QUARTO III. Response rate in cardiac resynchronization therapy patients implanted with a left ventricular quadripolar lead and the MultiPoint TM Pacing feature activated.

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Abstract

BACKGROUND: Although cardiac resynchronization therapy (CRT) is beneficial in most heart failure patients, up to 40% do not respond to CRT. It has been suggested that multipoint left ventricle pacing (MPP) would increase the response rate. **AIM**: To assess the CRT response rate at 6 months in patients implanted with a CRT device with the MPP feature activated early after the implant. **METHODS** This was a multicentre, prospective, open-label and non-randomized study. The primary endpoint was response to biventricular pacing defined as >15% relative reduction in left ventricular end-systolic volume (LVESV) comparing echocardiography measurements performed at baseline and 6 months by a core laboratory. Among secondary endpoints the combined endpoint of mortality or all-cause hospitalizations was evaluated. Primary study endpoint and clinical outcomes were compared to a Quarto II control cohort. **RESULTS:** 105 patients were included. The response rate was 64.6% (97.5% lower confidence bound 53%). Mean relative reduction in LVESV was 25.3% and mean absolute increase in LVEF was 9.4%. The subjects with device programmed using anatomical approach had showed a trend toward higher responder rate than those using the electrical approach (72% vs. 61.1%, p= 0.32). Compared with Quarto II, the combined endpoint of mortality and or all-cause hospitalizations was lower in Quarto III (12.4% vs 25.4%, p=0.004). **CONCLUSIONS**: Early activation of MPP was not associated to an advantage increasing echocardiography responders to CRT at 6 months of follow

up. Nevertheless, MPP was associated with better clinical outcomes in comparison to a historical control cohort. Patients programmed using widest pacing cathodes had a numerically higher responder rate.

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ABSTRACT.

BACKGROUND : Although cardiac resynchronization therapy (CRT) is beneficial in most heart failure patients, up to 40% do not respond to CRT. It has been suggested that multipoint left ventricle pacing (MPP) would increase the response rate.

AIM : To assess the CRT response rate at 6 months in patients implanted with a CRT device with the MPP feature activated early after the implant.

METHODS This was a multicentre, prospective, open-label and non-randomized study. The primary endpoint was response to biventricular pacing defined as >15% relative reduction in left ventricular end-systolic volume (LVESV) comparing echocardiography measurements performed at baseline and 6 months by a core laboratory. Among secondary endpoints the combined endpoint of mortality or all-cause hospitalizations was evaluated. Primary study endpoint and clinical outcomes were compared to a Quarto II control cohort.

RESULTS: 105 patients were included. The response rate was 64.6% (97.5% lower confidence bound 53%). Mean relative reduction in LVESV was 25.3% and mean absolute increase in LVEF was 9.4%. The subjects with device programmed using anatomical approach had showed a trend toward higher responder rate than those using the electrical approach (72% vs. 61.1%, p= 0.32). Compared with Quarto II, the combined endpoint of mortality and or all-cause hospitalizations was lower in Quarto III (12.4% vs 25.4%, p=0.004).

CONCLUSIONS : Early activation of MPP was not associated to an advantage increasing echocardiography responders to CRT at 6 months of follow up. Nevertheless, MPP was associated with better clinical outcomes in comparison to a historical control cohort. Patients programmed using widest pacing cathodes had a numerically higher responder rate.

KEYWORDS .

Heart Failure.

Cardiac Resynchronization Therapy.

Multipoint pacing.

Dyssynchrony.

Outcomes.

ABBREVIATIONS

Cardiac resynchronization therapy: CRT.

Heart failure: HF.

Left ventricular: LV.

LV ejection fraction: LVEF.

Multipoint pacing: MPP.

LV end-diastolic volume: LVEDV.

LV end-systolic volume: LVESV.

New York Heart Association: NYHA.

Left bundle branch block: LBBB.

Coronary sinus: CS.

BACKGROUND

Cardiac resynchronization therapy (CRT) is a well-accepted therapy for patients with heart failure (HF), left ventricular (LV) systolic dysfunction, and QRS prolongation. Large, randomized trials have shown improvement in symptoms, in LV structure and function, reduction in hospitalizations, and decrease of mortality in patients treated with CRT[1,2]. Unfortunately, a significant proportion of patients do not respond to CRT and this is related to poorer outcomes[3]. Suboptimal LV lead position and persistent mechanical dyssynchrony, affecting 25-30% of patients despite conventional biventricular pacing[4], have been some of the suggested reasons to explain the absence of response to CRT.

Multipoint LV pacing (MPP) through a quadripolar lead has been advocated to enhance the likelihood of response to CRT by stimulating and capturing a broader area of the LV. First studies with this new modality of LV pacing have reported benefits in terms of acute hemodynamic improvement, higher left ventricular ejection fraction (LVEF) and a higher ability to reduce dyssynchrony in comparison with conventional biventricular pacing[5-8]. Considering that LV mechanical dyssynchrony and contractile function are important determinants of long-term CRT benefit[9,10], MPP could offer advantages over conventional single LV site biventricular pacing.

It has been suggested that MPP would be especially useful for non-responder patients to CRT[11]. Nevertheless, the time necessary to evaluate the degree of response to CRT has not been established and the optimal moment to activate MPP remains a challenging issue. Whereas the strategy of activating MPP only in patients not responding to conventional biventricular pacing have been advocated and evaluated in randomized clinical trials, the possible advantages of the activation of MPP early after the device implantation have been poorly studied.

The objectives of this study were to prospectively assess the CRT response rate at 6 months in patients implanted with a CRT-D device with the MPP feature activated early after the implant.

METHODS.

Population

An open-label, multicentre, non-randomized, prospective study was designed. The study included patients implanted with a CRT-D device with the MPP feature under the current ESC or ACCF/AHA/HRS Class I or Class IIa indications for CRT-D implant (including upgrades from single or dual chamber ICD or PM). The following were the main exclusion criteria to participate in the study: myocardial Infarction, unstable angina or coronary revascularization within 40 days prior the enrolment, NYHA Class IV, Cerebrovascular Accident or Transient Ischemic Attack in the 3 months prior to enrolment, life expectancy $<$ 6 months or consideration for transplantation over the next 12 months, Primary valvular disease requiring surgical intervention and patients with persistent atrial fibrillation (AF)at the time of enrolment or 30 days prior to enrolment or permanent AF not treated with atrioventricular node ablation within 2 weeks after the CRT-D implant, pregnancy and finally, patients for whom suitable transthoracic echocardiographic images for determining the cardiac output and LV volumes cannot be obtained.

Enrolment was conducted between February 2016 and August 2018. The institutional review board at each center approved the study protocol, and written informed consent was obtained from each patient.

Device implantation

A biventricular pacemaker with implantable defibrillator with the MPP feature was implanted in all patients together with a quadripolar LV lead (Quartet(r), Abbott, Sylmar, CA). Immediately after implant and before discharge, if at least 2 MPP vectors options were available the MPP algorithm was turned ON. Investigators programmed devices and MPP based on their discretion. However, MPP configuration was recommended following one of the 2 different approaches:

Anatomical approach: choose the most anatomically separated vectors based on the position of each electrode, documented through fluoroscopic images.

Electrical approach: choose the most electrically separated vectors based on the data provided by the Conduction Delay Test (based on RV paced to LV sensed).

Clinical study endpoints

The primary endpoint of the study was to prospectively measure the CRT response rate at 6 months in subjects implanted with a Quartet^{TM} LV quadripolar lead with the MPP feature activated compared to no CRT pacing at baseline. A positive CRT response was defined as a relative reduction in the left ventricle end-systolic volume (LVESV) of at least 15 % at 6 months post-implant, measured by echocardiography.

Main secondary endpoints were reverse LV remodelling measured by changes in LV end diastolic volume and diameter (LVEDV and LVEDD) and by changes in LVESV and left ventricle end systolic diameter (LVESD); changes in NYHA class and in clinical composite score at 6 months; clinical outcomes at 6 months (mortality and all-cause hospitalization). Finally, a comparison of clinical outcomes with an historical control cohort corresponding to the patients involved in the previously conducted QUARTO II study[12] was prespecified. The Quarto II study was a prospectively study that evaluated the usefulness of the quadripolar lead Quartet, the patterns of programming and the response to CRT in 198 patients implanted with a CRT-D device programmed into conventional single-site biventricular pacing. The Quarto II showed a percentage of responders of 62% (reduction [?]15% in LVEV) at 6 months of follow-up[12].

All the echocardiography images were obtained by sites according to the study echo protocol at baseline and 6-month visit. They were submitted to the echo core lab for central evaluation and assessment. The echo core lab analysed and measured the echocardiographic images per the CIP and the echo protocol.

Statistical Analysis.

For the primary endpoint analysis, the following inequality hypothesis were tested: H0: Proportion of responders at 6 months with the MPP feature activated at baseline [?] 57%; H1: Proportion of responders at 6 months with the MPP feature activated at baseline $>$ 57%. The MPP responder rate was compared to 57%, which is the responder rate obtained from literature[13] for patients without the MPP feature activated.

The sample size calculation was based on the primary endpoint, proportion of CRT responders at 6 months who have the MPP feature activated at baseline. Using a one-sided, one sample Exact Binomial Test and a significance level of 2.5%, the study required 74 patients to reach a power of 90%. With the MPP feature activated at baseline, it was assumed that the proportion of responders at 6 months was 75%. In order to detect the 18% difference between the two responder rates, a total of 74 patients was needed to have analyzable endpoint data at 6 months. Assuming that, some patients would drop out of the study, the sample size increased to 103 subjects.

Mean +- standard deviation was reported for continuous data and frequencies and percentage for categorical data. The comparison of numerical variables was performed using Student's t test or Wilcoxon's rank-sum test, depending on the distribution of the variables. The Chi squared test, Fisher's exact test or Wald's test was used to compare qualitative variables as appropriate. Kaplan-Meier estimates with log-rank tests and multivariable Cox proportional hazards models were used to compare the QUARTO III study participants with the control cohort (Quarto II patients) for patient mortality, hospitalization, and the combined endpoint of mortality and/or hospitalization.

RESULTS

Patient demographics and electrical data.

One hundred and five patients at 13 investigational sites in Spain and Portugal were prospectively included in the study. The mean age was 65+-8 years, and most patients (78, 74%) were men. Baseline characteristics of the study population are summarized in table 1.

Of the 105 subjects who provided consent for study participation, 103 underwent an implant attempt, 1 subject had an unsuccessful implant due to the impossibility to cannulate the coronary sinus, and 102 subjects were successfully implanted with a CRT-D. Figure 1 shows the disposition of subjects during the study. Of the 102 implanted subjects, 96 were programmed with MPP ON. Among these 96 subjects, 30 (31.25%) were programmed following the anatomical approach and 66 (68.75%) following the electrical approach. After 6 months of follow-up there were 2 deaths, 12 patients were withdrawn before or at the 6-month visit. Finally, the 6 months echo follow-up was not performed in 3 patients. Accordingly, 79 patients were programmed with MPP ON, completed the follow-up and had a pair of echocardiographic images available (basal and 6 months). There were 2 subjects who had MPP not working properly during follow-up period and were excluded from the analysis.

Primary end-point results

The primary endpoint of the study was to prospectively measure the CRT response rate at 6 months in subjects with the MPP feature activated immediately after implant. Cardiovascular deaths were considered non-responder. There were 79 subjects considered for this analysis. The response rate was 64.6% (97.5% lower confidence bound (LCB): 53%). Despite having a higher numerical responder rate, the LCB was $<$ 57% and thus the primary endpoint was not met at the predefined 2.5% significance level.

There were 33 ischemic and 46 non-ischemic analyzable patients. Non-ischemic patients had a significant higher response rate in comparison to ischemic patients (73.9% vs 51.5%, p=0.039).

There were 25 subjects with device programmed using anatomical approach and 54 using electrical approach. Finally, the subjects with device programmed using anatomical approach had a numerically higher responder rate than those using the electrical approach (72.0% vs. 61.1%, p= 0.33).

Secondary end-point results

Table 2 shows the echocardiographic parameters at baseline, 6 months and the changes during the 6 months of follow-up. Mean reduction in LVESV (reverse remodeling) was 25.3% and mean increase in LVEF was 9.4 absolute points. The subjects with device programmed using anatomical approach had a non-significant higher reverse remodeling than those using the electrical approach (32.2%+-25.2% vs. 19.4%+-36.2%, p= 0.12) and a significant higher increase in LVEF (14.2%+-11.9% vs 8%+-12.6%, p=0.04). Finally, non-ischemic patients had a significant higher reverse remodeling in comparison to ischemic patients (32.6+-34.1% vs 10.5+-28.4%, p=0.04) and a significant higher increase in LVEF (12.5%+-12.1% vs 6.4%+-12.8%, p=0.04).

The percentage of super-responder (mean absolute LVEF increase of >14% at 6 months post-implant compared to no pacing at baseline) was 35.1%. It was observed a non-significant increase in percentage of super-responders in patients with device programmed using anatomical vs electric approach (48.0% vs 27.8%, p=0.08) and in non-ischemic vs ischemic patients (39.1% vs 27.3%, p=0.26)

The New York Heart Association (NYHA) class changes at 6 months are shown in Table 3. Before implant 35% of patients were on class III, whereas at 6 months only 12% of patients were on class III and most remained in class I or II. At 6 months, 8% and 14% of patients programmed using the anatomical and electrical approach, respectively, remained in class III.

We also evaluated the percentage of responders using the clinical composite score. A subject was defined as non-responder if suffered any of the following: death, heart failure hospitalization or worsening of the NYHA class. At 6 months of follow-up only 5% of patients were considered as clinical non-responders.

All 105 patients that consented to participate in the study were included for the evaluation of clinical outcomes. Mortality was 1.9% and 11.4% of patients were admitted to the hospital for any reason.

Finally, we compared the QUARTO III with QUARTO II clinical outcomes to evaluate potential benefits of MPP over conventional biventricular pacing. There were significant differences in baseline characteristics between both cohorts (Table 4). Statistically significant differences were evident for baseline age, NYHA class, LVEF and prevalence of hypertension and diabetes mellitus. The response rate in Quarto II was 61.8%, that was similar to the response rate found in Quarto III (p=0.684). Incidence of the combined endpoint of mortality and or all-cause hospitalizations was lower in Quarto III in comparison to QUARTO II (12.4% vs 25.4%, p=0.004, figure 2). A multivariate analysis was performed using a Cox's proportional hazard regression model to evaluate the benefits in clinical outcomes observed in the MPP cohort adjusting the demographic and baseline covariates. Patients included in QUARTO II had a significant higher risk of mortality and or all cause hospitalizations (HR: 1.99 (95% CI, 1.69-2.29), p=0.03).

DISCUSSION

This study shows, for the first time in a prospective study, the effects of early activation of MPP on reverse

remodelling, cardiac function and clinical response in patients with heart failure treated with CRT. The main findings of this study are (i) MPP was associated to a 6-month response rate of 64.6% that did not meet at a 2.5% significance level to be considered as significantly superior to current published CRT-D literature (calculated at 57%), (ii) similarly to previous studies with MPP, it was observed a numerically higher CRT response rate at 6 months in subjects programmed using widest pacing cathodes (72%) compared to other programming (61.1%), (iii) early activation of MPP was associated with an important 6-month LV reverse remodelling and improvement in cardiac function (i.e., LVEF) that was especially significant in patients programmed using anatomical approach, (iv) clinical response to early activation of MPP was high with only 12.2% of patients remaining in class III at 6 months with a percentage of negative responders to CRT according to the clinical composite score of 5%, and, (v) the incidence of mortality and or all cause hospitalizations was low and significantly lower in comparison with the observed in an recent cohort of patients treated with CRT using quadripolar leads and conventional biventricular pacing.

CRT by biventricular pacing is the only heart failure therapy that improves cardiac function, functional capacity and survival while decreasing hospitalizations[14]. Nevertheless, the response to BiV pacing is variable, ranging from complete normalization of cardiac function to lack of benefit. Suboptimal LV lead position, with less possibilities to pre-excite late activated left ventricular segments, and persistence of mechanical dyssynchrony despite biventricular pacing have been some of the suggested reasons to explain the absence of response to CRT[4]. The limited ability of conventional pacing to reduce dyssynchrony in some patients could be related to the important variability in the ventricular activation pattern, even in patients with LBBB[15,16]**.** In addition, the presence of diseased tissue and or lines of functional conduction block in the LV can induce slow myocardial impulse propagation or left ventricle latency, limiting the ability of a lateral LV lead to reduce the mechanical dyssynchrony. Consequently, intraventricular and interventricular dyssynchrony could persist in up to 30% of patients during conventional biventricular pacing[4]. MPP has been postulated to improve response by depolarizing large segments of the LV simultaneously and therefore activating early the area of latest electrical activation in left ventricle. Consequently, MPP could reduce LV activation time improving contractility and clinical outcomes.

Initial acute haemodynamic and echocardiographic studies of MPP showed a significant increase in LV dp/dt_{max}, LV stroke volume and a higher ability to reduce LV dyssynchrony in comparison to conventional biventricular pacing[5-8]. Nevertheless, the results observed in clinical trials have been somehow disappointing. In the MPP IDE study, patients received biventricular pacing for 3 months and were then randomized to MPP or biventricular pacing for 6 months[17]. MPP met the primary efficacy endpoint (non-inferiority of response rate based on Clinical Composite Score) in this study. However, MPP was not superior to conventional biventricular pacing reducing the percentage of patients with no response to CRT. In the More CRT MPP study[18], patients received conventional biventricular pacing and those not responding at 6 months were randomized to activate MPP or continue with biventricular pacing for another 6 months. In this study, MPP was not superior to biventricular pacing in the rate of conversion to echocardiographic response to CRT (31.8% vs 33.8%, P = 0.72). Similarly, we did not observe a significant benefit of MPP on the echocardiographic response rate to CRT in comparison to the estimated value previously published with conventional biventricular pacing.

Despite these neutral effects of MPP over the response rate to CRT, the MPP IDE study showed that patients randomized to MPP and programmed to pace from anatomically distant poles had a higher response rate to CRT in comparison to pace from close MPP poles. The rate of clinical responders at 9 months was 87% in the group of patients with the MPP programmed with the anatomic separation in comparison to 65% observed in patients with MPP and other programming or 70% in patients with conventional biventricular pacing[17]. The MORE CRT MPP study also observed a different non-responder to responder conversion rate according to the selection of poles for MPP, 46% in patient with the wide anatomical separation versus 26% in MPP and other programming and 34% in conventional biventricular pacing[18]. In our study, we also observed important differences in the effects of MPP according to the selection of poles for MPP. The patients programmed with an anatomical approach for MPP had a higher CRT response rate at 6 months (76%) compared to other programming (63%). Moreover, reverse remodelling and improvement in cardiac

function was especially important in patients programmed using anatomical approach with a mean absolute increase in LVEF of 14% in comparison to 8% in other MPP programming group. Finally, the percentage of super-responders was 48% in patients with MPP programmed using anatomical approach vs. 28% in other MPP programming. The observed percentage of super responders in this group is strikingly high in comparison to previous published data with conventional biventricular pacing. Interestingly, the QUARTO II study conducted by the same group using conventional biventricular pacing with quadripolar leads reported a super-responder rate of 38%[12].

These results are not surprising when considering the initial results of MPP evaluating acute hemodynamic and immediate dyssynchrony reduction in comparison to conventional biventricular pacing. These studies also reported a superiority of an empiric method of selecting MPP vectors based on maximizing anatomical spacing between pacing cathodes. These studies also reported that pacing with the minimum delay between pacing poles produced the best response in hemodynamics and dyssynchrony reduction[5-8]. The MPP IDE and the MORE CRT MPP trials also reported the highest benefits of MPP when pacing with the minimum delay between MPP electrodes.

All of these observations may be in accordance with the suggested benefits of MPP that entails the depolarization simultaneously of large segments of the left ventricle, reducing its activation time and resulting in a more efficient resynchronization. In this sense, wide separation of the 2 pacing sites seems to be crucial to obtain a benefit from MPP. When pacing sites are close, the area of initial myocardium activation is smaller than the area activated from 2 widely separated sites of pacing. Additionally, pacing from anatomically distant poles increases the probability of stimulate early the of latest activated area within the left ventricle and to avoid stimulation of overlying myocardial scar from at least one of 2 cathodes during MPP. On the other side, MPP by close pacing poles may be similar to conventional bipolar CRT. Indeed, it has been shown with conventional bipolar LV leads unwitting anodal capture in at least half of all cases[19]. This cathodal-anodal pacing of 2 adjacent LV lead poles may not be different from MPP from adjacent poles and would explain the absence of benefit of MPP over conventional CRT when pacing from narrow-spaced electrodes.

These results suggest the selection of widest-space electrodes with simultaneous pacing when considering MPP activation to increase CRT response. Otherwise, the probability of obtain a significant benefit could be null with a negative impact over device battery longevity.

Clinical outcomes of MPP have been less studied. In a registry, Forleo et al.[20] showed that MPP was associated with a better clinical outcome based on Clinical Composite Score, increased LVEF and reduction in QRS duration compared to biventricular pacing. In MORE CRT MPP study[18], patients randomized to the MPP arm showed a 21.8% reduction in heart failure events per 100 patient-years compared to before randomization and the biventricular arm showed a 9.1% reduction compared to before randomization (P=NS). In our study, we observed an important clinical response to MPP with only 12% of patients remaining in class III at 6 months of follow-up and a non-responder rate of 5% according to composite clinical score. Moreover, at 6 months mortality was only 1.9% and 11.4% of patients were admitted to the hospital for any reasons. Aiming to compare the clinical outcomes of MPP to conventional biventricular CRT the QUARTO III and QUARTO II cohorts were compared. Despite that groups were not completely equivalent; QUARTO II and QUARTO III cohorts were consecutives and were included, in most cases, by the same hospitals and investigators what entails a homogeneous plan of treatment and monitoring for the patients with heart failure involved in both studies. We observed better clinical outcomes in the group of patients treated with MPP with a significant reduction in the incidence of of mortality and or all cause hospitalizations in comparison to conventional biventricular pacing after adjusting for possible confounders variables.

Presently, MPP is available in devices from most of the companies. Despite the absence of an undoubtedly evidence of benefit, clinicians may have the opportunity of activating MPP in patients treated with CRT and a capable device. The published evidence may indicate a potential benefit from MPP only when it is possible to program wide separated pacing poles. The results of this study are in line with this observation and suggest a potential benefit in terms of clinical outcomes.

Study Limitations

Our study has several limitations. First, there were no specific recommendations for MPP programming and were left to the physician's discretion. Second, an important limitation of the study was the number of patients involved and the length of the follow-up that limits the identification of additional potential advantages of MPP further than 6 months. Third, the main limitation of the study, inherent to any registry, is the absence of a randomized comparator group of conventional biventricular pacing. Consequently, it cannot be concluded the superiority of any strategy for CRT. However, the better clinical outcomes observed in the group of patients treated with MPP merits to be analysed in future trials. Fourth, it was observed a benefit when programming MPP with the widest pacing electrodes. However, we did not address the percentage of cases in which it is possible to program MPP following this strategy. In our study, it was selected in 31% of patients, value similar to that observed in the MORE CRT MPP study (29%) or in the MPP IDE study (23%). We do not know if this programming was not possible in the remaining cases and factors as phrenic stimulation or unacceptable pacing thresholds limited the selection of the widest electrodes for MPP. If we accept that MPP could improve the results of CRT only when the selected pacing poles are enough separated it will be desirable to define the percentage of cases in which this is possible. Finally, we did not address the impact of MPP over device battery longevity that is an important issue when considering early activation of MPP.

Conclusions

Early activation of MPP was not associated to an advantage increasing echocardiography responders to CRT at 6 months of follow up. Nevertheless, MPP was associated to a low incidence of negative responders to CRT according to clinical composite score. Similar to previous studies, it was observed a higher CRT response rate and a higher improvement in left ventricular function at 6 months in subjects programmed using widest pacing cathodes. Finally, MPP in this study was associated with a low incidence of mortality and hospital admissions at 6 months of follow-up, which were significantly lower than those observed with conventional biventricular pacing in a comparative historical cohort of patients.

Ethical approval : All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Abbott provided funding for the study. The ClinicalTrials.gov Identifier is NCT02476201.

Informed consent : Informed consent was obtained from all individual participants included in the study.

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TABLES

Table 1. Baseline Demographics and Characteristics.

Variable	All Subjects (N=105)
Age (years)	
Mean ± SD (n)	64.5 ± 8.4 (105)
Range (Min, Median, Max)	(40, 64, 82)
Sex, (%) n/N	
Male	74.3% (78/105)
Female	25.7% (27/105)
NYHA Class (%) n/N	
Class I	5.7% (6/105)
Class II	57.1% (60/105)
Class III	37.1% (39/105)
Class IV	0.0% (0/105)
Cardiomyopathy Etiology (%) n/N	
Non-ischemic	58.1% (61/105)
Ischemic	41.9% (44/105)
Prior Cardiac Interventions (%) n/N	
ICD Implant	68.6% (72/105)
Valve Replacement	52.4% (55/105)
CABG	3.8% (4/105)
PCI	3.8% (4/105)
Valve Repair	1.0% (1/105)
Comorbidities (%) n/N	
Hypertension	68.6% (72/105)
Hypercholesterolemia	52.4% (55/105)
Smoker	49.5% (52/105)
Diabetes Mellitus	42.9% (45/105)
Dilated Cardiomyopathy	23.8% (25/105)
Renal Disease	10.5% (11/105)
CVA	9.5% (10/105)
COPD	9.5% (10/105)
Neoplastic Disease	5.7% (6/105)
Alcoholic	3.8% (4/105
Valvular Disease	3.8% (4/105)
Cardiac Medication (%) n/N	
Beta-Blockers	83.8% (88/105)
Diuretics	71.4% (75/105)
Aldosterone Antagonist	58.1% (61/105)
ACE	56.2% (59/105)
Antiplatelets	43.8% (46/105)
ARB	36.2% (38/105)
Anticoagulants	23.8% (25/105)

Table 2. **Echocardiographic parameters at Baseline and 6 months and LV reverse remodeling**

Measurements*	**Baseline**	**6-mo**
LVESD (cm) Mean ± SD (n) Range (Min, Median, Max)	5.45 ± 1.05 (3.10, 5.50, 7.50)	4.82 ±
LVEDD (cm) Mean ± SD (n) Range (Min, Median, Max)	6.38 ± 1.01 (3.90, 6.50, 8.00)	5.86 ±
LVESV (ml) Mean ± SD (n) Range (Min, Median, Max)	127.78 ± 48.87 (43.50, 124.67, 320.68)	95.12
LVEDV (ml) Mean ± SD (n) Range (Min, Median, Max)	180.50 ± 57.75 (79.75, 176.23, 400.58)	151.84
LVEF (Simpson method) (%) Mean ± SD (n) Range (Min, Median, Max)	31.38 ± 8.00 (10.00, 32.65, 47.00)	40.84

Table 3. Comparison of NYHA between Baseline and 6 Months.

NYHA Class		
Baseline		
% (n/N)		
6 Month		
% (n/N)		
I		
7.3% (6/82)		
19.5% (16/82)		
II		
57.3% (47/82)		
68.3% (56/82)		
III		
35.4% (29/82)		
12.2% (10/82)		
IV		
0.0% (0/82)		
0.0% (0/82)		

Table 4. Comparison of the baseline characteristics of Quarto II vs Quarto III.

	Subjects Analyzed (N = 303)	**Study Quarto II (N = 198)**	**Study Quarto III (N = 105)**	**Study p-value**
Age (years)	**Age (years)**	**Age (years)**	**Age (years)**	**Age (years)**
Mean ± SD (N) (Min, Median, Max)	65.5±9.7 (303) (29.0, 66.0, 94.0)	66.1±10.2 (198) (29.0, 67.0, 94.0)	64.5±8.4 (105) (40.0, 64.0, 82.0)	0.048[w]
Gender, n/N (%)	**Gender, n/N (%)**	**Gender, n/N (%)**	**Gender, n/N (%)**	**Gender, n/N (%)**
Female	79/303 (26.1%)	52/198 (26.3%)	27/105 (25.7%)	0.918[c]
Male	224/303 (73.9%)	146/198 (73.7%)	78/105 (74.3%)	
NYHa Class, n/N (%)	**NYHa Class, n/N (%)**	**NYHa Class, n/N (%)**	**NYHa Class, n/N (%)**	**NYHa Class, n/N (%)**
I	11/303 (3.6%)	5/198 (2.5%)	6/105 (5.7%)	0.002[c]
II	137/303 (45.2%)	77/198 (38.9%)	60/105 (57.1%)	

III	150/303 (49.5%)	111/198 (56.1%)	39/105 (37.1%)	
IV	5/303 (1.7%)	5/198 (2.5%)	0/105 (0.0%)	
Type of Cardiomyopathy, n/N (%)	**Type of Cardiomyopathy, n/N (%)**	**Type of Cardiomyopathy, n/N (%)**	**Type of Cardiomyopathy, n/N (%)**	**Type of Cardiomyopathy, n/N (%)**
ISCHEMIC	124/303 (40.9%)	80/198 (40.4%)	44/105 (41.9%)	0.800[c]
NON-ISCHEMIC	179/303 (59.1%)	118/198 (59.6%)	61/105 (58.1%)	
Medical History, n(%)	**Medical History, n(%)**	**Medical History, n(%)**	**Medical History, n(%)**	**Medical History, n(%)**
Unstable Angina	3/303 (1.0%)	2/198 (1.0%)	1/105 (1.0%)	0.961[c]
Hypertension	141/303 (46.5%)	69/198 (34.8%)	72/105 (68.6%)	<0.001[c]
Alcoholic	12/303 (4.0%)	8/198 (4.0%)	4/105 (3.8%)	0.922[c]
Diabetes Mellitus	109/303 (36.0%)	64/198 (32.3%)	45/105 (42.9%)	0.069[c]
COPD	23/303 (7.6%)	13/198 (6.6%)	10/105 (9.5%)	0.355[c]
CABG	26/303 (8.6%)	14/198 (7.1%)	12/105 (11.4%)	0.197[c]
Hypertrophic	4/303 (1.3%)	3/198 (1.5%)	1/105 (1.0%)	0.683[c]
Dilated	129/303 (42.6%)	87/198 (43.9%)	42/105 (40.0%)	0.509[c]
Idiopatic	44/303 (14.5%)	32/198 (16.2%)	12/105 (11.4%)	0.266[c]
LVESV at Baseline (mL)	**LVESV at Baseline (mL)**	**LVESV at Baseline (mL)**	**LVESV at Baseline (mL)**	**LVESV at Baseline (mL)**
Mean ± SD (N) (Min, Median, Max)	146.0±72.3 (283) (22.0, 130.0, 545.0)	155.2±75.1 (180) (22.0, 141.5, 463.0)	129.8±64.4 (103) (41.7, 118.3, 545.0)	0.003[w]
EF at Baseline(%)	**EF at Baseline(%)**	**EF at Baseline(%)**	**EF at Baseline(%)**	**EF at Baseline(%)**
Mean ± SD (N) (Min, Median, Max)	28.6±8.0 (292) (0.3, 29.0, 50.0)	26.9±7.4 (189) (0.3, 28.0, 46.7)	31.7±8.3 (103) (10.0, 33.0, 50.0)	<0.01[t]
[t] Two Sample t-test	[t] Two Sample t-test	[t] Two Sample t-test	[t] Two Sample t-test	[t] Two Sample t-test
[w] Wilcoxon Rank Sum test	[w] Wilcoxon Rank Sum test	[w] Wilcoxon Rank Sum test	[w] Wilcoxon Rank Sum test	[w] Wilcoxon Rank Sum test
[c] Chi-square test	[c] Chi-square test	[c] Chi-square test	[c] Chi-square test	[c] Chi-square test

FIGURES

Figure 1. Disposition of subjects during the study.

Figure 2. All cause death or hospitalization survival.

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