# Device Therapy for Heart Failure

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## Learning Objectives

- Overview of Heart failure stages and role of device-based therapies
- Implantable Cardioverter Defibrillator (ICDs) in primary prevention of SCD
- New defibrillation strategies (wearable ICD and subcutaneous ICD)
- Cardiac Resynchronization Therapy (CRT)

## Background

- In 2013, the ACC/AHA published an updated Guideline for the Management of Heart Failure
- New terminologies, concepts and recommendations were introduced
- An attempt was made to harmonize the guideline with other guidelines, consensus documents and position papers which are cross-referenced


## Terminology

- Guidelines Directed Medical Therapy (GDMT) - represents the optimal medical therapy recommended with a class 1 indication
- Heart Failure with reduced Ejection Fraction (HFrEF). LVEF ≤ 40 %
- Heart failure with preserved Ejection Fraction (HFpEF). LVEF ≥ 50 %
  - HFpEF, borderline (LVEF 41-49 %)
  - HFpEF, improved (LVEF >40 %)
- Maintained the concept of “stages”
**Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class**

<table>
<thead>
<tr>
<th>ACC/AHA HF Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>I: Asymptomatic</td>
</tr>
<tr>
<td>C</td>
<td>II: Symptomatic with moderate exertion</td>
</tr>
<tr>
<td>D</td>
<td>III: Symptomatic with minimal exertion</td>
</tr>
<tr>
<td></td>
<td>IV: Symptomatic at rest</td>
</tr>
</tbody>
</table>

**Therapeutic Options for Heart Failure Stages**

- **End Stage**
  - Impaired LV function
  - HF symptoms
  - Inadequate drug therapy
  - HF exacerbations
  - Inadequate LV remodeling
  - Symptoms: Dyspnea, fatigue, edema, anasarca
  - Treatments: Medical therapy, intensive care, hospice care

- **Symptomatic Stage**
  - Impaired LV function
  - HF symptoms
  - Inadequate drug therapy
  - HF exacerbations
  - Inadequate LV remodeling
  - Symptoms: Dyspnea, fatigue, edema, anasarca
  - Treatments: Medical therapy, intensive care

- **Preventive Stage**
  - Asymptomatic
  - Impaired LV function
  - Low risk of HF
  - Observation
  - Risk factor modification

**Heart Failure Device-Based Therapies**

- HFrEF (stage C)
  - Investigational devices to improve symptoms

- HFrEF (stage C)
  - Devices to improve survival (ICD)

- HFrEF (stage C)
  - Devices to improve symptoms and HF symptoms (CRT)

- Investigational devices
Heart Failure Device-Based Therapies

HRpEF (stage C)
- Investigational devices to improve symptoms
- Mechanical Circulatory Support (LVAD)

HFrEF
- Stage C
  - Devices to improve survival (ICD)
  - Devices to improve survival and HF symptoms (CRT)

Stage D
- Investigational devices

Device to reduce hospitalization (remote hemodynamic monitoring/CardioMEMS)

Mode of Death in Heart Failure

NYHA Class 2
- CHF 12%
- Sudden death 54%

NYHA Class 3
- CHF 26%
- Sudden death 59%

NYHA Class 4
- CHF 56%
- Sudden death 33%

MERIT-HF Lancet 1999

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

US Carvedilol (n = 1014 patients)
- Total: 3.2% (p = 0.001)
- Sudden: 7.5% (p = 0.001)

CIBIS-2 (n = 2647 patients)
- Total: 11.8% (p = 0.001)
- Sudden: 17.3% (p = 0.001)

MERIT-HF (n = 3991 patients)
- Total: 7.2% (p = 0.001)
- Sudden: 10.8% (p = 0.001)

Heart 2001;85:97–103
Implantable Cardioverter-Defibrillator (ICD) Basics

- Designed to treat a cardiac tachydysrhythmia
- Performs cardioversion/defibrillation
  - Ventricular rate exceeds programmed cut-off rate
- ATP (antitachycardia pacing)
  - Overdrive pacing in an attempt to terminate ventricular tachycardias
- All have pacemaker function (combo devices)

Schematic View of the Defibrillation Shock Generated by the ICD

Major Components of the ICD system

SCD Primary Prevention Trials (ICD Vs. Conventional Therapy)

- 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 ≥ 4 weeks, and
- LVEF ≤ 30%


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

Who should get an ICD?

- Ischemic CM, LVEF <0.30 (MADIT II)
- Ischemic and nonischemic dilated cardiomyopathy, NYHA class II/III CHF, LVEF < 35%. (SCD-HeFT).

Who should NOT get an ICD?

- CABG or PCI within the past 3 months- CABG-Patch ¹
- Acute MI within the past 40 days-DINAMIT ²
- Concomitant disease with less than 1 year likelihood of survival.

¹ Bigger et al. N Engl J Med 1997;337:1569-74

Wearable ICD System

- ECG Electrodes
  - Dry & non-adhesive
  - 4 electrodes providing 2 channels of monitoring
- Self-Gelling Defibrillation Electrodes
- Response Buttons
- Monitor
  - 150 joules biphasic
  - Stores ECG, compliance, etc.

ICDs and MRI

- It is becoming feasible to use MRI for certain ICD and lead models that are MRI compatible if done according to certain protocols
- Consulting with specialists is necessary before ordering MRIs in patients with ICDs
Indications for ICD Deactivation

- End-of-life care
- Recurrent inappropriate shocks due to lead failure or SVT/AF with rapid ventricular response
- During surgical procedures requiring the use to electrocautery in close proximity to the pulse generator

Case Presentation

- A 45-year-old female with history of breast cancer, s/p bilateral mastectomy and chemotherapy (2 years ago). Her cancer is currently in remission with favorable prognosis. She developed Adriamycin induced cardiomyopathy and despite >9 months of guideline directed medical therapy for heart failure, her LVEF remains 30%. She belongs to NYHA FC II. Her ECG shows NSR, normal intervals, QRS 90 ms, nonspecific T-wave abnormalities. Her L subclavian vein is occluded and she has a history of DVT in the R subclavian vein as a complication of prior Port-a-cath.
  - Intravenous ICD implant is recommended?
    A. True
    B. False

Subcutaneous ICD

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

Subcutaneous ICD vs. Transvenous ICD

Factors Favor S-ICD
- Young and active (less lead failure)
- CHD that limits lead placement, valve surgery
- Indwelling catheters
- Immuno-compromised
- 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)**

**Major CRT Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Patients</th>
<th>Mean follow-up</th>
<th>NYHA</th>
<th>LVEF inclusion criteria</th>
<th>QRS Inclusion criteria</th>
<th>Primary endpoint</th>
<th>Significance of intervention noted</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPANION (2004)</td>
<td>CRT-D + CRT-P + ICD</td>
<td>617 + 595 + 308</td>
<td>15</td>
<td>III, IV</td>
<td>≤35%</td>
<td>≥120 ms</td>
<td>All-cause mortality or hosp</td>
<td>+/−</td>
</tr>
<tr>
<td>CARE-HF (2005)</td>
<td>CRT-P + Med</td>
<td>409 + 404</td>
<td>29</td>
<td>III, IV</td>
<td>≤35%</td>
<td>≥120 ms</td>
<td>All-cause mortality or cardiovascular hospitalization</td>
<td>+</td>
</tr>
<tr>
<td>MADIT-CRT (2009)</td>
<td>CRT-D + ICD</td>
<td>1089 + 739</td>
<td>29</td>
<td>I, II</td>
<td>≤30%</td>
<td>≥130 ms</td>
<td>All-cause mortality or HF hosp</td>
<td>+</td>
</tr>
</tbody>
</table>

**Indications for CRT**

- **NYHA Class I**
  - LVST ≤ 35%  
  - QRS ≤ 150 ms  
  - LBBB pattern  
  - Sinus rhythm

- **NYHA Class II**
  - LVST ≤ 35%  
  - QRS ≤ 150 ms  
  - LBBB pattern  
  - Sinus rhythm

- **NYHA Class III & Ambulatory Class IV**
  - LVST ≤ 35%  
  - QRS ≤ 150 ms  
  - LBBB pattern  
  - Sinus rhythm

**Major CRT Trials**

- **COMPACTION (2004)**
  - CRT-D + CRT-P + ICD
  - Patients: 617 + 595 + 308
  - Mean follow-up: 15 months
  - NYHA: III, IV
  - LVEF inclusion criteria: ≤35%
  - QRS inclusion criteria: ≥120 ms
  - Primary endpoint: All-cause mortality or hosp care
  - Significance of intervention: +/−

- **CARE-HF (2005)**
  - CRT-P + Med
  - Patients: 409 + 404
  - Mean follow-up: 29 months
  - NYHA: III, IV
  - LVEF inclusion criteria: ≤35%
  - QRS inclusion criteria: ≥120 ms
  - Primary endpoint: All-cause mortality or cardiovascular hospitalization
  - Significance of intervention: +

- **MADIT-CRT (2009)**
  - CRT-D + ICD
  - Patients: 1089 + 739
  - Mean follow-up: 29 months
  - NYHA: I, II
  - LVEF inclusion criteria: ≤30%
  - QRS inclusion criteria: ≥130 ms
  - Primary endpoint: All-cause mortality or HF hosp
g
  - Significance of intervention: +
Devices to Reduce Readmissions

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Burden of Heart Failure
Heart failure is a big problem …

- HF affects 5.5-7 million Americans
- $31 Billion on HF hospitalizations
- Most frequent cause of rehospitalization in the US
- Importantly, repeat HF admissions lead to worsening mortality!

Heidenreich PA, et al, Circ Heart Fail 2013
Jencks SF, et al, NEJM 2009

Evolution of Acute Heart Failure

Weight Changes, HF Symptoms
Pressure Changes, Autonomic Adaptation
Impedance Changes
HF Hospitalization

Traditional Methods: Weights & Symptoms

Benefits
- Easy to understand
- Minimal equipment
- Low costs

Drawbacks
- Low compliance rates
- Variability in implementation
- Sensitivity <25%

Moser DK, Am Heart J 2005
van der Wal MH, Eur Heart J 2006
Abraham WT, Congest Heart Fail 2011

Telemedicine Trials to Reduce Readmissions

<table>
<thead>
<tr>
<th>TELE-HF</th>
<th>TIM-HF</th>
<th>BEAT-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH sponsored</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1600+ patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent phone interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>710 patients</td>
<td>1400+ patients</td>
</tr>
<tr>
<td></td>
<td>Telemonitoring of weight &amp; symptoms</td>
<td>Electronic telemonitoring</td>
</tr>
<tr>
<td></td>
<td>Not effective</td>
<td>Not effective</td>
</tr>
</tbody>
</table>

Bioimpedance

Benefits
- Can be obtained from devices already implanted
- Correlate well to invasive measures

Drawbacks
- Not a primary indication for device implant
- Unlikely to be an option for HFpEF
- Low positive predictive value

Bioimpedance Trials

<table>
<thead>
<tr>
<th>FAST</th>
<th>DOT-HF</th>
<th>OptiLink-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good sensitivity</td>
<td>No reduction in hospitalizations</td>
<td>Recently conducted</td>
</tr>
<tr>
<td>Good compliance</td>
<td>Hospitalizations</td>
<td>No hospitalization</td>
</tr>
<tr>
<td>Exploratory only</td>
<td></td>
<td>reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data did not induce</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clinical actions</td>
</tr>
</tbody>
</table>

Autonomic Adaptation: Biomarkers

Benefits
- Both HFpEF & HFrEF
- Repeatable and widely available

Drawbacks
- Requires phlebotomy (lab visit)
- Costs
- Confounding variables (e.g. obesity)
- Unclear what constitutes improvement

Yu CM, Circ 2005
Conraads VM, Eur Heart J 2011
### Biomarker Trials for Rehospitalization

<table>
<thead>
<tr>
<th>Trial</th>
<th>Biomarker</th>
<th>Size</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troughton, et al</td>
<td>BNP</td>
<td>69</td>
<td>Positive</td>
</tr>
<tr>
<td>STARS-BNP</td>
<td>BNP</td>
<td>220</td>
<td>Positive</td>
</tr>
<tr>
<td>Berger R, et al</td>
<td>NT-proBNP</td>
<td>278</td>
<td>Positive</td>
</tr>
<tr>
<td>PROTECT</td>
<td>NT-ProBNP</td>
<td>151</td>
<td>Positive</td>
</tr>
<tr>
<td>PRIMA</td>
<td>NT-ProBNP</td>
<td>345</td>
<td>Negative</td>
</tr>
<tr>
<td>BATTLE-SCARRED</td>
<td>NT-proBNP</td>
<td>364</td>
<td>Negative</td>
</tr>
<tr>
<td>TIME-CHF</td>
<td>BNP</td>
<td>499</td>
<td>Negative</td>
</tr>
<tr>
<td>GUIDE-IT</td>
<td>NT-proBNP</td>
<td>1100 (planned)</td>
<td>Stopped Early (ineffective)</td>
</tr>
</tbody>
</table>

### Hemodynamic Monitoring

#### Benefits
- Both HFpEF & HFrEF (CardioMEMSTM)
- Hemodynamics correlate well to HF events
- Occurs early in the decompensation process
- Known targets (PAD < 18 mmHg)

#### Drawbacks
- Invasive procedure
- Additional device (CardioMEMS)
- Monitoring by staff required

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### Hemodynamic Monitoring: Sensor Choice

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Benefits/Drawbacks</th>
</tr>
</thead>
</table>
| RV Lead| • Good for patients who need devices  
|        | • Unavailable to patients without device  
|        | • Worsening battery life |
| LA lead| • LA pressure better than PAD?  
|        | • An additional device implant  
|        | • Transseptal implant associated with increased complications |
| PA Sensor| • No battery  
|         | • Low implant complication rate  
|         | • Limited by body habitus  
|         | • Cost & reimbursement factors |

### Hemodynamic Monitoring: The Secret Sauce

- Early trials with hemodynamic monitoring did not improve outcomes. Why?
- Successful use of hemodynamics requires treatment to a numeric goal
- This must happen independent of symptoms
  - Physiologic changes will occur before symptoms

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Stevenson LW, Am J Cardiol 1990  
Morley D, Am J Cardiol 1994  
Stevenson LW, Circ Heart Fail 2010  
Bourge RC, JACC 2008
**PA Sensors**

- Implanted via right heart cath technique
- Typically placed in branch of left PA
- Provide PA systolic, diastolic, and mean pressures
- PA diastolic pressures typically mirror PCWP/LA pressures

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**Hypothesis of the CHAMPION Trial**

Change medications based on hemodynamic pressures instead of waiting for signs & symptoms

→ Heart failure hospitalizations

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**Protocol Guidelines: PA Pressure Management**

**Treatment Recommendations for Elevated PA Pressures**

- Add or increase diuretic
  - increase/add loop diuretic
  - change loop diuretic
  - add thiazide diuretic
  - IV loop diuretic
- Add or increase vasodilator
  - add or increase nitrate

---

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

- Trial Designed by Steering Committee with active FDA input
  - Prospective, multi-center, randomized, controlled single-blind clinical trial
  - All subjects followed in their randomized single-blind study assignment until the last patient reached 6 months of follow-up
  - 64 US Centers
  - PIs: William Abraham, Phil Adamson

550 Pts w/ CM Implants
All Pts Take Daily Readings

- 270 Pts: Treatment Management Based on Hemodynamics + Traditional Info
- 280 Pts: Control Management Based on Traditional Info

Primary Endpoint: HF Hospitalizations at 6 Months

Additional Analysis: HF Hospitalizations at All Days (~15 M mean FU)

Multiple Secondary Endpoints
### Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=270)</th>
<th>Control (n=280)</th>
<th>Relative Risk Reduction</th>
<th>p-value(^1)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy Endpoint: HF Related Hospitalizations (Rate for 6 months)</td>
<td>84 (0.32)</td>
<td>120 (0.44)</td>
<td>28%</td>
<td>0.0002</td>
<td>8</td>
</tr>
<tr>
<td>Supplementary Analysis: HF Related Hospitalizations (Full Duration - Annualized Rate)</td>
<td>158 (0.46)</td>
<td>254 (0.73)</td>
<td>37%</td>
<td>&lt;0.0001</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^1\)p-value from negative binomial regression

NNT = Number Needed to Treat


### Hemodynamic Monitoring Summary

- Implantable hemodynamic monitors provide direct and actionable measurements of intracardiac and pulmonary artery pressures.
- Management guided by such monitors reduces the risk of heart failure hospitalizations.
- This approach promises to revolutionize the management of heart failure patients:
  - Crisis management ➔ Stability management

### PA Monitoring Benefits Are Additive

<table>
<thead>
<tr>
<th>GDMT Class</th>
<th>HF Hospitalization Hazard Ratio</th>
<th>NNT</th>
<th>Mortality Hazard Ratio</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB</td>
<td>0.59</td>
<td>4</td>
<td>0.48</td>
<td>7</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.66</td>
<td>5</td>
<td>0.59</td>
<td>11</td>
</tr>
<tr>
<td>ACEi/ARB &amp; Beta-blocker</td>
<td>0.57</td>
<td>3</td>
<td>0.43</td>
<td>7</td>
</tr>
</tbody>
</table>

Abraham WT, JACC 2015

### CardioMEMSTM: Current Status

- Only approved PA pressure monitoring system at present.
- Approved for use in NYHA III HF patients.
- Intended to:
  - Reduced HF hospitalizations
  - Improved QoL
  - No indication to improve survival
Mechanical Circulatory Support Devices

HF Topography

NYHA I

NYHA II

NYHA III

NYHA IV

HF Topography

NYHA I

NYHA II

NYHA III

NYHA IV

HF Topography

NYHA I

NYHA II

NYHA III

NYHA IV

HF Topography

NYHA I

NYHA II

NYHA III

NYHA IV
NYHA Classification

1 year mortality of NYHA III HF is 10-15%

A HF hospitalization is a strong predictor of mortality (NYHA IIIb-IV)

Scrutenid et al, EHJ 1994
Gheorghiade et al, JACC 2013

NYHA Reproducibility

Inter-observer evaluation
Exact reproducibility: 56%
Within 1 functional class: 93%

NYHA III best correlated with exercise testing (75% of patients)

Goldman et al, Circ 1981
Franciosa et al, Am J Med 1979
Bennett et al, JHLT 2002
Cardiopulmonary Exercise Testing

- Also known as metabolic stress test, VO2 test
- Peak VO2 performance <14 ml/kg/min is associated increased risk of death within 24 months in HF patients

No VO2 testing? Try a 6-minute walk

- Distance ≤ 468 m (1535 ft) predicts higher mortality and hospitalization risk
- 6MWT is a good screening tool
- However, not as strongly correlated as VO2 data

The High-Risk HF Patient

1 or more of the following:
- HF Sx that fail to respond to medical therapy (persistent NYHA III or worse symptoms)
- Peak VO2 <14 ml/kg/min
- Intolerance to HF meds (esp new intolerance)
  - Hypotension
  - Renal dysfunction
  - Bradycardia
- Frequent hospitalizations
  - 2 in 3 months
  - 3 in 6 months
  - Need for inotropes during hospital stay

Treatment Options for High-Risk HF Patients

Transplant
- Good long term survival
- Strict selection criteria
- Limited supply of donor hearts
- Complex post-transplant medical regimen

Ventricular Assist Devices
- Improving long term survival (>70% at 2 years)
- Non-limited resource
- Can be bridge-to-transplant (BTT) or destination therapy (DT)
- Requires anti-coagulation
- Complex post-implant medical regimen

Palliative Care/Hospice
- Quality of life > survival
**VAD Criteria**

- Used as either Bridge to Transplant (BTT) or Destination Therapy (DT)
- EF ≤ 25%
- For BTT – must be listed for transplant
- For DT:
  - Failed optimal therapy for 45 of last 60 days
  - Or inotrope dependent (minimum 14 days)
  - Or IABP x 7 days
  - Peak VO₂ ≤ 14

**Summary of VAD Therapy for HF**

- Improves survival
- Improves functional status
- Improves quality of life
- Improving technology to reduce complications
- Part of guideline recommendations for treatment of HF

Rogers J, et al, JACC 2010
Yancy CW, et al, JACC 2013