ORIGINAL ARTICLE

Long-Term Outcomes of Resynchronization–Defibrillation for Heart Failure

John L. Sapp, M.D., Soori Sivakumaran, M.D., Calum J. Redpath, M.B., Ch.B., Ph.D., Habib Khan, M.D., Ratika Parkash, M.D., Derek V. Exner, M.D., Jeff S. Healey, M.D., Bernard Thibault, M.D., Laurence D. Sterns, M.D., Nhat Hung N. Lam, B.Sc., Jaimie Manlucu, M.D., Ahmed Mokhtar, M.D., Glen Sumner, M.D., Stuart McKinlay, B.H.Sc., Shane Kimber, M.D., Blandine Mondesert, M.D., Mario Talajic, M.D., Jean Rouleau, M.D., C. Elizabeth McCarron, Ph.D., George Wells, Ph.D., and Anthony S. L. Tang, M.D., for the RAFT Long-Term Study Team*

From QEII Health Sciences Centre, Dalhousie University, Halifax, NS (J.L.S., R.P.), the Mazankowski Alberta Heart Institute, University of Alberta, Edmonton (S.S., S.K.), the University of Ottawa Heart Institute, Ottawa (C.J.R., N.H.N.L., G.W.), Schulich School of Medicine and Dentistry, Western University, London, ON (H.K., J.M., C.E.M., A.S.L.T.), Libin Cardiovascular Institute, Calgary, AB (D.V.E., G.S.), McMaster University, Hamilton, ON (J.S.H.), Montreal Heart Institute, Montreal (B.T., B.M., M.T., J.R.), Royal Jubilee Hospital, Victoria, BC (L.D.S.), and the University of Toronto, Toronto (S.M.) — all in Canada; and King Abdulaziz University, Jeddah, Saudi Arabia (A.M.). Dr. Sapp can be contacted at john.sapp@nshealth.ca or at Halifax Infirmary, Rm. 2501B, 1796 Summer St., Halifax, NS Canada B3H2A7.

*A list of the RAFT Long-Term Study Team is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Sapp and Sivakumaran and Drs. Wells and Tang contributed equally to this article.

N Engl J Med 2024;390:212-20.
DOI: 10.1056/NEJMoa2304542

ABSTRACT

BACKGROUND

The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) showed a greater benefit with respect to mortality at 5 years among patients who received cardiac-resynchronization therapy (CRT) than among those who received implantable cardioverter–defibrillators (ICDs). However, the effect of CRT on long-term survival is not known.

METHODS

We randomly assigned patients with New York Heart Association (NYHA) class II or III heart failure, a left ventricular ejection fraction of 30% or less, and an intrinsic QRS duration of 120 msec or more (or a paced QRS duration of 200 msec or more) to receive either an ICD alone or a CRT defibrillator (CRT-D). We assessed long-term outcomes among patients at the eight highest-enrolling participating sites. The primary outcome was death from any cause; the secondary outcome was a composite of death from any cause, heart transplantation, or implantation of a ventricular assist device.

RESULTS

The trial enrolled 1798 patients, of whom 1050 were included in the long-term survival trial; the median duration of follow-up for the 1050 patients was 7.7 years (interquartile range, 3.9 to 12.8), and the median duration of follow-up for those who survived was 13.9 years (interquartile range, 12.8 to 15.7). Death occurred in 405 of 530 patients (76.4%) assigned to the ICD group and in 370 of 520 patients (71.2%) assigned to the CRT-D group. The time until death appeared to be longer for those assigned to receive a CRT-D than for those assigned to receive an ICD (acceleration factor, 0.80; 95% confidence interval, 0.69 to 0.92; P=0.002). A secondary-outcome event occurred in 412 patients (77.7%) in the ICD group and in 392 (75.4%) in the CRT-D group.

CONCLUSIONS

Among patients with a reduced ejection fraction, a widened QRS complex, and NYHA class II or III heart failure, the survival benefit associated with receipt of a CRT-D as compared with ICD appeared to be sustained during a median of nearly 14 years of follow-up. (RAFT ClinicalTrials.gov number, NCT00251251.)

Cardiac-resynchronization therapy (CRT) has been shown to reduce both mortality and heart-failure outcomes in patients with symptomatic heart failure, a reduced ejection fraction, and a wide QRS complex despite optimal medical therapy,[1-5] and it has been established as standard care in appropriate patients.[6] The implantation of a CRT device is a lifelong intervention for such patients, and clinical decision making is dependent on studies of the long-term outcomes of CRT.

The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) was a multicenter, double-blind, randomized, controlled trial that aimed to determine whether the addition of CRT to an implantable cardioverter–defibrillator (ICD), along with optimal medical therapy, would result in lower mortality and fewer hospitalizations for heart failure than an ICD and optimal medical therapy alone.[1] The trial included patients with a left ventricular ejection fraction of 30% or less, a QRS complex duration of more than 120 msec, and New York Heart Association (NYHA) class II or III heart failure. Patients with a right bundle-branch block, nonspecific intraventricular conduction delays, right ventricular pacing, or atrial fibrillation were not excluded. Enrollment in RAFT was completed in February 2009. During a mean (±SD) of 40±20 months of follow-up for the 1798 enrolled patients, CRT resulted in a significantly lower risk of death or hospitalization for heart failure (the composite primary outcome) than ICD (hazard ratio, 0.75; 95% confidence interval [CI], 0.64 to 0.87; P<0.001). The risks of secondary-outcome events, including death from any cause, death from any cardiovascular cause, and hospitalization for heart failure, were all significantly lower with CRT as well. To better understand the long-term effects of CRT on mortality, we analyzed the survival outcomes of patients enrolled at the eight highest-enrolling participating sites.

METHODS

TRIAL DESIGN AND OVERSIGHT

The design, protocol, and results of RAFT have been published previously.[1] The protocol and statistical analysis plan are available with the full text of this article at NEJM.org. All patients provided written informed consent to participate in the original RAFT trial. The long-term follow-up trial was approved by the institutional research ethics board at each participating site. Individual consent for use of data from long-term follow-up was waived; these data were obtained from the patients' clinical records. A data and safety monitoring committee was in place during the original RAFT trial but was not reconvened for the long-term follow-up trial. The long-term follow-up trial was designed by the steering committee, and data were gathered by the site investigators and site coordinators. The Dalhousie University Cardiac Arrhythmia Research unit and the Cardiovascular Trial Coordinating Center at Western University were responsible for the data management and for the analysis of the RAFT long-term follow-up data. The manuscript was drafted by the first authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol; all the authors made the decision to submit the manuscript for publication.

A Quick Take is available at NEJM.org

PATIENTS

Eligible patients with NYHA class II or III heart failure, a left ventricular ejection fraction of 30% or less, and an intrinsic QRS duration of 120 msec or more (or a paced QRS duration of 200 msec or more) were randomly assigned, in a 1:1 ratio, to receive an ICD or an ICD with CRT (CRT-D); randomization was stratified according to clinical center, atrial rhythm, and planned implantation of a single-chamber or dual-chamber ICD. In the trial, patients with NYHA class II or III heart failure were initially eligible for randomization. However, after the publication of a clinical trial showing a survival benefit for patients with NYHA class III heart failure and changes in clinical guidelines,[2,7,8] the protocol was modified, in February 2006, to exclude patients with NYHA class III heart failure. Patients were seen at follow-up visits 1 month after device implantation and then every 6 months until all patients had had at least 18 months of follow-up. At each follow-up visit, a clinical assessment and a device interrogation were performed. The patients and the general health care providers were unaware of the group assignments of the patients. Only the arrhythmia team that performed the device implantation and management were aware of

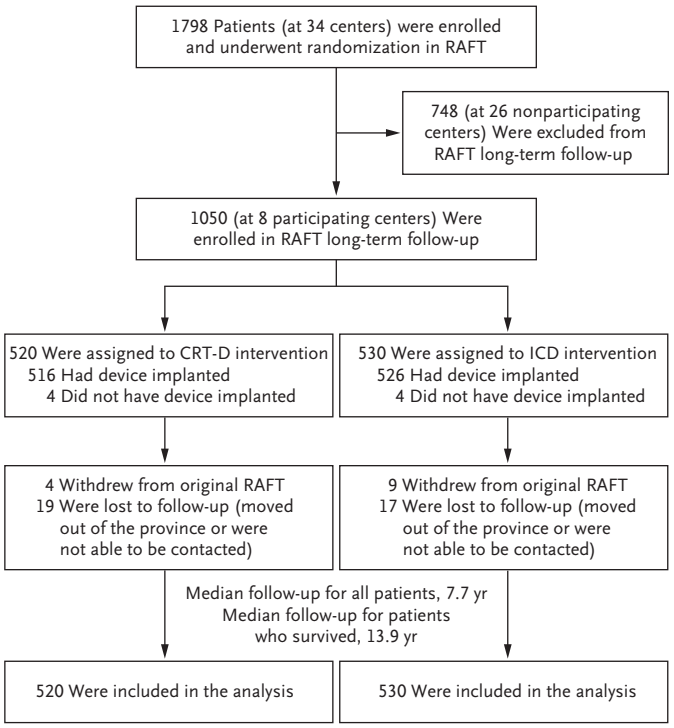

Figure 1. Randomization and Follow-up.

the trial-group assignments. Details on the representativeness of the trial patients are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

DATA ACQUISITION AND PATIENT FOLLOW-UP

The eight centers that enrolled the largest number of patients participated in the long-term follow-up trial (details can be found in the Supplementary Appendix). Survival data were obtained for all patients from clinical records. The data from patients who were lost to follow-up were censored at the date of their last clinical contact. The dates of heart transplantation or implantation of a ventricular assist device were collected from clinical records when relevant.

OUTCOMES

The primary outcome of this trial was death from any cause. The secondary outcome was a composite of death from any cause, heart transplantation, or implantation of a left ventricular assist device (Table S2).

STATISTICAL ANALYSIS

All analyses in this trial were conducted according to the intention-to-treat principle. The baseline characteristics of each treatment group were expressed as numbers of patients and percentages for categorical variables and as means with standard deviations or medians with interquartile ranges for continuous variables.

We used survival analysis techniques to compare the two treatment groups with respect to the primary and secondary outcomes. Survival in each of the two groups over the follow-up period was summarized with the use of Kaplan–Meier product-limit estimates. In order to estimate the treatment effect, we first examined the validity of the proportional-hazards assumption using plots of log of negative log of the estimated survival function,[9] time-dependent covariates in the Cox model, and the empirical score process.[10] We concluded that there was evidence of nonproportional hazards. Because of this possible violation of the proportional-hazards assumption and our prior knowledge of the likely shape of the baseline hazard, we adopted an exponential accelerated failure time model for our primary analysis, and we therefore present the estimates of the treatment effect as acceleration factors. We assessed the robustness of the results to alternative nonproportional-hazards models and distributional assumptions in a sensitivity analysis. The secondary outcome, a composite of death, heart transplantation, or implantation of a ventricular assist device, was analyzed in a similar fashion. Analyses based on patient characteristics were undertaken in subgroups defined according to age, sex, NYHA class, cause of cardiomyopathy, QRS duration, left ventricular ejection fraction, QRS morphologic features, and atrial rhythm. The P value is reported for the primary outcome of death. For the secondary outcome, a 95% confidence interval is presented without adjustment for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. Missing data were censored at the date of the patient's last follow-up contact (details can be found in the Supplementary Appendix). All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

RANDOMIZATION

A total of 1798 patients at 34 centers were included in RAFT. Eight centers that participated in the RAFT long-term follow-up enrolled a total of 1050 patients. The first patient was enrolled in January 2003, and all patients were followed until death or December 31, 2021. Among the 530 patients randomly assigned to receive an ICD, 526 (99.2%) underwent device implantation. A device was not implanted in 4 patients (3 because of patient or physician decision and 1 because the patient died before the device could be implanted). In the ICD group, 26 patients were lost to complete follow-up; outcomes at the end of the long-term follow-up trial could not be ascertained for 17 patients, and 9 patients withdrew from the trial. Among the 520 patients randomly assigned to receive a CRT-D, 516 (99.2%) underwent device implantation. A device was not implanted in 4 patients (2 because of patient or physician decision, and 2 because the patients died before the device could be implanted). In the CRT-D group, 23 patients were lost to complete follow-up; outcomes at the end of the long-term follow-up trial could not be ascertained for 19 patients, and 4 patients withdrew from the trial (Fig. 1).

PATIENT CHARACTERISTICS

The baseline characteristics of the patients appeared to be similar in the two treatment groups, except for aspirin and statin use (Table 1). The median duration of follow-up for the 1050 patients in the long-term survival trial was 7.7 years (interquartile range, 3.9 to 12.8), and the median duration of follow-up for those who survived was 13.9 years (interquartile range, 12.8 to 15.7). The patients who were assigned to the ICD group had a median duration of follow-up of 6.9 years (interquartile range, 3.2 to 12.0), and those who survived had a median duration of follow-up of 13.9 years (interquartile range, 12.8 to 15.4). The patients who were assigned to the CRT-D group had a median duration of follow-up of 8.5 years (interquartile range, 4.7 to 13.2), and those who survived had a median duration of follow-up of 14.2 years (interquartile range, 12.9 to 15.7). The median duration of follow-up for the patients who withdrew from the trial or who were lost to follow-up was 5.1

Table 1. Characteristics of the Patients at Baseline.*

Variable	ICD (N=530)	CRT-D (N=520)
Age — yr	66.8±9.1	66.3±9.3
Male sex — no. (%)	439 (82.8)	441 (84.8)
Underlying heart disease — no. (%)		
Ischemic	356 (67.2)	357 (68.7)
Nonischemic	174 (32.8)	163 (31.3)
NYHA class — no. (%)		
Class II	404 (76.2)	399 (76.7)
Class III	126 (23.8)	121 (23.3)
Left ventricular ejection fraction — %	22.1±5.1	22.3±5.4
Atrial rhythm — no. (%)		
Permanent atrial fibrillation or flutter	83 (15.7)	82 (15.8)
Sinus or atrial paced	447 (84.3)	438 (84.2)
Hypertension — no. (%)	247 (46.6)	233 (44.8)
Diabetes mellitus — no. (%)	194 (36.6)	157 (30.2)
Previous PCI — no. (%)	128 (24.2)	120 (23.1)
Previous CABG — no. (%)	194 (36.6)	182 (35.0)
Current cigarette smoking — no. (%)	71 (13.4)	70 (13.5)
Peripheral vascular disease — no. (%)	50 (9.4)	43 (8.3)
Hospitalization for heart failure within the previous 6 mo — no. (%)	121 (22.8)	128 (24.6)
Medication — no. (%)		
Beta-blocker	476 (89.8)	470 (90.4)
ACE inhibitor or ARB	513 (96.8)	501 (96.3)
Spironolactone	224 (42.3)	214 (41.2)
Digoxin	184 (34.7)	178 (34.2)
Aspirin	388 (73.2)	346 (66.5)
Warfarin	194 (36.6)	198 (38.1)
Clopidogrel	88 (16.6)	78 (15.0)
Statin	397 (74.9)	354 (68.1)
Diuretic	438 (82.6)	436 (83.8)
Calcium-channel blocker	59 (11.1)	64 (12.3)
Amiodarone	77 (14.5)	87 (16.7)
Other antiarrhythmic	6 (1.1)	9 (1.7)
Six-minute walk test — no.	452	461
Distance walked — m	351.3±110.2	347.0±105.4
Estimated glomerular filtration rate		
Mean — ml/min/1.73 m^2	58.9±22.5	58.3±19.6
Distribution — no./total no. (%)		
<30 ml/min/1.73 m^2	44/526 (8.4)	38/515 (7.4)
30–59 ml/min/1.73 m^2	235/526 (44.7)	234/515 (45.4)
≥60 ml/min/1.73 m^2	247/526 (47.0)	243/515 (47.2)

* Plus–minus values are means ±SD. The absolute values of all standardized differences were below the threshold of 0.10 except for diabetes mellitus (0.112), aspirin (0.118), and statin (0.122). ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, NYHA New York Heart Assocation, and PCI percutaneous coronary intervention.

Table 2. Electrocardiographic Characteristics of Patients at Baseline.*

Variable	ICD (N=530)	CRT-D (N=520)
Intrinsic QRS — no.	481	475
Intrinsic QRS duration — msec	159.3±24.2	158.1±23.8
Paced QRS — no.	49	45
Paced QRS duration — msec	209.1±16.8	211.6±21.2
QRS morphologic type — no. (%)		
Right bundle-branch block	52 (9.8)	36 (6.9)
Left bundle-branch block	364 (68.7)	373 (71.7)
NIVCD	65 (12.3)	66 (12.7)
Ventricular paced	49 (9.2)	45 (8.7)

* Plus–minus values are means ±SD. The absolute values of all standardized differences were below the threshold of 0.10. NIVCD denotes nonspecific intraventricular conduction delay.

years (interquartile range, 1.9 to 7.9 years). Details of randomization and follow-up are shown in Figure 1. The baseline characteristics of patients who were included in the long-term follow-up trial did not appear to differ meaningfully from those who were not included (Table S3). The number of patients per site for whom data were missing did not appear to differ meaningfully between the trial groups (Table S4).

Among the 1050 patients in the long-term follow-up trial, 880 (83.8%) were men, 713 (67.9%) had ischemic cardiomyopathy, and 337 (32.1%) had nonischemic cardiomyopathy; the mean age was 66.5±9.2 years. A total of 803 patients (76.5%) had NYHA class II heart failure. The criteria for participation in RAFT permitted the inclusion of patients with atrial arrhythmias or QRS morphologic features without left bundle-branch block. In the long-term follow-up trial, at baseline, 165 patients (15.7%) had a persistent atrial arrhythmia, 737 (70.2%) patients had left bundle-branch block, 88 (8.4%) had right bundle-branch block, 131 (12.5%) had a nonspecific intraventricular conduction delay, and 94 (9.0%) had paced QRS complexes (Table 2).

OUTCOMES

Death from any cause (the primary outcome) occurred in 405 of 530 patients (76.4%) assigned to the ICD group and in 370 of 520 patients (71.2%) assigned to the CRT-D group. The time until death appeared to be longer in the CRT-D group than in the ICD group (acceleration factor, 0.80; 95% CI, 0.69 to 0.92; P=0.002) (Fig. 2A).

A secondary-outcome event, a composite of death from any cause, heart transplantation, or implantation of a ventricular assist device, occurred in 392 patients (75.4%) in the CRT-D group and in 412 patients (77.7%) in the ICD group. The time until the composite outcome event occurred was longer in the CRT-D group than in the ICD group (acceleration factor, 0.85; 95% CI, 0.74 to 0.98) (Fig. 2B). Sensitivity analyses are shown in Table S5.

SUBGROUP ANALYSES

We conducted analyses of the relationship between the NYHA heart-failure class at baseline and the primary outcome. In this long-term follow-up trial, 23.5% of patients had had NYHA class III heart failure at baseline. The risk of death among patients with either NYHA class II or III heart failure at baseline according to the treatment group to which they were assigned (ICD or CRT-D) is shown in Figure S1. The outcomes in 11 prespecified subgroups of patients who were assigned to the CRT-D group or the ICD group are shown in Figure 3.

DISCUSSION

This long-term follow-up trial showed a benefit with respect to mortality among patients who received a CRT-D as compared with those who received a standard ICD, and this benefit appears to have been sustained over time. The median duration of follow-up among all patients was 7.7 years and among those who survived, 13.9 years. A similar association was observed for the composite of death from any cause, heart transplantation, or implantation of a ventricular assist device (the secondary outcome), although the event curves for the composite outcome appeared to begin to converge after 12 years.

RAFT included patients with mild-to-moderate symptoms of heart failure. These findings are complementary to the observations from other randomized, controlled trials. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) enrolled patients with NYHA class I or II heart failure.[4] During 7 years of extended follow-up, a reduction in mortality was observed among pa-

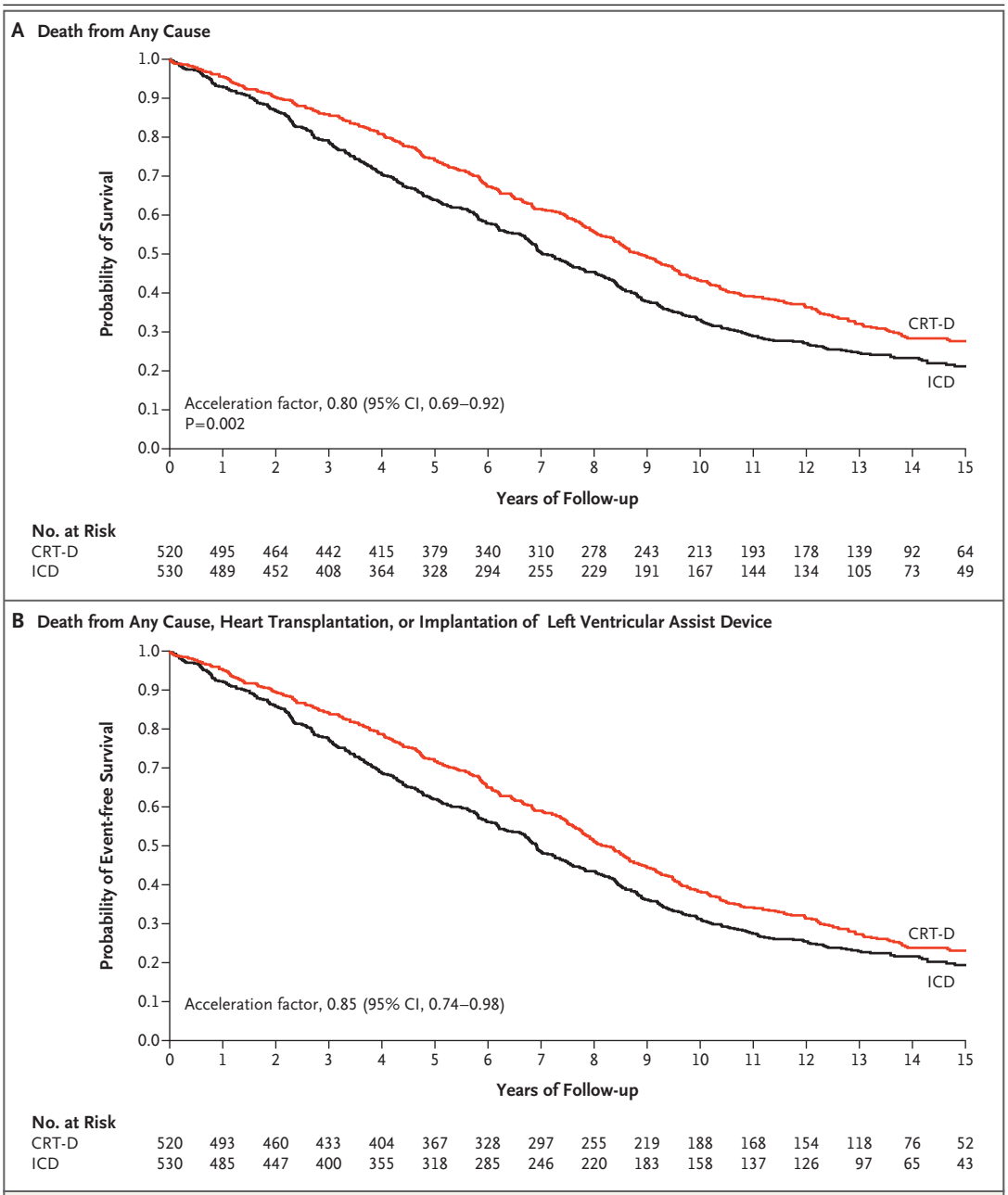

Figure 2. Kaplan–Meier Estimates of the Primary and Secondary Outcomes.

Panel A shows the probability of death from any cause (the primary outcome) in each group. Panel B shows the probability of a composite of death from any cause, heart transplantation, or implantation of a left ventricular assist device (the secondary outcome).

tients with left bundle-branch block.[11] Long-term (approximately 4.4 years) follow-up of patients with more severe heart failure in the CARE-HF trial (Cardiac Resynchronization–Heart Failure) showed the persistence of the original benefit of CRT implantation.[12] The present trial extends these observations over a longer follow-up time and supports the durability of the improvement in survival among patients with heart failure, reduced left ventricular ejection fraction, and

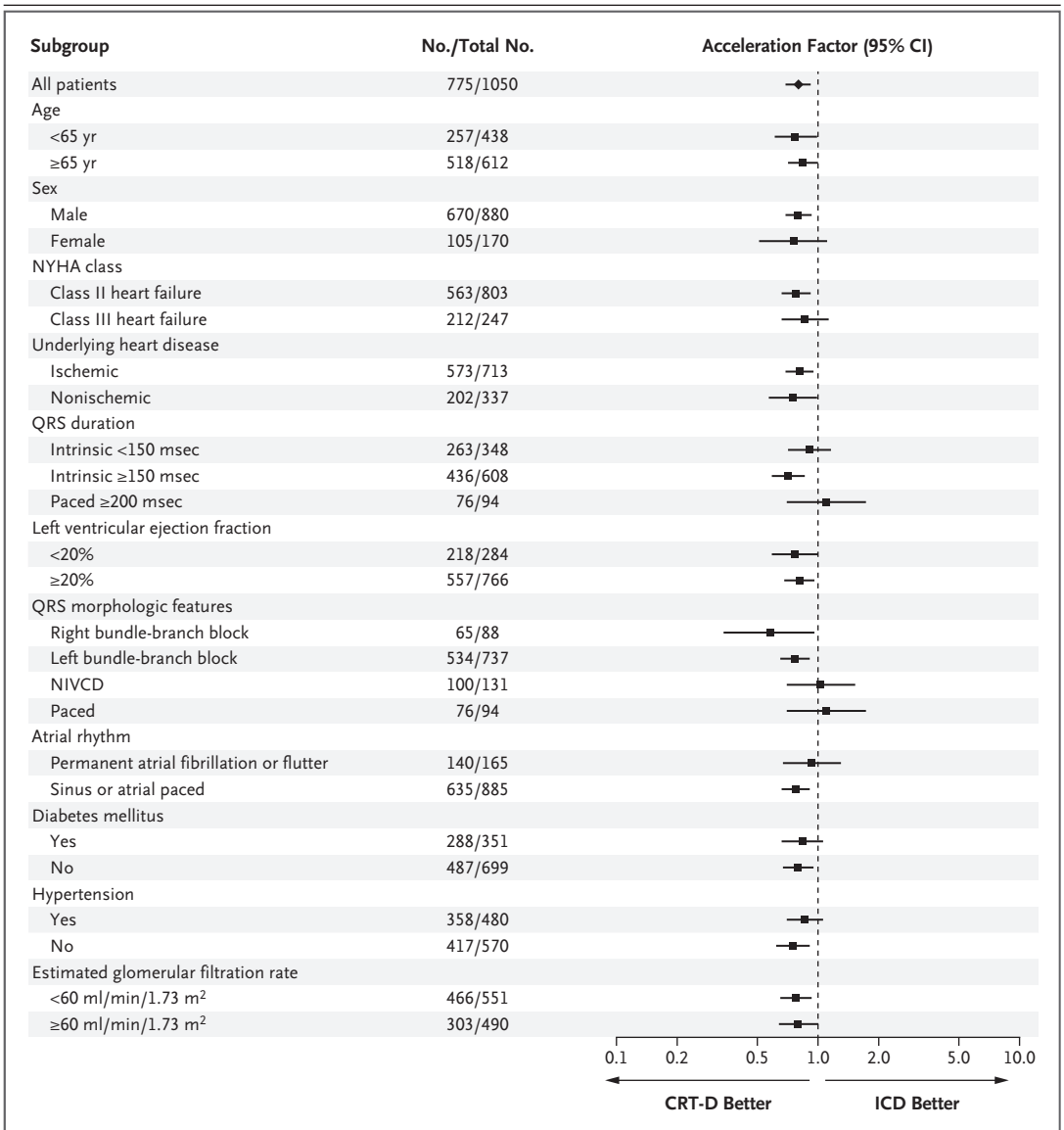

Figure 3. Subgroup Analyses of Death.

Estimates of the treatment effect (presented as acceleration factors) and 95% confidence intervals are shown for the primary outcome (death from any cause) in each prespecified subgroup. There was no plan for multiplicity in the statistical analysis, and the widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject treatment effects. Estimated glomerular filtration rates were not available for nine patients. NIVCD denotes nonspecific intraventricular conduction delay, and NYHA New York Heart Association.

prolonged QRS duration who received a CRT-D device.

CRT has been shown to result in significant improvement in cardiac performance[13] and to lead to reverse remodeling,[14,15] a reduction in new-onset ventricular arrhythmias,[16,17] and improved clinical outcomes.[1-4,13,14] It is possible that these beneficial early effects may be associated with the much longer-term improvements in overall survival shown in our trial.

The benefit with respect to mortality that we observed in this trial occurred despite the inclu-

sion of patients who have been shown to derive less clinical benefit or no clinical benefit from implantation of a CRT-D, including those with atrial fibrillation and those with QRS morphologic features without left bundle-branch block or with less-widened QRS complexes.[18] Furthermore, the survival benefit remained despite the fact that the long-term nature of this trial limited the analysis of subtle variations in clinical occurrences during the trial period, such as worsening of heart failure, changes to pharmacologic management, crossover between the treatment groups, or a change in the function of implanted leads — all examples of nonfatal, yet important changes that may reduce the effectiveness of CRT.

Our trial had limitations. Despite the survival findings among patients assigned to the CRT-D group, mortality within the overall long-term follow-up trial population was approximately 80% at 15 years. Since the initial trial was completed, pharmacologic therapy for heart failure has advanced, with the introduction of neprilysin inhibitors and sodium–glucose cotransporter 2 inhibitors.[19] CRT improves cardiac performance without increasing cardiac work[20] and would be anticipated to have a complementary effect to pharmacotherapy; however, the influence of CRT on survival for patients treated with newer drugs is uncertain. Although this trial included all patients at the eight highest-enrolling sites, this population is nonetheless a subset of the entire trial population, so our observations should be interpreted cautiously. Furthermore, the relatively low enrollment of women and the lack of racial diversity could influence the generalizability of the findings. The influence of crossover from the ICD group to the CRT-D group (or vice versa) was not examined in this trial. We have previously reported the characteristics of patients who crossed over from one group to the other within the initial follow-up period of RAFT.[21] The long-term nature of this trial makes it likely that a proportion of surviving patients will have had a variety of changes in their clinical course that could influence the decision to change the type of device they receive, which would confound any analysis of crossovers. Nonetheless, the persistence of benefit from an initial implantation of CRT-D appears to be consistent with an early and ongoing protective effect.

The survival benefit of CRT-D therapy over ICD alone for patients with a reduced ejection fraction, a widened QRS complex, and NYHA class II or III heart failure appears to have been sustained during a median of nearly 14 years of follow-up.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. Tang ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.
2. Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
3. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
4. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
5. 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;52:1834-43.
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145(18):e895-e1032.
7. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112(12):e154-e235.
8. Arnold JMO, Liu P, Demers C, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol 2006;22:23-45.
9. Borucka J. Extensions of Cox model for non-proportional hazards purpose. Ekonometria 2014;3:85-101 (https://www.dbc.wroc.pl/dlibra/docmetadata?id=27006).
10. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. Biometrika 1993;80:557-72.
11. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med 2014;370:1694-701.
12. 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;14:628-34.
13. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.

14. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
15. Daubert C, Gold MR, Abraham WT, 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 (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol 2009;54:1837-46.
16. Sapp JL, Parkash R, Wells GA, et al. Cardiac resynchronization therapy reduces ventricular arrhythmias in primary but not secondary prophylactic implantable cardioverter defibrillator patients: insight from the Resynchronization in Ambulatory Heart Failure Trial. Circ Arrhythm Electrophysiol 2017;10(3):e004875.
17. Ruwald MH, Solomon SD, Foster E, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation 2014;130:2278-86.
18. Cleland JG, Abraham WT, Linde C, et al. 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. Eur Heart J 2013;34:3547-56.
19. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145(18):e876-e894.
20. Ukkonen H, Beanlands RSB, Burwash IG, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. Circulation 2003;107:28-31.
21. Essebag V, Joza J, Birnie DH, et al. Incidence, predictors, and procedural results of upgrade to resynchronization therapy: the RAFT upgrade substudy. Circ Arrhythm Electrophysiol 2015;8:152-8.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/about-icmje/faqs/.