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Electrical storm is associated with impaired prognosis compared to ventricular tachyarrhythmias

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ABSTRACT

Background: Because data on electrical storm (ES) is limited, this study sought to compare the prognosis of patients with ES to those with ventricular tachyarrhythmias on mortality, rehospitalization and major adverse cardiac events (MACE).
Methods: In this retrospective study consecutive implantable cardioverter defibrillator (ICD) recipients presenting with ES were compared to patients surviving ventricular tachyarrhythmias (ventricular tachycardia (VT) or fibrillation (VF); non-ES) on admission from 2002 to 2016. The primary endpoint was all-cause mortality, secondary endpoints were rehospitalization and MACE at 2.5 years of follow-up.
Results: 764 consecutive patients with an ICD were included (11% with ES, 89% with VTA). ES was associated with higher rates of all-cause mortality (37% vs. 20%, log-rank $p = 0.001$; HR 2.084; 95% CI 1.416–3.065, $p = 0.001$). However, only in secondary preventive ICD recipients, ES remained significantly associated with mortality (39% vs. 20%; log rank $p = 0.001$; HR 2.235, 95% CI 1.378–3.625, $p = 0.001$). Furthermore, ES was associated with higher rates of rehospitalization (44% vs. 12%, log-rank $p = 0.001$; HR 4.763, 95% CI 3.237–7.009, $p = 0.001$), mainly due to VT (22% vs. 4%, $p = 0.001$) and acute heart failure (AHF) (17% vs. 4%, $p = 0.001$) and higher rates of MACE (40% vs. 23%; log rank $p = 0.001$; HR 1.838; 95% CI 1.273–2.654, $p = 0.002$). Increasing risks of death and rehospitalization were still observed even after multivariable adjustment.
Conclusion: ES was associated with increased rates of all-cause mortality, rehospitalization, respectively due to VT and AHF, as well as MACE at 2.5 years compared to patients with ventricular tachyarrhythmias apart from ES.

1. Introduction

An electrical storm (ES) represents a serious and possibly life-threatening heart rhythm disorder. ES is defined as ≥3 distinct episodes of sustained ventricular tachycardia (VT) or fibrillation (VF) episodes requiring implantable cardioverter defibrillator (ICD) therapy within one day [1]. ES constitutes an increasing epidemiological problem, especially in patients with ICD and heart failure (HF) [2]. The prevalence ranges from 4% in case of ICD implantation for primary prevention of sudden cardiac death (SCD) to 40% in case of secondary preventive ICD in patients with ischemic cardiomyopathy [2–4].

Clinical presentation of ES differs dramatically from asymptomatic delivery of anti-tachycardia pacing (ATP) to hemodynamic instability with multiple ICD-related shocks. Established first-line therapies against ES are antiarrhythmic drugs such as azimilide, amiodarone or dofetilide, overdrive ventricular pacing, hemodynamic support and sympathetic blockade by either beta-blockers or interventional sympathetic denervation. In selected patients also percutaneous catheter ablation has been recommended as another causative treatment option [5].

ES might result from a complex interplay between pre-existing pathological conditions creating a vulnerable electrical substrate and

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acute patient-specific initiating factors. Aberrant Ca^{2+}-handling and ionic imbalances have been identified as major contributors to the susceptibly and initiation of ventricular tachyarrhythmias. New-onset or worsening of heart failure, changes of antiarrhythmic drug therapies, psychological stress, diarrhoea, hypokalaemia or further comorbidities represent potential triggers for ES, whereas severe systolic dysfunction, chronic kidney disease and VT as an initial arrhythmia are regarded as independent and established predictors for ES [2,4].

However, little is known about the outcome of ES patients compared to patients with ventricular tachyarrhythmias in the absence of ES. In a meta-analysis, the presence of ES was recently shown to be associated with increased combined risk of death and hospitalization for heart failure compared to patients with a history of ventricular tachyarrhythmias [6]. However, in literature there is conflicting evidence whether ES could be considered as a reliable risk factor for mortality or rather an uninvolved third side-factor [2].

Therefore, the present study sought to re-evaluate the hypothesis whether ES may negatively impact long-term outcomes including mortality, rehospitalization and major adverse cardiac events (MACE) compared to patients with ventricular tachyarrhythmias apart from ES in consecutive ICD recipients at 2.5 years of follow-up.

2. Methods

2.1. Study population

The present study included all consecutive ICD recipients presenting with ES or ventricular tachyarrhythmias apart from ES (non-ES) on hospital admission from 2002 until 2016 at one institution. All types of ICD were allowed: transvenous, subcutaneous (s-ICD) and cardiac resynchronization therapy device with defibrillator function (CRT-D).

Ventricular tachyarrhythmias comprised VT and VF, as defined by current international guidelines [7,8]. VT was classified in the presence of a regular RR interval, large QRS morphology, changing polarity of QRS deflections during tachycardia compared to sinus rhythm and sudden onset of tachycardia. A heart rate >250/min with irregular RR intervals classified VF [7,8]. Electrical storm was defined as ≥3 episodes of ventricular tachyarrhythmias delimited by at least 5 min leading to appropriate ICD therapy during a single 24 hour time period [9,10]. Ventricular tachyarrhythmias were documented by ICD and in some cases additionally by 12 lead electrocardiogram (ECG), ECG tele-monitoring, or in case of unstable course or during resuscitation by external defibrillator monitoring. Documented VF was treated by external defibrillation and in case of prolonged instability with additional intravenous anti-arrhythmic drugs during cardiopulmonary resuscitation (CPR). Using the electronic hospital information system, all relevant clinical data related to the index event were documented. In detail, data documentation comprised baseline characteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, data derived from all non-invasive or invasive cardiac diagnostics and device therapies, such as coronary angiography, electrophysiological examination, as well as imaging modalities, such as echocardiography or cardiac magnetic resonance imaging (cMRI). Documentation period lasted from index event until 2016. Independent senior cardiologists analysed stored electrocardiograms and performed documentation of all medical data at the time of the patients' individual period of clinical presentation, being blinded to final data analyses.

Exclusion criteria comprised patients with acute myocardial infarction (AMI) as the primary cause of ventricular tachyarrhythmias or ES. Furthermore, patients with early cardiac death were excluded. Early cardiac death was defined as a cardiac death occurring within 24 h after onset of ventricular tachyarrhythmias (VT or VF) and ES or within 24 h of an assumed unstable cardiac condition leading to cardiac death, such as high degree AV-block, asystole, acute heart failure (AHF), cardiogenic shock or cardiopulmonary resuscitation (CPR) even in the absence of ventricular tachyarrhythmia [7]. Each patient was counted only once for inclusion.

The present study is derived from an analysis of the "Registry of Malignant Arrhythmias and Sudden Cardiac Death - Influence of Diagnostics and Interventions (RACE-IT)" and represents a single-centre registry including consecutive patients presenting with ventricular tachyarrhythmias and sudden cardiac arrest being admitted acutely to the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT02982473) from 2002 until 2016. The registry was carried out according to the principles of the declaration of Helsinki and was approved by the medical ethics committee II of the Faculty of Medicine Mannheim, University of Heidelberg, Germany.

Table 1
Baseline characteristics.

Characteristic	Non-ES (n = 677; 89%)	ES (n = 87; 11%)	p value
Age, median (range)	67 (16–88)	70 (22–86)	**0.001**
Male gender, n (%)	536 (79)	74 (85)	0.198
Cardiovascular risk factors, n (%)			
Arterial hypertension	411 (61)	55 (63)	0.651
Diabetes mellitus	173 (26)	22 (25)	0.957
Hyperlipidemia	251 (37)	37 (43)	0.323
Smoking	201 (30)	15 (17)	**0.015**
Cardiac family history	94 (14)	7 (8)	0.177
Comorbidities, n (%)			
Coronary artery disease	425 (63)	58 (67)	0.479
Myocardial infarction	239 (35)	32 (37)	0.786
Cardiogenic shock	41 (6)	2 (2)	0.152
CPR	142 (21)	5 (6)	**0.001**
Atrial fibrillation	228 (34)	36 (41)	0.155
Cardiomyopathy	118 (17)	11 (13)	0.262
Dilated cardiomyopathy	85 (13)	8 (9)	0.367
Hypertrophic cardiomyopathy	12 (2)	2 (2)	0.668
Hypertrophic obstructive cardiomyopathy	6 (1)	0 (0)	1.000
ARVD	10 (2)	1 (1)	0.809
Non-compaction cardiomyopathy	3 (1)	0 (0)	1.000
Tako-Tsubo cardiomyopathy	2 (1)	0 (0)	1.000
Long QT syndrome	21 (3)	2 (2)	1.000
Brugada syndrome	20 (3)	1 (1)	0.497
Intoxication	5 (1)	0 (0)	1.000
Electrolyte disorders	19 (3)	6 (7)	0.054
Electrophysiological examination, n (%)	308 (46)	21 (24)	**0.001**
VT ablation	44 (7)	18 (21)	**0.001**
Laboratory data, (mean ± SEM)			
Hemoglobin [g/dl]	13.4 ± 0.1	13.2 ± 0.3	0.208
Potassium [mmol/l]	4.3 ± 0.0	4.1 ± 0.1	**0.013**
Creatinine [mg/dl]	1.3 ± 0.0	1.5 ± 0.1	0.108
Troponin I [μg/l]	4.7 ± 3.5	0.3 ± 0.1	0.611
Medication at discharge, n (%)			
Beta-blocker	534 (82)	80 (95)	**0.002**
ACE-inhibitor/ARB	504 (77)	67 (80)	0.627
Statin	370 (57)	50 (58)	0.639
Amiodarone	116 (18)	45 (54)	**0.001**
ECG data, (mean ± SEM)			
PQ	185 ± 3	220 ± 11	**0.001**
QRS	113 ± 2	127 ± 13	0.146
QT	413 ± 5	440 ± 14	0.084
LVEF, n (%)			
≥55%	114 (19)	9 (11)	**0.025**
54–45%	61 (10)	7 (9)	
44–35%	115 (19)	9 (11)	
≤35%	302 (51)	55 (69)	
Type of ICD, n (%)			
ICD	595 (88)	76 (87)	0.966
CRT-D	57 (8)	8 (9)	
s-ICD	25 (4)	3 (3)	
ICD indication, n (%)			
Primary prevention	299 (44)	32 (37)	0.220
Secondary prevention	378 (56)	54 (63)	
ICD programming, bpm, median (IQR)			
VT detection threshold	171 (167–175)	171 (159–176)	0.133
VF detection threshold	214 (214–222)	214 (214–222)	0.393

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARVD, arrhythmogenic right ventricular dysplasia; CPR, cardiopulmonary resuscitation; CRT-D, cardiac resynchronization therapy defibrillator; ECG, electrocardiogram; ES, electrical storming; ICD, implantable cardioverter- defibrillator; IQR, inter quartile range; LVEF; left ventricular ejection fraction; SEM, standard error of measurement; VF, ventricular fibrillation; VT, ventricular tachycardia.

2.2. Definition of endpoints

The primary endpoint was all-cause mortality during the follow-up period until 2016. All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices ("bureau of mortality statistics") across Germany. Identification of patients was verified by place of name, surname, day of birth and registered living address.

Secondary endpoints comprised in-hospital mortality, first rehospitalization and MACE. First rehospitalization comprised first rehospitalization due to VT, VF, CPR, AHF, AMI, inappropriate ICD shock or stroke. MACE were defined as the composite of AMI,

Table 2
Primary and secondary endpoints.

Characteristic	Non-ES (n = 677; 89%)		ES (n = 87; 11%)		p value
Primary endpoint, n (%)					
Overall all-cause mortality	135	(20)	32	(37)	**0.001**
Secondary endpoints, n (%)					
In-hospital mortality	26	(4)	2	(2)	0.471
Mortality at follow up	109	(16)	30	(35)	**0.001**
First rehospitalization					
Overall	81	(12)	38	(44)	**0.001**
VT	24	(4)	19	(22)	**0.001**
VF	7	(1)	0	(0)	1.000
CPR	0	(0)	2	(2)	1.000
Acute heart failure	26	(4)	15	(17)	**0.001**
Acute myocardial infarction	8	(1)	1	(1)	0.979
Inappropriate ICD shock	16	(2)	0	(0)	1.000
Stroke	0	(0)	1	(1)	1.000
MACE	154	(23)	35	(40)	**0.001**

CPR, cardiopulmonary resuscitation; ES, electrical storming; ICD, implantable cardioverter- defibrillator; MACE, major adverse cardiac events; VF, ventricular fibrillation; VT, ventricular tachycardia.

target vessel revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and all-cause mortality [11].

2.3. Statistical methods

Quantitative data are presented as mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution of the data and were compared using the Student's *t*-test for normally distributed data or the Mann-Whitney *U* test for nonparametric data. Deviations from a Gaussian distribution were tested by the Kolmogorov-Smirnov test. Spearman's rank correlation for nonparametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies and compared using the Chi^2 test or the Fisher's exact test, as appropriate.

The following analyses were applied stepwise to evaluate the prognostic value of predefined variables on study endpoints: Kaplan-Meier curves were calculated with log-rank testing for statistical significance. Uni-variable hazard ratios (HR) are given together with 95% confidence intervals. Multivariable Cox regression models with mortality, rehospitalization and MACE as the dependent variables were developed using the "forward selection" option. Multivariable models were adjusted both by univariably statistically significant variables such as male gender, CPR, treatment with beta-blockers or amiodarone and impaired LVEF ($p < 0.05$), as well as with clinically relevant variables such as DCM, chronic kidney disease, diabetes mellitus and ablation of ventricular tachyarrhythmias.

The result of a statistical test was considered significant for $p < 0.05$, and a statistical trend was defined as $p < 0.1$. SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistics.

3. Results

3.1. Study population

A total of 764 consecutive ICD recipients were included retrospectively, of which 11% suffered from ES and 89% had ventricular tachyarrhythmias (62% VT, 27% VF). All patients were followed-up for 2.5 years (mean 5.3 years).

As shown in Table 1, most patients were males (at least 79%). ES patients were older (70 years vs. 67 years; $p = 0.001$), whereas non-ES patients underwent CPR more often (21% vs. 6%; $p = 0.001$) and were more commonly smokers (30% vs. 17%; $p = 0.015$). beta-blockers (95% vs. 82%; $p = 0.002$) and amiodarone (54% vs. 18%; $p = 0.001$)were more commonly prescribed in ES patients. Rates of electrophysiological examination were higher in non-ES patients (46% vs. 24%, $p = 0.001$), whereas VT ablation rate was higher in ES patients (21% vs. 7%, $p = 0.001$). Additionally, non-ES patients had higher mean potassium values (4.3 mmol/l vs. 4.1 mmol/l; $p = 0.013$). Notably, PQ intervals were longer in ES patients (220 ms vs. 185 ms; $p = 0.001$). Further, significantly more ES patients had left ventricular ejection fraction (LVEF) below 35% compared to non-ES patients (69% vs. 51%; $p = 0.025$).

Rates of AMI, coronary artery disease (CAD), atrial fibrillation (AF) and cardiomyopathies were not statistically different. Beyond, no further statistically significant differences in cardiovascular risk factors, comorbidities, laboratory data, electrocardiogram (ECG) data, ICD thresholds and discharge medication were present (Table 1).

Most patients had ICD implantation for secondary prevention, especially in patients with ES (63% vs. 56%). The most common ICD type was conventional transvenous ICD (88%) followed by CRT-D (8%) and s-ICD (4%) (Table 1).

3.2. Primary endpoint – all-cause mortality

At least 90% of patients were followed-up regularly within the median follow-up period of 2.5 years (*mean 5.3 years*) with at least one ICD check-up every 6 to 12 months.

ES patients were associated with increased rates of long-term all-cause mortality (37% vs. 20%; log rank $p = 0.001$; Table 2; Fig. 1, left panel) compared to non-ES patients, corresponding to 2-fold higher risk of all-cause death (HR 2.084; 95% CI 1.416–3.065, $p = 0.001$).

3.3. Secondary endpoints

Differences of all-cause mortality were more related to long-term follow-up of 2.5 years (35% vs. 16%; $p = 0.001$), whereas in-hospital mortality rates were similar in both groups (2% vs. 4%; $p = 0.471$). Furthermore, ES patients showed significantly higher rates of overall first rehospitalization (44% vs. 12%; log rank $p = 0.001$), which was mainly due to VT (22% vs. 4%; $p = 0.001$) and AHF (17% vs. 4%; $p = 0.001$). ES patients were 4.7 times more likely to be re-hospitalized (HR 4.763, 95% CI 3.237–7.009, $p = 0.001$; Table 2; Fig. 1, middle panel).

Additionally, increased rates of MACE were seen in ES patients (40% vs. 23%; log rank $p = 0.001$), corresponding to 1.8-fold higher risk of

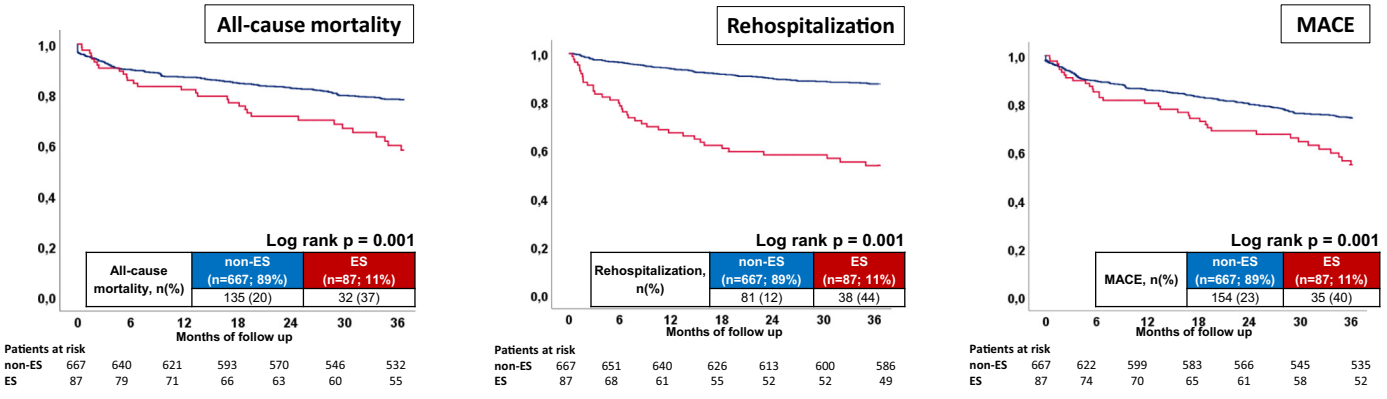

Fig. 1. Prognostic impact of ES on long-term all-cause mortality (left panel), overall rehospitalization (middle panel) and MACE (right panel) compared to ventricular tachyarrhythmias in ICD recipients.

future MACE at 2.5 years (HR 1.838; 95% CI 1.273–2.654, $p = 0.002$; Table 2; Fig. 1, right panel).

3.4. Multivariable Cox models

In multivariable Cox regression analyses, the presence of ES was still associated with 1.6 times higher risk of all-cause mortality at follow-up compared to non-ES patients (HR 1.615, 95% CI 1.004–2.598, $p = 0.048$), besides age (HR 1.041, 95% CI 1.021–1.061, $p = 0.001$), amiodarone treatment (HR 1.787, 95% CI 1.193–2.678, $p = 0.005$), LVEF ≤35% (HR 1.853, 95% CI 1.179–2.912, $p = 0.007$) and chronic kidney disease (HR 2.227, 95% CI 1.491–3.327, $p = 0.001$) (Table 3A).

Furthermore, ES was associated with a 4.5 fold higher risk for rehospitalization (HR 4.536, 95% CI 2.787–7.382, $p = 0.001$) and 3.0 times higher risk of MACE at 2.5 years (HR 3.031, 95% CI 1.844–4.985, $p = 0.001$) (Tables 3B and 3C).

3.5. Impact of ES in primary compared to secondary preventive ICDs

In ICD recipients for primary prevention, the occurrence of ES was not associated with higher risk for all-cause mortality (31% vs. 20%; log rank $p = 0.110$; Fig. 2, left panel), whereas ES influenced rehospitalization rates (59% vs. 8%; log rank $p = 0.001$; HR 10.917, 95% CI 5.977–19.941, $p = 0.001$; Fig. 2, middle panel) and MACE (37% vs. 22%; statistical trend log rank $p = 0.061$; HR 1.787, 95% CI 0.964–3.311, statistical trend $p = 0.065$; Fig. 2, right panel).

In ICD recipients for secondary prevention, all-cause mortality was higher among ES patients (39% vs. 20%; log rank $p = 0.001$; HR 2.235, 95% CI 1.378–3.625, $p = 0.001$; Fig. 3, left panel). Accordingly, also rehospitalization rates (35% vs. 15%; log rank $p = 0.001$; HR 2.822, 95% CI 1.676–4.750, $p = 0.001$; Fig. 3, middle panel) and MACE (41% vs. 24%; log rank $p = 0.014$; HR 1.784, 95% CI 1.199–2.846, $p = 0.015$; Fig. 3, right panel) were significantly higher in ES compared to non-ES patients.

3.6. Impact of ablation within ES patients

Ablation of ES was conducted in 18 ES patients. Ablation of ES did not reduce long-term all-cause mortality (50% vs. 33%; log rank $p = 0.205$; HR 1.639, 95% CI 0.758–3.546, $p = 0.209$). Furthermore, rehospitalization rates (55% vs. 40%; log rank $p = 0.099$; HR 1.820, 95% CI 0.883–3.752, $p = 0.105$), occurrence of MACE (50% vs. 38%; long rank $p = 0.416$; HR 1.368, 95% CI 0.641–2.921, $p = 0.418$) and recurrence of ES were not affected (17% vs. 28%; log rank $p = 0.380$; HR 0.593, 95% CI 0.175–2.004, $p = 0.593$).

Table 3A
Multivariable Cox regression for long-term all-cause mortality at 2.5 years.

Variable	HR	95% CI	*p* value
Age	1.041	1.021–1.061	**0.001**
Male gender	0.893	0.547–1.457	0.651
CPR	1.000	0.573–1.746	1.000
Beta-blocker treatment	0.956	0.516–1.771	0.886
Amiodarone treatment	1.787	1.193–2.678	**0.005**
LVEF ≤35%	1.853	1.179–2.912	**0.007**
DCM	1.015	0.573–1.800	0.958
Chronic kidney disease	2.227	1.491–3.327	**0.001**
Diabetes mellitus	1.389	0.944–2.045	0.096
VT ablation	1.054	0.568–1.956	0.867
ES	1.615	1.004–2.598	**0.048**

CI, confidence interval; CPR, cardiopulmonary resuscitation; DCM, dilative cardiomyopathy; ES, electrical storm; HR, hazard ratio; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia
Impaired renal function defines as creatinine >1.2 mg/dl.

Table 3B
Multivariable Cox regression for long-term rehospitalization at 2.5 years.

Variable	HR	95% CI	p value
Age	1.004	0.988–1.020	0.655
Male gender	1.267	0.722–2.223	0.409
CPR	0.765	0.402–1.458	0.416
Beta-blocker treatment	0.893	0.466–1.710	0.732
Amiodarone treatment	1.253	0.791–1.984	0.337
LVEF ≤35%	1.134	0.723–1.781	0.583
DCM	1.220	0.681–2.187	0.504
Chronic kidney disease	0.943	0.615–1.445	0.788
Diabetes mellitus	0.732	0.448–1.197	0.214
VT ablation	1.149	0.618–2.136	0.661
ES	4.536	2.787–7.382	**0.001**

CI, confidence interval; CPR, cardiopulmonary resuscitation; DCM, dilative cardiomyopathy; ES, electrical storm; HR, hazard ratio; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.
Impaired renal function defines as creatinine >1.2 mg/dl.

4. Discussion

The present study compares the prognostic impact of ES to ventricular tachyarrhythmias apart from ES on long-term all-cause mortality, rehospitalization and MACE in consecutive ICD recipients.

These data suggest that the presence of ES is an important independent predictor of adverse prognosis, even when compared to ventricular tachyarrhythmias apart from ES and even in the presence of an activated ICD. ES was associated with higher all-cause mortality, rehospitalization (mainly due to recurrent VT or AHF) and MACE. This prognostic impact was mainly observed in ICD recipients for secondary prevention. The higher risk of adverse prognosis was still proven after multivariable adjustment for age, gender, CPR, chronic kidney disease (CKD), diabetes, beta-blocker and amiodarone treatment, LVEF ≤35%, dilative cardiomyopathy and VT ablation.

Despite successful device therapies SCD still occurs in 2% of all patients with an ICD and death rates are directly related to the number of VT or VF recurrences [12]. A recent meta-analysis demonstrated 3.1 times higher risk of all-cause mortality for ES patients compared to patients without any history of ventricular tachyarrhythmias. Notably, ES patients were still associated with mortality when compared to patients with a history of ventricular tachyarrhythmias without ES [6]. However, this meta-analysis included all potential comorbidities triggering ventricular tachyarrhythmias and focused only on the risk for mortality and composite risk for all-cause mortality, heart transplantation and hospitalization for heart failure, whereas the present study explicitly excluded all patients with AMI related ventricular tachyarrhythmias and ES. ES in patients with non-ischemic cardiomyopathy was also associated with increasing mortality compared to non-ES patients [13,14]. The adverse prognostic impact of ES compared to ventricular

Table 3C
Multivariable Cox regression for MACE at 2.5 years.

Variable	HR	95% CI	*p* value
Age	1.041	1.018–1.064	**0.001**
Male gender	1.050	0.594–1.854	0.867
CPR	0.632	0.301–1.325	0.225
Beta-blocker treatment	0.875	0.429–1.781	0.712
Amiodarone treatment	1.588	1.002–2.514	**0.049**
LVEF ≤35%	1.456	0.894–2.369	0.131
DCM	0.818	0.404–1.653	0.575
Chronic kidney disease	1.666	1.070–2.596	**0.024**
Diabetes mellitus	0.877	0.547–1.404	0.584
VT ablation	0.705	0.334–1.485	0.357
ES	3.031	1.844–4.985	**0.001**

CI, confidence interval; CPR, cardiopulmonary resuscitation; DCM, dilative cardiomyopathy; ES, electrical storm; HR, hazard ratio; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia.
Impaired renal function defines as creatinine >1.2 mg/dl.

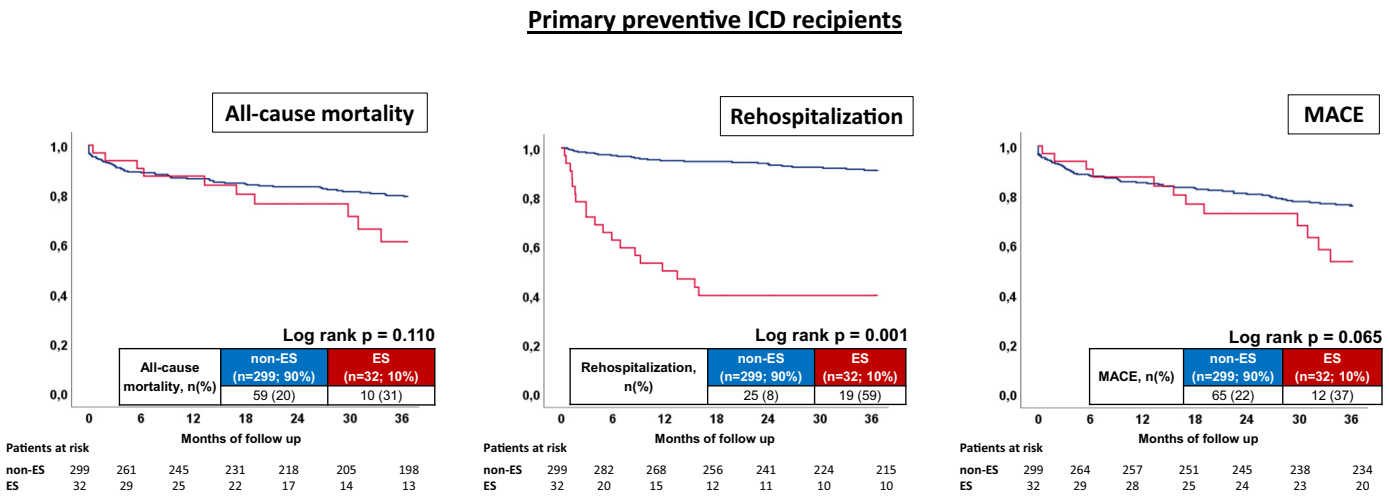

Fig. 2. Prognostic impact of ES on long-term all-cause mortality (left panel), overall rehospitalization (middle panel) and MACE (right panel) compared to ventricular tachyarrhythmias in ICD recipients for primary prevention.

tachyarrhythmias regarding all-cause mortality, rehospitalization and MACE was seen despite the fact the all patients in the present cohort were protected by an activated ICD.

In an experimental animal model of ES with recurrent ICD shocks for recurrent VF could show that episodes of ES cause a significant activation of Ca^{2+}/calmodulin-dependent protein kinase II and modification of Ca^{2+}-handling protein phosphorylation. This aberrant Ca^{2+}-handling might reveal molecular insights associated proarrhythmogenicity and mechanical dysfunction accompanying ES [15].

Some pathophysiological hypotheses are available explaining the increased risk of death among ES patients. Bänsch *et al.* propose recurrent VTs as a major driver for the increase in mortality, which in turn cause and promote LV dysfunction leading to end-stage heart failure, cardiogenic shock and death [16]. Accordingly, the results of the present study deliver further insights and enforce the hypothesis that ES might affect mortality via LV dysfunction since ES patients presented with significantly decreased LVEF. Another possible explanation delivers Sweeney *et al.* showing an increased mortality rate among patients with VT/VF terminated by shocks compared to patients treated only with anti-tachycardia pacing or without antiarrhythmic therapy [17]. The authors hypothesized that multiple shocks might contribute to transient systolic dysfunction and AHF in terms of cardiac decompensation [18]. Further, VT ablation in patients with drug-resistant ES provided optimal survival rates, enforcing the hypothesis that a decrease in VT/VF and ES might prevent associated decline in LVEF and favourably affects cardiac mortality [19,20].

Data from the MADIT II-study revealed a significantly higher risk for death for ES patients compared to non-VT/VF patients, especially within the first 3 months after the ES. However, data were derived from a post-myocardial infarction and only primary prevention cohort [21]. In contrast, survival rates in our study started to diverge from 6 months of follow-up. This might be related to increased VT ablation rates among ES patients. Vergara *et al.* demonstrated that ES patients are at high risk for VT recurrence and mortality, whereas successful ablation reduced VT recurrences and improved survival rates [22]. Nevertheless, rehospitalization rates due to VT were still significantly increased among ES patients in the present study at long-term follow-up of 2.5 years.

Most studies suggest that ES is associated with higher mortality in both primary and secondary preventive ICD recipients [1,23]. The results of the present study do not support this hypothesis since ES was only a significant risk factor for mortality in secondary preventive ICD recipients, whereas ES had no impact on mortality in the setting of

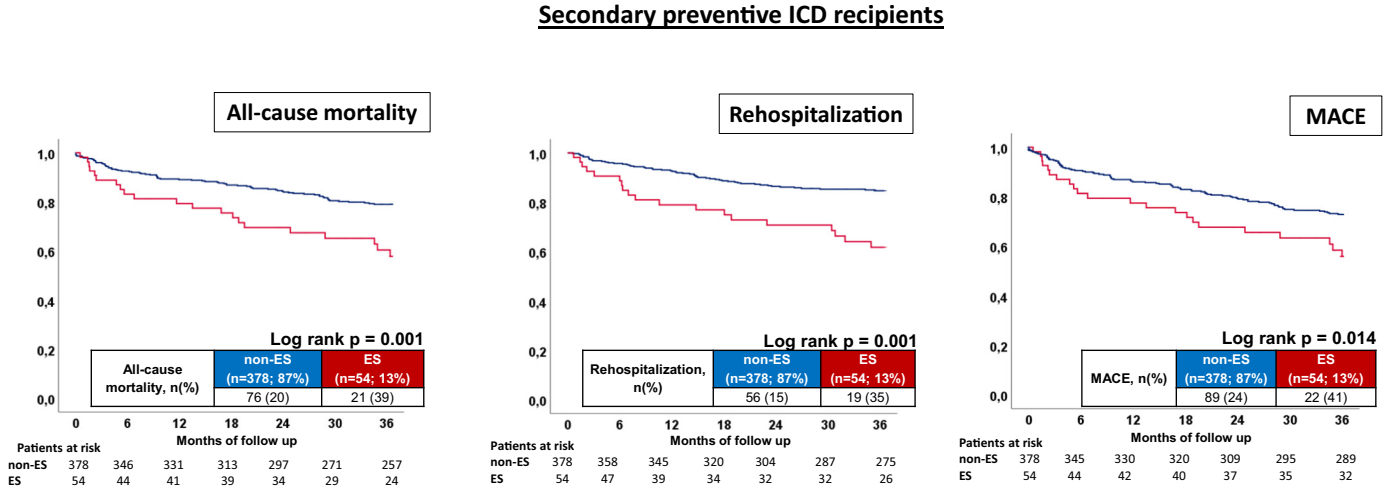

Fig. 3. Prognostic impact of ES on long-term all-cause mortality (left panel), overall rehospitalization (middle panel) and MACE (right panel) compared to ventricular tachyarrhythmias in ICD recipients for secondary prevention.

primary prevention. However, in this study post myocardial infarction patients were not included, whereas the majority of larger trials included patients with AMI [10,21]. Increased rehospitalization rates for ES patients were proven irrespective of primary or secondary prevention indication for ICD, which is in line with the current literature [6]. However, it is still under debate whether ES affects higher mortality rates directly or rather as a consequence of advanced heart failure stages or diseases such as acute myocardial infarction [24].

Despite increased VT ablation rates and higher treatment rates with beta-blockers and amiodarone, ES patients died significantly more often at follow-up time compared to non-ES patients. Notably, in non-ES patients smoking habits and CPR were more common compared to ES patients. Also in multivariable regression models the prognostic disadvantage of ES was proven and was comparable to the established risk factor LVEF <35%.

ES is also associated with increasing rates of rehospitalization alongside each shock delivery. In the presence of application of >3 shock rehospitalization rates increase up to 100% [16]. Also a sub-analysis of the SHIELD-trial revealed that ES was associated with a 3-times higher risk for arrhythmia-associated hospitalization compared to isolated VT/VF [9]. The higher overall rehospitalization rate within this study was particularly attributed to VT and AHF among ES patients. This data is in line with previous findings of Guerra *et al.* proposing ES as a clinical manifestation of worsening heart failure [6]. Further, the association between ES and increased rehospitalization rates due to VT was not unexpected. Monomorphic VT adverts the presence of a re-entry due to an electrophysiological substrate, which could fuel and sustain ES in many cases [2]. This could also explain the worsened LVEF in ES patients in this study, where re-entry pathways around anatomical barriers or scars could be favoured by structural cardiac remodelling [24]. The prognostic impact of ES compared to ventricular tachyarrhythmias in ICD recipients on all-cause mortality, rehospitalization rates and MACE in the absence of AMI at long-term follow up has never been investigated before. This study clearly demonstrated the adverse prognostic impact of ES compared to other forms of ventricular tachyarrhythmias. Therefore ES patients represent a population associated with highest risk. Based on this significant prognostic impact, ES patients are in need of a close clinical follow-up and optimal pharmacological heart failure treatment with beta-blockers and amiodarone, as well as ICD supply. Additionally, since the majority of ES consists of a basic re-entry mechanism, catheter ablation is a feasible option to stop ES onset shown to reveal further prognostic evidence since ES burden may be significantly decreased [19]. Notably, in some cases thoracic epidural anaesthesia, left cardiac sympathetic denervation and renal sympathetic denervation consist of further potential therapeutic options, which were shown to be associated with a decrease in arrhythmic burden [25–27]. However, this still needs to be investigated in future prospective randomized trials.

5. Study limitations

The present study is based on a rather small sample size with only 764 patients included in a retrospective and observational single-centre registry. VT zone programming with respect to detection length was retrieved from ICD reports retrospectively within our hospital documentation system. Further details beyond the presented have not been able to be consistently documented retrospectively. Rehospitalization rates were only documented within our own institution. Patients with prolonged hemodynamic instability and lethal outcome before admission and those not surviving out of hospital CPR without transfer to the heart centre were not included in this study. The present patient cohort comprised a wide range of cardiomyopathies potentially affecting prognostic outcomes further. Ablation rates among ES patients were low, possibly preventing to show a beneficial effect of ablation. Future prospective randomized controlled trials are needed to clarify further the prognostic impact of VT ablation in ES patients. Whether ES is a real risk factor or merely an “innocent bystander” for mortality in patients with VT or VF may not be drawn completely from the presented results, however need to be re-investigated in future trials.

6. Conclusions

ES is associated with higher rates of long-term all-cause mortality, rehospitalization rates and MACE compared to ventricular tachyarrhythmias in ICD recipients.

Conflict of interest

The authors report no relationship that could be construed as a conflict of interest.

Authors' contributions

JM and MB contributed equally to this study. JM, MB: substantially contributed to the conception and design of the work, data acquisition and analysis as well as interpretation of data for the work and drafted the work and revisited for critically important intellectual content. DE, TS, GT, LR, TR, NE, AB, SHK, CB, JR, KW, CN, KM, MA, TB, CW, MB: substantially contributed to data acquisition and analysis as well as interpretation of data for the work and revisited for critically important intellectual content. IA: conceived the study, substantially contributed to the conception and design of the work, data acquisition and analysis as well as interpretation of data for the work and drafted the work and revisited for critically important intellectual content. All authors read and approved the final manuscript.

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