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Implantable Cardioverter Defibrillators for Primary Prevention of Sudden Cardiac Death in CKD: A Meta-analysis of Patient-Level Data from 3 Randomized Trials

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Abstract

Background—The benefit of a primary prevention implantable cardioverter defibrillator (ICD) among patients with chronic kidney disease (CKD) is uncertain.

Study Design—Meta-analysis of patient-level data from randomized controlled trials.

Setting & Population—Patients with symptomatic heart failure and left ventricular ejection fraction of <35%.

Selection Criteria for Studies—From 7 available randomized control studies with patient level data, we selected studies with available data on important covariates. Studies without patient-level data on baseline eGFR were excluded.

Intervention—Primary prevention ICD versus usual care

Outcomes—Mortality, re-hospitalizations, and effect modification by estimated GFR (eGFR)

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Results—We included data from the Multicenter Automatic Defibrillator Implantation Trial I (MADIT-I), MADIT-II, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). 2,867 patients were included; 36.3% had at least stage 3 CKD (eGFR<60). The Kaplan-Meier estimate of the probability of death during follow-up was 43.3% among 1,334 patients receiving usual care and 35.8% among 1,533 ICD recipients. After adjustment for baseline differences, there was evidence that the survival benefit of ICDs in comparison to usual care depends on eGFR (posterior probability for null interaction $p < 0.001$). The ICD was associated with survival benefit among patients with an eGFR ≥ 60 (adjusted HR (aHR)=0.49 [95% posterior credible interval (PCI) 0.24-0.95]) but not among patients with eGFR < 60 (aHR = 0.80 [95% PCI 0.40-1.53]). eGFR did not modify the association between the ICD and re-hospitalizations.

Limitations—Few patients with eGFR < 30 were available. Differences in trial-to-trial measurement techniques may lead to residual confounding.

Conclusions—Reductions in baseline eGFR decrease the survival benefit associated with the ICD. These findings should be confirmed by additional studies specifically targeting patients with varying levels of eGFR.

Introduction

Chronic kidney disease (CKD) affects more than 20 million Americans. Compared with the general population, these patients have a four to twenty fold greater risk of sudden cardiac death (SCD).^{1,2} Primary-prevention implantable cardioverter-defibrillators (ICDs), used among patients who are at risk for but have not yet had life-threatening ventricular arrhythmias, have been proven to reduce SCD and overall mortality among selected patients with a reduced ejection fraction.³ However, the benefits and risks of this therapy among patients with CKD are not clear. Observational studies have consistently described decreased overall survival and increased complication rates among recipients of primary prevention ICDs who have CKD compared with those with preserved renal function.⁴⁻⁶ However, the absence of a control group who did not receive primary prevention ICD therapy in these studies makes assessment of risk/benefit in CKD patients uncertain. There is a paucity of randomized trial data in this subset of patients, since all the major clinical trials comparing ICDs to usual care excluded patients with advanced kidney disease.

A collaborative consortium involving the principal investigators of existing ICD trials was established to explore the effectiveness of the ICD in various subgroups. We conducted this pooled patient-level data analysis to assess whether kidney disease as estimated by the glomerular filtration rate modifies the effect of ICD treatment on mortality and rehospitalizations compared to usual care.

Methods

Data Sources and Study Selection

Individual data on patients enrolled in 7 primary prevention ICD trials were provided. We included clinical trials randomizing patients to a primary prevention ICD versus usual care for whom data on kidney function were available at enrollment. Patients from four clinical trials were excluded due to lack of available data on serum creatinine: the Coronary Artery

Bypass Graft Patch trial⁷, the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation trial⁸, the Defibrillator in Acute Myocardial Infarction Trial⁹, and the Multicenter Unsustained Tachycardia Trial¹⁰. The following 3 trials were included: the Multicenter Automatic Defibrillator Implantation Trial I (MADIT I)¹¹, MADIT II¹², and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)¹³. The criteria used by these trials to exclude patients with advanced CKD at baseline were as follows; for MADIT I, BUN >70 mg/dl or creatinine >3 mg/dl; for MADIT 2, creatinine >3 mg/dl; and for SCD-HeFT, creatinine >2.5 mg/dl. For our study, we included patients with symptomatic heart failure (New York Heart Association Class (NYHA) < IV), a left ventricular ejection fraction (LVEF) of $\geq 35\%$, and assignment to either an ICD or usual care. Patients without heart failure symptoms or with NYHA Class IV symptoms, a LVEF of $> 35\%$, who were missing data on prior MI, who had an MI in the 40 days preceding randomization, or whose time from randomization was unknown were excluded. Patients who were missing important covariates or who were assigned to other treatment arms besides ICD or usual care were also excluded.

Determination of eGFR group

Kidney function was determined by calculating the estimated glomerular filtration rate (eGFR) at study enrollment. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which utilizes serum creatinine concentration, age, race, and gender to determine estimated GFR and has been validated across populations with a wide range of GFR.¹⁴ For consistency with prior literature and for simplicity, we dichotomized the cohort into two strata of eGFR: eGFR < 60 (stage 3-5 CKD) and eGFR ≥ 60 ml/min/1.73 m². We also examined outcomes by finer categories of eGFR (eGFR < 45, 45-59, 60-89, and ≥ 90 ml/min/1.73 m²).

Baseline Characteristics

Patient characteristics at study enrollment were summarized according to eGFR group. The association of eGFR group with categorical and continuous baseline variables was tested using the χ^2 tests and tests of equality of means, respectively.

Endpoints

All-cause mortality was the primary endpoint of interest. Re-hospitalization was a secondary endpoint. Re-hospitalization was defined as admission to a hospital for any reason after ICD placement during each trial study period. In addition, we assessed ICD-related complications which were catalogued across trials included pneumothorax, hemothorax, pocket hematoma, lead dislodgement, ICD migration, impending ICD pocket erosion, ICD-related infection, and other clinical events deemed to be directly related to ICD implantation.

Statistical Analysis

To assess the relationship between CKD and ICDs on outcomes, our primary analysis was to examine the interaction between continuously-valued estimated GFR and ICD therapy on mortality. For interaction testing, statistical significance was assessed by computing the two-sided posterior probability of a null interaction. We also examined survival outcomes based

on eGFR classification (eGFR \geq 60 versus eGFR $<$ 60) using Kaplan-Meier survival curves. For ICD recipients, we assessed the association between eGFR group and ICD-related complications with the χ^2 test.

For the analyses of the primary and secondary endpoints, we used Bayesian Weibull survival and Bayesian logistic regression models, respectively, to combine trial data and address missing data.^{15,16} A Bayesian approach models uncertainty with prior distributions and establishes inferences based on posterior probabilities. The use of Bayesian modeling methods in pooled-data analyses is advantageous because it allows for inferences to be made about subgroups that may be under-represented in included trials by borrowing information across studies and subgroups. Variation within and between trials can be better accounted for by taking into account not only parameter uncertainty but also additional complexity such as missing data.¹⁶ (For further discussion on the advantages of Bayesian hierarchical models in pooled data analyses compared to classical Frequentist approaches, see Supplemental Item S1). In our models, missing covariate values were imputed based on their trial-specific empirical distribution. As an additional sensitivity analysis, we also created models that excluded patients who had missing data on any covariates. We adjusted for the following covariates: sex, race, age, LVEF, NYHA class, history of heart failure, history of hypertension, history of diabetes, history of coronary artery bypass grafting (CABG), presence of left bundle branch block, history of ischemic disease, and use of cardiac medications including antiarrhythmic, β -blockers, and ace-inhibitors. Assuming random effects for trial-specific treatment effects and for parameters defining trial-specific baseline hazard functions, a model including the main effects of the ICD and eGFR group as well as the multiplicative interaction of the ICD with eGFR group was fitted. Statistical significance for hazard ratios was established by whether the posterior credible interval (PCI) did not include unity. Analogously, a Bayesian logistic regression model was fitted to re-hospitalizations.

All analyses were performed using R version 3.0.1 and WinBUGS version 1.4.3 (WinBUGS code is provided as a Supplemental Item S2). All data were previously collected as part of the primary trials, and the use of the de-identified dataset was approved by the Duke Institutional Review Board.

Results

Figure 1 depicts a flow diagram summarizing the criteria used to select trials and select patients within included trials. From the 3 included clinical trials (MADIT-I, MADIT-II, and SCDHeFT), a total of 2,867 patients were included in our final study population. **Table 1** summarizes the characteristics of the clinical trials and the number of subjects from each trial that were included in this study. Excluded patients differed from included patients largely based on the exclusion criteria (Supplemental Table S1), but there was no significant difference in mortality risk between excluded and included patients. (log rank $p=0.2$)

Table 2 compares the baseline characteristics of subjects with eGFR $>$ 60 and eGFR \geq 60 ml/min/1.73m². More than one-third (36.3%) had at least stage CKD 3 (eGFR $<$ 60) upon study entry, and the mean eGFR of patients with eGFR $<$ 60 was 45.4 ml/min/1.73m².

Consistent with the exclusion criteria of the original trials, there were relatively few subjects with advanced (stage 4 or 5) CKD; only 3.6% of patients had an eGFR <30 ml/min/1.73m², and there were no patients with end stage renal disease enrolled in any of the trials. There were no significant differences in the proportion assigned to an ICD between the two eGFR groups. eGFR<60 patients were older (mean age 67 vs. 58 years) and had a higher prevalence of diagnosed heart failure (60.0% vs. 54.5%), prior CABG (47.1% vs. 36.0%), hypertension (59.8% vs. 49.6%), and diabetes (35.5% vs. 27.8%). Patients with eGFR<60 were less likely to be taking a β -blocker (59.0% vs. 66.2%) or an ACE inhibitor (82.9% versus 88.7%) at enrollment. LVEF, the presence of left bundle branch block, and use of antiarrhythmic medications did not differ between groups. Comparison of baseline characteristics by treatment assignment (ICD vs. no ICD) stratified by eGFR group is shown in Supplemental Tables S2 (eGFR \geq 60) and S3 (eGFR<60).

Unadjusted Outcomes

Overall, among 2,867 patients and 2.7 years of average follow-up (standard deviation = 1.5 years), the Kaplan-Meier estimate of the probability of death during follow-up was 43.3% in the 1,334 patients receiving usual care as compared with 35.8% in the 1,533 ICD recipients. **Figure 2** illustrates the survival curves for unadjusted all-cause mortality by treatment assignment stratified by eGFR grouping, showing the absence of a significant survival advantage with ICD assignment among patients with eGFR<60 ml/min/1.73m² (HR=0.92, 95% CI 0.74-1.14). A total of 1,805 (66.2%) patients were re-hospitalized at least once. **Figure 3** shows the overall rates of re-hospitalization and ICD-related complications. Patients who received an ICD were more likely to be re-hospitalized. Comparison of re-hospitalizations according to CKD categories showed that eGFR<60 patients in either treatment arm were more likely to be hospitalized. ICD-related complications in the ICD-treatment arms were also slightly higher among eGFR<60 patients, but the difference was not statistically significant (22.1% overall in the eGFR<60 group versus 18.8% in the eGFR \geq 60 group, p=0.1).

Adjusted Outcomes

Figure 4 shows the covariate-adjusted mortality hazard ratio of ICD versus usual care across the spectrum of eGFR. Overall, there was a significant interaction between eGFR and the benefit of ICD for all-cause mortality (posterior probability p <0.001). The survival benefit of ICD declines in proportion with declining eGFR; however, the 95% PCI does not exclude the possibility of benefit among those with low eGFR. There was no evidence of interactions between eGFR and re-hospitalizations (Supplemental Figure S1) or ICD-related complications.

Figure 5 summarizes the covariate-adjusted point estimates for the relative benefit of the ICD on outcomes according to four eGFR groups (eGFR<30, 30-59, 60-90, and >90 ml/min/1.73m²). The effect of the ICD in comparison to usual care on all-cause mortality for all eGFR groups \geq 60 ml/min/1.73m² was consistent with a survival benefit (eGFR >90 adjusted HR=0.45 95% posterior credible interval (PCI) 0.19-0.89; eGFR 60-90 aHR=0.46 [95% PCI 0.22-0.83]). We did not observe a significant benefit of the ICD in either of the eGFR subgroups <60 ml/min/1.73m² (eGFR 30-59 aHR = 0.8 [95% PCI 0.38-1.48];

eGFR<30 aHR=0.77 [95% PCI 0.36-1.32]). The risk of re-hospitalization between ICD and usual care arms did not differ substantially when compared according to eGFR subgroups (Figure 6).

We also performed additional sensitivity analyses removing patients with missing covariate data, and this analysis did not significantly alter the study findings.

Reported Mode of Death

We compared the trial-reported mode of death for the eGFR<60 and eGFR≥60 groups, focusing on the proportion of arrhythmia related vs. non-arrhythmic deaths. 24% of deaths were classified as cardiac deaths that could not be further classified as arrhythmic or nonarrhythmic. There was a higher proportion of arrhythmia-related death among patients with eGFR≥60 compared to patients with eGFR<60 (35.0% vs 23.8%, p=0.002). There was slightly greater proportion of non-arrhythmic deaths among eGFR<60 patients (48.4% vs. 40.7%) but this did not reach statistical significance (p=0.06). In the eGFR≥60 group, ICD treatment was associated with a significant reduction in arrhythmic death (unadjusted HR=0.22, 95%CI 0.14-0.35, P=0.001), whereas ICD treatment was not associated with a significant reduction in arrhythmic death in the eGFR<60 group (HR 0.68, 95% CI 0.44-1.07, p=0.3).

Discussion

To our knowledge, this meta-analysis of 2,867 subjects enrolled in primary prevention ICD trials is the largest collection of prospective data on the risks and benefits of a primary prevention ICD among patients with CKD, and the first meta-analysis to compare ICD outcomes against usual care in this patient population. In summary, we found that the mortality reduction associated with the ICD compared to control is significantly impacted by baseline kidney function, with decreasing benefit as GFR declines. As a group, patients with a GFR < 60 ml/min/1.73m² had a higher risk of re-hospitalization, but we did not observe a significant interaction between level of kidney function (as measured by the estimated GFR) and the risk of re-hospitalizations. There was no significant difference in the risk of ICD-related complications according to eGFR group.

Despite the fact that all published clinical trials to date excluded patients with severe kidney disease, more than one-third (36.3%) of the patients in our study had at least moderate CKD. Current guidelines do not provide any special consideration for eGFR group or level of kidney function in the decision to implant a primary prevention ICD.³ While there have been no clinical trials specifically designed to address the question of ICD benefit among CKD patients, a prior post hoc analysis of a small group of patients with GFR < 35 (N=60) enrolled in the MADITII study suggested that patients with did not derive a statistically significant benefit from an ICD (all-cause mortality hazard ratio 1.09, p = 0.8).¹⁷ Our study confirms and further extends these findings by showing that the beneficial effect of the ICD on mortality continuously declines with declining kidney function. Although our study population included a large number of patients with CKD, the small number of patients with advanced CKD enrolled in these trials prohibits a detailed assessment of a “threshold” eGFR at which the mortality advantage of ICD compared to usual care is abrogated. However,

these data should provide the impetus for further controlled clinical trials specifically designed to address the efficacy of the ICD in this patient population.

There are several lines of evidence that could explain a decreased efficacy of the ICD among CKD patients. First, CKD patients with heart failure may experience a higher proportion of non-arrhythmic death compared to arrhythmic death, thus limiting the ICD efficacy.¹⁸ A secondary analysis of the SOLVD study showed that the risk of non-arrhythmic death increases proportionally with worsening CKD, and the influence of CKD on the risk of non-arrhythmic death was most pronounced among patient with advanced heart failure.¹⁹ In the MADIT-II study, the small subgroup with GFR <35 showed a much higher risk of non-arrhythmic mortality compared to those with GFR>35%. These data support the notion that competing risks of nonarrhythmic mortality in CKD patients may overwhelm potential benefit from prevention of arrhythmic death. In support of this theory, we found that CKD patients experienced a lower proportion of arrhythmic deaths compared to eGFR≥60 patients. Second, multiple studies have documented markedly decreased survival time among ICD-recipients with CKD in comparison to their non-CKD counterparts.^{4,6,20} Decreased ICD exposure time because of decreased survival may also reduce opportunity of ICDs to prevent of arrhythmic death and reduce overall mortality. Finally, higher defibrillation thresholds observed in CKD patients might contribute to decreased ICD effectiveness in preventing arrhythmic death.²¹ Among 95 patients with a broad spectrum of baseline kidney function, Wase et. al. described a trend towards increasing defibrillation thresholds with worsening kidney function (mean defibrillation thresholds for stage 1–2 CKD, stages 3–4 CKD and ESRD/stage 5 CKD were 11.96 ± 4.56 J, 14.51 ± 5.16 J, and 16.33 ± 5.3 J, respectively.) Although our analysis was hampered by a significant proportion of cardiac deaths which could not be distinguished as either arrhythmic or nonarrhythmic, ICD treatment was only associated with reduction in arrhythmic death among patients with eGFR≥60, whereas no significant reduction was seen among patients with eGFR<60.

Our study has some limitations. First, although we provide the most robust published data on the efficacy of the ICD in patients with moderate CKD, we had limited data on patients with eGFR < 30 ml/min/1.73m² and no data on patients with end-stage kidney disease. A significant number of sudden deaths in CKD patients occur among those without decreased LVEF and those without CHF symptoms, and these patients were excluded from our study cohort. Therefore, we cannot generalize our conclusions to these important subgroups of patients at risk. Second, since we do not have information on the creatinine assay methodology used in the primary trials, we cannot exclude the possibility of measurement error introduced by the use of non-standardized assays, or the possibility that the CKD-EPI estimating equation may not be accurate among patients with CHF since it has never been validated in this population. Third, although we accounted for a large set of measured covariates that were available across trials, we cannot exclude the possibility that differences in trial-to-trial measurement techniques and unmeasured covariates contribute to residual confounding. Fourth, our analysis assumes that missing data occurred at random with missing covariate values imputed based on the trial-specific empirical distribution, which may or may not reflect the actual process leading to missing values. Finally, our data on mode of death is limited by non-uniformity of definitions across the included trials and missing data. A larger study of mode of death among ICD recipients with CKD would be

productive in order to better understand the relationship between competing risks of death and ICD efficacy.

In conclusion, our study provides evidence that the severity of CKD proportionally attenuates the benefit of the ICD. In the absence of randomized trial data geared towards addressing the efficacy of ICDs in this subgroup, clinicians should carefully counsel potential primary prevention ICD recipients with CKD about the likelihood of reduced benefit and increased risk compared to estimates generated from clinical trials enrolling predominantly patients with preserved renal function. While small pilot clinical trials are underway among patients with end stage kidney disease²², the uncertainty of the benefit of primary prevention ICD in the broader population of patients with CKD should provide the rationale for further investigation into appropriate risk stratification methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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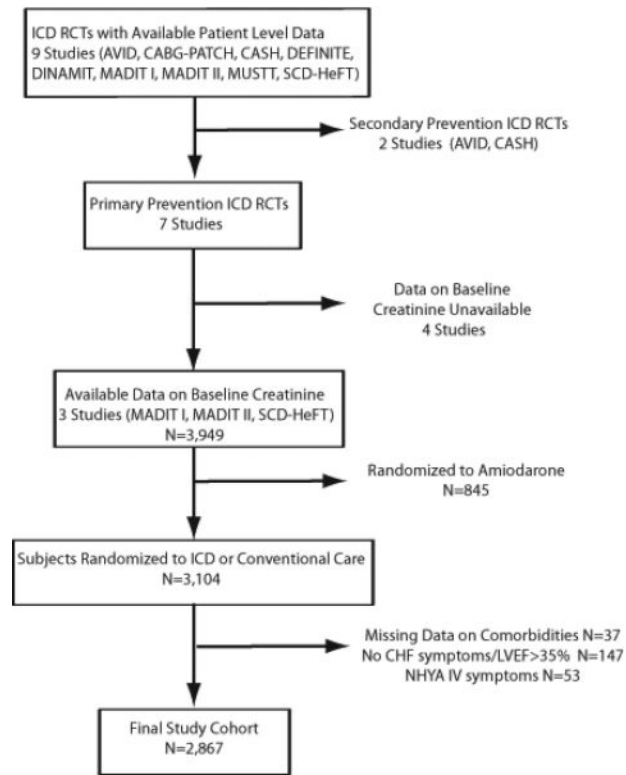


Figure 1.
Study selection and patient inclusion within selected studies

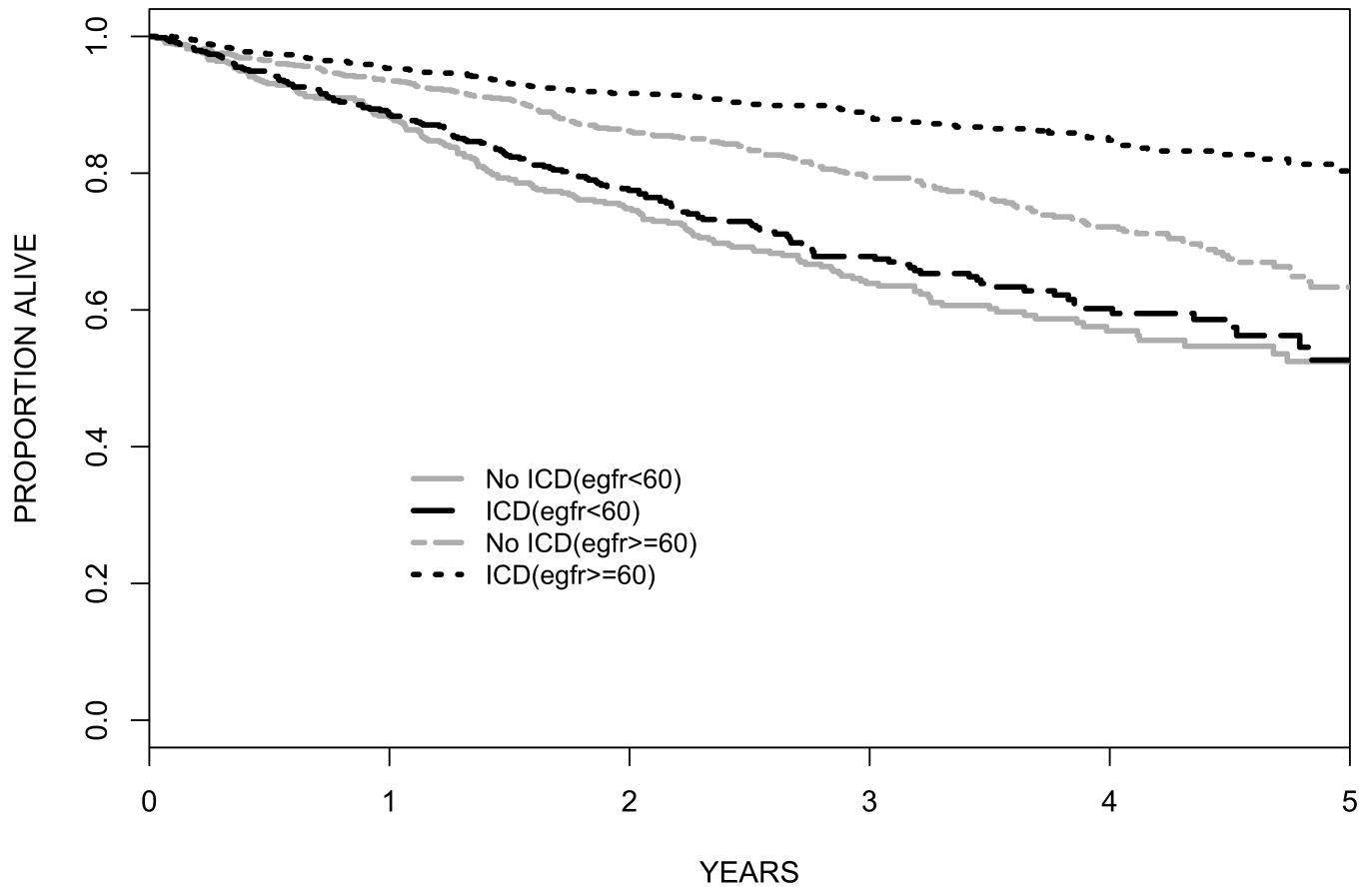


Figure 2. Kaplan-Meier Survival Curves in ICD Recipients vs. Non-recipients According to eGFR. Unadjusted HR for mortality benefit of ICD: eGFR \geq 60 HR=0.53, 95% CI 0.42-0.67; eGFR<60 HR=0.92, 95% CI 0.74-1.14.

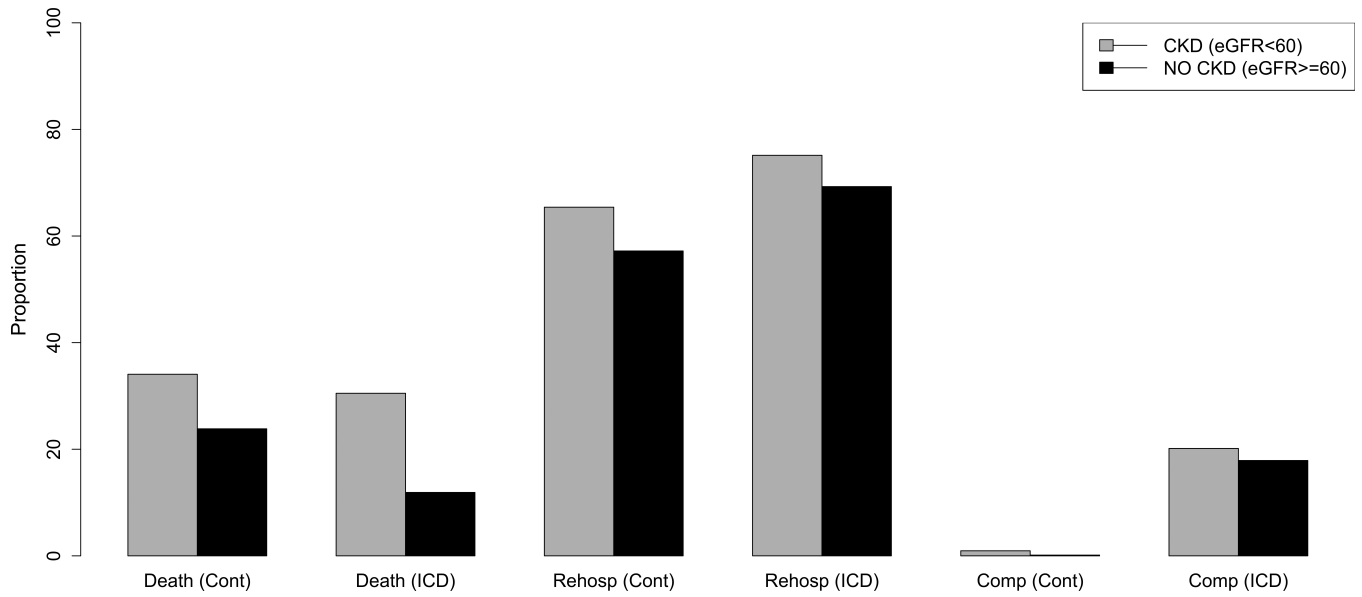


Figure 3. Proportion (%) of Study Participants with Adverse Outcomes by eGFR group. Abbreviations: Cont=control arm; Rehosp= rehospitalizations; Comp=complications

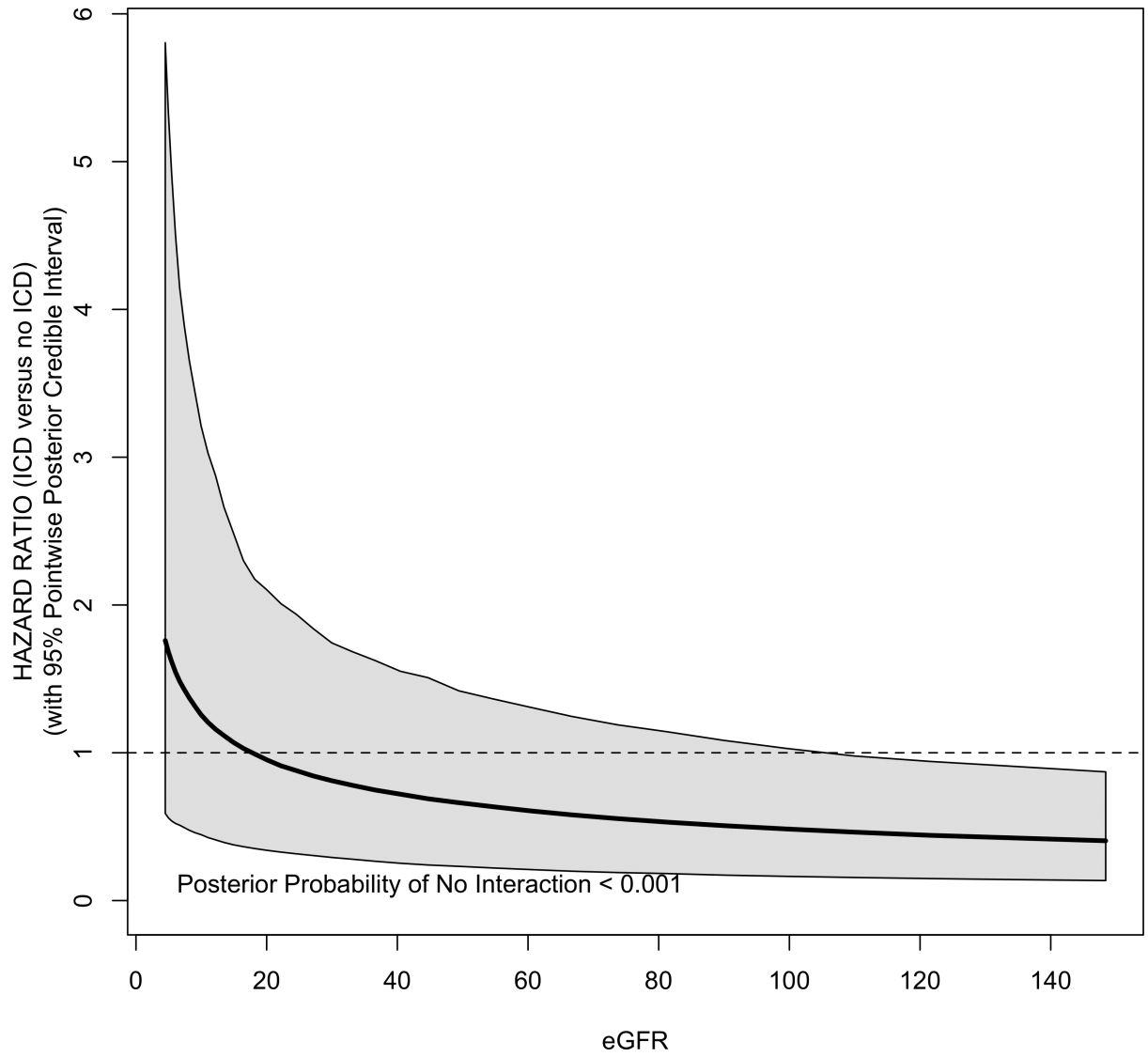
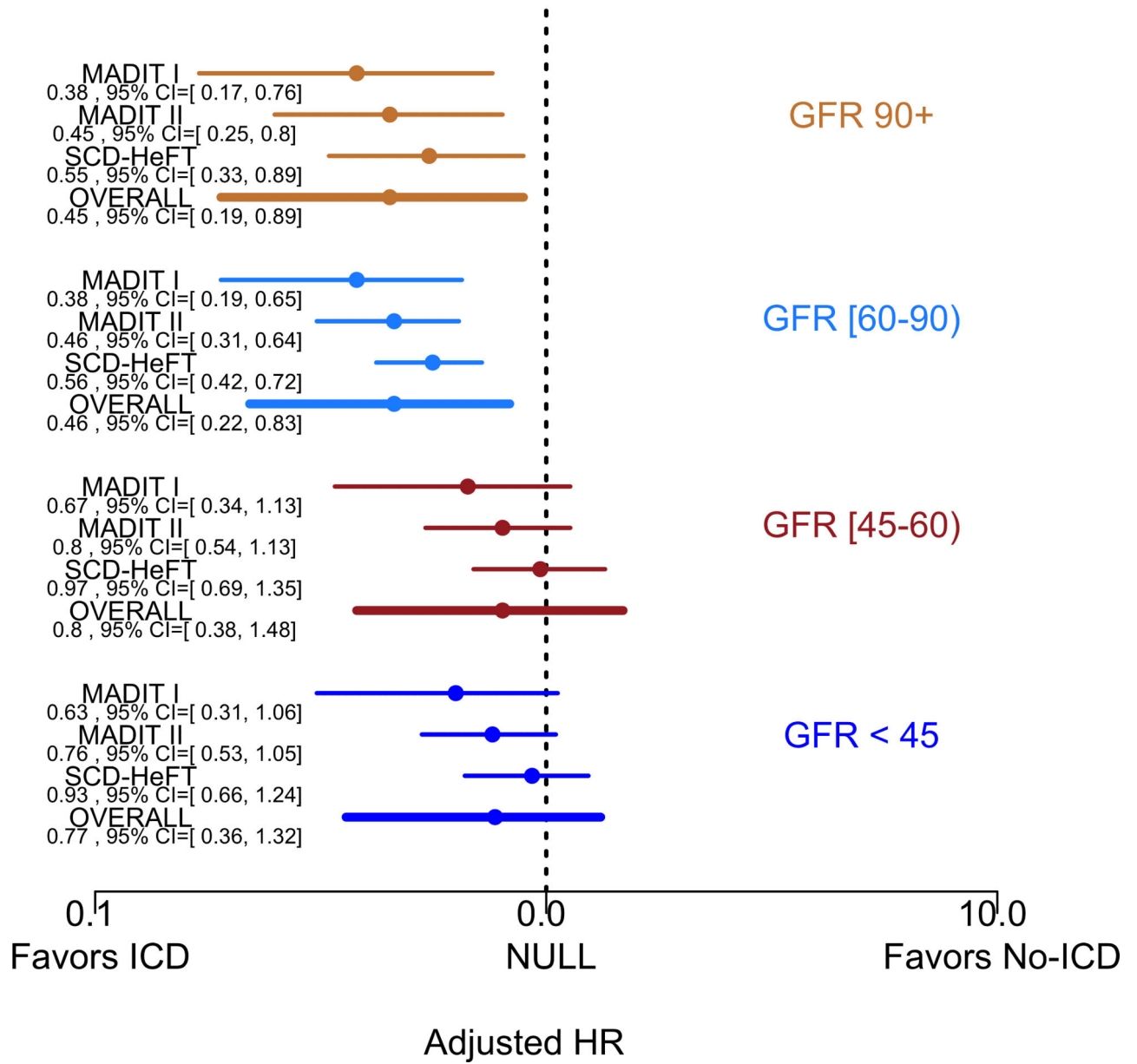


Figure 4. Bayesian-Weibull Covariate-Adjusted Hazard Ratio for Mortality Benefit of ICD as a function of baseline eGFR. Shaded areas reflect 95% pointwise posterior credible intervals.

All-Cause Mortality



Re-Hospitalizations

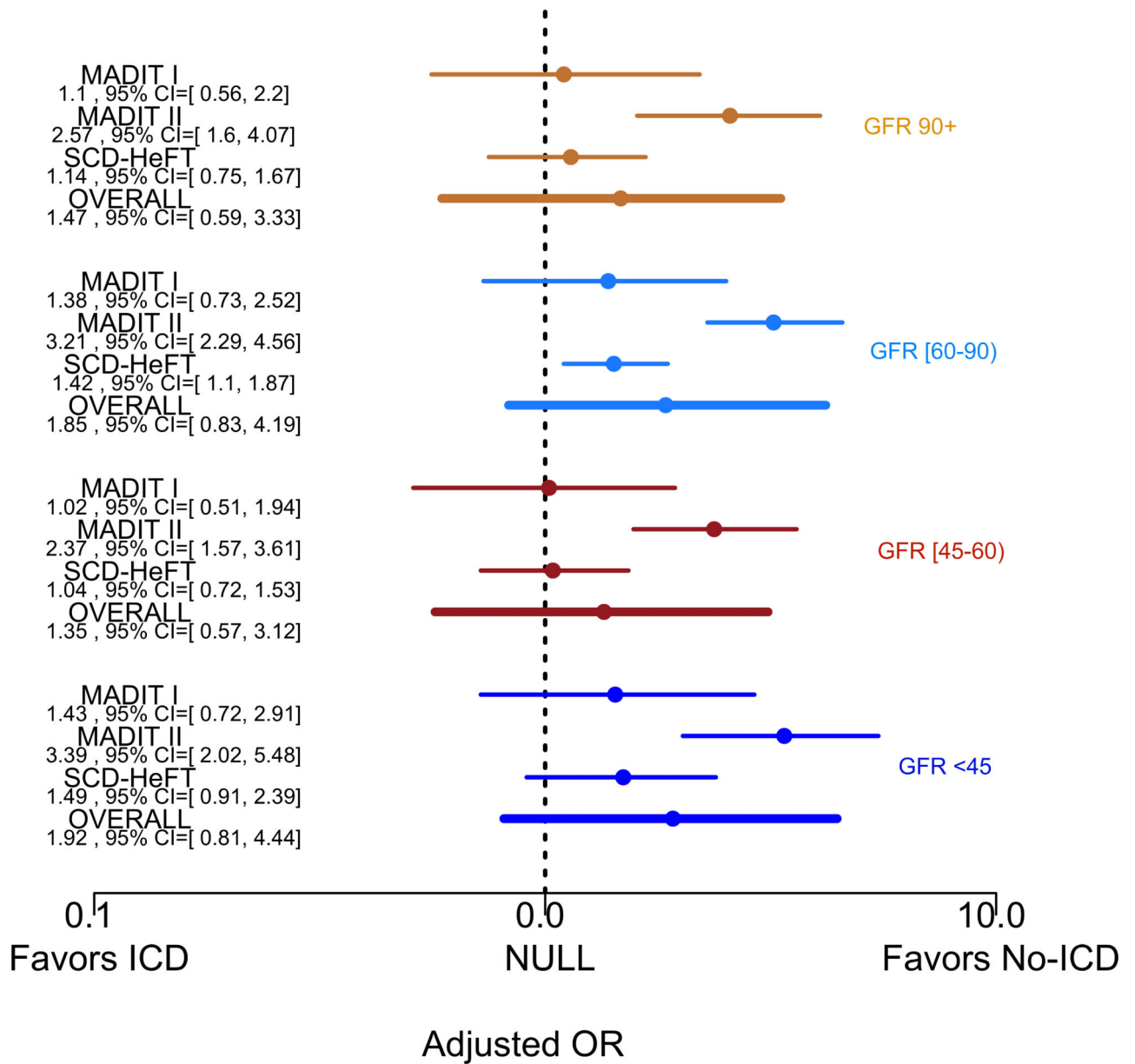


Figure 5. Forest Plots of covariate-adjusted HR and 95% PCI for A) all-cause mortality and B) re-hospitalizations by clinical trial and eGFR group, with x-axis displayed in the log-scale.

Table 1

Characteristics of Included Clinical Trials

Clinical Trial	Participating Countries	Publication Year	Mean follow-up (mos)	Eligible LVEF	Factorial Comparison	Total Subjects Enrolled	Subjects included in this study
MADIT-I	USA, Italy, Germany	1996	26.8	35%	ICD v. usual medical therapy	196	176
MADIT-II	USA, Netherlands, Germany, Israel	2002	20.2	30%	ICD v. usual medical therapy	1232	1080
SCD-HeFT	USA, Canada	2005	40.2	35%	ICD v. placebo v. amiodarone	2521	1611

Abbreviations: LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator.

Table 2

Baseline Characteristics of eGFR<60 and eGFR≥60 cohorts:

	eGFR < 60 N=1040	eGFR ≥ 60 N=1827	P-Value
Clinical Trial			
MADIT-I (%)	7.6	5.3	<0.001
MADIT-II (%)	40.7	36.0	
SCD-HeFT (%)	51.7	58.7	
Therapy assignment			
ICD (%)	52.0	54.3	0.2
Patient Demographics			
Age (mean, yrs)	66.6	57.9	<0.001
Female Gender (%)	20.5	18.1	0.1
Race			0.02
White (%)	84.2	79.9	
Black (%)	11.3	14.8	
Other (%)	4.5	5.3	
Comorbidities			
History of CHF(%)	60.0	54.5	0.005
Hypertension (%)	59.8	49.6	<0.001
Diabetes (%)	35.5	27.8	<0.001
Cardiac Disease characteristics			
LVEF % (mean)	23.5	23.8	0.2
Prior CABG (%)	47.1	36.0	<0.001
Left BBB (%)	21.7	19.0	0.09
NYHA class			<0.001
Class	15.7	17.4	
Class 2(%)	48.9	59.3	
Class 3(%)	35.4	23.3	
Medication use at enrollment			
Antiarrhythmic (%)	3.7	2.4	0.06
Beta-blockers (%)	59.0	66.2	<0.001
ACE inhibitor (%)	82.9	88.7	<0.001
Estimated GFR			
Mean (ml/min/1.73m ²)	44.7	78.4	<0.001
GFR<30 ml/min/1.73m ² (%)	10.3	0	

Abbreviations: LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; CHF, congestive heart failure; CABG, coronary artery bypass grafting; BBB, bundle branch block; NYHA, New York Heart Association; ACE, angiotensin converting enzyme.