Dual-Chamber Pacing or Ventricular Backup Pacing in Patients With an Implantable Defibrillator

The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial

The DAVID Trial Investigators*

Context Implantable cardioverter defibrillator (ICD) therapy with backup ventricular pacing increases survival in patients with life-threatening ventricular arrhythmias. Most currently implanted ICD devices provide dual-chamber pacing therapy. The most common comorbid cause for mortality in this population is congestive heart failure.

Objective To determine the efficacy of dual-chamber pacing compared with backup ventricular pacing in patients with standard indications for ICD implantation but without indications for antibradycardia pacing.

Design The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial, a single-blind, parallel-group, randomized clinical trial.

Setting and Participants A total of 506 patients with indications for ICD therapy were enrolled between October 2000 and September 2002 at 37 US centers. All patients had a left ventricular ejection fraction (LVEF) of 40% or less, no indication for antibradycardia pacemaker therapy, and no persistent atrial arrhythmias.

Interventions All patients had an ICD with dual-chamber, rate-responsive pacing capability implanted. Patients were randomly assigned to have the ICDs programmed to ventricular backup pacing at 40/min (VVI-40; n=256) or dual-chamber rate-responsive pacing at 70/min (DDDR-70; n=250). Maximal tolerated medical therapy for left ventricular dysfunction, including angiotensin-converting enzyme inhibitors and β-blockers, was prescribed to all patients.

Main Outcome Measure Composite end point of time to death or first hospitalization for congestive heart failure.

Results One-year survival free of the composite end point was 83.9% for patients treated with VVI-40 compared with 73.3% for patients treated with DDDR-70 (relative hazard, 1.61; 95% confidence interval [CI], 1.06-2.44). The components of the composite end point, mortality of 6.5% for VVI-40 vs 10.1% for DDDR-70 (relative hazard, 1.61; 95% CI, 0.84-3.09) and hospitalization for congestive heart failure of 13.3% for VVI-40 vs 22.6% for DDDR-70 (relative hazard, 1.54; 95% CI, 0.97-2.46), also trended in favor of VVI-40 programming.

Conclusion For patients with standard indications for ICD therapy, no indication for cardiac pacing, and an LVEF of 40% or less, dual-chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end point of death or hospitalization for heart failure.

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THE IMPLANTABLE CARDIOverter defibrillator (ICD) improves survival for most patients with life-threatening ventricular arrhythmias.[1] However, many of these patients have a reduced left ventricular ejection fraction (LVEF) and recurrent episodes of clinical congestive heart failure (CHF). In the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial, an admission to the hospital for an episode of CHF was highly predictive of subsequent death.[2]

The effectiveness of ICD therapy was established using single-chambered ICDs.[3-7] In these investigations, the bradycardia pacing rate was usually set below the intrinsic rate of the patient to avoid the detrimental hemodynamic consequences of single-chamber ventricular pacing and to preserve battery life.[8] Although the need for a pacemaker was not an exclusion for enrollment in the AVID Trial, the need for bradycardia pacing was overtly required in only 4% of the patients. Despite a paucity of evidence for need or benefit, most currently implanted ICDs are dual-chamber devices.[9]

Treatment of CHF has been improved by the routine administration of angiotensin-converting enzyme (ACE) inhibitors and β-adrenergic blocking agents.[10,11] However, treatment was

For editorial comment see p 3159.

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Box. Inclusion and Exclusion Criteria for Study Randomization*

Inclusion Criteria (1 of the following)

1. Documented VF and LVEF ≤40%
2. Syncopal sustained VT and LVEF ≤40%
3. Nonsyncopal VT and LVEF ≤40% and 1 of the following:
   a. Sustained VT, systolic blood pressure <80 mm Hg, or significant cardiac symptoms
   b. NSVT with significant symptoms and EPS-inducible sustained VT or VF
   c. NSVT (minimal or no symptoms) and EPS-inducible sustained VT or VF
4. Out-of-hospital unexplained syncope, heart disease, and EPS-inducible sustained VT or VF, and LVEF ≤40%
5. Hemodynamically stable sustained VT and LVEF ≤40%
6. EPS-inducible VT or VF within 6 weeks prior to randomization and LVEF ≤40%

All randomizations occurred in patients who had an index arrhythmia unrelated to transient or correctable causes and were either spontaneous or induced during an electrophysiologic study during the preceding 6 weeks.

Exclusion Criteria

1. Permanent pacemaker
2. Preexisting endocardial pacing leads
3. CABG, PCI, cardiac, or other arrhythmia surgery planned but not yet performed (temporary exclusion)
4. Symptomatic bradycardia or second- or third-degree AV block
5. Disqualifying atrial fibrillation
   a. Atrial fibrillation of unknown duration
   b. Atrial fibrillation of >6 months' duration
   c. Atrial fibrillation at the time of randomization
   d. Need for electrical or chemical cardioversion in the last month
6. Frequent, uncontrolled atrial tachyarrhythmia
7. Awaiting cardiac transplantation
8. Condition likely to limit cooperation
9. Geographically inaccessible
10. Enrolled in a conflicting study
11. Prisoner or ward of the state
12. Unable to give informed consent
13. Life expectancy <1 year

*VF indicates ventricular fibrillation; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; NSVT, nonsustained VT; EPS, electrophysiology study; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.

sometimes limited in previous ICD trials by bradycardia related to the chronotropic incompetence associated with coronary artery disease, β-blocker therapy, or by antiarrhythmic therapy for atrial or ventricular arrhythmias. Instead of adding a dual-chamber pacemaker to the single-chamber ICD, physicians often reduce the medication doses to prevent single-chamber right ventricular stimulation. Cardiac output is increased in proportion to heart rate, and atrial pacing has been shown to reduce the incidence of atrial fibrillation in some patients. These considerations were combined and produced the hypothesis that dual-chamber pacemakers would permit optimal drug therapy and improved hemodynamics and therefore would reduce CHF, heart failure hospitalizations, heart failure deaths, atrial fibrillation, strokes, ventricular arrhythmias, and total mortality.

This study evaluated patients with indications for ICD implantation but without indications for antibradycardia pacemaker therapy. We tested the hypothesis that aggressively treating left ventricular dysfunction with optimized drug therapy and with dual-chamber pacing could improve the combined end point of total mortality and heart failure hospitalization, compared with similarly optimized drug therapy supported by ventricular backup pacing.

METHODS

The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial was a multicenter, randomized, single-blinded, parallel-arm study of patients with ICDs, comparing VVI and DDDR paced modes.[12] Enrollment began in October 2000. Written informed consent was obtained from each patient. The study protocol was approved by the institutional review board at each institution. Target doses were specified for ACE inhibitor, β-blocker, and digitalis therapy.

Participants and ICD Implantation

All patients had a standard indication for ICD implantation for the treatment of ventricular tachyarrhythmias but without an indication for antibradycardia pacing. The study was designed to be adaptive to the rapidly changing indications for the ICD. Specifically, primary prevention indications were added to the original inclusion criteria during the course of the study. The inclusion and exclusion criteria are outlined in the BOX.

Transvenous dual-chamber pacemaker ICDs (Photon, Photon Micro, or Photon Atlas, St Jude Medical Inc, Sylmar, Calif) were implanted in all trial participants. Successful implantation of both the atrial and ventricular leads with a minimal defibrillation safety margin of 10 J was required before randomization.

Randomization

Any planned cardiac surgery (eg, ablation, endocardial resection, valve replacement, aneurysmectomy, revascularization) had to be completed before randomization. After successful ICD implantation, patients were randomly assigned to have the pacing function of the device initially programmed to the VVI mode with a lower rate of 40/min (VVI-40) without supraventricular tachycardia detection enhancements or

to the DDDR mode with a lower rate of 70/min (DDDR-70) and activation of supraventricular tachycardia detection enhancements.

This single-blind randomization (the patient blinded to pacing mode) was done centrally at the clinical trial center and was stratified by site, history of CHF, and history of atrial fibrillation. Within strata, randomization was based on permuted blocks with block size of 2 or 4, depending on the expected size of the stratum.

Programming

The intent of the DAVID Trial investigators was to allow flexibility of programming of the device so that the investigator could tailor the therapy to meet the clinical needs of the patient. However, some specific criteria were established to test the main hypothesis and provide for equivalent diagnostic data in both randomized assignments. Tachyarrhythmia detection was set to 150/min or slower, and diagnostics were set to collect atrial and ventricular bipolar electrograms and markers for all patients. However, the VVI-40 group was programmed to VVI with a lower rate of 40/min and supraventricular tachycardia (SVT) discrimination on the basis of the ventricular rate only. The DDDR-70 group was set to the DDDR mode with a base rate of 70/min, mode switching "on" and SVT discrimination to include atrial and ventricular intervals and relationships and ventricular electrogram morphology. All other parameters could be programmed according to the clinical judgment of the investigator.

Heart Failure Drug Therapy

Optimal pharmacologic therapy for left ventricular dysfunction and heart failure consisted of digoxin, diuretics, ACE inhibitors, and β-blockers. Initial and target doses for ACE inhibitors and β-blockers were defined in the protocol. Treatment adhered to the Heart Failure Society of America Practice Guidelines.[13]

ACE inhibitors were to be used as first-line agents for modification of the renin-angiotensin system. If a patient was unable to tolerate an ACE inhibitor (usually because of cough), an angiotensin II receptor blocker (ARB) was then to be tried. If neither an ACE inhibitor nor an ARB was tolerated, nitrates and hydralazine could be used for afterload reduction. β-Blockers were added after stabilization of the ACE inhibitor therapy. In the absence of local preference, metoprolol or carvedilol was administered.

Diuretics were added as needed. All patients with symptomatic CHF, New York Heart Association (NYHA) functional class II or III, were to receive digoxin, 0.125 mg/d. Spironolactone was to be administered at a dosage of 12.5 to 25 mg/d if a patient continued to have NYHA functional class III or IV CHF following maximum treatment with ACE inhibitors, β-blockers, digitalis, and diuretics, under close observation for occurrence of hyperkalemia.

Antiarrhythmic Drug Therapy and Other Therapy

Amiodarone was the preferred antiarrhythmic agent for both supraventricular and ventricular arrhythmias, but was given in as low a dose as possible to minimize the adverse effects of long-term administration. Antiarrhythmic medications for supraventricular tachycardia or atrial fibrillation at the time of randomization could be maintained, but prophylactic use of amiodarone for ambient ectopy, nonsustained ventricular tachycardia, and minimally symptomatic ventricular tachycardia was discouraged. Amiodarone for ventricular arrhythmias was given only for sustained or symptomatic episodes, or in an attempt to decrease ICD shocks. Warfarin was administered to patients who developed atrial fibrillation or who had a history of embolic events.

Ablation of the AV junction for rate control of atrial fibrillation appearing during the course of the study, of the atrium for atrial flutter, of the atrium for atrial fibrillation, or of the ventricle for ventricular tachycardia could also be implemented by the investigator during the course of follow-up, as clinically indicated.

Crossovers

Crossover from one pacing mode to another was considered only when compelling indications existed. Symptoms were treated by adjustment of both the rate and rate response of the ICD and the medications. If patients developed bradycardia in the VVI-40 group, negatively chronotropic medication doses were reduced or stopped before changing the pacing mode to VVIR. If patients developed unwanted tachycardia from the sensor, the sensor was reprogrammed to minimize this situation before reprogramming DDDR-70 randomized devices to the DDD mode. Crossover of the pacing mode required permission from the clinical trial center.

Objectives and Outcome Measures

The combined primary end point was freedom from death and absence of hospitalization for heart failure. The determination of heart failure hospitalization was made by an events committee, based on review of the hospital records with treatment group identifiers masked, and needed to satisfy both of the following criteria: (1) admission to hospital for more than 24 hours with a clinical history of worsening symptoms of heart failure as evidenced by clinical criteria including increased NYHA functional class, orthopnea, paroxysmal nocturnal dyspnea, edema, dyspnea on exertion, or gastrointestinal symptoms attributable to heart failure, and (2) 1 or more intensive treatment(s) for CHF within 24 hours of admission, such as intravenous diuretics, intravenous inotropic medications, or placement on the status 1 heart transplant list. Follow-up occurred every 3 months.

The events committee reviewed all hospitalizations meeting these 2 criteria, as well as any hospitalizations with admitting diagnosis of heart failure. Those judged by the committee to meet or to be equivalent to the above 2 conditions constituted a primary end point. Clinical death was considered to be when spontaneous respirations ceased and pulse and blood pressure disappeared.

Statistical Methods

The DAVID Trial used a 2-sided $\alpha = .05$ level test of the null hypothesis with monitoring for early rejection of the null hypothesis. The null hypothesis was that the time to death or hospitalization for treatment of heart failure would be similar in both treatment groups. Comparison was based on intention-to-treat. The log-rank statistic was used.[14]

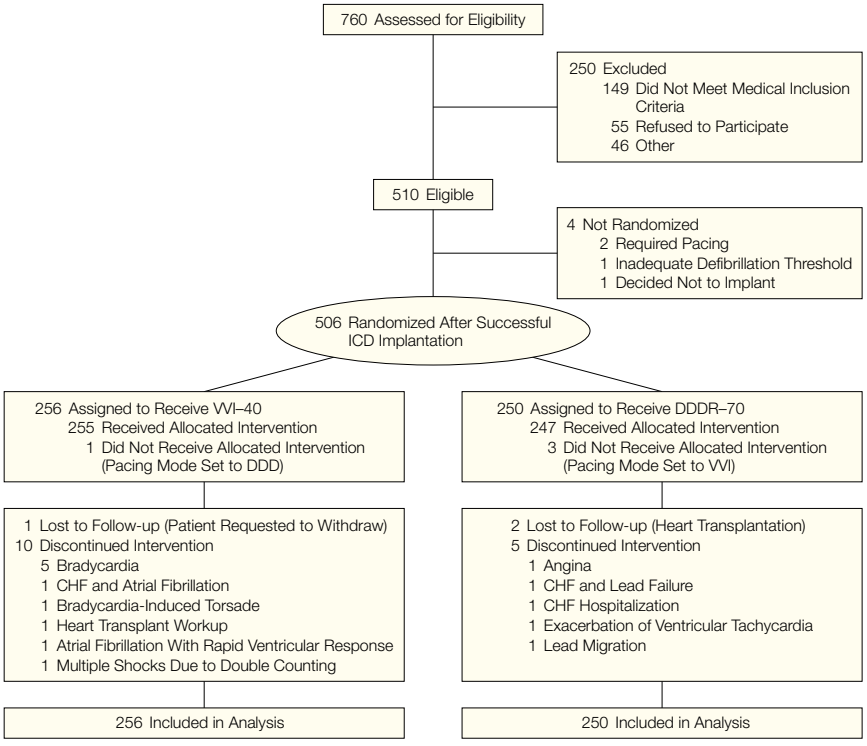
Based on data from the AVID database,[2] the control (VVI-40) survival rate free from death or hospitalization for CHF was expected to be 69.7% at 2 years. An absolute improvement of 8% was chosen as the alternative hypothesis, yielding a treatment group survival rate of 77.7% at 2 years, a relative improvement of 26.4%. With uniform accrual over 1.25 years and follow-up to a common termination date at approximately 3.5 years from start of enrollment, a desired power of 0.85 to detect the alternative, and a moderately conservative (up to 6 interim evaluations) sequential monitoring plan, the study needed to recruit 800 patients (625 per year). The study would have a maximum duration of 3.77 years, an expected duration under the null (DDDR = VVI) of 3.25 years, and an expected duration under the alternative (DDDR better than VVI) of 2.72 years. Approximately 300 primary end point events were expected during the course of the study.[15]

Event rates were estimated by the product-limit method (SPSS version 10; SPSS Inc, Chicago, Ill). In addition to the primary analysis, standard failure-time regression models were to be used for secondary analyses of the primary end points as well as for subgroup and exploratory analyses.[14]

Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) consisted of 4 individuals, including an arrhythmia expert, 2 heart failure experts, and a statistician/trialist. The primary responsibility of the DSMB was to monitor patient safety. However, board members were also responsible for reviewing the results of the sequential monitoring and making recommendations to the steering committee about continuation of the trial.

Figure 1. Flow of Patients Evaluated for the DAVID Trial



CHF indicates congestive heart failure; ICD, implantable cardioverter defibrillator. Many other patients would have been assessed and eligible, but for reasons related to a hospital's bulk purchase agreements, another manufacturer's device was to be used.

RESULTS

Discontinuation of the Trial

On September 27, 2002, the DSMB unanimously recommended stopping patient enrollment into the DAVID Trial. On September 30, the executive subcommittee of the steering committee accepted and implemented that recommendation. The primary consideration in the DSMB decision was that the conditional power for the original alternative (DDDR-70 being better than VVI-40) was less than 10%. Although the formal sequential monitoring boundary had not been crossed, a trend ($P \leq .03$) toward worse outcome with DDDR-70 pacing was established and was consistent with recently published corroborative data.[16,17]

Baseline Characteristics

A total of 506 patients were enrolled and randomized in the trial (FIGURE 1). The baseline characteristics of the randomized patients, outlined in TABLE 1, are representative of ICD recipients in previous trials.[3-7] The exceptions are related to the exclusion of patients with previous pacemaker therapy, significant bradycardia, sustained atrial tachyarrhythmias, and normal ventricular function. The mean age was 65 years, and the majority of patients were men with a history of coronary disease, myocardial infarction, hypertension, and hyperlipidemia. The mean LVEF was 27%. Half were NYHA functional class I, and only approximately 12% were functional class III-IV. Although the electrocardiogram had an average intrinsic QRS duration of 120 ms, 30.8% of patients had a QRS duration of at least 130 ms and 11.0% and 16.5% had a right or a left bundle-branch block pattern, respectively. The baseline mea-

surements were balanced in the 2 randomized groups.

Almost all patients were given pharmacologic therapy for left ventricular dysfunction. Only 4% of the patients ended the index hospitalization without β-blockers, ACE inhibitors, or ARBs. At hospital discharge, 80% had started taking β-blocking drugs; 83%, ACE inhibitor or ARB medications; 42%, digitalis; 54%, diuretics; 25%, nitrates; and 31%, antiarrhythmic drugs. There were no differences in drug use at hospital discharge (except diuretics: 49.4% in the DDDR arm vs 58.2% in the VVI arm, $P=.05$).

Subsequent to randomization, but during the baseline hospitalization, new or worsened CHF occurred in 4.2% of patients in the DDDR-70 group vs 0.8% of patients in the VVI-40 group. This new or worsened CHF occurring before discharge from the initial hospitalization was not counted as a primary end point. Only CHF occurring after discharge from any ICD implantation hospitalization counted toward our primary end point outlined below. Recurrent ventricular arrhythmias requiring therapy during the hospitalization for ICD implantation occurred in 7.5% of the DDDR-70 group and 5.9% of the VVI-40 group. Myocardial infarction during this initial hospitalization occurred in 3.8% of DDDR patients and 3.2% of VVI patients.

Follow-up Data

Median follow-up was 8.4 months (range, 0-23.6 months). Severe adverse events within 30 days of the original hospitalization for ICD implantation were equally distributed between the 2 groups, except for an apparent increase in early death of 2.2% (n=5) in the DDDR-70 group compared with 0.8% (n=2) in the VVI-40 group. Late complications of ICD implantation were rare in both groups.

In general, drug exposure at 6 months was similar in the 2 groups (TABLE 2). Drug formulations and doses for patients completing titration of ACE inhibitors, β-blockers, digoxin, furosemide, and spironolactone were also similar between groups.

Reflective of the programmed parameters, the electrocardiograms and ICD interrogations of the 2 groups showed major differences in the prevailing rhythm (TABLE 3). More DDDR patients exhibited right ventricular stimulation. Crossovers were rare in both groups, with only 5 DDDR patients having their pacing mode changed compared with 10 patients in the VVI arm.

Primary End Point

Primary end point event rates are shown in FIGURE 2A. The VVI-40 patients had

Table 1. Patient Baseline Characteristics*

Characteristic	VVI (n = 256)	DDDR (n = 250)	*P* Value
Age, mean (SD), y	66 (11)	64 (11)	.19
Male, No./total (%)	189/233 (81)	192/223 (86)	.15
Clinical history, No. (%)	(n = 233)	(n = 223)	
Ventricular fibrillation	9 (4)	8 (4)	.88
Ventricular tachycardia	19 (8)	37 (17)	.006
Atrial fibrillation or flutter	28 (12)	35 (16)	.26
Myocardial infarction	155 (67)	158 (71)	.32
Congestive heart failure	131 (56)	130 (58)	.66
Hypertension	148 (64)	135 (61)	.51
Diabetes	66 (28)	76 (34)	.19
Unexplained syncope	32 (14)	33 (15)	.75
Hyperlipidemia	135 (58)	128 (57)	.91
Coronary artery disease	196 (84)	186 (83)	.84
Hypertrophic cardiomyopathy	2 (1)	3 (1)	.62
Dilated cardiomyopathy	36 (16)	34 (15)	.95
Left ventricular ejection fraction, mean (SD), %	28 (8)	26 (8)	.17
	(n = 253)	(n = 241)	
No angina, No. (%)	174 (69)	150 (62)	.13
NYHA functional class, No. (%)			
I	127 (50)	112 (47)	.63†
II	98 (39)	97 (40)	
III or IV	28 (11)	32 (13)	
Electrocardiographic results, mean (SD)			
Rate, beats/min	72 (15)	73 (16)	.43
PR, ms	183 (38)	185 (39)	.51
QRS, ms	118 (27)	119 (27)	.71
QTc, ms	441 (42)	444 (41)	.36
Bundle-branch block, No./total (%)	59/241 (25)	70/233 (30)	.17
Indications for ICD therapy, No. (%)	(n = 256)	(n = 250)	
Ventricular fibrillation	48 (19)	44 (18)	.31†
Syncopal VT	17 (7)	16 (6)	
Symptomatic sustained VT	42 (16)	57 (23)	
Symptomatic NSVT + EPS positive	23 (9)	13 (5)	
Asymptomatic NSVT + EPS positive	63 (25)	57 (23)	
Unexplained syncope + EPS positive	37 (15)	44 (18)	
Hemodynamically stable VT	26 (10)	19 (8)	
Drugs at time of index arrhythmia	(n = 233)	(n = 223)	
Antiarrhythmic drugs	20 (9)	39 (18)	.005
β-Blocker	127 (55)	132 (59)	.31
ACE inhibitor	129 (55)	136 (61)‡	.20
Angiotensin II receptor blocker	18 (8)	17 (8)‡	.98
Calcium channel blocker	31 (13)	31 (14)‡	.84

*VVI indicates ventricular backup pacing; DDDR, dual-chamber rate-responsive pacing; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; NSVT, nonsustained VT; EPS, electrophysiology study; and ACE, angiotensin-converting enzyme.
†Global test for differences across categories.
‡Calculated in 222 patients.

fewer occurrences of the composite end point—death or hospitalization for new or worsened CHF (relative hazard, 1.61; 95% CI, 1.06-2.44; $P \leq .03$). One-year survival free of the composite end point was 83.9% for VVI-40 patients compared with 73.3% for DDDR-70 patients. Rates of CHF hospitalization (13.3% for VVI-40 vs 22.6% for DDDR-70 at 1 year), with patients censored at the time of death, are shown in Figure 2B, and the death rates (6.5% for VVI-40 vs 10.1% for DDDR-70 at 1 year) are displayed in Figure 2C. The CHF hospitalization differences did not appear to emerge until after the sixth month of follow-up, but the mortality curves diverged earlier after randomization. Although the VVI-40 patients had fewer events, the component end points (death [relative hazard, 1.61; 95% CI, 0.84-3.09; $P = .15$] and CHF hospitalization [relative hazard, 1.54; 95% CI, 0.97-2.46; $P = .07$]) did not individually reach statistical significance. The VVI group had 15 deaths and 30 hospitalizations for CHF compared with 23 deaths and 43 hospitalizations for CHF in the DDDR group.

The relationship between the percentage of right ventricular paced beats and the composite outcome variable in the DDDR-70 group was also explored. Patients who survived to the 3-month follow-up had worse 12-month event-free rates when the percentage of right ventricular pacing by ICD interrogation was 41% to 100% (75.9%) than when less than 40% (86.9%) ($P = .09$).

Table 2. Drugs Administered at 6 Months After Randomization*

Drug Therapy	No. (%) VVI (n = 156)	No. (%) DDDR (n = 149)	*P* Value
ACE inhibitor or ARB	131 (84)	130 (87)	.42
β-Blocker	134 (86)	126 (85)	.74
ACE inhibitor, ARB, or β-blocker	152 (97)	147 (99)	.44
Digoxin	64 (41)	63 (42)	.82
Diuretic	100 (64)	96 (64)	.95
Nitrate	39 (25)	33 (22)	.56
Spironolactone	23 (15)	32 (22)	.13
Amiodarone	36 (23)	47 (32)	.10
Sotalol	11 (7)	3 (2)	.04
Other antiarrhythmic drug	1 (1)	3 (2)	.29

*ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. A total of 176 VVI and 174 DDDR patients had been in the trial long enough to have a 6-month follow-up due. Follow-up data have not yet been verified and entered into the database for 20 and 25 of these patients, respectively.

Table 3. Follow-up ECG and ICD Results*

	VVI (n = 137)	DDDR (n = 140)	*P* Value
ECG (6 mo After Randomization)			
Sinus, No./total (%)	133/137 (97.1)	58/138 (42.0)	<.001
Paced, No. (%)	5 (3.6)	100 (71.4)	<.001
Atrial	2 (1.5)	83 (59.3)	<.001
Ventricular	4 (2.9)	78 (55.7)	<.001
Atrial fibrillation/flutter, No. (%)	0	3 (2.1)	.09
PR, mean (SD), ms	189 (43)	174 (34)	.004
QRS, mean (SD), ms	117 (29)	134 (39)	<.001
QTc, mean (SD), ms	434 (38)	452 (56)	.002
LBBB unpaced, No./total (%)	14/133 (10.5)	5/51 (9.8)	.89
RBBB unpaced, No./total (%)	11/133 (8.3)	4/51 (7.8)	.92
ICD Counters, % Beats Ventricular Paced, Mean (SD)			
3 mo	1.5 (8.0) (n = 193)	57.9 (35.8) (n = 188)	<.001
6 mo	0.6 (1.7) (n = 150)	59.6 (36.2) (n = 150)	<.001
12 mo	3.5 (14.9) (n = 78)	58.9 (36.0) (n = 77)	<.001

*ECG indicates electrocardiogram; ICD, implantable cardioverter defibrillator; LBBB, left bundle-branch block; and RBBB, right bundle-branch block.

COMMENT

Multiple studies have confirmed the benefit of ICDs for the treatment of patients who have already experienced serious ventricular arrhythmias (secondary prevention) as well as for patients at risk of ventricular arrhythmias (primary prevention).[3-7,16] Nevertheless, many ICD patients continue to have frequent episodes of CHF and heart failure–related mortality. With the exception of half of the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) ICD patients,[16] all of the ICD clinical trials documented improved survival using single-chamber ventricular pacing ICDs. These devices were programmed almost exclusively to permit intrinsic ventricular activation and inhibit right ventricular pacing.

Pacing modes have been compared in many studies of patients who have an indication for pacing. Andersen et al[18] evaluated the differences between AAI and VVI pacing for patients with the sick sinus syndrome. AAI pacing produced slightly better survival and was associated with a lower occurrence of severe CHF. The Pacemaker Selection in the Elderly[19] study compared VVI pacing with DDD pacing, with a better quality of life found in the patients with sinus node dysfunction treated with DDD pacing. However, there was no difference in overall outcome with respect to cardiovascular events or death. Single-chamber ventricular pacing has been compared with dual-chamber pacing in other studies,[19] but, in general, the improvements with DDD pacing have been modest at best. These studies suggest that atrioventricular synchrony may have some advantages, particularly reductions in the incidence of atrial fi-

brillation, but only the Danish pacemaker study evaluated the effect of right ventricular pacing compared with intrinsic ventricular activation through the His-Purkinje conduction network.[18]

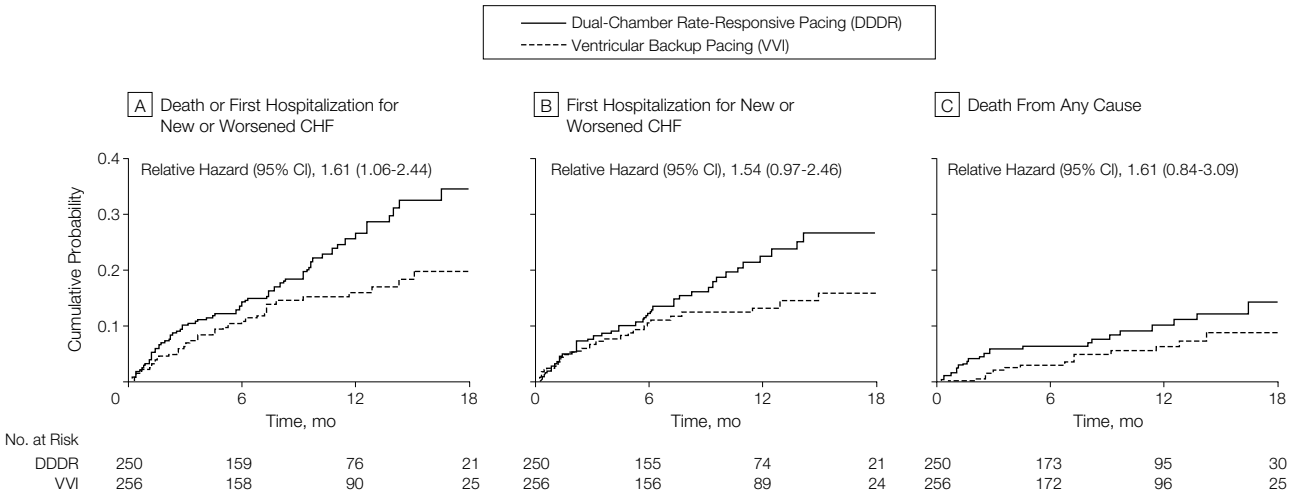
There were 2 distinct patient populations enrolled in the pacemaker mode selection and the ICD trials. Patients in the pacemaker trials required antibradycardia pacing, whereas only a small minority of the patients in the defibrillator trials had or developed the need for antibradycardia stimulation. A second difference is that left ventricular function was normal or near normal in most of the pacemaker trials but severely impaired in a large majority of the patients enrolled in the defibrillator trials. These 2 differences may contribute to the different clinical outcomes observed.

Not all patients in the pacemaker studies were completely pacemaker dependent, but the need for bradycardia support was evenly divided between the randomized groups. The Canadian Trial of Physiologic Pacing showed that the benefit of DDDR pacing was best demonstrated in patients who were paced a majority of the time.[20] However, recent data from the MOST (Mode Selection Trial in Sinus Node Dysfunction) pacemaker trial suggested that increased heart failure hospitalization was associated not with the pacing mode but with the prevalence of more than 40% right ventricular pacing.[21] Similarly, MADIT-II, the only ICD trial that included dual-chamber ICDs, reported that heart failure hospitalization was also associated with the presence of an ICD.[16] These data suggest that right ventricular stimulation may promote heart failure progression. Right ventricular stimulation may be more deleterious in patients with advanced left ventricular dysfunction, such as patients requiring ICD therapy.

Recent attention has been directed toward so-called resynchronization therapy, that is, pacing both the right and left ventricles simultaneously to improve the depolarization and contraction patterns in patients with NYHA functional class III-IV congestive heart failure and wide QRS durations. Resynchronization therapy applied to patients either with or without indications for ICDs has demonstrated improvement in functional status, including the 6-minute walk, NYHA functional class, Minnesota Living with Heart Failure quality of life, peak treadmill exercise oxygen consumption, and a reduction in heart failure hospitalization.[22-24]

We sought to compare intrinsic rhythm with ventricular backup VVI pacing with DDDR pacing in patients with left ventricular dysfunction, which translates into: Should ICDs with dual-chamber or single-chamber pacemaker function be implanted in these patients? Inherent in the hypothesis was that the DDDR mode with a lower rate of 70/min would provide rate support to increase cardiac output, suppress atrial and ventricular arrhythmias, and permit optimization of medications with negative chronotropic potential, such as the β-adrenergic-blocking drugs, sotalol, and amiodarone. The VVI mode could have provided the rate support if programmed at 70/min but at the expense of atrioventricular dyssynchrony. The sample size estimate for the DAVID trial used the equivalent end point (total mortality or CHF hospitalization) derived from the AVID ICD population.[2] The event-free survival rate for the VVI-40 group of the DAVID Trial was identical to that for patients randomized to receive the ICD in AVID, which was also programmed to VVI-40. In retrospect, the right ventricular

Figure 2. Survival to Main End Points in the Trial



For all plots, time zero is the day of randomization. CI indicates confidence interval. A, Survival to death or first hospitalization for congestive heart failure (CHF). Unadjusted $P=.02$; adjusted for sequential monitoring, $P=.03$. B, Survival to first hospitalization for CHF. Patients are censored at death. Log-rank $P=.07$. C, Survival to death from any cause. Log-rank $P=.15$.

stimulation intrinsic to the DDDR mode of pacing in the DAVID Trial imposed desynchronization therapy on these patients with existing significant ventricular dysfunction.

The specific programming choices could have affected the results. The lower rate for DDDR pacing was set to 70/min, and the atrioventricular interval (modifiable, but most commonly set at 180 ms) did not permit intrinsic conduction and activation of the ventricles in most patients. Although the QRS interval before pacing was slightly prolonged, 120 ms at baseline, it was not nearly as long as the QRS in most of the studies of biventricular pacing in CHF (averaging >160 ms). Overall, nearly 60% of all ventricular beats were paced in the DDDR-70 group compared with 1% in the VVI-40 group. Furthermore, the outcome appeared to worsen as the percentage of paced beats increased. It is possible that the outcome would have been different if the atrioventricular interval had been lengthened to allow intrinsic conduction.

Three aspects of DDDR pacing may be responsible for its detrimental impact on heart failure and mortality: (1) the heart rate is increased due to atrial pacing; (2) the PR interval is reduced due to ventricular pacing at the end of the AV interval; and (3) the ventricular electrical activation proceeds from the right ventricular apex instead of through the existing conduction system. It seems most likely that a slight increase in atrial rate would only increase cardiac output, although it could alter ventricular filling. Altering the AV interval may improve or reduce cardiac output, but it has generally been demonstrated to have a small effect. However, recent data summarized above suggest that right ventricular stimulation is maladaptive and causes increased heart failure by the mechanism of ventricular desynchronization.

There is a difference between saying that DDDR pacing is not beneficial for patients similar to those enrolled in the DAVID Trial and that there is no value to the atrial lead. It was initially proposed that heart failure therapy would be enhanced, atrial fibrillation would be reduced, ventricular arrhythmias would be reduced when heart failure was under better control, and the discrimination of supraventricular from ventricular tachyarrhythmias would improve with devices that provide DDDR pacing.[12] Given the increased cost and complexity of dual-chamber ICDs, the secondary outcomes data need to be further analyzed to see if the use of dual-chamber devices in patients without a bradycardia indication is appropriate. However when dual-chamber ICDs are implanted, then programming to backup ventricular pacing is justified unless there is a clear indication for pacing.

In addition, this study does not directly address the issue of biventricular pacing. However, only 12% of the patients in the DAVID Trial had NYHA functional class III-IV CHF, and only 30.8% had a QRS duration of at least 130 ms at the time of randomization. Further studies are needed to compare ventricular backup pacing with biventricular DDDR pacing in patients with less than NYHA functional class III CHF symptoms. However, conventional right ventricular stimulation in the DDDR mode seems clearly contraindicated in this patient population.

Our study has several limitations. This article reports only the primary end point data of the investigation, limited by the logistics associated with rapid reporting of the data after the early termination of randomization. We did not make sequential measurements of LVEF before and after pacing therapy, nor did drug therapy reach the recommended or target dose in many patients. The end point definitions for a CHF hospitalization were arbitrary, though chosen to ensure a high likelihood of the diagnosis of new or worsened CHF. A less stringent criterion of CHF hospitalization in the AVID trial predicted a 50% mortality over the ensuing 2 years.[2] Finally, it is impossible to say with statistical certainty that DDDR pacing was harmful because the investigation was halted prior to crossing the predetermined stopping boundary. It is uncertain why the survival curves diverge significantly after 6 months. However, the most likely explanation is that the right ventricular stimulation is a progressive influence expressing itself in most patients after several months of therapy. Alternatively, the exclusion of the heart failure exacerbations from the end point when they occurred during the index hospitalization may have permitted a tuning up of the heart failure therapy in those patients most likely to have decompensated in the first 6 months.

In conclusion, for patients who have no indication for bradycardia support but who have an indication for ICD implantation, there is no documented benefit derived from concomitant DDDR pacing at a rate of 70/min. The combined end point of death and hospitalization for new or worsened CHF is increased.

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