The Role of Meta-analysis in Identifying Diversity in Efficacy and Safety

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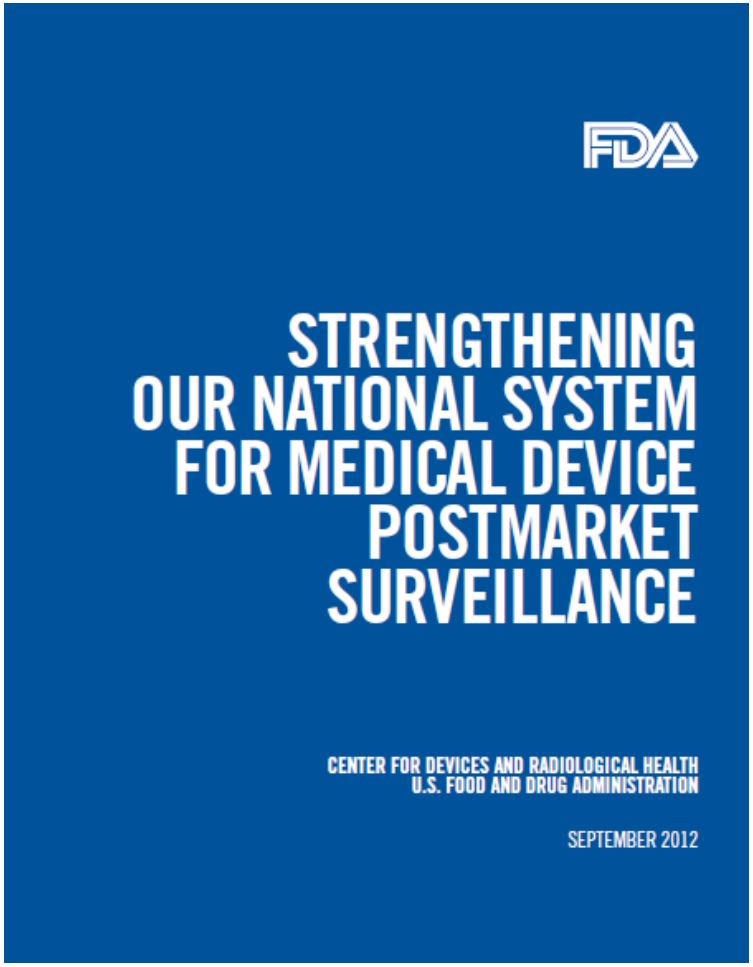
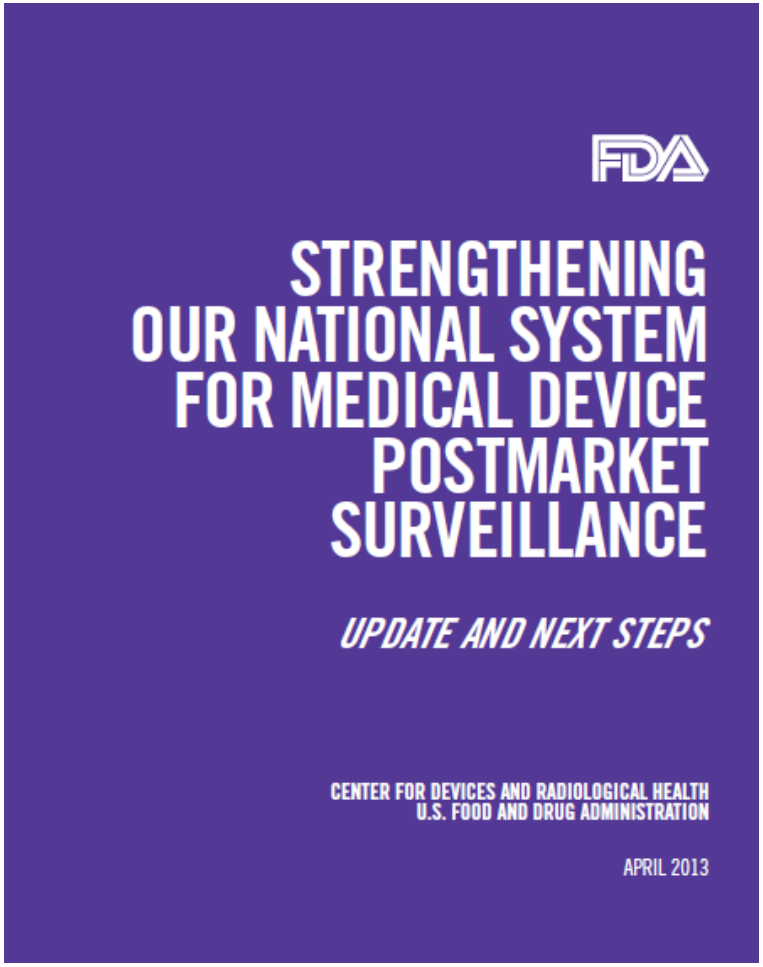
Vision: Strengthening Our National System

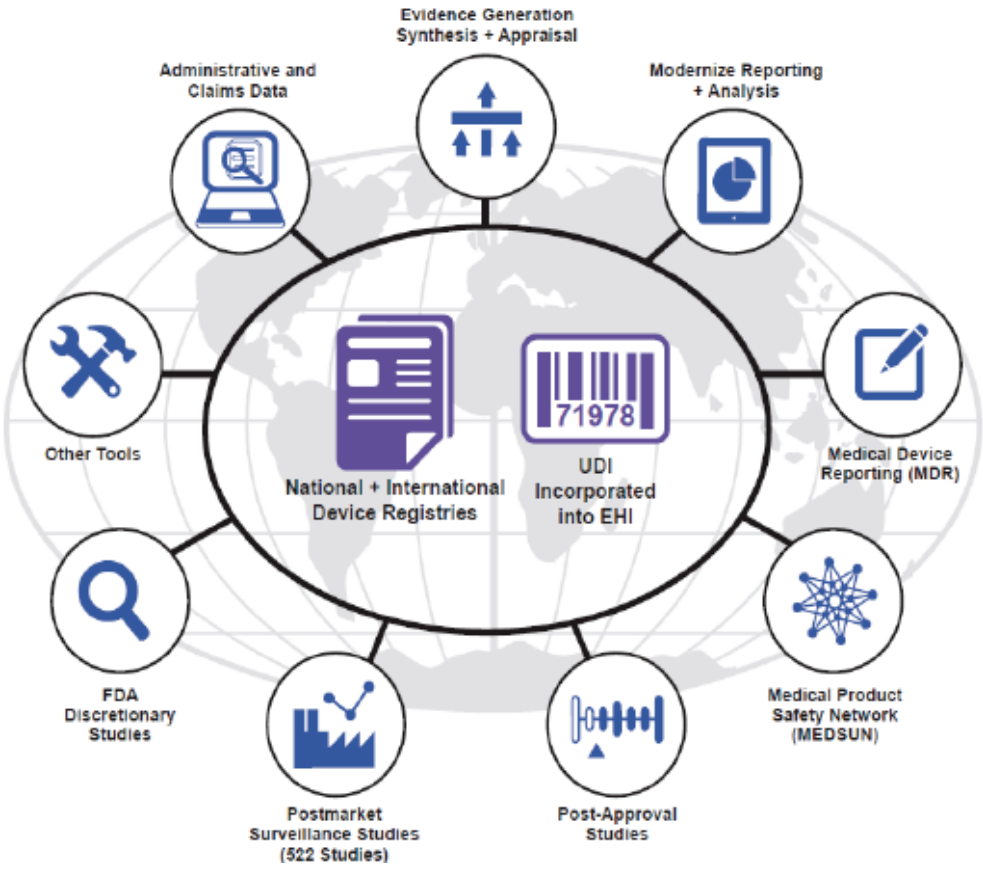




http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM301924.pdf
http://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf

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,

4. **Develop and Use New Methods for Evidence Generation, Synthesis and Appraisal.**

Food and Drug Administration Safety and Innovation Act (FDASIA) 2012

SEC. 907. Reporting of Inclusion of Demographic Subgroups in Clinical Trials and Data Analysis in Applications for Drugs Biologics and Devices

FDASIA Section 907 Requirement

1. FDA reported on how and to what extent information is available on safety and effectiveness differences by demographic subgroups (8/13)[1]
2. Action plan with recommendations (8/14):
   - to improve the completeness and quality of analyses of data on demographic subgroups
   - on the inclusion or lack of such data in labeling
   - improve the public availability of such data to patients, health care providers, and researchers

1. http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf
2. http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf

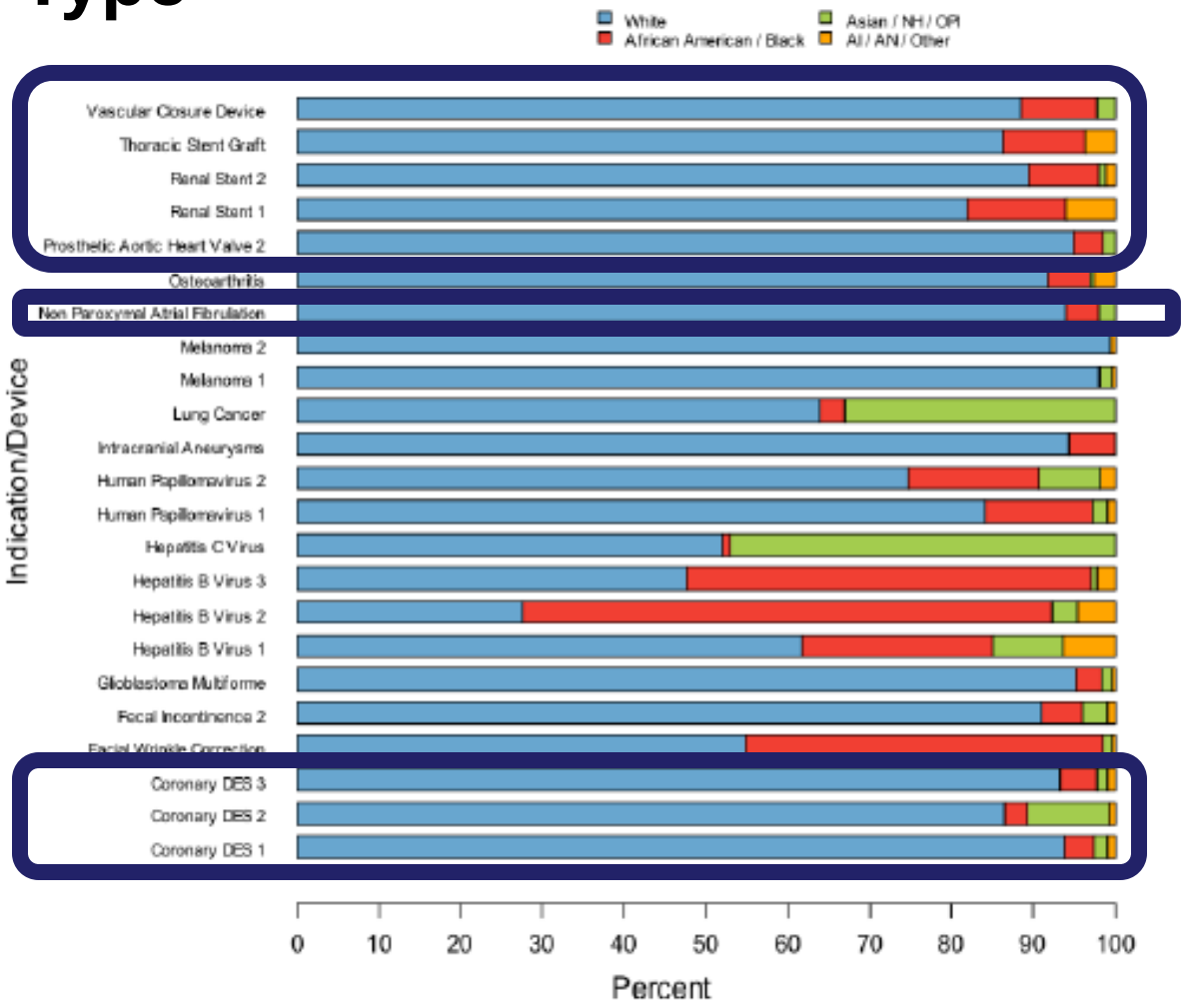
FDA Section 907 Report

- Inclusion of women varied by device product area, attributable to many factors that can influence interpretation and clinical relevance of demographic information (e.g., intended population, disease prevalence, etc.). [1]
- 88% of PMA applications contained sex subgroup analysis,
  - 63% of these contained labeling statements and/or FDA summary review on sex subgroup analysis.

1. http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf

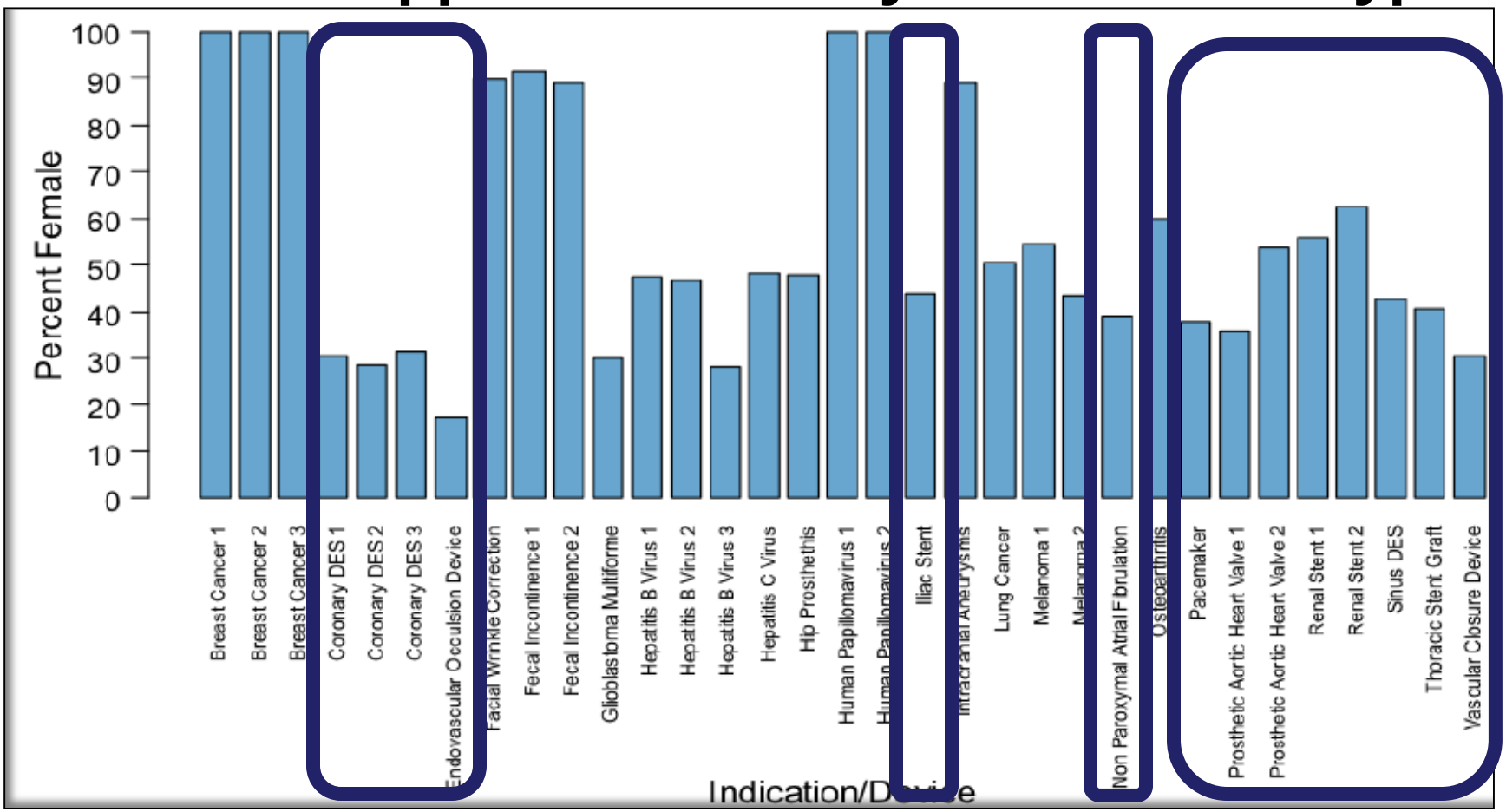
FDA Section 907 Report

2011 PMA Approvals: Race by Submission Type

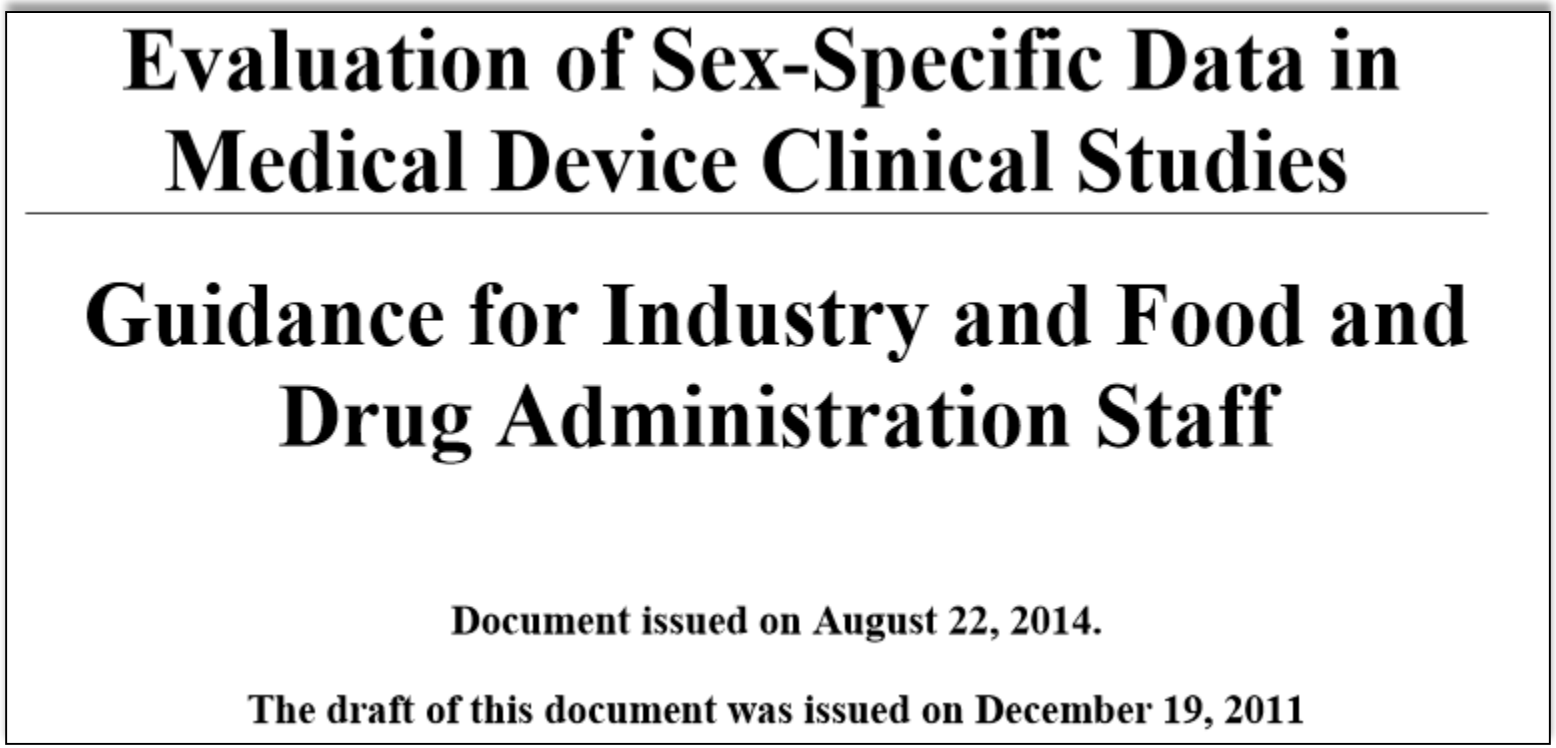


FDA Section 907 Report

2011 PMA Approvals: Sex by Submission Type



CDRH Guidance Document



Evaluation of Sex-Specific Data in Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 22, 2014.

The draft of this document was issued on December 19, 2011

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf

Goal

Fulfill CDRH's mission[1] to:

- Protect and promote public health
- Provide understandable and accessible science-based information about the products we oversee
- Advance regulatory science

AND

Address FDASIA 2012 Section 907 Action Plan Priorities:

- Priority 1: Improve the Completeness and Quality of Demographic Subgroup Data (Quality)
- Priority 3: Making demographic subgroup data more available and transparent (Transparency)

[1]CDRH Mission, Vision and Shared Values 2013

[2]http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf

Example of Regulatory Science

Research

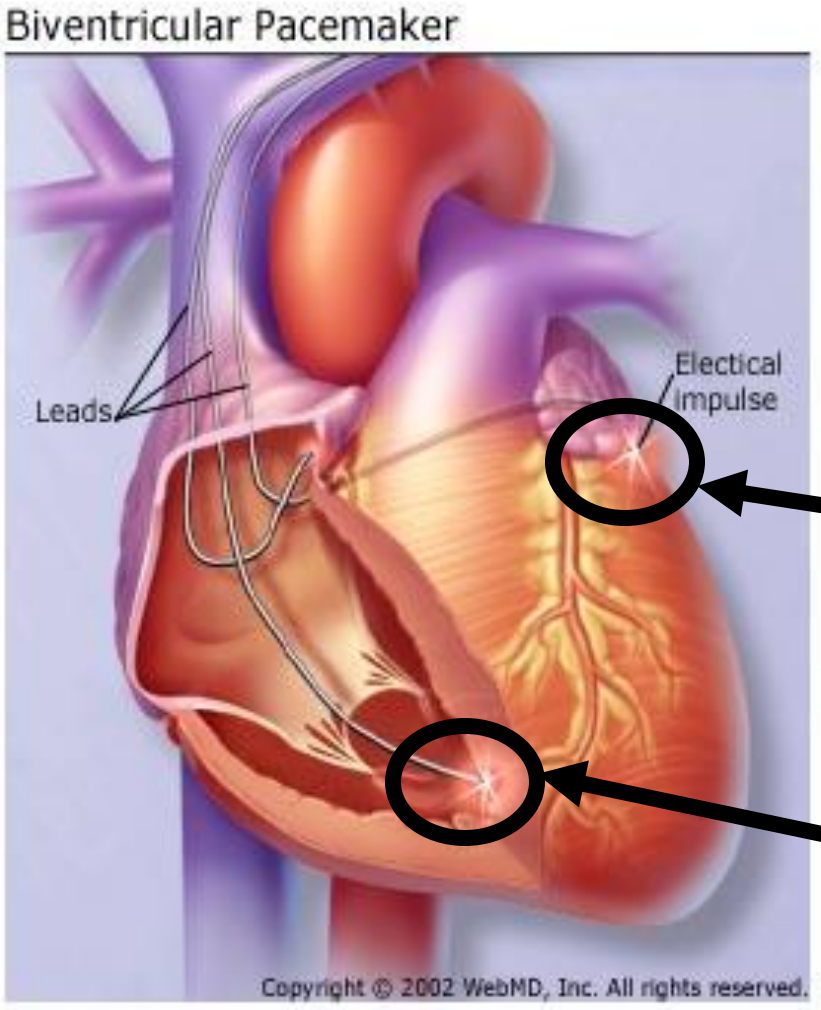
Original Investigation

Cardiac Resynchronization Therapy in Women
US Food and Drug Administration Meta-analysis of Patient-Level Data

Robbert Zusterzeel, MD; Kimberly A. Selzman, MD, MPH; William E. Sanders, MD, MBA; Daniel A. Caños, PhD, MPH; Kathryn M. O'Callaghan, BSE; Jamie L. Carpenter, MSPH; Ileana L. Piña, MD, MPH; David G. Strauss, MD, PhD

Zusterzeel, R., et al. (2014). Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med, 174*(8), 1340-1348, doi:10.1001/jamainternmed.2014.2717.

Cardiac Resynchronization Therapy



Additional LV lead for CRT

Traditional RV pacing lead

Shown to improve heart failure symptoms, reduce heart failure hospitalization and reduce mortality

Background

- Recent professional society guidelines limit the highest indication for CRT to LBBB and QRS ≥ 150 ms
- Per guidelines, decision largely based on 2 meta-analyses that looked separately at LBBB and QRS duration
- Prior meta analyses were unable to look at the interaction between these ECG characteristics
- Women only represented ~20% of patients in trials, thus findings “driven” by men

2012 Updated Guidelines

J Am Coll Cardiol. 2013;61:e6.
Circulation. 2013;127:e283.
Heart Rhythm 2012;9:1737.

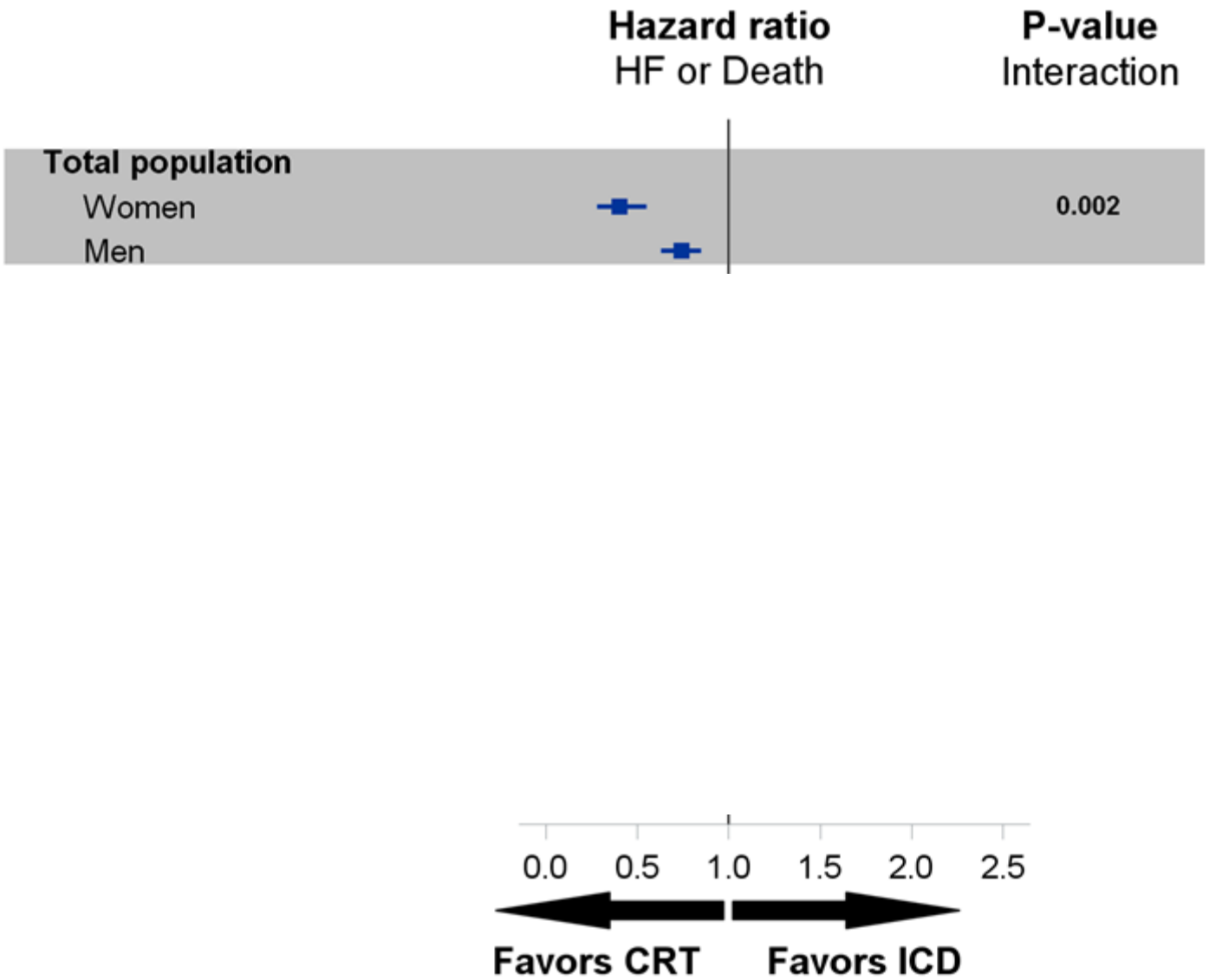
Meta-Analyses

Sipahi I, et al. *Arch Intern Med.* 2011;171:1454.
Sipahi, et al. *Am Heart J*. 2012;163:260.

Methods

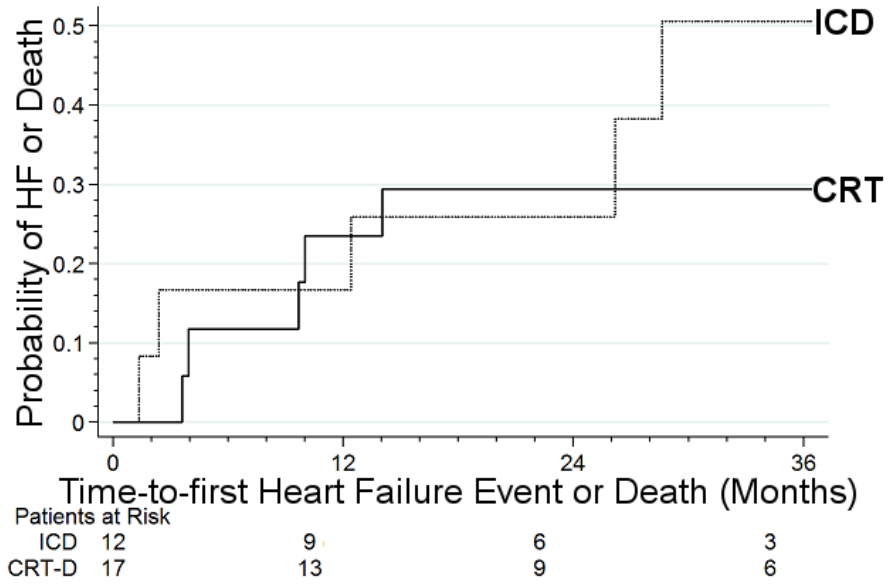
- Combined patient-level data from MADIT-CRT, RAFT and REVERSE
- Submitted to FDA as part of pre-market approval applications
- Calculated outcomes in CRT and ICD populations stratified by sex
  - In conventional LBBB patients across QRS duration
  - Used random effects modeling to address potential heterogeneity between trials
- End points:
  - Heart failure event or death (primary)
  - All-cause mortality (secondary)

Results by Sex and Subgroups



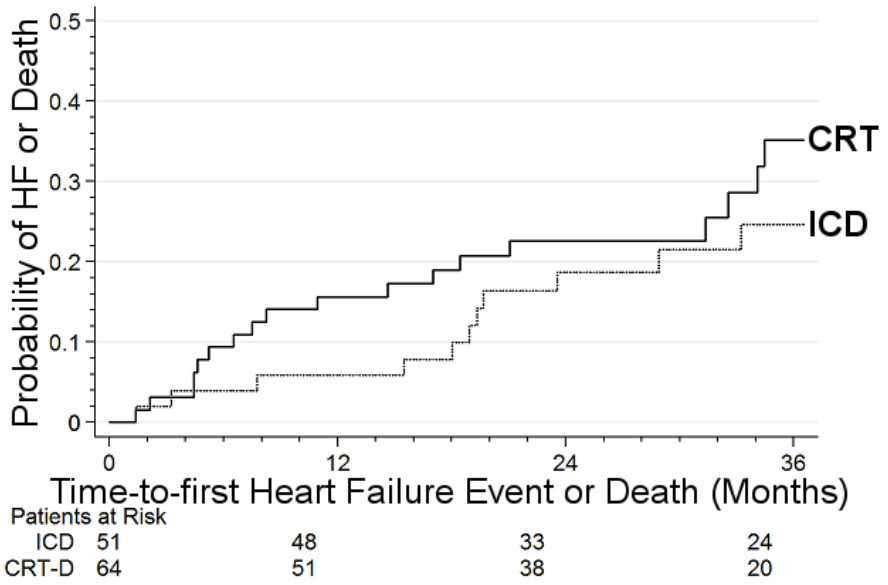
LBBB & QRS 120-129 HF or Death

Women



HR = 0.64 [0.18-2.20], p = 0.48

Men

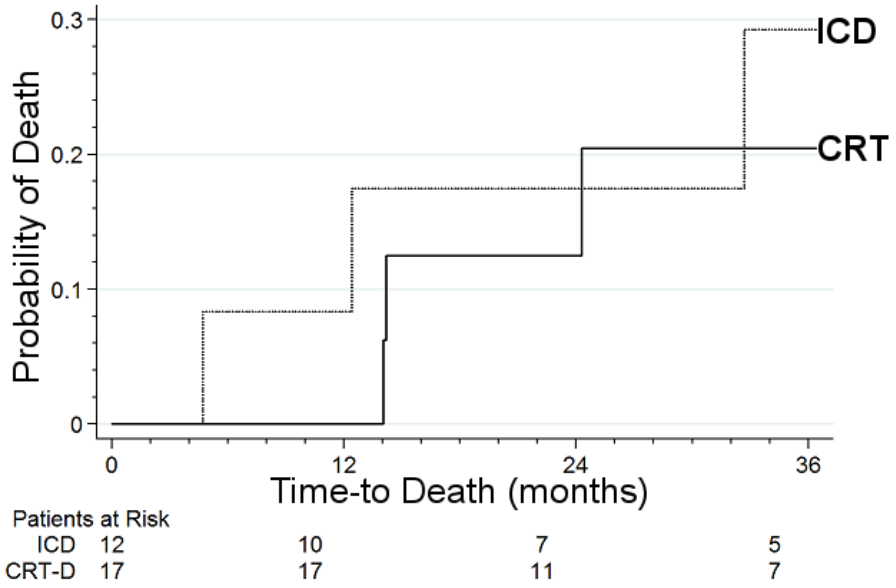


HR = 1.49 [0.70-3.16], p = 0.30

No effect in women or men with LBBB and QRS duration 120-129 ms

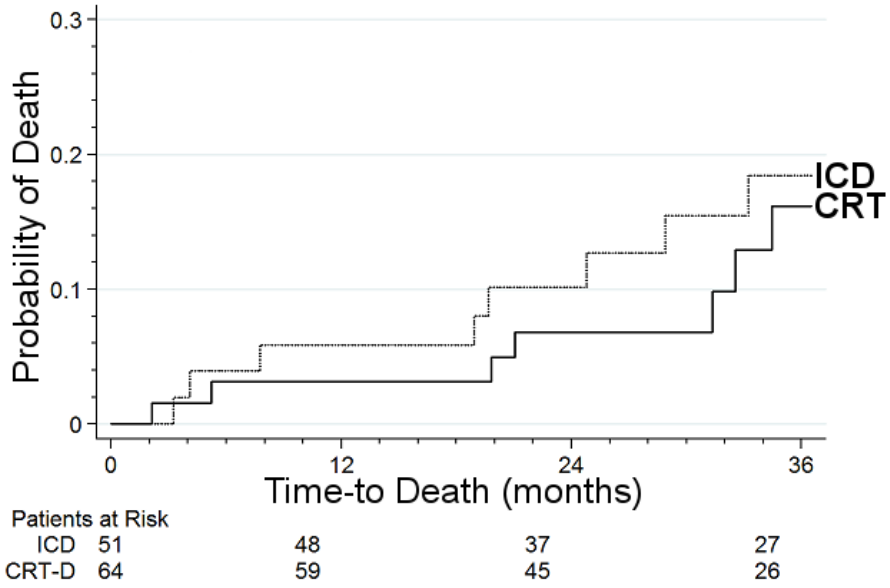
LBBB & QRS 120-129 Death

Women



HR = 0.63 [0.13-3.13], p = 0.57

Men

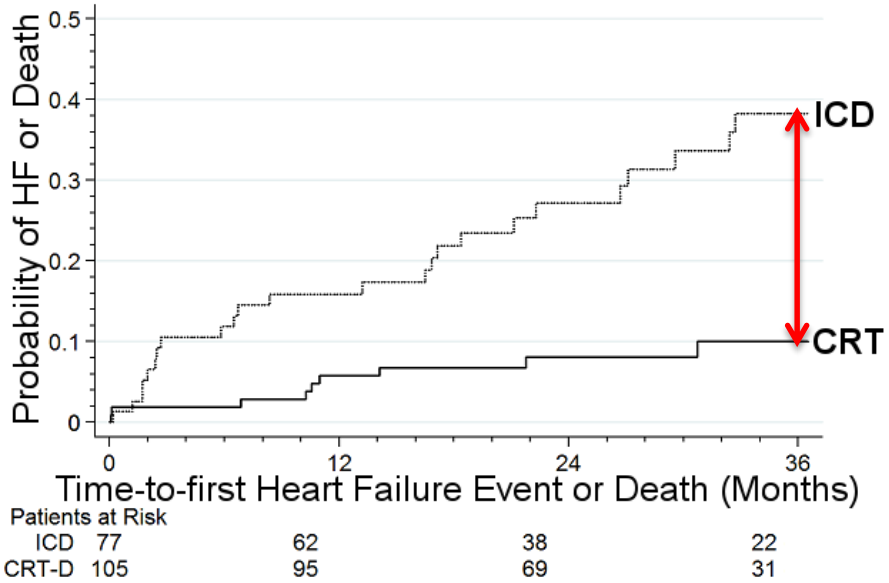


HR = 0.76 [0.27-2.09], p = 0.59

No effect in women or men with LBBB and QRS duration 120-129 ms

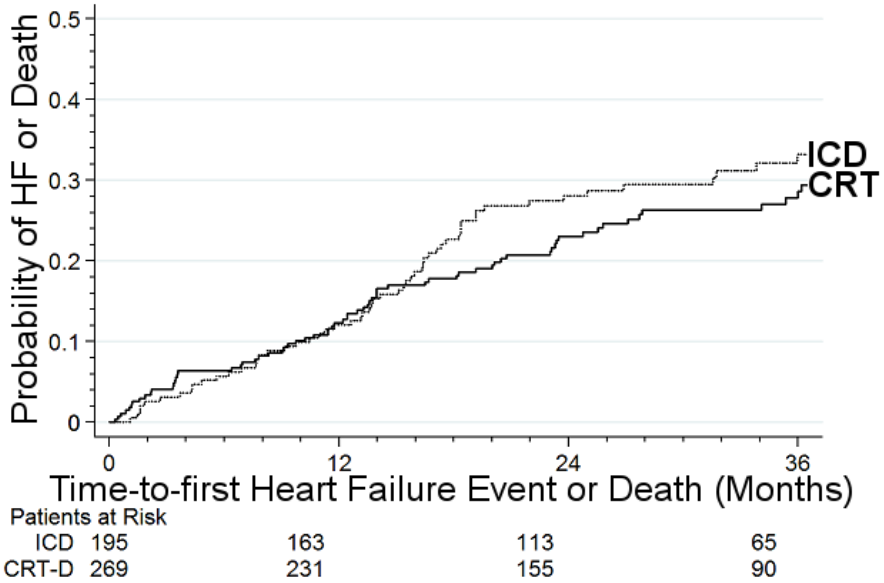
LBBB & QRS 130-149 HF or Death

Women



HR = 0.24 [0.11-0.53], p < 0.001

Men



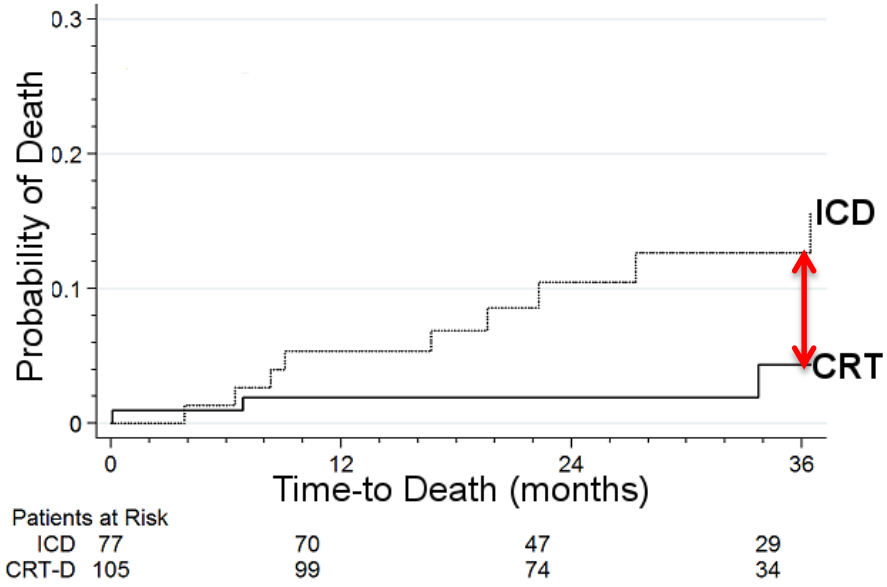
HR = 0.85 [0.60-1.21], p = 0.38

Significant 76% reduction in HF-event/death in LBBB women and QRS 130-149 ms

No significant effect in men

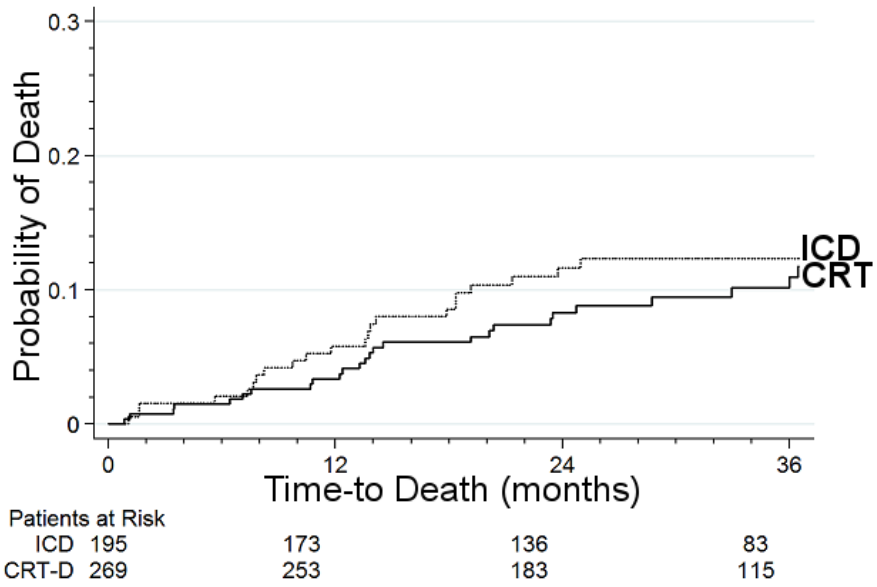
LBBB & QRS 130-149 Death

Women



HR = 0.24 [0.06-0.89], p = 0.03

Men



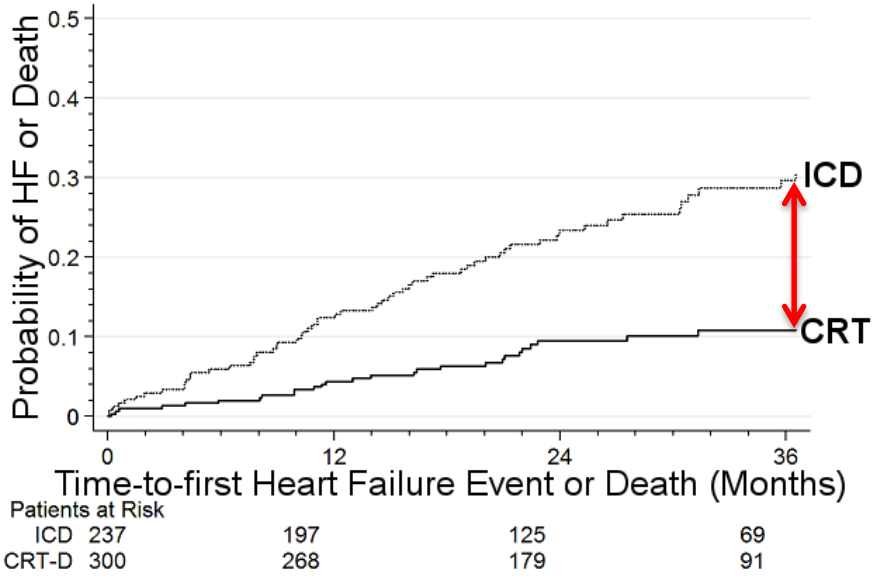
HR = 0.86 [0.49-1.52], p = 0.60

Significant 76% mortality reduction in LBBB women and QRS 130-149 ms

No significant effect in men

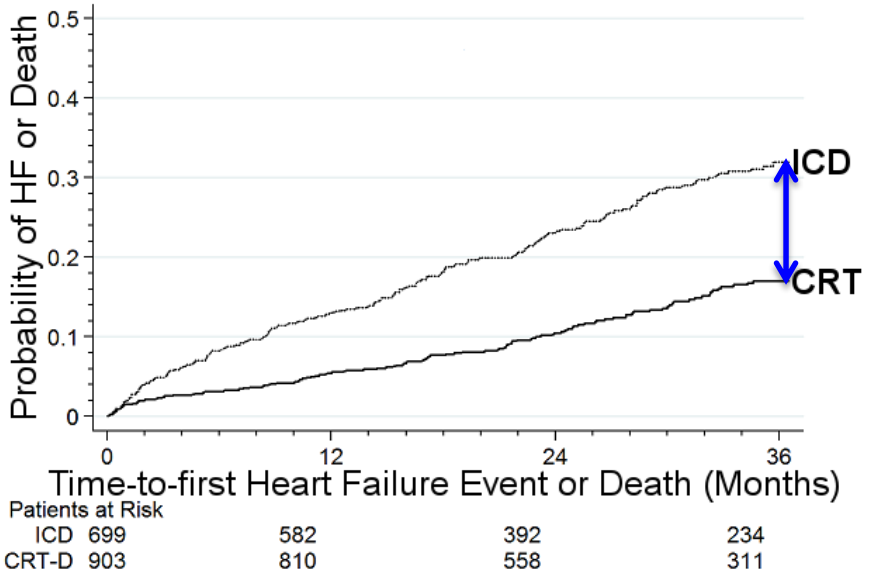
LBBB & QRS ≥ 150 HF or Death

Women



HR = 0.33 [0.21-0.52], p < 0.001

Men



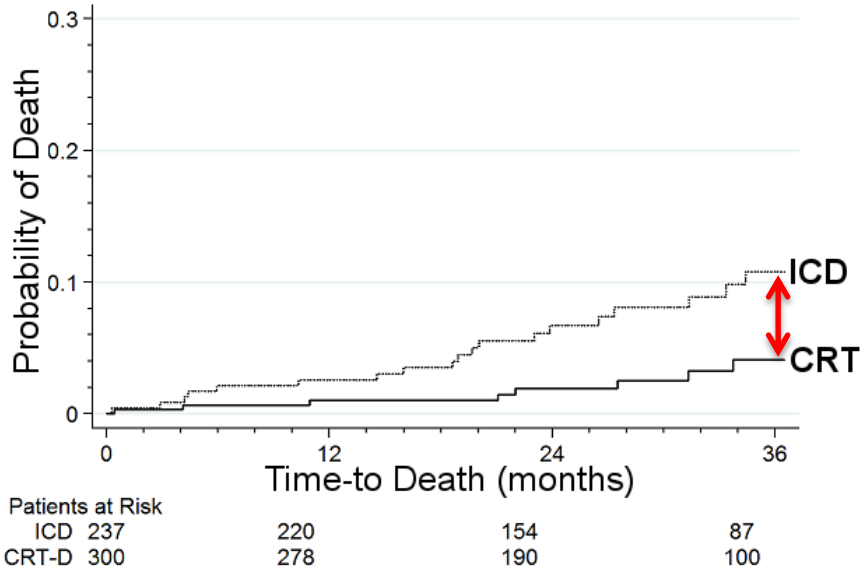
HR = 0.47 [0.37-0.59], p < 0.001

Significant 67% reduction in HF-event/death in LBBB women and QRS ≥ 150 ms

Significant 53% reduction in HF-event/death in LBBB men and QRS ≥ 150 ms

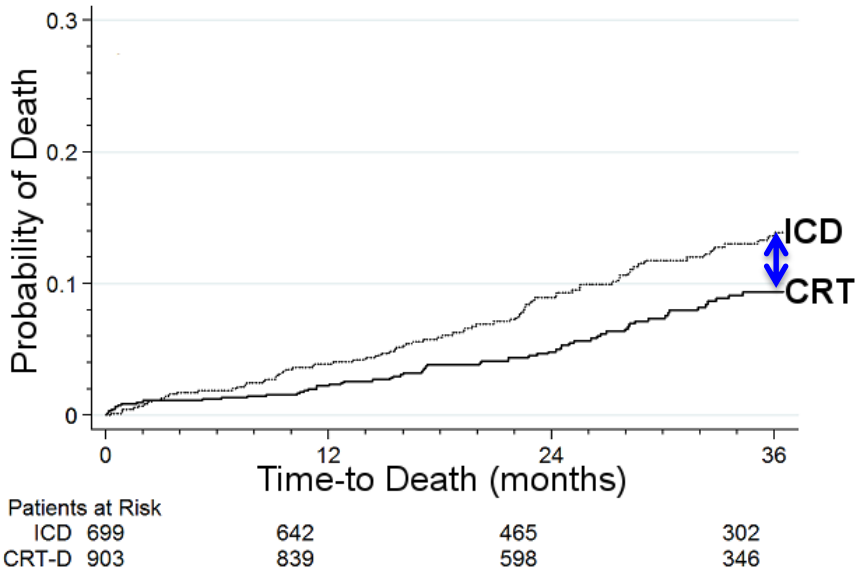
LBBB & QRS ≥ 150 Death

Women



HR = 0.36 [0.16-0.82], p = 0.01

Men



HR = 0.65 [0.47-0.91], p = 0.01

Significant 64% mortality reduction in LBBB women and QRS ≥ 150 ms

Significant 35% mortality reduction in LBBB men and QRS ≥ 150 ms

Study Findings – Women

- CRT causes a significant decrease in HF/death and death alone in women with conventional LBBB and QRS dur ≥ 130 ms
  - Specifically, 76% reduction in HF/death and 76% reduction in death alone with QRS 130-149 ms
  - Important to communicate because many physicians are most influenced by professional society guidelines and may not offer CRT to women with QRS <150 ms

Study Findings – Men

- CRT causes a significant decrease in HF/death and death alone in men with conventional LBBB and QRS ≥ 150 ms
  - Consistent with prior meta analyses that looked at men and women combined and professional society guidelines
- No significant effect of CRT in men with conventional LBBB and QRS 130-149 ms

Conclusions

- Women were underrepresented in CRT clinical trials and pooling data allowed for the investigation of CRT effects in women
  - FDA is in a unique position to perform this analysis due to availability of patient-level data
- We observed that women benefit from CRT at a lower QRS duration than men
  - Result could not have been obtained from study-level meta-analyses