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Do Implantable Defibrillators Help Patients With CKD?

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Individuals with chronic kidney disease (CKD) suffer from high rates of cardiovascular morbidity and mortality,(1) and they are at particularly high risk of sudden cardiac death.(2) Among individuals with myocardial infarction complicated by heart failure, for example, a stepwise increase in the 3-year risk of cardiac arrest has been observed in individuals with lower estimated glomerular filtration rate (eGFR).(3) Similarly, in a prior study by Pun and colleagues(2) of 19,440 patients undergoing cardiac catheterization, the rate of sudden death was 3.8 per 1000 patient years among individuals with an eGFR >60 mL/min/1.73m² but 7.9 per 1000 patient-years among individuals with eGFR <60 mL/min/1.73m²—an association that persisted in multivariable models.

Despite their high risk of cardiovascular and arrhythmic death, individuals with CKD are less likely to be treated with standard cardiovascular therapies than those without CKD even when standard indications for therapy are present.(4, 5) Although increased use of standard cardiovascular therapies in patients with CKD might lower mortality, evidence supporting their efficacy in this specific subpopulation remains elusive given the routine exclusion of individuals with CKD from cardiovascular trials.(6) The question of treatment efficacy is particularly important with regard to the use of automated implantable cardioverter defibrillators (ICDs) in patients with CKD, to which a meta-analysis by Pun et al. in this issue of AJKD provides important new evidence.(7)

Given the high incidence of sudden death in CKD, ICDs provide an intuitively appealing therapeutic option. However, questions about their appropriateness for individuals with CKD have been persistent for several reasons. First, clinical trials that established the benefit of ICDs for the primary prevention of sudden death in general excluded patients with Stage 4-5 CKD; thus, evidence of benefit in the advanced CKD population has never been

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established. Second, particularly in the hemodialysis population, ICD implantation can be associated with both technical difficulty (related to venous access) and the potential for increased short- and long-term complications, particularly bleeding and infection.(8, 9) Third and most importantly, the CKD population is known to face increased risk of mortality from myriad causes. There is good reason to believe that the benefit of ICDs may be attenuated in patients with elevated “competing” risks for death. With these concerns in mind, recently published appropriate use criteria for ICD implantation have expressed ambivalence about ICD implantation in patients with chronic kidney failure treated by dialysis, rating this practice as “May Be Appropriate”.(10)

A number of previous observational studies have indeed reported associations between even earlier stages of CKD and limited survival following ICD implantation.(11-13). While these studies have consistently shown the survival of CKD patients to be poor *despite* ICD implantation, they have been limited by the lack of control groups not receiving ICDs. Hence, the potential for ICDs to provide benefit in these patients could not be evaluated. Reports from one previous randomized trial have suggested the absence of benefit from ICDs in patients with eGFR <35 mL/min/1.73m² (HR, 1.09; P=0.84)(14, 15), but were limited by small numbers of such patients.

In their patient-level meta-analysis of data from 3 major randomized trials, Pun et al. (7) have provided important insights on the risks and benefits of ICD therapy in the setting of decreased eGFR. The patients enrolled in these trials all had symptomatic heart failure and left ventricular ejection fractions <35% without recent myocardial infarction and were randomized to ICD or standard therapy for the primary prevention of sudden cardiac death. The authors compared ICD therapy and standard medical therapy in terms of mortality, hospitalization, and ICD-related complications among individuals with and without CKD. Importantly, by combining data from 3 large trials, the analysis includes 1040 subjects with eGFR <60 ml/min/1.73 m²—significantly expanding randomized trial data in this area.

Although ICD therapy was associated with a significant survival advantage in the overall population, among individuals with decreased eGFR, no significant survival benefit with ICD-therapy was observed (HR for mortality, 0.92; 95% CI 0.74-1.14). In contrast, rehospitalization rates were higher among individuals receiving an ICD regardless of eGFR, and ICD-related complications were only slightly (and non-significantly) more frequent among patients with decreased GFR than those without decreased GFR (22.1% vs.18.8%, P=0.10). Bayesian multi-variable analyses confirmed the main findings, demonstrating a significant interaction between ICD therapy and eGFR for all-cause mortality (P<0.001) but not for hospitalization or ICD-related complications. Although the reasons for the reduced mortality benefit were uncertain, it is intriguing that arrhythmic deaths accounted for a smaller proportion of deaths among individuals with decreased eGFR than in those without decreased eGFR (23.8% vs. 35.0%, P=0.002), and that arrhythmic deaths were significantly reduced by 78% among individuals without decreased eGFR (HR, 0.22; 95% CI, 0.14-0.35) but the impact was attenuated and not significant among individuals with decreased eGFR (HR, 0.68; 95% CI, 0.44-1.07).

Based on Pun's findings, caution regarding the use of ICDs for primary prevention in patients with decreased eGFR appears warranted. Although their findings do not rule out a potential benefit and suggest that complications of therapy are at most slightly increased, it now seems clear that the presence of even moderate reduction in eGFR is associated with a dramatic attenuation in the survival advantages of ICDs when used for the primary prevention of sudden death. Although this study was not designed to explore the reason for this attenuation, the findings on arrhythmic death suggest two potential explanations. First, arrhythmic death may account for a lower proportion of overall mortality among individuals with decreased eGFR compared to those without decreased eGFR. This should serve as an important reminder to clinicians that competing risk from non-cardiovascular causes of death (as well as non-arrhythmic cardiovascular causes) in patients with CKD is an important determinant of the efficacy of cardiovascular therapies and must be particularly accounted for when assessing the value of invasive or costly therapies in this population. Second, although ICDs did appear to reduce arrhythmic death in the group with decreased eGFR, the effect was clearly attenuated. This is consistent with earlier analyses demonstrating higher defibrillation thresholds(16) in individuals with decreased eGFR and suggests that studying differences in the underlying mechanisms of sudden death according to eGFR may provide important therapeutic insights.

Lastly, several important facts should be noted. While important, these data apply only to the specific population analyzed. They should be extrapolated quite cautiously to individuals with ejection fractions >35%, with recent myocardial infarction, or those with prior cardiac arrest who would not have met the inclusion criteria of the analyzed trials. Similarly, although these data suggest that the impact of ICD therapy could be even more attenuated among individuals with stage 4-5 CKD, they provide imperfect answers as the 3 trials included a total of only 107 individuals with eGFR <30 mL/min/1.73m². Finally, it is worth mentioning that the authors attempted to include data from 4 additional clinical trials in their analysis, but were unable to do so due to a lack of information on the baseline kidney function of randomized participants. This is consistent with previous observations that, despite increasing recognition of the association of CKD with CV outcomes, large cardiovascular trials frequently exclude patients with CKD from participation or fail to measure or report on the baseline distribution of measures related to this important risk factor.(6)

Clinicians must be aware of important differences in patients with and without CKD, recognize that standard cardiovascular therapies may not be as effective in the setting of CKD, and carefully evaluate both the risk and benefit of these therapies within the context of the complexities of CKD. Increased use of patient-level meta-analysis of randomized trials should provide an important means of generating the necessary, high-quality data needed to more fully assess the risks and benefits of standard cardiovascular therapies in the growing CKD population. Nephrologists and cardiologists must strive to do better at demanding that patients with moderate or advanced CKD are included in cardiovascular trials with the necessary results on this population reported. In the meantime, as Pun et al's results emphasize, use of ICDs for primary prevention of sudden death in patients with advanced CKD should be limited.

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