Proposed Decision Memo for Implantable Defibrillators (CAG-00157R2)

Decision Summary

CMS has determined that the evidence is adequate to conclude that an implantable cardioverter-defibrillator (ICD) is reasonable and necessary for the following:

1. Patients with ischemic dilated cardiomyopathy (IDCM), documented prior myocardial infarction (MI) and measured left ventricular ejection fraction (LVEF) ≤ 30%.
2. Patients with nonischemic dilated cardiomyopathy (NIDCM) > 9 months and measured LVEF ≤ 30%.

The following criteria must be also met:

1. Patients must be able to give informed consent.
2. Patients must not have:
    - New York Heart Association classification IV;
    - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
    - Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 3 months;
    - Had an acute MI within the past month;
    - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
    - Irreversible brain damage from preexisting cerebral disease;
    - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than one year.
3. Ejection fractions must be measured by angiography, radionuclide scanning or echocardiography.
4. Myocardial infarctions must be documented and defined according to the consensus document of the *Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction*.[1]

In addition, CMS has determined that the use of ICDs for primary prevention of sudden cardiac death (SCD) is reasonable and necessary only if the beneficiary receiving the ICD implantation is enrolled in either an FDA-approved category B IDE clinical trial or a qualifying national database (registry). A registry must include criteria that ensure:

1. Hospitals and providers are certified as competent in the ICD implantation.
2. Participating hospitals and providers report data on all patients undergoing ICD implantation for primary prevention.
3. Hospitals and providers who do not comply with the data collection requirements are removed from the system.
4. The data set includes elements with the following characteristics:

- Baseline patient characteristics,
- Device type and characteristics,
- Facility and provider characteristics,
- Extent of disease progression,
- Periodic device interrogation for firing data,
- Long-term patient outcomes.

5. Specific hypotheses are addressed.

Data elements will be refined in the process of developing the national database. Specific hypotheses should be predefined and based upon analyses of combined data from all previous ICD trials. CMS strongly recommends that the sponsors and principal investigators of ICD trials engage an independent, reputable cardiology research center to pool the entire databases from their respective trials and conduct analyses to identify patient selection, device related issues and other research questions to more clearly define the data elements for the registry.

A provider implanting any ICD other than a single lead, shock only device for primary prevention must maintain and furnish upon request to CMS, its agents or other authorized personnel the documentation to verify the medical necessity for a more advanced ICD. This justification must be based on patient characteristics and supported by evidence from clinical studies.

Finally, all other indications for ICDs not currently covered in accordance with this decision will continue to be covered under Category B IDE trials and the CMS routine clinical trials policy (CIM 30-1).

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Proposed Decision Memo

To: Administrative File: CAG 00157R2
Implantable Defibrillators

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Subject: Coverage Decision Memorandum for Implantable Cardioverter Defibrillators

Date: September 28, 2004

I. Decision

CMS has determined that the evidence is adequate to conclude that an implantable cardioverter-defibrillator (ICD) is reasonable and necessary for the following:

1. Patients with ischemic dilated cardiomyopathy (IDCM), documented prior myocardial infarction (MI) and measured left ventricular ejection fraction (LVEF) ≤ 30%.
2. Patients with nonischemic dilated cardiomyopathy (NIDCM) > 9 months and measured LVEF ≤ 30%.

The following criteria must be also met:

1. Patients must be able to give informed consent.
2. Patients must not have:
    - New York Heart Association classification IV;
    - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
    - Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 3 months;
    - Had an acute MI within the past month;
    - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
    - Irreversible brain damage from preexisting cerebral disease;
    - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than one year.
3. Ejection fractions must be measured by angiography, radionuclide scanning or echocardiography.
4. Myocardial infarctions must be documented and defined according to the consensus document of the *Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction*.[1]

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1. Hospitals and providers are certified as competent in the ICD implantation.
2. Participating hospitals and providers report data on all patients undergoing ICD implantation for primary prevention.
3. Hospitals and providers who do not comply with the data collection requirements are removed from the system.
4. The data set includes elements with the following characteristics:
    - Baseline patient characteristics,
    - Device type and characteristics,
    - Facility and provider characteristics,
    - Extent of disease progression,
    - Periodic device interrogation for firing data,
    - Long-term patient outcomes.
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Data elements will be refined in the process of developing the national database. Specific hypotheses should be predefined and based upon analyses of combined data from all previous ICD trials. CMS strongly recommends that the sponsors and principal investigators of ICD trials engage an independent, reputable cardiology research center to pool the entire databases from their respective trials and conduct analyses to identify patient selection, device related issues and other research questions to more clearly define the data elements for the registry.

A provider implanting any ICD other than a single lead, shock only device for primary prevention must maintain and furnish upon request to CMS, its agents or other authorized personnel the documentation to verify the medical necessity for a more advanced ICD. This justification must be based on patient characteristics and supported by evidence from clinical studies.

Finally, all other indications for ICDs not currently covered in accordance with this decision will continue to be covered under Category B IDE trials and the CMS routine clinical trials policy (CIM 30-1).

II. Background

In June 2003, CMS released an NCD on ICDs that expanded coverage to specific patient populations for both primary and secondary prevention of sudden cardiac death.[2] Since our prior decision, new evidence has been presented and/or published on the use of ICDs in primary prevention.

In March 2004, CMS received a request from Medtronic Inc. for reconsideration of the prior decision on ICDs, based largely upon the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) results. SCD-HeFT was a prospective, randomized trial to test the hypothesis that amiodarone or an implantable cardioverter-defibrillator will improve survival compared to placebo in patients with NYHA Class II and Class III heart failure and reduced LVEF ≤ 35%. It included patients with nonischemic dilated cardiomyopathy (NIDCM) in addition to patients with ischemic dilated cardiomyopathy (IDCM). Since our prior decision limited coverage to patients with ICDM, LVEF ≤ 30% and prolonged QRS > 120 milliseconds, this request for reconsideration includes assessment of etiology of dilated cardiomyopathy, level of LVEF and QRS duration. As noted in the prior decision, the use of ICDs for the secondary prevention of SCD has been well studied and accepted. Therefore, secondary prevention will not be further evaluated in this memorandum.

Based on the National Health and Nutrition Examination Survey III, it has been estimated that 5 million Americans have congestive heart failure.[3] Congestive heart failure (CHF) is often a symptom of dilated cardiomyopathy, which is "characterized by ventricular remodeling that produces chamber dilation, with normal or decreased wall thickness, and diminution in systolic function."[4] Dilated cardiomyopathy may be further classified by etiology into IDCM (due to prior myocardial infarction and coronary artery disease) and NIDCM (due to non-ischemic conditions such as infections, inflammation, familial or genetic conditions or idiopathic causes); however, these two categories are not necessarily mutually exclusive.

Since there are various types of commercially available ICDs, a closer look at the type of ICD used in the various trials may provide insight into the necessary features of the device suitable for primary prevention. In general, current ICDs can be classified into single-chamber devices and dual-chamber devices, depending on the number of leads and lead placement. Single-chamber ICDs typically have one lead that ends in the right ventricle. Dual-chamber ICDs have at least one additional lead, usually in the right atrium. Once a ventricular tachyarrhythmia is detected, two methods may be used to treat the arrhythmia - antitachycardia pacing and direct current shocks.[5] The ICD can deliver one or more bursts of pacing to end ventricular tachycardia and restore a normal rate and rhythm. ICDs can also deliver "either synchronized, usually low-energy shocks (less than 5J) or unsynchronized high-energy shocks."[6] Another feature of some ICDs is antibradycardia pacing; however, the MADIT II[7] and DAVID[8] trials suggested that antibradycardia pacing may not be necessary and in some instances, may be detrimental. In SCD-HeFT, shock only, single-lead defibrillators were used.

A closely related device is the combined cardiac ventricular resynchronization and defibrillator (CRT-D), also referred to as a combined biventricular pacing and defibrillator device. Cardiac ventricular resynchronization refers to pacing techniques that aim to alter the amount of intraventricular asynchrony, most commonly identified by prolonged QRS interval. Although cardiac resynchronization therapy (CRT) devices were not completely reviewed in this decision, CRT-D devices were considered since these devices also have defibrillator functions.

III. History of Medicare Coverage

The Centers for Medicare & Medicaid Services (CMS), issued a Medicare National Coverage Determination (NCD) in 1986 providing limited coverage of implantable defibrillators. The policy has expanded over the years with revisions in 1991, 1999 and 2003. The most recent expansion of coverage is discussed in the June 6, 2003 decision memorandum that is available on our web site at www.cms.gov/coverage. This decision became effective for services on or after October 1, 2003 and expanded coverage to patients with a previous myocardial infarction, low ejection fraction and a wide QRS interval. The policy was also expanded to include coverage to patients enrolled in an Investigational Device Exemption Category B device trial. A follow up decision memorandum to clarify this specific aspect of the policy was published March 12, 2004 and is also available on our web site.

The benefit category for ICDs has been previously determined to fall within the prosthetic devices category.

On March 30, 2004, CMS accepted a request from Medtronic Inc. to expand coverage for ICDs. Medtronic Inc. made this request based on the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and specifically requested that Medicare expand coverage to the trial population. Since an NCD already exists for ICDs, this review is a reconsideration of the current policy. The current policy is:

A.Covered Indications

1. Documented episode of cardiac arrest due to ventricular fibrillation (VF), not due to a transientor reversible cause (effective July 1, 1991);
2. Documented sustained ventricular tachyarrhythmia (VT), either spontaneous or induced by an electrophysiology (EP) study, not associated with an acute myocardial infarction (MI) and not due to a transient or reversible cause (effective July 1, 1999);
3. Documented familial or inherited conditions with a high risk of life-threatening VT, such as long QT syndrome or hypertrophic cardiomyopathy (effective July 1, 1999);
   Additional indications effective for services performed on or afterOctober 1, 2003:
4. Coronary artery disease with a documented prior MI, a measured left ventricular ejection fraction $\leq$ 0.35, and inducible, sustained VT or VF at EP study. (The MI must have occurred more than 4 weeks prior to defibrillator insertion. The EP test must be performed more than 4 weeks after the qualifying MI.);
5. Documented prior MI and a measured left ventricular ejection fraction $\leq$ 0.30 and a QRS duration of > 120 milliseconds. Patients must not have:
   a. New York Heart Association classification IV;
   b. Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
   c. Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 3 months;
   d. Had an enzyme-positive MI within the past month;
   e. Clinical symptoms or findings that would make them a candidate for coronary revascularization;
   f. Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year.

B. All patients considered for implantation of a defibrillator must not have irreversible brain damage, disease or dysfunction that precludes the ability to give informed consent.

C. Myocardial infarctions must be documented by elevated cardiac enzymes or Q-waves onan electrocardiogram. Left ventricular ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography.

D. All other indications remain noncovered except in Category B IDE clinical trials (60 CFR 48417 [replace with 42 CFR 405.201]) or as a routine cost in clinical trials defined under CIM 30-1.

IV. Timeline of Recent Activities

6/6/2003	CMS issues the decision memorandum discussing the intent to expand coverage to patients with a previous myocardial infarction, low ejection fraction and wide QRS interval. This decision is based on data from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II).
10/1/03	Coverage in the June 2003 decision memorandum becomes effective.
3/8/04	The principal investigator of SCD-HeFT presents the primary trial results at the American College of Cardiology annual scientific session.
3/12/04	CMS issues a follow up decision memorandum to further explain the decision to allow coverage under IDE Category B clinical trials.
3/18/04	CMS meets with Medtronic Inc. to discuss results of SCD-HeFT.
3/30/04	CMS accepts a reconsideration request from Medtronic Inc. to expand coverage of ICDs to patients with SCD-HeFT indications. Tracking sheet is posted to our web site and the initial open public comment period begins.

4/14/04	Teleconference with the requestor.
4/22/04	CMS meets with St. Jude Medical to discuss recent clinical trials studying ICDs.
4/30/04	Initial open public comment period ends.
5/3/04	CMS meets with Guidant Corporation to discuss recent clinical trials studying ICDs.
5/17/04	Teleconference with requestor.
5/22/04	SCD-HeFT investigators present additional data from the trial at the Heart Rhythm Society's annual scientific session.
5/25/04	CMS requests a second open public comment period to receive comments on the COMPANION and DEFINITE trials that were published after the close of the initial comment period.
6/7/04	Posting of comments received in the initial public comment period.
6/8/04	CMS meets with the Heart Rhythm Society and the American College of Cardiology to discuss appropriate device selection.

6/23/04	CMS requests a third open public comment period to receive comments on threshold testing, anti-tachycardia pacing (ATP), risk associated with the ATP lead and an ICD patient registry.
6/25/04	Second public comment period closes.
6/28/04	Teleconference with requestor.
7/1/04	Posting of comments received in the second public comment period.
7/23/04	Third public comment period closes.
8/9/04	Posting of comments received in the third public comment period.

V. FDA Status

The FDA approved the first implantable defibrillator in 1985 while the first implantable cardioverter defibrillators were approved in 1988 and 1989.[9] The FDA approves each device individually and has granted premarket approvals (PMA)[10] for implantable defibrillators for the indications of providing antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias.

CMS assesses relevant health outcomes, above and beyond the safety and effectiveness regulatory mandate of the FDA. Although a device must receive FDA approval or clearance for at least one indication to be eligible for Medicare coverage, except for a category B device under an investigational device exemption (IDE) clinical trial (60 FR 48417, September 19, 1995), FDA approval/clearance alone does not entitle that device to coverage. The device must fall under a Medicare benefit category and be determined to be reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member to be covered by CMS. CMS has the authority to conduct a separate assessment of a device's appropriateness for Medicare coverage, including whether it is reasonable and necessary specifically for its intended use for Medicare beneficiaries (*see e.g.*, 60 FR 48417, 48420 September 19, 1995). Under a premarket approval application (PMA) review, the FDA determines whether or not there is reasonable assurance of safety and effectiveness for the device's intended use that is stated in its proposed labeling. Medicare NCDs consider the medical benefit and clinical utility of an item or service in determining whether the item or service is considered reasonable and necessary under the Medicare program. CMS determines whether or not the intervention improves net health outcomes in the Medicare population at least as well as established treatments. Thus, FDA PMA approval by itself is not sufficient for making a determination concerning Medicare coverage.

As we similarly stated in 66 FR 58788, 58797 (November 23, 2001) with regard to FDA 510(k) clearance, "[t]he criteria the FDA uses in making determinations related to substantial equivalency under section 510(k) of the Food, Drug, and Cosmetic Act is significantly different from the scientific evidence we consider in making "reasonable and necessary" determinations under Medicare. FDA does not necessarily require clinical data or outcomes studies in making a determination of substantial equivalency for the purpose of device approval under section 510(k) of the Food, Drug, and Cosmetic Act. Medicare NCDs consider medical benefit and clinical utility of an item or service in determining whether the item or service is considered reasonable and necessary under the Medicare program. Thus, a substantial equivalency approval under section 510(k) of FDA is not sufficient for making determination concerning Medicare coverage."

VI. General Methodological Principles

When making NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix III. In general, features of diagnostic studies that improve quality and decrease bias include the selection of a clinically relevant inception cohort, the consistent use of a single good reference standard, the inclusion of patients with and without the disorder in question, and the blinding of readers of the index test and of reference test results.[11]

VII. Evidence

A. Introduction

There have been numerous trials on the use of defibrillators to prevent sudden cardiac death. These trials have predominantly used mortality as the primary outcome. We have thus focused this reconsideration on mortality evidence released since our prior decision in June 2003. In addition, the definition of a myocardial infarction was changed. This redefinition will be included in the evidence section.

B. Discussion of evidence reviewed

1. Questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve final health outcomes for Medicare patients?"

The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared and the delivery setting. In this reconsideration, CMS sought to address the following questions:

- Is there evidence to conclude that ICDs decrease mortality for patients with ischemic dilated cardiomyopathy (IDCM) and reduced LVEF?
- Is there evidence to conclude that ICDs decrease mortality for patients with nonischemic dilated cardiomyopathy (NIDCM) and reduced LVEF?

2. External technology assessments

There was no external technology assessment commissioned.

3. Internal technology assessments

Medline was searched iteratively from 2002 using the following keywords: defibrillator with and without implantable. Studies on animal subjects and reports in languages other than English were excluded. Six original randomized clinical trials and several review articles were reviewed and classified into primary prevention and secondary prevention.

Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453-1458.

The Cardiomyopathy Trial (CAT) was a randomized trial to compare ICD therapy to standard medical therapy in patients with idiopathic dilated cardiomyopathy and impaired ejection fraction. Inclusion criteria were idiopathic dilated cardiomyopathy ≤ 9 months, LVEF ≤ 30%, NYHA Class II or III. Exclusion criteria included coronary artery disease, prior myocardial infarction, history of VT or VF, and significant valvular disease. The primary endpoint was all-cause mortality at 1 year of follow-up.[12]

A total of 104 patients were enrolled in the CAT pilot phase: 50 patients were randomly assigned to ICD treatment and 54 to the control group. Mean follow-up was 5.5 years. Mean age was 52 years. Men comprised 83% of the study population. Mean LVEF was 24%. Approximately 65% of the patients had NYHA Class II heart failure and 35% had NYHA Class III.

There were a total of 30 deaths: 13 in the ICD group compared to 17 in the control group (p-value=0.554). The investigators concluded "this trial did not provide evidence in favor of prophylactic ICD implantation in patients with DCM of recent onset and impaired left ventricular ejection fraction."[13]

In this study, Kaplan-Meier and Cox proportional regression analyses were used. No patients with NYHA Class IV were enrolled. Eleven patients received adequate ICD therapy. The sample size was relatively small. The authors found that "short- and long-term overall mortality rates in patients with DCM and significantly impaired LV function were surprisingly low."[14] The trial was stopped "after the inclusion of 104 patients because the all-cause mortality at 1 year did not reach the expected 30% in the control group."[15] The authors further noted, "even if 1348 patients had been included, as initially planned, the trial would have been underpowered."[16]

Strickberger SA, Hummel JD, Bartlett TG, 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;41:1707-1712.

The Amiodarone Versus Implantable Cardioverter-Defibrillator Trial (AMIOVIRT) was a prospective, randomized study "to compare the total mortality rates of patients with non-ischemic dilated cardiomyopathy (NIDCM)[17] and asymptomatic NSVT who were randomized to therapy with amiodarone or an ICD."[18] Inclusion criteria were nonischemic dilated cardiomyopathy, asymptomatic non-sustained ventricular tachycardia, LVEF ≤ 35% and NYHA Class I-III. Exclusion criteria included syncope, pregnancy, a contraindication to amiodarone or ICD, therapy with class I antiarrhythmic drug, or NIDCM within 6 months. The primary endpoint was total mortality.

A total of 103 patients were enrolled: 51 patients were randomly assigned to ICD treatment and 52 to amiodarone. Mean follow-up was 2.0 years. Mean age was 59 years. Men comprised 70% of the study population. Mean LVEF was 23%. Approximately 63% of the patients had NYHA Class II and 20% had Class III.

There were a total of 13 deaths: 6 in the ICD group compared to 7 in the amiodarone group (p-value=0.8). The investigators reported: "The study was stopped when the prospective stopping rule futility was reached. The percent of patients surviving at one year (90% vs. 6%) and three years (88% vs. 87%) in the amiodarone and ICD groups, respectively, were not statistically different (p=0.8)."[19]

In this study, there was no standard medical therapy group. The authors further stated: "The relatively small sample size in AMIOVIRT permits a mortality difference observed with a power of only 3%. The study was stopped due to the prospective rule used to identify inability to differentiate between ICD and amiodarone therapy."[20]

Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2152-2158.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was a prospective, randomized study to test "the hypothesis that an ICD will reduce the risk of death in patients with nonischemic cardiomyopathy and moderate-to-severe left ventricular dysfunction."[21] Inclusion criteria were a LVEF < 36%, the presence of ambient arrhythmias,[22] a history of symptomatic heart failure and the presence of nonischemic dilated cardiomyopathy. Patients were excluded if they had New York Heart Association (NYHA) Class IV congestive heart failure, were not candidates for the implantation of a cardioverter-defibrillator, had undergone electrophysiological testing within the prior three months, or had permanent pacemakers. Patients in whom cardiac transplantation appeared to be imminent, those with familial cardiomyopathy associated with sudden death and patients with acute myocarditis or congenital heart disease were also excluded. The primary endpoint was death from any cause. The secondary endpoint was sudden death from arrhythmia.

A total of 458 patients were enrolled: 229 patients were randomly assigned to receive standard medical therapy and 229 to receive standard medical therapy plus a single-chamber ICD. Mean follow up was 29.0 months. Mean age was 58.3 years. Men comprised 71.2% of the study population. Mean LVEF was 21%. Approximately 57% of the patients had NYHA Class II heart failure.

"There were 68 deaths: 28 in the ICD group, as compared with 40 in the standard-therapy group (hazard ratio, 0.65; 95 percent confidence interval, 0.40 to 1.06; P=0.08). The mortality rate at two years was 14.1 percent in the standard-therapy group (annual mortality rate, 7 percent) and 7.9 percent in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, as compared with 14 in the standard therapy group (hazard ratio, 0.20; 95 percent confidence interval, 0.06 to 0.71; P=0.006)."[23]

The authors concluded, "in patients with severe, nonischemic dilated cardiomyopathy who were treated with ACE inhibitors and beta-blockers, the implantation of a cardioverter-defibrillator significantly reduced the risk of sudden death from arrhythmia and was associated with a nonsignificant reduction in the risk of death from any cause."[24]

In this study, FDA approved, single chamber devices were used. The ICDs were programmed to back up VVI pacing at a rate of 40 beats per minute and to detect ventricular fibrillation at a rate of 180 beats per minute. Forty-one patients (17.9%) received appropriate ICD shocks. Forty-nine patients (21.4%) received inappropriate ICD shocks, primarily for atrial fibrillation or sinus tachycardia.

Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-2150.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial was a randomized trial to test the hypothesis that prophylactic cardiac-resynchronization therapy with a pacemaker (CRT) or with a pacemaker-defibrillator (CRT-D) would reduce the risk of death and hospitalization among patients with advanced chronic heart failure and intraventricular conduction delays. Enrollment criteria included New York Heart Association (NYHA) Class III or IV heart failure from either ischemic or nonischemic cardiomyopathy, LVEF $\leq$ 0.35, an electrocardiographically measured QRS interval $\geq$ 120 msec and a PR interval > 150 msec, sinus rhythm, no clinical indication for a pacemaker or implantable defibrillator, and a hospitalization for the treatment of heart failure or the equivalent in the preceding 12 months. Exclusion criteria included myocardial infarction within 60 days of randomization, CAD with surgical or percutaneous correction within 60 days of randomization, progressive or unstable angina, uncontrolled blood pressure and surgically uncorrected primary valvular heart disease.[25] The primary endpoint was a composite of "all-cause mortality and all-cause hospitalization, in which all-cause mortality is defined as death from all causes and all-cause hospitalization is defined as admission to a hospital for any reason."[26] The secondary endpoints included all-cause mortality and cardiac morbidity.

A total of 1520 patients were enrolled: 308 were randomly assigned to receive optimal pharmacologic therapy, 617 to optimal pharmacologic therapy plus CRT and 595 to optimal pharmacologic therapy plus CRT-D. Median follow-up for the primary endpoint was 11.9 months in the pharmacologic-therapy group, 16.2 months in the pacemaker group and 15.7 months in the pacemaker-defibrillator group (significantly longer for the groups that received devices compared to medical therapy). Mean age was approximately 67 years. Men comprised approximately 68% of the study population. Mean LVEF was approximately 21%. Approximately 55% of patients had ischemic cardiomyopathy.

For the primary endpoint, the 12-month rate of death from any cause or hospitalization for any cause was 68 percent in the pharmacologic therapy group as compared with 56 percent in the CRT group (hazard ratio= 0.81; 95% CI 0.69 to 0.96; P=0.014) and 56 percent in the CRT-D group (hazard ratio= 0.80; 95% CI 0.68 to 0.95; P=0.010).

For the secondary endpoint, there were 77 death (25%) in the pharmacologic therapy group, 131 deaths (21%) in the CRT group (hazard ratio= 0.76; 95% CI 0.58 to 1.01; P=0.0059), and 105 deaths (18%) in the CRT-D group (hazard ratio= 0.64; 95% CI 0.48 to 0.86; P=0.003).

The authors concluded, "in patients with advanced heart failure and a prolonged QRS interval, cardiac-resynchronization therapy decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality."[27]

In this study, there was a 1:2:2 randomization weighted towards device therapy. Kaplan-Meier analysis was used. In the pharmacologic therapy group, 26% of the patients withdrew from the study. Subsequently the study was modified to attempt to address this issue. The authors reported: "For the mortality endpoint analysis, data on patients whose vital status was not known at the end of the study were censored on the date of the last known contact."[28] The definition of all -cause hospitalization was changed after the trial had started, potentially influencing the primary endpoint of the trial.

Defibrillator in Acute Myocardial Infarction Trial (DINAMIT).[29]

DINAMIT was a randomized trial to test the hypothesis that an ICD will reduce the risk of death in patients with recent MI who are at high risk of arrhythmic death due to extensive myocardial scarring (low LVEF) and autonomic imbalance (low heart rate variability or high resting heart rate). Inclusion criteria included recent acute MI (6-40 days), LVEF $\leq$ 35%, and depressed HRV or elevated heart rate. Exclusion criteria included NYHA class IV heart failure, CABG surgery or 3-vessel PTCA since qualifying MI, and candidates for heart transplant. The primary outcome was mortality from all causes. Secondary outcomes included arrhythmic death, quality of life and cost effectiveness.

A total of 674 patients were enrolled; 332 were randomly assigned to ICD therapy and 342 to conventional medical therapy. Mean follow-up was approximately 30 months. Mean age was 62 years. Men comprised 76% of the study population. Mean LVEF was about 28%.

For the primary endpoint, there were 62 deaths in the ICD group compared to 58 deaths in the conventional therapy group (hazard ratio=1.08; 95% CI=0.76-1.55; p-value=0.66). For the secondary endpoint, there were 12 arrhythmic deaths in the ICD group compared to 29 deaths in the conventional therapy group (hazard ratio=0.42; 95% CI=0.22-0.83; p-value=0.009).[30]

Bardy GH. SCD-HeFT: The Sudden Cardiac Death in Heart Failure Trial. ACC meeting, 2004.
http://www.acc04online.org/ondemand/trials1/sessions.asp?link=R

SCD-HeFT was a prospective, randomized trial to test the hypothesis that amiodarone or an implantable cardioverter defibrillator will improve survival compared to placebo in patients with systolic dysfunction from ischemic or non-ischemic causes with either NYHA class II or class III heart failure, chronic stable congestive heart failure and reduced LVEF ≤ 35%. Randomization was stratified by cause of heart failure and NYHA class. The primary endpoint was all cause mortality based on a minimum of 2.5 years of follow-up. The secondary endpoints included arrhythmic cardiac mortality, non-arrhythmic cardiac mortality, morbidity, cost-effectiveness, and quality of life

Patient inclusion criteria included heart failure duration of at least 3 months, stable symptomatic CHF (NYHA class II and class III) due to ischemic or nonischemic dilated cardiomyopathy, CHF present for at least 3 months treated with a vasodilator, and LVEF ≤ 35%. Exclusion criteria included asymptomatic patients; history of cardiac arrest; restrictive, infiltrative or hypertrophic cardiomyopathy; and unexplained syncope.

A total of 2521 patients were enrolled; 847 were randomly assigned to placebo plus conventional heart failure therapy, 845 to amiodarone plus conventional heart failure therapy, and 829 to single lead ICD plus conventional heart failure therapy. Median follow-up was 45.5 months. Mean age was 59.5 years. Men comprised 77% of the study population. Mean LVEF was 23.8%. Approximately 52% of patients had ischemic cardiomyopathy.

For the primary endpoint at the end of the follow-up period, there was a significant reduction in mortality in the ICD group compared to the placebo group (hazard ratio compared to control=0.77; 97.5% CI=0.62-0.96; p-value=0.007). [31]

For patients with IDCM, there was a reduction in mortality hazard ratio for ICD therapy compared to control but it was not statistically significant (hazard ratio=0.79; 97.5% CI=0.60-1.04). For patients with NIDCM, there was a reduction in the mortality hazard ratio for ICD therapy compared to control but it was also not statistically significant (hazard ratio=0.73; 97.5% CI= 0.50-1.07).[32] Considering subgroups based on QRS interval, there were inconsistent findings depending on the definition of normal and abnormal intervals.

The SCD-HeFT authors provided a number of hazard ratios analyses that are provided in Appendix IV. Also, the Kaplan Meier curves for survival based on etiology of CHF are presented in Appendix V.

In this trial, there was equal randomization. The significance level was reduced to account for the additional comparisons in a 3-group trial. The follow-up time was extended by 1 year. Single lead, shock-only defibrillators were used in all patients in the ICD group. No dual chamber or bi-ventricular devices were used.

4. Medicare Coverage Advisory Committee (MCAC)

CMS did not convene an MCAC for this issue.

5. Evidence-based guidelines

At this time, professional society guidelines addressing the SCD-HeFT patient population are not available. We have been informed that the guidelines published in 2002 by American College of Cardiology (ACC), the American Heart Association (AHA) and the North American Society for Pacing and Electrophysiology (NASPE) will be reviewed and updated in the near future.

In 2002, the ACC/AHA recommendations for implantable defibrillator therapy, expressed in the standard format, [33] 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.]

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)*

Class IIa [Weight of evidence/opinion is in favor of usefulness/efficacy.]
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)* [34]

In 2000, the definition of a myocardial infarction was reevaluated by a joint committee of the Joint European Society of Cardiology and the American College of Cardiology in response to the need for a more precise definition and the availability of new diagnostic technologies. The joint committee stated the following:

Definition of Myocardial Infarction

Criteria for acute, evolving or recent MI.
Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a. ischemic symptoms;
   b. development of pathologic Q waves on the ECG;
   c. ECG changes indicative of ischemia (ST segment elevation or depression); or
   d. coronary artery intervention (e.g., coronary angioplasty).
2. Pathologic findings of an acute MI.

Criteria for established MI.
Any one of the following criteria satisfies the diagnosis for established MI:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathologic findings of a healed or healing MI.

6. Open Comment Period

CMS held three open comment periods during this national coverage analysis. Each comment period encouraged responses to different issues regarding ICDs. Most comments are available in full text on our web site at http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=108.

The first comment period was at the start of this national coverage analysis. CMS allowed the first 30 days for the public to comment on any issue related to the request to expand Medicare coverage of ICDs to the SCD-HeFT population. In addition to general comments, CMS encouraged commenters to focus on clinical trials and device selection.

In the second comment period, CMS specifically requested comments on the results of the COMPANION and DEFINITE trials.

In the third comment period, CMS asked for comments on three specific questions regarding the evidence of threshold testing, evidence of risks and benefits of anti-tachycardia pacing (ATP) and the justification of an ICD registry to better identify predictors of device firing (as a proxy for sudden cardiac death).

Comments received during these periods are summarized below according to classification of the commenter as a professional society, expert commenter or public commenter.

Professional Society Position Statements

The American College of Cardiology (ACC) comments that the SCD-HeFT data made available prior to the peer-reviewed publication is favorable but that review of peer reviewed data should be used to determine coverage. In addition, the ACC strongly supports that cardiovascular device selection be at the discretion of the treating physician. In comments by the Heart Failure Society of America (HFSA), the society points out that recent clinical trials show patients with heart failure and left ventricular dysfunction (with and without coronary artery disease as the underlying cause) but no history of a life-threatening arrhythmia treated with ICDs benefit from a reduced risk of death. The NASPE-Heart Rhythm Society supports full Medicare coverage of the SCD-HeFT patient population based on the currently available data. The society also strongly supports that cardiovascular device selection be at the discretion of the treating physician, particularly since some patients have multiple indications that may require a dual chamber defibrillator or biventricular pacing.

The Heart Rhythm Society submitted a clinical competency statement containing guidelines for non-electrophysiologists implanting defibrillators. They note that as the demand for these devices increases it is important to ensure patient safety through appropriate training of implanting physicians. The guidelines restrict non-electrophysiologist implanting physicians to those that meet high volume requirements of standard pacemakers in addition to receiving training for ICDs and cardiac resynchronization devices.

In comments from the Heart Failure Society of America, the society discusses recommendations for ICDs in patients eligible for cardiac resynchronization therapy (CRT) and in class IV heart failure, regardless of etiology. Both the ACC and Heart Rhythm Society support this recommendation.

In the third round of public comments the ACC and Heart Rhythm Society submitted joint comments. Both support threshold testing and note that clinical trials have used testing as part of their protocol and do not support the removal of threshold testing until clinical trials are available in support of changing clinical practice. The societies state that testing is necessary to determine lead re-positioning, need for device upgrade and assessment of device sensing. They also provide data in response to concern over ATP and note that ATP reduces the number of inappropriate shocks and should be available in defibrillators intended for the primary prevention of SCD. Although ACC and Heart Rhythm Society agree a registry could be beneficial they note many barriers to implementation.

Expert Opinion

Of the expert respondents in the first comment period, all support expanded coverage of ICDs. Although most experts cite results from SCD-HeFT, some experts note recent results from DEFINITE, COMPANION and MADIT-II as support for expanded Medicare coverage. CMS was cautioned against performing subgroup analyses of SCD-HeFT data. Some experts support defibrillator implantation in patients with LVEF ≤ 35% while one supports coverage of ICD implantation in patients with LVEF ≤ 39% regardless of etiology. Another expert supports extending coverage to all patients with a prior MI and LVEF ≤ 30% irrespective of QRS width in addition to patients with Class II or Class III CHF and LVEF ≤ 35% irrespective of the etiology of heart failure or the QRS width. Others support coverage of both ischemic and non-ischemic patients and Class II and Class III heart failure patients. One expert suggests that at least two different methods of measuring ventricular function be used to confirm LVEF. Real-world population registries are the suggestion of one expert to confirm the trial results. Overall, respondents strongly support that cardiovascular device selection be at the discretion of the treating physician.

Expert opinions received in the second comment period emphasize that MADIT II and SCD-HeFT prove ICDs beneficial to both ischemic and non-ischemic patients. In addition, they maintain that physician judgment, not grouping by QRS criteria, remains the most appropriate determinant of treatment. One expert supported coverage for the entire MADIT II and SCD-Heft populations and another notes a cost-effectiveness analysis that favors expanded coverage.

In response to the third comment period, Medicare received many comments from experts on the issue of threshold testing. Experts generally agree that threshold testing remains necessary to ensure the device will defibrillate the patient and make changes in the device setting or lead positioning if required. Another issue is the concern that physicians have appropriate specialty training to perform defibrillator implants. In regard to ATP, experts state that this function reduces inappropriate shocks and provides initial therapy for VT. However, some caution that inappropriately programmed ATP can increase risk of syncope or injury. For this reason, some recommend that only electrophysiologists be able to perform the procedure. Data is provided from MADIT II that demonstrates the value of ATP through the number of VT/VF episodes that were terminated by ATP. One expert argues that the primary goal of using ICDs as primary prevention is not to manage complex VT, therefore, recommends broad coverage of all class II and III patients with a simpler device. Expert comments varied on the issue of a registry. Some express that a registry at this point in time is unnecessary and that clinical trials have already proven the need for devices in these patients. Others state that additional information on clinical predictors of SCD would be valuable. Experts advise CMS that microvolt t-wave alternans testing offers a negative predictive value to rule out patients who will not benefit from an ICD.

Public Comments

In the first comment period, the majority of commenters support expanded coverage of ICDs to the SCD-HeFT population while some also recommend coverage of MADIT II patients. Many note support of ICDs for patients with LVEF ≤ 35% while some support coverage of patients with Class II and Class III heart failure. One respondent does not feel that ICDs should be routinely provided to all patients meeting SCD-HeFT criteria and feels strongly that an ICD should be available to selected patients with mild symptoms of heart failure with low ejection fraction, and otherwise good prognosis for meaningful survival extending past two years. Another respondent does not believe that CMS should cover ICDs for all patients with low LVEF or clinical heart failure, but should cover SCD-HeFT patients only with QRS > 0.12 sec. CMS is cautioned against performing subgroup analyses of the SCD-HeFT data by some commenters. Some commenters note the need for more data. Of the commenters that discussed device selection, most agreed that CMS should not determine device selection through coverage policy or cost information but that the treating physician makes the decision. A few commenters, however, note that there should be cost restrictions on cardiovascular devices. Microvolt T-wave alternations is suggested as a method of identifying patients who will not benefit from ICD therapy.

CMS received few public comments in response to the second comment period. Some of the public comments strongly support the COMPANION trial and suggest its results imply NYHA Class IV patients will be disenfranchised by a narrow CMS coverage determination. In order to allow another route to access for these patients, such commenters suggest Class IV patient coverage be left to local contractor discretion. Others recommend coverage of all or a combination of the MADIT II, SCD-HeFT, DEFINITE and COMPANION populations based on the favorable results of those trials. Commenters generally recommend the elimination of QRS as a condition of coverage and recommend using only LVEF. One commenter maintains that the differences in results between the DEFINTE (35% reduction in overall mortality) and SCD-Heft (25% reduction in overall mortality) trials are within expected limits for repeated trials. The same commenter points out a suggested benefit for Class III patients, though admitting this trend was statistically insignificant. Some commenters point out the evidence does not demonstrate a clear benefit for women treated with ICDs. Finally, most of the public commenters remain opposed to CMS determining device selection, stating that such decisions are best left to physician discretion.

In the third comment period, public commenters note that threshold testing is necessary to make sure it can deliver the required shock to the patient. The concern of some commenters is that removing threshold testing could encourage physicians to implant devices that are not adequately trained to do so. ATP comments received agree that this function reduces inappropriate shocks and contributes to a better quality of life for the patient since otherwise painful shocks are avoided. Commenters also note that clinical trials utilize threshold testing as part of the protocol therefore results of those studies cannot be extrapolated to patients who do not receive threshold testing. Most public commenters express concern for the reliability of information from a registry and do not expect it to provide more information than what is already available. Others determine that clinically useful information can come out of a registry but are unsure of how CMS would implement such a massive undertaking. Public commenters recommended the use of microvolt t-wave alternans testing to exclude certain patients from implants based on a prediction that they will not benefit from the device. They refer to the test's high negative predictive value.

VIII. CMS Analysis

A. Introduction

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

In this decision, we will be incorporating the new definition of a myocardial infarction as presented by the joint committee of the Joint European Society of Cardiology and the American College of Cardiology. In our prior decision, we did not use this new definition but used a definition based upon the inclusion criteria of the prior defibrillator trials. Since practice and technologies may change with time and trials may use varying inclusion criteria, we have decided to adopt the consensus definition of a myocardial infarction.

For this reconsideration of ICDs, the results of 6 trials (CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DINAMIT) involving defibrillators have been released or published since our prior decision in June 2003. DINAMIT studied patients with IDCM and will be discussed in the section on IDCM. CAT and AMIOVIRT studied patients with NIDCM and will be discussed in the section on NIDCM. COMPANION and SCD-HeFT studied both patients with IDCM and patients with NIDCM and are discussed below.

The COMPANION trial was a randomized controlled trial involving 1520 patients with nonischemic or ischemic dilated cardiomyopathy, LVEF $\leq$ 35%, QRS interval $\geq$ 120 msec. and PR interval > 150 msec. It demonstrated a reduction in mortality in the CRT-D therapy group compared to the optimal pharmacologic therapy group (18% versus 25%, respectively; hazard ratio =0.64; 95% CI=0.48-0.86; p-value=0.003).[35] However, there were several issues with the design, conduct and analysis of the trial. First there was an unequal, 1:2:2 randomization ratio weighted towards device therapy. An equal 1:1:1 randomization format is generally considered more neutral. Second, the definition of hospitalization was changed during the course of the trial without notifying the FDA. This potentially has a direct impact on the primary outcome since hospitalization was the dominating factor for the composite endpoint. Data should have been collected and reported using both definitions to determine if the change favored one group over another. Third, a high number of patients withdrew from the pharmacologic therapy group, many of whom obtained device therapy. Patients who were subsequently lost to follow-up were censored in the analyses, which may have lead to an inaccurate estimation of the mortality rate. These issues hamper the strength of the findings of the COMPANION trial. Since it was the only trial to evaluate mortality for patients with CRT and CRT-D therapy, additional research is needed to support the findings of this trial.

SCD-HeFT was a randomized controlled trial involving 2521 patients with both IDCM and NIDCM and LVEF $\leq$ 35%. It demonstrated a reduction in mortality in the ICD therapy group compared to the placebo group (hazard ratio =0.77; 97.5% CI=0.62-0.96; p-value=0.007) at the end of follow-up.

Overall, the absolute reduction in mortality was modest for a trial with a median follow-up of 45.5 months. Several potential explanations have been presented for the modest overall effect compared to prior ICD trials. In SCD-HeFT, appropriate medications for heart failure were recommended for all patients. SCD-HeFT also included patients with nonischemic dilated cardiomyopathy. As with other studies on patients with NIDCM, SCD-HeFT showed that overall morality is lower for patients with NIDCM compared to patients with IDCM.[36]

In SCD-HeFT, the follow-up period was extended by one year but the reason to do so has not been fully explained. In general, the extension of a clinical trial presents potential challenges: "Towards the scheduled end of a study, the investigator may find that he has nearly statistically significant results. He may be tempted to extend or expand the trial in an effort to make the test significant. Such a practice is not recommended. A strategy of extending assumes that the observed relative differences in rates of response will continue. The observed differences which are projected for a larger sample may not hold. In addition, because of the multiple testing issue and the design change, the significance level should be adjusted downward. However, appropriate adjustments in the significance level to account for the design changes may not easily be determined. Since a more extreme significance level should be employed, and since future responses are uncertain, extension may leave the investigator without the expected benefits. Whatever adjustments are made to either sample size or the length of follow-up should be done as early in the trial as possible. Early adjustments would diminish the criticism that the monitoring committee waited until the last minute to see whether the results would achieve some prespecified significance level before changing the study design."[37]

Overall SCD-HeFT was a well-conducted trial that had a large sample size and a lengthy follow-up period. The available results provide evidence on the benefits of single lead, shock only ICDs. Additional information such as ICD firing data, patient characteristics at last follow-up and disease progression should be forth coming.

B. Questions

For this reconsideration on ICDs, CMS focused on the following questions:

Question 1: Is there evidence to conclude that ICDs decrease mortality for patients with ischemic dilated cardiomyopathy (IDCM) and reduced LVEF?

- **What can we conclude from evidence for patients with either QRS $\geq$ 120 milliseconds or LVEF > 0.30?**

For patients with IDCM, evidence from DINAMIT, SCD-HeFT and COMPANION is relevant. DINAMIT was a randomized controlled trial involving 674 patients with recent myocardial infarction, LVEF $\leq$ 35% and depressed heart rate variability. It did not show a reduction in mortality when an ICD was implanted early after a myocardial infarction (6-40 days).[38]

Overall, SCD-HeFT showed a significant reduction in mortality. SCD-HeFT included 884 patients with IDCM and LVEF ≤ 35%. There was a reduction in mortality hazard ratio for ICD therapy compared to control but it was not statistically significant (hazard ratio=0.79; 97.5% CI=0.60-1.04). Overall, the COMPANION trial showed a significant benefit. COMPANION included 842 patients with IDCM, LVEF ≤ 35%, PR >150 ms. and QRS interval ≥ 120 msec. There was also a reduction in mortality hazard ratio for the CRT-D group compared to optimal pharmacologic therapy but it was not statistically significant (hazard ratio=0.73; 95%CI=0.52-1.04).[39]

In our June 2003 decision, we used prolonged QRS interval as a risk stratifier based on our concerns with the conduct of MADIT II [inclusion of patients with a high likelihood of benefit that should have been excluded by trial design (see previous decision memorandum - CAG-00157N: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=39) and subgroup analyses of the MADIT II data. The main results of the COMPANION trial are consistent with the use of prolonged QRS since it was one of the inclusion criteria; SCD-HeFT did not base inclusion on QRS interval. In subgroup analyses, SCD-HeFT showed that patients with QRS ≥ 120 msec. had a significant reduction in mortality (hazard ratio=0.67; 97.5% CI=0.49-0.93). Based on the findings from these trials, QRS interval appears to be a predictor of benefit; that is, in general, patients with longer QRS intervals have a greater benefit. This is also consistent with Nudell's statement: "When one looks at the combined results seen in MADIT II and SCD-HeFT, we estimate that patients with abnormal QRS widths (>120 milliseconds) have about 4 times the absolute ICD mortality benefit of that seen amongst patients with normal complex widths (<120 milliseconds)."[40] However, with the additional data from SCD-HeFT, one can conclude that patients with narrow QRS intervals also obtain a small benefit from ICD therapy (hazard ratio for QRS duration < 120 ms.=0.84; 97.5% CI=0.62-1.14).[41] Thus, we believe that the evidence is now sufficient to remove the QRS coverage limitation.

In addition to QRS prolongation in our June 2003 decision, we limited coverage to patients with LVEF ≤ 30% based upon the MADIT II inclusion criterion. SCD-HeFT included patients with LVEF ≤ 35%. Data from SCD-HeFT are included in the following table:

SCD-HeFT	Sample siz	Hazard Ratio, 97.5% Confidence Intervals
LVEF ≤ 0.30	2098	0.73 (0.57, 0.92)
LVEF > 0.30	422	1.08 (0.57, 2.07)

The other trials reviewed had LVEF inclusion criteria from 30 - 35% but did not stratify their results by LVEF categories. Other previously reviewed trials had varying LVEF inclusion criteria from 30% to 40%. The vast majority of patients in all trials had actual LVEFs in the mid to low 20% range. In addition, we received a number of comments suggesting that the 30% threshold is an appropriate threshold.

Thus, based on these observations, comments and the lack of benefit in the 30-35% subgroup in SCD-HeFT, we will continue the current coverage criterion of LVEF ≤ 30%.

Question 2: Is there evidence to conclude that ICDs decrease mortality for patients with nonischemic dilated cardiomyopathy and reduced LVEF?

For patients with nonischemic dilated cardiomyopathy, the evidence is not as substantial as for patients with IDCM since few defibrillator trials have been conducted on patients with NIDCM. In addition, prior reports have indicated that patients with NIDCM have better overall survival and outcomes than patients with IDCM. For patients with NIDCM, evidence from AMIOVIRT, CAT, DEFINITE, SCD-HeFT and COMPANION is relevant.

AMIOVIRT was a randomized controlled trial involving 103 patients with nonischemic dilated cardiomyopathy, asymptomatic non-sustained ventricular tachycardia and LVEF ≤ 35%. There was no statistically significant difference in mortality. The investigators reported: "Furthermore, in asymptomatic patients with ischemic cardiomyopathy, prophylactic implantation of an ICD is superior to treatment with amiodarone. This is in contrast to the observation from AMIOVIRT, where patients with NIDCM, left ventricular dysfunction and asymptomatic NSVT, had comparable survival with an ICD or amiodarone. These findings suggest that patients with cardiomyopathy secondary to coronary artery disease may respond differently to treatment than patients with NIDCM, highlighting the notion that ischemic and non-ischemic myocardial arrhythmogenic substrates may be fundamentally different."[42]

CAT was a randomized controlled trial involving 104 patients with recent onset nonischemic dilated cardiomyopathy and LVEF ≤ 30%. The investigators concluded: "ICD therapy did not reveal any survival benefit in the setting of DCM of recent onset and impaired LV function (EF ≤ 30%). This was most likely due to the low overall mortality rate in the control group. However, even in patients with a significantly increased mortality rate caused by a lower EF and nonsustained VTs, ICD therapy did not reveal any survival benefit. Therefore, the results of CAT do not favor prophylactic ICD implantation in patients with DCM of recent onset and impaired LVEF without any further risk stratification."[43]

The DEFINITE trial was a randomized controlled trial involving 458 patients with nonischemic dilated cardiomyopathy, LVEF < 36%, and PVC/NSVT. The investigators reported that "fewer patients died in the ICD group than in the standard-therapy group (28 vs. 40), but the difference in survival was not significant (P=0.08 by the log-rank test)."[44] The investigators concluded: "On the basis of our results, the routine implantation of a cardioverter-defibrillator cannot be recommended for all patients with nonischemic cardiomyopathy and severe left ventricular dysfunction. However, our findings of a reduction in sudden death from arrhythmia and an apparent benefit of ICDs in subgroup analyses suggest that the use of these devices should be considered on a case-by case basis."[45]

AMIOVIRT, CAT and the DEFINITE trial did not demonstrate a clear role for the use of a defibrillator for patients with NIDCM. SCD-HeFT enrolled 792 patients with NIDCM, as one prespecified subgroup, and showed a reduction in the mortality hazard ratio for ICD therapy compared to control but it was not statistically significant (hazard ratio=0.73; 95% CI= 0.50-1.07).[46] In the COMPANION trial, which added prolonged PR and QRS interval as inclusion criteria, there were 678 patients with NIDCM and a significant reduction in mortality in the CRT-D group compared to the optimal pharmacologic therapy group (hazard ratio =0.50; 95% CI=0.29-0.88). [47]

Considered together, CAT, AMIOVIRT, DEFINITE, SCD-HeFT and COMPANION present somewhat conflicting evidence on the use of defibrillators for patients with NIDCM and reduced LVEF. CAT, AMIOVIRT, DEFINITE indicated the need for further risk stratification of this population. CAT studied patients with recent onset NIDCM (≤ 9 months duration) and did not provide evidence to support the use in these patients. DEFINITE, COMPANION and SCD-HeFT evaluated patients with chronic NIDCM (average duration = 2.8 years; 3.6 years; and 2 years, respectively). COMPANION supported the use of prolonged PR and QRS duration as risk stratifiers; and showed that the mortality risk reduction was the greatest in the patients with prolonged QRS interval and NIDCM.[48]

Of the 5 relevant studies, 2 (COMPANION, SCD-HeFT) showed a significant reduction in mortality overall but not specifically for patients with NIDCM. SCD-HeFT presented evidence for a broad approach yet this evidence is tempered by the negative findings of AMIOVIRT, CAT and DEFINITE and the restricted population of the COMPANION trial. Based on these results, a more thoughtful approach may be more appropriate for patients with NIDCM compared to patients with IDCM. The firing data from SCD-HeFT for patients with NIDCM is forthcoming and should provide some reassurance that the devices are firing as expected in these patients.

Trial	Sample size - Nonischemic	Mortality - ICD	Mortality - Control	p-value
AMIOVIRT	103	11.8%	13.5%	0.8
CAT	104	26%	32%	0.6
COMPANION	678	not reported	not reported	Significant
DEFINITE	147	7.9%	14.1%	0.08
SCD-HeFT	792	not reported	not reported	NS

Based on the overall results of SCD-HeFT with support from the COMPANION trial, there is evidence that ICDs decrease mortality for patient with nonischemic dilated cardiomyopathy and reduced LVEF. Therefore, coverage will be expanded to include this group of patients.

C. Patient and Device Selection

Although SCD-HeFT demonstrated a statistically significant reduction in mortality, the absolute reduction was modest. In addition, a relatively small proportion (21.4%) of the defibrillator group received an appropriate shock over the course of the trial. This firing rate was slightly higher than the overall firing rate (19%) seen in MADIT II, which had a shorter average follow-up time (average 20 months).

Since the large proportion of patients who receive an ICD never received any therapy from their device, consideration of additional risk stratification methods would be reasonable. During SCD-HeFT's lengthy follow-up period, cardiac disease probably progressed and other relevant characteristics likely changed in many patients. Pending data from the last follow -up or measurement may help to predict which patients will likely receive defibrillator therapy and when therapy will likely occur.

1. Risk Reduction

In SCD-HeFT, a conscious attempt was made to ensure that all patients received optimal medical therapy. Appropriate use of beta-blocker therapy, angiotensin converting enzyme therapy, aldosterone blocking diuretics, aspirin and statin therapy was encouraged. The optimal medical therapy likely had an important role in reducing overall mortality rates in all groups. The mortality rate in the placebo medical therapy group was lower than the rates in most prior trials. Thus, optimizing medications for all patients should be emphasized. In addition, reduction of other major risk factors for sudden cardiac death should also be emphasized.

2. Pooled Data Analysis

CMS strongly encourages the sponsors and principal investigators of ICD trials to engage an independent, reputable cardiology research center to pool the databases from their respective trials and conduct analyses to identify patient selection, device related issues and other research questions that need further study. This information would be important for improving decision-making about defibrillator implantation.

3. QRS Interval

QRS prolongation has been studied as a potential risk stratifier for patients with congestive heart failure. Zareba and Moss reported that "sudden cardiac death occurs as a result of a complex interplay of changes in myocardial substrate, imbalance of autonomic regulation of the heart, and myocardial vulnerability."[49] The authors further explained that "electrical manifestation of changes in myocardial substrate include QRS and QTc prolongation, presence of conduction disturbances, presence of late potentials, abnormalities of repolarization morphology, and presence on nonsinus rhythm, namely atrial fibrillation."[50]

Given the total body of evidence from ICD and CRT trials, prolonged QRS interval remains a potentially useful risk stratifier which could be considered for defining the level of baseline risk and likely benefit from an ICD. With further research on CRT and CRT-D devices, more information may be available.

4. LVEF

As previously noted, LVEF is often considered an important prognostic indicator. In 2000, Moss reported that "the findings from MADIT, AVID, MUSTT, and CIDS paint a very clear picture - it is the sickest patients who benefit the most from ICD therapy."[51] Based on survival analysis of MADIT I data, Moss also noted "the survival benefit of ICD therapy was significantly greater than conventional therapy only in the subgroup with an ejection fraction < 26%."[52] In 2002, Skenkman and colleagues also reported "a linear relationship between QRS duration and decrease ejection fraction"[53] based on a prospective observational study of 3,471 patients with congestive heart failure. The authors also noted "systolic dysfunction was associated with graded increases in mortality across ascending levels of QRS prolongation."[54]

5. NYHA Class

Most studies on defibrillator therapy have only enrolled patients with NYHA Class I-III. Although it is likely to be a fairly subjective measure, it has been routinely used as a patient inclusion criterion. Patients with NYHA Class IV have been excluded in the large primary prevention trials such as SCD-HeFT and MADIT II. In addition, SCD-HeFT reported a surprising result for patients with NYHA Class III: there was no significant difference in mortality between the ICD and placebo groups. This finding has been difficult to explain. Additional consideration of this finding may be forthcoming from the trial investigators.

The COMPANION trial, a resynchronization therapy trial, was the only one of the trials reviewed in this decision and the prior decision that included patients with NYHA Class IV. Separate subgroup analyses of COMPANION patients with NYHA Class IV have not been reported, but only 14% of patients (219 of the 1520) were classified in NYHA Class IV. Given the extremely small number of NYHA Class IV patients that have been studied in the defibrillator trials (219 patients compared to over 8000 patients in total for Class I-III) and the methodologic issues with the COMPANION trial, there is insufficient evidence on the implantation of defibrillators in patients with NYHA Class IV CHF.

6. Microvolt T-Wave Alternans (MTWA)

Microvolt T-wave alternans refers to microvolt variations in the morphology of the electrocardiographic T-wave on an alternate beat basis during exercise. MTWA testing involves measurements of these T-wave variations during exercise stress testing. The testing is non-invasive but requires specific equipment. Several studies and reports have been published on the use of MTWA as a risk stratifier for defibrillator therapy.[55] Most recently, Bloomfield and colleagues reported that "among MADIT II-like patients, a microvolt T wave alternans test is better than QRS duration at identifying a high-risk group and also better at identifying a low-risk group unlikely to benefit from ICD therapy."[56] Peer-reviewed journal publications are expected in the near future which may provide further information on the utility of this test as a screening tool.

7. Age

Although chronological age is generally not an appropriate criterion for coverage, the implantation of any device should not be routinely recommended for patients with limited life expectancy (an exclusion criterion in most trials). Very few patients over the age of 75 years old have been enrolled in defibrillator studies. Of the two largest trials (MADIT II and SCD-HeFT), only 375 (10%) of the combined patients were over the age of 75 years. The actual benefits and harms of defibrillators in patients aged 75 years and older have not been adequately demonstrated. Therefore, the implantation of a defibrillator in the most elderly patients should be carefully considered and not routinely recommended. However, we will not restrict coverage by age in this decision.

Trial	total # patients	patients ≤ 75 years	patients > 75 years
MADIT II 2002	1232	1054 (86%)	178 (14%)
SCD-HeFT 2004	2521	2324 (92%)	197 (8%)
total	3753	3378 (90%)	375 (10%)

Trial	total # patients	patients ≤ 75 years	patients > 75 years

8. Gender

Like age, gender is usually not an appropriate criterion for coverage; however, female patients have been embarrassingly under-represented in all ICD trials. There may be different considerations for implantation of devices, type of device, size of device, longevity, shock energy and adverse events for women compared to men. In fact, no study has shown a significant improvement in mortality for women from ICD therapy compared to control therapy. A thorough assessment of whether the benefits and harms of ICDs differ by gender has not been published but is urgently needed.

Trial	total # patients	# men (percent)	# women (percent)	Significant ICD benefit in women
AMIOVIRT 2003	103	72 (70%)	31 (30%)	No
CAT 2002	104	83 (80%)	21 (20%)	No
COMPANION 2004	1520	1025 (67%)	495 (33%)	No
DEFINITE 2004	458	326 (71%)	132 (29%)	No
DINAMIT 2004	674	514 (76%)	160 (24%)	No
MADIT II 2002	1232	1040 (84%)	192 (16%)	No
SCD-HeFT 2004	2521	1933 (77%)	588 (23%)	No

Trial	total # patients	# men (percent)	# women (percent)	Significant ICD benefit in women
Total	6612	4993 (76%)	1619 (24%)	

9. Type of Defibrillator and Functions

In SCD-HeFT, single lead, single chamber defibrillators programmed for shock therapy only were used. These devices were not programmed for antitachycardia pacing. The evidence on the benefits of ATP is sparse and inconclusive. ATP has been found to be harmful in several clinical scenarios where pacing was initiated for a benign arrhythmia and resulted in ventricular fibrillation. In addition, the number of adverse events, including lead fractures, increases with the number of leads implanted. Since SCD-HeFT demonstrated a significant reduction in mortality from a single lead, shock only device and it enrolled by far the most patients of any trial, a single lead, shock only device is clinically appropriate and sufficient for primary prevention of sudden cardiac death. As mentioned in the prior decision, indiscriminate pacing may increase the risk of adverse events such as hospitalization for heart failure. This is consistent with the SCD-HeFT results, which had a lower adverse event rate compared to prior trials such as the DAVID trial and MADIT II.

CMS requested public comments on appropriate device selection (as noted in the public comments section). Few favored any device restrictions. At this time, CMS will not limit coverage based on type of defibrillator. However, the implantation of a device other than a single lead, shock only ICD requires medical justification of the necessity for a more advanced ICD that potentially has more adverse events. This justification must be based on patient characteristics and evidence from clinical studies and must be documented in writing in the medical records.

10. Cardiac resynchronization plus defibrillator therapy (biventricular pacing plus defibrillator)

Several prior trials on cardiac resynchronization therapy for advanced heart failure have been published.[57] The primary outcomes have focused predominantly on quality of life and functional status. The COMPANION trial studied the addition of a defibrillator to CRT on the outcomes of all-cause mortality and all-cause hospitalizations. As noted above, there were various issues with the COMPANION trial. The change in the definition of hospitalization during the trial is a potentially critical flaw influencing the primary outcome. The all-cause mortality outcome may have been influenced by the considerable withdrawal rate in the optimal pharmacological therapy group. Since there are no other published or reported trials powered to corroborate the findings of the COMPANION trial on the outcome of mortality, the evidence on the benefit of adding CRT to defibrillator therapy is insufficient. In addition, since CRT alone did not significantly reduce mortality, the observed benefit in the COMPANION trial from CRT-D was probably due to the defibrillator. Further research on CRT and CRT-D is needed. Thus, CMS will not propose any change in policy concerning CRT in this memorandum.

11. National ICD Registry

Finally, we desire to ensure that defibrillator implantation only occurs in those patients who are most likely to benefit and that the procedures are done only by competent providers in facilities with a history of good outcomes and a quality assessment/improvement program to identify providers with poor outcomes and other areas for improvement. As mentioned above, we are concerned that the available evidence does not allow providers to target these devices to patients who will clearly derive benefit. In order to provide maximum protection to our beneficiaries, CMS will require that reimbursement for ICDs for primary prevention of sudden cardiac death occur only if the beneficiary receiving the defibrillator implantation is enrolled in either a FDA approved category B IDE clinical trial or a qualifying national database (registry).

The submission of surveillance data on patients receiving an ICD for primary prevention to a national registry is reasonable and necessary to assure patient safety and protection. Data from the registry will help identify the appropriate ICD functions and settings and help reduce the incidence of inappropriate shocks. These patient protections and safeguards would only be available to the extent that registry data can be made available in some form to providers and practitioners to inform their decisions, monitor performance quality, benchmark and identify best practices. We do not set forth precise standards for data sharing practices. But we do require that the collection and distribution of health information be consistent with the *Standards for Privacy of Individually Identifiable Health Information*.[58]

The national registry for defibrillator implantation must meet several operational criteria for facility certification, assessment and data completeness. The national registry must include criteria to ensure that hospitals and providers are certified as competent in the implantation defibrillators. Participating hospitals and providers must be required to report data on all patients undergoing defibrillator implantation for primary prevention. Also, hospitals or providers who do not comply with the data collection requirements must be removed from the system. Complete prospective systematic data collection will ensure the registry's ability to achieve the objectives. Data elements in the national registry should address baseline patient characteristics, device type and characteristics, facility and provider characteristics, extent of disease, periodic device interrogation for firing data and long-term patient outcomes. After the appropriate objectives and hypotheses are developed, the minimum data necessary to answer the hypotheses can be identified, and simple processes for data collection and submission developed.

The registry must be designed to address specific hypotheses, some of which may come from the pooled data analysis outlined above. Examples of potential hypotheses for the data collection include the potential benefit of ICDs in the early (< 60 days) or late (> 10 years) post-MI period. Of particular interest would be hypotheses that identify appropriate risk factors, such as age, NYHA Class, QRS (or other ECG) interval and LVEF and screening tests, such as T-wave alternans, that predict which patients will receive defibrillator therapy. Finally, appropriate questions might identify those provider and facility attributes that predict good patient outcomes.

IX. Conclusions

ICD therapy has been shown in several trials to improve survival but there still is a considerable mortality rate for patients who have received defibrillators. Patients treated with an ICD in SCD-HeFT had a 22% mortality rate overall. Patients treated with a CRT-defibrillator in COMPANION had a 17.6% mortality rate at 1 year. Since ICDs only treat ventricular tachyarrhythmias, do not prevent death from other cardiac or noncardiac diseases, and cause adverse events, such as inappropriate shocks and lead fractures, they should not be perceived as or projected to be an ideal technology. Responsible use of ICDs should be encouraged. Risk factor reduction and optimal medical therapy, as encouraged in SCD-HeFT, remain crucial in reducing overall mortality from sudden cardiac death.

The Centers for Medicare and Medicaid Services has made the following determination regarding the use of ICDs:

CMS has determined that the evidence is adequate to conclude that an implantable cardioverter-defibrillator (ICD) is reasonable and necessary for the following:

1. Patients with ischemic dilated cardiomyopathy (IDCM), documented prior myocardial infarction (MI) and measured left ventricular ejection fraction (LVEF) $\leq$ 30%.
2. Patients with nonischemic dilated cardiomyopathy (NIDCM) > 9 months and measured LVEF $\leq$ 30%.

The following criteria must be also met:

1. Patients must be able to give informed consent.
2. Patients must not have:
    - New York Heart Association classification IV;
    - Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
    - Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 3 months;
    - Had an acute MI within the past month;
    - Clinical symptoms or findings that would make them a candidate for coronary revascularization;
    - Irreversible brain damage from preexisting cerebral disease;
    - Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than one year.
3. Ejection fractions must be measured by angiography, radionuclide scanning or echocardiography.
4. Myocardial infarctions must be documented and defined according to the consensus document of the *Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction*.[59]

In addition, CMS has determined that the use of ICDs for primary prevention of sudden cardiac death (SCD) is reasonable and necessary only if the beneficiary receiving the ICD implantation is enrolled in either an FDA-approved category B IDE clinical trial or a qualifying national database (registry). A registry must include criteria that ensure:

1. Hospitals and providers are certified as competent in the ICD implantation.

2. Participating hospitals and providers report data on all patients undergoing ICD implantation for primary prevention.
3. Hospitals and providers who do not comply with the data collection requirements are removed from the system.
4. The data set includes elements with the following characteristics:
    - Baseline patient characteristics,
    - Device type and characteristics,
    - Facility and provider characteristics,
    - Extent of disease progression,
    - Periodic device interrogation for firing data,
    - Long-term patient outcomes.
5. Specific hypotheses are addressed.

Data elements will be refined in the process of developing the national database. Specific hypotheses should be predefined and based upon analyses of combined data from all previous ICD trials. CMS strongly recommends that the sponsors and principal investigators of ICD trials[60] engage an independent, reputable cardiology research center to pool the entire databases from their respective trials and conduct analyses to identify patient selection, device related issues and other research questions to more clearly define the data elements for the registry.

A provider implanting any ICD other than a single lead, shock only device for primary prevention must maintain and furnish upon request to CMS, its agents or other authorized personnel the documentation to verify the medical necessity for a more advanced ICD. This justification must be based on patient characteristics and supported by evidence from clinical studies.

Finally, all other indications for ICDs not currently covered in accordance with this decision will continue to be covered under Category B IDE trials and the CMS routine clinical trials policy (CIM 30-1).

Appendix I

Table 1 - Inclusion and Exclusion Criteria for Defibrillator Trials

Study Sample Size	Inclusion Criteria	Exclusion Criteria	Baseline	Outcome
CAT 2002 ICD tx n=50; control n=54.	Age 18 to 70years; NIDCM ≤ 9 months; LVEF ≤ 30%; NYHA II -III.	CAD, prior MI, myocarditis, symptomatic bradycardia, VT, VF, sign. valvular disease, etc.	Mean f/u 23 mos, mean age 52 yrs, LVEF 24%, 65% NYHA II.	13 deaths in ICD group compared to 17 in the control group (p-value=0.554).
AMIOVIRT 2003. ICD tx n=51; Amio n=52.	NIDCM; LVEF ≤ 35%, NSVT, NYHA I-III.	Syncope, pregnancy, contraindications, NIDCM < 6 mos, etc.	Mean f/u 24 mos, mean age 59 yrs, LVEF 23%, 83% NYHA II-III.	No significant difference in survival between groups.
DEFINITE 2004. ICD tx n=229;	Age 21-80 yrs; NIDCM; LVEF < 36%; NSVT/PVCs, VT, VF.			

Study Sample Size	Inclusion Criteria	Exclusion Criteria	Baseline	Outcome
control n=229.		CAD, prior MI, symptomatic VT/VF, syncopy, arrest, NYHA IV, etc.	Mean f/u 29 mos, mean age 58 yrs, LVEF 21%, 57% NYHA II.	28 deaths in ICD group compared to 40 in control (hazard ratio= 0.65; 95% CI =0.40-1.06; p=0.08).
DINAMIT 2004. ICD tx n=332; control n=342.	Age 18-80 years, MI 6-40 days, LVEF ≤ 35%, depressed HRV.	NYHA IV, CABG w/I 4 wks, 3v PTCA, sustained VT/VCF, etc.	Mean f/u 30 mos, mean age 62 yrs, LVEF 28%.	62 deaths in ICD group compared to 58 in control (hazard ratio=1.08; 95% CI, 0.76-1.55; p=.0.66).
COMPANION 2004. CRT n=617; CRT-D n=595; control n=308.	Age ≥ 18 yrs., LVEF ≤ 35%, QRS ≥ 120 ms., PR > 150ms, NYHA III-IV.	MI within 60 days, syncope, unstable angina, indications for pace/ICD, etc.	Mean f/u variable, mean age 67 yrs, LVEF 21%, 86% NYHA III	77 death (25%) in the pharmacologic therapy group; 131 deaths (21%) in the CRT group; and 105 deaths (18%) in the CRT-D group (p=0.003 compared to control).
SCD-HeFT 2004. Amio n=845; ICD n=829; control n=847.	Age ≥ 18 yrs., LVEF ≤ 35%, NYHA II-III, CHF ≥ 3 mos.	LVEF > 35%, unable to conduct activities of daily living such as patients with NYHA Class IV CHF, cardiac arrest, pregnancy, patients likely to die from any non -cardiac cause within 12 months, etc.	Mean f/u 40.2 mos, mean age 59.5 yrs. Men comprised 77%, mean LVEF 24%. Approximately 52% ICM, NYHA.	244 deaths in placebo; 240 amiodarone (hazard ratio compared to control=1.06; 97.5% CI=0.86-1.30; p-value=0.529); 182 deaths in ICD (hazard ratio compared to control=0.77; 97.5% CI=0.62-0.96; p-value=0.007).

Appendix II

Table 1 - Inclusion and Exclusion Criteria for Defibrillator Trials (from June 2003 decision)

Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
MADIT I, 1996. Tx n=95; Conventional n=101.	age 25 to 80 years; myocardial infarction 3 wks or more; episode of asymptomatic unsustained VT unrelated to MI; LVEF ≤ 0.35; NYHA I-III; inducible, nonsuppressible VT on EPS; no indications for CABG or angioplasty.	prior cardiac arrest or VT causing syncope not associated with AMI; symptomatic hypotension; MI within past 3 wks; CABG within 2 months; angioplasty within 3 months; women of childbearing age not on med. contraceptives, adv cerebrovascular; noncardiac condition with reduced likelihood of survival.	all patients.	60% of defibrillator patients had shock discharge within 2 years. 15.8% (15 deaths) mortality rate in defibrillator group; 38.6% (39 deaths) in conventional therapy. hazard ratio=0.46; 95%CI=0.26-0.82.
CABG-Patch, 1997. Tx n=446; Control n=454.	scheduled for CABG; age < 80 years; LVEF < 0.36; Abn. signal averaged electrocardiogram.	h/o sustained VT or VF; diabetes m with poor control or infections; prior valve surgery; concomitant cerebrovascular surgery; serum creatinine >3mg/dl, emergency CABG; noncardiac condition with ex survival < 2 years; inability to attend f/u visits.	not required.	57% of defibrillator patients had shock discharge within 2 years. 22.6% (101 deaths) mortality rate in defibrillator group; 20.9% (95 deaths) in control group. hazard ratio=1.07; 95% CI=0.81-1.42.

Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
MUSTT, 1999. EP tx n=351; No tx n=353.	had coronary artery disease; LVEF&glt; 40%; asymptomatic unsustained ventricular tachycardia; EP induced sustained VT, VF.	H/o syncope or sustained ventricular tachycardia or fibrillation more than 48 hours after myocardial infarction; unsustained ventricular tachycardia only in acute ischemia, metabolic disorders, or drug toxicity.	all patients.	42% (132 deaths) overall mortality in antiarrhythmic therapy; 48% (158 deaths) in no antiarrhythmic therapy. Relative risk=0.80; 95%CI=0.64-1.01. Relative risk=0.45; 95%CI=0.32-0.63 for patients with defibrillators.
MADIT II, 2002. Tx n=742; Conventional n=490.	age >21 years, MI ≥ 1 month, LVEF ≤ 0.30.	had FDA approved indication for ICD; NYHA Class IV; coronary revascularization within 3 months; MI within past month; advanced cerebrovascular disease; were of childbearing age not using med contraceptives; condition other than cardiac disease with high likelihood of death; unwilling to consent.	not required.	19% of defibrillator patients had shock discharge within 2 years. 14.2% (105 deaths) mortality rate in defibrillator group; 19.8% (97 deaths) in conventional therapy. hazard ratio=0.69; 95% CI=0.51-0.93.

Appendix III General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. The goal of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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