Peer reviewed article

Therapy with an implantable cardioverter defibrillator (ICD) in patients with coronary artery disease and dilated cardiomyopathy: benefits and disadvantages

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Summary

Contemporary guidelines refer to ICD implantation in patients who experienced ventricular tachycardia or fibrillation as secondary prevention, and in well-defined high risk groups as primary prevention. Randomised studies were performed in patients with coronary artery disease and in non-ischaemic cardiopathies, chiefly dilated cardiomyopathy. After four years' follow-up the absolute risk reduction was some 10% in secondary prevention and 8–20% in primary prevention, depending on the patient population.

As only approx. 50% of ICD patients will receive appropriate therapies during long-term follow-up, reasonable risk stratification is crucial. However, apart from ejection fraction of <35%, all other echo- or electrocardiographic factors studied have thus far failed to have significant impact to determine risk in advance.

In a retrospective analysis comorbidities such as advanced age, renal failure and atrial fibrillation have been shown to influence the effect of an ICD.

During long term follow-up inappropriate shocks, lead complications, premature battery depletion and anxiety are some of the most significant problems for an ICD patient.

Key words: implantable cardioverter-defibrillator; coronary artery disease; dilated cardiomyopathy; competing risks; risk stratification

Introduction

In several large randomised studies the implantable cardioverter-defibrillator (ICD) has been shown to offer a significant survival benefit in primary and secondary prevention of sudden cardiac death (SCD), particularly in patients with coronary artery disease (CAD) [1–4]. Despite these obvious benefits, concerns have been expressed regarding certain disadvantages of ICD therapy. These include morbidity due to appropriate and inappropriate shocks, recalls, lead fractures and the high implantation and follow-up costs of the device. Finally, the optimal strategy for patient selection is still under debate, since only approx. half of patients experience ICD therapies (shocks or antitachycardia pacing [ATP]).

This review article will discuss all these topics. As more than 90% of ICD patients have either CAD or dilated cardiomyopathy (DCM), this review will confine itself to these pathologies. Indications for additional biventricular pacing (cardiac resynchronisation therapy, CRT) have been discussed in an earlier contribution [5] and exceed the scope of this review article.

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Indications for implantation

On the basis of the randomised trials mentioned above, the current guidelines [6] list the indications for ICD implantation in well defined patient groups. These indications are summarised in table 1. Briefly, a left ventricular ejection fraction (LVEF) of ≤35% is an indication for ICD implantation for primary prevention. In the secondary prevention setting, patients with sustained monomorphic ventricular tachycardias (VT) with or without haemodynamic compromise, and those

Table 1

Indication for ICD implantation according to current guidelines.

Coronary artery disease	
Primary prevention	
LVEF <35% >4 weeks after MI, NYHA II/III	Class I, Level A
LVEF <30% >4 weeks after MI, NYHA I	Class I, Level A
LVEF <40%, NSVT during Holter with inducible	Class I, Level B ventricular tachycardia
LVEF 30–35%, NYHA I	??
Secondary prevention	
SCD survivor	Class I, Level A
Sustained ventricular tachycardia (even asymptomatic)	Class I, Level B
Syncope with inducible ventricular tachycardia	Class I, Level B
Dilated cardiomyopathy	
Primary prevention	
LVEF <35%, NYHA II/III	Class I, Level B
LVEF <35%, NYHA I	Class 2b, Level C
Secondary prevention	
SCD survivor	Class I, Level A
Sustained ventricular tachycardia (even asymptomatic)	Class I, Level B
Syncope with inducible ventricular tachycardia	Class I, Level B

LVEF = left ventricular ejection fraction; NSVT = non-sustained ventricular tachycardia (>3 beats with frequency, >120 bpm); SCD = sudden cardiac death

with aborted SCD due to ventricular fibrillation (VF), qualify for ICD implantation irrespective of LVEF. However, there are caveats. Reversible causes of VF, such as, for example, VF during acute myocardial infarction, severe electrolyte dysbalances, critical coronary artery stenosis in combination with the occurrence of VF during exercise, or polymorphic VF associated with complete AV-block, need special consideration. In patients with coronary artery disease it is highly recommended that implantation be postponed for at least 40 days after acute myocardial infarction and for at least 3 months after bypass surgery, to allow for spontaneous or drug-induced recovery from LV dysfunction. If LVEF is >35% at that time, ICD implantation is not indicated. In addition, contemporary heart failure therapy aiming at target doses is mandatory, especially in patients with dilated cardiomyopathy. This approach with delayed ICD implantation is feasible and probably safe for patients, though it has not been tested prospectively. It is supported by the Kaplan-Meier curves from the SCD-HeFT trial [4], where the survival benefit of ICD patients could be demonstrated only beyond year one of follow-up. Similarly, in a subgroup analysis of the MADIT-II population [7], no benefit was seen in patients who received the ICD within six months of any revascularisation procedure.

One must bear in mind that cardiologists involved in decision-making regarding ICD implantation know much about inclusion criteria, but less about the respective exclusion criteria applied in the different trials and the resultant selection bias towards a patient group at high risk of SCD with otherwise low mortality and morbidity. Thus patient selection criteria from guidelines derived from trial efficacy considerations may not necessarily generalise to less selected patients from a common clinical population.

Finally, the risk of overall mortality and SCD is higher in patients with CAD than in those with DCM presenting with the same LVEF.

Evidence of ICD therapy

The evidence for secondary prevention stems from an individual patient data meta-analysis of Connolly [8] encompassing the three randomised trials AVID, CASH and CIDS, which compared ICD with medical therapy. Almost 2000 patients were included, more than 85% with coronary artery disease and 50% with ventricular fibrillation as the presenting arrhythmia. It is worthy of note that the mean baseline LVEF was 34%, whereas at discharge only 20–40% of patients were on beta-blocker and 65% on ACE-inhibitor therapy. This lack of optimal medical therapy, which should have been overcome in a contemporary population, certainly influenced overall mortality, even though we do not know these patients' mode of death. Overall, a significant reduction in relative mortality was observed (pooled hazard ratio 0.73, 95% CI 0.60–0.87). Absolute risk reduction attained some 8% after three and 9% after four years' follow-up. In the subgroup analysis, however, patients with an LVEF of >35% showed no survival benefit whereas those with an LVEF of

Table 2
Mortality rates and risk reductions based on four primary prevention ICD trials.

Randomised trial	MADIT	MUSTT	MADIT-2	SCD-HeFT
3-year absolute risk reduction	26%	20%	9%	7%
4-year absolute risk reduction	20%	21%	n.a.	8%
Relative risk reduction	54%	27%	31%	21%
NNT for one aborted SCD over 3 years	3.8	5	11.1	14.3
Mortality in ICD group	16%	17%	22%	16%
Mortality in control group	42%	37%	31%	23%

<35% had an absolute risk reduction of 14%. Patients with non-ischaemic cardiomyopathy did not derive significant survival benefit either, but this was probably due to lack of power.

The four large primary prevention trials in a heterogeneous ischaemic and non-ischaemic population included patients with various risk constellations [1–4] for arrhythmic death. With accruing evidence the inclusion criteria broadened. In the MADIT I trial [1], eligibility was defined as LVEF <35% and non-suppressible ventricular tachyarrhythmias on electrophysiological study. The only inclusion criterion in SCD-HeFT [4] was an LVEF <35% regardless of the underlying heart disease. Extending the indications was not reflected in a relative reduction of mortality but in a decreased absolute risk and consequently a larger number-needed-to-treat to save the life of one patient. Due to improved heart failure therapy over time the mortality rate in the control group decreased, whereas it remained stable in the ICD group. Detailed numbers are given in table 2.

In ischaemic cardiomyopathy there is strong evidence for benefit from ICD therapy stemming from the MADIT-I and II trials [1, 3], the MUSTT trial [2], in which only patients with CAD were included, and the subgroup analysis of SCD-HeFT [4].

In non-ischaemic cardiomyopathy the benefit from the ICD is still under debate, even though guidelines give clear indications when to implant an ICD. All four pure ICD trials for primary prevention [9–12] failed to show a significant survival benefit in the ICD group, most probably due to the lower than expected mortality rate in the control group and a resulting lack of power. Only a meta-analysis [13] was able to show improved survival with the ICD (relative risk reduction in all-cause mortality of 26%, 95% CI 0.58–0.96). However, the absolute risk reduction was calculated as 2%/year, thus leading to a high number-needed-to-treat.

Subgroup analysis in primary prevention trials

Regarding different subgroups the results are conflicting. In MADIT-II, patients aged over 70 years had similar benefit to younger ones, whereas SCD-HeFT patients over 65 did not have this benefit. In patients with a QRS duration of <150 ms [3] or <120 ms [4] the results were not clearly in favour of ICD therapy. Prolonged QRS duration, usually due to left bundle branch block, is often seen in more advanced cardiac disease. The use of CRT devices in these patients might have led to even greater benefit due to the reduced heart failure mortality rate documented in CRT trials [14].

Regarding the influence of the clinically apparent degree of heart failure the results are not congruent, even though it seems that sicker patients received more benefit. In MADIT-II, only patients in NYHA class I had a significant survival benefit, whereas SCD-HeFT patients in NYHA classes I to III showed favourable results with the ICD. Finally, in patients with an LVEF of >25% and >30% respectively, no benefit from ICD therapy was observed. A retrospective analysis of our own primary prevention patients (unpublished data) showed no difference regarding the occurrence of ICD interventions between groups during follow-up, irrespective of whether an LVEF of 20%, 25% or 30% was chosen as cut-off.

Risk scoring

Apart from LVEF alone, other electrophysiological predictors of mortality were tested for their ability in selecting candidates for ICD therapy, but neither T-wave alternans [15], inducibility in an electrophysiological study [16] nor heart rate turbulence [17] had any impact on mortality and arrhythmic events [15], arrhythmic events [16] or all-cause mortality [17] in substudies of MADIT-II and SCD-HeFT. However, in a study encompassing all patients from the MUSTT registry (i.e., those who received an ICD, those with antiarrhythmic therapy and those with only stan-

Table 3

Mortality according to the MADIT-II risk score [21]:

Risk score	ICD group	Non-ICD group	p-value
0	7%	8%	0.9
1	9%	22%	0.001
2	15%	32%	<0.001
≥3	29%	32%	0.45

The risk score is calculated by adding the following factors, if present: presence of atrial fibrillation, NYHA >II, QRS duration >120 ms, age >70 and BUN >9 mmol/l

dard cardiovascular drug therapy), both ejection fraction </> 30% and inducible/non-inducible VTs were combined [18]. Those patients with a LVEF >30% and non-inducibility had by far the lowest mortality. LVEF and inducibility were independent predictors of both total and arrhythmic mortality. In the light of results from the MUSTT trial, electrophysiological testing may thus be an option in patients with an LVEF of 30–35%

In a subanalysis of the ICD arm of the MADIT-II trial [19], predictors of subsequent ICD therapy for either VT or VF were determined. Sicker patients, i.e., those with a higher NYHA class, renal failure, obesity, digitalis therapy or lack of beta-blockade, had a higher risk, as those with interim hospitalisation for heart failure.

Another interesting aspect is the appropriate timing of ICD implantation. In primary prevention guidelines recommend an interval of 40 days after myocardial infarction and three months after bypass surgery. This is based on two observations. Firstly, the DINAMIT trial (in this study [20] patients were included 6–40 days after the infarction) showed no benefit from ICD therapy compared with best medical therapy. Secondly, a substantial proportion of patients experience a remarkable improvement in LVEF within a few weeks of infarction, due to early stunning and subsequent recovery of myocardial contractility. Similarly, a post-hoc analysis of the MADIT-II trial [7] also failed to show a benefit from the ICD if implanted within six months of any kind of revascularisation procedure. On the other hand, patients who received an ICD late (i.e., >60 months after revascularisation) had the greatest benefit. This is probably due to the treatment of incidental VF when the underlying cardiac disease progresses over time.

A simple and convincing risk scoring model to predict mortality has been developed recently, again using the MADIT-II database [21]. First, 17 prespecified parameters were tested in a univariate model. These factors included clinical, laboratory and electrocardiographic parameters. After an additional stepwise regression, five independent predictors determined at the time of ICD implantation emerged: presence of atrial fibrillation, NYHA >II, QRS duration >120 ms, age >70 and BUN >9 mmol/L. Finally, a score was derived where simply those predictors are added, given that they are present. It became obvious that only patients with an intermediate score benefited from ICD implantation. The details are shown in table 3. A subset of patients expected to represent a population with a very high risk of all-cause death was excluded upfront and analysed separately. Those were patients with severe renal dysfunction (BUN >18 mmol/L and/or creatinine >230 mmol/L). With or without an ICD they did indeed have a two-year mortality of more than 50% and did not benefit at all from ICD implantation. In their discussion, the authors mention that this score was derived retrospectively and could not be tested in a prospective cohort. However, due to the clear-cut ICD indications it will not be possible to test this or any other algorithm in a prospective trial in the near future, and the one presented should be used regularly from now on.

A similar score [22] was derived using the MUSTT population and including mainly clinical and echocardiographic parameters. Due to the much more complex scoring system (e.g., NYHA class II = 7 points; history of atrial fibrillation = 11 points) and other limitations, this algorithm is not easily applicable in everyday practice.

Apart from determination of LVEF, there are still no other convincing stratification methods of identifying more precisely those patients at very high risk of SCD. Identifying those patients would definitely be very important, since we know that only half of patients ever need their ICD. The risk score [21] designed by Goldenberg is a valuable tool pointing in the right direction.

Competing risks

Guidelines are not very precise regarding the impact of severe comorbidities on the indication for ICD. Only NYHA class IV and any disease limiting expected survival to less than one year are listed as “contraindications”. Severe renal failure has already been mentioned as another caveat. Advanced age in itself is not a limiting factor.

Our group has recently highlighted the importance of explicitly considering competing risks in decision-making before ICD implantation [23]. The concept is based on the fourfold table shown in figure 2. Applying this to ICD patients it is obvious that two mutually exclusive and therefore competing risks exist: appropriate ICD therapies and death prior to any ICD intervention. Using the fourfold table, there is one optimal fold (patient received ICD therapies and thus enjoys prolonged survival), one unwanted fold (patient dies without prior ICD therapy) and two intermediate folds (patient dies and has received ICD therapies,

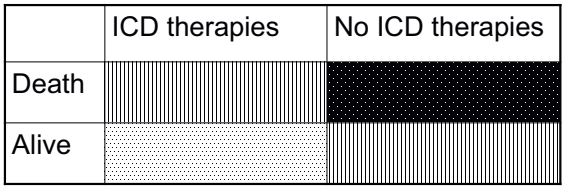

Figure 1

Fourfold table of dead/survival and occurrence of ICD therapies showing the optimal fold (bright dotted), the two intermediate folds (dashed) and the unwanted fold (dark dotted).

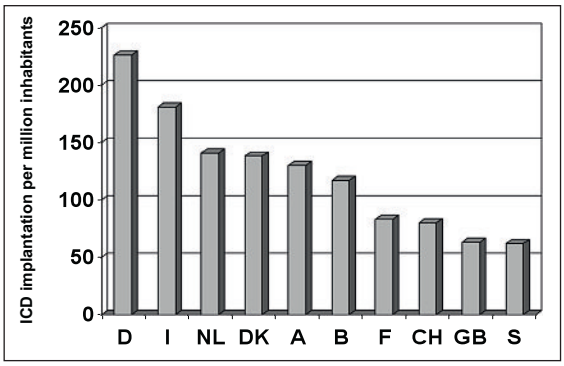

Figure 2

ICD implant rates in various Western European countries in 2006 (modified after [34]).
D = Germany,
I = Italy,
NL = the Netherlands,
DK = Denmark,
A = Austria,
B = Belgium,
F = France,
CH = Switzerland,
GB = Great Britain,
S = Sweden

which can be seen as a good event if he survived reasonably long after the ICD, or as a bad event if ICD therapy preceded death by only a few days or weeks; patient is alive and never needed ICD therapy, which is an undesirable fold from an economic point of view). Randomised trials did not consider this aspect of competing risks since patients with a high mortality risk for cardiac or non-cardiac reasons were excluded.

We studied the extent of competing risks on the basis of a prospective ICD registry. Almost 50% of patients received ICD therapy. However, 11% died prior to any ICD intervention, representing the black fold in figure 1. A relevant predictor for this competing risk was heart failure, as indicated by the need for diuretic therapy. Taking only true ventricular fibrillation as a surrogate marker for death, hardly any first episode of VF occurred after three years (one aspect of the competing risk model thus became negligible), while a further 15% of patients died without any ICD therapy, so that this aspect became more and more relevant.

Drawbacks of ICD therapy

Inappropriate shocks

The term inappropriate shock refers to all shocks delivered for non-ventricular arrhythmias, i.e., sinus tachycardia, atrial fibrillation, supraventricular re-entry tachycardia, and shocks delivered due to technical "failures", i.e., noise or T-wave oversensing. In the latter two situations the ICD senses either "noise" (e.g., due to lead fracture, pectoral muscle contraction, MRI signals etc) or both the QRS complex and the T wave (leading to a doubling of heart rate) and delivers a shock. As all these "arrhythmias" tend to have no major impact on cardiac output, these shocks therefore strike the patient unexpectedly, which renders the shock even more uncomfortable than appropriate shocks. It is difficult to give an exact rate of inappropriate shocks, as they depend heavily on the device settings (cut-off rate; time interval to detection and therapy etc) and on drugs influencing AV-nodal conduction. In some patients cardiologists programme a so-called "shock box" (VF detection e.g., >220 bpm) to keep inappropriate shocks to a minimum. In contrast, physically active patients with a cut-off zone of, for example, 170 bpm are much more prone to inadequate delivery of ICD therapy. The programming of discrimination algorithms able to differentiate between supraventricular and ventricular tachycardia can help to reduce the rate of inappropriate shocks.

The occurrence of inappropriate shocks has been investigated in MADIT-II patients [24]. However, interpretation of the results was complicated by the fact that cut-off rates (i.e., the heart rate above which the ICD starts to deliver therapy) were left to the discretion of the treating physicians and not reported in detail. After a follow-up of two years, 11% of patients suffered from at least one inappropriate shock and 30% of all shocks were delivered inappropriately. Rapidly conducted atrial fibrillation was the cause in 44%, regular supraventricular tachycardias in 38%, and sensing problems in 20%. Interestingly, patients with inappropriate shocks had a 2.3-fold higher mortality.

Future studies will focus on using more sophisticated discrimination algorithms or prolonged detection intervals to further reduce inappropriate shocks. Cardiologists and general practitioners must be aware of their responsibility for prescribing adequate drug therapy to support device programming and avoid inappropriate shocks.

ICD lead malfunction

Another relevant problem that is sometimes ignored is the limited longevity of ICD leads. They are susceptible to dislocation and fracture, resulting in loss of pacing and sensing functions and impeded delivery of shocks, or to inappropriate shocks due to noise sensing. Usually these problems require surgical revision, result in discomfort for the patient and carry a risk of infection. Two papers recently addressed this topic [25, 26]. A single centre registry [23] from Germany with 1000 patients reported a 10-year incidence of 20% lead failure necessitating surgical revision. Malfunction was independent of calendar year of implant. Most malfunctions were due to insulation problems (55%); fracture, impedance and sensing problems or exit block were seen less often (all approx. 10%). According to the problem encountered, malfunction occurred earlier (exit

block) or later (fracture) during follow-up. This high rate of lead malfunction was recently challenged by a paper from our group [26], where a different approach to calculate the malfunction incidence was adopted. In this series of 1300 patients lead revision was necessary in only 2.5% after five years. A feature of note was that patients who presented once with a lead problem had a much higher risk of developing a second or even third lead problem, irrespective of the chosen approach to solve the problem (i.e., implantation of a new ICD lead or of a pacemaker lead only). These patients warrant very careful observation during further follow-up.

Costs and device longevity

The high implantation costs in particular (€30000 to 35000 e.g., in Switzerland), not to mention follow-up costs (regular ICD interrogations, replacements, complications etc.), may result in limited implantation rates in countries with even more restricted health care budgets than Switzerland. Costs add up with higher numbers-needed-to-treat in certain risk categories, and can become unreasonably high. Device longevity, depending on several factors such as the need for additional pacing, number of shocks applied and manufacturer characteristics, can be as much as five years [27]. Then surgical replacement, again with additional costs and infection risk, is necessary.

Anxiety and depression

Psychological problems in ICD patients have been recognised as a major long-term problem, even though most cardiologists and general practitioners may not be aware of the implications for their patients' well-being. Ladwig et al. [28] stated that in most patients ICD implantation initially results in a feeling of relief and safety, which persists in the majority over a long period of time. This seems to be paired with some kind of dependence on the correct functioning of the device. Fortunately, only a minority of patients react to such feelings of dependence with serious maladaption and hopelessness.

Lemon et al. [29] followed 49 patients for up to six months after implantation. Initially, anxiety was present in about 30% and clinically significant depression in some 15%. Interestingly, anxiety decreased during follow-up, suggesting that it was associated with high-threat situations such as aborted SCD or device implantation, but became less important once there was some distance from the event.

Answering a standardised and well evaluated questionnaire on anxiety and depressive symptoms, 26% of Dutch ICD patients stated that they regularly used psychotropic drugs, 32% reported anxiety and 28% depressive symptoms [30]. The questionnaire differentiated between specific ICD concerns (e.g., thoughts of fear of ICD firing or becoming stressed in case of firing) and general anxiety and depression. "High concern" patients who never experienced ICD shocks had higher anxiety and depression scores than "low concern" patients with shocks. The authors recommend addressing such concerns as early as possible, even before device implantation, since otherwise they are bound to persist and impose serious morbidity problems on many patients.

End-of-life situation

In critically ill patients, e.g., end-stage heart failure or end-stage cancer, the situation should be discussed with the patient. In many cases it may be reasonable to deactivate the ICD, so that any tachyarrhythmia would no longer be treated.

Areas of uncertainty and need for patient-oriented clinical research

Determination of LVEF is crucial in decision-making, and cardiologists use different methods to determine it. Echocardiography is most often used, but MRI, radionuclear imaging and LV-laevogram may be used as well. All these methods have their limitations and offer considerable intra- and inter-observer variability. A gold standard has not been determined and current guidelines advise cardiologists to "use the LVEF determination that they feel is the most clinically accurate and appropriate in their institution" [6]. It might be reasonable in patients with a borderline LVEF of around 35% to use a second method of LVEF determination in a quest for greater precision.

Guidelines recommend an ICD for patients with a primary prevention indication whose LVEF is <35%. However, in the corresponding trials, mean LVEF was 23% [3] and 24% [4] respectively, with inclusion criteria being LVEF <35%!

Another aspect, which will become increasingly important, is the question how to counsel a patient who needs an ICD replacement but has never experienced an ICD intervention. Typical examples of this scenario in our experience are patients with idiopathic VF without arrhythmias during long-term follow-up, or patients with DCM whose LVEF improved to 45–50%. Many medical, economic, psychosocial and legal implications add to the complexity of this field. The current policy might be called "once ICD, always ICD". Industry-independent studies are urgently needed to collect data on issues such as risk assessment, patient preference, or downgrading to a simpler device at the time of impending ICD replacement.

New ICDs with subcutaneous instead of intravenous leads are currently being evaluated. They will be less expensive and do not involve the disadvantages of intravenous lead infection, but are able to deliver antitachycardia- and antibradycardia-pacing only for a short post-shock period. They might be used in primary prevention, in patients with genetic diseases such as Brugada or long-QT syndrome and in patients with aborted sudden death due to VF. The future will show whether these new ICDs are reliable and effective enough to challenge conventional ICDs.

Looking at the implant rate in Switzerland, it seems that this country, with still sufficient resources to offer optimal care, has adopted this duality of pros and cons of ICD therapy quite reasonably. Implant rate is about 80/million population, compared to front-runners such as Germany or Italy (230 and 180/million respectively) [31]. An overview of implant rates in various Western European countries is given in figure 2.

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