Unsolved issues in CRT: Problems after device implantation

Non Responders

ESC, Stockholm 2010

Daniel Gras, MD, Nantes, France
Unsolved issues after CRT device implant

Non Responders

- **Background**
- How to Define non Responders?
- Parameters Influencing CRT Response
- Potential Solutions to Optimize CRT
Today’s Patient Selection for CRT

Patient Selection for Cardiac Resynchronization Therapy

From the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Heart Rhythm Society

- Sinus rhythm
- LVEF ≤0.35
- Ischemic or nonischemic cardiomyopathy
- QRS complex duration ≥120 ms
- NYHA functional class III or IV
- Maximal pharmacological therapy + AF and PM patients …
- LVEF > 35 %: Echo ?
- Echo Investigation in IHD ++
- QRS < 150 ms (<130:Echo CRT)
- Earlier CRT consideration
- HF Hospitalization, BNP …
Natural History of Heart Failure: Curative versus Preventive Therapy

Most common mode of death

Pump Failure

Sudden Death

NYHA Class: I

CHF Stage: 1

Adapted from Bristow MR, in Heart Disease: A Textbook of CV Medicine 7th edition, 2004
How Much CRT Pacing is Really Needed?

Pts. with AT (n=617)  HF hospitalization/mortality

BiVpacing
100%
98-99%
93-97%
0-92%

Koplan et al., JACC 2009
Unsolved issues after CRT device implant

Non Responders

- Background
- **How to Define non Responders?**
- Parameters Influencing CRT Response
- Potential Solutions to Optimize CRT
How to define Non Responders (?)

1. Follow-up: 6 months, 1 year, Longer…
2. Clinical (Soft): NYHA, QoL, 6 MNW, VO2
3. Clinical (Strong): Morbidity (HFH), Mortality
4. Echocardiography: LVESV -10 or 15%, LVEF
5. Combined: Clinical and Echocardiography
6. Device-related complications: never considered
7. Other ….
Rethinking follow-up too short - Lessons from CARE-HF

![Graph showing percentage of patients free of death from any cause over days, comparing cardiac resynchronization and medical therapy.](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Cardiac resynchronization</th>
<th>Medical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>409</td>
<td>376</td>
<td>351</td>
</tr>
<tr>
<td>213</td>
<td>89</td>
<td>8</td>
</tr>
<tr>
<td>351</td>
<td>89</td>
<td>8</td>
</tr>
<tr>
<td>321</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>192</td>
<td>71</td>
<td>5</td>
</tr>
</tbody>
</table>

P < 0.002

Cleland NEJM 2005
Care-HF: Changes in LVES volume & LVEF

LV End-Systolic Volumes

LV ejection Fraction
Reverse Trial Primary End Point: Clinical Composite Response

Pre-Specified Analysis
Proportion: Worsened

- CRT OFF: 21% Worsened
- CRT ON: 16% Worsened

Conventional Analysis
Distribution: Worsened/Unchanged/Improved

- CRT OFF: 21% Worsened
- CRT ON: 16% Worsened
- CRT OFF: 39% Unchanged
- CRT ON: 30% Unchanged
- CRT OFF: 40% Improved
- CRT ON: 54% Improved

P-values:
- Pre-Specified Analysis: P=0.10
- Conventional Analysis: P=0.004
Reverse Trial Primary End Point: Clinical Composite Response: 12 vs 24 M FU

Pre-Specified Analysis
Proportion Worsened

<table>
<thead>
<tr>
<th>CRT OFF</th>
<th>CRT ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>79%</td>
<td>84%</td>
</tr>
<tr>
<td>21%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Improvement/Unchanged

<table>
<thead>
<tr>
<th>CRT OFF</th>
<th>CRT ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%</td>
<td>81%</td>
</tr>
<tr>
<td>29%/37%</td>
<td>54%/27%</td>
</tr>
</tbody>
</table>

Worsened

<table>
<thead>
<tr>
<th>CRT OFF</th>
<th>CRT ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>34%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Entire distribution analysis of worsened, unchanged and improved: P=0.0006
Consistency between REVERSE and MADIT CRT

**REVERSE**
Time to first heart failure hospitalization in the first 12 months (secondary end point)

RR - 53 %

**MADIT-CRT**
Kaplan-Meier estimate of heart-failure free survival probability (part of primary end point)

RR-34% and for HF only – 41 %
REVERSE: Remodeling Parameters

LVESVi  LVEDVi (ml/m²)  LVEF (%)

P-values compare 24-month changes.
Prospect Study
CCS versus Echo Response

Clinical response

Echocardiographic Response

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVESV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Unsolved issues after CRT device implant

Non Responders

• Background
• How to Define non Responders?
• Parameters Influencing CRT Response
• Potential Solutions to Optimize CRT
Parameters influencing CRT Response

1. Comorbidities: age-related, COPD, anemia …
2. Advanced CM vs Early Stage CM
3. Ischemic vs non ischemic origin
4. RV dysfunction
5. Lead Position, difficult anatomy
6. Device settings: AV & VV delays
7. Others ….
## Findings in the European CRT Survey

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75</td>
<td>31</td>
</tr>
<tr>
<td>HF hosp. within previous year</td>
<td>57</td>
</tr>
<tr>
<td>Prior device implantation</td>
<td>26</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23</td>
</tr>
<tr>
<td>QRS &lt;120 ms(^a) /120–129 ms</td>
<td>9/10</td>
</tr>
<tr>
<td>NYHA class I/II</td>
<td>2/22</td>
</tr>
<tr>
<td>LVEF &gt;35%(^b)</td>
<td>17</td>
</tr>
<tr>
<td>Moderate to severe mitral regurgitation</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^a\) mean baseline QRS in the survey 157 ms
\(^b\) mean baseline LVEF in the survey 27%

Bogale N. ESC 2009
# Prevalence of AF, very narrow QRS, and IHD by age in the European CRT Survey

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age &lt;75 (%)</th>
<th>Age ≥75 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>21</td>
<td>28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS &lt;120 ms</td>
<td>10</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ischemic disease</td>
<td>48</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bogale N. European Society of Cardiology 2009 Congress; August 30-September 2, 2009: Barcelona, Spain.
Limitations of CRT: Advanced Cardiomyopathy
MASCOT HFH 6 m < CRT (Univariate Analyses) Late vs Early Consideration for CRT

Kaplan-Meyer for time to death, based on number of HF hospit. in the 6 months preceding CRT implant.

0 HF Hosp
1 HF Hosp
>2 HF Hosp

p<0.001
Limitations of CRT: Ischemic Origin

LVEF: 25%, SR, LBBB (QRS 160 ms) , NYHA III/OMT
Limited impact of CRT in advanced ICM

Interaction Between CRT & Ischemic Etiology

LVESV

Control  CRT

P=0.01

LVEF

Control  CRT

P=0.003

Non-ischemic etiology  Ischemic etiology
Limitations of CRT: Reduced RV function
Limitations of CRT: Reduced RV function
Interaction at 18 Months in Care HF

- LVESV
  - Control: 302/40 (-52.1), CRT: 291/53 (-41.7)
  - Control vs CRT: P=0.002

- LVEF
  - Control: 2.1, CRT: 4.9
  - Control vs CRT: P=0.003

TAPSE >14 mm: Green
TAPSE ≤14 mm: Red
CRT failed to benefit

Key importance of CRT lead Placement
CRT Device Settings: Tuning of AV + VV Delays

DFT at Baseline: 280

DFT at 3 months: 400 ms

Septal to Lateral: 110 ms

Septal to Lateral: 10 ms
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FREEDOM Trial Results: Primary Endpoint
HF Clinical Composite Score
(Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th>HF CCS</th>
<th>Treatment</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Improved</td>
<td>551</td>
<td>67.52</td>
<td>559</td>
</tr>
<tr>
<td>Unchanged</td>
<td>76</td>
<td>9.31</td>
<td>86</td>
</tr>
<tr>
<td>Worsened</td>
<td>189</td>
<td>23.16</td>
<td>183</td>
</tr>
<tr>
<td>Total</td>
<td>816</td>
<td>100</td>
<td>828</td>
</tr>
</tbody>
</table>

No treatment differences in pre-specified ischemic and non-ischemic sub groups
Clear Study: Primary Endpoint

Clinical response rate to CRT (composite criterion*)

- **SonR group** (n=57): 86%
- **Control group** (n=99): 62%

**p=0.0013** (Fisher's exact test)

Mean FU: SonR group (367.5±41.3 days) vs. Control group (362.4±87.4 days) NS

*Composite criterion including NYHA functional class, death from any cause, deaths and hospitalizations for management of HF, and QOL
Dual site RV Pacing to optimize CRT
A randomized comparison of triple versus dual site ventricular stimulation in patients with congestive heart failure

Christophe Leclercq¹, MD, PhD, Fredrik Gadler², MD, PhD, Wolfgang Kranig³, MD, Sue Ellery⁴, MD, Daniel Gras⁵, MD, Arnaud Lazarus⁶, MD, Jacques Clémenty⁷, MD, Eric Boulogne⁸, MSc, Jean-Claude Daubert¹, MD, for the Triple Resynchronization In Paced Heart Failure Patients (TRIP-HF) study group

J Am Coll Cardiol 2008;51:1455-62
Existing Clinical Experience in Transseptal LV Endocardial Lead Implant

- VanGelder BM et al, Heart Rhythm, 2007
- Morgan et al, EuroPace, 2009
- Lau E, J Interv Card Electrophysiol., 2009

Right jugular vein or Left axillary vein or Subclavian vein

- Brockenbrough needle
- Mullins transseptal sheath/dilator
- Guidewire
- 6226 DEF or C304

Right femoral vein
Trans-septal left ventricular endocardial pacing through a persistent left-sided superior vena cava

Paul A. Scott, Paul R. Roberts, and John M. Morgan
Unsolved issues after CRT device implant

Non Responders

• Response to CRT:
  – CCS, Hospitalization, LV Reverse Remodeling, Mortality

• Limitations to CRT
  – Age and Comorbidities, advanced CM, Ischemic origin, Anatomical, RV Dysfunction, Lead Placement

• Management of non responders:
  – Earlier CRT Consideration: Madit CRT, Reverse, Raft …
  – Appropriate Lead Placement
  – Optimized CRT Settings (Automaticity, Telemonitoring …)
  – Triple site RV/LV CRT, LV Endocardial Pacing …