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АНАЛИЗ АНТИТРОМБОТИЧЕСКОЙ ТЕРАПИИ МЕРЦАТЕЛЬНОЙ АРИТМИИ В МЕЖДУНАРОДНЫХ И НАЦИОНАЛЬНЫХ РЕЕСТРАХ

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АННОТАЦИЯ

Внезапная сердечная смерть (ВСС) как необратимый исход и результат внезапной остановки сердца достигает 50% среди других исходов у лиц 35–50 лет, преимущественно мужского пола, однако в последнее время наметилась тенденция к увеличению доли и женского пола, как подростки и молодые люди. Риск внезапной сердечной смерти выше у мужчин и увеличивается с возрастом из-за более высокой распространенности ишемической болезни сердца среди пожилых людей. Число случаев ВСС колеблется от 1,4 на 100 тыс. человеко-лет (95% ДИ - 0,95-1,98) у женщин до 6,68 на 100 тыс. человеко-лет (95% ДИ - 6,24-7,14) у мужчин. Число случаев ВСС среди молодого поколения составляет 0,46–3,7 на 100 тысяч человеко-лет, что соответствует 1100–9000 смертей в Европе и 800–6200 смертей в США каждый год. Данные о распространенности ВСС в Узбекистане ограничены, включая особенности регистрации ВСС в разных странах.

Ключевые слова: аритмия, антитромботическая терапия, ишемическая болезнь сердца.

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ANALYSES OF ANTITHROMBOTIC THERAPY FOR ATRIAL FIBRILLATION IN INTERNATIONAL AND NATIONAL REGISTRIES

ABSTRACT

Sudden cardiac death (SCD) as an irreversible outcome and the result of sudden cardiac arrest reaches 50% among other outcomes in persons 35–50 years old, predominantly male, but recently there has been a tendency to increase the proportion of females, as well as adolescents and young adults. The risk of sudden cardiac death is higher in men and increases with age due to the higher prevalence of coronary artery disease among older people. The number of cases of SCD ranges from 1.4 per 100 thousand person-years (95% CI - 0.95-1.98) in women to 6.68 per 100 thousand person-years (95% CI - 6.24–7.14) in men. The number of cases of SCD among the younger generation is 0.46–3.7 per 100 thousand person-years,

which translates into 1100–9000 deaths in Europe and 800–6200 deaths in the United States each year. Data on the prevalence of SCD in Uzbekistan are limited, including the peculiarities of SCD registration in different countries.

Keywords: arrhythmia, antithrombotic therapy, coronary heart disease

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ANNOTATSIYA

To'satdan yuz beradigan yurakning birlamchi to'xtashi qaytarib orqaga bo'lmaydigan natija sifatida va to'satdan yurak to'xtashi natijasida 35-50 yoshdagi odamlarda, asosan erkaklarda, boshqa natijalar orasida 50% ga etadi, ammo so'nggi vaqtlarda ushbu kasallikning ayollar orasida ulishi ortishi kuzatilmoqda. Yurakning birlamchi to'xtashi xavfi erkaklarda yuqori bo'lib, keksa odamlarda yurak-qon tomir kasalliklarining ko'proq tarqalishi tufayli yosh bilan ortadi. YuK holatlari soni ayollarda 100 ming kishiga 1,4 dan erkaklarda 100 ming kishiga 6,68 (95% CI - 6,24-7,14) gacha. Yosh avlodlarda YBT bilan kasallanish har 100 ming kishiga 0,46-3,7 ni tashkil qiladi, bu Evropada 1100-9000 o'limga va Qo'shma Shtatlarda har yili 800-6200 o'limga to'g'ri keladi. O'zbekistonda YBTning tarqalishi to'g'risidagi ma'lumotlar cheklangan, jumladan, turli mamlakatlarda YBT ni ro'yxatga olishning oziga xos xususiyatlari mavjud.

Kalit so'zlar: aritmiya, antitrombotik terapiya, yurak qon tomir tizimi kasalligi.

The elements of prophylaxis of heart rhythm disorders caused by ischaemic myocardial damage include modulation of mitochondrial quality control mechanisms, which are positive regulation of mitochondrial biogenesis by activation of AMP-activated protein kinase and induction of upregulation of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha), which stimulates replacement of damaged mitochondria; effects on mitochondrial fusion and fission proteins - there is a restoration of balance in mitochondrial dynamics by positively regulating fusion through activation of dynamin-like 120 kDa protein (encoded by the OPA1 gene) and mitofusin-2 (encoded by the MFN2 gene), this helps to reduce fission by inhibiting dynamin-related protein 1 (Drp1), and prevents mitochondrial fragmentation; control of mitochondrial transient permeability pore opening is essential (prolonged opening leads to disruption of ultrastructure and arrest of ATP synthesis) [1, 5].

Induction of autophagy and mitophagy are important factors. Mitophagy can be activated through the PINK1/Parkin signalling pathway (PINK1 is PTEN-induced kinase 1; PTEN is a homologue of phosphatase and tensin) [2, 10]. Mitochondrial ATP-dependent potassium channels have also been reported as one of the additional contributors to the regulation of mitochondrial function, on the basis that they represent a potential mechanism to relate ATP availability to energy requirements, contributing to the homeostasis control of cellular metabolism during stress conditions, which include ischaemia-reperfusion [3, 4].

The cardiac vascular endothelium and related phenomena have been considered as an additional participant in the cardioprotective programme in the last few years. The endothelium regulates vascular tone by mediating both types of stimuli - vasoconstrictive and vasodilatory, is able to secrete vasodilatory molecules (nitric oxide, carbon monoxide, prostacyclin, bradykinin, adenosine), and stimulate the release of vasoconstrictive molecules (endothelin-1, angiotensin II, thromboxane A2). Endothelial cells contain one of three types of nitric oxide synthases, critical participants in the L-arginine to nitric oxide signalling pathway [5, 7]. A dysfunctional endothelial state causes reduced nitric oxide bioavailability (associated with a pro-thrombotic state), less response to vasodilators in vascular smooth muscle cells, and greater sensitivity to the development of an inflammatory state. On the other hand, endothelial progenitor cells contribute to vascular homeostasis and neovascularisation; the endothelium, together with cardiomyocytes and fibroblasts, is capable of releasing exerkins (microRNAs, long non-coding RNAs, neuregulin and Brain-derived neurotrophic factor), which have potential beneficial effects on treatment

in metabolic and cardiovascular diseases; endothelial small extracellular vesicles can be used in cardioprotective therapies [3, 6, 8].

Endothelial cells can express molecules that cause leukocyte migration into cardiac tissue, together with neutrophils can serve as additional sources of reactive oxygen species. As a consequence, endothelium may contribute to the pathogenesis of ischaemia-reperfusion and at the same time be one of the participants of cardioprotection [1].

Materials and Methods.

The work was structured in several stages. At the first stage, data from international and national registers of patients with cardiac rhythm disturbances were analysed. For this purpose, a search in PubMed and MEDLINE search engines was performed using the following **Keywords:** arrhythmia, coronary heart disease, rivaroxaban, dabigatran, warfarin, atrial fibrillation, new oral anticoagulants, direct oral anticoagulants, arrhythmia, coronary heart disease, real clinical practice, Rivaroxaban, Dabigatran, Apixaban, Warfarin, atrial fibrillation, new oral anticoagulants (NOACs), direct oral anticoagulants (DOACs). Registries included in the analysis had to fulfil the following criteria: international and national registries of patients with cardiac rhythm disturbances resulting from myocardial ischaemic injury and including information on the presence of antiplatelet therapy. The retrieved studies were analysed according to the following criteria: design, number and characteristics of included patients, risk stratification for stroke, antithrombotic therapy administered.

At the second stage, a retrospective pharmacoepidemiological study was conducted to investigate the pharmacoepidemiology of antithrombotic therapy in heart rhythm disorders. The object of the continuous retrospective pharmacoepidemiological study were medical records of inpatients (form 003/u) with the diagnosis of 'Atrial fibrillation' (ICD-10 code - I48), consecutively admitted to the cardiology department of the MU of Samarkand and Ufa. It was decided to focus on this category of patients due to the high frequency of thromboembolic complications in this group and the highest incidence among other manifestations of rhythm disorders. At this stage, 382 case histories of inpatients were included in the analysis. Inclusion criteria: age of patients older than 18 years, established diagnosis of atrial fibrillation (ICD-10: I48.0, I48.1, I48.2) of ischaemic genesis. Exclusion criteria: Cardiomyopathies of non-ischaemic genesis (I42-I43 according to ICD-10), thyrotoxicosis (E05 according to ICD-10), congenital heart defects (I34- I36 according to ICD-10), rheumatic heart lesions (I01, I05-I09 according to ICD-10), acute coronary syndrome (I20-I24 according to ICD-10), endocarditis (I33 according to ICD-10), myocarditis (I40-I41 according to ICD-10), pericarditis (I30-I32

according to ICD-10), pulmonary embolism (TELA) (I26 according to ICD-10).

Table 1. - Clinical and demographic characteristics.

Characteristic	Patients in total n=250	Healthy control group, n=50	CAG control group, n=100	R	IHD group with rhythm disturbance, n=100	R
Age, years	58.7±7.4	56.2±8.1	56.9±8.7	0.94	56.1±7.6	0.64
Male gender, abs (%)	97 (38.8)	17 (34.0)	35 (35.0)	0.75	35 (35.0)	0.87
Concomitant pathology of abs (%)						
Diabetes	16 (6.4)	4 (8.0)	6 (6.0)	0.92	6 (6.0)	0.78
Smoking	19 (7.6)	4 (8.0)	7 (7.0)	0.79	8 (8.0)	0.45
Oncology	4 (1.7)	0 (0.0)	2 (2.0)	0.34	2 (2.0)	0.57
Arterial hypertension	4 (1.7)	0 (0.0)	2 (2.0)	0.63	2 (2.0)	0.77
COPD	2 (0.8)	0 (0.0)	1 (1.0)	0.74	1 (1.0)	0.93

Note: p – level of statistical significance in comparison with the control group, CAG – coronary angiography.

Results. The frequency of prescription of antithrombotic drugs for heart rhythm disorders according to registries before the introduction of POAC into clinical practice is presented in Table 4.

Table 2 - Antithrombotic therapy according to the risk according to the CHADS2DS2-VASc scale

Prescribed drugs	Register name				
	ATRIUM (n=3163)			GLORIA-AF I phase (n=713)	
	0 (n=68)	1 (n=208)	2 or more (n=2881)	1 (n=184)	2 or more (n=529)
Antiplatelet agents	39.7	27.8	22.4	44.5	56.9
AVK	38.2	63.5	75.4	19	20.8
Absence antithromboticological therapy	22.1	8.7	2.2	36.4	22.3

Table 2 shows that in the GLORIA-AF phase I registry, all patients had an indication for anticoagulants. At the time of inclusion of patients in the AFNET registry, 84.5% of patients with atrial fibrillation with a history of stroke and 29.7% of patients with atrial fibrillation without a history of stroke had indications for anticoagulants (CHADS2≥2). In this group of patients at high risk of VTE, 70.5% of patients with a history of stroke received anticoagulants (81.4% of patients received AVCs, 5.2% heparin, and 13.4% received combined anticoagulant and antiaggregant therapy) and 61.7% of patients with atrial fibrillation without a history of stroke. At the time of inclusion in the ATRIUM register, 97.7% of patients had indications for OAC (6.3% had contraindications), of whom 74.6% were receiving OAC (isolated or in combination with antiaggregants).

At the time of follow-up in the AFNET registry, 85.4% of LDC patients with a history of stroke and 35.4% of HRD patients without a history of stroke had an indication for OAC (CHADS2≥2), with 76, 4% of HRD patients with a history of stroke (95.3% of patients received

AVCs, 4.6% heparin, and 10.4% received anticoagulants and antiaggregants together) and 69.2% of HRD patients without a history of stroke. One year later in the ATRIUM registry, 97.8% of HRD patients had an indication for OAC, of whom 70.4% received OAC in isolation or in combination with antiaggregants.

In the AFNET registry, in the group of patients with indications for OAC, 7.6% and 15.9% of HRD patients with a history of stroke were receiving antiaggregant therapy at the time of inclusion in the study and at the time of follow-up, respectively. In the GLORIA-AF registry, 53.7% of patients at moderate and high risk of ischaemic stroke were receiving antiaggregant therapy.

When analysing the data from GLORIA-AF, GARFIELD-AF and ORBIT-AF registries, it was found that on average over 4 years the frequency of OAC prescribing increased significantly, mainly due to a progressive increase in the frequency of POAC prescribing: in GLORIA-AF from 1.9% to 47.6%; in GARFIELD-AF from 3% to 43%; in ORBIT-AF from 2% to 71%. The opposite trend was observed for

antiaggregants, the frequency of prescription of which almost halved in all the registries compared over the same period of time. Due to the low rate of first-time atrial fibrillation in the ORBIT-AF I registry, this cohort of patients was not included in the analysis of antithrombotic therapy in registries of patients with first-diagnosed HRD. This analysis revealed that about half of the HRD patients with CHADS₂DS₂-VASc=0 received OAC: 46.1% in GLORIA-AF and 47% in GARFIELD-AF. This rate was highest in the ORBIT-AF II registry, where 57% at low risk of ischaemic stroke received OAC. When analysing antithrombotic therapy in the group of patients at high risk of VTE (CHADS₂DS₂-VASc≥2) according to the GLORIA-AF and GARFIELD-AF registries, it was found that 82.2% and 69% of atrial fibrillation patients, respectively, received OAC; in the ORBIT-AF

registry, the number of patients receiving OAC as indicated was significantly higher, reaching 87%.

The analysis of a number of large registries of patients with heart rhythm disorders has shown that there are common patterns in the clinical and demographic characteristics of patients and revealed inconsistency in the practice of anticoagulant therapy in real clinical practice with modern recommendations for the treatment of this pathology, including regional differences in the tactics of antithrombotic therapy. The obtained data indicate the need to develop registers of patients with heart rhythm disorders, including in the Republic of Uzbekistan. Registers of patients will allow to carry out detailed pharmacoepidemiological analysis of therapy in real clinical practice, to identify existing problems of its pharmacotherapy, on the basis of which to develop approaches to its optimisation.

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