Summary of Evidence
Medicare Coverage Advisory Committee
Implantable Defibrillators in the Primary Prevention of Sudden Cardiac Death

[NOTE: This document reflects the current CMS staff analysis of data related to this coverage decision. It is intended to serve as a basis for discussion at the Medicare Coverage Advisory Committee and does not reflect any staff conclusions. The final decision memorandum and National Coverage Determination will reflect the formal policy of CMS and DHHS.]

Primary prevention of sudden cardiac death has been defined as "the prevention of the first life-threatening arrhythmic event such as sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest."[1] Patients with a prior myocardial infarction and left ventricular dysfunction are at risk for sudden cardiac death and thus have been targeted for interventions. Therapeutic options include appropriate medications and implantable defibrillators. This review addresses only implantable defibrillators or implantable cardioverter defibrillators (ICDs).

To evaluate the evidence on effectiveness, Medline from 1996 was searched using the keyword defibrillator. Citations were limited to randomized controlled trials or randomized clinical trials and primary prevention of sudden cardiac death. Five trials and several related articles were located. The trials are summarized below and in Table 1. In addition, the ACC/AHA/NASPE 2002 guideline update is also included.

Multicenter Automatic Defibrillator Trial I (MADIT I) - 1996

Design: multicenter (30 in U.S. and 2 in Europe), randomized controlled trial of the use of implantable defibrillators in patients with coronary disease at high risk for ventricular arrhythmias.
Primary outcome: death from all causes
Sample Size: 196 patients enrolled and randomized.
defibrillator group (n=95); control group (n=101).
Inclusion Criteria
Men and women who were 25 to 80 years of age were eligible if they had:
(1) Q-wave or enzyme-positive myocardial infarction three weeks or more before entry;
(2) asymptomatic, unsustained ventricular tachycardia (VT);
(3) ejection fraction ≤ 0.35
(4) New York Heart Association functional class I, II, or III; and
(5) no indications for CABG or coronary angioplasty.
Exclusion Criteria
Patients were excluded if one or more of the following conditions were present:
(1) previous cardiac arrest or VT causing syncope, not associated with AMI;
(2) symptomatic hypotension while in a stable rhythm;
(3) myocardial infarction within the past three weeks.
(4) CABG within past two months or coronary angioplasty within past three months;
(5) women of childbearing age who were not using medically prescribed contraceptives;

---

[1] Myerburg, et al., 1998. Huikuri, et al. 2001.

(6) advanced cerebrovascular disease;

(7) any condition other than cardiac disease with a reduced likelihood of survival; or

(8) patients who were participating in other clinical trials.

Enrollment

Eligible patients underwent electrophysiologic (EP) study. Patients qualified for enrollment if sustained ventricular tachycardia or fibrillation was reproducibly induced and not suppressed after the intravenous administration of procainamide (or an equivalent intravenous antiarrhythmic agent if the patient had had a previous reaction to procainamide). Within 30 days after completing the qualifying EP study, the patients were randomly assigned to receive either an implanted defibrillator (n=95) or conventional medical therapy (n=101).

Results

"During an average follow-up of 27 months, there were 15 deaths (16%) in the defibrillator group (11 from cardiac causes) and 39 deaths (39%) in the conventional-therapy group (27 from cardiac causes) (hazard ratio for overall mortality, 0.46; 95 percent confidence interval, 0.26 to 0.82; P = 0.009)."[2] There were no reported hospitalizations for heart failure (adverse events).

Conclusions

"In patients with a prior myocardial infarction who are at high risk for ventricular tachyarrhythmia, prophylactic therapy with an implanted defibrillator leads to improved survival as compared with conventional medical therapy."[3]

Comments

Well designed and conducted.

Coronary Artery Bypass Graft (CABG) Patch Trial - 1997

Design: multicenter (35 in U.S. and 2 in Germany), randomized controlled trial on use of implantable defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass graft surgery.

Primary outcome: death

Sample size: 1055 patients enrolled; 900 randomly assigned.

defibrillator group (n=446); control group (n=454).

Inclusion Criteria

Men and women less than 80 years of age who were scheduled for coronary bypass surgery were eligible if they had:

(1) left ventricular ejection fraction < 0.36;

(2) abnormalities on a signal-averaged electrocardiogram.

Exclusion Criteria

Patients were excluded if they had:

(1) a history of sustained ventricular tachycardia or fibrillation;

(2) diabetes mellitus with poor blood glucose control or recurrent infections;

(3) previous or concomitant aortic- or mitral-valve surgery;

(4) concomitant cerebrovascular surgery;

(5) serum creatinine concentration greater than 3 mg per deciliter (265 mmol per liter);

(6) emergency coronary bypass surgery;

(7) noncardiovascular condition with expected survival of less than two years; or

---

[2] Moss et al., 1996.

[3] Ibid.

(8) inability to attend follow-up visits.

Enrollment

Patients were randomly assigned to the defibrillator (n=446) or control group (n=454) within randomly permuted blocks. Randomization took place in the operating room after bypass grafting had been completed and patients were on partial cardiopulmonary bypass.

Results

"During an average (+/-SD) follow-up of 32+/-16 months, there were 101 deaths in the defibrillator group (71 from cardiac causes) and 95 in the control group (72 from cardiac causes). The hazard ratio for death from any cause was 1.07 (95 percent confidence interval, 0.81 to 1.42; P = 0.64)."[4] There were no significant differences in new or worsened heart failure (adverse events).

Conclusions

The investigators found "no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal signal-averaged electrocardiogram in whom a defibrillator was implanted prophylactically at the time of elective coronary bypass surgery."[5]

Comments

Well-designed and conducted.

Multicenter Unsustained Tachycardia Trial (MUSTT) – 1999

Design: multicenter (85 sites in the US and Canada), randomized controlled trial on use of antiarrhythmic therapy guided by EP testing in patients with coronary artery disease, left ventricular dysfunction, and spontaneous unsustained ventricular tachycardia.

Primary outcome: cardiac arrest or death from arrhythmia

Secondary outcomes: death from all causes, death from cardiac causes, and spontaneous, sustained ventricular tachycardia.

Sample Size: 704 patients randomized.

EP guided therapy (n=351; 158 antiarrhythmic medications, 161 defibrillator therapy, 6 deaths, 7% refused) and medical therapy control (n=353).

Inclusion Criteria

Men and women with the following:

(1) coronary artery disease documented with catheterization or MI;

(2) left ventricular ejection fraction at or below 0.40 within 1 year of entry;

(3) asymptomatic nonsustained ventricular tachycardia;

(4) exercise stress test or cardiac catheterization within 6 months before enrollment.

Exclusion Criteria

Patients with the following were excluded:

(1) history of syncope or sustained VT/VF more than 48 hours after AMI;

(2) systemic disease likely to be fatal in less than 2 years.

Enrollment

After obtaining written consent, antiarrhythmic drugs were discontinued. Signal-averaged ECGs and EP studies were performed. A total of 2202 patients were enrolled: 767 patients with

---

[4] Bigger et al., 1997
[5] Ibid.

inducible, sustained ventricular tachyarrhythmias (704 agreed to undergo randomization), and 1435 patients without inducible tachyarrhythmias (as defined by the protocol).

Results

"Five-year Kaplan-Meier estimates of the incidence of the primary end point of cardiac arrest or death from arrhythmia were 25 percent among those receiving electrophysiologically guided therapy and 32 percent among the patients assigned to no antiarrhythmic therapy (relative risk, 0.73; 95 percent confidence interval, 0.53 to 0.99), representing a reduction in risk of 27 percent. The five-year estimates of overall mortality were 42 percent and 48 percent, respectively (relative risk, 0.80; 95 percent confidence interval, 0.64 to 1.01). The risk of cardiac arrest or death from arrhythmia among the patients who received treatment with defibrillators was significantly lower than that among the patients discharged without receiving defibrillator treatment (relative risk, 0.24; 95 percent confidence interval, 0.13 to 0.45; P<0.001)."[6] Adverse events were not reported.

Conclusions

"Electrophysiologically guided antiarrhythmic therapy with implantable defibrillators, but not with antiarrhythmic drugs, reduces the risk of sudden death in high-risk patients with coronary disease."[7]

Comments

Complex study design and analyses.

Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) - 2002

Design: multicenter (71 in U.S. and 5 in Europe), randomized controlled trial on the use of defibrillator or ICD in patients with a prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less.

Primary outcome: death from any cause

Sample size: 1232 patients were randomized 3:2.

ICD group (n=742); conventional medical therapy group (n=490).

Inclusion Criteria

Men and women who were more than 21 years of age were eligible if they had:

(1) MI one month or more before entry;

(2) elevated cardiac-enzyme levels during hospitalization for suspected MI;

(3) defect on thallium scanning, or akinesis with obs. coronary disease on angiography;

(4) ejection fraction of 0.30 or less within three months before entry;

(5) frequent or repetitive ventricular ectopic beats during 24-hour Holter monitoring (criteria eliminated after 23 patients since all had such arrhythmias).

Exclusion Criteria

Patients were excluded from enrollment if they had:

(1) Indication approved by the FDA for implantable defibrillator;

(2) New York Heart Association functional class IV at enrollment;

(3) Coronary revascularization within the preceding three months;

(4) MI within the past month, as evidenced by measurement of cardiac-enzyme levels;

(5) advanced cerebrovascular disease;

(6) were of childbearing age, not using medically prescribed contraceptive measures;

---

[6] Buxton et al., 1999.
[7] Ibid.

(7) any condition other than cardiac disease with a high likelihood of death; or

(8) unwilling to sign the consent form for participation.

Enrollment

When the trial began in July 1997, eligible patients had to have frequent or repetitive ventricular ectopic beats during 24-hour Holter monitoring. On January 1, 1998, after the enrollment of 23 patients, the executive committee eliminated this requirement because almost all eligible patients had such arrhythmias. Patients were randomly assigned in a 3:2 ratio to receive either an implantable defibrillator (n=742) or conventional medical therapy n=490).

Results

"During an average follow-up of 20 months, the mortality rates were 19.8 percent in the conventional-therapy group and 14.2 percent in the defibrillator group. The hazard ratio for the risk of death from any cause in the defibrillator group as compared with the conventional-therapy group was 0.69 (95 percent confidence interval, 0.51 to 0.93; P=0.016)."[8] Hospitalizations for new or worsened heart failure (adverse events) were higher in the defibrillator group compared to the control group (19.9% versus 14.9%, respectively).

Conclusions

"In patients with a prior myocardial infarction and advanced left ventricular dysfunction, prophylactic implantation of a defibrillator improves survival and should be considered as a recommended therapy."[9]

Comments

Adequately designed but exclusion criteria were not uniformly applied.

Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial – 2002

Design: multicenter (37 in U.S.), randomized, single-blinded, parallel-arm trial of patients with implantable cardioverter-defibrillators, comparing ventricular backup pacing at 40/min (VVI-40) and dual-chamber rate-responsive pacing at 70/min (DDDR-70).

Primary outcome: Composite end point of death or first hospitalization for heart failure.

Sample size: 506 patients randomized 1:1 after defibrillator implantation.

VVI-40 group (n=256), DDDR-70 (n=250).

Inclusion Criteria

Men and women with an indication for implantable defibrillator for ventricular tachyarrhythmias but without an indication for antibradycardia pacing.

(1) Documented VF and LVEF <=40%;

(2) Syncopal sustained VT and LVEF <=40%;

(3) Nonsyncopal VT and LVEF <=40%;

(4) Out-of-hospital unexplained syncope, heart disease, and EPS-inducible sustained VT or VF, and LVEF <=40%;

(5) Hemodynamically stable sustained VT and LVEF <=40%;

(6) EPS-inducible VT or VF within 6 weeks prior to randomization and LVEF <=40%;

Exclusion Criteria

(1) Permanent pacemaker;

(2) Preexisting endocardial pacing leads;

(3) CABG, PCI, cardiac, or other arrhythmia surgery;

---

[8] Moss et al., 2002.

[9] Ibid.

(4) Symptomatic bradycardia or second- or third-degree AV block;

(5) Disqualifying atrial fibrillation;

(6) Frequent, uncontrolled atrial tachyarrhythmia;

(7) Awaiting cardiac transplantation;

(8) Life expectancy <1 year.

Enrollment

All patients had an implantable defibrillator with dual-chamber, rate-responsive pacing capability implanted. Patients were randomly assigned to have the defibrillators programmed to either VVI-40 or DDDR-70.

Results

Patient enrollment into the DAVID Trial was stopped early (in September, 2002). One-year composite end point was 83.9% for patients treated with VVI-40 compared with 73.3% for patients treated with DDDR-70 (relative hazard, 1.61; 95% confidence interval [CI], 1.06–2.44).

Conclusions

"For patients with standard indications for ICD therapy, no indication for cardiac pacing, and an LVEF of 40% or less, dual-chamber pacing offers no clinical advantage over ventricular backup pacing and may be detrimental by increasing the combined end point of death or hospitalization for heart failure."[10]

Comments

Well designed and conducted.

Evidence-Based Practice Guidelines

In 2002, Gregoratos and colleagues published guidelines on the implantation of cardiac pacemakers and antiarrhythmia devices for the American College of Cardiology (ACC), the American Heart Association (AHA) and the North American Society for Pacing and Electrophysiology (NASPE).

Specifically for ICD therapy, the guidelines are as follows:

Class I - Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.[11]

1. Cardiac arrest due to VF or VT not due to a transient or reversible cause. *(Level of Evidence: A)*

2. Spontaneous sustained VT in association with structural heart disease. *(Level of Evidence: B*

3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred. *(Level of Evidence: B)*

4. Nonsustained VT in patients with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a Class I antiarrhythmic drug. *(Level of Evidence: BA)*

5. Spontaneous sustained VT in patients without structural heart disease not amenable to other treatments. *(Level of Evidence: C)*

---

[10] Wilkoff et al., 2002.

[11] Gregoratos et al., 2002.

Class II -Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.[12]
Patients with left ventricular ejection fraction of less than or equal to 30% at least 1 month post myocardial infarction and 3 months post coronary artery revascularization surgery. *(Level of Evidence: B)* [13]

CMS Staff Summary

Several randomized controlled trials have been classified in the literature as primary prevention trials: MADIT I, MUSTT, CABG-Patch and MADIT II. These trials may be further classified into two types: (1) trials on patients with inducible sustained ventricular tachyarrhythmias during EP study (MADIT I and MUSTT), and (2) trials on high risk patients with coronary disease who were not specifically required to have inducible sustained ventricular tachycardia during EP study (CABG-Patch and MADIT II).

Both MADIT I and MUSTT demonstrated significant improvements in survival for patients with prior myocardial infarction, left ventricular dysfunction and inducible, sustained ventricular arrhythmias during EP study that were treated with implantable defibrillators (54% and 55% reduction in mortality, respectively). Both trials were randomized controlled trials with relatively large sample sizes (196 patients and 704 patients, respectively). The results of these two trials are consistent and provide sufficient evidence on effectiveness for the population of patients with EP inducible ventricular tachyarrhythmias.

For patients with prior myocardial infarction and left ventricular dysfunction but who have not had documented ventricular tachyarrhythmias, the study results have been different. The CABG-Patch Trial and MADIT II focused on these types of patients at high risk for sudden death without requiring inducible ventricular arrhythmias or EP studies.

The CABG-Patch Trial investigators found "no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal signal-averaged electrocardiogram in whom a defibrillator was implanted prophylactically at the time of elective coronary bypass surgery."[14] The investigators also suggested that "the occurrence of sustained ventricular arrhythmias, either natural or induced, is a better marker than abnormalities on the signal-averaged electrocardiogram."[15]

The MADIT II found a significant improvement in survival (14.2% mortality rate in ICD group, 19.8% in conventional therapy group). However, there are concerns about the MADIT II study results. MADIT II evaluated patients with a prior myocardial infarction and left ventricular ejection fraction ≤ 0.30. The study design specified that patients who already had a FDA

---

[12] Gregoratos et al. 2002.
[13] Ibid.
[14] Bigger JT, et al., 1997.
[15] Ibid.

approved indication[16] for a defibrillator were to be excluded. However, Holter monitoring to identify arrhythmias was done in only the first 23 patients and EP studies were not required at all. Thus, the MADIT II study population included patients who likely would have had indications for a defibrillator if they had been appropriately tested.

Although EP testing was not required in MADIT II, 583 (82%) patients who received a defibrillator had EP testing done either prior to or during defibrillator implantation. Of these 583 patients, 210 (36%) were inducible.[17] Since nonsustained ventricular tachycardia (NSVT) is highly prevalent in patients with severe heart failure,[18] most of these inducible patients should have been excluded according to the MADIT II exclusion criteria but were not. By including a subset of patients (NSVT + EP inducible) known to have a large survival benefit (>50% reduction in mortality) from defibrillator therapy, a positive result could be demonstrated even if there was little or no effect in the rest of the study population.

If we consider mortality rates by inducibility, most of the observed benefits in MADIT II are due to the significant reduction in mortality in EP inducibile patients who received implantable defibrillators (9.5% vs.19.8% in the control group). For non-inducible patients who received a defibrillator, the difference is not statistically significant (16.6% vs. 19.8%, respectively). These comparisons and any regression analyses on EP inducibility are limited since we do not have inducibility data on the control group. Furthermore, regression analyses on the treatment group only are difficult to interpret without the corresponding control group data. With these design and data issues, the observed results are questionable. This raises the need for further research on the effectiveness of defibrillator therapy in patients who do not have EP inducible ventricular tachyarrhythmias.

The DAVID trial is important since it showed that patients with implantable defibrillators who received dual chamber pacing (DDDR-70) had a significantly worse outcome (composite end point of death and hospitalization for heart failure) compared to patients with implantable defibrillators who received ventricular backup pacing (VVI-40; hazard=1.61, 95% CI 1.06-2.24). The authors suggested that "right ventricular stimulation may promote heart failure progression." Of the other prior trials, only MADIT II used dual chamber devices. MADIT II similarly reported a higher number of hospitalizations for heart failure in the treatment group compared to the control group, overall (19.9% versus 14.9%, respectively) and in the first 12 months of follow-up. If we consider the same composite outcome for MADIT II, then there is no difference between the defibrillator and control groups (34.1% versus 34.7%, respectively). Since both devices were used in MADIT II, it would be interesting to look at the distribution of hospitalizations for heart failure by type of device (single versus dual chamber). MADIT I, CABG-Patch and MUSTT used only single chamber devices. None of these 3 trials reported increases in hospitalizations for heart failure.

---

[16] In 1997, the FDA approved indications for the VENTAK AICD were: (1) survival of at least one episode of cardiac arrest (manifested by a loss of consciousness) due to a ventricular tachyarrhythmia; (2) recurrent, poorly tolerated sustained VT; (3) prior MI, LVEF ≤ 35%, and documented episode of nonsustained VT, with an inducible ventricular tachyarrhythmia.

[17] FDA AICD Summary of Safety and Effectiveness, 2002

[18] Teerlink et al., 2000 and Singh et al., 1998.

In summary, MADIT I and MUSTT demonstrated that patients with documented coronary artery disease, left ventricular dysfunction and inducible ventricular tachyarrhythmias on electrophysiologic testing had a significant improvement in survival with ICD therapy (ACC/AHA/NASPE Class I indication). CABG-Patch did not provide evidence on effectiveness of implantable defibrillators for any other patient population, particularly those who do not have EP inducible ventricular tachyarrhythmias (ACC/AHA/NASPE Class IIa indication). Although MADIT II reported a positive outcome, the design and data issues may render the results inconclusive. The DAVID trial raises concerns about the safety and effectiveness of dual chamber defibrillators compared to single chamber devices for patients with implantable defibrillators but without an indication for pacing.

Additional Data Analyses

Since EP inducibility is a fundamental issue in MADIT II and there was no data on inducibility in the conventional treatment group, CMS asked Steve Goodman, M.D., Ph.D. to: (1) further evaluate EP inducibility; (2) model inducibility in the defibrillator group; (3) predict inducibility in the control group; (4) estimate treatment effects for the inducible and non-inducible groups; (5) calculate the uncertainty in these effects; and (6) interpret the analyses in the context of the entire trial.

Dr. Goodman's conclusions are as follows:
(1) The analyses strengthen the finding from MADIT I that inducible patients experience a substantive benefit from ICD's.
(2) These data provide weak to moderate evidence that the ICD effect is greater in inducible than non-inducible patients.
(3) *If taken in isolation from the results in inducible patients*, the evidence is suggestive but not definitive that non-inducible patients benefit from ICDs, albeit probably to a lesser degree than inducible patients.
(4) The adjudged strength of the evidence for an ICD effect in non-inducible patients must come from a qualitative, biologic judgment about the similarity of the physiologic mechanism producing the treatment effect in the two types of patients (i.e. how informative one effect is about the other).
    (a) Identical mechanism: The treatment effect and evidence should be estimated from the combined groups.
    (b) Different mechanism: The treatment effect and evidence should be estimated from each group separately.
    (c) Mechanisms similar but not identical: Grey Zone. The evidential strength and treatment effects lie somewhere between the separate and combined results. Data that is informative about the mechanism, together with results from other trials, must be used.

Questions for the Medicare Coverage Advisory Committee – February 12, 2003 Meeting

Voting Questions:

(1) a. Is the evidence adequate to draw conclusions about the net health outcomes in Medicare patients with evidence of a ventricular tachyarrhythmia either induced or spontaneous,

with or without documented coronary artery disease and reduced left ventricular ejection fraction undergoing implantable defibrillator therapy as primary prevention of sudden cardiac death?

    b. If yes, what is the size of the net health outcomes in this Medicare population as compared to established therapies?

(2) a. Is the evidence adequate to draw conclusions about the net health outcomes in Medicare patients with a prior myocardial infarction, a left ventricular ejection fraction of $\leq .30$, and without evidence of an induced or spontaneous ventricular tachyarrhythmia undergoing implantable defibrillator therapy as primary prevention of sudden cardiac death?

    b. If yes, what is the size of the net health outcomes in this Medicare population as compared to established therapies?

Discussion Question (background articles included in packet but not summarized):

(1) Two of the summarized trials used electrophysiologic testing to identify high risk patients. Two did not. What is the utility of electrophysiologic testing?

References

Bigger JT for the (for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators). Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass graft surgery. N Engl J Med 1997;337:1569-1575.

Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937-1945.

Buxton AE, Lee KL, Fisher JD, et al. for the Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-1890.

Buxton AE, Fisher JD, Josephson ME, et al. Prevention of sudden death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT). Prog Cardiovasc Dis 1993;36:215-226.

Gregoratos G, Cheitlin M, Conill A, et al. ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices. J Am Coll Cardiol 1998;31:1175-1209.

Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 Guideline Update Implantation of Cardiac Pacemakers and Antiarrhythmia Devices. American College of Cardiology Foundation and the American Heart Association, Inc., September 2002.

Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1473-1482.

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. N Engl Med 1996;335:1933-1940.

Moss AJ, Zareba W, Hall JW, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.

Myerburg RJ, Mitrani R, Interian A, Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. Circulation 1998;97:1514-1521.

Singh SN, Fisher SG, Carson PE, et al. Prevalence and significance of nonsustained ventricular tachycardia in patients with premature ventricular contractions and heart failure treated with vasodilator therapy. J AM Coll Cardiol 1998;32:942-947.

Teerlink JR, Jalaluddin M, Anderson S, et al. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. Circulation 2000;101:40-46.

US DHHS Food and Drug Administration. AICD Summary of Safety and Effectiveness PMA P910077/S037 and P960040/S026. July 2002.

US DHHS Food and Drug Administration. Premarket Approval Guidant Corporation VENTAK® (AICD), P960040. July 1997.

Wilkoff BL, Cook JR, Epstein AE, David Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115-3123.