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RISK STRATIFICATION OF DRUG-INDUCED LONG QT INTERVAL PROLONGATION CAUSED BY CLASS III ANTIARRHYTHMIC DRUGS

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Aim. To develop a personalized risk assessment score for the development of drug-induced QT interval prolongation while taking class III antiarrhythmic drugs (AAD).

Methods. We studied data from 110 patients with coronary artery disease and/or hypertension, who had heart arrhythmias and were taking class III AAD (amiodarone or sotalol) in a cardiology department. All patients underwent clinical, laboratory and instrumental studies, including history taking, 12-lead electricardiography recording, biochemical blood test, determination of the levels of neuronal NO-synthase (NOS1) and adapter protein of neuronal NO-synthase (NOS1AP) in blood plasma by ELISA, as well as the determination of polymorphisms G84A of the NOS1 gene using polymerase chain reaction. In order to stratify the risk of drug-induced QT interval prolongation, the method of linear discriminant analysis with stepwise inclusion was applied. The training sample consisted of 70 patients (63.6%), the test sample - of 40 patients (36.4%). The score was developed on a training sample, and the testing was performed on a test sample with the construction of an ROC curve, calculation of AUC, sensitivity, and specificity.

Results. The training and test samples were comparable in terms of the main clinical and anamnestic parameters and features of the pharmacological history. Patients with QT interval prolongation had significantly lower levels of magnesium (p=0.001), NOS1 (p=0.015) and NOS1AP (p=0.035). The discriminant analysis algorithm was stopped at the fourth step, as a result of which four statistically significant predictors were included in the model: thiazide or loop diuretic intake, blood serum magnesium level, plasma NOS1 and NOS1AP levels, each of which was assigned a certain number of points according to the received standardized coefficients. When conducting an ROC analysis on the initial sample, a threshold value of the scale of 6 points was obtained (AUC - 0.848 (0.759 - 0.937, p=0.002), sensitivity - 73.81%, specificity - 85.71%). The use of the scale on the test sample showed sensitivity of 77.27%, specificity of 77.77% and AUC of 0.834 (0.721 - 0.965, p=0.001), which corresponds to the good quality of the prognostic model.

Conclusion. Patients with a total score of ≥6 points have a high risk of drug-induced QT interval prolongation while taking class III AAD.

Key words: QT interval; drug-induced QT interval prolongation; antiarrhythmic drugs; magnesium; neuronal nitric oxide synthase; discriminant analysis

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Long QT syndrome (LQTS) is a potentially life-threatening channelopathy characterized by QT interval prolongation on the 12-lead electrocardiogram (ECG), syncope, and a high risk of sudden cardiac death (SCD) due to polymorphic ventricular tachycardia «torsades de pointes» [1, 2].

LQTS can be either congenital or acquired. Congenital variants of the syndrome occur due to rare mutations in genes encoding subunits of ion channels (sodium, potassium, and calcium) or their regulatory proteins [3]. The acquired form of LQTS is associated with the use of QT-prolonging drugs (antiarrhythmic, antibacterial, antihistamine, anticancer drugs, etc.), or other conditions, such as electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), slow heart rhythms, nervous and endocrine system diseases, hypothermia, systemic inflammatory processes, as well as autoimmune diseases associated with the presence of Anti-Ro SSA antibodies, etc [4-6]. Besides nowadays the role of the genetic component in the pathogenesis of drug-induced LQTS is beyond doubt. The list of possible candidate genes is quite extensive and includes the genes of many metabolic and physiological systems, including the nitric oxide (NO) synthesis system [7-9].

An epidemiological study conducted in Germany estimates the incidence of acquired LQTS as 2.5 cases per million in men and 4.0 cases per million in women, with 60% being drug-induced [10]. J.Tisdale et al. (2012) report that QT prolongation greater than 470 ms develops in 28% of patients, and greater than 500 ms in 6% of patients in intensive care units [11]. According to A.D.Ismagilov et al.

(2016), prevalence of drug-induced QT interval prolongation in Russian Federation is 7.5% among inpatients and 9.2% among outpatients [12]. There is no such statistical data available in Belarus.

To date, there are more than two hundred drugs that have the ability to cause QT interval prolongation and ventricular arrhythmias [6, 13]. Most often drug-induced LQTS is associated with antiarrhythmic drugs (AAD) of IA and III classes according to the Vaughan-Williams classification, the mechanism of action of which is based on slowing the rate of repolarization of the ventricular myocardium [13].

It is known that the frequency of AAD prescription throughout the world is steadily increasing. According to the results of C.Poulsen et al. (2020) from 1999 to 2017 in Europe it increased by 16%, amounting to 41.9 established daily doses per 1000 per day [14]. According to the results of T.M.Markman et al. (2020), a similar trend is observed in the USA, where from 2004 to 2016 the number of patients taking AAD increased from 345 to 979 per 100,000, with the most significant increase in the prescription of amiodarone and sotalol [15].

Risk stratification of the drug-induced QT interval prolongation remains a difficult, but extremely relevant and necessary problem. A different degree of QT interval prolongation in response to the same drug intake, different time of development and clinical manifestations of this electrocardiographic phenomenon - all this dictates an individual approach to each patient, taking into account clinical, demographic, electrophysiological, biochemical and genetic features.

Currently, there have been developed a number of scores and indices to assess the risk of drug-induced QT interval prolongation. The most common of them are the Tisdale score and QT-DDI score [16, 17]. However, neither of the above mentioned scores allows predicting the risk of QT prolongation with a sufficiently high degree of accuracy. Moreover, these scores were developed for patients admitted to intensive care units and are not recommended for use in patients in inpatient units and at the outpatient stage.

The aim of this study was to develop a personalized risk assessment score for the development of drug-induced QT interval prolongation while taking class III AAD.

METHODS

We evaluated the data of 110 patients with coronary artery disease and/or arterial hypertension that have cardiac arrhythmias and take class III AAD (amiodarone or sotalol) in the inpatient cardiology department. Patients with atrial fibrillation (AF) were referred to the hospital for electrical cardioversion or to select antiarrhythmic therapy. Patients with ventricular and supraventricular arrhythmias were hospitalized in order to clarify the diagnosis and determine tactics and strategies for further treatment.

Exclusion criteria from the study were: QTc interval greater than 450 ms in men and 470 ms in women before class III AAD initiation; taking any drugs other than Class III AAD with a confirmed or probable risk of torsades de pointes, listed in the «CredibleMeds» database [18]; taking class III AAD at the outpatient stage (prior to admission to the hospital); genotyped congenital LQTS; recent acute myocardial infarction, coronary artery bypass grafting, or coronary angioplasty (less than 3 months before enrollment in the study); left ventricular hypertrophy (Sokolov-Lyon index >35mm); an increase in the duration of the QRS complex ≥100 ms; permanent and long-term persistent form of AF; 24 hours after restoration of sinus rhythm in patients with paroxysmal and persistent AF; disorders of atrioventricular conduction; uncorrected pathology of the endocrine system; active inflammatory process of any localization of infectious, autoimmune or other etiology.

All patients underwent clinical, laboratory and instrumental studies, including history taking, 12-lead ECG recording, biochemical blood test, determination of the levels of neuronal NO-synthase (NOS1) and the neuronal NO-synthase adapter protein (NOS1AP) in blood plasma by ELISA, as well as the determination of polymorphism G84A of the NOS1 gene using polymerase chain reaction. The duration of the corrected QT interval was calculated using Bazett formula (QT/√RR). Determination of the duration of the waves and intervals was carried out manually using 12 standard ECG leads, with a record of at least five complete cardiac cycles. The definition of the end of the T wave was carried out

Table 1.

Clinical and anamnestic indicators and pharmacological history data of patients in the training sample and test sample

Parameters	Training sample	Test sample	p
Number of patients, n (%)	70 (63.6)	40 (36.4)	
Female sex, n (%)	38 (54.3)	18 (45)	0.416
Age, years	56 [51; 65]	57 [52; 62]	0.788
SCD family history, n (%)	3 (4.2)	1 (2.5)	0.874
Hypertension, n (%)	64 (91.4)	34 (85)	0.566
Atrial fibrillation, n (%)	40 (57.1)	24 (60)	0.799
Myocardial infarction history, n (%)	11 (15.7)	6 (15)	0.952
Non-sustained MVT history, n (%)	19 (27.1)	6 (15)	0.282
LVEF <50%, n (%)	6 (8.6)	3 (7.5)	0.926
Percentage of drugs*, %	21 [14; 24]	19 [14; 23]	0.673
Amiodarone intake, n (%)	46 (65.7)	28 (70)	0.707
Sotalol intake, n (%)	24 (34.3)	12 (30)	
Diuretic intake, n (%)	20 (28.6)	16 (40)	0.312
QT interval prolongation, n (%)	42 (60)	22 (55)	0.662

Note: here and further SCD - sudden cardiac death; MVT - monomorphic ventricular tachycardia; LVEF - left ventricular ejection fraction, * - QT prolonging drugs.

using the slope method, at the intersection of the baseline with a tangent drawn from the top of the T wave along its descending part. The average duration of QT and RR intervals was determined as the arithmetic mean of their duration in leads II, V2 and V5 in five cardiac cycles. QTc interval was considered prolonged if it was greater than 450 ms in men and greater than 470 ms in women in accordance with the recommendations of the European Medicine Agency (European Medicine Agency CHMP/ICH/2/04. ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) [19], as well as the 2009 AHA/ACCF/HRS Guidelines for Standardization and Interpretation of Electrocardiogram [20].

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Statistical analysis

Statistical analysis was performed using the STATISTICA 10.0 software package. Quantitative data, the distribution of which was not normal (the hypothesis of normal distribution was tested using the Liliefors and Shapiro-Wilk tests), were presented in the form of Me [Q1; Q3], where Me is the median, Q1, Q3 are the 1st and 3rd quartiles, respectively. The Mann-Whitney U-test was used to assess differences in quantitative traits between two independent groups. The statistical significance of differences between qualitative characteristics was assessed using the χ^2-Pearson test. The threshold value of the level of statistical significance was taken equal to 0.05.

In order to develop a prediction score for drug-induced QT interval prolongation and to assess its diagnostic accuracy, the initial sample was divided into two groups using a random number generator: a training sample (70 patients), on which the score was developed, and a test sample (40 patients), which was used for checking the model accuracy. The training and test samples were comparable in terms of the main clinical and anamnestic parameters and features of the pharmacological history (Table 1).

When conducting discriminant analysis, the method of stepwise inclusion was used. To convert the obtained indicators into standardized coefficients, a canonical analysis was carried out, after which the obtained scores were rounded up to an integer. To assess the prognostic significance of the score and find the threshold value, a ROC analysis was performed with the calculation of sensitivity and specificity. The score was tested on a test sample with the construction of a ROC curve, calculation of AUC, sensitivity and specificity.

Table 2.

Values of clinical, pharmacological, laboratory and molecular-genetic parameters in the studied groups of patients.

	With QT prolongation	Without QT prolongation	p
Number of patients, n (%)	42 (60)	28 (40)	-
Female sex, n (%)	26 (61.9)	12 (42.8)	0.237
Age, years	56 [49; 67]	54 [51; 61]	0.448
SCD family history, n (%)	2 (4.8)	1 (3.6)	0.867
Hypertension, n (%)	38 (90.5)	26 (92.8)	0.857
Atrial fibrillation, n (%)	24 (57.1)	16 (57.1)	1.000
Myocardial infarction history, n (%)	7 (16.7)	4 (14.3)	0.867
Non-sustained MVT history, n (%)	13 (30.9)	6 (21.4)	0.769
Diabetes mellitus (type 1 and 2), n (%)	3 (7.1)	1 (3.6)	0.799
LVEF <50%	5 (11.9)	1 (3.6)	0.547
Amiodarone intake, n (%)	29 (66.7)	17 (64.3)	0.908
Sotalol intake, n (%)	13 (33.3)	11 (35.7)	
Diuretic** intake, n (%)	15 (35.7)	5 (17.9)	0.125
Loop diuretic intake, n (%)	4 (9.5)	0 (0)	0.490
Potassium, mmol/l	4.22 [3.91; 4.50]	4.45 [4.14; 4.65]	0.283
Calcium, mmol/l	2.24 [2.09; 2.32]	2.32 [2.14; 2.48]	0.195
Magnesium, mmol/l	0.81 [0.84; 0.89]	0.92 [0.85; 0.99]	0.001
NOS1, μg/l	1.78 [1.41; 1.92]	2.13 [1.62; 2.49]	0.015
NOS1AP, ng/l	431 [280; 572]	543 [391; 738]	0.035
Pm$^{\#}$ G84A of the NOS1 gene, n (%)	6 (14.3)	2 (7.1)	0.608
Pm$^{\&}$ G84A of the NOS1 gene, n (%)	25 (59.5)	11 (39.3)	0.251

Note: here and further ** - loop or thiazide; NOS1 - neuronal NO-synthase; NOS1AP - neuronal NO-synthase adapter protein; Pm$^{\#}$ - AA genotype of the polymorhism; Pm$^{\&}$ - A allele of the polymorphism.

RESULTS

The training sample included 42 patients (60%) with drug-induced QT interval prolongation and 28 patients (40%) without QT interval prolongation. At the first stage of the analysis we assessed the clinical and pharmacological history, laboratory and genetic parameters of the studied patients. The results are presented in Table 2.

As it follows from Table 2, the patients of both groups were comparable in terms of clinical and anamnestic features, the structure of arrhythmias, and the antiarrhythmic therapy taken. In patients with QT interval prolongation, there was a trend towards more frequent use of diuretics compared with patients without LQTS (35.7% vs. 17.9%, p=0.125), but it did not reach statistically significant values. When analyzing electrolyte parameters, patients with QT interval prolongation had significantly lower serum magnesium levels compared with patients without QT interval prolongation (median 0.81 vs. 0.92 mmol/l, p=0.001), but comparable serum potassium (median 4.22 vs 4.45 mmol/l,

p=0.283) and calcium (median 2.24 vs 2.32 mmol/l, p=0.195) levels.

It should be noted that there were significant intergroup differences in the concentrations of NOS1 (median 1.78 vs. 2.13 μg/l, p=0.015) and NOS1AP (median 431 vs. 543 ng/l, p=0.035). However, the frequency of the recessive allele A and the homozygous genotype AA of the G84A polymorphism of the NOS1 gene in both groups were comparable (p>0.05).

Then we carried out a linear discriminant analysis, which allowed us to perform an in-depth study of the interaction of predictors and the response function. Using the stepwise inclusion method, we obtained a discriminant function with the following characteristics: Wilks' lambda - 0.603, Fisher's test - 10.719, p<10-12. Mahalanobis distance between the analyzed groups was 2.669935, p<10-14.

The stepwise discriminant analysis algorithm was stopped at the fourth step, as a result of which four statistically significant predictors were included in the model: thiazide or loop diuretic intake, serum magnesium levels, plasma NOS1 and NOS1AP levels.

To assess the risk of drug-induced QT interval prolongation caused by class III AAD, the following equation was obtained:

y=0.9*X1+1.36*X2+1.4*X3+0.93*X4-2.29, where

X1 - thiazide or loop diuretic intake (1 - yes; 0 - no);

X2 - serum magnesium level (1 - ≤ 0.85 mmol/l, 0 - > 0.85 mmol/l);

X3 - plasma NOS1 level (1 - ≤ 2.07 μg/l, 0 - > 2.07 μg/l);

X4 - plasma NOS1AP level (1 - ≤ 407.7 ng/l, 0 - > 407.7 ng/l).

Thus, if y≤0, drug-induced QT interval prolongation caused by class III AAD can be predicted with a sensitivity of 90.47%, specificity of 78.57% and overall accuracy of 84.52%. The distribution of classified objects is shown in Fig. 1. Correctly classified observations are presented as green markers, incorrectly classified ones are presented as red markers.

For practical application the data were recalculated. The standardized coefficients were multiplied by 5 and rounded to integers, and on the original sample the encrypted indicators were replaced with the values of the coefficients obtained in the course of the discriminant analysis.

As it follows from Table 3, the total score can vary from 0 to 10. When conducting a ROC analysis on the initial sample of patients, we received a threshold value of 6 points. AUC was 0.848 (0.759 - 0.937, p=0.002), sensitivity - 73.81%, specificity - 85.71%, which, according to the expert scale for AUC values, corresponds to the good quality of the model (Fig. 2, red line).

The applying of the score to the test sample demonstrated sensitivity of 77.27%, specificity of 77.77% and AUC of 0.843 (0.721 - 0.965, p=0.001), which also corresponds to the good quality of the predictive model (Fig. 2, green line).

Thus, patients with a score of ≥6 have a high risk of drug-induced QT interval prolongation while taking class III AAD. Therefore in this category of patients, it is advisable to prescribe other classes of antiarrhythmic drugs that do not cause QT interval prolongation, taking into account possible indications and contraindications.

DISCUSSION

Risk stratification in drug-induced LQTS remains challenging. To date, there is no comprehensive, easily measured and widely available indicator that would have sufficiently high ability to predict the development of drug-induced QT interval prolongation, and therefore, there is an active development of predictive models and indices.

Thus, to calculate the risk of QT interval prolongation in patients in intensive care units, it was proposed to use the J. Tisdale score (2013), which includes such indicators as age ≥68 years, female sex, loop diuretic intake, potassium level <3.5 mmol/l, QTc interval at admission >450 ms, acute period of myocardial infarction, sepsis, as well as taking 1 or 2 QT-prolonging drugs [16].

According to the developed algorithm, patients who scored less than 7 points belong to the low risk group for drug-induced QT interval prolongation, from 7 to 11 points - to the medium risk group, and more than 11 points - to the high risk group.

In accordance with the data obtained by J. Tisdale et al. (2013), this score has a sensitivity of 74% and a specificity of 77% for identifying patients at high risk of drug-associated QT interval prolongation [16].

In a study by K.Su et al. (2020), which included 264 patients admitted to intensive care units, sensitivity of J.Tisdale score for identifying patients at high risk of

Table 3.

Score for the risk assessment of drug-induced QT interval prolongation caused by class III antiarrhythmic drugs.

Criteria	Levels	Points
Diuretic intake**	yes	2
	no	0
Magnesium, mmol/l	≤ 0.85	3
	> 0.85	0
NOS1, μg/l	≤ 2.07	3
	> 2.07	0
NOS1AP, ng/l	≤ 407.7	2
		0

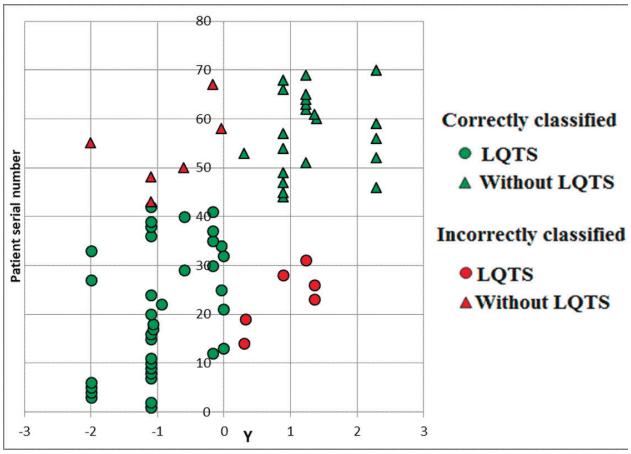

Fig. 1. Distribution of classified objects. Note: LQTS - long QT interval syndrome

LQTS was 97% (95% confidence interval (CI) 91-99%), but specificity was only 16% (95% CI 11-23%) [21]. Comparable data were obtained by W.Zhao et al. (2021), who used J.Tisdale score to identify a high risk of QT interval prolongation in patients with novel coronavirus infection [22]. Thus, sensitivity of this score was 85.7%, specificity - 7.6%, and area under the ROC-curve was 0.60 (95% CI 0.46-0.75). Risk factors independently associated with QT prolongation included end-stage renal disease (odds ratio (OR) - 6.42; 95% CI, 1.28-32.13) and serum potassium level ≤3.5 mmol/l at admission to the hospital (OR - 4.97; 95% CI 1.51-16.36) [22].

However, it should be noted that this score was developed for patients hospitalized in cardiologic intensive care units, and cannot be used in patients in inpatient departments and at the outpatient stage. Thus, patients included in the study by J.Tisdale et al. (2013), were hospitalized for exacerbation of chronic heart failure, acute coronary syndrome, acute kidney injury, pneumonia or sepsis [16]. All of the above conditions contribute to the development of acquired prolongation of the QT interval and make it difficult to assess the direct effect of drugs on the process of ventricular repolarization.

Another score for assessment of the risk of drug-induced QT interval prolongation was developed by F.Berger et al. (2020) based on a prospective follow-up study of 107 patients who underwent inpatient treatment at the Erasmus University Medical Center in Rotterdam [17]. The score was called QT-DDI (drug-drug interactions) and included such risk factors as female gender, age ≥75 years, hypertension, diabetes mellitus (type 1 and 2), chronic kidney disease with creatinine clearance ≤50 ml/min, potassium level <3.4 mmol/l, as well as taking QT-prolonging drugs.

Applying the developed score to an independent sample of 1579 patients, area under the ROC-curve was 0.54 (95% CI 0.51-0.56) when the QT prolongation was defined as > 450/470 ms, and 0.59 (95% CI 0.54-0.63) when QT prolongation was defined as >500ms. Threshold value of 6 points showed sensitivity of 76.6% and 83.9% and specificity of 28.5% and 27.5%, respectively [17].

Our score developed by stepwise discriminant analysis showed quite good results of sensitivity and specificity, as well as the area under the ROC-curve, both on the training and on the test sample of patients, which demonstrates its high predictive value in comparison with previously proposed models. Use of the discriminant analysis technique made it possible to derive a linear mathematical model, on the basis of which a personalized risk score for the development of drug-induced QT interval prolongation was proposed.

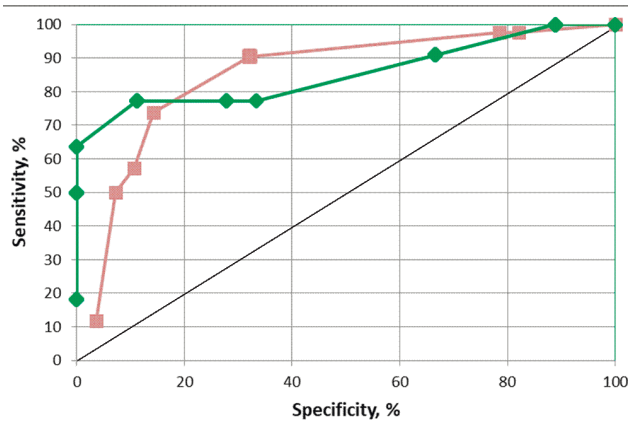

Fig. 2. ROC-curve of the predictive model for the training sample (red line) and test sample (green line).

The prognostic parameters included in this score combine both traditional risk factors for QT interval prolongation (diuretic intake and serum magnesium level) and new, little-studied indicators such as NOS1 and NOS1AP levels.

The effect of magnesium on the duration of the QT interval is mediated by complex molecular mechanisms involving potassium and calcium channels of cardiomyocytes, ryanodine receptors, and the calcium-binding protein calmodulin. A decrease in serum magnesium levels has been described in heart failure, CAD and hypertension, as well as in LQTS [23, 24]. K.Hoshino et al. (2002) found that more than half of patients with LQTS are in a magnesium-deficient state, which aggravates QT interval prolongation and stimulates the development of ventricular arrhythmias. When comparing the group of patients with congenital LQTS (n=22) and the control group (n=30), magnesium deficiency of less than 0.8 mmol/l was detected in 53% of patients in the main group and in 33% of participants of the control group ($p<0.01$) [24].

NO is a unique molecule involved in a wide range of biological functions, ensuring the normal functioning of the cardiovascular system under physiological conditions and its adaptation under pathological conditions [27]. NO, synthesized by almost all types of cardiac cells, is a universal cellular messenger that plays an important role in the regulation of the cardiovascular system. NO formed in cardiomyocytes can have an intracrine effect or change the functional properties of neighboring cardiomyocytes. NO generated from non-cardiomyocyte sources (endocardial and endothelial cells, autonomic nerves and ganglia) can have a direct effect on cardiomyocytes and an indirect effect by modulating coronary blood flow and/or the work of the autonomic nervous system [25].

The influence of NO on the ion channels and the electrical activity of the heart, as well as the role of its deficiency in the genesis of ventricular arrhythmias, is a relatively little-studied area. Studies on animal models have shown that NO deficiency leads to inhibition of the fast delayed rectifying current through potassium Kv 11.1 channels, blocking the alpha subunit of the potassium channel encoded by the hERG gene [26]. This coincides with the mechanisms of drug-induced LQTS, where potassium channels are blocked by variety of drugs, including class III AAD [27].

The production of the NO molecule is carried out from the amino acid L-arginine with the formation of L-citrulline with the participation of nitric oxide synthases [25]. To date, three such enzymes have been described: neuronal NO synthase (NOS1), cytokine-inducible NO synthase (NOS2), and endothelial NO synthase (NOS3).

In 1999 K.Y.Xu et al. demonstrated that NOS1 is expressed not only in brain neurons, but also in the sarcoplasmic reticulum of cardiomyocytes and regulates the reuptake of calcium ions by sarcoplasmic Ca2+-ATPase [28].

It is known that disturbances in intracellular calcium homeostasis play an important role in the development of ventricular arrhythmias leading to SCD. The main channel for the release of Ca2+ ions from the sarcoplasmic reticulum in cardiomyocytes is the ryanodine receptor-2 (RyR2) [29]. Neuronal NO synthase is responsible for endogenous S-nitrosylation of the RyR2 calcium channel [27, 28], and its deficiency leads to an increase in calcium levels and diastolic calcium waves. In turn, diastolic calcium waves are associated with early and delayed post-depolarizations, which lead to QT interval prolongation on the ECG and create a potential substrate for the development of polymorphic VT [30, 31].

The significance and functions of NOS1 have been shown in detail in animal model studies. In the study by S.Ronchi et al. it has been shown that inhibition of NOS1 function in guinea pig cardiomyocytes leads to the QT interval prolongation [31]. Pharmacological inhibition of NOS1 function led to an increase in the action potential, as well as an increase in the density of L-type calcium channels and a predisposition to the post-depolarizations caused by instability of the sarcoplasmic reticulum [32].

NOS1 contains an extended terminal domain that allows it to interact with adapter proteins. The most important of these proteins is NOS1AP, which binds the NOS1 molecule and regulates its activation [27]. Although NOS1 is capable of direct S-nitrosylation without an adapter protein, in this case there are certain difficulties in implementing S-nitrosylation as a signaling mechanism for NO. Therefore, the role of NOS1AP as an adapter protein for NOS1 is to direct it to other specific target proteins to perform the corresponding biological functions [30, 32].

NOS1AP presents significant clinical interest, primarily from the point of view of searching for genetic mutations associated with QT prolongation and an increased risk of SCD in the NOS1AP gene [7, 31, 33]. Thus, participants of the Rotterdam study with a homozygous GG genotype of the rs10494366 polymorphism of the NOS1AP gene, who took therapeutic doses of verapamil, had a more pronounced prolongation of the corrected QT interval (25.4 ms, p=0.0038) than patients with a homozygous TT genotype [33]. In the study by Y.Jamshidi et al. (2012) author s searched for associations between polymorphic variants of the NOS1AP gene, the degree of QT prolongation, and the risk of ventricular arrhythmias in patients taking class III AAD: amiodarone and sotalol [7]. There was conducted a study of 167 single nucleotide polymorphisms, the most significant of which was rs10919035, the mutant T allele of which was associated with the risk of drug-induced VT ($p=3.0\times10-4$). However, in these studies, plasma concentration of NOS1AP was not studied and only genetic methods of research were carried out.

A significant advantage of our score is the simplicity of calculating the total points, which does not require additional mathematical calculations. We recommend this score to be used before prescribing AAD, and therefore, if a patient scores more than 6 points, we suggest considering an AAD belonging to another class, taking into account individual indications and contraindications.

However, its use has some limitations, primarily due to the exclusion criteria from this study, as well as the small size of the sample of patients and the single-center nature of the study. It should also be noted that in this work we did not touch upon aspects of risk stratification for the development of ventricular arrhythmias caused by drug-induced QT interval prolongation, which are reflected in our previous publications [34].

Further research on the development of complex models for predicting the risk of drug-induced QT interval prolongation seems to be an extremely actual problem. Differentiated therapy of patients with cardiac arrhythmias based on such criteria will lead to a decrease in the number of side effects when taking class III AAD and will make it possible to make the right decision on the most appropriate AAD in each specific case.

CONCLUSION

As a result of the stepwise discriminant analysis, the risk assessment score for the drug-induced LQTS in patients receiving class III AAD included the following predictors: diuretic intake, serum magnesium level and plasma NOS1 and NOS1AP levels.

Patients who scored ≥6 points have a high risk of drug-induced QT interval prolongation caused by class III AAD (sensitivity - 77.27%, specificity - 77.77%, AUC - 0.834).

REFERENCES

1. Tester DJ, Ackerman MJ. Genetics of Long QT syndrome. *Methodist DeBakey Cardiovascular Journal.* 2014;10(1): 29-33. https://doi.org/10.14797/mdcj-10-1-29.
2. Rohatgi RK, Sugrue A, Bos JM, et al. Contemporary outcomes in patients with Long QT Syndrome. *J Am Coll Cardiol.* 2017;70(4): 453-462. https://doi.org/10.1016/j.jacc.2017.05.046.
3. Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA.* 2005;294(23): 2975-80. https://doi.org/10.1001/jama.294.23.2975.
4. Shah SR, Park K, Alweis R. Long QT Syndrome: A Comprehensive Review of the Literature and Current Evidence. *Curr Probl Cardiol.* 2019;44(3): 92-106. https://doi.org/10.1016/j.cpcardiol.2018.04.002.
5. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. *Pharmacol Rev*. 2010;62(4):760-781. https://doi.org/10.1124/pr.110.003723.
6. Balykova LA, Siprov AV, Parshina TS. Clinical and pharmacological aspects of drug-induced long QT syndrome. *Experimental and clinical pharmacology*. 2020;83(11): 35-44. (In Russ.) https://doi.org/10.30906/0869-2092-2020-83-11-35-44.
7. Jamshidi Y, Nolte IM, Dalageorgou C, et al. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. *J Am Coll Cardiol.* 2012;60(9): 841-50. https://doi.org/10.1016/j.jacc.2012.03.031.
8. Nesterec AM, Maksimov VN. Molecular genetic markers of QT interval duration and sudden cardiac death: a review of the literature. *Bulletin of Siberian Medicine.* 2022;21(1):

133-143. (In Russ.) https://doi.org/10.20538/1682-0363-2022-1-133-143.
9. Etheridge SP, Asaki SY, Niu MC. A personalized approach to long QT syndrome. *Curr Opin Cardiol.* 2019;34(1): 46-56. https://doi.org/10.1097/HCO.0000000000000587.
10. Sarganas G, Garbe E, Klimpel A, et al. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. *Europace.* 2014;16(1): 101-8. https://doi.org/10.1093/europace/eut214.
11. Tisdale JE, Wroblewski HA, Overholser BR, et al. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US. *Drug Saf.* 2012;35(6): 459-70. https://doi.org/10.2165/11598160-000000000-00000.
12. Ismagilov DA, Shih EV, Sizova ZM, et al. Clinical and pharmacological aspects of the use of drugs that affect the QT interval in the elderly. *Clinical gerontology.* 2016;3(4): 37-45. (In Russ.).
13. Schwartz PJ, Woosley RL. Predicting the Unpredictable: Drug-Induced QT Prolongation and Torsades de Pointes. *J Am Coll Cardiol.* 2016;67(13): 1639-1650. https://doi.org/10.1016/j.jacc.2015.12.063.
14. Poulsen CB, Damkjær M, Lofgren B, et al. Trends in Antiarrhythmic Drug Use in Denmark Over 19 Years. *Am J Cardiol.* 2020;125(4): 562-569. https://doi.org/10.1016/j.amjcard.2019.11.009.
15. Markman TM, Geng Z, Epstein AE, et al. Trends in Antiarrhythmic Drug Use Among Patients in the United States Between 2004 and 2016. *Circulation.* 2020;141(11): 937-939. https://doi.org/10.1161/CIRCULATIONAHA.119.044109.
16. Tisdale JE, Jaynes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes.* 2013;6(4): 479-87. https://doi.org/10.1161/CIRCOUTCOMES.113.000152.
17. Berger FA, van der Sijs H, Becker ML, et al. Development and validation of a tool to assess the risk of QT drug-drug interactions in clinical practice. *BMC Med Inform Decis Mak.* 2020;20(1): 171. https://doi.org/10.1186/s12911-020-01181-3.
18. CredibleMeds [Electronic resource]. - Available from: https://crediblemeds.org (accessed 02.05.2022).
19. Shah RR, Morganroth J. ICH E14 Q & A (R1) document: perspectives on the updated recommendations on thorough QT studies. *Br J Clin Pharmacol.* 2013;75(4): 959-65. https://doi.org/10.1111/j.1365-2125.2012.04442.x.
20. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part IV: The ST Segment, T and U Waves, and the QT Interval A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol.* 2009;53(11): 982-91. https://doi.org/10.1016/j.jacc.2008.12.014.
21. Su K, McGloin R, Gellatly RM. Predictive Validity of a QT_c Interval Prolongation Risk Score in the Intensive Care Unit. *Pharmacotherapy.* 2020;40(6): 492-499. https://doi.org/10.1002/phar.2400.
22. Zhao W, Gandhi N, Affas S, et al. Predicting QT interval prolongation in patients diagnosed with the 2019 novel coronavirus infection. *Ann Noninvasive Electrocardiol.* 2021;26(5): e12853. https://doi.org/10.1111/anec.12853.
23. DiNicolantonio JJ, O'Keefe JH, Wilson W. Subclinical magnesium deficiency: a principal driver of cardiovascular disease and a public health crisis. *Open Heart.* 2018;5(1): e000668. https://doi.org/10.1136/openhrt-2017-000668.
24. Hoshino K, Ogawa K, Hishitani T, et al. Studies of magnesium in congenital long QT syndrome. *Pediatr Cardiol.* 2002;23(1):41-8. https://doi.org/10.1007/s00246-001-0011-5.
25. Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. *J Physiol.* 2016;594(9): 2459-68. https://doi.org/10.1113/JP270526.
26. Garcia-Elias A, Benito B. Ion Channel Disorders and Sudden Cardiac Death. *Int J Mol Sci.* 2018;19(3): 692. https://doi.org/10.3390/ijms19030692.
27. Haselden WD, Kedarasetti RT, Drew PJ. Spatial and temporal patterns of nitric oxide diffusion and degradation drive emergent cerebrovascular dynamics. *PLoS Comput Biol*. 2020;16(7): e1008069. https://doi.org/10.1371/journal.pcbi.1008069.
28. Xu KY, Huso DL, Dawson TM, et al. Nitric oxide synthase in cardiac sarcoplasmic reticulum. *Proc Natl Acad Sci U S A.* 1999;96(2): 657-62. https://doi.org/10.1073/pnas.96.2.657.
29. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J.* 2012;33(7): 829-37, 837a-837d. https://doi.org/10.1093/eurheartj/ehr304.
30. Gonzalez DR, Beigi F, Treuer AV, et al. Deficient ryanodine receptor S-nitrosylation increases sarcoplasmic reticulum calcium leak and arrhythmogenesis in cardiomyocytes. *Proc Natl Acad Sci U S A.* 2007;104(51): 20612-7. https://doi.org/10.1073/pnas.0706796104.
31. Ronchi C, Bernardi J, Mura M, et al. NOS1AP polymorphisms reduce NOS1 activity and interact with prolonged repolarization in arrhythmogenesis. *Cardiovasc Res*. 2021;117(2): 472-483. https://doi.org/10.1093/cvr/cvaa036.
32. Tieu A, Akar FG. 'Social distancing' of the neuronal nitric oxide synthase from its adaptor protein causes arrhythmogenic trigger-substrate interactions in long QT syndrome. *Cardiovasc Res.* 2021;117(2): 338-340. https://doi.org/10.1093/cvr/cvaa179.
33. Cubeddu LX. Drug-induced Inhibition and Trafficking Disruption of ion Channels: Pathogenesis of QT Abnormalities and Drug-induced Fatal Arrhythmias. *Curr Cardiol Rev.* 2016;12(2): 141-54. https://doi.org/10.2174/1573403x12666160301120217.
34. Kalatsei LV, Snezhitskiy VA, Kopyckij AV. Assessment of the risk of polymorphic ventricular tachycardia in patients with drug-induced prolongation of the QT interval while taking class III antiarrhythmic drugs. *Journal of the Vitebsk State Medical University*. 2022;21(3): 15-24. (In Russ.) https://doi.org/10.22263/2312-4156.2022.3.15.