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STUDY DESIGN

Rationale and design of the EU-CERT-ICD prospective study: comparative effectiveness of prophylactic ICD implantation

Markus Zabel[1,2]*, Christian Sticherling[3], Rik Willems[4], Andrzej Lubinski[5], Axel Bauer[6], Leonard Bergau[1], Frieder Braunschweig[7], Josep Brugada[8], Sandro Brusich[9], David Conen[3,10], Iwona Cygankiewicz[11], Panagiota Flevari[12], Milos Taborsky[13], Jim Hansen[14], Gerd Hasenfuß[1,2], Robert Hatala[15], Heikki V. Huikuri[16], Svetoslav Iovev[17], Stefan Kääb[6], Gabriela Kaliska[18], Jaroslaw D. Kasprzak[19], Lars Lüthje[1], Marek Malik[20], Tomas Novotny[21], Nikola Pavlović[22], Georg Schmidt[23], Tchavdar Shalganov[24], Rajeeva Sritharan[1], Simon Schlögl[1], Janko Szavits Nossan[25], Vassil Traykov[26], Anton E. Tuinenburg[27], Vasil Velchev[28], Marc A. Vos[29], Stefan N. Willich[30], Tim Friede[2,31], Jesper Hastrup Svendsen[32], Béla Merkely[33] for the EU-CERT-ICD Study Investigators[†]

[1]*Department of Cardiology and Pneumology, Heart Center, University Medical Center, Göttingen, Germany;* [2]*DZHK (German Center for Cardiovascular Research), partner site Göttingen, Göttingen, Germany;* [3]*Department of Cardiology, University Hospital, Basel, Switzerland;* [4]*Department of Cardiovascular Sciences, University of Leuven, Belgium;* [5]*Department of Cardiology, Medical University of Lodz (MUL) WAM Hospital, Lodz, Poland;* [6]*Department of Cardiology, Klinikum Großhadern, Ludwig-Maximilians-Universität Munich, Munich, Germany;* [7]*Department of Cardiology, Karolinska Institutet, Stockholm, Sweden;* [8]*IDIBAPS, Department of Cardiology, Hospital Clinic Barcelona, Barcelona, Spain;* [9]*Department of Cardiovascular Disease, KBC Rijeka, Rijeka, Croatia;* [10]*Population Health Research Institute, McMaster University, Hamilton, ON, Canada;* [11]*Department of Electrocardiology, Medical University of Lodz (MUL), Lodz, Poland;* [12]*2nd Department of Cardiology, Attikon University Hospital, Athens, Greece;* [13]*Department of Cardiology, University Hospital, Olomouc, Czech Republic;* [14]*Gentofte Hospital, Copenhagen, Denmark;* [15]*Slovak Medical University NUSCH, Bratislava, Slovakia;* [16]*Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland;* [17]*Department of Cardiology, St. Ekaterina University Hospital, Sofia, Bulgaria;* [18]*Department of Cardiology, SUSSCH, Banska Bystrica, Slovakia;* [19]*Chair and Department of Cardiology, Bieganski Hospital, Medical University of Lodz (MUL), Lodz, Poland;* [20]*National Heart and Lung Institute, Imperial College, London, UK;* [21]*Department of Internal Medicine and Cardiology, University Hospital Brno, Brno, Czech Republic;* [22]*Department of Cardiology, KBC Sestre Milosrdnice, Zagreb, Croatia;* [23]*Med. Klinik und Poliklinik I, Technische Universität München, Klinikum rechts der Isar, Munich, Germany;* [24]*Department of Cardiology, National Heart Hospital, Sofia, Bulgaria;* [25]*Department of Cardiology, Magdalena Klinika, Krapinske Toplice, Croatia;* [26]*Department of Cardiology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria;* [27]*Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands;* [28]*Department of Cardiology, St. Anna Hospital, Sofia, Bulgaria;* [29]*Department of Medical Physiology, University Medical Center Utrecht, Utrecht, The Netherlands;* [30]*Institute for Social Medicine, Epidemiology and Health Economics, Charité Universitätsmedizin Berlin, Berlin, Germany;* [31]*Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany;* [32]*Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark;* [33]*Department of Cardiology, Semmelweis University Heart Center, Budapest, Hungary*

Abstract

Aims The clinical effectiveness of primary prevention implantable cardioverter defibrillator (ICD) therapy is under debate. The EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD) aims to assess its current clinical value.

Methods and results The EU-CERT-ICD is a prospective investigator-initiated non-randomized, controlled, multicentre observational cohort study performed in 44 centres across 15 European Union countries. We will recruit 2250 patients with ischaemic or dilated cardiomyopathy and a guideline indication for primary prophylactic ICD implantation. This sample will include 1500 patients at their first ICD implantation and 750 patients who did not receive a primary prevention ICD despite having an indication for it (non-randomized control group). The primary endpoint is all-cause mortality; the co-primary endpoint in ICD patients is time to first appropriate shock. Secondary endpoints include sudden cardiac death, first inappropriate shock, any ICD shock, arrhythmogenic syncope, revision procedures, quality of life, and cost-effectiveness. At baseline (and prior to ICD implantation if applicable), all patients undergo 12-lead electrocardiogram (ECG) and Holter ECG analysis using multiple advanced methods for risk stratification as well as detailed documentation of clinical characteristics and laboratory values. Genetic biobanking is also organized. As of August 2018, baseline data of 2265 patients are complete. All subjects will be followed for up to 4.5 years.

Conclusions The EU-CERT-ICD study will provide a necessary update about clinical effectiveness of primary prophylactic ICD implantation. This study also aims for improved risk stratification and patient selection using clinical and ECG risk markers.

Keywords Implantable cardioverter defibrillator; Risk factors; Mortality; Sudden cardiac death

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**Correspondence to: Markus Zabel, Department of Cardiology and Pneumology, Division of Clinical Electrophysiology, Heart Center, University Medical Center, Robert-Koch-Strasse 40, 37075 Göttingen, Germany. Tel: +49 (551) 39 69255; Fax: +49 (551) 39 19127. Email: markus.zabel@med.uni-goettingen.de*
†See Appendix for the complete list of EU-CERT-ICD clinical centres and EU-CERT-ICD project functionality.

Introduction

An estimated 500 000 sudden cardiac deaths (SCD) occur in the European Union (EU) annually, the majority of which are caused by malignant ventricular arrhythmias.[1] Large prospective, randomized multicentre studies have established that implantable cardioverter defibrillator (ICD) therapy is effective for primary prevention of SCD and improves total survival in patient populations.[2,3] ICDs are considered routine treatment after implementation to international guidelines.[4,5] More than a decade after publication of the landmark trials, there is evidence that all-cause mortality and appropriate shock rates have decreased and vary widely with age and co-morbidities.[6,7] Inappropriate and appropriate shocks have been reduced after optimization of ICD programming.[8,9] It was demonstrated from heart failure trials that the rate of SCD declined over the last decades.[10] As a consequence, a large number of ICD patients never receive appropriate shocks or die prior to any appropriate ICD therapy as the risk of non-arrhythmic death outweighs the risk of arrhythmic death.[11] Thus, improved selection of patient subgroups with a sufficiently high mortality benefit from ICD therapy is urgently required.[12,13] Useful parameters for risk stratification, for example, electrophysiological and electrocardiographic markers, parameters from cardiovascular history, biomarkers, and possible combinations are underused.[14–16] In 2012, the design of a randomized trial seemed ethically close to impossible due to the wide implementation of ICD therapy and unequivocal guidelines. Instead, we set out to conduct a large prospective non-randomized cohort study. We aimed to re-evaluate benefits from prophylactic ICD therapy and to test multiple combinations of risk factors to predict the risk of ICD shocks vs. the competing risk of non-arrhythmic mortality.

Study objectives

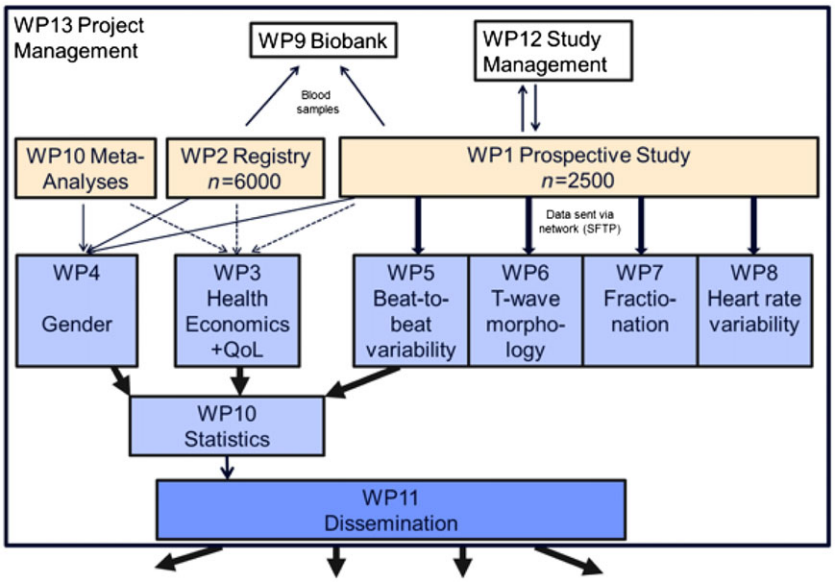
The 'EUropean Comparative Effectiveness Research to assess the use of primary prophylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD)' was funded by the European Community's Seventh Framework Programme as a modular research project to study the effectiveness of prophylactic ICDs. In addition to the described prospective study, a retrospective registry[17] and meta-analyses in primary prophylactic ICD patients were set up[18,19] (*Figure 1*). Over the course of the project, several original papers[20–27] and editorials[28–33] have been published from the various work packages. At the outset of the project, its primary objectives were as follows:

- to characterize all-cause mortality in a prospective patient cohort of ICD candidates newly implanted for primary prophylaxis of SCD and compare with a non-randomized control group;
- to determine prespecified clinical baseline characteristics contributing to the risk of the primary outcomes, that is, all-cause mortality and first appropriate shock;
- to define subgroups within the cohort with a lower or higher benefit from ICD treatment;
- to assess simple and cost-effective electrocardiographic noninvasive risk stratification techniques;
- to identify predictors for appropriate shocks using electrocardiogram (ECG)-related parameters and autonomic parameters as well as co-morbidities and laboratory parameters;
- to characterize subgroups within the cohort with a deviating risk for appropriate shock, in particular focusing on the role of sex category;
- to gather a blood sample from each participating patient (biobanking) to perform a genome analysis for risk stratification; and
- to provide outcome data as a basis for extensive health economic evaluation of ICD use and quality of life (QoL) including subgroups and country-specific differences.

Study design

The EU-CERT-ICD prospective trial is an investigator-initiated non-randomized, open, controlled, observational multicentre cohort study in 2250 analysable patients with ischaemic or dilated cardiomyopathy being candidates for receiving a primary prevention ICD by current guidelines. In the ICD treatment group, we aimed to enrol 1500 analysable patients at their first ICD implantation. Using the large disparities of ICD implant rates across Europe,[34] it was considered to find a non-randomized group of 750 comparable patients without ICDs to generate data on current ICD survival benefit. In the statistical design, differences between the ICD group and the control group in terms of relevant prognostic factors are compensated by appropriate statistical methodology yielding a hazard ratio that indicates the effect of the primary prophylactic ICD on the primary endpoint, all-cause mortality. All control patients are required to fulfil the primary prevention guideline indication, and reasons for non-ICD status have to be unrelated to the study, to be documented in the electronic case report form (eCRF) (did patient refuse to be implanted an ICD, did physician

Figure 1 Overview of the EU-CERT-ICD project structure. QoL, quality of life; WP, work package.



not recommend ICD implantation, and is ICD not sufficiently reimbursed by health care system). All patients receive optimal pharmacological treatment. In a total of 15 EU or EU-associated (Switzerland) countries, 44 clinical centres enrolled patients (*Figure 2*). Sites and countries were chosen to include highly experienced investigators representative of European cardiovascular medicine, often nationally leading centres. Expecting a dropout rate of 10%, a total number of 2500 patients was initially conceived; however, after the dropout rate was observed to be considerably lower, 2310 patients were targeted. All centres were encouraged to enrol patients consecutively from their screening sources. The Seventh Framework Programme project organization is shown in *Figure 1*.

Ethics

Approval was given by all local ethics committees. All patients gave their informed written consent prior to inclusion. The study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) principles. The study is registered at www.clinicaltrials.gov (NCT02064192).

Endpoints

Primary endpoints

The primary endpoint is all-cause mortality. Co-primary endpoints for risk prediction in the ICD patients are time to death and time to first appropriate shock.

Secondary endpoints

Secondary endpoints of the study are as follows:

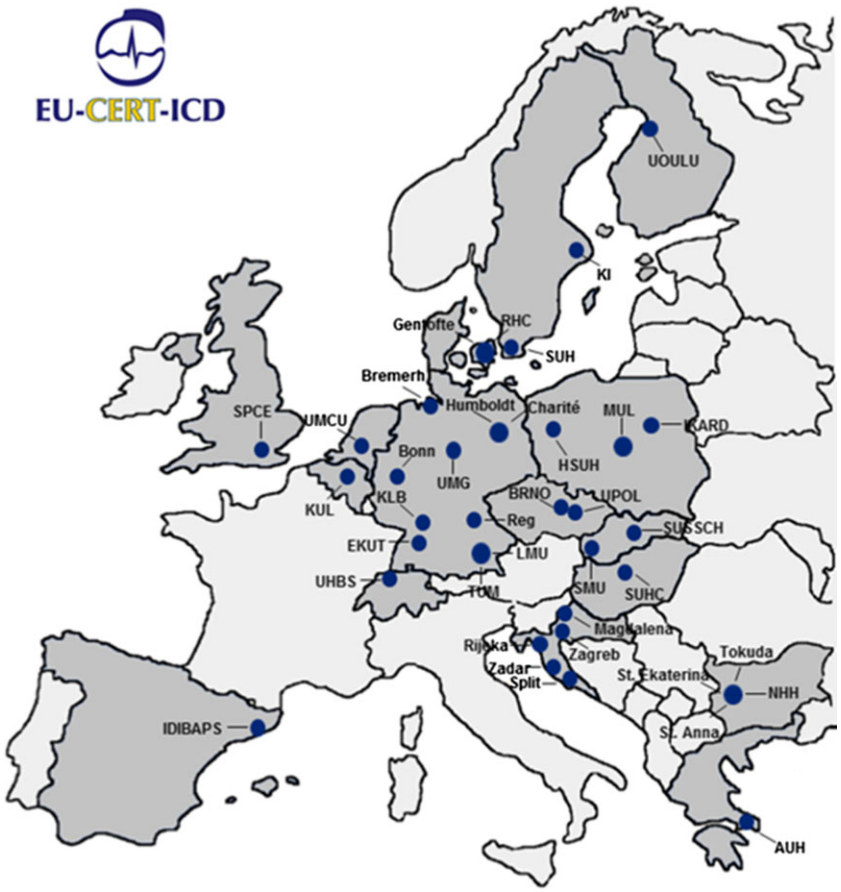
- cardiac mortality,
- SCD,
- non-cardiac mortality,
- first inappropriate shock,
- any ICD shock (appropriate or inappropriate),
- arrhythmogenic syncope or successful resuscitation for ventricular tachyarrhythmias,
- ECG-documented paroxysmal or permanent atrial fibrillation (defined as an atrial tachyarrhythmia $>$250/min lasting $>$30 s),
- revision, replacement, or upgrade/downgrade device procedures,
- QoL, and
- cost-effectiveness and estimated total costs.

Inclusion and exclusion criteria

Patients are eligible for enrolment if they fulfil the following inclusion criteria:

- patients with ischaemic or dilated cardiomyopathy;
- left ventricular ejection fraction (LVEF) $\leq$ 35% and New York Heart Association (NYHA) functional classes II–III (or NYHA functional class I and LVEF $\leq$ 30%);
- indication for primary prevention ICD treatment according to current European Society of Cardiology guidelines,[4] including pharmacologic treatment of heart failure and

Figure 2 Clinical study sites in the European Union.



correct timing from diagnosis of underlying heart disease and acute myocardial infarction;
- age ≥ 18 years; and
- written informed consent to participate in the study.

Patients may not fulfil one of the following exclusion criteria:

- patients with a secondary prophylactic ICD indication;
- planned implantation of a device for cardiac resynchronization therapy (CRT defibrillator or CRT pacemaker), or clearly indicated according to guidelines;
- unstable cardiac condition (i.e. acute ischaemia or NYHA IV);
- persistent higher degree atrioventricular block (in sinus rhythm);
- previous pacemaker or cardiac device therapy; and
- limited life expectancy ≤1 year.

Patients with atrial fibrillation are accepted up to a maximum of 15%.

Endpoint adjudication

The external endpoint committee will provide blinded adjudication of all death, shock, resuscitation, and syncope events. Each death will be classified as SCD,[35] cardiac, or non-cardiac. ICD shocks will be adjudicated based on review of device electrograms and classified as appropriate or inappropriate. An appropriate ICD shock is classified as (i) primarily delivered in the ventricular fibrillation (VF) zone, (ii) delivered as a backup to failed anti-tachycardia pacing (ATP) in the ventricular tachycardia (VT) zone, or (iii) delivered after acceleration of a failed ATP into the VF zone.

Crossover between study groups

Crossover of patients from the control group to the ICD group is not encouraged but is allowed at the discretion of the treating physicians. Typical reasons were the occurrence of malignant arrhythmias or the suspicion of arrhythmogenic syncope. The date of ICD implantation and manufacturer are noted in the eCRF; subsequently, the patient remains in the study with documentation of ICD events and programming. Statistical analysis will occur on an intention-to-treat basis; an on-treatment analysis is possible.

Study protocol

A graphic outline of the study protocol is shown in *Figure 3*. A 12-lead Holter ECG (CM 3000-12 BT; Getemed, Teltow/Germany) is recorded at 1 kHz sampling frequency for 24 h prior to ICD implantation in the ICD group. Holter data are collected for the purposes of ECG-based risk stratification. They will be analysed for the number of premature ventricular complexes, number of episodes and rate of non-sustained VT, short-term variability of the QT interval,[36] respiration triggered sinus arrhythmia,[37] modified moving average T-wave alternans,[38] periodic repolarization dynamics,[39] heart rate variability,[40] and heart rate turbulence including standard deviation of RR intervals, root mean square of successive differences in RR intervals, frequency domain heart rate variability parameters (low frequency/high frequency), turbulence onset, turbulence slope, acceleration capacity, and deceleration capacity.[41,42] From the 12-lead ECG extracted from suitable episodes of the 12-lead Holters, total cosine R-to-T (unitless), relative T-wave residuum (%), T-wave morphology dispersion (°), T-wave loop dispersion (unitless),[43] T-peak-to-T-end interval (ms), J-point elevation (mV), fractionation index (unitless),[44] fragmented QRS,[26] and early repolarization[45] will be determined. Some of these measurements are not possible in atrial fibrillation; therefore, the number of patients with atrial fibrillation is limited to 15%. During every Holter recording, a dedicated autonomic provocation schedule (10 min supine, 10 min standing, 10 min supine, and 10 min light exercise) is performed during the morning hours to allow subsequent study of autonomic responsiveness. Echocardiography is performed to measure LVEF using Simpson's method.[46] Underlying cardiac disease, NYHA functional class, pulse rate, resting blood pressure, weight, height, and cardiovascular pharmacological treatment are documented along with the presence or absence of the following co-morbidities: peripheral arterial disease, cerebral vascular disease, pulmonary disease, diabetes mellitus, hypertension, sleep apnoea, tobacco use, and any malignant disease within the last 5 years. Standard laboratory parameters are recorded, including creatinine, estimated glomerular filtration rate, serum blood urea nitrogen, and N-terminal pro BNP or BNP. An EDTA blood sample for biobanking will be taken. All study baseline tests had to be completed before implantation. Routine ICD implantation is not part of this observational study. Written informed consent for ICD implantation is obtained independently of the study.

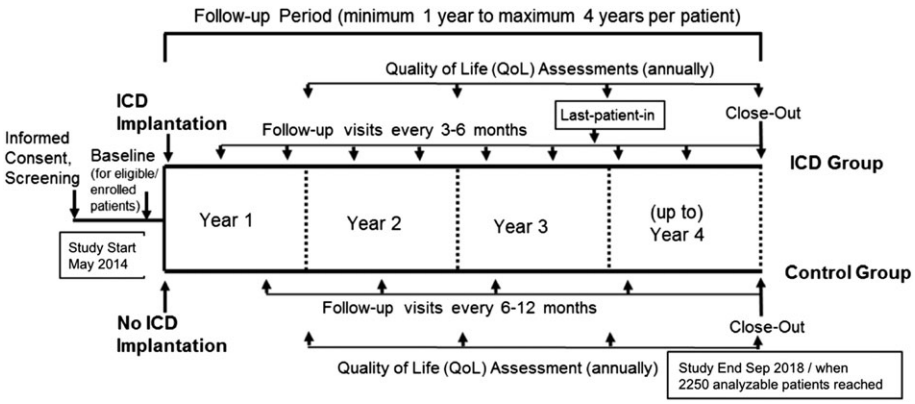
Follow-up

All ICD patients are followed in the outpatient clinic every 3 to 6 months or remotely by telecardiologic follow-up. Episodes of shock or ATP are stored as electrograms for adjudication; programming changes are recorded. Patients in the non-ICD control group are scheduled for visits every 6 to 12 months according to their clinical needs. In both groups, information can also be retrieved from hospital records, via telephone and/or mail from patients, relatives, general practitioners, or local authorities. If a patient undergoes heart transplant or implantation of a ventricular assist device, follow-up is censored on that date without an event counted.

Implantable cardioverter defibrillator programming

For this study, mandatory ICD programming was established. A VT therapy (200–250 b.p.m.) and a VF therapy (>250 b.p.m.) zone were programmed, with a supplementary monitor zone (170–200 b.p.m.). VT was treated by ATP followed by shocks of maximum output. VF was treated by ATP during charge (if applicable) and shocks of maximum output. ICD programming could be individualized by the physician on clinical grounds.

Figure 3 Study protocol. ICD, implantable cardioverter defibrillator.



Quality of life and health economics

Quality of life is assessed at baseline and annually during follow-up. Patients will fill out the SF-36 Questionnaire for general QoL,[47] the MacNew Questionnaire for disease-specific QoL,[48] and the Florida Patient Acceptance Survey for ICD acceptance.[49] Health economics questionnaires are assessed at baseline and during follow-up visits in German-speaking patients in Germany and Switzerland (questionnaire is validated only in the German language). QoL-adjusted cost-effectiveness will be estimated from actual cost comparisons and Markov decision models with attention to subgroups, regional, and sex comparisons.

Study organization

Clinical research organization services are provided by the Clinical Trial Unit (Klinisches Studienmanagement – Studienzentrum) of the University Medical Center Göttingen providing contract management, regulatory services, eCRFs, data management, and central and on-site monitoring. Web-based data capture and data collection are performed in secuTrial (current version, www.secutrial.com) according to GCP standards. Data quality is continuously monitored in all centres using central monitoring and query management. Regular on-site monitoring is additionally organized and conducted by the Clinical Trial Unit or a local freelancer. The main purpose of monitoring is to ensure optimal data quality and guarantee that the study is conducted, recorded, and reported in accordance with the study protocol and GCP guidelines. Patient safety is not an issue in an observational trial.

The Consortium Steering Committee is formed by the overall project coordinator, work package leaders, and the lead statistician.

Sample size calculation

Sample size calculations were carried out for the comparison of ICD patients with controls regarding mortality and for stratification of the ICD cohort with regard to appropriate shocks and mortality. We start here with the former. In the Identification and Therapeutic Targeting of Common Arrhythmia Trigger Mechanisms clinical study,[50] an annual all-cause mortality of about 4% was observed for high-risk patients. A similar mortality of 4.5% was observed by Smith *et al*.[51] Assuming an annual all-cause mortality of 4.5% in the ICD patients, exponential survival times, and a hazard ratio of 0.7 as observed in Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II),[2] recruitment over 3 years, and total study duration of 4 years, a sample of 1500 ICD patients and 750 control patients yields a power of 80% at the usual two-sided significance level of 5%. From preliminary analyses of registry data in 1272 ICD patients[23] and from own prospective data from 282 ICD patients,[22] we inferred that independent binary or dichotomized risk stratifiers (electrophysiological parameters, biomarkers, and other patients' characteristics) provide hazard ratios between 1.5 and 2.5. Thus, the sample size calculation of this study is based on a hazard ratio of 2 between a high-risk and a low-risk group of patients for some independent predictor variables. It was further assumed that about 20–40% of patients exhibit a lower overall risk with decreased annual all-cause mortality and that about 50% of patients exhibit a lower risk with regard to the annual appropriate ICD shock rate. Assuming a ratio of group sizes of 2:1, Schoenfeld's formula for time-to-event data[52] yielded that 122 deaths are required to achieve a power of 95% for a two-sided test at the usual two-sided significance level of 5% assuming a hazard ratio of 2. Correspondingly, 108 appropriate ICD shocks are required if the ratio of group sizes is 1:1 (equal group sizes for high-risk and low-risk patients). In the EUTrigTreat clinical study,[50] an annual appropriate ICD shock rate of about 4.5% was observed for high-risk patients. Higher rates of ICD shock (6%) as compared with the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study (5%) were published in 2005.[3] With a hazard ratio of 2, we assume an annual all-cause mortality and an annual appropriate ICD shock rate of about 2.25% for low-risk patients. Assuming exponentially distributed waiting times, 108 events can be expected to be observed within 4 years as long as at least a total of 1476 ICD patients are recruited into the study in two equally sized groups defined by the assessed prognostic markers over a 3 year period. Adjusting for some dropout, we aim to recruit 1500 patients with ICD into the study. Because risk rates can vary between men and women,[53,54] the derived sample size was also checked with respect to the detection of a gender-by-prognostic factor interaction. A total of 122 events are sufficient to detect a gender-by-prognostic factor interaction with power of at least 80% at a two-sided significance level of 10% if the groups are equally sized and the hazard ratios differ by a factor of 2.5 or larger. A total of about 37 events is expected in women,[54] providing a power of at least 80% (90%) for hazard ratios larger or equal to 2.5 (2.9) at the usual two-sided significance level of 5% assuming equally sized groups. If the group is split in a ratio of 2:1, the power is at least 80% (90%) for hazard ratios in excess of 2.6 (3.1). For the multivariate comparison of the primary endpoint between the ICD group and the control group (allocation ratio 2:1), a total number of 279 events are necessary for a clinically relevant hazard ratio of 0.7 at the usual two-sided significance level of 5%.

Statistical analyses

Patients who undergo an incomplete set of diagnostic baseline tests after enrolment will not be automatically excluded. Patients recruited and dropped out before the baseline

diagnostic tests will not be analysed. Time-to-event outcomes are summarized by Kaplan–Meier curves and estimates of event probabilities at appropriate follow-up times will be given with 95% confidence intervals. For appropriate and inappropriate shocks, death is considered a censoring event using competing risk adjustments.[55] Cox proportional hazards regression analyses or Fine and Gray proportional subdistribution hazard regression analyses are performed to quantify the predictive value of multiple categorical variables and dichotomized continuous variables on the primary and secondary time-to-event endpoints without (e.g. mortality) or with competing risks (e.g. shocks), respectively. The regression models will also include covariables such as age and sex category that potentially could confound the biomarkers of interest and ICD treatment. The independent predictive value of any variable will be determined. Useful combinations of independently predictive variables will be grouped together in order to establish prediction models or risk scores[6,56,57] for the prediction of mortality or ICD shocks or any of the predefined primary or secondary endpoints. Hazard ratios will be reported with 95% confidence intervals and *P*-values testing the hypothesis of no effect. Diagnostic techniques will be used to check the proportional hazards assumption. If necessary, missing data will be dealt with using multiple imputation. Classification models will be validated using cross-validation. The problem of unbalanced clinical characteristics between the ICD and control groups will be approached by using multivariate analyses of all patients with the presence of the ICD as one of the factors influencing outcomes but also by propensity score methods appropriate for non-randomized studies and centre-by-centre comparisons.

Discussion

The EU-CERT-ICD study will provide a necessary update on clinical effectiveness of primary prophylactic ICD implantation, following the recent publication of the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality trial.[58] Large disparities in ICD treatment that are multifactorial and cannot be explained by socioeconomic differences continue to exist between European countries.[34] Using multivariable regression statistics of the primary endpoint, we will be able to calculate an adequately powered hazard ratio of the ICD survival effect (as the primary measure of ICD benefit) in the overall cohort and predefined subgroups. Valid risk scores for mortality and shock can be provided. Concerning these outcomes, the results will be able to confirm known independent risk factors and possibly detect new ones. A large number of useful parameters for risk stratification, for example, electrocardiographic markers, cardiovascular history, biomarkers, and possible combinations can be used,[14–16] as exemplified by other conceptual publications from the field.[50,57,59,60] Cost-effectiveness in the overall trial population and in subgroups and the variation in EU countries can be analysed. The study will be an excellent tool to assess the predictive value of several state-of-the-art advanced ECG methods for application in the clinical decision-making in ICD candidates.

Implantable cardioverter defibrillator guidelines and implantable cardioverter defibrillator benefit

An update of the current European Society of Cardiology guidelines[4] and incorporating the DANISH trial as the only recent randomized ICD outcome trial (conducted 2008 to 2016) is still pending. DANISH showed that ICD therapy currently does not reduce mortality in all patients with non-ischaemic cardiomyopathy.[58] From the original DANISH data, it was shown that increasing age is associated with loss of ICD survival benefit.[61] Important outcomes in primary prevention ICD patients—that is, overall mortality and shocks—have improved considerably.[8,23,58,17] It is therefore uncertain whether the survival benefit of prophylactic ICDs is still the same. It had been hypothesized from original SCD-HeFT[56] and MADIT-II[62] data that patients with very high mortality do not benefit from prophylactic ICDs due to a high rate of non-arrhythmic or non-cardiac deaths.[63] Important subgroups, such as women,[3,62] patients with advanced heart failure,[3,50] renal failure,[64] or diabetics,[65] may have an ICD benefit below average. Net benefit of an ICD on survival depends on the underlying risk of malignant ventricular arrhythmias, as the device can reliably abort VT and VF, should they occur. Side effects of device therapy, such as device revisions, infections, and inappropriate shocks,[8,66] must be weighed in. In patients with low risk of life-threatening arrhythmias, risks may outweigh benefit; therefore, it is clinically useful to risk stratify accurately. As an example, in patients with hypertrophic cardiomyopathy, an ICD is generally not recommended, if the risk of SCD is predicted to be less than 0.8% per year.[67]

Current studies

In parallel to EU-CERT-ICD, the Dutch Outcome in Implantable cardioverter-defibrillator Therapy registry study funded by Dutch health insurers will report similar outcomes including cost-effectiveness in 1500 primary prophylactic ICD patients from multiple implant centres in the Netherlands in late 2018.[68] The randomized REevaluation of optimal treatment Strategies for prEvenTion of Sudden Cardiac Death in patients with ischemic cardiomyopathy trial was proposed to reassess the effects of primary prophylactic ICD therapy in ischaemic cardiomyopathy.[69] Another trial probing the prophylactic indication of defibrillators—the randomized Re-evaluation of Optimal Re-synchronisation Therapy in Patients with Chronic Heart Failure trial in 2000 patients with an LVEF $\leq$ 35% and

CRT treatment—is funded by the German health system[70] and starting up.

Conclusion

Appropriate identification of patient subgroups with significant mortality benefit from ICD therapy remains critical, and risk prediction models incorporating variables beyond LVEF and NYHA functional class are warranted. Further randomized ICD studies in prophylactic indications now seem feasible. The EU-CERT-ICD study will prospectively test indication criteria for primary prophylactic ICD implantation and is expected to provide important contemporary data to improve patient selection.

Conflict of interest

None declared.

Funding

The research leading to the results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement n0 602299, EU-CERT-ICD (starting 1 October 2013).

Appendix

List of EU-CERT-ICD clinical centres

Germany (13 centres, 507 patients): University Medical Center Göttingen: M. Zabel, J. Seegers, L. Bergau, G. Hasenfuß, P. Munoz-Exposito, T. Tichelbäcker, A. Kirova, S. Schlögl, R. Sritharan, K. Jörß, J. Macken, M. Misdaq, K. Rudolph (210); DZHK (German Center for Cardiovascular Research), partner site Göttingen: M. Zabel, G. Hasenfuß, T. Friede; University Hospital Tübingen: A. Bauer, C. Meyer-Zürn, C. Eick (65); Technische Universität München, Klinikum rechts der Isar: G. Schmidt, A. Müller, M. Dommasch, D. Sinnecker (49); Klinikum Großhadern und Innenstadt, Ludwig-Maximilians-Universität Munich: S. Kääb, M. Sinner, A. Bauer (44); Klinikum Reinkenheide Bremerhaven: R. Dissmann, U. Burmester (26); Vivantes Humboldt Klinikum Berlin: S. Behrens, M. Gregor (21); Klinikum Ludwigsburg: S. Stefanow, N. Rüb, C. Wolpert (20); Marienkrankenhaus Bonn: D. Bimmel, C. Lieberz (19); University Hospital Regensburg: J. Seegers, L. Maier (18); Klinikum Weiden: R. Schwinger (12); Charité Campus Virchow Klinikum: F. Blaschke, B. Pieske (12); Asklepios Klinik Hamburg-Barmbek: G. Grönefeld (10); Herz im Zentrum Hannover: G. Klein, A. Gardiwal (1).

Hungary (1 centre, 347 patients): Semmelweis University Hospital Budapest: B. Merkely, G. Szeplaki, P. Perge.

Croatia (5 centres, 226 patients): Magdalena Klinika Krapinske Toplice: J. Szavits Nossan, L. Rotkvić (110); KBC Sestre Milosrdnice Zagreb: N. Pavlovic, S. Manola, O. Vinter, I. Benko (70); KBC Rijeka: S. Brusic, E. Avdovic, M. Klasan (30); General Hospital Zadar: Z. Bakotic, A. Anic (8); KBC Split: Z. Jurisic (8).

Poland (5 centres, 184 patients): Medical University of Lodz (MUL) WAM Hospital: A. Lubinski, E. Kowalczyk, T. Kucejko, A. Czechowska, K. Wybor (86); MUL CKD Hospital: I. Cygankiewicz, P. Ptaszyński (41); MUL Bieganski Hospital, Chair and Department of Cardiology: J. Kasprzak, H. Qavoq (35); Poznan Medical University HSUH Hospital: P. Guzik, T. Krauze (19); Institute of Cardiology Warsaw: M. Sterlinski (3).

Slovakia (2 centres, 159 patients): Slovak Medical University NUSCH Bratislava: R. Hatala, M. Svetlosak (109); SUSSCH Banska Bystrica: G. Kaliska, J. Martinek (50).

Denmark (2 centres, 143 patients): Rigshospitalet Copenhagen: J. Hastrup Svendsen, K. Thamsborg (60); Gentofte Hospital, Copenhagen: J. Hansen, I.M. Schloett-Hyldelund, J. Laage-Petersen (83).

Belgium (1 centre, 131 patients): Department of Cardiovascular Sciences, University of Leuven and University Hospitals Leuven (KUL): R. Willems, B. Vandenberk, S. van Soest.

Greece (1 centre, 108 patients): Attikon University Hospital Athens: P. Flevari, D. Katsaras, A. Katsimardos, D. Leftheriotis, K. Papangelopoulou, C. Varlamos.

Bulgaria (4 centres, 105 patients): Acibadem City Clinic Tokuda Hospital: V. Traykov (34); St. Anna Hospital: V. Velchev (30); St. Ekaterina University Hospital: S. Iovev (22); National Heart Hospital: T. Shalganov (19); all in Sofia.

Switzerland (1 centre, 74 patients): University Hospital Basel: C. Sticherling, D. Conen, S. Giesebart.

Czech Republic (2 centres, 73 patients): University Hospital Brno: T. Novotny, M. Kozak (39); University Hospital Olomouc: M. Taborsky, J. Galuszka (34).

Netherlands (1 centre, 68 patients): University Medical Center Utrecht, Department of Cardiology: A. E. Tuinenburg, S. Wijers; Department of Medical Physiology: M.A. Vos, S. Wijers, A. Dunnink, D. Sprenkeler.

Spain (1 centre, 61 patients): Hospital Clinic Barcelona, Department of Cardiology, IDIBAPS: J. Brugada, E. Arbelo, E. Trucco, S. Vidorreta.

Finland (1 centre, 36 patients): University of Oulu Medical Center: H. Huikuri, T. Kenttä, A. Pelli, P. Huikuri, P. Koski.

Sweden (2 centres, 16 patients): Karolinska Institute Stockholm: F. Braunschweig, H. Karlsson, D. Ersgaard (14); Lund University Hospital: P. Platonov (2).

Endpoint Adjudication Committee: G. Grönefeld, T. Klingenheben.

List of EU-CERT-ICD project functionality

WP1 Prospective Study: Department of Cardiology, University Medical Center Göttingen/Germany: M. Zabel, J. Seegers, L. Bergau, G. Hasenfuß, P. Munoz-Exposito, T. Tichelbäcker, A. Kirova, S. Schlögl, R. Sritharan, K. Jörß, J. Macken, M. Misdaq, K. Rudolph.

WP02 Retrospective Registry: Department of Cardiology and Clinical Trial Unit, University Hospital Basel/Switzerland: C. Sticherling, M. Scharfe.

WP3 Health Economics: Charité Institute for Social Medicine, Epidemiology and Health Economics, Berlin/Germany: S. Willich, T. Reinhold, M. Cree.

WP4 Gender: Department of Cardiology, University Hospital - Basel/Switzerland: D. Conen, C. Sticherling.

WP5 ECG core lab beat-to-beat variability of repolarization: University Medical Center Utrecht, Department of Medical Physiology: M.A. Vos, S. Wijers, A. Dunnink, D. Sprenkeler.

WP6 ECG core lab T-wave morphology: St. Paul's Electrophysiology/Imperial College London: M. Malik, K. Hnatkova.

WP7 ECG core lab fractionation and early repolarization: Department of Cardiology, University of Oulu Medical Center Oulu/Finland: H. Huikuri, T. Kenttä, A. Pelli.

WP8 Holter Monitoring Core Lab: Department of Cardiology, Klinikum rechts der Isar, Technische Universität München Munich/Germany: G. Schmidt, A. Müller, J. Gerhardt, M. Dommasch, D. Sinnecker,

WP8 Periodic Repolarization Dynamics: Department of Cardiology, Klinikum Großhadern, Ludwig-Maximilians University Munich/Germany: A. Bauer, K. Rizas, W. Hamm.

WP9 Biobanking: Department of Cardiology Klinikum Großhadern, Ludwig-Maximilians University Munich/Germany: S. Kääb, M. Sinner.

WP10 Statistics: Department of Medical Statistics, University Medical Center Göttingen/Germany: T. Friede, C. Röver, M. Harden, B. Kessel.

WP11 Dissemination: Hospital Clinic Barcelona/Spain, Department of Cardiology, IDIBAPS: J. Brugada, E. Arbelo, E. Trucco.

WP12 Study Management: Institute for Clinical Studies/Clinical Trial Unit (IFS/KSM), Study Center and Staff Unit Clinical Studies at University Medical Center Göttingen/Germany: A. Berg, E. Müller, S. Apel, F. Walker, N. Kirchhof, S. Pfeiffer, A. Görlitz, A. Molitor, J. Heinrich.

WP13 Project Management: Gabo:mi Munich/Germany (2013–2016): S. Annetzberger, B. Fuchs; EU International Office University Medical Center Göttingen/Germany: A. Landwehr, A. Merk, A. Wilke, C. Hennecke, R. Mansch.

ECG, electrocardiogram
EU, European Union
WP, work package

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