VILNIUS UNIVERSITY

Vytautas
JUKNEVIČIUS

Evaluation of Patients with Resistant Arterial Hypertension before and after Pharmacological Treatment Correction or a Renal Artery Sympathetic Denervation Procedure

SUMMARY OF DOCTORAL DISSERTATION

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Rezistentiška arterine hipertenzija sergančių pacientų įvertinimas koregavus medikamentinį gydymą bei po simpatinės inkstų arterijų denervacijos

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CONTENTS

ABBREVIATIONS

AH – arterial hypertension
AHI – apnoea-hypopnea index
ABP – arterial blood pressure
ACC – American College of Cardiology
AHA – American Heart Association
AVN – atrioventricular node
BNP – B-type natriuretic peptide
DM – diabetes mellitus
DBP – diastolic blood pressure
US – ultrasound examination (echocardiography)
ECG – electrocardiogram
EF – ejection fraction
IQR – interquartile range
BMI – body mass index
CHD – coronary heart disease
CKD – chronic kidney disease
MED – Medication treatment corrective group
MI – myocardial infarction
NSAIDs – nonsteroidal anti-inflammatory drugs
CI – confidence interval
AF – atrial fibrillation
RAAS – renin-angiotensin-aldosterone system
ROC – receiver operating characteristics
SBP – systolic blood pressure
RASD – renal artery sympathetic denervation
SD – standard deviation
SNS – sympathetic nervous system
HR – heart rate
HF – heart failure
VUH SK – Vilnius University Hospital Santaros Klinikos

1. INTRODUCTION

1.1. The problem and relevance of the study

Arterial hypertension (AH) is a major risk factor for cardiovascular disease, stroke, disability, and overall mortality. According to the results of office arterial blood pressure measurements, in 2015, 1.13 billion people worldwide had arterial hypertension [1], of which 150 million in Europe [2, 3]. In 2015, 30% -45% of adults worldwide had hypertension of which 24% were adult men and 20% female [4]. The prevalence of hypertension is increasing regardless of a national level of economic development. As the world's population ages, obesity, sedentary lifestyle, and an unbalanced diet increase, the global prevalence of hypertension in the world is expected to increase (15-25%) and could reach 1.5 billion people in 2025. In large-scale follow-up studies, patients with poorly controlled arterial blood pressure had a 32% increased risk of end-stage chronic kidney disease, 24% increase in coronary heart disease, 46% increase in heart failure, and 6% overall risk of death [5].

Over the past 30 years, despite increasing public attention and awareness of the disease, some patients are still failing to meet their target blood pressure values.

In 2007, the European Society of Cardiology released guidelines [6] defining resistant hypertension as a condition in which the target arterial blood pressure (<130/80 mm Hg) cannot be reached with three different classes of antihypertensive drugs, one of which being a diuretic. In this document, resistant and refractory hypertension were used as synonyms, and all classes of antihypertensive drugs were recognized as suitable for initiating hypertension treatment, regardless of the pharmacological properties of individual classes of drugs and the etiology or pathophysiology of hypertension. However, this document emphasizes that non-compliance with the treatment regimen is identified as a major cause of uncorrected arterial blood pressure.

The 2008 definition of resistant arterial hypertension refers to a condition in which 3 different classes of antihypertensive drugs are administered at optimal doses (excluding drug classes), one of which is a diuretic, and the target ABP exceeds 140/90 mm Hg. This definition also recommends classifying resistant hypertension as conditions in which arterial blood pressure is corrected by the administration of 4 or more antihypertensive drugs [7, 8]. This document by the American Heart Association highlights that non-compliance with treatment regimens is more of a problem in the primary health care chain with only about 16% of patients not following treatment prescribed by medical professionals [7].

Introduced in 2009, catheter-based renal artery sympathetic denervation procedures have focused a great deal of attention on this topical problem among interventional cardiologists. The contradictory results of Simplicity HTN-3 study in 2014, which failed to demonstrate the benefit of renal artery sympathetic denervation in reducing ABP compared to a mock group, boosted the global focus on the problem of resistant hypertension in general [9]. In the course of the research, new concepts emerged in the scientific literature - *true* resistant hypertension, *presumed* resistant hypertension and *pseudo*-resistant hypertension. The true prevalence of resistant hypertension has long been questioned in the literature, ranging from 5 to 30% according to various sources and in different populations [10]. A number of meta-analyzes of the literature have been performed, one of the largest of which appeared in 2019 and covered 91 clinical trials in 3.2 million patients with hypertension, had demonstrated that true treatment-refractory resistant hypertension was confirmed in 10.3% of hypertensive patients, in 14.7% of patients with presumed resistant hypertension, and in 10.3% of patients with pseudo-resistant hypertension [11]. Therefore, the *presumed* resistant hypertension and *pseudo*-resistant hypertension, given the prevalence of AH globally and health risks of high blood pressure, has become a widely studied area, one of the most important being the treatment regimen, its optimization, and ways to ensure adherence.

An updated definition of resistant hypertension by the American Heart Association and the American College of Cardiology appeared in 2017 [12], and updated guidelines from the European Society of Cardiology appeared in 2018 [3]. In these important documents target ABP values (<130/80 mmHg and <140/90 mm Hg, respectively) and the groups of medications essential for the diagnosis of resistant hypertension differ. These methodological differences may lead to different study results in different treatment centres. Also, for demographic reasons, it is difficult to provide universal treatment guidelines for different countries, therefore, research even in relatively small centres and their adaptation to the local population is important.

Since 2012, catheter-based renal artery sympathetic denervation procedures have been performed in Vilnius University Hospital Santaros Klinikos after which significant long-term improvement in ABP control and regression of left ventricular hypertrophy persisted [13]. In practice, the need for detailed examination and selection of patients with resistant hypertension, optimal selection of medication and / or intervention treatment, and monitoring of these patients emerged. This research addresses the above issues.

1.2. Research hypothesis

Pharmalogical treatment optimization or catheter-based renal artery denervation reduces arterial blood pressure in patients with resistant arterial hypertension, however, the effects on target organ damage vary.

1.3. Research objective

To evaluate and compare different treatment strategies for the treatment of resistant arterial hypertension based on changes in arterial blood pressure and clinical trial data, as well as changes in factors for target organ damage.

1.4. Research tasks

1. Analyze and compare patients' office arterial blood pressure measurements and 24-hour measurements using pharmacological and non-pharmacological treatment of arterial hypertension.
2. Evaluate target organ damage with the help of instrumental methods (echocardiography, chest wall resistance measurements, pulse wave velocity measurements, overnight polysomnography), laboratory diagnostic methods and correlate them to the control of arterial hypertension over the observation period.
3. Analyze along-term (48 months after the procedure) effect of catheter-based renal artery sympathetic denervation on arterial blood pressure and arterial stiffness.
4. Assess the significance of chest wall resistance measurements in the dynamics of arterial hypertension treatment and in the optimization of pharmacological treatment.
5. Analyse the influence of polypharmacy in the treatment of patients with resistant arterial hypertension.

1.5. Statements to be defended

1. In patients with resistant arterial hypertension, arterial blood pressure is reduced by a medication optimization strategy based on patient-tailored examination or by catheter-based renal artery sympathetic denervation.
2. The positive effect of antihypertensive treatment on the reduction of target organ damage after 6 months (left ventricular hypertrophy and arterial stiffness) is observed only in the sympathetic renal artery sympathetic denervation group.
3. In catheter-based renal artery sympathetic denervation, the observed antihypertensive effect is long-term and lasting for 48 months.
4. Polypharmacy and comorbidities have a negative impact on the control of arterial blood pressure.

1.6. Novelty of the study

There are currently no approved standardized methods for the diagnosis and treatment of resistant arterial hypertension in clinical practice. The schemes used by many hypertension centres and researchers are individual, and highly variable, based largely on individual researchers' decisions and experience [14] .

One of the objectives of this research is to evaluate the significance of chest wall resistance measurements in the study and treatment of patients with resistant AH. To date, these non-invasive hemodynamic measurements have been performed worldwide to optimize the treatment of patients with AH compared to empirical treatment regimens [15]. Studies in patients with resistant AH are not extensive, with testing conducted primarily in local populations. In Lithuania, chest wall resistance measurements are not routinely widespread, they are mainly used in outpatient treatment of heart failure, while studies in the treatment of resistant AH have not been performed at all.

Long-term follow-up data on patients after catheter-based renal artery sympathetic denervation are also one of the features of this study. Following this procedure, outpatient 24-hour blood pressure monitoring and arterial pulse wave velocity measurements were collected for up to 48 months of follow-up. These data are unique in Lithuania and globally.

2. METHODOLOGY

This study was performed using a prospective (n = 34) and retrospective (n = 72) methodology. The study was conducted at Vilnius University Hospital Santaros Klinikos under the permission from the Vilnius Regional Biomedical Research Ethics Committee to conduct biomedical research (No 158200-18/3-1011-511).

Subjects with resistant arterial hypertension were enrolled in the prospective study if:

- at least one month after treatment adjustment, the target arterial blood pressure was not reached. The follow-up of these subjects lasted for 6 months from the time of enrolment.
- catheter-based renal artery sympathetic denervation was performed no more than 48 months ago.

In the retrospective part of the study, the monitoring data of the subjects who underwent **c**atheter-based renal artery sympathetic denervation at Vilnius University Hospital Santaros Klinikos (in 2012-2017) were analyzed. Data from these subjects were compared to those from the prospective study period during the analogous follow-up period (from enrolment to 6 months).

Prior to the enrolment in the study, all subjects signed an informed consent form.

Enrolled subjects were interviewed, and the anonymized data on their health records were stored in a database specially designed for the study. Data from clinical trials, epidemiological, laboratory and instrumental analyses were collected.

The enrolment protocol and monitoring of the retrospective part in the study a was developed by the supervisor prof. Aleksandras Laucevičius and dr. Andrius Berūkštis. In 2012-2017, dr. A. Berūkštis performed the selection of this research group, catheter-based renal artery denervation, and monitoring from enrolment until 24 months after the procedure. The research of this group of subjects on sleep apnea was performed by the doctoral student Vytautas Juknevičius.

The enrolment protocol and monitoring of the prospective part was developed by the supervisor prof. Aleksandras Laucevičius and the doctoral student Vytautas Juknevičius. The selection and monitoring of the subjects and the monitoring of the retrospective part subjects from months 24-48 after the intervention procedure were performed independently by the doctoral student.

2.1. Enrolment protocol

In the prospective group (medication treatment corrective group, MED group), patients with diagnosed or suspected resistant arterial hypertension were referred for outpatient consultation with a cardiologist at Vilnius University Hospital Santaros Klinikos. During the initial visit, the patients were asked questions to determine risk factors and obtain information on their health history. Special attention was paid to the antihypertensive drugs currently taken, their regimen, previously taken medicines, and the reasons why they were discontinued. Information was also collected on comorbidities and medications for their treatment. During the initial visit, a further plan for secondary arterial hypertension was developed based on a patient's medical history, objective examination data, and laboratory tests.

During the initial visit, patients were recommended to follow certain lifestyle changes, as well as they were explained the importance of regular medication regime, and their drug therapies were adjusted in accordance with 2013 and 2018 guidelines of the European Society of Cardiology and the European Society of Hypertension [3, 16].

The second visit was scheduled one month later. If patients followed the prescribed treatment regimen, in addition to a standard office clinical examination, mean 24-hour measurement of arterial blood pressure was performed. If patients who had office elevated blood pressure (> 140/90 mm Hg) and / or mean 24-hour blood pressure above 130/80 mm Hg during the second visit and met the enrolment criteria, they were offered to participate in a biomedical study. They were explained about the study and treatment plan, the potential benefits and risks. Patients who agreed to participate in the study signed an informed consent form. Those who refused were provided with standard health care.

In the retrospective group (catheter-based renal artery sympathetic denervation (RASD)), subjects were patients with resistant arterial hypertension who underwent catheter-based renal artery sympathetic

denervation at VUH SK at least 48 months ago. They were called by phone to consult a cardiologist at VUH SK. All subjects signed new informed consent forms for participation in the biomedical study. During the visit, a medical history was collected, a routine clinical examination was carried out, and outpatient measurements of 24-hour arterial blood pressure and arterial stiffness were performed. In addition, if necessary, medical treatment was adjusted, repeated visits were given, consultations with other specialists were provided.

In the prospective part of the study, out of 176 patients enrolled, 34 subjects were included in the main study group. The most common reasons for exclusion were pseudo-resistant hypertension, permanent atrial fibrillation, and severe sleep apnea (when apnea-hypopnea index AHI> 15 per hour). Patients with secondary hypertension who refused further treatment or those who did not complete the study protocol were also excluded from this group. In the retrospective group, 49 subjects out of 73 patients who underwent sympathetic renal artery denervation were included in the final analysis of the data at 48 months.

2.2. Testing for secondary causes of arterial hypertension

Subjects in the prospective study group were studied for secondary causes of hypertension.

To exclude renal parenchymal diseases, serum creatinine and potassium levels were measured in all subjects, and outpatient urinalysis as well as ultrasound to visualize renal and adrenal morphology were evaluated. Moreover, all subjects, if not previously performed, underwent two ultrasound scans of renal arteries to rule out renal vascular pathology. If the above-mentioned examinations could not be evaluated due to poor ultrasound imaging quality, abdominal computed tomography was performed in an angiography mode. Patients with significant renal artery stenosis (> 80%) or worsening of renal disease were referred to a nephrologist's consultation for further treatment (n = 3).

Subjects were interviewed for symptoms characteristic of sleep apnea. They completed the Epworth Sleepiness Scale questionnaire with eight situations, where a subject noted the likelihood of falling asleep. Despite the likelihood of sleep apnea in the questionnaire, everyone underwent an outpatient study of overnight polysomnography. If apnea-hypopnea index (AHI) exceeded 15 breathing events per hour in this study, subjects were referred to an otorhinolaryngologist and pulmonologist for treatment of sleep apnea. The latter patients were not included in further study selection. In addition, patients who were already being treated with non-invasive pulmonary ventilation devices were not included in the next phase of the study. All other subjects with AHI <15 per hour or no indication for specific treatment of sleep apnea after consultation with a pulmonologist continued their participation in the study (n = 1).

The study of primary hyperaldosteronism in this group of subjects was complicated. As it was not possible to guarantee a standardized blood collection and interpretation conditions according to the current protocol of the facility [17], plasma aldosterone and plasma renin tests were not performed in all primary patients based on the prevalence and potential risks of the disease.

If subsequent imaging tests (kidney and adrenal glands ultrasound or abdominal computed tomography) revealed abnormalities characteristic of this adrenal pathology, and if there was a high anamnestic and clinical likelihood of this pathology, these patients were referred to an endocrinologist for diagnosis of primary hyperaldosteronism.

Subjects were tested for plasma free methanephrine and normetanephrine if they were younger than 40 years of age or had standard symptoms of pheochromacytoma: sensations of rapid heartbeat and sweating, severe headache, extremely sudden and severe fluctuations in blood pressure, and frequent hypertensive crises. If an elevated blood test revealed an increase in free methanephrine, the subjects were referred to a physician endocrinologist for clarification of the diagnosis of pheochromacytoma or paraganglioma. In the

absence of confirmation of these diagnoses, patients continued to participate in the study if the diagnosis was neither ruled out nor confirmed (follow-up was assigned) - such patients discontinued the participation in the study and were provided with routine services.

2.3. Patient inclusion criteria

1. Female and male patients aged > 18.
2. Persons who understand Lithuanian and are able to read and sign an informed consent form in Lithuanian.
3. Criteria in patients with suspected resistant arterial hypertension: systolic ABP remaining $\geq$ 140 mm Hg and office diastolic > 90 mm Hg in the treatment of 3 or more drugs (including one diuretic), or 24-hour ABP> 130/80 mm Hg 1 month after the treatment correction in a specialized unit for hypertension.
4. Catheter-based renal artery sympathetic denervation procedure was performed in the 24-48 month period prior to the enrolment. This criterion applies to the retrospective group only.

2.4. Patient exclusion criteria

1. A diagnosis of secondary AH for which other forms of treatment are available.
2. A post-renal transplant or patients on dialysis.
3. Hemodynamically significant faulty heart valves when hypotension would be life threatening.
4. Bradycardia with heart rate <50 rpm.
5. Permanent atrial fibrillation.
6. Severe concomitant disease: actively treated oncological diseases, sepsis, autoimmune diseases, confirmed allergic reactions to drugs.
7. Pregnancy or breastfeeding.
8. A subject is participating in another study of a medical device or medicinal product.

9. Evident non-compliance with the treatment regimen.

2.5. Follow-up protocol

Patients in the prospective group (MED) who met the inclusion criteria and signed an informed consent form for the study were further examined. If a subject did not undergo a catheter-based renal artery denervation procedure, office blood pressure measurements, mean 24-hour arterial blood pressure measurement, electrocardiogram, resting echocardiography, arterial stiffness examination by applanation tonometry, chest wall resistance measurements, overnight polysomnography, examination of renal arteries, and blood tests were performed. Antihypertensive treatment was adjusted according to changes in the findings of these tests.

At 3 and 6 months of post-enrolment, a subject was re-examined, questioned, and further examined if medically indicated. The regimen of a medication taken by the subject, its adherence were also reviewed. The medications taken were adjusted as needed. The scheduling of study procedures is presented in Table 1.

Table 1. *Procedure schedule in the prospective study group.*

	Start of test	After 3 months	After 6 months
Informed consent form	X	-	-
Anamnesis, risk factors	X	-	-
Objective patient examination (ABP, HR etc.)	X	X	X
Blood tests	X	X	X
Electrocardiogram	X	X	X
Resting echocardiography	X		X
Chest wall resistance measurements	X	X	X

	Start of test	After 3 months	After 6 months
Overnight polysomnography, Epworth Sleepiness Scale questionnaire	X	-	-
Renal artery ultrasound	X	-	-
Questionnaire (MMAS - 4)	X	-	X
Assessment of arterial stiffness using applanation tonometry	X	X	X
24-hour monitoring of peripheral arterial blood pressure	X	X	X

If a subject form the prospective group underwent catheter-based renal artery sympathetic denervation 48 months ago, such subject signed a consent form. The subject underwent routine questioning and examination, office blood pressure measurements, measurement of mean 24-hour arterial blood pressure, assessment of arterial stiffness using applanation tonometry, and other examinations in medical indications.

3. RESULTS

3.1. Results of catheter-based renal artery denervation group and medication treatment group over 6-month period

3.1.1. General characteristics of the study participants

The catheter-based RASD group had 72 subjects, while MED group - 34. 34 (47.22 %) males and 38 (52.77 %) females were

enrolled in the catheter-based RASD, and 16 (47.1 %) males and 18 (52.94 %) females in MED group. The youngest patient in the study was 25 years old, and the oldest - 72 years old. The median age was 55 years in RASD group, and 57.5 years in MED group, and there was no statistically significant age difference between the two groups ($p = 0.112$, Mann-Whitney U test). There was also no significant age difference between the sexes in both groups.

The majority of subjects in both groups were overweight or obese. Mean BMI of both groups was 34.0 ± 5.85 kg/m^2, even though there was no statistically significant difference in BMI between men and women, however, men were slightly taller with higher body weights. Only 4 subjects had a normal BMI - 2 women and 2 men. The highest BMI (> 50 kg/m^2) was observed in 2 women.

There was no statistically significant difference between BMI and age in either study group.

By assessing patient history data, comorbidities were identified in both groups of subjects prior to enrolment in the study. There were statistically significantly more patients with diagnosed heart failure in RASD group 61 (83.6%) than in MED group 14 (41.2%) ($p < 0.001$). In MED group, the majority of patients had dyslipidemia 31 (91.2%), compared with only 32 subjects (43.84%) in RASD group ($p < 0.001$). The incidence of other diseases did not differ significantly between the two groups. The history of comorbidities in the subjects is presented in Table 2.

Table 2. *Distribution of history of comorbidities in study groups.*

History of co-morbidities	RASD group, n (%)	MED group, n (%)	p
Heart failure	61 (83.6 %)	14 (41.2 %)	-
- Retained ejection fractions	59 (81.9 %)	13 (38.2 %)	< **0.001**
- Moderately reduced ejection fractions	2 (2.7 %)	1 (2.9 %)	0.89

History of co-morbidities	RASD group, n (%)	MED group, n (%)	p
Smoking	5 (6.8 %)	6 (17.6 %)	0.446
Stroke	5 (6.8%)	2 (5.9 %)	0.823
Atrial fibrillation	5 (6.8 %)	1 (2.9 %)	0.743
Type 2 diabetes mellitus	29 (39.7 %)	16 (47.1%)	0.083
Coronary heart disease	16 (21.9 %)	8 (23.5 %)	0.789
Dyslipidemia	32 (43.84 %)	31 (91.2 %)	**<0.001**

3.1.2. Medications taken during the study

In both study groups, the total number of medications taken, measured by the number of pills, and the number of pills of antihypertensive drugs and the number of antihypertensive medications were evaluated separately (Table 3).

In both study groups, the median total number of pills at baseline was 7 pills and did not differ significantly between the groups. In both groups, the lowest number of pills taken was 2 and the highest was 14.

Table 3. *Number of medications and antihypertensive pills and antihypertensive medications taken during the study.*

Indicator	Months	Group	Min	Median	Mean	Max	SD	n	p
Total number of pills taken	0	RASD	2	7	7.48	14	2.22	72	0.369
		MED	2	7	7.03	12	2.6	34	
	3	RASD	2	7	7.53	13	2.69	66	0.321
		MED	2	7	6.91	11	2.67	34	

Indicator	Months	Group	Min	Median	Mean	Max	SD	n	p
	6	RASD	2	6, 5	6.79	12	2.73	66	0.674
		MED	3	7	7.38	17	3.43	34	
Number of pills of antihypertensive drugs taken	0	RASD	2	6	6.25	11	1.49	72	**<0.01**
		MED	2	5	4.79	7	1.45	34	
	3	RASD	2	6	6.04	11	1.81	66	**<0.01**
		MED	2	5	4.71	7	1.31	34	
	6	RASD	3	6	6.17	10	1.53	66	**<0.01**
		MED	2	5	4.88	10	1.70	34	
Number of antihypertensive medications	0	RASD	2	6	5.97	8	1.1	72	0.65
		MED	4	5	5.53	8	1.13	34	
	3	RASD	2	6	5.63	8	1.37	66	0.78
		MED	4	5	5.55	8	1.25	34	
	6	RASD	2	6	5.65	8	1.36	66	0.89
		MED	4	5	5.73	8	1.33	34	

RASD – catheter-based renal artery sympathetic denervation group; MED – medication treatment corrective group.

In the medication corrective group for the treatment of hypertension, subjects were treated with a smaller number of antihypertensive pills (median in RASD group: 6 IQR (2.0), in MED group: 5 IQR (2.0) (**p<0.01**)), however, the mean number of antihypertensive drugs did not differ between the two groups, see Table 3. The number of antihypertensive pills did not change significantly over the time interval (0-3-6 months) in either group, see Figure 1 and Figure 2.

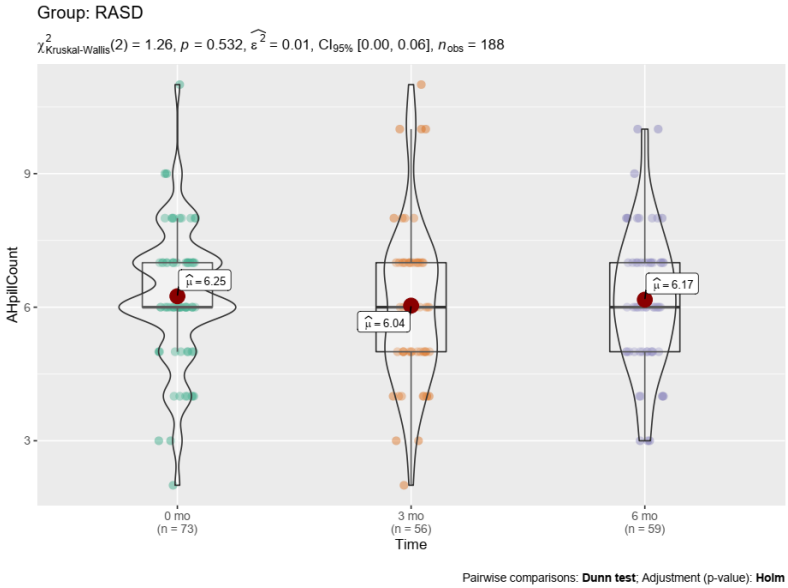

Figure 1. *Use of the number of pills of antihypertensive drugs in RASD group during the study period.*

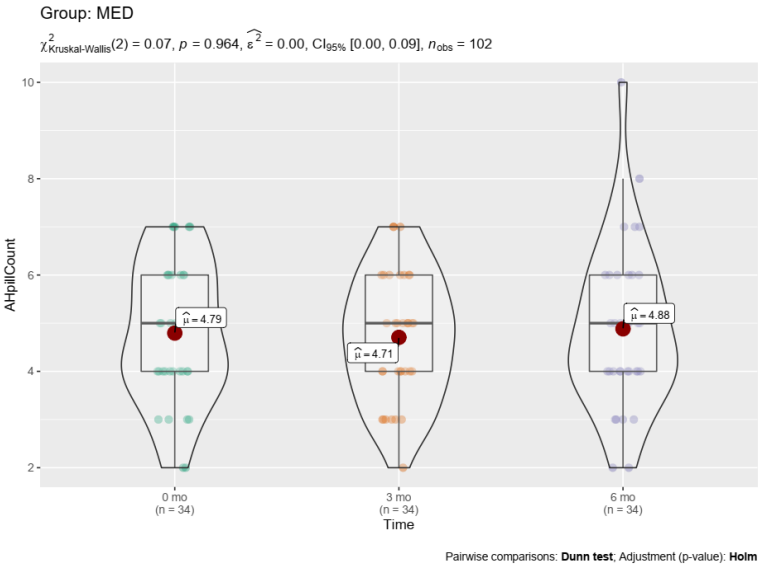

Figure 2. *Use of the number of pills of antihypertensive drugs in MED group during the study period.*

The comparison of antihypertensive medications by group shows that the majority of patients take medications that affect the renin-angiotensin-aldosterone system. Angiotensin-converting-enzyme inhibitors (ACEIs) were prescribed less frequently than angiotensin II receptor blockers (ARBs). The frequency of diuretic (DIU) use at the time of enrolment in the study differed significantly between the two groups (in RASD group 94.4 % and 73.4 % in MED group, p = 0.005) (Figure 3.). In the diuretic class, loop diuretics were administered to only 3 subjects (2 in RASD group and 1 in MED group). The remaining subjects were given thiazide or thiazide-like diuretics. There was a statistically significant increase in the prescription of aldosterone receptor antagonists in MED group at 3-month and 6-month follow-up periods (Figure 4.). The frequency of beta blockers (BBs) and calcium channel blockers (CCBs) did not differ between the two groups. Alpha blockers (αBs) were more commonly administered in the RASD group, however a statistically significant difference was observed only at the time of enrolment in the study (RASD 63.4 % and MED 35.2 %, p = 0.005). Centrally acting drugs were most rarely prescribed 3 months after catheter-based renal artery sympathetic denervation (68.3%); there was a significant difference between the two groups over this observation period. Detailed use of antihypertensive drugs and statistical comparison are given in Table 4.

Table 4. *Use of separate groups of antihypertensive drugs in both groups during the study period.*

Time, months	Group	ACE	ARB	CCB	DIU	MRA	BB	αB	CAAD
0 mo	RASD n=71	23 (32.4 %)	55 (77.5 %)	63 (88.73 %)	67 (94.4 %)	48 (67.6 %)	66 (92.9 %)	45 (63.4 %)	57 (80.3 %)
	MED n=34	6 (17.6 %)	28 (82.4 %)	28 (82.4 %)	25 (73.4 %)	27 (79.4%)	29 (85.3%)	12 (35.2 %)	29 (85.3 %)
	P	0,07	0.61	0.34	**0.005**	0.24	0.19	**0.005**	0.573
3 mo	RASD n=63	20 (31.7 %)	50 (79.4 %)	57 (90.5 %)	58 (92.1 %)	36 (57.1%)	54 (85.7 %)	37 (58.7 %)	43 (68.3 %)
	MED n=34	7 (20.6 %)	27 (79.4 %)	28 (82.4 %)	27 (79.4 %)	27 (79.4%)	29 (85.3%)	11 (32.4 %)	28 (82.4 %)
	P	0.45	0.242	0.61	0.89	**0.003**	0.19	0.076	**0.017**
6 mo	RASD n=66	19 (28.8 %)	51 (77.3 %)	57 (86. 4%)	64 (96.8 %)	39 (59.1 %)	59 (89.4 %)	38 (57.6 %)	46 (69.7%)
	MED n=34	7 (20.6 %)	27 (79.4 %)	31 (91.2%)	28 (82.4 %)	27 (79.4%)	30 (88.2 %)	11 (32.4 %)	26 (76.5 %)
	p	0.63	0.301	0.09	0.46	**0.01**	0.34	0.057	0.167

The table shows the number and percentage of patients taking the medication in the group. RASD – catheter-based renal artery sympathetic denervation group; MED – medication treatment corrective group; ACEI – angiotensin-converting-enzyme inhibitors; ARB – angiotensin II receptor blockers; CCB – calcium channel blockers; DIU – diuretics; ARA – aldosterone receptor antagonists; BB - beta blockers; αB – alpha blockers; CAAD – centrally acting antihypertensive drugs.

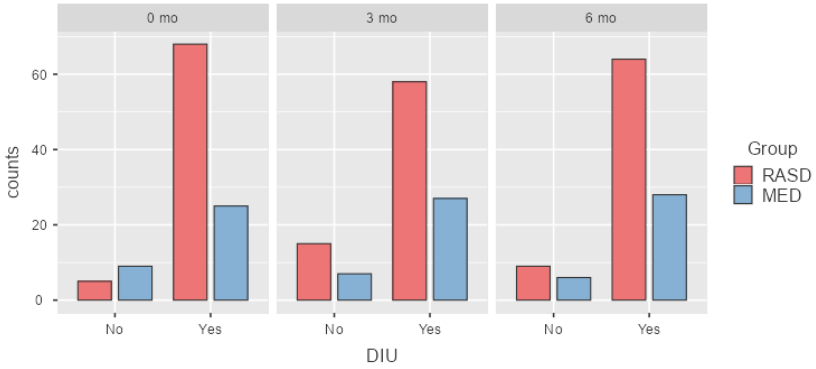

Figure 3. *Diuretic (DIU) use in study groups over the observation period.*

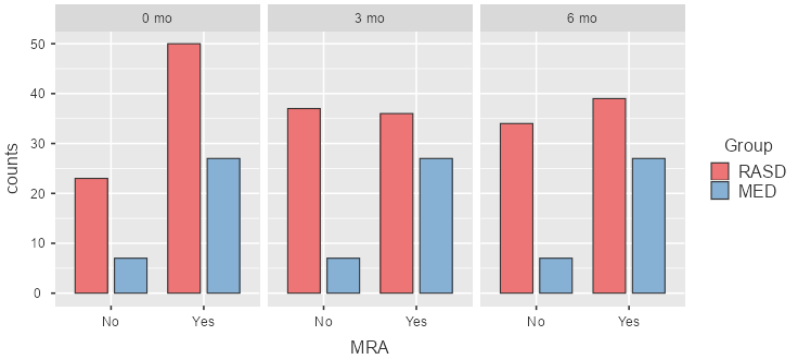

Figure 4. *Use of aldosterone receptor antagonists (ARAs) in study groups over the observation period.*

3.1.3. Changes in office arterial blood pressure and heart rate during the study

During the observation period, a significant decrease in office ABP was observed in both groups at 3 and 6 months. Baseline office systolic ABP was significantly higher in RASD group (190 mm Hg) than in MED group (175.5 mm Hg) (95 % CI: 2.02 – 15.7)

(p = 0.03), however, a steady decrease in systolic ABP was observed in both groups at subsequent 3 and 6 months. In RASD group, systolic ABP after 3 months decreased to 159.5 mm Hg (p < 0.001), and after 6 months dropped to 153 mm Hg (p < 0.001). In MED group, after 3 months, systolic ABP lowered to 152.8 mm Hg (p < 0.001), and at 6 months, the reduction in systolic ABP was not as significant as during the first 3-month follow-up period, however remained significantly lower than at the time of enrolment into the study (151.6 mm Hg) (p < 0.001). There was no significant difference in office systolic ABP between the two groups at 6 months (p = 0.329). The change in systolic ABP in the groups is shown in Figure 5. and Figure 6. The mean decrease in office systolic ABP after 6 months was significantly higher in RASD group: -33.8 mm Hg (± 3.01) than in MED group: -26.6 mm Hg (± 4.32) (p = 0.02).

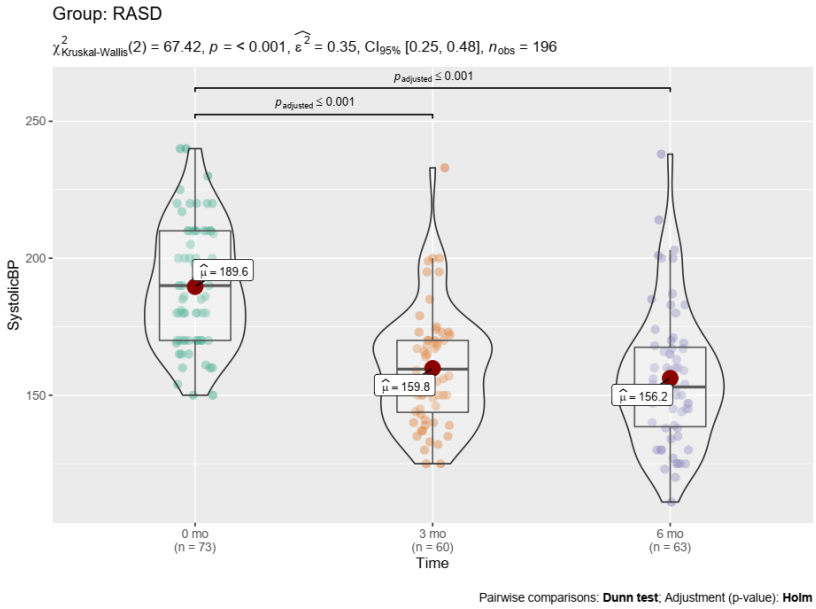

Figure 5. *Distribution of office systolic ABP (mm Hg) values in RASD group over the comparative period (box violin plot).*

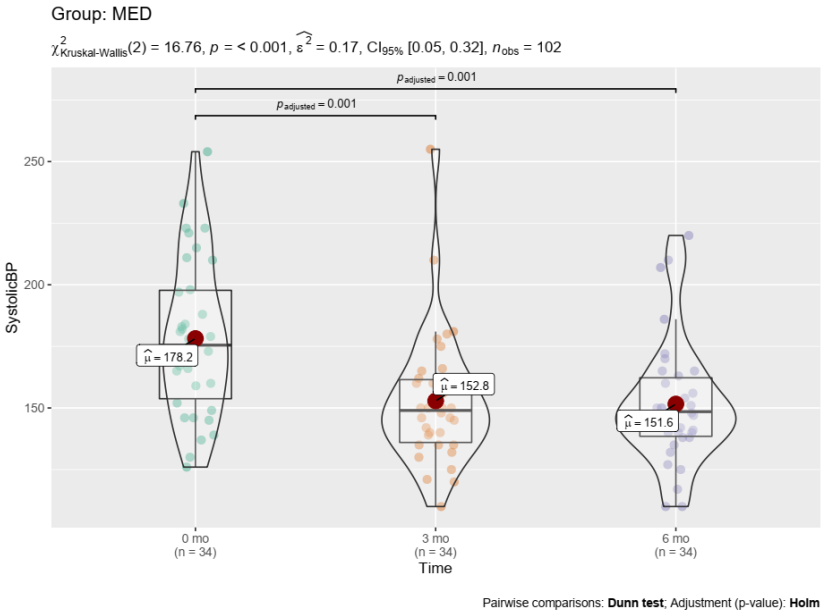

Figure 6. *Distribution of office systolic ABP (mm Hg) values in MED group over the comparative period (box violin plot).*

During the study, analogous changes were observed in the dynamics of the office diastolic ABP. The baseline diastolic ABP in RASD group was also higher than in MED group (105 mm Hg and 96 mm Hg, respectively) (95% CI: 2.64-10.1) ($p < 0.001$). In both groups, a significant reduction in diastolic ABP remained over the 3-month follow-up period, however the reduction in diastolic ABP was no longer as significant in the 3-6 month period as in the first follow-up period (Figure 7. and Figure 8.). After 6 months, the office diastolic ABP in RASD group was 90 mm Hg, while in MED group – 81 mm Hg, however, the difference between groups was not statistically significant ($p = 0.074$).

Mean reduction in ambulatory diastolic ABP at 6 months in RASD group: - 16.67 mm Hg (± 1.70), in MED group: - 13.9 mm Hg (± 3.2) ($p = 0.07$).

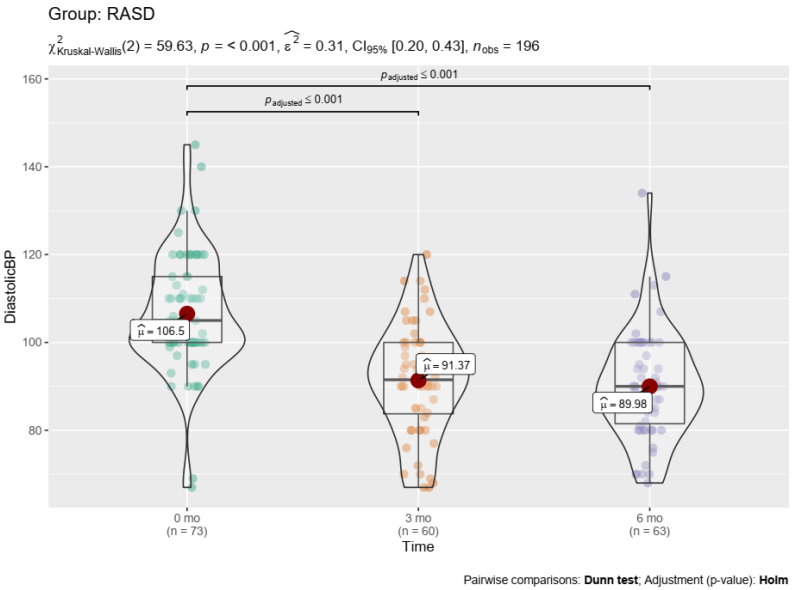

Figure 7. *Distribution of office diastolic ABP (mm Hg) values in RASD group over the comparative period (box violin plot).*

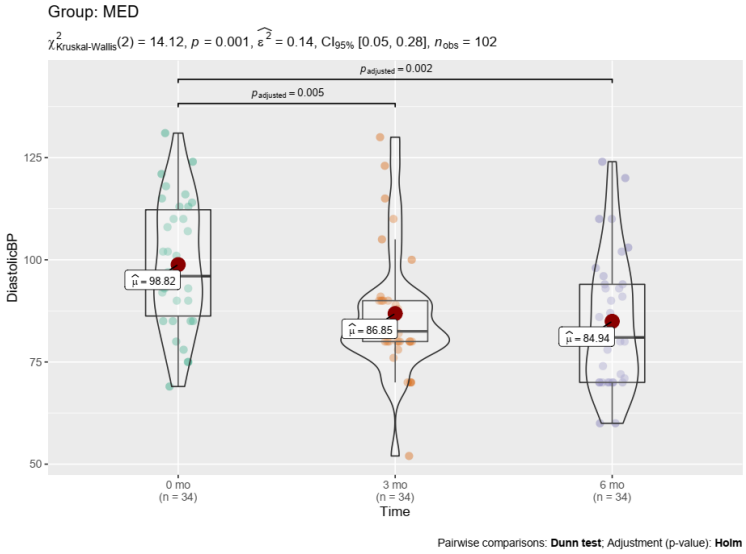

Figure 8. *Distribution of office diastolic ABP (mm Hg) values in MED group over the comparative period (box violin plot).*

When assessing the changes in office HR, the only significant reduction in HR was in RASD group over a period of 0-3 months from 72 to 65 bpm (p = 0.002). In other follow-up periods, there were no significant differences in HR either within or between the groups, see Figure 9. and Figure 10.

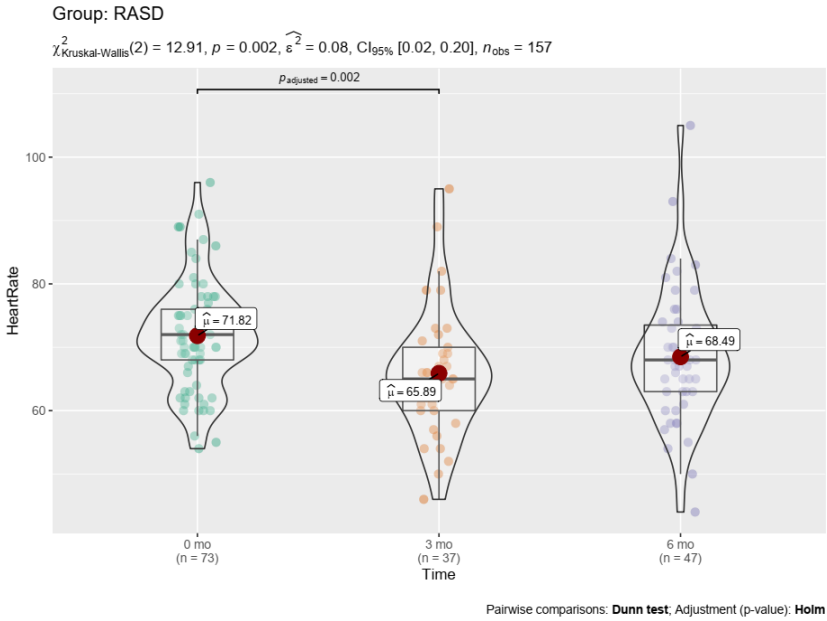

Figure 9. *Distribution of office heart rate (bpm) values in RASD group over the comparative period (box violin plot).*

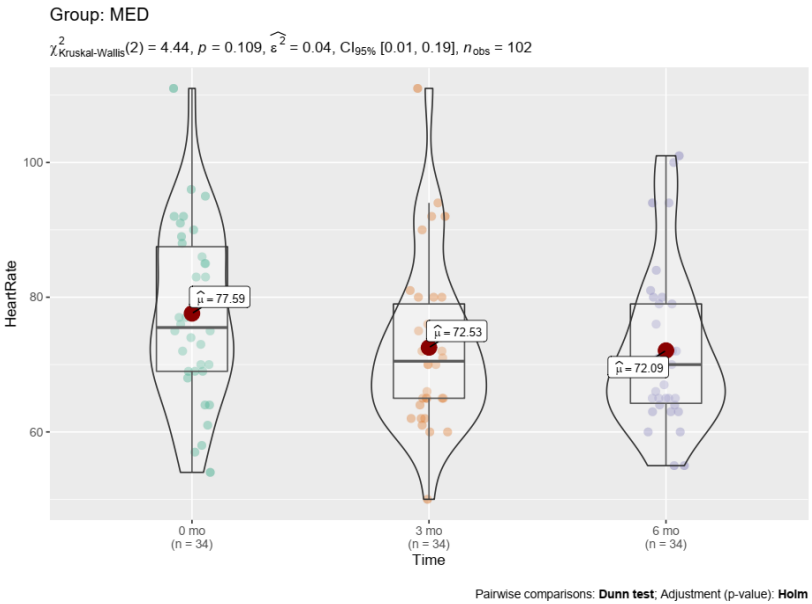

Figure 10. *Distribution of office heart rate (bpm) in MED group over the comparative period (box violin plot).*

3.1.4. Changes in 24-hour arterial blood pressure monitoring indicators

There was a significant reduction in 24-hour systolic and diastolic arterial blood pressure at both 3 and 6 months in both study groups. A significant decrease in 24-hour ABP was observed in RASD group from 161/97 mm Hg (IQR 23/14.3) to 153/91 mm Hg (IQR 31/19) within a period of 3 months ($p < 0.002$), the decrease in ABP continued after 6 months as well, when the median 24-hour ABP reached 145/89 mm Hg (IQR 26/13) ($p < 0.001$). The mean reduction in 24-hour systolic ABP in this group after 6 months was -14,82 mm Hg (±2.47; **p = 0.03**), diastolic ABP decreased on average by -7.28 mm Hg (± 1.66; **p = 0.03**). Distribution of 24-hour systolic and diastolic blood pressure values in both groups is given in Figure 11. and Figure 12.

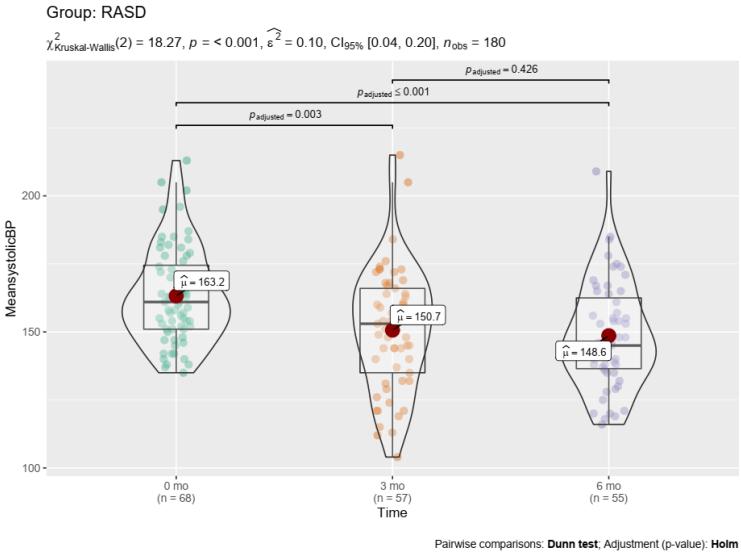

Figure 11. *Distribution of values of mean 24-hour systolic blood pressure of 24-hour ABP monitoring over the observation period in RASD group (box violin plot).*

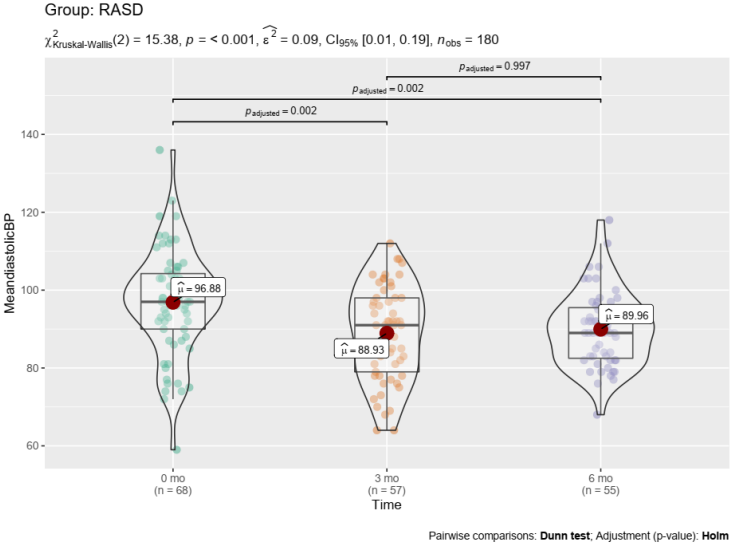

Figure 12. *Distribution of values of mean 24-hour diastolic blood pressure of 24-hour ABP monitoring over the observation period in RASD group (box violin plot).*

A significant decrease in 24-hour ABP was also observed throughout the follow-up periods in the medication treatment corrective group. In this group, median 24-hour ABP from baseline was 151/91.5 mm Hg (IQR 21.5 / 13.5), over 3 months ABP dropped significantly to 143/85 mm Hg (IQR 13.8 / 11.8) (p = 0.02), and after 6 months reached 141/83.5 mm Hg (IQR 11.8 / 12.3) (p = 0.001). The mean reduction in 24-hour systolic ABP in this group at 6 months was -15.4 mm Hg (± 2.98), diastolic ABP decreased on average by - 7.06 mm Hg (± 2.01). It is important to note that median 24-hour ABP from baseline was significantly higher in RASD group than in MED group (p = 0.03), however, no significant difference between the two groups remained in other follow-up periods (p = 0.09).

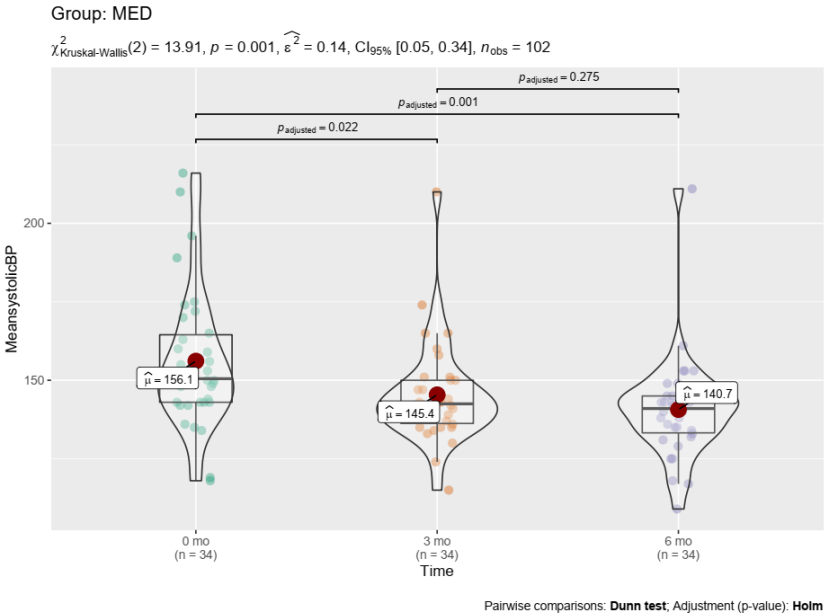

Figure 13. *Distribution of values of mean 24-hour systolic blood pressure of 24-hour ABP monitoring over the period of observation in MED group (box violin plot).*

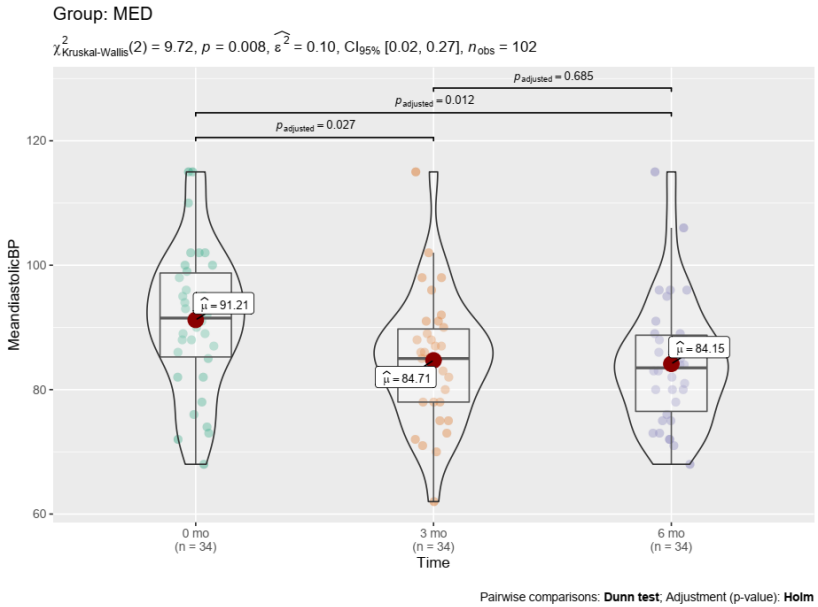

Figure 14. *Distribution of values of mean 24-hour diastolic blood pressure of 24-hour ABP monitoring over the period of observation in MED group.*

In MED group, when assessing day-time and night-time systolic and diastolic ABP, changes analogous to 24-hour ABP indicators throughout all follow-up periods remained.

When assessing the dynamics of 24-hour HR, mean 24-hour HR decreased from 75 (± 10.4) (bpm) to 71.4 (± 10.5) (bpm), yet the difference was not significant (p = 0.17). Changes in day-time and night-time mean heart rate were also insignificant. No significant dynamics of the ratio of day-time and night-time systolic and diastolic ABP over the 0-6 month period was not recorded either.

3.1.5. Changes in aortic pulse wave velocity

In comparison groups (0-6 months) over the observation period, significant changes in pulse wave velocity between carotid and femoral arteries (PWVcf) were observed in RASD group. In this group, the median PWVcf at baseline was 10.8 m/s, which after

3 months dropped to 9.98 m/s, and after 6 months was significantly lower and reached 9.2 m/s (p = 0.012) (Table 5). In medication treatment corrective group, the significant drop of PWVcf was not observed, at 3 and 6 months it reached 10.4 m/s and 10.8 m/s, respectively. It is important to note that after 6 months PWVcf in RASD group was statistically significantly lower than in MED group (p = 0,009) (the data are graphically presented presented in Figure 15 and Figure 16).

Table 5. *Numerical characteristics of changes in pulse wave velocity between carotid and femoral arteries in study groups.*

Indicator	Period	Group	Min	Median	Mean	Max	SN	IQR	n	p
PWV (m/s)	0 mo	RASD	6.4	10.8	10.8	15.9	2.22	3.25	55	
	3 mos	RASD	5.3	9.6	9.98	17.5	2.64	3.80	53	0.06
	6 mos	RASD	5.2	9.2	9.5	13.7	1.86	2.4	48	**0.012**
PWV (m/s)	0 mo	MED	7.5	11.3	11.0	15.2	1.77	2.35	34	-
	3 mos	MED	7.6	10.4	10.8	18.2	1.96	1.72	34	0.699
	6 mos	MED	7.1	10.8	10.8	17.8	2.27	2.4	34	0.699

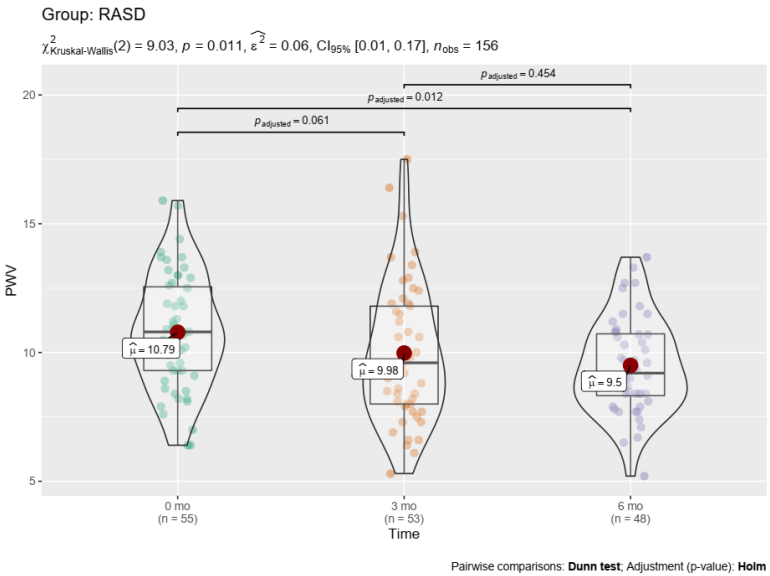

Figure 15. *Changes in pulse wave velocity between femoral and carotid arteries (m/s) in RASD group over the observation period (box violin plot).*

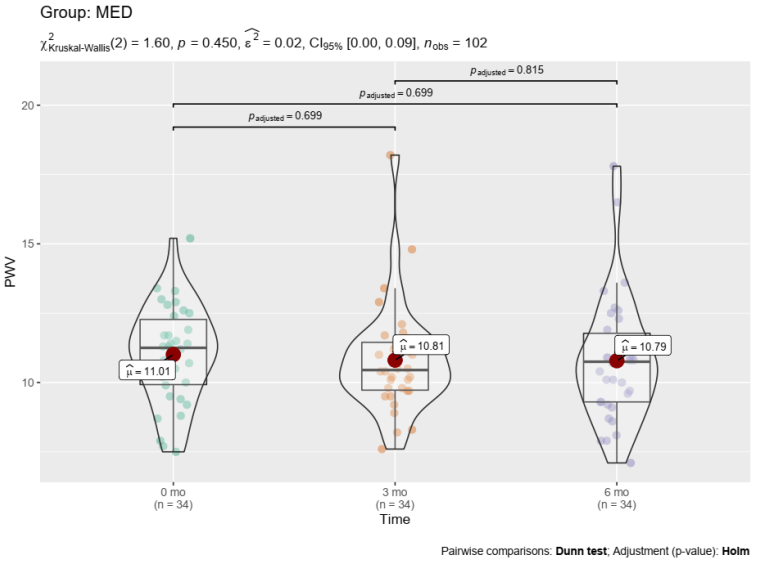

Figure 16. *Changes in pulse wave velocity between femoral and carotid arteries (m/s) in MED group over the observation period (rectangular – violin plot).*

3.1.6. Changes in cardiac ultrasound indicators in study groups

The dynamics of the left ventricular morphometry after 6 months was significant in RASD group. The thickness of the interventricular septum of the left ventricular changed in diastole from 1.14 ± 0.11 cm to 1.08 ± 0.05 cm **(p < 0.001)**, the thickness of the left ventricle posterior wall in diastole changed from 1.08 ± 0.09 cm to 1.02 ± 0.06 cm **(p < 0.001)**. The left ventricular mass index decreased significantly from 117 ± 29.4 (g/m^2) to 103.37 ± 24.35 (g/m^2) **(p = 0.004)** (Figure 17.). Other echocardiographic parameters examined did not change significantly.

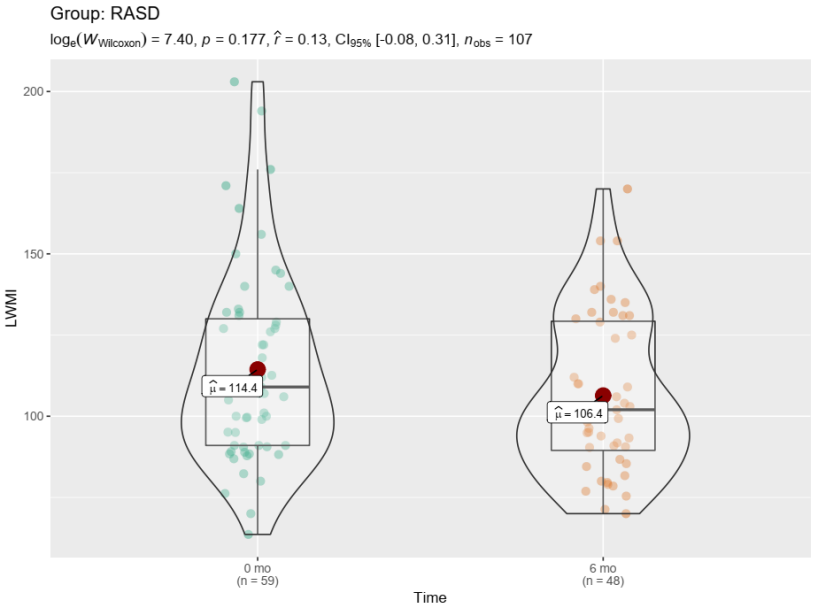

Figure 17. *Comparison of left ventricular mass index (g/m2) in RASD group over the initial and 6-month comparative period (rectangular – violin plot).*

In medication treatment corrective group (MED), no statistically significant echocardiographic changes were recorded when assessing dynamics at 6 months. The thickness of the interventricular septum of

the left ventricular changed in diastole from 1.08 ± 0.14 cm to 1.17 ± 0.17 cm (p = 0.052), the thickness of the left ventricle posterior wall in diastole changed from 1.13 ± 0.18 cm to 1.18 ± 0.16 cm (p = 0.351). The left ventricular mass index changed moderately as well from 112 ± 24.1 3 (g/m^2) to 120 ± 27.3 (g/m^2) (p = 0.274). There were also no significant changes in left ventricular systolic and diastolic function parameters in this group. It is important to note that the number of patients who underwent cardiac ultrasound re-examination at 6 months decreased to 21 (61.7% of the initial sample). Change of the left ventricular geometric mass index in MED group is given in the comparative rectangular-violin plot in Figure 18.

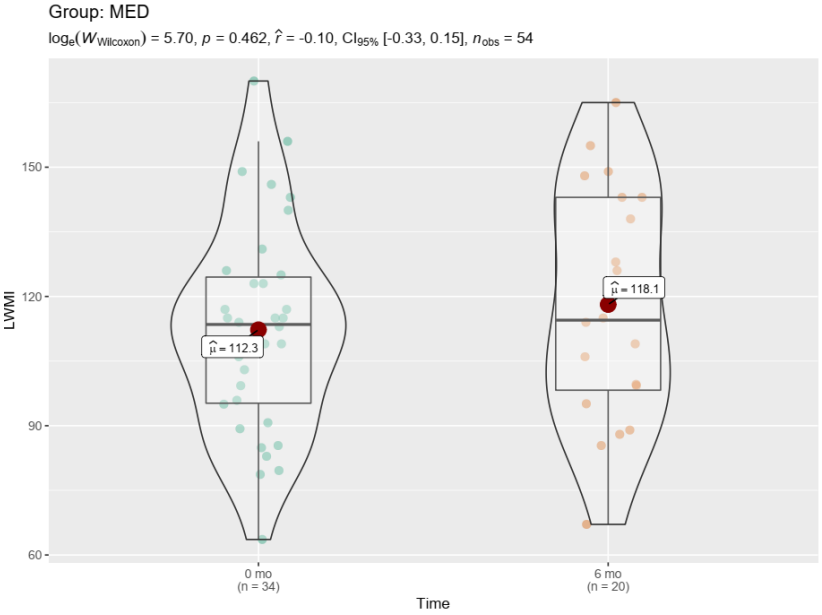

Figure 18. *Comparison of the left ventricular mass index (g/m2) in MED group during the study (over the initial and 6-month observation period) (rectangular – violin plot).*

3.1.7. Factors affecting the correction of 24-hour arterial blood pressure after 6 months

In both groups, despite different mean 24-hour ABP at baseline and different treatments applied, ABP decreased in both groups, however in RASD group, the proportion of subjects with mean 24-hour ABP lower than 140/90 mm Hg after 6 months was smaller (36%). MED group had 47% of such subjects. The comparative pie chart is given in Figure 19.

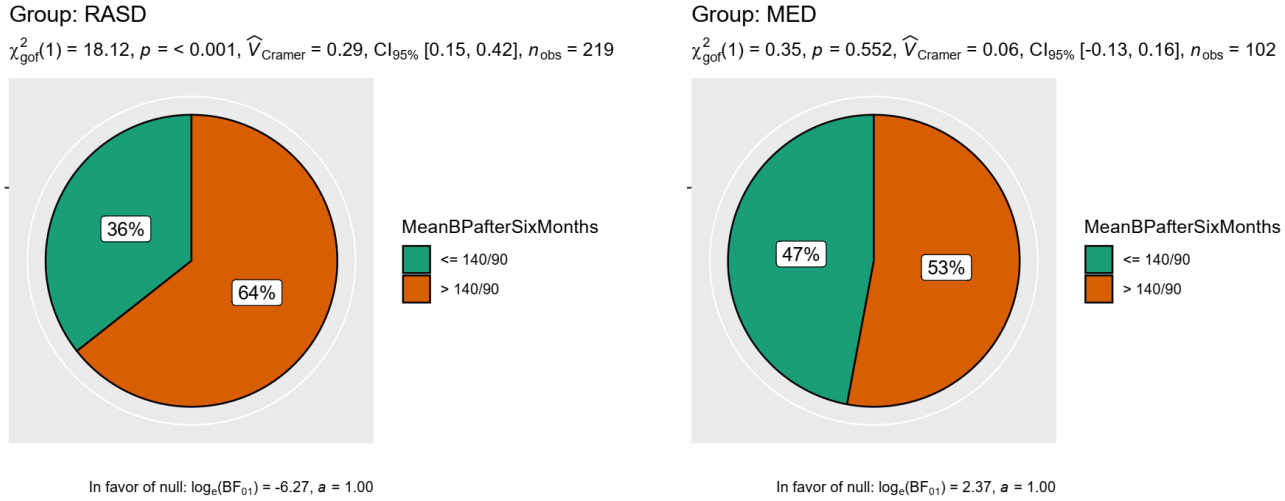

Figure 19. *The proportion of study patients in groups with mean 24-hour ABP after 6 months was below 140 / 90 mmHg (green colour) and higher or equal to 140 / 90 mm Hg (brown colour) (pie chart).*

We assessed which variables best predicted the correction of mean 24-hour arterial blood pressure after 6 months in both study groups by using a binary logistic regression method. The dependent variable "mean 24-hour ABP after 6 months": the predictive value is 1 when the monitoring median of ambulatory 24-hour ABP monitoring was equal to or higher than 140/90 mm Hg, and 0 when it was below 140/90 mm Hg. Independent variables were assessed: age, sex, body mass index, whether RASD was performed, comorbidities. Correlated variables were not included into a single model.

In addition, by using the binary logistic regression method, we aimed to evaluate the effect of changes in the number of medications used in the study and the individual groups of antihypertensive drugs on the mean 24-hour ABP after 6 months. In this model, the dependent variable is "mean 24-hour ABP after 6 months": when the monitoring median of ambulatory 24-hour ABP monitoring was equal to or higher than 140/90 mm Hg, and 0 when it was below 140/90 mm Hg. Odds rations of the change in the number of pills evaluated and of antihypertensive drug groups for the dependent variable "mean 24-hour ABP after 6 months" based on 24-hour ABP results are given in Figure 20.

When assessing the results of this regression model, it was observed that the use of calcium channel blockers (**p = 0.003**) and alpha blockers (**p = 0.002)** had a positive effect on the correction of 24-hour mean arterial blood pressure after 6 months. Moreover, we found that those subjects who had an increase in the number of pills prescribed compared to the enrolment into the study had a lower predictivity of adjusting their 24-hour mean ABP (odds ratio 3.14 (95% CI: 1.02-10.36, **p = 0.050)**). The reduction in the number of pills did not have a significant effect on the correction of the APB after 6 months. The results of this binary logistic regression are plotted in Figure 20.

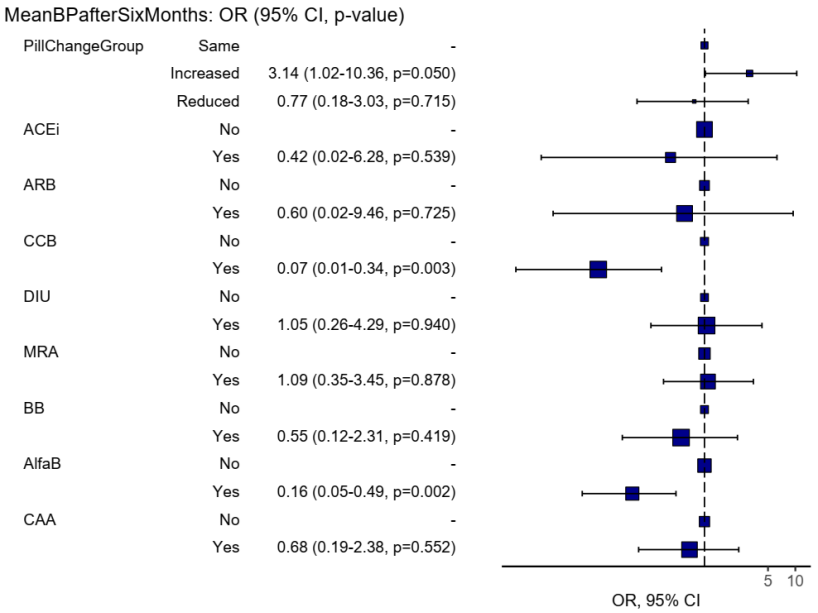

Figure 20. *Odds ratios of groups of antihypertensive drugs for a dependent variable "24-hour mean ABP after 6 months" based on 24-hour arterial blood pressure results after 6 months. ACEI – angiotensin-converting-enzyme inhibitors; ABP – arterial blood pressure; ARB – angiotensin II receptor blockers; CCB – calcium channel blockers; DIU – diuretics; ARA – aldosterone receptor antagonists; BB- beta blockers; αB – alpha blockers; CAA– centrally acting drugs; OR – odds ratio, CI – confidence interval.*

By using this binary logistic regression model, the exponents or odds ratios (ORs) of the coefficients of variables are as follows:

Free member OR = 6.4870;

"Age" OR = 0.8091;

"Creatinine" OR = 0.9536;

“LDL cholesterol” OR = 7.3518;

“Total number of pills (baseline)” = 3.0584;

“Calcium channel blockers: yes” OR = 0.0134;

The efficiency of the model was evaluated by compiling a classification table from the results calculated and actually determined Table 6 using the model and calculating its predicted values and plotting ROC curve (Figure 2). The model sensitivity 90.8 % (95 % CI: 81.0 % - 96.5 %), specificity 84.6 % (95 % CI: 65.1 % – 95.6 %), positive predictive value 93.7 % (95 % CI: 84.5 % - 98.2 %), negative predictive value 78.6 % (95 % CI: 59.0 % - 91.7 %) , accuracy 88,7 % (95 % CI: 80,7 % - 94,6 %). Kappa test value 0,=.502, McNemar’s test p-value 0.452 (there is no statistically significant difference between the observed values and the values obtained using the model). The area under ROC curve, in terms of the relationship between sensitivity and specificity of the study (model), describes the study as good. AUC 0.929 (95 % CI 0.853-0.982, $p<0.01$) was also obtained by calculating the predictive values of the model and plotting ROC curve. The model presented herein has a good diagnostic performance according to the AUROC of > 0.8. A graphical representation of the developed model is presented in Figure 21.

In this model, renal artery denervation procedure was excluded as a variable despite high sensitivity (92.1%) due to low specificity (33.3%), Cragg-Uhler method Pseudo-R2 = 0.173, the area under ROC curve AUC - 0.719.

Table 6. Classification table for comparison of the results calculated by the logistic regression model and mean 24-hour ABP after 6 months.

	Model result		
Observed	**<= 140/90 mm Hg**	**> 140/90 mm Hg**	**% of correctly predicted results**
<= 140/90 mm Hg	22	6	78.6
> 140/90 mm Hg	4	59	93.7

Note. Threshold level 0.5

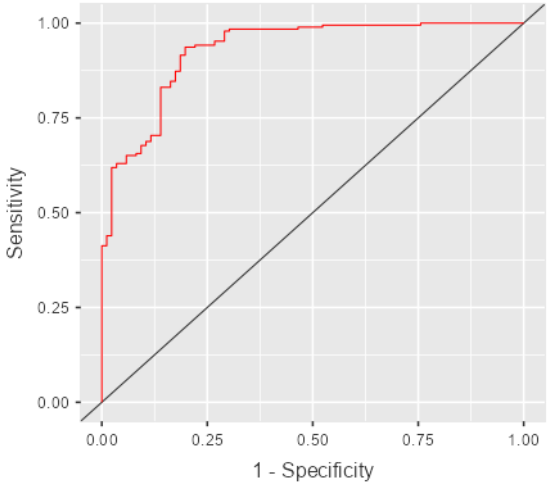

Figure 21. *ROC (Receiver Operating Characteristics) curve for regression model evaluation. Area under the curve - AUC 0.929 (95% CI 0.853-0.982, p<0.01).*

In this binary logistic regression model, the threshold values of the mean total number of pills and predictivity that the arterial blood pressure would exceed 140 / 90 mm Hg after 6 months were calculated and plotted. The chart is given in Figure 22**.**

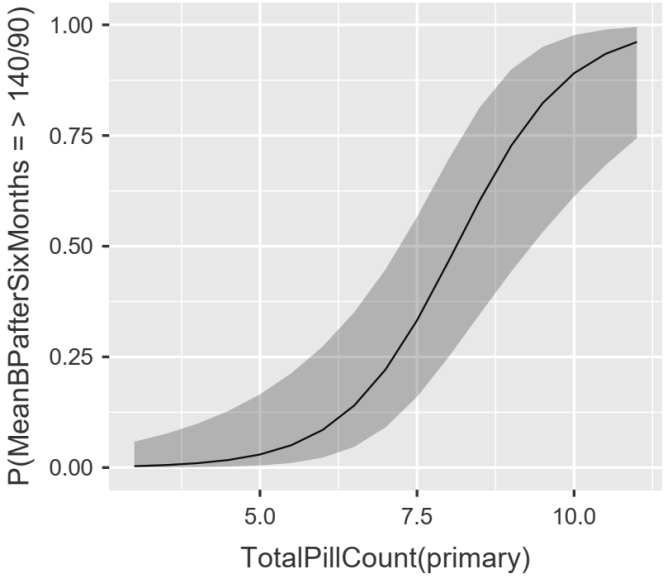

Figure 22. *Predictive relationship between the mean of the total number of pills and ABP (> 140/90 mmHg after 6 months) used in the regression model*

An analogous chart of predictive values of LDL cholesterol levels and ABP correction used in this model after 6 months is also given in Figure 23.

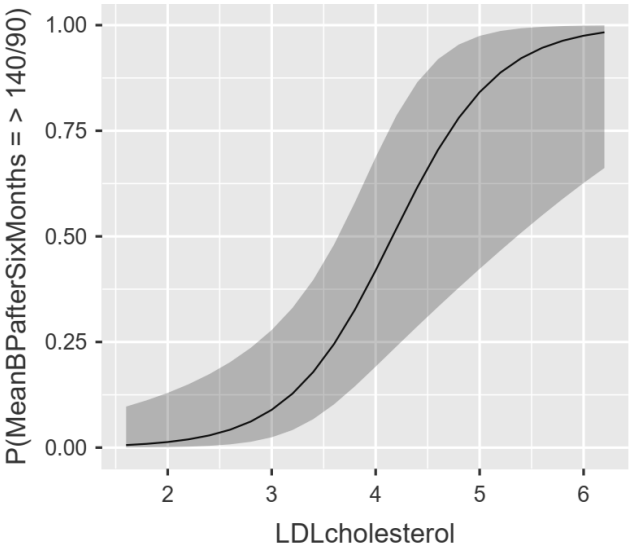

Figure 23. *Predictive relationship between LDL cholesterol (mmol/L) and ABP (> 140/ 90 mmHg after 6 months) used in the regression model.*

3.2. Results of additional diagnostic tests performed in the medication treatment group

In medication corrective group (MED), part of the additional questionnaire, laboratory, instrumental tests were performed according to the study protocol - they were performed in this group only, therefore, they will not be compared with catheter-based renal artery denervation group (RASD).

3.2.1. Changes in laboratory blood tests in the study group

In medication corrective group, subjects had normal baseline mean serum creatinine levels (76.2 ± 17.3 μmol/L), after 3 months rising slightly to 79.2 ± 20.9 μmol/L ($p = 0.31$), remaining the same after 6 months 79.2 ± 79.2 μmol/L ($p = 0.17$). Changes in serum creatinine are presented in Figure 24. Most subjects had a normal or slight

decrease in renal glomerular filtration rate according to the MDRD formula (GFR > 60 ml/min/1.72m^2), a moderate decrease in glomerular filtration rate was observed in 4 subjects (GFR 30-59 ml/min/1.72 m^2). Changes in serum creatinine are given in the flowchart, see Figure 24.

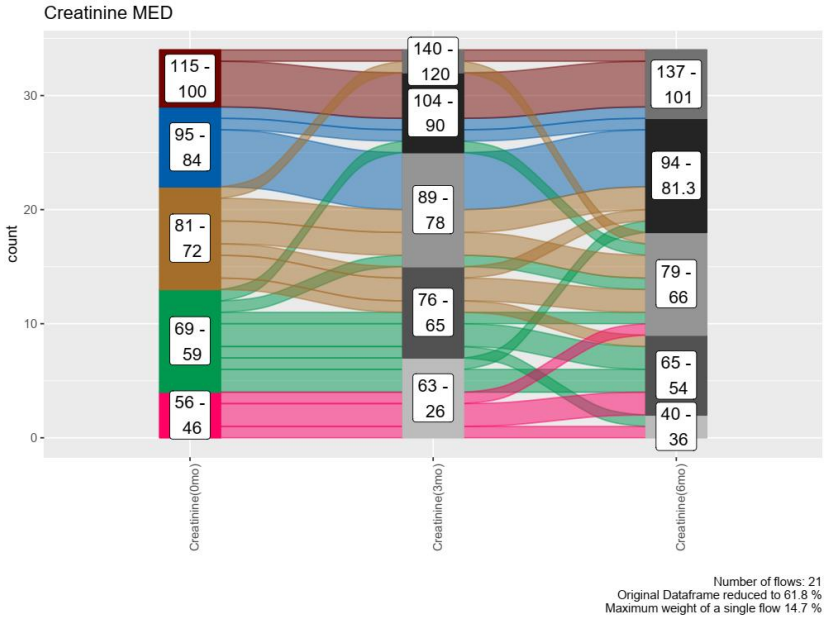

Figure 24. *Changes in serum creatinine (µmol / L) over the observation period (0-3-6 months) (flowchart).*

The median baseline serum potassium concentration was 4.4 mm/L, with a slight increase after 3 months up to 4,6 mmol/L ($p = 0.21$), and remained 4.5 mmol/L ($p = 0.08$) after 6 months. There were no significant cases of hypokalaemia or hyperkalaemia in the study leading to the adjustment or discontinuation of treatment.

Mean plasma concentrations of B-type natriuretic peptide (BNP) exceeded the diagnostic threshold for heart failure (<35 pg / mL) over all follow-up periods (93.9, 59.7 and 88.7 pg/mL, respectively), however, it did not change significantly in the group ($p = 0.95$).

Maximum analyte concentration (654 pg / mL) was recorded by including a subject into the study.

An impaired lipid metabolism was diagnosed in most subjects (n=31. 91 %), their median low-density lipoprotein (LDL-Ch) serum concentrations were 3.55 mmol / L. Despite a prescribed statin therapy, this rate did not change significantly at 3 and 6 months (3.65 and 3.33 mmol / L, respectively) (p = 0.32).

The vast majority of patients examined had a tendency to higher serum glucose or were treated for diabetes mellitus (47.1%). At enrolment, the median glucose concentration reached 6.6 mmol/L, after 3 months - 6.35 mmol/L (p = 0.74), and after 6 months - 6.5 mmol//L (p = 1). After 6 months, the largest fluctuations of glycemia were recorded as well, the lowest value recorded was 3.7 mmol/L, the highest - 22.2 mmol/L.

An increase in serum uric acid was also observed in the vast majority of subjects (laboratory rate in women: 155-357 μmol/L, men: 208-428 μmol/L). The median uric acid concentration in the subgroup of women at baseline was 406 μmol/L, after 3 and 6 months it increased slightly and reached 415 μmol/L (p = 0.74). In the subgroup of men, the median uric acid concentration at baseline was 431 μmol/L, after 3 months - 448 (p = 0.85), after 6 months it increased insignificantly and reached 442 μmol/L (p = 0.94). The highest uric acid concentration in the subgroup of men was found after 6 months, it reached 706 μmol/L, as a result, the medication treatment of 2 patients had to be adjusted.

3.2.2. Results and changes in chest wall resistance measurements in the study group

In medication treatment corrective group, clinical decisions were based on chest wall resistance measurement results. Informative results of the study were obtained for 31 subjects, a qualitative steady signal failed to be recorded for 3 subjects due to a high degree of

obesity. Based on the results of non-invasive blood flow measurements, 3 subgroups were formed, see Figure 25.:

- Vasoconstrictive (elevated peripheral vascular resistance > 3650 dyn * s * cm^5 , low cardiac index < 2.5 L/min * m^2) - 4 subjects (12%).
- Mixed (normal - elevated peripheral vascular resistance 3000-3650 dyn * s * cm^5, normal cardiac index 2,5-4 L/min * m^2) - 22 subjects (71%).
- Hyperdynamic (low peripheral vascular resistance 1600-3000 dyn * s * cm^5, high cardiac index > 4 L/min * m^2) - 5 subjects (16%).

A mixed hemodynamic model of hypertension was the most common (71 %).

Similar to the results of ambulatory 24-hour ABP measurements, there was also a significant reduction in systolic, diastolic, and mean arterial blood pressure in the group during this study. By assessing the overall group results of fluid in the chest wall, cardiac index, peripheral vascular resistance, and their dynamics, there were no statistically significant changes in the study sample.

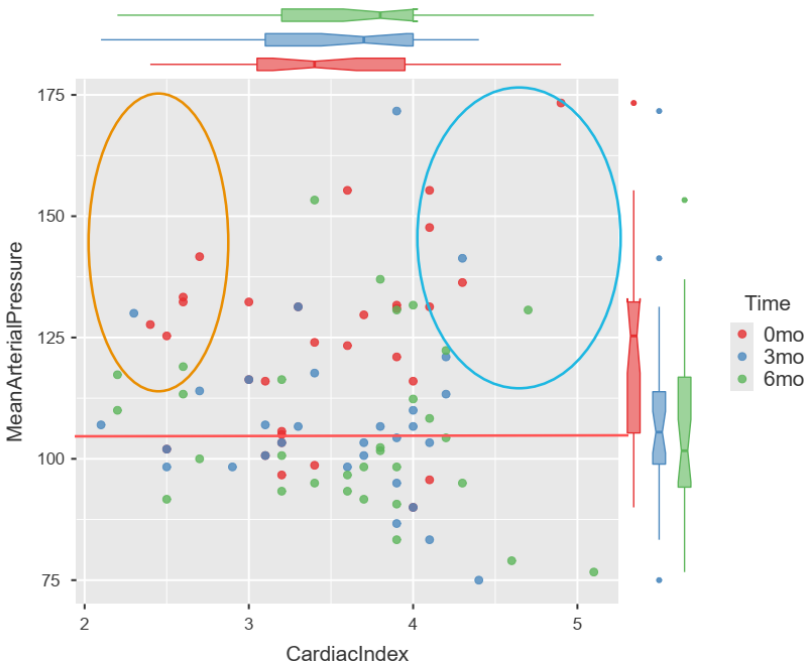

Figure 25. *Relationship between cardiac index and mean arterial pressure (MAP, mm Hg) in the study group (scatter plot). The red line shows VAS point separating normal blood pressure from elevated (> 105 mm Hg). The yellowy figure indicates vasoconstrictive hypertensive conditions (elevated peripheral vascular resistance > 3650 dyn * s * cm^5, low cardiac index < 2,5 L/min * m^2)). The bluey figure indicates hyperdynamic hypertensive conditions - low peripheral vascular resistance 1600-3000 dyn * s * cm^5, high cardiac index > 4 L/min * m^2). Scatter plot.*

By grouped subjects according to mean 24-hour systolic and diastolic ABP after 6 months (> 140/90 mm Hg and ≤ 140/90 mm Hg), 2 different trends in mean ABP dependence on cardiac index are observed. In the group of corrected blood pressure, a decreasing trend of mean ABP with increasing cardiac index was observed (Spearman's rank correlation coefficient -0.36, **p = 0,03**), in the poorly adjusted ABP group, on the contrary, mean ABP increases with an increasing cardiac index (Spearman's rank correlation coefficient 0.2,

p > 0.05). The confidence intervals of the equations of the linear mixed models in both groups overlap at low heart rates and split up when it increases (Figure 26.).

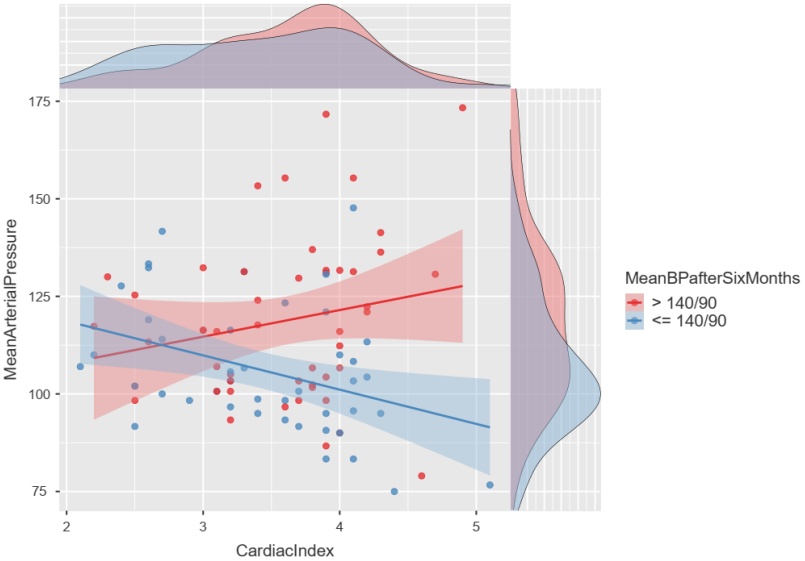

Figure 26. *Relationship between cardiac index (CI, L/min*m^2) and mean arterial pressure (MAP, mm H) in the groups of optimally corrected and uncorrected systolic arterial blood pressure after 6 months. Scatter plot.*

3.2.3. Outpatient overnight polysomnography results

In medication treatment correction group, all subjects (n = 34) underwent outpatient overnight polysomnography. The median of the apnea-hypopnea index of the subjects was 9.75 (IQR: 6.4) [min-max: 2.1 - 17.4 respiratory events / hour]. This indicator corresponds to mild sleep apnea syndrome. By assessing the number of respiratory events and the biometric data of the subjects, a strong positive correlation was found within the group between the body mass index and the apnea-hypopnea index (Kendall's Tau correlation coefficient r = 0.606, p < 0.001). In addition, a significant moderate correlation was

observed between mean 24-hour systolic arterial blood pressure after 6 months ir apnea-hypopnea index (Kendall's Tau correlation coefficient r_6 = 0.33, p_6 = 0.007). It is important to note that no significant correlation was observed between analogous 24-hour arterial blood pressure measurements at the time of enrolment to the study and after 3 months (Kendall's Tau correlation coefficient r_0 = 0.097, p_0 = 0.423; r_3 = 0.034, p_3 = 0.778, respectively).

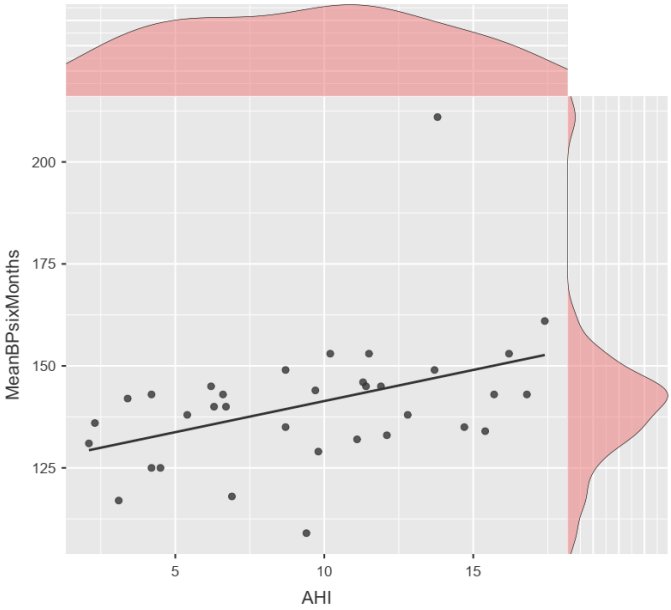

Figure 27. *Relationship between mean 24-hour arterial blood pressure (mm Hg) and apnea-hypopnea index (n/h) in the medication treatment corrective group. Scatter plot.*

No statistically significant correlations were detected between respiratory events during sleep and night-time / day-time systolic and diastolic ABP dipping.

By assessing the above data, and the correlations between body mass index, 24-hour arterial blood pressure after 6 months, and apnea-hypopnea index, we found a low, however statistically significant

correlation between body mass index and 24-hour arterial blood pressure after 6 months (Kendall's Tau correlation coefficient r = 0.272, p = 0.026). The data are shown in the plot below, see Figure 28.

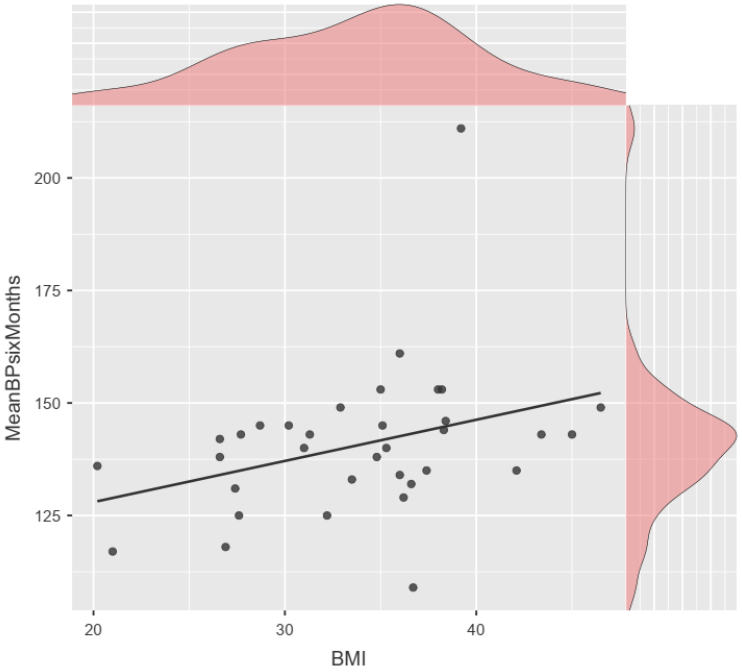

Figure 28. *Relationship between mean 24-hour arterial blood pressure (mm Hg) and body mass index (kg/m^2) in the medication treatment corrective group. Scatter plot.*

3.2.4. Morisky medication adherence scale results

Patient filled-in medication adherence questionnaires were completed at the beginning of the study by dividing them into 2 subgroups based on the median of the total number of pills taken in a group: the first subgroup included patients taking less than 7 pills, while the second subgroup included patients taking 7 or more pills.

Four standard answers, numbered 1-5, were provided to the four statements:

1) The first statement: “Sometimes I forget to take my medications”

After grouping the patients according to positive answers (“strongly agree” and “agree”) and negative answers (“disagree” and “strongly disagree”), up to 47% of respondents in the subgroup of those taking less than 7 pills indicated that they forgot to take medications, the other subgroup of those taking more pills was more numerous, even 71% of respondents. However, due to the small sample size, the difference was statistically significant (Fisher’s exact test $p = 0.227$).

2) The second statement: “Sometimes I have an irresponsible attitude towards taking medications”

Those who took fewer pills were more likely to disagree (76%) with the statement that they had the irresponsible attitude towards taking medication. In the subgroup of patients taking more pills, the positive and negative responses were distributed almost equally. In the latter subgroup, 48% of respondents admitted to being irresponsible about taking medications (Fisher’s exact test $p = 0.286$).

3) The third statement “When I feel better, sometimes I stop taking medications”

In both subgroups, respondents mentioned a little more often that they sometimes stop taking medications after feeling better. Such an answer was given in the subgroup of those taking less than 7 pills by 56% of the respondents, and in the subgroup of those taking more than 7 pills - by 63% of the respondents (Fisher’s exact test $p = 0.954$).

4) The fourth statement: “If I feel worse when taking medication, I sometimes stop taking it”

In both subgroups, the majority of respondents admitted that if they felt worse when taking medications, they stopped taking them. 83% of the respondents in the subgroup of those who take less than 7 pills responded positively, while the subgroup of those who take more than 7 pills had the absolute majority of those who responded similarly - 97% (Fisher’s exact test $p = 0.268$).

3.3. Long-term catheter-based renal artery sympathetic denervation monitoring results

The study included 72 subjects with resistant hypertension who underwent catheter-based renal artery sympathetic denervation. After 48 months of post-procedure follow-up, 5 subjects died (6.8%), two deaths were related to cardiovascular causes, but none were related to RASD procedure. 15 subjects (20.6%) failed to be contacted after 48 months or did not come to the study base for follow-up testing. Pulse wave velocity data from 4 (5.5%) subjects were not included in the final analysis due to permanent atrial fibrillation, and 49 subjects (67.1%) were included in the final analysis of this group.

3.3.1. Medication regimen

In RASD group, subjects took an average of 7.33 (± 2.44) pills before the procedure, of which 5.97 (± 1.1) were antihypertensive drugs. At 48 months of the post-procedure, the total mean number of pills decreased to 6.92 (± 3.37), of which 5.45 (± 2.2) were antihypertensive drug pills. It is important to note that there was a large variation in the amount of medication within this group: from 2 to 16 pills per day. The vast majority of subjects were treated with angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (100% at the enrolment and 95.9% after 48-month follow-up,

respectively). The combination of the latter medications was avoided and there were no cases where both groups were prescribed. The second most frequently prescribed group was diuretics (91.8% and 79.6% after 48 months). The rate of prescription of calcium channel blockers remained similar over the entire follow-up (86.3% and 85.7%, respectively). There was a significant reduction in the need for beta-blockers, from 90.4% to 55.1%, however, this difference was not statistically significant ($p = 0.08$). A downward trend in the use of centrally acting antihypertensive drugs has also been observed (78.1 % and 49.0 % after 48 months). The only group of medications with an increased prescription frequency by comparing the time interval analyzed was the group of aldosterone receptor antagonists, which was prescribed to 65.7% of subjects before RASD and increased to 87.8 % after 48 months of follow-up.

Absolute prescription frequency of oral antidiabetic drugs was related to changes in the sample size and number of diabetic patients, rather than changes in glycemic control.

Table 7. *Drug regimen in RASD group before the procedure and after 48 months*

Drug regimen	Before RASD procedure	48 months after RASD procedure
Number of antihypertensive drugs	5.97 (± 1.1) [4–11]	5.45 (± 2.2) [3–11]
Total number of pills	7.33 (± 2.44) [2–14]	6.92 (± 3.37) [2–16]
Prescribed drug classes		
ACEI/ARB	73 (100 %)	47 (95.9 %)
Diuretics	67 (91.8 %)	39 (79.6 %)
Calcium channel blockers	63 (86.3 %)	42 (85.7 %)
Beta blockers	66 (90.4 %)	27 (55.1 %)
Aldosterone receptor antagonists	48 (65.7 %)	43 (87.8 %)
Centrally acting drugs	57 (78.1 %)	24 (49.0 %)
Alpha blockers	45 (61.6 %)	32 (65.3 %)
Oral antidiabetic drugs *	29 (39.7 %)	18 (36.7 %)
Oral anticoagulants	5 (6.8 %)	8 (16.3 %)

Drug regimen	Before RASD procedure	48 months after RASD procedure
Antiplatelet drugs	21 (28.7 %)	23 (46.9 %)
Statins	32 (44.4 %)	24 (48 %)

RASD – catheter-based renal artery sympathetic denervation group; ACEIs – angiotensin-converting-enzyme inhibitors; ARB – angiotensin II receptor blockers; oral antidiabetic drugs – sulphonylureas and biguanides.

3.3.2. Arterial blood pressure monitoring results

There were long-term (after 48 months) positive results in the catheter-based renal artery denervation procedure in RASD group. In this group, the median ambulatory systolic and diastolic ABP remained statistically significantly lower at 165 / 95mm Hg (IQR: 34.0 / 16.5) after 48 months of follow-up than before the procedure at 180/110 mm Hg (IQR: 40.0/15.0) (**p = 0,02**). Mean decrease in 24-hour systolic ABP after 48 months in this group was -7 ± 23 mm Hg; (95% CI, -24 to -1) ($p < 0.02$). The data are graphically presented in Figure 29.

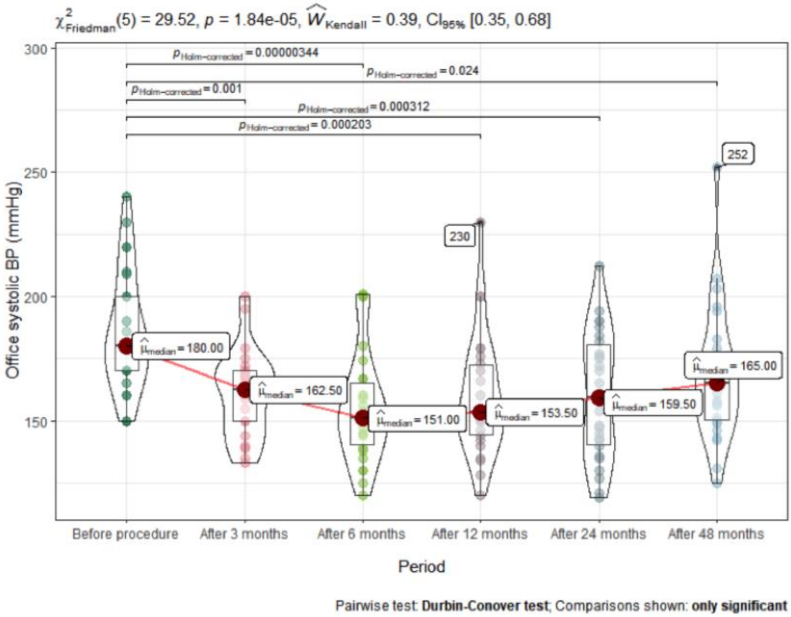

Figure 29. *Changes in office systolic arterial blood pressure over the observation period*

Similarly to systolic and diastolic office ABP, an analogous long-term, statistically significant reduction in blood pressure was observed after 24 hours in ABP monitoring, and in RASD group, median 24-hour ABP was 158/100 mm Hg (IQR: 23.5/14.2) before the procedure and remained significantly lower after 48 months at 140/86 mm Hg (IQR: 26.5 / 16.2) (systolic ABP **p <0.01**, diastolic ABP **p = 0.01**), mean 24-hour systolic ABP decrease in this group after 48 months was -11 ± 25mm Hg (95% CI: -20 to -2) (**p <0.001**). Data on changes of mean 24-hour systolic ABP are given in Figure 30.

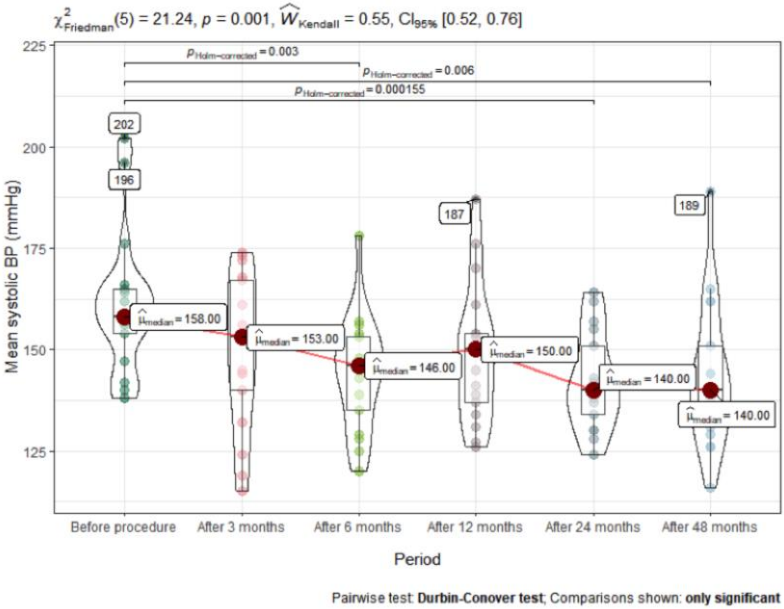

Figure 30. *Changes in mean 24-hour systolic arterial blood pressure over the observation period.*

3.3.3. Changes in aortic pulse wave velocity after catheter-based renal artery denervation

In the study group, there was a marked decrease in aortic pulse wave velocity, which was most distinct 12 months after the intervention. During this period, compared to the baseline median of PWVcf 11.2 [IQR: 3.15] m/s (95% CI 6.1, 16.2), PWVcf decreased statistically significantly to 9.8 [IQR: 2.1] m/s (95% CI 6.1, 13.7; (p = 0.002). The mean reduction in PWVcf in this group was -1.4 ± 0.98 m/s (95% CI -3.1, -0.3). Changes in PWVcf rate at 6, 24, and 48 months did not differ significantly from baseline. After 48 months, median pulse wave velocity was 10.3 [IQR: 4,0] m/s (95% CI 6,9, 17.8). Graphical data are provided in Figure 31.

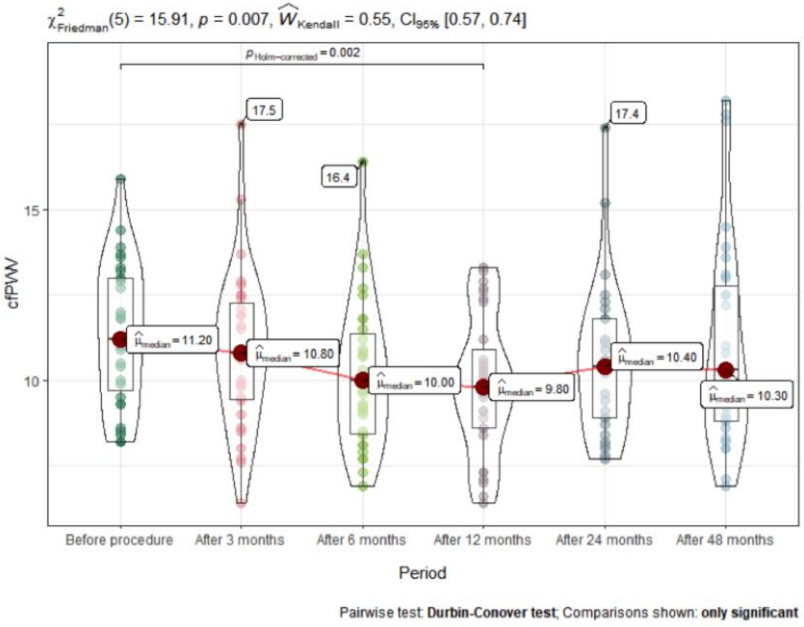

Figure 31. *Changes in pulse wave velocity between carotid and femoral arteries over the observation period*

3.3.4. Influence of medication number on arterial blood pressure and aortic pulse wave velocity

Subjects were divided into 3 groups according to the total number of pills taken: group 1 - taking 0-5 pills, group 2 - taking 6-10 pills, group 3 - taking > 10 pills. The analysis of mean 24-hour systolic blood pressure in the subjects reflected a trend towards higher mean systolic 24-hour ABP in the group where the subjects took more pills, however no statistically significant differences were observed in the groups in different follow-up periods as well as between groups over the same follow-up period. Graphical results are given in Figure 32.

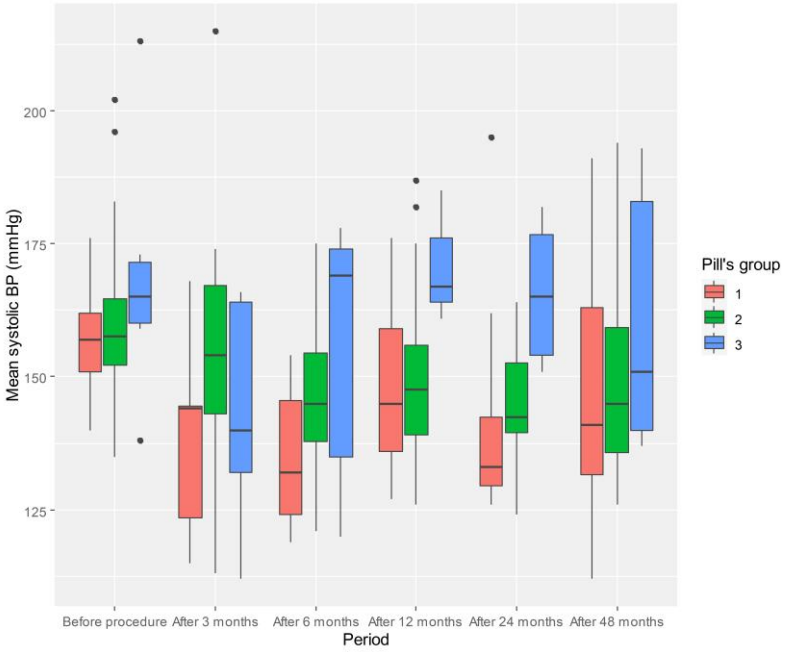

Figure 32. *Influence of the total number of pills on the mean 24-hour systolic arterial blood pressure over the observation period. Study groups: group 1: taking 0-5 pills, group 2: taking 6-10 pills, group 3: taking > 10 pills.*

By assessing the effect of the number of medications on mean aortic pulse wave velocity, the median upward trend in PWVcf with higher medication numbers was observed from the 12-month observation period, and a statistically significant difference was observed over the 48-month observation period. During this period, PWVcf was in group 1: 8.1 ± 1.6 m/s (95% CI 6.8 and 10.3); group 2: 10.9 ± 1.8 m/s (95% CI 8.4 and 14.8); group 3: 15.1 ± 2.6 m / s (95% CI 8.7 and 17.8) (p = 0.003). The data are shown in Figure 33.

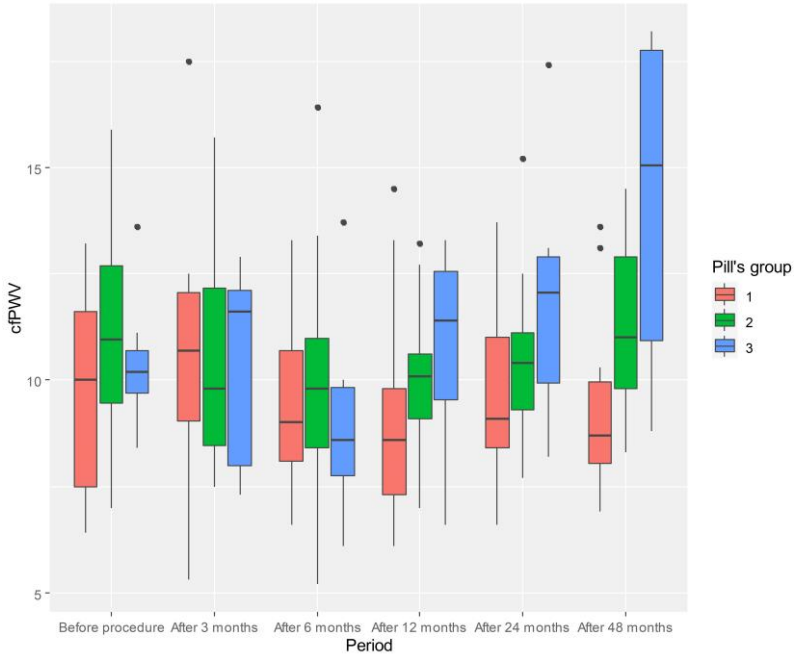

Figure 33. *Influence of the total number of pills on the mean aortic pulse wave velocity over the observation period. Study groups: group 1: 0-5 pills, group 2: 6-10 pills, group 3: > 10 pills.*

4. DISCUSSION

4.1. Discussion of a comparison of results between the catheter-based group and the medication treatment group over a 6-month period

There was a statistically significant reduction in mean systolic and diastolic 24-hour arterial blood pressure after 6 months in both RASD and MED groups. This decrease in systolic ABP was significantly higher in RASD group -33.8 mm Hg (± 3.01) than in MED group -26.6 mm Hg (± 4.32) ($p = 0.02$). This may have been influenced by the higher baseline ABP at the enrolment into the study in RASD group, and the benefit of the renal artery sympathetic denervation procedure itself, the efficiency of which was proven in SPYRAL-ON MED study, which had a greater reduction in mean 24-hour ABP in the intervention group (-7.4 mm Hg ; $p = 0.0051$) [18-20]. Similarly, there was a significant reduction in office blood pressure in both groups.

The median number of pills taken in both study groups was 7 and exceeded the definition of more than 5 pills applied for polypharmacy, which, although not uniform, is recognized by most authors [21]. In both groups, there were significant differences in the frequency of prescription of some groups of medications used for hypertension. Diuretics and α-adrenoceptor blockers were prescribed more frequently in RASD group than in MED group, and aldosterone receptor antagonists and centrally acting drugs were more commonly prescribed in MED group. These differences may have been significantly influenced by the timing of the study and the subsequent results of PATHWAY-2 study in 2015 [22]. Selection, procedures and monitoring of RASD group subjects took place in 2012-2017, while the selection and monitoring of MED group in 2017-2020. The positive benefits of spironolactone, bisoprolol and doxazosin in the treatment of resistant hypertension were demonstrated in PATHWAY-2 study.

As one of the hypotheses in this thesis was that a large number of pills prescribed by a physician had a negative effect on hypertension control, the prospective group followed the principle of administering the lowest possible number of pills to patients in two or three fixed-dose combinations. Due to a small sample size of the study, and the lack of objective determinations of drug metabolite concentrations, we were unable to randomize and ascertain the benefits of prescribing drug combinations described in the literature [23-26]. Despite these shortcomings, with the introduction of new combinations of fixed-dose antihypertensive agents throughout the study, there was a significant reduction in the number of antihypertensive pills prescribed in MED group (6.17 ± 1.53 and 4.88 ± 1.7; $p < 0.01$). The two groups were very heterogeneous in terms of the number of medications taken and comorbidities, yet at the same time similar to each other. In both groups, there was a huge gap between the minimum number of pills (non-antihypertensive drugs): in RASD group - 2, in MED group – 3, and the maximum number of pills: in RASD group - 14, in MED group - 17 according to the number of medicines prescribed. Therefore, in fact, in future large-scale similar studies, it would be more accurate to compare groups according to the number of medicines prescribed.

When analyzing the possible effect of treatment on target organ damage, different effects of arterial stiffness and left ventricular geometry were observed in both groups on cardiac ultrasound. A long-term steady decrease in pulse wave velocity was observed in RASD group, whereas no such change was observed in MED group, and there was a statistically significant difference between the two study groups at 6 months (9.5 m / s $\pm$ 1.86 and 10.8 m / s, $\pm$ 2.27; $p = 0.01$, respectively). Decreased arterial stiffness after RASD has been described by other authors, but so far PBG has not been proven out as a selective criterion for RASD [27–29].

The positive effect of RASD procedure on the left ventricular remodelling and regression of hypertrophy of subjects confirmed by cardiac magnetic resonance imaging was described in the doctoral

dissertation in biomedical sciences by dr. Berūkštis [13]. In MED group, significant changes in cardiac morphometry or diastolic left ventricular functions could not be detected after 6 months of repeated cardiac ultrasound despite an improved blood pressure control. These changes are consistent with a meta-analysis data by S. *Wang* and colleagues, and support the hypothesis that a decreased sympathetic tone in the body reduces BP hypertrophy and target organ damage [30].

We constructed a binary logistic regression model by analyzing factors that may have reflected the correction of a patient's ABP to less than 140/90 mm Hg after 6 months. Although an absolute reduction in ABP is, beyond question, a targeted goal, some patients and their treating physicians are satisfied with suboptimal ABP values [31], when a significant reduction in cardiovascular events occurs when target ABP values are reached [3, 12, 32, 33]. Thus, in this study, we applied a slightly more liberal threshold of 140/90 mm Hg approved by ESC in 2018 rather than the one of 2017 ACC/AHA for the analysis. We did not include RASD procedure as a separate factor into the model, as we looked for common factors for both study groups that could predict a decrease in mean 24-hour systolic ABP below 140/90 mm Hg after 6 months from the start of the study. The inclusion of age, creatinine, total number of pills, LDL cholesterol concentration, and use of calcium channel blockers resulted in a model with a sensitivity of 90.8%, a specificity of 84.6%, and an area under ROC curve (AUC 0.929). These findings enabled us to draw attention to certain features of the subjects that lead to the correction of hypertension and possibly the adherence to the treatment regimen as such.

In RASD group, 44% of subjects were diagnosed with dyslipidaemia and were treated with statins, compared with 91% of subjects in MED group. It is worth noting that there was no statistically significant reduction in LDL-cholesterol levels in MED group neither after 3, nor 6 months. This could be one of the evidences that the subjects did not fully adhere to the treatment regimen. In this study,

subjects in MED group partially acknowledged this in the Morisky (MMAS-4) questionnaire, however according to literature sources, Such questionnaires should be trusted least as a means of verifying a patient's adherence to treatment, as they are often overly optimistic about their condition, while more objective treatment control methods are needed in clinical trials [34–37].

In this model, the role of age and creatinine in predicting ABP correction after 6 months was determined. A negative multiplier for the effect of age in the regression equation (-0.2119) indicates that the target ABP was less likely to be achieved with a decreasing age of a subject. These data could be explained by literature data [38, 39] indicating that patients below 40 years of age have a statistically poorest adherence to treatment regimens and are therefore less likely to achieve target blood pressure in this age group. We related higher creatinine concentrations with the older age of the subjects and assumed that they were more adherent to the treatment regimen and took medicines that affect renin-angiotensin-aldosterone system and moderately increase serum creatinine [40, 41].

It is paradoxical, yet the total number of pills prescribed at the time of the enrolment into the study was significantly better at predicting ABP values after 6 months in this model than the number of antihypertensive pills. The use of calcium channel blockers was also a factor in the successful correction of ABP. Although the values of this group were not emphasized in the first definition of resistant hypertension in 2008 [8], the use of medications in this group in 2017-2018 became one of the mandatory criteria for the diagnosis of resistant hypertension [3, 33, 42].

4.2. Discussion of diagnostic tests performed in the medication treatment group

Part of the laboratory and instrumental tests were carried out in the medication treatment group that are not always performed or repeated at such intervals in the treatment of resistant hypertension.

The analysis of laboratory test results showed that there was no significant changes in creatinine or potassium levels by prescribing medications (ACEI / ARB + ARA) with a sufficiently intense effect on renin-angiotensin-aldosterone system that would indicate deterioration in renal function during treatment. There was also no significant increase in the dynamics of B-type natriuretic peptide, which would indicate worsening of heart failure.

In this group, the mean uric acid in the blood in both men and women exceeded the normal range during all follow-up periods, with some subjects taking medication to treat podagra. In adjusting medication treatment, efforts were made to account for these changes by avoiding combinations of antihypertensive drugs with thiazide diuretics, as studies have shown that uric acid in the endothelium reduces the production of vasodilators and increases peripheral vascular resistance [43, 44]. Therefore, in the absence of contraindications, aldosterone receptor antagonists have been selected that have less effect on uric acid metabolism compared to other diuretics.

Elevated LDL cholesterol levels during the treatment, as reflected in the logistic regression model given above, could be one of the evidences of incomplete adherence.

Chest wall resistance measurements were performed in this group - they show the instantaneous circulatory status of a subject in a non-invasive manner. In this low-scale study, the predominant pattern of hypertension was mixed with 22 (71%) subjects being treated with increasing doses of ACEI / ARB / CCB / ARA / BB / DIU in clinical practice or simply starting to take them. After 6 months, the antihypertensive effect was measured, and mean ABP in only 6 subjects exceeded 105 mm Hg threshold applied in this study. Accordingly, this subgroup could be made of pseudo-resistant subjects with medication misuse and enrolled in this study, or patients with true resistant AH with the need for hemodynamic optimization of treatment. Other subjects had a vasoconstrictive (13%) or hyperdynamic (16%) model of hypertension. Our data are consistent

with those described in the literature, in which the mixed model of hypertension is the most common, however differences in gender, age groups, and comorbidities have been identified with the wider use of impedance cardiography method [45–47]. Differences in ABP correction after 6 months suggest that hypertensive hyperdynamic conditions with high cardiac index due to sympathetic hyperactivation may be the cause of resistant hypertension due to failure to achieve target ABP. To confirm this hypothesis, more detailed studies would be required in combination with other methods to evaluate sympathetic activity. The majority of studies of the ICG method (2000-2015) were performed in patients with mild hypertension who were receiving monotherapy for AH and were compared with another empirically prescribed monotherapy. Most of these studies have demonstrated the superiority of the ICG-based method over empirical treatment [15, 47–49].

Our studied MED group noted that an average of 5-7 pills were prescribed for the treatment of hypertension, the vast majority of whom were treated with the combination of ACEI / ARB + CCB + DIU in the morning, which theoretically markedly reduces peripheral vascular resistance, and whereas ICG testing was also performed in the morning, this may have been one of the reasons for the lack of significant differences in the systemic vascular resistance index (SVRI) (0-3-6 month periods) despite significant differences in ABP measurements over the same period. These errors may also have been influenced by the increased arterial stiffness in most subjects, which resulted in a shorter left ventricular ejection time with a lower left ventricular end-systolic volume [45, 46, 50]. Other studies have described other positive benefits of ICG method, when a physician and patient had to perform additional disease-related test, to consider a circulatory status, to select a more suitable treatment [49]. There is a high likelihood that a part of such subjects were also in MED group. From a treatment adherence perspective, ICG can be used to monitor the hemodynamic response to treatment and to decide whether a subject has actually taken the prescribed medication [51]. Therefore,

in this study, the apparent benefits of the impedance cardiography method were not significant due to the large number of antihypertensive drugs that affect most pathophysiological mechanisms, increased arterial stiffness, and implied non-compliance with the treatment regimen.

In this study, a strong positive correlation between BMI and apnea-hypopnea index (Kendall's Tau correlation coefficient $r^2 = 0.606$, $p < 0.001$) was found in the overnight polysomnography in the MED group. In other testings of sleep apnea and body composition, this ratio is different ($r^2 = 0.424$) [174], as according to the research protocol we included only those subjects who did not have non-invasive pulmonary ventilation (AHI <15 per hour h).

Paradoxical as it may sound, no significant associations were found between AHI and the night-time / day-time systolic and diastolic ABP dipping in MED group, although other studies have proved an association between these indicators [54-57]. Even though polysomnography and 24-hour blood pressure monitoring were not performed simultaneously, ABP measurements during sleep may have affected sleep quality and the ABP measurement results. These results may also have been influenced by polypharmacy, potentially medications used by patients for insomnia, or different chronopharmacology of antihypertensive drugs.

4.3. Discussion of long-term catheter-based renal artery sympathetic denervation monitoring results

This part analyzes RASD group 48 months after renal artery denervation procedure. Based on the results of the observation, the effect of RASD procedure on the reduction of blood pressure has been shown to be long-term [58] and to last longer than 36 months, as previously published in the literature [59, 60]. In this group, the mean reduction in 24-hour systolic ABP was -11 ± 25 mm Hg (95% CI: -20 to -2) ($p < 0.001$), the median of mean 24-hour ABP was 140/86 mm Hg (IQR: 26.5 / 16.2).

Long-term effects on arterial stiffness have also been demonstrated. According to the literature, in the population of healthy people, the pulse wave velocity increases steadily with age, and at the age of 50 begins to increase faster (6-8% per year) [61-63]. The mean age of this group over the analyzed period was 60 years of age, and the median pulse wave velocity at 48 months was 10.3 m/s (IQR: 4.0, 95% CI 6.9, 17.8), and did not differ significantly from baseline, therefore, it can be assumed that RASD procedure partially suspended the progression of arterial stiffness in these subjects over a period of 48 months.

In addition, we analyzed the influence of the number of medications on treatment outcomes. After grouping patients according to the number of pills prescribed, we found no significant differences between subgroups in mean 24-hour ABP, yet there was an upward trend in arterial pulse wave velocity (those who took > 10 pills) in the subgroup from the 12th month, and at 48 months, this difference was statistically significant. This suggests that patients taking multiple pills are in the highest cardiovascular risk group, as described by other authors as well [64].

4.4. Study limitations

Unfortunately, it has to be admitted that this complex thesis has its limitations. First, the study is monocentric, which means that in another centre the results may differ from those presented here due to various causes: operator experience, logistical, technical features, social. Second, the prospective study sample is relatively small and was performed without a parallel intervention or control group, therefore some parameters, such as the efficacy of antihypertensive drugs, cannot be well evaluated due to the originator and generic drugs taken, while a relatively big time difference between the groups and newly emerged additional scientific knowledge may have influenced the results of the prospective group. Moreover, the concentrations of drug metabolites in blood or urine were not measured. The application

of recommendations in clinical work may also be influenced by the fact that patients for the study were selected according to strict criteria, with a large proportion of subjects not included into the final study group due to pseudo-resistance. A multicenter study with a wider scope may help answering the questions that arise from these limitations.

5. CONCLUSIONS

1) In patients with resistant arterial hypertension with a medication optimization strategy based on patient-tailored examination or catheter-based renal artery sympathetic denervation, a significant reduction in arterial blood pressure is maintained at 3 and 6 months.
2) Positive effects of antihypertensive treatment on target organ damage (left ventricular hypertrophy and arterial stiffness) at 6 months are observed in renal artery sympathetic denervation group only.
3) Chest wall resistance measurements are still of limited value in patients with resistant arterial hypertension, requiring additional large-scale testing in combination with determining drug concentrations.
4) Following catheter-based renal artery sympathetic denervation, the antihypertensive effect is long-lasting and persists after 48 months.
5) Negative association between polypharmacy and comorbidities with arterial blood pressure control and arterial stiffness indices.

6. PRACTICAL RECOMMENDATIONS

1) The most common cause of insufficient blood pressure control is non-compliance with medication regimen. When diagnosing and treating patients with poorly controlled hypertension, it is necessary to simplify the treatment regimen by prescribing the smallest number of pills possible, to treat concomitant conditions that may provoke hypertension, and improve the treatment adherence regimen.
2) In case of failure to achieve target arterial blood pressure with medications, catheter-based renal artery sympathetic denervation is one of the most effective and safe ways independent of a patient's medication regimen to improve arterial blood pressure control for at least 48 months that reduce target organ damage.
3) Chest wall resistance measurements can help specify the predominant circulatory mechanism, suspect non-compliance with medication regimen, and prescribe a more patient-tailored treatment.
4) Increased arterial stiffness may help identify patients at highest risk for cardiovascular events.

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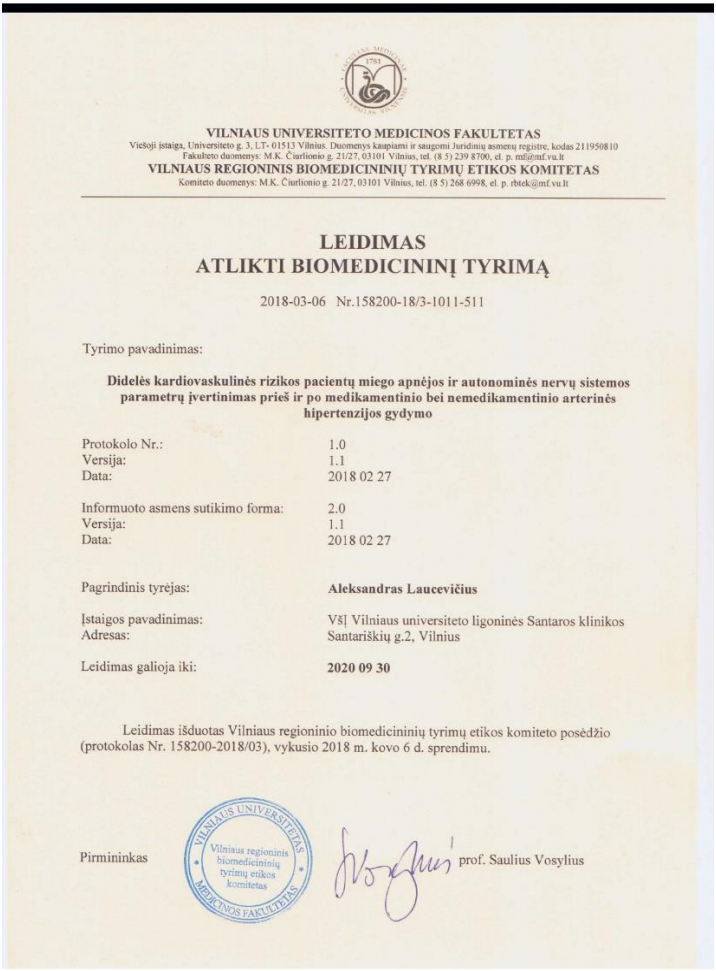
ANNEXES

Authorization provided by the Vilnius Regional Biomedical Research Ethics Committee



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PUBLICATIONS

Publications published in „Clarivate Analytics Web of Science“ and Index Copernicus databases

1. **Juknevičius, Vytautas**; Berūkštis, Andrius; Juknevičienė, Renata; Jasiūnas, Eugenijus; Šerpytis, Pranas; Laucevičius, Aleksandras. Long-term effects of renal artery denervation // Medicina. Basel: MDPI. ISSN 1010-660X. eISSN 1648-9144. 2021, vol. 57, iss. 7, art. no. 662, p. [1–13].DOI:10.3390/medicina57070662.
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1. **Juknevičius, Vytautas**; Berūkštis, Andrius; Juknevičienė, Renata; Saulė, Ieva Marija; Laucevičius, Aleksandras. Impact of polypharmacy and comorbidities to clinical outcomes in resistant hypertension renal denervation group // Journal of hypertension. Philadelphia: Lippincott Williams & Wilkins. ISSN 0263-6352. eISSN 1473-5598. 2021, vol. 39, suppl 1, p. 357–358. DOI: 10.1097/01.hjh.0000748672.74756.93.
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