Primary prevention with ICDs, are we on the right track?

A.A.M. Wilde, T.A. Simmers

There is little doubt that the introduction of internal defibrillators (ICD) has saved many lives over the last two decades. Initially, ICD use was only studied and propagated in resuscitated patients, but from the mid-1990s onwards primary prevention studies have been conducted in patients with ischaemic and non-ischaemic cardiomyopathy and a left ventricular ejection fraction (LVEF) ≤30 to 35%.[1-3] The study results, mostly indicating a beneficial effect of prophylactic ICD implant, were translated into the current guidelines and the use of ICDs has grown exponentially ever since.

In recent months a number of critical reviews, editorials and state-of-art papers question this seemingly unlimited use of ICDs in primary prevention care.[4-6] Since the vast majority of ICD recipients are primary prevention patients and since the growth in ICD use is based solely on prophylactic implants, we will briefly touch upon the most important issues.

Left ventricular ejection fraction (LVEF) is the one entry criterion that is common to all primary prevention studies. In this issue of the *Netherlands Heart Journal* the Eindhoven electrophysiology group nicely reviews the difficulties that exist with LVEF measurement.[7] Different techniques, uncertainty regarding the optimal timeframe of measurement and the evolution of LVEF over time, non-reproducibility even in stable patients and different levels of experience all contribute to inaccuracies in a parameter that is considered the single and most important determinant of ICD suitability. Moreover, the patients included in the primary prevention trials experiencing benefit from ICD therapy had a significantly lower LVEF than the value that appeared in the guidelines.[5,6] The 2006 ACC/AHA/ESC guidelines adapted a cut-off value of <40% (not relevant to any of the primary prevention trials!),[8] but the 2008 ACC/AHA/HRS guidelines abandoned a single cut-off value and brought it back to specific patient groups (still with a higher LVEF than actually studied!).[9] This is a very relevant issue because in the upper range of LVEF (>25 to 30%) no benefit from ICD therapy was observed (MADIT-I, MADIT-II & SCDHeFT data). The Dutch 2005-2006 guidelines mirror the European guidelines of those days.[8]

Further subanalyses of the primary prevention trials revealed that specific subsets of patients are more at risk than others. Detailed risk stratification by including a number of other easily ascertainable clinical variables revealed a simple risk score. In the MADIT-II population five risk factors appeared of importance: i.e. NHYA class >II/IV, atrial fibrillation, a QRS width of >120 msec, age >70 years and serum urea >9.3 mmol/l (>26 mg/dl).[10] In the absence of any of these risk factors (as was the case in about one-third of the MADIT-II study population) ICD therapy did not offer any benefit on mortality, but meanwhile patients were subject to (the full spectrum of) adverse effects of ICD therapy. When three or more of these factors were present no benefit was shown either. Equally, in patients with severe renal function alone (serum urea ≥17.85 mmol/l or creatinine ≥221 µmol/l) ICD therapy was not effective. Also in SCDHeFT, benefit from ICD was only seen in NYHA functional class II patients and not in class III/IV patients.[3] Finally, a recent analysis of almost 30,000 hospitalisations for heart failure and ICD implant revealed that the use of inotropic drugs around the time of ICD implant (±CRT) was associated with significant in(!)-hospital mortality (up to 15% when inotropic support was required after the implant) and increased costs.[11] In this respect, it is to be noted that predicted one-year mortality rates in patients hospitalised for heart failure can be as high as 79% when these patients have a number of associated not too uncommon conditions such as renal dysfunction, chronic obstructive pulmonary disease or anaemia (www.ccort.ca/CHFriskmodel.asp).[12]

A.A.M. Wilde
Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands
T.A. Simmers
Department of Cardiology, Amphia Hospital, Breda, the Netherlands

Correspondence to: A.A.M. Wilde
Department of Cardiology, Academic Medical Center
Amsterdam, PO Box 22660, 1100 DD Amsterdam,
the Netherlands
E-mail: a.a.wilde@amc.uva.nl

Another important issue to consider is the time-dependent benefit of ICD implant. In the primary intervention trials the time between the qualifying infarct and ICD implant was in general quite long (in MADIT-II almost 90% were over six months with a mean interval of 6.7 years; in SCDHeFT the median interval was 4.3 years). Actually in MADIT-II patients with qualifying infarcts <18 months did not benefit from ICD therapy.[13] Moreover, it is likely that, given the 'age' of these infarcts and the time interval in which these trials were executed, a significant subset of the qualifying infarcts were in the acute phase treated with thrombolysis or not treated at all. These infarcts may develop a different (late) arrhythmogenic substrate compared with PCI-treated infarcts. In the DINAMIT trial, by design only including recent infarcts (i.e. between 6 to 40 days after the qualifying infarct), no beneficial ICD effect was observed (the small effect that was observed was counterbalanced by non-arrhythmic deaths in the ICD group).[14] Also in the Valsartan in Acute Myocardial Infarction Trial (VALLIANT), a trial recently conducted in over 14,000 patients with acute myocardial infarction and low LVEF, sudden death rate in the patients group with LVEF <30% was only 2.5% per year.[15] Indeed, this is significantly lower than the event rate in the 'older' primary prevention trials. Finally, in a recent series of 465 ICD implants for primary prevention (SCDHeFT criteria) annualised firing rate was 4.5%.[16] The latter included shocks for rapid ventricular tachycardia which, as often thought or argued, is not similar to sudden death.[5] An important question to address is whether the lower event rate in these latter trials is in part explained by a lower than anticipated arrhythmia risk because the infarcts are PCI treated? And if so that would simply mean that nowadays PCI-treated infarcts carry a lower than anticipated arrhythmia risk in the long term. Clearly this will impact on cost-benefit ratio of prophylactic ICD implant.

ICD implants are not without complications. The often heard statement that implanting an ICD is similar to implanting a pacemaker is simply not true. In large volume centres primary ICD implants are associated with 10 to 11% mostly coded as 'mechanical complications of the ICD' and haemorrhage/haematoma.[17] Particularly patients after cardiac arrest and/or with chronic pulmonary or renal disease are at risk.[17] Death occurred before hospital discharge in 1% of patients! Obviously, costs increase significantly when complications occurred. In this issue of the *Netherlands Heart Journal* the results from the UMCU group are reported.[18] Equal to large US series ≥10% of their 677 patients had an implant-related complication. Infection constituted only a minority of complications and was not different between procedures performed in the operating room and in the cardiac catheterisation laboratory.[18]

In addition to the complications associated with the primo implant, complications on follow-up are equally frequent. Inappropriate shocks occur frequently (20% is no exception in various trials) and are more disabling then generally thought. In addition, devices and leads proved to be far from perfect. All companies had device or lead recalls in recent years leading to significant morbidity and even mortality (for a summary see reference 5). Long-term lead survival has also been studied recently; estimated survival rates were 85 and 60% at five and eight years after implantation respectively.[19] This high failure rate necessitates lead replacement with, easy to imagine, associated risks. And this at a time when we face potential problems with the Medtronic Sprint Fidelis and the St Jude Riata leads. The former has been implanted in over 250,000 individuals world-wide; the medium to long-term risk of failure is unknown but could well follow an exponential pattern over the years to come.[20] The latter may predispose to perforation. To the several case reports already published, the Zwolle group adds one more, notably and relevant to the above discussion, in a patient with a prophylactic implant.[21]

Obviously the above considerations will have significant impact on cost effectiveness of prophylactic ICD therapy. This issue is discussed at length by Tung et al. and the interested reader is referred to that paper.[5]

In conclusion, there is a growing awareness that ICD implant for primary prevention in patients with low LVEF should be reconsidered. Some refer to it as 'a bridge to far',[4] others question that current guidelines are 'not honest' to our patients.[5] It might well be that 'the clinical benefit has been overestimated by clinical trials, the adverse effects on morbidity, quality of life and the potential for proarrhythmia have been underestimated and that the unfavourable cost-effectiveness of ICD therapy is understated'.[5] There is no doubt that more accurate risk stratification is of utmost importance and that the cost-benefit ratio needs a thorough re-evaluation. To us there is little doubt that these guidelines need to be reconsidered and should take into account the critical remarks expressed in these articles that should be obligate literature to anyone dealing with ICDs. ■

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