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NON-INVASIVE PARAMETERS IN TREATED HYPERTENSIVE PATIENTS HAVE BETTER CORRELATION WITH TARGET ORGAN DAMAGE THAN THE POSSIBILITY OF PREDICTING 5-YEAR TREATMENT OUTCOME

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The objective of the research was to investigate which of routine non-invasive parameters could predict the occurrence of target organ damage and treatment outcome during 5-year follow-up in patients with arterial hypertension. The research included 176 patients (average age 66.9 ± 9.3) with arterial hypertension who were previously treated for 144 ± 90 months. Patient monitoring was continued for 63.6 months on average. Average values of 24-hour ABPM were 121.5 ± 14.6 mmHg for systolic (SBP) and 69.1 ± 9.2 mmHg for diastolic (DBP) pressure. The total of 36 (20.4%) patients had diabetes, while 115 (65.4%) patients had lipid disorder. Furthermore, 116 (63.4%) patients had left ventricular hypertrophy (LVH). Left ventricular mass index was, on average, 135.4 ± 30.7 g/m^2. During the follow-up period, we registered 21 (11.9%) new events, 3 (1.7%) of which were stokes, 6 (3.4%) were acute coronary events with accompanying revascularization, two stable angina pectoris (2.6%), two pacemaker insertions (2.6%), one acute thrombosis of leg artery (0.6%), one dementia (0.6%) and 6 (3.4%) new atrial fibrillations. Independent predictor for total new events was the size of left atrium (coefficient beta 0.295; $p < 0.01$). Patients with LVH had higher SBP and DBP values obtained from 24-hour ABPM and home measurement ($p < 0.01$). Independent predictor for the presence of LVH was the length of hypertension treatment (coefficient beta 0.180; $p < 0.03$). Predictors of lower values of creatinine clearance (for model $p < 0.01$) were age (beta 0.187; $p < 0.02$) and glycemic value (coefficient beta 0.232; $p < 0.01$). Routine non-invasive parameters in patients with arterial hypertension cannot predict 5-year treatment outcome during the treatment, but have a good correlation with damage of target organs.

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Key words: *arterial hypertension, treatment, target organs damage, cardiovascular events*

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Introduction

Blood pressure which is above the normal range leads to hypertensive damage of target organs and, along with risk factors for the occurrence of cardiovascular disease, leads to vascular, i.e. arteriosclerosis complications and adverse events. European Guidelines for Arterial Hypertension Recommendations state that the normal systolic pressure is below 140 mmHg and normal diastolic pressure is below 90 mmHg (1). Recently published American Guidelines have stated that normal values of systolic and diastolic blood pressure should be below 130 mmHg and 80 mmHg, respectively, and thus have defined the target values of blood pressure (2). Nowadays, there are numerous discussions on the values of normal blood pressure, as well as on target blood pressure in patients treated from high blood pressure. The Systolic Blood Pressure Intervention Trial (SPRINT) has confirmed that optimum value of systolic blood pressure in patients with arterial hypertension without diabetes is < 120 mmHg (3). If compared to the target value of < 140 mmHg, intensive reduction of blood pressure has led to the reduction of mortality by 27%. However, other studies, such as the study Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) have not confirmed the advantages of intensive reduction of systolic blood pressure below the standard target value (4).

Aside from blood pressure level, the presence of other risk factors was significant for the outcome of hypertensive disease. Joint effects of risk factors were shown in 10-year absolute risk tables in European Recommendations (1). However, reaching the target values defined in the guidelines was not possible in clinical practice. This was clearly shown by the results of EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) study which was conducted in 24 European countries and which focused on cardiovascular disease risk factors (5).

Having in mind the above stated, the expected outcome of hypertensive disease will be different depending on our ability to adjust the therapy and bring blood pressure and other relevant risk factors closer to the targeted values. It is important for clinical experts to review the results of their work and explore the possibility of predicting the disease outcome, all based on the success of correcting non-invasive parameters during treatment. The objective of the research was to determine which of routine non-invasive parameters could predict the occurrence of target organ damage and treatment outcome during 5-year follow-up in patients with arterial hypertension.

Materials and methods

The study was based on routine ambulatory medical examinations at Niška Banja Institute. The patients were referred to the institute from primary health protection unit due to high blood pressure. Treatment and monitoring were continued at the Institute. The second medical check-up was conducted after two weeks, the third was after a month, after which the check-ups were conducted each 5-6 months. All patients were subjected to clinical examination which included anthropometric measurements (waist, height and weight), electrocardiography, blood pressure measurement in ambulatory conditions, home conditions and 24-hour ambulatory monitoring, echocardiography and ergometric test. Patients with arterial hypertension and cardiovascular or cerebrovascular complications were not included in the study. The total of 176 patients, 72 males and 104 females, met the criteria for being included in the study. Table 1 shows the basic characteristics of the tested group. Median for risk factors, such as age, gender, smoking habits, diabetes, hypercholesterolemia, obesity, physical inactivity, alcoholism and heredity, was 4 risk factors for cardiovascular diseases. Thirty-six patients (20.4%) had diabetes, while 115 (65.4%) patients had lipid disorder. Ideal weight was recorded in 40 (21.9%) patients, while obesity was recorded in 56 (30.6%) patients. There were 61 (34.7%) smokers in the group, 19 (10.8%) of whom never stopped smoking. Physical inactivity was recorded in 62 (35.2%) patients.

Table 1. Basic features of the tested group

Parameters	Values
Male (%) / female (%)	72 (40.9)/104 (59.1)
Hypertension duration (months)	12.0 ± 7.5
Monitoring duration (years)	5.4 ± 3.0
Systolic blood pressure at outpatient unit (mmHg)	127.1 ± 14.4
Diastolic blood pressure at outpatient unit (mmHg)	77.7 ± 6.3
Body mass index (kg/m^2)	28.7 ± 4.7
Left ventricular mass (g)	255.3 ± 70.5
Left ventricular mass index (g/m^2)	135.3 ± 30.7
Left ventricular ejection fraction (%)	64.0 ± 5.8
Aortic root diameter (mm)	33.7 ± 3.3
Left atrial diameter (mm)	42.2 ± 6.5
Glycaemia (mmol/L)	6.0 ± 1.9
Cholesterol (mmol/L)	5.7 ± 1.2
HDL-cholesterol (mmol/L)	1.4 ± 0.7
LDL-cholesterol (mmol/L)	3.6 ± 1.1
Triglycerides (mmol/L)	1.9 ± 1.5
Creatinine (μmol/L)	87.8 ± 24.9
Number of risk factors	3.7 ± 1.3

In terms of important medications, at the end of the study 144 (81.1%) patients used beta blockers, 142 (80.7%) used ACE inhibitors or blockers of angiotensin 1 receptors , 85 (48.3%) patients used calcium channel blockers, 113 (64.2%) patients used diuretics and 72 (40.9%) patients used statins.

Blood pressure measurement

Blood pressure was initially measured in ambulatory conditions twice in two minutes at both hands. After the change of therapy, blood pressure reached the optimal limits, which was confirmed during the control check-ups. Corrected values of blood pressure were used in the study as average values monitored at control check-ups. The patients were trained to measure blood pressure at home twice a week, in the morning and in the evening for a period of one month, between the second and third check-up. Twenty-fourhour ambulatory blood pressure monitoring was conducted minimum once within the period of six months from the second medical check-up.

Laboratory analysis

We conducted the following standard laboratory analyses: complete blood count, glycaemia, lipid status, transaminase, urea, creatinine, uric acid, electrolytes and urine. The therapy was altered in accordance with the results of laboratory tests. Values of laboratory parameters which were taken minimum two months after taking the regular therapy were taken for the needs of this study. Total cholesterol larger than 5 mmol/L and/or triglycerides larger than 1.7 mmol/L were defined as lipid status disorder. Patients who suffered from diabetes mellitus needed endocrinologist report or evidence on prescribed medications for diabetes. Glomerular filtration rate was calculated by Cockcroft-Gault equation and identified five levels of kidney function (6).

Exercise testing

Exercise test, without beta blockers for minimum 24 hours, was done by standard Bruce protocol. The test was completed after reaching submaximal heart rate (85% of maximum theoretical heart rate) or due to pain in the chest or legs, fatigue or vertigo. Additionally, we respected patient's request to terminate the test if the patient felt bad. Ergometric test was conducted with the aim of excluding the patients due to coronary disease or discovering coronary disease as adverse vascular event during the later tests.

Echocardiography

Echocardiography was conducted by means of standard two-dimensional technique, while the measurement of heart structure was done by M-mode technique. Additionally, the assessment of valve function and testing the flow was done by means of Color Doppler, including pulse and/or Continuous-Wave Doppler. Having in mind that the patients had no segmental contractility disorder, all measurements were conducted in M-mode technique. Echocardiographic parameters which were taken into consideration were aortic root diameter, left ventricular diameter and ejection fraction. Left ventricular mass was calculated based on left ventricular wall thickness at the end of diastole and diastole diameter. Left ventricular mass index was obtained by dividing left ventricular mass by body surface area (7). Male patients with left ventricular mass index larger than 134 g/m^2 and female patients with mass index larger than 110 g/m^2 were considered to suffer from left ventricular hypertrophy. Patients with moderate and severe heart defects were excluded from the study.

Statistical data processing

Numerical parameters were shown as mean value ± standard deviation. Statistical significance between the subgroup was defined by means of Student's t-test. Distribution of attributive marks was shown by absolute values, percentage and median. Testing statistical significance between the groups was conducted by means of χ^2 test. Pearson correlation coefficient was obtained by bivariate correlation method. Multivariate linear regression analysis was used for defining significant predictors of adverse events and target organ damage. The value of p less than 0.05 was considered as statistically significant.

Results

During the follow-up period, we registered 21 (11.9%) new events, 3 (1.7%) of which were strokes, 6 (3.4%) were acute coronary events with revascularization, 2 (2.6%) stable angina pectoris, 2 (2.6%) pacemaker insertions, 1 (0.6%) acute arterial leg thrombosis, 1 (0.6%) dementia and 6 (3.4%) new atrial fibrillations.

Table 2 shows characteristics of patients with adverse event as compared to patients who have never experienced an adverse event. After including the parameters such as gender, age, hypertension duration, systolic and diastolic blood pressure values, factors of risk, body mass index, waist, glycaemia, total cholesterol, creatinine value and echocardiographic parameters, we obtained a model with one prognostic marker ($R = 0.277$; $R^2 = 0.077$; adjusted $R^2 = 0.070$; standard error of the estimate = 0.32600; $p < 0.001$). The only independent predictor of total new events was left atrial size (beta coefficient 0.277; $p < 0.01$). There was no difference in terms of the use of specific medications. After excluding non-vascular events from the analysis, there was not a single parameter that was statistically different between the groups.

Table 2. Most important characteristics of patients with and without adverse events

Parameters	Without adverse event	With adverse event
Age	66.6 ± 9.4	69.8 ± 8.6
Systolic blood pressure (mmHg)	127.2 ± 14.7	125.7 ± 12.8
Diastolic blood pressure (mmHg)	77.9 ± 6.6	75.7 ± 5.4
Ejection fraction (%)	64.0 ± 5.9	63.9 ± 5.5
Left atrial diameter (mm)	41.8 ± 5.9	46.1 ± 9.4*
Left ventricular mass index (g/m^2)	135.6 ± 30.2	134.4 ± 35.5
Glycaemia (mmol/L)	6.0 ± 2.0	5.6 ± 1.0
Total cholesterol (mmol/L)	5.7 ± 1.2	5.1 ± 1.0*
Creatinine (μmol/L)	88.1 ± 26.1	85.2 ± 15.3
Factors of risk	3.7 ± 1.3	3.3 ± 1.3

* - $p<0.05$

Both male and female patients with left ventricular mass index above limit value were older (age 68.4 ± 8.6 vs. 64.1 ± 10.0; $p < 0.01$), had longer history of treating arterial blood pressure (12.8 ± 7.4 vs. 10.3 ± 7.3 months), had higher values of 24-hour systolic (123.9 ± 10.0 vs. 119.2 ± 9.5 mmHg; $p < 0.05$) and diastolic (70.9 ± 10.2 vs. 66.1 ± 4.8 mmHg; $p < 0.05$) blood pressure. Additionally, these patients had higher values of home systolic (124.8 ± 11.2 vs. 118.3 ± 9.1 mmHg; $p < 0.05$) and diastolic blood pressure (71.5 ± 7.9 vs. 67.8 ± 5.3 mmHg; $p < 0.05$). Independent predictor for the presence of left ventricular hypertrophy was hypertension treatment duration (beta coefficient 0.180; $p < 0.03$; for model: $R = 0.180$; $R^2 = 0.032$; adjusted $R^2 = 0.026$; standard error of the estimate = 0.46992 $p < 0.03$). In terms of medication use, we found significant difference in the use of ACE inhibitors or angiotensin II receptor blockers in the group of patients with left ventricular hypertrophy (85.3% vs. 71.6%; $p < 0.05$), as compared to patients who did not suffer from left ventricular hypertrophy.

Predictors of higher creatinine values (for model: $R = 0.289$; $R^2 = 0.033$; adjusted $R^2 = 0.027$; standard error of the estimate = 24.23117 $p < 0.01$) were age (beta coefficient 0.178; $p < 0.02$) and glycaemia values (beta coefficient 0.231; $p < 0.01$). There was no significant correlation between eGFR and other parameters after excluding parameters which were parts of eGFR formula, except the value of systolic blood pressure ($r = 0.200$; $p < 0.05$). In terms of glomerular filtration rate, 53 (30.1%) patients had I-degree kidney function, 82 (46.6%) patients had II-degree kidney function, 38 (21.6%) patients had III-degree kidney function, only 3 (1.7%) patients had IV-degree kidney function, while there were no patients with V-degree of kidney function.

Figure 1 shows direct bivariate correlation between glycaemia and creatinine values. Correlation coefficient was not high, but it was statistically significant ($r = 0.231$; $p < 0.01$).

Ultrasound examination of carotid artery was conducted in 56 (31.8%) patients, 18 of whom had normal results (intima-media complex < 0.9 mm). Patients whose blood pressure could not be regulated despite the therapy (19 patients – 10.8%) were subjected to fundus examination, the result of which were changes of II degree.

Success in achieving the target values of specific parameters was shown in Graph 1.

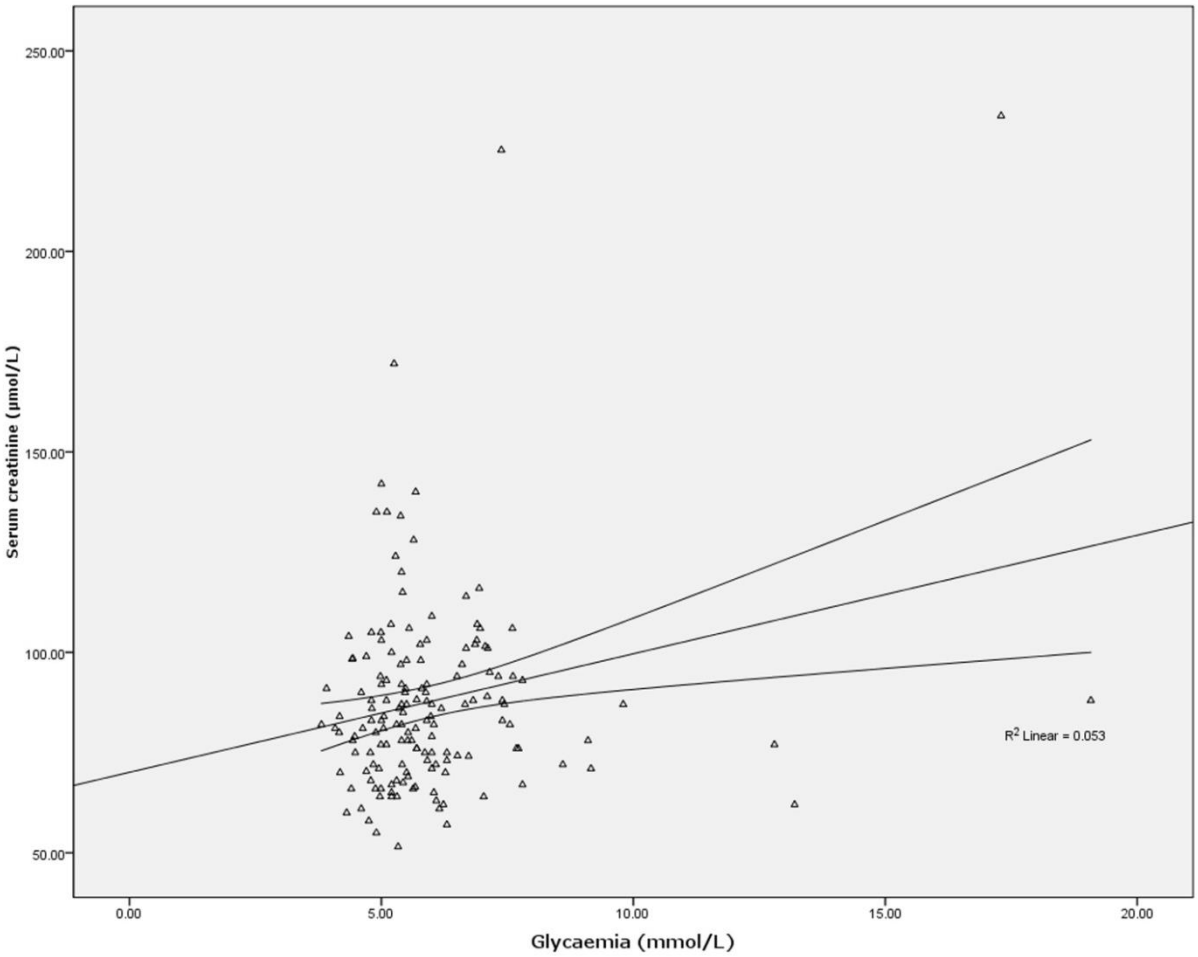
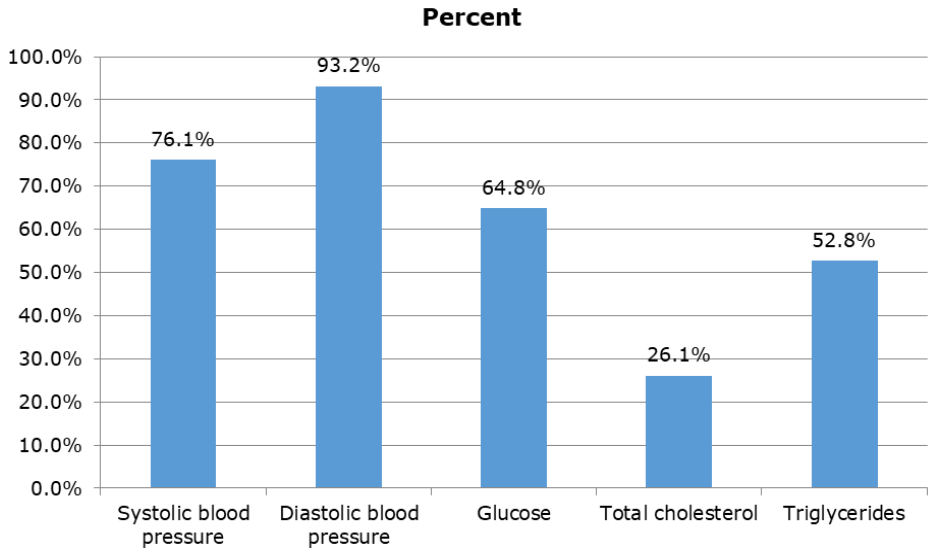


Figure 1. Direct bivariate correlation be-tween glycaemia and creatinine values.



Graph 1. Success in achieving the target values in accordance with European guidelines

Discussion

Vascular events (stroke and coronary disease) had a significant share in the structure of adverse events analyzed in this study. As for non-vascular events, atrial fibrillation was very important as well. This could account for the difference between the group with adverse event and the group without adverse events in terms of left atrial size. This difference became irrelevant if we observed patients with vascular complications only. Vaziri et al. proved that systolic and diastolic pressure level led to the increase of left ventricle, but that this was not the only cause (8). Moreover, age and body mass index played a very important role. According to the research of Dan et al. arterial hypertension was an important factor for the occurrence of composite events in patients with atrial fibrillation, but that it was not an independent prognostic marker in one-year total mortality (9). Higher value of total cholesterol in group of patients without adverse events could be explained by intensive statin therapy, as the difference in the use of statin was not recorded in the two subgroups.

Left ventricular hypertrophy occurred as a result of various factors, such as high arterial blood pressure, numerous neurohumoral factors and genetic factors (10). Patients with left ventricular hypertrophy who participated in this study were older, had longer history of treating arterial hypertension, higher values of systolic and diastolic blood pressure measured at home and during 24-hour ambulatory monitoring, but did not have high blood pressure measured in ambulatory conditions. Monitoring of blood pressure in ambulatory conditions was easier, but pressure was controlled better if home measurement was included in the entire process (11). This was cheaper and easier way of controlling blood pressure, and the studies showed that the results had good correlation with 24-hour ambulatory blood pressure measurement (12, 13). Niiramen et al. pointed out that even a one-day measurement could have prognostic significance. However, blood pressure should be measured at home for at least seven days in order to obtain the proper hypertension diagnosis (14). On the other hand, home measurement of blood pressure could predict morbidity and mortality of patients with arterial hypertension (15, 16). Having in mind literature data, the results of this research were compatible in terms of blood pressure rate and age. However, one could argue the fact that duration of arterial hypertension treatment correlated and acted as independent prognostic marker for the occurrence of left ventricular hypertrophy. It was hard to determine the moment when hypertension occurred and the moment when systematic treatment was initiated. Increased use of ACE inhibitors/angiotensin II receptor blocker was in accordance with the guidelines for treating arterial hypertension, having in mind that most potent medications for hypertrophy regression were the medications from this group (1, 17).

In terms of hypertension, kidney is the second target organ and its damage should be detected by non-invasive methods on regular basis. According to the consensus of the three European associations: the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the European Society of Hypertension, assessment of glomerular filtration rate, detection of microalbuminuria and definition of albumin-creatinine ratio in urine are recommended for early detection of kidney damage (18). However, due to insufficient availability, we usually measure creatinine and calculate glomerular filtration for all patients, as we have done to all patients who participated in this study. It is important to mention that it takes several years to change glomerular filtration arte (19). After diabetes, arterial hypertension is an important cause of kidney failure. Appropriate regulation of blood pressure reduces the frequency of kidney failure and vice versa, higher blood pressure measured by 24-hour ambulatory monitoring increases the frequency of kidney function deterioration (20, 21). Our study has demonstrated the connection between glomerular filtration rate and systolic blood pressure. Some studies have shown that dyslipidemia increases the risk of kidney failure (22). However, there are studies which have not confirmed the results illustrated in our study (23). Our study has found the correlation between glycaemia and creatinine. However, our study has not confirmed the correlation between glomerular filtration and diabetes, even though it has been confirmed in other studies (22).

Even though the guidelines emphasize the necessity of conducting ultrasound examination of carotid arteries as markers of vascular damage, it is not easy to conduct such examination in clinical conditions, and thus we have managed to conduct ultrasound examination in 31.8% patients (18). Even though they were mentioned in the guidelines, pulse velocity test and ankle–brachial index were not conducted during the study due to their unavailability. Detection of microvascular changes in the brain by means of magnetic resonance were not conducted because majority of patients had no neurological deteriorations, no deterioration of cognitive function, except one patient with verified dementia and changes during magnetic resonance of the brain. Patients with acute cerebrovascular events were subjected to detailed neurological diagnostics and therapy.

Conclusion

Routine non-invasive parameters in patients with arterial hypertension cannot predict five-year treatment outcome during the treatment, but have a good correlation with the degree of target organ damage.

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NEINVAZIVNI PARAMETRI KOD HIPERTENZIVNIH BOLESNIKA, KOJI SE LEČE, BOLJE KORELIRAJU SA OŠTEĆENJEM CILJNIH ORGANA U ODNOSU NA MOGUĆNOST PREDVIĐANJA PETOGODIŠNJEG ISHODA LEČENJA

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Cilj istraživanja bio je ispitati koji od rutinskih neinvazivnih parametara može, kod lečenih bolesnika od arterijke hipertenzije, predvideti nastanak oštećenja ciljnih organa i ishod bolesti, tokom pet godina praćenja. U istraživanje je uključeno 176 bolesnika (prosečne starosti 66,9 godina ± 9,3 godine) sa arteijskom hipertenzijom, koji su bili prethodno lečeni, prosečno 144 meseci ± 90 meseci. Praćenje bolesnika nastavljeno je još prosečno 63,6 meseci. Prosečne vrednosti dvadesetčetvoročasovnog ABPM bile su za sistolni (SBP) 121,5 mmHg ± 14,6 mmHg i za dijastolni (DBP) 69,1 mmHg ± 9,2 mmHg. Dijabetes je imalo 36 (20,4%) bolesnika, a poremećaj lipida 115 (65,4%) bolesnika. Hipertrofiju leve komore (LVH) imalo je 116 (63,4%) bolesnika. Indeks mase leve komore bio je prosečno 135,4 g/m^2 ± 30,7 g/m^2. Tokom perioda praćenja registrovan je 21 (11,9%) novi događaj, od toga 3 (1,7%) šloga, 6 (3,4%) akutnih koronarnih događaja sa sledstvenom revaskularizacijom, dve stabilne angine pektoris (2,6%), dve implantacije pejs-mejkera (2,6%), jedna akutna tromboza arterije nogu (0,6%), jedna demencija (0,6%) i 6 (3,4%) novih atrijalnih fibrilacija. Nezavisni prediktor za ukupne nove događaje bila je veličina leve pretkomore (koeficijent beta 0,295; p < 0,01). Bolesnici sa LVH imali su značajno veće SBP i DBP dobijenog iz dvadesetčetvoro-časovnog ABPM i kućnog merenja (p < 0,01). Nezavistan prediktor za prisustvo LVH bila je dužina lečenja hipertenzije (koeficijent beta 0,180; p < 0,03). Prediktori nižih vrednosti klirensa kreatinina (za model p < 0,01) bile su godine starosti (beta 0,187; p < 0,02) i vrednosti glikemije (koeficijent beta 0,232; p < 0,01). Rutinski neinvazivni parametri kod bolesnika sa artrijskom hipertenzijom tokom lečenja, ne mogu predvideti petogodišnji ishod lečenja, ali dobro korelišu sa oštećenjem ciljnih organa.

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Ključne reči: *arterijska hipertenzija, lečenje, oštećenje ciljnih organa, kardiovaskularni događaji*