DECISION MEMORANDUM

[This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction, program memorandum, CMS ruling or Federal Register Notice, giving specific directions to our claims processing contractors. That issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.]

TO: Administrative File CAG: # 00157N
Implantable Cardioverter Defibrillators

FROM: Steve Phurrough, MD, MPA
Acting Director, Coverage and Analysis Group

JoAnna Farrell
Health Insurance Specialist, Division of Medical and Surgical Services

Joseph Chin, MD, MS
Medical Officer, Division of Medical and Surgical Services

SUBJECT: National Coverage Determination (NCD) on Implantable Defibrillators

DATE: June 6, 2003

I. Decision

CMS determines that the evidence is adequate to conclude that an implantable defibrillator is reasonable and necessary for patients with

1) A documented episode of cardiac arrest due to ventricular fibrillation (VF), not due to a transient or reversible cause;
2) Documented sustained ventricular tachyarrhythmia, either spontaneous or induced by an electrophysiology (EP) study, not associated with myocardial infarction (MI) and not due to a transient or reversible cause;
3) Documented familial or inherited conditions with a high risk of life-threatening ventricular tachyarrhythmias, such as long QT syndrome or hypertrophic cardiomyopathy;
4) Coronary artery disease with a documented prior myocardial infarction, a measured left ventricular ejection fraction ≤ 0.35, and inducible, sustained ventricular tachycardia (VT) or VF at EP study. (The myocardial infarction must have occurred more than 4 weeks prior to implantable defibrillator insertion. The EP test must be performed more than 4 weeks after the qualifying myocardial infarction.)
5) CMS determines that the evidence is adequate to conclude that an implantable defibrillator is reasonable and necessary for patients with a documented prior

Appendix A

Table 1 – Patient Inclusion and Exclusion Criteria for Primary Prevention Trials

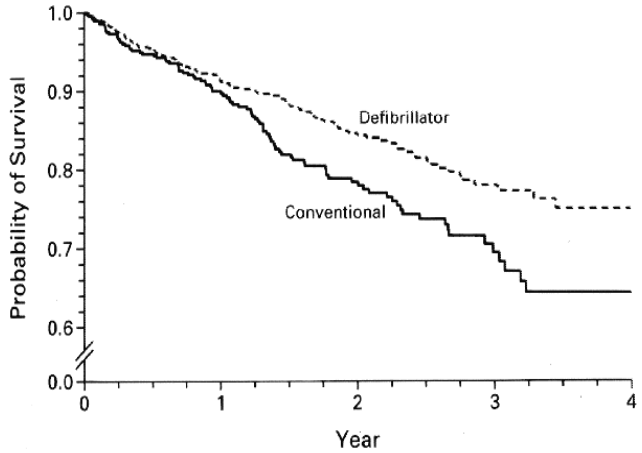
Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
MADIT I, 1996. Tx n=95; Conventional n=101.	age 25 to 80 years; myocardial infarction 3 wks or more; episode of asymptomatic unsustained VT unrelated to MI; LVEF ≤ 0.35; NYHA I-III; inducible, nonsuppressible VT on EPS; no indications 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.
MUSTT, 1999. EP tx n=351; No tx n=353.	had coronary artery disease; LVEF≤ 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.

Table 2 – Patient Inclusion and Exclusion Criteria for Secondary Prevention Trials

Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
AVID, 1997. Defib n=507; Drug tx n=509.	Resuscitated from near-fatal ventricular fibrillation; sustained ventricular tachycardia with syncope; sustained ventricular tachycardia with LVEF ≤ 0.40 and symptoms severe hemodynamic compromise.	not eligible for treatment with amiodarone.	not specified.	Overall survival = 89.3%, 81.6%, 75.4% at 1,2,3 years in defibrillator group; 82.3%, 74.7%, 64.1% at 1,2,3 years in antiarrhythmic drug group. P-value < 0/02.
CIDS, 2000. Defib n=328; Amio n=331.	In absence of AMI and electrolyte imbalance: documented VF; out of hosp cardiac arrest requiring defib or cardioversion; documented sustained VT causing syncope; other documented, sustained VT rate ≥ 150 causing presyncope or angina with LVDF ≤ 0.35; unmonitored syncope with documented spontaneous VT or sustained VT induced.	Defibrillator or amiodarone not appropriate tx; excessive perioperative risk for device implantation; previous amiodarone therapy for ≥ 6 weeks; nonarrhythmic medical condition with unlikely 1 year survival; long QT syndrome.	variable	25% (83 deaths) all cause mortality rate in defibrillator group; 29.6% (98 deaths) in amiodarone group; p-value=0.142.
CASH, 2000. Defib n=99; Drug n=189.	Resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias.	cardiac arrest within 72 hours of AMI, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect.	programmed electrical stimulation (PES).	36.4% death rate (95%CI=26.9%-46.6%) in defibrillator group; 44.4% (95%CI=37.2%-51.8%) in amiodarone/ metoprolol group.

Appendix B

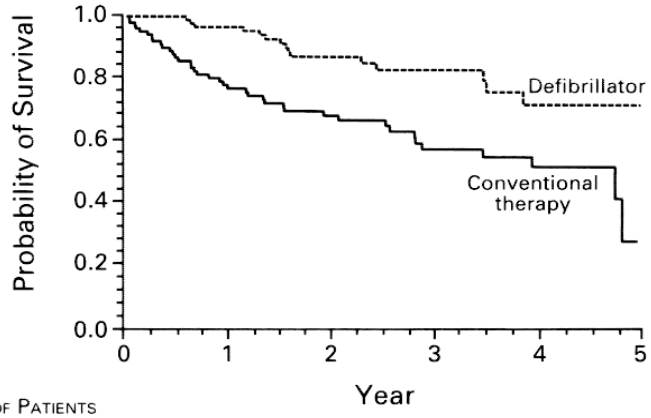
Figure 1 – Kaplan-Meier Survival Curve from MADIT II



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Kaplan-Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy.
From: Moss: N Engl J Med, Volume 346(12).March 21, 2002.877-883.

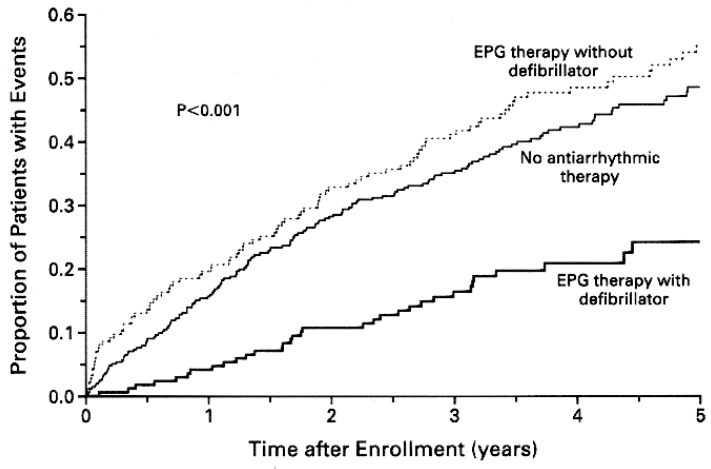
Figure 2 – Kaplan-Meier Survival Curve from MADIT I



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

Kaplan-Meier Analysis of the Probability of Survival, According to Assigned Treatment. The difference in survival between the two treatment groups was significant (P = 0.009) .
From: Moss: N Engl J Med, Volume 335(26).December 26, 1996.1933-1940

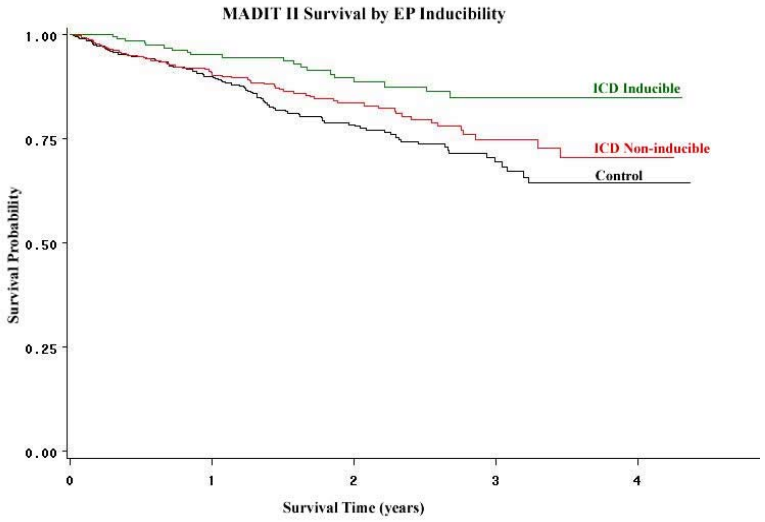
Figure 3 – Kaplan-Meier Mortality Curves from MUSTT



Kaplan-Meier Estimates of the Rates of Overall Mortality According to Whether the Patients Received Treatment with a Defibrillator.
From*:* Buxton: N Engl J Med, Volume 341(25).December 16, 1999.1882-1890

Appendix C

Figure 1 – Kaplan-Meier Survival Curves by EP Inducibility
(CMS analysis of the MADIT II dataset supplied by Guidant)



Appendix D

Table 1 - Deaths by LVEF and Group in MADIT II

	Treatment group			Control group			Total			p-value
	Deaths	N	%	Deaths	N	%	Deaths	N	%	
25%≤EF≤30%	43	385	11%	40	262	15%	83	647	13%	0.13
LVEF < 25%	62	357	17%	57	228	25%	119	585	20%	0.03

CMS analysis from MADIT II dataset supplied by Guidant.

Figure 1 - KM Survival Curves for Patients with LVEF>=25% by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)

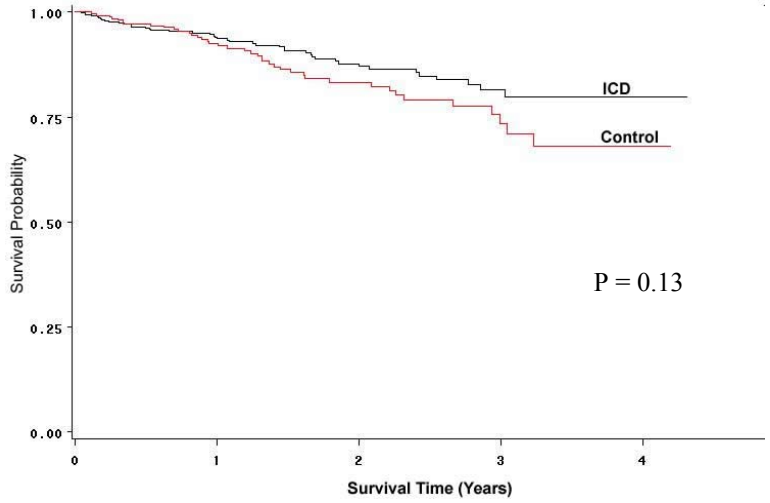
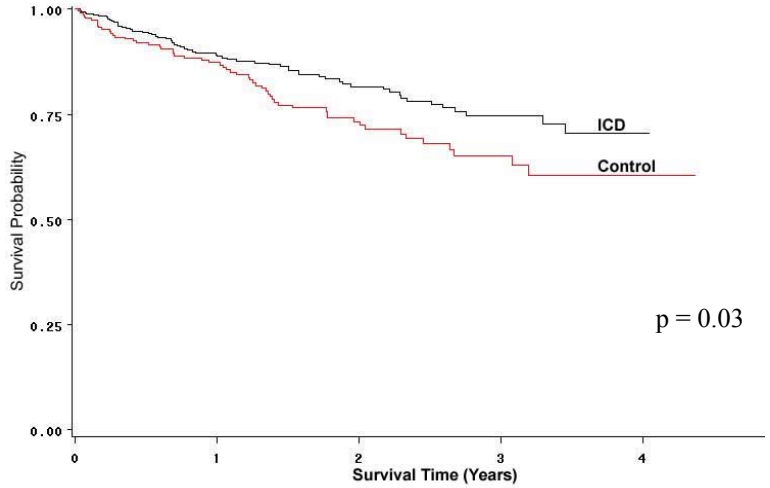


Figure 2 - KM Survival Curves for Patients with LVEF<25% by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)



Appendix E

Table 1 - Noninvasive Electrocardiology and Outcomes in MADIT II Patients
Presented by Wojciech Zareba MD, PhD

Noninvasive ECG Parameters in Multivariate Cox Model for Predicting Total Mortality in MADIT II Patients Randomized to Conventional Therapy

Variable	HR	(95% CI)	P value
Age≥65 years	1.47	(0.86-2.52)	0.164
NYHA ≥II	2.00	(1.20-3.34)	0.008
BUN>25	1.94	(1.17-3.21)	0.010
No BB use	1.57	(0.94-2.66)	0.089
A. Fib.	2.36	(1.14-4.89)	0.021
QRS>0.12 sec	1.90	(1.14-3.14)	0.013

From: NASPE 2002 Meeting - May 11, 2002.
http://naspehighlights.org/summary/summary.asp?sid=1&stid=19&ld=2002-05-11

Table 2 - Deaths by QRS Interval and Group in MADIT II

	Treatment group			Control group			Total			Hazard ratio
	Deaths	N	%	Deaths	n	%	Deaths	N	%	
QRS < 120 ms	43	357	12%	37	230	16%	80	587	14%	0.76
QRS = 120 ms	14	83	17%	13	84	16%	27	167	16%	1.03
QRS > 120 ms	35	225	16%	41	136	30%	76	361	21%	0.39

Results provided by Guidant.
98 pacemaker patients excluded; 19 missing QRS values.
Interaction p value = 0.052.

Table 3 - Deaths by QRS Interval and Group in MADIT II

	Treatment group			Control group			Total			p-value
	Deaths	N	%	Deaths	N	%	Deaths	N	%	
QRS ≤ 120 ms	57	451	13%	50	322	16%	107	773	14%	0.25
QRS > 120 ms	36	229	16%	41	138	30%	77	367	23%	0.001

CMS analysis of MADIT II dataset supplied by Guidant.
92 patients with pacemakers were excluded. 4 patients with unknown pacemaker status were included.
Interaction p value = 0.015

Figure 1 - KM Survival Curves for Patients with QRS ≤ 120 ms by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)

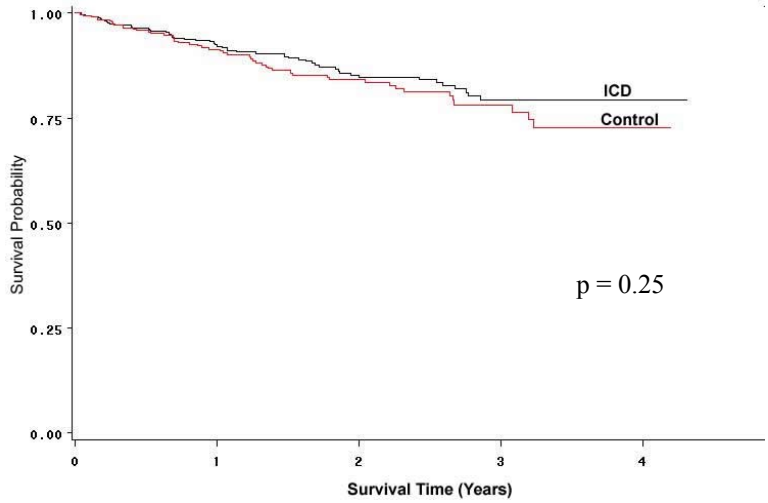


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Figure 2 - KM Survival Curves for Patients with QRS > 120 ms by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)

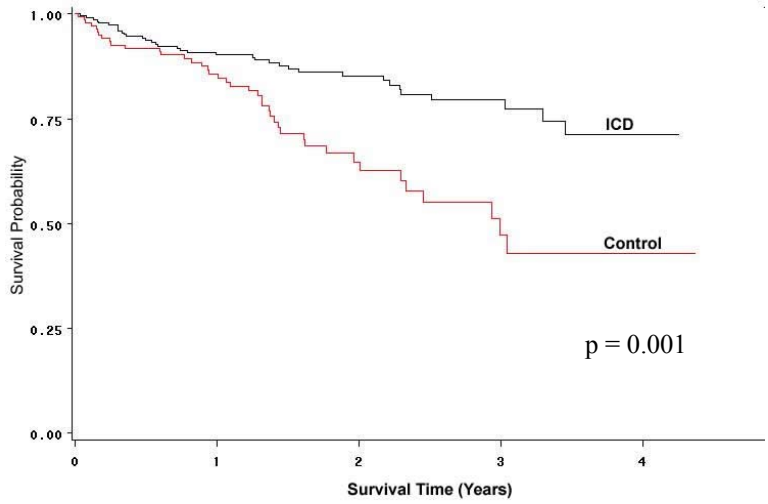

Table 4 - Cox Regression Model
(CMS analysis of the MADIT II dataset supplied by Guidant)

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Treatment	1	0.56531	0.45510	1.5430	0.2142	1.760
AGE	1	0.03462	0.00846	16.7428	<.0001	1.035
EF	1	-0.03811	0.01358	7.8739	0.0050	0.963
BUN	1	0.02896	0.00433	44.7956	<.0001	1.029
QRS>120ms	1	1.24498	0.48103	6.6985	0.0096	3.473
QRS interaction	1	-0.74071	0.30554	5.8771	0.0153	0.477

myocardial infarction and a measured left ventricular ejection fraction ≤ 0.30 and a QRS duration of > 120 milliseconds. Patients must not have:

- New York Heart Association classification IV;
- Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm; have
- Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within past 3 months;
- Had an enzyme-positive MI within past month;
- Clinical symptoms or findings that would make them a candidate for coronary revascularization; or
- 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;

and patients must be able to give informed consent.

Myocardial infarctions must be documented by elevated cardiac enzymes or Q-waves on an electrocardiogram. Ejection fractions must be measured by angiography, radionuclide scanning or echocardiography.

CMS determines that the evidence is not adequate to conclude that an implantable defibrillator is reasonable and necessary for all patients with a prior myocardial infarction, a left ventricular ejection fraction ≤ 0.30, and a QRS ≤ 120 ms.

All other indications are also noncovered.

II. Background

Cardiovascular disease is the single most common cause of death in the United States. Sudden cardiac death (SCD) is estimated to account for approximately 50% of all cardiovascular deaths. This represents an estimated 350,000 cases per year and only about 20% survive to hospital discharge. Ventricular tachyarrhythmias are the mechanism responsible for 75-80% of cases. The other events are precipitated by bradycardia, asystole, or electromechanical dissociation. Only 20% present with an acute MI though 75% have had a prior MI. Of the 1,100,000 MI's that occur each year in the US, 5-6% have heart failure with an ejection fraction < 30%. .[1][2]

Ventricular tachyarrhythmias include VT and VF`.[3] Ventricular tachycardia may be defined as three or more consecutive, ventricular ectopic beats at a rate of more than 120 beats per minute. The VT is considered "sustained" if it lasts longer than 30 seconds. VF may be defined as a fibrillatory state of the heart without coordinated contraction of the ventricle. There are a number of potential causes of ventricular tachyarrhythmias, including acute myocardial infarction and transient or reversible causes such as drug toxicity, severe hypoxia, acidosis, hypokalemia, hypercalcemia, hyperkalemia, systemic infections and myocarditis.[4]

The relative risk of experiencing SCD is highest for survivors of SCD, followed by patients with dilated congestive heart failure (CHF). In one series of SCD survivors, CHF was the primary diagnosis in 7 to 23 percent.[5] CHF can be evaluated clinically or evaluated by measuring the left

[1] Huikuri, et al., 2001.
[2] Willerson and Cohn, 1995
[3] Ibid.
[4] Ibid.
[5] Ibid

ventricular ejection fraction (LVEF). LVEF can be measured by angiography, radionuclide scanning or echocardiography.

Therapeutic strategies for the prevention of sudden cardiac death (SCD) may be divided into two general categories-- primary prevention and secondary prevention. "Primary prevention refers to the prevention of the first life-threatening arrhythmic event such as sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest. Secondary prevention refers to the prevention of a recurrence of a potentially fatal arrhythmia or cardiac arrest among patients who have had clinical events of that type."[6]

Typical diagnostic tests for the evaluation of individuals at risk of or survivors of SCD include routine electrocardiography and EP studies. Electrophysiologists attempt during testing to induce life-threatening arrhythmias and determining their suppressibility with drug therapy. As mentioned above, angiography, radionuclide scanning or echocardiography are also used to assess left ventricular function.

Therapeutic options for ventricular arrhythmias include medications and defibrillator devices (internal and external devices). This memorandum will focus exclusively on the implantable defibrillator, an electronic device that "continuously monitors the heart, identifies malignant ventricular tachyarrhythmias and then delivers electrical countershock to restore normal rhythm."[7] However, an implantable defibrillator will not detect or treat asystole or electromechanical dissociation, which account for a large proportion of sudden deaths.

Mirowski and colleagues reported the first use of this type of device in humans in 1980.[8] The first generation defibrillators had only one cardiac lead. Current implantable defibrillators typically have two leads and may be programmed to provide anti-tachycardia pacing and electrical defibrillation for the treatment and prevention of SCD. In May 2003, the FDA approved a new defibrillator that has fewer features than currently marketed defibrillators. It provides countershock for life-threatening arrhythmias; however, it does not offer lower energy pacing therapies. It is intended to provide ventricular defibrillation, for automated treatment of life-threatening ventricular arrhythmias in individuals not expected to have greater than 3 episodes of ventricular arrhythmia requiring ICD therapy during the anticipated lifetime of the device. .[9]

In May 2002, Guidant requested a national coverage decision to expand indications for implantable defibrillators to match the results from MADIT II. In accepting this request, CMS decided to reassess all indications for implantable defibrillators.

III. History of Medicare Coverage

The Centers for Medicare & Medicaid Services (CMS), issued a Medicare National Coverage Determination in 1986 providing limited coverage of implantable defibrillators. The policy has

[6] Huikuri, et al., 2001; Myerburg, et al., 1998.
[7] Mirowski, 1985.
[8] Mirowski, et al. 1980.
[9] Bardy, 2002.

expanded over the years with revisions in 1991 and 1999. The current Medicare Coverage Policy (as it appears in the Coverage Issues Manual) is:

> 35-85 IMPLANTATION OF AUTOMATIC DEFIBRILLATORS
>
> The implantable automatic defibrillator is an electronic device designed to detect and treat life-threatening tachyarrhythmias. The device consists of a pulse generator and electrodes for sensing and defibrillating. Effective for services performed on or after January 24, 1986 through July 1, 1991, the implantation of an automatic defibrillator (ICD-9 -CM codes 37.94-37.96 or CPT code 33246) is a covered service only when used as a treatment of last resort for patients who have had a documented episode of life-threatening ventricular tachyarrhythmia or cardiac arrest not associated with myocardial infarction. Patients must also be found, by electrophysiologic study, to have an inducible tachyarrhythmia that proves unresponsive to medication or surgical therapy (or be considered unsuitable candidates for surgical therapy). It must be emphasized that unless all of the above described conditions and stipulations are met in a particular case, including the inducibility of tachyarrhythmia, etc., implantation of an automatic defibrillator may not be covered.
>
> Effective for services performed on or after July 1, 1991, the implantation of an automatic defibrillator is a covered service for patients who have had a documented episode of life-threatening ventricular tachyarrhythmia or cardiac arrest not associated with myocardial infarction.
>
> Effective for services performed on or after July 1, 1999, the implantation of an automatic defibrillator is also a covered service for patients with the following conditions:
>
> 1. A documented episode of cardiac arrest due to ventricular fibrillation not due to a transient or reversible cause;
>
> 2. Ventricular tachyarrhythmia, either spontaneous or induced, not due to a transient or reversible cause; or,
>
> 3. Familial or inherited conditions with a high risk of life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy.[10]

IV. Timeline of Recent Activities

May 30, 2002	CMS accepts a request from Guidant Corporation (Guidant) to expand indications for implantable defibrillators.
July 18, 2002	The Food and Drug Administration (FDA) approved new indication for Guidant implantable defibrillators.
September 27, 2002	CMS meets with requestor and American College of Cardiology (ACC).
November 14, 2002	Referred to Medicare Coverage Advisory Committee (MCAC).
February 12, 2003	MCAC panel meeting convened.

[10] Centers for Medicare and Medicaid Services. Medicare Coverage Issues Manual § 35-85.

V. FDA Approval

The FDA approved the first implantable defibrillator in 1985 while the first implantable cardioverter defibrillators were approved in 1988 and 1989.[11] The FDA approves each device individually and has granted premarket approvals (PMA)[12] for implantable defibrillators for the indications of providing antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias.

On July 18, 2002 the FDA issued a specific indication for Guidant implantable defibrillators to include the "prophylactic treatment of patients with a prior myocardial infarction and an ejection fraction of ≤30%."[13] Labeled indications for other manufacturers' devices were not reviewed to determine if they may have language that includes a similar patient population.

VI. General Methodological Principles

When making national coverage determinations, we at CMS evaluate 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 extent to which we are confident that the intervention will improve net health outcomes for patients.

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 presented here 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.

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[11] Farley, Dixie. Implanted Defibrillators and Pacemakers: A Gentler Jolt and Tickle for Trembling Hearts. 29 Jul. 2002 <http://www.fda.gov/bbs/topics/CONSUMER/CON0279b.html>

[12] Medical Device Approvals. 29 Jul 2002 <http://www.fda.gov/cdrh/mda/index.html>

[13] Letter from Daniel G. Schultz, FDA, to Guidant Corporation. July 18, 2002. This letter is available on the FDA web site through a link at http://www.fda.gov/cder/approval/index.htm.

- 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.

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

CMS determines whether an intervention is reasonable and necessary by evaluating its risks and benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.

VII. Evidence

A. Introduction:

Implantable defibrillators have been used to treat life-threatening ventricular tachyarrhythmias and subsequently to prevent sudden cardiac death in certain high risk patients. Numerous randomized controlled trials have been conducted and reported in the peer reviewed journals. Since implantable defibrillators treat life-threatening ventricular tachyarrhythmias, the trials have predominately specified mortality as the primary outcome. Quality of life is also an important outcome since these devices are usually permanently implanted, may provide shocks erroneously and may have other potential adverse effect. However, quality of life as an outcome has not been adequately studied and was not evaluated in this NCD.

B. Discussion of evidence

1. Questions:

To assess both Guidant's request and the current coverage indications, CMS posed the following questions:

Is there adequate evidence to conclude that an implantable defibrillator is reasonable and necessary for patients with prior MI and LVEF ≤ 30%, but who have not had prior cardiac arrest or life-threatening ventricular tachyarrhythmias (primary prevention of sudden cardiac death)?

Is there adequate evidence to conclude that an implantable defibrillator is reasonable and necessary for patients with prior cardiac arrest or life-threatening ventricular tachyarrhythmias (secondary prevention of sudden cardiac death)?

2. **External Technology Assessment:**

CMS asked Steve Goodman, MD, PhD thru the Agency for Healthcare Research and Quality (AHRQ) to (1) further evaluate EP inducibility; (2) model inducibility in the defibrillator group; (3) predict inducibility in the control group; (4) estimate treatment effects for the inducible and non-inducible groups; (5) calculate the uncertainty in these effects; and (6) interpret the analyses in the context of the entire trial.

Dr. Goodman's conclusions are as follows:

(1) The analyses strengthen the finding from MADIT I that inducible patients experience a substantive benefit from ICDs.
(2) These data provide weak to moderate evidence that the ICD effect is greater in inducible than non-inducible patients.
(3) *If taken in isolation from the results in inducible patients*, the evidence is suggestive but not definitive that non-inducible patients benefit from ICDs, albeit probably to a lesser degree than inducible patients.
(4) The adjudged strength of the evidence for an ICD effect in non-inducible patients must come from a qualitative, biologic judgment about the similarity of the physiologic mechanism producing the treatment effect in the two types of patients (i.e. how informative one effect is about the other).
(a) Identical mechanism: The treatment effect and evidence should be estimated from the combined groups.
(b) Different mechanism: The treatment effect and evidence should be estimated from each group separately.
(c) Mechanisms similar but not identical: Grey Zone. The evidential strength and treatment effects lie somewhere between the separate and combined results. Data that is informative about the mechanism, together with results from other trials, must be used.[14]

3. **Internal Technology Assessment:**

Medline was searched iteratively from 1996 using the following keywords: defibrillator, cardioverter-defibrillator with and without implantable. Studies on animal subjects, reports in languages other than English, and cost-effectiveness studies were excluded. Seven original randomized clinical trials and several review articles were reviewed and classified into primary prevention and secondary prevention.

Primary Prevention: Implantable defibrillator use for individuals who have not had prior cardiac arrest or life-threatening ventricular tachyarrhythmias.

In 1996, Moss and colleagues reported the results of a randomized clinical trial (the Multicenter Automatic Defibrillator Trial (MADIT)) on the prophylactic use of implantable defibrillators in patients with coronary disease at high risk for ventricular arrhythmias. One hundred and ninety-

[14] CMS MCAC evidence summary

six patients were randomly assigned to implantable defibrillator therapy (n=95) or to conventional medical therapy (n=101). Patients were eligible if they were 25 to 80 years of age; had a Q-wave or enzyme-positive myocardial infarction three weeks or more before entry; had an episode of asymptomatic, unsustained ventricular tachycardia unrelated to an acute myocardial infarction; had inducible, nonsuppressible ventricular tachyarrhythmia on EP study; had a LVEF ≤0.35 as measured by angiography, radionuclide scanning or echocardiography; and were in NYHA class I, II or III. Patients who had previous cardiac arrest, coronary artery bypass graft within the past 2 months, or coronary angioplasty within the past 3 months were among those that were excluded. All patients received electrophysiologic (EP) study. Patients were followed for an average of 27 months. The investigators found a 16% total mortality rate in the defibrillator group compared to 39% in the conventional therapy group (p-value=0.009) with a hazard ratio=0.46 (95% CI= 0.26-0.82). The defibrillator group had a 12% cardiac mortality rate compared to 27% in the conventional therapy group.[15] Sixty percent of patients with an implanted defibrillator had a shock discharge within two years of enrollment. The authors concluded "in patients with a prior myocardial infarction who are at high risk for ventricular tachyarrhythmia, prophylactic therapy with an implanted defibrillator leads to improved survival as compared with conventional medical therapy."[16] In this study, intention to treat, Kaplan-Meier and Cox proportional hazards regression analyses were used.

In 1997, Bigger reported the results of a randomized clinical trial on the prophylactic use of implantable defibrillators in patients at high risk for ventricular arrhythmias for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Nine hundred patients were randomly assigned to implantable defibrillator therapy (n=446) or to control group (n=454). Patients were eligible if they were less than 80 years old, had a left ventricular ejection fraction of <0.36 and had abnormalities on signal-averaged electrocardiograms. Patients with a history of sustained ventricular tachycardia or fibrillation were among those that were excluded. No EP study was performed. Patients were followed for an average of 32 months. Fifty-seven percent of patients with an implanted defibrillator received a shock within the first two years after implantation. The authors found "no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal signal-averaged electrocardiogram in whom a defibrillator was implanted prophylactically at the time of elective coronary bypass surgery." They further noted that "the occurrence of sustained ventricular arrhythmias, either natural or induced, is a better marker than abnormalities on the signal averaged electrocardiogram of a high risk of sudden death that might be prevented by the prophylactic implantation of a defibrillator."[17] In this study, intention to treat, Kaplan-Meier and Cox regression analyses were used. Occurrence of infections (deep sternal-wound infection, infection at wound or catheter site and pneumonia) was significantly higher in the defibrillator group. Occurrence of myocardial infarction during long-term follow-up was significantly higher in the control group.[18]

In 1999, Buxton and colleagues reported the results of a randomized clinical trial on the prevention of sudden death in patients with coronary artery disease for the Multicenter

[15] Moss, et al.,1996.
[16] ibid.
[17] Bigger, et al.,1997.
[18] Bigger, et al., 1997.

Unsustained Tachycardia Trial (MUSTT) investigators. Seven hundred and four patients with sustained ventricular tachycardia induced during EP study were randomly assigned to antiarrhythmic therapy including medications and implantable defibrillators (n=351) or to no antiarrhythmic therapy (n=353). Patients were eligible if they had coronary artery disease, left ventricular ejection fraction ≤0.40 and asymptomatic unsustained ventricular tachycardia. Patients with syncope or sustained ventricular tachycardia or fibrillation more than 48 hours after the onset of myocardial infarction were among those excluded. The median duration of follow-up was 39 months. The investigators reported that "the five-year estimates of overall mortality were 42 percent and 48 percent, respectively (relative risk, 0.80; 95 percent confidence interval, 0.64 to 1.01)." For patients treated with a defibrillator, the relative risk of death from all causes was 0.45 (95 percent confidence interval 0.32-0.63).[19] In this study, intention to treat, Kaplan Meier and Cox proportional hazards regression analyses were used.

In 2002, Moss et al. reported the results of a clinical trial (the Multicenter Automatic Defibrillator Implantation Trial II) on prophylactic implantation of a defibrillator in patients with a previous myocardial infarction and reduced LVEF as measured by angiography, radionuclide scanning or echocardiography. Twelve hundred thirty two patients were randomly assigned (3:2) to receive an implantable defibrillator (n=742) or to conventional medical therapy (n=490). Patients were eligible if they had a prior myocardial infarction and a left ventricular ejection fraction of ≤0.30. In addition, "eligible patients had to have frequent or repetitive ventricular ectopic beats during 24-hour Holter monitoring." This requirement was eliminated after 23 patients "because almost all eligible patients had such arrhythmias." Patients with a New York Heart Association functional class IV or who had a myocardial infarction within the past month were among those excluded along with patients who had a FDA approved indication for an implantable defibrillator at the time of the study. Patients were not required to undergo EP study and were followed for an average of 20 months.

The authors stated that "in patients with a prior myocardial infarction and advanced left ventricular dysfunction, prophylactic implantation of a defibrillator improves survival." The mortality rate in the defibrillator group was 14.2%, whereas it was 19.8% in the conventional therapy group. The hazard ratio was 0.69 (95% confidence interval 0.51-0.93; p = 0.016). In this study, intention to treat and Kaplan-Meier analyses were used. Results of Cox regression analyses to adjust for potential confounders were not reported. The adverse event, occurrence of new or worsened heart failure, was higher in the defibrillator group (19.9%) compared to the conventional therapy group (14.9%).[20] Although EP study was not required in MADIT II, 583 patients had EP studies done either prior to or during defibrillator implant. Of these 583 patients, 210 (36%) were inducible.[21]

Additional analyses of the MADIT II data have been presented. At the North American Society of Pacing and Electrophysiology (NASPE) 2002 meeting, Zareba reported that "prolonged QRS duration and atrial fibrillation are significant and independent predictors of mortality in postinfarction patients with EF ≤ 30%".[22]

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[19] Buxton, et al. 1999.
[20] Moss, et al. 2002.
[21] FDA AICD Summary of Safety and Effectiveness, 2002.
[22] Zareba, NASPE 2002.

The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT), sponsored in part by the National Institutes of Health, is an ongoing study that will provide additional information on use of implantable defibrillators in patients at risk for sudden cardiac death. The primary goal is to identify therapy that will significantly reduce arrhythmic deaths inpatients with congestive heart failure resulting from ischemic cardiomyopathy and nonischemic dilated cardiomyopathy and reduced ejection fraction. The central hypothesis of the study is that amiodarone or an implantable defibrillator will improve survival in patients with NYHA Class II and Class III CHF and LVEF ≤ 35% compared to placebo. This is a large study with a sample size of 2521 patients. Many of these patients (about 30%) are similar to the MADIT II patients (prior MI and LVEF ≤ 30%). This study will provide important additional data on these patients.[23]

Secondary Prevention: Implantable defibrillator use for individuals who have had prior cardiac arrest or life-threatening ventricular tachyarrhythmias.

In 1997, the Antiarrhythmics Versus Implantable Defibrillators (AVID) investigators reported the results of a randomized clinical trial to compare antiarrhythmic drug therapy (amiodarone or sotalol) to implantable defibrillators in patients resuscitated from near fatal ventricular arrhythmias. One thousand and sixteen patients were randomly assigned to either implantable defibrillator therapy (n=507) or to antiarrhythmic drug therapy (n=509). Patients were eligible if they had been resuscitated from near fatal ventricular fibrillation, had sustained ventricular tachycardia with syncope, or had sustained ventricular tachycardia with LVEF ≤ 0.40 and symptoms suggesting severe hemodynamic compromise. Patients had to be eligible for treatment with amiodarone to be enrolled. Mean follow-up was 18.2 months. The investigators found a crude death rate (with 95 percent confidence limits) of 15.8±3.2% in the defibrillator group compared to 24.0±3.7% in the antiarrhythmic drug group. The adjusted hazard ratio from Cox regression analysis was 0.67. Patients with defibrillators were rehospitalized sooner than patients treated with antiarrhythmic drugs (p-value=0.04). The authors concluded, "Among survivors of ventricular fibrillation or sustained ventricular tachycardia causing severe symptoms, the implantable cardioverter-defibrillator is superior to antiarrhythmic drugs for increasing overall survival."[24]

In 1999, Connolly and colleagues reported the results of a randomized clinical trial to compare the efficacy of implantable defibrillator therapy to amiodarone treatment for the prevention of deaths in patients with previous sustained ventricular arrhythmia for the Canadian Implantable Defibrillator Study (CIDS) investigators. Six hundred fifty nine patients were randomly assigned to receive an implantable defibrillator (n=328) or amiodarone (n=331). Patients were eligible if they were resuscitated from ventricular fibrillation or ventricular tachycardia or had unmonitored syncope with documented spontaneous ventricular tachycardia. Patients with long-QT syndrome, excessive perioperative risk and previous amiodarone therapy were among those excluded. Mean follow-up times were 2.9 years for amiodarone patients and 3.0 years for implantable defibrillator patients. The investigators reported that "A 20% relative risk reduction occurred in all-cause mortality and a 33% reduction occurred in arrhythmic mortality with

[23] NIH communication, 2002.
[24] AVID, 1997.

implantable defibrillator therapy compared with amiodarone; this reduction did not reach statistical significance."[25] In this study, Kaplan-Meier and Cox's proportional hazards analyses were used. There was no control (non-treatment) group.

In 1999, Kuck and colleagues reported the results of a randomized clinical trial to compare the survival impact of implantable defibrillator therapy with 3 antiarrhythmic drugs (amiodarone, metoprolol, propafenone) for the Cardiac Arrest Study Hamburg (CASH) investigators. Assignment to propafenone was discontinued due to a high observed mortality rate. Two hundred eighty-eight patients were randomly assigned to implantable defibrillator therapy (n=99), amiodarone treatment (n=92) or metoprolol treatment (n=97). Patients were eligible if they had been resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias. Patients with cardiac arrest within 72 hours of an acute myocardial infarction were among those excluded. Mean follow-up was 57 months. The investigators found a 36.4% (95% confidence intervals=26.9% to 46.6%) crude death rate in the implantable defibrillator group compared to 44.4% (95% confidence intervals=37.2% to 51.8%) in the combined antiarrhythmic group.[26] In this study, Kaplan-Meier and Cox regression analyses were used. There was no control (non-treatment) group.

Reviews

In 2003, Lee and colleagues published a meta-analysis to compare the effectiveness of the implantable defibrillator and strategies for prevention of sudden death. Nine studies including over 5,000 patients were evaluated. The investigators concluded: "Although the ICD decreases the risk of arrhythmic death, its impact on all-cause mortality is related to the underlying risk of arrhythmia-related death relative to competing causes. Given the cost of the device strategy, policies of targeted intervention based on future risk of arrhythmia are warranted."[27]

In 2003, Ezekowitz and colleagues conducted a meta-analysis of randomized controlled trials on implantable defibrillators for prevention of sudden cardiac death. Eight primary and secondary prevention trials with a combined sample size of 4909 patients were included and analyzed. The authors reported: "Implantable cardioverter defibrillators are clearly more beneficial than drug therapy for secondary prevention of sudden cardiac death and for primary prevention in certain high risk groups. However, further research is needed to develop accurate risk stratification tools, to determine the economic impact of ICD therapy in different subgroups of patients, and to evaluate quality-of-life issues."[28]

In 1999, Pinski and Fahy conducted a review of implantable defibrillators. They assessed the clinical trials on implantable defibrillators and recommended indications and contraindications for their use. The authors stated:

- "Implantable defibrillators should be considered first-line therapy in patients who have survived episodes of cardiac arrest or of hemodynamically significant sustained

[25] Connolly, et al. 2000.
[26] Kuck, et al. 2000.
[27] Lee, et al., 2003.
[28] Ezekowitz, et al., 2003.

ventricular tachycardia that was not due to reversible causes, as well as in patients with clinical characteristics similar to those enrolled in MADIT."

- "Defibrillators should not be implanted in response to ventricular arrhythmias that have been triggered by myocardial infarction, correctable toxic or metabolic factors, or rapid atrial fibrillation complicating the Wolf-Parkinson-White syndrome."
- "Critically ill patients with frequent ventricular tachycardia or fibrillation unresponsive to drugs, ablation, or antitachycardia pacing should not receive defibrillators, as frequent painful shocks would be delivered."
- "Patients with a life expectancy of <1 year are not appropriate candidates for defibrillator therapy."[29]

In 2001, Gollob and Seger published a review of implantable defibrillators. They reviewed several prominent studies on the use of implantable defibrillators and stated that "In summary, the current evidence suggest that patients with a history of cardiac arrest or sustained VT and syncope are best treated with an implantable defibrillator. Patients with LVEF < 0.35, coronary artery disease, and NSVT should be referred for EP (electrophysiologic) study. If inducible, they should receive an implantable defibrillator."[30]

In 2001, Huikuri, Castellanos and Myerburg published a review article on sudden death due to cardiac arrhythmias. They reported that "The primary prevention of arrhythmias that may lead to sudden death remains problematic. Two studies support the idea that for a small but very high-risk subgroup, prophylactic cardioverter-defibrillator therapy provides a benefit over drug therapy, and this therapeutic strategy is gaining general acceptance. This high-risk subgroup consists of patients with nonsustained ventricular tachycardia and inducible sustained ventricular tachycardia (during EP study) with a reduced ejection fraction. At the other end of the spectrum, in more general populations of patients who have had a myocardial infarction and in other groups of patients such as those with dilated cardiomyopathy, no predictable and significant benefit of prophylactic therapy has been identified. As far as drug therapy is concerned, beta-blocker therapy, although nonspecific, is the only generally accepted therapeutic approach for the primary prevention of life-threatening arrhythmia."[31]

Medicare Coverage Advisory Committee

CMS convened an MCAC meeting on February 12, 2003 to discuss the evidence for implantable defibrillators in patients with an EF of ≤ 0.30 and a prior MI. CMS was interested in the MADIT II design issues, patient selection and recruitment, and potential risk stratifiers to more clearly define the appropriate population for defibrillator implantation.

The presentations from CMS, Guidant, and the scheduled public speakers are available as part of the MCAC documents available at http://www.cms.gov/ncdr/mcacdetails.asp?id=39.

The presentations focused on the overall MADIT II results and the subanalysis of EP inducibility. Dr. Arthur Moss, the principal investigator for MADIT II, presented MADIT data

[29] Pinski and Fahy , 1999.
[30] Gollob and Seger, 2001.
[31] Huikuri, et al. 2001

and results. In addition, new data on a subset of 257 patients that were classified as pre-enrollment EPS negative were presented without the ability to have premeeting analysis.

Dr. Mark Hlatky, a scheduled public presenter, had considerable reservations about the MADIT II trial, including patient selection and risk stratification. He stated: "I think the big question is whether an EF below 30 percent in and of itself is sufficient to put in an ICD, and I would say that the question here is whether the evidence is adequate. I would say MADIT II is suggestive, it's highly suggestive, but it doesn't really prove the case completely for this. The word that was used earlier by Dr. Moss and the representative of the company was a paradigm shift, a paradigm shift to say that we don't need any additional markers of patients with low EF. And I question that because this is a single study, it's very well done, but it's only a single study. And I think we have 25 years of research that says that there are other markers that are important and for that reason I am concerned that an indication from Medicare that says that ejection fraction alone is necessary to put in an ICD is overly broad, and would expose many patients who would not benefit from this device to risks, to say nothing of the large costs to the program."[32]

Another scheduled public presenter, Dr. Joanne Lynn also had concerns. She stated: "In sum, I would recommend that the Medicare Coverage Advisory Committee do the following: First, advise CMS to issue a national coverage determination for ICDs only for the populations where evidence is strong that they actually gain desired outcomes, which may mean that only a very small part of the Medicare population should be covered now, and certainly does not now include elderly who have multiple comorbidities and competing causes of death. Second, we should call on CMS to insure that Medicare patients have a high standard of informed consent. We should recommend that CMS institute methods to monitor outcomes, that they require evidence about all of the outcomes, including quality of life. That they monitor changes in the performance over time, and call on various parties to take up discussion of the priorities and values that are at stake."[33]

Many of the scheduled and unscheduled public commentators advocated strongly in favor of the benefits of ICD therapy for MADIT II patients and strongly encouraged CMS to provide coverage.

The panel voted on the following questions:

1. Is the evidence adequate to draw conclusions about the net health outcomes in Medicare aged patients who meet the inclusion and exclusion criteria in the MADIT II trial and who receive an implantable defibrillator as primary prevention for sudden cardiac death (SCD)?

2. Is the evidence adequate to apply the findings of MADIT II to all Medicare patients with a prior MI and an EF of ≤ 0.30 without requiring evidence of an arrhythmia?

3. Is the evidence adequate to apply the findings of the MADIT II trial to all Medicare patients who meet the inclusion and exclusion criteria for the MADIT II trial?

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[32] MCAC ICD transcript, 2003.
[33] Ibid

The panel voted unanimously "yes" to the first and third question and unanimously "no" to the second question.

Clinical Practice Guidelines

In 2002, Gregoratos and colleagues published guidelines on the implantation of cardiac pacemakers and antiarrhythmia devices for the American College of Cardiology (ACC), the American Heart Association (AHA) and the North American Society for Pacing and Electrophysiology (NASPE). The reported recommendations were expressed in the standard ACC/AHA format 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.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.[34]

Specifically for implantable defibrillator therapy, the guidelines are as follows:

Class I

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

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)* [35]

Expert and Public Comments

Many of the public comments received by CMS were in support of coverage for the MADIT II population, including letters from 37 individual practicing physicians. Separately signed form letters from 34 MADIT II investigators encouraging full coverage were also received.

[34] Gregoratos et al. 2002.
[35] Gregoratos, et al. 2002.

The ACC, NASPE and AdvaMed submitted comments in support of Medicare coverage of ICDs in patients who meet MADIT II criteria, largely based on the IIa recommendation generated by their joint guideline development committee.

Dr. Claude Lenfant, Director of the National Institutes of Health, National Heart, Lung, and Blood Institute, sent CMS a letter discussing MADIT II and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Dr. Lenfant expresses, "…the need for caution in making broad interpretations based solely on MADIT II." He describes the reasons why both of the studies are critical in assessing the clinical value of ICDs citing that the SCD-HeFT Data Safety and Monitoring Board has not made a recommendation to stop the study allowing the reasonable assumption that differences between treatment arms are not overwhelming.[36]

Dr. Alfred E. Buxton, Director of Electrophysiology and Arrhythmia Service, Rhode Island Hospital, commented, "While MADIT II results are quite clear, as applied to the study population, the difficulty we face as physicians, is to determine how generalizable the results are. The average duration of follow-up in the study was far too brief, in my opinion, to provide a realistic estimate of the benefits conferred by ICD treatment. …From my perspective, one potential logical option is for CMS to approve reimbursement for implantation of ICDs under a MADIT II indication contingent upon the results of more refined studies to demonstrate the true benefits and risks in this population."[37]

Mark E. Josephson, MD, Director of the Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service at the Beth Israel Deaconess Medical Center in Boston, MA submitted a paper to CMS urging caution in adopting new standards and recommendations for the use of ICDs when considering the evidence of only one study. Several other practicing and academic physicians urged similar caution.[38]

VIII. CMS Analysis

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 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).

An item or service may be considered reasonable and necessary only if it improves net health outcome(s). In addition, to be considered reasonable and necessary, the technology must, if FDA-regulated, have been approved or cleared by the FDA for at least one indication (unless it is a Category B device subject to an IDE) and the technology causes an equal or greater improvement in net health outcome(s) than any established alternatives used to treat the same indication in the same population in the same clinical setting.

[36] Correspondence
[37] Correspondence
[38] Correspondence

CMS focused on two general questions:

1. Is there sufficient evidence on the effectiveness of implantable defibrillators for individuals who have left ventricular dysfunction and have had a prior myocardial infarction, but have not had prior cardiac arrest or life-threatening ventricular tachyarrhythmias?

2. Is there sufficient evidence on the effectiveness of implantable defibrillators for individuals who have had prior cardiac arrest or life-threatening ventricular tachyarrhythmias?

Is there sufficient evidence on the effectiveness of implantable defibrillators for individuals who have left ventricular dysfunction and have had a prior myocardial infarction, but have not had prior cardiac arrest or life-threatening ventricular tachyarrhythmias (primary prevention of sudden cardiac death)?

Primary prevention of sudden cardiac death has been defined as "the prevention of the first life-threatening arrhythmic event such as sustained ventricular tachycardia, ventricular fibrillation, or cardiac arrest."[39] Patients with a prior myocardial infarction and left ventricular dysfunction are at risk for sudden cardiac death and thus have been targeted for interventions. The total population of patients who have left ventricular dysfunction and have had a prior myocardial infarction consists of patients who have EP inducible ventricular tachyarrhythmias and patients who do not. EP study is routinely considered and has been recommended for risk stratification,[40] although recent published commentaries have raised questions about the predictive value, reproducibility and clinical utility of EP in predicting which patients are likely to benefit from implantation of ICDs.

Several randomized controlled trials have been classified in the literature as primary prevention trials: MADIT I, MUSTT, CABG-Patch and MADIT II (Table 1 in Appendix A). These trials may be further classified into two types: (1) trials on patients with inducible sustained ventricular tachyarrhythmias during EP study (MADIT I and MUSTT), and (2) trials on high risk patients with coronary disease who were not specifically required to have inducible sustained ventricular tachycardia during EP study (CABG-Patch and MADIT II). Since the defibrillators were implanted, none of these trials were masked or blinded to either the investigators or patients.

Both MADIT I and MUSTT demonstrated significant improvements in survival for patients with prior myocardial infarction, left ventricular dysfunction and inducible, sustained ventricular

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[39] Myerburg, et al., 1998; Huikuri, et al. 2001.

[40] In 1996, Moss and colleagues reported the following: "We believe that the use of electrophysiologic testing enhanced the process of stratification for arrhythmia and helped select a population at particularly high risk that benefited from the defibrillator." In 1997, Bigger and colleagues reported: "For the present, electrophysiologic studies have a central role in identifying high-risk patients for whom the prophylactic implantation of a defibrillator is indicated." In 2001, Gollob and Seger reported: "EP testing is a well-established procedure that has been shown to predict the risk of SCD (sudden cardiac death) in patients with coronary artery disease." In 2001, Huikuri and colleagues reported: "The inducibility of sustained ventricular tachyarrhythmia by programmed electrical stimulation is a well-established marker of an increase risk of ventricular tachyarrhythmias."

arrhythmias during EP study that were treated with implantable defibrillators (54% and 55% reduction in mortality, respectively). Both trials were randomized clinical trials with sample sizes of 196 patients and 704 patients, respectively. MADIT I focused on patients who were inducible and nonsuppressible during EP test. MUSTT focused on the more general group of patients who were inducible, but without specification on suppressibility. The results of these two trials were consistent and provided sufficient evidence on effectiveness for this subpopulation and have been well accepted in practice. The 2002 ACC/AHA/NASPE evidence-based, clinical practice guidelines listed this indication (#4) in the Class I category. Several review articles have also reinforced the use of implantable defibrillators for this high-risk subpopulation.

For patients with prior myocardial infarction and left ventricular dysfunction but who have not had documented sustained (spontaneous or induced) ventricular tachyarrhythmias, the study results have been variable. The CABG-Patch Trial and MADIT II focused on these types of patients at high risk for sudden death but did not require inducible ventricular arrhythmias or EP study.

The CABG-Patch Trial investigators found "no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal signal-averaged electrocardiogram in whom a defibrillator was implanted prophylactically at the time of elective coronary bypass surgery."[41] The investigators also reported that "the occurrence of sustained ventricular arrhythmias, either natural or induced, is a better marker than abnormalities on the signal-averaged electrocardiogram."[42] The results of this trial also suggest that CABG revascularization sufficiently reduced the risk of SCD to a point where an implantable defibrillator did not improve survival in the specified time period.

MADIT II found a significant improvement in survival (14.2% mortality rate in implantable defibrillator group, 19.8% in conventional therapy group). Overall, this was a well-designed clinical trial. The study does, however, have a number of important methodological limitations. MADIT II evaluated patients with a prior myocardial infarction and left ventricular ejection fraction ≤ 0.30. The study design specified that patients eligible for an implantable defibrillator using MADIT I criteria (prior MI, LVEF ≤ 0.35, nonsustained VT, and inducible-nonsuppressible VT at EP study) were to be excluded. However, Holter monitoring to identify VT was done in only the first few patients and EP studies were required prior to enrollment. Thus, this study population included patients who had a high likelihood of meeting MADIT I criteria of inducibility and nonsustained VT, but who did not have testing to determine whether they met these criteria.

Although EP study was not required in MADIT II, 583 patients had EP studies done either prior to or during defibrillator implant. Of these 583 patients, 210 (36%) were inducible.[43] By including a subset of patients known to have a large survival benefit from an implantable defibrillator (>50% reduction in mortality), a positive outcome could have been shown in MADIT II even if there was little or no effect in the rest of the study population. It is unclear as

[41] Bigger, et al.,1997.
[42] ibid.
[43] FDA AICD Summary of Safety and Effectiveness, P910077/S037 and P960040/S026, July 18, 2002.

to why these patients who were found to have an inducible arrhythmia were not excluded from the trial.

Another important study consideration is the selection of the MADIT II population. The study population may not have been a representative sample of the general population of patients with prior MI and LVEF ≤ 35%. The MADIT II patients were referred by physicians or located using inpatient records, diagnostic laboratory records or catherization laboratory records. The selection method may have generated a higher risk group than a random sample, given the likelihood that patients identified from these settings were undergoing cardiac evaluation because of some ongoing signs or symptoms of their illness that had precipitated the admission or diagnostic evaluation.. This is supported by the high mortality rate in the conventional therapy group (19.8%) and the high frequency of patients with ventricular tachyarrhythmias. Other ICD studies have shown that the site from which patients are recruited can be an important determinant of baseline risk and absolute treatment benefit. Thus, the observed benefit from implantable defibrillators in MADIT II may be substantially higher than would be expected in the lower risk, general population of potentially eligible patients.

There are other limitations of the MADIT II study findings. Firstly, there is no clear explanation for the results that demonstrated no improvement in survival in the first 12 months (Figure 1 in Appendix B). Mirowski originally estimated a "52% decrease in the total mortality rate"[44] in the year after implantation of the device. Early improvements were seen in both MADIT I and MUSTT (Figures 2 and 3 in Appendix B). It is unclear why there was no survival benefit in the first 12 months of MADIT II. It is possible that there were very few episodes of ventricular tachyarrhythmias for the implantable defibrillator to treat. This is supported by the finding that only 134 (18.9%) of the 710 patients who had an implantable defibrillator implanted received therapy from their devices during the course of the trial.[45] By contrast, 60% of patients received therapy from their defibrillators in MADIT I.

Secondly, the higher rate of adverse events, such as hospitalization for new or worsened heart failure in the group receiving the implantable defibrillators compared to conventional therapy, is concerning (19.9% versus 14.9% respectively). Implantable defibrillators are invasive devices, require surgery to place, and are permanently implanted in most cases. While this finding of an increased risk for hospitalization may not be due to the ICD itself, this clearly documented but incompletely understood risk must be considered along side the potential benefits of this intervention.

Thirdly, there still was a substantial mortality rate in the treatment group (14.2%), due largely to non-arrhythmic cardiac deaths and non-cardiac deaths. The defibrillator group had improvements only in arrhythmic cardiac deaths compared to the conventional therapy group (3.8% versus 9.8% respectively), as expected since defibrillators only treat ventricular tachyarrhythmias. They do not prevent non-arrhythmic cardiac deaths (6.1% versus 4.5% respectively) or non-cardiac deaths (3.4% versus 4.3% respectively).[46] Since patients with

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[44] Mirowski M, et al., 1983.
[45] FDA AICD Summary of Safety and Effectiveness, P910077/S037 and P960040/S026, July 18, 2002.
[46] ibid.

serious co-morbidities such as diabetes and liver or renal disease are at risk for non-cardiac deaths, the benefits of implantable defibrillators in these patients would likely be reduced.

Another noteworthy feature of the MADIT II study is that only the primary results of the trial have so far been published in a full, peer-reviewed report. Numerous abstracts and presentations have been made containing additional analyses of the MADIT II data, including studies on quality of life, risk-stratification and cost-effectiveness. The MADIT II investigators have indicated that a number of additional publications will be available in the near future and these results should add significantly to a complete understanding of the results of this important trial.

As noted by a number of clinicians and experts, the mean duration of follow-up in the MADIT II trial was relatively short (20 months), primarily as a result of early termination of the trial. This leaves unanswered the question of whether the reported benefits would have been sustained over a period of time similar to the expected lifetime of the device (about 4-5 years).

In addition, the absolute reduction (5.6%) in mortality was small compared to MADIT I (23%).[47] This means that out of 100 patients with a defibrillator implanted for MADIT II indications only six (6) might benefit, and as noted above, the absolute benefit could be substantially less outside the study population. Greater knowledge is needed to more clearly identify the patients who would benefit and avoid implantation in those who don't. This is consistent with the ACC/AHA/NASPE 2002 evidence-based guideline update that listed this indication as a Class IIa. They stated: "Additional risk stratification studies are needed to better define which patient subgroups will benefit more or less from ICD therapy than that demonstrated in the above referenced population."[48] Also, the ACC stated during the MCAC that: "We support the ICD therapy for MADIT II indications in this particular subject population. We recommend strict adherence to the MADIT II inclusion and exclusion criteria. We recommend continued investigation of optimum risk stratification of patients in this group. And we recommend development of a registry of patients receiving ICDs for MADIT II indications; the registry very importantly should include the date and method of LVEF measurement in relation to the date of myocardial infarction and/or date of revascularization."[49]

After careful review of the information provided to them and presented on February 12, 2003, the MCAC determined that there was adequate evidence to conclude that ICDs improve net health outcomes for patients with a prior MI and LVEF ≤ 30% and who meet the inclusion and exclusion criteria of the MADIT II trial. CMS views the conclusion of the MCAC as a reasonable assessment of the information available to them at that time. Significant additional scientific evidence and expert input has been obtained since that time, much of which would have been highly relevant to the MCAC deliberations. For example, the panel devoted several hours of discussion to the role of EP inducibility as a risk stratifier. In addition to clarification of EP inducibility data presented by CMS, Dr. Moss presented data on a subset of 257 patients that were classified as pre-enrollment EP negative. CMS had not had any opportunity to review this data prior to the meeting because it had been inadvertently omitted from the MADIT II dataset provided by Guidant to CMS, and the analysis was not provided to CMS in advance of the

[47] In MADIT II, the number needed to treat (NNT) was 18 compared to 4 in MADIT I.
[48] ACC/AHA/NASPE 2002.
[49] MCAC ICD Transcript 2003

MCAC meeting. Subsequent analysis of this data by CMS found that 86 of the 257 patients who were originally EP negative had a repeat EP test at time of defibrillator implant and 38% of those patients were then found to be EP inducible. As has been noted previously, patients who are inducible on EP testing are known to have a large benefit from defibrillator implantation and defibrillator implantation for these patients is already considered reasonable and necessary by CMS. It would have been helpful for the MCAC to have had a complete, accurate understanding of this new data during their discussions.

Another topic receiving little attention during the MCAC meeting was the potential importance of QRS-width as a risk-stratification variable. Prior to the MCAC, Guidant provided CMS with an analysis stratified by QRS width clearly showing no difference in the mortality benefit of implantable defibrillators. Based on this information, CMS decided not to focus discussion on this variable. Subsequent review of the Guidant data by CMS led to discovery of an error in the data tables provided. Corrected data tables, survival curves and regression analyses presented in this decision memorandum would certainly have been important data for the MCAC to review and discuss had it been available and accurate when originally requested.

A final topic receiving little attention at the MCAC meeting was the significance of the NIH-sponsored SCD-HeFT trial. While representatives from this trial did attend the MCAC meeting, there was no discussion of the similarities and differences between these trials or the implications of the DSMB decision to continue that trial after review of the MADIT II results and their own confidential interim data. Subsequent to the MCAC meeting, CMS was made aware of the importance of this study and has engaged in numerous detailed discussions of the trial with the SCD-HeFT principal investigators, the DSMB chairperson, the lead statistician, and the trial sponsors (the National Heart, Lung and Blood Institute and Medtronic). We are convinced that the MCAC discussion would have been enriched had this information been available prior to the Feb 12 meeting.

In summary, while the MADIT II trial was a good randomized trial, it is a single clinical trial with a number of potentially significant methodological limitations. These issues have been expressed by a number of respected implantable defibrillator experts, have been written about in published editorials and commentaries, and are reflected in the IIa recommendation (conflicting evidence and/or divergence of expert opinion, weight of evidence in favor) assigned by the ACC and NASPE. The MCAC conclusion regarding the adequacy of the evidence reflected their assessment of the evidence available to them and was made in the absence of a substantial amount of additional and corrected information that may well have been influential in their deliberations. Based on these factors, CMS concludes that the evidence is not currently adequate to conclude that implantable defibrillator therapy is reasonable and necessary for the entire population of patients with prior myocardial infarction and left ventricular dysfunction who meet the MADIT II eligibility criteria.. CMS eagerly anticipates the availability of results from the SCD-HeFT trial and additional risk-stratification studies and will reconsider these conclusions when that additional data becomes available.

Risk Stratification

Implantable defibrillators have been shown to improve survival for patients at high risk for ventricular tachyarrhythmias and sudden cardiac death. MADIT II also demonstrated a benefit for a proportion of the population; however, many patients did not receive therapy. Identifying the patients at risk within the MADIT II population would allow for appropriate targeted therapy. Several methods for identifying those patients at risk have already been studied and reported in the literature, including EPS inducibility (mentioned above), severe left ventricular dysfunction, prolonged QRS interval, and T wave alternans. These factors may be directly applied to the MADIT II population to identify patients at high risk.

EPS inducibility has been adequately studied in MADIT I and MUSTT. CMS analysis of MADIT II data on EPS inducibility showed results consistent with prior studies on the risk of and the benefits of implantable defibrillators in patients with EPS inducible sustained ventricular tachyarrhythmias (please see Appendix C). However, EPS inducibility data were incomplete for patients in the conventional therapy group, thereby limiting our ability to fully consider this risk variable. Goodman further analyzed the MADIT II data and concluded that the data provided weak to moderate evidence that the ICD effect is greater in inducible than non-inducible patients.

Severe left ventricular dysfunction (left ventricular ejection fraction less than 25%) has been evaluated as a risk stratifier. 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."[50] Based on survival analysis of MADIT I data, Moss also noted that "the survival benefit of ICD therapy was significantly greater than conventional therapy only in the subgroup with an ejection fraction < 26%."[51] The risks associated with severe LV dysfunction and EP inducibility were further noted by Buxton and colleagues in 2002. The authors reported that "both low ejection fraction and inducible tachyarrhythmias identify patients with coronary disease at increased mortality risk."[52] CMS analysis of the MADIT II data on LVEF < 25% showed results that were consistent to prior findings (please see Appendix D). Patients with LVEF < 25% who received an implantable defibrillator had improved survival compared to the patients with LVEF < 25% in the conventional therapy group

Abnormal T wave alternans (electrical alternans) has been identified as a potential risk stratifier for sudden cardiac death in patients with prior myocardial infarct. In 1994, Rosenbaum and colleagues studied 83 patients referred for EP testing and found that positive alternans was a "significant and independent predictor of inducible arrhythmias" on EP testing.[53] In 1998, Armoundas and colleagues reported that T wave alternans measured during exercise appeared to "identify a substrate at risk for ventricular arrhythmias.[54] In 2002, Ikeda and colleagues studied 834 patients with prior MI and reported that T wave alternans was a "strong risk stratifier for SCD in infarct survivors."[55]

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[50] Moss, 2000.
[51] Ibid.
[52] Buxton, et al., 2002.
[53] Rosenbaum, et al., 1994.
[54] Armoundas, et al., 1998.
[55] Ikeda, et al., 2002.

Prolonged QRS interval (QRS>120 msec) may occur following myocardial infarction and subsequent development of myocardial scar tissue. It indicates "abnormal electrical activation of the ventricles or electrical ventricular dyssynchrony."[56] Several authors have reported the risk of prolonged QRS interval.[57] Prolonged QRS (intraventricular conduction delay) has been associated with "clinical instability and an increased risk of death in patients with heart failure."[58] The advancements of cardiac resynchronization and the conduct of several randomized controlled trials targeting ventricular dyssynchrony also provide indications of the risks associated with prolonged QRS interval and sudden cardiac death.[59]

The MADIT II data on prolonged QRS data has been further evaluated. Zareba, one of the MADIT II investigators, performed adjusted multivariate analyses of the MADIT II data and found that QRS duration > 120 msec was an "independent and significant" predictor of death (hazard ratio=1.90; 95% confidence intervals=1.14-3.14; p-value=0.013).[60] Guidant also provided additional analysis of the QRS interval. Using a three-category division of QRS interval (QRS < 120 ms, QRS = 120 ms and QRS > 120 ms), the interaction p-value was equal to 0.052, a marginally significant value (please see Appendix E).

CMS analysis of the MADIT II data on QRS interval (QRS ≤ 120 ms or QRS > 120 ms) showed results similar to those reported by to Zareba. Patients with a QRS ≤ 120 milliseconds in the implantable defibrillator group had a small (not statistically significant) reduction in mortality compared to the conventional therapy group (13% versus 16% respectively; p-value=0.25). Patients with a QRS > 120 milliseconds in the implantable defibrillator group had a significant reduction in mortality compared to the conventional therapy group (16% versus 30% respectively; p-value=0.001). Cox regression analysis controlling for prognostic factors showed a significant interaction (p-value=0.015; please see Appendix E), strongly suggesting that the QRS-width may be an important indicator of which patients are most likely to benefit from implantable defibrillator therapy.

Of the potential risk stratifiers that have been reported in the literature, there is more substantive data and prior indications of the risk associated with prolonged QRS interval (QRS > 120 milliseconds). It also provides a straightforward method to identify high-risk patients within the MADIT II population, based on readily available electrocardiogram (ECG) measurements. EP inducibility has been most studied and is covered under the MADIT I indication. However, EP inducibility data in MADIT II were incomplete. Severe LV dysfunction (LVEF < 25%) identifies a high risk group but LVEF values are often estimated and therefore a less objective, reproducible measure than QRS interval.. T wave alternans testing is a promising technology that may, with future study, provide a more accurate method of risk stratification. To better identify patients at risk, the well-designed risk stratification studies recommended by the ACC/AHA/NASPE guidelines and the registry recommended by ACC at the MCAC are still needed.

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[56] Bradley, et al., 2003.
[57] Shamim, et al., 1999; Xiao, et al., 1996.
[58] Abraham, et al., 2002
[59] Bradley, et al., 2003; Abraham, et al., 2002; Bristow, et al., 2000.
[60] Zareba W, NASPE 2002.

CMS is well aware of the hazards of drawing conclusions from subgroup analyses of randomized trials. Even highly significant interaction terms, such as was found for QRS-width, are more likely to be the result of chance than are the primary results of the study. However, given the possibility of a dramatic mortality benefit in this subgroup (88% reduction) and the expected availability of important new clinical data in less than one year, it was felt that implantable defibrillator therapy should be considered reasonable and necessary. CMS plans to closely monitor findings from future studies and will then assess whether narrower or broader coverage for the MADIT II population is indicated.

In summary, there is adequate evidence to conclude that an implantable defibrillator is reasonable and necessary for patients with a prior MI, LVEF ≤ 35% and inducible, sustained ventricular tachyarrhythmias during EP testing, as demonstrated in MADIT I and MUSTT. There is not adequate evidence to conclude that an implantable defibrillator is reasonable and necessary for the entire population of patients with a prior MI and LVEF ≤ 30% and who meet the other MADIT II eligibility criteria. Based on risk stratification studies, there is adequate evidence to conclude that an implantable defibrillator is reasonable and necessary for patients with a prior MI, LVEF ≤ 30% and QRS interval > 120 milliseconds. These patients must also meet the inclusion and exclusion criteria of MADIT II since the evidence for benefit of defibrillator therapy for this population is limited to the patients included in MADIT II. The myocardial infarction must be documented by elevated cardiac enzymes or Q-waves on an electrocardiogram. Ejection fractions must be measured by angiography, radionuclide scanning or echocardiography.

Is there sufficient evidence on the effectiveness of implantable defibrillators for individuals who have had prior cardiac arrest or life-threatening ventricular tachyarrhythmias (secondary prevention of sudden cardiac death)?

The survival benefits of implantable defibrillators in patients who have experienced life-threatening ventricular tachycardias or cardiac arrest have been demonstrated by 3 major randomized clinical trials (AVID, CIDS, CASH) with a large combined sample size (Table 2 in Appendix A). Prior to these trials, the standard treatment for these patients was antiarrhythmic medication therapy. All three trials compared implantable defibrillators therapy to medications and found improvements in survival. In AVID, the investigators detected a significant improvement in survival of patients treated with implantable defibrillators compared to patients treated with antiarrhythmic drugs. In CIDS, the investigators observed reductions in all-cause and arrhythmic mortality. In CASH, the investigators observed a reduction in all-cause mortality.

In addition, the 2002 ACC/AHA clinical practice guidelines listed these indications (#1 and #2) in Class I, the highest category of evidence. Several review articles have also supported the use of implantable defibrillators for high-risk patient populations derived from these clinical trials (Table 2 in Appendix A). Considered in aggregate, the evidence is adequate to conclude that an implantable defibrillator is reasonable and necessary for patients with a documented cardiac arrest due to ventricular fibrillation or life-threatening ventricular tachyarrhythmias.

Conclusions

Implantable defibrillators have been shown to improve survival for certain, well-defined patients at high risk for sudden cardiac death. Methods to identify these patients at high risk have been reported. Additional studies on effectiveness and risk stratification are needed. The NIH sponsored SCD-HeFT should provide much needed additional data. In addition, the development of a registry of all patients who received implantable defibrillators is highly desirable to allow continued follow-up and documentation of long-term benefits.

A CMS determination that a technology is reasonable and necessary does not imply that all patients meeting the covered indications should receive that technology. Clinical judgment is still required to appropriately select individuals for the technology.

A defibrillator is one of several options for prevention of SCD and treatment of ventricular tachyarrhythmias. Medications such amiodarone and beta blockers (such as sotalol) are effective and in many instances may be more appropriate. Medications for heart failure should also be optimized for maximum benefits.

Implantable defibrillators may expose patients to potential adverse events. Careful consideration and discussion of the harms and benefits with patients should be done prior to recommending an implantable defibrillator. This is especially significant for patients where the potential benefits are outweighed by the risks of noncardiac mortality. Careful consideration should also be given to the type of devices implanted. Almost all studies used only single chamber devices. The outcomes and results may not be entirely generalizable to other types of devices. More advanced devices are more difficult to implant and are not necessarily better than simple devices. The number of device leads should also be minimized since leads may break and need replacement, again subjecting the patient to potential harms. For many patients at relatively low risk, a simple, single lead defibrillator may be completely sufficient and should be considered as first line therapy.

Appendix A

Table 1 – Patient Inclusion and Exclusion Criteria for Primary Prevention Trials

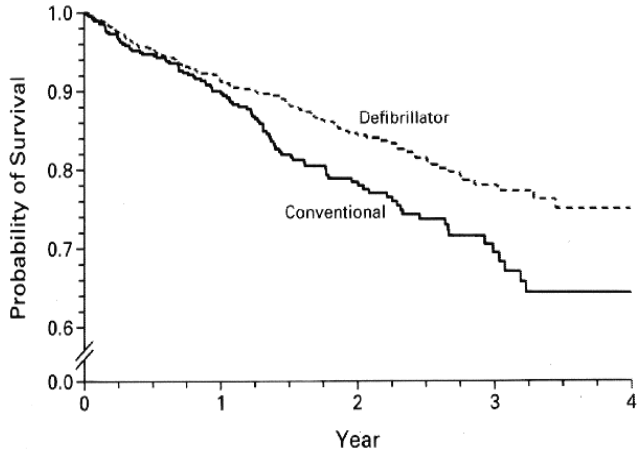
Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
MADIT I, 1996. Tx n=95; Conventional n=101.	age 25 to 80 years; myocardial infarction 3 wks or more; episode of asymptomatic unsustained VT unrelated to MI; LVEF ≤ 0.35; NYHA I-III; inducible, nonsuppressible VT on EPS; no indications 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.
MUSTT, 1999. EP tx n=351; No tx n=353.	had coronary artery disease; LVEF≤ 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.

Table 2 – Patient Inclusion and Exclusion Criteria for Secondary Prevention Trials

Study Sample Size	Inclusion Criteria	Exclusion Criteria	EP study	Outcome
AVID, 1997. Defib n=507; Drug tx n=509.	Resuscitated from near-fatal ventricular fibrillation; sustained ventricular tachycardia with syncope; sustained ventricular tachycardia with LVEF ≤ 0.40 and symptoms severe hemodynamic compromise.	not eligible for treatment with amiodarone.	not specified.	Overall survival = 89.3%, 81.6%, 75.4% at 1,2,3 years in defibrillator group; 82.3%, 74.7%, 64.1% at 1,2,3 years in antiarrhythmic drug group. P-value < 0/02.
CIDS, 2000. Defib n=328; Amio n=331.	In absence of AMI and electrolyte imbalance: documented VF; out of hosp cardiac arrest requiring defib or cardioversion; documented sustained VT causing syncope; other documented, sustained VT rate ≥ 150 causing presyncope or angina with LVDF ≤ 0.35; unmonitored syncope with documented spontaneous VT or sustained VT induced.	Defibrillator or amiodarone not appropriate tx; excessive perioperative risk for device implantation; previous amiodarone therapy for ≥ 6 weeks; nonarrhythmic medical condition with unlikely 1 year survival; long QT syndrome.	variable	25% (83 deaths) all cause mortality rate in defibrillator group; 29.6% (98 deaths) in amiodarone group; p-value=0.142.
CASH, 2000. Defib n=99; Drug n=189.	Resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias.	cardiac arrest within 72 hours of AMI, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect.	programmed electrical stimulation (PES).	36.4% death rate (95%CI=26.9%-46.6%) in defibrillator group; 44.4% (95%CI=37.2%-51.8%) in amiodarone/ metoprolol group.

Appendix B

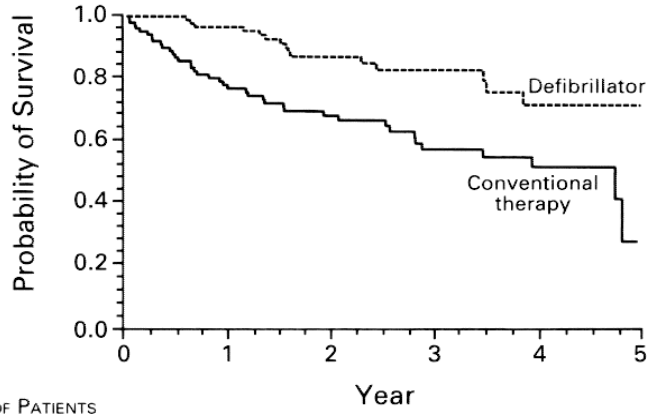
Figure 1 – Kaplan-Meier Survival Curve from MADIT II



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Kaplan-Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy.
From: Moss: N Engl J Med, Volume 346(12).March 21, 2002.877-883.

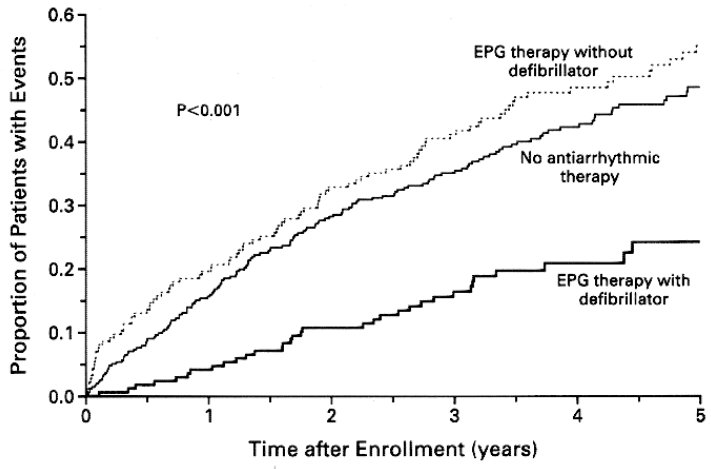
Figure 2 – Kaplan-Meier Survival Curve from MADIT I



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

Kaplan-Meier Analysis of the Probability of Survival, According to Assigned Treatment. The difference in survival between the two treatment groups was significant (P = 0.009) .
From: Moss: N Engl J Med, Volume 335(26).December 26, 1996.1933-1940

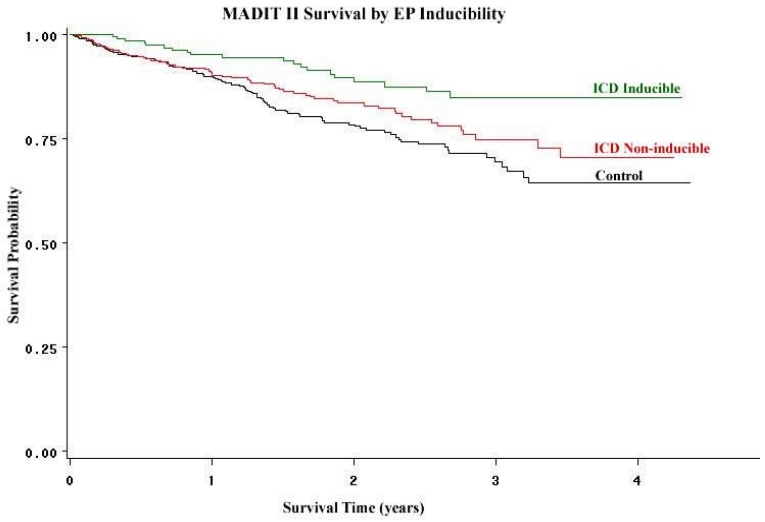
Figure 3 – Kaplan-Meier Mortality Curves from MUSTT



Kaplan-Meier Estimates of the Rates of Overall Mortality According to Whether the Patients Received Treatment with a Defibrillator.
From*:* Buxton: N Engl J Med, Volume 341(25).December 16, 1999.1882-1890

Appendix C

Figure 1 – Kaplan-Meier Survival Curves by EP Inducibility
(CMS analysis of the MADIT II dataset supplied by Guidant)



Appendix D

Table 1 - Deaths by LVEF and Group in MADIT II

	Treatment group			Control group			Total			p-value
	Deaths	N	%	Deaths	N	%	Deaths	N	%	
25%≤EF≤30%	43	385	11%	40	262	15%	83	647	13%	0.13
LVEF < 25%	62	357	17%	57	228	25%	119	585	20%	0.03

CMS analysis from MADIT II dataset supplied by Guidant.

Figure 1 - KM Survival Curves for Patients with LVEF>=25% by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)

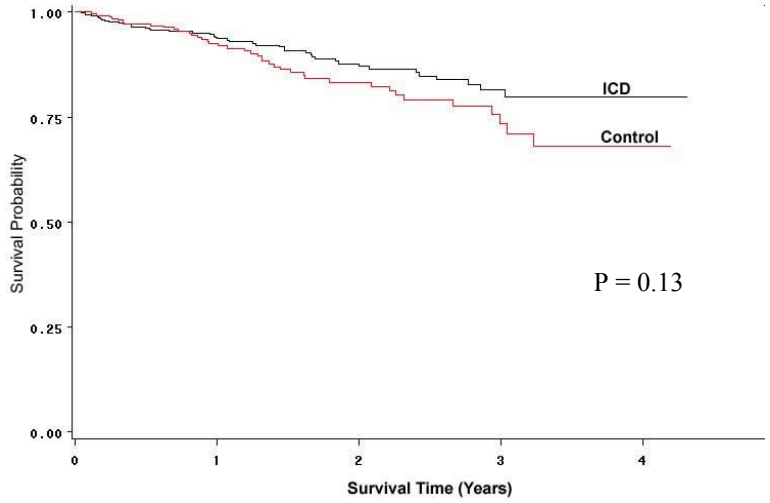
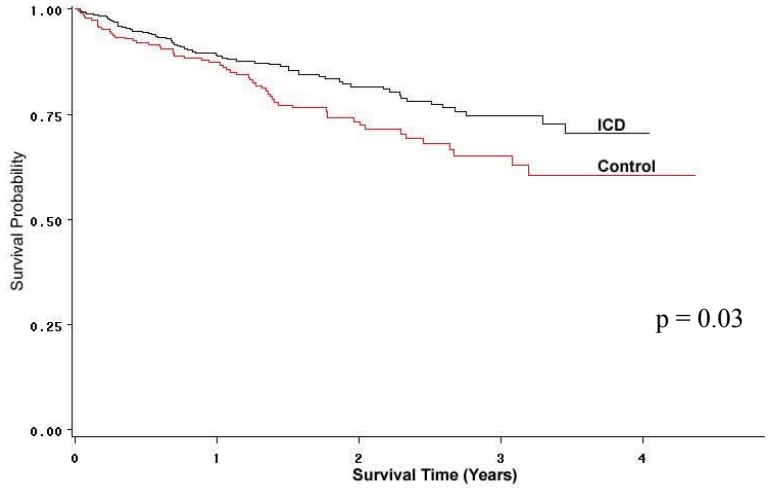


Figure 2 - KM Survival Curves for Patients with LVEF<25% by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)



Appendix E

Table 1 - Noninvasive Electrocardiology and Outcomes in MADIT II Patients
Presented by Wojciech Zareba MD, PhD

Noninvasive ECG Parameters in Multivariate Cox Model for Predicting Total Mortality in MADIT II Patients Randomized to Conventional Therapy

Variable	HR	(95% CI)	P value
Age≥65 years	1.47	(0.86-2.52)	0.164
NYHA ≥II	2.00	(1.20-3.34)	0.008
BUN>25	1.94	(1.17-3.21)	0.010
No BB use	1.57	(0.94-2.66)	0.089
A. Fib.	2.36	(1.14-4.89)	0.021
QRS>0.12 sec	1.90	(1.14-3.14)	0.013

From: NASPE 2002 Meeting - May 11, 2002.
http://naspehighlights.org/summary/summary.asp?sid=1&stid=19&ld=2002-05-11

Table 2 - Deaths by QRS Interval and Group in MADIT II

	Treatment group			Control group			Total			Hazard ratio
	Deaths	N	%	Deaths	n	%	Deaths	N	%	
QRS < 120 ms	43	357	12%	37	230	16%	80	587	14%	0.76
QRS = 120 ms	14	83	17%	13	84	16%	27	167	16%	1.03
QRS > 120 ms	35	225	16%	41	136	30%	76	361	21%	0.39

Results provided by Guidant.
98 pacemaker patients excluded; 19 missing QRS values.
Interaction p value = 0.052.

Table 3 - Deaths by QRS Interval and Group in MADIT II

	Treatment group			Control group			Total			p-value
	Deaths	N	%	Deaths	N	%	Deaths	N	%	
QRS ≤ 120 ms	57	451	13%	50	322	16%	107	773	14%	0.25
QRS > 120 ms	36	229	16%	41	138	30%	77	367	23%	0.001

CMS analysis of MADIT II dataset supplied by Guidant.
92 patients with pacemakers were excluded. 4 patients with unknown pacemaker status were included.
Interaction p value = 0.015

Figure 1 - KM Survival Curves for Patients with QRS ≤ 120 ms by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)

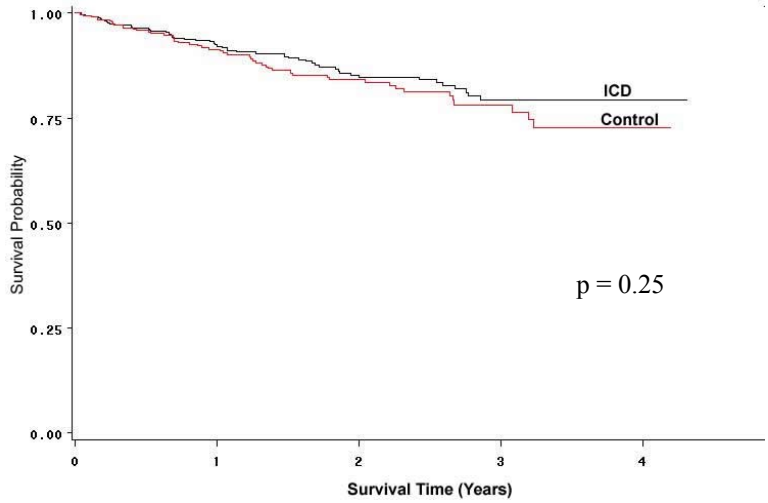


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Figure 2 - KM Survival Curves for Patients with QRS > 120 ms by Group
(CMS analysis of the MADIT II dataset supplied by Guidant)

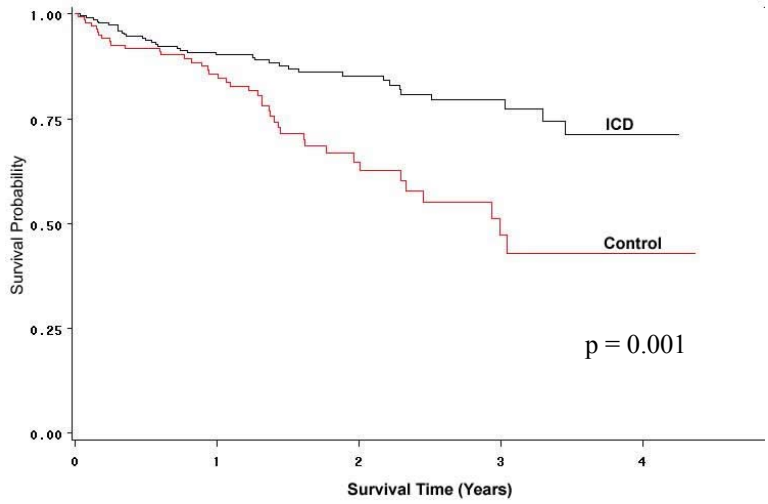

Table 4 - Cox Regression Model
(CMS analysis of the MADIT II dataset supplied by Guidant)

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Treatment	1	0.56531	0.45510	1.5430	0.2142	1.760
AGE	1	0.03462	0.00846	16.7428	<.0001	1.035
EF	1	-0.03811	0.01358	7.8739	0.0050	0.963
BUN	1	0.02896	0.00433	44.7956	<.0001	1.029
QRS>120ms	1	1.24498	0.48103	6.6985	0.0096	3.473
QRS interaction	1	-0.74071	0.30554	5.8771	0.0153	0.477

References

Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845-1853.

Armoundas AA, Osaka M, Mela T, et al. T-wave alternans and dispersion of the QT interval as risk stratification markers in patients susceptible to sustained ventricular arrhythmias. Am J Cardiology 1998; 82:1127-1129.

AVID Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576-1583.

Bardy G. ICDs for heart failure patients: do we know who needs one? Heart Failure Society Annual Meeting 2002.

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

Bigger JT. Expanding indications for implantable cardiac defibrillators. N Engl J Med 2002; 346:931-933.

Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure. A meta-analysis of randomized controlled trials. JAMA 2003; 289:730-740.

Bristow MR, Feldman AM, Saxon LA, et al. Heart failure management using implantable devices for ventricular resynchronization: comparison of medical therapy, pacing, and defibrillation in chronic heart failure (COMPANION) trial. J Cardiac Failure 2000; 6:276-285.

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

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

Buxton E, Lee KL, Hafley GE, et al. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: an analysis of patients enrolled in the Multicenter Unsustained Tachycardia Trial. Circulation 2002; 106:2466-2472.

Connolly SJ, Gent M, Roberts RS, et al. for the CIDS Investigators. Canadian Implantable Defibrillator Study (CIDS). A randomized trial of the implantable cardioverter-defibrillator against amiodarone. Circulation 2000; 101:1297-1302.

Ezekowitz JA, Justin A, Armstong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Annals Int Med 2003; 138:445-452.

Food and Drug Administration. Summary of Safety and Effectiveness: Request for New Indication as supported by Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). Rockville, MD: Food and Drug Administration, 2002.

Glikson M, Friedman PA. The implantable cardioverter defibrillator. Lancet 2001; 357:1107-1117.

Gollob MH, Seger JJ. Current status of the implantable cardioverter-defibrillator. Chest 2001; 119(4):1210-1221.

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

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

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

Ikeda T, Saito H, Tanno K, et al. T-wave alternans a predictor for sudden cardiac death after myocardial infarction. Am J Cardiology 2002; 79-82.

Kuck KH, Cappato, R, Siebels J, Ruppel R, for the CASH Investigators. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest. The Cardiac Arrest Study Hamburg (CASH). Circulation 2000; 102:748-754.

Lee, DS, et al. Effectiveness of Implantable Defibrillators for Preventing Arrhythmic Events and Death: A Meta-Analysis. Journal of the American College of Cardiology 2003; 41-9:1573-1582.

Mirowski M. The automatic implantable cardioverter-defibrillator: an overview. J Am Coll Cardiol 1985; 6:461-466.

Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980; 303:322-324.

Mirowski M, Reid PR, Winkle RA, et al. Mortality in patients with implanted automatic defibrillators. Ann Intern Med 1983; 98:585-588.

Moss AJ. Implantable cardioverter defibrillator therapy. The sickest patients benefit the most. Circulation 2000; 101:1638-1640.

Moss AJ, Hall WJ, Cannom DS et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl Med 1996; 335:1933-1940.

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

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

Pinski SL, Fahy GJ. Implantable cardioverter-defibrillators. American J Med 1999; 106(4):446-458.

Rosenbaum DS, Jackson LE, Smith JM, et al. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994; 330:235-241.

Shamim W, Fracis DP, Yousufuddin M, et al. Intraventricular conduction delay: a prognostic marker in chronic heat failure. Int J Cardiol 1999; 70:171-178.

Sheldon R, Connolly S, Krahn A, et al. for the CIDS investigators. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy. The Canadian Implantable Defibrillator Study. Circulation 2000; 101:1660-1664.

Willerson and Cohn (editors). *Cardiovascular Medicine*. Churchill Livingstone Inc. 1995 (ISBN 0-443-08781-4).

Xiao HB, Roy C, Fujimoto S, Gibson DG. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. Int J Cardiol 1996; 63:163-167.