UDC 616.12-008.331.1-07:577.17:577.152 https://doi.org/10.26641/2307-0404.2023.2.283252

***R.V. Hnizdiukh*** [*], ***V.V. Shmanko***

# STRUCTURAL AND FUNCTIONAL CONDITION OF THE HEART IN PATIENTS WITH ARTERIAL HYPERTENSION DEPENDING ON *A1166C-GENE* POLYMORPHISM OF ANGIOTENSIN II TYPE 1 AND *T786C*-PROMOTER OF ENDOTHELIAL *NO*-SYNTHASE GENE

*I. Horbachevsky Ternopil National Medical University*
*Maidan Voli, 1, Ternopil, 46001, Ukraine*
*Тернопільський національний медичний університет ім. І.Я. Горбачевського*
*вул. майдан Волі, 1, Тернопіль, 46001, Україна*
[*]*e-mail: hnizdyukh_rv@i.ua*

***Цитування: Медичні перспективи. 2023. Т. 28, № 2. С. 50-55***
***Cited: Medicni perspektivi. 2023;28(2):50-55***

**Key words:** *arterial hypertension, gene polymorphism*
**Ключові слова:** *артеріальна гіпертензія, генний поліморфізм*

**Abstract. Structural and functional condition of the heart in patients with arterial hypertension depending on *A1166C*-gene polymorphism of angiotensin II type 1 and *T786C*-promoter of endothelial *NO*-synthase gene. Hnizdiukh R.V., Shmanko V.V.** *It's known that pathological changes in structural and functional condition of the heart, which are caused by arterial hypertension, trigger development of chronic heart failure and disablement of population. Nowadays, it proven that candidate genes, expression products of which participate in regulating vascular tone, have considerable influence upon development of arterial hypertension, however their role in pathogenesis of arterial hypertension has not been fully clarified, and results of the respective researches significantly vary among different populations. To determine the structural and functional state of the heart in patients with hypertension depending on the polymorphism of the A1116C gene of the angiotensin II receptor type I and the T786C promoter of the endothelial NO-synthase gene we examined 86 patients, aged from 45 to 76 years. 30 people without signs of hypertension were in the control group. The structural and functional state of the heart was assessed by cardiac ultrasound according to standard methods. Studies of the A1166C allelic polymorphism of the angiotensin II receptor gene type 1 and the T786C promoter of the eNOS gene were performed by polymerase chain reaction with electrophoretic detection of results. Analysis of cardiac ultrasound showed, that in the patients – carriers of C-allele of both studied genes (AC+CC and TC+CC) left ventricular ejection fraction tended to decrease. We found a bigger thickness of the posterior wall of the left ventricle in patients with CC genotype compared to carriers of AA genotype A1166C – (1.3±0.07) cm vs. (1.1±0.05) cm ($p<0.005$). The mass of the left ventricular myocardium index in the group of patients with the genotype AC and CC was (157.5±7.3) g/m$^2$ and (161.5±7.1)) g/m$^2$, respectively, being by 16.7% and 19.6% more than in carriers of AA genotype of the AGTR1 gene. In the groups of patients-carriers of C-allele (TC+CC) of the eNOS gene the mass of the left ventricular myocardium index values were (155.2±11.4)) g/m$^2$ and (158.4±7.9)) g/m$^2$, respectively, which is by 5.4% and 7.5% more than in carriers of TT genotype. The mean size of the left atrium was significantly higher in patients who had AC and CC genotype of the AGTR1 gene, as well as TC and CC genotype of the eNOS gene compared with the control group. Carriers of C-allele (AC+CC genotype) of AGTR1 gene polymorphism had clearly bigger sizes of the left atrium, as compared to homozygotes by A-allele. The severity of diastolic dysfunction was higher in carriers of the CC genotype of the AGTR1 gene and the eNOS gene than in heterozygotes of the studied genes by 4.3% and 3.3%, respectively. The research shows that inheritance of CC genotype for A1166C polymorphism of the the angiotensin II type 1 receptor gene and of CC T786C polymorphism in the promoter of eNOS gene is associated with more noticeable changes in structural and functional heart condition among patients with arterial hypertension.*

**Реферат. Структурно-функціональний стан серця у хворих на артеріальну гіпертензію залежно від поліморфізму *A1166C*-гена рецептора ангіотензину II першого типу та *T786C*-промотора гена ендотеліальної *NO*-синтази. Гніздюх Р.В., Шманько В.В.** *Відомо, що патологічні зміни в структурно-функціональному стані серця, які виникають унаслідок артеріальної гіпертензії, є пусковим механізмом для розвитку хронічної серцевої недостатності та інвалідизації населення. На сьогодні доведено, що при експресії ряду генів-кандидатів утворюються речовини, які беруть участь у регуляції тонусу судин, проте їх роль у*



*На умовах ліцензії CC BY 4.0*

*патогенезі артеріальної гіпертензії до кінця не з'ясована, а результати таких досліджень можуть суттєво відрізнятися залежно від популяції. Метою роботи було з'ясувати структурно-функціональний стан серця в пацієнтів, які страждають на артеріальну гіпертензію залежно від поліморфізму досліджуваних генів. У дослідженні взяли участь 86 осіб, віком від 45 до 76 років. Група контролю складалась з 30 практично здорових осіб. Структурно-функціональний стан серця оцінювали за допомогою ультразвукового дослідження за стандартною методикою. Визначення алелей поліморфних ділянок (A1166C) гена AGTR1 та (T786C) гена eNOS проводили за допомогою полімеразної ланцюгової реакції з електрофоретичною схемою детекції результату. Аналіз показників ультразвукового дослідження серця показав, що у хворих носіїв С-алеля обох досліджуваних генів (AC+CC та TC+CC генотипи) спостерігалась тенденція до зниження фракції викиду лівого шлуночка. Нами виявлено більшу товщину задньої стінки лівого шлуночка в пацієнтів носіїв CC генотипу порівняно з носіями генотипу AA гена AGTR1 – 1,3±0,07 см проти 1,1±0,05 см (p<0,05). Індекс маси міокарда лівого шлуночка в групі хворих з генотипом AC та CC становив 157,5±7,3 г/м$^2$ і 161,5±7,1 г/м$^2$ віповідно, що на 16,7% і 19,6% більше порівняно з носіями AA генотипу гена AGTR1. У групах хворих-носіїв С-алеля (TC+CC) гена eNOS значення індексу маси міокарда лівого шлуночка становили 155,2±11,4 г/м$^2$ та 158,4±7,9 г/м$^2$ відповідно, що на 5,4% і 7,5% більше, ніж у носіїв TT генотипу. Середні розміри лівого передсердя виявились достовірно більшими в пацієнтів з AC та CC генотипами гена AGTR1, а також TC і CC генотипами гена eNOS порівняно з групою контролю. Носії С-алеля (AC+CC генотип) поліморфізму A1166C гена AGTR1 мали достовірно більші розміри лівого передсердя порівняно з гомозиготами за А-алелем. Вираженість діастолічної дисфункції була більшою в носіїв CC генотипу гена AGTR1 та гена eNOS, ніж у гетерозигот досліджуваних генів на 4,3% і 3,3% відповідно. Встановлено, що успадкування генотипу CC поліморфізму A1166C гена рецептора ангіотензину II першого типу та CC поліморфізму T786C промотора гена ендотеліальної NO синтази асоціюється з більш вираженими змінами структурно-функціонального стану серця в пацієнтів, хворих на артеріальну гіпертензію.*

Cardiovascular diseases (CVD) are the most common in Ukraine, so the pathology of the circulatory system affects about 22.3 million people, ie 52.4% of the population [1]. Arterial hypertension (AH) occupied the leading place in the structure of cardiovascular diseases [2]. Experts from the World Health Organization (WHO) note that hypertension is the most significant cause of death and disability among all CVDs [3].

The life and health prognosis of patients with hypertension largely depends on the effect of elevated blood pressure (BP) on target organs [4]. An uncontrolled BP level is the cause of left ventricular hypertrophy (LVH), which in turn leads to an increase in the LV myocardial mass (MM) and, as a result, an increase in the oxygen demand of the heart muscle and an increase in the risk of ectopic murmurs, dysmetabolic changes, as well as emergence and progression of diastolic and systolic dysfunctions [5].

It is known that a combination of hereditary factors and negative environmental influences plays an important role in the development of hypertension [6]. In recent years, influence of various genes on the development of hypertension has attracted considerable attention of medical science [7]. According to the hemodynamic theory of the hypertension development, a key role in its pathogenesis is played by an imbalance between the action of agents involved in the vasoconstriction and vasodilatation of blood vessels. Substances involved in the regulation of vascular tone are products of the expression of certain genes, thus, the human genotype can play an indirect role in the pathogenesis of hypertension. Such genes include the type 1 angiotensin gene and enotelial NO synthase [8].

The efforts of scientists from all over the world are aimed at studying the role of gene mutations in the pathogenesis of hypertension, however, as evidenced by research results, the prevalence of such mutations differs in different populations [9].

The purpose of this study was to find out the structural and functional state of the heart in patients with hypertension depending on the polymorphism of the *A1116C* gene of the angiotensin II receptor type I and the *T786C* promoter of the endothelial NO synthase gene.

**MATERIALS AND METHODS OF RESEARCH**

86 patients with arterial hypertension aged 45-76 (47 (55%) women and 39 (45%) men) took part in the study. The average age was (61.35±13.3) years; Treatment and examination were carried out in the Therapeutic Department of the Kozova Central Hospital. The control group consisted of 30 patients without signs of hypertension.

Family history regarding the early development of CVD (<55 years for men, <65 years for women) was found in 47 patients (55%). At the time of inclusion in the study, 27 people (31%) were active smokers, and 11 persons abused alcohol, which made up 13%. 30 patients (35%) suffered from obesity. Among the examined patients, 19 (22%) had hypertension stage I, and 67 (78%) had stage II. The study included patients diagnosed with hypertension 1-3 degree: 24% – degree 1, 55% – degree 2, and 21% – degree 3. The average daily blood pressure level by group is shown in Table 1.

The diagnosis of hypertension was established in accordance with the orders of the Ministry of Health of Ukraine No. 54 and 384 and the Recommendations of

the Ukrainian Association of Cardiologists on the prevention and treatment of hypertension by evaluating the anamnesis data, complaints, and the results of physical and clinical-instrumental examination.

Exclusion criteria were the presence of hypertension stage III (myocardial infarction and/or stroke in the anamnesis), secondary hypertension, any heart defects, rhythm and conduction disturbances, heart failure of functional class III–IV according to the NYHA, as well as severe concomitant diseases (chronic obstructive pulmonary disease, diabetes, chronic kidney disease, oncological and mental pathologies).

*Table 1*

**Average daily level of blood pressure by patient groups (M±m)**

| Indicator | Control group | AGTR1 (AA) | AGTR1 (AC) | AGTR1 (CC) | eNOS (TT) | eNOS (TC) | eNOS (CC) |
|---|---|---|---|---|---|---|---|
| SBP, mm Hg | 122.63±2.36 | 138±2.73 | 148.5±2.66 | 159±1.52 | 141±1.9 | 147.3±2.1 | 162.5±1.9 |
| DBP, mm Hg | 75.9±1.53 | 85±1.96 | 89.75±1.69 | 109.96±1.39 | 90±1.72 | 93.28±2.3 | 107.25±2.8 |

**Notes:** SBP – systolic blood pressure; DBP – diastolic blood pressure.

At the time of inclusion in the study, 63 patients were taking regular antihypertensive therapy, which was 73%. 43% of patients who constantly took antihypertensive drugs reached the target blood pressure level.

When performing the study, the principles of bioethics outlined in the Declaration of Helsinki "Ethical principles of medical research involving people", the "General Declaration on Bioethics and Human Rights (UNESCO)" and the order of the Ministry of Health of Ukraine "On approval of the procedure for conducting clinical trials of medicinal products and examination of materials of clinical tests and standard regulations on ethics commissions" No. 690 of September, 23, 2009. Written informed consent for the study was obtained from all patients. (Conclusion of the Commission on Biomedical Ethics of I. Horbachevsky Ternopil National Medical University No. 69 of April 12, 2022).

The structural and functional state of the heart was studied on the Acuson Sequoia 512 device according to the standard method according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography [10, 11]. Left ventricular wall thickness (LVWT) and interventricular septal thickness (IVST), and left atrial size (LAS) were determined using ultrasound of the heart. Left ventricular myocardial mass (LVMM) was determined using linear measurements, followed by calculation of the LVMM index (LVMMi) according to the Penn Convention formula. The state of LV systolic function was assessed by the ejection fraction (EF) indicator. Diastolic dysfunction of the left ventricle was assessed in all patients by Doppler echocardiography, taking into account the maximum speed of early (E, cm/s) and late (A, cm/s) diastolic filling of the LV, their ratio (E/A c.u.). A sign of diastolic disorders was considered to be a value of the E/A ratio of less than 1 c.u.

The polymerase chain reaction method with electrophoretic detection of the results was used to study the allelic polymorphism *A1166C* of the angiotensin II receptor gene type I and *T786C* – the promoter of the *eNOS* gene using SNP-EXPRESS reagent sets ("Litech" Ltd. LLC, RF). The frequency of distribution of polymorphic genes in the population was checked according to the Hardy-Weinberg law of genetic equilibrium.

Daily blood pressure monitoring was performed on a portable device SDM23 (Ukraine) according to a standard protocol. The indicators were analyzed using the software of this device. Monitoring took place every 15 minutes during the day and every 30 minutes during the night (every 30 minutes from 10:00 p.m. to 6:00 a.m.).

Statistical analysis of the results was carried out using the Statistica 10 program package ("Statsoft", USA, license number CDDR415X254504GVZ7) and the package of statistical functions of Microsoft Office Excel 2016 (Microsoft Corp., USA). The average arithmetic value (M) and its error (m) were determined. Checking the distribution of samples for normality was carried out according to the Shapiro-Wilk test. The reliability of changes in the average values of the study results between groups was calculated according to the Student's t-test with a normal distribution of independent samples. Statistically significant differences were considered to be $p<0.05$ [12].

**RESULTS AND DISCUSSION**

The structural and functional state of the heart in patients with hypertension depending on the



*На умовах ліцензії CC BY 4.0*

polymorphism *A1166C* and *T786C*, as well as healthy individuals are shown in Table 2.

When analyzing the indicators of systolic function of the myocardium, we did not find a significant difference between patients with hypertension and the control group, however, a tendency to a lower level of LVEF was observed in the carriers of the C-allele of both studied genes (AC+CC and TC+CC).

*Table 2*

**Cardiac ultrasound in patients with hypertension depending on the polymorphism of the *AGTR1* (*A1166C*) and e*NOS* (*T786C*) genes (M±m)**

| Genes | Genotypes, n=86 | Indicator value (M±m) in patients depending on gene polymorphism | | | | | |
|---|---|---|---|---|---|---|---|
| | | EF,% | TPWLV, cm | IVS, cm | LVMMi, g/m$^2$ | LA, см | E/A, cond. un. |
| Control (n=30) | | 66.2±2.4 | 0.8±0.1 | 0.9±0.1 | 113.4±8.3 | 3.2±0.1 | 1.3±0.1 |
| *AGTR1* | AA (n=18) | 66.2±2.4 | 1.1±0.05<br>p<0.01 | 1.2±0.06<br>p<0.01 | 135±10.1 | 3.8±0.09 | 1.16±0.07 |
| | AC (n=38) | 62.3±3.9 | 1.2±0.05<br>p<0.001 | 1.2±0.07<br>p<0.01 | 157.5±7.3<br>p<0.001 | 4.2±0.08<br>p<0.001<br>p$_1$<0.001 | 0.92±0.06<br>p<0.001 |
| | CC (n=30) | 58.1±3.4 | 1.3±0.07<br>p<0.001<br>p$_1$<0.02 | 1.2±0.06<br>p<0.01 | 161.5±7.1<br>p<0.001<br>p$_1$<0.03 | 4.6±0.2<br>p<0.001<br>p<0.001 | 0.88±0.07<br>p<0.001 |
| *eNOS* | TT (n=24) | 64.4±3.5 | 1.2±0.09<br>p<0.004 | 1.2±0.06<br>p<0.01 | 147.3±16.4 | 4.0±0.4 | 1.05±0.1 |
| | TC (n=31) | 62.7±3.1 | 1.2±0.06<br>p<0.001 | 1.2±0.07<br>p<0.01 | 155.2±11.4<br>p<0.004 | 4.3±0.3<br>p<0.001 | 0.93±0.1<br>p<0.01 |
| | CC (n=31) | 58.4±4.6 | 1.3±0.08<br>p<0.002 | 1.2±0.05<br>p<0.009 | 158.4±7.9<br>p<0.001 | 4.5±0.3<br>p<0.001 | 0.9±0.08<br>p<0.002 |

**Notes:** p – the difference between the indicators is significant compared to the control group; p$_1$ – the difference is significant in compared to with homozygotes by a single gene (AA, TT).

In patients with hypertension LVWT and IVST was significantly higher than in almost healthy individuals (p<0.01). We also found a bigger LVWT in patients with CC genotype compared to carriers of AA genotype *A1166C* – (1.3±0.07) cm vs. (1.1±0.05) cm (p<0.02).

LV myocardial infarction is considered an independent risk factor for overall and cardiac mortality, as well as the development of cardiovascular events such as myocardial infarction or stroke [13]. The study found that in patients with hypertension, the inheritance of AC and CC *A1166C* genotypes of the angiotensin II receptor gene type 1 and TC and CC *T786C – eNOS* promoter is characterized by more significant changes in LV MMi than in carriers of AA and TT genotypes. Thus, LV MMi in the group of patients with the genotype AC and CC was (157.5±7.3) g/m$^2$ and (161.5±7.1)) g/m$^2$, respectively, that is by 16.7% and 19.6% more than in carriers of AA genotype of the *AGTR1* gene. It should be noted that the difference in LV MMi in carriers of AA and CC genotypes was significant (p<0.03). Our results are consistent with the results of A.S. Shalimov, who established a probable increase in LVMMi in hypertensive patients in the presence of the C-allele of the *AGTR1* gene [14]. Regarding the *T786C* polymorphism, in the groups of patients – carriers of C-allele (TC+CC) LV MMi values were (155.2±11.4)) g/m$^2$ and (158.4±7.9)) g/m$^2$, respectively, which is 5.4% and 7.5% more than in carriers of TT genotype. The results of numerous experimental studies show that in carriers of the C allele there is a decrease in the expression of the eNO synthase gene and, as a result, a decrease in the production of nitric oxide, which is known to be involved in the regulation of vascular tone [15].

The mean sizes of LA were significantly higher in patients who had AC and CC genotype of the *AGTR1* gene, as well as TC and CC genotype of the *eNOS* gene compared with the control group (Table 2). Comparing the sizes of LA we found a significant difference (p<0.001) in patients-carriers of C-allele (AC+CC genotype) of the *A1166C* polymorphism of

the *AGTR1* gene and in patients – homozygous by the A allele.

We also analyzed the parameters of transmitral blood flow, which are known to be a marker of the left ventricular diastolic function.

We were able to find that patients – carriers of AA *AGTR1* gene genotype and homozygotes with the T allele of the *eNOS* gene did not have diastolic dysfunction. While the severity of diastolic dysfunction was higher in carriers of the CC genotype of the *AGTR1* gene and the *eNOS* gene than in heterozygotes of the studied genes by 4.3% and 3.3%, respectively, which may indicate a relationship between the C allele and the development of diastolic dysfunction in patients with hypertension.

**CONCLUSIONS**

1. In patients with hypertension, inheritance of AC and CC genotypes of the AGTR1 gene is characterized by significant changes in the structural and functional state of the heart than inheritance of the AA genotype. Homozygotes by C allele (CC genotype) showed significantly higher rates of the left ventricular wall thickness, left ventricular myocardial mass index and the left atrial size compared with patients with AGTR1 AA genotype ($p<0.05$).
2. In patients with hypertension who were detected a genotype with the presence of the C allele of the eNOS gene, significantly higher values left ventricular myocardial mass index and left atrial size were observed in comparison with the control group ($p<0.01$).
3. In patients with hypertension, residents of Ternopil region, inheritance of genotype CC polymorphism A1166C of angiotensin II receptor gene type 1 and CC polymorphism of T786C-promoter of eNOS gene is associated with greater changes in left ventricular diastolic dysfunction compared with heterozygotes.

**Contributors:**

Hnizdiukh R.V. – conceptualization, methodology, verification, formal analysis, research, writing – original draft, writing – review and editing, visualization;

Shmanko V.V. – conceptualization, methodology, verification, writing – review and editing, supervision.

**Funding.** This research received no external funding.

**Conflict of interests.** The authors declare no conflict of interest.

## REFERENCES

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-104. Erratum in: Eur Heart J. 2019 Feb 1;40(5):475.
doi: https://doi.org/10.1093/eurheartj/ehy686

2. Tseluyko VI. [Reality of arterial hypertension treatment in Ukraine: the results of «SYSTEMA 2» cohort study]. Ukrainskyi kardiolohichnyi zhurnal. 2018;25(1):13-20. Russian.

3. Kjeldsen SE. Hypertension and cardiovascular risk: General aspects. Pharmacol Res. 2018 Mar;129:95-99. doi: https://doi.org/10.1016/j.phrs.2017.11.003

4. Paini A, Tarozzi L, Bertacchini F, Aggiusti C, Rosei CA, De Ciuceis C, et al. Cardiovascular prognosis in patients admitted to an emergency department with hypertensive emergencies and urgencies. Journal of hypertension. 2021;39(12):2514-20.
doi: https://doi.org/10.1097/HJH.0000000000002961

5. Nesukay EG, Giresh II. [Left heart geometry changes in patients with essential hypertension and different heart rate]. Ukrainskyi kardiolohichnyi zhurnal. 2017;1:64-9. Ukrainian.

6. Brouwers S, Sudano I, Kokubo Y, Sulaica EM. Arterial hypertension. Lancet. 2021;398(10296):249-61. doi: https://doi.org/10.1016/S0140-6736(21)00221-X

7. Sakovych OO, et al. [Polymorphism of the second type angiotensin II receptor's gene in women with essential hypertension and the corresponding features of structural and functional parameters of myocardium]. Pathologia. 2018;15(2):169-75. Ukrainian.
doi: https://doi.org/10.14739/2310-1237.2018.2.141398

8. Singh M, Singh AK, Pandey P, Chandra S, Singh KA, Gambhir IS. Molecular genetics of essential hypertension. Clinical and experimental hypertension. Clin Exp Hypertens. 2016;38(3):268-77.
doi: https://doi.org/10.3109/10641963.2015.1116543

9. Rani B, Kumar A, Bahl A, Sharma R, Prasad R, Khullar M. Renin-angiotensin system gene polymorphisms as potential modifiers of hypertrophic and dilated cardiomyopathy phenotypes. Mol Cell Biochem. 2017 Mar;427(1-2):1-11.
doi: https://doi.org/10.1007/s11010-016-2891-y

10. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Associa-tion of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). Systemic Hypertension. 2017;14(2):6-28.
doi: https://doi.org/10.26442/2075- 082x_14.2.6-28

11. Perrone-Filardi P, Coca A, Galderisi M, Paolillo S, Alpendurada F, de Simone G, et al. Non-invasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus paper from the European Association of Cardiovascular Imaging



*На умовах ліцензії CC BY 4.0*

(EACVI), the European Society of Cardiology Council on Hypertension, and the European Society of Hypertension (ESH). Eur Heart J Cardiovasc Imaging. 2017 Sep 1;18(9):945-60. doi: https://doi.org/10.1093/ehjci/jex094

12. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. Kyiv: Medinform; 2018. p. 579. Russian.

13. Ma D, Mandour AS, Yoshida T, Matsuura K, Shimada K, Kitpipatkun P, et al. Intraventricular pressure gradients change during the development of left ventricular hypertrophy: Effect of salvianolic acid B and beta-blocker. Ultrasound. 2021 Nov;29(4):229-40.
doi: https://doi.org/10.1177/1742271X20987584

14. Shalimova A. Heart and vascular remodeling in essential hypertension and type 2 diabetes is dependent on genetic polymorphisms. Vessel Plus. 2017;1: 84-90. doi: https://doi.org/10.20517/2574-1209.2016.08

15. Mahmoodi K, Soltanpour MS, Kamali K. Assessment of the role of plasma nitric oxide levels, T-786C genetic polymorphism, and gene expression levels of endothelial nitric oxide synthase in the development of coronary artery disease. J Res Med Sci. 2017 Mar 15;22:34.
doi: https://doi.org/10.4103/1735-1995.202144

Стаття надійшла до редакції
04.07.2022