Prevention of sudden cardiac death in ischemic heart disease

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Figure 2: Causes of Sudden Cardiac Death

- Coronary heart disease: 75%
- Cardiomyopathies (DCM, HCM, ARVC): 15%
- Inherited arrhythmia syndromes (LQT, BrS, CPVT, ERS): 5%
- Valvular heart disease: 2%
- Others: 3%

ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; ERS = early repolarisation syndrome; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome.
# Preventing SCD with HF Medications

## Recommendation for Pharmacological Prevention of SCD

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation for Pharmacological Prevention of SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. In patients with HFrEF (LVEF ≤40%), treatment with a beta blocker, a mineralocorticoid receptor antagonist and either an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or an angiotensin receptor-neprilysin inhibitor is recommended to <strong>reduce SCD and all-cause mortality</strong>.</td>
</tr>
</tbody>
</table>

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death
Do we still need ICDs if we have ARNi?
Joachim R. Ehrlich MD, FHRS
Editorial to “Effects of angiotensin-neprilysin inhibition as compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices”
Beyond medication: Enter ICD
Randomised Trials of ICD Therapy

- “Primary prevention” - patients who have not yet had VT or VF, but are thought to be at high risk
- Multicenter Automatic Defibrillator Implantation Trial (MADIT 1) - 1996
- Multicenter UnSustained Tachycardia Trial (MUSTT) - 1999
- MADIT II – 2002
- COMPANION – 2004
- SCD-HeFT - 2004
Overview of Primary Prevention Trials

Results

• MADIT 54% reduction in mortality with ICD
• MUSTT 55-60% reduction in mortality with ICD
• MADIT II 31% reduction in mortality with ICD
• SCDHeFT 23% reduction in mortality with ICD
Major ICD Trials

- MADIT-I (47): 1996, N = 196, hazard ratio 0.46
- AVID (49): 1997, N = 1016, hazard ratio 0.62
- CABG-Patch (48): 1997, N = 900, hazard ratio 1.07
- CASH* (146): 2000, N = 191, hazard ratio 0.83
- CIDS (145): 2000, N = 659, hazard ratio 0.82
- MADIT-II (47): 2002, N = 1232, hazard ratio 0.69
- DEFINITE (150): 2004, N = 458, hazard ratio 0.65
- DINAMIT (150a): 2004, N = 674, hazard ratio 1.08
- SCD-HeFT (8): 2005, N = 1676, hazard ratio 0.77

LVEF, other features:
- 0.35 or less, NSVT, EP positive: aborted cardiac arrest
- 0.35 or less, abnormal SAECG and scheduled for CABG
- 0.30 or less, prior MI
- 0.35 or less, NICM and PVCs or NSVT
- 0.35 or less, MI within 6 to 40 days and impaired cardiac autonomic function
- 0.35 or less, LVD due to prior MI and NICM

Source: Cardiosource © 2007 by the American College of Cardiology Foundation
Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)

- It was designed to evaluate any possible benefit of ICD *early after MI*
- Total 674 patients with
- Recent (6-40 days) MI
- EF < 35%, depressed HRV
- Mean 24-hour HR > 80/min
- Tested ICD/ no ICD
- ICDs do not appear to be of benefit immediately after large MI (unexplained increase in non arrhythmic death)
Immediate Risk Stratification Improves Survival (IRIS) trial

- 898 pts recent AMI (<1 month)
- The mean LVEF in IRIS was 35%, compared with 28% in DINAMIT.
- There was an IRIS subgroup that had an LVEF >40%; they didn't show any survival benefit from ICDs either, according to Steinbeck.
- basically identical to DINAMIT; it's nice to see consistency.
DISCREPANCY?

- LV function
- Recurrent ischemia
- Non arrhythmic deaths
SECONDARY PREVENTION TRIALS

- AVID
- CIDS
- CASH
- Less benefit in EFLV>35%
- NNT
High risk post-PCI patients experience significant mortality during recovery from revascularization.

- The CADILLAC Trial post-PCI (1)
- Cleveland Clinic Registry: EF ≤35% - post-PCI (4)
- CATH PCI - NCDR Registry: EF <30% post-PCI >65yo (5)

3 month mortality:
- 11% Without STEMI
- 13% With STEMI

1 in 10 high-risk post-PCI patients die, with about 60% of this mortality due to Sudden Cardiac Death (1,5)

http://scdfacts.org
The CADILLAC Trial

- The CADILLAC Risk Score was developed to be a straightforward clinical scoring system for prediction of short- and long-term mortality after primary PCI.

- 7 risk factors constitute the CADILLAC risk score. Patients with a risk score $\geq 6$ are at highest risk for mortality.

- The CADILLAC trial included 2,082 patients who had a PCI procedure following an AMI. 20% of patients (1 in 5) scored $\geq 6$ and were at high mortality risk following a PCI procedure.

<table>
<thead>
<tr>
<th>CADILLAC Patient Score</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score $\geq 6$</td>
<td>HIGH</td>
</tr>
<tr>
<td>Score 3-5</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Score 0-2</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVEF $&lt;40%$</td>
<td>4</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>3</td>
</tr>
<tr>
<td>Killip Class II/III</td>
<td>3</td>
</tr>
<tr>
<td>Age $&gt;65$ years</td>
<td>2</td>
</tr>
<tr>
<td>Final TIMI flow 0-2</td>
<td>2</td>
</tr>
<tr>
<td>Three-Vessel Disease</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
</tr>
</tbody>
</table>
ICD implantation or temporary use of a WCD may be considered < 40 days after myocardial infarction in selected patients (incomplete revascularization, pre-existing LVEF dysfunction, occurrence of arrhythmias > 48 h after the onset of ACS, polymorphic VT or VF).

<table>
<thead>
<tr>
<th></th>
<th>IIb</th>
<th>C</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>170, 273</td>
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</table>

ICD implantation for the primary prevention of SCD is generally not indicated < 40 days after myocardial infarction.

<table>
<thead>
<tr>
<th></th>
<th>III</th>
<th>A</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>274, 275</td>
<td></td>
</tr>
</tbody>
</table>

Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death
ESC Clinical Practice Guidelines
Beyond LVEF

• Three distinct types of SCD risk stratifiers can be identified:
  1. Markers of abnormal substrate or structural heart disease
  2. Markers of abnormal repolarization or electrical instability
  3. Markers of abnormal autonomic balance
MARKERS OF ABNORMAL SUBSTRATE STRUCTURAL HEART DISEASE

1. Depressed Left Ventricular Ejection Fraction
2. Non-sustained Ventricular Tachycardia
3. Frequent Ventricular Ectopy
4. QRS Duration
5. MRI?
MARKERS OF ABNORMAL REPOLARIZATION OR ELECTRICAL INSTABILITY

1. T Wave Alternans (TWA)
2. Electrophysiology Studies (EPS)
3. Signal Averaged Electrocardiography
4. QT dispersion
MARKERS OF ABNORMAL AUTONOMIC BALANCE

1. Abnormalities in Resting Heart Rate
2. Heart rate variability (HRV)
3. Baroreceptor sensitivity (BRS)
4. Heart rate turbulence (HRT)
5. SAF
Beyond LVEF: heart rate turbulence

Heart Rate Turbulence as Risk-Predictor after Myocardial Infarction, Frontiers in Physiology · December 2011
Beyond LVEF
Prospective studies (or sub-studies) investigating heart rate turbulence as a post-infarction risk-predictor.

<table>
<thead>
<tr>
<th></th>
<th>ISAR-HRT</th>
<th>REFINE</th>
<th>ISAR-RISK++</th>
<th>CARISMA</th>
<th>ISAR-Sweet++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Barthel et al., 2003)</td>
<td>(Exner et al., 2007)</td>
<td>(Bauer et al., 2009a)</td>
<td>(Huikuri et al., 2009)</td>
<td>(Barthel et al., 2011)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1,455</td>
<td>322</td>
<td>2,343</td>
<td>312</td>
<td>481</td>
</tr>
<tr>
<td>Inclusion criteria*</td>
<td>MI ≤ 4 weeks, age ≤ 75 years</td>
<td>MI, LVEF &lt;50%</td>
<td>MI ≤ 4 weeks, age ≤ 75 years</td>
<td>MI &lt;21 days, LVEF ≤40%</td>
<td>MI ≤ 4 weeks, age ≤ 80 years, diabetes</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>22</td>
<td>47</td>
<td>60</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Mortality</td>
<td>Cardiac death&lt; sup&gt;†&lt;/sup&gt;</td>
<td>Mortality</td>
<td>VF/sustained VT on loop recorder</td>
<td>Mortality</td>
</tr>
<tr>
<td>Endpoints reached (%)</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Time of HRT assessment after MI</td>
<td>2nd week</td>
<td>2nd to 4th and 10th to 14th week</td>
<td>2nd week</td>
<td>1st and 6th week</td>
<td>2nd week</td>
</tr>
<tr>
<td>Treatment of acute MI</td>
<td>90% PCI, 6% lysis</td>
<td>45% PCI, 21% lysis</td>
<td>92% PCI, 3% lysis</td>
<td>14% PCI, 34 lysis</td>
<td>89% PCI</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>56</td>
<td>47</td>
<td>55</td>
<td>31</td>
<td>51</td>
</tr>
<tr>
<td>Betablockers (%)</td>
<td>93</td>
<td>92</td>
<td>96</td>
<td>96</td>
<td>94</td>
</tr>
</tbody>
</table>

**UNIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>ISAR-HRT</th>
<th>REFINE</th>
<th>ISAR-RISK++</th>
<th>CARISMA</th>
<th>ISAR-Sweet++</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT category 2</td>
<td>5.9 (2.9–12.2)</td>
<td>2.9 (1.1–7.5)&lt;sup&gt;++&lt;/sup&gt;</td>
<td>7.5 (5.3–10.7)</td>
<td>2.8 (1.1–7.2)&lt;sup&gt;‖&lt;/sup&gt;</td>
<td>6.6 (3.9–11.0)</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>4.5 (2.6–7.8)</td>
<td>4.5 (2.6–7.8)</td>
<td>3.0 (2.0–4.4)</td>
<td>2.4 (1.4–4.1)</td>
<td></td>
</tr>
</tbody>
</table>

**MULTIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>ISAR-HRT</th>
<th>REFINE</th>
<th>ISAR-RISK++</th>
<th>CARISMA</th>
<th>ISAR-Sweet++</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT category 2</td>
<td>5.9 (2.9–12.2)</td>
<td>Not specified</td>
<td>3.1 (2.1–4.6)</td>
<td>Not specified</td>
<td>4.1 (2.3–7.2)</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>4.5 (2.6–7.8)</td>
<td>Not specified</td>
<td>3.0 (2.0–4.4)</td>
<td>Not specified</td>
<td></td>
</tr>
</tbody>
</table>

* Sinus rhythm was inclusion criterion in all studies.
† Cardiac mortality included fatal and non-fatal cardiac arrest.
‡ Relative risks presented for turbulence slope < 2.5 ms/RR interval.
* LVEF was dichotomized at 35%.
++ HRT category ≥ 1 vs. 0 tested; HRT was assessed 10–14 weeks after MI.
+++ ISAR-RISK primarily tested the combination HRT category 2 and abnormal deceleration capacity (Bauer et al., 2006a).
We introduced a combined Non-Invasive and Invasive Risk Stratification Approach in post-MI patients 40 days after revascularization who had a LVEF > 40% (*Hellenic J Cardiol* 2014;55:361-368).
PRESERVE EF trial

7 Greek Centers

Hippokration Athinon
× 2

Attiko Athinon

Hippokration Thessaloniki

Eyaggelismos Athinon

Heraklion Kreta

Ioannina Epirus

Non Invasive markers combined with PVS

30 PVCs/hour
NSVT episode(s) /24 hour
2/3 positive criteria for LPs
QTc: 440 ms(♀) or QTc: 450ms (♂),
Ambulatory T wave alternans (TWA) ≥65 µV
SDNN/HRV ≤75 ms
Deceleration Capacity ≤4.5 ms & Heart Rate
Turbulence (HRT) Onset ≥0% and HRT slope ≤2.5 ms

PVS
5.3.1 Risk stratification

Risk stratification in patients with stable coronary artery disease after myocardial infarction with preserved ejection fraction

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVS should be considered in survivors of a myocardial infarction with preserved LV function and otherwise unexplained syncope.</td>
<td>IIa</td>
<td>C</td>
<td>280–282</td>
</tr>
</tbody>
</table>

LV = left ventricular; PVS = programmed ventricular stimulation.

\(^a\)Class of recommendation.

\(^b\)Level of evidence.

\(^c\)Reference(s) supporting recommendations.

There is limited evidence from subgroups of large-scale studies that programmed ventricular stimulation is helpful for risk stratification in patients after myocardial infarction with intermediate LVEF values or with an LVEF > 40\%.

This question is currently being addressed in the ongoing Risk Stratification in Patients With Preserved Ejection Fraction (PRESERVE-EF) trial (NCT02124018).

Risk Estimation Following Infraction Non-Invasive Evaluation - ICD Efficacy (Refine ICD) trial

Potentially eligible for study
- EF 36% to 50%
- No exclusion criteria
- All inclusion criteria met apart from Holter assessment

- ICD interrogation
- Follow-up assessment

Treatment (ICD) → Random Allocation

Abnormal HRT+ TWA

Core lab analysis

Registry (optional)
## Primary Prevention of SCD in Patients With Ischemic Heart Disease

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days’ post-MI and at least 90 days post-revascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>2. In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days’ post-MI and at least 90 days post-revascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected.</td>
</tr>
</tbody>
</table>
**Primary Prevention of SCD in Patients With Ischemic Heart Disease (contd.)**

<table>
<thead>
<tr>
<th>COR</th>
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<th>Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Value Statement:</strong> High Value (LOE: B-R)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. A transvenous ICD provides high value in the primary prevention of SCD particularly when the patient’s risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient’s burden of comorbidities and functional status.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>4. In patients with NSVT due to prior MI, LVEF of 40% or less and inducible sustained VT or VF at electrophysiological study, an ICD is recommended if meaningful survival of greater than 1 year is expected.</td>
</tr>
</tbody>
</table>

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### Primary Prevention of SCD in Patients With Ischemic Heart Disease (contd.)

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<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>5. In nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LVAD, an ICD is reasonable if meaningful survival of greater than 1 year is expected.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C-EO</td>
<td>6. An ICD is not indicated for NYHA class IV patients with medication-refractory HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities.</td>
</tr>
</tbody>
</table>

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2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death
Primary Prevention of SCD in Patients With Ischemic Heart Disease

- Primary prevention in pts with IHD, LVEF ≤40%
- MI <40 d and/or revascularization <90 d
- EP study (especially in the presence of NSVT)
- Inducible sustained VT
- GDMT (Class I)
- WCD (Class IIb)
- Reassess LVEF >40 d after MI and/or >90 d after revascularization
- NYHA class I or IV candidate for advanced HF therapy†

- Yes
  - ICD (Class I)*
  - GDMT (Class Ia)

- No
  - ICD should not be implanted (Class III: No Benefit)

- NYHA class II or III
- LVEF ≤40%, NSVT, inducible sustained VT on EP study
- ICD (Class I)
- GDMT
- No

- NYHA class I
- LVEF ≤30%
- ICD (Class I)

- NYHA class II or III
- LVEF ≤35%
- ICD (Class I)

- No

* MI <40 d and/or revascularization <90 d
** WCD
*** NYHA class II or III
**** LVEF ≤35%
***** NYHA class I
****** LVEF ≤30%
******* ICD
******** GDMT
********** No
*********** Yes
Thank you for your attention!