Selecting an Appropriate Population for Prophylactic Defibrillator Implantation after MI

Thato Nteso

A. Study Purpose and Rationale:

An important topic in the Cardiologic literature in recent years concerns the prophylactic use of implantable defibrillators in patients with ischemic heart disease. Patients who survive myocardial infarction are at increased risk of developing subsequent cardiovascular events. They also experience high mortality rates, both during the immediate post-infarct period and years later. An important cause of mortality in these patients is sudden cardiac death. Sudden death occurs primarily by an arrhythmic mechanism, generally v-tach or v-fib. Past research has focused on risk stratification of patients post-MI to identify those at highest risk of developing fatal arrhythmias. Recognized risk factors include: nonsustained v-tach during 24-hour ambulatory monitoring, left ventricular dysfunction, late potentials on signal-averaged ECG, repolarization alternans, reduced heart rate variability, and inducible v-tach at EP study.

Implantable cardioverter-defibrillators are devices that can detect potentially fatal cardiac arrhythmias and abort them, thus preventing sudden death. Previous research studies have assessed the effects of implanting ICDs in patient populations thought to be at high risk of sudden death. The MADIT I trial, published in 1996, enrolled survivors of MI with low EF and inducible v-tach at EP study, patients at exceptionally high risk of developing clinically significant ventricular arrhythmias. Compared to controls, patients with ICDs implanted demonstrated a significant survival benefit at an average follow-up of 27 months (hazard ratio=0.46, absolute risk reduction=22.8%). The MADIT II trial, published in 2002, focused again on MI survivors with low EF but dropped the requirement of a positive EP study for enrollment. In this study, patients with ICDs implanted also demonstrated a survival benefit, though less dramatic: at an average follow-up of 20 months, the hazard ratio was 0.69, with an absolute risk reduction of 5.6%.

Authors of MADIT II suggested that all patients who survive MI and have low EF should be treated prophylactically with implantable defibrillators. But their results leave unresolved several important issues. One question that remains is whether the survival benefit demonstrated in MADIT II derives completely from a subgroup of patients at exceptionally high risk of sudden death, patients who would have had v-tach inducible at EP study had they been tested. To address this question, I propose a study that focuses on the effect of ICD insertion in survivors of MI with low EF and *negative* EP studies.

B. Study Design and Statistical Analysis:

I propose a prospective, randomized trial that will involve multiple medical centers. The two study groups will differ in treatment with implantable defibrillators; both will receive maximal medical therapy. The number of subjects in each group will be 4914. This sample size should enable the detection of a 2% survival difference with 80% power at p=0.05. Statistical analysis will be performed using Chi-square test to compare proportions in the two groups; subgroup analyses will also be conducted using multiple logistic regression. Patients will be randomized in a 1:1 ratio to ICD insertion versus conventional medical therapy alone, with each center having equivalent numbers in each treatment group. There will be no designated crossovers.

C. Study Procedure:

Both treatment groups will receive standard medical therapy for secondary prevention post-MI and management of congestive heart failure. Patients will follow up with their primary physicians and

cardiologists, who will actively manage their medications. Additionally, subjects will be assessed at three month intervals by study investigators, who will be blinded to their treatment groups. At each follow-up visit, a record will be kept of the subject's maintenance medications, vital signs, body weight, and clinical symptoms. The anticipated duration of follow-up is two years.

D. Medical Device:

Subjects in the experimental group will receive implantable cardioverter-defibrillators. Insertion will be transvenous, using standard technique. These devices are approved by the FDA. Programming the defibrillators will be left to the discretion of each patient's physicians.

E. Study Subjects:

Inclusion criteria: age > 21, prior MI at least one month before entry, EF 30% or less, EP study performed and no inducible ventricular arrhythmia by accepted protocol. MI will be defined as follows: pathological Q wave on ECG, elevated cardiac enzymes during hospitalization for suspected MI, fixed defect on thallium scan, evidence of obstructive coronary artery disease on angiogram with wall motion abnormality. EF must be measured within three months before entry on echo, thallium scan, or ventriculogram.

Exclusion criteria: pre-existing indication for ICD, NYHA class IV at enrollment, revascularization procedure within preceding three months, women of childbearing age using no contraception, advanced cerebrovascular disease, MI within preceding month, significant co-morbidity associated with high likelihood of death within two years, participation in a concurrent trial, EP study performed with inducible v-tach.

F. Recruitment of Subjects:

To identify potential subjects, all patients hospitalized at participating centers with acute MI or unstable angina will be screened. Any patient referred for cardiologic evaluation, inpatient or outpatient, will also be screened. The treating physicians will approach potential subjects to solicit participation in the study.

G. Confidentiality:

Every effort will be made to protect patients' confidentiality. All study data will be coded and a unique code will be used for each subject. Data will be stored in a secure location, accessible only to the investigators.

H. Potential Risks/Benefits:

The experimental subjects will undergo insertion of an ICD. The control subjects will be treated with standard medical therapy and will not accrue any excess risk. All subjects may benefit from vigilant surveillance of their medical conditions. Alternative therapies include treatment with antiarrhythmic medications. All subjects may receive such therapy at the discretion of their treating physicians.

I. Compensation to Subjects:

The experimental subjects will receive ICD therapy free of charge. There will be no additional cost to patients who choose to participate in the study. There will be no additional compensation beyond free ICD therapy.

J. References:

1. Moss, A.J., Hall, W.J., Cannom, D.S., et al for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved Survival with an Implanted Defibrillator in Patients with Coronary Artery Disease at High Risk for Ventricular Arrhythmia. NEJM 1996; 335: 1933.
2. Moss, A.J., Wojciech, Z, Hall, W.J., et al for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. NEJM 2002; 346: 877.
3. UpToDate. Risk Stratification for Arrhythmic and Nonarrhythmic Death after Acute Myocardial Infarction
4. UpToDate. Epidemiology and Prognosis of Coronary Heart Disease.