Cardiac Resynchronization Therapy – A Cardiac Device with a Gender Gap in Outcomes

Kimberly A Selzman M.D. M.P.H. FHRS FACC
Associate Professor of Medicine, University of Utah
Director Cardiac Electrophysiology, Salt Lake City VA Hospital
Medical Officer, FDA, ODE, DCD, IEDB branch
Cardiac Resynchronization Therapy (CRT)
MADIT-CRT

- RCT of 1820 HF patients comparing ICD to CRT-D
- Mostly class II symptoms, ischemic class I
- QRS $\geq$ 130 ms
- Both ischemic and non-ischemic etiologies
- 25% of enrollees were women
- RESULTS: significant reduction in HF events
- FDA Panel: March 2010: subgroup analysis:
  - Women benefited more than men
  - Women had a greater reduction in HF events

Moss et al, NEJM 2009;361:1329-1338
MADIT-CRT Results

- Gender was a pre-specified analysis
- HFH/all cause mortality:
  - 69% reduction in women
  - 18% reduction in men
- Only women had a mortality benefit
- Women had greater LV remodeling

![Graph showing Kaplan-Meier Estimates of Cumulative Probability of Heart Failure or Death Stratified by Sex and ICD or CRT-D Therapy](image)
MADIT-CRT

• Why did women respond differently compared to men?
• More likely non-ischemic etiology (72% vs 36%)
• More likely left bundle branch block (LBBB) morphology (87% vs 65%)
• Less likely to have Afib, COPD
• Better response to Beta blockers?
• Of the 10 pre-specified subgroups, women and QRS $\geq$150ms showed greater benefit
• In the subset of subjects with non-ischemic CM and LBBB, HR of HR/death was 0.22
  Women 0.73 Men

They looked at all Super-Responders and performed a Regression Analysis.

- 191 Supers increased LVEF >14.5%
- Found 6 predictors;
  - Female sex
  - Non-ischemic
  - QRS > 150 ms
  - LBBB
  - BMI <30
  - Small LA volume

Hsu et al. JACC 2012;59:2366-73
Effect of gender on endpoints at 6 months

SMART AV Trial

- 846 CRT patients were enrolled and completed f/up
- 32% women
- Women had greater incidence of non-ischemic etiology and LBBB
- Only non-ischemic women responded to AV optimization

N=426 patients; 29% female
Longitudinal echo study
Looking at CCS and LVESVi
LV volumes: greater reduction in females
• Purpose: to look at subgroups in MIRACLE post hoc

• Looked at echo parameters, NYHA class, age, gender, HF etiology

• Women with CRT were more likely to be event free from first HF hospitalization or death, but not men
### Sex Related Differences in Patients’ Response to HF Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>arms</th>
<th>functional class</th>
<th>in efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT II(^{46,49})</td>
<td>Medical therapy vs ICD</td>
<td>≤30% I–IV</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>SCD-HeFT(^{48})</td>
<td>ICD vs amiodarone vs placebo</td>
<td>≤35% II–III</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>DEFINITE(^{47})</td>
<td>Medical therapy vs ICD</td>
<td>≤35% I–III</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>COMPANION(^{52})</td>
<td>Medical therapy vs CRT vs CRT-D</td>
<td>≤35% III–IV</td>
<td>Death or hospitalization for HF</td>
</tr>
<tr>
<td>CARE-HF trial(^{53})</td>
<td>Medical therapy vs CRT</td>
<td>≤35% III–IV</td>
<td>Death or hospitalization for HF</td>
</tr>
<tr>
<td>MADIT-CRT trial(^{55,58})</td>
<td>CRT-D vs ICD</td>
<td>≤30% I–II</td>
<td>Death or hospitalization for HF</td>
</tr>
<tr>
<td>REVERSE trial(^{56,59})</td>
<td>CRT (on vs off)</td>
<td>≤40% I–II</td>
<td>HF (clinical composite end point)</td>
</tr>
<tr>
<td>RAFT(^{57})</td>
<td>CRT-D vs ICD</td>
<td>≤30% II–III</td>
<td>Death or hospitalization for HF</td>
</tr>
</tbody>
</table>

Conclusions

- Women in the CRT trials tend to demonstrate greater benefit compared to men.
- Women in the CRT trials tend to have a greater proportion of non-ischemic CM and LBBB.
- However, the outcome difference cannot be solely explained by these baseline differences.
Cardiac Resynchronization Therapy – A Cardiac Device with a Gender Gap in Outcomes

Daniel Canos, MPH, PhD
FDA/CDRH/OSB/DEPI
FY 2009 OWH Grant

• Analysis of Sex Differences in Cardiac Resynchronization Therapy (CRT) Devices: Inclusion, Adverse Events, and Outcomes
  – Co-PI’s Kathryn O’Callaghan & Daniel Caños
  – Collaborators Ileana Piña & Kim Selzman

• Performed a systematic literature review to
  – Characterized the inclusion of women in CRT premarket studies;
  – Examined the published manuscripts on safety and effectiveness and reported on similarities and dissimilarities for men and women
SafeRx Project

- Collaboration among CMS, FDA, and Assistant Secretary for Planning and Evaluation (ASPE)
- Expands FDA’s capacity to evaluate postmarket product safety and performance, using information about exposure to medical products and outcomes in Medicare and Medicaid
- FDA has direct access to Medicare and Medicaid data through CMS SafeRx initiative with data management & programming via Acumen
Additional Efforts

• SafeRx Project CRT-D

• MDEpiNet
  – Evidence Synthesis Project with Harvard
National Medical Device Postmarket Surveillance Plan

Four specific actions to strengthen the U.S. postmarket surveillance system

1. Establish a Unique Device Identification (UDI) System and Promote Its Incorporation into Electronic Health Information;

2. Promote the Development of National and International Device Registries for Selected Products;

3. Modernize Adverse Event Reporting and Analysis; and,

SafeRx Project: CRT-D

CRT-D SafeRx Project Initiated in 2011

• **Study 1:** To examine the potential role of baseline characteristics in CRT-D utilization by characterizing these in the Medicare population and comparing this data to available premarket data.

• **Study 2:** To test the hypothesis that in CRT-D recipients, conventional LBBB diagnosis predicts better survival in women than men.
SafeRx Project: CRT-D

- FDA Principal Investigators
  - Daniel Caños
  - David Strauss

- CMS
  - Christopher Worrall
  - Jeffrey A. Kelman

- Funding: ASPE & FDA
All Medicare patients who:

- Received a CRT-D device (according to International Classification of Diseases, 9th revision [ICD-9], Clinical Modification codes);

- Between July 1, 2002 and December 31, 2008;

- And were continuously enrolled in Medicare Part A and B for ≥ 6 months prior to CRT-D implantation

144,642 CRT-D Patients

37,167 (26%) Female 107,475 (74%) Male
Study 1 Results Summary

• Comparison of Medicare post-market data to available premarket data shows characteristics that are:

  – Similar in pre- and post-market
    ▪ Proportion of women and men
  – Higher in post-market
    ▪ Diabetes
    ▪ Atrial fibrillation
    ▪ Hypertension
  – Lower in post-market
    ▪ Nonischemic cardiomyopathy
    ▪ LBBB

Study 2: Methods

- Compared prevalence and prognostic significance of co-morbidities and demographics of CRT-D recipients by sex

- Age
- Race
- Reason for Entry into Medicare
- Year of CRT-D Implantation
- Hypertension
- Ischemic Cardiomyopathy
- Prior MI
- LBBB
- RBBB
- Prior HF Hospitalization
- End Stage Renal Disease (ESRD)
- Diabetes
- Stroke
- Atrial Fibrillation

“Conventional LBBB”

• **Primary Endpoint**: All-cause mortality

• **Secondary Endpoint**: All-cause mortality or HF hospitalization
  • In-patient HF hospitalization as primary diagnosis (ICD-9-CM code)

• Determined univariate and multivariable Cox-proportional hazards associated with comorbidities (including LBBB)
  – Men
  – Women

Proportion of CRT-D Patients Surviving

Women had higher survival than men

LBBB had higher survival than non-LBBB

Mortality by Sex and LBBB:

- In women, LBBB associated with 31% lower death
- In men, LBBB associated with 16% lower death

Multivariable Adjusted Hazard Models

After controlling for comorbidities, conventional LBBB is associated with a larger mortality reduction in women than in men receiving CRT-D.

Confidence intervals do not overlap (interaction p<0.0001)

LBBB

HR: 0.74 [0.71-0.77]
26% lower hazard of mortality

HR: 0.85 [0.83-0.87]
15% lower hazard of mortality

SafeRx Study Conclusions

• LBBB diagnosis is associated with greater survival in women than men receiving CRT and this discrepancy is not explained by differences in comorbidities

• This may be because LBBB has different prognostic significance by sex

• However, we hypothesize that it is due to men having more false positive LBBB diagnoses by conventional LBBB ECG criteria
  – QRS duration was not available in Medicare to assess this … leads to next study in ACC ICD registry

Cardiac Resynchronization Therapy – A Cardiac Device with a Gender Gap in Outcomes

Robbert Zusterzeel, MD
FDA/CDRH/OSEL/DP
Why is LBBB Critical for CRT Response?

Minimal delay between septum and lateral wall

LARGE delay between septum and lateral wall

LBBB Criteria and QRS duration

• Conventional LBBB Criteria
  – QRS duration $\geq 120$ms & LV conduction delay (QS or rS in V1)

• Criteria are the same in women and men

• However, sex differences in QRS duration exist …

Average normal QRS duration Age 50+

- Men: 93 ms
- Women: 87 ms

$>5$ ms difference at baseline


With LBBB, Activation of septum and LV lateral wall is uncoupled

Thus difference in QRS duration doubles
Challenges to LBBB Criteria

• 1/3rd of patients diagnosed with LBBB by conventional criteria do not have activation consistent with LBBB

• New “strict” LBBB criteria were proposed
  • Require $\text{QRSD} \geq 130 \text{ ms}$ in women and $\text{QRSD} \geq 140 \text{ ms}$ in men, along with mid-QRS notching/slurring

Mechanical Dyssynchrony in Strict vs Non-strict LBBB

Two studies:
1\textsuperscript{st} comparison to MRI-tagging, 2\textsuperscript{nd} comparison to echocardiography

- Strict LBBB is significantly associated with a larger septal-to-lateral wall delay with MRI and unique LBBB mechanical activation pattern with echocardiography

Two Independent Studies Demonstrate that the new Strict LBBB Criteria Predict Benefit from CRT

**“False” LBBB Hazard Ratio 3.98 (p=0.005) for heart failure hospitalization or death**¹

**“True” LBBB leads to improvement in NYHA heart failure class and reduction in left ventricular dimensions**²

235 patients referred for ICD/CRT at Johns Hopkins underwent cardiac MRI

<table>
<thead>
<tr>
<th>CRT Subgroup</th>
<th>Women</th>
<th>Men</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar Size (% left ventricle)</td>
<td>5.0 ± 12.3</td>
<td>14.8 ± 12.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- Higher prevalence of nonischemic cardiomyopathy in women which is associated with smaller scar size
- Women had significantly lower scar size in the lateral wall, where the CRT left ventricular lead is placed

New FDA study

Sex Difference in Mortality Benefit from Cardiac Resynchronization Therapy

Follow-up of ~32,000 patients in the American College of Cardiology ICD Registry
Recent professional society guidelines limit the Class I indication for CRT to LBBB and QRS $\geq$ 150 ms

Women only represented $\sim$20% of patients in trials, thus findings primarily reflect outcomes in men.
Objective

• Based on our prior work on the importance of LBBB and sex differences in QRS duration, we will:

  – Compare long-term mortality outcomes of women and men receiving CRT-D among:
    • different combinations of ventricular conduction type and
    • QRS duration
Hypothesis

• We hypothesize that women have a mortality reduction at a lower QRS duration than men due to higher rate of false-positive LBBB diagnosis in men

• We hypothesize there to be no mortality difference in patients with non-LBBB conduction regardless of QRS duration
Methods

• ACC ICD registry
  – All primary prevention patients that received CRT-D between Jan 2006 – Sept 2009
  – QRS duration ≥ 120 ms
  – **LBBB or Other (RBBB+IVCD)**
  – No atrial fibrillation
  – No prior pacemaker or ICD

• Calculate mortality hazard ratios across QRS duration deciles for:
  – Women with LBBB
  – Men with LBBB
  – Women with Other conduction
  – Men with Other conduction

Corrected for important clinical covariates (including NYHA class, ischemic heart disease, diabetes, hypertension, ejection fraction, renal disease and heart failure duration)
Conclusions

• Strict LBBB criteria predict better response to CRT

• Need for more research to better define true LBBB and increase benefit-to-risk ratio for CRT separately in women and men

• Women have less myocardial scar than men

• FDA research on sex differences in CRT is ongoing
Take Home Messages

• Biological differences between women and men lead to a different response to medical therapy (CRT)

• Women benefit more than men from cardiac resynchronization therapy

• Increased benefit in women might be due to a higher prevalence of true left bundle branch block and non-ischemic cardiomyopathy and a lower prevalence of atrial fibrillation

• This highlights the importance of sex-specific analyses in medical device clinical trials
## Acknowledgements

<table>
<thead>
<tr>
<th>CDRH/OSEL/DP</th>
<th>CDRH/ODE/DCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• David Strauss</td>
<td>• William Sanders</td>
</tr>
<tr>
<td>• Loriano Galeotti</td>
<td>• Ileana Pina</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDRH/OSB/DEPI</th>
<th>CDRH/OCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Jamie Carpenter</td>
<td>• Kathryn O’Callaghan</td>
</tr>
<tr>
<td>• Naomi Herz</td>
<td></td>
</tr>
</tbody>
</table>

And all external collaborators
BACKUP SLIDES