Future of ICD Trials

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Medical Director of Cardiology
Hospital of the Good Samaritan
Clinical Professor of Medicine at
Keck Medical School at USC
Los Angeles, California
40 Years Ago ICD Trials Were Necessary

- Sudden cardiac death had been identified as a major unsolved public health issue
- Two widely different clinical approaches were available for SCD survivors: serial drug testing versus the newly available ICD
- Mirowski and Mower were intent on subjecting the ICD to randomized clinical trials
Drs Mirowski and Mower propose a new approach

1970-71: discussions at Medtronic with prototype of device
Protection Against SCD

“It is already becoming possible to protect the patient who has been resuscitated from VF against recurrence of cardiac arrest. Essential elements of a prophylactic program involve the use of anti-arrhythmic drugs. Therapy, however, needs to be individualized. The objective of treatment is reduction in frequency or complete abolition of advanced grades of VPCs rather than suppression of all ectopic activity”

Circulation 60, No. 7, 1593-1599, 1979
Long-Term Survival of Patients with Malignant Ventricular Arrhythmia Treated with Antiarrhythmic Drugs

Thomas B. Graboys, MD; Bernard Lown, MD; Philip J. Podrod, MD; Regis DeSilva, MB, FRCP
Boston, Massachusetts

123 VT/VF pts (60% CAD)
- Effective drug response = elimination (4B, 5 salvos or early VPCs) or reduction (4A - couplets) of ectopy
- Control (61 pts) 2.3% annual SCD

<table>
<thead>
<tr>
<th>EF</th>
<th>EF &lt;0.50</th>
<th>EF ≥0.50</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>32 (73)</td>
<td>29 (83)</td>
<td>61 (77)</td>
</tr>
<tr>
<td>No</td>
<td>12 (27)</td>
<td>6 (17)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>35</td>
<td>79</td>
</tr>
</tbody>
</table>

AJC 1982;50:437-443
Fraught with multitude of technical difficulties
Sensing of VF a difficult problem, probably insurmountable
Electric discharges can damage heart
No method to test operational readiness
No way of identifying candidates
Once in body, no way of testing device
Drugs a better way to treat bouts of VF
Authors engage in minor polemics
Wasteful of societal resources
Concept lacks common sense
ICD developed in same era

M. Mower
A. Moss
M. Mirowski
“Since when have answers to such questions been required before research is undertaken? Are Drs. Lown and Axelrod so clairvoyant that they can see the ultimate impracticality of someone else’s research energies thereby prematurely labeling that work ‘an imperfect solution in search of a plausible and practical application.’? Fortunately, sincere investigators will continue to attach problems even when the prospect of solution is slight and when sensible people shake their heads.”

Arthur J. Moss, M.D.
University of Rochester School of Medicine and Dentistry
Rochester, New York
EP Climate at Initiation of Prophylactic ICD Trials (~1990)

- Uncertainty about role of ICD (VT surgery, EPS-guided drug trials popular)
- All ICDs epicardial (4-5% operative risk)
- No secondary prevention ICD trials completed
- Long hospital stays
Risk Stratification and Survival after Myocardial Infarction

The Multicenter Postinfarction Research Group


% One-Year Cardiac Mortality

Radionuclide Ejection Fraction (%)

- (<20%) n=799
- (20-39%) mean EF = 46%
- (40-59%)
- (>60%)

MADIT II
SCD HeFT
MUSTT

Moss, et al.
NEJM 1983;309:331
# Major Implantable Cardioverter-Defibrillator Trials for Prevention of SCD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Pts. (n)</th>
<th>Inclusion Criteria: LVEF % &lt;</th>
<th>Other Inclusion Criteria</th>
<th>H.R.</th>
<th>95% C.I.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT I</td>
<td>1996</td>
<td>196</td>
<td>35</td>
<td>Prior MI, NSVT and + EP</td>
<td>0.46</td>
<td>0.26 to 0.82</td>
<td>0.009</td>
</tr>
<tr>
<td>MADIT II</td>
<td>2002</td>
<td>1232</td>
<td>30</td>
<td>Prior MI</td>
<td>0.69</td>
<td>0.51 to 0.93</td>
<td>0.016</td>
</tr>
<tr>
<td>CABG-Patch</td>
<td>1997</td>
<td>900</td>
<td>36</td>
<td>+ SAECG &amp; CABG</td>
<td>1.07</td>
<td>0.81 to 1.42</td>
<td>0.63</td>
</tr>
<tr>
<td>DEFINTE</td>
<td>2004</td>
<td>485</td>
<td>35</td>
<td>NICM, PVCs, or NSVT</td>
<td>0.65</td>
<td>0.40 to 1.06</td>
<td>0.08</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>2004</td>
<td>674</td>
<td>35</td>
<td>6-40 days after MI &amp; Impaired HRV</td>
<td>1.08</td>
<td>0.76 to 1.55</td>
<td>0.66</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>2005</td>
<td>1676</td>
<td>35</td>
<td>Prior MI or NICM</td>
<td>0.77</td>
<td>0.62 to 0.96</td>
<td>0.007</td>
</tr>
</tbody>
</table>
MADIT Family of Trials

- MADIT: 1996 NEJM (n=196; ↓ mortality)
- MADIT-II: 2002 NEJM (n=1232; ↓ mortality)
- MADIT-II LTFU: Circ 2010
- MADIT-CRT: 2009 NEJM (n=1820; ↓ HF)
- MADIT-RIT: 2012 NEJM (n=1500; ↓ inapp Rx & mortality)
- MADIT S-ICD: partially enrolled
- PI: Arthur J. Moss, MD

The MADIT trials have been sponsored by Boston Scientific, but were independently conducted by the MADIT executive Committee and the Heart Research Follow-up Program of the University of Rochester Medical Center.
Evidence for Changes in Incidence of SCD

- Consistent results shown for life-threatening clinical arrhythmias
- Higher risk of all-cause mortality in MADIT II compared to MADIT-CRT and MADIT RIT
Incidence of Sudden Cardiac Death

- General population
- High-risk subgroups
  - Any prior coronary event
  - EF <30% or heart failure
- Cardiac arrest survivor
- Arrhythmia risk markers, post MI

**Incidence**
- Percent

**Events**
- Absolute Number

**Studies**
- MADIT II
- SCD-HeFT
- AVID, CIDS, CASH
- MADIT I, MUSTT
### Influence of Ejection Fraction on Cardiovascular Outcomes in a Broad Spectrum of Heart Failure Patients

Scott D. Solomon, MD; Nagesh Anavekar, MD; Hicham Skali, MD; John J.V. McMurray, MD; Karl Swedberg, MD, PhD; Salim Yusuf, DPhil, FRCP; Christopher B. Granger, MD; Eric L. Michelson, MD; Duolao Wang, PhD; Stuart Pocock, PhD; Marc A. Pfeffer, MD, PhD; for the Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators

<table>
<thead>
<tr>
<th>LVEF</th>
<th>&lt;22% (n=1013)</th>
<th>23%-32% (n=1887)</th>
<th>33%-42% (n=1904)</th>
<th>43%-52% (n=1295)</th>
<th>&gt;52% (n=1500)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>405 (15.4)</td>
<td>573 (10.8)</td>
<td>406 (7.4)</td>
<td>197 (5.2)</td>
<td>250 (5.7)</td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td>345 (13.1)</td>
<td>475 (8.9)</td>
<td>330 (6.0)</td>
<td>152 (4.0)</td>
<td>158 (3.6)</td>
</tr>
<tr>
<td><strong>sudden death</strong></td>
<td>146 (5.6)</td>
<td>221 (4.2)</td>
<td>155 (2.8)</td>
<td>63 (1.7)</td>
<td>58 (1.3)</td>
</tr>
<tr>
<td><strong>CHF death</strong></td>
<td>130 (4.9)</td>
<td>156 (2.9)</td>
<td>88 (1.6)</td>
<td>44 (1.2)</td>
<td>51 (1.2)</td>
</tr>
<tr>
<td><strong>Non-CV death</strong></td>
<td>60 (2.3)</td>
<td>98 (1.85)</td>
<td>76 (1.4)</td>
<td>45 (1.2)</td>
<td>92 (2.1)</td>
</tr>
<tr>
<td><strong>CHF hospitalization</strong></td>
<td>329 (14.9)</td>
<td>507 (10.9)</td>
<td>364 (7.2)</td>
<td>203 (5.7)</td>
<td>272 (6.9)</td>
</tr>
</tbody>
</table>

*CHF* = congestive heart failure; *CV* = cardiovascular.
After MADIT I, II, & MADIT CRT, Drs Moss and Kutiyifa were interested in other risk markers besides EF and HF in a next generation of ICD trials.

Diabetes as a risk factor in CAD patients in the literature predicted a two-fold increase in mortality across all ejection fractions.

A trial hypothesis and sample size prediction was developed over two years in an iterative process led by Dr A. Moss with support of industry.
MADIT S-ICD

To test the hypothesis that post-MI diabetic patients with relatively preserved ejection fraction will have life-saving benefit from the subcutaneous implantable cardioverter defibrillator

Randomized, 2-arm study using Boston Scientific S-ICD devices
MADIT S-ICD Study Design

- Primary Hypothesis
  - S-ICD will reduce all-cause mortality in diabetic patients age \( \geq 65 \) years with prior MI and LVEF 35-50% when compared to conventionally-treated patients

- Study Design
  - 2:1 randomization with group sequential design
  - 1800 subjects
  - Hazard ratio of 0.75 with 80% power, two-sided 5% significance level \((\alpha)\), estimated dropout rate of 10%

- Participants
  - 1800 men and women from the United States (80%), Europe (15%), and Israel (5%)
MADIT S-ICD Endpoints

● Primary Endpoint
  • All-cause mortality in S-ICD when compared to conventional group

● Secondary Objectives
  • Evaluate the effects of S-ICD on all-cause mortality and on SCD in various subgroups

● Tertiary Objectives
  • Frequency and outcomes of S-ICD shocks for VT & VF
  • Frequency and outcomes of S-ICD inappropriate shocks
  • Frequency of S-ICD device complications

● Enrollment Duration
  • 42 to 48 months
Concerns about the Trial

- Will intense medical therapy in this high risk group mitigate positive effect of ICD as it did in the Danish Trial?
- Will asymptomatic patients enroll?
- Will diabetes physicians – who take care for these patients – allow enrollment?
- Has the EP community had enough of randomized trials?
- Slow enrollment so far
MADIT S-ICD Study Terminated

● Study Design:
  » 2:1 Randomization (S-ICD:CMT)

● Planned Enrollment:
  » 1800 men and women from 150 center in the United States, Europe, and Israel → enrollment was discontinued June 20, 2018

● Participants:
  » 40 men and women from 21 centers in the United States, Europe, and Israel
  » Follow-up continues per original study protocol

● Average length of follow-up:
  » Planned follow-up for a minimum of 5 years
What went wrong with MADIT S-ICD

Electrophysiologists do not control diabetic patients which was not the case with the other MADIT trials

Internists and diabetes physicians are very conservative about referring for ICDs

Cath lab logs showed that we had underestimated the prevalence of these patients anyway

We probably picked the wrong new risk stratifier (diabetes) but is there another one out there?

Electrophysiologists have lost interest in device trials

Large registries of patient groups difficult to randomize may give as much information as prospective trials
Ejection fraction is the preferred risk stratifier in ICD trials for the past 20 years: what is wrong with this?

- EF fails to select a population which will only die of arrhythmic cardiac events (it identifies both sudden and non-sudden cardiac deaths)
- EF is a measure of substrate abnormalities, not triggers: it measures populations at risk, not individuals
- EF does not clarify precise mechanisms of SCD & frustrates basic electrophysiologists
- However, clinical trials of therapies are simplified as EF is easy to measure, cheap and reproducible
- Combining EF with a second measure (eg SAEKG) does not work: not recognized by guidelines
The Future of MADIT Trials 2020

- The next MADIT trial will look at AF frequency in heart failure patients with preserved ejection fraction using a novel recording device.
- There are no further randomized ICD trials in a planning phase at this time.