The ICD in nonischemic cardiomyopathy: should we change our practice?
SCD Epidemiology in Heart Failure (HF)

- In the pre-implantable cardioverter defibrillator (ICD) era SCD accounted for ≈ 1/3 of all deaths in the HF population
  

- From 30% to 50% of all SCD events occur in a patient with known reduced left ventricular ejection fraction (LVEF)

  Chugh SS et al. *Prog Cardiovasc Dis* 2008; 51:213-228
  Stecker EC et al. *J Am Coll Cardiol* 2006; 47:1161-1166

- HF is one of the greatest risk factors for out-of-hospital cardiac arrest

  Rea TD et al. *Am J Cardiol* 2004; 93:1455-1460
Diverse Mechanisms of Unexpected SCD

157 patients with and without structural heart disease died while wearing Holter ECG

20 HF patients hospitalized with NYHA III/IV, severe LVSD experiencing cardiac arrest


Pathophysiology of SCD in HF

Modulating Factors

↑ Sympathetic Activation
↓ Parasympathetic Tone

Coumel’s Triangle

SCD

Substrate
Hypertrophy
LV Dilatation
LV Remodelling
Scar formation/Fibrosis
Conduction Abnormalities

Triggers
PVCs and VTs
Electrolyte Imbalances
Myocardial Ischaemia
Haemodynamic Changes
ICD and SCD Prevention

First Human Implant February 1980
John Hopkins Hospital, Baltimore, MD, USA

Drs Morton Mower (left) and Michel Mirowski (right) with their first prototype of an automatic defibrillator
### ICDs and Secondary SCD Prevention

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Resuscitated from VF</td>
<td>- VT with syncope</td>
<td>- Resuscitated from VF-VT</td>
<td>- Resuscitated SCD with documented sustained ventricular arrhythmias</td>
</tr>
<tr>
<td>- VT with syncope</td>
<td>- VT with syncope</td>
<td>- VT with syncope</td>
<td></td>
</tr>
<tr>
<td>- VT with LVEF&lt;40% and hemodynamic compromise (near syncope, angina, or heart failure)</td>
<td>- VT &gt; 150 bpm with LVEF &lt;35% and syncope or angina</td>
<td>- Unmonitored syncope with spontaneous or inducible VT</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>1016</th>
<th>659</th>
<th>288</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>65 y</td>
<td>64 y</td>
<td>58 y</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>31</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>18</td>
<td>36</td>
<td>57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug in control grp</th>
<th>Amiodarone 85% Sotalol 15%</th>
<th>Amiodarone</th>
<th>Amiodarone 49% Metoprolol 51%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other features</td>
<td>79% men 81% CAD 50% heart failure</td>
<td>85% men 80% CAD 50% heart failure</td>
<td>80% men 73% CAD 10% without SHD</td>
</tr>
</tbody>
</table>
ICDs and Secondary SCD Prevention

### Total mortality

<table>
<thead>
<tr>
<th>Name</th>
<th>n</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1016</td>
<td>80</td>
<td>0.62</td>
<td>0.47, 0.81</td>
</tr>
<tr>
<td>CIDS</td>
<td>659</td>
<td>83</td>
<td>0.82</td>
<td>0.61, 1.10</td>
</tr>
<tr>
<td>CASH</td>
<td>191</td>
<td>37</td>
<td>0.83</td>
<td>0.52, 1.33</td>
</tr>
</tbody>
</table>

Fixed effects HR = 0.72 95% = 0.60, 0.87

Test for association (U = 11.77 on 1 df) $P = 0.00060$
Test for heterogeneity ($Q = 2.37$ on 2 df) $P = 0.30550$

### Arrhythmic mortality

<table>
<thead>
<tr>
<th>Name</th>
<th>n</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1016</td>
<td>24</td>
<td>0.43</td>
<td>0.27, 0.66</td>
</tr>
<tr>
<td>CIDS</td>
<td>659</td>
<td>30</td>
<td>0.68</td>
<td>0.43, 1.08</td>
</tr>
<tr>
<td>CASH</td>
<td>191</td>
<td>7</td>
<td>0.32</td>
<td>0.15, 0.69</td>
</tr>
</tbody>
</table>

Fixed effects HR = 0.50 95% = 0.37, 0.67

Test for association (U = 21.73 on 1 df) $P = 0.00000$
Test for heterogeneity ($Q = 3.57$ on 2 df) $P = 0.16807$

ICDs and Secondary SCD Prevention

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations

Secondary Prevention
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for > 1 year with good functional status

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
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<tbody>
<tr>
<td>I</td>
<td>A</td>
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</tbody>
</table>

Eur Heart J 2016; 37(27):2129-200
Survival and QoL after Resuscitation

- 44% (amiodarone) vs. 34% (placebo) of patients reached the hospital alive after VF/CPR
- Only 13% (67 of 504) pts. were dismissed alive
- Only 6.9% (35 of 504) could lead an independent life after VF/CPR

ICDs and Primary SCD Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Therapy</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIOVIRT</td>
<td>103</td>
<td>NYHA I-II, DCM, asymptomatic NSVT, LVEF ≤ 0.35</td>
<td>ICD vs. amiodarone</td>
<td>0.87</td>
<td>0.31–2.42</td>
<td>NS</td>
</tr>
<tr>
<td>CABG-Patch</td>
<td>900</td>
<td>Scheduled for CABG, LVEF ≤ 0.35, positive SAECG</td>
<td>ICD vs. standard medical therapy</td>
<td>1.07</td>
<td>0.81–1.42</td>
<td>NS</td>
</tr>
<tr>
<td>CAT</td>
<td>104</td>
<td>NYHA II or III, DCM &lt; 9 months, LVEF ≤ 0.30</td>
<td>ICD vs. standard medical therapy</td>
<td>0.83</td>
<td>0.45–1.82</td>
<td>NS</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>458</td>
<td>DCM, LVEF ≤ 0.35, PVCs, or NSVT</td>
<td>ICD vs. standard medical therapy</td>
<td>0.65</td>
<td>0.40–1.06</td>
<td>0.08</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>674</td>
<td>Recent MI, LVEF ≤ 0.35, impaired cardiac autonomic function</td>
<td>ICD vs. standard medical therapy</td>
<td>1.08</td>
<td>0.76–1.55</td>
<td>NS</td>
</tr>
<tr>
<td>IRIS</td>
<td>898</td>
<td>Recent MI, LVEF ≤ 0.40, or NSVT</td>
<td>ICD vs. standard medical therapy</td>
<td>1.04</td>
<td>0.81–1.35</td>
<td>NS</td>
</tr>
<tr>
<td>MADIT</td>
<td>196</td>
<td>NYHA I–III, prior MI, LVEF ≤ 0.35, NSVT, and positive EPS</td>
<td>ICD vs. standard medical therapy</td>
<td>0.46</td>
<td>0.26–0.82</td>
<td>0.009</td>
</tr>
<tr>
<td>MADIT-II</td>
<td>1232</td>
<td>Prior MI, LVEF ≤ 0.30</td>
<td>ICD vs. standard medical therapy</td>
<td>0.69</td>
<td>0.51–0.93</td>
<td>0.016</td>
</tr>
<tr>
<td>MUSTT</td>
<td>351</td>
<td>CAD, LVEF ≤ 0.40, NSVT, and positive EPS</td>
<td>ICD vs. conventional antarrhythmic therapy</td>
<td>0.40</td>
<td>0.27–0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>1676</td>
<td>NYHA II or III, LVEF ≤ 0.35, ischaemic and nonischaemic cardiomyopathy</td>
<td>ICD plus standard medical therapy vs. placebo plus standard medical therapy</td>
<td>0.73</td>
<td>0.62–0.96</td>
<td>0.007</td>
</tr>
</tbody>
</table>
ICDs and Primary SCD Prevention in Ischaemic Cardiomyopathy
MADIT II (1997-2001)

- ≥ 1 months after myocardial infarction
- LVEF ≤ 30% + multiple / repetitive PVCs on Holter
- EP study not required

ARR = 5.6%
HR = 0.69 (0.51–0.93)  
p=0.016

Mean follow-up 20 months
ICDs and Primary SCD Prevention

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations

Primary Prevention
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II-III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:

- IHD (unless they have an MI in the prior 40 days)

<table>
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<tr>
<th>Class</th>
<th>Level</th>
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<tr>
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<td>A</td>
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</table>

Eur Heart J 2016; 37(27):2129-200
ICDs and Primary SCD Prevention in Nonischaemic Cardiomyopathy
ICD in Nonischaemic Cardiomyopathy
First Randomized Controlled Trials

**Cardiomyopathy Trial (CAT)**
- 104 patients, LVEF<30%
- Recent (<9 mo) onset DCM
- ACE-I 96%, β-blocker 4%

**Amio vs. ICD (AMIOVIRT)**
- 103 patients, LVEF<35%
- Non-ischaemic DCM + NSVT
- ACE-I 86%, β-blocker 52%

Strickberger AS. et al. *J Am Coll Cardiol* 2003; 41:1707-12
DEFINITE Trial (2004)

- Non-ischaemic cardiomyopathy, LVEF < 36%, NYHA I–III
- nsVT (3-15 cycles >120 bpm) or >10 PVCs/h (Ø EP Study)
- ICD (229 pts.) vs. Standard treatment (229 pts.)
- 86% pts. on ACE-I and 85% pts. on β-blocker

ARR = 5.2%
HR = 0.65 (0.40–1.06)

ARR = 4.8%
HR = 0.20 (0.06–0.71)

SCD-HeFT Trial (2005)

- 2521 patients with any cardiomyopathy (ICM + NICM)
- LVEF ≤ 35%, NYHA II – III
- 96% pts. on ACE-I / ARB and 69% pts. on β-blocker

Amiodarone vs. placebo  HR = 1.06 (0.86 – 1.30) p=0.53

ICD vs. placebo  HR = 0.77 (0.62 – 0.96) p=0.007

**ICDs and Primary SCD Prevention**

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
</tr>
<tr>
<td>An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II-III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:</td>
</tr>
<tr>
<td>• DCM (Dilated Cardiomyopathy)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
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<tr>
<td>I</td>
<td>B</td>
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</tbody>
</table>

*Eur Heart J 2016; 37(27):2129-200*
Primary Prophylactic ICD in Nonischaemic Cardiomyopathy

- Based on small to medium sized trials with neutral outcomes and subgroup analysis of larger trials
- Medical therapy has improved since the landmark ICD trials
1116 HF patients NYHA II-III (IV if planned CRT), LVEF ≤35% with non-ischaemic aetiology
Danish Trial – Study Overview

Randomized (n=1116)

- Preexisting CRT-P (n=19)
- Yes (n=626)
- No (n=471)

Randomization 1:1 CRT-D vs. CRT-P (n=645)

- CRT Stratum
  - CRT-D: N = 322
  - CRT-P: N = 323

Randomization 1:1 ICD vs. Medical Treat. (n=471)

- Non-CRT Stratum
  - ICD: N = 234
  - Medical Trt: N = 237

N Engl J Med 2016; 375(13) 1221-1230
## Danish Trial – Study Overview

### Means of exclusion of ischemic cause of heart failure — no. (%)

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheterization</strong></td>
<td>533 (96)</td>
<td>541 (97)</td>
</tr>
<tr>
<td><strong>Cause of heart failure — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>424 (76)</td>
<td>425 (76)</td>
</tr>
<tr>
<td>Valvular</td>
<td>20 (4)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (11)</td>
<td>55 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (9)</td>
<td>59 (11)</td>
</tr>
<tr>
<td><strong>Medications — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>533 (96)</td>
<td>544 (97)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>509 (92)</td>
<td>517 (92)</td>
</tr>
<tr>
<td>Mineralocorticoid-receptor antagonist</td>
<td>326 (59)</td>
<td>320 (57)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>34 (6)</td>
<td>32 (6)</td>
</tr>
<tr>
<td>CRT — no. (%)</td>
<td>322 (58)</td>
<td>323 (58)</td>
</tr>
</tbody>
</table>
At a median of 67.6 months, there was no significant difference in mortality between the two groups.

Hazard ratio = 0.87 (0.68–1.12)

p=0.28
Hazard ratio = 0.77 (0.57–1.09)  
\( p = 0.10 \)

Sudden Cardiac Death

Hazard ratio = 0.50 (0.31–0.82)  
\( p = 0.005 \)
Danish Trial – Interaction with Age

<table>
<thead>
<tr>
<th>CRT</th>
<th>No</th>
<th>58/234</th>
<th>65/237</th>
<th>0.83 (0.58–1.19)</th>
<th>0.31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>62/322</td>
<td>66/323</td>
<td>0.91 (0.64–1.29)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.87 (0.68–1.12)</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

N Engl J Med 2016; 375(13) 1221-1230
Most ICD recipients never experience ICD therapy

“Prediction is very difficult, especially about the future”

Niels Bohr (1885-1962)
Nonsustained VTs and risk of SCD in HF

Non-sustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: A meta-analysis

Marcos R. de Sousa, Carlos A. Morillo, Fábio T. Rabelo, Antônio M. Nogueira Filho, Antonio L.P. Ribeiro

Predictors of Appropriate Implantable Cardioverter Defibrillator (ICD) Therapy in Primary Prevention Patients with Ischemic and Nonischemic Cardiomyopathy

Atul Verma, M.D., Bradley Sarak, B.Sc., Alexander J. Kaplan, B.Sc., Richard Oosthuizen, B.Sc., Marianne Beardsall, R.N. M.S.N.

Increased SCD risk in patients with Non-sustained VT

Circulation
Nonsustained Ventricular Tachycardia in Severe Heart Failure
Independent Marker of Increased Mortality due to Sudden Death

Herman C. Doval, Daniel R. Nul, Hugo O. Grancelli, Sergio D. Varini, Saul Solfer, Gianni Corrado, Sergio Dubner, Omar Scapin and Sergio V.
Not All Nonsustained VTs Are Created Equal
How Can Optimization of Medical Treatment Avoid Unnecessary Implantable Cardioverter-Defibrillator Implantations in Patients With Idiopathic Dilated Cardiomyopathy Presenting With “SCD-HeFT Criteria?”

Baseline Evaluation

- Eligible for ICD: 162 pts
  - β-blockers 0%
  - ACE-I 41%

- Non-eligible for ICD: 109 pts (67%)
  - β-block 90%, ACE-I 95%

3-9 months Re-evaluation

- Eligible for ICD: 50 pts (31%)
  - β-block 85%, ACE-I 94%

- Non-eligible: 3 pts (2%)
  - NYHA IV

- Non-eligible: 106 pts (69%)

Impact of Comorbidities on ICD Benefit

CONCLUSIONS Patients with extensive comorbid medical illnesses may experience less benefit from primary prevention ICDs than those with less comorbidity; implantation should be carefully considered in sick patients. Further study of ICDs in medically complex patients is warranted.

Steinberg BA. J Am Coll Cardiol HF 2014; 2:623-9

1. Smoking
2. Diabetes
3. Ischaemic Heart Disease
5. Atrial Fibrillation
6. eGFR <60 ml/min
7. COPD
Role of Left Ventricular Midwall Fibrosis

Mid-Wall Fibrosis

No Mid-Wall Fibrosis

Leyva F. J Am Coll Cardiol 2017; 70:1216-1227
Take Home Messages

The role of ICD in treatment of Ventricular Arrhythmias and prevention of SCD among patients with HF and reduced LVEF is established

HOWEVER

- Evidence for nonischaemic CMP are less robust
- Optimized medical therapy is mandatory
- Risk stratification before implantation is crucial
- Comorbidities/fibrosis may influence ICD benefit
Thank you for your attention!
Treatment for patients with symptomatic HF-REF (NYHA II-IV)

Patient with symptomatic a HFrEF

- Therapy with ACE-I and beta-blocker (up-titrated to maximum tolerated evidence-based doses)
  - Still symptomatic and LVEF ≤ 35%
    - No
    - Yes
      - Add MR antagonist a
        (up-titrated to maximum tolerated evidence-based dose)
          - Yes
            - Still symptomatic and LVEF ≤ 35%
              - No
              - Yes
                - Diuretics to relieve symptoms and signs of congestion
                  - If LVEF ≤ 35% despite OMT or a history of symptomatic VT/VI, implant ICD
                    - Able to tolerate ACEI (or ARB) a
                      - Sinus rhythm, QRS duration ≥ 130 msec
                        - Sinus rhythm, a HR ≥ 70 bpm
                          - ARNI to replace ACE-I
                          - Evaluate need for CRT a
                            - Ivabradine
                              - These above treatments may be combined if indicated
                                - Resistant symptoms
                                  - Consider digoxin or H-ISDN or LVAD, or heart transplantation
                                    - No further action required
                                      - Consider reducing diuretic dose
                                        - Eur Heart J 2016; 37(27):2129-200
Nonpharmacological Treatments in Selected Patients

- If LVEF ≤35% do not relieve symptoms

- Able to tolerate ACEI (or ARB)
  - ARNi to replace ACE-I

- Sinus rhythm, QRS duration ≥130 msec
  - Evaluate need for CRT

- Sinus rhythm, HR ≥70 bpm
  - Ivabradine

These above treatments may be combined if indicated

- Resistant symptoms
  - Yes: Consider digoxin or H-ISDN or LVAD, or heart transplantation
  - No: No further action required Consider reducing diuretic dose
ICD Lead Performance

≈ 20-30% ICD transvenous lead fail by 10 yrs
ICDs and Primary SCD Prevention
2016 ESC Heart Failure GLs


ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.
COMPANION Trial (2005)

- 1520 patients with any cardiomyopathy (ICM + NICM)
- LVEF ≤ 35%, NYHA III – IV, QRS ≥ 120 msec
- 89% pts. on ACE-I / ARB and 67% pts. on β-blocker

![Graph showing event-free survival over days after randomization. Pharamacologic therapy vs. Pacemaker (105 events, P=0.003) vs. Pacemaker-defibrillator (131 events, P=0.059). CRT-D vs. Drugs HR = 0.64 (0.48 – 0.86) vs. CRT-P vs. Drugs HR = 0.76 (0.58 – 1.01).]