VENTRICULAR ARRHYTHMIAS

Definitions and Classification

Ventricular tachycardia (VT) is defined as a tachycardia (rate >100 beats/min) with three or more consecutive beats that originates in the ventricles. [1,2]

A*ccelerated idioventricular rhythm* denotes a ventricular rhythm <100 beats/min.

Sustained ventricular tachycardia lasts >30 s (unless requiring termination because of haemodynamic collapse), whereas *non-sustained tachycardia* terminates spontaneously within 30 s.

Monomorphic ventricular tachycardia has only one morphology during each episode (Figure 1).

Pleomorphic ventricular tachycardia has more than one morphology of monomorphic VT during the same or different episodes of VT, but the QRS is not continuously changing. In patients with implantable defibrillators (ICD), pleomorphic VT is associated with increased risk.[3]

In *polymorphic* ventricular tachycardia there is a constant change in QRS configuration indicating a changing ventricular activation sequence, usually at a heart rate <333 bpm (cycle length >180 ms). Rapid polymorphic ventricular tachycardia cannot easily be distinguished from ventricular fibrillation.

Bidirectional ventricular tachycardia is a rare form of tachycardia with two alternating morphologies, usually right bundle branch block with alternating left and right axis deviation. This typically occurs with catecholaminergic polymorphic ventricular tachycardia, digitalis toxicity, aconite poisoning, and genetic channelopathies such as Andersen-Tawil syndrome, and or other conditions that predispose cardiac myocytes to delayed afterdepolarizations (DADs) and triggered activity.[4]

Incessant VT denotes hemodynamically stable VT lasting hours.

VT storm indicates very frequent episodes of VT, more than 3 episodes in 24 h, monomorphic or polymorphic, requiring cardioversion.[5]

Torsades de pointes is a form of polymorphic ventricular tachycardia with characteristic beat-by-beat changes (twisting around the baseline) in the QRS complex associated with prolongation of the QT interval. It is triggered by an ectopic following a long coupling interval (>400 ms), and should be distinguished from the so-called *pseudo-TdP* that is triggered by short-coupled VPBs.[6,7]

Ventricular flutter indicates a monomorphic, regular ventricular arrhythmia with a rate of approximately 300 bpm (cycle length 200 ms) with no isoelectric interval between QRS complexes.

Ventricular fibrillation usually has a rate >300 bpm (cycle length ≤ 200 ms), and is a grossly irregular ventricular rhythm with marked variability in QRS morphology and amplitude. Fine VF is low amplitude VF that superficially could mimic asystole.

Pathophysiology

Electrophysiology

Ventricular tachycardia

Monomorphic VT may be focal or macroreentrant.[8] Focal VT has a point source of earliest ventricular activation with a spread of activation away in all directions from that site. The mechanism can be triggered activity, automaticity, or microreentry. The site of origin can be endocardial or epicardial with focal endocardial breakthrough. Macroreentry is due to myocardial scars secondary to prior myocardial infarction or other disease process.

Triggered activity due to delayed afterdepolarizations is the usual mechanism of *idiopathic outflow tract tachycardias*.[9] Termination of idiopathic ventricular outflow tract tachycardias by an intravenous bolus of adenosine or infusion of a calcium channel blocker, or by vagotonic maneuvers is consistent with triggered activity as the likely mechanism for some of these tachycardias. These tachycardias can be difficult to induce at electrophysiology testing; rapid burst pacing and/or isoproterenol infusion is often required. Although triggered arrhythmias typically occur in structurally normal hearts they may also be seen in association with congestive heart failure and ischemic heart disease.[10]

Automaticity that is provoked by adrenergic stimulation (not triggered) or disease processes that diminish cell-to-cell coupling may less commonly cause focal VT. This type of VT may become incessant under stress or during isoproterenol administration, but cannot be initiated or terminated by programmed electrical stimulation; it can sometimes be suppressed by calcium channel blockers or beta-blockers. Automaticity from damaged Purkinje fibres has been suggested as a mechanism for catecholamine-sensitive, focal origin VT. Automaticity can also occur in partially depolarized myocytes, as has been shown for VTs during the early phase of myocardial infarction as well as in some patients with ventricular scars. Automatic premature beats may, in addition, initiate reentrant VTs.

Reentry around a myocardial scar (scar-related reentry) characterized by regions of slow conduction and anatomic or functional unidirectional conduction block at some point in the reentry path, is the cause of the majority of monomorphic VT seen in patients with heart disease.[11] Myocardial scar is identified from low-voltage regions on ventricular voltage maps, areas with fractionated electrograms, unexcitability during pace mapping, evidence of scar on myocardial imaging, or from an area of surgical incision. Normal myocardium is typically characterized by bipolar voltage >1.5 mV, dense scar by bipolar voltage <0.5 mV, and border

zone tissue by bipolar voltage of 0.5 to 1.5 mV. It should be noted however, that voltage mapping has several limitations.[12] Prior myocardial infarction is the most common cause, but scar-related VT also occurs in cardiomyopathies, and after cardiac surgery for congenital heart disease or valve replacement. Evidence supporting reentry includes initiation and termination by programmed stimulation (although this does not exclude triggered activity), demonstrable entrainment or resetting with fusion, continuous diastolic electrical activity, and isolated diastolic potentials that cannot be dissociated from VT by perturbations introduced by pacing.

Following myocardial infarction, there is ion channel remodelling and regional reductions in I_{Na} and I_{Ca} within the scar, reduced coupling between myocytes by increased collagen and alterations in gap junction distribution and function, and intervening patchy fibrosis resulting in a zig-zag pattern of transverse conduction. Thus, scar remodelling contributes to the formation of channels and regions where conduction time is prolonged (isthmus sites ranging from 21-59 mm length by 15-47 mm width) facilitating reentry.[13] In the setting of ischemic cardiomyopathy, most ventricular tachycardia corridors, derived from late gadolinium enhanced cardiovascular magnetic resonance and validated through mapping, closely align with a 3-dimensional hyperboloid model.[14] Border zone corridors identified within areas of late gadolinium enhancement (LGE) are associated with malignant ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy.[15] Multiple VT morphologies caused by multiple re-entry circuits are often inducible in the same patient. The majority of reentrant circuits are located in the subendocardium, but subepicardial or intramyocardial reentry may also occur.[16]

Studies of Purkinje cell electrophysiology show multiple mechanisms responsible for ventricular arrhythmias, including enhanced automaticity, triggered activity, and reentry. The variation in functional properties of Purkinje cells in different areas of the His-Purkinje system underly the propensity for reentry within Purkinje fibers in both structurally normal and abnormal hearts.[17] Reentrant arrhythmias of the His-Purkinje system consist of bundle to bundle reentry, right bundle branch reentry due to longitudinal dissociation of the right bundle, interfascicular reentry, intrafascicular reentry, and macroreentry involving the myocardium. These tachycardias are usually seen in severe left ventricular dysfunction due to dilated cardiomyopathy, ischaemic heart disease, and valvular disease but they may also occur in apparently normal hearts.[17-19]

Ventricular Fibrillation

The mechanism of VF remains elusive and both reentrant (caused by multiple wavelets, mother rotor, or a combination of both) and focal mechanisms (rapidly firing focus initiated by triggered activity or automaticity) have been implicated.[20] In certain cases focal activity in the Purkinje network may be involved in VF initiation and maintenance.[21] Rapid pacing-

induced VF generally is attributed to reentrant mechanisms. Ischemia, drugs and genetic defects that prolong repolarization and alter intracellular calcium promote polymorphic ventricular arrhythmias degenerating to VF.

Presentation

The clinical presentation of ventricular arrhythmias depend on the haemodynamic disturbance they produce. Rapid tachycardias, long-lasting tachycardias, poor left ventricular function and atrioventricular dissociation tend to contribute to haemodynamic collapse which may present as *pre-syncope*, *syncope* or *sudden death*. When cardiac output and blood pressure are maintained, and when the episodes are short-lived, the arrhythmia may present as recurrent palpitations, breathlessness or chest pain. Occasionally, patients are completely *asymptomatic* during tachycardia. A history of ischaemic heart disease or congestive heart failure in men older than 35 years suggests that a wide-QRS tachycardia is probably ventricular in origin.[22] Figure 2 summarizes the genetic risk for ventricular arrhythmias/sudden cardiac death (VA/SCD), typical triggers, and clinical characteristics in different disease settings.

Physical Examination

Low blood pressure, heart failure and cardiogenic shock may be present as signs of haemodynamic distress.

Atrioventricular dissociation (apparent by a changeable pulse pressure or by Doppler assessment of flow in the ascending aorta[23]).

Irregular cannon waves in the jugular venous pulse.

Variable first heart sound may be seen if retrograde ventriculoatrial block is present.

None of these signs will be present if there is retrograde ventriculoatrial conduction which is present in 20-30% of cases. In this situation, atrial systole coincident with ventricular systole will produce ***regular cannon waves***.

ECG Morphologies

With ***monomorphic VT*** the ECG displays a wide QRS (>120 ms) tachycardia. A relatively narrow QRS (100-120 ms) may be seen in fascicular VT, or septal VT arising close to the His-Purkinje network. Prior MI, idiopathic VT, and arrhythmogenic cardiomyopathies (most often ARVC[24]) are the most common causes of monomorphic VT.

Polymorphic VT is usually seen in the context of QT prolongation (in the form of torsade de pointes), in patients with other genetic channelopathies (Brugada syndrome, CPVT, short QR or early repolarization syndrome), nonischaemic cardiomyopathies, idiopathic VT/VF, and in patients with acute STEMI or myocardial ischemia.[25] In STEMI, polymorphic VT may be seen during the acute phase, or up to 8 days following the MI,[26] and these patients are at high risk of developing arrhythmic storm.

***Torsades de pointes* (TdP)** occurs in most commonly in congenital LQTS, drug-related QT prolongation, metabolic abnormalities such as hypokalemia, and during marked bradycardia in patients with 3rd degree AV block with PVCs. It is characteristically triggered by ectopics with a long coupling interval (usually >500 ms).

Pseudo-TdP or ***short-coupling VF*** refers to polymorphic VT that is triggered by ectopic beats with a short coupling interval (such as approximately 350 ms) occurring in patients with or without QT prolongation.[6,7]

Polymorphic VT/VF storm in a patient with coronary disease is strongly suggestive of acute myocardial ischemia; pauses may occur prior to polymorphic VT even in the absence of QT prolongation. Usually, severe underlying heart disease is present. More rarely, VT storm can occur in patients who have a structurally normal heart, e.g, in Brugada syndrome, LQTS, catecholaminergic VT, or in drug overdoses.

Differential Diagnosis of Wide-QRS Tachycardias

The differential diagnosis of wide-QRS tachycardias is discussed in the Chapter on Differential Diagnosis of Arrhythmias

Acute Therapy of Ventricular Arrhythmias

Cardiac Arrest

The incidence of ventricular fibrillation or pulseless ventricular tachycardia as the first recorded rhythm in out-of-hospital cardiac arrest has declined to less than 30% in the past several decades.[27,28] Pulseless electrical activity (electromechanical dissociation) and asystole are proportionally more frequent with an incidence of 19-23%, while the remaining patients (approximately 50%) have asystole.[29] Survival rate is 30% for VT/VF arrests, but <10% for pulseless electrical activity. Public access defibrillation may increase this survival to 40% or even more.[30] VT/VF accounts for 67% of cardiac arrests in post-MI patients.[31] The use of thrombolysis during advanced life support for out-of-hospital cardiac arrest did not improve outcome,[32] and in patients without ST elevation coronary angiography has not improved outcome, with less than 15% of patients presenting with an occluded coronary artery (COAPT and PEARL RCTs), [33,34] A continuous review of peer-reviewed cardiopulmonary resuscitation science has also been initiated by the International Liaison Committee on Resuscitation (ILCOR).[35] Public basic life support and access to automated external defibrillators are important (Table 1). For pregnant patients see specific recommendations at the end of the Chapter. Table 2 and Figures 3-12 present the AHA and ESC recommendations for CPR and Emergency Care.

Important therapeutic points are:

- The ***basic life support (BLS)*** sequence of steps "A-B-C" (Airway, Breathing, Chest compressions) has been changed to "C-A-B" (Chest compressions, Airway, Breathing) in most guidelines for adults but variability exists, especially for pediatric patients. In addition, cardiac arrest from drowning is due primarily to lack of oxygen and CPR should follow the traditional ABC sequence.[36]
- ***Defibrillation*** using biphasic waveforms should be given, if possible within 2 min, for shockable cardiac arrest. Although the DOSE VF RCT, both anterior-posterior (vector change), and double sequential external defibrillator improved survival in refractory VF,[37] the value of vector change is not established.[38]
- A universal ***compression-ventilation ratio of 30:2*** is performed by lone rescuers for victims of all ages before an advanced airway (supraglottic airway or tracheal tube) is placed. One breath every 6 s (10 breaths/min) should be provided while continuous chest compressions are being performed. A rate of 10 breaths/min (1 breath every 6 sec) to provide asynchronous ventilation during continuous chest compressions is also acceptable. Chest compressions should be of adequate rate (100-120/minute) and of adequate depth of at least 2 inches (5 cm) in adults.
- Either ***bag-mask ventilation*** or an advanced airway strategy with ***endotracheal intubation*** or ***supraglottic airways*** may be considered during CPR for adult cardiac arrest in any setting. However, early, within 15 min, ***tracheal intubation*** for adult in-hospital cardiac arrest may not be beneficial.[39] Tidal volumes of 500-600 ml should be used. When positive pressure ventilation is given, continuous chest compressions are not superior to compressions interrupted for ventilation.[40]
- For most adults with out-of-hospital cardiac arrest, bystander CPR with chest compression only (***Hands-Only CPR***) appears to achieve outcomes similar or even better to those of conventional CPR (compressions with rescue breathing).[41,42] The predicted steep decline in arterial oxygen saturation does not occur until many minutes after the start of resuscitation and the volume of oxygen in the lungs is relatively great when arrest occurs suddenly. In addition, initial reperfusion with hypoxemic blood may result in fewer injurious oxygen free radicals and less reperfusion injury. Thus, continuous chest compression without active ventilation avoids risks associated with mouth-to-mouth contact, and is recommended when CPR is performed by a bystanding layperson.[43] Survival with continuous chest compression is better among patients whose arrests were due to cardiac causes and among patients whose initial cardiac rhythm was ventricular tachycardia or fibrillation rather than asystole or electromechanical dissociation.
- ***Precordial thumb*** may be beneficial only at the very early onset of VT when the arrhythmia is most vulnerable to lower-energy termination. However, if administered

on the electrically vulnerable portion of an organized rhythm (T wave), the thump (like an unsynchronized shock) risks acceleration or conversion of the rhythm to VF analogous to commotio cordis.[44]

- ***Epinephrine*** (1 mg every 3 to 5 min) is recommended, despite previous controversial results.[44] It is associated with increased survival in out of hospital cardiac arrest, especially in patients with non-shockable cardiac arrest.[45-48] High-dose epinephrine is not recommended.
- ***Lidocaine*** and ***amiodarone*** may be given in shock-refractory VT/VF, but the effect is limited.[49] In the ALPS trial, an IV bolus of 150 mg amiodarone or 60 mg lidocaine improved survival but just by 2.3% and 1.2% respectively, in patients with shock-resistant VT/VF.[50] Neither amiodarone nor lidocaine resulted in significantly higher rate of survival or favorable neurologic outcome compared to placebo in patients with out-of-hospital cardiac arrest (ROC trial). There was a suggestion for a significantly higher survival rate in the subgroup of patients with bystander-witnessed arrest, that is considered a surrogate for early recognition of cardiac arrest.[51]
- ***Magnesium*** is not of value in this setting, unless the arrest is due to torsade se pointes. Its routine use is not recommended in cardiac arrest. Routine use of ***sodium bicarbonate*** or ***calcium*** are also not recommended. Sodium bicarbonate may be considered in severe metabolic acidosis (pH<7.2, bicarbonate <20), and AKI stage 2 or 3.[52]
- ***Intraosseous*** drug administration should be considered only if intravenous access is not feasible.[44] Administration via an in-place endotracheal tube is no more recommended.[49]
- ***Mechanical CPR devices*** may be used in specific settings but their routine use is not recommended.[49] However, in the ARREST RCT, early ECMO-facilitated resuscitation for patients with out of hospital cardiac arrest and refractory VF significantly improved survival.[53]
- ***Gasping*** (ie agonal respiration) during CPR is independently associated with increased 1-year survival with favorable neurological function, defined as a Cerebral Performance Category (CPC) score ≤2, regardless of the first recorded rhythm. [54] CPR, therefore, should not be discontinued prematurely in gasping patients. Particular mechanical chest compression devices may be safe.[55]
- Induction of therapeutic ***hypothermia*** (Targeted Temperature Management-TTM between 32°C to 36°C) for at least 24 hours after resuscitation from a ventricular tachycardia or ventricular fibrillation arrest is recommended to improve survival and neurological recovery.[56] It seems that in patients with coma who had been resuscitated from cardiac arrest with nonshockable rhythm, hypothermia at 33°C for

24 hours is preferable.[57] However, rapid infusion of large volume cold saline may be harmful.[58] Hypothermia has not been found equally useful in the young (<18 years old).[59]

- Prehospital resuscitation efforts should be continued for at least ***40 minutes*** in all adults with out-of-hospital cardiac arrest.[60] Termination of Resuscitation (TOR) rules are provided in Figures 7 and 8.

Evaluation of Cardiac Arrest Survivors

Recommendations for cardiac arrest survivors are provided in Tables 3 and 4 and Figure 12. Recommendations for sudden death victims, in general, are provided in the relevant Chapter.

Monomorphic VT, Polymorphic VT, Torsade des Pointes, Incessant VT and VT storm

Acute management is presented in Table 5 and Figures 13-15. Recommendations for the management of ***wide-QRS tachycardias in the absence of established diagnosis*** are provide in the Chapter on Differential Diagnosis and Management of Tachyarrhythmias. The value of lidocaine is now refuted, while adenosine may be used in monomorphic VT, especially when the diagnosis of VT is not certain. In monomorphic wide-QRS tachycardia, intravenous procainamide (10 mg/kg/20 min) was associated with less major cardiac adverse events and a higher proportion of tachycardia termination within 40 min compared to amiodarone (5 mg/kg/20 min).[61] The prognostic value of electrical storm is rather debatable, most probably depending on the underlying heart condition.[5,62,63] Coronary angiography with a view to revascularization (if indicated) should be considered. Catheter ablation may be useful for the short-term management of VT storm,[64,65] and the combination of propranolol (160 mg/24h)with IV amiodarone is superior to metoprolol (200 mg/24h) and IV amiodarone in this setting.[66] Torsade de pointes (TdP) caused by a long QT syndrome (LQTS), responds to beta-blocker therapy, intravenous magnesium, and cardiac pacing. Other forms of polymorphic VT not associated with QT prolongation, including the polymorphic VT of Brugada syndrome, short QT syndrome, idiopathic VF, and the so-called pseudo-TdP, may respond to quinidine.[6] Short-term quinidine has also been found useful in patients developing polymorphic VT or electrical storm, especially in the healing phase of acute MI (3-8 days after the event).[26,67] Mexiletine may also be useful for VT storm in patients with ICD.[68] Cardiac sympathetic denervation may also be useful in patients with recurrent refractory VT but no overt heart failure.[69] Percutaneous stellate ganglion block is a novel, promising approach for electrical storm.[70]

Risk Stratification

Recommendations for investigations in patients with ventricular arrhythmias are provided in Table 6, and an ECG Score for risk of Sudden Arrhythmic Death in Table 7.

Resting 12-lead ECG

ECG during tachycardia is essential for differential diagnosis. ECG during sinus rhythm after interruption of tachycardia may reveal signs of ischemic heart disease, conduction defects, electrolyte disturbances, and syndromes of inherited arrhythmias (Brugada syndrome, ARVC, long QT syndrome). QRS duration >120 ms, ST-T abnormalities, and QT>440 ms or <400 ms have all been associated with increased mortality.[71] ECG measures have been found to be associated with sudden death in the general population. [72,73] An ECG score for the risk of sudden arrhythmic death in patients with coronary artery disease has been validated over a 5-year follow-up (PREDETERMINE) (Table 7).[74]

Laboratory Tests

Complete blood count, cardiac enzymes, serum electrolytes (including magnesium), creatinine, BUN, and liver and thyroid function tests should be checked.[75] Additional specific tests such as iron studies, HIV, etc should also be obtained when clinically indicated.

Thansthoracic Echocardiography

Thansthoracic echocardiography may detect signs of cardiomyopathy, ARVC and other structural abnormalities, and impaired LV function. There has been overwhelming evidence that in patients with heart disease in general, left ventricular ejection fraction is the major determinant of cardiac and total mortality. The results of several studies, including the SCD-Heft and MACAS, have also established the importance of LVEF as the most critical prognostic factor in patients with ischemic or non-ischemic LV dysfunction and NSVT.[76,77] However, LVEF alone has limited sensitivity and low specificity for arrhythmic versus nonarrhythmic cardiac death.[78-80] An overall mortality of 5.8% and 3% at one year has been found in patients with LVEF<=30%,[81] and 40%,[82] respectively, following primary intervention for acute myocardial infarction, and patients with a recent myocardial infarction and an LVEF<25% and/or wide QRS have not been shown to benefit from ICD therapy.[83] In the Swedish CPR Registry, predictors of cardiac arrest 90 days after MI (occurred in 0.3% of patients) in addition to LVEF were male sex, diabetes, renal impairment, heart failure, and newly identified atrial fibrillation or atrial flutter.[84]

Exercise Testing

Apart from demonstration of ischemia, exercise tasting may also be helpful in patients with long QT syndrome, exercise-triggered RVOT tachycardia, and cathecholaminergic polymorphic VT. NSVT induced by treadmill exercise testing aimed at evaluating presumed long QT syndrome suggests cathecholaminergic polymorphic VT rather than long QT

syndrome.[85] Although life-threatening arrhythmias may occur in up to 2% of individuals subjected to the test, exercise is recommended since it is better to expose arrhythmias under controlled circumstances.

Other Tests for Myocardial Ischemia

Functional tests such as myocardial perfusion, and stress echocardiography are required to demonstrate myocardial ischemia. Acute myocardial ischemia is an established cause of polymorphic ventricular rhythms,[86] preceding 35 to 80% of deaths due to a ventricular tachyarrhythmia.[87] The association of monomorphic ventricular tachycardia, a substrate-dependent arrhythmia, with acute ischemia is less well characterized, but ischemia may induce monomorphic ventricular tachycardia in the presence of a myocardial scar.[88] Refractory VT/VF is usually due to acute coronary syndrome or complex coronary artery disease.[89]

Coronary Angiography

It is mandatory in any patient with a life-threatening ventricular arrhythmia or aborted sudden death, even in the absence of ST-segment elevation, since the post-resuscitation ECG is rather unreliable.[90] However, the optimal timing (ie immediate vs delayed) is not established (COACT trial).[33] In cardiac arrest survivors, early coronary angiography may be of benefit even in the absence of ST-segment elevation on the presenting ECG.[52]

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) imaging with delayed hyperenhancement has been used for detecting an arrhythmogenic substrate in patients with underlying LV dysfunction.[91,92] Myocardial scar and LVEF are both risk markers for all-cause and cardiac death in patients with nonischemic cardiomyopathy. In nonischaemic cardiomyopathy, myocardial scar has strong and incremental prognostic value for SCD risk stratification, whereas LVEF, although a risk marker as well, has no incremental prognostic value over clinical measures.[93] LGE+ and LVEF<=35% appear to be strong predictor of ventricular arrhythmias and sudden death in this setting.[94] In patients with apparently idiopathic nonsustained ventricular arrhythmias, nonischemic LV scar with a ringlike pattern is associated with malignant arrhythmic events.[95] In this respect, cardiac MRI is also useful in hypertrophic cardiomyopathy, ARVC, sarcoidosis and other infiltrative myopathies.

Ambulatory Electrocardiography

Holter monitoring is valuable for detecting NSVT . Although previous studies have detected NSVT as a predictor of arrhythmic mortality, in the era of reperfusion and beta-blockers NSVT does not carry independent predictive power in identifying patients with ischemic or dilated cardiomyopathy at risk of sudden cardiac death, particularly in multivariate analyses when confounders such as the LVEF are taken into account.[96-98] Only in non-ST elevation

acute coronary syndrome NSVT occurring beyond 48 hours after admission indicates an increased risk of sudden death.[99] In non-ischaemic cardiomyopathy, NSVT on Holter is independently associated with sustained ventricular arrhythmias. NSVTs in this setting are typically short, predominantly irregular, slower than induced and spontaneous sustained VTs, and not related to late gadolinium enhancement on cardiac magnetic resonance.[92] In patients with HCM and most probably in patients with inherited channelopathies, detection of NSVT on Holter predicts arrhythmia episodes.[100] The use of Holter for evaluation of treatment is limited, since the suppression of frequent ventricular ectopy or NSVT by class IC antiarrhythmic drugs or amiodarone does not imply a favourable diagnosis. (CAST and CAST II and CHF-STAT).[101-103]

T-wave Alternans

T wave alternans are thought to reflect dispersion of repolarization and have been shown to predict future arrhythmic events better than SAECG and QRS duration.[104] In patients with reduced LV function (LVEF<40%) and NSVT, microvolt T-wave alternans has also predicted unstable ventricular tachyarrhythmias better than electrophysiology testing and LVEF<30%.[105] However, although TWA predicted higher total mortality in a MADIT II-like population, the risk of tachyarrhythmic events did not differ according to TWA results.[106] The ABCD (Alternans Before Cardioverter Defibrillator) study was the first trial to use micro-TWA to guide prophylactic ICD insertion in patients with LVEF<40% and NSVT. Risk stratification strategies using noninvasive TWA versus invasive EPS were comparable at 1 year with very low positive and very high negative predictive values, and complementary when applied in combination.[107]. Data from patients with ICD have also suggested that variability of TWA is greater before spontaneous VT/VF recordings[108] The test also has a significant negative predictive value for the occurrence of arrhythmic events in patients with dilated cardiomyopathy.[109]

Assessment of Autonomic Tone

Heart rate variability (HRV) has been identified as an independent risk factor for arrhythmic mortality in post-myocardial infarction patients.[110] Depressed baroreflex sensitivity has also been independently associated with an increased cardiac mortality and sudden death after MI, and with a higher predictive power than heart rate variability.[111] However, in the beta-blocking era, the common arrhythmia risk variables, particularly the autonomic and standard ECG markers such as QRS duration and QT dispersion, have limited predictive power in identifying patients at risk of sudden cardiac death.[112] In patients with nonischemic cardiomyopathy results on the value of heart rate variability have been conflicting.[77,113]

Signal Averaged Electrocardiography

Although in survivors of myocardial infarction an abnormal SAECG has been associated with increased risk of arrhythmic and total mortality, its value for risk stratification purposes is not established, especially in patients treated with thrombolysis or beta blockers.[114] In patients with dilated cardiomyopathy, SAECG does not predict sudden death,[77] but in arrhythmogenic right ventricular dysplasia SAECG can identify those with more extensive disease and a propensity for inducible ventricular tachycardia by programmed electrical stimulation, and is now considered a minor diagnostic criterion.

Periodic repolarization dynamics

Periodic repolarization dynamics (PRD) is a noninvasive electrocardiographic biomarker that most likely reflects the effect of phasic sympathetic activation on the myocardial cells, and quantifies low-frequency oscillations of ventricular repolarization instability. Increased PRD can identify patients with nonischemic cardiomyopathy in whom prophylactic ICD implantation leads to significant mortality reduction.[115]

Electrophysiology Testing

Electrophysiology study may be required for establishment of the **diagnosis** in patients presenting with nonsustained ventricular rhythms. Indications include the need for differentiation from SVT with aberration, AF in the context of an accessory pathway, or other forms of aberration, risk stratification in patients with repaired tetralogy of Fallot or sarcoidosis, and programmed electrical stimulation for induction of VT.

Programmed electrical stimulation (PES) may also be used for **risk stratification** purposes.[116] In ***post-infarction patients*** with NSVT, the induction of sustained ventricular tachycardia is associated with a two- to three-fold increased risk of arrhythmia-related death.[117] In patients with reduced LVEF (<40%) and NSVT, inducibility of sustained monomorphic ventricular tachycardia at baseline PES is associated with a 2-year actuarial risk of sudden death or cardiac arrest of 50% compared to a 6% risk in patients without inducible ventricular tachycardia.[118] Analysis of patients enrolled in the MUSTT as well as of those in the registry, revealed that non-inducible patients have a significantly lower risk of cardiac arrest or sudden death compared to inducible patients at 2 and 5 years (12% vs 24% and 18% vs 32%, respectively).[119] Noninducibility after VT ablation in patients with post-infarction VT is also independently associated with lower mortality during long-term follow-up.[120] Still, as these results indicate, patients with non-inducible sustained VT are not free of risk of sudden death, although in a recent trial, revascularized patents with non-inducible arrhythmias 4 days after the infarction and an LVEF<30% had a similar long-term survival free of death or arrhythmia as patients with LVEF>40%.[121]

In the MUSTT, total and arrhythmic mortality in patients who did not receive antiarrhythmic therapy were higher in those with an ejection fraction <30% than to those

whose ejection fractions were 30% to 40%. The relative contribution of arrhythmic events to total mortality was significantly higher in patients with inducible VT, and among patients with an ejection fraction ≥30%. This study therefore suggested that the major utility of electrophysiological testing may be restricted to patients having an ejection fraction between 30% and 40%.[122] There has been some recent evidence that programmed stimulation performed as early as 3 days after MI in patients with LVEF<=40% induces VT in up to 1/3 of patients, and may identify patients at high risk for spontaneous VT and sudden cardiac death. [123] Noninducibility after VT ablation in patients with post-infarction VT is independently associated with lower mortality during long-term follow-up.[120]

The ventricular stimulation protocol and the type of VT induced are important. Inducible monomorphic VT identifies patients at high risk of arrhythmia even when it is very fast (cycle length 200-250 ms, rate 240-300 bpm),[123,124] or is induced by 3 or 4 extrastimuli or by burst pacing.[125] [126] Inducibility of ventricular fibrillation or flutter (usually with a cycle length <200-250 ms) has been considered a nonspecific finding,[123,127,128] especially when induced with three extrastimuli at very short coupling intervals.[129] In the MUSTT trial, VF with 1-2 extrastimuli did confer an adverse prognostic significance.[119]

These results should be considered in the context of evidence from analysis of stored ICD data that have shown little association between spontaneous and induced ventricular arrhythmias.[130] The remodeling process after MI is ongoing with a resultant low correlation between induced and clinically occurring VT in the long term.[82]

In the patient with CAD and relatively preserved left ventricular function (LVEF>40%), the role of PES is not established, but there has been observational evidence that it may be of value for risk stratification.[131] Inducible monomorphic VT might prompt catheter ablation and if needed an ICD, while inducibility of VF may be a non-specific sign, especially if three extrastimuli are used.[129] However, further investigations for ischemia, cardiomyopathies, or inherited channelopathies may be appropriate.

In ***nonischaemic cardiomyopathy***, VT inducibility during electrophysiology study has also been found a powerful predictors of sustained ventricular arrhythmias during follow-up.[92]

Inducible sustained monomorphic or polymorphic VT is an independent risk factor for subsequent events in patients with ***repaired tetralogy of Fallot***,[132] and ***sarcoidosis.***[133] EPS before PVR in patients with Fallot identifies a substantial proportion of patients with inducible ventricular arrhythmias that are noninducible post PVR.[134] VT may be inducible in myotonic dystrophy type 1 but its prognostic significance is not established. However induced VT may display bundle branch reentry morphology and thus and respond to bundle branch ablation.[135]

Genetic Testing

Recommendations for genetic testing in patients with ventricular arrhythmias and/or aborted sudden cardiac death are provided in Table 8.

Long-term Therapy

Long-term therapy of patients with ventricular arrhythmias depends on the underlying substrate and mechanism of arrhythmia.

General measures

Management of any identifiable **underlying disorder** (ie heart failure, significant ischemia, etc) is essential (Table 9). Beta blockers, ACEIs, ARBs and statins have been shown in many studies to reduce mortality and sudden cardiac death.[136] Antiplatelet therapy in the SOLVD trial was also associated with reduced incidence of sudden cardiac death.[137] Although there has been evidence that omega-3 fatty acids may reduce life-threatening arrhythmic events, results have not been consistent.[138,139] Statins should be used in all patients with CAD. They do not reduce the risk of VTs or cardiac arrest, but result in a 11% reduction in the risk of SCD presumably by preventing coronary events.[140]

Smoking is strongly discouraged, and abstinence from **alcohol** is recommended in cases where there is a suspected correlation between alcohol intake and ventricular arrhythmias.

Correction of **hypokalemia and hypomagnesemia** are useful. Intravenous magnesium prolongs sinus node recovery time, reduces automaticity, and homogenise transmural ventricular repolarisation. It has been reported to be useful in preventing atrial fibrillation and ventricular arrhythmias after cardiac and thoracic surgery; in reducing the ventricular response in acute onset atrial fibrillation, including patients with Wolff-Parkinson-White syndrome; and in the treatment of digoxin-induced supraventricular and ventricular arrhythmias, multifocal atrial tachycardia, and polymorphic ventricular tachycardia or ventricular fibrillation from drug overdoses.[141,142] Intravenous magnesium has not been found useful in monomorphic ventricular tachycardia, and shock-resistant ventricular fibrillation.

Antiarrhythmic Drugs

With the exception of **beta blockers**, no currently available antiarrhythmic agent (Table 10) has been shown in randomized clinical trials to reduce mortality in patients with ventricular arrhythmias or to prevent sudden cardiac death in patients prone to arrhythmias.[143,144] In a meta-analysis of RCTs addressing the role of **amiodarone** for the prevention of sudden death, amiodarone reduced the risk of sudden cardiac death but not overall mortality, and was associated with a two- and five-fold increased risk of pulmonary and thyroid toxicity.[145] Concerns about increased mortality with amiodarone used in various clinical settings have been raised.[76,146-148] ICD remain the only means to reduce mortality in patients prone to life-

threatening ventricular arrhythmias (primary prevention) with clinical life-threatening ventricular arrhythmias (secondary prevention). In patients with ICD, **sotalol** may be used for reduction of the number of shocks in the absence of severely depressed LV function.[149] Mexiletine may also be useful in patients with ICD when catheter ablation is failed.[68]**Amiodarone** with **beta blockers** may be considered in patients who do not meet the criteria for an ICD. This combination is preferred to sotalol due to its proarrhythmic potential.[150] However, in the German DEVICRE Registry, amiodarone in combination with a beta blocker was not associated with a significantly reduced risk of ICD discharges or syncopal events compared to beta blocker only therapy, and data suggested suggested an increased all-cause mortality under amiodarone therapy, especially in the subgroups of patients with sinus rhythm or severely reduced left ventricular function.[151] In patients with recurrent VAs and structural heart disease who have limited treatment options, **quinidine** can be useful, particularly as a short-term therapy.[67] Quinidine has also been found effective in short-coupled VF and should be considered in patients with recurrent VF episodes or frequent appropriate ICD therapies.[7] Sodium channel blocking agents, and drugs associated with QT prolongation should be given only when absolutely necessary and under certain precautions (Figures 15 and 16). Ina phase 2 trial, ***varenicline***, a selective partial agonist of functional nicotinic acetylcholine receptors (an approved agent for smoking cessation) was found to reduce PVC burden and nonsustained VT incidence in post-MI patients without evidence of a proarrhythmic effects.[152] Significant antiarrhythmic drug interactions are presented in Appendix 3.

Implantable cardioverter defibrillator

General indications for Implantable cardioverter defibrillators (ICD) are presented in Table 11. Additional indications in patients with heart failure, post-MI, cardiomyopathies, and genetic channelopathies are discussed in the relevant chapters. Summarizing recommendations by ACCF/AHA/HRS 2017 GL on ventricular arrhythmias and sudden cardiac death, and ESC 2022 GL on ventricular arrhythmias, an ICD is indicated in:

- **Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.**
- **Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.**
- **Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation induced at electrophysiological study.**
- **Ischemic (>40 days post-MI) or dilated cardiomyopathy and LVEF <=35%.**
- **Post MI (>48h) sustained VT/VF, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.**

- **Post-MI (>40 days), NSVT, LVEF<40%, and inducible VF/VT.**
- **Sustained VT and normal ventricular function, cardiomyopathies and risk factors for sudden death, and genetic channelopathies with syncope.**

Other indications in specific clinical settings are discussed under Clinical Forms of VT. For optimum ICD programming see the relevant Chapter.

Current guideline-recommended medical therapy for at least 3 months is mandatory for patients with a newly diagnosed LVEF ≤35%, of ischaemic aetiology or not. If LVEF remains ≤35% or lower after this period and therefore the risk for SCD persists, an ICD is recommended for primary prevention of SCD.

Wearable cardioverter-defibrillator

The wearable cardioverter-defibrillator is an option for patients at risk of SCD who are not immediate candidates for ICD therapy (Table 11).[153] In the VEST trial on post-MI patients with LVEF<=35%, it reduced total mortality, although not significantly arrhythmic death defined a composite of sudden death or death from ventricular tachyarrhythmia at 90 days.[101] This trial, however, was probably underpowered, only 41% of patients wore the device at the end of follow-up, and of the 25 patients in the device group with adjudicated sudden death, 16 were not wearing the defibrillator at the time of death. In the SCD-PROTECT registry in patients with newly diagnosed reduced LVEF of ischaemic or non-ischaemic origin, there was a substantial risk of sudden cardiac death due to VT/VF during the early phase of guideline-recommended medical therapy optimization that was prevented by a wearable cardioverter-defibrillator.[154]

Catheter ablation

Catheter ablation is currently indicated for VT in various clinical settings either for eradication of the arrhythmia, as occurs in idiopathic VT, or for reducing the arrhythmia burden and consequent implantable cardioverter defibrillators (ICD) shocks in patients with ischaemic or structural heart disease (Table 12).[8,155,156] ICD shocks are associated with diminished quality of life and increased mortality.[157,158] Anti-arrhythmic drugs (AADs) have an important role in shock reduction; however these agents often have limited efficacy and significant side-effects.[159,160] Amiodarone reduces VT recurrence and ICD shocks,[161] but may be associated with increased mortality in this respect.[147] Thus, in cases of frequent monomorphic VT or VT storm in patients with ischaemic cardiomyopathy who already have an ICD, ablation can reduce the number of ICD shocks (without reducing mortality) and is preferable to drug therapy escalation.[162] In ischemic patients with ventricular arrhythmias, an initial strategy of catheter ablation leads to a lower risk of a composite primary end-point event than antiarrhythmic drug therapy (VANISH 2 RCT).[163] Preventive VT ablation before

ICD implantation does not reduce mortality or hospitalization for arrhythmia or worsening heart failure during 1 year of follow-up, but patients subjected to ablation have fewer ventricular arrhythmias and ICD interventions (BERLIN VT RCT).[164] Early catheter ablation of monomorphic VT at the time of ICD implantation (PAUSE-SCD RCT)[165] or after the first appropriate shock (PARTITA RCT), [166] significantly reduces the composite primary outcome of VT recurrence, CV hospitalization, and death.

In-hospital mortality rates for VT catheter ablation depend on the clinical condition of the patient.[167] In average, they are 2.5% for ischemic heart disease, 1.5% for non-ischemic structural heart disease, and 0.1% for patients without apparent heart disease.[168,169] After ablation, 30-60% of patients may also develop asymptomatic brain infarcts detected by MRI, and approximately half of them have a high likelihood of cognitive impairment.[170,171] Risk scores to identify patients at high peri-procedural risk have been developed.[156]

Although catheter ablation has not been proven to improve mortality in any randomized trial, retrospective cohort studies have provided evidence that successful ablation may be associated with both a higher rate of freedom from VT and also improved survival. A retrospective analysis of outcomes of VT ablation demonstrated that freedom from recurrent VT is associated with a significant reduction in all-cause mortality, independent of ejection fraction and heart failure status.[172] A meta-analysis of 8 cohort studies with 928 post-infarction VT patients demonstrated that patients who have VT rendered non-inducible by an ablation procedure have a lower VT recurrence rate compared with those who still have inducible arrhythmias after the ablation. Noninducibility translated to a significant reduction in all-cause mortality compared with partial success.[173] In a multicenter observational study of post-infarction patients, noninducibility was associated with a 35% reduction in mortality.[120] A similar finding has been reported in dilated cardiomyopathy patients.[174]

Ablation techniques

In haemodynamically stable VT ablation is guided by ***activation mapping*** and ***tachycardia entrainment*** techniques. Electroanatomic activation mapping is particularly useful in focal VT, but it can also be used to identify VT exit sites and diastolic corridors (isthmuses) of a reentrant VT. VT entrainment allows differentiation of critical isthmuses from bystanders. (Figure 17). [8] For haemodynamically unstable VT pace mapping during sinus rhythm can identify the site of origin of focal VTs, and the tachycardia exit site in reentrant VTs.[175]

In predominantly ***substrate ablation*** strategies abnormal electrograms such as fractionated/late potentials after the QRS complex, and local abnormal ventricular activity (LAVA) within the QRS are targeted. Creation of empiric ablation lines during sinus rhythm , electrical isolation of the scar, ablation of the core portion of the scar, and more extensive endocardial and epicardial scar ablation strategies (scar homogenization), have also been proposed.[8] Substrate ablation may offer similar or even higher success rates to

conventional ablation,[176] and is less cumbersome than mapping during VT. However, it does not distinguish bystander regions from re-entry circuit sites and therefore broad areas of ablation are often necessary, thus raising concern about the haemodynamic consequence of extensively ablating in proximity to normal myocardium at the edge of scar.

Indications for ***epicardial ablation*** include an unsuccessful prior endocardial ablation procedure, and VT unrelated to coronary artery disease (i.e., DCM, ARVC/D, HCM, and Chagas cardiomyopathy). The presence of midmyocardial or subepicardial scar on CMR may be useful in identifying patients that are likely to require epicardial mapping for successful abolition of VT.[177] VT circuits in post-MI patients are usually subendocardial, but up to 30% of patients may require epicardial ablation for mid-myocardial or sub-epicardial circuits.[178] A number of ECG criteria suggest an epicardial VT exit.[179] The most helpful criterion is delayed onset of ventricular activation with a pseudodelta >34 ms, and an RS >121 ms. [180]

Stereotactic radioablation is a new option for ablation of ventricular tachycardia where traditional ablation offers limited success.[181]

Clinical Forms of Ventricular Arrhythmias

Premature Ventricular Contractions and Non-sustained VT in Normal Subjects

Population-based studies have demonstrated that up to 69% of apparently healthy persons may have at least one premature ventricular contraction (PVC) on 24-h ECG recordings,[182] and even on a 2-minute rhythm ECG strip, ≥1 VPC is seen in 5.5% in the middle-age (45 to 64 years old).[183] In patients investigated for irregular pulse notification (iPhone or Apple Watch) up to 9% had frequent VPCs.[184]

The prognostic significance of PVC is apparently normal subjects had been controversial, but it seems that a higher frequency of PVCs is associated with reduced LVEF, incident heart failure, and increased mortality.[185-188] The effect appears to be additive when atrial premature beats occur concurrently.[186] In an analysis of NHANES III data, no significant association of PVC with total mortality was detected,[189] but, atrial premature beats were associated with total and cardiovascular mortality. [189] Rarely, right and left ventricular Purkinje-related or even RVOT PVC, may lead to polymorphic VT/VF. Frequent ventricular ectopy detected during exercise in apparently healthy persons, indicates increased cardiovascular mortality within the next decades,[190] but this seems to be true when ectopic beats occur during recovery.[191,192]

Ventricular ectopic beats are frequently observed at exertion in both recreational and elite **athletes**. They have been characterized as "***common***" i.e. LBBB/inferior axis, typical

RBBB and narrow QRS (<130 ms), and monomorphic without short coupling intervals, or "***uncommon***" i.e. LBBB/intermediate or superior axis, atypical RBBB and wide QRS (≥130 ms) and polymorphic with short coupling intervals.[193] Common ventricular ectopic beats are a physiological adaptation to training, whereas uncommon ventricular ectopic beats are not directly related to the physiological consequences of athletic training and may warrant closer evaluation.[194] Atypical common PVCs with emergence during exercise and >10 burden need a thorough investigation.[195]

The prevalence of **NSVT** in apparently healthy persons has been reported to be in the range of 0.5 to 1%.[196] A distinction between monomorphic and polymorphic NSVT is essential for prognostic and diagnostic purposes, and patients should be thoroughly evaluated for underlying cardiac disease (Figure 14).[197] Exercise-induced NSVT in older persons (>60 years) has not been found to carry an adverse prognosis.[198] In trained athletes, frequent PVC and NSVT may occurs at ambulatory monitoring or during exercise, and have no prognostic significance. [199-201] In the Apple Heart Study, among patients investigated for irregular pulse notification (iPhone or Apple Watch) up to 6.4% had NSVT.[184]

Therapy

Specific antiarrhythmic drug therapy is not indicated for PVCs or NSVT (Tables 13 and 14, Figures 18 and 19). In symptomatic cases β1 selective blockers may be given. Treatment of underlying hypertension is essential.[202] Catheter ablation may also be tried in drug-resistant, frequent monomorphic VPBs. In patients with frequent VPBs originating from the RVOT, catheter ablation is more efficacious than drug therapy, especially when there is a QS morphology in lead I.[203] Catheter ablation is especially indicated when PVC-induced cardiomyopathy is suspected.[185]

Idiopathic VT and VPBs

Idiopathic VT indicates VT that occurs in the absence of clinically apparent structural heart disease. Approximately 2/3 of idiopathic VT originate in the RV, and the rest in the LV (Figure 20). NSVT originating from the RVOT may occasionally cause syncope, but the risk of death is very low. However, malignant ventricular arrhythmias and sudden death have been reported in patients with ventricular ectopic activity.[204-206] In patients with apparently idiopathic non-sustained ventricular arrhythmias, the presence of a specific midmyocardial/subepicardial ring-like nonischaemic scar identified by late gadolinium enhancement (LGE) CMR, is associated with a particularly high risk of malignant arrhythmic events.[95] Thus, catheter ablation and ICD may be indicated in certain cases.[207]

Ventricular outflow tract arrhythmias

Idiopathic ventricular outflow arrhythmias are most probably due to triggered activity secondary to cAMP-mediated delayed after-depolarizations.[208] Defects of connexins (proteins

involved in cell to cell connections) may also be responsible.[209] Inducibility of sustained monomorphic VT (adenosine-sensitive) is possible with concomitant administration of isoprenaline in <50% of the cases of outflow tract tachycardias

These arrhythmias mainly originate from the RVOT (more often) or the LVOT below or above the semilunar valves. RVOT tachycardias produce a LBBB pattern with inferior axis and R/S transition beyond V_3. LVOT tachycardias usually produce a RBBB morphology with inferior axis or a LBBB morphology, inferior axis, and R/S transition at V_1 or V_2, due to the more posterior location of LVOT compared to RVOT.[210] LBBB morphology with notching in the limb leads and deep S waves in V1-V3 suggests a *free wall* origin of RVOT PVCs, whereas a r wave in V_1 and large R waves in the inferior leads suggests the *septum* or *pulmonary artery cusps* as site of origin.[211,212] If the R/S transition is in V_3, the tachycardia may originate from either the RVOT or the LVOT.[212] Ventricular outflow tract PVCs originating at the LV ostium and left or right *coronary cusps* (and usually at their junction) have a variable QRS morphology.[213] In outflow tract arrhythmias an *epicardial* site of origin is rare and may be indicated by a QRS>200 ms.[212]

Several ECG criteria to predict the origin of outflow tract ventricular arrhythmias have been published but they apply to PVCs rather than VT in this setting.[214-216] Rarely, polymorphic VT may also originate in the RVOT and usually, but not invariably, is induced by short-coupled ectopic beats.[25]

His-Purkinje System

Multifocal ectopic Purkinje-related premature contractions (MEPPC) syndrome is a rare cardiac disorder characterized by frequent multifocal ectopic ventricular beats, originating from various ectopic foci along the fascicular-Purkinje system, due to mutations in the *SCN5A* gene.[217] It is characterized by a high burden of frequent polymorphic PVCs exhibiting narrow QRS complexes, often presenting with both left bundle branch block and right bundle branch block patterns that disappear during a stress test. Catheter ablation is ineffective but class I antiarrhythmic drugs, such as flecainide and quinidine, which may reduce ventricular arrhythmias.[217]

Reentrant arrhythmias involving the His-Purkinje system include bundle branch reentry (typical or reverse), interfascicular reentry, and reentry through a concealed nodofascicular pathway.[18,19] Right bundle branch reentry due to longitudinal dissociation of the right bundle is also theoretically possible. [218,219]

Bundle branch reentry may be seen in apparently normal hearts,[220] and genetic causes have also been identified.[221] Mostly, however, they occur in patients with ventricular disease. Although these tachycardias are usually unstable, the 12-lead ECG when obtainable usually show a LBBB pattern with a leftward axis although a normal axis or a RBBB pattern with a leftward axis can also be seen.[222] A narrow-complex ECG during bundle branch

reentry has been attributed to right bundle reentry due to longitudinal right bundle dissociation, although a focal origin in the proximal right bundle could also be possible.[218,219] The necessary condition for bundle branch reentry is prolonged conduction in the His-Purkinje system, and this may be reflected in the HV interval which is prolonged during sinus rhythm and prolonged or equal to the baseline sinus rhythm during VT. The circuit involves the right and left brunch bundles with antegrade conduction occurring most of the time through the right bundle.[218,222] Bundle branch reentrant tachycardias usually respond to selective right bundle branch ablation.

Fascicular reentry tachycardias typically are due to reentry within the Purkinje network (interfascicular or intrafascicular), are verapamil-sensitive, and involve one or two of the fascicles of the left bundle branch. Although they can be idiopathic, they are more common in structurally abnormal hearts.[223] The mechanism is reentry that appears to involve a portion of the Purkinje fibres, most often in the region of the left posterior fascicle, giving rise to a characteristic right bundle branch block (RBBB) and left axis QRS configuration (although right axis deviation may also occur) and a QRS duration that is only slightly prolonged. [17,18,224] Tachycardias or premature ventricular beats originating from the proximal left anterior fascicle have a morphology close to that during sinus rhythm and can be safely ablated from the right coronary cusp.[225] Catheter ablation is accomplished by targeting the earliest or mid-diastolic Purkinje potential or by entrainment techniques.[8]

Other Sites of Origin

Tachycardias may also originate in the ***AV annuli*** either in the tricuspid (LBB pattern) or the mitral annulus (RBBB pattern or RS in V_1 and monophasic R or RS in V_2-V_6).[226] Tachycardias from the ***papillary muscles*** have a focal (no-reentrant) mechanism not involving the Purkinje network but, usually, the posterior papillary muscle, and present with have RBBB morphology.[227] Tachycardias may also originate around the His bundle or in the ***intraventricular septum*** (LBBB with inferior axis).[228]

Prognosis and Therapy

NSVT originating from the RVOT may occasionally cause syncope, although the risk of death is very low. However, malignant ventricular arrhythmias and sudden death may occur in patients with RVOT ectopic activity.[204-206] Short cycle length during NSVT, especially a second cycle length of NSVT < 317 ms, and history of syncope have been proposed as predictors of coexistence of VF or polymorphic VT.[229 230]

Differentiation from ARVC (see cardiomyopathies) is crucial, especially since rarely idiopathic VT may arise in the RV body, and subjects with RVOT VT, as well as with LVOT VT, may have subtle structural and functional abnormalities as detected by magnetic resonance imaging.[231] A detailed discussion on differential diagnosis is found in Chapter 40.

Frequent PVCs may also be the cause of ***tachycardia-induced cardiomyopathy***. For a

detailed discussion see the relevant Chapter.

Catheter ablation is the treatment of choice for idiopathic VT with success rates exceeding 80% for RVOT VT and fascicular tachycardias (Figure 21, and Tables 15-17). [232] It is especially indicated in tachycardia-induced cardiomyopathy in patients with a 24h PVC burden >10%. Catheter ablation of tachycardias from the papillary muscles may be difficult due to the contraction of the muscle. Success rates also are lower with epicardial or intraseptal sites of origin. The most common major complication is tamponade or pericardial effusion, reported to occur in 1-2% of cases.[8] Calcium channel blockers and beta blockers may also be considered.

Idiopathic VF

Idiopathic VF is diagnosed by exclusion of apparent causes, although a latent cardiomyopathy or channelopathy cannot be excluded. Several mutations of ion channels coding and other genes have been associated with idiopathic ventricular fibrillation. ICD is recommended in survivors (Table 18 and Figure 22). Certain cases of idiopathic VF can be attributed to specific PVC triggers that may be mapped and ablated. In patients without structural heart disease, polymorphic VT or VF can be initiated by isolated spontaneous PVCs that can be localized to the right or left Purkinje system in most of the cases and sometimes to the right ventricular outflow tract. [233,234] PVC triggers from the papillary muscles of the right and left ventricle and the right ventricular moderator band have also been implicated in polymorphic VT and VF.[235,236] VF storm in post-MI patients often is triggered by PVCs originating in the Purkinje fibers at the borders of scar, and also may respond to catheter ablation.[237] Published data on the long term results of catheter ablation in all of these settings are limited.

Short-coupled torsade de pointes or **pseudo TdP** is a rare variant of polymorphic VT of unknown aetiology. It is characterized by an extremely short-coupled interval of the first premature ventricular contraction (<=350 ms) initiating the tachycardia.[6] This predominantly affects young patients who often present with unclear syncope and a positive family history for SCD. In most cases torsade deteriorates into VF and an ICD is recommended for survivors with a definitive diagnosis. Short-coupled VF was responsible for at least 6.6% of unexplained cardiac arrest in otherwise healthy individuals of the CASPER registry.[7] It may occur in patients with or without QT prolongation, and may respond to quinidine.[6 7]

Ischaemic Heart Disease

Acute coronary syndromes

Ventricular arrhythmias in ACS are discussed in detail in ACS Therapy.

Chronic IHD

Compared with the pre-reperfusion era, late ventricular tachyarrhythmias are now less common, but they are still documented in approximately 20% of patients with recent MI (more than 7 days) and EF<0.40 within the next 2 years.[96]

NSVT after discharge from MI in the era of reperfusion and use of beta blockers, is not be an independent predictor of mortality, especially after ejection fraction is taken into account.[197] It may carry an adverse prognostic significance in patients with LVEF>35%.[238]

Monomorphic VT is usually due to scar-related reentry and its incidence has been reduced from 3% to 1-2% in the reperfusion era. A LBBB configuration in Lead V1 (dominant S wave) suggests an exit site in the right ventricle or the inter-ventricular septum. A dominant R wave or RBBB pattern in V1 indicates a LV exit site. The QRS axis defines VT origins in the vertical plane; an inferiorly directed QRS axis suggests a superior or anterior wall exit whereas a superiorly directed axis indicated an inferior wall exit. The precordial leads are more indicative of directionality in the horizontal plane. Deep S waves in the apical leads (V3–V6) indicate exit sites at the apex whereas prominent R waves in these leads point to a basal origin of activation. Sub-epicardial origin of VT is suggested by wider QRS complexes and delayed initial upstrokes in the precordial leads. Several algorithms have been published for identification of the exit site if postinfarction VT from the 12-lead ECG (Figure 23).[239-241]

Polymorphic VT or VF may be due to acute ischemia (acute coronary syndrome or spasm) or in the context of scar-related VT that degenerates into VF.[86,148]

Therapy. *Monomorphic VT* usually does not respond to revascularization.[242-244] *Polymorphic VT* or VF may or may not respond to revascularization and reassessment by means of LVEF and EPS if LVEF>35% is indicated 3 months after revascularization.[243,245-248] New-onset ventricular arrhythmias, especially VF occurring after the first 48h of cardiac surgery are associated with increased long-term mortality, especially in older patients with reduced LV function.[249] Flecainide,[102] and sotalol [150] increase mortality, whereas amiodarone shows a trend towards reducing arrhythmia episodes but without significantly affecting total mortality (EMIAT and CAMIAT studies),[250,251] or even showing a trend towards increasing it.[252] Therefore, no antiarrhythmic drug is suitable for primary prevention of cardiac death with exception for β-blockers, which were shown in several studies to reduce total and cardiac mortality in postinfarction patients, at least during the first year post-MI.[253] ICD implantation is recommended in patients who develop sustained VT/VF more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.[254] In addition, if new-onset VF occurs >48h after cardiac surgery and no reversible cause can be found, ICD implantation might be considered earlier.[249] Focally triggered VF storm in post-MI patients, usually originating in the Purkinje fibers at the borders of the scar, may respond to catheter ablation.[237]

Certain patients with *NSVT* in the context of reduced LV function need an ICD. In the

MADIT study,[255] on 196 patients with prior MI, EF≤35%, a documented episode of NSVT, and inducible and nonsuppressible sustained VT, ICD yielded a 54% reduction in total mortality compared to conventional (primary amiodarone) therapy during mean 27-month follow-up. The MUSTT enrolled 704 patients with coronary artery disease, asymptomatic NSVT, EF≤40%, and inducible sustained VT.[256] The risk of cardiac arrest or death from arrhythmia among patients who received treatment with ICD was significantly lower than that among patients who did not receive ICDs (relative risk, 0.24; 95% confidence interval, 0.13 to 0.45; *P <0*.001). Subsequently, in the MADIT II on 1232 postinfarction patients with markedly depressed LV function (LVEF≤30%), ICD resulted in 26% reduction of mortality over a 8-year follow-up, regardless of presence or absence of other risk stratifiers including NSVT.[257] Recommendations are provided in Figures 19-23, and Tables 24 and 25.

In patients ***without ventricular arrhythmias***, ICDs should be considered at least 40 days after MI in order to achieve reduction of total mortality (DINAMIT and IRIS studies),[258,259] and ≥3 months from a coronary revascularization procedure (Table 19, and Figures 26-28).[260,261] According to most published data, patients with a recent myocardial infarction do not benefit from ICD especially when they have LVEF <25% and/wide QRS,[262] but this is debatable.[263] Both DINAMIT and IRIS had excluded patients with sustained ventricular arrhythmias during this period, and sudden cardiac death was reduced despite no effect on overall mortality in the DINAMIT trial.[258] There is a substantial (10%) risk of arrhythmias within the first month following MI,[264] and between the first and three months after CABG.[265] There has also been some evidence for a benefit of early ICD implantation if sustained monomorphic VT (CL>=200 ms lasting more than 10 sec) is induced at electrophysiology study, 9 days post-MI,[266] whereas non-inducibility carries a good prognosis even in LVEF<30-35%.[121] In the DAPA RCT (underpowered) early ICD (within 4 days) following primary PCI in patients with LVEF < 30% within 4 days after STEMI, or primary VF, or Killip class ≥2 and/or TIMI flow < 3 after PCI, improved total and cardiac mortality.[267] Current guidelines recommend that patients with an initially reduced LVEF who are possible candidates for ICD therapy should undergo reevaluation of LVEF >=40 days after discharge.[254] During this period, 1.6% of them may have VT/VF, and the use of wearable cardioverter-defibrillator might be considered.[268]

Indications for *ICD implantation* are presented in Table 8 (see also Chapter on STEMI and Chapter on HF). ICD are generally indicated in patients who present with monomorphic VT or VF, and for patients with IHD (>40 days after MI and 90 days after revascularization) and:

LVEF<35% and NYHA I- III, or

LVEF<40% in the context of NSVT and inducible VT at EPS

In addition, ICD is recommended in:

Sustained VT/VF, >24 h after MI and not due to a treatable cause.

There have been concerns about the efficacy of ICD in the elderly (see Chapter 68.[269]

Catheter ablation is useful for reducing ICD discharges, and can be accomplished even for unmappable VTs. In post-infarction patients, several studies have reported that all inducible VTs were eliminated by ablation in 56-77% of patients. The procedure-related mortality rate was 0.5-5%, the VT recurrence rate within the next year was 12-50%.[8] Early referral of patients for catheter ablation results in improved freedom from VT compared with later referral.[270] Catheter ablation has also been shown to be effective in the treatment of VT storm in patients receiving long-term AAD therapy.[271] Procedure-related complications have been reported to occur in approximately 7% of patients.[8,172,272] Ablation-related early (<30 days) mortality ranges up to 3% in experienced centers, with more than one-half of patients dying before hospital discharge, most often because of refractory VT or heart failure (Table 2). Predictors of early mortality include LVEF, chronic kidney disease, presentation with VT storm, and the presence of unmappable VTs.[273] The reported 1-year mortality rate following VT ablation is 18%, with the primary causes of death being recurrent VT (37.5%) and heart failure (35%).[274] Other complications consist of cardiac perforation in 1.5%, major vascular injury in 2.3%, uncontrollable VT in up to 2.6%, high-degree AV block in 0.9%, coronary artery injury in 0.2%, and stroke or transient ischemic attack in 0.5%.[8]

Alternatively, beta blockers and amiodarone may prevent ICD shocks and are more effective than sotalol in this respect, but with a higher rate of complications.[149]

Heart Failure

In patients with heart failure and LVEF<30-40%, the reported prevalence of ***NSVT*** is 30-80%.[197,275] Although the GESICA-GEMA investigators identified NSVT as an independent predictor of total mortality in patients with heart failure (35-40% IHD) and LVEF<=35%,[276] in the CHF STAT (70-75% IHD) after adjusting other variables and especially for LVEF, NSVT was not an independent predictor of sudden death or total mortality in patients with heart failure and LVEF<35-50%. [277] Similar results were published by the PROMISE Investigators.[278] Only during the recovery period after exercise frequent ventricular ectopy has been found to carry an adverse prognostic significance in patients with heart failure.[279] However, in a recent analysis of ICD interrogation data in the SCD-HeFT population, long runs of rapid rate NSVT were associated with subsequent appropriate ICD shocks and an increase in mortality.[280]

Optimal medical therapy (*ACEI/ARBs, beta blockers and mineralocorticoid receptor antagonists*) is essential to reduce total mortality and sudden cardiac death in heart failure with a relatively preserved EF of 35-40% (ESC 2015 GL on VA and SCD, I-A). In patients with heart failure and LVEF<35% the GESICA study (516 patients of whom 75% with DCM) found *amiodarone* beneficial by means of reducing mortality and hospital admissions.[281]

However, the much larger SCD-HeFT (2521 patients, 52% ischemic), indicated substantial benefit only from ICD therapy in patients with low EF (<36%) and NYHA classes II and III. *ICD* therapy was associated with a decreased risk of death of 23 percent, and an absolute decrease in mortality of 7.2 percentage points after five years in the overall population.[76] In patients not eligible or who have no access to ICD, amiodarone may reduce the risk of sudden cardiac death but not overall mortality,[145] and it may increase noncardiac mortality in patients with NYHA class III heart failure.[282] Dronedarone is detrimental in heart failure patients.[283] There has been some evidence (MADIT-CRT) that ventricular resynchronization may reduce episodes of VT or VF in patients who respond it, whereas non-responders may have a higher event rate.[284] LVEF values and QRS duration do not appear to directly modify the survival benefit of ICD in patients with baseline LVEF<35%.[262] Changes in LVEF with medical therapy are inversely associated with all-cause mortality and appropriate shocks for ventricular tachyarrhythmias. In patients whose follow-up LVEF improved to >35%, the risk of an appropriate shock remains but is markedly decreased.[285] Amiodarone with a beta blocker or sotalol,[149] may be used to reduce appropriate shocks. Sudden death characterizes the mode of death in 30–50% of patients with chronic heart failure and a reduced ejection fraction. Death may be due to a first-time ventricular tachyarrhythmia that is responsive to the shock delivered by an ICD, or due to acute mechanical failure, which manifests as asystole, bradyarrhythmia, or electromechanical dissociation, or as incessant ventricular fibrillation that persists despite repetitive ICD discharges. Thus, 30–70% of the sudden deaths in clinical trials of HFrEF are not prevented by an ICD.**[286]** The MADIT-ICD benefit score weighs patient-specific risk of VT/VF against the competing risk of non-arrhythmic mortality in order to facilitate the improved selection of patients for primary prevention ICD therapy.**[287]**

Detailed recommendations for ICD and CRT are discussed in the Chapter on HF. The management of ventricular arrhythmias in acute heart failure is discussed in the relevant chapter.

Cardiomyopathies

Dilated Cardiomyopathy

Although VT or VF are the most common cause of death in dilated cardiomyopathy (DCM), other causes such as bradycardia, electromechanical dissociation, and pulmonary embolus account for up to 50% of sudden cardiac death in patients with advanced heart failure. NSVT on Holter, VT inducibility during electrophysiology study, and late gadolinium enhancement on cardiac magnetic resonance have been associated with sustained ventricular arrhythmias during follow-up in nonischemic dilated cardiomyopathy. ***NSVT*** may be detected in 40-50% of patients with DCM (deleted). LVEF and NSVT have been found significant predictors of

arrhythmic events,[288] but after medical stabilization with angiotensin-converting enzyme inhibitor and beta-blocker, the number and length of NSVT runs did not increase the risk of MVA in patients with LVEF ≤ 0.35 as opposed to those with LVEF > 0.35.[289] In the Marburg Cardiomyopathy Study,[77] on univariate analysis nonsustained VT and frequent ventricular premature beats showed a significant association with a higher arrhythmia risk, but on multivariate analysis only LVEF was found to be a significant predictor of major arrhythmic events. The combination of LVEF<=30% and NSVT denoted an 8-fold higher risk for subsequent arrhythmic events compared to LVEF<=30% and no NSVT. Signal-averaged ECG, baroreflex sensitivity, heart rate variability, and T-wave alternans were not helpful for arrhythmia risk stratification. In a more recent study, NSVT on Holter and VT inducibility during electrophysiology study were powerful predictors of sustained ventricular arrhythmias, independent of late gadolinium enhancement on cardiac magnetic resonance.[92] Midwall fibrosis identified by late gadolinium enhancement CMR, genetic testing for identification of malignant mutations and other electrocardiographic markers may be useful for risk stratification purposes.[109] Actually, myocardial scar detected by CMR is a more powerful risk stratification factor than LVEF.[93,94] LGE+ and LVEF<=35% appear to be strong predictor of ventricular arrhythmias and sudden death.[94] An EP study be useful in inducing a monomorphic VT that could be amenable to catheter ablation,[290] and as a risk stratifier since inducibility of ventricular arrhythmias,[291] and especially polymorphic VT or VF,[292] indicates increased likelihood of subsequent ICD therapies.

In patients with dilated or ischaemic cardiomyopathy and intraventricular conduction defects, VT may be due to ***bundle branch reentry***. Bundle branch reentrant tachycardia may also occur in the absence of any myocardial (see Idiopathic VT).[220] Catheter ablation is the treatment of choice in bundle branch reentry.

The majority of VT in non-ischemic cardiomyopathy arise near the **s**uperior and lateral perivalvular aortic and mitral regions, and many of them are epicardial in origin.[179] The use of contrast enhanced-CMR helps to identify an endocardial vs. epicardial origin. [293]
The role of ICD for primary prevention in DCM is controversial, but current guidelines endorse its use in patients with LVEF <= 35% and NYHA class II-III heart failure.[294-297] There was significant reduction of sudden death and a trend for reduced mortality with ICD in patients with non-ischemic heart failure and non-sustained VT (DEFINITE),[298] but, these results were not reproduced in the AMIOVIRT study [299] that failed to detect any difference between amiodarone and ICD in patients with DCM, and NSVT or the CAT study [300] that reported no difference between ICD and controls in DCM. Similarly, no benefit of ICD implantation in patients with nonischemic heart failure was seen in the DANISH trial, but 58% of patients in the medical therapy arm had received a CRT device, and ICDs reduced mortality in patients <59 years of age.[295] During a median follow-up of 9.5 years in the

DANISH trial, ICD implantation did not provide an overall survival benefit in patients with non-ischemic systolic heart failure. In patients <70 years, ICD implantation was associated with a lower incidence of all-cause mortality, cardiovascular death, and sudden cardiovascular death.[301] In subsequent meta-analyses, ICD implanted for primary prevention in non-ischaemic patients reduced sudden cardiac death,[302] and total mortality.[296] However, in an extended follow-up (13 years) of the DANISH, ICD did not reduce all-cause death but did reduce sudden cardiovascular death, with possible greater benefit in younger patients (<70 years).[303] The value of amiodarone is debatable. The overall success rate with ***catheter ablation*** than for patients with nonischemic cardiomyopathy (38 to 67%) is lower than that for patients with postinfarction ischemic cardiomyopathy (56 to 77%), [172,304-307] and an epicardial approach may be necessary. Complication rates are similar to those described in the ischaemic cardiomyopathy section. Catheter ablation is more efficacious for bundle branch re-entry with up to 100% success rates having been reported, but at a risk of up to 40% for inadvertent complete heart block.[272] Risk stratification and therapy of recurrent arrhythmias are presented in the Chapter on DCM.

Hypertrophic Cardiomyopathy

In hypertrophic cardiomyopathy 20 to 30% of patients may have ***NSVT***,[197] that is now considered a high risk factor. [100] ***Sustained VT*** has a similar prognostic impact to SCD, although it is relatively uncommon in HCM, and raises suspicion of a left ventricular apical aneurysm.[308] There are little published data on the results of VT ablation in patients with **HCM**, using a combined endocardial/epicardial approach.[309-312] Risk stratification and indications for ICD are discussed in the Chapter on HOCM.

Arrhythmogenic Right Ventricular Cardiomyopathy

Ventricular ectopic beats or runs of ventricular tachycardia occur early in the natural history of arrhythmogenic cardiomyopathy (AVRC). The main problem is with ARVC-associated VT that presents with inferior axis; in this case the differential diagnosis with idiopathic VT is of clinical importance. Risk stratification and indications for ICD are discussed in Chapter 40. Compared with patients with non-ischaemic dilated cardiomyopathy, patients with ARVC have better outcomes of ablation.[312] With the addition of epicardial mapping to the ablation strategy for ARVC/D patients, the success rates of catheter ablation have markedly improved.[313-315] A large, single-center study reported a 71% rate of freedom from recurrent VT following multiple procedures during a mean follow up of nearly 5 years.[315] Risk stratification and indications for ICD are discussed in the Chapter on ARVC.

Other Cardiomyopathies

The association between infiltrative cardiomyopathies and ventricular arrhythmias and sudden death is well documented. Specific conditions are discussed in relevant chapters on cardiomyopathies. Complex ventricular arrhythmias are common in **amyloidosis** (57% of

patients have PVCs, and 18% NSVT) and carry prognostic significance.[316] Cardiac **sarcoidosis** may present with non-sustained polymorphic or monomorphic VT that usually responds to steroids. Usually VT is either Purkinje-related (QRS<170 ms), or scar-related and may respond to catheter ablation.[317] Its clinical phenotype may mimic ARVC. An algorithm including a PR interval of 220 ms, the presence of an R' wave, and the surface area of the maximum R' wave in leads V1 through V3 of 1.65 mm^2 is sensate and highly specific for diagnosing CS.[318] Spontaneous development or EPS-induction of sustained monomorphic VT is an ominous sign and ICD may be indicated.[133] Catheter ablation in patients with cardiac sarcoidosis is challenging because of the complex underlying substrate. However it is feasible in selected patients and results in reduced arrhythmia burden.[319,320] Reported success rates approach 50% with a 5% risk of complications.[272] Patients with **Chagas' cardiomyopathy** presenting with either sustained VT or NSVT have a major risk for mortality in the presence of moderate LV systolic dysfunction (LVEF<40%).[321]

Congenital Heart Disease

Conditions that have been associated with the greatest risks of late sudden death are tetralogy of Fallot, D - and L -transposition of the great arteries, aortic stenosis, and functional single ventricle or significant systemic or single ventricular dysfunction. Periodic Holter monitoring is indicated in these patients, and electrophysiologic assessment is indicated in the presence of unexplained syncope.[322] Most data on patients with adult congenital heart disease are derived from patients with operated ***tetralogy of Fallot***. Anatomical isthmuses critical to the VT reentrant circuit often are identified between the septal defect patch or ventriculotomy and the pulmonary valve, and between the tricuspid annulus and the outflow patch or septal defect patch.[323] Part of the circuit may also be mapped at the left side of the ventricular septum and left-sided ablation may be successful.[324] Ablation offers an approximately 80% freedom from VT within the next 10 years.[323,325] Recommendations for the management of patients with congenital heart disease are presented in ACHD.

Valvular Disease

In patients with valvular disease the incidence of nonsustained ventricular tachycardia is considerable (up to 25% in aortic stenosis and in significant mitral regurgitation) and appears to be a marker of underlying left ventricular pathology.[326] The condition of ***arrhythmic mitral valve prolapse*** is discussed in the Chapter on Mitral Regurgitation.

Hypertension

In patients with arterial hypertension nonsustained ventricular tachycardia is correlated to the degree of cardiac hypertrophy and subendocardial fibrosis.[202] Approximately 12-28% of patients with hypertension and left ventricular hypertrophy present nonsustained ventricular tachycardia as opposed to 8% of patients with hypertension alone.[327]

Other Conditions

Acute myocarditis may be complicated by conduction disturbances or ventricular arrhythmias. Giant-cell myocarditis is a cause of monomorphic or polymorphic VT that is usually sustained and associated with high mortality. Recommendations for patients with inflammatory heart disease are discussed in the relevant Chapter.

Cardiovascular causes account for at least 40% of deaths in patients with **end-stage renal failure** and 20-30% of these are sudden.[328] Arrhythmias often occur during hemodialysis sessions and for at least 4 to 5 h afterward. During this period, hemodynamic status and fluctuations in electrolytes, especially potassium, magnesium, and calcium, are likely to play a crucial role in triggering events and should be monitored carefully. Risk factors predisposing to ventricular arrhythmias include LVH, hypertension, anemia, LV dysfunction, and underlying CAD.

Patients with **neuromuscular disorders** may present with ventricular arrhythmias or conduction defects.[329] Permanent pacemaker insertion may be considered for progressive muscular dystrophies such as myotonic muscular dystrophy type 1 (Steinert's disease), limb-girdle (Erb's) dystrophy, and Kearns-Sayre syndrome with any degree of AV block (including first-degree AV block) with or without symptoms, because there may be unpredictable progression of AV conduction disease. However, patients with myotonic muscular dystrophy type 1, as well as certain lamin A/C (LMNA- a cause of limb-girdle dystrophy), and desmin mutation carriers, may also need ICD back-up due to malignant ventricular arrhythmias.[135,330] Patients with lamin A/C mutations are prone to ventricular arrhythmias when at least two of the following independent risk factors are present: non-sustained ventricular tachycardia, ejection fraction <45%, male sex, and non-missense mutations. [331] Emery–Dreifuss muscular dystrophy is inherited as an X-linked or autosomal dominant disease caused by variants in genes encoding one or more of the proteins comprising the nuclear envelope. The two most commonly implicated genes are *EMD* (EDMD1) and *LMNA* (EDMD2).[332]
Male EMD variant-carriers have a risk of progressive heart failure and ventricular arrhythmias similar to that of male LMNA variant-carriers.[332]

Recommendations are provided in the Chapter on DCM.

Electrolyte and Metabolic Disorders

Rapid ***hyperkalemia, hypokalemia*** (< 3.5 mM), and ***hypomagnesemia*** are all associated with ventricular arrhythmias and SCD in patients with MI or even with structurally normal hearts (some of whom may have underlying channelopathies).[333] Potassium is the most abundant intracellular cation, and hypokalemia is the most common electrolyte abnormality encountered in clinical practice. Hypokalemia may be responsible for ventricular arrhythmias in subjects with hypertension and congestive cardiac failure treated with thiazide and/or loop diuretics, acute starvation, acute alcohol toxicity/withdrawal. The most significant ECG manifestation of hypokalemia is a prominent U wave. QT prolongation may also be seen.[25] Hyperkalemia affects up to 8% of hospitalized patients mainly in the setting of compromised renal function. The ECG manifestation of hyperkalemia depends on serum K^+ level. At 5.5-7.0 mmol/L K^+, tall peaked, narrow-based T waves are seen. At > 10.0 mmol/L K^+, sinus arrest, marked intraventricular conduction delay, ventricular tachycardia, and ventricular fibrillation can develop.[333] Although magnesium is the second most abundant intracellular cation, the significance of magnesium disorders are controversial partly because of the frequent association of other electrolyte abnormalities. However, IV magnesium by blocking the L-type Ca current can successfully terminate torsade de pontes without affecting the prolonged QT interval. Significant ***hypocalcemia*** and ***hypomagnesemia*** can prolong the QT interval due to prolongation in phase 2 of the action potential and hence a delay in the onset of repolarization. The long QT interval is the result of a long ST segment, and the T wave is normal in duration. ***Hypocalcemia*****,** frequently seen in the setting of chronic renal insufficiency, results in prolonged ST segment and QT interval while *hypercalcemia*, usually seen with hyperparathyroidism, results in shortening of both intervals. Occasionally, hyperparathyroidism can cause important elevations in serum calcium concentrations. Intracellular fluctuations in calcium concentration influenced by drugs (e.g., digitalis glycosides), exercise (e.g., catecholamines), and reperfusion following myocardial ischemia can trigger life-threatening arrhythmias. The protective effects of beta blockade in the latter settings may in part be due to the inhibition of calcium influx into myocytes.

Hypoglycaemia may also trigger arrhythmias and should be avoided in diabetic patients.[334]

Drug-induced Arrhythmias

With the exception of beta blockers, all antiarrhythmic drugs are proarrhythmic. In addition, drug interactions may also cause arrhythmia by means of intervening with metabolism and pharmacokinetics, such as inhibition of CYP3A4 that metabolizes certain drugs or impairment of renal function and drug excretion, and by combining drugs of similar

proarrhythmic action that was not apparent when each drug was used alone (macrolides with QT prolonging antiarrhythmics).[335]

Drug-induced Long QT syndrome

Marked QT prolongation, often accompanied by the development of torsades de pointes, occurs in ≥1% of patients receiving QT prolonging antiarrhythmic drugs and much more rarely in patients receiving noncardiac agents with QT prolonging potential (<0.01 to 0.1%).[336] Acute QTc increases (ie, ΔQTc >60 ms) are indicative of the exaggerated QTc response that accompanies increased risk of torsades de pointes/SCD in drug-induced LQTS.[337] Consumer mobile ECG devices and artificial intelligence–enabled mobile ECG devices may accurately detect QTc prolongation in settings where obtaining a traditional 12-lead ECG is not feasible.[338,339] QTc prolongation is also associated with an increased risk of stroke independent of traditional risk factors.[340] **Fluoroquinolones** that are currently on the market for example, present a very low risk of drug-induced torsades de pointes, with a frequency of this adverse event occurring at a rate of approximately 0.2 to 2.7 per million prescriptions.[341] Actually, numbers of drug-induced QT prolongation and torsades de pointes may be higher.[342] A small absolute increase in cardiovascular deaths, which was most pronounced among patients with a high baseline risk of cardiovascular disease, has been detected during 5 days of **azithromycin** therapy (47-245 additional cardiovascular deaths per million courses),[343] and a 3.7 times higher risk for arrhythmia in patients taking **clarithromycin** compared to amoxicillin.[344] Chronic exposure to azithromycin increases cardiac Na^+ current and can cause rapid, polymorphic ventricular tachycardia in the absence of QT prolongation.[345] In a meta-analysis, the risk of sudden cardiac death among patients taking macrolides was estimated as 1 :30,000.[346] In March 2013 an FDA warning was published regarding the use of azithromycin for patients who are already at risk for cardiovascular events. However, in a study on Danish national health care young and middle-aged adults, azithromycin use was not associated with an increased risk of death from cardiovascular causes compared to Penicillin V.[347] In a US case-control autopsy study of 525 presumed sudden cardiac deaths defined by standard consensus criteria and 104 matched control deaths due to trauma, QT-prolonging medications were associated with increased odds of presumed sudden cardiac death compared with deaths due to trauma, but this increased risk was specific for nonarrhythmic but not arrhythmic cause of death.[348] The risk of fatal anaphylaxis with penicillin is 1:50,000.[349]

Synthetic **opioids** and especially **methadone**, as well as the nonprescription drugs loperamide and mitragynine, and psychotropic drugs such as **clothiapine, haloperidol, prochlorperazine, thioridazine, olanzapine, quetiapine, risperidone,** and **sulpiride** are associated with increased risk of ventricular arrhythmias and sudden cardiac death.[350-352] **Clothiapine, haloperidole, henothiazines citalopram**, and **escitalopram** prolong the QT

and may increase arrhythmia propensity, especially when administered to patients with hypokalemia, abnormal T wave morphology, HCV infection, and HIV infection.[353] Use of medical cannabis is associated with an elevated of new-onset ventricular arrhythmias.[354] **Tricyclic antidepressants** such as amitriptyline are also associated with increased risk for modest QT prolongation, while selective serotonin reuptake inhibitors such as sertraline may be associated with much less risk.[355,356] An algorithm to reduce the risk of malignant arrhythmia in patients to be treated with psychotropic medications has been proposed.[357] If the QT-interval or QTc reaches a length >500 ms or increases by >60 ms compared with baseline, treatment with the particular drug should be ceased or dose reduced. Hypokalaemia should be avoided and concomitant treatment with more than one drug with the propensity of prolonging the QT interval should be avoided. [357]

The incidence of QT prolongation in patients with cancer is in general up to 22% across a variety of **chemotherapy drug** classes, with the exception of arsenic trioxide (used to treat patients with acute promyelocytic leukemia) that has been associated with QT prolongation in 26% to 93% of patients.[358,359] Cardiac arrhythmias are an emerging problem of most anticancer drugs with an increasing number of targeted therapies such as KI and anti-hormonal agents that are proarrhythmic by prolonging the QT interval or via other mechanisms. A comprehensive list has been published.[360]

Chloroquin and, especially, **hydroxychloroquine** may cause QT prolongation and torsades de pointes.[361]

While many drugs have been associated with isolated cases of torsades de pointes, Table 21 lists those generally recognized as having QT-prolonging potential. An up-to-date list is maintained at www.torsades.org and www.qtdrugs.org. Mutations, usually in KCNH2 are also found in one third of patients with drug- or hypokalemia- or bradycardia-induced LQTS.[362] Patients with classic LQTS mutations but normal or borderline QTc intervals are generally much more susceptible to QTc prolonging medications compared with the general population, yet they may be difficult to detect before drug exposure, and genetic scores are studies in this respect.[363] Most clinically relevant drug-related QTc prolongation occurs via inhibition of I_{Kr}, a potassium current mediated in humans by the ion channel KCNH2 encoded by the human ether-a-go-go–related gene (HERG), analogous to the genetic LQT2 form of the disease. However, some drugs may also prolong the QT by augmenting the late inward sodium current ($I_{Na\text{-}L}$) through the phosphoinositide 3-kinase pathway.[364] Risk amplifiers for QT prolongation include female gender, age, hypokalemia, hypomagnesemia, bradycardia, and the presence of underlying structural heart disease, particularly ventricular hypertrophy and congestive heart failure, and concomitant administration of drugs such as ketoconazole that are inhibitors of the cytochrome P4504A4 (CYP3A4) that metabolizes other drugs that may prolong QT.[336] Most cases of drug-induced TdP occur in the setting of substantial

prolongation of the QTc interval, typically to values >500 milliseconds, although QTc alone is a relatively poor predictor of arrhythmic risk in any individual patient.[365] The QT interval remains a predictor, although crude, of torsades de pointes.[366]

In clinical practice care should be taken when combining Class III antiarrhythmic agents with other drugs that prolong the QT. After initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include:[367]

- an increase in QTc from predrug baseline of 60 ms
- marked QTc interval prolongation >500 ms
- T-U wave distortion that becomes more exaggerated in the beat after a pause,
- visible (macroscopic) T-wave alternans
- new-onset ventricular ectopy, couplets and nonsustained polymorphic ventricular tachycardia initiated in the beat after a pause.

A reasonable strategy is to document the QT_c interval before and at least every 8 to 12 hours after the initiation, increased dose, or overdose of QT-prolonging drugs. Mexiletine may be useful in treating drug-induced torsades de pointes.[368] Recommendations on ECG monitoring have been published by AHA.[369] Management is presented in Table 22.

Digitalis

In mild cases of digitalis toxicity, discontinuation of the drug and maintenance of normal potassium levels is enough. Management of severe cases is presented in Table 22.

Sodium channel blockers

They delay depolarization and thus slow conduction and prolong the QRS, and to a less extent the QT interval. In the presence of ischemia or scar this may results in reentrant arrhythmias. The use of **flecainide** or **encainide** in the CAST was associated with a 3.6-fold increase in the risk of fatal arrhythmias in post-MI patients.[101] Genetic factors such as a SCN5A polymorphism may play a role in determining susceptibility to these effects. In addition to slowing of conduction velocity, sodium channel blocking drugs may also selectively abbreviate epicardial action potential duration, resulting in a transmural gradient of repolarization, elevation of the ST segment, and reentry.[336] Non-antiarrhythmic agents with sodium channel properties are tricyclic antidepressants, phenytoin, local anesthetic agents and drugs used to treat neuropathic pain. Recently, **nortriptyline** was found to increase the risk for sudden cardiac arrest in the general population, in the presence of genetic and/or non-genetic factors that block the cardiac sodium channel.[370]

Cytotoxic Chemotherapy Drugs

Chemotherapy-induced ventricular arrhythmias, including sustained ventricular tachycardia and fibrillation, are relatively rare. The incidence is higher in patients receiving chemotherapy for advanced metastatic disease but can also be attributable to the cancer itself (Tables 23 and

24, and Figure 29).[358,371]

Fluorouracil may cause lethal and potentially fatal arrhythmias irrespective of underlying coronary disease during the acute infusion period, the vast majority occurring during the first administration, usually occur in the context of coronary spasm produced by this drug.

Anthracyclines-induced cardiotoxicity is dose dependent, with intermittent high doses and higher cumulative doses increasing the risk of cardiomyopathy and lethal.[372] This form of cardiomyopathy can occur acutely soon after treatment, within a few months of treatment, or many years later. However, VT, as opposed to AF, is rare. For the effect of other chemotherapy agents see Chapters on Cardio-oncology.

Stimulant Drugs

Cocaine and **methamphetamine (substituted amphetamines)** cause structural and electrical remodeling of the atria and ventricles with subsequent ECG changes and atrial and ventricular brady and tachyarrhythmias (Table 25).[373] Non-selective betablockers (labetatlol or carvedilol) and sodium bicarbonate are used for the treatment of cocaine-induced arrhythmias, while selective or non-selective beta blockers and benzodiazepines are useful for merthamphetamine-induced arrhythmias.[373]

Ventricular Arrhythmias in Athletes

Vigorous exertion increases the incidence of acute coronary events in those who did not exercise regularly, whereas habitual physical activity reduces the overall risk of myocardial infarction and SCD. ECG and echocardiographic screening programs can reduce the incidence of SCD in professional athletes although differentiation between adaptive LV chamber enlargement from mild forms of cardiomyopathy may be impossible.[374] Electroanatomical substrate mapping may help diagnose concealed myocardial diseases in competitive athletes presenting with recent-onset VAs and an apparently normal heart.[375] Many athletes with ICDs can engage in vigorous and competitive sports without physical injury or failure to terminate the arrhythmia despite the occurrence of both inappropriate and appropriate shocks.[376] Athletes with nonsustained and asymptomatic exercise-induced ventricular arrhythmias may participate in low-intensity competitive sports provided that no structural heart disease has been demonstrated. Recommendations for disqualification from sports are discussed in the Chapter on Athletes.

Ventricular Arrhythmias in the Elderly

For older patients (>=75 years) and those with significant comorbidities, who meet indications for a primary prevention ICD, an ICD is reasonable if meaningful

survival of greater than 1 year is expected (ACC/AHA/HRS 2017 GL on VA/SCD, IIa-B-NR). However, older adults are prone to higher complication rates, shorter life expectancies (and thus, fewer years during which they could derive benefit from an ICD), and varying preferences. Thus, a particularly nuanced and patient-centered approach to treating these patients is necessary.

Ventricular Arrhythmias in Critically Ill Patients

The development of arrhythmias in the ICU patient may significantly worsen prognosis and requires thorough evaluation. Correction of the numerous precipitating causes should be part of the treatment, as arrhythmias may decrease or disappear after these measures are taken.[377]

Non-cardiac Surgery

Recommendations are provided in Table 26. See also the relevant Chapters.

Ventricular Arrhythmias in Pregnancy

VT may be related to elevated catecholamines, postpartum cardiomyopathy should be ruled out, especially if VT occurs during the last 6 weeks or in the early postpartum period.[378] In women with the congenital long QT syndrome, the risk of cardiac arrest is greater during the post-partum period compared with before or during pregnancy.[379] All antiarrhythmic drugs cross the placenta. Selective beta blockers may be used. There are some concerns about low weight for gestational age when used before the 6th week of pregnancy. No association with low weight for gestational age has been found for labetalol (started after the 6th week of gestation) as opposed to atenolol. Sotalol and flecainide are also considered safe, but experience is limited. Amiodarone may be used but foetal concentration is 20% of maternal concentration and may cause neonatal hypothyroidism (9% of newborns), hyperthyroidism, goiter and growth retardation. Ideally all antiarrhythmic drugs should be avoided during the first 8 weeks. In emergencies immediate cardioversion is safe. IV procainamide, IV sotalol (with normal QT) or IV amiodarone may also be used. The presence of an ICD is not a contra-indication for pregnancy. Recommendations of the ESC are presented in Table 27, and Figures 30 and 31. Recommendations for cardiac arrest are presented in Table 28 and Figures 32 and 33.

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