# Acute management of paroxysmal atrial fibrillation with beta-blockers plus intravenous flecainide using the real-world Chios registry (BETAFLEC-CHIOS)

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DOI: 10.33963/KP.a2022.0267

**Received:**
September 12, 2022

**Accepted:**
November 20, 2022

**Early publication date:**
November 23, 2022

## INTRODUCTION

Flecainide acetate is a class IC antiarrhythmic drug that was first synthesized in 1972. Nowadays after many years of clinical experience and with results of large trials, it is one of the first-line therapies for pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation (AF) without structural heart disease or coronary artery disease, according to the results of the CAST study [1]. Intravenous flecainide acetate was first introduced in Greek hospitals almost 18 months ago. Data on its use remain limited [2]. The BETAFLEC-CHIOS registry aimed to study the efficacy and safety of intravenous flecainide, co-administered with oral b-blockers in consecutive patients without structural heart disease or significant conduction abnormalities for cardioversion of paroxysmal AF.

## METHODS

### *Patient population*

BETAFLEC-CHIOS is a single-center registry that was initiated at the "Skylitseion" General Hospital of Chios in January 2020. Patients included in the registry presented with recent-onset (≤48 hours) AF lasting ≥30 min and documented by a 12-lead ECG; they received both intravenous (IV) flecainide and oral β-blocker. Exclusion criteria were severe structural or ischemic heart disease, left ventricular hypertrophy, significant valvular heart disease, previous cardiac surgery, any cardiomyopathy, atrial flutter, sick sinus syndrome, high degree atrioventricular block, abnormal electrolyte levels, or known sensitivity to flecainide. Continuous monitoring was applied during and after administration of IV flecainide. All patients underwent bedside heart echocardiography and cardiac enzymes measurement including high-sensitivity troponin-I to exclude structural or ischemic heart disease before flecainide administration. Monitoring and cardioversion of the patients with successfully restored sinus rhythm took place at the Emergency Department in the presence of a cardiologist. All patients were admitted to the Cardiology Department for further examination.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the Scientific Committee of the Skylitseio General Hospital of Chios, Greece (research project number: 81). Informed written consent was provided by all patients included in the registry. The study was registered in ClinicalTrials.gov with ID: NCT04991896.

### *Outcomes*

The primary outcome was conversion to sinus rhythm at 1 hour. Secondary outcomes were successful conversion at 2 hours, proarrhythmic events, severe hypotension, discontinuation of the IV flecainide infusion for any reason, and hospitalization duration. If no conversion to sinus rhythm was achieved at 2 hours after flecainide infusion, the patient was recorded as an "unsuccessful conversion attempt" and

referred for direct current cardioversion (DCC). All patients were anticoagulated according to the current European Society of Cardiology Guidelines (ESC) for the management of AF [2].

### Flecainide administration

Flecainide is given as an IV infusion of 1.5 mg/kg (max 150 mg) in 5% dextrose water over 10 min under continuous monitoring. Additionally, concomitant administration of a β-blocker, at least 45 min before initiation of flecainide infusion, was applied in all patients. The dose and type of β-blocker were selected by the treating physician according to the heart rate during AF and the patient's medical history. "Time to conversion" was calculated as the time interval from the end of the infusion up to when sinus rhythm was observed on the monitor and confirmed subsequently with a 12-lead ECG.

### Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows software, version 24.0 (IBM Corp., Armonk, NY, US). A Shapiro-Wilk test was used for normality tests. Normally distributed variables are expressed as mean (SD) and were compared with the t-test for independent samples. Not normally distributed variables are expressed as median (interquartile range [IQR]) and were compared with the Mann-Whitney U test for independent samples. Categorical variables were compared with the $\chi^2$ test. When any of the assumptions of the $\chi^2$ test was not met, Fisher's exact test was used instead. Binomial logistic regression was also used to reveal predictive factors of successful cardioversion. Statistical significance was defined as $P$ <0.05.

## RESULTS AND DISCUSSION

A total of 81 (49 males, 32 females) randomly selected patients, who complied with the study protocol were included in the registry before September 10, 2022. The baseline characteristics of the whole cohort and differences between the successfully and unsuccessfully cardioverted groups are presented in Supplementary material, *Table S1*. As expected, IV flecainide was administered in patients with no ischemic or structural heart disease, mainly middle-aged patients whose main comorbidities were arterial hypertension and dyslipidemia.

The duration of atrial fibrillation varied from 1 to 26 hours, and the initial heart rate from 75 to 160 bpm. All patients received an oral β-blocker before IV flecainide infusion.

Successful conversion to sinus rhythm at 1 and 2 hours (primary and secondary endpoint) after IV flecainide administration was achieved in 65 patients, resulting in a success rate of 80.2%. The median conversion time was 10 minutes (3–20 minutes) (Figure 1, Supplementary material, *Table S2*). The 16 patients that remained on atrial fibrillation underwent successful direct current cardioversion to sinus rhythm. No serious adverse events were recorded during flecainide administration (Supplementary material, *Table S2*).

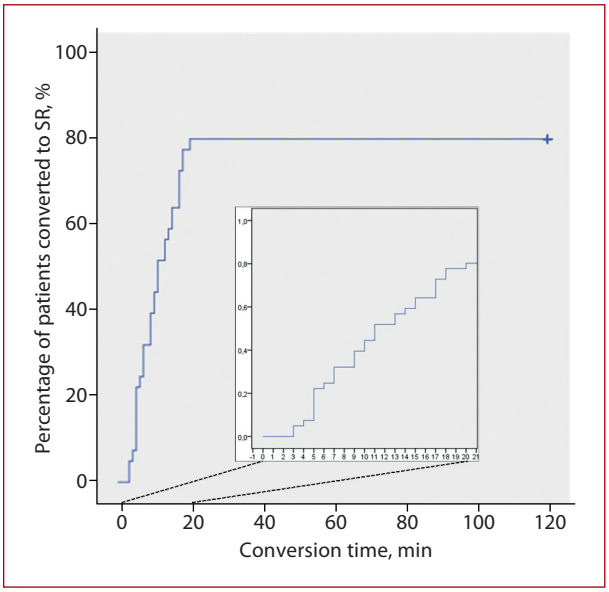


**Figure 1.** The figure depicts the relationship between the percentage of patients converted to SR and the conversion time. Successful conversion to sinus rhythm at 1 and 2 hours (primary and secondary endpoint) after IV flecainide administration was achieved in 65 patients, resulting in a success rate of 80.2%. The median conversion time was 10 min (3–20 min). Conversion rates with IV flecainide in recent-onset atrial fibrillation (AF) ≤72 hours varied from 50% to 96% in 1 hour after the infusion, slightly increased afterward for every hour, and almost reached a plateau at 3–8 hours, while shorter duration of AF ≤24 hours resulted in a higher success rate

Abbreviations: SR, sinus rhythm

When comparing the baseline characteristics between the successful and unsuccessful cardioversion groups, no statistically significant differences were found, except height (but this was not followed by a difference in body mass index [BMI] or body surface area [BSA]). Binomial logistic regression did not indicate any predictive factors of successful cardioversion either. Regarding duration of hospitalization, this was significantly shorter in patients who were successfully cardioverted with IV flecainide than in patients who failed to achieve sinus rhythm at 2 hours and had to wait for DCC (12 vs. 32 hours, $P$ <0.001) (Supplementary material, *Table 2*).

In acute AF cardioversion, flecainide is very effective in restoring sinus rhythm and with short conversion times compared with other antiarrhythmic drugs (amiodarone, propafenone, procainamide, ibutilide, dofetilide and vernakalant, antazoline) [2, 4–7]. Conversion rates with IV flecainide in recent-onset AF (≤72 hours) vary from 50% to 96% at 1 hour after the infusion, slightly increase afterward for every hour and almost reach a plateau at 3–8 hours, while shorter duration of AF (≤24 hours) results in higher success rate (Supplementary material, *Table S3, Figure S1*). Mean conversion time ranges from 14 to 53 minutes and usually is less than 30 minutes.

In conclusion, the BETAFLEC-CHIOS registry is, to our knowledge, one of the largest studies worldwide, evaluating the effectiveness and safety of IV flecainide in co-administration with a β-blocker in acute management of recent-onset AF, lasting less than 48 hours, in the emergency department. The success rate was high (80.2%) at 1 and 2 hours, and quick conversion to sinus rhythm was achieved in ≤20 minutes while no serious adverse events were observed. Appropriate selection of patients with shorter AF duration and the combination of flecainide with β-blocker, which is recommended by the ESC guidelines to increase the safety and efficacy of the medication in AF conversion, resulted in a high success rate of pharmacological cardioversion and fewer hospital admissions thanks to the short conversion time in short-stay units in the emergency department. Effective safe and fast AF cardioversion is of utmost importance, especially in the COVID-19 era when it is essential to minimize the need for hospitalization and use of valuable hospital resources.

### *Limitations*

The limitations of the BETAFLEC-CHIOS study are mainly associated with the type of the study (open-label, single-center registry). We tried to overcome inhomogeneities by establishing a pre-specified protocol and specific exclusion criteria for IV flecainide administration. Moreover, 20% of patients with AF received sotalol as a β-blocker (which was their baseline treatment of AF), even though the combination of two antiarrhythmic drugs is not suggested by the ESC 2020 AF guidelines [1]. However, there are articles regarding the combined use of flecainide and sotalol in AF in patients with arrhythmogenic right ventricular cardiomyopathy and recurrent supra-ventricular tachycardias [6].

### *Supplementary material*

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

### *Article information*

**Conflict of interest:** None declared.

**Funding:** No special funding was received for this registry. All treatments were available as standard treatments at the Skylitseio General Hospital of Chios, Greece.



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