Do Implantable Cardioverter Defibrillators Reduce Mortality in Patients With Chronic Kidney Disease at All Stages?

An Updated Meta-Analysis

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Summary

The benefits of implantable cardioverter defibrillator (ICD) implantation in chronic kidney disease (CKD) patients with high sudden cardiac death (SCD) risk are uncertain. To clarify the effects of receiving an ICD in CKD patients, we conducted this meta-analysis to identify the effects of ICDs on patients with CKD, including those on dialysis. We searched the Cochrane library, EMBASE, PubMed, and clinical trials for studies published before July 2016. Eleven studies including 20,196 CKD patients were considered for inclusion. The pooled analysis suggested that patients with an estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m² would benefit from receiving treatments with ICDs compared with patients without an ICD device (aHR = 0.77; 95% confidence interval [CI], 0.63 to 0.95). This is the first report of a subgroup analysis on the survival rate of ICD implantation in CKD patients according to an eGFR group. The subgroup analysis indicated a similar protective association of ICDs in stage 3 CKD patients (aHR = 0.71; 95%CI, 0.61 to 0.82) compared with the control group. However, there was no significant improvement in all-cause mortality in stage 4 CKD patients (aHR = 1.02; 95%CI, 0.75 to 1.37) or stage 5 CKD patients (aHR = 0.80; 95%CI, 0.60 to 1.31). This is the first meta-analysis reporting that ICD implantation reduces all-cause mortality in stage 3 CKD patients. However, the data do not indicate there is any benefit to ICD implantation in stage 4 or 5 CKD patients. (Int Heart J 2017; 58: 371-377)

Key words: Dialysis, Estimated glomerular filtration rate, Sudden cardiac death

Chronic kidney disease (CKD) is a rapidly increasing worldwide health problem with a high mortality rate and a high economic burden that affects millions of people.1,2 It is defined based on the presence of kidney damage or a glomerular filtration rate (GFR) < 60 mL/minute per 1.73 m² for ≥ 3 months, irrespective of cause. CKD is closely related to cardiovascular disease, such as atrial fibrillation and heart failure.3 In many clinical trials, worsening kidney function has been verified as an independent risk factor for SCD. Moreover, the risk of SCD increases with the progression of renal function deterioration.4,5 Furthermore, SCD is one of the main causes of mortality in CKD patients, especially those who undergo dialysis.6 Implantable cardioverter defibrillators (ICDs) have been proven to prevent SCD by terminating potentially lethal ventricular tachyarrhythmias in patients with congestive heart failure and a left ventricular ejection fraction (LVEF) ≤ 35%.7,8 However, there are no clinical randomized control trials (RCT) providing evidence for patients with CKD or people on dialysis.

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This study was supported by the National Basic Research Program of China [973 Program: 2013CB531100], and the National Natural Science Foundation of China [8153000545, 81530013, 81370288].

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Received for publication August 1, 2016. Revised and accepted October 6, 2016.

Released in advance online on J-STAGE May 23, 2017.

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Editorial p.303

In patients with CKD, the elevated risk of SCD is clear, but the ability of ICDs to prevent SCD is uncertain. Considering the high SCD risk in patients with CKD, ICD implantation may be helpful in reducing SCD occurrence. ICDs have played an important role in reducing mortality in CKD patients in numerous studies, particularly in patients on dialysis. Because the evidence supporting their utility in improving survival is conflicting, a meta-analysis is necessary to identify the effects of ICD implantation in patients with CKD, including patients on dialysis.

In 2014, a meta-analysis showed that an ICD implantation was associated with a survival benefit in CKD patients (aHR = 0.65, 95% CI, 0.47 to 0.91). However, another meta-analysis including patient-level data from 3 RCTs of primary prevention ICD implantation has shown no significant survival...
benefit of ICD implantation compared with controls in 1,040 patients with an estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m² not on dialysis (aHR = 0.92, 95% CI, 0.74 to 0.92). These meta-analyses have predominantly included patients recruited many years ago. Moreover, these meta-analyses did not conduct a subgroup analysis in patients with severe renal dysfunction, especially in dialysis patients. Furthermore, several new studies have investigated the effect of ICD implantation on the survival rate of patients with CKD. In the present analysis, we performed an updated meta-analysis on the effect of ICD implantation on the survival rate of patients with CKD. Moreover, this is the first report of a subgroup analysis on the survival rate of ICD implantation in patients with eGFRs < 60 mL/minute/1.73 m² according to an eGFR group.

**METHODS**

The methodology and presentation of the meta-analysis were based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement.

**Literature search:** Using electronic and manual retrieval methods, we searched the Cochrane library, EMBASE, PubMed, and Clinical trials for studies published before July 2016. Searches were limited to articles published in English. We performed the search with the following keywords and subject terms: ‘chronic kidney disease’, ‘dialysis’, ‘end stage renal disease’, ‘renal insufficiency’, ‘renal failure’, ‘hemodialysis’, ‘peritoneal dialysis’, ‘sudden cardiac death’, and ‘implantable cardioverter defibrillator’.

**Inclusion and exclusion criteria:** For inclusion in the meta-analysis, studies needed to satisfy the following criteria: 1) inclusion of patients with an eGFR < 60 mL/minute/1.73 m², including patients on dialysis; 2) ICD implantation used to treat CKD patients; 3) a follow-up period of at least 12 months; 4) an analysis of all-cause mortality; and 5) inclusion of patients with an indication to receive an ICD.

Studies with the following characteristics were excluded: 1) lack of a control group, 2) inclusion of patients with kidney transplants, 3) publication in only abstract form, and 4) inclusion of patients receiving cardiac resynchronization therapy or with a cardiac resynchronization therapy defibrillator device.

**Quality assessment of primary studies:** All studies were evaluated for quality using the Newcastle-Ottawa Scale. This risk of bias in the cohort studies was assessed on the basis of the following 3 terms: 1) selection of cohorts, 2) comparability of cohorts, and 3) assessments of outcome.

**Data extraction:** All papers retrieved by the search strategy were screened by two reviewers (Linghua Fu and Qiongqiong Zhou) independently. The first phase of screening was performed by reading abstracts, and the second phase of screening involved reviewing the full text. Ultimately, articles meeting the eligibility criteria were chosen. Disagreement was settled by discussion with a third author (Wengen Zhu).

From each study, extracted information included the following elements: 1) name of the first author, 2) year of publication, 3) country, 4) study design, 5) inclusion criteria, 6) total number of patients, 7) proportion of male patients, 8) age, 9) LVEF, 10) duration of follow-up, and 11) all-cause mortality.

**Determination of eGFR group:** Renal function was determined by calculating eGFRs at study enrollment. The equation used to calculate the eGFR was that of the Chronic Kidney Disease Epidemiology Collaboration (commonly known as the CKD-EPI), which takes into account sex, age, ethnic origin, and serum creatinine concentration. Based on the eGFR or evidence of damage, CKD is classified into 5 stages. A previous meta-analysis has shown that an eGFR < 60 mL/minute/1.73 m² is an independent predictor of all-cause mortality. In this meta-analysis, we only focused on patients with an eGFR < 60 mL/minute/1.73 m².

**Statistical analysis:** Statistical analysis was performed using Review Manager Version 5.3 (Copenhagen, The Nordic Cochrane Center, The Cochrane Collaboration, 2014, http://tech.cochrane.org/revman). The effect measurement estimate chosen was the adjusted hazard ratio (aHR), and risk ratios or odd ratios in the studies were considered to be adjusted hazard ratios. A Mantel-Hansel estimate was applied to yield a pooled aHR using a fixed-effect model, whereas a DerSimonian–Laird estimate used a random-effect model. Cochran’s chi-square test and I² statistic were measured to evaluate the heterogeneity among included studies. I² values of 25%, 50%, and 75% were considered to represent low, moderate, and large heterogeneity, respectively. If I² < 50% or P > 0.10, the fixed effects model was used for meta-analysis. If this was not the case, a random effects model was selected. The correction for publication was assessed by funnel plot analysis. The statistical significance threshold was set at P < 0.05.

**RESULTS**

**Search results:** A total of 324 potential studies were identified through the above-mentioned literature search strategy. A total of 279 records were excluded by screening based on the title and abstract, 37 records were excluded for other reasons, and 8 articles remained for full-text review. Three studies were obtained from a previously published patient-level meta-analysis. Finally, 11 eligible studies (7,8,11-13,18-23) from 9 articles (10-13,18-22) were included. The search steps are illustrated in Figure 1.

**Characteristics of included studies:** Eleven studies (7,8,11-13,18-23) enrolled 20,196 CKD patients (4,178 patients receiving ICD therapy and 16,018 patients in the control groups), and the duration of the studies ranged from 12 months to 96 months. There were 5 studies (11,18,19,21,22) involving 18,149 patients on dialysis. Most of the participants were male (62.9%). The mean age was 66.3 years old. Patients were implanted with an ICD for primary prevention in 7 studies (11,13,18,20-22) and secondary prevention in 4 studies (19,20,22). Among these studies, most were conducted in the United States. The main characteristics of the included studies are shown in Table I.

**Study quality:** The methodological quality of the included studies was generally good, with 7 to 9 stars and without high risk of bias.

**Survival of CKD patients with ICD implantation versus CKD patients without ICD implantation:** Eleven studies (7,8,11-13,18-23) enrolled 20,196 CKD patients, with 4,178 patients receiving ICD therapy and 16,018 patients in the control groups. Five studies (12,18-21) reported benefits in patients who had received an ICD implantation compared with patients who did not receive an ICD. Six studies (7,8,11,13,22,23) did not describe the association.
The pooled analysis suggested that patients with an eGFR < 60 mL/minute/1.73 m² benefited from receiving an ICD implantation compared with patients who did not receive an ICD (aHR = 0.78; 95%CI, 0.66 to 0.92) (Figure 2). High heterogeneity existed across the 11 studies (I² = 80%, P = 0.003).

Patients in stage 3 CKD (eGFRs 30-59 mL/minute/1.73 m²) Four studies involving 1441 patients reported the survival of patients in stage 3 CKD. The pooled analysis (Table II) showed a higher survival rate in stage 3 CKD patients with ICDs compared with the control group (aHR = 0.71, 95%CI, 0.61 to 0.82). We found moderate heterogeneity for all-cause mortality across the studies (I² = 47, P < 0.00001).

### Table I. Characteristics of the Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study or group</th>
<th>Country</th>
<th>ICD indication</th>
<th>eGFR (mL/minute/1.73m²)</th>
<th>Group</th>
<th>Simple</th>
<th>LVEF (%)</th>
<th>Age (years)</th>
<th>Men (%)</th>
<th>Follow-up (months)</th>
<th>Newcastle-Ottawa Scale</th>
</tr>
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<tr>
<td>Charytan et al 2011</td>
<td>USA</td>
<td>Secondary</td>
<td>Dialysis</td>
<td>ICD</td>
<td>2232</td>
<td>27</td>
<td>65.3</td>
<td>64.1</td>
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<td></td>
<td></td>
<td></td>
<td>Non-ICD</td>
<td>8928</td>
<td>27</td>
<td>65.0</td>
<td>65.8</td>
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<td></td>
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<tr>
<td>Herzog et al 2005</td>
<td>USA</td>
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<td>Dialysis</td>
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<td></td>
<td>Non-ICD</td>
<td>5582</td>
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<td>63.1</td>
<td>46.1</td>
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<tr>
<td>Khan et al 2010</td>
<td>USA</td>
<td>Primary</td>
<td>GFR &lt; 60</td>
<td>ICD</td>
<td>18</td>
<td>22</td>
<td>69</td>
<td>83.0</td>
<td>31</td>
<td>8</td>
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<td></td>
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<td>Non-ICD</td>
<td>15</td>
<td>26</td>
<td>71</td>
<td>53.0</td>
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<tr>
<td>Hiremath et al 2010</td>
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<td>Both</td>
<td>Dialysis</td>
<td>ICD</td>
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<td>20.4</td>
<td>70.3</td>
<td>84.0</td>
<td>29</td>
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<td>69.9</td>
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<td>Pun et al 2015</td>
<td>Canada</td>
<td>Primary</td>
<td>Dialysis</td>
<td>ICD</td>
<td>186</td>
<td>25</td>
<td>74</td>
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<td>Non-ICD</td>
<td>86</td>
<td>25</td>
<td>75</td>
<td>69.0</td>
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<tr>
<td>Singh et al 2014</td>
<td>USA</td>
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<td>eGFR &lt; 30</td>
<td>ICD</td>
<td>108</td>
<td>N</td>
<td>69.0</td>
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<td>12</td>
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<td>108</td>
<td>N</td>
<td>74.7</td>
<td>70.0</td>
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<tr>
<td>Nakhoul et al 2015</td>
<td>USA</td>
<td>Primary</td>
<td>eGFR &lt; 60</td>
<td>ICD</td>
<td>631</td>
<td>27.2</td>
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<td>Non-ICD</td>
<td>631</td>
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<td>72.0</td>
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<td>Genovesi et al 2015</td>
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<td>Dialysis</td>
<td>ICD</td>
<td>52</td>
<td>N</td>
<td>69.4</td>
<td>78.8</td>
<td>96</td>
<td>8</td>
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<td>Non-ICD</td>
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<td>N</td>
<td>71.8</td>
<td>74.8</td>
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<tr>
<td>Pun et al 2014</td>
<td>USA, Canada</td>
<td>Primary</td>
<td>Dialysis</td>
<td>ICD</td>
<td>541</td>
<td>23.5</td>
<td>67.1</td>
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<td>29.1</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Non-ICD</td>
<td>499</td>
<td>23.5</td>
<td>66.2</td>
<td>80.2</td>
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</tbody>
</table>

ICD indicates implantable cardioverter defibrillator; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and N, none. Pun’s article including MADIT-I 1996, MADIT-II 2002, SCD-HeFT 2005.
Patients in stage 4 CKD (eGFRs < 30 mL/minute/1.73 m² not receiving dialysis therapy) Two studies\(^{12,13}\) enrolled 403 CKD patients, with 204 patients receiving ICD therapy and 199 patients in the control group. In this analysis (Table II), there was no significant improvement in all-cause mortality in stage 4 CKD patients after ICD implantation (aHR = 1.02, 95%CI, 0.75 to 1.37), and there was low heterogeneity across these studies (\(I^2 = 19\%\), \(P = 0.53\)).

Patients in stage 5 CKD (patients on dialysis) There were 5 studies\(^{11,18,19,21,22}\) involving 18,149 patients receiving dialysis treatment, with 2,280 patients with ICD implantation and 14,765 patients in the control groups. In patients receiving dialysis treatment, a higher survival rate has been reported in the patients with ICD implantation in 3 studies,\(^ {18,19,21}\) whereas other studies\(^ {11,22}\) have shown an inconsistent conclusion. The pooled analysis (Table II) showed no difference between patients with ICD implantation and those without (aHR = 0.80, 95%CI, 0.60 to 1.31). There was high heterogeneity across these studies (\(I^2 = 89\%\), \(P < 0.00001\)).

Publication bias: Publication bias was assessed by subjective determination of funnel plot asymmetry. A funnel plot (Figure 3) suggested the absence of major publication bias.

**Discussion**

Current guidelines do not specifically consider eGFRs or the level of renal function in the decision to implant an ICD for primary or secondary prevention.\(^ {25,26}\) Two previous meta-analyses\(^ {9,10}\) have produced opposite conclusions and did not perform a subgroup analysis in patients with an eGFR < 60 mL/minute/1.73 m². This updated meta-analysis on the survival rate of ICD implantation in CKD patients is the largest study of its kind to date, accumulating information for over 20,196 patients and 11 studies. No previous article has described the differences in cardiac death between an ICD group and a control group, but all articles described the difference in all-cause mortality between these 2 groups. Therefore, we analyzed the effect of ICD implantation on the survival rate of patients with all-cause mortality. Our meta-analysis firstly demonstrated reduced all-cause mortality in patients receiving ICD implantation compared with the control group in stage 3 CKD patients. However, the association has not been confirmed in stage 4 or stage 5 CKD patients. A significant heterogeneity was apparent across the 11 studies. We found that high heterogeneity was partially related to kidney function. The subgroup analysis found a moderate or low heterogeneity association between all-cause mortality and ICD implantation in patients with stage 3 or 4 CKD; this result did not include dialysis patients.

**Stage 3 CKD patients with ICD implantation:** Compared with patients without CKD, CKD patients have more electrocardiographic abnormalities, including a wide QRS complex and atrioventricular conduction delay.\(^ {27}\) Compared with patients with an eGFR > 60 mL/minute/1.73 m², patients with an eGFR < 60 mL/minute/1.73 m² show a significantly higher rate of suffering from electrical storm (\(P = 0.003\)).\(^ {28}\)
The pooled analysis showed the significant benefit of ICD implantation in the prevention of SCD in stage 3 CKD patients (aHR = 0.71, 95%CI, 0.61 to 0.82). Bonato, et al have found that ventricular arrhythmias occurred in 35% of CKD patients who were assessed by 24-hour electrocardiograms. Patients with CKD have an increased risk of SCD due to numerous risk factors, such as left ventricular hypertrophy, autonomic imbalance, and rapid fluid and electrolyte shifts. At the cellular level, the cardiac sodium channel, the potassium channel, and calcium handling are abnormal in CKD rats, leading to increased vulnerability to early after depolarization and ventricular arrhythmias. Inherited factors are also considered to be a risk factor for SCD among CKD patients. Based on the reasons explained above, we were not surprised to obtain this result in stage 3 CKD patients.

**Stage 4 CKD patients with ICD implantation:** A lower eGFR is associated with an increased risk of SCD. Each 10 mL/minute/1.73 m² reduction in an eGFR increases the risk of all-cause mortality by 16% and SCD by 17%. Additionally, severe (eGFRs < 30 mL/minute/1.73 m²) but not moderate (eGFRs between 30 and 59 mL/minute/1.73 m²) CKD is an independent predictor of time to first appropriate shock.

However, the pooled analysis failed to indicate a similar protective association of ICD implantation in stage 4 CKD patients. Several reasons may explain why ICD implantation does not extend the life of stage 4 CKD patients. First, patients with stage 4 CKD are less responsive to ICD implantation due to an increase of defibrillation thresholds in patients with worsening renal failure. Increasing defibrillation thresholds to ICD therapy with declining renal function may be an important mechanism responsible for the observed attenuation of the device benefit among patients with severe renal disease in the present analysis. Second, the level of complications following device implantation is high, including an increased risk of device-related infections and non–cardiac related death, which may erode the survival benefit afforded by ICD implantation. Compared with patients with stage 3 CKD, patients with stage 4 or 5 CKD have higher rates of hematoma after ICD implantation. The risk of death after ICD implantation is proportional to the severity of CKD. Third, patients with stage 4 CKD sustain higher comorbidity burdens, such as heart failure, which may offset the potential benefit of ICD implantation.

**Patients on dialysis (stage 5 CKD) with ICD implantation:** Patients on dialysis often present with repolarization abnormalities, including a prolonged QT interval, microvolt T wave alternans, and abnormal T wave morphology. Moreover, repolarization abnormalities have been associated with SCD and all-cause mortality in patients on dialysis. Patients on dialysis have a 10 to 20-fold higher risk of suffering from SCD than patients without CKD. SCD is the most common cause of death in dialysis patients, accounting for 20-35% of all-cause mortality in patients on dialysis. Patients on dialysis are particularly vulnerable to SCD. The mechanisms that underlie SCD in dialysis patients are complicated, and many factors have been suggested to explain the increased arrhythmic risk in patients on dialysis. Left ventricular hypertrophy, which is a common echocardiographic finding in dialysis patients, has been linked to an increased risk of SCD as an arrhythmogenic substrate in CKD. Metabolic and electrolyte abnormalities, as well as fluid overload, may promote arrhythmias and increase the risk of SCD. Additionally, patients on dialysis are often characterized by increased sympathetic activity and activation of the renin–angiotensin–aldosterone system. Theoretically, an ICD implantation has a protective effect in reducing all-cause mortality in patients on dialysis. However, there is no significant advantage from receiving ICD implantation in patients on dialysis compared with controls.

There are some reasons for the limited benefits of ICD implantation in patients on dialysis. A large number of sudden cardiac arrest events that occur in dialysis are not due to ventricular fibrillation (VF) or ventricular tachycardia (VT) and would not be expected to respond to defibrillation therapy. Although the most common causes of patients dying of SCD are VF and VT, whether patients on dialysis exhibit the same proportion of arrhythmic events during SCD is unknown. Wong and colleagues conducted a study of 50 dialysis patients who received an implantable cardiac monitor. After a mean follow-up period of 18 months, they found that in patients on dialysis who had preserved left ventricular function, the vast majority of SCD events were due to bradycardia and asystole rather than to malignant ventricular arrhythmias. CKD was associated with a reduced heart rate response to subcutaneous nerve activity and conduction system diseases. Histological studies have shown myocardial calcification in CKD rats that involved the conduction system. An abrupt reduction of sympathetic tone precedes atrioventricular block, ventricular arrhythmia, and sudden death of the CKD rats.

An ongoing multicenter, observational, prospective cohort study of 66 patients with implantable loop recorders undergoing long-term hemodialysis may help to investigate arrhythmias and their association with SCD in dialysis patients. In an autopsy study, the majority of SCD events have been found to be due to vascular events instead of arrhythmic events. Moreover, patients on dialysis have a high risk of per-procedural complications, and approximately 5% of patients on dialysis have device infections during each year of follow-up. Furthermore, cardiovascular ICD implantation-related hospitalization is increasing among patients on dialysis and is associated with higher in-hospital mortality. Compared with controls, dialysis patients have markedly increased bleeding and device-related infections (12.5% versus 0.2%, P < 0.00001). In light of this information, the high incidence of complications may offset the potential survival benefit of ICD implantation in patients with stage 5 CKD. Finally, the presence of comorbidities such as atrial fibrillation, wide QRS, older age, and severe heart failure may counteract the benefit of ICD implantation in dialysis patients.

**Study limitations:** Several study limitations may affect the validity of this meta-analysis. First, all the studies included in this meta-analysis were observational studies. The findings therefore may have been influenced by selection bias, attrition bias, or other factors present in observational studies. There are no RCTs assessing the influence of ICD implantation on survival rates in CKD patients. The ongoing ICD2 trial may help to guide clinical decisions regarding the potential use of ICDs in dialysis patients. Future RCTs should be conducted to observe whether CKD patients should receive ICDs. Second, the data showing an association between ICD implantation and CKD demonstrated significant heterogeneity in patients on dialysis, which cannot be fully explored. Third, we focused on only all-cause mortality; other terms including cardiovascular
mortality, inappropriate shocks, and bleeding were not discussed. Fourth, the participants were nearly all individuals of European ancestry, and the effect of ICD implantation on Asians was not observed in the present study. Finally, eGFR data were based on serum creatinine, age, sex, and muscle mass. Nevertheless, age and sex can also affect survival in patients with ICD implantation.

**Conclusions:** This is the first meta-analysis reporting that ICD implantation reduces all-cause mortality in stage 3 CKD patients. However, the survival benefit of ICD implantation in CKD patients with stage 4 or 5 is not supported by these data. Future RCTs are needed to assess whether CKD patients should receive ICD therapy.

**DISCLOSURE**

**Competing interests:** None declared.

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