Survival of the Fittest:

Evolution of Left Ventricular Ejection Fraction after Acute Myocardial Infarction

Running title: Estes; Survival of the Fittest after MI

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Sudden cardiac death (SCD) from cardiac arrest remains the leading cause of cardiovascular mortality worldwide and accounts for approximately 250,000 deaths annually in the United States.\textsuperscript{1-4} The majority of cardiac arrests occur in patients with a prior myocardial infarction at a rate approximately five times that of the general population.\textsuperscript{3} Studies evaluating the time dependence of mortality immediately after an MI have consistently demonstrated that greatest risk for SCD is in patients with impaired LVEF.\textsuperscript{1-4} Despite revascularization and widespread use of beta-blockers, angiotensin-converting enzyme inhibitors, statins and antiplatelet agents, the risk of SCD remains highest in the first 30 days in these patients.\textsuperscript{1-4} Based on these observations, strategies for prevention of SCD need implementation early after an MI in high risk patients.

While depressed LVEF identifies patients with increased mortality risk immediately post MI, and is widely used as a risk stratification tool, it does not allow a distinction between those who will die of an arrhythmia and those who will die of other cardiovascular causes.\textsuperscript{4-8} Variable and unpredictable recovery of LV function after MI have been consistently noted immediately after a MI.\textsuperscript{5-7} Improvement in LVEF commonly begins within three days in patients who are revascularized with myocardial stunning and improved function of viable myocardium as the mechanisms.\textsuperscript{5-7} In the contemporary era of primary PCI for MI, of all revascularized patients with LVEF $\leq$40\% at day 3, 24\% will improve to have an LVEF $\geq$40\% at 6 months.\textsuperscript{5-7} Other noninvasive and invasive risk stratification techniques used alone or in combination with the LVEF also lack sufficient predictive value for SCD in the immediate post MI patient to have clinical utility for prevention of SCD.\textsuperscript{4-8}

Despite many limitations, reduced LVEF remains the most powerful predictor of survival after a MI.\textsuperscript{4-8} When used to select patients remote from MI or revascularization, it identifies patients who derive a mortality benefit from the ICD.\textsuperscript{9-12} Clinical trials assessing the ICD for
primary prevention of SCD have demonstrated a reduction in sudden death and total mortality among patients with left ventricular dysfunction due to ischemic heart disease.9-12 These trials have excluded patients with recent MI or revascularization.9-12 Notably, the trials assessing the role of the ICD for SCD prevention immediately after MI have failed to show any survival benefit.13-15 Both the IRIS and DINANITE Trials demonstrated a reduction in arrhythmic death which was offset by a significant increase in non-sudden death.13-15 This lack of benefit of the ICD in the immediate post MI period may be due to the high frequency of cardiac rupture or recurrent MI relative to arrhythmic deaths.16 It logically follows that the benefit of the ICD in post MI patients after 3 months may be due to a higher percentage of arrhythmic death than recurrent MI or cardiac rupture.16 Evidence based medicine strongly supports contemporary guidelines restricting ICD implants to patients at least 40 days after MI and 90 days after revascularization with continued impairment of left ventricular function while on optimal medical therapy.17

In this issue of Circulation, Sjöblom and colleagues further investigate the time dependence of LVEF after MI and the implications for ICD eligibility.18 These investigators specifically evaluate the proportion of MI patients who improved their LV function by three months such that that they would not qualify for an ICD implantation.18 Patients admitted for MI with reduced LVEF (≤40%) over a three year period to two hospitals were eligible for inclusion. Echocardiographic examinations were performed at the time of the diagnosis, at five days, one and three months after the MI.18 The main improvement in LVEF occurred by one month. The mean difference in LVEF over the next two months was small, 1.9%. During the first nine weeks nine patients, representing 10% of the final cohort studied, suffered from life-threatening arrhythmias.18 Remarkably, all nine patients survived cardiac arrest.18 Life-threatening
arrhythmias occurred in 10% of the patients illustrating the high risk for SCD in this population. Because there were no significant differences between the nine patients who had cardiac arrest and those who did not, the investigators note that is difficult to prevent SCD occurring shortly after an acute MI. The authors conclude that most patients improve their LVEF after AMI and in most patients the improvement could be confirmed after one month. They also note that these observations imply that further delay of ICD implantation may not be warranted.

Limitations acknowledged by the investigators include the subjective nature of the assessment of LVEF estimation due to lack of proper visualization of the endocardium. The authors also note the potential for intra- and inter-observer variations for calculating LVEF. A limitation not noted by the authors is exclusion from the study of an unspecified number of patients with a life expectancy less than one year or declining informed consent. Of the 121 patients enrolled, 21 were excluded from analysis due to disagreement of the LVEF estimation between the clinical echo and the echo core laboratory. Of the remaining 100 patients with an LVEF $\leq 40\%$, 9 patients dropped out of the study prior to hospital discharge. This includes six patients due to severe heart failure, one due to a cardiac embolus, and one due to a pulmonary embolus.

Accordingly, of the 121 patients originally enrolled only 91 patients were followed after hospital discharge for the duration of the study. An indeterminate exclusion rate prior to enrollment and a subsequent dropout rate of 25% confound interpretation of the outcomes. No additional information is provided on the 9 patients dropping out of the study prior to hospital discharge. Only two patients of the 91 remaining in the study after hospital discharge died, both from infection, representing a three month total mortality of 2.2%. There were no arrhythmic deaths. Survival of all 9 patients having a cardiac arrest in the study contrasts with the survival
rate averaging 10% of those receiving community based resuscitation. Based on these exclusions and study dropouts, there is considerable potential for a selection bias favoring survival of those completing three months of follow-up. In this respect, the evolution and LVEF after acute MI and implications for ICD eligibility presented by the investigators need to be carefully considered as potentially representing survival of the fittest. The short duration of follow-up (3 months) and the absence of any intervention showing improved survival further limit clinical utility of the study.

While the observations by Sjöblom and colleagues extend prior observations on the time dependence of LVEF after MI, the small selected patient population, short follow up, and absence of intervention limit the clinical utility of the observations. On the basis of prior interventional trials in high-risk patients immediately after MI, insufficient evidence still exists to support ICD implantation in those with impaired LVEF. Current guidelines restrict ICD implants to patients at least 40 days after MI and 90 days after revascularization with continued impairment of LVEF while on guideline based medical therapy. Unfortunately the strategy of home automated external defibrillator use in high-risk immediate post-MI patients has failed to improve survival compared with conventional resuscitation methods. While the short-term use of noninvasive vest defibrillation represents a reasonable approach for high-risk post-MI patients based on impaired LVEF, it has not been evaluated in prospective randomized trials. Since neither noninvasive or invasive risk stratification techniques, alone or in combination with the LVEF have proven to have clinical utility, improved risk stratification tests and interventions are essential to reduce SCD and mortality post MI. Currently a prospective randomized trial is being conducted to investigate of the role of CMR, with the ability to detect scar size and heterogeneity, in combination with programmed ventricular stimulation, to guide early post MI
ICD implantation. 20 Until this or other trails meet the standards of evidence based medicine by predicting and preventing SCD immediately after an MI, clinicians should focus on optimizing revascularization strategies and medical therapies. Clinical trials and current guidelines also support reappraisal of LVEF at least 40 days after MI and 90 days after revascularization to identify those with proven mortality benefit from ICD therapy.

Conflict of Interest Disclosures- Dr. Estes reports educational consulting for Boston Scientific (> $10,000), educational consulting for Saint Jude Medical (< $10,000), and quality and safety consulting for Medtronic (< $10,000).

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