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PROGNOSTIC SIGNIFICANCE OF CATESTATIN IN PATIENTS WITH PRIMARY HYPERTENSION AND TYPE 2 DIABETES MELLITUS

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The aim *of this study was to determine predictors of cardiovascular complications of arterial hypertension (AH) and type 2 diabetes mellitus (T2DM) and investigate the prognostic potential of catestatin (CST) and relaxin-2 (RLN-2) in this patient population.*

Materials and methods. *The research was performed in accordance with all ethical principles of the Declaration of Helsinki. All study participants signed a written informed consent. This study involved 106 patients with primary hypertension and 30 healthy volunteers. 55 hypertensive patients had comorbid T2DM. Plasma CST and RLN-2 levels were measured by an enzyme-linked immunosorbent assay. Major adverse cardiovascular events (MACE) were collected during 12-month follow-up via telephone interviews at visits in months 3, 6, 9, and 12. The end points of this study were acute myocardial infarction, ischemic stroke, acute heart failure and cardiac death. Statistical data analysis was performed using the SPSS 25.0 statistical software.*

Results. *13 end-points were registered in patients with AH during the 12-month follow-up period, but the difference in frequency of MACE occurrence between patients with AH and T2DM and hypertensive patients without T2DM was insignificant (p=0.181). The Cox proportional hazard model indicated CST (p=0.01), but not RLN-2 (p=0.20), as an independent predictor of MACE in hypertensive patients. Age (p=0.01), AH duration (p=0.03), presence of T2DM (p=0.03), HOMA-IR index (p=0.02), insulin (p=0.02) and uric acid levels (p=0.02) were also established as independent factors of end-points occurrence.*

Conclusions. *CST is an independent factor for predicting cardiovascular complications of AH, which allows us to consider it as a prognostic biomarker in patients with AH, especially hypertensive patients with comorbidity T2DM*

Keywords: *primary hypertension, type 2 diabetes mellitus, major adverse cardiovascular events, catestatin, relaxin-2, biomarker*

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death in the world population with the tendency to increase, accounting for 12.1 million deaths in 1990 and 20.5 million in 2021, which was a third of all-cause deaths globally. Coronary artery disease (CAD) and ischemic stroke (IS) account for 85 % of all deaths from cardiovascular disease worldwide. A lot of modifiable risk factors contributed to CVD death, especially air pollution, dyslipidemia, smoking, hyperglycemia, high body mass index (BMI), low physical activity, but the leading risk factor is elevated blood pressure (BP) [1, 2].

Arterial hypertension (AH) has multifactorial etiopathogenesis, including genetic predisposition, arterial stiffness and impaired arterial dilatation capacity, water-sodium retention, renin-angiotensin-aldosterone system hyperactivation and sympathetic dysregulation [3]. Elevated BP leads to the development of hypertension-mediated organ damage, which may induce the occurrence of major adverse cardiovascular events (MACE) due to further disease progression [4]. Thus, timely diagnosis and control of AH may prevent the development of MACE and reduce the rate of CVD mortality.

Catestatin (CST) and relaxin-2 (RLN-2) are involved in the key pathways of AH pathogenesis and considered as novel biomarkers of AH, as well as CVDs [5, 6]. Several studies demonstrated their prognostic potential in acute myocardial infarction (AMI) and heart failure (HF), but there is a lack of information about its significance in AH.

The aim of the present study was to determine predictors of cardiovascular complications of AH and T2DM and investigate the prognostic potential of CST and RLN-2 in this patient population.

2. Materials and methods

The present study was an observational prospective cohort single-centre by design with a 12-month follow-up. Patients were enrolled in the study from October 2021 to February 2022. This study was performed at the Department of Therapy of the Medical-Sanitary Base of JSC "Kharkiv Tractor Plant" and the Department of Gen-

eral Practice – Family Medicine of Kharkiv National Medical University.

The study protocol was approved by the Local Ethics Committee of the Medical-Sanitary Base of JSC "Kharkiv Tractor Plant" (date of approval: 21 September 2021). The research was performed in accordance with all ethical principles of the Declaration of Helsinki. All study subjects signed a written informed consent prior to enrollment in the study.

106 patients with primary hypertension and 30 healthy volunteers were enrolled in the study. Depending on the presence of comorbidity T2DM, hypertensive patients were divided into two groups: the first group included 55 patients with AH and T2DM, and the second group consisted of 51 hypertensive patients without T2DM.

Study design, methods of clinical examinations and laboratory assessments have been reported in our previous work [7]. The inclusion criteria were stage 2 of PH and patients over 50 years of age for men and 55 years for women. All participants underwent a clinical examination, including measurement of vital signs and anthropometric data, medical history interview, blood sampling, electrocardiography and echocardiography at the screening visit. Blood samples were collected by venipuncture after fasting for at least 8 hours at the screening visit according to the standards of laboratory practice. Plasma CST and RLN-2 levels were measured by an enzyme-linked immunosorbent assay (E4996Hu, BT Lab, Shanghai, China and E-EL-H1582, Elabscience, USA, respectively) according to the manufacturer's instructions.

Transthoracic echocardiography was performed using ultrasonography scanner Toshiba SSA-550 (Japan). Cardiac dimensions and volumes were measured using standard echocardiographic techniques [8]. The indices of left ventricular (LV) mass, LV end-diastolic (LV EDV) and end-systolic volume (LV ESV), and left atrium volume (LAV) were determined by indexing these values to body surface area (BSA). BSA was calculated using the DuBois formula:

$$BSA=0.007184\times height\ (cm)^{0.725}\times \times weight\ (kg)^{0.425} \quad (1).$$

Each study subject performed self-monitoring of BP every morning and evening for 31 days and registered systolic (SBP) and diastolic BP (DBP) values in the diary. Mean SBP (mSBP) and DBP (mDBP) were calculated based on these data.

MACE occurrence was collected during 12-month follow-up via telephone interviews with patients or their relatives at visits Month 3, 6, 9, 12. The end points of the present study were AMI, IS, acute HF (AHF) and CVD death.

Statistical data analysis was performed using SPSS (SPSS 25.0 for Windows, IBM, Armonk, NY, USA) and Microsoft Excel 2019 software. The Kolmogorov-Smirnov test was used to test the normality of data distribution. Data were presented as mean ± standard deviation for continuous variables with normal distribution, as median and interquartile range for continuous variables with skew distribution, and as whole numbers and percentages for categorical variables. The Student's t-test was used to compare differences between two groups of continuous variables with normal distribution, Mann-Whitney U test − for non-normality distributed data, and the χ^2 test – for categorical variables. The associations between plasma CST and RLN-2 levels and end-point occurrence were assessed with a Cox proportional hazard regression. Kaplan–Meier survival analysis was performed using the log-rank test. Statistical significance was defined as $p<0.05$. All tests of significance were two-tailed.

3. Results

Baseline characteristics of the study population have been reported previously [7]. Plasma CST levels were decreased in patients with AH compared to healthy volunteers (5.02±1.09 ng/ml vs 6.64±0.72 ng/ml; $p<0.001$), and patients with AH and T2DM had lower CST levels than hypertensive patients without T2DM (4.47±1.16 ng/ml vs 5.61±0.61 ng/ml; $p<0.001$) [7]. Besides, there was established a decline in RLN-2 levels in patients with AH (5.43 [5.02; 6.66] pg/ml vs 11.44 [10.85; 13.55] pg/ml; $p<0.001$), and patients with comorbidity T2DM had significantly lower RLN-2 concentrations (5.11 [4.97; 5.38] pg/ml vs 6.71 [6.00; 7.14] pg/ml; $p<0.001$).

13 end-points were registered in patients with AH during the 12-month follow-up period: 3 CVD death, 5 IS, 3 AMI and 2 AHF. 9 end-points (69,23 %) were observed in patients with AH and T2DM: 2 CVD death, 2 IS, 3 AMI and 2 AHF, while 4 end-points (30.77 %) were documented in hypertensive patients without T2DM: 1 CVD death and 3 IS, but the difference between these groups were insignificant (p=0.181) that was also confirmed in Kaplan-Meier analysis (p=0.170) (Fig. 1).

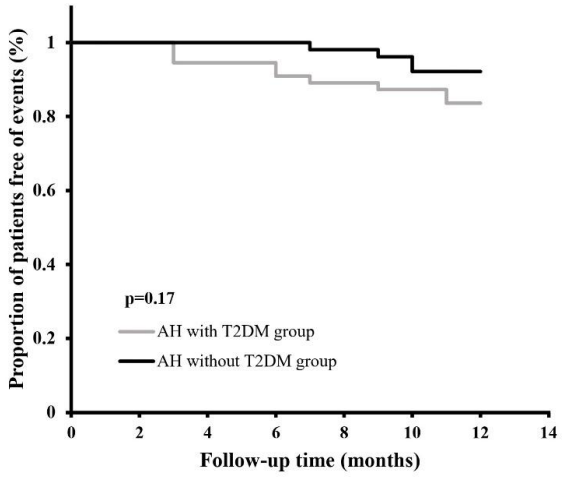

Fig. 1. Kaplan-Meier analysis in patients with AH depending on the presence of comorbidity T2DM

We performed the Cox proportional hazard model to estimate the independent predictors of MACE (Table 1). CST was established as an independent factor for predicting end-point occurrence (p=0.01), while there

was no detected association with RLN-2 levels (p=0.20). The age of patients (p=0.01) was also determined as a predictor of adverse events, while gender (p=0.65), BMI (p=0.14) and smoking (p=0.35) did not affect the frequency of events. Moreover, the analysis demonstrated a significant influence of AH duration (p=0.03) and the presence of T2DM (p=0.03) on the occurrence of cardiovascular complications. Notably, there were not determined any relationships with vital signs, particularly heart rate (p=0.32), office SBP (oSBP) (p=0.11) and DBP (oDBP) (p=0.56) as well as parameters of home BP monitoring, especially mSBP (p=0.06) and mDBP (p=0.22). Among laboratory parameters, HOMA-IR index, insulin and uric acid levels (p=0.02) were established as independent predictors, while another variable, including lipid profile parameters, did not show statistical significance (p>0.05).

Furthermore, only LV mass/BSA was determined as a predictor of cardiovascular events among echocardiography parameters (p=0.04).

Table 1

Independent factors for predicting major adverse cardiovascular events using the Cox proportional hazard model over a 12-month follow-up period

Parameter	HR	95 % CI	p-value
Catestatin	0.486	0.285–0.830	0.01*
Relaxin-2	0.841	0.644–1.097	0.20
Gender, male	0.774	0.253–2.365	0.65
Age	1.087	1.021–1.158	0.01*
BMI	1.106	0.968–1.264	0.14
oSBP	1.049	0.990–1.112	0.11
oDBP	1.034	0.925–1.156	0.56
Heart rate	1.032	0.969–1.099	0.32
mSBP	1.120	0.995–1.260	0.06
mDBP	1.106	0.941–1.301	0.22
AH duration	1.064	1.006–1.126	0.03*
Diabetes mellitus	3.578	1.102–11.619	0.03*
Smoking/ former smoker	0.567	0.175–1.841	0.35
Insulin	1.049	1.006–1.094	0.02*
Glucose	1.082	0.900–1.302	0.40
HOMA-IR index	1.157	1.023–1.309	0.02*
HbA1c	1.214	0.843–1.748	0.30
Uric acid	1.006	1.001–1.012	0.02*
LDL-C	0.842	0.504–1.405	0.51
HDL-C	0.662	0.147–2.986	0.59
VLDL-C	2.728	0.734–10.139	0.13
TGs	1.233	0.745–2.039	0.41
LV EF	0.908	0.782–1.054	0.21
LV mass/BSA	1.028	1.001–1.055	0.04*
LAV/BSA	1.038	0.976–1.104	0.23
LV EDV/BSA	1.034	0.985–1.086	0.18

*Note: *p<0.05; CI – confidence interval; HbA1c – glycated hemoglobin; HDL-C – high-density lipoprotein cholesterol; HR – hazard ratio; LDL-C – low-density lipoprotein cholesterol; TGs – triglycerides; VLDL-C – very low-density lipoprotein cholesterol*

4. Discussion

In the present study, we established that CST is an independent predictor of serious cardiovascular complications of AH. Recent studies demonstrated the diagnostic potential of CST [7, 9, 10] and RLN-2 [11, 12] in AH. Circulating CST levels were increased in hypertensive patients [9, 10], while we reported a decline of CST concentrations in patients with AH [7] that can be explained by different study designs. Patients involved in these studies had shorter duration of AH, so CST levels may be compensatory elevated at the early stage of AH due to its antihypertensive and antiadrenergic activities. On the other side, a part of the study subjects did not take antihypertensive medications [9, 10], while in our study, all patients received stable antihypertensive therapy. Our hypothesis about the influence of stable antihypertensive therapy and compensatory course of disease on CST concentrations is corroborated by observation that demonstrated elevated CST levels in untreated patients compared to treated ones [9]. Furthermore, other results confirmed our findings and shown decreased RLN-2 levels in patients with AH [11, 12]. On the other side, to the best of our knowledge, there are no data about the prognostic significance of CST and RLN-2 in hypertensive patients.

At the same, several research have shown the prognostic potential of CST and RLN-2 in cardiovascular disorders, especially CAD and HF. One study established that CST concentrations on the 3rd day after AMI is an independent predictor of MACE, such as cardiac death, recurrent AMI and decompensation of HF, while CST levels on the 7th day had no statistical significance [13]. At the same, another study did not show associations with CST on the 1st day of AMI and indicated only LV

EF as an independent factor in predicting MACE [14]. These contradictory results may be related to elevated catecholamine levels on the 3rd day that induce compensatory increasing of CST levels due to its antiadrenergic action [13].

Furthermore, CST may predict both all-cause and cardiac death in patients with chronic HF (CHF) [15] as well as unplanned hospitalization due to CHF [16]. We did not establish prognostic potential of RLN-2 in our study, although the RELAHF-4 study determined the association of RLN-2 with all-cause death among AHF patients with pregnancy-like RLN-2 concentrations (≥500 pg/ml) [17]. Moreover, RLN-2 may predict the occurrence of HF in patients with atrial fibrillation (AF) [18] and recurrence of AF after radiofrequency catheter ablation [19].

Study limitations. The present study had a relatively small sample size and only a 12-month follow-up period, so further studies with large sample sizes and longer time of observation are required to investigate the prognostic potential of CST and RLN-2 in this patient population.

Prospects for further research. Prospects for further research include the investigation of plasma CST and RLN-2 concentrations in dynamics in patients with AH and T2DM aimed at establishing the peculiarities of these biomarkers' metabolism, especially in patients with a high risk of cardiovascular complications.

5. Conclusions

1. According to the results of this study, impaired glucose metabolism did not significantly increase the frequency of cardiovascular complications of AH, although T2DM and parameters of carbohydrate metabolism were established as independent predictors of MACE.

2. CST was established as an independent factor for predicting cardiovascular complications of AH, which allows us to consider it as a prognostic biomarker in patients with AH, especially those with comorbidity T2DM.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

References

1. World Heart Report 2023: Confronting the World's Number One Killer (2023). World Heart Federation. Geneva, 48. Available at: https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf Last accessed: 25.11.2023

2. Lindstrom, M., DeCleene, N., Dorsey, H., Fuster, V., Johnson, C. O., LeGrand, K. E. et al. (2022). Global Burden of Cardiovascular Diseases and Risks Collaboration, 1990-2021. Journal of the American College of Cardiology, 80 (25), 2372–2425. doi: https://doi.org/10.1016/j.jacc.2022.11.001

3. Ma, J., Chen, X. (2022). Advances in pathogenesis and treatment of essential hypertension. Frontiers in Cardiovascular Medicine, 9. doi: https://doi.org/10.3389/fcvm.2022.1003852

4. Di Palo, K. E., Barone, N. J. (2022). Hypertension and Heart Failure. Cardiology Clinics, 40 (2), 237–244. doi: https://doi.org/10.1016/j.ccl.2021.12.011

5. Bozic, J., Kumric, M., Ticinovic Kurir, T., Urlic, H., Martinovic, D., Vilovic, M. et al. (2021). Catestatin as a Biomarker of Cardiovascular Diseases: A Clinical Perspective. Biomedicines, 9 (12), 1757. doi: https://doi.org/10.3390/biomedicines9121757

6. Aragón-Herrera, A., Feijóo-Bandín, S., Anido-Varela, L., Moraña-Fernández, S., Roselló-Lletí, E., Portolés, M. et al. (2022). Relaxin-2 as a Potential Biomarker in Cardiovascular Diseases. Journal of Personalized Medicine, 12 (7), 1021. doi: https://doi.org/10.3390/jpm12071021

7. Pankova, O., Korzh, O. (2023). Plasma catestatin levels are related to metabolic parameters in patients with essential hypertension and type 2 diabetes mellitus. Heart and Vessels. doi: https://doi.org/10.1007/s00380-023-02318-w

8. Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L. et al. (2015). Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography, 28 (1), 1-39.e14. doi: https://doi.org/10.1016/j.echo.2014.10.003

9. Kumric, M., Vrdoljak, J., Dujic, G., Supe-Domic, D., Ticinovic Kurir, T., Dujic, Z., Bozic, J. (2022). Serum Catestatin Levels Correlate with Ambulatory Blood Pressure and Indices of Arterial Stiffness in Patients with Primary Hypertension. Biomolecules, 12 (9), 1204. doi: https://doi.org/10.3390/biom12091204

10. Durakoglugil, M. E., Ayaz, T., Kocaman, S. A., Kirbas, A., Durakoglugil, T., Erdogan, T. et al. (2015). The relationship of plasma catestatin concentrations with metabolic and vascular parameters in untreated hypertensive patients: Influence on high-density lipoprotein cholesterol. The Anatolian Journal of Cardiology, 15 (7), 577–585. doi: https://doi.org/10.5152/akd.2014.5536

11. Gedikli, O., Yilmaz, H., Kiris, A., Karaman, K., Ozturk, S., Baykan, M., Ucar, U., Durmus, I., Karahan, C., Celik, S. (2009). Circulating levels of relaxin and its relation to cardiovascular function in patients with hypertension. Blood Pressure, 18 (1-2), 68–73. doi: https://doi.org/10.1080/08037050902864086

12. Sanidas, E., Tsakalis, K., Papadopoulos, D. P., Zerva, K., Velliou, M., Perrea, D. et al. (2018). The impact of apelin and relaxin plasma levels in masked hypertension and white coat hypertension. The Journal of Clinical Hypertension, 21 (1), 48–52. doi: https://doi.org/10.1111/jch.13449

13. Zhu, D., Xie, H., Wang, X., Liang, Y., Yu, H., Gao, W. (2015). Correlation of Plasma Catestatin Level and the Prognosis of Patients with Acute Myocardial Infarction. PLOS ONE, 10 (4), e0122993. doi: https://doi.org/10.1371/journal.pone.0122993

14. Xu, W., Yu, H., Wu, H., Li, S., Chen, B., Gao, W. (2016). Plasma Catestatin in Patients with Acute Coronary Syndrome. Cardiology, 136 (3), 164–169. doi: https://doi.org/10.1159/000448987

15. Peng, F., Chu, S., Ding, W., Liu, L., Zhao, J., Cui, X. et al. (2016). The predictive value of plasma catestatin for all-cause and cardiac deaths in chronic heart failure patients. Peptides, 86, 112–117. doi: https://doi.org/10.1016/j.peptides.2016.10.007

16. Wołowiec, Ł., Rogowicz, D., Banach, J., Gilewski, W., Sinkiewicz, W., Grześk, G. (2020). Catestatin as a New Prognostic Marker in Stable Patients with Heart Failure with Reduced Ejection Fraction in Two-Year Follow-Up. Disease Markers, 2020, 1–10. doi: https://doi.org/10.1155/2020/8847211

17. Miró, Ò., Herrero-Puente, P., Prieto, B., García-García, M., García-Hernández, P., Martín-Sánchez, F. J. et al. (2018). The subset of patients with acute heart failure able to secrete relaxin-2 at pregnancy concentrations could have a longer survival: a pilot study. Biomarkers, 23 (6), 573–579. doi: https://doi.org/10.1080/1354750x.2018.1463564

18. Zhou, H., Qu, X., Gao, Z., Zheng, G., Lin, J., Su, L. et al. (2016). Relaxin Level in Patients With Atrial Fibrillation and Association with Heart Failure Occurrence. Medicine, 95 (21), e3664. doi: https://doi.org/10.1097/md.0000000000003664

19. Qu, X., Chen, L., Sun, L., Chen, C., Gao, Z., Huang, W., Zhou, H. (2019). Serum relaxin level predicts recurrence of atrial fibrillation after radiofrequency catheter ablation. Heart and Vessels, 34 (9), 1543–1551. doi: https://doi.org/10.1007/s00380-019-01386-1

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