Defibrillator Therapy in Chronic Kidney Disease
Is It Worth It?

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Chronic kidney disease (CKD), affecting >6% to 9% of the US population, is a major public health problem that is increasing in incidence. Because of the overlapping clinical comorbidities of age, diabetes mellitus, atherosclerotic disease, and hypertension, heart failure (HF) and CKD are both inextricably linked and synergistic. CKD and HF often coincide, whereas the overall prevalence of cardiovascular disease in the Medicare population is 7% to 9%, in patients with CKD it is 31%. It is well established that patients with CKD have a markedly increased risk of death when compared with those without CKD; current estimates of mortality are 77 to 241 per 1000 patient years, with risk increasing in a step-wise fashion without CKD; current estimates of mortality are 77 to 241 per 1000 patient years, with risk increasing in a step-wise fashion according to severity of renal disease. The majority of deaths in patients with CKD are caused by cardiovascular disease (43%), and ≥60% of those are classified as sudden cardiac death (SCD), resulting in an annual SCD mortality rate of 7% in the dialysis population. In patients with coronary heart disease and CKD, the risk of SCD is strongly associated with severity of CKD, each 10 mL/min decrement in estimated glomerular filtration rate (eGFR) increases the risk for SCD by 11%.4

In this issue of Circulation: Arrhythmia and Electrophysiology, Hess et al10 report from the National Cardiovascular Data Registry ICD registry clinical factors associated with excess mortality in patients with CKD. Patients with CKD, not surprisingly, were more likely to be older, women, and have more comorbidities. The risk of death in the patients with CKD on dialysis was nearly 5x that of those without CKD. Less ill patients with CKD still had a markedly worse—twice (GFR, 30–60) and 4x higher (GFR, <30)—risk of death than those without CKD. These findings align with previous studies, suggesting a substantially increased mortality in patients with CKD, which reasonably leads one to question the benefit of ICD therapy in such high-risk patients. Medical practice guidelines suggest a somewhat arbitrary expected longevity of ≥1 year to justify implantation of an ICD.8 However, when considering a patient with end-stage CKD, the physician attempting to make the best decision on behalf of her patient is left without prospective randomized trial data.

In seminal prospective randomized clinical trials, ICD therapy reduced all cause mortality in moderate HF patients, entirely due to a reduction in arrhythmic death.3,8 However, the majority of ICD trials either excluded subjects with CKD or did not report the severity of renal dysfunction. Given the substantial mortality in patients with CKD, the competing risks of nonarrhythmic deaths are likely to attenuate any benefit achievable from an ICD. Furthermore, complications from ICD therapy are higher in these patients.9 Data exist to support these suppositions. A retrospective analysis of 61 patients with CKD enrolled in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) showed that each 10 mL/min per 1.73 m² decrement in eGFR increased the risk of SCD by 16% and overall mortality by 17%.10 ICD therapy was associated with a survival benefit in each eGFR category of ≥35 mL/min per 1.73 m²; however, no benefit was shown among patients with an eGFR <35 mL/min per 1.73 m².10

Numerous observational studies have reported a high mortality rate for patients with CKD after ICD placement.11 One representative analysis of 504 consecutive patients at ICD implant, 39% of which had CKD of varying degrees, showed a strong and step-wise association of mortality and renal dysfunction, even with milder levels of renal impairment.12 To date, ≥5 meta-analyses have been performed to evaluate the use of ICD therapy in the CKD population. In an appraisal of 7 studies, including 2516 patients, Sakhuja et al13 found a 2.7-fold higher risk of mortality in ICD patients undergoing dialysis when compared with those not receiving dialysis. Korantzopoulos et al14 also identified an increased risk of mortality (hazard ratio [HR], 3.44; 95% confidence interval [CI], 2.82–4.21) in ICD patients with CKD when compared with ICD patients with normal renal function. A subgroup analysis of 4 studies, including patients with milder renal dysfunction, showed a comparable HR for mortality of 3.06 (95% CI, 2.31–4.04) even in the moderately renal-impaired group of patients with eGFR<60 mL/min per 1.73 m².14

The data on ICD benefit in CKD has been derived primarily from meta-analyses, where the conclusions are somewhat divergent. A pooled patient-level analysis of MADIT-I, MADIT-II, and the Sudden Death in Heart Failure Trial (SCD-HeFT) showed no survival benefit in the 2867 primary prevention ICD patients and CKD, 36.3% of whom had an eGFR of <60 mL/min per 1.73 m² (adjusted HR, 0.80; 95% posterior credible interval, 0.40–1.53).15 Conversely, Chen et al16 reported a meta-analysis of 3 retrospective observational studies comparing survival in end-stage patients with CKD with and without ICD therapy (both primary and secondary indications). The 2-year survival was significantly better.
in patients treated with an ICD (odds ratio, 2.245; 95% CI, 1.871–2.685). Similarly, Makki et al. recently published the results of 2 separate meta-analyses to evaluate (1) the effect of CKD on mortality in patients with CKD and (2) the effect of CKD on mortality in ICD patients implanted for either primary or secondary prevention. Importantly, their evaluation of 5 observational studies comprising 17,460 patients with CKD showed a reduction in overall mortality in the CKD patients treated with an ICD when compared with matched CKD controls who were not treated with an ICD (HR, 0.65; 95% CI, 0.47–0.91). Their second analysis of 5233 CKD patients in 15 studies showed an unsurprising HR for mortality of 2.86 (95% CI, 1.91–4.27) in the group of ICD patients with CKD when compared with ICD patients without CKD.

In view of these studies, does the report by Hess et al help us to choose appropriate patients for ICD therapy or help us to guide the patient with CKD considering ICD therapy? The observation that in 2 patients with a GFR of <30 or on hemodialysis died within 3 years of ICD placement should give us pause. These investigators identified that the risk of death diverged from non-CKD patients immediately after ICD placement for the 2 groups with the most severe renal impairment. The strongest predictors of mortality by multivariable analysis were CKD severity, increased age, HF symptoms or low ejection fraction, diabetes mellitus, lung disease, low serum sodium, atrial fibrillation, ischemic heart disease, nonsustained ventricular tachycardia, and Medicare/Medicaid when compared with private insurance. Confirming previous data, they found a considerable number of significant interactions between clinical factors, indicating that patients with CKD may have differing causal factors for death when compared with the non-CKD population.

This study confirms previous analyses demonstrating an astonishing high risk of death in CKD, which is progressive and strongly related to degree of renal impairment. Most deaths are cardiac, and most cardiac deaths are sudden. However, the death rate of patients with CKD remains extremely high even with an ICD in place. This seeming paradox highlights the competing risks of death that may attenuate ICD benefit in this population. Without postmortem interrogations, it is impossible to know whether sudden deaths in this population are entirely caused by ventricular tachyarrhythmias. The metabolic abnormalities associated with end-stage CKD and, in particular, patients undergoing dialysis, raise the spectra of nontachyarrhythmic sudden deaths from pulseless electrical activity, or a primary bradyarrhythmia as contributing significantly to SCD. Despite backup pacing capabilities of an ICD, such an occurrence may not be salvageable in the setting of end-stage renal failure and HF.

Adding to these concerns, device-related complications, particularly infection and hematoma, are significantly more common in patients with CKD. Infection risk is further increased in patients undergoing dialysis, who often experience transient bacteremia, which can infect indwelling leads. Central access is a major issue for patients undergoing dialysis, and lead-related stenosis and thrombosis are common. Notably, both of these latter risks may be mitigated by implantation of the subcutaneous ICD system, a particularly appealing ICD option in the dialysis population.

In summary, SCD and HF are the prevailing modes of death in patients with CKD, yet the benefits of the ICD remain unclear. Published literature is inconsistent, largely because of the lack of randomized data and an inadequate understanding of competing modes of death. The abundant debate in the literature on the merits and disadvantages of ICD therapy in the setting of CKD reflects this vital knowledge gap. The scarcity of reliable facts precludes defining the optimum patient with CKD most likely to benefit from ICD therapy, and hampers clinician efforts to support patients in this decision-making process. One bright spot for this excessively vulnerable population is an observed declining risk of death in patients with CKD according to the United States Renal Data System. Overall death rates in patients with CKD have fallen 21% between 2002 and 2009, and this decline is particularly evident in cardiovascular and infectious causes. The rate of SCD has decreased since 2001 from 72 to 49 per 1000 patient years, nevertheless, only half of patients with CKD are still alive 3 years after the onset of dialysis.

The current study from Hess et al. extends previous observations highlighting the high mortality risk in patients with CKD and perpetuates the uncertainty of ICD benefit in the sickest of these patients. The ongoing Implantable Cardioverter Defibrillator in Dialysis patients (ICD2) trial, a prospective randomized study of the efficacy and safety of prophylactic transvenous ICD therapy in the reduction of SCD in dialysis patients aged 55 to 80 years, scheduled for completion in 2017, will be helpful in assessing some of these questions, at least in the dialysis population. Unfortunately, the answer to the clinically important question of whether primary prevention ICD therapy is worth it for the majority of patients with CKD remains unanswered. At present, the best we can do in assisting our patients with CKD to make decisions about ICD therapy is to have an honest and balanced conversation regarding the individual risk and benefit.

Disclosures
Dr Poole has received honoraria for speaking: Biotronik, Boston Scientific, Medtronic and St. Jude Medical. Advisory Board: Boston Scientific. consulting: Physio Control. Research: Sanoft Aventis. Fellowship educational grant support: Boston Scientific, Medtronic and St. Jude Medical. Equity options: Cameron Health. Dr Patton reports no conflicts.

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