16.4 Cardiac arrhythmias 3350 Matthew R. Ginks, D.

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ESSENTIALS The term cardiac arrhythmia (or dysrhythmia) is used to describe any abnormality of cardiac rhythm. The spectrum of cardiac arrhythmias ranges from innocent extrasystoles to immediately life-threatening conditions such as asystole or ventricular fibrillation. The key to the successful diagnosis of cardiac arrhythmias is the systematic analysis of an ECG of optimal quality obtained during the arrhythmia. Continuous monitoring is necessary for identification when ar- rhythmias are intermittent. Ambulatory ECG recordings are of most value when they provide correlation between the patient's symp- toms and the cardiac rhythm at that moment. Alternative strategies for the detection of infrequent arrhythmias include the use of a patient-activated recorder, which is applied and activated during symptoms, or an external or implanted loop recorder. More detailed investigation of cardiac arrhythmias is under- taken by invasive cardiac electrophysiological testing. Multipolar electrodes are inserted transvenously to record electrograms from the atrium, ventricle, His bundle, and coronary sinus. Electrophysiological mapping is an essential part of radiofrequency ablation. Bradycardias Bradycardia is defined as a ventricular rate of less than 60 beats/ min. The principal indications for active intervention in bradycardia are symptomatic (disturbances of consciousness, fatigue, lethargy, dyspnoea, or bradycardia-induced tachyarrhythmias) or prognostic (prevention of sudden cardiac death). In the presence of haemodynamic compromise, immediate at- tempts to increase heart rate should be employed, using atropine, isoproterenol (isoprenaline), and/or temporary cardiac pacing (transvenous or transcutaneous). Following stabilization, factors causing or contributing to the presentation should be sought and corrected—especially acute ischaemia and infarction, concomitant drug therapy, hypothermia, or electrolyte disorders. Specific disorders causing

bradycardia include: (1) sinoatrial dis- ease (‘sick sinus syndrome’); (2) neurocardiogenic syncope (e.g. ca- rotid sinus hypersensitivity); and (3) atrioventricular (AV) conduction disorders (‘heart block’). AV block—the commonest cause of AV block is idiopathic fibrosis of the His–Purkinje system, and the severity (degree) of block can be classified as (1) first-degree—defined as a PR interval greater than 0.2 s, which produces no symptoms and does not require treat- ment; (2) second-degree—when there is intermittent failure of con- duction from atrium to ventricle, either with a characteristic pattern of increasing PR interval duration preceding the nonconducted P-wave (Mobitz type I, Wenckebach) or without (Mobitz type II). Pacemaker implantation is not necessary for Mobitz type I in most cases, but is usually required for Mobitz type II; (3) third-degree (complete) AV block—when there is complete dissociation between atrial and ventricular activity, which is an indication for permanent pacemaker implantation, except in the context of an acutely revers- ible condition. Tachycardias The principal mechanisms responsible for tachyarrhythmias are (1) abnormal automaticity; (2) triggered activity; or (3) re-entry. Most clinically important sustained tachycardias appear to arise on the basis of re-entry, which requires the presence of a potential circuit comprising two limbs with different refractoriness and conduction properties. The first and most important step in the diagnosis and manage- ment of tachycardias is to determine whether the arrhythmia arises within the atria and/or AV junction, or from the ventricles, which can often be achieved by careful analysis of a 12-lead ECG. Diagnosis—it is safe to assume that virtually all narrow-complex tachycardias have a supraventricular origin, but wide-complex tachycardias (QRS duration ≥0.12 s) may arise either from the ven- tricle or from supraventricular mechanisms, and few areas in cardi- ology cause more difficulty—or result in more mismanagement—than the diagnosis of wide-complex tachycardias. Careful scrutiny of the 12-lead ECG may reveal diagnostic features, but the commonest reason for error is that the clinical context is not considered, or er- roneous conclusions are drawn from it: key issues to recognize are (1) elderly patients or those with a history of ischaemic heart dis- ease or heart failure are most likely to have ventricular arrhythmia; (2) the patient’s haemodynamic status is a poor predictor of the type of tachycardia; (3) ventricular tachycardia can present with a history of paroxysmal self-terminating episodes. 16.4 Cardiac arrhythmias Matthew R. Ginks, D.A. Lane, A.D. McGavigan, and Gregory Y.H. Lip

16.4 Cardiac arrhythmias 3351 Treatment—R-wave synchronized, direct current (DC) cardio version under general anaesthesia or deep sedation is the most
effective and immediate means of terminating sustained tachy cardias and should be employed when tachycardia is associated with haemodynamic compromise. In patients with tachycardia who are haemodynamically stable, manoeuvres that produce tran- sient vagal stimulation, such as the Valsalva manoeuvre or carotid sinus massage, may be employed. The response to intravenous ad- enosine, which will often terminate arrhythmias dependent on the AV node, may be of therapeutic or diagnostic value, and should be considered in all patients with tolerated regular tachycardia. In the long term, tachycardias can be treated with antiarrhythmic drugs (usefully categorized by the Vaughan Williams classification), implantable cardioverter–defibrillators, radiofrequency catheter ablation, or arrhythmia surgery. In all cases an assessment of the underlying precipitating cause (i.e. ischaemic heart disease, elec- trolyte disturbance, structural heart disease, genetic predispos- ition, or drug therapy) is required before planning subsequent long-term therapy. Atrial fibrillation Prevention of stroke—this is the most important priority and requires individualized assessment of stroke risk using the CHA2DS2-VASc score. Patients with one or more stroke risk factors should be con- sidered for oral anticoagulation. Formal assessment of a patient’s risk of bleeding with treatment should also be undertaken using the HAS-BLED score. The SAMe-TT2R2 scores can help

inform treatment decisions between use of a vitamin K antagonist (VKA, e.g. warfarin) or a non-VKA oral anticoagulant. Discussion and incorporation of patient preferences for treatment is advocated, and regular review of the treatment strategy over time is essential. Decisions on rhythm or rate control should be patient-centred and symptom-directed: a rate control strategy is noninferior to a rhythm-control strategy for long- term clinical outcomes. Rhythm or rate control management—rhythm control is by cardioversion (electrical or pharmacological) or catheter abla- tion. Unless the patient has been therapeutically anticoagulated for several weeks, cardioversion should not be attempted without transoesophageal echocardiography unless the known dur- ation arrhythmia has been less than 48 h because of the risk of thromboembolism. If it is clinically appropriate to attempt chem- ical cardioversion, the drugs of choice are class Ic agents (e.g. flecainide) for patients without significant underlying heart dis- ease; class III drugs (e.g. amiodarone) are safer in the presence of left ventricular dysfunction or ischaemic heart disease. For rate control, a β-blocker or rate-limiting (nondihydropyridine) calcium channel blocker, sometimes in combination with digoxin, should be considered. Paroxysmal atrial fibrillation—drug therapy may not be neces- sary for patients with infrequent paroxysms, or a 'pill in the pocket' approach can be used in those without structural heart disease, whereby they take a dose of an antiarrhythmic drug after the onset of arrhythmia. No drug is entirely satisfactory for recurrent parox- ysmal atrial fibrillation: although only modestly effective, a β-blocker is often prescribed as first-line therapy. Persistent atrial fibrillation—usually requires electrical cardioversion to achieve sinus rhythm and has a high recurrence rate even after successful cardioversion. The key decision is whether to employ a rhythm or rate control strategy. In general, a rate control strategy (AV nodal blocking drug, e.g. β-blocker, calcium channel blocker, or digoxin) should be considered in patients with few or minor symptoms, elderly patients, and those with contraindica- tions to antiarrhythmic therapy or cardioversion. A rhythm-control strategy (elective cardioversion) may be best in more symptomatic or younger patients (especially in those with structurally normal hearts), or in those with recent-onset atrial fibrillation due to a treated precipitant. If symptoms are clearly attributable to atrial fib- rillation and are refractory to antiarrhythmic drugs, then catheter ablation can be considered. Atrial flutter It is important to attempt to terminate atrial flutter since the ven- tricular rate is often poorly controlled by AV nodal blocking drugs: this may be achieved by electrical cardioversion (with pharmacological approaches being less effective), or by catheter ablation (which may be curative). Prophylaxis against thromboembolism should be given as for atrial fibrillation. Supraventricular tachycardias The term supraventricular tachycardia encompasses three types of arrhythmia: AV nodal re-entrant tachycardia (AVNRT), AV re- entry tachycardia, and atrial tachycardia (AT) in order of reducing frequency. Termination of an attack of AVNRT is achieved by producing transient AV nodal block by vagotonic manoeuvres, adenosine, or verapamil. Drug prophylaxis is undertaken with β-blockers, a com- bined β-blocker/class III agent such as sotalol, or with AV nodal blocking drugs such as verapamil or digoxin. Curative treatment is by radiofrequency ablation. Attacks of AV re-entry tachycardia are treated in the same way as AVNRT. Antiarrhythmic prophylaxis may be effective, but radiofrequency ablation offers high success rates with low incidence of complications and should be considered early. Pre-excitation syndromes The term 'pre-excitation' (e.g. seen as a δ-wave on the ECG) refers to the premature activation of the ventricle via one or more accessory pathways that bypass the normal AV node and His–Purkinje system. When seen in conjunction with palpitations this is Wolff-Parkinson– White syndrome. The main prognostic concern is pre-excited atrial fibrillation, which can be very rapid and degenerate into ventricular fibrillation. Patients with pre-excitation should be offered a car- diac electrophysiological study as first-line therapy, with a view to radiofrequency ablation.

Ventricular tachycardia Ventricular tachycardia (VT) normally occurs in individuals with overt heart disease but is also seen in young and apparently healthy subjects, when occult cardiac disease or cardiac genetic syndromes should be considered. Sustained VT is a medical emergency. Immediate DC cardioversion is necessary if the patient is hypotensive; haemodynamically tol- erated VT may be terminated pharmacologically, with intravenous β-blocker or amiodarone being the usual first-choice options. Unless there is a clear precipitating factor, the risk of sudden death

section 16 Cardiovascular disorders 3352 is high, and patients should be considered for an implantable cardioverter–defibrillator. Polymorphic VT, of which torsades de pointes is a well-recognized type associated with acquired or congenital prolongation of the QT interval, is an unstable rhythm with varying QRS morphology that undergoes spontaneous termination or degenerates into ventricular fibrillation. In patients with this condition, it is essential to discon- tinue predisposing drugs or other agents and to avoid empirical antiarrhythmic drug therapy. Intravenous magnesium sulphate is a safe and effective emergency measure. Intravenous isoprenaline or temporary pacing may also be required. Ventricular fibrillation The management of cardiac arrest due to ventricular fibrillation is discussed in this chapter. Patients who survive an episode should be assessed carefully to determine the risk of recurrence and may require an implantable cardioverter–defibrillator or antiarrhythmic therapy as for patients with ventricular tachycardia. Genetic syndromes These are inheritable causes of cardiac arrhythmia and can be divided into ion channel diseases (‘channelopathies’) and heart muscle diseases. Ion channel diseases include the congenital long-QT syndromes, short-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic VT. Heart muscle diseases include hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. General principles Definition The term cardiac arrhythmia (or dysrhythmia) is used to describe an abnormality of cardiac rhythm of any type. Normal cardiac electro- physiology is discussed in Chapter 16.3.1. The spectrum of cardiac arrhythmias ranges from innocent extrasystoles to immediately life- threatening conditions such as asystole or ventricular fibrillation. Arrhythmias may occur in the absence of cardiac disease but are more commonly associated with structural heart disease or external provocative factors. Symptoms of cardiac arrhythmias The symptoms produced by bradyarrhythmias depend on the ex- tent of cardiac slowing. They may include sudden death, syncope (Stokes–Adams attacks), or dizziness/presyncope. Continuous bradycardia without asystolic pauses may produce symptoms of fa- tigue, lethargy, dyspnoea, or cognitive impairment. The symptoms caused by tachyarrhythmias depend on a variety of factors including the heart rate, the difference between the rate during the arrhythmia and the preceding heart rate, the degree of ir- regularity of the rhythm, and the presence or absence of underlying cardiac disease. Symptoms of tachycardia include a feeling of rapid palpitation, chest discomfort or dyspnoea, syncope, or sudden death. The differential diagnosis of palpitation and syncope is dis- cussed in Chapter 16.2.2. Investigation of arrhythmias History-taking must include a detailed description of the symp- toms associated with the arrhythmia. Evidence should be sought for factors that may precipitate the arrhythmia (e.g. exercise, al- cohol, or drug therapy) and for the presence of underlying car- diac disease, in particular valvular heart disease, myocardial ischaemia/infarction, or congestive heart failure. Examination of the pulse may be unremarkable if the arrhythmia is intermittent. Physical examination for evidence of structural heart disease is essential. A 12-lead ECG should be performed both during the arrhythmia and once it has resolved (if possible, when the patient presents acutely). A full blood count (in cases of sinus tachycardia), thyroid func- tion (sinus tachycardia and atrial arrhythmias), and electrolyte testing (potassium for both atrial and

ventricular arrhythmias and calcium and magnesium for sustained ventricular arrhythmias) are routinely performed. Although troponin is often measured routinely in the patients presenting to the emergency department, a minor rise in troponin should not be regarded as diagnostic of an acute coronary syndrome as the precipitating cause. Further investigations to establish the presence of structural heart disease and to determine ventricular function may include chest radiog- raphy, echocardiography, exercise stress testing, coronary angiog- raphy, or MRI.
Electrocardiography The key to the successful diagnosis of cardiac arrhythmias is the systematic analysis of ECG (see Chapter 16.3.1) of optimal quality obtained during the arrhythmia (Table 16.4.1). Ideally, this should be a 12-lead ECG and may be compared to the ECG in intrinsic rhythm.
Ambulatory electrocardiography Continuous monitoring is necessary for identification when arrhyth- mias are intermittent. Ambulatory (Holter) ECG is normally per- formed for periods of 24–48 h using a portable recorder. High-speed

Table 16.4.1 Principles of ECG diagnosis of arrhythmias

Obtain 12-lead or multichannel recordings if possible	
Atrial activity	P-waves visible? Normal P-wave morphology and axis? Flutter/fibrillation waves? Atrial rate?
Ventricular activity	Ventricular rate? Regular or irregular? Normal QRS morphology and duration? Bundle branch block or bizarre QRS morphology? Variation in QRS morphology/axis?
Atrioventricular relationship	PR interval—fixed or varied? Retrograde P-waves? Atrial versus ventricular rate?

or automatic replay facilities enable the identification of intermit- tent arrhythmias, as well as the quantification of extrasystoles and assessment of parameters of heart rate variability. Interpretation of recordings requires knowledge of possible artefacts, such as those caused by movement or loss of electrode contact. It is important to allow for physiological variability in the sinus rate, also appreciating that minor abnormalities such as extrasystoles or brief (3–4 beat) runs of supraventricular arrhythmias are usually of no significance. Ambulatory ECG recordings are of most value when they provide correlation between the patient's symptoms and the cardiac rhythm at that moment. Patients should be issued with a diary card and asked to note any symptoms suggestive of arrhythmia during the recording. Alternative strategies for the detection of infrequent arrhythmias include the use of a patient-activated recorder, which is applied and activated during symptoms, or an external or implanted loop re- corder. Loop recorders continually record the ECG signal, but only have sufficient memory to retain a few minutes of data. In the event of symptoms, the patient activates the device, thus 'fixing' the pre- vious few minutes of recording for subsequent analysis. External loop recorders are usually used for up to 7 days, while an implanted event recorder can last for up to 3 years.
Cardiac electrophysiological study More detailed investigation of cardiac arrhythmias is under- taken by invasive cardiac electrophysiological testing. Multipolar electrodes are inserted transvenously to record electrograms from the atrium, ventricle, His bundle, and commonly from the coronary sinus (Fig. 16.4.1). The site of conduction delays within the heart may be identified, or accessory pathways lo- calized. Sustained arrhythmias may be initiated and their pat- tern of activation in the heart studied in detail; if necessary, the mechanism of the arrhythmia can be clarified using pacing manoeuvres (Fig. 16.4.2). Electrophysiological mapping is an es- sential part of radiofrequency ablation (see next), and modern three-dimensional mapping systems have facilitated ablation of complex arrhythmias.
Bradycardias
Aetiology and mechanisms Bradycardia is defined as a ventricular rate of less than 60/min, and results from a reduction in the rate of normal sinus pace- maker activity, or from disturbances of atrioventricular (AV) conduction. Sinus bradycardia may be physiological, for example, during sleep and in athletes. Pathological bradyarrhythmias can result from intrinsic degenerative disease of the sinus or AV node, or the conducting system. Bradycardia

may also be due to extraneous factors such as sympathetic withdrawal, vagal stimu- lation, drug effects, myocardial ischaemia/infarction, infiltra- tion, or surgical trauma, and also miscellaneous conditions such as hypothyroidism, hypothermia, jaundice, or raised intracranial pressure. General principles of management The principal indications for active intervention in bradycardia are symptomatic (disturbances of consciousness, fatigue, leth- argy, dyspnoea, or bradycardia-induced tachyarrhythmias) or prognostic (prevention of sudden cardiac death). Particular at- tention should be given to the history and ECG documentation of the rhythm disturbance. Drugs interfering with sinoatrial or AV nodal function should be withdrawn if possible, although under certain circumstances (e.g. tachycardia–bradycardia syndrome) it may be necessary to combine pacemaker implantation with con- tinued drug therapy. Acute management of bradycardia General principles can be applied to patients presenting with overt bradycardia, regardless of aetiology (Table 16.4.2). In the pres- ence of haemodynamic compromise, immediate attempts should be made to increase heart rate. Transient increases in sinus rate or the ventricular escape rate in complete AV block may be achieved with atropine or isoproterenol (isoprenaline). However, drug treat- ment is only of temporary value, and temporary or permanent car- diac pacing is indicated for persistent bradycardia (see ‘Pacemaker therapy’, later on). Temporary pacing is also indicated where ECG Right atrium His Right ventricle A H V 100 ms LV LA RA RV Fig. 16.4.1 Electrophysiological study. Illustration of lead placement (left). Quadripolar leads have been inserted from the femoral vein and the tips are shown positioned to allow recording and pacing from the high right atrium, His bundle, and the right ventricular apex. Intracardiac electrograms (right) show recordings from atrium (A), His bundle (H), and right ventricle (V). 1 s S1 S1 S2 S3 RV V1 aVF I Fig. 16.4.2 Induction of ventricular tachycardia by programmed stimulation. Ventricular pacing stimuli (S1) at 100 beats/min are followed by two extrastimuli (S2 and S3). Sustained monomorphic ventricular tachycardia is induced. Surface leads I, aVF, V1, and the intracardiac electrogram from right ventricular apex (RV) are shown.

section 16 Cardiovascular disorders 3354 frequent Stokes–Adams attacks are occurring. Pacing can be per- formed transcutaneously using an external pacing system in the emergency situation if facilities for transvenous pacing are not im- mediately available. Following stabilization, factors causing or contributing to the presentation should be sought and corrected, especially acute ischaemia and infarction, concomitant drug therapy, or electro- lyte disorders. Analysis of the ECG will allow identification of the conduction disorder and plans for long-term management can be instituted. Specific causes of bradycardia Sinoatrial disease Sinoatrial disease, often referred to as ‘sick sinus syndrome’, re- sults in inappropriate sinus bradycardia, sinus pauses, or junctional rhythm (Fig. 16.4.3) in the absence of extrinsic factors. The condi- tion is most commonly caused by idiopathic degeneration of the sinus nodal cells, particularly in older people, and is associated in about 20% of cases with idiopathic bundle branch fibrosis (see ‘Aetiology of atrioventricular block’). Occasionally, sinoatrial dis- ease is caused by ischaemia due to obstruction of the right coronary artery. Conduction block may occur between the sinus node and the atrium (sinoatrial exit block), resulting in ‘dropped’ P-waves (Fig. 16.4.4). More prolonged suppression of sinus node activity results in periods of sinus arrest, which are terminated by an es- cape beat from the sinus node, AV node, or ventricle (Fig. 16.4.5a). Where the sinus rate is permanently slower than the junctional rate, continuous AV junctional rhythm will be present. Patients with sinoatrial disease have an increased predisposition to atrial tachyarrhythmias (tachycardia–bradycardia syndrome), and pro- longed pauses may follow termination of tachycardia (Fig. 16.4.5b). Sinoatrial disease can cause symptomatic bradycardia, dizziness, or syncope, but may be asymptomatic. The diagnosis is

normally made from 12-lead or ambulatory ECG recording. Investigation should focus on excluding extrinsic causes of bradycardia, and on demonstrating the correlation between bradycardia or pauses and symptoms. Pacemaker implantation is indicated for the relief of symptoms (see next). Prognosis is not improved by pacemaker im- plantation in sinus nodal disease and thus pacemaker implantation in asymptomatic patients is not indicated. Neurocardiogenic syncope Conditions where patients suffer reflex-induced attacks of brady- cardia or hypotension are described in Chapter 16.2.2. Patients with carotid sinus hypersensitivity and reproducible symptoms of presyncope or syncope on carotid sinus massage should undergo permanent pacemaker implantation (see 'Permanent pace- maker therapy'). In patients with recurrent vasovagal syncope, it is recommended to maintain good hydration and salt intake. Isometric exercises may be helpful. Medical therapy with agents as diverse as α-agonists, β-blockers, vagolytic agents (disopyramide, hyoscine), ephedrine, mineralocorticoids, or antidepressants is often tried, but the evi- dence base for the efficacy of drug therapy is weak. Spontaneous resolution of symptoms occurs in many patients. There is little evi- dence to support pacemaker implantation even in those with pre- dominant bradycardia as the response to tilt testing, but it may be considered in selected individuals with intractable symptoms. Atrioventricular conduction disorders Impairment of AV conduction may occur either within the AV node (intranodal) or within the His–Purkinje system (infranodal). Intranodal block is not associated with QRS abnormalities, while distal (infranodal) block is commonly associated with bundle branch block. Bundle branch block (particularly left bundle branch block) is a common finding in elderly patients with a history of fa- tigue, dizziness, and syncope. Although both left and right bundle branch block are associated with an increased risk of developing complete AV block, bundle branch block as an isolated finding is not sufficient evidence to attribute symptoms to conduction disease; fewer than one-half of patients with bundle branch block and syn- cope have a final diagnosis of cardiac syncope. There are two ex- ceptions. Alternating left and right bundle branch block (although rare in the absence of higher-grade AV block) is an indication for pacemaker insertion in the absence of documented symptomatic 2:1

Table 16.4.2 General principles of acute management of the patient with bradycardia Assess the patient Respiratory status Blood pressure Symptoms Examine the ECG Sinus rate Ventricular rate AV relationship QRS morphology and duration If haemodynamic compromise Atropine Isoproterenol Temporary pacing Look for precipitants Ischaemia/infarction Vasovagal episode Thyroid status Electrolyte imbalance Hypothermia Drug therapy Fig. 16.4.3 Sinus bradycardia. The heart rate is less than 40 beats/min, and the sinus rate is so slow that an escape junctional beat is seen (open circle), preceding the P-wave.

 or third-degree AV block. Trifascicular block (a triad of first-degree heart block, left-axis deviation, and right bundle branch block) may be considered sufficient evidence for symptomatic conduction dis- ease requiring pacing where no other cause for symptoms has been identified. However, further evidence of more advanced conduction disease with prolonged ECG monitoring is usually sought. Aetiology of atrioventricular block The causes of AV block are shown in Box 16.4.1. The commonest is idiopathic fibrosis of the His–Purkinje system, which occurs with increasing frequency from the seventh decade of life onwards, is as- sociated with sinoatrial disease in up to 25% of cases, and results in progressive impairment of AV conduction. Atrioventricular block may occur acutely in myocardial infarction (Fig. 16.4.6). Inferior myocardial infarction predominantly affects AV nodal conduction by vagal overactivity, and possibly adenosine release from ischaemic myocardium. First-degree, second-degree, or third-degree AV block may occur, but are commonly transient, particularly with the advent of primary

percutaneous coronary intervention. Spontaneous recovery of normal conduction gener- ally occurs within 7–10 days. By contrast, AV block secondary to anterior myocardial infarction is normally due to extensive infarc- tion of the interventricular septum involving both the left and right bundle branches. This may result in type II second-degree block or complete AV block, with a low probability of recovery of normal conduction. Any drug-slowing AV conduction may potentially produce AV block. The risk is greater when such drugs are used in com- bination. Intravenous verapamil in patients already receiving β-adrenoceptor blockers is particularly hazardous. Vagally me- diated conduction disturbances occur as a physiological finding in highly trained athletes, and in young people during sleep, or in neurocardiogenic syncope. Atrioventricular conduction dis- turbances arise in structural congenital heart disease such as endocardial cushion defects, but also as an isolated congenital ab- normality, commonly in association with maternal systemic lupus erythematosus. First-degree atrioventricular block First-degree AV block is defined as a PR interval greater than 0.20 s (Fig. 16.4.7). This produces no symptoms and does not require treatment, although the risk of progression to higher-degree AV block should be considered. Second-degree atrioventricular block In second-degree AV block, there is intermittent failure of conduc- tion from atrium to ventricle. In type I (Wenckebach) second-degree block, a characteristic pattern of increasing PR interval duration followed by a nonconducted P-wave is seen (Fig. 16.4.8). The QRS morphology is commonly normal. Type I (Wenckebach) second- degree AV block usually indicates block in the AV node, and is nor- mally associated with a reliable subsidiary pacemaker and a low risk of progression to complete heart block. In most instances pacemaker implantation is not necessary unless recurrent presyncope or syn- cope suggest the occurrence of an intermittent higher-degree block. By contrast, in type II second-degree AV block (commonly called Mobitz type II AV block) there is a sudden failure of conduction, without a preceding increase in the PR interval (Fig. 16.4.9). Regular nonconducted P-waves may result in high-degree block, with 2:1 or 3:1 conduction. Type II second-degree AV block is generally indi- cative of extensive infranodal conduction abnormality, with a high risk of progression to complete AV block. Guidelines therefore (a) (b) Fig. 16.4.5 Sinus arrest. (a) A pause of 4 s results from failure of the sinus node to discharge. (b) Termination of atrial fibrillation is followed by a sinus pause of 2.5 s due to sinus arrest in a patient with bradycardia/tachycardia syndrome. Fig. 16.4.4 Sinoatrial exit block. A pause occurred because of the absence of a P-wave (open arrow). The timing of the sinus beats, however, is not interrupted, indicating that the sinus node discharged but the impulse failed to excite the atria.

 recommend permanent pacemaker implantation even in the ab- sence of symptoms. Third-degree atrioventricular block The characteristic feature of third-degree (complete) AV block is dissociation between atrial and ventricular activity (Figs. 16.4.6 and 16.4.10). The ventricular rate is regular and slower than the atrial rate. An escape rhythm arising above the bifurcation of the bundle of His will produce a narrow-QRS morphology, commonly with a relatively stable escape rhythm (50–60/min). A more distal escape rhythm results in widened bundle branch block morphology complexes with a slower escape rate (20–30/min). Complete AV block in patients with atrial fibrillation is often missed. It is recog- nized by the presence of a slow, regular ventricular response. High- degree AV block can be intermittent, and the resting ECG may be normal or only show evidence of mild conducting system disturb- ance such as first-degree AV block or bundle branch block. If there is clinical suspicion, ambulatory ECG recording is required, for pro- longed periods if necessary. The presence of complete AV block, except in the context of an acutely reversible condition, should be regarded as an indication for permanent pacemaker implantation. This is urgent in patients who are having Stokes–Adams attacks; their prognosis is

poor without pacemaker implantation, and markedly improved by permanent pacing, after which outcome will depend on the presence and extent of any underlying cardiac disease. Permanent pacing also improves prognosis in asymptomatic patients with complete AV block. One exception to this general rule is congenital complete heart block, where the escape rhythm is often relatively fast (50–60/min) with a narrow-QRS morphology. Many patients remain asymptomatic well into adult life, although there is a small risk of syncope or sudden death. Pacemaker implantation should be considered if there are symptoms, if there are abrupt pauses, if the average heart rate is below 50/min, or in patients over 40 years of age. Asystole The term asystole is used when the ECG shows a complete cessation of both atrial and ventricular activity. This appearance may be mimicked by disconnected ECG cables or other artefacts, but since asys- tole causes cardiac arrest the distinction is virtually always obvious. Ventricular standstill occurs when there in ongoing 'P' wave activity without QRS complexes. Pacemaker therapy Basic principles The basis of pacemaker therapy is the local depolarization of the myocardium by an electric current passed through an electrode in contact with the heart (atrium or ventricle). Activation of the re- mainder of the atria or ventricles occurs by direct cell-to-cell conduc- tion. The minimum current necessary to stimulate the heart during diastole is known as the pacing threshold. Pacemaker systems con- sist of one or more intracardiac catheter electrodes, introduced into the heart via the venous system, and a pulse generator, which con- tains the circuitry for generating and timing the pacing stimulus, as well as for sensing spontaneous cardiac depolarizations. The pacing stimulus is delivered between the active pole at the tip of the elec- trode catheter and an indifferent electrode sited either on the same Box 16.4.1 Causes of atrioventricular block • Idiopathic conducting system fibrosis • Acute myocardial ischaemia/infarction • Infiltration—calcific aortic stenosis, sarcoidosis, scleroderma, syphilis, tumour • Infection—diphtheria, rheumatic fever, endocarditis, Lyme disease • Drugs—digoxin, verapamil or diltiazem, β-blockers, antiarrhythmic drugs • Surgical trauma, radiofrequency ablation • Congenital heart block, congenital heart disease • Vagal—athletic heart, carotid sinus, and vasovagal syndrome • Myotonic dystrophy Fig. 16.4.6 Complete heart block in a patient with acute myocardial infarction. There is a narrow-QRS complex escape rhythm with ST-segment elevation, ventricular rate 45 beats/min. Fig. 16.4.7 First-degree heart block. The PR interval is prolonged (0.32 s). Fig. 16.4.8 Second-degree heart block, type I (Wenckebach). The PR interval progressively prolongs until there is a failure of conduction following a P-wave (arrow). Fig. 16.4.9 Second-degree heart block, type II. A nonconducted P-wave occurs without preceding prolongation of the PR interval.

 catheter 1–2 cm proximal to the tip (bipolar pacing), or utilizing the can of an implanted pulse generator (unipolar pacing). Satisfactory pacing requires stable electrode contact with the myocardium. The standard sites for endocardial atrial and ventricular pacing are the right atrial appendage and the right ventricular apex, respectively (Fig. 16.4.11), although screw-in active fixation leads allow place- ment at other atrial and ventricular sites. An external pulse generator is used for temporary pacing. For permanent pacing, it is usually implanted deep to the subcutaneous fat layer in the prepectoral region (Fig. 16.4.11). The generator con- tains a timer set to deliver pacing stimuli at a preset pulse interval (e.g. 1000 ms). Pacemakers normally operate in the demand mode, whereby if spontaneous activation of the cardiac chamber is sensed via the electrode, the delivery of a pacing stimulus is inhibited and the timer circuit of the generator is reset. Pacing in the fixed-rate mode results in the delivery of stimuli regardless of the spontaneous activity of the chamber being paced. Temporary ventricular pacing Temporary pacing is indicated in patients with bradycardia causing haemodynamic compromise, or

as a prelude to permanent pacemaker implantation in those with significant recurring symp- toms, or in high-grade AV block (i.e. Mobitz II or complete heart block). It is recommended that in those patients with an indica- tion for a permanent system this should arranged urgently where possible to avoid the complications associated with temporary pace- maker insertion. In patients undergoing anaesthesia for noncardiac surgery, the standard indications for pacing apply. Facilities for radiographic screening, continuous ECG moni- toring, and defibrillation are required. The pacing electrode is intro- duced under aseptic conditions via an intravascular sheath into the subclavian, internal jugular, or femoral vein and the tip advanced under radiographic guidance to the right ventricular apex. Non- sustained ventricular tachycardia, or occasionally ventricular fibril- lation, may occur during catheter manipulation. Once the electrode is at an acceptable site, pacing is initiated, and the minimum output necessary to achieve stable ventricular capture is determined. The pacing threshold should ideally be less than 1 V, at a pulse width of between 0.5 and 2 ms. If the pacing threshold is unsatisfactory, the electrode is repositioned until an acceptable site is found. Care should be taken to determine that the electrode is stable by asking the patient to take deep breaths or to cough while pacing at threshold. The electrode is then secured at the site of insertion and the pulse generator set to an output of at least 3 V above the pacing threshold. Permanent pacemaker therapy Indications for permanent pacing therapy are given in Table 16.4.3. Two scenarios are quite common and can cause confusion. Elderly patients presenting with symptomatic AV block (particularly in the context of permanent atrial fibrillation) or sinus node disease are fre- quently on rate-slowing drugs. It is usual to withdraw these agents be- fore assessing the need for pacing therapy. This is particularly common where multiple agents (e.g. digoxin and β-blockade) have been used. However, if patients have been on these agents for many years then the presentation with symptomatic bradycardia should be taken as an indication of progressive conduction disease and increasingly long- term pacing is required, particularly where these agents are required for control of tachyarrhythmias. The second scenario is the patient with evidence of conduction disease presenting with syncope where a class I indication is not met but there is a high index of suspicion and no other cause has been identified. These are patients with sinus node disease manifesting as pauses (>3 s) on a prolonged monitoring or advanced conduction disease (trifascicular block) on a 12-lead ECG. It should be remembered that there is no prognostic benefit in per- manent pacing in patients with either of these conditions. Ideally an attempt should be made to correlate pauses with symptoms or iden- tify a more extensive conduction disease with prolonged monitoring. Nocturnal pauses are common in this population and are not an in- dication for pacing unless they are very prolonged, associated with Fig. 16.4.10 Third-degree (complete) heart block. Atrial activity does not conduct to the ventricles, and there is a regular escape rhythm of 35 beats/min. Fig. 16.4.11 Dual-chamber permanent pacemaker. Chest radiograph showing the pacemaker generator (in a subcutaneous pocket in the pectoral region), which is connected to electrodes that pass via the left subclavian vein and superior vena cava to the heart. The tips of the electrodes are in the right atrial appendage and the right ventricular apex.

 symptoms, or the history is strongly suggestive of an arrhythmic cause for syncope (other causes having been excluded). Patients with sinus node disease have an increased susceptibility to neurally mediated bradycardia and hypotension, which may explain why some of these patients continue to have symptoms after pacemaker insertion. Pacing is not indicated in patients with unexplained falls; how- ever, there may be an argument for pacing in the context of conduc- tion disease and a classic history in selected cases, in an attempt

to prevent further events. Permanent pacing electrodes are normally inserted via the left or right cephalic, axillary, or subclavian vein. Once the electrode is in a satisfactory position, it is secured and connected to the implanted pulse generator. Most pulse generators are powered by lithium batteries and have a life of approximately 8–10 years, after which the generator is replaced. The rate, output voltage, pulse width, and other pacemaker parameters can be modified noninvasively using telemetry via a trans- mitter/receiver placed on the skin over the pulse generator. The amplitude and pulse width of the pacing stimulus are usually set at nominal values (e.g. 3.5 V, 0.5 ms), but are adjustable and can be reduced to pro- long the life of the battery, provided there is a sufficient safety margin between the pulse generator output and the pacing threshold. Pacing mode selection The nomenclature used to describe pacing mode is given in Table 16.4.4, and ECG examples of the principal pacing modes are shown in Fig. 16.4.12. Atrial demand (AAI) pacing is used for sino- atrial disease in the absence of AV block. Ventricular pacing (VVI) is the simplest and technically easiest mode of pacing, and is required Table 16.4.3 Indications for permanent pacing therapy Indications for pacing Conducting tissue disease Details Class of indication Level of evidence In patients with persistent bradycardia Sinus node disease Pacing is indicated when symptoms can clearly be attributed to bradycardia I B Acquired AV block Pacing is indicated in patients with third-or second-degree type 2 AV block irrespective of symptoms I C Acquired AV block Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS IIa C In patients with intermittent (documented) bradycardia Sinus node disease (including brady-tachy form) Pacing is indicated in patients affected by sinus node disease who have documentation of symptomatic bradycardia due to sinus arrest or sinus-atrial block I B Intermittent/paroxysmal AV block (including AF with slow ventricular conduction) Pacing is indicated in patients with intermittent/paroxysmal intrinsic third-or second-degree AV block I C Reflex asystolic syncope Pacing should be considered in patients ≫40 years with recurrent, unpredictable reflex syncope and documented symptomatic pause/s due to sinus arrest or AV block or the combination of the two IIa B Asymptomatic pauses (sinus arrest or AV block) Pacing should be considered in patients with a history of syncope and documentation of asymptomatic pauses >6 s due to sinus arrest, sinus-atrial block, or AV block IIa C In patients
with BBB BBB, unexplained syncope, and abnormal EPS Pacing is indicated in patients with syncope, BBB and positive EPS defined as HV interval of >70 ms, or second-or third- degree His–Purkinje block demonstrated during incremental atrial pacing or with pharmacological challenge I B Alternating BBB Pacing is indicated in patients with alternating BBB with or without symptoms I C In patients with undocumented reflex syncope Carotid sinus syncope Pacing is indicated in patients with dominant cardioinhibitory carotid sinus syndrome and recurrent unpredictable syncope I B AF, atrial fibrillation; AV, atrioventricular; BBB, bundle branch block; EPS, electrophysiology study. Table 16.4.4 Pacemaker mode nomenclature Chamber paced Chamber sensed Mode Additional features A Atrium A Atrium I Inhibited R Rate responsive V Ventricle V Ventricle T Triggered D Dual (A and V) D Dual (A and V) D Dual (I and T) O Neither O Fixed rate See text for examples.

 for AV conduction disturbances. However, VVI pacing does not permit AV synchrony or an increase in pacing rate in response to an increase in sinus (atrial) rate. Dual-chamber (DDD) pacemakers have electrodes in both the right atrium and ventricle. If the sinus cycle length is greater than the pulse interval, atrial demand pacing occurs. Following the atrial stimulus, a programmable AV delay commences. If no spontaneous ventricular depolarization

is sensed before the end of this interval, a pacing stimulus is delivered via the ventricular electrode. If the sinus cycle length is shorter than the pulse interval, no atrial stimulus is given, but the AV delay is trig- gered by the sensed atrial activity, followed by a paced ventricular beat, if a conducted ventricular activation does not occur. By this means, the ventricular rate tracks the atrial rate up to a program- mable maximum, allowing the heart to increase its rate in a physio- logical manner in response to metabolic demand. An alternative, and simpler, approach to achieve a rate response is the use of an ac- tivity sensor such as an accelerometer in the pulse generator. Such devices detect bodily movement and increase the pacing rate ac- cording to a programmable algorithm. Rate response can be utilized in either single-or dual-chamber pacemakers and is designated by the suffix 'R' (e.g. AAIR, VVIR, DDDR). The advantage of DDD pacing over VVI pacing lies in the maintenance of AV synchrony and rate responsiveness, but this is achieved at the expense of increased complexity, complications, and cost. DDD pacing reduces the risk of atrial fibrillation by virtue of pacing the atrium and avoiding retrograde atrial activation via the AV node and has a lower incidence of the pacemaker syndrome (see next). However, large-scale randomized trials comparing DDD with VVI(R) pacing have failed to substantiate survival benefits from DDD pacing, at least during follow-up periods of up to 3 years. Cardiac resynchronization pacing in patients with reduced ejec- tion fraction and an indication for permanent pacing is supported by evidence from several small randomized trials. The benefits have to be weighed against the added complexity of these devices and the complication rates. It should, however, be standard practice to perform an echocardiogram to assess left ventricular function in all patients undergoing permanent pacing, as up to 10% may have evi- dence of significant left ventricular dysfunction. Complications of pacemaker insertion Complications of temporary or permanent pacemaker implant- ation include those of central venous cannulation (e.g. bleeding, pneumothorax), perforation of the heart by the electrode tip leading to pericardial effusion and cardiac tamponade, and macroscopic or microscopic displacement of the electrode resulting in an increase in the pacing threshold or failure to capture. A chest radiograph should be taken after pacemaker insertion to exclude pneumothorax and to confirm that the electrode position is satisfactory. Permanent pacing may be complicated by the development of infection around the pulse generator, or by mechanical erosion of the generator through the skin. Once infection is established, or the skin is breached, it is almost never possible to eradicate infection with antibiotics: removal and replacement of the pacing system is required. The development of oedema and inflammation around the implanted electrode tip may result in a steady rise in the pacing threshold over the first few weeks, which can lead to an increase of the pacing threshold such that capture is lost (Fig. 16.4.13a), although the process is normally mild and self-limiting. Lead dis- lodgement occurs in up to 4.2% of patients with a dual-chamber and 1.4% with a single-chamber system. Demand pacemakers require an adequate intracardiac signal to recognize activation of the chamber in question, to inhibit output. The pacing stimulus will not be suppressed ('undersensing') if the intracardiac signal is of insufficient amplitude, resulting in in- appropriate pacemaker firing (Fig. 16.4.13b). This phenomenon is commoner in atrial pacing, owing to the lower amplitude of atrial compared with ventricular electrograms. Conversely, detection of extraneous electrical activity (e.g. skeletal muscle activity) via the pacing electrode can result in inappropriate inhibition of the pace- maker output (oversensing; see Fig. 16.4.13c). Oversensing is com- moner with unipolar than bipolar pacing modes because of the inclusion of the pulse generator can in the electrical circuit, and its proximity to the pectoral muscles. For the same reason, unipolar pacemaker systems are more prone to the problem of local skeletal muscle stimulation. Damage to the conductor or insulation of the pacing electrode may occur due to

trauma at the site of ligation or to compression between the clavicle and first rib. This may result in oversensing, skeletal muscle stimulation, or short-circuiting leading to premature battery depletion. Patients receiving AAI pacemakers may subsequently develop AV block, resulting in a recurrence of syncope and requiring up- grade of the pacing system to a DDD unit. Some patients with VVI pacemakers, particularly those with sinoatrial rather than AV dis- ease, will manifest retrograde ventriculoatrial conduction during ventricular pacing. This sometimes causes symptoms of fatigue, dizziness, or hypotension ('pacemaker syndrome'), which are asso- ciated with the presence of atrial cannon waves occurring as a result of simultaneous atrial and ventricular contraction. Upgrade of the system to a dual-chamber unit is necessary if symptoms are trouble- some. Newer pacing systems allow DDD pacemakers to act as VVI DDD AAI Fig. 16.4.12 Permanent pacemaker modes. Ventricular demand pacing, VVI (upper) with broad-complex ventricular complexes following the stimulus. Dissociated atrial activity can be seen. Atrial demand pacing, AAI (middle) with low amplitude bipolar pacing spike preceding the P- waves. Dual-chamber pacemaker, DDD (lower) with paced ventricular complexes following each P-wave (atrial tracking).

section 16 Cardiovascular disorders 3360 single-chamber atrial pacemakers, automatically switching to dual- chamber pacing should AV conduction fail, providing the benefits of atrial pacing with a lower risk of pacemaker syndrome. Follow-up Many patients with long-standing heart block treated by permanent pacing have no underlying cardiac rhythm, hence failure of the pacing system for whatever reason may be fatal and patients require follow-up in a pacemaker clinic. As well as detection of the com- plications described here earlier, the function of such a clinic is to assess the status of the pulse generator battery, and to maximize its life by programming the pulse generator output to the minimum consistent with a satisfactory safety margin. The design of pulse gen- erators and the battery characteristics normally allow prediction of the expected replacement date several months if not years ahead. However, premature battery depletion or pacemaker failure does occur, and patients should therefore be assessed at least annually by the clinic. Managing patients with permanent pacemakers Patients with a permanent pacing system can usually lead a perfectly normal life without limitations regarding physical activity. Driving is usually allowed 1 week after implantation. Patients should avoid strong electromagnetic fields and specific risks (arc welding ma- chines). Domestic appliances are not usually a problem unless faulty, and mobile phones are safe unless used in close proximity (<15 cm) to the device. Electronic surveillance systems and metal detectors at airports can affect pacemaker function. A significant proportion of patients with pacemaker and CRT de- vices will subsequently develop an indication for investigation with MRI. This has led to the development of MRI-compatible devices, which are now used routinely in younger patients or those where this form of imaging is likely to be required. Although the use of MRI in patients with pacemakers should be avoided, where the benefits of this investigation are thought to outweigh the risks, imaging can be relatively safely performed. Imaging should take place after consult- ation with the implanting cardiologist, and a cardiac physiologist or cardiologist should be in attendance during the procedure. Radiotherapy can also affect pacemaker function. Reprogramming is required before and after treatment in those patients who are pacing-dependent. Where the device lies directly within the radio- therapy field the pacemaker needs to be repositioned. In patients presenting with recurrent syncope, palpitations, or falls with a pacemaker in situ the cause is rarely due to pace- maker malfunction, although a pacing check is usually performed. Interrogation of modern pacing devices may also provide useful in- formation in patients with suspected tachyarrhythmias. Tachycardias Mechanisms of arrhythmogenesis The principal mechanisms responsible for tachyarrhythmias are those of

abnormal automaticity, triggered activity, or re-entry (Fig. 16.4.14). There is a complex interaction between the under lying substrate, such as previous myocardial infarction, a trig- gering event such as an extrasystole, and modulating influences, of which sympathetic stimulation and myocardial ischaemia are the most important. Automaticity Abnormal automaticity is defined as an inappropriate increase in the rate of discharge of a tissue that has physiological pace- maker properties (sinus node, AV node, or Purkinje fibres) or the pathological development of automaticity in atrial or ventricular myocytes (Fig. 16.4.14a). Such abnormalities are most commonly seen in the presence of ischaemia, sympathetic stimulation, or drug toxicity, especially digoxin. Automatic tachycardias are character- ized by an absence of initiation by extrasystoles, either spontan- eously or during electrophysiological testing. (a) (b) (c) Fig. 16.4.13 Pacemaker malfunction. (a) Failure to capture. The fourth stimulus fails to capture the ventricle. (b) Undersensing. The atrial pacemaker has failed to sense the preceding atrial activity and therefore delivered the second stimulus. This has captured the atrium, with the P-wave in the ST segment, and subsequent conduction to the ventricle. (c) Oversensing. This dual-chamber pacemaker has sensed an electrical artefact through the ventricular lead and as a result has suppressed ventricular pacing, with the absence of ventricular activation following the third P-wave. (a) (c) (b) (d) Fig. 16.4.14 Mechanisms of arrhythmia. (a) Increased automaticity. (b) Triggered activity due to early after-depolarizations. (c) Triggered activity due to delayed after-depolarizations. (d) Re-entry circuit. See text for details.

16.4 Cardiac arrhythmias 3361 Triggered activity The term ‘triggered activity’ is used to define an impulse initiation asso- ciated with a preceding action potential, and can be induced in vitro in tissues that do not demonstrate physiological automaticity. Two char- acteristic forms of depolarization may cause triggered activity. Early after-depolarizations These occur during the plateau phase of the action potential, prior to repolarization (Fig. 16.4.14b), and are more evident at slow heart rates, particularly in the presence of hypokalaemia and hypomag- nesaemia. Mutations in cardiac Na+ or K+ channels, or drugs that prolong myocardial repolarization by inhibiting one or more com- ponents of the outward potassium current, IK, (class IA and class III antiarrhythmics, tricyclic antidepressants, antihistamines, organo- phosphorus insecticides, and many others) predispose to the ap- pearance of early after-depolarizations in vitro. These changes are associated with the congenital and acquired long-QT syndromes and the arrhythmia torsades de pointes (see ‘Torsades de pointes and the long-QT syndromes’). Delayed after-depolarizations These are subthreshold depolarizations occurring after full repolari zation of the action potential (Fig. 16.4.14c). Their amplitude is in- creased by tachycardia or intracellular calcium overload and may reach a threshold at which an action potential is generated, potentially initiating a sustained tachycardia. Delayed after-depolarizations can be induced experimentally by digitalis overload and are the likely mechanism of digitoxic arrhythmias. Re-entry Most clinically important sustained tachycardias, whether of atrial, junctional, or ventricular origin, arise on the basis of re-entry. The establishment of a re-entry tachycardia requires the presence of a potential circuit comprising two limbs with different refractori- ness and conduction properties (Fig. 16.4.14d). A premature beat can be conducted in one limb of the circuit, but the other limb may still be refractory, resulting in unidirectional conduction block. If conduction is sufficiently slow, the tissue distal to the site of block in the refractory limb will have regained excitability before the ar- rival of the depolarizing wavefront, and conducts the activity retro- gradely. This results in reactivation of the initial conducting pathway and thus a circus movement tachycardia is established. Macro re- entry is defined as the occurrence of a re-entry circuit over a large area of the heart, such as in the presence of an accessory pathway (Fig. 16.4.15a). Micro re-entry occurs in a relatively small area

of the heart, for example at the border zone of an old myocardial infarc- tion, where conduction velocity is markedly slowed (Fig. 16.4.15b). The characteristic feature of a re-entrant tachycardia is that an ap- propriately timed extrastimulus can induce unidirectional block and initiate the arrhythmia. The tachycardia may be terminated by extrastimuli that depolarize the tissue ahead of the circulating wave- front and thus interrupt the circus movement. Differential diagnosis of tachycardias General principles The first and most important step in the diagnosis and manage- ment of tachycardias is to determine whether the arrhythmia arises within the atria and/or AV junction, or from the ventricles. An essential element in the differential diagnosis is to distinguish be- tween tachycardias with normal QRS-complex morphology and duration ('narrow-complex tachycardias'), and those where the QRS complexes are abnormal in morphology and increased in duration ('broad-complex tachycardias'). A guide to the differential diagnosis of tachyarrhythmias is provided in Fig. 16.4.16. Narrow-complex tachycardias Narrow-complex tachycardias arise through mechanisms that re- sult in ventricular activation via the AV node and His–Purkinje system and therefore show normal QRS morphology and duration (≤0.12 s) during tachycardia. Careful study of all leads of the ECG is necessary to assess regularity of QRS complexes and to iden- tify the presence of atrial activity (P-waves) (Fig. 16.4.16). The re- lationship of the PR to the RP interval is helpful in determining mechanism of narrow-complex tachycardias. In supraventricular tachycardias (see 'Supraventricular tachycardia'), P-waves may not be visible, or may occur immediately following the QRS com- plex. A long RP interval is found in atrial tachycardia, atypical AV nodal re-entry tachycardia and AV re-entry involving a slowly conducting accessory pathway as the retrograde limb. Atrial flutter waves are most commonly evident in the inferior limb leads or in lead V1. Broad-complex tachycardias Few areas in cardiology cause more difficulty, or result in more mis- management, than the diagnosis of broad-complex tachycardias. Whereas it is safe to assume that virtually all narrow-complex tachycardias have a supraventricular origin, broad-complex tachycardias (QRS duration ≥0.12 s) may arise either from the ven- tricle or from supraventricular mechanisms, the latter occurring if there is bundle branch block, either pre-existing or functional (ab- erration) as a result of the high rate (Fig. 16.4.16). An additional cause of aberrant conduction is activation of the ventricles via an accessory pathway. If the broad QRS morphology during tachycardia is identical to that in sinus rhythm, then a supraventricular origin is likely, with fixed bundle branch block. However, no ECG in sinus rhythm may be available, and difficulties in diagnosis and management arise when ventricular tachycardia is not recognized and is misdiagnosed as 'SVT with aberration'. This usually happens as a result of certain Accessory pathway Infarct border zone) b ( )a (Fig. 16.4.15 Examples of re-entry tachycardias. (a) Macro re-entry circuit involving an accessory pathway, which results in atrioventricular re-entry tachycardia. (b) Micro re-entry circuit at the border zone of a myocardial infarction.

 failings and misconceptions, the commonest being that the clinical context is not considered: • Age of the patient—middle-aged or older individuals presenting with a recent history of broad-complex tachycardia, and who give a history of myocardial infarction or congestive heart failure, are more likely to have ventricular than supraventricular tachycardia. However, ventricular tachycardia can also arise in young patients. • Haemodynamic status of the patient—it is often assumed that ventricular tachycardia should cause haemodynamic collapse, whereas patients may in fact be haemodynamically stable if the rate is not excessively fast or if underlying cardiac function is good. Conversely, supraventricular tachycardias may cause syn- cope, hypotension, or shock if sufficiently rapid, or if there is underlying heart disease. • Nature of the episodes of palpitation—it is often not appreciated that

ventricular tachycardia can present with a typical history of paroxysmal self-terminating episodes, just as in the case of supraventricular tachycardia. The importance of making a correct diagnosis in broad-complex tachycardia is twofold. First, inappropriate acute therapy of the tachyarrhythmia can be avoided. In particular, the use of verapamil in ventricular tachycardia misdiagnosed as supraventricular tachy- cardia is associated with a high risk of haemodynamic collapse as a result of its negative inotropic effect, coupled with its lack of efficacy in terminating ventricular tachycardia. Secondly, if the original ar- rhythmia has been misdiagnosed, then the adverse prognostic sig- nificance of ventricular tachycardia will be overlooked. Appropriate investigation and long-term management may not be instituted. It is therefore important that a diagnosis of SVT with aberration is made only if the ECG displays typical left or right bundle branch block with none of the features suggestive of VT listed in Fig. 16.4.16. In addition to attention to the history and 12-lead ECG, the response to transient AV nodal blockade with adenosine will assist diagnosis in many patients (Table 16.4.5). General principles of management Many cardiac arrhythmias are benign and require no interven- tion. The main indications for treatment are to relieve symptoms, or to prevent complications such as myocardial ischaemia, cardiac failure, embolism, or arrhythmic sudden death. Precipitating fac- tors such as myocardial ischaemia/infarction, infection, thyrotoxi- cosis, alcohol, electrolyte disorders, or drug toxicity must be sought and treated if possible. The therapy indicated will commonly be influenced by the presence of underlying structural heart disease such as myocardial ischaemia/infarction or left ventricular dys- function and can include drug therapy, device implantation, or radiofrequency ablation. Acute management of tachycardia An algorithm for the treatment of tachyarrhythmias is shown in Fig. 16.4.17. Assessment of the patient’s cardiorespiratory status takes precedence. R-wave synchronized, direct current (DC) QRS <120 ms Yes No Regular QRS Yes No Yes Atrial activity visible No • Atrial flutter • Atrial tachycardia Yes • Ventricular tachycardia No • AVNRT • AVRT • Atrial tachycardia No No Yes Yes A>V rate No RP > PR No • Atrial tachycardia • PJRT • Atypical AVNRT Yes • Atrial fibrillation • Atrial flutter • Atrial tachycardia • AF /Afl /AT with BBB* • Pre-excited AF • Polymorphic VT • Torsades de Pointes ECG features of VT** No QRS atypical for RBBB or LBBB* Yes or unknown 1:1 AV relationship Yes Regular QRS No or unknown No V>A rate Atrial activity visible No Yes Yes Yes *Atypical features of BBB favouring VT LBBB pattern:

qR or qS in lead V6

R in V1 >30 ms

Onset R to nadir of S >60 ms in V1 RBBB pattern:

qR, Rs, or Rr in V1

Axis > +90 or < −90 **Features favouring VT In 12-lead ECG:

Fusion or capture beats

Extreme axis deviation In precordial leads:

Concordance (all either positive or

negative)

Absence of RS pattern in any chest

lead

Onset R to nadir of S > 100ms QRS identical to that in sinus rhythm Fig. 16.4.16 Algorithm for diagnosis of tachycardia from 12-lead ECG. A, atrial rate; AF, atrial fibrillation; Afl, atrial flutter; AT, atrial tachycardia; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; BBB, bundle branch block; LBBB, left bundle branch block; PJRT, permanent junctional reciprocating tachycardia; PR, PR interval; RBBB, right bundle branch block; RP, RP interval; V, ventricular rate; VT, ventricular tachycardia. See text for details. Table 16.4.5 Diagnostic use of intravenous adenosine Arrhythmia Response Atrial tachycardia Atrial flutter Atrial fibrillation Transient AV block reveals atrial arrhythmia Rarely terminated AVNRT AVRT Terminates tachycardia by anterograde (AV) block Ventricular tachycardia Not terminated 1:1 VA conduction may be blocked, revealing AV dissociation For abbreviations, see Fig. 16.4.16.

16.4 Cardiac arrhythmias 3363 cardioversion under general anaesthesia or deep sedation is the most effective and immediate means of terminating sustained tachycardias, and should be employed when the tachycardia is associated with haemodynamic compromise (Fig. 16.4.18). Although atrial flutter may respond to low-energy cardioversion (50–100 J), other arrhythmias normally require energies of 100– 360 J for termination (150–200 J for biphasic shocks). The use of DC shock in the termination of ventricular fibrillation is discussed later in this chapter. In patients with haemodynamically stable tachycardias, manoeuvres that produce transient vagal stimulation such as the Valsalva manoeuvre or carotid sinus massage may be em- ployed. Similarly, adenosine is used pharmacologically to pro- duce transient slowing or block of the sinus node or AV node (see ‘Adenosine’). Vagal manoeuvres or adenosine will often terminate arrhythmias dependent on the AV node, and are also useful diagnostic tools, since transient interruption of AV nodal conduction may reveal the tachycardia mechanism (Table 16.4.5). Atrial tachyarrhythmias will not normally be terminated by vagal stimulation or adenosine, but an increase in AV block reveals the underlying atrial rhythm. Re-entry tachycardias may be terminated by the delivery of appropriately timed extrastimuli that depolarize part of the re- entry circuit prior to the arrival of the wavefront and interrupt the arrhythmia. Simple overdrive pacing can be effective in the termination of atrial flutter, AV nodal re-entry, AV (ortho- dromic) re-entry tachycardia, or sustained ventricular tachycardia (Fig. 16.4.19). The cardiac chamber in question is paced for brief periods (e.g. 6–12 beats), at a rate just above that of the tachy- cardia, with repeated attempts sometimes necessary at gradually increasing rates. Overdrive atrial or ventricular pacing may result in degeneration into atrial and ventricular fibrillation, respect- ively, hence facilities for immediate defibrillation must be avail- able. Implantable antitachycardia pacing facilities are incorporated into implantable cardioverter–defibrillators (see ‘Implantable cardioverter–defibrillators’). Haemodynamic compromise Yes No DC cardioversion Vagal manoeuvres IV adenosine* Terminated QRS <120ms Yes No IV amiodarone** IV lidocaine IV sotalol IV verapamil** IV β-blocker IV flecainide IV procainamide Overdrive pacing*** Persistent or re-initiated Terminated Terminated Persistent or re-initiated

- Caution with broad complex tachycardias or known pre-excitation. Adenosine is contraindicated in pre-excited AF and asthma ** Use only one drug from list *** If clinically appropriate, e.g. frequently recurring tachycardia Persistent or re-initiated Fig. 16.4.17

Algorithm for the acute management of tachyarrhythmias. 200 J I II III 1s Fig. 16.4.18 Synchronized DC cardioversion of atrial fibrillation.
A 200 J DC shock is delivered during atrial fibrillation to coincide with the R-wave of the QRS complex. This shock terminates the arrhythmia with restoration of normal sinus rhythm. I aVF V1 RV 1s S S S S S S S S Fig. 16.4.19 Termination of ventricular tachycardia by overdrive ventricular pacing. During ventricular tachycardia, a burst of eight stimuli (S) results in termination of the tachycardia and resumption of normal sinus rhythm. Surface leads I, aVF, V1, and intracardiac electrograms from the right ventricular apex (RV) are shown.

section 16 Cardiovascular disorders 3364 Treatments for tachycardias Antiarrhythmic drug therapy The Vaughan Williams classification is based on the effects of antiarrhythmic drugs in isolated normal tissue, and although many drugs act by more than one mechanism, the classification is still in widespread use. The effects of the major classes of antiarrhythmic drug activity at the tissue level, and the associated electrocardio- graphic changes, are listed in Table 16.4.6. Individual drugs are de- scribed in Table 16.4.7. Class I activity Class I antiarrhythmic drugs act by inhibiting the rapid inward so- dium current. Class Ia agents (e.g. quinidine, procainamide, and disopyramide) increase the cardiac action potential duration and have intermediate effects on the onset and recovery kinetics of the sodium channel and hence on intracardiac conduction. Class Ib agents (e.g. lidocaine and mexiletine) shorten the cardiac action potential duration and have very rapid offset kinetics that result in minimal slowing of normal intracardiac conduction. Class Ic drugs (e.g. flecainide and propafenone) have no major effect on ac- tion potential duration, but produce the most long-lasting effect on cardiac sodium channel kinetics and the most marked slowing of intracardiac conduction. Class II activity Class II activity is defined as antagonism of the arrhythmogenic effects of catecholamines. The commonest agents in this class are the competitive β-adrenoceptor blockers. Other agents such as propafenone have a weak β-receptor blocking activity, and amiodarone (see next paragraph) exhibits a noncompetitive sym- patholytic effect. Class III activity The class III mode of antiarrhythmic activity comprises length- ening of the cardiac action potential duration and hence of the effective refractory period. Drugs in this class possess a broad spec- trum of activity against atrial, supraventricular, and ventricular arrhythmias. Currently available class III agents act by inhibiting the rapid component of the outward potassium current IKr. Dofetilide and ibutilide are examples of drugs with ‘pure’ class III antiarrhythmic actions. Sotalol is a nonselective β-adrenoceptor antagonist that also possesses class III activity. Amiodarone pos- sesses antiarrhythmic activity in all four Vaughan Williams classes. Class IV activity Class IV drugs (e.g. verapamil and diltiazem) reduce the inward calcium current ICa in sinoatrial and AV nodal tissues. They are used to prevent or interrupt re-entry arrhythmias involving the AV node (e.g. AV nodal re-entry tachycardia), or to slow the ven- tricular response in atrial fibrillation or flutter. The dihydropyridine calcium antagonists, such as amlodipine and nifedipine, have no antiarrhythmic action. Digoxin The antiarrhythmic activity of digoxin is not explained within the Vaughan Williams classification and appears to be mediated pre- dominantly through vagal stimulation. It is used to slow ventricular rate in atrial fibrillation. Adenosine Adenosine, a naturally occurring purine nucleoside, is used pharmacologically to produce transient slowing or block of the sinus node or atrioventricular node. It is of particular value in view of its extremely short plasma half-life (c.2 s), which confers safety. It must be administered by rapid intravenous bolus injection, using incremental doses usually from 6 to 18 mg, to achieve the desired therapeutic effect. Adenosine is contraindicated in pre-excited atrial fibrillation or in severe

asthma and cautioned in patients with known pre-excitation syndrome (see ‘Pre-excitation syndromes (Wolff–Parkinson–White syndrome)’). Nonpharmacological therapy Cardioversion External electrical cardioversion, as just described, can be used electively to restore normal rhythm in patients with persistent ar- rhythmia. Failure of external cardioversion of atrial fibrillation occurs in some patients as a result of various factors, including in- creased transthoracic impedance due to obesity, prolonged atrial fibrillation, left ventricular dysfunction, and left atrial dilatation. Internal cardioversion can be successful in many of these patients. Table 16.4.6 Classification of antiarrhythmic drug activity ECG effect Tissue effect HR PR QRS QT SA node Atrium AV node Ventricle Class Ia 0 0/– + ++ 0 ++ – ++/– Ib 0 0 0 0/– 0 0 0 ++/– Ic 0 + ++ + 0 ++ 0/+ ++/– Class II – + 0 0 ++ ++ ++ +/0 Class III 0/– 0/+ 0 ++ 0/+ ++ 0/+ ++/– Class IV 0/– + 0 0 0/+ +/– ++ 0 Digoxin 0/– + 0 0 0/+ 0/– ++ 0/– Adenosine – + 0 0 ++ 0/– ++ 0 ECG effect: +, increases; −, decreases; 0, no effect; HR, heart rate. Tissue effect: +, antiarrhythmic activity; −, potential adverse or proarrhythmic effect; 0, no effect.

 The procedure involves the introduction of specialized electrode catheters that permit DC shock delivery between electrodes in the right atrium and the pulmonary artery or coronary sinus, providing a current field that achieves depolarization of both atria. Implantable cardioverter–defibrillators Patients identified as being at high risk of sudden cardiac death (e.g. a history of spontaneous ventricular arrhythmias, out-of-hospital cardiac arrest, or factors indicating high risk of developing a malig- nant arrhythmia) may be treated with an implantable cardioverter– defibrillator (ICD). A transvenous rate-sensing/shocking electrode is introduced via the subclavian vein to the right ventricular apex, with the generator implanted in the pectoral region (Fig. 16.4.20). If a heart rate above the threshold programmed by the device is recognized, a shock is delivered between the intracardiac shocking electrode and the generator casing. Some devices also include a right atrial electrode to sense atrial activation. A third lead lying in a tributary of the coronary sinus can be implanted to pace the left ventricle and help restore electromechanical synchrony in those with heart failure, reduced ejection fraction, and evidence of dyssynchrony (cardiac resynchronization therapy or ‘CRT’). An ICD can be programmed to deliver ventricular antitachycardia Table 16.4.7 Commonly used antiarrhythmic drugs Principal indication Dose Adverse effects IV Oral Class Ia Quinidine AF cardioversion – 1–2 g/day Hypersensitivity, GI symptoms, QT prolongation, hypotension Disopyramide AF prophylaxis VT termination 2 mg/kg 300–600 mg/day Negative inotropy, QT prolongation, parasympathetic blockade (accelerated AV conduction, urinary retention, dry mouth, blurred vision) Procainamide AF cardioversion VT termination 100 mg/5 min up to 1000 mg 1–6 mg/min 2–6 g/day Hypotension, QT prolongation, GI upset, lupus syndrome Class Ib Lidocaine (lignocaine) VT termination VT/VF prophylaxis 100 mg bolus
1–4 mg/min Ineffective CNS—confusion, dysarthria, fits Class Ic Flecainide AF cardioversion AF prophylaxis WPW prophylaxis 2 mg/kg 100–300 mg/day Proarrhythmia, negative inotropy, CNS disturbance Propafenone AF cardioversion AF prophylaxis WPW prophylaxis – 450–900 mg/day Proarrhythmia, negative inotropy, CNS disturbance, bronchoconstriction Class II Various, e.g. bisoprolol AF prophylaxis AF rate control SVT prophylaxis Sudden death prophylaxis – 5–10 mg/day Bradycardia, -ve inotropy, cold extremities, bronchoconstriction, lethargy Class III Sotalol AF termination AF prophylaxis WPW prophylaxis VT prophylaxis 2 mg/kg 160–320 mg/day Bradycardia, negative inotropy, cold extremities, bronchoconstriction, lethargy, QT prolongation Amiodarone AF termination AF prophylaxis WPW prophylaxis VT prophylaxis 300 mg in 30–60 min, then 900 mg/24 h 0.6–1.2 g/day loading first 2 weeks, then

100–400 mg/day Bradycardia, photosensitivity, skin pigmentation, hypo-or hyperthyroidism, alveolitis, hepatitis, peripheral neuropathy, epididymitis Class IV Verapamil SVT termination SVT prophylaxis AF rate control 5–10 mg 240–480 mg/day Negative inotropy, AV block, flushing, constipation Other Digoxin AF rate control 0.125–0.25 mg/day Anorexia, nausea, vomiting, AV block, atrial and ventricular arrhythmias Adenosine SVT termination 6–18 mg by incremental bolus Flushing, chest pain, bronchospasm, transient AV block AF, atrial fibrillation; SVT, supraventricular tachycardia (atrioventricular nodal and atrioventricular re-entrant tachycardia); VT, ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome.

section 16 Cardiovascular disorders 3366 pacing for tolerated tachycardias, with shock delivery available for faster rates or if pace-termination fails. ICDs are expensive, complex, and require regular specialist follow-up. For patients without an indication for pacing, cardiac resynchronization therapy or requirement for antitachycardia pacing (i.e. sustained monomorphic ventricular tachycardia), a subcutaneous ICD (S-ICD) is an alternative treatment option for prevention of sudden cardiac death. The lead is tunnelled super- ficial to the sternum and connected to a generator in an axillary pocket (Fig. 16.4.21). Radiofrequency ablation Selective ablation of part of a re-entry circuit, an arrhythmic focus, or the AV node is used increasingly in the management of arrhythmias and offers the opportunity of curative treat- ment. Radiofrequency energy is delivered between the tip of an intracardiac electrode positioned at the appropriate site and an indifferent surface electrode placed over the lower back or thigh. The energy produces a localized necrotic lesion 2–3 mm in diameter, which results in local conduction block. Current in- dications for radiofrequency ablation are listed in Table 16.4.8, and specific issues are discussed next in relation to individual arrhythmias. Arrhythmia surgery The ‘maze’ procedure for atrial fibrillation involves creating a series of lines of conduction block in the left and right atria, either by incisions or by ablation. This prevents the development of atrial re-entry circuits while permitting AV conduction. Surgical man- agement of recurrent ventricular tachycardia by mapping and re- section of the re-entry circuit is occasionally performed, but has been largely superseded by ablation or ICD therapy. Specific causes of arrhythmias Extrasystoles The term extrasystole is used to describe a premature beat arising from a focus other than the sinus node. Extrasystoles are also de- scribed as premature beats, premature contractions, premature de- polarizations, or ectopic beats. Atrial extrasystoles Atrial extrasystoles are recognized by a premature P-wave of dif- ferent morphology from the sinus P-wave (Fig. 16.4.22a), which can be hidden within the ST segment or T-wave of the preceding sinus beat. Premature atrial extrasystoles that occur before full re- covery of the AV node will be followed by prolongation of the PR (a) (b) Shock VP VP Fig. 16.4.20 Implantable cardioverter–defibrillator (ICD). (a) Chest radiograph showing the ICD generator in the left pectoral region, connected to a lead which passes via the left subclavian vein and superior vena cava to the heart. The tip of the lead is in the right ventricular apex. Cardiac rhythm is sensed from the electrodes at the tip of the lead, and shocks can be delivered between the metal casing of the generator and the right ventricular coil (thick portion of lead). (b) Discharge from an ICD. A rapid polymorphic ventricular tachycardia is terminated by a shock (typically 36 J) from the device. Electrograms shown are retrieved from the memory of the device, upper tracings from the shocking circuit (generator can to ventricular coil) and lower tracings from the sensing circuit (bipolar electrodes at the tip of the catheter in the right ventricle. The shock is followed by ventricular pacing (VP). Fig. 16.4.21 CXR showing subcutaneous ICD connected to a generator in an axillary pocket.

16.4 Cardiac arrhythmias 3367 interval, or, if sufficiently premature, complete failure of conduction (Fig. 16.4.22b). Nonconducted atrial extrasystoles must be distin- guished from sinus arrest or second-degree AV block. An atrial extrasystole will commonly reset the sinoatrial node, such that the next sinus beat occurs earlier than expected with respect to the preceding sinus beat, and the pause is less than compensatory. Atrial extrasystoles are a common finding in healthy people, par- ticularly with increasing age, but are more frequent in the presence of increased atrial pressure or stretch such as in cardiac failure or chronic mitral valve disease. Patients should be reassured that the arrhythmia is benign, and that drug treatment is rarely necessary. If treatment is required on symptomatic grounds, β-adrenergic blockers may be used, but class I antiarrhythmic drugs should be avoided in view of their proarrhythmic risk. Junctional extrasystoles Junctional extrasystoles are identified by the appearance of a premature, normal QRS complex in the absence of a preceding P-wave. The atria as well as the ventricles may be activated, re- sulting in an inverted P-wave simultaneous with the QRS com- plex, or inscribed within the ST segment. The significance and management of junctional extrasystoles are similar to those of atrial extrasystoles. Ventricular extrasystoles Ventricular extrasystoles are identified by the appearance of a bi- zarre, wide QRS complex not preceded by a P-wave (Fig. 16.4.23). There is commonly ST-segment depression and T-wave inversion. Ventricular extrasystoles may be intermittent or occur with a fixed relationship to the preceding normal beats, that is, 1:1, 1:2 (bigeminy or trigeminy). Ventricular extrasystoles occur in otherwise normal hearts but are found particularly in the presence of structural heart disease. Benign ventricular ectopy is common and indicated by the following: normal resting 12-lead ECG, structurally normal heart on echo, absence of other cardiac symptoms, resolution with ex- ercise, and the absence of a family history of early cardiac disease or sudden cardiac death. Ventricular ectopics occur commonly in the acute phase of myocardial infarction, but are also seen in the postinfarction phase, and in the presence of severe left ventricular hypertrophy or dysfunction of whatever cause. While the presence of frequent ectopy following myocardial infarction conveys an ad- verse prognosis, their suppression with class I agents (flecainide) actually increases mortality. Extrasystoles may produce symptoms that require treatment in a minority of cases. The safest option is β-blockade. Atrial arrhythmias Atrial fibrillation Mechanisms Studies of patients with paroxysmal atrial fibrillation suggest that the arrhythmia may be triggered by one or more rapidly discharging foci, which are commonly situated in the pulmonary veins. Table 16.4.8 Indications for radiofrequency ablation Diagnosis Ablation target Success Comments AVRT Accessory pathway +++ Pre-excited AF Accessory pathway +++ AVNRT Slow pathway +++ 0.5–1 % risk of CHB Atrial flutter TVA–IVC isthmus +++ Focal atrial tachycardia Tachycardia focus ++ Paroxysmal AF Pulmonary vein isolation ++ Moderate recurrence rate Persistent AF Extensive LA ablation + Often requires >1 procedure Permanent AF AV node +++ Requires permanent pacing, does not cure AF Scar-related ventricular tachycardia Re-entry circuit + High recurrence rate Focal ventricular tachycardia Site of origin ++ Especially RVOT focus AVRT, atrioventricular re-entry tachycardia; AF, atrial fibrillation; AVNRT, atrioventricular nodal re-entry tachycardia; LA, left atrial; CHB, complete heart block; TVA, tricuspid valve annulus; IVC, inferior vena cava; RVOT, right ventricular outflow tract. (a) (b) Fig. 16.4.22 Atrial extrasystoles. (a) An atrial extrasystole, with an abnormal P-wave at the end of the preceding T-wave, occurs following a sinus beat. (b) Blocked atrial extrasystoles. In the same patient, atrial extrasystoles occur following each sinus beat. They are earlier than those in (a), and the AV node is refractory because of the proximity of the atrial extrasystoles to the preceding beat, and conduction is blocked. Fig. 16.4.23 Ventricular extrasystole (open circle). No retrograde atrial activation occurs, and the P-wave sequence is undisturbed (arrowed).

section 16 Cardiovascular disorders 3368 In the presence of a heterogeneous substrate, it is thought that such a trigger gives rise to high frequency re-entry in certain areas (rotors) which perpetuate fibrillatory conduction. Rapid atrial ac- tivation induces a process of electrical remodelling, which renders cardioversion and maintenance of sinus rhytshm more difficult (‘atrial fibrillation begets atrial fibrillation’). The initial mechanism of remodelling is thought to be intracellular calcium overload re- sulting in shortening of the atrial refractory period, although more prolonged atrial tachyarrhythmias result in downregulation of cal- cium entry and dedifferentiation of atrial myocytes. Structural changes, including interstitial fibrosis, also occur and further per- petuate the arrhythmia. Classification and aetiology Atrial fibrillation is a common arrhythmia affecting 1% of the popu- lation, the incidence increases with advancing age to 5–10% in very elderly individuals. It is classified as paroxysmal (self-terminating episodes <7 days duration but usually <48 h), persistent (termin- ates after 7 days or following intervention, e.g. electrical cardiover sion), and permanent (where there is no strategy to terminate the arrhythmia). There are numerous causes of the arrhythmia (Box 16.4.2), but in many instances no obvious aetiological factor can be identified, and the patient is described as having ‘lone’ atrial fibrillation. Atrial fib- rillation carries adverse prognostic significance, in part through its association with organic heart disease but also as an important risk factor for mortality and the development of stroke and systemic em- bolism due to stasis and thrombus formation in the left atrium. The risk of stroke is particularly high in patients with mitral stenosis or mitral valve replacement and permanent atrial fibrillation. Presentation Patients with structurally normal hearts with a relatively slow ven- tricular rate may be asymptomatic and only picked up during routine screening. The onset of atrial fibrillation may trigger palpitations, fatigue, breathlessness, or angina in patients with underlying cor- onary disease. Presentation with syncope is relatively uncommon but may occur in the context of sinus node disease where spontan- eous reversion to sinus rhythm is associated with prolonged sinus node recovery. Atrial fibrillation may be detected at the time of presentation or during the investigation of stroke. Atrial fibrillation results in loss of the atrial contribution to left ventricular filling, which can result in a worsening of heart failure. Symptoms and impairment of left ventricular function (‘tachycardiomyopathy’) arise as a result of a rapid uncontrolled ven- tricular rate. In addition, uncontrolled atrial fibrillation can cause further impairment of ventricular filling in mitral stenosis and con- ditions associated with left ventricular diastolic dysfunction such as hypertensive left ventricular disease and aortic stenosis. Diagnosis The characteristic ECG findings in atrial fibrillation of recent onset are of rapid, irregular ‘f’ waves at a rate of 350–600/min. These are associated with an irregular ventricular response because of variable conduction through the AV node (Fig. 16.4.24a). With increasing duration of persistent atrial fibrillation, the amplitude of the ‘f’ waves diminishes until they are no longer visible. Under these cir- cumstances, atrial fibrillation is diagnosed by the absence of P-waves and the irregular ventricular response (Fig. 16.4.24b). Atrial fibrillation is classified into three patterns: paroxysmal, persistent, or permanent. In paroxysmal atrial fibrillation, spontan- eously terminating attacks of palpitation last anything from a few seconds to a few days. The ventricular rate is often rapid and the patient may be severely symptomatic. The term ‘persistent atrial fib- rillation’ is used to describe instances where the arrhythmia is not self-terminating, but where sinus rhythm can be restored by elec- trical or pharmacological cardioversion. Permanent atrial fibrilla- tion describes the situation where both patient and physician accept the arrhythmia and rhythm control (i.e. the restoration of sinus rhythm) is not being pursued. At this stage, the ventricular rate is often slower, and the patient may be unaware of the irregular pulse or of palpitations. General principles of management Appropriate management of atrial fibrillation depends on the pres- ence or absence of symptoms,

haemodynamic status, duration of arrhythmia, and the presence of factors affecting the successful maintenance of sinus rhythm. Management is based on the pre- vention of thomboembolic complications as the initial priority, and the use of a rate-or rhythm-control strategy in a patient-centred and symptom-directed approach. Trials in asymptomatic patients have failed to demonstrate a mortality or morbidity benefit from re- storing and maintaining sinus rhythm with antiarrhythmic therapy. In the elderly asymptomatic or mildly symptomatic patient, particu- larly with long-standing atrial fibrillation, a rate control strategy is sufficient. Box 16.4.2 Aetiology of atrial fibrillation • Increased atrial pressure—mitral valve disease, congestive heart failure, left ventricular hypertrophy, restrictive cardiomyopathy, pulmonary embolism • Atrial volume overload—atrial septal defect • Myocardial ischaemia/infarction • Thyrotoxicosis • Alcohol • Sinoatrial disease • Infiltration—constrictive pericarditis, tumour • Infection—systemic, e.g. pneumonia; cardiac: myo/pericarditis • Cardiac or thoracic surgery • Idiopathic—'lone' atrial fibrillation (a) (b) Fig. 16.4.24 Atrial fibrillation. (a) Coarse atrial fibrillation of recent onset. (b) Fine atrial fibrillation in a patient with long-standing valvular disease. Surface V1 leads are shown.

16.4 Cardiac arrhythmias 3369 Emergency presentation Atrial fibrillation of recent onset may terminate spontaneously, par- ticularly if associated with an acute febrile illness. Outside the con-text of an acute febrile illness, an attempt to restore sinus rhythm should be made unless the arrhythmia is obviously long-standing (>48 h) or is associated with advanced organic heart disease. Underlying precipitating factors such as thyrotoxicosis should be corrected before attempting cardioversion. Chemical or pharmacological cardioversion may be achieved with class Ia, Ic, or III agents. Class Ia agents accelerate the ven- tricular rate by virtue of their anticholinergic action on the AV node and must be used in combination with AV nodal blocking agent (e.g. digoxin, β-blocker, or calcium channel blocker). For patients without significant underlying heart disease, the current drugs of choice are the class Ic agents (e.g. flecainide 2 mg/kg intravenously over 30 min). Class III drugs are safer in the presence of left ven- tricular dysfunction or ischaemic heart disease (e.g. amiodarone 300 mg intravenously over 30 min, followed by 900 mg/24 h until cardioversion). The class III agents ibutilide and vernakalant have approval for this indication in some countries. Normally, only one drug should be tried in any individual patient. If drug therapy fails, DC cardioversion is commonly effective. Given that atrial fibrillation is a risk factor for the development of intracardiac thrombus formation, cardioversion, by chemical or electrical means, should not be attempted acutely if arrhythmia has clearly been present for longer than 48 h. Given that atrial fibril- lation may have developed asymptomatically, any doubt about the duration of arrhythmia onset should prompt thromboprophylaxis. Anticoagulation plus rate control with a β-blocker, calcium channel blocker, or digoxin should be considered in these circum- stances. However, in the presence of haemodynamic compromise, the benefit of achieving sinus rhythm may outweigh the poten- tial risk of embolism and attempt to restore sinus should be made. Transoesophageal echocardiography is useful in this situation to ex-clude left atrial thrombus. The strategy used will therefore depend upon the clinical presen- tation and is summarized in Box 16.4.3. Paroxysmal atrial fibrillation Paroxysmal atrial fibrillation is a self-terminating, recurrent ar- rhythmia, often associated with marked symptoms of palpitations. The goal of treatment is the maintenance of sinus rhythm and the amelioration of symptoms. In patients with infrequent paroxysms, drug therapy may not be necessary, or a 'pill in the pocket' approach can be used with selected patients without structural heart disease. For this, the patient takes a dose of an antiarrhythmic drug after the onset of arrhythmia (e.g. flecainide 100 mg), if this has previously been shown to be safe and effective under hospital supervision. In those with

recurrent paroxysmal atrial fibrillation, prophylactic therapy should be considered. No drug is entirely satisfactory and a β-blocker is often prescribed as first-line therapy. If this is ineffective, other antiarrhythmic therapy should be started. Class Ic agents (flecainide or propafenone) are effective and reasonably safe in the absence of underlying ischaemia, history of coronary artery disease, or left ventricular dysfunction, and are usually coprescribed with an AV nodal blocking drug. Amiodarone is effective but can be associ- ated with significant adverse effects and should be reserved for when the aforementioned measures fail. In the tachycardia–bradycardia syndrome, implantation of a permanent pacemaker may be required to control bradycardia and to allow antiarrhythmic therapy for the treatment of tachycardia. Catheter ablation may be considered as first line or for those in whom pharmacological therapy has failed. The goal of catheter ablation is to achieve electrical isolation of the pulmonary veins; clinical success rates are 70–80% from a single procedure. Persistent atrial fibrillation Persistent atrial fibrillation is not self-terminating, usually requires electrical cardioversion to achieve sinus rhythm, and has a high recurrence rate even after successful cardioversion. The key deci- sion is whether to employ a rhythm or rate control strategy. The AFFIRM trial showed no overall mortality benefit of a rhythm- control strategy in patients in whom a rhythm-control strategy in not indicated on the basis of symptoms. In general, a rate control strategy should be employed in asymptomatic or mildly symptom- atic individuals, in older people, and in those with contraindica- tions to antiarrhythmic therapy or cardioversion. This group should be treated as having permanent atrial fibrillation. In more severely Box 16.4.3 Cardioversion for atrial fibrillation 1 Defined onset <48 h with minor symptoms, haemodynamic stability, and no intercurrent illness 50% or more of patients will cardiovert spontaneously particularly in the context of prior paroxysmal symptoms. Rate control with oral β-blockade (e.g. bisoprolol 5 mg) may be all that is required ini- tially. Administration of LMWH is indicated in case cardioversion does not occur spontaneously within 24 h. Early echocardiography is required to assess for structural heart disease. In the presence of normal LV function and absence of a history of ischaemic heart disease consider oral flecainide loading (300 mg) or IV flecainide (2 mg/kg over 30 min). In the context of coronary disease or LV dys- function, consider oral amiodarone. 2 Defined onset >48 h/no defined onset, with minor symptoms, haemodynamic stability, and no intercurrent illness Rate control with oral β-blockade or rate-limiting calcium channel blocker as first line. Oral digoxin if other agents are contraindicated. Commence warfarin. Outpatient review and decision regarding rate or rhythm control depending on symptoms. 3 Defined onset >48 h/no defined onset, with haemodynamic in- stability, and no intercurrent illness Oral digoxin loading pending urgent echocardiographic assess- ment, then β-blockade if required (in the absence of cardiogenic shock or severe LV dysfunction or aortic stenosis on echo). Consider IV amiodarone and TOE-guided cardioversion in patients failing to respond (emergency cardioversion may be required without TOE in patients in imminent danger of cardiorespiratory arrest). 4 Rapidly conducted atrial fibrillation in conjunction with intercurrent illness In the context of a prior diagnosis of well-controlled permanent atrial fibrillation, treatment should be directed at the underlying illness and continuing the current rate of control medication. Patients with new-onset atrial fibrillation should be treated with rate control (as aforementioned) and anticoagulation with LMWH. Where haemodynamic compromise is felt to be due to atrial fib- rillation rather than the underlying illness, chemical or electrical cardioversion may be attempted depending on the duration of the arrhythmia (see earlier); however, the early recurrence rate is high. LMWH, low molecular weight heparin; LV, left ventricular; TOE, trans oesophageal echocardiography.

section 16 Cardiovascular disorders 3370 symptomatic or younger patients, or in those with atrial fibrilla- tion due to a treated precipitant, a rhythm-control strategy may be more appropriate. However, treatment choice has to be tailored to the individual and both options should be discussed with the patient. In patients with multiple comorbidities (e.g. chronic ob- structive pulmonary disease, heart failure, ischaemic heart disease), the contribution of atrial fibrillation to the patient's limitation may not be immediately clear. In such cases an attempt at restoring sinus rhythm may be worthwhile to clarify whether a rhythm-control strategy is justified. Prophylaxis of thromboembolism should be considered in both groups. If a rhythm-control strategy is adopted, elective cardioversion should be scheduled. Given that cardioversion may be associated with embolism, patients undergoing this procedure should be treated with warfarin or a non-VKA oral anticoagulants (NOAC) for at least 3 weeks beforehand, and this should be continued long term if warranted according to risk stratification, and for at least 4 weeks in those at low risk of thromboembolism, otherwise long- term anticoagulation is indicated irrespective of the apparent success of rhythm control. There is a high risk of recurrent atrial fibrillation (up to 50% at 1 year) and antiarrhythmic prophy- laxis should be considered. First-line therapy is often a simple β-blocker followed by a class Ic agent if there is no structural heart disease. Amiodarone may also be considered, and treatment prior to cardioversion increases the likelihood of its success. Finally, radiofrequency ablation may be employed but this requires more extensive left atrial ablation compared to paroxysmal atrial fibril- lation (Fig. 16.4.25), with a lower success rate, and often requires more than one procedure. Permanent atrial fibrillation In permanent atrial fibrillation, restoration of sinus rhythm is not feasible or is unsuccessful and chronic management involves con- trol of ventricular rate. Traditionally, the mainstay of treatment has been digoxin, at a dose titrated to achieve adequate slowing in the ventricular rate at rest, with therapeutic plasma concentrations. Despite adequate rate control at rest, patients commonly have an uncontrolled heart rate on exercise. Control of rate response with other AV nodal blocking drugs such as β-blockers or verapamil is associated with improved rate control which is especially important if the duration of diastole is critical, as in mitral stenosis or ischaemic heart disease. Often a combination of AV nodal blocking drugs is required. In cases where adequate rate control cannot be achieved despite combination therapy, radiofrequency ablation of the AV node and implantation of a permanent pacemaker (or cardiac resynchronization pacemaker) is an option, although this commits the patient to lifelong pacing therapy. Prevention of thromboembolism Atrial fibrillation patients have a fivefold increased risk of stroke compared to age-and gender-matched peers without atrial fibril- lation. However, individual stroke risk varies and is dependent upon the presence of other stroke risk factors such as increasing age, previous stroke, or transient ischaemic attack (TIA), hyper- tension, heart failure, diabetes mellitus, vascular disease (periph- eral artery disease, myocardial infarction), and female gender; the more risk factors that are present, the greater the risk of stroke. Importantly, when stroke occurs in the presence of atrial fibril- lation, the severity is greater, survival is poorer, residual neuro- logical deficit is greater, patients are more likely to require nursing home/residential care, and risk of recurrent stroke within 12 months is increased. Oral anticoagulation for stroke prevention. Anticoagulant therapy significantly reduces the risk of stroke and death in atrial fibrillation patients. Accordingly, current clinical guidelines (see Table 16.4.9) recommend effective stroke prevention with oral anticoagulation, either as a vitamin K antagonist (VKA, e.g. warfarin) or one of the non-VKA oral anticoagulants, for all atrial fibrillation patients ex- cept those patients at extremely low risk of stroke (see Table 16.4.10). These low-risk patients are defined as men and women aged under 65 years with no stroke risk factors. It is important to formally assess each patient's individual risk of stroke to inform

appropriate treat- ment decisions. Stroke risk assessment: CHA2DS2-VASc. The National Institute for Health and Care Excellence (NICE), American Heart Association/ American College of Cardiology/Heart Rhythm Society, and European Society of Cardiology (ESC) guidelines advocate the use of CHA2DS2-VASc to assess stroke risk (see Table 16.4.9). CHA2DS2- VASc is an acronym for the stroke risk factors which comprise it (see Table 16.4.10): congestive heart failure, hypertension, age 75 years or more, diabetes mellitus, previous stroke or TIA, vascular dis- ease, age 65–74 years, and female gender. The presence of each risk factor scores 1 point, except for age 75 years or over and previous stroke/TIA, which score 2 points each; the maximum score is 9. The ACCP9 guidelines recommend assessing stroke risk using the older CHADS2 score: congestive heart failure, hypertension, age 75 years or more, diabetes mellitus (1 point for each), and previous stroke or Fig. 16.4.25 Virtual geometry of the left atrium using the Carto 3 system (Biosense Webster, Diamond Bar, CA, USA). The view is a posterior view. The pulmonary veins are shown and the veins are labelled (RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein). Lesions produced by sequential application of radiofrequency energy are shown by the red spheres, encircling the pulmonary veins to produce electrical isolation, which is confirmed using a circular mapping catheter, seen inside the RSPV.

16.4 Cardiac arrhythmias 3371 TIA (2 points); maximum score is 6. In those with a CHADS2 score of 0, the American College of Chest Physicians (ACCP) guidelines recommend consideration of ‘non-CHADS2’ risk factors, that is, age 65–74, female gender, and vascular disease. The CHA2DS2-VASc score incorporates the CHADS2 score but offers a more compre- hensive assessment of stroke risk by including additional risk fac- tors (vascular disease, age 65–74 years, and female gender, placing greater emphasis on age ≥75 years) and it also allows further risk stratification of patients with a CHADS2 score of 0. Indeed, patients designated as ‘low risk’ on the basis of a CHADS2 score of 0 are not truly low risk, and thus treatment decisions made on the basis of CHADS2 score of 0 (i.e. no therapy or aspirin monotherapy) may result in ineffective stroke prevention. The duration of paroxysms of atrial fibrillation required to in- crease the risk of thromboembolism in patients who are asymp- tomatic has been studied in the ASSERT trial where atrial arrhythmias were detected in patients with pacemaker implants. The annual incidence of stroke increased markedly from around 1% in those with episodes less than 17 h to approximately 5% per annum in those with episodes greater than 17 h. Bleeding risk assessment: HAS-BLED. Decisions regarding OAC or antithrombotic therapy also require formal assessment of the patient’s risk of bleeding with treatment, the purpose of which is to ‘flag up’ those at increased risk of bleeding for more careful review and follow-up, and to address any modifiable bleeding risk factors. A high bleeding risk score should not necessarily lead to a decision to withhold anticoagulation, because for most patients the benefits of anticoagulation still outweigh the hazards. Appropriate and re- sponsible use of bleeding risk assessment is shown in Fig. 16.4.26. The NICE and ESC guidelines recommend the use of the HAS-BLED score to assess bleeding risk (see Table 16.4.9). The HAS- BLED acronym stands for uncontrolled hypertension, abnormal renal and/or hepatic function, previous stroke, prior bleed or bleeding predisposition, labile INRs (if on VKA), elderly, concomi- tant interacting drugs, and alcohol (drink) excess; with 1 point for the presence of each risk factor (see Table 16.4.10), with a maximum score of 9. Many factors within the HAS-BLED score are modifi- able and a patient’s HAS-BLED score can be reduced by ensuring blood pressure is well controlled (<140/90 mm Hg), maintaining INR control within the therapeutic range (INR 2.0–3.0), omitting Table 16.4.9 Current guidelines for the antithrombotic management of atrial fibrillation Guidelines Assessment of stroke

risk Assessment of bleeding risk Treatment recommendations Other recommendations NICE (2014) CHA2DS2-VASc HAS-BLED Offer OACa when CHA2DS2-VASc ≥2, taking into consideration bleeding risk Consider OACa for men with CHA2DS2-VASc ≥1, taking into consideration bleeding risk Review need for OAC at least yearly Do not offer aspirin monotherapy for stroke prevention in AF Only consider dual antiplatelet therapy if OAC contraindicated in patients with CHA2DS2-VASc ≥2 OAC with VKA TTR ≥65% Assess TTR at each visit Correct modifiable reasons for poor INR controlc Consider alternative OAC if TTR cannot be improvedd NOACs In accordance with NICE STAs ESC (2016) CHA2DS2-VASc No formal bleeding risk tool specified. Stresses attention to modifiable bleeding risk factors Consider patients' treatment preferences No antithrombotic therapy if patient <65 years with lone AF (i.e. CHA2DS2-VASc = 0 in males, 1 in females) OACa recommended if CHA2DS2-VASc ≥2 in males, or ≥3 in females Consider OACa if CHA2DS2-VASc 1 in males or 2 in females NOAC preferred to VKA in majority of AF patients initiating OAC NOACs Assess renal function before initiation (CrCl) Not recommended in those with severe renal impairment (CrCl<30 ml/min) In accordance with licensed indications VKAs INR 2–3; TTR control paramount ACCP (2012) CHADS2 but to consider other non-CHADS2 risk factors (age 65–74, vascular disease, female gender) No formal bleeding risk assessment or tool specified Tailor treatment decisions based on patients' treatment preferences and bleeding risk No therapy if CHADS2 = 0 If patients with CHADS2 = 0 choose therapy, aspirin monotherapy or dual APT is recommended; if non- CHADS2 risk factors are present (age 65–74, female gender, vascular disease), OAC recommended If CHADS2 = 1, OAC recommended over aspirin monotherapy or dual APT If CHADS2 ≥2, OAC recommended or aspirin monotherapy or dual APT if OAC refused/ contraindicated Dabigatranb preferred over VKAs ACCP, American College of Chest Physicians; APT, antiplatelet therapy; CHADS2, congestive heart failure (recent), hypertension, age ≥75 years, diabetes mellitus, previous stroke, or transient ischaemic attack; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke, or TIA, vascular disease, age 65–74 years, female gender; CrCl, creatinine clearance; ESC, European Society of Cardiology; HAS-BLED, uncontrolled hypertension, abnormal renal and/or hepatic function, previous stroke, prior bleed, or bleeding predisposition, labile INRs (if on VKA), elderly, concomitant interacting drugs and alcohol (drink) excess; INR, international normalized ratio; NICE, National Institute for Health and Care Excellence; NICE STA, National Institute of Clinical Excellence single technology appraisal; NOAC, nonvitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; TTR, time in therapeutic range, VKA, vitamin K antagonist. a Either vitamin K antagonist (most commonly warfarin) or nonvitamin K antagonist oral anticoagulant (apixaban, edoxaban, dabigatran, or rivaroxaban). b At the time the ACCP guidelines were published, dabigatran was the only NOAC approved by the US FDA. c Cognitive function; adherence to VKA; illness; drug interactions; lifestyle factors (diet and alcohol interactions). d If reason for poor TTR is nonadherence to OAC, switching to a NOAC is not recommended.

section 16 Cardiovascular disorders 3372 nonessential antiplatelets or NSAIDs, and minimizing alcohol in- take (≤8 units/week). A high HAS-BLED score (≥3) does not indi- cate that OAC should be withheld, but warrants caution and should encourage more regular review and control of modifiable bleeding risks. In addition, OAC should not be withheld exclusively because of the risk of falls. Prediction of INR control: SAMe-TT2R2. Oral anticoagulation treatment options for stroke prevention in atrial fibrillation include VKAs and NOACs (see Fig. 16.4.27). The SAMe-TT2R2 score (see Table 16.4.10), made up of routine demographic and clinical risk factors, can be used to identify upfront those newly diagnosed non- anticoagulated atrial fibrillation patients who are likely

to have poor INR control on a VKA (SAMe-TT2R2 score >2) and who may require more frequent INR monitoring and other interventions to help them achieve adequate time in therapeutic range (TTR) and for whom a NOAC might be a more effective option. Use of the SAMe-TT2R2 score is recommended by an ESC Task Force on Anticoagulants in Heart Disease to aid decision-making, rather than subjecting atrial fibrillation patients to a 'trial of warfarin' which may put such pa- tients at risk of stroke during the initial period of treatment. Patient preferences for treatment. All of the most recent clinical guidelines advocate the importance of eliciting patients' preferences regarding antithrombotic therapy and incorporating them into the decision-making process. Central to informed decision-making is patient education. The clinician's role is to provide patients with in- formation about their own risk of stroke, the benefits of OAC in re- ducing this risk, and their risk of bleeding with such treatment to allow them to make appropriate treatment decisions, and to respect their views and beliefs. Patients with better knowledge about atrial fibrillation, who understand the necessity of OAC for stroke preven- tion, despite having awareness and/or concerns about the bleeding risk associated with OAC, are more likely to adhere to treatment. Use of oral anticoagulation in the United Kingdom and globally. Despite the overwhelming evidence of the benefit of OAC for stroke prevention in atrial fibrillation, two recent sizeable observational
Table 16.4.10 Risk stratification scores to assess stroke risk (CHA 2DS 2-VASc), bleeding risk (HAS-BLED), and predict INR control (SAMe-TT 2R 2) CHA 2DS 2-VASc HAS-BLED SAMe-TT 2R 2 Definition Score Risk factor Definition Score Risk factor Definition Score Congestive heart failure Decompensated (i.e. hospitalized) HF irrespective of ejection fraction (i.e. HFrEF and HFpEF) and/or objective evidence of moderate-severe LV systolic dysfunction (on echocardiography) 1 Hypertension (uncontrolled) Systolic blood pressure

> 160 mm Hg 1 Gender Female 1 Hypertension Elevated blood pressure (>140/90 mm Hg) or history of hypertension (receiving antihypertensive medication) 1 Abnormal renal function Chronic dialysis, renal transplantation, serum creatinine ≥200 mmol/litre 1 Age <60 years 1 Age ≥75 years 2 Abnormal liver function Biochemical evidence of hepatic derangementa 1 Medical history ≥2 of the following: hypertension, diabetes, CAD/MI, PAD, CHF, stroke, pulmonary dx, hepatic, or renal dx 1 Diabetes mellitus 1 Stroke Ischaemic or haemorrhagic 1 Treatment Interacting drugs (e.g. amiodarone) 1 Stroke/TIA/TE Previous stroke, transient ischaemic attack, or thromboembolism 2 Bleeding History of bleeding or bleeding predisposition (e.g. anaemia) 1 Tobacco use Current or ex-smoker (within 2 years) 2 Vascular disease PAD, myocardial infarction, aortic plaque 1 Labile INR TTR <60% 1 Race Nonwhite ethnicity 2 Age 65–74 years 1 Elderly E.g. >65 years, extreme frailty 1 Gender Female 1 Drugs or alcohol excess Concomitant antiplatelets or NSAIDs or excessive alcohol (≥8 units/week (1 point for each) 1 or 2 Maximum score 9 9 8 CAD, coronary artery disease; CHF, congestive heart failure; dx, disease; HF, heart failure; HFrEF and HFpEF, heart failure with reduced or preserved ejection fraction; INR, international normalized ratio; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; PAD, peripheral arterial disease; TTR, time in therapeutic range. a

> Bilirubin >2 upper limit of normal (ULN) in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase>3 ULN.

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- Uncontrolled hypertension
- Labile INRs (if receiving a VKA)
- Concomitant use of aspirin or NSAIDs in anticoagulated patient
- Alcohol excess Identifies ‘at-risk’ patients for more regular review and follow-up A ‘high-risk’ bleeding risk score is not a reason or execuse to withhold oral anticoagulation For patients with an increased risk of bleeding the benefit of oral anticoagulation usually, but not always, outweighs the bleeding risk; thus, regular review and careful monitoring of bleeding risk is important Do not withhold oral anticoagulation solely because the patient is at risk of falls EHR and ‘electronic alerts’ Low risk = no action High risk = patient ‘flagged up’ for review Fig. 16.4.26 Bleeding risk assessment in AF—observations on the use and misuse of bleeding risk scores. EHR, electronic health record; INR, International Normalized Ratio; NSAID, nonsteroidal anti-inflammatory drug; VKA, vitamin K antagonist. From Lip GYH and Lane DA (2016). Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. J Thromb Haemost, 14, 1711–4, © 2016 International Society on Thrombosis and Haemostasis, with permission from John Wiley and Sons. Fig. 16.4.27 The approach to decision-making in the AF patient management pathway using the CHA2DS2-VASc, HAS-BLED, and SAMe-TT2R2 scores.

section 16 Cardiovascular disorders 3374 studies have demonstrated that large proportions of patients at risk of stroke (CHA2DS2-VASc score ≥2 or CHADS2 score of ≥2) still do not receive OAC. In the first cohort from the Global Anticoagulant Registry in the FIELD (GARFIELD) study, of 10 614 AF patients in 19 countries, 40.7% of patients with a CHA2DS2-VASc score of 2 or more did not receive OAC. More than one-half of the reasons given for withholding OAC therapy for patients at risk of stroke in the GARFIELD registry were linked to physician choice (i.e. bleeding risk, concerns over patient adherence, falls risk). Perhaps a more worrying finding from the GARFIELD registry revealed that ap- proximately one-quarter of patients with a CHA2DS2-VASc score of 2 or more were receiving antiplatelet monotherapy. A similar underuse of OAC in patients at high of stroke and overuse in those at low risk was seen in the Euro Heart Survey which was conducted a decade ago. The recent analysis in 1857 general practices in the United Kingdom, utilizing the GRASP-AF tool (which assessed stroke risk on the basis of the CHADS2 score and recommends treatment based on the 2006 NICE guidelines), demonstrated that 34.0% of patients with a CHADS2 score of 2 or more, with no docu- mented contraindication to OAC, were receiving OAC and the use of antiplatelet therapy rose as stroke risk increased. Use of OAC de- clined significantly among patients aged 80 years or over (47.4% vs. 64.5%; $p < 0.001$), while antiplatelet therapy increased in this age group. Consequently, those patients at greatest risk of stroke (i.e. elderly patients and those with multiple comorbidities) are the very patients who are least likely to receive adequate preventative therapy against stroke. This is despite very clear evidence from the Birmingham Atrial Fibrillation in The Aged (BAFTA) study which demonstrated that warfarin was more effective in

preventing strokes than aspirin in patients aged 75 years or over (2.5% vs. 4.9% per year; RR 0.52 [95% CI 0.33–0.80]), with a similar risk of major bleeding (1.9% vs. 2.0% per year; RR 0.96 [95% CI 0.53–1.75]) and from an individual patient-data meta-analysis of approximately 9000 atrial fibrillation patients which confirmed that OAC was efficacious in reducing ischaemic stroke regardless of the patient's age, whereas the protective effect of aspirin declined significantly with age. The lack of OAC prescription among atrial fibrillation patients at risk of stroke was not related to their bleeding risk or comorbidities. Guidelines for stroke prevention in atrial fibrillation. Effective prevention of stroke for atrial fibrillation patients requires OAC, ei- ther with a VKA or one of the NOACs (see Table 16.4.9 and Fig. 16.4.27). If patients are prescribed a VKA, the most important con- sideration is their anticoagulation control (INR 2.0–3.0), evidenced by a TTR of 65% or more. Patient education about factors that may affect their INR control (e.g. diet, alcohol intake, and interacting drugs) is important, and regular INR monitoring and assessment of the reasons for poor anticoagulation control is essential. Indeed, a recent trial demonstrated that a one-off intensive education ses- sion significantly improved TTR 6 months after warfarin initiation in an inception cohort compared to usual care. Consideration and correction (where possible) of the reasons for poor anticoagulation need to be addressed (see Fig. 16.4.27 and Table 16.4.9). Currently four NOACs—apixaban, dabigatran, edoxaban, and rivaroxaban— are NICE approved and available for stroke prevention in atrial fib- rillation (see Table 16.4.11 and Fig. 16.4.27). For patients who are OAC-naive, the NOACs are broadly preferred over a VKA for most patients. Strict adherence to licensed indications is essential and a recent European Heart Rhythm Association document offers excel- lent practical guidance on the use of NOACs in practice. Renal func- tion must be assessed prior to initiating a NOAC and the creatinine clearance, using the Cockcroft–Gault formula, must be calculated. NOACs should not be used in patients with severe renal impair- ment (CrCl <30 ml/min), although rivaroxaban 15 mg once daily, edoxaban 30 mg once daily, and apixaban 2.5 mg twice daily can be used with caution in patients with CrCl 15–29 ml/min. Regular monitoring of a patients' renal function for the duration of NOAC treatment is advocated; the frequency of renal function testing is de- pendent of the degree of renal impairment (see Table 16.4.11). Dose reductions are required in patients with moderate renal impairment and according to other factors (see Table 16.4.11 'Dose reductions' for specific criteria for each NOAC). Aspirin monotherapy is not an effective treatment strategy for stroke prevention in patients with atrial fibrillation and conse- quently the clinical guidelines actively discourage its use. Dual antiplatelet therapy, with aspirin and clopidogrel, should only be considered in patients with a CHA2DS2-VASc score of 2 or more in whom any OAC use is absolutely refused or contraindicated, given the increased risk of bleeding with dual antiplatelets and re- duced efficacy compared to OAC. Left atrial appendage occlusion devices should only be considered if OAC is absolutely contraindi- cated; they are not a first-line alternative to OAC and the risks of LAAO need to be carefully discussed with the patient. Regardless of the stroke prevention treatment strategy selected after discus- sion with the patient, treatment decisions and stroke and bleeding risk assessments should be reviewed at least annually as a patients' risk may change and treatment may need to be altered. One of the NICE 2014 recommendations is to offer patients with atrial fibrillation 'a personalized package of care including measures to prevent stroke'. This involves matching the right OAC drug to the patient on the basis of their stroke and bleeding risk assessment and overall clinical background/profile, which requires knowledge of the results of individual trials and of 'real world' observational studies supporting effectiveness or safety for particular patient profiles (Fig. 16.4.28). Net clinical benefit of OAC: NOACs versus warfarin. The most ap- propriate stroke prevention strategy involves balancing the benefit of treatment (i.e. reduction in stroke) against the possibility of serious

bleeding (i.e. intracranial haemorrhage) associated with treatment for each patient; an evaluation of the net clinical benefit. An analysis of the net clinical benefit of warfarin was undertaken in a large (>180 000) cohort of Swedish patients, with stroke and bleeding risk as- sessed by CHA2DS2-VASc and HAS-BLED, respectively. This study found that OAC treatment was associated with a positive net clinical benefit for all patients, except those with a CHA2DS2-VASc score of 0, confirming their truly low-risk status. Those with high stroke and high bleeding risk fared best from warfarin therapy; there were 12 fewer ischaemic strokes per 100 years at risk compared to not giving warfarin. What about the net clinical benefit of the NOACs against warfarin? There will never be a direct head-to-head comparison of the NOACs, therefore the next best option is an indirect comparison of the NOACs with warfarin. A similar analysis modelled the net clinical benefit of the NOACs apixaban, dabigatran, and rivaroxaban against warfarin in a real- world cohort of Danish atrial fibrillation patients. All four NOACs

16.4 Cardiac arrhythmias 3375 offered a net clinical benefit superior to warfarin among patients with a CHA2DS2-VASc score of 2 or more or a CHADS2 score of 1 or more, despite the risk of bleeding. Among patients with a CHA2DS2- VASc score of 1, both doses of dabigatran and apixaban were associ- ated with better net clinical benefit. In patients with a CHADS2 score of 0 and a high risk of bleeding, only dabigatran 110 mg twice daily and apixaban displayed a beneficial net clinical outcome. If the risk of stroke and the risk of bleeding are high, the NOACs have a risk- benefit profile superior to that of warfarin. To streamline decision-making for stroke prevention in patients with atrial fibrillation, a simple three-step process in the patient pathway can be considered, as shown in Fig. 16.4.29. Atrial flutter Typical atrial flutter is caused by a macro re-entrant circuit in the right atrium involving the cavo-tricuspid isthmus (Fig. 16.4.30), which produces a typical electrocardiographic ‘sawtooth’ pattern of atrial activity with a rate close to 300/min (Fig. 16.4.31). In the common form of the arrhythmia, flutter waves are negative in leads II, III, and aVF and positive in lead V1 and may be associated with either a regular or irregular ventricular response. Flutter with 2:1 AV conduction produces a regular tachycardia of 150/min and should always be considered in the differential diagnosis of a regular, narrow-QRS tachycardia of this rate. Occasionally, flutter occurs with 1:1 AV conduction producing a ventricular rate approaching 300/min. Class I antiarrhythmic drugs may predispose to this by causing a relative slowing of the atrial rate and allowing 1:1 conduc- tion through the AV node. The flutter waves may not be seen easily with faster ventricular rates, and transient slowing of AV conduction may be necessary to make the diagnosis (Fig. 16.4.31). The underlying risk factors for the development of atrial flutter are the same as those of atrial fibrillation (Box 16.4.2) and likely represent different manifestations of an atrial electrical myopathy. Indeed, the conditions often coexist and patients may manifest ei- ther flutter or fibrillation at different times. Atrial flutter is often poorly tolerated due to fixed, fast ventricular rates, and it can be difficult to rate control with AV nodal blocking drugs. Termination may be achieved by chemical or electrical cardioversion, as just described here for atrial fibrillation. Drug prophylaxis against atrial flutter uses the same agents as in parox- ysmal atrial fibrillation, although some antiarrhythmic drugs may slow conduction and be proarrhythmic. Radiofrequency ablation is increasingly used as first-line therapy, where a line of conduction block is created between the tricuspid valve annulus and the inferior vena cava, interrupting the isthmus through which the re-entry cir- cuit must pass (Fig. 16.4.30). This achieves cure in 90–95% of cases, Table 16.4.11 Novel oral anticoagulants for stroke prevention in atrial fibrillation Drug characteristics Apixaban Dabigatran Edoxaban Rivaroxaban Mechanism Oral direct factor Xa inhibitor Oral direct thrombin inhibitor Oral direct factor Xa inhibitor Oral direct factor Xa inhibitor

Half-life (h) 9–14 12–17 10–14 5–13 Excretion 25% renal; 75% faecal 80% renal 50% 66% liver, 33% renal Dose 5 mg twice daily 150 mg twice daily 60 mg once daily 20 mg once daily Dose in renal impairmentd (30–49 ml/min) 2.5 mg twice dailyc 110 mg twice daily 30 mg once dailya 15 mg once daily Dose reductions If ≥2 of following: serum creatinine >133 μmol/l; age ≥80 years; body weight ≤60 kg ≥80 years; concomitant verapamil; HAS-BLED score ≥3e ≥1 of the following: CrCl ml/min 15–50 ml/min; body weight ≤60 kg; on ciclosporin, dronedarone, erythromycin, or ketoconazole No dose reduction except for renal function Drug interactions Anticoagulants, antiplatelets, NSAIDs; ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors (ritonavir), rifampicin, St John's wort, phenobarbital, phenytoin, carbamazepine Anticoagulants, antiplatelets, NSAIDs; systemic ketoconazole, ciclosporin, tacrolimus, itraconazole, verapamil; quinidine, dronedarone, amiodarone, clarithromycin, rifampicin, St John's wort, phenytoin, carbamazepine, SSRIs, SNRIs Anticoagulants, antiplatelets, NSAIDsb Ciclosporin, dronedarone, erythromycin, or ketoconazoleb Quinidine, verapamil, amiodarone Phenytoin, carbamazepine, phenobarbital, or St John's Wort Anticoagulants, antiplatelets, NSAIDs; ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole quinidine, HIV protease inhibitors (ritonavir), clarithromycin, erythromycin, dronedarone, rifampicin, St John's wort, phenobarbital, phenytoin, carbamazepine Take with/after food No Yes No Yes Check renal function Divide CrCl by 10; e.g. CrCl 60 ml/min monitor every 6 months; if decline in renal function is suspected (e.g. hypovolaemia, dehydration) or concomitant use of certain medicinal products, check renal function a if CrCl 15–50 ml/min b Reduce dose to 30 mg once daily if use of concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole. c Dose reduction if serum creatinine >133 μmol/litre plus age ≥80 years and/or body weight ≤60 kg. d Dabigatran not to be used if CrCl <30 ml/min; edoxaban, rivaroxaban, and apixaban not be used if CrCl <15 ml/min; rivaroxaban and apixaban only to be used if CrCl 15–29 ml/min with caution and regular review (at least 3 monthly). e On an individual basis based on stroke and bleeding risk. Adapted from Camm AJ et al. (2012) ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J, 33, 2719–47; and Heidbuchel H et al. (2013) European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with nonvalvular atrial fibrillation. Europace, 15, 625–51.

section 16 Cardiovascular disorders 3376 Recurrent stroke, systemic embolic event, or transient ischaemic attack despite good anticoagulation control (TTR > 70%) Dabigatran 150 mg BID Apixaban 5 mg BID*, rivaroxaban 15 mg once daily, dabigatran (if CrCl 30–49 ml/min)†, or edoxaban 30 mg once daily Apixabin 5 mg BID* or dabigatran 110 mg BID§ Apixaban 5 mg BID*, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily Dabigatran 110 mg BID§, apixaban 5 mg BID*, or edoxaban 60 mg once daily VKA, rivaroxaban 20 mg once daily¶, or edoxaban 60 mg once daily Apixaban 5 mg BID*, dabigatran†, or edoxaban 60 mg once daily VKA with additional education and more regular follow-up, dabigatran†, rivaroxaban 20 mg once daily¶, apixaban 5 mg BID*, or edoxaban 60 mg once daily Moderate-to-severe renal impairment (CrCl 15–49 ml/min) High risk of gastrointestinal bleeding Gastrointestinal symptoms or dyspepsia High risk of bleeding (HAS-BLED ≥3) Once daily dosing or preference to have a lower pill burden Asian patients (consider drugs with reduced risk of intracranial haemorrhage and major bleeding in Asian subgroups) Choosing the oral anticoagulant drug to fit the patient profile Less likely to do well on VKA with good TTR (SAMe-TT2R2 score >2) Fig. 16.4.28 Stroke prevention in atrial fibrillation: fitting the

drug to the patient profile. CrCl, creatinine clearance; TTR, time in therapeutic range; VKA, vitamin K antagonist. *Reduced to 2.5 g BID with two or three criteria from age ≥80 years, bodyweight ≤60 kg, or serum creatinine concentration ≥133 μmol/litre. †110 mg BID for patients with a CrCl 30–49 ml/min (most countries, but not in the United States); in the United States only, 75 mg BID (available in the United States only) for patients with CrCl 15–29 ml/min (and only 150 mg BID dose available in the United States for CrCl >30 ml/min). ‡30 mg with CrCl 15–49 ml/min, P-glycoprotein inhibitors, or weight <60 kg. §110 mg BID dose not available in the United States for atrial fibrillation. ¶ Reduced to 15 mg if CrCl 15–49 ml/min. ‖Dose to be halved if the patient has any of the following: CrCl 15–49 ml/min, bodyweight ≤60 kg, or concomitant use of P-glycoprotein inhibitors. Reprinted from The Lancet, Vol. 388(10046), Freedman B, Potpara TS, Lip GY, Stroke prevention in atrial fibrillation, pp. 806–17, Copyright 2016, with permission from Elsevier. Step 1 identify low-risk patients Low stroke risk CHA2DS2-VASc score: 0 in males 1 in females Calculate SAMe-TT2R2 score SAMe-TT2R2 score >2 Regular review/INR checks/ counselling for VKA users SAMe-TT2R2 score 0–2 VKA treatment (eg. warfarin) … or try a NOAC Step 3 Decide on NOAC or VKA with high time in therapeutic range No antithrombotic treatment *Also calculate the HAS-BLED score. If HAS-BLED ≥3, address the modifiable bleeding risk factors and plan a closer clinical follow-up. Step 2 consider stroke prevention (i.e. oral anticoagulant) in all AF patients with ≥1 additional stroke risk factors* Fig. 16.4.29 The Birmingham ‘3-step’ to streamline decision-making for stroke prevention in patients with atrial fibrillation. Reprinted from Lip GYH (2017). Stroke prevention in atrial fibrillation. The Lancet, 38(1), 4–5, by permission of Oxford University Press.

16.4 Cardiac arrhythmias 3377 but does not, however, alter the risk of future development of atrial fibrillation. With regards to thrombo-prophylaxis, anticoagulation is indi- cated before and after cardioversion, as for atrial fibrillation. The role of longer-term anticoagulation is less clear and is currently not mandated. However, given the close link between atrial flutter and atrial fibrillation, the presence of silent atrial fibrillation should be considered, especially in those with high CHA2DS2-VASc scores. Finally, while it is important to note that although typical flutter accounts for more than 90% of all re-entrant circuits occurring spontaneously in the atria (others include incisional or scar-related re-entry), iatrogenic left atrial flutters are increasing in frequency as a consequence of increased use of ablation to treat AF. Focal atrial tachycardia Focal atrial tachycardia is an automatic arrhythmia, usually re- sulting in an atrial rate between 120 and 250/min. There may be a degree of AV block, although 1:1 AV conduction can occur. The ECG usually shows regular P-waves which do not show the same ‘sawtooth’ appearance as in atrial flutter (Fig. 16.4.32). In contrast to most other forms of supraventricular tachycardia, focal atrial tachycardia usually has a long RP interval (defined as >50% of the RR interval). The rate characteristically accelerates or ‘warms up’ before reaching a rate of 125–200/min, and careful analysis of morphology of the P-wave aids in localization of the source. Multifocal atrial tachycardia, in which rapid, irregular P-waves of three or four different morphologies are seen, may occur in se- verely ill elderly patients, or in association with acute exacerbation of pulmonary disease. Acute management includes drug treatment or cardioversion, as for atrial fibrillation. Focal atrial tachycardia may be amenable to treatment with radiofrequency ablation with success rates ap- proaching 80%, although recurrence rate is high. Supraventricular tachycardia Although all atrial arrhythmias are (by definition) supraventricular in origin, the term supraventricular tachycardia is commonly re- served for those in whom the AV node is an obligate part of a re- entry circuit—AV nodal re-entrant tachycardia (AVNRT) or AV re-entry tachycardia (AVRT). Correct recognition of these arrhyth- mias has achieved additional importance with the development of effective curative

measures. Atrioventricular nodal re-entry tachycardia Mechanism This is the commonest cause of paroxysmal re-entry tachycardia manifesting regular, normal QRS complexes. The basis of the ar- rhythmia is the presence of two functionally distinct pathways in the region of the AV node (Fig. 16.4.33). The ‘fast’ pathway conducts more rapidly but has a longer refractory period. The ‘slow’ pathway has slower conduction properties but a shorter refractory period. During sinus rhythm, AV nodal conduction occurs via the fast pathway with a normal PR interval (Fig. 16.4.33a). If a sufficiently premature atrial extrasystole arises, conduction in the fast pathway is blocked, but slow pathway conduction may continue, resulting in an abrupt increase in the AH interval as recorded in the His bundle electrogram. This corresponds to an increased PR interval on the surface ECG (Fig. 16.4.33b). If conduction down the slow pathway is sufficiently delayed to allow the fast pathway to recover excitability before activation reaches the distal end of the pathways, retrograde activation occurs via the fast pathway. The stage is then set for a re- entry circuit with anterograde conduction via the slow pathway and retrograde conduction via the fast pathway (‘slow/fast AV nodal re- entry’; Fig. 16.4.33c). Characteristically, anterograde activation of the ventricles and retrograde activation of the atria occur virtually simultaneously, resulting in the P-wave being ‘buried’ within the QRS complex, or producing a very small distortion of the terminal TVA RA IVC Fig. 16.4.30 Mechanism of atrial flutter. Typical atrial flutter results from a counterclockwise re-entry circuit in the right atrium. The isthmus between the tricuspid valve annulus (TVA) and inferior vena cava (IVC) forms a critical part of this circuit, and linear ablation to create block can prevent recurrent atrial flutter. Fig. 16.4.31 Atrial flutter with 1:1 AV conduction (top), 2:1 conduction (middle), and following adenosine administration (bottom) (6 mg intravenous injection 10 s previously). Fig. 16.4.32 Atrial tachycardia, with variable AV conduction. Lead V1.

section 16 Cardiovascular disorders 3378 QRS, recognition of which requires careful comparison with the ECG during sinus rhythm (Fig. 16.4.34). A less common variant of AV nodal re-entry tachycardia may arise where anterograde conduction during tachycardia is via the fast pathway with retrograde conduction via the slow pathway (‘fast/ slow AV nodal re-entry’, also termed ‘atypical AVNRT’). Under these circumstances, the atrium is activated well after the QRS com- plex, characteristically producing an inverted P-wave, with the RP interval greater than the PR interval during tachycardia, termed ‘long RP tachycardia’ (Fig. 16.4.35). Clinical features Atrioventricular nodal re-entry tachycardia commonly presents in young adults, although it may appear at any age. Episodes are char- acterized by sudden onset and sudden offset of symptoms of regular palpitations, which are normally well tolerated unless the tachy- cardia is particularly rapid, prolonged, or if the patient has other heart disease. The natural history is of episodic paroxysmal tachy- cardia, occurring at random intervals, although there may be clus- tering of attacks interposed with periods of relative freedom from symptoms. Atrioventricular nodal re-entry tachycardia has no spe- cific association with other organic heart disease. Management Termination of an attack of AV nodal re-entry tachycardia is achieved by producing transient AV nodal block. This may be achieved by vagotonic manoeuvres, by intravenous adenosine (3–18 mg; see Fig. 16.4.34), or by intravenous verapamil (6–18 mg). Drug prophylaxis of AV nodal re-entry tachycardia is undertaken with β-blockers, a combined β-blocker/class III agent such as sotalol, or AV nodal blocking drugs such as verapamil or digoxin, although curative treatment of AV nodal re-entry tachycardia by radiofrequency ablation is increasingly used as a first-line therapy. Radiofrequency energy is delivered to the ‘slow’ pathway, which lies between the compact AV node and the tricuspid annulus. Ablation at this site is normally curative in over 95% of cases but carries a small risk (0.5–1%) of inducing complete heart block. Atrioventricular re-entry tachycardia

Mechanism In contrast to AV nodal re-entry tachycardia, the substrate for AV re-entry is the presence of a second atrioventricular connection, separate from the AV node. This accessory pathway can lie any- where along the mitral or tricuspid annuli. Anterograde pathway conduction produces ventricular pre-excitation and is discussed in the ‘Pre-excitation syndromes’ section to follow. However, some ac- cessory pathways only conduct in the retrograde (ventriculoatrial) direction and are termed ‘concealed’, since there is no clue to their presence on the resting ECG. The anterograde limb of the re-entrant circuit is the AV node, with retrograde atrial activation occurring over the accessory pathway (see Fig. 16.4.36). This is termed ortho- dromic tachycardia and normally produces a narrow-complex QRS morphology. Retrograde atrial activation can be identified by the presence of a characteristic inverted P′-wave early in the ST seg- ment, an important diagnostic feature of AV re-entry tachycardia (Fig. 16.4.37). Rarely, an accessory pathway with slow retrograde Fig. 16.4.33 Atrioventricular nodal re-entry tachycardia. Mechanism of initiation by atrial extrasystole. See text for details. Fig. 16.4.34 Atrioventricular nodal re-entrant tachycardia. Rapid narrow- complex tachycardia with no apparent P-waves (upper) responding to 6 mg adenosine with restoration of sinus rhythm (lower). Close inspection reveals a positive deflection of the terminal QRS during tachycardia (pseudo R′, arrowed) which is absent during sinus rhythm. This is due to retrograde atrial activity coincident with ventricular activation. Lead V1. Fig. 16.4.35 Atypical atrioventricular nodal re-entry tachycardia (‘long RP’). Inverted P-waves precede the QRS complex during tachycardia (compare with preceding sinus beats).

16.4 Cardiac arrhythmias 3379 conduction may allow a stable, incessant re-entrant circuit with a long RP interval, referred to as permanent junctional reciprocating tachycardia. Clinical features Features are similar to AV nodal re-entry tachycardia, although ac- cessory pathways are the more common tachycardia substrate in children. Patients have a similar relapsing course of symptoms inter- spersed with periods of relative quiescence. Multiple pathways can be present within the same patient and are more common if there is coexisting structural heart disease such as Ebstein’s anomaly (see Chapter 16.12). Management As with AV nodal re-entry tachycardia, the AV node is an obligate part of the circuit and attacks may be aborted by vagotonic man- oeuvres or with intravenous adenosine. Antiarrhythmic therapy may be effective, but radiofrequency ablation offers high success rates with low incidence of complications and should be considered early in a patient’s treatment. Pre-excitation syndromes (Wolff–Parkinson–White syndrome) The term ‘pre-excitation’ refers to the premature activation of the ventricle via one or more accessory pathways that conduct in the antegrade direction (from atrium to ventricle), bypassing the normal AV node and His–Purkinje system. Accessory pathways with elec- trophysiological properties of normal myocardium may lie at any point in the AV ring, the commonest sites being in the left free wall or the posteroseptal region (Fig. 16.4.36). The characteristic electrocardiographic appearance is due to the fusion of wavefronts progressing down the normal His–Purkinje system and the antegradely conducting accessory pathway. Early ventricular activation through the pathway occurs more quickly than conduction through the AV node, producing a short PR interval, but thereafter intraventricular conduction is slow, resulting in slurred initiation of the QRS complex (the δ-wave; Fig. 16.4.38), before the remainder of the ventricle is excited via the normal His–Purkinje system. QRS morphology therefore reflects fusion of AV nodal and accessory pathway conduction. As such, the degree of pre-excitation during sinus rhythm is variable: it may be intermittent if the re- fractory period of the accessory pathway is close to the sinus cycle length (Fig. 16.4.38), or inapparent if the δ-wave is obscured due to rapid AV nodal conduction. In such instances, transient slowing of AV nodal conduction (e.g. by adenosine) will enhance the pro- portion of the ventricle

excited by the accessory pathway and reveal pre-excitation. The ECG appearances of a δ-wave occur in approximately 1.5 per 1000 of the population, but many individuals never experience paroxysmal tachycardias. The Wolff–Parkinson–White syndrome describes the combination of the symptoms of palpitation and the presence of pre-excitation on the ECG. (a) (c) (b) Fig. 16.4.36 Atrioventricular re-entry tachycardia. Mechanism of initiation by atrial extrasystole. See text for details: if the accessory pathway were concealed the ECG in sinus rhythm would not show the characteristic δ-wave. Fig. 16.4.37 Initiation of atrioventricular re-entry tachycardia. The third sinus beat is followed by the onset of narrow-complex tachycardia, initiated by an atrial extrasystole (obscured by T-wave). Retrograde atrial activation, with inverted P-waves in the ST segment (arrows), are seen during tachycardia.

section 16 Cardiovascular disorders 3380 Mechanisms of orthodromic and antidromic tachycardia The mechanism for orthodromic AV re-entry tachycardia is illus- trated in Fig. 16.4.35. A premature atrial extrasystole may find the pathway refractory but be conducted through the AV node to the ventricles (Fig. 16.4.36b). If sufficient delay has occurred by the time the ventricular insertion of the accessory pathway is depolarized, the pathway may have recovered excitability and allow retrograde activation from the ventricle to atrium, with the establishment of a re-entry circuit (Fig. 16.4.36c). Since the circuit involves activation of the ventricles via the His–Purkinje system, the QRS morphology during re-entry tachycardia is normal, unless a rate-related bundle branch block develops. If a bundle branch block is seen at a lower heart rate than a documented narrow-complex tachycardia, this is diagnostic of an accessory pathway ipsilateral to the bundle branch block (Coumel's sign). A rare form of AV re-entry tachycardia has anterograde conduc- tion via the accessory pathway and retrograde conduction via the AV node (antidromic tachycardia). The QRS morphology of this tachycardia is broad and grossly abnormal, with appearances de- pendent upon the site of insertion of the accessory pathway. Pre-excited atrial fibrillation The major prognostic concern in Wolff–Parkinson–White syn- drome is pre-excited atrial fibrillation. Conduction via an acces- sory pathway with a short refractory period, bypassing the normal AV nodal slowing, may result in very rapid conduction to the ven- tricle (Fig. 16.4.39) that can degenerate into ventricular fibrilla- tion. The degree of pre-excitation during atrial fibrillation varies, giving a characteristic pattern of an irregular ventricular response with QRS morphology ranging from normal to fully pre-excited. The risk of sudden death is increased if the shortest R-R interval is less than 250 ms during pre-excited atrial fibrillation, and is an indication for urgent cardioversion and early radiofrequency ablation. Management of the symptomatic patient
with ventricular pre-excitation The AV node is a part of the re-entry circuit in both ortho-and anti-dromic tachycardia, and adenosine and other AV nodal-blocking drugs may be effective. However, adenosine may precipitate pre- excited atrial fibrillation and should be used with caution. In pa-tients with known Wolff–Parkinson–White syndrome presenting with AV re-entrant tachycardia, drugs which also act on the acces- sory pathway such as flecainide or sotalol may be preferred. In pre- excited atrial fibrillation, AV nodal blocking drugs such as digoxin or verapamil should be avoided, because of the risk of ventricular fibrillation; treatment should be with antiarrhythmic therapy such as flecainide or by DC cardioversion. Patients with Wolff–Parkinson– White syndrome should be offered radiofrequency ablation as first- line therapy. This abolishes the risk of pre-excited atrial fibrillation as well as preventing further attacks of AV re-entry tachycardia. Careful mapping of the AV annulus using an electrode catheter is necessary to identify the site of the accessory pathway, at which the interval between the atrial and ventricular electrograms is at a min- imum. Passage of the radiofrequency current causes heating of the catheter tip and results in

the disappearance of accessory pathway conduction within a few seconds (Fig. 16.4.40). The success rate of Fig. 16.4.38 Intermittent pre-excitation in Wolff–Parkinson–White syndrome. The first two beats show the characteristic short PR interval and δ-wave. The middle two beats, however, show that the pre-excitation was intermittent. The pathway has become refractory, with normal PR interval and QRS morphology. Pathway conduction returns to cause pre-excitation in the final two beats. 1s Fig. 16.4.39 Pre-excited atrial fibrillation. Conduction via an accessory pathway results in an irregular broad-complex tachycardia. The third and fourth beats show less pre-excitation, with activation mainly through the normal conducting system, with more normal QRS-complex morphology. Lead V1. RF I V1 CS Map s 2 s 1 0 Fig. 16.4.40 Radiofrequency ablation of an accessory pathway. The patient had Wolff–Parkinson–White syndrome with evidence of ventricular pre-excitation on the surface electrogram during sinus rhythm (short PR interval, δ-wave). One beat after switching on the radiofrequency (RF) current the QRS becomes normal, indicating successful ablation of the accessory pathway. This was a left-sided accessory pathway, as shown by the short interval between left atrial and left ventricular activation recorded from the coronary sinus (CS). This interval is prolonged following ablation of the pathway. Surface leads I, V1, and intracardiac electrograms from CS and mapping catheter (Map) are shown.

16.4 Cardiac arrhythmias 3381 ablation varies according to the location of the pathway, but is usually over 90%. Approach to the asymptomatic patient
with ventricular pre-excitation Patients with Wolff–Parkinson–White syndrome should be evaluated carefully for the risk of pre-excited atrial fibrillation, even in the absence of symptoms. The risk of sudden death due to rapid pre-excited atrial fibrillation is very low among adults who have not had any symptomatic tachycardias, but is higher in symptomatic patients. If pre-excitation is intermittent, this indicates a long refractory period of the pathway and a low risk of life-threatening tachycardias. Abrupt disappearance of the δ-wave in response to exercise testing, or during Holter monitoring, or with the administration of a class Ia or Ic antiarrhythmic drug, also suggests a low risk. Some centres advocate diagnostic electrophysiological studies to identify a high-risk group with short pathway refractory periods and inducible tachycardia or pre-excited atrial fibrillation. The general tendency is for accessory pathway conduction to become slower with increasing age, and spontaneous disappearance of conduction is well documented. Other pre-excitation syndromes Other forms of pre-excitation include the Mahaim pathway, a direct AV, or atriofascicular connection with decremental conduction properties similar to AV nodal tissue. Ventricular tachycardia Definitions Ventricular tachycardia is defined as the presence of three or more consecutive ventricular beats at a rate of 120/min or greater. It is considered to be sustained if an individual salvo lasts for 30 s or more, and nonsustained if the duration is between 3 beats and 30 s. Monomorphic ventricular tachycardia has a consistent QRS morphology, whereas polymorphic ventricular tachycardia demonstrates a constantly changing QRS morphology, often without discrete QRS complexes. Polymorphic ventricular tachycardia may degenerate into ventricular fibrillation and the ECG distinction between the two is difficult. Torsades de pointes is a polymorphic VT in association with QT interval prolongation and is discussed in more detail later in the chapter. ECG characteristics The presence of AV dissociation is a particularly important feature to seek in a broad-complex tachycardia as it makes the diagnosis of ventricular tachycardia virtually certain (Fig. 16.4.41a). A careful search for P-waves perturbing the QRS complex or T-waves is necessary, ideally using multilead recordings. Occasionally, a fortuitously timed P-wave allows the development of a capture beat of normal QRS morphology without interrupting the tachycardia. A fusion beat occurs when activation of the ventricle is partly via the normal

His–Purkinje system and partly from the tachycardia focus (Fig. 16.4.41b). Fusion and capture beats are diagnostic of ven- tricular tachycardia but are commonly present only if the ventricular rate is relatively slow. Although AV dissociation is diagnostic of ven- tricular tachycardia, it is not invariable. Retrograde ventriculoatrial conduction may occur, giving either 1:1 conduction or higher de- grees of block (Fig. 16.4.41c). The QRS duration in ventricular tachycardia is commonly greater than 120 ms, and values greater than 140 ms are particularly sug- gestive of ventricular tachycardia. Although the QRS morphology may superficially resemble left or right bundle branch block, the morphology is commonly atypical (see Fig. 16.4.16). Ventricular tachycardia arising from the right ventricular free wall has a left bundle branch block-like pattern, whereas left ventricular free wall tachycardias show right bundle branch block morphology. The pres- ence of concordant positive or negative QRS complexes across the chest leads is suggestive of ventricular tachycardia, as is the existence of extreme axis deviation. ECG features consistent with VT are listed in Fig. 16.4.16. Aetiology Sustained monomorphic ventricular tachycardia commonly occurs in the presence of structural heart disease, but also arises in struc- turally normal hearts. It rarely occurs in the acute phase of myo- cardial infarction, but may be seen in the subacute phase (>48 h), or may arise many years later, particularly in association with left ventricular scar or aneurysm formation. The arrhythmia also occurs in other forms of structural heart disease associated with ventricular dilatation or fibrosis such as dilated cardiomyopathy, hypertrophic cardiomyopathy, or previous ventricular surgery (e.g. following re- pair of Fallot's tetralogy). Ventricular tachycardia may degenerate into ventricular fibrillation. Sustained monomorphic tachycardia can occur as a proarrhythmic response to antiarrhythmic drugs, particularly class I agents. Although ventricular tachycardia normally occurs in individ- uals with overt heart disease, it is also seen in young and apparently healthy subjects. In these, occult cardiac disease or cardiac genetic syndromes should be considered (see 'Genetic syndromes'). There (a) (b) (c) Fig. 16.4.41 Sustained monomorphic ventricular tachycardia. (a) Ventricular tachycardia with atrioventricular dissociation. P-waves (arrowed) are seen to have no relationship to the ventricular activation. Lead V1. (b) Ventricular tachycardia with fusion beat (arrow). Lead V1. (c) Ventricular tachycardia with 2:1 ventriculoatrial conduction. Lead III. P-waves (arrows) follow every second ventricular complex.

section 16 Cardiovascular disorders 3382 remain a few patients with documented ventricular tachycardia in whom no structural heart disease is evident on clinical, ECG, or echocardiographic examination. The tachycardia may arise from the outflow tract of the right or left ventricle, or from one of the fas- cicles of the left bundle branch, and is amenable to radiofrequency ablation. Acute management of ventricular tachycardia Rapid ventricular tachycardia may present with cardiac arrest, syn- cope, shock, anginal chest pain, or left ventricular failure, but slower tachycardias in patients with preserved cardiac function may be well tolerated. Sustained ventricular tachycardia is a medical emer- gency. If the patient is pulseless or unconscious, immediate DC cardioversion is necessary. If the patient is conscious but hypoten- sive, urgent DC cardioversion under general anaesthesia or deep sedation is used. Haemodynamically tolerated tachycardias may be terminated by drug therapy (see Fig. 16.4.17). Adenosine may be ad- ministered in the presence of haemodynamic stability to exclude the differential diagnoses of SVT with aberrancy or antidromic AVRT, but is likely to be ineffective in terminating VT (see Table 16.4.6). Amiodarone 300 mg over 20 min (ideally via a central vein) followed by 900 mg/24 h may be effective in restoring sinus rhythm. Second- line drugs for the termination of ventricular tachycardia include intravenous lidocaine (lignocaine) 100 mg, sotalol, procainamide, and disopyramide, although all may be proarrhythmic. Flecainide is contraindicated in view of the risk of developing incessant tachy-

cardia. Verapamil should be avoided as it may cause clinical deteri- oration. The only exception to this is in the rare instance of patients with structurally normal hearts who have ventricular tachycardia that is known to respond to verapamil (e.g. LV fascicular tachy- cardia). All antiarrhythmic drugs have significant negative inotropic actions that may further impair the haemodynamic status of the pa- tient if sinus rhythm is not restored. For this reason, no more than one antiarrhythmic drug should normally be given before recourse to alternative therapy, usually DC cardioversion. Overdrive termin- ation of ventricular tachycardia following insertion of a temporary pacing lead may be effective, particularly if the tachycardia is rela- tively slow. Facilities for cardioversion must be available in view of the risk of acceleration or degeneration into ventricular fibrillation. Secondary prevention Ventricular tachycardia is a potentially life-threatening condition. Unless the acute episode was clearly precipitated by some transient or reversible factor, there is a high probability of recurrent attacks, which may result in sudden death. Prognosis is worse if the ar- rhythmia was poorly tolerated, or if there is severe left ventricular dysfunction. Clinical evaluation of the patient after restoration of sinus rhythm should be supported by ECG, echocardiography, cardiac magnetic resonance imaging, and/or radionuclide ventriculography. Coronary angiography should be considered to identify the presence of sig- nificant coronary artery disease, which may act as a trigger to ven- tricular tachycardia. Unless there is a clear precipitating factor such as drug toxicity, electrolyte abnormality, or acute ischaemia, the risk of sudden death is high and patients should be considered for a sec- ondary prevention ICD (see Fig. 16.4.20). A meta-analysis of three secondary prevention trials of patients resuscitated from ventricular fibrillation or ventricular tachycardia causing haemodynamic compromise showed defibrillators to be better than antiarrhythmic drug therapy in preventing death from any cause (Fig. 16.4.42a). Primary prevention Patients with left ventricular dysfunction of any cause are at risk of sudden death from ventricular tachycardia or fibrillation and implantable defibrillators are appropriate for a subgroup of these patients as part of a primary prevention strategy. Those with non- sustained ventricular tachycardia, in whom sustained tachycardia can be induced at electrophysiological testing, have a better survival with defibrillator implantation compared with drug therapy. Primary prevention trials such as the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) have expanded the indication to include patients with class II/III heart failure and an ejection fraction less than 30%, even in the absence of known arrhythmia (Fig. 16.4.42b). Antiarrhythmic therapy Implantable defibrillator therapy is not affordable in all countries, and not appropriate for patients with New York Heart Association (NYHA) class IV heart failure or other conditions causing a se- verely limited prognosis. Medical therapy is necessary for many patients, but is limited by a relative lack of evidence from random- ized controlled trials. β-Adrenoceptor blockers are comparable to conventional antiarrhythmic agents in the prevention of recurrent ventricular tachyarrhythmias. Since they have been shown to reduce the risk of sudden death in unselected survivors of myocardial in- farction and in patients with chronic heart failure, they should be used routinely in the prophylaxis of ventricular tachycardia if toler- ated. Amiodarone did not improve mortality compared to placebo in the SCD-HeFT trial. The class I antiarrhythmics should not be used for this indication as they were associated with a higher rate of arrhythmic deaths in the Cardiac Arrhythmia Suppression Trial. Other therapies Radiofrequency ablation is used in the management of ventricular tachycardia, particularly in those with no structural heart disease. Right or left ventricular outflow tract tachycardia and fascicular tachycardia are particularly amenable to ablation. Radiofrequency ablation of critical areas of slow conduction in scar-related ven- tricular tachycardias is now frequently undertaken but success rates are lower than for other types of ablation and this approach is often reserved for the treatment of recurrent tachycardia in patients with implantable

defibrillators. Direct surgical management of recurrent ventricular tachycardia involves aneurysmectomy, endocardial mapping, and resection of the area containing the micro re-entry circuit. The indications for surgery have been reduced considerably since the advent of the ICD and the emergence of catheter ablation, since the surgical mor- tality is up to 10–15%. Where medically intractable ventricular tachyarrhythmias are associated with very poor left ventricular function, cardiac transplantation should be considered if catheter ablation fails. Nonsustained ventricular tachycardia The mechanism and causes of nonsustained ventricular tachy- cardia (Fig. 16.4.43) are similar to those of sustained ventricular tachycardia. There is often slight variation in the R-R interval, particularly if the salvo involves only a few beats. Short salvos of

16.4 Cardiac arrhythmias 3383 ICD Death Amio 50 40 30 20 10 0 1 2 3 Years Number at risk ICD: 934 715 467 273 159 104 Amio: 932 664 427 248 128 82 4 5 ICD Arrhythmic death Amio 50 40 30 20 10 0 1 2 3 Years 934 715 467 273 159 104 932 664 427 248 128 82 4 5 (a) (b) 0 0.0 0.1 0.2 0.3 0.4 Amiodarone (240 deaths; 5-yr event rate, 0.340) Amiodarone vs. placebo ICD therapy vs. placebo Hazard ratio (97.5% CI) 1.06 (0.86–1.30) 0.77 (0.62–0.96) P value 0.53 0.007 Placebo (244 deaths; 5-yr event rate, 0.361) ICD therapy (182 deaths; 5-yr event rate, 0.289) 12 24 36 Months of follow-up Mortality rate 48 No. at risk Amiodarone 845 772 715 484 280 97 Placebo 847 797 724 505 304 89 ICD therapy 829 778 733 501 304 103 60 Fig. 16.4.42 Improved survival with the implantable cardioverter–defibrillator (ICD). (a) Cumulative risk of fatal events for ICD or amiodarone (amio) from a meta-analysis of trials of secondary prevention, showing reduced death with ICD (left panel), due to reduced arrhythmic death (right panel). (b) Improved survival with ICD compared to amiodarone or placebo in a study of primary prevention in patients with heart failure. (a) Reproduced from Connolly SJ, et al. (2000). Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J, 21(24), 2071–8, by permission of Oxford University Press; (b) Bardy GH, et al. (2005), New Engl J Med, 352, 230. Copyright ©2005 Massachusetts Medical Society. All rights reserved. Fig. 16.4.43 Nonsustained ventricular tachycardia.

section 16 Cardiovascular disorders 3384 nonsustained ventricular tachycardia are often asymptomatic. Apart from the instances where nonsustained ventricular tachycardia pro- duces troublesome symptoms, the major clinical significance of the arrhythmia is as a risk marker for sustained ventricular tachycardia or sudden cardiac death in patients with left ventricular dysfunction or hypertrophy. Patients with structural heart disease, in particular those with severe left ventricular dysfunction, with QRS duration greater than 120 ms or heart muscle disease, should be considered for an implantable defibrillator as primary prevention of sudden car- diac death. If no structural heart disease or ion channel disease is present, and the patient is asymptomatic, no treatment is indicated as long-term follow-up of such patients indicates a good prognosis with no excess risk of sudden death. Polymorphic ventricular tachycardia Polymorphic ventricular tachycardia is an unstable rhythm with varying QRS morphology. It is most commonly seen in the acute phase of myocardial infarction. It either undergoes spontaneous ter- mination or degenerates into ventricular fibrillation. If episodes of polymorphic ventricular tachycardia are frequent in the early hours of myocardial infarction, they can be suppressed by β-blockade. Torsades de pointes and the long-QT syndromes Torsades de pointes is a characteristic type of polymorphic ven- tricular tachycardia with a typical undulating variation in QRS morphology as a result of variation in axis. It occurs in association with a prolonged QT interval during sinus rhythm. Long-QT syn- dromes may be acquired or congenital; the latter are discussed later in the chapter. Aetiology

Although class Ia and III antiarrhythmic drugs are the best-known causes of acquired long-QT syndrome, a very large number of non- cardiac drugs inhibit the outward potassium current IKr, and may cause significant lengthening of the QT interval either singly or in combination (Table 16.4.12). Episodes of torsades de pointes are often multifactorial in origin, with prolongation of the QT interval by an IKr inhibitor in association with predisposing factors such as bradycardia or pauses, hypokalaemia, or hypomagnesaemia. All of these predispose to early after-depolarizations in vitro and this mechanism appears to be the likely cause of torsades de pointes in the acquired syndromes. The prognosis of the acquired long-QT syndromes is excellent, provided the underlying predisposing fac- tors are identified and corrected. However, it is increasingly rec- ognized that there is a genetic predisposition to the development of acquired long-QT syndrome in the face of predisposing factors, leading to the concept that patients developing acquired long-QT syndrome have reduced 'repolarization reserve' as a result of a forme fruste of the congenital syndrome. ECG characteristics Torsades de pointes is an atypical ventricular tachycardia charac- terized by a continuously varying QRS axis ('twisting of points'; see Fig. 16.4.44). Episodes of torsades are commonly repetitive and normally self-terminating, although they may degenerate into ven- tricular fibrillation. Paroxysms of torsades de pointes are associated in the preceding beats with evidence of marked QT prolongation, and frequently with morphological abnormalities of the T-wave such as T-U fusion, gross increases in T-wave amplitude, or T-wave alternans. In the acquired long-QT syndromes a slowing of the heart rate, and in particular a postextrasystolic pause, is often associated with initiation of the arrhythmia. This produces a characteristic 'short–long–short' sequence of initiation (Fig. 16.4.44). Acute management The common clinical presentation is of recurrent dizziness or syncope, and the condition may easily be misdiagnosed as self- terminating polymorphic ventricular tachycardia or ventricular fib- rillation unless the characteristic morphology of torsades de pointes and the associated QT interval prolongation is recognized. It is es- sential to discontinue predisposing drugs or other agents and to avoid empirical antiarrhythmic drug therapy, which may worsen the arrhythmia. Individual paroxysms of torsades de pointes are nor- mally self-limiting, but if they are persistent, cardiac arrest will occur and emergency defibrillation is necessary. Intravenous magnesium sulphate (8 mmol over 10–15 min, repeated if necessary) is a safe and effective emergency measure for the prevention of recurrent parox- ysms of tachycardia. If torsades de pointes is associated with brady- cardia and pauses, the heart rate should be increased to between 90 Table 16.4.12 Causes or contributory factors in acquired long-QT syndromes Drug induced Antiarrhythmic drugs—classes Ia, III Macrolide antibiotics—erythromycin Antifungals—ketoconazole Psychotropics—tricyclic/tetracyclic antidepressants, antipsychotics Antihistamines—terfenadine, astemizole Antiemetics—domperidone, ondansetron Synthetic opioid—methadone Electrolyte disturbances Hypokalaemia, hypomagnesaemia, hypocalcaemia Metabolic Hypothyroidism, starvation, anorexia nervosa, liquid protein diet Bradycardia Sinoatrial disease, AV block Toxins Organophosphorus insecticides, heavy metal poisoning Fig. 16.4.44 Torsades de pointes. Note the marked QT interval prolongation in the sinus beats, and the 'short–long' pattern of R-R intervals immediately prior to initiation of the arrhythmia. Ambulatory monitoring recording is shown (continuous tracing).

 and 100/min by atrial or ventricular pacing or isoproterenol (iso- prenaline) infusion. Hypokalaemia and hypomagnesaemia should be sought and corrected if necessary. Accelerated idioventricular rhythm The term 'accelerated idioventricular rhythm' is used to describe a continuous ventricular rhythm with a rate less than 120/min. Idioventricular rhythm commonly occurs in the setting of acute myocardial infarction and appears to be a marker of

successful reperfusion therapy. No active treatment is necessary. Ventricular fibrillation Ventricular fibrillation is defined as a chaotic, disorganized ar- rhythmia with no identifiable QRS complexes (Fig. 16.4.45). The mechanism is of multiple, unstable re-entry circuits. The electrocar- diographic pattern depends on the duration of fibrillation: recent- onset fibrillation is described as ‘coarse’, with a peak-to-peak amplitude of around 1 mV (1 cm). With increasing duration of car- diac arrest, the amplitude of ventricular fibrillation diminishes and such ‘fine’ ventricular fibrillation is less likely to be amenable to suc- cessful electrical defibrillation. Ventricular fibrillation may occur during acute myocardial is- chaemia often initiated by an R on T extrasystole, and is the principal cause of death in the first 2 h following acute myocardial infarction (Fig. 16.4.45). Ventricular fibrillation during myocardial infarction is subdivided into primary, occurring without warning in an otherwise stable patient, and secondary, where fibrillation occurs in the context of left ventricular failure or cardiogenic shock. Ventricular fibrillation occurring in chronic heart disease is most commonly a result of de- generation of rapid ventricular tachycardia, whose causes have been described earlier. Rarer causes of fibrillation are listed in Box 16.4.4. Ventricular fibrillation is rarely self-terminating, and normally causes cardiac arrest with the rapid onset of pulselessness, uncon- sciousness, and apnoea. The management of cardiac arrest due to ventricular fibrillation is discussed in Chapter 17.2. Patients who survive an episode of ventricular fibrillation should be assessed carefully to determine the risk of recurrence. If ven- tricular fibrillation has occurred in the first few hours of a typical ST-elevation myocardial infarction, the risk of recurrent cardiac arrest is low, and no specific prophylactic therapy other than as- sessment and treatment of residual ischaemia and conventional postinfarction β-blockade is indicated. However, in many instances ventricular fibrillation arises as a result of acute ischaemia in pa- tients with known, extensive heart disease who have not sustained an acute infarction. These patients remain at high risk of recurrent ventricular fibrillation, and should be evaluated fully by exercise testing and coronary arteriography with a view to revascularization, and managed with an ICD or antiarrhythmic therapy as discussed in the section on ventricular tachycardia. Genetic syndromes Ion channel diseases Congenital long-QT syndromes The congenital long-QT syndromes (LQTS) are inherited conditions due to mutations in genes encoding ion channel proteins. They are mainly autosomal dominant and are subclassified according to the underlying gene defect (Table 16.4.13). Most cases are either LQT1 or LQT2, due to mutations affecting either the slow (IKs) or rapid (IKr) components of the outward potassium current. In the less common LQT3, the inward sodium current (INa) is affected. Lengthening of ventricular repolarization, and hence of the QT interval, occur as a result either of reduced outward current flow via IKr or IKs or in- creased duration of current flow via INa. The arrhythmia, torsades de pointes, has characteristics consistent with triggered activity. Attacks of torsades de pointes in the congenital syndromes are commonly associated with sympathetic stimulation such as exercise, waking, or fright, and are associated with increases in sinus rate. Cardiac events are particularly associated with exercise in LQT1, with auditory stimulation in LQT2, and can occur during sleep in LQT3. Paroxysms may produce syncope, which if prolonged may be complicated by convulsion, leading to misdiagnosis as epilepsy. A family history of recurrent syncope or sudden death may be obtained. Sinus bradycardia is commonly seen in these syndromes. The diagnosis of long-QT syndrome can be challenging and is not based on the ECG characteristics alone. The finding of a long QT interval on an ECG in patients with a history of syncope or palpi- tations or a routine ECG in asymptomatic patients can cause con- siderable anxiety among clinicians. The probability of LQTS can be assessed using the Schwartz score, with a score more than 3.5 sup- porting the diagnosis (Table 16.4.14). The prognosis of untreated congenital long-QT syndrome is poor, with a high incidence of sudden death in childhood. Factors associ- ated with high risk include personal history

of aborted sudden cardiac death or syncope, and corrected QT interval greater than 500 ms. Males with LQT3 are at increased risk regardless of the degree of QT interval prolongation. LQT1 has a better prognosis than other subtypes. Episodes of torsades de pointes and T-wave alternans on Holter monitoring also confer a higher risk. Fig. 16.4.45 Ventricular fibrillation complicating acute myocardial infarction. The arrhythmia is initiated by an 'R on T' ventricular extrasystole. Box 16.4.4 Causes of ventricular fibrillation • Acute myocardial ischaemia • Acute myocardial infarction—primary or secondary • Advanced organic heart disease with poor LV or RV function • Severe LV hypertrophy • Ventricular tachycardia/torsades de pointes • Electrical—electrocution, lightning, unsynchronized DC shock, com- petitive ventricular pacing • Pre-excited atrial fibrillation • Profound bradycardia • Hypoxia, acidosis • Genetic syndromes (e.g. long-QT syndrome, Brugada syndrome)

section 16 Cardiovascular disorders 3386 Table 16.4.13 Genetics of congenital long-QT syndromes Subtype Chromosome Gene Product Ion current affected Frequency LQT1 11 KCNQ1 KvLQT1 ↓IKs c.50% LQT2 7 KCNH2 HERG ↓IKr 30–40% LQT3 3 SCN5A Nav 1.5 ↑INa 5–10% LQT4 4 ANKB Ankyrin-B ↓Multiple Rare LQT5 21 KCNE1 minK ↓IKs Rare LQT6 21 KCNE2 MiRP1 ↓IKr Rare LQT7 17 KCNJ2 Kir2.1 ↓IK1 Rare LQT8 12 CACNA1C Cav1.2 ↑ICaL Rare LQT9 3 CAV3 Caveolin 3 ↑INa Rare LQT10 11 Sodium channel β4 SCN4B ↑INa Rare LQT11 7 AKAP9 Yotiao ↓IKs Rare LQT12 20 Syntrophin α1 SNTA1 ↑INa Rare LQT13 11 KCNJ5 Kir3.4 ↓IKr Rare LQT14 14 CALM1 Calmodulin 1 N/A Rare LQT15 2 CALM2 Calmodulin 2 N/A Rare LQT16 19 CALM3 Calmodulin 3 N/A Rare
Table 16.4.14 Schwartz score for the diagnosis of long-QT syndrome Clinic features Points ECG findingsa A QTcb ≥480 ms 3 460–479 ms 2 450–459 ms (male) 1 B QTcb 4th minute of recovery from exercise stress test ≥480 ms 1 C Torsade de pointesc 2 D T-wave alternans 1 E Notched T-wave in three leads 1 F Low heart rate for aged 0.5 Clinical history A Syncopec With stress 2 Without stress 1 B Congenital deafness 0.5 Family history A Family members with definite LQTSe 1 B Unexplained sudden cardiac death <age 30 among immediate family memberse 0.5 Score ≤1 point: low probability of LQTS 1.5–3 points: intermediate probability of LQTS ≥3.5 points: high probability of LQTS a In the absence of medications or disorders known to affect these ECG features. b QTc calculated using Bazett's formula where QTc = QT/√RR. c Mutually exclusive. d Resting heart rate below the 2nd percentile for age. e The same family member cannot be counted in A and B. Source: Schwartz PJ et al. (1993). Diagnostic criteria for the long-QT syndrome—an update. Circulation, 88, 782–4.

16.4 Cardiac arrhythmias 3387 β-Blockers are highly effective in LQT1 but are less protective in LQT2 and LQT3. Selective high left stellate ganglionectomy (cer- vical sympathectomy) has been employed successfully in cases with recurrent events despite β-blockers. Permanent pacing at rates of 70–80/min, in combination with β-blockers, may also be effective in reducing symptoms but defibrillator implantation is necessary for resistant cases, and is commonly used as first-line therapy if episodes of torsades de pointes have resulted in cardiac arrest or in those thought to be at high risk of sudden death. Short-QT syndrome This is a recently described entity with autosomal dominant inher- itance characterized by a gain of function mutation in the outward potassium currents (IKr and IKs). It produces a markedly shortened QTc, often less than 280 ms, and predisposes to atrial and ventricular fibrillation. Brugada syndrome The Brugada syndrome is an autosomal dominant condition which has a risk of sudden cardiac death associated with characteristic ECG abnormalities and a structurally normal heart. There is an unusual pattern of coved ST-segment elevation of at least 2 mm in two of the right precordial leads (Fig. 16.4.46).

Mutations of genes encoding the voltage-gated sodium channel (SCN5A), causing partial inactivation, have been identified in about 20% of patients, and although many other mutations have been identified (Table 16.4.15), genetic testing Fig. 16.4.46 Brugada ECG. Table 16.4.15 Genetics of Brugada syndrome Subtype Gene Protein Ion current affected Functional effect Frequency BrS1 SCN5A Nay1.5 INa Loss of function 20% BrS2 GPD1-L G3PD1L INa Loss of function Rare BrS3 CACNA1C Cav1.2 ICa-L Loss of function Rare BrS4 CACNB2 Cayβ2 ICa-L Loss of function Rare BrS5 SCN1B Nayβ1 INa Loss of function Rare BrS6 KCNE3 MiRP2 Ito/IKs Gain of function Rare BrS7 SCN3B Navβ3 INa Loss of function Rare BrS8 KCNH2 hERG1 IKr Loss of function Rare BrS9 KCNJ8 Kir6.1 IKATP Gain of function Rare BrS10 CACNA2D1 Cavα2δ-1 ICa-L Unknown Rare BrS11 RANGRF MOG1 INa Loss of function Rare BrS12 KCNE5 MiRP4 Ito/IKs Gain of function Rare BrS13 KCND3 Kv4.3 Ito Gain of function Rare BrS14 HCN4 HCN4 If Unknown Rare BrS15 SLAMP SLAMP INa Loss of function Rare BrS16 TRMP4 TRMP4 NSCCa Both Rare BrS17 SCN2B Navβ2 INa Loss of function Rare

section 16 Cardiovascular disorders 3388 is negative in most cases. Patients with a history of syncope and spon- taneous ECG features should be considered for defibrillator therapy. Catecholaminergic polymorphic ventricular tachycardia (CPVT) This is a rare arrhythmia characterized by polymorphic or bidirec- tional ventricular tachycardia occurring in situations of strenuous exercise, psychological stress, or emotion, often presenting in child- hood. It is associated with mutations of genes involved in controlling intracellular calcium handling. Mutations of the cardiac ryanodine receptor have autosomal dominant transmission, whereas mutations of the gene encoding for calsequestrin have autosomal recessive trans- mission. The resting ECG has no diagnostic features and the heart is structurally normal. β-Blockers may prevent syncope, but an ICD may be indicated for recurrent symptoms or high risk of cardiac arrest. Heart muscle diseases Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy has a prevalence of 0.2% in the popu- lation, and is associated with a variety of mutations encoding struc- tural or regulatory proteins of the cardiac myofibrillar apparatus. The mode of inheritance is autosomal dominant in 70% of cases, with vari- able penetrance. Although symptoms are often related to impaired haemodynamics, LV hypertrophy and myofibre disarray increase the risk of re-entrant arrhythmias and sudden death. Patients with sus- tained ventricular tachycardia or fibrillation should be considered for defibrillator therapy. Risk assessment should be performed in all patients with hypertrophic cardiomyopathy. Unexplained syncope, nonsustained ventricular tachycardia, ventricular septal thickness greater than 30 mm, a family history of sudden cardiac death, and a hypotensive response to exercise are all associated with increased risk. An ICD may be considered if one or more high-risk features are present. See Chapter 16.7.2 for further discussion. Arrhythmogenic right ventricular cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy (dysplasia) is an autosomal dominant condition associated with replacement of the right ventricular free wall with fat and fibrous tissue. These patients may have no symptoms or signs of cardiac disease, but typical ECG changes (epsilon wave in V1, or T-wave inversion in the right precordial leads) are associated with variable degrees of dilatation of the right ventricle demonstrable by echocardiography or MRI. This creates a substrate for heart failure or arrhythmia (ventricular tachycardia and fibrillation) and many patients will ultimately require defibrillator therapy. Dilated cardiomyopathy This is often used as an umbrella term for cardiomyopathy of non- ischaemic aetiology. In some cases, there is an inheritable cause which predisposes to arrhythmia, such as the lamin A/C, SCN5A, or titin mutations. Genetic testing A strong clinical index of suspicion may warrant targeted genetic testing for certain conditions (e.g. LQTS, CPVT). In many inherited cardiac

conditions, genetic testing may be indicated for family mem- bers and appropriate relatives once the causative mutation has been diagnosed in the index case. FURTHER READING Diagnosis and treatment Morady F (1999). Radio-frequency ablation as treatment for cardiac arrhythmia. N Engl J Med, 340, 534–44. Roden DM (2000). Antiarrhythmic drugs: from mechanisms to clin- ical practice. Heart, 84, 339–46. Screening Arnar DO, et al. (2019). Management of asymptomatic arrhythmias: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Failure Association (HFA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin America Heart Rhythm Society (LAHRS). Europace, pii: euz046, doi: 10.1093/europace/euz046. Donal E, et al. (2016). EACVI/EHRA expert consensus document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging, 17(4), 355–83. Freedman B, et al. (2017). Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. Circulation, 135(19), 1851–67. Lip GYH, et al. (2017). Hypertension and cardiac arrhythmias: execu- tive summary of a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Eur Heart J Cardiovasc Pharmacother, 3(4), 235–50. Mont L, et al. (2017). Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Europace, 19(1), 139–63. Bradycardia Brignole M, et al. (2013). ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J, 34, 2281–329. Fitzpatrick A, Sutton R (1992). A guide to temporary pacing. BMJ, 304, 365–9. Gammage MD (2000). Temporary cardiac pacing. Heart, 83, 715–20. Healey JS, et al. (2006). Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of random- ized trials, using individual patient data. Circulation, 114, 11–17. Morley-Davies A, Cobbe SM (1997). Cardiac pacing. Lancet, 349, 41–6. Atrial arrhythmias Apostolakis S, et al. (2013). Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT2R2 score. Chest, 144, 1555–63. Banerjee A, et al. (2012). Net clinical benefit of new oral anticoagu- lants (dabigatran, rivaroxaban, and apixaban) versus no treatment in a ‘real world’ atrial fibrillation population: a modelling analysis based on a nationwide cohort study. Thromb Haemost, 107, 584–9. Calkins H, et al. (2017). 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm, 14(10), e275–e444. Clarkesmith DE, et al. (2013). Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. PLoS One, 8, e74037. Cowan C, et al. (2013). The use of anticoagulants in the management of atrial fibrillation among general practices in England. Heart, 99, 1166–72.

16.4 Cardiac arrhythmias 3389 Freedman B, Potpara TS, Lip GY (2016). Stroke prevention in atrial fibrillation. Lancet, 388(10046), 806–17. Haïssaguerre M, et al. (1998). Spontaneous initiation of atrial fibrilla- tion by ectopic beats originating in the pulmonary veins. N Engl J Med, 339, 659–66. Healey JS, et al. (2012). Subclinical atrial fibrillation and the risk of stroke. N Engl J Med, 366, 120–9. Heidbuchel H, et al. (2015). Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antag- onist anticoagulants in patients with non-valvular atrial fibrillation. Europace, 17(10), 1467–507. Kakkar AK, et al. GARFIELD Registry Investigators (2013). Risk pro- files and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the inter- national, observational, prospective GARFIELD registry. PLoS One, 8, e63479. Kirchhof P, et al. (2016). 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace, 18(11), 1609–78. Lane DA, et al.

(2015). Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace, 17(12), 1747–69. Lip GY, et al. (2015). Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high- risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. Europace, 17(12), 1777–86. Lip GYH, Lane DA (2015). Stroke prevention in atrial fibrilla- tion: a systematic review. JAMA, 313(19), 1950–62. doi: 10.1001/ jama.2015.4369. Review. Erratum in: JAMA. 2015 Aug. Mant J, et al. BAFTA investigators; Midland Research Practices Network (MidReC) (2007). Warfarin versus aspirin for stroke pre- vention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet, 370, 493–503. National Clinical Guideline Centre (2014). Atrial fibrillation: the man- agement of atrial fibrillation. National Institute for Health and Care Excellence. Draft for consultation. Olesen JB, et al. (2012). The value of the CHA2DS2-VASc score for re- fining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: a nationwide cohort study. Thromb Haemost, 107, 1172–9. Pisters R, et al. (2010). A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrilla- tion: the Euro Heart Survey. Chest, 138, 1093–100. Sticherling C, et al. (2015). Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS). Europace, 17(8), 1197–214. Supraventricular tachycardias Calkins H. (2001). Radiofrequency catheter ablation of supraventricular arrhythmias. Heart, 85, 594–600. Katritsis DG, et al. (2017). European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular ar- rhythmias, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). Europace, 19(3), 465–511. Ventricular arrhythmias Al-Khatib SM, et al. (2018). 2017 AHA/ACC/HRS guideline for man- agement of patients with ventricular arrhythmias and the preven- tion of sudden cardiac death: executive summary: a report of the American College of Cardiology / American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. Heart Rhythm, 15, e190–e252. Bardy GH, et al. (2005). Amiodarone or an implantable cardioverterdefibrillator for congestive heart failure. N Engl J Med, 352, 225–37. Connolly SJ, et al. (2000). Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs implantable defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J, 21, 2071–8. Gupta A, et al. (2007). Current concepts in the mechanisms and man- agement of drug-induced QT prolongation and torsade de pointes. Am Heart J, 153, 891–9. Moss AJ, et al. (2002). Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med, 346, 877–83. Schwartz PJ, et al. (1993). Diagnostic criteria for the long QT syndrome—an update. Circulation, 88, 782–4. Stevenson WG, et al. (1998). Radiofrequency catheter ablation of ven- tricular tachycardia after myocardial infarction. Circulation, 98, 308–14. Genetic syndromes Brugada J, et al. (1998). Right bundle branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in pa- tients without demonstrable structural heart disease. Circulation, 97, 457–60. Garratt C, et al. (2010). Heart Rhythm UK position statement on clin- ical indications for implantable cardioverter defibrillators in adult patients with familial sudden cardiac death syndromes. Europace, 12, 1156–75. Goette A, et al. (2016). EHRA/HRS/APHRS/SOLAECE expert con- sensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace, 18(10),

1455–90. Hershberger RE, et al. (2018). Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med, 20, 899–909. Kies P, et al. (2006). Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment. Heart Rhythm, 3, 225–34. Maron BJ, et al. (2003). American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol, 42, 1687–713. Pedersen CT, et al. (2014). EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Europace, 16(9), 1257–83. Roden D (2008). Long QT syndrome. N Engl J Med, 358, 169–76. Shah M, et al. (2005). Molecular basis of arrhythmias. Circulation, 112, 2517–29.

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