sciendo Internal Medicine 2021 vol. XVIII No. 5 - www.srmi.ro 15
10.2478/inmed-2021-0179

ADVERSE DRUG REACTIONS AND ATRIOVENTRICULAR CONDUCTION DISORDERS - A FEMALE GENDER RELATED APROACH

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Rezumat

Introducere*. Deși bolile cardiovasculare rămân principala cauză de mortalitate indiferent de gen, genul feminin a rămas o populație subreprezentată în studiile în domeniu. Inițiative susținute ale Societății Europene de Cardiologie au adus în prim plan importanța studierii diferențelor de gen în privința profilului de siguranță al medicamentelor cardiovasculare în cazul femeilor. Printre efectele adverse medicamentoase frecvente, cardiovasculare, se numără tulburările de conducere atrio-ventriculară.*

Material și metodă*. Studiul prezentat a urmărit particularitățile clinico-paraclinice ale pacienților de gen feminin cu un diagnostic principal, la internare, de bradicardie, în relație cu medicația bradicardizantă. Am inclus un lot de 359 pacienți de gen feminin, împărțit în funcție de prezența sau absența medicației bradicardizante într-un lot studiu (n =206) și un lot martor (n =153).*

Rezultate*. Pacienții care au asociat medicație bradicardizantă au necesitat frecvent internare în urgență (P <0,001), cu o durată prelungită a spitalizării (P <0,001). Principalele tulburări de conducere atrio-ventriculară identificate au fost fibriația atrială cu alură ventriculară lentă (P =0,028), bradicardia sinusală (P =0,009) și pauzele sinusale (P =0,009). Dintre comorbidități, insuficiența cardiacă (P <0,001) și boala renală cronică (P <0,001), au fost frecvente în lotul de studiu. Parametrii ecocardiografici de dilatare ventriculară stângă (P =0,002) și biatrială (P <0,001), precum și disfuncția sistolică severă a ventriculului stâng (P =0,009), au prezentat semnificație statistică în acest lot. Cele mai frecvent utilizate medicamente au fost beta-blocantele, amiodarona și digoxinul.*

Concluzii*. Rezultatele noastre indică, ca factori asociați bradiaritmiilor legate de medicație, la genul feminin: insuficiența cardiacă cu disfuncție sistolică severă, disfuncția renală, fibrilația atrială și dilatarea ventriculară stângă.*

Cuvinte cheie: *tulburări de conducere atrio-ventriculară, gen feminin, medicație bradicardizantă.*

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Abstract

Introduction. *Although cardiovascular disease remains the leading cause of mortality regardless of gender, the female gender has remained an underrepresented population in studies in this field. Sustained initiatives by the European Society of Cardiology have brought to the fore the importance of studying gender differences regarding the safety profile of cardiovascular drugs in women. Common cardiovascular adverse drug reactions include atrio-ventricular conduction disorders.*

Materials and methods. *The present study followed the clinical and paraclinical features of female patients with a primary diagnosis of bradycardia in relation to bradycardic medication. We included a group of 359 female patients, divided according to the presence or absence of bradycardia medication into a study group (n=206) and a control group (n=153).*

Results. *Patients with associated bradycardic medication frequently required emergency admission (P < 0.001), with prolonged hospitalization (P < 0.001). The main atrioventricular conduction disorders identified were atrial fibrillation with slow ventricular response (P = 0.028), sinus bradycardia (P = 0.009) and sinus pauses (P = 0.009). Among comorbidities, heart failure (P<0.001) and chronic kidney disease (P<0.001), were common in the study group. Echocardiographic parameters of left ventricular (P=0.002) and biatrial (P<0.001) dilatation, as well as severe left ventricular systolic dysfunction (P=0.009), showed statistical significance in this group. The most used drugs were beta-blockers, amiodarone, and digoxin.*

Conclusions*. Our results indicate, as factors associated with medication-related bradyarrhythmias in female gender: heart failure with severe systolic dysfunction, renal dysfunction, atrial fibrillation, and left ventricular dilatation.*

Keywords*: atrioventricular conduction disorders, female gender, bradycardic medication.*

Introduction

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in both men and women[1]. Cardiovascular risk in women has been underestimated and little studied until today. The protective role of hormones disappears with the onset of menopause, leading to an increase in CVD incidence. After the age of 65, CVD are the leading cause of death in women. The lack of evidence on the gender difference in the efficacy and safety of cardiovascular therapeutic interventions are a consequence of is a consequence of the predominant inclusion of male patients in large clinical trials[2].

The influence of gender on the effects of medication in various cardiovascular pathologies is not fully known. Differences in anatomical structure and function are reflected in pharmacokinetics and pharmacodynamics characteristics. Body composition, drug absorption, plasma, and tissue distribution, metabolizing enzymes and transporters or drug excretion influence the pharmacokinetics of various drugs. Women have a lower gastric acid secretion and gastrointestinal transit time which leads to a decrease in the absorption of some beta-blockers (BB) such as metoprolol or verapamil (they need an acidic environment for absorption)[3]. Female specific hormones interfere in the metabolic process as plasma protein binding agents, but their effect needs further research in this field. In addition to the physiological aspects mentioned above, anatomical conformation plays a special role in drug metabolism in women as they have a higher percent of body fat and lower organ size, blood flow and plasma volume. Drugs which require loading-dosages such as amiodarone or digoxin reach higher serum level concentration than in men, leading to more adverse drug reactions (ADRs). Both renal and hepatic clearance depend on the cardiac output and are lower in women which leads to differences in drug-metabolizing enzymes and transporters as well as a more slowly clearance of drugs primarily excreted unchanged in the urine[2,4].

Objectives

The present study aimed to capture the clinical and paraclinical features of female patients with a main diagnosis on admission, of symptomatic bradycardia in relation to bradycardic medication.

Material and methods

We included a cohort of 359 female patients admitted to a single tertiary referral center in the North-East Romania for a symptomatic atrioventricular conduction disorder. We divided this group according to the presence or absence of bradycardic medication into a study group (n=206) and a control group (n=153), respectively. Age under 18 years, the diagnosis of an acute coronary syndrome, previous pacemaker implantation as well as post-interventional or post-surgical atrioventricular conduction disorders were exclusion criteria.

The statistical analysis covered a variety of parameters such as demographic characteristics, comorbidities, vital signs at presentation, laboratory results and use of β-blockers among the two groups (patients with β-blockers and controls). Descriptive statistics (frequency, percentage, mean, standard deviation) as well as inferential statistics were used. Numerical data was recorded as mean ± standard deviation (SD). Categorical data was presented as absolute

values and percentages. A Chi square test ($\chi 2$ test) or Fisher Exact test was used to assess differences between categorical variables. Independent t-test (parametric analysis) and Mann-Whitney U test (non-parametric analysis) was used to test the differences between numerical variables. The chosen significance threshold for P value was 0.05. All statistical calculations were performed using the SPSS statistics software (version 20, IBM).

Results

We included in our study 359 female patients, 206 in the study group (based on the use of medication) and 153 in the control group (without any bradycardic medication). The demographic characteristics and comorbidities associated are presented in Table 1. The mean age was slightly higher in the study group (73.66 ± 9.28 yrs *vs.* 74.18 ± 8.76 yrs, P=0,591) as well as the mean value of body mass index (27.99 ± 5.66 kg/m^2 *vs.* 28.07 ± 6.78 kg/m^2, P=0.628).

Both hypertension and diabetes mellitus were moreover present in the cases group (76.7% *vs.* 76.5%, P=0.181, respectively 26.2% *vs.* 18.3%, P=0.077). More patients in the first group associated acute kidney injury (18.0% *vs.* 9.8%, P = 0.030), chronic kidney disease (28.6% vs. 13.1%, P<0.001) or chronic kidney disease without exacerbation (20.9% *vs.* 7.2%, P<0.001), indicating a solid association between the use of antiarrhythmic medication and renal pathology. Statistical analysis revealed a statistically significant value for the association of heart failure in our study (31.6% *vs.* 14.4%, P<0.001).

Table 2 shows the vital signs at admission and the electrocardiographic findings. Emergency hospitalization (58.3% *vs.* 37.9%, P<0.001) and temporary cardiac pacing (14.6% *vs.* 13.1%, P =0.687) were more frequent in the cases group.

The mean values and SD of systolic blood pressure (142.85 ± 28.83 mmHg *vs.* 151.58 ± 28.81, P =0.005) and diastolic blood pressure (74.39 ± 13.83 mmHg *vs.* 75.78 ± 13.86 mmHg, P =0.348) were increased in the female group without antiarrhythmic medication, compared to the higher mean values of the heart rate in patients with antiarrhythmic medication (58.56 ± 24.62 bpm *vs.* 51.54 ± 22.00 bpm, P =0.003). Slow ventricular response atrial fibrillation was more frequent in the cases group (21.4% *vs.* 12.4%, P =0.028), while sinus bradycardia and sinus pauses were identified only in the first group, having a statistically significant value (P =0.009). The absence of bundle branch block morphology prior to conduction disorder was statistically significant (P =0.009) and more frequent in the control group (74.3% *vs.* 85.6%).

Parameters	Study group (with medication) *n* = 206	Control group (without medication) *n* = 153	P value
Age, yrs	73.66 ± 9.28	74.18 ± 8.76	0.591
Originating area (urban vs. rural)	115 (55.8%)	71 (46.4%)	0.077
Body mass index, kg/m^2	27.99 ± 5.66	28.07 ± 6.78	0.628
Duration of hospitalization, days	6.65 ± 3.59	4.89 ± 2.42	<0.001
Hypertension	158 (76.7%)	117 (76.5%)	0.181
Grade 1 hypertension vs. normal	8 (3.9%)	5 (3.3%)	0.758
Grade 2 hypertension vs. normal	38 (18.4%)	16 (10.5%)	0.036
Grade 3 hypertension vs. normal	112 (54.4%)	96 (62.7%)	0.112
Diabetes mellitus	54 (26.2%)	28 (18.3%)	0.077
Acute kidney injury	37 (18.0%)	15 (9.8%)	0.030
Chronic kidney disease	59 (28.6%)	20 (13.1%)	<0.001
Chronic kidney disease without exacerbation	43 (20.9%)	11 (7.2%)	<0.001
Heart failure	65 (31.6%)	22 (14.4%)	<0.001
Heart failure – NYHA class II vs. normal	42 (20.4%)	10 (6.5%)	<0.001
Heart failure – NYHA class III vs. normal	12 (5.8%)	-	0.002

Table 1. *Statistical analysis of demographic data and comorbidities in the two groups, n (%)*

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In terms of the assessed hematological parameters, the statistical analysis revealed slightly higher mean values in the cases group for white blood cells (9193.74 ± 5118.14 *vs.* 8659.74 ± 3252.30 P =0.210), red blood cells (4.42 ± 0.61 *vs.* 4.40 ± 0.57, P =0.899) and hemoglobin (13.00 ± 1.61 *vs.* 12.93 ± 1.58, P =0.889).

There were lower levels of serum natrium in the case group (137.95 ± 4.77 mmol/L *vs.* 139.22 ± 3.39 mmol/L, P =0.013) while the serum potassium levels were higher in the study group (4.52 ± 0.88 mmol/L *vs.* 4.39 ± 0.59 mmol/L, P=0.592). We found eGFR to be statistically significant in our study (P =0.006) as well as International Normalized Ratio (1.57 ± 1.19 *vs.* 1.20 ± 0.53, P <0.001). Gamma glutamyl transferase serum level was significantly higher in the study group (61.49 ± 81.08 U/L *vs.* 51.43 ± 65.29 U/L, P=0.054) (Table 3).

The inflammatory parameters evaluated (erythrocyte sedimentation rate, fibrinogen serum level and C reactive protein) had higher mean values in the study group (P=0.271, P=0.123, P=0.052). Regarding the lipid profile we identified similar mean values among total cholesterol (191.84 ± 47.98 mg/dl *vs.* 190.16 ± 46.92 mg/dl, P=0.284), low-density lipoprotein cholesterol (120.86 ± 38.44 mg/dl *vs.* 116.50 ± 37.38 mg/dl, P=0.852), high-density lipoprotein cholesterol (50.27 ± 16.15 mg/dl *vs.* 49.65 ± 13.58 mg/dl, P=0.371) and triglycerides (120.88 ± 60.54 mg/dl *vs.* 120.56 ± 68.51 mg/dl, P=0.962), but without statistical significance.

Table 4 illustrates the echocardiographic parameters included in the statistical analysis**.** The association of left ventricular dilation (8.7% *vs.* 1.3%, P=0.002), mitral stenosis (8.7% *vs.* 2%, P=0.007), and biatrial enlargement (67% *vs.* 48.4%, P<0.001) are parameters with statistically significance in our study. None of the valvular regurgitation proven to be statistically significant in our study. The mean value of left ventricular ejection fraction was higher in the control group (52.48 ± 11.62% *vs.* 54.73 ± 7.74%, P=0.494). The antiarrhythmic medication used by patients in the study group included a variety of therapeutic classes such as beta-blockers (150 cases, 72,8%), digoxin (54 cases, 26,2%), amiodarone (39 cases, 18,9%) and propafenone (15 cases, 7,3%) (Table 5).

Discussions

As early as about two decades ago, the first date about the vulnerability of female population to CVD, apeared. In 2006, CVD accounted for 55% of all deaths in the female population, with no significant improvement over time [5,6]. The low inclusion of female population in studies, as well as the neglect of the demographic aspect related to area

Parameters	Study group (with medication) *n* = 206	Control group (without medication) *n* = 153	P value
Clinical presentation			
Emergency hospitalization	120 (58.3%)	58 (37.9%)	<0.001
SBP, mmHg	142.85 ± 28.83	151.58 ± 28.81	0.005
DBP, mmHg	74.39 ± 13.83	75.78 ± 13.86	0.348
HR, beat/min	58.56 ± 24.62	51.54 ± 22.00	0.003
Temporary Cardiac Pacing	30 (14.6%)	20 (13.1%)	0.687
Syncope	110 (53.4%)	68 (44.1%)	0.093
Electrocardiogram			
Type 2 Second degree AV block	22 (10.7%)	27 (17.6%)	0.057
Third degree AV block	79 (38.3%)	70 (45.8%)	0.159
Slow ventricular response atrial fibrillation	44 (21.4%)	19 (12.4%)	0.028
Sinus bradycardia	9 (4.4%)	-	0.009
Sick sinus syndrome	43 (20.9%)	30 (19.6%)	0.768
Sinus pauses	9 (4.4%)	-	0.009
Heart rhythm prior to conduction disorder			
Sinus rhythm	149 (72.3%)	126 (82.4%)	0.027
Atrial fibrillation	57 (27.7%)	27 (17.6%)	0.027
Atrial flutter	-	-	-
QRS morphology prior to conduction disorder			
LBBB	21 (10.2%)	6 (3.9%)	0.026
RBBB	32 (15.5%)	16 (10.5%)	0.162
Absence of bundle branch block	153 (74.3%)	131 (85.6%)	0.009
Hemibundle during to conduction disorder			
LAFB	24 (11.7%)	26 (17.0%)	0.148
LPFB	1 (0.5%)	1 (0.7%)	0.832
QRS morphology during conduction disorder			
LBBB	28 (13.6%)	14 (9.2%)	0.195
RBBB	44 (21.4%)	26 (17.0%)	0.302
Absence of bundle branch block	134 (65.0%)	113 (73.9%)	0.075

Table 2. *Clinical presentation and electrocardiogram findings*

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Parameters	Analytical measurement	Study group (with medication) *n* = 206 mean ± SD, median	Control group (without medication) *n* = 153 mean ± SD, median	P value
Na	135 – 148 mmol/L	137.95 ± 4.77	139.22 ± 3.39	0.013
K	3.5 – 5.1 mmol/L	4.52 ± 0.88	4.39 ± 0.59	0.592
Ca	1.16 – 1.35 mmol/L	1.18 ± 0.08	1.20 ± 0.08	0.013
Serum creatinine	0.5 – 0.9 mg/dl	1.24 ± 0.65	1.08 ± 0.47	0.007
Urea	10 -50 mg/dl	61.75 ± 36.48	56.52 ± 33.55	0.126
eGFR		53.11 ± 21.05	59.03 ± 19.19	0.006
Uric acid	2.4-5.7 mg/dl	6.73 ± 2.13	6.39 ± 2.66	0.114
Glucose	75 – 115 mg/dl	127.52 ± 55.90	117.09 ± 33.33	0.252
Aspartate aminotransferase (AST)	0 – 31 U/L	50.82 ± 83.29	52.21 ± 125.17	0.222
Alanine aminotransferase (ALT)	0 – 31 U/L	43.48 ± 64.07	48.90 ± 104.99	0.190
Gamma glutamyl transferase (GGT)	7 – 32 U/L	61.49 ± 81.08	51.43 ± 65.29	0.054
Cholesterol	0-200 mg/dl	191.84 ± 47.98	190.16 ± 46.92	0.284
Low-density lipoprotein cholesterol	0-160 mg/dl	120.86 ± 38.44	116.50 ± 37.38	0.852

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High-density lipoprotein cholesterol	42-98 mg/dl	50.27 ± 16.15	49.65 ± 13.58	0.371
Triglyceride	35-150 mg/dl	120.88 ± 60.54	120.56 ± 68.51	0.962
International Normalized Ratio	0.76 – 1.24	1.57 ± 1.19	1.20 ± 0.53	<0.001
White blood cells	4000 – 10500/mm^3	9193.74 ± 5118.14	8659.74 ± 3252.30	0.210
Red blood cells	4.2 – 5.4 mil/mm^3	4.42 ± 0.61	4.40 ± 0.57	0.899
Hemoglobin	12.5 – 16 g/dl	13.00 ± 1.61	12.93 ± 1.58	0.889
Packed-cell volume	37 – 47%	39.27 ± 4.69	39.21 ± 4.96	0.833
Mean corpuscular volume	78 – 100 fl	89.23 ± 5.21	89.05 ± 5.85	0.599
Mean corpuscular hemoglobin	32 – 36 g/dl	29.81 ± 0.95	29.35 ± 2.21	0.906
Mean corpuscular hemoglobin concentration	27-31 pg	32.81 ± 0.95	32.84 ± 1.08	0.795
Thrombocytes	150000-450000/mm^3	222512.62 ± 75138.94	230809.80 ± 74133.58	0.118
Erythrocyte sedimentation rate	2-25 mm/h	36.83 ± 26.23	33.49 ± 24.89	0.271
C reactive protein	0-5 mg/L	21.74 ± 36.18	15.46 ± 22.15	0.123
Serum fibrinogen	160-500 mg/dl	522.38 ± 146.23	494.30 ± 133.36	0.052

Table 3. *Laboratory results*

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vulnerabilities even at European level, remains a problem that needs to be urgently addressed[7,8].

The present study addresses an unstudied field in the literature, that of atrioventricular conduction disorders related to the presence of medication as well as possible risk factors in female patients. Although the bradycardia-drugs relationship is well known and extensively studied, available studies do not specifically address the female gender issue [9,10].

However, there is evidence in the literature supporting the high vulnerability to adverse drug reactions of certain population groups, including women and the elderly[11-12].

In our study, although the mean age was higher for the study group, it did not show statistical significance, unlike available literature data regarding both genders or only the male gender. It should be noted that the mean age of 73 years is strictly higher than the threshold of 65 years, below which the effects of cardiovascular risk factors are reduced in this population. These findings once again reinforce the idea of the vulnerability of females to ADRs regardless of age[13-15]. At the same time, female patients in the study group were more likely to be admitted to the emergency department and to have an extended length of hospital stay, which is also consistent with other data in the literature[16].

Analyzing the main diagnoses at admission, we observed that the study group was statistically associated with atrial fibrillation (AFib) with slow ventricular reponse, sinus bradycardia and sinus pauses, the most frequently identified rhythm on the initial ECG also being AFib. On the other hand, the control group associated a diverse range of atrioventricular conduction disorders, with sinus rhythm on the initial ECG being significantly more prevalent. The statistically significant presence of LBBB prior to the bradycardic episode should also be mentioned, as a sign of degeneration of the excitoconduction system and in the context of more complex comorbidities.

Also, hypertension and diabetes mellitus, risk factors associated with ADRs, did not show statistical significance. However, it should be noted that the systolic blood pressure values were significantly lower in the study group, which can be attributed to the antihypertensive effect of the commonly used beta-blocker medication.

Among the identified comorbidities, heart failure (HF) of any grade showed a significant prevalence in the study group. Analyzing also echocardiographic parameters we observed a significant association dependent on comorbidities - ventricular and biatrial dilatation - frequently associated with HF and AFib or the presence of mitral stenosis - a rare but still present cause of HF. However, further

Parameters	Study group (with medication) *n* = 206	Control group (without medication) *n* = 153	P value
Left ventricular dilation	18 (8.7%)	2 (1.3%)	0.002
Aortic stenosis	39 (18.9%)	33 (21.6%)	0.537
Mitral stenosis	18 (8.7%)	3 (2.0%)	0.007
Mitral annular calcification	117 (56.8%)	95 (62.1%)	0.313
Biatrial Enlargement	138 (67.0%)	74 (48.4%)	<0.001
Mildly abnormal systolic dysfunction vs. normal	69 (33.5%)	67 (43.8%)	0.047
Moderately abnormal systolic dysfunction vs. normal	17 (8.3%)	7 (4.6%)	0.168
Severly abnormal systolic vs. normal dysfunction	12 (5.8%)	1 (0.7%)	0.009
Left ventricular septal hypertrophy	194 (94.2%)	142 (92.8%)	0.602
Pulmonary hypertension	104 (50.5%)	66 (43.1%)	0.183
Mitral regurgitation	159 (77.2%)	121 (79.1%)	0.155
Aortic regurgitation	86 (41.7%)	74 (48.4%)	0.143
Tricuspid regurgitation	148 (71.8%)	114 (74.5%)	0.560
Pulmonary regurgitation	23 (11.2%)	15 (9.8%)	0.313
Ejection fraction (%)	52.48 ± 11.62	54.73 ± 7.74	0.494
Left ventricular septum (mm)	12.22 ± 2.11	12.08 ± 1.95	0.644

Table 4. *Ecocardiography findings*

Medication	n (%)
Beta-blockers	150 (72.8%)
Digoxin	54 (26.2%)
Amiodarone	39 (18.9%)
Propafenone	15 (7.3%)
Verapamil	1 (0.5%)
Diltiazem	2 (1.0%)
Ivabradine	1 (0.5%)
Flecainide	2 (1.0%)

Table 5. *Medication used in the study group*

analyses are needed to determine the causality relationship, the drugs found in the study group representing guideline indications in the treatment of HF and AFib[17-19]. Also, both chronic kidney disease regardless of exacerbation and acute renal dysfunction were significantly associated with the study group. Added to this is the laboratory data, these patients associating high levels of serum creatinine and significantly lower eGFR and serum calcium values, data consistent with other studies in the field[20-21]. Among the biochemical parameters analyzed, it is worth mentioning the significantly lower serum sodium values in the study group, possibly in the context of HF-associated hyperhydration and renal dysfunction. At the same time, INR values were significantly higher in this group, which can be explained by the frequent association of AFib with the prevalent use of antivitamin K at the time of patients' admission.

Regarding the drugs used in the cases group, the vast majority of patients were treated with single therapy or combined therapy with one or more of beta-blockers, amiodarone or digoxin.

Under medication with amiodarone, women have a higher risk to develop Torsade de pointes or other ventricular tachycardias than men due to female predisposition to prolonged cardiac repolarization[22,23]. Sex hormones modulate cardiac K+ and Ca2+ ion channels involved in ventricular repolarization. Estrogens facilitate bradycardia-induced QT prolongation and the emergence of arrhythmias, whereas androgens shortened the QTc and blunted the QT response to drugs[24]. ADRs are more frequent in women, the main entities being represented by amiodarone-associated bradycardia which requires permanent pacemaker, dysthyroidism (29% in women vs. 17% in men) and phototoxicity (21% in women vs. 8% in men) as studies have shown[25,26].

Beta-blockers are class II antiarrhythmics used in various cardiovascular diseases. Drug-relates bradyarrhythmias have high prevalence among beta-blocker users. Current studies in this field suggest that older age and female gender are predictors of symptomatic bradyarrhythmias[27,28]. The extensive use of beta-blocker medication in these patients is most likely a result of their beneficial effects, suggested by current studies regarding heart failure[29,30].

Between the frequency of ADRs and eGFR there is an inversely proportional relationship. The high prevalence of metoprolol or nebivolol as beta-blockers with hepatic metabolism can be related to the comorbidities associated or the drug-drug interactions. Estrogens and progesterone have a cardiovascular protective role by modulating the cardiac expression of β1-

adrenoceptors and thus reducing β-adrenergic-mediated stimulation. Women have increased absorption and may reach higher maximum serum levels as well as slower clearance through CYP2D6 than man which results in a superior reduction in heart rate and blood pressure during physical activity in patients treated with metoprolol or propranolol[24,27].

In our study, digoxin was used by 26.2% of the female patients enrolled in the study group. Digoxin is widely used in heart failure, its effect being gender related[17]. Women develop more frequently ADRs (some studies mention an 50-75% increase than men) due to polymedication, drug bioavailability and differences in pharmacokinetics and pharmacodynamics. Digoxin is renally-excreted and requires dosage adjustment due to the slower renal clearance in women (lower serum concentrations of less than 0.8 ng/mL are recommended). Serum digoxin levels are influenced by the reduced activity of P-glycoprotein which leads to diminished excretion through the renal tubules[32,33]. The mortality rate of all causes in patients treated with digoxin is 5.8% higher in women. Women treated with digoxin had a smaller reduction in heart failure hospitalization due to recurrent decompensations than men[4,34].

Conclusions

Our study highlights the need for further research of ADRs in female patients in relation to atrioventricular conduction disorders. Our results show increased risk of medication-related bradyarrhythmias in women, regardless of age, with an increased need for emergency admission and prolonged period of hospitalization. These patients seem more prone towards AFib with slow ventricular response, especially in the case of pre-existing intraventricular conduction disorders (LBBB), and associate multiple important comorbidities such as HF and renal dysfunction. The main drug classes identified were beta-blockers, class III antiarrhythmics (amiodarone) and digoxin. However, our study presents several limitations due to its retrospective nature and further research on this topic is needed.

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