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Research Paper

Nocturnal respiratory rate predicts ICD benefit: A prospective, controlled, multicentre cohort study

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ABSTRACT

Background: Implantable cardioverter defibrillators (ICDs) prevent sudden cardiac death. ICD implantation decisions are currently based on reduced left ventricular ejection fraction (LVEF≤35%). However, in some patients, the non-arrhythmic death risk predominates thus diminishing ICD-therapy benefits. Based on previous observations, we tested the hypothesis that compared to the others, patients with nocturnal respiratory rate (NRR) ≥18 breaths per minute (brpm) benefit less from prophylactic ICD implantations.

Methods: This prospective cohort study was a pre-defined sub-study of EU-CERT-ICD trial conducted at 44 centers in 15 EU countries between May 12, 2014, and September 6, 2018. Patients with ischaemic or non-ischaemic cardiomyopathy were included if meeting primary prophylactic ICD implantation criteria. The primary endpoint was all-cause mortality. NRR was assessed blindly from pre-implantation 24-hour Holters. Multivariable models and propensity stratification evaluated the interaction between NRR and the ICD mortality effect. This study is registered with ClinicalTrials.gov (NCT0206419).

Findings: Of the 2,247 EU-CERT-ICD patients, this sub-study included 1,971 with complete records. In 1,363 patients (61.7 (12) years; 244 women) an ICD was implanted; 608 patients (63.2 (12) years; 108 women) were treated conservatively. During a median 2.5-year follow-up, 202 (14.8%) and 95 (15.6%) patients died in the ICD and control groups, respectively. NRR statistically significantly interacted with the ICD mortality effect (p = 0.0070). While the 1,316 patients with NRR<18 brpm showed a marked ICD benefit on mortality (adjusted HR 0.529 (95% CI 0.376–0.746); p = 0.0003), no treatment effect was demonstrated in 655 patients with NRR≥18 brpm (adjusted HR 0.981 (95% CI 0.669–1.438); p = 0.9202).

Interpretation: In the EU-CERT-ICD trial, patients with NRR≥18 brpm showed limited benefit from primary prophylactic ICD implantation. Those with NRR<18 brpm benefitted substantially.

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Research in Context

Evidence before this study

Current guidelines recommend prophylactic treatment with implantable cardioverter defibrillators (ICD) in patients with reduced ejection fraction. However, in patients at low risk of malignant arrhythmias or at high risk of non-arrhythmic death, e.g. due to pump failure, the ICD implantation offers little or no benefit.

Added value of this study

The study was a prospectively planned sub-study of the EU-CERT-ICD trial which showed an approximately 30% overall survival benefit from prophylactic ICD implantation. The sub-study that we report showed that an easy-to-determine mean nocturnal respiratory rate (NRR) allows the differentiation of groups of patients who benefit substantially from ICD implantation and who benefit much less, if at all.

Implications of all the available evidence

As an impact on the guidelines for prophylactic ICD implantation require independent confirmations, immediate use of NRR lies in facilitation of individual therapeutic decisions in borderline cases. In respect of an independent confirmation, we believe that based on our observation, a controlled outcome study is ethically justified with randomisation of patients with an LVEF $\leq$35% and an NRR $>$18 breaths per minute into ICD and control groups.

1. Introduction

The decision on primary prophylactic implantation of a cardioverter defibrillator (ICD) is currently based mainly on a reduced left ventricular ejection fraction (LVEF$\leq$35%) [1]. However, a number of patients who meet this criterion do not truly benefit from the device. They neither suffer from malignant arrhythmias after ICD implantation nor is their eventual death triggered by or related to a malignant arrhythmia.

In cardiac patients, respiratory rate at rest is an elementary measure of cardiovascular function [1,2,3,4]. Recent studies showed that in patients with acute coronary syndrome, increased respiratory rate indicates a poor prognosis [5,6]. In post-infarction patients, averaged respiratory rate assessed during night-time (nocturnal respiratory rate, NRR) predicted non-sudden rather than sudden cardiac death [7]. In this seminal study, a substantial proportion of patients with LVEF$\leq$35%, and thus eligible for primary ICD implantation, had an elevated NRR [7]. This made it reasonable to hypothesize that in contrast to ICD-recipients with lower NRR, primary ICD prophylaxis would be less effective in patients with LVEF$\leq$35% and increased NRR since they would more likely suffer from non-ICD preventable deaths.

To evaluate this concept prospectively, we predefined a sub-study of the EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD) [8]. The sub-study tested the hypothesis that patients with elevated NRR, the survival benefit from prophylactic ICD implantation is substantially reduced compared to patients with lower (normal) NRR. This text reports the sub-study results

2. Methods

2.1. Study design and participants

EU-CERT-ICD was a prospective investigator-initiated, non-randomised, controlled, cohort study carried out in 44 centres across 15 European countries between May 12, 2014, and September 6, 2018. The primary objective of EU-CERT-ICD was to identify subgroups of patients benefitting from ICD implantation [8]. Eligible participants were aged $\geq$18 years, met the criteria for primary prophylactic implantation of ICDs according to the current guidelines [1,9,10], had ischaemic or non-ischaemic cardiomyopathy, and LVEF$\leq$35%. Patients were excluded if they had an indication for secondary ICD prophylaxis, high-degree atrioventricular block ($\geq$II) at resting heart rates, a pacemaker implanted, unstable cardiac conditions such as decompensated heart failure (New York Heart Association - NYHA - functional class IV) or acute coronary syndrome, or a life expectancy of $\leq$1 year or if they were considered to be candidates for cardiac resynchronization therapy [8,11].

This study is registered with ClinicalTrials.gov, number NCT0206419. It was approved by local ethics committees of all participating centres and all patients provided written informed consent before inclusion. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The manuscript was written in accordance with the STROBE recommendations.

2.2. EU-CERT-ICD

EU-CERT-ICD included two groups of patients: the ICD group of patients who underwent ICD implantation, and the control group of patients treated conservatively. The decision to implant an ICD or to opt for conservative treatment was not determined by the study design. Rather, it was based on the decision of the treating physician and the patient, and was predominantly influenced by regional and national health policy practices [8]. In particular, economic differences amongst EU countries impact on the availability of prophylactic ICD implantations even for patients with identical demographic and clinical characteristics.

In the ICD group, ICDs were implanted according to local practice at the study centres. Mandatory baseline ICD programming was established, consisting of a ventricular tachycardia therapy zone of 200–250 beats per minute (bpm), a ventricular fibrillation therapy zone above 250 bpm, and a monitor zone of 170–200 bpm. Ventricular tachycardia was treated by antitachycardia pacing (ATP) followed by shocks of maximum output. Ventricular fibrillation was treated by ATP during charge (if applicable) and shocks of maximum output. ICD programming was permitted to be individualized for clinical reasons.

Underlying cardiac disease, New York Health Association functional class, pulse, resting blood pressure, weight, height, and cardiovascular pharmacological treatments and comorbidities (including peripheral arterial disease, cerebral vascular disease, pulmonary disease, diabetes mellitus, hypertension, sleep apnoea, tobacco use, and any malignant disease within the last 5 years) were recorded at baseline. Standard laboratory parameters - including creatinine concentrations, estimated glomerular filtration rates, serum blood urea nitrogen, N-terminal pro-B-type natriuretic peptide, and B-type natriuretic peptide - were also recorded.

A high-resolution (1 kHz) 12-channel 24-h Holter recording (CM 3000–12 BT; Getemed, Teltow, Germany) was obtained in all

patients the day before ICD implantation (for patients in the ICD group) or at study enrolment (for patients in the control group). The raw electrocardiographic data were digitally transferred and centrally stored at the University of Göttingen (Göttingen, Germany) by TF and MZ. Data pre-processing, including quality checks, exclusion of artefacts and beat annotations, was performed blindly at the Technical University of Munich (Munich, Germany).

2.3. NRR sub-study

The NRR sub-study was conducted in accordance with a predefined analysis plan within the EU-CERT-ICD framework.

NRR was calculated by a previously validated algorithm. Technical details of this algorithm calculating the respiratory rate based on Holter ECGs have been described elsewhere [12]. In short, the algorithm determined the respiratory rate using QRS amplitudes, QRS vectors, and heartbeat intervals, which are all influenced by respiration. NRR expressed the median value of respiratory frequency found in the period between midnight and 6AM.

Per a prospective definition, Holter recordings were excluded if they did not meet the predefined quality criteria for the NRR assessment (i.e., substantial baseline wander, significant noise, or recording artefacts) for more than one hour during the analysis interval.

To avoid possible bias, the centre in Munich has never received individual clinical data (clinical variables and mortality) of the EU-CERT-ICD population.

2.4. Follow-up

All patients in the ICD group were followed up every 3–6 months either in outpatient clinics or remotely. Episodes of shock or ATP were stored as electrocardiograms for adjudication, and programming changes were recorded. Patients in the control group had scheduled visits to outpatient clinics every 6–12 months. In both groups, information was also retrieved from hospital records, and via telephone or post from patients, relatives, general practitioners, and local authorities. If a patient underwent heart transplantation or implantation of a ventricular assist device, follow-up was censored on the relevant date without an event considered.

2.5. Outcomes

All-cause mortality was primary endpoint, and first appropriate shock was secondary endpoint. All endpoints were reviewed by an external blinded endpoint committee.

2.6. Statistical analysis

The primary endpoint all-cause mortality was visualized by Kaplan-Meier curves and analysed by Cox proportional hazards models stratified by region, which was scrutinized using standard model diagnostics including visual checks of the proportionality assumption. In order to consider possible differences in baseline variables, the primary analyses were adjusted for potential confounders which were selected based on a stepwise procedure using a p-value criterion with a two-sided level of 10% as threshold for entry and stay [13]. This resulted in a list of covariates including age, gender, NYHA class, body mass index, LVEF, diastolic blood pressure, QTc interval duration, creatinine, haemoglobin, and history or presence of atrial fibrillation, COPD or diabetes mellitus. A number of sensitivity analyses were conducted [14]. These included analyses stratified by quintiles of a propensity score [15], which was developed by fitting a logistic regression for treatment group as outcome and numerous baseline characteristics as independent variables. To check whether the propensity score stratification resulted in more balanced treatment groups within the strata, baseline characteristics within the strata were compared. The sensitivity analyses stratified by the propensity score are reported in the supplementary material (supplementary figures 1 and 2).

The interaction of NRR with ICD effects was assessed in Cox regressions that included ICD effect as a factor and NRR as a covariate. The optimum cut-off for NRR was identified by maximizing the interaction between ICD effect and the NRR effect using the cut-off to dichotomize the NRR values. The cut-off was varied between the 20% and 80% quantiles of the NRR values.

Significance was indicated by two-sided p-values less than 0.05; no correction for multiple testing was applied. The sample size calculation for the EU-CERT-ICD cohort has been reported previously [8]. All analyses were done in SAS (version 9.4).

2.7. Role of the funding source

The study was supported by the European Community's Seventh Framework Programme [HEALTH-F2-2009-602299] for 5 years (starting Oct 1, 2013). The sponsor had no input to the design or conduct of the study, to the evaluation of the results, to the writing of the report, and to the decision to submit the paper for publication. All authors were responsible for the interpretation of data, writing the manuscript and approval of the version to be published.

3. Results

During the recruitment period, 2247 patients were prospectively enroled, 1516 patients in the ICD group and 731 in the control group. 276 patients were subsequently excluded due to lack of complete follow-up data (n = 81) or disturbed ECG signals at night-time (n = 195). The population of the NRR sub-study thus included 1971 patients: 1363 in the ICD group and 608 in the control group (Fig. 1). Despite the non-randomized design, patients in the ICD and control groups were well balanced in terms of standardized differences for essential baseline clinical and demographic variables (table 1). Mean patient age was 61.7 years (SD 11.6) in the ICD group and 63.2 years (SD 11.7) in the control group, and more than 80% of patients of both groups were male (table 1). ischaemic cardiomyopathy, affecting 939 (68.9%) patients in the ICD group and 345 (56.7%) in the control group, was the leading cardiac disease. Pharmacological treatment corresponded to contemporary standards in both groups, with β blockers prescribed to 1291 (94.7%) and 566 (93.1%) patients in the ICD and the control group, respectively.

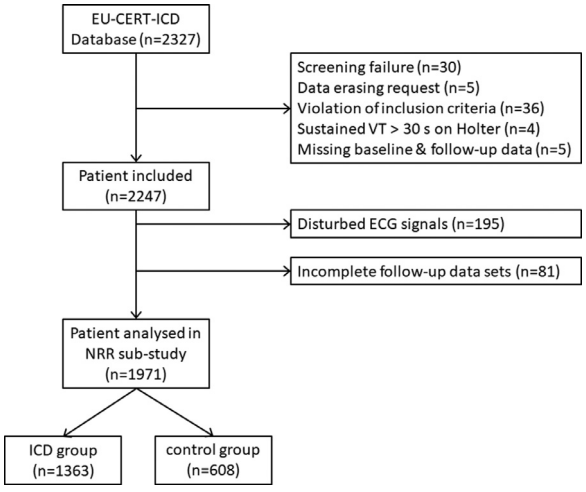


Fig. 1. Study flow chart

EU-CERT-ID=EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators. ECGs=electrocardiograms. ICD=implantable cardioverter defibrillator.

Table 1
Baseline characteristics and treatments of patients in the ICD and control groups.

Baseline characteristics	ICD group		Control group		Standardized difference
Number of patients	1363		608		
Female	244	(17.9)	108	(17.8)	0.00
Region					0.69
Eastern	578	(42.4)	400	(65.8)	
Northern	139	(10.2)	29	(4.8)	
Southern	70	(5.1)	75	(12.3)	
Western	576	(42.3)	104	(17.1)	
Age [years]	61.7	11.6	63.2	11.7	−0.13
BMI [kg/m^2]	27.7	5.2	28.1	4.9	−0.07
Creatinine [mg/dL]	1.2	0.6	1.2	0.6	−0.13
Diastolic blood pressure [mmHg]	73.8	11.1	74.9	10.9	−0.10
Haemoglobin [g/dL]	13.8	1.9	13.9	1.7	−0.01
LVEF [%]	27.5	5.5	29.0	5.6	−0.28
NRR [brpm]	17.1	3.1	17.9	3.8	−0.22
QTc [ms]	438.4	39.0	433.9	44.2	0.11
QRS [ms]	106.4	17.3	103.8	18.2	0.15
Sodium [mmol/L]	139.1	3.2	139.4	3.3	−0.09
AF (history or present)	334	(24.5)	169	(27.8)	−0.07
Chronic obstructive pulmonary disease	157	(11.5)	58	(9.5)	0.06
Diabetes	408	(29.9)	185	(30.4)	−0.01
Leading cardiac disease					−0.25
ischaemic cardiomyopathy	939	(68.9)	345	(56.7)	
Dilated cardiomyopathy	424	(31.1)	263	(43.3)	0.01
Malignant disease	60	(4.4)	25	(4.1)	−0.17
NYHA class					
Class I or II	857	(62.9)	333	(54.8)	
Class III or IV	506	(37.1)	275	(45.2)	
Sleep apnoea with or without airway pressure treatment	62	(4.5)	15	(2.5)	0.11
Tobacco use	887	(65.1)	298	(49.0)	0.33
Amiodarone	100	(7.3)	89	(14.6)	−0.24
AT1 antagonist	266	(19.5)	149	(24.5)	−0.12
Beta-blocker	1291	(94.7)	566	(93.1)	0.07
Loop diuretic	951	(69.8)	466	(76.6)	−0.16

Incidence variables are shown as absolute number (%), numerical variables as mean (standard deviation). Regions: Eastern Europe: Hungary, Bulgaria, Croatia, Poland, Slovakia, and the Czech Republic, Northern Europe: Denmark, Sweden and Finland, Southern Europe: Spain and Greece, Western Europe: Germany, Belgium, Netherlands, and Switzerland. ICD=implantable cardioverter defibrillator. AF=atrial fibrillation, AT1=angiotensin 1, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association.

Median follow-up was 2.7 years (IQR 2.1−3.4; maximum 4.8 years) in the ICD group and 1.2 years (IQR 0.8 −2.6; maximum 4.8 years) in the control group. Since the proportion of patients with missing items was small, complete case analyses were performed. During follow-up, 202 (14.8%) patients in the ICD group and 95 (15.6%) in the control group died. 100 (7.3%) patients in the ICD group received a first appropriate shock. There were 53 crossovers from the control group to the ICD group. Stratification by propensity score quintiles resulted in balanced treatment groups with regard to relevant baseline characteristics (supplementary Tables 1−5).

There was a 31.3% reduction in mortality in the ICD group compared to the control group (adjusted HR 0.687 [95% CI 0.529 − 0.894]; p = 0.0051). NRR showed a significant interaction with the ICD treatment effect in terms of mortality reduction: In patients with low NRR, ICD treatment was associated with a remarkable survival benefit. With increasing NRR the hazard ratio continuously worsens and the survival benefit is nearly eliminated (adjusted p = 0.0070; Fig. 2).

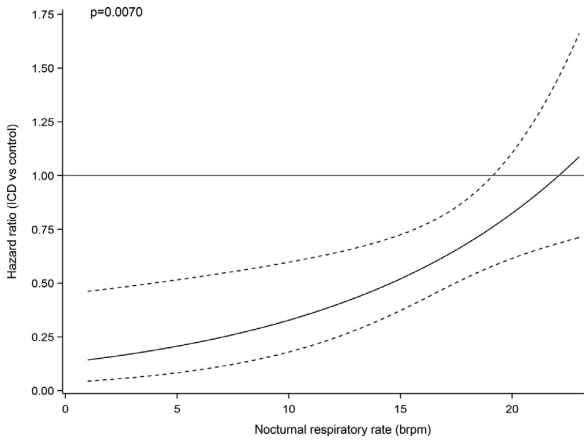
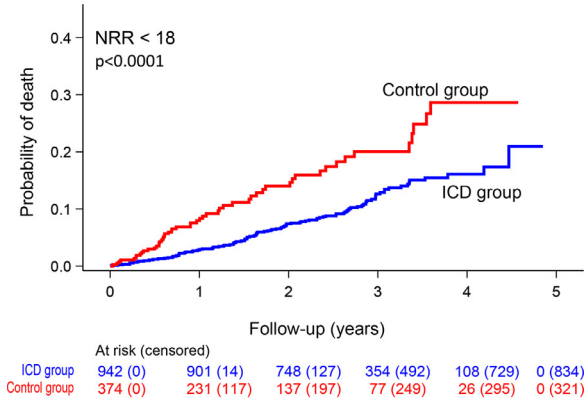


Fig. 2. ICD treatment effect as a function of nocturnal respiratory rate
Adjusted hazard ratios (ICD group vs control group) for mortality are shown. The solid line shows point estimates, and the broken lines show the 95% CIs. ICD=implantable cardioverter defibrillator.

There are no NRR cut-off values for prediction of the ICD treatment effect. In our study population, a cut-off of 18 brpm clearly distinguished patients who benefited from an ICD implantation from those in whom the device had little survival effect. In the 1316 patients with NRR <18 brpm (942 with ICD and 374 controls) there was a marked and statistically significant mortality benefit from ICD implantation (p = 0.0003). In the 655 patients with NRR ≥18 brpm there was no statistical or even practical difference in mortality between the ICD (n = 421) and control (n = 234) groups (p = 0.9202) (Fig. 3). Specifically, in patients with NRR <18 brpm, ICD therapy was



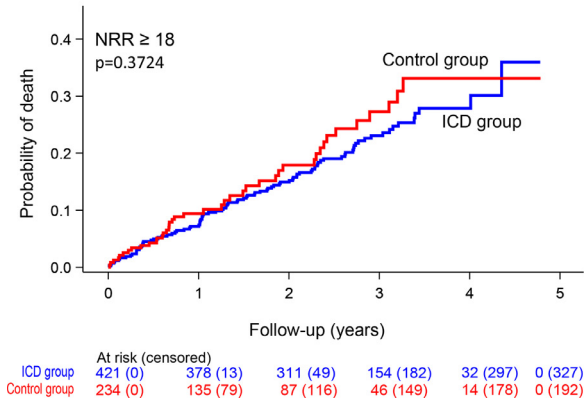


Fig. 3. Unadjusted cumulative mortality in the ICD and control groups in patients with nocturnal respiratory rate ≥18 brpm and <18brpm. ICD=implantable cardioverter defibrillator.

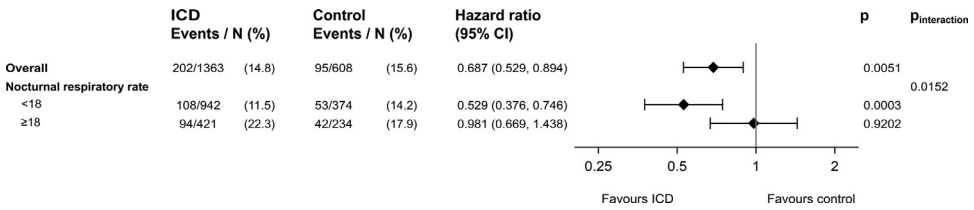


Fig. 4. Adjusted hazard ratios for the ICD group vs the control group
Error bars represent 95% CIs. ICD=implantable cardioverter defibrillator.

associated with a mortality reduction of almost 50% compared with the control treatment (adjusted HR 0.529 [95% CI 0.376 – 0.746]; $p = 0.0003$). In contrast, there was almost no reduction in mortality by ICD therapy in patients with NRR ≥18 brpm (adjusted HR 0.981 [95% CI 0.669 – 1.438]; $p = 0.9202$; interaction $p = 0.0152$; Fig. 4).

Consistent results were achieved by propensity score-adjusted sensitivity analyses (supplementary figures 1 and 2).

4. Discussion

The results of the NRR sub-study suggest that nocturnal respiratory rate predicts the mortality reduction effect of primary ICD prophylaxis in contemporarily treated patients. Overall, mortality reduction by prophylactic ICD implantation was 30% in the total study population. In patients with NRR <18 brpm, this reduction increased to 50% whilst the survival benefit of ICD treatment was almost absent in patients with NRR ≥18 brpm (non-significant survival benefit of only 1%).

Respiratory activity can be quantified by respiratory rate and tidal volume. It is mainly controlled by the brain stem activity which is influenced by peripheral and central chemoreceptors, peripheral mechanoreceptors and central respiratory network [16]. At night, the basal metabolic rate is down-regulated and less CO_2 is produced. A healthy organism reacts to this change by reduced respiratory activity.

In heart failure patients, this regulatory mechanism fails. Night-time respiration is not adequately reduced because of increased sympathetic activity and an increased chemoreflex gain [17,18]. This leads to relative hyperventilation also manifested by hypocapnia. Additionally, a progressive decrease in lung compliance requires higher distending effort for a specific tidal volume [19]. These patients often exhibit fast and shallow breathing as an adaptive mechanism to minimize the respiratory muscles workload and because of maladapted neurohormonal pathways with sympathetic control prominence and parasympathetic withdrawal [20,21,22]. Thus, increased NRR is probably an early indicator of heart failure triggered by subclinical pulmonary congestion, possibly exacerbated in the night-time resting supine position.

This is also consistent with the observation that the distinction between high and low NRR values was not associated with appropriate ICD shocks in the ICD group (details not presented). The lack of appropriate ICD shock prediction by NRR is not surprising since increased NRR appears to be indicative of hemodynamic disturbances rather than of electrical instability [7].

The NRR assessment may help individual decisions on the prophylactic ICD implantation, as patients with increased NRR did not appear to benefit from the therapy meaningfully. These patients need to have their hemodynamic situation optimized by heart failure treatment. However, it seems that they might be spared the side-effects of ICD implantation. A prospective randomized study comparing prophylactic ICD therapy against no ICD implantation in patients with LVEF≤ 35% and NRR ≥18 brpm is needed to confirm our findings.

Finally, combining NRR with parameters of electric instability (e.g. PRD) [14] that stratify patients at malignant arrhythmia risk might help to identify patients with the highest ICD implantation benefit.

Our study had several limitations. The EU-CERT-ICD study was not a randomized investigation. When the EU-CERT-ICD trial was designed in 2012, it appeared ethically impossible to conduct a randomised trial on prophylactic ICD implantation in patients with LVEF≤35%. Thus, the study design took the advantage of the different ICD implantation practices across Europe and used a non-randomised but strictly controlled design [8]. The ICD and control groups were well-balanced, and comprehensive statistical methods, like multiple adjustments and propensity scoring, were used to compensate for remaining differences. We used different statistical models for sensitivity analyses and obtained consistent results. This proved the validity of our results. Further, there has been no prior definition of predictive NRR cut-off value (to predict the ICD survival benefit). Nevertheless, the predictive value of 18.0 brpm is almost identical to the previously published prognostic cut-off value (to predict the outcome) of 18.6 brpm [7,11]. The follow-up was also rather short, especially in patients of the control group. Therefore, the findings of our study need to be confirmed with longer follow-up data. For obvious reasons of clinical practicality, the EU-CERT-ICD protocol included only one pre-implant 24 h Holter recording in each participant. We are therefore unable to comment on spontaneous intra-subject variability of NRR. Nevertheless, since the analysis of this sub-study was prospectively predefined, the possibility of the results being found by a chance can safely be excluded. Finally, the results of the NRR sub-study are based solely on data collected from a European patient population. We are unable to comment on possible differences to other populations.

In conclusion, NRR predicts the treatment effect of primary prophylactic ICD therapy on mortality in contemporarily treated patients. While patients with NRR<18 brpm benefitted substantially from prophylactic ICD implantation, those with NRR > 18 brpm showed little benefit. Assessment of NRR might help guiding treatment decisions about prophylactic implantation of ICDs in patients with ischaemic heart disease or non-ischaemic cardiomyopathy. Further studies are needed to confirm the correctness of NRR-guided treatment decision in prophylactic ICD therapy. In addition, it must be tested whether further improvement is possible by combining NRR with parameters for electrical instability.

Declaration of Competing Interest

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The study was supported by the European Community's Seventh Framework Programme [HEALTH-F2-2009-602299] for 5 years (starting Oct 1, 2013). The sponsor had no input to the design or conduct of the study, to the evaluation of the results, to the writing of the report, and to the decision to submit the paper for publication.

Data sharing

Deidentified individual participant data will be made available after the main analyses within the EU-CERT-ICD consortium are finished. Applications may be submitted to the consortium.

Author contributions

B.M., C.S., R.W., H.V.H., A.B., M.M., M.Z. and G.S. made substantial contributions to the conception and design of the study.

M.D., A.S., D.S., K.M.H., A.L., P.F. and S.K. acquired the data; P.B., A.M., K.-L.L., T.P., T.F., M.H. and G.S. made substantial contributions to the analysis and interpretation of data for the manuscript. M.D., A.S., M.M. and G.S. drafted the work.

All authors were responsible for the interpretation of data, writing the manuscript, approval of the version to be published.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100695.

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