Time efficiency and safety of antazoline in the rapid cardioversion of recent onset atrial fibrillation during supraventricular arrhythmias ablation

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INTRODUCTION

Pulmonary vein isolation (PVI) ablation is a minimally invasive treatment for atrial fibrillation (AF). Current guidelines recommend confirming electrical isolation, but periprocedural rapid-onset AF can complicate verification of whether a procedure was successful. In practice, rapid conversion to sinus rhythm can be achieved through electrical cardioversion (ECV) or pharmacological cardioversion (PCV) using antiarrhythmic drugs (AADs) like propafenone, flecainide, ibutilide, or amiodarone, with vernakalant being mostly inaccessible in general practice [1].

Antazoline, discovered in 1947, has shown its efficacy in converting AF to sinus rhythm since 1990. This led to its registration for treating supraventricular arrhythmias and widespread use in emergency departments and electrophysiology laboratories throughout Poland [2]. In our study, it was used according to this registration.

Despite its efficacy, safety, and registration in many European countries, antazoline is still not included in formal guidelines due to the lack of large randomized trials. Our study aimed to evaluate the time effectiveness and safety of intravenous antazoline in terminating recent-onset AF during ablation procedures.

METHODS

In this prospective, non-randomized, non-placebo-controlled observational cohort study, we assessed 42 patients treated for AF with antazoline during invasive electrophysiological studies or catheter ablation, from March 23, 2012 to March 20, 2014 in Central Veterans' Hospital in Lodz. All patients provided informed consent. The inclusion criteria required sinus rhythm at procedure start and cessation of AADs for at least five half-lives. The exclusion criteria included age <18 or >80 years, recent amiodarone usage within the past three months, structural heart disease, left ventricular ejection fraction (EF%) <40%, and the need for other AADs during the procedure. Data were collected for variables including age, history of atrial flutter (AFl), EF%, left atrial (LA) diameter, arterial hypertension (AH), diabetes mellitus (DM), time to conversion, and conversion to sinus rhythm (SR) status. Clinical and laboratory parameters (including electrocardiography and echocardiography) were evaluated according to the European Society of Cardiology and Polish Cardiac Society guidelines.

Upon AF onset, a 10-minute waiting period was observed for potential self-termination. For patients with interrupted oral anticoagulation, an intravenous injection of 5000 IU of unfractionated heparin was administered after AF onset. For those with AF, heparin boluses were administered under activated clotting time control (>300 sec) upon gaining left atrial access. If AF persisted, antazoline was administered in 100 mg/3-min boluses at 10-minute intervals, up to a maximum dose of 300 mg, in accordance with the Polish summary of product characteristics. Vital signs and potential antazoline-related side effects, such as tachycardia, bradycardia, hypotension, QT prolongation, and QRS prolongation, were

continuously monitored. Drug infusion was halted if significant complications arose. Each patient was observed for at least 30 minutes.

When AF was the underlying condition, PVI procedures continued. If AF persisted for over 30 minutes from the initial antazoline injection, ECV was performed. Metrics such as time to conversion and total antazoline dosage for AF termination were meticulously recorded.

Data were collected for variables including age, history of AFl, EF%, LA diameter, AH, DM, time to conversion, and conversion to SR status. The cohort was stratified into fast responders (dose ≤150 mg) and slow responders (dose >150 mg) for further subgroup analysis.

Statistical analysis

Numerical variables were reported as medians (interquartile ranges [IQR]), and categorical variables were reported as numbers and percentages. The differences in the variables were tested using the Wilcoxon rank-sum test, Fisher's exact test, or Spearman correlation (R). The statistical significance was set at a *P*-value of 0.05. Analyses were performed using R 4.0.3.

RESULTS AND DISCUSSION

The study cohort consisted of 42 patients, at a median (IQR) age of 59.5 (11.74) years (from 28 to 76 years old). The patients had median EF% of 60% (5%) and median LA diameter of 43.5 (4.75) mm. Among participants, 10 had a documented AFl history, 20 were hypertensive, and 6 were diabetic. We performed 29 PVI, 10 PVI and cavo-tricuspid isthmus ablation, 1 Wolff–Parkinson–White syndrome ablation, 1 atrioventricular nodal reentry tachycardia ablation and 1 electrophysiology study for risk stratification in Brugada syndrome.

The success rate of PCV in our cohort was 85.71% (n = 36) in 30 minutes of observation, with a median time to SR conversion of 15.5 minutes (IQR 18.75). As shown in Supplementary material, *Table S1,* there was no age difference between patients who achieved SR and those without conversion (median age 59 vs. 63 years; $P = 0.73$). Diabetes was significantly associated with conversion failure ($P = 0.03$), while AH, AFl history, and sex showed no significant associations with conversion.

Notably, patients who achieved SR had a significantly lower LA diameter (Figure 1; Supplementary material, *Table S1*), but LA diameter (r = 0.18; $P = 0.29$) and age (r = 0.27; $P = 0.11$) did not correlate with time to conversion. No significant differences in median time to conversion were observed between sexes ($P = 0.28$), DM ($P = 0.06$), AH ($P = 0.11$), or AFl history ($P = 0.55$).

Patients were subsequently assigned to fast or slow-responder subgroups based on the 150 mg antazoline dose (Supplementary material, *Table S2*). No factors showed significant associations with the response time.

Our study demonstrates that antazoline effectively converts new-onset AF during invasive electrophysiology procedures, addressing the challenge of periprocedural AF hindering successful PVI verification and impeding further ablation of supraventricular arrhythmias. Its efficacy is comparable to the results from the study by Balsam et al. [3], which reported a 90.9% success rate in 20 minutes for patients undergoing PVI with antazoline. The AnPAF study, a randomized trial, found similar results: a 72.2% success rate for SR conversion in 90 minutes with a median time of 16.0 minutes in the antazoline group [4]. In the AnPAF study, lower efficacy may be attributed to longer AF episode durations (11.2 h) compared to our study. Even though our mean antazoline dose, 194.44 (91.22) mg, was similar to AnPAF 190 mg, Balsam et al. [3] administered higher doses, mostly 400 mg, with a maximum of 500 mg. In contrast, vernakalant's efficacy in AF conversion is estimated at 52%, while propafenone reaches up to 60% [4]. In the newest AnProAF trial, antazoline showed a 63% success rate in converting nonvalvular paroxysmal AF to SR, compared to 52.1% for propafenone; also, it had a faster median conversion time (10 vs. 30 minutes) [5].

Our main findings are that an increase in LA diameter and diabetes were associated with unsuccessful SR conversion. This delay in action is significant, and enlarged LA size is a well-established factor for unsuccessful cardioversion and new-onset AF [6], which aligns with our results. Atrial hypertrophy causes structural and electrical remodeling, driven by ionic imbalance and interstitial fibrosis. Similar remodeling is influenced by AH duration and severity. Moreover, interstitial fibrosis promotes slow conduction areas and alters repolarization dynamics, fostering sustained arrhythmia episodes [7]. Conversely, antazoline enhances atrial post-repolarization refractoriness, promoting organized electrical activity, often via supraventricular tachycardia, with early P wave, PR, and QRS prolongation suggesting sodium channel blockade, and later QT prolongation indicating potassium channel inhibition [8, 9].

Analogically, our study identified 16 "fast responders" (≤150 mg) and 20 "slow responders" (>150 mg) to antazoline, indicating a dual-layered action pattern. This is in line with clinical observations of varying time to SR conversion. The CANT II study sub-analysis indicated slower propafenone response in males, suggesting potential sex differences [10]. While we observed a similar trend, the final results did not reach statistical significance.

In this study, we did not evaluate antazoline plasma concentrations or conduct systematic programmed atrial and ventricular stimulation, which underscores the need for further research on its effects on myocardial ion channels, conduction, and refractoriness.

Despite the modest sample size, antazoline demonstrated a favorable safety profile with no observed adverse effects. Our study lacked randomization and placebo control group, predominantly featuring PVI ablation in supraventricular arrhythmia groups. The small size of the study group render multivariable analysis unfeasible. We did not include a control group due to antazoline's effica-

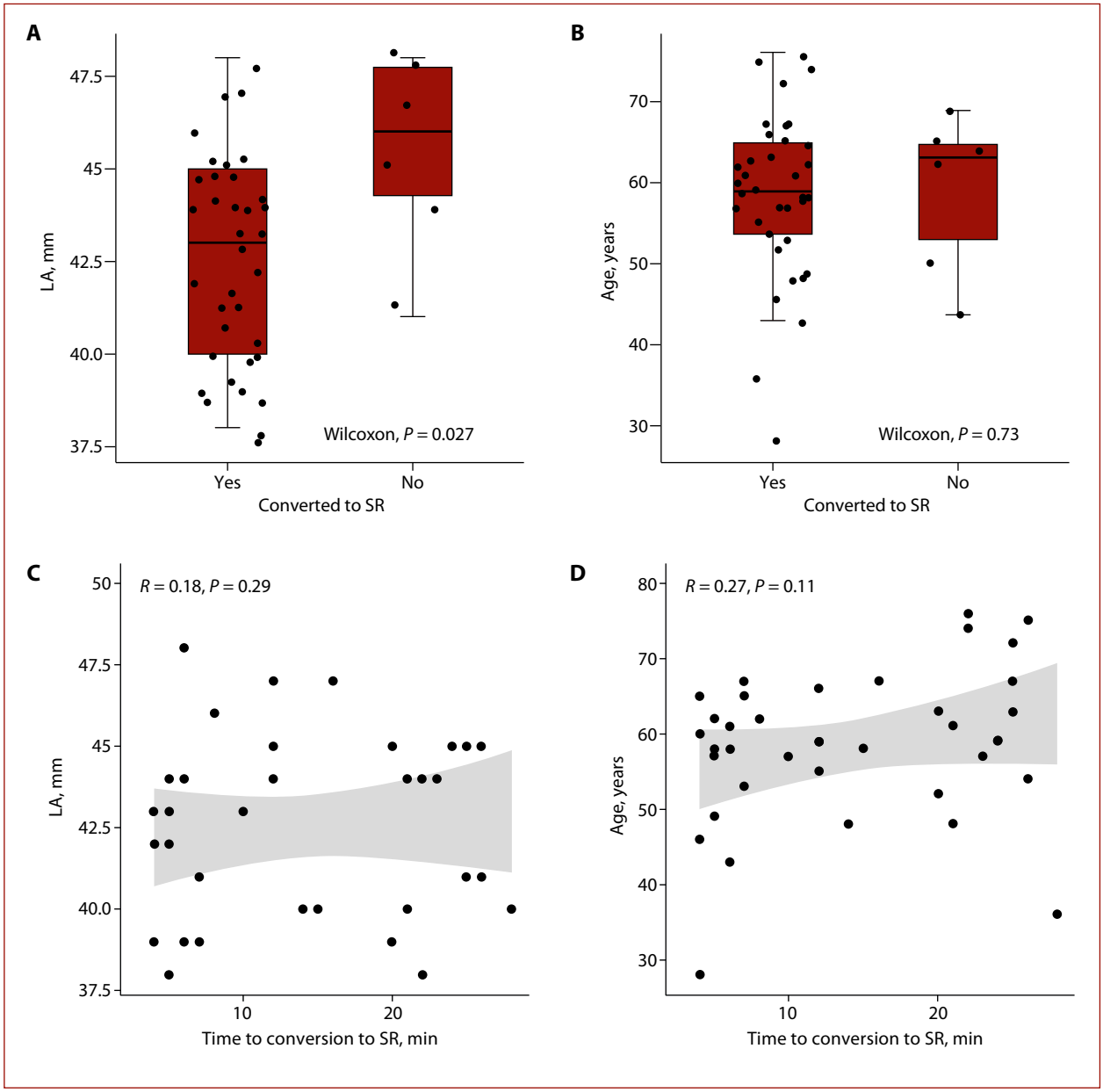

Figure 1. Intragroup associations depicted using boxplots and scatter plots

Abbreviations: LA, left atrium; SR, sinus rhythm

cy confirmed in various AF patient groups, particularly in emergency settings where it has outperformed other AADs [3–5, 8]. Comparisons with newer drugs like vernakalant, inhaled flecainide, and etripamil were not feasible due to their unavailability and cost constraints.

Antazoline offers high efficacy, rapidity, and safety, combined with low cost. It eliminates the need for general anesthesia, fasting, and extended recovery associated with ECV, which makes it a valuable treatment option.

Supplementary material

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

Article information

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