Rationale and Design for the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) Trial

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DETERMINE Trial. ***Background:*** **Cardiac magnetic resonance imaging (CMR) can accurately determine infarct size. Prior studies using indirect methods and CMR to assess infarct size have shown that patients with larger myocardial infarctions have worse prognoses. Implantable cardioverter defibrillators (ICD) have been shown to improve survival among patients with severe left ventricular (LV) dysfunction. However, the majority of cardiac arrests occur in patients with higher ejection fractions.**

Methods: **The Defibrillators To Reduce Risk By Magnetic Resonance Imaging Evaluation study (DETERMINE) is a prospective, multicenter, randomized, clinical trial in patients with coronary artery disease (CAD) and mild-to-moderate LV dysfunction. The purpose of this trial is to test the hypothesis that patients with an infarct size ≥10% of LV mass, randomized to ICD plus appropriate medical therapy will have improved survival compared with patients randomized to medical therapy alone. Cine and myocardial delayed contrast CMR will be performed in patients with CAD. The primary endpoint will be death from any cause. At least 10,000 patients with CAD will undergo CMR. The target enrollment is 1,550 patients with an estimated 36-month enrollment period. The patients will be followed up for 24 months after the last patient randomization. During the follow-up period, 330 deaths are estimated to occur. This study is powered to detect a 28% reduction in mortality by ICD therapy.**

Conclusion: **The DETERMINE trial will assess the efficacy of ICD therapy to improve survival among patients with CAD, mild-to-moderate LV dysfunction, and infarct size ≥10% of LV mass as measured by CMR.** *(J Cardiovasc Electrophysiol, Vol. 20, pp. 982-987, September 2009)*

MRI, ventricular tachycardia/fibrillation, ICD

Introduction

American Heart Association (AHA) statistics suggest that up to 400,000 people die suddenly every year presumably due to cardiac arrhythmias.[1] Prior myocardial infarction (MI) is the most common substrate for cardiac arrhythmias in patients with coronary artery disease (CAD).[2-4] Most patients who suffer an out-of-hospital cardiac arrest do not survive. Thus, using a prophylactic implantable cardioverter defibrillator (ICD) in patients at a risk of sudden cardiac death (SCD) is a conceptually attractive option. Several clinical trials have previously shown that the ICD reduces mortality in patients with CAD and low left ventricular (LV) ejection fraction who had not yet suffered a life-threatening arrhythmia.[5,6] However, the majority of out-of-hospital cardiac arrest occurs in patients with ejection fractions >35%. The relative risk of sudden death in such patients is lower than that for patients with a LV ejection fraction ≤35%.[1] Thus, risk stratification is needed to define a subgroup of patients with a better preserved LV ejection fraction who are at a risk of SCD. A number of noninvasive tests have been developed to help predict SCD. In randomized trials, only the LV ejection fraction, the presence of heart failure and possibly the presence of inducible ventricular tachycardia (VT) during programmed electrical stimulation (EPS) have been shown to identify patient who benefit from ICD therapy.[5,7]

Infarct size assessed with contrast-enhanced CMR can help predict risk in patients with healed MI. Roes *et al*. performed CMR in 231 patients. The spatial extent of infarct size and the total score of the scar were stronger predictors of total mortality than the LV ejection fraction or LV volumes.[8-19]

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TABLE 1
Eligibility

Inclusion Criteria: (Randomized Trial)
1. Evidence of coronary artery disease (CAD)[a]
2. Evidence of prior myocardial infarction defined by either Clinical history of prior myocardial infarction[b] OR Mild–moderate systolic LV dysfunction with an EF ≤50%
3. LVEF >35% by any current standard evaluation technique (e.g., echocardiogram, MUGA, angiography) Patients who have an EF between 30 and 35% and NYHA Class I heart failure who do not have a history of ventricular tachyarrhythmias, or inducible ventricular tachycardia during electrophysiological (EP) testing can be enrolled (target population)
4. CE-MRI measure of an infarct mass ≥ 10% of LV mass (as measured by the MRI core lab) If CE-MRI is performed ≤ 40 days after myocardial infarction, then the infarct mass must be ≥ 15% of the LV mass
5. Patients aged 18 years or above

[a]CAD will be confirmed by evidence of 1 of the following 3 criteria: (1) prior myocardial infarction, (2) significant stenosis of a major epicardial vessel (>50% proximal or 70% distal) by coronary angiography, and (3) prior revascularization (percutaneous coronary intervention or coronary artery bypass surgery). Patients may not be randomized until 90 days after revascularization.

[b]MI should be documented by the presence of 2 of the following 3 criteria: (1) symptoms consistent with myocardial infarction (i.e., chest pain, shortness of breath), (2) Q-waves on electrocardiogram, and (3) elevated cardiac enzymes (CPK elevation > 2 times or troponin elevation > 3 times the upper limit of normal for the lab). Patients may not be randomized until 40 days after myocardial infarction.

TABLE 2
Exclusions

Exclusion Criteria
1. History of cardiac arrest or spontaneous or inducible sustained VT (15 beats or more at a rate of 120 bpm or greater)
2. Unexplained syncope
3. Expected revascularization based on investigator's clinical assessment within the next 12 months (patients may be reevaluated 90 days after revascularization)
4. Currently implanted permanent pacemaker and/or pacemaker/ICD lead
5. Recent MI (<40 days) or revascularization (<90 days)
6. CVA within 90 days
7. Antiarrhythmics drug therapy for ventricular arrhythmias
8. New York Heart Association CHF functional class IV at enrollment
9. Pregnancy
10. Any condition other than cardiac disease that, in the investigator's judgment, would seriously limit life expectancy (poor 6-month survival)
11. Contraindication to a ICD implant (i.e., inadequate venous access, bleeding disorder)
12. Marked valvular heart disease requiring surgical intervention
13. Current alcohol or drug abuse
14. Participating in other trials with an active treatment arm (not to exclude patients who are in trials of diagnostic techniques or approved therapies)
15. Unwilling or unable to provide informed consent
16. Inability to comply with follow-up schedule due to a history of medical noncompliance, living a distance from the study center, or anticipated nonresidence in the area for the length of time required for follow-up

Based on these results and since the infarct mass has been found to be a better predictor of inducibility of VT during EPS than the LV ejection fraction,[12] we hypothesized that infarct size as measured by CMR may be a better predictor of arrhythmic risk and survival than the LV ejection fraction.

Methods

Study Objectives, Study Population, and Inclusion and Exclusion Criteria

The study objectives are to test the hypothesis that therapy with an ICD combined with appropriate medical therapy improves long-term survival compared with aggressive medical therapy alone in patients with CAD, and an infarct mass measuring ≥10% of the LV mass and mild-to-moderate LV systolic dysfunction will be randomized. Patients must have an ejection fraction >35% or have an ejection fraction of 30–35% without inducible VT and without New York Heart Association (NYHA) functional class II or greater heart failure. Details of the inclusion and exclusion criteria are shown in Tables 1 and 2.

Justification of Patient Selection Criteria

Several large-scale primary prevention trials have identified patients with clinical characteristics who appear to benefit from prophylactic ICD implantation.[20] A meta-analysis by Al Khatib *et al*.[21] demonstrated that the benefit of ICD implantation may be more modest in patients with LV ejection fractions between 30 and 35%. In this group of patients, heart failure class may provide additional risk stratification information. We thus carefully considered the appropriate ejection fraction cut-off for inclusion in the present trial and set the ejection fraction cut-off at 35% with NYHA functional class II and class III heart failure and 30% for those with class I CHF.

Infarct resorption and LV remodeling can occur weeks to months following MI. Yan *et al*. showed that after the acute phase of an MI, the extent of the scar defined by delayed contrast-enhanced CMR is an independent predictor of post-MI all-cause ($P = 0.005$) and cardiovascular mortality ($P = 0.01$).[22] Infarct size has also been shown to decrease over time.[23] Several studies have looked at the change in infarct size by measuring the infarct mass during the immediate post-MI period and then again during chronic follow-up. In a study by Wu *et al*., the late measure of the infarct mass decreased by 22% of the initial size with an absolute decrease of $4.3 \pm 5.5\%$.[15] Ingkanisorn *et al*. showed that the percent of infarcted myocardium decreased from $16 \pm 12\%$ to $11 \pm 9\%$.[24] Therefore, for DETERMINE in the instance where the infarct mass is measured within 40 days of a MI, the infarct mass required for randomization will be ≥15% of LV mass.

Study Design (Fig. 1)

Approximately 10,000 patients with CAD who have undergone CMR observational within 12 months will be enrolled in the DETERMINE registry. Of these 10,000 patients, those with an ejection fraction >35% (or 30–35% if they have class 1 heart failure) and the infarct mass measuring ≥10% of the LV mass will be eligible for the enrollment in the randomized portion of the trial. One thousand five hundred and fifty patients will be randomized to either medical therapy (control group) or ICD therapy in combination with medical therapy (treatment group) in a 1:1 fashion.

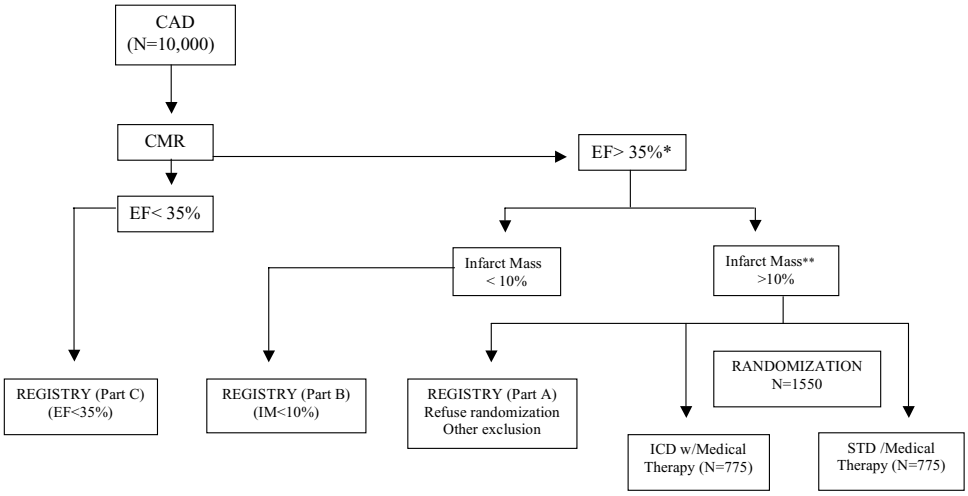

Figure 1. *DETERMINE study overview. *Eligibility for patients with an ejection fraction of 30–35% will be determined based upon their history of heart failure, ventricular tachyarrhythmias, or inducibility during electrophysiologic testing. **Infarct mass must be >15% if measured < 40 days after myocardial infarction.*

Observational Registry

The DETERMINE registry will enroll approximately 10,000 patients with a diagnosis of CAD who have undergone CMR. Patients enrolled in the registry who do not undergo randomization will be asked to consent to long-term follow-up. SCD and other causes of death will be documented over a 3–5 year follow-up period. One of the primary objectives of this cohort study will be to test the hypothesis that the infarct mass as measured by contrast-enhanced CMR is a better predictor for SCD than the LV ejection fraction.

Randomization

Randomizations will be stratified by enrolling center, an infarct mass of 10% or 15% (if IM was measured within 40 days of a MI), and the presence of chronic atrial fibrillation at the time of enrollment. Randomization will be considered time 0 for both groups for the purpose of the primary endpoint. Although LVEF measurements by CMR are more challenging in patients with atrial fibrillation, if the infarct mass can be calculated by CMR, these patients will be included.

Crossover and Loss to Follow-Up

Patients will be included in the analysis on an intention-to-treat basis. If there is a decision to use antiarrhythmic therapy and not to implant an ICD in the ICD arm or if the ICD is explanted or deactivated or if there is failure to implant the ICD system, then patients will be considered "crossed over." In addition, an attempt will be made to verify the vital status of subjects lost to follow-up through means including, but not limited to, the National Death Index/Social Security Index.

Baseline Evaluation

After the patient signs informed consent, a baseline examination will be performed that will include a clinical history and physical examinations, 12-lead ECG, and collection of blood sample for biomarker and genetic analysis. In addition, the patient will be asked to complete a 6-minute walk test and quality of life (QOL) questionnaires.

Follow-Up

Study follow-up will occur every 3 months and will include clinic visits at 6-month intervals alternating with telephone contact. It is anticipated that the average length of follow-up will be 3.5 years per patient. All patients will be followed until the last patient randomized completes 24 months of follow-up. All patients will be followed for evaluation of clinical status, vital status and QOL. In patients randomized to ICD, the follow-up will also include ICD interrogation. Additionally, a 6-minute walk test, QOL, and a standard ECG will be performed annually (Table 3). It is recommended that all patients, regardless of the randomization group, receive appropriate pharmacologic therapy as described in the ACC-AHA guidelines for patients after MI.[25]

Device Selection and ICD Implantation

The devices used in this clinical investigation include commercially available St. Jude Medical single and dual-chamber ICDs and lead systems. Dual-chamber devices may be implanted for sinus node dysfunction, atrioventricular block, or discrimination of atrial tachyarrhythmias. Biventricular pacing for cardiac resynchronization therapy is not currently indicated in this patient population and will not be used in this trial unless guidelines change. Defibrillation testing will consist of a standard clinically appropriate approach. A single defibrillation success with a 15 J safety margin or 2 consecutive successes with at least 7 J safety margin will be considered adequate for implantation. Noninvasive programmed stimulation will be performed to optimize device programming either during ICD implantation or prior to hospital discharge.

The following ICD programming parameters will be used:

- ICD should be programmed to minimize ventricular pacing and inappropriate shocks[26,27]
- Single- or dual-chamber ICD as appropriate
- VT and VF zones with long detection times
- Bradycardia at 40 bpm
- ATP will be programmed in the VT zone

TABLE 3
DETERMINE TRIAL: Follow-Up

	Screening Baseline	Postrandomization (Months)															
		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Medical history	X																
Physical exam	X		X		X		X		X		X		X		X		X
MRI data	X																
ICD interrogation			X		X		X		X		X		X		X		X
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X				X				X				X				X
6-minute walk test	X				X				X				X				X
QOL questionnaire	X		X		X		X		X		X		X		X		X
Genetic sample	X																
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact (vital status)		X		X		X		X		X		X		X		X	

All patients will continue the follow-up schedule (every 6 months clinic visit alternating with telephone follow-up) until the last randomized patient has been followed up for 24 months.

CMR Protocol

Participating centers will be required to submit corresponding sets of cine MR images and delayed enhancement MR images (DE-MRI) to the core laboratory. The cine images will be based on steady-state free precession (SSFP) using a phased-array cardiac coil during repeated breath holds.[28–30] The cine images will be acquired in the cardiac short-axis plane as a parallel stack extending from the base to the apex at 1-cm intervals. Either a 6-mm slice thickness with 4-mm gap or 8-mm slice thickness with 2-mm gap is acceptable. In addition, a single set of cine images will be acquired in each of 3 long-axis planes; horizontal long axis, vertical long axis, and LV outflow tract. Following intravenous administration of gadolinium-based contrast agent (GBCA) at a dose of 0.15–0.2 mmol/kg, a set of DE-MRI will be acquired in the same slice orientations and slice centers (positions) as the cine MR images. For DE-MRI, a segmented inversion-recovery sequence will be employed at least 10 minutes following intravenous GBCA injection. Depending on the pulse sequence portfolios available at specific field centers, DE-MRI sets with either magnitude-only or both magnitude- and phase-sensitive image reconstruction will be submitted to the core laboratory for analysis. If phase-sensitive image reconstruction is available and employed, a fixed inversion time may be used during image acquisition. Otherwise, the inversion time will be adjusted on a patient-specific basis to null normal myocardium. The cine and DE-MRI images will be evaluated separately by the consensus of 2 observers unaware of any patient information. Hyperenhanced myocardium on the DE-MRI will be assumed to represent the scar. In the event that the pattern and distribution of myocardial scar are inconsistent with ischemic infarction and more suggestive of another etiology such as myocarditis or cardiomyopathy, the scar will nonetheless be quantified and patients will be randomized or enrolled in the registry using the same criteria as for ischemic scar. For quantification, the myocardial borders will be segmented on all of the short-axis cine images and quantified by planimetry to determine LV volumes, ejection fraction, and mass (assuming density = 1.05 g/cm^3).[31] Myocardial gadolinium enhancement with respect to the planimetric extent of transmural MI as well as the total volume of hyperenhancement will be divided by the total volume of LV myocardial tissue to obtain the infarct mass as a percentage of LV mass. MRI core lab interobserver variability was assessed for 131 patients for both infarct mass and infarct percent of LV mass. The intraclass correlation for the infarct mass was 0.975 ($P < 0.001$), 95% CI (0.962, 0.983), and for infarct percent of LV mass was 0.977 ($P < 0.001$), 95% CI (0.968, 0.984).

Study Endpoints

Primary endpoint

The primary endpoint of the study will be all-cause mortality.

Secondary endpoint

A secondary endpoint of the study will be arrhythmic mortality. Cause-specific mortality will be determined by an independent events committee.[32]

Additional analysis

Additional analyses will look at appropriate ICD shocks and QOL. This study will include a careful assessment of the effects of ICD implantation and the presence of continued QOL and will be performed using two assessment tools. Changes in QOL throughout the trial will be assessed using one global [Short form 36 (SF-36)] and one disease-specific [Seattle Angina Questionnaire (SAQ)] instrument. In addition, 2 ICD-specific QOL tools, the Florida Patient Acceptance Survey (FPAS) and Florida Shock Acceptance Survey (FSAS), will also be administered.[33,34] QOL responses will be analyzed utilizing multilevel mixed models methodology.

Observational cohort substudy

Biological Markers and Genetics Substudy, NIH/NHLBI, and St. Jude Medical sponsored the observational cohort study, PRE-DETERMINE.

Blood samples will be collected and stored for future genetic and biomarker analyses from all patients enrolled in the randomized trial and the observational cohort study. At the end of the study, the predictive value of promising protein, genetic, and metabolic biomarkers on the risk of arrhythmic events will be examined in the 6,850 patients with a LV ejection fraction >35% enrolled both in observational cohort study and in parent DETERMINE randomized trial. The

goal of these analyses will be to identify a series of markers that alone or in combination with CMR imaging specifically predict the risk of arrhythmic death as compared with other causes of mortality among this at-risk, but understudied, population of CAD patients. Such markers may serve as relatively inexpensive methods to identify those at a risk for SCD. The public health impact of identifying such markers could be quite substantial and lead to (1) more efficient utilization of ICDs and (2) advances in our understanding of mechanisms that could ultimately lead to novel therapeutic approaches.

Statistical Methods

Death from any cause—Primary endpoint

A two-tailed test will be utilized to evaluate the primary endpoint.

H0: Rate of all-cause mortality in the ICD group = rate of all-cause mortality in control group

H1: Rate of all-cause mortality in the ICD group ≠ rate of all-cause mortality in control group

This hypothesis tests the effects of ICD implantation on all-cause mortality in the study population.

Sample Size

Based on the recent trials,[5,6,13,19,35-37] the mortality of the control patients was estimated to be 25% over an average of 3.5 years of follow-up. ICDs are expected to reduce the overall risk of death by 28%. In this group of patients with better preserved ventricular function, there should be less competing mortality from heart failure, and thus a 28% mortality reduction seems justified. Patients will be randomized to each study arm in equal numbers. We estimate that patients will be uniformly enrolled for 3 years and, after the last patient is enrolled, all patients will be followed up for an additional 2 years. It is estimated that 5% percent of the control group patients and 1% of the ICD arm will crossover. After crossover, patients' mortality rate will become that of their new study arm. Crossovers were modeled to occur at a constant rate. Two interim analyses will be performed after 60% and 80% of events have occurred. The benefit boundary will be more conservative in the early stages of the study (Power family with rho = 7). After the adjustment, the final analysis will be conducted at the 4.2% 2-sided significance level. Patients cannot be randomized until 40 days after a MI or 90 days after revascularization. Given those exclusions, no evidence is available to suggest that ICD effect will change during the course of the trial; therefore, proportional hazards assumption was adopted. Under these conditions, the number of events required to detect the difference that corresponds to HR = 0.6969 with 89.4% power and 5% 2-sided significance level will be 330, and 1,550 patients will be needed to reach this number of endpoints.

Primary Analysis

Total survival will be evaluated when all surviving patients have been seen for their 2-year follow-up visit. The survival time for patients who die during the study will be calculated as the number of the days from randomization to death. Analyses of survival times will be based on the log-rank test for comparison of survival curves using Kaplan–Meier methodology and implemented via the current version of the SPSS software. Interim analyses will take place after 198 and 264 deaths will have occurred.

Covariate Analysis

The impact of the following prespecified set of covariates—age, sex, race, time from the first MI, history of revascularization, descriptors of comorbidity (diabetes and hypertension), NYHA functional class, number of diseased coronary arteries, LV ejection fraction, atrial fibrillation, QRS duration and infarct mass—on the endpoint analysis will also be examined in a multivariate Cox regression. These baseline patient characteristics will be entered into the model ahead of the treatment assignment as a single block. Subsequently, the predictive power of ICD implantation will be assessed with the likelihood ratio test. The 2-sided alpha level of 10% will be used for all analyses.

Discussion and Conclusion

Several recent clinical trials have established the ICD as an important therapeutic modality for primary and secondary prevention of death in post-MI patients with severe LV dysfunction.[2-5,7] However, any strategy for primary prevention based on the ejection fraction alone has major limitations. For instance, the vast majority of patients who die suddenly following a MI have ejection fractions greater than 30 %.[6,35] Although these patients are at lower relative risk of SCD, they account for the majority of patients who die suddenly. Conversely, not all patients with low ejection fractions will experience arrhythmic death. Treating all patients with a depressed ejection fraction with an ICD may not be cost-effective. Infarct size determined by CMR in patients with known CAD has been found to be an independent predictor of overall mortality.[12,13,19] Thus, CMR may be useful in risk stratification in patients with a range of ejection fractions. DETERMINE will test this hypothesis.

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