VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2023, Vol. 30, No. 3, 473–482
DOI: 10.5603/CJ.a2023.0018

ISSN 1897–5593
eISSN 1898–018X

Flecainide in clinical practice

Mikołaj Basza[1], Cezary Maciejewski[2], Wojciech Bojanowicz[1], Paweł Balsam[2], Marcin Grabowski[2], Przemysław Mitkowski[3], Maciej Kempa[4], Oskar Kowalski[5], Zbigniew Kalarus[6], Miłosz Jaguszewski[7], Andrzej Lubiński[8], Ludmiła Daniłowicz-Szymanowicz[4], Łukasz Szumowski[9], Maciej Sterliński[9], Łukasz Kołtowski[2]

[1]Medical University of Silesia in Katowice, Poland
[2]1st Department of Cardiology, Medical University of Warsaw, Poland
[3]1st Department of Cardiology, University of Medical Sciences, Poznan, Poland
[4]Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland
[5]Department of Human Nutrition, School of Public Health in Bytom, Silesian Medical University in Katowice, Silesian Center of Heart Disease in Zabrze, Poland
[6]Department of Cardiology, DMS in Zabrze, Medical University of Silesia, Katowice, Poland
[7]1st Department of Cardiology, Medical University of Gdansk, Poland
[8]Department of Cardiology and Internal Disease, Medical University of Gdansk, Poland
[9]1st Arrhythmia Department, National Institute of Cardiology, Warsaw, Poland

This paper was guest edited by Prof. José Manuel Rubio Campal

Abstract

Flecainide, similar to encainide and propafenone, is IC class antiarrhythmic, inhibiting Nav1.5 sodium channels in heart muscle cells and modulates cardiac conduction. Despite its over 40-year presence in clinical practice, strong evidence and well-known safety profile, flecainide distribution in Europe has not always been equal. In Poland, the drug has been available in pharmacies only since October this year, and previously it had to be imported on request. Flecainide can be used successfully in both the acute and chronic treatment of cardiac arrhythmias. The main indication for flecainide is the treatment of paroxysmal supraventricular tachycardias, including atrial fibrillation, atrioventricular nodal re-entrant tachycardia, atrioventricular re-entrant tachycardia and ventricular arrhythmias in patients without structural heart disease. Beyond that, it may be used in some supraventricular tachycardia in children and for sustained fetal tachycardia. Many studies indicate its efficacy comparable to or better than previously used drugs such as propafenone and amiodarone, depending on the indication. This review aims to highlight the most important clinical uses of flecainide in the light of the latest scientific evidence and to provide an overview of the practical aspects of treatment, including indications, off-label use, contraindications, areas of use, monitoring of treatment and most common complications, taking into account special populations: children and pregnant women. (Cardiol J 2023; 30, 3: 473–482)

Key words: flecainide, atrial fibrillation, cardioversion, supraventricular arrhythmias, ventricular arrhythmias

Address for correspondence: Dr. Mikołaj Basza, Medical University of Silesia in Katowice, ul. Tadeusza Kościuszki 36/10, 44-100 Gliwice, Poland, tel: +48 666 351 061, e-mail: s73469@365.sum.edu.pl

Received: 8.11.2022 Accepted: 19.01.2023 Early publication date: 10.03.2023

Introduction

The Food and Drug Administration officially approved flecainide on October 31, 1985. Since then, major steps have been taken in diagnosing and managing supraventricular and ventricular arrhythmias; therefore, antiarrhythmic drugs play an essential role in contemporary clinical practice. To select the most appropriate treatment for a particular patient, fully understanding the advantages and limitations of loose molecules is necessary. In this article, we look at flecainide's pharmacological and clinical profiles.

Like, encainide and propafenone, flecainide is a class IC antiarrhythmic drug. Its main mechanism of action relies on strong inhibition of the Nav1.5 sodium channel, which is responsible for fast inward sodium flow during the 0 phase of action potential and rapid depolarization of the heart muscle. Despite the long-term clinical experience using flecainide in different patient subpopulations, its availability across European Union and European Economic Area countries was not always equal (Fig. 1). The drugs containing flecainide were previously imported to Poland from abroad as a targeted import on special demand and a doctor's recommendation; since October 2022, flecainide has been available on the Polish market. This review highlights the main application areas of flecainide, considering the latest guidelines and scientific evidence.

Flecainide: Scope of use

Flecainide is used in paroxysmal supraventricular tachycardias (SVT), including atrial fibrillation (AF), atrioventricular re-entrant tachycardia (AVRT), and atrioventricular nodal re-entrant tachycardia (AVNRT) in patients without structural heart disease. Flecainide is also used to prevent life-threatening sustained ventricular tachycardia (VT) and some channelopathies [1]. Additionally, the off-label use includes sustained fetal tachycardia (maternal/transplacental administration), premature ventricular beats (PVCs), and pharmacological cardioversion of AF. The main contraindications for treatment with flecainide are ischemic heart disease, hypertension with left ventricular hypertrophy (LVH), congestive heart failure, hypertrophic cardiomyopathy, degree 2 and 3 atrioventricular blocks, complete bundle branch block and significant liver and kidney disease (Table 1) [1]. The issue of the structural definition of heart disease in the context of the use of this drug is still under debate, and further studies are needed to determine flecainide's level of safety, allowing for a better understanding and differentiation of this term, especially in the context of ischemic heart disease. The current contraindica-

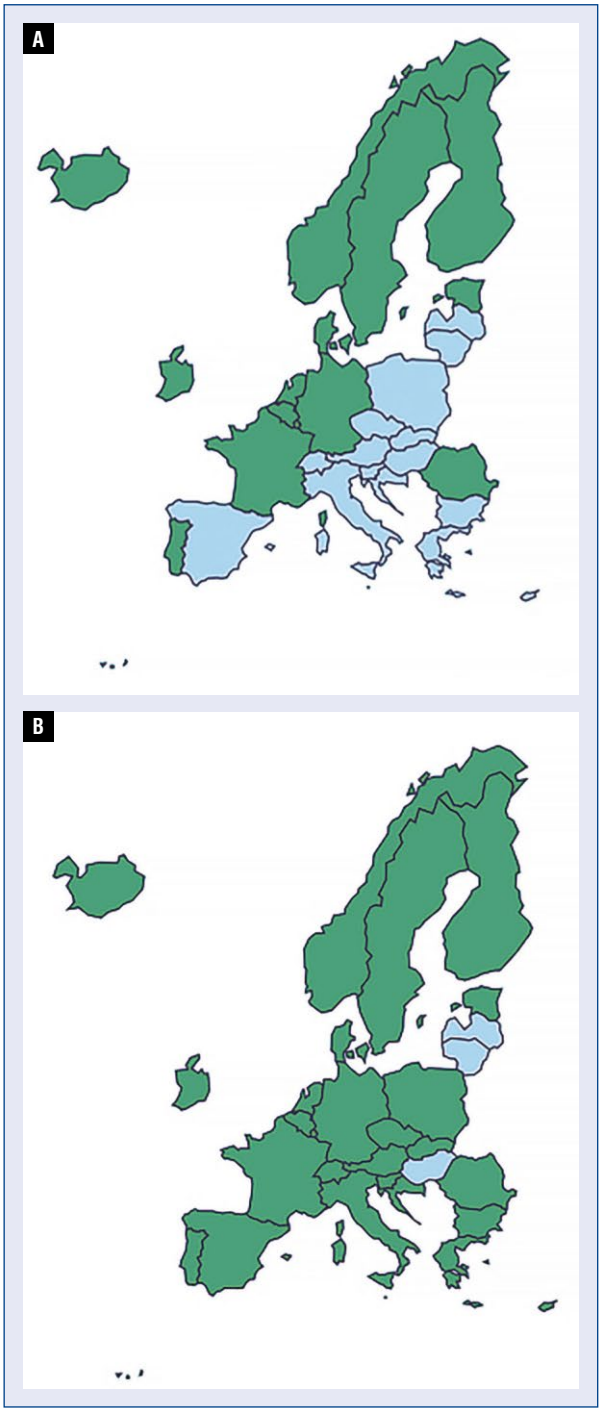


Figure 1. Flecainide availability across European Economic Area countries in 2018 (**A**) and 2022 (**B**). Source: National registers appointed by the European Medicines Agency.

Table 1. Flecainide indication and contraindications.

Flecainide indications	Flecainide contraindications
Atrial fibrillation/atrial flutter in patients who do not have structural heart disease	Ischemic heart disease
Pharmacological cardioversion of atrial fibrillation or flutter	Hypertrophic cardiomyopathy
Paroxysmal supraventricular tachycardia	Hypertension with left ventricular hypertrophy
Atrioventricular nodal re-entrant tachycardia	Congested heart failure
Atrioventricular re-entrant tachycardia	High-degree atrioventricular block
Wolff-Parkinson-White syndrome	Complete bundle branch block
Sustained ventricular tachycardia	Structural heart disease
Premature ventricular beats	Sick sinus syndrome
Sustained fetal tachycardia (maternal/transplacental administration)	Cardiogenic shock
	Acquired/congenital QT prolongation with a history of torsades de pointes
	Concurrent intake of ritonavir

tions for using flecainide in patients with structural heart disease are based on a prematurely interrupted CAST study and left much confusion. CAST was terminated 2 years after the start of enrollment due to increased mortality and sudden cardiac death in flecainide's group. That might have an impact not only on further contraindications but also on the underutilization of this drug, even in fields with strong clinical evidence of flecainide's safety [2–4].

Focus on atrial fibrillation

Emergency treatment

Flecainide may be successfully used in the pharmacological cardioversion of AF, and it is recommended for the cardioversion of new-onset AF in patients without structural heart disease [4–6]. Flecainide is characterized by a relatively high success rate in restoring sinus rhythm and a short median time to restore the rhythm, which makes this substance a reasonable alternative to propafenone and amiodarone [4, 7–9]. Martínez-Marcos et al. [7] compared these three substances administered intravenously in the single-blind trial and showed that flecainide was superior to others, with a 90% conversion rate in the first 12 hours to 72% and 64% for propafenone and amiodarone, respectively. Similar conclusions have been shown by Boriani et al. [8], a study in which they compared different drug protocols on AF conversion rate to sinus rhythm. Flecainide was administered per os and had a comparable conversion rate to orally and intravenously administered propafenone groups after 8 hours (75%, 76%, 75%, respectively).

The European Society of Cardiology (ESC) guidelines recommend considering flecainide for the induction of electrical cardioversion [5], although it is good to clarify that in evidence — Climent et al. [10] showed that flecainide does not significantly increase the rate of successful cardioversion and does not prevent AF relapses after the procedure. Moreover, 35% higher effectiveness of the first shock, compared to the placebo, was present in the subgroup of patients with successful cardioversion and not in the total study population. Some studies report that flecainide dose before cardioversion reduces energy requirements. On the other hand, studies show increased energy requirements in patients receiving flecainide's treatment. However, different methods were used to compare those results [11] reliably. Still, more research is needed to evaluate the role of this substance in cardioversion premedication. Nevertheless, it seems that flecainide does not reduce the effectiveness of electrical cardioversion and may have potential benefits without significant adverse effects in patients with persistent AF.

In selected patients, it is worth considering flecainide in the "pill in the pocket" strategy after evaluating the effectiveness and safety of such therapy in a hospital setting. Despite a lower conversion rate, this strategy may be preferred as it allows early conversion at a lower cost burden to the healthcare system with relatively low risk for a patient. It has been shown that if taken within 10 min from the onset of symptoms, the success rate of sinus rhythm recovery reaches 94% within 4 hours without needing further medical interven-

tion. The incidence rate of side effects remains low, at 7%. Only 1 in 165 patients in the study needed emergency room treatment due to atrial flutter (AFL). Others presented milder symptoms such as nausea, asthenia and vertigo [12]. The current ESC guidelines state that the "pill in the pocket" strategy with flecainide should be considered in everyday clinical practice (class IIa with confidence level B).

Long-term rhythm control

European Society of Cardiology guidelines recommend flecainide or propafenone for the long-term control of heart rhythm in AF patients with normal left ventricular function and no structural heart disease (defined as significant LVH and myocardial ischemia). These recommendations are strongly supported by several studies confirming flecainide's efficiency and safety profile [13–15]. The 2019 review of the Cochrane Antiarrhythmic Drugs database, based on four randomized controlled trials with over 511 participants, confirmed the effectiveness of chronic treatment with flecainide acetate compared to placebo or no treatment (relative risk [RR] 0.65). Flecainide, similar, to the previous 2015 review of Cochrane, had a better risk ratio than propafenone (RR 0.67) and was only second to amiodarone (RR 0.52) [13]. PITAGORA — randomized trial, on 127 patients paced for sinus node diseases in a mean follow-up of 20 months which showed that, among IC class agents, only flecainide was non-inferior to amiodarone in the management of atrial arrhythmias with comparable 1-year freedom from atrial tachyarrhythmia episodes. The findings of this study may apply to clinical practice; however small group count (37 randomized to flecainide) remains a significant limitation. In line with the new ESC guidelines, in patients with AF treated with flecainide for long-term heart rhythm control, concomitant use of an atrioventricular node blocking agent should be considered to avoid the transition to 1:1 conduction of AFL (class IIA recommendation) (Table 2).

Other supraventricular arrhythmias

Although electrical cardioversion remains the gold standard in acute settings and catheter ablation in the chronic treatment of supraventricular arrhythmias, flecainide might be considered in some cases where first-line treatment is unavailable or has no effect.

Flecainide may be considered in the acute treatment of focal atrial tachycardia in hemodynamically stable patients when adenosine, followed by beta-blockers or calcium channel blockers, are ineffective [16]. When ablation cannot be performed as a chronic treatment, it can be considered among non-dihydropyridine calcium channel blockers, beta-blockers, or propafenone. Treatment with flecainide was successful in 86% of patients with acute (intravenous) drug administration and 95% with chronic atrial tachycardia treatment [17]. An intravenous flecainide may effectively stop AVNRT and AVRT. It was effective in 14 (100%) patients with AVNRT and 11 (92%) patients with AVRT [18]. Flecainide is effective towards accessory pathways. Therefore, it can be considered in antidromic AVRT when vagal nerve manoeuvre and adenosine fail [16]. In 1986, Kim et al. [19] showed that, following intravenous or oral treatment with flecainide, recurrent SVT was non-inducible in 6 patients with recurrent atrioventricular tachycardia and three with recurrent atrioventricular node tachycardia. In these 9 patients, intravenous flecainide prevented the induction of recurrent SVT by inhibiting retrograde conduction in the reentry loop. Twelve patients continued treatment with oral flecainide for 16 months after hospital discharge in the same study. Tachycardia recurred in three of whom arrhythmia remained inducible after treatment with flecainide and in one of whom SVT was not inducible [19]. This indicates that flecainide is an antiarrhythmic agent worth considering in treating AVRT and AVNRT patients. In the chronic treatment of antidromic AVRT, flecainide should be considered, mainly when ablation is contraindicated or not feasible. Flecainide may also be considered in pre-excited AF (class IIB recommendation) (Table 3). Nevertheless, it is not recommended as first-line antiarrhythmics in patients with congenital heart disease, ventricular dysfunction, severe fibrosis, and sinus rhythm recovery in supraventricular macroreentry arrhythmias. Flecainide causes prolongation of AFL cycle length; however, it has a poor conversion rate, therefore, dofetilide is the first choice in hemodynamically stable patients [20].

Ventricular arrhythmias

Flecainide can be used in a provocation test to diagnose the Brugada type 1 pattern on the ECG as an alternative for ajmaline, but with much longer observation times (4 and 24 h vs. 0.5 and 4 h). Beyond diagnostics, flecainide is widely used in managing patients with ventricular arrhythmias, with its main application in catecholaminergic polymorphic ventricular tachycardia (CPVT). Several

Table 2. Recommendations with flecainide mentioned by European Society of Cardiology in the 2020 Guidelines for management of atrial fibrillation (adapted from: [5]).

Recommendations	Class of recommendation	Level of evidence
Recommendations for long-term antiarrhythmic drugs		
Flecainide or propafenone is recommended for long-term rhythm control in AF patients with normal left ventricle function and without structural heart disease, including significant LVH and myocardial ischemia	I	A
In AF patients treated with **flecainide** for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered	IIa	C
Recommendations for the management of AF during pregnancy		
Acute management		
Ibutilide or **flecainide** i.v. may be considered for termination of AF in stable patients with structurally normal hearts	IIb	C
Long-term management (oral administration of drugs)		
Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail	IIa	C
Recommendations for cardioversion		
For pharmacological cardioversion of recent-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or **flecainide** or propafenone (excluding patients with severe structural heart disease) is recommended	I	A
Pre-treatment with amiodarone, **flecainide**, ibutilide, or propafenone should be considered to facilitate the success of electrical cardioversion	IIa	B
In selected patients with infrequent and recent-onset AF and no significant structural or ischemic heart disease, a single self-administered oral dose of **flecainide** or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment	IIa	B

ACS — acute coronary syndrome; HF — heart failure; AF — atrial fibrillation; LVH — left ventricular hypertrophy

studies showed it reduces (24%) or reverses (42%) episodes of CPVT in patients without conventional therapy [21, 22]. Moreover, in patients on optimal beta-blocker therapy, after adding flecainide, CPVT suppression exceeded 85%; therefore, it should be considered as an addition to beta-blockers or alone if there are any contraindications for beta-blocker therapy [21, 23]. It is also highly recommended in CPTV patients after sudden cardiac arrest as a part of therapeutic intervention with implantable cardioverter-defibrillator implantation and beta-blockers (class I recommendation) [22, 24, 25]. 2022 ESC guidelines introduced changes and new concepts, including flecainide and its role in idiopathic PVC/VT and Andersen-Tawil syndrome (Table 4) [25].

An important consideration for clinical practice use

Before starting flecainide therapy, it is essential to rule out any contraindications. To rule out contraindications for the initiation of treatment, it is necessary to perform a 12-lead electrocardiogram (ECG), and it is also recommended to perform a cardiac stress test to exclude potential myocardial ischemia and an echocardiogram to assess the function of the left ventricle. An important parameter to be assessed before and during treatment is the width of the QRS complex, especially as flecainide should be viewed as a drug with a narrow therapeutic window [26]. During flecainide therapy, prolongation of QT and an increase in QRS between 12% and 20% can be expected. In cases of QRS width an increase of more than 25% from the baseline value bundle branch block or other blocks over 120 ms, ESC guidelines suggest discontinuing the treatment. Some authors propose reducing the dosage by half, and then, if the targeted QRS width still cannot be achieved, therapy should be discontinued (Central illustration) [5, 9, 25]. During flecanide treatment, a range of other adverse, proarrhythmic events with an incidence between

Table 3. Recommendations on using flecainide by European Society of Cardiology in 2019 Guidelines on supraventricular tachycardia (adapted from: [16]).

Recommendations	Class of recommendation	Level of evidence
Recommendations for the therapy of atrioventricular re-entrant tachycardia due to manifest or concealed accessory pathways		
Acute therapy — Hemodynamically stable patients		
In antidromic AVRT, i.v. ibutilide or procainamide or i.v. **flecainide** or profanenone or synchronized direct current cardioversion should be considered if vagal manoeuvres and adenosine fail	IIa	B
Chronic therapy		
Propafenone or **flecainide** may be considered in patients with AVRT and without ischemic or structural heart disease, if ablation is not desirable or feasible	IIb	B
Recommendations for the therapy of focal atrial tachycardia		
Acute therapy — Hemodynamically stable patients		
Adenosine (6–18 mg i.v. bolus) should be considered	IIa	B
Beta-blockers (i.v. esmolol or metoprolol) should be considered in the absence of decompensated heart failure, if adenosine fails	IIa	C
Verapamil or diltiazem (i.v.) should be considered for hemodynamically stable patients in the absence of hypotension or HFrEF, if adenosine fails	IIa	C
If the above measures fail, the following may be used:	IIb	C
• i.v. ibutilide		
• or i.v. **flecainide** or propafenone		
• or i.v. amiodarone		
Chronic therapy		
Beta-blockers or non-dihydropyridine calcium channel blockers (verapamil or diltiazem in the absence of HFrEF), or propafenone or **flecainide** in the absence of structural or ischemic heart disease, should be considered if ablation is not desirable or feasible	IIa	C
Recommendations for the acute therapy of pre-excited atrial fibrillation		
Hemodynamically stable patients		
Flecainide or propafenone (i.v.) may be considered	IIb	B
Recommendations for the therapy of supraventricular tachycardia in pregnancy		
Chronic therapy		
Flecainide or propafenone should be considered for prevention of SVT in patients with WPW syndrome, and without ischemic or structural heart disease	IIa	C
Flecainide or propafenone in patients without ischemic or structural heart disease should be considered if atrioventricular nodal blocking agents fail to prevent SVT	IIa	C

i.v. **flecainide** and propafenone are contraindicated in patients with ischemic or structural heart disease. They also prolong the QTc interval but much less than class III agents
AVRT — atrioventricular re-entrant tachycardia; HFrEF — heart failure with reduced ejection fraction; SVT — supraventricular tachycardia; WPW — Wolff-Parkinson-White

< 1% to 13%, may occur. This includes bradycardia, additional ventricular contractions, atrioventricular block, SVT, bundle branch block and AF, drug-induced Brugada, hypotension, 1:1 AFL, worsening heart failure, dizziness, tremor and nausea [4, 26, 27]. Lavalle et al. [4] proposed a practical guide for managing adverse events due to flecainide.

Safety in special populations

Pregnancy

Flecainide could be safely used in any supraventricular arrhythmia in pregnant women [5, 16]. Heart rhythm control is the preferred strategy in AF pregnant patients. Electrical car-

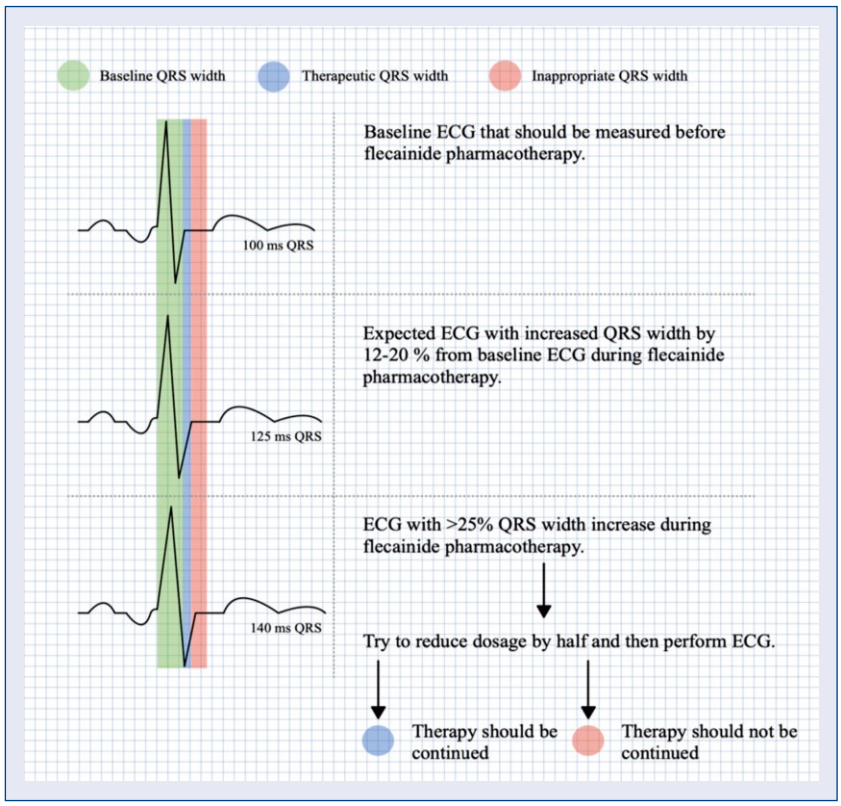
Table 4. Comprehensive recommendations for the use of flecainide as in the 2022 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (adapted from: [25]).

Recommendations	Class of recommendation	Level of evidence
Recommendations for management of patients with Andersen–Tawil syndrome		
Beta-blockers and/or **flecainide** with or without acetazolamide should be considered in patients with Andersen–Tawil syndrome to treat ventricular arrhythmia	IIa	C
Recommendations for the management of patients with catecholaminergic polymorphic ventricular tachycardia		
ICD implantation combined with beta-blockers and **flecainide** is recommended in CPVT patients after aborted cardiac arrest	I	C
LCSD should be considered in patients with diagnoses of CPVT when the combination of beta-blockers and **flecainide** at therapeutic dosage are either not effective, not tolerated, or contraindicated	IIa	C
ICD implantation should be considered in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/polymorphic VT while on the highest tolerated beta-blocker dose and on **flecainide**	IIa	C
Flecainide should be considered in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose	IIa	C
Recommendations for the management of patients with idiopathic premature ventricular complexes/ventricular tachycardia		
Beta-blockers, non-dihydropyridine CCBs, or **flecainide** should be considered when catheter ablation is not available, desired, or is particularly risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles	IIa	B
Catheter ablation or **flecainide** should be considered in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles	IIa	C
Recommendations for the prevention of sudden cardiac death and management of ventricular arrhythmia during pregnancy		
For acute conversion of hemodynamically tolerated SMVT during pregnancy, a beta-blocker, sotalol, **flecainide**, procainamide, or overdrive ventricular pacing should be considered	IIa	C
Recommendations for the acute management of sustained ventricular tachycardia and electrical storm		
In patients presenting with a hemodynamically tolerated SMVT in the absence of significant SHD, **flecainide**, ajmaline, or sotalol may be considered	IIb	C

CCB — calcium channel blockers; CPVT — catecholaminergic polymorphic ventricular tachycardia; ICD — implantable cardioverter-defibrillator; LCSD — left cardiac sympathetic denervation; PVCs — premature ventricular beats; RVOT — right ventricular outflow tract; SHD — structural heart disease; SMVT — sustained monomorphic ventricular tachycardia; VT — ventricular tachycardia

dioversion is recommended in hemodynamically unstable pregnant women; however, intravenous flecainide might be considered in hemodynamically stable women without structural heart disease [16].

In a series of cases, Chauvaue et al. [28] demonstrated the safe use of intravenous 100 mg flecainide to restore sinus rhythm in pregnant women and then followed by 200–300 mg of oral flecainide daily until delivery without complications for fetus growth and delivery. Similar case reports have been presented by Lewis and Currie [29], who performed successful pharmacological cardioversion on 38-year-old women in the 27th week of pregnancy. No evidence of congenital abnormality was observed [29]. Flecainide, despite limited evidence, is considered safe for the fetus and should be considered for managing fetal arrhythmia. In 1991 Allan et al. [30] conducted 12 successful rhythm conversions in 14 hydropic fetuses, with 1 case of spontaneous intrauterine death. In most cases, the time to conversion was under 48 hours. In the comparison of flecainide, sotalolol, and digoxin in



Central illustration. An important considerations for clinical practice use of flecainide; ECG — electrocardiogram.

SVT and AFL management on 159 fetuses, flecainide was superior to other drugs, with a 59% conversion rate and median 4 days to conversion in SVT; however, contrary, sotalol was more efficient than flecainide and digoxin in AFL patients [31].

Children

Flecainide is recommended as one of the first lines in some SVT in infants and children without structural heart disease and preserved ventricular function. It might be considered in symptomatic idiopathic VT and ion channelopathies such as long QT syndrome and catecholaminergic VT [32]. A retrospective cohort study on 175 children, including those with congenital heart disease and cardiomyopathy, showed that flecainide was well-tolerated. No significant difference in proarrhythmic effect was found in children with and without congenital heart disease. There was no cardiac arrest in this cohort; however, one death related to respiratory syncytial virus infection was reported [33]. In 2020 Vaquer et al. [34] reported 3 cases of flecainide intoxication in infants. Flecainide as a drug with a narrow therapeutic window, potential proarrhythmic effects, and interactions with dairy products, should be administered with caution and under ECG and plasma level monitoring, especially in the first 48–72 hours and in patients under 1 year old.

Summary

Flecainide, used in reference to the current state of the art and under proper supervision, can be seen as a highly effective and safe drug for arrhythmia management. The risk of side effects, in particular the proarrhythmic effect, can be minimized by diligently examining the patient for contraindications to treatment, using the drug according to current recommendations and guidelines, gradual dose increase under the supervision of a doctor in the hospital, and regular monitoring of the effects treatment with the use of ECG.

Conflict of interest: None declared

References

1. Arunachalam K, Alzahrani T. Flecainide. [Updated 2022 Aug 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/nbk542291/ (2022 January).

2. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991; 324(12): 781–788, doi: 10.1056/NEJM199103213241201, indexed in Pubmed: 1900101.
3. Anderson JL, Platia EV, Hallstrom A, et al. Interaction of baseline characteristics with the hazard of encainide, flecainide, and moricizine therapy in patients with myocardial infarction. A possible explanation for increased mortality in the Cardiac Arrhythmia Suppression Trial (CAST). Circulation. 1994; 90(6): 2843–2852, doi: 10.1161/01.cir.90.6.2843, indexed in Pubmed: 7994829.
4. Lavalle C, Magnocavallo M, Straito M, et al. Flecainide how and when: a practical guide in supraventricular arrhythmias. J Clin Med. 2021; 10(7), doi: 10.3390/jcm10071456, indexed in Pubmed: 33918105.
5. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
6. January CT, Wann LS, Alpert JS, et al. ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014; 130(23): 2071–2104, doi: 10.1161/CIR.0000000000000040, indexed in Pubmed: 24682348.
7. Martínez-Marcos FJ, García-Garmendia JL, Ortega-Carpio A, et al. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. Am J Cardiol. 2000; 86(9): 950–953, doi: 10.1016/s0002-9149(00)01128-0, indexed in Pubmed: 11053705.
8. Boriani G, Biffi M, Capucci A, et al. Conversion of recent-onset atrial fibrillation to sinus rhythm: effects of different drug protocols. Pacing Clin Electrophysiol. 1998; 21(11 Pt 2): 2470–2474, doi: 10.1111/j.1540-8159.1998.tb01203.x, indexed in Pubmed: 9825369.
9. Andrikopoulos GK, Pastromas S, Tzeis S. Flecainide: Current status and perspectives in arrhythmia management. World J Cardiol. 2015; 7(2): 76–85, doi: 10.4330/wjc.v7.i2.76, indexed in Pubmed: 25717355.
10. Climent VE, Marin F, Mainar L, et al. Effects of pretreatment with intravenous flecainide on efficacy of external cardioversion of persistent atrial fibrillation. Pacing Clin Electrophysiol. 2004; 27(3): 368–372, doi: 10.1111/j.1540-8159.2004.00444.x, indexed in Pubmed: 15009866.
11. Guarnieri T, Tomaselli G, Griffith LS, et al. The interaction of antiarrhythmic drugs and the energy for cardioversion of chronic atrial fibrillation. Pacing Clin Electrophysiol. 1991; 14(6): 1007–1012, doi: 10.1111/j.1540-8159.1991.tb04150.x, indexed in Pubmed: 1715060.
12. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med. 2004; 351(23): 2384–2391, doi: 10.1056/NEJMoa041233, indexed in Pubmed: 15575054.
13. Valembois L, Audureau E, Takeda A, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2019; 9(9): CD005049, doi: 10.1002/14651858.CD005049.pub5, indexed in Pubmed: 31483500.
14. Gulizia M, Mangiameli S, Orazi S, et al. PITAGORA Study Investigators. A randomized comparison of amiodarone and class IC antiarrhythmic drugs to treat atrial fibrillation in patients paced for sinus node disease: the Prevention Investigation and Treatment: A Group for Observation and Research on Atrial arrhythmias (PITAGORA) trial. Am Heart J. 2008; 155(1): 100–107, 107.e1, doi: 10.1016/j.ahj.2007.08.033, indexed in Pubmed: 18082498.
15. Gulizia M, Mangiameli S, Chiarandà G, et al. Design and rationale of a randomized study to compare amiodarone and Class IC anti-arrhythmic drugs in terms of atrial fibrillation treatment efficacy in patients paced for sinus node disease: the PITAGORA trial. EP Europace. 2006; 8(4): 302–305, doi: 10.1093/europace/eul003.
16. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020; 41(5): 665–720, doi: 10.1093/eurheartj/ehz467, indexed in Pubmed: 31504425.
17. Hohnloser SH, Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. Am J Cardiol. 1992; 70(5): 3A–9A, doi: 10.1016/0002-9149(92)91071-b, indexed in Pubmed: 1387287.
18. Gambhir DS, Bhargava M, Arora R, et al. Electrophysiologic effects and therapeutic efficacy of intravenous flecainide for termination of paroxysmal supraventricular tachycardia. Indian Heart J. 1995; 47(3): 237–243, indexed in Pubmed: 7558090.
19. Kim SS, Lal R, Ruffy R. Treatment of paroxysmal reentrant supraventricular tachycardia with flecainide acetate. Am J Cardiol. 1986; 58(1): 80–85, doi: 10.1016/0002-9149(86)90245-6, indexed in Pubmed: 3728336.
20. Crijns HJ, Van Gelder IC, Kingma JH, et al. Atrial flutter can be terminated by a class III antiarrhythmic drug but not by a class IC drug. Eur Heart J. 1994; 15(10): 1403–1408, doi: 10.1093/oxfordjournals.eurheartj.a060402, indexed in Pubmed: 7821320.
21. Van Der Werf C, Kannankeril PJ, Sacher F, et al. Wilde flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011; 57(22): 2244–2254, indexed in Pubmed: 21616285.
22. Kannankeril PJ, Moore JP, Cerrone M, et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. JAMA Cardiol. 2017; 2(7): 759–766, doi: 10.1001/jamacardio.2017.1320, indexed in Pubmed: 28492868.
23. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015; 36(41): 2793–2867, doi: 10.1093/eurheartj/ehv316, indexed in Pubmed: 26320108.
24. Paolini E, Stronati G, Guerra F, et al. Flecainide: Electrophysiological properties, clinical indications, and practical aspects. Phar-

macol Res. 2019; 148: 104443, doi: 10.1016/j.phrs.2019.104443, indexed in Pubmed: 31493514.
25. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022; 43(40): 3997–4126, doi: 10.1093/eurheartj/ehac262, indexed in Pubmed: 36017572.
26. Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. Am J Cardiol. 1984; 53(5): 89B–94B, doi: 10.1016/0002-9149(84)90509-5, indexed in Pubmed: 6695821.
27. Tamargo J, Le Heuzey JY, Mabo P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. Eur J Clin Pharmacol. 2015; 71(5): 549–567, doi: 10.1007/s00228-015-1832-0, indexed in Pubmed: 25870032.
28. Chauveau S, Le Vavasseur O, Morel E, et al. Flecainide is a safe and effective treatment for pre-excited atrial fibrillation rapidly conducted to the ventricle in pregnant women: a case series. Eur Heart J Case Rep. 2019; 3(2), doi: 10.1093/ehjcr/ytz066, indexed in Pubmed: 31449645.
29. Lewis G, Currie P. Atrial fibrillation during pregnancy: cardioversion with flecainide. Br J Hosp Med (Lond). 2015; 76(12): 720–721, doi: 10.12968/hmed.2015.76.12.720, indexed in Pubmed: 26646336.
30. Allan LD, Chita SK, Sharland GK, et al. Flecainide in the treatment of fetal tachycardias. Br Heart J. 1991; 65(1): 46–48, doi: 10.1136/hrt.65.1.46, indexed in Pubmed: 1899583.
31. Jaeggi ET, Carvalho JS, De Groot E, et al. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. Circulation. 2011; 124(16): 1747–1754, doi: 10.1161/CIRCULATIONAHA.111.026120, indexed in Pubmed: 21931080.
32. Brugada J, Blom N, Sarquella-Brugada G, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. EP Europace. 2013; 15(9): 1337–1382, doi: 10.1093/europace/eut082.
33. Cunningham T, Uzun O, Morris R, et al. The safety and effectiveness of flecainide in children in the current era. Pediatr Cardiol. 2017; 38(8): 1633–1638, doi: 10.1007/s00246-017-1707-5, indexed in Pubmed: 28840327.
34. Vaquer G, Marfil L, Ortega J, et al. Flecainide intoxication in pediatric patients with supraventricular tachycardia. Ann Pediatr Cardiol. 2020; 13(3): 264–266, doi: 10.4103/apc.APC_116_19, indexed in Pubmed: 32863668.