

**Initial Interim Public Comments for
Implantable Defibrillators
CAG-000157R1
March 30-April 30, 2004**

Comment #1:

Submitter: Dr. John Kall

Organization:

Date: April 28, 2004

Comment:

I have experienced several deaths in patients with QRS duration <120 ms who would otherwise met MADIT II criteria, and who otherwise have an intact functional class (including active employment and families). Today was one of those troubling days in this regard. I understand that AICDs should not be placed in all patients meeting "implant criteria", but excluding a large number of patients who would benefit from lifesaving therapy is very concerning. I have been placed repeatedly in a difficult situation when astute patients understand the role of prophylactic devices yet see their insurance companies deny reimbursement. I am pursuing alternative treatment strategies such as MADIT I protocols, and doing the best as possible. I am considering less expensive devices but I suspect that we will revisit the variety of technical issues experienced in the early '90's with "limited-capability" devices, likely ultimately resulting in more expensive therapy, not less. Hopefully we can strike a happy compromise and save more lives worth saving. Thank you again for your attention on this difficult but very important problem.

Comment #2:

Submitter: Rahul N. Doshi, MD, FACC

Organization: Sunrise Hospital and Medical Center/Cardiovascular Consults of Nevada

Date: April 28, 2004

Comment:

I am sending this email in regards to the upcoming CMS decision regarding the expanded population for ICD implantation after the results of the SCD-HeFT trial, presented by Dr. Bardy, at this year's ACC meeting in New Orleans.

I was fortunate enough to be at the presentation, and also at the ensuing press conference (because of the trial I presented).

There are three very striking things about the presentation and the data. The first is the absolute simplicity of the trial. Given this very straightforward comparison between the

ICD and amiodarone or placebo, the data is very powerful in supporting the use of prophylactic ICD implantation in the heart failure population with an ejection fraction of 35% or less. The trial is in this regards very similar to another very powerful trial, the MADIT II trial.

The second is how well treated this group of patients was. Despite the low overall mortality, the ICD was shown to be superior.

The third is the absolute insistence from Dr. Bardy in cautioning the interpretation of subgroup analysis. Post hoc analysis is always difficult to interpret and there will always be groups that fall out when enough groups are analyzed.

I strongly believe that it is time to change our mode of thinking. All this time, we have been looking for a way to predict ICD therapy, and in this population only implant ICDs. We have to start looking for a way to predict a complete lack of ICD therapy--ie, a test with perfect negative predictive value. Given that we have a way to save these patients with a procedure with so little morbidity/mortality, I do not see any other alternative.

Comment #3:

Submitter: Ron J. Haberman, MD

Organization: Health Care Rhythm Associates, P.C.

Date: April 28, 2004

Comment:

I am a cardiac electrophysiologist and I dedicate my life to treating patients with heart rhythm problems.

As you may be aware, sudden cardiac death (SCD) claims the lives of well over 300,000 Americans each year. The vast majority of these people die suddenly and without any warning. As such, most of them don't have the option of seeking help after a "small event" since they are already dead with that first event. The abnormal rhythms which kill these people are almost always as a result of scarring in the heart muscle from either prior heart attacks, viruses, or one of several other disease processes. The common denominator in all of these people is abnormal heart muscle function. Even without any extra beats on their EKGs or symptoms of dizziness or passing out all of these people are at higher risk of SCD. Specialists in my field have known this for years, but it took the SCD-HeFT trial to prove it. The people at the greatest risk are the elderly, and in the Medicare age range, since they are the ones most likely to have had prior heart attacks.

I urge you and your colleagues to adopt the criteria used in the SCD-HeFT patient population and apply them to Medicare patients without changing them (as was done with the MADIT II trial). In this manner we can save the lives

of hundreds of thousands of Americans each and every year.

Comment #4:

Submitter: Kataneh Maleki, MD

Organization:

Date: April 28, 2004

Comment:

I, Kataneh Maleki, am an electrophysiologist practicing in Pennsylvania. I see a lot of patients with depressed left ventricular function and ejection fraction less than 30%, meeting the criteria for ICD implant based on MADIT II trial. Some do not have wide QRS but have non sustained ventricular tachyarrhythmias; these patients usually undergo electrophysiology study and all of them are inducible easily and the electrophysiology study that usually takes 1-2 hours will be very short and only 10-20 minutes. I have seen patients who received biventricular ICD based on Companion trial and 1 month after implant the patient received an appropriate shock for VF, and some of them did not even have NSVT!

Patients with ejection fraction less than 35% are at high risk of sudden cardiac death and this has been shown with strong data in different trials (Definite, Companion, SCD-Heft and so on). Dont we have enough evidence already?

I personally think that based on the results of these trials, Medicare should review its policy and expand the coverage for ICD implant in appropriate patients. This will prevent unnecessary testing and of course cost.

To a brighter future

Comment #5:

Submitter: Hans J. Moore, MD, FACC

Organization: Tesatamur NASPE

Date: April 28, 2004

Comment:

As a practicing board certified electrophysiologist I would like to provide comment on the coverage issue for patients with LVEF <35% and NYHA FC II-III CHF. The concordant results of the SCD-Heft trial with the MADITI-II trial support the use of ICD's in this population.

I believe the therapy should be made available to all patients who fit the enrollment criteria of SCD-Heft. Additional data will be necessary for verification, but limited pre-implantation electrophysiologic testing seems prudent to allow for proper device selection, however that selection should be left up to the prescribing electrophysiologist.

The CMS should restrict the implantation of these devices to individuals with appropriate training and credentials, as has been recommended and set forth in guidelines promulgated by the American

College of Cardiology and NASPE- The Heart Rhythm Society. This will insure that a large pool of highly trained and knowledgeable specialists are involved in ICD prescriptions. Much the same way the FDA limits prescribing of certain pharmacotherapeutics. I am concerned that without this limitation, patients will receive improper therapy by less knowledgeable physicians, and there will be an increased potential for fraud and abuse related to remuneration.

Further clarification with regard to age limitations and comorbidities could (and probably should) be listed in trying to identify which patients should be excluded from this potentially life-prolonging therapeutic option.

Nevertheless, the opinion of a board certified electrophysiologist should be the determining factor.

Comment #6:

Submitter: Karthik Ramaswamy, MD, FACC

Organization: Northeast Georgia Heart Center

Date: April 28, 2004

Comment:

In view of the recent SCD-HFT trial, I encourage the Centers for Medicare and Medicaid Services to expand coverage for ICDs to include the population studied in the trial. I feel strongly that the appropriate cardiovascular device for heart rhythm and heart failure patients needs to be at the medical discretion of the treating physician, who is in the best position to select the most appropriate device for the specific patient. Stipulating device choice in regulation would be poor public health policy and could potentially harm patients.

Numerous Americans will benefit in terms of quality and quantity of life.

Comment #7:

Submitter: Arjun Sharma, M.D.

Organization:

Date: April 29, 2004

Comment:

I am commenting on the SCDHeFT trial as an investigator. The primary endpoints were prespecified and the data strongly suggest that in the patient population with LVEF <35% have improved survival with the ICD compared to either amiodarone or placebo. Dr. Bardy has examined a large number of subsets and while this is of academic interest to generate hypotheses for future studies it is not appropriate to base major clinical

decisions on subset analysis. It is my sincere hope that CMS uses only the primary trial results in the reimbursement scheme.

Comment #8:

Submitter: Robert A. Sorrentino, MD

Organization: Duke University Medical Center

Date: April 29, 2004

Comment:

I am the Clinical Director for the Cardiac Electrophysiology Service at Duke University Medical Center in Durham, NC. I work with 5 other electrophysiologists at this academic center. The recent results from DEFINITE, COMPANION, and SCD-HeFT trials DO support expanded Medicare coverage for ICD and CRT+ICD, for patients who meet the entry criteria demographics as stipulated by the specific clinical trials. Specifically, the data obtained from the patients enrolled in the SCD-HeFT trial shows a clinically and statistically significant benefit from ICDs implanted in heart failure patients with a left ventricular ejection fraction of $\leq 35\%$. I urge you and your colleagues to review the data available and I recommend that CMS provide full coverage for the heart failure patient population at risk as defined in these studies. I strongly feel that the appropriate cardiovascular device for heart rhythm and heart failure patients needs to be at the medical discretion of the treating physician and evidence based. The treating physician is in the best position to select the most appropriate device for the specific patient. Stipulating device choice in regulation would be poor public health policy and could potentially harm patients. Providing optimal care to patients is everyone's goal.

Comment #9:

Submitter: Robert M. Belt, M.D.

Organization:

Date: April 29, 2004

Comment:

I am an electrophysiologist practicing in Knoxville, Tennessee.

I am pleased that Medicare covers at least a portion of patients in the MADIT II population. T wave alternans helps me risk stratify the narrow QRS complex MADIT II that Medicare otherwise denies for AICD implantation. Except in rare cases, T Wave alternans positive patients are found to have inducible VT and subsequently get an AICD.

With the findings from SCD-HeFT, it is now apparent to me that all patients with left ventricular ejection fraction less than 35 % should have AICD implant if they are otherwise likely to live greater than one year and if the patient wants to prevent sudden arrhythmic death. An EP study is not as good at risk stratifying as we all once thought.

Please note that QRS duration was not a risk stratifying discriminator in this study. Thus it is my opinion that the restriction for covering AICD for only ischemic cardiomyopathy patients with QRS wider than 120 ms should be removed. The restriction for the presence of prior myocardial infarction should be removed.

AICD are too expensive. I would like to see the price tag for AICD come down. Hospitals do a good job of negotiating, but regardless of the hospital's efforts, the Medicare reimbursement to hospitals often does not even cover the cost of the device. AICD implant is a money loser for hospitals. This results in hospital administrators defining what type of device can be implanted, and even covert and overt discouragement for implanting or replacing AICD in their hospital. Why is the hospital responsible for paying for the difference that Medicare does not cover for AICD implantation?

I ask for CMS to fully cover AICD implantation for the population defined by SCD-HeFT. I ask that CMS not try to dilute the results by inappropriate subanalysis, as they did for the MADIT II. I ask for CMS to adequately reimburse hospitals an adequate amount for this life-saving therapy. Finally, I ask that device companies bring the cost of AICD down.

Thank you for your consideration in this matter.

Comment #10:

Submitter: Kevin Wheelan, MD

Organization: Baylor University Medical Center

Date: April 29, 2004

Comment:

I am writing in strong support of Medicare providing full coverage for prophylactic ICD implantation in patients with LVEF less than or equal to 35%. Recent data from 2 large well designed trials both resoundingly confirm the life preserving benefit of this therapy. The SCD-HeFT trial answered the question that this benefit applies to both ischemic and non-ischemic patients .

I believe that qualified specialists in the field of electrophysiology should be allowed to choose the appropriate type of device for this population and that not all patients would be best served by a simple VVI-ICD. Many of these patients have other types of rhythm disturbances or clinical problems and individualized care is always best.

The number of patients who receive this therapy will not be excessive or cause undo financial strain on our health care system. Cost effectiveness studies have shown ICD treatment to be less expensive than dialysis in life years saved. Electrophysiologists will use prudent clinical decision making in selecting patients with reasonable life expectancy before advocating a surgical procedure for these patients.

I appreciate your consideration of my thoughts

Comment #11:

Submitter: Peter Ott, MD, FACC

Organization: Sarver Heart Center, University of Arizona Health Sciences Center

Date: April 29, 2004

Comment:

Recent clinical trials overwhelmingly and clearly show that selected patient populations derive a clinically significant survival benefit when treated with an ICD on top of optimal medical therapy. Sudden cardiac death is prevented - the patient lives.

We as electrophysiologists see "saved" patients on a weekly basis in our defibrillator clinic! - The patients show up with documented ventricular fibrillation on the ICD log - successfully treated and sudden death prevented - a powerful testimony.

I strongly recommend the most recent publication in Circulation 2004; 109: 1848 - by Saluke et al: analysis of 7 large ICD trials revealed that in order to gain one year of life, one has to treat 2 - 11 patients with and ICD for 3 years - this is a far better number when compared to cholesterol lowering therapy and beta blocker therapy for CHF - two therapies widely accepted and supported.

Regarding costs: we have all seen a decrease in device cost - there is a large push to implant less complex ICD 's (less costly) - device companies are competing to become the "preferred" ICD vendor thus pushing prizes down without sacrificing quality and service.

Clinical trial results are publicized and patients - rightfully ask if they should have an ICD - the coverage issue must not be a factor in this decision process

Comment #12:

Submitter: James H. Kappler, MD

Organization: Michigan Heart PC

Date: April 29, 2004

Comment:

The electrophysiologists at St. Joseph Mercy Hospital and Michigan Heart have requested I speak on behalf of the five of us involved in the SCD-HeFT trial. We feel strongly that the data presented at the 2004 ACC meetings be assessed in total and that patients with both severe LV dysfunction and NYHA Class II and III CHF be considered to be at significant sudden death risk such that prophylactic ICD implantation is advised. We believe post-hoc sub-group analysis should be reserved for formulating questions for future study and that policy should not be generated on the basis of data which has inadequate power to provide a meaningful conclusion. We feel a situation similar to the decision put forth by CMS with respect to QRS duration as restriction to device implantation for a population (MADIT II) at risk should be avoided in this population being reviewed. Thanks for the opportunity to voice our concerns.

Comment #13:

Submitter: Michael L. Markel, MD

Organization:

Date: April 29, 2004

Comment:

I am writing to you regarding Medicare reimbursement for Implantable Cardioverter Defibrillators (ICDs). As you are aware there have been several trials that have demonstrated the efficacy of these devices for preventing Sudden Cardiac Death and thus also decrease total mortality. Most recently there have been studies (MADIT II, COMPANION, SCD-HeFT, and DEFINITE,) which have demonstrated the efficacy of these devices as primary prevention in patients with low ejection fractions (EF) below 30-35%. The patients in these studies have not had any documented spontaneous life threatening arrhythmia or even symptoms suggestive of life threatening arrhythmia (palpitations with pre-syncope or syncope). The data is becoming very clear. These devices definitely save lives and there are thousands and thousands of Medicare beneficiaries who would benefit from an ICD. Certainly cost issues have constrained the use of these devices. However, I suspect that if you or one of your family members had a low ejection fraction you would want to have the benefit of an ICD. I know I would.

As you are aware patients with heart disease and poor pumping function of their heart (low ejection fraction) also frequently have conduction system disease. Even if the degree of dysfunction is not severe enough to warrant pacing by itself we now know that patients in this situation

definitely get symptomatic benefit from digitalis and life prolonging benefit from Beta-Blockers. These drugs will tend to worsen borderline conduction system function and force the need for pacing. In patients with compromised pumping function of the heart we know that maintenance of the normal pattern of AV synchrony (atrium being activated before the ventricle) is best from a hemodynamic standpoint. If the patients conduction system disease is bad enough (i.e. the PR interval is long enough) right ventricular pacing will be forced. We know now that right ventricular pacing (and in particular right ventricular apical pacing) has deleterious effects on ventricular function and can trigger congestive heart failure (most recently demonstrated in the DAVID trial). In this situation bi-ventricular pacing is best. At the time of implant we also have to judge the likelihood of progression of the patients conduction system disease over the expected longevity of the device (generally 5 years). There are so many scenarios that can occur in a patient of this sort it would be difficult to make a regulation to define the type of ICD which can be implanted without the likelihood of compromising patient welfare and safety. I believe that the type of defibrillator implanted should be left up to the treating electrophysiologist.

Certainly with the thousands of patients involved cost is an issue since these devices are so expensive (especially the bi-ventricular devices). However, a device that is replaced before the end of its useful life because a nonavailable feature is needed (ex. dual rather than single chamber pacing) is much more costly. A new more expensive device is needed and there are the costs of another operation as well as (probably) more time in the hospital. Thus it is always cheaper to do it right the first time. It should not be forgotten that repeat operations also imply more chance for complications and morbidity.

From a cost containment standpoint, I think that it would be reasonable to state that Medicare will pay for these devices for primary prevention but that you can only pay a certain dollar amount (ex. \$8000 for a single chamber device, \$10,000 for a dual chamber device and \$15,000 for a bi-ventricular device). The companies can then offer a de-featured device for these prices (i.e. with some of the bells and whistles locked out of the software). If in the future some of these features are needed then for a fee (pro-rated for the remaining useful life of the device) the necessary feature can be programmed on. If it is presented such that it is either approve payment at "regulated" prices or no approval at all, then I think all of the companies will agree to lower the present prices. The companies already know that the system can't handle the number of expected ICD implants with the current price structure. Certainly with the much larger volume of sales anticipated this should still allow profit to be made. The companies make money, the

patients are taken care of, and hopefully we don't break the bank.

I hope these thoughts are of use to you

Comment #14:

Submitter: Bruce G. Hook, MD

Organization:

Date: April 30, 2004

Comment:

I am writing to ask for the support of CMS in expanding coverage for ICD implants to the entire Medicare population recently studied in the MADIT II and SCD-HeFT trials. I write as a SCD-HeFT investigator, NASPE member, ACC Governor and practicing clinical cardiac electrophysiologist for 11 years. The results of SCD-HeFT represent the largest ICD trial with the longest follow-up ever performed. The results show a significant 23% mortality reduction at 5 years in patients with both ischemic and nonischemic cardiomyopathy. These results essentially confirm the MADIT II data and for this reason I believe coverage should be extended in this population to all patients with an ischemic cardiomyopathy and ejection fraction less than 35%. With 2 trials now showing very similar findings it is clear that the mortality benefit from prophylactic ICD therapy is substantial and our patients should not be denied this treatment. Thank you for your consideration.

Comment #15:

Submitter: Kenneth M. Stein, MD

Organization: Weil Medical Center of Cornell University

Date: April 30, 2004

Comment:

Sudden cardiac death is epidemic in the United States. It accounts for approximately 450,000 deaths annually in the US (Zheng, et al, Circulation 2001;104:2158). This represents about one death every minute - 30 more Americans will die during the time it will take for me to compose and for you to read this email! Given the magnitude of the problem, newly available data from the DEFINITE, COMPANION, and SCD-HeFT trials urgently mandate a reevaluation of Medicare coverage policies for implantable cardiac defibrillators.

A wealth of data from well-conducted and well-performed prospective randomized clinical trials proves that ICDs prolong life in patients with severe ischemic cardiomyopathy (MADIT-II, SCD-HeFT) and in patients with congestive heart failure due to left ventricular dysfunction whether

ischemic or nonischemic in etiology (SCD-HeFT, DEFINITE, COMPANION). These data prove beyond all questioning that it would be appropriate to extend coverage to: A) all patients with a prior myocardial infarction and LVEF $\leq 30\%$ irrespective of QRS width as well as B) extending coverage to all patients with Class II or Class III congestive heart failure and LVEF $\leq 35\%$ irrespective of the etiology of heart failure or the QRS width.

In this context, and in the context of the issues raised during the prior national coverage determination, it is critical to address the effect of ICD implantation on quality of life. Although there are some real concerns regarding quality of life in ICD recipients (inappropriate shocks, driving, etc.) it is worthwhile to note that two prospective studies of ICD recipients have shown that quality of life is at least as good, and for many measures actually better, than quality of life in patients treated with antiarrhythmic medications (Irvine, et al, Am Heart J 2002;144:282 and Schron, et al, Circulation 2002;105:589).

As a community, we have an opportunity to save thousands upon thousands of lives, using an approved technology that has been proven to be safe and effective. I therefore urge you to act rapidly and act decisively so that we can transform this opportunity into reality.

Comment #16:

Submitter: Mark S. Kremers, MD

Organization: Mid/Carolina Cardiology & Electrophysiology Lab Presbyterian Hospital

Date: April 30, 2004

Comment:

I wish to urge CMS to support coverage of ICDs for patients meeting SCD-Heft enrollment criteria based on the excellent science of the study, its large enrollment and its clear outcome showing substantial survival improvement in patients receiving an ICD. As an investigator for the study with a substantial body of enrolled patients I have a first hand and credible experience upon which to support this opinion. I would add that consideration of parsing the coverage to selected subgroups for economic reasons is problematic as the study was not clearly designed to address these issues. While healthcare spending is and should be of concern to all of us, ICD coverage is a minor portion of the overall healthcare budget and ICD value is supported by similar strong scientific studies demonstrating comparable favorable outcomes. Lastly, dictating the type of device to be implanted is unprecedented and mitigates the considerable experience, knowledge, and insight of the MDs involved in these ill patients care. While quality healthcare should insure access to, and implementation of all appropriate therapies of proven benefit, this is not tantamount to "one

size fits all". Healthcare must be appropriately individualized under the direction of qualified and experienced healthcare providers. Thank you for consideration of these comments.

Comment #17:

Submitter: Eric N. Prystowsky, MD

Organization: Past-President of NASPE

Editor-in-Chief, Journal of Cardiovascular Electrophysiology

Date: April 30, 2004

Comment:

I write in support of expanded coverage by CMS for ICDs based on the results of SCD-HeFT.

I am on the Executive committee of the study, and have a conflict of interest as a consultant to Guidant. My comments deal strictly with data interpretation and are not affected by either of the perceived conflicts.

The results of SCD-HeFT support the MADIT 2 data and at the same time provide clinicians with valuable new data on the use of ICDs in patients with nonischemic cardiomyopathy, which has been an area of considerable controversy. Clearly, these data show the lifesaving ability of ICDs in patients who meet entrance criteria for SCD-HeFT, and I strongly recommend that CMS allow payment coverage for such individuals. I hope that CMS does not decide to do their own subgroup analysis to select only a small subgroup that they feel should receive reimbursement, as they did with the MADIT 2 study. The problems with using subgroup analyses for a clinical decision are well documented, and I reviewed them recently in an editorial for *Circulation* (PrystowskyEN: *Circulation* 2004;109:1073-1075). The previous decision by CMS to limit reimbursement in MADIT 2 to patients only if the QRS duration exceeds 120 msec has created a major problem for clinicians. We have data and society recommendations to give ICD therapy to patients who will not be reimbursed for it and cannot afford to pay for it--a tragic outcome for such patients and a source of incredible dismay and frustration for their families. Please do not let this happen again.

Thank you for the opportunity to express my views on this important topic to you.

Comment #18:

Submitter: Bruce L. Wilkoff, MD

Organization: The Cleveland Clinic Foundation

Date: April 30, 2004

Comment:

As the Director of Cardiac Pacing and Tachyarrhythmia Devices and of Clinical Electrophysiology Research at the Cleveland Clinic Foundation I have had the opportunity to directly oversee the care of over 5,000 ICD patients. Over the last 20 years, as an electrophysiologist specializing in pacemakers and ICDs, I have also participated in most of the multicenter randomized clinical trials of ICD therapy that have created the knowledge base on which we have based our current clinical indications for ICD care.

I would like to comment on translating the results of the current ICD clinical trials, including SCD-HeFT into clinical practice. Overall, it would be unwise to view any of the trials in isolation and it would also be unwise to limit the application of the trials to subsets of patients examined within the trials. The recent trials that need to be considered are the DAVID, DEFINITE, SCD-HeFT and COMPANION trials. The overall theme in these trials are the impact of implantable devices on heart failure symptoms and survival. Clearly our understanding is still incomplete, but there is no doubt that cardiac pacing can improve or deteriorate left ventricular function, heart failure symptoms and survival. Additionally and most importantly, ICDs improve survival in patients with significant heart failure symptoms.

The issue is how should we treat these patients in light of the trials. Also the question is what are the alternatives? Overall the theme seems to be that implantable defibrillation, avoidance of right ventricular pacing and inclusion of resynchronization therapy are directions that are supported by the data and that although further refinements of our understanding will occur it is likely that these principles will continue to be supported. In addition, and perhaps most troubling is that Amiodarone, once thought to be safe and most effective in patients with advanced heart failure appears to at very least not be effective in preventing sudden cardiac death, but perhaps dangerous in patients with advanced heart failure symptoms. This increases the importance of ICD therapy in patients with moderate to severe heart failure.

In data that has been submitted for publication from the DAVID dataset combined with the AVID dataset it appears that DDDR pacing in ICD patients may be as bad as (both heart failure hospitalization and death) Amiodarone in patients indicated for secondary prevention ICDs. However remember that the DAVID data was collected with patients implanted with Dual Chamber ICDs and that the only the mode was programmed to ventricular backup pacing. There are other important clinical reasons for implanting the atrial lead. Prominently is the use of tachyarrhythmia detection algorithms to reduce the incidence of inappropriate therapies for supraventricular arrhythmias and reducing the morbidity of ICD therapy. Currently, DAVID II is enrolling patients to explore the use of the AAI mode in these patients. We are not certain of the role of the atrial lead for these patients, but there is no data that says that the atrial lead is dangerous to the patient. The decision is a clinical decision and should be the purview of the physician. Many of these patients should get a single lead system, but many should get dual lead systems. The most expensive decision is the one that ends up with a second surgery to add the second lead when the patient subsequently proves the need for the other lead. This decision should be left up to the Cardiologist not to the reimbursement system. Almost

all of the randomized ICD clinical trial data has been collected with ventricular backup pacing, but if only single chamber devices are paid for in NYHA functional class II patients, it will be easy for the physician to discover times or days when the patient is NYHA functional class III and then justify the implantation of the still more expensive BiV device. The decision should be kept with the Cardiologist.

In my view, NYHA functional class II and III heart failure are ICD indications and NYHA functional class III symptoms with ventricular dysynchrony is a BiV ICD indication. This is supported by the entire mosaic of ICD and BiV studies. COMPANION is very compelling for ICD implantation in both ischemic and non-ischemic patients. SCD-HeFT is very compelling, particularly in NYHA functional class II patients, but in light of COMPANION and DEFINITE is supportive of ICD implantation particularly in non-ischemic patients. However excluding certain subgroups from ICD implantation payment, particularly NYHA functional class III patients, would be a mistake particularly since it would end up encouraging the physicians to choose the more expensive BiV system. Physicians are aware of the difficulty and expense associated with BiV systems and will make rational choices. Often the choice will be a single chamber device, but this should be modified according to the clinical situation as determined by the physician.

To be clear, I believe that CMS should designate patients with NYHA functional class II and functional class III heart failure with either ischemic or non-ischemic etiologies for their heart failure for payment of the ICD implantation and follow-up. In addition, I believe that if the patient also has ventricular dysynchrony that the patient is indicated for a BiV ICD provided the patient has NYHA functional class III heart failure symptoms. These patients should have these symptoms despite treatment with beta blockers and ACE inhibitors. Although I am a strong proponent of ventricular backup pacing in ICD patients with pacing indications and without functional class III heart failure, I often choose to implant a dual chamber device and use the atrial lead for AAI pacing to support the modest bradycardia these patients get from the beta blockers and use the atrial lead for SVT discrimination and diagnostics. Physicians should continue to have a choice of the mode of pacing required for their patients requiring ICD therapy.

Thank you for the opportunity to comment on these issues

Comment #19:

Submitter: Michael Cain, MD

Organization: NASPE Heart Rhythm Society

Date: April 30, 2004

Comment:



NASPE Heart Rhythm Society

April 30, 2004

Sean Tunis, MD
Chief Medical Officer
Director, Office of Clinical Standards and Quality
7500 Security Boulevard
Mailstop S3-02-01
Baltimore, MD 21244-1850

Dear Dr. Tunis,

NASPE-Heart Rhythm Society respectfully submit this letter regarding the **NCA Tracking Sheet for Implantable Cardioverter Defibrillators (ICDs) (CAG-00157R1)** as posted on the Centers for Medicare and Medicaid Services (CMS) website. NASPE-Heart Rhythm Society represents heart rhythm specialists who diagnose and treat Medicare beneficiaries with heart rhythm and heart failure diagnoses and work to prevent sudden cardiac death in specific patient populations.

We have reviewed data from the DEFINITE, COMPANION, and SCD-HeFT trials. The totality of the data support expanded coverage for ICD and CRT+ICD for patients who meet the entry criteria demographics as stipulated by the specific clinical trials. We look forward to discussing these data in much greater detail directly with CMS next month.

Specifically, the data obtained from the patients enrolled in the SCD-HeFT trial, which prompted the opening of the ICD coverage decision, shows a clinically and statistically significant benefit from ICDs implanted in heart failure patients with a left ventricular ejection fraction of $\leq 35\%$. We look forward to reviewing the data in greater detail once it is published in the peer reviewed medical literature. However, judging from the data available as of now, we do recommend that CMS work towards providing full coverage of the SCD-HeFT patient population.

We understand CMS is seeking evidence pertaining to the selection of the appropriate defibrillator for specific patient populations. NASPE-Heart Rhythm Society believes strongly that the appropriate cardiovascular device for heart rhythm and heart failure patients needs to be at the medical discretion of the treating physician who is in the best position to select the most appropriate device for the specific patient. For example, there are selected patients who require the atrial lead and a dual chamber device because of

standard "bradycardia" indications who also meet SCD-HeFT indications for an ICD. It would be poor public health policy to mandate and only reimburse for the single chamber ICD, when a dual chamber ICD is indicated because of coexisting sinus node dysfunction or significant conduction system disease. Moreover, other ICD candidates may have indications for biventricular pacing.

We look forward to our meeting in early June where we will have the opportunity to discuss these issues in greater detail. We appreciate your consideration of these comments and your willingness to meet with the leadership of our organization.

Comment #20:

Submitter: Michael J. Coyle

Organization: St. Jude Medical, Cardiac Rhythm Management Division

Date: April 30, 2004

Comment:

April 30, 2004

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: National Coverage Analysis (NCA) of Implantable Cardioverter Defibrillators (ICDs)
(# CAG-00157RI)

Dear Dr. Phurrough:

St. Jude Medical, Inc., a developer, manufacturer, and distributor of innovative medical devices including implantable cardioverter defibrillators (ICDs), commends the Centers for Medicare & Medicaid Services (CMS) for its consideration of expanded indications under the National Coverage Determination for Implantable Cardioverter Defibrillators (35-85) to include patients with a presence of NYHA Class II and III congestive heart failure, a left ventricular ejection fraction of equal to or less than 0.35, and no prior history of ventricular tachyarrhythmias (i.e. the SCD-HeFT study criteria).

St. Jude Medical strongly recommends that CMS cover the unrestricted use of ICD therapy for primary prevention of all-cause mortality in all patients who meet the SCD-HeFT criteria based upon the available scientific evidence.

We base this recommendation on the following:

- The SCD-HeFT clinical trial was a well-designed, high quality, NIH sponsored, randomized prospective controlled trial evaluating the use of ICD therapy versus

conventional medical therapy versus conventional medical therapy plus amiodarone in a large patient population with a high risk of arrhythmic mortality.

- ICD therapy is known, from previously performed controlled clinical trials, to clearly benefit patient populations at high risk of arrhythmic mortality, as well as all-cause mortality, as compared to conventional medical therapies.
- SCD-HeFT demonstrated a statistically significant reduction in all-cause mortality (the primary endpoint) associated with ICD treatment as compared with conventional medical therapy which included high compliance with appropriate prescription of ACE inhibitors, beta blockers, and lipid-lowering pharmacologic therapies, as well as compared to conventional medical therapy plus amiodarone.
- SCD-HeFT outcome results are compelling with a hazard ratio of 0.77 favoring ICD therapy and a relative reduction of overall mortality of 23% as compared with conventional medical therapy plus amiodarone. SCD-HeFT outcome results also demonstrated no statistically significant difference with the use of amiodarone alone as the primary therapy as compared with conventional medical therapy.
- SCD-HeFT outcome results are particularly compelling in that the data from the SCD-HeFT non-ischemic cardiomyopathy patient cohort corroborates the evidence for ICD therapy in that patient cohort provided by the DEFINITE Study. The DEFINITE Study outcome results demonstrated a hazard ratio of 0.65 favoring ICD therapy and a relative reduction of overall mortality of 35% as compared with conventional medical therapy.

SCD-HeFT provides very strong evidence that ICD therapy is indicated for primary prevention of all-cause death in patients with a presence of NYHA Class II and III congestive heart failure, a left ventricular ejection fraction of equal to or less than 0.35, and no prior history of ventricular tachyarrhythmias.

A decision to limit coverage to only a subset of SCD-HeFT patients, for example those who are NYHA Class II, would be inconsistent with the findings of the SCD-HeFT trial, which demonstrates a significant reduction in the risk of death for all patients who received ICD therapy. We believe it could be potentially misleading to perform sub-analysis of variables for which there were no a priori hypotheses and for which sufficient statistical power does not exist to answer these additional questions. Data resulting from these types of sub-analyses could be used to generate additional research questions, but are of questionable value in supplying evidence needed to make a coverage determination. Because SCD-HeFT is a landmark clinical trial that shows a clinically and statistically significant benefit from ICDs, full coverage of the SCD-HeFT patient population should be granted.

St. Jude Medical believes that significant and compelling scientific evidence has been provided to CMS in the SCD-HeFT clinical trial to clearly demonstrate that the use of ICD therapy significantly reduces all-cause mortality compared to conventional medical therapy and is appropriate, reasonable and necessary for the treatment of patients with

NYHA Class II and III congestive heart failure, a left ventricular ejection fraction of equal to or less than 0.35, and no prior history of ventricular tachyarrhythmias.

We feel strongly that coverage policy should not mandate device choice for specific patient populations since clinical differences between patients require different treatment strategies. We believe that physicians are in the best position to determine the most appropriate device for patients based on the specific and unique circumstances of each individual case. For example, for patients with paroxysmal AF or 1:1 retrograde VT, there is a need for dual chamber SVT/VT discrimination features which can reduce morbidity from inappropriate shocks. Patients with a standard indication for bradycardia pacing may require dual-chambered pacing as a treatment option in addition to receiving ICD treatment of their ventricular tachyarrhythmias. Various versions of ICD devices also provide diagnostic information for accurate arrhythmia management (e.g., dual chamber EGMs). And, finally, there is a need for flexibility as patients' conditions often change from disease progression resulting in the need to upgrade device therapy and tailor it to the patients' specific needs. For example, over 25% of patients develop or are first diagnosed with atrial fibrillation after they have had a device implanted. To optimize patient care, device choice must remain with the physician, not set in policy.

We are pleased that CMS is reviewing other recent clinical studies such as DEFINITE and COMPANION as part of the NCA. We believe that these studies are consistent with and add to the body of evidence supporting the use of ICDs in the SCD-HeFT patient population.

We believe that the DEFINITE clinical study provides significant and compelling scientific evidence, especially when combined with the SCD-HeFT clinical trial non-ischemic cardiomyopathy patient data, to clearly demonstrate that the use of ICD therapy significantly reduces all-cause mortality compared to conventional medical therapy and is appropriate, reasonable and necessary for the treatment of non-ischemic cardiomyopathy patients with NYHA Class II and III congestive heart failure, a left ventricular ejection fraction of equal to or less than 0.35, and no prior history of ventricular tachyarrhythmias. The combined results of DEFINITE and SCD-Heft in the non-ischemic cardiomyopathy population support a coverage decision of this patient group [the DEFINITE indications].

With regard to the COMPANION study, we believe that these results also support those of SCD-Heft and DEFINITE for Class III combined ischemic and non-ischemic patients with a hazard ratio of approximately 0.62 favoring CRT-D therapy and a relative reduction of overall mortality of 38% as compared with conventional medical therapy for heart failure.

We further recommend that all patient populations currently indicated for ICD therapy, including the patient population represented in the MADIT and MADIT II clinical trials, should continue to be covered as reasonable and necessary under CMS' National Coverage Determination. In addition, the results of the DINAMIT Study, a trial that investigated the benefit of implanting ICDs in the period immediately following an acute MI, do not support changing CMS coverage guidelines with regard to waiting 1 month after an AMI to implant an ICD in the MADIT II population.

St. Jude Medical appreciates the opportunity to comment regarding CMS' National Coverage Analysis of Implantable Cardioverter Defibrillators.

Comment #21:

Submitter: Nancy Miller

Organization: Thoracic & Cardiovascular Healthcare Foundation

Date: April 30, 2004

Comment:

Dr. Ip at our site was one of the highest enrollers in the Scdheft Trial. We enrolled 79 subjects. We strongly believe in the study results and totally support the implant of ICD for this patient population. We believe these patients would benefit from more than just a "shock box".

Comment #22:

Submitter: Harold R. Goldberg, MD, FACC

Organization: Spokane Cardiology

Date: April 30, 2004

Comment:

I am writing to you regarding CMS consideration of prophylactic defibrillator implantation and expanding indications.

I know that your department presently is evaluating new information regarding the sudden cardiac death in heart failure trial (SCD-HeFT).

It is clear that this study demonstrates a significant benefit in survival with prophylactic defibrillator implantation in patients with an ejection fraction of less than 35%.

Obviously we recognize the cost to the healthcare system to expand these indications. Nevertheless, the science unmasked by this type of study demands an appropriate response with regard to protecting patients from sudden death that can be avoided.

Further science dictates in the MADIT-II trial that patients even with narrow QRS benefited from defibrillator implantation. I do not believe it is appropriate for CMS to be restricting therapy based on the benefit of subgroup analysis when in fact subgroup analysis demonstrates that even patients with narrow QRS continue to benefit (albeit not to the extent of the wide QRS group).

I am looking forward to an objective review of the data and am fully

cognizant of the economic implications of this to the healthcare system. The cost benefit ratio of all modalities of therapy, for all medical problems frankly need to be on the table for discussion.

Your consideration is appreciated.

Comment #23:

Submitter: Mark Wathen, MD

Organization: Vanderbilt University

Date: April 30, 2004

Comment:

Dear CMS Panel,

I appreciate your efforts to read comments from the clinical field regarding heart failure mortality risk reduction. I am an Electrophysiologist, SCDHeFT investigator, and ICD researcher.

Survival from sudden death remains abysmal. AEDs will improve survival in selected sites

Consequent to the low survival rate, the best approach seems prophylactic therapy. Every therapy to date that has reduced cardiac mortality has done so principally through sudden death reduction: beta blockers, ACE inhibitors, spironolactone. Even coronary artery bypass therapy reduces mortality principally by reduced SCD. Direct SCD therapy with ICDs only logically follows. In fact, the amount of life saved by ICD therapy in the SCDHeFT trial is an absolute 7% whereas coronary artery bypass surgery yields only 7% risk reduction only in left main disease which represents only a small minority of surgeries. The absolute amount of mortality reduction by any other cardiovascular therapy is lesser. How could we justify coronary artery bypass expense in the US without also approving ICD therapy for CHF class II and III as per the SCDHeFT trial?

Should the ICD platform used in a trial be the only platform approved for implant by CMS? Should the ICD platform used in a trial be the only platform approved for implant by CMS? As expected from the standpoint of a clinician, this feels too restrictive. This seems like approval of carvedilol for CHF mortality reduction but not some other beta blocker. This approach to the approval process would halt medical therapeutic pharmaceutical development because the only way a new drug could be utilized for each indication is for it to be tested for each indication. No one is interested in such duplicative research and the costs would only climb. What would be the result? Less competition for each drug type and monopoly on therapy would become the standard. Ethical considerations would prevent 2nd or 3rd drugs being tested or new ICD platforms. Demanding the same ICD platform for approval would also be like demanding identical coronary artery bypass techniques used in the 1980's be performed in 2004. What would be the benefit? Reduced cost? How would a permitted monopoly for Medtronic lower cost of the ICD? Not likely.

Can we at least restrict ICD usage at another broader level. Say for example approving “shock only ICDs” as programmed in the SCDHeFT trial. I would not favor such approach. In this specific example, this approach would prevent use of anti-tachycardia pacing (ATP). ATP has been shown to reduce ICD shocks by over 90%. The PainFree trials have shown that 93-97% of all ventricular arrhythmias can be treated by ATP with around 90% success without increasing any of the adverse outcomes of: syncope, acceleration of VT to VF, duration of VT/VF, or sudden death. To patients who have received shocks, the single most important determinant of their quality of life is a subsequent shock. This quality of life effect is greater than CHF admissions or angina pectoris.

There seems to be a misperception about the quality of life of patients who wear ICDs. As with any therapy, quality of life has been assessed on a population basis. ICD patients have consistently shown improved quality of life compared to baseline whether measured at 3, 6 or 12 months post implant. As a population they have usually progressed to mid or late stage in their cardiac disease process. However, their QoL measurements have been shown to be equivalent to a general population of angina pectoris patients and also to a general pacemaker population. As mentioned above their QoL is adversely affected by shocks. However, even patients with > 5 shocks have not shown absolute reduction in QoL but rather simply lack of the expected improved QoL scores.

Comment #24:

Submitter: Michael J. Wolk, MD, FACC
Organization: American College of Cardiology
Date: May 18, 2004
Comment:

The American College of Cardiology (ACC) is a 30,000 member non-profit professional medical society and teaching institution whose purpose is to foster optimal cardiovascular care and disease prevention through professional education, promotion of research, and leadership in the development of standards and formulation of health care policy. The College represents more than 90 percent of the cardiologists practicing in the United States.

The ACC appreciates the ability to provide comments to CMS on the **NCA Tracking Sheet for Implantable Cardioverter Defibrillators (ICDs) (CAG-00157R1)** as posted on the Centers for Medicare and Medicaid Services (CMS) website.

ACC has reviewed data from recent ICD clinical trials (DEFINITE, COMPANION, AND SCD-HeFT) and believe it is important for CMS to evaluate coverage for these populations based on patients who meet the entry criteria demographics as stipulated by the specific clinical trials.

Preliminary review of the data obtained from the patients enrolled in the SCD-HeFT trial shows favorable results. We believe, however, that a more extensive review of the data is needed once peer reviewed medical literature is available and we welcome the

opportunity to provide further comments to CMS. This additional review will determine the appropriate expansion of ICD coverage to patients fitting the SCD-HeFT clinical criteria.

We understand CMS is seeking evidence pertaining to the selection of the appropriate defibrillator for specific patient populations. We feel strongly that the appropriate cardiovascular device needs to be at the medical discretion of the treating physician who is in the best position to select the most appropriate device for the specific patient.

We look forward to discussing these issues with CMS in greater detail in the near future.

Comment #25:

Submitter: Bruce Perlman

Organization:

Date: May 17, 2004

Comment:

I am an implanting electrophysiologist, but I have several reservations regarding SCD-Heft.

Neither SCD-Heft nor MADIT-II randomized patients to screening versus empirical therapy but rather used historical data. Since many of the patients were from prescreened referral populations, they may not directly apply to general populations.

There was a disproportionate benefit seen in patients from outside the US. I feel that the data set should be reevaluated for US sites only.

The study included only classes II and III CHF and no benefit was seen for class III. There should be more study regarding the potential benefit for classes III and IV, which may not have significant benefit at all.

Class II patients may receive a benefit but I would like to see the event rate and the number of devices required to achieve a significant benefit - class II may require prescreening to maximize benefit.

We need more data regarding the question of age on the results. A significant difference was seen between the < 65 and > 65 groups. Neither addressed the fact that a significant number of the patients referred for empirical ICD's are > 80.

I would also like to see data regarding the presence or absence of significant arrhythmia related symptoms - I did not see it in the data I personally received. This would include dizziness, syncope, palpitations, near syncope, and for cardiomyopathies, the family history of sudden death.

Comment #26:

Submitter: Richard J. Cohen

Organization:

Date: May 14, 2004

Comment:

I am writing in connection with your preparation for CMS of a national coverage determination for ICD implantation. I know that David Chazanovitz of Cambridge Heart, Inc has written to you with regard to use of Microvolt T-Wave Alternans (MTWA) testing as a non-invasive risk stratifier in patients being considered for ICD implantation, in view of the outstanding negative predictive value of MTWA testing. Patients who test MTWA negative are at an extraordinary low risk of sudden cardiac death and cardiac arrest. I believe that Mr. Chazanovitz requested a meeting to discuss this issue, and I would of course look forward to participating.

At the moment I wanted to send to you two publications. One paper is an outcomes study published in the Lancet of MADIT-II patients who had undergone MTWA testing. I believe that I sent you this paper in manuscript form during the previous National Coverage Determination for ICDs, but I am not sure that you have the published article. The second paper is a review article that I wrote for Cardiac Electrophysiology Review specifically addressing the clinical use of MTWA to risk stratify MADIT-II patients.

Research letters

T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation

S H Hohnloser, T Ikeda, D M Bloomfield, O H Dabbous, R J Cohen

In a trial of prophylactic implantation of a defibrillator, a mortality benefit was seen among patients with previous myocardial infarction and a left-ventricular ejection fraction of 0.30 or less. We identified 129 similar patients from two previously published clinical trials in which microvolt T-wave alternans testing was prospectively assessed. At 24 months of follow-up, no sudden cardiac death or cardiac arrest was seen among patients who tested T-wave alternans negative, compared with an event rate of 15.6% among the remaining patients. Testing of T-wave alternans seems to identify patients who are at low risk of ventricular tachyarrhythmic event and who may not benefit from defibrillator therapy.

Lancet 2003; **362**: 125–26

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In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)¹ among 1232 patients with previous myocardial infarction (MI) and left-ventricular ejection fraction of 0.30 or less, prophylactic defibrillator therapy reduced mortality from 19.8% to 14.2% (absolute mortality reduced by 5.6%) over an average of 20 months. Therefore, 18 defibrillators would need to be implanted to save 20 months of life. Thus, implantation of defibrillators in all MADIT II-type

patients would subject a large group of patients to costly invasive therapy to extend life in only a small proportion.

Microvolt T-wave alternans testing²⁻⁴ involves analysis of variation in microvolt level in the morphology of electrocardiographic T wave, on an alternate-beat basis, during exercise stress. T-wave alternans testing is non-invasive and is proven to be a highly specific and sensitive predictor of the occurrence of ventricular tachyarrhythmic events. The test compares favourably with invasive electrophysiology testing and other non-invasive risk-stratification methods. We assessed the role that non-invasive T-wave alternans testing might have in the prediction of tachyarrhythmia in MADIT II-type patients by analysis of data pooled from two previously published studies, in which microvolt T-wave alternans was prospectively assessed as a risk stratifier for ventricular tachyarrhythmias in patients without known previous sustained ventricular tachyarrhythmias. Ikeda and colleagues⁴ studied 850 consecutive MI survivors who underwent T-wave-alternans testing a mean of 2.7 months after MI. Klingenheben and colleagues³ studied 107 consecutive patients with New York Heart Association class II and III heart failure and no MI in the previous 6 weeks. We analysed all patients in the two studies who had previous MI and left-ventricular ejection

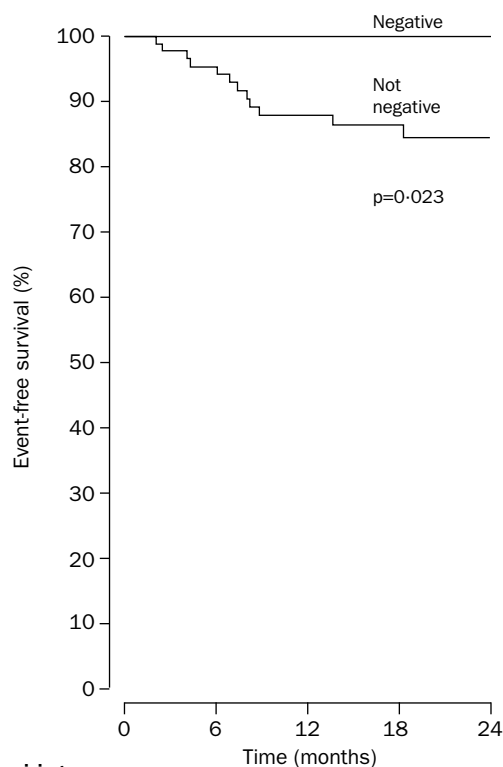


Figure 1: Event-free survival for primary endpoint according to outcome of T-wave alternans test

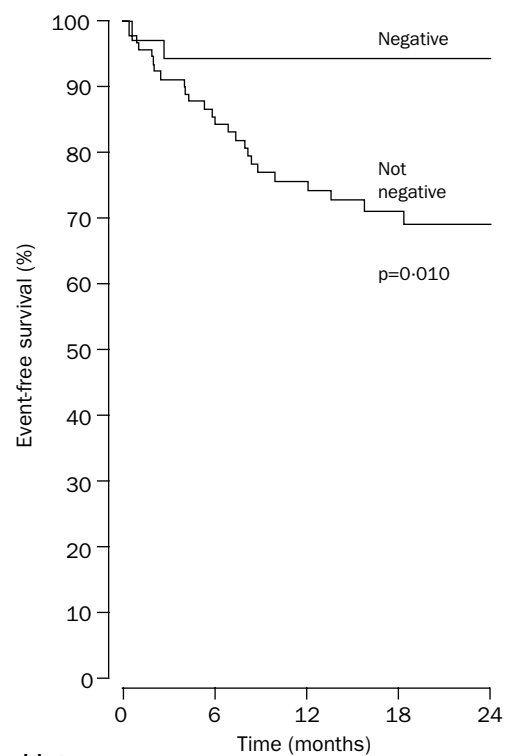


Figure 2: Event-free survival for secondary endpoint according to outcome of T-wave alternans test

fraction of 0.30 or less. Our primary endpoint was sudden cardiac death or cardiac arrest, the same as the primary endpoint of Ikeda and colleagues.⁴ Our secondary endpoint was ventricular tachyarrhythmic events, including sudden cardiac death, cardiac arrest, and sustained ventricular tachycardia, the endpoint of Klingenhoben and colleagues.³ We pooled the data from the two studies, including the original T-wave alternans and endpoint-event classifications, follow-up durations, and ejection fraction data, into a central database.

We used Kaplan-Meier analysis to assess event-free survival, with a two-sided log-rank test of significance. Relative risk at 24 months was calculated from the event-free survival at that time point. Follow-up data were capped at 24 months for each patient. Because our objective was to find out which patients do not require defibrillator therapy, we classified the T-wave alternans outcomes as negative or not-negative (positive and indeterminate).

129 patients (87 from Ikeda and colleagues, 42 from Klingenhoben and colleagues; 112 male, 17 female) had previous MI and left-ventricular ejection fraction of 0.30 or less. The mean age was 63 years (SD 11) and mean left-ventricular ejection fraction was 0.255 (0.045). Patients were followed up for a mean of 16.6 months (8.0). 35 (27%) patients tested T-wave alternans negative, 77 (60%) positive, and 17 (13%) indeterminate. The primary endpoint was experienced by no negative patient, ten positive patients (six sudden cardiac death, four cardiac arrests), and two indeterminate patients (both sudden cardiac death). For the secondary endpoint, the respective numbers were two, 21, and four.

For the primary endpoint, the event rate was 15.6% at 24 months of follow-up among patients who tested T-wave alternans positive or indeterminate, compared with an event rate of zero among patients who had negative results ($p=0.02$, figure 1). The overall event rate at 24 months for all 120 patients was 11.1%, and for patients with positive tests was 15.5%. For the secondary endpoint, the event rate was 31.1% at 24 months of follow-up among patients with positive or indeterminate results, compared with 5.7% among negative patients ($p=0.01$, figure 2). Relative risk at 24 months was 5.5. Event rate at 24 months for the population of all 120 patients was 24.0% and for positive T-wave alternans results was 31.4%.

In the negative, positive, and indeterminate groups, four, seven, and one patients, respectively, died from non-arrhythmic causes. The reasonably constant proportions of these deaths to the numbers of patients in each of these groups shows that T-wave alternans does not identify patients at risk of non-arrhythmic death. The all-cause mortality was 18.7% in the entire population at 24 months, and mortality was 12.5%, 21.4%, and 21.3% in the T-wave alternans negative, not-negative, and positive groups, respectively. The mortality rate in the entire population is consistent with the MADIT II results. The mortality rate among the patients with negative T-wave alternans tests was 42% lower than among the not-negative patients; this difference is larger than the 31% relative reduction in all-cause mortality in the defibrillator group compared with the control group in MADIT II. The difference in mortality between the negative and not-negative patients was not significant. A study population similar in size to the MADIT II trial would be required to show that a difference in mortality of the magnitude achieved in MADIT II was significant.

Our data suggest that MADIT II-type patients who test negative for microvolt T-wave alternans may not benefit from defibrillator therapy. Conversely, prophylactic defibrillator therapy might be more beneficial in such patients who have positive or indeterminate T-wave alternans results than in

similar patients who have not undergone risk stratification.

Contributors

All researchers participated in designing the study, assembling and analysing the data, and drafting and reviewing the report.

Conflict of interest statement

R J Cohen has an association with Cambridge Heart Inc, who manufacture equipment for the measurement of microvolt T-wave alternans. None declared for the other investigators.

Acknowledgments

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Johann Wolfgang Goethe University, Frankfurt, Germany

(Prof S H Hohnloser MD); Toho University, Tokyo, Japan (T Ikeda MD); Columbia University, New York, NY, USA (D M Bloomfield MD); University of Massachusetts, Worcester, MA, USA (O H Dabbous MD); and Massachusetts Institute of Technology, Cambridge, MA, USA (Prof R J Cohen MD)

Correspondence to: Prof R Cohen, Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Room E25-335a, 45 Carleton Street, Cambridge, MA 02142, USA (e-mail: rjcohen@mit.edu)

Human monoclonal thyroid stimulating autoantibody

J Sanders, M Evans, L D K E Premawardhana, H Depraetere, J Jeffreys, T Richards, J Furmaniak, B Rees Smith

A monoclonal autoantibody (MAb) with powerful thyroid stimulating activity has been produced from lymphocytes from a patient with Graves' disease. The autoantibody and its Fab fragment bind to the thyroid stimulating hormone (TSH) receptor (TSHR) with high affinity, inhibit labelled TSH binding to the receptor and stimulate cyclic AMP production in Chinese hamster ovary cells transfected with TSHR. TSHR autoantibodies with TSH agonist or antagonist activities from patients' serum samples are effective inhibitors of labelled monoclonal autoantibody binding to TSHR. Thus, the human monoclonal autoantibody has all the characteristics of serum TSHR autoantibodies. Its availability has important implications for new studies on the pathogenesis of Graves' disease.

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Since the discovery over 40 years ago of the thyroid stimulating autoantibodies that cause hyperthyroidism in Graves' disease many (but unsuccessful) efforts have been made to isolate and characterise the autoantibodies at the molecular level.^{1,2} The autoantibodies exert their stimulating effect by binding to the thyroid stimulating hormone receptor (TSHR) and we³ and others⁴ have produced animal monoclonal antibodies with similar characteristics to patient TSHR autoantibodies. We have now isolated and characterised a human monoclonal TSHR autoantibody that acts as a powerful thyroid stimulator.

Enhancing Specificity Without Sacrificing Sensitivity: Potential Benefits of Using Microvolt T-Wave Alternans Testing to Risk Stratify the MADIT-II Population

Richard J. Cohen *Harvard-MIT Division of Health
Sciences and Technology, Massachusetts Institute of
Technology Cambridge, MA, USA*

Abstract. The MADIT-II study (Moss et al., *N Engl J Med* 2002;346:877–883) demonstrated that implantation of a cardioverter/defibrillator (ICD) reduced mortality from 19.8% to 14.2% during 20 months of follow-up in patients with prior myocardial infarction and left ventricular ejection fraction ≤ 0.30 . Concerns have been raised both about the cost and potential morbidity of implanting ICDs in a large group of patients when only a small fraction of the patients would be expected to benefit from the treatment. This concern has given rise to the hope that an effective means of risk stratifying the MADIT-II population might be developed so that ICD therapy can be directed to only those patients who are at significant risk and thus likely to benefit from treatment for purposes of primary prevention of arrhythmic death. Electrophysiology study (EPS) is probably not suitable for this purpose because of its established relatively high false negative rate and because it is itself an invasive procedure. QRS width has been proposed for this purpose but prospective data demonstrating its effectiveness in stratifying the MADIT-II population for risk of arrhythmic death are absent. Initial data suggest that microvolt T-wave alternans (MTWA) testing does appear to be a suitable candidate for risk stratifying the MADIT-II population. These data indicate that approximately 30% of the MADIT-II population test negative for MTWA and that these patients are at extremely low risk for sudden cardiac death and cardiac arrest. Furthermore, MTWA is an inexpensive non-invasive test which can be repeated over time to monitor whether a patient who initially tests negative develops arrhythmic risk with the progression of the underlying disease. As studies of MTWA testing in the MADIT-II population come to publication, a database will likely be formed which will establish MTWA as an effective means of stratifying the MADIT-II population. ICD therapy may not be indicated in patients who test MTWA negative, and conversely the remaining patients may enjoy a greater mortality benefit than that observed in the MADIT-II trial. Furthermore, widespread MTWA testing might have the further benefit in those patients who do not test negative of serving as a call to action to referring physicians to direct those patients to ICD therapy, thereby greatly increasing the number of appropriate patients who actually receive potentially life saving therapy.

The MADIT-II trial [1] demonstrated that in patients with prior myocardial infarction and left ventricular ejection fraction ≤ 0.30 that implantation of an implantable cardioverter/defibrillator (ICD) reduced mortality from 19.8% to 14.2% over an average of 20 months of follow-up. The authors of the study estimated that there are approximately 400,000 new MADIT-II type patients each year in the United States, and that proceeding with ICD therapy in all MADIT-II patients would represent a significant cost to the health care system. In addition, placing ICDs in all MADIT-II patients would involve an invasive and expensive therapy for a large cohort of patients of which only a small fraction would be expected to benefit from the therapy. This is of concern because implantation of an ICD has morbidity associated with it. In this regard it is interesting to note that the authors of the MADIT-II study observed a higher incidence of hospitalization for heart failure in patients with ICDs than in the control group, although a causative relationship between ICD implantation and increased incidence of new or worsened heart failure was not established. While it is possible that the mortality benefit of ICD therapy might be greater than 5.6% over a longer duration of follow-up, that has not been proven at this point, and the benefit of ICD therapy would likely still be limited to a small fraction of the patients treated.

As a result of the medical concern of subjecting such a large group of patients to invasive therapy, and as a result of the concern related to the cost to the health care system of treating the entire MADIT-II population with ICDs, there has been increasing interest in the potential of subdividing the

Richard J. Cohen is a board member, consultant and has an equity interest in Cambridge Heart, Inc. a manufacturer of equipment for the measurement of microvolt T-wave alternans.

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MADIT-II population into a high risk group that might enjoy a greater mortality benefit from ICD therapy than that observed in the MADIT-II study, and a low risk group in which ICD therapy would not be indicated. This possibility was suggested in the editorial [2] which accompanied the publication of the MADIT-II study.

One potential strategy for accomplishing this goal would be to use programmed ventricular stimulation during electrophysiology study (EPS). However, the MUSTT registry data indicate that in patients with coronary artery disease, left ventricular ejection fraction ≤ 0.40 , and non-sustained ventricular tachycardia that at two years of follow-up there was a 12% rate of cardiac arrest and arrhythmic death in patients not inducible during EPS [3]. It would seem likely that MADIT-II patients (having a lower ejection fraction than the MUSTT patients) who are not inducible during EPS would be likely to have at least a comparable rate cardiac arrest and arrhythmic death as the MUSTT patients who were not inducible. Thus EPS would likely have too high a false negative rate to serve as a means of identifying which MADIT-II patients ought not receive ICD therapy. In addition, EPS suffers from the additional drawback of itself being an invasive procedure.

The United States Medicare system has chosen to limit reimbursement for MADIT-II patients to those patients with a QRS width greater than 120 milliseconds [4]. QRS width represents an easily obtained non-invasive measure. While QRS width might be associated with an increased mortality rate in patients with heart failure [5], in order for QRS width to serve as a useful risk stratifier to guide ICD usage, it must be demonstrated to be specifically and highly associated with risk of arrhythmic death—in the MADIT II population. The rationale for using QRS width as a risk stratifier in the MADIT II population was based on unpublished preliminary retrospective analysis of the MADIT-II data [4]. Unfortunately, there is an absence of prospective data demonstrating that

this measure is an effective risk stratifier in the MADIT-II population.

Data are now beginning to accumulate [6–8], demonstrating that microvolt T-wave alternans (MTWA) testing may be an effective risk stratifier specifically in the MADIT II population. These data indicate that MTWA, in contrast to EPS, appears to have a low false negative rate in this population. This feature may make MTWA a suitable means for identifying a sub-group of MADIT-II patients who may not benefit from ICD therapy.

Microvolt T-Wave Alternans Testing

MTWA testing [9] involves measuring variation in the morphology of the T-wave on an every other beat basis. The magnitude of the variation observed is typically on the order of a few microvolts, in comparison to the noise level in a standard electrocardiogram which is generally in the range of 10 to 20 microvolts. Thus in order to detect MTWA, specialized recording and signal processing methods must be employed for reliable measurement. In addition, MTWA is not generally present at rest even in patients at risk of ventricular tachyarrhythmias and therefore exercise stress, pharmacologic stress, or cardiac pacing must be utilized in order to elevate the heart rate. A positive MTWA test is one in which sustained T-wave alternans is present either at rest or with an onset heart rate of 110 bpm or less.

With current instrumentation, MTWA represents an inexpensive, convenient non-invasive testing modality. MTWA has been evaluated prospectively in a variety of patient populations [10–17] as a means of predicting occurrence of ventricular tachyarrhythmic events (see Table 1). Across a variety of patient populations, MTWA has been shown to be an effective non-invasive means of assessing which patients are at high and low risk of ventricular tachyarrhythmias and sudden cardiac death.

Table 1. Event rates in patients from prospective studies with spontaneous ventricular tachyarrhythmic event endpoints

Study	Patient population	Follow-up (months)	MTWA+ (%)	MTWA-(%)	RR
Rosenbaum et al. [10]	EPS ($n = 83$)	20	81	6	13.5
Gold et al. [11]	EPS ($n = 313$)	13	19	2	10.9
Klingenheben et al. [12]	CHF ($n = 107$)	18	21	0	∞
Hohnloser et al. [7]	DCM ($n = 137$)	18	22	6	3.44
Kitamura et al. [14]	DCM ($n = 83$)	21	24	3	8.8
Adachi et al. [18]	DCM ($n = 82$)	40	30	3	10.2
Grimm et al. [15]	DCM ($n = 263$)	72	~ 17	~ 12	~ 1.4
Ikeda et al. [16]	Post MI ($n = 102$)	13	28	2	16.8
Ikeda et al. [17]	Post MI ($n = 834$)	24	8*	1*	11.4

EPS: patients referred for electrophysiology study. DCM: dilated cardiomyopathy. CHF: congestive heart failure. MI: myocardial infarction. RR: relative risk. Percentages followed by an asterisk correspond to endpoint of sudden cardiac death or cardiac arrest. Percentages not followed by an asterisk also include sustained ventricular tachycardia as an endpoint. In the Grimm study, the event rate among MTWA indeterminates was reported as $\sim 34\%$.

Table 2. Ventricular tachyarrhythmic event rates among MADIT-II type patients followed prospectively after MTWA testing

Study	N	Pos (%)	Ind (%)	Neg (%)	Follow-up (months)	MTWA Pos	MTWA NotNeg	MTWA Neg	RR	P
Hohnloser et al. [7]	129	60	13	27	24	15.5%*	15.6%*	0%*	∞	0.02
					24	31.4%	31.1%	5.7%	5.5	0.01
Chow et al. [6]	193	50	20	30	18	11.8%		2.0%	6.0	0.035

Pos: positive. Neg: negative. Ind: indeterminate. NotNeg: not negative (positive or indeterminate). RR: relative risk (positive versus negative). Percentages followed by an asterisk correspond to endpoint of sudden cardiac death or cardiac arrest. Percentages not followed by an asterisk also include sustained ventricular tachycardia as an endpoint.

Prior to the MADIT-II study, the question that was usually raised with respect to MTWA testing was whether a positive MTWA test was sufficient evidence to guide a patient towards EPS and/or ICD therapy. With the advent of the MADIT-II study, in the MADIT-II population the question becomes whether a negative MTWA test is a sufficient indication to defer ICD therapy.

MTWA Testing in the MADIT-II Population

Several studies have now addressed the issue of using MTWA to risk stratify the MADIT-II population. Hohnloser et al. [7] reported on 129 MADIT-II type patients drawn from two previously published prospective studies which evaluated MTWA as a predictor of ventricular tachyarrhythmic events (see Table 2 and Figure 1). This subgroup analysis revealed that in this population at 24 months of follow-up there was a 15.6% rate of cardiac arrest and sudden cardiac death among patients who tested MTWA positive or indeterminate (*not-negative*) compared with no events among patients who tested MTWA negative ($P = 0.02$). Twenty-seven percent of the patients tested MTWA negative. If one also included sustained ventricular tachycardia as an endpoint, the event rate was 31.1% among the MTWA not-negative patients compared to an event rate of 5.7% among the MTWA negative Patients (relative risk 5.5, $P = 0.01$).

Chow et al. [6] reported in a published abstract on 193 MADIT-II type patients followed prospectively after MTWA testing. At eighteen months of follow-up the rate of ventricular tachyarrhythmic events (arrhythmic death, resuscitated cardiac arrest, or appropriate ICD discharge) was 11.8% among the patients who tested MTWA positive and 2.0% among the patients who tested MTWA negative (relative risk 6.0, $P = 0.035$).

In addition, Bloomfield [8] reported orally on 164 MADIT-II type patients from a multi-site study followed prospectively after MTWA testing. Using a total mortality endpoint after 18 months of follow-up he found no events among those patients who tested MTWA negative.

These three studies taken together suggest that MADIT-II patients who test MTWA negative have an extremely low risk of sudden cardiac death and cardiac arrest. The Chow et al. [6] and Bloomfield [8] studies have not yet been published as journal articles. One would expect when these studies come to publication and are taken together with the Hohnloser et al. study, there will be a substantial set of data comprising approximately 500 patients suggesting that MADIT-II patients who test MTWA Negative may not benefit from ICD therapy. In addition, the recently launched MASTER trial will also be examining event rates in MADIT-II patients segregated by the results of MTWA testing.

If MTWA were to be used to risk stratify MADIT-II patients, MTWA positive patients would certainly be expected to proceed to ICD therapy. MTWA negative patients might normally be expected to not receive ICD therapy. In the Hohnloser et al. [7] and Chow et al. [6] studies 13% and 20% of the patients tested MTWA indeterminate. Patients who test MTWA indeterminate should have their test repeated (generally immediately at the time of testing) for in about half the cases the repeat test is determinate. MADIT-II patients who remain MTWA indeterminate should probably proceed to ICD therapy because there is no evidence that their risk is low; in fact data suggest that an indeterminate test (particularly when due to a high level of ventricular ectopy [9]) is suggestive of elevated risk.

If ICD implantation is reserved for MADIT-II type patients who do not test MTWA negative, then the remaining patients would be expected to sustain a greater mortality benefit from ICD therapy than would the MADIT-II population as a whole. This result would be expected because the arrhythmic deaths would be expected to occur almost entirely among the patients who do not test MTWA negative.

One objection that may be raised to the MTWA studies discussed above, is that the follow-up data are 18 to 24 months in duration and that the patients may sustain events at a later point in time. One of the attractions of using a non-invasive, inexpensive test like MTWA is that it can easily be repeated on an annual basis. If a patient initially tests MTWA negative

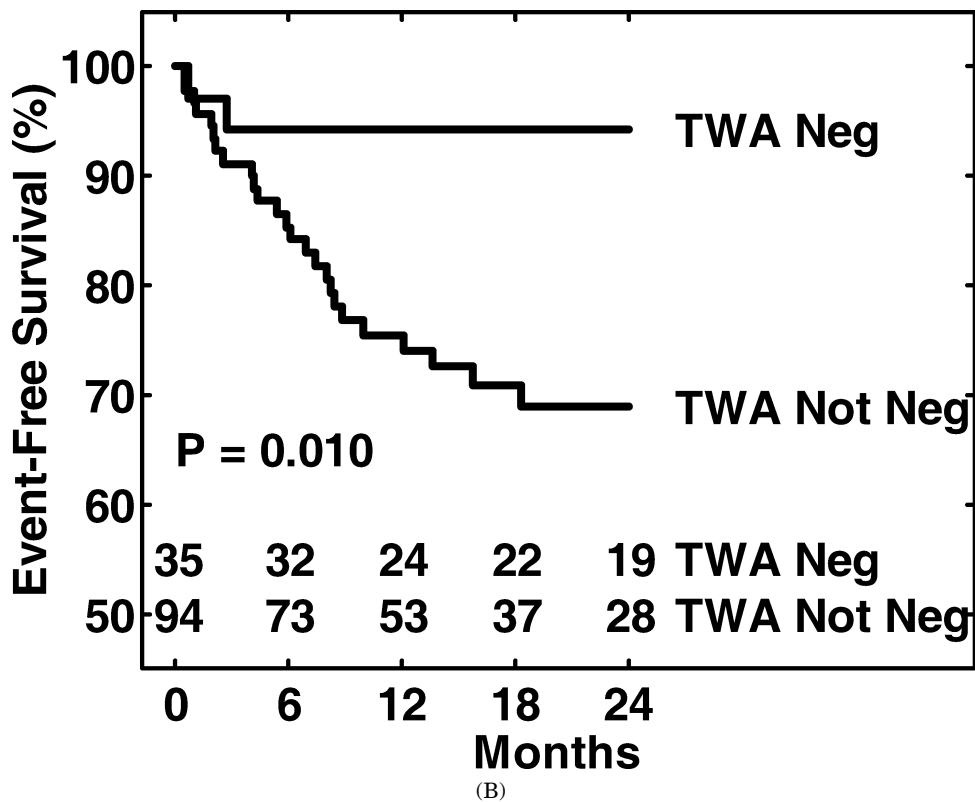
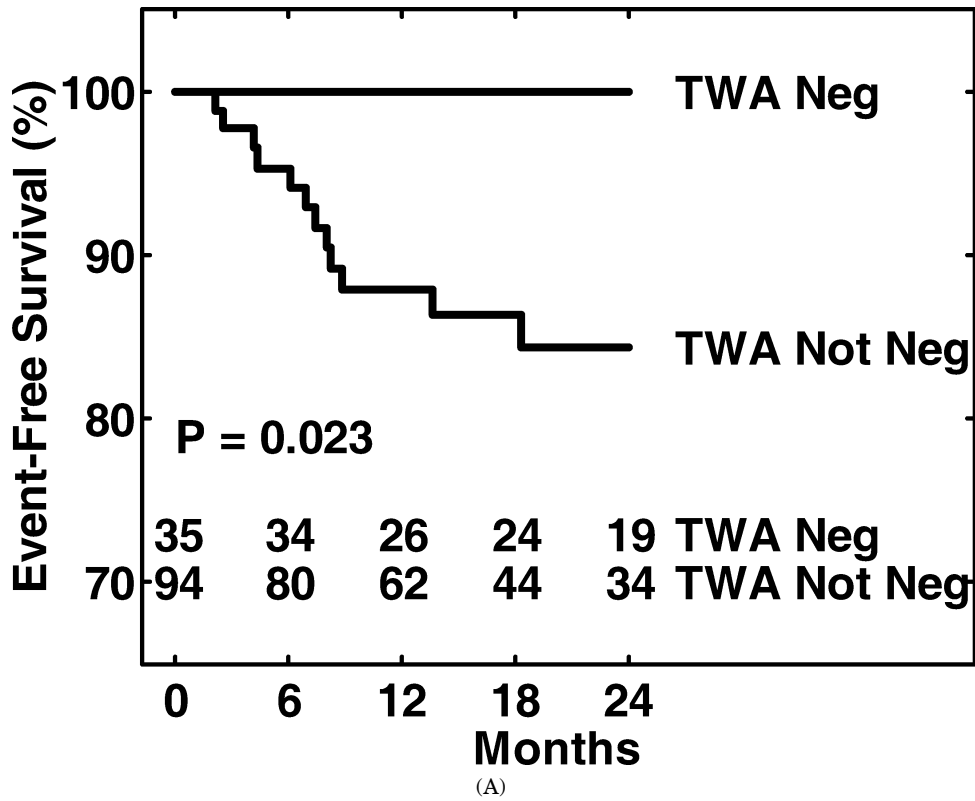


Fig. 1. Panel a. Event-free survival for primary endpoint segregated according to outcome of TWA test. Panel b. Event-free survival for secondary endpoint segregated according to outcome of TWA test. Redrawn, with permission, from Hohnloser et al. [7].

but later on tests positive or indeterminate, a decision to implant an ICD could be made at that time. Indeed, one might expect that the need for an ICD could certainly change as the myocardial substrate evolves.

Conclusion

In summary data from several independent studies suggest that MTWA testing is an effective means of risk stratifying MADIT II patients. Data that have become available to date suggest that MADIT-II type patients who test MTWA negative have an extremely low risk of arrhythmic death and cardiac arrest, and thus ICD therapy may not be indicated in such patients. Conversely, the remaining MADIT-II patients might be expected to obtain a greater mortality benefit than that observed in the entire MADIT-II population. When the not yet published studies come to journal publication one would expect that a sufficient data base may exist to support use of MTWA to guide therapy for MADIT-II patients.

We know that ICDs remain far under-utilized among patients who have well established indications for their use. Based on this historical record, one would expect that many physicians will not direct their MADIT-II patients to ICD therapy for purposes of primary prevention. One additional advantage of utilizing MTWA for risk stratifying MADIT-II type patients is that in patients who do not test negative the non-negative MTWA test will serve as a call to action to direct these patients to potentially life saving ICD therapy.

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Comment #27:

Submitter: Richard M. Luceri, M.D.

Organization:

Date: May 13, 2004

Comment:

I am a cardiac electrophysiologist and have devoted a good part of my medical career to the treatment and prevention of sudden cardiac death with the implantable defibrillator (ICD). In fact, I was one of the early investigators with Dr. Mirowski and I implanted the first ICD in the South almost 21 years ago when I was on the Faculty of the University of Miami School of Medicine.

Over the years, the scientific evidence has become more and more clear that ICDs save lives both in a secondary prevention capacity (i.e. AVID-type patients) and in primary prevention of “at-risk” patients (MADIT I & II, MUSTT, now SCD-HeFT). These well-conducted randomized trials have all demonstrated a significant reduction in mortality in those groups treated with an ICD. The recently presented SCD-HeFT trial, in particular, was the largest, longest and perhaps most significant of all the trials since it enrolled patients with both ischemic and dilated cardiomyopathies. CMS itself noted in the June 6, 2003 response to the MADIT II trial:

“CMS eagerly anticipates the availability of results from the SCD-HeFT Trial...”

Consequently, I am recommending that CMS cover the utilization of ICDs in the category of patients meeting the SCD-HeFT criteria. As a physician, it would be very difficult and perhaps unethical to select patients for prophylactic ICD therapy based on unproven sub-study analyses from this or any other trial. Thank you for the opportunity to express my opinion in this regard.

Comment #28:

Submitter: Lynne Warner Stevenson, MD

Organization: Brigham and Women’s Hospital

Date: May 9, 2004

Comment:

To ICD Review Committee

I would like to indicate that there are some well-recognized heart failure specialists who do not feel that ICD should be routinely provided to all patients meeting SCD-HeFT criteria. It should be recognized that there exists significant pressure upon us as well as CMS to endorse widespread ICD coverage. While the relative improvement in survival is highly statistically significant, the absolute increase in survival is 1.4% per year averaged over the 5 year period, and is 0 after the first 12 months. Thus the clinical significance for the individual patient may fall below the statistical significance for a population. Furthermore, the analysis of the

sizeable subset of 30% Class III patients shows no benefit (not a lack of statistically significant benefit, but no benefit). While the subjectivity of the Class II-III distinction has been emphasized, the separate analyses by objective measures of functional capacity (6 minute walk distance) and by the Duke Activity scale show parallel results that also demonstrate significant interaction - the sicker subgroup does not benefit. There are multiple possible reasons for this, which cannot be addressed until data is made available regarding the characteristics of patients in whom the ICD fired appropriately, and their subsequent outcomes.

I feel strongly, however, that ICD should be available to selected patients with mild symptoms of heart failure with low ejection fraction, and otherwise good prognosis for meaningful survival extending past 2 years. A key responsibility of all established bodies, however, should be to avoid imposition of any perceived mandate to insert ICD in patients who have not had prior events. The common trend to extend acceptance into required performance measures is strong. There is already interest in at least one major center in a performance metric identifying a denominator of patients with EF <30% to make sure that ICD implantation is explicitly addressed.

It is essential that the search for predictors of appropriate device discharge be intensified. There are no current market incentives to accelerate this search. However, with so many devices in place, it should have been possible by now, and should certainly be possible with an independent registry in future, to obtain a better profile of patients for whom devices are most likely to avert death.

Furthermore, even the United States cannot offer all things to all people. As has been discussed, we have progressed beyond the era when incremental therapies with small absolute benefit can be added infinitely until the asymptote of outcome is reached. There is no question that acceptance of SCD-HeFT criteria will expand the ICD-eligible population substantially. The majority of SCD-HeFT patients who received devices never got any benefit at all, while some had negative benefit from inappropriate shocks and other complications. This is very different from other heart failure therapies such as ACEI and beta blockers, which confer functional benefit for many patients on top of mortality benefit for a limited number. Thus number needed to treat to save X lives does not allow appropriate comparison of ICD with medical therapies that convey benefits in addition to survival. (CRT on the other hand, does improve functional capacity and may decrease disease progression, so is more in the category of drug therapies.

In this brief message, I will not go into the issues of shifting modes of death from sudden to slow, which is particularly important for elderly patients (average age of patients hospitalized with this type of heart failure in the US is 74, compared to this trial 60 yrs). At least with current costs of implantation, maintenance, and replacement, the financial implications of widespread increase in ICD implantation seem incompatible with the larger goals of providing adequate health care to a broad population. ICD are already used with much greater zeal in the US than in other countries. With relation to our approach to health care delivery and expectations, it has been said that only in the US is death considered optional. Are we that much richer? Can we really afford to invest in so many devices for such small return in absolute life benefit?

Comment #29:

Submitter: Alfred E. Buxton, MD

Organization: Rhode Island Hospital

Date: May 9, 2004

Comment:

SCD-HeFT was a well-designed trial carried out with a great deal of integrity. The average follow-up of approximately 45 months was quite long in comparison to most other trial of this type, lending much validity to the results. The relatively long follow-up (in comparison to the MADIT II study, for example) provides for a clearer picture of the true potential benefits of ICD therapy over the long term. The patient population was well defined, including patients with symptomatic heart failure, of any etiology with left ventricular ejection fractions of 35 % or less. The results of the trial cannot be applied to other patient populations. The trial results show a clear mortality benefit for patients who were treated with implanted defibrillators in comparison to both the empiric amiodarone as well as the placebo-therapy arms. The magnitude of improvement in mortality was relatively small at 1.2% yearly, but the benefit is quite clear. I personally believe, being intimately familiar with the results of this trial as a co-investigator, as well as being familiar with the MADIT II trial results, that the mandate for coverage for the SCD-HeFT population is far clearer than the MADIT II population. Let me explain my reasoning. Although it may not have been intentional, there is actually a great deal of overlap between the MADIT II and SCD-HeFT populations. Examination of the MADIT II report demonstrates that approximately two-thirds of patients enrolled in the MADIT trial had symptomatic heart failure, NY Heart Association class 2 or above. Furthermore, 51% of patients in the MADIT II trial had left bundle branch block or nonspecific IVCD. Thus, most of the MADIT II patients had additional markers of mortality risk. Therefore, the results of MADIT II are not valid for all asymptomatic patients with a prior infarct and ejection fraction of 30% or less. Further support for this statement can be seen from an analysis that was performed in the MUSTT population that was presented at last month's ACC meeting. In this abstract, we modeled mortality and sudden death risk in over 1500 untreated MUSTT patients. The results of that analysis show that the two-year total mortality risk for patients meeting the MADIT criteria (prior MI and ejection fraction of 30% or less), was actually only 6.2%, in contrast to the 19.8% mortality reported in the MADIT II population. However, when one adds additional risk factors to the MUSTT population, beyond ejection fraction, such as use of digitalis, presence of LBBB or nonspecific IVCD, nonsustained VT discovered while patients were hospitalized, or the presence of inducible sustained VT by EPS, then the mortality risk begins to approach that reported by the MADIT II investigators. The manuscript containing these results is submitted for publication.

The results of this analysis, MADIT, and the MUSTT trial are consistent with those of the SCD-HeFT trial: multiple factors in addition to ejection fraction impact on mortality of patients with coronary disease and left ventricular dysfunction. Patients with symptomatic heart failure and other markers elevate risks for total mortality, as well as sudden death. The subanalysis presented by the SCD-HeFT Investigators demonstrating that patients with wide QRS complexes demonstrated slightly greater benefit with ICD therapy can be explained by the fact that patients with wide QRS complexes have somewhat higher mortality than patients with narrow QRS complexes.

I believe that the results of the SCD-HeFT trial can probably be generalized to the majority of patients who meet the entry criteria for the study, and I would suggest applying very strict criteria to define this population. I suspect that the results of the SCD-HeFT are far more generalizable than those of the MADIT II study, for the reasons noted above.

These results should be confirmed in real world populations by performing one or more prospective registries testing the models.

Thank you very much for the chance to comment on this important trial

Comment #30:

Submitter: Andrew Rubin, MD
Organization: Eisenhower Medical Center
Date: May 8, 2004
Comment:

The issue of medical payment for the empiric implant of defibrillators continues to be a point of frustration for cardiac specialists as study after study has proven their efficacy in prolonging people's lives. Please strongly consider the importance of these devices in our society; a loved one may benefit someday.

Comment #31:

Submitter: Christopher Fellows, MD, Michael Belz, MD , John B. Sanders, MN, ARNP
Organization: Virginia Mason Medical Center
Date: May 3, 2004
Comment:

In response to an invitation for heart rhythm specialists to comment regarding CMS coverage for SCD HeFT indicated device implantations, we

would support expanded Medicare coverage for patients who meet the entry criteria of heart failure with left ventricular ejection fractions of less than or equal to 35%. We would support eventual full coverage of the SCD HeFT indicated patient population. The choice of appropriate device should remain the decision of the treating physician.

Comment #32:

Submitter: Eli Gang, MD, FACC, FACP

Organization: UCLA School of Medicine

Date: May 30, 2004

Comment:

I would like to emphasize the importance of the results of recent clinical trials to the care of patients at risk for sudden cardiac death. The population of patients who are likely to benefit from the implantation of an ICD has recently been further defined by the COMPANION, DEFINITE, DINAMIT and SCD-HeFT Trials. The latter, in particular, has helped us in treating patients with heart failure not related to prior myocardial infarctions. I strongly urge you to expand Medicare ICD coverage to patients defined in these trials. Furthermore, the choice of appropriate devices to implant in these and other high-risk patient populations should be left to the professional discretion of the physician who will perform this potentially life-saving procedure.

Comment #33:

Submitter: Omid Souresrafil, MBBS, Ph.D.

Organization:

Date: May 2, 2004

Comment:

There is no doubt that SCD-HeFT further reiterate the need for ICDs in a special patient group. As the results of trials such as AVID, MADIT and MADIT II have indicated in the past.

We should look at the results of these trials from two angles.

1. Although the above trials point to ICDs being indicated for the correct patient group, these indications should now be used to bridge the gap between several patient and most importantly physician groups as opposed to electrophysiologists who have been the primary centers of referrals for ICDs.

Cardiac hemodynamics plays a major role in disease progression, arrhythmias and mortality.

The advent and the success of CRT in a certain patient population has raised interest in expanding this therapy for other indications. The combination of CT and ICD therapy has also shown a statistically significant plus for the combination of devices.

However larger efforts are required to pass on this message to multiple physician groups.

Who will eventually get to refer patients to ICD therapy is the key to the success of the above therapies.

Primary care physicians with limited experience in these therapies need to be made aware of this further in order to refer patients directly, to the HF physician and to the implanting physician.

2. As primary care physicians with relatively limited exposure to scientific data, get inundated with results from tens of trials indicating ICDs and CRT devices, they need to be educated in interpreting scientific data. Most investigators in the above trials are experts in interpreting data, but I believe the main message needs to be passed on to the non-expert whose primary practice does not include referral of patients to EPs and HF specialists.

Physicians need to have access to tools for them to interpret data and applying it to their practice.

Comment #34:

Submitter: Paul C. Maccaro, MD

Organization: Huntington Hospital

Date: April 30, 2004

Comment:

This letter is written in response to the Center for Medicare and Medicaid Services request for public comment regarding the NCD for Implantable Defibrillators. I am a practicing Clinical Cardiac Electrophysiologist on the full time faculty of Huntington Hospital, a community hospital that serves north western Suffolk County in New York State. I am member of NASPE- Heart Rhythm Society, and I was an investigator for the SCD-HeFT trial.

Recent data from landmark studies such as SCD-HeFT, COMPANION, DEFINITE and MADIT-II demonstrate the benefit of CRT-D and ICD therapy in patients who meet entry criteria for each of these studies. I feel it is counter to the principals of evidence-based medicine to do anything but approve these life saving therapies to those who meet these entry criteria. Specifically, SCD-HeFT is a well designed, appropriately powered, and well executed study, and demonstrates a benefit to the complete population of patients with heart failure and an EF of $\leq 35\%$. The study was not designed to be powered to analyze for sub populations. Clearly we are all interested in seeing the complete data once published, but data already available warrants coverage of this patient cohort. Finally, your NCA tracking sheet states you are interested in recommendation for appropriate device selection for these specific populations. I feel very strongly that device selection needs to be at the discretion of the treating physician who

knows the specific patient needs. To legislate device selection would relegate medical care to the lowest bidder, potentially sacrificing quality of care for monetary purposes and would be poor public health policy and could potentially harm patients.

Thank you for this opportunity to comment on this important determination.

Comment #35:

Submitter: Marc Silver, MD

Organization: Raleigh Cardiology

Date: May 5, 2004

Comment:

I am writing to you regarding the upcoming CMS decision on ICD coverage for Medicare patients. I am a cardiologist in Raleigh, NC, and have great interest in the economic and ethical issues surrounding ICD therapy.

MADIT II demonstrated a clear mortality benefit in patient with prior MI and reduced LV function. SCD-HeFT and COMPANION have reinforced the data in CAD patients and expanded it to include non-ischemic cardiomyopathy patients. The number needed to treat in these trials ranges from 9 to 14 to save one life in five years.

As a society, we spend so much money on health care that has never been shown to reduce mortality or improve quality of life, that it seems unfair to judge the appropriateness of these therapies for Medicare coverage based on economic grounds. Only if CMS plans to review all covered procedures from an economic perspective would it be appropriate to ponder the economics of ICDs. When well run randomized clinical trials demonstrate unequivocal mortality benefit, the studied therapies or treatments should be covered. If CMS is going to start to weigh economic factors (which I suspect must be done), then all covered therapies, treatments, and diagnostic tests should be held to the same standard. It seems absurd that we cover expensive, unproven therapies in the treatment of disease (stenting coronaries without symptoms or provokable ischemia, routine use of adjunctive nuclear or echo imaging with stress testing in patients with interpretable ECGs, etc.) but will not fully cover ICDs in patients at high risk for sudden cardiac death.

I am a taxpayer. I hope to one day have Medicare coverage. I am well aware that we can't cover everything for everybody. HOWEVER, if proven therapies to reduce human suffering are not covered when unproven therapies are, then we have a system that is fundamentally flawed. I would applaud a careful economic look at what CMS should cover, if it is done across the board. It is hard to watch patients receive expensive, unproven therapies day after

day at my hospital, and then have to go to my office to tell a MADIT II patient that her insurance company (CMS) will not cover her ICD, even though I know it will on average reduce her risk of sudden death.

ICDs should be covered for patients who meet the strict MADIT II, COMPANION, and SCD-HeFT criteria. Further research should be done for better stratification of patients, but coverage should not be withheld pending that research. Use of subgroup analysis to find higher risk patients is a statistical no-no.

I have an ethical duty to inform my patients of therapies that can help them. Our society has an ethical duty to pay for those therapies, if it pays for even one therapy that is less cost-effective. If we are going to start rationing, let's do it fairly and as scientifically as possible.

Thanks for the opportunity to express my opinion.

Comment #36:

Submitter: Leon A. Feldman, MD, FACC

Organization: Desert Cardiology Center

Date: May 5, 2004

Comment:

I strongly encourage CMS to cover expanded indications for ICD implantation. The recent results from the SCD-HeFT trial show a clinically and statistically significant benefit for ICDs implanted in heart failure/cardiomyopathy patients (EF 35% or less). This is a wonderful opportunity to save numerous patients from premature death. The COMPANION, DEFINITE, MADIT, MADIT II and MUSTT trials all indicate similar benefit from prophylactic implantation of ICDs and CRT-D devices.

Please provide full coverage for the SCD-HeFT patient population.

Comment #37:

Submitter: Paul A. Levine, MD, FACC, FAHA

Organization: Loma Linda University School of Medicine

Date: May 5, 2004

Comment:

I am a board-certified cardiologist with a focused interest in electrophysiology and device therapy. I was recently notified by NASPE that CMS is seeking input with respect to a national coverage decision regarding expanding the reimbursable indications for implantable cardioverter defibrillator (ICD) implantation.

I would strongly recommend that CMS cover the unrestricted use of ICD therapy for primary prevention of all-cause mortality in all patients who meet the SCD-HeFT criteria based upon the available scientific evidence.

This recommendation is based on the following:

- The SCD-HeFT clinical trial was a well-designed, high quality, NIH sponsored, randomized prospective controlled trial evaluating the use of ICD therapy versus conventional medical therapy versus conventional medical therapy plus amiodarone in a large patient population with a high risk of arrhythmic mortality.
- ICD therapy is known, from previously performed controlled clinical trials, to clearly benefit patient populations at high risk of arrhythmic mortality, as well as all-cause mortality, as compared to conventional antiarrhythmic therapies.
- SCD-HeFT demonstrated a statistically significant reduction in all-cause mortality (the primary endpoint) associated with ICD treatment as compared with antiarrhythmic medical therapy. In addition, these patients with overt congestive heart failure demonstrated a high compliance with appropriate use of ACE inhibitors and beta blockers as well as and lipid-lowering pharmacologic therapies, all considered to be the current state-of-the-art therapy for these patients.
- SCD-HeFT outcome results are compelling with a hazard ratio of 0.77 favoring ICD therapy and a relative reduction of overall mortality of 23% as compared with conventional medical therapy plus amiodarone. SCD-HeFT outcome results also demonstrated no statistically significant difference with the use of amiodarone alone as the primary therapy as compared with conventional medical therapy.
- SCD-HeFT outcome results are particularly compelling in that the data from the SCD-HeFT non-ischemic cardiomyopathy patient cohort corroborates the evidence for ICD therapy in a similar patient population in the DEFINITE Study. The DEFINITE Study, sponsored by St. Jude Medical and presented in the Late Breaking Clinical Trials session at the American Heart Association meeting last November, demonstrated a hazard ratio of 0.65 favoring ICD therapy and a relative reduction of overall mortality of 35% as compared with conventional medical therapy.

SCD-HeFT provides very strong evidence that ICD therapy is indicated for primary prevention of all-cause death in patients with a presence of NYHA Class II and III congestive heart failure, a left ventricular ejection fraction of equal to or less than 0.35, and no prior history of ventricular tachyarrhythmias. This is compelling evidence and places both the clinician and the patient in an ethical bind if reimbursement is not provided for failure to prescribe an ICD for these patients would constitute substandard care, now that the results are available. Without CMS approval, many of my patients cannot afford this therapy on their own yet failure to provide this therapy is placing them at increased risk. In view of the available data, I will be discussing this with my patients and still recommend ICD therapy even if not approved by CMS or the various HMO and

other insurance carriers.

I fully realize that the Medicare budget is finite and limited. As a physician, I have great ethical difficulty not recommending life-saving therapy based on solid evidence. In view of SCD-HEFT and DEFINITE, I now believe that there is solid evidence in favor of ICD therapy for the non-ischemic cardiomyopathy patient. SCD-HEFT provides further evidence to support MADIT II in the ischemic heart disease population with serious impaired ventricular function. In an effort to minimize budgetary impact, it would be tempting to perform a subset analysis within the SCD-HEFT data. This would not be scientifically valid without an a priori hypotheses. In addition, sufficient statistical power does not exist to answer additional questions although conclusions from these types of sub-analyses could be used to generate additional research questions. These would be of questionable value in supplying evidence needed to make a coverage determination. Because SCD-HeFT is a landmark clinical trial performed under the auspices of the premier medical investigatory organization in the world, our own NIH and demonstrated a clinically and statistically significant benefit from ICDs, full coverage of the SCD-HeFT patient population should be granted.

SCD-HeFT reinforces my growing belief that the adage “say no to drugs” applies to more than just illicit drugs purchased on the street corner. Rather, virtually all antiarrhythmic drugs are less than totally effective and while they may reduce the number of VT or VF episodes and effectively reduce the number of potential shocks delivered by an ICD, they are not 100% effective. When used alone as primary therapy for a life-threatening arrhythmia, it is now recognized that they are woefully inadequate. While an ICD cannot prevent these arrhythmias, it can rescue the patient when such rhythms occur. The SCD-HeFT clinical trial clearly demonstrated that the use of ICD therapy significantly reduces all-cause mortality compared to conventional medical therapy. As such, it is appropriate, reasonable and necessary for the treatment of patients with NYHA Class II and III congestive heart failure, a left ventricular ejection fraction of equal to or less than 0.35 even in the absence of a prior history of ventricular tachyarrhythmias.

I also feel strongly that any coverage policy should not mandate device choice for specific patient populations since clinical differences between patients require different treatment strategies. I believe that my colleagues and I are in the best position to determine the most appropriate device for patients based on the specific and unique circumstances of each individual case. For example, for patients with paroxysmal AF or VT with 1:1 retrograde conduction, there is a need for dual chamber SVT/VT discrimination features that can reduce morbidity from inappropriate shocks. Patients with a standard indication for bradycardia pacing may require dual-chambered pacing as a treatment option in addition to receiving ICD treatment of their potential ventricular tachyarrhythmias. Various versions of ICD devices also provide diagnostic information for accurate arrhythmia and patient management (e.g., dual chamber EGMs). And, finally, there is a need for flexibility as patients’ conditions often change from disease progression and/or concomitant pharmacologic therapy resulting in the need to upgrade device therapy and tailor it to the patients’ specific needs. For example, over 25% of

patients develop or are first diagnosed with atrial fibrillation after they have had a device implanted. To optimize patient care, device choice must remain with the physician, not set in policy.

I encourage CMS to also review the other recent clinical studies such as DEFINITE and COMPANION as part of the NCA. These studies, although sponsored by industry, are consistent with and add to the body of evidence supporting the use of ICDs in the SCD-HeFT patient population. The combined results of DEFINITE and SCD-Heft in the non-ischemic cardiomyopathy population support a coverage decision of the patient group that was the focus of the DEFINITE study, non-ischemic cardiomyopathy with a reduced left ventricular EF.

With regard to the COMPANION study, those results also support those of SCD-HeFT and DEFINITE for Class III combined ischemic and non-ischemic patients with a hazard ratio of approximately 0.62 favoring CRT-D therapy and a relative reduction of overall mortality of 38% as compared with conventional medical therapy for heart failure.

I recommend that all patient populations currently indicated for ICD therapy, including the patient population represented in the MADIT and MADIT II clinical trials, should continue to be covered as reasonable and necessary under CMS' National Coverage Determination. In addition, the results of the DINAMIT Study, a trial that investigated the benefit of implanting ICDs in the period immediately following an acute MI, do not support changing CMS coverage guidelines with regard to waiting 1 month after an acute MI to implant an ICD , apropos of the MADIT II population.

I appreciate the opportunity to comment regarding CMS' National Coverage Analysis of Implantable Cardioverter Defibrillators.

Comment #38:

Submitter: Steven L. Higgins, MD

Organization:

Date: May 5, 2004

Comment:

I am a clinical cardiac electrophysiologist and must submit the following opinions:

1. CMS lost credibility with their response to MADIT II, rejecting excellent peer-reviewed science in exchange for a sham approval motivated by financial pressures. Your goal should be to save American lives and improve their health. MADIT II suggests that patients should get an ICD if they meet criteria regardless of QRS width. If you do not have enough funds, reevaluate other healthcare expenditures.

2. CMS has a chance to reestablish credibility by honestly reviewing COMPANION and providing approval for this indication without restriction. The science is sound. If CRT and CRT-D devices save lives and improve quality-of-life, Medicare recipients deserve to receive them. The finances should be considered separately. What would you want for your family member?

Comment #39:

Submitter: Jim Coman, MD
Organization: Oklahoma Heart Institute
Date: May 4, 2004
Comment:

SCD-HeFT showed a significant reduction in mortality for patients with class II and III CHF who underwent ICD implantation. This indication should be covered by CMS. The cost per life year saved for ICD intervention is well within the boundary of medical interventions already covered by CMS and certainly below the cost of other interventions which are mandated by the US government.

Substudy analysis can only be used for future trial design and hypothesis formation. Please do not use substudy analysis (as was done in MADIT II) to select a subpopulation of patients for implantation. The statistical validity of that process is lacking. The MADIT II population should likewise be covered entirely. Decisions of cost containment do not rest with CMS. Rationing of healthcare belongs elsewhere.

Comment #40:

Submitter: Aaron & Justine Jaffe
Organization:
Date: May 3, 2004
Comment:

I am a busy practicing electrophysiologist in northern Michigan. When strong data now support our previous belief that prophylactic ICD therapy for patients with idiopathic dilated cardiomyopathy saves lives, I very much would like to provide our patients with the best care. Currently I advise such patients that they would be best treated with a prophylactic ICD, but that CMS might not pay for it. If they wish to proceed (often) they must be prepared to cover the entire cost should CMS refuse coverage. I greatly dislike putting my patients in such a bind. PLEASE pass on my request to CMS to cover prophylactic ICD coverage for the SCD-HeFT patient base!

Comment #41:

Submitter: Mark E. Josephson
Organization:

Date: April 20, 2004

Comment:

I do not believe CMS should fund ICD's for all patients with low EF or SCD-HeFT patients with clinical heart failure (different than MADIT II). Dynamite was negative and definitely did not reach significance. Both MADIT II and SCD HeFT showed little benefit for patients with QRS < .12 sec.

MUSTT subgroup analysis presented by me in 2000 showed the importance of IVCD, LVH (with IVCD), LBBB on mortality in that patient population. The signal averaged ECG QRS duration was also an independent prediction of mortality. As such, I would recommend funding of SCD-HeFT patients ONLY with QRS > .12 sec. The new group of patients covered would be the cardiomyopathy patients. The very low absolute benefit of SCD-HeFT yields horrible cost-effectiveness. I suggest these studies should force a continued need for use of risk stratifiers - even EP's, since only MUSTT and MADIT demonstrated good cost-effectiveness.

Comment #42:

Submitter: Christian Machado, MD, FACC

Organization: Providence Hospital and Medical Centers

Date: April 21, 2004

Comment:

As a investigator for many of the Trial mentioned below, I have seen many of my heroe patients died on behalf of science so that the results of these trials be paid attention to and not be ignored.

I find it my duty to write a few lines, on my strong opinion, for a need to revise Medicare policy on ICD coverage Multiple Trials (MUSTT,MADIT, SCDHeFT) have proven the tremendous benefit in overall mortality that patients get from ICD implantation . This is a benefit for primary prevention that is before the patient suffers any irreversible clinical event This data is strong and comes from trials with different industry sponsors as well as NIH support

Though, we don't have an ideal way of screening the population at the 100% risk, we do not use this rationale for life or health insurance , that is we buy insurance because there is a clear risk

The lack of ideal tools do not keep us from treating or protecting patients, we treat cholesterol though we know not all heart attacks occur in patients with high cholesterol, we screen all passengers of a plain though we know they all are not terrorist, I think you get my point

The issue is, ICD coverage for our patients who are at real risk of SCD is needed, the sound data has arrived, there is no more waiting and is unfair the coverage be provided to subpopulations on the basis of sub analysis.

May I also remind you the financial impact of this decision on total Medicare expenditure is modest and worth it. It is your freind, your father,wife or neighbor who will benefit is not a statistic, is a LIFE the time is here to make the right decision please listen,

Comment #43:

Submitter: Kent Volosin, MD

Organization: University of Pennsylvania

Date: April 22, 2004

Comment:

We are familiar with rising health care costs and its overall impact on the economy, benefits rates, and taxes. However, it is inevitable that medical progress and technology will continue to advance, and people will live more productive and happier lives.

ICD's, in particular, not only treat conditions with a high mortality rate, but do so with so few complications and side effects that many people can return to work (improving the GNP and paying taxes), and spare immense costs associated with the treating these conditions without their use. Not to state the obvious, when calculating the economic impact of an expanded indication for ICD's, the cost of 'conventional' therapy needs to be included in the equation.

I want to pay a little tax as possible, and want Medicare to be around indefinitely. I do think that medical advances on the whole are economically beneficial. Lastly, expanding the 'approved' indications for ICD's is not forcing physicians to implant ICD's in everyone, but is allowing for a choice which can be made between the patient and their doctor.

Comment #44:

Submitter: David Schwartzman, MD

Organization: University of Pittsburgh School of Medicine

Date: April 22, 2004

Comment:

The landmark results of the trial SCD-HeFT were recently released. It has a scientific impact. SCD-HeFT greatly impacts patient access through Medicare coverage. Without Medicare coverage, guidelines will not work and my ability to decide my patients' care will be circumscribed.

As a clinical researcher, it is important that the next step be to obtain

Medicare coverage. Medicare coverage will utilize evidence-based medicine, which takes in to consideration study design, sample size, execution and results. SCD-HeFT is unprecedented in all of these dimensions and accordingly the PIs have voiced their opposition to sub-setting the trial results as unsupported by the trial design.

Full coverage for the SCD-HeFT patients would not result in a significant impact to the Medicare trust fund. The analyst community projects that the market for ICDs will continue to grow at or about its current rate with no real increase in growth. Only one in three currently indicated patients receive an ICD after five years of coverage. The ration is one in five patients, after five years, if MADIT II patients are added to the denominator.

Medtronic made a formal request on March 18, 2004. Because SCD-HeFT is a landmark clinical trial that shows a clinically and statistically significant benefit from ICDs, Medtronic requested full coverage of the SCD-Heft patient population. Given the dramatic results of the trial and the incremental monetary impact to the Medicare program, there is no justification for sub-setting the patient population for coverage purposes. Full coverage is needed to give full meaning to specialty society guidelines and to preserve physician based treatment decisions premised to those guidelines.

Since the publication of the results of the MADIT II trial, CMS has been interested in "low cost" ICDs for primary prevention populations. CMS is considering the use of coverage policy to mandate low-cost devices for SCD-HeFT patients. To optimize patient care, coverage policy should not specify devices for a given class of patients. Medicare coverage policy, with the force and effect of law, is too static to include a decision as individualized as device type, model, or manufacturer. The question at hand is: "Can the SCD-HeFT population be broken into homogeneous subsets that are so similar that a particular type of device can be specified in a coverage policy, or is physician judgment required to select the appropriate device for SCDHeFT patients?" Once written into policy, the only way device-specific requirements can be changed is when a large new clinical trial is completed, the results published, and CMS' review completed.

Medtronic's request to modify the current ICD coverage policy was accepted by CMS in March of 2004 initiating a thirty day comment period. The comment periods ends on April 30, 2004, at the end of the business day. CMS is seeking comments o each of the four most recent ICD trials, as well as evidence to support the appropriate selection of various types of devices for differing patient populations. I am contacting you to impress upon you the importance of full Medicare coverage.

Comment #45:

Submitter: Steve Singh
Organization: VA Medical Center, DC
Date: April 22, 2004
Comment:

SCD-HeFT is a land mark study and the results provide answers to the question of ICD use in patients with heart failure and reduced ejection fraction. The results are un-equivocal in that the ICD offers protection. I believe that saving 7 lives over 5 years in 100 patients is quite significant. While it is true that the ICD 'works' better in subsets, we should be cautious in the interpretation of such data. I do realize the issue of cost-effectiveness, but are we really qualified to put a price on a life? I do know it is difficult to draw a line

The ICD continues to show benefit and we must not ignore this fact. Please consider my letter as one voice in many, and feel free to contact me if so desired.

Comment #46:

Submitter: Mark A. Thompson, MD
Organization: The Sanger Clinic
Date: April 22, 2004
Comment:

As a cardiologist and implanter of pacemakers and ICD devices, I strongly ask you to consider coverage for ICD devices for the SCD-HeFT population and the MADIT-II population with narrow QRS duration, not just wide QRS duration. The science is rigorous and clearly shows substantial benefit for ICD implantation. Lack of CMS coverage limits the practical use of these devices in thousands of patients who would clearly benefit from them. In addition, limiting the sophistication of the devices by mandating a "low-cost ICD" is an inappropriate limitation and not supported by scientific data.

Comment #47:

Submitter: David L. Scher, MD, FACP, FACC
Organization:
Date: April 22, 2004
Comment:

I am a practicing cardiac electrophysiologist in Harrisburg, PA. I have been an investigator in multiple NIH ICD trials in the past, including CABG PATCH which was a neutral primary sudden death prevention trial for ICDs. Trials are done with a

hypothesis. When negative or neutral hypotheses are reached, it is easy for the CMS to deny approval for an indication, justifiably so. However, when sudden death is involved, and a study with as strong a positive outcome as SCD- HeFT is concluded, if CMS does anything but grant approval for an indication for prophylactic ICD implant in patients with class II and III heart failure and EF less than 35%, regardless of etiology, it will be sending a message that the number one killer in the USA is not a priority of health care in this country. The CMS decision granting approval only for QRS duration greater than 120 msec from the MADIT II study already gave a message that dollars (though a miniscule increase in NHC budget) are more important than saving lives. If this new indication request is denied, it will truly signal a policy of 'head in the sand' view of sudden cardiac death. The initiative of the Red Dress will be meaningless inasmuch as women are affected by sudden death as much as men. Cholesterol prostate, and breast cancer screening were high profile initiatives undertaken by this and other administrations. Yet prevention of the killer of more persons all these diseases combined need addressed in the wake of overwhelming evidence now in front of CMS. These studies will not be done again, and my patients will wait no longer for foot dragging by this government. When the long delay from FDA approval to the CMS ruling regarding MADIT II patients was taking place, I had no problems explaining to them that the government was hanging their lives out on the line. I didn't stand by and just complain. I presented MADIT II to the PA MCAC, of which I am a delegate. It was overwhelmingly approved without a QRS duration limit. Members were outraged at the long delay by CMS. Their feelings reflect the informed medical community as a whole, not just electrophysiologists whom the CMS may think have a self-serving interest in these approval processes. We deal with real people across a table everyday telling them they are at high risk of sudden death. Heed our pleas on our patients' behalves. For if we do not speak for them, no one will except the results of these studies which I hope will not be manipulated as MADIT II. Because this study not only confirms results of MADIT II and COMPANION, but solidifies the idea that the magnitude of this problem is huge and we must act now.

I urge you to approve new ICD indications based on the results of the SCD-HeFT trial.

Comment #48:

Submitter: Ken Ellenbogen, M.D.

Organization: Medical College of Virginia

Date: April 22, 2004

Comment:

I am writing as a practicing cardiologist seeking to have my opinion taken into account with respect to MEDICARE/CMS comments on the SCD-HeFT trial and ICD coverage.

My opinions are strongly felt, and represent the feeling of my colleagues and partners at the Medical College of Virginia and the McGuire VA Medical Center.

All decisions should be based on published medical data and evidence

based.

They can be summarized simply.

1. MEDICARE should cover ICD implantation for patients who are similar to those studied in SCD-HeFT and MADIT II. Namely, ALL patients with NYHA Class II and III CHF who have an ejection fraction less than 35%, whether due to ischemic or non-ischemic cardiomyopathy. This should be supported regardless of QRS width, etiology of CHF, age, or sex.
2. MEDICARE should not dictate what type of device is to be implanted, the doctor should decide what the most appropriate device is.
3. There is no data to support implantation of a "low cost" featureless ICD. Unless this is shown in a clinical trial to benefit patients, I do not believe this would be an appropriate device choice in > 90% of our patients.

Comment #49:

Submitter: Steve Ackerman, M.D.

Organization:

Date: April 22, 2004

Comment:

I am writing to urge you expand the coverage for ICD's into the idiopathic cardiomyopathy population as in SCD-HeFT. I remain distraught about your decision on MADIT II as I feel that you are limiting health care for those at highest risk.

Thank you for your consideration of this important topic.

Comment #50:

Submitter: Stephen Shorofsky, MD, Ph.D.

Organization: University of Maryland Medical Center

Date: April 23, 2004

Comment:

I am a practicing electrophysiologist in Maryland. I urge you to approve ICDs for the treatment of patients with class 2 and 3 heart failure that met the criteria for enrollment into the Scd-Heft trial. The trial showed a clear mortality benefit from the ICD in these patients. The magnitude of the benefit is equal to that seen with many of the drugs already approved for treating these patients. It would be difficult to withhold this proven treatment from the Medicare population

when it will be offered to those patients with private insurance. In addition, I caution against reading too much into any sub-analyses. All that sub-analyses can do is to propose hypotheses to study in future, randomized trial.

Thank you for your consideration of this matter.

Comment #51:

Submitter: L. Brent Mitchell, M.D.

Organization: University of Calgary and Calgary Health Region

Date: April 28, 2004

Comment:

I am an academic clinical cardiac electrophysiologist at the University of Calgary and Calgary Health Region. As a Site Investigator in the SCD-HeFT trial, I am intimately familiar with the results of this trial. As a Canadian, it makes no difference to me whether or not CMS chooses to provide or not to provide reimbursement of ICD health care related to the SCD-HeFT indication. Nevertheless, as a Physician, I am compelled to urge the CMS to "do the right thing".

The SCD-HeFT trial in and of itself provides definitive evidence that use of an ICD prevents death from all causes in patients with moderately severe congestive heart failure (NYHA functional class II-III) and left ventricular systolic dysfunction (LVEF less than or equal to 0.35). Just as importantly, the trial demonstrates that the only other potentially viable therapy for the prevention of the contribution of arrhythmic mortality to the problem of all-cause death (amiodarone) was of no value. These results, taken in conjunction with those of MADIT II, COMPANION, and DEFINITE make the benefits of the ICD in this patient population very clear. The treatment alternatives in these patients include no ICD or an ICD. The latter is associated with a 23% reduction in all-cause mortality. A choice not to implant the ICD is a choice to accept the higher all-cause mortality - a choice that is indefensible in many patients.

Our colleagues at CMS have previously expressed a willingness to ascribe patient benefits observed in a trial to a non-randomized subgroup (see the MADIT II decision). I would like to add my voice to the many that you have previously received pointing out the dangers of basing treatment decisions on subgroup analyses that can only be hypothesis generating.

As always, ask what treatment you would wish a loved one to receive. Facilitating the provision of that therapy to all is to "do the right thing".

Comment #52:

Submitter: Mark S. Link, MD

Organization: Tufts-New England Medical Center

Date: April 28, 2004

Comment:

I am a practicing cardiac electrophysiologist. I have watched closely the results of the clinical trials of ICDs. I am especially interested in MADIT-II and SCD-HEFT, trials which have shown a mortality benefit for individuals with heart failure and LV ejections fractions less than 35%. We all have seen too many of these individuals die suddenly, and I, for one, am very happy to see that there is finally some proof that ICDs save the lives of these individuals.

Please assist us in taking care of these individuals by broadening the coverage for ICDs to include these individuals. It is a very difficult position for the patients and us to be in when we have evidence that a technology can prolong their life, but that their insurance will or cannot cover it. Please help us in this regard.

Comment #53:

Submitter: Thomas Bigger

Organization: Columbia University

Date: April 24, 2004

Comment:

During hearings in February 2003, microvolt T-wave alternans was acknowledged as a promising test to select patients for ICD therapy. Evidence has continued to support this test for that purpose. At least two data sets have been analyzed and recently submitted for publication (Chow et al. and Bloomfield et al.). The SCD HeFT also has a microvolt T-wave alternans substudy. All of these data sets should be reviewed by CMS.

Comment #54:

Submitter: Paul Colavita, M.D.

Organization: Sanger Clinic

Date: April 24, 2004

Comment:

I am a practicing electrophysiologist and President of the Sanger Clinic, a 65 person cardiovascular group with its main office in Charlotte, NC. Our cardiologists,

cardiovascular surgeons and pediatric cardiologists care for more than 250,000 patients in western NC. Over 50% of our patient population is covered by Medicare. Your recent decision to limit the implantation of defibrillators to only those MADIT-II patients with QRS duration >120ms, was in effect a rationing of healthcare in the US. This had caused much consternation and angst within our practice, both for the physicians and patients who are affected by your decision. I can understand the fact that MADIT-II was only one study and more information was necessary before making a payment decision. But now , we have additional studies such as SCD-HeFT. Because SCD-HeFT is a landmark clinical trial, that shows a clinically and statistically significant benefit from ICDs, full coverage of the SCD-HeFT and MADIT-II should be granted. There is no justification for sub-setting the patient population for coverage purposes. Full coverage should be granted to give full meaning to specialty society clinical guidelines to and to preserve physician-based treatment decisions premised on those guidelines.

Since the publication of the results of the MADIT-II trial, CMS has been interested in "low cost" ICDs for primary prevention populations. CMS is also considering the use of coverage policy to mandate low cost devices. Medicare should not be prescribing therapy. This should be the responsibility of the physicians who care for these patients, not a governmental body. The financial risks of your decision can be handled in a more appropriate manner than a device specific coverage policy.

Thank you for your attention to these matters. I am sure you will make the right decision.

Comment #55:

Submitter: David Schwartzman, MD

Organization: University of Pittsburgh School of Medicine

Date: April 28, 2004

Comment:

PLEASE stick to the science. What is bullet-proof is the primary endpoint, which can be applied only to the population as a whole. If you are going to subset, then you must admit to the beneficiary who is denied that you are doing so for financial purposes alone.

Comment #56:

Submitter: Harry J. DeAntonio

Organization: East Carolina University

Date: April 28, 2004

Comment:

I support the findings of SCD-HeFT and believe that there is opportunity to save lives in this difficult to treat group of patients. These patients by study design include those with heart failure and a reduced left ventricular ejection fraction (< =35%). I believe that the type of device and the selection of the appropriate patient should be left in the hands of a

trained cardiac electrophysiologist. I appreciate your assistance in this matter.

Comment #57:

Submitter: Bradley P. Knight, MD

Organization: University of Chicago Hospitals

Date: April 28, 2004

Comment:

Based on the results of the NIH sponsored Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), it is my opinion that Centers for Medicare and Medicaid Services (CMS) should expand the Medicare covered indications for implantable defibrillators to include the population studied in the trial.

I would also like to offer a suggestion that might limit inappropriate device implantation. Given that the sole objective indication for defibrillator implantation would become a left ventricular ejection fraction $\leq 35\%$, I would suggest that at least 2 different measurements of ventricular function (echo, nuclear imaging, left ventriculogram) that confirm left ventricular ejection fraction $\leq 35\%$ be required for reimbursement. I feel that this simple requirement would substantially reduce the amount of unnecessary defibrillator implants. Erroneous measures of ventricular function are common in clinical practice.

Comment #58:

Submitter: Michael West

Organization:

Date: April 28, 2004

Comment:

CMS should utilize the results of well constructed trials to formulate coverage policies. When data proves a survival benefit and the proven therapy is altered for monetary reasons the result is an unhappy public. Ultimately, the providers bear the burden of the alterations. If CMS is genuinely interested in the public's well being, then proven life-saving therapies should not be altered to "fit the budget".

Comment #59:

Submitter: James B. Young, MD

Organization: Cleveland Clinic Foundation

Date: April 28, 2004

Comment:

In response to your request for commentary regarding new indications labeling for ICD's in heart failure patients I would like to point out that the trial design of landmark studies which clearly support that ICD insertion saves lives in ischemic dilated post myocardial infarction heart failure patients (MADIT II, COMPANION) as well as chronic ischemic and non-ischemic dilated cardiomyopathy patients more generally (SCD-HEFT) does not allow for retrospective parsing of data into subgroups to define those that should receive an implant. This violates a cardinal principal of clinic trials and you should not allow this to happen. Coverage decisions should simply be based on the science of the trial which means that patients meeting the entry criteria of the clinical investigation should be labeled as suitable for device insertion. Short of this would be duplicitous in view of the approval process that all devices and drugs must now be subjected to. It is highly unlikely that any procedure or therapeutic agent would receive widespread FDA or CMS approval based solely on a subset analysis of retrospectively identified subgroups. Furthermore, dictating the specific type of device to be inserted runs counter to the principal of treating our patients with the interventions specifically as described in the research effort.

Thank you for your consideration of this important issue.

Comment #60:

Submitter: Todd Florin, MD

Organization:

Date: April 27, 2004

Comment:

As a practicing electrophysiologist I am left with one overriding truth. Defibrillators save lives. When I finish this email, I will call a patient whose life has been saved three times from his defibrillator. I commissioned him to do a painting for my wife's anniversary present. This man is an active productive individual and has been for the 5 years I have known him. His story is repeated daily in every electrophysiologist office in the country.

Defibrillators are expensive. If we are going to ration care, than we need to be honest and open about it. There is no question that defibrillators are life saving machines. The science is clear.

Personally, I would favor a new DRG for prophylactic defibrillators at a lower reimbursement level to use market forces to push for cheaper defeatured devices. Regardless of how it comes about, we must either have an open, honest rationing discussion or begin to reimburse for implanted defibrillators. To tell a 64 year old that we need to do it now, because in a year, the government would consider it fraud, is an obscene problem

I look forward to your correction of this reimbursement problem

Comment #61:

Submitter: Sinan GURSOY, MD

Organization:

Date: April 27, 2004

Comment:

As practicing electrophysiologists, the recent uncertainty by CMS on ICD coverage has really put us on a bind as to how to approach the problem of counseling our patients at risk for Sudden Cardiac Death. Our difficulties in this matter are as follows:

1/ There are no other modalities in modern health care that have been shown to reduce overall mortality in patients with a cardiomyopathy, whether or ischemic or not, than the implantation of an ICD. Even when you look at the CASS trial from the early 80's or any interventional trial of recent years, no treatment modality has shown, that we know of, such a reduction in mortality.

2/ If the modern approach, to health care as a provider is and should be based on evidenced based medicine, we do not know how we can deny an ICD to any patients who meet the MADIT II and/or the SCD-Heft criteria.

3/ Granted if we find out some subsets that are at low risk, that is great, but until that data is available, we find it hard to accept dissecting available studies to try to answer this question, as that was not at all what either study was designed for. Like someone said "If you torture the data enough, it will admit". We believe at this point, that until further studies can identify lower risk subgroups, it would not be scientifically sound to try to read into subgroups in either study, as that is not what they were designed for and such statistical analysis would be at least flawed if not plainly inaccurate.

4/ We understand the financial implications of expanding coverage, but we are unaware of any similar previous stand by CMS, when the data seems so sound. Like Mr. Alan Greenspan pointed out recently, technology to make us live longer never stops to evolve and might end up being more expensive than we can afford as a society as a whole. Financial constraints will be a huge concern in the future of American medicine. Appropriate use of resources will be even more important as we go. If CMS's decision not to cover these studies is even partly a financial one, it should be dealt with more openly, and future guidelines jointly derived by CMS and associated medical and legislative bodies, as this, certainly, is the tip of the iceberg.

4/ In the interim, from an ethical, medical and legal perspective, we find it difficult not to be able to present this treatment alternative to our patients, at this point in time. While they are our "raison d'être", they would be the ones penalized. In conclusion, we strongly believe that our duty as physicians, scientists and providers, is to offer the best available treatment to our patients and a clear, unambiguous decision from CMS will certainly be welcome.

Comment #62:

Submitter: Imran Niazi, MD, FACC, FACP; Charles Lanzarotti, MD, FACC, FACP;
and Nguyen Phan, MD

Organization:

Date: April 27, 2004

Comment:

This email is sent to you in support of the SCD-HeFT study outcomes. Our medical practice has been treating this patient population since 1987. Each year the newest and most appropriate treatment plans have been offered to our patients. These choices have always been made with the patient's best interest as the first consideration. Government should not be placed into the position of making therapeutic choices for citizens.

Historically, the choice for this patient group was the basic implant or medication. Amiodarone has never been the best possible option, however for a long time it was considered a primary treatment option if devices were not the solution. As the implantable device technology has advanced, this treatment option has far exceeded medication/amiodarone as a prophylactic medication. Medication does not compare and the life expectancy of an implanted device.

It is medically important and significant that Medicare/CMS allows insured subscribers the opportunity to acquire this medical therapy for their well being and quality of life. No qualified patient should be denied appropriate proven treatment based upon governmental insurance sponsored limitations. As this population ages, the impact to the Medicare trust fund from the SCD-HeFT population will not be significant enough to limit coverage.

Comment #63:

Submitter: Bruce Stambler, MD

Organization:

Date: April 27, 2004

Comment:

Sudden cardiac death is a major public health problem in the United States accounting for over 300,000 deaths annually. Less than 10% of patients who suffer out-hospital cardiac arrest in the U.S. survive. The landmark results of the SCD-Heft will save countless lives if fully implemented. I urge CMS both as a citizen and a physician to approve full coverage for the SCD-Heft population. The evidence is clear. More lives should not be lost unnecessarily.

Comment #64:

Submitter: G. Neal Kay, MD

Organization: University of Alabama at Birmingham
Date: April 26, 2004
Comment:

The SCD-Hft and MADIT II trials tested the hypothesis that ICD implantation will improve survival in patients with low LVEF. Both trials demonstrate a significant improvement in overall mortality with an ICD.

There is no justification for post-hoc analysis trying to identify a high-risk subset of patients to cover. This is statistically invalid and potentially misleading. We should proceed to cover the scientifically valid conclusion-- that prophylactic ICDs are indicated and should be implanted in patients who meet the entry criteria (LVEF \leq 0.39, regardless of etiology). To deny coverage is to place physicians in a medico-legal and ethical dilemma. The physician is liable for malpractice if an ICD is not offered. On the other hand, patients are placed in the situation of having to pay for an indicated but not covered therapy. Please rectify this intolerable situation.

Comment #65:
Submitter: Jonathan Howlett
Organization:
Date: April 25, 2004
Comment:

As a SCD-HeFT investigator, I feel it is important to make my views regarding the CMS Coverage for ICD in the treatment of chronic congestive heart failure, known to you and the committee. I feel the most appropriate approach taken from analysis of several randomized trials, including SCD-HeFT, is to approve coverage of ICD insertion for primary prophylaxis of SCD in patients who meet the following criteria:

Chronic congestive heart failure for > 3 months
EF <35% while on maximal medical therapy for at least 6 weeks
No recent ACS, MI, PTCA or CABG within 3 months
Creatinine <2.5 mg/dl
NYHA FC II Symptoms, stable without recent worsening CHF
Careful discussion of risk and benefit of device insertion
Documentation of all of the above in the medical record.

I feel NYHA FC III should NOT be covered and that FC IV Symptoms represent a contraindication for device insertion.

I hope this email helps the discussion.

Comment #66:

Submitter: Brian Olshansky, MD

Organization: University of Iowa Hospitals

Date: April 25, 2004

Comment:

I am writing to you to express my strong support for changes in CMS recommendations regarding ICD implants in patients.

I have been an investigator in the SCD-HeFT Trial and was involved in the pilot study that preceded it. I have been involved with many prior clinical ICD trials including MADIT I, MADIT, II, and COMPANION. I have been involved with assessing the need for ICD implants in patients and have followed patients with ICDs for 20 years.

The SCD-HeFT trial is a landmark trial that has shown definitively that ICDs benefit patients who have a left ventricular ejection fraction no more than 0.35 and NYHA functional class II-III heart failure, otherwise treated properly. The study was not designed to address specific subgroups of this population.

There will be no other studies that will look into the need for ICDs in this population in the near future and this study supercedes any other data regarding the need for an ICD in this patient population.

I urge CMS to move to rapidly change the guidelines for ICD implant in this patient population as soon as possible. Full coverage should be granted to allow for ICD implant in this population who will clearly benefit.

The question can be asked: "Can the SCD-HeFT population be broken into subsets so that the need for a device or a particular type of device can be specified in a coverage policy"? I do not think so. The SCD-HeFT study was not designed to address this issue. The guidelines should reflect the intent of the study and the results of the study.

While there are smaller, less well designed, clinical trials in this country and in Europe that address specific subset populations of patients also included in SCD-HeFT, no other study is as definitive and none provides strong contradictory information from that provided in the SCD-HeFT trial. The SCD-HeFT trial provides the best data and no other similar trial is planned to my knowledge. Besides being the best study of its type involving heart failure patients, SCD-HeFT patients had excellent and complete long term follow-up and a placebo group was included. The study was NIH funded.

Based on the results of the study, a qualified physician can judge which patient fitting into the SCD-HeFT type of patient is best suited for an ICD device and which type of ICD device is best for a given patient.

If I can help further or you need me to expand on my opinions, I will be happy to do so.

April 29, 2004

Ms. JoAnna Baldwin
Lead Analyst
Mail Stop C1-09-06
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: Public Comment/Implantable Defibrillators (CAG-00157R1)

Dear Dr. Chin:

BIOTRONIK, one of the leading cardiac rhythm management companies worldwide, fully supports the petition to expand coverage of implantable defibrillators to include the population studied in the NIH-sponsored Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). The results of the SCD-HeFT study further support the conclusions reached in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), which were published in March, 2002. Both studies demonstrate that ICDs save lives for well-defined patient populations.

We recognize that as CMS considers expanding Medicare coverage for ICDs to be consistent with these clinical trial results, it will need to consider the increased costs the Medicare Program must bear to match this increased coverage. BIOTRONIK is committed to bringing safe and effective life saving technologies to market at a reasonable cost while improving the quality of care patients deserve.

As CMS considers the financial challenge of expanding coverage for implantable defibrillators, we would like to point out that following its FDA approval in May 2003, we successfully launched our prophylactic ICD known as the Cardiac Airbag® for under \$10,000. At less than half the price of the ICDs used in the SCD-HeFT, our introduction of Cardiac Airbag® clearly indicates our ability, willingness and determination to reduce Medicare expenditures while maintaining and often improving patient quality of care.

It is important to note that the SCD-HeFT clinical study was completed utilizing an ICD, which was conservatively programmed as a shock-only ICD, i.e., VF therapy only. This reprogramming of the ICD makes it the functional equivalent to our Cardiac Airbag®. Given the impressive results of this clinical study, we believe that ICDs designed as shock boxes, including our Cardiac Airbag®, should be expressly covered in CMS's expanded coverage policy. Doing so will enable CMS to expand ICD coverage

BIOTRONIK, Inc.
6024 Jean Road
Lake Oswego, OR 97035
Telephone 800-547-0394
Telefax 503-635-9936

Ms. JoAnna Baldwin
RE: Public Comment/Implantable Defibrillators (CAG-00157R1)
April 29, 2004



appropriately in a manner that will help reduce costs. Given the current financial strains on our health care system, we believe everyone must work cooperatively and diligently to find solutions that will have a positive impact on the future of health care in America.

BIOTRONIK has already taken the next step in this direction. Recognizing the ability to improve patient quality of life while also reducing overall health care costs, we combined our shock box with remote monitoring technology. Our Cardiac Airbag T®, which utilizes remote monitoring technology, also received FDA approval in May 2003. We would urge CMS to take into account the additional cost savings this type of technology offers to the Medicare Program as it modifies its ICD coverage policy. Not only should the initial cost outlay for the device be considered, but also the aggregate cost of following these patients must be factored into the decision-making process. Only with remote monitoring technologies can this cost paradigm be positively impacted.

I wish to thank you for your consideration of this important health care matter. We greatly appreciate the opportunity to provide you our insights and look forward to helping CMS provide top quality health care at a reasonable cost to Medicare beneficiaries. Please call me if you have any questions or if we can be of any further assistance.

Sincerely,

A handwritten signature in blue ink that reads 'Jake Langer'. The signature is stylized and includes a large, sweeping flourish at the end.

Jake Langer
President

cc: Joseph Chin, M.D., Medical Officer, CMS



BETH ISRAEL DEACONESS
MEDICAL CENTER
CARDIOVASCULAR DIVISION

Mark E. Josephson, M.D.
Chief, Cardiovascular Division
Director, Harvard-Thorndike Electrophysiology Institute
And Arrhythmia Service
Cardiology/Electrophysiology

330 Brookline Avenue
Boston, MA 02215
Phone: 617-632-7393
Fax: 617-632-7620

To: Joanna Baldwin From: Peter Zimetbaum, M.D.
Fax: 410-786-9286 Pages—Including cover: 2
Phone: Date: 4/30/03
Re: ICD's - SCD-HeFT CC:

Urgent For Review Please Comment Please Reply Confidential

Pls see attached comments re:
above subject.

Thanks!

The information contained in this fax is confidential and is intended only for the use of the individual or entity named above. If you are not the intended recipient, you are hereby notified that any dissemination, copying, or disclosure of this communication is strictly prohibited. If you have received this fax in error, please notify CareGroup at 617 975-6130 and destroy this communication immediately without making any copies of it or distributing it.

Comments to questions:

- 1) What do you think about the SCD – HeFT results?
- 2) How will you apply those results to clinical practice?
- 3) What should Medicare do in their coverage decision for ICS's?
- 4) Medicare is generally unable to require data collection or fund registries.

There is a need for stratification. The benefit is too small and the cost is too great. Devices have their own set of complications, which the majority has experienced. Using a wide QRS is the only reasonable way, but it needs to be used prospectively. Long term registry for all new funded devices is mandatory in order to allow new and better therapies to be funded and allow withdrawal of funding for old therapies that have become updated.

April 27, 2004

The Honorable Thomas Scully
Administrator
Centers for Medicare and Medicaid Services
7500 Security Boulevard
P.O. Box 8010
Baltimore, Maryland, 21244-8018

Dear Administrator Scully:

As a cardiology nurse specializing in the treatment of heart failure, I am writing to urge your active support in expanding Medicare coverage for heart failure patients who would benefit from Internal Cardioverter Defibrillator therapy.

Sudden cardiac death is the leading cause of death in the United States, claiming more than 400,000 lives every year or one person every two minutes.

As you know, the benefits of Internal Cardioverter Defibrillators (ICDs) for heart failure patients was underscored in a landmark study published in the March 21, 2002 *New England Journal of Medicine*. The study of 1,200 patients who suffered severe heart damage during a heart attack found that those with ICDs had a 31 percent decreased risk of death compared to those getting conventional, non-ICD treatment.

In your press release on June 6, 2003 you indicated that CMS would reevaluate its' decision regarding coverage of ICDs for Medicare beneficiaries when further data was available. On Monday, March 8, 2004, the results of the National Institute of Health's Sudden Cardiac Death in Heart Failure Trial were announced at the American College of Cardiology scientific sessions in New Orleans. This study, the largest ICD trial ever conducted to help determine the importance of ICDs, included 2,521 patients. The study demonstrated a 23 percent reduction in mortality for those with ICDs when compared to non-ICD treatment.

On behalf of the thousands of heart patients and their families whose lives may depend on ICD treatment, I strongly recommend that CMS reconsider the current guidelines for coverage and allow all eligible Medicare patients to receive ICDs.

I very much appreciate your attention to this important public health matter. I look forward to hearing back from you regarding your position. Should you have any questions or if I can be of any assistance, please do not hesitate to contact me.

Sincerely,

Beverly Bartlett, RN, BSN

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Bethesda, MD

John L. Fakunding, PhD
Bethesda, MD

Michel Komajda, MD
Saint Cloud, France

James B. Young, MD
Cleveland, OH

April 30, 2004

Sean Tunis, MD
Chief Clinical Officer
Centers for Medicare and Medicaid Services (CMS)
Deputy Director, Office of Clinical Standards and Quality
South Bldg Room S3-26-17 (MS: S3-01-02)
7500 Security Boulevard
Baltimore, MD 21244-1850

Dear Dr. Tunis:

The Heart Failure Society of America is a non-profit organization whose members consist primarily of health care providers with a primary focus on the care of patients with heart failure. In general, the professional services that we provide are primarily cognitive in nature, and in general, we do not implant devices and do not receive income from the implantation of devices by others. We do have a long tradition and record of patient advocacy. For all of these reasons, we respectfully submit this letter regarding the NCA Tracking Sheet for Implantable Cardioverter Defibrillators (ICDs) (CAG-00157R1) as posted on the Centers for Medicare and Medicaid Services (CMS) website.

The Society has reviewed the results of recent clinical trials that have evaluated the effects of implantable cardioverter defibrillators (ICDs) in patients with heart failure due to left ventricular dysfunction. In most cases, we have not been able to review the actual data from these studies and have relied instead on public presentations of preliminary results that (in many cases) have not yet undergone peer-review. We recognize that the final analyses (when completed) may differ from the results that have been presented to date, and we reserve the right to modify our recommendations to be consistent with the final data. We also appreciate the need to reach reimbursement decisions that are not only commensurate with the available evidence but also with the need for cost-effective policies.

In this regard, we would ask CMS to take notice of the following observations that have been made in recent clinical trials:

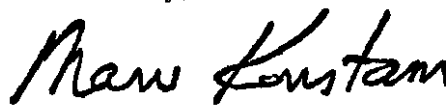
- The implantation of ICDs in selected patients with heart failure and left ventricular dysfunction who have not experienced a life-threatening ventricular arrhythmia has resulted in a meaningful reduction in the risk of death.

- This benefit has been observed in patients with and without underlying coronary artery disease as the cause of left ventricular dysfunction.
- This benefit has been observed in patients who have been receiving excellent treatment for their heart failure. The vast majority of patients who have benefited have been treated with ACE inhibitors and beta-blockers, two classes of drugs that are known to prolong life and which are frequently not optimally used.
- This benefit has been observed in patients with stable chronic heart failure. Patients with acutely decompensated heart failure (hospitalized or not) were generally not enrolled in these studies. Patients with end-stage heart failure or with major complicating medical illnesses were not enrolled.
- Subgroup analyses have suggested that the benefits of ICD placement may not be uniformly present in all patients who were adequately represented in these studies. However, subgroup analyses are very difficult to interpret and can lead to incorrect or conflicting recommendations. Furthermore, subgroup analyses frequently rely on characteristics that are largely subjective in nature or lend themselves to creative interpretation by physicians.

We bring these observations to your attention in the hope that they will be helpful to you in moving towards an appropriate reimbursement decision. We offer our experience and insights to you and our interest in meeting with you to discuss these issues.

If you have any questions, please contact Cheryl Yano, Executive Director, Heart Failure Society of America at 651-642-1633 or cyano@hfsa.org.

Sincerely,



Marvin A. Konstam, M.D.
President
Heart Failure Society of America

MAK/cjy



David A. Chazanovitz
President and CEO

April 29, 2004

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

Re: Public Comment Period – NCA/NCD – Implantable Defibrillators

Dear Dr. Phurrough:

Following the release of the SCD-HeFT results, and the subsequent reevaluation of the indications for implantable defibrillators by your agency, we thought it appropriate to request that you also reevaluate the utility of Microvolt T-Wave Alternans (MTWA) in the context of the various patient populations exhibiting increased risk of sudden cardiac death.

During the NCA process and MCAC Meeting associated with the Madit II trial, clinical information was presented by a number of physicians to CMS with respect to the utility of MTWA as a non invasive risk stratifier in this population. Clearly the stakes are very high, lives are at risk and significant expense issues loom in the potential decision to cover the million plus patient population which the various ICDs studies are now encompassing.

Various comments made by Dr. Tunis in public sessions, as well as the decision to utilize QRS duration as a risk stratifier in the Madit II population, suggest the realization of the important need to risk stratify this population to prevent patients in high risk general populations, who are actually at low risk personally, from receiving expensive and invasive therapy, which will prove to be unnecessary. The ability to discriminate those at low risk will have the impact of saving billions of dollars thus helping ease the burden of making implantable defibrillators available to those who truly are at risk and are in great need of these life saving devices.

During the NCA process in 2003 Drs. Theodore Chow and Richard Cohen presented clinical information to CMS regarding the utility of MTWA and its 98+% Negative Predictive value in the Madit II population (many of those patients would also be considered SCD-HeFT patients). Dr Daniel Bloomfield, in a separate session, also presented information from his NIH sponsored Congestive Heart Failure Trial further documenting the ability of MTWA to effectively rule out the need for ICD implantation in patients who test negative, as none of the MTWA negative patients in this multi-center study died. I am pleased to advise you that Dr Bloomfield has submitted his paper for publication. Additionally he has added QRS duration information on this population which will clearly suggest the superiority of MTWA with respect to non invasive risk stratification.

I have taken the liberty of preparing three exhibits with this transmittal letter. Exhibit A compares four of the landmark ICD studies. While it is obvious that you already have this information available to you, the point that the chart demonstrates is that while each study addresses larger and larger populations, the hazard ratios demonstrate a smaller and smaller benefit from the use of implantable defibrillators. We

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respect the statistical significance of these studies, but the declining difference in mortality between the ICD groups and the placebo / medicated groups suggests the importance of determining which patients are at minimal risk so as to best determine which patients will most likely benefit from ICD therapy.

Exhibit B addresses the significant financial impact which MTWA can have on these large and growing patient populations. While the discussion encompasses the total market, not just Medicare patients, the numbers suggest that there could be an annual potential saving of approximately \$2.4 billion dollars. Assuming that 50% of this market segment is represented by Medicare, well over \$1 billion could be saved annually by integrating MTWA testing into the diagnosis algorithm. The MTWA Test has FDA 510K concurrence with indications that would clearly cover all of the patients being discussed. Additionally the test has its own unique CPT Code (93025) which carries an average Medicare payment of approximately \$338. Our analysis also suggests that the ICD market is 25% penetrated. Should the penetration rate increase and more needy patients receive ICD therapy, the savings will increase as well.

Exhibit C discusses some relevant clinical studies, specifically to Madit II, however, Dr Bloomfield's study encompasses a substantially larger population of heart failure patients. Please note that of 486 Madit II type patients, the 147 or 30% who tested negative with MTWA fared quite well without invasive therapeutic intervention. There was only 1 death in this group, a rate substantially lower than reported in any of the ICD patient groups of the previously mentioned studies. MTWA has gained considerable market visibility and we continue to participate in multiple clinical studies as the product becomes more mainstream within the clinical cardiology community. I have listed some of the more significant clinical studies which are ongoing. As a point of information we believe that the 30% negative rate compiled from the 3 studies on Exhibit C will increase because of our ability to reduce indeterminate results.

For your convenience I am also attaching a copy of the Research Letter published in The Lancet detailing Dr Stephan Hohnloser's study. Additionally I have enclosed a CD-ROM containing presentations made by Drs. Bloomfield, Chow and Hohnloser at a symposium which we sponsored at the 2003 NASPE Meeting. At this year's NASPE Meeting there will be further presentations, abstracts, posters and even a core curriculum course on Microvolt T-Wave Alternans to be held on Friday, May 21st.

We strongly believe in the sound science and life saving abilities associated with implantable defibrillators. We have worked for many years developing a technology that would aid the process of finding the right patients truly in need of these valuable devices. The identification of large, broad based population groups requires better non-invasive risk stratification. This process can effectively be accomplished with MTWA. We would appreciate the opportunity to visit you with the physicians who have performed the various MTWA studies to elaborate on the role MTWA testing can play as part of your challenging ICD coverage determination.

Sincerely yours,



cc: JoAnna Baldwin
Dr Marcell Salive
Dr. Joseph Chin
Dr Sean Tunis

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Comparison and Summary of Major ICD Trials

Trail	MADIT	MUSTT	MADIT II	SCDHeFT
Study Objective	To evaluate if prophylactic therapy with ICD as compared with conventional medical therapy would improve survival in patients with a previous heart attack and left ventricular dysfunction	To test the hypothesis that EP guided therapy would reduce the risk of sudden death among patients with CAD, left ventricular dysfunction and asymptomatic, unsustained VT	To evaluate the effect of ICD therapy on survival in patients with reduced left ventricular function after heart attack	To evaluate if amiodarone and/or ICD therapy will improve survival compared to placebo in CHF patients without a history of sustained VT who have not had a previous life-threatening arrhythmic episode
Study Design	196 patients <ul style="list-style-type: none"> • 95 ICD • 101 Medical therapy 	704 patient <ul style="list-style-type: none"> • 351 Inducible, EP guided therapy • 161 ICD • 158 Drug • 353 non-inducible, medical therapy 	1232 patients <ul style="list-style-type: none"> • 742 ICD • 490 Medical therapy 	2521 patients <ul style="list-style-type: none"> • 847 Placebo • 845 Amiodarone • 829 ICD
Patient Criteria	Patients in NYHA class I, II or III with <ul style="list-style-type: none"> • Post MI • LVEF <= 35% (25%) • Documented asymptomatic non-sustained VT • EP inducible 	Patient with <ul style="list-style-type: none"> • CAD • LVEF <=40% (30%) • Documented asymptomatic non-sustained VT 	Patient with <ul style="list-style-type: none"> • Post MI • LVEF <= 30% (23%) 	Patients in NYHA class II or III with <ul style="list-style-type: none"> • LVEF <= 35% (25%) • Have ischemic or non-schemic DCM • Have had CHF for at least 3 months
Follow-up	27 months (mean)	39 months (median)	20 months (mean)	45.5 months (mean)
Endpoint	Death from all causes	Death from all causes	Death from all causes	Death from all causes
Mortality Rate	<ul style="list-style-type: none"> • NO ICD therapy 39% • ICD therapy 16% 	<ul style="list-style-type: none"> • No ICD therapy 55% • ICD therapy 24% 	<ul style="list-style-type: none"> • No ICD therapy 14.2% • ICD therapy 9.8% 	<ul style="list-style-type: none"> • Placebo 36.1% • Amiodarone 34% • ICD therapy 27.7%
Hazard Ratio¹	0.46 (54% relative reduction)	0.4 (60% relative reduction)	0.69 (31% relative reduction)	0.77 (23% relative reduction)
Prevalence	n/a ²	n/a ²	300,000 ⁴ patients (USA)	900,000 ³ patients (USA)

¹ Comparison of hazard ratios and prevalence reveals that these trials have identified larger and larger populations of patients indicated for ICD implantation, with treatment delivering a progressively declining reduction in mortality benefit, underscoring the growing need for an effective risk stratification tool.

² Prevalence is difficult to quantify as these patients groups require EP inducibility, however, the total pool of patients indicated for ICD implantation prior to Madit II was estimated at 300,000 individuals including Sudden Cardiac Arrest survivors, Madit, Mustt, etc.

³ Conservative estimate to eliminate double counting with overlapping Madit II population. Some estimates range as high as 1.2 to 1.5 million patients (USA).

⁴ Industry statements

ESTIMATED COST-SAVING POTENTIAL OF MICROVOLT T-WAVE ALTERNANS (MTWA) TESTING AMONG MADIT II AND SCD-HEFT PATIENTS

The MADIT II and SCD-HeFT studies have identified two additional large and overlapping populations of patients – totaling approximately 1.2 million people – who should be evaluated for a defibrillator implant (ICD). An ICD implant costs on average \$25,000 each.

Positive clinical data show that Microvolt T-Wave Alternans testing has convincing negative predictive value and has the potential to become a primary risk stratification tool. In other words, **it can allow physicians to determine which MADIT II and SCD-HeFT patients do not need an ICD.**

The MTWA test can spare many patients the risks associated with implanting an ICD unnecessarily, and also help the US medical delivery system realize substantial cost-savings in this large patient population.

THE CALCULATIONS BELOW REVEAL A SAVINGS OF ALMOST \$2.5 BILLION PER YEAR

Fundamental Costs and Statistics

Average cost to CMS of implantable defibrillator (ICD).....	\$25,000 ¹
Average cost to CMS of Microvolt T-Wave Alternans (MTWA) test.....	\$ 340 ²

Percentage of MADIT II patients who would likely test MTWA negative and thus not need an ICD implant.....	30% ³
--	------------------

Percentage of SCD-HeFT patients who would likely test MTWA negative and thus not need an ICD implant.....	34% ⁴
--	------------------

Penetration rate of ICD implants among indicated population.....	25% ⁵
--	------------------

Estimated Cost Saving Among MADIT II Patients

Estimated prevalence of MADIT II patients in the US indicated for an ICD.....	300,000 ⁶
---	----------------------

Estimated # of incremental MADIT II ICD implants, given 25% penetration rate.....	75,000
---	--------

Cost of providing MTWA tests to these patients (75,000 x \$340).....	\$25,500,000
--	--------------

Of these patients, # who would likely test MTWA negative and hence not need an ICD implant (75,000 x 30%).....	22,500
---	--------

Annual cost saving realized by <u>not</u> implanting 22,500 (x \$25,000) ICDs.....	\$562,500,000
--	---------------

Estimated Cost Savings Among Heart Failure (SCD-HeFT) Patients

Estimated prevalence of SCD-HeFT patients in US indicated for an ICD.....	900,000 ⁷
Estimated # of incremental ICD implants, given 25% penetration rate.....	225,000
Cost of providing MTWA tests to these patients (225,000 x \$340).....	\$76,500,000
Likely # of MTWA negative patients in this population (225,000 x 34%).....	76,500
Annual cost saving realized by <u>not</u> implanting 76,500 (x \$25,000) ICDs.....	\$1,912,500,000

Aggregate Savings (MADIT II + SCD-HeFT) Minus MTWA Costs

Cost saving from not implanting 99,000 (x \$25,000) ICDs.....	\$ 2,475,000,000
Total cost of MTWA testing 300,000 MADIT II and SCD-HeFT patients.....	-\$...102,000,000

Total Annual Savings.....\$2,373,000,000

¹ Extrapolated from various industry statements. In some markets, the cost of an ICD can be as high as \$40,000 or more per implant.

² The average reimbursement rate as published by CMS for CPT Code 93025 in 2004 is \$338, here rounded to \$340.

³ Exhibit C

⁴ In an oral presentation at the American College of Cardiology 2003 Latebreaking Clinical Trials Session, "TWA in CHF: A Prospective Study of T-Wave Alternans as a Predictor of Outcomes in Patients with Congestive Heart Failure," Dr. Dan Bloomfield reported that 34% of heart failure patients in an NIH-funded study tested MTWA negative. The patients in the NIH study were very similar in characteristics to those enrolled in the SCD-HeFT trial. Publication of this NIH-funded study in a peer-reviewed journal is pending.

⁵ Keusch, Lawrence. "US Healthcare, Medical Devices." Analyst Report, Goldman Sachs Global Investment Research, 3/18/04, p.2, cites a penetration rate of 30%, but we have adopted the more conservative rate of 25% in these calculations to reflect more usual consensus industry.

⁶ Extrapolated from various industry public statements. Some estimates are in excess of 400,000 patients.

⁷ Extrapolated from various industry public statements. Some estimates range as high as 1.2 to 1.5 million patients, but we have adopted a more conservative figure, in part to account for overlap with the MADIT II patient population.

**SUMMARY OF CLINICAL STUDIES OF MICROVOLT T -WAVE
ALTERNANS (MTWA) TESTING AMONG MADIT II-TYPE PATIENTS**

COMPLETED STUDIES

Study Author(s)	Number MADIT II Patients	MTWA-		MTWA +		MTWA – I	
		No	%	No	%	No	%
Bloomfield ¹	164	55	34	45	27	64	39
Cho ²	193	57	30	97	50	39	20
Hohnloser ³	129	35	27	77	60	17	13
TOTALS	486	147	30	219	45	120	25

Across these three studies, 30% of MADIT II-type patients (147 of 486) tested MTWA negative.

EVENT RATE AMONG MTWA NEGATIVE PATIENTS

Among the MTWA negative patients (*shaded in gray, above*):

- There were no deaths in the Bloomfield study
- There was 1 death in the Chow study
- There were no deaths in the Hohnloser study (and 2 non-fatal VTEs reported).
- The death rate among MTWA negative MADIT II patients across these three studies is less than 1% (1/147).
- The death rate in the Madit II study was 19.8% (drug group) and 14.2% (ICD group.)

(Note: Follow up period was approximately 12 months for Bloomfield and Chow studies, 24 months for Hohnloser study, and 20 months (mean) for MADIT II)

OTHER MTWA STUDIES (USA) PENDING RESULTS OR CURRENTLY IN PROGRESS

Study Name	Study Sponsor	Status	# of Patients	Results Expected
SCD-HeFT	NIH, Wyeth, Medtronic	Main results already reported. Prospective MTWA sub-study results expected later this year.	Approx. 500	End of 2004
ABCD	St. Jude	Completing enrollment	>500	Late 2005
MASTER	Medtronic	Enrolling in main study and registry study	600 main 1200 registry	Late 2005 Late 2006

1 Bloomfield, et al, T Wave Alternans in CHF: A Prospective Study of T Wave Alternans as a Predictor of Outcomes in Patients with Congestive Heart Failure. Late Breaking Clinical Trials, American College of Cardiology, March 2003 and "T-Wave Alternans as a Predictor of Outcomes in the Madit II Population" Cambridge Heart Seminar, NASPE, May 2003

2 Chow, Theodore, "Prospective Evaluation of Microvolt T Wave Alternans for Risk Stratification of Patients with Ischemic Cardiomyopathy" Medicare Coverage Advisory Committee Presentation -February 14, 2003 and "T-Wave Alternans as a Predictor of Outcomes in the Madit II Population" Cambridge Heart Seminar, NASPE, May 2003

3 Hohnloser S., Ikeda, T., et al, "T wave Alternans negative coronary patients with low ejection fraction and benefit from defibrillator implantation" THE LANCET, Vol. 362, July 12, 2003

Research letters

T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation

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In a trial of prophylactic implantation of a defibrillator, a mortality benefit was seen among patients with previous myocardial infarction and a left-ventricular ejection fraction of 0.30 or less. We identified 129 similar patients from two previously published clinical trials in which microvolt T-wave alternans testing was prospectively assessed. At 24 months of follow-up, no sudden cardiac death or cardiac arrest was seen among patients who tested T-wave alternans negative, compared with an event rate of 15.6% among the remaining patients. Testing of T-wave alternans seems to identify patients who are at low risk of ventricular tachyarrhythmic event and who may not benefit from defibrillator therapy.

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In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) among 1232 patients with previous myocardial infarction (MI) and left-ventricular ejection fraction of 0.30 or less, prophylactic defibrillator therapy reduced mortality from 19.8% to 14.2% (absolute mortality reduced by 5.6%) over an average of 20 months. Therefore, 18 defibrillators would need to be implanted to save 20 months of life. Thus, implantation of defibrillators in all MADIT II-type

patients would subject a large group of patients to costly invasive therapy to extend life in only a small proportion.

Microvolt T-wave alternans testing^{2,4} involves analysis of variation in microvolt level in the morphology of electrocardiographic T wave, on an alternate-beat basis, during exercise stress. T-wave alternans testing is non-invasive and is proven to be a highly specific and sensitive predictor of the occurrence of ventricular tachyarrhythmic events. The test compares favourably with invasive electrophysiology testing and other non-invasive risk-stratification methods. We assessed the role that non-invasive T-wave alternans testing might have in the prediction of tachyarrhythmia in MADIT II-type patients by analysis of data pooled from two previously published studies, in which microvolt T-wave alternans was prospectively assessed as a risk stratifier for ventricular tachyarrhythmias in patients without known previous sustained ventricular tachyarrhythmias. Ikeda and colleagues⁴ studied 850 consecutive MI survivors who underwent T-wave-alternans testing a mean of 2.7 months after MI. Klingeneben and colleagues³ studied 107 consecutive patients with New York Heart Association class II and III heart failure and no MI in the previous 6 weeks. We analysed all patients in the two studies who had previous MI and left-ventricular ejection

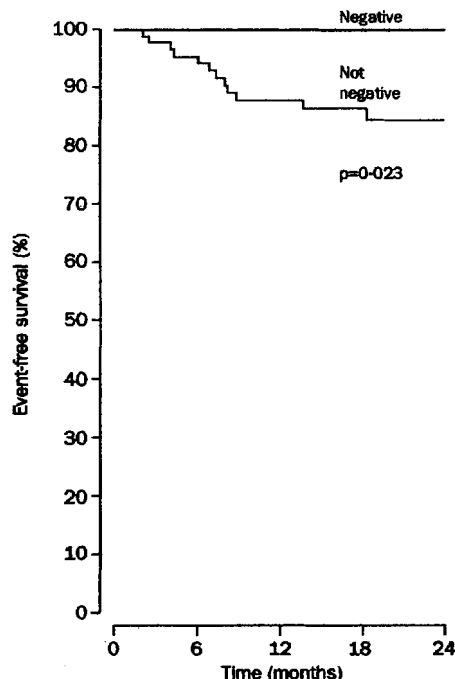


Figure 1: Event-free survival for primary endpoint according to outcome of T-wave alternans test

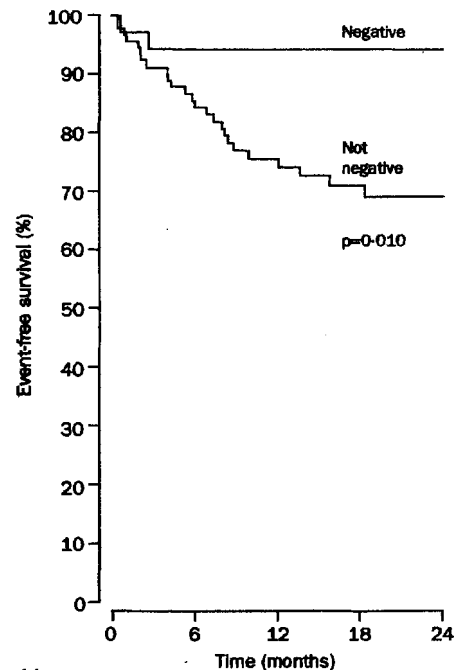


Figure 2: Event-free survival for secondary endpoint according to outcome of T-wave alternans test

fraction of 0.30 or less. Our primary endpoint was sudden cardiac death or cardiac arrest, the same as the primary endpoint of Ikeda and colleagues.⁴ Our secondary endpoint was ventricular tachyarrhythmic events, including sudden cardiac death, cardiac arrest, and sustained ventricular tachycardia, the endpoint of Klingenheben and colleagues.³ We pooled the data from the two studies, including the original T-wave alternans and endpoint-event classifications, follow-up durations, and ejection fraction data, into a central database.

We used Kaplan-Meier analysis to assess event-free survival, with a two-sided log-rank test of significance. Relative risk at 24 months was calculated from the event-free survival at that time point. Follow-up data were capped at 24 months for each patient. Because our objective was to find out which patients do not require defibrillator therapy, we classified the T-wave alternans outcomes as negative or not-negative (positive and indeterminate).

129 patients (87 from Ikeda and colleagues, 42 from Klingenheben and colleagues; 112 male, 17 female) had previous MI and left-ventricular ejection fraction of 0.30 or less. The mean age was 63 years (SD 11) and mean left-ventricular ejection fraction was 0.255 (0.045). Patients were followed up for a mean of 16.6 months (8.0). 35 (27%) patients tested T-wave alternans negative, 77 (60%) positive, and 17 (13%) indeterminate. The primary endpoint was experienced by no negative patient, ten positive patients (six sudden cardiac death, four cardiac arrests), and two indeterminate patients (both sudden cardiac death). For the secondary endpoint, the respective numbers were two, 21, and four.

For the primary endpoint, the event rate was 15.6% at 24 months of follow-up among patients who tested T-wave alternans positive or indeterminate, compared with an event rate of zero among patients who had negative results ($p=0.02$, figure 1). The overall event rate at 24 months for all 120 patients was 11.1%, and for patients with positive tests was 15.5%. For the secondary endpoint, the event rate was 31.1% at 24 months of follow-up among patients with positive or indeterminate results, compared with 5.7% among negative patients ($p=0.01$, figure 2). Relative risk at 24 months was 5.5. Event rate at 24 months for the population of all 120 patients was 24.0% and for positive T-wave alternans results was 31.4%.

In the negative, positive, and indeterminate groups, four, seven, and one patients, respectively, died from non-arrhythmic causes. The reasonably constant proportions of these deaths to the numbers of patients in each of these groups shows that T-wave alternans does not identify patients at risk of non-arrhythmic death. The all-cause mortality was 18.7% in the entire population at 24 months, and mortality was 12.5%, 21.4%, and 21.3% in the T-wave alternans negative, not-negative, and positive groups, respectively. The mortality rate in the entire population is consistent with the MADIT II results. The mortality rate among the patients with negative T-wave alternans tests was 42% lower than among the not-negative patients; this difference is larger than the 31% relative reduction in all-cause mortality in the defibrillator group compared with the control group in MADIT II. The difference in mortality between the negative and not-negative patients was not significant. A study population similar in size to the MADIT II trial would be required to show that a difference in mortality of the magnitude achieved in MADIT II was significant.

Our data suggest that MADIT II-type patients who test negative for microvolt T-wave alternans may not benefit from defibrillator therapy. Conversely, prophylactic defibrillator therapy might be more beneficial in such patients who have positive or indeterminate T-wave alternans results than in

similar patients who have not undergone risk stratification.

Contributors

All researchers participated in designing the study, assembling and analysing the data, and drafting and reviewing the report.

Conflict of interest statement

R J Cohen has an association with Cambridge Heart Inc, who manufacture equipment for the measurement of microvolt T-wave alternans. None declared for the other investigators.

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Human monoclonal thyroid stimulating autoantibody

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A monoclonal autoantibody (MAb) with powerful thyroid stimulating activity has been produced from lymphocytes from a patient with Graves' disease. The autoantibody and its Fab fragment bind to the thyroid stimulating hormone (TSH) receptor (TSHR) with high affinity, inhibit labelled TSH binding to the receptor and stimulate cyclic AMP production in Chinese hamster ovary cells transfected with TSHR. TSHR autoantibodies with TSH agonist or antagonist activities from patients' serum samples are effective inhibitors of labelled monoclonal autoantibody binding to TSHR. Thus, the human monoclonal autoantibody has all the characteristics of serum TSHR autoantibodies. Its availability has important implications for new studies on the pathogenesis of Graves' disease.

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Since the discovery over 40 years ago of the thyroid stimulating autoantibodies that cause hyperthyroidism in Graves' disease many (but unsuccessful) efforts have been made to isolate and characterise the autoantibodies at the molecular level.^{1,2} The autoantibodies exert their stimulating effect by binding to the thyroid stimulating hormone receptor (TSHR) and we³ and others⁴ have produced animal monoclonal antibodies with similar characteristics to patient TSHR autoantibodies. We have now isolated and characterised a human monoclonal TSHR autoantibody that acts as a powerful thyroid stimulator.