Non-Pharmacologic Treatment in Heart Failure

Zaza Iakobishvili, MD, PhD
Department of Cardiology
Rabin Medical Center
Severity of Heart Failure and Mode of Death

NYHA II
- CHF: 12%
- Other: 24%
- Sudden death: 64%
- N = 103

NYHA III
- CHF: 26%
- Other: 15%
- Sudden death: 59%
- N = 232

NYHA IV
- CHF: 56%
- Other: 11%
- Sudden death: 33%
- N = 27

N = number of deaths

Device-based treatment of heart failure

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<tr>
<th>Function of device</th>
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Adapted from Boehmer, Am J Cardiol, 2003
# Device-based treatment of heart failure

## Function of device

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## Examples

- Implantable hemodynamic monitors, home scales, home monitoring systems
- Pacemakers for bradycardia, ICD, LifeWest Wearable AED (LIFECOR, Inc, PA)
- Left ventricular or multisite pacing, Biventricular pacing, CorCap (Accorn, MN), Myosplint (Myocor, MN)
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*Adapted from* Boehmer, Am J Cardiol, 2003
Diagnostic capabilities

- Arrhythmia monitoring
- Heart rate
- Percent pacing
- Physical activity
- Heart rate variability
- Intrathoracic impedance
- RV pressures
The Chronicle®

Implantable continuous hemodynamic monitor (ICHM)

- Heart rate
- Syst RV pressure
- Diast RV pressure
- RV pulse pressure
- ePAD
- pos \( \frac{dP}{dt_{\text{max}}} \)
- neg \( \frac{dP}{dt_{\text{max}}} \)
- PEI
- STI
- Activity

External Pressure Reference
Primary Effectiveness end-point - the Chronicle group would have a 30% lower rate of combined HF-related events (hospitalizations, emergency department and urgent clinic visits requiring intravenous therapy) compared with the control group.

Bourke et al., JACC, 2008
* Hypothesized event rate was 1.2

**HF-related Hospitalization**

Cumulative Events

- **Chronicle**
- **Control**

RR: 22%
(p=0.27)

Bourge et al., JACC, 2008
Reduction in relative risk of a first heart failure related hospitalization

HR = 0.64 (0.42-0.96), p = 0.03

Bourge et al., JACC, 2008
Conclusions

- In patients with moderate to severe HF, the addition of an ICHM to optimal medical management did not significantly reduce the rate of all HF-related events.

- Additional trials will be necessary to establish clinical benefit of ICHM-guided care in this patient population.

Bourge et al., JACC, 2008
Intrathoracic impedance

Dryer lungs

Wetter lungs

Impedance ↑

Impedance ↓
Fluid Accumulation Notification Options

- Observations with Trends
- Device audible alert
- SentryCheck™
- Patient look indicator
Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure

- 640 pts with heart failure eligible for CRT-D (InSync Sentry®, Medtronic Inc, USA) implantation were enrolled in 42 countries.
- Lack of FU reports in 267 pts.
- Finally 373 pt files were analyzed.
Main Findings

- The device alert detected HF deterioration with an adjusted sensitivity and an adjusted PPV of 60% each.

- Failure of the alert algorithm to detect clinical HF deterioration was in 55% of the cases associated with an increase of the fluid index that was yet below the programmable alert threshold.

- Half of the false-positive alerts were related to other clinical findings or therapeutic interventions.

Vollmann et al., 2008
# Device-based treatment of heart failure

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*Adapted from Boehmer, Am J Cardiol, 2003*
HF Patients:
A Need for a New Therapy

- 40% of patients are not suitable for ACE Inhibitors Therapy
- 60% of Rehospitalizations
  Noncompliance with medications and diet
- Over 65 yrs of age HF is the leading cause of Hospitalization
- 50% of Mortality within five years for 50% of patients in NYHA Functional Class I through IV
CHF STAT Trial

QRS Duration and Mortality

**Total Death**

- **Wide QRS**
- **Narrow QRS**

P = 0.001

**Sudden Death**

- **Wide QRS**
- **Narrow QRS**

P = 0.0009

*BBBB* not *RBBB* associated with adverse outcomes

Juliano S. Am Heart J 143:1085, 2002
Contraction Depends on Activation
Normal vs Abnormal Contraction

Mechanical Dyssynchrony with IVCD

Normal

Dilated Cardiomyopathy

BASE

SEPTUM

APEX

Tagged MRI Imaging

Curry C. Circulation 2000;101:e2
Dysynchrony - Consequences

- Abnormal septal motion
- Reduced dP/dt
- Reduced pulse pressure
- Lower ejection fraction
- Reduced diastolic filling
- Mitral regurgitation

Dysynchrony Has Many Levels
Biventricular pacemaker leads
Intraventricular Synchrony

Atrioventricular Synchrony

Interventricular Synchrony

↑ dP/dt, ↑ EF, ↑ CO (↑ Pulse Pressure)

↓ MR

↓ LVESV

↓ LVEDV

Reverse Remodeling

↑ LA Pressure

↑ LV Diastolic Filling

↑ RV Stroke Volume

↓ LV Diastolic Filling

↑ EF, ↑ CO (↑ Pulse Pressure)

↓ LVESV

↓ LVEDV

Reverse Remodeling

CRT Background

• CRT has been shown to be consistently associated with:
  – Reductions in LV size and volume
  – Increased Stroke Volume
  – Increased Ejection Fraction
  – Reduced Mitral Regurgitation
  – Improved exercise capacity
  – Improved QOL and functional capacity

• Effects of CRT on hospitalisation and mortality remain uncertain
Quality of Life and CRT

McAlister FA. Ann Intern Med 2004;141:381-390
CHF Hospitalizations with CRT

McAlister FA. Ann Intern Med 2004;141:381-390
Does CRT Prevent Death?
## All Cause Mortality and CRT

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>CRT Group, (n/n)</th>
<th>Control Group, (n/n)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATH-CHF, 2002 (19)</td>
<td>2/24</td>
<td>0/17</td>
<td>3.6 (0.18–70.54)</td>
</tr>
<tr>
<td>Garrigue et al., 2002 (20)</td>
<td>0/6</td>
<td>0/7</td>
<td>Excluded</td>
</tr>
<tr>
<td>MUSTIC-SR, 2001 (12)</td>
<td>1/29</td>
<td>0/29</td>
<td>3 (0.13–70.74)</td>
</tr>
<tr>
<td>MUSTIC-AF, 2002 (18)</td>
<td>1/25</td>
<td>0/18</td>
<td>2.19 (0.09–50.93)</td>
</tr>
<tr>
<td>RD-CHF, 2003 (22)</td>
<td>2/22</td>
<td>4/22</td>
<td>0.5 (0.1–2.45)</td>
</tr>
<tr>
<td>CONTAK-CD, 2003 (15)</td>
<td>11/245</td>
<td>16/245</td>
<td>0.69 (0.33–1.45)</td>
</tr>
<tr>
<td>MIRACLE, 2002 (13)</td>
<td>12/228</td>
<td>16/225</td>
<td>0.74 (0.36–1.53)</td>
</tr>
<tr>
<td>MIRACLE-ICD, 2003 (14)</td>
<td>24/272</td>
<td>27/282</td>
<td>0.92 (0.55–1.56)</td>
</tr>
<tr>
<td>COMPANION, 2004 (21)</td>
<td>131/617</td>
<td>39/154</td>
<td>0.84 (0.61–1.14)</td>
</tr>
<tr>
<td>COMPANION-CD, 2004 (21)</td>
<td>105/595</td>
<td>38/154</td>
<td>0.72 (0.52–0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
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<td>0.79 (0.66–0.96)</td>
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The COMPANION Trial

- 1520 patients* enrolled at 30 centers
- NYHA FC III/IV, LVEF ≤0.35, QRS ≥120 ms
- Optimal medical therapy vs. CRTp vs. CRTd with optimal medical therapy

*stopped early by DSMB; 2200 planned
COMPANION: 1° Endpoint

Death, Hospitalization or Outpatient Medication

Maybe CRTp is all that is needed

36% reduction in all-cause mortality, 10% absolute risk reduction

Current Status of ICD and CRT Therapy in Heart Failure

- 2 major CRT trials showed mortality reduction and reduction in hospitalizations:
  - CARE- HF: CRT without defibrillator (CRT-P)
  - COMPANION: CRT alone and CRT-D

  Class I recommendation for CRT

- The main challenge is to identify appropriate pts and implement appropriate therapy
Current Status of ICD and CRT Therapy in Heart Failure

- ICD and CRT for selected pts now is standard of care added to optimal medical therapy (OMT).

- ICD trials:
  - MADIT-II: post MI/LV dx (EF <30%) – reduction in all-cause mortality.
  - SCD-HEFT: Ischemic and non-ischemic class II/III HF, EF ≤35% despite OMT – reduction in all-cause mortality.

- CLASS I RECOMMENDATION FOR THESE PTS IN THE ABSENCE OF CONTRAINDICATIONS.
SCD-HeFT
Mortality Rate Overall Results

Hazard Ratio (97.5% CI)  P-Value
Amiodarone vs. Placebo  1.06 (0.86-1.30)  0.53
ICD vs. Placebo        0.77 (0.62-0.96)  0.007

23% REDUCTION IN ALL-CAUSE MORTALITY

MADIT II: Multicenter Automatic Defibrillator Implantation Trial II

Hazard Ratio = 0.69
(P = 0.016)

31% Relative Reduction

Conventional Therapy: 19.8% (N = 490)
ICD Therapy: 14.2% (N = 742)
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

For patients who have left ventricular ejection fraction (LVEF) less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, cardiac resynchronization therapy (CRT) with or without an ICD is indicated for the treatment of New York Heart Association (NYHA) functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.

For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.

For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

For patients with LVEF less than or equal to 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered.

CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing.

CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
3. Cardiac Resynchronisation Therapy (CRT) in Patients with Heart Failure

Recommendations for the use of cardiac resynchronization therapy by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an ICD (CRT-D) in HF patients.

Heart failure patients who remain symptomatic in NYHA Class II/III despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), left ventricular dilatation*, normal sinus rhythm and wide QRS complex (≥ 120 ms)

- Class I - Level of evidence A for CRT-P to reduce morbidity and mortality.
- CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year, Class I - Level of evidence B.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m²; LV end diastolic diameter > 30 mm/m (height).
3. Cardiac Resynchronisation Therapy (CRT) in Patients with Heart Failure

**Recommendations for the use of biventricular pacing in HF patients with a concomitant indication for permanent pacing.**

Heart failure patients with NYHA Class II-IV symptoms, low ejection fraction (LVEF ≤ 35%), left ventricular dilatation* and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker).

- Class IIa - Level of evidence C

**Recommendations for the use of an ICD combined with biventricular pacemaker (CRT-D) in HF patients with an indication for an ICD.**

Heart failure patients with a Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), left ventricular dilatation*, wide QRS complex (≥ 120ms).

- Class I - Level of evidence B.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m²; LV end diastolic diameter > 30 mm/m (height).
3. Cardiac Resynchronisation Therapy (CRT) in Patients with Heart Failure

**Recommendations for the use of biventricular pacing in HF patients with permanent atrial fibrillation.**

Heart failure patients who remain symptomatic in NYHA Class III-IV despite optimal pharmacological treatment, with low ejection fraction (LVEF ≤ 35%), LV dilatation*, permanent atrial fibrillation and indication for AV junction ablation.

- Class IIa - Level of evidence C.

* Left ventricular dilatation/Different criteria have been used to define LV dilatation in controlled studies on CRT: LV end diastolic diameter > 55 mm; LV end diastolic diameter > 30 mm/m², LV end diastolic diameter > 30 mm/m (height).
Possible Risks for Implantable Devices

• Vascular complications
• Long-term risk of infections
• Leads may break/fracture
• Recalls

BUT:

Significant benefits – evaluate patients carefully

Devices are very reliable and improving constantly
The Importance of Patient Selection

• Maintain relationship with EP/patient and family
• Need to understand:
  – Why treatment is indicated
  – What are the downsides
  – Will continue with medical therapy
  – Possibility of inappropriate shocks
IMPROVE HF: Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting

- 167 outpatient cardiology practices surveyed in the USA
- 15,381 pts with HF, previous MI/LV Dx
- Results for utilization of device therapy in eligible patients:
  - ICD/CRT-D 51%
  - CRT – 39%
- Median 27% of pts received all HF therapies for which they were potentially eligible on the basis of chart documentation.
- Use of guideline-recommended therapies by practices varied widely
- Need to translate outcomes of RCTs and guidelines into clinical practice

Fonarow G, Circ Heart Fail, 2008
Trial design: Patients with LV dysfunction (NYHA class I-II) and wide QRS were randomized to cardiac resynchronization therapy (CRT) (n = 419) or optimal medical therapy (n = 191).

Results

- Patients worsened: 16% with CRT vs. 21% with optimal medical therapy (p = 0.1)
- LV end-systolic volume index: decreased 18.4 ml/m² vs. 1.3 ml/m² (p < 0.0001), respectively
- Risk of heart failure hospitalization reduced with CRT (p = 0.03)

Conclusions

- CRT for mild heart failure does not reduce the percentage of patients that clinically worsen
- CRT improves LV end-systolic volume index and reduces the risk of hospitalization compared with optimal medical therapy

Presented Dr. Cecilia Linde at SCAI-ACC i2 Summit/ACC 2008
MADIT-CRT: Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy

- N=1820
- EF < 30%. Class I or II HF
- Randomized to CRT_D (60%) or ICD-only (40%)
- OMT
- Combined end-point of all-cause mortality/HF events when compared with ICD-only therapy
- Ongoing study
### Inclusion Criteria

- NYHA class III HF
- LVEF ≤ 35%
- Evidence of mechanical dyssynchrony
- QRS duration < 130ms

### Exclusion Criteria

- NYHA class I, II, or IV
- Permanent Atrial Fibrillation
- Recent MI, unstable angina or cardiac revascularization
- Prior cardiac resynchronization therapy

**The Resynchronization Therapy in Normal QRS (RethinQ) Study**

Beshai et al., NEJM, 2007

Study Sponsored by St. Jude Medical
• CRT did not improve Peak VO$_2$ during exercise in patients with NYHA Class III heart failure, QRS duration $<130$ ms, EF $\leq 35\%$ and mechanical dyssynchrony as specified in this trial.

• While there was a statistically significant improvement of NYHA class, a secondary endpoint, there was no improvement in quality-of-life, 6-minute walking test, or echocardiographic measures of reverse LV remodeling.

• A subgroup of patients with QRS duration between $120$ ms and $130$ ms demonstrated an improvement from CRT, however patients with QRS duration $< 120$ ms did not demonstrate improvement.

• The subgroup of patients stratified on the basis of cardiomyopathy etiology did not demonstrate an improvement in peak VO$_2$. 
Post-Implant Follow-Up

• Management outside EP office:
  – Cardiologists with HF training
  – Need for more practitioners as number of patients with devices grows

Optimisation of Device

  – Important clinical data is recorded by device to evaluate patient progress
  – Optimisation of AV, VV delays in CRT devices
CRT Therapy – The Future

- Possible new indications
- Better optimization techniques (echo, etc.)
- Better programming (VV, AV algorithms)
- Better therapy (multiple activation sites)
- Auto-optimization
- More sophisticated monitoring
Conclusion

• CRT benefits many but not all patients with severe heart failure, low left ventricular ejection fractions and wide QRS complexes
Stages of Therapy

Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention
  - Hospice
  - VAD, transplantation
  - Inotropes
  - Aldosterone antagonist, nesiritide
  - Consider multidisciplinary team
  - Revascularization, mitral-valve surgery
  - Cardiac resynchronization if bundle-branch block present

Dietary sodium restriction, diuretics, and digoxin
ACE inhibitors and beta-blockers in all patients
ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
Risk-factor reduction, patient and family education

Pharmacologic and Device Therapy Across the Continuum

- Post-MI LV dysfunction:
  - AIRE/SAVE (ramipril/captopril)
- Mild CHF:
  - SOLVD Treatment (enalapril)
- Moderate CHF:
  - US Carvedilol/MERIT (carvedilol/metoprolol)
- Severe CHF:
  - COPERNICUS (carvedilol)

- Mild CHF:
  - EPHESUS (eplerenone)
- Moderate CHF:
  - CHARM/Val-HeFT (candesartan/valsartan)
- Severe CHF:
  - RALES (spironolactone)

- MADIT, MUSTT (ICD)
- SCD-HeFT, MADIT-II (ICD)
- MIRACLE, COMPANION, MUSTIC (CRT +/- ICD)
- CARE-HF