Clinical Trials

CRM Clinical Trials Summaries

Compiled by Diana Conti, CCDS

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Clinical Trial Acronyms - Organized by Therapy

Brady

ADOPT
ATTEST
CTOPP
Danish Mode Selection Trial
DAPPAF
DAVID II
INSYNC
MIRACLE (Pacing Study)
MIRACLE ICD
MOST
M-PATHY
PACE – Presented at AHA 2009
PASE
PASE (QoL)
PATH-CHF
SAVE PACe
TRIP-HF
UKPACE
VASIS
VPS
VPS II

Tachy

ADIOS
AMIOVIRT
ASSURE
AVID Electrical Storm Substudy
CABG PATCH
CASH
CAD
CIDS
COMPANION
CRT for the Treatment of HF in Patients with VTs
DAVID II
DAVID
DEBUT
DEFINITE
DINAMIT
Detect SVT
EMPIRIC
INTRINSIC RV
IRIS
InSync ICD
MADIT-CRT - Presented at ESC 2009
MADIT II
MADIT
MASTER
MIRACLE ICD
Maximizing Patient Benefit from CRT With the Addition of Structured Exercise Training
RBBB and ST-Segment Elevation Syndrome
SCD-HeFT Cost Effectiveness
SCD-HeFT
SMASH-VT
Slow VT in ICD Recipients
VTACH

ADIOS

General Information

Acronym
ADIOS

Full Name
Antiarrhythmic Drug Improve Outcome Study

Year Presented
1997

Year Published
not yet published

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients were randomized to ICD treatment with (n=31, 52%) or without (n=29, 48%) concomitant antiarrhythmic drug therapy, then followed up every 3 months or at recurrence. Data were evaluated according to an intention-to-treat analysis.

Principal Findings

Although first recurrence was the primary endpoint, patients in the discontinued therapy group were crossed over, if possible, to the opposing arm by returning the patients to EP-guided therapy.

Although continued use of antiarrhythmic drug therapy did not significantly reduce VT/VF recurrences, investigators found a trend to later recurrence of VT/VF episodes during follow-up in this group. After more than 2 years, 35% of patients in the ICD plus drug group had a recurrence at a mean of 12 months, while 45% of patients in the ICD-only arm recurred within a mean of 5±7 months. VT was the most common arrhythmia to recur.

Over the course of the study 8 patients died, the majority from heart failure.

The study was prematurely halted. In designing the study, the investigators assumed a 20% event rate in the group continuing on antiarrhythmic drug therapy and a 50%recurrence rate in the ICD-only group. With the event rate much less than anticipated in the ICD-only group and much greater in the drug therapy arm, the trial was discontinued early.

Interpretation

The investigators concluded that there is a limited value of serial drug testing in patients with VT/VF and an accepted indication for ICD implantation.

Reference

AHA 1997, Clinical Trials, presented by Ellen Hoffmann, MD, University of Munich, Munich, Germany

AMIOVIRT

General Information

Acronym
AMIOVIRT

Full Name
Amiodarone Versus Implantable Defibrillator in Patients with Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia study

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2000

Year Published
2003

Conditions

- Arrhythmias / Ventricular tachycardia
- Cardiomyopathy / Hypertrophic
- Arrhythmias

Therapies

- Antiarrhythmic / Class III / Amiodarone
- Implantable Cardioverter Defibrillator (ICD)
- Antiarrhythmic

Intervention

Patients were randomly assigned to have a defibrillator implanted (n=51) or to receive amiodarone (400 mg twice a day for 1 week, followed by 400 mg once a day for 51 weeks, and 300 mg once a day thereafter; n=52).

Principal Findings

There was no difference in survival at 1 year (90% vs 96%) or 3 years (88% vs 87%; p=0.8) in the amiodarone and ICD groups, respectively. Arrhythmia-free survival rates at 3 years trended higher with amiodarone vs ICD (73% and 63%, p=0.1). Syncope occurred in 5.8% of the patients treated with amiodarone and 3.9% of the patients treated with an ICD (p=0.7) during the duration of the study. Quality of life was also similar between the treatment arms at 1 year follow-up (p=NS). Costs trended lower during the first year of therapy with amiodarone vs ICD ($8,879 vs. $22,039, p=0.1).

Interpretation

Among patients with nonischemic dilated cardiomyopathy and asymptomatic, nonsustained ventricular tachycardia, treatment with an ICD was not associated with a reduction in total mortality compared with treatment with amiodarone during a mean 2-year follow-up. On the contrary, amiodarone therapy was associated with a trend towards improved arrhythmia-free survival. ICD has been shown to be more effective for survival than pharmacologic therapy in the MUSTT and MADIT trials. However, these trials enrolled patients with prior CAD, unlike the present trial which enrolled patients with NIDCM and NSVT. Given the lack of difference in mortality and the trend toward lower costs with amiodarone, it is unclear what the first clear-cut choice of therapy should be in patients with NIDCM and NSVT. The small sample size in the present trial limits the conclusions that can be drawn.

Reference

Strickberger SA et al. Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia—AMIOVIRT. J Am Coll Cardiol 2003;41:1707-12.

Presented at AHA 2000.

ASSURE

General Information

Acronym
ASSURE

Full Name
Arrhythmia Single Shock Defibrillation Threshold Testing Versus Upper Limit of Vulnerability: Risk Reduction Evaluation With Implantable Cardioverter Defibrillator Implantations

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2007

Conditions

- Arrhythmias
- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

During implantation, patients were randomized to vulnerability safety margin (VSM) or defibrillation safety margin (DSM) screening at 14 J. Each group then crossed over to the opposite testing. Patients then underwent confirmatory testing that required two VF conversions without failure at 21 J. If the first 14 J and confirmatory tests were passed, the devices were programmed to a 21 J shock for ventricular tachycardia (VT) or VF 200 bpm, irrespective of the results of their second 14 J test (the crossover testing).

Principal Findings

At study entry, 68% of patients had an ejection fraction 30%. New York Heart Association classification was predominantly class II (35%) or class III (48%). Coronary artery disease was present in 71% of patients, with 49% having had a prior myocardial infarction. Device type was ICD in 51% of patients and cardiac resynchronization therapy defibrillator in 49%.

Of those who underwent VSM, 75.5% passed the 21 J conversion; of those who underwent DSM, 81.3% passed 21 J conversion. There was a discrepancy between VSM and DSM screening following crossover in 65 patients, 94% of whom passed their 21 J confirmation testing. Testing results were similar when randomized to VSM versus DSM screening first.

During follow-up, the clinical VT/VF episode rate was 13.3% per year. The majority of clinical VT/VF episodes (86%) were terminated by the first shock, with no difference in first shock success by randomization group (92% in the VSM first group and 75% in the DSM first group). In all observed cases in which the first shock was unsuccessful, subsequent shocks terminated VT/VF.

Interpretation

Among patients receiving an ICD or cardiac resynchronization therapy defibrillator, device testing at the time of implantation using either vulnerability safety margin or defibrillation safety margin screening at 14 J was associated with similar rates of termination of clinical VT/VF episodes by the first shock.

While important to determine the function and integrity of the device, repeated VF induction at the time of device implantation can result in severe complications, particularly in certain high-risk populations such as those with advanced heart failure. VSM or DSM screening at 14 J were both shown to have similar positive predictive accuracy in the present trial.

Reference

Day JD, Doshi RN, Belott P, et al. Inductionless or limited shock testing is possible in most patients with implantable cardioverter-defibrillators/cardiac resynchronization therapy defibrillators: results of the multicenter ASSURE Study (Arrhythmia Single Shock Defibrillation Threshold Testing Versus Upper Limit of Vulnerability: Risk Reduction Evaluation With Implantable Cardioverter-Defibrillator Implantations). Circulation 2007;115:2382-9.

AVID Electrical Storm Substudy

General Information

Acronym
AVID Electrical Storm Substudy

Full Name
Electrical Storm Presages Nonsudden Death. The Antiarrhythmics vs. Implantable Defibrillators (AVID) Trial

Year Presented
2001

Year Published
2001

Conditions

- Arrhythmias / Ventricular tachycardia
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

A cardiovertor/defibrillator (ICD) was implanted in 457 patients with ventricular fibrillation (VF) or ventricular tachycardia (VT) associated with syncope or hemodynamic compromise and an ejection fraction < 0.40. Survival during a mean of 31 months of follow-up was compared among 90 patients who had an electrical storm, 184 patients who had VT/VF without electrical storm and 183 patients who did not have VT/VF.

Principal Findings

Patients who had VT/VF (with or without electrical storm) during follow-up had a lower ejection fraction than the other patients (0.29 vs. 0.35) and were less likely to have undergone revascularization after the index arrhythmia. Electrical storm occurred at a mean of 9 months after ICD implantation. The death rate was higher among patients with electrical storm (38%) than among patients with VT/VF without electrical storm (15%) and the remaining patients (22%). The most common type of death was nonsudden cardiac death. Electrical storm was independently associated with death (relative risk 2.4) but VT/VF without electrical storm was not. The risk of death was greatest during the first 3 months after electrical storm (relative risk 5.4).

Among patients with an ICD, electrical storm is a marker for subsequent nonsudden cardiac death, independent of other variables such as ejection fraction.

Interpretation

It is unclear whether electrical storm is a direct contributor to subsequent nonsudden cardiac death (perhaps by

causing myocardial injury) or simply a marker of more severe underlying heart disease. An implication of the former circumstance is that prevention of electrical storm with prophylactic antiarrhythmic drug therapy may improve prognosis. On the other hand, if electrical storm is a marker of more severe disease, it is possible that aggressive optimization of ventricular function might improve prognosis. However, whether survival after electrical storm can be improved by these interventions remains to be determined.

Reference

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1. Exner DV, Pinski SL, Wyse G, et al. and the AVID Investigators. Circulation 2001;103:2066-71.

CABG PATCH

General Information

Acronym
CABG PATCH

Full Name
The Coronary Artery Bypass Graft Patch Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
1997

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- CABG

Intervention

CABG and ICD insertion

Principal Findings

Among randomized patients, the initial phases of the trial have acceptable mortality (overall surgical mortality = 5.9%), morbidity (cardiopulmonary bypass = 23%; shock = 8%; deep sternal wound infection = 1.3%), and length of stay (median = 8 days). During an average follow-up of 32 ± 16 months, there were 101 deaths in the defibrillator group (71 from cardiac causes) and 95 deaths in the control group (72 from cardiac causes). The hazard ratio for death from any cause was 1.07 (95% confidence interval 0.81-1.42, p=0.64).

The original design called for 800 patients to be randomized to ICD prophylaxis or to no therapy, and followed for two to 6.5 years (average, 40 months) to a common termination date. Because the ICD pulse generators used in this trial lasted about 42 months, the original design required ICD replacement in many patients.

In June 1994, an unanticipated subpoena from the Office of the Inspector General made it impossible to replace about half of the ICD generators, and threatened to shorten follow-up substantially. After reviewing many options for restoring power, the Data Safety and Monitoring Board recommended that the sample size be increased from

800 to 900 patients, and that almost all patients be followed for 42 months. This recommendation extended follow-up for two years beyond the original termination date planned for the trial.

Interpretation

The interim analysis found no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction (LVEF), and an abnormal signal-averaged electrocardiogram (SAECG) in whom a defibrillator was implanted prophylactically at the time of elective CABG. Definitive comparisons of device and control groups will not be available until the completion of the trial.

Reference

1) Spotnitz HM, Herre JM, Baker LD Jr, Fitzgerald DM, Kron IL, Bigger JT Jr. Surgical aspects of a randomized trial of defibrillator implantation during coronary artery bypass surgery. The CABG Patch Trial. Circulation 1996;94:II248-53.
2) Curtis AB, Cannom DS, Bigger JT Jr, et al. Baseline characteristics of patients in the coronary artery bypass graft (CABG) Patch Trial. Am Heart J 1997;134:787-98.
3) Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med 1997;337:1569-75.
4) Bigger JT Jr, Parides MK, Rolnitzky LM, Meier P, Levin B, Egan DA. Changes in sample size and length of follow-up to maintain power in the coronary artery bypass graft (CABG) patch trial. Control Clin Trials 1998;19:1-14.

CASH

General Information

Acronym
CASH

Full Name
Cardiac Arrest Study Hamburg

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2000

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Antiarrhythmic / Class III / Amiodarone
- Antiarrhythmic / Class Ic / Propafenone
- Antiarrhythmic
- Beta blocker

Intervention

Patients were initially randomized in equal numbers to one of four groups: ICD, metoprolol, amiodarone, or propafenone. The propafenone group was terminated early (1992) when interim analysis revealed excess mortality in propafenone compared with ICD patients. Additional patients were then randomized to the three remaining arms. ICDs were epicardial from 1987-1991, and transvenous thereafter.

Principal Findings

Interim analysis revealed that propafenone treatment (n=56), as compared with ICD (n=59), was associated with increased sudden death (12% vs. 0%, $p< 0.05$) and sudden death or recurrent cardiac arrest (23% vs. 0%, $p< 0.05$), prompting discontinuation of the propafenone arm of the study.

Final results over 57 months' average follow-up reported a trend toward reduced all-cause mortality with ICDs (n=99), compared with the combined amiodarone (n=92) and metoprolol (n=97) groups (36.4% vs. 44.4%, one-tailed p=0.08). ICDs were associated with a reduction in sudden death (13.0% vs. 33.0%, one-sided p=0.005).

Interpretation

Cardiac arrest survivors treated with the class I-C antiarrhythmic drug propafenone had more frequent serious arrhythmic events than those treated with ICDs. When compared with amiodarone or metoprolol over longer-term follow-up, ICDs significantly reduced sudden death, but not total mortality. At its inception, this was the first randomized trial of ICDs versus pharmacologic therapy for secondary prevention of sudden cardiac death.

Unfortunately, the trial took approximately 10 years to enroll < 400 patients, and during this time, enormous changes took place in ICD technology, as well as thinking about antiarrhythmic drugs. The finding of early increased sudden death in the propafenone arm was very important in light of contemporary anti-arrhythmic drug trials. The trend toward reduced all-cause mortality was consistent with the much larger AVID trial, which started later, but was published sooner.

Reference

Preliminary results/interim analysis:

Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck KH. ICD versus drugs in cardiac arrest survivors: preliminary results of the Cardiac Arrest Study Hamburg. Pacing Clin Electrophysiol 1993;16:552-8.

Siebels J, Kuck KH. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). Am Heart J 1994;127:1139-44.

Final results:

Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748-54.

CAT

General Information

Acronym
CAT

Full Name
Cardiomyopathy Trial

Year Presented

Year Published
1992

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Heart failure / Ischemic
- Heart failure / Idiopathic
- Arrhythmias
- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

ICD, implanted transvenously, used with a subcutaneous patch electrode.
Programmed for maximum heart rate of 200 bpm.
Initial and all subsequent shocks programmed to 30 J with a 5-second delay and a detection rate for VF at 30 bpm higher than maximal heart rate.

Principal Findings

Not available

Interpretation

Not available

Reference

1. PACE 1992:15:697-700.
2. PACE 1993;16:576-81.

CIDS

General Information

Acronym
CIDS

Full Name
Canadian Implantable Defibrillator Study

Year Presented
not applicable

Year Published
1993

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Antiarrhythmic

Intervention

ICD.
Implantation as soon as possible after randomization.
Other surgical procedures (such as CABG) may be done concurrently.
Either thoracotomy or nonthoracotomy lead systems may be used.
ICD may be any device that can detect VT or VF and can electrically defibrillate and cardiovert the heart. Successful defibrillation threshold is 3 consecutive successful defibrillations at >10J below the maximum ICD output

Amiodarone (oral)
> 1200 mg/day for at least 1 week in the hospital
Followed by > 400 mg/day for at least 10 weeks
Followed by > 300 mg/day
If intolerable side effects occur, dose can be lowered to minimum of 200 mg/day
Patients who cannot tolerate minimum dose of amiodarone because of side effects, may receive another form of therapy, chosen by the investigator.
If VF or rapid sustained VT occurs while on amiodarone, investigator may consider other treatments. For patients randomized to not receive an ICD , the ICD should only be chosen as a last resort.

Principal Findings

Not yet available

Interpretation

Not yet available

Reference

1. Am J Cardiol 1993;72:103F-108F Design and baseline results
2. Circulation 1998;98(SupplI):I-93: EF subgroups

COMPANION

General Information

Acronym
COMPANION

Full Name
Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure

Year Presented
2003

Year Published
2009

Conditions

- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Subjects were randomized 1:2:2 open-label to: 1) OPT, 2) CRT + OPT, and 3) CRT-D + OPT. OPT was diuretics, angiotensin-converting enzyme inhibition (ACE-I) or angiotensin receptor blocker (ARB) substitution, β-blockade, and spironolactone; use of digoxin was optional.

Principal Findings

The trial was planned to include 2,200 patients; however, the Data Safety and Monitoring Board discontinued the trial early after the enrollment of 1,520 patients, due to superior efficacy of the primary endpoint in the CRT and CRT-D arms.

The primary endpoint of all-cause mortality or all-cause hospitalizations occurred in 68% of patients in the OPT arm, and was 56% in the CRT + OPT arm (hazard ratio [HR] 0.81, $p = 0.015$) and 56% in the CRT-D + OPT arm (HR 0.80, $p = 0.010$). Mortality alone through 1 year was 19% in the OPT arm, and was marginally reduced in the CRT arm (HR 0.76, $p = 0.06$) and reduced in the CRT-D arm (HR 0.64, $p = 0.003$). The rate of the combined endpoint of time to mortality or heart failure hospitalization was 60% in the OPT arm and was reduced with CRT (HR 0.75, $p = 0.002$) and with CRT-D (HR 0.72, $p < 0.001$). Similar treatment effects were seen in all subgroup analyses.

In the device arms, the implantation success rate was 87% in the CRT arm and 91% in the CRT-D arm. Serious adverse event rates were 10% and 8%, respectively.

After accounting for competing risks, CRT and CRT-D still reduced all-cause hospital admissions by 21% and 25%, respectively.

Interpretation

Among patients with advanced CHF, treatment with CRT or CRT-D was associated with a reduction in the composite of all-cause mortality or all-cause hospitalizations at a median follow-up of 14 months. The trial was discontinued early, due to the superior efficacy in the resynchronization arms.

Early trials have shown an improvement in the endpoints of quality of life, exercise capacity, and functional class with resynchronization in HF patients. However, this is the first large, randomized trial to show an improvement in all-cause mortality and rehospitalizations with resynchronization therapy and implantable cardioverter defibrillator use in severe HF patients.

The patient population was highly selective (severe HF defined by NYHA class III-IV with left ventricular dysfunction and wide QRS of ≥120 ms), and may not be generalizable to other lower-risk HF patients.

Reference

Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure. Results from the comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial. ***Circulation*** 2009;119:969-77.

Bristow MR, et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure. N Engl J Med 2004;350:2140-50.

Presented at Late-Breaking Clinical Trials, ACC 2003.

Presented at the European Society of Cardiology, Vienna, Austria, September 2003.

CRT for the Treatment of HF

General Information

Acronym
Cardiac resynchronization therapy for the treatment of heart failure

Full Name
Cardiac resynchronization therapy for the treatment of heart failure in patients with ventricular tachyarrhythmias

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2003

Conditions

- Heart failure
- Arrhythmias
- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia

Therapies

- Pacing
- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients with symptomatic HF, intraventricular conduction delay, and malignant ventricular tachyarrhythmias requiring therapy from an ICD were implanted with a device capable of providing both CRT and ICD therapy. Patients were randomized to CRT (n=245) or control (no CRT, n=245) for up to six months. The randomized therapy was programmed after 30 days without CRT.

Principal Findings

Although all patients were in New York Heart Association (NYHA) class II-IV at study entry, 40% of the patients who presented in NYHA class III/IV improved to NYHA class I or II, and 19% NYHA class II patients worsened to NYHA class III/IV during the 30-day medical therapy period.

The primary endpoint of HF progression did not differ significantly in the CRT versus the no CRT arm (relative 15% decrease with CRT, p=0.35). The secondary endpoints of peak VO_2 (0.8 ml/kg/min vs. 0.0 ml/kg/min, p=0.030) and six-minute walking test (35 m vs. 15 m, p=0.043) were significantly improved in the CRT arm versus the no CRT arm.

There was no difference in changes in NYHA class (p=0.10) or quality of life (QOL) (p=0.40) between the treatment arms. Ventricular dimensions were improved in the CRT arm (left ventricular [LV] internal diameter in diastole, -3.4 mm vs. -0.3 mm, p< 0.001; LV internal diameter in systole, -4.0 mm vs. -0.7 mm, p< 0.001), as was LV ejection fraction (EF) (5.1% vs. 2.8%, p=0.020). In a subgroup analysis, CRT therapy was associated with improvements in the secondary endpoints of peak VO_2, six-minute walking test, NYHA class, QOL, and LVEF in patients with advanced HF (NYHA class III/IV).

Interpretation

Among patients with symptomatic HF, intraventricular conduction delay, and malignant ventricular tachyarrhythmias, treatment with ICD therapy with CRT was not associated with an improvement in the primary endpoint of progression of HF compared with ICD therapy without CRT therapy, but was associated with improvements in many of the secondary endpoints of functional status.

CRT therapy was also associated with improvements in functional status, but not mortality in both the MIRACLE and MIRACLE ICD studies. The present study was underpowered to detect a significant difference in the primary endpoint because the actual event rate observed was approximately half that expected in the original study design.

Reference

Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42:1454-9.

DAVID II

General Information

Acronym
DAVID II

Full Name
Dual Chamber and VVI Implantable Defibrillator II

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2009

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arrhythmias / Atrial fibrillation
- Heart failure / Ischemic

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Pacing / VVI
- Pacing

Intervention

Patients with impaired LV systolic function who had received a defibrillator and without indication for pacing were randomized to atrial pacing (AAI-70) (n = 300) versus minimal ventricular pacing (VVI-40) (n = 300).

Principal Findings

Overall, 600 patients were randomized. There was no difference in baseline characteristics between treatment arms. In the VVI-40 group, the mean age was 63 years, 15% were women, mean LV ejection fraction was 27%, and ischemic cardiomyopathy was present in 93%.

There was no difference between the groups with respect to the primary endpoint, time to death, or heart failure hospitalization (24.6% for both groups, p = 0.95). There was no difference in the primary outcome among any of the tested subgroups.

There was no difference in death (p = 0.81), heart failure hospitalization (p = 1.0), syncope (p = 0.64), atrial fibrillation (p = 0.61), or first hospitalization (p = 0.46). Quality of life was also similar between the groups.

Interpretation

Among patients with LV dysfunction who had received a defibrillator and did not have a primary indication for pacing, the use of atrial pacing at 70 bpm was similar to minimal ventricular pacing at 40 bpm. This was evident in regard to the primary outcome of time to death or heart failure hospitalization, as well as the secondary outcomes.

The initial DAVID trial demonstrated that dual-chamber pacing was inferior to minimal ventricular pacing (i.e., back-up). The hypothesis was that the act of pacing may not be harmful, but rather the mode of pacing may be culprit (i.e., constant ventricular pacing). In the current trial, according to the authors, when pacing is determined to be necessary in defibrillator patients, atrial pacing may be a "safe alternative" to minimal ventricular pacing, although there is no clear advantage or disadvantage from either strategy.

Reference

Wilkoff BL, Kudenchuk PJ, Buxton AE, et al. The DAVID (Dual Chamber and VVI Implantable Debrillator) II Trial. ***J Am Coll Cardiol*** 2009;53:872-80.

DAVID

General Information

Acronym
DAVID

Full Name
Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2002

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

An ICD with dual-chamber, rate-responsive pacing capability was implanted in all patients. ICDs were programmed to 1) ventricular backup pacing at 40/min (VVI-40; n=256) or 2) dual-chamber rate-responsive pacing at 70/min (DDDR-70; n=250). All patients were also treated with medical therapy for LV dysfunction including ACE inhibitors, beta-blockers, digoxin, and diuretics.

Principal Findings

DAVID was discontinued early by the DSMB due to a trend toward worse outcome with DDDR-70 pacing vs VVI-40 ($p< 0.03$). Nearly all patients were treated with pharmacologic therapy for LV dysfunction during the index hospitalization (96%). Survival free of the composite end point (death or HF hospitalization) occurred in 83.9% of patients in the VVI-40 arm vs 73.3% of patients in the DDDR-70 arm at 1 year (relative hazard 1.61, $p=0.03$). Mortality occurred in 6.5% of the VVI-40 arm vs 10.1% for DDDR-70 (relative hazard 1.61, $p=0.15$). CHF hospitalization also trended higher in the DDDR-70 arm (13.3% for VVI-40 vs 22.6% for DDDR-70, relative hazard 1.54, $p=0.07$).

Interpretation

Contrary to the prespecified hypothesis, treatment with dual-chamber pacing was associated with an increase in

mortality or CHF hospitalizations by 1 year compared with ventricular backup pacing in patients with LV dysfunction and standard indications for ICD therapy but not for pacing. The effectiveness of single-chamber backup pacing ICDs has been previously established in many trials including the AVID and MADIT I trials. However, the DAVID trial addresses the effectiveness of dual chamber ICDs, which are frequently implanted. As the authors noted, two very different patient populations were enrolled in the pacemaker mode selection and the ICD trials. In the pacemaker trials, patients required antibradycardia pacing but only a small proportion of patients in the defibrillator trials needed antibradycardia stimulation. Additionally, in the pacemaker trials, LV function was normal or near normal in most patients but in the defibrillator trials LV function was severely impaired in a large majority of patients. Such differences may explain the dissimilar clinical outcomes in the trials. The authors speculate that the negative impact of DDDR pacing on mortality and heart failure may be due to 1) increased heart rate from the atrial pacing, 2) reduction in the PR interval due to ventricular pacing at the end of the AV interval or 3) the ventricular electrical activation proceeding from the right ventricular apex instead of through the existing conduction system. More than half of the patients in the MADIT II trial of patients without a prior episode of arrhythmia but with LV dysfunction had a dual-chamber defibrillator implanted. While MADIT II demonstrated a mortality benefit with ICD therapy compared with conventional medical therapy, the rate of hospitalization for heart failure trended to occur more frequently in the ICD arm (19.9% vs 14.9%, p=0.09). The possible explanation for this trend is more clearly understood with the current results of the DAVID trial.

Reference

JAMA 2002;288(24):3115-3123.

DEBUT

General Information

Acronym
DEBUT

Full Name
Defibrillator Versus Beta-Blockers for Unexplained Death in Thailand

Year Presented
not applicable

Year Published
2003

Conditions

- Arrhythmias / Ventricular tachycardia
- Arrhythmias / Ventricular fibrillation
- Syncope
- Arrhythmias

Therapies

- Beta blocker
- Implantable Cardioverter Defibrillator (ICD)

Intervention

The subjects of this study were 86 patients without structural heart disease who either survived an unexpected cardiac arrest, or who had syncope, a right bundle branch block, ST-segment elevation in V1-V3, and inducible ventricular tachycardia/fibrillation during electrophysiologic testing. The patients were randomly assigned to receive either an ICD (47 patients) or long-acting propranolol, 40-160 mg/day (39 patients). The duration of the study was 3 years.

Principal Findings

The mean age of the patients was approximately 42 years, and only 2 were women. The mortality rate during follow-up was 18% in the beta-blocker group, and there were no deaths in the ICD group. At least 1 episode of ventricular fibrillation (VF) was effectively terminated in 26% of patients who received an ICD. The annual event rate (sudden death and VF episodes) was 10% in the beta-blocker group and 20% in the ICD group.

Interpretation

Among SUDS patients, the ICD is more effective than beta-blockers for preventing arrhythmic deaths. This is the first study to demonstrate that the ICD is uniformly effective in preventing arrhythmic deaths in patients at risk of VF who do not have structural heart disease. Because there is considerable overlap between SUDS in Southeast

Asia and the Brugada syndrome, it is reasonable to expect that the results of this study also apply to symptomatic patients with the Brugada syndrome.

Reference

Nadamanee K, Veerakul G, Mower M, et al. Defibrillator Versus Beta-Blockers for Unexplained Death in Thailand (DEBUT). A Randomized Clinical Trial. Circulation 2003;107:2221-26.

DEFINITE

General Information

Acronym
DEFINITE

Full Name
Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2003

Year Published
2004

Conditions

- Arrhythmias
- Cardiomyopathy / Hypertrophic

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Medical

Intervention

Patients were randomized to standard medical therapy plus implantation of a single chamber ICD (n=229) or standard medical therapy alone (n=229). Standard medical therapy included angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and when needed digoxins and diuretics. ICD was programmed VVI 40 bpm, VF zone only; 180 bpm.

Principal Findings

Most patients were treated with ACE inhibitors (86%) and beta-blockers (85%). Baseline characteristics were similar in both treatment arms, with the exception of time from cardiomyopathy diagnosis, which was longer in the standard medical therapy arm (3.3 years vs. 2.4 years, p=0.04). The primary endpoint of all-cause mortality at two years was 13.8% in the standard medical therapy arm and 8.1% in the ICD arm (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.40-1.06; p=0.08).

While the difference in all-cause mortality did not reach statistical significance, there was a significant reduction in sudden cardiac death in the ICD arm (n=3 vs. n=14; HR 0.20, 95% CI 0.060-0.71; p=0.006). In the subgroup of patients with New York Heart Association (NYHA) class III, all-cause mortality was signficantly lower in the ICD arm (HR 0.37, 95% CI 0.15-0.90; p=0.02).

Interpretation

Among patients with nonischemic dilated cardiomyopathy, EF ≤35%, and spontaneous premature ventricular complexes or nonsustained ventricular tachycardia, treatment with standard medical therapy plus single chamber ICD implantation was associated with a nonsignificant reduction in all-cause mortality.

The present study is the first randomized trial of primary prevention therapy with ICDs in nonischemic cardiomyopathy patients. The MADIT II trial showed an improvement in mortality associated with ICD therapy in ischemic cardiomyopathy patients. A cost-effectiveness analysis will be performed.

Reference

Kadish A, et al. Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy. N Engl J Med 2004;350:2151-8.

Presented by Dr. Alan Kadish at the November 2003 American Heart Association Annual Scientific Sessions, Orlando, FL.

DINAMIT

General Information

Acronym
DINAMIT

Full Name
Defibrillator in Acute Myocardial Infarction Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2004

Year Published
2004

Conditions

- Coronary heart disease / Acute MI

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients were randomized to ICD therapy (n=332) versus no ICD therapy (n=342) in addition to best medical treatment in survivors of AMI. Cause of death was adjudicated by a committee blinded to treatment assignment.

Principal Findings

Randomization occurred an average of 18 days after the MI, and the ICD was implanted an average of 6.3 days after randomization. Medical therapy included beta-blockers (87%), angiotensin-converting enzyme inhibitors (95%), antiplatelet agents (92%), and lipid-lowering agents (78%).

Anterior MI was present in 72% of patients, and 48% of patients had chronic heart failure (CHF) associated with the index MI. Acute reperfusion therapy (percutaneous transluminal coronary angioplasty, thrombolytic, or both) was performed in 62% of patients.

The primary endpoint of all-cause mortality did not differ between treatment arms (7.5% per year in the ICD arm vs. 6.9% per year in the control arm, hazard ratio [HR] 1.08, 95% confidence interval [CI] 0.76-1.55, p=0.66). Death due to arrhythmia was lower in the ICD arm (1.5% per year vs. 3.5% per year, HR 0.42, 95% CI 0.22-0.83, p=0.009) while nonarrhythmia deaths were higher in the ICD arm (6.1% per year vs. 3.5% per year, HR 1.75, 95% CI 1.11-2.76, p=0.016).

Interpretation

Among recent post-MI patients, prophylactic implantable defibrillator therapy was not associated with a reduction in the primary endpoint of all-cause mortality compared with optimal medical therapy. As would be expected, the frequency of arrhythmia deaths was lower in the prophylactic ICD therapy arm. However, nonarrhythmia deaths were higher in the ICD arm.

The authors suggested that in patients with recent MI, ICD therapy changes the mode of death from arrhythmia to nonarrhythmia (a survival effect from arrhythmia death). In prior trials, prophylactic ICD therapy has been associated with improved survival in patients with ischemic cardiomyopathy, but prophylactic use had not previously been evaluated in recent post-MI patients.

Reference

Hohnloser SH, et al. Prophylactic Use of an Implantable Cardioverter–Defibrillator after Acute Myocardial Infarction. N Engl J Med 2004;351:2481-8.

Presented by Drs. Stewart Connelly and Stefan H. Hohnloser at the American College of Cardiology Annual Scientific Session, March 2004.

Detect SVT Study

General Information

Acronym
Detect Supraventricular Tachycardia Study

Full Name
Detect Supraventricular Tachycardia Study

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2006

Conditions

- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

All patients received a dual-chamber ICD and were randomized within 3 days of implantation to single-chamber (n = 199) or dual-chamber (n = 201) detection. Patients but not physicians were blinded to randomization. Programming was done to minimize ventricular pacing.

Principal Findings

The main reason for ICD implantation was for primary prevention of sudden death (67%). Twenty-five percent of patients had a known history of SVT, and 81% had coronary artery disease. SVTs occurred in 31% of the single-chamber group and 37% of the dual-chamber group, with 42% of the episodes in the single-chamber group and 69% of the episodes in the dual-chamber group due to SVT ($p = 0.06$). The crossover rate from single-chamber to dual-chamber detection was higher than crossover in the other direction ($n = 17$ vs. $n = 2$, $p < 0.001$).

The primary endpoint of inappropriate detection of SVT was 39.5% in the single-chamber group compared with 30.9% in the dual-chamber group ($p = 0.03$). The median number of episodes among patients with an SVT episode was 4 (range 1-58). The median number of episodes until the first inappropriate detection was 1.5 in the single-chamber group and 4 in the dual-chamber group, but there was no difference in the time to first inappropriate detection (103 days vs. 108 days, $p = 0.45$). Inappropriate therapy (antitachycardia pacing/shock) due to inappropriate detection occurred more frequently in the single-chamber group (33.0% vs. 24.8%, $p = 0.02$), but there was no difference in the overall rate of inappropriate shock ($p = 0.18$).

Mortality occurred in 3.5% of patients in each group. There was no difference in the frequency of complications, with 1 patient with atrial lead fracture/failure, 4 with atrial lead dislodgment, and 4 with atrial sensing errors.

Interpretation

Among patients with ICDs for a range of indications, use of dual-chamber detection was associated with a lower rate of inappropriate SVT detection through 6 months of follow-up compared with single-chamber detection.

Delivery of inappropriate shocks was a result of misclassification of SVT as VT causes undue pain and can be anxiety-provoking, impairing patients' quality of life. Several prior studies have not shown a difference in inappropriate therapies between single- and dual-chamber detection. The present study demonstrated a reduction in inappropriate detection and inappropriate therapies, but did not show a difference in inappropriate shock, due in part to a higher rate of pacing in the single-chamber group.

Reference

Friedman PA, McClelland RL, Bamlet WR, et al. Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the detect supraventricular tachycardia study. Circulation 2006;113:2871-9.

EMPIRIC

General Information

Acronym
EMPIRIC

Full Name
Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter Defibrillators Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2006

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients were randomized to standardized (n = 445) or physician-tailored (n = 455) ventricular tachycardia/ventricular fibrillation (VT/VF) programming of their ICD. In the standardized group, the programming was targeted to: 1) avoid detecting nonsustained tachycardias; 2) avoid detecting supraventicular tachycardias (SVTs) as VT; 3) empirical antitachycardia pacing (ATP) for slow and fast VTs; and 4) high-output first shocks.

Principal Findings

ICD indication was primary prevention in 46% of patients and secondary prevention in 54% of patients, with spontaneous sustained monomorphic VT the most frequently reported type of secondary prevention (26%). As expected, the programming in the tailored arm varied greatly. Detection of VF was programmed at 12-16 beats in 50% of patients and 18-24 beats in 49% of patients. The number of patients received 1 shock in both arms (18.2% for standardized arm vs. 19.1% for tailored arm). The number of SVT episodes detected was higher in the standardized arm (1,083 vs. 585, $p < 0.001$), but inappropriate shocks did not differ (125 vs. 118).

The primary endpoint of VT/VF (22.3% vs. 28.7%) and SVT or other non-VT/VF event episodes (11.9% vs. 26.1%) resulting in a shock met both the criteria for noninferiority and superiority in the standardized arm compared to the tailored arm. Time to first all-cause shock was noninferior in the standardized arm (hazard ratio [HR], 0.95; 90% confidence interval [CI], 0.74-1.23; noninferiority p = 0.0016). Time to first VT/VF shock in the standardized arm was nonsignificantly longer than the tailored group (HR, 0.80; 90% CI, 0.56-1.14; superiority p=0.297). The percent of patients with 5 shocks for all-cause VT/VF was lower in the standardized arm (3.8% vs. 7.0%, p = 0.039), as was true VT/VF (0.9% vs. 3.3%, p = 0.018). In the standardized arm, there were fewer unscheduled hospitalizations (n = 163 vs. n = 216, p = 0.001), but there were no differences in other clinical measures, including total mortality (n = 24 vs. n = 30), syncope (n = 2 vs. n = 3), emergency room visits (n = 44 vs. n = 46), or unscheduled outpatient visits (n = 308 vs. n = 293).

Interpretation

Among patients with standard indications for ICD placement, use of standardized VT/VF programming was associated with a reduction in the primary endpoints of VT/VF and SVT or other non-VT/VF event episodes resulting in shock compared with physician-tailored programming.

Programming of ICDs can be complicated, with multiple options for detecting and treating rhythms. The choice of programming is generally user specific, with some physicians favoring ATP for preventing shock, and can be tailored specifically to the patient. Delivery of inappropriate shocks as a result of misclassification of SVT as VT causes undue pain and can be anxiety-provoking, impairing patients' quality of life.

Reference

Wilkoff BL, Ousdigian KT, Sterns LD, Wang ZJ, Wilson RD, Morgan JM. A comparison of empiric to physician-tailored programming of implantable cardioverter-defibrillators: results from the prospective randomized multicenter EMPIRIC trial. J Am Coll Cardiol 2006;48:330-9.

INTRINSIC RV

General Information

Acronym
INTRINSIC RV

Full Name
Inhibition of Unnecessary RV Pacing With AV Search Hysteresis in ICDs

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2006

Year Published
not yet published

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients were implanted with a VITALITY AVT ICD that was programmed to dual-chamber rate-adaptive pacemaker (DDDR) mode. After one week, patients with right ventricular (RV) pacing < 20% were randomized to continued programming of DDDR AV search hysteresis (AVSH) 60-130 (n = 502) or reprogramming to VVI-40 (n = 486).

Principal Findings

At baseline, 67% of patients had coronary artery disease. Beta-blockers were used in 78% of patients, angiotensin-converting enzyme inhibitors in 64%, and diuretics in 50%.

The primary endpoint of death or heart failure hospitalization occurred in 6.4% of the DDDR AVSH group and 9.5% of the VVI-40 group, meeting the threshold for noninferiority. For superiority of DDDR AVSH, p = 0.072 and the risk ratio was 0.67. All-cause mortality also met the criteria for noninferiority (3.6% for DDDR AVSH vs. 5.1% for VVI-40 group, p < 0.001 for noninferiority, p = 0.23 for superiority). During follow-up, RV pacing in the DDDR AVSH group averaged 10%.

Interpretation

Among patients implanted with an ICD for standard indications, use of dual-chamber DDDR AVSH pacing was noninferior to single-chamber VVI-40 pacing for death or heart failure hospitalization at 1 year.

Results of the present trial differ from those of the DAVID trial, which showed treatment with dual-chamber pacing was associated with an increase in mortality or congestive heart failure hospitalizations by 1 year compared with ventricular backup pacing in patients with LV dysfunction and standard indications for ICD therapy, but not for

pacing. There are several major differences between the trials, including pacing at a lower threshold in the present trial (60 bpm vs. 70 bpm in DAVID) and the patient population, which in INTRINSIC RV excluded patients with >20% RV pacing in the first week.

Reference

Presented by Brian Olshansky, MD, at the Heart Rhythm Society Annual Scientific Sessions, Boston, MA, May 2006.

IRIS

General Information

Acronym
IRIS

Full Name
Immediate Risk-Stratification Improves Survival

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2009

Year Published
2009

Conditions

- Arrhythmias
- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Coronary heart disease
- Coronary heart disease / Acute MI
- Coronary heart disease / Acute MI / Arrhythmia
- Coronary heart disease / Acute MI / Arrhythmia / VT/VF
- Coronary heart disease / Acute MI / Heart Failure
- Heart failure / Ischemic
- Prevention
- Prevention/Primary

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients with high-risk criteria early after acute MI were randomized to ICD implantation (445) or no ICD implantation (453).

Principal Findings

Index diagnosis was ST-elevation MI in 77% of patients. Multivessel coronary disease was present in 57% of patients. Approximately two-thirds of patients received PTCA, and approximately 25% of patients received no reperfusion therapy. There was no difference in the primary endpoint of all-cause mortality between groups at 3 years (26.1% vs. 25.8%, p = 0.76).

Subgroup analysis failed to identify a subgroup of patients who benefited from early ICD implantation. While the incidence of sudden cardiac death was significantly reduced in the ICD group, the incidence of nonsudden cardiac death was increased.

Interpretation

The benefit of ICD implantation in patients with prior MI and left ventricular dysfunction was established in the MADIT II trial. However, the DINAMIT trial failed to demonstrate a benefit to routine early ICD implantation following MI.

The results from IRIS complement the findings from DINAMIT, and suggest that the reduction in sudden cardiac death with ICD implantation early after MI is counterbalanced by an increase in nonsudden cardiac death. Based on these findings, routine ICD implantation early after MI cannot be recommended at this time.

Reference

Steinbeck G, Andresen D, Seidel K, et al. Defibrillator implantation early after myocardial infarction. ***N Engl J Med*** 2009;361:1427-36.

A Randomised Study of the Effects of Optimal Medical Therapy Alone or in Combination With Cardioverter-Defibrillator Implantation on Survival in Patients Early After Myocardial Infarction. Presented by Dr. Gerhard Steinbeck at ACC.09/i2, Orlando, FL, March 2009.

InSync ICD

General Information

Acronym
InSync ICD

Full Name

Year Presented
2002

Year Published
not yet published

Conditions

- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients with NYHA Class II-IV heart failure, QRS duration of =130 ms, LVEF =35%, LVEDD =55 mm, who were stabilized on appropriate medical therapy, and indicated for an ICD were randomized to either implantation of the device with the cardiac resynchronization mode on, or to a control group, in whom the cardiac resynchronization mode was turned off. The ICD function was active in all patients. In all, there were a total of 636 subjects of NYHA Class II (n=215) or NYHA Class III/IV (n=421). Of the Class II subjects, 192 were randomized to either control or CRT. Of Class III/IV subjects, 362 were randomized to either control or CRT. In all, 371 patients received the implants. Patients in both the treatment and control groups were similar as far as heart rate, 6-minute walk distance, systolic and diastolic blood pressures, and the use of diuretic, ACE-I or ARB, and beta-blocker use. Similar percentages of patients with NYHA Class III were present in both groups (89% of controls and 88% in treatment group), and heart failure of ischemic etiology was present in 74% and 63%, respectively.

Principal Findings

Insertion of the device was achieved with 88% safety and efficacy, with roughly 90% of the implants implanted successfully. There were a total of 49 events observed in 44 patients, with an observed 6-month rate of 85.1%. Significant changes in NYHA functional class were seen in the treatment group, compared with controls; 63% of the treatment group improved, compared with 47% of the control group; 34% and 48% of the groups, respectively, stayed the same; while 3% of the treatment group worsened, compared with 5% of the control group. Clinical composite response results were improved in 55% of treatment patients, compared with 40% of controls; no change in 19% vs. 26%, respectively; and worsening in 26% vs. 33%, respectively.

Interpretation

n/a

Reference

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n/a

MADIT-CRT – Presented at ESC 2009

General Information

Acronym
MADIT-CRT—Presented at ESC 2009

Full Name
Multicenter Automatic Defibrillator Implantation TrialCardiac Resynchronization Therapy

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2009

Year Published
2009

Conditions

- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

All patients received Boston Scientific devices (who were the trial sponsors). Patients were randomized in a 3:2 fashion to receive either CRT-D or ICD alone. CRT was programmed to maximize biventricular programming, and atrioventricular delay was optimized using the latest optimization techniques. Single- or dual-chamber ICD devices were implanted, with a goal to minimize RV pacing.

Ventricular tachycardia zone was set at 180 bpm, and the ventricular fibrillation zone at 210 bpm. The programmed mode in the CRT-ICD arm was DDD with a lower rate of 40 bpm, with hysteresis off. In the ICD only arm, the programmed mode was VVI or DDI for single- and dual-chamber units, respectively, with a lower rate of 40 bpm, with hysteresis off.

Principal Findings

A total of 1,820 patients were enrolled from 110 hospitals in the United States and Europe, of which 1,089 received CRT-D, and 731 received ICD alone. The trial was terminated early, owing to a benefit noted in the CRT-D arm versus the ICD arm, which reached the prespecified efficacy boundary for interim analysis.

Baseline characteristics were fairly similar between the two arms. Patients enrolled in the trial were predominantly white (90.5%). About 55% had ICM, and about 10% of the patients had NYHA class III/IV symptoms >3 months prior to enrollment. The mean LVEF was 24%, with a mean 6-minute walk distance of about 361 ms. Atrial fibrillation (AF) was noted in about 12% of the patients, and diabetes in about 30.4%. The majority of patients had a left

bundle branch block on electrocardiogram (70.6%), and a QRS width ≥150 ms (64.6%). The mean LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) were 177 and 248 ml, respectively. Device implantation was successful in 98.4% of the patients, with 95.4% receiving the device to which they had been assigned. The device was removed in about 1% of the patients during follow-up.

The primary endpoint of death or nonfatal CHF events was less frequent in the CRT-D arm, compared with the ICD arm (17.2% vs. 25.3%, hazard ratio 0.66, 95% confidence interval 0.52-0.84, p = 0.001), driven predominantly by a reduction in CHF events (13.9% vs. 22.8%, p < 0.001), with no difference in all-cause mortality (6.8% vs. 7.3%, p = 0.99). This was true of patients with both ICM and NICM. Subgroup analyses demonstrated a greater benefit in women than in men (p = 0.01), and in those with a QRS duration ≥150 ms (p = 0.001). LVEF improved to a greater extent compared with baseline in the CRT-D arm (0.11 vs. 0.03, p < 0.001). Similarly, LVESV and LVEDV both reduced significantly compared to baseline in the CRT-D arm (57 ml vs. 18 ml, and 52 ml vs. 15 ml, respectively; p < 0.001 for both).

Adverse events in the 30 days after implantation were numerically higher in the CRT-D arm compared to the ICD arm, including pneumothorax (1.7% vs. 0.8%), infection (1.1% vs. 0.7%), and pocket hematoma needing evacuation (3.3% vs. 2.5%). About 4% of patients in the CRT-D arm needed coronary vein/sinus lead revision in the first 30 days.

Interpretation

The results of the MADIT-CRT trial indicate that CRT-D implantation in patients with systolic CHF (LVEF≤30%), with a wide QRS, and NYHA class I/II symptoms (asymptomatic or mildly symptomatic patients) is associated with a significant reduction in the primary endpoint of CHF events or mortality, as compared with ICD implantation alone, primarily due to a reduction in CHF events. Further, CRT-D implantation is associated with a significant albeit modest improvement in LVEF and LV volumes, as measured by echocardiography in a subgroup of patients.

Improvements in LV dimensions with CRT in mildly asymptomatic CHF patients have been noted earlier in the MIRACLE ICD-II and REVERSE trials. However, no significant difference in clinical endpoints was noted in these trials. MADIT-CRT is the largest trial on this topic, and noted an improvement in clinical endpoints, primarily CHF events.

One criticism is that investigators adjudicating on baseline functional status, and therapy or admission for CHF were not blinded to study group assignments, and could thus have biased the results toward a benefit in the CRT-D arm. Further, at least 10% of the patients in both arms had NYHA class III/IV symptoms >3 months prior to enrollment, and would thus have qualified for CRT-D, based on current criteria. The inclusion of these patients could also have biased the results in favor of the CRT-D arm.

Other considerations include analyzing the cost-effectiveness of CRT-D compared with ICD in future trials, since CRT-D implantation is significantly more expensive than ICD implantation alone.

Reference

Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. ***N Engl J Med*** 2009;Sep 1:[Epub ahead of print].

MADIT-CRT News Release, June 23, 2009.

MADIT II

General Information

Acronym
MADIT-II

Full Name
Multicenter Automatic Defibrillator Implantation Trial II

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2001

Year Published
2002

Conditions

- Coronary heart disease
- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

ICD placement in a 3(ICD):2(non-ICD) ratio

Principal Findings

The study was stopped early in November 2001 by the Data Safety Monitoring Board. Mortality was 14.2% in the ICD arm versus 19.8% in the conventional therapy arm (p=0.016), a 31% relative reduction (hazard ratio 0.69).

Kaplan-Meier estimates of survival show the two groups did not begin to diverge until nine months, and continued thereafter (p=0.007). The effect of defibrillator therapy on survival was similar in subgroup analyses stratified according to age, sex, EF, New York Heart Association (NYHA) class, and the QRS interval.

Hospitalization for heart failure trended to occur more frequently in patients implanted with an ICD compared with conventional therapy (19.9% vs. 14.9%, p=0.09).

Interpretation

ICD implantation was associated with a 31% reduction in overall mortality compared to conventional therapy over an average follow-up period of two years. Unlike MADIT I, which demonstrated an early survival benefit with ICD,

no mortality reduction was observed until nine months.

The trend toward higher rates of heart failure may be due to the longer time for heart failure to develop since ICD placement was associated with improved survival, but may also be due to defibrillator shocks resulting in myocardial injury or backup ventricular pacing impairing ventricular function.

If the FDA approves this modality, an additional 400,000 patients would be eligible for ICD placement annually. It remains to be determined if the substantial increased cost of this intervention can be borne by the health care system, and if sufficient manpower is available to place the defibrillators.

Reference

Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.

MADIT

General Information

Acronym
MADIT

Full Name
Multicenter Automatic Defibrillator Implantation Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
1996

Conditions

- Coronary heart disease / Acute MI / Arrhythmia
- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arrhythmias
- Coronary heart disease
- Coronary heart disease / Acute MI

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Medical

Intervention

ICD or conventional drug therapy, which included amiodarone (74% of patients in the nondevice arm), digitalis, disopyramide, mexiletine, procainamide, tocainide, beta-blockers, and sotalol; few patients received type IA agents and no patients received type IC agents.

Principal Findings

The Kaplan-Meier cumulative survival curve for the 196 patients after randomization showed improved survival in the ICD arm, with a separation that began early after implantation. This difference continued to the end of the trial. A log-rank statistic p value indicates that the likelihood of this benefit from the ICD by chance alone is <0.009.

The hazard ratio was 0.46. This means that there was a 54% reduction in total, all-cause mortality in the ICD arm relative to the best conventional treatment (p=0.009).

Most of the mortality reduction was caused by a decrease in arrhythmic death. Patients in the ICD group

experienced arrhythmic death much less frequently than conventionally treated patients.

The average survival for the defibrillator group over a four-year period was 3.66 years compared with 2.80 years for conventionally treated patients. Accumulated net costs were $97,560 for the defibrillator group compared with $75,980 for individuals treated with medications alone. The resulting incremental cost-effectiveness ratio of $27,000 per life-year saved compares favorably with other cardiac interventions.

Interpretation

The implantation of an ICD is associated with a significant 54% reduction in total mortality in high-risk coronary patients when compared with conventional medical therapy. An ICD is cost-effective in selected individuals at high risk for ventricular arrhythmias.

Reference

1) Multicenter automatic defibrillator implantation trial (MADIT): design and clinical protocol. MADIT Executive Committee. Pacing Clin Electrophysiol 1991;14:920-27.
2) Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.
3) Moss AJ. Update on MADIT: the Multicenter Automatic Defibrillator Implantation Trial. The long QT interval syndrome. Am J Cardiol 1997;79(6A):16-9.
4) Mushlin AI, Hall WJ, Zwanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. Multicenter Automatic Defibrillator Implantation Trial. Circulation 1998;97:2129-35.

MASTER

General Information

Acronym
MASTER

Full Name
Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2007

Year Published
2008

Conditions

- Coronary heart disease
- Heart failure / Ischemic
- Arrhythmias / Ventricular tachycardia
- Arrhythmias / Ventricular fibrillation

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

All patients underwent MTWA testing at baseline and were classified as MTWA negative or all others (positive or indeterminant). If testing was initially indeterminant, testing was to be repeated if possible. After testing, ICD implantation was then performed. Repeat MTWA testing was performed every 12 months.

Principal Findings

Baseline MTWA was negative in 37% of patients, positive in 51%, and indeterminate in 12%. Mean ejection fraction was 24%. A history of atrial fibrillation was present in 18% of the cohort. Cardiac resynchronization therapy was used in 23% of the population. Patients with a non-negative MTWA test were generally higher risk at baseline than patients with a negative MTWA, including being older (mean age 66 years for the non-negative group vs. 63 years for the negative group, p = 0.006), and more frequently having a QRS duration 120 msec (55% of the non-negative group vs. 44% of the negative group, p = 0.01).

The primary endpoint of life-threatening ventricular tachyarrhythmic events occurred in 10.3% of the MTWA-negative cohort and 13.3% of the non-negative cohort (hazard ratio [HR] 1.26, 95% confidence interval 0.76-2.09, p = 0.37). Results were similar when excluding the indeterminate MTWA group. Total mortality was lower in the MTWA-negative cohort compared with the non-negative cohort (6% vs. 13%, HR 2.04, p = 0.02), but among the

causes of death, the difference in mortality was not driven by sudden death, but by noncardiac deaths.

Interpretation

Among post-MI patients with impaired ejection fraction undergoing ICD implantation, risk stratification using MTWA testing was not associated with a difference in prediction of life-threatening ventricular tachyarrhythmic events.

According to the author, MTWA is thought to be a marker for electrophysiological abnormalities that predispose to re-entrant ventricular arrhythmias. A non-negative MTWA was associated with a higher risk of total mortality, but not specifically an increase in arrhythmic death. These findings suggest that a positive MTWA test may just identify a cohort of sicker patients, as evidenced by the increase in baseline risk and the increase in total mortality, but not identify a cohort at higher risk of sudden death. Similar results have been shown with other studies of MTWA testing. Predicting arrhythmic death has proven elusive, with limited clinical or physiologic parameters identified that correlate with sudden death.

Reference

Chow T, Keriakes DJ, Onufer J, et al., on behalf of the MASTER Trial Investigators. Does Microvolt T-Wave Alternans Testing Predict Ventricular Tachyarrhythmias in Patients With Ischemic Cardiomyopathy and Prophylactic Defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) Trial. ***J Am Coll Cardiol*** 2008;52:1607-15.

Presented by Dr. Theodore Chow at the American Heart Association Annual Scientific Session, Orlando, FL, November 2007.

MIRACLE ICD

General Information

Acronym
MIRACLE ICD

Full Name
Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2003

Conditions

- Heart failure

Therapies

- Pacing / Dual chamber
- Implantable Cardioverter Defibrillator (ICD)
- Pacing

Intervention

Following baseline assessment, patients underwent implant attempt within one week. Following successful lead placement, patients underwent a predischarge randomization to the control group (ICD on but CRT not on, n=182) or experimental group (both ICD and CRT on, n=187), then underwent a six-month period of double-blinded study with follow-up at one, three, and six months.

For patients in the CRT arm, the device was programmed to pace both ventricles simultaneously following atrial-sensed events at rates of ≤130/min, while atrial pacing occurred only for sinus rates < 35/min. In the control arm, the device did not provide atrial or ventricular pacing unless the intrinsic rate was < 35/min.

The electrophysiologist served as an unblinded third party, and the heart failure specialist, the managing physician, and the patient were kept blinded to study assignment during the six-month period of the study.

Principal Findings

Device implantation was unsuccessful in 50 patients who were subsequently not randomized. Compared with placebo, CRT was associated with a significantly improved New York Heart Association (NYHA) class by at least one class (median class change -1 vs. 0, p=0.007) and quality of life (-17.5 vs. -11 points, p=0.02), but no difference in six-minute walk distance (+55 vs. +53 m, p=0.36).

Many of the secondary endpoints were improved in the CRT arm, including time on the treadmill during exercise testing (+55.5 vs. -11 second, p< 0.001) and peak oxygen consumption (+1.1 vs. +0.1 ml/kg/min, p=0.04), and trend towards improved end-diastolic volume (-19.9 vs. -5.7 ml, p=0.06), end-systolic volume (-22.2 vs. -8.2 ml, p=0.06), and ejection fraction (+2.1% vs. +1.7%, p=0.12). The QRS duration was significantly lower in CRT patients compared with control (-20 vs. 0 ms, p< 0.001).

Using the change in overall clinical status, there was a trend for a higher percentage of CRT patients to be classified as improved (52% vs. 43%, p=0.07). There was no difference in mortality (7.6% vs. 7.8%, p=0.96) or the composite of death or repeat hospitalization for worsening HF (25.7% vs. 25.9%, p=0.69).

Interpretation

Among patients with CHF, a wide QRS interval, and arrhythmias, cardiac resynchronization with ICD was associated with improved functional class and improved quality of life, but no difference in six-minute walk distance over ICD alone.

While two of the three primary endpoints of the MIRACLE ICD trial were positive for CRT therapy, the data were not as consistent as the benefit seen in the MIRACLE trial, which had a similar design, but enrolled patients without an indication for ICD therapy. In the MIRACLE trial, CRT was associated with improvements in all three of the primary endpoints as well as all of the prespecified secondary endpoints, including clinical status, LV volume, and ejection fraction (EF).

The authors hypothesize that the difference in outcomes between the two similarly designed trials may be due to the fact the patients in the MIRACLE ICD trial were sicker, with less opportunity for morphometric remodeling from the CRT. Nonetheless, CRT was associated with improvement in two of the three primary endpoints in the MIRACLE ICD trial as well as many of the prespecified secondary endpoints (treadmill exercise duration, peak oxygen consumption, QRS duration).

Reference

Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003;289:2685–94.

Maximizing Patient Benefit From CRT With the Addition of Structured Exercise Training

General Information

Acronym
Maximizing Patient Benefit From Cardiac Resynchronization Therapy With the Addition of Structured Exercise Training

Full Name
Maximizing Patient Benefit From Cardiac Resynchronization Therapy With the Addition of Structured Exercise Training

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2009

Conditions

- Heart failure

Therapies

- Exercise
- Implantable Cardioverter Defibrillator (ICD)

Intervention

Three months after CRT implantation, patients were randomized into an exercise group and a control group. The exercise group underwent a program of physician-supervised exercise training consisting of three 30-minute visits/week. Each session consisted of 10-minute treadmill walking followed by 10-minute cycling, and then a further 10-minute treadmill walking. The intensity was 80% of the peak heart rate (HR) achieved at the 3-month test for the first 4 weeks, 85% for the next 4 weeks, and 90% for the final 4 weeks.

The exercise group was not provided with any specific instruction or guidance to perform exercise outside of the study. The control group was given no specific advice on exercise training and underwent no supervised training.

Principal Findings

A total of 50 patients were randomized, 25 to each arm. Baseline characteristics were fairly similar. Patients had predominantly NYHA functional class III congestive heart failure, with a mean peak VO_2 of 16.1 ml/kg/min, and exercise capacity of 374 seconds. Mean QRS duration was 160 ms, with a mean left ventricular end-diastolic diameter (LVEDD) of 7.1 cm and an ejection fraction (EF) of 24.0%. Sinus rhythm was noted in 66% of the patients.

Three months after CRT, there was a significant improvement in mean peak VO_2 to 18.4 ± 3.6 ($p < 0.001$), and

exercise duration to 562 seconds ($p < 0.001$). Cardiac indices such as peak cardiac power output and cardiac reserve also improved; however, peak VO_2 at the anaerobic threshold remained unchanged. Echocardiographic parameters such as LVEDD (7.07 ± 0.87 vs. 6.64 ± 0.77 cm, $p < 0.001$) and LVEF (23.7 ± 8.7 vs. 32.4 ± 6.2%, $p < 0.001$) were also significantly improved, while quality of life also improved.

Six months after CRT, the exercise arm was noted to have higher exercise duration (mean change: 171 vs. 30 seconds, $p < 0.001$), peak VO_2 (mean change 1.39 vs. -0.01, $p = 0.022$), with further improvements in quality of life, as compared with the standard therapy arm. Although significantly changed from baseline in both arms, there was no difference between the two arms at 6 months in LVEDD or LVEF. No side effects relating to exercise or arrhythmias were noted in the exercise arm.

Interpretation

The American College of Cardiology/American Heart Association guidelines currently recommend exercise training for all patients with chronic systolic heart failure, and its benefits were confirmed in the recently published HF-ACTION trial. Similarly, the beneficial effects of CRT on exercise capacity in these patients have been noted before. The results of this small, single-center, randomized, controlled trial indicate that exercise training in addition to CRT may be associated with even greater symptomatic and exercise capacity benefits in patients with chronic systolic heart failure.

Further follow-up may be necessary to document improvements in echocardiographic parameters such as LVEDD and LVEF. This is a simple, cost-effective, and safe intervention, and should be recommended in all such patients.

Reference

Patwala A, Woods PR, Sharp L, Goldspink DF, Tan LB, Wright DJ. Maximizing patient benefit from cardiac resynchronization therapy with the addition of structured exercise training: a randomized controlled study. ***J Am Coll Cardiol*** 2009;53:2332-9.

RBBB and ST-Segment Elevation Syndrome

General Information

Acronym
Right Bundle Branch Block and ST-Segment Elevation Syndrome

Full Name
Clinical and Genetic Heterogeneity of Right Bundle Branch Block and ST-Segment Elevation Syndrome: A Prospective Evaluation of 52 Families

Year Presented
2000

Year Published
2000

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Coronary heart disease / Acute MI
- Arrhythmias
- Coronary heart disease

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Observational series

Intervention

Sixty individuals from 52 families were diagnosed as having the Brugada syndrome based on clinical and ECG criteria. Thirty of these patients had a history of cardiac arrest/syncope, and 30 were asymptomatic. Pharmacologic challenge with intravenous flecainide or ajmaline was performed in 41 patients, and 39 patients underwent electrophysiologic testing to determine whether ventricular tachycardia (VT) or fibrillation (VF) was inducible. Genetic analysis for mutations of the SCN5A gene was performed in 52 of the probands and in 44 family members who had no clinical evidence of the Brugada syndrome. The patients were treated according to physician preference (cardioverter/defibrillator [ICD] in 26 patients and drug therapy in five patients).

Principal Findings

The pharmacologic challenge was positive (induction or worsening of ST elevation in V1-V3) in 85% of the patients. The test results were not reproducible in three of six patients in whom serial testing was performed. VT/VF was inducible in 67% of patients. The positive predictive value of inducible VT/VF for cardiac arrest/syncope during follow-up was 50%, and the negative predictive value was 46%. During a mean of 33 months of follow-up, the incidence of cardiac arrest/syncope was 29% in symptomatic patients, and 0% in the asymptomatic patients. A mutation of the SCN5A gene was found in 15% of the tested probands and in 45% of the tested asymptomatic family members. A drug challenge was positive in only 15% of silent gene carriers.

Interpretation

This is an important study because it challenges current views regarding the Brugada syndrome. From the clinical standpoint, perhaps the most important contrary finding is that asymptomatic patients are at low risk and need not necessarily be treated with an ICD. However, additional follow-up is needed to establish whether these patients maintain a benign prognosis beyond 3 years of follow-up.

Reference

1. Priori SG, Napolitano C, Gasparini M, et al. Circulation 2000;102:2509-15.

SCD-HeFT Cost-Effectiveness Study

General Information

Acronym
SCD-HeFT Cost-Effectiveness Study

Full Name
SCD-HeFT Cost-Effectiveness Study

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2004

Year Published
not yet published

Conditions

- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Antiarrhythmic / Class III / Amiodarone

Intervention

As previously described, randomization to a single-chamber ICD, amiodarone 200-400 mg/day, or placebo

Principal Findings

A total of 2,521 patients were enrolled in the study; 52% of patients had ischemic cardiomyopathy. In the overall study population, there was no effect of amiodarone on survival (the primary endpoint), while there was a highly significant 23% reduction in mortality among patients randomized to ICD therapy.

The cost-effectiveness substudy assessed 2003 US dollar costs to the health care system in an intent-to-treat analysis. Costs assessed were resource use, hospitalization costs (from billing data), physician costs (based on Medicare rates), outpatient medication costs, and ICD costs (mean of $17,500). Five-year total costs were $49,444 for amiodarone, $43,077 for placebo, and $61,967 for ICD therapy ($p=0.078$ for amiodarone vs. placebo; $p< 0.001$ for ICD vs. placebo).

The benefits of the various therapies over placebo were modeled from a societal perspective (not including nonmedical and productivity costs) over the lifetime of the study, given the assumptions that the benefit of a given therapy would be constant over time. Using this model, the life expectancy in the placebo arm was 8.4 years, while it was 10.8 years in the ICD arm. Thus, the cost-effectiveness of ICD therapy was $27,718 per life-year (undiscounted) or $33,192 (discounted 3%).

The cost-effectiveness of amiodarone therapy was not calculated, given that amiodarone was more costly than placebo without a survival benefit. The cost-effectiveness of ICD therapy appeared robust in sensitivity analyses, and was similar among patients with ischemic versus nonischemic cardiomyopathy. The cost per life-year was slightly greater among patients with NYHA class III heart failure than among patients with NYHA class II heart failure.

Interpretation

The SCD-HeFT trial demonstrated a survival benefit of a single-chamber ICD over placebo and amiodarone for patients with CHF. In this prespecified cost-effectiveness analysis, ICD therapy was demonstrated to be a cost-effective intervention (interventions costing < $40,000-50,000 are generally considered to be cost-effective from a societal perspective). Although ICD therapy was more costly than treatment with placebo, the survival benefit associated with ICD therapy appeared to offset the increased cost from a societal perspective.

Reference

Presented by Daniel B. Mark at the American Heart Association Scientific Sessions, November 2004, New Orleans, LA.

SCD-HeFT

General Information

Acronym
SCD-HeFT

Full Name
Sudden Cardiac Death in Heart Failure Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2004

Year Published
2005

Conditions

- Heart failure

Therapies

- Antiarrhythmic / Class III / Amiodarone
- Implantable Cardioverter Defibrillator (ICD)
- Antiarrhythmic

Intervention

Patients were randomized in a double-blind manner to either: 1) Conventional CHF therapy and placebo, 2) conventional CHF therapy plus amiodarone, or 3) conventional CHF therapy plus a conservatively programmed single lead ICD. Amiodarone was dosed at 800 mg during the first week, 400 mg during weeks 2-4, and chronically at 200 mg/day if < 150 lbs, 300 mg/day if 150-200 lbs, and 400 mg/day if >200 lbs.

ICDs were programmed for ventricular fibrillation (VF) treatment only. Patients underwent a six-minute walk test and Holter monitoring.

Principal Findings

At the end of follow-up, medication use included 72% on angiotensin-converting enzyme inhibitors, 78% on beta-blockers, 80% on loop diuretics, and 55% on aspirin. Baseline median six-minute walk was 1,130 feet. Prior duration of CHF was 24.5 months at baseline.

There was no difference in all-cause mortality between the amiodarone and placebo arm (28% vs 29%, hazard ratio [HR] 1.06, 97.5% confidence interval [CI] 0.86-1.30, p=0.53), but mortality was lower in the ICD arm compared with placebo (22% vs 29%, HR 0.77, 97.5% CI 0.62-0.96, p=0.007). Subgroup analysis showed similar results for the amiodarone versus placebo comparison in the prespecified subgroups, with the exception of NYHA class III, which

had an increased mortality in the amiodarone group (HR 1.44, 97.5% CI 1.05-1.97; n=497).

Interpretation

Among patients with NYHA class II or III CHF and reduced LVEF, treatment with an implantable ICD was associated with a reduction in all-cause mortality compared with placebo, but there was no difference between amiodarone and placebo. The ICD was programmed for VF treatment only.

Reference

Bardy GH, et al. Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure. N Engl J Med 2005;352:225-37.

Presented by Dr. Gust H. Bardy at the American College of Cardiology Annual Scientific Session, March 2004.

Bardy GH, Lee KL, Mauk DB, and the SCD-HeFT Pilot Investigators. The Sudden Cardiac Death in Heart Failure Trial: pilot study. PACE 1997;20:1148 (Abstract).

SMASH-VT

General Information

Acronym
SMASH-VT

Full Name
Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2006

Year Published
2007

Conditions

- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Arteriosclerosis
- Coronary heart disease / Acute MI / Heart Failure
- Heart failure / Ischemic
- Prevention/Secondary
- Syncope

Therapies

- Implantable Cardioverter Defibrillator (ICD)
- Electrophysiologic study

Intervention

Patients with prior MI and an unstable ventricular arrhythmia who had a defibrillator implanted were randomized (1:1) to prophylactic catheter ablation of arrhythmogenic ventricular tissue during sinus rhythm versus control (defibrillator only).

Principal Findings

The qualifying arrhythmic event was ventricular fibrillation (VF; 18%), unstable ventricular tachycardia (VT; 49%), syncope with inducible VT (21%), and defibrillator implanted for primary prophylaxis (12%). Baseline characteristics were well matched except for severe left ventricular (LV) dysfunction, which was marginally more common in the ablation group (25% vs. 11%, p = 0.06). There were three complications in the ablation group: 1) pericardial effusion without tamponade, 2) congestive heart failure exacerbation, and 3) deep venous thrombosis that required prolonged anticoagulation.

At 22.5 months of follow-up, appropriate defibrillator therapy occurred in 12% in the ablation group, compared with 33% in the defibrillator only group (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.15-0.78; p = 0.007). There was progressive separation of the Kaplan-Meier curves over the extent of follow-up. There was a consistent benefit in all subgroups that favored ablation.

Defibrillator shocks occurred in 9% of the ablation group versus 31% in the control group (HR, 0.27; 95% CI, 0.11-0.67; p = 0.003), defibrillator storms in 6% versus 19% (HR, 0.30; 95% CI, 0.09-1.00; p = 0.06), and death in 9% versus 17% (HR, 0.59; 95% CI, 0.22-1.59; p = 0.29), respectively. LV function and functional status remained stable in both groups during the extent of follow-up.

Interpretation

This trial revealed that in carefully selected patients, the use of prophylactic catheter ablation of arrhythmic tissue while in sinus rhythm reduces the need for subsequent defibrillator shocks or antitachycardia pacing. This is important since defibrillator therapy, especially defibrillator storms, can result in significant morbidity and impaired quality of life. There were only three complications in the ablation group with no long-term adverse events noted, such as decline in LV function or functional status. Although the trial was not designed to study survival, there was no suggestion of increased early or long-term mortality in the ablation group.

This trial was conducted at three specialized centers by highly skilled operators; therefore, the applicability of this therapy in community hospitals will need to be evaluated. The current treatment of patients who experience defibrillator shocks is antiarrhythmic drug therapy, coupled with defibrillator re-programming and antitachycardia pacing. This trial did not assess quality of life or address the role of catheter ablation versus antiarrhythmic drug therapy, which is still considered first-line therapy.

Reference

Reddy VY, Reynolds MR, Neuzil P, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med 2007;357:2657-65.

Slow VT in ICD Recipients

General Information

Acronym
Slow Ventricular Tachycardia in Implantable Cardioverter-Defibrillator Recipients

Full Name
Slow Ventricular Tachycardia in Implantable Cardioverter-Defibrillator Recipients

Year Presented
not applicable

Year Published
2005

Conditions

- Arrhythmias

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients previously implanted with a dual chamber ICD had a detection configuration into three groups: slow VT zone (101-148 bpm), conventional VT zone (>148 bpm) and a ventricular zone. Patients were randomized to antitachycardia pacing (ATP) with or without cardioversion activated in the slow VT zone (n=183) or a monitoring group with no activation in the slow VT zone (n=191).

Principal Findings

Underlying heart disease was coronary artery disease in the majority of patients (73%) followed by dilated cardiomyopathy (15%). ICD indication was spontaneous VT in 70% of patients, spontaneous VF in 19%, and induced VT/VF in 11%.

There were 10 deaths in the monitoring group and 13 deaths in the therapy group (p=NS). In the monitoring group, 181 slow VT occurred in 54 patients compared with 250 slow VTs in 60 patients in the treatment group. Mean duration was 15 minutes, and three patients required hospital re-admission. Of the 250 slow VTs in the treatment group, 245 were treated and 5 resolved spontaneously. The success rate of the 245 treated was 89.8%. Quality of life score improved from baseline to 12 months in both treatment groups (p=0.002 in the monitoring group and p=0.0007 in the treatment group), with no difference between groups.

Interpretation

Among patients previously implanted with a dual chamber ICD and without a history of slow VT, slow VT occurred in 30% of patients during one year follow-up, and were treated in 90% of episodes among patients with

antitachycardia pacing. Despite the high resolution with antitachycardia pacing, clinical events did not differ between the monitoring and the treatment group, with only 3 hospital admissions required. Additionally, quality of life improved in both groups from baseline, with no difference between groups.

Reference

Sadoul N, et al. Incidence and Clinical Relevance of Slow Ventricular Tachycardia in Implantable Cardioverter-Defibrillator Recipients. Circulation. 2005;112:946-953.

VTACH

General Information

Acronym
VTACH

Full Name
Ventricular Tachycardia Ablation in Coronary Heart Disease

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2010

Conditions

- Coronary heart disease
- Arrhythmias / Ventricular fibrillation
- Arrhythmias / Ventricular tachycardia
- Heart failure

Therapies

- Implantable Cardioverter Defibrillator (ICD)

Intervention

Patients undergoing implantation of an ICD had an electrophysiologic study to induce VT. They were then randomized to VT catheter ablation plus ICD (n = 54) versus ICD alone (n = 56).

Principal Findings

Overall, 110 patients were randomized. The mean age was 66 years, 7% were women, mean left ventricular ejection fraction (LVEF) was 34%, mean time since last myocardial infarction was 12.9 years, and mean follow-up was 22.5 months. Successful ablation was reported in 52% of patients.

The primary outcome, median time to first VT or ventricular fibrillation (VF) was 18.6 months in the ablation group versus 5.9 months in the control group ($p = 0.045$). The 24-month event-free survival from VT or VF was 47% versus 29% ($p = 0.045$), freedom from death was 92% versus 91% ($p = 0.68$), and the mean appropriate shocks per patient per year was 0.6 versus 3.4 ($p = 0.018$), respectively, for ablation versus control.

Considering freedom from VT or VF, patients with less severe LV dysfunction (EF >30%) appeared to benefit more from catheter ablation ($p = 0.016$) than patients with severe LV dysfunction (EF ≤30%) ($p = 0.76$).

Interpretation

Among patients with a history of stable VT eligible for ICD implantation, catheter ablation of VT at the time of the procedure appeared to be beneficial. Prophylactic catheter ablation reduced the time to first recurrence of VT or VF and improved freedom from VT or VF.

This is a technically demanding procedure, as evidenced by a success rate of approximately 50%. This will limit the generalizability of this procedure into the community setting; however, prophylactic catheter ablation may be appropriate for some carefully selected individuals. This procedure deserves further study.

Reference

Kuck KH, Schaumann A, Eckardt L, et al. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. ***Lancet*** 2010;375:31-40.

ADOPT

General Information

Acronym
ADOPT

Full Name
Atrial Dynamic Overdrive Pacing Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2001

Year Published
2003

Conditions

- Arrhythmias / Atrial fibrillation
- Arrhythmias

Therapies

- Pacing / Dual chamber
- Pacing

Intervention

Patients enrolled in the study received the St. Jude Medical Trilogy DR or Integrity Afx Autocapture Pacing System and were randomized into two groups: one with the DAO algorithm ON and DDDR pacing set at 60 ppm; the other with the DAO algorithm OFF and DDDR pacing at 60 ppm.

Principal Findings

Over 90% of the atrial arrhythmias observed during the six-month follow-up period were AF (vs. other organized atrial arrhythmias). The percentage of beats that were atrial paced was significantly greater in the DAO ON group (92.9%) than in the DAO OFF group (67.9%; $p< 0.0001$), demonstrating that the algorithm performed as specified in stimulating the patients' atrium a very high percentage of the time.

Overall AF burden was reduced in the DAO ON group compared with the DAO OFF group (2.50% for DAO OFF vs. 1.87% for DAO ON), and there was a consistent and decreasing AF burden observed over time ($p< 0.005$).

Patients in the DAO ON group showed a 60% reduction in symptomatic AF episodes from baseline levels (from 8.0 to 4.3 episodes), while patients in the DAO OFF group showed a 45% reduction in symptomatic AF episodes from baseline levels (from 8.3 to 3.2 episodes, both $p< 0.001$), but there was no difference between treatment groups in the number of episodes at six months (p=NS).

Quality of life scores improved during follow-up in both patient groups. Scores in the DAO OFF group improved significantly during follow-up in five of eight subscales and in the standardized mental component scales, and improved in the DAO ON in four of eight subscales and both the standardized physical and mental component scales. The only significant difference between the DAO OFF and DAO ON groups was a higher social function score in the treatment group at six months.

No DAO-related complications and no unanticipated adverse events were recorded. Total hospitalizations were similar in both arms (17 DAO OFF vs. 15 DAO ON).

Interpretation

Among patients with AF, dynamic atrial overdrive pacing with the AF suppression algorithm demonstrated overall reductions in atrial arrhythmia burden compared with conventional DDDR pacing alone. Despite the large relative decrease in AF burden (25%), the absolute difference was small (2.50% DAO OFF vs. 1.87% for DAO ON).

Reference

Carlson MD, Ip J, Messenger J, et al., for the Atrial Dynamic Overdrive Pacing Trial Investigators. A new pacemaker algorithm for the treatment of atrial fibrillation. Results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). J Am Coll Cardiol 2003;42:627–33.

Presented at AHA 2001

ATTEST

General Information

Acronym
ATTEST

Full Name
Atrial Therapy Efficacy and Safety Trial

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2003

Conditions

- Arrhythmias / Atrial fibrillation
- Arrhythmias

Therapies

- Pacing / DDD(R)
- Pacing

Intervention

All patients were implanted with a DDDRP pacemaker (AT500, Medtronic Inc., Minneapolis, Minnesota) with three atrial preventive pacing algorithms and two ATP algorithms. At implant, atrial detection was programmed ON in all patients, and DDDR pacing was programmed at a lower rate of 60 ppm and an upper rate of 120 ppm. After one month, patients were randomized to all prevention and ATP therapies ON (n=153) or OFF (n=171).

Principal Findings

Detection was confirmed in 99.9% of AT/AF episodes with stored electrograms (17,004/17,018), which occurred in 271 patients. The median amount of atrial pacing was 98% (IQ range 97% and 99%) in the ON group versus 75% (IQ range, 38% and 95%) in the OFF group ($p< 0.001$). For ventricular pacing, the median percentage was 99% (IQ range, 95% to 100%) in the ON group versus 98% (IQ range, 81% to 100%) in the OFF group ($p=0.005$).

Using device-defined criteria for successful termination, ATP terminated 54% of the 15,789 treated episodes in the ON group. No significant differences occurred in AT/AF burden (4.2 h/mo vs. 1.1 h/mo, $p=0.20$), total frequency (1.3 episodes/mo ON vs. 1.2 episodes/mo OFF, $p=0.65$), or symptomatic frequency ($p=0.62$) between the ON and OFF groups, respectively, during the three-month study period.

There were no differences in burden or total frequency in subgroup analysis by presence of episodes during the

run-in period, baseline characteristics, or the use of antiarrhythmic drugs. System-related, complication-free survival at four months was 90.2% by Kaplan-Meier estimate, with the most frequent complications being atrial lead dislodgement (n=11), ventricular lead dislodgement (n=5), and pericardial effusion (n=4).

Interpretation

Among patients with symptomatic AF or AT, there was no difference in the burden or frequency of atrial tachyarrhythmias with atrial prevention and termination therapies combined in a DDDRP pacemaker, despite an increase in the relative amount of atrial pacing and an ATP efficacy of 54%.

The authors hypothesized that the high proportion of ventricular pacing (median 99%) may have had a negative effect and limited any potential benefit from the atrial therapies. Additionally, bradycardia-induced AT/AF may have been suppressed by the DDDR pacing. An important limitation of the trial was that the device stored 35 episodes between interrogations and, as such, only about 10% of all episodes logged by the daily counters were available for review. Additionally, the daily counters did not store the episode type (AT or AF).

Reference

Lee MA, Weachter R, Pollak S, et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency. Results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. J Am Coll Cardiol 2003;41:1926–32.

CTOPP

General Information

Acronym
CTOPP

Full Name
Canadian Trial of Physiologic Pacing

Year Presented
1998

Year Published
2000

Conditions

- Arrhythmias / Atrial fibrillation
- Arrhythmias

Therapies

- Pacing / VVI(R)
- Pacing / Dual chamber
- Pacing

Intervention

Ventricular vs. physiologic pacing

Principal Findings

Among the 1474 patients randomized to VVI pacing, 25.2% received VVI devices, 73.3% received VVIR, 0.7% crossed over to a DDD, DDDR, or AAI device, and 0.2% did not receive a pacer. For the 1094 randomized to physiologic pacing, 52.8% received a DDD device, 35.2% received DDDR, 1.9% received AAI, 3.5% received AAIR, 5.7% crossed over to a VVI device, and 0.9% did not receive a pacer. The complication rate in the physiologic pacing group was 9.0% compared to 3.8% for the VVI arm, and was attributed to the additional lead needed for dual-chamber pacing. The two groups were equal with respect to pacer dependency, indication for implantation, and concomitant anti-ischemic, anti-platelet, and anti-arrhythmic therapy. The total study duration was 5 years, with a mean follow-up of 36 months. The event rate for the primary endpoint was 5.43 events per year for the VVI group and 4.78 events per year for the physiologic pacing group (p=.205). For all cause mortality, the event rate was 6.54 for the VVI group, and 6.25 events per year for the physiologic group. There were 1.09 strokes per year in the VVI group compared to 1.02 strokes per year in the physiologic pacing group. The incidence of CHF was 3.62 events per year in the VVI group compared to 3.02 per year in the physiologic group. None of these differences were statistically significant. Physiologic pacing was associated with a significant 18% relative reduction in the occurrence of atrial fibrillation (6.59 to 5.34 events per year, p = 0.0357), although this benefit did not become apparent until after 2 years. Seventy-five percent of patients were tested with a six-minute walk to assess their functional capacity. There was no significant difference in pre- or post- walk heart rates or in the total distance

walked (VVI: 350+127 m, Phys: 356+127 m).

Interpretation

Ten nonrandomized studies have suggested a reduction in death and stroke from physiologic pacing. Previous suggestions for benefit have been prevention of atrial fibrillation and subsequent risk of stroke. Although there was a significant reduction in the occurrence of atrial fibrillation by physiologic pacing, the risk of death or stroke from atrial fibrillation is low. As a result, this large, randomized study provides little support for a reduction in cardiovascular death by physiologic pacing strategies. This study suggests that we rethink the role of physiologic pacing compared to ventricular pacing alone. Because the only differences are in the late development of AF between the two groups, there may be little evidence to support the use of physiologic pacing in many patients. The cost implications of this study are equally important. It is possible that a difference in incidence of atrial fibrillation between the two modalities would increase with time.

Reference

1. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators.N Engl J Med 2000 May 11;342(19):1385-91.

Danish Mode Selection Trial

General Information

Acronym
Danish Mode Selection Trial

Full Name
Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome.

Year Presented
1994

Year Published
1997

Conditions

- Arrhythmias

Therapies

- Pacing / AAI
- Pacing / VVI
- Pacing

Intervention

Patients were randomized to atrial or ventricular pacing with unipolar leads and passive fixation. Screw-in fixation was employed if passive fixation was not successful. Follow-up visits wre obtained at 3 months, 12 months and yearly thereafter.

Principal Findings

Atrial pacing was associated with a decreased rate of all cause mortality and cardiovascular death (relative risk 0.66 [95% CI 0.44-0.99]; p=0.045 and 0.47 [0.27-0.82; p=0.0065 repectively), however in multivariate analysis atrial pacing was associated with less cardiovascular death but not overall mortality. The incidences of atrial fibrillation and chronic atrial fibrillation were also significantly lower atrially paced patients(0.54 [0.33-0.89], p=0.012 and 0.35 [0.16-0.76], p=0.004, respectively). Thromboembolic events were also less frequent in the atrially paced group (0.47 [0.24-0.92], p=0.023). Heart failure was less severe in the atrial group than in the ventricular group ($p< 0.05$). The risk of developing atrioventricular block in the atrial group was approximately 0.6% annually.

Interpretation

Atrial pacing is associated with a significantly lower rate of cardiovascular death, lower rates of atrial fibrillation, fewer thromboembolic complications, reduced heart failure, and a low-risk of atrioventricular block.

Reference

1. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome.Lancet 1994 Dec 3;344(8936):1523-8 2. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997 Oct 25;350(9086):1210-6.

DAPPAF

General Information

Acronym
DAPPAF

Full Name
Dual Site Atrial Pacing to Prevent Atrial Fibrillation

Year Presented
1998

Year Published
1998

Conditions

- Arrhythmias / Atrial fibrillation
- Arrhythmias

Therapies

- Pacing / DDD(R)
- Pacing

Intervention

Patients undergo implantation of a pacing system with a DDDR pulse generator with programmable polarity, rate response, and mode switching ability. An activation fixation lead for placement in the coronary sinus and a Y adaptor for connection of the two atrial leads to the generator are implated as well. Patients cross over every 6 months to the other 2 modes of pacing until all three modes have been used.

Principal Findings

Final results have not been reported

Interpretation

n/a

Reference

1. Fitts SM, Hill MR, Mehra R, Friedman P, Hammill S, Kay GN, Prakash A, Webb C, Saksena S. Design and implementation of the Dual Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) clinical trial. DAPPAF Phase 1 Investigators. J Interv Card Electrophysiol 1998 Jun;2(2):139-44.

INSYNC

General Information

Acronym
INSYNC

Full Name
Multisite pacing as a supplemental treatment of congestive heart failure: the Medtronic Inc. InSync Study

Year Presented
1998

Year Published
1998

Conditions

- Heart failure

Therapies

- Pacing / Dual chamber
- Pacing

Intervention

A multisite pacemaker (Medtronic InSync)was implanted with left ventricular pacing leads (Medtronic 2187 and 2188) implanted via a cardiac vein

Principal Findings

7 of 10 patients during follow-up who exited the study had died. 4 of these were sudden deaths. There was a clinical benefit among surviving patients, which was corroborated by a significant improvement in NYHA functional class (improvement by 1.2) and in the Minnesota Living with Heart Failure Quality of Life Questionnaire Score (+40%) and by a longer distance covered during a 6-minute walk test (+25%). The clinical improvement was associated with a significant narrowing of the paced QRS complex during biventricular pacing, a significant decrease in the interventricular mechanical delay, and a trend towards an increase in the duration of ventricular filling.

Interpretation

This small study shows that multisite pacing is safe during a limited follow-up period and is associated with an improvement in exercise capacity. The results of this small, nonrandomized registry should be taken in the context of other small trials and larger randomized trials that support the efficacy of biventricular pacing in refractory congestive heart failure.

Reference

1. Gras D, Mabo P, Tang T, Luttikuis O, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. Pacing Clin Electrophysiol 1998 Nov;21(11 Pt 2):2249-55. 2. Leclercq C, Kass DA. Retiming the failing heart and clinical status of cardiac resynchronization. JACC 2002; 39:194-201.

MIRACLE (Pacing Study)

General Information

Acronym
MIRACLE (Pacing Study)

Full Name
Multicenter InSync Randomized Clinical Evaluation

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2001

Year Published
2002

Conditions

- Heart failure

Therapies

- Pacing / Dual chamber
- Pacing

Intervention

Following baseline assessment, patients underwent implant attempt within one week. Following successful lead placement (93%), patients underwent a predischarge randomization to the control group (no CRT, n=225) or CRT group (n=228), then underwent a six-month period of double-blinded study with follow-up at one, three, and six months. The electrophysiologist served as an unblinded third party, and the heart failure specialist, the managing physician, and the patient were kept blinded to study assignment during the six-month period of pivotal study.

Control arm patients could then go into the resynchronization mode. These patients were then followed up at nine months, and all patients continue to be followed at six-month intervals following the double-blind period of the controlled study.

Principal Findings

Device implantation was unsuccessful in 8% of patients, and was complicated by refractory hypotension, bradycardia, or asystole in four patients (two that died) and by perforation of the coronary sinus requiring pericardiocentesis in two patients.

Compared with placebo, CRT was associated with a significantly improved six-minute walk distance (+39 vs. +10 m, p=0.005), improved New York Heart Association (NYHA) class by at least one class (68% vs. 38%, p< 0.001), quality of life (-18.0 vs. -9.0 points, p=0.001), time on the treadmill during exercise testing (+81 vs. +19 seconds, p=0.001),

and ejection fraction (+4.6% vs. -0.2%, p< 0.001). CRT was also associated with a significantly improved peak oxygen consumption (+1.1 vs. +0.2 ml/kg/min, p=0.009).

The QRS duration was significantly lower in CRT patients compared with control (-20 vs. 0 ms, p< 0.001). Need for hospital admission (8% vs. 15%, p=0.02) and intravenous medication (7% vs. 15%, p=0.004) were lower in CRT patients compared to controls.

Using the Heart Failure Clinical Composite Outcome Measure, a significantly higher percentage of CRT patients were classified as improved (67% vs. 39%, p< 0.001) and fewer CRT patients were classified as worsened (16% vs. 27%). Death or worsening heart failure requiring hospitalization occurred less frequently in the CRT arm (28% vs. 44%, hazard ratio 0.60, 95% confidence interval 0.37–0.96; p=0.03).

Interpretation

Among patients with CHF and ventricular dysynchrony, biventricular pacing was associated with improved functional class, increased six-minute walk distance and maximal oxygen uptake, and improved quality of life.

Recently, CRT, or biventricular pacing, has emerged as a potential treatment option for patients with severe heart failure. Patients thought to benefit include those with intraventricular conduction delay who are refractory to medical therapy.

The optimal performance of biventricular pacing devices has yet to be determined. Lead placement remains problematic, and reliable predictors of response have yet to be identified.

The MIRACLE trial is one of the largest clinical trials of CRT in CHF reported to date. The results are encouraging, with 67% of CRT patients showing improvement in the clinical composite endpoint that included NYHA functional class and global assessment compared with 39% of placebo patients. This difference in clinical improvement is striking compared to other heart failure trials that have applied this same composite clinical endpoint.

The MIRACLE data suggest that CRT is safe and well tolerated, with no serious adverse events among those patients receiving active therapy.

Reference

1. Main Results: Abraham WT, Fisher WG, Smith AL,et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.

2. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). J Card Fail 2000;6:369-80.

3. Abraham WT. Late breaking clinical trials: results from late breaking clinical trial sessions at ACC 2001. J Am Coll Cardiol 2001;38:604-5.

MOST

General Information

Acronym
MOST

Full Name
Mode Selection Trial (MOST) in sinus node dysfunction

Year Presented
not applicable

Year Published
2000

Conditions

- Arrhythmias

Therapies

- Pacing / DDD(R)
- Pacing / VVI(R)
- Pacing

Intervention

All patients will receive a DDDR pacemaker noninvasively programmed to VVIR or DDDR before implantation

Principal Findings

n/a

Interpretation

n/a

Reference

American Heart Journal 2000;140:541-51.

M-PATHY

General Information

Acronym
M-PATHY

Full Name
Multicenter Pacing Therapy

Year Presented

Year Published
1998

Conditions

- Cardiomyopathy / Hypertrophic

Therapies

- Pacing / DDD(R)
- Pacing

Intervention

Randomization to 3 months of dual chamber pacing (DDD) or backup mode (AAI-30) followed by crossover to the alternative mode for another 3 months. This was followed by 6 months of unblinded DDD pacing.

Principal Findings

The first 6 months of the study conformed to a randomized, double-blind, crossover design. Specifically, patients were randomized to either 3 months of DDD pacing or to an AAI-30 back-up mode. All patients were subsequently crossed over to the alternative mode for the next 3 months. Finally, patients underwent 6 additional months of DDD pacing in an uncontrolled/unblinded fashion. Patients completing this 12-month protocol experienced a total of 9 months of DDD pacing.

Of the 48 patients originally enrolled, 4 did not participate in the cross over. The remaining 44 constitute the primary study group. Twelve of these 44 patients deviated from the protocol design, including 8 who elected for early and unscheduled crossover from AAI-30 to DDD. One patient, age 67, died unexpectedly after 8.5 months. Thus, 32 patients completed the original protocol.

Symptomatic improvement was the same for patients randomized between DDD and AAI-30. In the uncontrolled phase of DDD pacing, quality-of-life scores were significantly improved compared to baseline, but the scores were no different from those recorded during AAI-30.

None of the objective measures analyzed, including treadmill exercise duration, peak oxygen consumption during treadmill exercise, and outflow gradient, improved significantly with DDD pacing.

Some modest hemodynamic benefit was achieved in most patients. In a small subset of older patients (>65 years), a significant clinical response was seen, suggesting that DDD pacing could be a viable therapeutic option for elderly patients.

Interpretation

Permanent dual chamber (DDD) pacing has been proposed as an alternative to septal myotomy/myectomy surgery for reducing symptoms in severely symptomatic patients with obstructive hypertrophic cardiomyopathy (HCM). M-PATHY is the first controlled test of this hypothesis. The similarity results from DDD and control (AAI-30) pacing modes suggests a substantial placebo effect. On the other hand, it is difficult to obtain sufficient sample sizes in this area to control type II error. Investigators could not confirm prior claims that chronic pacing produces left ventricular remodeling in HCM. They concluded that overall, pacing should not be regarded as a primary treatment for patients with obstructive HCM, and previous uncontrolled results should be interpreted with caution.

Reference

1. Circulation 1998;98(Suppl I):I-506. Preliminary results

PACE – Presented at AHA 2009

General Information

Acronym
PACE—Presented at AHA 2009

Full Name
Pacing to Avoid Cardiac Enlargement

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2009

Year Published
2009

Conditions

- Arrhythmias
- Prevention

Therapies

- Pacing / Dual chamber

Intervention

Patients with bradycardia and normal LV ejection fraction (EF) were randomized to biventricular pacing (n = 89) versus RV pacing (n = 88).

Principal Findings

Overall, 177 patients were randomized. There was no difference in baseline characteristics between the groups. In the biventricular pacing arm, the mean age was 69 years, 47% were women, body mass index was 25 kg/m^2, LVEF was 62%, and history of diabetes was 26%.

At 12 months, LVEF was 62% with biventricular pacing versus 55% with RV pacing ($p < 0.001$). LV end-systolic volume was 28 ml versus 36 ml ($p < 0.001$), respectively. There was no difference in the primary outcome according to the prespecified subgroup of pre-existing LV diastolic dysfunction.

There were no periprocedural deaths. Hospitalization for heart failure within 12 months occurred in 6% versus 7%, respectively. Distance in 6-minute walk test was 380 m versus 374 m ($p = 0.81$) and quality of life was similar between the groups ($p = 0.75$).

Interpretation

Among patients with bradycardia due to sinus-node dysfunction or atrioventricular block, and with normal LV function, the use of biventricular pacing is beneficial. In contrast to RV pacing, biventricular pacing resulted in preserved LV function and dimensions. Hospitalization for heart failure, distance in 6-minute walk test, and quality of life were similar between the groups.

Although this was a relatively small study, it builds upon our accumulating knowledge of the deleterious effects of RV pacing. While these findings are compelling, future studies will be needed to determine if similar patients should routinely receive a biventricular device, which is more expensive and requires more expertise for implant.

Reference

Yu CM, Chan J, Zhang Q, et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. ***N Engl J Med*** 2009;Nov 15:[Epub ahead of print].

Presented by Dr. Cheuk-Man Yu at the American Heart Association Scientific Sessions, Orlando, FL, November 15, 2009.

PASE

General Information

Acronym
PASE

Full Name
Pacemaker Selection in the Elderly

Year Presented
1998

Year Published
1998

Conditions

- Arrhythmias

Therapies

- Pacing / DDD(R)
- Pacing / VVI(R)
- Pacing

Intervention

Intermedics dual-chamber rate-adaptive pacemakers (models 294-03, 293-03, 294-03R, and 294-05) were implanted and were randomly programmed to VVIR versus DDDR modes.

Principal Findings

Quality of life improved significantly after pacemaker implantation ($P < 0.001$), but there were no differences between the two pacing modes in either the quality of life or prespecified clinical outcomes (including cardiovascular events or death). However, 53 patients assigned to ventricular pacing (26 percent) were crossed over to dual-chamber pacing because of symptoms related to the pacemaker syndrome. Patients with sinus-node dysfunction, but not those with atrioventricular block, had moderately better quality of life and cardiovascular functional status with dual-chamber pacing than with ventricular pacing. Trends of borderline statistical significance in clinical end points favoring dual-chamber pacing were observed in patients with sinus-node dysfunction, but not in those with atrioventricular block.

Interpretation

The implantation of a permanent pacemaker improves health-related quality of life. The quality-of-life benefits associated with dual-chamber pacing as compared with ventricular pacing are observed principally in the subgroup of patients with sinus-node dysfunction

Reference

N Engl J Med 1998;338:1097-104

PASE (QoL)

General Information

Acronym
PASE(QOL)

Full Name
Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing.

Year Presented

Year Published
1998

Conditions

- Pacing

Therapies

- Pacing / Dual chamber
- Pacing

Intervention

Intermedics dual-chamber rate-adaptive pacemakers (models 294-03, 293-03, 294-03R, and 294-05), programmed to either DDDR or VVIR modes.

Principal Findings

A total of 203 patients were randomized to dual-chamber pacing; the remaining 204 patients were assigned to ventricular pacing. The indications for the implantation of a permanent pacemaker included atrioventricular block in 201 patients (49 percent, of whom 119 patients, or 59 percent, had third-degree block), sinus-node dysfunction in 175 patients (43 percent), and other diagnoses in 31 (8 percent). Ventriculoatrial (retrograde) conduction at the time of implantation was present in 29 percent.

Follow-up visits and health-status assessments took place 3, 9, and 18 months after enrollment and at the end of the study. Assessment of health status before randomization was performed at the local clinical site, before the pacemaker mode was assigned. Subsequent assessments were made by telephone from the coordinating center.

During the course of the trial, pacemaker syndrome severe enough to warrant reprogramming from ventricular to dual-chamber pacing was diagnosed in 53 patients assigned to ventricular pacing (26 percent), in 45 percent of whom sinus-node dysfunction was the reason for implantation. Crossover from ventricular to dual-chamber pacing occurred early: 44 percent of the 53 crossovers occurred within one month after implantation, and 77 percent within six months. After crossover, the patients had improvement in SF-36 scores, including scores for physical function (+22, P = 0.03) and emotional role (+27, P = 0.01).

In the overall group, there was significant improvement in health-related quality of life between base line (before implantation) and three months after implantation, as measured by several SF-36 subscales (social function, P< 0.001; physical role, P< 0.001; emotional role, P< 0.001; mental health, P< 0.001; energy, P< 0.001).

There were no significant differences in scores between the ventricular-pacing group and the dual-chamber-pacing group in any of the SF-36 subscales at 3 months or 18 months. After nine months of follow-up, there was a significant difference favoring dual-chamber pacing only in scores for the mental health subscale (P = 0.03)

Longitudinal analyses, detected a borderline improvement in scores on the emotional-role subscale in patients assigned to dual-chamber pacing (P= 0.04).

There were no significant differences in cardiovascular functional status between groups, as assessed by the Specific Activity Scale, at either the three-month or the nine-month assessment. However, there was a significant difference favoring dual- chamber pacing at the 18-month visit (Table 4), and longitudinal analysis demonstrated a significant difference favoring dual-chamber pacing (P = 0.045).

There were no significant differences between the ventricular-pacing group and the dual-chamber-pacing group in the rates of death from all causes, stroke or death, stroke or death or hospitalization for heart failure, and the development of atrial fibrillation.

Among the patients who received pacemakers because of sinus-node dysfunction, there were significant differences favoring dual-chamber pacing at three months in scores on the physical-role subscale (P = 0.02), social-function subscale (P = 0.03), and emotional-role subscale (P = 0.002) of SF-36.

Among the patients with atrioventricular block at implantation, there were no significant differences between groups in any of the SF-36 subscales, in longitudinal analyses of the Specific Activity Scale, or in any of the prespecified clinical endpoints.

Interpretation

The design of the study did not permit maintenance of an accurate registry to compare the screened and enrolled populations. However, the demographic and clinical characteristics of the participants were very similar to those of recipients of dual-chamber pacemakers in the Medicare data base. In this study, pacemaker placement led to dramatic improvements in health-related quality of life. This uncontrolled observation is consistent with the reported low rate of recurrence of symptoms after pacemaker implantation. However, when patients with ventricular pacing were compared with patients with dual-chamber pacing, there were no convincing differences in general health-related quality of life. Analysis of two prespecified subgroups - patients with sinus-node dysfunction and those with atrioventricular block at implantation - did reveal a favorable response to dual-chamber pacing in patients with sinus-node dysfunction. Nonetheless, these differences are considerably smaller than were previously thought.

Reference

N Engl J Med 1998; 338:1097-104. Final results.

PATH-CHF

General Information

Acronym
PATH-CHF

Full Name
The Pacing Therapies for Congestive Heart Failure (PATH-CHF) Study

Year Presented
1999

Year Published
2001

Conditions

- Heart failure

Therapies

- Pacing / Dual chamber
- Pacing

Intervention

Patients received an implantable pacemaker system with te ability to switch from univentricular to biventricular pacing capability. At the time of the initiation of this study, this necessitated implantation of two pulse generators. The patient was then randomized to univentricular or biventricular pacing. The optimal pacing site and AV delay when pacing the right, left, or right and left ventricles were determined using a computer generated protocol. Patients were paced for 4 weeks followed by 4 weeks without pacing, and finally crossed over the the other modality (biventricular or univentricular) of pacing for 4 weeks. Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire. Changes in ejection fraction, chamber sizes and filling pattern were obtained by echocardiography.

Principal Findings

An analysis of echocardigraphic data from 25 of the 42 enrolled patients showed that after 6 months of pacing, the left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD, respectively) were significantly reduced (LVEDD from 71 ± 10 to 68 ± 11 mm, p=0.027; LVESD from 63 ± 11 to 58 ± 11 mm, p=0.007). LV end-diastolic and end-systolic volumes were also reduced(LVEDV from 253 ± 83 to 227 ± 112 ml, P = 0.017; LVESV from 202 ± 79 to 174 ± 101 ml, p=0.009), and the ejection fraction was significantly increased (from 22 ± 7% to 26 ± 9%, p=0.03). Those patients who did not experience LV volume reduction had significantly higher baseline LVEDVs compared with those who did (351 ± 52 vs. 234 ± 74 ml, p=0.018).

Interpretation

In patients with advanced heart failure and increased QRS duration, there is a decrease in LV dimensions at 6 months in some patients. The small sample size, slected population and lack of a control group limit the generalizability of these findings and clinical applicability to the heart failure population at large.

Reference

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1. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Mortensen P, Klein H. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study.Am J Cardiol 1999 Mar 11;83(5B):130D-135D. 2. The PATH-CHF (PAcing THerapies in Congestive Heart Failure) Investigators; CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 2001 Dec;38(7):1957-65.

SAVE PACe

General Information

Acronym
SAVE PACe

Full Name
Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2007

Conditions

- Arrhythmias
- Arrhythmias / Atrial fibrillation

Therapies

- Pacing
- Pacing / Dual chamber

Intervention

All patients received dual-chamber pacemakers, either the Kappa 700, Kappa 900, EnPulse, or EnRhythm. Patients were then randomized to dual-chamber minimal ventricular pacing (n = 530) or conventional dual-chamber pacing (n = 535). Patients but not physicians were blinded to treatment assignment.

The atrioventricular (AV) interval with conventional dual-chamber pacing was 120-180 msec. The minimal pacing group programming allowed for automatic lengthening of or elimination of the pacemaker's AV interval in order to withhold ventricular pacing and prevent ventricular desynchronization. Dual-chamber pacing was maintained in the event of AV block.

Principal Findings

The trial was discontinued early after an interim analysis met the prespecified criteria for superiority of the dual-chamber minimal ventricular pacing on persistent atrial fibrillation compared with conventional dual-chamber pacing group.

At study entry, mean ejection fraction was 58% and only 20% had a history of heart failure. Previous atrial fibrillation was present in 38% of patients and 20% were on an antiarrhythmic agent. Minimum pacing rate was set at 61 bpm in each group and the detection of atrial fibrillation was 179 bpm.

The median percentage of ventricular beats paced was lower in the dual-chamber minimal ventricular pacing group compared with the conventional dual-chamber pacing group (9.1% vs. 99.0%, $p < 0.001$). There was no difference in the percentage of atrial beats paced between the two groups (71.4% vs. 70.4%, $p = 0.96$). The primary endpoint of persistent atrial fibrillation occurred in significantly fewer patients in the dual-chamber minimal ventricular pacing group (7.9%) compared with the conventional dual-chamber pacing (12.7%; hazard ratio 0.60, 95% confidence interval 0.41-0.88; $p = 0.009$).

There was no difference in the mortality rate between the two groups (4.9% for dual-chamber minimal ventricular pacing vs. 5.4% for conventional dual-chamber pacing, $p = 0.54$). There was also no difference in hospitalization for heart failure (2.8% vs. 3.1%, respectively, $p = 0.62$). Cardioversion was performed in 4.2% of the dual-chamber minimal ventricular pacing group and 4.9% for conventional dual-chamber pacing group ($p = 0.58$).

Interpretation

Among patients with sinus-node disease, use of dual-chamber minimal ventricular pacing was associated with a reduction in atrial fibrillation compared with conventional dual-chamber pacing through a mean follow-up of 1.7 years.

Right ventricular stimulation during dual-chamber pacing has been thought to be the culprit factor in the adverse effects on left ventricular pump function, leading to no mortality benefit with dual-chamber pacing, and in some cases, increased heart failure. The present study sought to evaluate whether minimizing right ventricular stimulation would result in a reduction in atrial fibrillation.

Dual-chamber minimal ventricular pacing was associated with reduced ventricular desynchronization and with a reduction in atrial fibrillation. Despite these reductions, there was no difference in mortality between the two groups, although the trial was underpowered to detect such a difference.

Reference

Sweeney MO, Bank AJ, Nsah E, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med 2007;357:1000-8.

TRIP-HF

General Information

Acronym
TRIP-HF

Full Name
Triple Resynchronization in Paced Heart Failure Patients

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2008

Conditions

- Heart failure

Therapies

- Pacing / Dual chamber

Intervention

Patients with drug-refractory CHF were implanted with a 3-lead biventricular pacemaker (i.e., 2 leads in the left ventricle [LV] and 1 lead in the right ventricle [RV]). After 3 months of conventional biventricular pacing, 33 patients were randomized to 3-lead followed by 2-lead pacing for 3 months each versus 2-lead followed by 3-lead pacing for 3 months each.

Principal Findings

Two LV leads were unable to be implanted in six patients for an 85% success rate; however, four of these patients received at least 1 LV lead. There was one adverse event during implantation: an uncomplicated coronary sinus dissection. During follow-up, two patients died from end-stage HF.

There was no change in the primary outcome, the Z ratio (0.76 with 3 leads and 0.78 with 2 leads; $p = 0.94$).

LV ejection fraction was 35% versus 27% ($p = 0.0010$), LV end-systolic volume was 134 cm^3 versus 157 cm^3 ($p = 0.019$), and LV end-systolic diameter was 53.9 mm versus 57.0 mm ($p = 0.024$), respectively for 3 leads versus 2 leads.

The distance covered during a 6-minute walk test was 402 m versus 431 m ($p = 0.058$), and the quality-of-life score was 22 versus 22 ($p = 0.75$), respectively for 3 leads versus 2 leads.

Interpretation

Among patients with refractory HF symptoms, the use of 3 leads (2 in the LV and 1 in the RV) failed to improve global ventricular resynchronization as assessed by the Z ratio, compared with 2 leads. The authors postulated that this may have been partly due to the fact that 30% of the patients had a QRS duration less than 150 ms and therefore started with a higher Z ratio.

This therapy also did not improve the distance covered in a 6-minute hall walk or the quality of life. Despite this, 3-lead cardiac resynchronization improved LV ejection fraction and reduced LV end-systolic volume and diameter. Since this therapy did improve some parameters of LV reverse remodeling, further studies are warranted.

Reference

Leclercq C, Gadler F, Kranig W, et al. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. ***J Am Coll Cardiol*** 2008;51:1455-1462.

UKPACE

General Information

Acronym
UKPACE

Full Name
United Kingdom Pacing and Cardiovascular Events

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
2003

Year Published
2005

Therapies

- Pacing / DDD(R)
- Pacing / VVI
- Pacing / VVI(R)
- Pacing

Intervention

Patients at 46 sites in the UK were randomized to either dual chamber (DDD/R) pacing (n=1012) or single chamber ventricular pacing. Patients in the single chamber arm were randomized to either fixed rate (VVI; n=504) or adaptive rate (VVI/R; n=505) pacing.

Principal Findings

All cause mortality did not differ between the VVI, VVI/R, and DDD/R arms (hazard ratio [HR] 0.96 for VVI and VVI/R combined vs. DDD/R, p=0.56; HR 1.03 for VVI vs. DDD/R, p=0.74; HR 0.89 for VVI/R vs. DDD/R, p=0.22). There was also no difference in stroke or transient ischemic attack (TIA) for the VVI and VVI/R combined versus DDD/R analysis (HR 1.28, p=0.20) or the VVI/R versus DDD/R (HR 0.98, p=0.93), but there was an increase associated with DDD/R versus VVI (HR 1.58, p=0.035).

Heart failure also did not differ between the arms (8% with VVI vs. 11% with VVI/R vs. 10% with DDD/R) or did myocardial infarction (2.4% with VVI vs. 2.2% with VVI/R vs. 3.2% with DDD/R).

Interpretation

Among elderly patients with high-grade AV block, treatment with DDD/R was not associated with a difference in all-cause mortality compared with VVI or VVI/R. The trial was designed given the observed lower use of dual chamber pacing in elderly patients in a UK utilization analysis.

It is possible that longer follow-up would be needed to see an effect on atrial fibrillation or heart failure such as in the Danish Mode trial, which had a mean follow-up of 5.5 years compared with only three years for nonfatal clinical events in the present trial. Quality of life, exercise tolerence test, and other secondary end point data are not yet available.

Reference

Toff WD, et al. Single-Chamber versus Dual-Chamber Pacing for High-Grade Atrioventricular Block. N Engl J Med 2005;353:145-55.

Presented at Late-Breaking Clinical Trials, ACC 2003.

VASIS

General Information

Acronym
VASIS

Full Name
Vasovagal Syncope International Study

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2000

Conditions

- Syncope

Therapies

- Pacing / Dual chamber

Intervention

Patients were randomized to dual-chamber pacemaker implantation or no pacemaker implantation. All pacemakers were programmed to the DDI mode at 80 bpm, with an AV interval of 150 ms and a rate hysteresis of 45 bpm.

Principal Findings

Recurrent syncope occurred in 1/19 patients (5%) in the pacemaker group versus 14/23 (61%) in the no pacemaker group, p=0.0006. The median time to first recurrent syncope in the no pacemaker group was five months. This effect occurred despite a lack of change on repeat tilt table testing within 15 days after enrollment (tilt positive 59% with pacemaker, 61% without, p=NS).

Interpretation

Dual chamber pacemakers appear to reduce the frequency of recurrent syncope in highly selected patients with frequent vasovagal syncope and cardioinhibitory responses to tilt table testing. The authors caution that a placebo effect from pacemaker implantation could not be excluded—an effect that appeared to be present in the larger North American Vasovagal Pacemaker Study II.

Reference

Sutton R, Brignole M, Menozzi C, et al. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. Circulation 2000;102:294-9.

VPS

General Information

Acronym
VPS

Full Name
The North American Vasovagal Pacemaker Study

Year Presented
1999

Year Published
1999

Conditions

- Pacing
- Syncope

Therapies

- Pacing / Dual chamber
- Pacing / DDD(R)
- Pacing

Intervention

Patients were randomized to permanent pacemaker (Medtronic Thera DR with rate drop sensing) implantation or usual therapy.

Principal Findings

The study was terminated early after interim analysis demonstrated a large treatment effect. The primary endpoint of first recurrence of syncope was less frequent in those who underwent pacemaker implantation compared to those who did not (70% versus 22%; $p < 0.05$). The relative risk reduction was 85.4% (95% confidence interval, 59.7% to 94.7%).

Interpretation

n/a

Reference

1.Pacing & Clinical Electrophysiology 1997;20:844-8. Study design 2. Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the

prevention of vasovagal syncope. J Am Coll Cardiol 1999 Jan;33(1):16-20.

VPS II

General Information

Acronym
VPS II

Full Name
Vasovagal Pacemaker Study II

Image
Slide image available for online review in the Clinical Trials section at www.cardiosource.com

Year Presented
not applicable

Year Published
2003

Conditions

- Syncope

Therapies

- Pacing
- Pacing / Dual chamber

Intervention

All patients in the trial were implanted with a dual-chamber pacemaker. Patients were randomized to receive dual-chamber pacing (DDD; n=48) with rate drop response or to have only sensing without pacing (n=52).

Principal Findings

There were significantly more women randomized to the dual-chamber pacing group (72.9% vs. 48.1%), but other baseline characteristics were well balanced. Median number of syncope events in the prior year was four in each group, with the time from most recent event one month in each group. Mean duration of tilt table test was 30 minutes.

Syncope episodes occurred in 42% of the sensing only group compared with 33% of the pacing group (relative risk reduction [RRR] 30.2%, log-rank p=0.14). In an analysis excluding the one patient in the pacing group who had the pacemaker removed, the RRR was 35% (p=0.10). Self-reported presyncope occurred in nearly all study patients (94% in sensing only group and 96% in pacing group, p>0.99).

There was one major pacemaker complication in each group (one pericardial tamponade in the pacing group and one infection requiring reimplantation in the sensing only group). Additionally, seven patients had lead dislodgement or needed repositioning.

Interpretation

Among patients with vasovagal syncope, use of dual-chamber pacing was not associated with a reduction in the primary endpoint of recurrent syncope compared with no pacing.

Earlier studies, including VPS I, demonstrated a reduction in recurrent syncope episodes compared with usual care, but these studies were not blinded, as only patients randomized to the pacing group were implanted with a pacemaker. The present study is the first double-blind, randomized trial of pacemaker therapy in syncope patients. Given the lack of demonstrated benefit and the not infrequent complications associated with the pacemaker implantation (whether it was pacing or not), the authors concluded pacemaker therapy should not be recommended as first-line therapy for patients with vasovagal syncope.

Reference

Connolly SJ, Sheldon R, Thorpe KE, et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. JAMA 2003;289:2224-9.