Primary prevention implantable cardioverter defibrillators in end-stage kidney disease patients on dialysis: a matched cohort study

Patrick H. Pun1,2, Anne S. Hellkamp1, Gillian D. Sanders1, John P. Middleton2, Stephen C. Hammill3, Hussein R. Al-Khalidi1, Lesley H. Curtis1, Gregg C. Fonarow4 and Sana M. Al-Khatib1,2

1Duke Clinical Research Institute, Durham, NC, USA, 2Department of Medicine, Duke University Medical Center, Durham, NC, USA, 3Mayo Clinic, Rochester, MN, USA and 4Ahmason-UCLA Cardiomyopathy Center, Ronald Reagan-UCLA Medical Center, Los Angeles, CA, USA

Correspondence and offprint requests to: Patrick H. Pun; E-mail: patrick.pun@duke.edu

ABSTRACT

Background. Sudden cardiac death is the leading cause of death among end-stage kidney disease patients (ESKD) on dialysis, but the benefit of primary prevention implantable cardioverter defibrillators (ICDs) in this population is uncertain. We conducted this investigation to compare the mortality of dialysis patients receiving a primary prevention ICD with matched controls.

Methods. We used data from the National Cardiovascular Data Registry’s ICD Registry to select dialysis patients who received a primary prevention ICD, and the Get with the Guidelines-Heart Failure Registry to select a comparator cohort. We matched ICD recipients and no-ICD patients using propensity score techniques to reduce confounding, and overall survival was compared between groups.

Results. We identified 108 dialysis patients receiving primary prevention ICDs and 195 comparable dialysis patients without ICDs. One year (3-year) mortality was 42.2% (68.8%) in the ICD registry cohort compared with 38.1% (75.7%) in the control cohort. There was no significant survival advantage associated with ICD [hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.66–1.13, log-rank P = 0.29]. After propensity matching, our analysis included 86 ICD patients and 86 matched controls. Comparing the propensity-matched cohorts, 1 year (3 years) mortality was 43.4% (74.0%) in the ICD cohort and 39.7% (76.6%) in the control cohort; there was no significant difference in mortality outcome between groups (HR = 0.94, 95% CI: 0.67–1.31, log-rank P = 0.71).

Conclusions. We did not observe a significant association between primary prevention ICDs and reduced mortality among ESKD patients receiving dialysis. Consideration of the potential risks and benefits of ICD implantation in these patients should be undertaken while awaiting the results of definitive clinical trials.

Keywords: cardiovascular disease, defibrillator, dialysis, end-stage kidney disease, sudden cardiac death

INTRODUCTION

Sudden cardiac death (SCD) is the leading cause of death in end-stage kidney disease (ESKD) patients receiving dialysis, accounting for >25% of all deaths [1]. Although all patients with cardiovascular disease are at risk of SCD, the risk among dialysis patients is 10–20-fold higher than among patients without chronic kidney disease (CKD) [2]. In patients with preserved renal function, implantable cardioverter defibrillators (ICDs) have been proved to effectively reduce mortality among survivors of cardiac arrest (so-called secondary prevention) and in patients with reduced left ventricular ejection fraction (LVEF) who have not had prior arrhythmia events (primary prevention) [3]. Given the increased risk of SCD in patients with ESKD, it is vitally important to address whether primary prevention ICDs are associated with improved survival in such a vulnerable population of patients with ESKD. Despite the lack of consensus on the benefit of ICDs in dialysis patients, the number of primary prevention ICD implants in these patients has steadily increased over the past decade [4].

No randomized clinical trial has addressed whether primary prevention ICDs are beneficial among dialysis patients [1]. Observational data suggest that ESKD patients on dialysis who receive ICDs have markedly increased overall mortality and complication rates compared with ICD recipients without ESKD [5]. The high burden of comorbidity, risk of non-cardiovascular death, increased rate of bacteremia,
bleeding tendency and advanced age of the dialysis population are also potential factors that may limit the benefit of primary prevention ICDs. Since there are no prior studies in ESKD patients specifically examining the potential survival advantage associated with primary prevention ICDs, we conducted this investigation to compare the survival of dialysis patients receiving a primary prevention ICD with that of propensity-matched controls without an ICD.

**Materials and Methods**

**Data sources and available covariates**

We used data from the National Cardiovascular Data Registry’s ICD registry, the Get with the Guidelines-Heart Failure (GWTG-HF) database and the Centers for Medicare & Medicaid Services claims. The National Cardiovascular Data Registry ICD registry was launched in 2005 in response to a mandate from Centers for Medicare and Medicaid Services that data on all beneficiaries receiving a primary prevention ICD be entered into a national registry. Periodic audits indicate >90% of fields accurately reflect the data from the medical charts [6].

The GWTG-HF program was established as a quality improvement initiative that involves data collection on patients hospitalized for acute heart failure. Data quality is ensured by data checks to prevent out-of-range or duplicate entries and data audits. Data collected include patient demographics, comorbidities, clinical characteristics, historical therapies and interventions, in-hospital outcomes and recorded contraindications to evidence-based therapies. Specific data were collected regarding the presence or absence of an ICD on admission, any ICD implantation during the index hospitalization, scheduled outpatient ICD implantation at the time of discharge and contraindications that preclude an ICD implantation.

Only variables that were identically defined in the ICD and the GWTG-HF registries were used in this analysis. Apart from determination of dialysis-dependency at enrollment, these include demographic characteristics, LVEF, comorbid conditions (history of ischemic heart disease and arrhythmias), blood pressure readings, cardiovascular medication use and serum creatinine values.

**Study population**

For both ICD and the non-ICD cohorts, only patients receiving chronic dialysis with documented cardiomyopathy and an LVEF ≤35% were included. Patients with Class IV heart failure symptoms, myocardial infarction within 40 days prior to implant, coronary artery bypass surgery within 90 days prior to implant and new-onset heart failure (<3 months) were excluded, in accordance with evidence-based guidelines for primary prevention ICD implantation [3]. All patients were Medicare patients ≥65 years old to ensure linkage to Medicare data on all-cause mortality.

The ICD cohort consisted of patients drawn from the ICD registry who received a primary prevention ICD during an admission for heart failure and were discharged home alive between 1 January 2006 and 31 December 2007. Patients receiving a cardiac resynchronization therapy defibrillator device (CRT-D) were excluded from this analysis in order to avoid confounding and indication bias specific to benefits and risks of CRT-D implantation. The index implant was used for patients with several device implants in the registry.

To select a comparator cohort of patients without an ICD, we included chronic dialysis patients in the GWTG-HF registry who were hospitalized with heart failure between 1 January 2005 and 31 December 2009, had LVEF ≤35%, and were discharged alive without an ICD at admission, during hospitalization, or prescribed at discharge. Patients with new-onset heart failure and patients who were discharged to hospice care, a skilled nursing facility, a rehabilitation center and those transferred to another acute care facility or left against medical advice were excluded. Patients with no reasonable expectation of survival for at least 1 year or those with a physician-documented contraindication for not receiving an ICD were excluded.

Qualifying records were matched with Centers for Medicare and Medicaid Services enrollment files and inpatient claims data to identify unique patients. For patients who appeared in both registries, the ICD registry record was retained. Only the first hospitalization for each patient among matching records was selected.

**Primary outcome**

Our primary outcome was all-cause mortality. For both cohorts, vital status was available for patients via the Medicare denominator file through 31 December 2011. Patients without a record of death were considered alive as of 31 December 2011, or the date at the patient was no longer enrolled in Medicare, whichever came first.

**Statistical analysis**

Baseline characteristics were compared between the two cohorts using the Pearson’s Chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. The standardized difference between groups for each variable was calculated as the absolute value of the difference in means or proportions, divided by the average standard deviation, and expressed as a percentage. Covariates with standardized difference value <10% were considered a good match.

To reduce confounding between the two cohorts, we matched ICD registry patients to similar GWTG-HF patients as follows. A propensity model was built using a multivariable logistic regression model in which the dependent variable was an indicator of whether each patient was recipient of an ICD or not, and the independent variables were the available baseline characteristic variables. From the logistic regression model, the estimated probability (P) of being an ICD registry patient and a corresponding logit \[\text{logit} = \log\left(\frac{P}{1-P}\right)\] were calculated for each patient. For a given ICD registry patient, we identified GWTG-HF patients whose logit differed from the ICD registry patient by <0.25*(standard deviation of the logit) [7]. ICD patients without a suitable matching GWTG-HF patient were omitted from the analysis, and each GWTG-HF patient was matched only once.

Kaplan–Meier estimates, log-rank statistic and unadjusted Cox proportional hazards models were used to compare all-
cause mortality outcome for the ICD and non-ICD cohorts. A two-sided P-value of <0.05 was considered statistically significant. For all analyses, SAS version 9.2 (SAS Institute, Cary, NC, USA) was used.

RESULTS

We identified 651 chronic dialysis patients in the ICD registry between 2006 and 2007. Of these patients, 281 (43%) received an ICD for a non-evidence-based indication; after applying other exclusion criteria, 108 unique dialysis patients received primary prevention ICDs according to evidence-based guidelines. For the comparison cohort, we identified 1647 chronic dialysis patients in the GWTG-HF registry between 2005 and 2009. Seventy-two percent had either missing data on LVEF or LVEF >35%; after applying other exclusion criteria, there were 195 unique non-ICD heart failure patients who did not receive an ICD (Table 1).

Baseline characteristics of the two cohorts are shown in Table 2. At baseline, there were no significant differences in age, gender, race, history of ischemic heart disease and history of diabetes between the two cohorts. ICD recipients had a higher prevalence of prior atrial arrhythmias, a lower systolic blood pressure, lower creatinine values and a higher prevalence of statin use.

After propensity matching, the cohorts consisted of 86 ICD registry patients and 86 matched patients from the GWTG-HF cohort. All baseline variables were balanced after matching with <10% standardized difference between cohorts for any given variable (Table 2, Figure 1). The median duration of follow-up was 4.7 years in the ICD Registry cohort and 2.9 years in the GWTG-HF cohort.

For the unmatched cohorts, 1- and 3-year mortality rates were 42.2 and 68.8% in the ICD registry cohort compared with 38.1 and 75.7% in the GWTG-HF cohort; there was no significant difference in mortality outcome between the groups [Figure 2, hazard ratio (HR) 0.87 [95% confidence interval (CI) 0.66–1.13], log-rank P = 0.29]. Comparing the propensity-matched cohorts, the 1- and 3-year mortality rates were 43.4 and 74.0% in the ICD cohort and 39.7 and 76.6% in the GWTG-HF cohort; similarly, there was no significant difference in mortality outcome between the groups [Figure 3, HR: 0.94 (95% CI: 0.67, 1.31), log-rank P = 0.71].

Table 1. Inclusion and exclusion criteria applied to eligible ESRD patients to derive study population

<table>
<thead>
<tr>
<th>ICD registry patients</th>
<th>n</th>
<th>GWTG-HF patients</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis patients receiving primary ICD</td>
<td>651</td>
<td>Dialysis patients hospitalized for CHF without ICD implantation</td>
<td>1647</td>
</tr>
<tr>
<td>Missing EF</td>
<td>8</td>
<td>Missing EF</td>
<td>341</td>
</tr>
<tr>
<td>EF &lt;35</td>
<td>18</td>
<td>EF &lt;35</td>
<td>845</td>
</tr>
<tr>
<td>Non-evidence-based implantation*</td>
<td>281</td>
<td>Documented contraindication to implantation</td>
<td>45</td>
</tr>
<tr>
<td>Secondary prevention ICD</td>
<td>12</td>
<td>New-onset heart failure</td>
<td>98</td>
</tr>
<tr>
<td>Cardiac Resynchronization therapy-defibrillator</td>
<td>204</td>
<td>Left AMA or transfer to acute care facility</td>
<td>11</td>
</tr>
<tr>
<td>Device replacement</td>
<td>7</td>
<td>Discharge to hospice, SNF, rehab</td>
<td>99</td>
</tr>
<tr>
<td>Non-unique patients</td>
<td>13</td>
<td>Non-unique patients</td>
<td>13</td>
</tr>
<tr>
<td>Final population</td>
<td>108</td>
<td>Final population</td>
<td>195</td>
</tr>
</tbody>
</table>

*Myocardial infarction within 40 days n = 101; Class IV heart failure n = 91; CABG in previous 3 months (n = 2); new-onset heart failure n = 87.

DISCUSSION

To our knowledge, this is the first study that specifically compares survival with and without a primary prevention ICD in dialysis patients. In summary, among dialysis patients with congestive heart failure (CHF) and LVEF ≤35%, we did not observe a significant survival advantage associated with primary prevention ICD compared with propensity-matched controls.

Among patients without kidney disease, primary prevention ICDs are a proven but costly therapy to reduce SCD and overall mortality in at-risk patients. Currently, there are no special considerations for dialysis status or level of kidney function in the guidelines for primary prevention ICD implantation [3, 4]. While it is appealing to consider managing the risk of SCD in patients with CKD with ICDs, the evidence supporting efficacy of these devices is inconsistent. Randomized trials of ICDs excluded patients with advanced CKD, but post hoc analyses from pivotal trials suggested that the benefit of ICDs was abrogated by the presence of reduced kidney function [8]. One meta-analysis suggested that CKD patients at high risk for SCD had improved survival with an ICD compared with similar patients who did not have a device in place [9]. A retrospective analysis of 696 patients who had an ICD at a single center determined that patients with CKD [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²] but not on dialysis had higher mortality and higher likelihood of appropriate ICD shock compared with patients without CKD when the devices were placed for primary prevention [10]. However, a meta-analysis that included patient-level data from three randomized trials of primary prevention ICDs found no significant benefit of ICD compared with controls among 1040 patients with eGFR <60 mL/min/1.73 m² not on dialysis (adjusted HR: 0.8, 95% CI: 0.4–1.5) [11].

The risk of ICDs may outweigh any benefit for CKD patients who require dialysis. Prior studies have reported increased mortality and increased complication rates in ICD recipients on dialysis compared with patients without CKD when the devices were placed for primary prevention [12, 13]. One study examining the short-term outcomes of dialysis patients in the National Cardiovascular Data Registry (NCDR) ICD registry found a 5-fold increase in in-hospital mortality and a 20% increase in ICD-related complications compared with non-dialysis patients [5]. Another recent study examined 9528 hemodialysis patients who received a primary...
or secondary ICD between 1994 and 2006 found disturbingly high annual rates of bacteremia (52%), device infection (4.2%) and death (45%). Furthermore, the most frequent cause of death after ICD implantation was determined to be arrhythmia (38% of all deaths) [4].

A significant number of sudden cardiac arrest events that occur in dialysis are not due to ventricular fibrillation or ventricular tachycardia and would not be expected to respond to defibrillation therapy [14, 15]. Increased risks of non-arrhythmic causes of death that would not be prevented by ICD therapy among dialysis patients may blunt the overall mortality benefit. Indeed, heart failure patients with CKD enrolled in clinical trials experienced a higher proportion of non-arrhythmic deaths compared with patients without kidney disease [8, 11, 16]. The high overall annual rate of mortality among dialysis patients receiving ICDs may also reduce the overall exposure time to ICD, thus reducing the opportunity for ICDs to reverse life-threatening arrhythmias. Consistent with

| Table 2. Baseline characteristics for ICD Registry and GWTG-HF patients before and after matching |
|----------------------------------|----------------------------------|----------------------------------|
| Baseline characteristic         | All ESKD dialysis patients qualifying for analysis | 1:1 matched ESKD patients |
| GWTG-HF (n = 195)                | Registry (n = 108)               | P-value | GWTG-HF (n = 86) | Registry (n = 86) | P-value |
| Age, years                       | 73 (69, 80)                     | 75 (68, 79) | 0.68 | 74 (70, 80) | 75 (68, 80) | 0.91 |
| Male                             | 59% (115)                       | 69% (75) | 0.069 | 71% (61) | 69% (59) | 0.74 |
| White race                       | 67% (129)                       | 56% (61) | 0.066 | 64% (54) | 62% (53) | 0.80 |
| LVEF (%)                         | 25% (20, 32)                    | 25% (20, 30) | 0.011 | 25% (20, 30) | 25% (20, 30) | 0.61 |
| Ischemic heart disease           | 70% (137)                       | 73% (79) | 0.59 | 78% (67) | 74% (64) | 0.59 |
| Prior atrial arrhythmia          | 25% (48)                       | 40% (43) | 0.0052 | 36% (31) | 36% (31) | 0.95 |
| Systolic blood pressure          | 141 (121, 160)                  | 132 (114, 146) | 0.0025 | 134 (114, 152) | 133 (118, 147) | 0.96 |
| Creatinine (mg/dL)               | 4.9 (3.5, 7.0)                  | 4.1 (2.1, 5.6) | 0.0002 | 3.9 (2.9, 5.3) | 4.5 (2.5, 5.9) | 0.53 |
| Diabetes                         | 54% (105)                       | 49% (53) | 0.43 | 56% (48) | 53% (46) | 0.76 |
| Hypertension                     | 86% (167)                       | 83% (90) | 0.59 | 90% (77) | 88% (76) | 0.81 |
| ACE-inhibitor or ARB             | 65% (127)                       | 61% (65) | 0.51 | 58% (50) | 61% (51) | 0.73 |
| Beta-blocker                     | 83% (161)                       | 76% (81) | 0.20 | 77% (66) | 80% (67) | 0.63 |
| Diuretic                         | 43% (72)                       | 50% (53) | 0.27 | 47% (34) | 43% (36) | 0.58 |
| Statin                           | 43% (81)                       | 58% (61) | 0.014 | 52% (44) | 55% (46) | 0.76 |

**FIGURE 1:** Standardized difference in baseline characteristics before and after propensity matching.
previous reports, we noted a very high rate of mortality in our study population regardless of ICD implantation status (38%/42% 1-year mortality and 69%/76% 3-year mortality in ICD/no-ICD cohorts). Besides the potential safety concerns raised by an increased rate of implantation-related and infectious ICD complications, other authors have also reported higher defibrillation thresholds in dialysis patients, perhaps further reducing the effectiveness of ICDs [17].
Current evidence-based primary prevention implantation guidelines suggest that ICDs should be reserved for patients with cardiomyopathy and left ventricular systolic dysfunction [3]. Accordingly, in this study, we examined only patients with an LVEF ≤35%. However, diastolic dysfunction due to left ventricular hypertrophy, instead of systolic dysfunction, is seen more often among CKD patients who experience SCD [18, 19]. An increase in left ventricular mass index over time was found to be the most potent predictor of SCD death risk in 10-year observational study of hemodialysis patients [20]. The role of primary prevention ICDs among hemodialysis patients with left ventricular hypertrophy and preserved systolic function is worthy of further study.

Ultimately, controlled clinical trials will be needed to determine the potential benefits of ICDs among dialysis patients. The ongoing ICD2 randomized trial may help guide clinical decisions regarding the potential use of ICDs in dialysis patients [21]. While awaiting further data from this and other studies, increased communication between nephrologists and cardiologists is needed to counsel potential ICD recipients about the likelihood of increased risks and reduced benefits compared with estimates obtained from the general population, and to coordinate ICD placement when indicated to reduce the possibilities of vascular access compromise. Newer leadless defibrillator devices such as the subcutaneous implantable defibrillator and the wearable external defibrillator may be especially advantageous among dialysis patients to avoid vascular complications and minimize infectious risks, and these novel therapies should be tested in ESKD patients on dialysis.

There are several limitations of our analysis that should be noted. First, we examined only patients aged 65 years and older enrolled in Medicare; therefore, the generalizability of our findings to younger dialysis patients may be limited. However, this concern is reduced by the observation that only 10% of dialysis patients receiving primary ICDs in the NCDR registry between 2006 and 2007 were <65 years old. Additionally, the United States Renal Data System reported that the mean age of dialysis patients who receive ICDs in the USA was 67 years [5]. Second, our analysis was limited by relatively small numbers of patients, and it is possible that a significant effect was missed due to lack of statistical power. However, this concern is balanced against a large number of events observed in both cohorts, which partially offsets the reduction in power from reduced number of patients. Finally, our findings might be affected by bias by indication or confounding due to imbalance in unmeasured variables such as additional laboratory data or dialysis characteristics. However, this concern is alleviated by our decision to include only variables that were identically defined in both ICD and control cohorts to minimize measurement bias. Additionally, our propensity matching technique was successful at minimizing the absolute standardized difference to <10% across all defined variables, reducing the possibility of residual confounding.

In conclusion, we did not observe a significant association between primary prevention ICDs and reduced mortality among ESKD patients receiving dialysis. Cautious consideration of the potential risks and benefits of ICD implantation in these patients should be undertaken while awaiting the results of more definitive clinical trials. In the absence of more definitive data, optimal care of dialysis patients who have reduced LVEF will require collaboration among care providers in organ transplantation, vascular surgery, cardiology and nephrology.

ACKNOWLEDGEMENT
This work was supported by National Institutes of Health research grants 1R01-HL093071-01A1 to Dr S.M.A. K. from the National Heart, Lung, and Blood Institute and K23-DK098281 to Dr P.H. from the National Institute of Diabetes and Digestive and Kidney Diseases. Results of this study were presented in an abstract at the annual meeting of the American Society of Nephrology, November 2014, in Philadelphia, PA.

CONFLICT OF INTEREST STATEMENT
The Get With The Guidelines-Heart Failure (GWTG-HF) program is provided by the American Heart Association and has been funded in the past through support from Medtronic, GlaxoSmithKline, Ortho-McNeil, and the American Heart Association Pharmaceutical Roundtable. The ICD Registry is an 370 initiative of the American College of Cardiology Foundation with partnering support from the Heart Rhythm Society. Dr G.C.F. reports receiving consultancy fees from Medtronic and honorarium from Boston Scientific.

REFERENCES
Criteria for HNF1B analysis in patients with congenital abnormalities of kidney and urinary tract

Anke Raaijmakers1, Anniek Corveleyn2, Koen Devriendt2, Theun Pieter van Tienoven3, Karel Allegaert4, Mieke Van Dyck1, Lambertus van den Heuvel1, Dirk Kuypers5, Kathleen Claes6, Djalila Mekahl11,∗ and Elena Levtchenko1,∗

1Department of Pediatric Nephrology, UZ Leuven, Leuven, Belgium, 2Department of Human Genetics, UZ Leuven/KU Leuven, Leuven, Belgium, 3Department of Sociology, Vrije Universiteit Brussel, Brussels, Belgium, 4Neonatal Intensive Care Unit, UZ Leuven, Leuven, Belgium, 5Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium and 6Department of Nephrology, UZ Leuven, Leuven, Belgium

Correspondence and offprint requests to: Anke Raaijmakers; E-mail: anke.raaijmakers@uzleuven.be

These authors contributed equally to this work.

ABSTRACT

Background. Congenital anomalies of kidneys and urinary tract (CAKUT) are the most predominant developmental disorders comprising ~20–30% of all anomalies identified in the prenatal period. Mutations in hepatocyte nuclear factor 1-beta (HNF-1β) involved in the development of kidneys, liver, pancreas and urogenital tract are currently the most frequent monogenetic cause of CAKUT found in 10–30% of patients depending on screening policy and study design. We aimed to validate criteria for analysis of HNF1B in a prospective cohort of paediatric and adult CAKUT patients.

Methods. We included CAKUT patients diagnosed in our paediatric and adult nephrology departments from January 2010 until April 2013 based on predefined screening criteria. Subjects presenting with at least one major renal criterion or one minor renal criterion combined with one or more extra-renal criteria in the personal history or a familial history of renal or extra-renal manifestations were considered eligible.

doi: 10.1093/ndt/gfu370
Advance Access publication 13 December 2014