

## AICD TREATMENT IN 2004 – STATE OF THE ART

Thomas Budde

Department of Internal Medicine/Cardiology, Alfried Krupp Hospital, Essen, Germany

### Abstract

Primary and secondary prevention of sudden cardiac death is not sufficiently assured by medication. The (automatic) implantable cardioverter/defibrillator ((A)ICD) is able to terminate life-threatening arrhythmias (ventricular fibrillation/flutter, ventricular tachycardia) reliably. The identification and care of risk patients is of crucial importance. Initially, only survived resuscitation for ventricular fibrillation or ventricular tachycardia was regarded as a confirmed indication. Several studies (CABG patch, MADIT, MADIT II, MUSTT, DINAMIT, CAT AMIOVIRT, DEFINITE, COMPANION, SCD-HeFT) have examined the prophylactic indication for ICD therapy in risk groups. Patients with chronic state after myocardial infarction with markedly impaired left ventricular function and/or spontaneous, non-sustained ventricular tachycardia have been documented to benefit. Patients with moderately severe or severe heart failure also profit from ICD implantation, where appropriate in combination with cardiac resynchronization therapy in conduction disorders. There is divergent data on dilated cardiomyopathy. ICD is not indicated in patients with acute infarctions or undergoing elective bypass surgery.

*Key words:* AICD, cardioverter, defibrillator, ICD, ventricular tachycardia, ventricular fibrillation

### INTRODUCTION

The development of the automatic implantable cardioverter/defibrillator (AICD) for treatment of life-threatening arrhythmias has a long history. In 1775, Abildgarrd [1] succeeded for the first time in inducing and terminating ventricular fibrillation in animal experiments. In 1889, McWilliam [23] established the causal connection between ventricular fibrillation and sudden cardiac death. At the end of the 1930s, the number of accidents with electrical current in the US electricity industry increased, giving rise to several commissions to develop defibrillators. In 1947, Beck et al. [8] succeeded for the first time in performing a defibrillation during an operation on the exposed heart. The first transthoracic defibrillation was achieved in 1956 by Zoll et al. [31]. In 1961, Zacouto et al. developed a "resuscitation block" consisting of a "heart minder", pacemaker and a defibrillator. Following the studies of Lown et al. [22] at the beginning of the 1960s, more modern and more effective transthoracic defibrillators were developed. Mieczyslaw

("Michel") Mirowski (1924 – 1990) and co-workers commenced the development of an implantable defibrillator at the beginning of the 1970s [24]. The intellectual impetus for this project was the death of Mirowski's erstwhile boss from sudden cardiac death. In 1980, Mirowski presented the first clinically applicable automatic implantable cardioverter/defibrillator [25].

### TECHNOLOGICAL DEVELOPMENT OF IMPLANTABLE DEFIBRILLATORS

Implantable defibrillators are capable of instant detection and elimination of spontaneously occurring ventricular tachycardias or ventricular fibrillation. They can themselves immediately monitor the result of cardioversion or defibrillation and deliver further shocks with higher energies if required. The number of functions integrated into the AICDs has continuously increased in the course of their development. The size of these very complex devices could be substantially reduced in the period from 1980 until the present day. Whereas the first implantable defibrillator was still larger than a cigarette packet, some of the devices of the current generation already have volumes of less than 40 cm<sup>3</sup>. In the beginning, it was only possible to suture the defibrillation electrodes onto the heart epicardially in an open operation [30]. The aggregate was also initially implanted abdominally in a large-scale operation under general anesthesia. In consequence of the continuous reduction in size of devices, a purely subcutaneous transvenous technique for implanting the defibrillation electrodes [10, 12] became possible owing to the increase in effectiveness also of lower-energy shocks with new shock impulse forms and algorithms. The defibrillation electrodes could be advanced via the superior vena cava into the apex of the right ventricle. Besides the electrode in the apex of the right ventricle, more advanced electrode catheters have a further electrode at the transition between the superior vena cava and the right auricle. The aggregate itself is situated under the skin and in the current generation with its metallic envelope serves as a third electrode (active can principle) (Fig. 1). The appreciable reduction in the energy necessary for defibrillation was attained by biphasic, sequential [5, 7, 12, 14, 16, 18-20] (Fig. 2) and (in some cases using new electrode positions) [4] (Fig. 3) also bidirectional, orthogonal [3, 12, 14, 16-18, 20] impulse shock delivery. It could be shown that the energy required for defibrillation decreases substantially if two defibrillation impulses fol-

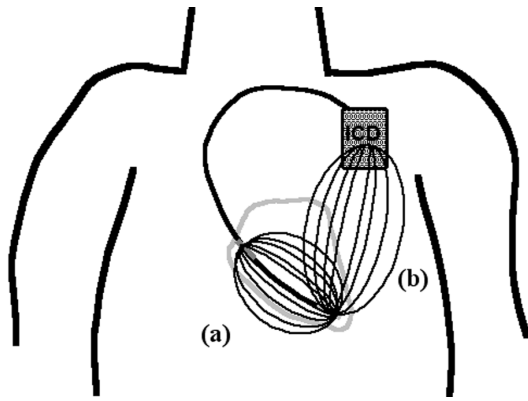


Fig. 1. Sequential, bidirectional shock delivery between two catheter electrodes (a) and then between one catheter electrode and the ICD housing ('active can') (b).

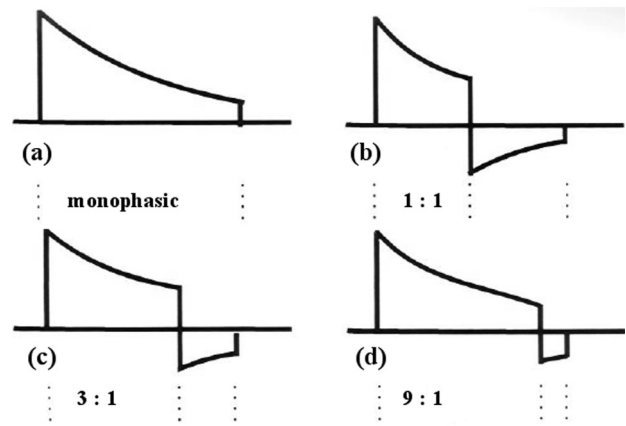


Fig. 2. Monophasic (a) versus biphasic, sequential defibrillation shock (b, c, d) impulses.

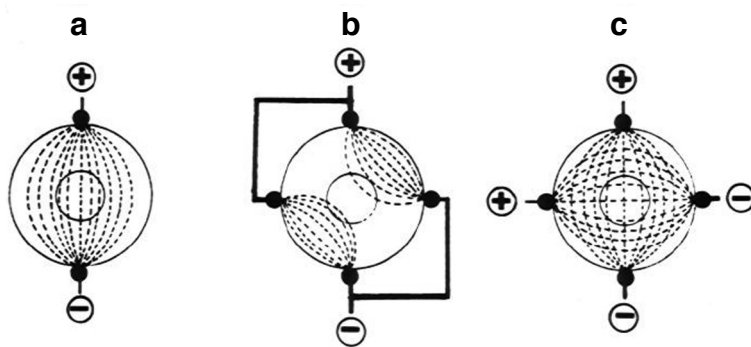


Fig. 3. Monodirectional (a), bidirectional (b) and orthogonal (c) defibrillation shock delivery.

lowing each other at a close interval in the perpendicular direction are administered instead of a single shock. The AICDs were further developed in such a way that not only defibrillation and cardioversion, but also antibradycardic and antitachycardic pacemaker stimulation techniques became possible. The first single-chamber systems could be programmed with few arrhythmia detection zones and detection criteria. On the other hand, two-chamber systems developed the capacity for separate detection and stimulation in the atria and ventricles of the heart. They can also administer antitachycardic atrial treatment such as preventive, burst or high-rate pacing. In the latest development phase of ICD, the three-chamber system, the additional option of resynchronization therapy for treatment of severe heart failure was rendered feasible by placing a further electrode in the coronary sinus. With the increase of functional capability, the range of indications has been substantially extended since the 1980s and the implantation figures have risen appreciably. The number of implantations worldwide was still less than 10,000 in 1990. On the other hand, about 30,000 ICDs were implanted in 1995 and the number of implanted devices was about 80,000 per year in 2000. In the meantime, there are more than 100,000 implantations per year. The clear demonstration of the clinical benefit of AICDs which are at the same time restricted by economic considerations leads today to a noteworthy problem in establishing or limiting the indication for AICD implantation.

### PREVENTION OF SUDDEN CARDIAC DEATH AND/OR TOTAL MORTALITY AFTER MYOCARDIAL INFARCTION

A reduction of the overall mortality after myocardial infarction could be demonstrated in large-scale study populations e.g. for ACE inhibitors, aldosterone receptor antagonists, beta blockers, statins, polyunsaturated omega-3 fatty acids or thrombolytics and acetylsalicylic acid in acute myocardial infarction (Table 1) [28]. However, also a reduction of the incidence of sudden cardiac death was also demonstrated e.g. for ACE inhibitors, aldosterone antagonists and omega-3 fatty acids (Table 1) [28]. A systematic protection from the occurrence of sudden cardiac death cannot be achieved to date by any medication strategy. Consequently, clinical testing of ICDs was clearly indicated. The spontaneous course is expected to entail an especially high risk. Clinical studies were therefore initially undertaken in patients with condition after resuscitations because of ventricular tachycardia or ventricular fibrillation as a secondary prevention measure. Studies on the primary prevention of lethal arrhythmias were then carried out in patients with coronary heart disease and poor left ventricular function. A series of further clinical studies followed: these extended the spectrum of the underlying diseases to include dilated cardiomyopathy or heart failure. The patients to be included were selected on the basis of left ventricular function, clinical occurrence of nonlethal arrhythmias as well as noninvasive or invasive electrophysiological or other cardiological investigation findings.

Table 1. Sudden death and total mortality after myocardial infarction: effects of chronic drug therapy (28).

Therapy	# Patients	■ Total mortality	□ SCD
ACE inhibitors, post acute infarction	15,104	0.85	0.95
Aldosterone receptor blockers	1,663	0.75	0.85
Betablockers, post myocardial infarction	24,298	0.80	0.80
Statins	30,817	0.75	0.75
Polyunsaturated fatty acids	11,324	0.75	0.65
Nitrates, early treatment	81,908	0.95	0.95
Magnesium, early treatment	61,860	1.05	1.05
Thrombolytics, during infarction	58,600	0.85	0.85
Aspirin, after myocardial infarction	17,187	0.80	0.80

0.4    0.6    0.8    1.0    1.1  
lower    relative risk    higher

### CLINICAL STUDIES, INCLUSION CRITERIA

Studies in patients with coronary heart disease: In 1996, 196 patients with left ventricular ejection fraction  $\leq 35\%$  and clinically non-sustained ventricular tachycardia but with inducibility in the electrophysiological investigation were included in the MADIT study [26]. The CABG patch study [9] followed in 1997 and included 900 patients with indication for bypass operation. The left ventricular ejection fraction was also  $\leq 35\%$ . In addition, the detection of positive late potentials was required. The patients underwent a bypass operation and epicardial patch electrodes were implanted intraoperatively. Up to 1999, the MUSTT study [13] investigated 704 patients with a left ventricular ejection fraction  $< 40\%$  and non-sustained ventricular tachycardia which could be induced in the electrophysiological study. Whereas the MADIT study [26] still specified the clinical occurrence of arrhythmias as an inclusion criterion and was oriented to the results of the electrophysiological investigation, up to 2000 1,232 patients were included in the MADIT II study [27] without consideration of clinical arrhythmia or electrophysiological findings. The main inclusion criteria were merely a coronary heart disease and a left ventricular ejection fraction  $\leq 30\%$ . In 2004, the DINAMIT study [15] devoted to acute myocardial infarction included 674 patients with acute myocardial infarction, a left ventricular ejection fraction  $\leq 35\%$  and a reduced heart rate variability.

#### *Studies in patients with dilated cardiomyopathy (DCM):*

After the investigation of patients with coronary heart disease, the effectiveness of ICD therapy was re-examined also in patients with restriction of left ventricular function resulting from dilated cardiomyopathy. In 2002, the CAT study [2] included 104 patients with dilated cardiomyopathy and a left ventricular ejection fraction  $\leq 30\%$  and heart failure of NYHA classes II to III for  $\leq 9$  months. The AMIOVIRT study [29] up to 2003 comprised 103 patients with a DCM and a left ventricular ejection fraction  $\leq 35\%$  and non-sustained

clinical tachycardia. Up to 2004, 458 patients with the same characteristics were included in the DEFINITE study [21].

#### *Studies in patients with heart failure in poor left ventricular function:*

"Prophylactic" ICD implantation was investigated up to 2004 in two large-scale studies. In the COMPANION study [11], 1,520 patients with heart failure of NYHA classes III to IV and a left ventricular ejection fraction  $\leq 35\%$  with a PR interval  $\geq 120$  ms and QRS duration  $> 150$  ms were studied, whereas the SCD-HeFT study [6] reported on 2,521 patients with heart failure of NYHA classes II to III and likewise a left ventricular ejection fraction  $\leq 35\%$ .

### CLINICAL STUDIES, RESULTS

#### PROPHYLACTIC ICD THERAPY IN CHD PATIENTS

In the CABG patch (Coronary Artery Bypass Graft Patch Trial) study [9], 900 patients with coronary heart disease, an ejection fraction of  $\leq 35\%$ , positive late potentials and indication for bypass operation were randomized to treatment with an ICD (446 patients) with epicardial electrodes or to a control group (454 patients). The primary endpoint was the overall mortality. The average age was  $64 \pm 9$  years, the mean left ventricular ejection fraction  $27 \pm 6\%$ . Myocardial infarction had occurred in 82% of patients, and 22% had undergone revascularizing procedures. 73% of the patients were in the NYHA classes II and III. After an average follow-up duration of  $32 \pm 16$  months, there were 101 deaths (71 cardiac) in the ICD group and 95 (72 cardiac) in the control group. The hazard ratio for deaths from any cause was 1.07 (95% confidence range 0.81 – 1.42;  $p = 0.64$ ) for the ICD group.

The MADIT (Multicenter Automatic Defibrillator Implantation Trial) study [26] randomized 196 post-infarct patients with an ejection fraction  $\leq 35\%$ , clinical occurrence of non-sustained ventricular tachycardia and inducible, nonsuppressable ventricular tachycardia

in the electrophysiological study to an ICD treatment ( $n = 95$ ) or conventional therapy (101). The average age was  $63 \pm 9$  years, the mean left ventricular ejection fraction  $26 \pm 7\%$ . 35% of the patients belonged to the NYHA class I, and 65% to NYHA classes II and III. The infarct event occurred more than six months previously in 88% of the patients. 71% had been treated with revascularizing procedures. After an average follow-up duration of 27 months, there were 15 deaths in the ICD group (11 cardiac) and 39 deaths (27 cardiac) in the group receiving conventional treatment (hazard ratio for the overall mortality 0.46; 95% confidence range 0.26 – 0.82;  $p = 0.009$ ). Medication with amiodarone, beta blockers or other antiarrhythmics did not have any effect on the result.

The MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) study [27] comprised 1,232 patients with myocardial infarction that had occurred more than four weeks previously and with a left ventricular ejection fraction  $\leq 30\%$ . Spontaneous occurrence of arrhythmias or electrophysiological testing were not required as inclusion criteria. The patients were randomized in the ratio 3:2 to an ICD therapy (742 patients) or conventional medication (490 patients). Death from any cause was defined as the endpoint. The average age of the patients was  $65 \pm 10$  years, the average ejection fraction was  $23 \pm 6\%$ . The infarct had occurred more than six months previously in 87%. 57% had a bypass operation, 44% had received a PTCA. After an average follow-up of 20 months, deaths occurred in 19.8% of the patients treated with medication alone and in 14.2% of the ICD group (hazard ratio 0.69; 95% confidence range 0.51-0.93;  $p = 0.016$ ).

The MUSST (Multicenter Unsustained Tachycardia Trial) study [13] was designed to establish whether the prognosis can be improved by treatment on the basis of electrophysiological findings in patients with coronary heart disease and a left ventricular ejection fraction of  $\leq 40\%$  as well as clinically occurring spontaneous non-sustained ventricular tachycardia. 704 patients with inducible ventricular tachycardia were randomized either to an antiarrhythmic therapy with medication or ICD or to no antiarrhythmic treatment. ACE inhibitors and beta blockers were allowed as concomitant medication. The risk of cardiac arrest or arrhythmic death and the total mortality were not affected by an electrophysiologically based antiarrhythmia medication. The risk of cardiac arrest or death due to arrhythmia was significantly less for the patients with ICD therapy (relative risk 0.24; 95% confidence range 0.13-0.45;  $p < 0.001$ ).

#### ICD THERAPY IMMEDIATELY AFTER ACUTE INFARCTION

The effectiveness of ICD implantation in the acute infarct stage was investigated in the DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) study [15]. 674 patients aged from 18 – 80 years with a left ventricular ejection fraction  $\leq 35\%$  and a reduced heart rate variability were included six to 40 days after infarction and randomized to ICD therapy (332 patients) vs. no ICD treatment (342 patients). The pri-

mary endpoint was the total mortality of any cause, the secondary endpoint was arrhythmia-related deaths. After a mean follow-up duration of  $30 \pm 13$  months, no difference was shown in the overall mortality (62 deaths in ICD group, 58 in the control group) (hazard ratio for death in the ICD group 1.08; 95% confidence range 0.76-1.55;  $p = 0.66$ ). A marked reduction of arrhythmia-related deaths (12 vs. 29; hazard ratio 0.42; 95% confidence interval 0.22-0.83;  $p = 0.009$ ) was shown in the ICD group, but there was also a raised number of deaths not due to arrhythmia (50 vs. 29; hazard ratio 1.75; 95% confidence range 1.11-2.76;  $p = 0.02$ ). There was thus a shift from death due to arrhythmia to death not due to arrhythmia in the ICD group.

#### ICD TREATMENT IN CARDIOMYOPATHY

The CAT (Cardiomyopathy Trial) study [2] investigated prophylactic ICD implantation in patients with dilated myopathy (beginning of symptoms before  $\leq 9$  months) and a left ventricular ejection fraction  $\leq 30\%$ . The patients were randomized to ICD therapy (50 patients) or a control group (54 patients). The study was ended prematurely after inclusion of 104 patients, since the overall mortality after one year did not reach the expected 30%. After a mean follow-up of  $5.5 \pm 2.2$  years, the cumulative survival rates (93% and 80% in the control group as compared to 92% and 86% in the ICD group after two and four years) did not differ significantly between the two groups.

The AMIOVIRT (Amiodarone Versus Implantable Cardioverter Defibrillator Randomized Trial) study [29] comprised 103 patients with dilated cardiomyopathy, left ventricular ejection fraction  $\leq 35\%$  and asymptomatic non-sustained ventricular tachycardia. It compared an amiodarone and an ICD therapy with the endpoint of overall mortality in this group of patients. Secondary endpoints were arrhythmia-free survival, quality of life and costs. The one-year (90% vs. 96%) and three-year actuarial survival rates (88% vs. 87%) were not statistically different ( $p = 0.8$ ) and the quality of life did not differ either ( $p = \text{NS}$ ). There was merely a trend to longer arrhythmia-free survival ( $p = 0.1$ ) and lower costs during the first year of treatment ( $p = 0.1$ ) in favor of amiodarone.

In 458 patients with dilated cardiomyopathy with a left ventricular ejection fraction  $\leq 35\%$  and ventricular extrasystoles or non-sustained ventricular tachycardias, the DEFINITE (Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation) study [21] compared the implantation of a one-chamber ICD (229 patients) with a control group receiving standard medication (229 patients). 86% received ACE inhibitors, 85% beta blockers. The mean left ventricular ejection fraction was 21%. During a follow-up of  $29.0 \pm 14.4$  months, 28 patients died in the ICD group, and 40 patients in the control group (hazard ratio 0.65; 95% confidence range 0.40-1.06;  $p = 0.08$ ). A significant difference was shown solely with regard to sudden cardiac death. Three patients died acutely in the ICD group as compared to 14 patients of the control group (hazard ratio 0.20; 95% confidence range 0.06-0.71;  $p = 0.006$ ).

## ICD THERAPY IN HEART FAILURE

In the COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) study [11], 1,520 patients with a heart failure of NYHA classes III - IV, a left ventricular ejection fraction  $\leq 35\%$  and intraventricular conduction disorders (PR interval  $> 120$ ms; QRS  $> 150$  ms) were included in the study. They were randomized in a ratio 1:2:2 to an optimal medication (diuretics, ACE inhibitors, beta blockers and spironolactone) alone, combination with cardiac resynchronization treatment with a biventricular pacemaker or a combination with resynchronization and ICD treatment. Combined endpoints were the time up to death or hospitalization for any reason. The risk of dying or going to hospital because of heart failure was lowered by 34% by the pacemaker treatment ( $p < 0.002$ ) and by 40% by the pacemaker defibrillator treatment ( $p < 0.0001$  compared to the control group receiving medication). The overall mortality was reduced by 24% ( $p = 0.059$ ) by the pacemaker and 36% ( $p = 0.003$ ) by the pacemaker/defibrillator.

The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study [6] randomized 2,521 patients with heart failure of NYHA classes II and III and a left ventricular ejection fraction  $\leq 35\%$  to conventional heart failure therapy and placebo (847 patients), to conventional heart failure therapy and amiodarone (845 patients) or a conventional therapy plus a therapy with a one-chamber ICD programmed only to deliver shocks (829 patients). The median of the ejection fraction was 25%. 70% of the patients were in NYHA class II, 30% in NYHA class III. In 52% of the patients, the heart failure was due to ischemia. After a mean follow-up duration of 45.5 months, there were 244 (29%) deaths in the placebo group, 240 (28%) in the amiodarone group and 182 (22%) in the ICD group. Whereas the risk of death was similar in the amiodarone group to that in the placebo group, the overall mortality was reduced by 23% by ICD treatment (hazard ratio 0.77; 97.5% confidence range 0.62-0.96;  $p = 0.007$ ). The results were equally valid for ischemic and nonischemic causes of heart failure, but varied depending on the NYHA class.

## CONCLUSIONS

Concepts for medication alone have not led to an adequate reduction of sudden or arrhythmia-related cardiac death. The implantable cardioverter/defibrillator is able reliably to prevent arrhythmia-related deaths. Identification of the patient groups that will profit most from its use is of crucial importance. Besides facilitating implantation, its further technological developments since the first presentation in 1980 has led to an increase of technical functions and the durability of the devices and also to an extension of the indications. Whereas the treatment of patients who had survived resuscitation for ventricular tachycardia or ventricular fibrillation was initially at the forefront, the "prophylactic" indication is becoming of even greater significance in the light of these considerations. Table 2 shows the prophylactic indications tested up to now in relation to the underlying disease, the NYHA class and

Table 2. 'Prophylactic' indications for ICD implantation in patients with low ejection fraction with regard to underlying heart disease, NYHA class and clinical arrhythmias.

EF $\leq 40\%$		EF $\leq 35\%$		EF $\leq 30\%$
CAD	NYHA I	NYHA II	NYHA IV	CAD
nsVT inducible	DCM nsVT	NYHA III	QRS $> 150$ PR $\geq 120$	
MUSTT MADIT	DEFINITE	SCD-HeFT	COMPANION	MADIT II

Presupposition:  
Constantly low left ventricular ejection fraction despite optimal conservative therapy.

Negative studies: CABG-Patch, CAT, DINAMIT

the spontaneous as well as the electrophysiologically inducible arrhythmias that have been investigated.

In post-infarct patients with restricted left ventricular function in the chronic state without continuing ischemia and with spontaneous non-sustained as well as electrophysiologically inducible left ventricular tachycardia, ICD implantation leads to a major improvement of the prognosis [13, 26]. This does not apply to the results obtained with antiarrhythmic medication [13]. On the other hand, it is indeed known from the data of MADIT II [27] that ICD treatment does indeed generally improve the prognosis of patients in the post-infarct stage with highly restricted LV function irrespective of spontaneous or inducible arrhythmias. However, prophylactic ICD implantation in patients with coronary heart disease and restricted left ventricular function cannot be recommended during elective bypass operation even though the study concerned [9] must be seen in the light of the use of "old" epicardial ICD electrodes. ICD implantation in the acute infarct stage does not lower the overall mortality, although the number of deaths due to arrhythmia is reduced [15].

The data on prophylactic ICD implantation in dilated cardiomyopathy shows a picture that is less clear [2, 21, 29]. There are indications that the risk of dying of sudden cardiac death is reduced [21], but the overall mortality does not appear to be appreciably affected in the patient groups with dilated cardiomyopathy [21, 29].

Current data indicates that patients with heart failure and severely restricted left ventricular function likewise benefit from ICD implantation [6, 11]. In chronic heart failure of NYHA classes II and III, ICD therapy reduces the overall mortality [6], but this is not the case for treatment with amiodarone. Together with a pacemaker resynchronization therapy, ICD therapy also reduces the mortality in patients with heart failure of NYHA class III-IV and intraventricular stimulus conduction disorders [11].

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*Address for correspondence:*

Prof. Dr. Thomas Budde, F.E.S.C., European Cardiologist  
Department of Internal Medicine/Cardiology  
Alfried Krupp Hospital  
Alfried Krupp Str. 21  
D-45117 Essen, Germany  
Tel: ++49-201-434-2524/-2525  
Fax: ++49-201-434-2376  
E-mail: budde.thomas@krupp-krankenhaus.de