ICD for Primary Prophylaxis of Sudden Cardiac Death: An Indian Perspective

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INTRODUCTION

The implantable cardioverter defibrillator (ICD) is perhaps one of the greatest inventions of modern medicine, culminating from a dream in 1969 to the first clinical implant in 1980 in just 11 years. The conviction (not dream), of Michel Mirowski developed after having helplessly watched his former chief of Medicine, die of recurrent ventricular arrhythmias. The fascinating history of its development culminated with NASA being involved in preclinical testing, applying techniques of assuring reliability of an orbiting spacecraft and similar other methods before declaring it fit for human trial in July 1979- till the final implant in Feb 4, 1980. And what a shock, when the first device fell down before implanting, and the one implanted took an agonizing 35 seconds before firing!

This small beginning, in less than two decades, has changed the outlook of patients with coronary artery disease (CAD) and ventricular dysfunction surviving a sudden death episode/ hypotensive ventricular tachycardia (VT).12 Although the device does precious nothing in preventing the recurrence of the arrhythmia, it has shown tremendous efficacy in treating these tachyarrhythmias. The growth of the device also got a major impetus because of the lack of suitable anti-arrhythmic medications for such patients. True to the evolutionary pattern of almost all major discoveries and inventions, the ICD is in its growing phase, wherein, implant recommendations appear to be stemming from the “heart”, rather than for the heart, with unseeming haste. One maybe left to wonder that the day is not far when anyone could buy the device over the counter thinking it grants immortality!

The acceptance and implementation of a single parameter, ejection fraction (EF) as being sufficient to qualify for an implant in patients of CAD and no prior arrhythmia, is proof of this evolutionary phase. While MADIT II and SCDHeFT results continue to get debated and analyzed in depth at various scientific and economic platforms, the American College of Cardiology / American Heart Association / North American Society for Pacing and Electrophysiology (ACC / AHA / NASPE) have already accepted CAD with old myocardial infarction (MI) and left ventricular ejection fraction (LVEF) ≤ 30% as an accepted indication to implant an ICD for primary prevention of SCD.23 The CMS (Center for Medicare and Medicaid Services, US) has approved this indication to claim reimbursement from insurance firms. The economic repercussions of accepting the above guidelines are going to be mind boggling for the rest of the world and unthinkable for India with a population of over 100 crores (109 individuals). The incidence of SCD in the general population is 0.1%, meaning thereby that 1 million Indians are at risk of SCD annually. The risk factor for SCD for the vast majority of these individuals is CAD. Even as of today, it is not possible to reliably identify the vast majority of those who would have such a catastrophic event. The MADIT and MUSTT criteria (the largest primary prophylaxis trials) form only a meager 10% of these CAD patients, meaning thereby; that 90% of SCD’s will still and as of now the focus through invasive strategies is to address this 10%. This would translate into approximately 100, 000 ICD implants per year in India for primary prophylaxis in this subgroup. Given the present cost of an ICD (Rs. 4 lakhs) in India (without adding any overheads like implant charges, follow-up charges etc.) we need 40 billion rupees just for primary prevention of SCD in this population alone!3,4 So, here’s a “therapy” that may benefit 5.6 individuals in a group of 100, and that too over a period of 30 months. How many “quality” of months or years gained would also depend on the underlying condition/s, but could as be low as 2.7 months! (from AVID data?)

As “educated physicians and cardiologists” we have therefore to decide for ourselves; armed with the knowledge of an “effective” therapy that greatly strains the health budget of our economy do we blindly extend its use for all indications approved by the American Heart Association or should we be more prudent and advise only for select high risk groups, that are still not well known. What should be the recommendation for physicians when it comes to third party payment, be it the CGHS/Railways or an insurance company. Should these be different for a person who can pay on his own meaning thereby, can, a person buy an ICD from the shop and get it implanted by xyz? If we follow the AHA guidelines we know we will have a bankrupt health budget within months, but if we try to be patriotic the net savvy patient would drag you to the court for medical negligence?

In these days of evidence based medicine (or is it industry driven, evidence based?), we wish to apprise our physicians of the role of ICD in LV dysfunction in the Indian context through this article. The questions posed, are, not only identifying the populations who will benefit most; but also by how much, for how long and at what cost? Equally important who are those who don’t stand to benefit despite a low EF? Have the published large-scale randomized trials given us all the answers? What then should be our policy vis a vis device implantations? A highly qualified, multidisciplinary team is the needs of the hour, to address these complex issues and prevent misuse. Our article intends to bring forth some of the above issues.

A. Primary Prevention of SCD in CAD

All patients with CAD, regardless of severity, are at risk for SCD. An asymptomatic person with <50% lesion in the left anterior descending artery is at risk for SCD because of sudden plaque rupture and an acute MI. The probability of this event would be very low compared to a patient with multiple MIs, LVEF of 25% and frequent ectopy. Both these patients are candidates for primary prophylaxis for SCD. The second is the more obvious patient, although they represent only a small, though not negligible, fraction of sudden deaths in the community. Fig 1 shows how the risk of SCD in CAD evolves around LVEF and how other markers substratify an individual’s risk. The line depicts that although the core theme maybe LVEF in deciding mortality, many other clinical and electrophysiological markers modify the overall mortality.

Myerburg illustrated this effect of coronary risk factors on SCD risk in an earlier publication.5 While the absolute risk of arrhythmic death is high in patients with CAD, LV dysfunction and NSVT (and even higher in patients who have survived an SCD episode), these patients comprise only a small fraction of the overall population who actually have an SCD event. The vast majority of patients who have an SCD event every year are instead derived from the general population pool who have CAD risk factors and a much better ventricular function.

I. The Primary Prevention Trials:
**Patient Subgroups Studied**

The MADIT II trial was the first trial to look at primary prevention and recruited 196 patients at high-risk for SCD: the high risk was because of the inducible, non suppressible VT in the setting of a low EF. The mean LVEF of these patients was 26% (Table 1). They had baseline non sustained ventricular tachycardia (NSVT) and inducible, non-suppressible VT at electrophysiologic study (EPS), a well known positive predictor for spontaneous VT. The results were remarkably in favor of ICD compared to the medically treated arm, although the drug arm was sub-optimally treated with beta-blockers. The other trial that used EPS to randomize its patients was MUSTT, which used an LVEF of 40% as a cut-off for recruitment. The benefit in this study was also obvious, demonstrating the importance of ambient ventricular arrhythmias in determining arrhythmic risk of death.

In an attempt to do away with EPS (that is expensive in the US and also has a small risk) the MADIT II investigators followed with the MADIT II trial. During the enrollment phase the investigators did away with the need for baseline ventricular ectopy/NSVT (as this was hindering recruitment) and therefore the trial changed to answer the question whether ICD could be used as a blanket therapy for all patients with LVEF ≤ 0.30. The important points in recruitment that need to be emphasized are: exclusion of patients with MI in past 3 weeks, revascularization within the past 3 months or comorbid illness precluding survival for the duration of the trial. After randomization, 742 patients received an ICD while 490 were on conventional therapy (beta-blockers 70%, ACE inhibitors 70%, statins 65%). Of note, more than 50% of patients in MADIT II were on digoxin. In addition, two thirds of patients in MADIT II had symptomatic heart failure (NYHA class ≥ II). Over a follow-up of 20 months (6 days to 53 months), the two-year mortality in the ICD arm was 14.2% and 19.8% in the conventional therapy arm. This led to premature termination of the trial as this was associated with a relative risk reduction of 31% though the absolute risk reduction was small (5.6%). At this juncture, we would wish to deviate a little to explain the concept of relative and absolute risks and how these figure in the cost-benefit analysis.

How do we judge cost-efficacy of an intervention that is directly life saving? One could argue that nothing is more precious than life and there cannot be a cost attached to it, but the fact remains that someone has to pay for the ICD. It could be a “crorepati” (from KBC!) himself or a middle class person who may have to shell all his savings or it maybe the CGHS/Railways/other governmental agencies. It is somewhat peculiar that most cardiologists are happy when the government is the ICD provider, without realising the fact that it is the tax-payers money and is limited; it has to be divided in proper proportion into various other diseases wherein outcomes maybe much better.

The efficacy of an intervention is judged by its effect on mortality, morbidity and quality of life. When we say mortality, it not only means how many lives are saved but also the number of life-years gained which could again be adjusted for quality of life in this period % providing an ICD to a 80 year old, Class IV patient with metastatic prostate cancer would hardly help the individual, family and society. The AVIT trial just added 2.7 months of life over the control of 3 years! Life-years added can be roughly made out from the area between the two survival curves while effectiveness is judged by relative risk (RR) reduction. Thus if the control arm at 3 years has a mortality of 30% and the ICD arm has a mortality of 20%, we would say the relative risk reduction was by 33%, while the absolute risk reduction over 3 years was 10%. This would mean that 10 lives were saved over 3 years when 100 patients were treated with the ICD. It is possible that the risk reduction was spread over 3 years equally or it maybe that there was no benefit in first year and it came in only after that. In clinical decision making, absolute risk reduction is more important to derive the cost effectiveness. A valid benchmark has to be provided to measure cost effectiveness and other interventions should be measured against it. In the US renal dialysis at a cost of $ 50,000 per year is the benchmark and supposed to be cost effective. Given our economy, per capita income and the burden of communicable diseases this figure for us is like asking for the moon. Once again, the above arguments should not be misconstrued into the argument that “then we should stop doing all coronary interventions”. The issue here is that all patients should be

### Table 1: Major randomized primary prevention ICD trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
<th>Mean LVEF</th>
<th>Symptomatic CHF (NYHA)</th>
<th>Trial Duration</th>
<th>Absolute RR</th>
<th>Relative RR</th>
<th>Numbers Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT</td>
<td>CAD, Prior MI, LVEF ≤ 0.35, NSVT, non-suppressible VT on EPS</td>
<td>0.26±0.07</td>
<td>63%</td>
<td>Average FU</td>
<td>22.8%</td>
<td>56%</td>
<td>4.4</td>
</tr>
<tr>
<td>MUSTT</td>
<td>CAD, LVEF ≤ 0.40, NSVT, Inducible VT</td>
<td>0.28±0.08</td>
<td>63%</td>
<td>Median FU</td>
<td>25%</td>
<td>76%</td>
<td>16.7</td>
</tr>
<tr>
<td>CABG</td>
<td>CAD, LVEF ≤ 0.35, Undergoing CABG, abnormal SAE G</td>
<td>0.27±0.06</td>
<td>71%</td>
<td>32±16 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT II</td>
<td>CAD, Prior MI, LVEF ≤ 0.30</td>
<td>0.23±0.05</td>
<td>65%</td>
<td>Average 20 months (6 days -53 months)</td>
<td>5.6% (ICD 14.2%, Conventional arm 19.8%)</td>
<td>31%</td>
<td>17.9</td>
</tr>
<tr>
<td>SCDHeFT</td>
<td>CAD, DCM, LVEF ≤ 0.35</td>
<td>0.25</td>
<td>100%</td>
<td>Median FU</td>
<td>7.2% (ICD 28.9% vs. Conventional arm 36.1%)</td>
<td>23%</td>
<td>—</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>DCM, LVEF ≤ 0.35, NSVT/ PVC</td>
<td>0.21</td>
<td>88.4%</td>
<td>29±14.4 months</td>
<td>6.2% (ICD 7.9% vs. Conventional arm 14.1%)</td>
<td>—</td>
<td>Hazard ratio 0.66 (p=NS)</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>Recent MI, LVEF ≤ 0.35, depressed heart rate variability</td>
<td>0.28±0.05</td>
<td>86.5%</td>
<td>30±13 months</td>
<td>ICD 7.5% vs. Conventional arm 6.9%</td>
<td>—</td>
<td>Hazard Ratio 1.08 (p=NS)</td>
</tr>
</tbody>
</table>
provided with the best possible care within the economic framework especially when the government is the paying party.

The MADIT investigators concluded that the ICD should be considered in all patients with advanced LV dysfunction (read LVEF ≤ 0.30) as it improves their survival (a conclusion further endorsed by Arthur Moss, principal investigator of this trial in a subsequent article10). This conclusion from the MADIT II investigators, which has been endorsed by the ACC/ AHA/ NASPE as a class IIa indication for ICD, has sparked a debate that refuses to die even three years after the results of this trial were published.

SCDHeFT is the largest randomized ICD trial that also has the longest follow-up; it evaluated the benefit of ICD over amiodarone in heart failure patients11. The trial enrolled patients with symptomatic heart failure (ischemic and non-ischemic) with LVEF ≤ 0.35. Over a period of 45 months a 23% relative reduction in mortality with the ICD. Amiodarone was no better than placebo in reducing overall mortality in this trial.

**II. IS ONLY LVEF < 30% ENOUGH EVIDENCE FOR A PROPHYLACTIC ICD?**

The central theme that has polarized cardiologists is the use of LVEF as the sole determinant of cardiovascular risk for deciding on ICD implant in patients with CAD and LV dysfunction. The use of LVEF only may greatly simplify the implant indications but lumps together patients with a widely varied risk of SCD. Do patients with EF < 30%, no ventricular ectopy and non-inducible VT on EPS benefit? (this patient is depicted in Fig 1 as the arrow within the shaded box). We don’t know; but this answer could have been provided by the MADIT II investigators who did an EPS in over 3/4th of its patients but have not provided details of the EP evaluation. It is unlikely that any trial can now be done separately to answer the above issue. It thus becomes pertinent to estimate the quantum of risk for different patient subgroups by analyzing the evidence accumulated till date and also going into the various subgroups of these trials, especially MADIT II.

Before proceeding to the step of dissecting population subgroups based on EF one also needs to give a hard look at the sanctity of using one-time echo estimation of LVEF as a reliable tool. LVEF estimation by echocardiography is a variable that is subject to significant intra- and inter-observer variability. In some studies, measurements have varied by as much as 8.5% between sessions12. LVEF is a highly load dependant parameter that can actually vary markedly between two studies done at different times in the same patient. It is surprising and intriguing that such a crucial decision stands atop such an imprecise measurement and based on it purports sizeable benefits!

**i) Patients with CAD Who Have Shown No Benefit of Prophylactic ICD**

The CABG Patch trial randomized 1055 patients with CAD, LVEF ≤ 0.35 and an abnormal signal averaged ECG who were undergoing CABG to either an ICD or medical therapy (only 3% were on amiodarone and 24% were on beta-blockers).11 This trial did not find any benefit of a prophylactic defibrillator on mortality in this population. The DINAMIT trial used a very different population than all earlier trials – it randomized 674 high-risk CAD patients within 6-40 days of an acute MI to either an ICD or medical therapy (~85% on beta-blockers).12 High-risk status of these post MI patients was based on abnormal autonomic function tests (depressed heart rate variability or elevated 24-hour average heart rate on Holter). Although the ICD could significantly reduce arrhythmic death, overall death was similar in both groups as the ICD merely changed the mode of death from arrhythmic to pump failure death. The negative results of the above two trials are important in several ways: they highlight the importance of revascularization and the importance of ambient electrical instability in the form of frequent VPC’s/NSVT and the importance of the timing of the implant vis a vis the MI. It may be noted that in a sub-analysis of the MADIT II data, there was no survival benefit of the ICD in patients who received their ICD within 18 months of their MI. Data from the Maastricht registry also documented that the average time of SCD was 9 years after their index MI. This is quite contrary to what has always been believed that the patient with MI is at maximal risk of arrhythmic death in the early years after MI.13

**ii) Patients with CAD, LVEF <0.30 Who Do Not Benefit With Prophylactic ICD**

For LVEF alone to qualify as the ideal risk stratifier, the probability of SCD in patients with LVEF below 0.30 should be significantly higher than in those with better LVEF (Table 2). However, a subgroup analysis from the MUSTT trial demonstrated that the proportion of arrhythmic death was not higher in patients with LVEF ≤ 0.30 versus those with LVEF between 0.30 to 0.40.14 Subanalysis from the same investigators demonstrated that even amongst patients with the same LVEF (≤ 0.40), outcomes differed, depending upon the clinical setting in which the arrhythmia occurred15. Mortality rates in those who were recruited as in-patients at two and five years was 24% and 48% that was significantly higher than amongst those recruited as out-patients (18% and 36% at two and five years respectively, p = 0.018).15 In addition, significantly more in-patients who had CAD and poor LV function with asymptomatic NSVT had inducible VT on EP study than out-patients. Significantly more in-patients in the MUSTT trial with NSVT had a history of congestive heart failure and more advanced NYHA functional class, testifying to the importance of symptomatic heart failure in predicting arrhythmic events.

The MUSTT investigators made a predictive model for arrhythmic death based on a number of clinical and electrocardiographic variables such as age > 65 years, presence of LBBB or intraventricular conduction delay, EF ≤ 0.30, digitalis therapy and non-sustained VT diagnosed during in-hospital stay. Using this model, the two-year total mortality in patients whose only risk factor was LVEF ≤ 0.30 was only 6.2% and two-year risk of arrhythmic death was only 3.5%.16

The importance of clinical factors in defining the risk of arrhythmic death in a given patient is highlighted on examination of the mortality rate in the control arm of the various clinical trials. One would expect that the patients in the secondary prevention trials are sicker than the patients in primary prevention trials as these patients have had a clinical event like VT/VF or syncope. Paradoxically, the mortality rates in the control arm of all these ICD trials reveals just the converse: mortality rates in the control arm were actually higher in some of the primary prevention than in the secondary prevention trials (Table 3). This is due to recruitment of far sicker patients in the primary prevention trials than what is suggested by the innocuous statement “LVEF < 30%”. It is interesting to note that the mortality of the control arm...
Table 2: Limitations of LVEF in predicting SCD

1. Patients with same LVEF may have differing outcomes depending upon type of recruitment (out-patient vs. in patient)
2. Proportion of arrhythmic deaths not higher in patients with LVEF <0.30 vs. LVEF 0.30-0.40
3. Arrhythmic events higher in patients with LVEF <0.30 if they have symptomatic heart failure, than when they do not
4. Most sudden deaths in post MI patients occur in those with LVEF >0.30
5. Risk scores incorporating additional clinical data predict low clinical event rate in patients whose only risk factor is low LVEF

of MADIT II is more than the mortality of the control arm of SCDHeFT trial, a heart failure trial that required patients to have symptomatic heart failure for recruitment. This demonstrates that the MADIT II population is not merely a patient with an LVEF <0.30, but a patient with LV dysfunction and a host of additional risk factors. Therefore, generalization of this data to all patients with LVEF <0.30 would be like comparing apples with oranges.

(iii) Patients with CAD, LVEF >0.30 Who Are at Also at High Risk of SCD

Another misconception arising from the current controversy is that the patient with an LVEF > 30% is a relatively better candidate than an EF < 30%, under any circumstances. This is also not borne out from the Maastricht Circulatory Arrest Registry, which revealed that majority of sudden deaths occurred in patients with LVEF > 0.30. The mean LVEF of patients with SCD was 0.41 in this study. The ATRAMI study also showed that of the 49 deaths that occurred amongst 1284 patients with recent MI over an average follow-up of 21 months, only 22 occurred in patients with EF <0.35. In addition, the average EF of survivors was not different from patients who had sudden death. Thus this preoccupation with LVEF <0.30 excludes a sizeable portion of the CAD population who are also at risk of SCD.

III. UNANSWERED QUESTIONS AND LIMITATIONS OF AVAILABLE DATA FROM

Table 3: Major primary and secondary prevention trials of ICD

<table>
<thead>
<tr>
<th>Secondary Prevention Trials</th>
<th>Year of Publication</th>
<th>No. of Patients</th>
<th>LVEF</th>
<th>Annual Control Group Mortality, %</th>
<th>Trial Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1997</td>
<td>1016</td>
<td>0.35±0.12</td>
<td>12</td>
<td>NHLBI</td>
</tr>
<tr>
<td>CASH</td>
<td>2000</td>
<td>228</td>
<td>0.45±0.17</td>
<td>9</td>
<td>CPI/ Guidant, ASTRA GmbH</td>
</tr>
<tr>
<td>CIDS</td>
<td>2000</td>
<td>659</td>
<td>0.34±0.14</td>
<td>10</td>
<td>Medical Research Council, Canada and Wyeth-Ayerst Lab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Prevention Trials</th>
<th>Year of Publication</th>
<th>No. of Patients</th>
<th>LVEF</th>
<th>Annual Control Group Mortality, %</th>
<th>Trial Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT</td>
<td>1996</td>
<td>196</td>
<td>0.26±0.07</td>
<td>17</td>
<td>CPI/Guidant</td>
</tr>
<tr>
<td>MUSTT</td>
<td>1999</td>
<td>704</td>
<td>0.28±0.08</td>
<td>13</td>
<td>NHLBI, CR Bard, Berlex Lab, Boehringer-Ingelheim Pharma, Guidant, Knoll Pharma, Medtronic, Merck, Searle, Ventritex, Wyeth-Ayerst Lab</td>
</tr>
<tr>
<td>CABG Patch</td>
<td>1997</td>
<td>900</td>
<td>0.27±0.06</td>
<td>8</td>
<td>NHLBI, Guidant/CPI</td>
</tr>
<tr>
<td>MADIT II</td>
<td>2002</td>
<td>1232</td>
<td>0.23±0.05</td>
<td>11.88</td>
<td>Guidant</td>
</tr>
<tr>
<td>SCDHeFT</td>
<td>2005</td>
<td>2521</td>
<td>0.25</td>
<td>9.5</td>
<td>NHLBI, NIH, Medtronic, Wyeth-Ayerst Lab, Knoll Pharma</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>2005</td>
<td>458</td>
<td>0.21</td>
<td>7</td>
<td>St. Jude Medical</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>2005</td>
<td>674</td>
<td>0.28±0.05</td>
<td>6.9</td>
<td>St. Jude Medical</td>
</tr>
</tbody>
</table>


CURRENT ICD TRIALS

Analysis of various subgroups from the MADIT II database demonstrates many inconsistencies in survival patterns in these subgroups. Although there was a survival benefit for the overall survival, there were only four subgroups that clearly benefited from the ICD: those with age ≥ 70 years, male sex, NYHA class I and QRS width > 0.15. Analysis of other subgroups (like QRS width <0.12, NYHA class > II) showed wide confidence intervals. Although these subgroups were not pre-defined and these results can be a statistical aberration, the arguments put forward by Dr. Rahimtoola are extremely pertinent. How can we dismiss data of 618 patients (3 times the MADIT trial) with QRS width < 0.12, showing no clear survival benefit, as imperfect data because this was not a predefined subgroup? A recent committee convened to examine the benefits of the ICD (that included Arthur Moss, principal investigator of both the MADIT trials), concluded that the magnitude of benefit in many clinically relevant subgroups within the overall high-risk primary prevention group remains uncertain and needs to be addressed in future studies.

IV. UTILITY OF ADDITIONAL RISK STRATIFICATION TOOLS

These limitations of LVEF in predicting sudden death have rekindled interest in additional markers for risk stratification. Non-invasive markers such as baroreflex sensitivity, heart rate turbulence, microvolt T-wave alternans and signal averaged ECG are being investigated for their role in further risk stratification. The ATRAMI investigators reported on the utility of baroreflex sensitivity (BRS) and heart rate variability (HRV) in identifying patients at risk for life-threatening arrhythmias. The combination of all three risk factors i.e. non-sustained VT, depressed BRS and abnormal HRV increased the mortality more than 22-fold. Amongst patients with LVEF <35%, depressed BRS was associated with a higher mortality even in the absence of non-sustained VT. This comprised about 20% of the trial population. More importantly, among patients with LVEF <35%, absence of non-sustained VT and a normal BRS was associated with a very low mortality rate. This group accounted for more than 50% of the trial population, demonstrating that not all patients with LVEF<35% were at a high risk for sudden death.

Barthel et al also demonstrated the importance of additional risk markers to stratify risk of arrhythmic death. They evaluated the role of heart rate turbulence in risk stratifying 1455 post MI patients. HRT
category 2 was the strongest predictor of death followed by LVEF $\leq 0.30$. In patients in HRT category 2 and LVEF $\geq 0.30$, the 2-year mortality was almost 35% in patients with diabetes mellitus and age $\geq 65$ years. Thus HRT is a strong risk stratifier even in patients with an LVEF $\geq 0.30$, showing that this empiric cut-off of LVEF $\leq 0.30$ is flawed in its ability to demarcate between high and low-risk patients. Rather, a more comprehensive battery of tests maybe required to correctly identify the high-risk patient. Moreover, the degree of risk may not remain static, but fluctuate with time. Wilber et al., in a subanalysis of the MADIT II trial, demonstrated that the ICD was not useful in patients who received their defibrillator < 18 months from their MI. 21 In fact, the mean duration of the most recent MI to enrollment in the MADIT II trial was 81±28 months. Although the exact reasons for the lack of benefit needs to be investigated, these patients had less high-risk factors; they were younger, had better EF, were more often on beta-blockers and had a narrower QRS. This again attests to the importance of the clinical setting in which these arrhythmias occur in governing long-term prognosis. Table 4 provides a summary of known additional risk markers.

### B. Primary Prevention of SCD in Dilated Cardiomyopathy

The role of the ICD in primary prevention of SCD in dilated cardiomyopathy has been examined in the CAT, AMIOVIRT, DEFINITE and SCHeFT trials. 22-24 The AMIOVIRT and CAT trials were small trials that did not find a mortality difference with the use of the ICD. Both these trials had low rate of events in both arms, probably related to the absence of a requirement for symptomatic heart failure as enrollment criteria. The DEFINITE trial randomized 458 patients with non-ischemic DCM with LVEF $<0.35$ and asymptomatic NSVT to ICD or conventional medical therapy. 24 Although there was a 35% relative risk reduction in the ICD arm, this did not reach statistical significance. In the SCHeFT trial patients with both ischemic and non-ischemic DCM and LVEF $\leq 0.35$ were randomized to ICD or conventional medical therapy. 24 There was a significant survival benefit with the use of the ICD in patients in NYHA class II but not in class III patients. However, the absolute risk of a SCD event was much lower in non-ischemic DCM (5-year event rate of 25.8% in amiodarone arm and 21.4% in ICD arm) than ischemic DCM (5-year event rate of 41.7% in amiodarone arm and 35.9% in ICD arm), even though the relative risk reduction was similar (27% reduction in mortality in non-ischemic DCM vs. 23% reduction in ischemic DCM). As the ICDs reduce the relative risk for SCD by approximately 50%, the cost-effectiveness of this intervention is reduced in patients with lower absolute risks.

### D. Societal Factors and Public Health Effects of Indiscriminate Use of ICD

Despite the proven efficacy of ICD, significant disparities in ICD implantation rates exist in the developed world. These global variations have been well documented in a number of studies. 24 The United States stands out as the only country with an extremely high implant rate amongst these developed nations. National registries may offer important perspectives on the role of non-invasive high-risk markers such as T-wave alternans in predicting arrhythmic death. Till then it would be prudent for cardiologists in developing countries to exercise more restraint in extending the ICD for primary prevention to a MADIT II population.

### E. Ethical Issues

Physicians and cardiologists should also take note of the fact that contrary to what most of us believe the ACC/AHA/NASPE guidelines are not legally binding even to the US physicians. The US FDA is a regulatory body that, justifiably, approves therapy based on its scientific merit alone without considering its economic implications. The CMS takes the tough decision regarding broad clinical coverage of a therapy within the economic framework. In the absence of any such body in India, it is the duty of the Indian medical community to address this dilemma. Although it would be easy to take an escapist route and be aghast at having double standards for Indians, it is rather the call of the hour to boldly and justly assess the actual risk for an individual patient.

### Suggested Recommendations

- CHF: NYHA 2 or 3
- CAD load: multivessel disease, inducible ischemia
- Extent of infarction
- ECG: QRS width, LBBB, LVH
- Holter: Nonsustained VT
- Signal Averaged ECG — T wave alternans
- Baroreceptor response
- Electrophysiological study

<table>
<thead>
<tr>
<th>Table 4: SCD risk modifiers with low LVEF</th>
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<tr>
<td>CHF: NYHA ≥ 2</td>
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<td>CAD load: multivessel disease, inducible ischemia</td>
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<tr>
<td>Extent of infarction</td>
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<td>ECG: QRS width, LBBB, LVH</td>
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<td>Holter: Nonsustained VT</td>
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<td>Signal Averaged ECG — T utility</td>
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<td>T wave alternans</td>
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<td>Heart rate variability</td>
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<td>Heart rate turbulence</td>
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have not been closely scrutinized, they have been related to the national economic status. Correlations have been drawn between the gross domestic product (GDP) and both pacemaker and ICD implant rates amongst these developed nations 26. As these devices are reimbursed using taxpayers money, and each nation has to draw a ceiling to the amount that can be used for budgeting health costs, cost-effectiveness for the society for each physician initiated intervention needs to be scrutinized. This is especially true for the developing world, which have finite health budgets and are also burdened with both communicable and non-communicable diseases. Indiscriminate diversion of funds for expensive devices in patients who may not gain much from the ICDs will only accentuate health inequities in these developing nations. Projections from the SCHeFT trial (which demonstrated 23% relative risk reduction over 5 years) implied that of 100 such patients followed over 5 years, 7-5 lives would be saved due to the ICD, 29 would have died despite the ICD while 64 would have never used the ICD. The EP study in MADIT population reduced the numbers needed to treat to prevent a clinical outcome from roughly 18 (in MADIT II) to 4 (in MADIT I). This made this intervention significantly more cost-effective. For the developing world cost-effectiveness is extremely relevant as interventions that have been deemed cost-effective in developed nations are not necessarily inexpensive for a public health program in the developing world. Indeed, when absolute benefits of a therapy are small and lower-risk groups can be reliably excluded, these nations stand to gain substantially in saving costs with a negligible effect on overall survival. Moreover, the public health impact of indiscriminate use of ICD on incidence of sudden death in the community will be minimal. As majority of sudden deaths occur in patients with near normal ventricular function, and less than 10% of all sudden deaths are in high-risk patients, a substantial portion of the national health budget will be drained in an ineffectual exercise. It has to be realized that an ICD is not a public health tool; it is a tool designed to improve mortality in a particular individual. To make it more cost effective, we have to identify those individuals who will benefit the most and in turn from this subpopulation give it to the most deserving depending on health and societal “economics”. The issue is not to deny the ICD to a deserving patient but to more reliably identify the high-risk patient with more appropriate tools than a mere assessment of ejection fraction. Indeed, a study published by Tanno et al did not concur with the MADIT II results and did not find the LVEF cut-off useful in Japanese patients. 25 National registries may need to be created to follow patients who are denied an ICD to assess outcomes in such patients. An independent group, separate from the industry should monitor these outcomes; one can make out from Table 1 that several of the ICD trials have actually been sponsored by the device manufacturers. MADIT II and the SCHeFT are the only two large clinical trials that have explored the utility of the ICD for primary prevention, although both had significant differences in their patient selection. Additional trials such as ABCD trial will offer important perspectives on the role of non-invasive high-risk markers such as T-wave alternans in predicting arrhythmic death. Till then it would be prudent for cardiologists in developing countries to exercise more restraint in extending the ICD for primary prevention to a MADIT II population.
The use of ICD for primary prevention should be based not only on available trial data, but also incorporates the unanswered links. An approach is suggested below that incorporates relevant current data

1. Patients with CAD, LV dysfunction <0.40 should be treated aggressively with anti-ischemic therapy including revascularization when necessary. They should have a Holter to check for ambient ventricular ectopy and subsequently restratified. An EPS may be indicated in case of presence of other risk markers.

2. Patients with CAD, LVEF <0.35 with NSVT should undergo an EP study to determine inducibility of VT. If inducible, the patient should receive an ICD. Before implantation of the ICD, it should be ensured that the patient has not had a recent MI (within 1 month), revascularization procedure within 3 months or has significant co-morbid illness that precludes survival beyond a year. Patients who are NYHA class IV should be stabilized before ICD implantation.

3. Patients with CAD, LVEF <0.30 and no ambient ventricular ectopy should not be advised an ICD indiscriminately. Further risk stratification in this group should be based on clinical (NYHA class, QRS width and morphology) and electrophysiologic risk markers (EP study, non-invasive risk markers such as HRT, BRS, TWA, etc) before using an ICD.

4. Patients with CAD, LVEF <0.35, no ambient ventricular ectopy but symptomatic CHF NYHA class II/III should undergo non-invasive tests/ EPS for assessing arrhythmic risk. They form a high risk group and may need an ICD.

5. Patients with CAD, poor LV function and recurrent hospitalizations for heart failure should probably not receive an ICD in the absence of a heart failure program/ cardiac resynchronization therapy. Survival in these patients is poor due to competing risk of pump failure death and significant longevity will not be achieved by addressing arrhythmic risk alone.

6. Role of non-invasive tests for assessing arrhythmic risk should be encouraged in all CAD patients, especially for those with LVEF <0.40. These also include presence of left ventricular hypertrophy and left bundle branch block.

**Conclusions**

The ICD has undoubtedly revolutionized therapy of serious ventricular arrhythmias. However as medical science steadfastly forges ahead to provide high-tech answers to increase longevity, physicians, especially in the developing world need to reflect on the appropriate indications for this therapy. A bustling economy that spends up to 15% of its GDP on health can afford to advise even exorbitantly expensive therapy to its people. However, smaller economies would bleed their bottoms in trying to blindly emulate them. Indeed, if a patient needs to spend 4 lakh rupees every five years for a device that in all probability would not fire even once in up to two-thirds of its recipients suggests the need for more rational utilization. Further risk stratification with additional risk markers may help in better assessment of the risk of SCD in the coming years. It is also a clarion call to the ICD industry to reexamine their product line. Optimal patient selection must not be denied the device on monetary grounds alone. Relevant national guidelines need to be formulated urgently to justify appropriate use of these life-saving but expensive medical technologies.

**References**


