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Original Article

Cardiac resynchronization therapy is associated with improvement in clinical outcomes in Indian heart failure patients: Results of a large, long-term observational study

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ABSTRACT

Background: Heart failure (HF) is a common health problem in South Asia, and its incidence and prevalence are projected to rise. Cardiac resynchronization therapy (CRT) has been shown to improve mortality, reduce hospitalizations, and improve symptoms in selected patients with HF. The South Asian Systolic Heart Failure Registry (SASHFR) was designed to be a large and comprehensive registry of Indian HF patients with the purpose of enhancing the quality of care and clinical outcomes of HF patients by promoting the adoption of evidence-based, guideline-recommended therapies, in particular CRT.

Methods: Overall, 471 patients on optimized medical therapy and meeting CRT implantation guidelines were followed up in 12 Indian hospitals. During the 2-year follow-up period, clinical response in terms of clinical composite score, overall performance and changes in HF performance metrics, mortality and hospitalizations rates were evaluated.

Results: Of 471 patients, 116 (24.6%) accepted to be implanted with a CRT device, while 355 (75.4%) refused, financial constraints being the main reason for refusing a CRT device. The study met its primary outcome, as the number of patients associated with an improvement in clinical composite score at 24 months was significantly higher (69.1%) in the CRT group than in the no-CRT group (44.7%) [odds ratio = 2 (95% confidence interval 1.25–3.20), $p = 0.004$]. Also, changes in HF metrics, mortality and hospitalizations rates indicated a more favorable response among patients who underwent CRT.

Conclusions: The results from the SASHFR registry show a clear superiority of CRT over optimal pharmacological therapy in terms of improvement in clinical conditions among HF patients. The low rate of CRT acceptance, in patients indicated to this therapy, highlights the need for new health-care policies to improve awareness about HF disease and its therapies and possibly to enhance financial coverage of indicated therapies.

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1. Introduction

Heart failure (HF) is a common health problem in South Asia. The estimated prevalence of HF in India ranges from 1.3 to 4.6 million, with an annual incidence ranging from 491,600 to 1.8 million.¹ The HF burden on health-care resources is expected to grow rapidly all over the world because of the increasing aging population,¹ specifically in India, because the incidences of HF risk factors, such as coronary heart disease (CHD), hypertension, rheumatic heart disease (RHD), obesity, and diabetes, are growing.^{2,3}

At the moment, little is known about the current status of HF clinical management in India, together with other aspects such as its impact on patient mortality and morbidity, incidence and prevalence of the disease, cardiovascular and co-morbidity profile of HF patients, hospitalization rates, and economic burden.

Several studies demonstrated the safety and effectiveness of cardiac resynchronization therapy (CRT) combined with optimal drug therapy in the management of patients with moderate-to-severe HF.^{4–6} Based on the evidence of these trials, the American College of Cardiology, American Heart Association, and the Heart Failure Society of America have incorporated CRT in the guidelines for the management of HF.⁷

Patients with HF in India, compared with their western counterparts, have specific characteristics; they are younger, sicker, and have a much higher morbidity and mortality.⁸ These specificities warrant development of surveillance systems and HF therapy guidelines which are specific to Indian patients.

We performed the South Asian Systolic Heart Failure Registry (SASHFR) study to characterize the current management of patients with systolic HF in South Asia, following an educational intervention of current guidelines and delivery of disease management tools and to characterize the effect of current therapy on clinical outcomes. The study seeks to enhance the quality of care and clinical outcomes of the systolic HF patients by promoting the adoption of evidence-based, guideline-recommended therapies, in particular CRT, in eligible patients.

2. Methods

2.1. Study design

The SASHFR study was a nonrandomized prospective study designed to characterize the current management and the clinical outcomes up to 24 months after inclusion of patients with systolic HF enrolled across 12 Indian sites from October 2008 to December 2013. The study was closed on December 2015, when the last patient performed the 2-year follow-up visit.

The registry was conducted in compliance with the protocol and in accordance with the International Harmonised Tripartite Guidelines for Good Clinical Practice, the ethical principles laid down in the Declaration of Helsinki, and the “Ethical Guidelines for Biomedical Research on Human Subjects” issued by the Indian Council of Medical Research. The study protocol was approved by the institutional review board of each site. All patients were required to provide written informed consent before enrollment.

The registry included patients with moderate-to-severe HF [New York Heart Association (NYHA) class III or IV] who had ejection fraction (EF) $\leq 35\%$, QRS duration ≥ 120 ms, and a sinus rhythm, according to the CRT device implantation guidelines.^{7,8} In addition to the usual exclusion criteria, patients who experienced unstable angina, acute myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within the past 3 months, or with a CRT device previously implanted, were not enrolled.

Eligible patients who accepted to get implanted and in whom the implant was successful were grouped under the “CRT group”, while the remaining patients were categorized under the “no-CRT group”.

The main objective of the registry was to characterize the long-term outcomes of CRT and no-CRT patients, in terms of clinical composite score (as improved, worsened, or unchanged) and health-care utilization (based on hospitalization days), and to determine the overall performance and changes in HF performance metrics at each clinic visit. In addition, reasons why CRT-indicated patients did not receive implant were investigated.

The secondary objectives of the study were to determine the demographics of HF patients enrolled in the registry, to characterize the profile of HF patients with a positive response to CRT, and to determine the overall performance and changes in HF performance metrics at each visit.

No safety end points were considered for this study.

2.2. Education on HF guidelines

At the beginning of the study, before enrolling any patient, all the investigators and their medical staff attended an educational workshop designed to help developing a clinical care pathway that could be used in practice to implement existing HF guidelines into the quality of care for HF patients. After this initial training, the medical staff underwent refresher training, at least annually. Education on salt-restricted diet, daily weight monitoring, warning signs of worsened HF, and activity recommendations was provided to HF patients at initial visit, 6 months, and 12-month follow-up.

2.3. Patient groups

Patients meeting guidelines for CRT device implantation and who confirmed their participation by signing informed consent form were enrolled and categorized in one of the three following groups:

- CRT group: patients meeting CRT indication, on optimal medical therapy, who accepted to receive CRT-P (pacemaker) or CRT-D (defibrillator) device.
- No-CRT group: patients meeting CRT indication, on optimal medical therapy, who did not accept to be implanted with a CRT-P or CRT-D device.
- Patients meeting CRT indication but not on optimal medical therapy. These patients were appropriately managed with optimal pharmacological therapy per consensus guidelines for a period of 3 months after enrollment. At the end of this period, if they were still recommended for an implant of a CRT-P or CRT-D device were categorized in one of the first two groups. Otherwise, or in the case of not compliance to the therapy, they were exited.

The study flowchart is summarized in [Fig. 1](#).

2.4. CRT devices

Patients included in the CRT group received an InSync[®] III Model 7298 (Medtronic plc, Minnesota, USA) pacemaker if meeting guidelines for CRT-P device implantation or an InSync Sentry[™] Model 7298 (Medtronic plc) or Concerto[®] CRT-D (Medtronic plc) if meeting guidelines for CRT-D device implantation. All Medtronic leads, CRT-P and CRT-D devices, programmers, software, and accessories used in this study are approved for market release.

2.5. Follow-up schedule

Clinical data collection for all the enrolled patients was carried out at baseline and at 6-, 12-, 18- and 24-month follow-up visits. In addition, telephone follow-up visits were performed at 3, 9, 15, and 21 months for no-CRT patients.

2.6. Primary efficacy end points

The primary efficacy end point was the Packer clinical composite score, composed by death, HF hospitalization, NYHA class, and patient global assessment score. This score has been used in several HF studies.⁹ Patients were defined as either worsened (defined as patient died/hospitalized for worsening HF/worsening in the NYHA class or in patient global assessment score/discontinued CRT for worsening HF), improved (defined as not worsened and improvement in the NYHA class and/or in patient global assessment score), or unchanged (defined as neither improved nor worsened). Results at 12 and 24 months were reported and compared between groups.

2.7. Secondary efficacy end points

The key reasons for not receiving CRT were assessed.

Clinical outcomes of 6-min hall walk distance, Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life score, clinical composite score, and NYHA class were characterized at baseline and for all follow-up visits and compared between patients treated with CRT-P and CRT-D.

2.8. Statistical analysis

Being a registry study, no formal sample size calculation was performed. Intention-to-treat population, which included all patients enrolled in the registry, was considered for the analysis.

Demographic data and other continuous variables were summarized using descriptive statistics by study groups. Gender, intake

of hormone replacement therapy, and other categorical variables were summarized using count and percentage by the study groups. The homogeneity of the continuous variables across the study groups was evaluated using analysis of variance (ANOVA) or using nonparametric Kruskal–Wallis test (if assumptions of ANOVA were not satisfied). The homogeneity of the categorical variables was evaluated using Fisher's exact test.

The comparison of clinical composite score at 12 months and 24 months was performed using a logistic regression method, and the odds ratio (OR) were reported together with their 95% confidence intervals (95% CI). The baseline categories including age, sex, QRS duration, ischemic/nonischemic, left bundle branch block, NYHA class, left ventricular ejection fraction, beta-blocker use, angiotensin I–converting enzyme (ACE)/angiotensin II receptor blocker (ARB) use were included in the analysis as covariates if found significant. Subjects who shifted from the no-CRT group to the CRT group anytime during the follow-up visit were considered under CRT group for the same follow-up visit, and for these subjects, post-implant visits were also considered. For handling missing data at follow-up visits, the last observation carried forward technique was used for the end point clinical composite score.

The analysis, presented adjusted for baseline confounders through a multivariable model, was repeated without adjustment. A further analysis on the subset of patients without major protocol deviations (per-protocol population) was also performed to check the robustness of the results. Overall performance and changes in HF performance metrics was assessed between baseline, 12, and 24 months in all patients and was calculated in both CRT and no-CRT groups based on assessment of seven metrics (use of ACE inhibitors and/or ARBs, beta-blockers, aldosterone receptor antagonists, anticoagulation therapy, implantable cardioverter-defibrillator (ICD), CRT, and impartment of HF education).

Survival and risk of HF hospitalizations were also studied and compared between groups by means of the Cox regression for proportional hazards. The proportionality of risks was studied

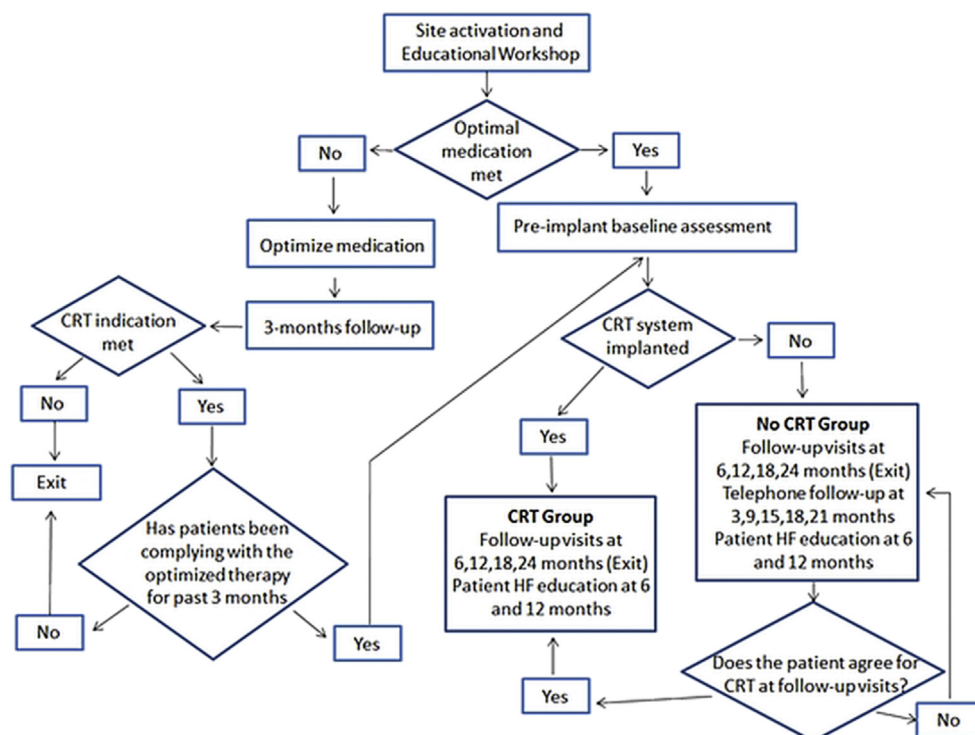


Fig. 1. Study design. CRT, cardiac resynchronization therapy; HF, heart failure.

through the Schoenfeld residual method, and the hazard ratio (HR) was presented with their 95% CI. For the computation of the HF performance metrics, scores of 1 and 0 were assigned for “yes” and “no” answers, and the total score was calculated and summarized. Changes in this score at each visit from baseline, for each question, were compared using Fisher's exact test.

Percentages of HF patients meeting CRT implant guidelines after 3 months of optimal medical therapy after enrollment were summarized using descriptive statistics as frequency and percentages and were compared using chi-square test or the Fisher's exact test, as appropriate.

3. Results

Overall, 501 patients were screened across 12 sites, 497 of them were enrolled in the study, and 471 were included in the analysis. Among them, 116 (24.6%) accepted to get implanted with a CRT device and formed the CRT group, while the remaining 355 (75.4%) formed the no-CRT group (Fig. 2). Baseline characteristics are reported in Table 1.

3.1. Clinical composite score

The patients' distribution between the two study groups is shown in Fig. 2. The study results, reported in Fig. 3 and in Table 2, show that the primary objective of the study was successfully achieved, as the number of patients associated with an

improvement in clinical composite score at 24 months was significantly higher among CRT patients, compared with no-CRT patients ($p < 0.001$). These results, corrected by using multivariate analysis, to take into account possible differences in patients' baseline characteristics, were confirmed when analyzing the per-protocol population. The difference between the two study groups became significant from 12 months onward, with the maximum at 24 months [1/9 patients (11.11%) in the CRT group versus 5/124 (4.03%) in the no-CRT group; OR = 0.19 (95% CI 0.07–0.45), $p < 0.001$].

3.2. NYHA functional class and quality of life

At baseline, 78 (67.24%) and 38 (32.76%) patients in CRT group were in NYHA class III and IV, respectively. The corresponding numbers in the no-CRT group were 338 (96.57%) and 12 (3.43%). Despite a worse baseline condition, at 24 months, there was a better improvement in NYHA functional status among CRT patients, with 15 patients (37.50%) in NYHA class III and none in NYHA IV, compared with the no-CRT group, where the respective numbers were 68 (73.12%) and 0, respectively.

Regarding quality of life, the baseline score for all the three domains of KCCQ was less in the CRT group as compared with the no-CRT group, with mean scores of 47.97 and 80.00, respectively. At the end of 24 months, the CRT group showed a better improvement in KCCQ scores compared with the no-CRT group, with mean scores of 76.01 and 85.43, respectively. Similarly, the changes in the KCCQ

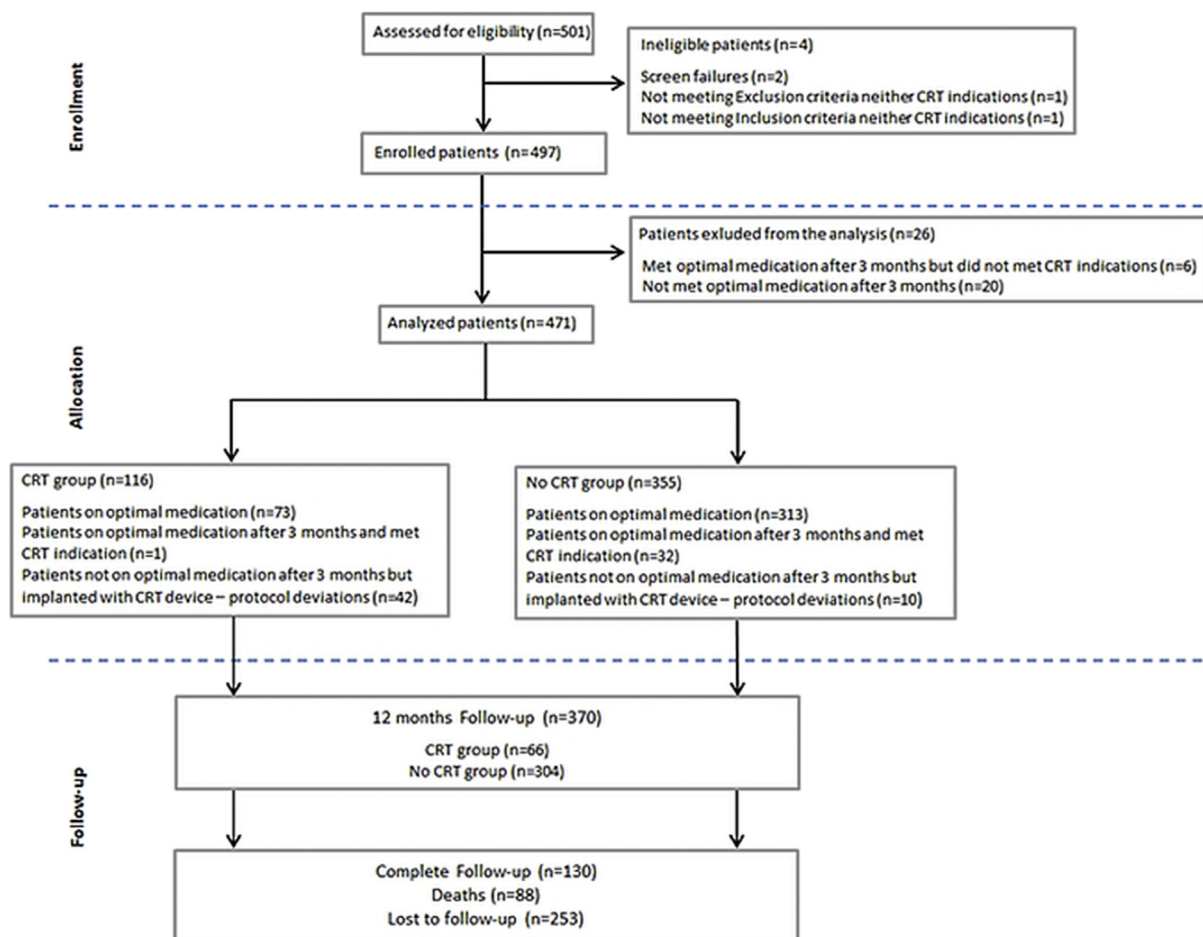


Fig. 2. Study flow diagram. CRT, cardiac resynchronization therapy.

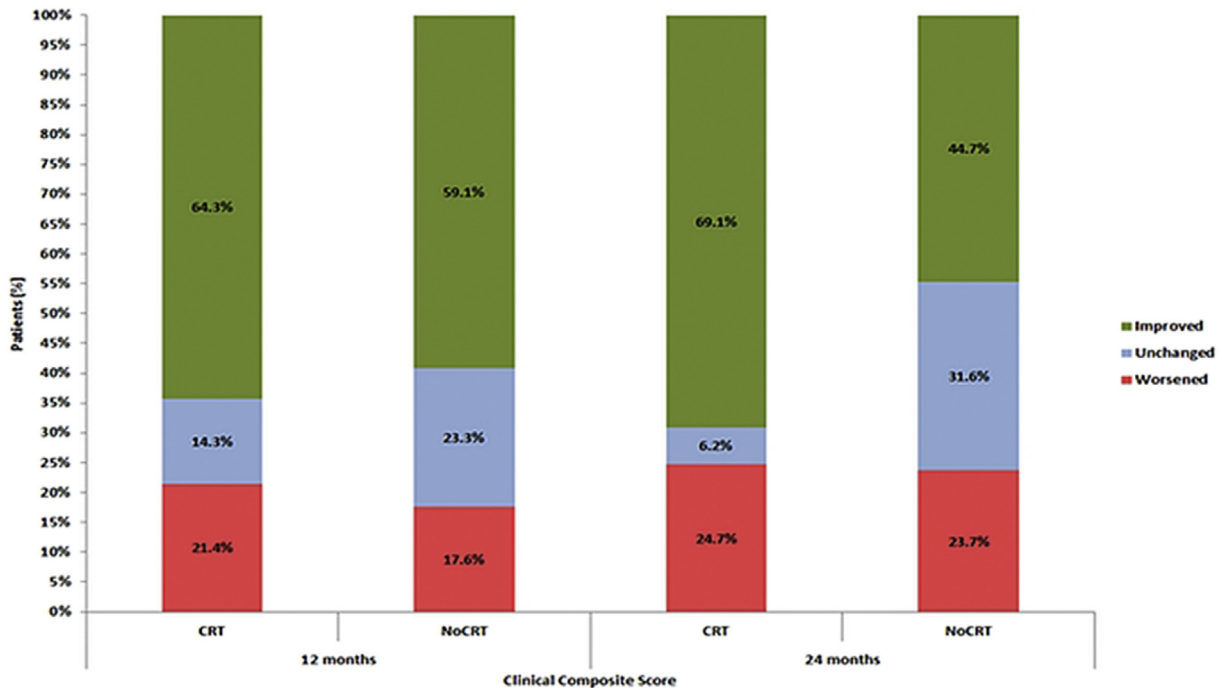


Fig. 3. Primary study end point (clinical composite score at 12 and 24 months for patients in the CRT and no-CRT groups). CRT, cardiac resynchronization therapy.

score from baseline to 6, 12, and 24 months were statistically significant between the groups with maximum change noted at 24 months (<0.0001).

3.3. Mortality and HF-related hospitalizations

Any-cause death occurred in 24 of 116 (20.7%) CRT patients and 64 of 355 (18.0%) no-CRT patients ($p =$ not significant).

HF-related deaths occurred in 7 (6.0%) CRT patients vs. 41 (11.5%) no-CRT patients ($p =$ not significant).

HF-related hospitalizations occurred in 14 of 116 (12.1%) CRT patients and 19 of 355 (5.4%) no-CRT patients ($p =$ not significant).

3.4. CRT acceptance

Out of the 355 patients who decided to not get implanted with a CRT device, 320 of them (90.1%) refused because of financial constraints, 7 patients (1.97%) declined because they felt better or improved with medication, one patient was a candidate for transplantation, and the remaining patients refused for other personal reasons.

3.5. CRT-related adverse events

No CRT-related adverse events were reported.

4. Discussion

HF is a major component of the noncommunicable disease burden in the Indian population.¹⁰ In India, using calculations based on morbidity and mortality profiles and prevalence of risk factors such as CHD, hypertension, RHD, and increasing aging, there would be at least 1 million patients with HF at any time.² The aim of the SASHFR study was to characterize the current management and long-term clinical outcomes among systolic HF population in India.

4.1. Main results

In our study, CRT therapy was associated with (1) improved clinical composite score, (2) improved NYHA functional status, (3) improved quality of life, and (4) decreasing trend toward HF-related deaths and hospitalizations.

The clinical composite score, composed by survival rate, HF hospitalizations, changes in NYHA class, and patient global assessment, was associated with a statistically significant improvement in the CRT group compared with the no-CRT group, by the end of 24 months. Similarly, a positive response calculated on improvements in clinical composite score and reduction in left ventricular end-systolic volume (LVESV), that is related to improvement in clinical outcomes,¹¹ was significantly higher among CRT patients, compared with the no-CRT patients, with the difference becoming significant from 12 months onwards. These results confirm the ones previously obtained in the resynchronization reverses remodeling in systolic left ventricular dysfunction (REVERSE) trial, in which patients programmed with CRT therapy ON showed a better response at 1 year than those programmed with CRT therapy OFF, not significant in terms of improvement in Packer clinical composite score but statistically significant in terms of LVESV reduction (-18.4 ± 29.5 ml/m² for CRT-ON group; -1.3 ± 23.4 ml/m² for CRT-OFF group; $p < 0.0001$).¹¹ The 24-month results of the European cohort of the REVERSE trial showed that CRT improves the HF clinical composite response and the LV structure and function.⁹

Our results also indicate that the subjects included in the CRT group showed a marked improvement in NYHA functional status and functional exercise tolerance, as evidenced by the mean distance walked in 6-min hall walk test.

Moreover, the CRT group patients experienced an improvement in quality of life assessed by mean of the KCCQ scores, with a statistically significant difference at 24 months with respect to baseline.

Finally, also the HF-related deaths and the hospitalization days indicate a more favorable response in the CRT group, although this

Table 1
Patient characteristics at enrollment.

Baseline characteristics	CRT	No CRT	Total	p value
<i>Demographics</i>				
Age (years), mean ± SD	60 ± 12	57 ± 12	58 ± 12	0.040
Height (cm), mean ± SD	164 ± 9	160 ± 9	161 ± 9	0.001
Weight (Kg), mean ± SD	66 ± 12	63 ± 11	64 ± 11	0.022
Male gender, n (%)	79 (68.1%)	264 (74.4%)	343 (72.8%)	0.188
<i>Medical/surgical history</i>				
Ischemic cardiomyopathy, n (%)	32 (27.6%)	153 (43.1%)	185 (39.38%)	0.003
Cardiac arrest, n (%)	20 (17.2%)	8 (2.2%)	28 (5.9%)	<0.001
Myocardial infarction, n (%)	17 (14.7%)	120 (33.8%)	137 (29.01%)	<0.001
Coronary artery bypass graft, n (%)	20 (17.2%)	61 (17.2%)	81 (17.2%)	1.0
Coronary artery intervention (stent or angioplasty), n (%)	23 (19.8%)	62 (17.45%)	85 (18.15%)	0.57
History of atrial fibrillation, n (%)	6 (5.2%)	2 (0.6%)	8 (1.7%)	0.003
History of ventricular fibrillation, n (%)	1 (0.89%)	1 (0.3%)	2 (0.4%)	0.42
History of ventricular tachycardia, n (%)	24 (20.79%)	13 (3.7%)	37 (7.9%)	<0.001
NYHA class IV, n (%)	38 (32.8%)	12 (3.4%)	50 (10.7%)	<0.001
Left bundle branch block, n (%)	90 (77.69%)	170 (47.9%)	260 (55.2%)	<0.001
QRS wave duration, mean ± SD	152 ± 32	158 ± 34	157 ± 33	0.11
Complete AV block, n (%)	1 (1.0%)	1 (0.3%)	2 (0.4%)	0.42
AV node ablation, n (%)	1 (0.96%)	0	1 (0.2%)	–
History of syncope, n (%)	20 (17.2%)	2 (0.6%)	22 (4.7%)	<0.001
Valve dysfunction, n (%)	35 (30.2%)	49 (13.8%)	84 (17.8%)	<0.001
Valve surgery, n (%)	3 (2.69%)	5 (1.4%)	8 (1.7%)	0.41
Diabetes, n (%)	0	1 (0.3%)	1 (0.2%)	–
LVEF (%), mean ± SD	24 ± 5	27 ± 6	26 ± 6	<0.001
LVESV (ml), mean ± SD	163 ± 99	126 ± 47	132 ± 61	<0.001
LVEDV (ml), mean ± SD	197 ± 114	169 ± 53	174 ± 67	0.004
LVESD (mm), mean ± SD	192 ± 243	77 ± 118	101 ± 159	<0.001
LVEDD (mm), mean ± SD	218 ± 277	95 ± 138	121 ± 183	<0.001
<i>Medications at enrollment</i>				
ACE inhibitor/ARBs, n (%)	87 (75.0%)	337 (94.9%)	424 (90.0%)	<0.001
Beta-blockers, n (%)	74 (63.79%)	330 (93.0%)	404 (85.78%)	<0.001
Diuretics, n (%)	103 (88.79%)	305 (85.9%)	408 (86.6%)	0.43

ACE-ARB, angiotensin I–converting enzyme or angiotensin II receptor blocker; AV, atrioventricular; CRT, cardiac resynchronization therapy; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; SD, standard deviation.

was not statistically significant. Results from the REVERSE study showed that in addition to the highest rate in HF-related hospitalizations for patients included in the CRT-OFF group, time-to-first HF hospitalization was significantly delayed in the CRT-ON group (HR 0.47, $p = 0.03$).¹¹ Large trials confirmed this trend and also underlined that delay in implanting a CRT device in patients with HF appears to be associated with an irrevocable reduction in survival.^{5,6}

One of the secondary objectives of the study was to characterize the demographics of the HF population included in the registry. No significant difference regarding age was found, and the mean age of the HF patients enrolled was 60 years. In a recent acute HF registry of 90 patients in India, the patients were middle aged (50.8 years) with a mean EF of 27.8%. They had a high mortality (in-hospital mortality rate of 30.8%) with post-discharge 6-month rehospitalization and mortality rates of 39.5% and 26.3%.¹² This supports the concept that

Table 2
Study end points.

	CRT (n = 116)	No CRT (n = 355)	OR (95% CI)	p value
Clinical composite score: 12 months ^a				
Improved	63 (64.3%)	185 (59.1%)	1.19 (0.69–2.06)	0.53
Unchanged	14 (14.3%)	73 (23.3%)		
Worsened	21 (21.4%)	55 (17.6%)		
Clinical composite score: 24 months ^a				
Improved	67 (69.1%)	130 (44.7%)	2.00 (1.25–3.20)	0.004
Unchanged	6 (6.2%)	92 (31.6%)		
Worsened	24 (24.7%)	69 (23.7%)		
Survival and HF hospitalizations				
Any-cause deaths	24 (19.4%)	64 (18.4%)	0.97 (0.60–1.57)	0.90
HF hospitalizations	14 (12.1%)	19 (5.4%)	0.53 (0.26–1.09)	0.087
Positive response ^b				
12 months	3 (10.7%)	4 (3.4%)	0.42 (0.18–0.95)	0.037
24 months	1 (11.1%)	5 (4.0%)	0.19 (0.08–0.41)	<0.001

The baseline categories including age, sex, QRS duration, ischemic/nonischemic, left bundle branch block, NYHA class, LVEF, beta-blocker use, ACE/ARB use were included in the analysis as covariates if found significant.

The table includes data on clinical composite score and percentage of HF patients with positive responses at 12 and 24 months and mortality and HF hospitalization during the study.

CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; HR, hazard ratio; OR, odds ratio.

^a 18 CRT and 42 no CRT missing at 12 months; 19 CRT and 64 no CRT missing at 24 months.

^b 75 CRT and 169 no CRT missing at 12 months; 19 CRT and 108 no CRT missing at 24 months.

cardiovascular disease affects patients in India at a younger age than the Western HF cohorts, that typically range from 65 to 73 years.² Our data confirm the previous findings of the panarrhythmia and heart failure (PANARM HF) registry¹⁰ about the imbalance between males and females among recipients of implantable devices or interventional therapies. This result could be because of a combination of factors such as reduced cardiovascular disease prevalence among females, reluctance to seek health care and, more likely, a lower priority and willingness to finance female health in Indians.

4.2. Therapy acceptance

One of the most important results of our study is the great number of patients who were unwilling to receive a device. Of the 471 enrolled patients, only 24.6% of them opted for CRT-P/CRT-D during the 2-year study duration. Among the remaining 75.4% of patients, financial constraints were the key reason why they refused the implant. This trend appears to be quite common across India. The PANARM HF registry¹⁰ showed that of the 1011 screened patients who needed to be referred to an interventional cardiologist (IC), only ~25% of them consulted the IC. Moreover, half the HF patients who consulted the IC, and were indicated for a CRT device, were in HF stage C or D. This finding is a clear reflection of the lack of health awareness and low priority to proactively seek out health care in the Indian community.

5. Conclusions

Our data show a clear superiority of CRT therapy over optimal pharmacological therapy in terms of improvement in clinical conditions among selected patients with HF. The low rate of CRT acceptance, in patients indicated to this therapy, highlights the need for new health-care policies to improve awareness about HF disease and its therapies and possibly to enhance financial coverage of indicated therapies.

6. Limitations

The SASHFR study is an observational study; while a randomized design would have allowed to account for selection bias or other kind of biases, the observational nature of our study allowed us to evaluate acceptance of HF guidelines-indicated therapies.

The study met its prespecified primary end point; therefore, even in a nonrandomized design, the study confirmed the hypothesis that CRT on top of optimized pharmacological therapy improves clinical outcomes in patients with HF in India. The fact that the clinical composite score showed a significant difference between the CRT and no-CRT groups only 12 months after enrollment may be related to the small sample size which likely caused the analysis to be underpowered. Further data from future randomized trials are needed to validate the important findings of our study.

The study was associated with a relevant number of lost to follow-up patients; while this aspect reflects real-world clinical practice, we cannot exclude that this partially influenced the study results.

We cannot exclude underreporting of clinical events and device-related complications.

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Conflicts of interest

V. Rajan and R. Radhakrishnan are employees of Medtronic.

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References

- Huffman MD, Prabhakaran D. Heart failure: epidemiology and prevention in India. *Natl Med J India*. 2010;23:283–288.
- Seth S, Bhargava B, Maulik S, et al. Consensus statement on management of chronic heart failure in India. *J Pract Cardiovasc Sci*. 2015;1:105.
- Chaturvedi V, Parakh N, Seth S, et al. Heart failure in India: the INDUS (India Utkeri Study) study. *J Pract Cardiovasc Sci*. 2016;2:28.
- Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834–1843.
- Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure results from the comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial. *Circulation*. 2009;119:969–977.
- Cleland JGF, Freemantle N, Erdmann E, et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. *Eur J Heart Fail*. 2012;14:628–634.
- Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *Heart Rhythm*. 2008;5:934–955.
- Seth S. Heart Failure in India: Need for Indian Guidelines. http://www.csi.org.in/Cardio_pdf/21.pdf.
- Daubert C, Gold M, Abraham W, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE trial. *J Am Coll Cardiol*. 2009;54:1837–1846.
- Vora A, Naik A, Lokhandwala Y, et al. Profiling cardiac arrhythmia and heart failure patients in India: the Pan-arrhythmia and Heart Failure Observational Study. *Indian Heart J*. 2017;69:226–239.
- Gold MR, Daubert C, Abraham WT, et al. The effect of reverse remodeling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: results of the REVERSE study. *Heart Rhythm*. 2015;12:524–530.
- Seth S, Khanal S, Ramakrishnan S, Gupta N, Bahl VK. Epidemiology of acute decompensated heart failure in India the AFAR study (acute failure registry study). 2015;1:2015–2018.