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Outcomes of Cardiac Resynchronization Therapy by New York Heart Association Class: A Patient-Level Meta-Analysis

Nishkala Shivakumar, MD, MBA,[3] Daniel J. Friedman, MD,[1,2], Marat Fudim[1,2], MD, William T. Abraham, MD,[4] John G. F. Cleland, MD, PhD,[5,6] Anne B. Curtis, MD,[7] Michael R. Gold, MD, PhD[8] Valentina Kutyifa, MD,[9] Cecilia Linde, MD,[10] James Young, MD,[11] Anthony Tang, MD,[12] Antonio Olivas-Martinez, MD,[13] Lurdes Y.T. Inoue, PhD,[13] Gillian D. Sanders, PhD, [2,14,15,16,] Sana M. Al-Khatib, MD, MHS,[1,2]

1, Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC

2. Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

3, Department of Medicine, Duke University School of Medicine, Durham, NC

4, Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH

5, National Heart and Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London, United Kingdom (J.G.F.C.).

6, British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Health, University of Glasgow, United Kingdom (J.G.F.C.).

7, Department of Medicine, University at Buffalo, Buffalo, NY

8, Department of Medicine, Medical University of South Carolina, Charleston, SC

9, Division of Cardiology, Department of Medicine, University of Rochester Medical Center Rochester, NY

10, Karolinska Institutet and Department of Cardiology, Karolinska University, Stockholm, Sweden

11, Cleveland Clinic, Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

12, Department of Medicine, Western University, Ontario, Canada

13, Department of Biostatistics, University of Washington, Seattle, WA

14, Duke-Margolis Center for Health Policy, Duke University, Durham, NC

15, Evidence Synthesis Group, Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

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16, Department of Population Health Sciences, Duke University School of Medicine, Durham, NC

Corresponding author:

Sana M. Al-Khatib, MD, MHS

Duke Clinical Research Institute, 300 Morgan Street, Durham, NC 27701. Phone: 919-668-8649; Fax: 919-668-7058.

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Abstract

Data on the benefits of cardiac resynchronization therapy (CRT) in patients with severe heart failure (HF) symptoms are limited. We investigated the relative effects of CRT in patients with ambulatory NYHA IV vs. III functional class at the time of device implantation. In this meta-analysis, we pooled patient-level data from the MIRACLE, MIRACLE-ICD, and COMPANION trials. Outcomes evaluated were time to the composite endpoint of first HF hospitalization (HFH) or all-cause mortality and time to all-cause mortality alone. The association between CRT and outcomes was evaluated using a Bayesian Hierarchical Weibull survival regression model. We assessed if this association differs between NYHA III and IV groups by adding an interaction term between CRT and NYHA class as a random effect. A sensitivity analysis was performed by including data from the RAFT trial. Our pooled analysis included 2309 patients. Overall, CRT was associated with a longer time to HFH or all-cause mortality (adjusted hazard ratio [aHR] 0.79, 95%CI 0.64 – 0.99, p = 0.044), with a similar association with time to all-cause mortality (aHR 0.78, 95% CI 0.59 – 1.03, p = 0.083). Associations of CRT with outcomes were not significantly different for those in NYHA III and IV classes (ratio of aHR 0.72, 95% CI 0.30 – 1.27, p = 0.23 for HFH/mortality; ratio of aHR 0.70, 95% CI 0.35 – 1.34, p = 0.27 for all-cause mortality alone). The sensitivity analysis, including RAFT data, did not show a significant relative CRT benefit between NYHA III and IV classes. Overall, there was no significant difference in the association of CRT with either outcome for patients in NYHA functional class III compared with functional class IV.

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Introduction

Cardiac resynchronization therapy (CRT) has improved the treatment of heart failure (HF) by reducing hospitalization rates and mortality among patients across a wide range of HF symptom severity. Trials such as MADIT-CRT [1] and RAFT [2] demonstrated the benefit of CRT in patients with mild to moderate HF symptoms while MIRACLE [3], CARE-HF [4], and COMPANION [5] demonstrated similar benefit for patients with advanced HF symptoms. Unfortunately, even in the latter set of trials, patients with the most advanced symptoms, i.e. NYHA class IV symptoms, were not well represented. COMPANION, MIRACLE and CARE-HF only enrolled ~14%, ~10% and ~7% of patients with NYHA class IV symptoms respectively. Thus, whether CRT benefits patients with NYHA class IV symptoms is uncertain. This is an important question to answer as patients with HF are living longer, and therefore, the number of patients with advanced HF symptoms is increasing.

In this analysis, we aimed to evaluate whether CRT is associated with improvement in time to the combined endpoint of HF hospitalization (HFH) or all-cause mortality and time to all-cause mortality alone for patients in NYHA functional class IV compared with class III.

Methods

Data Sources

We performed a patient level meta-analysis of the following CRT trials that included patients in NYHA III or IV classes: MIRACLE, MIRACLE-ICD [6], and COMPANION trials. These trials compared patients with CRT with a control group (either optimal medical therapy or ICD with no CRT). These three trials included only patients with NYHA III and IV functional class. In MIRACLE, all patients underwent CRT-P implantation, but only the treatment group had the

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biventricular pacing function turned on. In MIRACLE-ICD, outcomes were compared between patients with a CRT-D and those with an ICD. In COMPANION, both patients with CRT-D and CRT-P were enrolled, and outcomes of CRT were compared with those randomized to pharmacological therapy alone.

In a sensitivity analysis, the RAFT trial was included; this trial enrolled patients with NYHA II or III functional class, but only NYHA III data were used in this analysis. In RAFT, patients with CRT-D were compared with those with an ICD with no CRT. Due to data privacy restrictions, we were not given access to European patient data, which precluded inclusion of the CARE-HF trial.

Study Population

Patients in NYHA III or IV classes who had data available on HFHs and all-cause mortality were included. We excluded patients with a left ventricular ejection fraction (LVEF) >35%, QRS width <120ms, RV pacing, combined left bundle and right bundle branch block, and time to HFH/mortality of 0.

Outcome

Outcomes of interest were time to the composite of first HFH or all-cause mortality and time to all-cause mortality alone.

Statistical analysis

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Categorical variables are presented as medians and 25th and 75th percentiles. Continuous variables are presented as counts and frequencies.

For each endpoint, the overall CRT effect (versus no CRT) was estimated using a Bayesian Hierarchical Weibull survival regression model with a random intercept and a random treatment effect at the trial level adjusting for the presence of an ICD and baseline characteristics (age, sex, NYHA class, LVEF, QRS duration, LBBB morphology, atrial fibrillation, diabetes, hypertension, ischemic etiology, use of beta-blockers, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers). CRT effect by NYHA class (class IV versus class III) was evaluated using a similar model but including a random interaction term between CRT and NYHA class. The null hypothesis of no interaction was tested with the 2-sided posterior probability that the mean component of the random interaction term between CRT and NYHA group was zero. All priors are non-informative. Normally distributed priors were used for fixed effects and mean components of the random effect distributions. Half-normal distributions priors were used for the variance components of the random effect distributions, and a log-normal distribution prior was chosen for the shape parameter of the Weibull model. The scaled Schoenfeld residuals from an adjusted Cox proportional hazard mixed effects model with random intercepts and random treatment effects at the trial level were used to assess the validity of the proportional hazard assumption for each model.

In a sensitivity analysis, the above analyses were repeated after including patients in NYHA class III enrolled in the RAFT trial. For the adjusted regression models, a fixed interaction term

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was used instead of a random interaction term because patients in NYHA class IV were excluded from RAFT and a random interaction variable between NYHA classes could not be estimated.

Results

A total of 2360 patients were considered for inclusion from the MIRACLE, MIRACLE-ICD, and COMPANION trials; after applying exclusion criteria, 2309 patients were available for analysis. Tables 1 and 2 provide the baseline characteristics of the study cohort sorted by trial and NYHA functional class. Patients in NYHA class IV comprised 13% of the total study population. Of those assigned to CRT, slightly more than half received CRT-P. The median age of patients was 66 years, they were predominantly men (69%), and the median LVEF was 23%. Both ischemic (57%) and non-ischemic (43%) cardiomyopathy were well represented. QRS duration was similar across NYHA classes and CRT groups. Common comorbidities included diabetes (39%), hypertension (49%), and atrial fibrillation (17%). The burden of diabetes and history of atrial fibrillation were similar among the CRT groups. However, there were more patients with a history of diabetes and atrial fibrillation in the NYHA class IV group. Medical therapy was similar among the CRT groups, but patients with NYHA class IV functional class were less likely to be on an ACE/ARB and a beta-blocker.

The median follow-up for the overall cohort was 10 months (IQR 6-18 months). The adjusted (Figures 1 and 2 and Table 3) associations of CRT overall and by NYHA class with time to HFH/mortality and overall survival times are shown using Kaplan-Meier curves and forest plots. The results in figure 1, figure 2, and table 3 were adjusted for ICD, age, sex, NYHA class, EF, QRS duration, LBBB, atrial fibrillation, diabetes, hypertension, ischemic etiology, use of beta

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blockers, and use of ACE/ARB. Table 4 shows the results for the sensitivity analysis including data from RAFT.

Overall, CRT was associated with a longer time to the composite outcome (aHR 0.79, 95% CI 0.64-0.99, p 0.044) with a similar trend for all-cause mortality alone though not statistically significant (aHR 0.78, 95% CI 0.59-1.03, p 0.083). The ratio of hazard ratios failed to demonstrate a significant interaction between NYHA class and the association of CRT with either outcome. The ratio of hazard ratios (NYHA IV/III) for time to the composite outcome was 0.72 (95% CI 0.30-1.27, p 0.23) and for time to all-cause mortality alone was 0.70 (95% CI 0.35-1.34, p 0.27).

There was not a statistically significant association of CRT with both endpoints in the individual NYHA functional classes. For patients with NYHA III functional class, the aHR for time to the composite outcome was 0.82 (95% CI 0.66-1.04, p 0.10), and the aHR for time to all-cause mortality alone was 0.87 (95% CI 0.62-1.20, p 0.40). For patients with NYHA IV functional class, the aHR for time to the composite outcome was 0.59 (95% CI 0.26-1.04, p 0.23) and the aHR for time to all-cause mortality alone was 0.61 (95% CI 0.31-1.09, p 0.088).

A sensitivity analysis that included data from the RAFT trial showed significant association of CRT in the overall group with longer time to both outcomes (time to all-cause mortality/HFH: aHR 0.76, 95% CI 0.64-0.91, p 0.009; all-cause mortality: aHR 0.74, 95% CI 0.59-0.92, p 0.007). In this analysis, there was also no significant interaction between NYHA class and the association of CRT with time to both outcomes. The ratio of hazard ratios (NYHA IV/III) for

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time to all-cause mortality/HFH was 0.85 (95% CI 0.59-1.25, p 0.41) and time to all-cause mortality alone was 0.78 (95% CI 0.51-1.23, p 0.27).

There was CRT benefit for both outcomes in the individual NYHA groups as well. For patients in NYHA Class III, the aHR for time to the composite outcome was 0.78 (95% CI 0.65-0.95, p 0.020) and for time to all-cause mortality alone was 0.79 (95% CI 0.63-1.00, p 0.051). For patients with NYHA IV, the aHR for time to all-cause mortality/HFH was 0.67 (95% CI 0.46-0.97, p 0.037) and the aHR for time to all-cause mortality alone was 0.61 (95% CI 0.41-0.94, p 0.027).

Discussion

This patient level meta-analysis provides data on the outcomes of CRT for patients with the most severe HF symptoms, i.e. NYHA class IV. Most studies that have included patients with NYHA Class III and IV symptoms have a very small proportion of patients with NYHA class IV functional class. Therefore, it was important to combine available data to examine outcomes of CRT in patients with NYHA class IV functional class.

In this study, there was significant association of CRT with improved outcomes in the overall group of patients; i.e., those in NYHA class III and those in NYHA class IV. In the primary analysis, there was not a statistically significant improvement in time to all-cause mortality/HFH or time to all-cause mortality when patients with NYHA class III and those with NYHA class IV symptoms were analyzed separately. However, in the sensitivity analysis that included data from RAFT, there was a statistically significant improvement in time to both endpoints for patients

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with NYHA class III and those with class IV symptoms separately. These results along with the results of the interaction tests (for the primary and the sensitivity analysis) show that CRT is associated with improved outcomes in patients with NYHA class III as well as those with NYHA class IV functional class. The difference in results between the primary analysis and the sensitivity analysis strongly suggests that the primary analysis lacked statistical power to show an improvement in the two endpoints with CRT for the individual NYHA classes. The statistical power was augmented by inclusion of the RAFT trial in the sensitivity analysis. The differences in NYHA class IV results between the primary analysis and the sensitivity analysis can be explained by the utilization of one model for both data sets with the same assumed class interaction term.

The role of CRT in patients with advanced HF symptoms may be affected by several clinical factors. The extent of cardiac remodeling in patients with advanced HF symptoms may impact response to CRT. There is likely a level of remodeling (left ventricular dilatation, EF, etc.) beyond which CRT may not confer any benefit. While data on this issue are badly needed, echocardiographic parameters were not available for examination in the current study. Also, patients with advanced HF commonly have other comorbidities. Whereas a prior study [7] has suggested that CRT is beneficial in patients with several comorbidities, that study did not include an adequate number of patients with NYHA class IV symptoms. How the number, type, and severity of comorbidities affect outcomes of CRT deserves more study. In addition, many patients with advanced HF are not able to tolerate guideline-directed target doses of medical therapies, either due to a low blood pressure and/or an elevated creatinine. Therefore, CRT may be especially beneficial in such patients. This, too, deserves further study.

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It is important to note that patients in NYHA class IV enrolled in traditional randomized clinical trials of CRT and examined in the current study are likely not representative of patients seen in clinical practice. Patients enrolled in randomized clinical trials are generally less morbid and are more closely monitored than "real-world" patients. Therefore, data from clinical trials should be complemented with data from registries. In US registry-based studies, it has been shown that patients with advanced HF have greater peri-procedural complications and higher 30-day all-cause mortality after device (ICD or CRT) implantation compared with patients with mild to moderate HF symptoms [8]. In the Israeli ICD Registry, the risk associated with CRT implantation was found to be similar among patients with mild and advanced HF symptoms while the risk associated with ICD implantation was greater in patients with advanced HF symptoms [9]. An analysis of the InSync Italian registry compared the benefit of CRT in patients with mild HF symptoms (NYHA II) versus patients with moderate to advanced HF symptoms (NYHA Class III-IV) [10]. This analysis showed similar improvement in EF among patients with mild and advanced HF but less improvement in functional status and lower all-cause mortality in patients in NYHA class II compared with patients with more advanced HF. Additionally, there are meta-analyses that have demonstrated CRT benefit for time to HFH/all-cause mortality [11] and time to all-cause mortality [12] for patients in NYHA class IV. The former looked at 5 randomized trials to evaluate what pre-implantation variables predict response to CRT (most important variable found to be QRS duration). The latter analyzed data from CARE-HF and COMPANION trials to evaluate the same outcomes for CRT-P (QRS duration not found to be significant factor predicting CRT benefit).

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Despite these studies, data remain limited regarding CRT in patients with advanced HF symptoms. Until more data are generated in larger and more contemporaneous cohorts of patients with HF, this patient-level meta-analysis will hopefully inform clinical practice and shared-decision making.

Limitations

Although our analysis included the largest number of patients in NYHA class IV (302 patients) to date, and it was conducted at the patient level, some limitations should be acknowledged. The power of this study was limited by the relatively small number of patients in NYHA class IV. For this reason, we were underpowered in our interaction analysis further highlighting the need for new studies with greater recruitment of patients with advanced HF symptoms. Studies included in this analysis were published more than a decade ago; medical therapy of patients with HF and CRT devices and implantation techniques have evolved drastically since the publication of those trials. Whether and how contemporary CRT technology and medical therapy for patients with advanced HF might impact the outcomes of CRT is uncertain. Other important endpoints such as quality of life and implant-related complications were not reported in a sufficient number of studies for this meta-analysis, and procedural complications that are higher in patients with more advanced HF might influence the net clinical benefit from CRT. Although the endpoints of the trials were all independently adjudicated by blinded clinical endpoint committees, endpoint definitions varied slightly across the trials. While advanced Bayesian techniques were applied to account for this heterogeneity, the possibility of confounding cannot be ruled out.

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Conclusions

In this meta-analysis of patient level data from randomized controlled trials, CRT appeared to be beneficial in improving the time to all-cause mortality or HFH, as well as all-cause mortality alone, in patients in NYHA class III as well as those in NYHA class IV. However, given the relatively small number of patients in NYHA class IV, these results highlight the need for further studies on patients in NYHA class IV that are reflective of contemporaneous CRT devices, implantation techniques, and medical therapy for advanced HF.

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References

[1] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W and Investigators M-CT. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329-38.

[2] Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL and Resynchronization-Defibrillation for Ambulatory Heart Failure Trial I. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363:2385-95.

[3] Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J and Evaluation MSGMIRC. Cardiac resynchronization in chronic heart failure. The New England journal of medicine. 2002;346:1845-53.

[4] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539-49.

[5] Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140-50.

[6] Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K and Multicenter InSync ICDRCETI. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685-94.

[7] Zeitler EP, Friedman DJ, Daubert JP, Al-Khatib SM, Solomon SD, Biton Y, McNitt S, Zareba W, Moss AJ and Kutyifa V. Reply: The Benefit of Cardiac Resynchronization Therapy Is Not Hindered by the Number of Comorbidities. J Am Coll Cardiol. 2017;70:2097-2098

[8] Fudim M, Ali-Ahmed F, Parzynski CS, Ambrosy AP, Friedman DJ, Pokorney SD, Curtis JP, Fonarow GC, Masoudi FA, Hernandez AF, Al-Khatib SM. Periprocedural Risk and Survival Associated With Implantable Cardioverter-Defibrillator Placement in Older Patients With Advanced Heart Failure. JAMA Cardiol. 2020 Jun 1;5(6):643-651. doi: 10.1001/jamacardio.2020.0391. PMID: 32211811; PMCID: PMC7097837.

[9] Suleiman M, Goldenberg I, Samniah N, Rosso R, Marai I, Pekar A, Khalameizer V, Militianu A, Glikson M. Outcome of Patients with Advanced Heart Failure Who Receive Device-Based Therapy for Primary Prevention of Sudden Cardiac Death: Insights from the Israeli ICD

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Registry. Pacing Clin Electrophysiol. 2015 Jun;38(6):738-45. doi: 10.1111/pace.12627. Epub 2015 Apr 13. PMID: 25754272.

[10] Landolina M, Lunati M, Gasparini M, Santini M, Padeletti L, Achilli A, Bianchi S, Laurenzi F, Curnis A, Vincenti A, Valsecchi S, Denaro A; InSync/InSync ICD Italian Registry Investigators. Comparison of the effects of cardiac resynchronization therapy in patients with class II versus class III and IV heart failure (from the InSync/InSync ICD Italian Registry). Am J Cardiol. 2007 Sep 15;100(6):1007-12. doi: 10.1016/j.amjcard.2007.04.043. Epub 2007 Jul 5. PMID: 17826388.

[11] John G. Cleland, William T. Abraham, Cecilia Linde, Michael R. Gold, James B. Young, J. Claude Daubert, Lou Sherfesee, George A. Wells, Anthony S.L. Tang, An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure, *European Heart Journal*, Volume 34, Issue 46, 7 December 2013, Pages 3547–3556, https://doi.org/10.1093/eurheartj/eht290

[12] Cleland, J.G.F., Bristow, M.R., Freemantle, N., Olshansky, B., Gras, D., Saxon, L., Tavazzi, L., Boehmer, J., Ghio, S., Feldman, A.M., Daubert, J.-C. and de Mets, D. (2022), The effect of cardiac resynchronization without a defibrillator on morbidity and mortality: an individual patient data meta-analysis of COMPANION and CARE-HF. Eur J Heart Fail, 24: 1080-1090. https://doi.org/10.1002/ejhf.2524

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Table 1. Patient characteristics overall and by study cohort

Characteristic	Overall, N = 2,309	MIRACLE N = 452	MIRACLE-ICD N = 338	COMPANION N = 1,519
Female	721 (31%)	147 (33%)	81 (24%)	493 (32%)
Age (years)	67 (58, 74)	65 (56, 73)	69 (60, 75)	67 (59, 74)
Treatment				
OMT	540 (23%)	233 (52%)	0 (0%)	307 (20%)
ICD recipients	167 (7.2%)	0 (0%)	167 (49%)	0 (0%)
CRT-P recipients	836 (36%)	219 (48%)	0 (0%)	617 (41%)
CRT-D recipients	766 (33%)	0 (0%)	171 (51%)	595 (39%)
Ischemic	1,312 (57%)	240 (53%)	235 (70%)	837 (55%)
Non-ischemic	1,004 (43%)	219 (48%)	103 (30%)	682 (45%)
NYHA				
III	2,007 (87%)	403 (89%)	301 (89%)	1,303 (86%)
IV	302 (13%)	49 (11%)	37 (11%)	216 (14%)
LBBB	1,700 (74%)	379 (84%)	247 (73%)	1,074 (71%)
QRS width (ms)	160 (142, 176)	160 (155, 180)	160 (150, 180)	160 (140, 175)
EF (%)	22 (18, 28)	23 (18, 28)	22 (19, 27)	21 (17, 28)
Atrial fibrillation	393 (17%)	53 (12%)	0 (0%)	340 (22%)
Hypertension	1,141 (49%)	186 (41%)	166 (49%)	789 (52%)
Diabetes	898 (39%)	152 (34%)	125 (37%)	621 (41%)
Medications				
Betablocker	1,488 (64%)	256 (57%)	206 (61%)	1,026 (68%)
ACE/ARB	2,071 (90%)	413 (91%)	306 (91%)	1,352 (89%)
Amiodarone†	180 (23%)	62 (14%)	118 (35%)	0 (NA%)
Diuretics	2,187 (95%)	426 (94%)	315 (93%)	1,446 (95%)

Summaries presented in median (IQR) or n (%). †Information available only for 790 patients.
ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CRT-D: cardiac resynchronization therapy with defibrillation, CRT-P: cardiac resynchronization therapy, ICD: implantable cardioverter defibrillator, LBBB: left bundle branch block, EF: ejection fraction, NA: Not available information, NYHA: New York Heart Association, OMT: optimal medical treatment.

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Table 2. Patient characteristics by treatment assignment and age category

	Overall		NYHA III		NYHA IV	
Characteristic	**CRT,** N = 1,602	**No-CRT,** N = 709	**CRT,** N = 1,398	**No-CRT,** N = 610	**CRT,** N = 204	**No-CRT,** N = 99
Female	513 (32%)	209 (29%)	444 (32%)	168 (28%)	69 (34%)	41 (41%)
Age (years)	66 (58, 74)	68 (59, 74)	66 (58, 74)	68 (59, 74)	67 (60, 75)	68 (60, 75)
ICD recipients	766 (48%)	167 (24%)	663 (47%)	150 (25%)	103 (50%)	17 (17%)
Ischemic	874 (55%)	440 (62%)	749 (54%)	371 (61%)	125 (61%)	69 (70%)
Non-ischemic	731 (46%)	273 (39%)	652 (47%)	243 (40%)	79 (39%)	30 (30%)
LBBB	1,174 (73%)	526 (74%)	1,033 (74%)	451 (74%)	141 (69%)	75 (76%)
QRS width (ms)	160 (142, 178)	160 (142, 175)	160 (142, 177)	160 (142, 172)	160 (144, 178)	160 (144, 180)
EF (%)	21 (17, 27)	23 (19, 29)	22 (18, 27)	23 (19, 29)	20 (15, 25)	20 (16, 27)
Atrial fibrillation	291 (18%)	103 (15%)	248 (18%)	79 (13%)	43 (21%)	24 (24%)
Hypertension	806 (50%)	337 (48%)	702 (50%)	289 (47%)	104 (51%)	48 (48%)
Diabetes	615 (38%)	284 (40%)	526 (38%)	229 (38%)	89 (44%)	55 (56%)
Medications						
Betablocker	1,058 (66%)	430 (61%)	949 (68%)	382 (63%)	109 (53%)	48 (48%)
ACE/ARB	1,438 (90%)	635 (90%)	1,269 (91%)	550 (90%)	169 (83%)	85 (86%)
Amiodarone†	94 (24%)	86 (21%)	79 (23%)	77 (22%)	15 (36%)	9 (20%)
Diuretics	1,519 (95%)	670 (94%)	1,318 (94%)	571 (94%)	201 (99%)	99 (100%)

Summaries presented in median (IQR) or n (%). †Information available only for 791 patients.

ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CRT: cardiac resynchronization therapy, LBBB: left bundle branch block, EF: ejection fraction, NYHA: New York Heart Association.

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Table 3. CRT effect in time to mortality and time to mortality/HFH overall and by NYHA class

	Estimate	95% Credible interval	Posterior probability
Time to all-cause mortality or HFH			
HR for CRT overall†	0.79	0.64 – 0.99	0.044
By NYHA class group¥			
HR for CRT in NYHA class III	0.82	0.66 – 1.04	0.10
HR for CRT in NYHA class IV	0.59	0.26 – 1.04	0.067
Ratio of hazard ratios (IV / III)	0.72	0.30 – 1.27	0.23
Time to all-cause mortality			
HR for CRT overall†	0.78	0.59 – 1.03	0.083
By NYHA class group ¥			
HR for CRT in NYHA class III	0.87	0.62 – 1.20	0.40
HR for CRT in NYHA class IV	0.61	0.31 – 1.09	0.088
Ratio of hazard ratios (IV / III)	0.70	0.35 – 1.34	0.27

†Estimates obtained from a model with an overall CRT effect. ¥Estimates obtained from a model with a CRT effect by NYHA class group.
CRT: cardiac resynchronization therapy, HFH: heart failure hospitalization, HR: hazard ratio

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Table 4. Sensitivity analysis including RAFT data. CRT effect in time to mortality and time to mortality/HFH overall and by NYHA class

	Estimate	95% Credible interval	Posterior probability
Time to all-cause mortality or HFH			
HR for CRT overall†	0.76	0.64 – 0.91	0.009
By NYHA class group¥			
HR for CRT in NYHA class III	0.78	0.65 – 0.95	0.020
HR for CRT in NYHA class IV	0.67	0.46 – 0.97	0.037
Ratio of hazard ratios (IV / III)	0.85	0.59 – 1.25	0.41
Time to all-cause mortality			
HR for CRT overall†	0.74	0.59 – 0.92	0.007
By NYHA class group ¥			
HR for CRT in NYHA class III	0.79	0.63 – 1.00	0.051
HR for CRT in NYHA class IV	0.61	0.41 – 0.94	0.027
Ratio of hazard ratios (IV / III)	0.78	0.51 – 1.23	0.27

†Estimates obtained from a model with an overall CRT effect. ¥Estimates obtained from a model with a CRT effect by NYHA class group.
CRT: cardiac resynchronization therapy, HFH: heart failure hospitalization, HR: hazard ratio

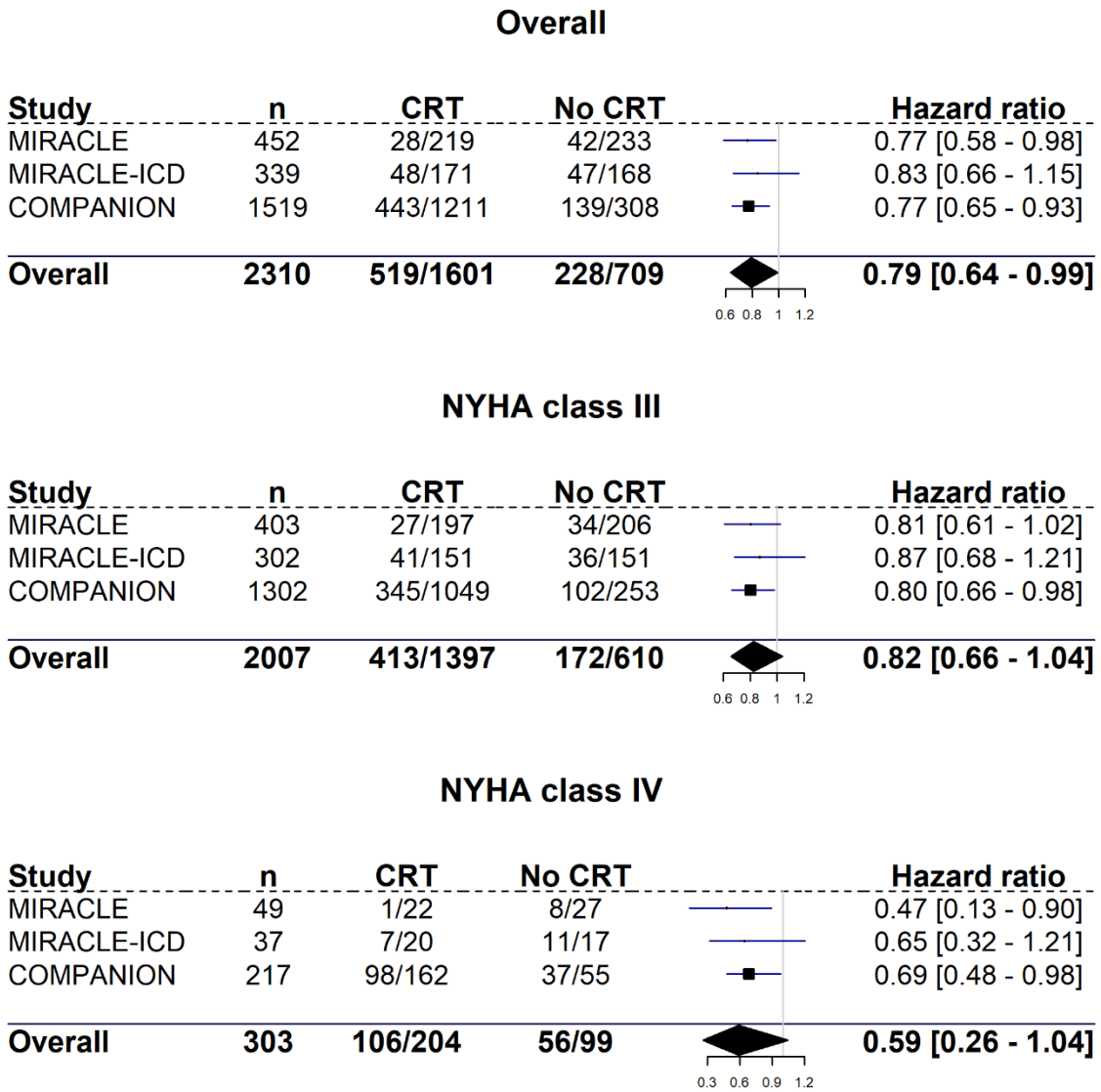

Figure 1. Forest plots for CRT effect on all-cause mortality or HFH overall (A) and by NYHA group (B) class III and (C) class IV.

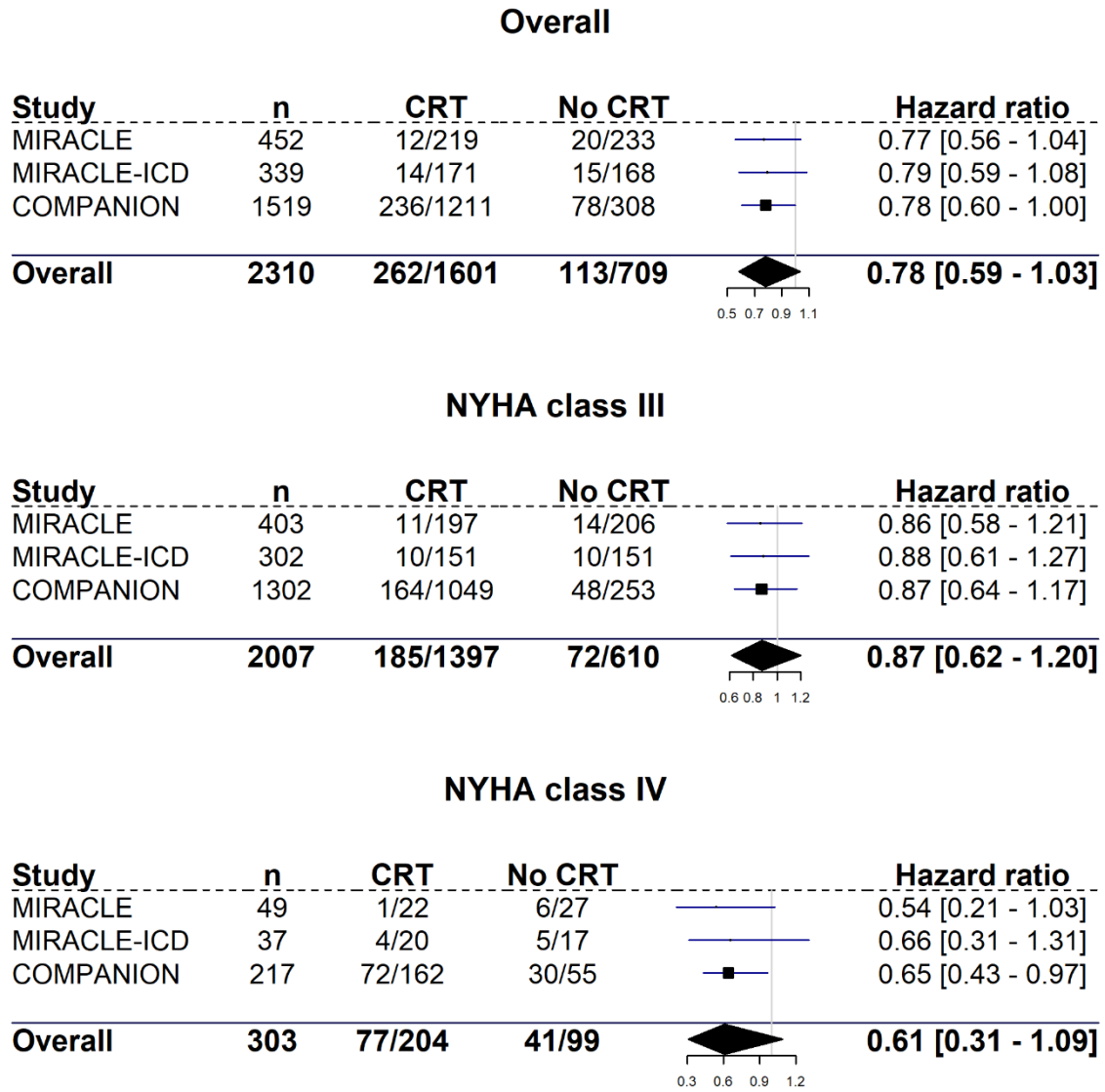

Figure 2. Forest plots for CRT effect on all-cause mortality overall (A) and by NYHA group (B) class III and (C) class IV