Syvolap V.V.,
PhD, professor
Headof the department of multimodal diagnostics and propedeutics
At Zaporizhzhia State Medical University
NovikovE.V.,
PhD student
of the department of multimodal diagnostics and propedeutics
At Zaporizhzhia State Medical University
PotapenkoM.S.
PhD, docent of the department
of an esthesiology and intensive therapy at
Zaporizhzhia State Medical University
Al Kaddah D.
Intern of the department
of multimodal diagnostics and propedeutics
at Zaporizhzhia State Medica lUniversity

INFLUENCE OF A STATIN THERAPY ON THE ELECTRICAL PROPERTIES OF ATRIAL AND VENTRICULAR MYOCARDIUM IN PATIENTS WITH ARTERIAL HYPERTENSION COMBINED WITH A SUBCLINICAL HYPOTHYROIDISM.

Annotation. The influence of atorvastatin therapy on the dynamics of indicators characterizing late potentials of the atria and ventricles in patients with arterial hypertension (AH) combined with a subclinical hypothyroidism (SH)was investigated. Addition of statins to the antihypertensive therapy during the year in patients with AH andaconcomitant subclinical hypothyroidism does not have a corrective effect on the late potentials of the atria, howeverit is associated with a probable decrease in the number of premature atrial contractions (PAC), a decrease by half ($p = 0.001$) of the percentage of patients with the prolonged duration of the filtered QRS complex and of the minimal root mean square (RMS) amplitude of the QRS complex over the last 40 ms by 17.6% ($p = 0.040$).

Keywords:Arterial hypertension, subclinical hypothyroidism, 24h-monitoring of electrocardiogram, late atrial potentials, late ventricular potentials, statin therapy.

MainProblem. Arterial hypertension is one of the main causes of atrial and ventricular disorders of the heart rhythm [1]. To the most common factors that have a proarrhythmic effect in patients with AH belong systolic and diastolic pressure overload, secondary neurohormonal activation, left ventricular hypertrophy (LVH), myocardial fibrosis.

The described changes cause a decrease in the speed of the impulse conduction, formation of the ectopic foci and a substrate for the appearance of the "re-entry" mechanism [2,3,4,5,6]. Left atrial dilatation due to the increased diastolic pressure of the left ventricle causes an increased risk of atrial fibrillation (AF) [7,8,9.].The existence of an association of mentioned changes with the onset and progression of the ventricular arrhythmias has also been proved [10]. Late potentials of the atria and ventricles are considered as one of the earliest criteria fora proarrhythmic myocardial readiness in patients with AH [11,12,13,14]. These are electrical oscillations at the end of the "P" wave or of the ventricular ECG complex, which have a low amplitude (5-20 μV) and a high frequency (more than 20-50 μV) but are not registered on a normal ECG. Thanks to a special processing, the signals are available for recording and analysis on the modern Holter ECG-monitoring devices [15,16,17].

Analysisofthelatestinvestigationsandpublishings: The analysis of the literature sources and the results of our own studies on the effect of SH on the electrical properties of the myocardium of atria and ventricles are reported in the previous publication [18]. The aim of this work is to study changes in these parameters in patients with AH with the concomitant SH under the influence of statin therapy.In the past years, a conclusive data on the antiarrhythmic activity of medicationsthat don't belong to the antiarrhythmic drug group have been obtained. This is aso called "upstream" or "additional" therapy [19]. These drugs include angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), aldosterone antagonists, and statins [20-27].All of these medical substances can affect the pathogenetic mechanisms of arrhythmias, so unlike the antiarrhythmic therapy, which is mostly symptomatic, "upstream" therapy can be considered pathogenetic.The antiarrhythmic effect of statins can be connected to a number of factors: improved lipid metabolism; endothelial function; anti-inflammatory, antioxidant action; change in the permeability of membranes and conductivity of ion channels, influence on the autonomic nervous system. [19,20,21]. Most of the data regarding the antiarrhythmic properties of statins have been accumulated in the group of patients with persistent or paroxysmal form of atrial fibrillation.Thus, the meta-analysis of 2014 did not prove such an impact except in cases of AF prevention after coronary artery bypass surgery [28]. Neither did Prof. V.I. Podzolokov et al. [29] obtain a significant reduction in the frequency and duration of arrhythmia in the secondary prevention of AF with the help of statins. However, researchers from Volgograd (Russia) concluded that the addition of atorvastatin to standard

antiarrhythmic therapy for 6 months in patients with ischemic heart disease with a paroxysmal form of AF statistically significantly reduces the frequency of recurrence and the duration of the AF paroxysms, improves their subjective tolerance and reducesthe supraventricular and ventricular ectopic activities.Positive changes in temporal and spectral indicators of heart rate variability (increase in SDNN, RMSSD, TP, HF and the decrease in LF / HF) are considered by the authors as one of the mechanisms of the antiarrhythmic effect of statins [30].

Highlighting the parts of the main problem that were unsolved previously:

Data on the antiarrhythmic properties of statins are conflicting. The effect of atorvastatin on the late potentials of the atria and ventricles in patients with arterial hypertension combined with subclinical hypothyroidism has not been studied previously.

Formulationofthemaingoalsofthearticle: To study the effect of the statin therapy on the electrical properties of atrial and ventricular myocardium in patients with arterial hypertension combined with subclinical hypothyroidism.

Presentation of the main material of the investigation with the full explanation of the scientific results received.

The studies were conducted on the clinical base of the Department of Multimodal Diagnostics and Propedeutics of ZSMU in the cardiology department of CNC "City Hospital No. 6" ZMR in Zaporizhzhia. After the informed consent was signed, 74 patients with AH were included in the study, 43 of them without and 31 with the concomitant subclinical hypothyroidism. The diagnosis of AH was established in accordance with the recommendations of the Association of Cardiologists of Ukraine [31], and the diagnosis of subclinical hypothyroidism in accordance with the recommendations [32].

Depending on the therapy, patients were divided into three groups. The first group included 22 patients (54 ± 9 years, 91% women) with AH without concomitant subclinical hypothyroidism, who were prescribed only first line antihypertensive drugs without statins. The second group included 21 patients (56 ± 6 years, women 86%) with AH without the concomitant subclinical hypothyroidism, who were prescribed first-line antihypertensive drugs with statins. The third group was formed with 31 patients (mean age 58 ± 10 years, women 90%) withAH with the concomitant subclinical hypothyroidism who were prescribed first-line antihypertensive drugs with statins.The groups were compared by age, gender, main anthropometric indices. Prior to treatment and after one year of observation, all patients underwent echocardiographic examination on a My Lab Seven device (Italy) to examine changes in structural, geometric, and functional cardiac parameters. 24h-monitoring of arterial blood pressure and electrocardiogram with the analysis of late potentials of the atria and ventricles was performed before the beginning of therapy and after one year of therapy on the bifunctional device "Cardiotechnics-04" ("Incart", S.-P., R.F.) with a simultaneous registration of blood pressure and ECG.Statistical processing was performed using the software package "STATISTICA 13.0" ("Statsoft", USA), license number JPZ8041382130ARCN10-J. The normality of quantitative indices distribution was analyzed using the Shapiro-Wilk test. Parameters that had a normal distribution are presented as arithmetic mean and standard deviation (M ± SD). For indicators that had a distribution that was different from normal, data of the descriptive statistics were provided in the form of median and interquartile range - Me (Q25 - Q75). Comparisons of quantitative indices across the groups were performed using Student and Mann-Whitney criteria, depending on the character of the distribution. Qualitative indicators were compared with the help of Pearson's $\chi 2$. A difference of $p < 0.05$ was considered statistically significant. All tests were two-sided.

Results:

Changes in the late potentials of the atria and ventricles in patients with AH without the concomitant subclinical hypothyroidism under the influence of antihypertensive therapy without the addition of statins. In patients with AH without a concomitant subclinical hypothyroidism under the influence of treatment with antihypertensive drugs for a year without addition of statins, the maximal duration of the filtered P-wave decreased from 150.36 ± 41.86 ms to 136.91 ± 19.89 ms, (p = 0.176), without changes in the mean duration of the filtered P wave (before treatment 115,91 ± 9,28 ms, after treatment 114,05 ± 11,07 ms, p = 0,573).The value of P total was higher than the recommended values before the treatment in 35.00 ± 28.83% of patients, and in 26.86 ± 28.13% of patients after one year of therapy (p = 0.209). That is, changes in the filtered P-wave under the influence of treatment were characterized by a tendency to decrease its duration and specific gravity in patients with P total value exceeding critical values.

The value of the maximum RMS amplitude of the P-wave over the last 20 ms in patients with AH without a concomitant subclinical hypothyroidism did not change significantly under the influence of treatment (6.14 ± 1.17 μV before treatment, 6.2 ± 1.48 μV after treatment, (p = 0,888)), as well as the mean RMS amplitude of the P-wave over the last 20 ms (3.79 ± 0.52 μV before treatment, 3.93 ± 0.74 μV after treatment, (p = 0.432).At the same time, there was a probable increase in the minimal RMS amplitude of the P-wave over the last 20 ms from 1.85 ± 0.72 μV to 2.29 ± 0.73 μV, (p = 0.049). RMS20 values less than 3.5 μV were recorded before the treatment in 43.41 ± 27.23% of patients, and after 1 year of therapy in 35.32 ± 28.82% of the treated patients, however, this difference also did not reach the statistical probablity (p = 0.348).

The analysis of the specific gravity of patients with the present late atrial potentials revealed that before the beginning of therapy, 100% (n = 22) of patients with AH without a concomitant subclinical hypothyroidism had late atrial potentials. After one year of treatment with antihypertensive drugs without the addition of statins, specific gravity of patients with

present late atrial potentials decreased significantly down to 73% (n = 16) (p = 0.0106). The criteria for the presence of late atrial potentials we considered to be Ptotal ≥120 ms, RMS20 <3.5 μV.

The decrease in frequency of registration of late atrial potentials was accompanied by a tendency for a decrease of the number of premature atrial contractions from 14 (4; 22) to 8.5 (4; 15); p = 0.221.

During the analysis of indices of processes of ventricular depolarization before and after treatment with antihypertensive drugs without the addition of statins in patients with AH without a concomitant subclinical hypothyroidism, an unreliable reduction in the duration of the filtered complex QRS (TotalQRS) was established: maximum duration of the filtered QRS complex from 93.65 ± 8.34 ms to 91.75 ± 7.67 ms, (p = 0.491), the minimal duration of the filtered QRS complex from 80.32 ± 6.29 ms to 77.5 ± 8.02 ms (p = 0.249), the average duration of the filtered QRS complex from 87.51 ± 7.59 ms to 85.82 ± 7.78 ms (p = 0.588).Indicators of RMS40 and LAS40 in patients with AH without a concomitant subclinical hypothyroidism had no probable difference before and after the treatment. The percentage of patients who had RMS40 and LAS40 values beyond the reference values before and after treatment also did not change significantly.

Unlike late atrial potentials, a probable difference in the frequency of registration of late ventricular potentials before and after one year of treatment in patients with AH without a concomitant subclinical hypothyroidism was not detected by us - 41% (n = 9) of patients had late ventricular potentials before the treatment and 45% (n = 10)after treatment, the difference was statistically unreliable (p = 0.790).

Changes in the late potentials of the atria and ventricles in patients with AH without a concomitant subclinical hypothyroidism under the influence of antihypertensive therapy with addition of statins. In patients with AH without a concomitant subclinical hypothyroidism under the influence of treatment with antihypertensive drugs with addition of statins for a year, a significant decrease in the average duration of the filtered P-wave was observed from 112.71 ± 11.93 ms to 104.24 ± 14.28 ms, (p = 0.043).There were no significant changes in the maximal and minimal duration of the filtered P-wave before and after the treatment. The value of P total was higher than the recommended values before treatment in 30.10 ± 29.95% of patients, and after a year of treatment decreased almost by two times -down to 15.95 ± 24.64%, (p = 0.032).

That is, changes in the filtered P-wave in patients with AH without a concomitant subclinical hypothyroidism under the influence of treatment with addition of statins were characterized by a reliable decrease by 7.5% of its average duration and almost two times the specific gravity of patients with P total values exceeding critical numbers.

The value of the maximal RMS amplitude of the P-wave over the last 20 ms in patients with AH without a concomitant subclinical hypothyroidism under the influence of treatment with the addition of statins did not change significantly (6.07 ± 1.46 μV before treatment, 5.74 ± 1.47 μV after treatment, (p = 0.443)), as well as the mean and minimal RMS amplitude of the P wave over the last 20 ms. An RMS20 value of less than 3.5 μV before and after also did not reach the statistical probability limit (p = 0.910).

Analysis of thespecific gravity ofpatients withthepresent late atrial potentials (using two Ptotal criteria ≥120 ms, RMS20 <3.5 μV) established that 90.5% (n = 19) of patients with AH without aconcomitant subclinical hypothyroidism had late atrial potentials prior to the start of therapy.

After one year of treatment with antihypertensive drugs with addition of statins, the specific gravity of patients with present late atrial potentials decreased reliably- down to 61.9% (n = 13), with an absolute reduction of 28.6% (p = 0.0399).

Analysis of indices of ventricular depolarization in patients with AH without a concomitant subclinical hypothyroidism before and after treatment with antihypertensive drugs with addition of statins (second group) did not reveal any significant changes in the maximal duration of the filtered QRS complex (before treatment 93.57 ± 10.93, after treatment 95,33±10,71ms, (p=0,439)) the minimal duration of the filtered QRS complex (before treatment 78.76 ± 8.50 ms, after treatment 77.5 ± 8.02 ms, (p = 0.722)); mean duration of the filtered QRS complex (before treatment 82.24 ± 7.55 ms, after treatment up to 87.00 ± 8.98 ms, (p = 0.588)).Indices of RMS40 and LAS40 in patients with AH without a concomitant subclinical hypothyroidism also did not reliably change under the influence of antihypertensive therapy with addition of statins after one year of treatment, except for maximal RMS40 (before treatment 68.67 ± 9.20 μV, after treatment 63.38 ± 7 , 21 μV; p = 0.044).

The percentage of patients whose RMS40 and LAS40 values would fall outside the reference values before and after one year of treatment also did not reliably change. Before the beginning of treatment, the specific gravity of patients with RMS40 less than critical values was 9.86 ± 21.43% and 21.43 ± 35.10% after treatment (p = 0.344). With definitive LAS40 values before treatment, there were 5.67 ± 13.45% of patients, and after treatment 15.67 ± 24.77%, the difference almost reached the statistical probability limit (p = 0.072).

There was no reliable difference detected in the frequency of registration of late ventricular potentials before and after one year of treatment with antihypertensive drugs with the addition of statins in patients with AH without a concomitant subclinical hypothyroidism. Before the treatment24% (n = 5) of patients had late ventricular potentials, and after treatment - 48% (n = 10), the difference is statistically unreliable (p = 0.113).

Changes in the late potentials of the atria and ventricles in patients with AH with a concomitant subclinical hypothyroidism under the influence of antihypertensive therapy with the addition of statins. In patients with AH with a concomitant subclinical

hypothyroidism under the influence of treatment with antihypertensive drugs with addition of statins for a year, there was no change in the maximal duration of the filtered P-wave (141 ± 21 ms vs.143 ± 28 ms, (p = 0.898)), minimal duration of the filtered P-wave(85 ± 18 ms vs. 80 ± 19 ms, p = 0.522),mean duration of the filtered P-wave (113 ± 10 ms vs. 108 ± 11 ms, p = 0.701).The value of P total was higher than the recommended values before the treatment in 27 ± 27% of patients and in 20 ± 20% of patients after one year of therapy (p = 0.159). That is, changes in the filtered P-wave under the influence of treatment were characterized only by a tendency for a decrease of its duration and specific gravity of patients with a value of P total that exceeds the critical values.

The value of the maximal root mean square amplitude of the P-wave over the last 20 ms in patients with AH with a concomitant subclinical hypothyroidism also did not change significantly under the influence of treatment (6 ± 1 μV vs 5 ± 1 μV, (p = 0.159)); as well as the mean and minimal RMS amplitude of the P wave over the last 20 ms. RMS20 values less than 3.5 μV were recorded before treatment in 45 ± 26% of patients, and after 1 year of treatment in 37 ± 29% of treated patients, but this difference was statistically unreliable (p = 0.898).

Analysisof the specific gravity of patients with the present late atrial potentials (using two Ptotal criteria ≥120 ms, RMS20 <3.5 μV) established that 87% (n = 27) of patients with AH with a concomitant subclinical hypothyroidism had late atrial potentials before the initiation of therapy. A year after the treatment with antihypertensive drugs with addition of statins the specific gravity of patients presenting late atrial potentials increased up to 94% (n = 29) but unreliably (p = 0.351).

Analysis of indices of ventricular depolarization processes before and after treatment in patients with AH with a concomitant subclinical hypothyroidism established a tendency for a reduction of the maximal duration of the filtered QRS complex (TotalQRS) after a year of therapy with antihypertensive drugs with addition of statinsfrom 100 ± 17 ms to 95 ± 20 ms, (p = 0.071), while there is no change in the minimal duration of the filtered QRS complex (85 ± 15 ms versus 85 ± 15 ms, (p = 0.370)), mean duration of the filtered QRS complex (92 ± 15 ms vs. 90 ± 15 ms (p = 0.701). However, the percentage of patients with AH with a concomitant subclinical hypothyroidism with the prolonged duration of the filtered QRS complex after a year of antihypertensive therapy with addition of statins decreased by two times from 6 ± 23% to 3 ± 18%, (p = 0.001). Indices RMS40 and LAS40 in patients with AH with a concomitant subclinical hypothyroidism had no probable difference before and after treatment, with the exception of RMS40 minimal (before 17 ± 15 μV, after 14 ± 8 μV; p = 0.040). Before the treatment, the specific gravity of patients with less than critical RMS40 values was 49 ± 40%, and after treatment 47 ± 40%, (p = 0.701).

The percentage of patients whose LAS40 values exceeded the reference values before and after treatment also did not change significantly. With definitive values of LAS40 before treatment there were 42 ± 36% of patients and after treatment 35 ± 36% (p = 0,442).

There was no probable difference establishedin the frequency of registration of late ventricular potentials before and after a year of treatment in patients with AH with a concomitant subclinical hypothyroidism - 81% (n = 25) of patients had late ventricular potentials before the treatment, and 74% (n = 23) after treatment,the difference was statistically unreliable (p = 0.5118).

Therefore, the presence of the concomitant subclinical hypothyroidism in patients with AH completely inhibits the positive action of pleiotropic effects of statins on the processes of slowing down and fragmentation of the processes of atrial depolarization. Prescribing statins in addition to antihypertensive therapy for patients with AH contributes to a two times decrease (p = 0.001) of the percentage of patients with a prolonged duration of the filtered QRS complex and reduction of the minimal RMS amplitude value of the QRS complex by 17.6% (p = 0.040) over the last 40ms, however these changes in the activity of the processes of ventricular depolarization are not accompanied by a statistically probable decrease in the number of premature ventricular contractions (p = 0.798).

Conclusions and proposals:

1. A long-term therapy during the year with antihypertensive drugs without the addition of statins is accompanied with a probable reduction in the specific gravity of patients with AH without a concomitant subclinical hypothyroidism with late atrial potentials from 100% to 73%, and the increase of the minimal value of RMS amplitude over the last 20 ms from 1.85 ± 0.72 μV to 2.29 ± 0.73 μV, (p = 0.049). Indices that reflect the slow and fragmented activity of the ventricular depolarization processes had no statistically significant difference before and after treatment in this category of patients with AH.

2. A long-term therapy during the year with antihypertensive drugs with the addition of statins is accompanied with a reduction in the specific gravity of patients with AH without the concomitant subclinical hypothyroidism (second group) with late atrial potentials from 90.5% to 61.9%, (p = 0.0399), reduction by 7.5% (p = 0.043) of the mean duration of the filtered P-wave and almost by two times (p = 0.032) of the specific gravity of patients with a P total that exceeded critical values. At the same time, antihypertensive therapy with statins did not affect the late ventricular potentials in this category of patients.

3. Addition of statins to the antihypertensive therapy during the year in patients with AH with the concomitant subclinical hypothyroidism does not have a corrective effect on the late atrial potentials, howeverit is associated with a probable reduction in the number of premature atrial contractions, decreasing twice(p=0,001)the percentage of patients with the prolonged duration of the filtered QRS complex and minimal RMS amplitude of the QRS complex over the last 40 ms by 17.6% (p = 0.040).

The prospects for the further research are to study the effects of statin therapy on the structural and geometric restructuring of the heart in patients with AH with the concomitant subclinical hypothyroidism.

Literature:

1. Radulescu D, Stoicescu L, Buzdugan E, Donca V. Patterns of left ventricular remodeling among patients with essential and secondary hypertension. Revista médica de Chile. 2013;141(12):1520-1527. doi:10.4067/s0034-98872013001200004

2. Sultana R, Sultana N, Rashid A, Rasheed SZ, Ahmed M, Ishaq M, Samad A. Cardiac arrhythmias and left ventricular hypertrophy in systemic hypertension. J Ayub Med Coll Abbottabad. 2010;22(4):155-8.

3. Shenasa M, Shenasa H, El-Sherif N. Left Ventricular Hypertrophy and Arrhythmogenesis. Cardiac Electrophysiology Clinics. 2015;7(2):207-220. doi:10.1016/j.ccep.2015.03.017

4. Kahan T, Bergfeldt L. Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. Heart. 2005;91(2):250-256. doi:10.1136/hrt.2004.042473

5. Yiu K-H, Tse H-F. Hypertension and cardiac arrhythmias: a review of the epidemiology, pathophysiology and clinical implications. Journal of Human Hypertension. 2008;22(6):380-388. doi:10.1038/jhh.2008.10

6. Santangeli P, Infusino F, Sgueglia GA, Sestito A, Lanza GA. Ventricular late potentials: a critical overview and current applications. Journal of Electrocardiology. 2008;41(4):318-324. doi:10.1016/j.jelectrocard.2008.03.001

7. Baseline characteristics of patients with atrial fibrillation: The AFFIRM Study. American Heart Journal. 2002;143(6):991-1001. doi:10.1067/mhj.2002.122875

8. Kannel W, Wolf P, Benjamin E, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates 11Reprints are not available. The American Journal of Cardiology. 1998;82(7):2N-9N. doi:10.1016/s0002-9149(98)00583-9

9. Verdecchia P, Reboldi G, Gattobigio R, et al. Atrial Fibrillation in Hypertension. Hypertension. 2003;41(2):218-223. doi:10.1161/01.hyp.0000052830.02773.e4

10. Madu EC, Baugh DS, David Gbadebo T, Dhala A, Cardoso S. Effect of ethnicity and hypertension on atrial conduction: Evaluation with high-resolution p-wave signal averaging. Clinical Cardiology. 2001;24(9):597-602. doi:10.1002/clc.4960240906

11. Baguet J-P, Erdine S, Mallion J-M. Hypertension and arrhythmia. European Society of Hypertension Scientific Newsletter: Update on Hypertension Management. 2005;6:24. https://www.eshonline.org/esh-content/uploads/2014/12/24_Newsletter-Hypertension-and-Arrhythmia.pdf

12. Mozoş I, Şerban C, Mihăescu R. Late Ventricular Potentials in Cardiac and Extracardiac Diseases. Cardiac Arrhythmias - New Considerations. February 2012. doi:10.5772/25415

13. Barbosa PRB, de Souza Bomfim A, Barbosa EC, et al. Spectral turbulence analysis of the signal-averaged electrocardiogram of the atrial activation as predictor of recurrence of idiopathic and persistent atrial fibrillation. International Journal of Cardiology. 2006;107(3):307-316. doi:10.1016/j.ijcard.2005.03.073

14. Galinier M, Balanescu S, Fourcade J, et al. Prognostic value of arrhythmogenic markers in systemic hypertension. European Heart Journal. 1997;18(9):1484-1491. doi:10.1093/oxfordjournals.eurheartj.a015476

15. Benchimol-Barbosa PR, Barbosa EC, Bomfim AS, Ginefra P, Nadal J. Clinical assessment of the effect of digital filtering on the detection of ventricular late potentials. Brazilian Journal of Medical and Biological Research. 2002;35(11):1285-1292. doi:10.1590/s0100-879x2002001100005

16. Ramos JA, dos Santos PJL. Parametric Modeling in Estimating Abnormal Intra-QRS Potentials in Signal-Averaged Electrocardiograms: A Subspace Identification Approach. IFAC Proceedings Volumes. 2012;45(16):565-570. doi:10.3182/20120711-3-be-2027.00402

17. Abdelghani SA, Rosenthal TM, Morin DP. Surface Electrocardiogram Predictors of Sudden Cardiac Arrest. Ochsner J. 2016;16(3):280–289.

18. Сыволап В.В. Новиков Е.В. Электрические свойства миокарда у больных артериальной гипертензией, сочетанной с субклиническим гіпотиреозом // Запорожский медицинский журнал. 2019. Т. 21, № 5(116). С. 582–589

DOI: 10.14739/2310-1210. 2019.5.179405[Syvolap, V. V., Novikov, Ye.V. (2019). Electrical properties of the myocardium in patients with arterial hypertension combined with subclinical hypothyroidism. Zaporozhye medical journal, 5(116), 582–589. DOI: 10.14739/2310-1210. 2019.5.179405]

19. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010t;12(10):1360-420.

20. Savelieva I., Camm A.J. Statins and polyunsaturated fatty acids for treatment of atrial fibrillation. Nat Clin Pract Cardiovasc Med 2008; 5: 30-41.

21. Savelieva I., Kourliouros A., Camm J. Primary and secondary prevention of atrial fibrillation with statin and polyunsaturated fatty acids: review of evidence and clinical relevance. Naunyn Schmiedebergs Arch Pharmacol 2010; 381: 1-13.

22. Santangeli P., Ferrante G., Pelargonio G., et al. Usefulness of statins in preventing atrial fibrillation in patients with permanent pacemaker: a systematic review. Europace 2010; 12: 649-54.

23. Patti G., Chello M., Candura D., et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3

(Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation 2006; 114:1455-61.

24. Liakopoulos O.J., Choi Y.H., Kuhn E.W., et al. Statins for prevention of atrial fibrillation after cardiac surgery:a systematic literature review. J Thorac Cardiovasc Surg 2009; 138: 678-86e1.

25. Almroth H., Hoglund N., Boman K., et al. Atorvastatin and persistent atrial fibrillation following cardioversion:a randomized placebo-controlled multicentre study. Eur Heart J 2009; 30: 827-33.

26. Fauchier L., Pierre B., de Labriolle A., et al. Antiarrhythmic effect of statin therapy and atrial fibrillation:a meta-analysis of randomized controlled trials. JACC 2008; 51: 828-35.

27. Liu T., Li L., Korantzopoulos P., et al. Statin use and development of atrial fibrillation: a systematic reviewand meta-analysis of randomized clinical trials and observational studies. Int J Cardiol 2008; 126:160-170.

28. Yang Q, Qi X1, Li Y.The preventive effect of atorvastatin on atrial fibrillation: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2014;14:99.

29. Подзолков В.И., Тарзиманова А.И., Гатаулин Р.Г. Статины во вторичной профилактике фибрилляции предсердий.//Рациональная фармакотерапия в кардиологии2016;12(5). С. 517-521. DOI: 10.20996/1819-6446-2016-12-5-517-521. [Podzolkov V.I., Tarzimanova A.I., Gataulina R. Statiny vo vtorichnoy profilaktike fibrillyatsii predserdiy // Ratsional'naya farmakoterapiya v kardiologii 2016; 12 (5). S. 517-521. DOI: 10.20996 / 1819-6446-2016-12-5-517-521.]

30. Е. С. Козлова , Немчук Ф.А., Лопатин Ю.М. Аторвастатин и нарушения ритма сердца. Взгляд на механизм действия.//Вестник Волгоградского государственного медицинского университета. 2010. 1(33). С. 86-90 [E. S. Kozlova, NemchukF.A., LopatynYU.M. Atorvastatin i narusheniya ritma serdtsa.. Vzglyad na mekhanizm deystviya.// Vestnik Volgogradskogo gosudarstvennogo meditsinskogo universiteta. 2010. 1 (33). S. 86-90]

31. Артеріальна гіпертензія. Оновлена та адаптована клінічна настанова, заснована на доказах (2012 рік): практичні рекомендації [Текст] / Робоча група з артеріальної гіпертензії Укр. Асоц. Кардіологів // Артериальная гипертензия. – 2012. - №1[Arterial′nahipertenziya. Onovlena ta adaptovana klinichna nastanova, zasnovana na dokazah (2012 rik): Praktychni rekomendatsiyi [Tekst] / Robocha hrupa z arterial′noyi hipertenziyi Ukr. Asots. Kardiolohiv // Arterial′na hipertenziya. - 2012. - №1]

32. Pearce, Brabant, G., Duntas, L., Monzani, F., Peeters, R., Razvi, S., &Wemeau, J. (2013).ETAGuideline: Managemen to Subclinical Hypothyroidism. EurThyroidJ, 2, 215-228.