

## New Treatments for Heart Failure

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## Disclosure

Company	Nature of Affiliation	Unlabeled Product Usage
• St. Jude Medical	• Consultant	• None

## Objectives

- Understand the mechanism of action and indications for sacubitril-valsartan
- Understand the mechanism of action and indications for ivabradine
- Understand how remote hemodynamic management of heart failure can be used to decrease heart failure hospitalizations

## Heart Failure Definitions

- HFrEF (“systolic HF”): LVEF  $\leq$  40%
- HFpEF (“diastolic HF”): LVEF  $\geq$  40%

## Heart Failure Treatment

- Medical therapy for HFrEF has been unchanged for years
  - ACE / ARB
  - B-blockers
  - Aldosterone antagonists
  - Hydralazine / Nitrates

Yancy, et al. Circulation 2013

## Heart Failure Treatment

Medical Therapy for HFrEF: Magnitude of Benefit in RCTs

GDMT	RR Reduction in Mortality (%)	NNT for Mortality Reduction	RR Reduction in HF Hospitalizations (%)
ACEi or ARB	17	26	31
B-blocker	34	9	41
Aldosterone antagonist	30	6	35
Hydralazine / Nitrate	43	7	33

Yancy, et al. Circulation 2013

## Neprilysin

- Enzyme that degrades several endogenous vasoactive compounds
  - Natriuretic peptides
  - Bradykinin
  - Adrenomedullin
- Inhibition of neprilysin increases levels of these substances
  - Vasodilation
  - Natriuresis
  - Diuresis

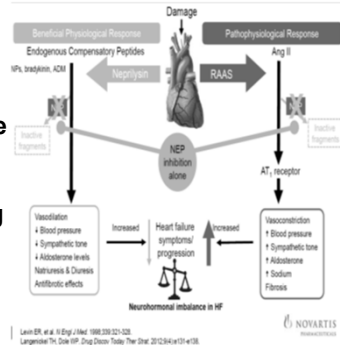
## Neprilysin

- Inhibiting neprilysin was a therapeutic target for several other compounds
- Combination neprilysin inhibitor and ACE inhibitor (Omapatrilat)
  - Promising, but associated with severe angioedema
  - Angioedema d/t inhibition of 3 enzymes involved in bradykinin degradation
    - ACE
    - Neprilysin
    - Aminopeptidase P

Fryer RM, et al. Br J Pharmacol 2008

## Sacubitril-valsartan

- Combo of neprilysin inhibitor sacubitril and ARB valsartan
- Designed to minimize risk of angioedema by only blocking 1 bradykinin degrading enzyme



Gu J, et al. J Clin Pharmacol 2010

Hegde LF, et al. J Cardiovasc Pharmacol 2011

## PARADIGM-HF

- 8442 patients
- LVEF  $\leq 40\%$
- NYHA II-IV
- Randomized to sacubitril-valsartan (200 mg – equivalent to valsartan 160 mg BID) or enalapril 10 mg BID
- Primary outcome was composite CV death or first HF hospitalization
- Stopped early (median follow up 27 months) because of benefit seen in interim analysis

McMurray J, et al. NEJM 2014

## PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 $\pm$ 11.5	63.8 $\pm$ 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 $\pm$ 6.1	29.4 $\pm$ 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 $\pm$ 15	121 $\pm$ 15
Heart rate (beats/min)	72 $\pm$ 12	73 $\pm$ 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

## PARADIGM-HF: Results

- Sacubitril-valsartan reduced primary endpoint by 20%
  - NNT = 21
- Secondary endpoints
  - 20% reduction in CV death
  - 21% reduction in HF hospitalization
  - 16% reduction in all cause mortality

## Sacubitril-Valsartan

- Approved by the FDA July 7, 2015
- “Entresto”
- NYHA Class II-IV
- EF  $\leq$  40%
- Used in place of ACE or ARB

## Sacubitril-Valsartan: Contraindications

- Patients with history of angioedema due to ACE or ARB
- Pregnancy
- Do not use concurrently with ACE - hold for 36 hours after switching from ACE
- Avoid using with another ARB (i.e. avoid dual ARB therapy)

## Ivabradine

- Selective inhibitor of sinoatrial pacemaker modulating “f-current” (If)
- Slows the sinus heart rate
- Mechanism of ivabradine in HFrEF likely due to heart rate reduction

Dobre D, et al. Eur J Heart Fail 2014

## SHIFT Trial

- 6558 patients
- LVEF  $\leq$  35%
- Sinus rhythm and resting HR  $\geq$  70 bpm
- Randomized to ivabradine or placebo
- Primary endpoint: composite CV death or HF hospitalization
- Median follow-up 23 months

Swedberg K, et al. Lancet 2010

## SHIFT Trial: Baseline Characteristic

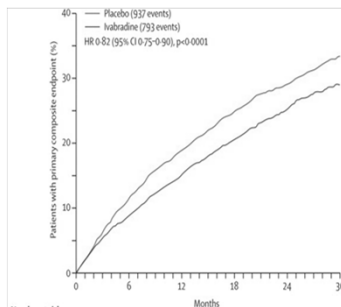
	Ivabradine N=2052	Placebo N=2098
Mean age, years	60	60
Male, %	77	77
BMI, kg/m <sup>2</sup>	28	28
Mean HF duration, years	3.4	3.4
HF, ischemic cause, %	66	65
NYHA Class III, %	50	51
NYHA Class IV, %	2	2
Mean LVEF, %	28.7	28.5
Mean HR, bpm	84.3	84.6

## SHIFT Trial: Baseline Characteristics

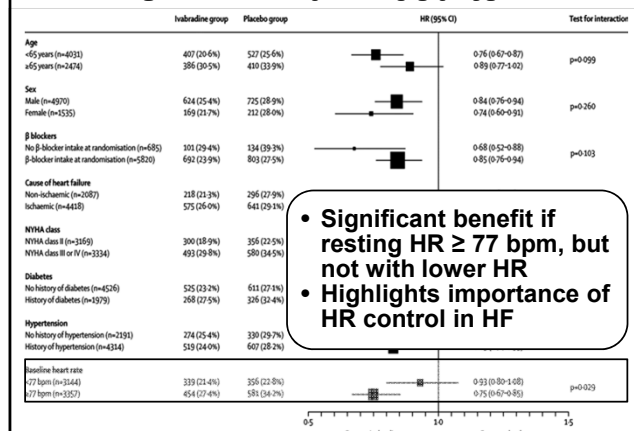
GDMT	Ivabradine N=2052	Placebo N=2098
<b>B-blocker, %</b>	<b>87</b>	<b>87</b>
At least ½ target dose	55	56
At target dose	26	26
<b>ACEi / ARB, %</b>	<b>77</b>	<b>77</b>
<b>Diuretics, %</b>	<b>28</b>	<b>28</b>
<b>Aldosterone antagonists, %</b>	<b>3.4</b>	<b>3.4</b>

## SHIFT Trial: Results

- 24% reduction in primary end-point in ivabradine group
- Results largely d/t ↓ HF hospitalization (HR 0.74, 95% CI 0.66-0.83) and ↓ HF death (HR 0.74, 95% CI 0.58-0.94)



## SHIFT Trial: Results



- Significant benefit if resting HR ≥ 77 bpm, but not with lower HR
- Highlights importance of HR control in HF

## Ivabradine

- Approved by the FDA on April 15, 2015
- “Corlanor”
- Stable HF with LVEF  $\leq 35\%$
- Sinus rhythm with resting HR  $\geq 70$  bpm
- Either on max tolerated dose of  $\beta$ -blocker or have contraindication to  $\beta$ -blockers
- Not a full or partial substitute for  $\beta$ -blockade

## Ivabradine: Contraindications

- Acute decompensated heart failure
- Hypotension (BP < 90/50)
- Sick sinus syndrome, sinoatrial block, or 3<sup>rd</sup> degree AV block
- Patients who are pacemaker dependent
- Severe hepatic impairment
- In combo with strong CYP3A4 inhibitors

## Remote Hemodynamic Monitoring

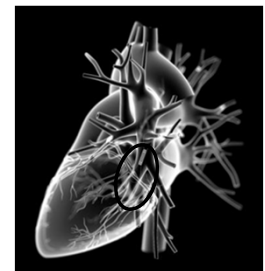
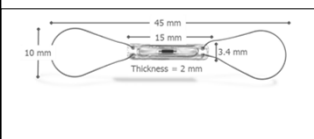
Pulmonary Artery Pressure Sensor	Patient Electronics System	CardioMEMS™ HF System Website
		

CardioMEMS™ HF System

## CardioMEMS™ HF System

The pulmonary artery pressure sensor is implanted via a right heart catheterization procedure via femoral vein approach.

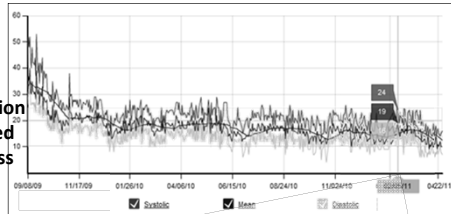
Target location for pulmonary artery pressure sensor



## Patient Management Database

### Trend Data

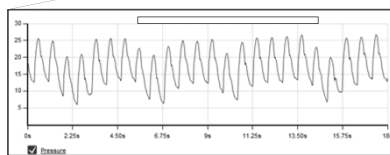
- Easy-to-read
- Physician alerts
- Home transmission
- Secure, encrypted web-based access



### Discrete Data

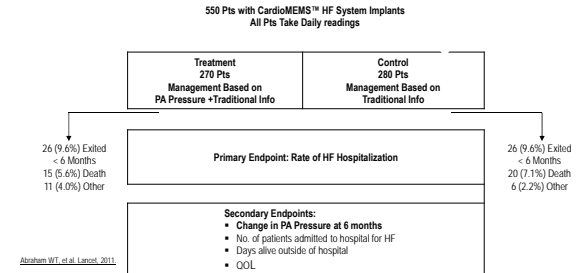
#### Reading

Systolic: 24  
Mean: 19  
Diastolic: 16  
Heart Rate: 81



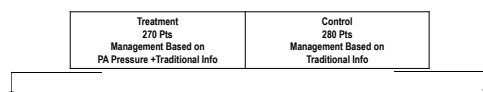
## CHAMPION: CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients

Patients with NYHA III HF for at least 3 months, irrespective of LVEF and a HF hospitalization within past 12 months.



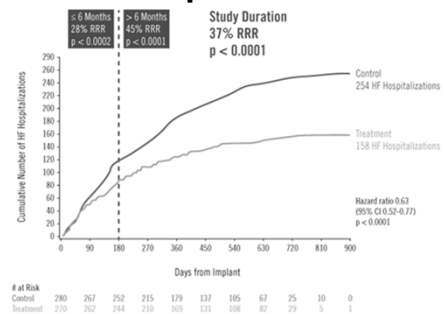
## CHAMPION Clinical Trial: Managing to Target PA Pressures

550 Pts with CardioMEMS™ HF System Implants  
All Pts Take Daily readings



Abraham WT, et al. Lancet, 2011.

## CHAMPION Clinical Trial: PA Pressure-guided Therapy Reduces HF Hospitalizations



NNT = 4

Abraham WT, et al. Lancet, 2011.

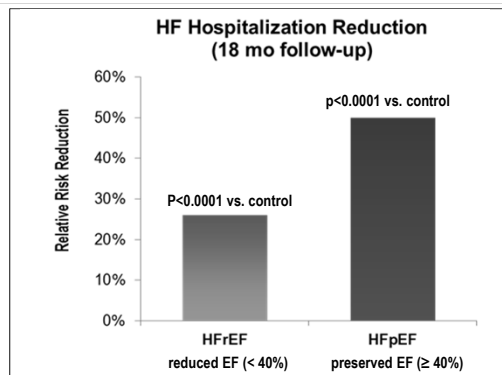
Patients managed with PA pressure data had **significantly fewer HF hospitalizations** as compared to the control group.

### CHAMPION Clinical Trial: PA Pressure-Guided Therapy Improves Outcomes in Patients with Preserved Ejection Fraction

- HFpEF (diastolic HF) represents ~50% of all HF patients
- PAP-guided therapy significantly reduced hospitalizations in HFpEF patients in the treatment group by 46% at 6 months ( $p < 0.0001$ ) and by 50% at 18 months ( $p < 0.0001$ )
- **NNT = 2**

Adamson PB, et al. Circ Heart Fail. 2014.

### CHAMPION Clinical Trial: PA Pressure-Guided Therapy Improves Outcomes in Patients with Preserved Ejection Fraction



Adamson PB, et al. Circ Heart Fail. 2014.

### All Secondary Efficacy Endpoints Met

	Treatment (n=270)	Control (n=280)	p-Value
Change from Baseline in Mean Pulmonary Artery Pressure at 6 Months Mean AUC	-156	33	0.008
Subjects Hospitalized for Heart Failure at 6 Months # (%)	54 (20)	80 (29)	0.022
Days Alive Outside Hospital at 6 Months Mean	174.4	172.1	0.022
Minnesota Living with Heart Failure Questionnaire at 6 Months Mean	45	51	0.024

Abraham WT, et al. Lancet 2011

### CardioMEMS

- Approved by the FDA on May 28, 2014
- NYHA Class III patients
- HFrEF or HFpEF
- HF hospitalization within the past year



## **CardioMEMS: Contraindications**

- Active infection
- Recurrent PE or DVT
- Unable to tolerate right heart catheterization
- GFR < 25 ml/min
- Hypersensitivity or allergy to ASA and/or clopidogrel
- CRT within the past 3 months
- Chest circumference > 165 cm

## **What is New in Device Therapy for Heart Failure**

**Rami Kahwash, MD**  
Assistant Professor of Internal Medicine  
Heart Failure and Cardiac Transplant Program  
Division of Cardiovascular Medicine  
The Ohio State University Wexner Medical Center

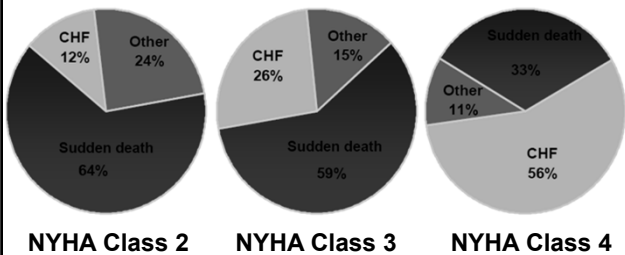
## **Learning Objectives**

- Mode of death in heart failure and the impact of Sudden Cardiac Death (SCD)
- Implantable Cardioverter Defibrillator (ICDs) in primary prevention of SCD
- New defibrillation strategies (wearable ICD and subcutaneous ICD)
- Update in the indication of cardiac resynchronization therapy

## **Epidemiology of Symptomatic Heart Failure in the U.S.**

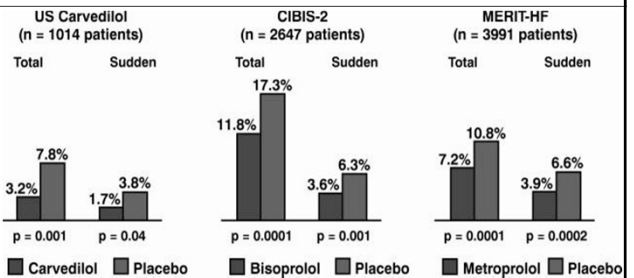
- Major public health problem
- Final manifestation of many cardiac diseases
- ≈ 5 million Americans with heart failure (increasing)
- 500,000 new cases diagnosed each year
- Most frequent cause of hospitalization in patients older than 65 years
- Causes or contributes to 250,000 deaths/year
- 1-Year mortality rate is about 10-15%
- 5-Year mortality rate approaches 50%

## Mode of Death in Heart Failure



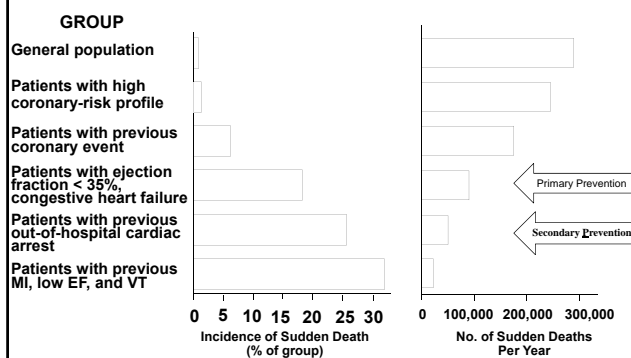
MERIT-HF Lancet 1999

## Beta Blockers' Effects on total Mortality and Sudden Death in Patients with HF



Heart 2001;85:97-103

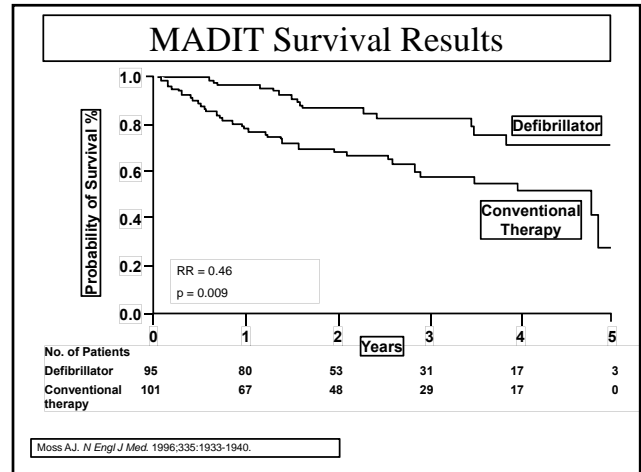
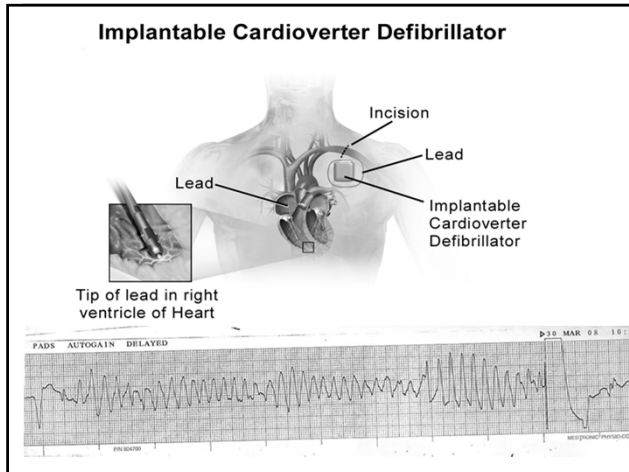
## Incidence of SCD in Specific Populations and Annual SCD Numbers



Myerburg RJ. Circulation.1998;97:1514-1521.

## SCD Primary Prevention Trials (ICD Vs. Conventional Therapy)

- MADIT
- MADIT II
- SCD-HeFT

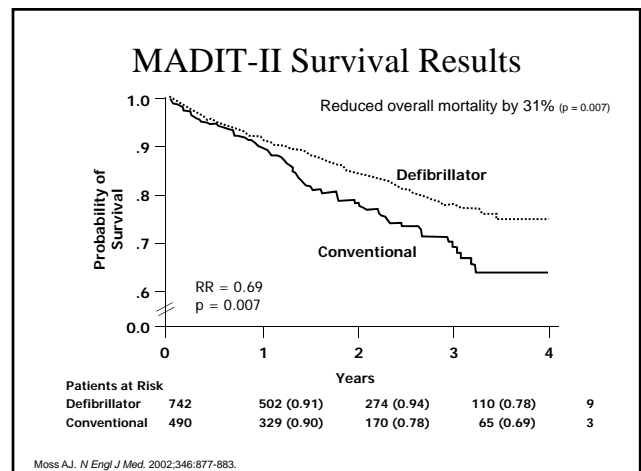


## MADIT-II

**Objective:**

- Evaluate the effectiveness of ICD therapy (n = 742) compared to conventional therapy (n = 490) in high-risk post-MI patients
- Post-MI  $\geq$  4 weeks, and
- LVEF  $\leq$  30%

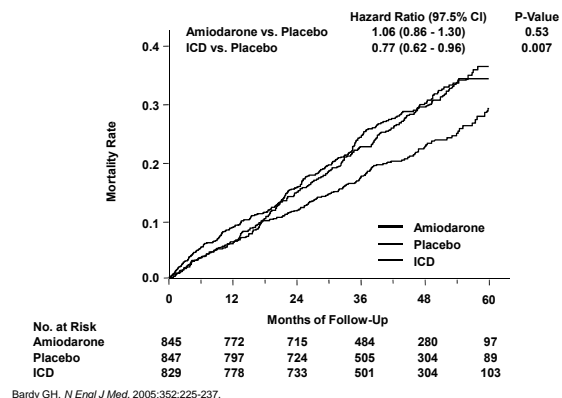
Moss AJ. *N Engl J Med.* 2002;346:877-883



## SCD-HeFT Sudden Cardiac Death in Heart Failure Trial

- Determine if amiodarone or ICD will decrease the risk of death from any cause in patients with mild-to-moderate heart failure (Class II and III).
- Maximally treated CHF for  $\geq 3$  months with a LVEF of  $\leq .35$

## SCD-HeFT Mortality Rate Overall Results



## SCD-HeFT: Primary Conclusions

- In class II or III CHF patients with EF  $\leq 35\%$  on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years
- Simple, single lead, shock-only ICDs decrease mortality by 23%
- Amiodarone, when used as a primary preventative agent, does not improve survival

## Who should get an ICD?

- All secondary prevention indications, e.g. sustained VT, cardiac arrest, syncope with induced VT, etc. (AVID, CASH, CIDS)
- CAD, Prior MI, LVEF  $<0.35$ , inducible VT (MADIT I)
- CAD, Prior MI, LVEF  $<0.30$  (MADIT II)
- Ischemic and nonischemic dilated cardiomyopathy, NYHA class II/III CHF, LVEF  $< 35\%$ . (SCD-HeFT).

## Case 1

- 75 year old man with HTN, DM II and HLP admitted to the CCU with NSTEMI. Coronary angiography revealed 3 vessel CAD. He underwent successful 3V CABG. He was established on BB, ACE I, statin and ASA. LVEF at time of discharge was 25%. His functional class was c/w NYHA FC III. ECG: NSR, QRS: 100 ms, nonspecific ST changes

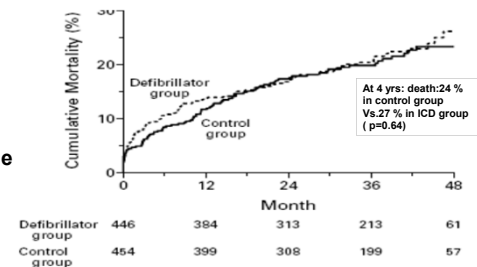
- ICD should be implanted before discharge

A. True

B. False

## Primary Prevention ICDs with CABG Surgery CABG-Patch

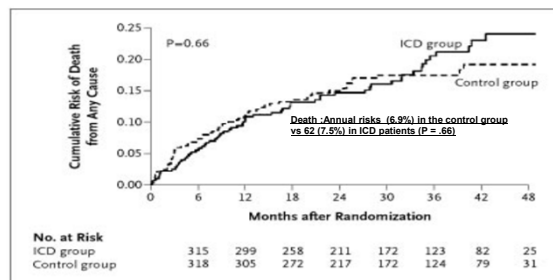
- CAD
  - CABG
  - LVEF < 0.35
  - ++ SAECG
- ICD at the time of CABG



Bigger et al. N Engl J Med 1997;337:1569-74.

## Prophylactic Use of ICDs After Acute Myocardial Infarction DINAMIT

6-40 day post MI, LVEF < 35 %, evidence of autonomic dys



Hohnloser S et al. N Engl J Med 2004;351:2481-2488

## Do NOT implant an ICD if:

- CABG or PCI within the past 3 months (CABG-Patch).
- Acute MI within the past 40 days (DINAMIT).
- Concomitant disease with less than 1 year likelihood of survival.

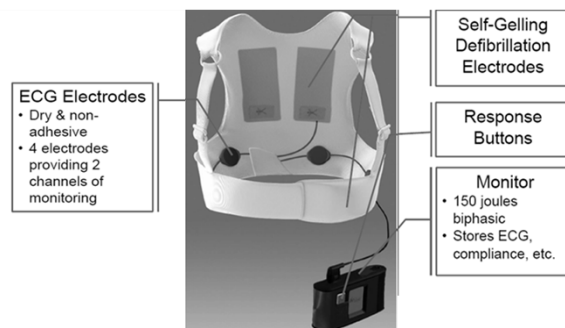
## Case 2

- 22 year old female college student presented to the ED with history of 1 week of progressive dyspnea on exertion. She reported flu like illness 3 weeks ago. Exam c/w sinus tachycardia 110, elevated JVP, + S3 gallop and rales in the lower lung fields. CXR c/w pulmonary edema. Echo showed severely decreased LVEF of 20% with global hypokinesis. ECG: sinus tachycardia, QRS: 88 ms, diffuse nonspecific ST changes. Cardiac biopsy reveals lymphocytic myocarditis. Symptoms improved to NYHA FC II with conventional heart failure therapy and she is ready for discharge.

- ICD is indicated before discharge

A. True  
B. False

## Wearable ICD System



## Wearable Defibrillator Indications

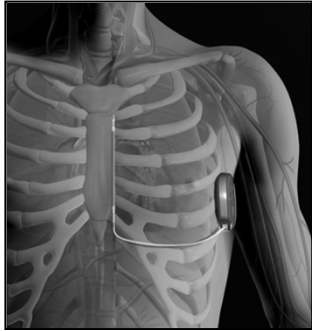
- Post MI with low ejection fraction < 35 %
  - ☐ < 40 days after MI
  - ☐ < 90 days after PCI or CABG
- New onset nonischemic cardiomyopathy < 3 months up to 9 months
- Pretransplant in NYHA FC IV
- ICD extraction due to infection, requires time for treatment with IV antibiotics.

## Case 3

- 45 year old female patient with long standing history of type 1 DM, and Hx of ESRD s/p kidney-pancreas transplant on immunosuppressive therapy. She was also diagnosed with cardiomyopathy 3 years ago. Coronary angiography reveals small vessel disease not suitable for intervention. Despite 6 months of guideline directed medical therapy for heart failure, her LVEF remains 25%. She belongs to NYHA FC II. Her ECG shows NSR, normal intervals, QRS 90 ms, nonspecific Tw abnormalities.
- Intravenous ICD is favored over S-ICD.

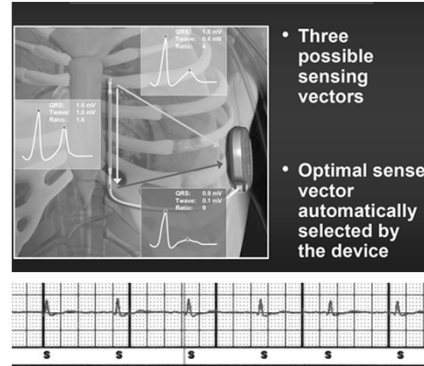
A. True  
B. False

## Subcutaneous ICD



- 80 joules (delivered)
- 69cc, 145 grams
- Active can
- 5 year longevity
- Post-shock pacing
- Single lead connection
- Full featured episode storage
- No Brady pacing or ATP

## S-ICD Sensing Features



## Subcutaneous ICD VS. Transvenous ICD

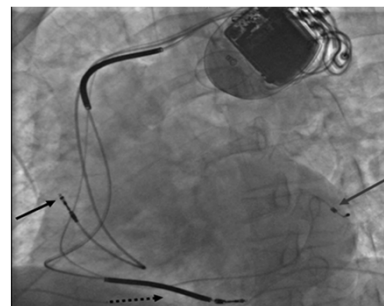
### Factors Favor S-ICD

- Young and active (less lead failure)
- CHD that limits lead placement, valve surgery
- Indwelling catheters
- Immunocompromised
- Inherited channelopathies (low VT risks).

### Factors Favor TV- ICD

- Recurrent monomorphic VT (role of ATP)
- Bradycardia requiring pacing
- Indication for CRT
- High risk for VT (e.g. sarcoidosis, ARVD).
- Preference for remote monitoring

## Cardiac Resynchronization Therapy (CRT)

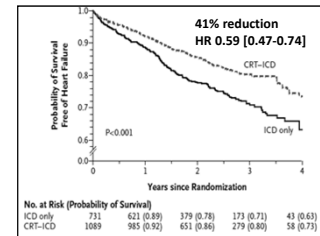


## CRT Class I Indication

- There is strong evidence that CRT reduces mortality and hospitalization and improves cardiac function and structure in symptomatic chronic HF patients (Class III, IV) with optimal medical treatment, severely depressed LVEF (i.e.  $\leq 35\%$ ) and complete LBBB (QRS  $> 120$  ms).

## CRT in NYHA Class I-II Heart Failure MADIT-CRT:

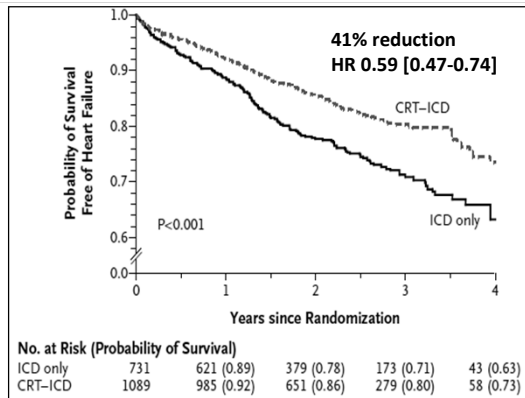
n=1820  
Ischemic: NYHA Class I & II  
Non-ischemic: NYHA Class II  
LVEF  $\leq 30\%$   
QRS  $\geq 130$  ms  
ICD vs. CRT-D (2:3 randomization)



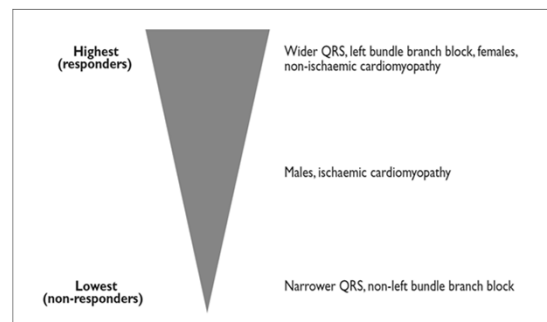
Primary endpoint of all-cause mortality or nonfatal HF events:  
17.5% in CRT-D vs. 25.3% in ICD, HR 0.66 [0.52 to 0.84],  $p=0.001$

Moss et al. N Engl J Med 2009;361

## CRT in NYHA Class I-II Heart Failure MADIT-CRT:



## Magnitude of Benefit from CRT



2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, Brignole et al. Europace (2013) 15, 1070-1118



## 2012 Focused Update Recommendations

### **Class I**

**CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT. (*Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II*)**