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REVIEW

Prevention of sudden cardiac death in patients with chronic kidney disease: risk and benefits of the implantable cardioverter defibrillator

Jana M. Hoffmeister · N. A. Mark Estes III · Ann C. Garlitski

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Abstract Implantation of implantable cardioverter defibrillators (ICDs) for primary prevention has been shown to significantly reduce mortality in several randomized controlled trials. However, many of these trials have excluded patients on hemodialysis as well as patients with advanced chronic kidney disease (CKD). Whether the benefits of ICD therapy extend to patients with CKD is not clear. This review will examine the relationship between advancing stage of CKD and risk/benefit of ICD placement. Furthermore, we will review the recent evidence for the rates of complications as CKD advances. The intent is to assist the clinician who is considering the risks and benefits of ICD implantation in patients who have significant competing comorbidities and have not been specifically studied in randomized controlled trials.

Keywords Implantable cardioverter defibrillator (ICD) · Chronic kidney disease · End stage renal disease · Mortality · Complications

1 Introduction

The introduction of the implantable cardioverter defibrillator (ICD) as a primary and secondary preventative strategy against sudden cardiac death (SCD) has significantly decreased mortality in multiple patient populations [1–5]. Over a decade ago, Multicenter Automatic Defibrillator Implantation Trial (MADIT-I) demonstrated that in patients with a prior myocardial infarction with impaired left ventricular (LV) function, nonsustained ventricular tachycardia (VT) and inducible VT, prophylactic therapy with an ICD improves survival compared to standard medical therapy [1]. MADIT-II confirmed that even those patients without documentation of an arrhythmia (spontaneous or inducible) but with a prior myocardial infarction and an ejection fraction (EF) ≤30 % derive a mortality benefit from ICD implantation [2]. Multicenter Unsustained Tachycardia Trial (MUSTT) reinforced these findings while SCD-HeFT expanded our understanding to non-ischemic cardiomyopathy with heart failure [4, 5]. Furthermore, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) illustrated that those patients with non-ischemic dilated cardiomyopathy, EF≤35 %, and premature ventricular complexes or nonsustained VT, who underwent ICD placement versus optimal medical therapy had a significant reduction in arrhythmic mortality (although there was no statistically significant difference in all-cause mortality) [3].

A subset of patients who are candidates for primary prevention of SCD via ICD placement are those with chronic kidney disease (CKD). CKD is defined as either (1) kidney damage, i.e., pathologic abnormalities or markers of damage such as abnormalities in blood or urine tests or imaging studies or (2) glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months. The stages of CKD are as follows: stage 1 is kidney damage with normal or GFR ≥90 mL/min/1.73 m^2, stage 2 is kidney damage with mildly decreased GFR 60–89 mL/min/1.73 m^2, stage 3 is moderately decreased GFR 30–59 mL/min/1.73 m^2, stage 4 is severely decreased GFR 15–29 mL/min/1.73 m^2, and stage 5 is GFR <15 mL/min/1.73 m^2 or dialysis [6]. The prevalence of CKD, as defined by GFR of <60 mL/min/1.73 m^2, in the USA was estimated at 13.1 % in 2004 and is rapidly on the rise [7]. CKD is extremely common in patients with severe left ventricular dysfunction and

J. M. Hoffmeister · N. A. M. Estes III · A. C. Garlitski (✉)
The New England Cardiac Arrhythmia Center, The Cardiovascular Center, Department of Medicine, Tufts Medical Center,
750 Washington Street,
Boston, MA 02111, USA
e-mail: agarlitski@tuftsmedicalcenter.org

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threatens a poor prognosis [7]. Cuculich et al. performed a retrospective study of patients who underwent ICD implantation for primary prevention of SCD. When treating CrCl as a continuous variable, a 1-ml/min reduction in CrCl was associated with a 5.5 % increase in hazard of death. With an 18-ml/min reduction in CrCl, there was an impressive doubling in the risk of death. Patients with the most advanced CKD stage (i.e., lowest GFR) have a much greater risk of dying an arrhythmic death compared to patients with stage 1 CKD [8]. Cardiac disease is the most common cause of death in patients with end-stage renal disease (ESRD), with arrhythmic death responsible for over 60 % of cardiac mortality [9]. As a result, there is reason to suspect higher absolute benefit with ICD therapy in CKD patients given higher absolute risk of SCD. On the other hand, there is plausible reason to suspect that CKD modifies the efficacy of the ICD. Competing modes of death may be at play in this population. For example, SCD in CKD is not necessarily a result of a ventricular arrhythmia but rather a non-shockable rhythm such as asystole. Therein lies a complicated assessment of risks and benefits which would be ideally answered with a randomized controlled trial of patients who are stratified according to stage of CKD and risk of SCD. In the absence of such a trial, we present a synthesis of the available evidence of ICD therapy in patients with CKD according to stage of disease.

2 Representation of renal function in randomized controlled trials

Although one review revealed that patients with any form of renal disease were excluded in 86 (56 %) out of 153 cardiovascular trials, subsets of CKD patients have been included in major ICD trials albeit using variable criteria [10]. Table 1 is a summary of the renal characteristics in major primary prevention trials which either support or dispute the mortality benefit derived from ICD placement in patients with heart failure [1, 2, 4, 5, 11–16]. Two major trials, CABG-Patch and SCD-HeFT, excluded patients with a creatinine above 3 and 2.5 mg/dl, respectively [5, 16]. MADIT included 43 patients (22 %) with BUN >25 mg/dl and excluded ESRD patients [1, 15]. MADIT-II included 61 patients (5 %) with BUN >25 mg/dl, estimated GFR 68.8±23.9 ml/min/1.73 m^2 [2, 15]. ESRD patients were also excluded in MADIT-II [15]. Thus, the primary prevention trials that reported renal function either implicitly or explicitly excluded patients with ESRD. Several major trials did not report any renal exclusion, including MUSTT, Cardiomyopathy Trial (CAT), AMIOVIRT, DEFINITE, and Immediate Risk-Stratification Improves Survival (IRIS) [3, 4, 11, 12, 15, 17].

In the three major secondary prevention trials Antiarrhythmics Versus Implantable Defibrillators (AVID), Cardiac Arrest Study Hamburg (CASH) and Canadian Implantable Defibrillator Study (CIDS), there were no explicit exclusion criteria for CKD [18–20]. The data is summarized on Table 2. However, AVID and CIDS excluded patients with life expectancies under 1 year which may have impacted the decision to enroll ESRD patients, although this is a speculation.

3 Stages 1 and 2 CKD

Some studies have noted improved survival of patients with stage 1 CKD, mild kidney damage with normal or increased GFR 90 to 120 ml/min, following ICD placement for primary prevention [9, 21, 22].

In a retrospective cohort study, 958 patients with a EF ≤40 % who underwent primary prevention ICD placement between 2000 and 2006 were stratified into five groups: stage 1, GFR 90 to 120 ml/min; stage 2, GFR 60 to 89 ml/min; stage 3, GFR 30 to 59 ml/min; stage 4, GFR 15 to 29 ml/min; and stage 5, GFR 0 to 14 ml/min. The primary outcome was 1-year mortality with a secondary outcome of mean survival time. They found that there was a stepwise increase in mortality for each stage of CKD. Those with stages 1 and 2 CKD had a median survival of 78 and 90 months, respectively [21].

Amin et al. created a decision analysis model to evaluate the risks and benefits of ICD implantation in patients with CKD who meet current criteria for a primary prevention ICD. Variables included patient's age, GFR, probability of SCD, and device implantation mortality. For patients with a GFR ≥60 mL/min, mortality benefits of ICD implantation are not calculated to be affected by renal impairment. Although age decreases net survival, it is independent of renal impairment. Amin and colleagues also concluded that the mortality benefit in stage 2 CKD patients is calculated to be the same as those without CKD [22].

The most robust data is obtained from Goldenberg et al. who performed a retrospective analysis of the outcome associated with renal dysfunction in patients enrolled in the MADIT-II [23]. They showed that those with stages 1 and 2 CKD had 2-year all-cause mortality estimates at 11 %, compared to the conventional group at 16 %. Adjusting for age >65 years, NYHA functional class ≥II, smoking at anytime, EF ≤25 %, diabetes mellitus, diastolic blood pressure ≤80 mmHg, heart rate ≥80, body mass index ≥30 kg/m^2, and treatment with beta blockers, ICD therapy in patients with an GFR ≥60 ml/min/1.73 m^2 did confer a survival benefit reflected by a 34 % risk reduction in all-cause mortality. Furthermore, there was a risk reduction of 68 % for SCD [23]. Thus, those with stages 1 and 2 CKD tend to have similar survival advantages as their counterparts without CKD, all other factors being equal.

Table 1 Renal characteristics in primary prevention ICD trials

Trial	*N*	Inclusion criteria	Intervention	Mortality benefit	Renal function
MADIT [1, 15]	196	NYHA I, II, or III with prior MI (≥3 weeks), EF ≤35 %, asymptomatic NSVT and inducible, nonsuppressible VT on EPS	ICD vs optimal medical therapy (AADs were used at the discretion of the physician.)	Yes	43 Patients (22 %) with BUN>25 mg/dl. ESRD excluded
CABG-Patch [12]	1,055 enrolled; 900 underwent random group assignment	Undergoing CABG, EF ≤35 %, abnormal SAECG	ICD vs optimal medical therapy	No	Cr >3 mg/dl excluded
MUSTT [4, 15]	2,202 enrolled; 704 with inductible sustained VT underwent random group assignment	Documented CAD; asymptomatic NSVT, EF ≤40 %, inducible sustained VT	ICD±AADS	Yes	No renal function exclusion reported
CAT [15, 17]	104	Recent diagnosis of NICMP (≤9 months), EF ≤30 %, NYHA II or III	ICD vs optimal medical therapy	No	No renal function exclusion reported
MADIT-II [3, 15]	1,232	Prior MI (>1 month), EF ≤30 %	ICD vs optimal medical therapy	Yes	61 patients (5 %) with BUN>25 mg/dl, estimated GFR 68.8±23.9 ml/min/1.73 m^2; ESRD excluded.
AMIOVIRT [11]	103	NICMP, EF ≤35 %, NSVT, NYHA I, II, or III	ICD vs amiodarone	No	No renal function exclusion reported
DEFINITE [3, 15]	458	NICMP, EF ≤35 %, NYHA I, II, or III, and NSVT or an average of 10 PVCs/hour on Holter monitoring	ICD vs optimal medical therapy	Yes	No renal function exclusion reported
DINAMIT [14]	674	Recent MI (6–40 days), EF ≤35 %, standard deviation of normal-to-normal RR intervals of 70 ms or less or a mean RR interval of 750 ms or less (heart rate, 80 bpm or greater) over a 24-h period at least 3 days after infarct	ICD vs optimal medical therapy	No	No renal exclusion reported. However, non-cardiac illness with life expectancy <2 years were excluded.
SCD-HeFT [5, 15, 23]	2,521	ICMP or NICMP, EF ≤35 % and NYHA II or III	ICD vs placebo vs amiodarone	Yes	Median Cr=1.1 mg/dl, interquartile ranges 0.9–1.4 for ICD and placebo groups, 0.9–1.3 for amiodarone group. Cr≥2.5 mg/dl excluded.
IRIS [12]	898	Recent MI (5–31 days), EF ≤40 % and fulfill 1 and/or 2 (1) ECG HR ≥90 bpm (1–2 days post MI) and EF ≤40 % (5–31 days post-MI); (2) ≥1 episode of NSVT ≥150 bpm (Holter, 5–31 days post-MI)	ICD vs optimal medical therapy	No	No renal function exclusion reported

The table is modified from Cannizzaro et al. [15]

NSVT nonsustained ventricular tachycardia, *EPS* electrophysiology, *AADs* antiarrhythmic drugs, *CABG* coronary artery bypass graft surgery, *SAECG* signal-averaged electrocardiogram, *CAD* coronary artery disease, *ICMP* ischemic cardiomyopathy, *NICMP* non-ischemic cardiomyopathy, *MI* myocardial infarction, *EF* ejection fraction, *PVCs* premature ventricular contractions, *GFR* glomerular filtration rate, *ESRD* end-stage renal disease, *Cr* creatinine

Acknowledging the absence of trials randomizing patients to ICD versus medical therapy according to presence of renal disease, these data, as summarized on Table 3, support a survival benefit of ICD placement for primary prevention of SCD in the presence of stages 1 or 2 CKD.

4 Stage 3 CKD

Based on available evidence, stage 3 CKD (GFR 30–59 mL/min/1.73 m^2) appears to be the threshold at which the risk/benefit ratio may be altered [21–23]. Median survival for stage 3 CKD patients after ICD placement for primary prevention has been estimated at 80 months [21]. In their decision analysis model, Amin et al. calculated that the mortality benefit is less significant in stage 3 CKD and is dependent on the patient's age. This is attributed to a higher procedural risk and decreased life expectancy. For stage 3 CKD patients, they found that those under 80 years of age derive the greatest benefit [22].

Goldenberg et al. showed that among MADIT-II patients, there was an increase in the all-cause mortality rate to 20 % with further progression of CKD to stage 3 (defined by GFR 35–59 mL/min/1.73 m^2), as compared to 11 % in those with GFR >60 mL/min/1.73 m^2. Despite these differences, patients with mild to moderate CKD still obtained a mortality benefit. Overall there was a risk reduction of 26 % in all-cause mortality and a risk reduction of 63 % in SCD [23].

5 Stage 4 CKD

The median survival for stage 4 CKD patients following ICD placement for primary prevention has been estimated at

Table 2 Renal characteristics in secondary prevention ICD trials

Trial	Number of patients	Inclusion criteria	Intervention	Mortality benefit from ICD	Renal function
AVID [15, 20]	1,016	Patients resuscitated from near-fatal VF; sustained with syncope; or sustained VT with an EF ≤40 % and symptoms suggesting severe hemodynamic compromise	ICD vs AADs	Yes	No renal exclusion reported. However, non-cardiac illness with life expectancy <1 year excluded.
CASH [19]	288 (after elimination of patients assigned to propafenone)	Resuscitated from cardiac arrest due to documented sustained ventricular arrhythmia	ICD, amiodarone, or metoprolol	Yes	No renal function exclusion reported
CIDS [18]	659	Patients were eligible in the absence of either recent acute MI (≤72 h) or electrolyte imbalance and manifested any of the following: (1) documented VF; (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion; (3) documented, sustained VT causing syncope; (4) other documented, sustained VT at a rate ≥150 beats/min, causing presyncope or angina in a patient with EF ≤35 %; (5) unmonitored syncope with documentation of spontaneous VT ≥10 s or sustained (≥30 s) monomorphic VT induced by programmed ventricular stimulation	ICD vs amiodarone	Yes	No renal exclusion reported. However, non-cardiac illness with life expectancy <1 year was excluded.

The table is modified from Cannizzaro et al. [15]

VF ventricular fibrillation, *VT* ventricular tachycardia, *EF* ejection fraction, *AADs* antiarrhythmic drugs, *MI* myocardial infarction

42 months. At 1 year, mortality is significantly greater for these patients compared to stages 1 and 2 [21]. Based on one decision analysis model for placement of ICDs for primary prevention, patients with stage 4 CKD who are under age 75 are calculated to benefit the most. Those who are older have a calculated higher procedural risk and decreased life expectancy [22]. Overall, there is a paucity of data specifically on patients with stage 4 CKD as it relates to the risk/benefit ratio of ICD implantation. The data relating to increased mortality in these CKD patients is consistent. However, the degree to whether the ICD modifies the adverse effect of CKD is unclear.

6 Stage 5 CKD

Table 3 further illustrates the significant mortality differences found in patients with ESRD following ICD placement. Hager et al. revealed that the median survival for stage 5 CKD after ICD placement for primary prevention has been estimated at 21 months. At 36 months, survival of patients with stage 5 CKD was 0 %. The risk of death within 1 year for stage 5 CKD was significantly greater than stage 1 CKD (OR 35, 95 % confidence interval 5.85 to 209.6, $P<0.0001$). After adjustment for other comorbidities, CKD remained an independent predictor of 1-year overall survival (relative risk 10.08, 95 % confidence interval 4.2 to 24.1, $P<0.0001$) [21].

A secondary analysis of MADIT-II illustrated that GFR was the most powerful predictor of mortality risk. No ICD benefit was found in patients with an GFR≤35 ml/min/1.73 m^2 (all-cause mortality hazard ratio 1.09, $P=0.84$, SCD hazard ratio 0.95, $P=0.95$) [23]. In the decision analysis model previously discussed, patients under the age of 65 were calculated to benefit most [22].

A recent study by Charytan et al. provides perhaps the most striking mortality data in which ESRD patients in the USRDS database who received ICDs were examined [24]. During the mean follow-up of 1.4 years, 53.4 % of patients died with cardiovascular causes attributed to 63.2 % and, specifically, an arrhythmic cause to 38.2 %. Also, the survival benefit associated with ICD use for secondary prevention was lost after 3 years. This data reflects an overall high mortality rate with frequent arrhythmic cause of death in spite of ICD implantation in ESRD patients [24].

In contrast, some investigators support a mortality benefit, albeit for secondary prevention. Herzog et al. studied ESRD patients having ICD implantation for secondary prevention within 30 days of admission, discharged alive, and surviving at least 30 days from admission. Among 460 patients (7.6 %) with ICD and 5,582 patients (92.4 %) without ICD, the estimated 1-, 2-, 3-, 4-, and 5-year survivals after day 30 of admission in the ICD group versus no ICD group were 71, 53, 36, 25, and 22 %; 49, 33, 23, 16, and 12 % ($P<0.0001$), respectively. ICD implantation was

Table 3 Mortality observations following ICD placement by stage of CKD

Author	Study design	Indication	Stage of CKD	Major findings
Hager [21]	Retrospective cohort study	Primary prevention	1	Mean survival=78 months
			2	Mean survival=90 months
			3	Mean survival=80 months
			4	Mean survival=42 months
			5	Mean survival=21 months. At 36 months, survival of patients with stage 5 CKD was 0 %. Compared to stage 1, significant increase in risk of death (OR 35, 95 % confidence interval 5.85 to 209.6 $P<0.001$)
Goldenberg [23]	Retrospective sub-group analysis of MADIT-II	Primary prevention	1	All-cause mortality 11 %. ICD conferred a 34 % risk reduction in all-cause mortality and 68 % risk reduction in SCD
			2	
			3	Increase in all-cause mortality to 20 %. Risk reduction of 26 % in all-cause mortality and risk reduction of 63 % SCD
			4	For GFR ≤35 ml/min/1.73 m^2, no benefit of ICD. (All-cause mortality HR 1.09, $P=0.84$, SCD HR 0.95, $P=0.95$)
			5	
Amin [22]	Decision analysis model	Primary prevention	1	Mortality benefit calculated to be age-independent
			2	
			3	Mortality benefit calculated to be greatest in those under the age of 80
			4	Mortality benefit calculated to be greatest in those under age 75
			5	Mortality benefit calculated to be greatest in those under age 65
Charytan [24]	Retrospective cohort study	Secondary prevention	5	ICD use is associated with an estimated 22 % mortality decrease (95 % Cl, 16–27 %) when restricting follow-up to 2 years; the survival benefit is lost at 3 years
Herzog [25]	Retrospective cohort study	Secondary prevention	5	Estimated 1-, 2-, 3-, 4-, and 5-year survivals after day 30 of admission in the ICD group versus no ICD group were 71, 53, 36, 25, and 22 %; 49, 33, 23, 16, and 12 % ($P<0.0001$) 42 % reduction in death risk [RR 0.58 (95 % CI 0.50, 0.66)]
Sakhuja [26]	Meta-analysis	Primary and secondary prevention	5	2.7-Fold higher mortality in patients with ICDs on dialysis versus no dialysis

HR hazard ratio, *OR* odds ratio, *CI* confidence interval, *SCD* sudden cardia death, *GFR* glomerular filtration rate, *RR* relative risk

independently associated with a 42 % reduction in death risk [relative risk 0.58 (95 % CI 0.50, 0.66)] [25].

One meta-analysis which looked at both primary and secondary prevention found a 2.7-fold higher mortality in patients with ICDs on dialysis versus no dialysis, implying that despite the burden of SCD in patients with ESRD, there are other mechanisms which limit the ability of ICDs to reduce mortality. Of note, the most common cause of death in this meta-analysis was heart failure [26].

There are several proposed explanations for why ESRD patients do not derive the same mortality benefit as their counterparts. Alsheikh-Ali et al. examined the association of HF and CKD severity with arrhythmic and nonarrhythmic death risk in a secondary analysis of the SOLVD trial. They found that the severity of CKD was significantly associated with risk of arrhythmic death, after adjusting for age, enalapril allocation, and gender. Patients with an GFR <30 mL/min/1.73 m^2 had 4.3 times (95 % CI 2.3–8.0) the hazard of dying an arrhythmic death compared with patients in stage 1 CKD [8]. Those with class IV HF and GFR <30 mL/min/1.73 m^2 had 13 times (95 % CI 4.9–34.2) the hazard of dying of an arrhythmia compared with patients in the least advanced stages. Patients with the most advanced CKD stage had 6.5 times (95 % CI 2.9–14.8) the hazard of dying of a nonarrhythmic death compared with patients in stage 1 CKD. Furthermore, there was a statistically significant and synergistic interaction between HF and CKD, meaning that the presence of more advanced CKD amplified the effects of HF. Subjects with class IV HF and GFR <30 mL/min/1.73 m^2 had 100.8 times (95 % CI 53.0–192.0) the hazard

of dying of a nonarrhythmic death compared with patients in the least advanced stages. They propose that although arrhythmic death is highest in more advanced HF and CKD, the increased risk of nonarrythmic death means lower ratio of arrhythmic to nonarrythmic death. Consequently, there is decreased mortality benefit in these patients because a smaller proportion of deaths are due to arrhythmic causes that are potentially preventable by ICD therapy [8].

Another proposed mechanism is the trend toward increasing defibrillator thresholds (DFTs) in ICDs of those with ESRD. Wase et al. investigated the impact of ICDs in 95 patients with VT/VF and CKD defined as GFR <60 mL/min/1.73 m^2. In addition to a significant difference in all-cause mortality in those with normal GFR versus ESRD, they found a trend toward increased DFTs. For patients with stages 1–2 CKD, stages 3–4 CKD and ESRD/stage 5 CKD, average DFTs were 11.96±4.56 J, 14.51±5.16 J, and 16.33 ±5.3 J, respectively. There was a significant difference comparing overall trend in DFT differences between stages 1–2 and ESRD/stage 5 (P=0.004). Although there was a trend, increasing DFTs were not a significant independent predictor for mortality [27]. Whether patients with CKD and higher DFTs have worse outcomes remains unanswered.

7 Complications

Most of the literature on ICD complications in CKD focuses on ESRD patients with little data describing complications in earlier stages of CKD. Aggarwal et al. showed that unadjusted rates of major and total complications of ICD placement for both primary and secondary prevention were significantly greater in ESRD patients compared with patients without ESRD. The length of stay was significantly longer among patients with ESRD compared with those without ESRD (8.3±11.9 vs. 4.4±13.1 days; P<0.0001). However, it is unclear whether this is merely a reflection of baseline need for care, such as peri-procedural dialysis, or secondary to complications. Since patients with ESRD had significantly longer stays, when the authors limit complications to two days of device implantation, the incidence of cardiac arrest (0.7 vs. 0.2 %, P<0.0001), drug reaction (0.3 vs. 0.1 %, P<0.0001), and implantation site hematoma (1.5 vs. 0.8 %, P<0.0001) were still significantly greater in patients with ESRD [28]. The unadjusted in-hospital mortality was almost 5-fold in patients with ESRD compared with patients without ESRD [28]. They conclude that the presence of ESRD is an independent predictor of in-hospital complications even when adjustments are made for the longer length of hospital stay [28].

Another recent study stratified complications by stage of CKD. Tompkins et al. reviewed the medical records of 1,440 patients and noted an incremental increase in the risk of developing both bleeding and infectious complications as renal function declines. Patients with stage 2 CKD had no difference when compared to controls with regards to bleeding complications (4.9 vs 3.2 %, P>0.05). However, patients with stage 3 CKD had an increased risk of bleeding complications statistically significant compared to controls (7.4 vs 3.2 %; P<0.005), and stage 4 CKD patients suffered even greater rates that were statistically significant compared to controls (9.8 vs 3.2 %, P<0.005). Those with ESRD exhibited markedly elevated incidence of bleeding complications compared to controls (21.9 vs 3.2 %; P< 0.0001). Although the overall bleeding risk was greatest in stage 4 or 5 CKD, addition of antiplatelet agents did not specifically increase the risk of bleeding. Rather, patients with moderate dysfunction such as those with GFR ≥30 cc/min had a significant increase in bleeding when adding aspirin/clopidogrel, warfarin with INR ≥1.5, or heparin (P=0.0014, P=0.0004, and P<0.00001, respectively). This study revealed that 0.5 % of the patients had infectious complications [29]. There are limitations as the study was retrospective without standardized protocol for anticoagulants or antibiotics.

A recent study by Charytan et al. showed that device infections and need for lead removal or revision is quite common. Bacteremia occurred at rates in excess of one infection/2 person-years of follow-up. Device infection occurred frequently at a rate of 42 infections per 1,000 person-years. Furthermore, generator replacement (39 events/1,000 person-years) and lead removal or exchange (34 events/1,000 person-years) were not uncommon [24].

Future management strategies which may minimize the risk and complications associated with endovascular lead placement include the use of a wearable defibrillator as a bridge in patients in whom renal function may improve or the subcutaneous ICD.

8 Conclusions

There are several limitations to the available evidence related to the benefits and risks of ICD placement in patients with CKD and, accordingly, with this review. There is significant heterogeneity across studies in their stratification of CKD, i.e., use of GFR versus BUN versus creatinine. Many groups have combined categories of CKD and dichotomized on the basis of dialysis dependence. Additionally, studies utilized variable inclusion and exclusion criteria with respect to primary versus secondary indications. Most of the data is derived from retrospective cohorts, registries, and models rather than randomized controlled trials with, ideally, stratification according to stage of CKD. Although no prospective randomized controlled trials have been performed, the available retrospective studies and meta-analyses reveal

higher complication and mortality rates in patients with ESRD. The data suggests that more advanced CKD may result in less benefit via ICD therapy. However, teasing out whether CKD modifies ICD efficacy versus whether the ICD modifies the adverse effect of CKD is extraordinarily difficult. A randomized trial is needed to assess both the benefit and risk of ICD placement in these patients. It should be noted, however, that current guidelines for device implantation recommend primary ICD implantation in patients with an EF≤35 % regardless of renal function. Thus, designing a prospective randomized trial of ICD versus medical therapy by renal function may be difficult at this stage. Clinicians must carefully consider age, heart failure status, infection and competing comorbidities in making recommendations in the individual patient.

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Editorial Commentary

This comprehensive review summarizes the literature regarding the influence of CKD on outcomes in patients with ICDs, and reinforces its impact on morbidity and mortality in this population. Perioperative complication rates are higher, and late infections not insignificant. A unique aspect of the manuscript is that it summarizes the literature from the perspective of grades of dysfunction.

Many unknowns about these patients exist: What are the mechanisms by which CKD degrades ICD benefit? How do other comorbidities interact with CKD to impact survival? It may be that CKD is such a powerful modifier of ICD benefit that it alone may predict lack of ICD benefit. Is it possible that CRT in selected patients can improve renal function? Also, nonarrhythmic causes of sudden death including coronary and other vascular disease, and bradycardia cannot be ignored. Recall also the negative impact of peripheral vascular disease on outcomes, even in the absence of CKD. Given the vascular and infectious risks of transvenous ICD therapy in dialysis patients, might a subcutaneous ICD be preferable?

From an aerial perspective, the consistency of the conclusion begs the question why have we not done a RCT specifically addressing these patients? Patients with significant CKD were not included in the pivotal trials of ICD therapy, and given the fact that as a sole comorbidity it is such a powerful predictor of poor outcome, such a study would be ethically sound. It would be most appropriate for primary prevention since for those surviving a life-threatening ventricular arrhythmia it would be difficult to not advise device therapy. Unfortunately, since current guidelines for primary prevention do not distinguish patients with and without CKD, it may be difficult to ever proceed with such a venture. Nevertheless, I think it should be done. For now, we need to very carefully counsel patients with CKD about the significant debate that exists about attenuated benefit from ICD therapy afforded to their predecessors.