Implantable cardioverter-defibrillators and cardiac resynchronization therapy

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Frontiers of heart failure controversies, ESC - Paris 2011

Conflict of interest: consulting fees from St Jude Medical and Biotronik; research grants and speaker honoraria from Biotronik, St Jude Medical, Medtronic, and Boston Scientific; and is a co-principal investigator in EchoCRT. No Stocks/Options from a medical device company. Stocks/Options from Cardiorentis (Biotech)
Implantable Defibrillators

Mieczysław (Michel) Mirowski
ICD Landmark Trials

<table>
<thead>
<tr>
<th>Acronym, Pub Year</th>
<th>Hazard ratio</th>
<th>LVEF, other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT-I 1996</td>
<td>N = 190</td>
<td>0.35 or less, NSVT, EP positive</td>
</tr>
<tr>
<td>AVID 1997</td>
<td>N = 1016</td>
<td>Aborted cardiac arrest</td>
</tr>
<tr>
<td>CABG-Patch 1997</td>
<td>N = 900</td>
<td>0.35 or less, abnormal SAECG and scheduled for CABG</td>
</tr>
<tr>
<td>CASH 2000</td>
<td>N = 191</td>
<td>Aborted cardiac arrest</td>
</tr>
<tr>
<td>CIDS 2000</td>
<td>N = 659</td>
<td>Aborted cardiac arrest or syncope</td>
</tr>
<tr>
<td>MADIT-II 2002</td>
<td>N = 1,032</td>
<td>0.30 or less, prior MI</td>
</tr>
<tr>
<td>DEFINITE 2004</td>
<td>N = 458</td>
<td>0.35 or less, NICM and PVCs or NSVT</td>
</tr>
<tr>
<td>DINAMIT 2004</td>
<td>N = 674</td>
<td>0.35 or less, MI within 6 to 40 days and impaired cardiac autonomic function</td>
</tr>
<tr>
<td>SCD-HeFT 2005</td>
<td>N = 912</td>
<td>0.35 or less, LVD due to prior MI and NICM</td>
</tr>
</tbody>
</table>
ESC Guidelines for Heart Failure (2008)

<table>
<thead>
<tr>
<th>Class IA</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA II/III, LVEF ≤35%, ischaemic cause, &gt;40 days of MI, reasonable expectation of survival with good functional status for &gt;1 year, optimum medical therapy</td>
<td>Reduce mortality</td>
</tr>
<tr>
<td>Survivor of VF</td>
<td>Reduce mortality</td>
</tr>
<tr>
<td>LVEF ≤40%, haemodynamically unstable VT and/or VT with syncope, reasonable expectation of survival with good functional status for &gt;1 year, optimum medical therapy</td>
<td>Reduce mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IB</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA II/III, LVEF ≤35%, non-ischaemic cause, reasonable expectation of survival with good functional status for &gt;1 year, optimum medical therapy</td>
<td>Reduce mortality</td>
</tr>
</tbody>
</table>

ICD=implantable cardioverter defibrillator. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. MI=myocardial infarction. VF=ventricular fibrillation. VT=ventricular tachycardia.

_Table 2: Class I recommendations for ICDs in patients with chronic heart failure according to the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure, 2008, by indication_
First Implantable Cardioverter Defibrillator (ICD)

Components of the one of the earliest ICDs:
Incl. battery and capacitors the weight was 895 g
The ICD Lead is the „weak spot“ of ICD Systems
Active Treatment with Cardiac Resynchronisation Therapy (CRT)

Pre CRT

Post-CRT
CRT: State of the art and expanding indications

• Patients with less severe heart failure (asymptomatic LVD and mild HF)

• Patients with chronic RV pacing due to conduction disease and heart failure

• Patients with less severe LVD (e.g., LVEF 36% to 50%) or normal LVEF and a chronic pacing indication

• Patients with a narrow QRS and ventricular dysynchrony measured by echocardiography

• Changing the definition of ventricular dysynchrony (QRS duration → ECHO)
CRT: State of the art and expanding indications

- Patients with less severe heart failure (asymptomatic LVD and mild HF)
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- Patients with less severe LVD (e.g., LVEF 36% to 50%) or normal LVEF and a chronic pacing indication
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- Changing the definition of ventricular dysynchrony (QRS duration → ECHO)
CRT in NYHA Class I-II Heart Failure

2003: Contak CD
6 months, n =263

Primary Obj:
composite (mortality, HF hospitalization, and VT/VF)

Peak V02

2004: MICD II
6 months, n=186

Primary Obj:
HF Clinical Composite Score

2008: REVERSE
12 months, n=610
24 months, n=262

Primary Obj: composite (total mortality and HF hospitalization)

2009: MADIT CRT
Average 29 months, n=1820

Primary Obj: composite (mortality or HF event)

2010: RAFT
Minimum 18 months, n=1800

Primary Obj: composite (total mortality and HF hospitalization)
REVERSE at 24 Months
Powered Secondary End Point: LVESVi

P-value compares 24-month changes
**REVERSE: Time to First HF Hospitalization or Death from Any Cause**

Percentage Hospitalized for HF or Died

- CRT ON: 24.0%
- CRT OFF: 11.7%

P = 0.003
HR = 0.38

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>CRT OFF</th>
<th>CRT ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>82</td>
<td>180</td>
</tr>
<tr>
<td>6</td>
<td>79</td>
<td>176</td>
</tr>
<tr>
<td>12</td>
<td>76</td>
<td>173</td>
</tr>
<tr>
<td>18</td>
<td>70</td>
<td>168</td>
</tr>
<tr>
<td>24</td>
<td>39</td>
<td>77</td>
</tr>
</tbody>
</table>

Patients censored at their 24-month follow-up. Some were before 24 months (730 days), hence the low number at risk. Some were after 24 months, hence the curves rising past 24 months.
MADIT-CRT

MADIT-CRT

RAFT - Resynchronization/Defibrillation for Ambulatory Heart Failure Trial

Hazard ratio, 0.75 (95% CI, 0.64–0.87)
P < 0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD–CRT</td>
<td>894</td>
<td>790</td>
<td>615</td>
<td>429</td>
<td>278</td>
<td>130</td>
<td>41</td>
</tr>
<tr>
<td>ICD</td>
<td>904</td>
<td>770</td>
<td>572</td>
<td>384</td>
<td>214</td>
<td>101</td>
<td>19</td>
</tr>
</tbody>
</table>

Tang et al., NEJM November 14, 2010
Effect of Intrinsic QRS Duration on Outcomes

Primary Outcome
Death or hospitalization for heart failure

Death from any cause

CRT in mild HF?

<table>
<thead>
<tr>
<th></th>
<th>MADIT CRT</th>
<th>REVERSE</th>
<th>RAFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF Inclusion criteria</td>
<td>LVEF &lt; 0.30 NYHA I/II</td>
<td>LVEF &lt; 0.40 NYHA I/II</td>
<td>LVEF &lt; 0.30 NYHA II/III</td>
</tr>
<tr>
<td>QRS duration</td>
<td>&gt; 130 msec</td>
<td>&gt; 120 msec</td>
<td>&gt; 120 msec</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Death or HF event</td>
<td>1- HF composite 2- LVESVI</td>
<td>HF Hospitalization or death</td>
</tr>
<tr>
<td>NNT to reduce 1 HF event</td>
<td>12 over 24 mos</td>
<td>20 / 12 mos</td>
<td>14 / 60 mos (death) 11 / 60 mos (hosp)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Improved HF morbidity</td>
<td>Increased time to first event; decreased volumes</td>
<td>Morbidity and mortality benefit</td>
</tr>
<tr>
<td>Concerns</td>
<td>Severity of HF?</td>
<td>Short follow-up</td>
<td>Inclusion of class III HF</td>
</tr>
</tbody>
</table>
CRT in NYHA Class I-II Heart Failure

- >4000 patients evaluated in randomized controlled trials completed as of November 2010

- Strong evidence for reverse remodeling
  - ↓ LV volumes and dimensions
  - ↑ LV ejection fraction
  - ↓ Mitral regurgitation

- Improvement in functional status and outcomes, as measured by
  - clinical composite endpoints
  - combined endpoint of heart failure morbidity and all-cause mortality
Is QRS duration a good marker of ventricular dyssynchrony?

• In the CARE-HF trial patients with a QRS duration between 120 – 149 msec had to fulfill 2 out of 3 echocardiographic dyssynchrony criteria to be included.

• In the subgroup analysis of the Companion trial, patients with a QRS < 160 msec did not benefit from CRT.

• In the subgroup analysis of the MADIT-CRT and RAFT trial, patients with a QRS < 150 msec did not benefit from CRT.
2010 Focused Update of ESC Guidelines on
device therapy in heart failure

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref.&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D is recommended to reduce morbidity and</td>
<td>NYHA function class III/IV</td>
<td>I</td>
<td>A</td>
<td>5–19</td>
</tr>
<tr>
<td>mortality&lt;sup&gt;d&lt;/sup&gt;</td>
<td>LVEF ≤35%, QRS ≥120 ms, SR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal medical therapy</td>
<td>Class IV patients should be ambulatory&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

<sup>d</sup>Reasonable expectation of survival with good functional status for > 1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.

<sup>e</sup>No admissions for HF during the last month and a reasonable expectation of survival > 6 months.

CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.
## 2010 Focused Update of ESC Guidelines on device therapy in heart failure

### Recommendation in patients with heart failure in New York Heart Association function class II

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent</td>
<td>NYHA function class II</td>
<td>I</td>
<td>A</td>
<td>9, 20–22</td>
</tr>
<tr>
<td>disease progression(^d)</td>
<td>LVEF ≤35%, QRS ≥150 ms, SR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal medical therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Class of recommendation.  
\(^b\)Level of evidence.  
\(^c\)References.  
\(^d\)The guideline indication has been restricted to patients with HF in NYHA function class II with a QRS width ≥ 150 ms, a population with a high likelihood of a favourable response. CRT = cardiac resynchronization therapy; CRT-D = CRT with defibrillator function; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.
Who Benefits From CRT? – The Latest

• Patients with less severe heart failure (asymptomatic LVD and mild HF)
• Patients with chronic RV pacing due to conduction disease and heart failure
• Patients with less severe LVD (e.g., LVEF 36% to 50%) or normal LVEF and a chronic pacing indication
• Patients with a narrow QRS and ventricular dysynchrony measured by echocardiography
• Changing the definition of ventricular dysynchrony (QRS duration → ECHO)
CRT reverses LV remodeling in heart failure patients with chronic RV pacing in a similar way as in primary CRT recipients, even after very long periods of RV pacing.

Georg Fröhlich, Jan Steffel, David Hürlimann, Frank Enseleit, Thomas F. Lüscher, Frank Ruschitzka, William T. Abraham and Johannes Holzmeister, Eur Heart J. 2010 Jun;31(12):1477-85
Chronic RV pacing in systolic heart failure patients is deleterious and biventricular pacing is the appropriate pacing mode for systolic heart failure patients.
## 2010 Focused Update of ESC Guidelines on device therapy in heart failure

### Recommendations in patients with heart failure and a concomitant class I pacemaker indication

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient population</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D is recommended to reduce morbidity</td>
<td>NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms</td>
<td>I</td>
<td>B</td>
<td>41–48</td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered to reduce morbidity</td>
<td>NYHA function class III/IV LVEF ≤35%, QRS &lt;120 ms</td>
<td>IIa</td>
<td>C</td>
<td>—</td>
</tr>
<tr>
<td>CRT-P/CRT-D may be considered to reduce morbidity</td>
<td>NYHA function class II LVEF ≤35%, QRS &lt;120 ms</td>
<td>IIb</td>
<td>C</td>
<td>—</td>
</tr>
</tbody>
</table>

*a Class of recommendation.
*b Level of evidence.
*c References.
*d Reasonable expectation of survival with good functional status for >1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D. CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

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European Heart Journal (2010) 31, 2677–2687
# Recommendations in patients with heart failure and permanent atrial fibrillation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient population</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D&lt;sup&gt;d&lt;/sup&gt; should be considered to reduce morbidity</td>
<td>NYHA function class III/IV</td>
<td>IIa</td>
<td>B</td>
<td>27–40</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤35%, QRS ≥130 ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacemaker dependency induced by AV nodal ablation</td>
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</tr>
<tr>
<td></td>
<td>Slow ventricular rate and frequent pacing&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup>Class of recommendation.
<sup>b</sup>Level of evidence.
<sup>c</sup>References.
<sup>d</sup>Reasonable expectation of survival with good functional status for > 1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.
<sup>e</sup>Frequent pacing is defined as ≥95% pacemaker dependence.

CRT = cardiac resynchronization therapy; CRT-P = CRT with pacemaker function; CRT-D = CRT with defibrillator function; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

European Heart Journal (2010) 31, 2677–2687
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- Patients with a narrow QRS and ventricular dysynchrony measured by echocardiography
- Changing the definition of ventricular dysynchrony (QRS duration → ECHO)
CRT and Heart Failure

LV Function vs. Time

- CRT
- OMT
- OMT + CRT(D)

Reverse Remodeling
Clinical-Non Progressor
Non responder
Clinical outcome trials are necessary to determine the future role of CRT in patients with less severe LVD or normal LVEF and indication for chronic RV pacing.
Who Benefits From CRT? – The Latest

- Patients with less severe heart failure (asymptomatic LVD and mild HF)
- Patients with chronic RV pacing due to conduction disease and heart failure
- Patients with less severe LVD (e.g., LVEF 36% to 50%) or normal LVEF and a chronic pacing indication
- Patients with a narrow QRS and ventricular dysynchrony measured by echocardiography
- Changing the definition of ventricular dysynchrony (QRS duration → ECHO)
Rationale for Studying CRT in Narrow QRS Patients

- Recent small studies\textsuperscript{1,2,3} have indicated that HF patients with a narrow QRS duration and \textit{echocardiographic} evidence of ventricular dysynchrony may benefit from CRT
- Lack of definitive evidence and other contradictory studies\textsuperscript{4} provide the rationale for a long-term, randomized, controlled trial of CRT in these patients

\textsuperscript{1}Khan et al, Eur J Heart Fail 2007; 9:491-501
\textsuperscript{3}Bleeker et al, Am J Cardiol 2005; 95:140-2.
\textsuperscript{4}Beshai JF et al, N Engl J Med 2007; 357:2461-71
Rationale for Studying CRT in Narrow QRS Patients

• Hundreds of thousands of needy heart failure patients could benefit if the indication for CRT was expanded to those with a narrow QRS

• Study investigates the controversy between electrical and mechanical dysynchrony
Potential for CRT in Narrow QRS Patients

More than 70% of HF patients present with narrow QRS

HF patient population in NYHA III/IV $^{1,2,3}$

50% of patients with narrow QRS have ventricular dyssynchrony

1 Schoeller et al, Am J Cardiol 1993; 71:720-726
3 Farwell et al, Eur Heart J 2000; 21:1246-1250
Mechanical Dyssynchrony
Speckle Tracking – Radial Strain

LBBB Dyssynchrony
Opposing Wall Delay Method by TDI

140 ms

Lateral

Apical 4-Chamber View
Dyssynchrony in relation to QRS width in Heart Failure Patients (EF < 35%)

Mechanical Dyssynchrony (% Patient Population)

- Intraventricular dyssynchrony
- Global dyssynchrony

Mean QRS CARE-HF, Companion
Presence of pre-defined dyssynchrony measures in patients with a narrow QRS complex

Echocardiography Guided Cardiac Resynchronization Therapy

Prospective, international, multicenter, double-blinded, randomized study which all patients followed for 24 months

1,258 patients

NYHA III/IV, OPT, NSR, LVEF ≤ 35%, LVEDD ≥ 55 mm
QRS<130ms, Echo Dysynchrony

Primary endpoint:
Effectiveness: Combination of all-cause death or HF-Hospitalization
Safety: Complication-free rate at 6 months

Sponsor: Biotronik
Dyssynchrony in relation to QRS width in Heart Failure Patients (EF < 35%)

Mechanical Dyssynchrony (% Patient Population)

Intraventricular dyssynchrony

Global dyssynchrony

EchoCRT Patients

Mean QRS CARE-HF, Companion

QRS width (msec)

80  100  130  160  200
Dependence of Future CRT Indication on Echo Dyssynchrony

Mechanical Dyssynchrony (% Patient Population)

- ECHO necessary for CRT indication
- Patient population EF < 35%
- Mean QRS CARE-HF Companion

QRS width (msec)
<table>
<thead>
<tr>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III</th>
<th>NYHA IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic therapy</td>
<td>ACE-Inhibitors</td>
<td>β-Blocker</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>also if</td>
<td></td>
<td></td>
<td>Antagonisten</td>
</tr>
<tr>
<td>asymptomatic</td>
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<tr>
<td>Post MI</td>
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<td>ICD for</td>
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<td>Survivors of</td>
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<td>SCA or with</td>
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<tr>
<td>sustained VT</td>
<td></td>
<td></td>
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</tbody>
</table>

- ICD (EF < 35% on OMT)
- CRT or CRT-ICD patients with „dyssynchrony“ on OMT