SUMMARY

PH.D. THESIS

MANAGEMENT OF RESISTANT HYPERTENSION

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Resistant hypertension is a priority issue for primary and secondary care settings, given its rising prevalence and the special diagnostic and therapeutic approach it requires, not only for gaining control over blood pressure values and meeting the targets, but also for reducing the risk of cardiovascular diseases, as well as the high morbidity and mortality related to this pathology. Patients suffering from resistant hypertension represent an important public health issue in our country, as they present a high or very high absolute cardiovascular risk, imposing considerable expenses on the healthcare system, and have a high prevalence of organ damage as they are difficult to control.

Since there are relatively few data collected from studies on the prevalence and clinical and biological characteristics, as well as on the control of resistant hypertension in the western part of Romania, we have proposed to perform a study on resistant hypertension (RH) in GP surgeries, the healthcare facilities to which most hypertensive patients initially refer.

We have performed an observational study of hypertensive patients in 17 GP surgeries in Timis County, in collaboration with cardiologists from specialized medical centres and clinical units in Timis County. The diagnosis made in the GP surgery and based on measuring the BP and on the ambulatory blood pressure monitoring (ABPM); pathological ABPM cases are investigated in specialized clinics by performing complementary investigations such as echocardiography, carotid ultrasonography, abdominal ultrasound, biochemical, hormonal, CT and MRI investigations.

THE OBJECTIVES OF THIS STUDY were the following:

- Identifying the prevalence of RH in hypertensive patients monitored at the level of GP surgeries in Timis county
- Assessing their epidemiological profile
- Assessing the risk factors associated with RH
- Assessing the clinical profile or RH

- Identifying the demographic and clinical factors associated with treatment resistance
- Exploring, at the level of family medicine, the blood pressure profile during the daytime, overnight and for 24 h using the ambulatory BP monitoring, determining the dipper or non-dipper night-time blood pressure profile
- Making a comparison between patients with RH and patients with controlled hypertension
- Establishing a RH patient assessment algorithm
- Analyzing the renal impairment, focusing on tracking down microalbuminuria and on determining the eGFR based on tables, using creatinine and the gender of patients
- Tracking the predictive factors for the presence of microabuminuria
- Analyzing the cardiac damage in RH based on the electrocardiogram and echocardiography
- Analyzing the subclinical vascular damage highlighted by the carotid ultrasonography
- Identifying the diagnostic errors met in the studied pathology
- Developing a close relationship with specialists in clinical centres for continuing the investigation on cardiac organ damage, renal and vascular impairment and associated cardiovascular, renal, cerebral and vascular diseases.
- Analyzing and monitoring the administered therapy and recommendations on lifestyle changes for the control of resistant hypertension
- Collaborating with specialists for establishing the optimal therapeutic scheme, which would provide control over resistant hypertension and over the regression of organ damage
- Establishing a RH patient assessment algorithm
- Monitoring treatment adherence and the results obtained with decreasing the BP and the regression of organ damage on the longest possible period.

MATERIAL AND METHODS

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A number of 5146 hypertensive patients from 17 GP surgeries in Timis County, treated for at least 3 months, were evaluated between 2012 and 2018. The inclusion criteria were: adult hypertensive patients, over 18 years of age, newly identified with office BP values higher than 140/and or 90 mmHg or controlled or uncontrolled patients under treatment. The study excluded patients with secondary hypertension, patients known for being non-compliant to treatment, and those who did not accept to be part of the study and to go through the control and investigation stages, as well as patients with atrial fibrillation, for whom a satisfactory ABPM cannot be obtained. The database included office BP measurements and

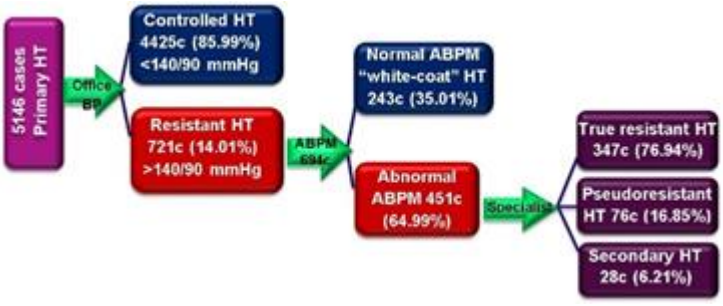
ambulatory BP monitoring. The laboratory tests provided data on (1) the presence of risk factors, (2) presence of target organ damage and (3) main causes of secondary hypertension, and initially included the routine ones. More complex investigations were necessary only for a limited number of cases, where history, physical examinations and laboratory data suggested a secondary cause for hypertension.

In hypertensive patients, general practitioners performed ECG and the albumin/creatinine ratio using the Arkray sticks, and MAU+ cases were subsequently confirmed in accredited laboratories.

RESULTS

From the total number of 5146 patients enrolled in the study, 4425 (85.99%) patients were therapeutically controlled, reaching the target BP values, i.e. under 140/90 mm Hg. These patients formed the controlled hypertension group. The study included both patients with newly identified hypertension and patients who were already suffering from hypertension. The newly identified hypertensive patients have been evaluated for three months, a period considered to be necessary for the physician to establish the optimal therapeutic scheme and to include the patient, based on the office measured BP, in one of the 2 groups, i.e. the 1st therapeutically controlled group and the 2nd group of patients who was not controlled with three therapies.

A number of 721 (14.01%) cases had office BP values >140/90 mmHg, being treated with three agents in maximum doses, including a diuretic. These cases met, based on office BP measurements, the criteria for treatment resistant hypertension.



Flow chart of the study

In order to exclude from this group the white-coat effect hypertension or “white-coat” effect for HT measured in the medical practice, the ABPM was further performed using BTL 08 devices in all uncontrolled HT cases.

Out of the 694 cases evaluated by ambulatory blood pressure monitoring, 451 (64.99%) patients were found with abnormal values of the 24h BP profile. This

study group presented a correspondence between the office BP and the BP recorded automatically using the ABPM. This group was further explored in order to exclude false resistance due to non-adherence to treatment or to secondary hypertension.

When evaluated using the ambulatory blood pressure monitoring device, a number of 243 (35.1%) patients with apparently resistant office BP (group II) had normal BP values, both during daytime (under 135/85 mm Hg) and over 24 h (under 130/80 mm Hg), which allowed us to exclude RH. In this group, the normal ABPM values confirmed the "white-coat" effect hypertension or "white-coat" effect, which explained the high BP values measured in the medical practice.

In the following stage of the study, patients with pathological ABPM values were evaluated in specialized clinics for excluding secondary hypertension or pseudo-resistant HT. After the investigations performed, out of the 451 patients with pathological ABPM values, resistant HT was confirmed in only 347 (76.94%) cases.

RH was excluded in 104 (23%) patients as following: pseudo-resistant HT was confirmed in 76 (16.85%) cases and secondary HT was confirmed in 28 (6.21%) cases. Out of the total number of 721 (14.1%) patients considered to suffer from treatment resistant hypertension based on office measurements, only 347 cases were finally diagnosed with true RH, which corresponds to a true RH prevalence of 6.47% of the total evaluated hypertensive population in Timis County.

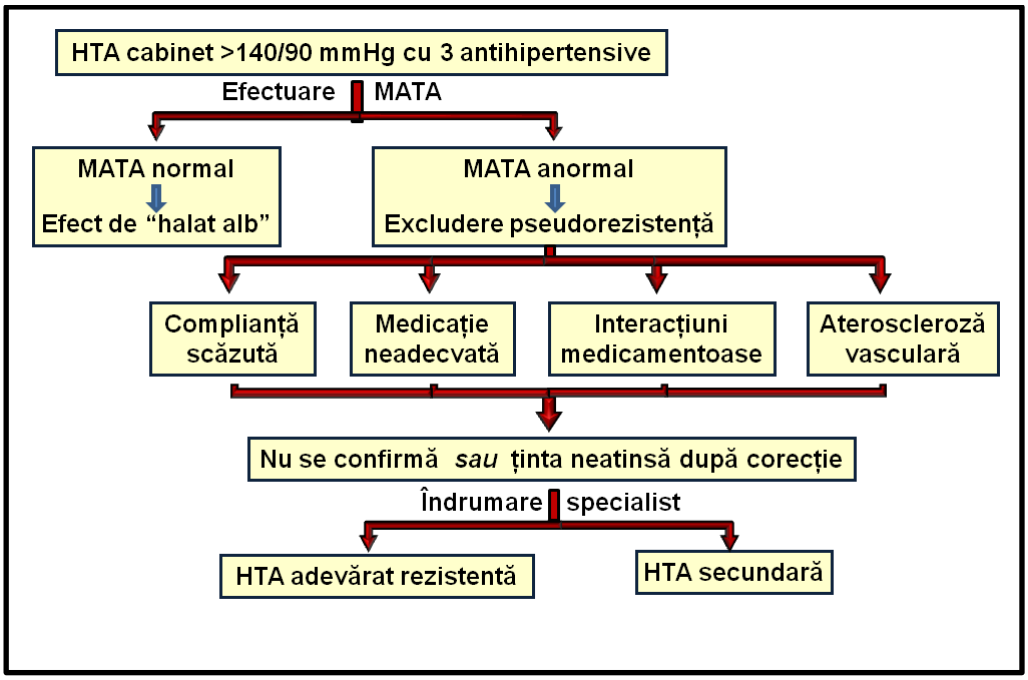
The causes of treatment pseudo-resistance were the following: lack of treatment adherence in 44 (57.89%) cases, inappropriate therapy in terms of doses and combinations in 22 (28.96%) cases, associated administration of drugs leading to the increase of BP in 6 (7.89%) cases and other different causes for pseudo-resistance in 4 (5.26%) patients.

A number of 28 cases with secondary HT (6.21% of 5146 patients) have also been identified. The most frequent causes for secondary HT were sleep apnoea syndrome in 10 (35.71%) cases, renal artery stenosis in 6 (21.43%) cases, renal parenchymal disease in 4 (14.28%) cases, primary hyperaldosteronism in 3 (10.71%) cases, Cushing's syndrome in 1 (3.57%) case and other causes in 2 (7.14%) cases.

In order to analyse the characteristics of RH and the differences compared to controlled HT, we carried out a comparative study between a group of 721 hypertensive controlled patients and a group of 347 patients suffering from treatment resistant hypertension. Office BP values and ABPM values were statistically significantly higher in RH patients compared to HT controlled patients. The analysis of the patients' lifestyle identified the presence of many factors which have contributed to the development of RH. The factors present in RH patients were: obesity in 204 (58.79%) patients, sedentary lifestyle in 187 (57%) patients,

high salt intake in 25.07%, smoking in 17.87%, and excessive alcohol ingestion in 41 (11.81%) patients. By preventive education actions, medical assistants and physicians involved in the study made efforts for fighting these risk factors and changing the patients' lifestyle.

The general practitioners involved in the research, together with the cardiologists with whom they collaborated, based on the experience and data collected in the study, have elaborated a RH diagnostic algorithm. The diagnostic algorithm was disseminated among general practitioners in Timis County, in order to be applied on a large scale at the level of GP surgeries and specialized clinics when assessing the patients suspected for treatment resistant hypertension. In this diagnostic algorithm, the normal ABPM values confirm the white-coat HT. In case of pathological ABPM, first, we need to exclude pseudo-resistance due to low adherence, inappropriate medication, drug interactions and vascular atherosclerosis in the elderly. When a pseudo-resistance cause cannot be objectified and BP targets are not met, collaboration with consultants becomes necessary, their experience and professional training being highly important for solving severe HT cases.



Office HT > 140/90 mmHg with 3 antihypertensive drugs
Performing the ABPM
Normal ABPM →"White coat" effect
Abnormal ABPM → Excluding the pseudo-resistance → Low adherence Inadequate medication Drug interactions Vascular atherosclerosis → Not confirmed

or *target* not reached after correction → Referral to consultant → True RH Secondary HT

Diagnostic algorithm in RH

The blood pressure profile was characterised by high blood pressure values in RH compared to controlled hypertension, the highest values being recorded when measuring blood pressure in the medical practice. The biggest differences between the 2 groups referred to daytime SBP, office SBP and night-time SBP. The analysis of the circadian blood pressure profile over 24 h lead to the identification of a 65.53% non-dipper BP profile in RH patients vs. 60.89% in controlled HT patients.

Compared to controlled HT patients, the following clinical factors were more frequently met in RH patients: longer progression of the disease - in years, older age, family history of cardiovascular diseases more frequently present, higher prevalence of diabetes mellitus, obesity, target organ damage and cardiovascular diseases. No statistically significant changes referring to gender, presence of dyslipidemia and reduced glucose tolerance have been identified in the 2 groups.

The evaluation of urinary albumin excretion by determining the urinary albumin/creatinine ratio in RH patients has lead to identifying the presence of microalbuminuria (MAU+) in 76 (21.9%) cases, the absence of MAU (MAU-) in 243 (70.02%) patients and presence of macroalbuminuria in 28 (8.08%) patients. The prevalence of MAU was influenced by age, being more reduced in the 30-40 years age group compared to the older age group, with the highest prevalence in the 60-70 years age group (35.52%) and in the 70-80 years age group (30.26%). The comparison between the MAU+ and MAU- study groups has pointed out the differences between the 2 groups in terms of biochemical and clinical data. RH patients, identified with MAU+, were older, with significantly older mean ages (66.10 ± 11.20 vs. 62.30 ± 10.20 years, $p = 0.0060$), age ranges varying between 31 and 76 years. The male gender was present in 43 (56.58%) cases with MAU+, compared to 124 (51.03%) cases in the MAU- group. The systolic BP measured in the medical practice was higher than RH with MAU+ compared to the MAU- group (165 ± 13.50 vs. 148 ± 12.40 mmHg, $p<0.0001$). Also, diastolic BP was higher in the RH group with MAU+ (94 ± 12.20 mmHg vs. 88 ± 14.6 mmHg, $p = 0.0013$), who presented an unfavourable BP profile over 24 hours (68.11% non-dippers + risers). We noticed a longer BP progression, in years, in the MAU+ group, but this was not statistically significant (15.20 ± 9.90 vs. 14.10 ± 9.80, $p = 0.1048$).

Statistically significant differences between the RH groups with MAU+ and MAU- were noticed concerning the presence of obesity (64.47% vs. 48.97%, $p = 0.0184$), diabetes mellitus (44% vs. 34 %, $p = 0.001$), a LVH on ECG (8.93% vs.

2.08%, p = 0.0034), LVH detected on the ultrasound in 28% (p=0.001), ischaemic cardiac diseases (42.10% vs. 23.87%, p = 0.0021), peripheral artery diseases (30.26% vs. 18.10%, p = 0.0233), and the increased number of drugs administered (3.72 ± 0.78 vs. 3.44 ± 0.46, p = 0.001). No significant differences were noticed in terms of gender distribution (p = 0.3986), living area (urban 57.89% vs. rural 55.97%, p = 0.7686), family history of cardiac diseases (39.47% vs. 37.04%, p = 0.7031), sedentary lifestyle (59.21% vs. 57.91%, p = 0.062), smoking (18.47% vs. 17.05%, p = 0.7413) and concerning the incidence of cerebrovascular diseases (25.00% vs. 23.04%, p = 0.7255). The analysis of biochemical data in RH patients showed significant differences between the MAU+ and MAU- groups. Statistically significant differences were noted for glycaemia (118.80 ± 32.02 vs. 108.01 ± 26.01 mg/dL), HbA1c (6.56 ± 0.98 vs. 5.96 ± 0.91 %), eGFR (56.10 ± 15.4 vs. 69.30 ± 17.5 mL/min/1.73 m^2) and potassium (4.59 ± 0.44 vs. 4.71 ± 0.43 mg/dL). No statistically significant differences were noted for serum creatinine, uric acid, LDL-cholesterol, HDL- cholesterol, TG and reduced glucose tolerance.

The univariate logistic regression analysis indicated the following factors that were correlated with MAU+: age (OD 1.028, 95% CI 1.018-1044, p < 0.001), BMI (0.987, 95% CI 0.977-0.998, p = 0.01), systolic BP over 24 hours (OD 1.023, 95% CI 1.014-1.032, p < 0.001), eGFR (OD 0.99, 95% CI 0.982-0.997, p < 0.001), glycaemia (OD 1.003, 95% CI 1.002-1.008, p = 0.01), HbA1c (OD 1.384, 95% CI 1.231-1.692, p < 0.001), ischaemic cardiac diseases (OD 1.018, 95% CI 1.003-1.032, p = 0.04), peripheral artery diseases (OD 1.520, 95% CI 1.150-2.015, p = 0.010), and diabetes mellitus (OD 1.560, 95% CI 1.256-1.904, p < 0.001).

In the multivariate analysis, the factors correlated with the presence of MAU were systolic BP (OD 1.024, 95% CI 1.011-1.039, p < 0.001), HbA1c (OD 1.324, 95% CI 1.078-1.724, p = 0.008), and eGFR (OD 0.989, 95% CI 0.977-0.999, p = 0.01). The study also indicated that MAU+ in RH resistant patients is an early marker of progressive CV and renal diseases.

MAU was identified in all stages of CKDs. In the 1st, 2nd, 3rd and 4th stages of CKD the prevalence was the following: 3.95%, 18.43%, 38.15% and 39.47%, respectively. From the 76 cases with MAU+, 32 (42%) cases were patients suffering from diabetes, with a statistically significantly high percent compared to the RH patients with MAU- (patients with diabetes 34%). Regarding glucose tolerance, no significant differences were found. MAU+ was present in 42.10% of the patients with ischaemic cardiac diseases, in 30.26% of those with peripheral artery diseases and in 25% of the patients with cerebrovascular diseases (figure 52).

The carotid ultrasonography indicated that the carotid intima-media thickness was greater in RH patients with MAU+ (0.95±0.15 mm) compared to RH

patients with MAU– (0.89±0.12mm). Carotid artery atheromatous plaques were identified in 22 (28.90%) RH patients with MAU+ compared to 37 (15.22%) patients with MAU-.

Concerning the presence of left ventricular hypertrophy, detected on the electrocardiogram, it was identified in 31 (8.93%) RH patients with MAU+, and in 123 (2.08%) patients with MAU-, which is a statistically significant difference.

The structure of the LV was analyzed on the echocardiography in 258 hypertensive patients with RH. The LV modifications identified on the echocardiography included four subtypes: I. normal geometry in 84 (31%) patients; II. concentric remodelling in 54 (20.9%) echocardiography; III. eccentric hypertrophy in 60 (23.2%) patients and IV. concentric hypertrophy in 63 (24.4%) patients. Please note that the most frequent modification encountered in RH patients was the concentric hypertrophy of the left ventricle, followed by the concentric remodelling of the left ventricle and by the eccentric hypertrophy of the LV.

In RH, compared to controlled hypertension, the following drug classes were administered: ACE inhibitors (61.09% vs. 48.96%), ARB1 (38.9% vs. 34.95%, diuretics (100% vs. 42%), calcium blockers (74.93% vs. 38.00%), spironolactone (17.87% vs. 0.00%) and other classes (57.92% vs. 5.96%).

In RH identified in the MAU+ vs. MAU- groups the following drug classes were administered: ACE inhibitors (55.26% vs. 60.90%), ARB_1 (44.74% vs. 37.86%), diuretics (100% in both groups), calcium blockers (76.31% vs. 69.96%), beta blockers (51.31% vs. 46.09%), spironoclactone (19.74% vs. 16.87%) and other antihypertensive drugs (58.37% vs. 57.92%).

76.13% of the RH patients with MAU - underwent triple therapy. 64.47% of the patients with MAU+ were recommended triple therapy. 18.43% of the RH patients with MAU+ and 16.05% of the RH patients with MAU- were administered quadruple therapy. 17.10% of the RH patients with MAU+ 7.82 % and of the RH patients with MAU- benefited from therapy with ≥ 5 drugs. We noticed that for the RH group with MAU+ the association of 4 or ≥ 5 drugs for controlling the BP was more frequently needed compared to the MAU- patients.

Based on the accumulated experience and on the study of literature data, we have prepared a RH treatment algorithm. The initiation was performed by the consultant, and the monitoring was subsequently carried out in collaboration with the general practitioner. In stage 1, a blocker of the renin-angiotensin system is administered, associated with a calcium blocker and, obligatorily, with a thiazide-type diuretic (provided that there are no contraindications such as heart failure or stage 4 chronic kidney disease). If after one month of treatment targets were not met, doses were increased. In case the eGFR was under 30ml/min or in case of

heart failure, Furosemid was administered twice a day. In this stage, either spironolactone or an alpha or beta blocker was also added.

If targets were not met after another month, the 5th or 6th antihypertensive was added. This was either a vasodilator, or an alpha-blocker or central blocker, such as Clonidine and Dopegyt. In case of drug intolerance to high doses, with SBP≥160 mmHg and DBP≥100 mmHg, when possible, invasive treatment methods were used, such as renal sympathetic denervation. In our casuistry only 2 RH cases underwent renal sympathetic denervations by catheter ablation, performed in foreign clinics. In all cases, the risk factors such as hyperlipidemia, and diabetes mellitus were treated. When necessary, the primary and secondary prophylaxis of atherosclerosis was performed with aspirin in an 80-100 mg/day dose.

CONCLUSIONS

1. RH has a growing prevalence and it requires a special diagnostic and therapeutic approach, in order to reduce the associated cardiovascular risk, as well as high morbidity and mortality
2. The prevalence of treatment resistant hypertension, according to the assessments performed in GP surgeries in collaboration with consultants from Timis County was of 6.7% of the total number of hypertensive patients.
3. In order to confirm a high office BP, BP must be monitored outside the medical practice, the method with the best results being the ambulatory blood pressure monitoring.
4. In the patients who met the RH requirements based on the office BP, the ABPM was normal for 35%, which confirmed the "white-coat" and pathological HT diagnostic in 64.99% of the patients.
5. Patients who showed a correspondence between high office BP and increased BP values on the ABPM presented a true RH in 76.94% cases, pseudo-resistant HT in 16.85% cases and secondary HT in 6.21% cases.
6. Lifestyle related risk factors, which contributed to the development of RH, were: obesity (58.79%), sedentary lifestyle (57%), high salt intake (25.07%), smoking (17.87%), and excessive alcohol ingestion (11.81%).
7. The circadian BP profile in RH patients was predominantly of the non-dipper type (65.53% vs. 60.89% non-dipper in controlled HT).
8. The diagnostic algorithm prepared in order to be used by general practitioners for RH includes ABPM as a compulsory stage, so as to exclude the "white-coat" HT. In case of pathological ABPM, pseudo-resistance must also be excluded, followed by the exclusion of secondary HT, in collaboration with a consultant.
9. After having compared RH with controlled HT, we reached the conclusion that the following clinical factors were statistically significantly associated with RH:

old age (<0.05), family history of cardiovascular diseases (<0.0001), sedentary lifestyle (0.0465), BMI >30 kg/m^2 (<0.001), HT duration in years (<0.001), organ damage as a result of HT (<0.001), LVH (<0.001), and present cardiovascular diseases (<0.001).

10. The investigation of asymptomatic and symptomatic organ damages is absolutely necessary in RH. Such a patient approach can lead to the regression of cardiovascular and renal impairments and it can improve the diagnostic procedure.

11. The prevalence of asymptomatic organ damage, expressed by: left ventricular hypertrophy, intima-media carotid thickening and microalbuminuria was higher in RH patients.

12. The investigation of asymptomatic and symptomatic organ damages is absolutely necessary in RH. Such a patient approach allows the detection, application of prophylactic and curative measures that can favour the regression of cardiovascular and renal impairments, thus improving the prognosis.

13. Hypertensive nephropathy can be detected in RH patients by early signs such as the presence of microalbuminuria (MAU 30-300 mg/24h) or mild decrease of the eGFR (60-30 ml/min), both parameters being easy to assess in GP surgeries and becoming, within our study, a routine procedure in the diagnostic assessment of resistant hypertension.

14. Microalbuminuria was present in 21.90% of the RH patients, and absent in 70.02% RH patients, while macroalbuminuria was present in 8.08%.

15. MAU was statistically significantly correlated with age (p=0.006), SBP (p< 0.0001), DBP (p = 0.0013), non-dipper profile (p<0.05), obesity (p = 0.0184), diabetes mellitus (p = 0.001), LVH on the ECG (p = 0.0034), LVH on the ultrasound (p = 0.001), ischaemic cardiac diseases (p = 0.0021), peripheral artery diseases (p = 0.0233), CIMT (p = 0.02), presence of carotid artery atheromatous plaques (p=0.001), and increased number of administered drugs (p = 0.001).

16. The factors correlated to the presence of MAU in the multivariate regression analysis were systolic BP (OD 1.024, 95% CI 1.011-1.039, p < 0.001), HbA1c (OD 1.324, 95% CI 1.078-1.724, p = 0.008), and eGFR (OD 0.989, 95% CI 0.977-0.999, p = 0.01).

17. RH patients needed a more aggressive therapy, focused on fighting the physiopathological mechanisms involved in the genesis of hypertension

18. The drug classes administered to RH patients, compared to controlled HT patients, were: ACE inhibitors (61.09% vs. 48.96%), ARB_1 (38.9% vs. 34.95%, diuretics (100% vs. 42%), calcium blockers (74.93% vs. 38.00%), spironolactone (17.87% vs. 0.00%), and other classes (57.92% vs. 5.96%).

19. The drug classes administered to RH patients with MAU+ compared to MAU- were: IE ACE inhibitors CA (55.26% vs. 60.90%), ARB_1 (44.74% vs. 37.86%),

diuretics (100% in both groups), calcium blockers (76.31% vs. 69.96%), beta blockers (51.31% vs. 46.09%), spironoclactone (19.74% vs. 16.87%), and other antihypertensive drugs (58.37% vs. 57.92%).

20. In order to exclude secondary HT and pseudo-resistant HT, general practitioners must collaborate with consultants and complex investigations must be carried out.

21. By preventive education actions, medical assistants and general practitioners can contribute to fighting risk factors and changing the lifestyle of RH patients.

22. Considering the unfavorable prognosis of RH, the increased effort of general practitioners for improving this condition by prophylaxis, diagnostic and therapeutic measures is fully justified.