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The DAVID (Dual Chamber and VVI Implantable Defibrillator) II Trial

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Objectives The purpose of this study was to determine whether atrial pacing is a safe alternative to minimal (backup-only) ventricular pacing in defibrillator recipients with impaired ventricular function.

Background The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial demonstrated that dual chamber rate responsive pacing as compared with ventricular backup-only pacing worsens the combined end point of mortality and heart failure hospitalization. Although altered ventricular activation from right ventricular pacing was presumed to be the likely cause for these maladaptive effects, this supposition is unproven.

Methods In all, 600 patients with impaired ventricular function from 29 North American sites, who required an implanted defibrillator for primary or secondary prevention, with no clinical indication for pacing, were randomly assigned to atrial pacing (at 70 beats/min) versus minimal ventricular pacing (at 40 beats/min) and followed up for a mean of 2.7 years.

Results There were no significant differences between pacing arms in patients' baseline characteristics, use of heart failure medications, and combined primary end point of time to death or heart failure hospitalization during follow-up, with an overall incidence of 11.1%, 16.9%, and 24.6% at 1, 2, and 3 years, respectively. Similarly, the incidence of atrial fibrillation, syncope, appropriate or inappropriate shocks, and quality of life measures did not significantly differ between treatment groups.

Conclusions The effect of atrial pacing on event-free survival and quality of life was not substantially worse than, and was likely equivalent to, backup-only ventricular pacing. Atrial pacing may be considered a "safe alternative" when pacing is desired in defibrillator recipients, but affords no clear advantage or disadvantage over a ventricular pacing mode that minimizes pacing altogether. (Dual Chamber and VVI Implantable Defibrillator [DAVID] Trial II; NCT00187187) (J Am Coll Cardiol 2009;53:872–80) © 2009 by the American College of Cardiology Foundation

Implantable defibrillators save lives by treating life-threatening ventricular tachycardia or fibrillation. However, some patients may require bradycardia pacing in addition to antitachycardia therapy from their defibrillator. The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial demonstrated that dual chamber rate responsive pacing at 70 beats/min (DDDR-70) worsens the combined end point of mortality and hospitalization for heart failure compared with ventricular backup-only pacing at 40 beats/min (VVI-40) in patients with impaired ventricular function (1). Although cardiac resynchronization studies suggest that altered ventricular activation from right ventricular pacing was the likely explanation for these maladaptive effects in

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the DAVID trial (2), this supposition is unproven. Such an adverse outcome might occur through a variety of mechanisms other than ventricular dyssynchrony. These include the increased heart rate from pacing or a sensor-driven rate response, creation of a nonphysiologic atrioventricular (AV) conduction interval during AV sequential pacing, and/or effects from atrial pacing itself (such as disruption of left-sided heart AV synchrony by right atrial stimulation) (3). Although not required for most defibrillator patients, addressing the most suitable modality when pacing is desired is important because it potentially affects the future design and application of such therapies in this population (4), particularly among those who are not candidates for biventricular systems. Notably, only ventricular backup pacing and biventricular stimulation, for some heart failure patients, have thus far been safely combined with implantable defibrillator therapy.

The purpose of this trial was to isolate the effects of the atrial pacing mode itself from those other proposed mechanisms for the outcome of the DAVID trial. Our specific objective was to determine if atrial pacing mimics the adverse consequences of the AV sequential, rate responsive pacing observed in the DAVID trial, or whether it is a viable and safe alternative to a mode that attempts to minimize ventricular pacing in defibrillator recipients.

Methods

The DAVID II trial was a randomized, parallel arm, noninferiority trial with implantable defibrillator recipients who had left ventricular dysfunction, comparing atrial pacing at 70 beats/min (AAI-70) to minimal ventricular pacing (VVI-40). The AAI-70 pacing was selected to insure receipt of atrial pacing for evaluation of this pacing mode at a physiologic but not unduly rapid rate. Eligibility criteria are described in Table 1, and included patients previously randomized in the VVI-40 arm of the DAVID trial who had not yet met that trial's clinical end point. Patients received defibrillators for primary or secondary prevention; none had clinical indications for bradycardia pacing. Twenty-nine North American sites participated, most had enrolled patients in the DAVID trial (1), and maintained the same infrastructure for both studies.

Randomization. All patients received commercially approved St. Jude Medical (St. Paul, Minnesota) dual chamber defibrillators (Epic or Atlas DR Family) and leads (Riata Family). The precise right-side heart lead implant sites were not pre-specified, but were commonly in the vicinity of the right atrial appendage and ventricular apex. Immediately after successful implantation with testing of defibrillation efficacy, patients were randomly allocated to bradycardia support (AAI-70 or VVI-40). Antitachycardia parameters of defibrillators were programmed as described in the DAVID trial, using pre-specified criteria with flexibility to meet the clinical needs of patients (1). Randomization was done centrally and stratified by newly enrolled patients (substratified by investigational site, heart failure history, and implantable defibrillator indication) and re-randomized DAVID trial patients (substratified by heart failure history). Patients were blinded to their pacing mode and followed up every 3 months until the common termination date.

Other therapies. Patients were required to be taking appropriate heart failure medications at study entry, and continued treatment with angiotensin-converting enzyme inhibitors or receptor blockers, beta-blockers, digitalis, diuretics, and spironolactone, the titration of which was reviewed at every follow-up visit, with the goal of achieving ≥50% of the target daily doses recommended in the Heart Failure Society of America Practice Guidelines (5). Antiarrhythmic medications required for treatment of supraventricular arrhythmias at the time of randomization were maintained, as were antithrombotic therapies.

Occurrences of symptomatic bradycardia during follow-up were treated by adjustment or discontinuation of medications having such effects and, when required, by adjustment

Abbreviations and Acronyms

AAI-70 = atrial pacing at a rate of 70 beats/min
AV = atrioventricular
DDDR-70 = dual chamber rate responsive pacing at 70 beats/min
MLHF = Minnesota Living with Heart Failure Questionnaire
NYHA = New York Heart Association
VVI-40 = ventricular backup pacing at a rate of 40 beats/min

Table 1 Inclusion and Exclusion Criteria for Study Randomization

Inclusion criteria (1 of the following):
1. Prior enrollment in and randomization to the VVI-40 treatment arm of the DAVID trial without having met that trial's clinical end point
2. LVEF ≤0.40 and 1 of the following spontaneous sustained ventricular arrhythmias unrelated to a transient or correctable cause within the preceding 6 weeks:
a. Cardiac arrest due to VF or VT
b. VT with syncope
c. VT with significant symptoms or systolic blood pressure <80 mm Hg
3. LVEF ≤0.40 with or without spontaneous ventricular arrhythmias and EPS-inducible VT or VF within the preceding 6 weeks
4. LVEF ≤0.30 due to coronary artery disease and >1 month from acute myocardial infarction and >3 months from an invasive coronary intervention
Exclusion criteria (any of the following):
1. Permanent pacemaker
2. Symptomatic bradycardia, or PR interval >0.24 s, or second- or third-degree atrioventricular block
3. Atrial fibrillation ≥6 months or of unknown duration
4. Frequent, uncontrolled supraventricular tachycardia
5. NYHA functional class IV heart failure or ≤3 months of optimal therapy for NYHA functional class III heart failure
6. Awaiting cardiac transplantation
7. Prisoner or ward of the state
8. Unable to give informed consent
9. Life expectancy <1 yr

DAVID = Dual Chamber and VVI Implantable Defibrillator; EPS = electrophysiologic study; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia; VVI-40 = ventricular back-up pacing at 40 beats/min.

of the paced rate before addressing pacing mode. If required for clinical indications, a change in pacing mode (a change in the site of pacing to the alternate chamber, or to a multichamber pacing mode) was permitted.

End points. The primary combined end point was time to death or heart failure hospitalization. Heart failure hospitalization was determined by an Events Committee who reviewed all records (blinded to treatment assignment) pertaining to hospitalization with an admitting or contributory diagnosis of heart failure. Qualifying heart failure required both >24-h hospitalization with clinically worsening heart failure symptoms, and at least 1 intensive treatment for heart failure (intravenous diuresis, intravenous inotropic medications, or dialysis) within 24 h of admission. Secondary end points included all appropriate implantable defibrillator therapies delivered for ventricular fibrillation or tachycardia, all inappropriate therapies for conditions unrelated to ventricular tachyarrhythmias (each adjudicated by blinded review of implantable defibrillator electrograms), and quality of life measurements. Additional end points included time to first occurrence of confirmed atrial fibrillation, syncope, and other hospitalization.

Quality of life. General measures of quality of life were assessed using the Short Form 36-Item Health Survey and the Minnesota Living with Heart Failure Questionnaire (MLHF), both of which were obtained at baseline and at 6-month follow-up; the Global Rating Change and the Simple Outcome Screen, obtained at baseline and at each follow-up visit; and a modified Short Form-36 Health Survey at trial completion. With the exception of the Simple Outcome Screen (administered by study personnel), sites were blinded to quality of life survey results, which were self-administered and conveyed directly to the central coordinating center. The Short Form-36 Health Survey is a commonly used general assessment of quality of life (6–8). It consists of 36 items, providing an overall score with mental and physical components. The MLHF has been used in almost all assessments of quality of life in heart failure studies, using 21 items particularly relevant to heart failure patients (9,10). The Simple Outcome Screen consists of 2 questions designed to assess outcome after stroke (11), but is also useful for assessing recovery from cardiac arrest. Finally, the Short Form-36 Health Survey was substantially modified to provide a much shorter instrument with a high correlation to the original Short Form-36 Health Survey physical summary score. An algorithm constructed theoretically, that is, without attention to the actual data, to translate responses from the Short Form-36 Health Survey into "presumed" responses to the Modified Short Form-36 Health Survey yielded correlations of 0.94 when applied to the baseline and 6-month Short Form-36 Health Survey data.

Follow-up. Patients were followed up at 3-month intervals. After the 6-month follow-up, alternative 3-month visits could be conducted by telephone with remote implantable defibrillator interrogation and download of parameters and events and verbal assessment of the patient's condition. Remote or in-person implantable defibrillator interrogations were also performed when patients received a shock therapy. Death, possible heart failure hospitalization, serious complications related to the device, leads, or medications, change of pacing modality, or withdrawal from the study were reported within 24 hours of discovery.

Oversight. The study was approved by the Institutional Review Boards at all sites; all participants gave written informed consent. An independent Data and Safety Monitoring Board reviewed data and end points approximately every 6 months and could recommend design changes or early trial termination.

Statistical design and analysis. The DAVID II trial was designed as a 1-sided (noninferiority) trial testing the null hypothesis that the effect of atrial pacing, like DDDR-70 in the DAVID trial, will worsen the combined end point of total mortality and heart failure hospitalization, as compared with ventricular backup-only pacing. Specifically, the null hypothesis for the DAVID II trial was H_O: $\Delta = -0.425$ years, where Δ is the difference between the median event-free survival time in the AAI arm and the VVI arm. By comparison, in the DAVID trial, the difference in median time to an event between the DDDR-70 and VVI-40 arms was $\Delta = -0.48$ years. The alternative hypothesis was H_A: $\Delta = 0$. That is, the effect of atrial pacing would be no worse than VVI-40 on the combined end point.

It was planned to enroll 600 patients and follow until 200 events had occurred. Assuming event rates similar to those observed in the DAVID trial (median time to the primary end point of 3.85 years), it was anticipated this would require an average follow-up of 2.5 years. A sequential testing design was used that included a boundary for rejecting the null and a futility boundary for not being able to reject the null. Testing was to occur at increments of approximately 50 events. The number of events was chosen, using the Simulator of Sequential Trials in East 2000 (12), so that the alpha level of the study (the probability of rejecting the null, that AAI-70 is worse than VVI-40, when it was true) = 0.025. The power of the study (the probability of rejecting the null if the alternative, H_A: $\Delta = 0$, was true) = 0.746. The sequential boundaries were chosen such that if AAI-70 trended superior to VVI-40, the trial would be terminated in short order to conduct a typical 2-sided superiority trial, whereas if AAI-70 trended inferior to VVI-40, in particular if H_O were true, the trial would be terminated in approximately 2 years.

Differences in continuous and dichotomous variables were analyzed with the use of Student's *t* test, the chi-square test, or the Mann-Whitney *U* test. Failure-time regression models were used for secondary analyses of the primary end points, as well as for subgroup and exploratory analyses. Generalized linear models were used to analyze the repeated quality of life measures. Statistical significance was indicated by $p \leq 0.05$.

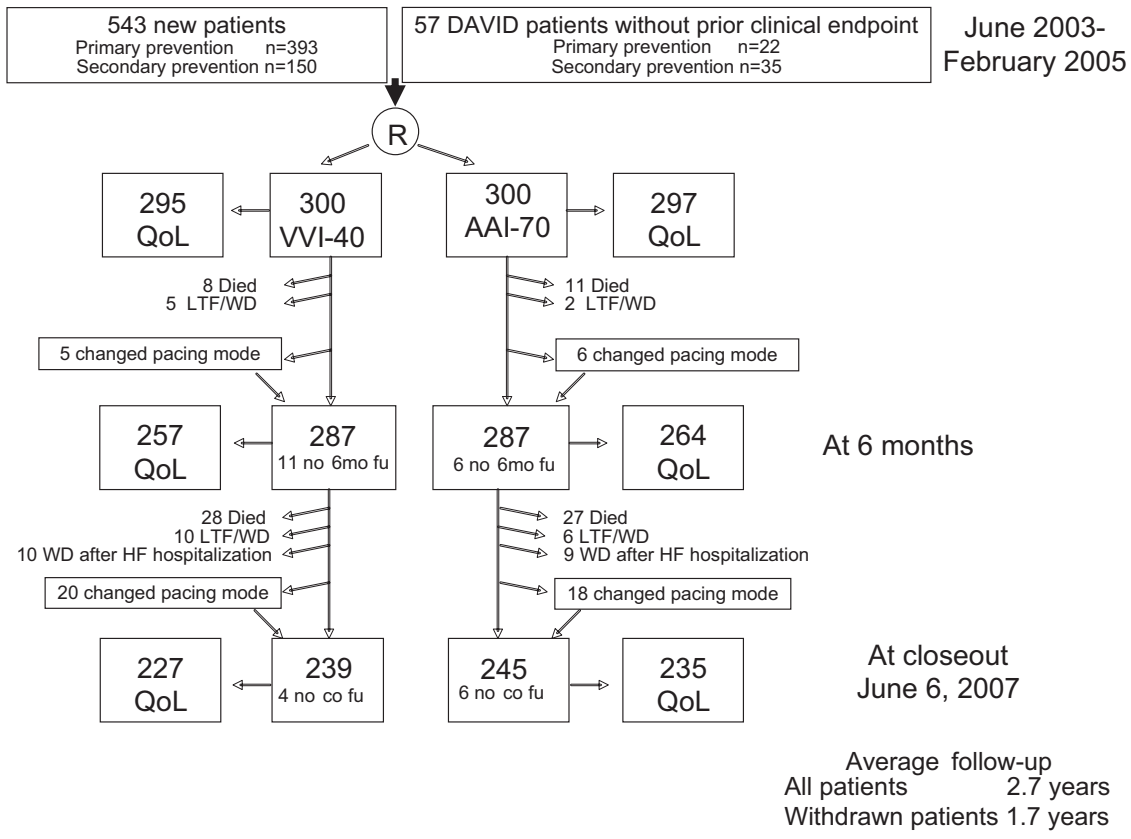

Figure 1 **Flow of Patients in the DAVID II Trial**

The diagram depicts randomization of the DAVID II (Dual Chamber and VVI Implantable Defibrillator II) trial patients, baseline evaluation, and the number of patients available for evaluation at 6-month follow-up and at study close-out. AAI-70 = atrial pacing at 70 beats/min; co = close-out; fu = follow-up; HF = heart failure; LTF = lost to follow-up; QoL = quality of life assessment; R = randomized; VVI-40 = ventricular back-up pacing at 40 beats/min; WD = withdrawn.

Results

Population. Between June 2003 and February 2005, 600 patients were enrolled and 300 randomly assigned to each pacing treatment group (Fig. 1). Baseline patient characteristics are described in Table 2. There were no significant differences in these characteristics between treatment groups, including the factors identified in the DAVID trial as being associated with increased heart failure hospitalization or death (1). As shown in Figure 1, a total of 49 patients changed pacing mode assignment during the follow-up period before reaching a primary end point. These included 7 patients who were reprogrammed to the alternate single-chamber pacing mode, and 42 who were changed to dual chamber pacing. These changes in pacing mode during follow-up were equally distributed between both treatment cohorts. In addition, after an average follow-up period of 1.7 years, 23 patients (a comparable proportion from both treatment groups) were lost to follow-up. Another 19 were withdrawn by protocol after meeting the heart failure hospitalization end point (12 received a biventricular defibrillator, 4 underwent heart transplantation), or voluntarily (2 relocated, 1 refused further follow-up), and thus were not available for the final quality of life assessment.

Pacing. At 3-month follow-up, 7.5% of patients in the AAI-70 treatment arm received no atrial pacing, whereas the frequency of atrial pacing ranged from 1% to 20% in 22.5% of patients, from 21% to 40% in 18%, and >40% in 52% of patients. By comparison, ventricular pacing was rare in the VVI-40 group at 3-month follow-up; 13% of patients received none, and the frequency of ventricular pacing averaged <2% in the remainder. At 24-month follow-up, the overall frequency of atrial pacing averaged 47% in the AAI-70 group, and ventricular pacing 2% in the VVI-40 group. Heart rates (mean ± SD) differed modestly between AAI-70 and VVI-40 groups at 3 and 24 months (72 ± 8 beats/min vs. 66 ± 13 beats/min, and 73 ± 6 beats/min vs. 65 ± 12 beats/min, respectively; $p < 0.001$).

Medications. Use of heart failure medications, statins, and antiarrhythmics was similar between treatment groups at hospital discharge after study enrollment (Table 2), and remained so during follow-up. At 24 months of follow-up, angiotensin-converting enzyme inhibitors or receptor blockers were taken by, respectively, 88% and 86% of

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Table 2 Baseline Characteristics

	Overall	
	VVI-40	AAI-70
Number enrolled	300	300
Mean age, yrs	63	64
Male, %	85.3	84.7
Mean LVEF	26.6	26.3
Primary prevention, %	68.7	69.7
Clinical history before randomization, %		
AF/flutter	15.3	13.0
MI	88.3	86.0
CHF	65.3	67.0
Hypertension	65.7	66.3
Diabetes mellitus	33.3	31.0
Ischemic cardiomyopathy, %	93.0	93.0
NYHA functional class, %		
I	45.7	41.3
II	44.7	49.0
III	9.7	9.7
Discharge medications after enrollment, %		
ACEI or ARB	87.7	90.0
Beta-blocker	90.3	88.0
Diuretic	56.7	56.7
Digoxin	27.0	31.3
Spironolactone	18.3	19.0
Statin	75.3	76.3
Antiarrhythmic medications	16.7	17.0
Baseline electrocardiogram available, n	296	292
Heart rate, mean (SD)	69 (13)	70 (14)
PR, mean (ms) (SD)	181 (33)	179 (39)
QRS, mean (ms) (SD)	110 (25)	111 (24)
First-degree AV block (PR >200 ms), %	21.3	20.2
Left bundle branch block, %	11.5	12.0
Right bundle branch block, %	4.7	5.5
Nonspecific intraventricular conduction defect, %	25.7	25.3
Baseline quality of life available, n	295	297
SF-36 physical score, mean (SD)	37 (10)	37 (11)
SF-36 mental score, mean (SD)	48 (11)	49 (10)
MLHF physical score, mean (SD)	18 (11)	17 (11)
MLHF emotional score, mean (SD)	9.0 (7.0)	8 (6)

AAI-70 = atrial pacing at 70 beats/min; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; AV = atrioventricular; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLHF = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; SF-36 = Short Form-36 Health Survey; VVI-40 = ventricular back-up pacing at 40 beats/min.

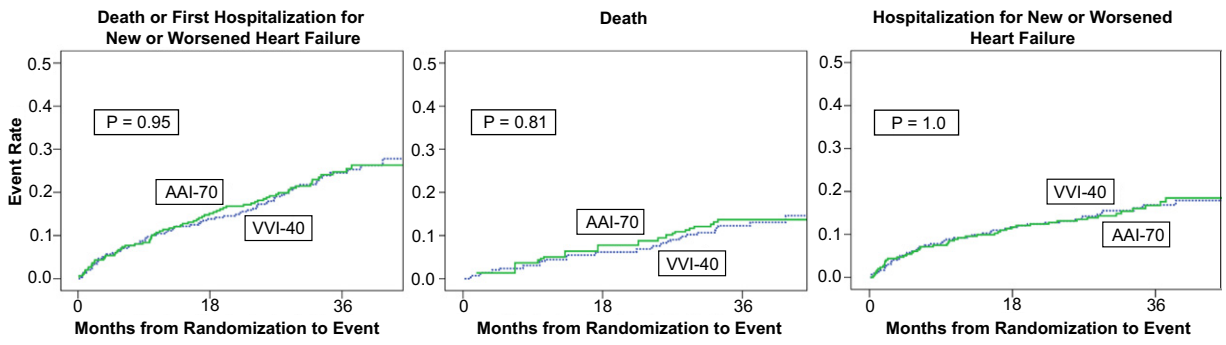
patients assigned to VVI-40 and AAI-70 pacing, diuretics by 61% and 55% of these treatment groups, beta-blockers by 91% and 93%, digoxin by 28% and 30%, spironolactone by 16% and 17%, statins by 79% and 81%, and antiarrhythmic medications by 22% of patients. Similarly, doses of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers did not significantly differ between treatment groups at study entry or during follow-up, and were comparably titrated upward over time in both treatment groups. At study entry, 68% of patients in the VVI-treatment arm versus 73% of those in the AAI-70 treatment arm were at ≥50% of targeted daily doses for angiotensin-converting enzyme inhibitors and receptor blockers, and 49% versus 52% of patients for beta-blockers; at 24 months, the corresponding values were 78% versus 80% of patients for angiotensin-converting enzyme inhibitors and receptor blockers, and 66% versus 69% of patients for beta-blockers ($p < 0.001$ compared with dosing levels of these drugs at study entry in each pacing arm).

Trial termination. By the December 2006 meeting of the Data Safety Monitoring Board, the test statistic had crossed the boundary for rejection of the null hypothesis, with no difference in the primary outcome, but potentially contradictory differences in quality of life measures. Accordingly, the Board recommended continuing the study to obtain additional quality of life measures, for which the modified Short Form-36 Health Survey physical questionnaire was developed and study termination rescheduled to allow sufficient time for each patient to accrue at least 1 more follow-up before trial close-out. The average time of follow-up was 2.7 years (range 1 week to 4 years).

Clinical end points. There were no significant differences between the treatment arms in the primary combined end point of time to heart failure hospitalization or death, with an overall incidence of 11.1%, 16.9%, and 24.6% at 1, 2, and 3 years, respectively (Fig. 2). Nor was any significant effect observed on the primary outcome that might be attributable to the frequency of atrial pacing in the AAI-70 treatment group. There were also no differences observed between treatment arms when time to death and heart failure hospitalization were examined separately, nor among subgroups examined for implantable defibrillator indication, sex, age, resting heart rate, ejection fraction, heart failure history, QRS duration or PR interval (Fig. 3). Similarly, the incidence of atrial fibrillation, syncope, (Fig. 4) or appropriate/inappropriate shocks (Fig. 5) did not differ between pacing groups.

Quality of life. Baseline Short Form-36 Health Survey and MLHF summary scores are displayed in Table 2. Comparing the changes from baseline to 6 months, the VVI-40 group experienced a greater improvement in the Short Form-36 Health Survey physical subscale, of 2.6 compared with 1.2 points for the AAI-70 group ($p = 0.04$ after adjustment for baseline factors affecting the physical subscale: age, heart failure history, diabetes mellitus, depression, and atrial fibrillation). The MLHF physical subscale changes also trended weakly in favor of VVI-40 pacing, an improvement of 4.0 versus 3.0 points ($p = 0.19$). Modest improvements in the Short Form-36 Health Survey mental subscale (improvement of 1.2 points) and the MLHF emotional subscale (improvement of 2.0 points) were observed, but without significant differences between treatment arms.

In contrast, responses to the Global Rating Change indicated an improved sense of health between 3 and 6 months for the AAI-70 group compared with the VVI-40 group. That is, 43% of the patients reporting worse health, 48% of those reporting the same health, and 57% of those reporting better health were in the AAI arm ($p = 0.026$).



Number of Patients at Risk at Month Shown				Number of End Point Events in Follow-up	
	0	18	36	Deaths	Heart Failure Hospitalizations
VVI-40	300	252	109	36	47
AAI-70	300	251	109	38	47

Figure 2 **Primary Outcome**

Event rates are depicted for the primary (composite) end point **(left)** and its components **(middle and right)** in the 2 treatment groups: atrial pacing at 70 beats/min (AAI-70 **[green lines]**) and ventricular back-up pacing at 40 beats/min (VVI-40 **[blue lines]**). The tables indicate the number of patients at risk by month of follow-up, and the total number of deaths and number of patients hospitalized for heart failure in each treatment group.

Corresponding proportions at the 3-month follow-up were 51%, 50%, and 49%. No differences were observed for Simple Outcome Screen measures between treatment groups during follow-up.

At 6 months, the modified Short Form-36 Health Survey physical subscale was highly correlated with the 6-month Short Form-36 Health Survey physical score (0.94), and was slightly improved in the VVI-40 cohort, but did not indicate any treatment effect when administered at study close-out.

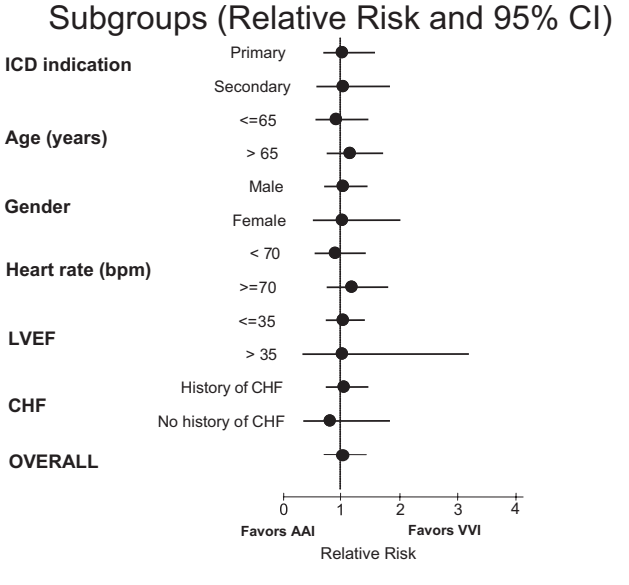


Figure 3 **Primary Outcome Depicted by Patient Subgroups**

No differences favoring one or the other treatment arm were observed when death and heart failure hospitalization were examined among the subgroups shown. AAI = atrial pacing at a rate of 40 beats/min; bpm = beats/min; CHF = congestive heart failure; CI = confidence interval; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; VVI = ventricular back-up pacing at a rate of 40 beats/min.

Discussion

At the time the first DAVID trial was conducted, dual chamber defibrillators were increasingly being implanted, regardless of whether bradycardia pacing support was needed. In this climate of practice, the DAVID trial tested the hypothesis that heart failure hospitalizations and mortality would be reduced as a result of the more aggressive use of heart failure medications afforded by active pacing or perhaps because of the benefits resulting from pacing itself. That the outcome of the DAVID trial was unexpectedly worse in the actively paced group did not necessarily disprove this hypothesis. Rather, it is possible that the mode of pacing chosen for the trial (DDDR-70) was merely the wrong mechanistic approach to achieve its ends, as suggested by the growing appreciation of the ill effects from right ventricular pacing that the DAVID trial was largely responsible for initially bringing to clinical attention. The DAVID II trial tested this alternate mode hypothesis. As such, it examined the safety of atrial compared with minimal ventricular pacing in a population of implantable defibrillator recipients who were comparable in their baseline characteristics and in risk stratifiers associated with worse outcome in the DAVID trial. No differences in the primary combined end point of time to heart failure hospitalization or death were found between treatment arms. These findings were in significant contrast to those of the DAVID trial, in which AV sequential pacing increased the risk of heart failure hospitalization or death, but were insufficient to suggest that atrial pacing, while as "safe," offers any inherent advantage in this population over a ventricular mode that

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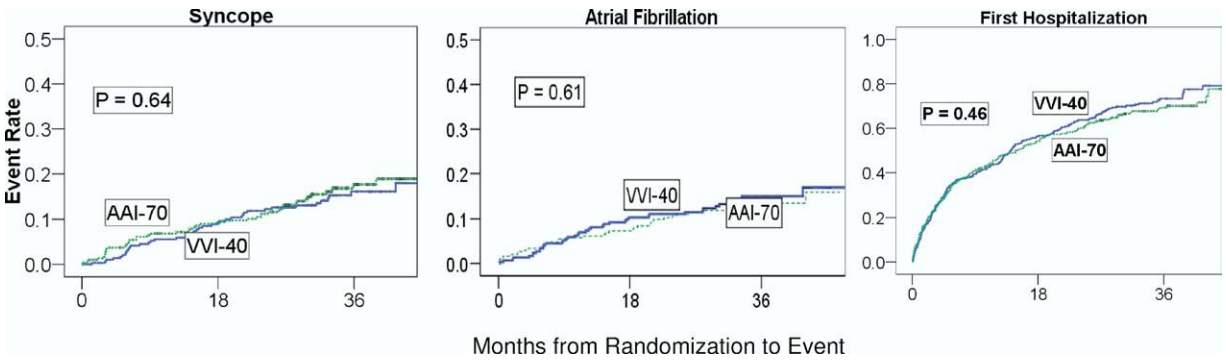

Figure 4 **Secondary Outcomes**

Event rates are shown for syncope **(left)**, atrial fibrillation **(middle)**, and first hospitalization **(right)** for any cause in each treatment group: atrial pacing at 70 beats/min (AAI-70 **[green lines]**) and ventricular back-up pacing at 40 beats/min (VVI-40 **[blue lines]**).

minimizes pacing altogether. The DAVID II trial was designed to test for noninferiority, but, as in most studies of 600 patients, was not powered to conduct definitive subgroup analyses.

Secondary end points. In addition to the primary end point, all secondary end points also failed to demonstrate differences between the 2 pacing strategies. The incidence of death, heart failure hospitalization, atrial fibrillation, syncope, first hospitalization, and appropriate and inappropriate shocks did not differ between randomized groups (Fig. 4). There was a trend toward fewer inappropriate shocks in the AAI-70 treatment arm, but that did not reach statistical significance (Fig. 5).

Atrial fibrillation. The incidence of atrial fibrillation in the DAVID II study population was 13.7% at 3 years, which should have allowed for detecting substantial differences in its occurrence between treatment groups. In a previous trial, atrial pacing reduced the incidence of atrial fibrillation when pacemakers were implanted for sinus node dysfunction (13). Failure to see a comparable effect in the DAVID II trial may be because atrial rate support improves atrial fibrillation rhythm control primarily when it prevents bradycardia in predisposing conditions such as sick sinus syndrome. It is also possible that the presence of significant left ventricular dysfunction in DAVID II trial patients diminished the beneficial effect of a more rapid atrial rate on the incidence of atrial fibrillation. Notably, a higher incidence of atrial fibrillation during cardiac resynchronization therapy was recently associated with the frequency of right atrial pacing, indicating that a rhythm benefit from pacing is not necessarily a foregone conclusion in a heart failure population (14).

Syncope. Syncope was observed in equal frequency in both treatment groups. This finding suggests that when such symptoms are attributable to bradycardia, neither atrial nor VVI pacing offers any inherent advantage. For example,

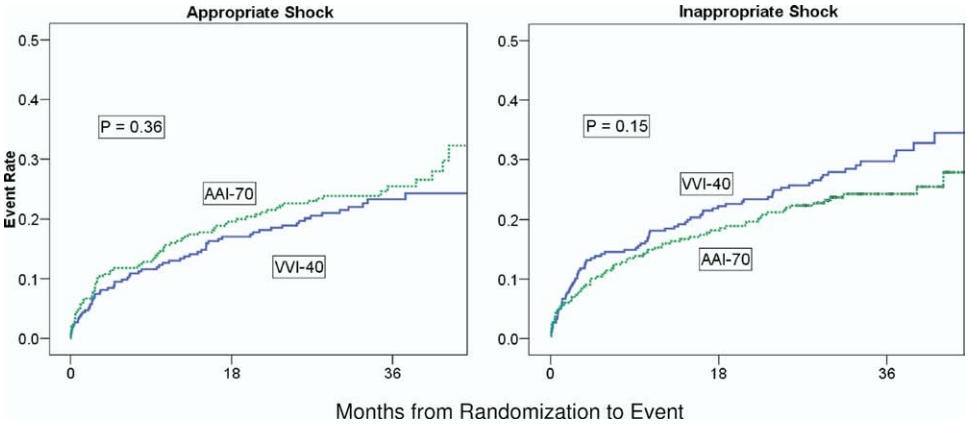

Figure 5 **Appropriate and Inappropriate Shocks**

Event rates are shown for appropriate shocks **(left)** and inappropriate shocks **(right)** in each treatment group: atrial pacing at 70 beats/min (AAI-70 **[green lines]**) and ventricular back-up pacing at 40 beats/min (VVI-40 **[blue lines]**).

VVI-40 pacing may afford protection from asystole during sinus pauses, but may result in syncope from the slow ventricular rate and loss of AV synchrony. Conversely, atrial pacing prevents atrial asystole and enables AV synchrony, but the resulting ventricular rate is completely dependent upon the integrity of intrinsic AV conduction. Because patients enrolled in the DAVID II trial had no indication for pacing, it is also possible that syncopal events of bradycardia etiology were uncommon during the study, regardless of treatment assignment. Taken together, our data do not support the need for either mode of pacing for protection from syncope or atrial fibrillation in implantable defibrillator recipients without the presence of other indications.

Comparison with previous studies. Event rates were lower in the DAVID II trial population than in the DAVID trial; this finding was explainable by a shift in the demographics of enrolled patients. Primary prevention patients comprised 69% of the DAVID II trial population, compared with 49% in the DAVID trial; 87% of the patients had a history of myocardial infarction compared with 49% in the DAVID trial. In addition, the qualifications for primary prevention ICDs changed between the trials. In the DAVID trial, eligible patients were required to undergo electrophysiologic testing with inducible ventricular tachycardia, similar to the MADIT (Multicenter Automatic Defibrillator Implantation Trial) and MUSTT (Multicenter Unsustained Tachycardia Trial) study patients (1,15,16). Conversely, >60% of primary prevention patients in the DAVID II trial were enrolled without electrophysiologic testing, in keeping with updated treatment guidelines based on the MADIT II trial (17). Neither DAVID trial enrolled primary prevention patients with nonischemic cardiomyopathy (Table 2) (1).

In having achieved relatively frequent atrial pacing without major changes in heart rate (which averaged only 6 to 8 beats/min), the DAVID II trial suggests that the deleterious effects of DDDR-70 pacing observed in the DAVID trial were not the consequence of atrial pacing itself, as this would have also resulted in worse outcomes in the current study. Rather, DDDR-70 pacing probably accounted for the worse outcomes due to unnecessary RV pacing in a susceptible population. This observation is in keeping with the recent retrospective analysis of the DAVID and MADIT II trial data, suggesting such an explanation was the most likely cause for their increased incidence of death and heart failure hospitalization (18,19).

The results of the DAVID II trial are similar to those of the recently published INTRINSIC RV trial (20). As in our trial, no significant differences were found in the combined primary end point between a dual chamber pacing mode that used an algorithm to minimize ventricular pacing, compared with backup pacing (VVI-40). However, the DAVID II trial comprised sicker patients, with a higher incidence of heart failure (66% vs. 37%), coronary artery disease (93% vs. 67%), and a higher event rate in its control group (11.1% vs. 9.5%). Furthermore, the frequency of either right atrial or right ventricular pacing in the DDDR arm of the INTRINSIC (Inhibition of Unnecessary RV Pacing With AVSH in ICDs Study) trial was low (averaging only 13%), arguably resulting in its having only compared 2 minimally paced treatment groups. In contrast, the higher prevalence of atrial pacing (averaging 47%) in the AAI-70 arm of the DAVID II trial affords a truer comparison between more frequent atrial pacing and minimal pacing (VVI-40). Taken together, the results of these 2 studies suggest that atrial pacing, of whatever frequency, is as safe as the avoidance of pacing in a heterogeneous group of implantable defibrillator recipients.

Quality of life. The conflicting quality of life observations at 6 months in the DAVID II trial likely reflect chance variation. This chance variation was exemplified by Global Rating Change responses that did not differ between treatment arms at 3 months and by Global Rating Change and Short Form-36 Health Survey physical responses that differed significantly between treatment arms at 6 months, but in opposite directions; and it was confirmed by the modified Short Form-36 Health Survey physical score, which mimicked the Short Form-36 Health Survey score at baseline and 6 months, but showed no difference at close-out between treatment arms.

Study limitations. Limitations of the DAVID II trial include those that are inherent to a noninferiority study. Although the sample size was sufficiently large to reject the null hypothesis, our alternative hypothesis (that the effect of AAI-70 on the combined end point was no worse than VVI-40 backup pacing) could be compromised by the rate of patients who changed pacing assignment, or missing data from those withdrawn or lost to follow-up. The rate of such events was low and was similar in both treatment arms (Fig. 1). Furthermore, the average interval before withdrawal or loss to follow-up was 1.7 years, such that substantial information about treatment course was still derived in such instances.

This study did not specifically address effects of more rapid heart rates or rate-responsive pacing, which invite further study. Moreover, it did not address the differential risks from implantation and long-term morbidity between single and dual chamber defibrillators, as all patients received only the latter. Nor did it address the effect of more frequent (AAI-70) pacing on implantable defibrillator generator life, and whether potentially offset by other battery savings (such as the trend toward fewer inappropriate shocks). The frequency of shocks was also not a primary study end point, and could have been influenced by factors other than pacing mode. In addition, the study addressed patients who had no clinical indication for permanent pacing, and therefore cannot be extrapolated to those with pacing indications. The DAVID II trial included a small number of patients who were originally included in the VVI-40 arm of the DAVID trial and subsequently re-randomized to the treatment arms of the DAVID II trial. The inclusion or exclusion of these patients did not alter the

results presented. Finally, it could be argued that titration of heart failure medications was not sufficiently aggressive to accentuate the potential differences between pacing modes that might otherwise have been observed, particularly among recipients of atrial pacing. However, the dosing levels achieved with heart failure medications compare well with those targeted in heart failure patients and conformed to published guidelines. Our results suggest that active pacing is not necessarily required to attain adequate dosing levels of such medications.

Conclusions

Among implantable defibrillator recipients with left ventricular dysfunction and no clinical indications for pacing, the effect of atrial pacing on event-free survival and quality of life was not substantially worse than, and was likely equivalent to, backup-only ventricular pacing. Atrial pacing may be considered a "safe alternative" when pacing is desired, but affords no clear advantage or disadvantage over a ventricular pacing mode that minimizes pacing altogether.

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Key Words: implantable defibrillator ■ heart failure ■ pacing.

APPENDIX

For a list of the DAVID II principal investigators and coordinators, please see the online version of this article.