■ ORIGINAL ARTICLE

The occurrence of drug-induced side effects in women and men with arterial hypertension and comorbidities

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ABSTRACT

Background: Women have been underrepresented in large clinical trials in hypertension, and the incidence of adverse drug reactions by sex has been not sufficiently described.

Aims: The aim of the study was to determine the prevalence of adverse drug reactions in women and men with arterial hypertension and comorbidities and to assess the specific predisposing factors for adverse drug reactions by sex.

Methods: The study population comprised consecutive hospitalized patients diagnosed with arterial hypertension and patients treated in an outpatient clinic, whose recruitment started in January 2019 aiming to reach 1000 participants. A structured questionnaire was used to gather the patients' demographic and clinical data and current or past cases of adverse drug reactions.

Results: The study included 560 women and 440 men, with mean (standard deviation) age of 62.84 (14.96) years. Women were older than men, had a longer hypertension history, and suffered less frequently from other cardiovascular diseases. Women reported more frequently adverse drug reactions. The risk of drug-induced side effects in women increased with age ($P = 0.03$) and with coexistence of any respiratory disease ($P = 0.04$). In the case of male sex, the risk of adverse drug reactions increased with the occurrence of hypercholesterolemia ($P = 0.03$), and coexistence of any analyzed metabolic diseases ($P = 0.04$).

Conclusions: Adverse drug reactions were reported more frequently by women. Older age and the presence of any respiratory disease increased the risk of adverse drug reactions in women, while in men, the risk was increased mainly by the presence of hypercholesterolemia or other metabolic diseases.

Key words: comorbidities, drug-related adverse events, hypertension

INTRODUCTION

Elevated blood pressure is one of the leading causes of premature morbidity and mortality worldwide. The number of patients with arterial hypertension has been steadily increasing, according to the Non-Communicable Diseases Risk Factor Collaboration analysis, doubling between 1990 and 2019 to amount to over 1.2 billion people by the end of that period. According to a data forecast for 2025, 1.5 bil-lion people will have hypertension by 2025 [1]. Such a high prevalence of arterial hypertension is being reported throughout the world, regardless of the wealth of a given country [2].

Hypertension rarely occurs as an isolated disease entity. It is often accompanied by other risk factors for cardiovascular diseases, such as type 2 diabetes, hypercholesterolemia, gout, or obesity, as well as clinically overt complications of the cardiovascular system,

WHAT'S NEW?

Among men and women with arterial hypertension, older age and the presence of any respiratory disease are associated with a more frequent history of adverse drug reactions in women, while in men such association of adverse drug reactions was detected mainly for the presence of hypercholesterolemia or other metabolic diseases.

such as ischemic heart disease, heart failure (HF), and atrial fibrillation (AF), which thus constitute an additional therapeutic challenge [3].

Treatment for high blood pressure involves two main approaches applied alone or most often in combination, i.e., lifestyle changes and drug therapy. For patients with hypertension and comorbidities, pharmacological treatment is necessary in the vast majority of cases since the cardiovascular risk for these patients is high or very high.

The main goal of treatment is to maintain blood pressure within the correct range, which thereby reduces the risk of complications and premature cardiovascular mortality and is also of key importance in ensuring patient adherence to a pharmacotherapy regimen [4].

Patients with arterial hypertension and comorbidities are for the most part elderly subjects on multiple medications. Such a patient profile is closely associated with the problem of disease acceptance, which is defined as acknowledging and coming to terms with the existence of a medical condition that cannot be changed permanently and to which the patient must become accustomed [5]. Poor disease acceptance is often associated with arbitrary discontinuation of drug therapy [6].

The current European Society of Cardiology/European Society of Hypertension 2018 guidelines for the management of arterial hypertension recommend the same target blood pressure values and therapeutic management program for both sexes, although in actual clinical practice a correlation exists between a patient's sex and the management and effects of their treatment [3]. Population-wise, control of arterial hypertension is least effective in young men and older women. Sex is another factor that impacts the choice of antihypertensive drug class [7, 8]. Men are more often prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists and beta-blockers than women, while more women than men receive diuretics and calcium antagonists [8]. Despite a large number of clinical drug trials for hypertension, women are underrepresented in these trials, or no sex sub-analysis is performed with regard to the effects of treatment. Likewise, the incidence of adverse drug reactions by sex is insufficiently reported in the literature. Meanwhile, the occurrence of adverse drug reactions may significantly affect the quality of life of patients with arterial hypertension and comorbidities, as well as their disease acceptance, and result in arbitrary drug discontinuation, thereby leading to a poorer cardiovascular prognosis.

This study aimed to determine the frequency of adverse drug reactions in women and men with arterial hypertension and comorbidities and to assess the sex-specific predisposing factors leading to their occurrence.

METHODS

The study included patients of both sexes hospitalized in the Department of Cardiology, Interventional Electrocardiology and Hypertension at the University Hospital in Kraków, in whom arterial hypertension was the underlying diagnosis or had been identified as comorbidity, as well as patients undergoing chronic treatment in the outpatient hypertension clinic. The recruitment started in January 2019 aiming to reach 1000 participants.

The study population comprised 1000 people, of whom 560 were women.

The inclusion criteria for the study were as follows: age over 18 years, a diagnosis of essential arterial hypertension, duration of the disease of more than one year, and signed informed consent to participate in the study. Exclusion criteria were as follows: symptoms of dementia severe enough to prevent the participant from completing the questionnaires, secondary arterial hypertension.

The study was conducted in line with the Declaration of Helsinki and approved by the local Bioethics Committee (no. 1072.6120.261.2017). Before the study began, each participant had signed informed consent.

For the study, the authors used a structured proprietary questionnaire, which the patients filled in independently or with the help of a research team member either during their hospitalization or while waiting for an appointment at the clinic. The survey consisted of 22 questions covering various demographic and clinical factors. The patients' declared comorbidities and risk factors for cardiovascular diseases, as well as all medications currently being taken. All those data were verified by analyzing available medical documentation. The patients also indicated when their arterial hypertension was diagnosed and they started to be treated.

The next part of the questionnaire focused on the occurrence of any drug-related adverse events experienced by the patients either at present or in the past. If the answer was affirmative, the patient was asked to provide the name of the drug, the type of symptoms they experienced, and their severity. The patients also provided information about their reactions to the occurrence of side effects (arbitrary drug discontinuation, additional consultation with a doctor, reading medication leaflets). Multiple-drug intolerance was

defined as the occurrence of side effects after taking 3 or more classes of drugs.

Statistical analysis

The analysis was performed using the R statistical package, version 3.5.1 (http://cran.r-project.org). The normality of the distribution of quantitative variables was verified with the Shapiro-Wilk test, as well as on the basis of a visual assessment of the histograms. Nominal data were described using frequency measures: n count and % of the group. The ordinal data were presented on the basis of the median (interquartile range [IQR]) and quantitative variables using the mean and standard deviation. A comparison of the groups with regard to individual parameters was made using the following tests: χ^2 or Fisher's exact tests for nominal variables and Student's t-tests, Mann-Whitney U tests for ordinal and quantitative variables, depending on the situation. Additionally, logistic regression analysis was performed to identify the parameters that predict the occurrence of drug-induced side effects. A multivariable analysis was performed with selected variables based on the stepwise "backward" method and applying the Akaike information criterion. As a starting point for the multivariable models, the variables applied were those that in one-dimensional models had a value of $P < 0.25$ in the Wald test.

A multivariable regression model was provided using the stepwise method based on the Akaike information criterion. The model evaluation criteria included: the χ^2 test ($P < 0.001$), Nagelkerke's pseudo r-squared measures = 0.08, the Hosmer-Lemeshow goodness-of-fit test ($P = 0.14$), and variance inflation factor index (range: 1.01–1.12).

The significance level adopted in the tests was $\alpha = 0.05$.

RESULTS

A total of 1 000 patients participated in the study, 560 of whom were women and 440 men. The mean (standard deviation [SD]) age of the group as a whole was 62.84 (14.96) years, and their ages ranged from 19 to 103 years. The average (SD) body mass index of the study cohort was 27.86 (4.84) kg/m^2.

A comparison between men and women in the study group revealed significant differences in terms of age ($P = 0.004$), the duration of hypertension ($P = 0.04$), and the number of cardiovascular diseases reported ($P < 0.001$). Women were significantly older, had longer hypertensive disease duration, and had fewer comorbid cardiovascular diseases than men.

Women suffered from certain comorbidities significantly less frequently than men: coronary artery disease (CAD) ($P < 0.001$), past myocardial infarction (MI) ($P < 0.001$), HF ($P < 0.001$), AF ($P = 0.004$), and hypercholesterolemia ($P = 0.001$), but they reported a higher prevalence of rheumatoid diseases ($P = 0.001$) and endocrine disorders ($P < 0.001$).

Women took significantly fewer drugs of any class ($P = 0.02$), as well as fewer cardiac drugs (per tablet),

other than antihypertensive drugs ($P < 0.001$). As regards particular classes of drugs, women received the following significantly more frequently than men: angiotensin receptor antagonists ($P = 0.008$) and rheumatological drugs ($P = 0.03$). On the other hand, they were prescribed the following far less frequently: antiplatelet drugs ($P < 0.001$), statins ($P = 0.003$), and cardiac drugs, other than antihypertensive drugs ($P = 0.02$) (Table 1).

More women than men reported a history of drug intolerance ($P < 0.001$). The same was true in the case of multiple-drug intolerance ($P = 0.006$). Far more women than men experienced intolerance to such drugs as antibiotics ($P = 0.004$) and analgesics ($P = 0.004$). Women were also far more likely to report side effects ($P < 0.001$). As regards specific side effects, women reported the following conditions far more frequently than men: hypotension ($P = 0.02$), coughing ($P < 0.001$), edema ($P = 0.001$), bradycardia ($P = 0.04$), and skin lesions ($P = 0.01$) (Table 2).

Significant differences in terms of age were observed between women reporting adverse drug reactions and women not reporting such effects ($P < 0.001$), with women from the former group being older. Women who experienced side effects also reported a significantly higher number of cardiac diseases ($P = 0.02$), other diseases ($P < 0.001$), and any diseases in general ($P < 0.001$). The following specific comorbidities were more common among women reporting adverse drug reactions compared to women without such reactions: CAD ($P = 0.02$), past MI ($P = 0.02$), HF ($P = 0.002$), respiratory diseases ($P = 0.02$), and rheumatoid diseases ($P = 0.03$) (Table 3).

No significant difference was observed between the two groups of women in terms of the number of drugs taken of any class ($P = 0.51$), in the number of tablets of antihypertensive drugs taken ($P = 0.34$), or in the number of cardiovascular drugs taken per tablet without antihypertensive drugs ($P = 0.44$). In the case of specific drug classes, antiplatelet drugs were prescribed significantly more frequently to women reporting adverse drug reactions than to women without adverse drug-induced symptoms (24% vs. 12%; $P < 0.001$), but calcium antagonists were received significantly less frequently by women with adverse drug reaction than by women who had no adverse drug reactions (30% vs. 48%; $P < 0.001$) (Table 3).

Then, a multivariable analysis was performed to determine the occurrence of drug-induced side effects in women. First, single-factor models were constructed, on the basis of which the variables were selected in the multi-factor model.

The multivariable logistic regression model indicated that the risk of drug-induced side effects in women increased significantly with age, odds ratio (OR), 1.01; 95% confidence interval (CI), 1.002, 1.03; $P = 0.03$, as well as with the presence of respiratory diseases; OR, 1.76; 95% CI, 1.02, 3.10; $P = 0.04$. The other variables in the multivariable model remained insignificant for the risk of drug side effects (Figure 1A).

Table 1. Characteristics of the study population by sex

	Men (n = 440)	Women (n = 560)	*P*-value
Age, years, mean (SD)	61.29 (15.43)	64.05 (14.49)	0.004
BMI, kg/m², mean (SD)	27.96 (4.52)	27.78 (5.07)	0.55
Duration of hypertension, median (IQR)	10.00 (5.00–17.25)	23.00 (10.00–30.00)	0.04
Cardiovascular diseases, number, median (IQR)	3.00 (1.00–4.00)	2.00 (1.00–2.00)	<0.001
Other diseases, number, median (IQR)	1.00 (0.00–3.00)	2.00 (1.00–3.00)	0.44
Diseases in general, number, median (IQR)	4.00 (2.00–7.00)	3.00 (2.00–5.25)	0.05
Comorbidities, n (%)			
CAD	136 (30.9)	105 (18.8)	<0.001
Past MI	90 (20.5)	56 (10.0)	<0.001
HF	104 (23.6)	75 (13.4)	<0.001
Heart arrhythmia	55 (12.5)	66 (11.8)	0.81
AF	84 (19.1)	69 (12.3)	0.004
Hypercholesterolemia	244 (55.5)	248 (44.3)	0.001
Other cardiovascular diseases	123 (28.0)	144 (25.7)	0.47
Respiratory diseases	52 (11.8)	68 (12.1)	0.95
Gastrointestinal diseases	55 (12.5)	80 (14.3)	0.47
Neurological diseases	40 (9.1)	47 (8.4)	0.78
Dermatological diseases	12 (2.7)	11 (2.0)	0.56
Rheumatoid disorders	28 (6.4)	74 (13.2)	0.001
Metabolic disorders	99 (22.5)	120 (21.4)	0.74
Diabetes	130 (29.5)	144 (25.7)	0.20
Mental disorders	12 (2.7)	24 (4.3)	0.25
Endocrine disorders	36 (8.2)	136 (24.3)	<0.001
Cancer	26 (5.9)	37 (6.6)	0.75
Non-cardiovascular diseases	172 (39.1)	189 (33.8)	0.09
Concomitant diseases, n (%)	327 (74.3)	430 (76.8)	0.41
Total number of drugs taken, median (IQR)	6.00 (3.00–7.00)	5.00 (3.00–7.00)	0.02
Classes of drug, n (%)			
ACEI	246 (55.9)	293 (52.3)	0.29
Beta-blockers	282 (64.1)	331 (59.1)	0.12
ARB	64 (14.5)	119 (21.3)	0.008
Calcium antagonists	167 (38.0)	215 (38.4)	0.94
Diuretics	231 (52.5)	281 (50.2)	0.51
Antihypertensive drugs	91 (20.7)	93 (16.6)	0.12
Antiplatelet medications	140 (31.8)	103 (18.4)	<0.001
Anticoagulants	81 (18.4)	77 (13.8)	0.06
Statins	243 (55.2)	255 (45.5)	0.003
Other cardiovascular drugs	211 (48.0)	267 (47.7)	0.98
Cardiovascular medications	418 (95.0)	525 (93.8)	0.48
Antihypertensive drugs	410 (93.2)	508 (90.7)	0.20
Cardiovascular medications without antihypertensive drugs	327 (74.3)	378 (67.5)	0.02
Number of cardiovascular medications in tablet form without antihypertensive drugs, median (IQR)	2.00 (0.00–3.00)	1.00 (0.00–2.00)	<0.001
Number of antihypertensive drugs in tablet form, median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.43
Drugs for respiratory disorders	23 (5.2)	28 (5.0)	0.99
Drugs for neurological disorders	20 (4.5)	14 (2.5)	0.11
Drugs for mental disorders	15 (3.4)	19 (3.4)	0.99
Drugs for dermatological disorders	1 (0.2)	3 (0.5)	0.79
Drugs for metabolic disorders	120 (27.3)	140 (25.0)	0.46
Drugs for rheumatoid disorders	2 (0.5)	13 (2.3)	0.03
Other non-cardiovascular drugs	130 (29.5)	182 (32.5)	0.35
Any other medications	223 (50.7)	294 (52.5)	0.61
Any drugs in total	421 (95.7)	535 (95.5)	0.99

The data are presented as n (of the group) unless otherwise stated. The groups were compared using the χ² test or Fisher's exact test for percentages and Student's t-test or the Mann-Whitney U test for quantitative variables

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; SD, standard deviation

Table 2. Prevalence of drug intolerance and side effects by sex

	Men (n = 440)	Women (n = 560)	*P*-value
Drug intolerance, n (%)	179 (40.7)	300 (53.6)	<0.001
1 drug	133 (30.2)	184 (32.9)	0.40
2 drugs	23 (5.2)	59 (10.5)	0.003
3 drugs or more	23 (5.2)	57 (10.2)	0.006
Incidences of drug intolerance, median (IQR)	0.00 (0.00–1.00)	1.00 (0.00–1.00)	<0.001
ACEI	18 (4.1)	27 (4.8)	0.69
Beta-blockers	7 (1.6)	14 (2.5)	0.44
ARB	5 (1.1)	5 (0.9)	0.95
Calcium antagonists	9 (2.0)	18 (3.2)	0.35
Diuretics	7 (1.6)	10 (1.8)	>1.00
Antihypertensive drugs	4 (0.9)	11 (2.0)	0.27
Antiplatelet medications	7 (1.6)	21 (3.8)	0.063
Anticoagulants	7 (1.6)	6 (1.1)	0.66
Statins	6 (1.4)	13 (2.3)	0.39
Antibiotics	52 (11.8)	105 (18.8)	0.004
Analgesics	26 (5.9)	64 (11.4)	0.004
Other cardiovascular drugs	6 (1.4)	12 (2.1)	0.50
Other non-cardiovascular medications	80 (18.2)	137 (24.5)	0.02
Adverse effects, n (%)	178 (40.5)	292 (52.1)	<0.001
1 adverse effect	84 (19.1)	116 (20.7)	0.58
2 adverse effects	30 (6.8)	57 (10.2)	0.08
3 adverse effects	43 (9.8)	62 (11.1)	0.58
4 adverse effects	10 (2.3)	26 (4.6)	0.07
5 or more	11 (2.5)	31 (5.5)	0.03
Adverse effects, median (IQR)	0.00 (0.00–1.00)	1.00 (0.00–2.00)	<0.001
Type of adverse effect, n (%)			
Electrolyte imbalances	1 (0.2)	4 (0.7)	0.53
Hypotonia	15 (3.4)	39 (7.0)	0.02
Cough	15 (3.4)	53 (9.5)	<0.001
Edema	14 (3.2)	48 (8.6)	0.001
Bradycardia	8 (1.8)	24 (4.3)	0.04
Skin lesions	64 (14.5)	117 (20.9)	0.01
Gastrointestinal disorders	21 (4.8)	43 (7.7)	0.08
Other	139 (31.6)	226 (40.4)	0.005
Allergic reaction	76 (17.3)	125 (22.3)	0.06
Bleeding	9 (2.0)	11 (2.0)	>0.999
Abnormal laboratory test results	3 (0.7)	7 (1.3)	0.57
Muscle pain	5 (1.1)	10 (1.8)	0.56

Data are presented as n (% of the group) unless otherwise stated. The groups were compared using the χ^2 test or Fisher's exact test for percentages and the Mann-Whitney U-test for quantitative variables

Abbreviations: see Table 1

A comparison of men reporting adverse drug reactions with those not confirming such reactions revealed a significant age difference (*P* = 0.001), with men from the former group being older. The men who experienced no side effects also reported a significantly greater number of cardiovascular diseases (*P* <0.001), other diseases (*P* <0.001), and any diseases in general (*P* <0.001) compared with other men. For specific comorbidities, men reported adverse drug reactions from the following conditions significantly more frequently than men without adverse drug reactions: CAD (*P* <0.001), past MI (*P* = 0.004), HF (*P* = 0.001), AF (*P* = 0.01), hypercholesterolemia (*P* = 0.02), and metabolic diseases (*P* = 0.02) (Table 4).

Men reporting side effects took significantly more drugs of any class (*P* = 0.04) and received far more cardiovascular drugs per tablet except antihypertensive drugs (*P* <0.001). When it came to specific classes of drugs, men reported adverse drug reactions for the following medications more frequently than men without adverse drug reactions: antiplatelet drugs (*P* = 0.02), anticoagulants (*P* = 0.03), and cardiovascular medications, except for antihypertensive drugs (*P* = 0.006). For calcium antagonists (CA), men receiving CA significantly less often reported adverse drug reactions than those not treated by CA (*P* = 0.02) (Table 4).

First, single-factor models were constructed, on the basis of which variables were selected for the multi-factor model. Then, a multivariable analysis was performed to determine predictors of drug-induced side effects in men.

The multivariable logistic regression model for men indicated that the risk of drug-induced side effects increased with hypercholesterolemia (OR, 1.53; 95% CI, 1.03–2.27;

Table 3. Comparison of women reporting adverse drug reactions with women not reporting adverse drug reactions in association with comorbidities and classes of drug taken

Women	Reporting no adverse drug reactions (n = 260)	Reporting adverse drug events (n = 300)	P-value
Age, years, mean (SD)	61.74 (13.81)	66.06 (14.78)	<0.001
BMI, kg/m², mean (SD)	27.74 (5.01)	27.81 (5.14)	0.86
Cardiovascular diseases, number, median (IQR)	2.00 (1.00–2.00)	2.00 (1.00–3.00)	0.02
Other diseases, number, median (IQR)	1.00 (0.00–3.00)	2.00 (1.00–3.00)	<0.001
Diseases in general, number, median (IQR)	3.00 (2.00–5.00)	4.00 (2.00–6.00)	<0.001
Comorbidities, n (%)			
CAD	37 (14.2)	68 (22.7)	0.02
Past MI	17 (6.5)	39 (13.0)	0.02
HF	22 (8.5)	53 (17.7)	0.002
Heart arrhythmia	33 (12.7)	33 (11.0)	0.63
AF	28 (10.8)	41 (13.7)	0.36
Hypercholesterolemia	113 (43.5)	135 (45.0)	0.78
Other cardiovascular drugs	57 (21.9)	87 (29.0)	0.07
Cardiovascular system	259 (99.6)	299 (99.7)	>0.99
Respiratory system	22 (8.5)	46 (15.3)	0.02
Gastrointestinal system	30 (11.5)	50 (16.7)	0.11
Nervous system	22 (8.5)	25 (8.3)	>0.99
Dermatological diseases	4 (1.5)	7 (2.3)	0.71
Rheumatoid disorders	25 (9.6)	49 (16.3)	0.03
Metabolic disorders	50 (19.2)	70 (23.3)	0.28
Diabetes	67 (25.8)	77 (25.7)	>0.99
Mental disorders	9 (3.5)	15 (5.0)	0.49
Endocrine disorders	55 (21.2)	81 (27.0)	0.13
Cancer	13 (5.0)	24 (8.0)	0.21
Non-cardiovascular diseases	182 (70.0)	248 (82.7)	0.001
Concomitant diseases	260 (100.0)	300 (100.0)	>0.99
Total number of drugs taken, median (IQR)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	0.51
Classes of drug, n (%)			
ACEI	144 (55.4)	149 (49.7)	0.21
Beta-blockers	157 (60.4)	174 (58.0)	0.63
ARB	52 (20.0)	67 (22.3)	0.57
Calcium antagonists	124 (47.7)	91 (30.3)	<0.001
Diuretics	132 (50.8)	149 (49.7)	0.86
Antihypertensive drugs	51 (19.6)	42 (14.0)	0.10
Antiplatelet medications	30 (11.5)	73 (24.3)	<0.001
Anticoagulants	32 (12.3)	45 (15.0)	0.42
Statins	124 (47.7)	131 (43.7)	0.39
Other cardiovascular drugs	120 (46.2)	147 (49.0)	0.56
Cardiovascular medications	247 (95.0)	278 (92.7)	0.34
Antihypertensive drugs	239 (91.9)	269 (89.7)	0.44
Cardiovascular medications without antihypertensive drugs	175 (67.3)	203 (67.7)	0.99
Number of cardiovascular medications in tablet form without antihypertensive drugs, median (IQR)	1.00 (0.00–2.00)	1.00 (0.00–3.00)	0.44
Number of antihypertensive drugs in tablet form, median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.34
Drugs for respiratory disorders	8 (3.1)	20 (6.7)	0.08
Drugs for neurological disorders	4 (1.5)	10 (3.3)	0.28
Drugs for mental disorders	8 (3.1)	11 (3.7)	0.88
Drugs for dermatological disorders	1 (0.4)	2 (0.7)	0.99
Drugs for metabolic disorders	66 (25.4)	74 (24.7)	0.92
Drugs for rheumatoid disorders	5 (1.9)	8 (2.7)	0.76
Other non-cardiovascular drugs	76 (29.2)	106 (35.3)	0.15
Any other medications	127 (48.8)	167 (55.7)	0.13
Any drugs in total	252 (96.9)	283 (94.3)	0.20

Data are presented as n (% of the group) unless otherwise stated. The groups were compared using the χ² test or Fisher's exact test for percentages and Student's t-test or the Mann-Whitney U test for quantitative variables

Abbreviations: see Table 1
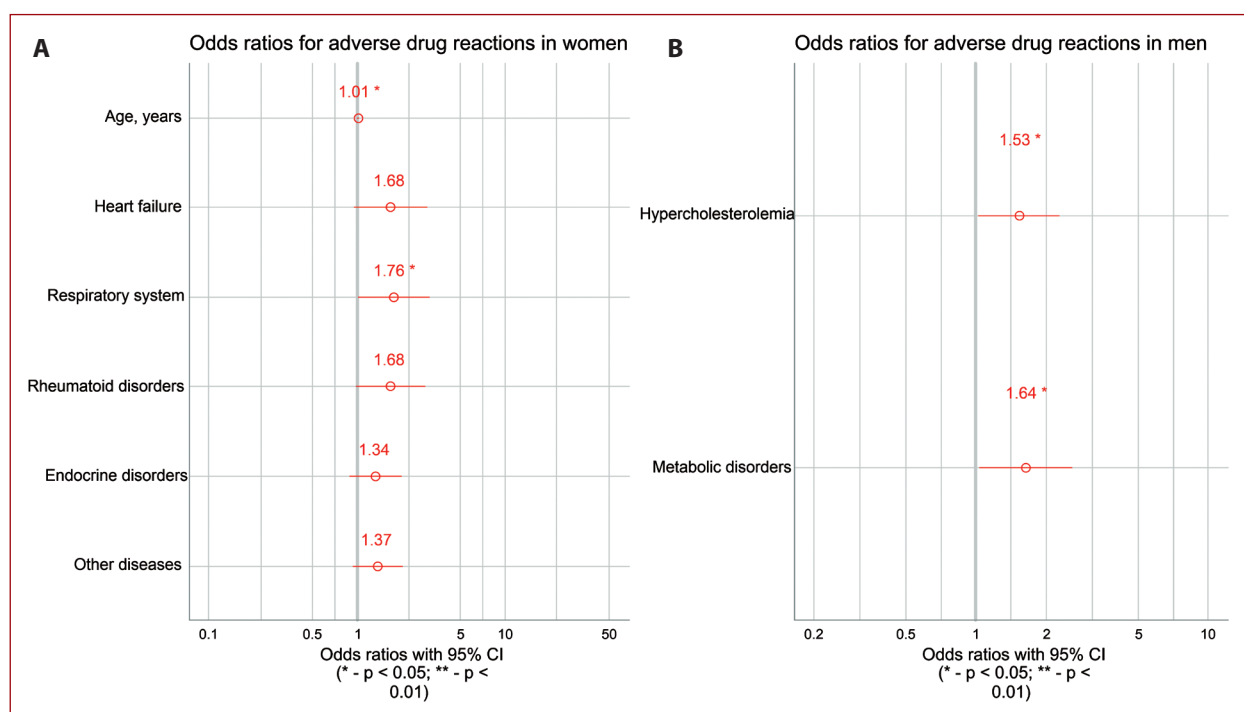
Figure 1. Multivariable logistic regression analysis for adverse drug reactions in women (**A**) and men (**B**)

P = 0.03) and metabolic diseases (OR, 1.64; 95% CI, 1.03, 2.59; P = 0.04) (Figure 1B).

DISCUSSION

In the present study, we observed the frequent incidence of adverse drug reactions in women and men with hypertension. The occurrence of drug-induced adverse events is a common phenomenon in healthcare and is inevitable given the polypharmacotherapy regimens followed today.

In a meta-analysis of 33 studies covering a total of over 1.5 million patients in general practice, the average incidence of drug-induced adverse events was estimated at 8.32%. However, this figure depended largely on the characteristics of the study population and ranged from 0.87% in a Spanish study of young healthy participants up to 65.35% in a study of American general practice treating elderly patients with comorbidities [9].

The frequency of adverse drug-induced symptoms in our participants, i.e., 54% in the case of the female patients and 41% for the male patients, was related with the age of the study population, the average being 62.84 years, as well as the presence of various comorbidities such as CAD, HF, AF, hypercholesterolemia, diabetes, respiratory disorders, and diseases of the digestive system, i.e., factors which promote polypharmacy and, as a result, increase a patient's risk of any drug-related events [10].

A review of the literature, encompassing 47 articles describing the incidence of drug-induced adverse reactions in European hospitals or clinics, showed that, based on 22 studies, the average rate of hospitalization for drug-in-

duced adverse reactions was 3.5%, while drug-induced symptoms observed during hospitalization affected on average 10.1% of patients, based on 13 studies.

Only 5 studies were included that assessed outpatient drug-related adverse events. This indicates a lack of information on the epidemiology of drug-induced adverse events among general practitioners or specialist clinics.

However, it can be assumed that the incidence of such events may be higher than in patients requiring hospitalization [11].

The factors that increased the risk of drug-induced adverse events in our female study participants included age and respiratory diseases, while the predisposing factors leading to an increased risk of adverse drug reactions in men were hypercholesterolemia and other metabolic diseases such as diabetes, gout, obesity, and osteoporosis. The occurrence of adverse effects after taking drugs used to treat respiratory diseases, especially inhaled drugs, has been described in the data collected by the pharmaceutical regulatory authority in Portugal over a period of 10 years [12]. A review of the literature covering 75 studies, including 3 meta-analyses, found that the incidence of adverse reactions increased significantly with age, e.g., in the case of cardiovascular drugs, the rate was 20% of the general population, and this percentage increased to 50% in older populations [13].

The frequent occurrence of drug-induced adverse events in patients with metabolic diseases, especially diabetes, was also noted in the Portuguese data, although in the latter case the problem was more frequently ob-

Table 4. A comparison of men reporting adverse drug reactions associated with comorbidities and classes of drug taken with men not reporting adverse drug reactions

Men	Not reporting adverse drug reactions (n = 261)	Reporting adverse drug reactions (n = 179)	P-value
Age, years, mean (SD)	59.28 (14.86)	64.21 (15.83)	0.001
BMI, kg/m², mean (SD)	27.97 (4.78)	27.95 (4.14)	0.97
Cardiovascular diseases, number, median (IQR)	2.00 (1.00–3.00)	3.00 (2.00–4.50)	<0.001
Other diseases, number, median (IQR)	1.00 (0.00–2.00)	2.00 (1.00–4.00)	<0.001
Diseases in general, number, median (IQR)	3.00 (2.00–5.00)	5.00 (3.00–8.00)	<0.001
Comorbidities, n (%)			
CAD	60 (23.0)	76 (42.5)	<0.001
Past MI	41 (15.7)	49 (27.4)	0.004
HF	46 (17.6)	58 (32.4)	0.001
Heart arrhythmia	30 (11.5)	25 (14.0)	0.53
AF	39 (14.9)	45 (25.1)	0.01
Hypercholesterolemia	132 (50.6)	112 (62.6)	0.02
Other cardiovascular drugs	53 (20.3)	70 (39.1)	<0.001
Cardiovascular system	261 (100.0)	179 (100.0)	1
Respiratory system	25 (9.6)	27 (15.1)	0.11
Gastrointestinal system	29 (11.1)	26 (14.5)	0.36
Nervous system	22 (8.4)	18 (10.1)	0.68
Dermatological diseases	5 (1.9)	7 (3.9)	0.34
Rheumatoid disorders	19 (7.3)	9 (5.0)	0.45
Metabolic disorders	48 (18.4)	51 (28.5)	0.02
Diabetes	77 (29.5)	53 (29.6)	1
Mental disorders	5 (1.9)	7 (3.9)	0.34
Endocrine disorders	21 (8.0)	15 (8.4)	1
Cancer	12 (4.6)	14 (7.8)	0.23
Other non-cardiovascular diseases	80 (30.7)	92 (51.4)	<0.001
Other diseases	188 (72.0)	139 (77.7)	0.22
Diseases of any kind	261 (100.0)	179 (100.0)	1
Total number of drugs taken, median (IQR)	5.00 (3.00–7.00)	6.00 (3.50–8.00)	0.04
Classes of drug, n (%)			
ACEI	154 (59.0)	92 (51.4)	0.14
Beta-blockers	166 (63.6)	116 (64.8)	0.88
ARB	35 (13.4)	29 (16.2)	0.50
Calcium antagonists	111 (42.5)	56 (31.3)	0.02
Diuretics	145 (55.6)	86 (48.0)	0.15
Antihypertensive drugs	55 (21.1)	36 (20.1)	0.90
Antiplatelet medications	71 (27.2)	69 (38.5)	0.02
Anticoagulants	39 (14.9)	42 (23.5)	0.03
Statins	136 (52.1)	107 (59.8)	0.14
Other cardiovascular drugs	110 (42.1)	101 (56.4)	0.004
Cardiovascular medications	249 (95.4)	169 (94.4)	0.81
Antihypertensive drugs	246 (94.3)	164 (91.6)	0.38
Cardiovascular medications without antihypertensive drugs	181 (69.3)	146 (81.6)	0.006
Number of cardiovascular medications in tablet form without antihypertensive drugs (IQR)	1.00 (0.00–2.00)	2.00 (1.00–3.00)	<0.001
Number of antihypertensive drugs in tablet form, median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.53
Respiratory system	10 (3.8)	13 (7.3)	0.17
Nervous system	12 (4.6)	8 (4.5)	1
Psychotropic	7 (2.7)	8 (4.5)	0.46
Dermatological	1 (0.4)	0 (0.0)	1
Metabolic group	77 (29.5)	43 (24.0)	0.25
Rheumatoid	2 (0.8)	0 (0.0)	0.65
Other	66 (25.3)	64 (35.8)	0.02
Other medications	130 (49.8)	93 (52.0)	0.73
All drugs in total	249 (95.4)	172 (96.1)	0.91

Data are presented as n (% of the group) unless otherwise stated. The groups were compared using the χ² test or Fisher's exact test for percentages and Student's t-test or the Mann-Whitney U test for quantitative variables

Abbreviations: see Table 1

served in women [12]. Our observations of a correlation between age and the frequency of adverse reactions in women, but not in men, could be due to the fact that the female participants were significantly older than their male counterparts. On the other hand, in the present study population, we observed in men a higher prevalence of certain risk factors for cardiovascular diseases such as hypercholesterolemia and other metabolic diseases, and as a consequence, they were also more inclined to suffer from other cardiovascular diseases. Such a combination of numerous cardiovascular risk factors, on the one hand, and cardiovascular diseases on the other, could promote polypharmacy and, as a result, make men with metabolic disorders more susceptible to the occurrence of adverse drug reactions.

In our patients' history, we noted both non-specific symptoms, such as skin lesions or gastrointestinal disorders, as well as symptoms specific to a particular drug class. Drug-induced side effects were significantly more common in women than in men. As regards specific side effects, women were significantly more likely to experience hypotension, cough, edema, bradycardia, and skin lesions.

An analysis of different classes of drugs revealed that both single-drug intolerance and multiple-drug intolerance were significantly more common in women than in men. A multivariable analysis showed that intolerance of such drugs as antibiotics and analgesics occurred far more often among women. In the case of women, adverse reactions following antibiotic administration were most frequently reported, for example, after using ceftriaxone and for anti-tuberculosis drugs [14]. In a retrospective cohort study evaluating the incidence of adverse reactions after analgesics, women reported such symptoms almost twice as often as men [15].

It should also be noted that the frequency of adverse reactions after taking analgesics, especially nonsteroidal anti-inflammatory drugs, may be underreported because in many countries, including Poland, they are available as over-the-counter drugs.

The women in our study received fewer drugs of any class than the men, and fewer cardiovascular drugs (tablets) other than antihypertensive drugs. When it came to specific types of drugs, women took angiotensin receptor blockers and rheumatological drugs more frequently than men. The female study participants who received angiotensin receptor blockers were older and post-menopausal. In addition, rheumatic disorders were significantly more common in women than in men. On the other hand, women used antiplatelet drugs, statins, or cardiological drugs other than antihypertensive drugs more rarely than men, which was due to the more frequent presence of cardiovascular risk factors and concomitant cardiological diseases in men.

A comparison between women reporting side effects and women not reporting them showed that the former group was significantly older and had more comorbidities, including cardiovascular diseases. Specific diseases that were significantly more prevalent in women with side effects included CAD, history of MI, HF, respiratory diseases, and rheumatic disorders. Our analysis indicates once more that morbidity-related polypharmacy is a major risk factor for a history of drug-induced adverse reactions.

There was, however, no difference between the two groups of women in terms of the number of drugs taken of any class, the number of antihypertensive medications (in tablet form), and the number of non-antihypertensive cardiovascular medications (in tablet form). Women who reported adverse drug-induced symptoms took antiplatelet medications far more often than those who did not report such symptoms, but, at the same time, received fewer calcium antagonists. Antiplatelet medications, e.g., acetylsalicylic acid, are indicated for hypertensive patients with atherosclerotic cardiac complications, while calcium antagonists are used mainly for female patients of reproductive age, which explains their less frequent application in the study population.

A comparison of men reporting adverse drug reactions with men not reporting such reactions showed that patients in the former group were older and had a significantly higher number of cardiovascular diseases and comorbidities. When it came to specific diseases, men reporting side effects were more likely to suffer from coronary heart disease, past MI, HF, AF, hypercholesterolemia, and metabolic diseases. In addition, men reporting adverse drug reactions were significantly more likely to take more classes of drugs, including antihypertensive medications, and cardiovascular medications other than antihypertensive drugs, than men who did not report such events. When it came to specific classes of drugs, men reporting adverse drug reactions much more frequently used antiplatelet medications, anticoagulants, and cardiovascular medications other than antihypertensive drugs than men not reporting drug-induced side effects, but at the same time they took fewer calcium antagonists. Our male subgroup analysis showed a correlation between polypharmacy and an increased risk of adverse reactions. We also observed a correlation between adverse reactions and the number of medications and tablets taken. The use of combination drugs, recommended in the European guidelines, not only makes it possible to reduce the number of tablets taken by a patient per day, but also to reduce the dosage of single drugs. As a consequence, the use of single-pill combination medications may prevent the occurrence of drug-induced side effects [16].

The guidelines for the treatment of chronic diseases, including hypertension, emphasize the need to ensure safe treatment by monitoring a patient's tolerance to such treatment over a short period of approximately 1 month after the introduction of one drug because only such an approach would allow the patient to avoid arbitrary drug withdrawal as a result of adverse reactions in connection with taking a particular medication [3, 17, 18].

At every medical visit, the patient should be asked about the tolerance of the medications they are taking. Poorer drug tolerance affects the overall quality of a patient's life, which in hypertensive patients translates into worse blood pressure control and thus a higher risk of premature morbidity and mortality.

Based on the current analysis, special attention should be paid to female patients and elderly patients, as well as people with numerous comorbidities.

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