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REVIEW

Preventive implantable cardioverter defibrillator therapy in contemporary clinical practice: need for more stringent selection criteria

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Abstract

While the efficacy of the intracardiac defibrillators (ICDs) for primary prevention is not disputed, the relevant studies were carried out a long time ago. Most pertinent trials, including MADIT-II, SCD-Heft, and DEFINITE, recruited patients more than 20 years ago. Since then, improved therapeutic modalities including, in addition to cardiac resynchronization therapy, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and, most recently, inhibitors of sodium-glucose cotransporter 2, have lowered present-day rates of mortality and of sudden cardiac death. Thus, nowadays, ICD therapy may be less effective than previously reported, and not as beneficial as many people currently believe. However, criteria for ICD implantation remain very inclusive. The patient must (only) be symptomatic and have ejection fraction (EF) $\leq$ 35%. The choice of EF 35% is notable because the average EF in all large trials was much lower, and clinical benefit was mainly limited to EF $\leq$ 30%. This EF cut-off value defines a substantial portion of potential ICD recipients. It seems therefore reasonable to limit ICD eligibility criteria in the EF range 30–35% to patients at highest risk only. We discuss and present some rational criteria to assist the clinician in improving risk stratification for preventive ICD implantation.

Keywords Intracardiac defibrillator; Ischaemic cardiomyopathy; Non-ischaemic cardiomyopathy; Left ventricular ejection fraction; Primary prevention

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Introduction

Each month, over 10 000 implantable cardioverter defibrillator (ICD) are being implanted in the USA alone, while the overall volume of worldwide implantations continues to increase as well.[1–3] Most devices are implanted in patients at high risk of sustained ventricular tachycardia or fibrillation.[2] While the efficacy of the ICDs for this indication—primary prevention—is not disputed, it is fair to say that the relevant studies were carried out a long time ago.[4–10] Most trial reports date from early this century, implying that their results were obtained in—and in theory thus only applicable to—patients treated over 20 years ago. Since then, the principle of electric shock for life-threatening arrhythmias has not changed much, while other therapeutic options have progressed and rates of sudden cardiac death have decreased.[11] Thus, present-day ICD therapy may be less effective than previously reported, and not as beneficial as many people currently believe. This assessment is validated by the results of the most recent and large study on preventive ICD implantation, which reported only a minor survival advantage of ICD placement compared with usual clinical care in individuals with a cardiomyopathy of non-ischaemic origin.[12] Admittedly, patients with ischaemic heart disease (IHD) are at higher risk of sudden cardiac death, but their recruitment in the applicable trials also dates back two decades, and the therapy that they received reflects that. Therefore, time has

come for an updated qualitative assessment of current indications for preventive ICD therapy, and that is the aim of our paper.

The trials

In ischaemic heart disease

Preventive ICD implantation in IHD has been investigated in seven randomized trials.[4–10] MADIT I and MUSTT started enrolment in 1990 (see *Table 1* for characteristics of both studies). Electrophysiological investigation (EP) was needed prior to inclusion in both, a requirement that has been abandoned in subsequent trials.[4,6] In fact, MUSTT was a comparison of EP guided versus 'conventional' therapy, and, among the 351 randomized to EP guided therapy, 161 (46%) patients initially received defibrillators. Two 'negative' trials—DINAMIT and IRIS—took place shortly (within 40 days) after myocardial infarction (MI) and resulted in the contra-indication of ICD implantation in early post-MI survivors.[8,10] The CABG Patch trial was performed in patients undergoing surgical coronary revascularization but found no benefit of ICD insertion in that population.[5] Thus, MADIT II and SCD-Heft comprise the most recent trials favouring ICD implantation in IHD.[7,9] Because of their significance, both—so-called landmark—trials are described in some detail. Additional details are presented in *Table 1*.

Starting in July 1997, MADIT II randomized 1232 post-MI patients with advanced left ventricular (LV) dysfunction, defined as LV ejection fraction (EF) $\leq$ 30% (*Table 1*).[7] The hazard ratio for mortality was 0.69, but the plausible effect range was wide [95% confidence interval (CI) 0.51–0.93].

From September 1997 onwards, SCD-Heft evaluated prophylactic ICD therapy versus placebo (as well as vs. amiodarone) in three groups each of about 840 patients with symptomatic congestive heart failure and EF $\leq$ 35%.[9] The cardiomyopathy was of ischaemic origin in approximately 50% of the patients. Compared with placebo, ICD implantation was associated with a 23% (95% CI 4–38%) reduction in mortality. The largest survival benefit was observed in patients with New York Heart Association (NYHA) class II heart failure and with LVEF $\leq$ 30%, characteristics present in 70–80% of patients included.

In non-ischaemic cardiomyopathy

As described earlier, SCD-Heft was a mixed trial of patients with ischaemic as well as non-ischaemic heart disease. Randomized trials of preventive ICD therapy in patients with exclusively non-ischaemic heart disease include—in chronological order—CAT, AMIOVIRT, DEFINITE, and the DANISH study.[12–15] Both CAT and AMIOVIRT were quite small, each

Table 1 Characteristics and outcome of randomized trials of intracardiac defibrillator implantation and novel pharmacotherapies in ischaemic and non-ischaemic heart disease

Trial name	Intervention	Year of publication	Number[a]	Number with IHD[a]	Annual death rate	Inclusion EF	Mean EF	Mortality reduction	ACE inhibition	Beta-blockers	MRAs
MADIT-I	ICD in IHD	1996	93	93	12%	≤35%	26%	54%	54%	23%	Unk
MUSTT	EP guided therapy	1999	351	351	10%	≤40%	30%	60%	Unk	40%	Unk
MADIT-II	ICD in IHD	2002	742	742	9%	≤30%	23%	31%	70%	70%	Unk
SCD-Heft	ICD 'mixed'	2005	829	431	10%	≤35%	25%	23%	94%	69%	20%
DEFINITE	ICD dilated CM	2004	229	NA	6%	≤35%	21%	35%	84%	85%	Unk
Danish trial[b]	ICD dilated CM	2016	556	NA	4%	≤35%	25%	13%	97%	92%	57%
EPHESUS[c]	MRA	2003	3319	3319	8%	< 40%	33%	15%	87%	75%	100%[e]
EMPHASIS	MRA	2011	1364	951	7%	≤30%	26%	22%	94%	87%	100%[e]
PARADIGM	LCZ696	2014	4187	2506	7%	≤35%[d]	30%	16%	100%[e]	93%	54%
DAPA-HF	SGLT2	2019	2373	1316	7%	≤40%	31%	17%	95%	96%	71%

ACE, angiotensin-converting enzyme; CM, cardiomyopathy; EF, ejection fraction; ICD, intracardiac defibrillator; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NA, not applicable; SGLT2, sodium-glucose cotransporter 2 inhibitor; Unk, unknown.
[a]Number of patients in the active treatment arm.
[b]Cardiomyopathy of non-ischaemic origin.
[c]Early post-myocardial infarction patients, high initial mortality.
[d]After protocol modification.
[e]By trial design.

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including about 100 patients. Enrolment in CAT began in 1991 and required—among others—EF $\leq$ 30%.[13] The number of deaths in patients randomized to ICD (n = 13) or medical therapy (n = 17) was not different; the main predictor of mortality was low EF. Recruitment in AMIOVIRT commenced in August 1996 and was completed by September 2000, with the purpose to compare total mortality during therapy with amiodarone or ICD.[14] The inclusion EF was $\leq$35%, but the mean EF of the included patients was much lower, namely, 23%. Survival at 3 years was similar among patients treated with ICD (88%) and amiodarone (87%).

DEFINITE randomized 458 symptomatic patients with LVEF $\leq$ 35% and ambient arrhythmias.[15] The first patient was randomized in 1998; mean EF was 21%. With 28 and 40 deaths in the ICD and control groups, respectively, the point estimate of the difference in mortality was sizeable (hazard ratio 0.65, 95% CI 0.40–1.06), although not statistically significant.

The DANISH study is the most recent and largest trial in non-ischaemic cardiomyopathy.[12] This study randomized 556 patients with symptomatic systolic heart failure and EF $\leq$ 35% to ICD, and 560 to usual clinical care. After a median follow-up of almost 6 years, 120 patients in the ICD and 131 patients in the control groups had died (hazard ratio 0.87, 95% CI 0.68–1.12, P = 0.28). Although ICD placement was effective in lowering the rate of sudden cardiac death, from 8.2% to 4.3%, the authors concluded that prophylactic ICD implantation did not reduce long-term mortality.

When the data from the various trials are combined, the mortality benefits associated with preventive ICD insertion in non-ischaemic disease typically range from 19% to 25%.[16–19] Details of the two largest trials, DEFINITE and the DANISH study, are presented in *Table 1*.

Current therapeutic options

Medical treatment in the two first landmark trials in IHD, MADIT-II and SCD-Heft, was probably standard for that time period, although usage of beta-blockers and mineralocorticoid receptor antagonists was relatively modest while, as a reflection of previous clinical practice, digoxin was used frequently. But in the next 20 years, further therapeutic advancements have become available for patients with LV dysfunction, with significant bearing on their outcome.

One relevant development in the treatment of patients with heart failure includes the introduction of cardiac resynchronization therapy (CRT) and with or without ICD. The COMPANION investigators established the worth of this treatment modality in 1520 patients with advanced (NYHA class III and IV) heart failure, 57% of them with IHD. Most patients, with mean EF of 22%, received contemporary medical treatment. One-year mortality, almost 20%, was very high. The combination of CRT and defibrillator was successful in reducing all-cause mortality with 34%.[16] CRT has since become recommended standard therapy in patients with symptomatic heart failure in sinus rhythm and with EF $\leq$ 35%, QRS duration $\geq$ 150 ms, and left bundle branch block QRS morphology.[17]

The most relevant developments in the medical treatment of patient with symptomatic heart failure include the mineralocorticoid receptor antagonists, the angiotensin receptor-neprilysin inhibitors, and, most recently, inhibitors of sodium-glucose cotransporter 2 (SGLT2).[18–21] Both eplerenone and spironolactone—not separately reported in DEFINITE, infrequently used in MADIT-II and SCD-Heft, and employed in about 60% of patients in the DANISH trial—were found to lower mortality with 20% in advanced heart failure.[18,19] Neprilysin inhibition with LCZ696 *in lieu* of angiotensin-converting enzyme inhibition and associated with a relative and absolute reduction in mortality of 16% and 1.8%, respectively, was not used in any of the preventive ICD trials.[20] And neither was the SGLT2 inhibitor, a relatively novel drug that lowered mortality with (relative) 17% and (absolute) 2.8% compared with recommended therapy in symptomatic patients with heart failure.[21] The main characteristics of the largest modern-day heart failure drug trials are also given in *Table 1*.

The data in *Table 1* illustrate the limited use of currently available optimal medical treatment in the early trials, just as the—probably partly ensuing—high event rates of the early studies compared with the more recent. In addition, it is obvious that event rates in non-ischaemic cardiomyopathy are lower than in IHD. The data in *Table 1* make it also clear that the benefits of each of the new therapeutic modalities clearly fall within the plausible effect ranges of the most recent ICD trials (while their combined effects could be larger).

Complications and costs

Immediately after their introduction, controversy about the costs and complications associated with ICD implantation was unleashed.[7,22] This debate has continued ever since. The ICD implantation itself carries approximately 9% peri-procedural risk of complication.[23–26] During follow-up, in addition to the regular device interrogations, inappropriate shocks and re-hospitalizations are not uncommon, while generator replacement every 4 to 7 years carries a risk of minor and major complications.[27] A list of short-term and long-term ICD complications is summarized in *Table 2*.

As it currently stands, 25 ICDs are required to save one life.[17,28] In view of their high levels of current employment, the financial burden of preventive ICD implantation

Table 2 Short-term, medium-term, and long-term complication rates of intracardiac defibrillator implantation

Early (peri-implant) [23,24]	
Any	9%
Mortality	0.5%
Pneumothorax	1%
Bleeding	1%
Infection	2%
Other	4%
During 3 to 4 years of follow-up [25,26]	
Inappropriate ICD shock	12%
Device malfunction or lead failure	6%
Device or lead infection	2%
Hospitalization (for other reasons)	3%
Device replacement related [27]	
Any	4%
Stroke	0.5%
Infection/inflammation	2%
Haematoma requiring intervention	2%

ICD, intracardiac defibrillator.

apparently seems to be acceptable at individual levels in rich countries. However, this is much less the case from a societal point of view. Rising numbers of implantations and the prospect of even larger numbers of future patients with heart failure in aging populations are unwelcome from that perspective. It is thus logical that measures have been taken in some countries to minimize the rate of implantations, for instance, by limiting the number of implanting centres. It is unknown whether this has been effective.

Intracardiac defibrillator cost-effectiveness decreases when event rates decline. There can be no doubt that—in addition to the observed decrease in overall mortality observed in the pharmacological trials depicted in *Table 1*—the risk of sudden death has also decreased substantially, reportedly by 44%, in the last decades.[11] Importantly, the absolute rate of sudden death was found to be lower among patients with a recent diagnosis of heart failure, consistent with the cumulative benefit of evidence-based medication on this mode of death. These findings can probably be extrapolated to the population at large.[29] In our region, we have witnessed a reduction of about 40% in the rate of sudden cardiac death in middle-aged and elderly men and women, a much larger decrease than the observed decline in overall mortality in the same population.[30]

Ejection fraction and intracardiac defibrillator selection criteria

Historically, when new and—in their early phase—expensive pharmaceutical agents were introduced, for instance, with the early clinical introduction of angiotensin-converting enzyme inhibitors, statins, and—now—PCSK9 inhibitors, their clinical application has been tailored to men and women at highest risk.[31–33] But this has not been the practice for preventive ICDs. Despite many attempts to identify specific patient groups in whom the devices would be more (cost) effective, such efforts have not resulted in modification of guidance on their use in clinical practice. In fact, with time, the criteria for ICD implantation have only become more inclusive and lenient. Both the European and American guidelines currently state that the patient (only) needs to be symptomatic (NYHA class II or III) and have an EF $\leq$ 35% (while receiving 'optimal' medical treatment).[17,34] In patients with a non-ischaemic cardiomyopathy, treatment with 'optimal' medical treatment for 3 months is additionally advised, although improvement in LV function ('remodelling') may happen after longer period of times.[35,36]

The cut-off value of EF 35% is important because this criterion identifies and defines a large group of potential ICD recipients. For example, exactly 50% of the patients in PARADIGM-HF had an EF between 30% and 35%.[20] Of note, the EF inclusion criterion in SCD-Heft was $\leq$35% and $\leq$30% in MADIT-II, but the average EF in both trials, 25% and 23%, respectively, was much lower, just as in the DANISH study and in DEFINITE. The evidence of ICD benefit in the low EF range is considerable, but this is much less the case when LV function is better preserved. For instance, the positive effects of ICD implantation in SCD-Heft were only observed in patients with EF $\leq$ 30%, who—importantly—comprised 80% of the study population.[9] In MUSTT, with EF $\leq$ 40% as LV function inclusion criterion, the relation between EF and event rates was highly significant whether EF was treated as continuous or dichotomized variable, and total mortality in patients with EF $\leq$ 30% was more than 50% higher compared with EF between 30% and 40%.[37]

Of course, sudden arrhythmic death will continue to occur, but—given the currently available therapeutic options—at a much lower rate than observed in the landmark and other trials.[11] The conclusion that this affects ICD therapy effectiveness is not new and has led to multiple attempts to identify patients at highest risk. But individualized prediction of sudden cardiac death remains notoriously difficult,[38–42] and, despite the development of innovative clinical risk models, the continuing increase in ICD insertions as well as the

Table 3 Factors associated with intracardiac defibrillator benefit or harm in ejection fraction range 30–35%

Factors favouring ICD implant
Ischaemic heart disease
QRS width $\geq$ 150 ms and LBBB[a]
Presence of fibrosis on MRI
Factors not favouring ICD implant
Limited life expectancy
Myocarditis $<$ 6 months
QRS width $<$ 120 ms

ICD, intracardiac defibrillator; LBBB, left bundle branch block; MRI, magnetic resonance imaging.
[a]With cardiac resynchronization therapy.

unchanged guidance in their use indicate that such methods of selection have not been successful.[43,44]

There can be little doubt that, within the EF range between 30% and 35%, the evidence for ICD benefit in primary prevention is limited. This is in particular true in non-ischaemic cardiomyopathy where event rates are lower than in IHD. Of note, the risk of arrhythmic endpoints is reportedly larger in the presence of myocardial fibrosis assessed with late gadolinium enhancement.[45,46] And the finding of such fibrosis, although its relevance has not yet been confirmed in randomized comparisons, may tip the balance in favouring ICD implantation in non-ischaemic cardiomyopathy. In patients with myocarditis, longer duration of medical therapy than 3 months may be necessary to establish improvement of LV function.[35,36] Lastly, patients with normal QRS duration have often been reported to be at relatively low risk, and ICD implantation may be deferred in such instances.[40] *Table 3* provides a summary of these recommendations.

Summary and conclusions

Findings from the landmark ICD trials, interpreted in combination with the clinical evidence and effective therapeutic options since accumulated and set against the costs and the potential complications of ICD implantation, now demand and allow for better and more stringent ICD implant selection criteria in primary prevention. Moreover, while it must be acknowledged that the relationship between LVEF and ICD effectiveness is not straightforward—benefit is both low in those at extremely high and at very low risk—LV function is a major determinant of prognosis in all studies of patients with heart failure, regardless of their cause.[17,47,48] In the most recent and largest trials, ICD benefit was mainly confined to patients with LVEF $\leq$ 30%. At this moment, it seems reasonable to limit the ICD eligibility criteria in the EF range 30–35% to patients at highest risk only and to defer ICD implantation in subjects within this EF range without features suggesting high risk. In *Table 3*, such criteria have been presented. We realize that these cover only a limited selection of risk categories and will only be applicable to a limited number of patients and implant decisions. Nevertheless, we hope that the rational and considerations presented in this paper will gain following and will encourage modifications in clinical practice as well as in future guidance.

It goes without saying that a proper assessment of the contemporary benefit of preventive ICD in patients with relatively mild LV dysfunction, with or without CRT, will require a new randomized clinical trial. The study should include symptomatic patients with heart failure of any cause with an EF above the range currently debated, thus with LVEF over 30%, and must employ baseline imaging techniques detailed enough to establish their worth in subsequent clinical risk stratification. Given the current ICD implantation rates, the recruitment of such patients should be relatively straightforward.

Conflict of interest

None declared.

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