ORIGINAL ARTICLE

Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

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ABSTRACT

BACKGROUND

The benefit of an implantable cardioverter–defibrillator (ICD) in patients with symptomatic systolic heart failure caused by coronary artery disease has been well documented. However, the evidence for a benefit of prophylactic ICDs in patients with systolic heart failure that is not due to coronary artery disease has been based primarily on subgroup analyses. The management of heart failure has improved since the landmark ICD trials, and many patients now receive cardiac resynchronization therapy (CRT).

METHODS

In a randomized, controlled trial, 556 patients with symptomatic systolic heart failure (left ventricular ejection fraction, ≤35%) not caused by coronary artery disease were assigned to receive an ICD, and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. The secondary outcomes were sudden cardiac death and cardiovascular death.

RESULTS

After a median follow-up period of 67.6 months, the primary outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (hazard ratio, 0.87; 95% confidence interval [CI], 0.68 to 1.12; P=0.28). Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (hazard ratio, 0.50; 95% CI, 0.31 to 0.82; P=0.005). Device infection occurred in 27 patients (4.9%) in the ICD group and in 20 patients (3.6%) in the control group (P=0.29).

CONCLUSIONS

In this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. (Funded by Medtronic and others; DANISH ClinicalTrials.gov number, NCT00542945.)

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*A complete list of investigators in the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) is provided in the Supplementary Appendix, available at NEJM.org.

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In both European and U.S. guidelines, prophylactic implantation of an implantable cardioverter–defibrillator (ICD) is a class 1 recommendation for patients with heart failure and reduced left ventricular systolic function.[1,2] However, the evidence for a benefit is much stronger for patients with ischemic heart disease than it is for patients with heart failure from other causes. Over the past two decades, ICD implantation has been shown to be associated with substantial reductions in the rate of sudden cardiac death and total mortality in patients with ischemic heart disease.[3-6] In the case of patients without ischemic heart disease, one trial showed an association between ICD implantation and a reduction in the rate of death attributed to arrhythmias, but no single trial has shown a convincing effect on total mortality.[7-9] The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study, which randomly assigned 1520 patients with New York Heart Association (NYHA) class III or IV heart failure to receive medical therapy, a cardiac resynchronization therapy (CRT) pacemaker, or a CRT defibrillator, showed significantly lower all-cause mortality in association with a CRT defibrillator than with medical treatment alone, but a CRT defibrillator was not shown to be superior to a CRT pacemaker.[10] The only randomized trial involving patients with nonischemic systolic heart failure in which a significant benefit with regard to all-cause mortality has been reported in association with the implantation of an ICD is the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which included 2521 patients, half of whom had nonischemic systolic heart failure.[6] However, the positive effect of ICD treatment was confined to patients in NYHA class II, and no patients received concomitant CRT. In addition, medical treatment for heart failure has changed since SCD-HeFT was conducted.

Given the limited evidence of a benefit from the implantation of an ICD in patients with chronic nonischemic heart failure, we conducted a randomized trial in which patients whose condition was stable and who had chronic symptomatic heart failure, reduced ejection fraction, and increased levels of natriuretic peptide with or without a need for CRT were randomly assigned either to receive or not to receive an ICD.

Methods

Trial Oversight

The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) was an investigator-initiated multicenter, randomized, unblinded, controlled trial that was conducted at all centers in Denmark at which ICDs were implanted. The trial design and baseline characteristics of the patients have been published previously.[11] The trial was designed and overseen by a steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) and was supported by unrestricted grants from Medtronic, St. Jude Medical, TrygFonden, and the Danish Heart Foundation; the funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis, in the writing of the manuscript, or in the decision to submit it for publication. The trial protocol, available at NEJM.org, was approved by the regional scientific ethics committee for the Capital Region of Denmark and the Danish Data Protection Agency. The trial was performed in accordance with the principles of the Declaration of Helsinki. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial and this report to the protocol.

Patients

Symptomatic patients (NYHA class II or III, or NYHA class IV if CRT was planned) with nonischemic systolic heart failure (left ventricular ejection fraction ≤35%) and an increased level (>200 pg per milliliter) of N-terminal pro–brain natriuretic peptide (NT-proBNP) were eligible for enrollment. The qualifying left ventricular ejection fraction and NT-proBNP level had to be measured after the doses of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers and beta-blockers had been increased to target levels, which were the guideline-specified levels whenever possible. A nonischemic cause of heart failure was usually determined by coronary angiography, although a normal computed tomographic (CT) angiogram or nuclear myocardial perfusion imaging study was acceptable. Patients could be included even if they had one or two coronary arteries with

stenoses, if the extent of coronary artery disease was not considered to be sufficient to account for the reduced left ventricular systolic function. Patients with an existing conventional pacemaker or CRT pacemaker device could be included if the patients were willing to have the device changed or upgraded. Patients who had permanent atrial fibrillation with a resting heart rate higher than 100 beats per minute or renal failure that was being treated with dialysis were excluded. A complete list of the inclusion and exclusion criteria is provided in the Supplementary Appendix. All participants provided written informed consent.

TRIAL PROCEDURES

Participants were randomly assigned in a 1:1 ratio to either the ICD group or the control group (usual clinical care). Randomization was performed with the use of a Web-based system, in permuted blocks, with block sizes ranging from 2 to 6 patients, and was stratified according to center and according to whether patients were scheduled to receive CRT. The decision to implant a CRT device had to be made before randomization. Implantation of an ICD (or a CRT pacemaker or CRT defibrillator) was planned to be performed no later than 4 weeks after randomization; all patients were seen at follow-up visits after 2 months and every 6 months thereafter until the end of the trial. Device programming and monitoring of the ICD followed routine clinical practice (see the Supplementary Appendix).

OUTCOMES

The primary outcome was death from any cause. The secondary outcomes were sudden cardiac death, cardiovascular death, resuscitated cardiac arrest or sustained ventricular tachycardia, and change from baseline in quality of life (quality-of-life outcomes are not discussed in this report). The outcome designated as "sudden cardiac death" probably included some instances of sudden vascular death, because, as we realized during the adjudication of outcomes, a clear distinction often could not be made between sudden cardiac death and sudden vascular death. However, because the term "sudden cardiac death" was used in the protocol and event definitions, we have retained this term throughout. The safety outcome of device infection was prespecified; all other safety outcomes were based on adverse-event reporting. An end-point classification committee, the members of which were unaware of the treatment assignments, used prespecified criteria to adjudicate all prespecified clinical outcomes (see the Supplementary Appendix for criteria).

STATISTICAL ANALYSIS

The study was designed to have 80% power to detect a 25% difference in total mortality between the treatment groups. At least 246 primary outcome events were required for the study to be conclusive, and we planned to include 1000 patients. Because the event rate and enrollment rate were lower than expected, the steering committee decided to prolong enrollment until June 30, 2014, or until 1200 patients were included (whichever came first) and to follow the last randomly assigned patient for at least 2 years. The baseline characteristics were compared between the treatment groups with the use of chi-square and Wilcoxon tests. Outcomes were analyzed with the use of time-to-event methods. Kaplan–Meier plots were calculated for total mortality, and cumulative incidence curves were calculated for events with competing risk (sudden cardiac death and cardiovascular death). The analysis of the primary outcome was performed with a log-rank model stratified according to center and status with respect to planned implantation of a CRT device. The proportional-hazard assumption was assessed with Schoenfeld residuals. Post hoc annual event rate ratios were derived from a Poisson regression. Prespecified subgroup analyses of the primary outcome were performed for the variables shown in Table 1. All analyses were performed in the intention-to-treat population. Two-sided P values of 0.05 or less were considered to indicate statistical significance. Analyses were performed with SAS software, version 9.4 (SAS Institute), and R software, version 3.3.1 (R Project for Statistical Computing).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From February 7, 2008, to June 30, 2014, a total of 1116 patients were enrolled at five centers; 556 patients were randomly assigned to the ICD group, and 560 patients were assigned to the control group (Fig. 1). Overall, the two groups were balanced with respect to baseline characteristics

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	ICD Group (N=556)	Control Group (N=560)
Median age (IQR) — yr	64 (56–72)	63 (56–70)
Female sex — no. (%)	151 (27)	156 (28)
Median blood pressure (IQR) — mm Hg		
Systolic	123 (110–139)	124 (111–138)
Diastolic	74 (65–81)	74 (66–82)
Median body-mass index (IQR)†	26.8 (23.9–30.5)	26.8 (23.8–30.1)
Median NT-proBNP level (IQR) — pg/ml	1244 (616–2321)	1110 (547–2166)
Median QRS duration (IQR) — msec	146 (114–166)	145 (110–164)
Median left ventricular ejection fraction (IQR) — %	25 (20–30)	25 (20–30)
Median estimated GFR (IQR) — ml/min/1.73 m^2	74 (58–91)	73 (58–92)
NYHA class — no. (%)		
II	297 (53)	300 (54)
III	252 (45)	253 (45)
IV	7 (1)	7 (1)
Median duration of heart failure (IQR) — mo	20 (8–72)	18 (8–60)
Coexisting conditions — no. (%)		
Hypertension	181 (33)	167 (30)
Diabetes	99 (18)	112 (20)
Permanent atrial fibrillation	135 (24)	113 (20)
Means of exclusion of ischemic cause of heart failure — no. (%)		
Nuclear study	5 (1)	8 (1)
CT angiogram	18 (3)	11 (2)
Catheterization	533 (96)	541 (97)
Cause of heart failure — no. (%)		
Idiopathic	424 (76)	425 (76)
Valvular	20 (4)	21 (4)
Hypertension	62 (11)	55 (10)
Other	50 (9)	59 (11)
Medications — no. (%)		
ACE inhibitor or ARB	533 (96)	544 (97)
Beta-blocker	509 (92)	517 (92)
Mineralocorticoid-receptor antagonist	326 (59)	320 (57)
Amiodarone	34 (6)	32 (6)
CRT — no. (%)	322 (58)	323 (58)
Preexisting pacemaker or CRT pacemaker — no. (%)	56 (10)	46 (8)

* There were no significant differences (P<0.05) between the study groups. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CRT cardiac resynchronization therapy, CT computed tomography, GFR glomerular filtration rate, ICD implantable cardioverter–defibrillator, IQR interquartile range, NT-proBNP N-terminal pro–brain natriuretic peptide, and NYHA New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

(Table 1). In both groups, 58% of patients received CRT. The majority of patients received target doses of heart failure medication in accordance with the guidelines that were available at the time of the trial (Table S1 in the Supplementary Appendix), and among the patients

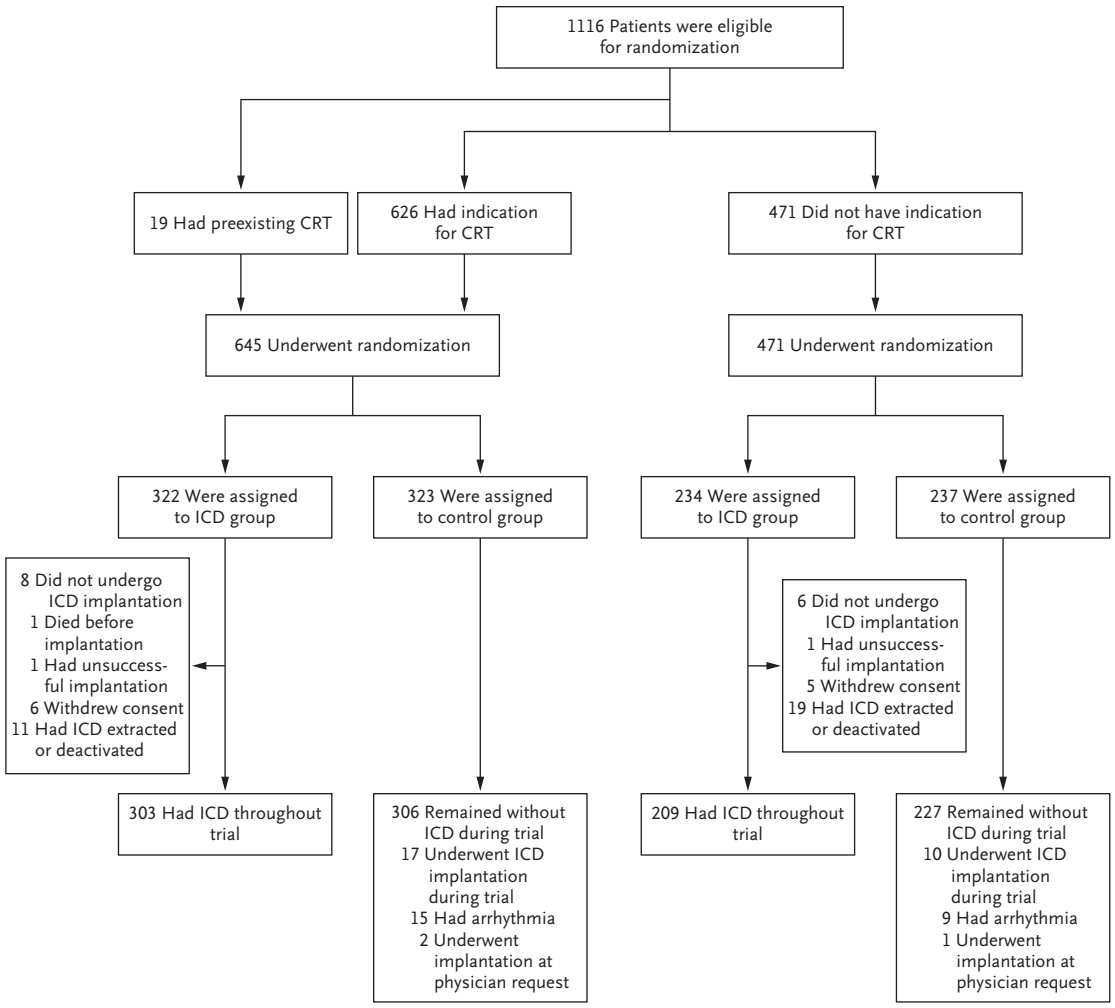

Figure 1. Enrollment and Randomization of Patients.

Details regarding device implantation and upgrades in the control group are provided in the Supplementary Appendix. CRT denotes cardiac resynchronization therapy, and ICD implantable cardioverter–defibrillator.

with wide left bundle-branch block (QRS duration, ≥150 msec), 93% received CRT (see Table S2 in the Supplementary Appendix for baseline demographic characteristics according to CRT status and treatment group).

DEVICE IMPLANTATION

In the ICD group, 4 patients required two attempts at implantation, and 14 patients did not receive an ICD (1 patient died before implantation, implantation was unsuccessful in 2 patients, and 11 patients withdrew consent before implantation). The median time from randomization to implantation was 31 days (interquartile range, 19 to 43). A total of 27 patients in the control group received an ICD (24 because of an arrhythmic event and 3 at the request of their physician). During the trial, 85 patients (15.3%) in the ICD group had the battery in their ICD replaced, and 30 patients had the device removed or permanently deactivated because of an infection or by request (Fig. 1).

FOLLOW-UP AND OUTCOMES

Follow-up data for all outcomes were available through June 30, 2016. The median follow-up period was 67.6 months (interquartile range, 49 to 85), and no patients were lost to follow-up for the primary outcome.

The primary outcome, death from any cause,

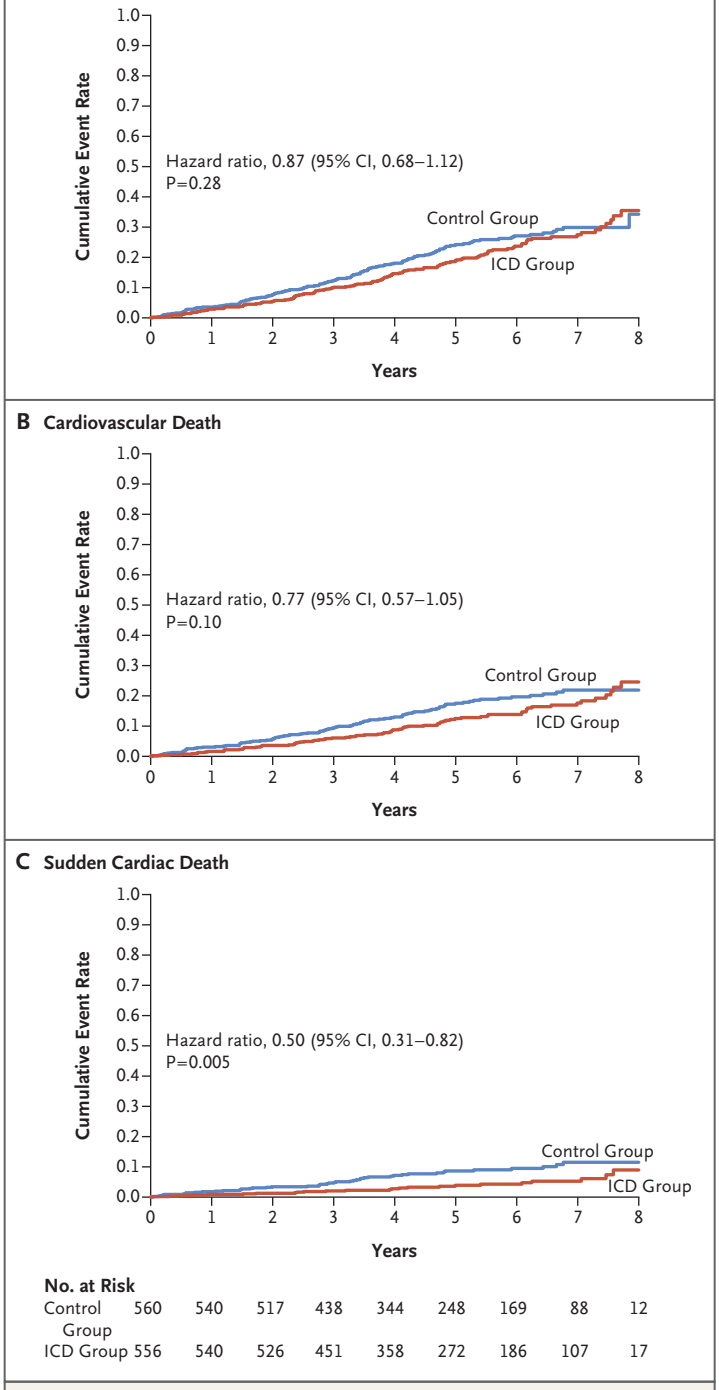

Figure 2. Time-to-Event Curves for Death from Any Cause, Cardiovascular Death, and Sudden Cardiac Death.

occurred in 120 patients (21.6%) in the ICD group (4.4 events per 100 person-years) and in 131 patients (23.4%) in the control group (5.0 events per 100 person-years) (Fig. 2A and Table 2). The hazard ratio for death from any cause in the ICD group, as compared with the control group, was 0.87 (95% confidence interval [CI] 0.68 to 1.12; P=0.28). The test for the proportional-hazard assumption with Schoenfeld residuals gave a P value of 0.054. Annual event rate ratios from post hoc analyses are provided in Table S3 in the Supplementary Appendix. Cardiovascular death occurred in 77 patients (13.8%) in the ICD group and in 95 patients (17.0%) in the control group (hazard ratio, 0.77; 95% CI, 0.57 to 1.05; P=0.10) (Table 2 and Fig. 2B). Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (hazard ratio, 0.50; 95% CI, 0.31 to 0.82; P=0.005) (Table 2 and Fig. 2C). The clinical outcome of resuscitated cardiac arrest or sustained ventricular tachycardia occurred with similar frequency in the two groups (Table 2); termination of ventricular tachycardia by antitachycardia pacing occurred in 97 patients (17.4%) in the ICD group, and appropriate shock for ventricular fibrillation or rapid ventricular tachycardia was given for 64 patients (11.5%) in the ICD group.

The results of subgroup analyses are shown in Figure 3. The results were similar across all subgroups with the exception of age, for which there was a significant treatment-by-subgroup interaction (P=0.009 for the interaction) (Fig. 3, and Fig. S1 in the Supplementary Appendix). The rate of death from any cause was significantly lower among patients younger than 68 years of age than among patients 68 years of age or older (hazard ratio, 0.64; 95% CI, 0.45 to 0.90; P=0.01). The effect of ICD implantation was independent of CRT status (P=0.73 for the interaction) (Fig. S2 in the Supplementary Appendix).

SAFETY

Device infections occurred in 27 patients (4.9%) in the ICD group and in 20 patients (3.6%) in the control group (P=0.29) (Table 2). Among patients who were not receiving CRT, the risk of device infection was higher in the ICD group than it was in the control group (12 of 234 patients [5.1%] vs. 2 of 237 patients [0.8%]; hazard ratio, 6.35; 95% CI, 1.38 to 58.87; P=0.006). Inappropriate shocks occurred in 33 patients (5.9%) in the ICD group (Table 2); 28 of the shocks were due to atrial fibrillation, 4 were due to oversensing, and 1 was due to supraventricular arrhyth-

Table 2. Outcomes and Adverse Events.*

Outcome	ICD Group† (N=556)	Control Group† (N=560)	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Death from any cause	120 (21.6)	131 (23.4)	0.87 (0.68–1.12)	0.28
Cardiovascular death	77 (13.8)	95 (17.0)	0.77 (0.57–1.05)	0.10
Sudden cardiac death	24 (4.3)	46 (8.2)	0.50 (0.31–0.82)	0.005
Other cardiovascular death	53 (9.5)	49 (8.8)	1.03 (0.70–1.52)	0.89
Noncardiovascular death	43 (7.7)	36 (6.4)	1.12 (0.72–1.76)	0.60
Resuscitated cardiac arrest or sustained VT	26 (4.7)	25 (4.5)	1.03 (0.59–1.79)	0.91
Cardiac arrest	11 (2.0)	14 (2.5)	0.79 (0.36–1.75)	0.56
Sustained VT requiring medical intervention or electrical conversion	16 (2.9)	14 (2.5)	1.12 (0.54–2.30)	0.76
			Odds Ratio (95% CI)	
Device infection	27 (4.9)	20 (3.6)	1.38 (0.73–2.63)	0.29
CRT‡	15/322 (4.7)	18/323 (5.6)	0.83 (0.38–1.78)	0.60
No CRT‡	12/234 (5.1)	2/237 (0.8)	6.35 (1.38–58.87)	0.006
Serious device infection§	15 (2.7)	13 (2.3)	1.17 (0.51–2.69)	0.69
CRT‡	9/322 (2.8)	11/323 (3.4)	0.82 (0.29–2.20)	0.65
No CRT‡	6/234 (2.6)	2/237 (0.8)	3.09 (0.54–31.56)	0.24
Bleeding requiring intervention	1 (0.2)	0	—	—
Pneumothorax	11 (2.0)	6 (1.1)	1.86 (0.68–5.08)	0.22
Inappropriate shocks	33 (5.9)	0	—	—

* VT denotes ventricular tachycardia.
† Total numbers are included when they differ from those in the overall study group. A total of 348 patients in the control group received a device (CRT pacemaker, ICD, CRT defibrillator, or bradycardia pacemaker) after randomization and were susceptible to device complications. Details regarding device implantation and upgrades in the control group are provided in the Supplementary Appendix.
‡ Percentages were calculated with the numbers of patients scheduled for CRT and the numbers of patients not scheduled for CRT as the denominators.
§ A serious device infection was defined as infection requiring lead extraction or lifelong antibiotic treatment or causing death (see the Supplementary Appendix).

mia other than atrial fibrillaton. One patient had the ICD deactivated because of several shocks. Other complications during implantation were uncommon and occurred in both groups, because many of the control patients received a CRT device (Table 2).

DISCUSSION

We found that implantation of an ICD in patients who had heart failure that was not caused by ischemic heart disease did not provide an overall survival benefit, although the risk of sudden cardiac death was halved with an ICD. There was an important interaction with age that suggested that younger patients may have a survival benefit in association with ICD implantation. The results were independent of whether a patient received a CRT device.

All time-to-event curves appeared to diverge during the initial 5 years of the trial and then to converge (Fig. 2). Post hoc analysis of annual event rate ratios (Supplementary Appendix) supports this interpretation. This observation lends support to the rationale for long-term studies, since the most common causes of death may change over time in patients with heart failure. In previous trials that showed a benefit from ICD implantation in patients with ischemic heart disease, the number needed to treat in order to save one life was as low as 6 over an 8-year period.[3,12,13] There may be several explanations for the difference between these results and our findings. Patients with nonischemic heart failure may be

Subgroup	ICD Group	Control Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no.				
Age					0.009
<59 yr	17/167	34/181	0.51 (0.29–0.92)	0.02	
≥59 to <68 yr	36/173	50/202	0.75 (0.48–1.16)	0.19	
≥68 yr	67/216	47/177	1.19 (0.81–1.72)	0.38	
Sex					0.66
Female	22/151	23/156	1.03 (0.57–1.87)	0.92	
Male	98/405	108/404	0.85 (0.64–1.12)	0.24	
NT-proBNP					0.06
<1177 pg/ml	32/266	74/268	0.59 (0.38–0.91)	0.02	
≥1177 pg/ml	57/292	88/290	0.99 (0.73–1.36)	0.96	
LV ejection fraction					0.69
<25%	70/264	65/242	0.87 (0.62–1.22)	0.42	
≥25%	50/292	66/318	0.79 (0.54–1.14)	0.21	
Estimated GFR					0.86
<73 ml/min/1.73 m^2	75/272	80/278	0.88 (0.64–1.21)	0.42	
≥73 ml/min/1.73 m^2	45/283	50/280	0.82 (0.55–1.23)	0.33	
NYHA functional class					0.71
II	52/297	54/300	0.92 (0.63–1.35)	0.68	
III–IV	68/259	77/260	0.81 (0.58–1.13)	0.21	
Heart failure duration					0.73
<18 mo	31/254	36/277	0.88 (0.54–1.43)	0.61	
≥18 mo	89/301	95/283	0.81 (0.61–1.09)	0.17	
Hypertension					0.63
No	78/375	87/392	0.90 (0.66–1.22)	0.48	
Yes	42/181	44/167	0.79 (0.51–1.21)	0.27	
Diabetes					0.60
No	87/457	95/448	0.85 (0.63–1.31)	0.26	
Yes	33/99	36/112	0.92 (0.57–1.50)	0.74	
Permanent atrial fibrillation					0.30
No	83/421	91/447	0.92 (0.68–1.24)	0.58	
Yes	37/135	40/113	0.76 (0.48–1.20)	0.24	
Cause of heart failure					0.80
Idiopathic	90/424	100/425	0.88 (0.66–1.17)	0.37	
Valvular	4/20	5/21	0.59 (0.13–2.71)	0.50	
Hypertension	13/62	12/55	0.68 (0.29–1.63)	0.39	
Other	13/50	14/59	1.02 (0.47–2.20)	0.96	
Preexisting pacemaker					0.71
No	108/500	120/514	0.88 (0.68–1.14)	0.34	
Yes	12/56	11/46	0.88 (0.36–2.20)	0.79	
CRT					0.73
No	58/234	65/237	0.83 (0.58–1.19)	0.31	
Yes	62/322	66/323	0.91 (0.64–1.29)	0.59	
Overall			0.87 (0.68–1.12)	0.28	

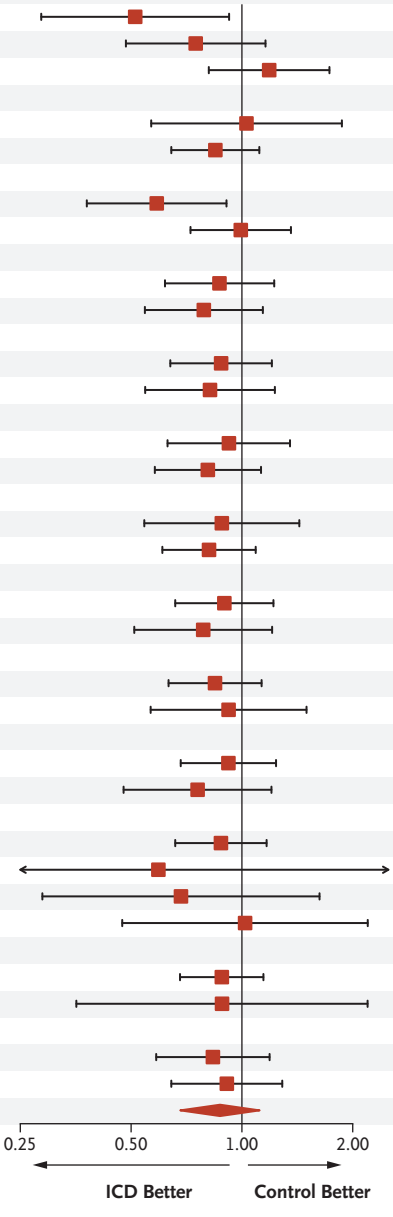

Figure 3. Rate of Death from Any Cause (Primary Outcome) in Prespecified Subgroups.

GFR denotes glomerular filtration rate, LV left ventricular, NT-proBNP N-terminal pro–brain natriuretic peptide, and NYHA New York Heart Association.

less prone to death from arrhythmia than patients with ischemic heart failure, but better medical treatment and CRT also may have reduced the risk of death from arrhythmia for all patients with heart failure. Our event rate was lower than that observed in older studies, which reflects the fact that our study population consisted predominantly of outpatients who were in stable condition and who were treated medically in accordance with the guidelines, with almost

every patient receiving beta-blockers and inhibitors of the renin–angiotensin system and 60% of the patients receiving mineralocorticoid-receptor antagonists.

We did not find a difference in the relative effect of an ICD between patients who received CRT and patients who did not. However, data on causes of death from observational studies involving patients receiving CRT suggest that an ICD may not be beneficial in the majority of these patients.[14] In the COMPANION trial, the overall difference in mortality between the CRT defibrillator group and the CRT pacemaker group was not tested statistically.[10] In later analyses of the data by independent authors, the crude P value based on overall mortality in the CRT pacemaker group versus the CRT defibrillator group was calculated as 0.12.[15,16] At present, it is therefore unclear whether patients who are eligible for CRT should routinely receive an ICD, and a study in which patients are randomly assigned to receive a CRT pacemaker or a CRT defibrillator would be of potential clinical importance.[16]

In the current study, 31% of deaths were attributed to noncardiovascular causes. This is not surprising in an elderly population, but it highlights the importance of selecting patients for ICD implantation carefully. The rate of death among the patients we included in our trial was relatively low, and patients at higher risk may be more likely to benefit from ICD implantation. However, the subgroup data that suggest a lower likelihood of benefit in older patients might be used as an argument for not implanting ICDs in frail patients. Also, the benefit of ICD implantation with respect to sudden cardiac death that was seen in our trial is convincing, and patients who are not expected to die from other causes may be good candidates for ICD implantation. Long-term data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II indicate that clinical risk scores may make it possible to identify the patients with ischemic heart disease who will benefit most from ICD implantation.[12] Such a method for identifying patients with nonischemic heart failure who are at high risk for death from arrhythmia would be very useful.

The side effects associated with device implantation in our trial were not trivial. Device-related infections were not infrequent, but we did have a high proportion of patients in both groups who were receiving CRT (which requires implantation of an additional lead in the coronary sinus). In addition, 10% of our patients already had a pacemaker and were randomly assigned either to receive or not to receive an ICD upgrade; this is a patient group that has not been included in most of the previous trials. In a recent study, major device-related complications occurred within the first 6 months after implantation in approximately 6% of patients who received an ICD and 11% of patients who received a CRT defibrillator.[17] Rates of inappropriate shocks or inappropriate antitachycardia pacing have decreased in recent years with the use of less aggressive ICD settings, but even with these modifications, 6% of patients have inappropriate shocks within 2.5 years after implantation of a dual-chamber ICD.[13] These figures are similar to the 5.9% of patients who received inappropriate shocks in our trial.

The DANISH trial adds to the available body of data to consider in formulating the indications for ICD implantation in patients with nonischemic systolic heart failure. In the current American Heart Association guidelines, ICD implantation for primary prevention of sudden cardiac death in patients with symptomatic systolic heart failure is a class 1A recommendation, with no differentiation between patients with ischemic and nonischemic causes.[1] In the European guidelines, ICD implantation is a class 1B recommendation for patients with nonischemic heart failure, as opposed to a class 1A recommendation for patients with ischemic heart failure.[2] The American Heart Association guidelines refer solely to the SCD-HeFT trial for their recommendations regarding ICD implantation in patients with nonischemic causes of heart failure, whereas the European guidelines also refer to the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial. However, SCD-HeFT enrolled patients between 1997 and 2001, and only 69% of enrolled patients received beta-blockers at baseline, 20% of patients received a mineralocorticoid-receptor antagonist, and no patients received concomitant CRT.[6] In addition, the designation of ischemic or nonischemic causes in the SCD-HeFT trial was based primarily on patient history, with results from coronary angiography used to designate the cause only if such results were avail-

able. The DEFINITE trial, which enrolled patients between 1998 and 2002, included a larger proportion of patients who received beta-blockers (85%) but, again, no patients who received CRT.[9]

In conclusion, in our trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure that was not caused by coronary artery disease was not found to reduce long-term mortality.

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

APPENDIX

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