

# Shades of Grey: The Conundrum of Implantable Defibrillators in Individuals with Advanced CKD

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CKD contributes significantly to the global health burden, with a prevalence estimated at 10%–12% of individuals worldwide (1). Morbidity and mortality rates remain high in these individuals (2–5), and they are at a particularly magnified risk of sudden cardiac death (SCD) (6,7). To wit, in a study by Pun *et al.* (6) of 19,440 patients with coronary artery disease undergoing cardiac catheterization, declining renal function was associated with a progressive increase in risk of SCD. Similarly, in a seminal study, Anavekar *et al.* (3) studied 14,527 patients with acute myocardial infarction and found an increase in risk of death because of cardiovascular etiologies and higher rates of cardiac arrest at lower eGFRs.

There appears to be lower utilization, even when objective indications are present, of standard cardiovascular diagnostic and interventional procedures in individuals with CKD compared with those without CKD, despite the potential for increased benefits in this high-risk group (8). Whether lower utilization represents a nihilistic bias, a phenomenon dubbed as renalism, (9) is uncertain. Increased use of standard cardiovascular therapies in patients with CKD may be associated with lower mortality (10); however, evidence supporting the short- and long-term efficacy of standard therapies or analyzing the risk-to-benefit ratio in this subpopulation is lacking given the routine exclusion of individuals with CKD and ESRD from cardiovascular trials (11).

Implantable cardioverter defibrillators (ICDs) would seem to be an intuitive therapeutic option for the primary prevention of SCD in the CKD population given the well established mortality reduction when used for this purpose in individuals with coronary artery disease or heart failure and reduced left ventricular ejection fraction (12,13). There are, however, persistent concerns regarding their efficacy and survival benefit in the CKD population, particularly in advanced CKD, because of a scarcity of randomized data in this population. Additionally, a limited number of observational studies suggest that the presence of CKD is associated with a reduced survival benefit and an elevated rate of health care resource utilization after ICD implantation compared with individuals with preserved renal function (4,14).

In this edition of *CJASN*, a new analysis by Nakhoul *et al.* (15) makes an important attempt at addressing the

deficiencies in existing data. Using a retrospective cohort design, the authors provide key insights on the risks and benefits of ICD therapy in the setting of varying levels of renal dysfunction. This large cohort of 1053 patients with CKD, who had ICDs placed for primary prevention of SCD, offers a comprehensive study of a diverse population with sufficient follow-up for the observation of primary outcomes. Strict propensity score matching of controls in combination with both adjusted and unadjusted Cox proportional hazard models were used in the analysis to address baseline differences in the cohort and adjust for confounding. Similarly, a sensitivity analysis of the full (unmatched) study cohort used a primary multivariable regression model without matching to assess outcomes. No observational study can guarantee freedom from residual confounding or indication bias—in this case the possibility that, despite similar overall comorbidity burdens, the decision to implant or withhold ICDs was clinically driven and motivated by unmeasured differences in risk, clinical indication, or contraindication to ICD placement, which is compatible with the small but persistent postmatch between-group differences in age and history of ventricular arrhythmia. However, reasonably consistent results across the myriad analytic methods used by the authors of the study provide reassurance about the robustness of their results. Importantly, use of an ICD was associated with lower mortality among patients with CKD stage 3, but no such association was present for eGFR < 30 ml/min per 1.73 m<sup>2</sup>. Furthermore, in sensitivity analyses including patients with ICD placement before diagnosis of CKD or those with known CKD at the time of ICD placement, the direction of effect estimates consistently suggests an attenuation of benefit in advanced CKD; however, the interaction between CKD stage and ICD placement did not achieve statistical significance ( $P=0.11$  and  $P=0.20$ , respectively).

In short, the authors convincingly demonstrate a reduced efficacy from ICD placement as CKD progresses with uncertain benefits in those with advanced CKD. This is consistent with prior conclusions from Pun *et al.* (16) and Charytan *et al.* (17) on ICD placement for primary prevention in patients with ESRD on dialysis. Interestingly, Hess *et al.* (18) previously demonstrated that 1-year death rates after ICD placement was 20% higher in patients with eGFR < 30 ml/min per

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1.73 m<sup>2</sup> when compared with patients without CKD. A higher comorbidity burden in the CKD population and hence a greater, competing risk for death from nonsudden causes may explain this attenuation of ICD benefit. In other words, ICD benefit may be limited in advanced CKD if arrhythmic death accounts for a lower proportion of overall mortality among individuals with CKD despite the higher overall mortality rate and higher incidence of both sudden and nonsudden cardiovascular death and death from noncardiovascular causes (19). Alternatively, the benefits of ICD implantation in advanced CKD, particularly in patients on dialysis, compared with those with preserved renal function may be limited by a differential defibrillation threshold in the setting of advanced myocardial fibrosis and capillary rarefaction (20), frequent electrolyte shifts (5), and occurrence of noncardiovertible rhythms such as bradycardia (21) and asystole. Finally, advanced CKD may increase the likelihood of short- and long-term complications from ICDs as a result of an increased risk of bleeding and infection (16,22), with mortality risks further increased when ICD replacement is required (23). Each of these factors may limit utility of ICDs in CKD and are important considerations for clinicians when assessing the value of invasive or costly therapies in this population.

Several weaknesses of the analysis should be noted. These include absence of information on differences in duration of renal dysfunction between the patients and controls, which could have introduced a length-time bias. Further, only 60% of patients with ICD could be matched, thereby limiting the reliability and generalizability of the primary analysis. As previously mentioned, age and ventricular arrhythmias were not well matched in the propensity score and had to be included as factors in the adjusted models. In particular, this raises the question of whether, despite careful chart review, some patients in fact had ICD placement for secondary rather than primary prevention. Finally, data were missing on the cause of death; therefore, the article leaves unanswered the important question of whether the efficacy of ICDs at preventing death from arrhythmia is preserved in CKD but masked by a high incidence of nonarrhythmic death, as previously noted. It is important to note that details regarding prior history of myocardial infarction, hospitalizations for heart failure, and admissions to nursing facility were lacking, which is a reminder that the results of this study should be extrapolated cautiously beyond the specified patient population.

Despite these limitations, the new analysis by Nakhoul and coauthors provides a strong argument for equipoise regarding the benefits of using ICDs for the primary prevention of SCD in advanced CKD. In conclusion, clinicians must be aware of important differences between patients with and without CKD and should carefully assess both the risk and benefit of standard therapies within the context of the complexities of CKD. In the case of ICDs for primary prevention, the best evidence consistently suggests, at most, a limited benefit from their use. High-quality randomized trials inclusive of patients with moderate and advanced CKD are needed to help nephrologists and cardiologists better understand the risks and benefits of standard cardiovascular therapies, including but not limited to ICDs, in the growing CKD population.

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