What is the Optimal Therapy
: Korean Reimbursement Criteria for ICD (current issue)

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Wonju College of Medicine
57, M No past medical alcohol Hx
DOE and Abd distension for 6 months
Chest PA and Echo

Echo
- LVd 6.5cm
- Lad 5.9cm
- EF 33%
- BNP 994.45 pg/mL

Dx

Medical therapy
Which?
How long?
When? – Fu study

Need for ICD?
Korean Reimbursement Criteria for ICD (current issue)
## Primary prevention in LV dysfunction

<table>
<thead>
<tr>
<th>2012 ACC AHA guideline</th>
<th>2015 ESC guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A</td>
<td>I A</td>
</tr>
<tr>
<td>I B</td>
<td>I B</td>
</tr>
</tbody>
</table>

### ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI

- **I A** LVEF ≤ 30%, and NYHA Class I. (Class I)
- **I A** LVEF ≤ 35% and NYHA Class II or III. (Class I)
- **I B** LVEF ≤ 40%, and inducible VF or sustained VT at electrophysiological study. (Class I)
- **I B** Nonischemic DCM and LVEF ≤35% and NYHA functional Class II or III. (Class I)

### Symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy

- **I A** Ischaemic aetiology (at least 6 weeks after myocardial infarction).
- **I B** Non-ischaemic aetiology.
Primary prevention for heart failure

<table>
<thead>
<tr>
<th>ICD 인정기준</th>
</tr>
</thead>
</table>

(1) 심근경색 발생 후 40일 경과한 허혈성 심부전
  (가) 심구혈률(EF) \( \leq 30\% \)
  (나) 심구혈률(EF) 31~35%로 NYHA class II, III의증상
  (다) 심구혈률(EF) \( \leq 40\% \) 환자로 비지속성 심실빈맥이 있으며 임상전기생리학적검사에서 혈역동학적으로 의미있는 심실세동이나 지속성 심실빈맥이 유발되는 경우

(2) 비허혈성 심부전으로 3개월 이상의 적절한 약물치료에도 불구하고 NYHA class II, III의 증상을 보이는 심구혈률(EF) \( \leq 35\% \)인 환자에서 1년 이상 생존이 예상되는 경우
# Primary prevention of SCD: 2017 ACC/AHA

## Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease

References that support the recommendations are summarized in Online Data Supplement 21.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</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 postrevascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1, 2).</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 postrevascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (2, 3).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Value Statement:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>High Value (LOE: B-R)</strong></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 (4).</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 (5).</td>
</tr>
<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 (6-9).</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>
### Primary prevention of SCD

: 2017 ACC/AHA

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. In patients with NICM, HF with NYHA class II–III symptoms and an LVEF of 35% or less, despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1-6).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>2. In patients with NICM due to a <em>Lamin A/C</em> mutation who have 2 or more risk factors (NSVT, LVEF &lt;45%, nonmissense mutation, and male sex), an ICD can be beneficial if meaningful survival of greater than 1 year is expected (7-10).</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>3. In patients with NICM, HF with NYHA class I symptoms and an LVEF of 35% or less, despite GDMT, an ICD may be considered if meaningful survival of greater than 1 year is expected (5).</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C-EO</td>
<td>4. In patients with medication-refractory NYHA class IV HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities, an ICD should not be implanted.</td>
</tr>
</tbody>
</table>

For all patients with NICM, it is imperative that patients be on GDMT for HF for at least 3 months before a primary prevention ICD is offered.
The ICD in Heart Failure — Time for a Rethink?

1. Heart failure classification
   Only ICMP vs NICMP
Problem

• Diagnosis
  – HF with AF : HF cause AF
  – AF with HF : AF cause AF
  – Idiopathic DCM?
# Diagnosis and Classification of HF

<table>
<thead>
<tr>
<th>Diseased Myocardium</th>
<th>Ischemic CMP</th>
<th>Non-Ischemic CMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>Myocardial scar</td>
<td>Non-ischemic myocardial damage</td>
</tr>
<tr>
<td></td>
<td>Myocardial stunning/hibernation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epicardial coronary artery disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal coronary microcirculation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endothelial dysfunction</td>
<td></td>
</tr>
<tr>
<td>Toxic damage</td>
<td>Recreational substance abuse</td>
<td>Alcohol, cocaine, amphetamine, anabolic steroids.</td>
</tr>
<tr>
<td></td>
<td>Heavy metals</td>
<td>Copper, iron, lead, cobalt.</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>Cytostatic drugs (e.g., anthracyclines), immunomodulating drugs (e.g., interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressants, antiarrhythmics, non-steroidal anti-inflammatory drugs, anaesthetics.</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>Immune-mediated and inflammatory damage</td>
<td>Related to infection</td>
<td>Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).</td>
</tr>
<tr>
<td></td>
<td>Not related to infection</td>
<td>Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g., Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg-Strauss).</td>
</tr>
<tr>
<td>Infiltration</td>
<td>Related to malignancy</td>
<td>Direct infiltrations and metastases.</td>
</tr>
<tr>
<td></td>
<td>Not related to malignancy</td>
<td>Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g., Pompe disease), lysosomal storage diseases (e.g., Fabry disease).</td>
</tr>
<tr>
<td>Metabolic derangements</td>
<td>Hormonal</td>
<td>Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolism, CCM’s disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.</td>
</tr>
<tr>
<td></td>
<td>Nutritional</td>
<td>Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g., malignancy, AIDS, anorexia nervosa), obesity.</td>
</tr>
<tr>
<td>Genetic abnormalities</td>
<td>Diverse forms</td>
<td>HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopaties.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal Loading Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Valve and myocardium structural defects</td>
<td>Acquired Mitral, aortic, tricuspid and pulmonary valve diseases.</td>
</tr>
<tr>
<td></td>
<td>Congenital Atrial and ventricular septum defects and others (for details see a respective expert document).</td>
</tr>
<tr>
<td>Pericardial and endomyocardial pathologies</td>
<td>Pericardial Constrictive pericarditis Pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>Endomyocardial HES, EFM, endocardial fibroelastosis.</td>
</tr>
<tr>
<td>High output states</td>
<td>Severe anaemia, sepsis, thyrotoxicosis, Paget’s disease, arteriovenous fistula, pregnancy.</td>
</tr>
<tr>
<td>Volume overload</td>
<td>Renal failure, iatrogenic fluid overload.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arrhythmias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachyarrhythmias</td>
<td>Atrial, ventricular arrhythmias.</td>
</tr>
<tr>
<td>Bradyarrhythmias</td>
<td>Sinus node dysfunctions, conduction disorders.</td>
</tr>
</tbody>
</table>
The ICD in Heart Failure — Time for a Rethink?

2. 3개월 이상의 적절한 약물 치료
# Optimal Medical Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class a</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE-I is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A beta-blocker is recommended, in addition an ACE-Id, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-Id and a beta-blocker, to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
The concept of ‘optimal medical therapy’ relies on recommendations of current consensus-derived guidelines, most of which are supported by ‘level of evidence C’ (no scientific evidence). However, guidelines recommendations for commonly employed cardiovascular drugs often are based on strong evidence (‘level A’). Generally, such drugs are recommended at ‘target doses’ employed in the trials on which their putative efficacy and regulatory approval are based, and are considered ‘optimal medical therapy’. Information about the effectiveness of other doses, lower, or higher, seldom is available.
Optimal Medical Therapy

• Target dose vs. Target effect

• How to optimize (eg, biomarker guided)

• Duration of therapy

• New agent : ARNI
Table 2. Results of 13 Univariable Meta-regressions Evaluating the Effect of Individual Covariates on Death Benefits of \( \beta \)-Blockers in Heart Failure

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th>Trials, ( n )</th>
<th>Patients, ( n )</th>
<th>Ratio of Relative Risks (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of men</td>
<td>21</td>
<td>18,773</td>
<td>0.93 (0.79–1.10) per 10% increment</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean age</td>
<td>21</td>
<td>18,773</td>
<td>1.04 (0.86–1.24) per decade</td>
<td>0.69</td>
</tr>
<tr>
<td>Percentage with an ischemic cause</td>
<td>21</td>
<td>18,773</td>
<td>0.99 (0.86–1.14) per 20% increment</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean baseline LVEF</td>
<td>20</td>
<td>18,392</td>
<td>1.04 (0.92–1.18) per 5% increment</td>
<td>0.54</td>
</tr>
<tr>
<td>Percentage with NYHA class III or IV symptoms</td>
<td>21</td>
<td>18,773</td>
<td>1.00 (0.96–1.05) per 10% increment</td>
<td>0.84</td>
</tr>
<tr>
<td>Percentage with atrial fibrillation</td>
<td>8</td>
<td>8,915</td>
<td>1.00 (0.91–1.09) per 5% increment</td>
<td>0.95</td>
</tr>
<tr>
<td>Percentage of digoxin use</td>
<td>19</td>
<td>18,336</td>
<td>1.01 (0.96–1.06) per 10% increment</td>
<td>0.64</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>19</td>
<td>17,981</td>
<td>1.07 (0.88–1.32) per 5 beats/min</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart rate reduction*</td>
<td>17</td>
<td>17,831</td>
<td>0.82 (0.71–0.94) per 5 beats/min</td>
<td>0.006</td>
</tr>
<tr>
<td>( \beta )-Blocker dose</td>
<td>17</td>
<td>17,660</td>
<td>1.02 (0.93–1.10) per increment</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean baseline SBP</td>
<td>17</td>
<td>17,516</td>
<td>1.00 (0.73–1.35) per 20 mm Hg</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean SBP reduction</td>
<td>10</td>
<td>5,462</td>
<td>1.02 (0.87–1.20) per 2 mm Hg</td>
<td>0.78</td>
</tr>
<tr>
<td>Agent</td>
<td>21</td>
<td>18,773</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>–</td>
<td>–</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>–</td>
<td>–</td>
<td>1.05 (0.82–1.35)</td>
<td>0.68</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>–</td>
<td>–</td>
<td>1.03 (0.77–1.38)</td>
<td>0.85</td>
</tr>
<tr>
<td>Atenolol</td>
<td>–</td>
<td>–</td>
<td>0.89 (0.29–2.76)</td>
<td>0.83</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>–</td>
<td>–</td>
<td>1.36 (1.09–1.69)</td>
<td>0.009</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>–</td>
<td>–</td>
<td>1.30 (0.99–1.71)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.

* For every 5-beat/min reduction in mean heart rate, the risk ratio for death decreases by 18% (relative risk ratio, 0.82 [95% CI, 0.71 to 0.94]). Therefore, starting with our pooled risk ratio of 0.76 for death and our median heart rate reduction of 12 beats/min, it would be reasonable to expect that a mean heart rate reduction of 17 beats/min would confer a relative risk for death of approximately 0.62.
Optimal Medical Therapy: Target dose vs. Target effect

Figure 4. Meta-regression line for magnitude of heart rate reduction and risk ratio of all-cause mortality.
How Can Optimization of Medical Treatment Avoid Unnecessary Implantable Cardioverter-Defibrillator Implantations in Patients With Idiopathic Dilated Cardiomyopathy Presenting With “SCD-HeFT Criteria?”

Massimo Zecchin, MDa-*, Marco Merlo, MDa, Alberto Pivetta, MDa, Giulia Barbati, PhDb, Cristina Lutman, MDa, Dario Gregori, PhDb, Laura Vitali Serdoz, MDa, Stefano Bardari, MDa, Silvia Magnani, MDa, Andrea Di Lenarda, MDc, Alessandro Proclemer, MDd, and Gianfranco Sinagra, MDa

SCD-HeFT criteria
NICMP NYHA II or III
LVEF ≤ 35%
Naïve to BB

nonSCD-HeFT criteria
NICMP NYHA II or III
LVEF > 35%
Naïve to BB

Improvement at 2nd evaluation
LVEF 0.35 and/or
NYHA class I
Duration of OMT

SCD-HeFT criteria
254 pts (49%)
ACEI 41%

Mean FU duration: 5.4 ± 2 mo

2nd evaluation at 3-9mo
162 pts (66%)
BB 87%, ACE 95%

Death/HT (9 pts 4%)

Remained
50 pts (31%)
BB 85%, ACE 94%

Improved
109 pts 67%
BB 90%, ACE 95%

NYHA IV (3pts 2%)

Aggravated to SCD-HeFT
13 pts (10%)
BB 75%, ACE 92%

Remained
111 pts 89%
BB 83%, ACE 86%

Mean FU duration: 5.5 ± 2 mo

nonSCD-HeFT criteria
227 pts (41%)
ACEI 50%

2nd evaluation at 3-9mo
125 pts (55%)
BB 82%, ACE 86%

Death/HT (4 pts 2%)
Duration of optimal Medical Therapy

• ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 Appropriate Use Criteria for ICD and CRT
  – Once a patient with a nonischemic cardiomyopathy is on guideline-directed therapy for at least 3 months, ICD implantation was rated Appropriate for LVEF ≤35% and NYHA class I to III symptoms
  – It is generally recommended that patients receive a period of guideline directed medical therapy following a new diagnosis of nonischemic cardiomyopathy with the hope that LV function will improve.
Optimal medical therapy

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</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 reduce SCD and all-cause mortality (1-8).</td>
</tr>
</tbody>
</table>
The ICD in Heart Failure — Time for a Rethink?

3. Need for Primary prevention of ICD
Declining Risk of Sudden Death in Heart Failure

Trends in the Rate of Sudden Death across Trial Groups over Time.

Declining Risk of Sudden Death in Heart Failure

Trends in the all-cause death rate

The falling rates of sudden death were in line with the downward trend in the overall death rates. Li Shen et al N Engl J Med 2017;377:41-51.
## Declining Risk of Sudden Death in Heart Failure

<table>
<thead>
<tr>
<th>Trial and Group</th>
<th>Concomitant Medication</th>
<th>Annual Rate</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RALES</strong></td>
<td>ACE inhibitor (94%), beta-blocker (10%)</td>
<td>7.6 (6.3–9.1)</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor (93%), beta-blocker (11%), MRA (100%)</td>
<td>5.4 (4.3–6.7)</td>
<td>0.71 (0.54–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (97%), MRA (4%)</td>
<td>6.3 (5.4–7.3)</td>
<td>0.84 (0.66–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>BEST</strong></td>
<td>ACE inhibitor or ARB (96%), beta-blocker (100%), MRA (3%)</td>
<td>4.9 (4.2–5.9)</td>
<td>0.66 (0.51–0.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (96%), beta-blocker (100%), MRA (11%)</td>
<td>2.7 (2.0–3.6)</td>
<td>0.35 (0.25–0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (96%), MRA (10%)</td>
<td>4.8 (3.9–6.0)</td>
<td>0.62 (0.47–0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CIBIS-II</strong></td>
<td>ACE inhibitor or ARB (95%), beta-blocker (100%), MRA (7%)</td>
<td>3.9 (3.2–4.9)</td>
<td>0.49 (0.37–0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (95%), beta-blocker (100%), MRA (7%)</td>
<td>6.7 (5.6–7.9)</td>
<td>0.83 (0.64–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (93%), beta-blocker (55%), MRA (5%)</td>
<td>4.6 (4.0–5.2)</td>
<td>0.60 (0.48–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MERIT-HF</strong></td>
<td>ACE inhibitor or ARB (93%), beta-blocker (35%), MRA (5%)</td>
<td>4.9 (4.3–5.6)</td>
<td>0.65 (0.52–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (98%), beta-blocker (69%), MRA (19%)</td>
<td>3.2 (2.6–4.0)</td>
<td>0.46 (0.35–0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (97%), beta-blocker (69%), MRA (20%)</td>
<td>2.7 (2.2–3.4)</td>
<td>0.59 (0.39–0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>SCD-HeFT</strong></td>
<td>ACE inhibitor or ARB (98%), beta-blocker (69%), MRA (24%)</td>
<td>3.0 (2.4–3.7)</td>
<td>0.59 (0.46–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>Beta-blocker (54%), MRA (23%)</td>
<td>4.4 (3.6–5.3)</td>
<td>0.59 (0.46–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ARB (100%), beta-blocker (54%), MRA (24%)</td>
<td>3.0 (2.4–3.7)</td>
<td>0.40 (0.30–0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CHARMA-Alternative</strong></td>
<td>ACE inhibitor or ARB (96%), beta-blocker (10%), MRA (17%)</td>
<td>4.6 (4.0–5.4)</td>
<td>0.64 (0.50–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (100%), beta-blocker (54%), MRA (17%)</td>
<td>5.3 (4.7–5.9)</td>
<td>0.71 (0.57–0.88)</td>
<td>0.002</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (91%), beta-blocker (75%), MRA (19%)</td>
<td>5.1 (4.6–5.7)</td>
<td>0.69 (0.56–0.86)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CHARMA-Added</strong></td>
<td>ACE inhibitor or ARB (93%), beta-blocker (63%), MRA (41%)</td>
<td>2.5 (2.2–3.0)</td>
<td>0.36 (0.28–0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (94%), beta-blocker (64%), MRA (39%)</td>
<td>2.9 (2.5–3.3)</td>
<td>0.41 (0.32–0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (92%), beta-blocker (75%), MRA (39%)</td>
<td>3.3 (2.6–4.1)</td>
<td>0.43 (0.32–0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CORONA</strong></td>
<td>ACE inhibitor or ARB (92%), beta-blocker (86%)</td>
<td>3.3 (2.6–4.1)</td>
<td>0.43 (0.32–0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (93%), MRA (100%)</td>
<td>2.5 (2.0–3.3)</td>
<td>0.34 (0.25–0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Experimental therapy</td>
<td>ACE inhibitor or ARB (94%), beta-blocker (85%), MRA (100%)</td>
<td>2.5 (2.0–3.3)</td>
<td>0.34 (0.25–0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>GISSI-HF</strong></td>
<td>ACE inhibitor or ARB (93%), beta-blocker (92%), MRA (57%)</td>
<td>3.7 (3.3–4.1)</td>
<td>0.49 (0.40–0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Control</td>
<td>ACE inhibitor or ARB (100%), beta-blocker (93%), MRA (54%), LCZ696</td>
<td>3.0 (2.7–3.4)</td>
<td>0.41 (0.32–0.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
ICD Trials: Primary prevention

Coronary artery disease

- MADIT
- MUSTT
- MADIT II
- SCD-HeFT

Non-ischemic CMP

- CABG-Patch
- DINAMIT
- IRIS

Positive

- SCD-HeFT
- DEFINITE
- COMPANION

Negative

- CAT
- AMIOVIRT

- Multicenter RCT of ICD vs. OMT vs OMT with amiodarone
- 10 centers/2521 patients, Follow-up 48 months
- **Inclusion criteria: Ischemic and non ischemic cardiomyopathy, EF ≤ 35 %**
- Additional risk factors: Not specified
- CRT : not implanted
- Outcomes:
  - 22% mortality in ICD group, 28% in amiodarone, 29% in control. 7% of absolute risk reduction ICD vs control. p=0.007

Bardy GH et al. NEJM 2002;346:877-83
SCD-HeFT: Baseline Patient Characteristics

- Average Age = 60 Years
- Gender
  - Male = 77%
  - Female = 23%
- Minorities made up 23% of the patient population
- Median LVEF was 25%
- More NYHA Class II than Class III
  - NYHA II = 70%
  - NYHA III = 30%
- Roughly even split between ischemic and non-ischemics
  - Ischemic = 52%
  - Non-ischemic = 48%
SCD-HeFT Primary Endpoint: All Cause Mortality

- 23% Reduction in All Cause Mortality For ICD Therapy (p-value 0.007)

![Graph showing Kaplan-Meier Estimates of Death from Any Cause.](image)

Figure 1. Kaplan-Meier Estimates of Death from Any Cause.
CI denotes confidence interval.
SCD-HeFT All Cause Mortality: subgroup analysis

• Multicenter RCT of ICD vs. optimized medical therapy
• 47 centers/458 patients, Follow-up 29 months
• Inclusion criteria: NIDCM, EF < 36 %
• Additional risk factors: NSVT or frequent premature complexes

• Outcomes:
  • 8.1% overall mortality in ICD vs. 13.8% in optimized therapy.
  • Absolute risk reduction 5.7%, but not significant (p=0.6). The risk for sudden death from arrhythmia was significantly reduced (p=0.006).

Kadish, Levine et al. NEJM 2004;350:2151-58
DEFINITE Trial: Survival results

Kadish, Levine et al. NEJM 2004;350:2151-58
COMPANION :2000-2002

- Multicenter RCT of CRT-P, CRT-D vs. optimized medical therapy
- 128 US centers/1520 patients
- Inclusion criteria:
  - NYHA class III or IV, EF ≤ 35% with wide QRSd ≥ 120ms
  - Ischemic or non-ischemic

- Outcomes:
  - A pacemaker reduced the risk of the secondary end point of death from any cause by 24 percent (P=0.059), and a pacemaker–defibrillator reduced the risk by 36 percent (P=0.003).

COMPANION Trial: Survival results

A Primary End Point (Any cause of death and hospitalization)

No. at Risk
Pharmacologic therapy 308 176 115 72 46 24 16 6 1
Pacemaker 617 384 294 228 146 73 36 14 3
Pacemaker–defibrillator 595 385 283 217 128 61 25 8 0

B Secondary End Point (Any cause of death)

No. at Risk
Pharmacologic therapy 308 284 255 217 186 141 94 57 45 25 4 2
Pacemaker 617 579 520 488 439 355 251 164 104 60 25 5
Pacemaker–defibrillator 595 555 517 470 420 331 219 148 95 47 21 1

CRT-P vs. OPT HR 0.81; 95% CI 0.69-0.96; P=0.014; adjusted P=0.015
CRT-D vs. OPT HR 0.80; 95% CI 0.68-0.95, P=0.010; adjusted P=0.011

All cause of death subgroup analysis

Ischemic CAMP CRT-D vs. OPT HR 0.73; 95% CI 0.52-1.04
Non-ischemic CMP CRT-D vs. OPT HR 0.50; 95% CI 0.29-0.88

COMPANION Trial: Survival results

- The addition of a defibrillator to cardiac-resynchronization therapy did not appreciably affect the combined outcomes of death from or hospitalization for any cause, which are heavily influenced by the hospitalization components.

Multicenter RCT of ICD vs. Antiarrhythmic drugs as conventional therapy

15 centers/104 patients, Follow-up 23 months

Inclusion criteria: Symptomatic recent onset non ischemic DCM (≤9mo), LVEF ≤ 30 %, NYHA II or III

Additional risk factors: Not specified

Outcomes:

- Mortality 8% in ICD vs. 7% in control (not significant! P = 0.54)
- Issues: Low baseline risk for death due to improved therapy options. Early termination after 1 year

AMIOVIRT: 1996 – 2000

• Multicenter RCT of ICD vs. Antiarrhythmic drugs as conventional therapy
• 10 centers/101 patients, Follow-up 24 months
• Inclusion criteria: NIDCM, EF ≤ 35%, asymptomatic NSVT, NYHA class I to III
• Additional risk factors: NSVT

• Outcomes:
  • Survival 88% in ICD vs. 87% with Amiodarone (p=NS).
  • Issues: Low baseline risk for death due to improved therapy. Early termination after 3 years due to low 3 year mortality in both arms.

Strickberger SA et al. JACC 2003; 41:1707-12
After exclusion of COMPANION (fixed effects RR, 0.74; 95% CI, 0.58-0.96; \(P=.02\)).
DANISH

- Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH)
  - Investigator initiated multicenter, randomized, unblinded, controlled trial that was conducted at all centers in Denmark at which ICDs were implanted
  - Inclusion
    - Symptomatic patients (NYHA class II or III, or NYHA class IV if CRT was planned)
    - Nonischemic systolic heart failure (left ventricular ejection fraction ≤35%)
    - increased level (>200 pg per milliliter) of N-terminal pro–brain natriuretic peptide (NT-proBNP)
  - Exclusion
    - permanent AF with a resting HR > 100 bpm
    - renal failure with dialysis

Køber L et al. N Eng J Med 2016 Sep 29;375(13)
Køber L et al. N Eng J Med 2016 Sep 29;375(13)
The effect of ICD implantation was independent of CRT status (P = 0.73 for the interaction)
Recent meta analysis
Recent meta analysis

NICM Patients Without CRT (ICD vs. Medical Therapy Alone)

### All-cause Mortality Non-CRT Group

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIOVIRT</td>
<td>0.87 (0.31, 2.43)</td>
<td>3.16</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>0.65 (0.40, 1.06)</td>
<td>14.06</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>0.74 (0.57, 0.96)</td>
<td>47.97</td>
</tr>
<tr>
<td>CAT</td>
<td>0.83 (0.45, 1.52)</td>
<td>8.94</td>
</tr>
<tr>
<td>DANISH Non-CRT Group</td>
<td>0.83 (0.58, 1.19)</td>
<td>25.86</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p=NS)</td>
<td>0.76 (0.63, 0.91)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis

(n = 2,347)

Recent meta analysis

### Sudden Cardiac Death (Non-CRT)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIOVIRT</td>
<td>0.51 (0.05, 5.45)</td>
<td>6.55</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>0.21 (0.06, 0.74)</td>
<td>24.17</td>
</tr>
<tr>
<td>SCD-HEFT</td>
<td>0.28 (0.13, 0.58)</td>
<td>69.29</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.27 (0.15, 0.50)</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis

(n=1,172)

**Risk Ratio**

- Favors ICD
- Favors No-ICD

Recent meta analysis

NICM Patients With CRT (CRT-D vs. CRT-P)

All-cause Mortality CRT Group

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPANION</td>
<td>0.57 (0.36, 0.90)</td>
<td>44.82</td>
</tr>
<tr>
<td>DANISH CRT Group</td>
<td>0.91 (0.64, 1.29)</td>
<td>55.18</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p=NS)</td>
<td>0.74 (0.47, 1.16)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: Weights are from random effects analysis

(n=1,197)

Recent meta analysis
The ICD in Heart Failure — Time for a Rethink?

4. Risk Stratification for SCD
- identification of patients who are most likely to benefit from an ICD
### Age

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ICD Group</th>
<th>Control Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;59 yr</td>
<td>17/167</td>
<td>34/181</td>
<td>0.51 (0.29–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥59 to &lt;68 yr</td>
<td>36/173</td>
<td>50/202</td>
<td>0.75 (0.48–1.16)</td>
<td>0.19</td>
</tr>
<tr>
<td>≥68 yr</td>
<td>67/216</td>
<td>47/177</td>
<td>1.19 (0.81–1.73)</td>
<td>0.38</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22/151</td>
<td>23/156</td>
<td>1.03 (0.57–1.87)</td>
<td>0.92</td>
</tr>
<tr>
<td>Male</td>
<td>98/405</td>
<td>108/404</td>
<td>0.85 (0.64–1.12)</td>
<td>0.24</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1177 pg/ml</td>
<td>32/266</td>
<td>74/268</td>
<td>0.59 (0.38–0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥1177 pg/ml</td>
<td>57/292</td>
<td>88/290</td>
<td>0.99 (0.73–1.36)</td>
<td>0.96</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25%</td>
<td>70/264</td>
<td>65/242</td>
<td>0.87 (0.62–1.22)</td>
<td>0.42</td>
</tr>
<tr>
<td>≥25%</td>
<td>50/292</td>
<td>66/318</td>
<td>0.79 (0.54–1.14)</td>
<td>0.21</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;73 ml/min/1.73 m²</td>
<td>75/272</td>
<td>80/278</td>
<td>0.88 (0.64–1.21)</td>
<td>0.42</td>
</tr>
<tr>
<td>≥73 ml/min/1.73 m²</td>
<td>45/283</td>
<td>50/280</td>
<td>0.82 (0.55–1.23)</td>
<td>0.33</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>52/297</td>
<td>54/300</td>
<td>0.92 (0.63–1.35)</td>
<td>0.68</td>
</tr>
<tr>
<td>III–IV</td>
<td>68/259</td>
<td>77/260</td>
<td>0.81 (0.58–1.13)</td>
<td>0.21</td>
</tr>
<tr>
<td>Overall</td>
<td>68/259</td>
<td>77/260</td>
<td>0.87 (0.68–1.12)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
In the subgroup of patients who were younger than 68 years of age, the rate of death from any cause was significantly lower in the ICD group than in the control group (hazard ratio, 0.64; 95% CI, 0.45 to 0.90; \( P = 0.01 \)).
LGE on CMR

Meta analysis: Annual rate of VF/VF or SCD according to LGE status.

Ongoing trial NCT01918215
Cardiac Magnetic Resonance GUIDEd Management of Mild-moderate Left Ventricular Systolic Dysfunction. (CMR_GUIDE) LVEF (36%–50%).

# Risk stratification of SCD in ICD era

<table>
<thead>
<tr>
<th>Risk stratification of SCD</th>
<th>LVEDD</th>
<th>LVEF</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic parameters</td>
<td>BRS</td>
<td>HRT</td>
<td>HRV</td>
</tr>
<tr>
<td>Arrhythmia-based parameters</td>
<td>EP study</td>
<td>NSVT</td>
<td></td>
</tr>
<tr>
<td>Depolarization parameters</td>
<td>fQRS</td>
<td>QRS duration/LBBB</td>
<td>SAECG</td>
</tr>
<tr>
<td>Repolarization</td>
<td>TWA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jeffrey J. Goldberger et al. J Am Coll Cardiol 2014;63:1879–89
Risk stratification of SCD in ICD era

A

Autonomic parameters

BRS
Hohloser
Grimm
TOTAL

HRV
Benesch
Rashba
Heinloser
Grimm
TOTAL

HRT
Mises
Klingelhofer
Grimm
TOTAL

B

Functional parameters

LVEDD
Morgera
Adachi
Kitamura
Grimm
TOTAL

LVEF
Kron
Iacoviello
Morgera
Adachi
Kitamura
Schaefer
Heinloser
Hoffman
Grimm
Levitt
Zecchin
DEFINITE
TOTAL

C

Arrhythmia-based parameters

EP Study
Stamato
Meinhertz
Kron
Geisinger
Kadish
Das
Morgera
Vorma
Poli
Becker
Brennula
Grimm
Tuttilo
Rankevich
DEFINITE
TOTAL

NSVT
Adachi
Morgera
Brennula
Hoffman
Becker
Schaefer
Kitamura
Brennula
De Maria
Fauciier
Heinloser
Vorma
DEFINITE
Iacoviello
Rankovic
Watahabe
Grimm
Zecchin
TOTAL

D

Depolarization parameters

Fragmented QRS
She
Pai
TOTAL

QRS Duration/LBBB
Morgera
Brennula
Hombach
Schaefer
Heinloser
Fauciier
Iacoviello
Iuliano
Grimm
DEFINITE
TOTAL

E

Repolarization

T-Wave Alternans
Sarzi
Barenbrug
Sakabe
Barenbrug
Shohda
Blomfield
Adachi
Kitamura
Hohloser
Santen
Cantillon
Grimm
TOTAL
Risk stratification of SCD in ICD era

Bar chart showing the major adverse cardiac event (%) for different categories:
- fQRS: 28.3, p=0.015
- Non-fQRS: 6.3
- DE: 27, p=0.097
- Non-DE: 12.2
- fQRS+/DE-: 12.8
- fQRS-/DE+: 5.9
- fQRS-/DE-: 40.9, p=0.008

MS Ahn, JB Kim IJC 2013:168:1417–1422
Conclusion

- Decreasing rate of SCD among patients with HF with reduced EF
- Cumulative benefit of evidence-based medications on sudden death.
- NICM pts should be treated with OMT for enough duration.
- ICD therapy is of benefit among appropriately selected patients with NICM, particularly if they are younger (<68yo).
Initial presentation 2014-05-12

- Sx improved after medication
- Candesartan 4mg
- Bisoprolol 2.5mg
- Furix 40
- Aldactone 25
- Warfarin

2015.04.13
Transfer to Local Hosp

2015.07.26
SCD
Real World Conclusion