

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

Zabel, Markus; Sticherling, Christian; Willems, Rik; Lubinski, Andrzej; Bauer, Axel; Bergau, Leonard; Braunschweig, Frieder; Brugada, Josep; Brusich, Sandro; Conen, David; ...

Source / Izvornik: **ESC Heart Failure, 2019, 6, 182 - 193**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1002/ehf2.12367>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:462300>

Rights / Prava: [Attribution-NonCommercial-NoDerivatives 4.0 International](#)/[Imenovanje-Nekomercijalno-Bez prerada 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-08-29**



Repository / Repozitorij:

[Repository of the University of Rijeka, Faculty of Medicine - FMRI Repository](#)



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

Markus Zabel^{1,2*}, Christian Sticherling³, Rik Willems⁴, Andrzej Lubinski⁵, Axel Bauer⁶, Leonard Bergau¹, Frieder Braunschweig⁷, Josep Brugada⁸, Sandro Brusich⁹, David Conen^{3,10}, Iwona Cygankiewicz¹¹, Panagiota Flevari¹², Milos Taborsky¹³, Jim Hansen¹⁴, Gerd Hasenfuß^{1,2}, Robert Hatala¹⁵, Heikki V. Huikuri¹⁶, Svetoslav Iovchev¹⁷, Stefan Kääh⁶, Gabriela Kaliska¹⁸, Jaroslaw D. Kasprzak¹⁹, Lars Lüthje¹, Marek Malik²⁰, Tomas Novotny²¹, Nikola Pavlovic²², Georg Schmidt²³, Tchavdar Shalghanov²⁴, Rajeeva Sritharan¹, Simon Schlögl¹, Janko Szavits Nossan²⁵, Vassil Traykov²⁶, Anton E. Tuinenburg²⁷, Vasil Velchev²⁸, Marc A. Vos²⁹, Stefan N. Willich³⁰, Tim Friede^{2,31}, Jesper Hastrup Svendsen³², Béla Merkely³³ for the EU-CERT-ICD Study Investigators[†]

¹Department of Cardiology and Pneumology, Heart Center, University Medical Center, Göttingen, Germany; ²DZHK (German Center for Cardiovascular Research), partner site Göttingen, Göttingen, Germany; ³Department of Cardiology, University Hospital, Basel, Switzerland; ⁴Department of Cardiovascular Sciences, University of Leuven, Belgium; ⁵Department of Cardiology, Medical University of Lodz (MUL) WAM Hospital, Lodz, Poland; ⁶Department of Cardiology, Klinikum Großhadern, Ludwig-Maximilians-Universität München, Munich, Germany; ⁷Department of Cardiology, Karolinska Institutet, Stockholm, Sweden; ⁸IDIBAPS, Department of Cardiology, Hospital Clinic Barcelona, Barcelona, Spain; ⁹Department of Cardiovascular Disease, KBC Rijeka, Rijeka, Croatia; ¹⁰Population Health Research Institute, McMaster University, Hamilton, ON, Canada; ¹¹Department of Electrophysiology, Medical University of Lodz (MUL), Lodz, Poland; ¹²2nd Department of Cardiology, Attikon University Hospital, Athens, Greece; ¹³Department of Cardiology, University Hospital, Olomouc, Czech Republic; ¹⁴Gentofte Hospital, Copenhagen, Denmark; ¹⁵Slovak Medical University NUSCH, Bratislava, Slovakia; ¹⁶Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland; ¹⁷Department of Cardiology, St. Ekaterina University Hospital, Sofia, Bulgaria; ¹⁸Department of Cardiology, SUSSCH, Banska Bystrica, Slovakia; ¹⁹Chair and Department of Cardiology, Bieganski Hospital, Medical University of Lodz (MUL), Lodz, Poland; ²⁰National Heart and Lung Institute, Imperial College, London, UK; ²¹Department of Internal Medicine and Cardiology, University Hospital Brno, Brno, Czech Republic; ²²Department of Cardiology, KBC Sestre Milosrdnice, Zagreb, Croatia; ²³Med. Klinik und Poliklinik I, Technische Universität München, Klinikum rechts der Isar, Munich, Germany; ²⁴Department of Cardiology, National Heart Hospital, Sofia, Bulgaria; ²⁵Department of Cardiology, Magdalena Klinika, Krapinske Toplice, Croatia; ²⁶Department of Cardiology, Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria; ²⁷Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; ²⁸Department of Cardiology, St. Anna Hospital, Sofia, Bulgaria; ²⁹Department of Medical Physiology, University Medical Center Utrecht, Utrecht, The Netherlands; ³⁰Institute for Social Medicine, Epidemiology and Health Economics, Charité Universitätsmedizin Berlin, Berlin, Germany; ³¹Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany; ³²Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; ³³Department 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

Received: 15 August 2018; Accepted: 30 August 2018

*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

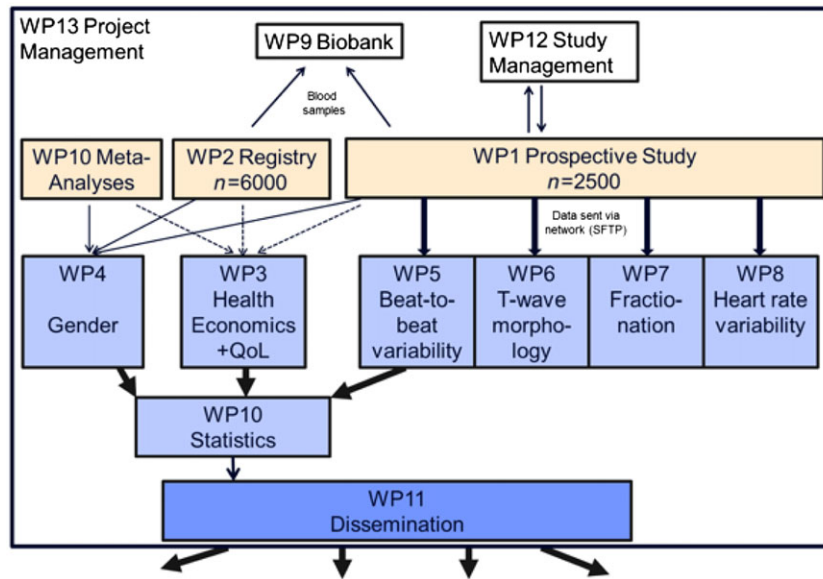
The ‘European Comparative Effectiveness Research to assess the use of primary prophylactic Implantable Cardioverter Defibrillators (EU-CERT-ICD)’ was funded by the European Community’s Seventh Framework Programme as a modular research project to study the effectiveness of prophylactic ICDs. In addition to the described prospective study, a retrospective registry¹⁷ 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

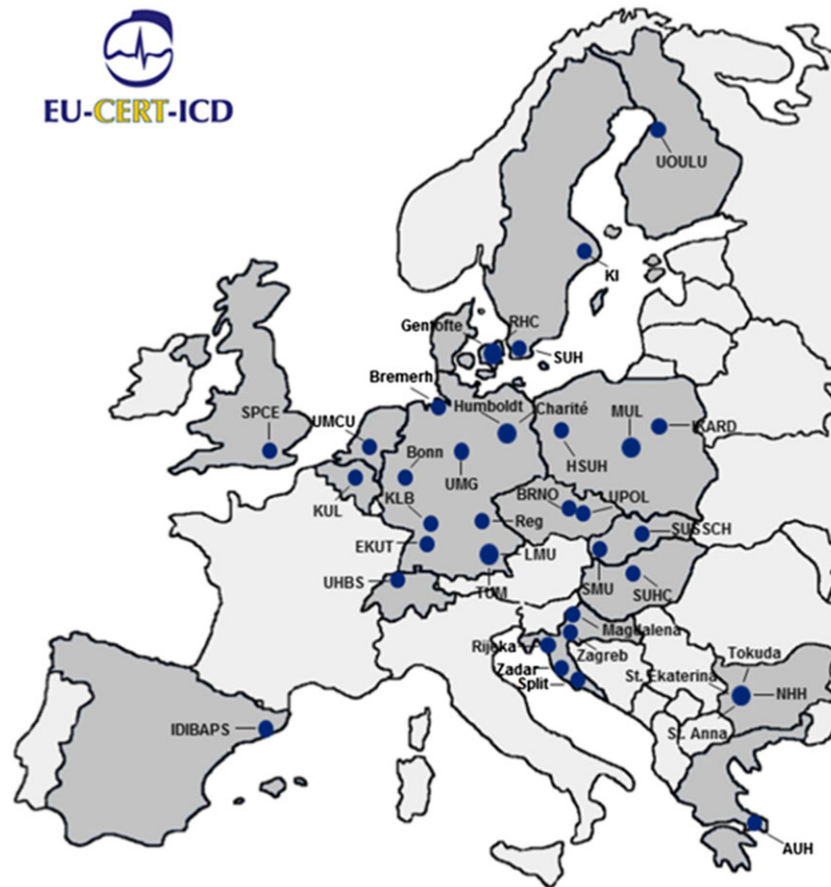
Secondary endpoints of the study are as follows:

- 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 \geq 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 \leq 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 repolarization⁴⁵ 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.

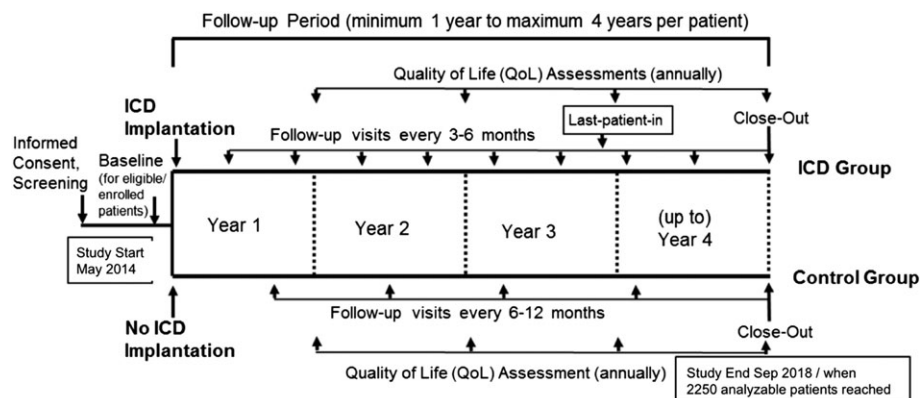
Follow-up

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

patients²³ 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 data⁵² 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 sub-distribution 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 socio-economic 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 guidelines⁴ 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-HeFT⁵⁶ and MADIT-II⁶² 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 system⁷⁰ 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. Kääh, 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. Vandenberg, 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. Iovet (22); National Heart Hospital: T. Shalganov (19); all in Sofia.

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

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. Tuinburg, 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. Kääh, 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

References

- Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001; **345**: 1473–1482.
- Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877–883.
- Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352**: 225–237.
- Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen S, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ, Group ESCSD. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; **36**: 2793–2867.
- Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of

- sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2018; **138**: e210–e271.
6. Kramer DB, Friedman PA, Kallinen LM, Morrison TB, Crusan DJ, Hodge DO, Reynolds MR, Hauser RG. Development and validation of a risk score to predict early mortality in recipients of implantable cardioverter-defibrillators. *Heart Rhythm* 2012; **9**: 42–46.
 7. Bilchick KC, Stukenborg GJ, Kamath S, Cheng A. Prediction of mortality in clinical practice for medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. *J Am Coll Cardiol* 2012; **60**: 1647–1655.
 8. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA 3rd, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W, for the MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012; **367**: 2275–2283.
 9. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JB, Hersi A, Gulaj M, Wijfels MC, Santi E, Manotta L, Arenal A. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *JAMA* 2013; **309**: 1903–1911.
 10. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Kober L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray JJV. Declining risk of sudden death in heart failure. *N Engl J Med* 2017; **377**: 41–51.
 11. Koller MT, Schaer B, Wolbers M, Sticherling C, Bucher HC, Osswald S. Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. *Circulation* 2008; **117**: 1918–1926.
 12. Barsheshet A, Moss AJ, Huang DT, McNitt S, Zareba W, Goldenberg I. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. *J Am Coll Cardiol* 2012; **59**: 2075–2079.
 13. Goldberger JJ, Buxton AE. Personalized medicine vs guideline-based medicine. *JAMA* 2013; **309**: 2559–2560.
 14. Goldberger JJ. Evidence-based analysis of risk factors for sudden cardiac death. *Heart Rhythm* 2009; **6**: S2–S7.
 15. Wellens HJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, Huikuri HV, Kääh S, La Rovere MT, Malik M, Myerburg RJ, Simoons ML, Swedberg K, Tijssen J, Voors AA, Wilde AA. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J* 2014; **35**: 1642–1651.
 16. Huikuri HV, Makikallio TH, Raatikainen MJ, Perkiomaki J, Castellanos A, Myerburg RJ. Prediction of sudden cardiac death: appraisal of the studies and methods assessing the risk of sudden arrhythmic death. *Circulation* 2003; **108**: 110–115.
 17. Sticherling C, Arendacka B, Svendsen JH, Wijers S, Friede T, Stockinger J, Dommasch M, Merkely B, Willems R, Lubinski A, Scharfe M, Braunschweig F, Svetlosak M, Zürrn CS, Huikuri H, Flevari P, Lund-Andersen C, Schaer BA, Tuinenburg AE, Bergau L, Schmidt G, Szeplaki G, Vanderberk B, Kowalczyk E, Eick C, Juntilla J, Conen D, Zabel M, for the EU-CERT-ICD Investigators. Sex differences in outcomes of primary prevention implantable cardioverter defibrillator therapy: combined registry data from eleven European countries. *Europace* 2018; **20**: 963–970.
 18. Conen D, Arendacka B, Röver C, Bergau L, Munoz P, Wijers S, Sticherling C, Zabel M, Friede T. Gender differences in appropriate shocks and mortality among patients with primary prophylactic implantable cardioverter-defibrillators: systematic review and meta-analysis. *PLoS One* 2016; **11**: e0162756.
 19. Bergau L, Tichelbäcker T, Kessel B, Luthje L, Fischer TH, Friede T, Zabel M. Predictors of mortality and ICD shock therapy in primary prophylactic ICD patients – a systematic review and meta-analysis. *PLoS One* 2017; **12**: e0186387.
 20. Tomzik J, Koltermann KC, Zabel M, Willich SN, Reinhold T. Quality of life in patients with an implantable cardioverter defibrillator: a systematic review. *Front Cardiovasc Med* 2015; **2**: 34.
 21. Baumert M, Porta A, Vos MA, Malik M, Couderc JP, Laguna P, Piccirillo G, Smith GL, Tereshchenko LG, Volders PG. QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology. *Europace* 2016; **18**: 925–944.
 22. Seegers J, Bergau L, Exposito PM, Bauer A, Fischer TH, Lüthje L, Hasenfuss G, Friede T, Zabel M. Prediction of appropriate shocks using 24-hour holter variables and T-wave alternans after first implantable cardioverter-defibrillator implantation in patients with ischemic or nonischemic cardiomyopathy. *Am J Cardiol* 2016; **118**: 86–94.
 23. Seegers J, Conen D, Jung K, Bergau L, Dorenkamp M, Lüthje L, Sohns C, Sossalla ST, Fischer TH, Hasenfuss G, Friede T, Zabel M. Sex difference in appropriate shocks but not mortality during long-term follow-up in patients with implantable cardioverter-defibrillators. *Europace* 2016; **18**: 1194–1202.
 24. Hnatkova K, Seegers J, Barthel P, Novotny T, Smetana P, Zabel M, Schmidt G, Malik M. Clinical value of different QRS-T angle expressions. *Europace* 2018; **20**: 1352–1361.
 25. Seegers J, Hnatkova K, Friede T, Malik M, Zabel M. T-wave loop area from a pre-implant 12-lead ECG is associated with appropriate ICD shocks. *PLoS One* 2017; **12**: e0173868.
 26. Vandenberg B, Robyns T, Goovaerts G, Van Soest S, Floré V, Garweg C, Van Huffel S, Ector J, Willems R. Inferior and anterior QRS fragmentation have different prognostic value in patients who received an implantable defibrillator in primary prevention of sudden cardiac death. *Int J Cardiol* 2017; **243**: 223–228.
 27. Sprenkeler DJ, Tuinenburg AE, Ritsema van Eck HJ, Malik M, Zabel M, Vos MA. Circadian pattern of short-term variability of the QT-interval in primary prevention ICD patients – EU-CERT-ICD methodological pilot study. *PLoS One* 2017; **12**: e0183199.
 28. Aro AL, Kenttä TV, Huikuri HV. Microvolt T-wave alternans: where are we now? *Arrhythm Electrophysiol Rev* 2016; **5**: 37–40.
 29. Huikuri HV, Zabel M, Lombardi F, Malik M, on behalf of the e-Health, Digital Rhythm Study Group of the European Heart Rhythm Association. Measurement of cardiovascular autonomic function: where to go from here? *Int J Cardiol* 2017; **249**: 73–74.
 30. Huikuri HV. Prediction of benefits from prophylactic implantable cardioverter-defibrillator therapy. *Int J Cardiol* 2017; **243**: 274–275.
 31. Malik M, Camm AJ, Huikuri H, Lombardi F, Schmidt G, Schwartz PJ, Zabel M, on behalf of e-Rhythm Study Group of EHRA. Electronic gadgets and their health-related claims. *Int J Cardiol* 2018; **258**: 163–164.
 32. Malik M, Huikuri H, Lombardi F, Schmidt G, Zabel M, e-Rhythm Study Group of EHRA. Conundrum of the Tpeak-Tend interval. *J Cardiovasc Electrophysiol* 2018; **29**: 767–770.
 33. Malik M, Buxton AE, Huikuri H, Lombardi F, Schmidt G, Zabel M, e-Rhythm Study Group of EHRA. Noninvasive electrophysiology in risk assessment and screening. *Heart Rhythm* 2018; **15**: 803–804.
 34. Raatikainen MJ, Arnar DO, Merkely B, Camm AJ, Hindricks G. Access to and clinical use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology countries: 2016 Report from the European Heart Rhythm Association. *Europace* 2016; **18**: iii1–iii79.
 35. Goldstein S, Friedman L, Hutchinson R, Canner P, Romhilt D, Schlant R, Sobrino R, Verter J, Wasserman A. Timing,

- mechanism and clinical setting of witnessed deaths in postmyocardial infarction patients. *J Am Coll Cardiol* 1984; **3**: 1111–1117.
36. Oosterhoff P, Tereshchenko LG, van der Heyden MA, Ghanem RN, Fetis B, Berger RD, Vos MA. Short-term variability of repolarization predicts ventricular tachycardia and sudden cardiac death in patients with structural heart disease: a comparison with QT variability index. *Heart Rhythm* 2011; **8**: 1584–1590.
 37. Sinnecker D, Dommasch M, Steger A, Berkefeld A, Hoppmann P, Müller A, Gebhardt J, Barthel P, Hnatkova K, Huster KM, Laugwitz KL, Malik M, Schmidt G. Expiration-triggered sinus arrhythmia predicts outcome in survivors of acute myocardial infarction. *J Am Coll Cardiol* 2016; **67**: 2213–2220.
 38. Verrier RL, Kligenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, Ikeda T, Martinez JP, Narayan SM, Nieminen T, Rosenbaum DS. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrophysiology. *J Am Coll Cardiol* 2011; **58**: 1309–1324.
 39. Rizas KD, McNitt S, Hamm W, Massberg S, Käb S, Zareba W, Couderc JP, Bauer A. Prediction of sudden and non-sudden cardiac death in post-infarction patients with reduced left ventricular ejection fraction by periodic repolarization dynamics: MADIT-II substudy. *Eur Heart J* 2017; **38**: 2110–2118.
 40. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; **17**: 354–381.
 41. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, Bigger JT Jr, Schömig A. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999; **353**: 1390–1396.
 42. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K, Hnatkova K, Schömig A, Huikuri H, Bunde A, Malik M, Schmidt G. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet* 2006; **367**: 1674–1681.
 43. Zabel M, Malik M. Practical use of T wave morphology assessment. *Card Electrophysiol Rev* 2002; **6**: 316–322.
 44. Terho HK, Tikkanen JT, Junttila JM, Anttonen O, Kenttä TV, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Prevalence and prognostic significance of fragmented QRS complex in middle-aged subjects with and without clinical or electrocardiographic evidence of cardiac disease. *Am J Cardiol* 2014; **114**: 141–147.
 45. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009; **361**: 2529–2537.
 46. Otterstad JE. Measuring left ventricular volume and ejection fraction with the bi-plane Simpson's method. *Heart* 2002; **88**: 559–560.
 47. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473–483.
 48. Dixon T, Lim LL, Oldridge NB. The MacNew heart disease health-related quality of life instrument: reference data for users. *Qual Life Res* 2002; **11**: 173–183.
 49. Burns JL, Serber ER, Keim S, Sears SF. Measuring patient acceptance of implantable cardiac device therapy: initial psychometric investigation of the Florida Patient Acceptance Survey. *J Cardiovasc Electrophysiol* 2005; **16**: 384–390.
 50. Bergau L, Willems R, Sprenkeler DJ, Fischer TH, Flevari P, Hasenfuss G, Katsaras D, Kirova A, Lehnart SE, Lüthje L, Röver C, Seegers J, Sossalla S, Dunnink A, Sritharan R, Tuinenburg AE, Vandenberk B, Vos MA, Wijers SC, Friede T, Zabel M. Differential multivariable risk prediction of appropriate shock versus competing mortality – a prospective cohort study to estimate benefits from ICD therapy. *Int J Cardiol* 2018; <https://doi.org/10.1016/j.ijcard.2018.06.103>.
 51. Smith T, Levy WC, Schaer BA, Balk AH, Sticherling C, Jordaens L, Theuns DA. Performance of the Seattle Heart Failure Model in implantable defibrillator patients treated with cardiac resynchronization therapy. *Am J Cardiol* 2012; **110**: 398–402.
 52. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983; **39**: 499–503.
 53. Peterson PN, Daugherty SL, Wang Y, Vidaillet HJ, Heidenreich PA, Curtis JP, Masoudi FA, on behalf of the National Cardiovascular Data Registry. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation* 2009; **119**: 1078–1084.
 54. MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P, Birnie D, Simpson CS, Khaykin Y, Pinter A, Nanthakumar K, Calzavara AJ, Austin PC, Tu JV, Lee DS. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. *Ann Intern Med* 2012; **156**: 195–203.
 55. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496–509.
 56. Levy WC, Lee KL, Hellkamp AS, Poole JE, Mozaffarian D, Linker DT, Maggioni AP, Anand I, Poole-Wilson PA, Fishbein DP, Johnson G, Anderson J, Mark DB, Bardy GH. Maximizing survival benefit with primary prevention implantable cardioverter-defibrillator therapy in a heart failure population. *Circulation* 2009; **120**: 835–842.
 57. Lee DS, Hardy J, Yee R, Healey JS, Birnie D, Simpson CS, Crystal E, Mangat I, Nanthakumar K, Wang X, Krahn AD, Dorian P, Austin PC, Tu JV, on behalf of the Investigators of the Ontario ICD Database. Clinical risk stratification for primary prevention implantable cardioverter defibrillators. *Circ Heart Fail* 2015; **8**: 927–937.
 58. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, Investigators D. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016; **375**: 1221–1230.
 59. Shadman R, Poole JE, Dardas TF, Mozaffarian D, Cleland JG, Swedberg K, Maggioni AP, Anand IS, Carson PE, Miller AB, Levy WC. A novel method to predict the proportional risk of sudden cardiac death in heart failure: derivation of the Seattle proportional risk model. *Heart Rhythm* 2015; **12**: 2069–2077.
 60. Bilchick KC, Wang Y, Cheng A, Curtis JP, Dharmarajan K, Stukenborg GJ, Shadman R, Anand I, Lund LH, Dahlstrom U, Santand U, Maggioni A, Swedberg K, O'Conner C, Levy WC. Seattle heart failure and proportional risk models predict benefit from implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2017; **69**: 2606–2618.
 61. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, Olesen LL, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, Kober L, Thune JJ. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017; **136**: 1772–1780.
 62. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, Zareba W, McNitt S, Andrews ML, for the MADIT-II Investigators. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008; **51**: 288–296.
 63. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, Boehmer JP, Carlson MD, Frantz RP, McNulty SE, Rogers JG, Anderson J, Johnson GW, Walsh MN, Poole JE, Mark DB, Lee KL, Bardy GH. Impact of implantable cardioverter-defibrillator,

- amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation* 2009; **120**: 2170–2176.
64. Bansal N, Szpiro A, Reynolds K, Smith DH, Magid DJ, Gurwitz JH, Masoudi F, Greenlee RT, Tabada GH, Sung SH, Dighe A, Go AS. Long-term outcomes associated with implantable cardioverter defibrillator in adults with chronic kidney disease. *JAMA Intern Med* 2018; **178**: 390–398.
65. Junttila J, Huikuri H, Pelli A, Kenttä T, Friede T, Willems R, Sticherling C, Bergau L, Malik M, Vandenberk B, Vos MA, Schmidt G, Merkely B, Lubinski A, Svetlosak M, Braunschweig F, Harden M, Zabel M, for the EU-CERT-ICD Investigators. Appropriate shocks and mortality in diabetic and vs. non-diabetic patients with prophylactic implantable cardioverter-defibrillator. *Heart Rhythm* 2018; **15**: S300.
66. Ranasinghe I, Parzynski CS, Freeman JV, Dreyer RP, Ross JS, Akar JG, Krumholz HM, Curtis JP. Long-term risk for device-related complications and reoperations after implantable cardioverter-defibrillator implantation: an observational cohort study. *Ann Intern Med* 2016; **165**: 20.
67. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**: 2733–2779.
68. van Barneveld M, Dijkgraaf MGW, Hulleman M, Boersma LVA, Delnoy P, Meine M, Tuinenburg AE, Theuns D, van der Voort PH, Kimman GP, Buskens E, Tijssen JPG, Bruinsma N, Verstraelen TE, Zwinderman AH, van Dessel P, Wilde AAM, for the DO-IT investigators. Dutch outcome in implantable cardioverter-defibrillator therapy (DO-IT): registry design and baseline characteristics of a prospective observational cohort study to predict appropriate indication for implantable cardioverter-defibrillator. *Neth Heart J* 2017; **25**: 574–580.
69. Dagnes N, Hindricks G. Devices for management of sudden cardiac death: successes, challenges and perspectives. *Int J Cardiol* 2017; **237**: 34–37.
70. <https://innovationsfonds.g-ba.de/projekte/versorgungsforschung/reset-crt-reevaluation-der-optimalen-resynchronisationstherapie-bei-patienten-mit-herzinsuffizienz.167> (29 September 2018).