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FOR SUDDEN CARDIAC DEATH RISK ASSESSMENT AND PREVENTION

(SECOND EDITION)`

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GLOSSARY OF ABBREVIATIONS

AAA – antiarrhythmic agents
AV – atrioventricular
AVRT – atrioventricular reciprocating tachycardia
AVNRT – atrioventricular nodal reentrant tachycardia
AH – arterial hypertension
BP – blood pressure
ARVD – arrhythmogenic right ventricular dysplasia
ACM – alcoholic cardiomyopathy
AED – automatic external defibrillator
BLS – basic life support
LBBB – left bundle branch block
CD – circulatory diseases
SCD – sudden coronary death
CHD – congenital heart defects
HRV – heart rate variability
SCD – sudden cardiac death
LVOT – left ventricular outflow tract
RVOT – right ventricular outflow tract
HCM – hypertrophic cardiomyopathy
LVH – left ventricular hypertrophy
AACP – accessory atrioventricular conduction pathway
CI – confidence interval
DCM – dilated cardiomyopathy
CTD – connective tissue dysplasia
VA – ventricular arrhythmia
VRD – ventricular rhythm disorder
VT – ventricular tachycardia
PVC – premature ventricular contractions
ACE inhibitors – angiotensin-converting enzyme inhibitor
CAD – coronary artery disease
ALV – artificial lung ventilation
ICD – implantable cardioverter-defibrillator
IE – infective endocarditis
LV – left ventricle
CMP – cardiomyopathy
CPVT – catecholaminergic polymorphic ventricular tachycardia
ICSD – International Classification System of Diseases
NVT – non-sustained ventricular tachycardia
AMI – acute myocardial infarction
ACS – acute coronary syndrome

RR – relative risk
OR – odds ratio
RV – right ventrical
MVP – mitral valve prolapse
PUFA – polyunsaturated fatty acids
PTH – parathyroid hormone
ALS – advanced life support
SIDS – sudden infant death syndrome
DM – diabetes mellitus
CPR – cardiopulmonary resuscitation
OSAS – obstructive sleep apnea syndrome
EVRS – early ventricular repolarization syndrome
SSS – sick sinus syndrome
TGA – transposition of the great arteries
SVT – sustained ventricular tachycardia
LVEF – left ventricular ejection fraction
VF – ventricular fibrillation
AF – atrial fibrillation
HM-ECG – Holter ECG monitoring
CRD – chronic renal disease
cAMP – cyclic adenosine monophosphate
HR – heart rate
ECG – electrocardiogram
CP – cardiac pacing (cardiac pacemaker)
ES – electrophysiological study
EchoCG – echocardiography
CHADS-2 – clinical prediction rules for estimating the risk of stroke in patients with fibrillation /flutter
CRT –cardioresynchronizing treatment
CRT-D – triple chamber cardioverter defibrillator
$etCO_2$ – carbon dioxide partial pressure in the last portion of the expired-air
LQTS – long QT syndrome
NSTEMI – non-ST segment elevation myocardial infarction
QT – QT interval
QTc – QT interval corrected
$PaCO_2$ – carbon dioxide tension in arterial blood
PAP – positive airway pressure
SaO_2 – arterial oxygen saturation
SDNN – standard deviation of NN intervals
STEMI – ST segment elevation myocardial infarction
WPW – Wolff-Parkinson-White

I. INTRODUCTION

Cardiovascular mortality in Russia is one of the highest in the world reaching 614 deaths per 100,000 per year [1]. The main causes of death from cardiovascular diseases are the progression of congestive heart failure (about half of all cases) and sudden cardiac death (SCD) (the other half) [2, 3]. According to the Federal State Statistics Service, about 899,000 people died from cardiovascular diseases in the Russian Federation in 2016. Thus, we can assume that the number of sudden cardiac deaths in our country in 2016 was no less than 300,000 people [1]. SCD is one of the major problems of the national health care. This problem raises additional concerns due to the fact, that there is an opportunity for effective interventions aimed at changing this negative situation.

In the submitted Russian Guidelines, as well as in the first edition published in 2012 [4], we continued to use the principles of algorithmic decision-making in various clinical situations.

In the development of this edition of the Guidelines, the group of experts used the latest achievements in SCD risk assessment and prevention in various populations and patient categories, as stated in the recently issued domestic, European and American Guidelines [5–7].

In contrast to the above mentioned guidelines, our group of experts found it appropriate to consider in more detail the issues of SCD risk stratification and prevention in such patient categories as elderly patients, patients with a transplanted heart.

These Guidelines allow to identify risk factors for SCD in routine clinical practice and to develop optimal approach for SCD prevention in every individual clinical case a wide range of physicians (internists, cardiologists, cardiac surgeons, interventional radiologists, intensivists).

These Guidelines are a continuation of the work on the development and implementation of the effective sudden cardiac death prevention system in our country, which we started in 2012.

As well as their first edition, the Guidelines are based on a notion of major and secondary SCD risk factors.

Identification of the major risk factors implies use of more aggressive means of SCD prevention (interventional and/or surgical procedures).

Presence of secondary SCD risk factors steers toward more conservative approach, which includes the individual patient risk factors modification (e.g., smoking cessation, weight loss) and optimization of the medical treatment.

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II. MECHANISMS AND CAUSES OF SCD. TERMS AND DEFINITIONS

Definition of SCD. Sudden cardiac death (SCD) is non-violent death that has developed instantly or within 1 hour of the onset of acute changes in the patient clinical status [1].

One should distinguish between *sudden **cardiac** death* and *sudden death*. Diagnostic criteria for the latter are similar to the ones in SCD definition, except that sudden death develops due to noncardiac causes such as massive pulmonary embolism, rupture of a cerebral aneurysm, etc.

Mechanisms of SCD. According to Holter monitoring data obtained from patients who died suddenly, in most cases the underlying cause of SCD were ventricular tachyarrhythmias (85%) – ventricular tachycardia (VT) and ventricular fibrillation (VF), followed by asystole. The remaining 15% are caused by bradyarrhythmias and asystole [2–4] (Figure II.1). Arrhythmia complicated by acute left ventricular failure leads to systemic and regional (primarily CNS) hemodynamic derangements. This may cause irreversible changes in the vital organs and death. In this context, the key to the clinical interpretation of any malignant arrhythmias as life-threatening is presence of the following signs and symptoms: syncope, presyncope, dizziness, hypotension, progression of CHF signs, angina pectoris. The presence or absence of preexisting structural heart defects may be crucial to adaptive changes of cardiac output parameters, and thus to the clinical course of the arrhythmia.

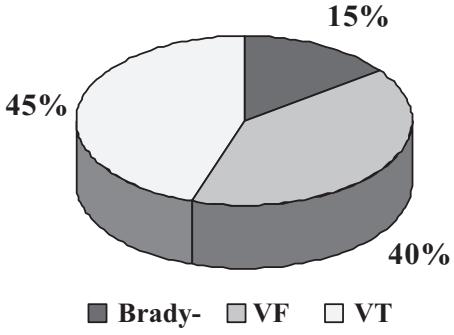

Figure II.1. Mechanisms of SCD. The diagram shows contributions of different types of arrhythmias and cardiac conduction abnormalities to SCD. Brady – percentage of bradyarrhythmias leading to SCD, VF – ventricular fibrillation, VT – ventricular tachycardia

In patients without severe structural heart disease, SCD usually is a result of polymorphic VT or torsades de pointes [5]. While in patients with structural heart disease, particularly coronary after diseases (CAD), ventricular arrhythmias occur either as a result of acute myocardial ischemia, or due to re-entry mechanisms, mainly caused by scarred tissue following a myocardial infarction (in such case, coronary flow abnormalities are not the cause of arrhythmia) [1, 6–8]. As for bradyarrhythmic mechanisms, they are typical for patients with terminal stages of structural heart disease and are relatively rare (about 15%) [6–8].

The following factors may be triggers of fatal arrhythmias: change in autonomic nervous system tone (increase or decrease in sympathetic/parasympathetic tone), physical activity, intake of certain drugs, electrolyte disturbances, toxin exposure, hypoxia.

Table II.1

Causes of sudden cardiac death (adapted from J. Ruskin, 1998)

CAD
dilated cardiomyopathy
left ventricular hypertrophy
hypertrophic cardiomyopathy
acquired heart defects
acquired heart defects
acute myocarditis
arrhythmogenic right ventricular dysplasia
coronary arteries anomalies
sarcoidosis
amyloidosis
heart tumors
left ventricular diverticula
WPW syndrome
long QT syndrome
Brugada syndrome
catecholaminergic polymorphic ventricular tachycardia
short QT syndrome
drug-induced proarrhythmia
cocaine intoxication
severe electrolyte imbalance
idiopathic ventricular tachycardia

Causes of SCD. The probability of SCD within one year in individuals with structural heart disease is 7.5 times higher than in patients without structural heart disease [8]. Among the cardiac pathology that may lead to SCD, coronary artery disease is the most common cause accounting for 80% of all cases [6–8]. In addition to CAD, SCD, as a dramatic outcome of the disease, occurs in patients with dilated cardiomyopathy (DCM) [1, 6], hypertrophic cardiomyopathy (HCM) [1, 6], arrhythmogenic right ventricular dysplasia (ARVD) [1, 6], Brugada syndrome and long QT syndrome, anomalies of the coronary arteries and other pathological conditions, listed in Table II.1.

Definitions and terms. It believe it is prudent to define here basic terms that will be used in these guidelines hereinafter (Table II.2).

Table II.2

Glossary

Bidirectional ventricular tachycardia − ventricular tachycardia with electrical axis alternation in the frontal plane; it is often associated with digitalis toxicity overdose.

Monomorphic ventricular tachycardia − ventricular tachycardia with consistent QRS complex morphology in 12-lead ECG.

Non-sustained ventricular tachycardia (NVT) − VT that presents with at least 4 consecutive ventricular complexes with maximum duration of no more than 30 seconds and self-terminates spontaneously.

Torsades de pointes − VT which is usually associated with long QT or QTc intervals. ECG tracing demonstrates characteristic «twisting» of the QRS complex around the isoelectric baseline.

Polymorphic ventricular tachycardia − VT with varying QRS complex configuration in 12-lead ECG. The QRS complex frequency ranges from 100 to 250 per minute.

Bundle-branch re-entrant tachycardia − is a result of re-entry circut within His-Purkinje system. Surface ECG tracing is usually characterized by VT with QRS complex configuration similar to the one in left bundle branch block (LBBB); heart rate is high (about 200 beats per minute); it often develops in patients with dilated cardiomyopathy.

Sustained ventricular tachycardia (SVT) − VT that lasts longer than 30 seconds, it often does not terminate spontaneously.

Hemodynamically unstable ventricular arrhythmias − VF, VT, sustained/non-sustained VT and/or PVCs that are accompanied by signs/symptoms of significant hemodynamic compromise (dizziness, presyncope, syncope, hypotension, CHF progression, angina).

Hemodynamically stable ventricular arrhythmias − sustained/non-sustained VT and/or frequent PVCs that are accompanied by minimal clinical manifestations (e.g., dizziness, palpitations, tendency to hypotension).

Odds ratio − a measure of strength of association between a condition or exposure and an outcome. Chance of event occurrence is the ratio between the probability of its occurrence and the probability of its non-occurrence. The odds ratio is calculated by dividing the probability of event occurrence in one group by the probability of its occurrence in other group.

Penetrance − population term that means the proportion of individuals who exhibit particular trait (disease) among all individuals with the corresponding mutation;

Proband − the first family member, for whom medical and genetic investigation is conducted;

Sudden cardiac death prevention − a set of activities carried out in patients who survived cardiac arrest (secondary prevention) or in patients with high risk of SCD without history of cardiac arrest (primary prevention).

Prevalence − the proportion of individuals in the population with the disease at a given time period.

Relative risk − ratio of event frequency in a treatment group to the event frequency in a control group.

Cardiac arrest − cessation of cardiovascular activity as a result of ventricular tachycardia and/or ventricular fibrillation, documented by ECG tracing (this definition requires ECG verification).

Table II.2 (continuation)

Ventricular flutter − organized (cycle length variability does not exceed 30 ms) ventricular arrhythmia with frequency of ventricular activation of about 300 per minute (cycle length – 200 ms), characterized by a monomorphic configuration of QRS complexes and lack of an isoelectric interval between adjacent ventricular complexes.

Risk factors − clinical parameters indicating the risk of SCD in a specific patient during current calendar year.

Ventricular fibrillation − high frequency, usually over 300 beats per minute (cycle length of 180 ms or less), irregular ventricular rhythm with marked variability in cycle length, morphology and amplitude of QRS complexes.

Incidence − proportion of people in the population who develop a disease within a certain period of time.

Expressivity − degree of expression of a trait (disease).

Arrhythmogenic effect − a direct result of unpredictable electrophysiological effect of an antiarrhythmic drug on the conduction system of the heart and myocardium, causing new arrhythmias

Proarrhythmic effect − worsening of current arrhythmia sings/symptoms and/or deterioration of the pre-existing arrhythmia characteristics due to use of antiarrhythmic therapy

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III. CLASS OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

These guidelines statements are based on modern principles of evidence-based medicine and presented in indication classes along with level of evidence for both diagnostic methods used for SCD risk stratification and SCD prevention methods (Table III.1).

Levels of evidence for a statement are classified as follows:

- *The highest* (Class A) – data from large number of randomized clinical trials and/or meta-analysis are available.
- *Moderate* (Class B) – data from limited number of randomized clinical trials (one) and/or non-randomized trials are available.
- *The lowest* (Class C) – statement is only based on individual case reports data and/or expert opinions.

Table III.1

Indication classes

Indication class	Comments
Class I	Conditions for which there is evidence and/or consensus regarding the usefulness and effectiveness of the diagnostic or treatment procedure
Class II	Conditions for which there is conflicting evidence and/or disagreement regarding the usefulness and effectiveness of the diagnostic or treatment procedure
Class IIa	Evidences or opinions in favor of the diagnostic or treatment procedure predominate
Class IIb	Usefulness and effectiveness of the diagnostic or treatment procedure are less substantiated by evidence and expert opinions
Class III	Conditions for which there is evidence and/or consensus regarding the fact that this diagnostic or treatment procedure is neither useful nor effective, and in some cases is harmful

IV. PATHOLOGICAL ANATOMY OF SUDDEN CARDIAC DEATH

SCD does not represent an independent nosological unit, it is a group concept that includes a number of different independent diseases and conditions:

Among all forms of SCD, the most common one is death due to coronary artery disease (CAD), which is referred to as sudden (acute) coronary death. Often the terms sudden cardiac death and sudden coronary death are used as synonyms. However, we must remember that these concepts are generic and specific in relation to each other.

The causes of SCD can be cardiomyopathies, among which the greatest importance in terms of prevalence and social significance belongs to alcoholic cardiomyopathy (ACM), myocarditis, vascular malformations, arrhythmic syndromes, etc.

Genetically determined diseases are represented by arrhythmogenic cardiomyopathy / right ventricular dysplasia (ACRVD), as well as diseases combined in the group of canalopathies (hereditary violations of the functioning of the cardiomyocytes cytomembrane ion channels): long QT-syndrome, short QT-syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia as well [1–3].

Sudden coronary death. The main pathoanatomical evidences

The main pathoanatomical manifestations of sudden coronary death, found at autopsy, correspond to the signs of CAD. They include stenosing arteriosclerosis of the coronary arteries of the heart, in some cases with their thrombosis, as well as focal and diffuse cardiosclerosis, cardiac muscle hypertrophy with dilated heart cavities, acute venous plethora of internal organs [4, 5].

Stenosing coronary artery atherosclerosis is an almost obligate sign of SCD and occurs in more than 90% of patients with CAD who suddenly died. Stenosing atherosclerosis may be absent in young people, and in the genesis of sudden coronary death, a primary role can be those of a coronary arteries spasm (Prinzmetal angina). In the overwhelming majority of the deceased, the degree of the coronary arteries stenosis exceeds 75% of the area of the vessel lumen with a lesion usually of at least two major branches. Most of the stenosis is expressed in the anterior descending branch of the left coronary artery. The degree of stenosis of the coronary arteries of the heart with sudden coronary death correlates with the degree of myocardial fibrosis, and the localization of fibrosis sites coincides with the pool of the obstructively altered artery [6, 7].

Thrombosis of the coronary arteries is rare in sudden coronary death, according to different authors, in 5–25% of cases. Moreover, a clear pattern is noted: the shorter the time interval from the onset of a heart attack to the moment of death, the less often there are thrombi. This is understandable, since thrombosis formation takes time. In case of a so-called instant death, when the duration of a heart attack is calculated in minutes, thrombosis occurs in 4% of sudden coronary deaths.

Due to autotrombolysis or thrombolytic therapy at autopsy, thrombi of the coronary arteries of the heart may no longer be diagnosed during life (angiographically, etc.). Even without thrombolytic therapy 24 hours after death, angiographically documented thrombi of the coronary arteries of the heart are retained only in 30% of the deceased [1, 8].

Information on the frequency of large-scale cardiosclerosis in sudden coronary death is controversial and varies widely (from 34 to 82% of cases). Moreover, it is more often localized in the interventricular septum, which indicates involvement in the pathological process of the *conducting* system, since the structures of the conducting system are localized precisely in this region. Hypertrophy of the myocardium is observed in the prevailing number of sudden deaths and reflects the role of the arterial hypertension factor.

Myocardial infarction with formed necrosis is not common in sudden coronary death, i.e. not more than in 2% of cases, except for the earliest, pre-necrosis evidences of the developing infarction when it is mainly about acute coronary syndrome (ACS) concerning a new type of CAD isolated to an independent form.

Acute coronary syndrome

At present, ACS is a group clinical concept in CAD that combines various evidences of acute myocardial ischemia caused by a **complicated unstable atherosclerotic plaque of the coronary artery of the heart** [1, 6, 9–11]. The introduction of the concept of ACS in the practice led to the elimination of the term "pre-infarction state", and sudden coronary death called "acute coronary insufficiency" appears in ICD-10 in "other acute forms of CAD" group with general code I24.8 [2, 11–13].

The following nosological units are included in ACS [1, 10, 11, 13]:

- unstable angina;
- non-ST-elevation myocardial infarction (NSTEMI);
- ST-elevation myocardial infarction (STEMI).

They can lead to sudden coronary death, which in some classifications is included in the ACS. In ICD-10, these types of myocardial infarctions have been included (and have been assigned with separate codes) only since April 2017, therefore these terms and codes are applied in practical work not in all countries yet.

The cause of development of ACS is a sharply developed partial (with unstable angina and non ST-elevation MI) or complete occlusion (with ST-elevation MI) of the coronary artery by the thrombus with complicated unstable atherosclerotic plaque. Complications of unstable atherosclerotic plaque include hemorrhage into the plaque, erosion or rupture, dissection of its cap, thrombus, thrombotic or atheroembolism of distal sections of the same artery [9–11, 13, 14]. At autopsy (and microscopically), the rupture is often documented by a hemorrhage into the intima of the coronary artery. In order not to miss the presence of hemorrhage, it is recommended that during the pathological anatomical examination, in addition to transverse incisions, longitudinal sections of the artery to be made. Unstable atherosclerotic plaque is characterized by microscopic loosening of the connective tissue of the cap as a result of the destruction of the collagen lattice and the accumulation of foamy cells, thereby taking a characteristic "moiré pattern"; lymphocytes and macrophages are diffusely distributed among the *altered* connective tissue.

Complicated (often unstable) atherosclerotic plaque of the coronary artery of the heart is an obligatory morphological criterion for the diagnosis of nosological units included in ACS. It is important to note that the stenosis of the coronary arteries by atherosclerotic plaques before the development of their complications in 50% of patients is negligible and is less than 40%.

Definitions of the concepts of ACS and type 1 myocardial infarction (MI) (see below) dictate the requirements for the examination of coronary arteries of the heart on autopsy for the detection of unstable atherosclerotic plaque: it is necessary to cut the coronary arteries longitudinally, the limitation only to transverse sections is unacceptable [10, 11, 13–15]. It is advisable to use the heart dissection method by G.G. Avtandilov [10, 11, 13–15]. In pathoanatomical and forensic medical diagnoses, it is necessary to indicate localization, the type (stable, unstable) and the nature of the complications of atherosclerotic plaques, the degree of stenosis of specific arteries, and the description of the stage and extent (area) of arterial atherosclerosis is optional.

For pathoanatomical diagnosis of nosological units in ACS, morphological verification of focal myocardial ischemia is necessary. Although irreversible necrotic changes in cardiomyocytes develop within 20–40 min of ischemia, the speed of necrosis development is affected by the state of collaterals and microcirculatory bloodstream, as well as the cardiomyocytes themselves and individual sensitivity to hypoxia. In addition, macro- and microscopic morphological signs of necrosis that do not require the use of special diagnostic methods appear no earlier than 4–6 hours (up to 12 hours) [10, 11, 13, 14].

In practical terms, the *phenomenon of sarcomeres hyperrelaxation*, determined with polarization microscopy in longitudinally cut cardiomyocytes, is the most informative and obvious. The phenomenon is characterized by an increase in the distance between the centers of neighboring isotropic (dark) disks – from normal 1.6–1.8 microns to 2–2.5 microns. Normally, the width of dark discs is one and a half to two times less than that of light ones. When hyperrelaxation, the width of the dark discs increases and exceeds the width of the light discs. The sensitivity of the polarization-optical method of determining ischemia is not inferior to electron microscopy, allowing detecting ischemia within 10–15 minutes after cessation of coronary blood flow, but at the same time, polarization microscopy provides an overview of histotopographic evaluation of the prevalence of ischemic injury [16]. Large areas of ischemia with hyperrelaxed sarcomeres in the myocardium of the deceased are detected in sudden coronary death by polarization microscopy, which occupy up to 30–50% of the area of the left ventricle myocardium.

In search of histological signs of myocardial ischemia, the researchers drew attention to the phenomenon of *wave-like deformation of muscle fibers*, although this sign is not so specific, as it is observed in non-ischemic (toxic, metabolic) myocardial damages [17]. Ischemia is also evidenced by *circulatory disorders at the level of microcirculation vessels*. This is expressed by the stasis of blood in the capillaries with the formation of the so-called "pillars" of erythrocytes (a sludge phenomenon), which is accompanied by stromal edema. It is advisable to apply histological staining according to Li and Selye (red-colored ischemia), histochemical (PAS reaction – disappearance of glycogen in the ischemic zone), and electron microscopy (signs of mitochondrial damage) methods.

For reliable verification of myocardial ischemia in sudden coronary death, it is recommended to use a macroscopic *sample with nitroblue tetrazolium* (nitro-ST reaction), which makes it possible to clearly identify areas of ischemic heart muscle in the form of light-lilac enzyme activity foci on the dark purple general background of unaffected myocardium [18].

Ventricular fibrillation and the phenomenon of reperfusion

The mechanism of cardiac arrest in sudden coronary death is most often ventricular fibrillation (VF), less often – asystole. In this case, at autopsy, the heart has a flabby consistency, its cavities are dilated, the blood is liquid, acute venous plethora of the internal organs is noted.

The histological marker of VF is the widespread *fragmentation of muscle fibers*, which is combined with the formation of multiple *contracture damages of cardiomyocytes*, which are detected by staining with iron hematoxylin according to Rego by areas of sarcoplasm stained in black at the places of their dissociation.

Thus, with sudden coronary death, two oppositely directed processes are observed in cardiomyocytes: on the one hand, hyperrelaxation of sarcomeres as an evidence of myocardial ischemia, on the other hand, contractural damage to cardiomyocytes as a consequence of the release of norepinephrine from sympathetic nerve terminals. Moreover, the alternation of these processes occurs in parallel and is simultaneously observed in the same field of view, affecting neighboring cellular structures. Such a picture of hyperrelaxation and contractures combination is a morphological evidence of the ischemic myocardium **reperfusion phenomenon**. With sudden coronary death, extensive areas of reperfusion damages are found in the left ventricle myocardium. A similar pattern is observed in the border zone of the MI, where reperfusion of the ischemic myocardium occurs due to collateral circulation.

It has been established that reperfusion developing in an irreversibly ischemic myocardium is a factor provoking ventricular fibrillation. This process occurs indirectly by washing away from the ischemic zone into the bloodstream of the so-called *arrhythmogenic substances* accumulating there which are biologically active substances that cause electrical instability of the myocardium [19, 20]. These include, first of all, lysophosphoglycerides (lysophosphatidylcholine and lysophosphatidylethanolamine) and free fatty acids as the cell membranes destruction products. Due to their high reactogenic properties, lysophosphoglycerides disrupt the structure of cell membranes, in particular sarcolemma of cardiomyocytes, contributing to the uncontrolled flow of calcium ions into the cell under conditions of increased membrane permeability (hypoxic ischemia), which leads to electrical instability of the myocardium. In mitochondria isolated from the myocardium of suddenly died patients with CAD, an increase in the content of lysophosphatidylcholine, lysophosphatidylethanolamine and free fatty acids was detected, which is regarded as the initiating substrate for electrophysiological disturbances in the cardiac muscle [21].

The arrhythmogenic substances also include cyclic adenosine monophosphate (cAMP), catecholamines (mainly noradrenaline released from adrenergic nerve terminals), free radical peroxide compounds of lipids and some others. It was found that the higher the content of cAMP in myocardial tissue, the more it is prone to fibrillation in response to adrenaline stimulation. An elevated concentration of cAMP is attributed to the excessive intake of calcium ions into the cardiomyocyte, increase of glycogenolysis and lipolysis, the development of electrical instability of the myocardium [9].

In the classic course of myocardial infarction, the arrhythmogenic substances "become embedded" in the area of coagulation necrosis that is forming and do not exert their pathogenic effect. If deep ischemia is interrupted by the reperfusion process development, the arrhythmogenic substances are washed

out of the ischemic zone into the bloodstream and exert a damaging effect on the membranes of the cardiomyocytes, provoking the VF. Moreover, ischemia should be sufficiently deep and irreversible, that is, long enough to exceed the permissible threshold of arrhythmogenic substances accumulation and, as a result, substantially impair the permeability of cardiomyocytes membranes. This is why the definition of SCD (sudden coronary death) includes the time interval of a heart attack duration within one hour, this is the period of irreversible ischemia, for which the arrhythmogenic substances accumulate in the ischemic zone and the cell membranes of the cardiomyocytes are damaged.

Thus, it is reperfusion that is the factor provoking the switching of acute coronary syndrome towards the development of sudden coronary death. Without reperfusion, ACS progression and myocardial ischemia result in the formation of a myocardial infarction.

Coding of sudden coronary death according to ICD-10 and the formulation of the diagnosis

In the International Statistical Classification of Diseases and Related Health Problems of the 10th revision (ICD-10) there is no "Sudden coronary death" heading, but there is "Sudden cardiac death" with the cipher I46.1. This heading unites all forms of SCD, after exclusion of CAD and sudden coronary death. However, according to the rules of ICD-10, it cannot be used in diagnoses after autopsy and, even clinically, it can be used only as an exception, in the absence of other possible death causes, especially violent ones.

For the encoding of sudden coronary death, the heading "Other acute forms of CAD" (code I24.8) and the term "acute (sudden) coronary insufficiency" are used. As already mentioned above, according to the rules of ICD-10 terms with "death" word are inaccurate and forbidden to be used in diagnosis. However, the "Acute (sudden) coronary insufficiency" nosological unit should not be confused with "Acute heart failure" syndrome and one of death (thanatogenesis) mechanisms bearing the same name.

In the final clinical, pathoanatomical or forensic diagnosis, either acute (sudden) coronary insufficiency (ICD-10 code – I24.8) or myocardial infarction (ICD-10 codes – I21.-), depending on the situation, should be recorded. In pathoanatomical and forensic medical diagnoses, ST segment changes with MI are indicated only if there are relevant data in the final clinical diagnosis, with the reference "according to inpatient or outpatient case record", "according to clinical record") [1, 2, 10–13]. After the introduction in practice in Russia of a new version of ICD-10 dated April 2017 or ICD-11, the formulation and coding of the diagnosis of myocardial infarction, taking into account changes in the ST segment, are mandatory.

In the event of myocardial ischemia that can be identified in a sudden dead, for example, through a reaction with nitro-ST, the diagnosis should be formulated as a myocardial infarction with the addition of "in the ischemic stage" using the codes of block I21.

The long-standing mistake of the Russian-language translation of ICD-10 of 1995 was the requirement to code a recurrent myocardial infarction or reinfarction with I22.- codes, while these codes were offered by WHO experts only for recurrent myocardial infarction. In ICD-10 version of 2016 it was clarified that in order to avoid misinterpretations and from prospective of evaluating any myocardial infarction as acute, the use of I22.- codes for any myocardial infarction in case of deaths in clinical, pathoanatomical and forensic medical diagnoses is forbidden. Codes I22.- may be used only for live persons with recurrent myocardial infarction.

Unfortunately, due to the lack of clear explanations of ICD-10 requirements in the recommendations of the Ministry of Health of Russia, contradictory recommendations of professional medical communities, various domestic medical organizations currently use both outdated and modern requirements with regard to both acute coronary death and myocardial infarction.

It is not recommended to use the code I25.1 – atherosclerotic heart disease (or atherosclerotic cardiosclerosis) with sudden coronary death, which, unfortunately, is often due to the fact that it is not always possible to document signs of ACS or acute myocardial ischemia at autopsy. In this case, the acute form of CAD is coded by means of the CAD chronic form heading, which is incorrect since it distorts the statistics of the CAD forms.

Up to 15% of cases of SCD are associated with pathological processes affecting the heart, in addition to CAD.

Myocarditis

SCD development may rest on latent myocarditis, caused most often by a viral infection, less often by other pathogens. Among the viruses, enteroviruses, in particular Coxsackie B4 virus, as well as cytomegalovirus and influenza viruses, are more often detected as myocarditis pathogens. Latent myocarditis was found in 50% of HIV-infected patients. Myocarditis pathogens also include rickettsia. Myocarditis can be allergic, in particular with drug and serum allergies. Autoimmune reactions play their role in the development of myocarditis chronic forms, where an infectious agent triggers the process, and then myocarditis progresses often in a latent form. These latent myocarditis forms can cause SCD [13, 14].

Postmortem diagnosis of myocarditis in the absence of clinical data is possible only with microscopic confirmation. At autopsy, there are an increase

in the heart size, myocardial flabbiness, dilatation of the cavities noted. Hemorrhages can occur in the endocardium and the epicardium. Fibrotic lesions can occur in the heart muscle at the far-advanced stage. There are evidences of acute and chronic circulatory disorders. Focal inflammatory infiltrates in the heart muscle, represented by lymphocytes, macrophages, plasma cells, areas of scarring granulation tissue, fibrosis foci, which further contributes to electrical instability of the myocardium, as a cause of ventricular tachyarrhythmia are microscopically noted [15]. Different forms of myocarditis have their own characteristic features, described in the corresponding pathology sections. Thus, in case of Abramov-Fiedler's myocarditis, giant cells resembling Pirogov–Langhans cells are observed in the inflammatory infiltrate, with Chagas' myocarditis, peculiar inclusions of the parasite are observed in the sarcoplasm of cardiomyocytes.

Thanatogenesis of sudden death in myocarditis is associated with acute heart rhythm disorders leading to VF or asystole.

Cardiomyopathies

Cardiomyopathy (CMP) is one of the most common causes of SCD after sudden coronary death. Sudden death mechanism in all forms of cardiomyopathies is mainly associated with the progression of fatal heart arrhythmias developing into VF, less often into asystole.

There are two main groups of CMP: primary, or idiopathic (CMPs of unknown etiology) and secondary (CMPs of defined etiology). Secondary cardiomyopathies, as a rule, are not independent nosological units, but serve as evidences of other diseases.

Dilated cardiomyopathy (DCM) is characterized *macroscopically* by an increase in the mass of the heart with a sharp expansion of its cavities and frank evidences of heart failure. The heart mass reaches significant values of 600, 700, 800 grams and even more than a kilogram. Cardiac apex is smooth, and the transverse dimension is equalized with the longitudinal one, and sometimes even exceeds it, therefore the heart acquires a spherical shape. Left ventricle wall thickness increases, but not so much as to correspond to such a high heart mass. The parietal endocardium is vulnerable to fibroelastosis, which is usually found in heart defects. Along with this, there are characteristic signs of chronic heart failure syndrome: nutmeg liver, cyanotic induration of spleen, kidney, dropsy of cavities, anasarca, brawny induration of lungs [22].

Microscopic signs of DCM are evidenced quite well, but are not specific, therefore DCM diagnosis is based on clinical and morphological data, taking into account the autopsy results and macroscopic changes in the heart. Multiple focal lesions of cardiomyocytes predominantly of contracture type, widespread

foci of fibrosis, small focal lymphohystiocyte clusters in the stroma, hypertrophy of cardiomyocytes, undulating deformation of muscle fibers are histologically observed in the myocardium in DCM.

Severe mitochondrial damage (swelling, matrix washout, crista destruction, focal electron-dense deposits), dilatation of the sarcoplasmic reticulum tubules, deformation changes in the gaps between the membranes of the intercalated discs are detected at the ultrastructural level, which significantly affects the electrical stability of the myocardium.

Hypertrophic cardiomyopathy (HCM) is characterized *macroscopically* by an increase in the muscular mass of the left ventricle predominantly in the absence of cavities dilatation. Attention is drawn to the asymmetric nature of hypertrophy; interventricular septum thickness is usually one and a half to two times greater than the thickness of left ventricle free wall. Because of the increase in muscle mass of the myocardium in the subaortic region of the left ventricle, the narrowing of the outflow tract often occurs, which is referred to as muscular (hypertrophic) subaortic stenosis.

Microscopically, HCM is characterized by a violation of the architectonics of myocardial muscle fibers, their disordered arrangement. In the same microscope field of view, one can simultaneously observe bundles of muscle fibers that run both in the longitudinal and transverse directions, along with tangentially cut bundles of cardiomyocytes. There is hypertrophy of cardiomyocytes with diffuse cardiosclerosis. Distinctive histological features are also the serration of the hypertrophied cardiomyocytes nuclei contours, and the presence the so-called lucent halo around the nuclei. This halo is due to the accumulation in the perinuclear space of glycogen granules, which are washed out during preparation [23].

The genetic predisposition to HCM, caused by eleven mutant genes with the presence of more than five hundred individual transmutations accompanied by a defect of myocardial proteins such as myosin, troponin, actin, is proved.

Restrictive CMP (derived from English "restriction") is evidenced by pronounced sclerosis and hyalinosis of the parietal endocardium with an intact valve apparatus, which is accompanied by impairment (restriction) of myocardial contractile function. It is assumed that the restrictive CMP is a consequence of past Löffler parietal (mural) endocarditis. Restrictive CMP is accompanied by signs of cardiac decompensation and heart rhythm disorders leading to sudden death.

Right ventricular arrhythmogenic dysplasia

According to the definition of the ESC Working Group on Myocardial and Pericardial Diseases (2008) [24], arrhythmogenic cardiomyopathy/right ventricular dysplasia (ACRVD) is a heart muscle disease characterized by progressive

replacement of the right ventricular myocardium with fat and fibrous tissue first with regional, and then with overall damage of the right ventricle. It has been established that this type of cardiomyopathy is caused by mutations in genes encoding desmosome proteins, i.e. specialized structures that provide intra- and intercellular interaction. Genetically determined disorders lead to disruption of plakoglobin, i.e. intercellular adhesion protein, transport [25]. The remodeling of the intercalated discs and the decrease in the number of desmosomes lead to a disruption of the mechanical adhesion of the cardiomyocytes, which contributes to their death with progressive replacement by fibrotic and fat tissue [26], which is an anatomical substrate for the occurrence of ventricular arrhythmias. In 2010, F. Marcus et al. [27] suggested the morphometric diagnostic criterion of ACRVD, developed for myocardial biopsy and based on the principle of counting the number of residual cardiomyocytes not involved in the pathological process. Less than 60% is regarded as a "big" diagnostic sign, and 60–75% as a "small" diagnostic sign. M.V. Gordeeva et al. [28] suggested to extrapolate this morphological criterion proposed for intravital myocardial biopsies to the results of pathoanatomical analysis.

A new form of primary CMPs, i.e. **non-compaction myocardium**, or spongy CMP, has been recently included in the group of primary CMPs. This form of CMP is characterized by an overgrowth of the heart muscle trabecular apparatus of the left, or rarely of the right, ventricle with deep intertrabecular recesses (trabecular layer), with an active thinning of the true left ventricular wall (compact layer), at the ratio of the trabecular layer to the compact one of more than 2.

Secondary cardiomyopathies

As a rule, secondary CMPs are not separated nosological units, but are regarded as syndromes or evidences of other diseases. All varieties of secondary CMPs are usually described when characterizing the corresponding nosologies.

Alcoholic cardiomyopathy (ACM) is of the greatest interest due to its wide occurrence and social significance, being one of the frequent but not mandatory evidences of chronic alcoholism or chronic alcohol intoxication. It often leads to SCD. As in sudden coronary death, sudden death in alcoholic cardiomyopathy occurs due to fatal cardiac arrhythmias with an outcome of VF [29].

Morphological evidences of ACM, even where clearly pronounced, are not specific enough. Therefore, the diagnosis of ACM should be only clinicopathologic and taking into account the complex of all signs in relation to anamnestic (follow-up) data and intravital clinical evidences. There is also a misconception that the morphology of ACM is identical to DCM. Although there is much in common between them, these are different states.

In a *macroscopic* study, grade of the cardiac muscle hypertrophy with ACM never reaches those values that are inherent to DCM. Heart mass in ACM is 400–500 grams, max. 600 grams ("beer heart"), and normal mass (300–350 grams) is also possible. The heart is usually flabby to the touch; the chambers (of the left ventricle mainly) are dilated. There is often a large accumulation of fat under the epicardium. Coronary arteries are usually not affected by atherosclerosis, but its severity is not significantly different from population indices in individuals of older age groups. Myocardial profile is often of a yellowish tinge due to fatty degeneration.

The *microscopic picture* of ACM is also nonspecific, although the changes are quite pronounced. A combination of hypertrophy and atrophy of cardiomyocytes is typical, small round-cell infiltrates are encountered in the stroma as a reaction to muscle cells damage, and the sarcoplasm of cardiomyocytes is vacuolated. Small-drop sarcoplasm obesity is noted. Lipomatosis of the myocardial stroma (especially of the left ventricle), perivascular sclerosis, and clusters of lipofuscin in the sarcoplasm are definitive [30]. To confirm the diagnosis of ACM, a histochemical determination of the decrease in the activity of alcohol dehydrogenase in myocardial tissue on autopsy material is suggested.

If SCD occurs with underlying acute alcohol intoxication, the above signs are layered with acute changes: plasmorrhagia, perivascular edema, myocardial stromal edema, swelling and proliferation of vascular endotheliocytes of microvasculature, myolysis, contracture damages of cardiomyocytes, sludge.

In the structure of the *pathoanatomical diagnosis*, ACM can appear as an evidence of chronic alcohol intoxication (cipher F10.1) or chronic alcoholism (cipher F10.2), which are established as underlying disease. If immediate cause of death is associated with ACM, ACM is established as underlying disease being separate nosological unit (cipher I 42.6).

In this case, chronic alcohol intoxication or chronic alcoholism with all its evidences are placed under the background disease heading. In case of death from ethanol poisoning, acute alcohol intoxication is put first in the underlying disease heading (cipher T51.0) with the use of an additional cipher (X45), indicating external circumstances, i.e. the accidental nature of poisoning. In this case, chronic alcohol intoxication or chronic alcoholism with multisystemic evidences, if any, is placed in the background disease heading, and ACM is not separately encoded, but appears in the background disease as an evidence [31].

Rare forms of sudden cardiac death

SCD development may be based on the abnormality of heart and great vessels development. Among adult patients with congenital heart defects, the incidence of SCD is 5.3 per 1000. Cases of SCD in *aortic coarctation*,

congenital heart defects are described. There are cases of death in *coronary artery hypoplasia* and even in the complete absence of one of the three great coronary arteries. There are defects with *anomalous coronary arteries* from the pulmonary artery. Observations of SCD in the so-called "*myocardial bridge*", a peculiar developmental disease (many experts recognize it as a variant of normal development), are described when a great coronary artery (most often the anterior descending one) passes in a peculiar tunnel or is blocked from the outside by a bundle of myocardial muscle cells [32]. This bundle can pinch the artery lumen, causing an acute ischemia episode. As a rule, with the above-mentioned defects SCD occurs in the perinatal period or early childhood.

Persons at risk of SCD include patients with various ***hereditary and acquired forms of cardiac conduction disease***. A number of pathological conditions with high risk of SCD due to life-threatening ventricular arrhythmias are united in the "primary electrical heart diseases" group and denoted as congenital cardiac channelopathies [33]. As a rule, in this category of suddenly died patients, specific morphological changes in the myocardium were not detected.

Sudden cardiac death in children

The vast majority of observations of sudden death in children occur during the first year of life. The sudden death in infants, developed for no apparent cause, is commonly referred to as sudden infant death syndrome (SIDS). By definition, SIDS is an unexpected non-violent death of an infant, in which there are no adequate causes for death, historical and pathoanatomical study data. In ICD-10, SIDS has a separate heading, i.e. R95, and is referred to as sudden infant death.

SIDS is the most common cause of death in children in the age range from 2 weeks to 1 year, accounting for about 30% of all deaths in this age. SIDS incidence in the United States is about 1.5 per 1,000 of live-born children. SIDS incidence peak is between 2 and 4 months of life. In most cases of SIDS, a child dies in his/her sleep, so this death is often referred to as "cot death".

The diagnosis of SIDS in forensic and pathoanatomical practice is usually made through elimination of violent death, as well as other possible causes of death, verified in pathoanatomical research. It is impossible to detect any macroscopic changes that could explain the death mechanism. As for histological changes, they are insignificant and nonspecific and cannot explain the cause of sudden death.

In 1997, I.M. Vorontsov et al. [34] proposed to distinguish the following specific, in their opinion, morphological signs of SIDS, which they designated as "chronic hypoxia histological markers":

- hyperplasia of the muscular layer of medium and small vessels in the lesser circulation in combination with myocardial hypertrophy of the right ventricle;
- excessive content of periadrenal brown fat;
- multiple petechial hemorrhages under serosa (under epicardium, pleura, thymus capsule);
- brainstem gliosis;
- an excessive number of extramedullary hematopoiesis foci in liver;
- hyper- and hypoplasia of carotid bodies glomus tissue;
- hyperplasia of chromaffin adrenal tissue.

Among the morphological changes in SIDS, attention is drawn to the condition of the thymus, the so-called "thymomegaly", which earlier, along with such signs as generalized hyperplasia of lymphoid tissue, hypoplasia of the adrenal cortex, etc. was called "lymphoidotoxemia".

Thanatogenesis mechanisms in SIDS are a subject of discussion and remain largely unexplained. The generalization of SIDS study results suggests that there are two options for thanatogenesis, i.e. respiratory and cardiac ones. In the first case, we are talking about death from respiratory failure due to apnea that occurs in one's sleep. Cardiac mechanisms of thanatogenesis are mainly associated with functional impairment of cardiac conduction system. In children of the first year of life at high risk of SIDS, the so-called Wolff-Parkinson-White syndrome or LQTS is significantly often detected on the ECG.

The studies of S.L. Parilov [35] have established that the mechanism of sudden death in children of the first year of life can be a consequence of birth injuries of the central and parasympathetic nervous system that, in combination with acute infections, contributes to the sudden development of acute respiratory or heart failure.

There are isolated cases of sudden death in children due to congenital or acquired pathology of the coronary arteries of the heart.

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V. EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

Over the past 20 years, the epidemiology of sudden cardiac death (SCD) has changed significantly. In economically developed countries due to the implementation of effective programs for the prevention and treatment of cardiovascular disease (CVD) has led to a significant reduction in mortality from CVD, and as a result – from the SCD [1]. However, the number of deaths from cardiovascular disease in the world remains high and is about 17 million, 25% of which is SCD [2]. Thus, the coefficients of SCD in the general mortality (up to 20%) and cardiovascular mortality (up to 40%), wich were established 15–20 years ago were revised today.

At the present time in developed countries the average frequency of BCC is 1.40 per 100 000 person-year in women and 6.68 per 100 000 person-years in men [3]. The incidence of SCD in young people naturally lower – 0,46–3,7 per 100 000 population per year [4, 5]. In absolute values, this corresponds to 9,000 deaths in Europe and 6200 deaths each year in the United States [6].

In Russia, there is no official statistical reporting on the frequency of SCD. Approximate number of SCD can be calculated using the coefficient 25% [2] of mortality from CVD (for example, in 2014 940,489 people died due to CVD in Russia [7]). Thus, we can assume that approximately 235 thousand people dies suddenly in Russia a year.

Most domestic studies on the epidemiology of BCC, was carried out in 1970 and was limited to the scope of the WHO program "Register of myocardial infarction" [8–12]. It is obvious that in the last fifty years there have been dramatic changes in the treatment of myocardial infarction (MI), which had an impact on its associated mortality statistics.

A large domestic study REZONANS, conducted in three Russian cities (Ryazan, Voronezh, Khanty-Mansiysk) in a population of 285,736 patients with coronary artery disease was designed to assess SCD prevalence as a result of coronary heart disease (ie, sudden coronary death) [13], because CHD is the most common cause of SCD. According to diagnoses in medical death certificates, SCD incidence in male patients with CAD was 69 cases per 100,000 men per year, in female patients it was 26 cases per 100,000 women per year, while peak of SCD frequency in patients with CHD accounted for males in the age group 50–59 years, women – 70–79 years old, in the older age groups of patients with CHD incidence of SCD, according to the officially registered data, is rapidly declining. However, a more detailed analysis with additional

review of medical records, interviewing relatives, death witnesses, attending physicians and ambulance crews led to the conclusion that actual SCD incidence in men and women 2.3 and 2.8 times higher, respectively (156 and 72 cases per 100 000 population per year in males and females, respectively). Thus, according to Resonance study, SCD is underdiagnosed in Russia with half SCD cases in male CAD patients and 2/3 cases in female CAD patients being undiagnosed. The main reasons for this are lack of active diagnostic investigation while determining cause of death (45.4%) and errors in medical records (55.6%).

The register of SCD GERMINA was conducted in five major areas of the Bryansk region among the working age population (25–64 years) numbering 417,740 people. It demonstrated SCD frequency equal to 25.4 per 100 thousand population [14]. Considering the gender the frequency of SCD among men was 46.1 per 100 thousand people, women – 7.5 per 100 thousand people a year, ratio of male: female was 6.1:1. The proportion in cardiovascular mortality was 7.3% and in the total mortality – 2.9%.

Among the reasons of SCD in the working-age population, coronary heart disease (CHD) dominates – up to 80–85%, and at least half of these deaths occur in acute forms of CHD [15]. Various cardiomyopathy and inflammatory heart diseases occupy the second place in the list of etiological factors (15–20%), while the share of valvular heart disease (5–7%) and inherited primary arrhythmia syndromes (2–3%) is substantially less [1,14]. In some cases, when the cause of death remains unclear despite clinical, laboratory, instrumental and morphological studies, the diagnosis «sudden cardiac death» (ICD I46.1 code) can be established [16].

In the GERMINA study [14] as the most frequent causes of SCD were: chronic coronary heart disease (43%), less often – acute forms of coronary artery disease (37%). Share of cardiomyopathies accounted for 18%. In 2% of cases was established diagnose of SCD.

Patients suffering from CVD have a maximum risk of SCD, especially persons with a history of MI with reduced left ventricular systolic function and / or ventricular arrhythmias [15,17]. At the same time more than half cases of SCD occurs in the general population and in the group of people who have the well-known risk factors for CHD and in whom the risk of SCD is relatively low (Fig. 1). These data demonstrate the importance of a proactive approach to the prevention of SCD in all these groups of people, regardless of the level of risk of SCD.

The etiological factors of SCD are different in different age populations. In young most frequent causes of SCD are inflammatory heart diseases, cardiomyopathies and inherited primary arrhythmia syndromes. As we age,

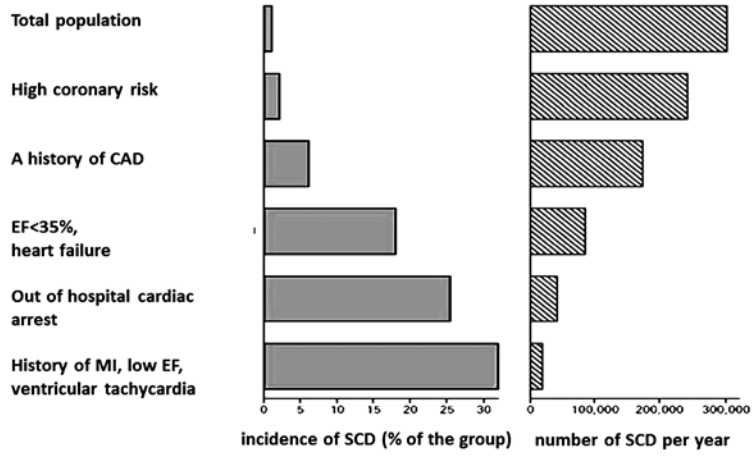

Fig. 1. The frequency of and the absolute number of SCD in the general population and specific groups of patients (adapted from R.J.Myerburg et al., 1992)

significantly increases the role of CHD, valvular heart disease and associated heart failure [1, 14, 18].

A number of epidemiologic features of SCD were defined in numerous studies. In particular, the direct or exponential correlation between SCD rate and age was established, as well as the significant predominance of men over women [8–14, 18]. It is known that more than 75% of SCD cases occur out of hospitals, of which about 20–25% – in public places (airports, train stations, stadiums, etc.) [10, 14, 18].

A significant role in tanatogenesis belongs to alcohol abuse, which is a characteristic feature of the epidemiology of SCD in the Russian Federation [14, 19]. Proof of this is the high percentage of anamnestic data on alcohol abuse, established in the medical records (36%), in the survey of relatives of died people (43%) and high frequency (27%) of alcohol detected in the blood at postmortem examination. Also, in 7% cases of SCD the alcoholic cardiomyopathy (I42.6 ICD code) was detected as main diagnosis.

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VI. SCD RISK FACTORS AND SCD RISK STRATIFICATION IN CLINICAL PRACTICE

SCD risk factors

SCD incidence is the lowest in the general population where the largest number of SCD is registered. Among patients with risk factors SCD incidence is higher, but in absolute numbers it is much smaller than that of the general population. In this context, the question of prognostic significance of such factors and their combinations for SCD prediction is extremely important.

The risk of SCD depends on individual risk factors and their significance for each individual patient. The presence of several risk factors allows to put a patient in a specific clinical subgroup, determine SCD risk, predict timing and, ultimately, determine the optimal prevention approach.

In our view, it is appropriate to distinguish *major* and *secondary* SCD risk factors. The *major* risk factors include history of cardiac arrest episode and/or hemodynamically significant sustained VT, history of myocardial infarction (MI), syncope, confirmed systolic dysfunction with decreased left ventricular ejection fraction (LVEF) of less than 40%, PVCs and/or episodes of non-sustained ventricular tachycardia. In the presence of *major* risk factors in an individual patient, there is a high or moderate likelihood of recurrence of malignant ventricular arrhythmias with development of acute heart failure, and, ultimately, SCD. The *secondary* risk factors include: left ventricular hypertrophy (LVH), hypertension (HTN), hyperlipidemia, diabetes mellitus (DM), smoking, obesity, increased heart rate (HR), hypersympathicotonia and other signs and symptoms discussed below.

Major risk factors

Major risk factors are clinical signs that increase the likelihood of SCD within the calendar year to moderate or high level (probability may reach 5–15% or 20–50%, respectively).

History of cardiac arrest and/or hemodynamically significant sustained ventricular tachycardia. The most important SCD risk factor is the history of previous cardiac arrest. According to JT Bigger, risk of SCD within a year in these patients is 30–50% [1]. These results were confirmed at the end of the last century in studies of ICD use for secondary SCD prevention (AVID, CASH, CIDS) in such patients [2-5].

History of previous myocardial infarction. According to studies of antiarrhythmic agents in post-AMI patients (EMIAT, CAMIAT and DIAMOND-MI),

Требуется уточнить уровни вложения заголовков. В исходнике они никак не согласованы

arrhythmic mortality as a result of ventricular tachycardia and ventricular fibrillation during one year is 5%, and during 2 years is 9% [5-7].

Left ventricular systolic dysfunction. Reduced left ventricular ejection fraction is an independent predictor of total, cardiovascular and arrhythmic mortality. This assumption has been confirmed by epidemiological data (including EPOHA study) as well as results of trials of ICDs effectiveness in primary and secondary SCD prevention; systolic dysfunction was one of the inclusion criteria to many of these trials [2-4, 8-12].

Syncope. SCD risk in patients with syncope may be a result of structural heart disease or may be associated with mechanism of the syncope.

SCD risk associated with the underlying disease. More and more convincing evidence that, to a large extent, the presence of syncope and SCD risk are related to the nature of the underlying disease. In the absence of a heart disease, syncope is a minor burden on the prognosis, and the main dangers are associated with the possibility of trauma in recurrent syncopal episodes [15].

The risk of death in a patient with syncopal states in ***coronary artery disease*** (CAD) is directly proportional to the severity of left ventricular dysfunction. Causes of syncope in CAD may be repeated episodes of ischemia and associated arrhythmias, primarily ventricular tachycardia (VT) or bradycardia [10, 12, 16].

In ***dilated cardiomyopathy*** (DCM), the presence of syncopal states is also associated with increased mortality [17, 18]. The most common cause of death in patients with syncope in DCM is considered to be VT [19, 20]. The mortality of patients with history of DCM and syncope can exceed 30% in 2 years [20-23].

In ***hypertrophic cardiomyopathy*** (HCM), syncope refers to one of the "big" SCD risk factors. It is unfavorable if syncope develops repeatedly, occurs at the load peak of or is combined with young age, heart failure and sudden deaths in close relatives [24-26].

Syncope occurring within 6 months after the initial examination in these patients is also a sign of a poor prognosis. Therefore, with syncope of unknown etiologyin patients with HCM older than 16 years without indication of the history of episodes of cardiac arrest, ventricular arrhythmias causing syncope or subconscious state, it is recommended to determine the SCD risk using the HCM Risk-SCD calculator (http://www.doc2do.com/hcm/webHCM.html) [27-29].

In ***aortic stenosis***, the average survivability of patients without aortic valve replacement after the occurrence of syncope is 2 years, most patients die within 3 years [30]. Half of patients with aortic stenosis who had angina episodes for 5 years, or syncope states for 3 years, or dyspnoea and other evidences of heart failure for 2 years, die suddenly [31].

Structural heart diseases [32-36] are a major SCD risk factor and overall mortality in patients with syncope. It was found that the presence of syncope in patients with severe heart failure and implanted resynchronizing devices (CRT-D) is associated with higher mortality [37, 38].

The risk of SCD associated with the nature of syncope. The risk of SCD is directly related to the syncope development mechanism. Framingham Heart Study demonstrated that mortality in patients with ***cardial syncope*** **(Table VI.1)** over a year is much higher (up to 33%) than in patients with noncardiac syncope (up to 12%) or syncope of unknown etiology (up to 6%) [39]. Although in the presence of organic damage to the heart and blood vessels, the mechanism of syncope is not always clear and can be mixed [27, 40, 41].

Syncope associated with orthostatic hypotension and other forms of transient hypotension may increase the risk of cardiovascular complications (risk of developing acute myocardial infarction, stroke) and be associated with mortality from all causes as well [42-47].

Table VI.1

Signs that characterize the increase in the likelihood of cardiac and non-cardiac causes of syncope

The most commonly associated with cardiac causes of syncope
• Elderly age (> 60 y.o.)
• Male
• Ischemic heart disease, structural heart disease, previous arrhythmias or decreased ventricular function
• Sudden loss of consciousness without a prodromal period or with a short prodromal period, for example, palpitation
• Syncope during exercise
• Syncope when lying on the back
• Small number of syncopal episodes (1 or 2)
• Abnormalities in the study of the heart
• Family history of hereditary heart diseases or premature sudden cardiac death (up to 50 years)
• Congenital heart diseases
The most commonly associated with non-cardiac causes of syncope
• Young age
• Lack of heart diseases
• Syncope only in standing position
• Changes in well-being when going from a prone position or sitting to a standing position
• Prodromal period with symptoms such as nausea, vomiting, feeling of heat
• The presence of specific triggers: dehydration, pain, stress, medical manipulation
• Situational triggers: cough, laughter, urination, defecation, swallowing
• Frequent repetition and a long history of syncope with similar characteristics

Regarding the SCD risk in syncope caused by orthostatic hypotension, it has been established that this form of hypotension is associated with a twofold increase in the risk of death (compared to that in the overall population) due to the concomitant diseases severity [42, 48].

The ARIC study (16,000 people) found that mortality from all causes and stroke was higher in people with orthostatic hypotension (13.7%) than those who did not have it (4.2%) [49], and not only in the elderly, but in middle-aged people as well [50].

In ***reflex syncope***, which often develops in young adults without structural heart disease or myocardial electrical instability, the prognosis is favorable [13]. However, there are observations indicating a possible connection between reflex syncope and SCD [51].In young athletes prone to vasovagal syncope, there is a possibility that the reflex mechanisms may be involved in syncope induced by physical activity, in rare cases they may result in death due to asystole. [52].

In ***patients with syncope of unknown origin***, mortality in the first year of follow-up (if there are no cardiac causes of syncope) is about 5% [53]. 15% of deaths by unclear causes in the past had at least one syncope of unknown origin. ¾ of them were seated, at rest - in 31%, on exertion in 38% of patients. Among the people who were clinically dead due to the sinus node arrest, a history of syncope was present in 23%, seated - in 79%, at rest - in 55%, on exertion - in 36% of patients [54]. Syncope of unknown etiologyis a marker of high SCD risk or resistant VT with a frequency of these states development amounting to more than 20% per year [55, 56].

Based on the available data, patients with syncope of unknown etiologyare now recommended as candidates for the implantation of a cardioverter-defibrillator [57].

Criteria for a high SCD risk of in syncope. Numerous studies have shown that organic heart diseases [58-61] and primary myocardial electrical instability of the myocardium [61] are the main risk factors for SCD and overall mortality in patients with syncopal states. In a number of prospective studies, there have been established risk factors that suggest an unfavorable prognosis in patients with syncope **(Table VI.2).**

EGSYS-2 study was conducted to estimate the early (within 1 month) and late (within 2 years) mortality in patients with syncope. Criteria of bad short-term prognosis were abnormal ECG changes, shortness of breath, hematocrit <30%, systolic blood pressure <90 mmHg, history of congestive heart failure (The San Francisco Syncope Rule) [62]. The risk of death in high-risk patient group was the highest during the first few days following the syncope. Four out of five deaths occurred within 48 hours after admission to the emergency department due to syncope (STePS study) [63].

Таблица VI.2

Risk stratification during the first examination in prospective population-based studies

Study	Risk factors	Index	End point	Results
San Francisco Syncope Rule [62]	- ECG changes - Congestive heart failure - Shortness of breath - Hematocrit <30% - SBP <90 mm Hg.	No risk = 0 Risk ≥1	Serious outcomes within 7 days	Sensibility 98% Specificity 56%
Martin et al. [34]	- ECG changes - History ventricular arrhythmias in anamnesis - Congestive heart failure - Age> 45 years	0–4 (1 score for each factor)	Severe arrhythmias or «arrhythmic» death within 1 year	0% – index 0 5% – index 1 16% – index 2 27% – index 3 or 4
OESIL index [35]	- ECG changes - Cardiovascular disease - Absence of a prodromal period - Age > 65 years	0–4 (1 score for each factor)	Death for 1 year	0,6% – index 1 14% – index 2 29% – index 3 53% – index 4
EGSYS index [32]	- Palpitation before syncope (+4) - Changes in ECG or heart disease (+3) - Scope at the load (+3) - Fainting in prone position (+2) - The prodromal period[a] (-1) - Predisposing factors[b] or triggers (-1)	Total score	2-year total mortality	2% – index <3 21% – index ≥3 2% – index <3 13% – index 3 33% – index 4 77% – index >4

Notes: The table shows the results of various studies in which clinical data were analyzed in patients with syncope. In general, the presence of changes in the ECG, elderly age or symptoms of heart disease indicate a more unfavorable prognosis within 1-2 years.

[a] – Nausea, vomiting.

[b] – Warm and crowded rooms, long standing, fear, pain, emotional stress.

Signs of unfavorable long-term prognosis were structural heart diseases and abnormalities on the ECG, and not the syncope development mechanism (the prognosis for arrhythmogenic syncope did not differ from the prognosis for reflex and orthostatic syncope) **(Table VI.3.)** [64].

Syncope can be a precursory symptom of SCD, especially in patients with cardiovascular diseases. Studies show that high overall and sudden mortality are mainly related to the most common structural heart diseases and ventricular arrhythmias. Therefore, at the examination it is necessary to assess the presence of structural diseases and coronary heart disease, and also to exclude less common causes of cardial syncope associated with the SCD risk such as WPW syndrome, hereditary electrical diseases of the heart, for example, LQTS.

Non-sustained VT and frequent PVCs. Studies, conducted in the 1970s, showed that patients with history myocardial infarction and frequent PVCs

Table VI.3

Risk factors for unfavorable short-term and long-term prognosis in syncope

Risk factors for unfavorable short-term prognosis	Risk factors for unfavorable long-term prognosis
Evaluation at an outpatient stage or emergency room	
Male	Male
Elderly age (> 60 years)	Elderly age (> 60 years)
Absence of a prodromal period	Absence of nausea / vomiting preceding syncope event
Palpitation before loss of consciousness	Ventricular arrhythmias
Syncope during exercise	Cancer
Cerebrovascular diseases	Structural heart diseases
Family history of sudden cardiac death	Heart failure
Traumatism	Cerebrovascular diseases
	Diabetes mellitus
	High risk as per CHADS-2 scale
	Study results
Signs of bleeding	ECG changes
Signs of disability	Reduction in glomerular filtration rate
Pathological ECG changes	
High level of troponin	

and/or episodes of non-sustained ventricular tachycardia have higher risk of SCD. Based on the results of MADIT I and MUSST studies, that were assessing the effectiveness of ICDs in patients with PVCs and non-sustained ventricular tachycardia, it can be argued that the resistance of these arrhythmias to class IA antiarrhythmic agents and their transformation into sustained VT during endocardial electrophysiological study are risk factors for SCD. [9].

Secondary risk factors

The *secondary* risk factors are clinical signs that are associated with increase of SCD risk to a higher level than that in the general population.

Arterial hypertension and left ventricular hypertrophy. Hypertension is a well known risk factor for coronary artery disease, although the data that hypertension is a risk factor for SCD are inconclusive [65, 66]. LVH is a morphological basis that increases the risk of SCD in patients with hypertension due to predisposition to VA. Factors contributing to the development of LVH include age, obesity, impaired glucose tolerance, genetic predisposition [67]. It is known that the presence of ECG signs of LVH (increased R-wave voltage and repolarization abnormalities) is associated with 33% and 21% mortality within 5 years in men and women, respectively [67].

The risk of SCD in patients with ECG signs of LVH is comparable to that in patients with CAD and CHF. A number of studies have shown that increased

myocardial mass, detectable on echocardiography, is a risk factor for SCD. According to Framingham Heart Study, relative risk (RR) of SCD was 1.45 (95% CI 1.10–1.92, P = 0.008) for every 50 g/m2 increase in LV mass, in subjects with other risk factors [68]. Diagnosed by ECG or cardiac echo LVH is an independent risk factor for cardiovascular events. And the presence of LVH signs on both ECG and echocardiogram, increases the risk even more. Results from randomized controlled trials do not provide a comprehensive answer to the question about effects of lowering blood pressure on the SCD risk. It is known that in older men with isolated systolic hypertension, the risk of SCD is higher than in women [66]. This fact indirectly agrees with the results of isolated systolic hypertension treatment studies in the elderly that showed a 17% decrease in total mortality and mortality from AMI, including 25% decrease in SCD, with hypertension treatment [69]. Meta-analysis of randomized trials data on blood pressure reduction in middle-aged patients with predominantly diastolic hypertension [70] revealed a 14% (95 CI: 4–22%, P <0.01) decrease in mortality from coronary artery disease and nonfatal AMI.

Lipids. The correlation between high cholesterol level and the risk of coronary heart disease, including SCD, is well-known [71–73]. In clinical trials evaluating lipid lowering for primary prevention of CAD, the risk of SCD was not studied specifically and reliable data on this are not available. If we assume that the reduction of SCD risk would occur in parallel with the reduction in mortality from CAD and AMI, then statins administration may reduce the relative risk of SCD by 30–40% [73]. Many epidemiological studies have shown that the risk of coronary artery disease (and possibly SCD) is associated with a diet containing high levels of saturated fatty acids and low levels of polyunsaturated fatty acids [74]. To date, there is no evidence that a diet high in saturated fatty acids increases risk of SCD. However, in US Physicians Study that included 20,551 male subjects aged 40 to 84 years with history of AMI, it was shown that weekly consumption of fish reduces the relative risk of SCD 2-fold (95% CI 0.24 -0.96; P = 0.04). This effect was independent of other risk factors [75]. Intake of seafood with high PUFA content was also associated with reduced risk of SCD.

Physical activity. There is a relationship between intense physical activity and development of SCD. However, the mechanism of this remains unclear. In most cases, those who die suddenly during exercise, previously did not work out on a regular basis [76]. Thus, the risk of SCD or AMI increases in untrained individuals during intense exercise. A population-based study has shown that after modifying the CAD risk factors the relative risk of SCD in individuals with moderate physical activity (work in the garden, walking) or intensive regular activity (more than 60 minutes/week) is 3–4 times lower

than in individuals without such physical activity [77]. The results of this study showed that the lack of physical activity causes coronary events (angina, acute coronary syndrome, acute myocardial infarction) in 43% (95% CI 26–60), even with the effective management of other risk factors, such as smoking, AH and excessive alcohol consumption.

Alcohol. Data on the relationship between alcohol intake and SCD are inconclusive. Excessive intake of strong alcoholic beverages increases the risk of SCD [72, 78]. This fact can be explained by the increase of the interval QT duration, which often occurs in alcoholics [79]. On the other hand, there are data on the protective effect of small doses of alcohol from life-threatening ventricular arrhythmias [80]. British Regional Heart Survey, a prospective study, has demonstrated that the consumption of alcohol in small quantities is associated with reduced risk of fatal outcome from a first major coronary event (RR 0.61, P <0.05) [72].

Heart rate and heart rhythm variability. Increase in HR is an independent risk factor for SCD [71, 72]. The correlation between high heart rate and risk of SCD is present in individuals with or without previously diagnosed heart disease, regardless of body mass index and physical activity [71]. The mechanism of this correlation is not clearly known. One explanation is the reduction of parasympathetic nervous system activity. Studies of heart rate variability suggest that in male population the total relative risk of death during 5 years of follow-up was 2.1 times higher (95% CI 1.4–3.0) in middle-aged patients with SDNN index less than 20 ms, compared with those of similar age with SDNN index of 20–39 ms [81].

Smoking. Population studies have shown that smoking is an independent risk factor for both BCC and AMI [72, 73]. This also applies to persons with no signs of coronary artery disease [82, 83]. Smoking is an important long-term risk factor for SCD [71]. We also know that smoking is a strong predictor of SCD, not SCD as a result of CAD [72]. However, results of a number of studies did not support the disproportionate effects of smoking on SCD [72]. Continued smoking after experiencing a cardiac arrest out of a medical institution is an independent predictor of recurrent episode of SCD [83].

Diabetes Mellitus. It is unknown whether glucose intolerance is an independent predictor of SCD. In Honolulu Heart Program Study, 8006 patients were followed up for 23 years. It was found that in individuals with impaired glucose tolerance and diabetes mellitus relative risk of SCD was 2.22 and 2,76, respectively (P = 0.05) [84]. Similar results were obtained in Austria (OR = 4.2, 95% CI 1.39–12.81). [72] In France, a retrospective analysis of more than 18,000 SCD cases showed that diabetes is a risk factor for SCD only in patients with coronary artery disease [85]. Prospective studies in Finland and

the UK confirmed the hypothesis that diabetes is not an independent predictor of SCD [72, 85].

ECG abnormalities. ST segment depression and T-wave deviations are informative in diagnosing coronary artery disease and left ventricular hypertrophy. There is a correlation between ST segment depression, T wave changes, and high risk of cardiovascular death. For instance, analysis of ECG tracings of 9117 men and women in Belgium who had no history of anginal episodes or myocardial infarction, showed that ischemic ECG changes were present in 8.4% of men and 10.6% women. After the correction of other cardiovascular disease risk factors, relative risk of cardiovascular mortality was 2.45 (95% CI 1.70–3.53) in men and 2.16 (95% CI 1.30–3.58) in women [86]. These data have also been confirmed by a number of other studies [87]. QT interval duration and dispersion are relevant for SCD prediction. The analysis of population studies data showed that an increase of QT interval may also be associated with structural heart disease (LVH). The length of interval QTc > 420 ms is a predictor of SCD [88, 89]. Convincing evidence that the QT interval dispersion is a predictor of SCD are lacking [88-91].

SCD risk stratification

In 1984, J.T. Bigger specified factors that determine SCD risk during a calendar year **(Table VI.4)**. In our guidelines, these factors are considered as major. They were used as inclusion criteria in the study of implantable cardioverter-defibrillator (ICD) effectiveness in SCD prevention [2-4, 9–12].

The cause of SCD is arrhythmia and hence the identification of a particular type of arrhythmia in every particular patient requires their prognostic assessment regarding the risk of SCD. In this connection, SCD risk stratification

Table VI.4

Risk of SCD development (adapted from Bigger JT, 1984)

	Annualy SCD risk
Moderate risk group	
History AMI or LVEF less than 40%	5%
AMI + LVEF less than 40% or ОИМ + frequent PVC, or LVEF less than 40% + PVC	10%
AMI + LVEF less than 40% + PVC	15%
High risk group	
Post-SCD patients	30–50%
VT + syncope	30–50%
VT + minimal clinical evidences	20–30%

Note: AMI - acute myocardial infarction; LVEF - left ventricular ejection fraction; PVC – premature ventricular contractions; SCD - sudden cardiac death; VT - ventricular tachycardia

in patients with cardiac arrhythmias regardless of the structural heart disease presence, proposed R. Fogoros, is worth mentioning [92] **(Table VI.5).** This classification, in our view, clarifies understanding of life-threatening arrhythmias. Thus, it is possible to decide on the course of malignant arrhythmias not only based on its hemodynamic significance, but also on its electrocardiographic features.

Table VI.5

Risk of sudden cardiac death in patients with cardiac rhythm and conduction abnormalities (adapted from R. Fogoros, 2006)

High
1. Ventricular fibrillation
2. Ventricular tachycardia
3. III degree AV block with low rate escape rhythm
4. WPW syndrome with anterograde conduction along accessory AV pathway with atrial fibrillation
Moderate
1. Ventricular ectopy with structural heart disease
2. II degree AV block
3. III degree AV block with adequate rate escape rhythm
4. Atrial fibrillation
Low
1. Atrial ectopy
2. Ventricular ectopy without structural heart disease
3. Supraventricular tachycardia
4. I degree AV block

Note: AACP –accessory atrioventricular conduction pathway; WPW – Wolff–Parokinson–White, AV – atrioventricular

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VII. THE RESEARCH METHODS REQUIRED FOR THE SCD RISK STRATIFICATION

The definition of SCD risk is based on a clinical assessment of a patient, which includes the history, results of physical and instrumental examinations. **Table VII.1** provides a list of the main instrumental and laboratory studies required to determine the risk of SCD, as well as classes of indications for their conduct and levels of evidence.

Table VII.1

Diagnostic tests that may be required for SCD risk stratification

Test	Comments	Indication class	Level of evidence
Electrocardiography:			
12-lead surface ECG	Allows to discover congenital anomalies associated with high risk of SCD (e.g. long QT syndrome, short QT syndrome, Brugada syndrome, arrhythmogenic right ventricular dysplasia), and to identify other ECG criteria (e.g., signs of electrolyte abnormalities, His–Purkinje conduction blocks, LVH signs) [1-3].	I	C
	12-lead surface ECG at rest is indicated in all patients during examination for VRD [1-3]	I	A
Holter monitoring	Indicated in patients with symptoms of arrhythmia to determine if they are caused by life-threatening arrhythmias [4-12]	I	B
	Indicated in patients with PVCs on the ECG tracing without any other symptoms [4]	I	B
Stress tests	Recommended for adult patients who have coronary artery disease risk factors and symptoms that may be associated with arrhythmias	I	B
	Indicated in patients with previously verified or suspected VRD arising during physical activity, including catecholamine-dependent ventricular tachycardia [13]	I	B
	Indicated in middle-aged and elderly patients with PVCs on the ECG tracing without any other symptoms.	IIb	C
	Execution of the ECG-stress test should be considered in order to assess the effectiveness of drug therapy or catheter ablation in patients with diagnosed VRD induced by physical stress [14].	IIa	C
Implantable recorders	Implantable recorders are indicated for patients with mild symptoms that may be associated with arrhythmias, for example, in case of syncope when standard diagnostic ECG cannot establish a causal relationship between the event and heart rhythm abnormality [15]	I	B

Test	Comments	Indication class	Level of evidence
Echocardiography	Indicated in patients with suspected structural heart disease [15-18]	I	B
	Indicated in patients with high risk of SCD and cardiomyopathy (DCM, HCM, ARVD), postinfarction myocardial fibrosis and family history of diseases with high risk of SCD [15-18].	I	B
	Stress echocardiography to detect silent myocardial ischemia is recommended in patients with VRD, moderate risk of CAD, treated with glycosides; patients with left ventricular hypertrophy; patients with ST-segment depression > 1 mm at rest, in patients with WPW syndrome or with LBBB [15-18].	I	B
	Echocardiography with pharmacological stress is recommended to identify painless myocardial ischemia in patients with moderate risk of CAD who cannot exercise 15, 16].	I	B
Genetic counseling and genetic testing (DNA diagnosis).	Aimed to identification and/or clarification of a hereditary disease diagnosis. Recommended for all patients and their families with hereditary diseases, and must include discussion of clinical examination of the risk and benefits of genetic testing [13, 15]	I	C
Biomarkers	Determination of BNP serum level in patients with structural heart pathology may carry additional information on the SCD prognosis [13, 15]	IIa	B
Magnetic resonance imaging (MRI)	Indicated in patients with VRD, when echocardiography is not able to precisely evaluate LV and RV function and/or identify structural abnormalities [15, 17-20].	IIa	B
	Indicated to confirm the diagnosis of ARVD or noncompact cardiomyopathy [15, 21, 22]	IIa	B
Magnetic resonance imaging (MRI) with delayed gadolinium medications contrast	Indicated in patients with HCM to detect the presence and severity of intramyocardial fibrosis as a predictor of SCD [23, 24]	IIa	B
	Indicated for the detection of inflammatory or scar lesions of the myocardium with myocarditis and coronary artery disease as a possible arrhythmogenic substrate [15, 17, 19, 20]	IIb	C
CT of heart and coronary arteries	Identification of prognostically unfavorable congenital anomalies of coronary arteries leads from sinuses of Valsalva [15, 19, 20]	IIb	C
	CT of heart can be used as an alternative to MRI with contraindications to the latter or its inaccessibility 19, 20].	IIb	C

Test	Comments	Indication class	Level of evidence
Coronary angiography	Indicated in patients with coronary artery disease and life threatening VRD (high and medium risk of SCD, see table V.2), as well as in those who survived cardiac arrest [15, 25]	I	C
Endocardial electrophysiological study (ES)	Conducting endocardial ES is recommended for post-MI patients with CAD who have the following symptoms: palpitation, pre-fainting conditions and syncope [15, 26-28]	I	B
	Conducting endocardial ES is recommended for patients with structural heart pathology and having the following symptoms: palpitation, pre-fainting conditions and syncope, bradyarrhythmia (including noninvasive methods) [15, 26-28]	I	C

Note: ARVD – arrhythmogenic right ventricular dysplasia; LVH – left ventricular hypertrophy; PVCs – premature ventricular contractions, VA – ventricular arrhythmia; DCM – dilated cardiomyopathy, HCM – hypertrophic cardiomyopathy; LBBB – left bundle branch block, ICD – implantable cardioverter defibrillator; Echo – echocardiography.

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VIII. SCD PREVENTION

SCD prevention is a set of activities carried out to prevent or decrease likelihood of SCD in patients who survived cardiac arrest (secondary prevention) or in patients with high risk of SCD without history of cardiac arrest (primary prevention). SCD prevention should include modification of risk factors and an adequate treatment of the primary disease and comorbidities. Modern SCD prevention is based on an integrated approach that includes the use of medications, interventional and surgical methods. The choice of preventive measures depends on patient risk category.

Medical treatment

The use of different groups of drugs for primary or secondary prevention of SCD has different indication classes and level of evidence, those depend on primary diagnosis, CHF FC, LV systolic function, signs and symptoms and nature of the rhythm disturbance. For this purpose, medications for the underlying disease treatment or specific antiarrhythmic agents (AAA) can be used.

Beta-blockers. Benefits of β-adrenergic blocking agents and their various effects are well studied in experiments and in clinical practice. Antiarrhythmic effect of β-adrenergic blocking agents is associated with both their anti-ischemic effects and the decrease in sympathetic activity. A meta-analysis of 25 studies of β-adrenergic blocking agents' effects on post-MI patients' survival, which included nearly 25,000 patients, showed that β-adrenergic blocking agents increased survival, reduced total and cardiovascular mortality and decreased SCD incidence [1]. Positive effects of β-adrenergic blocking agents on ventricular arrhythmias and SCD are also proved in patients with CHF of ischemic and non-ischemic nature (DCM, HCM, long QT syndrome, catecholaminergic polymorphic VT, ARVD, aortic stenosis) [2–5]. Another advantage of β-adrenergic blocking agents is that they also can be combined with other antiarrhythmic agents, for instance amiodarone [6]. The choice of β-adrenergic blocking agents and approaches to dose titration are determined by the underlying disease that is present in the patient (past AMI, CHF, AH and others). Thus, β-adrenergic blocking agents are safe and effective, in case of proper selection of patients and approaches to dose titration, agents that have the largest evidence base and must be considered as first-line agents for primary and secondary prevention of SCD (**I, A**) [7].

ACE inhibitors and angiotensin receptor blockers. Benefits of ACE inhibitors in coronary artery disease treatment are well known. They affect

electrophysiological processes in the myocardium, altering the function of the K- and Ca-channels and increasing refractoriness and ventricular repolarization, preventing re-entry arrhythmias in patients with CHF and ischemic VF. Antiarrhythmic effects of ACE inhibitors are also due to inhibition of the sympathetic nervous system. They inhibit circulating catecholamines and angiotensin-2, and increase plasma potassium level. Several studies have shown that ACE inhibitors increase baroreceptors sensitivity and improve heart rate variability. Finally, the antiarrhythmic effect of ACE inhibitors may be due to anti-inflammatory properties and a decrease in postinfarction remodeling processes.

Evidence of ACE inhibitors positive effects on the survival of patients with acute myocardial infarction, and patients with CHF of ischemic and nonischemic nature obtained in a large number of clinical studies showed that ACE inhibitors significantly reduced total and cardiovascular mortality in these patients [8–13]. However, SCD was not evaluated as an end point in most of these clinical trials, in contrast to β-adrenergic blocking agents. The exception is a TRACE randomized trial that studied the effects of trandolapril on the SCD; the positive result was proven [13]. It should be noted that the verification of mechanism of death, especially in SCD, presents certain difficulties, especially in clinical trials, when deaths are usually evaluated retrospectively. However, there is no doubt of the fact that almost half of patients with CHD, especially individuals with previous history of MI, die suddenly. Clearly, we may extrapolate the strong evidence on the reduction of cardiovascular mortality with ACE inhibitors to SCD. A large meta-analysis that evaluated effects of ACE inhibitors on the SCD risk is a confirmation of the above [11]. This analysis included data of 15,104 patients from 30 studies (15 of the studies were blind, randomized, placebo-controlled) and showed that ACE inhibitors use was associated with reduced total and cardiovascular mortality in patients with history of MI, and the incidence of SCD in these patients decreased by 20% (2,356 deaths, including 900 SCDs). In this regard, the statement about effectiveness of ACE inhibitors in SCD prevention in patients with history of myocardial infarction and with chronic heart failure (systolic dysfunction) is present in all current domestic and international guidelines on SCD prevention and has the highest level of evidence **(I, A).**

As for the data on ACE inhibitors effectiveness in SCD prevention in patients with preserved left ventricular function, there are much less data available. Several studies (HOPE, EUROPA) have shown the benefits of ACE inhibitors, such as ramipril and perindopril, in SCD prevention in patients with high risk of cardiovascular events [78, 79]. It should be noted that in these studies SCD is not evaluated as an independent endpoint. However, ACE inhibitors are

recommended for patients with CHF and preserved left ventricular function, as they prevent CHF development and progression **(IIa, B).**

Thus, ACE inhibitors are also one of the medications required for SCD prevention, especially in post-MI patients and patients with CHF.

As for the angiotensin receptor blockers, there are less data on their effects on reducing mortality in CHF patients than that of ACE inhibitors. There are positive results on reducing risks of cardiovascular mortality in patients with CHF treated with losartan and valsartan. In CHARM study [14], an ARB (candesartan) showed clear efficacy in reducing mortality from cardiovascular causes and characteristics of sudden death (15% reduction of risk, $p = 0.036$) in patients with congestive heart failure and reduced left ventricular systolic function. Therefore, candesartan can now be used for SCD prevention in patients with chronic heart failure and reduced left ventricular ejection fraction on a par with ACE inhibitors. Regarding use of other angiotensin receptor blockers for SCD prevention in patients with preserved LV function, no conclusive data are currently available.

Aldosterone antagonists. A retrospective analysis of SOLVD study data (6,797 patients, 424 deaths) showed a correlation between the use of diuretics in CHF patients and risk of SCD. However, no such correlation has been observed in case of potassium-sparing diuretics use, either alone or in combination with other diuretics. RALES study (1,663 patients) was ended before scheduled time because patients with severe CHF treated with spironolactone after 2 years of follow up had significantly lower overall mortality (35% vs. 46%) and SCD rates (10% vs. 13%) compared with patients managed with loop diuretics. No significant reduction in ventricular arrhythmias detection rates was noted [15]. It was shown that electrolyte disturbances arising from administration of diuretics not belonging to the class of potassium-sparing agents might contribute to fatal arrhythmias, while aldosterone antagonists are likely to play a protective role. Further, it was shown that the antiarrhythmic effect of these drugs was more complex. Aldosterone receptor blockade in addition to the conservation of potassium and magnesium leads to the elimination of systemic vasoconstriction, prevents stimulation of collagen synthesis and fibrosis in myocardium, and has an impact on the autonomic nervous system that actively influences hearth rate. It improves heart rate variability and increases baroreceptors sensitivity [16, 17]. In recent years, studies of a new aldosterone antagonist, eplerenone, have been conducted; they confirm the effectiveness of this class of medications in reducing risk of SCD. Therefore, SCD prevention in patients with CHF should include aldosterone antagonists **(I, A),** it concerns not only patients with severe heart failure but also patients with CHF FC II [18].

Sacubitril/valsartan supramolecular complex is a new medication with the properties of simultaneous blockade of AT_1 receptors and neprilysin, consisting of 6 molecules of valsartan and 6 molecules of sacubitril, sodium and water cations. Sacubitril provides for a blockade of neprilysin (Zn-containing metalloproteinase produced by the vascular endothelium, which ensures the degradation of Na-uretic peptides and bradykinin), valsartan provides for a blockade of AT_1 receptors. Both components in a single molecule are represented at the ratio of 1:1 [19]. The supramolecular complex of sacubitril+valsartan (Uperio) promotes the restoration and sustention of neurohormonal systems balance due to the complex influence on RAAS and natriuretic peptides activation, belongs to ARNI (angiotensin receptors and neprilysin inhibitor) which is a new class of drugs. Comparison of patients groups treated with the supramolecular complex of sacubitril + valsartan (Uperio) 200 mg 2 times a day or enalapril ACE inhibitor 10 mg twice a day within a PARADIGM-HF study (8,442 FC II-IV NYHA patients included) showed that total mortality decreased by 16% (OR **0.84**, 95% CI 0.76-0.93) $p < 0.001$), and sudden cardiac death decreased by 20% (OR 0.80, 95% CI 0.68-0.94) $p = 0.008$ [20]. The experts expressed cautious optimism in the interpretation of these data, since only those patients who did not demonstrate intolerance to ACE inhibitors (with average therapy duration of 15 days) and Uperio (with average duration therapy of 29 days) were included in the study according to the protocol.

Aspirin. It has been clearly proven that aspirin has positive effects for both primary and secondary prevention of coronary events. In addition to the antiplatelet properties, the medication has anti-inflammatory properties and reduces remodeling processes in healthy tissues. A retrospective analysis of the SOLVD study showed that in CHF patients aspirin reduced incidence of SCD by 24% [21]. According to current guidelines, both domestic and foreign, the drug is included in standard preventive care of post-AMI patients, as well as patients with stable angina and acute coronary syndrome **(I, A).**

Statins. A literature review regarding the use of statins in patients with coronary artery disease suggests that they significantly reduce cardiovascular mortality. In most of the conducted clinical trials, SCD was not evaluated as an endpoint. However, the 4S study demonstrated a significant decrease as cardiac mortality and SCD rate during simvastatin use. Similar results were obtained with respect to pravastatin (LIPID). Large meta-analysis of 90,000 patients who participated in 14 randomized trials in 2005, conclusively proved statins effectiveness in prevention of SCD in CAD patients [22]. Therefore, current guidelines on SCD prevention in patients with CAD include statins as a mandatory medication class **(I, A)** [7, 23]. Statins are recommended for all high cardiovascular risk group patients to prevent cardiovascular complications.

Regarding the statins use for SCD prevention in patients with nonischemic CHF, there are currently no evidence to recommend these medications for such patients.

Omega-3 polyunsaturated fatty acids (PUFA). The first reports on the effectiveness of PUFA in SCD prevention were obtained in the DART study that showed that individuals who consumed oily fish two times a week or more often had 30% reduction in cardiovascular mortality, mainly due to the decrease in VF incidence.

Later the hypothesis was tested in animal models, and for instance, it was shown that ω-3-PUFAs (main fatty acids of oily fish) had a protective effect against VF. The mechanisms of antiarrhythmic action of ω-3-PUFAs were studied; it was shown that they stabilize cardiomyocytes membrane in ischemia or adrenergic stimulation, interfering with sodium, potassium and calcium ion channels. They act like class Ib antiarrhythmic agents (mexiletine-like effect), but without proarrhythmic or antiarrhythmic effects. From the electrophysiological point of view, the protective effect of ω-3-PUFA is that for the «arrhythmic» action potential to be induced higher electric amplitude is required during their use; the duration of cardiomyocytes effective refractory period in also increased, which decreases likelihood of fatal arrhythmias, including ventricular fibrillation [24].

In addition to the antiarrhythmic effect, these drugs demonstrate anti-inflammatory effects, reduce the formation of oxygen radicals and reperfusion complications, increase mitochondrial activity, improve endothelial function, reduce thromboxane level and platelet aggregation. Several studies have shown that ω-3-PUFAs increase LVEF parameters and improve HRV parameters, thus modifying major and minor risk factors of SCD [25].

Convincing evidence in support of ω-3-PUFAs was obtained in two large clinical trials. In GISSI-prevenzione study, use of the Omacor medication, 1 g/day, in AMI patients was associated with significant reduction in SCD risk by 45%, cardiovascular mortality by 30% and total death risk by 20% [26]. Results of a multicenter, double-blind, placebo-controlled trial GISSI-HF, published in 2008, showed that in patients with CHF Omacor 1 g/day combined with optimal medical therapy was associated with reduction of total mortality rate by 9% and reduction in hospitalizations for ventricular arrhythmias. The number of side effects in ω-3-PUFA group did not differ from the one in control group [27].

There is a number of publications that describe effects of Omacor on the severity of ventricular arrhythmias. In one of them, a month of adjunctive therapy with ω-3 fatty acids in patients with stable CAD resulted in a statistically significant decrease in a number of non-sustained ventricular tachycardia episodes and PVCs [28].

Thus, to date, the preventive effect of ω-3 fatty acids on SCD risk reduction in patients with history of myocardial infarction has been convincingly demonstrated. According to current guidelines, post-MI patients should consume 1 gram of ω-3 fatty acids (namely, Omacor) per day and arrange «fish days» (about 200 g of oily fish) at least twice a week [29, 30]. Data about the use of ω-3 fatty acids for secondary prevention of SCD in patients who survived circulatory arrest is currently limited, but trials on this subject, particularly in patients with ICDs, are being conducted.

Nitrates. Since one of the mechanisms of SCD is an ischemic event, nitrates may be beneficial in SCD prevention in such patients. No long-term randomized trials evaluating effects of antianginal therapy on ventricular arrhythmias has been conducted. These medications are not included in the international and national guidelines. Nevertheless, there are data supporting a positive effect of nitrate therapy on ventricular ectopic activity, and their use in treatment ischemic ventricular arrhythmias may be discussed [31].

IC class antiarrhythmic agents. Use of AAA for SCD prevention has significant limitations, and in some cases, according to multicenter randomized trials, they may increase risk of serious adverse outcomes. In particular, according to CAST and CAST-II trials, IC class agents use in patients with ventricular arrhythmias and history of acute myocardial infarction is accompanied by a significant increase in SCD characteristics [32, 33]. However, there is a number of situations in which AAA use can be justified.

First of all, they can be used in patients with implantable cardioverter-defibrillators (ICD) and frequent ICD interventions for recurrent VT/VF. The worst case of this situation is called arrhythmic storm and requires additional antiarrhythmic therapy of VT and reduction of the number of ICD interventions.

Amiodarone and sotalol. Antiarrhythmic effects of class III agents such as amiodarone and sotalol are associated with action potential prolongation and increased duration of refractory period, which contributes to interruption of the re-entry loop and also suppresses arrhythmias arising from the triggered activity. Positive effects of amiodarone and sotalol on arrhythmia are also due to their anti-ischemic effects, decrease in heart rate, neuromodulating action and effects on left ventricular function [34]. Data regarding their effects on long-term survival are inconclusive. A number of clinical trials and one meta-analysis (that included data of several large studies) have shown reductions in SCD rate with amiodarone treatment in patients with left ventricular dysfunction after myocardial infarction and nonischemic dilated cardiomyopathy [35]. However, most of the patients in these clinical trials were treated with combination of amiodarone and β-adrenergic blocking agents. Large, well-designed SCD-

HeFT study that evaluated amiodarone effectiveness for SCD prevention in patients with CHF did not show benefit over placebo in patients with CHF FC NYHA II–III [36].

At the same time, it should be noted that sotalol and amiodarone as are effective agents for the ventricular arrhythmias treatment. They lengthen QT interval and may therefore have proarrhythmic effect.

Currently, there are no data supporting class III AAA use to improve survival in patients with cardiac disease and VRD. Their administration may be warranted in patients with ventricular arrhythmias in combination with β-adrenergic blocking agents (for amiodarone – **IIa, B**; for sotalol – **IIa, C**) with careful monitoring for possible side effects as well as arrhythmogenic and proarrhythmic effects.

In conclusion, the highest level of evidence for SCD prevention is available for β-adrenergic blocking agents that should be administered (unless contraindicated) for primary prevention of SCD in all patients who have had a myocardial infarction, and patients with left ventricular systolic dysfunction (both ischemic and non-ischemic origin), regardless of the history of arrhythmias [7, 37, 38, 42].

For the same purpose, post-MI patients are administered with ACE inhibitors/ARBs, statins, aspirin, ω-3 fatty acids [39–41]. In patients with non-ischemic heart failure, ACEI/ARBs, aldosterone antagonists, ω-3 fatty acids are indicated [27].

Interventional methods

This section discusses the use of current interventional methods for SCD prevention. Each of them has different indication classes and level of evidence, those depend on primary diagnosis, CHF FC, LV systolic function, signs and symptoms and nature of the rhythm disturbance.

Implantable cardioverter-defibrillator

Nowadays, ICD therapy has become one of the main methods of SCD preventing in a group of high-risk patients. For example, in 2014 in 56 European countries in 2,052 centers there were 85,289 ICD implantations performed (including 13 operations per 1 million of population in Russia) [43].

The risk of recurrent episodes of persistent ventricular tachycardia or VF in patients who survived the first arrhythmic episode is 19%, 33% and 43% after 1, 3 and 5 years of follow-up, respectively [44].

ICD effectiveness in SCD prevention has been proven in several large clinical trials (**Table VIII.1**) which were designed to assess survival in patients with major SCD risk factors identified by JT Bigger in 1984) [45]. The results of these

Table VIII.1

Studies evaluating ICD for primary and secondary prevention of SCD

Study, year of the results publication	Study objective	Number of subjects	Follow-up period	Results
Secondary prevention				
AVID 1997 [95]	Comparison of antiarrhythmic agents and ICD in patients with history of cardiac arrest	1,016	13 months	Total mortality reduction in ICD subgroup by 29%
CASH 2000 [97]	Comparison of antiarrhythmic agents and ICD in patients with history of cardiac arrest	288	57 months	In ICD group, overall mortality was 23% lower and arrhythmic mortality was 61% lower
CIDS 2000 [96]	Comparison of amiodarone therapy and ICD in patients with history of cardiac arrest	659	3 years	In ICD group, overall mortality was 20% lower and arrhythmic mortality was 31% lower
Primary prevention				
MADIT 1996 [98]	Comparison of ICD and antiarrhythmic agents in patients with history of myocardial infarction, ejection fraction of less than 35%, non-sustained ventricular tachycardia and induced sustained VT during endocardial ES	196	27 months	Total mortality reduction in ICD subgroup by 54%
GABG-Patch 1997 [100]	Comparison of ICD+CABG and antiarrhythmic therapy+ CABG effects on overall mortality in patients with ejection fraction of less than 35%	900	32 months	Indicators of overall mortality did not differ between groups
MUSTT 1999 [99]	Comparison of ICD and standard CAD therapy in patients with history of acute myocardial infarction, ejection fraction of less than 40%, non-sustained ventricular tachycardia and induced sustained VT during endocardial ES	659	5 years	Total mortality decreased in ICD subgroup by 31% and 24% compared with antiarrhythmic therapy group and standard CAD therapy group, respectively
MADIT II 2002 [101]	Comparison of ICD and standard CAD therapy in patients with history of acute myocardial infarction, ejection fraction of less than 30%	1,232	20 months	Absolute risk of total mortality reduction in ICD subgroup by 56%
CAT 2002 [102]	Comparison of standard CHF therapy and its combination with ICD in patients with DCM, EF < 30%	104	66 months	Absolute risk of total mortality reduction in ICD subgroup by 55%

Study, year of the results publication	Study objective	Number of subjects	Follow-up period	Results
AMIOVIRT 2003 [103]	Comparison of ICD and amiodarone therapy in patients with DCM, ejection fraction of less than 35% and non-sustained ventricular tachycardia	103	24 months	Absolute risk of total mortality reduction in ICD subgroup by 17%
DEFINITE 2004 [104]	Comparison of standard CHF therapy and its combination with ICD in patients with DCM, EF < 36%, non-sustained ventricular tachycardia and PVCs	468	29 months	Absolute risk of total mortality reduction in ICD subgroup by 52%
DINAMIT 2004 [105]	Comparison of standard treatment of AMI and its combination with ICD placement during subacute (6 to 40 days) period of AMI	674	30 months	ICD implantation in subacute period of AMI does not reduce total mortality, but reduces arrhythmic mortality
COMPANION 2004 [106]	Comparison of ICD in combination with cardiac resynchronization therapy (CRT), isolated cardiac resynchronization therapy and standard CHF therapy	1,520	12 months	Absolute risk of total mortality reduction in ICD-CRT subgroup by 36%
SCD-HeFT 2005 [34]	Comparison of ICD, amiodarone and placebo in patients with CHF NYHA FC II–III, EF < 35% (etiology: CAD – 55%, DCM – 45%)	2,521	45 months	Total mortality reduction in ICD subgroup by 23%

Note: CAD – coronary artery disease; PVCs – premature ventricular contractions; VT – ventricular tachycardia; DCM – dilated cardiomyopathy; EF – ejection fraction; LBBB – left bundle branch block; ICD – Implantable Cardioverter Defibrillator; Echo – echocardiography; NVT – non-sustained ventricular tachycardia; AMI – acute myocardial infarction; CHF – congestive heart failure; ICD-CRT – implantable cardioverter-defibrillator with cardiac resynchronization function.

trials formed the basis for current Guidelines for ICD use and management of patients with ventricular arrhythmias and the prevention of SCD [46].

Radiofrequency ablation

Catheter radiofrequency ablation (RFA) is one of the interventional procedures that can effectively eliminate or modify the substrate of one of the major SCD risk factors, namely, VT and/or VF. Possibility of RFA use depends on arrhythmia etiology and its particularities. RFA is warranted in patients with frequent ICD shocks and so-called «electrical storm» (more than three justified ICD shocks within 24 hours) due to recurrent sustained ventricular tachycardia refractory to multiple antiarrhythmic agents [47–49]. However,

data on RFA effectiveness for SCD prevention are currently limited, largely because the cohort of patients with ventricular tachycardia is heterogeneous and randomization of these patients is complicated.

There are different methods of VT RFA. The technique of entering the reentry tachycardia cycle with the purpose of determining its critical zone with subsequent ablation is considered to be classical. In a number of cases, in clinical practice, it is necessary to deal with a hemodynamically unstable VT, long-lasting mapping of which is impossible. In these cases, it is advisable to use hemodynamic support systems during the operation, but this increases the cost and risks of the procedure [50]. Many patients with VT, caused by the presence of cicatricial changes in the myocardium, have a complex structure of the tachycardia substrate, which can be evidenced by a multitude of VT morphologies.

An alternative to this technique can be the mapping of the tachycardia substrate by means of the navigation system by identifying the scar tissue and slow conduction zones inside the cicatrix followed by their ablation. The end point of this procedure will be not only the absence of tachycardia induction, but also the elimination of delayed activity within the scar tissue [51].

In a number of cases, mainly in patients with right ventricular arrhythmogenic dysplasia [52], dilated cardiomyopathy [53], and with coronary artery disease with myocardial infarction of lower localization [54], the incidence of epicardial localization of scar tissue is high. The use of epicardial approach is related to an additional risk of damage to the heart walls and coronary arteries and should be performed only in clinics with extensive experience in these procedures.

Conduction of repeated shock therapy in patients with ICD is associated with a decrease in the quality of patients' life [56], and an increase in overall mortality [57]. The implementation of RFA in this category leads to a significant decrease in the probability of repeated ICD shock discharges in comparison with antiarrhythmic drug therapy [58, 59].

X-ray endovascular treatment of IHD in SCD prevention

SCD, the main etiological factor of which is the arterial sclerotic disease, is one of the leading causes of mortality in CAD patients. It is true that all measures aimed at improving the prognosis, survival rates in patients with coronary heart disease are preventive in reducing the risk of sudden cardiac death [7, 60].

In accordance with the European recommendations on myocardial revascularization, coronary angiography (and PCI, if necessary) is indicated as soon as possible in survivors or resuscitated after sudden cardiac death

(IIa class of recommendations, B level of evidence), in patients with electrical storm, emergency coronary angiography and, if necessary, direct myocardial revascularization **(IIa class of recommendations, C level of evidence)** should be considered [61].

Methods of direct myocardial revascularization, introduced into clinical practice since the 1970s, fundamentally improved the quality of life and prognosis in patients with CAD and, therefore, play a crucial role in secondary prevention of SCD [60, 61]. X-ray endovascular treatment is currently a highly effective and widely used method of direct myocardial revascularization in CAD patients, being in a rather large number of cases a direct alternative to traditional surgical correction, i.e. aorto-coronary bypass graft [61, 62]. The use of stents with a medicinal antiproliferative coating in performing percutaneous coronary interventions (PCI) has significantly improved the long-term results of X-ray-endovascular treatment in the most complex forms of coronary bed lesion [61, 62]. The high effectiveness of the intervention method in the treatment of patients with acute disorders of coronary circulation has been convincingly proven, in the observance of the time interval, PCI is a method of choice in the treatment of patients with ST segment elevation acute myocardial infarction (STEAMI) and non-ST segment elevation acute myocardial infarction (NSTEAMI) [61, 62].

When determining indications for direct myocardial revascularization – surgical or x-ray endovascular one – it is necessary to take into account the clinical form, the morphology of the coronary arteries disease, the functional state of the myocardium, the presence and severity of concomitant cardiac and extracardiac pathology, risk factors associated with one or another treatment method [62 , 63]. The aim of direct myocardial revascularization is to improve the quality of life: improvement of the clinical state, pain management, increase in stress tolerance, and decrease of circulatory insufficiency evidences [62, 63]. Another and even more important task is to improve the disease prognosis: increase in life expectancy by reducing the number of major cardiac complications, i.e. mortality and myocardial infarction, including cases of SCD caused by these complications of coronary heart disease [62, 63].

The greatest positive effect on both clinical condition and prognosis is achieved if the stenoses causing myocardial ischemia are eliminated. In acute coronary artery circulation disorders, identification of these target stenoses does not cause any complications [61], whereas in patients with stable CAD, especially in the case of multiple coronary artery disease, this can be difficult [61, 63, 64]. In addition to angiographic evaluation, both non-invasive diagnostic methods, i.e. stress tests, stress echocardiography, myocardial scintigraphy, and intravascular imaging methods, measurement of the coronary blood flow

fractional reserve against the background of maximal coronary hyperemia [62, 63, 64], are essential. The precise identification and elimination of ischemia-causing stenoses and the rejection of routine coarctation stenting that do not cause myocardial ischemia make it possible to significantly improve the results of x-ray endovascular treatment in this group of patients [62–65].

Acute coronary artery circulation disorders are associated with extremely poor prognosis and high mortality. It is in this group of patients that x-ray-endovascular methods of treatment can significantly reduce the frequency of mortality and, thereby, improve the disease prognosis [7, 61]. In patients with stable angina in determining the benefits of direct revascularization over conservative therapy, the option and prevalence of coronary artery disease is important: the greater myocardial volume is susceptible to ischemia, the less effective drug therapy is, the more expedient the direct (surgical or X-ray-endovascular) revascularization is. Thus, left coronary artery (LCA) trunk disease is associated with an extremely unfavorable prognosis and is a direct indication for direct myocardial revascularization [61, 62, 66]. In the 1970s it was demonstrated that SCD in the group of patients with disease of the LCA trunk develops 3–4 times more often than in other variants of coronary bed lesion [66], on the basis of which N.S. Gotsman et al., indicating a high risk of SCD in these patients, called the LCA trunk “the artery of sudden death” [67]. In addition, stenosis of the proximal segment of the LCA anterior interventricular branch, isolated or in combination with lesions of other sites [61, 68, 69] is associated with an unfavorable prognosis.

The most preferred method of treating patients with complicated forms of lesion is still surgical one **(Table VIII.2).** It should be borne in mind that the recommendations in Table VIII.2 are only valid for patients at low risk of surgical correction. Thus, in a number of cases in patients at high risk of surgical treatment, the expected long-term benefits can be leveled by the likelihood of serious complications at the hospital stage, which may be an argument in favor of choosing an interventional method of treatment [65, 68]. When determining possible indications for X-ray endovascular treatment, one must also take into account the probability of successful elimination of all hemodynamically significant lesions. Since a more complete volume of revascularization is associated with better long-term results, with comparable risks of performing a particular treatment method, a preference should be given to this type of revascularization, which will allow the most complete volume of ischemic myocardium revascularization [64]. Incomplete, inadequate myocardial revascularization leads to unsatisfactory clinical results in a separated follow-up period [70, 71]. In the study of A. Colombo et al., it was demonstrated on a rather large clinical material (1,345 patients) that the presence of unresolved

large epicardial artery occlusion leads to an increase in mortality in the long-term follow-up period, including that due to SCD [71]. Thus, by 4 years of follow-up, in the group of patients with successful recanalization of occluded arteries (847 patients), the incidence of cardiac mortality was 2.5%, whereas in patients with failed recanalization (498 patients), this index reached 8.5% (p <0 , 0001). The incidence of SCD in the first group was 0.5%, and in the second group it was 2.7% (p = 0.001) [71]. Additional risk factors for cardiac mortality and SCD in the group of patients with incomplete revascularization were chronic renal failure, decreased left ventricular ejection fraction, insulin-dependent diabetes mellitus. Achievement of an adequate revascularization volume in the case of multivessel lesions, including stenosis of the LCA trunk, is of particular importance. Thus, the presence of unresolved occlusion of the right coronary artery in patients subjected to the stenting of the LCA is associated with a higher risk of cardiac mortality, by 5 years of follow-up this indicator was 22.7% in this group compared with 6.6% in patients with complete revascularization (p <0.001) [71]. Thus, the achievement of an adequate volume of revascularization can significantly reduce the risk of cardiac mortality associated, among other things, with SCD in patients with coronary artery disease [64, 70, 71].

Patients with stable coronary artery disease with a reduced left ventricular ejection fraction of less than 35% have an increased risk of SCD development and may be considered candidates for the implantation of a cardioverter-

Table VIII.2

Indications for coronary artery bypass graft surgery or percutaneous coronary intervention in patients with stable angina with lesions appropriate for both procedures and associated with a low predictable surgical lethality

Anatomical variant of coronary bed lesion	Coronary artery bypass grafting preferred	Percutaneous coronary intervention preferred
Single or double vessel disease without proximal stenosis of anterior interventricular branch (AIVB)	IIb C	IC
Single-vessel disease with AIBV proximal stenosis	IA	I A
double vessel disease with AIBV proximal stenosis	I B	I C
Three-vessel disease, SYNTAX score ≤22	IA	IB
Three-vessel disease, SYNTAX score 23–32	IA	IIIB
Three-vessel disease, SYNTAX score >32	IA	IIIB
LCA trunk disease, SYNTAX score ≤22	I B	I B
LCA trunk disease, SYNTAX score 23–32	IA	IIa B
LCA trunk disease, SYNTAX score >32	IA	III B

defibrillator, but in the presence of a viable myocardium, revascularization may potentially improve systolic LV function, reduce the risk of ventricular arrhythmias and prevent SCD [61]. Myocardial revascularization is justified as the first stage in these patients, ideal solution is in eliminating the narrowing of all arteries supplying viable myocardium with the decision to implant a cardioverter-defibrillator 3 months after assessing the effectiveness and effect of revascularization on the contractile function of the left ventricle [61].

It is necessary to single out a group of patients resuscitated after SCD. Patients with established or probable coronary artery disease, SCD survivors or those who have life-threatening ventricular arrhythmias should necessarily undergo angiographic examinations to assess the state of the coronary arteries and cardiac risk (**I recommendation class, B level of evidence)** [72]. Direct revascularization, i.e. CABG or PCI, is certainly indicated in SCD survivors who can be suspected to have ventricular rhythm disturbances induced by ischemia due to hemodynamically significant (> 70%) stenosis of the major epicardial artery (**recommendation class I, level of evidence for CABG is B, for PCI is C**) [72]. Coronary revascularization in order to reduce SCD risk is indicated in patients with stable coronary artery disease in cases of acute myocardial ischemia accompanied by ventricular fibrillation (**I recommendation class, B level of evidence**) [62].

Acute coronary artery disorders, i.e. STEAMI, unstable angina and NSTEAMI, occupy a leading place in the structure of mortality associated with coronary artery disease [61,73] and are the cause of SCD in more than 50% of patients with coronary heart disease [1, 2, 4]. Acute occlusion in the case of STEAMI development, or acute myocardial ischemia without total occlusion (with NSTEACS) in the vast majority of cases lead to ventricular rhythm disturbances, which are the leading cause of SCD. Over the last decades, PCI with stenting has convincingly proved its effectiveness as a method of primary reperfusion therapy in patients with STEAMI [61, 73–75]. The greatest effectiveness of endovascular treatment is achieved when performing interventions in the early periods (90–120 minutes) from the development of AMI. The main task practical healthcare face in providing effective assistance to the population is the organization of a round-the-clock network of X-ray and endovascular treatment departments with the possibility of implementing PCI as early as possible as the primary method of reperfusion therapy [61, 73].

Patients with NSTEACS represent an extremely heterogeneous group with respect to the risk of developing serious cardiac complications. Undoubtedly, destabilization of atherosclerotic plaque leading either to the debut of the disease or to the “exacerbation” of stable coronary artery disease, without timely and adequate treatment, can lead to the progression of lumen obstruction

(up to complete occlusion) and development of extensive transmural AMI [61]. In determining the indications for early or delayed invasive treatment, a comprehensive assessment of the patient's condition should be conducted, which determines the possible risk of unfavorable cardiac complications, on the basis of which a decision on the expediency and timing of coronary angiography and, if there are indications, PCI should be made [61].

It should be noted that NSTEACS is the most frequent evidence of coronary artery disease, its lethality remains high and is generally comparable in the long-term period with lethality in STEAMI [61]. The tasks of coronary angiography and subsequent revascularization are improvement of symptoms and prognosis (lifetime). The quality of life, period of hospitalization and potential risks associated with invasive and conservative treatment should be taken into account when choosing a treatment strategy [61]. Early stratification is extremely important for identifying patients at high early and long-term risk of adverse cardiovascular complications in whom an early invasive strategy with adjuvant pharmacotherapy can improve the prognosis [61]. Patients with

Table VIII.3

Recommendations for the implementation of myocardial revascularization in patients with NSTEACS

Recommendations	Class of recommendations	Level of evidence
An emergency (<2 hours) coronarography is indicated in patients at a very high risk of ischemic complications (refractory angina with concomitant heart failure or cardiogenic shock, life-threatening ventricular CRD, or hemodynamic instability.	I	C
An early invasive strategy (<24 hours) is indicated in patients who have ≥1 of primary risk criterion	I	A
Invasive strategy (<72 hours after symptom development) is indicated in patients who have ≥1 of primary high-risk criterion (Table 7) or recurrent clinical evidences.	I	A
Non-invasive documentation of induced ischemia is indicated in low-risk patients without recurrent symptoms before choosing invasive strategy.	I	A
The choice of the revascularization method (PCI for ischemia responsible artery / multivessel stenting / CABG) is performed on the basis of the clinical condition, severity and prevalence of the lesion, concomitant pathology in conjunction with cardiologists, cardiovascular surgeons, i.e. the "cardiological team".	I	C
Stents with a 2-3-generation coating are indicated for x-ray endovascular treatment of severe lesions in patients with ACS.	I	A

cardiogenic shock or SCD resuscitated should undergo immediate (<2 hours) coronary angiography because of the high probability of having significant coronary artery lesions, but it is also extremely important to identify low-risk patients in whom the invasive strategy leads to less pronounced benefits or even leads to increased risk of adverse complications [61].

Table VIII.3 provides recommendations on the implementation of revascularization in patients with NSTEACS [61].

As follows from the data in Table VIII.3, patients at high risk should necessarily undergo coronary angiography. The choice of the revascularization method (CABG or PCI) is carried out in accordance with the general principles given earlier, however, preference should be given to the X-ray endovascular method, as in this group of patients it is associated with a lower risk of complications [61]. Only in case of a complex multivessel lesion with a high-risk morphology and a high risk of complications in the implementation of PCI a decision about the emergency CABG operation can be made [61].

Surgical myocardial revascularization

In recent years, the success in the surgical and medical treatment of coronary artery disease has been associated with a decrease in the number of sudden deaths. However, the proportion of SCD in the mortality of patients with coronary artery disease has not decreased, a decrease in the total number of SCD cases is associated with a reduction in total mortality from coronary artery disease [76, 77]. The most revealing are the statistics on SCD in the Framingham study. Fox et al. [76] compared the mortality of patients with coronary artery disease in studies of 1950–1969 and 1990–1999. According to the authors, the overall mortality of patients with CAD decreased by 59%, and the number of sudden cardiac deaths decreased by 49% in two time samples.

Myocardial revascularization is one of the main methods of CAD treatment. In the Russian Federation, according to the Ministry of Health, 280 coronary artery bypass graft operations (CABG) and 420 coronary artery (CA) stenting operations per 1 million of population were performed in 2011. Considering the large number of patients who underwent these operations, the problem of SCD risk stratification and prevention after myocardial revascularization is very relevant.

SCD pathophysiology in patients with CAD is determined by three related factors: coronary artery damage, myocardial damage and chronic changes in the physiology of the left ventricular myocardium. All these factors are interrelated, and, together or separately, can be a cause of SCD.

Potentially fatal ventricular arrhythmias can occur both during the very myocardial ischemia, when the transmembrane potential of the cardiomyocyte

changes, and during myocardial reperfusion [78]. With the blood flow recovery, a local action potential lengthening, a sort of local "long QT", occurs in the area of the myocardium [79]. This may be the reason for trigger ventricular arrhythmias, which, in their turn, can initiate the occurrence of reentry tachycardia in patients with structurally altered myocardium. Probably, transient myocardial ischemia is a trigger factor in those cases when CAD debuts a sudden death. Myocardial revascularization in the detection of hemodynamically significant stenoses of the coronary arteries reduces the risk of repeated ischemic events and associated episodes of ventricular tachyarrhythmias.

In the acute phase of myocardial infarction (up to 48 hours), various pathophysiological processes take place in the affected areas of the heart muscle. In addition to the changes that are characteristic of myocardial ischemia and reperfusion, changes in the local cardiac impulse conduction velocity are observed in the affected area of the cardiac muscle. Early interventions blood flow recovery in the infarction zone can stabilize the myocardium and lead to a reduction in the risk of SCD in the acute phase of myocardial infarction [80].

In the subacute period, the process of scar formation takes place in the affected area. The main mechanism of SCD in this period is reentrant tachycardia. With long-term follow-up of post MI-patients, the likelihood of sudden death increases. This is not only due to the presence of left ventricular cicatrix as a ventricular tachycardia substrate, but also to myocardial remodeling, i.e. ischemic cardiomyopathy development [81]. Episodes of myocardial ischemia in this group of patients may trigger triggering of ventricular arrhythmias and worsen the course of heart failure.

Myocardial ischemia is a SCD trigger, and the potential risk reduction after myocardial revascularization has been evaluated by different investigators. Current evidence indicates a positive effect of hibernating myocardium revascularization on the contractile function of the left ventricle.

CASS (Coronary artery surgery study) [82] and VA (Veterans administration) [83] studies have shown a statistically significant reduction in mortality in the group of post myocardial revascularization patients compared with drug therapy. Other studies have shown the maximum benefits of myocardial revascularization to improve patient survival with viable myocardium [84, 85]. The reduction in mortality in these studies was also associated with an increase in the ejection fraction and a decrease in the volume of the left ventricle after revascularization.

Despite the fact that myocardial revascularization is associated with a reduction in the risk of ischemic events that may be a trigger for ventricular tachyarrhythmias, its impact on the risk mitigation of SCD not associated with acute myocardial ischemia remains insufficiently investigated. In the

study of Brugada et al. [86], the induction of ventricular arrhythmias in ES and the recurrence of spontaneous ventricular arrhythmias were estimated during follow-up after myocardial revascularization. Despite revascularization, induction and recurrence risk of ventricular arrhythmias remained high in patients with pre-existing arrhythmias. This observation is an evidence of the fact that myocardial revascularization does not lead to a modification of the already formed substrate of ventricular tachycardia.

However, not in all clinical situations, ICD implantation brings significant advantages in survival in post-MI patients. Patients referred for coronary artery bypass grafting with an ejection fraction of less than 36% and an abnormal signal-averaged ECG were included in a randomized study of Coronary Artery Bypass Graft (CABG) Patch Trial [87]. The first key feature of the study was the inclusion of patients referred for aorto-coronary bypass grafting with an assessment of the ejection fraction before revascularization. The ejection fraction observed after revascularization in these patients became higher than at the time of implantation of the device. The second feature of this study was epicardial implantation of defibrillation electrodes, which was not widely used in the future. The result of the study was approximately the same overall mortality in groups with ICDs and with drug therapy. The ICD group had fewer arrhythmic deaths (4.0% in the ICD group and 6.9% in the control group), however, had more nonarrhythmic ones [88].

The MADIT II study showed no benefit in the survival of patients who had been implanted with the ICD immediately after myocardial revascularization compared to patients who had been implanted with the ICD 6 months or more after revascularization. In the group of patients without ICD therapy, the overall cardiac mortality increased six months or more after revascularization, mainly due to an increased risk of SCD [89].

Veenhuyzen G.D. et al. study [90] showed the effect of CABG surgery on survival in a large group of 5,410 patients with a left ventricular ejection fraction of less than 36%. Myocardial revascularization was associated with a 25% reduction in the risk of total mortality and a 46% reduction in the risk of SCD, regardless of the degree of reduction in the left ventricular ejection fraction and the severity of heart failure symptoms.

Thus, myocardial revascularization in the group of patients with a low ejection fraction and viable myocardium is associated with a significant reduction in overall and sudden mortality. The left ventricular ejection fraction and other above described risk factors of SCD should be reassessed in the long term after revascularization. On the strength of all the evidence available in existing recommendations [91], myocardial revascularization in patients with a left ventricular ejection fraction of less than 36% belongs **to the first class**

of evidence (B level of evidence), with stenosis of left main coronary artery, its equivalent, proximal stenosis of the anterior interventricular branch of the left coronary artery with of two- or three-vessel lesions. The left ventricular ejection fraction should be reassessed 3 months after revascularization for risk re-stratification and addressing the need for ICD implantation in patients in the absence of sustained ventricular arrhythmias prior to surgery. In patients with the large scar tissue area, restoration of the left ventricular ejection fraction is less likely, and indications include the possibility of implanting ICDs at earlier times. In patients who have had episodes of cardiac arrest or recorded sustained ventricular arrhythmias, the risk of arrhythmia recurrence may persist regardless of myocardial revascularization. ICD implantation prior to the revascularization procedure can be recommended to these patients.

One of the main problems in the treatment of post myocardial revascularization patients is the determination of the necessary timing of ICD implantation. Surveys of survival after CABG and coronary artery stenting showed a significant risk of early death after revascularization in patients with a reduced left ventricular ejection fraction. Implantation of ICD earlier than 6 months after revascularization did not show an effective reduction in mortality in this group of patients.

However, high mortality in the first month after myocardial revascularization was registered in large national registers. According Society of Thoracic Surgeons Adult Cardiac Surgery Database [92] register, which included 348,341 post-CABG patients older than 64 years, mortality in patients with LV ejection fraction was less than 30% in 30 days after surgery was 7.6%, and a year after – 18.6%, and mortality in patients with LV ejection fraction from 30 to 45% was 4.4% and 11.6% accordingly. Thus, mortality in the first 30 days after revascularization was more than a third of mortality in the first year after surgery. According to the National Cardiovascular Data Registry [93], which included 343,466 patients underwent stenting of the coronary arteries; the total mortality after surgery was 3% after 30 days and 6% after 6 months. Thus, mortality in the first 30 days after revascularization was half of the total mortality in this group of patients.

Reduction of the overall mortality in the evaluation of long-term results of myocardial revascularization is due to myocardial remodeling processes leading to an improvement in the systolic function of the left ventricle. Many patients after 3 months after revascularization cease to meet the criteria for primary SCD prevention and do not need ICD therapy due to the increase in the left ventricular ejection fraction.

A modern measure for protecting patients with a low fraction of left ventricular ejection in the first months after myocardial revascularization is wearable

cardioverter-defibrillators. This therapy has become widespread in the US and Europe, but it is not used in Russia at the moment. The results of using a wearable cardioverter-defibrillator according to the Canadian national register, which included 4,958 patients with LV ejection fraction of less than 36%, were evaluated by Zishiri E. T. et al. [94]. Therapy with a wearable cardioverter-defibrillator was associated with a 39% reduction in overall mortality compared to the control group at a 90-day follow-up. In the analysis of the subgroup of post-CABG patients, the total death rate among patients with wearable cardioverter-defibrillator was 3%, in the control group – 7%, in the subgroup of patients who underwent stenting of the coronary arteries, the total mortality in patients with worn cardioverter-defibrillator was 2%, in the control group – 10%.

At the end of the 90-day follow-up period after myocardial revascularization, patients with LV ejection fraction of less than 36% should be implanted with an ICD for primary SCD prevention, patients who have an increase in left ventricular ejection fraction greater than 35%, and episodes of resistant ventricular arrhythmia, ICD implantation is not indicated. The use of wearable cardioverter-defibrillators is a promising direction in improving the survival of patients with low ejection fraction after myocardial revascularization.

It is also necessary to improve the risk stratification in post-MI patients in the long term after myocardial revascularization. Not all post MI and myocardial revascularization patients with ICD for primary SCD prevention have motivated actuations at long-term follow-up. A large number of patients with ICD for primary SCD prevention die from heart failure during long-term follow-up, without suffering any ICD shock discharge. The definition of patients who will potentially have ventricular arrhythmias in the long term after myocardial revascularization is an important problem in modern research

In making a clinical decision, we must understand that myocardial revascularization has a greater effect on the triggers of ventricular arrhythmias than on their substrate. The risk of life-threatening ventricular arrhythmias in post-MI patients remains the highest in the group of patients with a low fraction of the left ventricular ejection. Improvement of risk stratification in the long term after myocardial revascularization is a promising direction for future studies. Implantation of a cardioverter-defibrillator and myocardial revascularization in accordance with existing indications should be used in CAD patients to reduce the risk of sudden cardiac death

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IX. RESUSCITATION PROCEDURE FOR SUDDEN CARDIAC DEATH (ALGORITHMS OF THE NATIONAL COUNCIL FOR RESUSCITATION AND THE EUROPEAN RESUSCITATION COUNCIL)

Cardiopulmonary resuscitation (CPR) is a system of measures aimed at restoring effective blood circulation in case of clinical death.

Basic life support (BLS) includes ensuring airway patency, maintaining blood circulation and breathing without the use of special devices other than barrier ones (facial screen, mask) and automatic external defibrillators (AED). Basic life support can be provided both by persons with or without medical education.

Advanced life support (ALS) is carried out by medical personnel and includes invasive and special techniques (heart rythm analysis, manual defibrillator application, airway patency assurance, assurance of intravenous or intraosseous access, medication administration, etc.) [1–4].

Justification of the importance of early resuscitation activities

Only four events in case of SCD are essential, i.e. providing an increase in the percentage of patients' survival before hospital discharge:

1. **Early detection of SCD and ambulance call-out;**
2. **Immediate beginning of chest compression;**
3. **Immediate defibrillation;**
4. **Set of measures in the postresuscitative period.**

In conditions where cardiac rhythm monitoring is not available, SCD is to be diagnosed for no more than 10 seconds on the following grounds: unconsciousness, absence of normal respiration or agonal breathing, absence of carotid pulse.

In the first minutes after SCD, agonal respiration develops in 40% of the affected persons. Cardiac arrest in the beginning can cause a short convulsive episode, which can be mistaken for epilepsy. The final changes in skin color, usually pallor or cyanosis, are not diagnostic criteria for cardiac arrest. After diagnosing SCD, an emergency service should be immediately notified (at pre-hospital stage – an ambulance, in hospital – intensivists) and CPR should be stared. In most countries of the world the average time from a call to an emergency medical service to the time it arrives at the destination is

5–8 minutes. During this time, the survival of the patient depends on other people being around who should start CPR and use the AED [1, 5–6].

The early start of chest compression increases survival at SCD by 2–3 times. Chest compression and defibrillation performed within 3–5 min of SCD ensure survival in 49–75% of cases. Every minute of delay with defibrillation reduces the likelihood of survival by 10–15%. Early defibrillation is possible if an AED available in a public place [7–9].

Basic life support and automatic external defibrillation

algorithm of basic resuscitation activities (fig. IX.1) [1, 10]

- **Make sure that you, the patient and others are safe; eliminate possible risks** (for example, bare wires, broken glass, moving vehicles, aggressive people, etc.)
- **Check patient's reaction**: shake him/her by the shoulders gently and ask loudly "What's the matter with you?". Persons without medical education should not spend time checking the carotid pulse. *If the patient reacts*, leave him in the same position, try to find out the reasons for what is happening and call for help, assess the patient's condition regularly.
- If the patient does not react – move him/her so that he/she lies on his/her back and open the airways by tilting the head and pushing the chin – press the forehead with a hand, and push the chin down with the other hand. Keeping the airways open, you need to **see, hear and feel <u>normal respiration</u>**, watching the movements of the chest, listening to the noise of breathing and feeling the movement of air on your cheek. Investigate for no more than 10 seconds. Persons with medical education should also assess the presence of carotid pulse during the breath test.
- **Make a decision: respiration is normal, abnormal, or absent**. It should be remembered that in 40% of the affected persons agonal respiration may develop (rare, short, deep convulsive respiratory movements) in the first minutes after the circulatory arrest.
- If the patient breathes normally, accommodate him/her in a safe position, call an ambulance, assess the condition and the presence of normal respiration regularly.
- If the patient has agonal breath or absent one, ask others to **call for help** (ambulance, intensivists) and **bring an automatic external defibrillator** (or do it yourself); **start CPR with chest compression**.
- THUS, CLINICAL SIGNS OF THE CIRCULATION OF THE CIRCULATION ARREST ARE:

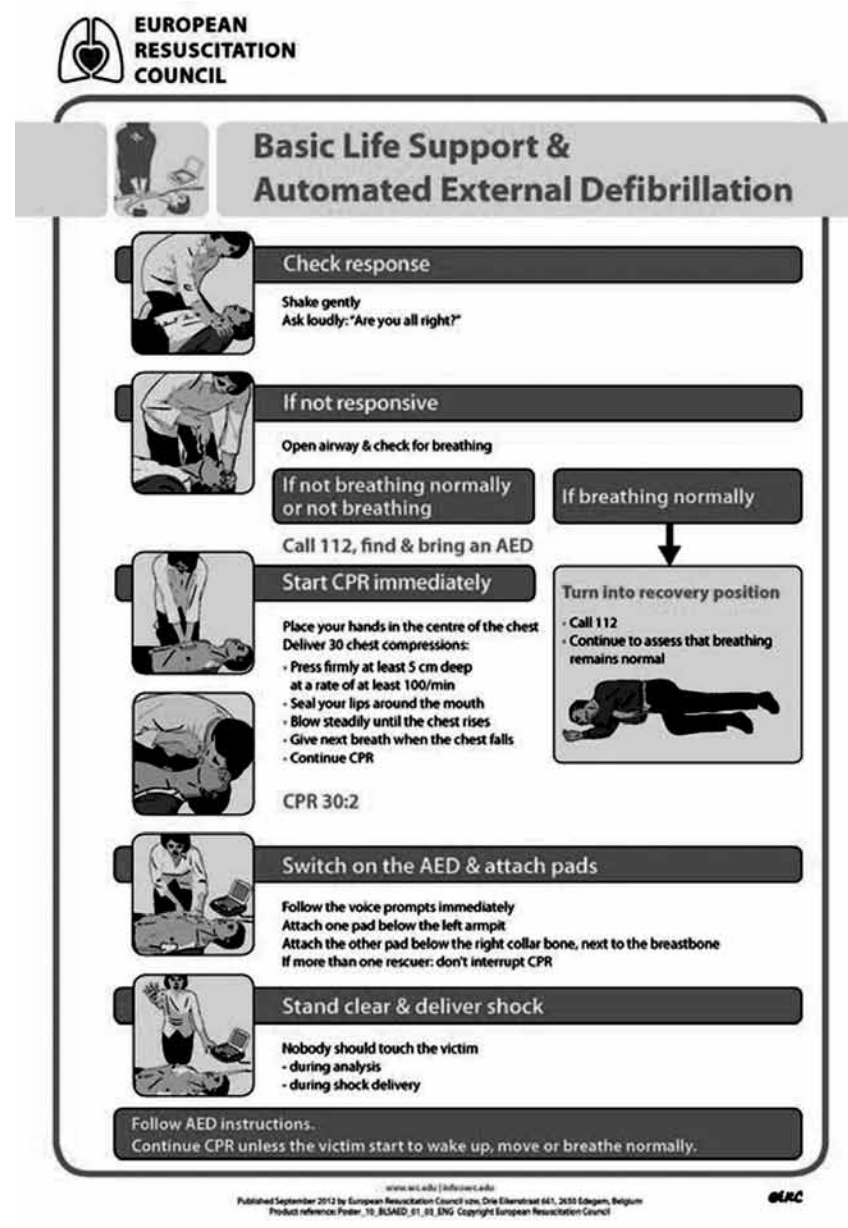

Fig. IX.1 Algorithm for basic resuscitation with the use of an automatic external defibrillator

– unconsciousness
– absence of normal respiration or an agonal respiration
– absence of carotid pulse (this symptom to be assessed only by persons with medical education).

- **Start chest compression:**
  – kneel alongside of the patient;
  – place the heel of one palm on the center of the patient's chest (i.e., on the lower half of the sternum);
  – place the heel of the other palm over the first palm;
  – interlock your fingers and make sure that you do not put pressure on the ribs; bend arms in the elbow joints; do not put pressure on the upper abdomen or lower sternum; we have just placed the hell of the resuscitator's palm in this position
  – place the body vertically above the chest of the patient and press down to a depth of at least 5 cm, but not more than 6 cm;
  – provide complete chest decompression without loss of hands contact with the sternum after each compression;
  – continue chest compression with a frequency of 100 to 120/min;
  – compression and decompression of the chest should take equal time;
  – chest compression should be done only on a hard surface. It is necessary to decompress the pressure reducing support surfaces before starting CPR, using special emergency valve.
  – chest compression should be combined with artificial breaths («mouth-to-mouth», «mouth-to-nose», «mouth-to-tracheostoma»):
  – open the airways as described above after 30 compressions;
  – clamp nose alar with the thumb and forefinger of the hand located on the forehead;
  – open the mouth, pushing the chin;
  – make a normal breath and tightly grasp the patient' mouth with your lips;
  – make a uniform breath for 1 second, while observing the chest lifting, which corresponds to a respiratory volume of about 500–600 ml (sign of an effective inspiration); avoid forced breaths;
  – keeping the airways open, lift your head and watch the chest going down during expiration;
  – if the first artificial breath is ineffective, it is necessary to remove foreign bodies from the patient's mouth and check the adequacy of the airway opening before the next breath. Do not make more than two attempts of artificial breaths;
  – make another artificial breath. In total it is necessary to make 2 artificial breaths, which should take no more than 10 sec. It is not clear: resuscitation is not limited to two breaths. It is necessary to avoid hyperventilation, which worsens the venous return to the heart.

Continue CPR at the compression : ventilation ratio of 30:2. Chest compressions should be performed with minimal intervals.

Algorithm of using the automatic external defibrillator (AED) [1, 10]

1. Start the BLS using the algorithm described above. If the rescuer is alone, and there is already an AED available, start the BLS using the AED.
2. As soon as the AED is delivered to the scene of the event:
   – **turn on the AED** and continue to follow its voice and visual commands;
   – **place electrodes** on the exposed chest of the patient (Fig. IX.1). One electrode is applied to the right side of the chest (under the collarbone, to the right of the sternum, *not onto the sternum*!). The second electrode is applied to the left half of the chest. In the presence of a second rescuer during the application of electrodes, continuous chest compressions should be continued;
   – if the chest is heavily covered with hair, it should be shaved before applying the electrodes (to avoid bad contact of the electrodes with the skin, sparking and burns)! Electrodes cannot be applied to the area of an implanted pacemaker or a cardioverter-defibrillator and transdermal drug systems!
   – **then follow the voice and visual commands of the AED**;
   – make sure that during the rhythm analysis **no one touches the patient** – this can disrupt the rhythm analysis algorithm;
   – the automatic external defibrillator performs an automated heart rhythm analysis according to a specially developed computer algorithm: VF and with wide complex tachycardia are recognized as rhythms requiring defibrillation.
   – if the defibrillation is indicated (VF or wide complex tachycardia), **make sure that no one touches the patient, and press the button** (in case of fully automatic operation mode of AED the button does not need to be pressed); **immediately after the discharge, continue the BLS at the ratio of 30:2;**
   – if the defibrillation is not indicated, **continue the BLS at the ratio of 30:2 without delay, follow the voice and visual commands of the AED**.

Programs of publicly-available defibrillation

It is advisable to place AED in areas where one can expect one cardiac arrest in 5 years (airports, train stations, shopping centers, etc.). At the same time, it is mandatory to train the personnel of such an institution. AED in public

places are labeled with an international symbol. However, placing AEDs in public places does not solve the problem of SCD, which develops at home, and such SCDs have the largest number.

Data on the intrahospital use of AEDs are contradictory. The use of AED may be advisable in those places of the hospital where the resuscitation team will arrive with a delay (more than 3 minutes). In other situations, the use of manual (i.e. non-automatic) defibrillators is preferable [11–13].

When performing ***CPR by two rescuers***, one rescuer performs chest compressions, the other performs artificial ventilation. The rescuer, performing chest compression, loudly counts the number of compressions and gives the command to the second rescuer to perform two breaths. Rescuers change places every 2 minutes. If an AED is available, then one rescuer performs CPR 30:2, the second one works with the AED. AED electrodes should be applied to the chest, without interrupting chest compression.

Advanced life support (fig. IX.2) [14]

The initial part of the algorithm for extended resuscitation is similar to the BLS algorithm [10]:

– **diagnosis of circulatory arrest** (unconsciousness, absent / agonal respiration, no pulse on the main artery);
– **calling for help**;
– **start of chest compressions, continuation of CPR 30:2 until the arrival of specialists**. The technique of chest compressions and artificial ventilation is the same as in BLS.

- If the medical worker is alone, then he must inevitably leave the victim for a while in order to bring equipment and a defibrillator; if there are several medical workers, then it is necessary to immediately identify the leader who will manage the team work.
- An important addition to the SCD diagnostics at the stage of advanced resuscitation is a carotid pulse check (do not spend more than 10 seconds on this).
- Artificial ventilation at the hospital stage, before the arrival of resuscitators, can be provided for with a breathing bag. Always avoid hyperventilation. Use oxygen as soon as possible.

Advanced resuscitation activities differ depending on the initial rhythm, determined by the cardiac monitor. Heart rhythm monitoring is performed either with the help of three standard cardiac monitor leads or with self-adhesive defibrillator electrodes. The latter is preferable for ALS.

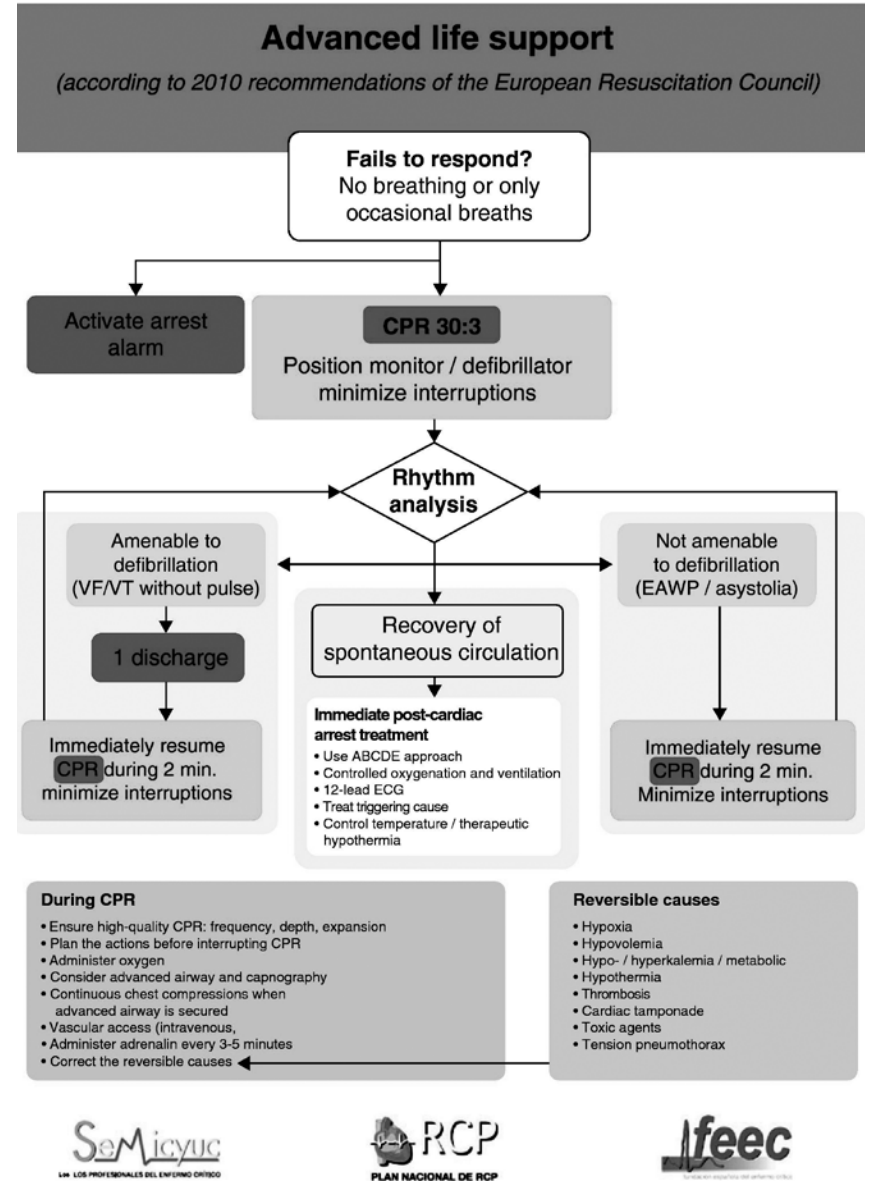

Fig. IX.2 Algorithm of advanced resuscitation.
It is necessary to explain in the text what the ABCDE algorithm is, it is desirable to give a reference

Algorithm to follow in the event of the determination of a rhythm to be defibrillated (ventricular fibrillation or wide complex tachicardy) [14]

- Start CPR at the ratio of 30:2. If there is a cardiac monitor, connect it to the patient.
- **If the SCD occurred in a situation where the patient is connected to the monitor, but there is no defibrillator nearby, then resuscitation can begin with one *chest thrust***: deliver a jerky thrust at the lower part of the sternum from a height of 20 cm with the ulnar margin of the tightly clenched fist. **There are no other indications for the use of a chest thrust**.
- As soon as a defibrillator is delivered/available, apply electrodes to the victim's chest. Begin the heart rhythm analysis. Stop chest compression during the rhythm analysis.
- **Discharge No. 1**. If according to the monitoring data ventricular fibrillation (VF) or wide complex tachycardia is confirmed, apply one discharge (*360 J for monophasic impulse, 150–200 J for biphasic one*) minimizing pauses between ceasing chest compressions and discharge application. The pause between the ceasing of chest compression and discharge is critical and should not exceed 5 seconds [15–17].
- Always remember the safety of the rescuer and others during defibrillation!
- **Always apply only one defibrillator discharge, the next discharge should be applied if there are appropriate indications after 2 minutes**, i.e. immediately after the discharge, without losing time to check the rhythm, immediately resume CPR 30:2 for 2 minutes. The interval between discharge and the resumption of chest compressions should be minimal! Any intervals in chest compressions should be planned by the leader of the resuscitation team in advance. The person performing chest compression should be changed every 2 minutes. **Ensure airway patency** (intubation of the trachea is a priority) and **artificial lung ventilation** (respiratory volume of 6–8 ml/kg, lung ventilation rate to be 8–10/min, oxygen fraction at inspiration to be 100%).
- **After 2 minutes of CPR, stop and check the rhythm on the monitor, spending a minimum amount of time for it**.
- **Discharge No. 2.** If according to the cardiac monitor data VF or wide complex tachycardia is detected again, apply the second discharge (of the same power or more, 150–360 J for the biphasic discharge) and resume 30:2 CPR immediately for 2 min.
- After 2 minutes of CPR, stop and check the rhythm on the monitor, spending a minimum amount of time for it.

- **Discharge No. 3.** If VF or wide complex tachycardia is detected again, apply the third discharge (of the same power or more) and continue CPR 30:2 immediately for 2 min. After applying the third discharge, it is possible to administer medications (adrenaline 1 mg, amiodarone 300 mg intravenously or intraosseously) in parallel with CPR [18–20].
- Next, evaluate the heart rhythm through the cardiac monitor every 2 minutes. If VF or wide complex tachycardia is preserved, continue administration of adrenaline 1 mg intravenously or intraosseously every 3–5 minutes until the spontaneous circulation is returned; administrate another dose of amiodarone 150 mg IV after the 5th defibrillator discharge.
- In case the asystole develops, see the Algorithm to follow in the event of determination of a rhythm that cannot be defibrillated.
- If an organized heart rhythm or signs of spontaneous circulation return are detected on the monitor (*targeted movements, normal respiration, cough, etCO2 increase on the monitor*), **it is necessary to palpate the pulse on the main artery, spending no more than 10 seconds.**
  - If there is a pulse, start treatment according to the postresuscitation algorithm.
  - If there is any doubt about the pulse presence, continue CPR 30:2.

Algorithm to follow in the event of determination of a rhythm that cannot be defibrillated (asystolia, electromechanical dissociation) [14]:

- **Start 30:2 CPR and inject 1 mg adrenaline as soon as access** (intravenous or intraosseous) **is available**. If there is a cardiac monitor, connect it to the patient.
- **Check that the ECG electrodes are correctly applied**! In the presence of P-waves with underlying asystole, cardiac pacing should be applied. If there are doubts about the rhythm (asystole or fine FV), continue CPR, do not attempt defibrillation, which will only increase the damage to the myocardium.
- Ensure airway patency (intubation of the trachea is a priority) and artificial lung ventilation (respiratory volume of 6–8 ml/kg, lung ventilation rate to be 8–10/min, oxygen fraction at inspiration to be 100%). Continue CPR for 2 minutes [21].
- After 2 minutes of CPR, check the rhythm through the cardiac monitor, spending a minimum amount of time.
- **If asystole is detected, continue CPR, inject adrenaline 1 mg every 3–5 minutes intravenously or intraosseously.** If during CPR there are signs of blood circulation return, stop administration of adrenaline and continue CPR until the end of the two-minute cycle.

- Atropin with CPR is not recommended (excluded from the guidelines from 2010)
- If an organized heart rhythm or signs of spontaneous circulation return are detected on the monitor (*targeted movements, normal respiration, cough, etCO2 increase on the monitor*), it is necessary to palpate the pulse on the main artery, spending no more than 10 seconds.
  – If there is a pulse, start treatment according to the postresuscitation algorithm.
  – If there is any doubt about the pulse presence, continue 30:2 CPR.

Notes

Typical mistakes in resuscitation: late onset of chest compressions and defibrillation, delay in calling for specialized care; incorrect technique of chest compressions (*hand position, frequency, depth, decompression, continuity of chest compressions*); untimely and inefficient change of rescuers (*which leads to a decrease in the effectiveness of chest compressions*); ineffective teamwork (*lack of a single leader, inefficient distribution of roles within the team, the presence of unauthorized persons, lack of accounting and control of ongoing resuscitation activities*); loss of time for minor diagnostic, organizational and therapeutic procedures (*which leads to unjustified interruptions in chest compressions and increases lethality)* [1].

When conducting ALS, one should remember **the potentially reversible causes of circulatory arrest** and correct them in a timely manner (hypoxia, hypovolemia, hyper/hypokalemia, hypocalcemia, acidosis, hypothermia, tension pneumothorax, cardiac tamponade, intoxication, pulmonary embolism) [1, 14, 22].

If VF/wide complex tachycardia developed in the presence of medical personnel under monitoring conditions and the defibrillator is available (reanimation department, interventional cardiology department, post anesthesia care unit, etc.), then after SCD diagnosis **three consecutive defibrillator discharges should be applied immediately with evaluation after each discharge of the rhythm through the cardiac monitor**. If an organized rhythm is recorded from on the cardiac monitor (i.e. not VF or asystole), check the carotid pulse. If three consecutive discharges are ineffective, start 30:2 CPR and then follow the algorithm described above.

Persistent VF/wide complex tachycardia is an indication for percutaneous coronary intervention to eliminate the cause of arrhythmia, i.e. coronary artery thrombosis. In this situation, the patient undergoes percutaneous coronary intervention with continuing CPR. In this case, the use of devices for mechanical CPR should be considered for the time of patient transportation and percutaneous coronary intervention.

During ALS it is necessary to periodically check the **contact closeness of the defibrillator plates and the cardiac monitor electrodes with the skin**, loose contact can cause sparking during defibrillation and errors in the rhythm analysis.

Use of oxygen in defibrillation: masks or nasal cannulas, breathing bags should be taken off and removed for at least 1 m from the patient during defibrillation; the contour of the lung ventilator should not be disconnected.

Echocardiography has a good potential for detecting reversible causes of circulatory arrest. Integration of echocardiography into the algorithm of advanced resuscitation activities requires a certain preparation to minimize intervals in chest compressions [23–25].

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X. SCD RISK STRATIFICATION AND PREVENTION IN PATIENTS WITH DIFFERENT COMORBIDITIES

X.1. SCD risk stratification and prevention in patients with CAD

X.1.A. SCD risk stratification and prevention in patients with postinfarction cardiosclerosis and left ventricular systolic dysfunction

Risk stratification

To determine the risk of SCD and choose prevention approach in this group of patients, it is first necessary to determine clinical course of CHD in every patient (stable/unstable).

In patients with history of myocardial infarction (not less than 40 days ago), SCD risk stratification algorithm is presented in **Table X.1.1.** Consistent implementation of the algorithm in these patients primarily implies identifying of *major* SCD risk factors which ultimately will determine the list of activities for primary/secondary SCD prevention in every individual patient.

Consistent implementation of the algorithm in these patients primarily implies ruling out of unstable angina and identification of *major* SCD risk factors which ultimately will determine the list of activities for primary/secondary SCD prevention in every individual patient.

Recommendations for SCD prevention

The following is a list of measures to be implemented for SCD prevention in patients with history of myocardial infarction, according to evidence-based medicine principles.

Class I

1. Adequate medical therapy of CAD and CHF that includes mandatory administration (if there are no contraindications and side effects) of the following medication classes:
   - β-adrenergic blocking agent (A);
   - ACE inhibitors (A);
   - acetylsalicylic acid (A);
   - statins (A);
   - eplerenone after MI with a reduced LVEF in combination with left ventricular failure or diabetes mellitus (B).

Table X.1.1

SCD risk stratification in patients with postinfarction cardiosclerosis and left ventricular systolic dysfunction

1. Is there a verified episode of cardiac arrest due to VF/VT?	
yes	no
see item 2	
2. Is there angina and/or signs of CAD destabilization*?	
yes	no
Coronary angiography, consider revascularization	See section on recommendations for SCD prevention
3. Are there registered non-sustained ventricular arrhythmias**?	
yes	no
Holter monitoring, consider coronary angiography, endocrinal ES	see item 4
4. Are there any clinical and instrumental signs of chronic left ventricular aneurysm?	
yes	no
consider cardiac surgery	see item 5
5. LVEF is less than 40%	
yes	no
see section on recommendations for SCD prevention	see section on SCD risk stratification and prevention in patients with chronic CAD and normal left ventricular systolic function

** – CAD destabilization includes unstable angina (according to the defined of National guidelines for management of ACS without persistent ST elevation), stable angina FC III–IV refractory to the adequate antianginal therapy, angina after myocardial revascularization procedures (stenting, CABG).*
*** – Non-sustained ventricular tachycardia includes non-sustained ventricular tachycardia and PVCs.*

2. Restoration of coronary blood flow with surgical or interventional methods if possible (B).

3. For secondary SCD prevention, ICD placement is recommended for patients who survived ventricular fibrillation or hemodynamically unstable ventricular tachycardia episodes (major risk factors) who receive ongoing optimal medical therapy, have good functional status and prognosis for survival over a year and more (A).

4. For primary SCD prevention, ICD placement is recommended for patients with left ventricular dysfunction due to prior MI (not less than 40 days after MI; a major risk factor of SCD) with LVEF lower than 40%, CHF NYHA FC I–III, good functional status, who receive continuous optimal medical therapy and have a favorable prognosis of survival for a year or more (A).

5. For primary SCD prevention, ICD placement is recommended for patients with following major risk factor of SCD: left ventricular dysfunction due to prior MI (not less than 40 days after MI), LVEF lower than 40%, CHF NYHA FC I–III, non-sustained VT (based on ECG, Holter monitoring) or sustained VT and/or VF (induced on endocardial ES), with good functional status, who receive continuous optimal medical therapy and have a favorable prognosis of survival for a year or more (A).

Class IIa

1. Radio frequency ablation (RFA) in patients with hemodynamically stable ventricular tachycardia (a major risk factor for SCD) and EF > 40% (B).

2. RFA for VT in patients managed with ICD and antiarrhythmic agents with frequent (more than 2 times a year) justified ICD interventions (C).

Class IIb

1. Amiodarone in combination with β-adrenergic blocking agents in patients with symptomatic ventricular arrhythmias (a major risk factor for SCD) when β-adrenergic blocking agents are not effective (B).

2. Amiodarone in patients with VA (a major risk factor for SCD), who are intolerant and/or refuse ICD placement (C).

3. Sotalol in patients with symptomatic ventricular arrhythmias (a major risk factor for SCD) when β-adrenergic blocking agents are not effective (C).

4. Surgical treatment of chronic heart aneurysm (C).

5. PUFA (B).

Class III

1. Antiarrhythmic agents administration is not mandatory in patients with asymptomatic PVCs or non-sustained ventricular tachycardia (a major risk factor for SCD) (B).

2. IC class antiarrhythmics are contraindicated (B).

X.1.Б. SCD risk stratification and prevention in patients with chronic CAD and normal left ventricular systolic function

Risk stratification

It should be emphasized that any patient with confirmed coronary artery disease is potentially at risk of SCD, and the majority of sudden deaths in absolute numbers occur in individuals without severe left ventricular systolic dysfunction [1–6].

In this group of patients it is crucial to verify and then modify *secondary* risk factors for SCD, which are, in fact, risk factors for CHD as well. Thus, diagnostic tests and medical therapy (secondary prevention of CAD), recommended by the National Guidelines for the diagnosis and treatment of chronic CAD are, in fact, measures for SCD risk stratification and prevention [7].

The emergence of various ventricular arrhythmias (VA) types in patients with chronic coronary artery disease can often be related to destabilization of CAD and/or progression of CHF.

In most cases, non-sustained ventricular tachycardia episodes in patients with chronic coronary artery disease are asymptomatic. To date there are no unequivocal evidence to support NSVT suppression to decrease mortality. Treatment of sustained ventricular tachycardia in patients with chronic coronary artery disease depends on clinical manifestations and frequency of its episodes. In patients with history of cardiac arrest due to ventricular fibrillation/ventricular tachycardia that occurs 48 hours after AMI manifestation, there is a high risk of another episode of ventricular fibrillation [8–12].

It is important to take into account the clinical signs and verify possible causes of ventricular arrhythmias to determine SCD risk and administer appropriate treatment. The algorithm of risk stratification in patients with history of acute myocardial infarction is presented in **Table X.1.2.**

Table X.1.2

SCD risk stratification in patients with chronic CAD and normal left ventricular systolic function

1. Is there transient or permanent myocardial ischemia and/or recurrent acute coronary episodes?	
yes	no
Coronary angiography in order to choose revascularization method	see item 2
2. Are there registered sustained/non-sustained ventricular arrhythmias?	
yes	no
Coronary angiography in order to choose revascularization method	See the guidelines for diagnosis and treatment of chronic coronary artery disease [13]

Recommendations for SCD prevention

Class I

1. Adequate medical therapy of CAD and CHF that includes mandatory administration (if there are no contraindications and side effects) of the following medication classes:
   - β-adrenergic blocking agents (A);
   - ACE inhibitors (A);
   - acetylsalicylic acid (A);
   - statins (A);
   - PUFA (B).

2. Restoration of patency of the coronary arteries is recommended if indicated for secondary SCD prevention in patients who survived ventricular fibrillation or hemodynamically unstable ventricular tachycardia (major risk factors), since acute myocardial ischemia usually provokes VT (B).

3. For secondary SCD prevention, ICD placement is recommended for patients who survived ventricular fibrillation or hemodynamically unstable ventricular tachycardia episodes (major risk factors), when coronary revascularization is not possible, and who receive ongoing optimal medical therapy, have good functional status* and prognosis for survival over a year and more (A).

Class IIa

1. Administration of amiodarone in combination with β-blockers is advisable to reduce severity of symptoms caused by recurrent hemodynamically stable ventricular tachycardia (major risk factors for SCD) in patients with LV dysfunction due to acute myocardial infarction, who may not have an ICD implanted or refuse the procedure (C).

2. Surgical and/or interventional restoration of coronary blood flow for primary SCD prevention is indicated in patients with chronic coronary artery disease and hemodynamically significant stenoses of the coronary arteries (C).

3. ICD implantation is suitable for the treatment of recurrent sustained ventricular tachycardia in patients with a history of previous myocardial infarction (the main risk factors for SCD) with normal or near-normal systolic ventricular function, receiving continuous optimal medical therapy and have a favorable prognosis for survival with a good functional status for a year or more (C).

Class IIb

1. Radiofrequency catheter ablation or amiodarone administration can be seen as an alternative to ICD placement in patients with moderate left ventricular dysfunction (ejection fraction 40%) and recurrent hemodynamically stable ventricular tachycardia (a major risk factor for SCD) (B).

Class III

1. Antiarrhythmic agents are not recommended as a preventive measure to reduce mortality in patients with non-sustained asymptomatic VA (a major risk factor for SCD) (B).

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X.2. SCD risk stratification and prevention in patients with chronic heart failure

In patients with chronic heart failure associated with decreased systolic function, VA occurs often and SCD risk is increased. The etiology of CHF is likely to affect mechanisms and types of VA. Additional predictors of SCD in patients with CHF are severe mitral regurgitation, decrease in hemoglobin level and concomitant end stage renal disease, with progressive increase in SCD risk at the stage when chronic dialysis is required [1–4]. Other parameters of the greatest prognostic value in patients with CHF are: ejection fraction, QRS complex length, left bundle branch block, signal-averaged ECG, heart rate variability, baroreflex abnormalities, T-wave alternans, QT interval dispersion, heart rate turbulence [5–7].

Risk stratification

To determine the risk of SCD and choose prevention approach in this group of patients, it is necessary to determine CHD etiology in every individual case.

The algorithm for SCD risk stratification in patients with CHF is shown in Table X.2.1. Consistent implementation of this algorithm will determine a

Table X.2.1

SCD risk stratification in patients with CHF

1. Is there evidence of ischemic etiology of CHF?	
yes	no
Coronary angiography, consider revascularization	see item 2
2. Is there history of cardiac arrest episodes?	
yes	no
(see recommendations for SCD prevention – class I, item I)	Prevention measures depend on: CHF NYHA FC; LVEF; VA presence/absence; signs of ventricular dyssynchrony presence/absence (see recommendations for SCD prevention)
Are there registered sustained/non-sustained ventricular arrhythmias?	
yes	no
Holter monitoring, consider endocrinal ES	see recommendations for SCD prevention

list of activities required for primary/secondary prevention of SCD in each individual case.

Recommendations for SCD prevention

Class I

1. Adequate medical treatment of CHF according to current national guidelines for the treatment of CHF [7] includes mandatory administration (in the absence of contraindications and side effects) of β-adrenergic blocking agents (A), ACE inhibitors or angiotensin II receptor blockers (A), diuretics (C), spironolactone (A), PUFAs (B).

2. For secondary SCD prevention, ICD placement is recommended for patients who survived ventricular fibrillation or hemodynamically unstable ventricular tachycardia episodes that were not due to reversible causes (major risk factors), and who receive ongoing optimal medical therapy, have good functional status* and prognosis for survival over a year and more (A).

3. For primary SCD prevention, ICD placement is recommended for patients with left ventricular dysfunction due to prior MI (not less than 40 days after MI; a major risk factor of SCD) with LVEF lower than 40%, CHF NYHA FC I–III, good functional status*, who receive continuous optimal medical therapy and have a favorable prognosis of survival for a year or more (A).

* You can read about functional status assessment methods at http://www.chcr.brown.edu/pcoc/functi.htm

4. For primary SCD prevention, ICD placement is recommended for patients with non-ischemic heart diseases with LVEF of less than 35%, CHF NYHA FC I–III (a major risk factor), who receive continuous optimal medical therapy, have good functional status* and have a favorable prognosis of survival for a year or more (A).

5. Concomitant therapy with amiodarone, sotalol alone or in combination with β-blockers is recommended for patients with ICDs, receiving CHF treatment, to reduce symptoms of ventricular tachycardia (both sustained and non-sustained) (C).

6. Amiodarone is indicated for treatment of hemodynamically significant VT and non-sustained ventricular tachycardia if cardioversion and/or correction of the arrhythmia causes did not effectively resolve of prevent its early recurrence (B).

Class IIa

1. For primary SCD prevention, biventricular pacemaker placement (CRT) is indicated for patients with CHF NYHA FC III–IV (a major risk factor), who receive continuous optimal medical therapy, who have sinus rhythm and QRS complex duration of more than 120 ms and have a favorable prognosis of survival for a year or more (A).

2. ICD placement is indicated in patients with recurrent hemodynamically stable ventricular tachycardia (a major risk factor), normal or near normal left ventricular ejection fraction, who receive optimal CHF treatment with good functional status* and have a favorable prognosis of survival for a year or more (C).

3. Biventricular pacemaker placement without ICD function is appropriate to prevent SCD in patients with CHF NYHA FC III–IV, LVEF of less than 35% (major risk factors), QRS complex duration of 160 ms (or at least 120 ms if other signs of asynchronous ventricular contraction are present), who receive continuous optimal medical therapy and have a favorable prognosis of survival for a year or more (B).

Class IIb

1. Amiodarone, sotalol and/or β-adrenergic blocking agents may be prescribed to patients with major and minor risk factors for SCD, receiving optimal CHF treatment, who may not have an ICD placed.

2. For primary SCD prevention, ICD placement may be considered for patients with non-ischemic heart diseases with LVEF of 30–35% (a major risk factor), CHF NYHA I, who receive continuous optimal medical therapy,

* You can read about functional status assessment methods at http://www.chcr.brown.edu/pcoc/functi.htm

have good functional status and have a favorable prognosis of survival for a year or more (B).

Class III

1. IC class antiarrhythmics administration for VA treatment (a major SCD risk factor) is not recommended in patients with CHF (A).

2. ICD placement is not indicated in patients with refractory heart failure who are not expected to achieve the compensation of its manifestations and without favorable prognosis (A)

Since about 50% of deaths in patients with CHF are SCD, the primary SCD prevention is a crucial issue. In other words, a physician should clearly estimate at what stage of the disease the ICD placement is recommended. **Table X.2.2.** presents indication classes for ICD placement for primary SCD prevention depending on CHF etiology, CHF FC, LVEF values and presence of VA.

Table X.2.2

ICD for primary SCD prevention in patients with CHF

NYHA FC	LVEF, %					
	Less than 30		31–35		36–40	
	CHF etiology					
	Ischemic	*Non-ischemic*	*Ischemic*	*Non-ischemic*	*Ischemic*	*Non-ischemic*
NYHA I	I (not earlier than 40 days after AMI)	IIb	I (NSVT +)	IIb	I (NSVT +)	III
NYHA II	I (not earlier than 40 days after AMI)	I	I (not earlier than 40 days after AMI)	I	I (NSVT +)	III
NYHA III	I (not earlier than 40 days after AMI)	I	I (not earlier than 40 days after AMI)	I	I (NSVT +)	III
NYHA IV	III	III	III	III	III	III

Note: Roman numerals in the table show the indication class for ICD placement. LVEF – left ventricular ejection fraction, CHF – congestive heart failure, SNVT – non-sustained ventricular tachycardia, AMI – acute myocardial infarction, FC – functional class.

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X.3. SCD risk stratification and prevention in patients with bradyasystolic arrhythmias and conduction disorder

Bradyarrhythmia include a wide range of diseases, the pathogenesis of which involves reduction of cardiac output by reducing the heart rate due to sinus node dysfunction and/or abnormalities in action potential propagation along the conducting system of the heart. SCD due to bradyarrhythmias occur in 15% of cases [1–3]. However, it is important to realize that the coexistence of bradyarrhythmias and LV systolic dysfunction in the same patient suggests high and moderate risk of ventricular tachyarrhythmias.

X.3.A. SCD risk stratification and prevention in patients with sinus node dysfunction

Patients with sick sinus syndrome (SSS) accounts for about half of the total number of pacemaker implantation [4].

SCD risk in this group of patients depends on the severity of signs and symptoms and the nature of the underlying disease. It is believed that permanent pacing improves clinical symptoms, but does not modify the prognosis of patients with SSS. However, these data were obtained long time ago in small, non-randomized studies and non-prospective [5]. It is known that lack of a permanent pacemaker in patients with SSS is accompanied by deterioration in the quality of life, increased morbidity and mortality. As for SCD, the systematic estimation of its contribution to the total death rate in these patients was not carried out [6].

Risk stratification

Sinus node dysfunction as a cause of severe bradycardia or sinus pauses, can manifest with syncope, pre-syncope, dizziness, hypotension, symptoms of heart failure progression, angina pectoris. SCD in patients with SSS is more likely if there are signs of LV systolic dysfunction. Pathophysiological mechanism of this scenario is a long asystole pause without escape rhythm and/or VA, those are a result of pause-dependent repolarization abnormalities, the manifestation of which leads to disturbances in both systemic and regional hemodynamics, particularly within central nervous system. This may cause irreversible changes in the vital organs and death. The presence or absence of preexisting structural heart defects may be crucial to adaptive changes of cardiac output parameters, and thus to the clinical course of the arrhythmia. History of such risk factors as syncope, structural heart disease, long-term symptomatic asystolic pause during Holter monitoring correlate with poor prognosis, including high risk of SCD. At the same time, it should be mentioned that the key is symptomatic significance of the pause, not its duration (Table VI.5).

SCD prevention

Permanent atrial and/or dual-chamber pacing in patients with SSS improves symptoms and quality of life, reduces incidence of atrial fibrillation and its episodes frequency [7]. To date, long-term results on permanent pacing and its effects on survival and SCD incidence are unknown.

X.3.B. SCD risk stratification and prevention in patients with AV- and interventricular conduction abnormalities

Diseases with AV- and intraventricular conduction abnormalities were assessed in several non-randomized and observational studies [8, 9]. These studies have shown that these abnormalities are often associated with syncope and presyncope and in rare cases with SCD. Permanent pacing improves quality of life, regarding the SCD risk, data are inconclusive.

AV-conduction abnormalities

Prognosis is favorable for patients with I and II degree Mobitz I AV blocks, whereas II degree Mobitz II AV block, intra-Hisian and infra-Hisian blocks often progress to III degree AV block (see Table VI.5) which requires a permanent pacing. [10]

III degree AV block is the most common in patients with CAD or degenerative diseases of the heart. Several small non-randomized studies have shown that the permanent pacing increases survival parameters in these patients [10].

Two- and tree-fascicular blocks

Data obtained in prospective studies of asymptomatic patients with chronic blockade of two fascicules, suggest a relatively slow progression of the disease to III degree AV block. [10] However, SCD incidence in this group of patients is relatively high due to malignant ventricular tachyarrhythmias. Risk factors for SCD are CAD, CHF, and/or advanced age [11]. It is known that patients with two- and tree-fascicular blocks and history of syncope as well as patients with intermittent III degree AV block more likely to have SCD. Permanent pacing does not reduce SCD incidence significantly [12]. There are conflicting data on the prognostic value of the long HV interval for the SCD risk. Some studies show, that presence of HV interval >75 ms is an insignificant prognostic factor, but HV interval >100 ms indicates very high risk and requires urgent permanent pacing initiation [13–15].

Data regarding the role of the left bundle branch fascicular blocks as independent predictors of SCD are also inconclusive. It is hypothesized that addition of one of the left bundle branch fascicular blocks may be considered as a risk factor of SCD.

In patients without severe structural heart disease new or preexisting left bundle branch block is not associated with SCD risk worsening. On the other hand, for patients with history of AMI and thrombolytic therapy, new or preexisting left bundle branch block is an additional factor that contributes to the risk of SCD [16–18].

Congenital AV block

Several studies have shown that the pacemaker implantation may improve survival in patients with complete congenital AV block [18–20]. SCD may be the first manifestation of complete congenital AV block in previously asymptomatic patients without structural heart disease. SCD in these patients may be due to complete AV block without any escape rhythms or due to bradycardia-dependent malignant ventricular tachyarrhythmias.

In these patients prolongation of the QT interval, early afterdepolarizations and dispersion of refractoriness in ventricular myocardium contribute to the emergence of fatal ventricular arrhythmias by long-short mechanism* [20, 21]. In patients with congenital cardiac conduction system abnormalities, SCD risk factors include: heart rate less than 50 bpm, QT interval prolongation, structural heart disease [22].

AV block after RF ablation or RF modification of AV node

SCD risk remains a problem in patients with AV node RFA, including RF modification of AV node, since incidence of malignant ventricular

* *a long-short sequence.*

arrhythmias in these patients reaches 2–3%, especially in patients with severe CHF manifestations [23, 24]. The mechanism of worsening the arrhythmias in this cohort of patients remains unclear. It is believed that it depends on bradycardia-dependant increase in ventricular repolarization time and their refractoriness parameters during the first day after RFA procedure, especially when repolarization abnormalities were preexistent [25, 26]. SCD prevention in these cases includes cardiac pacing with a relatively high rate and continuous ECG monitoring for first 24 hours after the procedure.

According to Zehender et al., 12–31% of patients die suddenly during the first year of follow-up after cardiac pacemaker implantation [27]. The authors have also noted that SCD incidence is three times higher during the first year after implantation of the pacemaker implantation than in subsequent years. This is consistent with domestic data, showing that SCD incidence in patients after pacemaker implantation and AV node RFA with chronic atrial fibrillation reaches 10% [10, 28]. It is thought that device sensitivity loss or asynchronous stimulation promotes initiation of malignant ventricular arrhythmias [10].

Specific risk group is the patients with AV nodal reentrant tachycardia (AVNRT) with coexisting I degree AV block. RF modification of the AV node to eliminate AVNRT in these cases may be associated with worsening of AV conduction abnormalities and potentially SCD. AV node RF-modification technique, developed by Russian authors, eliminates this risk [29].

Recommendations for SCD prevention

Permanent atrial and/or dual-chamber pacing in accordance with the National guidelines for artificial cardiac pacing [7] in patients with AV conduction abnormalities improves symptoms and quality of life reduces SCD incidence. Current data on the long-term effects of permanent pacing on the survival and the risk of SCD are contradictory.

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X.4. SCD in patients with cardiomyopathies

Cardiomyopathy is a myocardial disease, in which structural and/or functional disorders in the absence of coronary atherosclerosis, hypertension, congenital or acquired heart defects are recorded. As per its morphological characteristics, cardiomyopathy is divided into hypertrophic, dilated and restrictive CMP, arrhythmogenic right ventricular dysplasia, and unclassifiable form as well. In its turn, each of the types is divided into a familial or genetically determined form and nonfamilial form.

X.4.A. SCD risk stratification and prevention in patients with DCM

Dilatation cardiomyopathy (DCM) is a group of diseases phenotypically combined by the presence of a disturbance of left ventricular systolic function and its dilatation, which develop not due to hemodynamic overload (due to falure or hypertension) and not due to CAD. In this case, the expansion of the right ventricle can also be registered, but this is not a diagnostic criterion of DCM. There are familial form with known mutations and familial form with an unknown type of mutation distinguished. Nonfamilial forms include DCM due to myocarditis, Kawasaki's disease, DCM associated with pregnancy, endocrine DCM, alcoholic, tachycardic forms, DCM due to excessive use of selenium, carnitine, thiamine, etc.

The five-year survival rate among Caucasians with DCM is 31.4% [1]. Mortality rate from this disease ranges from 0.10 to 1.16 per 10 000 population

in ages from 35–39 to 55–57 years [2]. At the same time, SCD is responsible for 20% of deaths [3, 4].

SCD is rarely the first manifestation of the disease, other signs and symptoms of a progressing disease are more common [5, 6]. In most cases, SCD is caused by life-threatening VA [7].

Genetic testing

It is advisable to test all next-of-kin relatives, particularly in the case of a malignant DCM progression or pathological phenotype, allowing to suspect a genetic mutation [8]. Based on available data, genetic testing for LMNA gene mutation may play a role in SCD risk stratification in patients with DCM [9, 10]. However, in most cases, screening for genetic mutations has a low efficiency (less than 20% in isolated DCM without concomitant skeletal muscle abnormalities) [8]. A standard screening approach should include family history of at least three generations (cases of CHF, cardiomyopathy, heart transplantations, SCD, cardiac rhythm and conduction abnormalities, stroke or other thromboembolic events), physical examination, ECG, echocardiography, Holter monitoring (in case of proband SCD).

Recommendations for SCD prevention

Class I

1. All patients with DCM are recommended to carefully study the family history of at least 3 generations (A).

2. Cardiologic screening of first-degree relatives is recommended: anamnesis, examination, ECG, Echo-CG, Daily monitoring of ECG (in case of proband death) (A).

3. If relatives have signs of DCM, regular cardiac examinations starting with early childhood (from 10–12 years with laminopathy) every 12–36 months up to 10 years, every 12–24 months up to 20 years and then every 2–5 years up to 50–60 years and cardiological screening of proband descendants of each subsequent generation are recommended (B).

4. If the signs of DCM are not found in the relatives and genetic testing is impossible, regular cardiac examination is recommended, starting from early childhood every 12–36 months up to 10 years, every 12–24 months up to 20 years and then every 2–5 years up to 50–60 years. (B).

5. If a proband mutation is detected in a proband with DCM in the result of genetic testing, genetic screening of first-degree relatives (B) is recommended.

6. If there are no causative mutations in the relatives, a further examination should be stopped (C).

7. If there are no causative mutations in relatives, genetic testing of descendants should not be carried out (C).

Class IIa

In case of causative mutations in relatives of asymptomatic carriers of causative mutations, a regular cardiological examination is recommended every year from 10 to 20 years and then every 1–3 years with the use of additional survey methods if necessary (C).

Risk stratification

Approaches to SCD risk stratification in patients with dilated cardiomyopathy do not differ from those used for risk stratification in patients with non-ischemic heart failure (see Table VII.2.1). In DCMC, an extremely high risk of SCD is associated with mutations in the LMNA gene.

Recommendations for SCD prevention

Class I

1. Optimal medical treatment of CHF according to current national guidelines for the treatment of CHF includes mandatory administration (in the absence of contraindications and side effects) of β-adrenergic blocking agents (A), ACE inhibitors (A), aldosterone antagonists (A).

2. For secondary SCD prevention, ICD placement is recommended for patients who survived ventricular fibrillation or hemodynamically unstable ventricular tachycardia episodes that were not due to reversible causes (major risk factors), and who receive ongoing optimal medical therapy, have good functional status* and prognosis for survival over a year and more (A).

3. For primary SCD prevention, ICD placement is recommended for patients with non-ischemic heart diseases with LVEF of less than 35%, CHF NYHA FC I–III (a major risk factor), who receive continuous optimal medical therapy, have good functional status* and have a favorable prognosis of survival for a year or more (A).

4. Catheter ablation of right bundle is indicated in patients with bundle branch re-entry ventricular tachycardia (a major risk factor), confirmed with endocrinal ES (C).

5. Concomitant therapy with amiodarone, sotalol alone or in combination with β-blockers is recommended for patients with ICDs, receiving DCM treatment, to reduce symptoms of ventricular tachycardia (both sustained and non-sustained) (C).

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* You can read about functional status assessment methods at http://www.chcr.brown.edu/pcoc/functi.htm

6. Amiodarone is indicated for treatment of hemodynamically significant VT and non-sustained ventricular tachycardia (major risk factors) if cardioversion and/or correction of the arrhythmia causes did not effectively resolve of prevent its early recurrence (B).

Class IIa

1. For primary SCD prevention, biventricular pacemaker placement (CRT) is indicated for patients with DCM and CHF NYHA FC III–IV (a major risk factor), who receive continuous optimal medical therapy, who have sinus rhythm and QRS complex duration of more than 120 ms and have a favorable prognosis of survival for a year or more (B).

2. ICD placement is indicated in patients with recurrent hemodynamically stable ventricular tachycardia (a major risk factor), normal or near normal left ventricular ejection fraction, who receive optimal DCM treatment with good functional status and have a favorable prognosis of survival for a year or more (C).

3. Biventricular pacemaker placement without ICD function is appropriate to prevent SCD in patients with DCM and CHF NYHA FC III–IV, LVEF of less than 35% (a major risk factor), QRS complex duration of 160 ms (or at least 120 ms if other signs of asynchronous ventricular contraction are present), who receive continuous optimal medical therapy and have a favorable prognosis of survival for a year or more (B).

Class IIb

1. Amiodarone and/or β-adrenergic blocking agents may be prescribed to patients with major and minor risk factors for SCD, receiving optimal CHF treatment, who may not have an ICD placed.

2. For primary SCD prevention, ICD placement may be considered for patients with DCM, LVEF of 30–35% (a major risk factor), CHF NYHA FC I, who receive continuous optimal medical therapy, have good functional status and have a favorable prognosis of survival for a year or more (B).

Class III

1. The use of IC class drugs for VA (the main risk factor of SCD) treatment is not recommended in patients with CHF (A).

2. ICD placement is not indicated in patients with refractory heart failure who are not expected to achieve the compensation of its manifestations and without favorable prognosis (A).

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X.4.B. SCD risk stratification and prevention in patients with hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is left ventricle myocardial hypertrophy development without arterial hypertension or valvular heart disease. Incidence is about 1 case per 500 people. In addition, in modern classification, there are HCM associated with obesity, rare cases of excessive LVH in athletes, HCM in children whose mothers have diabetes mellitus and HCM due to amyloidosis are distinguished. Usually determined by the thickening of the walls of the left ventricle (LV) of 15 mm or more (for children of 2 SD or more for age) in the absence of other causes that could potentially cause of hypertrophy and is not accompanied by the chambers dilatation [1]. Hypertrophic cardiomyopathy characterized by focal myocardial hypertrophy and changes in the spatial orientation of cardiomyocytes (chaotic positioning), which is essential for diagnosis [2]. It is assumed that these changes serve as arrhythmias substrate.

Epidemiology

According to various studies of Western, European, Asian and African countries, the frequency of the left ventricle thickness gain in adults has recently increased [3–12]. The studies show age-dependent nature of the frequency, which is significantly lower in patients younger than 25 years [9]. In pediatric registers, the incidence of HCM in children is unknown, but population

studies report incidence of 0.3 to 0.5 per 100,000 per year [13, 14]. Although HCM inheritance is mostly autosomal dominant, most studies indicate a slight predominance of men. The frequency of HCM in patients with different races is similar [3–12].

Since HCM is primarily of genetecal origin, careful collection of a family history acquires a diagnostic meaning, and, if possible, the relatives of the patient should be examined [1, 15–18].

SCD risk stratification

American College of Cardiology and European Society of Cardiology categorized known risk factors for SCD as major and possible, or secondary, for certain groups of patients with HCM (**Table X.4.1**). The clinical evaluation of patients with HCM is recommended for SCD risk stratification every 12–24 months [1, 19–24].

Table X.4.1

SCD risk factors in patients with HCM

«Major» SCD risk factors	SCD is possible in some patients
– Cardiac arrest – Spontaneous sustained ventricular tachycardia – Family history of SCD – Unexplained syncope – Thickening of the left ventricular wall ≥ 30 mm – Spontaneous non-sustained ventricular tachycardia	– Atrial fibrillation – Myocardial ischemia – The presence of a high risk gene mutations – Intensive (competitive) physical activity

Recently, in a multicentre retrospective long-term study involving 3,675 patients, known as HCM Risk-SCD*, a new model for SCD risk predicting was developed and validated [25]. HCM Risk-SCD uses a variable risk predictor associated with an increased risk of sudden death in at least one published multivariate analysis [25]. This eliminates the abnormal response of blood pressure to physical stress from risk markers. This model allows to estimate the individualized 5-year risk, and is consistent with the model using 4 main risk factors, the effectiveness of this predictive model is constantly improving (C-index from 0.54 to 0.7) [25]. In HCM Risk-SCD, a non-linear relationship between SCD risk and the maximum left ventricle wall thickness was established [25]. This parameter is taken into account in the model as a quadratic term. Online-calculator HCM Risk-SCD is available at: (http://doc2do.com/hcm/webHCM.html).

* *HCM Risk-SCD model should not be used for patients of <16 years old, professional athletes and for persons with metabolic/infiltrative diseases (eg, Anderson-Fabry disease) and syndromic forms (eg, Noonan syndrome). This model does not use a stress-induced gradient in the LV outlet tract and has not been validated in individuals before and after myoectomy or septal alcohol ablation.*

The role of genetic testing in patients with HCM for SCD risk stratification of now remains unclear (**IIb, B**). Genetic testing for HCM is recommended in patients with atypical clinical features of HCM (**I, B**). Family screening should include ECG, echocardiography and clinical follow up on a regular basis (from 12 to 18 months in children and adolescents, and about every 5 years in adults). The genetic testing is recommended in first-degree relatives of a HCM patient (**I, B**) [1, 15–18].

Holter monitoring is recommended for the initial SCD risk evaluation in patients with HCM (I, B), and then, every 1–2 years in patients with no history ventricular tachycardia episodes (IIa, C) [1, 22, 26].

Stress testing with blood pressure and ECG monitoring is also possible for SCD risk stratification in patients with HCM (**IIa, B**). Pathological BP response during testing (defined as either failure to increase blood pressure more than 20 mmHg or a drop in blood pressure of over 20 mmHg during the test) is considered as a major risk factor for SCD [27–29].

Some authors propose to consider cardiac MRI with gadolinium as an additional method to help clinicians with risk stratification and make tactical decisions (**IIa, C**) in patients diagnosed with HCM when SCD risk stratification based on common factors is impossible [1, 30].

Recommendations for SCD prevention

Studies of cardiovascular disease have shown that ICD implantation for primary and secondary prevention can reduce mortality [31, 32]. ICD implantation can be considered for patients with a projected 5-year risk of sudden death of ⩾4% (calculated by the HCM Risk-SCD model) and a life expectancy of > 1 year, after a detailed clinical examination, taking into account the lifelong risk of complications and the effect of ICD on the way of life, socio-economic status and psychological health.

Secondary prevention

Patients with HCM survived an episode of VF or persistent ventricular tachycardia have a high risk of subsequent fatal cardiac arrhythmias and should receive ICD treatment [30, 33–36].

On the other hand, the number of patients with indications for ICD implantation, especially for *primary prevention* of SCD, even in the United States and Western Europe is significantly higher than the number of implants. According to Shah B. et al. [37], in average about 20% of patients with indications for ICD implantation undergo the necessary operation. In Russia, given the small number of ICD implantations (2,381 operations in 2015), less than 1% of the likely number of patients who need ICDs actually receive them.

Table X.4.2

Primary SCD prevention in HCM patients

Risk factor	Comments
Age	• Some risk factors are more significant in young patients, especially NVT, pronounced LVH, and unexplained syncope.
Nonsustained ventricular tachycardia	• HTV (defined as> 3 consecutive contractions with a frequency of ≥120 beats / min lasting <30 seconds) develops in 20–30% of patients during outpatient monitoring of the ECG and is an independent SCD risk factor. • **SCD prevention measures:** prescription of β-adrenoblockers **(I, B),** amiodarone **(IIb, C),** according to indications **–** ICD-therapy **(I, B**).
Max. left ventricle wall thickness	• The severity and prevalence of LVH measured by transthoracic echocardiography is associated with the risk of SCD. • Several studies have shown the highest risk of SCD in patients with a maximum wall thickness of ≥30 mm.
Family cases of sudden cardiac death at a young age	• Although the definitions differ, family cases of SCD are usually considered clinically significant if one or more relatives of the first degree died suddenly at the age of <40 years, with HCM or without it; or when SCD developed from a first-degree relative of any age with an established diagnosis of HCM.
Syncope	• Syncope is often found in patients with HCM, but their causes can be diverse. • Non-neurocardiogenic syncope, for which no explanation is given after the examination, is a risk factor for SCD. • Episodes for 6 months from the examination can have the greatest predictive value in relation to SCD. • **SCD prevention of in the presence of indications**: septal myomectomy (**I, C**), alcohol ablation (**IIb, B**), ICD therapy **(I, B**), implantation of a two-chamber ECS (**IIb, B**)
Obstruction of the left ventricular outflow tract	• A large number of studies have shown a significant association between LVEF obstruction and SCD. • **SCD prevention measures**: prescription of β-adrenoblockers (**I, B**), septal myomectomy (**I, C**), alcohol ablation (**IIb, B**), implantation of a two-chamber ECS (**IIb, B**)
Blood pressure response to the load	• Approximately one-third of adult patients with HCM have an abnormal response of systolic pressure to the load, characterized by progressive hypotension. • An abnormal response of systolic pressure to the load is defined as the inability to increase the pressure by at least 20 mm Hg. from the rest level at the peak of physical activity or a pressure drop of > 20 mm Hg. of the peak pressure. • An abnormal response to systolic pressure to the load is associated with an increased risk of SCD in patients younger than 40 years.

Recommendations for primary SCD prevention in patients with HCM are given in **Table X.4.2**. [38]

Class I

1. ICD placement should be performed in patients with HCM with a projected 5-year risk of sudden death of ⩾4% (calculated by the HCM Risk-SCD model) and such major risk factors for SCD as a sustained ventricular tachycardia or ventricular fibrillation, who receive continuous optimal medical therapy, have good functional status and a favorable prognosis of survival for a year or more (B).

2. Beta-adrenergic blocking agents are recommended for the symptomatic adult patients with obstructive or non-obstructive HCM, but they should be used with caution in patients with sinus bradycardia or AV conduction disorders (B).

3. Septal myotomy is indicated for patients with severe and refractory to medical therapy symptoms* and obstruction of LVOTO (C)**.

Class IIa

1. ICD placement is indicated for primary and secondary prevention of SCD in patients with HCM who have at least one major risk factor (see Table VII.4.1): heart arrest, spontaneous sustained VT, family history of SCD, unexplained syncope, thickness of LV wall more than 30 mm, BP abnormalities during stress testing, spontaneous non-sustained ventricular tachycardia, who receive continuous optimal medical therapy, have good functional status and have a favorable prognosis of survival for a year or more (B).

2. Ethanol embolization is indicated for adult HCM patients with obstructive LVOTO (a major risk factor in these patients) if signs and symptoms are refractory to medical therapy and there are contraindications for myotomy/myoectomy (such as serious concurrent medical condition and/or advanced age) (B).

3. Amiodarone may be the drug of choice for patients with hypertrophic cardiomyopathy and history of persistent ventricular tachycardia and/or ventricular fibrillation (main risk factors), when ICD placement is contraindicated (C).

4. Expanded myoectomy may be considered in patients with obstructive HCM and resistance to drug therapy (C).

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* Signs and symptoms include angina FC III–IV, syncope, presyncope, dizziness, hypotension that are refractory to optimal medical therapy. LVOTO pressure gradient at rest or during exercise should not exceed 50 mmHg.

** The surgery should be performed only by experienced surgeons (who have performed at least 20 procedures or practicing at a center, where at least 50 of such procedures performed in a year).

Class IIb

1. ICD implantation can be considered for patients with HCM with a projected 5-year risk of sudden death of ⩽4% (calculated by the HCM Risk-SCD model) only if there are clinical manifestations that have proven prognostic significance (B).

2. Amiodarone may be used for the primary prevention of SCD in patients with HCM who have one or more major SCD risk factors, when ICD placement is impossible (C).

3. Permanent dual chamber pacing with a short AV delay may be indicated for patients with obstructive HCM with severe signs and symptoms that are refractory to medical therapy and who are not candidates for septal reduction procedure if LVOTO systolic gradient falls by 25% or more during preliminary dual-chamber pacing with optimal AV delay (B).

4. Experience with sotalol in patients with hypertrophic cardiomyopathy is limited, but it may be used in certain clinical situations, particularly in patients with ICDs (C).

Class III

1. ICD implantation is not recommended for patients with HCM having no major SCD risk factors (C).

2. ICD implantation is not recommended for patients with HCM with a projected 5-year risk of sudden death of ⩽4% (calculated by the HCM Risk-SCD model) (B).

3. ICD placement is not recommended for HCM patients with positive genotype (a possible risk factor) and without clinical signs and symptoms (C).

4. Ethanol embolization should not be performed in patients with severe septal hypertrophy (over 30 mm) due to uncertain effectiveness of the procedure in these patients (C).

5. Ethanol embolization should not be performed in asymptomatic patients, patients with medically controlled symptoms or patients with a planed cardiac surgery when myoectomy may be performed as a part of this surgery (C).

6. Nitrates, nifedipine and high doses of diuretics are potentially dangerous in patients with obstructive hypertrophic cardiomyopathy (C).

7. Cardiac glycosides use in HCM patients without AF is potentially dangerous (B).

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X.4.1.C. SCD risk stratification and prevention in patients with ARVD

Currently, "arrhythmogenic dysplasia / cardiomyopathy of the right ventricle" is defined as the pathology of the heart muscle, often familial one, characterized by a structural and functional anomaly of the right ventricle, associated with the replacement of the myocardium with fat or fibrous tissue [1]. Recent data indicate involvement in the pathological process of the left ventricle in 50% of cases [2]. Most clinical and histological data suggest that the pathological process is of an acquired nature and progresses over time. However, this does not exclude the possibility of having genetically determined myocardial dystrophy, manifesting in childhood or adolescence. A characteristic feature of the pathology is local or diffuse transmural replacement of the right ventricle free wall myocardium with fatty or fibrous-fat tissue at the usually normal left ventricle of the heart.

Manifestations of ARVD are derivatives of electrical instability of the myocardium and progressive ventricular dysfunction.

Ventricular arrhythmias are estrasystole, unsustained or sustained tachycardia, can cause ventricular fibrillation and sudden death at any stage of the pathology development. Progressive deterioration of the pumping function of the myocardium leads to the development of right ventricular and biventricular heart failure and up to 20% of all cases occur during prolonged follow-up [3].

The existing diagnostic criteria are based on histological, genetic, electrocardiographic parameters and data of various methods of visualizing the myocardial structure (MRI, CT, echocardiography). There are three categories of patients: with an obvious, border or possible form [4].

The incidence of ARVD in general population varies from 1 per 1,000 to 1 per 5000 population and is a significant cause of SCD in athletes and young adults [5].

Treatment as a method of SCD prevention

Specific treatment aimed at the elimination of pathological process itself with ARVD, currently does not exist. With the development of myocardial dysfunction, heart failure is being corrected. However, the determining factor in the treatment of these patients is antiarrhythmic therapy aimed at the prevention and management of ventricular arrhythmias.

Prevention of sudden cardiac death in this pathology is aimed at correcting the arrhythmic component.

All forms of therapy are used in the treatment of ARVD: medication, surgical methods, catheter destruction, implantation of cardioverter-defibrillators.

Drug therapy. At present, there is no consensus on the strategy of treatment in asymptomatic patients with minor changes in the morphology of the right ventricle and without ventricular arrhythmias. In these cases, the use of β-adrenoblockers is justified for reducing the risk of adrenergic-stimulated arrhythmias. If a patient has symptomatic ventricular extrasystoles, episodes of unsuatainable ventricular tachycardia, it is also advisable to start treatment with β-adrenoblockers. Patients with paroxysms of sustained ventricular tachycardia should be evaluated in terms of the need for implantation of a cardioverter-defibrillator, with the possible preservation of antiarrhythmic therapy to reduce the number of discharges.

Drug treatment of symptomatic ventricular arrhythmias in patients with ARVD, even with the use of AAA of the III class, may be unsuccessful or associated with a risk of side effects. In these cases, surgical or catheter methods of treatment can be used.

Surgical methods. The first attempt to influence the substrate of tachycardia was ventriculotomy in the area of the earliest epicardial activation, performed by G.Guiraudon and co-authors in 1974. Subsequently, for the treatment of patients with ARVD, this group of authors proposed an operation for complete isolation of the right ventricle free wall [6]. However, this operation was not widely used because of the frequent development of acute right ventricular failure. Individual cases of a long-term effect of right ventricular isolation are described with a slight decrease in function with two-chamber pacing [7].

Modification of the technique with partial isolation of the free wall of the right ventricle was not widely used due to frequent recurrences of tachycardia [8]. Heart transplantation can be considered an options for surgical treatment of arrhythmogenic dysplasia. As a method of treating heart failure in this group of patients, it is possible to use cardiomyoplasty of the right ventricle [9].

Catheter methods. Ventricular arrhythmias in arrhythmogenic dysplasia are associated with either abnormal ectopic activity or the presence of "slow" conduction zones and reentry tachycardia. The heterogeneity of morphological changes and the progression of the pathological process in ARVD are the cause of the polyfocal character and the transformation of ventricular arrhythmias.

In 1984, P. Puech et al. reported for the first time on successful catheter destruction in a 27-year-old patient with arrhythmogenic right ventricular dysplasia [10].

Reentry mechanism is associated with the presence of a "slow conduction" zone, which is the critical link of tachycardia and the purpose of catheter intervention. Often, the polymorphism of ventricular tachycardia is due to the presence of several "exit" points around one area of "slow conduction".

As in reentry coronary ventricular tachycardia, the most effective are the effects in the zone of "slow conduction" [11, 12].

New opportunities in the treatment of patients with ARVD have been discovered with the advent of electro-anatomical mapping techniques. Registration of amplitude and directivity of signals from the endocardium surface allows not only to determine the mechanism of tachycardia, but also visualize the prevalence of the pathological process. M. Boulos et al. found a correlation between magnetic resonance imaging and echocardiography and electro-anatomical mapping [13].

Efficacy and long-term results of catheter destruction in ARVD are determined by two factors: the polymorphism of the tachycardia substrate, the difficulties in identifying the critical zone, and the further development of the disease. ARVD is a progressive pathology with a high probability of occurrence of new ventricular arrhythmias. The prevalence of the substrate and its development in arrhythmogenic dysplasia often makes it impossible to completely eliminate the arrhythmogenic zone, but it allows it to be modified and to achieve a sustainable effect. Often patients need several operations to be performed. According to Fontaine G. et al., the effectiveness of the first operation was 32%. After the second – operation the effect was achieved in 45% of patients. And as a result of three procedures, a sustained result was achieved during follow-up period of 5.4 years [14].

Implantation of cardioverter-defibrillators. Like post-MI patients patients with arrhythmogenic right ventricular dysplasia have a risk of sudden cardiac

death. Implantation of cardioverter-defibrillators is indicated to the patients at risk. Unlike coronary artery disease, there is no consensus on the need for implantation of cardioverter-defibrillators for primary prevention of sudden cardiac death. At present, this operation, as a measure of primary prevention, is justified in patients with compromised history (the presence of suddenly died immediate relatives and verified arrhythmogenic right ventricular dysplasia) and having signs of this pathology. An additional factor may be data from genetic analysis, especially the detection of type ARVD2, which is characterized by the onset of polymorphic ventricular tachycardia and sudden death at a young age.

Patients who have had episodes of ventricular fibrillation, or who have sustained paroxysms of ventricular tachycardia, are unconditional candidates for the secondary prevention of sudden cardiac death using implantable cardiovertors-defibrillators.

The use of these devices can significantly reduce the risk of arrhythmic death. However, most patients still need to take antiarrhythmic drugs to reduce the number of discharges of the defibrillator [15].

Implantation of cardioverter-defibrillators in patients of this group, taking into account changes in the right ventricle, is associated with a higher frequency of the system dysfunction, i.e. detection falure with a reduced amplitude of R wave, high thresholds of stimulation, as well as a risk of myocardium perforation with an electrode.

Choice of treatment tactics

Given the different forms and variants of the clinical course of arrhythmogenic right ventricular dysplasia, there is no single algorithm for therapeutic tactics. Conventionally, patients with arrhythmogenic dysplasia can be divided into five groups.

1. Patients with a limited form of dysplasia in combination with asymptomatic or low-symptomatic ventricular extrasystole, without a compromised family history. In these cases, systemic antiarrhythmic therapy, with the exception of β-blockers, is not justified. Of course, these patients, like all patients with ARVD, should avoid intense physical activity and exercise.

2. In the presence of local forms of ARVD in combination with symptomatic ventricular extrasystole, paroxysms of unstable or persistent ectopic tachycardia, antiarrhythmic therapy is indicated. In cases of inefficiency or impossibility of drug treatment, it is advisable to perform catheter destruction of the tachycardia zone.

3. To prevent episodes of a stable, hemodynamically significant ventricular tachycardia without distinct right ventricular myocardial dysfunction, an antiarrhythmic drug can be selected using an endocardial electrophysiological study. If the recurrence of the tachycardia persists, a catheter operation or implantation of a cardioverter-defibrillator is indicated.

4. Patients with paroxysms of persistent ventricular tachycardia in the presence of severe myocardial dysfunction, as well as those who had a sudden cardiac death, require the implantation of a cardioverter-defibrillator while preserving antiarrhythmic drugs and concomitant correction of heart failure.

5. In rare cases of ARVD, when the effects of myocardial dysfunction (Uhl disease) or biventricular pathology without episodes of ventricular tachycardia or ventricular fibrillation prevail, correction of manifestations of heart failure is prevalent. Implantation of a cardioverter-defibrillator can be considered, but there is currently no reliable data on the effectiveness of its use in this group of patients.

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X.5. SCD in patients with WPW syndrome

WPW syndrome is a combination of ECG pattern illustrating ventricular pre-excitation via the accessory (anomalous) atrioventricular conduction pathway and paroxysmal atrioventricular reciprocating (re-entry) tachycardia (AVRT), resulting from electrical circuit via accessory AV conduction pathway, normal auriculoventricular node, atrial and ventricular myocardium [1–3].

Term WPW phenomenon is used when a patient has sinus rhythm and evidence of anterograde (from atria to ventricles) impulse conduction via the accessory electrical conduction pathway (ventricular pre-excitation) on ECG without clinical manifestations; or AVRT is confirmed by ECG [1, 2].

WPW syndrome is the term that applies to patients who have ventricular pre-excitation combined with symptomatic tachycardia other than AVRT, e.g. fibrillation or atrial flutter [202–204].

According to various authors WPW syndrome prevalence in the general population is 0.1 – 0.3% [1–4].

Among patients with WPW syndrome risk of SCD in 3–10 years varies from 0.15 to 0.39%, which is higher than in general population [1–3, 10, 11]. Cardiac arrest is often the first manifestation of WPW.

The *main* risk factors for SCD in patients with WPW syndrome/phenomenon (in decreasing order of importance) are: an episode of atrial fibrillation with RR interval 260 ms or less with anterograde conduction along accessory AV conduction pathway, history of syncope, structural heart defects, family history of WPW syndrome or SCD, anterograde refractory period of accessory AV conduction pathway < 270 ms [3, 6, 7, 10–12].

Risk stratification

SCD risk stratification algorithm is presented in **Table X.5.1**. It is based on the identification of the major SCD risk factors in patients with WPW syndrome [3, 7, 9]. Consistent implementation of this algorithm will determine a list of activities required for primary/secondary prevention of SCD in each individual case.

For SCD risk stratification in this group of patients, the primary goal is to identify the clinical signs (the main risk factors and their combination) associated with high risk of SCD. Ultimately, this will determine the sequence of activities for SCD prevention.

Table X.5.1

SCD risk stratification in patients with WPW syndrome

1. Is there evidence of pre-excitation on ECG	
Yes	No
see item 2	
2. Is there a symptomatic tachycardia and/or history of syncope	
Yes	No
Endocrinal EPS and RFA of the accessory AV conduction pathway	see item 2
2. Is there a family history of WPW syndrome or SCD	
Yes	No
Endocrinal EPS and RFA of the accessory AV conduction pathway	see item 3
3. Is there a structural abnormality of the heart	
Yes	No
Endocrinal EPS and RFA of the accessory AV conduction pathway	see item 4
4. Ventricular pre-excitation is asymptomatic	
See recommendations for SCD prevention	

Recommendations for SCD prevention

Class I

1. Patients with evidence of ventricular pre-excitation on the ECG, history of cardiac arrest, unexplained syncope (major risk factors) or symptomatic tachycardia should have RFA of accessory AV conduction pathway performed (B).

2. RFA is indicated in patients with atrial fibrillation (or other atrial tachycardia), accompanied by high-frequency activation of ventricular myocardium (RR interval of 260 ms or less with anterograde conduction via accessory AV conduction pathway – the main risk factor for SCD) (B).

3. In patients with WPW syndrome and major risk factors who prefer medication therapy to RFA, class I antiarrhythmic agents or amiodarone are preferred (C).

4. Patients of high risk occupations (aircraft pilots, public transport drivers, athletes) who are diagnosed WPW syndrome/phenomenon should have RFA of accessory AV conduction pathway performed regardless of the presence of symptoms and the magnitude of anterograde effective refractory period (ERP) in accessory AV conduction pathway, and even if major SCD risk factors are absent (B).

5. Patients with WPW phenomenon and anterograde effective refractory period in accessory AV conduction pathway of less than 270 ms (a major risk factor) (B).

Class IIa

1. Regular cardiology checkups are indicated for patients with ECG ventricular pre-excitation signs and absence of major risk factors (history of symptomatic tachycardia, syncope, family history of SCD, structural heart disease, anterograde effective refractory period in accessory AV conduction pathway <270 ms) (C).

2. Antiarrhythmic agents are not indicated for patients with ECG ventricular pre-excitation signs and without history of symptomatic tachycardia, syncope, family history of SCD, structural heart disease, anterograde effective refractory period in accessory AV conduction pathway >270 ms (C).

Class IIb

1. RFA should be considered in patients with WPW phenomenon with anterograde effective refractory period in accessory AV conduction pathway >270 ms (C).

Class III

1. Digoxin, β-adrenoblockers, verapamil and ATP are contraindicated for patients with WPW syndrome/phenomenon (C).

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X.6. SCD in atrial fibrillation

Atrial fibrillation (AF) is associated with an increased risk of developing heart failure, cardiogenic thromboembolism, in particular cerebral strokes and, as a result, an increase in overall mortality [1, 2]. In addition, it is known that in some diseases, atrial fibrillation increases the risk of SCD. This concerns, in particular, the syndrome of WPW [3], hypertrophic cardiomyopathy [4] and the syndrome of the short QT interval [5], as discussed in the relevant chapters of these Guidelines. Moreover, the results of studies over the past few years indicate that AF may be an independent risk factor for ventricular fibrillation (VF) and SCD [6–9].

In patients suffering this arrhythmia, the risk of SCD due to the development of ventricular fibrillation or asystole is more than twice that of patients without AF [10]. The causes and mechanisms of a possible connection between atrial fibrillation and ventricular fibrillation have not been adequately studied. One of the most fundamental works on this issue is the analysis conducted on the basis of the ENGAGE AF-TIMI 48 Trial study, in which the results of 2,8-year treatment with anticoagulants, warfarin or edoxaban of 21,105 patients with AF were studied. Among other indicators, possible predictors of SCD [8] were studied. According to the results of this analysis, among the many parameters, the most frequent factors that can significantly increase the risk of SCD in patients with AF are: a previous myocardial infarction, CHF III–IV NYHA, LVEF <50%. Among the additional significant predictors of SCD in these patients are: age over 75 years, male gender, ECG signs of left ventricular hypertrophy, an increase in the number of heartbeats over 80/min, non-recognition of β-adrenoblockers, appointment of digitalis. A certain role

as risk factors for CSD may be an increase in the content of creatinine in the blood, the presence of a permanent or persistent form of AF, diabetes mellitus. Many of these factors are modifiable, but the possibility of reducing the risk of SCD by influencing them requires further research. The data available to date do not allow to believe that adequate therapy with anticoagulants can reduce SCD risk in AF, despite the reduction in the risk of stroke [2].

Risk stratification

AF may manifest as a sharp tachy- or bradycardia, causing hemodynamic disorders and accompanied by syncopal conditions, arterial hypotension, signs of myocardial ischemia, the appearance or exacerbation of heart failure. These symptoms are the most important risk factors for SCD, especially in patients with structural cardiac pathology, in particular, with myocardial infarction, pronounced left ventricular hypertrophy with signs of CHF III–IV NYHA. Among the main risk factors for SCD in patients with AF are WPW syndrome with episodes of tachycardia with an RR interval of less than 260 ms with an anterograde for AACP, and episodes of bradyarrhythmia with a rhythm frequency of less than 40 rpm or pauses exceeding 3 s due to AV blockade, especially of distal type.

Recommendations for SCD prevention

Class IIa

1. Adequate medical therapy of patients with CAD, post-MI cardiosclerosis, according to the current National Recommendations, including the use (in the absence of contraindications) of β-blockers, ACE inhibitors, acetylsalicylic acid, statins and other agents that reduce the risk of SCD in patients with this disease.

2. Adequate medical therapy of CHF, according to the current National Recommendations, including the use (in the absence of contraindications) of β-blockers, ACE inhibitors, aldosterone antagonists and other agents that reduce the risk of SCD in patients with CHF.

Class IIb

1. Adequate medical therapy of diseases accompanied by severe left ventricular hypertrophy (hypertrophic cardiomyopathy of arterial hypertension, etc.), according to the current National Recommendations, including the use (in the absence of contraindications) of β-adrenoblockers and other agents that reduce the risk of SCD in patients with these diseases.

2. In the presence of arrhythmic syndromes that threaten with the possibility of SCD, in particular WPW syndrome with threatening tachyarrhythmia, RFA is advisable.

3. In the presence of hemodynamically significant bradyarrhythmias, as well as severe bradycardia (<40 min) and pauses more than 3 seconds it is advisable to use permanent ECS.

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X.7. SCD in patients with congenital and acquired heart defects

X.7.A. SCD in patients with congenital heart defects

Congenital heart disease (CHD) is a heterogeneous group of patients with different structural pathologies, but with common mechanisms of atrial and ventricular remodeling. Depending on the degree of severity and duration of the defect, the process of remodeling and the formation of a substrate for ventricular arrhythmias is different. The main arrhythmogenic factors in these cases are myocardial hypertrophy and left and right ventricular dysfunction. The performed interventions on the one hand lead to correction of hemodynamics, on the other – can cause reentery tachycardias in the area of cicatricial fields.

Therefore, with all the variety of congenital malformations, risk stratification and prevention of sudden cardiac death are determined precisely by these three factors: the nature and degree of myocardial hypertrophy, the decrease in ventricular myocardial function, the presence or likelihood of sustainable ventricular tachycardias.

The incidence of SCD in patients with correlated CHD is 0.9–1.4 per 1000 patient-years, which is 25–100 times higher than in the general population [1, 2]. 90% of all sudden deaths occur in 4 groups of patients: having transposition of the main arteries, Fallot's tetralogy, aortic stenosis and coarctation of the aorta with increasing risk over time, especially with left ventricular and tetralogy of Fallot. 6–9% of patients after correction of Fallot tetralogy die suddenly during observation from 21 to 35 years (2–3% per year), accounting for up to 50% of all deaths in this group [2–4]. The highest incidence of SCD is observed in patients with aortic stenosis – 10–13% during 15 to 20 years of follow-up [2, 5].

Most cases of SCD in patients with correlated CHD are associated with ventricular arrhythmias: hemodynamically significant stable monomorphic ventricular tachycardias (VT) in patients who underwent ventricular and filling with a patch of an interventricular septal defect, or monomorphic or polymorphic VT and ventricular fibrillation in the absence of surgical scars. In the absence of a substrate for postinstitutional arrhythmias, the trigger mechanism of SCD is associated with pathological hypertrophy, fibrosis and heart failure.

Violation of the myocardial function of the right and left ventricles in this group of patients leads to disruption of cellular currents work. The decrease in potassium current activity and the increase in the action potential observed in cardiomyocytes of patients with myocardial dysfunction causes an early post-depolarization. Changes in calcium currents lead to late post-depolarization and trigger activity. Severe hypertrophy of the myocardium can be the result of chronic high blood pressure in the chambers of the heart in obstructive processes and uncorrected tetralogy of Fallot. Myocardial dysfunction occurs if the right ventricle remains systemic after an operation of arterial switching during transposition of the main arteries or in congenital correlated transposition of the main arteries. Left ventricular dysfunction may be associated with long-term cyanosis if the correction of the Fallot tetralogy was performed at adulthood or if there was a chronic volume overload after a palliative bypass procedure.

Verification of various mechanisms of arrhythmogenesis in congenital heart diseases is the key in assessing risk stratification and treatment. Existing data on late mortality and the risk of complications are based on patients who have

been corrected during adolescence. Early surgical correction and changes in surgical strategy, particularly in the tetralogy of Fallot and transposition of the main arteries, can affect not only early lethality, but also the frequency and potential mechanisms of arrhythmia, the risk of sudden death in adult patients in the future.

Fallot's tetrad

The tetralogy of Fallot occurs in 7.5% of cases of CHD and is characterized by subpulmonary stenosis, a subaortic defect of the interventricular septum with aortic dextrose and the development of right ventricular hypertrophy.

For the first time the correction of tetralogy of Fallot was performed by Lillehei in 1954. The high lethality of the first operations led to the development of a two-step correction technique – palliative bypass surgery at the beginning of life with subsequent radical correction in childhood. A complete correction includes the closure of the perimembranous or muscle defect of the interventricular septum (IVS) with a patch to remove the infundibular or valvular obstruction of the right ventricular outflow tract. Correction is performed using vertical or transverse right ventriculotomy in combination with a patch to expand the RV output tract. The characteristics of the defect and the type of correction are the main factors determining the conditions for the occurrence of reentery tachycardias. Areas of post-cicatricial scars, in combination with patch material and the fibrous ring of the pulmonary and tricuspid valves, form the slow-conduction areas and the substrate for reentry tachycardia.

Right ventriculotomy and frequent use of a transannular patch with subsequent pulmonary regurgitation with chronic volume overload leads to right ventricular dilatation and dysfunction with the risk of ventricular tachycardia and SCD in the future.

Changes in the myocardium in the tetralogy of Fallot, in particular, the development of myocardial fibrosis in the muscular part of the crista supraventricularis, are more pronounced in patients operated over the age of 4 years. The use of magnetic resonance imaging with gadolinium makes it possible to assess the degree of fibrosis of the right and left ventricles in the tetralogy of Fallot, which correlates with the frequency of occurrence of atrial and ventricular arrhythmias.

Although the high frequency of ventricular extrasystoles and episodes of unstable VT correlates with the induction of stable VT, there is no convincing data on the relationship with SCD in these cases, and treatment of asymptomatic ventricular extrasystoles is not indicated.

Primary correction in infancy up to 18 months is a common practice today and can be performed with low peri-operative mortality. Prevention of

long-existing hypoxemia and volume overload prevents the development of structural changes and the formation of a substrate for slow conduction and ventricular arrhythmias. However, despite the early operation, progressive pulmonary regurgitation occurs in almost all patients after a transannular correction by a patch, and this is one of the factors affecting the need for a repeat operation.

Moderate or severe pulmonary regurgitation and abnormal right ventricular hemodynamics and increased end-systolic pressure are associated with VT and SCD. In addition, the width of the QRS complex of over 180 msec is a risk factor for stable VT and SCD.

Violation of the function of the right and left ventricles (EF less than 40%) are important in assessing the prognosis of patients with the tetralogy of Fallot. The diastolic pressure of the left ventricle is less than 12 mm Hg. is an independent predictor of adequate shock discharges in patients with the Fallot tetrad and implanted ICDs [6].

Despite a noticeable decrease in the volume of the right ventricle and improvement of hemodynamics after correction of the pulmonary valve, a simple valve replacement does not eliminate the substrate of ventricular arrhythmias, mainly having a rientry mechanism. In one series of patients with a QRS complex width of more than 180 ms after a late correction of the defect, the 5- and 10-year total freedom from death and VT was 80% and 41% and did not differ from the control group similar in age, pulmonary regurgitation, right ventricular dilation and QRS width, which did not perform valve correction. The addition of the operation with mapping and cryodestruction of the arrhythmogenic zone resulted in freedom from VT in 96% at a follow-up of 7.5 years [7].

At present, there is no data on the efficacy of AAA in patients with VA and tetralogy of Fallot. However, in general, the prescription of AAA for the prevention of recurrent reentry VT has ambiguous efficacy and is complicated by side effects. A real alternative to AAA is a catheter technology aimed at destroying zones of slow conduction in hemodynamically stable VT, at which activation mapping is possible. In cases of fast and hemodynamically unstable VT, it is possible to use the technique of mapping the arrhythmia substrate and destroying possible components of the reentry chain.

Verification of the connection between the anatomical transitions and the macro-reentry of the VT can help for intraoperative mapping and destruction in repeated operations with regurgitation of the pulmonary valve.

In accordance with the existing recommendations, the ICD in patients with CHD and VT should be implanted after ineffective catheter destruction and after the SCD episode. Implantation of the ICD should be considered in

patients after unexplained syncope without specific and reversible reasons. In these cases, the induction of VT and NVT can be useful.

Preventive implantation of the ICD in patients after correction of the tetralogy of Fallot is a matter of discussion, but can be considered in the presence of right and left ventricular dysfunction, severe fibrosis, QRS width of more than 180 ms, and induction of VT during electrophysiological examination. It is important that more than 80% of the VAs cured by the ICD are monomorphic fast VTs, but 70% require a shock discharge to stop VT. In these cases, catheter destruction of the VT substrate is justified, however, there are no remote results in this group of patients yet. Complications associated with the ICD, 25–30% of which are unreasonable discharges associated with the NVT and electrode problems, should be remembered [6].

Transposition of the main arteries (TMA)

TMA is the most common «blue» heart disease in newborns, representing 5% of all CHDs. Complex TMA is associated with a defect of the interventricular septum and obstruction of the outflow tract of the left and right ventricles.

Until the early 1980s, patients with TMA underwent a two-stage surgical correction. The atrial septectomy of Blalock-Hanlon, proposed in 1950, was replaced by balloon atrial septostomy with the Raskind balloon after 1966 and was performed shortly after the birth of the child. Then, in the first year of life, a switching operation is performed using the Senning or Mustard technique. In the Senning operation, first performed in 1959, an atrial septum is used to create a separation barrier and redirect blood flow from the hollow veins to the left ventricle. Mustard operation, proposed in 1964, uses a patch made of pericardium or synthetic material. According to the observations of patients after the operation of «switching», SCD is the main cause of death of these patients in the long term and is $4 \pm 7\%$ in terms of up to 10 years and $9 \pm 4\%$ in terms of up to 20 years of follow-up [2].

More than 80% of cases of SCD occur at load, which is the result of the inability of the myocardium to increase cardiac output. Atrial arrhythmias often precede SCD, reducing the atrial systole and filling the ventricles of the heart. Symptomatic arrhythmias with signs of heart failure and documented episodes of flutter or atrial fibrillation are predictors of SCD in patients after Mustard or Senning operations [8].

Since 1975, anatomical correction of the arterial switching operation becomes a method of choice. This approach not only reduces the likelihood of atrial arrhythmias and sinus node dysfunction, but reduces the likelihood of fatal ventricular arrhythmias, since the left ventricle maintains systemic blood flow. Correction of a simple TMA does not require surgical access to the

ventricles or the use of patches and is not associated with a risk of occurrence of postinversion monomorphic VT, as in patients with the tetralogy of Fallot. The use of plastic materials is necessary in cases of correction of complex forms of TMA, if it is necessary to close the defect of IVS, and may be the cause of the development of the macro-reentry VT. Complex anatomy of the defect and operations for its correction require the use of computerized tomography data integration systems in electrophysiological mapping, which makes it possible to visualize the substrate of arrhythmia.

The risk of SCD with TMA is 4% within 10 years after correction (5–8 cases per 1000 patient-years). In most cases, ventricular arrhythmias and SCD in this group of patients were preceded by atrial arrhythmias. Other SCD risk factors are RV dysfunction, venous obstruction and width of the QRS complex of more than 140 ms, but there are no specific criteria determining ICD implantation.

It is important to understand that implantation of the ICD can be technically difficult with intra-atrial patches and implantation of the electrode in the morphologically left ventricle. Patients in this group have a high incidence of unmotivated discharges (6.6% per year) associated with atrial arrhythmias [9].

Congenital aortic stenosis

Despite surgical correction, aortic stenosis has the greatest risk of SCD (5.4 per 1000 patient-years) [2].

The obstruction of the output tract of the LV includes a heterogeneous group with obstruction at different levels: subvalvular, valvular and supravalvular. Valvular stenosis is usually the result of degeneration of the bicuspid aortic valve and occurs most often. Subvalvular stenosis is caused by the valve membrane. Rare cases of non-valvular stenosis are associated with other malformations, such as Williams syndrome, or are the result of a previous surgical procedure (for example, an ascending aortic suture after a TMA switching operation).

The risk of SCD in this group of patients depends on the time of the existence of the defect and is associated with left ventricular myocardial dysfunction and myocardial hypertrophy.

Aortic coarctation

The frequency of SCD in patients after correction of aortic coarctation is 1.3 per 1000 patient-years [2]. Coarctation of the aorta can occur at different levels, but classically occurs in the so-called «isthmus,» below the left subclavian artery. One third of patients have a bicuspid valve. Even after correction of coarctation, patients may remain prone to hypertension and concomitant hypertension of the LV, which may be the cause of an increased risk of SCD in this group of patients.

IX.7.B. SCD in patients with acquired heart defects

Operations with acquired heart defects are usually not associated with ventriculotomy and are limited to plastic surgery or replacement of heart valves – more often aortic and mitral. The process of pathological remodeling in these cases is limited to a change in the structure of the myocardium of the left and right ventricles with underlying disease and hemodynamic disorders that occur in the heart disease. In patients after correction of heart valves, without signs of a previous myocardial infarction, the occurrence of stable VT is rarely observed. Registration Stable VT is usually associated with the presence of scar changes and is the basis for electrophysiological examination and ICD implantation [10].

Typical and most significant risk factors for the occurrence of life-threatening arrhythmias in this group of patients is myocardial hypertrophy and a decrease in its pumping function. Myocardial dysfunction with a reduction in the ejection fraction of less than 35% is an indication for ICD implantation, and in cases of combination with signs of blockage of the left bundle branch – a system of resynchronizing therapy. The need for simultaneous implantation of these systems and correction of heart disease is required rarely – only in cases of secondary prevention of SCD or obvious doubts about the prospects of improving myocardial function after correction of the defect.

Risk stratification

At present, there is no evidence that mitral valve repair or replacement reduce the risk of VA in patients with valvular heart disease. Therefore, these patients are managed based on the current guidelines for every individual diseases.

Clinical workup and treatment of patients with valvular heart disease and VA should be based on current guidelines for the diagnosis and treatment of heart defects and the identification of major and minor risk factors and other clinical and instrumental data, in particular a low EF.

Positive effects of mitral valve repair or replacement on SCD prevention in patients with mitral valve prolapse, severe mitral regurgitation with hemodynamically significant VA (a major risk factor) are not proven.

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X.8. SCD risk stratification and prevention in patients heart connective tissue development abnormalities

Over the past two decades, the idea of connective tissue dysplasia (CTD) of the heart, manifested by changes in the connective tissue framework and valvular apparatus, has been actively developing with the formation of so-called small cardiac anomalies [1].

The arrhythmia developing with small heart anomalies is of great interest to researchers [2,3]. Both structure and functions anomalies of the heart conduction system (dysfunction of the sinus node and sinoatrial zone, additional pathways and interfascicular connections), and hemodynamic disorders that occur with regurgitation of blood due to valve prolapse lie at the heart of the development of arrhythmias in these conditions. A significant pro-arrhythmic role is played by deformation of the left ventricular (LV) cavity arising from extracardiac causes and under the influence of the heart's anomaly [4].

Rhythm and heart conduction disorders with CTD are recorded quite often. In the electrocardiographic study, in 2/3 patients with undifferentiated heart CTD, some deviations are detected, in Holter monitoring, in 95% of patients [5, 6].

Mitral valve prolapse

The frequency of sudden death in MVP syndrome depends on many factors, the main ones of which are electrical instability of the myocardium in the

presence of the syndrome of the long QT interval, ventricular arrhythmias, concomitant mitral insufficiency, neurohumoral imbalance [7].

Sudden death in patients with MVP is recorded in less than 0.2% of cases during a long-term follow-up [8, 9, 10]. In the absence of mitral regurgitation, the risk of SCD is low and does not exceed 2:10,000 per year, while with concomitant mitral regurgitation the risk increases 50–100 times [7, 11].

Meanwhile, in children with MVP, ventricular arrhythmias and variance of the QT interval are significantly more often compared with the control group [12]. In addition, MVP is a frequent (3–5%) cause of sudden cardiac death (SCD) in athletes with congenital coronary artery anomalies and hypertrophic cardiomyopathy. In most cases, SCD with MVP is arrhythmogenic and is caused by the occurrence of idiopathic ventricular tachycardia or with long QT interval syndrome [3, 7, 9].

The special attention should be paid to the special subgroups of MVP with a high risk of developing SCD, i.e. to patients with severe mitral insufficiency due to the flail leaflet of the mitral valve – a formidable complication of prolapse, which significantly affects the prognosis. Based on the results of a long-term follow-up of patients with severe mitral insufficiency, valid SCD predictors based on multivariate analysis included: NYHA functional class, LV ejection fraction and presence of atrial fibrillation. Surgical correction of mitral insufficiency in most cases leads to a significant reduction in the risk of sudden death [13].

False tendon of the heart

False tendons (FT) in recent years are referred to small heart anomalies by most authors and are considered as the cause of violations of intracardiac hemodynamics, diastolic LV function, electrical stability of the heart. According to the literature, FT demonstrated their high arrhythmogenic significance [14].

To explain the participation of FT in the origin of heart rhythm disorders, various mechanisms are proposed. First, FT can function as a conductor due to the presence of cells in the conducting system, generating the phenomenon of re-entry. Secondly, mechanical stretching of the myocardium at the site of FT attachment can generate the appearance of ectopic impulses [4,15]. Thirdly, the FT attachment sites can act as sites with a reduced speed of impulses, or they can be blocked altogether, causing local «swirls» in the conducting system, which can also trigger a re-entry mechanism, significantly increasing the risk of life-threatening rhythm disturbances. Also, FT can participate in cardiac remodeling, which in itself is a pro-arrhythmic factor [4].

The cause of bioelectric instability of the heart can serve as a morphological heterogeneity of the myocardium, arising from local disturbances of

microcirculation due to traction of tissues adjacent to FT attachment sites. In addition, changes in myocardial microcirculation due to CTD also cause the development of sclerosis (or apoptosis) sites. Alternating with functionally active zones, they cause electrical heterogeneity of the heart tissue. Endocardial irritation resulting from excessively long FT may lead to the formation of foci of ectopic activity and the development of ventricular arrhythmias. The turbulent flow of blood arising from the obstruction in its path in the form of a transverse strand is also a factor contributing to the bioelectric instability of the myocardium [4].

Ventricular extrasystole and left ventricular false tendons

In 1984, the first opinion about the arrhythmogenic role of drugs in practically healthy individuals with ventricular extrasystole (VE) was expressed [16,17]. In people with LVFT VE is significantly more frequently noted. In turn, the prevalence of LVFT among people with VE is significantly higher, compared with people without it [18]. Moreover, the prevalence of the left ventricular lesion among people with frequent VE (more than 1000 per day) is significantly higher than among those with a more rare extrasystole, and bifoccus and paired extrasystoles were recorded by the authors only in persons with LVFT [17].

LVFT, MVP, and their combination are significantly more often detected in patients with frequent (more than 3 in 1 min.) monotopic VE in comparison with patients without heart rhythm disturbances. According to the multivariate analysis, the presence of LVFT and MVP is significantly associated with the frequency of VE, while the effect of MVP and LVFT, taken separately, is insignificant. [19].

VE is more often observed in the presence of FT in the basal part of the interventricular septum (IVS) [20–23]. The frequency of VE increases with FT thickening, in the presence of several FT, as well as in the case of FT attachment IVS and papillary muscles [5, 20, 21, 23].

In patients with LVFT, in the absence of organic damage to the heart, the occurrence of ventricular arrhythmia (VA), including ventricular fibrillation, paroxysmal ventricular tachycardia, has been described. Spontaneous rupture of FT is associated with cessation of cardiac arrhythmia [24]. The development of VA in patients with FT is facilitated by dilatation of the LV cavity, as well as a violation of its diastolic filling and local disturbance of intracardiac hemodynamics in the area of FT location. An analysis of echolocation shows that with a significant increase in the echosomalency of drugs over the acoustic solidity of the intact myocardium, there is a decrease in the frequency of VA development. Since the cause of high acoustic solidity is an increase in the

content of collagen fibers, this indicates that an increase in the content of connective tissue in the FT leads to a decrease in the likelihood of heart rhythm disturbances. That is, with VE associated with drugs, consisting primarily of muscle and Purkinje's cll cells [24].

Heart rhythm disorders in myocardial infarction and the presence of false tendons

In patients in the acute period of myocardial infarction (MI), ventricular fibrillation (VF) is significantly more frequent in patients with LVFT. In patients with MI, the development of VF has a reliable relationship with the presence of LVFT, high Killip class, the presence of LV asynergy (sensitivity 83.3%, specificity 92.7%) [14].

According to the results of discriminant analysis, there have been identified five factors that have a high ability to discriminate against patients survived FV: LVFT, LVFT localization, LV cavity size, LV asynergy size, intracavitary cardiac calcification (sensitivity 87.5%, specificity 95.0%). When the model was tested, a sensitivity of 80% and a specificity of 92.5% were demonstrated in a group of patients with acute MI [4, 25].

Connection of false heart tendon with the syndrome of early ventricles repolarization

Among patients referred by doctors to EchoCG, the incidence of electrocardiographic syndrome of early ventricular repolarization (EVRS) in patients with left ventricular FT is more than 80% [20, 26–30]. When LVFT combined with MVP and other manifestations of connective tissue dysplasia, the EVRS is determined in 93% of cases [23]. As the severity of the EVRS increases, the number of registered signs of undifferentiated CTD increases [25].

In persons of military age with LVFT, the EVRS occurs in 42.9% of cases. The most characteristic is the presence of EVRS in persons with transverse LVFT – 55.5% and with multiple LVFT – 77.3% compared with 18.7% of EVRS with diagonal location of the left ventricle FT. Thus, EVRS in persons with FT can be considered as a syndrome marker of heart CTD syndrome [28, 31].

A number of authors consider the cause of the EVRS in changing the process of normal propagation of excitation, premature excitation of individual areas of the myocardium, leading to an earlier onset of repolarization of these regions as a result of the passage of a pulse along FT starting from MVP [29, 32–35]. Other things being equal, FT reduces the distance from the MVP to the free wall of the LV or the papillary muscle. The change in the process of normal activation, as is known, leads to violations of repolarization. Perhaps, this can explain the cases of pronounced changes in repolarization in the left ventricle.

Clinical examination of patients with structural heart anomalies

The questions of prevention and medical examination of persons with small heart anomalies remain unexplored. Most researchers agree on the need for regular follow-up and regular echographic examinations once a year. Carrying out EchoCG at the present time allows to diagnose the presence of small anomalies with sufficient accuracy, to determine their location and potential value in LV remodeling, hemodynamic disturbances and heart rhythm disturbances, which serves as an additional tool for determining the tactics with which to prevent SCD in each specific the case.

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X.9. SCD in patients with metabolic and inflammatory diseases

X.9.A. . SCD risk stratification and prevention in patients with myocarditis and infective endocarditis

Myocarditis

Myocarditis is a predominantly inflammatory disease of heart muscle, caused directly or indirectly by immune mechanisms during infection, parasitic or protozoal infestations, chemical or physical agents exposure, as well as lesions that occur in allergic and autoimmune diseases [1]. Myocarditis in combination with heart dysfunction is referred to as inflammatory cardiomyopathy [2], both these terms are presented in the recommendations of ESC [3].

A viral infection is the most common etiologic factor causing myocarditis, it is responsible for more than 60% of cases (in European population, the most common are adenoviruses, enteroviruses (Coxsackie B), parvovirus B – 19 and human herpes virus – 6 and their associations) [1]. Among bacterial pathogens, intracellular pathogens (Chlamidia) have gained the greatest importance in recent years [4]. Other reasons of myocarditis include: direct and indirect effects of toxic substances (e.g. drugs) allergic and autoimmune reactions in patients with systemic diseases (autoimmune diseases, cancer, sarcoidosis, ulcerative colitis) [1, 2, 4].

The incidence of myocarditis in different European countries varies significantly and ranges from 0.12% to 12% [5, 6]. Diagnosis of myocarditis is made in less than 1% of hospitalized patients, while according to autopsy data the disease signs are present in 3–9% of cases [4].

Verification of myocarditis is a complex multicomponent process. The gold standard of diagnosis is endomyocardial biopsy, in which there are signs of inflammation in the myocardium, necrosis of cardiomyocytes, as well as the pathogen of the inflammatory process or its fragments [7]. The diagnosis of myocarditis is established in accordance with the criteria described by Caforio et al. [3].

Apparently, in clinical practice there is a significant hypodiagnosis of myocarditis. A comprehensive examination of a large group of patients with "idiopathic" different variants of rhythm and conduction disorders, including endomyocardial biopsy, allowed O.V. Blagovoy et al. [8] to establish the diagnosis of a certain myocarditis in 55% of cases. Another 22% of those surveyed had probable myocarditis, and in 9% of cases there was a combination of myocarditis with genetic cardiomyopathies.

Autopsy of individuals who died suddenly shows morphological signs of myocarditis in 8.6% of cases [9], and in up to 40 % of individuals younger than 40 year [10,11].

The direct mechanism of SCD in patients with myocarditis is sustained arrhythmias that according to an epidemiological study ESETCID, conducted in Europe, are present in 18% of patients [112]. A correlation between the arrhythmias incidence and severity and morphological variant of myocarditis is present, e.g. the worst arrhythmias occur in patients with giant cell myocarditis. In another study [13], about 5% of cases of myocarditis manifested with ventricular tachycardia.

There are two different clinical scenarios depending on the nature of the VA associated with myocarditis: 1. Acute and fulminant myocarditis with refractory malignant VA and an unfavorable short-term prognosis. 2. Prolonged progression of the disease with the development of inflammatory cardiomyopathy and LV dysfunction associated with high risk of SCD, as in the case of CMD.

Acute and fulminant myocarditis

Fulminant myocarditis is a separate form of inflammatory myocardial infarction, the characteristic features of which are a high incidence of refractory malignant VA, acute HF and a poor immediate prognosis. Prognostically unfavorable signs in the early period are a progressive decrease in LV systolic function, persistent elevation of cardiac troponin, development of unstable VA, and signs of intraventricular conduction disturbances [14]. Short-term prognosis with fulminant form of myocarditis is unfavorable, however, long-term prognosis is optimistic for survivors. According to the Japanese registry, short-term survival with fulminant myocarditis does not exceed 58% [15].

Acute myocarditis in Lyme disease and diphtheria is characterized by a high frequency of conduction disorders of the heart, often requiring the setting up of a temporary ECS.

Giant cell myocarditis is a severe form of myocarditis with an extremely unfavorable course, often found in young people. The diagnosis is confirmed by endomiocardial biopsy data, in which typical giant multinucleate cells are detected in inflammatory foci. A frequent symptom is the development of severe cardiac conduction abnormalities that require the implantation of ECS. Combined antiarrhythmic therapy is often not effective, the prognosis in such patients is extremely unfavorable due to refractory electric storms, continuous VT or VF.

In all cases of acute and fulminant myocarditis, hospitalization, restriction of motor activity and monitoring of basic vital functions are required. In the presence of signs of heart failure, basal therapy of ACE inhibitors, β-blockers with the purpose of creating a neurohormonal blockade, symptomatic, including antiarrhythmic therapy, is often required, and implantation of ECS, cardiopulmonary support systems or intra-aortic balloon counterpulsation is often required [14].

The question of ICD implantation, as a rule, is considered after the end of the acute phase of myocarditis. Indicators in favor of an earlier resolution of this issue are recurrent life-threatening VA, giant cell myocarditis and sarcoidosis. An effective temporary solution in such cases may be the use of a dressed cardioverter-defibrillator.

Myocarditis leading to inflammatory cardiomyopathy

A number of large prospective studies found that the cause of 10–21% of cases of DCM is myocarditis [16]. On the other hand, two-thirds of patients with an unstated nature of systolic myocardial dysfunction have a viral genome in the cardiac muscle [17].

Drug therapy and interventional treatment of arrhythmias, including for the prevention of SCD, with this version of myocarditis do not have any specific features and should be conducted in accordance with recommendations for the treatment of arrhythmias in patients with CHF.

Reccomendations

Class I

1. Patients with life-threatening clinical manifestations of resistant ventricular tachyarrhythmias in the presence of myocarditis are recommended with treatment in specialized centers capable of monitoring hemodynamics, cardiac catheterization and endomyocardial biopsy, the use of mechanical assist devices for cardiopulmonary support, and the possibility of providing specialized types of care for arrhythmias (C).

2. Patients with acute myocarditis with the development of severe bradycardia and / or conduction disorders of the heart, accompanied by clinical manifestations, implantation of temporary ECS (C).

Class IIa

1. AAA is suitable in patients with unstable and resistant VT in the acute phase of myocarditis (C).

2. ICD implantation can be effective in patients with stable hemodynamically significant VT outside the acute phase of myocarditis, receiving constant optimal drug therapy and having a favorable prognosis for survival for 1 year or more (C).

3. Consideration should be given to the possibility of implantation of an ICD or a permanent pacemaker in patients with inflammatory diseases of the heart after arresting an acute condition (C).

4. Wearing an external defibrillator should be considered as a transitional therapy before complete recovery or implantation of a permanent ICD in patients after an inflammatory myocardial disease with persistent

severe LV dysfunction and / or electrical instability of the ventricular myocardium (C).

Class IIb

1. ICD implantation can be considered earlier in patients with giant cell myocarditis or sarcoidosis in the presence of resistant VT with a violation of hemodynamics or history of cardiac arrest episode, given the unfavorable prognosis for these conditions, provided an expected life span > 1 year with a good functional status (C).

2. Additional indicators of adverse prognosis and increased risk of SCD in inflammatory myocardial diseases are signs of myocardial infiltration according to immunohistochemical data and / or pathological focal fibrosis from the results of MRI of the heart after myocarditis (C).

Infective endocarditis

Infective endocarditis (IE) is inflammation of the valve structures, parietal endocardium or endothelium by the great vessels congenital defect caused by direct penetration of a pathogen, it usually resembles sepsis (acute or subacute) with pathogen circulation in the blood, venous thromboembolism, immunological changes and complications [18].

The major pathogens causing IE in the past decade are staphylococci and streptococci, which are identified in 75–90% of patients with positive blood cultures [19]. The specific weight of other pathogens, i.e. fungi, chlamydia, rickettsia, mycoplasmas, viruses, is significantly lower. There is a correlation between the causative agent and the clinical course of the disease. Thus, subacute IE is usually caused by various types of Streptococcus, while acute IE is often associated with Staphylococcus infection [20].

Epidemiology of IE in recent years is characterized by the emergence of specific forms: IE in drug addicts (with tricuspid valve involvement), IE in patients with valve prosthesis, IE in patients with implanted pacemakers, IE in patients on hemodialysis, IE in transplanted organ recipients [21, 22].

Nowadays, one of the major problems of IE is the increasing resistance of pathogens to commonly used antibiotics, which largely determines high mortality in IE patients that reaches 10–26% even in hospital settings [23–25]. Most of the sudden deaths are due to acute heart failure as a result of valve destruction or fulminant septic shock that is typically associated with valve abscess formation; although such cases can not be classified as SCD [26].

At the same time, the formation of an abscess in the interventricular septum (IVS) or the extension of a purulent process from the aortic valve to IVS may lead to the destruction of the heart conduction system, that

may cause complete AV block and SCD [27]. In this regard, AV block in a patient with IE should always raise a concern about presence of such severe complications as abscess. VE in patients with infective endocarditis is an extremely unfavorable prognostic sign [28], while at the same time there are no specific recommendations for the treatment of arrhythmias in this group of patients.

Treatment of IE patients with should prolonged, integrated and multi-component. In all cases, antibiotic treatment should be administered taking into account the etiological factor, in most cases a combination of antibacterial agents is required [19,21–23,26]. The other major directions of treatment in addition to antibiotic therapy are surgical treatment and immune replacement therapy.

Recommendations

Class I

1. Surgical correction of severe aortic valve regurgitation associated with ventricular tachycardia in patients without contraindications is indicated (C).

2. Surgical treatment of acute endocarditis complicated by abscess of aorta or aortic valve, associated with AV block in patients without contraindications is indicated (C).

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X.9. B. SCD risk stratification and prevention in patients with metabolic syndrome, obesity, dieting and anorexia

Introduction and Epidemiology.

Metabolic syndrome is a set of interrelated risk factors of cardiovascular diseases as a result of atherosclerosis. There are different criteria for diagnosing the metabolic syndrome; abdominal obesity, arterial hypertension, atherogenic dyslipidemia (increased triglycerides, decreased high-density lipoprotein cholesterol in the blood), insulin resistance (impaired glucose tolerance, fasting hyperglycemia, type 2 diabetes mellitus) are considered [1–5]. The prevalence of the metabolic syndrome varies greatly depending on the region, the patient population studied, and the diagnostic criteria. So, according to various data received in the Russian Federation, it can be from 12 to 65% [6, 7].

The metabolic syndrome describes a number of changes potentially contributing to the onset of SCD – an increase in the duration and dispersion of the QT interval [8–12], changes in heart rate variability indicating a predominance of sympathetic effects on the sinus rhythm and / or decreased vagal activity [12–21], hypertrophy of the left ventricle [22–24]. In addition, with expressed metabolic disorders, there may be additional risk factors for SCD: hypokalemia, hypoglycemia, promoting sympathetic nervous system activation and disturbance of myocardial repolarization with prolongation of the QT interval, obstructive sleep apnea syndrome.

Obesity and excessive measures on rapid weight loss contribute to SCD. The risk of SCD is particularly high in patients with severe obesity and its presentce in young age [30, 32]. It is most likely due to the emergence of life-threatening ventricular arrhythmias, although conduction system abnormalities were also identified in young individuals who died suddenly [33]. Factors that increase SCD risk in obese individuals are: increased duration and dispersion of QT interval, changes in heart rate variability, characteristic structural changes of the heart (cardiomegaly, dilatation of the left ventricle, myocardial hypertrophy with no signs of interstitial fibrosis) and obstructive apnea [31, 35–37]. Risk of SCD in obese individuals can be significantly reduced by weight loss. Manifestations of cardiomyopathy and QT prolongation are also reversible, especially in the early stages of the disease [38–40]. There are reports on arrhythmias and SCD in patients following long-term, not balanced, very low calorie diets (especially liquid protein diets) [41–45]. Accordingly, a low-calorie diet that promotes weight loss should be well balanced

Mortality in anorexia nervosa patients is likely to be about 6% [46]. It is believed that almost one third of deaths, including deaths after food intake resumption is due to heart disease, but the exact data on SCD causes are

lacking. Prolonged fasting leads to heart muscle atrophy, sinus bradycardia, QT interval prolongation as well as electrolyte disturbances that exacerbate these disorders. Most myocardial abnormalities are completely reversible after appropriate food intake resumption [47–49]. Resumption of food intake after prolonged starvation may be associated with cardiac, neurological and hematological disorders caused by imbalance of fluids and electrolytes. Cardiac complications usually arise during first week after feeding resumption and are commonly associated with severe nutritional deficiencies, hypophosphatemia and use of parenteral nutrition only [50–53].

SCD risk stratification algorythm

Every major component of metabolic syndrome (obesity, hypertension, impaired lipid carbohydrate metabolism) can be a risk factor for SCD if severe enough [54]. At present, it is unclear whether the combining of these predisposing factors into the metabolic syndrome adds information on SCD risk stratification as the published data are contradictory [32, 55, 56].

Measures for SCD prevention

Class I

1. There are no specifics on treatment of life-threatening VA (including idications for ICD and ECS implantation) in patients with metabolic syndrome, obesity, anorexia or dieting. (C).

Class IIa

1. Weight loss program for obese patients and carefully controlled feeding resumption in anorexia patients can reduce risk of VA and SCD (C).

Class III

1. Long-term, nonbalanced, very low-calorie diet and fasting are not recommended since they may be dangerous and may cause life-threatening VA (C).

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X.9. C. SCD risk stratification and prevention in patients with endocrine disorders

Risk stratification

Hormonal regulation abnormalities may be the direct or indirect cause of SCD due to life-threatening arrhythmias and conduction blocks. Endocrine disorders have both the direct effect on the myocardium (e.g., pheochromocytoma, hyperthyroidism, hypothyroidism) and may cause conditions that increase risk of arrhythmias (e.g., electrolyte abnormalities associated with adrenals dysfunction). Some endocrine disorders contributes the development of conditions that lead to structural heart disease that, in turn, may increase risk

of SCD (e.g., dyslipidemia increases risk of coronary artery disease; secondary hypertension leads to left ventricular hypertrophy).

Diabetes Mellitus

It is known that in post-MI patients, diabetes increases risk of SCD [1–3]. Thus, in patients with type 2 diabetes, the risk increased not only with an increase in the level of glucose (RR 1.73, 95% CI, 1.28–2.34), but also in the presence of microvascular complications (RR 2.66, 95% CI 1, 84–3.85). However, in women, risk factors such as smoking, hypertension and diabetes mellitus, increased the risk of SCD by 2.5–4 times [2–4].

In the development of SCD syndrome in patients with diabetes, regardless of the presence of coronary atherosclerosis, both the electrical instability of the myocardium and the actual myocardial damage contribute to it. One of the proposed mechanisms underlying the development of SCD is cardiac autonomic neuropathy and the associated lengthening of the QTc interval. Thus, with QTc interval in the upper quartile, the risk of SCD was 2.8 times higher than in patients who had a normal QTc interval [5]. The prolongation of the QTc interval in patients with type 1 diabetes, especially in conditions of hypoglycemia, can lead to the development of fatal arrhythmias (VT and FF) and SCD [6].

At present, the issue of the relationship between hyperglycemia and the risk of SCD remains open, as the available data are rather contradictory. However, most researchers agree that such an association exists if fasting glycemia exceeds 7.7 mmol / L [5].

It is known that diabetes mellitus may increase the risk of SCD in the population of patients with myocardial infarction [4,7], and those with diabetes have a heavier coronary lesion compared to those without diabetes [8]. It is believed that the presence of diabetes, regardless of other factors, significantly increases the risk of SCD, supplementing such factors as low fraction of the left ventricular ejection and high functional class of heart failure. The mechanism of SCD in such patients is realized through the development of atrial fibrillation [9]. In addition to the above reasons, the thrombogenic effect of metabolic disorders, namely, the increase in plasma clotting factors (in particular, thrombin, factor VII), the reduction of endogenous anticoagulants (thrombomodulin, protein C), the production of an inhibitor of the plasminogen activator type 1 – PAI-1 [10].

Thus, the identification of potential factors for the development of SCD syndrome in patients with diabetes and their timely correction are an important component of the prevention of SCD syndrome. Normalization of the level of glycemia reduces the risk of cardiovascular diseases. However, there is no evidence that there is a decrease in the number of sudden deaths. In contrast, a number of studies have demonstrated that intensive glycemic control,

accompanied by an increased risk of hypoglycemic conditions, when combined with cardiac autonomic neuropathy and hypokalemia, can lead to an increased risk of fatal outcomes.

Recommendations for the prevention of SCD in patients with diabetes (aimed at the prevention and treatment of arrhythmias) [11]

Class I

1. Patients with diabetes and AF show oral anticoagulants (K Vvtamin antagonists or new: dabigatran, rivaroxaban, apixaban) in the absence of contraindications (A).

2. Patients with diabetes and ischemic cardiomyopathy with LVEF <35%, as well as survivors of ventricular fibrillation and stable ventricular tachycardia, are recommended to implant a cardioverter defibrillator (A).

3. To prevent SCD in patients with diabetes and heart failure, and after myocardial infarction, the administration of β-blockers (A).

Class IIa

1. Patients with diabetes should be screened for AF because it is a common cause of SCD (C).

2. Patients with diabetes and AF should undergo an assessment of the risk of bleeding (HAS-BLED scale) when prescribing antithrombotic therapy (C).

3. Patients with diabetes should undergo a screening for risk factors SCD (C).

Obesity, metabolic syndrome

Obesity, in itself, is considered one of the important causes of SCD. It is known that obesity is a risk factor for CAD and type 2 diabetes. However, the independent role of obesity as a cause of SCD is also established. This is confirmed by the findings of the Framingham study, indicating an increased risk of SCD as body weight increases, both in men and women [12]. In addition, according to different population-based studies, obesity was the cause of SCD non-ischemic origin in about 20% of cases [12], which indirectly confirmed not ischemic but arrhythmogenic character of death [12, 13]

Metabolic syndrome, the main component of which is abdominal obesity, according to prospective studies increases the risk of SCD. Thus, according to the results of the Paris prospective study, the metabolic syndrome was associated with a 68% increase in the risk of SCD in a population of middle-aged men who did not suffer from diabetes or ischemic heart disease at the time of enrollment [14]. Such components of the metabolic syndrome, as hypertension, hypercholesterolemia and hypertriglyceridemia, increased the risk of both sudden and any other cardiac death. At the same time, patients with metabolic syndrome with SCD often showed fasting hyperglycemia and an increase in the

amount of abdominal fat. The closest correlations were established between the waist circumference and the risk of SCD [14].

One of the possible mechanisms linking obesity and SCD, is the phenomenon of long QTc interval [15]. Despite the obvious association of abdominal obesity with the prolongation of the QTc interval, specific mechanisms of arrhythmogenic effects are under study [16]. Perhaps, an important role is played by a high level of free fatty acids, leading to a violation of repolarization, as well as an increase in the concentration of catecholamines. An important factor in regulating the activity of the cardiovascular system and the risk of developing life-threatening arrhythmias is the violation of autonomic regulation, as well as the development of dilated cardiomyopathy in obese patients [17].

Thus, abdominal fat in excess can realize its pro-arrhythmic effect both through structural changes in the myocardium and through the syndrome of sleep apnea, increasing the risk of life-threatening arrhythmias. At the same time, the results of studies on the effect of weight loss on mortality rates, including SCD, are controversial. It is well known that weight loss reduces the risk of cardiovascular diseases and type 2 diabetes. In small clinical studies, weight loss as a result of bariatric surgery has been shown to improve heart rate variability and normalize the QTc interval [18]. However, one should take into account the fact that fasting, a very low-calorie diet, surgical treatment of obesity can lead to hypocalcemia, hypokalemia, hypomagnesemia, which in turn increases the risk of developing life-threatening rhythm disturbances.

Acromegaly

The main cause of death in patients with acromegaly is cardiovascular system damage [19]. Long-term and active acromegaly (with autonomous secretion of growth hormone) causes so-called acromegalic cardiomyopathy that is characterized by concentric hypertrophy, diastolic, and later systolic dysfunction with severe heart failure that is refractory to conservative therapy. chronic hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) also leads to development of insulin resistance, type 2 diabetes mellitus, dyslipidemia, and contributes to the emergence of hypertension and left ventricular hypertrophy. Coronary atherosclerosis is not typical for acromegaly. Patients with acromegalic cardiopathy have various rhythm and conduction disorders (atrial and ventricular extrasystoles, AF and VT) more often than in the general population. It is believed that the frequency of ventricular rhythm disturbances correlates with the duration of the disease, and severity is greater with the severity of left ventricular hypertrophy than with biochemical signs of disease activity. According to some reports, about 75% of patients with acromegaly have a sleep apnea syndrome, which can also contribute to the

occurrence of life-threatening rhythm disorders. The cause of SCD in patients with acromegaly is considered ventricular tachycardia and ventricular fibrillation [20]. As for the specific treatment of acromegaly, it has been shown that the normalization (or reduction) of growth hormone and IGF-1 leads to a decrease in the frequency of ventricular ectopic complexes [21].

Primary aldosteronism

Primary aldosteronism is the most frequent endocrine cause of hypertension and occurs in 5–10% of patients. It is known that a high level of aldosterone is associated with an increased risk of cardiovascular events, including myocardial infarction, arrhythmias and strokes [22]. Hypokalemia, characteristic of primary aldosteronism, is accompanied by an elongation of the QTc interval [23], which can contribute to the development of arrhythmias. Most often, with primary aldosteronism, AF occurs [24], but in a number of cases pirouette tachycardia, polymorphic ventricular tachycardia [25] is also observed. Treatment of patients with a violation of left ventricular systolic function with the help of blockers of mineralocorticoid receptors led not only to a 30% reduction in total mortality, but also to a 29% decrease in the risk of sudden cardiac death [26].

Primary hyperparathyroidism

It has been established that excessive secretion of parathyroid hormone (PTH) in patients with primary hyperparathyroidism is associated with an increased risk of developing cardiovascular diseases and lethality [27]. This can be explained by the fact that smooth muscle cells of the vascular wall, endothelium, cardiomyocytes are target cells for PTH. In conditions of increased parathyroid hormone concentration, endothelial dysfunction, an increase in the thickness of the intima-media complex, damage to the coronary arteries are observed, which indicates its pro-atherogenic effect [28]. Another possible cause contributing to an increase in the mortality of patients with high PTH levels can be arterial hypertension, as well as the direct effect of PTH on the myocardium, which leads to cardiomyocyte hypertrophy, increases the heart rate, and arrhythmia may occur [29].

It is known that an increase in PTH levels is accompanied by an increase in the calcium concentration associated with significant ECG changes in the form of lengthening PR and QRS intervals, shortening the QTc interval and the ST segment [30]. The arrhythmogenic effect of hypercalcemia can be realized due to early and late post-depolarization, shortening of the effective refractory period and the start of the re-entry mechanism.

Thus, parathyroid hormone, either independently or through increasing the level of calcium, has a positive inotropic and chronotropic effect on the heart, promotes the development of arterial hypertension, diastolic dysfunction and, possibly, atherosclerosis. However, the mechanisms by which patients with primary hyperparathyroidism increase the risk of sudden cardiac death require further study.

Thyroid dysfunction

Dysfunctions of the thyroid gland worsen the course of cardiovascular diseases. Cases of sudden death are described in Graves's disease, one of the most common causes of thyrotoxicosis. Fatal consequences can lead to unrecognized severe thyrotoxicosis with the development of thyrotoxic crisis in Graves's disease. Typical thyrotoxicosis disorders of the heart rhythm (FP), accompanied by progressive heart failure, can lead to death of the patient [31,32]. It should be said that the appointment of amiodarone to a patient with atrial fibrillation and unrecognized thyrotoxicosis can significantly complicate the subsequent therapy.

Other diseases of the endocrine system

Sudden cardiac death in patients with Addison's disease and hypoparathyroidism, is described extremely rarely and, as a rule, its development is due to severe electrolyte disorders (hyperkalemia or hypocalcemia) due to deficiency of glucocorticoids, mineralocorticoids and parathyroid hormone, respectively.

The literature mentions single clinical cases, where nonclassical manifestations of excessive secretion of catecholamines in patients with pheochromocytoma were cardiogenic shock, pulmonary edema and sudden death [33].

More recently, there has been evidence of an association between the risk of sudden cardiac death and D vitamin deficiency [34]. Such patterns are most often described for patients with chronic kidney disease receiving hemodialysis [35]. At present, there is no doubt that vitamin D deficiency is a risk factor for the development of type 2 diabetes, hypertension, and inflammation, the appearance of which contributes to the increased mortality of patients [36]. It is believed that all these changes in the heart and blood vessels in conditions of vitamin D deficiency can lead to an increased risk of arrhythmias and sudden cardiac death [37].

Recommendations for SCD prevention

Class I

1. VA therapy, that is secondary to endocrine disorders, should be directed to the correction of electrolyte imbalance and management of the underlying disease (C).

2. There are no specifics on prevention and treatment of life-threatening VA (a major risk factor) and SCD in patients with endocrine disorders. SCD

prevention measures should be the same as for patients with other diseases. This implies that the SCD risk stratification and prevention in these patients is based on the detection of major and secondary risk factors. SCD prevention includes ICD or pacemaker placement in patients with good functional status who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (C).

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X.9. D. SCD risk stratification and prevention in patients with end-stage renal disease

Risk stratification

About 40% of patients with end-stage renal disease die from cardiovascular disease, including 20% who die suddenly [1–2]. In addition to coronary atherosclerosis, other risk factors of sudden cardiac death in patients with chronic kidney disease include LVH, uremic cardiomyopathy, anemia, QT interval prolongation and dispersion, reduced heart rate variability, rapid changes in blood volume and electrolytes, as well as inadequate dialysis, hyperphosphatemia, hyperparathyroidism etc. [2, 3].

Recommendations for SCD prevention

Class I

1. SCD prevention measures in patients with end stage renal disease include major risk factors identification (history of ventricular arrhythmias, systolic dysfunction, syncope, cardiac arrest) and modification of secondary risk factors (hypertension, dyslipidemia, hyperglycemia), and the risk factors associated with chronic kidney disease and dialysis (treatment of renal anemia, hyperparathyroidism, vitamin D deficiency, adequate dialysis, avoidance the dialysis fluid with low potassium and calcium content) (C).

Class IIa

1. For secondary prevention of SCD in patients on hemodialysis or continuous ambulatory peritoneal dialysis, angiotensin II receptor blockers (C) and class III antiarrhythmic agents are indicated (C).

2. For primary prevention of SCD in patients on hemodialysis or continuous ambulatory peritoneal dialysis, ACE inhibitors are indicated (B).

3. In patients with chronic kidney disease and major SCD risk factors (life-threatening arrhythmias and left ventricular systolic dysfunction) ICD placement is superior to medical therapy. However, in patients on dialysis

beneficial effect of ICD placement on survival has not been proven. The decision on ICD placement should be individual and based on the patient's condition and life expectancy (C). However, the fact the patient is on regular hemodialysis treatment or continuous ambulatory peritoneal dialysis should not be regarded as a decisive argument against ICD implantation.

Class IIb

1. For primary prevention of SCD in patients on hemodialysis or continuous ambulatory peritoneal dialysis, selective β-adrenoblockers may be considered (C).

2. For primary prevention of SCD in patients on hemodialysis or continuous ambulatory peritoneal dialysis without signs of coronary arteries involvement, nicorandil may be considered (C).

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X.10. SCD in patients with pericardial disease

Risk stratification

According to the etiological classification of pericardial diseases of the European Society of Cardiology [1], they are divided into infectious and non-infectious. The main causes of pericardial diseases are viruses (in developed countries), as well as bacteria (more often mycobacterium tuberculosis), there are less frequent tumoral pericarditis and pericarditis associated with a systemic (usually autoimmune) disease. Pericarditis is an inflammation of the heart sac, including the serous visceral (epicardium) and fibrous parietal layers with the pericardial fluid located between them. Pericarditis can be both isolated and manifestation of systemic diseases. Classical pericardial syndromes include pericarditis, effusion into the pericardial cavity, cardiac tamponade, and constrictive pericarditis.

In case of suspected pericarditis, the definition of inflammatory markers (leukocytosis, C-reactive protein, etc.), renal, hepatic and thyroid gland function, myocardial damage markers (cardiac troponins, creatine kinase), ECG registration, radiography of organs chest, echocardiography. At the second level of diagnosis, with insufficient information on the first level, computer tomography or magnetic resonance imaging of the heart can be performed, as well as pericardial fluid analysis

for detection of bacteria, tumor cells with large efflorescence, which does not respond to standard anti-inflammatory therapy. Additional studies to determine the etiology of pericarditis should be carried out in view of the clinical picture in the presence of predictors of high risk of adverse outcome.

SCD in cases of pericardial diseases can occur as a result of various pathological processes: inflammation, constriction, etc. However, there is no conclusive evidence of a link between ventricular tachyarrhythmias and pericardial diseases. It is assumed that the SCD in these patients lead mainly hemodynamic causes, rather than cardiac arrhythmias [2].

In the modern literature there are only descriptions of single cases of SCD in pericarditis after catheter ablation of atrial fibrillation in a young man with probable hereditary canalopathy [3], successful resuscitation with sudden cardiac arrest on the background of tuberculous pericarditis [4].

Recommendations for SCD prevention

Class I

1. SCD risk stratification and prevention in patients with pericardial disease are based on the detection of major and secondary SCD risk factors. SCD prevention includes ICD placement in patients with major SCD risk factors, good functional status who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (C).

X.11. SCD in patients with COPD

Chronic obstructive pulmonary disease (COPD) is one of the most common diseases of the adult population in the world, affecting between 7 and 18.2% of persons older than 40 years [1–3]. In the last 25 years, there has been a steady increase in mortality from COPD, and according to expert predictions the disease will take third place among all causes of death by 2020 [4].

COPD is a chronic disease characterized by persistent airflow limitation in the airways, which are usually progressive and associated with an inflammatory response to prolonged exposure to particles or gases. The severity of COPD is largely determined by the exacerbations frequency and present comorbidities [5]. The most common associated problem in COPD patients is cardiovascular diseases, in most cases, coronary artery disease, heart failure, atrial fibrillation and hypertension. According to a large study of more than 1,800 patients, the COPD patients risk of death from cardiovascular events and from coronary artery disease is 3.36 and 5.65 times higher than that in general population, respectively [6]. There is a direct correlation between the risk of death and forced expiratory volume in 1 second (FEV1) which is the major quantitative criterion of airflow obstruction [7].

At the same time, patients with milder COPD have a much higher risk of dying from respiratory failure than from cardiovascular disease [311].

Available epidemiological data on COPD combination with heart disease vary significantly. For example, in VALIANT study that included 14 703 patients with acute myocardial infarction, about 9% of patients had concomitant COPD; mortality rate in patients with COPD was 30% while mortality rate in patients without COPD was 19%. More than 27% of COPD patients in this study had heart failure before the enrollment [312].Another large study analyzed 400000 hospitalizations of patients with COPD in the veterans affair department, concomitant coronary artery disease was present in 33.6% of cases [313].

Such high association between COPD, coronary heart disease, heart failure and arrhythmias is due to a number of factors: First, there is a common dominant risk factor – smoking. Second, both types of pathology are age dependent, their incidence increases progressively after 50 years of age. Third, remodeling of the right heart is a reaction to pulmonary hypertension. Fourth, systemic inflammation, oxidative stress, hypercapnia that are characteristic for COPD accelerate atherogenesis and provoke arrhythmias. Finally, there is a reciprocal negative effect of drug therapy, when drugs to treat heart disease may worsen COPD and bronchodilators may provoke life-threatening arrhythmias.

Risk stratification

To determine SCD risk in patients with COPD the following two major factors should be taken into account:

– the degree of airflow limitation, determined by spirometry;
– patient history, in particular presence of concomitant or prior diseases that increase SCD risk and medication history.

Patients with FEV1 greater than 60% have no additional risk of SCD, so their management does not differ from that of patients without COPD.

In patients with FEV1 of less than 60% and without risk factors in the history, Holter monitoring on a regular basis for early detection of latent cardiac disease is recommended.

Most attention regarding SCD prevention requires a group of COPD patients with lowered FEV1 (⩽60%) and cardiovascular diseases. In such patients, changes of the management plan to introduce SCD prevention measures are indicated as follows (**Figure. X.11.1**).

Class I

1. SCD prevention specifics in patients with COPD are based on the detection of major and secondary SCD risk factors. This includes ICD placement

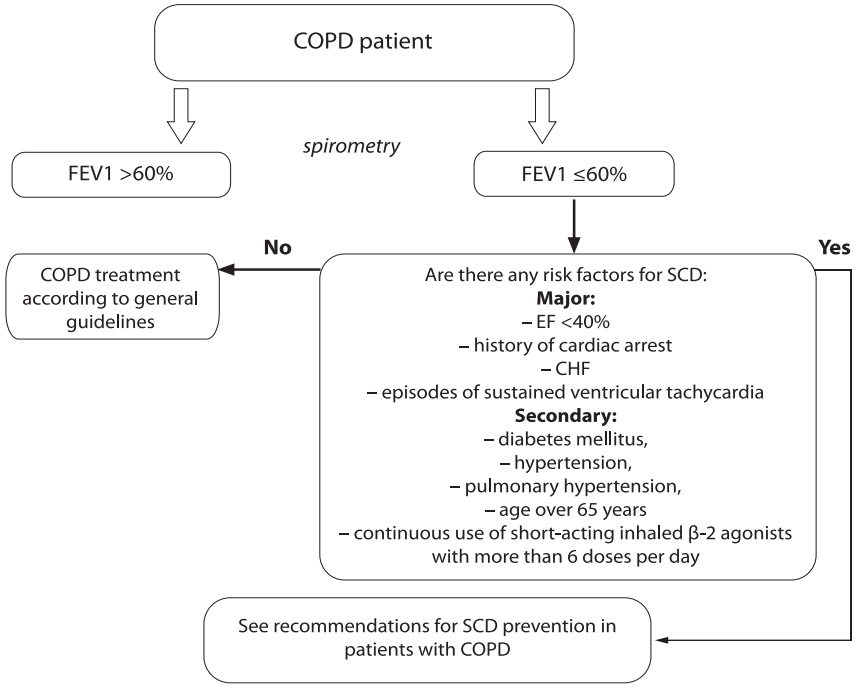

Figure. X.11.1. SCD risk stratification in patients with COPD

in patients with major SCD risk factors, good functional status* who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (B).

2. When β-adrenoblockers are indicated, preference should be given to selective β-1-blockers (A).

Class IIa

1. In patients with CHF, bisoprolol is the preferred drug that does not reduce FEV1 (a major risk factor) and quality of life (B).

2. Stable COPD patients treated with theophylline and long-acting β-2 agonists have do not have increased risk of SCD *(B)*.

Class IIb

1. Inhaled corticosteroids reduce the risk of SCD in patients with COPD (B).

2. Elderly patients (over 65 years old) with COPD have a lower risk of SCD when treated with long-acting inhaled β-2 agonists than with long-acting inhaled anticholinergic agents (B).

* You can read about functional status assessment methods at http://www.chcr.brown.edu/pcoc/functi.htm

3. Powder tiotropium for inhalation does not increase the risk of SCD in patients with COPD (B).

Class III

1. Avoid high doses of β-2 agonists in patients with unstable angina (A).

2. The use of 14-membered macrolides (erythromycin, clarithromycin) may lead to QT prolongation and increased risk of ventricular arrhythmias (a major risk factor for SCD) (B).

3. Inhaled ipratropium bromide use in patients with COPD is associated with increased risk of SCD (B).

4. Patients with COPD and CHF, treated with short-acting inhaled β2 agonists, have a higher risk of SCD comparing with those not taking these medications (A).

5. While considering coronary artery bypass grafting in COPD patients with FEV1 < 60% it should be taken into account that in these patients the risk of death in the postoperative period is significantly higher (B).

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X.12. SCD with neuromuscular diseases

Hereditary neuromuscular diseases (myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb myodystrophy, Emery–Dreifuss muscular dystrophy and other myopathies) may predispose to the development of atrial arrhythmias, conduction abnormalities, AV block, monomorphic or polymorphic VT and SCD [1–7]. Clinical signs that may indicate higher risk of SCD are quite diverse. SCD is well known complication of some neuromuscular diseases but the progression of conduction abnormalities is such patients may be unpredictable [8–17]. In the case of concomitant heart disease in patients with muscular dystrophy, it is necessary to pay attention to minimal clinical signs or electrocardiographic manifestations when deciding on ICD or pacemaker placement and endocrinal EPS.

Recommendations for SCD prevention

SCD risk stratification in patients with neuromuscular diseases is based on the detection of major and secondary SCD risk factors as well as the diagnosis and therapy of pathological conditions associated directly with neuromuscular diseases.

1. Accurate genetic diagnosis (**I, A**).
2. Conduction of studies determining the state of the cardiovascular system:
   A) Registration of the surface ECG (I, C) (once for three months).
   B) Echo-CG (I, B) (once every three months):
   – increased attention should be paid to the echocardiographic signs of latent cardiac failure:
     - an increase in the final diastolic diameter of the left ventricle during the last three months;
     - an increase in the mass of the heart during the last three months;
     - decreased left ventricular ejection fraction within the last three months;
     - the presence of dyskinesia of the walls of the left ventricle;
     - the ratio of the distance from the highest point of the opening of the mitral valve leaflet to the interventricular septum to the end diastolic diameter of the left ventricle is > 16;
     - an increase in the ratio of the left ventricle pre-ejection period to the left ventricle ejection period within the last three months.

If all six of the above signs are identified in the patient, one should expect the development of a manifest heart failure within the next six months. It should be noted that during the first two months of the patient's loss of ability to move independently, there is a decrease in the mass of his left ventricle, as well as his final diastolic diameter by 20%, and therefore it is necessary to adjust the normative indices for patients at the given time.

   C) Holter monitoring of ECG (**I, B**).
3. Biopsies of:
   - Myocardium;
   - Skeletal muscle (I, A).
4. Adequate medication, including the appointment of the following groups of drugs (in the absence of contraindications and unacceptable side effects):
   - ACE inhibitors (I, A);
   - sartans (I, B);
   - β-adrenoblockers (I, A).

It should be noted that the therapy of patients with cardiomyopathy, which develops with progressive muscular dystrophy, has some peculiarities in comparison with the treatment of patients with isolated cardiomyopathy. The use of combined symptomatic therapy with cardiac glycosides and diuretics practically does not lead to an increase in the contractility of the myocardium and, although it allows temporarily improving the patient's condition, nevertheless does not contribute to an increase in his life. In this case, the combination of selective β-adrenoblockers and cardiotrophic drugs is more optimal.

With regard to antiarrhythmic therapy, the advisability of their use in patients with neuromuscular diseases seems to be rather doubtful, since there are data on the lesser survival of patients with Duchenne and Becker muscular dystrophies who have ventricular ectopy and receive antiarrhythmic drugs compared to patients who do not receive these medications [18, 19]. With sinus tachycardia against the background of the normal fraction of the left ventricular ejection, preference should be given to selective β1-adrenoblockers.

In the presence of latent heart failure, it is advisable to adhere to the following algorithm for managing patients [20] (**I, B**):

- clinical examination of the patient every four weeks;
- early antibiotic treatment of any infectious diseases;
- use of preparations containing magnesium administration of amiodarone to patients with frequent and / or severe arrhythmias;
- use of anticoagulants;
- increase in cardiac output by the use of cardiac glycosides at usual therapeutic doses, diuretics, coenzyme Q10, angiotensin converting enzyme inhibitors.

Also we have to ensuring normal respiration function (**I, A**):

В оригинале отсутсвует п.5 списка.

- evaluation of breathing function at an early age of the patient – 4–6 years*;
- regular consultation of the patient by a pediatrician specializing in the evaluation of respiratory functions;
- testing of respiratory functions at each consultative visit of the patient;
- training the patient and his relatives for various options of auxiliary ventilation, which will help to avoid emergencies;
- providing the patient and his relatives with guidance on the proper process of eating;
- regular assessment of sleep quality and respiratory state during sleep – carrying out night oximetry and / or polysomnography);
- regular assessment of cardiac activity, including annual ECG and EchoCG, starting at least from school age;
- regular assessment of the ability to self-sanitize the broncho-pulmonary tree – check the availability of cough;
- providing manual assistance or mechanical support for coughing with normalizing pressure in the bronchopulmonary tree of insufflator-exuflator;
- training the patient and his relatives to use the pulse oximeter at home, in order to independently control the patency of the airways;
- non-invasive ventilation support through the nasal inhaler, which ensures the periodic creation of positive pressure in the airways;
- use of artificial ventilation to prevent additional consumption of oxygen to compensate for night hypoventilation caused by inadequate breathing;
- non-invasive daytime ventilation support, when the function of breathing is disrupted in the daytime, using a mouth inhaler that provides periodic positive pressure in the airways, or an inflatable toy that promotes increased intra-abdominal pressure simulating breathing;
- training the patient how to breathe in the tongue (the so-called «big-pharynx» breathing), used during the shutdown of mechanical ventilation;
- performing artificial ventilation by imposing a tracheostomy, if non-invasive ventilation is not feasible or rejected by the patient and his relatives;
- prevention of the use of so-called preventive artificial ventilation;

* *The evaluation of respiratory function should be performed 2 times a year after a patient begins using the wheelchair and until the vital air volume exhaled after the maximum inspiration (80% of the normal volume) or until the patient reaches the age of 12 and every 3-6 months after the start carrying out artificial ventilation of the lungs or the use of various auxiliary mechanical means facilitating the act of breathing.*

- assessment of the state of the respiratory and cardiovascular systems during sleep before surgical interventions and ensuring free airway patency and support of respiratory functions during the postoperative period;
- lifelong observation and treatment of the patient, which includes therapy of respiratory and pain syndromes, as well as a comprehensive psychosocial rehabilitation.

Implantation of ECS (**IIa, B**) can be discussed in patients with such hereditary neuromuscular diseases as myodystrophy of Duchenne, Becker, Emery-Dreyfus, Mabry, or Rottauf-Mortier-Beier, amyotrophy of Verdnig-Hoffmann, Davidenkov's myodystrophy, Pompe and Girke disease, Cairns- Seira syndrome, myotonic dystrophy of Rossolimo-Kurshman-Steinert-Butten in the presence of such SCD risk factor as AV-blockade (including AV-blockade of I degree), which is often the main manifestation of cardiac pathology among patients of this group.

The possibility of ECS implantation is considered even in the absence of clinical symptoms, which is due to the fact that patients in this category may have an acute progression of AV conduction abnormalities.

Implantation of the ICD in patients with left ventricular ejection of less than 35% for the purpose of primary prevention of SCD belongs to indications IIa class, with a level of evidence of B.

There are various opinions on the advisability of heart transplantation in patients with muscular dystrophy and concomitant cardiomyopathy, which is associated with a high enough perioperative risk due to reduced physical activity of patients and in connection with the alleged rapid development of the cardiomyopathic process in the transplanted heart. However, according to some authors, such a view is not entirely justified. So, in the work of W. Rees et al. [21] reported patients with Duchenne myopathy who underwent heart transplantation. The average age of patients with an extreme stage of the cardiomyopathic process was 25 years (from 9 to 45), the duration of postoperative follow-up was from 10 months to 7 years. There was an uncomplicated postoperative period in all patients described, they all received immunosuppressive therapy using azathioprine, cyclosporine and corticosteroids. Annual studies of the condition of the transplant with cardiac catheterization showed normal functioning of the left ventricle. There have been no cases of coronary artery disease, and up to the present day, no patient has experienced a progression of pre-operative muscular dystrophy.

Correction of genetic disorders

Despite the obvious success in studies of the structure of the dystrophin gene, real progress in the gene therapy of neuromuscular diseases has not been achieved yet, primarily due to the giant size of the gene and its mRNA, and the lack of effective means of delivering the gene to the muscles.

It is believed that the achievement of therapeutic effect is possible with successful transfection of at least 20%, and according to the latest data – 40%, of all muscle fibers of only skeletal muscles, heart muscles and diaphragm. The main criteria for the effectiveness of transfection are the appearance of dystrophin-positive muscle fibers, normalization of the level of biochemical markers of Duchenne's myodystrophy, changes in physiological parameters (strength, muscle tone).

Correction of genetic disorders in patients with Duchenne and Becker's myodystrophies suggests:

- introduction of the dystrophin gene (IIa, B);
- replacement of the dystrophin gene (B);
- skipping of the dystrophin gene, i.e. removing (missing) a mutation in the gene and connecting together the surrounding genetic instructions (C);
- ignoring the stop codon of the dystophin gene, since in some cases the development of Duchenne's myodystrophy is caused by a stop signal in the dystrophin gene – a type of mutation called a «premature stop codon» or «nonsense mutation» (C);
- the introduction of a minigen (a c-DNA component coding for the synthesis of a region of dystrophin at the level of which a deletion has occurred) both in the skeletal muscle and directly into the cardiac muscle (B);
- cell transplantation (C);
- influence on calcium channels of muscles (B);
- restoration of muscle cell membranes (A);
- suppression of the dystrophic process (C);
- stimulation of regeneration of muscle tissue (B).

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X.13. SCD in patients with channelopathies and early ventricular repolarization syndrome

Long QT syndrome, short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia are rare inherited diseases caused by disorders in ion channels functioning (channelopathies). Early ventricular repolarization syndrome (EVRS) should be considered as

pathogenetically related to the abovementioned diseases. However, strictly speaking, EVRS has not yet been assigned to the channelopathies category. They are caused by a mutation(s) of the genes either encoding pore-forming structure proteins or specific ion channels, receptors and enzymes proteins that are key structural and functional components of normal or anormally changed electrophysiological system of the heart. The clinical significance of channelopathies is due to the fact that all of them are associated with a genetically determined high risk of SCD in the absence of structural abnormalities of the heart.

X.13.A. Long QT syndrome

Long QT syndrome (LQTS) is a genetic disorder characterized by abnormal lengthening of the QT interval on ECG at rest (QTc> 460 ms in females and QTc> 440 ms in males), syncope and a high risk of SCD due to torsades de pointes.

There are several classifications of LQTS. The classification based on type of inheritance and associated clinical features distinguishes two types of the syndrome:

Type 1 – Romano–Ward syndrome (RWS) is caused by mutations in 12 different genes, has autosomal dominant inheritance.

Type 2 – Jervell and Lange–Nielsen syndrome (JLNS), caused by mutations in 2 genes, has autosomal recessive inheritance. It accounts for about 1% of all cases of congenital deaf-mutism. Congenital deafness is a mandatory sign, it is two-sided, perceptor type and does not affect low frequency audio spectrum. It is due to loss of organ of Corti function as a result of critical reduction in the number of potassium ions in perilymph. LQTS occurs in patients of all ethnic groups. Congenital long QT syndrome incidence is 1–2:10000 and it causes about 3,000 deaths annually. The first type of syndrome (RWS) is more common (1:5000–7000), the second type (JLNS) is less common (1,6–6:1000000), but in Denmark its incidence is significantly higher (1:200 000).

Depending on the clinical manifestations, following LQTS variants are defined:

1. Isolated QT prolongation (40%);
2. QT prolongation with syncope (38%);
3. Syncope without QT prolongation (11%);
4. Latent variant (11%), it implies a high risk of syncope and SCD without any obvious clinical manifestations of the disease. This option can be diagnosed with high amount of certainty only in retrospect, after sudden death of the proband relatives that were considered healthy.

In males of all age groups and especially teenagers, the disease has more severe and malignant form. In females risk of syncope and SCD increases during puberty.

LQTS is caused by mutations in 13 genes, and so 13 LQTS genotypes exist. These are mutation in 6-potassium channel genes (KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2, KCNJ5), 2 sodium channel genes (SCN5A, SCN4B), one calcium channel gene (CACNA1C) and 4 genes of specific binding and structural proteins (AKAP9, ANK9, CAV3, SNTA1). As a result, the concentration of potassium ions in the cell is reduced, or sodium and calcium concentrations are increased, which leads to abnormal Na/Ca exchange and as a result prolonged action potential duration.

The first syndrome genotype (LQT1) is the most common and accounts for 35–50% of all LQTS variants; in 90% of cases it leads to Jervell and Lange–Nielsen syndrome while the remaining 10% are related to the fifth genotype (LQT5). The second syndrome genotype (LQT2) accounts for 25–40% of cases. The sixth syndrome genotype (LQT6) is phenotypically similar to LQT2 but is much rarer. The third syndrome genotype (LQT3) accounts for 5–10% of cases. The remaining genotypes are the rarest variants and occur in less than 1.5% of cases.

Andersen syndrome

Andersen's syndrome (or LQT7) is a rare, inherited disease characterized by intermittent hyper- and hypokalemic palsy, skeleton abnormalities, dysmorphic features, long QT interval, ventricular arrhythmias, specific T wave and often very pronounced U wave [1, 2]. Syndrome is associated with mutations in gene KCNJ2 that encodes K1 type potassium channel.

Life-threatening VA are rather rare in patients with Andersen syndrome, although sudden death episodes have been described in these patients [3–4]. The management experience is limited. Treatment with amiodarone and acetazolamide of a young female with Andersen syndrome and R218W mutation in the gene KCNJ2 caused lasting improvement of cardiac and muscle symptoms. Periodic paralysis in most cases can be prevented by oral potassium supplements [5]. Positive effects of β-blockers in these patients has not been proven. Positive effects of calcium channel blockers in arrhythmia treatment in these patients have also been based on a single case report. There have been reports on effectiveness of IC class antiarrhythmics: flecainide [6, 7] and ethacyzin [8].

Timothy syndrome

Timothy syndrome (or LQT8) is a rare genetic condition characterized by QT prolongation, fatal arrhythmias, syndactyly, hypoglycemia, hypothermia, mental retardation, congenital heart defects, immune deficiency, congenital

abnormalities and autism. A transient AV blockade 2–1 due to extension of ventricular repolarization periods (and not because of abnormal conduction in AV node) has been described [9, 10]. Timothy syndrome is associated with mutations in gene CACNA1C that encodes α1 subunit of potassium channels. The mutation contributes to cell overload with calcium ions in all tissues [11].

Genetic features of LQTS

1. 2 of 5 carriers of mutant alleles do not have QT prolongation.
2. Penetrance is low and varies with different types of the syndrome: LQT1<LQT2<LQT3.
3. Penetrance increases significantly with administration of medications that prolong QT interval.
4. Asymptomatic carriers of pathological alleles have a lower risk of fatal arrhythmias, but this risk is significantly increased when they are administered medications that prolong QT interval. Specific LQTS mutations are identified in approximately 20% of patients with secondary QT lengthening.
5. The correlation between genotype and phenotype is present only in patients with LQT1–LQT8 syndromes.
6. High genetic heterogeneity: 13 genes, more than 760 mutations.
7. The inheritance type is autosomal dominant, LQT1 and LQT5 syndroms may also be inherited via autosomal recessive mechanism.
8. In 5–10% of cases, LQTS is a result of spontaneous sporadic mutations.
9. In 20–25% of cases, exact genetic causes of LQTS are not identified, which requires further research of possible new causative mutations.
10. In some patients, mutations in several genes are present which leads to more severe clinical manifestations of the disease.

Currently, there are means to study a complete sequence of the encoding part of the corresponding gene [12–14].

Risk stratification

Based on knowledge of genotype, sex, and QT interval length risks of syncope, ventricular arrhythmias and SCD are stratified (**Table X.13.1**). [15, 16]. The following stress test results are additional risk factors for life-threatening arrhythmias: polymorphic ventricular tachycardia and/or severe (more than 520 ms) prolongation of QTc interval, alteration of T wave in a patient with a history of syncope [17]. There are individual data showing that the type of mutation may be significant in determining a patient prognosis and may be an indication for preventive ICD placement. This is the case for gene KCNQ mutation A341V [18]. Patients with JLNS, Timothy syndrome and other homozygous syndromes are at the highest risk of SCD during childhood.

Table X.13.1

Risk stratification in patients with congenital long QT syndrome

Risk of cardiac events by age of 40	QTc at rest	Genotype	Gender
High (>50%)	>500 ms	LQT1 LQT2 LQT3	male/female male/female male
Medium (30–49%)	> or < 500 ms < 500 ms	LQT3 LQT3 LQT2	female male female
Low (<30%)	< 500 ms	LQT2 LQT1	male male/female

Patients resuscitated after SCD have the worst prognosis with a relative risk of another cardiac arrest of 12.9.A mutation in the pore-forming region of the protein is considered to be independent genetic risk factor for SCD, comparable with QTc> 500 ms [19]. The risk of death in asymptomatic carriers of LQT1 mutations is the highest at a young age [20].

Recommendations for genetic testing

Class I

1. It is recommended to order genetic testing for congenital long QT syndrome for all children and adolescents with QT prolongation at rest (QTc> 460 ms in females and QTc> 440 ms at males) with major SCD risk factors (history of unexplained syncope, cardiac arrest history, family history of SCD), and for children with epilepsy without effect from a specific therapy (B).

Class IIa

1. Genetic testing is recommended for all patients with high probability of long QT syndrome based on the history and ECG-phenotyping of disease (based on the 12 lead ECG at rest and/or during stress tests with physical exercise or catecholamines infusion) (C).
2. Genetic testing is recommended for all asymptomatic patients with QTc> 480 ms (children) or QTc> 500 ms (adults) on 12 lead ECG in the absence of diseases or conditions that may cause prolongation of QT interval (such as electrolyte disturbances, myocardial hypertrophy, bundle-branch block, etc.) (C).
3. If a genetic testing of the proband led to identification of a mutation responsible for LQTS, first and second degree relatives, regardless of the clinical phenotype, should have selective genetic testing performed (C).

Class IIb

1. If prolonged QT, caused by medications, is identified, genetic testing provides an opportunity to identify carrier state mutations responsible for primary forms of LQTS (B).

2. In case it is impossible to test for all the known mutations, a selective testing of genes responsible for LQT1-3 (KCNQ1, KCNH2, SCN5A) may be conducted (C).

3. 12-lead ECG at rest is recommended for first and second degree relatives of a patient with secondary QT prolongation (C).

SCD prevention

Lifestyle modification. If syndrome genotype is known, it is recommended to make lifestyle modifications considering the influence of the specific triggering mechanisms of fatal outcomes [15, 21–24].

It is recommended for patients with LQT1 and LQT5 syndrome to limit excessive physical activities, especially competitive sports [25], swimming, sprinting, dance or exercise them under medical supervision.

Patients with LQT2 and LQT6 should avoid strong emotional stress (fear, anger, crying, examinations), sudden acoustic stimuli (alarm clock, vehicle horn, phone ringing), especially during sleep. Risk of cardiac events (VA, SCD) is also highly increased in these patients during postpartum period. In addition, medications that prolong the interval QT may serve a trigger [26]*. Food supplements with unknown chemical composition should be avoided.

Treatment. When a specific LQTS genotype is determined it is possible to choose an individual therapeutic strategy, including recommendations for lifestyle modifications, use of specific medications and ICD placement if needed [12, 27–29].

Timely administration of medical therapy (mostly β-adrenoblockers) effectively prevents syncope in more than 87% of patients. However, β-blockers are less effective in patients with LQT2 genotype and and even contraindicated in patients with LQT3 genotype [30].

ICD placement is the method of choice for such patients with history cardiac arrest episodes and ineffectiveness of conservative therapy [12, 30].

Surgical removal of the left stellate ganglion to eliminate asymmetric sympathetic autonomic innervation of the heart (an arrhythmogenic factor) results in some shortening of QT interval [31].

Prophylactic use of β-blockers can be recommended for asymptomatic carriers of the mutation [28, 29].

Recommendations for SCD prevention

Class I

1. Lifestyle modifications are recommended for patients diagnosed (clinically and/or by molecular genetic testing) with long QT syndrome (B).

* *For the list of medications please visit www.qtdrug.org*

2. Patients diagnosed (clinically and/or by molecular genetic testing) with long QT syndrome should not take medications that may prolong QT interval (B).

3. For primary prevention of SCD in patients diagnosed with long QT syndrome (LQT3) by molecular genetic testing, ICD placement is recommended (B).

4. For secondary prevention of SCD in patients diagnosed with long QT syndrome (LQT1, LQT2, LQT5 and LQT6) by molecular genetic testing and history of a cardiac arrest episode, ICD placement is recommended (B).

Class IIa

1. In patients diagnosed with long QT syndrome (LQT1 and LQT5) by molecular genetic testing, beta blockers are recommended (B).

2. In patients diagnosed with long QT syndrome (LQT2 and LQT6) by molecular genetic testing, potassium supplements are recommended (B).

3. In patients diagnosed with long QT syndrome (LQT3) by molecular genetic testing, IB class antiarrhythmics are recommended (B).

4. ICD implantation is justified in patients with clinical diagnosis of long QT syndrome with major risk factors for SCD (syncope and/or ventricular fibrillation), treated with β-adrenoblockers (B).

Class IIb

1. In patients diagnosed with long QT syndrome (LQT2 and LQT6) by molecular genetic testing, calcium channel blockers and IB antiarrhythmic agents may be used (B).

2. Prophylactic use of β-blockers can be recommended for asymptomatic carriers of the mutations [358, 359].

3. Left-sided sympathectomy can be considers in patients with clinical diagnosis of long QT syndrome, with major risk factors for SCD (history of a cardiac arrest episode, torsades de pointes) who are treated with β-adrenoblockers (B).

Class III

1. In patients diagnosed with long QT syndrome (LQT3) by molecular genetic testing, beta blockers and nicorandil are contraindicated (C).

X.13. B. Short QT syndrome

Short QT syndrome (SQTS) is a genetically determined disorder characterized by shortening of both absolute (QT $\leqslant$ 300–340 ms) and corrected (QTc <320 ms) QT interval as well as high, symmetrical, peaked T waves and a wide range of heart rhythm abnormalities ranging from AF to VA.

Syncope and SCD usually occur at rest or during sleep. Syncope in patients with SQTS is less common than SCD that is the first manifestation of the disease in most patients.

Diagnostic criteria of SQTS [362], based on the point scale evaluation of clinical and genotyping data, are presented in **Table X.13.2**.

QT interval length may vary significantly with HR changes in patients with this syndrome, therefore it is advisable to make all the measurement at heart rate of about 60 bpm to avoid results distortion introduced by Bazett's formula. It is important to rule out secondary causes of the syndrome since various conditions may shorten QT interval, including: hypercalcemia, hypokalemia, cardiac glycoside overdose, acidosis, hypo- or hyperthermia, some antiarrhythmic agents (mexiletine, tocainide). SQTS prevalence is not known.

Typical clinical manifestations of congenital SQTS occur in patients with mutations in five different genes, therefore 5 SQTS genotypes are allocated. These are mutations in 3 potassium channel genes (KCNQ1, KCNH2, KCNJ2) and in 2 calcium channels genes (CACNA1C, CACNB2B).The result of these mutations is either an increase in potassium concentration in the cell, or a decrease in the calcium concentration, which leads to a shortening of the action potential in cardiac myocytes.SQTS genotypes, associated with calcium genes mutations, are always phenotypically combined with Brugada syndrome.

Table X.13.2

SQTS diagnostic criteria

Diagnostic criteria	Score
QT_c length, ms <370	1
<350	2
<330	3
The interval from J point to T wave peak is less than 120 ms	1
Medical history	
History of cardiac arrest	2
Documented ventricular tachycardia or ventricular fibrillation	2
Syncope with no known cause	1
Atrial fibrillation	1
Family history	
First and second degree relatives with high likelihood of SQTS	2
First and second degree relatives who died suddenly without known cause	1
Sudden infant death syndrome	1
Genotype http://www.sciencedirect.com/science/article/pii/S0735109710047212 – tblfn5	
Previously described mutation is identified	2
A mutation of unknown significance is identified in genes KCNH2, KCNQ1, KCNJ2	1
Assessment of SQTS diagnosis likelihood	
STQS is very likely	4 and more
STQS is likely	3
STQS is unlikely	1–2

Quinidine may normalize the length of QT interval [33]. The only method of SCD prevention in these patients is ICD placement [34]. It seems that genetic analysis does not carry additional information on risk of SCD.

Genetic features of SQTS:

1) low penetrance;
3) asymptomatic carrier state of pathological alleles is possible;
4) there is no correlation between genotype and phenotype;
5) high genetic heterogeneity: 5 genes, more than five mutations;
6) autosomal dominant inheritance;
7) may be sporadic.

Recommendations for genetic testing

Class IIa

1. Genetic testing should be performed to confirm the diagnosis in patients with low or intermediate likelihood of SQTS (C).

Class IIb

1. If a pathogenic mutation in proband is identified, testing of the patient relatives is recommended (C).

Recommendations for SCD prevention

Class I

1. ICD placement is recommended for secondary prevention of SCD in patients with the diagnosis of short QT syndrome with major risk factors for SCD (history of cardiac arrest, syncope, hemodynamically significant sustained ventricular arrhythmias induced by endocrinal ES) (C).

Class IIa

1. ICD placement is recommended for patients with high probability of SQTS (B).

2. Quinidine may effectively reduce risk of SCD in patients with short QT syndrome, if ICD placement is impossible (C).

X.13. C. Brugada syndrome

Brugada syndrome is a genetically determined disease that develops as a result of abnormal electrophysiological activity of the right ventricular epicardium near the outflow tract.

Syncope and SCD in patients with Brugada syndrome often occur at rest or during sleep.

Brugada syndrome is characterized by a specific ECG changes:

– continuous or transient right bundle branch block;
– ST segment elevation (point J) in V1–V3 leads (there are three ECG types);
– inverted T waves in V1–V3 leads;

– periodic PQ prolongation;
– paroxysmal ventricular tachycardia during syncope;
– «epsilon» is a wave in V1 that looks like a «notch» of the ST segment (30% of cases).

The exact prevalence of Brugada syndrome is unknown. The prevalence of congenital Brugada syndrome on average is 1–60:10 000 in the world and 1:10 000 in Europe, whereas it is 1:100 000 in one of the regions of Belgium. In Europe, Brugada syndrome is more prevalent among people of Eastern European descent. In South-East Asia and Far East, the prevalence is >5 per 10,000, it is the highest in Thailand, Philippines and Japan. In Thailand, approximately 2500 people die from this syndrome each year. In Russia, the disease prevalence is roughly equivalent to that in Europe [35]. It is known that the Brugada syndrome does not occur in African Americans.

There are several clinical variants of Brugada syndrome:
1. Isolated classic ECG changes;
2. Syncope with specific ECG changes;
3. Syncope without specific ECG changes;
4. Hidden variant – latent, silent clinical course.

Typical clinical manifestations of Brugada syndrome occur in patients with mutations in 8 different genes, therefore 8 Brugada syndrome genotypes are allocated. These are mutations in 3 sodium channel genes (SCN5A, SCN1B, SCN3B), in 2 potassium channels genes (KCNE3, KCNJ8), in 2 calcium channels genes (CACNA1C, CACNB2B) and in a glycerol-3-phosphate dehydrogenase gene (GPD1L).The result of these mutations is either a decrease in sodium and calcium concentrations in the cell or an increase in the potassium concentration, which leads to a shortening of the action potential in right ventricular epicardium [12, 36]. In Russia, there is limited experience with genotyping of patients with Brugada syndrome, but at least in a third of the patients mutations of SCN5A gene are detected; all identified mutations have not been registered previously [37].

Risk stratification

Predictors of poor outcome in Brugada syndrome patients are: male gender, history of syncope or family history of sudden death, spontaneous ST segment elevation in V1–V3 combined with syncope, spontaneous ST segment deviations and the first ECG type of the syndrome.

Hemodynamically significant ventricular tachyarrhythmias (often clinically verified by the patients) may be induced in patients with Brugada syndrome during endocrinal EPS. However, EPS can not be considered a gold standard for SCD risk stratification since it has little diagnostic value [38].

No data on routine use of genotyping for SCD risk assessment are available. In one study, it was shown that gene SCN5A mutations may cause loss of function of this ion channel, which may indicate a poor prognosis [39].

Genetic features of Brugada syndrome
1. Low penetrance (~ 25%);
2. Sodium channel blockers (ajmaline) to identify affected people increases penetrance to 80%;
3. Asymptomatic carrier state is possible;
4. Not at all genotypes correlate with phenotype;
5. High genetic heterogeneity: 8 genes, more than 400 mutations;
6. Autosomal dominant inheritance.

Only 25% of patients have the abovementioned mutations.

Recommendations for genetic testing

Class I

1. Genetic testing for congenital Brugada syndrome is recommended for all children and adolescents with the specific ECG changes, who have major risk factors for SCD, including syncopal episodes, history of cardiac arrest, ventricular arrhythmias, family history of SCD (B).

Class IIb

1. Identification of the mutation type in SCN5A gene may provide additional information about SCD risks (B).

2. If a pathogenic mutation in proband is identified, testing of the patient relatives is recommended.

Class III

1. Genetic testing is not indicated for asymptomatic patients with 2 or 3 type Brugada-like ECG changes.

Recommendations for SCD prevention

Class I

1. ICD placement is recommended for patients diagnosed with Brugada syndrome clinically and/or based on molecular analysis and with history of cardiac arrest (a major risk factor for SCD) (C).

Class IIa

1. ICD placement is recommended for patients with Brugada syndrome, spontaneous ST segment elevation in leads V1–V3, history of syncopal episodes (a major risk factor for SCD) and verified causal mutations in SCN5A gene (C).

2. Clinical monitoring of the spontaneous ST segment elevation frequency is appropriate in patients with clinical manifestations of the disease as well as in patient with ST segment elevation only during pharmacological stress tests (C).

3. ICD implantation is indicated in patients with Brugada syndrome, good functional status, favorable survival prognosis for a year or more and verified VT that did not cause cardiac arrest (C).

Class IIb

1. Endocrinal EPS may be considered for SCD risk stratification in patients with Brugada syndrome with spontaneous ST elevation, without SCN5A mutations and any clinical signs or symptoms (C).

2. Quinidine can be used to reduce the severity of ST segment elevation and treatment of the «arrhythmic storm» in patients with Brugada syndrome (C).

Class III

1. IC class (e.g. flecainide and propafenone) and IA class (e.g. procainamide, disopyramide) antiarrhythmic agents are contraindicated in patients with Brugada syndrome.

X.13. D. Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a hereditary syndrome characterized by electrical instability of cardiomyocytes due to acute activation of the sympathetic nervous system (during physical or emotional stress) which may lead to sudden death.

There are no abnormalities on resting ECG. The arrhythmia may be reproduced on physical or medical (with intravenous catecholamines) stress tests. Therefore, CPVT patients need to limit physical activity, they are strictly prohibited from professional sports [40].

For children with a malignant form of CPVT syncope, a number of features of sinus rhythm, which may contribute to the early, pre-clinical identification of patients with CPVT in the population, have been identified. These features constitute a characteristic ECG picture:

– permanent or transient PQ shortening (< 0,11 c) without other ECG manifestations of WPW syndrome;
– sinus bradycardia;
– high circadian index on Holter monitoring (> 1.45).

There are 2 CPVT genotype identified.The first CPVT genotype (CVPT1) is associated with mutations of ryanodine receptor RYR2, the second CPVT genotype (CVPT2) is associated with mutations in calsequestrin 2 (CASQ2) gene. This results in an increase of calcium release from the sarcoplasmic reticulum in response to calcium ions entering the cell, causing an overload of cells with calcium ions, which causes a reversal ventricular wall activation, enhances transmembrane dispersion of repolarization and starts ventricular tachycardia by re-entry mechanism [41, 42]. Beta adrenoblockers are sometimes not effective in arrhythmias prevention. There is some evidence on the effectiveness of verapamil, which may be due to direct interaction with the ryanodine receptors.

Other genes may cause CPVT. It is believed that a mutation in KNJ2 gene is associated not only with Andersen/LQT7 syndrome, but also is the cause of CPVT 3 genotype (CPVT3). One patient with CPVT had a mutation in ankyrin B gene, that is also present in patients with long QT syndrome type 4 [43]. It is possible that mutations in RYR2 gene cause the so-called sudden infant death syndrome [12]. Recently, assumptions have been made that idiopathic ventricular fibrillation may be a variant of these disease (CPVT).

Risk stratification

Risk factors for SCD in these patients include: VF, family history of SCD, the disease manifestation in childhood, history of syncope, physical activity.

Genetic features of CPVT:

1. Low penetrance.
3. Asymptomatic carrier state is possible;
4. There is no correlation between genotype and phenotype;
5. High genetic heterogeneity: 4 genes, more than 170 mutations.
6 The disease is usually inherited in autosomal dominant manner, rarely in autosomal recessive manner.

Recommendations for genetic testing

Class I

1. Genetic screening for congenital CPVT syndrome is recommended for all children and adolescents with the following SCD risk factors: polymorphic ventricular tachycardia induced by physical or severe emotional stress, syncope, cardiac arrest, family history of SCD (B).

2. Genetic testing is recommended for patients with high probability of CPVT diagnosis based on medical history, family history, ECG phenotype of the disease, physical (treadmill) or pharmacologic (catecholamines) stress test results (C).

Class IIb

1. If a pathogenic mutation in proband is identified, genetic testing of the patient first and second relatives is **recommended**.

Recommendations for SCD prevention

Class I

1. Lifestyle modifications (avoidance of any physical stress, competitive sports, emotional distress) are recommended for patients diagnosed (clinically and/or by molecular genetic testing) with CPVT (B).

2. B-adrenoblockers are recommended for patients diagnosed clinically with CPVT (C).

3. For secondary prevention of SCD in patients diagnosed with CPVT (clinically or/and by molecular genetic testing) and a major SCD risk factor such as history of a cardiac arrest episode, ICD placement and beta blockers administration are recommended (C).

Class IIa

1. For secondary prevention of SCD in patients diagnosed with CPVT (clinically or/and by molecular genetic testing) and a major SCD risk factor such as history of a cardiac arrest episode during treatment with beta blockers, ICD placement is recommended (C).

Class IIb

1. Patients diagnosed with CPVT during childhood or adulthood (using molecular genetic testing) without clinical manifestations of the disease should be treated with β-adrenoblockers (C).

X.13. E. SCD in patients with early ventricular repolarization

Early ventricular repolarization syndrome (EVRS) was first described in 1936, but its prognostic significance has still not been determined [44]. EVRS is characterized by the following electrocardiographic manifestations: 1) horizontal or downward segment ST elevation > 0.1 mV with downward convexity, and; 2) presence the junction point or junction wave (J wave) on the downward slope of R wave; 3) counterclockwise heart electrical axis deviation in longitudinal axis, and; 4) rapid and sharp increase in R wave amplitude in precordial leads with simultaneous diminishing or disappearance of S wave.

Until 2008, most of authors agreed that EVRS is nothing more than a benign electrocardiographic phenomenon [44, 45]. In 2008, two groups of authors almost simultaneously have published case-control studies questioning the favorable prognosis of EVRS [376, 377]. In both studies, J point was 3–6 times more frequent in the lower (II, III, avF) and lateral (V4–6) leads, and J wave amplitude was higher in patients with idiopathic ventricular fibrillation compared to healthy individuals.

A retrospective analysis of Social Insurance Institution's Coronary Heart Disease Study data have shown that, in general population, presence of J waves in the inferior leads is associated with a higher risk of cardiovascular death, but the survival curves begin to diverge after 15 years of follow-up [48]. Similar data were obtained in a retrospective analysis of a German part of the MONICA project [49]. Antzelevitch C. and Yan G-X. have proposed a new classification of EVRS that qualifies 2 and 3 type of EVRS as potentially arrhythmogenic, and type 3 syndrome as a likely cause of the electrical storm [50].

Recommendations for SCD prevention

Class IIa

1. The presence of J waves in the inferior leads (II, III, avF) may be a major risk factor for ventricular fibrillation (or even SCD), and a factor that increases susceptibility to fatal arrhythmias due to myocardial ischemia (B).

2. The treatment of choice in case of VA (a major risk factor) or an electrical storm in patients with EVRS in inferior leads is to increase heart rate by means of temporary cardiac pacing or isoproterenol administration (B).

3. Prolonged treatment with quinidine is indicated for SCD prevention if ECG signs of EVRS in the inferior leads are present (B).

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X.14. SCD in patients with obstructive sleep apnea syndrome

Information on the risk assessment of SCD in adults with obstructive sleep apnea syndrome (OSAS) is limited. Risk factors SCD were studied only in single randomized and non-randomized trials. In all patients with OSAA, a non-invasive examination should be performed to assess the risk and identify possible triggers of SCD, the presence of which may serve as the basis for targeted therapy. At the same time, the category of patients with severe OSAS should be included in the group of increased risk of SCD development. Additional prognostic criteria for adverse prognosis include the following [1]: age 60 years and older (OR 5.53), oxygen saturation during sleep, namely, a decrease in the mean to 93% (OR 2.93) and a minimum value of up to 78% (OR 2.60), the index of apnea / hypopnea more than 20 events / h (OR 1.6), the presence of associated diseases (arterial hypertension, IHD, chronic heart failure, ventricular arrhythmias). **Table X.14.1** presents the algorithm for stratifying the risk of SCD in the OSAS.

At present, there is no evidence that ventricular arrhythmias should be treated in some special way in patients with OSAS [2]. The role of non-invasive respiratory support with positive inspiratory and expiratory pressure (PAP (positive airway pressure)-therapy), and the role of oral applicators for the prevention of ventricular arrhythmias and SCD in cases of OSAS is not defined [3–7]. It remains unclear whether the appropriate treatment of OSAS will change the clinical manifestations and avoid implantation of the pacemaker

Table X.14.1

SCD risk stratification in patients with sleep apnea

1. OSAHS diagnosis verification	
yes	no
See item 2	SCD risk stratification and prevention based on general principles
2. Apnea/hypopnea index >15	
yes	no
CPAP therapy or non-invasive ventilation choice	Weight reduction, correction of ENT disorders, elimination of OSAHS risk factors
3. Has 24h Holter monitoring revealed a rhythm and conduction disturbances during the night or daytime sleep?	
yes	no
see recommendations for SCD prevention in patients with OSAHS	SCD risk stratification and prevention in these patients are based on the detection of major and secondary SCD risk factors and general principles of SCD prevention

Note: AHI – Apnea/hypopnea index, OSAHS – sleep apnea/hypopnea syndrome, SCD – sudden cardiac death.

in the category of patients whose cardiac impulse conduction disorders are associated with obstructive respiratory events [8–14].

However, there is evidence that long-term treatment of patients with severe OSAs with PAP-therapy and oral applicators equally effectively reduces the increased risk of cardiovascular mortality. Thus, the risk of an unfavorable prognosis was 0.56 per 100 people per year with PAP therapy and 0.61 per 100 people per year with oral applicators. The highest risk of developing a fatal event was observed in the group of patients who refused any type of treatment – 2.1 per 100 people per year, and the lowest in the group of patients without OSAs – 0.28 per 100 people per year [15].

The clinical efficacy of the above, as well as new innovative methods for treating OSAS, in particular electric stimulation of the hyoid nerve, continue to be actively studied [16–19].

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X.15. SCD in patients with ventricular arrhythmias of structurally normal heart

The term «structurally normal heart» is becoming more and more relative, since new methods of ultrastructural analysis of myocardium, specific immunological tests, biopsies, are being actively implemented in clinical practice. Their use has significantly reduced the proportion of patients with clinically significant ventricular rhythm as well as number of patients with intact heart muscle. Such concepts as «minimal changes of myocardium» of the right or left ventricles of the heart, which are usually associated with idiopathic ventricular arrhythmias, have successfully entered the professional language of arrhythmologists. In fact, mounting evidence showing that the causes of «minimal changes of myocardium» of right or left ventricle in patients with ventricular arrhythmias (VA) may be first manifestations of arrhythmogenic right ventricular dysplasia (ARVD), an arrhythmogenic variant of latent myocarditis or some other more rare conditions [1–3, 5, 7–9, 11].

The most common site of idiopathic ventricular arrhythmias are the basal regions of the heart, namely left ventricular outflow tract (LVOT) and

right ventricular outflow tract (RVOT). The origin of the so called fascicular tachycardia is the point of division of the back or medial (much less frontal) His bundle branches. Other places of origin of arrhythmias can be found in the group of idiopathic ventricular arrhythmias in a statistically insignificant percentage of cases [5, 9].

The arrhythmic syndrome manifests clinically at the age less that 35 years, in the case of FT – before 25 years [9].

Idiopathic left ventricular arrhythmias

The most typical location of the arrhythmogenic zones is LVOT in the projection of the left, right and noncoronary sinuses of Valsalva aorta. Epicardial localization of arrhythmia zones in the projection of LCA or LAD trunks, as well as left ventricular supply tract (LVST) under the anterior and posterior flaps of mitral valve at the place of attachment of cross chords of left ventricle [401].

VA commonly manifests in males aged 25–30 years. Clinically the arrhythmia is benign with rare hemodynamically significant ventricular tachycardia (VT) paroxysms, but, in typical cases, characteristic ectopic activity is present in the form of isolated, paired or grouped PVCs or non-sustained VT with the cycle length of more than 400 ms with tendency to sinus bradycardia. There have been reports of patients with a history of the long lasting condition (over 5 years), who have not been treated with antiarrhythmic agents and developed arrhythmogenic cardiomyopathy [5, 9].

Idiopathic RVOT arrhythmias

Most of the RVOT arrhythmias after a detailed clinical analysis classified as manifestations of ARVD or latent arrhythmogenic variant of focal myocarditis. A significant reduction in the number of genuinely idiopathic ventricular arrhythmias from RVOT is facilitated by the widespread introduction into clinical practice of such examination methods as MRI of myocardium with contrasting, the study of the immunological status of patients with VA with the determination of antibody titres to various myocardial structures, genetic screening for ARVD, HCM, noncompact myocardial syndrome and various canalopathies. In addition, more and more information about the results of biopsy in right ventricular arrhythmias accumulates, in the overwhelming majority of cases demonstrating diagnostically significant changes at the histological and cytological level in patients with VA without macrostructural changes in the myocardium [1–3, 5–7, 9, 11]. Thus, today, the view that the most common origin of idiopathic VA is RVOT may be revised due to the improvement of diagnostic techniques.

The most common RVOT origin area is RVOT septal area under the pulmonary valve (typical for arrhythmogenic variant of latent myocarditis), the

less common is anterior septal area under the pulmonary valve and the septal area above the pulmonary valve. Other right ventricular origin areas (anterior wall of RVOT, supply tract, RV apex) are much less common, and almost always indicate presence of latent pathology (early stage of ARVD) [1–3, 5, 9].

Clinically the arrhythmia is charactrized with rare hemodynamically significant VT paroxysms. Severity of ectopic activity can vary from single PVCs per day to high Lown grades. The tendency to a background sinus bradycardia is rarely noted. Arrhythmia manifestation usually occurs before the age of 35 years [9].

Fascicular left ventricular tachycardia

In the group of fascicular tachycardia, male patients predominate, the disease manifestation usually occurs before the age of 25 years. Clinical manifestations of this arrhythmia are episodes of sustained ventricular tachycardia that usually have minimal hemodynamic significance, they easily terminated with intravenous isoptin administration. Between the sustained VT episodes, the majority of patients lack any signs of ventricular ectopic activity. Genetic determinants of the condition are unknown. There have been reports on arrhythmogenic cardiomyopathy development in patients with constant recurrent VT, with good size and LVEF recovery after VT treatment [9, 12].

SCD risk stratification in patients with VA and structurally normal heart

Table X.15.1

SCD risk stratification and prevention algorithm (clinical data) [11–13]

1. History of SCD episode	
Yes	No
Consider ICD placement	see item 2
1.1. SCD episode with reversible reasons	
Yes	No/unknown
Elimination of causes of cardiac arrest, observation	Consider implantation of a cardioverter-defibrillator
1.2. The cause of cardiac arrest was a monomorphic VT (ECG data during resuscitation)	
Yes	No/unknown
Consider ES, RFA	see item 2
2. VT with dizziness, syncope	
Yes	No
Consider ES, RFA	see item 3
3. Shortness of breath during exercise due to VA	
Yes	No
Consider antiarrhythmic agents, ES and RFA	see item 4

4. Ventricular tachycardia induction or increase in PVCs rate during physical exercise or recovery period	
Yes	No
AAT β-adrenoblockers, sotalol; consider the possibility of ES, RFA	see item 5
4.1. Suppression of VA at load	
Yes	No
AAT 1 C Class\ observation / discuss the feasibility of ES, RFA	see item 5
5. Effectiveness of the ongoing antiarrhythmic therapy	
Yes	No
Prospective observation	see the recommendations

Table X.15.2

SCD risk stratification and prevention algorithm (medical history) [5, 9, 19]

1. History of syncope of unknown cause	
Yes	No
Multi-day ECG monitoring Remote ECG monitoring Tilt-test Implantation of a long-term monitor (REVEAL) Consider EPS	see item 2
2. Syncope in relatives	
Yes	No
Genetic counseling, cardiac screening of close relatives, including children	see item 3
3. Data on the presence of ventricular arrhythmias in relatives	
Yes	No
Genetic counseling, cardiac screening of close relatives, including children	see item 4
4. Proarrhythmic effects of antiarrhythmic agents	
Yes	No
Adjunct treatment with antiarrhythmic agents, discuss EPS. Genetic counseling	see the recommendations

Table X.15.3

SCD risk stratification and prevention algorithm (ECG and Holter monitoring data) [3, 7–10, 13, 14, 16–22, 24, 25]

1. Sustained paroxysms of ventricular tachycardia	
Yes	No
Discuss EPS, RFA (ICD if ineffective)	see item 4
2. VT cycle length of less than 360 ms	
Yes	No
Consider EPS for VF induction (except FT). If VF is not induced – see item 1	see item 1

3. The width of the ectopic QRS complex during ventricular tachycardia is more than 160 ms	
Yes	No
Consider EPS for polymorphic VT/VF induction (except the VT from the right/non-coronary sinuses of Valsalva or LVOT)	see item 1
4. Ventricular arrhythmia of Lown class IIb and above	
Yes	No
Antiarrhythmic agents, discuss EPS, RFA	see item 5
5. Detection of ventricular late potentials	
Yes	No
Consider stress tests, EPS	see item 6
6. A transient change in QTc duration beyond the standard values according to Holter monitoring data	
Yes	No
Analysis of the antiarrhythmic agents; genetic counseling	see item 7
7. QT dispersion of more than 100 ms	
Yes	No
Consider stress tests, EPS	see item 8
8. The presence of epsilon waves, including transient ones, according to Holter monitoring	
Yes	No
Genetic counseling for ARVD	see item 9
9. The presence of J waves, including transient ones, according to Holter monitoring	
Yes	No
Genetic counseling	see item 10
10. The presence of R notches at in ectopic QRS	
Yes	No
Consider stress tests, EPS	see item 11
11. Detection of microvolt T wave alternans according to Holter monitoring	
Yes	No
Consider stress tests, EPS	see item 12
12. Transient conduction abnormalities (AV, idioventricular)	
Yes	No
Consider stress tests, EPS; immunological test for latent myocarditis	see item 13
13. Polytopic Ventricular arrhythmia of Lown class IIb and above	
Yes	No
Consider stress tests, EPS; immunological test for latent myocarditis	see item 14
14. The combination of atrial and ventricular arrhythmias	
Yes	No
Immunological test for latent myocarditis	Prospective observation

Table X.15.4

SCD risk stratification and prevention algorithm (instrumental diagnostic methods data) [1, 2, 5, 9]

1. MRI: areas of fibrosis/thinning in the ventricular myocardium	
Yes	No
Differential diagnosis between ARVD onset and latent myocarditis	see item 2
2. MRI: intramyocardial areas of fat inclusions	
Yes	No
Analysis of ARVD diagnostic criteria	see item 3
3. MRI: epicardial areas of fat inclusions	
Yes	No
Immunological test for latent myocarditis	see item 4
4. MRI: intramyocardial contrast accumulation in the early phase	
Yes	No
Immunological test for latent myocarditis	see item 5
5. MRI: intramyocardial contrast accumulation in the delayed phase	
Yes	No
Differential diagnosis between ARVD onset and latent myocarditis	see item 6
6. MRI: expansion of RVOT/LVOT	
Yes	No
Differential diagnosis between ARVD onset and latent myocarditis	see item 7
7. Scintigraphy: areas of mosaic hypoperfusion in LV	
Yes	No
Immunological test for latent myocarditis	Prospective observation

Table X.15.5

SCD risk stratification and prevention algorithm (endocrinal ES data) [5, 9, 11, 12, 22, 23]

1. VF induction with standardized protocol of ventricular pacing	
Yes	No
Consider ICD placement	see item 2
2. Induction of polymorphic VT with standard programmed stimulation	
Yes	No
Consider ICD placement	see item 3
3. Induction of monomorphic high-rate hemodynamically significant VT with standard programmed stimulation	
Yes	No
Consider RFA/ICD placement	Consider RFA/antiarrhythmic agents

The abundance of parameters included in the analysis is due to the identification difficulty of SCD risk in patients with structurally normal myocardium. In addition, it is understandable that behind many arrhythmias of the structurally normal heart there is the genetically determined pathology, not yet studied,

whose phenotypic manifestations can be the so-called «nonspecific» changes on the transient ECG. With idiopathic VA, one should also not forget about the early stages of ARVD and the arrhythmogenic variant of latent myocarditis; a differential diagnosis between these two nosological forms is extremely difficult to make without conducting a genetic study.

SCD prevention in patients with VA and structurally normal heart.

Class I

1. RFA is indicated in patients without structural heart disease with paroxysmal or continuous recurrent ventricular tachycardia originating from RVOT/LVOT with, ineffectiveness antiarrhythmic agents (B).
2. RFA is indicated in all patients with fascicular left ventricular tachycardia (A).
3. Preventive antiarrhythmic therapy is indicated in patients with structurally normal heart and daily index of arrhythmia load of more than 20% (C).
4. If the «minimal change» in RV/LV that fits arrhythmogenic variant of latent myocarditis criteria are identified as a cause of VA etiotropic and pathogenetic treatment of the underlying disease, regardless of the duration, is indicated (C).
5. If the «minimal change» in RV (rarely in LV) that fit arrhythmogenic variant of latent myocarditis criteria are identified as a cause of VA MRI of the myocardium with constriction and analysis of diagnostic criteria are indicated.
6. Cardioverter-defibrillator (ICD) placement is indicated in patients with ventricular arrhythmias without structural heart disease who have survived an SCD episode without reversible causes. (B).
7. ICD is indicated in patients without structural heart disease with sustained VA, that requires medical or shock cardioversion when preventive use of antiarrhythmic agents is ineffective and RFA has failed (C).

Class IIa

1. RFA is indicated in patients without structural heart disease with sustained or continuous recurrent ventricular tachycardia as an alternative forsuccessful antiarrhythmic agents if patient prefers (C).
2. Preventive use of antiarrhythmic agents (β-adrenoblockers or sotalol) is indicated for patients without structural heart disease and with daily index of arrhythmia load of more than 20% that is provoked by physical exercise and registered on Holter monitoring mainly during daytime (C).
3. Preventive use of IC antiarrhythmic agents is indicated for patients without structural heart disease and with daily index of arrhythmia load of more than 20% that is provoked by sinus bradycardia and suppressed by physical exercise and registered on Holter monitoring mainly during the night (C).

4. Endocrinal ES is appropriate in patients with VA without structural heart disease and with history of palpitations, episodes of dizziness and syncope, if VT is expected to be the cause (B).

Class IIb

1. RFA is indicated in patients without structural heart disease with sustained unifocal VA originated from RVOT/LVOT with daily index of arrhythmia load of more than 20% as an alternative for successful antiarrhythmic agents if patient prefers (C).
2. Adjunctive therapy with omega-3 polyunsaturated fatty acids is recommended in patients with VA without structural heart disease (C).

Class III

1. Preventive use of antiarrhythmic agents is indicated for patients without structural heart disease and with daily index of arrhythmia load of not more than 20% (C).
2. Preventive use of antiarrhythmic agents is indicated for patients without structural heart disease and with VA manifestation (history is up to 3 months) (C).
3. RFA is not indicated in patients without structural heart disease with sustained unifocal VA originated from RVOT/LVOT with daily index of arrhythmia load of not more than 20% (C).
4. RFA is not indicated for patients without structural heart disease and with VA manifestation (history is up to 6 months) (C).
5. RFA is not indicated in patients with known «minimal changes in RV/LV» that fit arrhythmogenic variant of latent myocarditis criteria before the pathogenetic and etiologic treatment of the underlying disease, in case of arrhythmia history of less than a year with multifocal VA.

X.16. SCD risk stratification and prevention in patients with electrolyte disturbances

Clinically significant electrolyte imbalance may lead to life-threatening arrhythmias and conduction abnormalities in structurally normal myocardium. Most frequent causes of electrolyte imbalance encountered in clinical practice are the following:

1. The use of diuretics (mainly thiazide diuretics);
2. Digitalis toxity;
3. Acute and chronic renal failure, including chronic hemodialysis;
4. Electrolyte disturbances directly related to the cardiopulmonary bypass;
5. Massive blood transfusion;
6. Chronic intoxications: alcohol/drug abuse;
7. Starvation and anorexia.

In these cases the following abnormalities may cause SCD:

1. Hypokalemia. The use of diuretics, a complication of cardiopulmonary bypass, hemodilution, hyperinsulinemia, respiratory or metabolic alkalosis, activation of renin-angiotensin-aldosterone system.
   Complications: atrial and ventricular arrhythmias.
2. Hyperkalemia. level of potassium in blood may increase as a result of: renal failure, metabolic acidosis, hemolysis and hemoglobinuria caused by perfusion damage of blood cells, hemothorax, massive blood transfusion, high doses of potassium-containing drugs, such as IV bolus of more than 10 million units of penicillin potassium salt.

Complications: heart blocks, cardiac arrest in systole.

3. Hypomagnesemia. Use of large doses of diuretics, transfusion of citrated blood, cardiopulmonary bypass, cardiac toxicity of adrenaline.
   Complications: with magnesium deficiency cardiomyocytes lose potassium that is replaced by sodium and water. This process of ionic imbalance considerably worsens ischemic damage of cardiomyocytes and sometimes may lead to cardiac arrest as a result of torsades de pointes.
4. Hypermagnesemia. Acute renal failure with anuria, excessive magnesium supplements administration.
   Complications: atrioventricular conduction abnormalities with magnesium plasma concentration of 2.5–3.0 mmol / L. The concentration of 3.5–4.0 mmol x L–1 causes deep depression of the central nervous system, the so-called «magnesium anesthesia».
5. Hyperkalemia. Thiazide diuretics, cancer, lithium, pheochromocytoma, endocrine pathology.
   Complications: ventricular arrhythmias, conduction disorders.
6. Hypocalcemia. Chronic uncompensated alkalosis due to various intoxications, endocrine pathology, hypoalbuminemia, hypomagnesemia.
   Complications: QT prolongation, torsades de pointes.

SCD prevention in patients with electrolyte disturbances and structurally normal heart

Class I

1. Administration of potassium and magnesium supplements is justified for treatment and prevention of ventricular arrhythmias in patients with structurally normal heart treated with thiazide diuretics (B).

2. Administration of potassium and magnesium supplements is justified for treatment and prevention of ventricular arrhythmias in patients with structurally normal heart after cardiopulmonary bypass surgeries with mandatory correction of blood pH values (B).

Class IIa

1. In patients with confirmed life-threatening VA and structurally normal heart it is appropriate to maintain serum potassium levels in the range of 4.5 – 5.5 mmol/L (C).

2. Administration of potassium and magnesium supplements is justified for treatment and prevention of of ventricular arrhythmias in patients with structurally normal heart with cardiac glycosides overdose (B).

Class IIb

1. Administration of potassium and magnesium supplements is justified for treatment and prevention of ventricular arrhythmias in patients with structurally normal heart and acute or chronic alcohol or narcotic intoxications, anorexia (C).

Class III

1. Administration of potassium and magnesium salts is not justified in patients with acute and chronic renal failure (B).

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X.17. SCD risk stratification and prevention in specific population groups

X.17.A SCD in athletes

According to Italian researchers [1, 2], SCD incidence in athletes is 2.6 and 1.1 per 100 000 individuals per year in males and females, respectively. It is 2.4 times higher than that in individuals of comparable age who do not work out on a regular basis. SCD incidence is higher among French athletes: 6.5

cases per 100 000 [3]. Data from a national register of SCD in young athletes of the United States show a progressive increase in SCD incidence during the past 2.5 decades, an average of 6% per year [4]. Currently in Russia no such statistical reports are available.

Most frequently SCD is registered in individuals who are professionally engaged in football (from 30% to 40% of all SCD cases among athletes in Europe and the US). SCD reported incidence is somewhat less in basketball, cycling and contact sports [1, 2]. There is a clear correlation between SCD and gender – over 90% of athletes who died suddenly are males, and an increase in the incidence of SCD with age [1, 5, 6]. Thus, the main risk factors for SCD in athletes are age, male gender and intensity of exercise

The most common causes of SCD in young athletes are hereditary arrhythmogenic diseases (cardiomyopathy and canalopathy) and ischemic heart disease (congenital or acquired). In young people, the main causes are CMP and canalopathy, whereas as the age increases, the role of CAD increases significantly as a cause of sudden death [7]. In the American National Register of sudden death among athletes, which was organized in the 1980s at the Heart Institute of Minneapolis, among athletes under the age of 40, there were 1,866 cases of SCD. Only 36% of all sudden deaths were associated with confirmed CVD, and HCM (36%), congenital coronary artery anomalies (17%), myocarditis (6%), AAD (4%) and canalopathy (3% , 6%) were the mosr frequent [8]. However, doubts are expressed about the legitimacy of the HCM diagnosis in all cases when marked left ventricular hypertrophy is detected at died athlets autopsy [1, 9]. Some domestic authors propose the term compensatory-hypertrophic stress cardiomyopathy, with the main difference of this condition from HCM being the reversibility of the hypertrophy after cessation of training [9]. It is obvious that the presence of LVH in an athlete is a risk factor of SCD.

In an Italian prospective incidence study, which included persons engaged in competitive sports, it was shown that in athletes under the age of 35 the most frequent cause of SCD is ARVD (24%), then goes ischemic arteriosclerosis (20%), abnormal coronary artery distention (14 %) and mitral valve prolapse (12%) [10]. Among athletes of 36 years of age and older, more than half of cases of SCD are associated with CHD [7].

SCD prediction in sport is an extremely difficult task, since about 80% of people who died suddenly, did not have any symptoms before the death and there were no history of SCD among their relatives [1, 6]. However, in some European countries and the United States several protocols proposed for SCD prevention in athletes, that include recommendations on history taking, including family history and physical examination; and in some countries

include additional studies such as ECG and/or echocardiography. In Italy, the introduction of such protocol allowed to reduce SCD incidence in athletes in 3.5–5 times within a period from 1980s and 2000s [11].

In 2011, Russia has published first National Guidelines for admission of athletes with cardiovascular system abnormalities to the training and competition process [12]. The guidelines recommend a two-step algorithm of screening athletes to address the question of admission to the sport: 1) analysis of medical history, physical examination and 12-lead ECG, and 2) in-depth medical examination (in case of positive family history, symptoms, abnormalities on physical examination or ECG changes, not related to the training process).

Special attention requires a decision on admission to the sport activities patients with cardiovascular abnormalities. This question is beyond the scope of this document, it is detailed in the National Guidelines for admission of athletes with cardiovascular system abnormalities to the training and competition process [12].

The recommendations of the European Association for the Prevention of CVD and Rehabilitation (EACPR) on cardiac screening and the determination of the level of physical activity of middle-aged and elderly people engaged in amateur sports are also published [13].

It should be noted the importance of training trainers and personnel of sports centers in the event of emergencies, cardiopulmonary resuscitation and the use of automatic external defibrillators [13, 14].

Recommendations for SCD prevention: athlets

Class I

1. Athletes are recommended to carefully collect history in order to identify the background pathology of CVS, rhythm disturbances, syncopal episodes or cases of SCD in the family (C).

2. When ECG changes are detected, suggesting the presence of structural pathology of the heart, Echocardiography and / or MRI of the heart are recommended. (C).

Class IIa

1. Young athletes with a view to screening before the competition are recommended a thorough physical examination and registration of the resting ECG (C).

2. For middle-aged people participating in high-intensity strength training, a physical examination with assessment of complaints and history data, registration of resting ECG and determination of SCORE (C) risk should be performed for screening purposes.

3. Training of personnel participating in the organization of sports competitions, skills of cardiopulmonary resuscitation and the correct use of automatic external defibrillators (C).

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X.17.B. SCD risk stratification and prevention in elderly patients

Incidence of sudden cardiac death (SCD) increases with age, regardless of sex, race of the patient. In the United States, the annual occurrence of SCD in a 50-years-old population is 100 people per 100,000 population. In the

population of patients older than 75 years, the incidence of SCD is 8 (!) times higher and is 800 cases per 100,000 population [1].

To high risk of SCD in elderly and senile age predispose the following moments:

- 83% of men and 87.1% of women older than 80 years have any cardiovascular disease;
- risk of SCD in patients who survived myocardial infarction (MI) is 4–6 times higher than in the general population [2]. The very incidence of myocardial infarction also significantly increases with age: the average age of patients with first-time angina / MI is 64.7 years for men and 72.2 years for women;
- features of the functioning of the body in elderly and senile patients: decreased kidney and liver function;
- polymorbidity, multiple drug interactions with multicomponent therapy of various diseases.

At the moment, there are no separate indications for the implantation of ICDs in elderly patients. ICD implantation is not indicated in patients with an expected life expectancy of less than 1 year [3]. In the MADIT II study, it was shown that the effectiveness of ICD in patients before and older than 75 years did not differ from that in younger patients. However, a meta-analysis of the 5 largest studies did not reveal the benefits of ICD implantation in this group of patients. It should be noted that the frequency of complications of the ICD implantation procedure itself did not differ in the group from that in the general sample. Consequently, the age itself cannot be an obstacle to ICD implantation. Since statistically significant benefits from ICD implantation are traced only 1 year after surgery, it should not be performed if the patient's expected life expectancy is less than 1 year. In this regard, the evaluation of those factors that can significantly reduce the patient's life expectancy is of paramount importance.

It should be clearly understood that the ICD is able to prevent SCD, but cannot reduce mortality from other causes. These are situations of severe polymorbidity and senile asthenia (fragility) in elderly and senile patients. In this unjustified setting ICD patient with a terminal status, can lead to a long and painful death of the patient with repeatedly recurring episodes of unnecessary defibrillation. The recommendations of the American Association of Cardiologists indicate the possibility of switching off electrodes of an already implanted ICD in such patients after a preliminary consultation involving the patient and his relatives [10–14].

Passport age as a risk factor cannot fully reflect the heterogeneous group of elderly patients. The process of aging the organism itself is a factor leading

to acceleration of unfavorable pathogenetic mechanisms of the development of diseases [4, 5]. Elderly patients are a special group of patients who need specialized geriatric diagnostics for making clinical decisions. In the evaluation of health risks in elderly patients, the concept of senile asthenia is becoming increasingly widespread [4–6]. This approach is extremely important in patients with high risk of SCD.

Senile asthenia is a syndrome that is characterized by the presence of the following symptoms: weight loss – sarcopenia, a decrease in the strength of the hand muscles when measured by a dynamometer, severe fatigue (the need to perform daily activities with effort), slowing down the movement speed, a significant decrease in physical activity. In the presence of three or more symptoms, senile asthenia occurs, one or two – senile overgrowth. The age-related asthenia with CHF is 6–7.5 times more likely than in the general population of elderly patients and significantly aggravates the prognosis of such patients, decreasing their survival [7–9]. At the same time, today there is no unified approach to senile asthenia and the estimated life expectancy of such patients.

For the adoption of an appropriate solution, it is advisable to use the criteria of terminal cardiac disease. CARING criteria: cancer, 2 or more hospital admissions per year (admissions $\geqslant$2); stay in a hospice home, stay in an intensive care unit with two or more non-cancerous diseases requiring external patient care ($\geqslant$2 non-cancer hospice Guidelines) [15] or criteria for terminal heart failure NHO (National Hospice Organization): IV FC of CHF, despite optimal drug therapy; FV <20%; impossibility to control arrhythmias with the help of drug therapy; cardiopulmonary resuscitation in the anamnesis; a syncope in the anamnesis; embolisms from the heart cavities in the anamnesis; HIV infection.

NHO criteria are highly sensitive and specific for death in the next year (and even 6 months). In addition, unlike other models for determining terminal status, they are designed specifically for patients with cardiac pathology [15].

Recommendations for SCD stratification and prevention

Class I

1. Management of elderly patients with VA, as a rule, should not differ from that in younger patients. This implies that the SCD risk stratification and prevention in elderly patients is based on the detection of major and secondary risk factors. SCD prevention includes ICD or pacemaker placement in patients with good functional status* who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (C).

* You can read about functional status assessment methods at http://www.chcr.brown.edu/pcoc/functi.htm

2. All elderly patients should be advised to stop smoking and alcohol abuse (B).

3. Beta-blockers (A). Nebivolol has the largest evidence base among patients older than 70 years (B).

4. ACE inhibitors (ramipril, enalapril, perindopril, trandolapril) in elderly patients with LV systolic dysfunction effectively prevent SCD (B).

5. ACE inhibitors (elderly under 70 years and ramipril – no age limit) in patients with persistent EF. The possibilities of other ACE inhibitors in this category of patients have not been studied to date (B).

6. APA II can be used as an alternative to ACE inhibitors with intolerance of the latter for prevention of SCD in elderly patients.

7. With proper selection of patients (initially normal levels of potassium, blood creatinine), the addition of spironolactone / eplerenone to ACE inhibitors, β-adrenoblockers effectively reduces the likelihood of SCD in elderly patients with CHF III-IV FC with systolic LV myocardial dysfunction. Moreover, eplerenone significantly improves prognosis also in patients with II FC of CHF (A).

8. The use of acetylsalicylic acid in doses of 75–100 mg is indicated for all patients with CAD, regardless of age or patients with a high cardiovascular risk not older than 70 years (A).

9. Stentin is indicated for all patients with CAD or high cardiovascular risk regardless of age (B).

10. In the absence of contraindications to β-adrenoblockers and high risk of SCD, amiodarone may be used together with β-adrenoblocker to prevent arrhythmic death in patients with existing ventricular arrhythmias (B).

11. Dosage and choice of antiarrhythmic agents should be adjusted to reflect changes of pharmacokinetics in elderly patients (C).

Class IIa

1. The use of omega-3-PUFA is safe. However, their effectiveness in the prevention of SCD in patients older than 70 years requires additional confirmation in clinical studies (C).

2. It is possible to use ARA II directly as a starting agent for blockade of RAAS (without prior administration of ACE inhibitors) (C).

Class III

1. ICD placement in patients with life expectancy of less than one year due to severity of the primary disease or comorbidities is not justified (C).

2. Class I antiarrhythmic agents should not be given to elderly patients with organic heart disease (A).

3. Do not combine ARA with ACE inhibitors. This combination increases the number of side effects, without giving any therapeutic benefits (B).

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X.17.C. SCD in patients after heart transplantation

At present, there is no official information on the prevalence of SCD in patients after heart transplantation in the central statistical database of the Federal Service of State Statistics of the Russian Federation [1], as well as prospective domestic and foreign studies. Data on the literature on the frequency of SCD after cardiac transplantation, obtained during epidemiological studies in the US and European countries, varies widely from 0.5 to 50% [2–9], which is explained not only by the possible errors in observational, retrospective

epidemiological studies, but and the difference in the interpretation of terms and definitions of SCD by different authors. Thus, E.Y. Birati et al. [10] considered deat after the onset of new symptoms within 24 hours to be the deterministic SCD time, which significantly differs from the opinion of the experts ESC, RKO, ANA / ACC, postulating SCD as death within an hour interval from the onset of symptoms of destabilization of the condition [11–13]. Criteria for inclusion and exclusion of patients from the study range from one week, or one month after surgery to six months post-implantation period, a number of authors included in the sample all patients with SCD irrespective of the time elapsed after surgery [4–10].

ESC experts in 2015 emphasize the rather high incidence of SCD after heart transplantation, citing relatively small long-term studies in which SCD is recorded at a frequency of more than 10%. In particular, a retrospective analysis of the biopsies of 74 patients who died in the period from 1984 to 2002 of heart recipients was mentioned, among which SCD was detected in 37% [3]. The results of a large multicentre retrospective study of the causes, predictors, and time trends of incidence of SCD in patients with a transplanted heart for the period from 1987 to 2012 were recently published [14]. Data of medical documentation of more than 37 thousand patients from the UNOS-register was analyzed. During six years 46% of recipients died, sudden death was detected in 9.6% cases. The age of the recipient (RR 0.90, 95% CI 0.86–0.95, P <0.0001), and the Caucasoid race (RR 0.61, 95% CI 0.54–0.69, P <0.0001) correlated with SCD risk mitigation, while graft rejection (RR 1.51, 95% CI 1.35–1.70, P <0.0001), the age of the donor (RR 1.17, 95% CI of 1,13–1.23, P <0.0001) and a decrease in the left ventricular ejection fraction ⩽40% (RR 3.67, 95% CI 3.23–4.17, P <0.0001) were significant predictors of SCD development. In contrast to the findings from this register on the relationship between low contractility of the left ventricle and SCD, in a later study of E.Y. Birati et al. came to the conclusion that there was no effect of EF on the risk of SCD in the recipients of the heart [10]. Out of 11 deaths with EF ⩽35%, only 2 patients (18%) had sudden death, which is significantly less than in 9 died suddenly out of 29 (31%) with FV> 35%. In general, the authors confirmed a higher mortality rate in recipients with an EF <35%, but with regard to SCD, there was a conclusion that there was no correlation between the decreased EF and an increased risk of sudden cardiac death after heart transplantation. The independence of the frequency of arrhythmias, especially ventricular fibrillation, from contractility is also shown by researchers in a retrospective analysis of medical records and autopsy records of 257 deceased patients with a transplanted heart [4]. Although most of them have a EF of ⩽ 50%, there is no significant difference in the number of potentially fatal arrhythmias in comparison with recipients

with a documented EF > 50%. It is well known to reduce EF of the left ventricle as an independent predictor of total, cardiovascular and arrhythmic mortality in the general population. This provision is confirmed both by the results of epidemiological data and by the results of studies evaluating the effectiveness of the ICD for primary and secondary prevention of SCD, in many of which systolic dysfunction was one of the inclusion criteria [11, 15–17]. Apparently, at the present stage of knowledge about the genesis of SCD in patients after heart transplantation, the absence of significant correlations between EF and SCD frequency is the dominant difference from the general population.

In patients with a transplanted heart, the issue of the imbalance in the functioning of the autonomic nervous system as a significant factor in the development of fatal arrhythmias and, accordingly, sudden cardiac death is widely discussed [18–22]. Chang HY et al. [5] demonstrated the significance of high heart rate as a predictor of SCD in patients at rest, without finding a connection with the basal and adjusted QT interval. In a retrospective analysis of the causes of death of patients who underwent heart transplantation from 2007 to 2013 at the University of Pennsylvania clinic, the authors suggested that an increase in sympathetic and / or a decrease in the parasympathetic tone of the autonomic nervous system is the cause of SCD. Thus, the researchers interpreted the fact that they had no influence on the risk of SCD as coronary vasculopathy, and the level of contractility in the ranking of patients in groups with EF <35% and with EF > 35% in the cohort of patients studied by them. The uneven recovery of sympathetic and parasympathetic innervation of the heart has been studied in recent decades. In particular, it has been shown that the process of sympathetic re-innervation starts from the first year of the post-implantation period and can be delayed up to 15 years, being the basis for the heterogeneity of sympathetic influences [23, 24]. It is with uneven sympathetic reinnervation of the sinus node and the left ventricle of the transplanted heart, Stecker EC et al. [25] associated an increase in arrhythmogenic risk in the genesis of SCD, which indirectly corresponds to E.Y. Birati et al. [10] on the high incidence of lethal arrhythmias and a significant proportion of SCD after the first year of the posttransplant period with the SCD peak in the second year after heart transplantation. According to numerous autopsy data [3, 26, 27], an important cause of SCD is the processes of graft rejection. A number of studies discuss hypotheses about the role of epicardial disease, microvessel diseases in potentially fatal cardiac arrhythmia in patients after heart transplantation [28–30].

In a study by Patel V.S. et al. [31] the conclusion about SCD authors compared with the severity and frequency of episodes of rejection, a history of arrhythmia, the presence of IHD, hypertension, diabetes, dysfunction of the left ventricle. A total of 25 patients were identified as sudden deaths (9.7%),

20% died within 12 months after transplantation, 80% after> 12 months, 20% of them died after more than 60 months. Survival of patients ranged from 2.5 to 138 months (an average of 45.7 months). The average number of episodes of rejection per patient was 2.6, most occurred within the first 12 months after transplantation. And analysis of the data from the angiograms available to the researchers indicated the presence of coronary heart disease in 53% of patients. The timing of CHD debut after transplantation was from 29 to 85 months (on average, 51.4 months). In accordance with the protocols of autopsies, signs of coronary heart disease are fixed in 92%, signs of transplant rejection – in 15%. The authors concluded about the high incidence of SCD in the recipients of the heart, highlighting the particular importance of coronary pathology present in most patients who died suddenly. Given that the most common cardiovascular diseases after organ transplantation are vascular diseases, all patients with this pathology are recommended to take acetylsalicylic acid in a dose of 75–100 mg to prevent cardiovascular complications [32–34].

Despite dozens of publications devoted to the analysis of data from both individual transplant centers and multicenter retrospective observations, ESC experts in 2015 in clinical «Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death» [11] included in SCD section only three publications, focusing primarily on the extremely high incidence of coronary artery disease found in pathoanatomical studies of patients who underwent heart transplantation and died suddenly [3]. Death in such cases is often associated with predominantly arrhythmic genesis, hyperkalaemia, hemodialysis or plasmapheresis procedures are suggested as triggers. Hemodynamic stress in hemodialysis or plasmapheresis, episodes of severe transplant rejection with disruption of the functioning of the conduction system of the heart are discussed as conditions that initiate ventricular arrhythmias and SCD [11, 14].

A number of studies have revealed a correlation between QT interval dispersion and SCD risk in the posttransplant period, which is probably associated with ischemic processes as a result of coronary blood supply pathology. Vasculopathy of the allograft can also lead to the development of fibrotic processes, which are a substrate for ventricular arrhythmias [3, 28–30, 35, 36]. In addition to antiproliferative and immunosuppressive drugs, statins are routinely used in the treatment of heart recipients to prevent and treat vasculopathy of the graft [32–34, 37].

Conclusions:

1. Determining SAD pathological conditions of the transplanted heart are recognized as the violation of coronary blood supply and acute rejection of the graft by most researchers.

2. In most studies, the absence of the effect of the ejection fraction on the risk of SCD in the recipients of the heart has been proven.

3. The main measures for the prevention of SCD in patients with a transplanted heart should be concentrated on the identification of high SCD risk groups, primarily recipients with coronary artery disease.

4. Given that the most common cardiovascular diseases after organ transplantation are vascular diseases, all patients with atherosclerotic lesions of the arteries are recommended taking statins and acetylsalicylic acid in a dose of 75–100 mg to prevent cardiovascular complications.

5. As in the general population, the therapy of patients after transplantation is based on the use of medicines in accordance with established standards of treatment. With the progression of atherosclerosis, drug therapy can be combined with endovascular and surgical methods of treating heart and vascular diseases.

6. ICD placement should be considered in individuals at high risk for sudden death, taking into account possible complications associated with the implant and immunosuppression.

7. An in-depth study of the role of the sympathetic and parasympathetic system in heart recipients in the genesis of SCD would identify a high SCD risk group of in recipients in the long-term post-transplant period. It is necessary to update prospective studies with the identification of causes, predictors, temporal trends in frequency of occurrence and effective methods of preventing SCD in patients after heart transplantation.

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CONCLUSION

Cardiovascular mortality continues to be an actual problem in Russia. Sudden cardiac death accounts for about half of all the deaths.

SCD occurs as a result of acute left ventricular failure due to malignant ventricular arrhythmias complicated by systemic and regional (primarily CNS) hemodynamics derangements. This may cause irreversible changes in the vital organs and death. The presence or absence of preexisting structural heart defects may be crucial to adaptive changes of cardiac output parameters, and thus to the clinical course of the arrhythmia. In this context, the key to the clinical interpretation of any malignant arrhythmias as life-threatening is presence of the following signs and symptoms: syncope, presyncope, dizziness, hypotension, progression of CHF signs, angina pectoris.

The use of modern medical technology, including implantation of cardioverter-defibrillators, can be effective in sudden cardiac death prevention. In recent years, several federal centers of cardiac surgery in different regions of the country were opened within the «Health» national project. However, the rate of cardioverter-defibrillator implantations does not meet current average needs and is significantly below than that in leading European countries and the US.

The main cause of this situation is not so much a lack of funding, but, above all, the lack of a systematic approach to adequate clinical assessment of patients with cardiovascular diseases; different approaches to the patients by cardiologists, internists, interventionists, cardiac surgeons, mediocre graduate education level on the subject and the lack of quality assurance of measured directed at SCD prevention.

These guidelines are one of the measures aimed at prompt development and implementation of an effective sudden cardiac death prevention system in our country.