Clinical Research in Cardiology (2019) 108:878–891
https://doi.org/10.1007/s00392-019-01416-y

ORIGINAL PAPER

Prognostic impact of recurrences of ventricular tachyarrhythmias and appropriate ICD therapies in a high-risk ICD population

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Received: 22 September 2018 / Accepted: 17 January 2019 / Published online: 12 February 2019

Abstract

Purpose The study sought to evaluate the prognostic impact of recurrences of ventricular tachyarrhythmias in consecutive ICD recipients with ventricular tachyarrhythmias on admission.

Methods All consecutive patients surviving at least one episode of ventricular tachyarrhythmias from 2002 to 2016 and discharged with an ICD (pre-existing ICD or ICD implantation at index hospitalization) were included. The primary endpoint was all-cause mortality according to the presence or absence of recurrences of ventricular tachyarrhythmias at 5 years. Secondary endpoints comprised the impact of different types of recurrences, appropriate ICD therapies, as well as predictors of recurrences and appropriate ICD therapies. Kaplan–Meier, multivariable Cox regression and propensity score matching analyses were applied.

Results A total of 592 consecutive ICD recipients was included (44% with recurrences of ventricular tachyarrhythmias and 56% without). Recurrences of ventricular tachyarrhythmias were associated with increased all-cause mortality at 5 years (HR = 1.498; 95% CI = 1.052–2.132; $p = 0.025$). Worst survival was observed in patients with sustained VT or VF as first recurrences compared to non-sustained VT, as well as in patients with cumulative recurrences of non-sustained or sustained VT plus VF, whereas mortality was not affected by the number of recurrences of ventricular tachyarrhythmias (> 4 vs. ≤ 4). Moreover, appropriate ICD therapies were associated with increased all-cause mortality (HR = 1.874; 95% CI = 1.318–2.666; $p = 0.001$), mainly attributed to secondary preventive ICDs. Finally, atrial fibrillation, LVEF < 35% and non-ischemic cardiomyopathy were identified as predictors of recurrences of ventricular tachyarrhythmias and appropriate ICD therapies.

Conclusions Recurrences of ventricular tachyarrhythmias and recurrent appropriate ICD therapies are associated with increased long-term all-cause mortality in consecutive ICD recipients. Non-ischemic cardiomyopathy, AF and LVEF < 35% revealed to be significant predictors of both endpoints.

Keywords Recurrences · Ventricular tachyarrhythmia · Ventricular tachycardia · Ventricular fibrillation · ICD · Mortality

Introduction

Implantable cardioverter defibrillators (ICD) represent an established clinical therapy for more than 30 years [1]. Although ICDs have the risk of adverse clinical outcomes in approximately 20% of ICD recipients, including inappropriate device therapies and device-related infections [2–4], treatment with ICDs was shown to be more effective than treatment with antiarrhythmic drugs in patients surviving episodes of ventricular tachyarrhythmias [5–7]. During the past decades, an enormous increase of ICD supply by 51% has been observed in the United States and in the overall Western World. Most commonly an ICD is implanted in

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-019-01416-y) contains supplementary material, which is available to authorized users.

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males above 65 years [8]. Due to the wide-spread use of an ICD, the identification of reliable predictors of recurrences of ventricular tachyarrhythmias and ICD therapies has become of major medical interest [9].

Some studies evaluated predictors for the future onset of ventricular tachyarrhythmias. They found low left ventricular ejection fraction (LVEF < 35%), increased stages of the New York heart association (NYHA) classification and the presence of a secondary preventive ICD to be significant predictors of ventricular tachyarrhythmias. In contrast, other studies were not able to identify any reliable predictor for appropriate ICD therapies [10]. Accordingly, such studies usually focus on prespecified questions in preselected cohorts. However, studies evaluating the real-world prognostic impact of the different types of recurrences of ventricular tachyarrhythmias and ICD-related therapies (i.e. anti-tachycardia pacing (ATP) and ICD shocks) are needed. Unfortunately, even data from all-comers, real-life ICD cohorts from the last 2 decades, which evaluate all prognostic aspects regarding recurrences of ventricular tachyarrhythmias and associated ICD therapies, are not common [11–14].

Therefore, this all-comers study aims to comprehensively evaluate the prognostic impact of recurrences of ventricular tachyarrhythmias and ICD-related therapies on long-term all-cause mortality and cardiac rehospitalization in consecutive ICD recipients with index episodes of ventricular tachyarrhythmias on admission. The prognostic impacts will be analyzed for different aspects including the different types of recurrent ventricular tachyarrhythmias and ICD-related therapies, their individual predictors, time dependency, implant indication and device types.

Methods

Study population

The present all-comers study retrospectively included all consecutive patients with index episodes of ventricular tachyarrhythmias on index hospital admission, who were discharged from our institution with an ICD from 2002 until 2016. This includes either patients with a pre-existing ICD and a documented index episode of ventricular tachyarrhythmias, or patients presenting with an index episode of ventricular tachyarrhythmias undergoing ICD implantation at index hospitalization. Transvenous single-chamber ICD, cardiac resynchronisation therapy with defibrillator (CRT-D) or subcutaneous ICD (s-ICD) were included. Patients with a primary preventive ICD comprised those with persistent LVEF < 35% without sustained ventricular tachyarrhythmias of irreversible causes at the time of prior ICD implantation, or non-sustained VT at index with persistent LVEF < 35% and ICD implantation at index. Patients with a secondary preventive ICD comprised those with a prior history of sustained ventricular tachyarrhythmias of irreversible causes and prior consecutive ICD implantation before index hospitalization. Furthermore, patients with a secondary preventive ICD may have received ICD implantation at index hospitalization after the index episode of ventricular tachyarrhythmias of irreversible causes [1, 15, 16].

Patients without an ICD at discharge or with death at index hospitalization were excluded from the present analysis. To guarantee a sufficient documentation of recurrent ventricular tachyarrhythmias, patients not presenting for at least one ICD check at follow-up were also excluded.

Definition of ventricular tachyarrhythmias

All patients presented with an index episode of ventricular tachyarrhythmias. Ventricular tachyarrhythmias comprised ventricular tachycardia (VT) and fibrillation (VF) as defined by current international guidelines [1, 17]. Sustained VT was defined by VT with a duration of more than 30 s or additional hemodynamic collapse within 30 s. Non-sustained VT was defined by a duration of less than 30 s. VT comprised of wide QRS complexes (≥ 120 ms) at a rate greater than 100 beats/min [1]. Ventricular tachyarrhythmias at index were documented by 12-lead electrocardiogram (ECG), ECG tele-monitoring, ICD or in case of unstable course or during resuscitation by external defibrillator monitoring. Documented VF was treated by ICD-related shock or external defibrillation and in case of prolonged instability with additional intravenous antiarrhythmic drugs during cardiopulmonary resuscitation (CPR). Electrical storm (ES) was defined as ≥ 3 episodes of ventricular tachyarrhythmias requiring appropriate device therapy and occurring during a period of 24 h [1, 18].

Recurrences of ventricular tachyarrhythmias comprised recurrent non-sustained, sustained VT, ES or VF according to the above criteria when occurring after discharge from index hospitalization and documented clinically or by the existing ICD.

Clinical follow-up

ICD recipients routinely presented every 3–6 months for device check and unscheduled in case of noticed device interrogations at our clinic. Device settings and programming was performed according to current international guidelines by specialized cardiologists in electrophysiology during routine clinical care [1, 17, 19]. Device recordings were re-evaluated retrospectively by independent cardiologists being blinded to final data analysis.

All relevant clinical data related to the index ventricular tachyarrhythmias, recurrences of ventricular tachyarrhythmias after discharge and re-hospitalizations were

documented using patients' files, daily records and the electronic hospital information system. These comprised baseline characteristics, prior medical history, prior medical treatment, length of index and rehospitalization stay, detailed findings of laboratory values at baseline, data derived from all non-invasive or invasive cardiac diagnostics and device therapies (i.e. coronary angiography, electrophysiological examination, prior or newly implanted cardiac devices (ICD, pacemakers or cardiac contractility modulators (CCM)) and imaging modalities (i.e. echocardiography or cardiac magnetic resonance imaging (cMRI)).

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)", a single-center registry including consecutive patients presenting with ventricular tachyarrhythmias and aborted cardiac arrest being admitted acutely to the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT02982473), from 2002 until 2016. The study 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.

Long-term follow-up period was set at the median time period of follow-up. Accordingly, long-term 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 until 2016. Identification of patients was verified by place of name, surname, day of birth and registered living addresses.

Primary and secondary endpoints

The primary endpoint was long-term all-cause mortality in patients with and without overall recurrences of ventricular tachyarrhythmias at 5 years.

Secondary endpoints comprised the prognostic impacts on long-term all-cause mortality according to the following criteria: first recurrences of ventricular tachyarrhythmias; cumulative recurrences; number of recurrences; ICD therapies in all patients; recurrences of ventricular tachyarrhythmias and appropriate ICD therapies in primary vs. secondary preventive ICDs; overall ICD therapies in patients with recurrences only. Further secondary endpoints comprised of predictors of recurrences of ventricular tachyarrhythmias and ICD-related therapies. The final secondary endpoints comprised of the impact of yearly recurrences, respectively, appropriate ICD therapies, at 1, 2, 3, 4 and 5 years of follow-up.

Endpoint analyses were based on the following subdefinitions: overall recurrences of ventricular tachyarrhythmias comprised of patients with any type or number of recurrent ventricular tachyarrhythmias. Overall ICD therapies comprised of patients with any types or numbers of appropriate ICD therapies, including anti-tachycardia pacing (ATP), ICD-related shock or both ATP and shock in the presence of documented ventricular tachyarrhythmias. Patients with overall recurrences of ventricular tachyarrhythmias were stratified by the type of first recurrence (i.e. non-sustained VT vs. sustained VT vs. VF), the cumulative types of recurrences (i.e. patients with sustained or non-sustained VTs only vs. patients with episodes of documented sustained or non-sustained VTs plus VF) and finally the number of recurrences of ventricular tachyarrhythmias (i.e. above or equal to the median of recurrences per patient).

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 non-parametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies, and compared using the chi-squared test or the Fisher's exact test, as appropriate.

First, univariable Kaplan–Meier method was applied to evaluate prognostic differences of long-term survival within the entire cohort and propensity-matched subgroups.

1:1 propensity-score matching was used to reduce potential selection bias and performed including the entire study cohort ($n = 592$ patients) for the analyses of (1) non-recurrence vs. recurrence and (2) non-ICD therapy vs. ICD therapy [20, 21]. Propensity scores were created according to the presence of the following independent variables: age, gender, diabetes, chronic kidney disease (glomerular filtration rate < 60 mL/min/1.73 m^2), prior coronary artery disease (CAD), left ventricular dysfunction, CPR, atrial fibrillation, non-ischemic cardiomyopathy, indication of ICD implantation (primary vs. secondary preventive ICDs) and index ventricular tachyarrhythmias (VT vs. VF). Based on the propensity scores counted by logistic regression, for each patient in the overall recurrence group (ICD therapy group, respectively), one patient in the control group (non-recurrence and non-ICD therapy) with a similar propensity score value was found (accepted difference of propensity score value < 5%).

Second, multivariable Cox regression models were applied with "overall recurrences of ventricular tachyarrhythmias" and "overall appropriate ICD therapies" as dependent variables for the identification of specific predictors within the unmatched entire cohort. Multivariable Cox regression models were developed using the "forward

selection" option, where only statistically significant variables ($p < 0.05$) were included and analyzed simultaneously. The following predefined variables being statistically different between the groups were used for multivariable Cox-regressions: age, sex, non-ischemic cardiomyopathy (NICM), atrial fibrillation (AF), indication of ICD implantation, acute myocardial infarction (AMI) and LVEF < 35%. Hazard ratios (HR) are given together with 95% confidence intervals. Patients without complete follow-up were censored (accepted lost-to follow-up rate < 10%).

The result of a statistical test was considered significant for $p < 0.05$, and a statistical trend was defined as $p < 0.10$. SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS (Version 25, IBM, Armonk, New York) were used for statistics.

Results

Study population

A total of 592 consecutive patients was included retrospectively (Fig. 1, flow chart). All patients survived the index episode of ventricular tachyarrhythmias and were discharged with an ICD. 18% presented with a pre-existing ICD, whereas 82% of patients underwent ICD implantation at index hospitalization before discharge. Most patients presented with VT of any type compared to VF (69% vs. 31%). Patients were median-aged at 66 years with a higher rate of males (80%). Most patients had a secondary compared to primary preventive ICD (57% vs. 43%). The most common device types were transvenous single-chamber ICD (91%), followed by a CRT-D (7%) and s-ICD (2%).

Survival according to recurrences of ventricular tachyarrhythmias

Median follow-up time was 6.3 years (IQR 3.5–9.3 years). At least 90% of patients were followed-up regularly at 5 years (1825 days) with at least one ICD check-up every 6–12 months.

First recurrences of ventricular tachyarrhythmias occurred at a median follow-up time of 1.05 years (IQR 0.34–2.11 years) after discharge from index hospitalization. At 5 years, 44% had recurrences of ventricular tachyarrhythmias, respectively, 42% at 4 years, 38% at 3 years, 33% at 2 years and 22% at 1 year (Table 1, left panel). Table 2 presents patient characteristics according to the presence of overall recurrences of ventricular tachyarrhythmias at long-term follow-up. Patients with recurrences of ventricular tachyarrhythmias had higher rates of chronic kidney disease

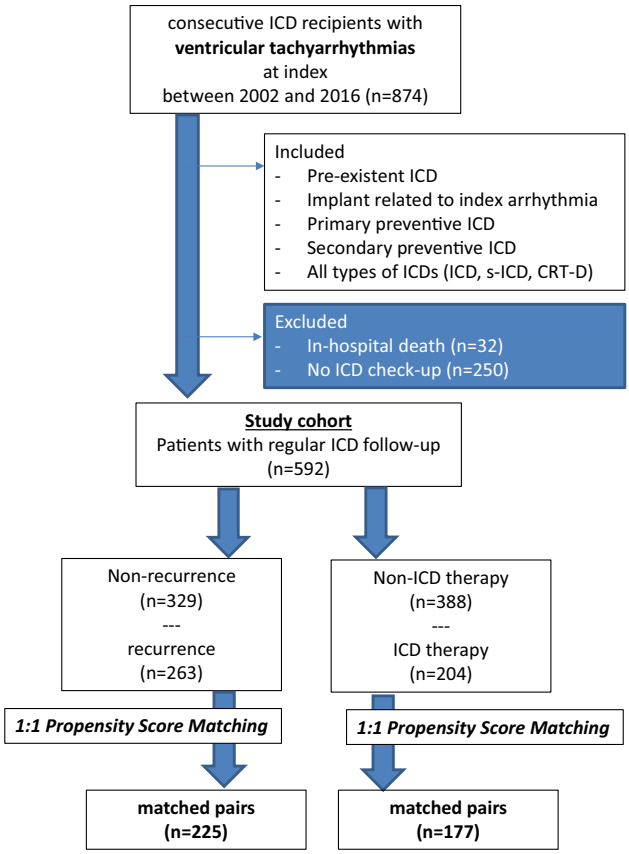

Fig. 1 Flow chart of study population

(48% vs. 39%), LVEF < 35% (54% vs. 44%) and secondary preventive ICDs (62% vs. 54%) (Table 2, left panel).

Patients with recurrences of ventricular tachyarrhythmias were associated with increased long-term all-cause mortality at 5 years (mortality rates 26% vs. 17%, log rank p = 0.024; HR = 1.498; 95% CI = 1.052–2.132; $p = 0.025$) (Fig. 2, left panel). Recurrences of ventricular tachyarrhythmias were associated with impaired survival from the second year of follow-up on already, whereas at the first year a statistical trend for impaired survival was observed only (Table 1, left panel). Accordingly, the rates of re-hospitalization were higher in patients with recurrences (Table 2).

After propensity-score matching (225 matched pairs) significant differences between both groups were no longer seen, except for a higher rate of smoking in the non-recurrence group (Table 2, right panel). Thereafter, recurrences of ventricular tachyarrhythmias were still associated with impaired long-term survival at 5 years (mortality rate 26% vs. 18%, log rank $p = 0.034$; HR = 1.542; 95% CI = 1.030–2.307; $p = 0.035$) (Fig. 2, right panel).

Focusing on the type of first recurrences of ventricular tachyarrhythmias in the unmatched cohort, both patients with sustained VT and VF were associated with impaired long-term survival compared to patients with non-sustained

Table 1 Unmatched HRs and 95% CI for recurrence as well as for ICD therapy according to follow-up period

Follow-up time	Analysis of recurrence					Analysis of appropriate ICD therapy				
	n (%)*	*n* (%)†	HR	95% CI	*p* value	*n* (%)*	*n* (%)†	HR	95% CI	*p* value
1 year	128 (22)	128 (22)	2.254	0.934–5.437	0.071	98 (17)	98 (17)	2.054	0.797–5.294	0.136
2 years	193 (33)	65 (11)	2.209	1.247–3.914	**0.007**	153 (26)	55 (9)	2.581	1.445–4.577	**0.001**
3 years	227 (38)	34 (6)	1.945	1.223–3.092	**0.005**	178 (30)	25 (4)	2.239	1.411–3.555	**0.001**
4 years	246 (42)	19 (3)	1.699	1.146–2.517	**0.008**	191 (32)	13 (2)	2.152	1.454–3.184	**0.001**
5 years	263 (44)	17 (3)	1.498	1.052–2.132	**0.025**	204 (34)	13 (2)	1.874	1.318–2.666	**0.001**

Bold values indicate $p < 0.05$

Level of significance $p < 0.05$, statistical trend $p < 0.1$

*Sum (percentage) of events according to follow up period

†Number (percentage) of new events according to each year of follow up

VT (log rank $p < 0.015$) (Fig. 3, left panel). Regarding the cumulative recurrences, patients with sustained or non-sustained VTs plus VF were associated with worse survival compared to patients with sustained or non-sustained VTs only (log rank $p = 0.045$) (Fig. 3, middle panel). Finally, patients with ≤ 4 recurrences of any type and patients with > 4 recurrences (according to the median of overall recurrences) revealed comparable long-term survival (log rank $p = 0.249$) (Fig. 3, right panel).

Survival according to appropriate ICD therapies

First appropriate ICD therapies occurred at a median follow-up time of 1.1 years (IQR 0.3–2.0 years) after discharge from index hospitalization. Table 3 presents patient characteristics according to the presence of overall ICD-related therapies at long-term follow-up. More patients with ICD therapies survived an index episode of VT compared to the non-therapy group (75% vs 66%) despite higher rates of CKD, NICM, atrial fibrillation and LVEF < 35%. Smoking was higher in the non-therapy group (Table 3, left panel).

Patients with appropriate ICD therapies were associated with increased long-term mortality (mortality rates 30% vs. 16%, log rank $p = 0.001$; HR = 1.874; 95% CI = 1.318–2.666; $p = 0.001$) (Fig. 4, left panel; Table 3). Both patients with ICD shocks (mortality rate 36% vs. 18%, log rank $p = 0.001$; HR = 2.276; 95% CI = 1.572–3.294; $p = 0.001$) and patients with episodes of ATP only were associated with increased mortality at long-term follow-up (mortality rate 30% vs. 18%, log rank $p = 0.003$; HR = 1.711; 95% CI = 1.191–2.460; $p = 0.004$) (data not shown). Impaired mortality in patients with ICD therapies was evident already at 2 years of follow-up (Table 1, right panel).

After propensity-matching (177 matched pairs) (Table 3, right panel), appropriate ICD therapies were still associated with increased mortality at 5 years (mortality rates 30% vs. 16%, log rank $p = 0.001$; HR = 2.007; 95% CI = 1.280–3.147; $p = 0.002$) (Fig. 4, right panel).

Focusing on those patients with recurrences of ventricular tachyarrhythmias at 5 years only within the unmatched cohort, those with appropriate ICD therapies still revealed increased long-term mortality (mortality rates 30% vs. 10%, log rank $p = 0.008$; HR = 2.949; 95% CI = 1.275–6.821; $p = 0.011$) (Fig. 5a).

Stratification by indication of ICD implantation

Focusing on patients with a primary preventive ICD (43%), recurrences of ventricular tachyarrhythmias were not associated with differences of long-term all-cause mortality (unmatched: HR = 1.458; 95% CI 0.807–2.636; $p = 0.211$; matched: HR = 1.475; 95% CI 0.772–2.818; $p = 0.239$). In contrast, those recurrences of ventricular tachyarrhythmias treated by appropriate ICD therapy were associated with increased mortality (unmatched: HR = 1.857; 95% CI 1.026–3.362; $p = 0.041$; matched: HR = 1.802; 95% CI 0.890–3.649; $p = 0.102$) (not shown).

In patients with a secondary preventive ICD (57%), recurrences of ventricular tachyarrhythmias were also not associated with differences of long-term all-cause mortality (unmatched: HR = 1.454; 95% CI 0.933–2.264; $p = 0.098$; matched: HR = 1.536; 95% CI 0.915–2.578; $p = 0.104$). However, patients with appropriate ICD therapy were associated with increased mortality even after propensity-score matching (unmatched: HR = 1.832; 95% CI 1.182–2.840; $p = 0.007$; matched: HR = 2.100; 95% CI 1.166–3.785; $p = 0.0014$) (not shown).

Subgroup of s-ICD patients

Characteristics of patients with an implanted s-ICD ($n = 13$; 2%) are given in Supplemental Table 1. At 5 years of follow-up, five patients (39%) had recurrences of ventricular tachyarrhythmias and four patients (31%) had an appropriate ICD therapy (no episodes of ATP only, four patients

Table 2 Characteristics according to recurrences of ventricular tachyarrhythmias

Characteristics	Before propensity score matching			After propensity score matching		
	Non-recurrence ($n=329$;56%)	Recurrence ($n=263$;44%)	p value	Non-recurrence ($n=225$;50%)	Recurrence ($n=225$;50%)	p value
Age, median (range)	66 (19–84)	67 (15–87)	0.263	66 (19–84)	67 (21–87)	0.526
Males, *n* (%)	256 (78)	215 (82)	0.238	184 (82)	182 (81)	0.809
Tachyarrhythmia at index, *n* (%)						
Ventricular tachycardia	221 (67)	187 (71)	0.305	157 (70)	162 (72)	0.604
Ventricular fibrillation	108 (33)	76 (29)		68 (30)	63 (28)	
Cardiovascular risk factors, *n* (%)						
Arterial hypertension	210 (64)	158 (60)	0.349	146 (65)	135 (60)	0.284
Diabetes mellitus	87 (26)	69 (26)	0.954	57 (25)	57 (25)	1.000
Hyperlipidemia	132 (40)	103 (39)	0.813	99 (44)	90 (40)	0.390
Smoking	106 (32)	67 (26)	0.073	73 (32)	51 (23)	**0.020**
Cardiac family history	54 (16)	29 (11)	0.061	39 (17)	26 (12)	0.081
Comorbidities at index, *n* (%)						
Coronary artery disease	224 (68)	178 (68)	0.917	163 (72)	156 (69)	0.468
Atrial fibrillation	98 (30)	96 (37)	0.084	74 (33)	81 (36)	0.487
Acute myocardial infarction	44 (13)	33 (13)	0.766	26 (12)	29 (13)	0.666
Cardiogenic shock	27 (8)	24 (9)	0.692	18 (8)	21 (9)	0.615
CPR	78 (24)	59 (23)	0.715	48 (21)	47 (21)	0.908
Out of hospital	52 (16)	42 (16)	0.957	32 (14)	35 (16)	0.691
In hospital	26 (8)	17 (7)	0.503	16 (7)	12 (5)	0.435
Non-ischemic cardiomyopathy	27 (8)	33 (13)	0.082	24 (11)	30 (13)	0.384
Chronic kidney disease	127 (39)	125 (48)	**0.029**	98 (44)	103 (46)	0.635
Medication at discharge, *n* (%)						
Beta-blocker	279 (85)	233 (87)	0.180	197 (88)	204 (91)	0.289
ACE-inhibitor	224 (68)	187 (71)	0.428	163 (72)	162 (72)	0.916
ARB	42 (13)	33 (13)	0.954	28 (13)	28 (13)	1.000
Aldosterone antagonist	45 (14)	46 (18)	0.201	28 (12)	39 (17)	0.145
Amiodarone	61 (19)	50 (19)	0.884	46 (20)	43 (19)	0.723
ECG intervals, (mean ± SEM)						
PQ	170 ± 4	180 ± 5	0.156	170 ± 5	180 ± 5	0.182
QRS	106 ± 4	110 ± 5	0.569	109 ± 5	109 ± 5	0.939
QT	421 ± 7	408 ± 5	0.145	425 ± 10	407 ± 4	0.073
LVEF, *n* (%)						
≥ 55%	71 (24)	35 (15)	0.051	50 (22)	34 (15)	0.287
54–45	34 (11)	23 (9)		22 (10)	23 (10)	
44–35%	60 (20)	49 (21)		44 (20)	48 (21)	
< 35%	132 (44)	125 (54)		109 (48)	120 (53)	
Not documented	29 (–)	31 (–)	–	– (–)	– (–)	–
Electrical therapies at index, *n* (%)						
Electrophysiological examination	155 (47)	114 (43)	0.360	111 (49)	127 (56)	0.219
Ablation therapy	17 (5)	16 (6)	0.629	13 (6)	13 (6)	1.000
Type of ICD, *n* (%)						
ICD	296 (90)	245 (93)		206 (92)	211 (94)	
CRT-D	25 (8)	13 (5)	0.376	17 (8)	12 (5)	0.631
s-ICD	8 (2)	5 (2)		2 (0.9)	2 (0.9)	
Implant indication, *n* (%)						
Primary prevention	153 (47)	99 (38)	**0.030**	103 (46)	90 (40)	0.216
Secondary prevention	176 (54)	164 (62)		122 (54)	136 (60)	

Table 2 (continued)

Characteristics	Before propensity score matching			After propensity score matching		
	Non-recurrence ($n=329$;56%)	Recurrence ($n=263$;44%)	p value	Non-recurrence ($n=225$;50%)	Recurrence ($n=225$;50%)	p value
ICD programming, bpm, median (IQR)						
VT detection threshold	171 (167–176)	170 (167–171)	**0.004**	171 (167–176)	167 (167–171)	**0.005**
VF detection threshold	214 (214–222)	214 (214–222)	0.451	214 (214–222)	214 (214–220)	0.716
All-cause mortality, at 5 years, *n* (%)	57 (17)	67 (25)	**0.015**	40 (18)	58 (26)	**0.040**
First rehospitalization, *n* (%)						
Overall	54 (17)	113 (43)	**0.001**	43 (19)	96 (43)	**0.001**
Ventricular tachycardia	0 (0)	51 (20)	**0.001**	0 (0)	44 (20)	**0.001**
Ventricular fibrillation	0 (0)	14 (5)	**0.001**	0 (0)	12 (5)	**0.001**
Acute myocardial infarction	4 (1)	4 (1)	1.000	3 (1)	4 (2)	0.703
Acute heart failure	19 (6)	21 (8)	0.287	14 (6)	18 (8)	0.463
Inappropriate device therapy	18 (6)	10 (4)	0.342	16 (7)	8 (4)	0.093
Other	13 (4)	13 (5)	0.559	10 (5)	10 (5)	1.000

Bold values indicate $p<0.05$

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CPR* cardiopulmonary resuscitation, *CRT-D* cardiac resynchronization therapy plus defibrillator, *ICD* implantable cardioverter-defibrillator, *s-ICD* subcutaneous ICD

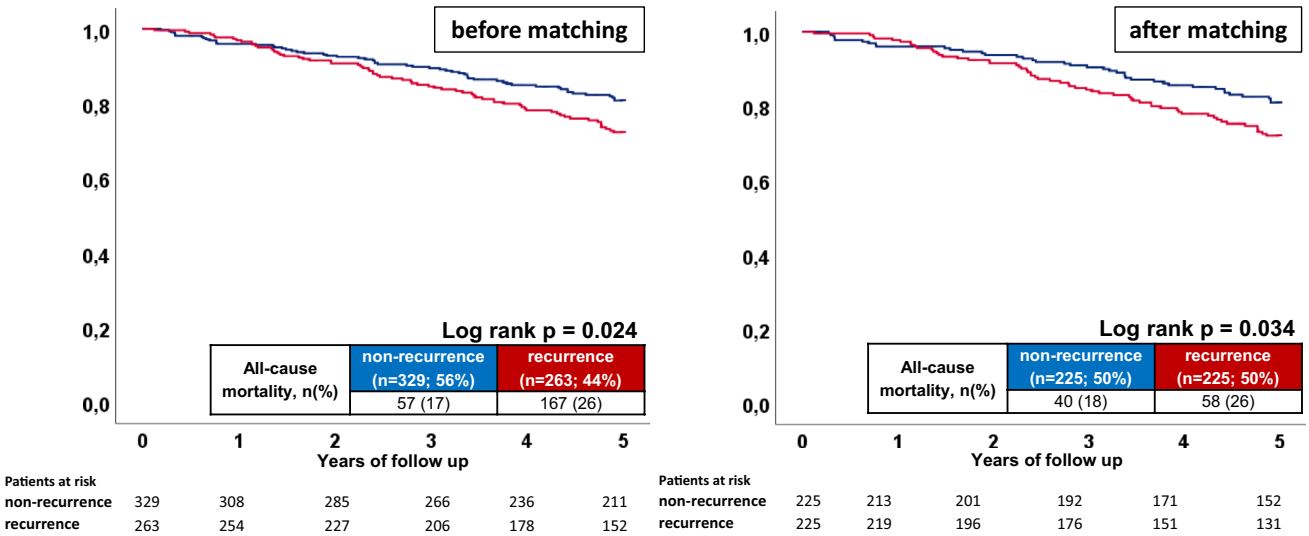

Fig. 2 Kaplan–Meier survival curves evaluating the impact of recurrences of ventricular tachyarrhythmias on all-cause mortality at 5 years before (left panel) and after propensity score matching (right panel)

with ICD shocks). Two patients (15%) died within 5 years of follow-up.

Predictors of recurrences of ventricular tachyarrhythmias

After 5 years of follow-up, 263 patients (44%) had recurrences of ventricular tachyarrhythmias, with highest rates of recurrences at year 1 ($n=128$; 22%) (Table 1, left panel). From an overall perspective, most patients had sustained VT (mean 5.0 episodes ± 0.9 per patient), followed by non-sustained VT (mean 4.8 episodes ± 1.4 per patient) at 5 years of follow-up (Table 4).

Within multivariable Cox regression analyses, non-ischemic cardiomyopathy (HR = 1.503; 95% CI = 1.019–2.217; $p=0.040$) and AF (HR = 1.319; 95% CI = 1.003–1.734; $p=0.048$) were strongest predictors of

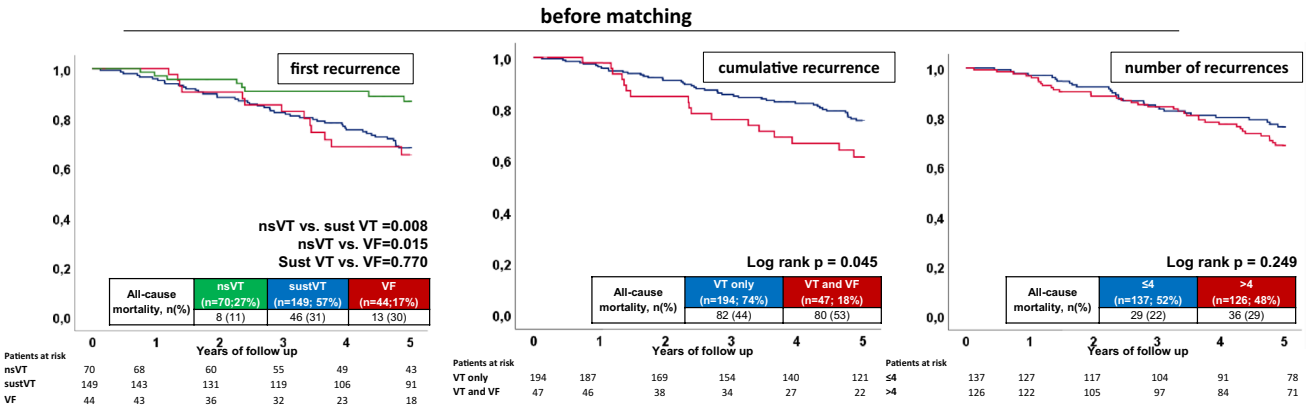

Fig. 3 Kaplan–Meier survival curves demonstrating the impact of type of first recurrent ventricular tachyarrhythmias (left panel), cumulative types of ventricular tachyarrhythmias at follow-up (middle panel) and numbers of recurrences at 5 years (right panel)

recurrences of ventricular tachyarrhythmias at long-term follow-up (Fig. 5b, left panel).

Predictors of appropriate ICD therapy

ICD therapies were highest in the first year of follow-up in 98 patients (17%) (Table 1, right panel). Age (HR = 1.016; 95% CI = 1.002–1.029; $p = 0.023$), LVEF < 35% (HR = 1.431; 95% CI = 1.053–1.947; $p = 0.022$), AF (HR = 1.327; 95% CI 0.974–1.807; $p = 0.073$, statistical trend) and NICM (HR = 1.713; 95% CI = 1.126–2.607; $p = 0.012$) were strongest predictors of appropriate ICD therapy at long-term follow-up (Fig. 5b, right panel).

Discussion

The present study evaluates the prognostic impact of recurrences of ventricular tachyarrhythmias and appropriate ICD therapies on all-cause mortality in consecutive all-comer ICD recipients with index episodes of ventricular tachyarrhythmias on admission. This real-world ICD cohort reveals that patients with recurrent ventricular tachyarrhythmias on admission were associated with increased long-term all-cause mortality at 5 years. Worst survival was seen in patients with a first recurrence episode of sustained VT plus VF compared to non-sustained VT, as well as in patients with cumulative episodes of overall VT plus VF compared to cumulative overall VT in the absence of VF. Long-term survival was not affected by the number of recurrences per patient. Numbers of recurrences were highest in the first year of follow-up after index hospitalization. Increased mortality related to appropriate ICD therapies was mainly attributed to patients with a secondary preventive ICD. LVEF < 35%, AF and NICM were identified as strongest predictors of recurrences of ventricular tachyarrhythmias and appropriate ICD therapies.

Focusing on the impact of ventricular tachyarrhythmias and ICD therapies on long-term survival, Grimm et al. [11] demonstrated in the last century that appropriate or inappropriate ICD shocks were not associated with arrhythmic and all-cause mortality in 241 patients at long-term follow-up of 5 years. They found a higher rate of appropriate ICD shocks (63%) compared to our study (34%). In contrast, our study identifies both recurrences of ventricular tachyarrhythmias—especially those treated by appropriate ICD therapies—to be significantly associated with long-term mortality. Results were confirmed even after propensity matching, and specifically evident in patients with a secondary preventive ICD. However, there are varying rates between 8–13% or up to 60% of appropriate ICD therapies in recent studies [11, 22]. A meta-analysis by Qian et al., including 13 cohort studies with 75% of patients with a primary preventive ICD revealed increased mortality associated with appropriate ICD shocks, but not with sole ATP [12–14]. In contrast, the present study differentiates even into patients with episodes of ATP only, which were in turn also associated with increased mortality.

With regard to the different types and cumulative numbers of recurrent tachyarrhythmias and appropriate ICD therapies, Pacifico et al. [23] analyzed the impact of single vs. non-ICD-shock and multiple vs. single ICD shock in 421 consecutive patients. They found increased death associated with both single and multiple ICD shocks compared to patients without. In contrast to their findings, the present study demonstrates increasing long-term mortality related to cumulative overall VT plus VF vs. overall VT in the absence of VF, whereas an increasing number of recurrences per patient (≤ 4 episodes vs. > 4 episodes) was not affecting long-term mortality.

Regarding the different types of ventricular tachyarrhythmias, non-sustained VT were recently shown to be

Table 3 Characteristics according to appropriate ICD therapies

Characteristics	Before propensity score matching			After propensity score matching		
	Non-ICD therapy ($n=388$;66%)	ICD therapy ($n=204$;34%)	p value	Non-ICD therapy ($n=177$;50%)	ICD therapy ($n=177$;50%)	p value
Age, median (range)	66 (19–84)	67 (15–87)	0.059	67 (39–84)	67 (21–87)	0.595
Male gender, *n* (%)	304 (78)	167 (82)	0.314	144 (81)	144 (81)	1.000
Tachyarrhythmia at index, *n* (%)						
Ventricular tachycardia	256 (66)	152 (75)	**0.033**	127 (72)	134 (76)	0.398
Ventricular fibrillation	132 (34)	52 (26)		50 (28)	43 (24)	
Cardiovascular risk factors, *n* (%)						
Arterial hypertension	248 (64)	120 (59)	0.225	118 (67)	106 (60)	0.186
Diabetes mellitus	104 (27)	52 (26)	0.730	46 (26)	43 (24)	0.713
Hyperlipidemia	152 (39)	83 (41)	0.721	78 (44)	76 (43)	0.830
Smoking	124 (32)	49 (24)	**0.044**	62 (35)	38 (22)	**0.005**
Cardiac family history	58 (15)	25 (12)	0.370	27 (15)	23 (13)	0.542
Comorbidities at index, *n* (%)						
Coronary artery disease	265 (68)	137 (67)	0.777	130 (73)	123 (70)	0.410
Atrial fibrillation	114 (29)	80 (39)	**0.015**	60 (34)	67 (38)	0.438
Acute myocardial infarction	56 (14)	21 (10)	0.155	19 (11)	18 (10)	0.862
Cardiogenic shock	32 (8)	19 (9)	0.660	11 (6)	17 (10)	0.237
CPR	101 (27)	36 (18)	**0.038**	31 (18)	28 (16)	0.669
Out of hospital	68 (18)	26 (13)	0.130	25 (14)	22 (12)	0.638
In hospital	33 (9)	10 (5)	0.108	6 (3)	6 (3)	1.000
Non-ischemic cardiomyopathy	31 (8)	29 (14)	**0.017**	24 (14)	27 (15)	0.650
Chronic kidney disease	150 (39)	102 (50)	**0.011**	83 (47)	86 (49)	0.750
Medication at discharge, *n* (%)						
Beta-blocker	331 (85)	181 (89)	0.248	158 (89)	159 (90)	0.862
ACE-inhibitor	271 (70)	140 (69)	0.760	136 (77)	123 (70)	0.119
ARB	47 (12)	28 (14)	0.555	19 (11)	25 (15)	0.303
Adosterone antagonist	52 (13)	39 (19)	0.067	23 (13)	33 (19)	0.145
Amiodarone	68 (18)	43 (21)	0.293	37 (21)	37 (21)	1.000
ECG intervals, (mean ± SEM)						
PQ	169 ± 4	186 ± 7	**0.014**	177 ± 7	186 ± 7	0.341
QRS	105 ± 4	114 ± 6	0.149	111 ± 7	113 ± 6	0.808
QT	418 ± 6	108 ± 6	0.249	418 ± 7	105 ± 6	0.158
LVEF, *n* (%)						
≥ 55%	85 (24)	21 (12)	**0.001**	24 (14)	21 (12)	0.909
54–45	42 (12)	15 (8)		17 (10)	15 (9)	
44–35%	69 (20)	40 (22)		35 (20)	39 (22)	
< 35%	153 (44)	104 (58)		101 (57)	102 (58)	
Not documented	39 (–)	24 (–)	–	– (–)	– (–)	–
Electrical therapies at index, *n* (%)						
Electrophysiological examination	176 (45)	93 (46)	0.958	85 (48)	83 (47)	0.831
Ablation therapy	21 (5)	12 (6)	0.813	7 (4)	9 (5)	0.609
Type of ICD, *n* (%)						
ICD	352 (91)	189 (93)		158 (89)	166 (94)	
CRT-D	27 (7)	11 (5)	0.725	15 (9)	10 (6)	0.223
s-ICD	9 (2)	4 (2)		4 (2)	1 (0.6)	

Table 3 (continued)

Characteristics	Before propensity score matching			After propensity score matching		
	Non-ICD therapy ($n=388$;66%)	ICD therapy ($n=204$;34%)	p value	Non-ICD therapy ($n=177$;50%)	ICD therapy ($n=177$;50%)	p value
Implant indication, *n* (%)						
Primary prevention	173 (45)	79 (39)	0.170	83 (47)	71 (40)	0.198
Secondary prevention	215 (55)	125 (61)		94 (53)	106 (60)	
ICD programming, bpm, median (IQR)						
VT detection threshold	171 (167–176)	170 (165–171)	**0.001**	171 (167–176)	170 (165–171)	**0.009**
VF detection threshold	214 (214–222)	214 (214–222)	0.673	214 (214–220)	214 (214–221)	0.698
All-cause mortality, at 5 years, *n* (%)	63 (16)	61 (30)	**0.001**	29 (16)	55 (31)	**0.001**
First rehospitalization, *n* (%)						
Overall	60 (15)	107 (52)	**0.001**	37 (21)	88 (50)	**0.001**
Ventricular tachycardia	2 (0.1)	49 (24)	**0.001**	2 (0.1)	42 (24)	**0.001**
Ventricular fibrillation	0 (0)	14 (7)	**0.001**	0 (0)	12 (7)	**0.001**
Acute myocardial infarction	4 (1)	4 (1)	0.408	1 (0.6)	4 (2)	0.177
Acute heart failure	22 (6)	18 (9)	0.146	11 (6)	16 (9)	0.319
Inappropriate device therapy	19 (5)	9 (5)	0.792	13 (7)	7 (4)	0.169
Other	13 (4)	13 (4)	0.088	10 (6)	7 (4)	0.457

Bold values indicate $p<0.05$

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CPR* cardiopulmonary resuscitation, *CRT-D* cardiac resynchronization therapy plus defibrillator, *ICD* implantable cardioverter-defibrillator, *s-ICD* subcutaneous ICD

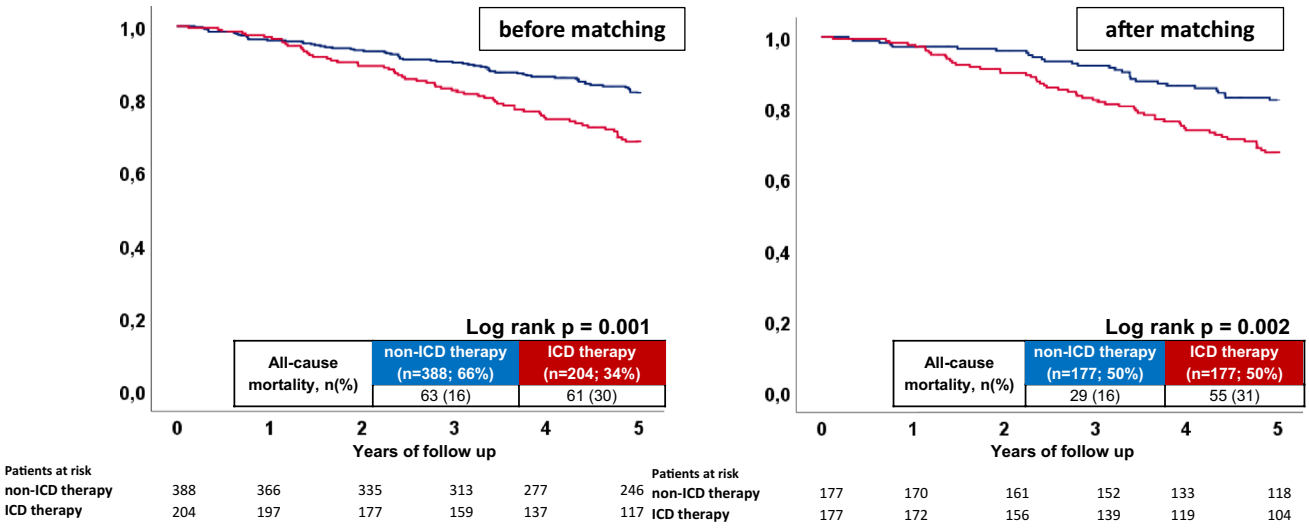

Fig. 4 Kaplan–Meier survival curves evaluating the impact of appropriate device therapies on all-cause mortality at 5 years before (left panel) and after propensity score matching (right panel)

associated with rehospitalization due to acute heart failure compared to non-VT patients in 104 ICD recipients [24]. In contrast, the present study demonstrates decreasing long-term mortality associated with recurrent non-sustained VT vs. sustained VT plus VF.

Implantation of an s-ICD represents a more common alternative type of ICD worldwide with a higher comfort for patients compared to a transvenous ICD [25–29]. However, the number of s-ICD patients was very low in the present study (2%). The prognostic impact of recurrences of

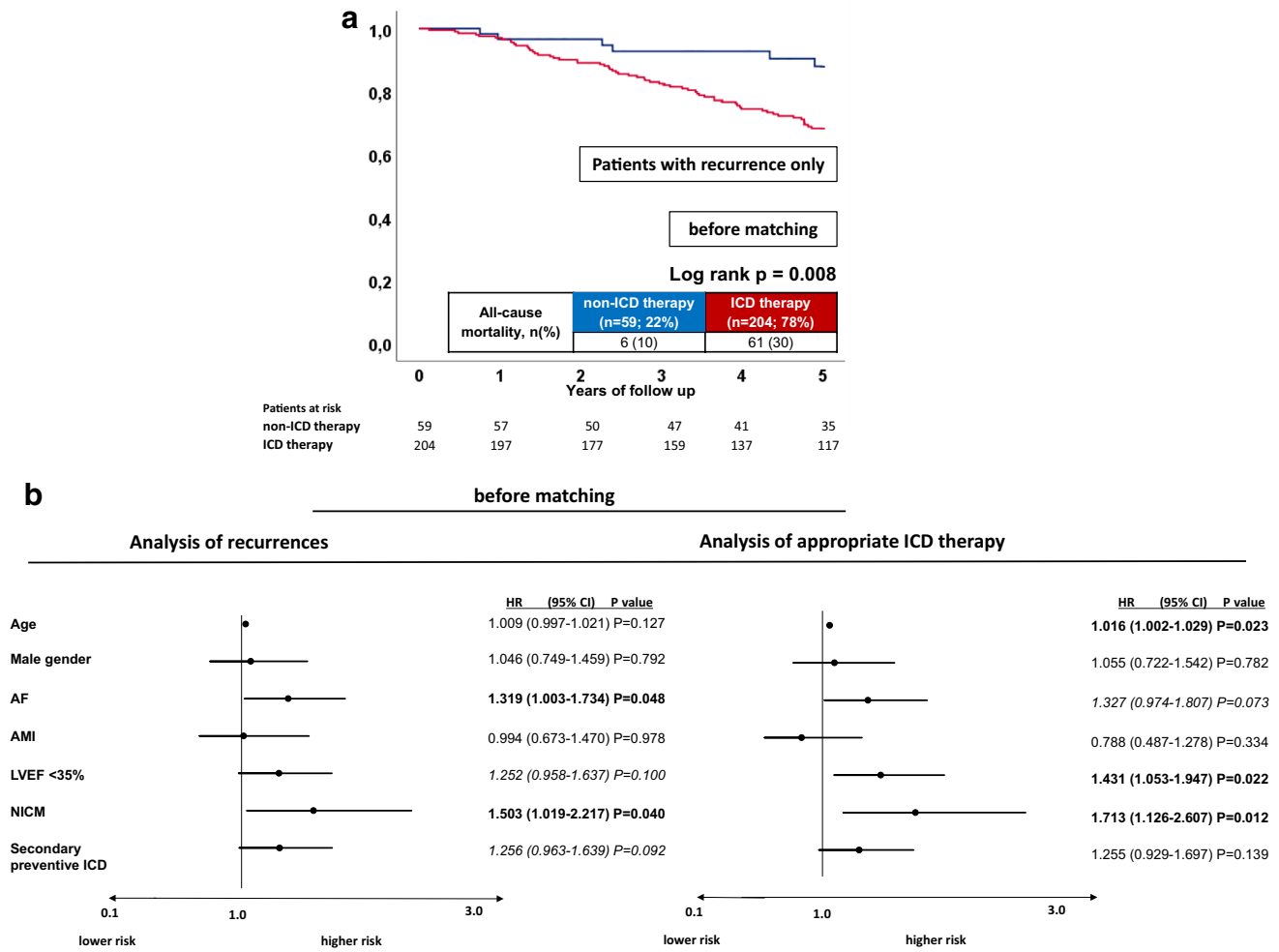

Fig. 5 **a** Appropriate ICD therapies were still associated with increased mortality in patients with recurrences only. **b** Multivariable Cox regression models demonstrating predictors of recurrences of ventricular tachyarrhythmias (left panel) and appropriate device therapies (right panel) at 5 years

ventricular tachyarrhythmias and appropriate ICD therapies specifically in s-ICD recipients needs further investigation. Furthermore, the prognostic benefit of a wearable defibrillator is still under debate with conflicting results of recent studies focussing on the prevention of SCD in patients with LVEF < 35% [30, 31] and peripartum cardiomyopathies [32, 33].

Since ventricular tachyarrhythmias are caused by multifactorial pathways and associated comorbidities such as also cardiac anxiety, the identification of reliable predictors remains an ongoing challenge [9, 34–38]. Zaman et al. demonstrates especially patients with a secondary preventive ICD to be at risk of recurrent ventricular tachyarrhythmias [39, 40]. Fang et al., demonstrated that the presence of dilative cardiomyopathy was also associated with increased mortality in 132 consecutive patients with a secondary preventive ICD at 3.6 years [41, 42]. The present study identifies LVEF < 35%, AF and non-ischemic cardiomyopathy as predictors of both recurrent ventricular tachyarrhythmias and appropriate ICD therapies, whereas only the latter was also different in patients with a secondary preventive ICD. A 1.6-fold increased risk of ventricular tachyarrhythmias and SCD was associated with AF in 350,000 patients from Taiwan [43]. However, AF has been proven as a modifiable arrhythmia by physical activity [44] and medical treatment including ablation therapy [45–47].

Conclusions

Taken together, the present study is derived from a real-life cohort of all-comer ICD recipients presenting with index episodes of ventricular tachyarrhythmias. The prognostic impacts of recurrences of ventricular tachyarrhythmias

Table 4 Types of recurrences of ventricular tachyarrhythmias and ICD therapies at 5 years of follow-up

Characteristics	
First recurrence of ventricular tachyarrhythmia, *n* (%)	
Overall	263 (44)
Non-sustained VT	70 (11)
Sustained VT	149 (25)
VF	44 (7)
Electrical storm	41 (7)
VT cycle length, median (IQR)	320 (280–340)
Overall recurrences at follow-up, *n* (%)	
Non-sustained VT	112 (19)
Sustained VT	189 (32)
VF	64 (11)
Electrical storm	41 (7)
Recurrences per patient, mean ± SEM	
Overall	10.8 ± 1.7
Non-sustained VT	4.8 ± 1.4
Sustained VT	5.0 ± 0.9
VF	0.9 ± 0.6
Electrical storm	0.1 ± 0.0
First appropriate device therapies, *n* (%)	
Overall appropriate device therapy	204 (34)
Appropriate shock	87 (15)
Appropriate ATP only	117 (20)
Overall device therapies at follow-up, *n* (%)	
Appropriate shock	119 (20)
Appropriate ATP only	155 (26)
Inappropriate device therapy	78 (13)
Device therapies per patient, mean ± SEM	
Appropriate shock	0.8 ± 0.1
Appropriate ATP only	4.0 ± 0.8
Inappropriate shock	0.4 ± 0.1
Inappropriate ATP only	0.1 ± 0.0

ATP anti-tachycardia pacing, *ICD* implantable cardioverter-defibrillator, *SEM* standard error of mean, *VF* ventricular fibrillation, *VT* ventricular tachycardia

and appropriate ICD therapies were analyzed for different aspects including the different types of recurrent ventricular tachyarrhythmias and ICD-related therapies, their individual predictors, time dependency, implant indication and device types. Recurrences of ventricular tachyarrhythmias and appropriate ICD therapies were associated with increased long-term all-cause mortality. LVEF < 35%, AF and NICM revealed strongest predictors of both endpoints.

Study limitations

This observational and retrospective registry-based analysis reflects a realistic picture of consecutive health-care supply of high-risk ICD recipients presenting with ventricular tachyarrhythmias on admission. Lost-to-follow-up rate regarding the evaluated endpoint of all-cause mortality was minimal. ICD check-ups and re-hospitalization were only documented within our institution. However, to minimize lost-to-follow-up rate, all patients not meeting ICD follow-up at least once after discharge were excluded. Therefore, we can guarantee a routine follow-up every 3–6 months for over 90% of analyzed patients. All clinical data were documented reliably by individual cardiologists during routine clinical care being blinded to final analyses, alleviating the use of an independent clinical event committee. Subgroup analyses stratified by the indication of ICD implantation may be influenced by the small numbers of patients in these subgroups. Also the small number of s-ICD patients (2%) does not allow reliable conclusions regarding the impact of recurrences of ventricular tachyarrhythmias and appropriate ICD therapies on mortality in this subset of patients. The present results need to be re-evaluated within even larger representative multi-centre registries or even prospective randomized trials, especially focusing on patients undergoing s-ICD implantation.

Compliance with ethical standards

Conflict of interest The authors declare that they do not have any conflict of interest.

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