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Outcomes of patients with chronic kidney disease and implantable cardiac defibrillator: Primary versus secondary prevention

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ABSTRACT

Background: Chronic kidney disease (CKD) is associated with worse survival in patients with implantable cardiac defibrillators (ICDs). This study examined the association of outcomes with CKD in patients receiving an ICD for primary versus secondary prevention.
Methods: The study included 696 patients who underwent ICD placement for clinical reasons (59% primary, 41% secondary prevention) at the University of Alabama at Birmingham between January 2002 and September 2007. CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 but not on dialysis. Outcomes of interest included overall mortality and first appropriate ICD therapy (shocks or anti-tachycardia pacing).
Results: After a follow-up of 50 ± 24 months, 213 patients died (31%) and 111 (16%) received appropriate ICD therapy. Patients with CKD had higher mortality than patients with no CKD in the primary (43% vs. 15%, $p<0.001$) and secondary prevention (37% vs. 23%, $p=0.003$) groups. Patients with CKD were at higher risk of receiving an appropriate ICD therapy than patients without CKD in the primary ($p<0.001$) but not secondary prevention ($p=0.9$) cohort. After adjusting for age, gender and multiple risk factors, CKD was independently associated with all-cause mortality and ICD therapy in the primary prevention group (HR 2.08 [1.34–3.23] and 3.53 [1.75–7.10], $p=0.001$ and <0.0001, respectively) but not in the secondary prevention group (HR 1.27 [0.81–2.00], and 0.63 [0.35–1.13], $p=0.3$ and 0.2, respectively).
Conclusions: CKD is independently associated with increased mortality and appropriate ICD therapy in patients undergoing ICD implantation for primary but not secondary prevention.

1. Introduction

Chronic kidney disease (CKD) is now recognized as an important risk factor in patients with and without known cardiovascular disease [1]. The prevalence of CKD is increasing at an alarming rate with an estimated 11% of the US population having CKD, and more than 2 million patients expected to be on dialysis by 2030 [2,3]. Sudden cardiac death (SCD) accounts for 25% of all death in patients with CKD and up to 60% of those on dialysis [3–5]. While large randomized clinical trials have shown survival benefits with implantable cardiac defibrillators (ICD) in high-risk patients, they have excluded patients with advanced CKD [6,7]. The implantation of ICD devices is increasing in patients with CKD, but there is a significant concern that mortality remains elevated in this population despite ICD implantation [3]. The mortality rate increases exponentially with advancing CKD and reaches 50% at 4 years in patients on dialysis [8]. In individuals with less advanced CKD, there is 12%–55% increase in the death rate for every 10% decrease in the estimated glomerular filtration rate (eGFR) [8,9]. Currently, there are limited data on outcomes in patients with CKD based on the indication for ICD placement and it is not clear if the risk associated with CKD is present in patients receiving an ICD who have a history of SCD (secondary prevention) as well as in those who are at high risk of, but with no personal history of SCD (primary prevention). The purpose of this study was to examine the impact of CKD on outcomes in patients with ICD implants for primary vs. secondary prevention as defined in the Multicenter Automatic Defibrillator Implantation Trial II and the Anti-arrhythmics versus Implantable Defibrillators Trial, respectively [6,10].

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2. Methods

Patients who underwent implantation of an ICD (with or without a bi-ventricular pacing device) for either primary or secondary prevention at the hospital of the University of Alabama at Birmingham between January 2002 and September 2007 were included in this study. Exclusion criteria included: 1) age<18 years, 2) unavailability of laboratory measurements needed for calculating eGFR at the time of device implantation, 3) unavailability of follow-up data, and 4) patients on dialysis. The database included 930 patients, of whom 234 (25%) were excluded based on the above criteria. The patients included in this study and those excluded did not differ in age, gender, left ventricular (LV) ejection fraction (EF) and whether the indication for ICD implantation was primary or secondary prevention.

Characteristics of the cohort including the demographics, co-morbidities, medications, and laboratory results at the time of ICD implantation were extracted through chart reviews. The LVEF was determined using transthoracic echocardiography, gated radionuclide angiography, single photon emission computed tomography, or contrast left ventriculography. The eGFR was calculated using the Modification of Diet in Renal Disease formula (MDRD) based on age, race, gender, and baseline serum creatinine level [11,12]. For the purposes of this analysis, CKD was defined as eGFR<60 ml/min/1.73 m^2.

Follow-up data were obtained at 3–6 month intervals in the electrophysiology clinic with device interrogation. All devices were programmed similarly at implantation regardless of CKD status. ICD therapy (shocks or anti-tachycardia pacing) was determined as appropriate or inappropriate by an experienced clinical electrophysiologist who reviewed the intra-cardiac electrograms. All-cause mortality was determined using the social security death index master data file assessed on March 26th, 2010. The outcomes of interest were all-cause mortality and the occurrence of first appropriate ICD therapy.

All statistical analyses were carried out using SPSS version 11.5 for Windows (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean ± SD and discrete variables as frequencies and percentages. The Chi-square test was used for the comparison of categorical variables between the groups. Continuous variables were compared between the groups by the unpaired *t* test, the Mann–Whitney *U* test, or one-way analysis of variance (ANOVA) as appropriate. When ANOVA was used and a significant difference was detected among the groups, a post-hoc least significant difference test was conducted to determine which groups were significantly different from each other. All tests were 2-tailed, and a p value<0.05 was considered statistically significant. Event-free survival curves were constructed using the product-limit method (Kaplan–Meier) and differences among survival curves were estimated by the log-rank test. Proportional hazard analysis was performed using Cox regression modeling and adjusted for age, gender, hypertension, atrial fibrillation, myocardial infarction, CKD, LVEF, left bundle branch block, biventricular pacing, anti-arrhythmics including (but not limited to) amiodarone, and beta blocker therapy. Estimated risks were reported as hazard ratios (HR) with correspondent 95% confidence intervals (CI).

The institutional review board at the University of Alabama at Birmingham approved the study.

3. Results

The cohort consisted of 696 patients with a follow-up of 50 ± 24 months. The baseline characteristics of the cohort are summarized in Table 1. There were 454 patients with ICD alone (65%) and 242 patients with ICD plus biventricular pacing device (35%). The ICD was implanted for primary prevention in 409 patients (59%) of whom 141 had CKD (34%), and for secondary prevention in 287 patients (41%) of whom 115 had CKD (40%). Most patients (81%) had heart failure symptoms, predominately New York Heart Association Class II and III. The LVEF was 28 ± 15% (interquartile range 20–33%). There was a preponderance of Caucasian men in our cohort. Patients with CKD were older, more likely to have atrial fibrillation, prior myocardial infarction and peripheral vascular disease and more likely to be treated with amiodarone but less likely to be treated with beta-blockers than patients without CKD (Table 1).

During the follow-up period, 213 patients died (31%) and 111 patients (16%) received an appropriate ICD therapy. Kaplan–Meier survival analysis showed that CKD patients had lower survival than non-CKD patients in both the primary and secondary prevention groups. In the primary prevention group, the 1 and 5 years all-cause mortality were 11% and 43% for patients with CKD vs. 4% and 15% for patients without CKD, respectively (log-rank p<0.001). In the secondary prevention group, the 1 and 5 years all-cause mortality were 10% and 37% for patients with CKD vs. 8% and 23% for patients without CKD, respectively (log-rank p = 0.003) (Fig. 1). CKD patients had a higher risk of receiving appropriate ICD therapy vs. non-CKD in the primary prevention group (p<0.001) but not in the secondary prevention group (p = 0.9) (Fig. 2).

Table 1
Baseline demographics.

Variable	Primary prevention		Secondary prevention	
	CKD (N = 141)	Non-CKD (N = 268)	CKD (N = 115)	Non-CKD (N = 172)
Demographics				
Age	66 ± 11†	54 ± 14†	66 ± 11†	55 ± 17†
Men	101 (72%)	186 (69%)	84 (73%)	126 (73%)
Caucasians	127 (90%)*	209 (78%)*	102 (89%)	143 (83%)
Co-morbidities				
Hypertension	107 (76%)†	157 (59%)†	82 (71%)	112 (65%)
Hyperlipidemia	102 (72%)*	159 (59%)*	71 (62%)	97 (56%)
Diabetes mellitus	52 (37%)	85 (32%)	40 (35%)	42 (24%)
Myocardial infarction	67 (48%)*‡	95 (35)*	71 (62%) *‡	74 (43%)*
Percutaneous coronary intervention	41 (29%)	68 (25%)	31 (27%)	41 (24%)
Coronary artery bypass graft	63 (45%)†	73 (27%)†	44 (38%)	55 (32%)
Smokers	42 (30%)$	92 (34%)	41(36%)$	75 (44%)
Stroke	22 (16%)*	23 (8%)*	20 (17%)	23 (13%)
Peripheral vascular disease	24 (17%)*	21 (8%)*	25 (22%)*	21 (12%)*
Atrial fibrillation	60 (42%)†	44 (16%)†‡	46 (40%)	50 (29%)‡
Left bundle branch block	59 (41%)*‡	79 (29%)*	33 (29%)‡	38 (22%)
Biventricular pacing (%)	81 (57%)†§	93 (35%)†§	37 (32%)*§	31 (18%)*§
QRS (ms)	139 ± 34*	130 ± 33*	140 ± 44	134 ± 37
Glomerular filtration rate (ml/kg/1.73 m^2)	46 ± 10†	82 ± 18†	45 ± 11†	85 ± 22†
Congestive heart failure New York Heart Association¶	125 (89%)§	233 (87%)§	92 (80%)*§	116 (67%)*§
I	16 (12%)	44 (17%)	34 (35%)	71 (46%)
II	54 (39%)	98 (39%)	23 (24%)	47 (30%)
III	59 (43%)	101 (40%)	33 (34%)	34 (22%)
IV	8 (6%)	11 (4%)	6 (7%)	3 (2%)
Left ventricular ejection fraction%	25 ± 11	27 ± 14§	28 ± 13*	32 ± 16*§
Medications				
Aspirin	85 (57%)	176 (66%)	79 (69%)	106 (62%)
Beta blockers	121 (82%)§	241(90%)§	78 (68%)§	135 (78%)§
ACE-I/ARB	107 (72%)	217 (81%)	85 (74%)	131 (76%)
Aldactone	54 (36%)	111(41%)‡	66 (57%)*	127 (74%)*‡
Loop diuretics	120 (81%)†	177 (66%)†‡	91(79%)†	96 (56%)†‡
Digoxin	65 (44%)	116 (43%)‡	50 (43%)	57 (33%)‡
Amiodarone	27 (18%)†§	18 (7%)†§	52 (45%)*§	56 (32%)*§
Other antiarrhythmics	4 (3%)	6 (2%)†	8 (7%)	17 (10%)†
Statins	93(63%)*	148 (53%)*	63 (55%)	88 (51%)

ACE-I (angiotensin converting enzyme inhibitor); ARB (angiotensin receptor blocker); CKD (chronic-kidney-disease); hyperlipidemia (low density lipoprotein higher than ATP III goal or taking statins); hypertension (blood pressure>140/90 or taking anti-hypertensive medications).
*p<0.05; †p<0.001 [in-group CKD vs. non-CKD (primary prevention) and CKD vs. non-CKD (secondary prevention)].
‡p<0.05; §p<0.001 [between groups of CKD (primary vs. secondary) and non-CKD (primary vs. secondary)].
¶ Available N = 493; (missing values: 4, 14, 19 and 17, respectively).

After adjusting for age and multiple risk factors, CKD was predictive of all-cause mortality (Table 2) and ICD therapy (Table 3) in the primary prevention group (HR 2.08 [1.34–3.23] and 3.53 [1.75–7.10], p = 0.001 and <0.0001, respectively) but not in the secondary prevention group (HR 1.27 [0.81–2.00], and 0.63 [0.35–1.13], p = 0.3 and 0.2, respectively). A significant interaction was present between CKD and ICD indication (primary vs. secondary) for mortality and ICD therapy (p<0.05 for both).

In patients with CKD, as well as in those without CKD, the indication for ICD implantation (secondary vs. primary) was not predictive of overall mortality (HR 0.72, p = 0.2 for CKD; and HR 1.22, p = 0.4 for non-CKD). Finally, in patients with CKD, a history of SCD or sustained ventricular tachycardia (ICD implanted for secondary prevention) was not associated with a higher risk of having a first appropriate ICD therapy (multi-variate adjusted HR 0.99, p = 1.0) unlike those without CKD (multi-variate adjusted HR 2.59, p = 0.002) (Fig. 2).