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Gender Differences in the Utilization & Response to Implantable Device Therapy (Implantable Cardioverter Defibrillators/ Cardiac Resynchronization Therapy)



BACKGROUND

- Cardiovascular disease has been a cause of more deaths in women than men since 1985

Historical perspective:

1977- Women of childbearing age restricted from phase 1 and early phase 2 clinical trials in the wake of birth defects from thalidomide and diethylstilbestrol.

1985 CV mortality exceeded in women vs men causing alarm in health care communities.



BACKGROUND

- Public Health Service TF on Women's Health Issues: compromise in quality of Health information and the health care available to and received by women.
- NIH establishes Office of Research on Women's Health.
- US Dept of Health and Human Services (HHS) establishes Office on Women's Health (OWH) promoting inclusion of women in research.
- In 2008 HHS-OWH provided with funding for women's health research and suggest to Congress future research.



Gender Differences or Gender Disparities?

- Lack of equality or the presence of inequality.
- WHO: unnecessary, avoidable and considered unfair and unjust differences in health define inequity.
- WHO: equity in healthcare as equal access for equal need, equal utilization and equal quality of care.

Classes of Recommendation

Definition : Suggested wording to use

Class I Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective : Is recommended /Is indicated

Class II Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.

--Class IIa Weight of evidence/opinion is in favor of usefulness/efficiency : Should be considered

--Class IIb Usefulness/efficiency is less well established by evidence/opinion : May be considered

Class III Evidence or general agreement that Is not recommended the given treatment or procedure is not useful/effective, and in some cases may be harmful : Is not recommended.

Level of Evidence A

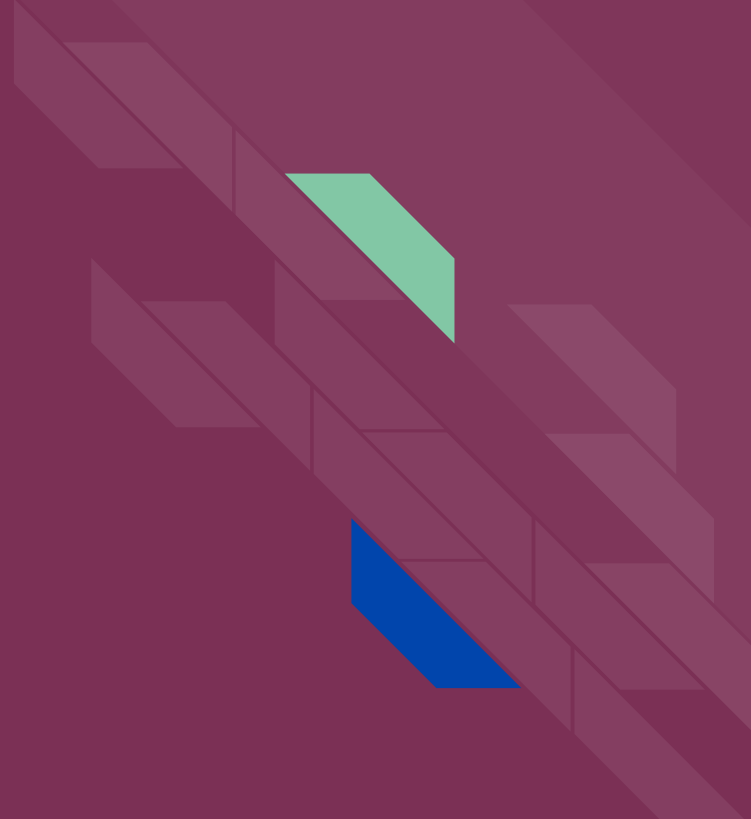
- Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B

- Data derived from a single randomized clinical trial or large non-randomized studies.

Level of Evidence C

- Consensus of opinion of the experts and/or small studies, retrospective studies, registries.





Indications for CRT-D

CRT has been shown to reduce morbidity and mortality in selected patients with systolic heart failure.

Guidelines.

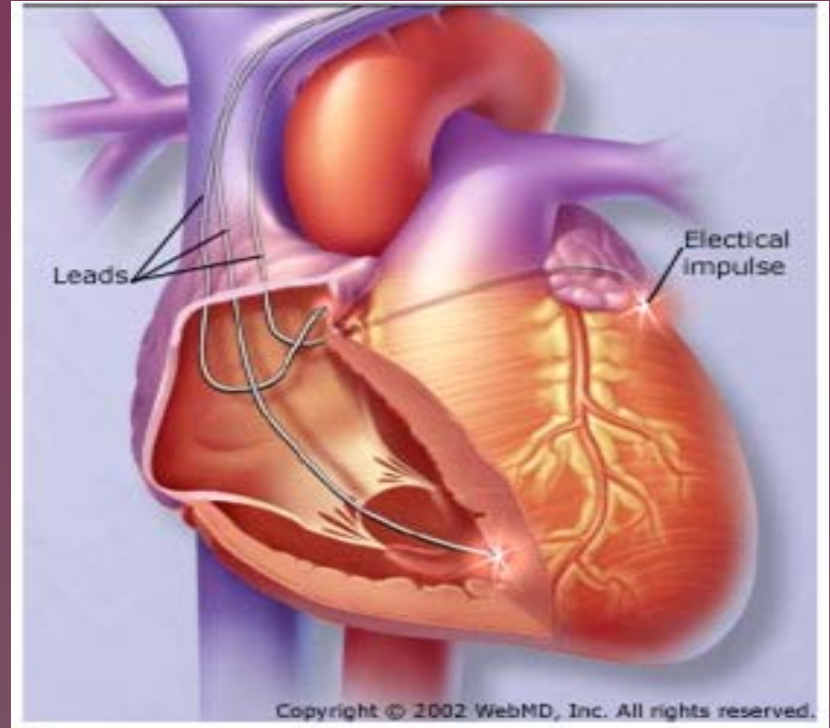
- All cardiac societies' guidelines agree that all patients with a LBBB and or a QRS duration of ≥ 150 ms should be offered a CRT device provided they are in NYHA heart failure functional class III
- International Guidelines:
 - All patients with LBBB/ QRS d of ≥ 150 ms should get a CRT device with NYHA functional class II and ambulatory class IV.
 - Patients with LBBB and QRSd > 120 ms have shown a better prognosis with CRT implantation.

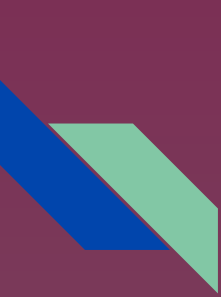
Guidelines

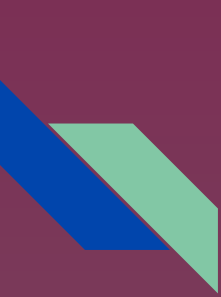
- BiVentricular pacing superior to RV pacing in patients with Heart failure and high degree of AV block or those that require a high % pacing.
- Class I recommendations for CRT-D in patients requiring an ICD with CRT criteria met
 - >QRS duration between 130 and 149 ms and
 - >recommended for QRS >150 ms.

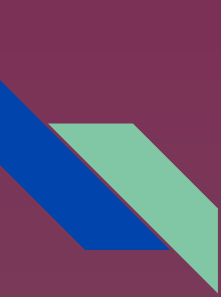
What is **C**ardiac **R**esynchronization Therapy (**CRT**)

Bi Ventricular or Multisite Ventricular pacing to synchronize the interventricular synchrony and improve the ejection fraction.



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- The largest studies of cardiac resynchronization therapy (CRT) implants in the U.S. show men were significantly more likely to undergo CRT therapy with an implantable cardioverter-defibrillator (ICD) than women—despite predictors that indicate women demonstrate greater ICD efficacy
 - Sexual disparity in implants increased significantly from pacemaker implant to CRT-D implants.
 - With increasing clinical demand there is an urgent need for implant practices to improve alignment of device selection with those most likely to benefit

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- Annual incidence of SCD 200,000 to 450,000 in the US.
 - Major risk factor is heart failure with reduced ejection fraction.
 - Several large RCT have demonstrated mortality benefit from ICD implantation for both primary and secondary prevention.
 - Significant under-representation of women in these trials.

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- Numerous studies have demonstrated ICDs and CRTS benefit eligible patients with better outcomes in women.
 - Women remain severely underrepresented in these trials.
 - Women less likely to receive this life-saving therapy



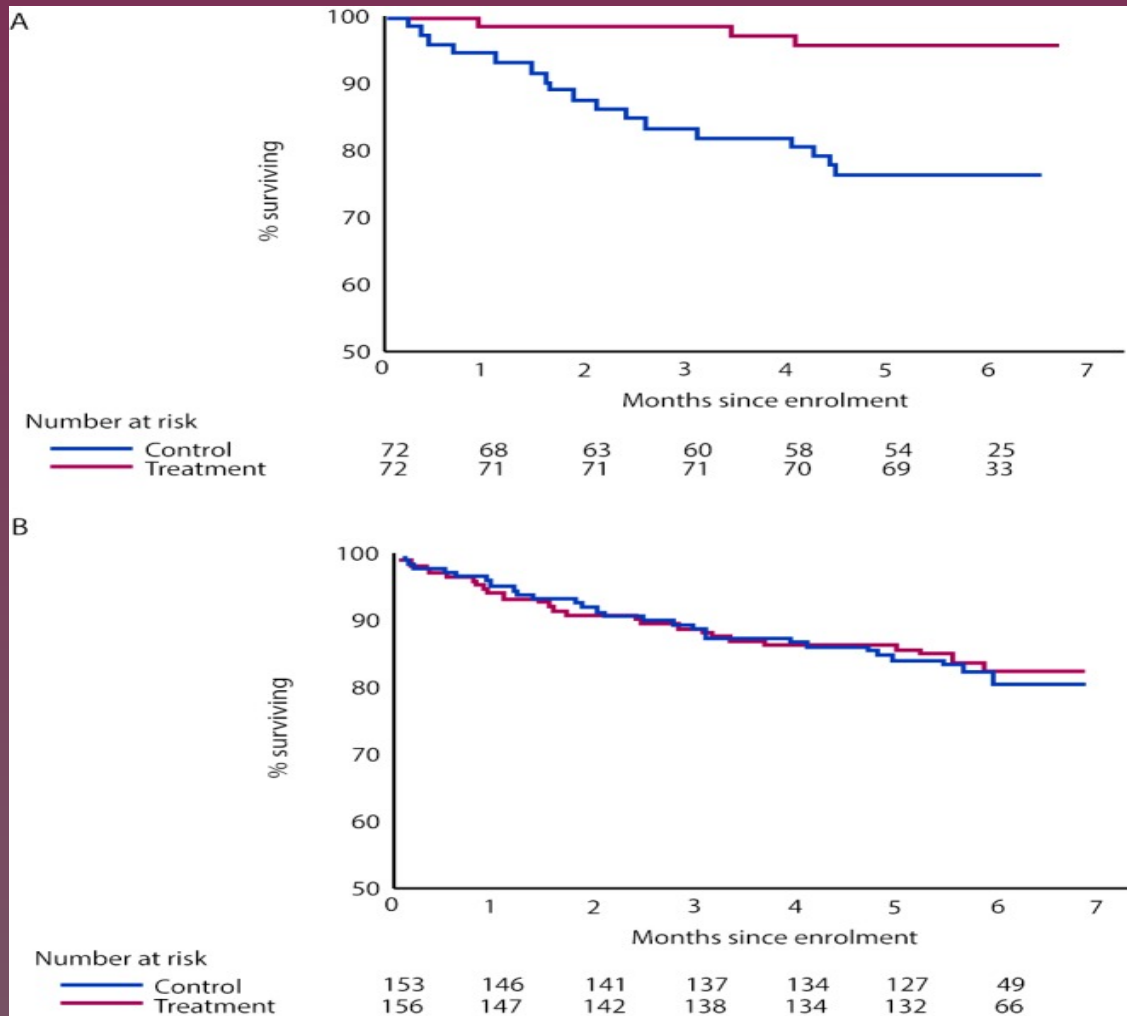
Analyses form Trials

MIRACLE: Women receiving CRT had reduced hospitalizations for heart failure and reduce combined endpoints of HF hospitalization and death.

MADIT-CRT Trial: 34% reduction in risk of HF or death with CRT-D vs ICD alone. Women showed greater reductions in HF, HF or death and all cause mortality with CRT-D than men.

Women had greater reverse cardiac remodelling than men.

Time to first HF hospitalization or death in Women (top) and Men (bottom) treated with CRT vs control.





Analyses from Trials.

MASCOT: For management of AF suppression in AF-HF: reduced all cause mortality, cardiac death and hospitalizations in women.

Independant swedish study: Female gender the only independent predictor of lower all-cause mortality.

Varma, Heart Rhythm 2014: NICMP with LBBB favorable response women vs men 86% vs 36% for QRS < 150 ms and 83% vs 39% for QRS > 150 ms

33% ♂

CRT Response Score for Men

47% ♀

CRT Response Score for Women

More Men
Received
CRT Device

80%

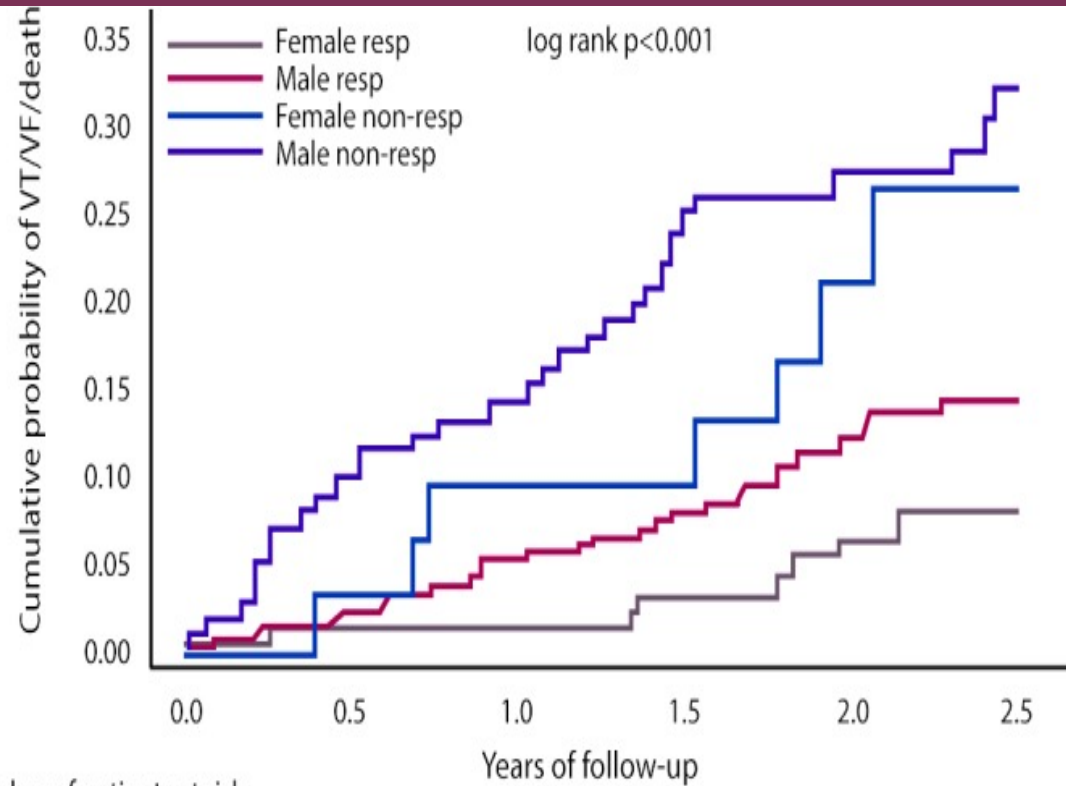


Fewer Women
Received
CRT Device

73%



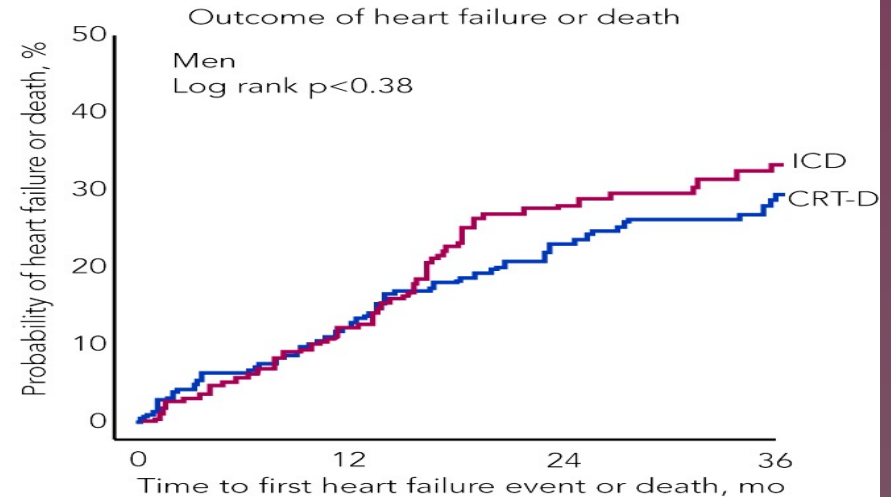
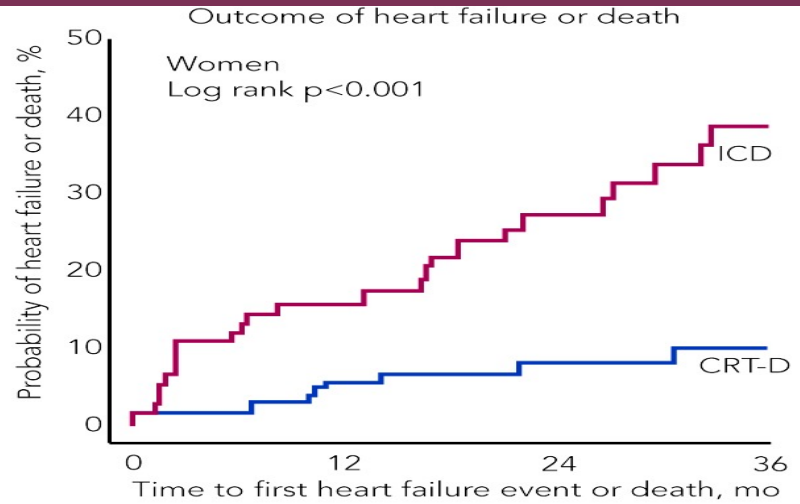
Mortality benefit for heart failure or death higher in women than men receiving CRT-D based on the CRT response in the subject, showing superiority favoring women.



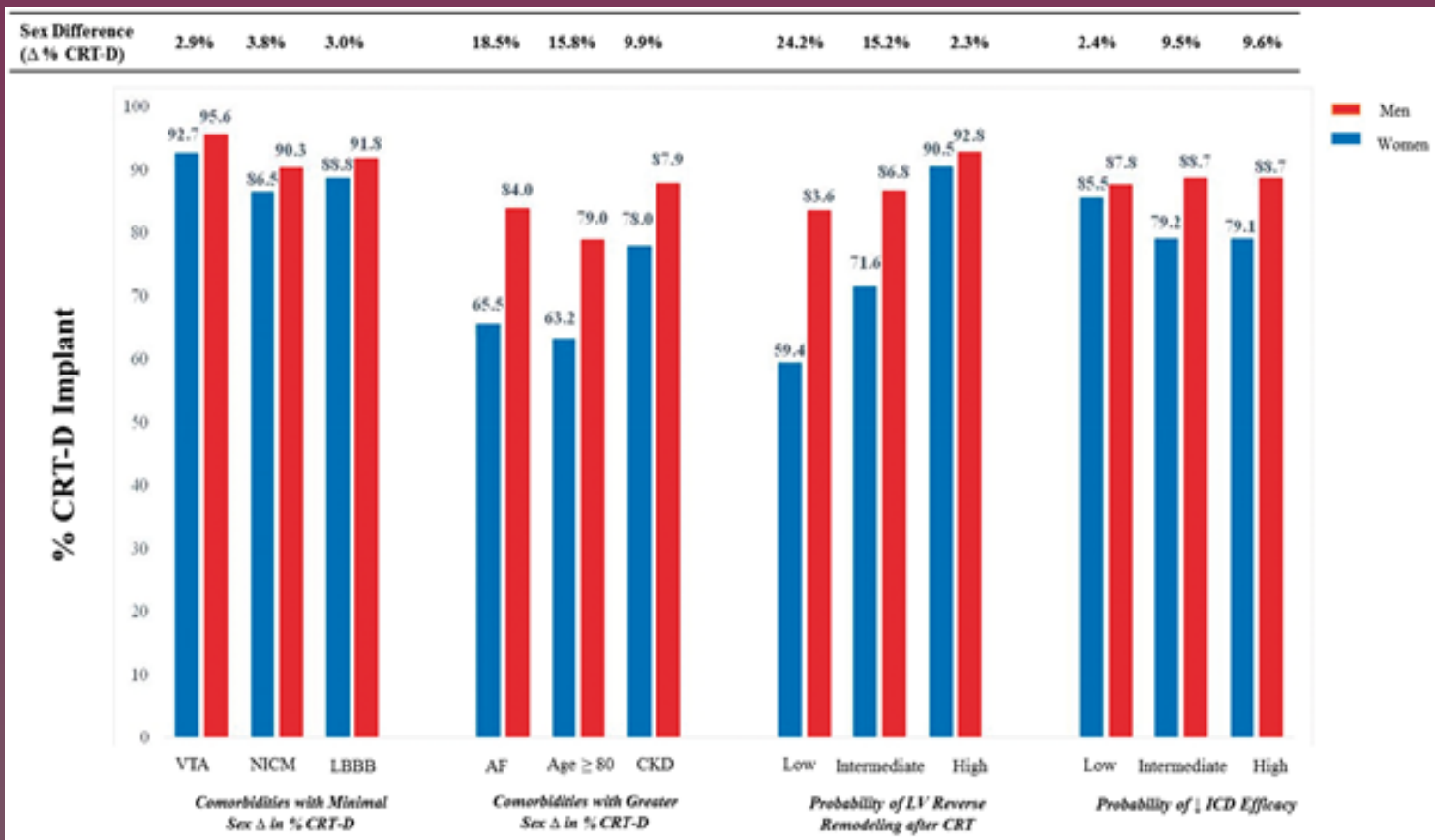
Number of patients at risk

Female resp	129	127 (0.02)	123 (0.02)	104 (0.03)	78 (0.07)	48 (0.08)
Male resp	262	255 (0.02)	242 (0.05)	193 (0.08)	141 (0.12)	82 (0.14)
Female non-resp	31	30 (0.03)	28 (0.10)	26 (0.10)	17 (0.21)	12 (0.25)
Male non-resp	112	101 (0.10)	94 (0.14)	73 (0.25)	58 (0.27)	36 (0.32)

Gender based outcomes in
LBBB and wide QRS of 130 to
149 ms.



Sex differences in CRT-D implantation: impact of demographics, comorbidities, and predicted device efficacy





ICD trials

- MUSTT: women made up 10% of the randomised patients and 16% of those in registry .

-No difference in mortality in the EP vs registry group.
Insufficient power due to small number of women enrolled.

- MADIT-2: 16% women, Sicker women (more advanced HF, DM, HTN, LBBB). No difference in ICD vs standard medical therapy in both groups

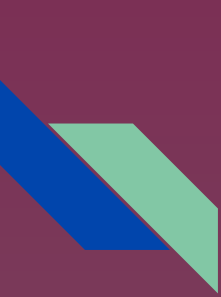
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- SCD-HeFT and DeFINITE both showed no mortality benefit for women in receiving ICD vs placebo or medication.
 - Analysis of multiple trials randomized 490 eligible women to ICD compared to 490 eligible women with no ICD showing survival benefit in the ICD arm. It concluded that both sexes derived equal survival benefit from ICD implant for primary prevention.

Table 1: Major Implantable Cardioverter-Defibrillator Trials and their Outcomes

Study	Total Population	Indication	% Women	Groups	Mortality
MADIT I ²	196	Primary prevention of SCD	8	Antiarrhythmic drug therapy versus ICD	54 % relative reduction in mortality in ICD group; not stratified by sex
MADIT II ⁴	1,232	Primary prevention of SCD	16	ICD versus medical therapy	Men: HR 0.66; p=0.011 Women: HR 0.57; p=0.132
SCD-HeFT ⁵	2,521	Primary prevention of SCD	23	ICD versus medical therapy + amiodarone versus medical therapy alone	Men: HR 0.73; CI [0.57–0.93] Women: HR 0.96; CI [0.58–1.61]
MUSTT ³	704	Primary prevention of SCD	10	Standard medical therapy versus medical therapy plus EP-guided therapy	Mortality in EP-guided therapy group – men: 21 % women: 32 % (p=0.13)
DEFINITE ⁷	458	Primary prevention of SCD	29	Medical therapy versus ICD	Men: HR 0.49; CI [0.27–0.90]; p=0.019 Women: HR 1.14; CI [0.50–2.64]; p=0.754
AVID ⁶	1,885	Secondary prevention of SCD	22	Antiarrhythmic drug therapy versus ICD	Mortality in women – 15.5 %, men: 14.4 % compared with 24.5 % in patients without ICD

AVID = Antiarrhythmics Versus Implantable Defibrillators; DEFINITE = Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation ; EP = electrophysiology; ICD = implantable cardioverter-defibrillator; MADIT = Multicentre Automatic Defibrillator Implantation Trial; MUSTT = Multicentre Unsustained Tachycardia Trial; SCD = sudden cardiac death; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.



Why Women...?

- Shorter QRSduration in women than men, therefore greater prolongation and greater interventricular delay and dyssynchrony for any degree of QRSwidening.
- Ignoring gender differences of CRT response may lead to the exclusion of women with shorter QRSwho would derive the most benefit.
- Differences in cellular electrophysiology properties, autonomic modulation, hormonal effects on ion channel expressions



Why the Bias??

- Women make up less than 25% of total population enrolled. Studies underpowered to detect significant mortality benefit for women receiving ICDs.
- A Meta Analysis showed 8.6/1000 women received ICD vs 32.3/1000 men within 1 year of known eligibility.
- Sufficient evidence of survival benefit with ICD in both sexes, decision for eligible patients should not be gender based.



Conclusions

- Underrepresentation of Women in clinical CV trials.
 - inadequate volume of evidence to guide treatment decisions for female patients.
- Women much less likely to receive advanced therapies
- Women referred LATE for invasive treatment, have more comorbidities therefore worse outcomes.
- Even though, women have better survival benefit from advanced therapies, they are less likely to be referred for them



Interventions.

- Awareness campaigns such as this one.
- Educate health care providers about gender differences
- Increase gender specific research to reduce gender disparity contributing to elevated mortality rates in women with CVD.
- Enroll more women in cardiac and cardiac device implant trials



Food for thought..

- Are the current practice guideline more restrictive in recommendations for the QRSduration to make a woman eligible for CRT ?
- After all these recommendations were based mostly on outcomes of male dominated trials...



"Sorry to be a nuisance, but I think my phone charger got mixed up in here somehow."

Thank You!

