Primary prevention with the ICD in clinical practice: not as straightforward as the guidelines suggest?

F.A.L.E. Bracke, L.R.C. Dekker, P.H. van der Voort, A. Meijer

At first sight, guidelines for implantation of an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death in patients with left ventricular systolic dysfunction seem unambiguous. There are clear cut-off values for ejection fraction, and functional class. However, determination of the ejection fraction itself is not unambiguous, and other risk factors for sudden death that may have a profound effect on risk are not used for decision-making. Furthermore, to obtain a clinically significant impact on survival, expected longevity is important as it can greatly compromise the benefit in elderly patients but underestimate the long-term potential of ICD therapy in younger patients. (*Neth Heart J* 2009; 17:107-10.)

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Guidelines for implantable cardioverter defibrillator (ICD) implantation are a necessary reference for clinical decision-making in primary prevention of sudden cardiac death in patients with left ventricular systolic dysfunction. They may seem straightforward at first sight with clear cut-off values for inclusion primarily based on the ejection fraction.[1-3] However, risk is not dichotomous as suggested, nor equally distributed: some patient groups may profit more while in others ICD therapy may even be futile. Furthermore, patients may differ from the trial populations from which the predictive models have been derived and remain exposed to the risk of sudden death beyond the duration of the trials in real life. Recently, there has been a reappraisal of benefits and potential hazards of ICD therapy.[4] The purpose of this paper is to reflect on the guidelines considering known and potential risk factors that may help in risk stratification in clinical practice.

F.A.L.E. Bracke
L.R.C. Dekker
P.H. van der Voort
A. Meijer
Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands

Correspondence to: F. Bracke
Department of Cardiology, Catharina Hospital, PO Box 1350, 5602 ZA Eindhoven, the Netherlands
E-mail f.bracke@skynet.be

Limitations of current guidelines

The guidelines for primary prevention of sudden arrhythmic death with an ICD in patients with left ventricular systolic dysfunction are factually based on two pivotal trials: MADIT II and SCD-HeFT.[5,6] MADIT II included patients aged <80 years with a history of myocardial infarction for at least one month before inclusion and an LVEF of <30%. SCD-HeFT included both ischaemic and dilated cardiomyopathy patients with an LVEF <35% and stable heart failure class II or III, but had no age limit.

The guidelines, therefore, state that preventive ICD implantation is indicated in patients with LV dysfunction due to prior myocardial infarction who are at least 40 days postmyocardial infarction, have an LVEF <30%, and are in NYHA functional class I (based on MADIT II) and ICD therapy is indicated in patients with nonischaemic or ischaemic dilated cardiomyopathy who have an LVEF ≤35% and who are in NYHA functional class II or III (based on SCD-HeFT).

The implementation of specific cut-off values for LVEF suggests a dichotomous distribution of the risk for SCD.[7] However, mortality increases linearly with ejection fractions <45%.[8] Secondly, patients are selected for ICD implant in daily practice after a single determination of LVEF interpreted at face value without considering the considerable levels of variability due to acquisition and reader interpretation, and especially biological and temporal factors: loading conditions may differ due to variations in intravascular volume, adrenergic state or postabsorptional state after a meal.[9,10] In a recent study, Hare et al. found a 6.4±8.9% variation over time even in clinically stable patients in a single experienced echo lab.[10] Otterstat et al. dem-

onstrated that a difference of 11% was necessary to obtain 95% certainty that a change in LVEF was not the result of confounding factors.[9] On top of this comes the variation from different techniques and levels of experience in acquisition and interpretation of the results. This questions the strict reliance on a difference of the LVEF of one point on either side of the cut-off value to implement ICD therapy.

For patients with ischaemic cardiomyopathy, the guidelines are solely based on an LVEF <30%. But recently Buxton et al. demonstrated in a critical reappraisal of the MUSTT trial that other variables have a similar prognostic significance.[11] Additional risk factors for sudden or arrhythmic death were a history of heart failure, left bundle branch block or QRS width >0.11 s and inducible ventricular arrhythmia. By including these variables, a group of patients with an LVEF of >30% could be defined who had a higher-risk profile than those with only an LVEF of <30% and no additional risk factors in whom two-year total mortality approximated 5%. This is in contrast to the mortality for control patients in the MADIT II population of 22% and of 18% in the SCD-HeFT, suggesting that these trials recruited from a higher risk population. Indeed, two-thirds of patients enrolled in the MADIT II study had symptomatic heart failure (NYHA functional class II or more), and a similar number had an LVEF ≤25%. Furthermore, approximately 50% of the population had a QRS duration of ≥120 ms. Likewise, the prerequisite of heart failure NYHA class II or III in SCD-HeFT resulted in a sicker population. Thus, more risk factors are influencing the outcome of MADIT II and SCD-HeFT populations than suggested by the inclusion criterion of LVEF alone.[6]

Do trials represent current patient populations?

As many of the participants in both trials had indeed one or more additional risk factors, it can be questioned if the patients included in these studies are representative of the general postmyocardial infarction population with a low ejection fraction in the present era. In the VALIANT study, which included more than 14,000 patients with acute myocardial infarction complicated by left ventricular dysfunction, total mortality in patients with an ejection fraction of <30% was 5% per year after the first year with a sudden death rate 2.5% per year.[12,13] Also current aggressive revascularisation strategies may yield different substrates for arrhythmia than in the era of the primary prevention studies, even in the presence of similar ejection fractions.[14,15]

Even in the MADIT II study, Goldenberg et al. reported that the one-third of the study population who possessed no other risk factors than an LVEF <30% had no mortality benefit from the ICD.[16] Conversely, these authors demonstrated that patients with one or two additional risk factors (age >70 years, NYHA functional class >II, blood urea nitrogen (BUN) >9.3 mmol/l and <17.8 mmol/l, atrial fibrillation and QRS duration >120 ms) who comprised more than half of the study population had the greatest benefit from ICD therapy with a two-year mortality of 15% compared with 28% in the control population.

At the other end of the spectrum, in the most diseased patients, the benefit of the ICD is annihilated. In MADIT II patients, when three or more of the mentioned risk factors were present, survival was not superior in the ICD group compared with the conventional group.[16] Especially severe chronic kidney disease delineates a very high-risk population in whom any possible benefit of the ICD is attenuated by the high overall mortality: with BUN >25 mmol/l or creatinine >250 µmol/l, two-year mortality was approximately 50% in both the ICD and conventional therapy group (hazard ratio 1.00, CI 0.5 to 2.2).[16] In a retrospective study of 35 patients with chronic kidney disease, out of 229 who had an ICD implanted for primary prevention, Cuculich et al. registered a one-year survival of 61.8% in patients with a serum creatinine of >177 µmol/l or on chronic dialysis, compared with 96.3% in controls.[17] This lack of benefit in the more diseased population was also apparent in the SCD-HeFT trial: whereas in NYHA class II patients there was a 46% reduction in risk of death, patients in NYHA class III had no advantage with an ICD compared with placebo.

The downside of ICD therapy

What objections, apart from economic considerations, can be made against implanting an ICD in a low-risk patient? First, ICD therapy is not without complications. Although complications in new implants may be low, they are multiplied at the time of generator replacement. In a survey of generator replacements because of device recalls, major complications have been reported in 4.1 to 5.8% of patients.[18,19] Also lead longevity is a major concern in the long term: Kleemann et al. reported that only 60% of leads functioned properly after an eight-year follow-up.[20] Secondly, most patients are not aware of an imminent risk of sudden death when offered ICD therapy, and labelling them as such may profoundly influence the quality of life. It is therefore not surprising that up to 38% of ICD recipients experience symptoms that meet criteria for anxiety disorders, with younger patients and those receiving multiple shocks at greater risk.[21,22] The quality of life is also greatly influenced by inappropriate shocks. These occurred in 11.5% of the MADIT II ICD patients and 15% in the PainFREE RX II trial.[23,24] Younger patients may be more susceptible for inappropriate shocks.[25,26]

Elderly patients and primary ICD implant: an unspoken territory

Guidelines for primary prevention do not refer to any age limits, possibly reflecting that the influence of age on outcome during the study period in both pivotal

trials is ambiguous. When the SCD-HeFT population is dichotomised for age, only patients <65 years showed advantage from an ICD. In contrast, MADIT II showed no significant difference between the predefined age groups. However, in the post-hoc risk analysis of the MADIT II population by Goldenberg et al. age >70 years was one of the risk factors improving the benefit of the ICD.[16] It should be noted that the division according to age in the studies does not reflect what is contemporarily considered as an elderly patient. Nevertheless, it is important to realise that the average age of MADIT II patients was around 64 years, and three quarters of the patients in SCD-HeFT were <69 years: so one can easily argue that both trials generally avoided ICD therapy in the truly elderly patients.

As the life-saving benefit of ICD therapy already commences after about one year, guidelines endorse implantation if life expectancy is at least one year.[1-3] But cost-effectiveness studies of both the MADIT II and SCD-HeFT trial have shown that the cost per life-year saved only started to look acceptable from about five years after device implant for MADIT II and eight years for SCD-HeFT patients under the condition of persistent benefit of ICD therapy after the empirical follow-up of both studies.[27,28] However, the assumption of persistent benefit of the ICD in the elderly population is questionable, as any advantage of the ICD on arrhythmic death may be largely attenuated by a higher total mortality.[29]

Also a combined analysis of the secondary prevention defibrillator trials showed a lack of survival advantage in the >75 years age group due to a high incidence of nonarrhythmic death.[29] Implantation of an ICD in elderly patients has further only been addressed directly in a few nonrandomised cohort studies, recently reviewed by Grimm.[30] Although these studies registered a similar low incidence of sudden death or appropriate shocks in patients below and above 75 years of age, they registered a noticeably increased total mortality in the older group. In this context it is good to note that shocks labelled as appropriate should not automatically considered to be lifesaving as well. In SCD-HeFT 21% of the patients had shocks considered appropriate for fast ventricular tachycardia or fibrillation, yet the absolute reduction in mortality was only 7.2% at five years.[5] Also in the DEFINITE trial, patients in the ICD group experienced twice as many appropriate shocks than there were fatal events in the control group, yet there was no survival difference.[31]

A matter much related to primary implant of an ICD in elderly patients is generator replacement in this patient group. Some patients – often never having received therapy from the ICD – need generator replacement at an age and stage of health at which primary implant would not be considered appropriate. In these circumstances, it may be in the interest of the patient to avoid the discomfort and risks of a generator exchange. In clinical practice, the subject is rarely discussed with the patient and family, and there are no guidelines to assist in handling the situation. However, a timely discussion is necessary as at the time of the generator exchange, the emotional impact of abandoning ICD therapy might be insurmountable.

Conclusions and perspectives

Despite all previous considerations, ICD therapy has proven to be life-saving for many patients, and no other therapy provides such compelling documentation of its effectiveness. Following the guidelines, a multitude of patients who will actually benefit from the ICD need to be treated to achieve this result. However, subgroups of patients who potentially do not benefit from the device are subjected to the therapy if a strict interpretation of the guidelines is applied. Borleffs et al. showed that the current practice of ICD implantation in the Netherlands shows a restrained implementation of the guidelines.[32] The authors related this partly to logistics and the restriction of the number of implanting centres, resulting in a concentration on patients considered to have the most potential clinical benefit and cost-effectiveness from the device.

Before a more liberal implementation of the guidelines will drive the number of implants, further randomised long-term studies are needed to better target ICD therapy in various subgroups as simple registries will not suffice to answer these questions. As argued, there is a rationale for targeting a prospective study aimed at the elderly patient population of ≥75 years.[33] In contrast, attention should be paid to younger patients who may be at risk for a longer period of time than observed in the current studies and may have a potential for a meaningful benefit if followed for a longer time. This has been hinted in a single-centre follow-up study of the CIDS secondary prevention trial, were it is suggested that the benefit of ICD therapy over amiodarone increases over time.[34]

There may be a reluctance to withhold a potential life-saving therapy from patients when randomised in such a study. But it should be realised that half of the victims of sudden cardiac death after myocardial infarction have an LVEF of more than 30% and are currently not eligible for ICD therapy according to the guidelines.[35] In effect, only 10% of all sudden death victims are currently deemed to be at high risk.[36]

There is still a long way to go before we are able to better stratify patients at risk for sudden death. Older and new modalities testing various aspects of electrical stability are used to stratify patients at high and low risk, including T-wave alternans and VT induction for which studies show mixed results.[37-39] Recent studies indicate that genetic factors are strongly involved in sudden death risk caused by common diseases, such as coronary artery disease.[40,41] It is to be expected that these developments will guide the way to the development of additional genetic risk markers helping us to safely withhold ICD therapy in patients at alleged risk,

as well as identify future sudden death victims among patients with heart disease.

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