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ORIGINAL ARTICLE

Impact of chronic kidney disease on recurrent ventricular tachyarrhythmias in ICD recipients

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Abstract

The study sought to assess the impact of chronic kidney disease (CKD) on recurrences of ventricular tachyarrhythmias in implantable cardioverter defibrillator (ICD) recipients. Data regarding the outcome of patients with CKD in ICD recipients is limited. A large retrospective registry was used including consecutive ICD recipients surviving episodes of ventricular tachycardia (VT) or fibrillation (VF) from 2002 to 2016. CKD patients were compared to non-CKD patients. The primary endpoint was the first recurrence of ventricular tachyarrhythmias at 5 years. Secondary endpoints were ICD-related therapies, rehospitalization and all-cause mortality at 5 years. Kaplan–Meier, multivariable Cox regression and propensity score matching were applied. A total of 585 consecutive patients were included (non-CKD: 57%, CKD: 43%). CKD had higher rates of the primary endpoint of recurrent ventricular tachyarrhythmias compared to non-CKD patients (50% vs. 40%; log rank $p=0.008$; HR = 1.398; 95% CI 1.087–1.770; $p=0.009$), which was irrespective of a primary or secondary preventive ICD and mainly attributed to recurrent VF (11% vs. 5%; $p=0.007$) and electrical storm (ES) (10% vs. 5%; $p=0.010$). Accordingly, CKD patients had higher rates of the secondary endpoint of appropriate ICD therapies (41% vs. 30%; log rank $p=0.002$; HR = 1.532; 95% CI 1.163–2.018; $p=0.002$), mainly attributed to appropriate ICD shocks (19% vs. 11%; $p=0.005$). After multivariable Cox regression CKD was associated with a 1.4-fold higher risk of appropriate device therapies (HR = 1.353; 95% CI 1.001–1.825; $p=0.049$), but not with first recurrence of ventricular tachyarrhythmias ($p=0.177$). Irrespective of propensity score matching, CKD was associated with increasing all-cause mortality at 5 years ($p=0.001$). The presence of CKD is associated with increased rates of recurrent ventricular tachyarrhythmias, appropriate device therapies, mainly attributed to appropriate shock, and all-cause mortality in ICD recipients at 5 years.

Keywords Ventricular tachycardia · Ventricular fibrillation · Mortality · Chronic kidney disease · ICD

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Introduction

The risk of ventricular tachyarrhythmias and sudden cardiac death (SCD) in patients with chronic kidney disease (CKD) is high and represents the leading cause of death in haemodialysis patients [1]. A reduced glomerular filtration rate (GFR) was shown to be associated with increased risk of death, cardiovascular events and rehospitalization [2]. Notably, CKD patients are usually excluded in about 80% from randomized controlled trials (RCT) [3–5]. The most common risk factor for the development of ventricular tachyarrhythmias is coronary artery disease (CAD) [6]. Several pathomechanisms for CAD in CKD patients are described. Progressive coronary calcification due to Monckeberg sclerosis or hyperparathyroidism might induce arterial wall thickening and stiffness up to ossification of vascular smooth muscle cells of coronary vessels and heart valves [7]. Increased cardiovascular risk factors such as diabetes and dyslipidemia are associated with CKD and in further consequence with CAD [8, 9]. Especially CKD patients suffer from ongoing oxidative stress and elevated homocysteine levels, which are also present in CAD and CKD patients [8, 9].

Implantable electronic cardiac devices are frequently used for the management of patients with cardiac arrhythmias [10]. Amongst these, implantable cardioverter defibrillators (ICD) have become therapeutic cornerstones for an effective primary and secondary prevention of ventricular tachyarrhythmias and SCD. They were shown to primarily decrease long-term mortality in patients with left ventricular ejection fraction (LVEF) < 35%, ischemic and dilated cardiomyopathy [11–15]. The prognostic benefit of an ICD was shown for patients suffering from channelopathies such as Brugada syndrome, long- and short-QT-syndrome, as well as cardiomyopathies, including hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy [16]. In secondary prevention, patients with prior haemodynamically relevant ventricular tachyarrhythmias were shown to benefit from ICD therapy, irrespective of the underlying disease [14, 17]. However, the potential survival benefit of an ICD is still unclear in CKD patients compared to the general population. Especially in primary prevention, ICD-related complications such as venous thromembolism and infections may further limit the assumed benefit [10, 18–20]. Furthermore, it is important to identify subgroups of patients at higher risk to develop recurrent ventricular tachyarrhythmias to ensure their optimal long-term survival.

Data is rare whether CKD may affect future recurrences of ventricular tachyarrhythmias in ICD recipients. Therefore, this study evaluates the impact of CKD on recurrences of ventricular tachyarrhythmias, device-related therapies, rehospitalization and all-cause mortality in ICD recipients surviving index episodes of ventricular tachyarrhythmias.

Methods

Data collection and documentation

The present study included all consecutive patients with an activated ICD presenting with ventricular tachyarrhythmias on admission from 2002 until 2016 at our institution. All relevant clinical data related to the index event, as well as to recurrences of ventricular tachyarrhythmias and rehospitalization—as being documented during routine clinical care by independent cardiologists and medical staff—was retrospectively derived from the electronic hospital information system, patient files, discharge letters, results from diagnostic testings and the laboratory system. Data was transferred into a standardized electronic database, where the quality and accuracy of documented data was re-assessed by two independent cardiologists (M.Be.) and (I.A.).

Ventricular tachyarrhythmias comprised ventricular tachycardia (VT) and fibrillation (VF), as defined by current international guidelines [21, 22]. Sustained VT was defined by the duration of more than 30 s or causing hemodynamic collapse within 30 s. Non-sustained VT was defined by a duration of less than 30 s. Both types of VT had wide QRS complexes ($\geq$ 120 ms) at a rate greater than 100 beats per minute [23]. Ventricular tachyarrhythmias at index was documented by 12-lead electrocardiogram (ECG), ECG tele- monitoring, ICD or in case of unstable course or during cardiopulmonary resuscitation (CPR) by external defibrillator monitoring. Documented VF was treated by ICD-related shock or external defibrillation and in case of prolonged instability with additional intravenous anti-arrhythmic drugs during CPR. Electrical storm (ES) was defined as $\geq$ 3 episodes of ventricular tachyarrhythmias requiring appropriate device therapy and occurring during a period of 24 h [23, 24].

Clinical data 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, 12-lead or holter ECG, echocardiography, cardiac magnetic resonance imaging (cMRI), coronary angiography, pharmacological therapy and ICD protocols.

The following device types were allowed: ICD, cardiac resynchronisation therapy with defibrillator (CRT-D) and subcutaneous ICD (s-ICD). 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 were performed according to current international guidelines by specialized cardiologists in electrophysiology during routine clinical care [21, 23, 25].

Every re-hospitalization of each patient—either ambulatory or in-hospital at our institution—was reviewed and documented for recurrent ventricular tachyarrhythmias, in-hospital death and upcoming relevant cardiac events.

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 sudden cardiac arrest being acutely admitted 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.

Inclusion and exclusion criteria

Only patients with an activated ICD were included (i.e. ICD recipients). All patients had a documented episode of ventricular tachyarrhythmias, which defines the index event. Each patient was counted only once for inclusion when presenting with the first episode of ventricular tachyarrhythmias. All analyzed patients had to survive index hospitalization.

Risk stratification was performed according to the presence of CKD and non-CKD according to the clinical practice guideline of the "kidney disease improving global outcome" (KDIGO) executive committee for the evaluation of chronic kidney disease [26]. According to the KDIGO guideline a CKD was defined as abnormalities of kidney function with implication for health. Patients with GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5) and a duration > 3 months were included [27].

Patients without a prior history of CKD or no evidence of renal function at index presentation were excluded. Furthermore, patients on hemodialysis were excluded.

Primary and secondary outcomes

Follow-up period was set at 5 years for all outcomes. The primary endpoint was the first recurrence of ventricular tachyarrhythmias (VT or VF) as documented within ICD protocols. Secondary endpoints were overall recurrences at follow-up, recurrences per patient, associated appropriate or inappropriate device therapies (first, overall, per patient), first re-hospitalization and all-cause mortality at follow-up. Further stratification was performed into subgroups of primary or secondary prevention and appropriate or inappropriate device therapies.

Appropriate device therapy was defined as device interrogation in the presence of VT or VF including antitachycardia pacing (ATP), ICD-related shock or both ATP and shock. Inappropriate device therapy was defined as ATP or ICD shock in the absence of VT or VF. First re-hospitalization comprised rehospitalizations due to VT, VF, acute myocardial infarction (AMI), acute heart failure and inappropriate device therapy.

All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices ("bureau of mortality statistics") all across Germany. Identification of patients was verified by place of name, surname, day of birth and registered living addresses.

Statistical methods

CKD patients were compared to non-CKD patients. 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. Data 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.

Firstly, univariable Kaplan–Meier method was applied to evaluate differences in primary and secondary endpoints within the entire unmatched cohort between CKD and non-CKD patients. Furthermore, differences were tested in subgroups of primary versus secondary prevention. Hazard ratios (HR) are given together with 95% confidence intervals (CI). Secondly, multivariable Cox regression models were developed using the "forward selection" option in the unmatched cohort, where only statistically significant variables ($p < 0.05$) or clinically relevant variables were included and analyzed simultaneously. Predefined variables being used for multivariable Cox regressions included: age, diabetes, CAD, CPR, beta-blocker, CKD. Thirdly, Kaplan–Meier analyses were repeated in propensity matched cohorts for primary and secondary endpoints. Details on propensity-score matching are outlined below. Patients without

complete follow-up were censored (accepted lost-to follow-up rate < 10%).

The result of a statistical test was considered significant for $p < 0.05$, 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.

Propensity score matching

In RCT patients with or without a specific disease (such as CKD and non-CKD) would have a 50% chance to be treated. Also balanced measured and unmeasured baseline characteristics would be expected. In an observational study, recruiting real-life patients, no randomization results in varying chances between 0 and 100% resulting in imbalances of baseline characteristics. Consecutively, differences of outcomes in specific disease groups might, therefore, also be explained by heterogenous distribution of baseline characteristics. To reduce this selection bias, we used 1:1 propensity score for the presence of CKD to assemble a matched cohort in which CKD and non-CKD patients would be well balanced on all measured baseline characteristics. 1:1 propensity score matching was performed including the entire study cohort performing a non-parsimonious multivariable logistic regression model using patients with CKD as the dependent variable [28, 29]. Propensity scores were created according to the presence of the following independent variables: age, gender, diabetes, left ventricular dysfunction and underlying ventricular tachyarrhythmias (i.e. VT/VF) on admission. Based on the propensity score values counted by logistic regression, for each patient in the CKD group one patient in the non-CKD group (control group) with a similar propensity score value was found (accepted difference of propensity score value < 5%).

Results

Study population

A total of 585 consecutive ICD recipients (CKD: 57%; non-CKD: 43%) surviving an episode of ventricular tachyarrhythmias were included (Table 1). Most patients were males. VT was more common than VF (68–70% vs. 30–33%) at index in both groups. CKD patients were older and had higher rates of diabetes, CAD, CPR, LVEF < 35%, atrial fibrillation (statistical trend) and beta-blockers. No further differences were seen in both groups. Table 2 outlines ICD-related data of the study population. Most patients had an activated transvenous ICD (89–93%), whereas CRT-D or subcutaneous ICD were present in minor part (3–8%). Indication for ICD implantation was equally distributed (about 42% primary and 58% secondary prevention). The median detection thresholds for VT (171 bpm) and for VF (214 bpm) were similar in both groups, as well as the median cycle length of VT 280 ms (Table 2).

Follow-up data, primary and secondary endpoints

At least 90% of patients were followed-up regularly within the follow-up period of 5 years (1825 days) with at least one ICD check-up every 6–12 months.

The primary endpoint of first recurrence of ventricular tachyarrhythmias was increased in CKD patients (50% vs. 40%, log-rank $p = 0.008$; HR = 1.398; 95% CI 1.087–1.770; $p = 0.009$) (Table 2 and Fig. 1, left panel), irrespective of the presence of primary and secondary preventive ICD indication (primary: 45% vs. 36%; log rank $p = 0.057$; HR = 1.468; 95% CI 0.986–2.186; $p = 0.059$; secondary: 53% vs. 44%; log rank statistical trend $p = 0.089$; HR = 1.306; 95% CI 0.959–1.778; $p = 0.090$) (Fig. 1, middle and right panel). Differences of recurrences of ventricular tachyarrhythmias were attributed to higher rates of VF (11% vs. 5%) and ES (10% vs. 5%).

Regarding secondary endpoints, freedom from first appropriate device therapy was decreased in CKD patients (41% vs. 30%, log rank $p = 0.002$; HR = 1.532; 95% CI 1.163–2.018; $p = 0.002$) (Fig. 2, left panel), whereas no difference was found for inappropriate device therapies (Fig. 2, right panel). The difference of first appropriate device therapies was driven by increasing rates of appropriate ICD shocks (19% vs. 11%). No differences were seen for overall rehospitalization at 5 years in both groups, whereas CKD patients had higher rates of all-cause mortality compared to non-CKD patients (30% vs. 14%, $p = 0.001$; HR = 2.451;95% CI 1.707–3.519; $p = 0.001$) (Table 2).

Multivariable cox regression models

After multivariable adjustment, CKD patients were not associated with first recurrences of ventricular tachyarrhythmias (HR = 1.201; 95% CI 0.921–1.568; $p = 0.177$) (Table 3). However, there was a 1.4-fold higher risk of appropriate ICD therapy (HR = 1.353; 95% CI 1.001–1.825; $p = 0.049$) (Table 3) in CKD patients. Patients ≥ 74 years were associated with a 1.5-fold higher risk and patients with an LVEF < 35% were associated with a 1.4-fold higher risk of appropriate ICD therapy.

Table 1 Baseline characteristics and comorbidities before and after propensity score matching according to chronic kidney disease (CKD)

Characteristic	Before matching ($n=585$)					After matching ($n=435$)				
	Non-CKD ($n=333$; 57%)		CKD ($n=252$; 43%)		p value	Non-CKD ($n=218$; 50%)		CKD ($n=217$; 50%)		p value
Male gender, n (%)	263	(79)	202	(80)	0.726	178	(82)	178	(82)	1.000
Age, median (range)	56	(15–75)	61	(44–72)	**0.001**	60	(33–75)	62	(44–72)	0.255
Ventricular tachyarrhythmias at index, n (%)										
Ventricular tachycardia	234	(70)	170	(68)	0.467	154	(71)	153	(70)	0.916
Ventricular fibrillation	99	(30)	82	(33)		64	(29)	65	(30)	
Serum creatinine, mg/dl (IQR)	0.97 (0.9–1.1)		1.45 (1.3–1.8)		**0.001**	0.99 (0.88–1.08)		1.45 (1.29–1.73)		**0.001**
Renal Replacement Therapy	–	–	37	(15)	–	–	–	32	(15)	–
Cardiovascular risk factors, n (%)										
Arterial hypertension	204	(61)	161	(64)	0.516	146	(67)	140	(64)	0.546
Diabetes mellitus	76	(23)	78	(31)	**0.027**	61	(28)	62	(28)	0.915
Hyperlipidemia	135	(41)	100	(40)	0.834	104	(48)	88	(40)	0.123
Smoking	101	(30)	71	(28)	0.571	68	(31)	60	(28)	0.400
Cardiac family history	53	(16)	30	(12)	0.169	35	(16)	27	(12)	0.273
Comorbidities, n (%)										
Atrial fibrillation	100	(30)	94	(37)	0.064	69	(32)	79	(36)	**0.321**
Coronary artery disease	215	(65)	183	(73)	**0.039**	163	(75)	159	(73)	0.663
Acute myocardial infarction	38	(11)	38	(15)	0.191	25	(12)	32	(15)	0.320
Non-iscaemic cardiomyopathy	35	(11)	25	(10)	0.816	25	(12)	15	(12)	1.000
CPR	40	(12)	52	(21)	**0.018**	25	(12)	44	(20)	**0.021**
LVEF at discharge, n (%)										
LVEF ≥ 55%	69	(23)	35	(16)	**0.016**	36	(17)	35	(17)	0.460
LVEF 54–45%	36	(12)	21	(9)		27	(12)	20	(9)	
LVEF 44–35%	65	(22)	42	(19)		49	(23)	42	(19)	
LVEF < 35%	128	(43)	128	(57)		106	(49)	121	(56)	
Not documented	35	–	26	–		–	–	–	–	–
Medication at discharge, n (%)										
Beta-blocker	279	(84)	228	(91)	**0.01**8	199	(91)	197	(90)	0.740
ACE-inhibitor/ARB	231	(70)	177	(70)	0.821	164	(75)	151	(69)	0.164
Adosterone antagonist	45	(14)	45	(18)	0.149	32	(15)	39	(18)	0.364
Amiodarone	54	(16)	54	(21)	0.108	35	(16)	45	(21)	0.216
ECG intervals (mean ± SD)										
PQ	160	±12	160	±21	0.418	160	±11	160	±22	0.850
QRS	80	±14	80	±20	**0.004**	80	±18	80	±21	**0.043**
QT	400	±18	400	±15	0.051	400	±22	400	±16	0.226

Bold type indicates $p < 0.05$

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *CKD* chronic kidney disease, *CPR* cardiopulmonary resuscitation, *ICD* implantable cardioverter-defibrillator, *IQR* interquartile range, *CPR* cardiopulmonary resuscitation, *LVEF* left ventricular ejection faction

Propensity score matching

After propensity score matching similar baseline characteristics were achieved in both subgroups (Table 1; right panel). CKD was not associated with the the primary endpoint of recurrences of ventricular tachyarrhythmias (41% vs. 48%; log rank $p=0.111$) (Fig. 3, left panel), but with the secondary endpoint of appropriate device therapies (39% vs. 33%, log rank statistical trend $p=0.076$; HR = 1.329; 95% CI 0.965–1.823; $p=0.077$) (Fig. 3, right panel) and appropriate ICD shocks (26% vs. 14%, log rank $p=0.001$, HR = 2.249; 95% CI 1.444–3.502; $p=0.001$).

Table 2 ICD data and study endpoints before and after propensity score matching according to chronic kidney disease (CKD)

Characteristic	Before matching ($n=585$)			After matching ($n=436$)		
	Non-CKD ($n=333$; 57%)	CKD ($n=252$; 43%)	p value	Non-CKD ($n=218$; 50%)	CKD ($n=218$; 50%)	p value
Type of ICD, n (%)						
ICD	309 (93)	225 (89)	0.329	203 (93)	198 (91)	0.595
CRT-D	18 (5)	20 (8)		13 (6)	16 (7)	
s-ICD	6 (2)	7 (3)		2 (1)	4 (2)	
Implant indication, n (%)						
Primary prevention	148 (44)	102 (40)	0.337	103 (47)	92 (42)	0.289
Secondary prevention	185 (56)	150 (60)		115 (53)	12 (58)	
ICD programming, bpm, median (IQR)						
VT detection threshold	167 (164–171)	169 (162–171)	0.726	167 (158–171)	167 (160–171)	0.107
VF detection threshold	214 (214–219)	214 (214–222)	0.992	214 (214–214)	214 (214–222)	0.412
VT cycle length, median (IQR)	320 (283–350)	315 (280–336)	0.667	320 (298–350)	320 (280–330)	0.987
Primary endpoint, n (%)						
First recurrence of ventricular tachyarrhythmias						
Overall	136 (40)	125 (50)	**0.026**	90 (41)	104 (48)	0.163
Non-sustained VT	43 (13)	25 (10)	0.263	27 (12)	21 (10)	0.367
Sustained VT	79 (24)	73 (29)	0.152	58 (27)	63 (29)	0.572
VF	16 (5)	28 (11)	**0.007**	6 (3)	21 (10)	**0.003**
Electrical storm	15 (5)	25 (10)	**0.010**	9 (4)	21 (10)	**0.001**
Secondary endpoints						
Overall recurrences at follow-up, n (%)						
Non-sustained VT	63 (19)	48 (19)	0.969	39 (18)	41 (19)	0.805
Sustained VT	99 (30)	88 (35)	0.182	67 (31)	75 (34)	0.414
VF	28 (8)	36 (14)	**0.024**	15 (7)	30 (14)	**0.018**
Electrical storm	15 (5)	25 (10)	**0.010**	9 (4)	21 (10)	**0.001**
Recurrences per patient, mean ± SEM						
Non-sustained VT	4.2 ± 2.0	5.4 ± 2.1	0.431	4.3 ± 1.4	4.5 ± 2.3	0.904
Sustained VT	4.2 ± 0.9	5.4 ± 1.4	0.157	5.4 ± 1.5	4.5 ± 1.0	0.253
VF	1.9 ± 1.3	0.2 ± 0.1	**0.009**	0.2 ± 0.1	2.1 ± 1.5	**0.028**
Electrical storm	0.1 ± 0.0	0.1 ± 0.0	**0.013**	0.0 ± 0.0	0.1 ± 0.0	**0.014**
First appropriate device therapies, n (%)						
Overall	101 (30)	102 (41)	**0.011**	71 (33)	66 (39)	0.162
Appropriate shock	37 (11)	49 (19)	**0.005**	19 (9)	39 (18)	**0.005**
Appropriate ATP only	56 (17)	49 (19)	0.412	44 (20)	43 (10)	0.924
Overall device therapies at follow-up, n (%)						

Table 2 (continued)

Characteristic	Before matching ($n=585$)			After matching ($n=436$)		
	Non-CKD ($n=333$; 57%)	CKD ($n=252$; 43%)	p value	Non-CKD ($n=218$; 50%)	CKD ($n=218$; 50%)	p value
Appropriate shock	50 (15)	68 (27)	**0.001**	30 (14)	57 (26)	**0.001**
Appropriate ATP only	78 (23)	76 (30)	0.063	60 (28)	65 (30)	0.575
Inappropriate device therapy	51 (15)	27 (11)	0.109	34 (16)	22 (10)	0.089
Device therapies per patient, mean ± SEM						
Appropriate shock	0.5 ± 0.1	1.1 ± 0.3	**0.013**	0.4 ± 0.1	1.0 ± 0.3	**0.018**
Appropriate ATP only	4.4 ± 1.3	3.4 ± 0.8	0.551	4.4 ± 1.3	3.8 ± 0.9	0.667
Inappropriate shock	0.5 ± 0.2	0.4 ± 0.2	0.744	0.3 ± 0.1	0.4 ± 0.2	0.513
Inappropriate ATP only	0.1 ± 0.1	0.1 ± 0.0	0.642	0.1 ± 0.1	0.1 ± 0.0	0.500
Re-hospitalization, *n* (%)						
Overall	93 (28)	75 (30)	0.627	72 (33)	65 (30)	0.490
VT	23 (7)	31 (12)	**0.026**	15 (7)	27 (12)	**0.049**
VF	4 (1)	10 (4)	**0.030**	3 (1)	9 (4)	0.078
AMI	2 (1)	6 (2)	0.066	2 (1)	5 (2)	0.250
Acute heart failure	25 (8)	1 (6)	0.461	19 (9)	14 (7)	0.373
Inappropriate device therapy	20 (6)	8 (3)	0.112	16 (7)	6 (3)	**0.029**
Other	19 (6)	5 (2)	**0.025**	17 (8)	4 (2)	**0.004**
All-cause mortality, at 5 years, *n* (%)	48 (14)	7 (30)	**0.001**	35 (16)	68 (31)	**0.001**

Bold type indicates $p < 0.05$

ATP anti-tachycardia pacing, *HF* heart failure, *SEM* standard error of mean, *VF* ventricular fibrillation, *VT* ventricular tachycardia

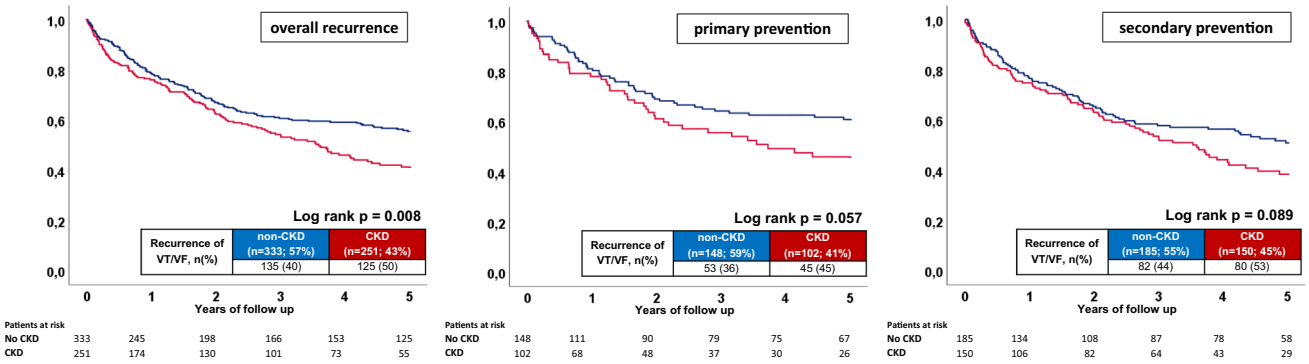

Fig. 1 Freedom from first recurrences of ventricular tachyarrhythmias (left panel), stratified to primary (middle panel) and secondary preventive ICD recipients (right panel)

Fig. 2 CKD patients were associated with decreased rates of freedom from appropriate device therapies (left panel), but not with inappropriate device therapies (right panel)

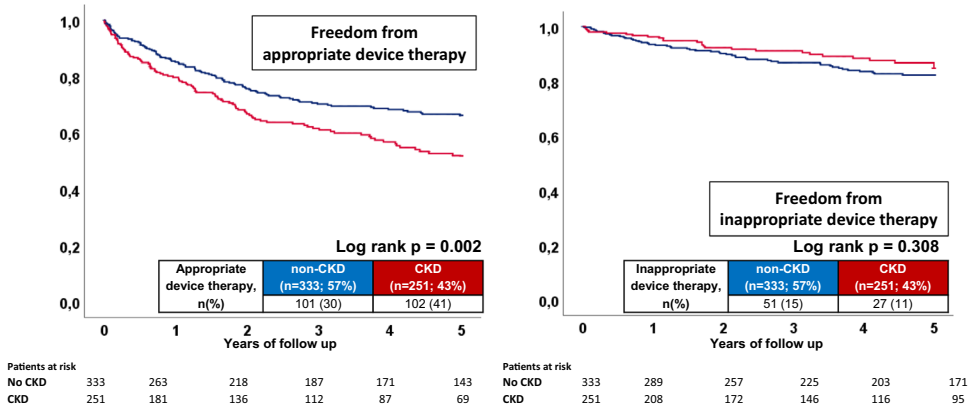

Table 3 Multivariable Cox regression analyses within the unmatched cohort ($n = 585$)

Endpoint	First recurrence			First appropriate therapy		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥ 75	1.425	1.046–1.942	0.177	1.499	1.065–2.108	**0.020**
Diabetes	0.893	0.697–1.214	0.472	0.878	0.619–1.248	0.469
CAD	0.846	0.588–1.217	0.367	0.926	0.606–1.417	0.725
CPR	0.939	0.741–1.467	0.602	0.734	0.537–1.002	0.052
LVEF < 35%	1.275	0.962–1.691	0.091	1.389	1.007–1.917	**0.045**
CKD	1.201	0.921–1.568	0.177	1.353	1.001–1.825	**0.049**

Bold type indicates $p < 0.05$

CAD coronary artery disease, *CI* confidence interval, *CKD* chronic kidney disease, *CPR* cardiopulmonary resuscitation, *HR* hazard ratio, *LVEF* left ventricular ejection faction

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

Discussion

The present study evaluates the prognostic impact of CKD on recurrences of ventricular tachyarrhythmias, device-related therapies, rehospitalization and all-cause mortality at five years of follow-up in consecutive ICD recipients surviving episodes of ventricular tachyarrhythmias. This study suggests, that CKD may decrease freedom from first recurrent ventricular tachyarrhythmias (mainly attributed to VF and ES), as well as from first appropriate device-related therapies (predominantly ICD related shock). The prognostic impact of CKD on first appropriate device therapy was seen also after multivariable adjustment and propensity score matching. Furthermore, CKD patients

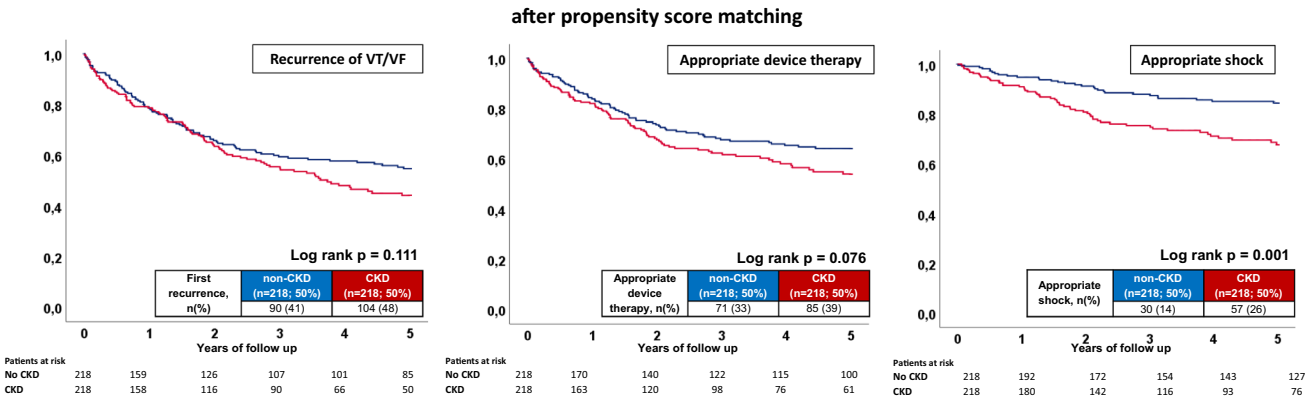

Fig. 3 After propensity score matching, CKD patients were not associated with higher rates of recurrent ventricular tachyarrhythmias (left panel), but higher rates of appropriate device therapy (statistical trend, middle panel) and appropriate shock (right panel)

revealed higher all-cause mortality at 5 years. Both CKD and LVEF < 35% were associated with a higher risk of appropriate ICD therapy.

CKD is a well-known cardiovascular risk factor for heart failure and CAD, which themselves are common risk factors for the development of ventricular tachyarrhythmias [6, 30]. In particular, LVEF < 35% increases the risk of ventricular tachyarrhythmias [31]. In the present study both, the presence of CKD and LVEF < 35%, were associated with a 1.4-fold higher risk of first appropriate ICD therapy. In turn, LVEF < 35% is associated with CKD and in this context reflects the cardio-renal (CRS) or reno-cardiac syndrome (RCS), where heart and kidney dysfunctions overlap [32]. The cardio-renal syndrome can be subdivided in five types. Type I and II are caused by acute or chronic heart failure with limitation of kidney function by decreased renal blood flow due to cardiac low output [32]. Type III and IV are caused by an acute or chronic kidney failure with vascular and myocardial damages by oxidative stress, inflammation and increased volume-dependant pre- and afterload [32–34]. Type V CRS describes the simultaneous occurrence of cardiac and renal injury [32–34]. The different types of CRS cannot be identified exactly in this retrospective cohort. However both LVEF < 35% and CKD appear to have relevant and significant impact in patients presenting with ventricular tachyarrhythmias.

Treatment with ICD has become a therapeutic cornerstone for an effective primary and secondary prevention of ventricular tachyarrhythmias and SCD. It was shown to effectively decrease long-term mortality in patients with LVEF < 35%, irrespective of the underlying disease [11–15]. ICD therapy in the chronic post-infarct period (≥ 30 days) was shown to be associated with decreased long-term mortality in patients with ischemic cardiomyopathy and LVEF < 30% [15, 35], whereas the prognostic benefit of an ICD in the acute postinfarct period (< 30 days) is limited [15, 35]. Whether CKD patients may be associated with a prognostic benefit related to ICD therapy has not yet been completely understood. In contrast, CKD patients with ICD were shown to be associated with higher rates of device-related complications including central venous thrombosis and bloodstream infections [10, 18–20, 36].

The Cleveland clinic CKD registry included 631 pairs of CKD patients with and without an implanted ICD. At a median follow-up of 2.9 years, the presence of an ICD was associated with lower risk of death among patients with an estimated GFR 45–49 ml/min, which was not observed in patients with a GFR < 30 ml/min [37]. Beyond, the potential benefit of ICD in non-dialysis CKD patients is still unclear and concise studies evaluating the risk of recurrent ventricular tachyarrhythmias in CKD patients are rare at all.

A prospective study from Brazil focused on ventricular tachyarrhythmias in 76 ICD recipients with CKD and non-ischemic cardiomyopathy (LVEF < 35%) at 12 months of follow-up [38]. Patients with LVEF > 35%, ischemic heart disease and valvular heart disease were excluded [38]. The study suggested that the risk of SCD or recurrent ventricular tachyarrhythmias increased with advanced stages of CKD [38]. In contrast to previous studies, the strength of the present study is the longer follow-up period of 5 years, the larger sample size and the comparison to non-CKD patients.

Besides the CRS, different approaches, explaining the association between CKD and ventricular tachyarrhythmias do exist. Firstly, CKD patients are at risk for QTc-prolongation of more than 500 ms due to an impairment of cardiac repolarization [39]. QTc-prolongation is a risk factor of ventricular tachyarrhythmias, affecting two-thirds of all CKD patients [39]. Secondly, CKD and hemodialysis patients are affected by electrolyte shifts, such as sudden potassium and calcium shifts and rapid changes of volume and blood pressure. This might also sustain a milieu of mechanical and electrical imbalance of myocytes, which might alleviate

the onset of ventricular tachyarrhythmias [40]. Thirdly, the electrical imbalance might be influenced by oxidative stress, elevated homocysteine levels, hyper-phosphatemia, and the accumulation of several cardiotoxic substances such as b2-microglobulin, nucleosides, parathyroid hormone and many more [41, 42].

Whether CKD patients may significantly benefit from ICD implantation is still unclear, even when focussing on primary or secondary preventive indication. It may be speculated whether the risk of device-related complications may justify the potential, not yet proven, benefits for the prevention of ventricular tachyarrhythmias in CKD patients compared to the general population. Accordingly, the present study contributes to a better understanding of this important high-risk sub-group. The use of epicardial or subcutaneous leads may further prevent central venous thrombosis and device-related infections in future [10].

Conclusion

The present study demonstrates that ICD recipients with CKD are associated with an increased risk for recurrent ventricular tachyarrhythmias, appropriate ICD therapies and higher all-cause mortality at five years.

Study limitations

This observational and retrospective registry-based analysis reflects a realistic picture of consecutive health-care supply of high-risk patients presenting with ventricular tachyarrhythmias. Lost to follow-up rates regarding the evaluated endpoint of all-cause mortality was minimal. To minimize lost to follow-up rates, all patients not meeting ICD follow-up for at least once after discharge were excluded from the present analysis. All clinical data was documented reliably by individual cardiologists during routine clinical care being blinded to final analyses, alleviating the use of an independent clinical event committee. The effect of CKD is only based on the assessment of CKD at index presentation. CKD development at follow-up was not documented. Therefore, the present results need to be re-evaluated within even larger and more representative multi-centre registries, especially focusing on the impact of CKD in selected subgroups with ICD therapies.

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Compliance with ethical standards

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

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