











ORIGINAL RESEARCH

# Estimated Glomerular Filtration Rate and Implantable Cardioverter-Defibrillator in Nonischemic Systolic Heart Failure: Extended Follow-Up of DANISH

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**BACKGROUND:** Patients with heart failure and chronic kidney disease (CKD) may have an increased risk of death from causes competing with arrhythmic death, which could have implications for the efficacy of implantable cardioverter-defibrillators (ICDs). We examined the long-term effects of primary prophylactic ICD implantation, compared with usual care, according to baseline CKD status in an extended follow-up study of DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality).

**METHODS AND RESULTS:** In the DANISH trial, 1116 patients with nonischemic heart failure with reduced ejection fraction were randomized to receive an ICD (N=556) or usual care (N=550). Outcomes were analyzed according to CKD status (estimated glomerular filtration rate  $\geq$ / $<$ 60 mL/min per 1.73 m<sup>2</sup>) at baseline. In total, 1113 patients had an available estimated glomerular filtration rate measurement at baseline (median estimated glomerular filtration rate 73 mL/min per 1.73 m<sup>2</sup>), and 316 (28%) had CKD. During a median follow-up of 9.5 years, ICD implantation, compared with usual care, did not reduce the rate of all-cause mortality (no CKD, HR, 0.82 [95% CI, 0.64–1.04]; CKD, HR, 1.02 [95% CI, 0.75–1.38];  $P_{\text{interaction}}=0.31$ ) or cardiovascular death (no CKD, HR, 0.77 [95% CI, 0.58–1.03]; CKD, HR, 1.05 [95% CI, 0.73–1.51];  $P_{\text{interaction}}=0.20$ ), irrespective of baseline CKD status. Similarly, baseline CKD status did not modify the beneficial effects of ICD implantation on sudden cardiovascular death (no CKD, HR, 0.57 [95% CI, 0.32–1.00]; CKD, HR, 0.65 [95% CI, 0.34–1.24];  $P_{\text{interaction}}=0.70$ ).

**CONCLUSIONS:** ICD implantation, compared with usual care, did not reduce the overall mortality rate, but it did reduce the rate of sudden cardiovascular death, regardless of baseline kidney function in patients with nonischemic heart failure with reduced ejection fraction.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT00542945.

**Key Words:** chronic kidney disease ■ clinical trial ■ estimated glomerular filtration rate ■ heart failure ■ implantable cardioverter-defibrillator

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## CLINICAL PERSPECTIVE

### What Is New?

- This extended follow-up study of the DANISH (Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators in Patients With Nonischemic Systolic Heart Failure on Mortality) trial, which included 1116 patients with nonischemic heart failure with reduced ejection fraction, confirmed the strong association between chronic kidney disease and mortality.
- Implantable cardioverter-defibrillator implantation, compared with usual care, did not reduce the overall mortality rate, regardless of baseline kidney function.
- The beneficial effect of an implantable cardioverter-defibrillator on sudden cardiac death was not modified by kidney function.

### What Are the Clinical Implications?

- Although our findings indicate that the effect of implantable cardioverter-defibrillator implantation was not modified by kidney function, further study in a clinical trial designed and powered to answer this question, especially in those with severely impaired kidney function, is required.

## Nonstandard Abbreviations and Acronyms

<b>CRT</b>	cardiac resynchronization therapy
<b>DANISH</b>	Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators in Patients With Nonischemic Systolic Heart Failure on Mortality
<b>HFrEF</b>	heart failure with reduced ejection fraction

**C**hronic kidney disease (CKD) is common in patients with heart failure (HF) with reduced ejection fraction (HFrEF).<sup>1,2</sup> The presence of CKD is associated with more severe HF and worse clinical outcomes,<sup>3,4</sup> and it influences the decision to initiate, up-titrate, and discontinue life-saving guideline-recommended medical therapies. Although kidney function does not appear to modify the effects of HFrEF therapies,<sup>2</sup> there is evidence to suggest that the effect of a primary prophylactic implantable cardioverter-defibrillator (ICD) may be modified by CKD status. In a recent meta-analysis of 3 primary prevention ICD trials, there was a significant interaction between estimated glomerular

filtration rate (eGFR) and the effect of ICD implantation on all-cause mortality, with a benefit in patients with an eGFR  $\geq 60$  mL/min per 1.73 m<sup>2</sup> but not in those with an eGFR  $< 60$  mL/min per 1.73 m<sup>2</sup>.<sup>5</sup> However, the trials enrolled both patients with ischemic and nonischemic pathogenesis. More important, the trials included in this meta-analysis were conducted decades ago, and the evidence-based treatment armamentarium in HFrEF has evolved substantially since then. Therefore, it is important to examine the effects of ICD therapy in a more contemporary cohort of patients with HFrEF receiving guideline-recommended therapies according to kidney function.

In the DANISH (Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality) trial, a primary prophylactic ICD did not reduce the long-term rate of death from any cause compared with usual care, but it did reduce sudden cardiovascular death (SCD).<sup>6</sup> Here, we provide a detailed report of the effects of primary prophylactic ICD implantation in an extended follow-up study of the DANISH trial, adding 4 years of additional follow-up, according to baseline eGFR level.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. DANISH was a randomized, controlled, unblinded multicenter trial, which evaluated the efficacy and safety of primary prevention ICD implantation compared with usual care in 1116 patients with nonischemic HFrEF. The design and main findings of the trial have been published and described in detail previously.<sup>6,7</sup> The ethics committee for the Capital Region of Denmark approved the protocol (H-D-2007-0101), and all participants gave written informed consent.

### Study Participants

Key inclusion criteria were nonischemic cause of HF (preferably determined by coronary angiography, but a normal computed tomographic angiogram or nuclear myocardial perfusion imaging was accepted), a left ventricular ejection fraction  $\leq 35\%$ , New York Heart Association functional class II or III (or class IV if cardiac resynchronization therapy [CRT] was planned), an NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration  $> 200$  pg/mL, and optimal treatment with medical therapy for HF. Patients with preexisting pacemakers or CRT-pacemakers were also eligible if they were willing to accept a potential upgrade. Patients fulfilling indications for a CRT device received a CRT-defibrillator (if randomized to ICD arm) or CRT-pacemaker (if randomized to control arm). Key exclusion criteria were a resting heart rate  $> 100$  beats per

minute in patients with permanent atrial fibrillation and renal replacement therapy including dialysis. A full list of exclusion criteria is provided in the main paper.<sup>6</sup>

### eGFR Measurement

eGFR values were calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.<sup>8,9</sup> Plasma creatinine was measured at baseline in all randomized patients with contemporary clinical routine assays at the local laboratories of the enrollment sites. The assessment of the effect of ICD implantation according to baseline eGFR was a prespecified subgroup analysis.

In the present study, patients were divided in 2 subgroups according to the presence of CKD (defined as an eGFR below 60 mL/min per 1.73 m<sup>2</sup>). eGFR was also analyzed as a continuous measure and a dichotomized measure at the median, as prespecified in the primary analysis of DANISH.

### Follow-Up and Outcomes

In the main trial, patients were followed until June 30, 2016. In the present study with extended follow-up, patients were followed until May 18, 2020. No patients were lost to follow-up. The primary outcome was death from any cause, and secondary outcomes were cardiovascular death, SCD, and noncardiovascular death. All outcomes were adjudicated by an event committee blinded to treatment allocation.

In addition, device complications among patients randomized to an ICD were also examined, although these data were available only for the original follow-up duration.

### Statistical Analysis

Baseline characteristics were summarized as frequencies with percentages or medians with interquartile ranges, and differences were tested using the  $\chi^2$  test for categorical variables and unpaired *t* test or the Wilcoxon test for normally distributed and nonnormally distributed continuous variables, respectively.

The association between eGFR and outcomes (regardless of treatment allocation) was examined with the Kaplan–Meier estimator (for death from any cause), Aalen–Johansen estimator (for cardiovascular death, SCD, and noncardiovascular death, taking the competing risk of other causes of death into account), and restricted cubic spline analyses based on Cox proportional hazards regression models, adjusted for treatment assignment, age, sex, systolic blood pressure, log of NT-proBNP, left ventricular ejection fraction, prior HF hospitalization, New York Heart Association functional class, diabetes, atrial fibrillation, CRT implantation (preexisting or planned), and center. In these

analyses, an eGFR of 60 mL/min per 1.73 m<sup>2</sup> served as the reference.

The effect of ICD implantation versus usual care according to eGFR was examined with Cox proportional hazards regression models, stratified according to center and CRT implantation (preexisting or planned). In addition, models were adjusted for certain key variables that were significantly different between the ICD and control arm in each of the eGFR categories. The effect of ICD implantation was also examined according to continuous eGFR modeled as a fractional polynomial.

The effect of ICD implantation on death from any cause was also examined according to continuous age, modeled as a fractional polynomial, in patients with and without CKD, respectively.

Data were analyzed according to the intention-to-treat principle. All analyses were conducted using STATA version 17.0 and SAS version 9.4. A *P* value of 0.05 was considered statistically significant.

## RESULTS

Of the 1116 patients randomized in DANISH, eGFR values at baseline were available in 1113 individuals. Median eGFR at baseline was 73 (25th–75th 58–92) mL/min per 1.73 m<sup>2</sup>. In total, 28.4% of the participants had CKD, of whom 61.4% had stage 3A CKD (ie, eGFR 45–59 mL/min per 1.73 m<sup>2</sup>), 31.6% stage 3B CKD (ie, 30–44 mL/min per 1.73 m<sup>2</sup>), and 7.0% stage 4 (ie, 15–29 mL/min per 1.73 m<sup>2</sup>). Median follow-up was 9.5 years (interquartile range, 7.9–10.9 years).

### Patient Characteristics

Patient characteristics according to CKD status (ie, eGFR above/below 60 mL/min per 1.73 m<sup>2</sup>) are presented in [Table S1](#). Compared with patients without CKD, those with CKD were older and more likely to be men and have a higher body mass index, NT-proBNP, longer QRS duration, and lower left ventricular ejection fraction. Patients with CKD were also more likely to have a history of hypertension, diabetes, and atrial fibrillation, worse New York Heart Association functional class, and longer duration of HF than those without CKD. With respect to background HF therapy, patients with CKD were less frequently treated with a renin-angiotensin-system inhibitor and a beta blocker, but they were more likely to be treated with amiodarone and a loop diuretic and more often had a preexisting or planned CRT implantation.

Patient characteristics according to treatment assignment and CKD status are shown in [Table 1](#). Overall, patient characteristics were similar between the ICD and usual care groups in both patients with and without CKD. When baseline characteristics were examined

**Table 1. Baseline Characteristics of the Study Population According to Treatment Assignment in Patients With and Without Chronic Kidney Disease (eGFR Above/Below 60mL/min per 1.73m<sup>2</sup>)**

	No CKD eGFR ≥60mL/min per 1.73m <sup>2</sup> N=797			CKD eGFR <60mL/min/1.73m <sup>2</sup> N=316		
	Control group N=403	ICD group N=394	P value	Control group N=155	ICD group N=161	P value
Age, y, median (interquartile range)	61 (54–67)	62 (54–70)	0.40	67 (61–73)	70 (63–75)	0.10
Male sex, N (%)	274 (68.0)	277 (70.3)	0.48	128 (82.6)	128 (79.5)	0.49
Physiologic measures, median (interquartile range)						
Systolic blood pressure, mmHg	125 (112–139)	123 (110–138)	0.17	120 (109–135)	123 (108–140)	0.53
Heart rate, bpm	69 (61–78)	69 (61–77)	0.60	70 (60–78)	68 (60–76)	0.65
Body mass index, kg/m <sup>2</sup>	26 (23–30)	27 (24–30)	0.19	28 (25–32)	28 (24–31)	0.35
N-terminal pro-B-type natriuretic peptide, pg/mL	924 (501–1905)	1095 (526–2135)	0.17	1522 (808–3067)	1795 (887–3191)	0.73
eGFR, mL/min per 1.73cm <sup>2</sup>	83 (71–97)	82 (72–97)	0.88	50 (41–57)	47 (39–54)	0.05
QRS duration, msec	140 (108–164)	145 (111–165)	0.46	150 (119–166)	150 (122–168)	0.90
Left ventricular ejection fraction, %, mean (SD)	24.4 (6.3)	24.2 (6.3)	0.62	23.1 (5.5)	23.9 (6.3)	0.27
Duration of HF, median (interquartile range), months	15 (8–51)	16 (8–58)	0.65	20 (10–93)	50 (12–96)	0.14
Main cause of HF, N (%)			0.82			0.89
Idiopathic	314 (77.9)	309 (78.4)		109 (70.3)	114 (70.8)	
Valvular	12 (3.0)	13 (3.3)		9 (5.8)	7 (4.4)	
Hypertension	33 (8.2)	36 (9.1)		22 (14.2)	26 (16.2)	
Other	44 (10.9)	36 (9.1)		15 (9.7)	14 (8.7)	
New York Heart Association class, N (%)			0.58			0.28
II	239 (59.3)	226 (57.4)		59 (38.1)	71 (44.1)	
III/IV	164 (40.7)	168 (42.6)		96 (61.9)	90 (55.9)	
Medical history, N (%)						
Hospitalization for HF	263 (65.8)	246 (62.8)	0.38	98 (64.1)	113 (70.2)	0.25
Hypertension	99 (24.6)	114 (28.9)	0.16	67 (43.5)	67 (41.6)	0.73
Diabetes	69 (17.1)	53 (13.5)	0.15	41 (26.5)	46 (28.6)	0.67
Atrial fibrillation	128 (31.8)	145 (36.8)	0.13	80 (51.6)	92 (57.1)	0.32
Stroke	45 (11.2)	35 (8.9)	0.28	19 (12.3)	16 (10.0)	0.52
Treatment, N (%)						
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	396 (98.3)	388 (98.5)	0.81	146 (94.2)	144 (89.4)	0.12
Beta blocker	378 (93.8)	363 (92.1)	0.36	137 (88.4)	145 (90.1)	0.63
Mineralocorticoid receptor antagonist	237 (58.8)	237 (60.2)	0.70	81 (52.3)	88 (54.7)	0.67
Amiodarone	15 (3.7)	14 (3.6)	0.90	17 (11.0)	20 (12.4)	0.69
Loop diuretic	278 (69.0)	273 (69.3)	0.93	138 (89.0)	141 (87.6)	0.69
Thiazide	31 (7.7)	29 (7.4)	0.86	14 (9.0)	17 (10.6)	0.65
Metolazone	4 (1.0)	4 (1.0)	0.97	2 (1.3)	0 (0)	0.15
Erythropoietin	0 (0)	1 (0.3)	0.31	3 (1.9)	1 (0.6)	0.30
CRT-P/CRT-D	222 (55.1)	223 (56.6)	0.67	100 (64.5)	98 (60.9)	0.50

CKD indicates chronic kidney disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; and ICD, implantable cardioverter-defibrillator. According to the protocol, patients fulfilling criteria for CRT devices received a CRT-D if randomized to the ICD arm or received a CRT-P device if randomized to the control arm.

according to eGFR above or below the median level (73mL/min per 1.73m<sup>2</sup>), duration of HF was longer and atrial fibrillation was more common in the ICD arm than

in the usual care arm in patients with CKD, whereas diabetes was more prevalent in the usual care arm than in the ICD arm in individuals without CKD (Table S2).

## Outcomes According to Baseline eGFR

The cumulative incidence of outcomes according to CKD status (ie, eGFR above/below 60 mL/min per 1.73 m<sup>2</sup>) is shown in Figure S1. In restricted cubic spline analyses, after adjustment for prognostic variables, an eGFR <60 mL/min per 1.73 m<sup>2</sup> was associated with a greater risk of all outcomes examined although the association was not statistically significant for noncardiovascular death (Figure 1). Among patients randomized to an ICD, there was no difference in the risk of device infection, and other ICD-related complications, between patients with and without CKD (Table S3).

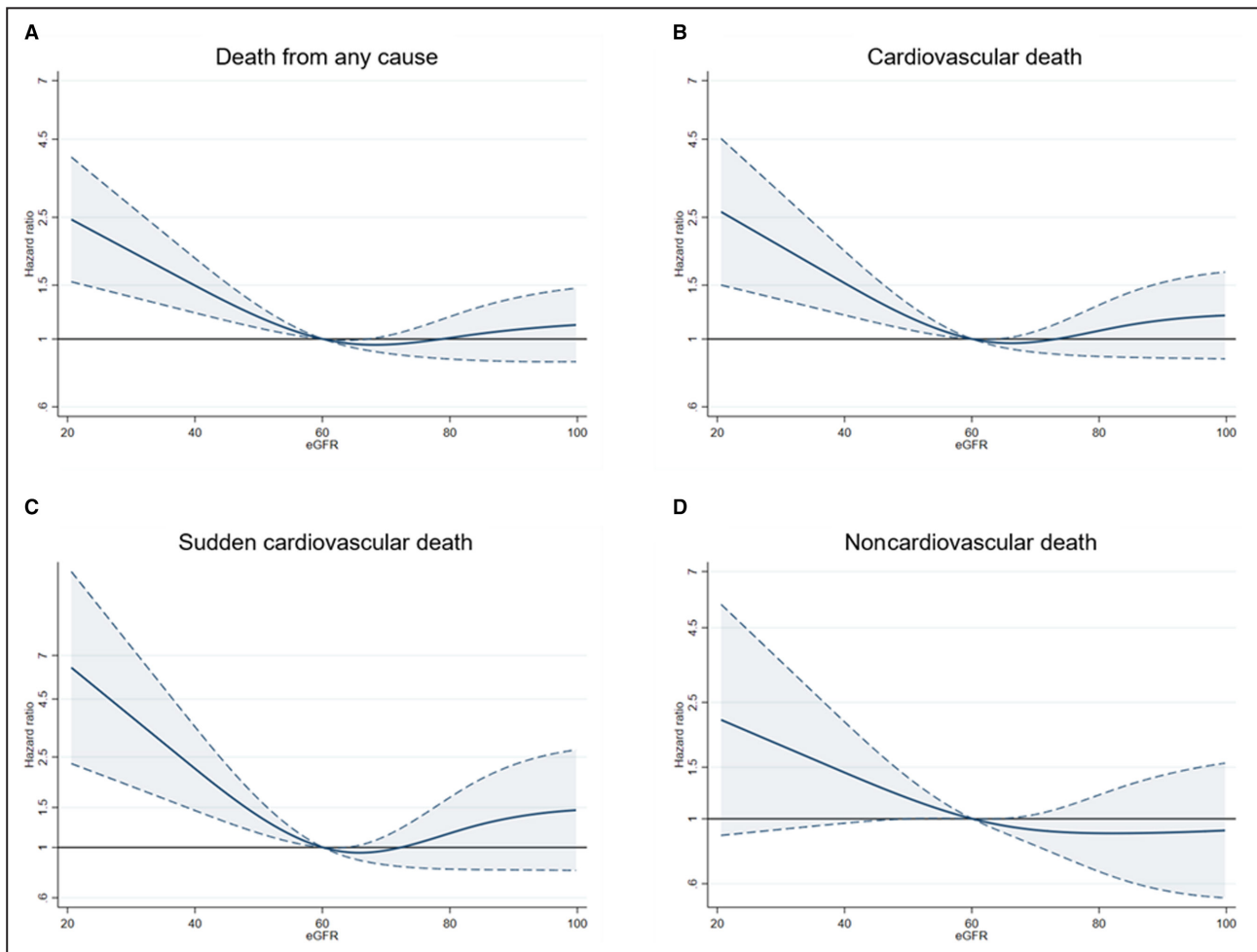
## Effect of ICD Implantation on Outcomes According to Baseline eGFR

The effects of ICD implantation on outcomes according to CKD status are shown in Figures 2 and 3 and

Table S4. ICD implantation did not significantly reduce the rate of death from any cause or cardiovascular death in patients with and without CKD, and there was no significant interaction between CKD status and the effect of ICD implantation on either of these outcomes ( $P_{\text{interaction}}=0.31$  and 0.20, respectively). Similarly, there was no significant interaction between eGFR, examined as a continuous variable, and the effect of ICD implantation on death from any cause and cardiovascular death (Figure 4A and 4B).

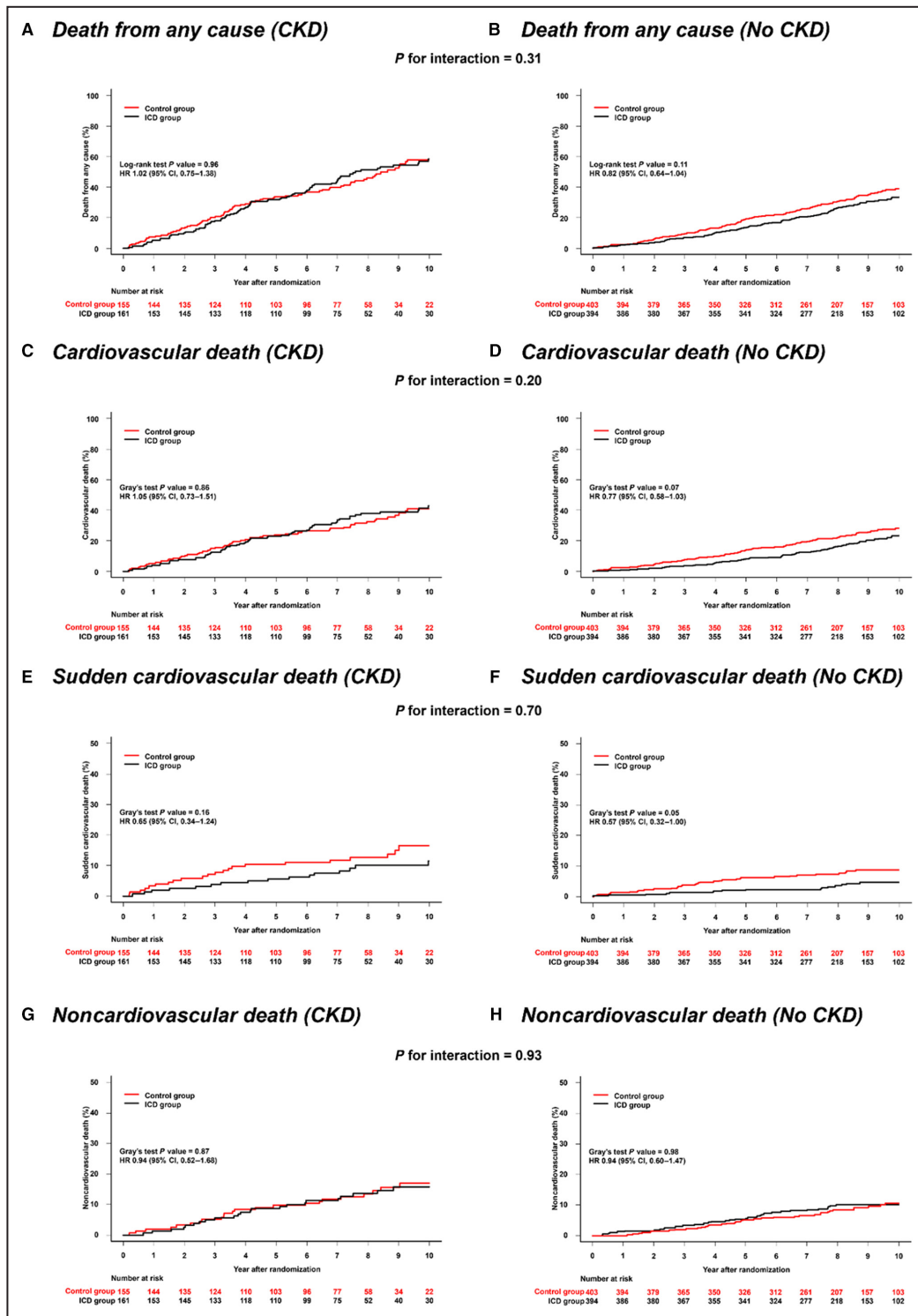
CKD status did not modify the beneficial effects of ICD implantation on the rate of SCD ( $P_{\text{interaction}}=0.70$ ). Similarly, there was no significant interaction between eGFR, examined as a continuous variable, and the effect of ICD implantation on SCD ( $P_{\text{interaction}}=0.65$ ) (Figure 4C).

ICD implantation neither reduced the rate of noncardiovascular death in patients with CKD nor in those

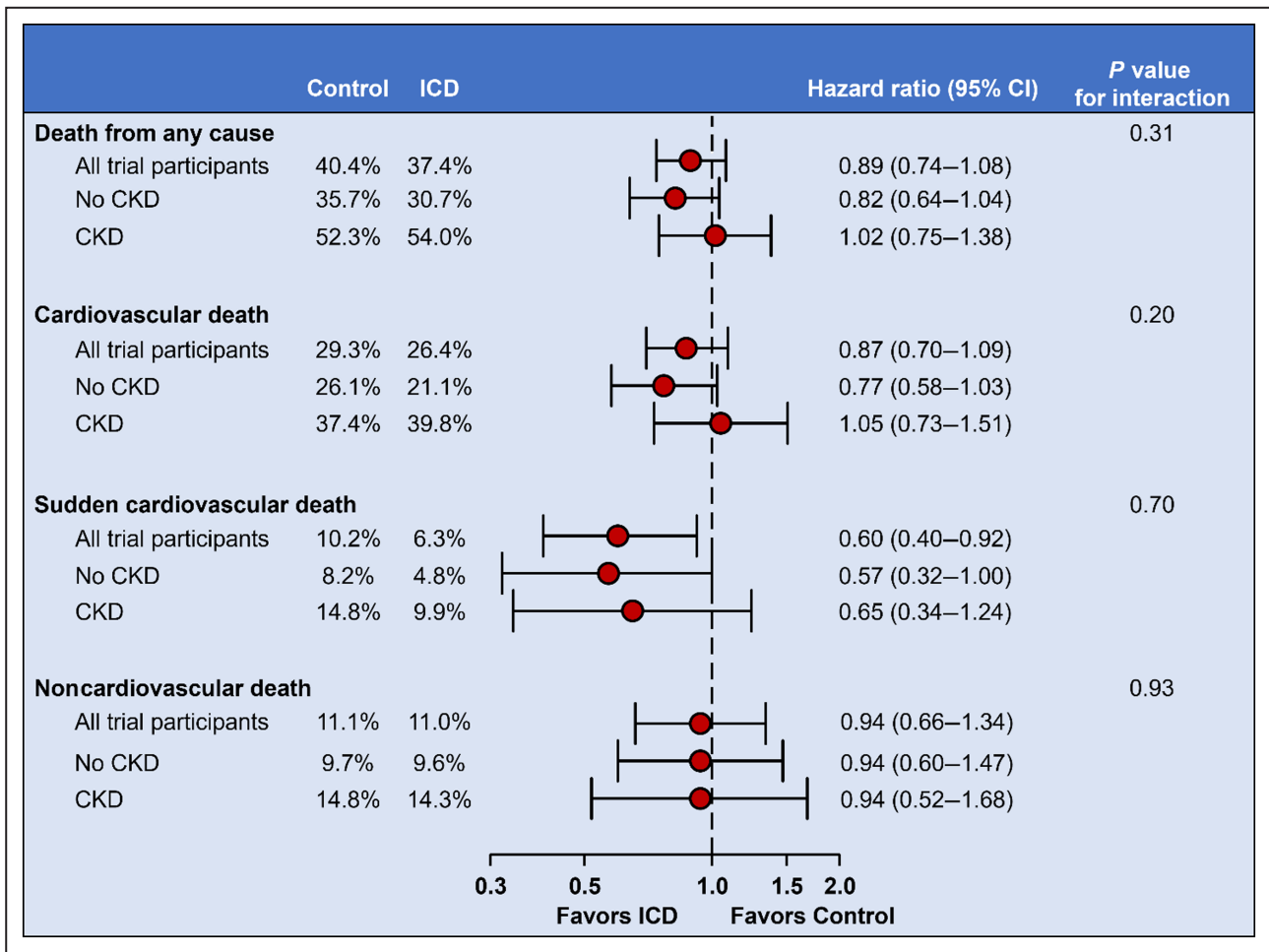


**Figure 1. Absolute risk of outcomes according to chronic kidney disease.**

**A**, Death from any cause; **B**, Cardiovascular death; **C**, Sudden cardiovascular death; **D**, Noncardiovascular death. The figures show the association between eGFR (as a continuous variable) and outcomes. The reference is 60 mL/min per 1.73 m<sup>2</sup>. The Cox models were adjusted for treatment assignment, age, sex, systolic blood pressure, log of NT-proBNP, LVEF, prior HF hospitalization, NYHA functional class, diabetes, atrial fibrillation, CRT implantation (preexisting or planned), and center. CRT indicates cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.



**Figure 2. Effect of ICD implantation compared with usual care according to CKD.** **A**, Death from any cause: eGFR <60mL/min per 1.73m<sup>2</sup>; **B**, Death from any cause: eGFR ≥60mL/min per 1.73m<sup>2</sup>; **C**, Cardiovascular death: eGFR <60mL/min per 1.73m<sup>2</sup>; **D**, Cardiovascular death: eGFR ≥60mL/min per 1.73m<sup>2</sup>; **E**, Sudden cardiovascular death: eGFR <60mL/min per 1.73m<sup>2</sup>; **F**, Sudden cardiovascular death: eGFR ≥60mL/min per 1.73m<sup>2</sup>; **G**, Noncardiovascular death: eGFR <60mL/min per 1.73m<sup>2</sup>; **H**, Noncardiovascular death: eGFR ≥60mL/min per 1.73m<sup>2</sup>. All hazard ratios are stratified according to center and cardiac resynchronization therapy implantation (preexisting or planned). CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; and ICD, implantable cardioverter defibrillator.



**Figure 3. Effect of ICD implantation compared with usual care according to CKD.** All hazard ratios are stratified according to center and cardiac resynchronization therapy implantation (preexisting or planned). CKD, chronic kidney disease; and ICD, implantable cardioverter defibrillator.

without CKD, with no interaction between eGFR and the effect of treatment (Figure 4D).

We also examined the effect of ICD implantation according to baseline eGFR levels above or below median. In line with the main findings, there was no statistically significant interaction between eGFR and the effect of ICD implantation for any of the outcomes (Table S5).

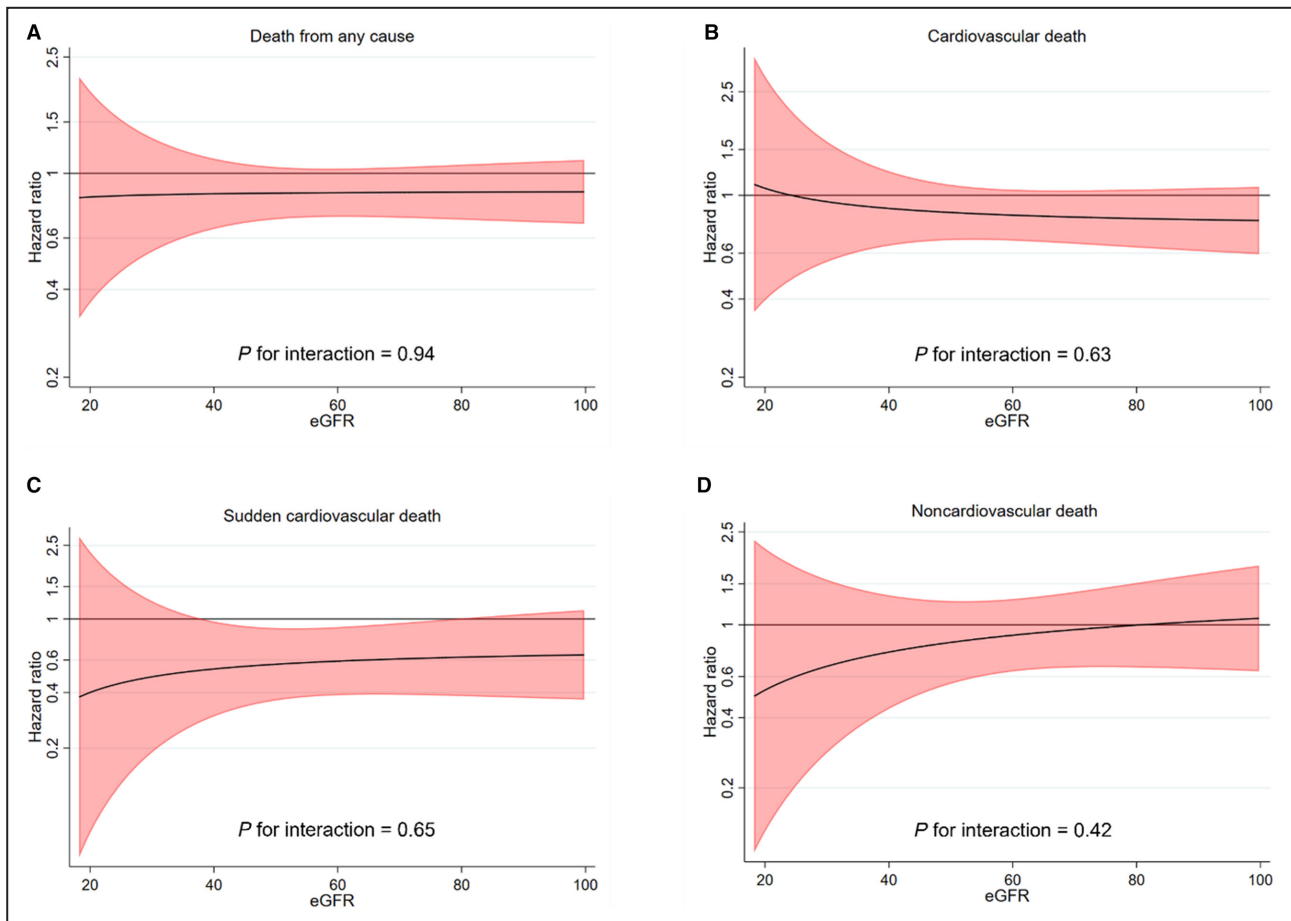
### Effect of ICD Implantation on Death From Any Cause According to Baseline eGFR and Age

In patients without CKD, age did not modify the effect of ICD implantation on death from any cause ( $P_{\text{interaction}}=0.98$ ; Figure S2A). In patients with CKD, there was a trend toward an interaction between age and the effect of ICD implantation on death from any cause, with a greater mortality reduction with ICD implantation in younger individuals ( $P_{\text{interaction}}=0.11$ ) (Figure S2B).

## DISCUSSION

In this extended follow-up study of the DANISH trial, we confirmed the strong association between CKD and mortality in patients with nonischemic HFrEF. ICD implantation, compared with usual care, did not reduce the overall mortality rate, regardless of baseline kidney function. The beneficial effect of an ICD on SCD was not modified by kidney function.

There were large differences in the clinical characteristics and outcomes between HFrEF patients with and without CKD, most of which confirmed prior findings.<sup>5,10</sup> Thus, patients with CKD were older and more often men, and they had a greater comorbidity burden, a longer duration of HF, and a higher mortality rate (irrespective of cause of death) than individuals without CKD. However, the proportion of patients with severe CKD was low, with only 2% of the DANISH population having stage 4 CKD (ie, 15–29 mL/min per 1.73 m<sup>2</sup>). The low proportion highlights the substantial underrepresentation of patients with severely impaired kidney



**Figure 4.** Effect of ICD implantation compared with usual care on outcomes according to continuous eGFR.

**A,** Death from any cause; **B,** Cardiovascular death; **C,** Sudden cardiovascular death; **D,** Noncardiovascular death. The figures show the effect of ICD implantation vs usual care on outcomes according to continuous eGFR modeled as a fractional polynomial. The model was stratified according to center and cardiac resynchronization therapy implantation (preexisting or planned). eGFR indicates estimated glomerular filtration rate; and ICD, implantable cardioverter defibrillator.

function in HFrEF trials (including those of primary prevention ICD), and greater efforts should be made to increase the representation of these patients in clinical trials to establish the effect of therapies in individuals with more severe CKD.

Nevertheless, the effects of disease-modifying, guideline-recommended HFrEF therapies, including beta blockers,<sup>11–14</sup> renin-angiotensin-system inhibitors,<sup>15,16</sup> mineralocorticoid-receptor antagonists,<sup>17,18</sup> angiotensin receptor-neprilysin inhibitors,<sup>10,19</sup> and sodium-glucose cotransporter 2 inhibitors,<sup>20–22</sup> appear to be consistent across the range of eGFRs included in landmark clinical trials. However, this may not be the case with primary prophylactic ICD implantation. In an individual participant-level data meta-analysis of MADIT-I (Multicenter Automatic Defibrillator Implantation Trial), MADIT-II, and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), there was a survival benefit with a primary prophylactic ICD,

compared with usual care, in patients without CKD but not in those with CKD.<sup>5</sup> Similarly, the beneficial effect of an ICD on arrhythmic death was attenuated in patients with CKD. An ICD can prevent SCD caused by ventricular tachyarrhythmia, severe bradycardia, or complete heart block but cannot provide protection against other causes of death, and because patients with CKD have an increased risk of competing causes of death to arrhythmic death (ie, patients with a longer duration of HF or more severe HF more often die from pump failure or terminal HF, and those with more noncardiovascular comorbidities are more likely to die from noncardiovascular causes), this potential interaction between kidney function and the effect of an ICD is biologically plausible. However, our findings from a large and well-treated cohort of patients with nonischemic HFrEF are in contrast with those from this meta-analysis. Specifically, we found that the effects of ICD implantation were not modified by kidney function, and



these results were supported by the statistically more powerful analyses of eGFR as a continuous variable, in which the treatment effect was entirely consistent across the range of baseline eGFR levels included in the DANISH trial.

The reasons for the discrepancy in results between the meta-analysis and the DANISH trial are not clear, although there are several possible explanations. First, the evidence-based treatment armamentarium in HFrEF has evolved and expanded substantially since the landmark ICD trials included in the meta-analysis were conducted,<sup>23–26</sup> and due to the cumulative benefit of these evidence-based, disease-modifying therapies, the incidence of SCD has declined in patients with HFrEF during the past decades.<sup>27</sup> Indeed, the use of renin-angiotensin-system inhibitors, beta blockers, and mineralocorticoid-receptor antagonists was markedly higher in the DANISH trial than in any previous ICD trial, and more than 50% of the DANISH participants received CRT.<sup>6,28–30</sup> Therefore, the lack of interaction between an ICD and kidney function (and the lack of efficacy of ICD implantation in patients without CKD) in the DANISH trial may be due to the low rate of SCD. Second, the majority of the patients in the meta-analysis had HF of ischemic origin,<sup>28,29</sup> whereas individuals enrolled in the DANISH trial were required to have HF of nonischemic origin, and patients with ischemic HF may be more susceptible to ventricular arrhythmias, originating from myocardial scar tissue, than those with nonischemic HF.<sup>31,32</sup> Finally, given the limitations of subgroup analyses, a significant interaction (or the lack thereof) could simply have resulted by chance, and the findings should therefore be considered as hypothesis generating. Thus, it remains uncertain whether kidney function, especially in the lower eGFR range or in patients on dialysis, modifies the effect of an ICD. Therefore, there is a need for a randomized clinical trial specifically designed and powered to address this question. Although the DANISH trial and the ICD trials included in the meta-analysis described here excluded patients undergoing dialysis, the ICD2 (Implantable Cardioverter-Defibrillator in Dialysis Patients) trial examined the effects of prophylactic ICD implantation, compared with usual care, in dialysis-treated patients with a left ventricular ejection fraction  $\geq 35\%$ . In this trial, ICD implantation did not reduce the rate of SCD or all-cause mortality, but <200 patients were included, and because <5% had HF, these findings cannot be extrapolated to patients with HFrEF.<sup>33</sup>

## Limitations

This study has some limitations that need to be acknowledged. First, although the assessment of the effect of ICD implantation on death from any cause according to baseline eGFR, dichotomized at the

median, was prespecified, the examination of secondary outcomes was done post hoc, as was the assessment of the effect of ICD implantation according CKD status. Because the trial was not powered to examine the effect of ICD in a subgroup of patients, the results should be interpreted with caution and considered as hypothesis generating at best. Second, as in any clinical trial, the prespecified inclusion and exclusion criteria in DANISH precluded the enrollment of very high-risk patients, and the study population was predominantly White. Third, the number and proportion of patients with stage 4 CKD were low (2% of the DANISH population; 7% of the DANISH population with CKD) and patients on dialysis were excluded. Consequently, these findings cannot be generalized to individuals with severely impaired kidney function. Fourth, the requirement of optimal medical therapy might have resulted in a lower proportion of patients with CKD in the DANISH trial, because these patients have a lower tolerance to HF therapies. Fifth, although it would have been interesting to examine longitudinal changes in eGFR, we did not have data on eGFR during follow-up. Finally, in the analysis comparing outcomes between patients with and without CKD, the risk of residual confounding cannot be excluded despite comprehensive adjustment. Therefore, causal inference cannot be drawn from these analyses.

## CONCLUSIONS

In an extended follow-up study of the DANISH trial, ICD implantation, in comparison with usual care, did not reduce the overall mortality rate, but it did reduce the rate of SCD, regardless of baseline kidney function in patients with nonischemic HFrEF.

## ARTICLE INFORMATION

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## Supplemental Material

Tables S1–S5  
Figures S1–S2

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