CHAPTER XI

Chronic kidney disease and ICD related complications, 16 years of experience

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ABSTRACT

Introduction: ICD implantation has become an accepted therapy for the prevention of sudden cardiac death. However, serious co-morbidities such as chronic kidney disease (CKD) are influencing the beneficial effects of ICD therapy. In this study the association between kidney function and the occurrence of ICD related complications was assessed.

Methods: All patients receiving an ICD or CRT-D between 1996 and 2012 were included. Renal function was categorized as: glomerular filtration rate (GFR)>90, GFR 30-90 or GFR<30 mL/min/1.73m^2. Registered complications were pocket hematoma, pneumothorax, lead complications and device infection.

Results: In 3147 device recipients, 236 patients (7.5%) suffered from at least one complication. Patients with a GFR<30 (n=110)had a higher event rate for hematoma, pneumothorax and infection. These patients were older, had a higher incidence of hypertension, diabetes and a lower BMI ($p<0.05$). After correcting for these risk-factors, hematoma remained independently associated with a GFR<30ml/min(OR 2.7 CI:1.05-6.9, $p=0.04$).Device infection, pneumothorax and lead complications were not independently associated with a GFR<30ml/min.

Conclusions: Patients with CKD suffered from more ICD related complications than patients without kidney disease. Partially, this was associated with kidney dysfunction itself. However, the high burden of risk-factors associated with device complications in patients with renal disease played an important role as well.

INTRODUCTION

Since implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy-defibrillators (CRT-D) were proven effective in the prevention of sudden cardiac death and the treatment of heart failure, worldwide implantation rates increased significantly.[1-4] Given the growing number of eligible patients, it is expected that implantation rates will continue to rise in the future.[5]

As with all interventions, device therapy is associated with complications, such as hematoma, pneumothorax, lead related complications and device infection.[6-8] These complications significantly influence morbidity, mortality and healthcare cost.[9;10] Therefore, identification of patients at risk for complications and the prevention of these complications is paramount for the future of device therapy.

Patients with chronic kidney disease (CKD) represent such a high risk patient group. The prevalence of cardiovascular disease is high in these patients, and sudden cardiac death the most frequent cause of death.[11;12] Since patients with renal dysfunction have been excluded from most ICD-trials, there are no prospective data on ICD safety and effectiveness in this patient group.[1-3] Several retrospective studies suggested that patients with CKD are at an increased risk for ICD related complications, however either follow-up duration or population size was limited in these studies.[13-15]

Therefore the purpose of this study was to assess the incidence of device related complications in a large observational registry and to investigate the association with CKD during long term follow-up.

METHODS

Patient population

Since 1996, all recipients of an ICD or CRT-D in the Leiden University Medical Centre (LUMC) were registered in the departmental Cardiology Information System (EPD-Vision, LUMC). Clinical characteristics at baseline, data on implant procedure and follow-up were noted in this system. For the current analysis, all patients receiving their first ICD or CRT-D between 1996 and 2012 for primary prevention (left ventricular ejection fraction <35%) or secondary prevention (survival of cardiac arrest or syncope due to suspected ventricular arrhythmia) were included. Device replacement were included only if the patients received their initial ICD between 1996 and 2012.

Patient groups were created in accordance with the National Kidney Foundation classification system using the MDRD formula.16 A GFR>90 ml/min/1.73m^2 was defined as normal kidney function, GFR 30-90 ml/min/1.73m^2 as mild to moderate CKD and a GFR<30 ml/min/1.73m^2 as advanced CKD. Patients without available GFR measurements around the time of device implant were excluded from this study.

Follow-up

All ICD recipients were followed-up two months post-implant and every 3-6 months thereafter. Data on follow-up were collected until the 1st of July 2012, until a new implantation if this took place in 2012, or until the moment patients were lost to follow-up or died.

Device implantation and settings

All defibrillator systems used were implanted transvenously and without thoracotomy. Implanted systems were manufactured by Biotronik (Berlin, Germany), Boston Scientific (Natick, United States, formerly CPI, Guidant), Medtronic (Minneapolis, United States) or St. Jude Medical/Ventritex (st. Paul, United States). In the CRT-D devices, LV-lead placement was performed after obtaining a coronary sinus venogram. Subsequently the LV lead was inserted and positioned using an 8F guiding catheter. LV lead positioning was preferred in a lateral or posterolateral vein. The right atrial and right ventricular leads were positioned conventionally.

In patients using oral anticoagulants, periprocedural, target INR for patients without mechanical valves was 1.5-2.0 and in case of a mechanical valve, target INR was 2.0-2.5. Flucloxacillin was administered immediately before device implant and 4 hours after the procedure. In case of generator replacement without lead replacement, antibiotics were only administered before device implant.

Definition of variables

Ischemic heart disease was defined as the presence of significant coronary artery disease (a diameter of stenosis of at least 50% in at least one coronary artery). Hypertension was defined as a documented history for hypertension or a repeatedly measured office blood pressure of >140/90mmHg. Data on both vitamin-K antagonists (OAC's) and the use of dual antiplatelet therapy (Clopidogrel with acetylsalicylic acid or Prasugrel combined with acetylsalicylic acid, DAT) were collected.

Complications

All adverse events as registered in EPD-Vision were analyzed retrospectively by M.S.B. and M.K.B. Adverse events were categorized as pneumothorax, pocket hematoma, lead related complications or device infection. Pneumothorax was defined as all cases of pneumothorax present on routine chest X-ray after device implantation. Hematoma was defined as all cases of hematoma severe enough to be documented in patient file or requiring surgical intervention after device implantation. Since most hematomas occur immediately after device implant, hematoma was likely to be discovered during routine post-operative wound control or at the routine appointment 2 months post-implant. Lead related complications were defined as all cases of lead failure or lead dislocation requiring the implantation or relocation of an atrial, left ventricular (LV) of right ventricular (RV) lead. Device infection was

defined as all cases of device explantation due to suspected infection regardless of the presence of a positive lead or device culture.

Statistical analysis

For the initial data presentation patient groups were created according to kidney function (GFR>90, GFR 30-90, GFR<30). Continuous data were described by their mean and SD, and analyzed using an independent student t-test. Categorical data were described as proportions (percentage) and compared using a Chi-square test for independence. For the analysis of differences between the GFR groups, the patients with normal kidney function served as controls.

For the different complications, various models were built, to take into account that each complication has different characteristics. The inclusion of variables in these models was determined by univariate analysis ($p<0.1$), biological considerations and potential confounding effects.

Hematoma may occur after every device procedure, so a generalized estimating equations (GEE) model was used. In this model, every implantation is a new risk factor for hematoma and the fact that patients sometimes receive several consecutive devices is taken into account.

Pneumothorax occurs directly after 1st implant (or after lead replacement), so a standard binary logistic regression analysis was used.

Lead problems can occur at any given moment during follow-up, independent of the implantation of a new device, therefore a standard Cox regression analysis was used to investigate the time to first lead problem.

The occurrence of 1st infection was analyzed using Cox regression analysis with second and third device implant as a time-dependent covariate. This was done to adjust for the increased risk for infection attributed bydevice replacement.[17]

All statistical analyses were performed Using SPSS (version 20.0, SPPS Inc. Chicago, Illinois).

RESULTS

Patients

Between 1996 and 2012, 3282 patients received an ICD or CRT-D for primary (63%) or secondary prevention(37%). In 3147 patients (96%), a GFR measurement was available around the time of device implantation and these patients were included for further analysis. Due to either battery depletion or device infection 1101 patients received a second device, 296 a third and 61 a fourth. As shown in table 1, the average age of patients at time of implant was 62±13 years, 78% were males, average GFR was 82±36 mL/min/1.73m^2 and most patients received a dual chamber ICD (48%).

Table 1: *Patient Characteristics*

Characteristics	Total cohort	Glomerular Filtration Rate (mL/min/1.73m²)		
	(n=3147)	GFR> 90 (n=1116)	GFR 30-90 (n=1921)	GFR<30 (n=110)
Age, years	62±13	52±13	67±10*	71±10*
Sex (%, male)	78	83	76*	68*
Follow-up, years	3.5±2.8	3.7±3.0	3.4±2.7*	2.4±2.2*
BMI, kg/cm²	26±4	28±5	26±4*	24±5*
LVEF, %	37±21	42±21	35±21*	31±18*
GFR, mL/min/1.73m²	82±36	119±30	64±15*	23±7*
Primary prevention (%)	63	63	65	65
Hypertension (%)	44	42	44	52‡
Diabetes mellitus (%)	23	21	24	34†
Prior Myocardial Infarction (%)	63	55	68*	68[0]
Atrial Fibrillation (%)	26	18	29*	37*
β -Blocker (%)	58	58	59	49
ACEi/ARB (%)	76	72	80*	68
Acetylsalicylic acid(%)	34	38	32†	23†
OAC (%)	58	46	65*	72‡
DAT (%)	11	14	10*	6†
INR	1.6±0.6	1.6±0.5	1.6±0.6‡	1.8±0.7†
Single chamber ICD (%)	10	12	10*	11*
Dual chamber ICD (%)	48	59	43	30
CRT-D (%)	41	29	48	59

BMI; body mass index, LVEF; Left ventricular ejection fraction, GFR; glomerular Filtration Rate, OAC; oral anticoagulants, DAT; Dual antiplatelet therapy, INR; International Normalized Ration, ICD; Implantable Cardioverter Defibrillator, CRT-D; Cardiac Resynchronization Therapy- Defibrillator. *;p<0.001, †; p<0.01, ‡; p<0.05

Baseline characteristics stratified for renal function

Patients with normal kidney function were compared to those with advanced CKD. Patients with a GFR<30mL/min/1.73m² were older (71 vs. 52years, p<0.001), were less often male (68 vs. 83%, p<0.001), had a lower body mass index (BMI, 24 vs. 28 kg/m², p<0.001), had a lower left ventricular ejection fraction (LVEF, 31 vs. 42%, p<0.001) and more often had hypertension (52 vs. 42%, p<0.05), diabetes mellitus (34 vs. 21%, p<0.01) and atrial

fibrillation (AF, 37 vs. 18%, p<0.001). Medication use in both groups was similar, with the exception of the use of oral anticoagulants (OAC's), which was more frequent in patients with advanced CKD (72 vs. 46%, p<0.001) and the use of DAT, which was more frequent in patient with normal kidney function (14 vs. 6%, p=0.01). The INR of patients with a GFR<30mL/min/1.73m^2 was significantly higher than that of patients with normal kidney function (1.8 vs. 1.6, p=0.001). Furthermore, patients with advanced CKD more often received CRT-D (59 vs. 29%, p<0.001) (Table 1). In the group of patients with advanced CKD (n=110), 17 (15%) patients received dialysis around the time of device implant.

Complications

During a median follow-up of 3.5±2.8 years, 238 out of 3147 patients suffered from at least 1 complication (7.6%). In these 238patients 303 complications were observed. Observed complications were hematoma (n=57), pneumothorax (n=37), lead related complications (n=88) and device infection (n=121). Patients with advanced CKD had a higher event rate for hematoma (2.3 versus 0.3/100 patient years), pneumothorax (1.2 versus 0.3) and infection (2.3 versus 1.3) but not for lead problems (0.8 vs. 0.8). Crude, unadjusted event rates were shown in figure 1.

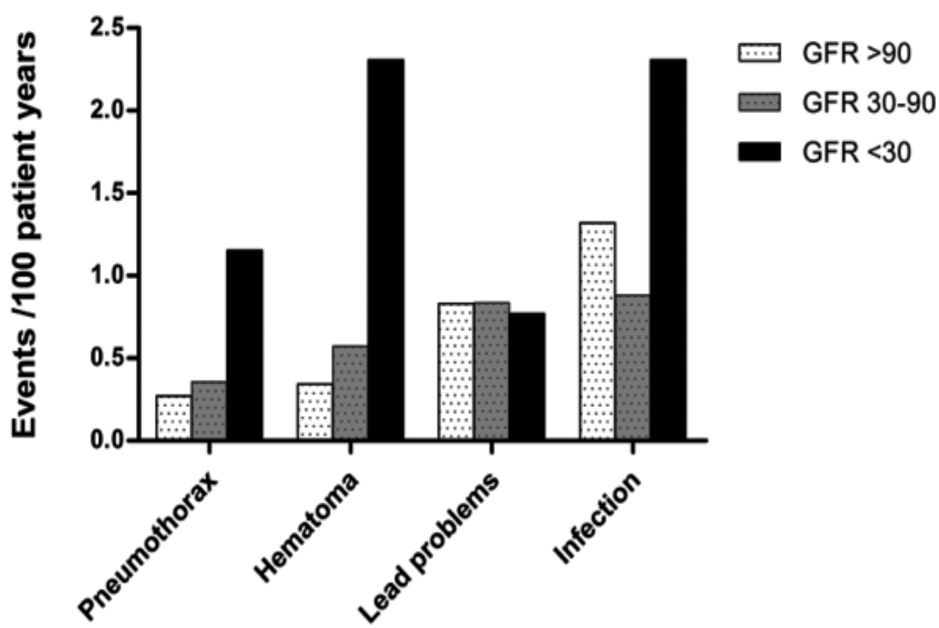

Figure 1. Crude event rates of the different complications

Hematoma

Out of the 3147 patients, fifty-three patients (1.7%) suffered from at least one hematoma. Hereof 2 patients suffered from two hematomas and 1 patient suffered from three events. There were 57 hematomas among the 4605 device implants (1.2%). Age, gender, BMI, hypertension, advanced CKD, the use of OAC's, acetylsalicylic acid, INR and DAT, were added in the univariate model. In the multivariate model a GFR<30 ml/min/1.73m^2 was the only parameter significantly associated with the occurrence of hematoma (OR 2.69, CI;1.05-6.90, p=0.04, table 2).

Table 2: *Factors associated with the occurrence of hematoma.*

	Univariate p-value	Multivariate p-value	OR	95% CI
Age	0.05	0.13	1.02	1-1.04
Sex	0.38	-		
BMI	0.21	-		
HT	0.19	-		
GFR<30	0.01	0.04	2.69	1.05-6.90
OAC	0.07	0.49	1.26	0.66-2.43
Ascal	0.08	0.19	0.62	0.31-1.27
DAT	0.81	-		
INR	0.78			

OR; Odds ratio, CI; Confidence interval, BMI; Body Mass Index, HT; Hypertension, GFR; Glomerular Filtration Rate, OAC; Oral anticoagulants, Ascal; Acetylsalicylic acid, DAT; Dual antiplatelet therapy INR; International Normalized Ration.

Pneumothorax

Thirty-seven patients (1.2%) suffered from a pneumothorax. A total of 32 pneumothoraxes occurred after the 1st implant and 5 occurred after the 2nd implant (0.5% of 2nd implants). These 5 cases were all related to the implantation of an extra lead. Logistic regression was performed, simultaneously adjusting for age, gender, BMI , CRT-D, and a GFR<30 mL/min/1.73m^2. The occurrence of pneumothorax was independently associated with female gender (OR=0.21 for males, CI;0.11-0.42, p<0.001) and a lower BMI (OR=0.9 per unit increase, CI;0.83-0.97, p<0.01). Kidney function was not associated with the occurrence of pneumothorax (OR 0.76, CI; 0.20-2.79, p=0.7).

Lead dysfunction

In 86 patients (2.7%) there was at least one lead problem requiring hospital admission. Two patients experienced 2 of these events. When analyzing the 1st lead related complication, 24% were LV-lead related, 68% RV-lead and 8% atrial lead related. After correcting for age,

gender, CRT-D a GFR<30 ml/min/1.73m^2, time to any first lead problem was significantly associated with the implantation of a CRT-D device (HR 2.3, CI; 1.40-3.75, p<0.001). Out of the 88 lead problems registered, 39 (44%) occurred within a period of 30days post-implant. There was no association between lead dysfunction and a GFR<30 (HR 0.98 CI; 0.24-4.06, p=0.98) nor was there an (univariate) association between lead complications and the dialysis procedure (HR 0.05, p=0.7).

Infection

Device infections occurred in 113 (3.6%) patients. Among these 113 patients, 8 patients suffered from a second infection. Age, gender, LVEF, hypertension, diabetes, BMI, 2nd and 3th device, GFR<30 ml/min/1.73m^2,the use of OAC's and the use of CRT-D were analyzed in the univariate model. Variables with p≤0.1 were added to the multivariate model (fig 2). Device infection was independently associated with device replacement (2nd device, HR 4.4, CI;2.27-8.60, p<0.001) and the use of CRT-D (HR 1.7, CI;1.10-2.59, p=0.02). There was a trend for an association with gender (HR 0.6, p=0.08) and GFR<30 (HR 2.1, p=0.08). Of interest, a strong univariate association was found in patients receiving dialysis (HR

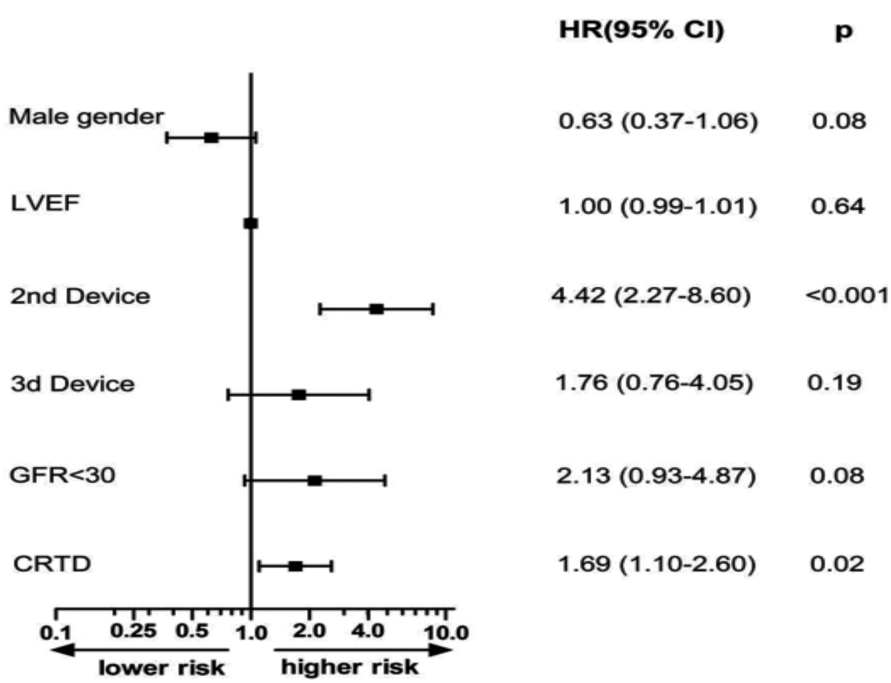

Figure 2. Hazard ratio's for the occurrence of device infection
LVEF; Left ventricular ejection fraction, GFR; Glomerular Filtration Rate, CRT-D; Cardiac Resynchronization Therapy- Defibrillator.

9.14 CI; 2.88-28.99, p<0.001). In this group 3 patients suffered from an infection. The small number of patients receiving dialysis however (n=17) made it unfeasible to add this variable to the multivariate model.
Out of the 121 infections observed, 26 (21%) occurred within 30 days post-implant. In 33patients (26 and an additional 7) the infection occurred within one year (1%).
The most frequent causes of infection were Staphylococcus Aureus (S. Aureus, 28%) followed by Coagulase-negative staphylococcus (CNS, 21%). In 15% of the cases no cause of infection was found. In these patients a vegetation was observed using echocardiography in 14% and in the remaining cases local decubitus of the skin was present around the device pocket.
In patients with advanced kidney disease, S.Aureus was the cause of infection in 5 out of the 6 (83%) observed infections compared to 27 out of 107 (25%) infections in patients with a GFR>30 (p=0.07).

DISCUSSION

In the present study, data from 3147consecutive patients who received an ICD or CRT-D were examined. The most important findings were; (1) During an average follow-up of 3.5 years 7.5% of patients suffered from at least one device related complication (2) Patients with advanced CKD, most of them not on dialysis, showed an increased incidence of device related complications (3) This high incidence of device related complications was partially associated with renal failure itself. However, it appears that the advanced CKD patients' heavy burden of multiple risk factors associated with complications plays an even more important role.

The current data provides unique information on risk factors for ICD-related complications during a long follow-up period. Several large registries recently reported on ICD related complications, with follow-up limited to initial hospitalization or limited clinical data.[10;14;15;18] Since most infections and lead problems occur after initial hospitalization, a longer follow-up is necessary to provide an accurate account on these complications. Smaller studies reported an incidence of complications of 4-14% up to 12 months after device implantation.[19-21] At present, the only study on this topic with a longer follow-up had a small sample size, making multivariate analysis impossible.[22] Furthermore, whereas several papers have reported on a complication rates in dialysis patients, this is one of the few studies reporting on complications in patients with advanced kidney disease not on dialysis .[15;18]

Hematoma

The occurrence of hematoma in the study population (1.7% of patients) was similar to that reported in other trials (0.9-3.2%).[10;14;20] Hematoma was independently associated with aGFR<30 mL/min/1.73m^2. This association might be caused by platelet dysfunction

and abnormal nitric oxide production associated with kidney disease.[23;24] An increased incidence of OAC use in patients with CKD was observed. This might be explained by the high burden of AF, left ventricular dysfunction and valvular replacement in these patients. However the association between advanced CKD and risk of hematoma was independent of medication use. It is possible that the strict peri-procedural INR control in our center ,mitigated the effect of OAC use on the risk of hematoma.

Lead complications

A total of 2.7% of the patients implanted with an ICD or CRT-D suffered from at least one lead complication. Patients that received a CRT-D experienced more complications when compared to patients with a conventional ICD. This is not surprising since CRT-D implantation is technically challenging and the presence of more leads in the venous system could predispose to lead complications.[8]

Pneumothorax

In the study population, 1.2% of patients suffered from a pneumothorax, an incidence similar to that reported in the literature (0.4-1.3%).[14;20;22] Independent predictors for pneumothorax were female gender and a lower BMI. Female gender as a predictor for complications and specifically as a predictor for pneumothorax has been described in the past.[20;25] However an association between pneumothorax and BMI has not been shown before[14;19] An explanation might be that in patients with less body mass, the subclavian vein lies relatively closer to the skin, making it more likely to puncture through the vein and subsequently puncturing the pleura, causing a pneumothorax.[26] After adjusting for co-morbidity, renal function was not associated with the occurrence of pneumothorax.

Infection

Device explantation due to suspected infection occurred in 3.6% of patients. This slightly higher incidence compared to current literature (0.5-3%) is probably due to the longer follow-up in the study population.[10;21;22] This is confirmed by the incidence of device infection within one year post-implant, which was approximately 1% in the present study. CRT-D therapy and a 2nd device implantation were both independently associated with time to ICD related infection. Device replacement has previously been described as an important risk factor for device infection.[17] It has been proposed that this is due to local, perioperative wound contamination.[17;27] Indeed, S.Aureus and CNS, both present in the normal skin flora, were the most frequently found pathogens in the current study. A logical explanation for CRT-D as a risk factor for device infection might be that the average CRT-D implantation takes longer than the implantation of an ICD.

After adjustment for the risk factors associated with device infection (gender, LVEF, device replacement, advanced renal disease and CRT-D), only a trend remained for the association between a GFR<30 and infection. However, in the univariate analysis a strong independent

association was found between the time to infection and dialysis therapy. This finding is in line with results from several previous studies that suggested the dialysis procedure might carry a risk factors for device infection.[13;28] A possible cause might be due repeated microbial exposure due to repeated intravenous access in dialysis patients.

Clincial Implications

This study illustrates that there are several risk factors for device complications and advanced CKD is one of these. These results suggest that withholding device therapy based solely on the presence of CKD would be inappropriate. Especially given the recent observations that patients with CKD receive more appropriate device therapy and appear to experience a benefit in mortality after device implant.[29;30]

Furthermore, it is of utmost importance to be aware of the high risk of both hematoma and infections when implanting a device. To reduce these risks it is important to carefully consider anticoagulation regimens, antibiotic prophylaxis, to screen for any signs of pre-existing infection and to limit the performance of high risk operations to experienced cardiologists.[31] The observation that device replacement is a major risk factor for infection stresses the need to develop ICD's with longer longevity and to reconsider antibiotic treatment in device replacements.

Limitations

Guidelines for ICD implantations have changed over the years, resulting in a somewhat heterogeneous patient population. Moreover in the 16 years span of our registry, the clinical strategy in anticoagulation therapy has changed, which might influence the reported rate of events. Furthermore, no periodical eGFR measurements were available in our population to assess the potential effect of eGFR worsening on complication rate. However, in the group of ICD recipients who underwent device replacement, 140 experienced worsening of CKD stage, which is 5% of our total population. This suggests that the effect of worsening CKD stage on complications in the total population might be limited. However this data does represent device recipients that cardiologists see in actual clinical practice. The occurrence of reporting bias cannot be excluded, since all information was retrospectively collected from a patient database.

CONCLUSION

In ICD recipients, device related complications are common, as shown by the 7.5% of patients suffering from at least one complication. Patients with CKD suffered from more ICD related complications than patients without kidney dysfunction. Partially, this can be explained by factors unique for renal disease. However, the high burden of risk-factors associated with device complications in patients with renal disease played an important role as well.

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