PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

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Heart 2006;**92**:1873–1878. doi: 10.1136/hrt.2006.087957

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Sudden cardiac death (SCD) causes more than 300 000 deaths per annum in Europe, with the same number occurring in the United States, according to current estimations.[1 2] This amounts to a death toll of 1–1.5 per 1000 people per year in the industrialised world.[w1] In low-income regions of the world, the estimations are less valid. These estimates are based on clinical definitions of "sudden" and "cardiac". "Sudden" implies that death occurred unexpectedly and that the sequence of events that led to death occurred within a short time span, usually one hour before death. It is generally assumed that the patient was in a stable condition before the sudden and lethal event. "Cardiac" implies that the primary pathology occurred in the heart. This is usually confirmed by the absence of other lethal diseases upon inspection and, whenever available, autopsy. At times, signs of acute myocardial infarction or of acute heart failure can substantiate the assumption of "cardiac" death. Within the limitations of such a definition, it is generally assumed that the majority (85%) of SCD victims die of ventricular tachyarrhythmias, usually in the form of ventricular fibrillation (VF).[1] The remaining SCD victims die either of bradyarrhythmias or of acute pump failure.

PRIMARY PREVENTION OF SCD: A DIAGNOSTIC DILEMMA

SCD urgently requires primary prevention because the first clinical event is often fatal, especially in patients with ventricular tachyarrhythmias. Patients with acute bradyarrhythmias often retain a basal circulation—for example, due to ventricular escape rhythms. Thereby, the appropriate treatment (often a pacemaker) can usually be deployed in time to prevent irreversible organ damage when a sudden bradyarrhythmia occurs. VF, in contrast, results in a rapid and complete loss of blood circulation. If left untreated, this condition results in irreversible organ (most notably brain) damage after a few minutes.[1] Even in regions of the world with highly developed emergency medical care systems, only a small proportion of patients suffering from VF will leave the hospital alive.[1 w2] This is despite recent efforts to improve the treatment of SCD in the community setting by the use of semi-automatic external defibrillators.[1 w3] Primary prevention of SCD is therefore in part a diagnostic challenge—that is, it requires identification of future sudden death victims before the first arrhythmia episode. Correct identification of future SCD victims is especially important as there is an effective treatment, namely defibrillation via an external or internal (implanted) defibrillator.[w4]

This effectiveness of the cardioverter-defibrillator has been proven in selected high-risk patient groups. At first, defibrillators were implanted for secondary prevention of ventricular arrhythmias. More recently, their effectiveness has been demonstrated for primary prevention of SCD in patients with severely reduced left ventricular function (below 30–35% left ventricular ejection fraction), caused either by coronary artery disease or by cardiomyopathies.[3 4] Unfortunately, only every third SCD victim can be identified by the markers for SCD risk that are currently known.[1] Identification of other patient groups at high risk for SCD is required to save the remaining 0.6 per 1000 annual SCD victims in the population.

PRIMARY PREVENTION OF SCD BY PRIMARY AND SECONDARY PREVENTION OF CORONARY ARTERY DISEASE AND OPTIMAL TREATMENT OF HEART FAILURE

Coronary artery disease causes acute or chronic myocardial ischaemia and myocardial necrosis and remains the major cause of heart failure. SCD may be the first clinical manifestation of coronary artery disease in as many as one in five coronary heart disease patients.[1] Actions for primary prevention of coronary artery disease, most notably reduction of blood lipids, cessation of smoking, and sufficient treatment of diabetes and arterial hypertension, are therefore paramount to the prevention of SCD (fig 1).

In addition, several drugs are useful to prevent SCD in patients with known coronary artery disease or heart failure (table 1). Drugs that prevent acute ischaemic cardiac events (aspirin, hydroxymethylglutarate CoA (HMG-CoA) reductase inhibitors or "statins", β blockers) appear to have a moderate effect in reducing SCD caused by ischaemic heart disease. Heart failure patients, a group at high risk for sudden death, may further benefit from aldosterone antagonists and

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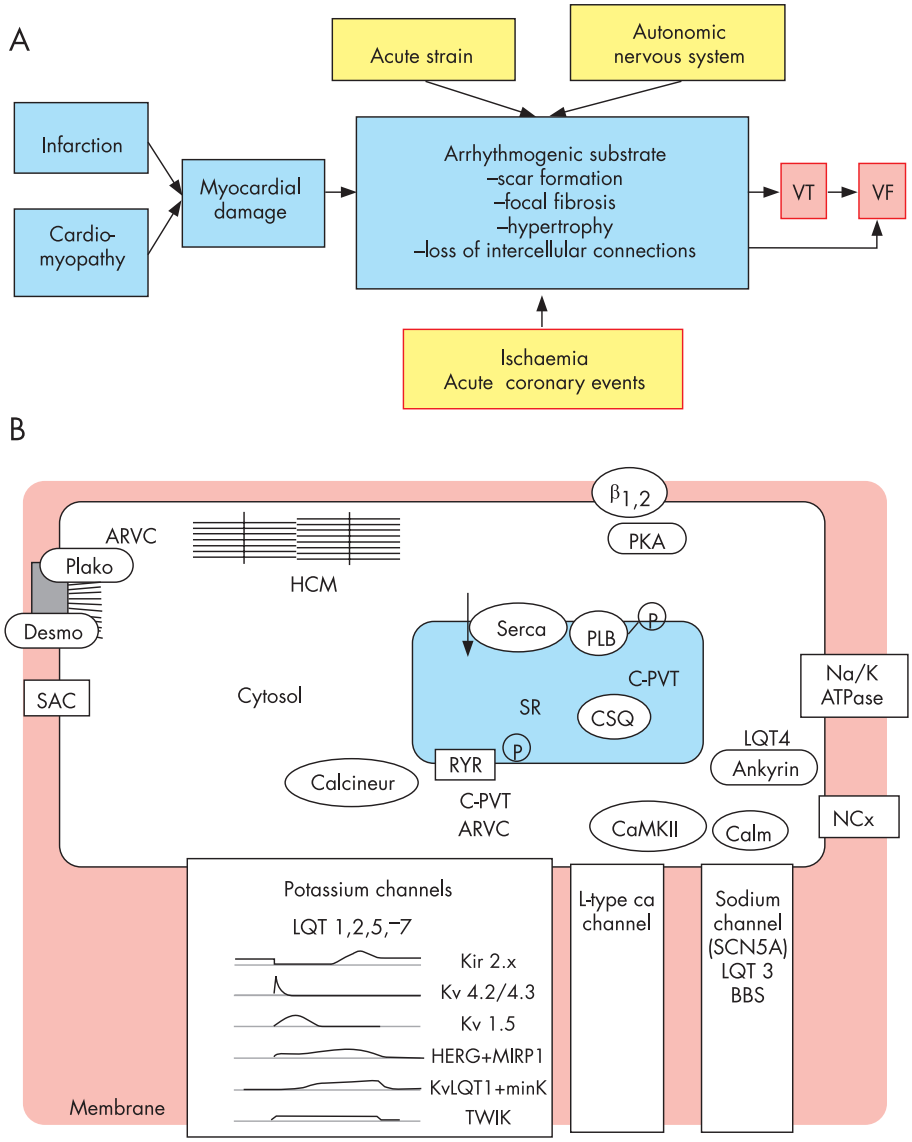

Figure 1 Causes of sudden arrhythmic death. (A) Structural heart disease forms a substrate for ventricular arrhythmias—for example, by damage to the left ventricular myocardium after myocardial infarction or as a consequence of cardiomyopathy. Ventricular tachycardia (VT) or ventricular fibrillation (VF) are often triggered by acute myocardial ischaemia, autonomic imbalance, or acute strain/stress. (B) Molecular mechanisms of sudden arrhythmic death. Shown is a schematic of a myocardial cell. The major proteins implicated in inherited arrhythmogenic diseases and the respective disease entities are indicated. ARVC, arrhythmogenic right ventricular cardiomyopathy; BBS, Brugada syndrome; Calm, calmodulin; CaMKII, calmodulin kinase II; CPVT, catecholaminergic polymorphic ventricular tachycardia; CSQ, calsequestrin; Desmo, desmoplakin; HCM, hypertrophic cardiomyopathy; LQT, long QT syndrome; NCx, sodium calcium exchanger; PKA, protein kinase A; Plako, plakoglobin and plakophilin; RYR, ryanodine receptor; SAC stretch-activated channel; SR, sarcoplasmic reticulum. Adapted with permission from Kirchhof P, Breithardt G. *Zeitschr Elektrophysiol Schrittmacherth* 2003;**14**:168–79.

angiotensin-converting enzyme (ACE) inhibitors. Among the interventions that lower blood lipid values, consumption of fish oil may have a special effect on the reduction of sudden death,[5 w5] although this has been disputed recently.[w6] Finally, cardiac resynchronisation therapy by biventricular stimulation may decrease sudden death rates in heart failure patients.[w7 w8] Amiodarone is the only ion channel blocking drug that may, under certain circumstances, prevent SCD in patients with known coronary heart disease,[6 w9] or at least not cause SCD.[7]

RECOGNITION OF PATIENTS AT HIGH RISK FOR SCD DUE TO INHERITED DISEASE

The majority of SCD events (approximately two-thirds) occurs in patients with normal left ventricular function, and approximately one in 10 of these patients suffers from an identifiable arrhythmogenic cardiac disease. At present, there are no prospectively validated algorithms or "risk factors" to identify these patients before the first arrhythmia episode, but there are several well-described disease entities associated with a high risk for SCD. Most of these diseases are inherited or genetically determined (fig 1).

A simple and powerful clinical tool to identify patients with inherited arrhythmogenic diseases is an appropriate family history of sudden death. Sudden deaths before the age of 60 in first-degree relatives, but also unexplained "accidents" (for example, car crashes without the involvement of alcohol, bad weather conditions or other explanations for the crash) should trigger further investigations. Palpitations and syncope may also raise a small flag, but they are relatively frequent and most often not due to ventricular arrhythmias.

Table 1 Drugs to prevent sudden cardiac death by preventing progression of coronary artery disease or heart failure

Drugs	Main mode of action	Mortality reduction proven for CAD/CHF	Prevention of SCD
β blockers	Modification of response to catecholaminergic stimulation in the heart	CAD/CHF	Shown[2 16]
Aldosterone-antagonists (spironolactone and eplerenone)	Blockade of aldosterone in kidney and heart	CHF	Shown (secondary end point)[17 w22]
ACE inhibitors	Inhibition of the stimulation of cardiomyocytes by angiotensin II	CHF	Shown in meta-analysis[17]
Angiotensin-receptor inhibitors	Alternative to ACE inhibitors	CHF[w23]	Likely[18]
Aspirin	Prevention of coronary thrombotic events (acute coronary ischaemia)	CAD (unstable situations)[19]	Not established, but likely[1]
HMG-CoA reductase inhibitors (''statins'')	Reduction of LDL cholesterol, possibly additional ''pleiotrophic'' effects	CAD	Not established, but likely[1]

While the main effect of these drug treatments is usually prevention of progression of known coronary heart disease or heart failure, some agents may have more direct antiarrhythmic effects.
ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, chronic heart failure; HMG-CoA, hydroxymethylglutarate CoA; LDL, low density lipoprotein; SCD, sudden cardiac death.

Depending on the penetrance of a specific disease and on the likelihood of spontaneous ''de novo'' mutations, a positive family history may identify up to two-thirds of the patients with inheritable arrhythmogenic diseases.

In addition, the standard ECG can identify some patients with inherited arrhythmogenic diseases (fig 2, table 2). Other diseases—for example, familial hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy—may require echocardiography and further cardiac investigations to be diagnosed correctly. At present, genetic tests are usually reserved to confirm a clinically suspected diagnosis. Once the diagnosis is made, further diagnostic tests and treatment decisions should be performed or guided by individual recommendations from specialised centres.

Identification of arrhythmogenic diseases in the ECG

Figure 2 shows the ECG changes associated with arrhythmogenic diseases that predispose to sudden cardiac death.

Congenital long QT syndromes

The congenital long QT syndromes, which predispose the affected individual to torsades de pointes tachyarrhythmias, can be identified by a corrected QT interval > 0.44–0.46 s in the resting ECG. There is, however, a relevant overlap between normal QT intervals and QT intervals of patients with long QT syndrome,[w10] and the diagnosis should be made based on clinical and ECG criteria,[w11] ideally confirmed by genetic testing. There are at least seven different gene defects known to cause long QT syndromes (LQT1 to LQT7), that code for ion channels or their regulatory proteins. β blockers are often effective to prevent SCD in asymptomatic and some symptomatic patients with the long QT syndrome. Oral potassium supplementation may support arrhythmia prevention in long QT syndrome. Some patients require more

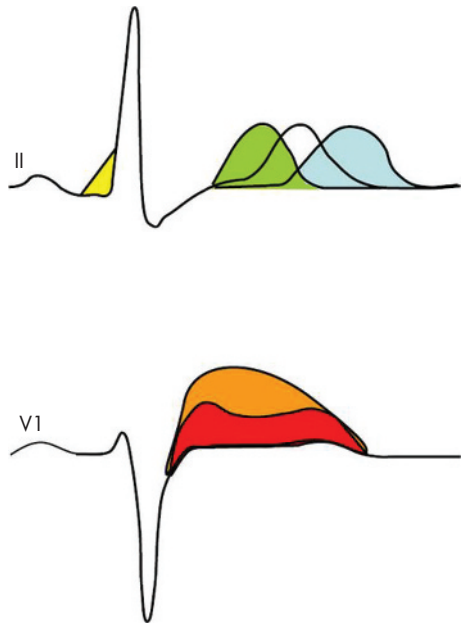

Figure 2 ECG changes associated with ''electrical'' diseases that predispose to sudden cardiac death. These include long QT and short QT syndromes, identifiable by an abnormally long (blue) or abnormally short (green) QT interval, the Brugada syndrome, identifiable by reversible ST segment elevation in the right precordial chest leads (coved type, orange; or saddle-type, red), and Wolff-Parkinson-White syndrome, of which the characteristic is the delta wave, a sign of ventricular pre-excitation (yellow). All changes are depicted in lead II (upper recording), with the exception of the changes associated with Brugada syndrome, which are only found in the right precordial chest leads and are therefore depicted in lead V1 (lower recording). In addition, T wave inversion in V1-V3 may be a sensitive, non-specific sign of ARVC.

Table 2 List of ECG signs indicative for electrical arrhythmogenic diseases

ECG sign	Suspected disease
Corrected QT interval >0.46 s	Long QT syndrome
Corrected QT interval <0.32 s	Short QT syndrome
Coved-type/saddle-type ST segment elevation in the right precordial chest ECG leads (V1–V3) in the absence of myocardial infarction, either spontaneous or provoked by flecainide or ajmaline	Brugada syndrome
Delta wave, ventricular pre-excitation	Wolff-Parkinson-White syndrome
Abnormal left ventricular hypertrophy, especially in septal precordial leads	Familial hypertrophic cardiomyopathy

With the exception of Wolff-Parkinson-White syndrome, these diseases are classical inherited diseases.

aggressive treatments, including continuous rapid atrial pacing or defibrillator implantation, usually for secondary prevention. In the future, gene-specific treatment options for long QT syndromes may become available.[8]

Short QT syndrome

The short QT syndrome is a very rare familial syndrome characterised by a short QT interval (corrected QT interval < 0.3 s), frequent palpitations and "lone" atrial fibrillation, syncope and sudden death, short atrial and ventricular refractory periods, and inducible VF.[9] The entity has only recently been identified. Although defibrillator implantation may expose patients at relatively high risk to inadequate shock therapies, implantation of a defibrillator is the only suggested antiarrhythmic treatment for these patients at present.

Wolff-Parkinson-White syndrome

Wolff-Parkinson-White syndrome is caused by an additional, usually atrioventricular, electrically conducting connection between the atria and the ventricles. The ECG sign is ventricular pre-excitation, identified by a delta wave and a shortened PQ interval. SCD occurs in a subset of Wolff-Parkinson-White patients, and is believed to be caused by rapid conduction of atrial fibrillation to the ventricles and subsequent induction of VF. SCD may be cured by catheter ablation of the accessory pathway,[10] although some patients may remain at risk of SCD after ablation of the pathway.[w12]

Brugada syndrome

Brugada syndrome is characterised by a right bundle branch block pattern with coved or saddle-type ST segment elevation in the right precordial ECG leads (V1–V3) and a predisposition to ventricular arrhythmias and sudden death.[11] The ECG pattern is at times only visible after administration of slowly dissociating sodium channel blockers (usually flecainide or ajmaline).[11] A history of syncope and a suspicious ECG should trigger a drug test. Genetic testing can confirm the diagnosis in the 10–20% of affected patients who suffer from mutations in the *SCN5A* gene that encodes for the cardiac sodium channel. Defibrillator implantation is the only established effective treatment to prevent SCD in Brugada syndrome, but identification of the patient groups at highest risk for SCD remains controversial.[11 w13]

Identification of arrhythmogenic diseases by echocardiography

Valvular heart disease

Aortic stenosis, especially when associated with left ventricular hypertrophy, and mitral valve prolapse are clinical entities that are associated with SCD, although the risk is not high enough to justify specific antiarrhythmic treatment. Again, the individual history—and at times family history—of SCD should alert the cardiologist to a potential risk for SCD in patients with these conditions. It has been suggested that a long QT interval is an indicator for SCD in patients with aortic stenosis or mitral valve prolapse, although systematic data are not available.

Familial hypertrophic cardiomyopathy

Familial hypertrophic cardiomyopathy (FHC) is a genetically determined disease that is characterised by varying degrees of asymmetric left ventricular hypertrophy and sudden death caused by polymorphic ventricular tachycardia (VT) or VF. Asymmetric left ventricular hypertrophy or hypertrophy that cannot be adequately explained by the degree of hypertension should alert the cardiologist to this disease, especially when a history or family history of palpitations or sudden death is concomitant. The gene defects (at least eight) are found in the contractile apparatus.[12] β blockers and possibly amiodarone can probably reduce SCD in FHC patients.

Aetiology of sudden cardiac death (SCD)

- SCD is common and caused by ventricular tachyarrhythmias in the majority of patients. The first clinical event is often lethal
- There are currently four major identifiable aetiologies of SCD:
  - ventricular fibrillation in the setting of acute cardiac ischaemia
  - ventricular arrhythmias in patients with heart failure or valvular heart disease
  - ventricular arrhythmias in patients with inherited arrhythmogenic disease
  - drug-induced proarrhythmia ("iatrogenic" SCD)

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) usually manifests as ventricular tachycardia with an origin from the right ventricle (that is, with a left bundle branch block pattern on the ECG). Genetically, it is a disease of the desmosome.[w14] The diagnosis is based on the identification of right ventricular enlargement and dysfunction and of ventricular tachycardias with right ventricular origin. Sotalol and, possibly to a lesser extent, amiodarone have been effective in preventing VT in ARVC patients.[13] Patients who survived VT/VF are candidates for defibrillator therapy, but complication rates after implantation are higher than in general implantable cardioverter-defibrillator patient cohorts, mostly due to electrode sensing problems in the diseased right ventricle.[w15] A combination of drug treatment and catheter ablation can also be effective.[w16]

Fabry disease

Fabry disease is caused by an inherited lack of α-galactosidase and results in renal, facial, and myocardial amyloid deposits.[w17] The combination of renal dysfunction, red papulae on the face, and left ventricular hypertrophy with a salt-and-pepper pattern on echocardiography should trigger the clinical suspicion of Fabry disease.[w17] The renal phenotype is often life limiting, but sudden death has been reported. Sudden death can be due to either bradycardia caused by progressive conduction block, sinus nodal dysfunction, or ventricular arrhythmia due to the formation of anatomical re-entrant circuits.[w18] Unlike other inherited arrhythmogenic diseases, there is a specific drug treatment for Fabry disease—that is, substitution of α-galactosidase.[w17] This treatment is possibly a specific antiarrhythmic treatment option in Fabry disease patients.

DO NO HARM! PREVENTION OF DRUG-INDUCED PROARRHYTHMIA (TORSADES DE POINTES)

Fatal ventricular arrhythmias, usually in the form of torsades de pointes tachycardias, are a rare but potentially fatal side effect of a wide variety of cardiac and non-cardiac drugs (fig 3).[14] As some of these drugs are frequently prescribed, proarrhythmia contributes to sudden death.[15] Torsades de

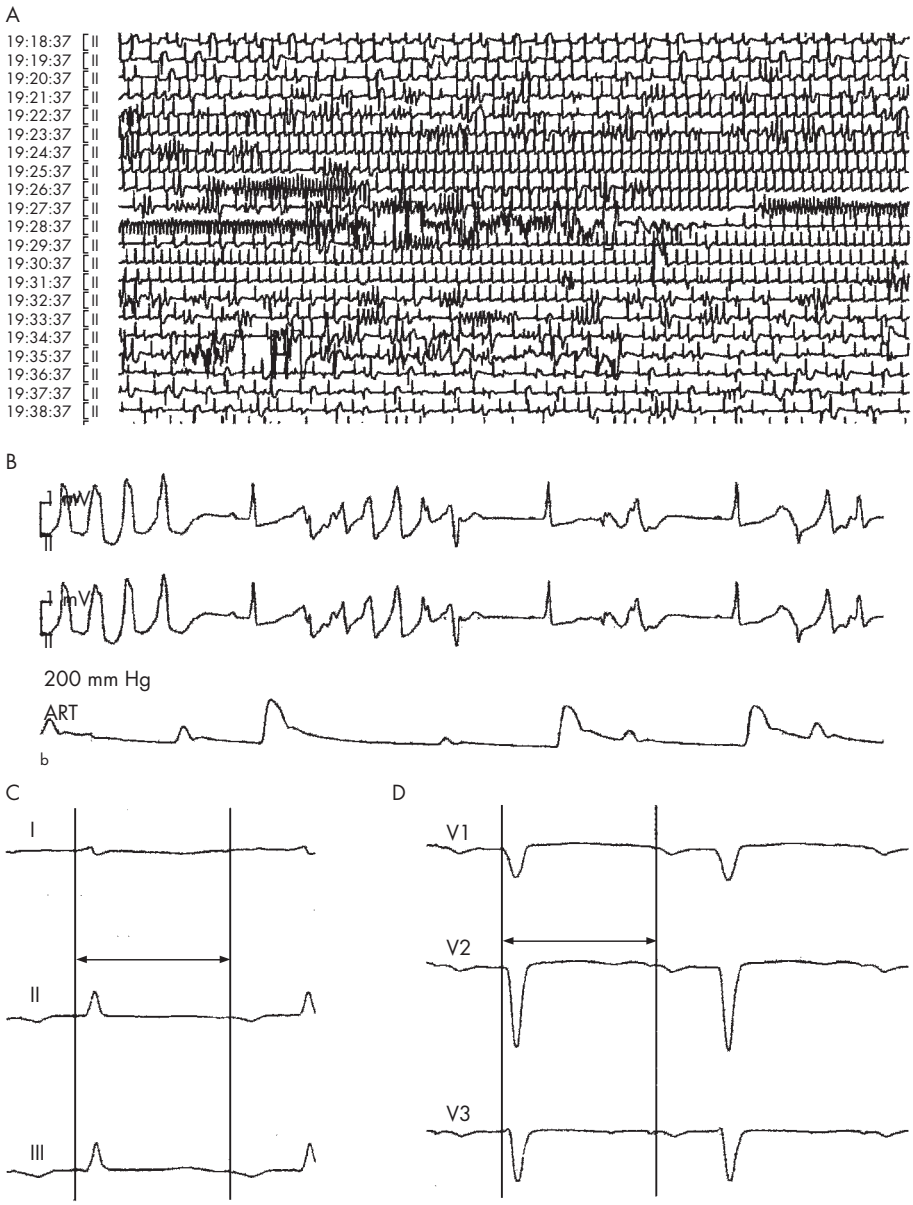

Figure 3 Ventricular tachycardias provoked by ciprofloxacin. A 71-year-old female patient with left ventricular hypertrophy was admitted to an intensive care unit with bilateral pneumonia that required mechanical ventilation. Antibiotic treatment included ciprofloxacin. She developed torsades de pointes which were recorded in a Holter ECG and were successfully defibrillated (A, B). At that time, the QT interval was notably prolonged (C). After stopping ciprofloxacin treatment, the QT interval returned to normal duration (D). Arrows indicate QT intervals.

pointes are believed to be triggered by afterdepolarisations and maintained in a functional substrate for re-entry formed by increased dispersion of refractoriness and repolarisation. Altered intracellular calcium handling appears to be relevant for afterdepolarisations, while altered function of the physiological repolarising currents is paramount for the formation of the substrate for functional re-entry.

Drug-induced proarrhythmia is an unresolved problem for physicians, pharmaceutical companies and regulatory bodies.[14] Drug-induced prolongation of the QT interval is a sign of potential pro-arrhythmic effects, but it is neither specific nor sensitive. Clinical data suggest that only a special group of patients are at risk for these arrhythmias,[w19 w20] and the majority of patients will never suffer from them. Susceptible patients appear to have a ''reduced repolarisation reserve''—that is, an abnormal prolongation of the action potential upon treatment with action potential-prolonging drugs.[w21] Subclinical forms of long QT syndromes[w20] or other genetically determined arrhythmogenic diseases are likely to contribute to drug-induced proarrhythmia. The list of drugs that convey such a risk is continuously expanding and includes antibiotics,[15] antipsychotic drugs, and antihistaminic compounds[14] (see also www.torsades.org). Knowledge of the clinical characteristics that identify patients at increased risk for drug-induced torsades de pointes (a combination of female sex, longer-than-average QT interval, left ventricular hypertrophy, bradycardia, and/or hypokalaemia) and of the drugs known to provoke such arrhythmias can help to prevent the occurrence of drug-induced proarrhythmia. Careful observation of an abnormal QT interval prolongation

How to prevent SCD: current status and perspective

- Prevention of SCD is ineffective at present
- Currently, prevention of SCD can be achieved through four types of interventions:
  - prevention of acute ischaemic events by prevention of coronary artery disease
  - optimal treatment of heart failure and protection of high-risk patients with a defibrillator
  - identification of an inherited risk for arrhythmias in the surface ECG and subsequent treatment of the underlying disease
  - prudent use of drugs with a potential for proarrhythmic side effects.
- Future diagnostic tests and therapeutic interventions will be based on a more comprehensive understanding of the cellular and electrical events that trigger SCD. The diagnostic aim is to identify patients at risk for SCD with sufficient accuracy to warrant implantation of a defibrillator before the first arrhythmic event. Future disease- or gene-specific interventions may, in the future, help to prevent SCD in patients with inherited arrhythmogenic disorders

upon initiation of a treatment with a QT-prolonging drug may allow identification of patients before the first occurrence of torsades de pointes.[14 w19 w21]

Additional references appear on the *Heart* website—http://www.heartjnl.com/supplemental

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Supported by the IZKF Münster

In compliance with EBAC/EACCME guidelines, all authors participating in Education in *Heart* have disclosed potential conflicts of interest that might cause a bias in the article

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