Renal function and the long term clinical outcomes of cardiac resynchronization therapy with or without defibrillation

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Short title: Renal function and CRT

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ABSTRACT

Background and Aims: Patients with moderate-to-severe chronic kidney disease (CKD) are underrepresented in clinical trials of cardiac resynchronization therapy (CRT)-defibrillation or CRT-pacing (CRT-P). We sought to determine whether outcomes after CRT-D are better than after CRT-P over a wide spectrum of CKD.

Methods and Results: Clinical events were quantified in relation to pre-implant estimated glomerular filtration rate (eGFR) after CRT-D (n=410 [39.2%]) or CRT-P (n=636 [60.8%]) implantation. Over a follow-up period of 3.7 years (median, interquartile range: 2.1-5.7), the eGFR<60 group (n=598) had a higher risk of total mortality (adjusted hazard ratio [aHR]:1.28; p=0.017), total mortality or heart failure (HF) hospitalization (aHR:1.32; p=0.004), total mortality or hospitalization for major adverse cardiac events (MACEs, aHR:1.34; p=0.002) and cardiac mortality (aHR:1.33; p=0.036), compared to the eGFR≥60 group (n=448), after covariate adjustment. In analyses of CRT-D vs CRT-P, CRT-D was associated with a lower risk of total mortality (eGFR≥60 HR: 0.65; p=0.028; eGFR<60 HR 0.64, p=0.002), total mortality or HF hospitalization (eGFR≥60: aHR:0.66; p=0.021; eGFR<60 aHR: 0.69, p=0.007), total mortality or hospitalization for MACEs (eGFR≥60: aHR:0.70; p=0.039; eGFR<60 aHR: 0.69, p=0.005) and cardiac mortality (eGFR≥60: aHR:0.60; p=0.026; eGFR<60 aHR:0.55; p=0.003).

Conclusion: In CRT recipients, moderate CKD is associated with a higher mortality and morbidity compared to normal renal function or mild CKD. Despite less favourable absolute outcomes, patients with moderate CKD had better outcomes after CRT-D than after CRT-P.

Keywords

chronic kidney disease; cardiac resynchronization therapy; heart failure; implantable cardioverter defibrillator

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure (HF), impaired left ventricular (LV) function and a wide QRS complex. (1) Some observational studies have suggested that CRT may be undermined by renal dysfunction. (2; 3) In the 'real world', more than half of patients with HF have chronic kidney disease (CKD) stages 3-5. (4)

The higher risk of sudden cardiac death (SCD) in CKD (5; 6) enhances the 'substrate' for defibrillation. In keeping with the hypothesis that the 'sickest benefit the most' (7), the proportional benefit of CRT-D should be greater in patients with CKD. There is, however, uncertainty as to the benefit of implantable-cardioverter defibrillators (ICDs) in patients with CKD. (8) In this respect, a meta-analysis of patient-level data from 3 randomized trials of primary prevention ICD found no benefit of ICD among 1,040 patients with eGFR<60 ml/min. (9) Comparisons between CRT-D and CRT-P in patients with CKD have not been undertaken.

In this observational study of real-world clinical practice, we have assessed the long-term outcomes of CRT according to pre-implant renal function. Because of the restrictions on CRT-D placed by national guidelines, (10) our study population comprises a substantial

proportion of CRT-P recipients. This provides a unique opportunity for a comparison of long-term outcomes of CRT-D and CRT-P.

METHODS

The study population consisted of patients undergoing a successful CRT device implantation for primary prevention in the period from October 2005 to January 2017 at 2 centres (Good Hope Hospital and Queen Elizabeth Hospital, Birmingham, United Kingdom). Device choice was governed by the National Institute of Clinical Excellence guidelines, which in 2007 recommended CRT-P rather than CRT-D for patients with non-ischemic cardiomyopathy and indications for CRT. With a subsequent guideline change in 2014 recommending CRT-D in non-ischemic cardiomyopathy, (10) the proportion of CRT-D recipients increased thereafter. The study was approved by the local Ethics Committee or the local Clinical Audit Departments, which do not require informed consent for audits of clinical care delivery and outcomes. The study conforms with the Declaration of Helsinki.

The diagnosis of HF was made on the basis of clinical features plus echocardiographic evidence of LV systolic dysfunction. The etiology of HF was based on the findings from a clinical history (myocardial infarction, coronary revascularization) and/or investigations (eg. cardiovascular magnetic resonance and nuclear imaging). Patients with hypertrophic or restrictive cardiomyopathy, primary valvular disease, sarcoidosis, amyloidosis, congenital heart disease or myocarditis were excluded. Patients who were recruited to clinical trials were also excluded.

Device therapy. Standard transvenous techniques under local anesthesia and intravenous sedation were used for device implantation. Thereafter, patients were followed up in

dedicated device therapy clinics on a 6-monthly basis, patients with events were assessed opportunistically according to clinical need. Device optimization using trans-mitral Doppler-directed optimization of atrioventricular delay using an iterative technique was undertaken up to 2013. In the light of emerging evidence, routine echocardiographic optimization was abandoned. Thereafter, optimization was only undertaken in symptomatic non-responders. In patients in sinus rhythm, backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an inter-ventricular delay of 0-4 ms. In patients with permanent atrial fibrillation, right ventricular and LV leads were implanted and a CRT generator was used, plugging the atrial port and programming to a ventricular triggered mode. Atrioventricular junction ablation was undertaken according to physicians' discretion.

Endpoints. The primary endpoint was total mortality. Secondary endpoints included: cardiac mortality, which included cardiac transplantation or implantation of a left ventricular assist device; the composite endpoint of total mortality or HF hospitalization; the composite endpoint of total mortality or unplanned hospitalization for major adverse cardiac events (MACEs), which included hospitalization for HF, myocardial infarction, acute coronary syndrome and arrhythmia (ventricular tachycardia, ventricular fibrillation and atrial fibrillation). Stroke and pulmonary embolism were not considered as MACEs. Therapies delivered by CRT-D devices (anti-tachycardia pacing and shocks) were evaluated for appropriateness using electrograms. Only appropriate therapies were considered. In composite endpoints, the first event was used for censoring. Mortality data was collected through medical records and from interviews with patients' caregivers. Clinical events were collected every 6 months by investigators who were blinded to all other patient data, apart from demographics. These were adjudicated by blinded investigators on a 6-monthly basis.

Renal function. The GFR was estimated (eGFR) using the simplified formula derived from the Modification of Diet in Renal Disease (MDRD) study, which has been validated in patients with heart failure. (11) In data analysis, we have used the eGFR threshold of <60 mL/min per 1.73 m^2 in the definition of renal dysfunction. This cut-off has been used extensively in CRT studies. (12-14)

Statistical analysis

Baseline characteristics were compared between patients with eGFR<60 and ≥60 mL/min per 1.73 m^2 as well as across device types. Continuous variables were expressed as mean ± standard deviation (SD). Normality was tested using the Shapiro-Wilk test. Comparisons between normally distributed continuous variables were analyzed using ANOVA and categorical variables were analyzed using chi-squared tests. Kaplan-Meier curves and the log-rank test were used to assess cumulative survival. Multivariate Cox proportional hazard models were used to assess relative hazard rates comparing eGFR<60 and ≥60 mL/min per 1.73 m^2 as well the impact of eGFR as a continuous measurement. Variables with a p <0.10 on univariable analyses were entered in multivariate models, and further backward elimination was applied for the final multivariate models. Interactions between eGFR and device type was tested and interaction p values for CRT-D versus CRT-P were reported for the 2 eGFR groups. Proportionality hypotheses were verified by visual examination of log (survival) graphs to ensure parallel slopes and by examining Schoenfeld residuals. In P-spline analyses, predicted risks of total mortality were calculated considering eGFR as a continuous variable and a eGFR of 60 mL/min per 1.73 m^2 was used as reference. Separate analyses were undertaken for the interaction between CRT-D and CRT-P. Statistical analyses were undertaken using Stata 14 (StataCorp, Texas). A two-sided p ≤0.05 was considered statistically significant.

RESULTS

Baseline characteristics according to renal function. Of a total of 1,046 patients, 488 (42.8%) had a pre-implant eGFR ≥60 and 598 (57.2%) a eGFR<60. As shown in **Table 1**, patients in eGFR<60 were 6.8 years older (p<0.001), were less likely to receive a CRT-D (p=0.026) and were more likely to have ischemic cardiomyopathy (p=0.001), diabetes (p=0.030), hypertension (p=0.009), a previous CABG (p=0.004) and atrial fibrillation (p=0.009). In addition, the eGFR<60 group had a higher uptake of loop diuretics (p=0.018) and a lower uptake of ACEIs/ARAs (p<0.001). The 2 groups were well matched for sex, NYHA class, upgrade from pacemakers, QRS morphology, QRS duration, LVEF, as well as uptake of beta-blockers and MRAs.

Outcomes according to renal function. As shown in **Figure 1**, patients with eGFR<60 had a higher total mortality, total mortality or HF hospitalization, total mortality or hospitalization for MACEs, and cardiac mortality. Total mortality was 273/598 (45.7%); 14.0 per 100 person-years) in the eGFR<60 group and 162/488 (33.2%); 9.11 per 100 person-years) in the eGFR ≥60 group (**Table S1, Online Appendix**). Over a maximum follow-up period of 12 years (median of 3.7 years (interquartile range [IQR]: 2.1-5.7; 3.4 years [IQR, 1.9-5.4] for eGFR<60 and; 3.9 years [IQR: 2.2-6.0] years for eGFR ≥60), the eGFR<60 group had a higher risk of total mortality (HR:1.53; 95% CI 1.26-1.86), total mortality or HF hospitalization (HR:1.55; 95% CI 1.29-1.86), total mortality or hospitalization for MACEs (HR:1.51; 95% CI 1.26-1.80) and cardiac mortality (HR:1.55; 95% CI 1.23-1.95). Analyses of crude hazard ratios of total mortality and of eGFR in subgroups is shown in **Figure S1, Online Appendix.**

The survival benefit of eGFR≥60 was seen in most subgroups except for age <59 or ≥80 years, female sex, NYHA class IV, with diabetes and LVEF≤0.25. In multivariate analyses (**Table 2**), the eGFR<60 group had a higher risk of total mortality (aHR:1.28; 95% CI 1.04-1.57), total mortality or HF hospitalization (aHR:1.32; 95% CI 1.09-1.59), total mortality or hospitalization for MACEs (aHR:1.34; 95% CI 1.11-1.61), and cardiac mortality (aHR:1.33; 95% CI 1.02-1.74), after covariate adjustment. When eGFR was considered as continuous variable, a eGFR decrement of 10 mL/min per 1.73 m^2 was associated with a higher total mortality (aHR:1.09; 95% CI 1.04-1.15), a higher total mortality or HF hospitalization (aHR:1.11; 95% CI 1.05-1.16) and a higher total mortality or hospitalization for MACEs (aHR:1.10; 95% CI 1.05-1.15), after covariate adjustment.

Baseline characteristics according to device type. Over the study period, 1,046 patients underwent primary prevention CRT-D (n=410 [39.2%]) or CRT-P (n=636 [60.8%]). As shown in **Table 1**, significant differences emerged between CRT-D and CRT-P patients with respect to most baseline characteristics. Notably, CRT-D patients were 4.6 years younger (p<0.001) and a greater proportion were men (p<0.001). In addition, CRT-D patients had a lower NYHA class (76.4% in class III or IV, compared with 86.2% in CRT-P patients, p<0.001) and a higher eGFR (by 2.6 mL/min per 1.73 m^2, p=0.042).

Outcomes according to device type. In univariate analyses, CRT-D patients had a lower crude total mortality (HR: 0.68; 95% CI 0.55-0.84), total mortality or HF hospitalization (HR: 0.73; 95% CI 0.60-0.88), total mortality or hospitalization for MACEs (HR:0.74; 95% CI 0.62-0.90) and cardiac mortality (HR:0.67; 95% CI 0.52-0.86). **Figure 2** shows that the benefit of CRT-D over CRT-P was evident for both eGFR<60 and ≥60 groups.

In multivariate analyses (**Table 2**), CRT-D was associated with a lower total mortality in both eGFR groups (eGFR≥60 aHR: 0.65; 95% CI 0.45-0.95; eGFR<60 aHR 0.64, 95% CI 0.48-0.85). A similar trend was observed for total mortality or HF hospitalization, total mortality or hospitalization for MACEs and cardiac mortality. We did not find any device type / eGFR interaction when comparing CRT-D with CRT-P (all p>0.5) (**Table S2, Online Appendix**). The relative risks of total mortality increased and difference between CRT-D and CRT-P narrowed as the eGFR decreased below 60 (**Figure S2, Online Appendix**)

To explore possible effects of date of implantation on outcomes, we used different year dummies on survival analyses and found that date of implantation did not predict any of the endpoints (data not shown).

DISCUSSION

This is the largest study comparing mortality and morbidity after CRT-D and CRT-P in relation to pre-implant renal function. We found that a eGFR<60 was associated with a higher risk of total mortality, total mortality or HF hospitalization, total mortality or hospitalization for MACE, and cardiac mortality, compared to a eGFR≥60. Moreover, despite less favourable outcomes compared to eGFR≥60 group, CRT-D was associated with a lower total mortality and composite endpoints in the eGFR<60 group.

Renal function and outcomes. We have observed that CKD was associated with a higher total mortality. Every 10 mL/min per 1.73 m^2 decrement in eGFR was associated with a 15% higher crude total mortality (9% after covariate adjusment). This is broadly consistent with several observational studies. In a registry of 716 consecutive CRT recipients, a 10 mL/min

per 1.73 m^2 decrement in eGFR was associated with a 18% higher total mortality. (15) In a study of 432 CRT-D recipients, the estimated 5-year mortality rose from 36.3% for CKD stage 1 to 62.1% for CKD stage 4 and 5. (16) In the National Cardiovascular Data Registry (ICD Registry), the 3-year mortality for CRT-D patients with end-stage renal failure was 54%. (2)

In subgroup analyses (**Figure 2**), the survival benefit of eGFR≥60 was seen in most subgroups on total mortality, except for age (<59 years or ≥80 years), female sex, NYHA class IV, diabetes or LVEF <25%. With respect to female sex, several studies have shown a more favourable outcome from device therapy in women. (17-19) and it appears that the protective effect of female sex somehow overrides the effects of renal dysfunction. With respect to age, it is conceivable that the natural mortality expected at the age of ≥80 years overrides the effects of renal dysfunction. Arguably, severe pump failure, in the context of NYHA class IV or a LVEF<25%, may also be expected to override renal dysfunction.

CRT-D versus CRT-P: We found that CRT-D was superior to CRT-P with respect total mortality, total mortality or HF hospitalization, total mortality or hospitalization for MACEs, and cardiac mortality. Importantly, the lower risk of these endpoints with CRT-D over CRT-P evident in patients with a eGFR<60, despite that these outcomes were worse than in the eGFR≥60 group. This suggests that in CRT recipients, CRT-D is superior to CRT-P, regardless of renal function.

A subanalysis of MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) showed that although total mortality was higher in patients with a GFR<60, compared to patients with a eGFR ≥60, the reduction in total

mortality and total mortality or HF hospitalization was actually greater in the GFR<60 group. (12) Importantly, MADIT-CRT compared CRT-D with ICD and therefore, the reported findings relate to the effects resynchronization rather than defibrillation. In the present study, which compares CRT-D versus CRT-P rather than CRT-D with ICD, the superior outcomes of CRT-D must, intuitively, be due to delivered antitachycardia pacing and shocks. However, the rate of delivered therapies were similar in both eGFR groups. Why the same rate of such therapies should translate to better outcomes, in terms of total and cardiac mortality, even in patients with an eGFR<60, is not immediately apparent. The possibility arises that, over and above the benefits of CRT, antitachycardia pacing or shocks carry a greater proportional survival advantage in advanced CKD (eGFR<60).

Clinical application

Physicians may be tempted to avoid device therapy in patients with renal dysfunction, (20) given reports of poor outcomes and an increased risk of complications. (2) This study shows that after CRT, patients with CKD had a worse prognosis than patients with normal or mildly impaired renal function. Nevertheless, patients lived longer and were less likely to be hospitalized for HF or MACE after CRT-D than after CRT-P. These findings support the preferential use of CRT-D over CRT-P in patients with moderate CKD.

Limitations

This study has the limitations of an observational study. We did not include patients without CRT-D or CRT-P therapy as a control group and we cannot therefore comment on the relative benefit of device therapy over optimal medical therapy. Although we have included more patients with severe renal dysfunction than any other study (n=84 with eGFR<30 or end-stage renal failure), we lack statistical power to adequately compare CRT-D versus CRT-

P in patients at these extremes of renal dysfunction. In addition, it is possible that renal dysfunction influenced the prescription and choice of device therapy, which was based on physician's decisions rather than by study design. The national guidelines on CRT represent an *a priori* selection bias on device type selection which may have influenced outcomes. Notwithstanding, the group difference in eGFR was only marginal (2.6 mL/min per 1.73m^2). We have no data as to the number of patients who were excluded from device therapy on the basis of renal dysfunction. A further limitation is the lack of data with regard to optimization of medical therapy following device implantation. Unfortunately, we lack data on the exact number of clinic visits per patient, or the reasons behind them. It is possible that differences in clinical follow-up could have influenced our results. Differences in the biventricular pacing uptake between the CRT-D and CRT-P groups, which were not addressed, could also account for differences in outcomes.

CONCLUSIONS

In CRT recipients, moderate CKD was associated with a higher total mortality and morbidity compared to normal renal function or mild CKD. Despite less favourable absolute outcomes, patients with moderate CKD had better outcomes from CRT-D than after CRT-P. These findings support the preferential use of CRT-D over CRT-P in patients with moderate CKD who are considered candidates for CRT.

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FIGURE LEGENDS

Figure 1. Primary and Secondary Endpoints According to Renal Function.

Kaplan-Meier survival curves for clinical outcomes according to renal function. Patients were grouped according to a eGFR < or ≥60 mL/min per 1.73m^2.

CRT-D = cardiac resynchronization therapy-defibrillation.; CRT-P = cardiac resynchronization therapy-pacing; HF = heart failure; MACE = major adverse cardiovascular events.
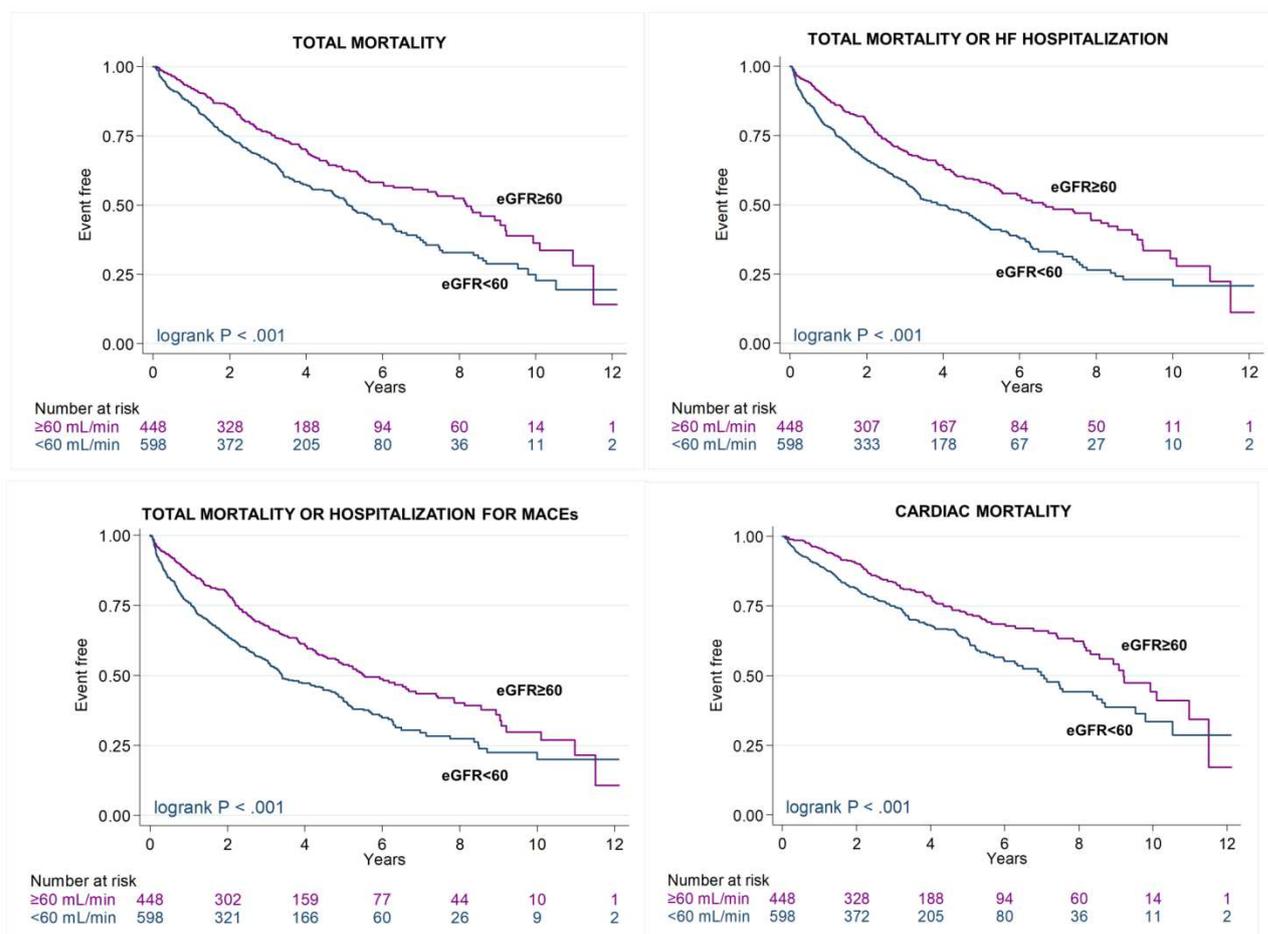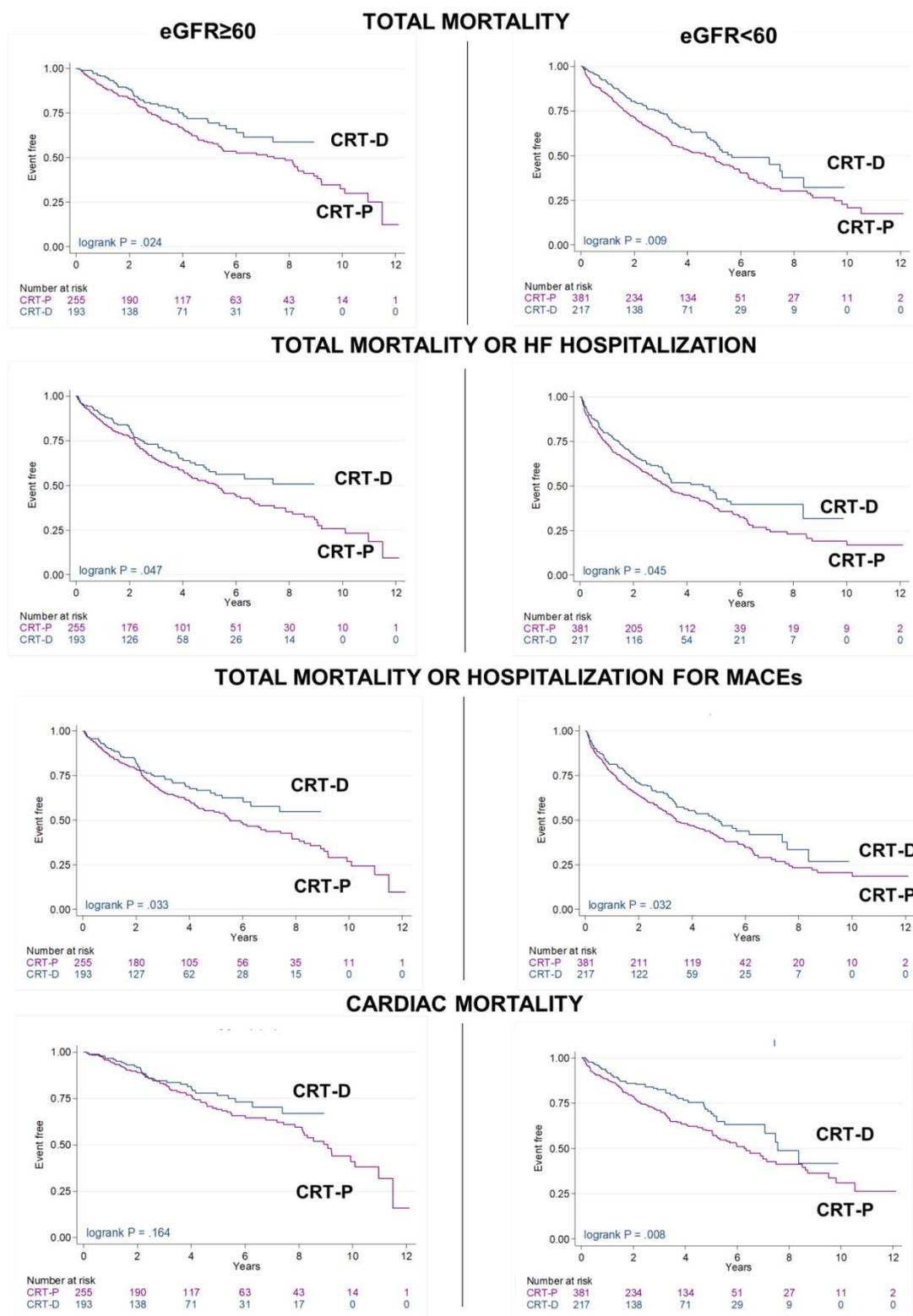
Figure 2. Primary and Secondary Endpoints According to Device Type and Renal Function.

Kaplan-Meier survival curves for clinical outcomes according to device type, in the categories of renal function according to a eGFR < or ≥60 mL/min per 1.73m^2.

CRT-D = cardiac resynchronization therapy-defibrillation.; CRT-P = cardiac resynchronization therapy-pacing; HF = heart failure; MACE = major adverse cardiovascular events.

Table 1. Baseline Characteristics.

	All	eGFR≥60	eGFR<60	p*	CRT-D	CRT-P	p*
N	1,046	448	598		410	636	<0.001
eGFR (mL/min per 1.73m^2)	57.1±20.2	75.9±12.7	43.1±11.8	<0.001	58.7±19.8	56.1±20.6	0.042
eGFR≥60	-	-	-	-	193 (47.07)	255 (40.09)	0.026
eGFR<60	-	-	-	-	217 (52.93)	381 (59.91)	
Sex (male), n (%)	756 (72.28)	331 (73.88)	425 (71.07)	0.314	322 (78.54)	434 (68.24)	<0.001
Age, yrs	72.8±10.8	68.9±11.5	75.7±9.2	<0.001	70.0±9.8	74.6±11.1	<0.001
≤59	130 (12.43)	94 (20.98)	36 (6.02)	<0.001	61 (14.88)	69 (10.85)	<0.001
60-69	260 (24.86)	139 (31.03)	121 (20.23)		133 (32.44)	127 (19.97)	
70-79	377 (36.04)	135 (30.13)	242 (40.47)		161 (39.27)	216 (33.96)	
≥80	279 (26.67)	80 (17.86)	199 (33.28)		55 (13.41)	224 (35.22)	
NYHA class							
I	50 (4.82)	26 (5.84)	24 (4.05)	0.120	33 (8.13)	17 (2.69)	<0.001
II	133 (12.83)	64 (14.38)	69 (11.66)		63 (15.52)	70 (11.09)	
III	723 (69.72)	308 (69.21)	415 (70.10)		281 (69.21)	442 (70.05)	
IV	131 (12.63)	47 (10.56)	84 (14.19)		29 (7.14)	102 (16.16)	
Device type, n (%)							

CRT-D	410 (39.20)	193 (43.08)	217 (36.29)	0.026	-	-	-
CRT-P	636 (60.80)	255 (56.92)	381 (63.71)		-	-	-
Upgrade from pacemaker	174 (16.63)	71 (15.85)	103 (17.22)	0.554	48 (11.71)	126 (19.81)	0.001
Etiology of cardiomyopathy, n (%)							
Ischemic	561 (53.63)	213 (47.54)	348 (58.19)	0.001	300 (73.17)	261 (41.04)	<0.001
Non-ischemic	485 (46.37)	235 (52.46)	250 (41.81)		110 (26.83)	375 (58.96)	
Co-morbidities, n (%)							
Diabetes mellitus	237 (22.66)	87 (19.42)	150 (25.08)	0.030	102 (24.88)	134 (21.07)	0.150
Hypertension	311 (29.73)	114 (25.45)	197 (32.94)	0.009	108 (26.34)	203 (31.92)	0.054
CABG	193 (18.45)	65 (14.51)	128 (21.40)	0.004	102 (24.88)	91 (14.31)	<0.001
ECG variables							
Sinus rhythm, n (%)	701 (67.02)	320 (71.43)	381 (63.71)	0.009	296 (72.20)	405 (63.68)	0.004
Atrial fibrillation, n (%) †	345 (32.98)	128 (28.57)	217 (36.29)		114 (27.80)	231 (36.32)	
QRS morphology (LBBB), n (%)	828 (79.69)	357 (80.04)	471 (79.43)	0.806	322 (78.92)	506 (80.19)	0.620
QRS duration (ms)	154.9±23.2	154.5±22.4	155.2±23.8	0.662	152.7±23.1	156.3±23.1	0.015
Medication, n (%)							
Loop diuretics	991 (94.74)	416 (92.86)	575 (96.15)	0.018	398 (97.07)	593 (93.24)	0.007
ACEIs / ARAs	923 (88.24)	419 (93.53)	504 (84.28)	<0.001	381 (92.93)	542 (85.22)	<0.001
Beta-blockers	720 (68.83)	311 (69.42)	409 (68.39)	0.723	315 (76.83)	405 (63.68)	<0.001
MRAs	431 (41.20)	188 (41.96)	243 (40.64)	0.666	207 (50.49)	224 (35.22)	<0.001
LVEF (%)	24.8±9.8	25.1±9.5	24.5±10.0	0.338	23.7±9.0	25.5±10.2	0.006

Patients were grouped according to pre-implant estimated glomerular filtration rate (eGFR) <60 or ≥60 mL/min per 1.73 m^2 and device type.

Variables are expressed as mean ± SD, unless indicated otherwise.*, refers to differences

between the groups from ANOVA for continuous variables and from chi-squared tests for

categorical variables; †, includes permanent, persistent and paroxysmal atrial fibrillation (AF).

ACEIs indicates angiotensin-converting enzyme inhibitors; ARAs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; MRA, mineralocorticoid receptor antagonists.

Table 2. Multivariate Analyses.

	TOTAL MORTALITY				TOTAL MORTALITY OR HF HOSPITALIZATION				TOTAL MORTALITY OR MACEs				CARDIAC MORTALITY			
	HR	95% C.I.		p	HR	95% C.I.		p	HR	95% C.I.		p	HR	95% C.I.		p
eGFR<60	1.28	1.04	1.57	0.017	1.32	1.09	1.59	0.004	1.34	1.11	1.61	0.002	1.33	1.02	1.74	0.036
Sex (male)	1.70	1.34	2.16	<0.001	1.51	1.22	1.88	<0.01	1.47	1.19	1.81	<0.001	1.68	1.22	2.32	0.002
Age (yrs)	1.03	1.02	1.04	<0.001	1.02	1.01	1.03	<0.01	1.02	1.01	1.03	0.01	1.02	1.00	1.03	0.029
NYHA class																
III	1.77	1.17	2.68	0.007	1.44	1.03	2.03	0.035	1.51	1.08	2.11	0.017	-			
IV	3.85	2.47	6.00	<0.001	3.13	2.15	4.57	<0.01	3.08	2.12	4.48	<0.001	2.51	1.85	3.40	<0.001
Device type (CRT-D)	0.67	0.53	0.84	0.001	0.70	0.57	0.87	0.001	0.72	0.58	0.89	0.002	0.64	0.47	0.87	0.004
Etiology (ischemic)	1.24	1.00	1.53	0.049	1.29	1.06	1.58	0.012	1.39	1.14	1.69	0.001	1.41	1.06	1.87	0.017
Diabetes mellitus	-				1.26	1.02	1.55	0.033	1.25	1.02	1.54	0.034	1.40	1.06	1.87	0.020

Atrial fibrillation		-				-				-			1.30	0.99	1.70	0.057
QRS duration (ms)	0.99	0.99	1.00	0.004	0.99	0.99	1.00	<0.01	0.99	0.99	1.00	<0.001	0.99	0.98	1.00	0.01
Loop diuretics		-			1.56	1.01	2.42	0.046		-				-		
Beta-blockers		-				-			0.82	0.68	0.98	0.032	0.77	0.59	1.00	0.047
LVEF (%)		-				-				-			0.98	0.97	1.00	0.008

Data is expressed in terms of hazard ratios (HR) and 95% confidence intervals (95% CI).

CRT-D indicates cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing.