Antiarrhythmic drugs for pharmacological cardioversion of atrial fibrillation and sex differences: Insights from the CANT II Study

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ABSTRACT

Background: Data on sex differences in terms of action of antiarrhythmic agents (AADs) are limited. This study aimed to evaluate the clinical profile of patients with atrial fibrillation (AF), and efficacy and safety of AADs used for pharmacological cardioversion (PCV) of AF.

Methods: This research was a sub-analysis of the retrospective multicenter Cardioversion with ANTazoline II (CANT) registry, which comprised 1365 patients with short-duration AF referred for urgent PCV with the use of AAD. Patients were categorized according to and compared in terms of clinical parameters and PCV outcomes. The primary endpoint was return of sinus rhythm within 12 hours after drug infusion, and the composite safety endpoint involved bradycardia <45 bpm, hypotension, syncope, or death.

Results: The sex distribution of patients qualified for PCV was even (men, n = 725; 53.1%). Females were older and more symptomatic and had higher CHA_2DS_2-VASc scores, higher prevalence of tachyarrhythmia, and higher use of chronic anticoagulation. The overall efficacy (71.4% vs. 70.1%; $P = 0.59$) and safety (5.2% vs. 4.6%; $P = 0.60$) of PCV was comparable in men and women. Amiodarone (68.3% vs. 65.9%; $P = 0.66$) and antazoline (77.1% vs. 80.0%; $P = 0.19$) had similar efficacy in men and women, but propafenone had a lower rate of rhythm conversion in men (64.7% vs. 79.3%; $P = 0.046$). None of the assessed AADs differed in terms of safety profile in both sexes.

Conclusion: Female patients with AF have different clinical profiles but similar efficacy and safety of AADs as compared to male participants. Propafenone has significantly lower efficacy in men, which requires further investigation.

Key words: antazoline, amiodarone, atrial fibrillation, pharmacological cardioversion propafenone, sex differences

WHAT'S NEW?

Accumulating data indicate significant sex disparities in terms of clinical presentation and management in patients with atrial fibrillation. The present analysis aimed to evaluate the clinical profile of patients with atrial fibrillation referred for pharmacological cardioversion and assess efficacy and safety of different antiarrhythmic agents with reference to the patient's sex. The study showed that overall efficacy and safety of pharmacological cardioversion are similar in men and women. Although efficacy and safety of amiodarone and antazoline seem independent of sex, propafenone use may be linked to lower efficacy of cardioversion in men than in women.

INTRODUCTION

Atrial fibrillation (AF) represents a global burden for healthcare systems due to a greater risk of ischemic stroke, stroke-related disability, progression of heart failure, and death [1]. Although age-adjusted AF prevalence is higher in men [2, 3], women tend to have a higher risk of AF-related complications [4, 5], lower quality of life and symptom management [6], more pronounced risk of systemic thromboembolism, reflected by the routinely used CHA_2DS_2-VASc score [7]. Conversely, female patients less frequently receive adequate anticoagulation [8] and physicians are more reluctant to qualify women for the rhythm control strategy involving pulmonary vein isolation, electrical cardioversion, or antiarrhythmic drug (AAD) therapy [9]. Still, women who undergo AF catheter ablation are more likely to develop complications [10]. On the other hand, AADs are thought to confer a greater risk of adverse reactions in women [11]. Notably, women have a higher propensity for QT interval prolongation and resultant malignant ventricular arrhythmias [11]. The RACE trial provided worrisome data on the potentially higher rate of complications of chronic AAD therapy in women [12]. Taking into consideration all these aspects, sex disparities in terms of clinical presentation of AF seem vital for management of patients suffering from AF. Still, there is a paucity of data on the use of different AADs with reference to patient's sex. Thus, this sub-analysis of the CANT II study (Cardioversion with ANTazoline in Atrial Fibrillation II registry) aimed to evaluate the efficacy and safety of different AADs for pharmacological cardioversion of short-duration AF with regard to patients' sex.

METHODS

This research represents a sub-analysis of the real-life cardioversion with intravenous ANTazoline in the Atrial Fibrillation II registry (CANT II study), which comprised 1365 consecutive patients with short-duration AF qualified for urgent pharmacological cardioversion. The rationale, design, and main results of the study were thoroughly described earlier [13]. In brief, this was a retrospective multicenter registry conducted in 6 centers throughout Poland using the Scientific Platform of the "Club 30" of the Polish Cardiac Society between June 2019 and February 2020. The study included eligible patients with paroxysmal or persistent atrial fibrillation, who did not meet exclusion criteria [13]. Patients were qualified for pharmacological cardioversion in the emergency department according to local practice. The allocation to a specific AAD was left to the discretion of the attending physician and was in line with the 2016 European Society of Cardiology guidelines on AF management [14]. The primary endpoint of the study was the return of sinus rhythm confirmed in 12-lead electrocardiographic recording within a 12-hour monitoring period. The composite safety endpoint comprised bradycardia <45 bpm or hypotension (decrease in systolic blood pressure of >40 mm Hg), syncope, or death. The study definitions and therapeutic arms were thoroughly described previously [13].

In this sub-analysis, baseline demographic and clinical variables as well as efficacy and safety of AADs were compared between women and men. Additionally, the success rate of different AADs was compared separately in the sub-population of women and men.

The choice of AAD included: (1) intravenous (*i.v.*) amiodarone (Cordarone®, Sanofi-Aventis), (2) *i.v.* antazoline mesylate (Phenazolinum®, Polfa, Warszawa, Poland), (3) *i.v.* or oral propafenone (Rytmonorm®, Mylan Healthcare, Warszawa, Poland), or (4) ≥2 medications. AAD administration was preceded by meticulous assessment of anticoagulation status. The use of beta-blockers and *i.v.* electrolyte supplementation was optional in the respective clinical settings.

The study protocol complied with the Declaration of Helsinki guidelines and was approved by the Ethics Committee of the Medical University of Silesia in Katowice number KNW/022/KB1/9/18 on 13 February 2018. All the patients signed written informed consent for treatment and participation in the registry.

Statistical analysis

Statistical analysis was carried out using SPSS v.25.0 software (IBM Corp, Armonk, NY, US). All the continuous variables were assessed using the Shapiro-Wilk test and expressed as medians (interquartile ranges [IQR]) in the case of non-normally distributed variables or means and standard deviations (SD) in the case of normally distributed variables. All the qualitative parameters were expressed as crude numbers and percentages. The inter-group differences were compared using the Mann-Whitney U test, Kruskal-Wallis test, Student's t-test, or analysis of variance (ANOVA). Qualitative variables were compared using the χ^2 test. The relative risk (RR) ratio with 95% confidence interval (CI) limits, number needed to treat (NNT), and

number needed to harm (NNH) were calculated for the efficacy and safety of AAD in AF termination. In subgroups of women and men, separate univariable analyses of different predictors of rhythm conversion were established with calculation of the odds ratio (OR). All the variables with P <0.1 were incorporated into two separate logistic regression models of independent predictors of successful pharmacological cardioversion. The area under the receiver operating characteristics curve (AUROC) was calculated for two separate models in women and men. The goodness of fit of the model was verified using the Hosmer–Lemeshow test. A P-value <0.05 was regarded as statistically significant.

RESULTS

This retrospective analysis included 1365 patients with short-duration AF. The baseline characteristics and the results concerning efficacy and safety of different AADs were described earlier [13]. The analysis showed a higher prevalence of males (53.1%) in the study population qualified for urgent pharmacological cardioversion. The comparison between women and men in terms of demographic and clinical variables is presented in Table 1. Women qualified for urgent rhythm control were older and had a similar prevalence of arterial hypertension and diabetes as men (Table 1). Notably, women had lower rates of coronary artery disease (CAD) and structural heart disease but higher left ventricular ejection fraction (LVEF) and smaller left atrial diameter than men undergoing pharmacological cardioversion of AF. In contradistinction to men, women were characterized by lower potassium concentration and estimated glomerular filtration rate (eGFR), higher symptomatic EHRA class and CHA_2DS_2-VASc scores, greater extent of tachyarrhythmia, and higher prevalence of chronic anticoagulation. The analysis showed more frequent use of amiodarone in women and antazoline in men, while the use of propafenone was similarly distributed between both sexes (Table 1).

The success rate (risk ratio [RR], 0.981; 95% confidence interval [CI], 0.917–1.051; P = 0.59) and the risk of adverse events (RR, 0.883; 95% CI, 0.551–1.413; P = 0.60) of pharmacological cardioversion were comparable in women and men (Table 1). The efficacy of different AADs by sex is highlighted in Figure 1. Amiodarone alone shared similar efficacy (RR, 1.037; 95% CI, 0.881–1.221; P = 0.66) and safety (RR, 0.267; 95% CI, 0.032–2.254; P = 0.19) in men and women. The success rate (RR, 0.964; 95% CI, 0.886–1.049; P = 0.40) and safety of antazoline as a single AAD (RR, 1.13; 95% CI, 0.559–2.287; P = 0.73) was also comparable in males and females. Still, the efficacy of propafenone used as a stand-alone agent was significantly lower in men than in women (RR, 0.480; 95% CI, 0.231–0.995; NNT 7; P = 0.046), while a trend towards higher rate of adverse reactions of propafenone in women was reported (RR, 0.268; 95% CI, 0.060–1.199; NNH 12; P = 0.06).

The proportion of peri-cardioversion beta-blocker use (P = 0.44) and *i.v.* potassium infusion (P = 0.53; Table 1) was comparable between women and men. The distribution of beta-blocker use was also similar in women and men in the cohorts of patients treated with amiodarone (27.4% vs. 28.3%, P = 0.86), antazoline (59.3% vs. 61.5%; P = 0.61), and propafenone (31.7% vs. 28.3%, P = 0.39). The proportions of patients who received *i.v.* potassium infusion were comparable between women and men in the amiodarone (55.4% vs. 59.3%, P = 0.51), antazoline (45.7% vs. 52.0%, P = 0.18), and propafenone subgroups (28.0% vs. 25.6%, P = 0.42).

In women, antazoline and propafenone exhibited similar efficacy in terms of rhythm conversion, which was significantly higher than in the amiodarone group (80.0% vs. 79.3% vs. 65.9%, respectively; P <0.001). Conversely, in men, antazoline showed the highest efficacy in AF termination, which was higher than in the case of propafenone and amiodarone (77.1% vs. 64.7% vs. 68.3% respectively, P <0.001).

The results of univariable analysis of different predictors of successful PCV in women and men are presented in Supplementary material, *Table S1*. The results of logistic regression analysis in women and men are presented in Table 2. In women, return of sinus rhythm was independently associated with higher eGFR (P = 0.001) and higher LVEF (P = 0.04), while AF episode duration >7 days (P <0.001) and the use of amiodarone, in contrast to other AADs (P = 0.03), were linked to cardioversion failure. In men, an increased baseline heart rate (P = 0.04) and intravenous potassium supplementation (P = 0.02) predicted successful pharmacological cardioversion, whereas AF episode duration >7 days and the use of propafenone (P = 0.002) or amiodarone (P = 0.001), in opposition to other AADs, were associated with a lower rate of AF termination.

DISCUSSION

In this sub-analysis of the multicenter CANT II registry, we found that women with AF undergoing acute rhythm control with pharmacological cardioversion were older, and had higher CHA_2DS_2-VASc scores and a higher prevalence of chronic anticoagulation. They were more symptomatic, less frequently underwent pulmonary vein isolation, and had a lower prevalence of structural heart disease. They more frequently presented with tachyarrhythmia in the course of AF episodes and had lower eGFR and potassium concentration (Table 1) than men. Notably, as this study enrolled consecutive patients without exclusion criteria, one should underline the slight predominance of men represented in the registry. These observations are consistent with former reports, which documented a significantly diverse profile of female patients suffering from AF [15, 16]. In the Euro Observational Research Programme (EORP) pilot survey on AF performed on 3119 patients, women with AF had a similar profile to our findings, including older age, higher European Heart Rhythm Association class, higher estimated risk of systemic embolism reflected by higher CHA_2DS_2-VASc score, and more common chronic use of

Table 1. Comparison of selected demographic, clinical, laboratory, and echocardiographic characteristics between men and women with short duration atrial fibrillation subject to urgent pharmacological cardioversion

Variable	Women n = 640 (46.9%)	Men n = 725 (53.1%)	*P*-value
Demographic characteristics			
Age, years, median (IQR)	71 (65-77)	66 (56-74)	<0.001
Body mass index, kg/m^2, mean (SD)	28.0 (4.6)	28.1 (4.0)	0.68
Obesity, n (%)	201 (31.4%)	223 (30.8%)	0.67
Comorbidities			
Arterial hypertension, n (%)	444 (69.3%)	503 (69.4%)	0.89
Diabetes mellitus, n (%)	128 (20.0%)	134 (18.5%)	0.78
Coronary artery disease / peripheral artery disease, n (%)	145 (22.7%)	298 (41.1%)	<0.001
History of ischemic stroke / transient ischemic attack, n (%)	39 (6.1)	25 (3.4)	0.06
Structural heart disease, n (%)	168 (26.3)	337 (46.5)	<0.001
Selected echocardiographic parameters			
LVEF, %, median (IQR)	58 (54–60)	55 (50–60)	<0.001
Left atrial diameter, mm, median (IQR)	43.0 (39.0–47.0)	44.0 (41.0–47.5)	0.008
Laboratory tests			
Serum creatinine concentration, mg/dl, median (IQR)	0.88 (0.74–1.10)	1.05 (0.91–1.21)	<0.001
eGFR, ml/min/1.73 m^2, median (IQR)	66.0 (50.4–83.0)	77.0 (63.0–89.0)	<0.001
Potassium concentration, mEq/l, mean (SD)	4.20 (0.44)	4.29 (0.46)	0.003
White blood cell count, ×1000/µl, median (IQR)	7.69 (6.40–9.32)	7.34 (6.21–8.79)	0.02
Hemoglobin, g/dl, mean (SD)	13.6 (1.6)	14.8 (1.6)	0.001
AF characteristics			
Persistent atrial fibrillation, n (%)	52 (8.1)	51 (7.0)	0.14
AF episode duration, hour, median (IQR)	10 (5–24)	10 (4–24)	0.27
CHA_2DS_2–VASc score, points, median (IQR)	3 (3–5)	2 (1–3)	<0.001
EHRA class, mean (SD)	2.46 (0.82)	2.32 (0.84)	0.03
History of pulmonary veins isolation, n (%)	39 (6.1)	82 (11.3)	<0.001
Chronic anticoagulation, n (%)	339 (53.0)	314 (43.3)	0.002
VKA, n (%)	92 (14.4)	82 (11.3)	0.023
NOAC, n (%)	247 (38.6)	238 (32.0)	0.01
Heart rate ≥130 bpm, n (%)	202 (31.6)	117 (16.1)	<0.001
Adjuvant treatment and antiarrhythmic therapy			
Beta-blocker use, n (%)	259 (40.5)	299 (41.2)	0.44
Intravenous potassium, n (%)	275 (43.0)	318 (43.9)	0.53
Amiodarone[a], n (%)	265 (41.4)	243 (33.5)	0.003
Propafenone[a], n (%)	138 (21.6)	147 (20.3)	0.56
Antazoline[a], n (%)	380 (59.4)	517 (71.3)	<0.001
≥2 antiarrhythmic drugs, n (%)	144 (22.5)	184 (25.4)	0.29
Dose of antazoline, mg, median (IQR)	200 (100–200)	200 (150–200)	0.74
Dose of amiodarone, mg, median (IQR)	425 (300–600)	450 (300–600)	0.97
Dose of propafenone, mg, median (IQR)	140 (70–300)	220 (120–450)	0.12
Primary efficacy and safety endpoints			
Successful pharmacological cardioversion, n (%)	457 (71.4)	508 (70.1)	0.59
Composite safety endpoint, n (%)	33 (5.2)	33 (4.6)	0.60
Hypotension, n (%)	5 (0.8)	9 (1.2)	0.40
Bradycardia <45 bpm, n (%)	28 (4.4)	27 (3.7)	0.54
Syncope, n (%)	1 (0.2)	0 (0.0)	0.29
Death, n (%)	0 (0.0)	0 (0.0)	–

[a]Overall use including overlapping antiarrhythmic therapy

Abbreviations: AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association classification; IQR, interquartile range; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulants; SD, standard deviation; VKA, vitamin K antagonists

anticoagulation [16]. Notably, Lip and colleagues demonstrated that female patients were less likely to be qualified for rhythm control strategies, including AF ablation and electrical cardioversion but were more often referred for pharmacological cardioversion (28.2% vs. 22.4%; P <0.001), while they received chronic AAD therapy as frequently as men (39.7% vs. 36.6%; P = 0.15) [16]. Still, the EORP study did not provide detailed information on the efficacy and mode of pharmacological cardioversion [16]. On the other hand, Duran-Bobin et al. [15] showed similar tendencies, including a lower prevalence of chronic treatment with AADs in females than in males (31.3% vs. 42.3%, P = 0.001). Still, they did not provide data on use of AADs for pharmacological cardioversion [15].

In our study, the body mass index and prevalence of obesity were comparable between women and men

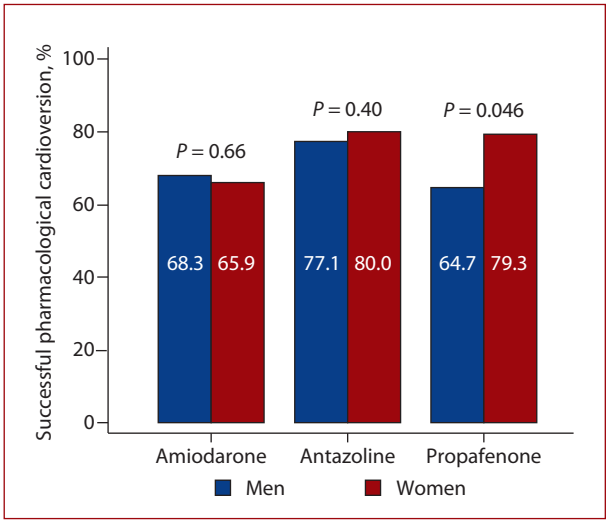

Figure 1. Comparison of efficacy of pharmacological cardioversion with different antiarrhythmic drugs depending on patients' sex

(Table 1). Cichoń et al. [17] demonstrated that obesity represents a strong negative predictor of the efficacy of electrical cardioversion; however, this variable was not associated with cardioversion outcomes in our report (Supplementary material, *Table S1*).

The sex-related differences do not pertain merely to AF presentation and treatment but have been reported in other cardiovascular disorders, most notably CAD [17]. Andreotti et al. [18] showed that women tend to have delayed onset of atherosclerosis, less pronounced cardiovascular risk factors in age-matched cohorts, less frequent obstructive CAD, and tend to be undertreated and underrepresented in cardiovascular trials. These findings speak in favor of the sex-specific approach to management of patients with cardiovascular disease, including AF and CAD [19].

In our study, more women than men were treated with amiodarone, while class Ia AAD antazoline was more frequently used in males than females. This study is so far the first report in the literature that provides data on efficacy and safety of different AADs for pharmacological cardioversion depending on sex in a real-world setting. Although the overall efficacy and safety of AADs were similar in men and women, propafenone showed far worse efficacy in men than in women (Figure 1). The multivariable analysis provided evidence that the use of amiodarone or propafenone was linked to cardioversion failure in men, while in women, only amiodarone was associated with unsuccessful rhythm conversion (Table 2). The reason for this lack of efficacy of propafenone in males remains unknown, but this phenomenon requires further research as the current European AF guidelines do not propose different approaches to men and women in terms of AAD use [20].

Our data provide evidence for relative AAD safety in acute rhythm control in the female AF population. On the other hand, women treated with propafenone had numerically higher rates of mild adverse reactions, mainly transient bradycardia (Table 1). These data should be confronted with a former report suggesting a higher risk of proarrhythmia in females treated with AAD [12]. The RACE trial delivered evidence that during 2.3-year follow-up, female patients with persistent AF qualified for the rhythm control strategy exhibited more AAD-related complications than men (4.7% vs. 1.5%), accompanied by more frequent indications for pacemaker implantation (5.2% vs. 1.8%) [12]. Still, our study investigated only acute, non-chronic, administration of AAD and showed no difference in terms of adverse reactions between both sexes. One should note, however, that a former report suggested a higher risk of QTc interval prolongation in women, translating into a greater risk of torsade de pointes in females [21]. Still, no such case was reported in our population, presumably given the lack of sotalol administration.

Our analysis showed that antazoline represents a sound and efficient AAD for acute rhythm conversion in short-duration AF both in women and men. In women, antazoline exhibited comparable efficacy to propafenone and better than amiodarone, while in men, antazoline was superior to both propafenone and amiodarone. Antazoline belongs to antihistamine drugs with potent and rapid antiarrhythmic

Table 2. Logistic regression analysis of independent predictors of successful pharmacological cardioversion in men and women

Variable	OR	95% CI	*P*-value
Women			
AF episode duration >7 days	0.083	0.037–0.182	<0.001
eGFR (per a 1 ml/min increase)	1.021	1.008–1.034	0.001
LVEF (per a 1% increase)	1.033	1.002–1.065	0.04
Amiodarone use[a] vs. other AAD	0.569	0.340–0.955	0.03
AUROC, 0.758; 95% CI, 0.710–0.802; Hosmer–Lemeshow *P* = 0.76			
Men			
AF episode duration >7 days	0.047	0.015–0.144	<0.001
Baseline heart rate, per a 1 bpm increase	1.012	1.001–1.024	0.04
Intravenous potassium infusion	1.928	1.091–3.408	0.02
Propafenone use[a] vs. other AAD	0.331	0.163–0.672	0.002
Amiodarone use[a] vs. other AAD	0.379	0.210–0.686	0.001
AUROC, 0.744; 95% CI, 0.692–0.791; Hosmer–Lemeshow *P* = 0.93			

[a]Relative to the whole population of women treated with antiarrhythmic agents

Abbreviations: AAD, antiarrhythmic drugs; AUROC, area under the receiver operating characteristic curve; other — see Table 1

activity resembling Vaughan-Williams class Ia with atropine-like properties [22]. Antazoline has been registered and used in emergency departments in Poland for urgent termination of atrial fibrillation [13]. In the earlier CANT I study [23] and the current high-volume CANT II study [13], antazoline has been shown to have comparable efficacy to propafenone and superior efficacy to amiodarone in terms of the rate of rhythm conversion. Also, Farkowski et al. found that antazoline is characterized by even better efficacy than propafenone [24], and its efficacy extended to the elderly population [25]. What is more, none of the above-mentioned results indicated serious adverse events related to the use of antazoline in comparison to other AADs. In patients with advanced chronic kidney disease with an estimated glomerular filtration rate <45 ml/min, antazoline lost its efficacy with a rhythm conversion rate of 35% [26]. To date, the use of antazoline is not supported by the current ESC guidelines on AF [20] as no large randomized controlled trial prospectively confirmed its safety, especially in patients with structural heart disease. Still, the present analysis indicates that the favorable efficacy and safety profile of antazoline extends to both sexes.

Limitations of the study

This analysis represents a retrospective registry and is subject to the limitations of retrospective design. The study involved a relatively small number of patients treated with propafenone. The time between AAD administration and return of sinus rhythm was not studied. A considerable proportion of patients received ≥2 AADs, which might have modified the results of the registry. The study did not investigate the electrocardiographic alterations following AAD infusion, or QRS and QTc interval prolongation.

CONCLUSIONS

Our study indicates that the general efficacy and safety of pharmacological cardioversion for short-duration AF is similar in men and women. Amiodarone and antazoline are characterized by similar success rates of pharmacological cardioversion in both sexes, but propafenone seems to be less efficient in men.

Supplementary material

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

Article information

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