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ICD risk stratification studies – EU-CERT-ICD and the European perspective☆

Joachim Seegers, MD,[a,b] Leonard Bergau, MD,[a] Tobias Tichelbäcker, MD,[a] Marek Malik, PhD, MD,[c] Markus Zabel, MD[a,*]

[a] Department of Cardiology and Pneumology, Division of Clinical Electrophysiology, University Medical Center Göttingen, Germany
[b] Department of Internal Medicine II, Division of Cardiology, University Hospital Regensburg, Germany
[c] National Heart and Lung Institute, Imperial College, London, United Kingdom

Abstract

Background and rationale: In patients with ischemic or non-ischemic cardiomyopathy and impaired left ventricular ejection fraction, treatment with implantable cardioverter-defibrillator (ICD) has been shown to improve survival and guidelines recommend their use for primary prevention of sudden cardiac death. Experts disagree regarding the validity of decade-old trial results as the basis for this recommendation, therefore, reconsideration of prophylactic ICD treatment is needed.

EU-CERT-ICD, DANISH-ICD and DO-IT: In order to update the evidence on prophylactic ICD treatment, several prospective studies are underway in Europe. The prospective EU-CERT-ICD cohort study (NCT 02064192) is enrolling 2500 patients and compares patients undergoing first ICD implantation with controls with an earlier clinical decision to go without ICD implantation strictly unrelated to the study. The DANISH ICD study (NCT 00542945) has randomized 1000 patients with dilated cardiomyopathy and an LVEF ≤35% (1:1 ICD implantation vs. control). The prospective DO-IT multicenter registry will include 1500 ICD patients in multiple Dutch high-volume implanting centers. Due to the widespread use of ICD therapy, new randomized trials seem not straightforward to envisage in many countries.

Conclusion: The above described ICD studies will provide additional evidence regarding the effectiveness of primary prophylactic ICDs in Europe and may have an impact on ICD treatment guidelines. They could also help to design randomized trials in low risk patients.

Keywords: Cardioverter defibrillator, implantable; Risk factors; Mortality; Sudden cardiac death

Introduction

In patients with impaired left ventricular ejection fraction (LVEF, ≤35%), treatment with an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) has become a guideline indication more than 10 years ago. This recommendation was largely based on two landmark trials, the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) [1] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [2], showing a survival benefit of 23% to 31% of ICD recipients compared to patients without ICD treatment. Participants of these studies were enrolled between 1997 and 2003. Therefore, experts disagree regarding the validity of decade-old trial results as the basis for this recommendation, and a reconsideration of primary prophylactic ICD treatment is needed. First, clinical decision-making based on left ventricular ejection fraction (LVEF) as the only factor must over-simplify the stratification of patients at risk. Second, important outcomes such as overall mortality and appropriate shock rate have decreased over the years [3], after many improvements of pharmaceutical and interventional treatment options of coronary artery disease and heart failure having emerged in between [4,5]. Furthermore, improved ICD programming has led to

Abbreviations: ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial-II; SCD, sudden cardiac death; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

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* Corresponding author at: Department of Cardiology and Pneumology, Division of Clinical Electrophysiology, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany.

E-mail address: markus.zabel@googlemail.com

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substantially reduced numbers of both appropriate and inappropriate ICD therapies, especially of anti-tachycardia pacing therapies [6]. In Europe, low annual mortality rates of 5% [7,8] and annual appropriate shock rates of 4–5% are typical [7]. Third, important subgroups such as women [7,9] or elderly patients [10] have been described to potentially exhibit a lower than average benefit from the ICD. In the current overview, ongoing European ICD studies are presented, with particular focus on the EU-CERT-ICD risk stratification study.

Ongoing prospective ICD studies in Europe

Several prospective studies are currently enrolling patients in Europe. One of them is a randomized ICD trial in patients with dilated cardiomyopathy (DANISH-ICD, NCT00542945), the other two are prospectively designed cohort studies for the purpose of improved risk stratification (EU-CERT-ICD and DO-IT).

European Comparative Effectiveness Research to assess the use of primary prophylactic Implantable Cardioverter Defibrillators (EU-CERT-ICD)

The EUropean Comparative Effectiveness Research to assess the use of primary prophylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD, NCT02064192) project is funded by the European Commission and is conducted in 26 academic institutions in 14 European countries from 2013 to 2017. In the main part – the prospective cohort study will enroll 2500 patients with ischemic or non-ischemic cardiomyopathy and primary prophylactic ICD indications for reduced LVEF according to the current treatment guidelines. A dropout rate of 10% is expected. Two non-randomized cohorts are established according to the treating physician's decision and patient's preference: 1500 patients undergo primary prophylactic implantation of an ICD at baseline (ICD group), and 750 are enrolled as control patients which are not implanted with an ICD due to an earlier clinical decision to go without ICD implantation strictly unrelated to the study (Fig. 1). Mortality rates of both groups will be compared after adjustment for pre-specified defined multiple confounders. In particular, it will be analyzed whether the presence of an ICD is a multivariate factor influencing mortality. In addition, several ECG and Holter-based risk markers, among them QRS- and T-wave morphology as well as markers of autonomic tone are obtained at inclusion in order to investigate their value to define subgroups with particularly high or low risk of the major outcomes all-cause mortality and appropriate ICD shock. In detail, state-of-the-art digital analyses from the 12-lead ECG, such as QRS duration, QTc, T-peak to T-end, early repolarization patterns, fractionation of QRS complex and a variety of QRS complex and T-wave loop variables as well as state-of-the-art analyses of digital 24 h-Holter-recordings for the number of PVCs, the number and rate of non-sustained ventricular tachycardias, mean heart rate, three selected heart rate variability parameters (standard deviation of all intervals between normal beats, root mean square of successive differences, low frequency heart rate fluctuation/high frequency heart rate fluctuation), two heart rate turbulence parameters (onset and slope) and deceleration capacity are included. After enrollment, all patients will be followed for at least 1 year and up to 4 years. Co-primary endpoints are all-cause mortality and appropriate ICD shocks; in addition, secondary endpoints are defined: time to first inappropriate shock, death, subdivided to a) sudden cardiac death, b) cardiac death and c) non cardiac death, respectively, arrhythmic syncopes, resuscitations, occurrence of any ICD shock or atrial fibrillation, costs and estimated costs, quality of life data from several questionnaires. Furthermore, blood samples for later genetic analyses are collected from all patients in a biobank. The study has currently enrolled 1100 patients and expects to complete enrollment in the first half of 2017. The ICD patient's standard programming calls for prolonged detection times to arrhythmia (12 s) and programming with a high-rate cut off (arrhythmias below a cycle length of 300 ms are ignored).

In addition, the project also features a multicenter European ICD retrospective registry now compiled with 4900 ICD patients from 14 of the participating centers implanted with an ICD for primary prevention in ischemic and non-ischemic cardiomyopathy are analyzed; first results

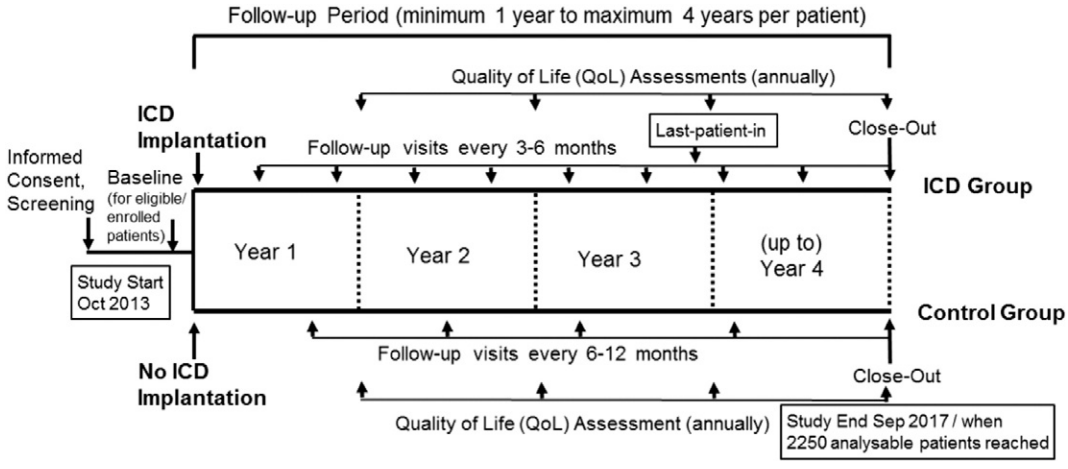

Fig. 1. Study flowchart of EU-CERT-ICD.

showed that two third of patients died without ever appropriately using their ICD. Finally, meta-analyses are performed to provide the best possible information on the prognostic value of any marker for all-cause mortality, appropriate shocks, inappropriate shocks, ICD revision operations, and other complications of ICD therapy.

Danish ICD Study in patients with dilated cardiomyopathy (DANISH)

Very important in the context of a reevaluation of primary prophylactic ICD indications, the results of the randomized DANISH ICD study (NCT00542945) will be released in a hotline session at the ESC congress in late August 2016. After the publication of the SCD-HeFT results, the Danish national treatment guidelines did not endorse primary prophylactic ICD implantation in non-ischemic cardiomyopathies (they did for ischemic cardiomyopathy), but instead entered into conducting this study. The study has randomized 1000 patients with dilated cardiomyopathy and an LVEF ≤35% in a 1:1 fashion to ICD implantation and control group without ICD implantation) between 2007 and 2014 and closed an extended follow-up in 2016.

Dutch Outcome in ICD therapy (DO-IT)

The Dutch Outcome in ICD therapy (DO-IT) trial is a prospective multicenter registry study conducted in the Netherlands. This study investigates the current practice of primary prophylactic ICD therapy in the Netherlands and aims to identify patients that do not derive benefit from ICD therapy. Enrollment at multiple Dutch high-volume implanting centers started in 2014 and 1500 patients are anticipated to be enrolled in 2016 [20]. A follow-up of 1–2 years is intended.

To add to the described prospective activities in Europe, the retrospective French Observatoire Multicentrique Français Des Porteurs de Défibrillateur Automatique Implantable en Prévention Primaire (DAI-PP) multicenter registry (NCT 01992458) has enrolled 5539 patients between 2002 and 2012, with a mean follow-up of 3.1 years. The group has published papers on the prognostic effect of age on ICD patients [8], the effects of major risk factors on non-arrhythmic mortality and ICD therapies, and the effects of gender on the major outcomes mortality and ICD therapies [21].

Discussion

Current practice of ICD implantation in Europe

ICD implantation rates have substantially increased in Europe between 2000 and 2010, with some leveling off between 2010 and 2014 [11]. Large differences are found between European regions and countries (Fig. 2). Disparities may be explained by different medical infrastructures (e.g. number of implanting centers, number of implanting physicians) or socio-economic differences between the individual health care system (e.g. different modes of reimbursement). Nonetheless, variation in ICD implants can also be seen between equally wealthy countries in Europe. For example, a threefold higher implantation rate per million inhabitants is reported for Germany as compared to the United Kingdom. Thus, the phenomenon of different ICD implantation rates between European countries is not fully explained and probably multifactorial.

ICD benefits and risks

The net benefit of ICD therapy depends on several factors. First, ICD systems reliably abort malignant ventricular arrhythmias such as sustained ventricular tachycardia

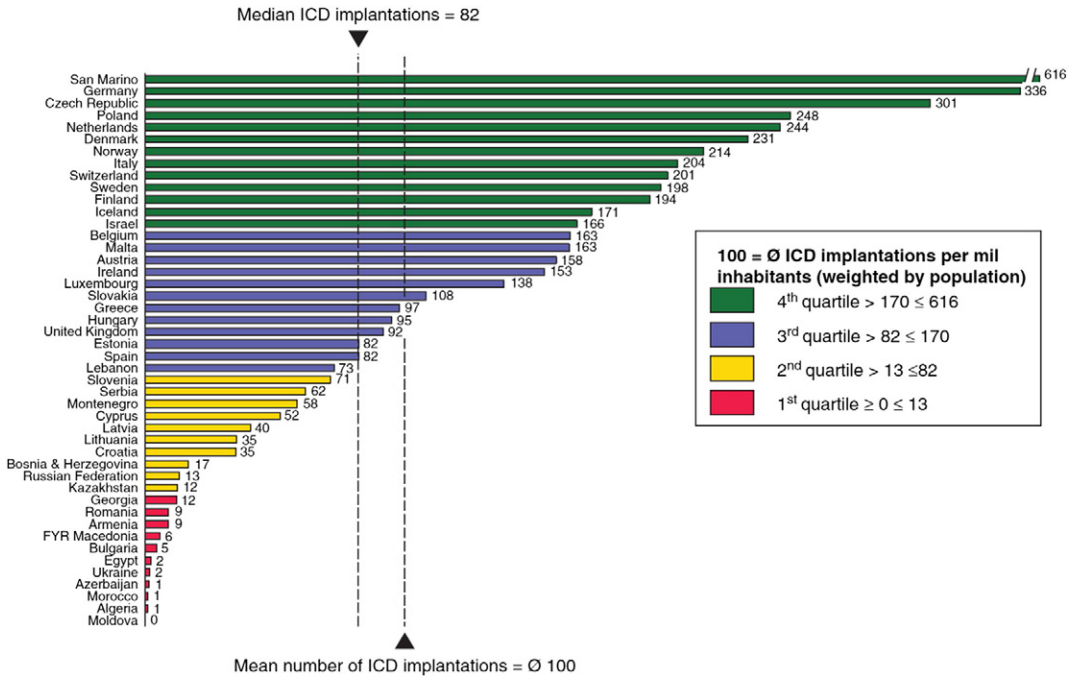

Fig. 2. ICD implantation per million inhabitants per European country (from Raatikainen [11] with permission).

and ventricular fibrillation, should they occur. The realization of this major benefit of the device thus depends on the underlying malignant arrhythmia risk. On the other hand, device side effects must be weighed against this expected benefit. Electrode dysfunction, system infections, and inappropriate therapies may contribute to potential harm [6,12]. In patients at very low risk of life-threating arrhythmia, these risks may outweigh the benefit; e.g. in patients with hypertrophic cardiomyopathy, an ICD is generally not recommended, if the risk for SCD falls below 0.8% per year [13]. As a consequence, a large number of patients decease without having ever received an appropriate shock from their device [7,14]. Therefore, accurate predictors of all-cause mortality and appropriate ICD shocks are needed in order to improve patient selection for prophylactic ICD therapy.

Different ICD benefit in subgroups

In patients defined by a chronic LVEF ≤35%, several publications have suggested higher or lower survival benefit from ICD treatment in some well-defined subgroups [10,15,16]. These subgroups need to be prospectively investigated, since a retrospective identification is not sufficient as proof. Recently, in a population of 3445 ICD patients prescribed for primary prevention, Lee at al. [10] were able to identify several subgroups at different risk of appropriate ICD shocks using a scoring system (Fig. 3): whereas patients in the lowest risk group revealed a cumulative incidence of 0.9% of appropriate shock, an incidence of 9.3% at 1 year follow-up was observed in the highest risk group. Annual mortality ranged between 0.6% and 17.7% in the group with the lowest and the highest risk. Elderly patients as well as patients with co-morbidities like kidney disease, obstructive lung disease or peripheral artery disease revealed a high mortality risk. In general, risk scores predicting mortality in ICD patients have been derived from a large number of patients enrolled, a better definition of appropriate shock is yet to be developed using various risk stratification methods, in particular electrocardiographic methods, such as in the EU-CERT-ICD risk stratification study. In general, it should be noted that patients with high mortality such as with heart failure of NYHA class IV could potentially derive a poor benefit from their ICD while patients with low mortality but a high proportion of arrhythmia related sudden death may have high ICD benefit.

We have tested several ECG-based mortality and ICD shock predictors in a series of 672 ICD patients [17]. As presented at ESC 2015, appropriate shocks are independently predicted by VT/VF inducibility and non-negative T-wave alternans [18]. Mortality risk did not coincide with appropriate shock risk. Patients with very low annual shock and mortality risks could be identified presuming low benefit of ICD therapy, vice versa high shock risks were also identifiable indicating higher than average ICD benefit.

Study designs for ICD studies a decade after SCD-HEFT and MADIT

For ethical reasons, new randomized trials on ICD therapy have been deemed particularly difficult to conceive. As an exception and because of a national decision in Denmark, we expect the results of the DANISH ICD study to be released at the ESC congress 2016. These will largely supplement the ongoing discussion as to whether new study data are necessary to adapt the ICD guidelines. Depending on these results, discussion about randomized trials may increase. Beyond, an observational and prospective cohort study is the best study design possible. Results from cohort studies identifying low risk patients could then be used in order to conceive randomized trials in certain patient groups. In this regard, EU-CERT-ICD study utilized a cohort study design and further makes use of the described European diversities that permit enrollment of true control patients without an ICD but fulfilling guideline criteria due to participating centers from countries with lower implantation

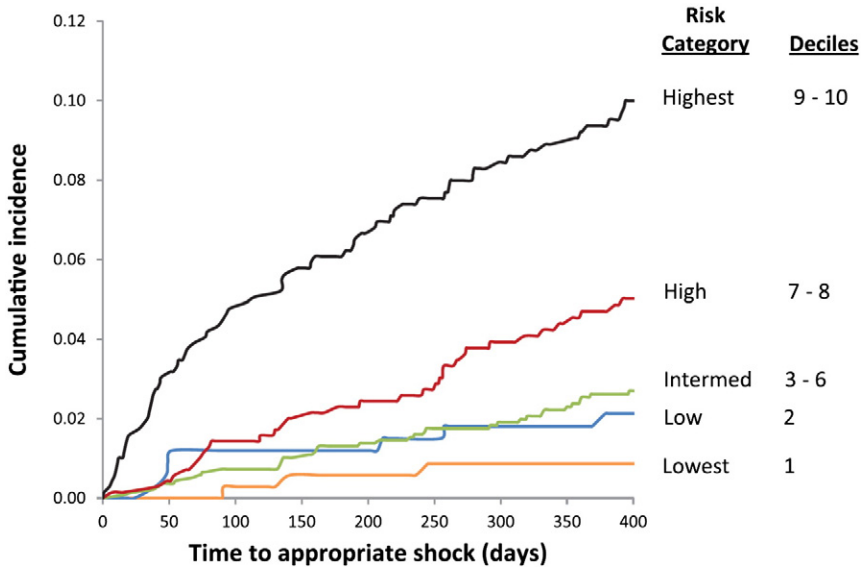

Fig. 3. Cumulative incidence of shock between different risk groups – from Lee et al. [10] with permission.

rates. In the final data set, multivariate analysis is necessary to correct for the unrandomized distribution of outcome confounders between the ICD and control groups. Furthermore, presence of the ICD can be factored into multivariate models and its influence on all-cause mortality determined without randomization. A prospective list of possible confounders has been identified, hidden confounders cannot be ruled out. Control patients in Europe, however, are not confined to low income countries. Estimation of ICD benefits also rests on quantifying appropriate shock rates as a surrogate outcome of SCD. From earlier randomized studies, it was projected that only a proportion of appropriate ICD shocks represent truly survived SCDs [19], and a range of 25–40% of appropriate shocks may have led to an SCD. This number needs a reassessment soon, as researchers and clinicians need to set a minimum risk of SCD and appropriate shock which may be acceptable to societies not to be treated with an ICD, for instance a 2% annual appropriate shock rate, translating into a <1% SCD risk. It is both possible that the number needed to treat becomes excessively high or there is a lower end of absolute mortality where the benefit of the ICD ends.

There is ongoing discussion whether ATP therapies should be counted as endpoints. A number of studies report ICD therapies as a combination of shocks plus ATP therapies, quantitative differentiation among these is important. EU-CERT-ICD and its preceding risk stratification study, the EUTrigTreat clinical study [17] have chosen appropriate shock as a major endpoint, this was also the choice in the Ontario ICD study [9,10]. In the MADIT-RIT study [6] where programming largely reduced the number of ATP therapies, this was neutral to mortality. It is essential that ICD programming is kept uniform in studies evaluating ICD benefit.

Summary and outlook

The guidelines for primary prophylactic ICD treatment have not been changed substantially for more than 10 years. Improvements in pharmacological heart failure therapy and interventional cardiology have been implemented in clinical routine. As a consequence, lower mortality and shock rates in ICD patients have been clearly observed. These facts lead to a necessity of re-evaluation of indications of primary prophylactic ICD therapy. Upcoming prospective studies such as the EU-CERT-ICD project aim to identify patients not deriving a benefit from ICD therapy. LVEF alone seems no longer suitable when decision on ICD treatment is made. The upcoming study results could also lead to the design of randomized trials in low risk patients.

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