

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Clinical Indications for Therapeutic Cardiac Devices

*Ida Åberg, Gustav Mattsson and Peter Magnusson*

## Abstract

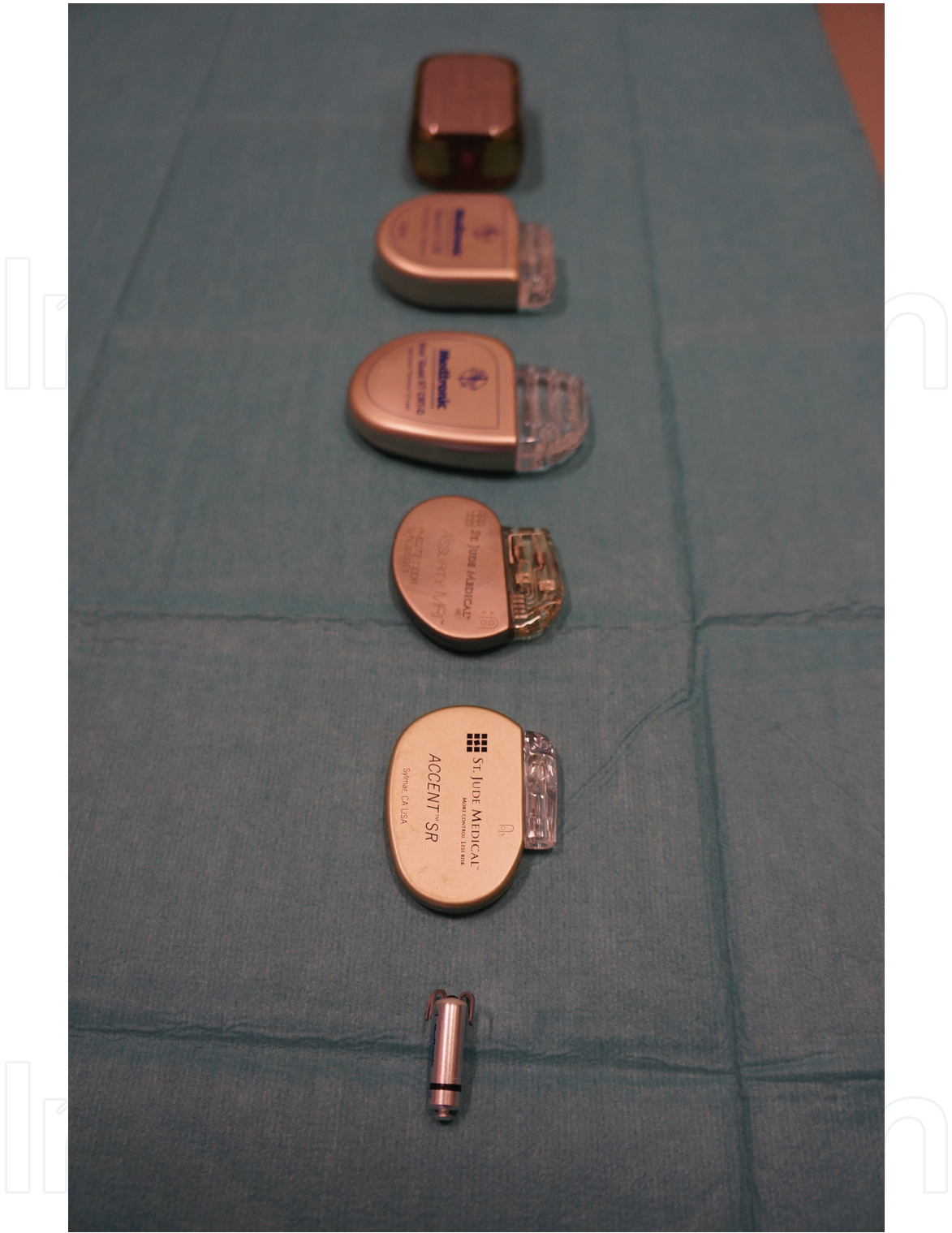
Both technology and clinical indications have changed since the first cardiac devices. Choosing the right therapy, or abstaining from it, is the key to good clinical management. Pacemakers effectively reduce symptoms of bradycardia, prevent syncope in patients with sick sinus syndrome, and reduce mortality in high-degree atrioventricular block. Cardiac resynchronization therapy improves symptoms and survival in heart failure patients with reduced ejection fraction and ventricular dyssynchrony. Implantable cardioverter defibrillators terminate life-threatening ventricular arrhythmias and are indicated for the prevention of sudden cardiac death, either as secondary prevention in survivors of ventricular fibrillation or ventricular tachycardia with hemodynamic compromise or as primary prevention due to heart failure with reduced ejection fraction or other miscellaneous diseases. More recently, leadless pacemakers and subcutaneous implantable cardioverter defibrillators have been developed as alternatives in specific conditions.

**Keywords:** bradycardia, cardiac devices, cardiac resynchronization therapy, heart failure, implantable cardioverter defibrillator, indication, pacemaker, sudden cardiac death

## 1. Introduction

“Those who suffer from frequent and strong faints without any manifest cause die suddenly”, Hippocrates stated more than 2000 years ago [1]. This is likely a description of arrhythmia-related death, which nowadays often is avoidable due to the improvements in diagnostics and treatment the world has seen since antiquity.

The majority of patients receiving a pacemaker today are above the age of 65, owing to increasing problems with impulse generation and conduction with age [2]. With the world population getting older, the prevalence of permanent pacemakers will likely continue to rise [3]. This chapter aims to present a concise description of current guidelines regarding the indications for cardiac devices, including pacemakers, cardiac resynchronization therapy (CRT), and implantable cardioverter defibrillators (ICD) (**Figure 1**).



**Figure 1.**  
*Cardiac devices. From the top: older pacemaker, dual-chamber implantable cardioverter defibrillator, cardiac resynchronization therapy-defibrillator, dual-chamber pacemaker, single-chamber pacemaker, and leadless pacemaker.*

## 2. Pacemaker therapy

The medical properties of electricity have been known for some time. The physicians of ancient Rome treated acute gout with electric sea creatures. Alexander von Humboldt tested the theory of electrical conduction in biological tissue on himself. The first artificial pacemaker, powered by a hand-cranked motor, was invented by Albert Hyman in 1932. The first patient to receive an implantable pacemaker, Arne Larsson, had to wait until 1958, when he underwent the procedure at the Karolinska

University Hospital in Stockholm. He outlived both the surgeon Åke Senning and the engineer Rune Elmqvist who developed the system [1].

## **2.1 Etiology**

The most common etiology of bradycardia leading to pacemaker implantation is conduction tissue fibrosis, but there are several others etiologies responsible for slow heart rates according to data from registers, for example the Swedish pacemaker registry [4]. Some of these are reversible, such as infection/inflammation, metabolic conditions, and medications while others are congenital such as third-degree atrio-ventricular (AV) block associated with maternal systemic lupus erythematosus [5].

## **2.2 Pacing mode**

A code of four to five letters is used to describe the pacing mode. The first letter indicates where pacing occurs (where A stands for atrium, V for ventricle, and D for dual); the second describes which chamber is sensed. In the third position, the letters I (inhibit), T (trigger), or D (dual) are used to describe in which way the device responds to sensed events. An R in the fourth position means that rate response (increased pacing rate during physical exertion) is active. Finally, a fifth letter is occasionally used to describe where multicenter pacing is employed (A, V, or D) [6].

## **2.3 Rate response**

The purpose of rate response is to increase the heart rate in response to altered demand, and there are different solutions available to achieve this. Activity sensors are widely used; one example is the accelerometer that identifies postural changes and movement. Minute ventilation sensors can change the heart rate according to variations of respiratory rate and tidal volume [7].

## **2.4 Pacemaker syndrome**

The pacemaker syndrome is a condition brought on by the loss of AV synchrony caused by ventricular pacing. There are no specific diagnostic criteria, but symptoms include orthopnea, dyspnea upon exertion, orthostatic hypotension, and syncope. The mode selection trial (MOST), a prospective study of patients with sick sinus syndrome (SSS) randomized to VVIR or DDDR pacing, concluded that the incidence of pacemaker syndrome was 19.7% at 4 years after implantation. The incidence of pacemaker syndrome varies between less than 2 and 83% in multiple studies [8].

## **2.5 Mode switch**

This is crucial in patients with paroxysmal atrial tachyarrhythmias. The cut-off for mode-switch is based on sensing of electrical activity of an atrial lead and is programmable, typically 180 beats per minute. Atrial flutter activity is sometimes hidden in the so-called post-ventricular blanking period and often requires reprogramming. Furthermore, nonphysiological electrical activity may lead to oversensing which results in mode-switch.

## **2.6 Indications for permanent pacing**

In bradycardia caused by reversible etiologies, permanent pacing is not warranted, and temporary pacing should instead be considered. Generally, once



reversible causes for bradycardia are excluded, the indication for pacing is based on the severity of bradycardia rather than its etiology [9]. It should be noted though that symptomatic sinus bradycardia as a result of medical therapy is an indication for permanent pacing if there are no alternative treatment options [10].

### 2.6.1 Sinus node dysfunction

Persistent sinus bradycardia, chronotropic incompetence, and sinus arrest can all be seen in sinus node disease (SND), a condition that primarily affects the elderly [10]. When diagnosing chronotropic incompetence (the inability to increase the heart rate as a response to activity or other demands), the fact that heart rate is affected by aging, medication, and physical conditioning must be taken into account. Exercise testing is the basis for diagnosis [11]. It is important to separate physiological bradycardia from inappropriate bradycardia, since sinus bradycardia in trained athletes is normal and not an indication for pacemaker therapy [10].

#### 2.6.1.1 Persistent bradycardia

In patients with SND, pacing has not been proven to prolong survival and is therefore used to relieve symptoms. Symptoms of bradycardia include impaired tolerance to exercise, symptoms of heart failure (HF), syncope, and more subtle symptoms like dizziness and forgetfulness. Untreated patients with SSS, however, are commonly affected by systemic thromboembolism [9]. A significant reduction in stroke and atrial fibrillation (AF) among these patients has been seen with AAI or DDD compared with VVI. The DANPACE trial shows that the incidence of paroxysmal AF is higher with AAIR pacing than DDDR, and there is a two-fold increase in the risk of re-operation [12]. In the Canadian Trial of Physiologic Pacing (CTOPP) where physiologic pacing (dual-chamber or atrial) was compared to ventricular pacing in patients with symptomatic bradycardia, a reduction in the risk of AF was seen for patients who received dual-chamber pacing. No significant reduction in the risk of stroke, death, or hospitalization for HF in the first 3 years after implantation was seen with dual-chamber pacing, but the risk of perioperative complications was significantly higher in this group [13]. The MOST trial compared ventricular- to dual-chamber pacing in patients with SSS, and no reduction in stroke with dual-chamber pacing was observed. However, a reduction of AF, signs and symptoms of HF, and a slight improvement in quality of life was seen [14]. Between 0.6 and 1.9% of all patients with SND develop AV block every year, which can of course be a problem when AAIR is used [9]. Rate response should be considered (class IIa recommendation) in people with SND and chronotropic incompetence according to the guidelines of the European Society of Cardiology (ESC). The indication is strengthened in those who are young and physically active. There is evidence for improvement in quality of life and exercise capacity with VVIR compared to VVI. When it comes to comparing DDD with DDDR there have been inconsistent results [9]. In extrinsic (functional, induced by for example drugs or high vagal tone) bradycardia, the prognosis is benign, and pacing is only indicated to prevent recurrent syncope [9].

#### 2.6.1.2 Intermittent bradycardia

Documented symptomatic bradycardia due to sinoatrial block or sinus arrest in patients with intrinsic SND (including the brady-tachy form) is a class I recommendation for pacemaker therapy by the ESC [9]. When there is no documented correlation between symptoms and electrocardiography (ECG), people with intrinsic sinus node dysfunction may still be candidates for cardiac pacing if they have

experienced syncope and there are documented asymptomatic ventricular pauses of more than 3 seconds. This does not apply to young, well-trained, or medicated persons and during sleep. Alternative explanations such as hypotension should be ruled out before deciding on pacemaker therapy [9]. The recommendations regarding pacing mode for permanent bradycardia apply for intermittent bradycardia as well, based on the fact that there are not enough studies including only patients with intermittent bradycardia. Dual-chamber pacing is preferred to reduce the risk of pacemaker syndrome [9].

### *2.6.2 Atrioventricular block*

#### *2.6.2.1 Persistent bradycardia*

Pacing improves survival in people with AV block (third-degree and second-degree type 2), as well as prevents recurrence of syncope. There are no randomized controlled trials (RCTs), but observational studies from the beginning of the pacemaker era suggest this. One study describes a one-year mortality of about 50% in patients with complete AV block [15]. Therefore, pacemaker therapy is recommended by the ESC in these patients, even if they are asymptomatic [9]. Permanent pacing is controversial in second-degree type 1 AV block; although not if it is symptomatic or the conduction delay is situated at intra- or infra-His levels, in these cases pacing should be considered (class of recommendation IIa). If the QRS complex is wide, development of complete AV block is more likely [9].

Studies have shown that above one quarter of people with VVI develop pacemaker syndrome. Dual-chamber pacing reduces the risk of these symptoms. Since they require an additional lead and have longer implantation times and a higher risk of complications, dual-chamber devices are more expensive. When the risk of AF and pacemaker syndrome is taken into account, the cost difference is small over a five-year period. Since there is no reduction in morbidity or mortality with dual-chamber pacing compared to ventricular pacing, the choice should be made on an individual basis where increased risk of complications and cost is considered [9]. The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial compared dual-chamber pacing to ventricular pacing in elderly patients with high grade AV block and found that pacing mode does not affect survival, and in contrast with the CTOPP trial, no reduction in AF in dual-chamber compared to ventricular pacing was seen. Fixed-rate single-chamber pacing was associated with an increased risk of stroke, transient ischemic attack, and thromboembolism compared with dual-chamber pacing, but there was no difference between the rate-adaptive single-chamber and dual-chamber groups [16].

In permanent AF and AV block, the ESC recommendation (class I recommendation) is ventricular pacing with rate response [9].

#### *2.6.2.2 Intermittent bradycardia*

Correlations between symptoms and ECG are not as important in intrinsic third- or second-degree AV block as it is in SSS. The ESC states that cardiac pacing is indicated in people suffering from intrinsic intermittent AV block, regardless of documentation of correlation between symptoms and ECG findings [9].

#### *2.6.3 Suspected (undocumented) bradycardia*

In patients with syncope, the presence of bundle branch block (BBB) suggests that the cause may be complete heart block. In spite of this, less than half of patients with

BBB and syncope are diagnosed with cardiac syncope. According to the ISSUE 1 study and the Bradycardia detection in Bundle Branch Block (B4) study [17] (that included patients with normal or preserved systolic function), it is safe to wait until the correct diagnosis is made before starting cardiac pacing [9]. ICD or CRT-D should be considered in patients with syncope who have BBB and HF, previous myocardial infarction, or ejection fraction (EF)  $\leq 35\%$ . This is because a high incidence of total and sudden cardiac death (SCD) has been observed in patients with BBB, and mostly those with HF, previous myocardial infarction, or low EF [9]. In patients with BBB who have experienced syncope but have normal EF, an electrophysiological study should be considered. If this study is abnormal, pacing is a class I recommendation in the ESC guidelines [9]. If the electrophysiological study is normal, an insertable cardiac monitor should be considered since EPS cannot rule out intermittent or paroxysmal AV block [9].

Cardiac pacing is generally indicated in alternating BBB (block involving all three fascicles on successive ECGs) since it is known to progress toward AV block fast, even if there is no history of syncope [9]. Asymptomatic BBB is not an indication for pacemaker therapy. In some cases though, patients with unexplained syncope and BBB are candidates for pacemaker therapy, especially old people with unpredictable syncope [9].

#### 2.6.4 Carotid sinus syncope

Carotid sinus syncope is defined as a drop in blood pressure of 50 mmHg or asystole of more than 3 s as a result of carotid sinus massage [9]. Dual-chamber pacing is indicated when asystole of 6 s and syncope follows carotid sinus massage (to be performed for a full 10 s, supine and erect), and the patient has recurrent and unpredictable syncope [9].

#### 2.6.5 Tilt-induced vasovagal syncope

Tilt-induced vasovagal syncope often affects young people and is in itself a benign condition. When deciding whether to implant a pacemaker, this must be taken into consideration [9]. Pacing may be considered (class IIb recommendation according to ESC) in these patients if they suffer from recurrent and unpredictable episodes, are older than 40 years, and have a documented cardio-inhibitory reflex, but only after other therapies have failed [9]. As with carotid sinus syncope, dual-chamber pacing is recommended [9].

### 2.7 Indications for pacing in specific conditions

#### 2.7.1 Pacing in acute myocardial infarction

Primary angioplasty and thrombolytic therapy have led to a decrease in AV block associated with acute myocardial infarction, but it still occurs and when it does, mortality is high [10]. When advanced second- or third-degree AV block is seen with left bundle branch block (LBBB) or when right bundle branch block occurs with left anterior or posterior fascicular block, the prognosis is particularly bad [10]. Intraventricular conduction delays develop as a result of extensive damage to the myocardium, meaning greater injury to the heart than an isolated electrical problem [10]. If the AV block is expected to be temporary, permanent pacemaker therapy should be avoided [10]. AV block associated with acute myocardial infarction resolves spontaneously in 2–7 days in most cases [9]. Permanent AV pacing is recommended by the American Heart Association (AHA) in persistent and

symptomatic second- or third-degree AV block following acute myocardial infarction. Persistent second-degree AV block in the His-Purkinje system associated with alternating bundle branch block also constitutes an indication for permanent ventricular pacing, as well as third-degree AV block within or below the His-Purkinje system following ST elevation myocardial infarction. In the case of associated bundle branch block, permanent ventricular pacing is indicated in transient advanced second-degree and third-degree infra-nodal AV block according to AHA, whereas ESC states that there is no evidence that pacing improves outcomes in these patients [9, 10]. Permanent AV pacing may be considered in the case of persistent second-degree or third-degree AV block at the AV node level, even if there are no symptoms, according to the AHA [10]. According to the ESC, the recommendations for pacemaker therapy in permanent AV block following acute myocardial infarction are the same as those for AV block of other etiologies [9].

#### *2.7.2 Pacing after cardiac surgery, transcatheter aortic valve implantation, and heart transplantation*

Both AV block and SND may appear as complications after cardiac interventions, and if they persist, permanent pacing must be considered. An observation time of up to 7 days is recommended before implanting a permanent pacemaker in high degree or complete AV block following cardiac surgery or transcatheter aortic valve implantation. A shorter observation time can be used in case of complete AV block with a low escape rhythm, where resolution is not likely. SND as a result of cardiac surgery or heart transplantation should be observed from 5 days up to some weeks before deciding on pacemaker therapy [9].

#### *2.7.3 Pacing in children and in congenital heart disease*

When implanting a pacemaker in a young person, several considerations have to be made. For one, they will have the pacemaker for a whole lifetime, increasing the risk of experiencing complications sometime during this period. They usually have higher activity levels than adults, and because of this and the fact that they grow the risk of stress on the device and electrode dislodgement is increased. The presence of right to left-shunt is a contraindication for endocardial leads; hence, epicardial pacing is used instead in this congenital defect. Small body size and the absence of transvenous access are other reasons why epicardial pacing is often preferred in children. Second-degree type 2 and third-degree AV block are indications (class I according to ESC) for pacemaker therapy in children who are symptomatic or if any of the following risk factors are present: ventricular dysfunction, prolonged QTc interval, complex ventricular ectopy, wide QRS complex escape rhythm, slow ventricular rate (<50 beats per minute, ventricular pauses more than three times the cycle length of the underlying rhythm) with or without symptoms. For children without any risk factors, the ESC states that pacing may be considered in high-degree and complete AV block, adding that opinions regarding the benefit of pacing differ. Pacemaker therapy is indicated for children with SND if they are symptomatic and there is a clear correlation between symptoms and bradycardia. The decision to implant a pacemaker in a child should be made after discussion with pediatric cardiologists, and it is recommended that it is done in a specialized center [9].

#### *2.7.4 Pacing in hypertrophic cardiomyopathy*

Patients who have symptoms because of left ventricular outflow tract obstruction can be treated medically, surgically, with septal alcohol ablation, and



sequential AV pacing [9]. Sequential AV pacing is an alternative when myectomy or septal alcohol ablation are contraindicated or when the risk of AV block after these procedures is considered high [9].

### *2.7.5 Pacing in pregnancy*

Complete heart block with a slow escape rhythm with wide QRS complexes should be treated with pacemaker implantation during pregnancy, using echoguidance or electro-anatomic navigation to avoid fluoroscopy. The procedure is safe, especially when the fetus is beyond 8 weeks of gestation. In case of stable, junctional escape rhythm with narrow complexes, pacemaker implantation can be delayed until after delivery [9].

### *2.7.6 Leadless pacemakers*

Malfunction of the electrodes is the most common cause of surgical pacemaker revision. Pocket hematoma and erosion are other complications associated with pacemaker implantation [18]. There are currently two self-contained leadless pacemaker systems available: Nanostim™ and Micra™. Nanostim™ has been evaluated in the prospective nonrandomized study LEADLESS, and the complication-free rate compares favorably with traditional pacemaker systems [18]. As for Micra™, the risk of major complications in the first 12 months after implantation was 48% lower compared to historical control patients with transvenous systems [19]. Currently, solely the VVI-mode is available via leadless pacemaker systems. Considering this, the higher cost and the fact that there is not much experience outside clinical trials with these systems yet, use of leadless pacemakers should for now be reserved for when VVI-mode is indicated and transvenous leads are unfeasible or undesirable.

## **2.8 Emergency temporary pacing**

Bradycardia can be a life-threatening condition where immediate action is crucial. When the hemodynamics is affected resulting in symptoms of acute HF, ischemic chest pain, or signs of shock, the first step is to administer atropine intravenously. If atropine is not effective or appropriate, a continuous infusion with beta-adrenergic agonists such as isoproterenol, dopamine, or epinephrine is sometimes needed to uphold an adequate pulse until pacemaker therapy can be initiated. Another alternative is transcutaneous pacing, which can be used while waiting for implantation of a temporary transvenous- or permanent pacemaker [20]. The pads are preferably attached with anterior-posterior placement and are then connected to the defibrillator/monitor [21]. Transcutaneous pacing can be performed on a conscious patient, but sedation is preferred [21, 22]. During transcutaneous pacing, the patient must be monitored closely with ECG and with regard to hemodynamic stability [9]. Seeing that there are a number of risks associated with temporary transvenous pacing (for example, accidental extraction of the pacemaker lead by the patient, risk of infection, and thromboembolic events), the ESC recommends avoiding this treatment if possible, and otherwise keeping the treatment time as brief as possible [9].

## **3. The implantable cardioverter defibrillator**

The first patient to receive an ICD was a woman who had survived repeated episodes of ventricular fibrillation (VF) and continued to experience arrhythmias

refractory to medical therapy [23]. This was at The Johns Hopkins Hospital in the US in 1980, after extensive work by Michel Mirowski and his colleagues. After the death of his mentor, who suffered from recurrent ventricular tachyarrhythmias, Mirowski's goal was to create a device that could monitor the heart rhythm and administer a defibrillating shock to treat life-threatening tachyarrhythmias [24]. Today the ICD is the treatment of choice for both primary and secondary prevention of SCD due to VT/VF [25].

### **3.1 Etiology**

Every year, cardiovascular diseases cause around 17 million deaths worldwide, of which SCD makes up approximately 25% [25]. The vast majority of these deaths are due to ventricular tachyarrhythmias. According to epidemiological data, 80% of the fatal arrhythmias occur as a consequence of structural coronary artery abnormalities. Dilated- and hypertrophic cardiomyopathies are the second most common reasons for SCD [26]. Among the young, channelopathies, cardiomyopathies, myocarditis, and drug-induced arrhythmias are more common, while coronary artery disease, valvular heart diseases, and HF predominate in older individuals [25].

### **3.2 Cardioversion and antitachycardia pacing**

Cardioversion implies that shock delivery is synchronized with the QRS complex to avoid inducing VF by delivering a shock during the refractory period of the cardiac cycle, and it is recommended for the treatment of several supraventricular arrhythmias and monomorphic ventricular tachycardia (VT) with pulses. It should not be used to treat VF or pulseless or polymorphic VT, since these arrhythmias require unsynchronized high-energy doses, also known as defibrillation [27]. Antitachycardia pacing is an alternative way to terminate monomorphic ventricular arrhythmias; it can reduce the number of shocks and is generally tolerated well since it is rarely noticed by the patient. The mechanism is that a short sequence of pacemaker pulses (typically 8–12), with a rate slightly faster than the detected tachycardia, is delivered as a response to ventricular arrhythmia. The success rate varies but has in some cohorts been shown to exceed 90% [28].

### **3.3 Indications for ICD**

In patients with high risk of SCD, ICD therapy prevents SCD and prolongs life (given that life expectancy is not for other reasons less than 1–2 years) [25]. Both patients who have experienced previous ventricular arrhythmias and those who are at increased risk of future arrhythmia can be protected by ICD therapy.

#### *3.3.1 Secondary prevention*

In patients who have survived an episode of documented VF or VT that is not hemodynamically tolerated, ICD is a class I recommendation according to the ESC, provided that there are no reversible causes and that the expected survival with good functional status is at least 1 year [25]. Recurrent sustained VT (not including the first 48 hours after myocardial infarction) in patients who are treated with optimal medical therapy and have a normal left ventricular EF (LVEF) should be considered for ICD therapy (class IIa recommendation). Survival must be expected for at least a year with good functional status [25]. Three trials have studied the effect of ICD compared to medical treatment as secondary prevention in patients who have survived VF or sustained VT: the antiarrhythmics vs.

implantable defibrillator (AVID) study (patients with VT had syncope or serious cardiac symptoms and an LVEF of 40% or less) [29], the Cardiac Arrest Study Hamburg (CASH) (patients were survivors of cardiac arrest secondary to documented ventricular arrhythmias) [30], and the Canadian Implantable Defibrillator Study (CIDS) (patients with VT had syncope or cardiac symptoms and an LVEF of 35% or less; patients with unmonitored syncope and subsequent documentation of VT were also included) [31]. The AVID study showed an increase in overall survival in the ICD group. In the CASH study, the reduction in all-cause mortality in the ICD group did not reach statistical significance but there was a 61% reduction in SCD. The reduction in all-cause mortality and SCD seen in the ICD group in the CIDS study was not statistically significant. A meta-analysis of these three trials concluded that there is a 28% reduction in total mortality with ICD therapy compared to amiodarone, mainly due to a 50% reduction in arrhythmic mortality [32]. In the following sections, current guidelines regarding secondary prevention in specific circumstances are addressed.

### *3.3.1.1 Acute coronary syndromes*

Approximately 6% of patients with acute coronary syndrome experience VT/VF within 48 hours after the first symptoms, the majority during or before reperfusion therapy [25, 33]. As stated above, ICD is recommended after an episode of VF or hemodynamically compromising VT, unless the episode occurred within 48 hours of myocardial infarction, in a patient who receives optimal medical treatment [25].

### *3.3.1.2 Cardiomyopathies*

In patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular noncompaction cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy, ICD therapy is indicated after a survived episode of cardiac arrest due to VT/VF, or in patients who have experienced syncope or hemodynamic compromise because of spontaneous sustained VT—in accordance with the guidelines in general [25]. When it comes to arrhythmogenic right ventricular cardiomyopathy, the ESC suggests that ICD should be considered (class IIa) in patients who have experienced hemodynamically well tolerated sustained VT as well. For patients with light-chain amyloidosis or hereditary transthyretin-associated amyloidosis who have had a sustained VT with hemodynamic impact, and have a life expectancy of more than a year with good functional status, ICD should be considered. This recommendation is upgraded to a class I (is recommended) regarding restrictive cardiomyopathy [25].

### *3.3.1.3 Hereditary primary arrhythmia syndromes*

ICD therapy and beta-blockers are recommended for patients with long QT syndrome and previous cardiac arrest and should be considered in these patients if they have experienced syncope or VT while on an adequate dose of beta-blockers [25]. In catecholaminergic polymorphic VT, ICD as an addition to beta-blockers is recommended after a survived cardiac arrest, recurrent syncope, or polymorphic/bidirectional VT during treatment with optimal medical therapy [25]. In short QT syndrome and Brugada syndrome, ICD is recommended for patients who have survived a cardiac arrest or those who have experienced documented spontaneous sustained VT [25]. In Brugada syndrome, an ICD may be indicated in primary prevention, especially when syncope is likely due to an arrhythmic event [34].

### 3.3.2 Primary prevention

#### 3.3.2.1 Heart failure

In the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial a decrease in the overall mortality of 23% was seen in patients with both ischemic and nonischemic HF in New York Heart Association (NYHA) functional class II and III and an LVEF of 35% or less who received an ICD [35]. An LVEF of 35% or less and symptomatic HF (NYHA II-III) after 3 months of optimal medication is a class I indication for ICD therapy according to the ESC (provided that the expected survival with good functional status is at least 1 year) [25]. More recently, the DANISH trial randomized patients with symptomatic HF (LVEF of 35% or less) of nonischemic origin to ICD therapy or usual clinical care, and found no overall survival benefit with ICD therapy, although the risk of SCD was halved [36]. However, all-cause mortality was significantly reduced by ICD in patients younger than 59 years old. There is currently no indication for ICD therapy in patients with HF in NYHA class IV, unless they are listed for heart transplantation since their risk of SCD is generally high and the wait is often a year or more [25].

#### 3.3.2.2 Acute coronary syndromes

In 1996, results from the MADIT trial were published, showing that in patients with a prior myocardial infarction, NYHA class I-III, LVEF of less than 35%, a documented asymptomatic nonsustained VT, and nonsuppressible VT on an electrophysiological study, prophylactic ICD therapy leads to improved survival [37]. The MADIT-II trial enrolled patients with reduced left ventricular function (LVEF 30% or less) after myocardial infarction and found that the patients who received ICD therapy had a 31% decrease in all-cause mortality [38]. LVEF should be assessed before discharge from the hospital in all patients with acute coronary syndrome, and re-assessed 6–12 weeks later, to evaluate whether or not primary prevention ICD implantation is indicated. As in nonischemic etiology with LVEF of 35% or lower, symptomatic HF (NYHA class II-III), expected survival with good functional status for at least 1 year, and optimal medical therapy for at least 3 months, ICD therapy is recommended (class I recommendation) by the ESC. At least 6 weeks must have passed since the myocardial infarction before deciding on ICD therapy [25]. The use of an ICD as prophylaxis in patients with a recent myocardial infarction (6–40 days previously) does not reduce the overall mortality; a reduction in SCD was offset by an increase in nonarrhythmic death [39]. Hence, ICD implantation within 40 days of acute myocardial infarction as primary prevention of SCD is generally not indicated but it may be considered in specific cases: preexisting impairment in LVEF, incomplete revascularization, and arrhythmia that occurs more than 48 hours after acute myocardial infarction [25].

#### 3.3.2.3 Cardiomyopathies

The DEFINITE trial studied patients with nonischemic dilated cardiomyopathy with an EF of less than 36% and premature ventricular complexes or nonsustained VT, and found that ICD implantation significantly reduced the risk of SCD [40]. The same indications for ICD therapy regarding patients with symptomatic heart failure apply to patients with dilated cardiomyopathy and left ventricular noncompaction cardiomyopathy. In addition to this, ICD should be considered in patients with dilated cardiomyopathy who have a verified disease-causing LMNA mutation (frequently seen in patients with conduction diseases) and clinical risk factors [25].



Regarding primary prevention in HCM, a calculator that estimates the 5-year risk of SCD (HCM Risk-SCD) is recommended by the ESC to evaluate the need for ICD therapy in patients aged 16 or older. Based on the risk score, the class of recommendation regarding ICD therapy varies [25]. When it comes to primary prophylactic ICD in patients with arrhythmogenic right ventricular cardiomyopathy, the ESC suggests that ICD should be considered in patients who have experienced unexplained syncope. ICD may be considered in patients with arrhythmogenic right ventricular cardiomyopathy who have at least one risk factor for ventricular arrhythmias, including family history of premature SCD and extensive right ventricular disease. The risks of ICD therapy should be taken into account when considering it as primary prophylactic therapy [25]. Finally, ICD therapy should be considered in patients with Chagas disease (a cardiomyopathy caused by the parasite *Trypanosoma cruzi*) who have an EF of less than 40% [25].

#### 3.3.2.4 Hereditary primary arrhythmia syndromes

In patients with long QT syndrome, ICD may be considered (as a complement to beta-blockers) in patients who are asymptomatic carriers of a pathogenic *KCNH2*- or *SCN5A*-mutation (high-risk genetic profiles) and have a QTc of more than 500 ms [25]. An ICD may be considered as primary prevention in short QT syndrome, if there is a family history of SCD and evidence of shortened QT in some of these patients. The available data is too scarce for any specific recommendations to be made regarding this. As for Brugada syndrome, primary prevention with an ICD should be considered in patients with a spontaneous type I ECG pattern and suspected arrhythmic syncope in their medical history, and may be considered in patients who develop VF during programmed ventricular stimulation [25].

#### 3.3.2.5 Pediatric patients

A number of different etiologies are responsible for the risk of SCD in children: channelopathies, cardiomyopathies, and congenital heart disease. The same guidelines for when ICD is indicated apply to both adults and children, with the exception of dilated cardiomyopathy and advanced dysfunction of the left ventricle since the incidence of SCD is low in this group [25].

### 3.4 The subcutaneous ICD

This system is placed completely outside the thoracic cavity, eliminating problems with vascular access and transvenous leads. Subcutaneous ICD therapy is not appropriate for patients with bradycardia that requires pacing, for those who have indications for CRT or for those who need antitachycardia pacing. When these patients are excluded, subcutaneous defibrillators should be considered as an alternative to transvenous defibrillators (class IIa recommendation) in patients with an ICD indication [25]. According to the ESC, subcutaneous ICD could be considered (class IIb recommendation) as an alternative to transvenous defibrillators when there are difficulties with venous access, after ICD removal secondary to infection or in young patients who will require long-term ICD therapy [25].

### 3.5 The wearable cardioverter defibrillator

As the name suggests, this defibrillator is entirely external; defibrillator, leads and electrode pads are attached to a wearable vest. It may be considered for adult patients with reduced LVEF who are waiting for a more permanent solution (cardiac

transplantation, transvenous implant) or those who are at a temporary risk of SCD, as in peripartum cardiomyopathy or active myocarditis [25, 41].

### **3.6 Contraindications and considerations**

All through the European guidelines concerning ICD indications, it is emphasized that the expected survival with good functional status should be at least 1 year for ICD to be an option. As mentioned before, symptomatic HF with NYHA class IV is considered a contraindication, unless the patient is waiting for heart transplantation. VT or VF due to reversible causes should not be treated with ICD [25]. Psychiatric illness that might be aggravated due to ICD implantation is sometimes considered a contraindication [42], although it is not mentioned as such in the ESC guidelines. Up to a fifth of terminally ill patients with an ICD experience shocks in the last weeks of life, and deactivation of the ICD should be considered when the patient's condition worsens. This issue should be discussed before implantation and as the illness progresses [25]. A magnet placed over the ICD will deactivate tachyarrhythmia therapies, and this stops inappropriate defibrillations or unnecessary defibrillations at the end of life.

### **3.7 Health-related quality of life**

In its guidelines, the ESC emphasizes the importance of discussing health-related quality of life issues with the patient before ICD implantation and during progression of the disease, by making it a class I recommendation. In addition to this, they recommend that patients who experience inappropriate shocks are assessed psychologically and treated for any distress [25]. Depression and anxiety are common in ICD patients; one systematic review reports anxiety in 8–63% of these patients and depression in 5–41% [43]. Similar effects on quality of life have been seen in patients with ICD and with medical therapy, with impairment in quality of life associated with adverse symptoms in both groups and experience of sporadic shocks in the ICD group [44]. Some patients develop post-traumatic stress disorder, and these symptoms have been associated with nonconstructive support (information that leads to insecurity and fear) from healthcare professionals; further studies are needed [45].

## **4. Cardiac resynchronization therapy**

In around 30% of patients suffering from chronic HF, the conduction pathways are affected, leading to cardiac dyssynchrony [46]. The aim of CRT is to, as the name suggests, improve synchrony in the heart's contraction [9]. Patients eligible for this therapy are those with a wide QRS complex, HF, and impaired left ventricular function [47]. Biventricular pacing was first introduced in the early 1990s by Bakker et al. and Cazeau et al. [48, 49]. CRT with the ability to work as an ICD is termed CRT-D, whereas the term used for a CRT that solely has a pacing function is CRT-P.

### **4.1 Cardiac dyssynchrony**

The dyssynchrony that is targeted with CRT is caused by delays in electrical conduction, and the main way to identify this is by assessing the QRS duration (in particular LBBB) [50]. A prolonged QRS duration has been associated with decreased LVEF [51]. In patients with HF, prolongation of the QRS complex has been shown to be an independent predictor of increased total mortality and SCD. LBBB is related to worse survival but not sudden death [52]. Partially, the mechanism behind

dyssynchrony is prolongation of the AV interval, leading to late systolic contraction which may take the place of early diastolic filling as well as cause mitral regurgitation. Furthermore, conduction delays between and in the ventricles themselves result in asynchronous contraction in the left ventricular walls with subsequent loss of cardiac efficiency [9]. Long-standing cardiac dyssynchrony can result in remodeling of the heart, causing dilation of the left ventricle, deteriorating diastolic and systolic function and worsening of HF [53].

## 4.2 Important trials

Several trials have been conducted in order to optimize indications for CRT. The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial compared optimal medical therapy, CRT-D, and CRT-P, and found that all-cause mortality and hospitalization was reduced in both CRT groups. Reduction in mortality was however only marginally significant with CRT-P, but significant in the CRT-D group [54]. In the CARDiac RESynchronization in Heart Failure (CARE-HF) trial, optimal medical therapy was compared to CRT-P, with the result that CRT-P reduced all-cause mortality and hospitalization as well as improved symptoms and quality of life [55]. Both of these trials enrolled patients in NYHA class III-IV with a QRS duration of 120 ms or more. The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) compared the rate of all-cause mortality and hospitalization due to HF between patients in NYHA class II or III with a QRS duration of at least 120 ms, randomized to either CRT-D or ICD, finding a reduction in the primary outcome in the CRT-D group [56].

In the RESynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, patients with HF in NYHA class I and II were randomized to CRT (with or without defibrillator) or control. The results showed an improvement in the ventricular structure and function in the CRT group and a decrease in hospitalization for HF [57]. MADIT-CRT was designed to evaluate the effect on death and HF events in patients in NYHA class I-II who received a CRT-D compared to an ICD. The risk of HF events was reduced, left ventricular volumes were reduced, and EF improved in the CRT-D group, but no significant difference in all-cause mortality was seen between the groups [58]. When the outcomes in MADIT-CRT were studied in relationship to whether or not the patient had LBBB, CRT-D led to a reduction in HF progression and a reduced risk of ventricular tachyarrhythmias in patients with LBBB while patients with non-LBBB morphology did not benefit clinically [59].

## 4.3 General indications for CRT

### 4.3.1 Patients in sinus rhythm

CRT is recommended by the ESC (class I recommendation) in patients with symptomatic HF in sinus rhythm, with a QRS duration of 130 ms or more, LBBB morphology, and an LVEF of 35% or less despite optimal medical therapy, to reduce symptoms, morbidity, and mortality [60]. CRT should be considered (class IIa recommendation) in patients who meet these criteria but do not have LBBB morphology and have a QRS duration of 150 ms or more and may be considered (class IIb recommendation) in non-LBBB morphology if the QRS duration is between 130 and 149 ms [60]. Patients with HF with reduced EF in any NYHA class who have an indication for bradycardia pacing with a high proportion of right ventricular pacing (high degree AV block, permanent AF) should receive CRT instead of a conventional pacemaker in order to reduce morbidity (class I recommendation) [60]. Lastly, patients with HF with reduced EF who already have a pacemaker or ICD and develop worsening HF



despite optimal medical therapy and have a high rate of ventricular pacing may be considered for upgrade to CRT [60].

Since there have been few patients included in RCTs who are in NYHA class I or IV, the evidence for CRT in these patients is inconclusive. When it comes to NYHA class IV, individual consideration should be made. The recommendations from the ESC include patients in NYHA class IV who are ambulatory (no HF hospitalizations in the last month) [9].

#### *4.3.2 Patients in atrial fibrillation*

Since AF results in irregular and often fast ventricular rates, there is a risk that biventricular pacing delivery does not work adequately in these patients, and most of the patients with AF and an intact AV node require AV junction ablation in order for biventricular pacing to work properly. When considering AV junction ablation before CRT implantation, the risk that pacemaker dependency poses must of course be taken into account [9]. In its 2013 guidelines, the ESC suggests that CRT should be considered in patients with AF who have an EF of 35% or less, are in NYHA class III-IV despite optimal medical therapy, and have a QRS duration of at least 120 ms—provided that bi-ventricular capture of as close to 100% can be achieved. In case bi-ventricular pacing is incomplete, AV junction ablation should be performed [9]. CRT is not an indication for AV junction ablation in any other situation than when it is necessary because of consistently high ventricular rates despite optimal medical therapy [60]. In addition to this, CRT should be considered in patients with reduced EF who are candidates for AV junction ablation because of uncontrolled heart rate; a QRS duration of more than 120 ms is not necessary [9]. In the slightly more recent guidelines from 2016 regarding acute and chronic HF, a QRS duration of 130 ms is the cut off for when CRT is indicated (applies to patients in sinus rhythm as well as in AF) [60].

#### *4.3.3 Patients with indications for bradycardia pacemakers*

Right ventricular pacing might be associated with harmful effects on the cardiac function and structure; therefore, upgrading from a conventional pacemaker to CRT is recommended in patients with optimal medical therapy who have HF in NYHA class III and ambulatory class IV, EF of less than 35%, and a high percentage of right ventricular pacing [9]. It should be noted that upgrade to CRT implies a higher risk of complications compared to primary implantation [9]. In patients who have indications for bradycardia pacing and have not yet received a pacemaker, the ESC guidelines from 2013 recommend that CRT should be considered if they have a history of HF with reduced EF and an expected high rate of ventricular pacing in order to decrease the risk of worsening HF [9]. In its 2016 guidelines regarding acute and chronic HF, the ESC made CRT a class I recommendation (is recommended) in patients with HF with reduced EF regardless of NYHA class, who have an indication for ventricular pacing (patients with AF included) [60].

#### *4.3.4 Patients with indications for ICD*

Several studies, including the aforementioned RAFT and MADIT-CRT, that have compared ICD to CRT-D have found that CRT-D reduces morbidity and mortality. Therefore, when a patient is to receive an ICD, the presence of CRT indications (as mentioned) should be assessed [9]. According to the ESC guidelines, when ICD therapy is indicated in a HF patient who has a QRS complex duration between 130 and 149 ms, CRT-D should be considered. If the QRS duration is 150 ms or more, CRT-D is recommended [60].



#### 4.3.5 The choice between CRT-P and CRT-D

In order to improve prognosis, evidence points toward the use of CRT-D therapy for patients in NYHA class II and CRT-P for patients in NYHA classes III-IV [60]. There is not sufficient evidence based on RCTs for the ESC to make a specific recommendation on when to choose one over the other, but they offer some advice. In addition to patients with advanced HF, the ESC suggests CRT-P in patients with severe renal insufficiency and those who have other major comorbidities, cachexia, or frailty. CRT-D, on the other hand, is more appropriate in patients with a life expectancy of at least a year, stable HF, no comorbidities, and ischemic heart disease [9].

#### 4.4 Contraindications

According to the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study, there is a risk of increased mortality when CRT is used in patients with systolic HF and a QRS duration of less than 130 [61]; QRS of less than 130 ms is therefore considered a contraindication to CRT by the ESC [60].

#### 4.5 Cardiac contractility modulation

Patients who lack indications for CRT but still suffer from symptomatic HF with reduced EF in spite of optimal medical therapy might be candidates for cardiac contractility modulation (CCM). It provides nonexcitatory stimulation of the ventricle in its refractory period in order to improve contractility but not cause extra systolic contractions [60].

### 5. Future perspectives

An interesting area of research is the attempt to build biological pacemakers. Stem cells and viral vectors have been used to introduce ion-channel genes into the heart [62]. These preclinical attempts are promising but much remains until they are ready to be considered a clinical option [63]. Nevertheless, electronic devices have been developed over decades with proven efficacy, and devastating complications are rare.

Leadless pacing provides a landmark in the development of pacemaker technology. However, it is basically limited to pacing from the right ventricle. Because most patients will benefit from AV synchronization and even additional cardiac resynchronization, efforts are made to fulfill this demand. The AV-sequential challenge could potentially be solved by a VDD mode that would rely on atrial sensing from a subcutaneous integrated ECG device. Furthermore, device systems that are able to communicate between them are being developed. The subcutaneous ICD could be combined with a leadless pacemaker, which could provide sensing/pacing in the right ventricle, including anti-tachycardia pacing. The ultrasound-based technology WiCS™ system for endocardial pacing of the left ventricle is another option that is currently being developed [64]. The energy is transmitted from a subcutaneous transmitter subcutaneously to a receiver in the endocardium. Leadless pacing in the right ventricular chamber combined with the left-ventricular endocardial unit and a subcutaneous pulse generator could be a possibility in the near future.

### 6. Conclusions

Pacemaker therapy has revolutionized the treatment of bradycardia, and with an aging population, the use of permanent pacemakers is likely to increase. SCD,

a major cause of death worldwide, can now be prevented with ICD therapy. CRT reduces symptoms and risk of death in patients who have HF with reduced EF and ventricular dyssynchrony. The indications for these therapies continue to evolve as new evidence emerges and novel technologies become available.

### **Conflict of interest**

Peter Magnusson has received lecture fees from Abbott, Bayer, Boehringer-Ingelheim, Boston Scientific, Medtronic, MSD, Orion Pharma, and Pfizer.

### **Author details**

Ida Åberg<sup>1</sup>, Gustav Mattsson<sup>1\*</sup> and Peter Magnusson<sup>1,2</sup>

1 Centre for Research and Development, Uppsala University, Gävle, Sweden

2 Cardiology Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

\*Address all correspondence to: [gustav.mattsson@regiongavleborg.se](mailto:gustav.mattsson@regiongavleborg.se)

### **IntechOpen**

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Aquilina O. A brief history of cardiac pacing. *Images in Paediatric Cardiology*. 2006;**8**(2):17-81
- [2] Gregoratos G. Permanent pacemakers in older persons. *Journal of the American Geriatrics Society*. 1999;**47**(9):1125-1135
- [3] Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG, Hobbs MS. Trend in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. *Open Heart*. 2014;**10**(1):e000177
- [4] Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: Data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. *Europace*. 2015;**17**(1):69-77
- [5] Åberg I, Mattsson G, Magnusson P. Bradycardia: A clinician's guide to slow heart rates. *EC Cardiology*. 2018;**5**(6):316-325
- [6] Mulpuru SK, Madhavan M, McLeod CJ, Cha YM, Friedman PA. Cardiac pacemakers: Function, troubleshooting, and management: Part 1 of a 2-part series. *Journal of the American College of Cardiology*. 2017;**69**(2):189-210
- [7] Dell'Orto S, Valli P, Greco EM. Sensors for rate responsive pacing. *Indian Pacing and Electrophysiology Journal*. 2004;**4**(3):137-145
- [8] Link MS, Hellkamp AS, Estes NA III, Orav EJ, Ellenbogen KA, Greenspon A, et al. High incidence of pacemaker syndrome in patients with sinus node dysfunction treated with ventricular-based pacing in the mode selection trial (MOST). *Journal of the American College of Cardiology*. 2004;**43**(11):2066-2071
- [9] Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: The task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace*. 2013;**15**(8):1070-1118
- [10] Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology*. 2013;**61**(3):e6-e75
- [11] Brubaker PH, Kitzman DW. Chronotropic incompetence: Causes, consequences, and management. *Circulation*. 2011;**123**(9):1010-1020
- [12] Nielsen JC, Thomsen PE, Højberg S, Møller M, Vesterlund T, Dalsgaard D, et al. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. *European Heart Journal*. 2011;**32**(6):686-696
- [13] Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *The New England Journal of Medicine*. 2000;**342**(19):1385-1391
- [14] Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction.

The New England Journal of Medicine. 2002;**346**(24):1854-1862

[15] Johansson BW. Longevity in complete heart block. *Annals of the New York Academy of Sciences*. 1969;**167**(2):1031-1037

[16] Toff WD, Camm AJ, Skehan JD. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. *The New England Journal of Medicine*. 2005;**353**(2):145-155

[17] Moya A, García-Civera R, Croci F, Menozzi C, Brugada J, Ammirati F, et al. Diagnosis, management, and outcomes of patients with syncope and bundle branch block. *European Heart Journal*. 2011;**32**(12):1535-1541

[18] Reddy VY, Knops RE, Sperzel J, Miller MA, Petru J, Simon J, et al. Permanent leadless cardiac pacing: Results of the LEADLESS trial. *Circulation*. 2014;**129**(14):1466-1471

[19] Duray GZ et al. Long-term performance of a transcatheter pacing system: 12-month results from the Micra Transcatheter Pacing Study. *Heart Rhythm*. 2017;**14**(5):702-709

[20] Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;**122**:S729-S767

[21] Bektas F, Soyuncu S. The efficacy of transcutaneous cardiac pacing in ED. *The American Journal of Emergency Medicine*. 2016;**34**(11):2090-2093

[22] Gammage MD. Temporary cardiac pacing. *Heart*. 2000;**83**(6):715-720

[23] Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, et al.

Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *The New England Journal of Medicine*. 1980;**303**(6):322-324

[24] Glikson M, Friedman PA. The implantable cardioverter defibrillator. *Lancet*. 2001;**357**(9262):1107-1117

[25] Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *European Heart Journal*. 2015;**36**(41):2793-2867

[26] Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *The New England Journal of Medicine*. 2001;**345**(20):1473-1482

[27] Link MS, Atkins DL, Passman RS, Halperin HR, Samson RA, White RD, et al. Part 6: Electrical therapies: Automated external defibrillators, defibrillation, cardioversion, and pacing: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;**122**:706-719

[28] Schaumann A, von zur Mühlen F, Herse B, Gonska BD, Kreuzer H. Empirical versus tested antitachycardia pacing in implantable cardioverter defibrillators: A prospective study including 200 patients. *Circulation*. 1998;**97**(1):66-74

[29] The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients



resuscitated from near-fatal ventricular arrhythmias. *The New England Journal of Medicine*. 1997;**337**(22):1576-1583

[30] Kuck KH, Cappato R, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation*. 2000;**102**(7):748-754

[31] Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation*. 2000;**101**(11):1297-1302

[32] Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. 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. European Heart Journal*. 2000;**21**(24):2071-2078

[33] Mehta RH, Yu J, Piccini JP, Tcheng JE, Farkouh ME, Reiffel J, et al. Prognostic significance of postprocedural sustained ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention (from the HORIZONS-AMI Trial). *The American Journal of Cardiology*. 2012;**109**(6):805-812

[34] Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. *Journal of the American College of Cardiology*. 2018;**72**(9):1046-1059

[35] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable

cardioverter–defibrillator for congestive heart failure. *New England Journal of Medicine*. 2005;**352**(3):225-237

[36] Køber L, Thune JJ, Nielsen JC, Haarbo J, Vidbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *The New England Journal of Medicine*. 2016;**375**(13):1221-1230

[37] Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *The New England Journal of Medicine*. 1996;**335**(26):1933-1940

[38] Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *The New England Journal of Medicine*. 2002;**346**(12):877-883

[39] Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter–defibrillator after acute myocardial infarction. *The New England Journal of Medicine*. 2004;**351**(24):2481-2488

[40] Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *The New England Journal of Medicine*. 2004;**350**(21):2151-2158

[41] Reek S, Burri H, Roberts PR, Perings C, Epstein AE, Klein HU, et al. The wearable cardioverter-defibrillator: Current technology and evolving indications. *Europace*. 2017;**19**(3):335-345

[42] DiMarco JP. Implantable cardioverter–defibrillators. *The New England Journal of Medicine*. 2003;**349**(19):1836-1847

- [43] Magyar-Russell G, Thombs BD, Cai JX, Baveja T, Kuhl EA, Singh PP, et al. The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: A systematic review. *Journal of Psychosomatic Research*. 2011;**71**(4):223-231
- [44] Schron EB, Exner DV, Jenkins LS, Steinberg JS, Cook JR, Kutalek SP, et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: Impact of therapy and influence of adverse symptoms and defibrillator shocks. *Circulation*. 2002;**105**(5):589-594
- [45] Morken IM, Bru E, Norekvål TM, Larsen AI, Idsoe T, Karlsen B, et al. Perceived support from healthcare professionals, shock anxiety and post-traumatic stress in implantable cardioverter defibrillator recipients. *Journal of Clinical Nursing*. 2014;**23**(3-4):450-460
- [46] Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *The New England Journal of Medicine*. 2002;**346**(24):1845-1853
- [47] Leyva F, Nisam S, Auricchio A. 20 years of cardiac resynchronization therapy. *Journal of the American College of Cardiology*. 2014;**64**(10):1047-1058
- [48] Bakker PF, Meijburg HW, de Vries JW, Mower MM, Thomas AC, Hull ML, et al. Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function. *Journal of Interventional Cardiac Electrophysiology*. 2000;**4**(2):395-404
- [49] Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, et al. Four chamber pacing in dilated cardiomyopathy. *Pacing and Clinical Electrophysiology*. 1994;**17**(11 Pt 2):1974-1979
- [50] Kass DA. Cardiac resynchronization therapy. *Journal of Cardiovascular Electrophysiology*. 2005;**16**(s1):S35-S41
- [51] Murkofsky RL, Dangas G, Diamond JA, Mehta D, Schaffer A, Ambrose JA. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction [see comment]. *Journal of the American College of Cardiology*. 1998;**32**(2):476-482
- [52] Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN. QRS duration and mortality in patients with congestive heart failure. *American Heart Journal*. 2002;**143**(6):1085-1091
- [53] Jaffe LM, Morin DP. Cardiac resynchronization therapy: History, present status, and future directions. *The Ochsner Journal*. 2014;**14**(4):596-607
- [54] Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England Journal of Medicine*. 2004;**350**(21):2140-2150
- [55] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *The New England Journal of Medicine*. 2005;**352**(15):1539-1549
- [56] Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *The New England Journal of Medicine*. 2010;**363**(25):2385-2395
- [57] Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *Journal of the American College of Cardiology*. 2008;**52**(23):1834-1843

[58] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *The New England Journal of Medicine*. 2009;**361**(14):1329-1338

[59] Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT). *Circulation*. 2011;**123**(10):1061-1072

[60] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2016;**37**(27):2129-2200

[61] Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *The New England Journal of Medicine*. 2013;**369**(15):1395-1405

[62] Rosen MR. Gene therapy and biological pacing. *The New England Journal of Medicine*. 2014;**371**(12):1158-1159

[63] Rosen MR, Robinson RB, Brink PR, Cohen IS. The road to biological pacing. *Nature Reviews. Cardiology*. 2011;**8**(11):656-666

[64] Sperzel J, Burri H, Gras D, Tjong FV, Knops RE, Hindricks G, et al. State of the art of leadless pacing. *Europace*. 2015;**17**(10):1508-1513