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 ≤ 40%
- HFpEF ("diastolic HF"): LVEF ≥ 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

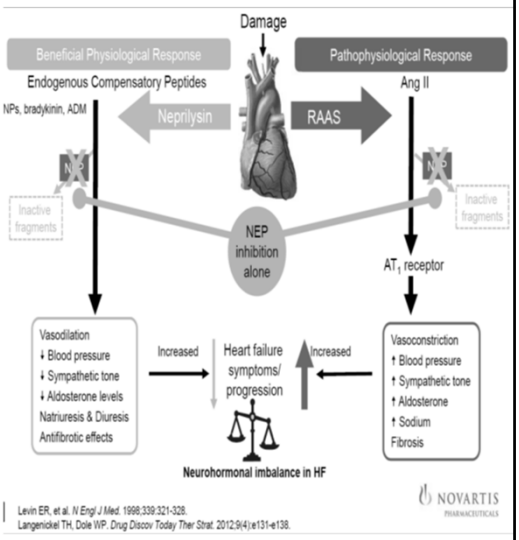
Neprilysin

- 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 ≤ 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 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 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 ≤ 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 ≤ 35%
- Sinus rhythm and resting HR ≥ 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

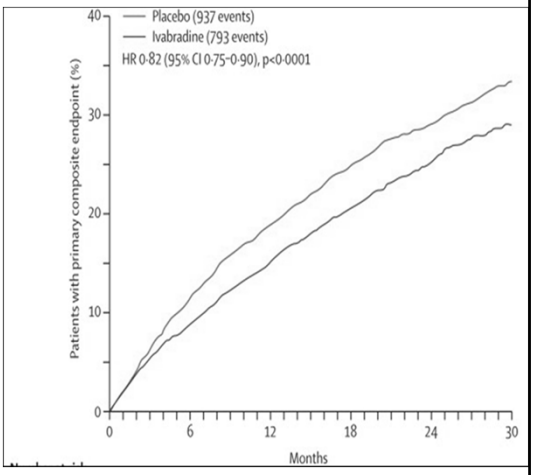
	Ivabradine N=2052	Placebo N=2098
Mean age, years	60	60
Male, %	77	77
BMI, kg/m^2	28	28
Mean HF duration, years	3.4	3.4
HF, ischemic cause, %	66	65
NYHA Class III, %	50	51
NYHA Class IV, %	2	2
Mean LVEF, %	28.7	28.5
Mean HR, bpm	84.3	84.6

SHIFT Trial: Baseline Characteristics

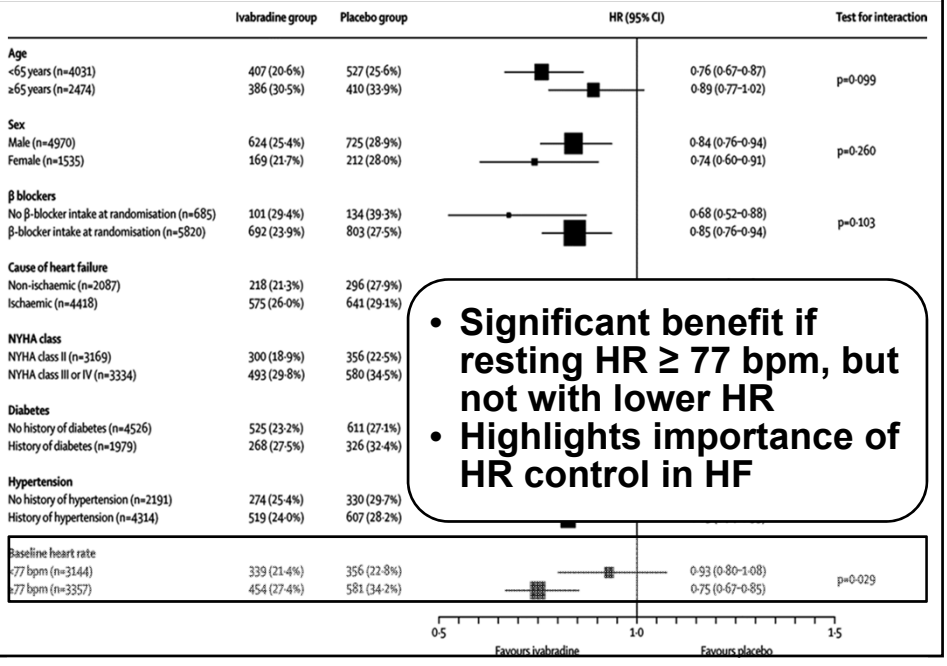
GDMT	Ivabradine N=2052	Placebo N=2098
B-blocker, %	**87**	**87**
At least ½ target dose	55	56
At target dose	26	26
ACEi / ARB, %	**77**	**77**
Diuretis, %	**28**	**28**
Aldosterone antagonists, %	**3.4**	**3.4**

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 ≤ 35%
- Sinus rhythm with resting HR ≥ 70 bpm
- Either on max tolerated dose of β-blocker or have contraindication to β-blockers
- Not a full or partial substitute for β-blockade

Ivabradine: Contraindications

- Acute decompensated heart failure
- Hypotension (BP < 90/50)
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block
- Patients who are pacemaker dependent
- Severe hepatic impairment
- In combo with strong CYP34A inhibitors

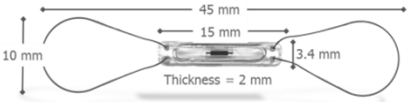
Remote Hemodynamic Monitoring

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

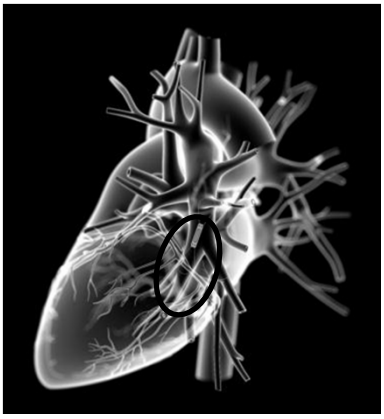
CardioMEMS™ HF System

CardioMEMS™ HF System

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



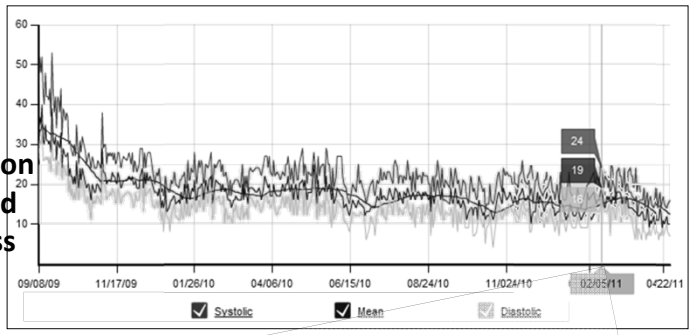
Target location for pulmonary artery pressure sensor



Patient Management Database

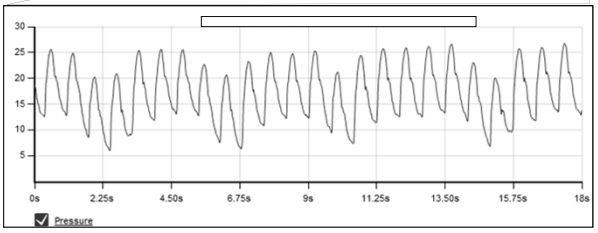
Trend Data

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



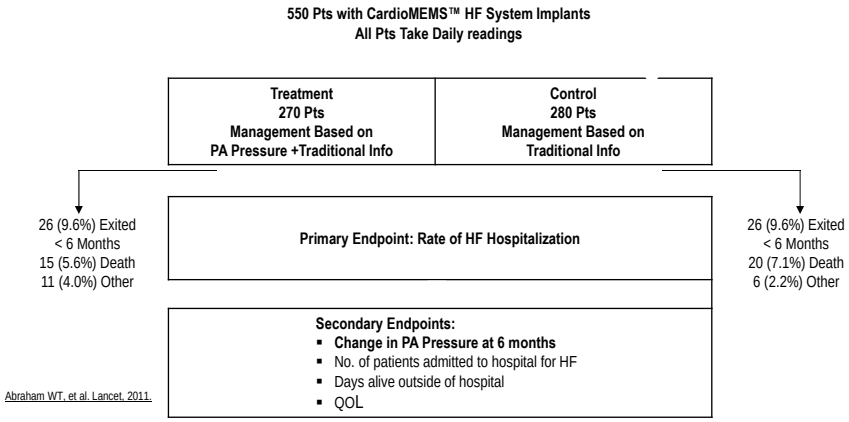
Discrete Data

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.



Abraham WT, et al. Lancet, 2011.

CHAMPION Clinical Trial: Managing to Target PA Pressures

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

Treatment	Control
270 Pts Management Based on PA Pressure +Traditional Info	280 Pts Management Based on Traditional Info

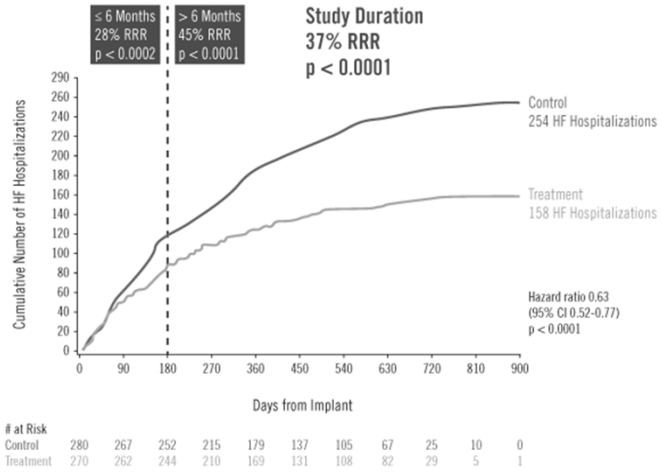
PA pressures were managed to target goal pressures by physicians with appropriate titration of HF medications.

Target Goal PA Pressures:

- PA Pressure Systolic 15 – 35 mmHg
- PA Pressure diastolic 8 – 20 mmHg
- PA Pressure mean 10 – 25 mmHg

Abraham WT, et al. Lancet, 2011.

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



NNT = 4

Abraham WT, et al. Lancet, 2011.

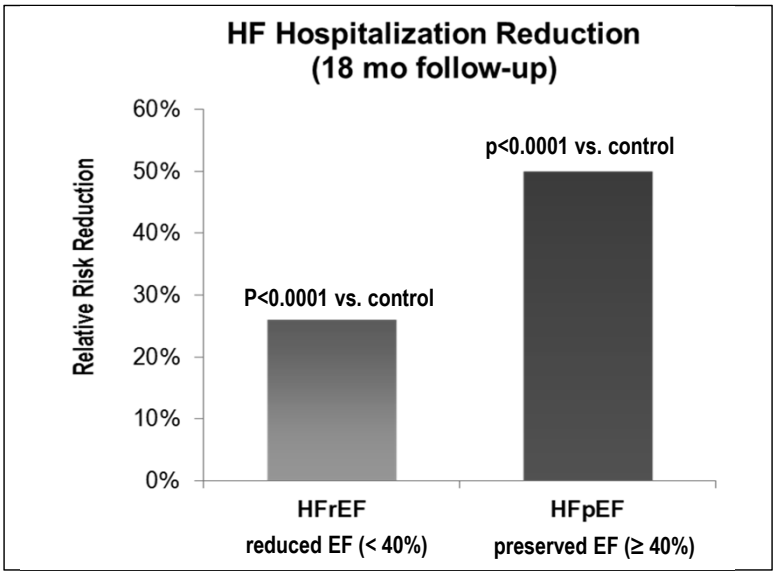
Patients managed with PA pressure data had **significantly fewer HF hospitalizations** as compared to the control group.

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

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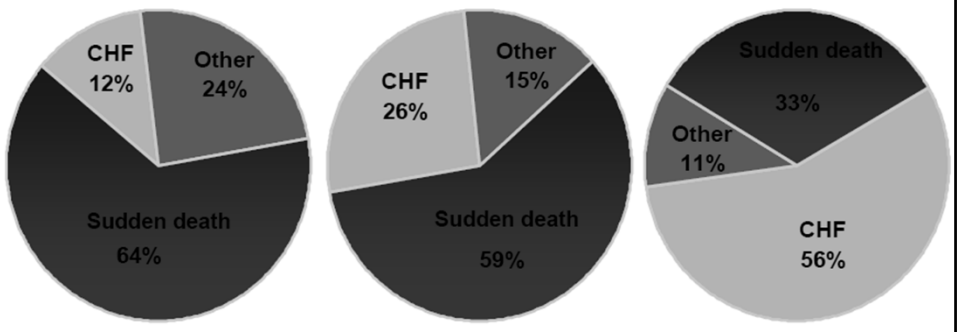
Learning Objectives

- 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%

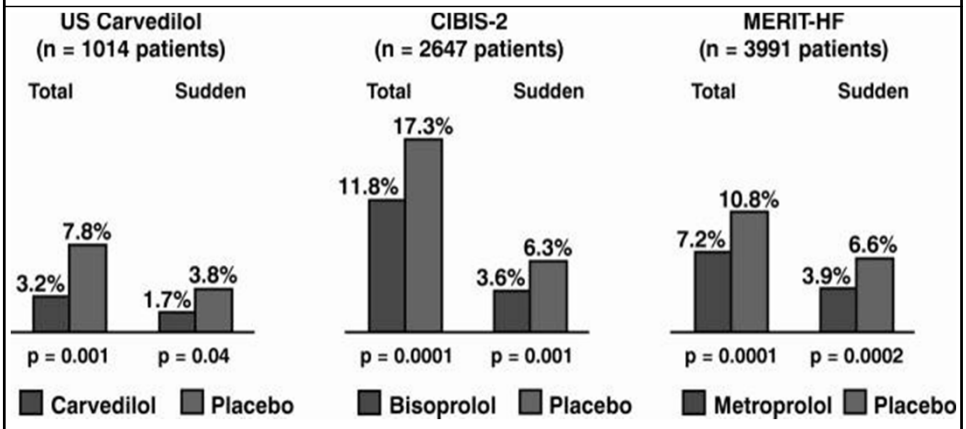
Mode of Death in Heart Failure



NYHA Class 2 NYHA Class 3 NYHA Class 4

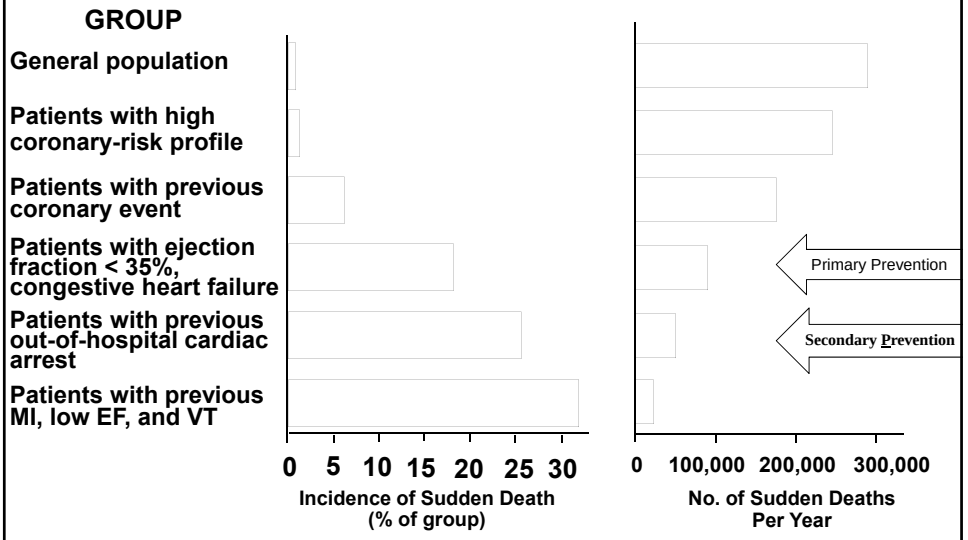
MERIT-HF Lancet 1999

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

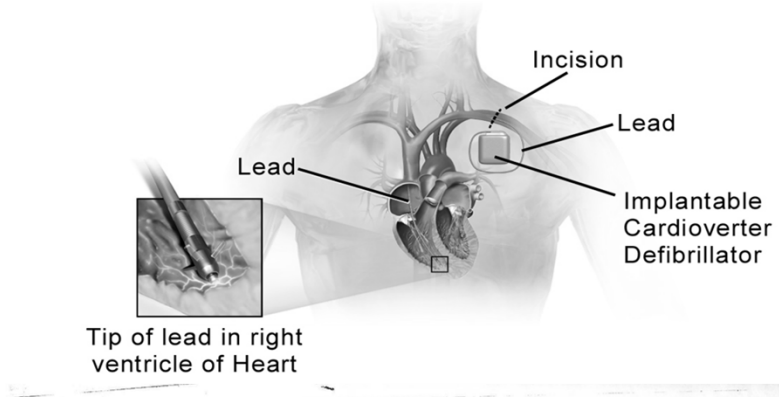


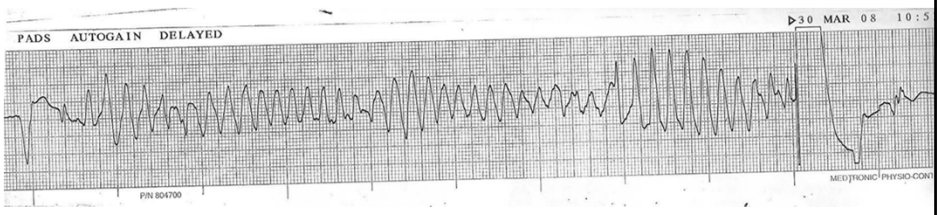
Myerburg RJ. *Circulation*.1998;97:1514-1521.

SCD Primary Prevention Trials (ICD Vs. Conventional Therapy)

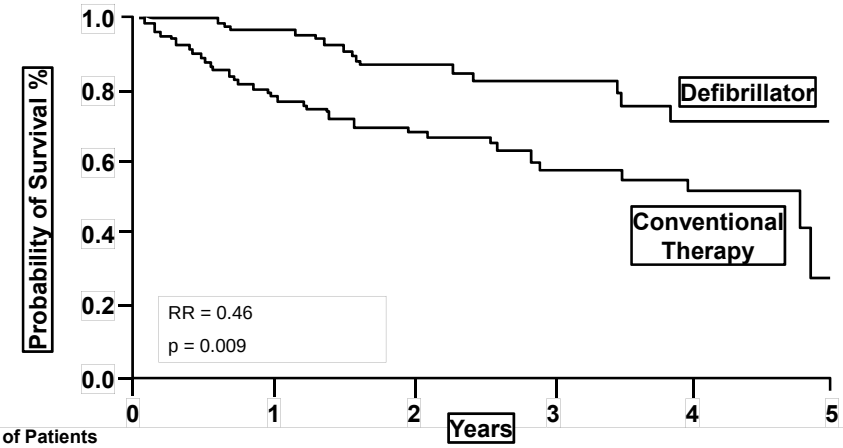
- MADIT
- MADIT II
- SCD-HeFT

Implantable Cardioverter Defibrillator





MADIT Survival Results



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

Moss AJ. *N Engl J Med*. 1996;335:1933-1940.

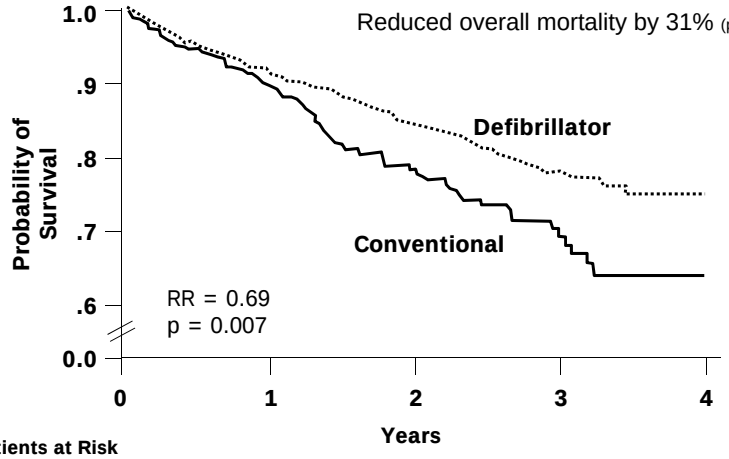
MADIT-II

Objective:

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

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

MADIT-II Survival Results



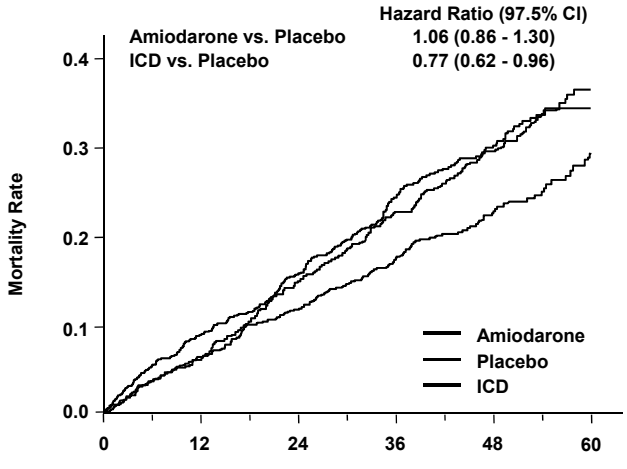
Patients at Risk					
Defibrillator	742	502 (0.91)	274 (0.94)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

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 ≥ 3 months with a LVEF of ≤ .35**

SCD-HeFT Mortality Rate Overall Results



No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD	829	778	733	501	304	103

Bardy GH. *N Engl J Med.* 2005;352:225-237.

SCD-HeFT: Primary Conclusions

- In class II or III CHF patients with EF ≤ 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

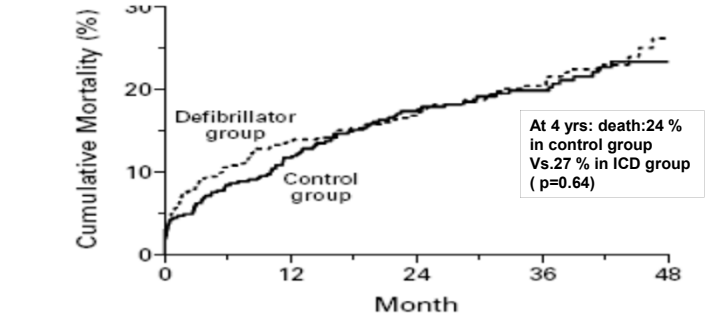
- ICD should be implanted before discharge

A. True

B. False

Primary Prevention ICDs with CABG Surgery
CABG-Patch

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

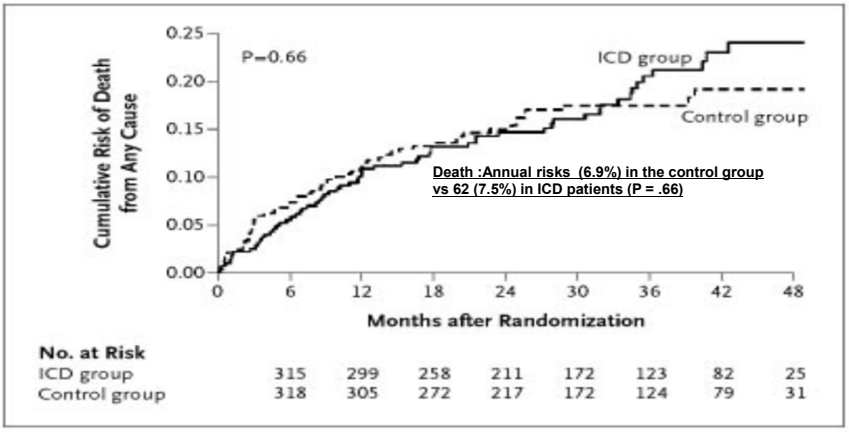


Defibrillator group	446	384	313	213	61
Control group	454	399	308	199	57

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.

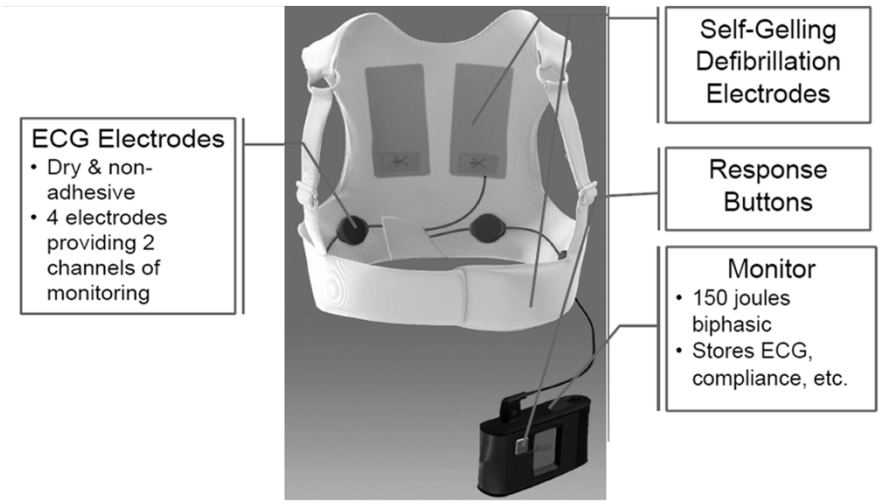
Case 2

- **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 rails 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

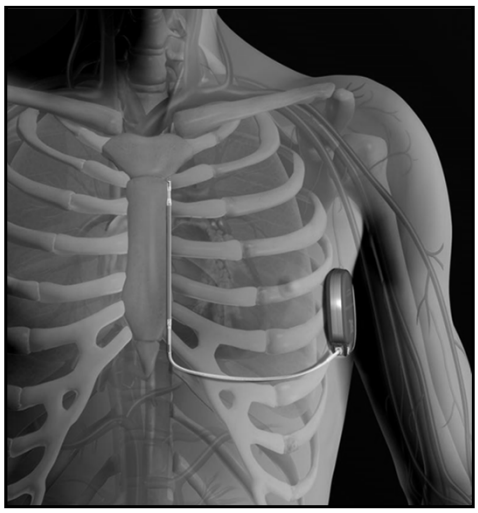
- Post MI with low ejection fraction < 35 %
  - < 40 days after MI
  - < 90 days after PCI or CABG
- New onset nonischemic cardiomyopathy < 3 months up to 9 months
- Pretransplant in NYHA FC IV
- ICD extraction due to infection, requires time for treatment with IV antibiotics.

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.

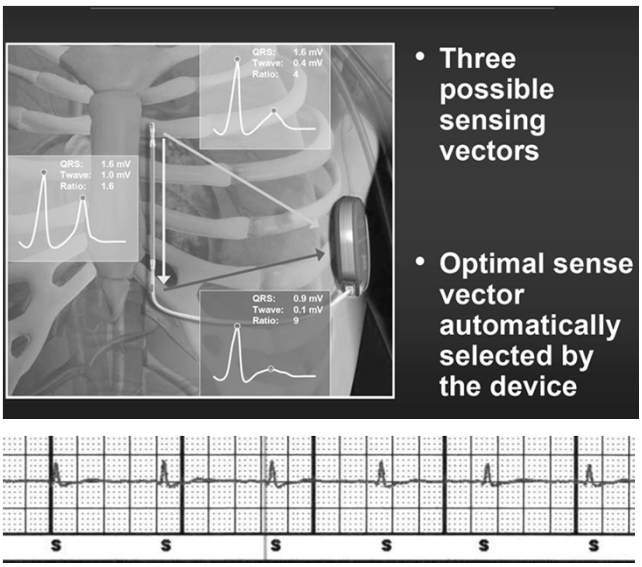
A. True
B. False

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

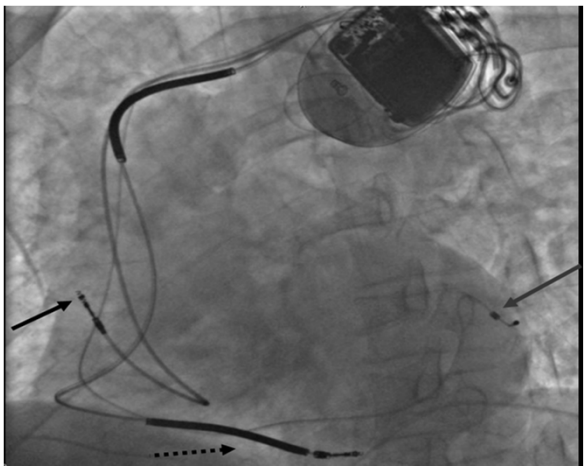
S-ICD Sensing Features



Subcutaneous ICD VS. Transvenous ICD

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

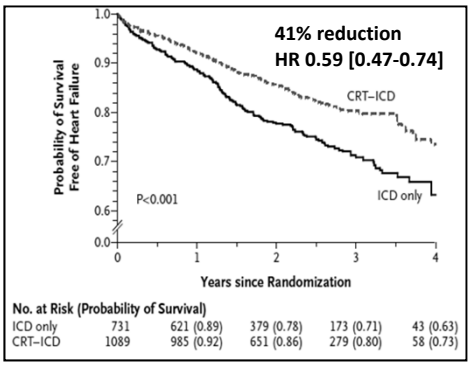


CRT Class I Indication

- **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. ≤35%) and complete LBBB (QRS> 120 ms).**

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

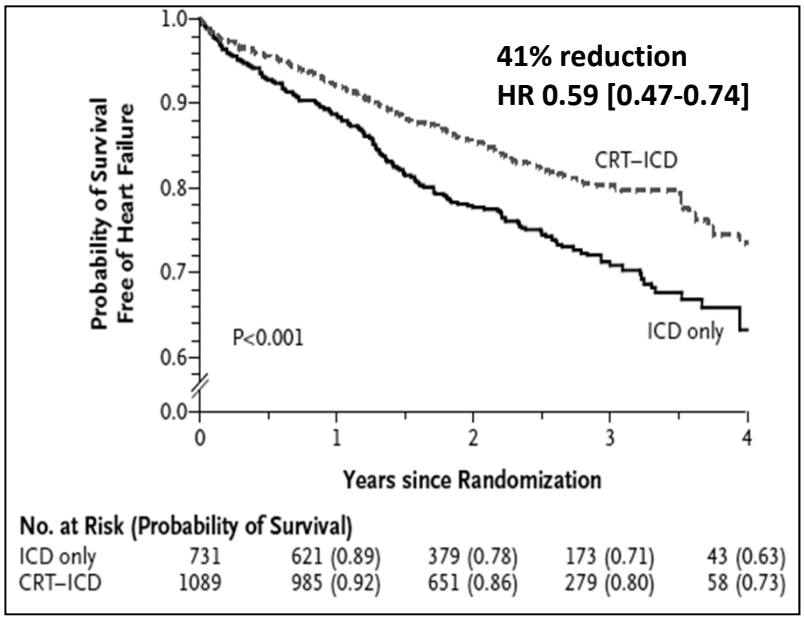
n=1820
Ischemic: NYHA Class I & II
Non-ischemic: NYHA Class II
LVEF ≤30%
QRS ≥130 ms
ICD vs. CRT-D (2:3 randomization)



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

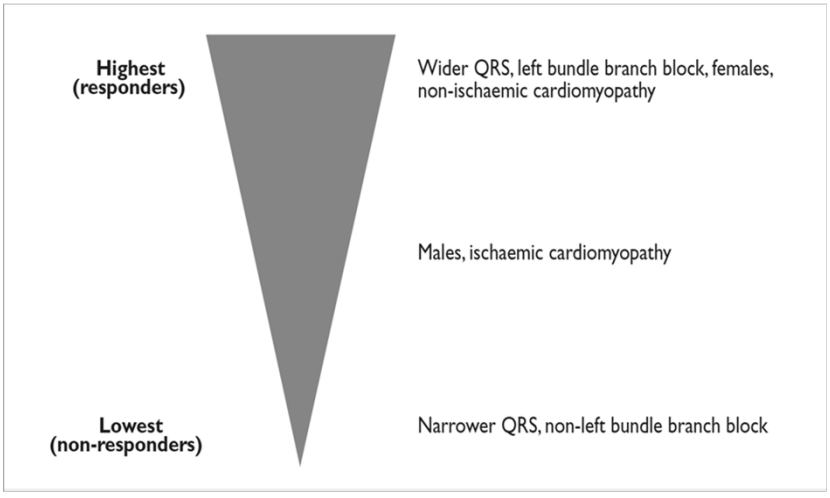
CRT in NYHA Class I-II Heart Failure MADIT-CRT:



No. at Risk (Probability of Survival)

ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

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)***