DOI 10.26724/2079-8334-2022-2-80-89-93
UDC 616.12-008.331.1: 616.12-07

N.V. Kuzminova, A.V. Ivankova, S.E. Lozinsky, I.I. Knyazkova[1], E.I. Ivanova, O.M. Kulchytska, Yu.L. Shkarivsky
National Pirogov Memorial Medical University, Vinnytsia; [1]National Medical University, Kharkiv

ACCORDANCE OF CLINICAL AND INSTRUMENTAL PROFILE TO CYSTATIN C LEVEL IN PATIENTS WITH STAGE II HYPERTENSION AND FREQUENT EXTRASYSTOLE

e-mail: kuzminova5517@gmail.com

156 patients with essential arterial hypertension of the II stage were examined, 124 of them had frequent symptomatic extrasystoles: 74 – of supraventricular and 50 – of ventricular origin. Another 32 patients had no arrhythmias and were a comparison group. The control group included 30 practically healthy normotensive persons. All patients underwent a complete clinical and laboratory and anthropometric examination, blood pressure measurement, daily blood pressure monitoring, daily electrocardiogram monitoring, echocardiography, and serum cystatin C determination. The value of glomerular filtration rate and the presence of paired ventricular extrasystole showed the greatest predicting level of serum cystatin C in patients with hypertension (OR 5.32 and 3.22, respectively, p<0.0001). It is proved that relatively high levels of cystatin C in patients with stage II hypertension are accompanied by the electrical instability of the left ventricular myocardium and can be considered as a marker of frequent and paired ventricular extrasystoles in these patients. Patients with hypertension with relatively high cystatin C are characterized by higher blood pressure, more severe structural remodelling of the left ventricle, and impaired renal function.

Key words: essential hypertension, extrasystole, cystatin C, cystatin ratio, cystatin background.

Н.В. Кузьмінова, А.В. Іванкова, С.Е. Лозинський, І.І. Князькова, Є.І. Іванова, О.М. Кульчицька, Ю.Л. Шкарівський

КЛІНІКО-ІНСТРУМЕНТАЛЬНИЙ ПРОФІЛЬ ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ ІІ СТАДІЇ ТА ЧАСТУ ЕКСТРАСИСТОЛІЮ ВІДПОВІДНО ДО РІВНЯ ЦИСТАТИНУ С

Обстежено 156 хворих на есенціальну артеріальну гіпертензію ІІ стадії, 124 з них мали часту симптомну екстрасистолію (74 – суправентрикулярний варіант і 50 – шлуночковий варіант), 32 пацієнти не мали аритмій і склали групу порівняння. До групи контролю увійшли 30 практично здорових нормотензивних осіб. Усім хворим проведено повне клініко-лабораторне та антропометричне обстеження, вимір артеріального тиску, добове моніторування артеріального тиску, добове моніторування електрокардіограми, ехокардіографія та визначення рівня цистатину С сироватки крові. Найбільшу інформативність в прогнозуванні рівня цистатину С сироватки в пацієнтів з гіпертонічною хворобою показали величина швидкості клубочкової фільтрації і наявності парних шлуночкових екстрасистол (ВШ 5,32 і 3,22 відповідно, p<0,0001). Доведено, що відносно високий рівень цистатину С у пацієнтів з гіпертонічною хворобою ІІ стадії супроводжується розвитком електричної нестабільності міокарда лівого шлуночка і може розглядатись у якості маркеру виникнення частої і парної шлуночкової екстрасистолії у цих пацієнтів. Для хворих на гіпертонічну хворобу з відносно високим рівнем цистатину С сироватки характерні більш високі цифри артеріального тиску, більш тяжке структурне ремоделювання лівого шлуночка і порушення функціонального стану нирок.

Ключові слова: артеріальна гіпертензія, екстрасистолія, цистатин С, цистатиновий індекс, цистатиновий фон.

The study is a part of the research project "Metabolic risk factors, cardiovascular remodeling and functional status of the kidneys in patients with cardiovascular disease. Possibilities of pharmacological correction", state registration No. 0119U101849.

Essential Hypertension (EH) is a pressing problem of our time. It leads to premature disability and death, especially in combination with other well-known cardiovascular risk factors [1, 4, 14, 15]. Today, the world is actively studying various metabolic markers of cardiovascular risk, including cystatin C (Cys C) [5].

Cys C is a more sensitive marker of decreased glomerular filtration rate (GFR) than creatinine because its level is not affected by factors such as age, sex, muscle mass, diet, physical activity, or race. It serves as an effective early predictor of renal failure, even at normal creatinine levels [1, 2, 4, 5, 9, 12]. These properties allow us to consider Cys C as an indicator that reflects the kidneys' function in different categories of patients. Cys C acquires special diagnostic value in pediatrics, in patients with diabetes, and cardiovascular diseases [4, 5].

Cys C is produced by almost all cells in the body that contain the nucleus. It is often referred to as a marker of inflammation. It is believed that 99 % of Cys C is eliminated by the kidneys. Cys C is freely filtered in glomerular capillaries, and since its molecule is not subject to tubular reabsorption or secretion, it can be considered an almost ideal marker of GFR. The concentration of Cys C in the serum should be inversely related to the value of GFR because when it enters the tubular space during reabsorption, Cys C is metabolized in the proximal convoluted tubule almost completely [1, 3, 10].

MESA and COR studies, involving about 12000 people, showed that Cys C-only based GFR was a more reliable criterion for predicting cardiovascular mortality than GFR based on creatinine or the combined use of Cys C and serum creatinine [6, 13].

A large American population study showed that high levels of Cys C were associated with the presence of hypertension in adults without clinical manifestations of chronic kidney disease. However, such dependence was observed only in women [1, 5]. In patients with hypertension, serum Cys C correlated with albuminuria, left ventricular myocardial mass index, intima thickness of the common carotid artery, and mean systolic blood pressure measured by daily monitoring [7, 8, 13].

The purpose of the study was to assess the difference in the clinical and instrumental profile of patients with stage II hypertension and frequent extrasystoles with different neurohumoral backgrounds – relatively high or low levels of serum cystatin C.

Materials and methods. The study involved 156 patients with stage II hypertension. The main clinical array of the study was presented by 124 patients (aged 27 to 75 years) with frequent concomitant extrasystoles (>30 extrasystoles per 1 hour). Another 32 patients with stage II EH (aged 32 to 72 years) had no cardiac arrhythmias and were referred to the comparison group. 50 (40.3 %) patients in the main group were male and 74 (59.6 %) were female. The comparison group included 15 (46.9 %) men and 17 (53.1 %) women. The statistical analysis showed no significant differences ($p>0.05$) by age and sex between the main and the comparison group which indicated their age and gender homogeneity.

Frequent supraventricular extrasystoles were found in 74 (59.7 %) of 124 patients in the main group, and another 50 (40.3 %) patients had ventricular extrasystoles (VE). Arrhythmic history ranged from 1 to 27 years and averaged 8.062±0.421 years.

All patients and healthy individuals agreed to participate in the study. The agreement was signed following the bioethical standards of the Helsinki Declaration and the International Code of Medical Ethics.

A complete comprehensive clinical, biochemical, and instrumental examination was performed for all patients at the stage of their inclusion to verify the underlying diagnosis and comorbidities, as well as assess the metabolic status. After verification of the diagnosis, patients who agreed to participate in the study were examined by the following methods: general clinical and anthropometric examination, measurement of blood pressure (BP); electrocardiogram (ECG) in 12 leads, daily Holter ECG monitoring, daily blood pressure monitoring, echocardiography; determination of the level of cystatin C in the serum.

The establishment of the main diagnosis and concomitant pathology, identification of indications and contraindications to the inclusion of patients in the study, assessment of the anamnesis, and the formation of clinical groups of the study were completed during the clinical examination.

Blood pressure was measured according to the Recommendations of the Ukrainian Society of Cardiology (2013) using a sphygmomanometer (Microlife, Switzerland).

Electrocardiography was performed according to the standard method in 12 leads on a UKARD device (Hungary).

Daily BP (DBPM) and ECG (DM ECG) monitoring were performed using the software and hardware complex of the DiaCard system (Solvaig JSC, Ukraine) according to the standard protocol.

The structure and function of the heart were assessed using echocardiography in one-dimensional and two-dimensional modes with color, pulse, and continuous-wave Doppler using “My Lab 25” equipment (Italy).

The serum cystatin C level was determined by enzyme-linked immunosorbent assay using the “Human Cystatin C” kit (BioVendor, Czech Republic) following the manufacturer's instructions.

Statistical processing was performed using the software “Statistica” v. 12.0 (StatSoft corp.) following the recommendations for medical and biological research. The results were presented as the median meanings. Spearman's rank correlation analysis was used to determine the relationship between the parameters. To determine the independent predictors of Cys C, we chose the procedure of the logistic regression in the “Nonlinear Estimation” module, (“Logistic regression or logit model”). This statistical method is usually used if the dependent variable is of binary value and can have only two values: 1 or 2.

The peculiarity of the results of logistic regression is that the value of the initial parameter (Y) is its logit transformation: $\text{logit}(Y)=\ln(Y/(1-Y))$, which significantly increases the sensitivity of this function to changes in combinations of different prognostic factors (predictors).

In our case, the dependent variable (or the initial parameter of the analysis) was serum Cys C, which can have only two values – 1 or 2, where 1 reflected the value of Cys C lower and 2 – equal or higher than the median value for the overall sample (n=156). As the median value was 1.16 mg / l then the binary Cys C variable was estimated as 1 in the case of levels <1.16 and 2 – ≥1.16 mg/l, respectively. Multiple regression was performed for each initial parameter separately.

The basic statistical matrix included only those clinical, instrumental, and laboratory parameters, which passed the preliminary Spearman rank correlation analysis with Cys C serum level and had a significant correlation level ($p<0.05$).

One of the conditions for the effective application of the logit regression method is the independence of variables (factors) from each other. This hypothesis was tested by using Spearman's rank correlation method. Only those variables that had a higher Cys C correlation coefficient were left for further analysis.

Results of the study and their discussion. Table 1 demonstrates the final results of Spearman's rank correlation, which convincingly show the absence of significant correlation (associative) relationships between the parameters selected for further logit-regression analysis. This preliminary statistical "filtering" of independent variables ensures the maximum efficiency of the logit-regression model for predicting the level of serum Cys C. It should be noted that these factors were included in the subsequent multiple logistic regression analysis.

The independent factors taken for further logit-regression analysis of the Cys C level, the value of Spearman's rank correlation coefficient with the Cys C level, and the confidence level (p) are shown in Tab. 1. According to this table, the following independent factors were involved for further logit-regression analysis: the degree of hypertension, smoking (determined by history), DBPn (determined by DBPM), LVMI (determined by echocardiography using the Pen Convention formula according to existing recommendations), the VE1 and VEp (determined according to DM ECG) and GFR calculated by creatinine using the CKD-EPI equation. The latter was the only factor that met an inverse correlation with serum Cys C levels.

Table 1

Spearman's rank correlation between Cystatin C level and possible predictors selected for logit regression (taken from Statistica v. 12.0 software analysis)

	Spearman Rank Order Correlations						
	Degree of AH	Smoking	DBPn	LVMI	VE1	VEp	GFR (CKD-EPI)
GFR (CKD-EPI)	-0.037756	0.078414	-0.039012	-0.178913	-0.137593	0.104279	1.000000
Degree of AH	1.000000	0.110480	-0.026478	0.120161	-0.056685	0.023023	-0.037756
Smoking	0.110480	1.000000	-0.141960	-0.118259	0.062515	-0.037422	0.102433
DBPn	-0.026478	-0.141960	1.000000	0.013875	-0.112548	-0.076575	-0.039012
LVMI	0.102579	0.118259	0.037466	1.000000	0.037904	-0.066771	-0.071482
VE1	-0.056685	-0.062515	-0.014714	-0.066771	1.000000	0.094120	-0.074589
VEp	0.023023	-0.037422	-0.076575	-0.178913	-0.070144	1.000000	-0.099875

Clinical and instrumental parameters	**Spearmen R**	**p-value**
Degree of Hypertension, points (1 degree – 1 point, 2 – 2 and 3 – 3 points)	0.312	0.0001
Smoking (binary value: 0 – non-smoker and 1 – smoker)	0.264	0.0009
PBPn, mm Hg	0.344	<0.0001
LVMI	0.307	0,0007
VE1	0.425	<0.0001
VEp (binary value: 0 – absent and 1 – present)	0.511	<0.0001
GFR by creatinine	-0.632	<0.0001

Note. Degree of hypertension – the degree of hypertension in points (1 degree – 1 point, 2 – 2 and 3 – 3 points, respectively), smoking (binary value: 0 – non-smoker and 1 – smoker), DBPn – median night diastolic blood pressure (mm Hg), LVMI – left ventricular myocardial mass index in g / m^2, VE1 – the average frequency (per 1 h) of ventricular extrasystole, VEp – paired ventricular extrasystole (binary value: 0 – absent and 1 – present), GFR (CKD-EPI) –glomerular filtration rate (ml/min/1.73 m^2), determined by creatinine.

After the exclusion of non-significant predictors based on the logistic regression analysis the final model for predicting Cys C level in patients with stage II EH included 6 independent predictors that revealed statistically significant ($p<0.05$) relationships with the initial parameter: degree of AH in points (OR=2.57, p=0.0003), the history of smoking (yes/no) (OR=1.77, p=0.02), and LVMI in g/m^2 (OR=1.37, p=0.03), the average number of VE per 1 h (OR=2.47, p=0.0004), the presence/absence of paired VE per 24-hour ECG monitoring (OR=3.22, $p<0.0001$) and GFR in ml/min/1.73 m^2 (OR=5.32, $p<0.0001$) (Table 2). It is noteworthy that the value of GFR and the presence of paired VE (OR 5.32 and 3.22, respectively, $p<0.0001$) had a greatest contribution in predicting the Cys C level in patients with EH.

The model with the highest χ^2 criterion (table 2 χ^2-Chi=51.546 and p=0.00000) was chosen as a final among all the models obtained by combining different independent factors. It was observed that almost all independent predictors had positive log coefficients (LK) with the initial parameter. The exception was the value of GFR, which showed a negative LK and had feedback from the original

parameter. Accordingly, the history of such risk factors like smoking and the presence of paired VE increases the probability of "relatively high", as well, as reducing "relatively low" (<1.16 mg/l) level of serum Cys C (≥ 1.16 mg/l) by 1.77 times and 3.22 times respectively. In addition, the increase in blood pressure and the degree of hypertension in patients with AH of stage II increases the chances of relatively high and reduces the chances of relatively low levels of Cys C by 2.57 times, while the average number of VE1 – by 2.47 times, LVMI – by 1.37 times and reducing the value of GFR by creatinine – by 5.32 times.

Implementing the data of the obtained model on the clinical course of hypertension, we proposed the term "cystatin background" for a "relatively high" level of Cys C (≥ 1.16 mg/l) in hypertensive patients, which was accompanied by higher blood pressure and more severe course of the disease. The latter is characterized by the presence of such a risk factor as smoking, more prominent structural remodeling of the left ventricle, namely, an increase in LVM of concentric type (correlation with LVM and RWT, respectively r=0.299; p=0.001 and r=0.284; p=0.001), more severe renal impairment (the decrease in GFR and close direct correlations between Cys C and creatinine levels (r=0.627; p< 0.0001), as well as an increase in the frequency of VE and the presence of paired VE. The latter is a manifestation of electrical instability of the left ventricular myocardium and disorders of its physiological properties.

We have identified critical (median) values for all independent predictors and calculated their predictive value (%) for Cys C level prediction (table 2).

Table 2

Results of logistic regression analysis of independent predictors of serum cystatin C levels, their critical and predictive values (transferred from the results of software analysis Statistica v. 12.0)

N=156	Model: Logistic regression (logit) N of 0's: 68 1's: 86 Final loss: 79,917326229 Chi?(7)=51,546 p=,00000					
	Smoking	Degree of AH	VE1	VEp	LVMI	GFR (CKD-EPI)
Estimate (LK)	0.5793126	0.9442157	0.905714	0.841258	0.317122	-1.67067
Odds ratio	1.76826705	2.570796	2.4736975	3.219282	1.373002	5.315356
p-value	0.01885581	0.0002928	0.0004224	0.00007	0.03247	0.000009

Independent predictors for Cys C level	**Critical value**	**Number of positive cases (n) and predictive value (%)**
Degree of AH, points (1 degree – 1 point, 2 – 2 and 3 – 3 points)	2	N=99 **62.7 %**
Smoking (binary value: 0 – non-smoker and 1 – smoker)	1	N=90 **57.0 %**
LVMI	154	N=86 **54.4 %**
Mean VE frequency	4	N=103 **65.2 %**
Presence of VEp (binary value: 0 – absent and 1 – present)	1	N=112 **70.9 %**
GFR by creatinine	48	N=130 **82.3 %**

Note. The regression logit coefficient (LK) is the natural logarithm of the odds ratio (OR) for the initial parameter of the model (in this case for a relatively high/low level of Cys C – ≤1.16 and > 1.16 mg/l, respectively). The table below shows the log transformations for each factor, which are considered OR (Odds ratio).

The GFR had the highest predictive value for Cys C level (82.3 %) in patients with EH. The calculated creatinine GFR value <48 ml/min/1.73 m^2 determined a "relatively high" level of Cys C (≥1.16 mg/l), while GFR ≥ 48 ml/min/1.73 m^2 – "relatively low" level of Cys C (<1.16 mg/l) hormone in serum. In turn, the degrees 2 or 3 of hypertension (predictive value 62.7 %), a history of smoking (57.0 %), LVMI ≥ 154 g/m^2 (54.4 %), mean VE frequency > 4/h (65.2 %), and the presence of paired VE during the day (70.9 %) predicted "relatively high", while 1 degree of hypertension, no history of smoking, LVMI <154 g/m^2, mean VE frequency <4/h and the absence of paired VE during 24-hour ECG monitoring – "relatively low" level of Cys C.

In addition to the concept of "cystatin background", we have developed a "cystatin ratio" for a more accurate prediction of the course of hypertension. For this purpose, we proposed using the average Cys C levels ratio in patients and healthy individuals [4]. Thus, the average level of cystatin C in patients with stage II EH was 1.162 (1.003; 1.371) mg/l, and in healthy individuals – 0.892 (0.631; 1.043) mg/l. Accordingly, we obtained the "cystatin ratio" value, equal to 1.3.

Implementing the data of the obtained model on the clinical course of hypertension, it should be assumed that the relatively high "cystatin background" and/or "cystatin ratio" in hypertensive patients will be accompanied by higher BP and more severe disease course, LV structural remodeling, and functional

impairment. The state of the kidneys and an increase in the frequency of registration of VE and the appearance of paired VE. The latter is a manifestation of electrical instability of the left ventricular myocardium and its impaired physiological properties. The connection of cystatin C with the functional state of the kidneys is not in doubt, and our results allow us to consider cystatin C also as a marker of cardiovascular dysfunction. This assumption meets confirmation in the literature [1, 4, 9, 11, 12].

Interestingly that the frequency of VE showed an association with cystatin profile in patients with EH while the frequency of SVE did not. Based on this fact, it can be assumed that the development of supraventricular arrhythmogenesis in patients with EH, to a greater extent depends on the severity of hemodynamic overload of the left atrium and, to a lesser extent, changes in the neurohumoral background of patients, namely cystatin C. On the other hand, VE is a direct manifestation of electrical instability of the left ventricular myocardium. In turn disorders of left ventricular electrophysiological state in stage II EH depend primarily on several neurohumoral factors, namely cystatin C.

Thus, this study showed the difference in clinical and instrumental profiles in patients with stage II hypertension and frequent extrasystoles with different neurohumoral backgrounds – relatively high and low levels of cystatin C. It was found that an increase in cystatin C (≥1.16 mg/l) in this cohort of patients is associated with known cardiovascular risk factors, namely: smoking, higher blood pressure, BMI, more frequent VE, the presence of paired VE, and lower GFR, which in turn increases cardiovascular risk and contributes to the worsening the prognosis. The concepts of "cystatin background" and "cystatin index" were proposed based on the results which may simplify the routine cardiovascular risk stratification.

Conclusions

1. The level of cystatin C in patients with stage II EH may be predicted by several independent predictors: the degree of hypertension, the presence/absence of smoking history, the value of LVM, the average VE frequency, the presence of paired VE and the value of GFR, calculated by the formula CKD-EPI.

2. We proposed the terms high "cystatin background" (≥1.16 mg/l) and high "cystatin ratio" (>1.3) that may be accompanied by more severe arterial hypertension and an increase in known cardiovascular risk factors.

3. The most significant predictors of the Cys C level are the GFR by creatinine (82.3 %) and the presence of paired VE (70.9 %).

References

1. Chekalina N, Burmak Y, Petrov Y, Borisova Z, Manusha Y, Kazakov Y, et.al. Quercetin reduces the transcriptional activity of NF-kB in stable coronary artery disease. Indian Heart J. 2018; 70 (5): 593-97. DOI: 10.1016/j.ihj.2018.04.006.
2. Dangle PP, Ayyash O, Kang A. Cystatin C-calculated glomerular filtration rate-a marker of early renal dysfunction in patients with neuropathic bladder. Urology. 2017; 100: 213–17. https://doi.org/10.1016/j.urology.2016.08.011
3. Filler G, Rodriguez Cuellar C, Medeiros M. Overcoming the limitations of glomerular filtration rate estimation by using a novel rapid bedside measurement? Ann Transl Med. 2018; 6 (15): 312. https://doi.org/10.21037/atm.2018.06.51
4. Ivankova AV, Kuzminova NV, Lozinsky SE, Ivanov VP. Comparative assessment of renal function by cystatin C level in patients with hypertension and extrasystole. 2020; Biomedical and biosocial anthropology 41: 11-17. https://doi.org/10.31393/bba41-2020-02
5. Kuzminova NV, Ivankova AV, Ivanov VP, Lozinsky SE. Diagnostic and prognostic value of cystatin C as an early marker of renal dysfunction in patients with cardiovascular pathology. 2018; Likarska sprava 7-8: 17-23. https://doi.org/10.31640/JVD.7-8.2018(3)
6. Jin S, Xu J, Shen G, Gu P. Predictive value of circulating cystatin C level in patients with acute coronary syndrome: a meta-analysis. Scand J Clin Lab Invest. 2021; 81 (1): 1–7. https://doi.org/10.1080/00365513.2020.1846212
7. Lee HC, Lin YH. The Pathogenic Role of Very Low-Density Lipoprotein on Atrial Remodeling in the Metabolic Syndrome. Int J Mol Sci. 2020; 21 (3): 891. https://doi.org/10.3390/ijms21030891
8. Parsi E, Bitterlich N, Winkelmann A, Rösler D, Metzner C. Dietary intervention with a specific micronutrient combination for the treatment of patients with cardiac arrhythmias: the impact on insulin resistance and left ventricular function. BMC Cardiovasc Disord. 2018; 18 (1): 220. https://doi.org/10.1186/s12872-018-0954-6
9. Pottel H, Delanaye P, Schaeffner E. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. 2017; Nephrol. Dial. Transplant. 32 (3): 497–507. https://doi.org/10.1093/ndt/gfw425
10. Sherief LM, Youssef DM, Sherbiny HS. Screening of renal dysfunction among Burkitt lymphoma survivors by novel markers. Hematology. 2017; 22 (5): 265–73. https://doi.org/10.1080/10245332.2016.1259713
11. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR. et al. Cystatin C versus creatinine in determining risk based on kidney function. N. Engl J. Med. 2013; 369 (10): 932–43. https://doi.org/10.1056/NEJMoa1214234
12. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Workgroup. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Ann. Intern. Med. 2013; 158 (11): 825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007
13. Sun Y, Lu Q, Cheng B, Tao X. Prognostic value of cystatin C in patients with acute coronary syndrome: A systematic review and meta-analysis. Eur. J. Clin. Invest. 2021; 51 (3): e13440. https://doi.org/10.1111/eci.13440
14. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D. [et al.] 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75: 1334–57. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026
15. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M. [et al.] ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39 (33): 3021–3104. https://doi.org/10.1093/eurheartj/ehy339

Стаття надійшла 23.04.2021 р.