Clinical Effectiveness of Primary Prevention ICDs: Results of the EU-CERT-ICD Non-Randomised, Controlled, Multicentre Study

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Declaration of interest

- Others (Biotronik: travel grants, minor)

Background

- Use of the ICD for VT/VF unquestioned, eg. for secondary prophylaxis

- Primary prophylaxis: Guidelines (Class I indication) unchanged since >10 years, > 100.000 ICD implanted in Europe per year at high cost

- Overall mortality in HF pts has improved, explained by better drug-treatment, cardiac revascularisation techniques and better prevention

- Shocks are now <4% per year, many patients die without shock

- Has ICD benefit decreased in primary prophylactic therapy?

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Objectives

- To characterise all-cause mortality in a prospective cohort of ICD candidates newly implanted for primary prophylaxis and compare with a non-randomised no-ICD control cohort

- To determine prespecified clinical baseline characteristics contributing to the risk of the primary outcome all-cause mortality

- To define subgroups within the cohort with a lower or higher benefit from ICD treatment

STUDY DESIGN

Rationale and design of the EU-CERT-ICD prospective study: comparative effectiveness of prophylactic ICD implantation
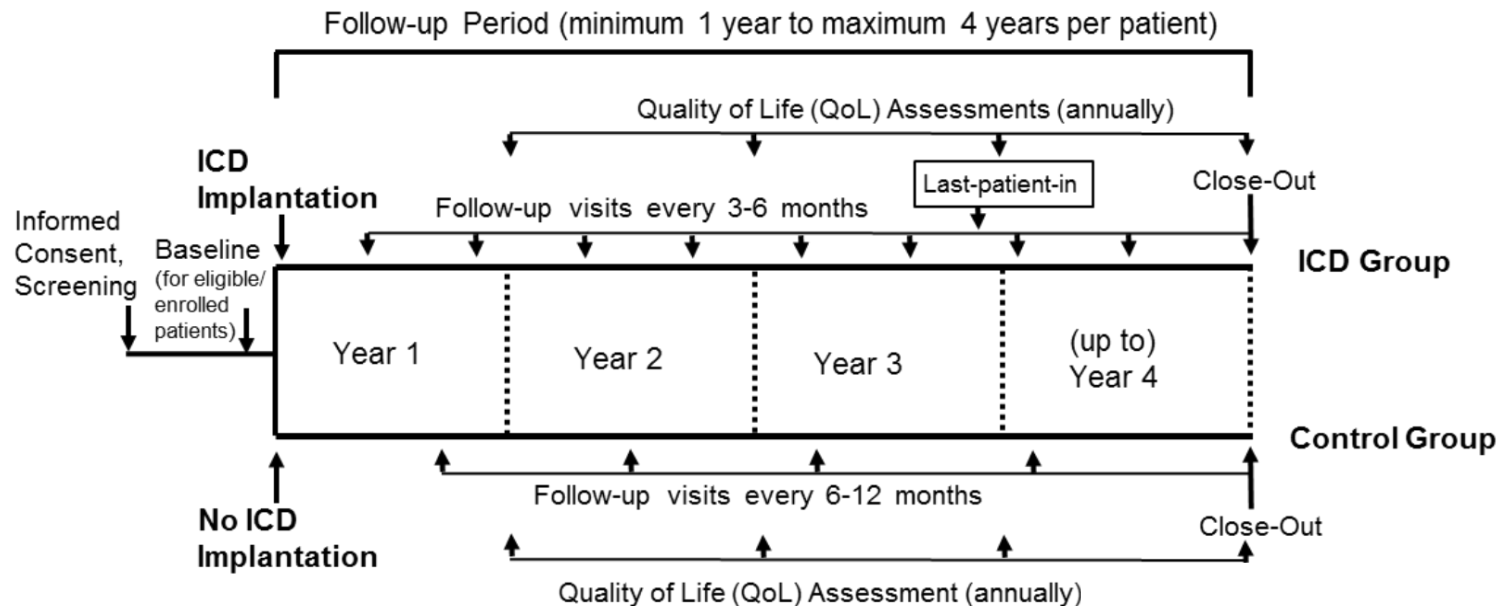
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ESC Congress Paris 2019 **World Congress of Cardiology**

Zabel et al, ESC Heart Fail 2019

EU-CERT-ICD prospective study

- EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD; NCT0206419)
- Investigator-initiated, prospective, controlled, non-randomised, multicentre cohort study
- Funded 2013-2018 by EU 7th Framework Program (FP7)
- 44 clinical centres, 15 countries
- Coordinated by UMG Göttingen
- Enrolment from 12 May 2014 – 7 Sep 2018

Study Protocol

Follow-up Period (minimum 1 year to maximum 4 years per patient)

Quality of Life (QoL) Assessments (annually)

ICD Implantation

Follow-up visits every 3-6 months

Last-patient-in

Close-Out

Informed Consent, Screening

Baseline (for eligible/ enrolled patients)

ICD Group

| Year 1 | Year 2 | Year 3 | (up to) Year 4 |

Control Group

Follow-up visits every 6-12 months

Close-Out

No ICD Implantation

Quality of Life (QoL) Assessment (annually)

Inclusion/Exclusion Criteria

Inclusion:
- Ischaemic or dilated cardiomyopathy
- LVEF ≤ 35% with optimal medical therapy
- Class-I ICD indication according to ESC guidelines
- Age ≥ 18 y

Exclusion:
- CRT planned or clearly indicated
- Previous pacemaker or device
- Higher degree AV block
- Unstable cardiac condition
- Limited life expectancy < 1 y

Outcomes

- Primary endpoint: All-cause mortality
- Co-primary endpoint: First appropriate ICD shock
- Secondary endpoints included: Sudden cardiac death

Statistics

- Kaplan-Meier curves, Cox regression analyses
- Stratification by region after grouping of countries and centres into regions: Western/Central, Northern (Scandinavia), Southern (Spain, Greece), Eastern
- For adjustment of remaining baseline differences between ICD and control group, we used stepwise multivariate models (p≤0.10 entry and stay) and propensity-score based techniques (propensity strata, propensity score as covariate, propensity matching)
- Interaction of ICD effect with sex, age, ICM/DCM, mortality risk group, diabetes, and region was determined
- Sample size of 1500 ICD vs. 750 controls (2:1 ratio) with 279 mortality events sufficient for 80% power, two-sided $p < 0.05$

Patient Flowchart

EU-CERT-ICD prospective study database (n=2327) → Screening failure (n=30) / Data erasing request (n=5)

Included patients (n=2292) → Valvular cardiomyopathy (n=34) / Sustained VT > 30 sec on Holter (n=4) / Centre dropout (n=3) / Life expectancy < 1 year (n=2) / FU < 13 days without fatal event (n=1) / Study withdrawal and missing baseline information (n=1)

Analysis set (n=2247)

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Baseline characteristics: ICD vs. control group

Table 1: Patient characteristics at baseline (n=2247)

Baseline characteristics	ICD group		Control group		Total		p-value
Number of patients	1516		731		2247		
Female	274	(18.1)	134	(18.3)	408	(18.2)	0.8822
Region							<.0001
Eastern	644	(42.5)	492	(67.3)	1136	(50.6)	..
Northern	150	(9.9)	35	(4.8)	185	(8.2)	..
Southern	90	(5.9)	78	(10.7)	168	(7.5)	..
Western	632	(41.7)	126	(17.2)	758	(33.7)	..
Age [years]	61.9	11.5	63.4	11.7	62.4	11.6	0.0040
BMI [kg/m2]	27.8	5.2	28.3	5.1	27.9	5.2	0.0050
Creatinine [mg/dL]	1.156	0.589	1.225	0.600	1.179	0.594	<.0001
Diastolic blood pressure [mmHg]	74.0	11.1	75.2	11.2	74.4	11.1	0.0061
Haemoglobin [g/dL]	13.8	1.9	13.9	1.8	13.8	1.8	0.4227
LVEF [%]	27.5	5.6	29.1	5.5	28.0	5.6	<.0001
QTc [ms]	438.8	38.7	431.9	51.5	436.6	43.3	0.0015
QRS [ms]	106.3	17.2	103.8	18.5	105.4	17.7	<.0001
Sodium [mmol/L]	139.1	3.2	139.4	3.2	139.2	3.2	0.0135
AF (history or present)	370	(24.4)	210	(28.7)	580	(25.8)	0.0283
COPD	174	(11.5)	76	(10.4)	250	(11.1)	0.4453
Diabetes	458	(30.2)	223	(30.5)	681	(30.3)	0.8866
Leading cardiac disease							<.0001
Ischaemic cardiomyopathy	1045	(68.9)	416	(56.9)	1461	(65.0)	..
Dilated cardiomyopathy	471	(31.1)	315	(43.1)	786	(35.0)	..
Malignant disease	70	(4.6)	29	(4.0)	99	(4.4)	0.4817
NYHA functional class							0.0067
Class I or II	947	(62.5)	413	(56.5)	1360	(60.5)	..
Class III or IV	569	(37.5)	318	(43.5)	887	(39.5)	..
Stroke or TIA	162	(10.7)	61	(8.3)	223	(9.9)	0.0820
Tobacco use	976	(64.4)	343	(46.9)	1319	(58.7)	<.0001
Amiodarone	115	(7.6)	111	(15.2)	226	(10.1)	<.0001
Digitalis glycosides	100	(6.6)	60	(8.2)	160	(7.1)	0.1640
ACE or AT1 antagonist	1414	(93.3)	635	(86.9)	2049	(91.2)	<.0001
Beta-blocker	1436	(94.7)	683	(93.4)	2119	(94.3)	0.2167
Loop diuretic	1068	(70.4)	555	(75.9)	1623	(72.2)	0.0066
MRA	1183	(78.0)	506	(69.2)	1689	(75.2)	<.0001

Main results

- Eastern Europe: 1136/2247 patients (50%), 492/774 controls (63%)
- 1-ICD: 1192/1516 pts (79%), 2-ICD: 299 pts (20%), S-ICD: 25 (1.6%), CRT: none
- Crossovers: 61 pts control to ICD, 9 pts ICD to control (mean 0.9 y)
- Overall FU (May 15, 2019): 2.4 ± 1.1 y (max. 4.8), ICD group: 2.7 ± 1.0 y, control: 1.7 ± 1.2 y
- Annualised mortalities: Overall: 6.3%/y. (342 deaths), ICD: 5.5%/y, control: 9.2%/y
- Annualised first appropriate shock rate: 2.8%/y, 107 patients (7.0%) had 148 appr. shocks

All-cause mortality: ICD vs. control group

Hazard ratio 0.682
95% CI 0.537-0.865
p=0.0016

ICD group

Control group

Survival probability

Follow-up time (years)

	0	1	2	3	4	5
ICD group	1516	1417	1159	547	152	0
Control group	731	441	260	140	49	0

All-cause mortality: ICD vs. control group

Sudden cardiac death: ICD vs. control group

Hazard ratio 0.166
95% CI 0.089-0.310
p<0.0001

Control group

ICD group

Cumulative incidence

Follow-up time (years)

Final multivariate prediction model for mortality

Parameter	Stratified by region			
	p-value	HR	95% CI	
Age (per 10 yrs)	<.0001	1.411	1.255	1.583
LVEF (per 5 %)	<.0001	0.762	0.688	0.841
QTc (per 40 ms)	<.0001	1.322	1.173	1.431
COPD (yes vs no)	<.0001	2.191	1.691	2.837
BMI (kg/m^2)	0.0004	0.954	0.929	0.979
Haemoglobin (g/dL)	0.0008	0.887	0.827	0.951
Creatinine (mg/dL)	0.0015	1.224	1.080	1.386
NYHA (III vs. I-II)	0.0016	1.454	1.153	1.833
Sex (male vs. female)	0.0045	1.580	1.152	2.166
Diabetes (yes vs. no)	0.0506	1.265	0.999	1.600

Adjusted hazard ratios for comparison of mortality ICD vs. no-ICD (multivariate predictors), and sensitivity analyses (propensity score techniques)

Model	n	Events	p-value	HR ICD vs. control	95% CI	
Unadjusted Strata by region	2247	342	0.0016	**0.682**	0.537	0.865
Adjusted by mortality predictors	2154	326	0.0140	**0.731**	0.569	0.938
Propensity score as covariate	2221	334	0.0029	**0.675**	0.521	0.874
Strata by propensity score quintiles	2221	334	0.0016	**0.667**	0.519	0.858
Propensity score matching (2:1)	1776	259	<.0001	**0.587**	0.451	0.763

CI confidence interval, HR hazard ratio

Mortality hazard ratios (adjusted by multivariate risk score) for selected subgroups

	ICD Events / N (%)		Control Events / N (%)		Hazard ratio (95% CI)		p	p_interaction
Overall	223/1470	(15.2)	103/684	(15.1)	0.731 (0.569, 0.938)		0.0140	
Age								0.0902
<75 years	168/1270	(13.2)	78/560	(13.9)	0.641 (0.486, 0.847)		0.0017	
≥75 years	55/200	(27.5)	25/124	(20.2)	1.063 (0.628, 1.800)		0.8206	
Diabetes								0.0887
no	136/1030	(13.2)	66/474	(13.9)	0.616 (0.451, 0.842)		0.0024	
yes	87/440	(19.8)	37/210	(17.6)	0.945 (0.637, 1.403)		0.7797	
Disease								0.2727
ICM	170/1014	(16.8)	66/387	(17.1)	0.786 (0.582, 1.061)		0.1162	
DCM	53/456	(11.6)	37/297	(12.5)	0.588 (0.380, 0.910)		0.0172	
Mortality predictors								0.1416
lower risk groups	110/1171	(9.4)	56/552	(10.1)	0.622 (0.445, 0.870)		0.0055	
highest risk group	113/299	(37.8)	47/132	(35.6)	0.831 (0.578, 1.195)		0.3173	
NYHA								0.1816
classes I or II	97/926	(10.5)	44/382	(11.5)	0.604 (0.417, 0.874)		0.0075	
classes III or IV	126/544	(23.2)	59/302	(19.5)	0.835 (0.605, 1.153)		0.2739	
Region								0.6136
eastern	119/616	(19.3)	69/460	(15.0)	0.767 (0.567, 1.038)		0.0853	
non-eastern	104/854	(12.2)	34/224	(15.2)	0.674 (0.453, 1.004)		0.0521	
Sex								0.2717
female	33/269	(12.3)	14/124	(11.3)	1.015 (0.534, 1.931)		0.9631	
male	190/1201	(15.8)	89/560	(15.9)	0.691 (0.529, 0.903)		0.0067	

Limitations

- Possible biases of a non-randomised, controlled cohort study despite adjustment techniques

- Control group follow-ups were shorter and not as frequent

Conclusions

- In contemporary ICM/DCM patients (LVEF ≤35%, narrow QRS), primary prophylactic ICD treatment was associated with a 27% lower mortality after adjustment.

- There appear to be patients with less survival advantage, such as older patients or diabetics.

- Randomised ICD studies are now clearly warranted.

Thank you for your attention!

EU-CERT-ICD investigators

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