# Chapter 13
# Devices for Heart Failure: Implantable Cardioverter Defibrillator

**Mihran Martirosyan, Dominic A.M.J. Theuns, and Tamas Szili-Torok**

## Abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| ATP | Antitachycardia pacing |
| CAD | Coronary artery disease |
| CRT | Cardiac resynchronization therapy |
| CRT-D | Cardiac resynchronization therapy with an ICD function |
| CVD | Cardiovascular disease |
| HF | Heart failure |
| ICD | Implantable cardioverter defibrillator |
| LV | Left ventricle |
| LVEF | LV ejection fraction |
| QOL | Quality of life |
| SCD | Sudden cardiac death |
| S-ICD | Subcutaneous implantable defibrillator |
| VF | Ventricular fibrillation |
| VT | Ventricular tachycardia |

M. Martirosyan, MD • Dominic A.M.J. Theuns, PhD
Department of Clinical Electrophysiology, Erasmus Medical Center, Rotterdam, The Netherlands

T. Szili-Torok, MD, PhD (✉)
Department of Clinical Electrophysiology, Erasmus Medical Center, Rotterdam, The Netherlands

Department of Clinical Electrophysiology, Thoraxcenter, Erasmus MC, `s Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
e-mail: t.szilitorok@erasmusmc.nl



M. Dorobanţu et al. (eds.), *Current Approach to Heart Failure*,
DOI 10.1007/978-3-319-45237-1_13

Implantable cardioverter defibrillator is an implantable battery-powered device, which consists of a device and lead(s), and aimed to convert life threatening ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation) to a sinus rhythm by means of an antitachycardia pacing and direct biphasic current shock. The implantable cardioverter defibrillators usually have pacemaker function as an additional function.

Heart failure is a chronic disease with a high prevalence and incidence worldwide. Despite the current approach to the early diagnosis and treatment, heart failure associated morbidity and mortality is still high and will continue to rise in the future. The progression of heart failure is irreversible. Current approach to the treatment of heart failure with an optimal medical therapy and device therapy can slow down the progression of the disease, but not reverse or stop the progression. Consequently, efforts should be made to decrease heart failure incidence and prevalence and improve survival among heart failure patients. The main two causes of death among heart failure patients are ventricular tachyarrhythmias and progressive pump failure. A significant advance in the use of implantable devices (implantable cardioverter defibrillator, cardiac resynchronization therapy with and without defibrillation function) to monitor and treat HF patients has been performed. During the last decades the large randomized studies have demonstrated that implantable cardioverter defibrillators are highly effective for primary and secondary prevention of sudden cardiac death in heart failure patients.

Nowadays, implantable cardioverter defibrillators are considered the standard therapy for patients at high risk for ventricular tachyarrhythmias, both for primary and secondary prevention.

Implantable cardioverter defibrillator (ICD) is an implantable battery-powered device, which consists of a device and lead(s), and aimed to convert life threatening ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation) to a sinus rhythm by means of an antitachycardia pacing (ATP) and direct biphasic current (DC) shock. The ICDs usually have pacemaker function as an additional function.

Development of ICDs has started since mid of twentieth century when Claude Beck performed the first electrical defibrillation of ventricular fibrillation (VF). The first human implantation of an ICD was performed at the John Hopkins Hospital by the group of Mirowski in the early 80s [1, 2]. During the last decades ICDs have evolved from bulky pulse generators which were placed in the abdominal region with epicardial patches requiring thoracotomy to a sophisticated rhythm management devices with an endocardial defibrillation leads. The implantable cardioverter defibrillator has been proven to be a highly effective tool for primary and secondary prevention of sudden cardiac death in selected patients. The annual number of implantations have increased substantially during the last years. A worldwide cardiac pacing and implantable cardioverter-defibrillator survey with 61 included countries was conducted in 2009 and was compared with the results of 2005. This survey demonstrated a significant increase in the number of ICD implantations among all involved countries [3].

The effectiveness of ICDs in the primary and secondary prevention of sudden cardiac death (SCD) among HF patients has been demonstrated in large randomized studies [5, 19] and will be discussed in details in this chapter.

## Epidemiology of Heart Failure: Insight into the Device Therapy

According to the current definition of the European Society of Cardiology "Heart failure is a clinical syndrome in which patients have typical symptoms and signs resulting from an abnormality of cardiac structure and function" [4].

Heart failure (HF) and atrial fibrillation (AF) are considered to be new cardiovascular epidemics over the last decades and are considered to be an increasing healthcare problem worldwide due to a high morbidity and mortality and the high rate of disability among HF patients. HF affects nearly five million patients in the USA and more than 550,000 patients are diagnosing with new HF annually. The incidence of HF remained stable over the last decades, meanwhile the prevalence of disease has steadily increased worldwide due to an ageing of the population and high incidence of coronary artery disease (CAD) which is among the main risk factors of HF. Approximately 15,000,000 patients have HF in the USA and Europe [5–9].

According to the Framingham Heart Study, the 5-year survival of HF patients is less than 40 % after the first manifestation of the disease [10]. The absolute mortality of HF is still high, nearly 50 % within 5 years [9, 11]. The ARIC study, which was published in 2008, has demonstrated that 1- and 5-year mortality among HF patients after hospitalization for HF were 22 % and 42.3 %, respectively [12].

Another important aspect of the current problem of HF is the HF-related costs. Treatment of HF is associated with a repetitive, prolonged and costly hospitalizations and expensive treatment, such as a therapy with an implantable devices, heart transplantation, etc. (i.e. HF related direct and indirect annual costs were estimated around $30,000,000,000 in the United States in 2006 and $33 billion in 2007) [13, 14].

The above mentioned data predispose to understand the fact that, despite the current approach to the early diagnosis and treatment, HF associated morbidity and mortality is still high and will continue to rise in the future. It is important to emphasize that the progression of HF is irreversible. Current approach to the treatment of HF with an optimal medical therapy and device therapy can slow down the progression of the disease, but not reverse or stop the progression.

Consequently, efforts should be made to decrease HF incidence and prevalence and improve survival among HF patients. The early prediction of the outcome of HF is as important as the early identification of the disease itself and the group of patients who will benefit from the certain intervention and might allow more rational or cost-effective use of specific heart failure medications and devices. Different risk factors and multivariable risk scores, such as a brain natriuretic peptide (BNP) and the Seattle Heart Failure Model (SHFM) have been prescribed during the last decades and recommended for the risk stratification of HF patients [15].

To summarize, HF is a chronic disease with a high prevalence and incidence worldwide, the prognosis of which is remaining poor and mortality among affected patients is still high.

## Evolution of the Implantable Cardioverter Defibrillator from Thoracotomy to the Subcutaneous Implantable Defibrillator

The first implantation of a defibrillator was performed in a patient with two previous cardiac arrests in 1980 at the John Hopkins Hospital by the group of Mirorowski. Thereafter ICD implantation was performed in a few centers in patients with a history of cardiac arrest (i.e. secondary prevention). In 1985 the US Food and Drug Administration (FDA) approved commercial implantable cardioverter-defibrillators.

The ICD-system consists of a pulse generator and lead(s). The ICD can be divided into three groups: single-chamber ICDs, dual-chamber ICDs and cardiac resynchronization therapy (CRT) with an ICD function (CRT-Ds). The generator consists of the battery, capacitor and the circuit (pacing pulse and shock generation, signal filtering and analysis, data storage). The basic components of ICDs have not changed during the last decades. Initially, the pulse generator was a single-chamber device and placed in the abdominal region with epicardial patches requiring thoracotomy to implant the system. A significant improvement was the shift from epicardial defibrillation patches to endocardial defibrillation leads, which simplified the implantation procedure (Fig. 13.1). The dual-chamber ICDs were produced and represented thereafter. During the last decades, technology evolved from shock boxes to a sophisticated rhythm management devices. Defibrillation efficacy has been improved by invention of biphasic shock waveforms and by using the generator as one of the electrodes for defibrillation. Modern ICDs can perform a variety of sophisticated functions, including atrial and ventricular therapy, ATP, bradycardia pacing, biventricular pacing, electrogram storage, and diagnostics e.g. HF, burden of AF [16, 17].

The concept of the biventricular pacing (i.e. CRT) was introduced more than 20 years ago. CRT was developed as a technique to provide a synchronize pacing of right and left ventricles and reduce the morbidity and mortality of HF patients by improving the whole contractility of the left ventricle (LV) and ejection fraction of the left ventricle (LVEF).

Recently, subcutaneous implantable defibrillator (S-ICD) was introduced into the clinical practice. Both the generator and the lead of an S-ICD are implanted subcutaneously, and logically avoid of the use of endocardially placed leads [18]. Both the rationale and the scientific data regarding the CRT-Ds and S-ICDs will be discussed in details in this chapter.

A significant advance in the use of implantable devices (ICD, CRT-P/D) to monitor and treat HF patients has been performed during the last decade. Nowadays, ICDs are considered to be the standard therapy for patients at high risk for ventricular


**Fig. 13.1** Original implantable cardioverter defibrillator pulse generator, on the *left*, and a modern device on the *right* (Gasparini and Nisam [17]. [16] Copyright 2016 by Springer)

tachyarrhythmias, both for primary and secondary prevention. The current state of art of the device therapy of HF patients will be discussed in details below in this chapter.

## Current Tendencies in the Treatment of Heart Failure (Prevention of Sudden Cardiac Death): From Optimal Medical Therapy to the Idea of Implantable Cardioverter Defibrillators

The main guidelines focused on the diagnosis and treatment of HF, primary and secondary prevention of SCD are represented by the European Society of Cardiology, the American Heart Association and the American College of Cardiology [4, 19–21, 68].

The current management of HF targets the modification of the existent and the identified risk factors and elimination of their influence on the natural course of

disease, treating the main heart disease, improving the quality of life (QOL) and reducing the mortality, and including the following approaches: optimal medical therapy (OMT), device based therapy (ICD, CRT-P/D), LV assist devices (LVAD) and heart transplantation. Prevention of SCD among HF patients is the most challenging issue in the treatment of HF.

The main two causes of death among HF patients should be emphasized. More than half of HF associated deaths are due to ventricular tachyarrhythmias (ventricular tachycardia (VT), VF) and the rest is due to a progressive pump failure (progressive failure of cardiac function) [22].

Several studies have been performed to demonstrate the effect of OMT on the reduction of HF mortality. Among medications used for the treatment of HF only beta blockers has shown to have an impact on the reduction of HF mortality. The US Carvedilol trial has showed a 65 % reduction in mortality with carvedilol in patients with HF with systolic dysfunction (LVEF <35 %). Arrhythmia associated death had decreased from 3.8 to 1.7 % [23]. The CIBIS-II trial has demonstrated a significant reduction of arrhythmic mortality from 6.4 to 3.6 % with bisoprolol. All-cause mortality was reduced by 34 % [24]. The MERIT-HF study has showed a significant 41 % relative risk reduction of arrhythmia associated mortality with metoprolol [25]. The impact of carvedilol on the reduction of SCD among severe HF patients was checked in the COPERNICUS trial, which showed a significant reduction in SCD from 6.1 % in the placebo group to 3.9 % in the carvedilol group, all-cause mortality has significantly reduced by 35 % [26]. A meta-analysis of a randomized controlled trials of the role of beta-blockers in the prevention of SCD in HF patients were recently performed by Al-Gobari et al. 30 randomized controlled trials with the comparison of the use of beta-blockers vs. placebo/control for the prevention of SCD in HF patients were included. The total number of involved patients was 24,779. Beta-blockers were effective in the prevention of SCD (OR 0.69; 95 % CI, 0.62–0.77, $P < 0.00001$), cardiovascular death (OR 0.71; 95 % CI, 0.64–0.79, $P < 0.00001$) and all-cause mortality (OR 0.67; 95 % CI, 0.59–0.76, $P < 0.00001$). The results of the analysis have suggested that beta-blockers reduce the risk of SCD by 31 %, cardiovascular death by 29 % and all-cause mortality by 33 % [27].

The usefulness of amiodarone as an antiarrhythmic medication in the reduction of the incidence of SCD among HF patients was evaluated in several studies. A total of 1013 patients resuscitated from SCD or presenting with VT and/or VF patients were enrolled in the AVID study to compare the effectiveness of ICD versus antiarrhythmic drugs (mostly amiodarone). The primary endpoint of the study was overall mortality. A total of 45 % of the patients in the defibrillator group and 40 % of patient in antiarrhythmic drug-group had a HF at the time of inclusion to the study. ICD was superior to antiarrhythmic drugs for increasing overall survival among patients. Overall survival with an ICD was 89.3 % vs 82.3 % with an amiodarone at 1 year, 81.6 % vs 74.7 % at 2 years and 75.4 % vs 64.1 % at 3 years respectively ($p < 0.02$ %). The effect of an ICD was not significant in a patients with LVEF > 35 %, which is a very important point to emphasize [28]. Authors had concluded that the implantation of an ICD should be offered as a first-line therapy to survivors of SCD.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) had a crucial role on the future understanding of the possible ways of the prevention of SCD

among HF patients, e.g. the role of antiarrhythmic drugs and ICDs [29]. The ability of amiodarone to decrease the mortality among HF patients and the primary prevention effect of ICDs especially among patients with non-ischemic cardiomyopathy were not clarified before. A total of 2521 consecutive patients with New York Heart Association (NYHA) class II-III HF (70 % class II, 52 % ischemic HF) and an impaired systolic function (LVEF < 35 %) of the LV (median LVEF 25 %) were randomized into three groups: conventional therapy plus amiodarone, conventional therapy plus placebo and conventional therapy plus a conservatively programmed, shock-only, single-lead ICD. The primary end point was death from any cause.

The median follow-up was 45.5 months. 244 (29 %) patients were died in the placebo group, 240 (28 %) and 182 (22 %) were died in the amiodarone and in the ICD group, respectively. There was no significant difference in the reduction of risk of SCD in amiodarone and placebo groups (HR 1.06; 97.5 %, 0.86–1.30; P = 0.53). ICD therapy was associated with a decreased risk of death of 23 % (HR 0.77; 97.5 %, 0.62–0.96; P = 0.007) and an absolute decrease in mortality of 7.2 % points after 5 years in the overall population.

## Prevention of Sudden Cardiac Death Among Heart Failure Patients

As it was mentioned above the primary and secondary prevention of SCD in patients with HF is the greatest challenge in the management of HF patients.

The following concepts have to been clarified at this point. The term SCD is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life; OR an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event; OR no obvious extra-cardiac causes have been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death [21].

A primary prevention of SCD includes therapies to reduce the risk of SCD in individuals who are at risk of SCD but have not yet experienced an aborted cardiac arrest or life-threatening arrhythmias [21].

A secondary prevention of SCD comprises of therapies to reduce the risk of SCD in patients who have already experienced an aborted cardiac arrest or life-threatening arrhythmias [21].

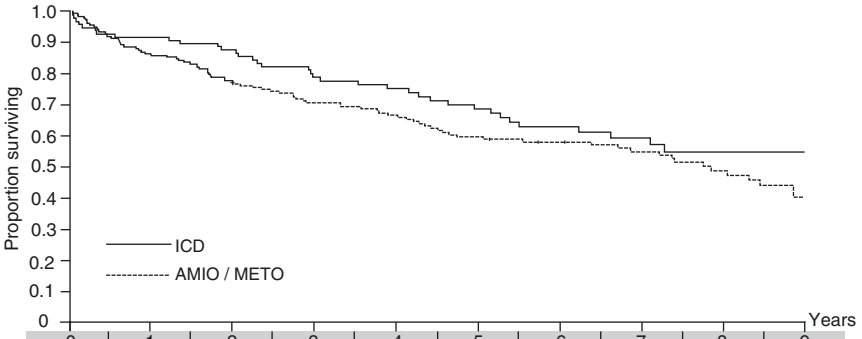
## Secondary Prevention of Sudden Cardiac Death Among Heart Failure Patients

Several studies were performed at the beginning of the “ICD-era” with the intention to demonstrate the effectiveness of such a therapy in the reduction of mortality among survivors of SCD (secondary prevention).

One of the first studies which were performed among SCD survivors was the above mentioned AVID study [28]. Among SCD survivors (VT, VF) ICD was superior to an antiarrhythmic drugs for increasing overall survival among patients. It is important to emphasis one more time that the study showed that the effect of an ICD was not significant in a patients with LVEF > 35 %.

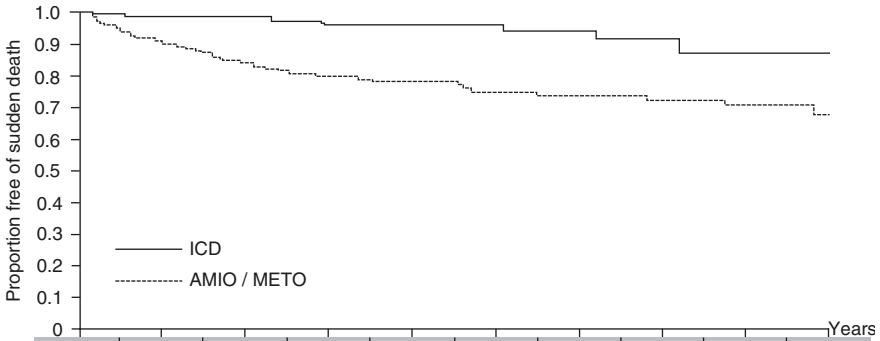
The next study which was performed among survivors of SCD was the Cardiac Arrest Study Hamburg (CASH) study [30], which was published in 2000. A prospective, multicenter, randomized comparison of ICD vs. antiarrhythmic drug therapy among survivors of cardiac arrest was performed. An inclusion criteria was a cardiac arrest secondary to documented sustained ventricular arrhythmias. Patients with cardiac arrest within 72 h of an acute myocardial infarction (MI), cardiac surgery, electrolyte abnormalities or pro-arrhythmic drug effects were excluded from the study. Included patients were randomized to ICD-group and antiarrhythmic drug group (amiodarone-, metoprolol- and propafenone-group). The primary end point of the study was all-cause mortality. The secondary end points were sudden death and recurrence of cardiac arrest at 2-year follow-up. All the patients included in the ICD-group had received an epicardial ICD until June 1991 and an endocardial ICD from July 1991. Appropriate functioning of the devices was proved by the pre-discharge DFT-test. The recruitment of patients was performed from 1987 to 1998. Assignment to propafenone was discontinued in 1992 due to a high prevalence of all-cause mortality among propafenone-group as compared with an ICD-group. The remained of included patients (n = 288) were randomized into ICD- (n = 99), metoprolol- (n = 97) and amiodarone-group (n = 92). The minimum follow-up was 2 years. The baseline parameters of the recruited patients were similar in an ICD- and antiarrhythmic drug-group (metoprolol + amiodarone). The mean LVEF of the recruited patients were higher compared to the patients included in the AVID study. Fifty-nine percent and 56 % of patients in the ICD-group and antiarrhythmic drug-group were in NYHA functional class II, respectively. During the mean follow-up of 57 ± 34 months the overall mortality rates were 36.4 % (CI 26.9–46.6 %) in the ICD-group and 44.4 % (CI 37.2–51.8 %) in the antiarrhtyhmic drug-group. Overall survival was non-significantly higher in the ICD-group compared to the antiarrhythmic drug-group. The overall mortality rates among metoprolol- and amiodarone –group was 45.4 % (CI 35.2 % to 55.8 %) and 43.5 % (CI 33.2 % to 54.2 %) respectively (P = 0.845).

The secondary analyses demonstrated that the overall sudden death rates were 13 % (CI 7.9–19.6 %) in the ICD-group and 33 % (CI 27.2–41.8 %) in the antiarrhythmic drug-group. The sudden death free survival was significantly higher in the ICD-group as compared to the antiarrhythmic drug-group [1-sided P = 0.005, HR 0.423 (97.5CI upper bound 0.721)]. The overall rates of nonfatal cardiac arrest were 11.1 % (CI 6.9–16.5 %) in the ICD-group and 19.5 % (CI 12.2–25.6 %) in the antiarrhythmic drug-group. In ICD patients, the percent reductions in all-cause mortality were 41.9, 22.8 and 24.7 % at years 1, 5 and 9 of follow-up. Kuck et al. had concluded that therapy with an ICD was associated with a non-significant 23 % reduction in all-cause mortality as compared to the treatment with metoprolol/amiodarone. The benefit of an ICD implantation as secondary prevention was more visible during the first 5 years after the index event (Figs. 13.2 and 13.3).




| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| ICD | 99 | 91 | 82 | 68 | 61 | 50 | 36 | 29 | 15 | 9 |
| AMIO/METO | 189 | 161 | 142 | 115 | 90 | 79 | 64 | 51 | 34 | 22 |
| % reduction in all-cause mortality of ICD ptd | | 41.9 | 39.3 | 28.4 | 27.7 | 22.8 | 11.4 | 9.1 | 10.6 | 24.7 |

**Fig. 13.2** Long-term overall survival in ICD and drug arms. *AMIO* indicates amiodarone, *METO* metoprolol, *pts* patients. (Kuck et al. [30] Copyright 2016 by Springer)




| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| % reduction in sudden death of ICD pts | | 81.8 | 86.7 | 76.2 | 78.3 | 80.8 | 73.1 | 64.3 | 56.7 | 60.6 |

**Fig. 13.3** Long-term survival free of sudden death in ICD and drug arms. *AMIO* indicates amiodarone, *METO* metoprolol, *pts* patients (Kuck et al. [30] Copyright 2016 by Springer)

The Canadian Implantable Defibrillator Study (CIDS) had similar design and have been performed in Canada. Six hundred and fifty nine resuscitated patients (with documented VF, sustained VT, unmonitored syncope) were included in the trial and were randomized in an ICD-group and an amiodarone-group [31]. During the 5-years of follow-up arrhythmic mortality was reduced by 33 % with an ICD therapy compared with amiodarone, which was not statistically significant. 50.5 %

of patients in an amiodarone group and 48.8 % of patients in an ICD group had a congestive heart failure.

Meta-analysis of the above mentioned AVID, CASH and CIDS secondary prevention trials was performed by Connolly et al. in 2000, which has demonstrated an overall reduction of arrhythmia induced mortality with ICD by 50 and 28 % relative reduction in death [32]. All three trials have demonstrated consistent results regarding the comparison of an ICD vs. amiodarone. A significant reduction in death from any cause with an ICD was demonstrated with these trials, with a summary hazard ration (ICD: amiodarone) of 0.72 (95 % confidence interval 0.60, 0.87; P = 0.0006). For the outcome of arrhythmic death, the hazard ratio was 0.50 (95 % confidence interval 0.37, 0.67; P < 0.0001). Survival was extended by a mean of 4.4 months by the ICD over a follow-up period of 6 years. Patients with an impaired systolic function of LV (LVEF ≤ 35 %) benefit more from an ICD implantation as compared with those with a better preserved systolic function of LV.

Consequently, based on these trials current guidelines suggest that "an ICD is recommended to reduce the risk of sudden cardiac death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for >1 year with good functional status" (Class of recommendation – I, Level of evidence – A) [4, 21, 68].

## Primary Prevention of Sudden Cardiac Death Among Heart Failure Patients

According to the major guidelines on the management of HF and prevention of SCD ICD implantation is indicated for the primary prevention of SCD among HF patients who have an estimated life expectancy at least 1 year and more [4, 19–21, 68]. These recommendations are based on the major trials performed during the last decades.

ICD therapy was compared to amiodarone therapy in a patients with NYHA class II-III HF and LVEF < 35 % in the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial in improving 5-year survival [29]. The primary endpoint of the study was all-cause mortality. All the included patients were randomized into a placebo-, an amiodarone- and an ICD-shock only-group. ICD therapy was associated with a 23 % reduction of all-cause mortality as compared with placebo.

One of the earliest trials which has compared ICD therapy with an OMT was the Multicenter Automatic Defibrillator Implantation (MADIT) Trial [33]. A comparison of an ICD vs conventional medical therapy among high-risk patients was investigated. A total of 196 consecutive patients with ischemic cardiomyopathy, NYHA class I-III HF, LVEF ≤ 35 %, a documented episode of asymptomatic unsustained VT and inducible, non-suppressible ventricular tachyarrhythmia on electrophysiological study (EP study) were included in the study and randomized into an ICD-group (n = 95) and conventional medical therapy group (n = 101). The mean follow-up of the trial was 27 months. A total of 15 deaths (11 cardiac deaths) were

registered in the ICD-group as compared with the 39 deaths in the conventional therapy group (HR 0.46, 95 % CI, 0.26–0.82, P = 0.009). Antiarrhythmic therapy (amiodarone, beta-blockers, etc.) in the involved population were not associated with the improved survival. Hence, all-cause mortality was reduced by nearly 60 % over the 27-month of follow-up in the ICD-group.

The second Multicenter Automatic Defibrillator Implantation Trial (MADIT II trial) was conducted later and involved patients with ischemic cardiomyopathy and prior myocardial infarction (at least 1 month or more before inclusion in the study), LVEF < 30 %, NYHA class I-III HF (59 % of involved patients were in NYHA class II-III HF, patients with NYHA class IV HF were not included in the study) who were randomized in a 3:2 ratio to receive an ICD (n = 742) or a conventional medical therapy (n = 490). ICD implantation was associated with a 31 % relative risk reduction in mortality [34]. The most important aspect of the MADIT II trial which has to be emphasized is the fact that due to a very poor predictive value EP studies were not performed for risk stratification and current guidelines are focused on class of HF (NYHA) and LVEF.

According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [68], which has been published recently, an ICD implantation is indicated for the primary prevention of SCD among HF patients in the following settings:

1. An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II-III), and an LVEF ≤ 35 % despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status, and they have:
   - Ischemic heart disease (unless they have had an MI in the prior 40 days) – Class I, Level A.
   - Dilated cardiomyopathy – Class I, Level B.
2. ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis – Class III, Level A.
3. ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation – Class III, Level C.
4. Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's need and clinical status may have changed – Class IIa, Level B.
5. A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device – Class IIb, Level C.

Unless patients after MI are at high risk of SCD due to life-threatening ventricular tachyarrhythmias, as it was mentioned above, ICD implantation is indicated at least 40 days after MI. The hypothesis that patients with an acute MI can benefit more in case of an early implantation of ICD was checked in randomized trials.

Patients at 6–40 days after an acute MI (LVEF ≤ 35 % and impaired cardiac autonomic function, manifested as depressed heart-rate variability or an elevated average 24-h heart rate on Holter monitoring) was involved in the Defibrillator in Acute Myocardial Infarction Trial [35] and randomized in an ICD therapy group (n = 332) and no ICD therapy group (n = 342). The primary endpoint of the study was mortality from any cause. The secondary endpoint was death from arrhythmia. No significant difference in overall mortality was observed during a follow-up period of 30 ± 13 months (62 vs 58 patients died in the ICD and in the control group, respectively; HR for death in the ICD group 1.08, 95 % CI, 0.76–1.55, 9 = 0.66). However, the prevalence of nonarrhythmic deaths were significantly higher in the ICD group as compared with the control group (50 vs 29, HR in the ICD group 1.75, 95 % CI, 1.11–2.76, p = 0.02).

A total of 898 consecutive patients at 5–31 days after an acute MI (LVEF ≤ 40 %, heart rate≥90 bpm on the first available electrocardiogram, nonsustained VT (≥150 bpm) during Holter monitoring or both criteria) were randomized in the ICD treatment group (n = 445) and medical therapy group (n = 453) in the study of Steinbeck et al. [36]. No significant difference in the overall mortality during a follow-up of 37 months was observed (116 vs 117 in the ICD and control group, respectively, p = 0.78). Though the prevalence of SCD in the ICD group was less than in the control group (27 vs. 60; HR, 0.55; 95 % CI, 0.31 to 1.00; p = 0.049) the number of non-SCD was higher in the ICD group (68 vs. 39, HR, 1.92; 95 % CI, 1.29 to 2.84; p = 0.001).

Hence, prophylactic ICD implantation early after an acute MI (≤40 days) among HF patients is not associated with a better survival.

## Cardiac Dyssynchrony

Many of HF patients have a LV contraction dyssynchrony associated with conduction delay which led to the reduction of systolic function of LV [13]. The presence of the mentioned dyssynchrony worsens contraction of LV due to heterogeneity of LV contraction and reduces the LVEF which leds to the increasing of mortality among HF patients. According to the studies performed at the beginning of the noughties dyssynchrony is an independent risk factor of HF patients' mortality. According to some studies the prevalence of dyssynchrony among HF patients varies from 25 to 30 % based on the ECG and up to 60 % based on echocardiography [37, 38]. In the EuroHeart Failure survey 41 % of those patients who had an EF < 35 % had a QRS duration ≥ 120 ms. (7 % – RBBB, 34 % – LBBB or the intraventricular conduction delay) and 17 % had a QRS ≥ 150 ms. [39]. In the Italian Network on congestive heart failure (IN-CHF) 25 % of the involved patients had complete LBBB, 6 % had complete RBBB and 6 % had other forms of intraventricular conduction delay [40].

Two levels of cardiac dyssynchrony are present: electrical dyssynchrony, which is mainly represented by a prolonged PR interval and widened QRS complexes, and

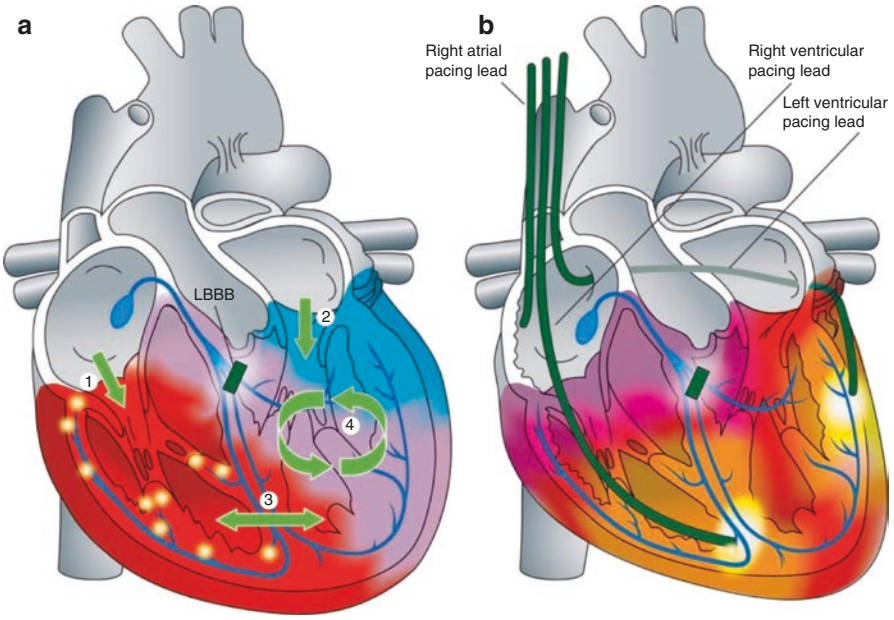



**Fig. 13.4** Relation of the cardiac conduction system, mechanical dyssynchrony, and CRT. (**a**) Electrical disturbances induce mechanical dyssynchrony at different levels: atrioventricular (1, 2), interventricular (3), and intra left ventricular dyssynchrony (4), resulting in an impaired mechanical efficiency of the cardiac cycle and decreased cardiac output. LBBB has been indentified to have an effect most on mechanical dyssynchrony. Early electrical activation is marked in *red*, whereas late electrical activation is marked in *blue*. (**b**) A standard CRT system consists of a right atrial lead, a right ventricular lead (in CRT pacemaker systems) or a right ventricular defibrillation lead (in CRT defibrillator systems), and a left ventricular lead. The left ventricular lead is placed in a tributary of the coronary sinus on the left lateral or posterolateral wall. CRT works by biventricular pacing and subsequent resynchronisation of the impaired mechanical contraction patterns. *CRT* cardiac resynchronisation therapy. *LBBB* left bundle branch block (Holzmeister and Leclercq [41] Copyright 2016 by Springer)

mechanical dyssynchrony, which is the result of an electrical dyssynchrony and represented by interatrial dyssynchrony, AV dyssynchrony, interventricular dyssynchrony and intraventricular dyssynchrony.

Current main approaches to diagnose the dyssynchrony are ECG (based on the QRS widening), echocardiography and magnetic resonance imaging. 12-lead ECG is considered to be a basic tool, which can suggest the presence of a broad QRS complex. The above mentioned abnormal electrical activation, mainly represented by the prolonged PR interval and widened QRS complexes, which is mostly attributable to a left bundle branch block (LBBB), frequently detected in HF patients lead to the concept of biventricular pacing (i. e. synchronize pacing). HF patients with broad QRS complexes (which suggests LV contraction dyssynchrony) have a worse prognosis than those patients with a narrow QRS complexes. According to the MADIT CRT trial patients with an intraventricular conduction delay, RBBB and LBBB had 3-year mortality rates of 4 %, 7 % and 8 % respectively [42]. Figure 13.4

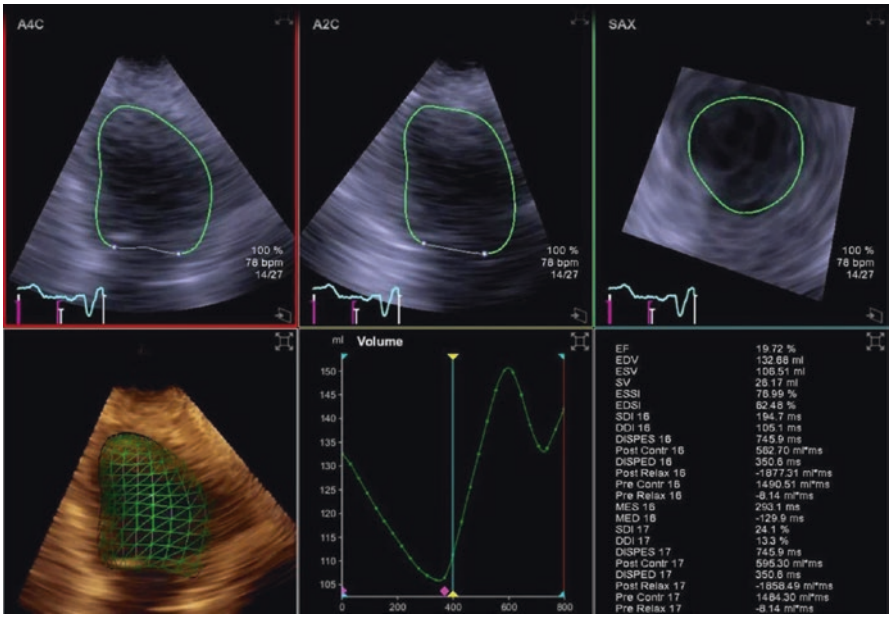



**Fig. 13.5** 3D echocardiography in a patient with LBBB. A substantial systolic dyssynchrony represented by SDI 17 = 24.1 %. LVEF = 20 %. *SDI 17* systolic dyssynchrony index of 17 segments of LV

represent the relation of the cardiac conduction system, mechanical dyssynchrony, and the concept of CRT [41].

One of the easy reproducible tools to visualize dyssynchrony is an echocardiography. During the last decades echocardiography evolved and developed as one of the modern and developed tools, which plays an important role in the diagnosis and risk stratification of HF patients. Currently, 3D echocardiography (along with M-mode, 2D echocardiography and tissue doppler imaging) plays an important role in the assessment of LV dyssynchrony and evaluation of the CRT response after an implantation [43]. Figure 13.5 shows a 3D transthoracic echocardiography of a patients with LBBB, QRS duration is 160 ms., no CAD, who reffered for CRT implantation.

## The Concept of Biventricular Pacing: Cardiac Resynchronization Therapy

Cardiac resynchronization therapy was developed in the mid of ninetieth with the intention to improve the quality of life (QOL) and survival of HF patients by synchronizing LV contraction. The concepts of the short-term hemodynamic effects of a synchronize stimulation of right and left ventricles, or left ventricle alone were published in 1960–1970 by Vagnini et al., Tyers et al., Gibson et al. and De Teresa et al. [44].

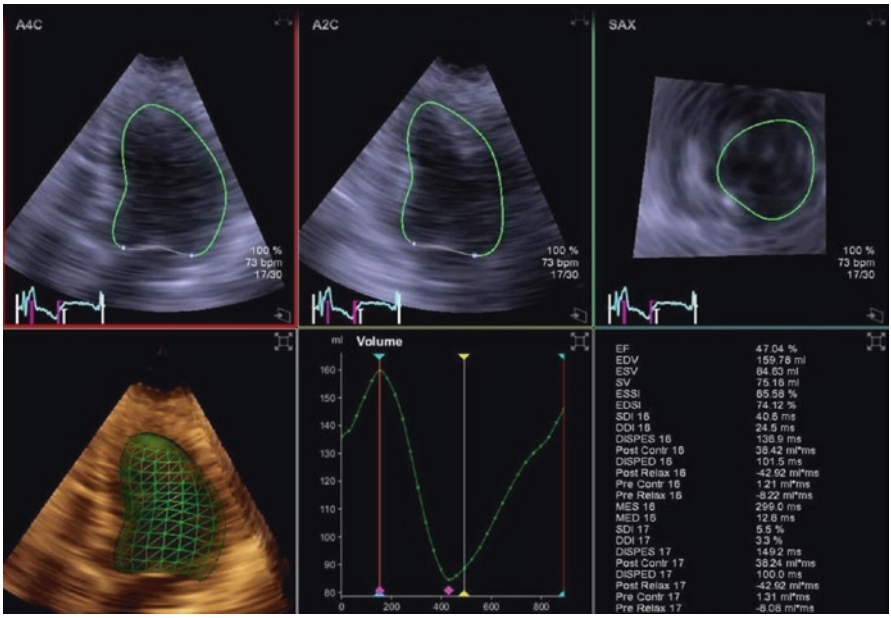



**Fig. 13.6** 3D transthoracic echocardiography after CRT implantation. A substantial improvement of systolic function of the LV (LVEF = 47 %) and synchronize contraction of the LV (SDI 17 = 5.5 %) was registered within a 24 h after implantation

The first steps of resynchronization were done in the early 90s. Gazeau et al. have performed an epicardial stimulation of LV in 1994 and the first endocardial stimulation of LV through the coronary sinus was done in 1996 by Bakker et al. in the Netherlands [45, 46]. In 2001 CRT was approved by the FDA of the USA to use in selected patients with HF. During the last two decades several studies have been performed and the substantial effect of CRT implantation on the improvement of the mechanical synchrony of LV, energetic efficiency and regional metabolism have been demonstrated. CRT-therapy aimed to influence on the most of the above mentioned mechanisms of cardiac dyssynchrony and led to the improvement of LV function, reduction of the functional mitral regurgitation and induction of LV reverse remodeling [47]. Figure 13.6 represents a 3D echocardiography of the same patient after CRT implantation, as was discussed above in Fig. 13.5 (<24 h after implantation). A substantial improvement of the LVEF (LVEF = 47 %) and narrowing of QRS complex (QRS = 130 ms) was registered with 24 h after implantation of a CRT.

According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [68] the following patients have an indication for CRT-therapy:

1. CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class I, Level A.

2. CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class IIa, Level B.
3. CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class I, Level B.
4. CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 ms and non-LBBB QRS morphology and with LVEF ≤ 35 % despite OMT in order to improve symptoms and reduce morbidity and mortality – Class IIb, Level B.
5. CRT rather than RV pacing is recommended for patients with HF with reduced EF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF – Class I, Level A.
6. CRT should be considered for patients with LVEF ≤ 35 % in NYHA Class III–IV despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 ms provided a strategy to ensure biventricular capture is in place or the patient is expected to return to sinus rhythm – Class IIa, Level B.
7. Patients with HF with reduced EF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF – Class IIb, Level B.
8. CRT is contraindicated in patients with a QRS duration < 130 ms – Class III, Level A.

Clinical benefits of biventricular pacing alone (CRT-P) and in combination with defibrillation function (CRT-D) were demonstrated in several studies during the last years. The MUSTIC trial (the Multisite Stimulation in Cardiomyopathy) was the first multi-center, randomized trial which has demonstrated the clinical benefits of CRT therapy. Sixty-seven patients with impaired LV function (LVEF ≤ 35 %), NYHA class III HF, sinus rhythm and QRS duration>150 ms. Were involved in the trial. The initial programming of the devices was <40 bpm backup pacing for the first 3 months, which was later reprogrammed to the biventricular pacing. Biventricular pacing was associated with significant improvement in 6-min. Walking test and QOL (58 % of patients reported an improvement in QOL with CRT), peak oxygen uptake and decreased hospitalizations [48]. A similar parameters were evaluated in the MIRACLE trial (the Multicentre InSync Randomised Clinical Evaluation trial) which consistent with a larger population of included patients (n = 453). [49].

The comparison of biventricular pacing alone (CRT-P) with optimal medical therapy was performed in the CARE-HF trial (the Cardiac Resynchronization in Heart Failure). Eight hundred and thirteen consecutive patients with LVEF ≤ 35 %,

NYHA class III–IV heart failure, QRS duration ≥120 ms. And echocardiography evidence of a ventricular dyssynchrony were included in the trial and randomized into optimal medical therapy and CRT-P groups [50]. A composite primary endpoint of the trial was all-cause mortality or hospitalization for a major cardiac event, and a secondary endpoint was all-cause mortality. Biventricular pacing was associated with a 26 % significant reduction in the composite primary endpoint at 29 months of follow-up. CARE-HF was the first trial which has demonstrated a significant improvement in survival of HF patients even with a biventricular pacing alone, without an ICD-function.

The COMPANION trial (the Comparison of Medical Therapy, Pacing and Defibrillation trail) has included 1520 patients (ischemic or nonischemic cardiomyopathies) with NYHA class III-IV HF, LVEF ≤ 35 % and QRS duration>120 ms, who were randomized in a 1:2:2 ration to receive optimal medical therapy, medical therapy with a CRT-P, and medical therapy with a CRT-D [51]. The primary composite end point of the trial was the time to death from or hospitalization for any cause. The risk of the combined end point of death from or hospitalization for HF was reduced by 34 % in the CRT-P group ($p < 0.002$) and by 40 % in the CRT-D group ($p < 0.001$). The risk of the secondary end point of death from any cause was decreased by 24 % ($p = 0.059$) in the CRT-P group and by 36 % in the CRT-D group ($p = 0.003$). This trial has demonstrated that in patients with advanced HF and a prolonged QRS interval CRT-D was superior to CRT-P in reduction the combined risk of death from any cause or first hospitalization.

The average CRT implantation rate in western and central Europe in 2011 was 140/per million population (CRT-D – 107 units, CRT-P – 33 units) [20].

## The Concept and Rational of the Subcutaneous Implantable Defibrillators

Recently, an entirely subcutaneous implantable defibrillator has been developed. One of the reasons to develop a S-ICD-system was the relatively high risk of complications associated with the implantation of transvenous ICD lead(s) (such as pneumothorax, cardiac perforation, dislodgement, pericardial effusion and cardiac tamponade) and chronic transvenous lead complications (such as systemic infections, insulation breaches, conductor breaks), which will be discussed below [52].

The investigational device exemption (IDE) trial has demonstrated the safety and effectiveness of the S-ICD system for treatment of ventricular arrhythmias [53]. The results of the European Regulatory trial, the US Investigational Device Exemption trial and the EFFORTLESS registry demonstrated the safety and efficacy of the subcutaneous implantable defibrillators as a viable alternative for primary and secondary prevention of SCD in selected patients without an indication for bradycardia, resynchronization therapy or the need for ATP [29, 52, 53, 54]. A limitation of the S-ICD system is the absence of cardiac pacing [52, 54].

## Peri- and Post-procedural Complications of Implantable Cardioverter Defibrillators Implantation

As it was mentioned in the introduction of this chapter the design and programming of ICDs have been significantly improved to maximize therapeutic benefit and minimize patients' discomfort [55]. Despite the fact that the implantation procedure has been simplified since the initial experience the implantation of transvenous ICD systems is still associated with a certain risk of complications (up to 4–11 % of new ICD implantations are associated with complications [56–60]) both peri- and post-procedurally (such as mechanical complications, infections, lead damages, malfunctions, etc.).

Peri-procedural adverse outcomes associated with an ICD implantation can be categorized as major or minor [61]. Major complications are lead dislodgement, pneumothorax, cardiac arrest, coronary venous dissection, pericardial tamponade, device-related infection, cardiac perforation, transient ischemic attack or stroke, myocardial infarction, urgent cardiac surgery, hemothorax, peripheral embolus and valve injury. Minor complications are hematoma, drug reaction, conduction block, set screw problem, venous obstruction and peripheral nerve injury.

According to the data published by Dewland et al. dual-chamber ICD implantation was associated with increased periprocedural complications and in-hospital mortality as compared with single-chamber ICDs [62]. 104,049 consecutive patients who received either a single-chamber or a dual-chamber ICD from January 1, 2006 to December 31, 2007 were enrolled to the National cardiovascular data Registry ICD Registry. Sixty-two percent of patients were received a dual-chamber ICD, the rest underwent a single-chamber ICD implantation. The frequency of periprocedural adverse events as well as the rate of an in-hospital mortality were higher in the dual-chamber ICD group (3.17 % vs 2.11 %. $p < 0.001$; 0.40 % vs. 0.23 %, $p < 0.001$, respectively).

The frequency and the risk of post-procedural complications (such as systemic infections, insulation breaches, conductor breaks) are relatively high as well. Removal of infected or damaged transvenous leads is associated with a substantial morbidity and mortality [63, 64]. According to the study of Kleemann et al. published in 2007 ICD lead dysfunction appeared among nearly 40 % of patients, during the 8-year follow-up period [65]. The systematic review by Persson et al. in 2014 demonstrated 2.8–3.6 % of adverse events from 35 independent cohorts reported in 53 articles. Post-hospitalization device-related complications rate varies from <0.1 to 6.4 % (2–49 months), lead-related complications varies from <0.1 to 3.9 % (1.5–40 months), infections 0.2–3.7 % (1.5–49 months) and thrombosis 0.2–2.9 % (1.5–49 months) [66].

Therefore, nowadays a transevenous endocardial lead is considered as a weak chain of the whole ICD-system.

Although ICD implantation prolongs life in patients at risk, it does not improve the quality of life (QOL) or symptoms of HF [67]. Given the fact that 2/3 to 3/4 of patients underwent ICD implantation never receive a therapeutic defibrillation but

the implantation of ICD is associated with the above mentioned peri- and post-procedural complications potential benefits and harms of the implantation procedure, as well as at least 1 year life expectancy of the recipient have to be thorough investigated before implantation.

**Future Developments**

Future development of ICDs will refer to both the generator and lead(s). Current generators are still big and cause discomfort for the vast majority of patients. The evolution of the generators have to go toward smaller and thinner devices with improved shape, extended longevity and improved remote monitoring system. Improvement of the sensing and detection, diagnostic algorithm and antitachycardia pacing has to be performed to decrease the number of appropriate and inappropriate shocks. Recently, quadripolar ICD leads were represented with a better productivity, as well as leads with hemodynamic sensors are already present in the systems of some manufacturers. These sensors will allow to continuously monitor hemodynamic values, such as pressure, volume, intracardiac impedance and improve follow-up of patients. The number of long-term complications associated with ICD leads are still high, which has to be improved with the new generation of leads and possibly new techniques for implantation.

Overall, the effect of an implantable cardioverter defibrillator therapy on the reduction of sudden cardiac death among heart failure patients is indisputable. During the last decades and based on the substantial number of randomized clinical trials ICDs became one of the most powerful lifesaving therapies in cardiology.

## References

1. Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. JAMA. 1947;135:985.
2. 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. N Engl J Med. 1980;303:322–4.
3. Mond HG, Proclemer MD. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009–a World Society of Arrhythmia's project. Pacing Clin Electrophysiol. 2011;34(8):1013–27.
4. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–847.
5. Braunwald E. Shattuck lecture: cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med. 1997;337:1360–9.
6. Heart disease and stroke statistics: 2005 update. Dallas: American Heart Association; 2005.

7. Go AS et al. Executive summary: heart disease and stroke statistics: 2013 update—a report from the American Heart Association. Circulation. 2013;127(1):143–52.
8. Curtis LH, Whellan DJ, Hammill BG, et al. Incidence and prevalence of heart failure in elderly persons, 1994–2003. Arch Intern Med. 2008;168:418–24.
9. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292:344–50.
10. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev. 2000;5(2):167–73.
11. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397–402.
12. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival from the Atherosclerosis Risk in Communities study. Am J Cardiol. 2008;101(7): 1016–22.
13. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007;115:e69–e171.
14. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff Jr DC, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. Heart disease and stroke statistics–2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113:e85–e151.
15. AbouEzzeddine OF, French B, Mirzoyev SA, et al. From statistical significance to clinical relevance: a simple algorithm to integrate brain natriuretic peptide and the Seattle Heart Failure Model for risk stratification in heart failure. J Heart Lung Transplant. 2016. pii: S1053–2498(16)00063–2.
16. Glikson M, Friedman PA. The implantable cardioverter defibrillator. Lancet. 2001;357:1107–17.
17. Gasparini M, Nisam S. Implantable cardioverter defibrillator harm? Europace. 2012;14:1087–93.
18. Bongiorni MG, Viani S, Zucchelli G, et al. Subcutaneous implantable cardiac defibrillators: indications and limitations. Curr Heart Fail Rep. 2015;12:79–86.
19. Russo AM et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2013;61(12):1318–68.
20. Brignole M 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). Eur Heart J. 2013;34(29):2281–329.
21. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, 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). Eur Heart J. 2015; 36:2793–867.
22. Mozaffarian D et al. Prediction of mode of death in heart failure: the Seattle Heart Failure Model. Circulation. 2007;116(4):392–8.
23. Packer M, Bristow MR, Cohn JN, et al. Effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med. 1996;334:1349–55.
24. Philippe L, CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.

25. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353:2001–7.
26. Packer M, Coats AJ, Fowler MB, Carvedilol Prospective Randomised Cumulative Survival Study (COPERNICUS) Study Group, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure. Circulation. 2002;106:2194–9.
27. Al-Gobari M, El Khatib C, Pilon F, Gueyffier F. Beta-blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2013;13:52.
28. The Antiarrhythmic Versus Implantable Defibrillator (AVID) investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576–83.
29. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–37.
30. Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of anti-arrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000;102:748–54.
31. Connoly SJ, Gent M, Roberts RE, et al. Canadian implantable defibrillator study (CIDS). Circulation. 2000;101:1297–302.
32. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta analysis of ICD secondary prevention trials – AVID, CASH & CIDS. Eur Heart J. 2000;21:2071–8.
33. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996;335:1933–40.
34. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Multicenter Automatic Defibrillator Implantation Trial II Investigators, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877–83.
35. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Prophylactic use of an implantable cardioverter defibrillator after acute myocardial infarction. N Engl J Med. 2004;351:2481–8.
36. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgartner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361:1427–36.
37. Chalil S, Stegemann B, Muhyaldeen S, et al. Intraventricular dyssynchrony predicts mortality and morbidity after cardiac resynchronization therapy: a study using cardiovascular magnetic resonance tissue synchronization imaging. J Am Coll Cardiol. 2007;50:243–52.
38. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart. 2003;89:54–60.
39. Rao RK, Kumar UN, Schafer J, Viloria E, De Lurgio D, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. Circulation. 2007;115:2136–44.
40. Ritter P, Delnoy PP, Padeletti L, Lunati M, Naegele H, Borri-Brunetto A, Silvestre J. A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs. standard methods. Europace. 2012;14:1324–33.
41. Holzmeister J, Leclercq C. Implantable cardioverter defibrillators and cardiac resynchronization therapy. Lancet. 2011;378(9792):722–30.

42. Perkiomaki JS, Ruwald AC, Kutyifa V, et al. Risk factors and the effect of cardiac resynchronization therapy on cardiac and non-cardiac mortality in MADIT-CRT. Europace. 2015;17(12):1816–22.
43. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization therapy. Part 1-issues before device implantation. J Am Coll Cardiol. 2005;46(12):2153–67.
44. Daubert JC, Leclercq C, Donal E, Mabo P. Cardiac resynchronisation therapy in heart failure: current status. Heart Fail Rev. 2006;11:147–54.
45. Cazeau S, Ritter P, Bakdach S, et al. Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol. 1994;17:1974–9.
46. Bakker P, Meijburg H, De Jonghe N, et al. Beneficial effects of biventricular pacing in congestive heart failure. Pacing Clin Electrophysiol. 1994;17:820 (abstract).
47. Kass DA. Zipes Lecture. Pathophysiology of cardiac dyssynchrny and resynchronization. Heart Rhythm. 2009;6(11):1660–5.
48. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344:873–80.
49. Abraham WR, Fisher WG, Smith A, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845–53.
50. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539–49.
51. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350: 2140–50.
52. Theuns DAMJ, Crozier IG, Barr CS, et al. Longevity of the subcutaneous implantable defibrillator: long-term follow-up of the European Regulatory Trial Cohort. Circ Arrhythm Electrophysiol. 2015;8(5):1159–63.
53. Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W, Burke MC. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation. 2013;128:944–53.
54. Lambiase PD, Barr C, Theuns DA, Knops R, Neuzil P, Johansen JB, Hood M, Pedersen S, Kääb S, Murgatroyd F, Reeve HL, Carter N, Boersma L, EFFORTLESS Investigators. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J. 2014;35:1657–65.
55. Miller JD, Yousuf O, Berger R. The implantable cardioverter-defibrillator: an update. Trends Cardiovasc Med. 2015;25:606–11.
56. Ezekowitz JA, Rowe BH, Dryden DM, Hooton N, Vandermeer B, Spooner C, et al. Systematic review: implantable cardioverter defi brillators for adults with left ventricular systolic dysfunction. Ann Intern Med. 2007;147:251–62.
57. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Culler SD, et al. The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators. J Am Coll Cardiol. 2006;47:2493–7.
58. Lee DS, Krahn AD, Healey JS, Birnie D, Crystal E, Dorian P, Investigators of the Ontario ICD Database, et al. Evaluation of early complications related to de novo cardioverter defibrillator implantation insights from the Ontario ICD database. J Am Coll Cardiol. 2010;55:774–82.
59. Al-Khatib SM, Greiner MA, Peterson ED, Hernandez AF, Schulman KA, Curtis LH. Patient and implanting physician factors associated with mortality and complications after implantable cardioverterdefibrillator implantation, 2002-2005. Circ Arrhythm Electrophysiol. 2008;1:240–9.
60. Curtis JP, Luebbert JJ, Wang Y, et al. Association of physician certification and outcomes among patients receiving an implantable cardioverter-defibrillator. JAMA. 2009;301:1661–70.
61. Hsu JC, Varosy PD, Parzynski CS, Chaudrhy SI, Dewland TA, Curtis JP, Marcus GM. Procedure timing as a predictor of inhospital adverse outcomes from implantable cardioverter-defibrillator implantation: insights from the National Cardiovascular data Registry. Am Heart J. 2015; 169(1):45–52.e3.
62. Dewland TA, Pellegrini CN, Wang YW, et al. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among

patients enrolled in the NCDR implantable cardioverter-defibrillator registry. J Am Coll Cardiol. 2011;58(10):1007–13.
63. Hauser RG, Katsiyiannis WT, Gornick CC, Almquist AK, Kallinen LM. Deaths and cardiovascular injuries due to device-assisted implantable cardioverter-defibrillator and pacemaker lead extraction. Europace. 2010;12:395–401.
64. Brunner MP, Cronin EM, Duarte VE, Yu C, Tarakji KG, Martin DO, Callahan T, Cantillon DJ, Niebauer MJ, Saliba WI, Kanj M, Wazni O, Baranowski B, Wilkoff BL. Clinical predictors of adverse patient outcomes in an experience of more than 5000 chronic endovascular pacemaker and defibrillator lead extractions. Heart Rhythm. 2014;11:799–805.
65. Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation. 2007;115(19):2474–80.
66. Persson R, Earley A, Garlitski AC, Balk EM, Uhlig K. Adverse events following implantable cardioverter defibrillator implantation: a systemic review. J Interv Card Electrophysiol. 2014;40:191–205.
67. Theuns D, Thornton AS, Klootwijk PJ, et al. Outcome in patients with an ICD incorporating cardiac resynchronization therapy: differences between primary and secondary prophylaxis. Eur J Heart Fail. 2005;7:1027–32.
68. Ponikowski P, Voors AA, Anker SD, 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). Eur Heart J. doi:10.1093/eurheartj/ehw128.