ORIGINAL ARTICLE

# Multiple drug intolerance in patients with arterial hypertension: prevalence and determining factors

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**KEY WORDS**

chronic disease, drug-related side effects and adverse reactions, drug tolerance, hypertension

**ABSTRACT**

**INTRODUCTION** One of the reasons for poor medication compliance among patients is the occurrence of adverse drug reactions.

**OBJECTIVES** The aim of this study was to determine the prevalence of multiple drug intolerance syndrome (MDIS), defined as adverse reactions to 3 or more classes of drugs, among patients with arterial hypertension, and to assess the predisposing factors.

**PATIENTS AND METHODS** The study population included hospitalized patients diagnosed with arterial hypertension as well as patients undergoing chronic treatment in an outpatient hypertension clinic. The authors used a structured proprietary questionnaire, which focused on demographic and clinical data, including current or past history of adverse drug reactions.

**RESULTS** The study population comprised 1000 patients, including 560 women. The mean (SD) age was 62.8 (14.9) years. Eighty patients (8%) suffered from MDIS. There were more women in this group, as compared with the entire study population (71% vs 55%; $P = 0.01$). The patients with MDIS had a longer history of hypertension (median 15 vs 10 years; $P = 0.01$), and were more likely to suffer from respiratory ($P = 0.01$), gastrointestinal ($P = 0.003$), rheumatoid ($P < 0.001$), and endocrine ($P = 0.01$) disorders. The risk of MDIS was the highest with the concomitant use of analgesics, followed by β-blockers, antiplatelet drugs, and antibiotics.

**CONCLUSIONS** MDIS in patients with hypertension is common and more frequently affects women and patients with a longer known disease duration. Comorbidities increase the risk of MDIS. Its risk is strongly associated with the use of analgesics, β-blockers, antiplatelet drugs, and antibiotics.

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**INTRODUCTION** Elevated blood pressure is one of the leading causes of premature morbidity and mortality worldwide, including fatal and non-fatal strokes, heart attacks, other vascular diseases, and kidney disease.[1] The prevalence of arterial hypertension is steadily increasing and nowadays over 1.2 billion people worldwide are suffering from the disease. Unfortunately, less than half of the treated hypertensive patients meet the criteria set for target blood pressure values.[2] Currently, in both developed and developing countries, several classes of antihypertensive drugs are available that provide effective treatment for arterial hypertension and reduce the risk of its complications.[3] Despite the availability of pharmacotherapy, blood pressure control remains suboptimal around the world. This is due to a number of factors, including patient failure to adhere to doctor's recommendations.[4] One of the reasons for insufficient patient adherence to medical advice is the occurrence of drug-induced adverse events. An adverse drug reaction (ADR) is any unwanted, uncomfortable, or dangerous effect that a drug may have.

A meta-analysis of 38 randomized, placebo-controlled clinical trials and 37 randomized active clinical trials showed that, with the exception of angiotensin receptor antagonists, all classes

## WHAT'S NEW?

Drug-related adverse reactions are an important cause of drug discontinuation among patients. Multiple drug intolerance syndrome (MDIS), that is, intolerance to 3 or more drug classes, is an even more serious clinical problem. We explored the prevalence of this clinical entity in patients with hypertension and identified the groups of patients particularly prone to MDIS. At each medical appointment, attention should also be paid to the patient's medical history, including adverse drug reactions.

of antihypertensive agents are associated with an increased risk of treatment withdrawal due to adverse events, as compared with placebo. In the studies comparing active treatment regimens, the use of angiotensin receptor antagonists was associated with less frequent discontinuation of treatment due to drug-induced adverse events than for the other classes of antihypertensive drugs.[5] Current guidelines on the management of hypertension usually recommend a combination therapy, that is, a therapy including 2 or more classes of drugs. In addition, comorbidities require many patients to take other classes of drugs, for example, analgesics, steroids, statins, hypoglycemic drugs, and others, which also expose them to drug-induced adverse events. Multiple drug intolerance syndrome (MDIS) is diagnosed when a patient reports ADRs to 3 or more different classes of drugs. A typical effect of MDIS is self-reported nonadherence, where a patient reports drug discontinuation after noticing a side effect.[6]

The aim of the study was to determine the prevalence of MDIS in a group of patients with arterial hypertension and to assess the predisposing factors.

**PATIENTS AND METHODS** The study population comprised patients hospitalized at the Department of Cardiology and Interventional Electrocardiology and Hypertension of the University Hospital in Kraków, in a stable medical condition, with a diagnosis of arterial hypertension as their underlying disease or a comorbidity, as well as patients undergoing chronic treatment for hypertension in an outpatient hypertension clinic. The study was conducted until reaching the prespecified number of 1000 patients, 560 of whom were women. The inclusion criteria were as follows: age of 18 years or older, a diagnosis of essential arterial hypertension, known disease duration of more than 1 year, and signed informed consent to participate in the study. The exclusion criteria were a lack of the patient consent, advanced stage of dementia preventing the patient from completing the questionnaire, age below 18 years, and secondary arterial hypertension.

Participation in the study was voluntary. Each participant was informed about its purpose and methodology, as well as of their right to withdraw from the study at any stage. The study obtained the approval of the Bioethics Committee of the Jagiellonian University in Kraków, Poland (1072.6120.261.2017).

The patients completed a survey containing questions covering various demographic and clinical factors. The data provided by the patients regarding comorbidities and risk factors for cardiovascular diseases, as well as currently taken medications, were verified based on the available medical documentation. The patients were also asked to indicate how long they had been suffering from hypertension.

The next part of the questionnaire focused on the occurrence of any current or past drug-related adverse events. If the answer was affirmative, the patient was asked to provide the name of the drug and the type of adverse events. The patients also provided information on their behavior following the occurrence of the adverse reaction. The questionnaire is included in Supplementary material.

**Statistical analysis** The analysis was performed using the R statistical software package, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria, http://cran.r-project.org). Normality of the distribution of interval variables was checked with the Shapiro–Wilk test and assessed visually on the histograms. The nominal data were described by means of frequency measures: n count and percent of the group. The ordinal data and not normally distributed variables were presented using the median (interquartile range [IQR]), and normally distributed interval variables were presented with their mean and SD. A comparison of groups according to individual parameters was performed using the following tests: the $\chi^2$ test or the Fisher exact test for nominal variables, and the *t* test and the Mann–Whitney test for ordinal and interval variables, depending on their distribution. Furthermore, logistic regression analysis was performed in order to identify the parameters predicting the occurrence of drug-induced side effects or multiple-drug intolerance. Multivariable analysis was performed to select variables via the stepwise "backward" method based on the Akaike information criterion. As a starting point for the multivariable models, we used the variables that in univariable models had a *P* value below 0.25 in the Wald test. The obtained multivariable models were evaluated by means of the following: the $\chi^2$ test, the Nagelkerke R2 coefficient, and the goodness of fit test by Hosmer and Lemeshow. The degree of autocorrelation between the predictors was also verified using the variance inflation factor. A significance level of $P < 0.05$ was adopted.

**RESULTS** The study population comprised a total of 1000 patients, including 560 women and 440 men. The mean (SD) age of the group was 62.84 (14.96) years, and it ranged from 19 to 103 years. The average (SD) body mass index was 27.86 (4.84) kg/m$^2$. A total of 48% of the participants reported intolerance to at least 1 drug. Only 48

patients who experienced a side effect after taking a drug declared discontinuation of the drug before consulting a doctor. In most cases, intolerance concerned 1 drug (32% of the group). Multiple drug intolerance was reported by 80 patients (8% of the entire group). The highest number of drug classes to which a patient reported intolerance was 8.

The group of patients with MDIS had a higher proportion of women than the entire study group (71% vs 55%; $P = 0.01$). The patients with MDIS had a longer history of hypertension (median, 15 years vs 10 years; $P = 0.01$). They were also characterized by a significantly higher prevalence of noncardiac diseases ($P = 0.02$). In comparison with the other study participants, the group with MDIS suffered significantly more frequently from the following comorbidities: diseases of the respiratory system (21% vs 11%; $P = 0.01$), digestive tract disorders (25% vs 13%; $P = 0.003$), rheumatoid diseases (24% vs 9%; $P < 0.001$), and endocrine disorders (29% vs 16%; $P = 0.007$).

No significant differences were observed between the 2 groups in terms of the number of consumed classes of drugs ($P = 0.28$), the number of tablets of cardiovascular drugs taken other than antihypertensive drugs ($P = 0.25$), and the number of antihypertensive drugs in terms of tablets consumed (median 1 vs 2; $P = 0.05$). When it came to specific drug classes, the study participants reporting MDIS consumed rheumatology drugs significantly more frequently than the rest of the study group (5% vs 1.2%; $P = 0.03$). They consumed the following medications significantly less frequently than the group without MDIS: angiotensin-converting enzyme inhibitors (ACEIs) (36% vs 55%; $P = 0.001$), diuretics (38% vs 52%; $P = 0.01$), other antihypertensive drugs (8.8% vs 19%; $P = 0.03$), and statins (35% vs 51%; $P = 0.01$), as shown in TABLE 1. The patients with MDIS experienced ADRs from all analyzed drug classes significantly more often than the remaining participants, with the exception of anticoagulants. ADRs in any form were indicated by 93.8% of the patients with MDIS and 43% of the other patients ($P < 0.001$). The number of side effects was also significantly higher in the group suffering from MDIS. The most common side effect reported by the group with MDIS was an allergic reaction (66%). The patients with MDIS reported all the analyzed ADRs significantly more often than the remaining patients, with the exception of the following: bleeding, laboratory abnormalities, muscle pain, and electrolyte disturbances, for which no significant differences were confirmed between the groups (TABLE 2). Of 80 patients with MIDS, 47 reported pharmacologically specific side effects (32 for calcium channel blockers, 47 for ACEIs, 38 for β-blockers, 27 for diuretics, 17 for angiotensin receptor blockers), and 33 nonspecific side effects. The results do not sum up to 100%, as the patients, according to current guidelines, were on a combination therapy, and they reported intolerance to multiple drugs.

A multivariable analysis was then performed to determine the occurrence of MDIS. First, univariable models were constructed, on the basis of the variables selected for the multivariable model. They are summarized in TABLE 3. The multivariable logistic regression model showed that the risk of MDIS increased significantly in the event of gastrointestinal disease (odds ratio[OR], 3.65; 95% CI, 1.28–10.44; $P = 0.01$). In terms of drug intolerance, the risk of MDIS was the highest in the case of analgesics (OR, 65.59; 95% CI, 23.73–208.46; $P < 0.001$), β-blockers (OR, 48.42; 95% CI, 8.30–285.90; $P < 0.001$), antiplatelet drugs (OR, 47.26; 95% CI, 8.65–272.95; $P < 0.001$), and antibiotics (OR, 30.04; 95% CI, 11.69–87.76; $P < 0.001$) (TABLE 4).

**DISCUSSION** In our study, we observed a high frequency of ADRs. Another frequent phenomenon was the occurrence of MDIS, which in the studied population affected on average 1 in 12 patients. The risk of MDIS was higher in women, in the patients with known longer disease duration, in those taking analgesics, β-blockers, and antiplatelet medications, as well the individuals suffering from comorbidities. ADRs are a common phenomenon in the health care, and they are inevitable with the currently administered polypharmacotherapies.

In a meta-analysis of 33 studies involving a total of over 1.5 million patients cared for by general practitioners, the average prevalence of drug-induced adverse events was estimated at 8.32%. However, it depended largely on the characteristics of the study population and ranged from 0.87% in a Spanish study of a young healthy population, to 65.35% in a study of a health care practice in the United States treating elderly patients and patients with numerous comorbidities.[7]

A diagnosis of MDIS is based primarily on compiling the patient's history regarding current and previous medications and taking into account the side effects that a patient associates with their use. A common feature of MDIS is patient-reported noncompliance with medical recommendations, where a patient reports drug discontinuation due to the occurrence of side effects. Regardless of MDIS diagnosis, a patient with MDIS still requires further treatment for each of their chronic diseases, excluding the cases of allergic reactions or a need of a consultation for psychiatric disorders.[8]

The prevalence of MDIS in the literature is reported to be in the range of 2.1% to 10%.[9-13] In the general population of California, the prevalence of MDIS was estimated at 2.1%,[13] while in a population of the United Kingdom patients taking any type of medication and reporting any side effects, 4.9% met the criteria for MDIS.[9] On the other hand, 10.1% of 786 selected patients at a reference center for the treatment of arterial hypertension met the MDIS criteria, which is a level similar to that observed in our population of patients with chronic hypertension.[10]

**TABLE 1** Comparison of patients with and without multiple-drug intolerance in terms of comorbidities and classes of drugs taken (continued on the next page)

| Parameter | | No multiple-drug intolerance (n = 920) | Multiple-drug intolerance (n = 80) | *P* value |
|---|---|---|---|---|
| Sex | Women | 503 (54.7) | 57 (71.3) | 0.006 |
| | Men | 417 (45.3) | 23 (28.8) | |
| Age, y, mean (SD) | | 62.8 (14.9) | 62.9 (16) | 0.1 |
| BMI, kg/m$^2$, mean (SD) | | 27.89 (4.88) | 27.53 (4.3) | 0.49 |
| Known duration of hypertension, y | | 10 (6–20) | 15 (10–29.5) | 0.008 |
| Number of cardiovascular diseases | | 2 (1–3) | 1 (1–3) | 0.07 |
| Total number of noncardiovascular diseases | | 1 (1–3) | 2 (1–4) | 0.02 |
| Total number of diseases of any kind | | 4 (2–6) | 3.5 (2–6) | 0.41 |
| Comorbidities | | | | |
| Coronary artery disease | | 221 (24) | 20 (25) | 0.95 |
| Previous myocardial infarction | | 135 (14.7) | 11 (13.8) | 0.95 |
| Heart failure | | 166 (18) | 13 (16.3) | 0.8 |
| Arrhythmia without atrial fibrillation | | 115 (12.5) | 6 (7.5) | 0.26 |
| Atrial fibrillation | | 146 (15.9) | 7 (8.8) | 0.12 |
| Hypercholesterolemia | | 461 (50.1) | 31 (38.8) | 0.07 |
| Other cardiovascular diseases | | 247 (26.8) | 20 (25) | 0.82 |
| Respiratory system diseases | | 103 (11.2) | 17 (21.3) | 0.01 |
| Digestive system diseases | | 115 (12.5) | 20 (25) | 0.003 |
| Nervous system diseases | | 79 (8.6) | 8 (10) | 0.82 |
| Skin diseases | | 20 (2.2) | 3 (3.8) | 0.61 |
| Rheumatoid diseases | | 83 (9) | 19 (23.8) | <0.001 |
| Metabolic disorders | | 208 (22.6) | 11 (13.8) | 0.09 |
| Diabetes | | 259 (28.2) | 15 (18.8) | 0.09 |
| Mental disorders | | 32 (3.5) | 4 (5) | 0.7 |
| Endocrine disorders | | 149 (16.2) | 23 (28.8) | 0.007 |
| Oncological diseases | | 61 (6.6) | 2 (2.5) | 0.22 |
| Other noncardiovascular diseases | | 330 (35.9) | 31 (38.8) | 0.69 |
| Total noncardiovascular diseases | | 691 (75.1) | 66 (82.5) | 0.18 |
| Number of drug classes | | 5 (3–7) | 5 (2–6.25) | 0.28 |
| Class of drug | | | | |
| ACEIs | | 510 (55.4) | 29 (36.3) | 0.001 |
| β-Blockers | | 561 (61) | 52 (65) | 0.56 |
| Angiotensin II receptor blockers | | 162 (17.6) | 21 (26.3) | 0.08 |
| Calcium channel blockers | | 360 (39.1) | 22 (27.5) | 0.053 |
| Diuretics | | 482 (52.4) | 30 (37.5) | 0.02 |
| Other antihypertensive drugs | | 177 (19.2) | 7 (8.8) | 0.03 |
| Antiplatelet drugs | | 225 (24.5) | 18 (22.5) | 0.80 |
| Anticoagulants | | 148 (16.1) | 10 (12.5) | 0.49 |
| Statins | | 470 (51.1) | 28 (35) | 0.008 |
| Other cardiovascular drugs | | 443 (48.2) | 35 (43.8) | 0.52 |
| Cardiovascular drugs | | 868 (94.3) | 75 (93.8) | 0.99 |
| Antihypertensive drugs | | 847 (92.1) | 71 (88.8) | 0.41 |
| Cardiovascular drugs other than antihypertensive drugs | | 653 (71) | 52 (65) | 0.32 |
| Number of cardiovascular drugs taken in a tablet form excluding antihypertensive drugs | | 1 (0–2) | 1 (0–2) | 0.24 |
| Antihypertensive drugs in terms of number of tablets | | 2 (1–3) | 1 (0–2) | 0.05 |
| Respiratory system drugs | | 45 (4.9) | 6 (7.5) | 0.45 |
| Nervous system drugs | | 29 (3.2) | 5 (6.3) | 0.25 |
| Psychotropic drugs | | 28 (3) | 6 (7.5) | 0.07 |
| Dermatological drugs | | 4 (0.4) | 0 | 0.99 |
| Metabolic group | | 247 (26.8) | 13 (16.3) | 0.05 |

**TABLE 1** Comparison of patients with and without multiple-drug intolerance in terms of comorbidities and classes of drugs taken (continued from the previous page)

| Parameter | No multiple-drug intolerance (n = 920) | Multiple-drug intolerance (n = 80) | *P* value |
|---|---|---|---|
| Rheumatology drugs | 11 (1.2) | 4 (5) | 0.03 |
| Other noncardiovascular drugs | 284 (30.9) | 28 (35) | 0.52 |
| Total noncardiovascular drugs | 472 (51.3) | 45 (56.3) | 0.46 |
| All drugs taken together | 879 (95.5) | 77 (96.3) | 0.99 |

Data are presented as number (percentage) or median (interquartile range) unless otherwise stated.

Men and women were compared using the $\chi^2$ test, the Fisher exact test, the *t* test, or the Mann–Whitney test.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; BMI, body mass index

**TABLE 2** Comparison of patients with and without multiple-drug intolerance in terms of drug intolerance and side effects

| Parameter | No multiple-drug intolerance (n = 920) | Multiple-drug intolerance (n = 80) | *P* value |
|---|---|---|---|
| Drug intolerance | | | |
| Any drug | 399 (43.4) | 80 (100) | <0.001 |
| ACEIs | 29 (3.2) | 16 (20) | <0.001 |
| β-Blockers | 14 (1.5) | 7 (8.8) | <0.001 |
| Angiotensin II receptor blockers | 3 (0.3) | 7 (8.8) | <0.001 |
| Calcium channel blockers | 15 (1.6) | 12 (15) | <0.001 |
| Diuretics | 10 (1.1) | 7 (8.8) | <0.001 |
| Other antihypertensive drugs | 8 (0.9) | 7 (8.8) | <0.001 |
| Antiplatelet drugs | 18 (2) | 10 (12.5) | <0.001 |
| Anticoagulants | 10 (1.1) | 3 (3.8) | 0.13 |
| Statins | 12 (1.3) | 7 (8.8) | <0.001 |
| Antibiotics | 120 (13) | 37 (46.3) | <0.001 |
| Analgesics | 55 (6) | 35 (43.8) | <0.001 |
| Other cardiovascular drugs | 11 (1.2) | 7 (8.8) | <0.001 |
| Other noncardiovascular drugs | 164 (17.8) | 53 (66.3) | <0.001 |
| Side effects | | | |
| Presence of symptoms | 395 (42.9) | 75 (93.8) | <0.001 |
| 1 symptom | 192 (20.9) | 8 (10) | – |
| 2 symptoms | 72 (7.8) | 15 (18.8) | – |
| 3 symptoms | 95 (10.3) | 10 (12.5) | – |
| 4 symptoms | 18 (2) | 18 (22.5) | – |
| 5 or more symptoms | 18 (2) | 24 (30) | – |
| Number of side effects, median (IQR) | 0.00 (0–1) | 4 (2–5) | <0.001 |
| Type of side effect | | | |
| Electrolyte imbalance | 3 (0.3) | 2 (2.5) | 0.07 |
| Hypotension | 30 (3.3) | 24 (30) | <0.001 |
| Coughing | 46 (5) | 22 (27.5) | <0.001 |
| Swelling | 34 (3.7) | 28 (35) | <0.001 |
| Bradycardia | 23 (2.5) | 9 (11.3) | <0.001 |
| Skin lesions | 131 (14.2) | 50 (62.5) | <0.001 |
| Gastrointestinal disorders | 40 (4.3) | 24 (30) | <0.001 |
| Other | 302 (32.8) | 63 (78.8) | <0.001 |
| Allergic reaction | 148 (16.1) | 53 (66.3) | <0.001 |
| Bleeding | 16 (1.7) | 4 (5) | 0.11 |
| Abnormalities in laboratory results | 8 (0.9) | 2 (2.5) | 0.41 |
| Muscular pains | 12 (1.3) | 3 (3.8) | 0.21 |

Data are presented as number (percentage) unless otherwise stated.

Groups were compared using the $\chi^2$ test, the Fisher exact test, or the Mann–Whitney test.

Abbreviations: see TABLE 1

**TABLE 3** Univariable logistic regression for the occurrence of multiple-drug intolerance

| Parameter | OR | 95% CI | *P* value |
|---|---|---|---|
| Sex, women | 2.05 | 1.26–3.45 | 0.005 |
| Age, y | 1.00 | 0.99–1.02 | 0.1 |
| BMI, kg/m$^2$ | 0.98 | 0.94–1.03 | 0.53 |
| Comorbidities | | | |
| Coronary artery disease | 1.05 | 0.61–1.76 | 0.84 |
| Previous myocardial infarction | 0.93 | 0.45–1.73 | 0.82 |
| Heart failure | 0.88 | 0.46–1.58 | 0.69 |
| Arrhythmia excluding atrial fibrillation | 0.57 | 0.22–1.23 | 0.19 |
| Atrial fibrillation | 0.51 | 0.21–1.05 | 0.1 |
| Hypercholesterolemia | 0.63 | 0.39–1.001 | 0.05 |
| Other cardiovascular diseases | 0.91 | 0.52–1.51 | 0.72 |
| Circulatory system diseases | NA | NA | NA |
| Respiratory system diseases | 2.14 | 1.17–3.72 | 0.009 |
| Digestive system diseases | 2.33 | 1.33–3.95 | 0.002 |
| Nervous system diseases | 1.18 | 0.51–2.41 | 0.67 |
| Skin diseases | 1.75 | 0.41–5.26 | 0.37 |
| Rheumatoid diseases | 3.14 | 1.75–5.42 | <0.001 |
| Metabolic disorders | 0.55 | 0.27–1.01 | 0.07 |
| Diabetes | 0.59 | 0.32–1.02 | 0.07 |
| Mental disorders | 1.46 | 0.43–3.80 | 0.49 |
| Endocrine disorders | 2.09 | 1.23–3.45 | 0.005 |
| Oncological diseases | 0.36 | 0.06–1.19 | 0.16 |
| Other noncardiovascular diseases | 1.13 | 0.70–1.80 | 0.607 |
| Total noncardiovascular diseases | 1.56 | 0.89–2.95 | 0.14 |
| Any kind of disease | NA | NA | NA |
| Class of drug | | | |
| ACEIs | 0.46 | 0.28–0.73 | 0.001 |
| β-Blockers | 1.19 | 0.74–1.94 | 0.48 |
| Angiotensin II receptor blockers | 01.67 | 0.96–2.78 | 0.06 |
| Calcium channel blockers | 0.59 | 0.35–0.97 | 0.04 |
| Diuretics | 0.54 | 0.34–0.87 | 0.01 |
| Other antihypertensive drugs | 0.40 | 0.17–0.83 | 0.02 |
| Antiplatelet drugs | 0.90 | 0.51–1.52 | 0.69 |
| Anticoagulants | 0.75 | 0.35–1.41 | 0.4 |
| Statins | 0.52 | 0.32–0.82 | 0.007 |
| Other cardiovascular drugs | 0.84 | 0.53–1.32 | 0.45 |
| Total cardiovascular drugs | 0.90 | 0.38–2.64 | 0.82 |
| Antihypertensive drugs | 0.68 | 0.34–1.51 | 0.3 |
| Cardiovascular drugs other than antihypertensive drugs | 0.76 | 0.47–1.24 | 0.26 |
| Respiratory system drugs | 1.58 | 0.59–3.55 | 0.31 |
| Nervous system drugs | 2.05 | 0.68–5.02 | 0.15 |
| Psychotropic drugs | 2.58 | 0.94–6.04 | 0.04 |
| Dermatological drugs | NA | NA | NA |
| Metabolic group | 0.53 | 0.27–0.94 | 0.04 |
| Rheumatology drugs | 4.35 | 1.18–13.06 | 0.01 |
| Other noncardiovascular drugs | 1.21 | 0.74–1.93 | 0.44 |
| Total noncardiovascular drugs | 1.22 | 0.77–1.94 | 0.4 |
| All drugs taken together | 1.20 | 0.42–5.02 | 0.8 |

Abbreviations: NA, not analyzed; OR, odds ratio; others, see TABLE 1

In our study population, MDIS occurred more frequently in women, and this observation was consistent with previous studies in the general population, among patients taking prescription drugs, and in a selected population of patients with arterial hypertension.[9,10,12,13]

A longer known duration of arterial hypertension was associated with a more frequent occurrence of MDIS, which is a new observation not documented in the available literature. This relationship may be due to the more advanced age of the patients reporting any drug-induced side effects in our population, as well as may have originated from a reduced acceptance of arterial hypertension in the patients with longer disease duration.[14] The comorbidities that increased the risk of MDIS among our patients included diseases of the respiratory and digestive systems, rheumatoid, and endocrine diseases. Increased morbidity associated with the digestive system, in particular in the form of gastroesophageal reflux disease, was observed in patients with MDIS and arterial hypertension in a specialized clinic in the United Kingdom.[10] To date, the literature has provided no reports on a more frequent occurrence of respiratory, rheumatoid, or endocrine diseases in patients with MDIS. A higher number of comorbidities increases the risk of reduced acceptance of the underlying disease, that is, arterial hypertension,[14] which may translate into more meticulous patient reporting of ADRs, and further lead to a situation where the criteria for MDIS are met more frequently.

A multivariable analysis designed to establish the drug classes most strongly associated with the risk of MDIS showed that in our group these drugs were analgesics, followed by β-blockers, antiplatelet drugs, and antibiotics. The side effects following the consumption of analgesics are frequent.[15] However, it should also be noted that the frequency of reporting adverse events associated with analgesics, especially nonsteroidal anti-inflammatory drugs, may be underestimated, as in many countries, including Poland, they are available as over-the-counter drugs. The relationship between analgesics and the occurrence of MDIS has already been described in large cohorts of patients.[16]

The relationships between antiplatelet drugs, especially aspirin, and antibiotics, and the occurrence of MDIS, are similarly well-known. Acetylsalicylic acid and antibiotics are often associated with nonspecific symptoms, such as gastrointestinal complaints, and more typical symptoms, such as allergic reactions. In our study, the use of antiplatelet drugs was higher than in the general population, because a significant proportion of patients suffered from cardiovascular disorders.

A new observation, however, is a relationship between MDIS and the use of β-blockers. β-blockers are commonly used in the treatment of cardiovascular diseases, including hypertension, heart failure, tachyarrhythmia, and coronary artery disease. They also have a number of

**TABLE 4** Multivariable logistic regression for the occurrence of multiple drug intolerance

| Parameter | OR | 95% CI | *P* value |
|---|---|---|---|
| Comorbidities | | | |
| Arrhythmia | 0.39 | 0.08–1.39 | 0.18 |
| Digestive system diseases | 3.65 | 1.28–10.44 | 0.01 |
| Rheumatoid diseases | 2.13 | 0.81–5.57 | 0.12 |
| Metabolic disorders | 0.35 | 0.10–1.02 | 0.07 |
| Intolerance of the following drugs | | | |
| ACEIs | 17.74 | 5.04–65.77 | <0.001 |
| β-Blockers | 48.42 | 8.3–285.9 | <0.001 |
| Angiotensin II receptor blockers | 13.85 | 1.06–174.86 | 0.04 |
| Calcium channel blockers | 26.38 | 4.16–186.26 | 0.001 |
| Diuretics | 40.24 | 4.60–287.57 | <0.001 |
| Other antihypertensive drugs | 13.40 | 1.86–82.74 | 0.006 |
| Antiplatelet drugs | 47.26 | 8.65–272.95 | <0.001 |
| Statins | 16.60 | 2.57–132.65 | 0.005 |
| Antibiotics | 30.04 | 11.69–87.76 | <0.001 |
| Analgesics | 65.59 | 23.73–208.46 | <0.001 |
| Other cardiovascular drugs | 41.08 | 7.63–220.05 | <0.001 |
| Other noncardiovascular drugs | 34.16 | 13.89–96.07 | <0.001 |

Model evaluation: $\chi^2$ test ($P$ <0.001), pseudo R2 Negelkerky = 0.72; goodness of fit Hosmer and Lemeshow test ($P$ = 0.366), variance inflation factor (range, 1.07–1.75).

Abbreviations: see **TABLES 1** and **3**

noncardiac applications, such as the treatment of hyperthyroidism, migraine headaches, and anxiety.[17] β-blockers, however, may cause significant side effects such as hypotension, bradycardia, and depression. The observed relationship between MDIS and β-blockers is most likely due to the characteristics of our study group. In the populations characterized by a lower percentage of cardiovascular diseases, ACEIs were indicated as cardiovascular drugs associated with MDIS.[13] In our study, ACEIs were also associated with MDIS, albeit to a lesser extent than β-blockers.

The study has some limitations. First, it was conducted in a single center. The outpatient clinic at our department provides a follow-up to a total of 1500 hypertensive patients a year. We aimed at recruiting 1000 participants, to resemble the general population of patients managed at our center per year, taking into account the dropouts due to the exclusion criteria, including unwillingness to participate. Second, the designed questionnaire was not externally validated. We are aware that the collected information reflects more the patients' beliefs and memories than an accurate estimate of causal effect of a drug on the reported side effect. However, the patient's beliefs and experiences related to particular medications are an important issue to consider when planning a long-term therapy aimed at reducing cardiovascular risk, in which medication compliance is crucial.[18,19]

To summarize, the occurrence of MDIS is a common phenomenon in the patients with arterial hypertension. Making such a diagnosis may facilitate understanding of the patient's problems and implementing effective measures to reintroduce antihypertensive drugs. The history of ADRs should be collected in detail from each hypertensive patient, as multiple drug intolerance might lead to worse acceptance of the treatment and arbitrary drug discontinuation leading to increased cardiovascular risk. The most effective method of treatment appears to be a combination of drugs at low therapeutic doses.[10] A reduced dose ensures fewer side effects as compared with a standard dose.[20] The patient's concern about possible side effects of particular medication increases the possibility of arbitrary drug discontinuation.

## SUPPLEMENTARY MATERIAL

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

## ARTICLE INFORMATION

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**CONTRIBUTION STATEMENT** MP and KSS conceived the concept of the study. MP and KSS contributed to the design of the research. All authors were involved in data collection. MP and KSS analyzed the data. All authors were involved in writing the manuscript draft. All authors edited and approved the final version of the manuscript.

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