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EDITORIAL

Flecainide and atrial fibrillation cardioversion: what solutions at present and in the near future?

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This editorial refers to 'Flecainide acetate inhalation solution for cardioversion of recent-onset, symptomatic atrial fibrillation: results of the phase 3 RESTORE-1 trial' by M. Rienstra *et al.*, https://doi.org/10.1093/europace/euaf064.

Atrial fibrillation (AF) is an increasing healthcare challenge that significantly contributes to emergency department (ED) overcrowding and hospital admissions worldwide.[1,2] Over the past decade, the burden of ED visits due to AF has steadily increased, with a growing proportion of patients now managed directly in the ED without hospitalization.[3,4] Symptomatic episodes of AF remain a major driver of healthcare resource utilization and costs, significantly impacting patients' quality of life.[5,6] This highlights the need for standardized and safe strategies to optimize AF management, particularly in terms of rhythm control in the setting of recent-onset AF.[7-9]

Flecainide was synthetized in 1972 as a result of studies on analogues of procainamide and over the past 40 years has become one of the most widely used antiarrhythmic drugs, expanding beyond its original indication for ventricular arrhythmias.[7,9-11] Clinical use of flecainide was significantly impacted by the CAST trial, and its use is now contraindicated in patients with structural heart disease.[3,7,10,11] Recent observational data suggest that flecainide among select patients with nonobstructive coronary artery disease and without a history of ventricular tachycardia or non-revascularized myocardial infarction may be used without an increased risk of mortality. This evidence should be confirmed in future randomized controlled trials. Despite the safety concerns raised by the CAST trial, flecainide remains a key drug for AF rhythm control strategies in patients without structural heart disease. Additionally, the availability of different formulations (intravenous, immediate-release, and controlled-release) has proved its clinical applicability and patient adherence. Flecainide is now recognized as a cornerstone in the pharmacological cardioversion of recent-onset AF in appropriately selected patients.[3,11] The synthesis of flecainide in the early 70s was the result of a systematic search for fluorinated local anaesthetic analogues of procainamide. Its chemical structure is based on the amide linkage found in procainamide, but it incorporates two fluorinated phenyl groups, which improve its lipophilicity and sodium channel binding affinity. In the 1985, flecainide was approved by the FDA for the treatment of ventricular arrhythmias and later found its place in the management of AF and supraventricular tachycardias. Its primary mechanism of action involves potent sodium channel blockade, causing inhibition of the transient peak inward sodium current. The electrophysiological characteristics that are likely to play a central role in AF cardioversion include rate-dependent prolongation of atrial refractoriness, a greater prolongation of atrial refractoriness compared to action potential duration, a reduction in excitability, and inhibition of spontaneous diastolic SR Ca2+ release.[3,7,10]

Flecainide has been used through various administration routes, including intravenous, oral and recently, inhaled formulations[3,10-12] (*Figure 1*). Available data suggest that both intravenous and oral flecainide are highly effective in the pharmacological cardioversion of recent-onset AF.[11] Success rates for conversion are high, with intravenous administration achieving rates between 65% and 96%, and oral loading (with a single dose) ranging from 78% to 95%.[11] While intravenous flecainide typically restores sinus rhythm within 0.4–0.9 h, oral loading regimens take longer, ranging from 1.8 to 5 h, depending on the dosing protocol.[11,12] In recent years, significant efforts have been made to explore alternative administration routes and formulations for antiarrhythmic drugs that are better tolerated and may offer more immediate effectiveness.[10,13] Inhaled flecainide acetate has been developed to achieve a superior administration form: the breath-actuated inhaler generates a flecainide aerosol upon inhalation, allowing for rapid absorption and capillary delivery of the drug directly to the left atrium via the pulmonary veins.[10,13,14] This method enables a rapid clearance and a decreased systemic exposure of the drug, while obtaining faster and higher plasma concentrations for acute pharmacological

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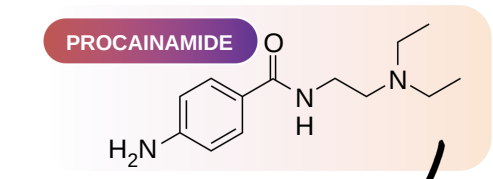

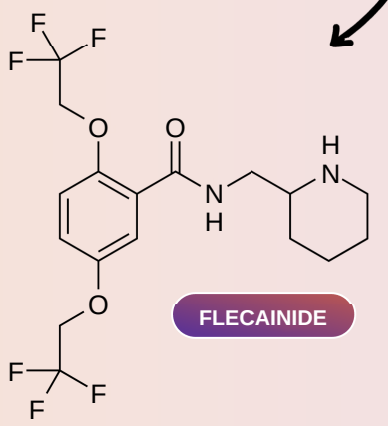

Route of administration	Standard dose	Time to sinus rhythm	Mean peak plasma levels	Efficacy, %	Serious adverse events, %
Intravenous	1.5–2 mg/kg	10–30 minutes	400–600 ng/mL	65–96	~2–3%
Oral	300 mg (200 mg if body weight <70 kg)	2–4 hours	300–500 ng/mL	78–95	~0.5–1%
Inhaled	120 mg	12–20 minutes	200–400 ng/mL	30–53	~1%

Figure 1 Flecainide, synthetized in 1972 as a result of studies on analogues of procainamide, is used for conversion of atrial fibrillation, with various routes of administration, including the classical intravenous and oral administrations, as well as the novel inhaled formulation. The standard doses, times to conversion to sinus rhythm, efficacy, and occurrence of adverse events are shown.

cardioversion than orally administered flecainide. The phase 2 INSTANT trial[13,14] was the first study to investigate this approach, with encouraging preliminary findings. The overall conversion rate was 42.6% (95% CI: 33.0–52.6%) with the majority (75.0%) of the conversions occurring within the first 30 min (median time of 14.6 min).[13] The inhaled formulation was found to be safe, and reported adverse events were mostly of mild intensity and limited duration.[13]

In the present Issue of *EP Europace*, Rienstra *et al.*[15] report the intriguing results of the Phase 3 RESTORE-1 trial. This multicentre study, conducted across 24 sites in Europe, Canada, and the USA, was a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of orally inhaled flecainide acetate (FlecIH-103) in patients with recent-onset, symptomatic, newly-diagnosed, or paroxysmal AF.[15] Patients were randomized in a 3:1 ratio to receive FlecIH-103, with an estimated total lung dose (eTLD) of up to 120 mg, or a placebo inhalation solution. The primary efficacy endpoint was the proportion of patients whose AF converted to sinus rhythm during a 90 min observation period. Unfortunately, the trial was prematurely stopped after enrolling 55 of the planned 400 patients, due to lower-than-expected conversion rates and plasma flecainide levels. Indeed, the conversion rate in the FlecIH group was 30.8% (95% CI: 14.7%, 43.8%), which was lower than anticipated and below the 42.6% conversion rate observed in the INSTANT-1 trial.[13,15] The median time to conversion in the active treatment group was substantially comparable (12.8 min, IQR: 17.2, range: 5.6–61.6 min).

One of the important factors to highlight is that the plasma flecainide levels in the RESTORE-1 trial achieved a mean maximum concentration of only 198 ng/mL.[15] This was nearly two-fold lower than the 367 ng/mL observed in the INSTANT-1 trial for the same target dose (eTLD of 120 mg), which likely contributed to the significantly lower conversion rates and limited overall efficacy.[13] This discrepancy in plasma levels may be the key factor behind the study's suboptimal outcome and warrants careful consideration for drug delivery formulations in future investigations. Of note, patients with successful AF cardioversion had a mean maximum plasma concentration of 260 ng/mL, which was ~50% higher than the mean plasma concentration of patients in whom cardioversion was not effective (172 ng/mL).[15]

Furthermore, the mean plasma levels in the present RESTORE-1 trial were approximately half of those observed in INSTANT-1, corresponding to a reduced eTLD of ~60 mg rather than the targeted 120 mg.[13,15] This reduction in the drug-delivered dose likely played a significant role in conditioning the suboptimal efficacy seen in this trial. As the authors nicely showed, when plotting the mean peak plasma levels and conversion rates from both trials, it becomes evident that the plasma levels reached in RESTORE-1 closely mirrored those seen with the 60 mg eTLD group in INSTANT-1.[15] This reinforces the hypothesis that the reduced conversion rate in the RESTORE-1 trial is probably due to the lower plasma concentrations, which likely resulted from a diminished dose delivery during the inhalation process. The authors hypothesize that the lower-than-expected dose was primarily due to variability in the performance of the drug-device combination product used in RESTORE-1, leading to a suboptimal nebulization rate of the inhaled solution. This batch-to-batch variability may have resulted in only ~50% of the intended dose being delivered over the 8 min inhalation period, directly affecting the plasma concentrations and, consequently, the efficacy of the treatment.[15]

It is important to note that AF conversion rate below 50% is lower than expected, especially when compared to the historically higher success rates of intravenously or orally administered flecainide.[11,12] On the other hand, it is important to emphasize that the safety profile of inhaled flecainide remains potentially advantageous over other formulations, also considering its rapid onset of action.[10] Moreover, a crucial factor is the difficulty in classifying the entity of recent-onset AF, as no cut-off time has not been established yet.[11] Historically, a 48 h cut-off has been

used to define recent-onset AF, although there is a growing trend towards more restrictive timeframes, with the 24 h threshold suggested by the latest 2024 AF ESC guidelines for maximizing safety.[8] Actually, in literature, several studies have adopted varying definitions of 'recent-onset AF' with time intervals from arrhythmia onset ranging from 12 h to 7 days, or <24 h. While this inconsistency in terminology presents challenges for study comparisons, it also underscores the need for a standardized operative definition. Such a definition is crucial not only for the accurate classification of patients but also for guiding clinical decisions. Future research should focus on refining these definitions to ensure more accurate comparisons and improve clinical decision-making.

The authors of the RESTORE-1 trial deserve commendation for undertaking such a complex randomized study in an era of rapidly evolving treatment options, including advanced pharmacological therapies and catheter ablation.[5,8] Overall, despite the premature termination of the trial, the data are of great interest, since show that inhaled flecainide is not only safe but have the potential to offer a practical option for rapid cardioversion of AF, providing prompt symptom relief and reducing emergency department stays. Furthermore, the study paves the way for new research into alternative administration routes for antiarrhythmic drugs. If ongoing researches confirm the safety profile and demonstrate significantly improved efficacy, the inhalation method could become a viable out-of-hospital therapeutic alternative, enabling faster restoration of sinus rhythm compared to the traditional 'pill-in-the-pocket' strategy.[10] Indeed, the 2024 AF ESC guidelines reaffirmed the role of flecainide for the 'pill-in-the-pocket' strategy with a class IIa recommendation.[8] Historically, this approach has not gained widespread acceptance due to concerns over potential proarrhythmic effects and the preference for hospital-based flecainide administration. However, when appropriately implemented with prior in-hospital safety oral testing, this strategy may serve as a safe and effective alternative, potentially reducing ED visits and hospitalizations.[11,12] In this context, inhaled flecainide could be implemented as a valid 'on-demand' strategy for AF out-of-hospital cardioversion in patients without structural heart disease.

As the field continues to explore innovative approaches to AF treatment, it is evident that a wide range of options is available. As The Doors' song '*Break On Through (To the Other Side)*' suggests, exploring new horizons is essential for uncovering innovative solutions. This includes revisiting historically established drugs, which may still prove efficacy when reassessed through the lens of modern scientific understanding.

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Data availability

No new data were generated or analysed in support of this research.

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