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

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Short title: BETAFLEC-CHIOS registry

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INTRODUCTION
Flecainide acetate is a class IC antiarrhythmic drug that was first synthesized in 1972. Nowadays given the many years of clinical experience and the 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 firstly introduced in the Greek hospitals almost 18 months ago. Data from its use still remain limited [2]. The aim of the BETAFLEC-CHIOS registry was 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 the 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-lasting ≥30 min AF (≤48 hours of onset), documented by a 12-lead ECG, and 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 a bedside heart echo and cardiac enzymes measurement including high sensitivity troponin-I to exclude structural or ischemic heart disease, prior to flecainide administration. Monitoring and cardioversion of the patients with successfully restored sinus rhythm took place at the Emergency Department, under the presence of cardiologist. All patients were admitted in the Cardiology clinic 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, hospitalization duration. If no conversion to sinus rhythm was achieved at 2 hours after flecainide infusion, the patient was recorded as “unsuccessful conversion attempt” and forwarded 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 DW 5% over 10 min under continuous monitoring. Additionally, concomitant administration of a b-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 heart rate during the AF and 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 the software IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, US). 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-square test. When any of the assumptions of the χ² test was not met, Fisher’s exact test was used instead. Binomial logistic regression was used to reveal predictive factors of successful cardioversion, as well. 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 have been included in the registry until September 10, 2022. The baseline characteristics of the whole cohort as well as the differences between the successfully and not-successfully 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, with the main comorbidities being arterial hypertension and dyslipidemia.

The duration of the atrial fibrillation varied from 1-26 hours and the initial heart rate from 75 to 160 bpm. All patients received an oral b-blocker prior to 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 min (3–20 min) (*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*).

When comparing the baseline characteristics between the successful and not-successful cardioversion groups, no statistical differences were found, except from height (but this was not followed by a difference in body mass index [BMI] or body surface area [BSA]). Binomial logistic regression did not also reveal any predictive factor of successful cardioversion.
Regarding duration of hospitalization, this was significantly shorter in patients who were successfully cardioverted with IV flecainide than in patients who failed to achieve SR 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 \( \leq 72 \) hours vary from 50%–96% in the 1 hour after the infusion, slightly increase afterwards for every hour and almost reach a plateau at 3–8 hours, while shorter duration of AF \( \leq 24 \) hours results in higher success rate (Supplementary material, Table S3, Figure S1). Mean conversion time ranges from 14–53 min, usually being less than 30 min.

In conclusion, 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 b-blocker in the acute management of recent-onset AF, lasting less than 48 hours, in the emergency department. Success rate is high at 80.2% at 1 and 2 hours and quick with conversion to sinus rhythm achieved in \( \leq 20 \) minutes, while no serious adverse events were observed. Appropriately selected patients with shorter AF duration and the combination of flecainide with b-blocker which is proposed by the ESC Guidelines to increase the safety and efficacy of the medication in AF conversion) result in high success rate of pharmacological cardioversion and less hospital admissions due to the short conversion time that can be spent 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 b-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 \([1]\). Despite that, there are articles regarding the combined used of flecainide and sotalol in AF and 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.

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**REFERENCES**


**Figure 1.** Figure depicts the relationship between the percentage of patients converted to sinus rhythm 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 vary from 50%–96% in the 1 hour after the infusion, slightly increase afterwards for every hour and almost reach a plateau at 3–8 hours, while shorter duration of AF ≤24 hours results in higher success rate.