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Ventricular arrhythmias and prevention of sudden cardiac death

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Abstract
This review article presents updated European guidelines for the management of patients with ventricular arrhythmias (VA) and prevention of sudden cardiac death (SCD). New understanding of SCD epidemiology, modern concepts on genetics, imaging and a large volume of clinical data for stratification of VA and SCD risk, as well as advances in diagnostic assessment and therapeutic strategies contributed to the revision of the previous recommendations. In the given recommendations the leading role is given to genetic analyses, invasive and noninvasive methods of diagnostics, such as electrophysiological examination, programmed electric stimulation of heart, magnetic resonance imaging (MRI). In terms of preventive treatment, recommendations on expanding general education of the population, the principles of first aid to persons with sudden cardiac arrest and ensuring the availability of out-of-hospital cardiac defibrillation have been prioritized. The indications for beta-blockers, flecainide, implantable cardioverter-defibrillators, catheter ablation, implantable programmed antitachycardia stimulation devices, and left-sided sympathetic cardiac denervation have expanded considerably.
Keywords: prevention, genetic risk factors, ventricular arrhythmias, sudden cardiac arrest, sudden death.

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Introduction

Sudden cardiac death (SCD) accounts for about 50 % of all deaths from cardiovascular disease (CVD), with 50 % of SCDs occurring as the first manifestation of heart disease, i.e. as a cardiac cause of sudden death [1, 2]. Regardless of gender, the incidence of CHD increases significantly with age. With a very low incidence in infancy and childhood (1 per 100.000 person-years), the incidence of CHD in middle-aged people (in the fifth to sixth decade of life) is approximately 50 per 100.000 person-years [3]. In the eighth decade, the incidence is at least 200 per 100.000 person-years. At every age, and even after the correction of the risk factors for coronary heart disease (CHD), men have a higher rate of CHD than women[4]. CHD accounts for 75–80 % of all cases of CHD. Studies by various authors suggest that there is a correlation between age and the cause of CHD. In 20–30 years, primary electrical diseases and cardiomyopathies, as well as myocarditis and coronary anomalies [5]; in 30–40 years, 50 % of cases of VSS are associated with CHD, especially acute coronary syndrome [6]. In the 40–50 year age group, CHD is associated with potentially inherited electrical or structural non-ischemic heart disease [7]. Chronic structural diseases such as acute coronary events or chronic coronary artery stenoses, heart defects and heart failure (HF) are prevalent in the elderly. 10–20 % of all deaths in Europe are SCDs. Over the course of a year, 300.000 people in Europe experience episodes of out-of-hospital cardiac arrest requiring emergency medical care [8].

Let us briefly review the current definition of sudden cardiac arrest (SCA) and SCD:

- SCA is the sudden cessation of normal cardiac activity with haemodynamic collapse.
- SCD is sudden natural death presumed to be due to cardiac disease, witnessed and occurring within 1h of symptom onset or, in the absence of witnessing, within 24 h of the last time the deceased was seen alive. SCD at autopsy is defined as sudden death from unknown or cardiac causes.

Updates

Here are the key updates for 2022 on VA prophylaxis in SCD. The new guidelines call for the optimisation of implantable cardioverter defibrillator (ICD) programming and algorithms for the management of patients with the "electrical storm" type sustained ventricular tachycardia (SVT). This term refers to SVT occurring three or more times within 24 hours (at least 5 minutes apart), each requiring emergency intervention. New sections on diagnostic evaluation are described in detail, including pharmacological provocation tests, genetic testing and systematic screening of probands and relatives with primary electrical heart disease. Detailed flowcharts and guidelines for the diagnostic evaluation of VA in patients with no known heart disease are presented. ICD guidelines are updated and algorithms for the management of patients with SVT and frequent recurrent ICD discharges are proposed.

New sections and concepts are covered in detail, such as provocative diagnostic tests, genetic testing, diagnostic evaluation at first presentation with ventricular tachycardia (VT) in patients without known cardiac disease, management of patients with electrical storm, and features of device therapy. The focus is on the universal availability of basic life support and access to automated external defibrillators (AEDs). The primary requirements in this regard are the public availability of AEDs in locations with the highest probability of SCA [9] and the increase of emergency out-of-hospital cardiopulmonary resuscitations (CPRs) by bystanders. It is recommended that life support education be promoted in the community for the later[10]. It is important to use all means of alerting bystanders who have received basic life support training.

General aspects of the VA treatment

General aspects of the treatment of UA emphasise that optimal drug therapy (ODT), including angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/angiotensin receptor blockers and neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), beta-blockers (BBs) and SGLT2 inhibitors, is indicated in all patients with HF with reduced left ventricular ejection fraction (LVEF). Direct current cardioversion (DC) is recommended as a first-line therapy for patients with sustained monomorphic VT (SMVT) with high tolerance to therapy. ICD implantation is recommended for patients with an estimated survival of > 1 year. In patients with haemodynamically tolerable SMVT and high risk of SCD, intravenous (IV) procainamide (novocainamide) should be administered, and IV amiodarone may be discussed in the absence of an established diagnosis. In SMVT/non-sustained

polymorphic VT (NPVT)/ventricular fibrillation (VF) caused by premature ventricular complexes (PVCs), catheter ablation may be considered as an alternative to ICDs. In the early phase after myocardial infarction (MI), the use of a portable cardioverter defibrillator is recommended in some patients.

CHD patients

Catheter ablation is preferable to escalating antiarrhythmic drug (AAD) therapy in patients with CHD despite ongoing amiodarone therapy for the persistence of recurrent symptomatic SMVT or recurrent ICD discharges. In CHD patients with an abnormal aortic bifurcation of the coronary artery and a history of prevented SCAs, postoperative cardiac imaging under exercise conditions is recommended as an adjunct to cardiopulmonary exercise testing [11]. ICD is recommended in patients with coronary artery spasm, survivors of SCAs, CHD patients with LVEF ⩽ 30 % despite ODT for ⩾ 3 months [12], and CHD patients with LVEF ⩽ 40 % and non-sustained VT (NVT) converting to SMVT during programmed electrical stimulation (PES). Catheter ablation can replace ICDs in CHD patients with well-tolerated SMVT and LVEF ⩾ 40 % [13], as well as augment ICDs when treatment with BB or sotalol is ineffective, manifested by recurrent symptomatic SMVT or recurrent ICD discharges.

Idiopathic VT or PVCs

Catheter ablation is recommended as first-line therapy for symptomatic idiopathic VT or PVC from the right ventricular outflow tract (RVOT) or left bundle branch of the His [14]. BBs, non-dihydropyridine calcium channel blockers (CCBs) or flecainide are only prescribed when catheter ablation is not possible or undesirable. The same applies to symptomatic idiopathic PVC/VT from other parts of the heart [15]. In patients with non-idiopathic PVC/VT, even with normal echocardiography (ECHO), even in patients with unexplained EF reduction with a PVC rate of at least 10 %, if PVC-induced cardiomyopathy is suspected, cardiac MRI should be scheduled[16]. Catheter ablation is also important in patients who are tolerant to resynchronisation therapy (RST) and who, despite medical therapy, have frequent, predominantly monomorphic PVCs that limit optimal biventricular pacing, and may be used for idiopathic PVC/VT in asymptomatic patients with a PVC frequency > 20 % per day [16, 17]. Amiodarone is not recommended as first-line therapy in patients with idiopathic PVC or VT.

Dilated cardiomyopathy (DCMP) or hypokinetic non-dilated cardiomyopathy (HNDC)

Genetic testing (including at least the LMNA, PLN, RBM20 and FLNC genes) is recommended in patients with DCMP or HNDC with atrioventricular (AV) conduction slowing under the age of 50 years, or with a history of first-degree relatives with DCMP/HNDC or SCD (age < 50 years) [18]. Prescription of MRI with delayed gadolinium enhancement (DGA) should be discussed to assess the aetiology and risk of VA/SCD. ICD implantation is required both in symptomatic patients with LVEF < 50 % and in the presence of ⩾ 2 risk factors (syncope, DGA on MRI, SMVT in PES, pathogenic mutations in LMNA, PLN, FLNC and RBM20 genes) and in patients with DCMP/HNDC with haemodynamically tolerable SMVT. Electrocardiography (ECG) and echocardiography are desirable in close relatives of patients with apparent sporadic DCM/HNDC. Participation in high-intensity exercise, including competitive sports, is not recommended for individuals with DCM/HNDC and the LMNA gene mutation [19].

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

MRI, genetic counselling and testing are recommended in patients with suspected ARVC [20]. BBs treatment may be considered in all patients diagnosed with ARVC. ICD implantation should be considered in symptomatic patients with moderate RV or LV dysfunction or NVT or PES-inducible SMVT. If ICDs are contraindicated, antitachycardia pacing (ATC) should be considered [21]. PES may be used for risk stratification in patients with suspected UA [22]. Carriers of ARVC-associated pathogenic mutations should avoid high-intensity exercise.

Hypertrophic Cardiomyopathy (HCMP)

MRI with DGA is recommended for the diagnostic evaluation of patients with HCMP, with genetic counselling and testing being an essential feature for the diagnosis and further follow-up of these patients [23]. ECG and EchoCG are recommended for the first-degree relatives. ICD implantation is important primarily in patients with HCMP aged ⩾ 16 years with

an intermediate 5-year risk of SCD (4-6 %) and with significant DGA on MRI (usually ⩾ 15 % of LV mass), or LVEF < 50 %, or abnormal blood pressure response during exercise testing, or LV apex aneurysm, or the presence of a sarcomeric pathogenic mutation. ICD should also be discussed in children < 16 years of age with an estimated 5-year risk of SCD ⩾ 6 % (based on the HCM Risk-Kids score) and in patients with stable haemodynamics on SMVT [24]. Patients with recurrent symptomatic VA or recurrent ICD discharges should be prescribed with antiarrhythmic drugs (AD). ICD implantation may be considered in patients with HCMP aged ⩾ 16 years with a low estimated 5-year risk of SCD (< 4 %) but significant DGA on MRI (usually ⩾ 15 % of LV mass) or LVEF < 50 % or LV apex aneurysm [25]. Catheter ablation is indicated in selected patients with recurrent, symptomatic SMVT or recurrent ICD discharges in whom AD treatment is ineffective. Asymptomatic adult patients without the above-mentioned risk factors can participate in high-intensity exercise [26].

Left ventricular noncompaction (LVNC) and restrictive cardiomyopathy (RCMP)

The diagnosis of LVNC and RCMP is based on MRI or echocardiography. To prevent SCD in patients with LVNC and RCMP, as well as in patients with light-chain or transthyretin-associated cardiac amyloidosis and haemodynamically intolerable VT, the decision to implant an ICD is made according to the guidelines regarding DCMP/HNDC.

Myotonic dystrophy

Invasive electrophysiological evaluation is recommended in patients with myotonic dystrophy and palpitations or syncope associated with VA, or in patients who have survived SCA. This method of evaluation is also acceptable in patients with myotonic dystrophy and a PR interval ⩾ 240 m/s on ECG or a QRS complex duration ⩾ 120 m/s, or in patients older than 40 years with supraventricular arrhythmias or significant DGA on MRI. ICD implantation is recommended in patients with myotonic dystrophy and SMVT or prevented SCA not caused by reentrant VT. ICD should also be discussed in patients with myotonic dystrophy without atrioventricular conduction slowing and syncope, where there is a reasonable suspicion of VA [27]. In addition, an ICD may be considered in patients with limb-girdle type 1B or Emery-Dreyfus muscular dystrophy with an indication for electrocardiostimulation, in patients with significant DGA on MRI, and over a permanent pacemaker in patients with myotonic dystrophy and additional risk factors for VA and SCD[28]. In patients with myotonic dystrophy, frequent electrophysiological assessment of AV conduction and arrhythmia induction is not recommended in the absence of suspected arrhythmias or progressive conduction disturbances.

Myocarditis

In patients with haemodynamically intolerable SVT or ventricular fibrillation (VF) in the acute or chronic phase of myocarditis, ICD implantation should be considered before hospital discharge or during outpatient follow-up [29]. In post-myocarditis patients with recurrent symptomatic VT, treatment with ADs should be considered and, if ineffective, catheter ablation should be discussed. In patients with haemodynamically well-tolerated SMVT in the chronic phase of myocarditis, with preserved LV function and an expected small post-ablation scar, catheter ablation may be used as an alternative to ICD therapy.

Cardiac sarcoidosis

In patients with cardiac sarcoidosis with LVEF > 35 % but significant DGA on MRI, ICD implantation should be considered after resolution of the acute inflammation [30]. In the case of small DGA on MRI, PES should be discussed for risk stratification and ICD implantation should be considered in the case of induced SMVT. In patients with Chagas cardiomyopathy with symptomatic PVCs or VT, AD treatment with the possibility of amiodarone should be the first line of treatment [31]. If ADs are ineffective, catheter ablation should be considered.

Congenital heart defects (ConHD)

In patients with ConHD and persistent VA, evaluation for residual lesions or new structural abnormalities is recommended. Treatment of supraventricular tachycardia with delayed intraventricular conduction should be discussed in selected patients with ConHD (including atrial septal repair for transposition of the main arteries, Fontaine surgery and Ebstein's anomaly) presenting with SCA [32]. In patients with corrected tetralogy of Fallot requiring surgical or transcatheter pulmonary valve replacement, pre- or intra-operative catheter mapping and crossing of an-

atomical isthmuses that induce VT can be discussed. If biventricular function is preserved in patients with symptomatic SMVT, catheter-based or concomitant surgical ablation may be considered as an alternative to ICD therapy [33]. In the absence of arrhythmia but in the presence of its risk factors, electrophysiological study including PES may be considered.

Idiopathic VF

It is recommended that idiopathic VF in SCA be diagnosed, preferably with documented VF, after exclusion of underlying structural changes of canalopathic, metabolic or toxicological etiology. In idiopathic VF with "electrical storm" or recurrent ICD discharges, emergency infusion of isoproterenol, verapamil or quinidine followed by long-term quinidine therapy is preferred [34]. In patients with idiopathic VF, genetic testing for canalopathy and cardiomyopathy genes and clinical evaluation (history, ECG and high thoracic ECG, exercise testing, echocardiogram) in first-degree family members is desirable [35].

Long QT syndrome (LQT)

Genetic counselling and testing is recommended in patients with clinically diagnosed LQT. Non-selective BBs (nadolol or propranolol) are recommended to reduce the risk of arrhythmias in patients with LQT with documented QT prolongation. Mexiletine is indicated in patients with type 3 LIQT[36]. The risk of arrhythmia, which depends on genotype and QT interval length, should be calculated before starting treatment for LIQT. ICD implantation can be used in asymptomatic LQT, in patients with a high risk profile (on a scale of 1-2-3 on the LQT risk calculator), as an adjunct to genotype-specific therapy[37]. Routine diagnostic testing with adrenaline provocation is not recommended in patients with SUIQT.

Andersen-Tawil syndrome

Genetic testing is recommended for all patients suspected of having Andersen-Tawil syndrome. In the absence of structural heart disease, Andersen-Tavila syndrome is suspected in patients with at least two of the following features: prominent U teeth with/without QT prolongation, bidirectional and/or polymorphic premature ventricular complexes/VT, dysmorphic features, periodic paralysis, and a pathogenic loss-of-function mutation of KCNJ2 [38, 39]. For unexplained syncope, implantation of an implanted loop recorder (ILR) should be discussed. ICD implantation is used in patients with prevented SCA or intolerable SVT and a history of unexplained syncope or tolerable SVT. Prescription of BB and/or flecainide with or without acetazolamide should be considered as an AD therapy.

Brugada syndrome (BrS)

Genetic testing for the SCN5A gene is recommended for probands with BrS[40]. The diagnosis of BrS is made in patients without other heart disease and induced type 1 BrS on ECG if at least one of the following features is present: arrhythmic syncope or nocturnal agonal breathing, family history of BrS, family history of SCD (< 45 years) with negative autopsy and presence of situations suspicious for BrS. In cases with unexplained syncope, implantation of an ILR should be considered. BrS can be suspected in patients with an induced ECG pattern of type 1 BrS without other cardiac disease [41]. PES can be used to detect VA in asymptomatic patients, with spontaneous manifestation of type 1 BrS on ECG. A test with sodium channel blockers is not recommended in patients with a previous episode of type 1 BrS. Catheter ablation is also not necessary in asymptomatic patients.

Early repolarisation syndrome (ERS)

It is recommended that ERS be diagnosed as J-point elevation ⩾ 1 mm in the two adjacent inferior and/or lateral ECG leads and in patients with the above-mentioned ECG features with unexplained VF/PVCs [42]. The diagnosis of ERS is made in a case of SCD with a negative autopsy result if the physical examination and pre-mortem ECG show ERS. In patients with suspected ERS, genetic testing for ERS is desirable [43]. First-degree relatives of the patient should be clinically evaluated for additional risk factors. For the diagnosis of arrhythmias, ILR should be considered in individuals with at least one risk factor or arrhythmic syncope [44]. ICD implantation is recommended for all patients who have experienced SCA. Intravenous infusion of isoproterenol is required for the medical management of patients with electrical storm. In recurrent VF, the use of quinidine in addition to an ICD should be discussed. PVC ablation is required in patients with recurrent episodes of VF caused by similar ventricular extrasystoles (VEs) that do not respond to medical therapy [45]. ICD implantation or quinidine treatment is used in selected individuals

with arrhythmic syncope and additional risk factors, and in the absence of symptoms in individuals with high-risk ERS and a family history of unexplained juvenile SCD [46]. Routine clinical evaluation and ICD implantation is not recommended in asymptomatic individuals with ERS [47].

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Genetic counselling and testing is indicated in all patients with a clinical diagnosis of CPVT. If physical stress testing is not possible, provocation with adrenaline or isoproterenol may be considered to diagnose this condition. In terms of treatment, BBs, preferably non-selective, are recommended for all patients [48].

Short QT syndrome (SQT)

Genetic testing is required in SQT patients when the QTc duration is ⩽ 320 m/s[49]. In arrhythmic syncope, the diagnosis of SQT is suspected when the QTc duration is between 320 m/s and 360 m/s. In addition, this diagnosis may be considered in patients with a QTc of 320–360 m/s if there is a family history of SCD before the age of 40 years. In younger patients, implantation of an ILR should be discussed, and an ICD should be considered in patients with arrhythmic syncope. In some cases, quinidine may be used if the patient refuses an ICD or in asymptomatic patients with a family history of SCD [50]. In the case of "electrical storm", intravenous isoproterenol is preferred [51].

Some population groups

Athletes with CVD and at risk of SCD are treated according to current eligibility guidelines. In women with ARVC, the continuation of BB during pregnancy should be considered. Metoprolol, propranolol or verapamil are preferred for long-term treatment of idiopathic sustained VT during pregnancy. In women with symptomatic recurrent SMVT refractory to ADs, it is advisable to consider catheter ablation after the first trimester of pregnancy using neuroimaging techniques [52]. ICD implantation may be discussed in selected patients with vasculopathy of the transplanted heart or who are taking immunosuppressants. ICD implantation for primary prevention of SCD in elderly patients may be discouraged because of the lack of expected defibrillator benefit associated with age and comorbidities [53].

Conclusion

Prevention of ventricular arrhythmias and SCD therefore requires an individualised approach to each case, taking into account the nosology of CVD, arrhythmia characteristics, results of genetic counselling and testing, imaging data and appropriately selected treatment.

Measures to prevent SCD through out-of-hospital emergency cardiopulmonary resuscitation with universal availability of defibrillation are an integral task not only for health authorities, but also for the all state structures in general.

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