ORIGINAL ARTICLE

Efficacy and safety of antazoline for cardioversion of atrial fibrillation: propensity score matching analysis of a multicenter registry (CANT II Study)

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KEY WORDS

amiodarone, antazoline, atrial fibrillation, pharmacological cardioversion, propafenone

EDITORIAL

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ABSTRACT

INTRODUCTION Due to safety concerns about available antiarrhythmic drugs (AADs), reliable agents for termination of atrial fibrillation (AF) are requisite.

OBJECTIVES The aim of the study was to evaluate the efficacy and safety of antazoline, a first-generation antihistamine, for cardioversion of recent-onset AF in the setting of an emergency department.

PATIENTS AND METHODS This multicenter, retrospective registry covered 1365 patients (median [interquartile range] age, 69.0 [61.0–76.0] years, 53.1% men) with new-onset AF submitted to urgent pharmacological cardioversion. AAD allocation was performed by the attending physician: antazoline alone was utilized in 600 patients (44%), amiodarone in 287 (21%), propafenone in 150 (11%), and ≥2 AADs in 328 patients (24%). Antazoline in monotherapy or combination was administered to 897 patients (65.7%). Matched antazoline and nonantazoline groups were identified using propensity score matching (PSM, n = 330). The primary end point was return to sinus rhythm within 12 hours after initiation of the treatment.

RESULTS Before PSM, antazoline alone was superior to amiodarone (78.3% vs 66.9%; relative risk [RR], 1.17; 95% CI, 1.07–1.28; P <0.001) and comparable to propafenone (78.3% vs 72.7%; RR, 1.08; 95% CI, 0.97–1.20; P = 0.14) in terms of rhythm conversion rate. In the post-PSM population, the rhythm conversion rate was higher among patients receiving antazoline alone than in the nonantazoline group (84.2% vs 66.7%; RR, 1.26; 95% CI, 1.11–1.43; P <0.001), and the risk of adverse events was comparable (P = 0.2).

CONCLUSIONS Antazoline appears to be an efficacious agent for termination of AF in real-world setting. Randomized controlled trials are required to evaluate its safety in specific patient populations.

INTRODUCTION The clinical significance of atrial fibrillation (AF) extends further than just the risk of excessive stroke-related disability and mortality[1] and is related to emotional stress and increased health care costs caused by a growing number of consults in the emergency department (ED) due to acute debilitating symptoms.[2] Although a debate about the supremacy of heart

WHAT'S NEW?

Pharmacological cardioversion represents a core element of rhythm control strategy. Antazoline is an antihistamine which causes termination of atrial fibrillation, and its efficacy is comparable to that of propafenone and superior to that of amiodarone in a real-world setting of an emergency department. Antazoline appears to be a safe antiarrhythmic compound; however, its safety should be further evaluated in randomized controlled trials.

rate or rhythm control strategy continues,[3] an attempt to terminate arrhythmia in individuals with recent-onset AF seems the most viable option in the population with recent-onset AF on adequate anticoagulation with high clinical probability of sinus rhythm (SR) maintenance.[4]

Although electrical cardioversion (EC) confers a nearly 90% chance of rhythm conversion,[5-7] it requires general anesthesia and may not be acceptable to all patients. Thus, the majority of patients are initially submitted to pharmacological cardioversion (PC) using a variety of antiarrhythmic drugs (AADs), which results in suboptimal success rate of roughly 70%.[6] Other limitations of the available AADs are linked to increased risk of proarrhythmia in patients with structural heart disease (Vaughan–Williams class Ic),[8] high cost and low availability (vernakalant),[9] or delayed onset of action in the case of amiodarone,[10] which leads to prolonged stay in the ED or the need for a potentially preventable hospital admission.

Antazoline mesylate belongs to a group of first-generation antihistaminic agents, and it was shown to exert antiarrhythmic effects on supraventricular and ventricular arrhythmias in the 1960s.[11] Forgotten by cardiologists for decades, antazoline had been widely used as a safe parenteral antihistamine compound, until the 1990s, when it was demonstrated to be a potent class Ia AAD capable of converting AF to SR,[12] which led to its registration for treatment of supraventricular arrhythmias and resultant widespread use, initially in electrophysiology laboratories,[13] and subsequently in EDs throughout Poland. Properties of antazoline include rapid rhythm conversion within a median time of 16 minutes from the drug infusion,[14] anticholinergic action leading to transient increase of heart rate, as well as increasing the corrected QT interval, left atrial refractory period, and inter-atrial conduction time.[15-17] Of note, antazoline was initially shown to be superior to placebo[14] and PC with propafenone in terms of rhythm conversion rate.[18] A recent retrospective study performed at our institution demonstrated that antazoline led to termination of AF in 85.3% of patients and was superior to amiodarone and comparable with propafenone, while not being associated with serious adverse actions.[19] These findings were also confirmed in the elderly population.[20] Given this promising preliminary results, the aim of this registry was to evaluate the efficacy and safety of intravenous antazoline for PC of AF in relation to other AADs in the real-world setting of ED.

PATIENTS AND METHODS

Study design

The CANT (Cardioversion with Intravenous Antazoline Mesylate) study represents a multicenter, retrospective real-world registry, which was designed to investigate the efficacy and safety of intravenous antazoline mesylate for PC of AF. The study was an extension of a formerly single-center analysis of PC initiated in the Upper Silesia Medical Center in Katowice, Poland.[19] The subsequent recruitment of centers to the CANT study was performed using the Scientific Platform of the "Club 30" of the Polish Cardiac Society between June 2019 and February 2020. In total, 6 academic centers throughout Poland reported 1365 patients with recent-onset AF subjected to ad hoc PC. The choice of the AAD and adjuvant β-blocker administration or electrolyte supplementation were left at the discretion of the attending physician in the emergency or cardiology department. The flowchart of the study is shown in FIGURE 1. The protocol was formulated in adherence to the guidelines of the Declaration of Helsinki. The study protocol was accepted by the Ethics Committee of Medical University of Silesia in Katowice (KNW/022/KB1/9/18) on February 13, 2018 and the patients signed written informed consent for treatment and registry participation.

The primary inclusion criterion was an unscheduled admission to the emergency or cardiology department with the diagnosis of paroxysmal or persistent AF confirmed using 12-lead electrocardiogram and referral for urgent PC.

The electronic database was queried with the use of the I48 code of the *International Classification of Diseases, Tenth Revision* (ICD-10), and the exclusion criteria were as follows: (i) permanent AF; (ii) atrial flutter; (iii) sick sinus syndrome or AF with bradycardia <60 bpm; (iv) elective admission; (v) spontaneous termination of AF during stay in the emergency department without AAD administration; (vi) termination of AF only following β-blocker or electrolyte infusion; (vii) contraindication to acute rhythm control due to lack of adequate anticoagulation if the AF episode lasted longer than 48 hours; (vii) chronic antiarrhythmic therapy defined as the use of propafenone or sotalol within 7 days preceding the admission to the ED or antiarrhythmic therapy with amiodarone in the preceding 3 months, if amiodarone was used for at least 1 month (FIGURE 1).

Efficacy and safety end points

The primary end point was successful AF termination reflected by return to SR confirmed on 12-lead electrocardiogram in the ED or cardiology department. In general, the study covered patients in whom follow-up for rhythm conversion was at least 12 hours. The patients were subjected to continuous

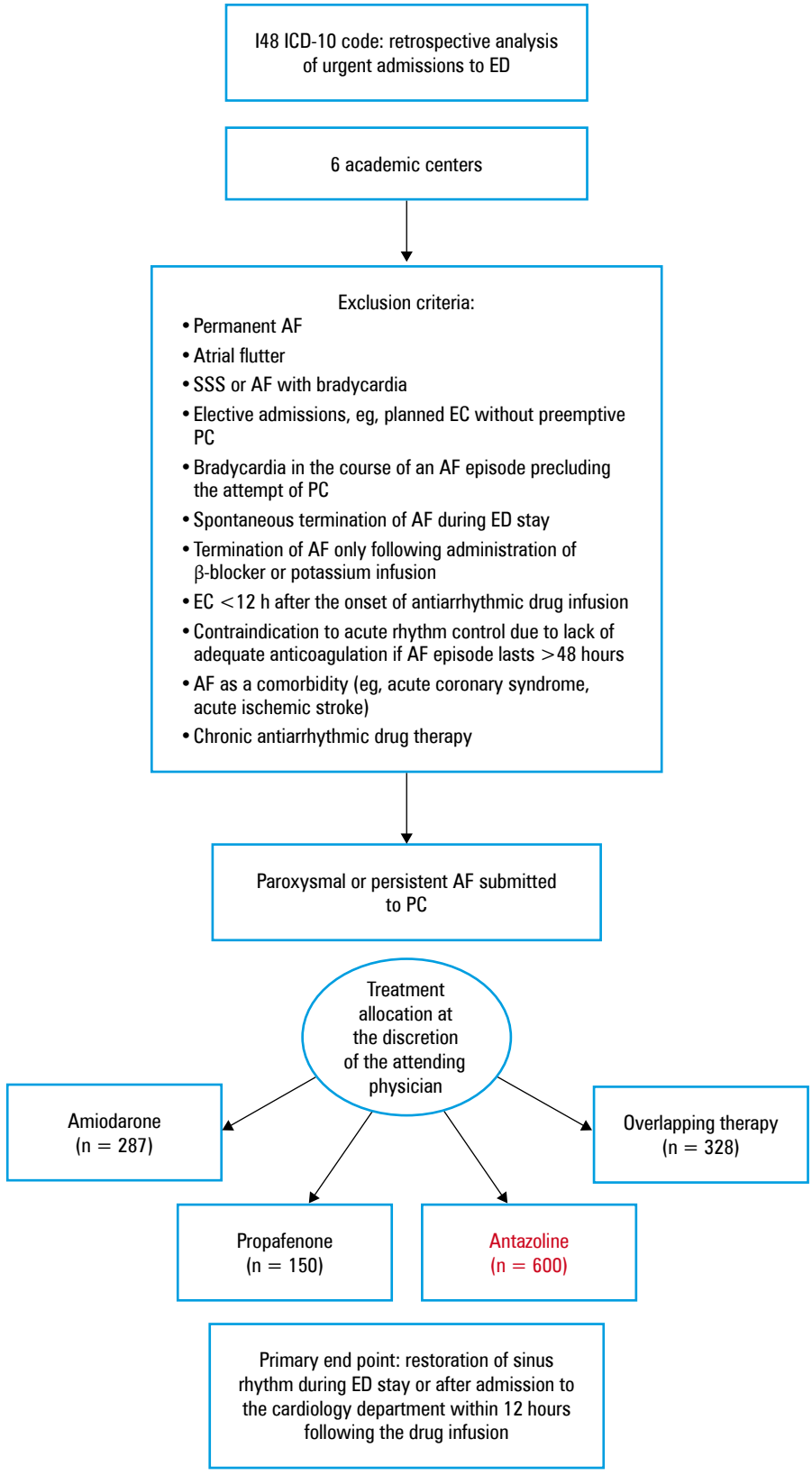

FIGURE 1 Study flowchart

Abbreviations: AF, atrial fibrillation; EC, electrical cardioversion; ED, emergency department; ICD, *International Classification of Diseases, 10th Revision*; PC, pharmacological cardioversion; SSS, sick sinus syndrome

electrocardiographic monitoring until the return to SR or for 12 hours following the start of the drug infusion. If EC was performed within 12 hours following AAD administration, the patients were excluded from the trial, as this could lead to underestimation of efficacy of an AAD, particularly amiodarone. In the event of an admission to the cardiology department, the patients were included in the analysis if PC or observation was continued for at least 12 hours. Termination of AF by means of EC after 12 hours of follow-up was considered a failure of PC.

The composite safety end point was the occurrence of any serious adverse event following the administration of AAD, including bradycardia below 45 bpm, hypotension (decrease of systolic blood pressure of >40 mm Hg), syncope, or death.

Data acquisitions and definitions Detailed description of data acquisition and the definitions can be found in Supplementary material, *Definitions*.

Antiarrhythmic therapy Treatment allocation was based on individual decision of the attending physician depending on the clinical setting, taking into consideration the 2016 European Society of Cardiology guidelines on the management of AF.[5] Antiarrhythmic therapy comprised either 1) intravenous (IV) amiodarone (Cordarone, Sanofi-Aventis), or 2) IV or oral propafenone hydrochloride (Rytmonorm, Mylan), or 3) IV antazoline mesylate (Phenazolinum, Polfa, Warsaw, Poland), or 4) a combination of 2 or more agents. Prior to PC, the status of anticoagulation was checked and the AAD was administered under electrocardiographic and hemodynamic supervision.

As far as the anticoagulation was concerned, the patients had to either (i) be on adequate chronic anticoagulation; or (ii) if not anticoagulated, have an overt duration of the AF episode of less than 48 hours; or (iii) undergo transesophageal echocardiography within 48 hours prior to cardioversion. All patients who were not chronically anticoagulated received a weight-adjusted dose of heparin prior to cardioversion.

The regimen of AAD administration varied depending on the center and the attending physician. In general, the patients received amiodarone diluted with 5% glucose in an infusion pump with an optional initial IV bolus at a dose of 150 mg. Propafenone hydrochloride was used either in the form of 150-mg oral pills or an IV bolus of 70-mg propafenone in 100 ml of 0.9% saline formulation. Sotalol was available in the form of 40- or 80-mg tablets.

The mode of antazoline mesylate infusion comprised either a single or repeated slow undiluted IV bolus (3 min) of 100 to 200 mg or diluted with a 100-ml solution of 0.9% sodium chloride and infused over 5 to 15 minutes. The total dose of each drug, as well as the use of a β-blocker (IV or oral) or IV electrolyte supplementation in the pericardioversion period were not prespecified but left to the best judgement of the attending physician. β-Blockade most commonly comprised IV metoprolol (2.5 or 5 mg bolus).

Statistical analysis Statistical analysis was performed using SPSS v. 25.0 software (IBM Corp, Armonk, New York, Unites States) and MedCalc v. 14.8.1 software (MedCalc Software, Ostend, Belgium). Qualitative parameters were presented as absolute numbers and percentages. Quantitative variables were expressed as mean and SD in the case of normal distribution or as median and interquartile range (IQR) in the case of nonnormal distribution. For the comparison of normally distributed variables, the *t* test or analysis of variance (ANOVA) was applied, while in variables that did not follow the normal distribution, the 2-tailed Mann–Whitney test or the Kruskal-Wallis test was utilized. The significance of proportions in contingency tables was calculated using the χ^2 test. In the analyses with multiple comparisons, the Bonferroni adjustment was performed. Relative risk (RR) with 95% CI was calculated. The Altman formula was utilized for the purpose of RR calculation, while in the case of 0 cases per group, the formula developed by Pagano and Gauvreau (2000) was applied. Propensity score matching (PSM) analysis with the nearest neighbor algorithm was performed to match the antazoline and nonantazoline cohorts, as well as antazoline vs amiodarone and antazoline vs propafenone in terms of the set of core baseline variables including sex, age, presence of arterial hypertension, diabetes mellitus (DM), coronary artery disease (CAD) or peripheral artery disease (PAD), structural heart disease, history of ischemic stroke or transient ischemic attack (TIA), estimated glomerular filtration rate (eGFR), serum potassium concentration, transcatheter pulmonary vein isolation (PVI) in anamnesis, persistent AF, IV potassium supplementation, β-blocker administration, heart rate, and CHA_2DS_2-VASc score.

RESULTS

Baseline characteristics and study end points Following detailed revision of all exclusion criteria, a total of 1365 patients with short-duration AF were included in the final analysis (FIGURE 1). Data on the demographic and clinical characteristics are summarized in TABLE 1. The study population was characterized by the median (IQR) age of 69.0 (61.0–76.0) years and a slight overrepresentation of men (53.1%). The majority of patients had paroxysmal AF and only 103 patients (7.5%) had persistent AF. Tachyarrhythmia was reported in 23.4% of patients and the median (IQR) CHA_2DS_2-VASc score was 3 (2–4) points. Nearly half of the population was on chronic oral anticoagulants, while 8.9% of patients had a history of PVI. Adjuvant therapy in the form of β-blocker or IV potassium administration was used in 40.9% and 43.4% of the patients, respectively.

General information about the antiarrhythmic therapy is presented in FIGURE 1. Antazoline alone or in combination was administered in 897 patients (65.7%). Antazoline alone was utilized in 600 patients (44.0%), amiodarone alone in 287 (21.0%), propafenone alone in 150 (11.0%), antazoline and amiodarone in 184 (13.5%), antazoline and propafenone in 97 (7.1%), amiodarone and propafenone in 22 (1.6%), antazoline, amiodarone and propafenone in 14 (1.0%), propafenone and sotalol in 8 (0.6%), amiodarone and sotalol in 1 (0.1%), and antazoline and sotalol in 2 (0.2%). In summary, 328 patients (24.0%) received 2 or more AADs (overlapping therapy).

TABLE 1 Baseline characteristics of the overall study population

Variable	Overall population (n = 1365)
Demographic characteristics	
Male sex	725 (53.1)
Age, y	69.0 (61.0–76.0)
Weight, kg	79.99 (14.99)
BMI, kg/m^2	28.05 (4.32)
Comorbidities	
Arterial hypertension	947 (69.4)
Diabetes mellitus	262 (19.2)
CAD/PAD	443 (32.5)
Ischemic stroke/TIA	64 (4.7)
Structural heart disease	505 (37.0)
Echocardiographic parameters	
LVEF, %	56.0 (50.0–60.0)
LVEF <50%	128 (9.4)
LAd, mm	43.82 (5.81)
Laboratory tests	
Serum creatinine concentration, mg/dl	0.99 (0.82–1.16)
eGFR, ml/min/1.73 m^2	72.3 (56.0–86.0)
eGFR <60 ml/min/1.73 m^2	233 (17.1)
Potassium level, mEq/l, mean (SD)	4.24 (0.45)
WBC, × 1000/μl	7.55 (6.30–9.04)
Hemoglobin, g/dl	14.3 (13.1–15.3)
AF characteristics	
Persistent AF	103 (7.5)
AF episode duration, h	24 (7–32)
CHA_2DS_2-VASc score	3 (2–4)
EHRA class	3 (2–3)
History of PVI	121 (8.9)
Chronic anticoagulation	653 (47.8)
Heart rate ≥130 bpm	319 (23.4)
Time of admission to the ED	1 pm (10 am–6 pm)
Adjuvant treatment	
β-Blocker use	558 (40.9)
IV potassium	593 (43.4)
Antiarrhythmic therapy	
Amiodarone[a]	508 (37.2)
Propafenone[a]	291 (21.3)
Antazoline[a]	897 (65.7)
Dose of antiarrhythmic drugs	
Antazoline, mg	200 (100–200)
Amiodarone, mg	450 (300–600)
Propafenone, mg	150 (70–370)

Data are presented as number (percentage) of patients or median (interquartile range) unless indicated otherwise.

a Drugs used also alone or in combination

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; ED, emergency department; EHRA, European Heart Rhythm Association classification; eGFR, estimated glomerular filtration rate, IV, intravenous; LAd, left atrial diameter; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; PVI, pulmonary vein isolation; TIA, transient ischemic attack, WBC, white blood cell count

The median (IQR) dose of antazoline was 200 (100–200) mg. The number of patients receiving specific doses of antazoline was as follows: 50 mg, n = 14 (1.6%); 100 mg, n = 200 (22.3%); 150 mg, n = 36 (3.6%); 200 mg, n = 446 (49.7%); 250 mg, n = 11 (1.2%); 300 mg, n = 180 (20.1%); 400 mg, n = 7 (0.7%); 500 mg, n = 2 (0.2%); 600 mg, n = 1 (0.1%). The median (IQR) dose of amiodarone was 450 (300–600) mg, and of propafenone, 150 (70–370) mg. Due to PC failure, 190 patients (13.9%) were further subjected to EC.

Successful PC was achieved in 965 patients (70.7%). The composite safety end point was reported in 66 patients (4.8%). In detail, 56 patients (4.1%) exhibited bradycardia, 1 patient (0.1%) had syncope, and 14 patients (1.0%) had hypotension, whereas no in-hospital death was recorded.

Successful vs unsuccessful cardioversion Stratification of different clinical variables depending on the success of PC is presented in Supplementary material, *Table S1*.

Comparison of antazoline vs other antiarrhythmic drugs The comparison between different forms of PC in terms of particular clinical variables and study end points is presented in TABLE 2. Full analysis comprising the overlapping therapy is shown in Supplementary material, *Table S2*. The rate of successful PC per treatment allocation is shown in FIGURE 2, while the forest plot of RR of successful PC with antazoline vs other AADs is presented in FIGURE 3.

The groups of patients stratified by AADs differed substantially in terms of baseline characteristics. The group treated with antazoline alone had a higher prevalence of CAD (P <0.001) and a lower prevalence of chronic kidney disease (P <0.001), greater left atrial diameter (P = 0.002), a lower rate of IV potassium supplementation (P = 0.001), and a higher rate of pericardioversion β-blocker administration (P <0.001) than the amiodarone cohort. Conversely, the group of patients who received antazoline alone had a higher prevalence of arterial hypertension (P <0.001), DM (P = 0.02), CAD (P <0.001), structural heart disease (P <0.001), and persistent AF (P = 0.02), greater left atrial diameter (P <0.001), and more frequently received adjuvant therapy in the form of IV potassium (P <0.001) or β-blockers (P <0.001) than the propafenone group.

The efficacy of antazoline alone was superior to that of amiodarone alone (78.3% vs 66.9%; RR, 1.17; 95% CI, 1.07–1.28; P <0.001) and overlapping antiarrhythmic therapy (78.3% vs 59.2%; RR, 1.32; 95% CI, 1.20–1.46; P <0.001), whereas the rhythm conversion rate associated with antazoline monotherapy was comparable with that of propafenone (78.3% vs 72.7%; RR, 1.08; 95% CI, 0.97–1.20; P = 0.14) (FIGURES 2 and 3).

The rate of composite safety end point was higher in the group treated with antazoline alone than in the amiodarone cohort (5.2% vs 2.1%; RR, 2.47; 95% CI, 1.04–5.86; P = 0.03), but comparable for the antazoline alone and the propafenone group (5.2% vs 7.3%; RR, 0.70; 95% CI, 0.36–1.37;

TABLE 2 Clinical characteristics and cardioversion outcome per antiarrhythmic drug used for pharmacological cardioversion

Variable	Amiodarone[1] (n = 287)	Propafenone[2] (n = 150)	Antazoline[3] (n = 600)	*P* value[a,c] 1 vs 2	*P* value[a,c] 1 vs 3	*P* value[a,c] 2 vs 3	*P* value[b,c]
Male sex	123 (42.9)	68 (45.3)	350 (58.3)	0.57	<0.001	0.004	<0.001
Age, y	69.0 (61.0–76.0)	70.0 (60.0–77.0)	68.0 (61.0–76.0)	0.96	0.17	0.30	0.31
Weight, kg	86.0 (72.0–99.0)	65.0 (62.0–90.0)	80.0 (71.0–91.5)	0.21	0.33	0.29	0.28
BMI, kg/m^2, mean (SD)	28.74 (4.79)	26.41 (3.35)	28.06 (4.24)	0.59	0.80	0.57	0.94
Arterial hypertension	210 (73.2)	80 (53.3)	401 (66.8)	<0.001	0.14	<0.001	<0.001
Diabetes mellitus	50 (17.4)	17 (11.3)	111 (18.5)	0.002	0.35	0.02	<0.001
CAD/PAD	82 (28.6)	35 (23.3)	231 (38.5)	0.03	<0.001	<0.001	<0.001
Ischemic stroke/TIA	14 (4.9)	3 (2.0)	19 (3.2)	0.46	0.14	0.67	0.07
Structural heart disease	102 (35.5)	38 (25.3)	247 (41.2)	0.03	0.11	<0.001	0.003
LVEF, %	55.0 (50.0–60.0)	60.0 (55.0–60.0)	57.0 (51.0–60.0)	0.003	0.44	0.01	0.02
LAd, mm, mean (SD)	42.62 (4.95)	39.57 (5.93)	44.34 (6.27)	0.002	0.002	<0.001	<0.001
SCr, mg/dl	0.92 (0.79–1.12)	0.94 (0.75–1.10)	0.98 (0.82–1.15)	0.58	0.20	0.19	<0.001
eGFR, ml/min/1.73 m^2	74.0 (57.0–86.0)	75.0 (56.0–90.0)	73.7 (57.8–86.0)	0.77	0.42	0.80	0.23
eGFR <60 ml/min/1.73 m^2	68 (23.7)	16 (10.7)	69 (11.5)	<0.001	<0.001	0.87	<0.001
Potassium level, mEq/l, mean (SD)	4.28 (0.48)	4.27 (0.41)	4.20 (0.45)	0.68	0.03	0.24	0.13
WBC, × 1000/µl	7.80 (6.54–9.40)	7.40 (6.48–8.91)	7.30 (6.10–8.77)	0.49	0.04	0.50	0.16
Hemoglobin, g/dl	14.2 (13.1–15.1)	14.6 (13.7–15.6)	14.5 (13.4–15.3)	0.02	0.01	0.36	0.01
Persistent AF	14 (4.9)	3 (2.0)	44 (7.33)	0.14	0.22	0.02	<0.001
CHA_2DS_2-VASc score	3 (2–4)	3 (1–3)	3 (2–4)	0.01	0.16	0.12	0.03
EHRA class	3 (2–3)	2 (2–3)	3 (2–3)	0.59	0.20	0.19	<0.001
History of PVI	12 (4.2)	13 (8.7)	71 (11.8)	0.001	<0.001	0.31	<0.001
Chronic anticoagulation	191 (66.6)	47 (31.3)	199 (33.2)	<0.001	<0.001	0.69	<0.001
HR ≥130 bpm	94 (32.8)	30 (20.0)	109 (18.2)	<0.001	<0.001	0.56	0.02
β-Blocker use	77 (26.8)	37 (24.7)	333 (55.5)	0.51	<0.001	<0.001	<0.001
IV potassium	160 (55.7)	33 (22.0)	225 (37.5)	<0.001	0.001	<0.001	<0.001
Successful PC	192 (66.9)	109 (72.7)	470 (78.3)	0.22	<0.001	0.14	<0.001
Composite safety end point	6 (2.09)	11 (7.33)	31 (5.17)	0.007	0.03	0.30	0.07
Death	0	0	0	–	–	–	–
Bradycardia ≤45 bpm	5 (1.7)	8 (5.3)	29 (4.8)	0.04	0.03	0.80	0.14
Syncope	0	1 (0.7)	0	0.17	–	0.045	0.04
Hypotension	2 (0.7)	3 (2.0)	5 (0.8)	0.23	0.83	0.21	0.56

Data are presented as number (percentage) of patients or median (interquartile range) unless indicated otherwise.

a χ^2 test, Mann–Whitney test, or *t* test

b χ^2 test for multiple comparisons, Kruskal–Wallis test, or analysis of variance (ANOVA)

c The Bonferroni adjustment for multiple testing was performed and the *P* value threshold was set for 0.017.

Abbreviations: HR, heart rate; SCr, serum creatinine concentration; others, see **FIGURE 1** and **TABLE 1**

P = 0.30). Bradycardia up to 45 bpm was reported in 29 (4.8%), while hypotension in 5 patients (0.8%) treated with antazoline. No incidents of syncope or in-hospital death were reported in the antazoline group (**TABLE 2**).

Antazoline alone vs combined nonantazoline cohort: crude data and propensity score analysis The comparison between the patients treated with antazoline alone and the truly nonantazoline cohort (amiodarone and propafenone and a combination of these agents without overlapping antazoline), both in unmatched and matched cohorts, is presented in **TABLE 3**. The PSM analysis employed a set of core variables listed in the *Statistical analysis* section.

The pre-PSM analysis revealed that the antazoline alone group had a higher success rate (78.3% vs 68.8%; RR, 1.14; 95% CI, 1.06–1.23; *P* <0.001) (**FIGURE 3**) and a comparable composite end point rate (5.2% vs 4.1%; *P* = 0.40), as compared with the nonantazoline group (**TABLE 3**). The post-PSM

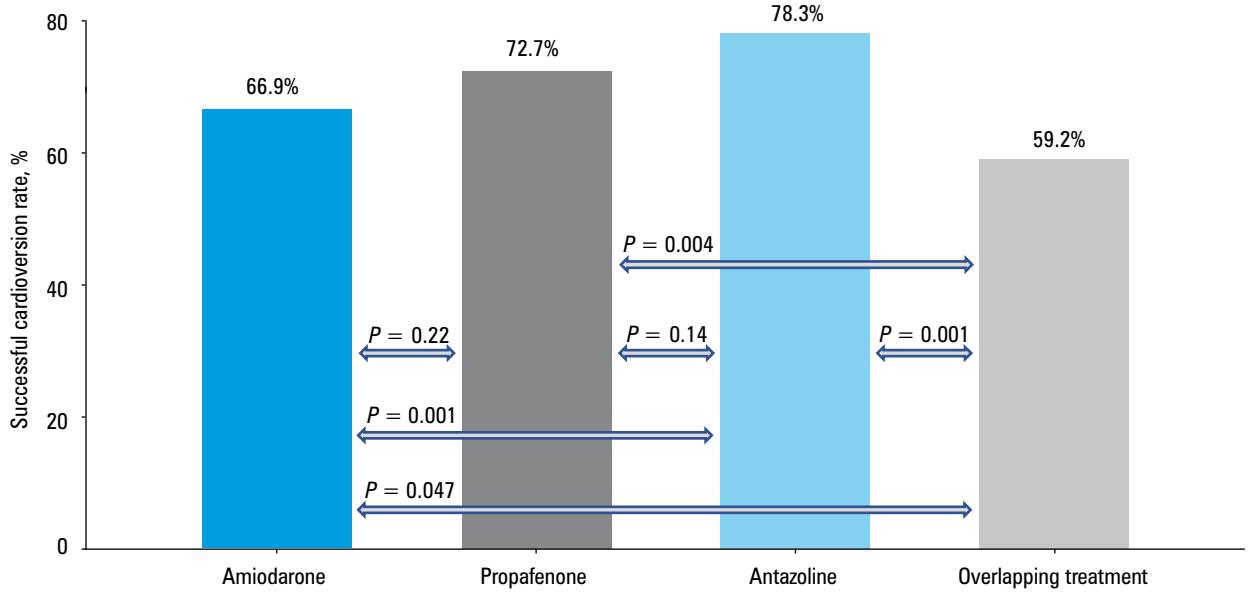

FIGURE 2 Efficacy of different pharmacological agents in terms of successful pharmacological cardioversion

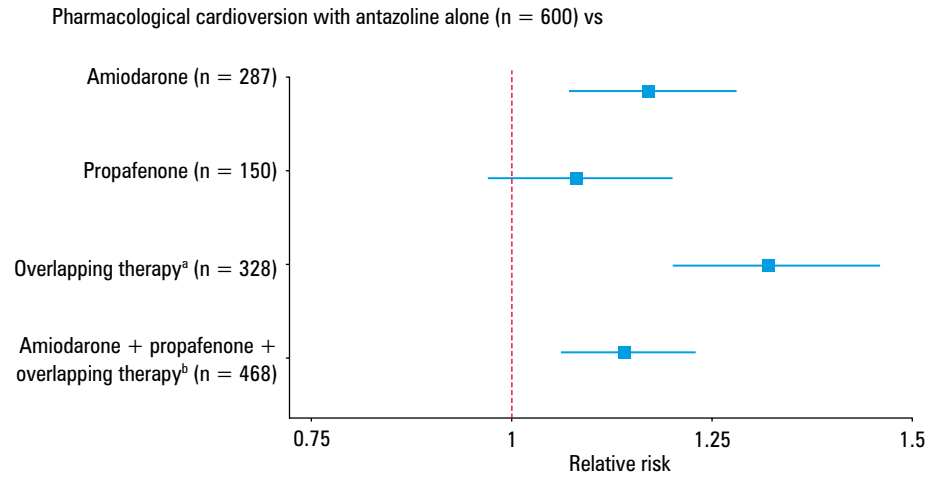

FIGURE 3 Efficacy of antazoline vs other pharmacological agents in an unmatched population: forest plot of relative risk of successful pharmacological cardioversion

a ≥2 antiarrhythmic drugs including antazoline in combination with other agents

b ≥ 2 antiarrhythmic drugs except for antazoline used in combination with other agents

analysis confirmed that antazoline alone was superior to nonantazoline treatment in terms of AF termination (84.2% vs 66.7%; RR, 1.26; 95% CI, 1.11–1.43; number needed to treat, 5.7; P <0.001) (FIGURE 3) and comparable in terms of the risk of composite safety end point occurrence (0.0% vs 1.8%; RR, 0.14; 95% CI, 0.01–2.74; P = 0.2).

A separate PSM analysis revealed that antazoline used in monotherapy was more successful in terms of rhythm conversion than amiodarone alone (84.1% vs 65.5%; RR, 1.24; 95% CI, 1.06–1.44; P = 0.001) and comparable with propafenone alone (80.9% vs 76.6%; RR, 1.05; 95% CI, 0.86–1.30; P = 0.61) (TABLE 4). The rates of adverse events in both PSM analyses were comparable between the treatment arms (TABLE 4).

DISCUSSION This multicenter registry provided evidence that intravenous antazoline represents a highly efficacious AAD in a population of patients with recent-onset AF, as it was superior to combined amiodarone and propafenone groups matched in terms of baseline parameters (84.2% vs 66.7%; P <0.001). Furthermore, in the post-PSM analysis, antazoline administered as a single AAD was associated with a comparable risk of safety end point occurrence to that observed in the nonantazoline group (0.0% vs 1.8%; P = 0.2). In the unmatched pre-PSM

TABLE 3 Clinical characteristics and cardioversion outcome in the antazoline and nonantazoline cohorts before and after propensity score matching

Variable	Crude analysis			Propensity score matching with nearest neighbor algorithm 1:1		
	Antazoline alone (n = 600)	Nonantazoline (n = 468)	*P* value	Antazoline alone (n = 165)	Nonantazoline (n = 165)	*P* value
Male sex	350 (58.3)	203 (43.4)	<0.001[a]	75 (45.5)	70 (42.4)	0.58[a]
Age, y	68.0 (61.0–76.0)	69.0 (60.0–76.0)	0.29[b]	67.0 (60.0–74.0)	66.0 (58.0–76.0)	0.90[b]
Age ≥65 y	367 (61.2)	293 (62.6)	0.63[a]	100 (60.6)	94 (57.0)	0.50[a]
Arterial hypertension	401 (66.8)	306 (65.4)	0.63[a]	130 (78.8)	124 (75.2)	0.43[a]
Diabetes mellitus	111 (18.5)	70 (15.0)	0.28[a]	33 (20.0)	33 (20.0)	1.00[a]
CAD/PAD	231 (38.5)	124 (26.5)	<0.001[a]	49 (29.7)	45 (27.3)	0.63[a]
Ischemic stroke/TIA	19 (3.2)	17 (3.6)	0.90[a]	13 (7.9)	10 (6.1)	0.52[a]
Structural heart disease	247 (41.2)	148 (31.6)	<0.001[a]	57 (34.6)	55 (33.3)	0.82[a]
LVEF, %	57.0 (51.0–60.0)	55.0 (50.0–60.0)	>0.99[b]	56.0 (52.0–60.0)	55 (50.0–60.0)	0.25[b]
eGFR, ml/min/1.73 m^2	73.7 (57.8–86.0)	74.0 (57.0–87.0)	0.62[b]	75.0 (58.0–88.9)	77.0 (58.0–90.0)	0.91[b]
eGFR <60 ml/min/1.73 m^2	69 (11.5)	89 (19.0)	<0.001[a]	44 (26.7)	42 (25.5)	0.80[a]
Potassium level, mEq/l	4.20 (0.45)	4.28 (0.46)	0.02[c]	4.25 (0.46)	4.25 (0.43)	0.83[c]
Potassium level ≤3.5 mEq/l	20 (3.3)	16 (3.4)	0.97[a]	9 (5.5)	6 (3.6)	0.43[a]
WBC, × 1000/μl	7.3 (6.1–8.8)	7.8 (6.5–9.2)	0.06[b]	7.2 (5.9–8.8)	8.0 (6.7–9.3)	0.34[b]
Hemoglobin, g/dl	14.5 (13.4–15.3)	14.2 (13.2–15.2)	0.08[b]	14.6 (13.4–15.3)	14.3 (13.2–15.3)	0.26[b]
Persistent AF	44 (7.33)	19 (4.1)	<0.001[a]	10 (6.1)	12 (7.3)	0.66[a]
AF episode duration, h	18 (5–28)	28 (6–36)	<0.001[b]	16 (5–20)	18 (6–26)	0.23[b]
CHA_2DS_2-VASc score	3 (2–3)	3 (2–4)	0.80[b]	3 (2–4)	3 (2–4)	0.88[b]
History of PVI	71 (11.8)	26 (5.6)	<0.03[a]	12 (7.27)	12 (7.27)	1.00[a]
Heart rate ≥130 bpm	109 (18.2)	141 (30.1)	<0.001[a]	60 (36.4)	58 (35.2)	0.82[a]
β-Blocker use	333 (55.5)	126 (26.9)	<0.001[a]	64 (38.8)	69 (41.8)	0.58[a]
IV potassium	225 (37.5)	206 (44.0)	0.02[a]	67 (40.6)	74 (44.9)	0.44[a]
End points						
Successful PC	470 (78.3)	322 (68.8)	<0.001[a]	139 (84.2)	110 (66.7)	<0.001[a]
Composite safety end point	31 (5.2)	19 (4.1)	0.40[a]	0	3 (1.8)	0.2[a]
Death	0	0	–	0	0	–
Bradycardia ≤45 bpm	29 (4.8)	14 (3.0)	0.13[a]	0	2 (1.2)	0.16[a]
Syncope	0	1 (0.2)	0.26[a]	0	0	–
Hypotension	5 (0.8)	6 (1.3)	0.47[a]	0	1 (0.6)	0.32[a]

Data are presented as number (percentage) of patients or median (interquartile range).

a χ^2 test

b Mann–Whitney test

c *t* test

Abbreviations: see FIGURE 1 and TABLES 1 and 2

population, antazoline alone more frequently restored SR (78.3%) than amiodarone alone or overlapping therapy. The rhythm conversion for antazoline alone was also comparable with that for propafenone-based cardioversion. In the separately matched cohorts following PSM, antazoline alone was also more efficacious than amiodarone and comparable with propafenone in terms of rhythm conversion. The crude analysis showed that the use of antazoline alone was associated with a higher rate of complications than the use of amiodarone but the rate was comparable with that observed in patients using propafenone. In the overall population, the use of antazoline as a single AAD was linked to 31 safety end points (5.2%), which was similar to 19 incidents in the nonantazoline cohort (4.1%, *P* = 0.40). No cases of in-hospital death or syncope were documented.

The present study constitutes by far the largest analysis of PC and the largest study focused on the assessment of efficacy and safety of antazoline mesylate in a broad population of patients with short-duration AF. The current findings mostly recapitulate data from the formerly reported single-center study,[19] which showed that antazoline alone (AF conversion rate of 85.3%) was superior to amiodarone (66.7%), and comparable with propafenone-based strategy (78.6%). The present study provides

TABLE 4 Propensity score matching analysis comparing antazoline vs amiodarone and antazoline vs propafenone

Variable	PSM with nearest neighbor algorithm 1:1 antazoline vs amiodarone			PSM with nearest neighbor algorithm 1:1 antazoline vs propafenone		
	Antazoline (n = 113)	Amiodarone (n = 113)	*P* value	Antazoline (n = 47)	Propafenone (n = 47)	*P* value
Male sex	52 (46.0)	47 (41.6)	0.50[a]	17 (36.2)	13 (27.7)	0.38[a]
Age, y	67.0 (60.0–73.0)	68.0 (62.0–75.0)	0.27[b]	68.0 (62.0–74.0)	69.0 (53.0–76.0)	0.89[b]
Arterial hypertension	87 (77.0)	87 (77.0)	1.00[a]	32 (68.1)	32 (68.1)	1.00[a]
Diabetes mellitus	24 (21.2)	21 (18.6)	0.62[a]	6 (12.8)	5 (10.6)	0.75[a]
CAD/PAD	33 (29.2)	32 (28.3)	0.88[a]	8 (17.0)	6 (12.8)	0.56[a]
Ischemic stroke/TIA	7 (6.2)	7 (6.2)	1.00[a]	2 (4.3)	3 (6.4)	0.65[a]
Structural heart disease	30 (26.5)	32 (28.3)	0.68[a]	13 (27.7)	9 (19.2)	0.33[a]
LVEF, %	58.0 (54.0–60.0)	56.0 (50.0–60.0)	0.97[b]	55.0 (50.0–60.0)	55 (50.0–60.0)	0.86[b]
eGFR, ml/min/1.73 m^2	76.0 (57.4–88.6)	76.0 (61.0–86.0)	0.88[b]	75.0 (57.0–85.0)	75.0 (61.0–90.0)	0.75[b]
eGFR <60 ml/min/1/73 m^2	34 (30.1)	25 (22.1)	0.17[a]	13 (27.7)	11 (23.4)	0.64[a]
Potassium level, mEq/l, mean (SD)	4.21 (0.43)	4.27 (0.47)	0.17[b]	4.22 (0.45)	4.17 (0.30)	0.47[b]
CHA_2DS_2-VASc score	3 (1–4)	3 (2–4)	0.64[b]	3 (2–4)	3 (1–4)	0.92[b]
Persistent AF	6 (5.3)	7 (6.2)	0.87[a]	3 (6.4)	2 (4.3)	0.65[a]
AF episode duration, h	18 (7–24)	19 (7–32)	0.53[b]	14 (6–16)	12 (4–18)	0.29[b]
Heart rate > 130 bpm	42 (37.2)	43 (38.1)	0.89[a]	25 (53.2)	19 (40.4)	0.22[a]
β-Blocker use	40 (35.4)	38 (33.6)	0.78[a]	24 (51.1)	25 (53.2)	0.84[a]
IV potassium	61 (54.0)	67 (59.3)	0.20[a]	23 (48.9)	24 (51.1)	0.84[a]
Successful PC	95 (84.1)	74 (65.5)	0.001[a]	38 (80.9)	36 (76.6)	0.61[a]
Composite safety end point	0	1 (0.9)	0.16[a]	0	1 (2.1)	0.32[a]
Death	0	0	–	0	0	–
Bradycardia ≤45 bpm	0	0	–	0	0	–
Syncope	0	0	–	0	1 (2.1)	0.32[a]
Hypotension	0	1 (0.9)	0.16[a]	0	0	–

Data are presented as number (percentage) of patients or median (interquartile range) unless indicated otherwise.

a χ^2 test

b Mann–Whitney test

Abbreviations: PSM, propensity score matching; others, see **FIGURE 1** and **TABLES 1** and **2**

high-volume confirmation of the formerly acquired results. More importantly, the PSM analysis allowed compensation for the uneven distribution of variables, which could otherwise alter the success and complication rates of each of the AADs.

The acquired results should be compared with those of the AnPAF study,[14] the only randomized placebo-controlled trial evaluating antazoline vs placebo for PC of AF, which covered 74 patients and showed that intravenous antazoline terminated AF in 72.2% of patients in a median time of 16 minutes (vs 10.5% in placebo). The study reported only mild symptoms secondary to antazoline use, most commonly hot flush (19.4%) and drowsiness (8.3%), while no serious adverse events (only a single episode of hypotension and a single episode of mild dyspnea) were documented.[15] On account of the abovementioned report, a recent meta-analysis by deSouza et al[21] evaluating the efficacy of different AADs for PC in the ED indicated that antazoline was characterized by the highest efficacy among all AADs (odds ratio, 24.9; 95% credible interval, 7.4–107.8).

In a study by Farkowski et al[18] performed on 432 patients with AF admitted to the ED, antazoline was demonstrated to be superior to propafenone in terms of cardioversion success rate (71.6% vs 55.1%). The safety analysis was consistent with the current research, as adverse actions of antazoline were uncommon and benign, including 6 episodes of hypotension below 100 mm Hg (1.8%) and 32 cases of bradycardia (9.6%).[18]

The application of antazoline for cardioversion of AF in the setting of electrophysiology laboratory was validated by Balsam et al[13] on 141 consecutive patients with AF submitted to PVI. The efficacy of antazoline in terms of AF termination reached 83.6% in patients with paroxysmal and 31.1% in patients with persistent AF.[13]

The properties of antazoline resemble those of quinidine and other Vaughan-Williams class Ia agents.[22] Following infusion, antazoline triggers an increase of atrial postrepolarization

refractoriness, translating into more organized electrical activity of atria in the form of supraventricular tachycardia and, eventually, return to SR.[22] Antazoline modifies the electrophysiologic properties of the myocardium by increasing the duration of the QRS complex and corrected QT interval, and exerts an anticholinergic action resulting in improved atrio-ventricular conduction.[15-17]

It is vital to note that in crude analysis, the patients treated with antazoline exhibited a higher rate of composite safety end point occurrence than the amiodarone group, predominantly driven by a higher rate of bradycardia, which was consistent with the results of the study by Farkowski et al.[18] This phenomenon might be explained by the propensity of antazoline for transient increase of heart rate, which is routinely prevented by administration of β-blockers. In the postcardioversion period, this may lead to transient sinus bradycardia. Indeed, the antazoline group had a higher rate of β-blocker use than the amiodarone cohort (55.5% vs 26.8%; P <0.001). PSM led to an even distribution of β-blocker utilization, which translated into a similar rate of bradycardia between the antazoline and nonantazoline cohorts (P = 0.13). The low rate of adverse actions and a considerable representation of patients with structural heart disease in the present registry (37% in the overall population; 41.2% in the antazoline group) speak in favor of antazoline's cardiovascular safety.

The present findings underscore the safety and efficacy of antazoline use, which leads to rapid rhythm conversion,[14] translating into shorter stay in the ED and presumably lower costs of hospitalization. This should be contrasted with vernakalant, which is now recommended by the European guidelines[5] for rapid and effective PC (median time to rhythm conversion, 11 min), yet its applicability is limited in certain regions due to economic issues.[9,10] Antazoline is routinely used in EDs throughout Poland and it was registered for termination of supraventricular arrhythmias. Although randomized controlled trials with an active comparator are warranted, the role of antazoline in the treatment of AF in the real-world scenario should not be neglected. The unique story of antazoline, a drug once designed for treating allergic reactions, is an example of reverse evidence-based medicine, in which the undeniable clinical efficacy is now being confirmed by scientific research.

Furthermore, the real-world nature of the present registry highlights the need for revision of the current practice, as the utilization of antiarrhythmic drugs for PC was highly nonadherent to contemporary guidelines.[5,7] In the current registry, 64.5% of patients treated with amiodarone did not have structural heart disease, while 25.3% of patients who received propafenone had some form of structural heart disease. This merits urgent attention of scientific societies to implement guidelines on daily clinical management of patients with AF.

Study limitations The current study is subject to limitations inherent to its retrospective design; however, the PSM analysis aimed to minimize the impact of heterogeneity of the population on the study results. The exact number of screened patients who were excluded is unknown as the study represented a registry; however, the exclusion criteria of this registry were solely used to identify consecutive patients diagnosed with an ICD-10 I48 code subjected to PC of AF who were not using antiarrhythmic agents, and who were eligible for PC in terms of the anticoagulation status. The study results might have been altered by the exclusion criterion of EC prior to the end of the 12-hour follow-up. Still, this criterion was designed to compensate for the possible underestimation of the efficacy of amiodaron, which is characterized by a delayed onset of action. Due to the study design, some episodes of mild adverse effects of AADs might have been underreported, such as rash and other skin reactions, nausea, vomiting, and others. For this reason, the present study did not consider these phenomena as safety end points. A considerable proportion of patients treated with antazoline (41.2%) and propafenone (25.3%) had structural heart disease and the treatment did not comply with current guidelines; however, it did not lead to a higher rate of complications in these subgroups of patients. All patients underwent PC under strict electrocardiographic and hemodynamic monitoring and all arrhythmic events were recorded. Episodes of high-rate supraventricular tachycardia were not regarded as a complication since antazoline frequently converts AF to transient supraventricular tachycardia prior to eventual restoration of SR. The study did not cover other AADs, such as vernakalant, ibutilide, or flecainide, which are currently unavailable in Poland. This registry did not include data on time to successful rhythm conversion.

Conclusions Antazoline mesylate represents an efficacious antiarrhythmic agent with a relatively safe clinical profile, which is noninferior to other available AADs in terms of adverse effects. Given its regional widespread utilization, randomized controlled trials comparing antazoline with other AADs are of crucial importance in order to unequivocally confirm its safety profile and verify its applicability in specific patient populations, including patients with structural heart disease.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT MTW conceived the concept of the study, collected data, performed statistical analysis, and drafted the manuscript; AM, DM, BC-S, PB, MW, and W. Wańha collected data, drafted the manuscript, and verified the final version of the manuscript; W. Wróbel, MF, EĆ-R, MS, KO, RB, KB, TD, MP, and BK collected data and drafted the manuscript; MK, JDK, and HS collected data, drafted the manuscript, and supervised the project; KM-S drafted the manuscript and supervised the project.

CONFLICT OF INTEREST None declared.

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