The Relationship Between Glomerular Filtration Rate and Survival in Patients Treated with an Implantable Cardioverter Defibrillator

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ABSTRACT

Objectives: We explored the association between renal insufficiency (RI) and mortality among patients treated with an implantable cardioverter defibrillator (ICD).

Background: Randomized trials have shown improvements in survival among select patients treated with an ICD. Renal insufficiency patients have a high risk of cardiac death; however, it is not clear whether the ICD has a positive effect on survival in this group of patients.

Methods: This was a retrospective review of a single-center experience of 346 patients treated with an ICD. Patients were stratified into 4 groups according to their glomerular filtration rate (eGFR; expressed as mL/min/-1.73 m^2) at implantation: group I, > 75.0; group II, -60.0 to 74.9; group III, -45.0 to 59.9; and group IV, $- \leq 45.0$. All-cause mortality was the primary end point, with differences in survival times among the 4 groups of patients expressed in Kaplan-Meier curves.

Results: Mean follow-up was 3.5 y (range 0.1 to 12.9 y), during which 67 patients died (19%). Mortality in each eGFR group was: I -6.8%, II -13.8%, III -11.5%, IV -45.8% ($p<0.001$). Survival times (mean, y) were I, 3.74; II, 3.66; III, 3.38, and IV, 2.82. The presence of diabetes was not a factor in the outcomes.

Conclusions: Patients treated with an ICD with an eGFR of $\leq$ 45.0 mL/min/1.73 m^2 have a significantly shorter survival time than those patients with an eGFR > 45.0 mL/min/1.73 m^2. Patients with an eGFR $>45.0\ mL/min/1.73\ m^2$ appear to have equally good outcomes when treated with an ICD. This may have implications for patient selection for ICD therapy.

Key words: implantable cardioverter defibrillator, defibrillator, renal function, renal failure, sudden death

Introduction

Implantable cardioverter defibrillator (ICD) therapy has been proven to significantly reduce all-cause mortality in patients treated for prior cardiac arrest (secondary prevention)[1] and in patients at high risk for cardiac arrest (primary prevention).[2–5] Once ICD therapy had been shown to be effective, guidelines for practice and utilization were written,[6] and clinical use became common.[7] However, clinicians are often presented with patients who meet the criteria for entry into a clinical trial, but who have comorbidities that may have caused similar patients to be excluded from such a trial. These comorbidities may or may not affect the beneficial effects of an ICD upon survival. Also, there are groups of patients in whom the ICD was shown not to improve survival.[8–10]

Renal insufficiency (RI) presents as a common comorbidity in patients referred for ICD therapy. Renal insufficiency is also associated with a particularly high risk for cardiovascular events and for cardiac arrest.[11–15] Patients with RI might benefit from ICD therapy or have competing potential causes for death that limit the benefit of ICD therapy.[16] Passman et al. have previously shown that renal dialysis patients experience frequent ICD shocks, while Wase et al. have previously shown that RI in ICD patients was associated with a shortened survival time.[17,18]

To determine whether there is a relationship between renal function and survival outcome in patients treated with an ICD, we examined our center's experience with patients treated with an ICD in whom renal function was evaluated at the time of ICD implantation.

Methods

We reviewed the records of all patients implanted with an ICD at our center between 1992 and 2004. Of the 362 identified, 346 were available for follow-up. Patients were selected for ICD implant using indications current at the time of implantation.[6] Exceptions to this included patients implanted with an ICD as part of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, the Multicenter

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Unsustained Tachycardia Trial (MUSTT), and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), all of which showed improvement in mortality outcomes in ICD-treated patients.[1,3,19] Gender, age, height, weight, and serum creatinine (SCr) were collected in all patients within 1 wk of ICD implant (Table 1).

We used the estimate of renal function and renal function groupings of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) study group. This study of the impact of renal dysfunction on mortality after myocardial infarction (MI) utilized the abbreviated Modification of Diet in Renal Disease equation to estimate the glomerular filtration rate (eGFR).[11,20]

The abbreviated formula is as follows:

$$\text{eGFR (mL/min/1.73 m}^2) = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if Female}) \times (1.210 \text{ if Black})$$

As in the VALIANT study, patients were stratified into 4 groups based on the eGFR: group I, ≥75.0 mL/min/1.73 m^2 (n = 78); group II, −60.0 to 74.9 mL/min/1.73 m^2 (n = 96); group III, −45.0 to 59.9 mL/min/1.73 m^2 (n = 99); and group IV, ≤45.0 mL/- min/1.73 m^2 (n = 72) (Table 1). Patients were followed for a mean of 3.5 y. Mortality from any cause was compared among the 4 groups. Data is presented as mean and standard deviation. The chi-square analysis of variance, and a *t*-test were performed where appropriate, for comparisons between groups. Survival time was analyzed using Kaplan-Meier survival analysis and Cox regression; p<0.05 is considered significant.

Results

A total of 362 patients were implanted with an ICD. Sixteen patients were lost to follow-up yielding 346 for analysis, and data sets were complete in 326 patients (Table 1). Follow-up averaged 3.5 y (range 0.1 to 12.9 y), and 67 patients (19.4%) died. The groups by eGFR had a mortality of I −6.8%, II −13.8%, III −11.5%, IV −45.8% (I, II, III versus IV, p<0.001) (Figure 1 and Table 2). Each eGFR group was analyzed for interaction with common clinical factors that might affect survival time: gender, diabetes, age >80 years, presence of significant coronary artery disease, previous MI, and ejection fraction <30%. In all analyses, the impact of eGFR remained significant.

To adjust for imbalances in the 4 eGFR groups, Cox regression analysis was conducted with the forward, or conditional, method (Table 3). With diabetes and left ventricular ejection fraction (LVEF) variables in the final equation, the hazard of death for patients in the <45 eGFR group was 8.82 times that of patients in the >75 eGFR group.

Patients with a Glomerular Filtration Rate <45

Patients with an eGFR <45 mL/min/1.73 m^2 (eGFR <45) were reviewed in detail. There were 72 patients with an eGFR <45 treated with an ICD; follow-up was complete in 67 patients. Mean follow-up was 3.5 y (range 0.1 to 12.9 y), and 28 patients died (42%). Six patients were on dialysis at the time of ICD implantation and 5 of these patients died during follow-up. Shocks from the ICD occurred in 17 of the 28 (61%) patients who died during follow-up and in 8 of the patients (21%) who survived through follow-up. Patients who died and experienced an ICD shock had a mean of

TABLE 1: Patient characteristics in eGFR groups

	eGFR group mL/min/1.73 m^2				
Characteristics	Group I >75.0 n = 78	Group II 60–74.9 n = 96	Group III 45.0–59.9 n = 99	Group IV <45.0 n = 72	p
Age	60.1 ± 2.48	62.9 ± 2.74	66.7 ± 2.74	72.1 ± 2.59	<0.001
LVEF	33.0 ± 15.4	31.5 ± 16.4	29.2 ± 13.8	26.5 ± 15.7	0.096
eGFR	87.4 ± 11.6	67.4 ± 4.0	53.0 ± 4.5	31.7 ± 8.8	<0.001
CAD (%)	58 (74.4)	64 (66.75)	80 (80.8)	55 (76.4)	0.150
DM (%)	15 (19.2)	30 (31.3)	29 (29.3)	24 (33.3)	0.212
MI (%)	46 (59.0)	46 (48.4)	68 (68.7)	50 (69.4)	0.011
Male (%)	60 (76.9)	81 (84.4)	77 (77.8)	58 (80.6)	0.587

Abbreviations: CAD = coronary artery disease; DM = diabetes mellitus; eGFR = glomerular filtration rate; MI = myocardial infarction.

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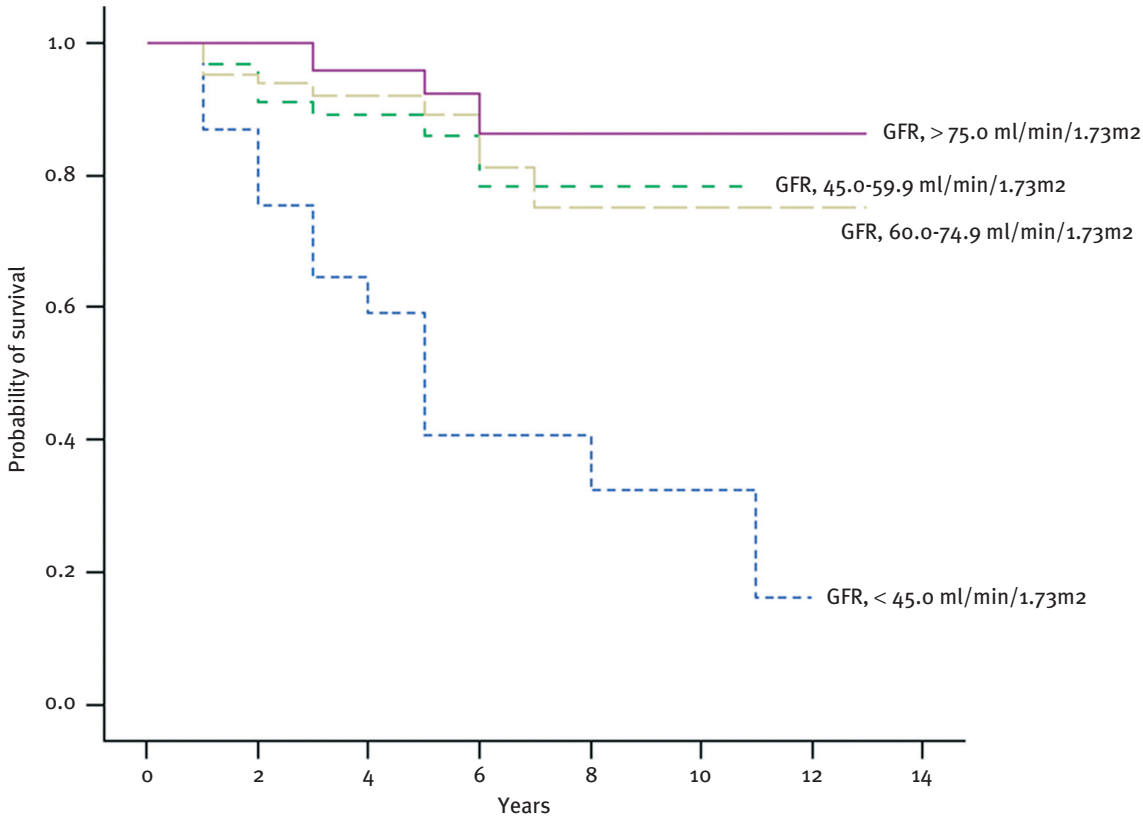

Figure 1: Kaplan-Meier display of survival among 326 patients treated with an ICD. GFR = glomerular filtration rate.

6.3 shocks per patient, while in survivors who received shocks the mean number of shocks was 3.9 shocks per patient. Among the 28 patients who died during follow-up, 10 were in hospice care or had asked not to be resuscitated prior to their death. The most common causes for death were congestive heart failure, renal failure, carcinoma, and stroke or head trauma.

Discussion

The treatment decisions physicians must make to guide patient management are often not addressed by large randomized trials. Many trials have shown a benefit for patients treated with an ICD,[1–5] while others have failed to show a survival advantage in the group undergoing coronary artery bypass graft (CABG) surgery and those early after MI.[8,9] It is likely that within the group of patients identified by randomized trials as benefiting from an ICD, there are subgroups in whom ICD therapy may not demonstrate a survival advantage.[21]

The recent large multicenter trials of ICD use have all had entry criteria that excluded patients with significant comorbidities: generally patients expected to live less than 1 to 2 y. The AVID trial did not collect data on renal function, but did ask a yes/no question if renal disease was present, and patients were excluded if the investigator believed they had a life expectancy of less than 1 y.[22] The Multicenter Automatic Defibrillator Implantation Trial (MADIT) excluded patients with uremia[23] and found that 22% of patients enrolled had a blood urea nitrogen (BUN) >25 mg/dL.[2] The Multicenter Unsustained Tachycardia Trial (MUSTT) did not record renal function and excluded patients with comorbidities likely to limit longevity. The SCD-HeFT trial did record renal function, BUN and

TABLE 2: Years survived by eGFR

eGFR Groups	Mean	Median
Group I (>75)	3.74	3.53
Group II (60–75)	3.66	2.96
Group III (45–60)	3.38	2.62
Group IV (<45)	2.82	2.14
Total	3.43	2.77

Abbreviation: eGFR = glomerular filtration rate.

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TABLE 3: Cox regression model for survival, eGFR, and other associated variables

eGFR (compared with >75.0)	Adjusted HR (95.0% CI)	p-Value	
<45.0	8.823	(3.066–25.388)	0.000
45.0–59.9	1.699	(0.522–5.523)	0.378
60.0–74.9	1.764	(0.550–5.655)	0.340
DM	2.159	(1.207–3.859)	0.009
LVEF >30%	0.969	(0.945–0.994)	0.015

Variables in the Cox model that were dropped during forward conditional method were age, gender, CAD, and MI. *Abbreviations*: CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; eGFR = glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

creatinine, but excluded patients with a creatinine >2.5 mg/dL.[19]

Patients with RI represent a group that may meet the criteria established for ICD use but experience less of a survival benefit from such therapy owing to the established reduction of survival in this group of patients, especially those with end-stage renal disease.[15] There are limited data from the large randomized trials to address this group. In the VALIANT study the group with eGFR <45 had a 3-y mortality of 40%, similar to our patient population.[11]

The SCD-HeFT database may offer some insight into the outcomes of patients with decreased renal function. However, patients with a serum creatinine >2.5 mg/dL were excluded from that trial, thereby limiting any statements to this group. A preliminary report from the SCD-HeFT group presents data with findings similar to the present study.[24] This adds support to the conclusion that ICD therapy should not be routinely used in the group of patients with an eGFR <60 mL/min.[24] Wase et al. examined a similar group of patients, showing that patients with RI had higher defibrillation thresholds (DFTs) at implantation of the ICD, while our data suggests ICDs did function appropriately in the low eGFR group, and that death was from noncardiac causes.[18]

Although the data in our review is limited by the retrospective, nonrandomized nature of the review, it does point to a significantly worse outcome for patients with renal disease treated with an ICD in clinical practice. It is very likely that within the group of patients with RI, some receive benefit from ICD therapy. However, it is also possible that patients meeting criteria for ICD therapy who also suffer from significant renal disease will experience worse outcomes than those without RI, and may benefit very little or not at all from ICD therapy. Given the increase in the incidence of RI and the increase in the utilization of ICDs, this question deserves further study. We believe that until there is evidence available to show an improved outcome in patients with RI who qualify for an ICD, such patients considered for ICD therapy should be selected carefully.

References

1. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators: A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576–1584
2. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, et al.: the Multicenter Automatic Defibrillator Implantation Trial Investigators: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933–1940
3. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, et al.: the Multicenter Unsustained Tachycardia Trial Investigators: A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882–1890
4. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, et al.: the Multicenter Automatic Defibrillator Implantation Trial II Investigators: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–883
5. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, et al.: the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–2150
6. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, et al.: ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee on Pacemaker Implantation). *J Am Coll Cardiol* 2002;40:1703–1719
7. Jauhar S, Slotwiner DJ: The economics of ICDs. *N Engl J Med* 2004;351:2542–2544
8. Bigger JT: the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators: Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997;337:1569–1575
9. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, et al.: Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481–2488
10. Gillis AM: Prophylactic implantable cardioverter-defibrillator after acute myocardial infarction–not for everyone. *N Engl J Med* 2004;351:2540–2542
11. Anavekar NS, McMurray JJV, Velazquez EJ, Solomon SD, Kober L, et al.: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351:1285–1295

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DOI:10.1002/clc.20209

12. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C: Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *N Engl J Med* 2004;351:1296–1305
13. Gupta R, Birnbaum Y, Uretsky BF: The renal patient with coronary artery disease. *J Am Coll Cardiol* 2004;44:1343–1353
14. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Grady D, et al.: Renal insufficiency as an independent predictor of mortality among women with heart failure. *J Am Coll Cardiol* 2004;44:1593–1600
15. Keith DS, Nicholas GA, Gullion CM, Betz Brown J, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;164:659–663
16. Herzog CA: Cardiac arrest in dialysis patients: approaches to alter an abysmal outcome. *Kidney Int* 2003;(Suppl 84) S197–S200
17. Passman R, Robin J, Weinberg K, Tiongson J, Quadrini M, et al.: Increased risk of appropriate ICD therapy in renal dialysis patients. *Heart Rhythm* 2004;1:S33A
18. Wase A, Basit A, Nazir R, Jamal A, Shah S, et al.: Impact of chronic kidney disease upon survival among implantable defibrillator recipients. *J Interv Card Electrophysiol* 2004;11(3): 199–204
19. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, et al.: the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators: Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–237
20. National Kidney Foundation K/DOQI Clinical Practice Guidelines for CKD: Evaluation, classification and stratification. *Am J Kidney Dis* 2002;39:S1–S000
21. Tinetti ME, Bogardus ST, Agostini JV: Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med* 2004;351:2870–2874
22. The AVID Investigators: Antiarrhythmics versus implantable defibrillators (AVID)—rationale, design, and methods. *Am J Cardiol* 1995;75:470–475
23. MADIT Executive Committee: Multicenter Automatic Defibrillator Implantation Trial (MADIT): design and clinical protocol. *Pacing Clin Electrophysiol* 1991;14:920–927
24. Dickinson MG, Ip JH, Hellkamp AS, Anderson J, Poole JE, et al.: SCD-HeFT Investigators: Decreased impact of implantable defibrillators on sudden cardiac death in patients with renal insufficiency and heart failure: an analysis of the SCD-HeFT. *Heart Rhythm* 2006;3:S38

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