ORIGINAL ARTICLE

Declining Risk of Sudden Death in Heart Failure

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ABSTRACT

BACKGROUND

The risk of sudden death has changed over time among patients with symptomatic heart failure and reduced ejection fraction with the sequential introduction of medications including angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and mineralocorticoid-receptor antagonists. We sought to examine this trend in detail.

METHODS

We analyzed data from 40,195 patients who had heart failure with reduced ejection fraction and were enrolled in any of 12 clinical trials spanning the period from 1995 through 2014. Patients who had an implantable cardioverter–defibrillator at the time of trial enrollment were excluded. Weighted multivariable regression was used to examine trends in rates of sudden death over time. Adjusted hazard ratios for sudden death in each trial group were calculated with the use of Cox regression models. The cumulative incidence rates of sudden death were assessed at different time points after randomization and according to the length of time between the diagnosis of heart failure and randomization.

RESULTS

Sudden death was reported in 3583 patients. Such patients were older and were more often male, with an ischemic cause of heart failure and worse cardiac function, than those in whom sudden death did not occur. There was a 44% decline in the rate of sudden death across the trials ($P=0.03$). The cumulative incidence of sudden death at 90 days after randomization was 2.4% in the earliest trial and 1.0% in the most recent trial. The rate of sudden death was not higher among patients with a recent diagnosis of heart failure than among those with a longer-standing diagnosis.

CONCLUSIONS

Rates of sudden death declined substantially over time among ambulatory patients with heart failure with reduced ejection fraction who were enrolled in clinical trials, a finding that is consistent with a cumulative benefit of evidence-based medications on this cause of death. (Funded by the China Scholarship Council and the University of Glasgow.)

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Many patients with heart failure and reduced ejection fraction die suddenly, often owing to a ventricular arrhythmia.[1] Implantable cardioverter–defibrillators (ICDs) reduce this risk and are currently recommended in patients with New York Heart Association (NYHA) functional class II or III symptoms and a left ventricular ejection fraction of 35% or less, regardless of cause.[2-5] However, ICDs are costly, have occasional complications early after implantation (e.g., infection), and may have later adverse outcomes including inappropriate shocks and device malfunction that lead, in some patients, to a diminished quality of life.[6]

The currently recommended medications for heart failure with reduced ejection fraction, including angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers,[7,8] beta-blockers,[9] and mineralocorticoid-receptor antagonists,[10] reduce the risk of sudden death. After the accrual of evidence from randomized, controlled trials, these drugs have increasingly been used in combination, with the latest guidelines recommending treatment with all three in most patients. More recently, combination therapy with sacubitril and valsartan resulted in a lower risk of sudden death than the ACE inhibitor enalapril.[11] With the increasing use of evidence-based medications, rates of sudden death over time may have diminished such that ICDs may not significantly reduce overall mortality when added to appropriate medical therapy in some groups of patients, such as those with nonischemic cardiomyopathy.[12] To investigate this issue, we examined the risk of sudden death during follow-up in 12 randomized, controlled trials involving patients with symptomatic heart failure with reduced ejection fraction that were conducted during the period from 1995 through 2014.

Methods

Population of Patients

We attempted to obtain patient-level data from all randomized trials enrolling more than 1000 broadly representative patients with chronic ambulatory and symptomatic (NYHA class II, III, or IV) heart failure with reduced ejection fraction (≤40%) that were conducted over the past 20 years and that included adjudication of cause of death (excluding trials in which all the patients in each randomized group had an ICD) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Among 42 trials identified, 20 trials were excluded for the reasons indicated in Figure S1 in the Supplementary Appendix. A total of 22 trials were eligible for inclusion in our analysis, but data were not obtained for 10 of them (Table S1 in the Supplementary Appendix), so 12 trials were included in this analysis (Table 1). The design and results of these trials have been published in detail,[2,13-23] and their main characteristics are summarized in Table S2 in the Supplementary Appendix.

Outcome of Interest

In the present study, the outcome of interest was sudden death. The adjudication of sudden death in each trial was carried out by an independent committee in a blinded fashion with the use of prespecified criteria. Similar but not identical criteria were used in most trials (Table S3 in the Supplementary Appendix). The cumulative incidence rates of sudden death in each trial were calculated at 30 days, 60 days, 90 days, 180 days, 1 year, 2 years, and 3 years after randomization. The risk of sudden death was also calculated according to the length of time between the diagnosis of heart failure and randomization (≤3 months, >3 to 6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, or >5 years).

Adjustment for Potential Confounding Variables

We examined the confounding effect of a number of baseline variables on the risk of sudden death, including age, sex, left ventricular ejection fraction, NYHA class, cause (ischemic vs. nonischemic), previous myocardial infarction, and history of hypertension or diabetes; these data had been collected in all the trials. The estimated glomerular filtration rate (GFR) was not available in most patients in the two CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) trials (measured only in patients from North America).[18,19] The plasma level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) was measured only in Val-HeFT (Valsartan Heart Failure Trial),[17] CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure),[20] GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure Trial),[21] and the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure)[23] trial. We examined the

Table 1. Trials Included in the Analysis, According to Trial Period.

Trial Acronym*	Trial Period	No. of Patients		Randomized Comparison
		Included in Original Report	Included in This Analysis†	
RALES	March 1995–Aug. 1998	1663	1663	Spironolactone vs. placebo
BEST	May 1995–July 1999	2708	2617	Bucindolol vs. placebo
CIBIS-II	Nov. 1995–March 1998	2647	2647	Bisoprolol vs. placebo
MERIT-HF	Feb. 1997–Oct. 1998	3991	3991	Metoprolol vs. placebo
Val-HeFT	March 1997–May 2000	5010	5010	Valsartan vs. placebo
SCD-HeFT	Sept. 1997–Oct. 2003	2521	1692	ICD vs. amiodarone vs. placebo
CHARM-Alternative	March 1999–March 2003	2028	1960	Candesartan vs. placebo (in patients who could not take ACE inhibitors)
CHARM-Added	March 1999–March 2003	2548	2448	Candesartan vs. placebo (added to ACE-inhibitor therapy)
CORONA	Sept. 2003–May 2007	5011	4875	Rosuvastatin vs. placebo
GISSI-HF	Aug. 2002–March 2008	4574	3820	Rosuvastatin vs. placebo
EMPHASIS-HF	March 2006–May 2010	2737	2316	Eplerenone vs. placebo
PARADIGM-HF	Dec. 2009–March 2014	8399	7156	Angiotensin–neprilysin inhibitor vs. enalapril

* The full trial names, trial registration numbers, and citations of the trials are as follows: RALES (Randomized Aldactone Evaluation Study)[13]; BEST (Beta-Blocker Evaluation of Survival; ClinicalTrials.gov number, NCT00000560)[14]; CIBIS-II (Cardiac Insufficiency Bisoprolol Study II)[15]; MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure)[16]; Val-HeFT (Valsartan Heart Failure Trial)[17]; SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial; NCT00000609)[2]; CHARM-Alternative (the alternative trial of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program; NCT00634400)[18]; CHARM-Added (the added trial of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program; NCT00634309)[19]; CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure; NCT00206310)[20]; GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure Trial; NCT00336336)[21]; EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; NCT00232180)[22]; and PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; NCT01035255).[23] There are no trial registration numbers for RALES, CIBIS-II, MERIT-HF, or Val-HeFT because these trials were conducted before the requirement to register trials. ACE denotes angiotensin-converting enzyme.

† A total of 91 patients in the BEST trial were excluded from this analysis because data from 1 patient were not available in the public-use copy of the BEST database we obtained from the National Heart, Lung, and Blood Institute and 90 patients had an implantable cardioverter–defibrillator (ICD) at the time of enrollment in the trial. A total of 829 patients in SCD-HeFT were excluded from this analysis because they had been randomly assigned to receive an ICD. Also excluded from this analysis for having an ICD at the time of enrollment in the trial were 68 patients in the CHARM-Alternative trial, 100 patients in the CHARM-Added trial, 136 patients in CORONA, 293 patients in GISSI-HF, 421 patients in the EMPHASIS-HF trial, and 1243 patients in the PARADIGM-HF trial. In addition, 461 patients in GISSI-HF were excluded from this analysis because they had a left ventricular ejection fraction of more than 40%.

additional prognostic importance of the estimated GFR and the NT-proBNP level on sudden death in patients with full data and after imputation of missing values.

STATISTICAL ANALYSIS

The characteristics of all the patients at baseline, and the characteristics of the patients with sudden death and those without, in each trial were summarized as means with standard deviations for continuous variables and as percentages for categorical variables. The characteristics at baseline were compared between the patients with sudden death and those without sudden death with the use of Student's t-tests for continuous variables and chi-square tests for categorical variables. Because NT-proBNP values were not normally distributed, they are presented as medians and interquartile ranges and were analyzed with the use of the Mann–Whitney U test.

The annual rate of sudden death in each trial and in each group in each trial was calculated per 100 patient-years. The cumulative incidence rates of sudden death in each trial were calculated and were also shown by means of cumulative incidence curves, with the use of the nonparametric cumulative incidence function of Fine and Gray,[24] in which death from nonsudden causes was treated as a competing risk (i.e., dependent censoring). The hazard ratio for sudden death in each trial group was calculated with the use of a cause-specific Cox proportional-hazards

model, and we used the placebo group of the earliest trial, RALES (Randomized Aldactone Evaluation Study),[13] as the reference.

In a Cox model we then examined the association between calendar year and the risk of sudden death with adjustment for randomized group, with the trial as a random effect. This model was then further adjusted for the confounding variables listed above. The association between calendar year and the rate of sudden death was assessed in a multiple linear regression model with the randomization year and randomized group as covariates, weighted by the inverse variance of the rate, with the trial as a random effect. To examine whether, and to what extent, outliers influenced the overall trends, we undertook sensitivity analyses that excluded each outlier trial in turn and reproduced the regression analysis. Additional analyses were performed to examine the influence of the duration between the diagnosis of heart failure and randomization on the cumulative incidence of sudden death and to evaluate whether and how the risk of sudden death varied according to the left ventricular ejection fraction. Further details about the statistical analyses are provided in the Supplementary Appendix.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. The cumulative incidence analysis was undertaken with the use of R software, version 3.2.3, with the cmprsk package. All other data analyses were performed with the use of Stata software, version 14 (StataCorp).

RESULTS

STUDY POPULATION

We analyzed data from 40,195 patients with heart failure with reduced ejection fraction who were enrolled in any of 12 clinical trials conducted over a 20-year period (Table 1), after excluding 3180 patients who had an ICD or were receiving cardiac-resynchronization therapy with a defibrillator and 461 patients with a left ventricular ejection fraction greater than 40% in GISSI-HF. Of the participants included in the analysis, 3583 (8.9%) had sudden death.

BASELINE CHARACTERISTICS OF STUDY POPULATION

The characteristics of the patients in each trial are summarized in Table S4 in the Supplementary Appendix. The mean age of the patients across the trials was 65 years, and 77% of the patients were men. Most of the patients (95%) had NYHA class II or III heart failure. The mean left ventricular ejection fraction varied across the trials, ranging from 23% in the BEST (Beta-Blocker Evaluation of Survival)[14] trial to 32% in GISSI-HF; the overall mean ejection fraction was 28%. A total of 62% of the patients across the trials had an ischemic cause of heart failure. The use of ACE inhibitors and angiotensin-receptor blockers was consistently high (>90%) across these trials (with the exception of the CHARM-Alternative trial, which enrolled patients who could not take an ACE inhibitor). As a general trend, there was a substantially greater use of beta-blockers and mineralocorticoid-receptor antagonists in more recent trials. An estimated GFR measurement was available in 36,959 patients (92%), and both the estimated GFR and the NT-proBNP level were available in 15,308 patients (38%).

BASELINE CHARACTERISTICS OF PATIENTS WITH SUDDEN DEATH

The characteristics of the patients with sudden death and those without sudden death in each trial are shown in Table S5 in the Supplementary Appendix. Overall, older age, male sex, lower left ventricular ejection fraction, lower systolic blood pressure, higher heart rate, worse heart-failure symptoms, an ischemic cause of heart failure, and a history of myocardial infarction, diabetes, or renal dysfunction were positively associated with sudden death. Patients with sudden death were less likely to have undergone coronary revascularization than those without sudden death. The NT-proBNP levels were substantially higher in patients who had sudden death in the Val-HeFT, CORONA, GISSI-HF, and PARADIGM-HF trials than in patients who did not have sudden death. Patients with sudden death were less likely than those without sudden death to have been treated with a beta-blocker but were more likely to be receiving a diuretic, digitalis, or a mineralocorticoid-receptor antagonist.

SUDDEN DEATH RATES IN EACH TRIAL

The annual rate of sudden death fell over time, from 6.5% in the earliest trial (RALES, which was completed in 1998) to 3.3% in the most recent trial (PARADIGM-HF, which was completed in 2014) (Table 2 and Fig. 1); the P value for trend was 0.02. The CORONA trial (completed in

2007) was an outlier, with a rate of sudden death of 5.2% (Table 2). The rate of death from any cause in the CORONA trial also lay outside the declining trend for all trials, which suggests that the higher rate of sudden death was likely to be due to specific clinical characteristics of the patients in the CORONA trial; the trial enrolled only patients 60 years of age or older who had ischemic heart failure. A sensitivity analysis that excluded the CORONA trial showed a steeper trend line for sudden death over time. In the BEST and Val-HeFT trials, sudden death that was preceded by worsening of heart failure was excluded from the analyses in order to be consistent with the definitions used in the remaining trials; a sensitivity analysis that included these events showed a steeper trend line for the decline in sudden death over time. The proportion of sudden death relative to overall mortality did not change across trials, which indicates that the falling rates of sudden death were in line with the downward trend in the overall death rates. Details are provided in Figures S2, S3, and S4 in the Supplementary Appendix.

The rate of sudden death was lower in the experimental-therapy group than in the control group in all the trials, with the exceptions of Val-HeFT and GISSI-HF (Fig. 2). With adjustment for randomized group, with the trial as a random effect, there was a decline in the risk of sudden death of 44% over the 19 years (hazard ratio, 0.56; 95% confidence interval [CI], 0.33 to 0.93; P=0.03). The reduction in risk over time was attenuated with further adjustment for baseline covariates (adjusted hazard ratio, 0.90; 95% CI, 0.61 to 1.32; P=0.60) although the randomized group remained associated with a lower risk of sudden death (hazard ratio, 0.86; 95% CI, 0.81 to 0.92; P<0.001). Additional analyses that took into account the individual randomized groups in each trial are presented in the Supplementary Appendix.

SUDDEN DEATH ACCORDING TO DURATION OF FOLLOW-UP AND TIME SINCE DIAGNOSIS

At 90 days after randomization, the cumulative incidence rates of sudden death ranged from 2.4% (95% CI, 1.6 to 3.1) in RALES to 1.0% (95% CI, 0.8 to 1.3) in the PARADIGM-HF trial (Table 2 and Fig. 3). Generally, in each trial, the cumulative incidence of sudden death at 180 days was approximately double that at 90 days, with a similar general trend toward lower rates in more recent trials. This trend was evident through the latest follow-up interval assessed (3 years).

The cumulative risk of sudden death during follow-up increased significantly according to the length of time between the diagnosis of heart failure and randomization in the nine trials that had this information available (involving 31,866 patients [79% of the total study sample]) (Fig. S8 in the Supplementary Appendix). There was no evidence that the cumulative incidence of sudden death among patients with recently diagnosed heart failure (≤3 months before randomization) was greater than among those with a longer duration of heart failure.

SUDDEN DEATH ACCORDING TO LEFT VENTRICULAR EJECTION FRACTION

We examined the annual rate and the cumulative incidence rates of sudden death at different time intervals during follow-up according to subgroups that were defined according to the left ventricular ejection fraction (<30% vs. 30 to 35% and <25% vs. 25 to 35%) in each trial (Tables S6 and S7 in the Supplementary Appendix). Generally, there was a downward trend in the rate of sudden death, similar to the trend in the entire population, across the trials within each of the ejection fraction subgroups. Consistently in each trial, a higher rate of sudden death was observed in the subgroup of patients with a lower ejection fraction. Details are provided in the Supplementary Appendix.

DISCUSSION

In this analysis involving 40,195 patients with heart failure with reduced ejection fraction who were enrolled in any of 12 clinical trials conducted over a period of 19 years, we found that the rate of sudden death has declined by 44%. The decline in the rate of sudden death over this period paralleled the increasing use of evidence-based pharmacotherapies that are known to reduce the incidence of sudden death. The contemporary cumulative incidence of sudden death (according to the three most recent trials in our study) is approximately 1% by 3 months and 2% or less by 6 months among patients treated with an ACE inhibitor or angiotensin-receptor blocker, a beta-blocker, and a mineralocorticoid-receptor antagonist; the 6-month rate was 1.7% among patients receiving combination therapy with sac-

Table 2. Annual Rates and Cumulative Incidence Rates of Sudden Death in the Clinical Trials Included in this Study, with Randomized Groups Combined.*

Variable	RALES (N=1663)	BEST (N=2617)	CIBIS-II (N=2647)	MERIT-HF (N=3991)	Val-HeFT (N=5010)	SCD-HeFT (N=1692)	CHARM-Alternative (N=1960)	CHARM-Added (N=2448)	CORONA (N=4875)	GISSI-HF (N=3820)	EMPHASIS-HF (N=2316)	PARADIGM-HF (N=7156)
No. of patients with sudden death	192	294	131	211	442	168	186	311	631	367	125	525
No. of patients with death from any cause	670	839	384	362	979	484	540	762	1452	1055	342	1344
Percent of sudden deaths in total mortality	28.7	35.0	34.1	58.3	45.1	34.7	34.4	40.8	43.5	34.8	36.5	39.1
Annual rate of sudden death per 100 patient-yr (95% CI)	6.5 (5.6–7.4)	5.6 (5.0–6.3)	3.8 (3.2–4.5)	5.3 (4.6–6.1)	4.7 (4.3–5.2)	3.0 (2.6–3.5)	3.7 (3.2–4.2)	4.3 (3.8–4.8)	5.2 (4.8–5.6)	2.7 (2.5–3.0)	2.9 (2.4–3.4)	3.3 (3.1–3.6)
Cumulative incidence (95% CI) — %												
At 30 days	1.0 (0.5–1.5)	0.5 (0.2–0.8)	0.4 (0.1–0.6)	0.3 (0.1–0.5)	0.6 (0.4–0.8)	0.5 (0.2–0.9)	0.6 (0.2–0.9)	0.6 (0.3–0.9)	0.5 (0.3–0.7)	0.3 (0.2–0.5)	0.3 (0.1–0.5)	0.4 (0.3–0.6)
At 60 days	1.5 (0.9–2.0)	1.1 (0.7–1.6)	0.9 (0.6–1.3)	0.7 (0.4–0.9)	1.0 (0.7–1.3)	0.9 (0.4–1.3)	1.1 (0.6–1.5)	1.0 (0.6–1.4)	0.9 (0.6–1.1)	0.6 (0.3–0.8)	0.7 (0.3–1.0)	0.7 (0.5–0.9)
At 90 days	2.4 (1.6–3.1)	1.8 (1.3–2.3)	1.3 (0.9–1.7)	1.3 (0.9–1.6)	1.3 (1.0–1.7)	1.4 (0.9–2.0)	1.6 (1.1–2.2)	1.5 (1.0–1.9)	1.3 (1.0–1.7)	1.0 (0.7–1.3)	1.0 (0.6–1.5)	1.0 (0.8–1.3)
At 180 days	4.2 (3.2–5.2)	3.1 (2.4–3.7)	2.0 (1.5–2.5)	2.5 (2.0–3.0)	2.6 (2.2–3.1)	2.5 (1.7–3.2)	2.5 (1.8–3.2)	2.5 (1.9–3.2)	2.6 (2.2–3.1)	1.5 (1.2–1.9)	2.1 (1.5–2.7)	2.0 (1.7–2.3)
At 1 yr	6.7 (5.5–7.9)	5.8 (4.9–6.7)	3.8 (3.0–4.5)	5.0 (4.3–5.7)	4.5 (3.9–5.1)	3.7 (2.8–4.6)	4.2 (3.3–5.1)	4.5 (3.7–5.3)	5.0 (4.4–5.6)	3.2 (2.6–3.8)	3.0 (2.3–3.7)	3.7 (3.3–4.2)
At 2 yr	10.9 (9.3–12.4)	9.7 (8.5–10.9)	6.8 (5.4–8.2)	NA	8.4 (7.5–9.2)	6.4 (5.2–7.5)	6.7 (5.6–7.8)	8.2 (7.1–9.3)	9.1 (8.3–9.9)	5.6 (4.9–6.4)	5.3 (4.3–6.4)	6.5 (5.9–7.1)
At 3 yr	13.4 (11.4–15.4)	13.2 (12.0–15.1)	NA	NA	12.2 (10.6–13.9)	8.7 (7.4–10.1)	9.5 (8.1–10.8)	11.2 (9.9–12.4)	13.2 (12.2–14.2)	7.6 (6.7–8.4)	7.4 (6.0–8.7)	8.8 (8.0–9.5)

* CI denotes confidence interval, and NA not available.

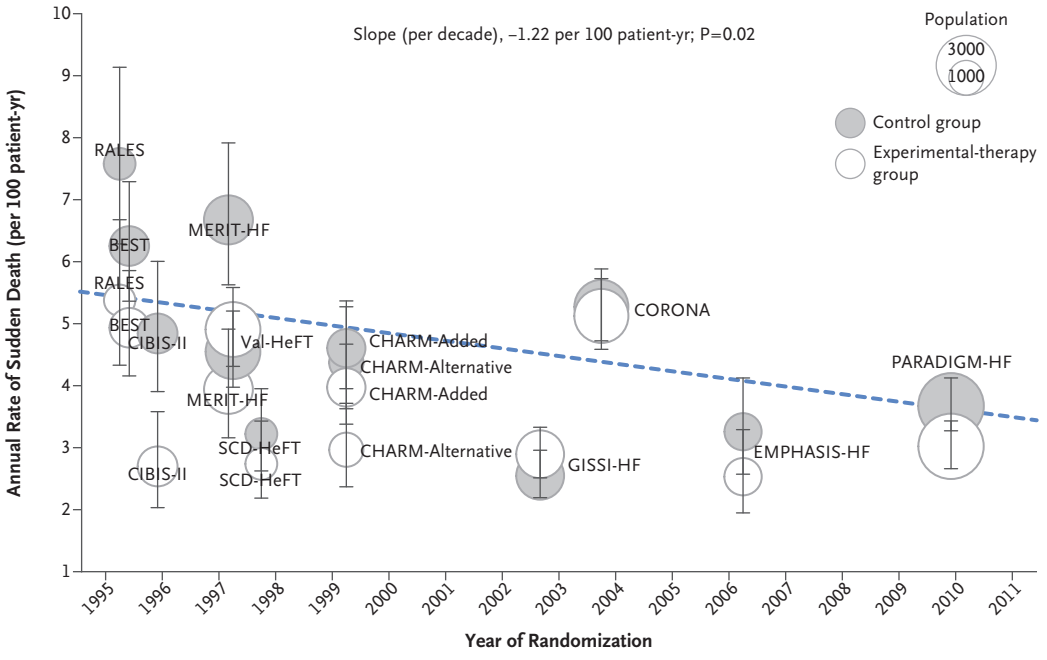

Figure 1. Trends in the Rate of Sudden Death across Trial Groups over Time.

Shown are the annual rates of sudden death per 100 patient-years. Data are shown according to the respective start dates of each trial. Each circle represents a group from each trial as labeled, with the control group shaded and the experimental-therapy group unshaded. For the SCD-HeFT trial, this analysis used the placebo group as the control group and the amiodarone group as the experimental-therapy group (the group of patients assigned to receive an implantable cardioverter–defibrillator was not used in this analysis). The center of each circle corresponds to the randomization year and the annual rate of sudden death in each group, and I bars indicate 95% confidence intervals. The area of each circle represents the sample size in each group (reference sizes are shown in the key). The dotted line is based on the multiple linear regression of the annual rate of sudden death in each trial group with the randomization year and randomization group as covariates, weighted by its inverse variance and with trial as a random effect. The P value for the slope represents the P value for the randomization year on the basis of the linear model.

ubitril and valsartan. After 3 years, the cumulative incidence was 8.8%.

The decreased risk of sudden death in contemporary trials involving patients with a high use of guideline-recommended therapies, coupled with data from previous trials and registries on the likely benefits and complications of ICDs, suggests that it may be difficult to show a significant benefit of ICD implantation for primary prevention in most patients with heart failure with reduced ejection fraction in the current era. This view is reinforced by the recent findings of the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH), which showed no reduction in overall mortality among patients with nonischemic cardiomyopathy with high rates of guideline-recommended pharmacologic treatment and cardiac-resynchronization therapy.[12]

Our study suggests that new efforts are needed to find a high-risk subgroup of patients who benefit from ICD implantation and in whom it is cost effective.[25] The identification of such patients is important, because not all sudden deaths occur in patients with ischemic cardiomyopathy in whom myocardial scar (the dominant substrate for ventricular dysrhythmias) is present. Although the burden of myocardial scar may help identify patients who are at higher risk for sudden death, alternative risk predictors are needed, particularly in patients with nonischemic cardiomyopathies.[12] Although we found some subgroups that had higher rates of death, well-developed and validated prognostic models are needed to identify high-risk patients.

Trial and Group	Concomitant Medication	Annual Rate	Hazard Ratio (95% CI)		P Value
RALES					
Control	ACE inhibitor (94%), beta-blocker (10%)	7.6 (6.3–9.1)		Reference	—
Experimental therapy	ACE inhibitor (95%), beta-blocker (11%), MRA (100%)	5.4 (4.3–6.7)		0.71 (0.54–0.95)	0.02
BEST					
Control	ACE inhibitor or ARB (97%), MRA (4%)	6.3 (5.4–7.3)		0.84 (0.66–1.07)	0.15
Experimental therapy	ACE inhibitor or ARB (96%), beta-blocker (100%), MRA (3%)	4.9 (4.2–5.9)		0.66 (0.51–0.85)	0.001
CIBIS-II					
Control	ACE inhibitor (96%), MRA (10%)	4.8 (3.9–6.0)		0.62 (0.47–0.83)	0.001
Experimental therapy	ACE inhibitor (96%), beta-blocker (100%), MRA (11%)	2.7 (2.0–3.6)		0.35 (0.25–0.49)	<0.001
MERIT-HF					
Control	ACE inhibitor or ARB (96%), MRA (8%)	6.7 (5.6–7.9)		0.83 (0.64–1.07)	0.15
Experimental therapy	ACE inhibitor or ARB (95%), beta-blocker (100%), MRA (7%)	3.9 (3.2–4.9)		0.49 (0.37–0.66)	<0.001
Val-HeFT					
Control	ACE inhibitor or ARB (93%), beta-blocker (35%), MRA (5%)	4.6 (4.0–5.2)		0.60 (0.48–0.76)	<0.001
Experimental therapy	ACE inhibitor or ARB (100%), beta-blocker (35%), MRA (5%)	4.9 (4.3–5.6)		0.65 (0.52–0.81)	<0.001
SCD-HeFT					
Control	ACE inhibitor or ARB (98%), beta-blocker (69%), MRA (19%)	3.2 (2.6–4.0)		0.46 (0.35–0.60)	<0.001
Experimental therapy	ACE inhibitor or ARB (97%), beta-blocker (69%), MRA (20%)	2.7 (2.2–3.4)		0.39 (0.29–0.52)	<0.001
CHARM-Alternative					
Control	Beta-blocker (54%), MRA (23%)	4.4 (3.6–5.3)		0.59 (0.46–0.77)	<0.001
Experimental therapy	ARB (100%), beta-blocker (54%), MRA (24%)	3.0 (2.4–3.7)		0.40 (0.30–0.54)	<0.001
CHARM-Added					
Control	ACE inhibitor (100%), beta-blocker (55%), MRA (16%)	4.6 (4.0–5.4)		0.64 (0.50–0.81)	<0.001
Experimental therapy	ACE inhibitor or ARB (100%), beta-blocker (54%), MRA (17%)	4.0 (3.4–4.7)		0.55 (0.43–0.70)	<0.001
CORONA					
Control	ACE inhibitor or ARB (92%), beta-blocker (75%), MRA (39%)	5.3 (4.7–5.9)		0.71 (0.57–0.88)	0.002
Experimental therapy	ACE inhibitor or ARB (91%), beta-blocker (75%), MRA (39%)	5.1 (4.6–5.7)		0.69 (0.56–0.86)	0.001
GISSI-HF					
Control	ACE inhibitor or ARB (93%), beta-blocker (63%), MRA (41%)	2.5 (2.2–3.0)		0.36 (0.28–0.46)	<0.001
Experimental therapy	ACE inhibitor or ARB (94%), beta-blocker (64%), MRA (39%)	2.9 (2.5–3.3)		0.41 (0.32–0.52)	<0.001
EMPHASIS-HF					
Control	ACE inhibitor or ARB (93%), beta-blocker (86%)	3.3 (2.6–4.1)		0.43 (0.32–0.59)	<0.001
Experimental therapy	ACE inhibitor or ARB (94%), beta-blocker (85%), MRA (100%)	2.5 (2.0–3.3)		0.34 (0.25–0.47)	<0.001
PARADIGM-HF					
Control	ACE inhibitor or ARB (100%), beta-blocker (92%), MRA (57%)	3.7 (3.3–4.1)		0.49 (0.40–0.61)	<0.001
Experimental therapy	ACE inhibitor or ARB (100%), beta-blocker (93%), MRA (54%), LCZ696	3.0 (2.7–3.4)		0.41 (0.32–0.51)	<0.001

Figure 2 (facing page). Hazard Ratios for Sudden Death across Trial Groups, with Incremental Use of Each Class of Medications Indicated.

Hazard ratios were compared with the control (placebo) group in the RALES trial. Shown are the annual rates of sudden death per 100 patient-years. The percentages in the concomitant-medication column indicate the percentages of patients who were taking each type of medication. LCZ696 is an angiotensin–neprilysin inhibitor (sacubitril–valsartan). ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CI confidence interval, and MRA mineralocorticoid-receptor antagonist.

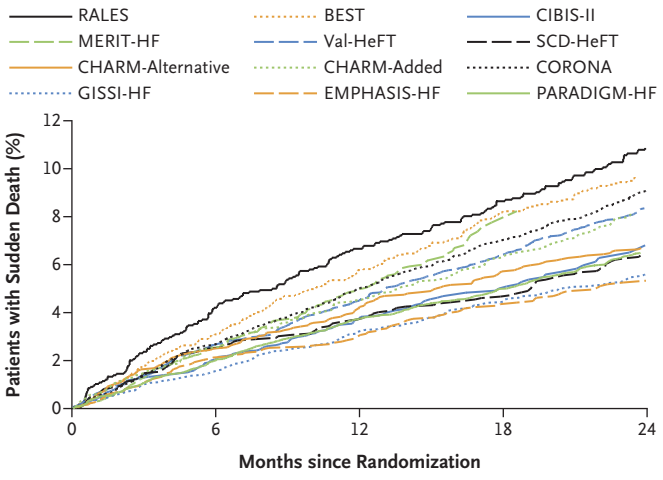

Figure 3. Cumulative Incidence Rates of Sudden Death in the Trials Included in this Study, with Randomized Groups Combined.

The rate of sudden death in our analysis was not higher among patients with a recent diagnosis of heart failure than among those with longer-standing heart failure with reduced ejection fraction; indeed, the reverse was true. Current guidance states that the use of evidence-based pharmacologic therapy for at least 3 months is appropriate in most patients, with repeat measurement of the ejection fraction before device implantation.[26] However, in patients with a new diagnosis, the initiation and increase in dose of three neurohumoral blockers may take many weeks, and there is evidence that reverse remodeling is both dose-dependent and greater with multiple drugs than with one or two agents.[27-31] Moreover, a reduction in left ventricular volumes and an increase in the left ventricular ejection fraction may still occur between 6 and 12 months after the initiation of treatment.[32] Consequently, 3 months may be too short a period to wait to see whether there is sufficient recovery of left ventricular function to obviate the need for an ICD.

One limitation of our study is that it is retrospective and based on clinical trials, in which the majority of patients were white and male, rather than in real-world cohorts in which patients tend to be older, have more coexisting conditions, and receive fewer, and lower doses of, evidence-based drugs.[33-35] However, the rates of sudden death have also been shown to be decreasing among less-selected patients over a time span similar to that covered in our study.[36] Moreover, it is in patients who are similar to those in the present studies that ICDs are most clearly indicated. The rates of sudden death that we found are also in keeping with a report on the national experience of wearable cardioverter–defibrillators in the United States.[37]

Other limitations of our analysis include the fact that the trials we studied did not share a standardized definition of sudden death, although sensitivity analyses suggest that the lack of such standardization does not explain the falling rate of sudden death over time. The measurement of NT-proBNP levels, an important prognostic factor, was not available in all patients, but on the basis of the available data, additional adjustment for NT-proBNP levels did not substantially alter the observed decline in the rate of sudden death. We did not exclude patients who received an ICD during follow-up in each trial; the available data suggest that these numbers were small. Finally, we did not include 10 other trials that were conducted during the period from 1995 through 2014, although the characteristics of the patients enrolled in those trials were very similar to those of the patients in the included trials (Table S1 in the Supplementary Appendix).

In conclusion, the rate of sudden death among patients with heart failure with reduced ejection fraction who were enrolled in clinical trials has fallen over the past two decades, a finding that is consistent with a cumulative benefit of evidence-based medications on sudden death. The absolute rate of sudden death was lower among patients with a more recent diagnosis of heart failure than among those with a longer-standing diagnosis of heart failure.

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APPENDIX

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