Prediction of mortality benefit by means of Periodic repolarization dynamics in patients undergoing prophylactic implantation of a defibrillator: EU-CERT-ICD substudy

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and the EU-CERT-ICD investigators

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LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

EU-CERT-ICD

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

ESC Congress Paris 2019 Together with World Congress of Cardiology

Declaration of interest

- Research contracts (Medtronic Research Grant (partial funding of the SMART-MI study))

Prediction of ICD mortality benefit by PRD – EU-CERT-ICD

Background

- Current guidelines recommend prophylactic ICD implantation in patients with ischemic or non-ischemic cardiomyopathy and LVEF ≤35%[1]
- Management of heart failure has improved significantly since publication of landmark trials
- Presently, only a small proportion of patients treated with prophylactic ICD implantation ever experience adequate ICD interventions

[1]Priori et al., Eur Heart J 2015

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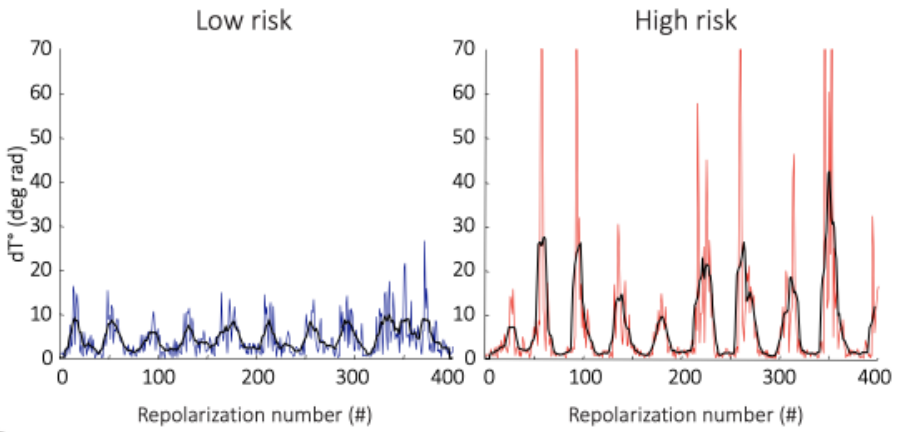
- Management of heart failure has improved significantly since publication of landmark trials
- Presently, only a small proportion of patients treated with prophylactic ICD implantation ever experience adequate ICD interventions
- Identification of patients who actually benefit from prophylactic ICD implantation in terms of mortality reduction is an unmet clinical need

[1]Priori et al., Eur Heart J 2015

Prediction of ICD mortality benefit by PRD – EU-CERT-ICD

Background

- Periodic Repolarization Dynamics (PRD) is a novel ECG-based marker that quantifies sympathetic-activity related low-frequency oscillations of cardiac repolarization instability[1]
- In previous studies, increased PRD was associated with malignant tachyarrhythmias, appropriate ICD shocks and sudden cardiac death[2,3]



[1]Rizas … Bauer, J Clin Invest 2014
[2]Rizas … Bauer, Eur Heart J 2017
[3]Rizas … Bauer, Heart Rhythm 2019

Prediction of ICD mortality benefit by PRD – EU-CERT-ICD

Hypothesis

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- In previous studies, increased PRD was associated with malignant tachyarrhythmias, appropriate ICD shocks and sudden cardiac death[2,3]
- We therefore hypothesized that PRD predicts the ICD treatment effect on mortality in contemporarily treated patients with ischemic or non-ischemic cardiomyopathy and LVEF ≤35%

[1]Rizas … Bauer, J Clin Invest 2014
[2]Rizas … Bauer, Eur Heart J 2017
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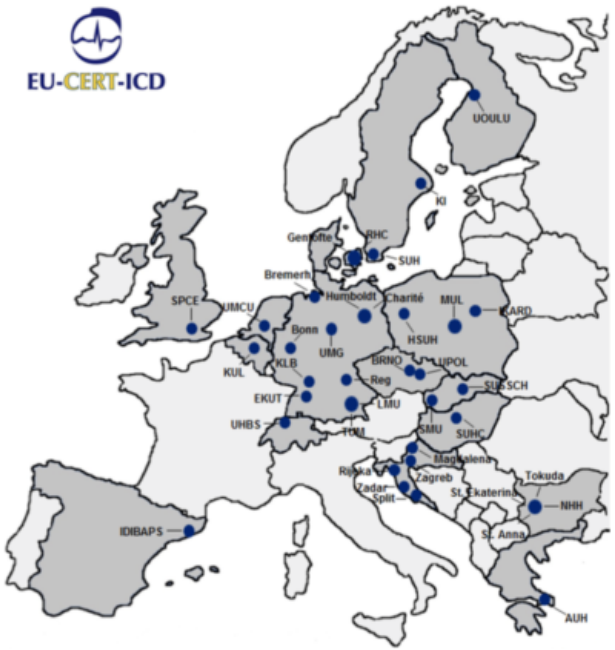
Prediction of ICD mortality benefit by PRD – EU-CERT-ICD

Methods

- Predefined substudy of the EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD; NCT0206419)
- Funded under the 7th Framework Programme (EU 602299)
- Prospective, investigator-initiated, non-randomized, controlled cohort study
- Conducted at 44 centres in 15 European countries
- Enrollment from May 2014 to September 2018



Zabel et al., ESC Heart Fail 2019

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Procedures

- The decision to implant an ICD or opt for a conservative approach was not determined by the study design, but rather was based on the decision of the treating physician and the patient, and was influenced by regional and national health policy practices
- In the ICD group, mandatory ICD programming was established
- At enrollment, a high-resolution 12-lead 24h Holter recording was obtained in all patients
- PRD was blindly assessed from night hours (0000 h - 0600 h) by an ECG Corelab at the LMU Munich using validated technologies (SMARTLab 1.5)

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Outcomes and statistical analyses

- Primary endpoint was total mortality
- Co-primary endpoint in ICD patients was occurrence of a first appropriate shock
- Primary analyses were stratified by quintiles of a propensity score
- The propensity score was developed by logistic regression analysis with the treatment group (ICD or control) as dependent variable and 28 baseline characteristics as independent variables

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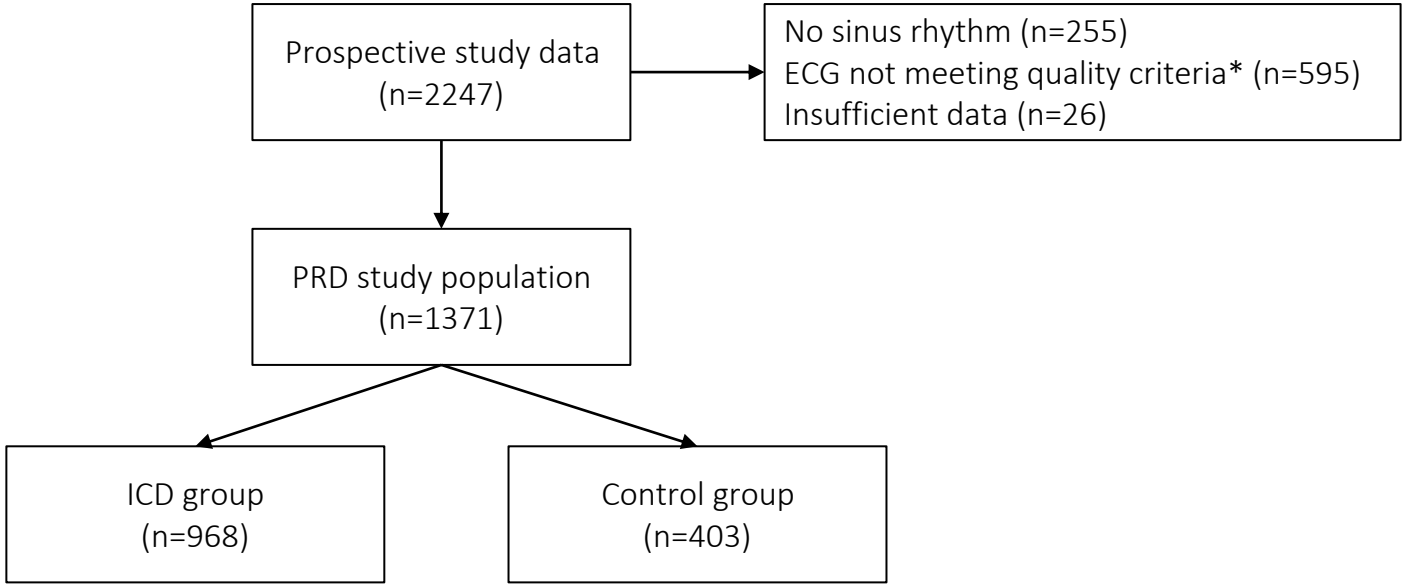
Flow chart



* ≥ 4.5 h of high-quality signal (0000 h - 0600 h)

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Patients' characteristics

	ICD group (n=968)	Control group (n=403)	p-value
Female	174 (18%)	78 (19%)	0.55
Age (years)	61.5 (11.8)	62.7 (11.7)	0.12
Creatinine (mg/dL)	1.2 (0.6)	1.2 (0.7)	0.077
LVEF (%)	28 (6)	29 (5)	<0.0001
PRD (deg)	5.3 (2.5)	5.2 (2.4)	0.64
Diabetes mellitus	293 (30%)	115 (29%)	0.52
Ischemic CMP	699 (72%)	249 (62%)	0.00014
NYHA Class ≥III	337 (35%)	163 (40%)	0.048
Beta-blocker	917 (95%)	376 (93%)	0.30

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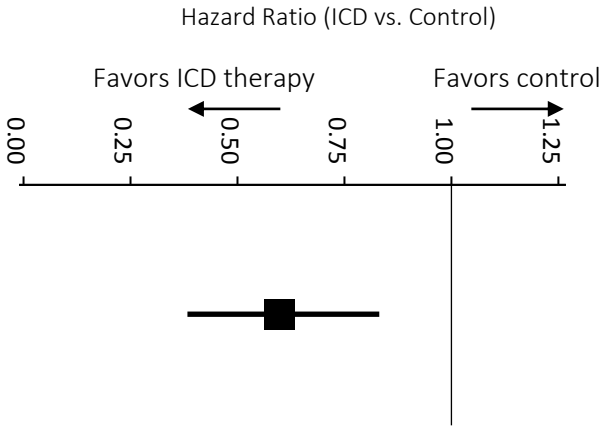
ICD treatment effect on mortality



Overall ICD treatment effect

0.57 (0.41-0.79); p=0.0008

Number of deaths	138	64
Follow-up time, years (IQR)	2.7 (1.3)	1.2 (1.9)

Model adjusted by propensity quintiles

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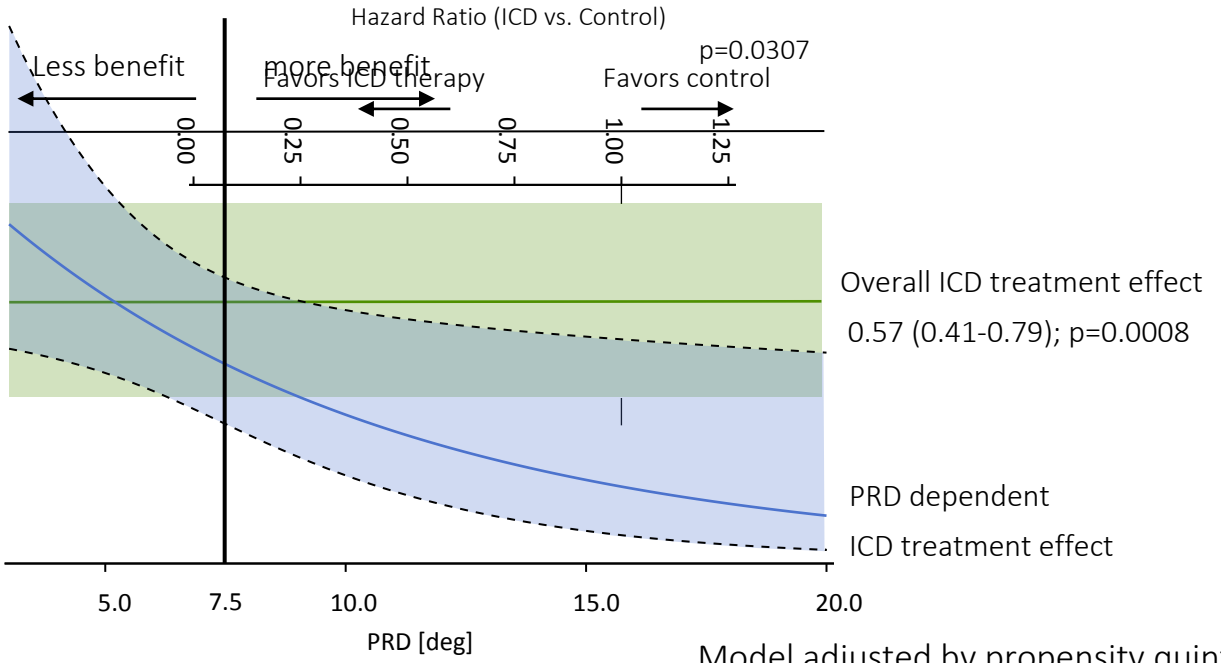
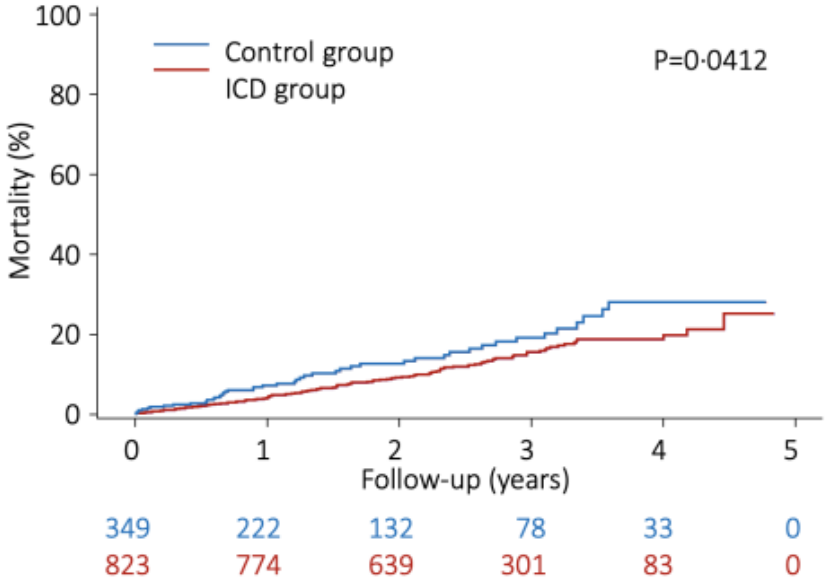
ICD treatment effect on mortality

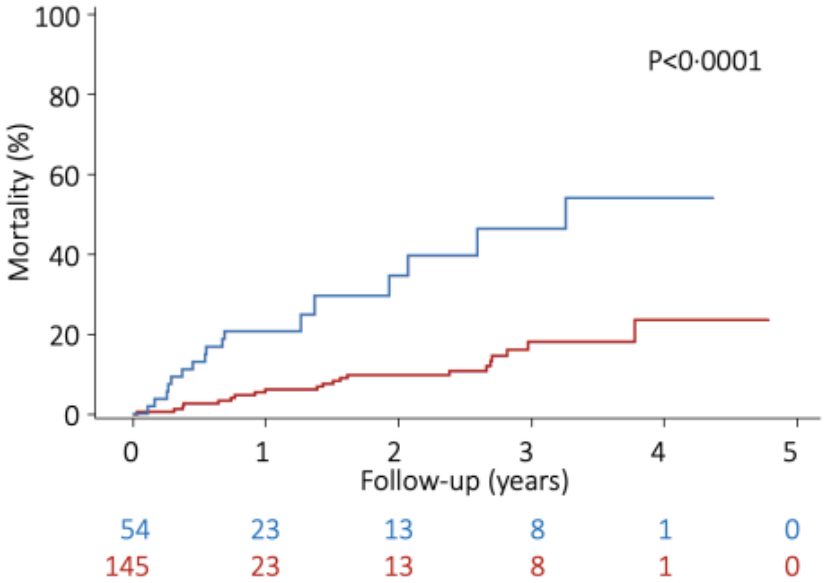


Model adjusted by propensity quintiles

Prediction of ICD mortality benefit by PRD – EU-CERT-ICD

Prediction of ICD treatment effect on mortality





unadjusted mortality rates

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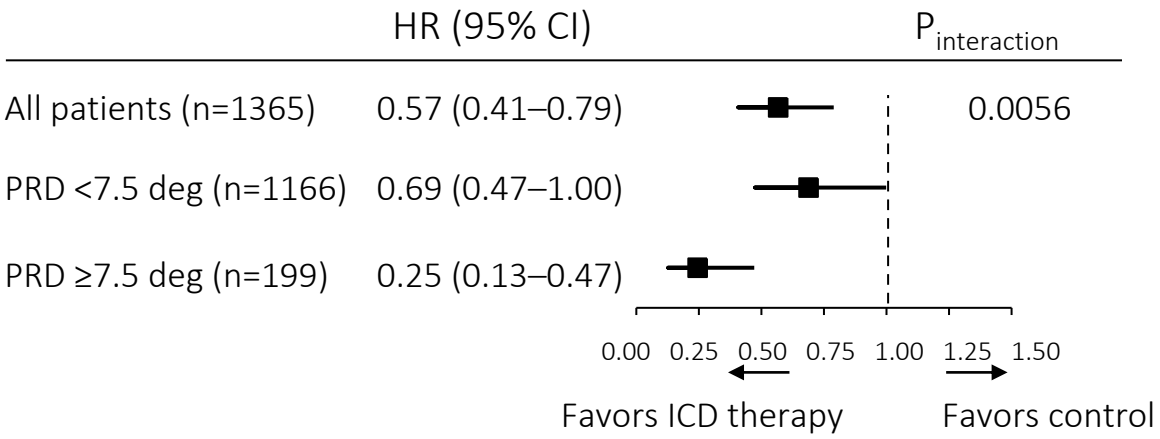
Prediction of ICD treatment effect on mortality



Model adjusted by propensity quintiles

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Appropriate ICD shocks

There were 65 (6.7%) first appropriate shocks in the ICD group, corresponding to an annualized shock rate of 2.6%

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Prediction of appropriate shocks

Fine & Gray competing risk analysis in ICD patients for prediction of a first appropriate shock (n=968)

	HR (95% CI)	p-value
COPD	0.57 (0.30–1.10)	0.0941
BMI (per kg/m^2)	1.24 (1.04–1.50)	0.0195
Creatinine (mg/dl)	1.15 (0.97–1.35)	0.1018
Digitalis glycoside	2.56 (0.89–7.69)	0.0800
Male gender	2.94 (0.06–8.17)	0.0384
QRS (ms)	1.09 (0.90–1.34)	0.3839
PRD (per SD)	1.30 (1.08–1.56)	0.0050

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Limitations

- EU-CERT-ICD is a non-randomized study
- Strict pre-defined ECG quality criteria led to exclusion of a significant number of patients
- Results cannot be extrapolated to patients with atrial fibrillation
- Proposed cut-off value of PRD for predicting an ICD treatment effect needs to be independently confirmed
- Follow-up time was short. The results should be confirmed by longer follow-up.

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Conclusions

- PRD predicts the treatment effect of primary prophylactic ICD therapy in terms of mortality reduction in contemporarily treated patients
- PRD assessment may help to guide prophylactic ICD-implantation in patients with ischemic heart disease or non-ischemic cardiomyopathy
- It could be promising to combine PRD with complementary markers that identify patients who do not benefit from ICD implantation due to competing risks
- Further studies are needed to validate that PRD-guided treatment decisions improve the efficacy of prophylactic ICD therapy

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Thanks to all EU-CERT-ICD investigators

Dept. of Cardiology, Semmelweis University Heart Center, Budapest/Hungary
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Doctopic: Primary Research

Prediction of mortality benefit based on periodic repolarisation dynamics in patients undergoing prophylactic implantation of implantable cardioverter defibrillators: a prospective, controlled, multicentre cohort study

Axel Bauer, Mathias Klemm, Konstantinos D Rizas, Wolfgang Hamm, Lukas von Stülpnagel, Michael Dommasch, Alexander Steger, Andrezej Lubinski, Panagiota Flevari, Markus Harden, Tim Friede, Stefan Kääb, Bela Merkely, Christian Sticherling, Rik Willems, Heikki Huikuri, Marek Malik, Georg Schmidt, Markus Zabel*, and the EU-CERT-ICD investigators†*

Prediction of ICD mortality benefit by PRD – EU-CERT-ICD

Thank you very much for your attention.