Lessons from the DEFINITE Trial

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The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was a prospective, randomized multicenter trial of ICD therapy in 458 patients with a nonischemic dilated cardiomyopathy.[1] The trial was designed based on the premise that: patients with nonischemic cardiomyopathy are at an increased risk of sudden cardiac death and prior studies examining the role of ICD therapy in these patients had not shown a definite benefit. The primary purpose of this trial was therefore to determine whether ICDs have a role as primary prevention therapy in this group of patients.

Patient Population

The inclusion criteria were any patient with a left ventricular ejection fraction less than 36%, a history of symptomatic heart failure, presence of nonischemic cardiomyopathy and the presence of an episode of nonsustained ventricular tachycardia on Holter monitoring (3-15 beats at a rate of > 120 beats/minute or an average of >10 PVC's/hour). Exclusion criteria included NYHA Class IV symptoms or confirmed significant coronary artery disease on angiography responsible for the cardiomyopathy. Additional exclusion criteria consisted of the presence of a permanent pacemaker, prior electrophysiologic testing within three months of study inclusion, acute myocarditis, congenital heard disease, familial cardiomyopathy associated with sudden cardiac death and imminent heart transplantation.

A total of 229 patients were randomized to medical therapy alone. The other 229 patients were randomized to medical therapy plus a single chamber ICD. Medical therapy consisted of angiotensin converting enzyme inhibitors in 85%, beta blockers in 85% (carvedilol in 57%, metoprolol in 22% and other beta blockers in 5%), diuretics in 87%, amiodarone in 5%, digoxin in 42% and nitrates in 11%. The doses of these medications were adjusted to those recommended for patients with heart failure or the highest doses tolerated. The mean left ventricular ejection fraction was 21% (range: 7-35%), and the mean QRS interval was 115.1 msec (range: 78-196 msec). Twenty-three percent of patients had a history of diabetes mellitus, and 24.5% had a history of atrial fibrillation. The mean duration of heart failure was 2.83 years (range: 0.0-38.5 years). NYHA Class II hear failure was present in 57.4% of patients, and 21% of patients had either NYHA Class I or Class III symptoms. The mean distance walked during the 6 minute wak

test was 319.4 meters. Clinical characteristics were similar in both groups except for a slightly increased duration of heart failure (0.88 years) in the standard therapy group (p=0.04).

Study Design

Patients were randomly assigned to one of the two study arms. There were no significant differences in the patient populations. ICDs were programmed to back up VVI pacing at a rate of 40 bpm and to single zone tachycardia therapy assigned for all arrhythmias faster than 180 bpm. All patients were followed up at three month intervals. Patients were crossed over from standard medical therapy to ICD therapy if they had a cardiac arrest or an episode of unexplained syncope that was felt to be due to an arrhythmic event. The cause of death was determined by an events committee. The trial was monitored by a separate data and safety committee. The blinding process included removal of any information from progress notes or laboratory testing that would indicate whether the patient had an ICD. The mean follow-up was 29.0±14.4 months.

Lessons Learned

Lesson #1: ICD's prevent arrhythmic death and probably overall mortality

1. **The risk of sudden death from arrhythmias was statistically significantly reduced by ICD therapy.**
2. **The risk of death from any cause was reduced by borderline statistical significance by ICD therapy**

In this trial, there were a total of 68 deaths: 28 in the ICD group, compared to 40 in the standard therapy group (hazard ratio: 0.65; 95% confidence interval, 0.40 – 1.06; p=0.08 by the log rank test). The mortality rate of death from any cause was 6.2% in the standard therapy group and 2.6% in the ICD therapy group at one year, at two years it was 14.1 % in the standard therapy group and 7.9 % in the ICD group. There were 17 sudden deaths from arrhythmia: 3 in the ICD group, compared to 14 in the standard therapy group (hazard ratio, 0.20; 95% confidence interval, 0.06 – 0.71; p=0.0006).

There were two patients who refused ICD implantation after informed consent and randomization. There were no procedure related deaths. Thirteen patients received ICD upgrades during follow-up; 2 were upgraded to dual chamber ICD's due to sinus node dysfunction and 11 were upgraded to biventricular (CRT, cardiac resynchronization therapy) ICDs due to congestive heart failure. Twenty-three of the 229 patients randomized to medical therapy received ICDs during follow-up, because of syncope or heart failure with a prolonged QRS duration. An analysis based on treatment actually received showed almost identical findings.

Of the 68 deaths, 26 deaths were classified as noncardiac, 10 were due to cancer, 5 to stroke, and 1 each due to drug overdose, suicide, liver failure and renal failure. Four deaths could not be definitively characterized. Twenty of the 68 deaths were due to heart failure, 11 in the standard medical therapy group and 9 in the ICD group.

Lesson #2: Benefit is similar in patients with recently diagnosed cardiomyopathy vs. patients with cardiomyopathy of longer duration

This sub-study analyzed the effect of the duration of cardiomyopathy relative to the risk of sudden cardiac death. This is a retrospective study that looked at the data from the DEFINITE trial and divided groups into patients who were recently diagnosed with cardiomyopathy (≤ 3 months and ≤ 9 months) and compared to patients with longer durations of cardiomyopathy. There were significant differences in the patient subgroups, with respect to race, QRS duration, NYHA functional classification and the presence of diabetes.[2] Patients with a longer duration of cardiomyopathy had longer QRS durations, more severe NYHA Class, and a higher prevalence of diabetes mellitus.

Overall survival was similar in patients when a cut point of 3 or 9 months was selected (Figures 1 and 2). The ICD group was associated with a reduced risk of death for patients who were recently diagnosed within 3 months (hazard ratio 0.37; 95% confidence intervals: 0.14- 0.998; p = 0.049) and the difference at nine months was of borderline significance (hazard ratio: 0.48; 95% confidence interval: 0.48; 95% CI: 0.23-1.025, p = 0.058). The ICD insertion was not significantly related to survival for patients who had been diagnosed with cardiomyopathy for longer periods of time. Importantly, despite the fact that treatment assignment was significantly related to improved survival in patients with shorter duration of cardiomyopathy, the association of treatment assignment with outcome was not different in the groups of patients as indicated by nonsignificant interaction terms between the three and nine month cut points. In other words, the relative differences in survival between recently and remotely diagnosed groups of patients with cardiomyopathy was not significant. Adjusting for the covariates did not substantially alter the findings of the unadjusted model. It is also worthwhile noting, the survival curves between the ICD group and the medically treated group continued to diverge throughout the entire follow-up period.

These results are similar to those of Makati et al. who reviewed their data base of 131 patients with an implanted ICD in the setting of nonischemic dilated cardiomyopathy and categorized patients into those with symptoms of > 9 months duration and < 9 months duration.[3] They found *no* difference in occurrence of ICD treated ventricular arrhythmias between the two groups (p= 0.49) or ICD treated malignant ventricular arrhythmias (p= 0.16). The SCD-HeFT trial also found

no basis for exclusion of patients from ICD therapy with the time from diagnosis of nonischemic cardiomyopathy of a short duration.[4]

It is important to point out this analysis was retrospective and post hoc, and DEFINITE was not powered to assess the effect of the time of diagnosis on ICD related survival. Nevertheless, these results do *not* support the national coverage decision by CMS that excludes coverage of ICD therapy in patients with a duration of non ischemic cardiomyopathy of less than 3-9 months.

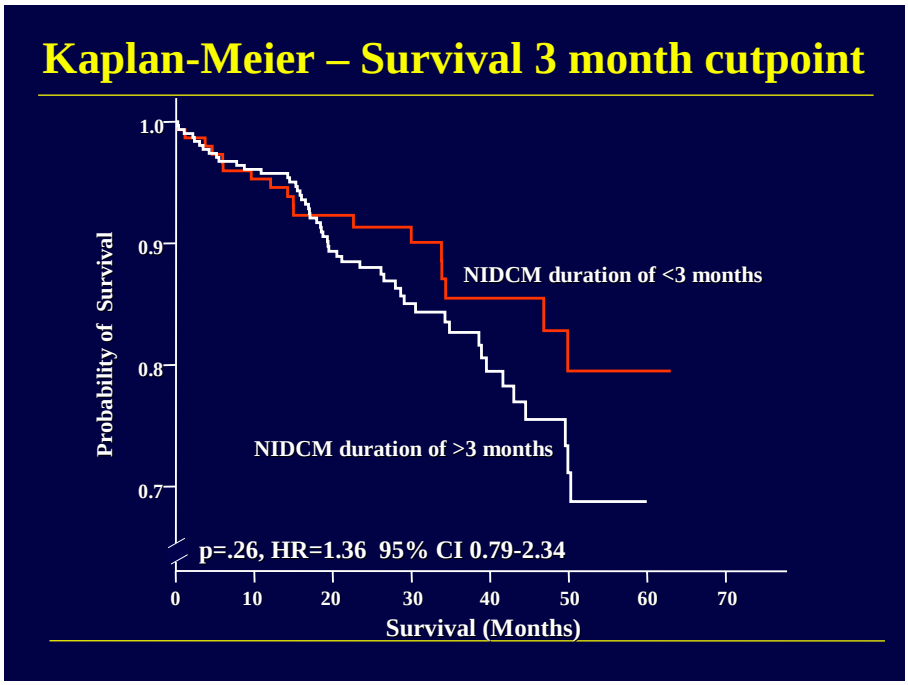

Figure 1: Overall survival with a 3 month cutpoint for the duration of cardiomyopathy using Kaplan-Meier analysis for probability of survival.

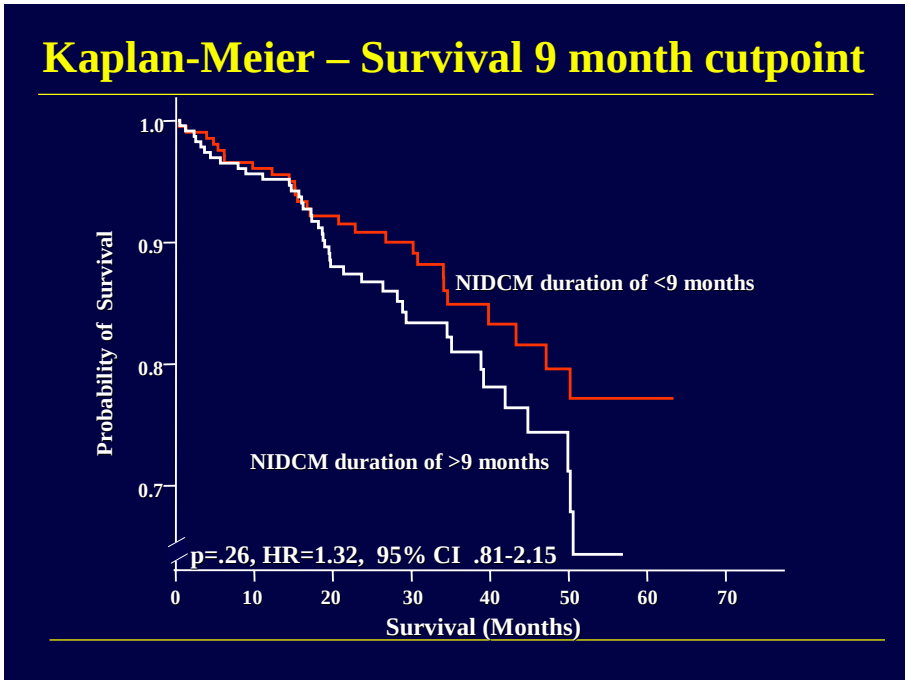

Figure 2: Overall survival with a 9 month cutpoint for the duration of cardiomyopathy using Kaplan-Meier analysis for probability of survival.

Lesson # 3: Shocks are *NOT* a surrogate for sudden cardiac death

In this retrospective analysis, the investigators sought to answer the question of whether ICD shocks could serve as a surrogate for sudden cardiac death. This is a particularly important question as many studies of patients with ICDs have equated "appropriate" shocks or shocks for rapid ventricular tachycardia as equivalent to an episode of aborted sudden cardiac death. It would be easier and quicker to do studies of ICD therapy with the primary endpoint being appropriate ICD therapy than having to do a longer, larger study with the primary endpoint being mortality. This issue has major imiplications for future clinical trials of ICD therapy.[5]

The authors analyzed all shocks and classified them as "appropriate" or "inappropriate", and then further classified shocks as being due to monomorphic ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation. In this study data was analyzed for two different primary end points.[6] In the first analysis, the primary end point was sudden arrhythmic death or being resuscitated from sudden cardiac death in the standard medical therapy treatment arm. In the ICD arm, the primary end points were appropriate shock or sudden arrhythmic death. Data was also analyzed for a primary endpoint in the standard medical therapy group for syncope plus

resuscitated sudden cardiac death plus sudden arrhythmic death compared to shock or syncope or sudden arrhythmic death in the ICD arm. Only the earliest event was counted, and patients were censored after they reached an endpoint. For example, if a patient experienced in chronological order syncope followed by sudden death, he was censored from further analysis after the first event, because theoretically it could be fatal. The 26 patients who crossed over from the standard medical therapy to the ICD arm were censored at the time of crossover.

A total of 33 patients received 70 appropriate shocks and 47 patients received 86 inappropriate shocks. Twelve patients received 18 shocks that could not be reliably classified as either appropriate or inappropriate. Of the 70 shocks that were classified by a separate committee as appropriate, 37 were for monomorphic ventricular tachycardia, 13 for polymorphic ventricular tachycardia and 19 for ventricular fibrillation. One episode could not be definitively classified as monomorphic or polymorphic. The mean cycle length for monomorphic ventricular tachycardia was 272 ± 9 msec, for polymorphic ventricular tachycardia it was 211 ± 11 msec and for ventricular fibrillation it was 183 ± 14 msec. Of the 86 inapprorpriate shocks, 46 were due to atrial fibrillation and 31 were due to supraventricular tachycardia and in 9 episodes a definite diagnosis of the arrhythmia could not be made.

The most important message from this study is as follows: the number of total events in each arm was similar when we compared syncope PLUS sudden cardiac death PLUS resuscitated sudden cardiac arrest in the standard medical therapy arm with the number of episodes of sudden cardiac death plus ICD shocks plus syncope in the ICD arm. Patients in the ICD arm were more likely to have an arrhythmic event (ICD shock plus sudden cardiac death) than patients in the standard medical therapy arm (hazard ratio 2.12, 95% confidence interval: 1.153-3.893, p = 0.013). The number of arrhythmic events when one includes syncope as a potential arrhythmic event was similar in both groups (hazard ratio 1.20, 95% confidence interval: 0.774-1.865, p = 0.414).

The take home message is that appropriate ICD shocks occur more frequently than sudden cardiac death in patients with nonischemic cardiomyopathy. This means that episodes of nonsustained ventricular tachycardia frequently terminate spontaneously in such patients, and are presumed to be the cause of some episodes of syncope in this patient population. One may hypothesize, that similar episodes of nonsustained ventricular tachycardia may less frequently terminate spontaneously in the milieu of ischemic heart disease. Transient ischemia in those patients may increase the likelihood of initiation and maintenance of ventricular fibrillation through multiple mechanisms. Our findings clearly demonstrate that ICD shocks cannot be reliably used as an estimate of the incidence of sudden cardiac death, and the number of ICD shocks cannot be used to estimate the number of lives saved or mortality benefit of ICD therapy. Our findings are corroborated further by the PAIN-Free II trial where at least one third of episodes of very rapid

monomorphic ventricular tachycardia terminated spontaneously before antitachycardia pacing therapy was delivered.[7]

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