Long-term Impact of Body Mass Index on Survival of Patients Undergoing Cardiac Resynchronization Therapy: A Multi-Centre Study

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Abstract

Obesity is a risk factor for heart failure (HF), but its presence among HF patients may be associated with favorable outcomes. We investigated the long-term outcomes across different body mass index (BMI) groups, after cardiac resynchronization therapy (CRT), and whether defibrillator back-up (CRT-D) confers survival benefit. One thousand two-hundred seventy-seven (1,277) consecutive patients (mean age: 67.0±12.7 years, 44.1% women, and mean BMI: 28.3±5.6 Kg/m^2) who underwent CRT implantation in 5 centers between 2000-2014 were followed-up for a median period of 4.9 years (IQR 2.4-7.5). More than 10% of patients had follow-up for ≥10 years. Patients were classified according to BMI as normal: <25.0 Kg/m^2, overweight: 25.0-29.9 Kg/m^2 and obese: ≥30.0 Kg/m^2. 364 patients had normal weight, 494 were overweight and 419 were obese. CRT-Ds were implanted in >75% of patients, but were used less frequently in obese individuals. The composite endpoint of all-cause mortality or cardiac transplant/left ventricular assist device (LVAD) occurred in 50.9% of patients. At 10-year follow-up, less than a quarter of patients in the lowest and highest BMI categories were still alive and free from heart transplant/LVAD. After adjustment BMI of 25-29.9 Kg/m^2 (HR=0.73 [95%CI 0.56-0.96], p=0.023) and use of CRT-D (HR=0.74 [95% CI 0.55-0.98], p=0.039) were independent predictors of survival free from LVAD/heart transplant. BMI of 25-29.9 Kg/m^2 at the time of implant was independently associated with favourable long-term 10-year survival. Use of CRT-D was associated with improved survival irrespective of BMI class.

Introduction

The risk of heart failure (HF) is significantly increased among obese individuals compared to non-obese individuals even after adjustment for established risk factors for HF [1]. On the contrary, studies have demonstrated that among patients with established HF, overweight (OW) or obese (OB) individuals have better prognosis compared to their normal weight (NW) counterparts [2, 3]. Cardiac resynchronization therapy (CRT) improves left ventricular (LV) systolic function, symptoms of HF and survival of patients with reduced ejection fraction (HFrEF) ≤35% and evidence of electrocardiographic dyssynchrony [1, 4, 5]. Recent evidence from an analysis of a selected elderly Medicare beneficiaries implanted with CRT-defibrillator (CRT-D) showed that the majority were OW or OB and that the risk of death was significantly lower across all body-mass index (BMI) categories above 25 Kg/m^2 [6]. Furthermore, a single-center study of 113 patients implanted with CRT-D demonstrated improved survival with higher BMIs at median follow-up of 4.5 years [7]. Currently, no studies have assessed the impact of CRT-D versus CRT-pacemaker (CRT-P) across different BMI categories. We sought to investigate the long-term impact (at 10-years and beyond) of BMI in a population of patients referred for CRT (with or without defibrillator), and whether or not there is a survival benefit from CRT-D.

Methods

This was a retrospective, multi-center study which involved 1,277 consecutive HF patients who underwent successful implantation of CRT devices (with or without a defibrillator) at: Heart Hospital/University College London Hospital, UK; Hospital of Santa Cruz, Carnaxide, Portugal; Royal Papworth Hospital, Cambridge UK; Regional Hospital Liberec, Liberec, Czech Republic, and Guys and St Thomas' NHS Foundation Trust, London, UK. CRT is part of routine clinical practice, while no experiments were involved in this study. All patients provided written, informed consent for the procedure. The data were collected

retrospectively through hospital electronic records, while additional information, where needed, was retrieved from paper notes. We searched for specific causes of death based on hospital records, primary care data and coroner reports. We also collected data from our local clinic records and stored device electrograms (EGMs).

Briefly, in order for patients to undergo CRT implantation they had documented HF of New York Heart Association (NYHA) class II-IV symptoms despite optimal therapy, LV ejection fraction (LVEF) ≤35%, and QRS duration ≥120ms, in line with the European Society of Cardiology (ESC) guidelines [1]. Choice of pacemaker or defibrillator was based on the patient's clinical history, risk profile and history of arrhythmias. We excluded patients requiring of intravenous inotropic drug therapy or having an estimated life expectancy of less than 12 months due to comorbidities other than HF.

Body mass index (BMI) was calculated as weight divided by height squared (Kg/m^2). Height and weight of patients for the BMI calculation were obtained at pre-assessment prior or at the day of the procedure. Subjects were grouped into tertiles rounded to the closest World Health Organization BMI categories as follows: normal weight, BMI <25.0 kg/m^2; overweight, BMI 25.0-29.9 Kg/m^2; and obese BMI ≥30.0 Kg/m^2. Routine bloods were obtained from all patients. Estimated creatinine clearance (CrCl) was calculated based on the Cockroft-Gault formula (CrCl (male) = (140-age) × weight / (0.814 × serum creatinine umol/L).

Devices were programmed with two ventricular tachycardia zones *ab initium*, according to the patient's age and previously documented ventricular arrhythmias, as some patients had CRT implanted before the MADIT-RIT trial [8]. Adjustment of therapies and detection zones was applied during follow-up or following documented arrhythmic events.

The patients were followed-up for a median period of 4.9 years (IQR 2.4-7.5) post-CRT implantation. More than 10% of patients had follow-up for ≥10 years. The study endpoints were: (i) the composite of all-cause mortality or heart transplantation/LV assistant

device (LVAD), (ii) all-cause mortality, and (iii) ventricular tachycardia (VT) requiring defibrillator therapies.

Data are presented as mean ± standard deviation (SD) for continuous variables and as valid percentages for categorical variables. For the assessed endpoints, incidence rates per 100 patient-years were also estimated. Sub-analyses were conducted for the composite endpoint in primary prevention CRT-P and CRT-D devices. Continuous variables were tested for normality of distribution with Kolmogorov-Smirnov test and by visual inspection of P-P plots. To examine the differences in demographic and clinical characteristics according to BMI categories and CRT device type one-way analysis of variance (ANOVA) and X^2 test were used for continuous and categorical variables. Multivariate Cox regression analysis was used to test the time dependency of association of BMI classes and use of CRT-D with all-cause mortality or heart transplant/LVAD, after adjustment for baseline differences (Method: Enter). Exact values of $p < 0.05$ were considered statistically significant. Data analysis was performed with SPSS software, version 18.0 (SPSS Inc., Chicago, IL).

Results

In the present study, we enrolled 1,277 HF patients in whom a CRT was implanted. Demographic characteristics of the study population and survival rates are presented in Table 1. Patients were divided into 3 groups according to BMI: 28.5% NW (18.5-24.9 Kg/m^2), 38.7% OW (BMI 25.0-29.9 Kg/m^2) and 32.8% OB (BMI ≥30 Kg/m^2) respectively. A small proportion of patients was underweight (1.5% of patients had a BMI below 18.5Kg/m^2) or overweight (1.6% had a BMI of 35 to 40 and 3.1% had BMI ≥ 40 Kg/m^2). CRT-D was implanted in 75.6% of patients. The mean age of all patients was 67 years, with OB patients (BMI ≥30 Kg/m^2) being younger (p<0.001), more likely to have diabetes (p<0.001) and with higher creatinine clearance (p<0.001). In addition, the NW group had lower EF (26±9%) compared to OW (29±10%) and OB (29±10%) patients (p<0.001). There were no differences in the use of

cardioprotective medications such as beta blockers, angiotensin converting enzyme inhibitors and spironolactone among the groups. However, obese individuals were less likely to receive CRT-P (p=0.004).

The composite endpoint of all-cause mortality or cardiac transplant/LVAD occurred in 50.9% of patients. The unadjusted incidence rate of the composite endpoint was 14.64 per 100-patient years in the NW group versus 10.41 in the OW group and 9.37 in the OB (Table 2). Figure 1 shows the survival curves for the 3 BMI groups with adjustment for baseline differences, with pre-obese patients having a significant survival benefit. After adjustment, no significant interaction was observed with cardiomyopathy type (p=0.348), and the primary endpoint was observed less frequently in the pre-obese group both for ischemic and non-ischemic cardiomyopathy (Supplementary Figure S1).

Survival rate free from all cause-mortality and cardiac transplant/LVAD at 10-years ranged from 15 to 51% in the different BMI groups. Lower survival was observed for extreme BMI levels (<18.5 Kg/m^2 and ≥40 Kg/m^2) and was more favourable for patients with BMI between 25.0-39.9 Kg/m^2, with a two-fold higher survival rate (Figure 2; unadjusted data). After adjustment for possible confounders BMI of 25.0-29.9 Kg/m^2 had a protective effect for the primary endpoint (HR=0.73 [95%CI 0.56-0.96], p=0.023) (Table 3). In addition, use of CRT-D was significantly associated with reduced all-cause mortality/heart transplant/LVAD (HR=0.74 [95% CI 0.55-0.98], p=0.039). Other independent predictors identified in the model were: female sex, atrial fibrillation, NYHA class III, NYHA class IV, LV ejection fraction, QRS width, eGFR, haemoglobin, and use of oral loop diuretics (Table 3). Similarly, BMI 25.0-29.9 Kg/m^2, female sex, NYHA IV, LV ejection fraction, use of CRT-D and loop diuretics, and eGFR were also independent predictors of all-cause mortality. Diabetes was also included as a significant predictor of mortality in this model (HR=1.34 [95%CI 1.03-1.74], p=0.030; Supplementary Table S1).

At least 1 appropriately treated VT was observed in 27.4% of patients. Incidence per 100 patient-years was comparable across the 3 BMI classes: 3.79 in NW vs. 3.25 in OW vs. 3.70 in OB individuals (Table 2). After adjustment, survival curves visually illustrate that the survival benefit of CRT-D appears to be independent from BMI class (Figure 3) and patients implanted with CRT-D have numerically or significantly better survival than their CRT-P counterparts. The sample was not powered for multiple comparisons (6 groups with adjustment for several co-variables). Further sub-group analysis was performed for CRT-P versus CRT-D across different BMI groups (Supplementary Table S2).

Discussion

In the present study, we found that most patients implanted with CRT were either OW or OB as indexed by BMI measurements. In addition, OW patients and OB patients with BMI <40 Kg/m^2 had higher long-term 10-year survival. Moreover, defibrillator backup and being OW were independent predictors for improved survival free from Heart Transplantation/LVAD. Despite its survival benefit, CRT-Ds were underutilized in OB patients.

Body mass index is a parameter dependent on height and weight, hence it can be affected by increased adipose tissue, cachexia and loss of muscle mass as well as fluid overload, particularly in HFrEF patients. The inability of BMI to distinguish fat tissue from muscle mass and also the fact that adipose tissue may play protective role during acute severe illnesses, where caloric intake is severely disrupted, are possible explanations for the obesity paradox in HF. Previous analyses of HF cohorts referred for CRT demonstrated that underweight and NW patients had worse outcomes [9]. Furthermore, an analysis of a randomized control trial suggested a stepwise decrease in the risk of death in patients with BMI 30-34.9 and >35 Kg/m^2 [10]. In-hospital mortality in the setting of decompensated HF is also affected by BMI [11]. A recent meta-analysis suggested that underweight HF patients were at the highest risk and OW

patients at the lowest risk of adverse outcomes [12]. The main limitation of all these studies is the use of BMI to identify OB patients despite the limited accuracy of this marker to quantify adiposity. Body composition can be more accurately measured by CT or MRI based techniques, but these are limited by radiation and/or cost. An analysis of the Framingham Heart study (FHS) and the Multi-Ethnic Study of Atherosclerosis (MESA) cohorts demonstrated that patients with lower LV ejection fraction had lower epicardial adipose tissue and higher mortality compared with counterparts with higher LV ejection fraction and this association was independent of BMI [13]. Regardless of the approach to measure adiposity, cachexia is associated with worse outcomes in HF patients. HF is a catabolic disease and patients with advanced HFrEF may experience unintentional weight loss [14]. On the other hand, OB patients may seek specialized care earlier in their disease course because of greater functional impairment, leading to earlier treatment with medical and device therapies. Furthermore, OB patients may be able to maintain higher blood pressures and thus tolerate uptitration of beta blockers, antagonists of the renin-angiotensin-aldosterone system and neprilysin inhibitors [15]. Obese patients may also be exposed to the protective effects of various anti-inflammatory adipokines and have higher muscle mass [16]. However, obesity is a heterogeneous disease with certain negative effects on cardiovascular risk, hence the observed obesity paradox may be due to survival bias or index event bias as these patients tend to be in earlier stages of HF compared with underweight or NW HF patients.

Our cohort analysis has longer follow-up time than the previous cohorts and highlights the long-term effects of BMI on 10-year or longer survival after CRT implantation (with or without a defibrillator), and suggests that the long-term impact of BMI may be translated by a U-shape curve (higher mortality in BMI extremes). When comparing CRT-D with CRT-P, our study showed that the presence of a defibrillator was independently associated with survival irrespective of BMI status. These findings support the decision to implant a defibrillator

irrespectively of a patient's BMI as there is no difference in appropriate therapy delivery across the range of BMI. This observation is of great interest as it points out that the protective benefit of a higher BMI is likely by reducing the risk of pump failure-related death rather than sudden arrhythmic deaths. Also, it should help address the issue of underutilization of CRT-Ds in OB patients.

Limitations of our study are inherent to any study with observational, retrospective design. The timing from HF onset to CRT implantation could affect outcomes after implantation regardless of the BMI, and we did not adjust for other important parameters of long-term survival in HF such as maximum oxygen consumption during cardiopulmonary exercise testing.

In conclusion, our study of long-term outcomes in this large cohort of CRT recipients suggests that less than a quarter of patients in the lowest and highest BMI categories at the time of implant are alive after 10-years. In addition, use of CRT-D and being OW were independently associated with improved survival.

Declarations

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Tables

Table 1. Demographic characteristics of the study population.

Table 2. Outcomes across the different BMI groups.

Table 3. Prediction of survival free from all-cause mortality or heart transplant/LVAD.

Figure Legends

Figure 1. Death or heart transplant/LVAD across different BMI groups.

Figure 2. Survival across all BMI groups.

Figure 3. Death or heart transplant/LVAD: CRT-P versus CRT-D across different BMI groups.

Supplementary material

Table S1. Prediction of survival free from all-cause mortality.

Table S2. CRT-P versus CRT-D across different BMI groups.

Figure S1. Time to Event for primary composite endpoint (ischemic vs. non-ischemic

cardiomyopathy sub-analysis)

Table 1. Demographic characteristics of the study population.

Variable	All Patients (n=1277)	Body Mass Index (Kg/m^2)			p
		≤24.9 (n=364)	25.0-29.9 (n=494)	≥30.0 (n=419)	
Age (years)	67.0±12.7	68.7±14.4	68.2±11.7	64.2±11.7	<0.001
Men	714 (59.9%)	210 (57.7%)	269 (54.5%)	235 (56.1%)	0.638
Diabetes mellitus	331 (25.9%)	64 (17.5%)	125 (25.3%)	143 (34.8%)	<0.001
Hypertension	585 (45.8%)	158 (43.4%)	225 (45.5%)	202 (48.2%)	0.400
Dyslipidemia	371 (29.1%)	94 (25.8%)	141 (28.5%)	136 (32.5%)	0.119
Ischemic CM	616 (48.2%)	190 (52.2%)	221 (44.7%)	205 (48.2%)	0.091
Secondary prevention	156 (12.2%)	40 (11.0%)	62 (12.6%)	54 (12.9%)	0.691
NYHA					0.011
I	37 (2.9%)	14 (3.9%)	10 (2.1%)	12 (2.9%)	
II	350 (27.4%)	107 (29.5%)	141 (28.5%)	102 (24.3%)	
III	764 (59.8%)	193 (52.9%)	302 (61.1%)	269 (64.2%)	
IV	127 (9.9%)	50 (13.7%)	41 (8.3%)	36 (8.6%)	
AF	414 (32.5%)	119 (33.0%)	161 (32.7%)	134 (31.9%)	0.946
LVEF (%)	28±10	26±9	29±10	29±10	<0.001
QRS width (msec)	157±31	157±31	159±31	156±30	0.384
LBBB	810 (65.8%)	225 (64.1%)	317 (66.2%)	268 (66.8%)	0.492
Haemoglobin (gr/dl)	12.7±1.9	12.5±1.7	12.8±2.0	12.9±1.8	0.041
eGFR CG (ml/kg/min)	71±35	55±24	66±27	93±42	<0.001
CRT-P	311 (24.4%)	90 (24.7%)	141 (28.5%)	80 (19.1%)	0.004
Oral anticoagulants	506 (39.6%)	154 (42.1%)	197 (39.8%)	156 (37.2%)	0.434
Antiplatelets	600 (46.9%)	165 (45.2%)	226 (45.8%)	209 (47.0%)	0.334
Beta-blockers	875 (68.5%)	249 (68.4%)	327 (66.2%)	299 (71.3%)	0.320
ACEi/ARB-II	1069 (83.7%)	305 (83.7%)	411 (83.2%)	353 (84.3%)	0.662
MRA	700 (54.7%)	193 (53.0%)	263 (53.3%)	243 (58.1%)	0.358
Oral loop diuretic	945 (74.0%)	278 (76.4%)	357 (72.2%)	310 (74.1%)	0.372
Statins	682 (53.4%)	181 (49.7%)	264 (53.4%)	237 (56.6%)	0.160

Abbreviations. NYHA: New York Heart Association; ACEi: angiotensin converting enzyme inhibitors; ARB-II: angiotensin II receptor blockers; MRA: mineralo-receptor antagonist; eGFR: estimated glomerular filtration rate; CM: cardiomyopathy; LVEF: left ventricular ejection fraction; AF: atrial fibrillation; BMI: body mass index; p-values are based on ANOVA for continuous variable and on chi-square test for categorical variables.

Table 2. Outcomes across the different BMI groups.

Variable	All Patients (n=1277)	Body Mass Index (Kg/m²)			p
		≤24.9 (n=364)	25.0-29.9 (n=494)	≥30.0 (n=419)	
All-cause Mortality n (%) **Incidence per 100 py, 95%CI**	604 (48.6%) 10.6, 9.70-11.47	195 (56.2%) 13.91, 11.97-16.15	232 (47.8%) 9.81, 8.57-11.22	177 (43.2%) 9.04, 7.75-10.54	0.002
All-cause Mortality or LVAD/HT n (%) **Incidence per 100 py, 95%CI**	632 (50.9%) 11.09, 10.22-12.04	204 (58.8%) 14.64, 12.64-16.96	245 (50.5%) 10.41, 9.13-11.88	183 (44.6%) 9.37, 8.06-10.90	0.001
All-cause Mortality or LVAD/HT in PP CRT-Ds n (%) **Incidence per 100 py, 95%CI**	390 (49.4%) 13.46, 12.11-14.96	116 (52.7%) 14.22, 11.71-17.27	149 (51.6%) 14.09, 11.87-16.72	125 (44.5%) 12.19, 10.13-14.68	0.121
All-cause Mortality or LVAD/HT in PP CRT-Ps n (%) **Incidence per 100 py, 95%CI**	169 (56.5%) 18.67, 15.85-22.00	64 (72.7%) 29.64, 22.45-39.14	66 (48.9%) 14.31, 11.07-18.51	39 (51.3%) 17.11, 12.20-23.99	<0.001
Appropriate Therapies in PP CRT-Ds n (%) **Incidence per 100 py, 95%CI**	113 (27.4%) 3.56, 2.95-4.29	34 (27.9%) 3.79, 2.69-5.33	38 (27.3%) 3.25, 2.36-4.49	41 (27.0%) 3.70, 2.71-5.04	0.986

Abbreviations. LVAD: left ventricular assist device; CRT (D/P): cardiac resynchronization therapy (defibrillator/pacemaker); py: patient years

Legend: PP – Primary prevention; * 6 patients had LVAD (4 normal weight, 1 overweight, 1 obese); all remaining received heart transplant.

Table 3. Prediction of survival free from all-cause mortality or heart transplant/LVAD.

Variable	HR	95%CI	P
Age	0.99	0.98-1.00	0.362
Women	0.55	0.42-0.73	<0.001
Diabetes mellitus	1.23	0.95-1.59	0.114
BMI <25 Kg/m^2 (ref)			
BMI 25-29.9 Kg/m^2	0.73	0.56-0.96	0.023
BMI ≥30 Kg/m^2	0.96	0.70-1.32	0.808
AF	1.29	1.02-1.63	0.032
Ischemic CM	0.93	0.72-1.20	0.574
Secondary prevention	1.30	0.94-1.79	0.117
CRT-D	0.74	0.55-0.98	0.039
NYHA I (ref)			
NYHA II	1.50	0.74-3.04	0.267
NYHA III	2.08	1.04-4.12	0.037
NYHA IV	4.57	2.14-9.72	<0.001
LVEF	0.99	0.98-1.00	0.013
QRS (ms)	0.99	0.99-1.00	0.031
Antiplatelet agents	0.90	0.71-1.16	0.418
Oral loop diuretics	1.98	1.44-2.70	<0.001
Hemoglobin	0.99	0.98-1.00	0.003
eGFR	0.99	0.98-0.99	<0.001

Abbreviations. NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; CM: cardiomyopathy; LVEF: left ventricular ejection fraction; AF: atrial fibrillation; BMI: body mass index; CRT-D: cardiac resynchronization therapy defibrillator. Note: Multivariate Cox Regression Model, Method Enter.

Figure 1
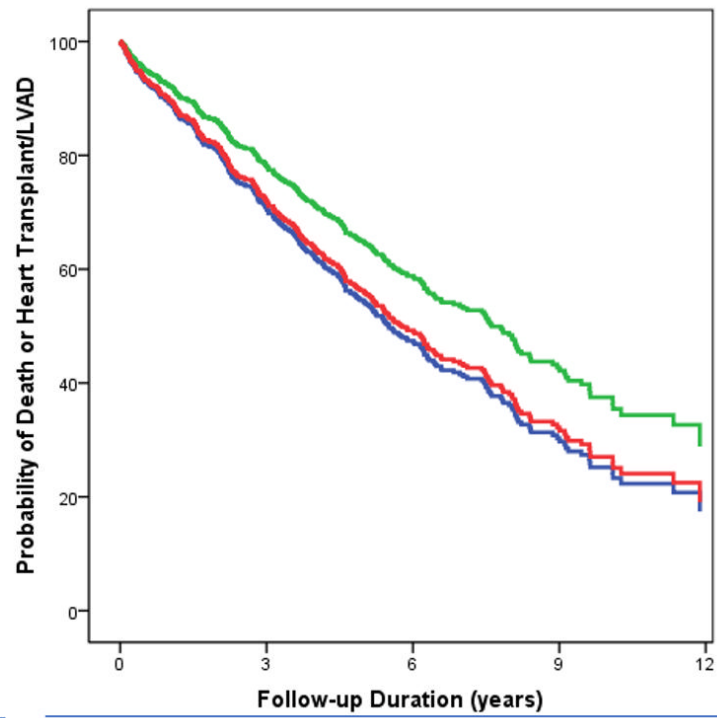
BMI Class		0	3	6	9	12	HR
<25 Kg/m²		364	211	110	43	3	Ref
25 to <29.9 Kg/m²		494	347	202	80	7	0.73 0.56-0.96
≥30 Kg/m²		419	285	163	59	3	0.95 0.69-1.31

Figure 2

Survival across BMI strata
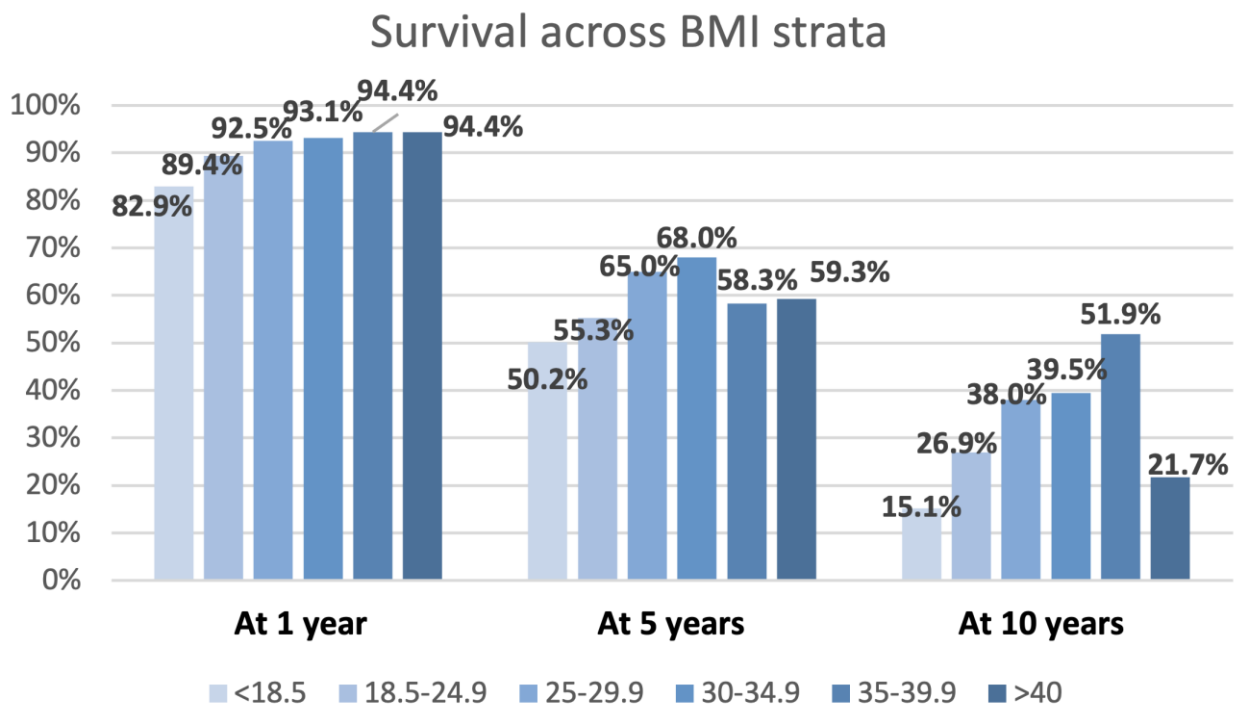
Figure 3
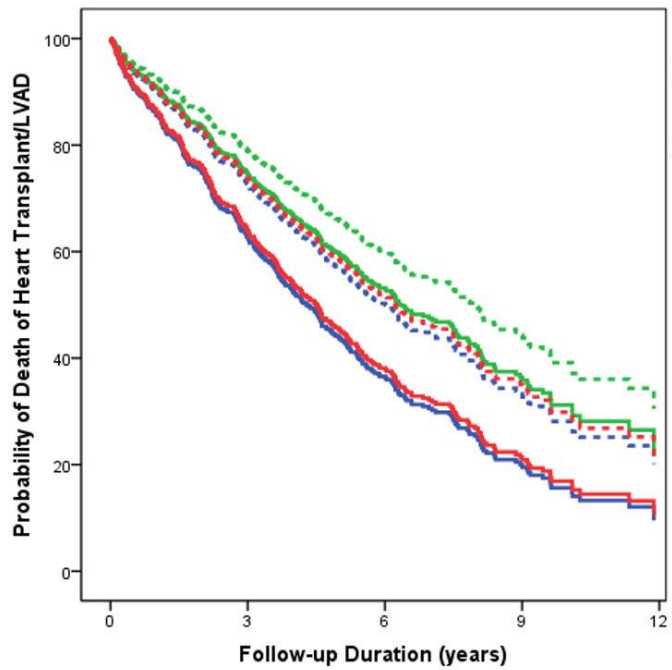
Group		0	3	6	9	12	HR
CRT-P <25Kg/m^2		90	47	19	8	1	Ref
CRT-D <25Kg/m^2		274	164	89	35	2	0.68 0.44-1.05
CRT-P 25 to <29.9 Kg/m^2		141	94	51	21	4	0.63 0.36-1.09
CRT-D 25 to <29.9 Kg/m^2		353	253	150	58	2	0.51 0.33-0.78
CRT-P ≥30 Kg/m^2		80	50	24	10	1	0.96 0.50-1.86
CRT-D ≥30 Kg/m^2		339	247	139	50	2	0.65 0.41-1.03

Table S1. Prediction of survival free from all-cause mortality.

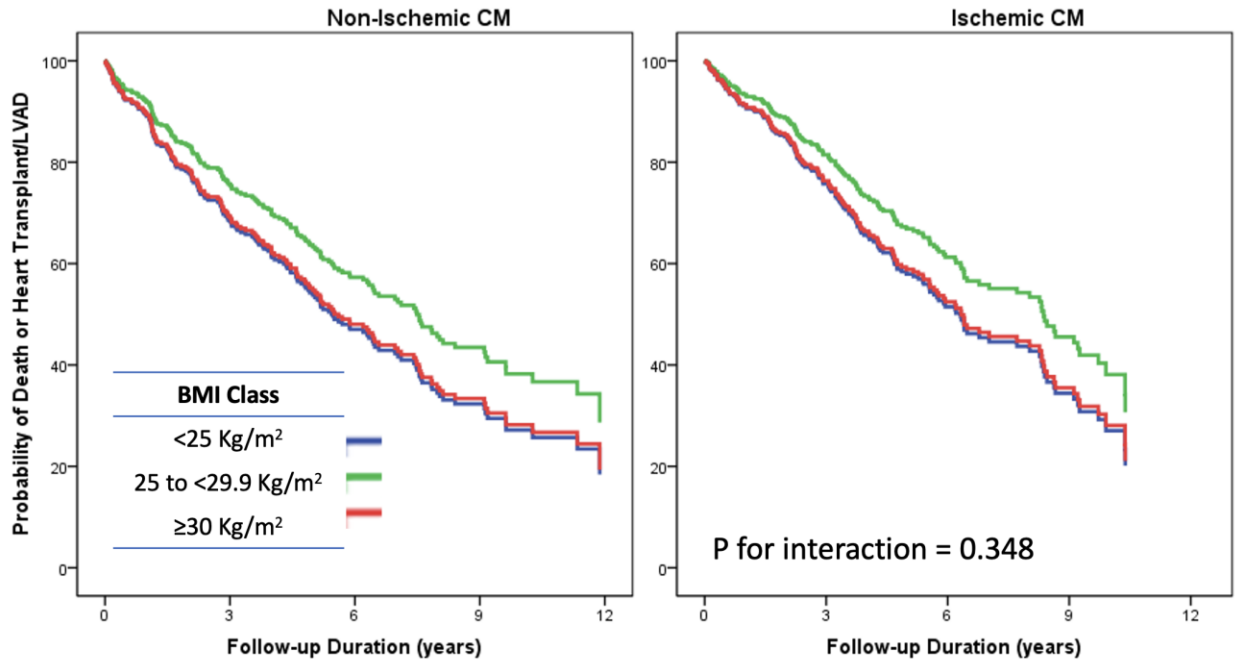| Variable	HR	95%CI	P
Age	1.01	0.99-1.02	0.481
Women	0.55	0.41-0.73	<0.001
Diabetes mellitus	1.34	1.03-1.75	0.030
BMI <25 Kg/m^2 (ref)			
BMI 25-29.9 Kg/m^2	0.70	0.52-0.94	0.016
BMI ≥30 Kg/m^2	1.06	0.76-1.47	0.733
AF	1.25	0.98-1.60	0.076
Ischemic CM	0.92	0.70-1.21	0.542
Secondary prevention	1.40	1.00-1.97	0.048
CRT-D	0.68	0.50-0.91	0.010
NYHA I (ref)			
NYHA II	1.41	0.66-3.01	0.381
NYHA III	1.99	0.96-4.14	0.064
NYHA IV	4.63	2.08-10.31	<0.001
LVEF	0.98	0.97-0.99	0.002
QRS (ms)	0.99	0.99-1.00	0.092
Antiplatelet agents	0.89	0.69-1.15	0.392
Oral loop diuretics	2.01	1.43-2.83	<0.001
Hemoglobin	0.99	0.98-1.00	0.010
eGFR	0.99	0.98-0.99	<0.001

Abbreviations. NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate; CM: cardiomyopathy; LVEF: left ventricular ejection fraction; AF: atrial fibrillation; BMI: body mass index; CRT-D: cardiac resynchronization therapy defibrillator. Note: Multivariate Cox Regression Model, Method Enter.

Variable	CRT-P BMI ≤24.9 Kg/m² (n=90)	CRT-D BMI ≤24.9Kg/m² (n=274)	CRT-P BMI 25.0-29.9 Kg/m² (n=141)	CRT-D BMI 25.0-29.9 Kg/m² (n=494)	CRT-P BMI ≥ 30.0 Kg/m² (n=80)	CRT-D BMI ≥ 30.0 Kg/m² (n=419)
Age (years)	75.6±11.8	66.4±14.5**	72.2±10.8	66.6±11.9**	65.5±12.3	63.9±11.6
Men	44 (48.9%)	166 (60.6%)	67 (47.5%)	202 (57.2%)	33 (41.3%)	202 (59.6%)*
Diabetes mellitus	21 (23.3%)	41 (15.0%)	45 (31.9%)	85 (24.1%)*	30 (37.5%)	110 (32.4%)
NYHA						
I	2 (2.2%)	12 (4.4%)	2 (1.4%)	9 (2.5%)	0 (0%)	14 (4.1%)
II	24 (26.7%)	84 (30.7%)	40 (28.4%)	100 (28.3%)	21 (26.3%)	81 (23.9%)
III	46 (51.1%)	146 (53.3%)	75 (53.2%)	227 (64.3%)**	50 (62.5%)	217 (64.0%)
IV	18 (20.0%)	32 (11.7%)	24 (17.0%)	17 (4.8%)**	9 (11.3%)	27 (8.0%)
AF	38 (42.2%)	81 (29.6%)*	61 (43.3%)	101 (28.6%)*	32 (40.0%)	102 (30.1%)
Ischemic CM	51 (56.7%)	139 (50.7%)	50 (35.5%)	171 (48.4%)*	26 (32.5%)	179 (52.8%)*
Secondary prevention	1 (1.1%)	39 (14.2%)*	4 (2.8%)	58 (16.4%)**	2 (2.5%)	52 (15.3%)*
LVEF (%)	27±9	26±9	32±12	28±9**	32±12	28±10**
QRS width (msec)	165±32	153±31*	167±34	155±29**	154±29	156±31
LBBB	55 (62.5%)	170 (64.6%)	89 (63.6%)	228 (67.3%)	52 (67.5%)	216 (66.7%)
Haemoglobin (gr/dl)	12.4±1.7	12.5±1.7	12.6±2.0	12.9±2.0	12.8±19.4	12.9±17.7
eGFR CG (ml/kg/min)	44±18	58±25**	62±25	69±28*	80±38	92±43*
Oral anticoagulants	34 (37.8%)	121 (44.2%)	68 (48.2%)	142 (40.2%)	39 (48.8%)	127 (37.5%)
Antiplatelets	42 (46.7%)	127 (46.4%)	51 (36.2%)	174 (49.3%)*	31 (38.8%)	177 (52.2%)*
Beta-blockers	58 (64.4%)	195 (71.2%)	89 (63.1%)	237 (67.1%)	63 (78.8%)	248 (73.2%)
ACEi/ARB-II	77 (85.6%)	231 (84.3%)	120 (85.1%)	284 (80.5%)	64 (80.0%)	277 (81.7%)
MRA	43 (47.8%)	153 (55.8%)	72 (51.1%)	189 (53.5%)	49 (61.3%)	205 (60.5%)
Oral Loop diuretic	79 (87.8%)	198 (72.3%)*	106 (75.2%)	246 (69.7%)	57 (71.3%)	255 (75.2%)

Table S2. CRT-P versus CRT-D across different BMI groups.

Note: * P<0.05; ** P<0.001; Abbreviations. NYHA: New York Heart Association; ACE-I: angiotensin converting enzyme inhibitors; ARB-II: angiotensin II receptor blockers; MRA: mineralo-receptor antagonist; eGFR: estimated glomerular filtration rate; CM: cardiomyopathy; CRT (D/P): cardiac resynchronization therapy (defibrillator/pacemaker); LVEF: left ventricular ejection fraction; AF: atrial fibrillation; BMI: body mass index; p-values are based on ANOVA for continuous variable and on chi-square test for categorical variables.

1   **Figure S1.** Time to Event for primary composite endpoint (ischemic vs. non-ischemic
2   cardiomyopathy sub-analysis).
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