

Factors associated with resistant hypertension in a large cohort of hypertensive patients: the Pol-Fokus study

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KEY WORDS

antihypertensive treatment, cardiovascular risk, resistant hypertension

ABSTRACT

INTRODUCTION Patients with resistant hypertension (RHT) are at high risk for coronary artery disease (CAD) and cerebrovascular disease (CVD), compared with the general hypertensive population.

OBJECTIVES The aim of the study was to evaluate factors associated with RHT in a large sample of hypertensive patients under the care of general practitioners and specialists in Poland.

PATIENTS AND METHODS We included 12 375 patients (mean age, 64.0 ± 12.3 years; age range, 18–98 years; women, 59%) with hypertension treated for at least 1 year. Patients were divided into 3 groups: with controlled hypertension, uncontrolled hypertension (not fulfilling the criteria for RHT), and RHT.

RESULTS Controlled hypertension, uncontrolled hypertension, and RHT were found in 47.3%, 27.9%, and 24.7% of the patients, respectively. The RHT rate was higher in patients visiting specialist offices (29.8%) and in patients with diabetes (32.5%), CAD (31.5%), CVD (33.3%), and impaired renal function (31.9%). Patients with RHT were characterized by the highest rate of high (23.5%) and very high (60.5%) added cardiovascular risk. An underuse of preferred antihypertensive drug combinations and aldosterone antagonists in patients with uncontrolled hypertension and RHT was observed. In a multivariate analysis, RHT was independently associated with male sex, higher pulse pressure, metabolic syndrome, diabetes, CAD, CVD, diseases requiring treatment with nonsteroidal anti-inflammatory drugs and an estimated glomerular filtration rate of less than 60 ml/min/1.73 m².

CONCLUSIONS The vast majority of patients with RHT carry a high or very high cardiovascular risk. In addition, the underuse of preferred antihypertensive drug combinations and aldosterone antagonists has been observed.

INTRODUCTION The recent data from a large representative sample of the adult populations showed that awareness and all aspects of hypertension management have improved systematically across the national surveys that have been focusing on cardiovascular disease for the past 20 years. A recent increase in the hypertension control rate appears to be almost exclusively driven

by a significant rise in the proportion of hypertensive people who are taking multiple antihypertensive agents, and hypertensive patients on polytherapy regimens were the most likely to meet their blood pressure (BP) goals.^{1–4}

It has been shown that patients with resistant hypertension (RHT) are at a disproportionately higher risk for target organ damage and

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cardiovascular events, compared with the general hypertensive population. Therefore, the recognition and identification of individuals with RHT is of particular importance, given the fact that they may require further diagnostic evaluation for specific interventions.⁵⁻⁷

An emerging subpopulation with therapy-resistant disease is becoming more evident in the United States and Western Europe. However, limited data are available so far on the prevalence and clinical characteristics of RHT in Central and East European countries known for their high cardiovascular risk.^{6,8,9}

Therefore, the aim of the Pol-Fokus study was to evaluate factors associated with RHT in a large sample of hypertensive patients treated for at least 1 year by general practitioners (GPs) and specialists (cardiologists and hypertension specialists) in Poland.

PATIENTS AND METHODS Pol-Fokus was a large, observational, cross-sectional survey of hypertensive subjects followed up by GPs, cardiologists, and hypertension specialists throughout Poland. The study was approved by the Ethics Committee of the Jagiellonian University in Kraków, Poland, and all participants provided informed consent.

A total of 1500 GPs and 500 specialists in cardiology or hypertension from all Polish provinces in Poland were drawn randomly from the registry of medical practices and then contacted individually. The sample reflected the distribution of medical care in individual Polish provinces. From that group, 979 GPs and 286 specialists participated in the Pol-Fokus study (FIGURE 1).

The Pol-Fokus study included hypertensive patients meeting the following criteria: age of 18 years or older, hypertension treated for at least 1 year, with at least 1 visit to a doctor who had been participating in the study over the previous year. Patients had to be free from any acute disease in the preceding 4 weeks and free from known secondary causes of hypertension. Each of the participating GPs had to include 6 to 8 patients and each specialist had to include 8 to 10 patients. During each day of the enrollment, the second and third hypertensive patient visiting the practice that day and meeting the inclusion criteria was included.

After discarding data from doctors who did not achieve the specific quota or who provided incomplete questionnaires, as well as from patients who were included despite not meeting the inclusion criteria, we finally analyzed data from 12 436 patients. For the purpose of this analysis, we also excluded 61 patients with no data regarding antihypertensive treatment (*Supplementary material online, Figure S1*).

All patients underwent standard clinical evaluation. The known duration of hypertension was recorded. Weight and height as well as waist circumference were measured. Body mass index (BMI) was calculated and obesity was considered

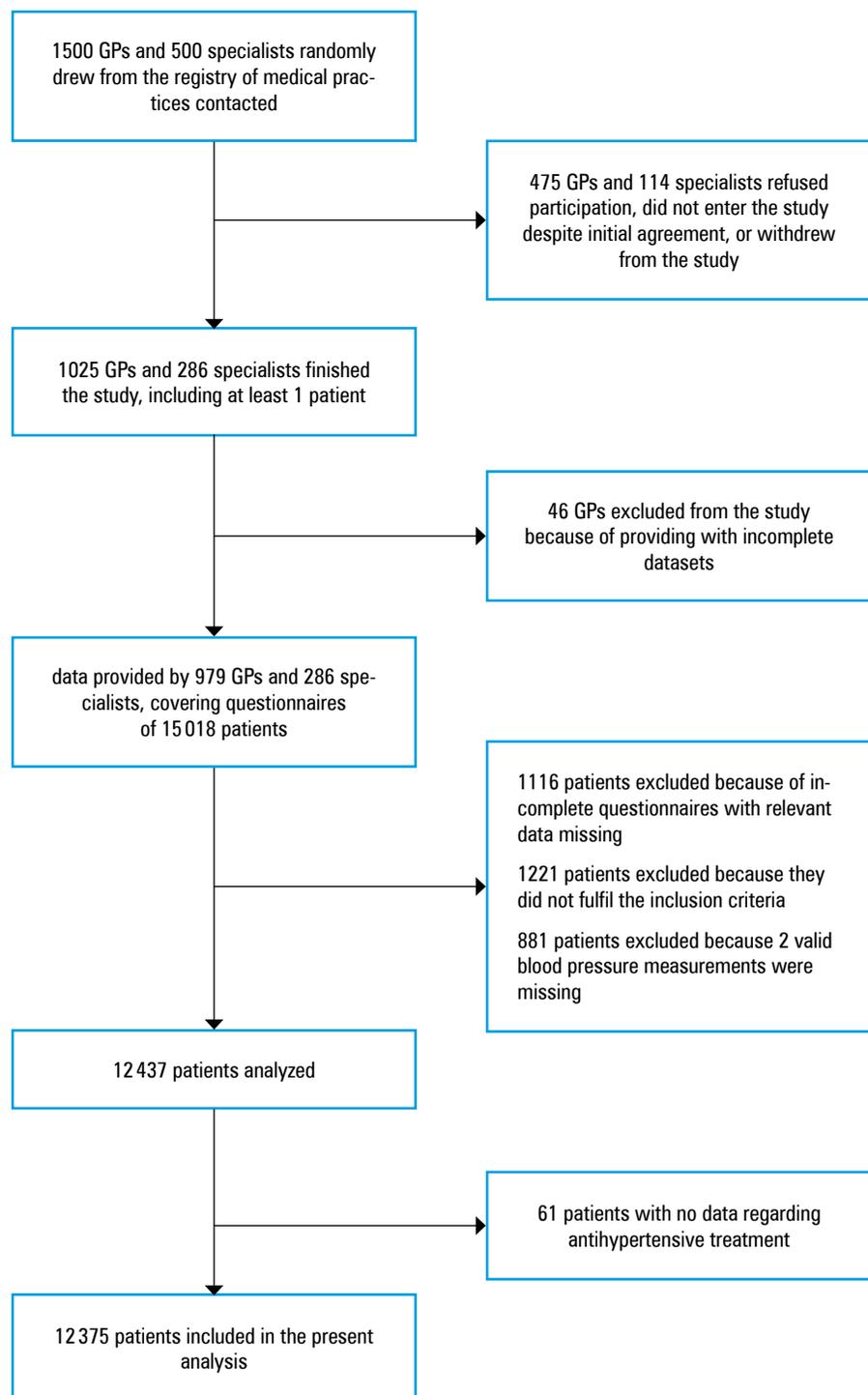
as having a BMI of 30 kg/m² or higher. Abdominal obesity was defined as a waist circumference exceeding 102 cm for women and 88 cm for men.²⁻¹⁰ Data on the current use of medications including antihypertensive, glucose, and lipid-lowering drugs as well as antiplatelet agents were also documented. BP levels during the previous visit (within 1 year of the current visit) and the levels of plasma sodium, potassium, glucose, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were recorded together with a history of coronary artery disease (CAD), cerebrovascular disease (CVD), as well as metabolic and other diseases. Each participating doctor was provided with specific instruction for these assessments. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease formula.¹¹ The LDL cholesterol goal was defined as less than 2.5 mmol/l in patients with diabetes or known cardiovascular disease and less than 3.0 mmol/l in the remaining patients.² Cardiovascular risk was evaluated according to the criteria of the 2013 European Society of Hypertension / European Society of Cardiology (ESH/ESC) guidelines (stratification into 4 groups: with low, moderate, high, and very high added risk).²

BP was measured with a patient in the sitting position after a 5-minute rest. Based on the upper arm circumference, an appropriately sized cuff was placed on the arm with the lower edge of the cuff 2 cm above the antecubital fossa. Three consecutive readings were taken, and the average was recorded. Each participating doctor was provided with a detailed instruction for BP measurement. The use of devices with confirmed accuracy was recommended.

We defined hypertension control as BP levels lower than 140 mmHg for systolic BP and lower than 90 mmHg for diastolic BP. RHT was defined as uncontrolled hypertension despite using 3 antihypertensive drugs including a diuretic.² For the purpose of this analysis, we divided patients into 3 groups: with controlled hypertension, uncontrolled hypertension (not fulfilling the criteria of RHT), and RHT.

Data collection and preparation of the dataset were performed by an independent office—Medycyna Praktyczna. Data analysis was carried out using the statistical software, PASW Statistics 18 (SPSS Inc., Chicago, Illinois, United States). The results are presented as mean ± 1 standard deviation or median and interquartile range. The values of variables were compared between groups: continuous and discrete variables, using the *t* test, Mann-Whitney test, or univariate analysis of variance with the Duncan post-hoc test; and categorical variables, using the χ^2 test or Fisher exact test. Multivariate logistic regression models were performed to determine the combined effect of several variables on the prevalence of the characteristic. For the multivariate analysis, the variables with a significant association

FIGURE 1 Study flow-chart
Abbreviations: GP, general practitioners



were included. Multicollinearity was tested using the variation inflation factor. A *P* value of less than 0.05 was considered statistically significant.

RESULTS We included 12 375 patients (mean age, 64.0 ±12.3 years; age range, 18-98 years; women, 59%) Among these, 5857 patients had controlled hypertension (47.3%), 3458 had uncontrolled hypertension (27.9%), and 3060 had RHT (24.7%). The rate of patients with RHT was higher and that of patients with uncontrolled hypertension was lower in specialist offices, as compared with those of GPs (FIGURE 2). The rate of RHT varied between individual provinces of Poland, with the highest prevalence being 30.0%

and the lowest—17.3% (Supplementary material online, Figure S1).

The rates of uncontrolled hypertension and RHT also varied significantly across the age categories: <40 years, 40-65 years, and ≥65 years (Supplementary material online, Figure S2). Patients aged 65 years or older were characterized by the lowest eGFR compared with those aged 40 to 65 years and less than 40 years (67.2 ±21.6 vs 79.0 ±23.3 and 91.6 ±28.9 ml/min/1.73 m², respectively; *P* <0.001). There were no differences in sex distribution between the groups (TABLE 1). Patients with RHT were older as compared with those with controlled and uncontrolled hypertension (TABLE 1). BMI, waist-to-hip ratio, and

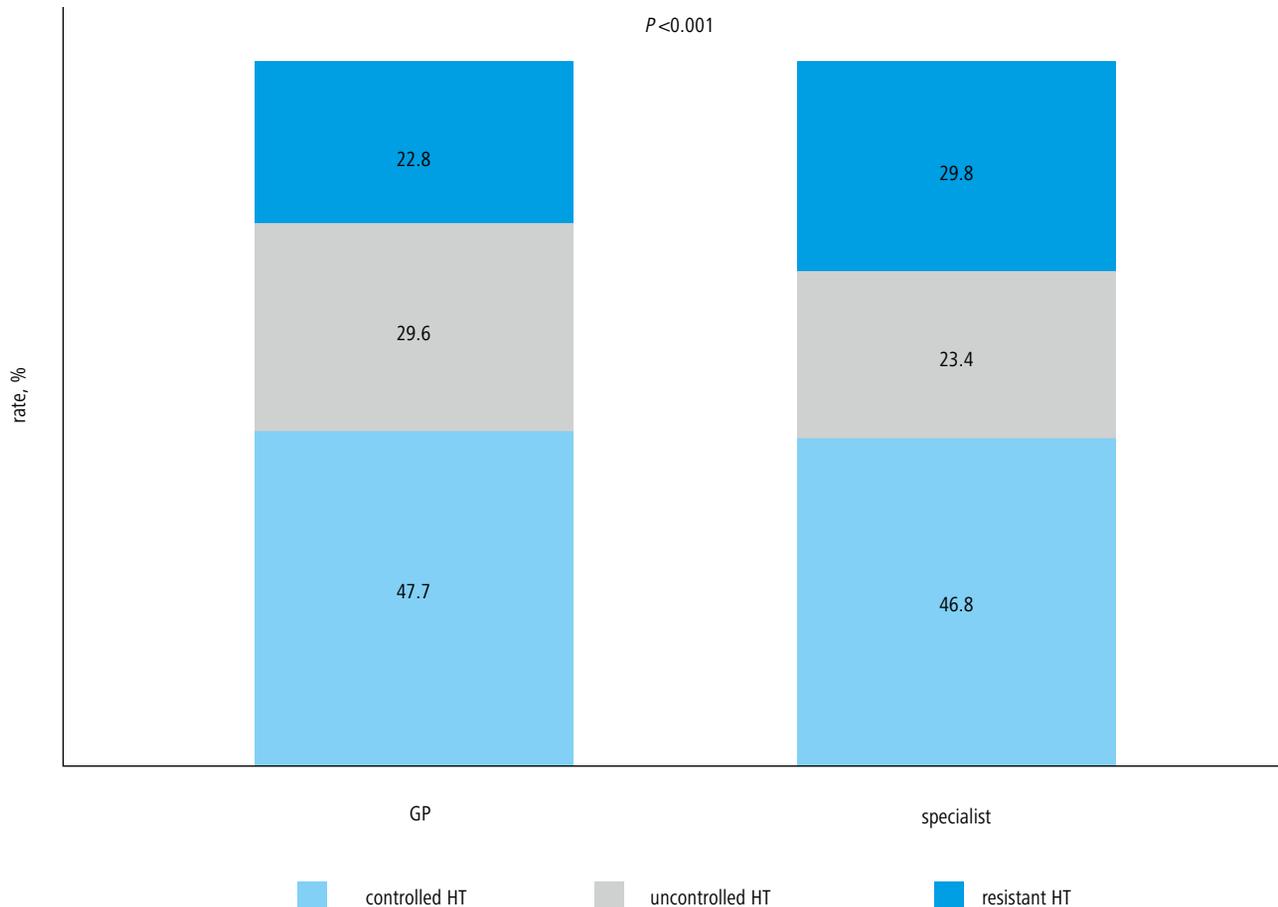


FIGURE 2 Prevalence of controlled, uncontrolled, and resistant hypertension (HT) in general practitioner (GP) and specialist offices

the rate of abdominal obesity were higher in patients with RHT as compared with patients with controlled hypertension (TABLE 1). No differences in these parameters were found between controlled and uncontrolled hypertensive patients. The RHT group was characterized by the highest rate of patients with high or very high added cardiovascular risk (FIGURE 3).

Patients with RHT and uncontrolled hypertension had higher sodium and glucose concentrations and lower potassium concentrations as compared with patients with controlled hypertension. eGFR was lower in patients with RHT as compared with patients with controlled hypertension (TABLE 1). The rate of RHT was higher among patients with eGFR of less than 60 ml/min/1.73 m² (31.9%), as compared with patients with an eGFR of 60 to 89 ml/min/1.73 m² and of 90 ml/min/1.73 m² or more (25.1% and 20.8%, respectively, $P < 0.001$).

In addition, total cholesterol, LDL cholesterol, and triglyceride levels were higher in patients with resistant and uncontrolled hypertension, as compared with patients with controlled hypertension (TABLE 1). Patients with RHT and uncontrolled hypertension had LDL cholesterol levels within the therapeutic range less often than those with controlled hypertension (TABLE 2). Also, among patients treated with statins, the rate of achieved LDL goals was lower in patients with resistant and uncontrolled hypertension, as compared with those with controlled hypertension (36.3% and 35.4% vs. 49.2%; $P < 0.001$).

Patients with diabetes, CAD, and CVD had a higher rate of RHT compared with patients without these diseases (32.5% vs. 22.6%; $P < 0.001$, 31.5% vs. 19.7%; $P < 0.001$; 33.3% vs. 23.6%; $P < 0.001$, respectively). Also, these diseases were more frequent among patients with RHT compared with patients with controlled hypertension (TABLE 2). There were no differences in the rates of these diseases between patients with controlled and uncontrolled hypertension. Other diseases including arrhythmias, heart failure, chronic kidney disease (CKD), chronic obstructive pulmonary disease, diseases requiring the use of non-steroidal anti-inflammatory drugs, benign prostatic hyperplasia in men, depression or anxiety, and diseases causing disability were more frequent in patients with RHT, but not in patients with uncontrolled hypertension, as compared with controlled hypertension (TABLE 2).

TABLE 3 shows the analysis of antihypertensive treatment in relation to BP control. Patients with uncontrolled hypertension, as compared with patients with controlled hypertension, received a lower number of antihypertensive medications (TABLE 1) and less often used thiazide diuretics, β -blockers, and calcium channel blockers, but not drugs inhibiting the renin-angiotensin-aldosterone system (TABLE 3). Patients with RHT more often used antihypertensive drugs of all classes, as compared with patients with controlled hypertension (TABLE 3).

We analyzed the rate of use of antihypertensive drug combinations and showed an underuse

TABLE 1 Characteristics of patients with controlled, uncontrolled and resistant hypertension in the studied group

	n	Controlled HT	Uncontrolled HT	Resistant HT	<i>P</i> ^a	<i>P</i> ^b	<i>P</i> ^c
number	12 375	5857	3458	3060	–	–	–
sex, % of women	12 375	59.3	57.8	59.9	0.17	0.13	0.61
age, y	12 375	63.6 ± 12.4	62.6 ± 12.8	66.3 ± 11.3	<0.001	<0.001	<0.001
BMI, kg/m ²	12 094	28.5 ± 4.4	28.8 ± 4.5	30.1 ± 4.9	<0.001	0.010	<0.001
abdominal obesity, %	12 264	50.6	51.8	62.7	<0.001	0.28	<0.001
systolic BP, mmHg	12 375	128 ± 8	150 ± 13	152 ± 13	<0.001	<0.001	<0.001
diastolic BP, mmHg	12 375	80 ± 6	89 ± 13	90 ± 13	<0.001	0.023	<0.001
pulse pressure, mmHg	12 375	50 ± 7	60 ± 16	63 ± 17	<0.001	<0.001	<0.001
number of antihypertensive drugs, n	12 375	2 (2–3)	2 (2–2)	3 (3–4)	<0.001	<0.001	<0.001
sodium, mmol/l	7230	140.0 ± 3.6	140.3 ± 4.2	140.2 ± 3.9	0.008	0.014	0.030
potassium, mmol/l	7911	4.40 ± 0.42	4.37 ± 0.43	4.37 ± 0.43	0.023	0.024	0.024
creatinine concentration, μmol/l	8669	97.8 ± 90.6	97.1 ± 91.3	96.1 ± 69.3	0.78	0.95	0.69
eGFR, ml/min/1.73 m ²	8669	73.7 ± 23.7	74.9 ± 24.1	70.1 ± 22.7	<0.001	0.13	<0.001
glucose, mmol/l	10 647	5.58 ± 1.28	5.64 ± 1.36	5.92 ± 1.40	<0.001	0.073	<0.001
total cholesterol, mmol/l	9406	5.2 ± 1.1	5.5 ± 1.1	5.5 ± 1.1	<0.001	<0.001	<0.001
LDL cholesterol, mmol/l	8710	3.1 ± 0.9	3.3 ± 1.0	3.3 ± 1.0	<0.001	<0.001	<0.001
HDL cholesterol, mmol/l							
women	5143	1.5 ± 0.7	1.5 ± 0.7	1.4 ± 1.0	0.38	0.99	0.34
men	3653	1.3 ± 0.7	1.3 ± 0.9	1.3 ± 0.6	0.70	0.80	0.91
triglycerides, mmol/l	9734	1.6 ± 0.7	1.7 ± 0.7	1.8 ± 0.9	<0.001	<0.001	<0.001

Data are presented as mean ± 1 standard deviation or median (interquartile range). Categorical variables are shown as proportions.

a for comparison between 3 groups; **b** for comparison between patients with controlled and uncontrolled hypertension; **c** for comparison between patients with controlled and resistant hypertension

Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein

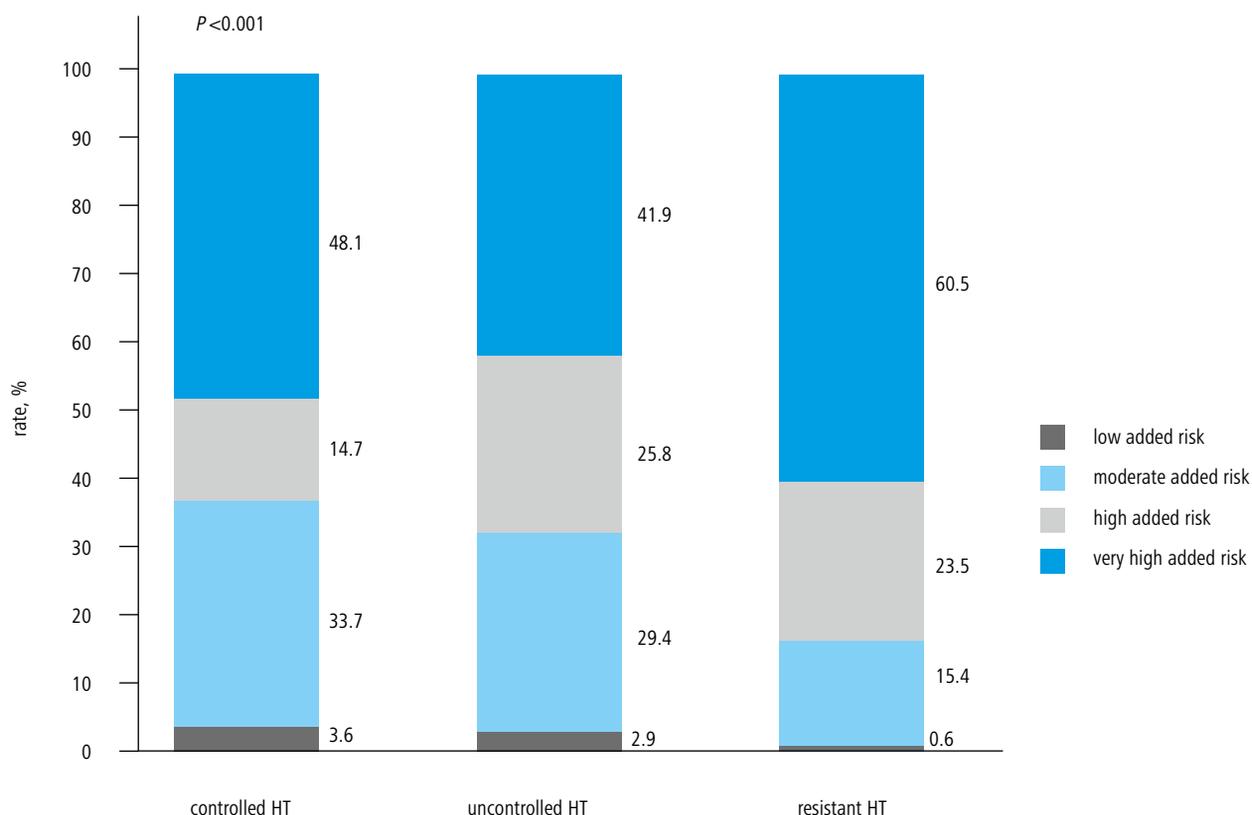


FIGURE 3 Cardiovascular risk stratification in patients with controlled, uncontrolled, and resistant hypertension (HT), according to the 2013 European Society of Hypertension/European Society of Cardiology

TABLE 2 Frequency of coexisting diseases in patients with controlled, uncontrolled, and resistant hypertension in the study group

	n	Controlled HT	Uncontrolled HT	Resistant HT	P ^a	P ^b	P ^c
number	12 375	5857	3548	3060			
diabetes, %	12 227	20.7	19.0	29.3	<0.001	0.052	<0.001
metabolic syndrome, %	12 375	50.8	47.5	66.3	<0.001	0.002	<0.001
coronary artery disease, %	11 553	42.2	37.1	55.9	<0.001	<0.001	<0.001
cerebrovascular disease, %	11 373	10.8	9.8	15.8	<0.001	0.17	<0.001
arrhythmias, %	11 451	29.0	24.0	38.3	<0.001	<0.001	<0.001
heart failure, %	11 414	15.8	11.4	26.9	<0.001	<0.001	<0.001
eGFR <60 ml/min/1.73 m ² , %	8669	26.7	24.6	34.4	0.001	0.064	<0.001
LDL cholesterol below the goal, %	8710	50.8	38.4	38.5	<0.001	<0.001	<0.001
LDL cholesterol below the goal, % ^d	6529	49.1	35.9	36.4	<0.001	<0.001	<0.001
chronic diseases requiring NSAIDs treatment, %	11 411	20.9	22.3	28.9	<0.001	0.106	<0.001
depression / anxiety, %	11 401	15.9	16.0	19.3	<0.001	0.85	<0.001
benign prostatic hyperplasia M, %	4649	28.3	26.0	35.2	<0.001	0.095	<0.001
COPD, %	11 277	8.7	7.5	10.0	0.003	0.060	0.045
diseases causing disability, %	11 341	10.0	11.4	15.5	<0.001	0.047	<0.001

Variables are shown as proportions.

a for comparison between 3 groups; **b** for comparison between patients with controlled and uncontrolled hypertension; **c** for comparison between patients with controlled and resistant hypertension; **d** patients treated with lipid lowering drugs

Abbreviations: COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs, others, see **TABLE 2**

TABLE 3 Antihypertensive treatment in patients with controlled, uncontrolled, and resistant hypertension in the study group

	n	Controlled HT	Uncontrolled HT	Resistant HT	P ^a	P ^b	P ^c
number	12 375	5857	3548	3060			
ACEIs, %	12 375	60.0	60.0	65.3	<0.001	0.97	<0.001
ABRs, %	12 375	32.9	31.5	44.2	<0.001	0.17	<0.001
ACEIs or ARBs, %	12 375	88.3	87.0	96.4	<0.001	0.064	<0.001
β-blockers, %	12 375	56.7	42.9	74.1	<0.001	<0.001	<0.001
CCBs, %	12 375	32.2	28.4	53.6	<0.001	<0.001	<0.001
TDs, %	12 375	45.4	24.0	80.2	<0.001	<0.001	<0.001
loop diuretics	12 375	10.1	2.3	23.4	<0.001	<0.001	<0.001
mineralocorticoid receptor antagonists, %	12 375	9.2	5.6	14.7	<0.001	<0.001	<0.001
any diuretic, %	12 375	54.2	26.4	100.0	<0.001	<0.001	<0.001
β-blockers, %	12 375	2.2	1.4	4.8	<0.001	0.012	<0.001
centrally acting drugs, %	12 375	0.4	0.5	1.9	<0.001	0.60	<0.001
statins, %	11 502	71.0	65.3	79.1	<0.001	<0.001	<0.001
fibrates, %	9726	8.5	8.6	14.1	<0.001	0.98	<0.001
acetylsalicylic acid, %	10 957	64.1	56.7	76.9	<0.001	<0.001	<0.001

Variables are shown as proportions.

a for comparison between 3 groups; **b** for comparison between patients with controlled and uncontrolled hypertension; **c** for comparison between patients with controlled and resistant hypertension

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; TDs, thiazide/thiazide-type diuretics; others, see **TABLE 1**

of preferred drug combinations (**FIGURE 4** and *Supplementary material online, Figures S3-6*). The rate of use of preferred drug combinations was lower in patients with uncontrolled hypertension, as compared with those with controlled hypertension (*Supplementary material online, Figure S6*). Patients with RHT were characterized by a higher

rate of use of preferred drug combinations (*Supplementary material online, Figure S6*); however, the rate of use of the most preferred 3-drug combination (angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker and calcium channel blocker and thiazide/thiazide-type diuretic) was 41.7%. We observed significant differences

FIGURE 4 Rate of use of the most preferred 3-drug combinations (angiotensin-converting enzyme inhibitor / angiotensin II receptor blocker and calcium channel blocker, and thiazide/thiazide-type diuretic) in relation to coexisting clinical conditions in patients with resistant hypertension. P value for comparison between patients with and without coexisting clinical condition. Abbreviations: see TABLES 1 and 3

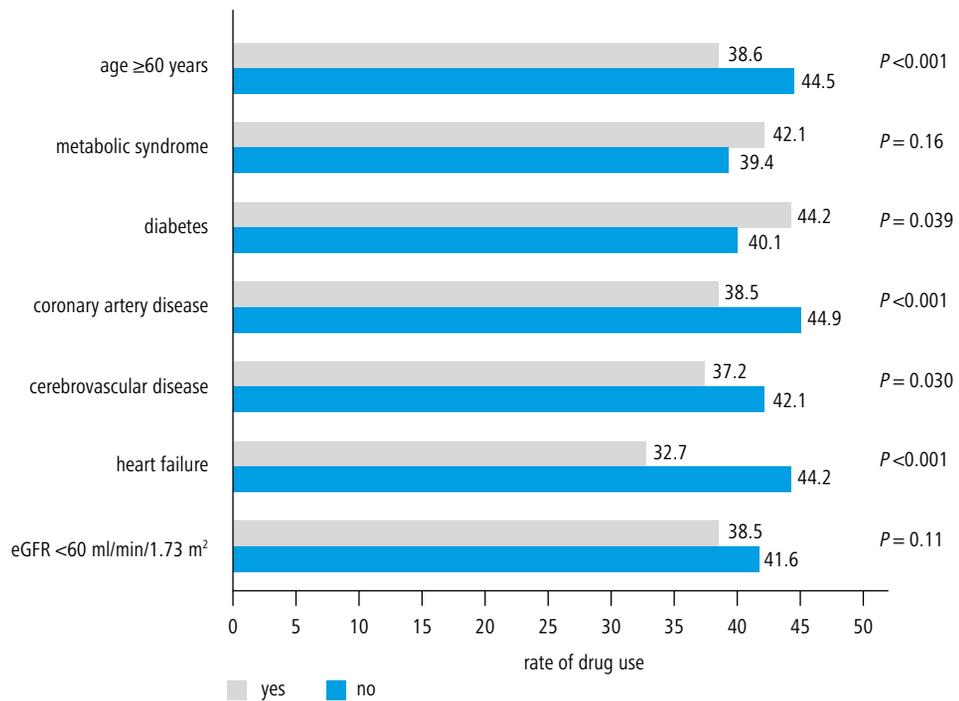


TABLE 4 Multivariate model assessing an independent association of factors with the presence of resistant hypertension

Factors related with resistant hypertension	OR	95% CI	P value
male sex	1.17	1.03–1.32	0.015
age ^a	–	–	–
pulse pressure ^b	1.77	1.69–1.86	<0.001
abdominal obesity	1.20	1.03–1.39	0.017
metabolic syndrome	1.46	1.24–1.72	<0.001
diabetes	1.16	1.01–1.33	0.031
coronary artery disease	1.62	1.45–1.82	<0.001
cerebrovascular disease	1.20	1.01–1.42	0.036
treatment with NSAIDs	1.25	1.10–1.43	0.001
diseases causing disability	–	–	–
depression / anxiety	–	–	–
eGFR <60 ml/min/1.73 m²	1.27	1.12–1.45	<0.001

a for 10-year increase; **b** for 10-mmHg increase

Abbreviations: CI, confidence interval; OR, odds ratio; others, see TABLES 1 and 2

in the rate of use of this combination in relation to coexisting clinical conditions in patients with RHT (FIGURE 4). Further analysis also revealed that in patients with RHT, a decline in eGFR was accompanied by an increase in the use of loop diuretics and decrease in the use of thiazide/thiazide-type diuretics. However, still in patients with an eGFR of less than 30 ml/min/1.73 m², the rates of use of the respective drug classes were 53.1% and 58.1% (Supplementary material online, Table S1).

To assess which factors are independently related to RHT, we performed a multivariate analysis including sex, age, pulse pressure, abdominal obesity, metabolic syndrome, diabetes, CAD, CVD, diseases requiring treatment with nonsteroidal anti-inflammatory drugs, diseases causing disability, depression or anxiety, and an eGFR

of less than 60 ml/min/1.73 m². The presence of RHT was independently associated with male sex, higher pulse pressure, abdominal obesity, metabolic syndrome, diabetes, CAD, CVD, diseases requiring treatment with nonsteroidal anti-inflammatory drugs, and an eGFR of less than 60 ml/min/1.73 m² (TABLE 4).

DISCUSSION Our study has shown that the prevalence of RHT in treated patients with hypertension was 24.7%, indicating a relatively high rate of apparent RHT. Our data indicates also variability in the prevalence of RHT between individual Polish provinces. This might be due to the differences in patients' clinical characteristics, social and economic status, as well as access to health care facilities. Interestingly, the differences in hypertension control rate between

individual Polish provinces were also revealed in the WOBASZ study.¹²

Observational studies have reported a prevalence of RHT of 12% to 15%, whereas randomized control trials have shown higher rates, leading us to conclude that the prevalence of RHT in treated patients with hypertension is somewhere in the range between 15% and 30%. Based on a recent meta-analysis by Achelrod et al.,¹³ the prevalence of RHT in this population is 13.72%, according to 20 observational studies and 16.32% according to 4 randomized control trials performed in Western Europe and North America. However, limited data are available on the prevalence and clinical characteristics of RHT in Central and East European countries.^{9,13-15}

The results of the BP-CARE study⁸ allowed to assess the prevalence and main clinical features of RHT in a group of 1312 subjects from 9 countries of Central and Eastern Europe. The results based on the clinical values of BP showed that the prevalence of apparent RHT was 32.3% and was higher than in our Pol-Focus study. In the BP-CARE study, after implementation of screening based on 24-hour ambulatory BP measurement, the prevalence decreased to 19.4%.⁸

Our results indicate that the prevalence of RHT increased with age and was the highest in the group of patients over 65 years of age (28.1%), as compared to those younger than 40 years of age (12.8%). Various independent studies have shown that older age was among the main clinical features that differentiate patients with RHT from those with controlled hypertension. Also, a large international survey showed that BP control is largely unsuccessful with increasing age, and the use of more than 3 antihypertensive drugs increased with age, from 16.1% at the age of 18 to 40 years to 37.8% at the age of more than 75 years. However, despite an increase in the number of drugs prescribed and the usage of efficacious drug classes, the age-related rise in systolic BP was not balanced by a more effective hypertension management, as evidenced by an age-related decrease in the rate of systolic BP control.¹⁶⁻¹⁸

Our results indicate that the prevalence of vascular risk factors including obesity, hyperlipidemia, diabetes, CAD, or CVD was higher in subjects with RHT, as compared with patients with controlled hypertension. The results of the other studies performed so far indicate that patients with a diagnosis of RHT often present with a cluster of cardiovascular risk factors such as obesity, diabetes, CAD, CVD, or some degree of CKD. On the other hand, several studies have reported a higher prevalence of subclinical target organ damage in patients with RHT as compared with those with controlled hypertension.^{16,14-21}

The evaluation of cardiovascular risk according to the 2013 ESH/ESC guidelines showed that, in our RHT group, the prevalence of the high and very high cardiovascular risk was significantly more frequent, as compared with the controlled and uncontrolled hypertension groups. Also, the

results of the BP-CARE study confirmed the relationship between true RHT and other conditions characterized by high or very high cardiovascular risk in East European populations.⁸ Therefore, our data and BP-CARE study results support the concept that both the presence of concomitant conditions such as obesity, history of diabetes, CAD, or CVD and persistent elevation of BP potentiate the cardiovascular risk in patients with RHT, making it much higher than that observed in patients without RHT.⁸ This may also partially explain the higher percentage of subjects with RHT seen by specialists, since the referred patients may carry a higher burden of cardiovascular diseases contributing to the development and progression of RHT, as compared with those treated by GPs.²⁰⁻²³

Recent studies, including the Cardiovascular Research Network hypertension registry and the REACH registry,⁷ have also indicated that the presence of RHT is associated with an increased risk of major cardiovascular events and death, regardless of BP control. Specifically, compared with controlled hypertension, RHT was strongly associated with an increased risk of all-cause mortality, cardiovascular mortality, and nonfatal stroke; however, an association with nonfatal myocardial infarction was not observed in all studies.^{7,16,22,24-26}

Our results indicate that the prevalence of CAD was higher in subjects with RHT, as compared with patients with controlled hypertension. CAD was also independently associated with the presence of RHT in a multivariate model. Thus, it seems reasonable that patients with RHT had more severe vascular diseases in general. The post hoc analysis from the INVEST study²⁰ suggested that RHT is common in individuals with hypertension and CAD, with a prevalence of approximately 38%. It has also been found that the presence of RHT is associated with an increased risk of major cardiovascular events and death, regardless of BP control, compared with controlled hypertension.^{19,20}

Our study showed that the percentage of subjects with impaired kidney excretory function (eGFR <60 ml/min/1.73 m²) was significantly higher in patients with RHT compared with those with controlled hypertension. Also, in our study, lower eGFR was associated with RHT in a multivariate model. Renal data from clinical studies are consistent with a well-established relationship between RHT and CKD, the nature of which is likely to be bidirectional. RHT may be adversely affecting renal function and also CKD may be reducing the response to antihypertensive treatment, due to sodium retention and increased activity of the renin-angiotensin-aldosterone and sympathetic nervous systems. Therefore, CKD could be both the cause and effect of RHT.^{16,21,22,27}

In addition, the higher prevalence of renal dysfunction in patients with versus those without RHT may be due to higher pulse pressure values seen in our study, which were shown to

be associated with a detrimental effect on renal vasculature. There is also evidence that elevated pulse pressure, which reflects reduced vascular compliance in large arteries, may predict negative outcomes better than either systolic or diastolic BP alone.²⁸

Our results showed that both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were used in most of the patients with RHT, followed by thiazide/thiazide-type diuretics, β -blockers, and calcium channel blockers. The evaluation of the preferred drug combination scheme based on the 2013 ESH/ESC guidelines showed that a regimen consisting of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, calcium channel blocker and thiazide/thiazide-type was used in less than half of the patients with RHT, more often in those with coexisting metabolic syndrome or diabetes. Other drug combinations within the triple-drug regimens are rather difficult to explain, and several reasons should be taken into consideration, including physicians' perceptions, the level of co-payment, or patients' belief in the effectiveness of medications and side effects of particular drug classes.^{2,29,30} Secondly, for certain classes of medications, such as angiotensin-converting enzyme inhibitors, β -blockers, and diuretics, it is unknown whether they were prescribed for the treatment of hypertension or for other indications such as CAD or heart failure.²²

Our study also indicates the inadequate use of loop diuretics in patients with RHT associated with impaired kidney excretory function. It is particularly seen in subjects with an eGFR of less than 30 ml/min/1.73 m², and, in this group, 58% of the patients were taking thiazide/thiazide-type diuretics insufficient to counteract the sodium retention typical for this condition. It might be postulated that this might be contributed to the higher rate of RHT in patients with impaired kidney excretory function.

In our study, although the rate of treatment with aldosterone antagonists was higher in patients with RHT than in patients with controlled hypertension, it was relatively low (14.7%). Similar results were described recently by other authors indicating that the underuse of aldosterone antagonists may explain why therapeutic strategies fail to bring BP to its goal and such an optimization of the therapy should help to control BP.^{22,31-34}

A major strength in this study is that we analyzed RHT in a large cohort of patients in Poland characterized by clinical features and cluster of cardiovascular risk factors being treated by both specialists and GPs. The clinical setting of our study have been successfully used before in Poland in other studies.^{35,36}

Our study has certain limitations. First, the adherence to antihypertensive treatment could not be assessed or controlled. Our estimation was based on the physician's judgment of the patient's adherence to treatment. The lower rate of

patients with LDL cholesterol levels below the treatment goal among patients with RHT might suggest their nonadherence to a recommended treatment.

Moreover, we based our analysis on clinical BP measurements, and BP monitoring was not used to exclude those with white coat hypertension. Another limitation, typical for observational studies, is the lack of forced titrated treatment. Therefore, among patients with uncontrolled hypertension treated with 2 or even 3 drugs (without diuretic), there is a potential subgroup of patients with RHT. Yet another limitation was the cross-sectional design of the study, which did not allow to examine the effect of RHT on the development and progression of complications. The prevalence of RHT could have been overestimated, since secondary forms of hypertension were not assessed; therefore, we cannot exclude the possibility that some patients with secondary hypertension were misclassified as having RHT.

Also, most participating patients underwent a laboratory examination and a substantial percentage did not undergo a carotid ultrasound or microalbuminuria estimation before the evaluation. The lack of this information about vascular and renal target organ damage may have led to an underestimation of cardiovascular risk in these patients.

In conclusion, our study based on a large group of treated hypertensive patients has shown that RHT is relatively common both in GP and specialist offices. The underuse of preferred antihypertensive drug combinations may contribute to uncontrolled BP levels. Moreover, patients with RHT are characterized by a high or very high cardiovascular risk.

Contribution statement AP, MK, JG, MK, DC, KKJ, KN, and AJ conceived the idea for the study. AP, MK, JG, RTM, and WL contributed to the design of the research. RTM and WL were involved in data collection. AP, MK, JG, RTM, and AJ analyzed the data. AP and AJ coordinated the funding of the project. All authors edited and approved the final version of the manuscript.

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Conflict of interest AP has received lecturer's honoraria and travel expenses from Servier, Krka, Berlin-Chemie/Menarini, Polpharma, Medtronic, and Zentiva. KKJ has received lecturer's honoraria from Polpharma and travel expenses from Servier. KN has received lecturer's honoraria and travel expenses from Servier, Krka, Berlin-Chemie/Menarini, Polpharma, Medtronic, Bayer, and Adamed. AJ has received lecturer's honoraria and travel expenses from Servier, Krka, Berlin-Chemie/Menarini, Polpharma, Medtronic, Zentiva, Abbott, and Adamed.

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Czynniki związane z nadciśnieniem tętniczym opornym oceniane w dużej grupie chorych na nadciśnienie tętnicze – badanie Pol-Fokus

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SŁOWA KLUCZOWE

leczenie nadciśnienia tętniczego, nadciśnienie tętnicze oporne, ryzyko sercowo-naczyniowe

ABSTRAKT

WPROWADZENIE Chorzy z nadciśnieniem tętniczym (NT) opornym charakteryzują się wysokim ryzykiem zdarzeń związanych z chorobą wieńcową (ChW) i chorobą naczyniowo-mózgową (ChNM) w porównaniu z ogólną populacją chorych na NT.

CELE Celem badania była ocena czynników ryzyka związanych z NT opornym w dużej grupie chorych na NT będących pod opieką lekarzy rodzinnych i specjalistów w Polsce.

PACJENCI I METODY Do badania włączono 12 375 chorych (średni wiek 64,0 ± 12,3 roku; zakres 18–98 lat; 59% kobiet) z NT leczonym od co najmniej roku. Chorych podzielono na trzy grupy: z kontrolowanym NT, niekontrolowanym NT (nie spełniającym kryteriów dla NT opornego) i NT opornym.

WYNIKI Kontrolowane NT, niekontrolowane NT i NT oporne stwierdzono odpowiednio u 47,3%, 27,9% i 24,7% chorych. NT oporne występowało częściej u chorych pod opieką specjalistów (29,8%) oraz u chorych z cukrzycą (32,5%), ChW (31,5%), ChNM (33,3%) i upośledzoną funkcją nerek (31,9%). Chorzy z NT opornym charakteryzowali się najwyższą częstością występowania wysokiego (23,5%) i bardzo wysokiego (60,5%) dodanego ryzyka sercowo-naczyniowego. Stwierdzono niewystarczające stosowanie preferowanych skojarzeń leków hipotensyjnych i antagonistów aldosteronu u chorych z niekontrolowanym NT i NT opornym. W analizie wieloczynnikowej NT oporne było niezależnie związane z: płcią męską, wyższym ciśnieniem tętna, zespołem metabolicznym, cukrzycą, ChW, ChNM, chorobami wymagającymi leczenia niesteroidowymi lekami przeciwzapalnymi i szacunkowym współczynnikiem filtracji kłębuszkowej < 60 ml/min/1,73 m².

WNIOSKI Chorzy z NT opornym w znaczącej większości są obciążeni wysokim lub bardzo wysokim ryzykiem sercowo-naczyniowym. Ponadto wykazano niezadawalające wykorzystanie preferowanych skojarzeń lekowych i antagonistów aldosteronu.

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Supplementary material online

Factors associated with resistant hypertension in a large cohort of hypertensive patients

- Pol-Fokus study

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Supplementary figure 1.

Prevalence of controlled, uncontrolled and resistant hypertension in individual provinces of Poland (respective rates on the map).



$P < 0.001$

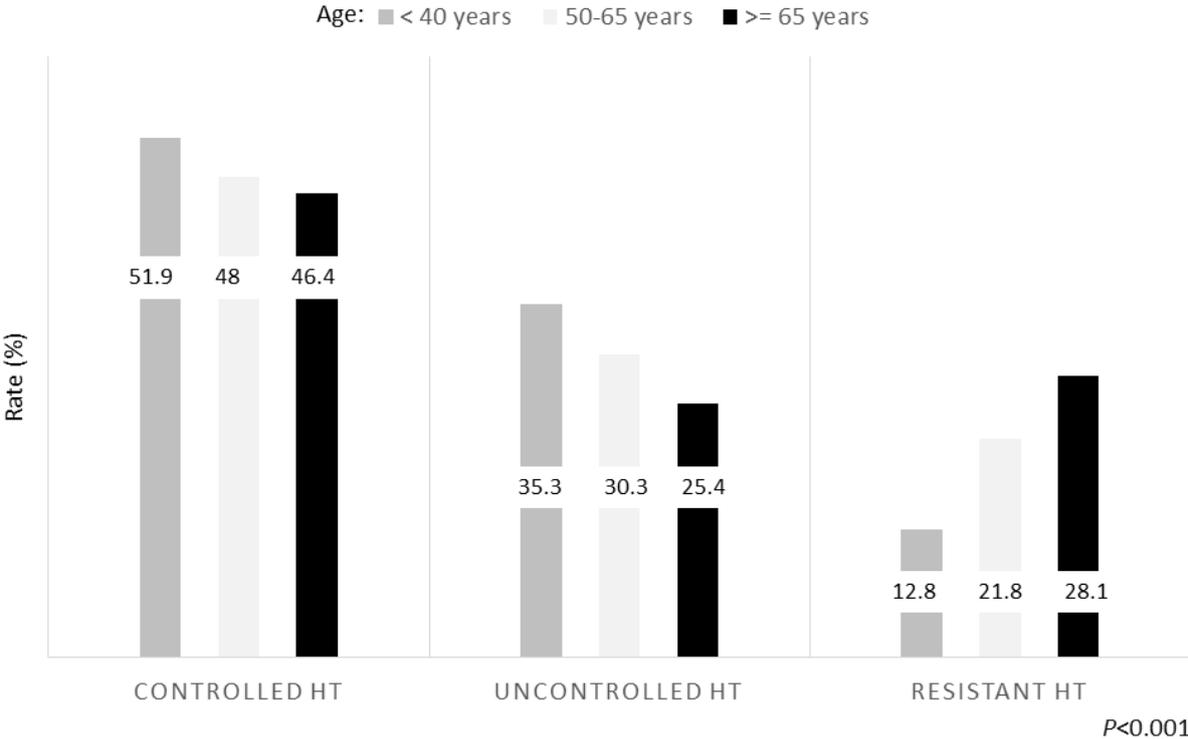
Supplementary table 1. Frequency of use of thiazide/thiazide-type diuretics, loop diuretics and aldosterone antagonists in patients with resistant hypertension in relation to eGFR category.

e GFR, ml/min/1.73m ²	eGFR category				<i>P</i>
	<30	30-60	60-90	≥90	
Number of patients, n	43	737	1122	363	
Thiazide/thiazide-type diuretics, n; %	25; 58.1	510; 69.2	908; 80.9	302; 83.2	<0.001
Loop diuretics, n; %	23; 53.5	253; 34.3	256; 22.8	70; 19.3	<0.001
Aldosterone antagonists, n; %	5; 11.6	132; 17.9	192; 17.1	38; 10.5	<0.001

eGFR – estimated glomerular filtration rate, n – number of patients

Supplementary figure 2. Prevalence of controlled, uncontrolled and resistant hypertension (%) across the age categories <40 years, 40-65 years and ≥65 years.

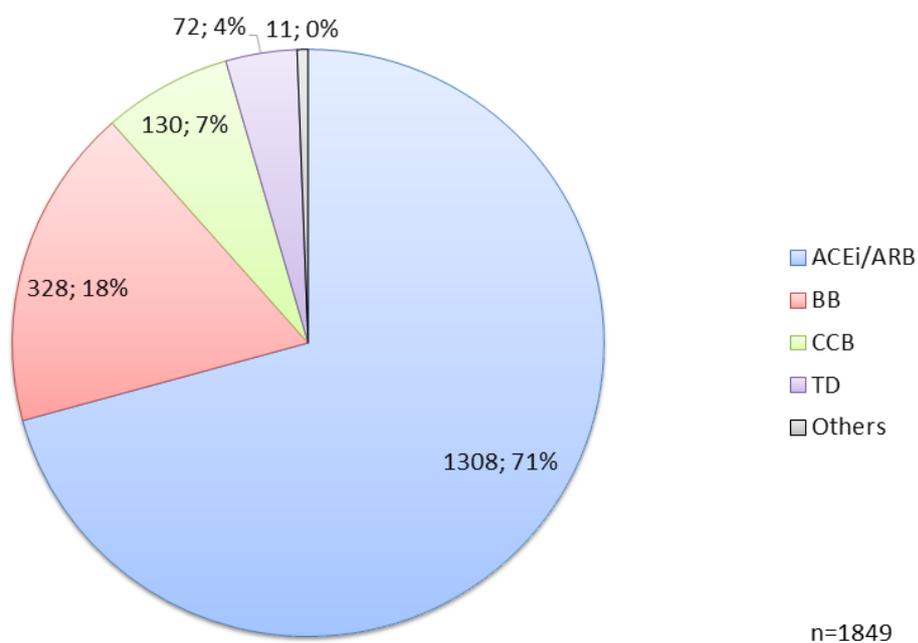
HT - hypertension



Supplementary figure 3.

Rate of use of antihypertensive drugs among patients on one antihypertensive drug. Data are presented as a number of patients and rate.

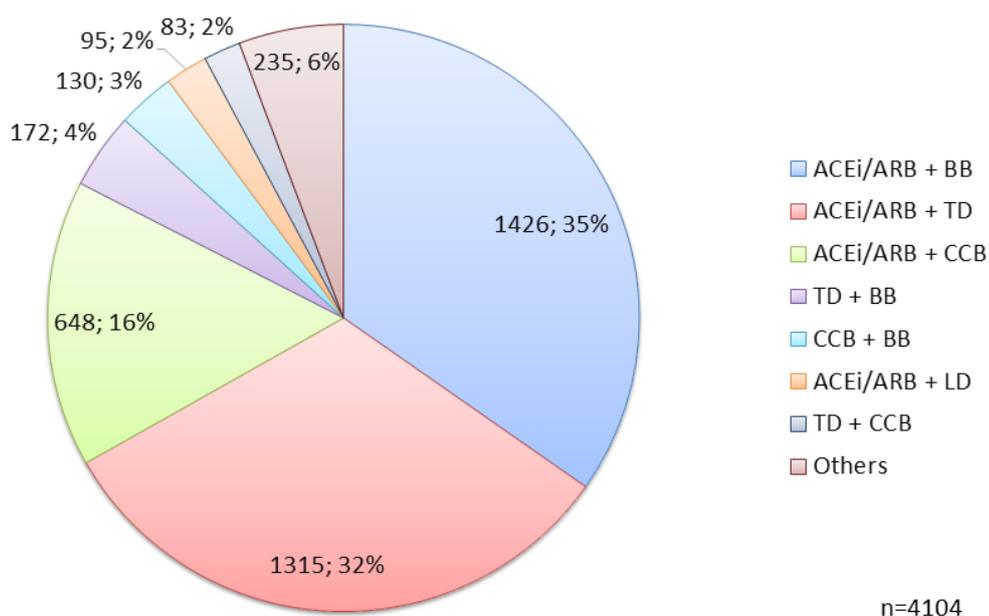
ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin II receptor blocker, BB – beta-blocker, CCB – calcium channel blocker, n – number of patients, TD – thiazide/thiazide-type diuretic.



Supplementary figure 4.

Rate of use of antihypertensive drugs combinations among patients on two antihypertensive drugs. Data are presented as a number of patients and rate.

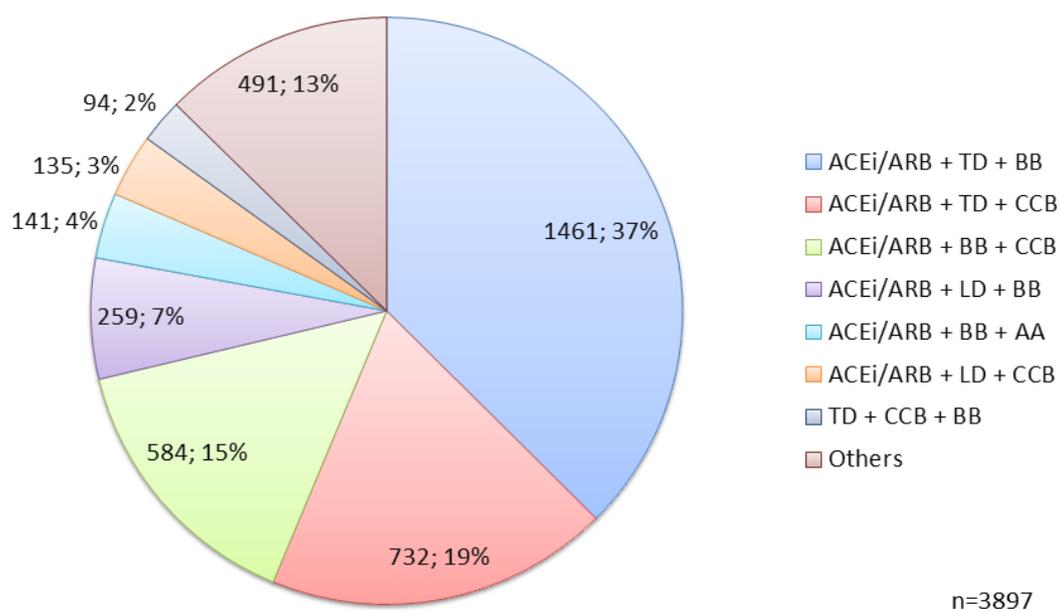
ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin II receptor blocker, BB – beta-blocker, CCB – calcium channel blocker, LD – loop diuretic, n – number of patients, TD – thiazide/thiazide-type diuretic.



Supplementary figure 5.

Rate of use of antihypertensive drugs combinations among patients on three antihypertensive drugs. Data are presented as a number of patients and rate.

AA – aldosterone antagonists, ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin II receptor blocker, BB – beta-blocker, CCB – calcium channel blocker, LD – loop diuretic, n – number of patients, TD – thiazide/thiazide-type diuretic.



Supplementary figure 6.

Rate of use of preferred antihypertensive drugs combinations among patients with controlled, uncontrolled and resistant hypertension.

ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin II receptor blocker, CCB – calcium channel blocker, HT – hypertension, TD – thiazide/thiazide-type diuretic

