ORIGINAL ARTICLE

Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure

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ABSTRACT

BACKGROUND

We tested the hypothesis that prophylactic cardiac-resynchronization therapy in the form of biventricular stimulation with a pacemaker with or without a defibrillator would reduce the risk of death and hospitalization among patients with advanced chronic heart failure and intraventricular conduction delays.

METHODS

A total of 1520 patients who had advanced heart failure (New York Heart Association class III or IV) due to ischemic or nonischemic cardiomyopathies and a QRS interval of at least 120 msec were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy (diuretics, angiotensin-converting–enzyme inhibitors, beta-blockers, and spironolactone) alone or in combination with cardiac-resynchronization therapy with either a pacemaker or a pacemaker–defibrillator. The primary composite end point was the time to death from or hospitalization for any cause.

RESULTS

As compared with optimal pharmacologic therapy alone, cardiac-resynchronization therapy with a pacemaker decreased the risk of the primary end point (hazard ratio, 0.81; P=0.014), as did cardiac-resynchronization therapy with a pacemaker–defibrillator (hazard ratio, 0.80; P=0.01). The risk of the combined end point of death from or hospitalization for heart failure was reduced by 34 percent in the pacemaker group (P<0.002) and by 40 percent in the pacemaker–defibrillator group (P<0.001 for the comparison with the pharmacologic-therapy group). A pacemaker reduced the risk of the secondary end point of death from any cause by 24 percent (P=0.059), and a pacemaker–defibrillator reduced the risk by 36 percent (P=0.003).

CONCLUSIONS

In patients with advanced heart failure and a prolonged QRS interval, cardiac-resynchronization therapy decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality.

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Intraventricular conduction delays are associated with dyssynchronous left ventricular contraction caused by regional delays in the electrical activation of the chamber.[1,2] This phenomenon, which occurs in 15 to 30 percent[3-5] of patients with heart failure due to dilated cardiomyopathy, reduces systolic function and increases systolic volume.[6-8] In patients with primary or secondary dilated cardiomyopathies characterized by intraventricular conduction delays, biventricular stimulation synchronizes the activation of the intraventricular septum and left ventricular free wall and thus improves left ventricular systolic function.[6-8] In short-term studies, cardiac-resynchronization therapy in the form of biventricular stimulation improved symptoms,[9-12] improved the quality of life,[9] and increased exercise tolerance and partially reversed maladaptive remodeling.[9,13-15] These salutary effects support the hypothesis that long-term cardiac-resynchronization therapy decreases the risk of death and complications related to heart failure in patients with intraventricular conduction delays.

Implantable cardioverter–defibrillators (referred to hereafter as defibrillators) can reduce the risk of death among patients who have ischemic cardiomyopathy and no history of sustained ventricular arrhythmia,[16] but it is not clear whether such prophylactic therapy would be beneficial in patients who have advanced heart failure with severe left ventricular dysfunction or in those with nonischemic cardiomyopathies. Nor is it clear that in these settings, any benefit would be additive to those of cardiac-resynchronization therapy. To address these questions, we conducted a large-scale, multicenter, controlled clinical trial comparing optimal pharmacologic therapy plus cardiac-resynchronization therapy with a pacemaker, optimal pharmacologic therapy plus cardiac-resynchronization therapy with a pacemaker–defibrillator, and optimal pharmacologic therapy alone in a population with advanced heart failure and intraventricular conduction delays.

METHODS

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial was conducted at 128 U.S. centers. The complete protocol has been described elsewhere.[17] Enrollment criteria included New York Heart Association (NYHA) class III or IV heart failure resulting from either ischemic or nonischemic cardiomyopathy, a left ventricular ejection fraction of 0.35 or less, an electrocardiographically measured QRS interval of at least 120 msec and a PR interval of more than 150 msec, sinus rhythm, no clinical indication for a pacemaker or implantable defibrillator, and a hospitalization for the treatment of heart failure or the equivalent in the preceding 12 months.[17] Patients, physicians, independent statisticians, and members of the data-management group and the data safety and monitoring board were not blinded to the treatment assignments, whereas the steering committee, the end-points committee, and the sponsor were unaware of the treatment assignments.

Eligible patients who provided written informed consent were randomly assigned in a 1:2:2 ratio to treatment with protocol-mandated optimal pharmacologic therapy alone, optimal pharmacologic therapy plus cardiac-resynchronization therapy with a pacemaker, or optimal pharmacologic therapy plus cardiac-resynchronization therapy with a pacemaker–defibrillator. The pharmacologic therapy used in all groups consisted of diuretics (unless they were not needed), angiotensin-converting–enzyme inhibitors (unless they were not tolerated, whereupon angiotensin-receptor blockers could be substituted), beta-blockers (unless they were not tolerated or were contraindicated), and spironolactone (unless it was not tolerated). Digoxin and other medications used to treat heart failure could be given at the investigator's discretion. The research protocol was approved by the institutional review board of each center.

Patients who were randomly assigned to receive cardiac-resynchronization therapy underwent implantation of a pacemaker (Contak TR model 1241, Guidant) or a pacemaker–defibrillator (Contak CD model 1823, Guidant), with the use of commercially available leads for right atrial pacing and right ventricular pacing or for pacing with defibrillation (Endotak models 0125, 0154, and 0155, Guidant). An over-the-wire lead (Easytrak models 4510 through 4513, Guidant) was placed with the aid of a guiding sheath into a distal branch of the coronary sinus vein chosen by the physician for left ventricular stimulation. Correct placement of the coronary venous or left ventricular lead was subsequently verified radiographically. The programmed atrioventricular delay was calculated from a proprietary algorithm based on measures of the intrinsic PR interval, the QRS interval, and the intracardiac atrioventricular interval at the time of implantation.[18] The final pacing setting for both devices was VDD

with a lower rate well below the patient's lowest intrinsic heart rate, in order to maintain atrial tracking under resting conditions.

The primary end point was a composite of death from any cause or hospitalization for any cause, analyzed from the time of randomization to the time of the first event. Unscheduled intravenous administration of inotropic or vasoactive drugs for more than four hours in the emergency department or on an outpatient basis was considered an instance of the primary end point with respect to hospitalization. Hospitalizations for the initial implantation of the device in the groups assigned to cardiac-resynchronization therapy were not considered to be primary end points, nor were hospitalizations for elective implantation of a device (in the absence of an electrophysiological indication or an ongoing hospitalization for heart failure requiring intravenous therapy). Death from any cause was a secondary end point. We also analyzed the outcomes of death from or hospitalization for cardiovascular causes and death from or hospitalization for heart failure, which were not specified in the protocol but are commonly reported in heart-failure trials. Adverse events were defined as any undesirable clinical outcome and included device-related events as well as events related to the patients' general condition.

Table 1. Clinical Characteristics of the 1520 Patients.*

Characteristic	Optimal Pharmacologic Therapy (N=308)	Cardiac-Resynchronization Therapy	
		Pacemaker (N=617)	Pacemaker–Defibrillator (N=595)
Age (yr)	68	67	66
Male sex (%)	69	67	67
NYHA class III (%)	82	87	86
Duration of heart failure (yr)	3.6	3.7	3.5
Left ventricular ejection fraction	0.22	0.20	0.22
Left ventricular end-diastolic dimension (mm)	67	68	67
Heart rate (beats/min)	72	72	72
Blood pressure (mm Hg)			
Systolic	112	110	112
Diastolic	64	68	68
Distance walked in 6 min (m)	244	274	258
QRS interval (msec)	158	160	160
Ischemic cardiomyopathy (%)	59	54	55
Diabetes (%)	45	39	41
Bundle-branch block (%)			
Left	70	69	73
Right	9	12	10
Pharmacologic therapy (%)			
ACE inhibitor†	69	70	69
ACE inhibitor or angiotensin-receptor blocker†	89	89	90
Beta-blocker	66	68	68
Loop diuretic	94	94	97
Spironolactone	55	53	55

* Median values are given for continuous measures. There were no significant differences among the groups.
† Patients who could not tolerate an angiotensin-converting–enzyme (ACE) inhibitor received an angiotensin-receptor blocker.

During the course of the study, an unanticipated and substantial number of patients withdrew from the pharmacologic-therapy group to receive commercially available implants because of arrhythmia or heart failure. To mitigate the withdrawal rate, the independent statistical group recommended and the steering committee implemented a policy of asking patients who had withdrawn before December 1, 2002, to consent to the collection of data on vital status and hospitalizations for the duration of the study. For mortality and hospitalization end-point analyses, data on patients who withdrew before reaching an end point who were not known to have died and for whom complete post-withdrawal information on hospitalization could not be obtained by this means were censored at the time of elective hospitalization for device implantation or on the date of the last contact. For the mortality end-point analysis, data on patients whose vital status was not known at the end of the study were censored on the date of the last known contact. All analyses were censored at the time of cardiac transplantation.

First events for hospitalization related to cardiovascular causes or heart failure, the use of outpatient intravenous-medication therapy, and the cause of death were adjudicated by an end-points committee. All analyses were conducted according to the intention to treat. Efficacy analyses were based on the time to a first event (unless otherwise stated), with differences between groups determined by the log-rank statistic and the time to an event plotted according to the Kaplan–Meier method. Both nominal P values and P values adjusted for sequential monitoring were reported for the primary end point and mortality. All hazard ratios were unadjusted for covariates, and the Wald chi-square statistic was used for determining P values for the hazard ratios in subgroups. Differences in baseline characteristics

between groups were evaluated with the use of the Wilcoxon rank-sum test for continuous and ordered categorical data and Pearson's chi-square test for all other categorical data. All P values are two-sided and nominal unless otherwise specified.

Assumptions with respect to the sample size have been described previously.[17] The trial was designed to detect a reduction of 25 percent both in the primary end point and in the rate of death from any cause at an alpha value of 0.02 in the pacemaker group and an alpha value of 0.03 in the pacemaker–defibrillator group, each as compared with the phar-

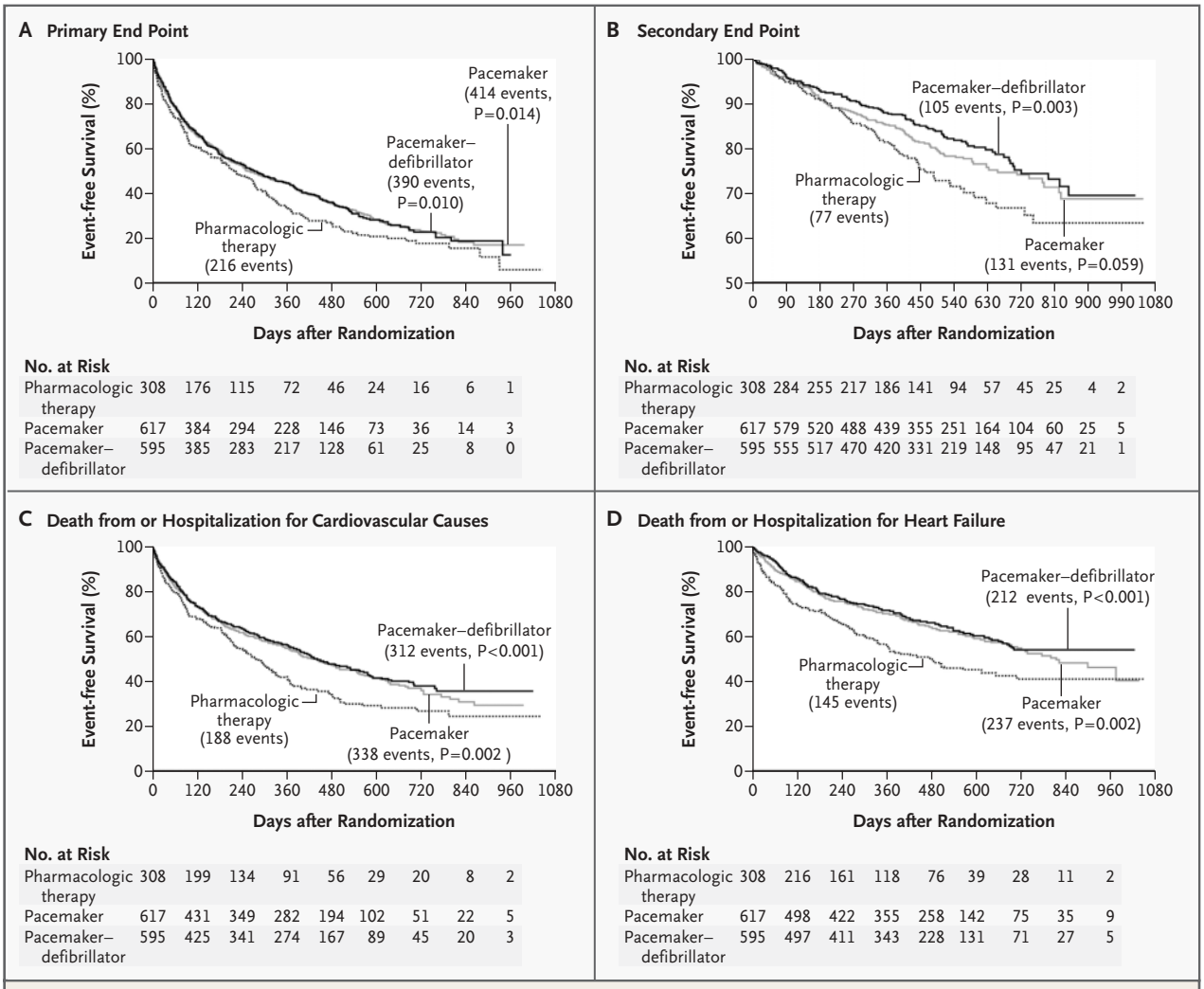


Figure 1. Kaplan–Meier Estimates of the Time to the Primary End Point of Death from or Hospitalization for Any Cause (Panel A), the Time to the Secondary End Point of Death from Any Cause (Panel B), the Time to Death from or Hospitalization for Cardiovascular Causes (Panel C), and the Time to Death from or Hospitalization for Heart Failure (Panel D).

In Panel A, the 12-month rates of death from or hospitalization for any cause — the primary end point — were 68 percent in the pharmacologic-therapy group, 56 percent in the group that received a pacemaker as part of cardiac-resynchronization therapy, and 56 percent in the group that received a pacemaker–defibrillator as part of cardiac-resynchronization therapy. In Panel B, the 12-month rates of death from any cause — the secondary end point — were 19 percent in the pharmacologic-therapy group, 15 percent in the pacemaker group, and 12 percent in the pacemaker–defibrillator group. In Panel C, the 12-month rates of death from or hospitalization for cardiovascular causes were 60 percent in the pharmacologic-therapy group, 45 percent in the pacemaker group, and 44 percent in the pacemaker–defibrillator group. In Panel D, the 12-month rates of death from or hospitalization for heart failure were 45 percent in the pharmacologic-therapy group, 31 percent in the pacemaker group, and 29 percent in the pacemaker–defibrillator group. In the pharmacologic-therapy group, death from heart failure made up 24 percent of the events, hospitalization for heart failure 72 percent of events, and the intravenous administration of inotropes or vasoactive drugs for more than four hours 4 percent of events. P values are for the comparison with optimal pharmacologic therapy.

macologic-therapy group.[17] Under the design assumptions[17] and given a target of 1000 primary events, the study had a statistical power of more than 90 percent for each of the comparisons of the primary end point and 80 percent for the secondary end point of death from any cause. Stopping guidelines for the trial were based on O'Brien–Fleming monitoring boundaries[19] as implemented by Lan and DeMets,[20] with the final critical boundaries for end points adjusted on the basis of the interim analyses.

Enrollment began on January 20, 2000. On November 18, 2002, the data safety and monitoring board reported to the steering committee that 941 potential end point events had been identified and that the trial had most likely already met or would soon reach the target of 1000 events. In addition, at this time preestablished boundaries for the termination of the trial had been crossed in the pacemaker–defibrillator group for both the primary end point and the secondary end point of death from any cause and in the pacemaker group for the primary end point. As recommended by the data safety and monitoring board, the steering committee stopped enrollment and directed that all efficacy follow-up end on December 1, 2002. At the time enrollment was stopped, 1520 patients had undergone randomization.

The study was managed by Clinical Cardiovascular Research, Gaithersburg, Maryland, and the independent statistical data-analysis center was the Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison. The data were held at the University of Wisconsin, where they were analyzed by Dr. DeMets and colleagues. The sponsor had no role in data analysis.

RESULTS

STUDY POPULATION

There were no clinically significant differences in baseline variables or mandated background therapy among the three groups (Table 1).

SUCCESS OF IMPLANTATION IN THE GROUPS ASSIGNED TO CARDIAC-RESYNCHRONIZATION THERAPY

In the groups assigned to cardiac-resynchronization therapy, implantation was successful in 87 percent of the patients in the pacemaker group (539 of 617) and 91 percent of patients in the pacemaker–defibrillator group (541 of 595). For patients who underwent randomization on or after July 1, 2001, when collection of data regarding this outcome was begun, the median duration of the procedure (including lead revisions) was 164 minutes for the pacemaker and 176 minutes for the pacemaker–defibrillator.

Figure 2 (facing page). Hazard Ratios and 95 Percent Confidence Intervals for the Primary End Point of Death from or Hospitalization for Any Cause and the Secondary End Point of Death from Any Cause, According to the Baseline Characteristics of the Patients.

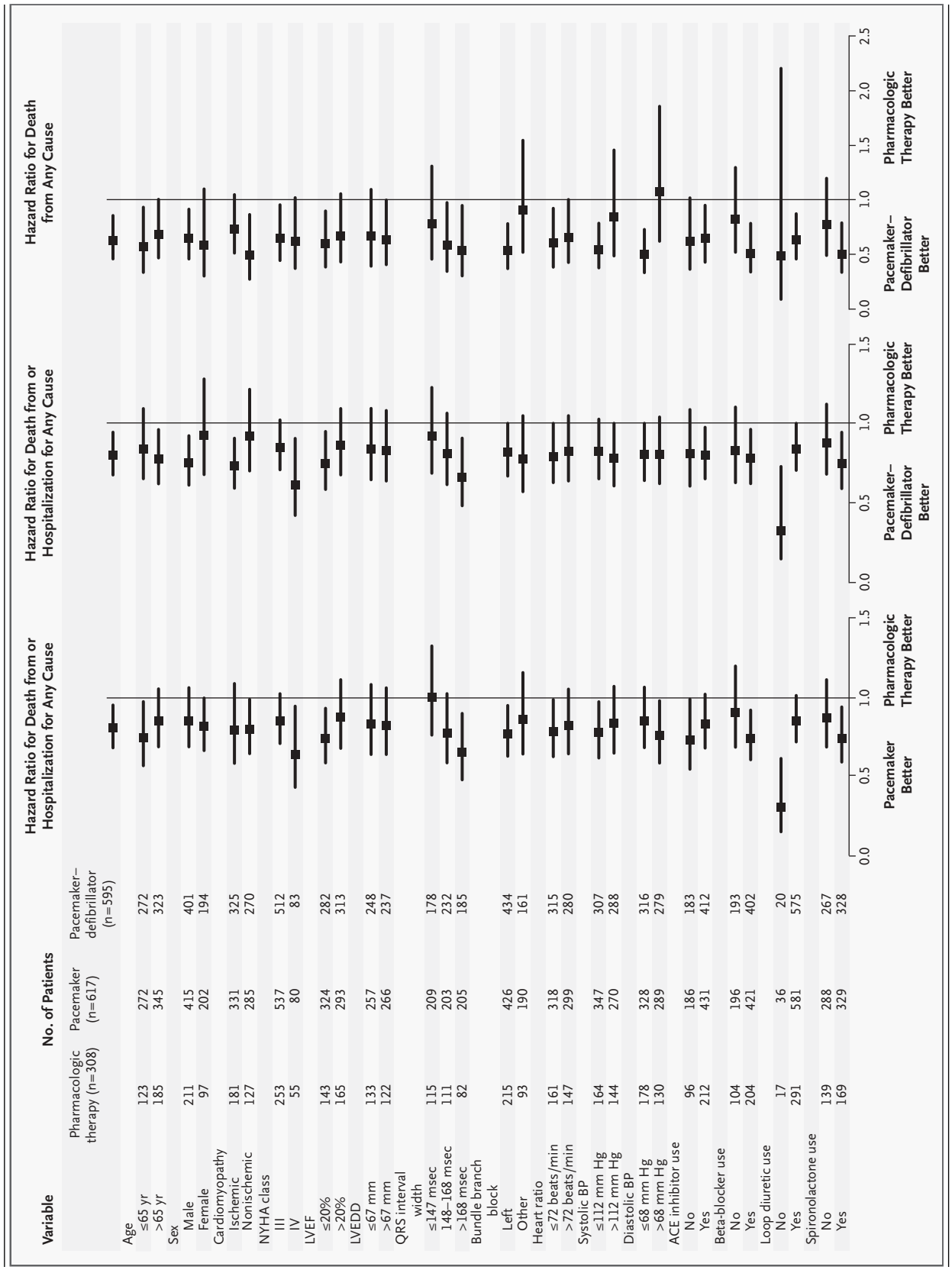
Not all patients had echocardiographically determined values for left ventricular end-diastolic dimension (LVEDD). NYHA denotes New York Heart Association, LVEF left ventricular ejection fraction, BP blood pressure, and ACE angiotensin-converting enzyme.

Five deaths (0.8 percent of enrolled patients) in the pacemaker group and three (0.5 percent) in the pacemaker–defibrillator group were adjudicated as related to procedural complications. The mortality rates 30 days after randomization were similar among the three groups: 1.0 percent in the pacemaker group and 1.8 percent in the pacemaker–defibrillator group, as compared with 1.2 percent in the pharmacologic-therapy group ($P=0.34$ and $P=0.79$, respectively).

WITHDRAWAL FROM THE STUDY AND LENGTH OF FOLLOW-UP

The withdrawal rate differed among the groups: 26 percent of patients in the pharmacologic-therapy group withdrew, as compared with 6 percent of those in the pacemaker group and 7 percent of those in the pacemaker–defibrillator group. For patients who had not reached a primary end point at the time of withdrawal, the rate was 13 percent, 2 percent, and 2 percent, respectively. In the pharmacologic-therapy group, there were no significant differences in baseline characteristics between patients who withdrew from the study and those who did not, with the exception of the prevalence of ischemic cardiomyopathy (68 percent vs. 55 percent).

After consent was again obtained ("reconsent"), the status for the primary end point through the end of the study was known for 91 percent of the patients in the pharmacologic-therapy group and 99 percent of the patients in each of the other groups; data on mortality were complete for 96 percent of the patients in the pharmacologic-therapy group and 99



percent of the patients in each of the other groups. Including the data gathered after reconsent, the median duration of follow-up for the primary end point was 11.9 months in the pharmacologic-therapy group, 16.2 months in the pacemaker group (P<0.001 for the comparison with the pharmacologic-therapy group), and 15.7 months in the pacemaker–defibrillator group (P<0.001 for the comparison with the pharmacologic-therapy group). For mortality, the median duration of follow-up was 14.8 months, 16.5 months (P=0.028), and 16.0 months (P=0.129), respectively.

PRIMARY END POINT

Eighteen first hospitalizations in the pharmacologic-therapy group and one in the pacemaker group were considered by the end-points committee to be elective for the purpose of device implantation or upgrade and were excluded from the end-point analysis. A total of 1020 primary end points were analyzed. The 12-month rate of the primary composite end point of death from any cause or hospitalization for any cause was 68 percent in the pharmacologic-therapy group as compared with 56 percent in the pacemaker group (hazard ratio for the primary end point, 0.81; 95 percent confidence interval, 0.69 to 0.96; P=0.014; adjusted P=0.015 by the log-rank test) and 56 percent in the pacemaker–defibrillator group (hazard ratio, 0.80; 95 percent confidence interval, 0.68 to 0.95; P=0.010; adjusted P=0.011) (Fig. 1A). Thus, either type of cardiac-resynchronization therapy reduced the risk of the primary end point by approximately 20 percent (Fig. 1A).

SECONDARY END POINT

In the pharmacologic-therapy group, 77 of 308 patients died (25 percent) during the entire study period; 58 (75 percent) of these deaths were classified as due to cardiac causes. The one-year mortality rate in the pharmacologic-therapy group was 19 percent. The effect of cardiac-resynchronization therapy on the secondary end point of death from any cause is shown in Figure 1B. The implantation of a pacemaker was associated with a marginally significant reduction in the risk of death from any cause (hazard ratio, 0.76; 95 percent confidence interval, 0.58 to 1.01; P=0.059; adjusted P=0.06), whereas the implantation of a pacemaker–defibrillator was associated with a significant, 36 percent reduction in risk (hazard ratio, 0.64; 95 percent confidence interval, 0.48 to 0.86; P=0.003; adjusted P=0.004).

DEATH FROM OR HOSPITALIZATION FOR CARDIOVASCULAR CAUSES OR HEART FAILURE

Data on the outcome measure of death from or hospitalization for cardiovascular causes are shown in Figure 1C. The 12-month event rate was 60 percent in the pharmacologic-therapy group. As compared with optimal pharmacologic therapy, cardiac-resynchronization therapy with a pacemaker reduced the risk by 25 percent (hazard ratio, 0.75; 95 percent confidence interval, 0.63 to 0.90; P=0.002), whereas cardiac-resynchronization therapy with a pacemaker–defibrillator reduced the risk by 28 percent (hazard ratio, 0.72; 95 percent confidence interval, 0.60 to 0.86; P<0.001).

Data for the rates of death from or hospitalization for heart failure are shown in Figure 1D. The 12-month event rate was 45 percent in the pharmacologic-therapy group. As compared with optimal pharmacologic therapy, cardiac-resynchronization therapy with a pacemaker reduced the risk by 34 percent (hazard ratio, 0.66; 95 percent confidence interval, 0.53 to 0.87; P=0.002), whereas cardiac-resynchronization therapy with a pacemaker–defibrillator reduced the risk by 40 percent (hazard ratio, 0.60; 95 percent confidence interval, 0.49 to 0.75; P<0.001).

SUBGROUP ANALYSES

As compared with optimal pharmacologic therapy alone, the addition of cardiac-resynchronization therapy with either a pacemaker or a pacemaker–defibrillator (Fig. 2) resulted in hazard ratios for the primary end point according to baseline characteristics that were consistently below 1.0, indicating consistent efficacy for each device. Both devices resulted in a progressive lowering of the hazard ratio with an increasing QRS interval. Cardiac-resynchronization therapy reduced the risk of the primary end point among both patients with and those without ischemic cardiomyopathy, and cardiac-resynchronization therapy in combination with beta-blockers or spironolactone reduced the risk further than did cardiac-resynchronization therapy in combination with other agents.

Hazard ratios for the secondary end point of death from any cause, according to baseline characteristics for the pacemaker–defibrillator group as compared with the pharmacologic-therapy group, are shown in Figure 2. An increasing QRS interval had less of an effect on the mortality secondary end point in the pacemaker–defibrillator group than it did on the primary end point for either device, and

again, patients who received a pacemaker–defibrillator and beta-blockers or spironolactone tended to have a lower risk of death from any cause than their counterparts who received other agents. Among patients with nonischemic cardiomyopathy, pacemaker–defibrillator therapy was associated with a significantly lower risk of death from any cause, as compared with pharmacologic therapy (hazard ratio, 0.50; 95 percent confidence interval, 0.29 to 0.88; P=0.015). Among patients with ischemic cardiomyopathy, the reduction in the risk of death from any cause was not statistically significant in the pacemaker–defibrillator group, as compared with the pharmacologic-therapy group (hazard ratio, 0.73; 95 percent confidence interval, 0.52 to 1.04; P=0.082). A test for interaction between the treatment effects in the subgroup with nonischemic cardiomyopathy and the subgroup with ischemic cardiomyopathy was not statistically significant. In the pacemaker group (data not shown), as compared with the pharmacologic-therapy group, the implantation of a device reduced the risk of death from any cause by 9 percent in the subgroup with nonischemic cardiomyopathy (hazard ratio, 0.91; 95 percent confidence interval, 0.55 to 1.49; P=0.70), as compared with 28 percent in the subgroup with ischemic cardiomyopathy (hazard ratio, 0.72; 95 percent confidence interval, 0.51 to 1.01; P=0.058).

OTHER OUTCOME VARIABLES

As shown in Table 2, the NYHA class, the distance walked in six minutes, and the quality of life, as assessed by the Minnesota Living with Heart Failure questionnaire, were significantly better in both cardiac-resynchronization therapy groups than in the pharmacologic-therapy group at three and six months. Median changes in systolic blood pressure from baseline to 3, 6, and 12 months in the two cardiac-resynchronization therapy groups were also significantly better than those in the pharmacologic-therapy group (Fig. 3A). There were no significant changes in diastolic pressure in any of the groups (Fig. 3B).

ADVERSE EVENTS

A total of 61 percent of patients in the pharmacologic-therapy group had a moderate or severe adverse event from any cause, as compared with 66 percent of patients in the pacemaker group (P=0.15) and 69 percent of patients in the pacemaker–defibrillator group (P=0.03). There was no significant difference between cardiac-resynchronization therapy groups in the proportion of patients with moderate or severe device-related adverse events (P=0.42).

Moderate or severe adverse events related to the implantation procedure occurred in 10 percent of patients in the pacemaker group and 8 percent of

Table 2. Changes in Distance Walked in Six Minutes, Quality of Life, and New York Heart Association (NYHA) Class.

Variable	3 Months			6 Months		
	No. of Patients	Mean ±SD Change	P Value*	No. of Patients	Mean ±SD Change	P Value*
Increase in distance walked in 6 min (m)						
Optimal pharmacologic therapy	170	9±84	—	142	1±93	—
Cardiac-resynchronization therapy						
Pacemaker	422	33±99	<0.001	373	40±96	<0.001
Pacemaker–defibrillator	420	44±109	<0.001	378	46±98	<0.001
Increase in quality of life (%)†						
Optimal pharmacologic therapy	243	−9±21	—	207	−12±23	—
Cardiac-resynchronization therapy						
Pacemaker	510	−24±27	<0.001	460	−25±26	<0.001
Pacemaker–defibrillator	514	−24±28	<0.001	478	−26±28	<0.001
Improvement in NYHA class symptoms (%)						
Optimal pharmacologic therapy	242	24	—	199	38	—
Cardiac-resynchronization therapy						
Pacemaker	551	58	<0.001	489	61	<0.001
Pacemaker–defibrillator	543	55	<0.001	497	57	<0.001

* P values are for the comparison with the group given optimal pharmacologic therapy.
† The quality of life was measured with the Minnesota Living with Heart Failure questionnaire. This questionnaire contains 21 questions regarding patients' perceptions of the effects of heart failure on their daily lives. Questions are rated on a 6-point scale (total score, 105), with higher scores indicating a poor quality of life.

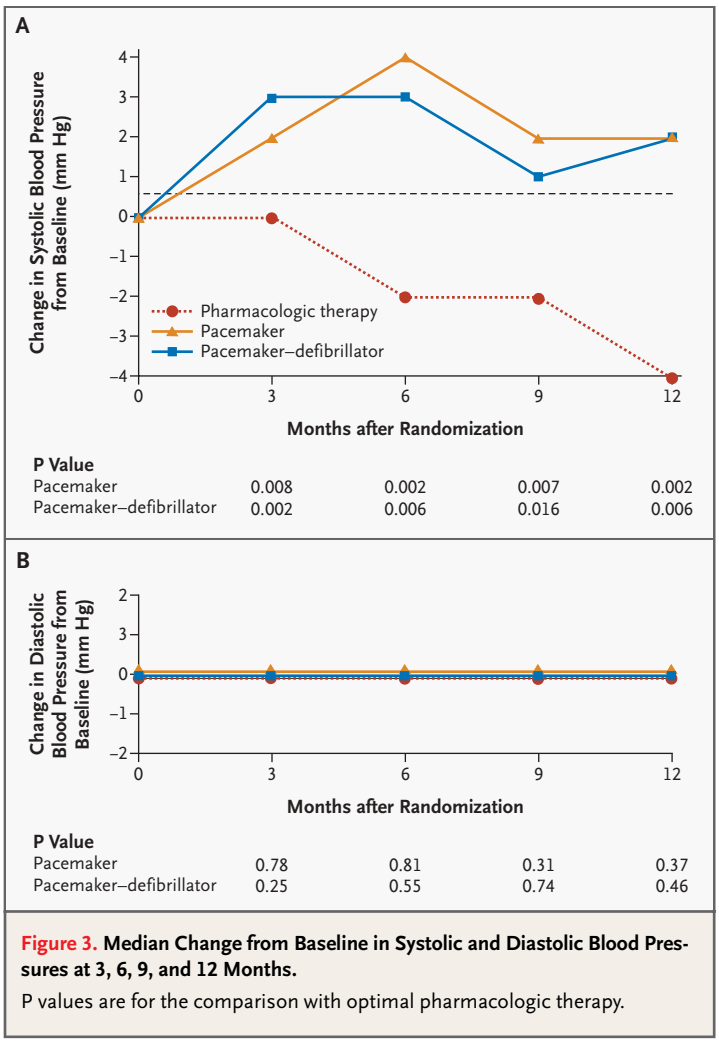


Figure 3. Median Change from Baseline in Systolic and Diastolic Blood Pressures at 3, 6, 9, and 12 Months.

P values are for the comparison with optimal pharmacologic therapy.

those in the pacemaker–defibrillator group. Included in these events were coronary venous dissection (0.3 percent in the pacemaker group and 0.5 percent in the pacemaker–defibrillator group), coronary venous perforation (1.1 percent and 0.8 percent, respectively), and coronary venous tamponade (0.5 percent and 0.3 percent, respectively).

DISCUSSION

Our results indicate that the use of biventricular stimulation to resynchronize left ventricular contraction can improve major clinical outcomes in patients with a prolonged QRS interval and advanced, symptomatic heart failure as a result of moderate-to-severe left ventricular systolic dysfunction. The primary composite end point of the COMPANION trial — the rate of death from any cause or hospitalization for any cause — was reduced by approximately 20 percent in both groups that received cardiac-resynchronization therapy in addition to optimal pharmacologic therapy, as compared with the group that received optimal pharmacologic therapy alone. The even larger reduction in the outcome of death from or hospitalization for heart failure suggests that much of the reduction was related to the favorable effects of the devices on the clinical syndrome of heart failure. This is further supported by the augmentation of systolic blood pressure in these two groups, which was consistent with a favorable effect of cardiac-resynchronization therapy on systolic function.[6] The addition of a defibrillator to cardiac-resynchronization therapy did not appreciably affect the combined outcomes of death from or hospitalization for any cause, which are heavily influenced by the hospitalization components. However, the addition of a defibrillator to cardiac-resynchronization therapy incrementally increased the survival benefit, resulting in a substantial, 36 percent reduction in the risk of death (P=0.003), as compared with optimal pharmacologic therapy.

Each of the devices used in the study became commercially available during the trial. Since neither investigators nor patients were blinded in this trial, the subsequent effect was a disproportionately high rate of withdrawal from the pharmacologic-therapy group so that patients could receive cardiac-resynchronization therapy with one of these devices. This change was particularly common among patients with ischemic cardiomyopathy, for whom such treatment had become an option with the publication of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II).[16] We addressed the disproportionate withdrawal rate by excluding elective implantation of devices from analyses of the primary end point and other hospitalization end points and, when possible, again obtaining consent from patients who withdrew ("reconsent") so that we could complete the intention-to-treat analysis. The latter approach substantially increased the completeness of the data and greatly reduced the potential effect of the withdrawal rate on end-point analyses.

Our results extend those of earlier, short-term studies that evaluated the effects of cardiac-resynchronization therapy on exercise tolerance,[9-12] symptoms of heart failure,[9-12] and the quality of life.[9] Taken together, these data indicate that, in a population with advanced heart failure and an increased QRS interval, cardiac-resynchronization

therapy improves most major factors that affect the quality of life. Moreover, our data demonstrate that adding a defibrillator to cardiac-resynchronization therapy significantly reduces the risk of death. The clinical efficacy of cardiac-resynchronization therapy with a pacemaker–defibrillator is especially noteworthy, since the therapy was delivered in conjunction with the best evidence-based pharmacologic therapy for heart failure.

Before our study, the case for defibrillator therapy in patients with left ventricular dysfunction had been based on MADIT II,[16] which was conducted exclusively in a population with ischemic cardiomyopathy. We demonstrated a 36 percent reduction in the risk of death from any cause in the patients who received a pacemaker–defibrillator. When the patients were stratified according to the cause of heart failure, cardiac-resynchronization therapy with a pacemaker–defibrillator, as compared with optimal pharmacologic therapy, was associated with a 27 percent reduction in the risk of death from any cause in the subgroup with ischemic cardiomyopathy (hazard ratio for death, 0.73; 95 percent confidence interval, 0.52 to 1.04) and a 50 percent reduction in risk in the subgroup with nonischemic cardiomyopathy (hazard ratio, 0.50; 95 percent confidence interval, 0.29 to 0.88). The 27 percent reduction in risk is similar to the 31 percent reduction reported in MADIT II, whereas the 50 percent reduction provides evidence of the efficacy of adjunctive defibrillator therapy in patients with nonischemic cardiomyopathy.

In summary, in selected patients, cardiac-resynchronization therapy with a pacemaker or a pacemaker–defibrillator can improve the clinical course of chronic heart failure due to a dilated cardiomyopathy. The pacemaker is associated with a reduction in hospitalizations and symptoms and improved exercise tolerance and quality of life, and the addition of a defibrillator to cardiac-resynchronization therapy further reduces mortality. The decision of which of these two therapeutic options is appropriate for a particular setting is best determined on an individual basis by patients and their physicians.

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Dr. Krueger reports having received lecture fees from Guidant. Drs. Kass, Feldman, Boehmer, Saxon, De Marco, and Bristow are consultants to and report having received lecture fees from Guidant. Drs. White and DeMets are under contract to Guidant, and Dr. White holds equity in Guidant. Mr. DeVries is an employee of Guidant, and Dr. DiCarlo is an employee of Pfizer.

APPENDIX

The following investigators and institutions participated in the COMPANION trial (listed in descending order of the number of patients enrolled): S. Krueger, Bryan Medical Center, Lincoln, Nebr.; F. McGrew, Baptist Memorial, Memphis, Tenn.; L. Wagoner, University of Cincinnati, Cincinnati; J.K. Ghali, Willis-Knighton Hospital; Shreveport, La.; G.W. Botteron, St. Anthony's–St. Louis, Kirkwood, Mo.; P. Kirlin, Methodist Hospital of Indianapolis, Indianapolis; P. Fenster, University of Arizona Medical Center, Tucson; G. Kidwell, Akron General Medical Center, Akron, Ohio; S.O. Gottlieb, St. Joseph's Medical Center, Baltimore; P. Desai, Amarillo Heart Group, Amarillo, Tex.; M. Harvey, Presbyterian Hospital, Oklahoma City; J. Aranda, University of Florida, Gainesville; R. Starling, Cleveland Clinic Foundation, Cleveland; J. Coman, Hillcrest Medical Center, Tulsa, Okla.; D. Mann, Baylor and Veterans Affairs Medical Center, Houston; J.T. Heywood, Loma Linda University Medical Center, Loma Linda, Calif.; B. Lowes, University of Colorado Health Sciences Center, Denver; J.L. Anderson, Baptist Medical Center, Oklahoma City; J. Kennett, Boone Hospital–Missouri Heart Center, Columbia; P. Steiner, University of California San Francisco, San Francisco; A. Ciuffo, Sentera Norfolk General Hospital, Norfolk, Va.; A. Banks, United Hospital–St. Paul Heart Clinic, St. Paul, Minn.; G. Tomassoni, Central Baptist Hospital, Lexington, Ky.; D. Cannom, Good Samaritan Hospital, Los Angeles; K. Crossen, North Mississippi Medical Center, Tupelo; J.G. Rogers, Washington University–Barnes, St. Louis; M. Gilbert, University of Utah Medical Center, Salt Lake City; J. Franklin, Baylor–Dallas, Dallas; G. Hendrix, Medical University of South Carolina, Charleston; M. Johnson, Orlando Regional Medical Center, Orlando, Fla.; J. Zeigler, St. Mary's Hospital, Hobart, Ind.; K. McGrath, St. Joseph's Hospital, Atlanta; N. Erenrich, John F. Kennedy Medical Center, West Palm Beach, Fla.; J. Weber, Our Lady of Lourdes Medical Center, Camden, N.J.; F.W. Smart, Tulane Hospital and Clinic, New Orleans; S.P. Graham, Buffalo General Hospital, Buffalo, N.Y.; A. Smith, Emory University School of Medicine, Atlanta; J. Bailey, Presbyterian Hospital, Charlotte, N.C.; M. Jessup, Hospital of the University of Pennsylvania, Philadelphia; D. Steinhaus, St. Luke's Hospital, Kansas City, Mo.; J. Goldstein, William Beaumont Hospital, Royal Oak, Mich.; G.S. Greer, Baptist Medical Center–Arkansas Cardiology, Little Rock; J.P. Boehmer, Milton S. Hershey Medical Center, Hershey, Pa.; J. Finkle, Lankenau Hospital, Wynnewood, Pa.; A. Seals, Memorial Hospital, Jacksonville, Fla.; M. Kukin, Mount Sinai Medical Center, New York; G. Bhat, Jewish Hospital–University of Louisville, Louisville, Ky.; J. Chin, Mercy General Hospital, Sacramento, Calif.; A. Massumi, St. Luke's Episcopal Hospital, Houston; P.S. Bernstein, St. Luke's Medical Center, Milwaukee; R.L. Berkowitz, Hackensack University, Hackensack, N.J.; T.A. Frank, Carolinas Medical Center–The Sanger Clinic, Charlotte, N.C.; A. Interian, Jr., Jackson Memorial Hospital, Miami; D. Salerno, Memorial Hospital, Chattanooga, Tenn.; A. Heroux, Rush–Presbyterian–St. Luke's Medical Center, Chicago; D. Nabert, Baptist Memorial, Jacksonville, Fla.; M.A. Silver, Christ Hospital and Medical Center, Oaklawn, Ill.; D. Renlund, LDS Hospital, Salt Lake City; R. McBride, Cardiovascular Associates of Virginia, Roanoke; J. Steinberg, St. Luke's–Roosevelt, New York; M. Flemming, St. John Hospital–Detroit, St. Clair Shores, Mich.; B. Alpert, Western Pennsylvania Hospital, Pittsburgh; S. Khan, Cedars-Sinai Medical Center, Los Angeles; R. Corbisiero, Deborah Heart and Lung Center, Brown Mills, N.J.; J. Ruskin, Massachusetts General Hospital, Boston; G. Haas, Riverside Methodist Hospital, Columbus, Ohio; P. Fattal, St. Mary's Medical Center, Saginaw, Mich.; D. Chilson, Spokane Heart Institute, Spokane, Wash.; B.S. Clemson, St. Francis Medical Center, Peoria, Ill.; R. Bourge, University of Alabama, Birmingham; L. Miller, Arlington Hospital, Arlington, Va.; W. Colgate, Clinical Research Center, Sarasota, Fla.; J. Hare, Johns Hopkins Hospital, Baltimore; D. Pawlush, Pinnacle Health Hospitals, Wormleysburg, Pa.; C. Liang, Strong Memorial Hospital, Rochester, N.Y.; K. Roush, Toledo Hospital, Toledo, Ohio; C. O'Connor, Duke University Medical Center, Durham, N.C.; J.T. O'Brien, Fairfax Hospital, Falls Church, Va.; S. Erhlich, Mission Hospital Regional Medical Center, Mis-

sion Viejo, Calif.; J. Navas, Morton Plant, Clearwater, Fla.; R. Hershberger, Oregon Health Sciences University, Portland; R. Tung, Research Medical Center, Kansas City, Mo.; B. Jaski, Sharp Memorial Hospital, San Diego, Calif.; W. Hepp, Heart Center of Sarasota, Sarasota, Fla.; D. Haggman, Southwest Florida Regional Medical Center, Fort Myers; S. Bennett, Washington Hospital Center, Washington, D.C.; J. Sandberg, Lehigh Valley Hospital, Allentown, Pa.; R. Frantz, Mayo Clinic–Rochester, Rochester, Minn.; A. Labib, St. Elizabeth's Hospital, Youngstown, Ohio; R. Doshi, Sunrise Medical Center, Las Vegas; R. Oren, University of Iowa Hospitals and Clinics, Iowa City; K.F. Browne, Lakeland Regional Medical Center, Lakeland, Fla.; J. Beard, Providence Hospital, Columbia, S.C.; M. Borganelli, Sacred Heart Hospital, Pensacola, Fla.; S. Gottlieb, University of Maryland, Baltimore; C. Porter, University of Kansas Medical Center, Kansas City; S. Murali, University of Pittsburgh Medical Center, Pittsburgh; S. Menon, Christ Hospital, Cincinnati; K. Turk, St. Elizabeth Regional Medical Center, Lincoln, Nebr.; E. Prystowsky, St. Vincent Hospital, Indianapolis; B. Knight, University of Michigan Hospital, Ann Arbor; D. Wilber, Loyola University of Chicago, Maywood, Ill.; R. Malik, Marion General Hospital, Marion, Ohio; S. Klein, Moses H. Cone Memorial Hospital, Greensboro, N.C.; F. Abi-Samra, Ochsner Hospital, New Orleans; J. Bergin, University of Virginia, Charlottesville; M.T. Olivari, Abbott Northwestern, Minneapolis; J. Schmedtje, Carillion Medical Center, Roanoke, Va.; G. Michaud, Rhode Island Hospital, Providence; J. Holmberg, St. Joseph Hospital, Omaha, Nebr.; A. Anderson, University of Chicago, Chicago; P. Narayan, Veterans Affairs Medical Center, Washington, D.C.; E. Horn, Columbia Presbyterian Hospital, New York; J. Goldberger, Northwestern Memorial Hospital, Chicago; M. Ruder, Sequoia Hospital, Redwood City, Calif.; W. Mecca, St. Vincent Medical Center, Erie, Pa.; G. Fonarow, University of California Los Angeles Medical Center, Los Angeles; J. Dinerman, Huntsville Hospital, Huntsville, Ala.; D. Martin, Lahey Clinic, Burlington, Mass.; M. O'Shaughnessy, Parkview Memorial Center, Fort Wayne, Ind.; C. Sueta, University of North Carolina, Chapel Hill; F. Lee, Yale University School of Medicine, New Haven, Conn.; S. Greenberg, St. Francis Hospital, New York; T. Donohue, Hospital of St. Raphael, New Haven, Conn.; S. Chun, Stanford University Hospital, Stanford, Calif.; A. Zivin, Swedish Hospital, Seattle; J. Hayes, Marshfield Medical Research Foundation, Marshfield, Wis.; A. Greenspon, Thomas Jefferson University Hospital, Philadelphia; **Executive Committee** — M. Bristow (chair), A. Feldman, L. Saxon, T. DeMarco, D. Kass, J. Boehmer, D. Mann, S. Singh; **Mortality and Morbidity Committee** — P. Carson (chair), B. Jaski, J. Steinberg, C. O'Connor, J. Lindenfeld, J. Ghali; **Data and Safety Monitoring Board** — S. Goldstein (chair), W. Parmley, E. Powers, P. Wang, W. Brown; **Biostatisticians** (University of Wisconsin) — D. DeMets, S. Anderson, J. Barnet; **Clinical Cardiovascular Research** — B. White, A. Lwin; **Guidant Clinical Staff** — L. Voshage-Stahl, S. McQuillan, P. Yong, D. Breiter, F. Ecklund, K. Selander, J. Leigh.

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