Implantable Cardioverter Defibrillators and Chronic Kidney Disease

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Abstract: Use of implantable cardioverter defibrillators (ICDs) is the treatment of choice for heart failure patients with ejection fraction <35% to prevent sudden cardiac death. Whether this benefit remains among patients with chronic kidney disease (CKD) or end stage renal disease (ESRD) is yet to be elucidated. We conducted a systematic review of studies in PubMed that have investigated the use of ICDs among patients with CKD or ESRD. From the 470 studies identified, we selected 42 for the current review. Patients with CKD/ESRD were more likely to get antitachycardia pacing or shocks and had higher cardiac and/or all-cause mortality compared to patients without CKD/ESRD. These associations had an inverse dose-response effect with worse outcomes with decreasing kidney function. In conclusion, use of ICDs in CKD/ESRD is associated with increased antitachycardia pacing/shocks and mortality suggesting that their routine use in this patient population may be associated with more adverse outcomes than benefits. (Curr Probl Cardiol 2021;46:100639.)

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Introduction

About 37 million people or 15% of the adult population in the United States (US) have chronic kidney disease (CKD), based on the latest statistics from the Centers of Disease Control and Prevention.[1] In addition, approximately 800,000 people have end stage renal disease (ESRD).[2] Of note, patients with CKD/ESRD are associated with a very high burden of heart failure (HF). For example, according to the US renal data system statistics, about 30% of patients with CKD who were 66 years or older had HF in 2015.[3]

Despite significant strides in treatment approaches, HF remains one of the leading causes of death in the US and all over the world.[4] In 2017, HF was a contributory cause in 1 out of every 8 deaths in the US.[4] On the other hand, it is well known that adults with CKD/ESRD have a higher mortality rate compared to age-matched adults without CKD/ESRD.[2] According to the American Heart Association 2019 statistical update, arrhythmias and sudden cardiac death (SCD) account for more than 40% of all deaths among patients with CKD/ESRD.[3,5] Nevertheless, the presence of CKD/ESRD complicates HF treatment and makes the prognosis bleak.

Unfortunately, many SCDs are usually unwitnessed but malignant ventricular arrhythmias are thought to be the main underlying causal factor.[6,7] Implantable cardioverter defibrillators (ICDs) are currently indicated as a prophylactic measure against SCDs among HF patients with left ventricular ejection fraction less than 35%.[8,9] However, it is yet to be elucidated whether this benefit remains among patients with HF and CKD/ESRD. Notably, most studies that have investigated the use of ICDs among patients with diminished kidney function exclude patients with advanced kidney disease especially CKD stage G4-5 and ESRD. These patients are particularly challenging because of technical difficulties regarding access, short- and long-term complications associated with bleeding, infections, and competing causes of death. We sought to investigate whether the use of ICDs among patients with CKD/ESRD is appropriate for primary or secondary prevention of SCDs through a systematic review of the current literature.

Methods

We conducted a systematic review of studies in PubMed that have investigated the use of ICDs among patients with CKD/ESRD. The following Medical Subject Headings (MeSH) terms were used: ("ICD" OR "implantable cardioverter defibrillator" OR "defibrillator") AND ("CKD" OR "chronic kidney disease" OR "kidney failure" OR "ESRD" OR "end

stage renal disease"). We also conducted a manual search for additional studies using references in the manuscripts accrued through the aforementioned MeSH criteria. The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology[10] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statements.[11] All studies that had data on study design, sample, ICD use among participants, renal function, antitachycardia pacing (ATP) events, shocks events, and mortality were included in the current systematic review study.

Results

Our search using the specified MeSH terms showed 470 studies out of which we selected 42 studies with relevant data for the current review study (Fig 1).

Use of ICDs and Antitachycardia Therapy/Shocks

In our review, multiple studies in diverse populations showed that patients with CKD/ESRD have higher rates of appropriate ICD therapy compared to those without CKD/ESRD. Appropriate therapy was defined as ATP or shock events occurring after an experience of ventricular tachycardia or ventricular function episode. On the other hand, inappropriate therapy was defined as ATP/Shock events without ventricular tachycardia or ventricular function episodes.

One of the early studies exploring this association was a single-center retrospective study by Robin et al.[12] who showed a 2.3-fold increased risk of appropriate ICD therapy among patients with ESRD compared to participants without ESRD. However, there were only 19 participants in this study who had ESRD making its findings susceptible to chance observation. A follow-up study by Blumer et al.[13] using data from patients undergoing first-time ICD implantation at the University Hospital Zurich, Switzerland, showed that ICD use in CKD is associated with 59% risk of appropriate ICD therapy. However, this study did not stratify the outcome by the different categories of CKD. Using data from patients who underwent ICD placement at the Creighton University Medical Center, Nebraska, from January 2000 to December 2004, Alla et al.[14] showed that appropriate shock free survival was significantly lower in patients with severe CKD (glomerular filtrate rate [GFR] < 30 mL/min/1.73 m^2) compared to mild disease (GFR > 60 mL/min/1.73 m^2) and concluded that severe, but not moderate (GFR 30-59 mL/min/1.73 m^2), CKD is an

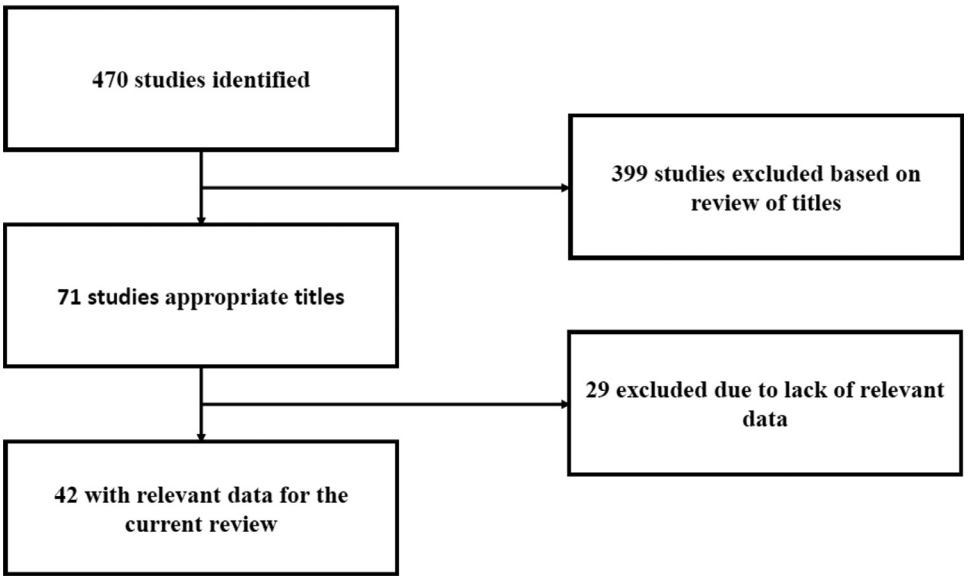

FIG 1. A flow chart of the study selection process for the current review.

independent predictor for time to first appropriate shock. Using data from 321 patients who underwent ICD placement for primary prevention of SCDs between April 2004 and September 2008 at the Regions Hospital University of Minnesota Medical School, Ahmed et al.[15] also showed that CKD is an independent predictor of appropriate ICD therapy. Williams et al.[16] using data from 199 patients in the Duke Electrophysiology Genetic and Genomic Studies biorepository who had undergone ICD between 2002 and 2010 for primary or secondary prevention of SCDs showed that patients with CKD/ESRD had an annual incidence rate of 7.3% per year for appropriate ICD therapy. Notably, Williams et al. also showed that these patients had an incidence rate of 8.0% for inappropriate ICD therapy. Another study using data from 696 patients who underwent ICD placement for primary and secondary prevention at the University of Alabama at Birmingham between January 2002 and September 2007 showed that patients with CKD had a 3.5-fold increased risk for appropriate ICD therapy compared to patients without CKD in primary prevention but not for secondary prevention[17]. Weidner et al.[18] showed that CKD patients had higher rates of ventricular tachyarrhythmias compared to non-CKD patients after 5 years of follow up. In this study, CKD was associated with 1.4-fold higher risk of appropriate therapy (Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI): 1.00-1.83). Interestingly, a prospective study conducted in Brazil among patients who received ICDs for primary and secondary prevention of SCDs, Kiuchi et al.[19] categorized participants into 4 CKD categories (stage 1-4) and showed a dose-response association between CKD category and ATP with the highest incidence/risk for stage 4 CKD patients[19]. Similar findings were also reported for ICD shocks with the highest incidence among patients with CKD stage 4.

Subcutaneous ICDs

Due to concern of complications associated with the use of ICDs in dialysis patients, especially with regard to infection,[20] subcutaneous ICDs have been advocated over traditional transvenous ICDs. However, there are very few studies that have investigated the use of subcutaneous ICDs in ESRD suggest a higher incidence of appropriate therapies among ERSD patients compared to non-ESRD patients. In a small study using data from patients who underwent subcutaneous ICD placement at Emory University hospital between April 2010 to January 2015 (n = 79), El-Chami et al.[21] compared patients on hemodialysis vs no hemodialysis and showed a significantly higher rate of appropriate shocks in the

hemodialysis group (17.9% vs 1.4% per year, $P = 0.02$). In a similarly designed study conducted using data from patients who underwent subcutaneous ICD placement at Hahnemann University Hospital (n = 86), Koman et al.[22] also showed a nominally higher rate of appropriate ICD therapies (22% vs 6%, $P = 0.058$) in hemodialysis patients compared to nonhemodialysis patients. Notably, findings from both studies were based on small sample sizes and their results are not adjusted for covariates making them susceptible to chance observations and bias.

ESRD/CKD and Mortality

Multiple studies have investigated the use of ICDs among patients with CKD/ESRD and their findings consistently show that ICDs are associated with increased mortality. However, very few studies have listed the specific causes of death. One of the early findings came from a small study (n = 95) by Wase et al.[23] who used chart review data of patients who underwent ICD placement between 1997 and 2001 and showed that patients with GFR < 60 mL/min/1.73 m^2 were associated with 2.59-fold increased odds of death compared to those with GFR ≥ 60 mL/min/1.73 m^2 ($P = 0.009$). Interestingly, Wase et al. further showed that half of the deaths were due to a noncardiac or cardiac but nonarrhythmic cause. Similarly, a small case-control study by Hreybe et al.[24] among patients on hemodialysis showed that ICDs are associated with increased risk for mortality (HR = 10.3; $P = 0.03$) and time to mortality (HR = 2.9; $P = 0.02$). However, the cause of death was only determined in less than half of the patients who died (9 out of 22 deaths). Bruch et al.[25] also showed that ICDs are associated with 73% increased risk of death among patients with CKD. However, the study did not list any specific cause of death. A case-control study (n = 78) by Khan et al.[26] among patients with CKD (GFR < 60 mL/min/1.73 m^2)/ESRD and LVEF $\leq 35\%$ showed that ICDs are protective against mortality among patients who were not on hemodialysis but not among those on hemodialysis. However, only half of the deaths had a cause listed with the majority from multiorgan failure.

Findings from multiple studies have showed that decreasing kidney function is associated with increased mortality regardless of ICD placement and that the mortality benefit of ICDs is lost in advanced renal failure. El-Chami et al.,[27] through a retrospective study using data from Emory University hospital, showed that ESRD is an independent predictor of mortality among patients with ICDs. Ahmed et al.[15] also showed that CKD was an independent predictor of appropriate ICD therapy and that appropriate ICD therapy was associated with a 2.3-fold increased

risk for cardiovascular mortality. Hage et al. 2013[17] also showed that patients with CKD had lower survival compared to non-CKD patients. In adjusted results, Hage et al. showed that CKD was an independent predictor for all-cause mortality (HR = 2.08, $P < 0.01$) and ICD therapy (HR = 3.53, $P < 0.01$) in the primary prevention but not in the secondary prevention group. Another retrospective study from Italy among patients on hemodialysis by Genovesi et al.[28] showed that ICD use was associated with increased risk of death. Interestingly, Genovesi et al. showed that patients who qualified for ICD, based on echocardiographic findings, but did not have ICDs placed were associated with even lower survival. Notably, a large prospective cohort study (n = 3542) by Goldenberg et al.[29] showed that the risk of death without receiving appropriate ICD shock therapy at 5 years was 2.5-fold ($P < 0.001$) higher among advanced CKD patients (GFR < 30 mL/min/1.73 m^2 or being on dialysis) compared to those without advanced CKD.

Despite ICD placement, there is evidence of a progressive dose-response association between decreasing renal function and mortality. Using data from the National Cardiovascular Data Registry's ICD registry linked with the Social Security Death Master File, Hess et al.[30] also showed an inverse dose-response association between GFR level and mortality. Similarly, Eisen et al.[31] used data from the Israeli ICD registry and showed that patients with GFR < 30 mL/min/1.73 m^2 had 5.4-fold increased risk of death compared to patients with GFR ≥ 30 mL/min/1.73 m^2. Nakhoul et al.[32] through a large case-control study (cases 1053, controls 9435) showed that ICDs were protective among patients GFR ≥ 30 mL/min/1.73 m^2 but not among those with GFR < 30 mL/min/1.73 m^2. A retrospective cohort study of patients who underwent ICD placement at the Barnes Jewish Hospital between 1999 and 2005 by Cuculich et al.[33] showed an inverse dose-response association between GFR and mortality with patients having GFR of 45-60, 30-45, and <30 mL/min/1.73 m^2 associated with 2.5-, 7.7-, and 40.3-fold increased risk of dying, respectively, compared to patients with GFR > 60 mL/min/1.73 m^2. Hager et al.[34] also showed a stepwise decrease in survival among patients with LVEF ≤ 40% undergoing ICD placement, with patients with CKD stage G4 and G5 having a 3.1- and 10.2-fold increased risk of mortality, respectively, compared to patients in CKD stage G1. There was no statistically significant difference in mortality between patients in stages G2 and G3 compared to those in G1. Alla et al.[14] in a stratified study by GFR (≥ 60, 30-59, <30 mL/min/1.73 m^2) showed an inverse dose-response association between kidney function and mortality with the highest mortality in the severe CKD group (GFR < 30 mL/min/1.73 m^2). Using data

from the Duke Electrophysiology Genetic and Genomic Studies biorepository, Williams et al.[16] showed 48% increased risk of all-cause mortality for every 10 mL/min/1.73 m^2 reduction in GFR despite ICD placement.

For greater statistical power, some investigators have combined data from multiple studies to get a better estimate of the association between use of ICDs and mortality in CKD/ESRD. Korantzopoulos et al.[35] combined data from 11 observational studies and showed that ICDs are associated with increased mortality (HR = 3.49; 95% CI: 2.82-4.21) among patients with CKD. Similarly, Makki et al.[36] combined data from 15 studies and showed that CKD was associated with 2.86-fold increased risk of death among patients with CKD despite placement of ICDs. A more recent meta-analysis by Fu et al.[37] combined data from 11 studies and showed that ICDs are protective against mortality among patients with CKD (HR = 0.78; 95% CI: 0.68-0.92). Similarly, Shurrab et al.[38] combined 11 studies and also showed that ICDs are protective against mortality in patients with CKD (OR = 0.66; 95% CI: 0.45-0.98). Focusing on patients with ESRD, Sakhuja et al.[39] combined data from 7 studies and showed that ICDs are associated with 2.67-fold increased risk of death among patients on hemodialysis.

Interestingly, a meta-analysis (n = 2867) combining data from 3 randomized controlled trials (MADIT-I, MADIT-II, and SCD-HeFT) showed that ICDs are associated with increased survival among people with GFR $\geq$ 60 mL/min/1.73 m^2 but not among patients with GFR $<$ 60 mL/min/1.73 m^2.[40] Notably, recent findings from the ICD2 trial (n = 200), a randomized controlled trial among patients with ESRD on HD with LVEF $\geq$ 35% that was conducted at Leiden University Medical Center, Netherlands, showed no mortality benefit after ICD placement.[41] However, the study had to be stopped prematurely by the data and safety monitoring board due to futility.

Discussion

Our systematic review of existing studies has shown that the use of ICDs for primary and/or secondary prevention of SCDs among patients with CKD/ESRD is associated with increased ATP and shock events. In fact, studies that looked at this association by GFR levels have shown an inverse dose response association between GFR level ATP/shock events. Moreover, studies that looked at the impact of ICD use on mortality among patients with CKD/ESRD have not shown a mortality benefit.

It is important to note that the current recommendations for ICD use are based on early studies that showed reduced mortality and this benefit

was assumed to apply in patients with severe kidney function.[42,43] However, patients with ESRD and CKD stage G4-5 were frequently excluded from these studies[44] and ICD use in this patient population was mainly based on extrapolation. Interestingly, findings from more recent studies specifically looking at patients with severe renal dysfunction have failed to show a mortality benefit in this patient population. In fact, a recent randomized controlled study, the ICD2 trial, was stopped prematurely by the data and safety monitoring board due to futility.[41] The current systematic review highlights a need to re-examine current recommendations on the use of ICDs among patients with decreased kidney function.

Worsening kidney function is associated with multiple cardiovascular changes that could partly explain the increased risk for arrhythmias CKD/ESRD. Left ventricular hypertrophy (LVH) is the most common cardiovascular complication in CKD with worsening kidney function associated with increasing prevalence of LVH.[45,46] In addition, there is a well-established association between LVH and cardiac arrhythmias and this could partly explain the higher prevalence of ventricular arrhythmias with worsening kidney function.[47] Furthermore, CKD is associated with QTc prolongation which in turn could predispose patients to ventricular arrhythmias.[48] Electrolyte disturbances are also common among patients with CKD/ESRD further increasing their risk for arrhythmias.[18,49] Moreover, the rapid flux in potassium and calcium during hemodialysis could cause destabilizing changes in the myocardium thus creating a proarrhythmogenic state.[18,50] Notably, hemodialysis has been associated with myocardial stunning which could contribute to worse heart function and consequently, to a proarrhythmogenic state.[51] In addition, elevated levels of PTH and phosphorus in CKD/ESRD patients contribute to hypertrophy and myocardial fibrosis, which creates electrical instability and thus increased risk for ventricular arrhythmias.[52] Sympathetic hyperactivity has also been cited as a possible cause of ventricular arrhythmias in CKD patients, it is possibly the result of renal damage.[53] Uremic toxins such as FGF23 and indoxyl sulfate have been shown to have an arrhythmogenic effect on cardiomyocytes and cause adverse cardiovascular events in some studies.[54,55]

Multiple factors could contribute to the increased mortality associated with decreasing kidney function. Worsening renal function could be associated with decreased efficiency of ICDs.[23] In addition, competing causes death are known to increase with decreasing renal function which could further contribute to the observed increased mortality. Furthermore, the use of ICDs in CKD is associated with increased risk for infection which could to decreased survival.[20] Of note, patients with CKD are likely to be

older, with multiple comorbidities, and on multiple medications; all this complicate treatment and increase mortality.[14] Moreover, the factors that contribute to the increased risk for arrythmias in CKD/ESRD could also potentially increase the risk for mortality.

According to the current American Heart Association/American College of Cardiology guidelines, ICD use is indicated in patients who have at least 1-year survival with reasonable quality of life.[9] Our review findings consistently showed a trend of increasing ATP/shock events with decreasing renal function in a dose-response association. Of note, ATP/shock events are not benign, especially when they happen to a conscious patient, and may require hospitalization for further investigation and increased utilization of healthcare resources.[56,57] Moreover, increased ATP/shock events are associated with increased mortality and increased hospitalizations which further limit patients' quality of life and increase healthcare spending.[58]

Conclusion

Our systematic review of existing data from studies on the use of ICDs in patients with CKD/ESRD shows that ICDs in this patient population are associated with increased ATP/shocks and mortality perhaps due to arrhythmias, infection, electrolyte imbalance or competing causes of death. This suggests that their routine use in patients with renal disease may be associated with more adverse outcomes than benefits. Larger and better designed studies to further investigate the usefulness of ICDs in CKD and ESRD are warranted.

Author Contributions

Study concept and design: Khouzam. Acquisition of data: Kiage, Latif, and Craig. Drafting the manuscript: Kiage, Latif, and Craig. Critical revision of manuscript for important intellectual content: All authors. Final manuscript approval: All author.

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