RUSSIAN GUIDELINES
FOR SUDDEN CARDIAC DEATH RISK ASSESSMENT AND PREVENTION

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Eurasian Arrhythmology Association (ЕврА[3])

CONTENTS

I. INTRODUCTION

Cardiovascular mortality in Russia is one of the highest in the world reaching 1,462 deaths per 100,000 per year [1]. There are two major dramatic outcomes of cardiovascular diseases – death due to progression of congestive heart failure (about half of all cases) and sudden cardiac death (the other half). It is estimated that 200,000–250,000 people die in Russia each year from sudden cardiac death (SCD) [2].

SCD is one of the major problems of the national health care. This problem raises additional concerns due to present increasing trend in SCD incidence. It is also clear that there is an opportunity for effective interventions aimed at changing this negative situation.

These guidelines, based on the latest achievements of domestic and foreign experts, address SCD risk assessment and prevention in various populations and patient categories. 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 one of the measures aimed at prompt development and implementation of an effective sudden cardiac death prevention system in our country.

These 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.

For those readers whose are not familiar with SCD and who desire to understand this topic deeper, we recommend:

First, read the chapters I–VI;

Second, when managing a patient, to assess SCD risk and introduce the prevention measures it is important to establish main diagnosis and identify SCD risk factors. After that, read the corresponding section on the specific condition in Chapter VII SCD risk stratification and prevention;

Third, we suggest using the recommendations provided in the specific section of Chapter VII as a practical guidance.

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 [3–5].

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 [6–8] (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.

In patients without severe structural heart disease, SCD usually is a result of polymorphic VT or torsades de pointes [3]. 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

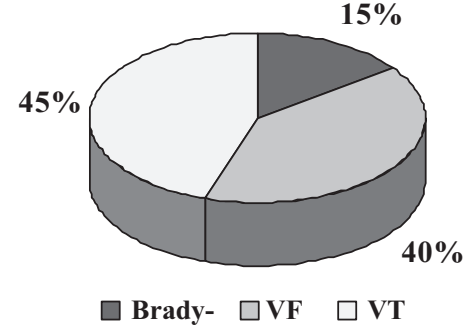

Figure II.1. Mechanisms of SCD. The diagram shows contributions of different types of arrhythmias and cardiac conduction abnormalities to SCD. Brady – percentage of bradyarrhythmias leading to SCD, VF – ventricular fibrillation, VT – ventricular tachycardia

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

mechanisms, mainly caused by scarred tissue following a myocardial infarction (in such case, coronary flow abnormalities are not the cause of arrhythmia) [3–5, 9]. As for bradyarrhythmic mechanisms, they are typical for patients with terminal stages of structural heart disease and are relatively rare (about 15%) [3–8].

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.

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 [10, 11]. Among the cardiac pathology that may lead to SCD, coronary artery disease is the most common cause accounting for 80% of all cases [3–8]. In addition to CAD, SCD, as a dramatic outcome of the disease, occurs in patients with dilated cardiomyopathy (DCM) [3–8], hypertrophic cardiomyopathy (HCM) [3–8], arrhythmogenic right ventricular dysplasia (ARVD) [3–8], 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

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. SCD EPIDEMIOLOGY

There is no official statistical data of the Russian Federation (Central Statistical Database of the Federal State Statistics Service, www.gks.ru/dbscripts/Cbsd) on specific SCD mortality rate in Russia. Estimated data, calculated with coefficients obtained from U.S. and European epidemiological studies, show a wide range of possible SCD incidence in Russia: from 141 thousand to 460 thousand a year (Table IV.1). However, the most feasible values probably lie between 200–250 thousand cases a year. [12]

The first epidemiological studies of SCD in the former USSR were carried out in the 1970s as part of WHO program «Registry of acute myocardial infarction». [13] In Moscow, annual sudden death rate was 78 for males and 37 for females per 100 000. Later, similar data were obtained in Novosibirsk [14] and Vologda [15]. These studies have identified a number of epidemiological features, in particular, a clear association between prevalence of myocardial infarction and SCD as well as higher SCD incidence in men compared with women. Male-to-female sudden death ratio was 2.1–6.6:1.

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 well as to evaluate diagnosing and statistical reporting in the medical institutions [16]. 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. 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

Table IV.1

Population (2009) and mortality rate (2010) of Russia

Parameter	Total number, n	Proportion, %
Permanent population[1]	141 909 244	
Crude death rate[2]	2 028516	100.0
Number of deaths from natural causes[2]	1 711 528	84.4
Number of deaths from cardiovascular diseases [2]	1 151 917	56.8
Estimated number of SCD[3]	141 909 – 460 766	

[1] – The central statistical database of the Federal State Statistics Service, 2009 (www.gks.ru/dbscripts/Cbsd)

[2] – The central statistical database of the Federal State Statistics Service, 2010 (www.gks.ru/dbscripts/Cbsd)

[3] – Estimated number (the minimal number corresponds to 1% of the population, the maximal number corresponds to 40% deaths from cardiovascular diseases).

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, 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%).

According to another epidemiologic study conducted in Moscow [17], among all deaths that happened out of medical institutions, SCD was responsible for 39.4% of cases (reaching 92.5 cases per 100,000 individuals per year).

In the U.S., the annual incidence of SCD is 1–2 cases per 1000 population, in absolute numbers it corresponds to 200 000 – 450 000 deaths a year [18, 19]. Such discrepancies are mainly due to differences in diagnostic criteria, mainly related to different SCD time frames (24 hours figure was used in 1980–1990 and up to 1 hour in current guidelines). The U.S. averaged epidemiological data suggests that the proportion of SCD (assuming one hour inclusion criteria) in overall mortality rate is about 13%, and in mortality from cardiovascular diseases is about 40%. [19] At the same time the results of a Dutch study, in which a 24-hour diagnostic criteria was used, have shown that the SCD constitutes 18.5% of all deaths [20]. In the aforementioned Russian study РЕЗОНАНС (REZONANS) [16], 12 hours were used as a threshold for SCD diagnosis, and the estimated proportion of SCD in overall mortality rate was 16.3%.

In Europe, the SCD incidence is, in general, comparable to that in the U.S., however, it varies greatly in different European countries depending on the economic state and geographical location [21]. In addition, a clear correlation can be traced between the SCD incidence and age, gender and CAD prevalence in the population [12, 22]. The vast majority of SCD cases (80–85%) is associated with coronary artery disease, and more than half of them are related to acute coronary circulation disorder [23]. The absolute number of SCD cases is higher in men and it increases with age, but the proportion of SCD in overall mortality rate is the highest in those aged 35–44 years [23]. The same study showed that in 80% of cases death occurs at home, in 15% – on the street and in another 15% – in a public place. There are no witnesses in more than third of death cases.

Thus, only a small number of patients dies in the presence of medical personnel and in theory has a better chance of successful resuscitation and therefore survival. These findings lead to the conclusion that the major efforts should be focused on identifying high-risk groups for SCD and preventive activities.

Figure IV.1 clearly demonstrates this situation. SCD incidence is the lowest in the general population compared to high risk groups, on the other hand this category has the largest absolute number of SCD. Conversely, in a high-risk

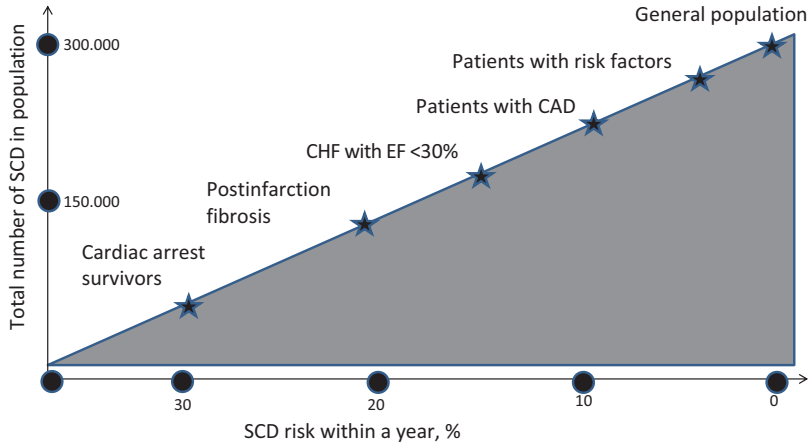

Figure IV.1. Incidence and absolute number of SCD in the general population and in special patient subgroups (adapted from R.J. Myerburg et al., 1992). The general population includes all patients older than 35 years, high-risk subgroup include patients with various risk factors for the first coronary event. SCD incidence is the lowest in the general population compared to the high risk groups, on the other hand this category has the largest absolute number of SCD. In a high-risk group the SCD proportion is the highest, but in absolute numbers it is much smaller than that of the general population

group, for example, in patients with history of cardiac arrest and/or myocardial infarction with ventricular arrhythmias the SCD proportion is the highest, but in absolute numbers it is much smaller than that of the general population.

These data demonstrated for the first time almost 20 years ago are still valid today. They show that the effectiveness of SCD prevention has clearly not improved enough, and on the other hand it is very important to look for new criteria that would allow to identify the high-risk patient groups in the general population [12] .

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

SCD incidence is the lowest in the general population compared to the high risk groups, on the other hand this category has the largest absolute number of SCD. 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.

SCD risk factors

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 an year in these patients is 30–50% [24]. 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 [25–27].

History of previous myocardial infarction. According to studies of antiarrhythmic agents in post-AMI patients (EMIAT, CAMIAT and DIAMOND-MI), arrhythmic mortality as a result of ventricular tachycardia and ventricular fibrillation during one year is 5%, and during 2 years is 9% [28–30].

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 [20, 25–27, 31–34].

Syncope. High risk of SCD in patients with syncope may be a result of structural heart disease or may be associated with mechanism of the syncope. Framingham Heart Study demonstrated that mortality in patients with cardiogenic syncope in a calendar year is much higher (33%) than in patients with noncardiac syncope (12%) or syncope of unknown etiology (6%) [35, 36].In vasovagal syncope, which often develops in young adults without structural heart disease or myocardial electrical instability, the prognosis is favorable [35]. However, there are observations indicating a possible connection between vasovagal syncope and SCD [37].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. [38] 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, shortness of breath, hematocrit <30%, systolic blood pressure <90 mmHg, history of congestive heart failure (The San Francisco Syncope Rule). 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) [39].

Non-sustained ventricular tachycardia and frequent PVCs. Studies, conducted in the 1970s, showed that patients with history myocardial infarction and frequent PVCs 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 intracardiac electrophysiological study are risk factors for SCD. [31]

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 [40, 41]. 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 [42]. 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 [42].

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. [43] 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 [41]. 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 [44]. Meta-analysis of randomized trials data on blood pressure reduction in middle-aged patients with predominantly diastolic hypertension [45] 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 [46–48]. 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% [49, 50]. 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 [51]. 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. [52] 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 [53]. 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 [54]. 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, high blood pressure 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 [47, 55]. This fact can be explained by the increase of the interval QT duration, which often occurs in alcoholics [56]. On the other hand, there are data on the protective effect of small doses of alcohol from life-threatening ventricular arrhythmias [57]. 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) [47].

Heart rate and heart rhythm variability. Increase in HR is an independent risk factor for SCD [46, 47]. 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 [46]. The bases 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 [58].

Smoking. Population studies have shown that smoking is an independent risk factor for both BCC and AMI [47, 48]. This also applies to persons with no signs of coronary artery disease [59, 60]. Smoking is an important long-term risk factor for SCD [46]. We also know that smoking is a strong predictor of SCD, not SCD as a result of CAD [47]. However, results of a number of studies did not support the disproportionate effects of smoking on SCD [47]. Continued smoking after experiencing a cardiac arrest out of a medical institution is an independent predictor of recurrent episode of SCD [60].

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) [61]. Similar results were obtained in Austria (OR = 4.2, 95% CI 1.39–12.81). [47] 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 [62]. Prospective studies in Finland and the UK confirmed the hypothesis that diabetes is not an independent predictor of SCD [47, 62].

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. [63] These data have also been confirmed by a number of other studies [64]. 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 QT> 420 ms is a predictor of SCD [65, 66]. Convincing evidence that the QT interval dispersion is a predictor of SCD are lacking [66–68].

SCD risk stratification

In 1984, J.T. Bigger specified factors that determine SCD risk during a calendar year (Table V.1). 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 [24–26, 30–34].

Table V.1

SCD risk (from Bigger J.T., 1984)

	SCD risk within a current year
Moderate risk group	
History of AMI or EF less than 40%	5%
AMI+EF below 40% or AMI + frequent PVCs or EF less than 40% + PVCs	10%
AMI + EF below 40% + PVCs	15%
High risk group	
Patients who experienced SCD	30–50%
VT + syncope	30–50%
VT + minimal clinical manifestations	20–30%

Note: AMI – acute myocardial infarction, EF – ejection fraction, PVCs – premature ventricular contractions, SCD – sudden cardiac death, VT – ventricular tachycardia

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 in patients with cardiac arrhythmias regardless of the structural heart disease presence, proposed R. Fogoros, is worth mentioning [69] (Table V.2). 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.

Diagnostic tests for SCD risk stratification

SCD risk assessment is based on a clinical evaluation of a patient, including medical history, physical examination and additional diagnostic tests. Table V.3 presents the basic instrumental and laboratory tests, which are required to assess risk of SCD, as well as indication classes for their administration and levels of evidence.

Table V.2

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

High	Moderate	Low
Ventricular fibrillation Ventricular tachycardia III degree AV block with low rate escape rhythm WPW syndrome with antero-grade conduction along ac-cessory AV pathway with atrial fibrillation	Ventricular ectopy with struc-tural heart disease II degree AV block III degree AV block with ad-equate rate escape rhythm Atrial fibrillation	Atrial ectopy Ventricular ectopy without struc-tural heart disease Supraventricular tachycardia I degree AV block

Note: WPW – Wolff–Parokinson–White, AV – atrioventricular

Table V.3

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 abnormali-ties, His–Purkinje conduction blocks, LVH signs).	I	C
Holter monitor-ing	Indicated in patients with symptoms of arrhythmia to determine if they are causes by potentially life-threatening arrhythmias (see Table V.2)	I	B
	Indicated in patients with PVCs on the ECG tracing without any other symptoms	I	B
Stress tests	Recommended for adult patients who have coro-nary artery disease risk factors and symptoms that may be associated with arrhythmias	I	B
	Indicated in patients with previously verified or sus-pected ventricular arrhythmias arising during physi-cal activity, including catecholamine-dependent ventricular tachycardia, to establish the diagnosis and determine the VT clinical significance for the patient	I	B
	Indicated in middle-aged and elderly patients with PVCs on the ECG tracing without any other symptoms.	IIb	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 can not establish a causal relationship between the event and heart rhythm abnormality.	I	B
Echocardiog-raphy	Indicated in patients with suspected structural heart disease	I	B
	Indicated in patients with high risk of SCD and car-diomyopathy (DCM, HCM, ARVD), postinfarction myocardial fibrosis and family history of diseases with high risk of SCD.	I	B
	Stress echocardiography to detect silent myocar-dial ischemia is recommended in patients with VA, 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.	I	B

Table V.3 (continuation)

Test	Comments	Indication class	Level of Evidence
	Echocardiography with pharmacological stress is recommended to identify painless myocardial ischemia in patients with moderate risk of CAD who can not exercise.	I	B
Genetic counseling and genetic testing (DNA diagnosis).	Aimed to identification and/or clarification of a hereditary disease diagnosis. Includes a discussion with the patient and/or family members about the hereditary nature of the disease, type of inheritance, risk of a child with the disease or risk of disease in future generations. Providing information on the natural history of the disease, specific risk factors, possible prevention measures, treatment and/or maintenance management as well as possible reproductive methods options. 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		
Magnetic resonance imaging (MRI), computed tomography (CT) of the heart	Indicated in patients with VA, when echocardiography is not able to precisely evaluate LV and RV function and/or identify structural abnormalities.	IIa	B
Coronary angiography	Indicated in patients with coronary artery disease and life threatening VA (high and medium risk of SCD, see table. V.2), as well as in those who survived cardiac arrest	I	C
Electrophysiology study (EP)	EP study with pharmacological agents may be used to evaluate the clinical significance of arrhythmias and to stratify risk of SCD. EP is also used for VT induction and verification, monitoring the effectiveness of antiarrhythmics, previous catheter ablation, to determine risks of VT or SCD, diagnosis syncope, to determine indications for ICD implantation.	Indication classes and levels of evidence are determined in every clinical case and are regulated by BHOA National Guidelines, 2011 [70].	

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; BHOA – Pan-Russian Scientific Society of Arrhythmologists.

VI. SCD PREVENTION

SCD prevention is a set of activities carried out to prevent of 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 medical 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 to prevent SCD. 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 can be used.

Beta blockers. Benefits of beta-blockers and their various effects are well studied in experiments and in clinical practice. Antiarrhythmic effect of beta blockers is associated with both their anti-ischemic effects and the decrease in sympathetic activity. A meta-analysis of 25 studies of beta blockers effects on post-MI patients survival, which included nearly 25,000 patients, showed that beta blockers increase survival, reduce total and cardiovascular mortality and decrease SCD incidence [71]. Positive effects of beta blockers on VA and SCD are also proved in patients with CHF of ischemic and non-ischemic nature (dilated cardiomyopathy, hypertrophic cardiomyopathy, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, ARVD, aortic stenosis) [72–75]. Another advantage of beta blockers is that they also can be combined with other antiarrhythmic agents, for instance amiodarone [76]. It should be noted that not all beta blockers were equally effective in reducing the risk of SCD. Preference is nowadays given to lipophilic drugs, including: metoprolol succinate, bisoprolol, carvedilol, nebivolol (in elderly) [76]. Thus, beta blockers are safe and effective agents that have the largest evidence base and must be considered as first-line agents for primary and secondary prevention of SCD**(I, A)** [4, 12].

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 have shown that ACE inhibitors significantly reduce total and cardiovascular mortality in these patients [77–82].However, SCD was not evaluated as an end point in most of these clinical trials, in contrast to beta-blockers. The exception is a randomized trial TRACE that studied the effects of trandolapril on the SCD; the positive result was proven [82]. 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 on 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 [80]. 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 is associated with reduced total and cardiovascular mortality in patients with history of MI, and the incidence of SCD in these patients decreases by 20% (2356 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 are 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 [83], 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. So, apparently, 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 (6797 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. Study RALES (1663 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 [84]. It is shown that electrolyte disturbances arising from administration of potassium non-sparing diuretics may 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 is 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 also has an impact on the autonomic nervous system that actively influences hearth rate. It improves heart rate variability and increases baroreceptors sensitivity [85, 86] . 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 [87].

Acetylsalicylic acid. It has been clearly proven that acetylsalicylic acid 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 acetylsalicylic acid reduces incidence of SCD by 24% [88]. 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 also obtained with respect to pravastatin (LIPID). In IDEAL clinical study (2005), patients with stable CAD were treated with simvastatin (20 mg) or atorvastatin (80 mg), both medications have shown positive results in respect to cardiac arrest (intermediate endpoint). 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 [89]. Therefore, current guidelines on SCD prevention in patients with CAD include statins as a mandatory medication class **(I, A)** [4, 12, 90]. 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.

ω3-polyunsaturated fatty acids (PUFA). The first reports on the effectiveness of PUFA in SCD prevention were obtained in DART study that showed that individuals who consumed oily fish two times a week or more oftenly 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 ω3-PUFAs (main fatty acids of oily fish) have a protective effect against VF. The mechanisms of antiarrhythmic action of ω3-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 ω3-PUFA is that for the «arrhythmic» action potential to be induced higher electric amplitude in required during their use; the duration of cardiomyocytes effective refractory period in also increased, which decreases likelihood of fatal arrhythmias, including ventricular fibrillation [91].

In addition to the surrogate mild antiarrhythmic effect of these drugs, they 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 ω3-fatty acids increase LVEF parameters and improve HRV parameters, thus modifying major and minor risk factors of SCD [92].

Convincing evidence in support of ω3-PUFAs was obtained in two large clinical trials. GISSI-prevenzione study, use of Omacor, 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% [93]. 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 is associated with reduction of total mortality rate by 9% and reduction in hospitalizations for ventricular arrhythmias. The number of side effects in ω3-PUFA group did not differ from the one in control group [94].

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 [95].

Thus, to date, the preventive effect of ω3-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 ω3-fatty acids (Omacor) per day and arrange «fish days» (about 200 g of oily fish) at least twice a week [96, 97]. Data about the use of omega-3 fatty acids for secondary prevention of SCD in patients who survived cardiac 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 [98].

IC class antiarrhythmic agents. Use of antiarrhythmic agents 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 [99, 100]. However, there is a number of situations in which antiarrhythmic agents use can be justified.

First of all, they can be used in patients with implantable cardioverter-defibrillators (ICD) and frequent ICD interventions for 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 [101]. 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 [102]. However, most of the patients in these clinical trials were treated with combination of amiodarone and beta-blockers. Large, well-designed study SCD-HeFT that evaluated amiodarone effectiveness for SCD prevention in patients with CHF did not show benefit over placebo in patients with NYHA FC IV [103].

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

Currently, there are no data supporting class III agents use to improve survival in patients cardiac disease and ventricular arrhythmias. Their administration may be warranted in patients with VA in combination with beta-blockers (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 beta-blockers 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 [1, 4, 12, 104–106].

For the same purpose post-MI patients are administered with ACE inhibitors/ARBs, statins, aspirin, ω3-fatty acids [107–109]. In patients with non-ischemic heart failure, ACEI/ARBs, aldosterone antagonists, ω3-fatty acids are indicated [87].

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.

ICD

Modern implantable cardioverter-defibrillator (ICD) consists of a device that is enclosed in a small titanium box which is implanted subcutaneously or intramuscularly in the left subclavian area, and one or more electrodes installed in the heart chambers. To date, there are one-, two-and three-lead (biventricular) system are available. In most vehicles the device enclosed in a titanium box that is part of the discharge circuit of the defibrillator [110] (Figure VI.1).

The arrhythmias detection is based on the analysis of RR-intervals, forms of ventricular signal, RR-interval stability, ratios of atrial and ventricular activity (in dual chamber systems). The input signal is filtered resulting in elimination of low-frequency (due to T-wave) and high-frequency components (due to skeletal muscles activity) which are therefore not detected by ICD.

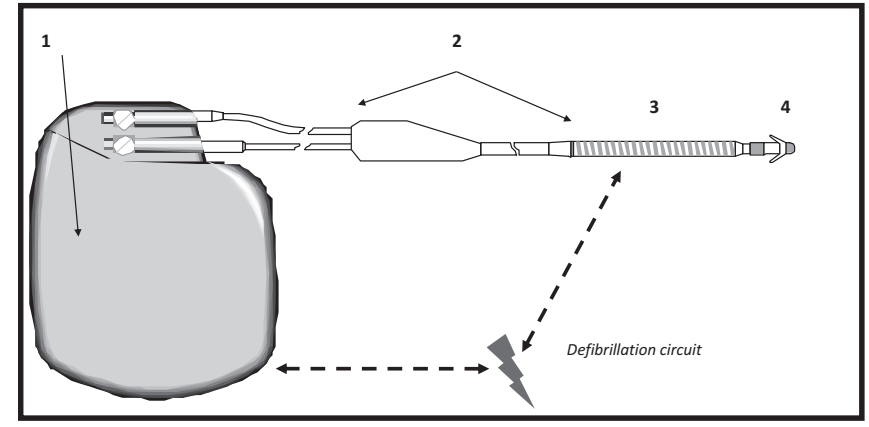

Figure VI.1 Modern ICD circuit. The device consists of a titanium body (1) and an intracardiac electrode (2). ICD discharge chain lies between the ICD body and the coil (3), located on the electrode. The distal tip of the electrode (4) detects arrhythmic events and performs antitachy- and antibrady-pacing

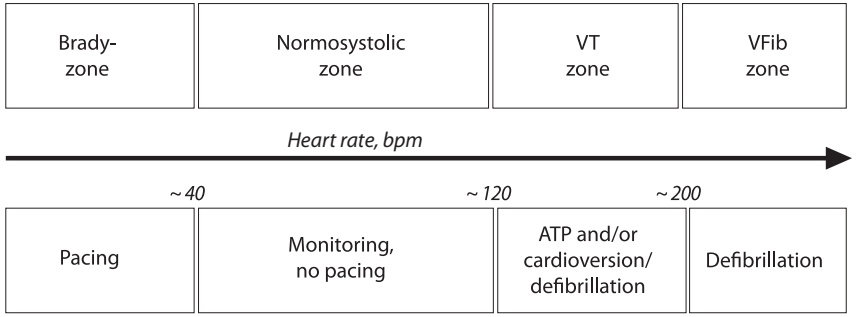

Figure VI.2. ICD detection zones. The diagram shows detection zones of modern ICDs that depend on ventricular contraction rate. In the so-called bradyasystolic zone (heart rate below 40 per minute), pacing is conducted in a set mode; in the normosystolic zone (heart rate 40–150 per minute), the device monitors cardiac activity without pacing; in ventricular tachycardia zone (heart rate of 150–200 per minute), the antitachycardia pacing (ATP) or cardioversion may be performed; cardiac defibrillation is applied in ventricular fibrillation zone (heart rate > 200 per minute)

Defibrillators have different heart rate detection zones. For example, if an arrhythmia rate falls into so-called ventricular fibrillation zone (where the ventricular rate is higher than 200 per minute), then defibrillator discharge occurs to treat ventricular fibrillation or high rate ventricular tachycardia (Figure VI.2). In the so-called VT zone various antitachycardia pacing modes can be applied to suppress the arrhythmia. As a result, hemodynamically nonsignificant, relatively slow VT recorded in the low-rate zone detection can be successfully terminated by antitachycardia pacing. VT can be terminated by ***BURST*** mode (stimulation with short bursts at a rate 10–30% above the rate of tachycardia), ***RAMP*** mode (stimulation with gradually increasing rate of impulses when each subsequent impulse shortens the stimulation cycle compared to the previous one) or ***RAMP+*** mode (stimulation with a single scanning impulse that is applied depending to the tachycardia cycle length with set coupling interval). When these are ineffective cardioversion is performed (Figure VI.3). In so-called normosystolic zone (heart rate is between 40–150 beats per minute), an ICD monitors the rhythm, and in bradyasystolic zone (heart rate below 40 beats per minute) the device performs previously programmed pacing.

Detection parameters and pacing algorhythms for every zone are set during initial device testing and set up. Depending on the clinical situation and medical therapy, these values may be adjusted accordingly. To prevent unnecessary discharges during supraventricular arrhythmias and sinus tachycardia, the RR interval stability (in case of tachysystolic atrial fibrillation) and ventricular complex morphology, registered by ventricular electrode, are analysed. There is a possibility to assess suddenness of tachyarrhythmia (when VT VF starts

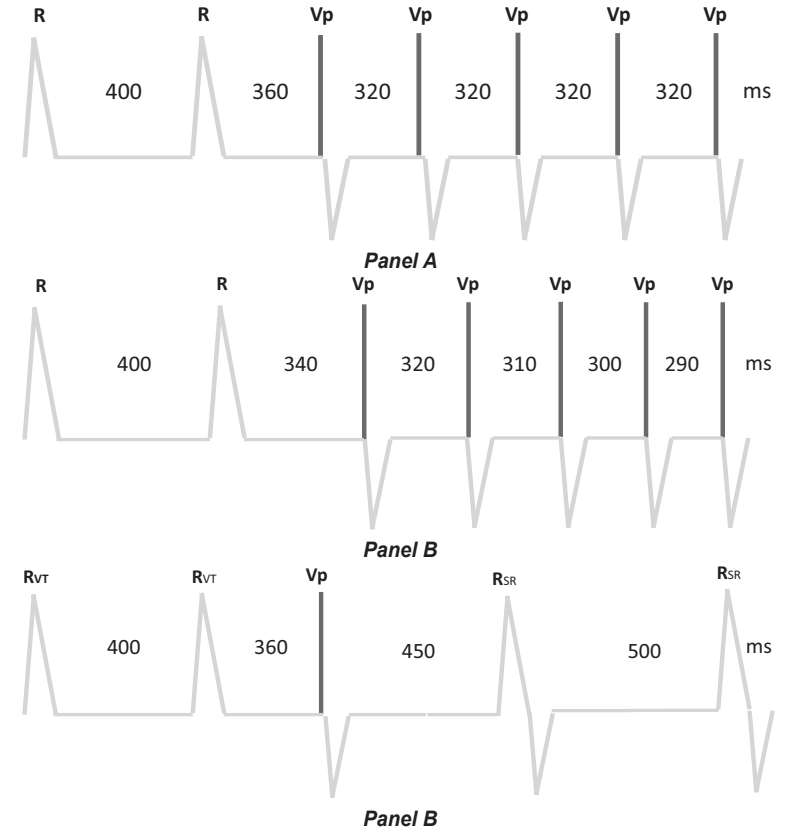

Figure VI.3. Modes of antitachycardia pacing. Panel A schematically presents Burst ATP Mode. VT cycle length (interval RR) is 400 ms. ATP is delivered with a fixed cycle length (range Vp–Vp) 320 ms, representing 80% of the VT cycle length. Panel B schematically represents Ramp ATP Mode. VT cycle length (interval RR) is 400 ms. The pacing rate is gradually increasing with every next impulse shortening the cycle by 10 ms compared to the previous one. Panel B schematically represented Ramp+ or Scanning ATP Mode. VT cycle length (interval RVT–RVT) is 400 ms. Pacing is performed with single scanning stimulus (Vp), which is applied depending on the tachycardia cycle length. In this example, the scanning stimulus interrupts VT

RR interval length suddenly decreases), and register impulses in the atria and ventricles. ICD treatment criteria are selected by a physician based on patient tachycardia signs and symptoms. For instance, first step of treatment in hemodynamically significant VF or fast VT is defibrillation with a shock of 10 J higher than intraoperative defibrillation threshold with subsequent automatic power increase in power to the maximum value of 40 J, and with a change in the circuit polarity from the ICD body to intracardiac electrode and vice versa [110].

ICD effectiveness in SCD prevention has been proven in several large clinical trials (Table VI.1) which were designed to assess survival in patients with major SCD risk factors (JT Bigger, 1984). [24] The results of these studies formed the basis for current American and European Guidelines for ICD use and Guidelines for management of patients with ventricular arrhythmias and the prevention of SCD. [4]

Thus, new approaches to the primary prevention of SCD require preventive defibrillation in a significant number of patients. From a practical point of view, this situation implies need of a single shock in one patient

Table VI.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 [25]	Comparison of antiarrhythmic agents and ICD in patients with history of cardiac arrest	1016	13 months	Total mortality reduction in ICD subgroup by 29%
CASH 2000 [27]	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 [26]	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 [31]	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 EPS	196	27 months	Total mortality reduction in ICD subgroup by 54%
GABG-Patch 1997 [111]	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

Table VI.1 (continuation)

Study, year of the results publication	Study objective	Number of subjects	Follow-up period	Results
MUSTT 1999 [33]	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 EPS	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 [32]	Comparison of ICD and standard CAD therapy in patients with history of acute myocardial infarction, ejection fraction of less than 30%	1232	20 months	Absolute risk of total mortality reduction in ICD subgroup by 56%
CAT 2002 [112]	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%
AMIOVIRT 2003 [113]	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 [114]	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 [115]	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

Table VI.1 (continuation)

Study, year of the results publication	Study objective	Number of subjects	Follow-up period	Results
COMPANION 2004 [116]	Comparison of ICD in combination with cardiac resynchronization therapy (CRT), isolated cardiac resynchronization therapy and standard CHF therapy	1520	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%)	2521	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.

over a relatively long period of time (e.g. a couple of years). In this regard, the clinical use of the new ICD-technologies, that were development with participation of domestic scientists, acquires considerable clinical significance [117–119].

RFA

Catheter 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 [120–122]. However, data on RFA effectiveness for SCD prevention are currently limited, largely due to the fact that the cohort of patients with ventricular tachycardia is heterogeneous and randomization of these patients is complicated.

Considering the above said, a meta-analysis of 5 studies evaluating effectiveness of RFA in patients with VT, published in 2012, is worth mentioning. The meta-analysis included data on 457 patients with structural heart disease (mostly *ischemic*) [67]. The study compared RFA and antiarrhythmic therapy effects on arrhythmias and mortality rate (without specifying its mechanism),

and estimated rate of complications during RFA of VA patients. The meta-analysis results have shown that RFA of VA patients significantly reduces the number of VT episodes and the number of ICD interventions. However, RFA was not associated with reduced mortality (including sudden death). Discussing the results, the authors note that many publications, included in this meta-analysis, were descriptive, and the proportion of randomized trials was limited [123].

Despite the fact that publications on RFA in patients with non-ischemic ventricular arrhythmias (including patients with ARVD, DCM, channelopathies) show positive impact of RFA on arrhythmic syndrome, currently it is difficult to determine the exact role of RFA in SCD prevention. The number of patients enrolled in these studies was relatively small, and duration of clinical follow up was limited.

Thus, RFA is currently the most effective method of treatment for patients with ventricular arrhythmias and lack of structural heart disease [4]. Improvement of hemodynamic parameters as a result of RFA therapy in patients with idiopathic PVCs can be considered as an important positive modifier of systolic dysfunction, a risk factor for SCD [124]. However, in the era of evidence-based medicine, data from randomized trials with long-term follow-up of these patients is required to confirm this hypothesis.

Surgical treatment of arrhythmias

Methods of direct surgical excision or resection of arrhythmogenic focus are still used in the leading surgical centers to treat recurrent VA that is refractory to multiple antiarrhythmic agents; patients with frequent ICD shocks; patients with failure of RFA. Surgical treatment necessitates careful preoperative preparation and precise intraoperative determination of one or few tachycardia sources. To eliminate arrhythmogenic sites, a number of centers uses an approach based on resection of scar fields in the myocardium. Since these procedures are rather traumatic, nowadays endocardial resection of postinfarction scar, circular endocardial ventriculotomy and endoventriculoplasty are usually combined with Coronary artery bypass surgery. Endocardial RF ablation or cryoablation of arrhythmia focuses can also be used intraoperatively.

Thus, in cases of recurrent ventricular tachycardia in patients with ICD, refractory to medical therapy and catheter RFA, surgical resection, direct RFA or cryoablation of the VT focus is possible.

In patients with congenital long QT syndrome (LQTS), left cervicothoracic sympathetic ganglionectomy is used as an adjunctive therapy in case of frequent ICD discharges or beta-blockers intolerance [126].

Myocardial revascularization in arrhythmia management

VA development is directly related to acute or chronic coronary artery disease. In this regard, surgical or interventional revascularization of hibernating myocardium can improve the electrical stability and reduce the risk of ventricular arrhythmias. Thus, CAD screening and treatment should be the first steps in risk stratification and prevention of SCD, since viable myocardium revascularization can modify such a major SCD risk factor as contractile left ventricular dysfunction [127]. In a number of post-MI patients life-threatening ventricular arrhythmias can be eliminated with myocardial revascularization, but only if a VA has ischemic etiology. Early revascularization with beta-blocker administration can also reduce VT/VF rate during acute period of myocardial infarction.

Nevertheless, despite the myocardial revascularization risk of SCD during one year reaches 13% [128]. It is worth emphasizing that, in patients with a large scar area recovery of LVEF is less likely and ICD implantation may be required soon after revascularization.

Literature review of relevant publications suggests that myocardial revascularization results in increased survival and reduced incidence of SCD during long-term follow up [129]. If coronary heart disease is complicated by VA, especially in patients with left main coronary artery lesions and proximal left anterior descending artery, then there is a high likelihood that myocardial revascularization would reduce the rate and decrease the severity of arrhythmias, and some patients would allow to completely eliminate them.

In our opinion, special attention must be given to revascularization in patients with CHF of ischemic etiology without significant anginal symptoms for primary and secondary prevention of SCD. For this category of patients very limited data on revascularization effects on SCD incidence and overall survival are available.

In this context, the diagnostic evaluation of patients with ischemic CHF should include an assessment of myocardial viability. A number of prospective and retrospective studies and meta-analyzes have demonstrated that revascularization in patients with ischemic but still viable myocardium significantly improves left ventricular contractile function and survival parameters [127]. In contrast, revascularization is ineffective in patients without viable myocardium, and thus it should be avoided in such patients. A standard method for assessing myocardial anatomy, its regional and general contractility, viability, and, more importantly, size of infarction including its depth (determined with late gadolinium enhancement) is MRI [130].

Table VI.2

Recommendations for patients with CHF and left ventricular systolic dysfunction (EF ≤ 35%), with predominance of anginal signs and symptoms

	Indication class	Evidence
PCI is possible with suitable anatomy and the presence of viable myocardium.	IIb	C

Table VI.3

Recommendations for patients with CHF and left ventricular systolic dysfunction (EF ≤ 35%), with predominance of signs and symptoms of CHF (angina I–II class or absent)

	Indication class	Evidence
PCI is possible with suitable anatomy and the presence of viable myocardium.	IIb	C
If lack of viable myocardium is confirmed, revascularization is not recommended.	III	B

The choice between the main direct revascularization methods (CABG or interventional angioplasty) should be based on a thorough assessment of the coronary lesions anatomy, the expected «completeness» of revascularization, the nature of comorbidities and the presence of severe concomitant valvular heart disease.

Nevertheless, successful revascularization in patients with coronary artery disease and systolic dysfunction does not waive need of relevant SCD preventive measures and ICD implantation [4, 12].

Tables VI.2 and VI.3 provide recommendations for CHF patients with left ventricular systolic dysfunction (EF ⩽ 35%) and predominance of signs and symptoms of angina or CHF.

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

VII.1. SCD risk stratification and prevention in patients with coronary artery disease

VII.1.A. SCD risk stratification and prevention in patients with previous myocardial infarction 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 presented in Table VII.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:
   - beta-blockers (A)
   - ACE inhibitors (A)
   - acetylsalicylic acid, (A)
   - statins (A)
   - PUFA (B)

Table VII.1.1

SCD risk stratification in patients with previous MI 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, EPS	see item 4
4. Are there 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 (C).

3. 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).

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

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

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 EPS), 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. Amiodarone in combination with beta-blockers in patients with symptomatic ventricular arrhythmias (a major risk factor for SCD) when beta-blockers alone are not effective (B).

2. Sotalol in patients with symptomatic ventricular arrhythmias (a major risk factor for SCD) when beta-blockers alone are not effective (C).

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

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

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

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 (A).

3. Amiodarone is not recommended in patients with hyperthyroidism (C).

VII.1.B. 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 [9–12, 19].

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 [131].

The emergence of various 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 [132–134].

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 VII.1.2.

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:
   - beta-blockers (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

Table VII.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 [131]

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).

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

Heart failure is a pathological condition in which the cardiac output does not meet the needs of the body due to reduced pumping function of the heart. In clinical practice, acute and chronic heart failure is distinguished. Heart failure is not a separate disease. Usually it is a complication or outcome of various diseases and pathologic states.

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

Table VII.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 EPS	see recommendations for SCD prevention

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 [135–138]. 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 [139].

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 VII.2.1. Consistent implementation of this algorithm will determine a 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 [83] includes mandatory administration

(in the absence of contraindications and side effects) of beta-blockers (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).

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

Class IIb

1. Amiodarone, sotalol and/or β-blockers 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, 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)

Table VII.2.2

ICD for primary SCD prevention in patients with CHF (adapted from Bradley, 2009)

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.

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

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 VII.2.2. presents indication classes for ICD placement for primary SCD prevention depending on CHF etiology, CHF FC, LVEF values and presence of VA.

VII.3. SCD risk stratification and prevention in patients with bradyasystolic arrhythmias

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 [6–8]. 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.

VII.3.A. SCD risk stratification and prevention in patients with sinus node dysfunction (SND)

Patients with sick sinus syndrome (SSS) accounts for about half of the total number of pacemaker implantation [140].

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 [141]. 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 [142].

Risk stratification

SND 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 CNS. 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. Unfortunately, to date, there are no generally accepted risk factors for SCD in patients with SSS. However, 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 (see Table V.2).

SCD prevention

Permanent atrial and/or dual-chamber pacing in accordance with the National guidelines for artificial cardiac pacing [70] in patients with SSS improves symptoms and quality of life, reduces incidence of atrial fibrillation and its episodes frequency. To date, long-term results on permanent pacing and its effects on survival and SCD incidence are unknown.

VII.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 [143, 144]. 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 V.2) which requires a permanent pacing. [110]

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 [110].

Two- and tree-fascicular blocks

The 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. [110] 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 [145]. 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 [146]. There

are conflicting data on the prognostic value of the long HV interval for the SCD risk. In particular, HV interval >75 ms is an insignificant prognostic factor, but HV interval >100 ms indicates very high risk and requires urgent permanent pacing initiation [147–149].

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 [150–152].

Congenital AV block

Several studies have shown that the pacemaker implantation may improve survival in patients with complete congenital AV block [153–155]. 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 * [156, 157]. In patients with congenital cardiac conduction system abnormalities, SCD risk factors include: heart rate less than 50 bpm, QT interval prolongation, structural heart disease. [5]

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 arrhythmias in these patients reaches 2–3%, especially in patients with severe CHF manifestations [5, 159]. 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 [160]. SCD prevention in these cases includes cardiac pacing with a relatively high rate and continuous ECG monitoring for first 24 hours after the procedure.

* – a long-short sequence

According to Zehender et al., 12–31% of patients die suddenly during the first year of follow-up after cardiac pacemaker implantation [161]. 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% [110, 202]. It is thought that device sensitivity loss or asynchronous stimulation promotes initiation of malignant ventricular arrhythmias [110].

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 [158].

Recommendations for SCD prevention

Permanent atrial and/or dual-chamber pacing in accordance with the National guidelines for artificial cardiac pacing [70] 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.

VII.4. SCD in patients with cardiomyopathies

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

DCM is noncoronary diffuse myocardial disease of unknown etiology, characterized by dilatation and systolic dysfunction of the left or both ventricles [162, 163]. The main manifestation of the disease is a syndrome of chronic heart failure; CHF is biventricular, progressive and in general has poor prognosis in 90% of patients.

The five-year survival rate among Caucasians with DCM is 31.4% [164]. 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 [165]. At the same time, SCD is responsible for 20% of deaths [166, 167].

SCD is rarely the first manifestation of the disease, other signs and symptoms of a progressing disease are more common [168, 169]. In most cases, SCD is caused by life-threatening VA [170].

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 addition, genetic testing seems justified in patients with dilated cardiomyopathy and their relatives.

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 [171]. Based on available data, genetic testing for LMNA gene mutation may play a role in SCD risk stratification in patients with DCM [172, 173]. However, in most cases, screening for genetic mutations has a low efficiency (less than 20% in isolated DCM without concomitant skeletal muscle abnormalities) [171]. 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. Optimal medical treatment of CHF according to current national guidelines for the treatment of CHF [87] includes mandatory administration (in the absence of contraindications and side effects) of beta-blockers (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 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 EPS (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).

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

Class IIb

1. Amiodarone, sotalol and/or β-blockers 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. 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).

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

Hypertrophic cardiomyopathy (HCM) is a disease characterized by 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

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

cause of hypertrophy and is not accompanied by the chambers dilatation [174]. Hypertrophic cardiomyopathy characterized by focal myocardial hypertrophy and changes in the spatial orientation of cardiomyocytes (chaotic positioning), which is essential for diagnosis [175].

Multiple gene defects, especially the DD angiotensin-converting enzyme gene polymorphism, mutations of Arg403Gln and Len908Val genes and mitochondrial genome play a leading role in the development of hereditary and sporadic forms of HCM, they cause qualitative abnormalities of myocardial contractile proteins structure (myosin heavy chain (chromosome 14) – 30–40% of cases; troponin T (chromosome 1) – 10–20% of cases; α-tropomyosin (chromosome 15) – 5% of cases, myosin binding protein C – 15% of cases; myosin light chain – 1% of cases) [174].

About 0.2% of the world population suffer from HCM with a significant proportion of the patients are of the working-age [174].

The very fact of the HCM diagnosis places the patients at high risk group for SCD. SCD may be caused by ventricular arrhythmias (as a result on myocardial ischemia), left ventricular outflow tract obstruction (LVOTO) and/or tachysystole during atrial fibrillation or flutter.

SCD risk stratification

The relatively low incidence of the disease makes it difficult to stratify the risk of SCD in these patients, as there is a high risk of false-positive results for any stratification factor that may prevail over the true positives. In one study, 23 of 480 patients died suddenly, although they were expected to live another 6.5 years according to their clinical condition. SCD risk was directly related to the wall thickness of the left ventricle. It was found that in over 20 years, there were very few fatalities among patients with hypertrophic cardiomyopathy with left ventricular wall thickness of 20 mm, whereas mortality rate in patients with left ventricular wall thickness of 30 mm or greater reached nearly 40% over the same time period. Several studies have determined the ration of interventricular septum thickness to the left ventricle posterior wall thickness of 1:1 as a major risk factor for SCD [174, 176, 177].

ACC and the ESC categorized known risk factors for SCD as «major» and «possible» (in these guidelines as *major* and *secondary*) for certain groups of patients with HCM (Table VII.4.1). The clinical evaluation of patients with HCM is recommended for SCD risk stratification every 12–24 months (**II A, C**) [174, 178–181].

The role of genetic testing in patients with HCM for SCD risk stratification of now remains unclear (indication class 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

Table VII.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

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**) [174, 182–185].

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**) [174, 179, 186].

Stress testing with blood pressure and ECG monitoring is desirable 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 [187–189].

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 [174, 190].

Recommendations for SCD prevention

Class I

1. ICD placement should be performed in patients with HCM 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 have a favorable prognosis of survival for a year or more (B).

2. Beta-blockers 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)**.

* – 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 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): cardiac 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 (C).

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).

Class IIb

1. 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).

2. 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).

3. 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 placement is not recommended for patients with HCM without major risk factors for SCD (C).

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

3. 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).

4. 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).

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

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

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

Arrhythmogenic right ventricle dysplasia/cardiomyopathy (ARVD) is mostly genetically determined abnormality of the heart muscle which is pathologically characterized by fibro-fatty infiltration of right ventricular myocardium and usually manifested by ventricular arrhythmia [191–193].

According to epidemiological studies of ARVD, the disease prevalence in general population ranges from 1:1000 to 1:5000, male to female ratio is 3:1 [194–197]. In the developed world, ARVD is one of the most common causes of sudden cardiac death (SCD) in persons younger than 35 years [196, 197]. Russian epidemiological data correspond to the international data: ARVD is the second leading cause of SCD in patients ⩽ 35 years (14.1%) (after alcoholic cardiomyopathy) with gender ratio of patients who died of 3:1, males to females, respectively [197]. Familial variants of ARVD constitute at least 50% of all cases with predominantly autosomal dominant inheritance (12 genes encoding different components of myocardial desmosomes are identified) and variable penetrance [4, 191, 359].

ARVD is diagnosed based on a set of «major» and «minor» diagnostic criteria according to the ARVD International Diagnostic Criteria, 1994, as modified in 2010 [191, 198].

Risk stratification

VA, ranging from single PVCs to sustained ventricular tachycardia and ventricular fibrillation leading to SCD are rather pathognomonic clinical manifestations of ARVD. VT, in turn, may be the first and the only clinical manifestation of the disease [191]. The most common signs/symptoms of ARVD are tachycardia and/or palpitations, syncope and SCD, which are observed at 27, 26 and 23% of patients, respectively [191–194]. VF is a cause of SCD in young patients with ARVD who were previously asymptomatic. In patients with a long history of ARVD, the likelihood of sustained monomorphic hemodynamically stable VT is higher [193]. Progression of the disease may be accompanied by manifestations of biventricular heart failure.

VA with the LBBB type of QRS complexes morphology is a distinctive feature of ARVD and points to the right ventricular origin of the arrhythmia. In patients with diffuse ARVD, several morphological classes of VA may occur [191–194].

SCD is the leading cause of death in these patients with 0.08–9.0% of patients dying suddenly in a year [191, 194, 199–201]. In patients with ARVD, SCD occurs relatively often during exercise, and prevalence of ARVD among athletes, who died suddenly, reaches 25% [191].

A retrospective clinical and pathologic analysis indicates that in addition to the major risk factors for SCD (history of cardiac arrest, syncope, episodes of sustained ventricular tachycardia) the following factors may have clinical significance in these patients: young age, positive family history, professional sport, contractile dysfunction of the right ventricle, left ventricle involvement, dispersion of the complex QRS duration > 40 ms, repolarization abnormalities in precordial ECG leads [199, 200]. However, the prognostic significance of these factors (individually and in combinations) is not clear. In 2011, data from a 10 years long follow up study of 96 ARVD patients have shown that the addition of the LV dysfunction to the preexisting RV dysfunction was the most unfavorable prognostic factor for the patients survival [191].

Genetic testing

Data on genetic typing of ARVD patients are currently very limited. It makes it impossible to draw conclusions about the role of genetic typing for the SCD risk stratification and choice of treatment strategies for patients with ARVD. The following are the criteria which justify genetic testing in ARVD patients when present [191].

Comprehensive genetic testing for genes that encode proteins of myocardial desmosomes (DSC2, DSG2, DSP, JUP, PKP2, TMEM43) is useful in patients diagnosed with ARVD according to The International Criteria, as modified in 2010.

Genetic testing ***may be recommended*** for patients with a high likelihood of ARVD according to the International Criteria, as modified in 2010, i.e. when 1 major or 2 minor ARVD criteria are present.

Genetic testing ***is not indicated*** in patients with only one minor ARVD criterion present, according to the International Criteria, as modified in 2010.

Focused mutation-specific genetic testing is ***indicated*** for family members and close relatives of a patient with confirmed genetically determined ARVD after the defective gene identification (index-case).

However, there is evidence that healthy carriers of the defective gene do not require specific preventive management. This group of individuals requires

regular screening for early diagnosis of asymptomatic VA, which includes thorough history, genealogical analysis, 12-lead ECG, Holter monitoring, analysis, ventricular late potentials, cardiac stress testing and transthoracic echocardiogram [191, 200].

Recommendations for SCD prevention

Class I

1. ICD placement is indicated for SCD prevention in patients with ARVD if the following criteria are men: confirmed sustained VT or VF episode (major risk factors), good functional status*, life expectancy of more than 1 year (B).

Class IIa

1. ICD implantation can be effective in preventing the SCD in patients with severe ARVD who have such risk factors as: left ventricle involvement, family history of SCD in one or more family members (or family members with episodes of syncope of unknown etiology, when VT or VF were not excluded as a cause of syncope), good functional status and life expectancy of more than 1 year (C).

2. Amiodarone or sotalol can be effective for sustained ventricular tachycardia or ventricular fibrillation (major risk factors) treatment in patients with ARVD when ICD placement is not possible or justified (C).

3. Radiofrequency catheter ablation is warranted as an additional method of management in ARVD patients who experience recurrent sustained VT episodes, despite ongoing treatment with antiarrhythmic agents (C).

Class IIb

1. EPS may be performed in patients with an confirmed ARVD for SCD risk stratification and to assess the effectiveness of antiarrhythmic therapy (C).

VII.5. SCD in patients with WPW syndrome

WPW syndrome is a combination of ECG phenomenon 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 VA node, atrial and ventricular myocardium [202–204].

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 [202, 203].

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

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% [202–205].

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 [202–204, 211, 212]. 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 magnitude 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 [204, 207, 208, 211–213].

Risk stratification

SCD risk stratification algorithm is presented in the Table VII.5.1. It is based on the identification of the major SCD risk factors in patients with WPW syndrome [204, 208, 210]. Consistent implementation of this algorithm will determine a list of activities required for primary/secondary prevention of SCD in each individual case.

Table VII.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
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
EPS and RFA of the accessory AV conduction pathway	see item 3
3. Is there a structural abnormality of the heart	
Yes	No
EPS and RFA of the accessory AV conduction pathway	see paragraph 4
4. Ventricular pre-excitation is asymptomatic	
See recommendations for SCD prevention	

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.

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 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, beta-blockers, verapamil and ATP are contraindicated for patients with WPW syndrome/phenomenon (C).

VII.6. SCD in patients with valvular heart disease

VII.6.A. SCD in patients with congenital heart defects

Risk stratification

Congenital heart defects (CHD) is a diverse range of anatomical and physiological defects with various clinical manifestations. The risk of arrhythmias before and after the surgical correction of the defect implies the possibility of SCD. It should be noted that more than 75% of infant and child deaths from CHD occur in the hospital, most of them during the surgery. The remaining deaths occur either outside the hospital or in intensive care units due to other congenital anomalies or sepsis. Progressive increase in SCD incidence and cardiovascular mortality is noted in patients operated for CHD at the age of 20 years or older.

Five types of CHD are associated with high long-term risk of SCD: tetralogy of Fallot, D-and L-transposition of the great arteries, aortic stenosis, and single functional ventricle. The highest SCD incidence among patients with CHD is in patients with tetralogy of Fallot. Invasive hemodynamic monitoring and EPS should be performed in patients after the surgery and with history of near SCD episodes. Positive EPS results, regardless of the clinical status of the patient, allow identification of patients at high long-term risk of SCD.

The most common congenital anomaly of the coronary arteries associated with high risk of SCD in young age is aberrant right coronary artery origin from the left aortic sinus. The possible mechanisms of SCD are either acute angulation of the coronary artery mouth and as a result its bending or compression of the left coronary artery, leading to acute myocardial ischemia and subsequent VT or VF. The diagnosis is made during coronary angiography and is an indication for surgical revascularization.

Amount of experimental data to recommend specific approach to these patients management is limited. Management of emergency conditions that developed in patients with CHD is addressed without any specifics.

Recommendations for SCD prevention

Class I

1. ICD placement is indicated in patients with congenital heart defects (CHD) with history of cardiac arrest (the main risk factor for SCD) if the cause of the disease is determined during the workup and other reversible causes are excluded. ICD placement is indicated in patients with good functional status* who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (B).

2. Invasive study of intracardiac hemodynamics parameters and EPS are indicated in patients with CHD and spontaneous sustained VT (a major risk factor for SCD). The recommended methods of treatment are catheter ablation or surgical treatment of VT. If these methods are not effective, ICD placement is recommended (C).

Class IIa

1. Invasive evaluation of intracardiac hemodynamic parameters and EPS are indicated in patients with CHD and major risk factors for SCD such as: history of unexplained syncope episodes, impaired ventricular contractile function.

2. When certain or potentially determinable cause of cardiac arrest (a major risk factor) is absent, ICD placement is indicated in patients with good functional status* who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (B).

Class IIb

1. EPS may be considered in patients with CHD and paired PVC or non-sustained ventricular tachycardia to determine the risk of sustained ventricular tachycardia (C).

Class III

1. Prophylactic use of antiarrhythmic agents is not indicated in patients with asymptomatic CHD and isolated PVCs (C).

VII.6.B. SCD in patients with acquired heart defects

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.

Recommendations for SCD prevention

Class I

1. 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 for SCD (C).

Class IIb

1. 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 (C).

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

VII.7. SCD in patients with metabolic and inflammatory diseases

VII.7.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 [214].

A viral infection is the most common etiologic factor causing myocarditis, it is responsible for more than 60% of cases [215]. In the European population, the most common viral genomes identified on myocardial biopsy are parvovirus B – 19 and human herpes virus – 6 [216]. Among bacterial pathogens, intracellular pathogens (genus Chlamidia) have gained the greatest importance in recent years [218]. 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) [214, 217, 219].

The incidence of myocarditis in different European countries varies significantly and ranges from 0.12% to 12% [215, 216]. 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 [218].

Autopsy of individuals who died suddenly shows morphological signs of myocarditis in 8.6% of cases [219], and in 40–12% of individuals younger than 40 year [220]. According to some reports, myocarditis is the leading cause of sudden death in children. [8]

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 [221]. 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 [222, 223], about 5% of cases of myocarditis manifested with ventricular tachycardia.

However, the prognostic value of various arrhythmias, as well as other clinical and instrumental data (e.g. low EF) at the early stage of myocarditis has not yet been established. In many cases, adequate therapy leads to complete resolution of these symptoms [218].

Therefore, recommendations for SCD prevention in patients with myocarditis are very limited and mainly are related to the acute stage of the disease. Amiodarone is effective for ventricular tachyarrhythmias management [224]. A temporary pacemaker placement in the acute state of myocarditis is indicated for patients with hemodynamically significant bradyarrhythmias, when ICD implantation is not considered. However, at a later stage, if hemodynamically significant ventricular arrhythmias persist despite adequate antiarrhythmic therapy and the patient prognosis is favorable for at least a calendar year, the ICD implantation may be recommended.

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 [225].

The major pathogens causing IE in the past decade are staphylococci, streptococci and enterococci, which are identified in the vast majority of patients with positive blood cultures [226, 227]. 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 [228].

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 [229, 230].

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 [231–233]. 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 [234]. 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 [234]. In this regard, AV block in a patient with IE should always raise a concern about presence of such severe complications as abscess.

Treatment of IE patients with should prolonged, integrated and multicomponent. In all cases, antibiotic treatment should be administered taking into account the etiological factor, in most cases a combination of antibacterial

agents is required [231–234]. The other major directions of treatment in addition to antibiotic therapy are surgical treatment and immune replacement therapy.

Recommendations for SCD prevention

Class I

1. Ethiologic, pathogenetic and symptomatic therapy during the acute phase of myocarditis should be performed (C).

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

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

Class IIa

1. ICD placement may be effective in patients with life-threatening VA (a major risk factor) after the acute phase of myocarditis, who receive optimal medical treatment and have a favorable prognosis of survival for a year or more (B).

2. Antiarrhythmic agents may be used in patients with sustained and non-sustained ventricular tachycardia in the acute phase of myocarditis (C).

Class III

1. ICD placement during the acute phase of myocarditis is not indicated (C).

VII.7.B. SCD risk stratification and prevention in patients with metabolic syndrome, obesity, dieting and anorexia

Metabolic syndrome is a set of interrelated risk factors of cardiovascular diseases as a result of atherosclerosis [235–238]. Its major components are abdominal obesity, high blood pressure, atherogenic dyslipidemia (elevated plasma triglycerides and decreased plasma HDL cholesterol), insulin resistance (impaired glucose tolerance, fasting hyperglycemia and type 2 diabetes mellitus). The metabolic syndrome is characterized by prothrombotic and proinflammatory changes of hemostasis system as well as numerous metabolic and endocrine abnormalities [236, 2373, 239]. Metabolic syndrome diagnostic criteria continue to be discussed and clarified. For instance, experts of Russian Scientific Society insist on the leading role of abdominal obesity (excessive accumulation of visceral fat) in the pathogenesis of the metabolic syndrome and emphasize its importance over the other diagnostic criteria [240]. The waist circumference criterion has also been revised to account for patient's ethnicity and country of residence [237]. A number of changes in patients with metabolic syndrome that may increase risk of SCD have been reported: increase in duration and dispersion of QT interval [241–245], changes in heart rate variability,

indicating the predominance of sympathetic effects on sinus rhythm and/or reduction of vagal activity [245–255], left ventricular hypertrophy [256–258]. In addition, when metabolic disorders are severe, emergence of new SCD risk factors may not be ruled out: hypokalemia [259], hypoglycemia that facilitate sympathetic nervous system activation and repolarization deviations with QT prolongation [260, 261] as well as obstructive sleep apnea with coexists with many components of the metabolic syndrome, including sympathetic activity predominance [262–265].

Severe eating disorders and excessive measures on their rapid correction may contribute to SCD. The risk of SCD is particularly high in patients with severe obesity with this parameter 40–60 times that in general population stratified by age [266, 267]. 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 [268]. Factors that increase SCD risk in obese individuals are: increased duration and dispersion of QT interval, characteristic structural changes of the heart (cardiomegaly, dilatation of the left ventricle, myocardial hypertrophy with no signs of interstitial fibrosis) and obstructive sleep apnea [270–274]. 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 [275–277]. Low-calorie diet that promotes weight loss should be well-balanced. There are reports on arrhythmias and SCD in patients following long-term, not balanced, very low calorie diets (especially liquid protein diets) [278–282].

Mortality in *anorexia nervosa* patients ranges from 5 to 20%, and the actual figure is likely to be about 6% [283]. 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 [284–286]. 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 [287–290].

SCD risk stratification

Every major component of metabolic syndrome (obesity, hypertension, impaired lipid metabolism, diabetes mellitus) can be a risk factor for SCD if severe enough [291, 292]. At present, it is unclear whether the combining of

these predisposing factors into the metabolic syndrome adds information on SCD risk stratification [292].

Recommendations for SCD prevention

Class I

1. There are no specifics on prevention and treatment of life-threatening VA (a major risk factor) and SCD in patients with metabolic syndrome, obesity, anorexia or dieting. 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 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).

Class IIa

1. Weight loss program for obese patients (secondary SCD risk factor modification) and carefully controlled feeding resumption in anorexia patients can effectively 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).

VII.7.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 may 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 are accompanied by the development of conditions that predispose to structural heart disease that, in turn, may increase risk of SCD (e.g., dyslipidemia increases risk of coronary artery disease; secondary hypertension of endocrine etiology may lead to left ventricular hypertrophy).

Diabetes Mellitus

It is known patients with prior of MI, the diagnosis of diabetes increases risk of SCD [293–295]. Possible mechanisms causing SCD in these patients

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

are autonomic neuropathy that increases QT interval duration as well as severe silent myocardial ischemia that increases risk of VT and VF.

Normalization of blood glucose and HbA1c levels reduces cardiovascular risk. However, there are no data that it leads to reduction in number of sudden deaths. In contrast, several studies have demonstrated that intensive glycemic control, especially in the presence of autonomic neuropathy, increases risk of SCD, which may be associated with an increased risk of hypoglycemia, accompanied by QT interval lengthening and hypokalemia.

Acromegaly

The main cause of death in patients with acromegaly is cardiovascular system damage [296]. Long-term and active acromegaly (with continuous hypersecretion of growth hormone) causes so-called acromegalic cardiomyopathy that is characterized by concentric hypertrophy, diastolic, and later left ventricular systolic dysfunction with severe heart failure that is refractory to medical therapy, chronic hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). It is also accompanied by the development of insulin resistance, type 2 diabetes mellitus, dyslipidemia, and contributes to the emergence of hypertension and left ventricular hypertrophy. In patients with acromegalic cardiomyopathy, various arrhythmias are more frequent than in general population [297]. Risk of ventricular arrhythmias correlates with duration of the disease, the arrhythmias hemodynamic significance depends more on severity of LVH than on biochemical parameters of the disease activity. According to some data, about 75% of patients with acromegaly suffer from sleep apnea/hypopnea [298], which is often accompanied by life-threatening arrhythmias. Late ventricular potentials are registered in 56% of patients with active acromegaly, their present does not depend on patient age, sex, duration of illness or severity of left ventricular hypertrophy [299, 300]. However, the exact prognostic significance of the late ventricular potentials for SCD risk in patients with acromegaly remains unknown. Normalization (or decrease) of GH and IGF-1 reduces PVCs frequency.

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).

VII.7.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 [301–302]. 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. [302, 303].

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 beta-blockers 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).

VII.8. SCD in patients with pericardial disease

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).

VII.9. 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 [304–306]. 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 [307].

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 [308]. 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 [309]. 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 [310].

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

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

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 400 000 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

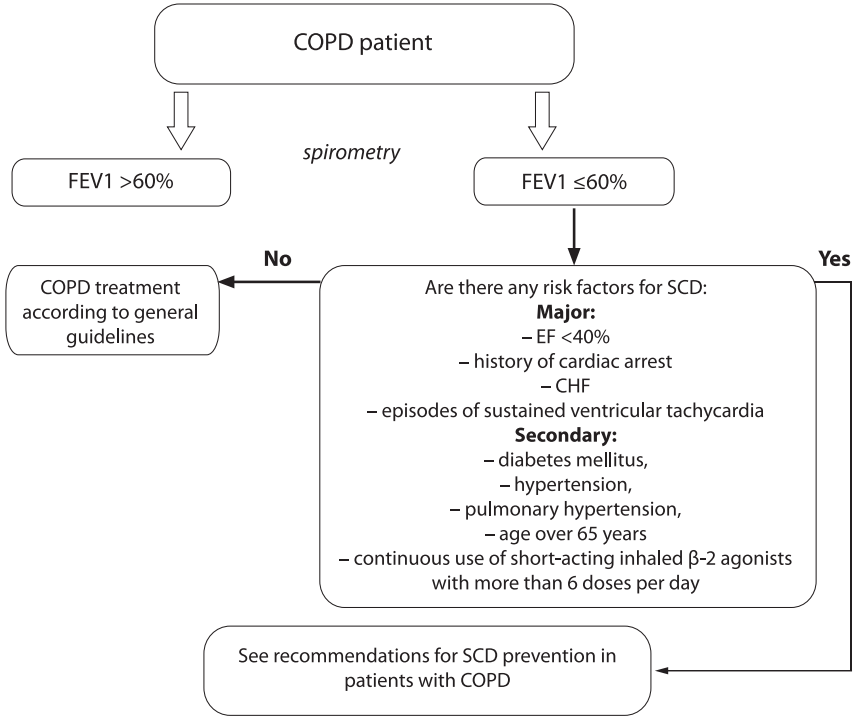

Fig. VII.9.1. SCD risk stratification in patients with COPD. FEV1 – forced expiratory volume in 1 second

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 FEV1 ⩽60% and cardiovascular diseases. In such patients, changes of the management plan to introduce SCD prevention measures are indicated as follows (Figure VII.9.1).

Recommendations for SCD prevention

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 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-blockers 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 β-2 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).

VII.10. 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 [314–320]. 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 [321–330]. 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 EPS.

Recommendations for SCD prevention

Class I

1. SCD risk stratification in patients with neuromuscular diseases is based on the detection of major and secondary SCD risk factors. Principles of SCD prevention do not differ from those in patients without neuromuscular diseases (A).

Class IIb

1. Pacemaker implantation may be considered in patients with hereditary progressive neuromuscular diseases (e.g., myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb myodystrophy, Emery–Dreifuss muscular dystrophy etc.) with such SCD risk factor as AV block (including I degree AV block), which is a major risk factor in this group of patients, even without clinical signs. This is due to the fact that in these patients acute progression of AV conduction abnormalities is possible (B).

VII.11. 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 abnormal 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.

VII.11.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. The latter 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 [331, 332]. 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 [332–334]. 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 [335]. 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 [336, 337] and ethacyzin [338].

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 [339, 340]. 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 [341].

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 LQT1–LQT8.
6 High genetic heterogeneity: 13 genes, more than 760 mutations.
7 The inheritance type is autosomal dominant, LQT1 and LQT5 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 [342–344].

Risk stratification

Based on knowledge of genotype, sex, and QT interval length risks of syncope, ventricular arrhythmias and SCD are stratified (Table VII.11.1). [345, 346]. The following stress test results are additional risk factors for life-

Table VII.11.1

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

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 [347]. 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 [348]. Patients with JLNS, Timothy syndrome and other homozygous syndromes are at the highest risk of SCD during childhood. 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 [349]. The risk of death in asymptomatic carriers of LQT1 mutations is the highest at a young age [350].

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 [345, 351–354].

It is recommended for patients with LQT1 and LQT5 syndrome to limit excessive physical activities, especially competitive sports [355], 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 [356]*. 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 [342, 357–359].

Timely administration of medical therapy (mostly β-blockers) effectively prevents syncope in more than 87% of patients. However, β-blockers are less effective in patients with LQT2 genotype and completely ineffective (and even contraindicated) in patients with LQT3 genotype [360].

ICD placement is the method of choice for such patients with history cardiac arrest episodes and ineffectiveness of conservative therapy [342, 360].

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

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 [361].

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

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).

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-blockers (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 beta-blockers (B).

Class III

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

VII.11.B. Short QT syndrome

Short QT syndrome (SQTS) is a genetically determined disorder characterized by shortening of both absolute (QT ⩽ 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 VII.11.2.

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,

Table VII.11.2

SQTS diagnostic criteria

Diagnostic criteria	Score
QT_c, 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 unlikely	1–2

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. Quinidine may normalize the length of QT interval [363]. The only method of SCD prevention in these patients is ICD placement [364]. 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 EPS) (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).

VII.11.C. Brugada syndrome

Brugada syndrome (BrS) 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 pattern:

– 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 [365]. 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. 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 [367].

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 EPS. However, EPS can not be considered a gold standard for SCD risk stratification since it has little diagnostic value [368].

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 [369].

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.
7. 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 pattern, 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 (C).

Class III

1. Genetic testing is not indicated for asymptomatic patients with 2 or 3 type Brugada-like ECG pattern.

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. 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.

VII.11.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 [370].

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 pattern:

– 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 [371, 372]. Beta blockers 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 [373]. It is possible that mutations in *RYR2* gene cause the so-called sudden infant death syndrome [342]. 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*** (C).

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. Beta blockers 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 (B).

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-blockers (C).

VII.11.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 [374]. 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 [374, 375]. 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 [378]. Similar data were obtained in a retrospective analysis of a German part of the MONICA project [379]. 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 [380].

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)

VII.12. SCD in patients with sleep apnea

Sleep apnea is defined as cessation of airflow through nose and mouth for 10 seconds or more [381].

Depending on the mechanism, there are two main types of apnea: obstructive and central. Currently, it is known that about 90% of all episodes of sleep apnea is associated with upper airway obstruction (UAO).

Recently, another term, *hypopnea*, has been introduced into clinical practice. It was first described by Block et al. as episodes of shallow breathing accompanied by desaturation [382].

RERA that stands for «respiratory effort-related arousal» is a term used in English language publications for more accurate accountability of abnormal respiration episodes, we can translate it as «EEG activation [383] as a result of respiratory effort». Thus, RERA implies an episode of respiratory disorders

accompanied by EEG activation or micro-awakening of the brain, usually as a result of increased upper airway resistance. At the same time, changes in the respiration recording channels (oronasal airflow, thoracoabdominal movements) should not meet apnea or hypopnea criteria [384].

Thus, the term «obstructive sleep apnea/sleep hypopnea» is currently used instead of «obstructive sleep apnea». The former name better reflect the syndrome's pathophysiological entity.

Currently, the standard for severity evaluation of respiratory abnormalities during sleep is apnea–hypopnea index (AHI) that implies quantitative assessment of apneas, hypopneas, and RERA during one hour of sleep. Obstructive sleep apnea hypopnea syndrome (OSAHS) is a sleep disorder characterized by AHI$\geqslant$5 accompanied by clinical signs.

According to the International Classification of Sleep Disorders, obstructive signs of apnea syndrome or OSAHS are present in at least 1–2% of the total population. In the age group of 30–60 years, 4% of men and 2% of women have AHI$\geqslant$5 accompanied by clinical signs of OSAHS.

Polysomnography allows objective assessment of not only sleep structure, but also for accurate quantitative and qualitative evaluation of respiratory disturbances during sleep. Polysomnography can also detect episodes of sinus arrest or transient I–III degree AV block.

Currently, OSAHS is considered an independent predictor of hypertension [385].

Hypoxemia due to sleep apnea can lead to myocardial ischemia [385] and ventricular arrhythmias [386]. Potentially fatal arrhythmias may be present in OSAHS patients during sleep [387, 388]. In a randomized study of 41 patients with OSAHS treated with CPAP, it was shown that in the subgroup of patients who were transitioned from therapeutic pressure level to subtherapeutic level in two weeks (i.e. sleep apnea symptoms were present again due to excessively low pressure), there was a significant prolongation of QTc interval and the TpTe(c) interval as well as dispersion of repolarization (TpTe/QT) [389].

OSAHS role in sudden cardiac death during sleep is significant. In contrast to the generally accepted fact that the peak of cardiovascular mortality in the general population falls on early morning hours (6.00 to 12.00), the highest incidence of sudden cardiovascular deaths in OSAHS patients is during the night (from 00.00 to 6.00) [390].

Sleep apnea leads to sinus arrest [390], AV blocks of varying degrees, up to the full AV block [391].

Currently, OSAHS treatment of choice is nCPAP (nasal continuous positive airway pressure), which is a method of creating of a continuous positive pressure

within airways. In Russian publications, English abbreviation «CPAP» became accepted in recent years.

One of the main benefits of CPAP therapy in hypertensive patients is decrease and sometimes complete normalization of blood pressure, often observed during the treatment [392–394]. Sinus pauses associated with episodes of apnea often disappear with CPAP therapy as well; other sleep apnea associated cardiac arrhythmias also became significantly reduced with the treatment [394]. 7 year long follow-up of OSAHS patients showed significant reduction of sudden cardiac death in CPAP therapy group compared with those patients who felt this therapy was unacceptable for them [395].

Risk stratification

Table VII.12.1

SCD risk stratification in patients with sleep apnea/hypopnea

1. OSAHS diagnosis verification	
yes	no
See item 2	SCD risk stratification and prevention based on general principles
2. AHI >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.

Recommendations for SCD prevention

Class I

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

Class IIa

1. CPAP therapy is indicated for patients with bradyasystolic arrhythmias associated with SOAGS. Pacemaker implantation in these patients should be considered if a bradyasystolic arrhythmia persists during adequate CPAP therapy (B).

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

VII.13. SCD in patients with ventricular arrhythmias and structurally normal heart

VII.13.A. SCD risk stratification and prevention in patients with idiopathic ventricular arrhythmias

To date, the term «structurally normal heart» is becoming more and more relative, since new methods of ultrastructural analysis of myocardium, specific immunological tests, biopsies, and others 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. In fact, mounting evidence showing that the causes of «minimal changes of myocardium» of right or left ventricle in patients with VA may be first manifestations of ARVD, an arrhythmogenic variant of latent myocarditis or some other more rare conditions [202, 396–400].

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 (FT) is the point of division of the back or medial (much less frontal) His bundle branches. Other places of origin of arrhythmias are much less common [202, 401]. The arrhythmic syndrome manifests clinically at the age less that 35 years, in the case of FT – before 25 years [401].

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. 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 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 a 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 [202, 401].

Idiopathic RVOT arrhythmias

To date, most of the RVOT arrhythmias after a detailed clinical analysis classified as manifestations of ARVD or latent arrhythmogenic variant of focal myocarditis [202, 396–400]. Thus, today, the view that the most common

origin of idiopathic VA is RVOT may be revised. The cause is 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) [202, 396–400].

Clinically the arrhythmia is benign with rare hemodynamically significant VT paroxysms. Severity of ectopic activity can vary from single PVCs per day to non-sustained ventricular tachycardia. There is no significant difference in the ectopic activity severity depending on patient gender. Arrhythmia manifestation usually occurs before the age of 35 years [401].

Fascicular left ventricular tachycardia

The condition more often occurs in males, the disease usually manifests at the age younger than 25 years.

The 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 [4].

Risk stratification

Tables VII.13.1–VII.13.5 contain algorithm for SCD risk stratification in patients with VA and structurally normal heart.

[5, 9, 19]

Table VII.13.1

Clinical data

1. History of SCD episode	
Yes	No
Consider ICD placement	see item 2
2. VT with dizziness, syncope	
Yes	No
Consider EPS, RFA	see item 3
3. Shortness of breath during exercise due to VA	
Yes	No
Consider antiarrhythmic agents, EPS and RFA	see item 4

Table VII.13.1 (continuation)

4. Ventricular tachycardia induction or increase in PVCs rate during physical exercise or recovery period	
Yes	No
Antiarrhythmic agents: β-blockers/sotalol, consider EPS, RFA	see item 5
5. Effectiveness of the ongoing antiarrhythmic therapy	
Yes	No
Monitoring by a cardiologist	see the recommendations

Table VII.13.2

Medical history (including family history)

1. History of syncope of unknown cause	
Yes	No
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 and/or arrhythmogenic effects of antiarrhythmic agents	
Yes	No
Adjunct treatment with antiarrhythmic agents, discuss EPS. Genetic counseling	see the recommendations

Table VII.13.3

ECG and Holter monitoring data

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

Table VII.13.3 (continuation)

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
Review 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 (arrhythmia of Lown class IIb and above)	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	Monitoring by a cardiologist

Table VII.13.4

Additional diagnostic methods data

1. MRI: areas of fibrosis/thinning in the ventricular myocardium	
Yes	No
Differential diagnosis between ARVD onset and latent myocarditis	see item 2

Table VII.13.3 (continuation)

2. MRI: intramyocardial areas of fat inclusions	
Yes	No
Genetic study to exclude/verification ARVD	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	Monitoring by a cardiologist

Table VII.13.5

EPS data

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, VA of a structurally normal heart can be largely due to not yet known genetically determined disorders that may phenotypically manifest with so-called «non-specific» transient ECG changes. In patients with idiopathic VA it is importance to be alert about the early stages of ARVD

and arrhythmogenic variant of latent myocarditis; it can be very difficult to differentiate between these two diagnoses without genetic testing.

Recommendations for SCD prevention

Class I

1. RFA is indicated in patients without structural heart disease with paroxysmal or continuous recurrent ventricular tachycardia originating from RVOT/LVOT (a major risk factor for SCD) with intolerance, ineffectiveness or refusal of antiarrhythmic agents (B).

2. RFA is indicated in all patients with fascicular left ventricular tachycardia (FT) (A).

3. Preventive antiarrhythmic therapy is indicated in patients with structurally normal heart and arrhythmia Lown class above IIb (a major risk factor for SCD) (C).

4. If the «minimal change» in RV/LV that fit arrhythmogenic variant of latent myocarditis criteria are identified as a cause of VA (a main risk factor for SCD), 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 (a main risk factor for SCD), genetic testing to rule out ARVD manifestation is indicated.

6. ICD placement is indicated in patients with VA without structural heart disease who have survived an SCD episode (a major risk factor for SCD) without reversible causes. (B).

7. ICD placement is indicated in patients without structural heart disease with sustained VA (a major risk factor for SCD) that requires medical or shock cardioversion when preventive use of antiarrhythmic agents is ineffective and RFA has failed.

Class IIa

1. RFA is indicated in patients without structural heart disease with sustained or continuous recurrent ventricular tachycardia (a major risk factor for SCD). RFA in these cases is considered as an alternative for antiarrhythmic agents if patient prefers the intervention treatment (C).

2. Preventive use of antiarrhythmic agents (β-blockers or sotalol) is indicated for patients without structural heart disease and with antiarrhythmia of Lown class above IIb (a major risk factor for SCD) 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 antiarrhythmia of Lown class above IIb (a major risk factor for SCD) that is provoked by sinus bradycardia and suppressed by physical exercise and registered on Holter monitoring mainly during the night (C).

4. EPS 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 (a major risk factor for SCD) (B).

Class IIb

1. RFA is indicated in patients without structural heart disease with sustained monomorphic VA originated from RVOT/LVOT that is above Lown class IIb (a major risk factor for SCD). RFA in these cases is considered as an alternative for antiarrhythmic agents if patient prefers the intervention treatment (C).

2. Adjunctive therapy with Omacor is recommended in patients with VA (a major risk factor for SCD) without structural heart disease (C).

Class III

1. Preventive use of antiarrhythmic agents is indicated for patients without structural heart disease and with antiarrhythmia of Lown class below IIa (C).

2. Preventive use of antiarrhythmic agents is indicated for patients without structural heart disease and with VA manifestation (history of arrhythmia is no longer than 2 months) (C).

3. RFA is not indicated in patients without structural heart disease with sustained monomorphic VA originated from RVOT/LVOT that is below Lown class IIb (C).

4. RFA is not indicated for patients without structural heart disease and with VA manifestation (history of arrhythmia is no longer than 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 until the pathogenetic and etiologic treatment of the underlying disease is completed.

VII.13.B. 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. Postperfusion 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:

Hypokalemia. The use of diuretics, a complication of cardiopulmonary bypass, hemodilution, hyperinsulinemia, respiratory or metabolic alkalosis, activation of renin-angiotensin-aldosterone system, and others.

Complications: atrial and ventricular arrhythmias.

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 and others.

Complications: heart blocks, cardiac arrest in systole.

Hypomagnesemia. Use of large doses of diuretics, transfusion of citrated blood, cardiopulmonary bypass, cardiac toxicity of adrenaline and others.

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.

Hypermagnesemia. Acute renal failure with anuria, excessive magnesium supplements administration.

Complications: atrioventricular conduction abnormalities with magnesium plasma concentration of 2.5–3.0 mmol x L^{-1}. The concentration of 3.5–4.0 mmol x L^{-1} causes deep depression of the central nervous system, the so-called «magnesium anesthesia».

Hyperkalemia. Thiazide diuretics, cancer, lithium, pheochromocytoma, endocrine pathology.

Complications: ventricular arrhythmias, conduction disorders.

Hypocalcemia. Chronic uncompensated alkalosis due to various intoxications, endocrine pathology, hypoalbuminemia, hypomagnesemia, and others.

Complications: QT prolongation, torsades de pointes

Recommendations for SCD prevention

Class I

1. Administration of potassium and magnesium supplements is justified for treatment and prevention of VA in patients treated with thiazide diuretics (B).

2. Administration of potassium and magnesium supplements is justified for treatment and prevention of VA in patients after cardiopulmonary bypass surgeries (e.g. CABG) (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 VA in patients with cardiac glycosides overdose (B).

Class IIb

1. Administration of potassium and magnesium supplements is justified for treatment and prevention of VA 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 indicated in patients with acute and chronic renal failure (B).

VII.14. SCD correlation with physical factors and toxins

VII.14.A. Smoking and SCD

Smoking is responsible for 30% of all deaths related to coronary artery disease, but regarding the SCD prevention, it is an independent risk factor (it does not depend on CAD presence) [46, 59, 402].Activation of the sympathetic nervous system by nicotine may reduce heart rate variability and increase the likelihood of VA and SCD [403–407].Smoking cessation reduces the risk of SCD.

Recommendations for SCD risk stratification and prevention

Class I

1. It is strongly recommended to avoid smoking (passive smoking) for all patients with major (verified VA and/or a prevented SCD episode) and secondary risk factors for SCD (B).

2. Smoking status should be determined in all patients with such major SCD risk factor as VA, it should be reflected in medical records, and programs on smoking cessation should be recommended for the patients (C).

VII.14.B. Lipids and SCD

Statins reduce risk of VA/SCD in patients with coronary artery disease and ischemic cardiomyopathy, probably due to antiischemic and not antiarrhythmic effect. In patients with non-ischemic cardiopathy, statins do not reduce risk of VA/SCD [408].

Despite the fact that in CAD patients there is a correlation between increased risk of VT/SCD and high levels of total cholesterol, VLDL, LDL, low levels of HDL combined with high levels of triglycerides and apolipoprotein B, the effectiveness of statin therapy in reducing the risk of VA/SCD does not depend on the lipid changes [409]. Studies on effects of lipid lowering on SCD incidence (SCD primary prevention) have not been conducted. However, such effects can be predicted based on the fact that the reduction in lipid levels is

accompanied by a decrease in relative risk of death from coronary heart disease and other causes by 20–40% [49, 410, 411].

Low levels of polyunsaturated fatty acids and low omega-3 index are independent risk factors for death from CAD, especially in patients with history of cardiac arrest [412, 413]. Several studies, primarily experimental models, have shown that fatty acids can reduce the incidence of SCD due to VA prevention [412–415]. Adding of PUFAs to standard therapy may reduce likelihood of SCD in patients with coronary artery disease [95, 416]. However, to date, discrepancies remain between the experimental and clinical data with respect to VA risk reduction as well as PUFAs use for SCD prevention [417].

Recommendations for SCD risk stratification and prevention

Class I

1. Statin therapy effectively reduces risk of VA/SCD in patients with coronary artery disease (A).

Class IIb

1. PUFAs are indicated in patients with coronary artery disease and VA, as an adjunct to standard therapy (B).

VII.15. SCD risk stratification and prevention in specific population groups

VII.15.A. SCD risk stratification and prevention in athletes

According to Italian researchers [418, 419], 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 [420]. 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 [421]. 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 [418, 419]. There is a clear correlation between SCD and gender – over 90% of athletes who died suddenly are males [418, 422].

According to some studies, the most common cause of SCD in young athletes is hypertrophic cardiomyopathy, a portion of which can reach 28–36% of all cases [18, 421, 424]. Among other causes of SCD, various anomalies of coronary vessels (14–17%) (with left coronary artery emergence from right

sinus of Valsalva being the most common), myocarditis (about 5%), ARVD (about 5%) are noted.

However, doubts are expressed about the legitimacy of the HCM diagnosis in all cases when marked left ventricular hypertrophy is detected at autopsy [418, 425, 426]. 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 [424]. It is obvious that the presence of LVH in an athlete is a risk factor of SCD.

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 [418]. 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 [427, 428].

In 2011, Russia has published first National Guidelines for admission of athletes with cardiovascular system abnormalities to the training and competition process [355]. 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 surface 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 [355].

Recommendations for SCD risk stratification and prevention

Class I

1. The clinical evaluation of athletes should include detailed history (including family history of premature death or SCD), physical examination and 12-lead ECG (C).

2. If cardiovascular diseases are diagnosed, it should be decided on whether to recommend professional sports activities as well as nature and degree of possible physical activity (C).

Class IIa

1. If positive family history, symptoms or signs (including ECG abnormalities) not related to the sport are identified it is recommended to conduct an in-depth medical examination, including echocardiography and other specific tests if required.

VII.15.B. Risk stratification and prevention in relatives of patients who died of SCD

Recommendations for SCD risk stratification and prevention

Class I

1. Genetic testing is recommended for all patients with a family history of SCD (LQT, SQT, CPVT, Brugada syndromes, etc.) (B).

2. Careful specialized examination (ECG, echocardiography, laboratory tests, etc.) is recommended for all patients with a family history of SCD (C).

Assessment of possible risk factors is recommended for all patients with a family history of sudden death in order to identify individuals at high risk of SCD [429]. However, for each disease (hypertrophic cardiomyopathy, long QT syndrome, Brugada syndrome and others) there are separate target risk stratification factors [429–432]. Genetic testing is justified in patients with a family history of SCD [432].

VII.15.C. SCD risk stratification and prevention in elderly

SCD incidence increases with age [429, 430]. VA is a frequent sign in older people, especially in those with a structural heart disease [433–435]. VA may be the harbingers of CAD destabilization and SCD [436, 438].

SCD prevention in elderly patients with VA is not fundamentally different from that described above. Beta blockers, if not contraindicated, are recommended for VA management in the elderly, especially in patients with coronary artery disease. However, despite the proven efficacy in reduction of all-cause mortality and SCD, the isolated beta blockers use may not be sufficient in elderly patients. In life-threatening VA, a combination of beta blockers with amiodarone or amiodarone monotherapy, in case of beta blockers intolerance, is preferred [29, 437].

Several randomized prospective studies have demonstrated the efficacy of ICD for primary and secondary prevention of SCD in patients with coronary artery disease, compared with antiarrhythmic agents in all age groups [25–27, 31–34]. All these studies enrolled a significant number of patients over the age of 65 years. Several experimental studies show that invasive treatment methods of patients with life-threatening VA are equally effective in the elderly and in young patients [439–441]. Elderly patients with multiple comorbidities and

limited life expectancy may not be suitable candidates for ICD placement, even if they meet the criteria for the procedure.

Recommendations for SCD risk 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).

2. Dosage and choice of antiarrhythmic agents should be adjusted to reflect changes of pharmacokinetics in elderly patients (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).

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

VIII. 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.