Chapter 1
The Use of Implantable Cardioverter-Defibrillators in Nonischemic Cardiomyopathy

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Introduction

In people with cardiac arrest due to ventricular arrhythmia, the application of an electrical shock to the myocardium may terminate the ventricular arrhythmia and resuscitate the patient. In 1985, the approval of the implantable cardioverter-defibrillator made it possible to protect persons at high risk of cardiac arrest. While the first versions of the ICD were bulky and had to be placed in the abdomen with epicardial shock wires placed surgically, improvements in the design has made ICD implantation no more complicated than conventional pacemaker placement. Hence, ICDs today may be implanted in almost any patient and the decision to implant an ICD is based on an assessment of the likelihood of obtaining lifesaving therapy from the device compared to the short- and long-term risks associated with implantation, such as infection and inappropriate shocks.

Nonischemic cardiomyopathy is an umbrella term for a wide array of myocardial diseases where the impaired myocardial function is not caused by coronary artery disease. Thus, nonischemic cardiomyopathy may be secondary to valvular heart disease, congenital heart disease, or hypertension; it may be part of a systemic disease such as sarcoidosis, systemic lupus, or amyloidosis; it may be genetic such as hypertrophic cardiomyopathy, arrhythmogenic ventricular cardiomyopathy, or familial dilated cardiomyopathy; it may be caused by drugs such as cocaine or antineoplastic compounds; it may be caused by infection; or it may be idiopathic.

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This chapter discusses the use of ICDs in patients with heart failure and reduced left ventricle systolic function, which is not explained by coronary artery disease.

Secondary Prevention

As ICDs work by terminating malignant ventricular arrhythmia, the persons most likely to benefit are those who have already had such an arrythmia. Therefore, ICDs are offered to everyone with nonischemic cardiomyopathy, who have had ventricular fibrillation or sustained ventricular tachycardia, where the arrythmia was not due to obviously reversible factors such as severe hypokalemia, or the patient has a very high risk of death within a year due to other causes.

Three secondary prevention trials included a combined 292 patients with nonischemic cardiomyopathy, the Antiarrhythmics versus Implantable Defibrillators Trial (AVID) [1], the Canadian Implantable Defibrillator Study CIDS) [2], and the Cardiac Arrest Study Hamburg (CASH) [3]. Of these trials, only AVID and CIDS reported outcomes for the subgroup of patients with nonischemic cardiomyopathy. Both trials found a trend towards reduction in mortality with ICD implantation, but because of the low number of patients, neither was statistically significant. In a combined analysis of the two trials, ICD implantation was associated with a hazard ratio of 0.69 with a statistically nonsignificant p-value of 0.22 [4]. However, when including the much larger number of patients with ischemic heart disease in the analysis, the reduction in mortality becomes statistically significant and with no hint of a difference in effect of ICD implantation between patients with and without ischemic heart disease [5]. For this reason, guidelines recommend that all patients who have survived a sustained ventricular arrhythmia should be offered an ICD.

Primary Prevention

Some patients with nonischemic systolic heart failure are at such high risk of death due to ventricular arrhythmia that an ICD is recommended for primary prevention. However, the risk of sudden cardiac is lower than for patients who have already experienced arrhythmia. This means that other competing causes of death become relatively more likely and that the survival benefit from an ICD decreases while the risk of complications is unchanged.

There have been six primary prevention trials in which patients with nonischemic cardiomyopathy were included, Table 1.1.

The trials were comparable in some respects such as the typical patient being a middle-aged Caucasian male with severely reduced left ventricular ejection fraction. But because trials were conducted over a 15-year period, there was a marked

Table 1.1 Trials of ICD implantation for primary prevention including patients with nonsischemic cardiomyopathy

	CAT [6]	AMIOVIRT [7]	DEFINITE [8]	SCD-HeFT[a] [9]	COMPANION[b] [10]	DANISH [11]
Number of patients in trial	104	103	458	2521	1520	1117
Number of patients in ICD arm	50	51	229	829	595	557
Age (years)	52 (mean)	59 (mean)	58 (mean)	60	66	63
Nonischemic etiology	100	100	100	48	45	100
Male	80	71	71	77	67	72
Duration of heart failure	3 months (mean)	3.2 years (mean)	2.8 years (mean)	NR	3.5 years	1.8 years
CRT	–	–	–	–	100 [c]	58
Atrial fibrillation	16	NR	25	17	0	22
Diabetes	NR	34	23	31	41	19
LVEF	24 (mean)	23	21 (mean)	24	22	25
QRS (ms)	108 (mean)	NR	112ms (mean)	NR	160	146
NYHA						
I		15	22	–	–	–
II	65	63	57	68	–	54
III	35	20	21	32	86	45
IV			–	–	14	1
Medication						
ACE/ARB	96	85	86–97	94	90	97
Beta blocker	4	51	85	69	68	92
MRA	NR	19	NR	20	55	58
Follow-up time (months)	66 (mean)	24 (mean)	29 (mean)	46	16	68

Numbers represent percent or median unless indicated

ARB angiotensin receptor blocker, *MRA* mineralocorticoid receptor antagonist, *CRT* cardiac resynchronization therapy, *CAT* the cardiomyopathy trial, *AMIOVIRT* amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia, *DEFINITE* defibrillators in nonischemic cardiomyopathy treatment evaluation, *NR* not reported, *SCD-HeFT* sudden cardiac death in heart failure trial, *COMPANION* comparison of medical therapy, pacing, and defibrillation in heart failure, *DANISH* Danish study to assess the efficacy of ICDs in patients with nonischemic systolic heart failure on mortality

[a]Descriptive statistics are presented for the ICD group ($n = 829$)

[b]Descriptive statistics are presented for the CRT-D group ($n = 595$)

[c]No patients received an ICD only, patients who got a device received cardiac resynchronization therapy with or without a defibrillator

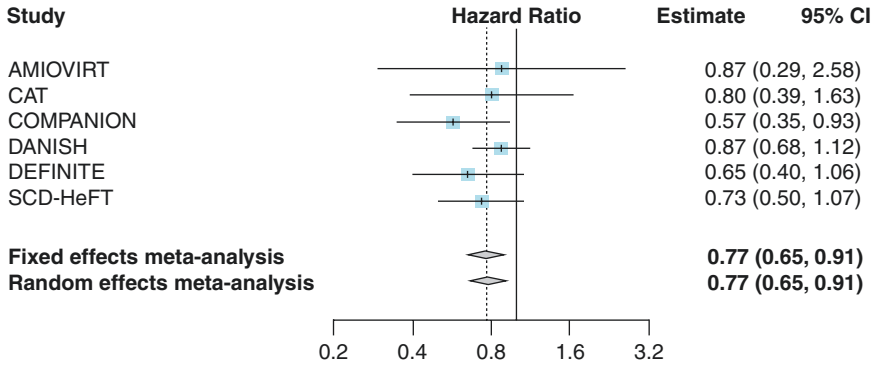

Fig. 1.1 Meta-analysis of the effect of ICD-implantation on all-cause death in patients with nonsichemic cardiomyopathy. lower hazard ratio favors ICDw

difference in concomitant medical therapy, and consequently a wide difference in risk of all-cause and sudden cardiac death. Most of the trials had fewer patients on betablockers and mineralocorticoid receptor antagonist than would be acceptable with current medical management of heart failure patients. Four trials included only patients with nonischemic heart failure, while the two remaining trials included both patients with ischemic and nonischemic etiology.

Only DEFINITE and DANISH were designed and powered to detect a difference in all-cause mortality for patients with nonischemic heart failure. Both trials were neutral. The SCD-HeFT trial did not specifically find a p-value below 0.05 in the subgroup of patients with nonischemic heart failure, but this was very likely due to low power as there was no interaction between ischemic or nonischemic etiology on the effect of ICD implantation. The only trial with a p-value below 0.05 for the effect of ICD implantation in patients with nonischemic heart failure was the post hoc comparison of patients with nonischemic etiology who received cardiac resynchronization therapy with or without a defibrillator function in COMPANION. Yet, all trials trended towards a mortality lowering effect of ICD implantation, and taken together there is a statistically significant 23% reduction in hazard of all-cause death with ICD implantation (Fig. 1.1). This reduction in all-cause mortality is driven by a substantial 60% reduction in sudden cardiac death. Because of these results, international guidelines recommend ICD implantation in patients with nonischemic systolic heart failure [12, 13].

Individual Risk Stratification

For some patients with nonischemic systolic heart failure, an ICD is not likely to substantially prolong life. This is the case for patients who are either simply at a low risk of sudden cardiac death in general or patients with a nonnegligible risk of sudden cardiac death but whose risk of death from nonsudden causes overshadows this risk. For such patients, the risk-benefit ratio with ICD implantation is reduced.

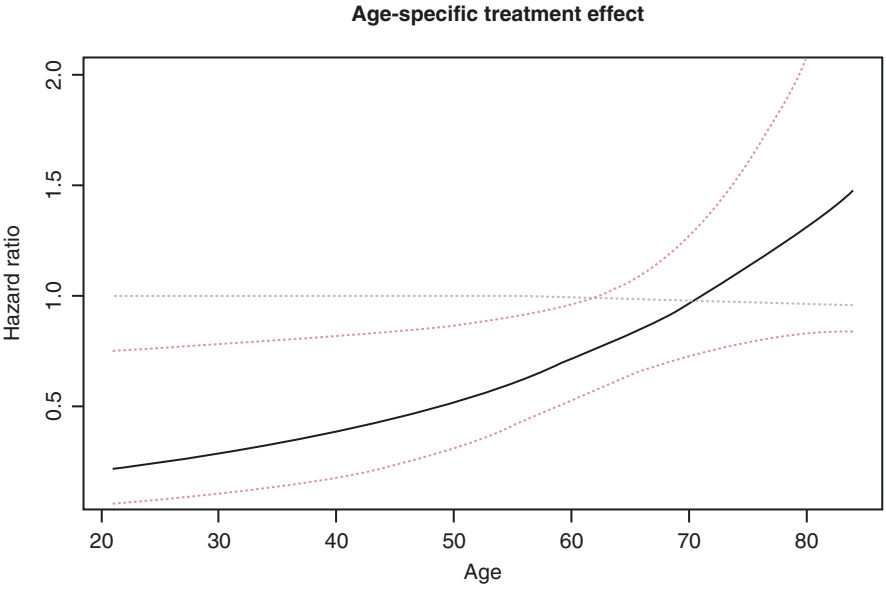

Fig. 1.2 The relation between age and risk of all-cause mortality regarding ICD treatment or control. On the x-axis age in years and on the y-axis the hazard ratio (HR). The dashed blue line indicates hazard ratio =1, which corresponds to an equal mortality in patients treated with ICD and control. The black line illustrates the risk for all-cause mortality according to age, and the dashed red lines are the 95% confidence interval. ICD denotes implantable cardioverter-defibrillator

An example of this is older patients. In the DANISH trial, there was a significant interaction between the age and the effect of ICD implantation on all-cause mortality in that older patients did not benefit from ICD implantation as opposed to younger patients (Fig. 1.2) [14]. This decline in effect of ICD implantation with age was due to a decrease in relative risk of sudden cardiac death compared to other modes of death with age. While the absolute risk of sudden cardiac death was unchanged in older patients, the risk of nonsudden death was markedly increased. And as ICD implantation only affects sudden cardiac death, the benefit of ICD implantation decreased, not because of a reduced effect on sudden cardiac death, but because of a much higher risk of other modes of death.

In line with this thinking, investigators attempt to identify patients at high absolute and relative risk of sudden cardiac death. It does remain, however, very difficult to identify risk factors that increase the risk of dying suddenly as opposed to dying nonsuddenly, as most risk factors increase the risk of both sudden and nonsudden death equally. The Seattle Proportional Risk Model was developed to determine the likelihood of death being sudden or nonsudden in patients with heart failure who died (Fig. 1.3) [15]. This model has been validated in several cohorts, and it has been shown to identify patients who benefitted from ICD implantation in SCD-HeFT and DANISH. As can be seen from the figure, factors that are usually associated with more advanced heart failure such as low sodium levels and high New York

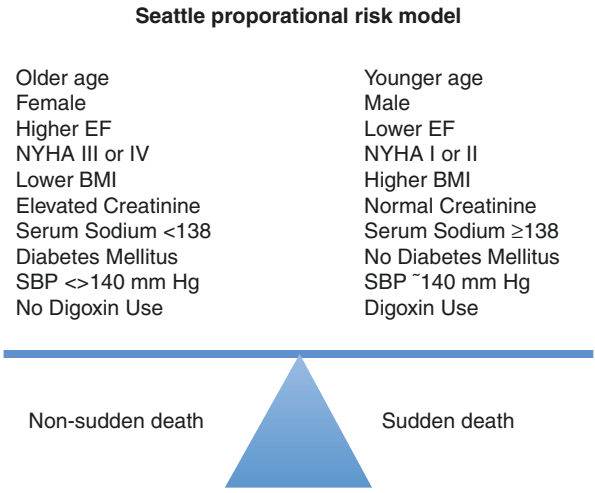

Fig. 1.3 Illustration of factors that increase the relative likelihood of sudden or non-sudden death in the Seattle Proportional Risk Model

Heart Association Class confer a relatively higher likelihood of dying suddenly as opposed to nonsuddenly. Hence, The Seattle Proportional Risk Model indicates that ICDs are more favorable in patients with less advanced and less symptomatic heart failure.

Another way to potentially identify patients at higher risk of sudden cardiac death and hence higher likelihood of benefit from ICD implantation is by cardiac imaging. A left ventricular ejection fraction below 35% is already used as a risk marker, but it is far from perfect. Currently, most attention is paid to the possibility of using gadolinium-enhanced cardiac magnetic resonance imaging to identify localized cardiac fibrosis, which may serve as a substrate for ventricular arrhythmia. Localized fibrosis, identified by late gadolinium enhancement, is strongly correlated to the risk of overall and sudden cardiac death, and theoretically this late gadolinium enhancement might therefore serve as an indicator as to which patients should be offered an ICD [16]. However, there have been no prospective randomized studies on the effect of ICD in patients with late gadolinium enhancement, and in the subgroup of patients in the DANISH study that underwent cardiac magnetic resonance imaging, there was no sign of an increased effect of ICD in the group of patients who had late gadolinium enhancement. It therefore remains to be seen if late gadolinium enhancement on cardiac magnetic resonance imaging will improve selection of patients for ICD implantation.

An additional marker with potential for identifying risk of sudden cardiac death is bilateral ventricular dysfunction. Patients with right ventricular dysfunction in addition to left ventricular dysfunction have a much higher risk of sudden cardiac death. In the DANISH cardiovascular magnetic resonance subgroup, patients with right ventricular dysfunction lived longer with ICD implantation, whereas patients with only left-sided dysfunction did not benefit from ICD implantation [17].

Several, less common causes of nonischemic systolic heart failure are associated with a particular high risk of SCD (e.g., certain genetic cardiomyopathies) and

guidelines recommend prophylactic ICD implantation for an increasing number of patients without specific trial data being available. This may be the correct strategy. However, as these patients at particular high risk of SCD have most likely been included (without knowledge of the mutation) in the trials that have convinced cardiologists of recommending ICD to patients with nonischemic systolic heart failure in general, it is likely that there are some other subsets of patients who then benefit very little from this general strategy.

Effect of ICD in Patients Who Are Candidates for Cardiac Resynchronization Therapy

Cardiac resynchronization therapy reduces morbidity and mortality for patients with left ventricular dysfunction and left bundle branch block. Patients who are candidates for cardiac resynchronization therapy often also fulfil criteria for ICD implantation. However, as the benefit of ICD implantation is related to the risk of sudden cardiac death and this risk decreases markedly with cardiac resynchronization therapy, the benefit of ICD implantation might be considerably less than in patients who do not receive concomitant cardiac resynchronization therapy. Indeed, observational data suggest this is the case [16, 18]. In addition, while the COMPANION trial did find an effect of adding a defibrillator to cardiac resynchronization therapy in patients with nonischemic heart failure, DANISH did not, and taken together, there is no statistical evidence of effect (Fig. 1.4).

Thus, there is not much evidence to support the use of defibrillators in patients with nonischemic heart failure who are candidates for cardiac resynchronization therapy. However, guidelines advocate the use of a defibrillator with cardiac resynchronization therapy, and given that the risk associated with implantation of a defibrillator electrode instead of a normal right ventricular electrode is small, it might be argued that any benefit from adding a defibrillator, however small, is risk- and cost-effective.

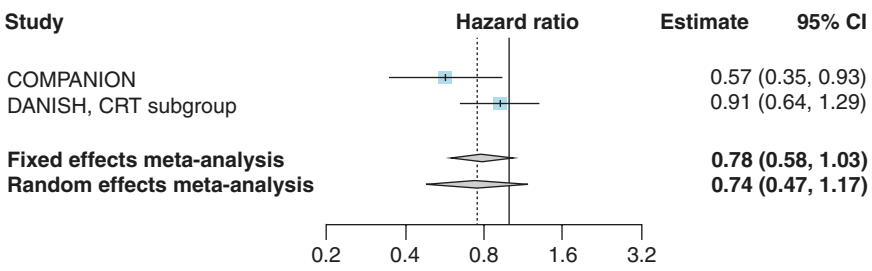

Fig. 1.4 Meta-analysis of the effect of ICD implantation in addition to cardiac resynchronization therapy on all-cause death in patients with nonsichemic cardiomyopathy. Lower hazard ratio favors ICD

Conclusion

In summary, ICD implantation for patients with nonischemic heart failure is recommended by international guidelines for secondary prevention, as well as for primary prevention in patients who are symptomatic with left ventricular ejection fraction below 35%. Further efforts to identify patients who are likely to benefit from ICD implantation are under way. In the meantime, individual patient characteristics indicating likelihood of dying suddenly should be taken into account, particularly for older patients.

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