Contemporary Advanced Heart Failure Therapy

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40 yo male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min.
Lisinopril 5 mg qd and Toprol XL 150 mg qd.

Next step should be:

a) Add aldactone 25 mg qd
b) Add digoxin 0.125 mg qd
c) Refer for CRT-D
d) Increase Lisinopril to 10 mg qd
e) Add corlanor
Audience Response Question

40 yo AA male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min
Lisinopril 40 mg qd and Toprol XL 150 mg qd.

Next step should be:
a) Add aldactone 25 mg qd
b) Add digoxin 0.125 mg qd
c) Refer for CRT-D
d) Add hydralazine/nitrates
e) Add corlanor
40 yo white male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min. QRS duration 170 msec. Lisinopril 40 mg qd, Toprol XL 150 mg qd, aldactone 25 mg qd.

Next step should be:

a) Refer for CRT-D

b) Add hydralazine/nitrates

c) Add corlanor (ivabradine)

d) Add entresto (sacubitril/valsartan)

e) Change to Lisinopril to entresto (sacubitril/valsartan)
Epidemiology of Heart Failure

- Approximately 5.7 million Americans have CHF
- 670,000 new cases annually
- Five-year mortality rate as high as 50%
- Most frequent cause of hospitalization in patients older than 65 years
- Prevalence: 11.7% of population > 85 years old
- DRG 127 (Congestive Heart Failure):
  - Primary Dx 990,000 hospitalizations/yr
  - Secondary Dx 2,000,000 hospitalizations/yr
- Single largest expense for Medicare

AHA. 2011 Heart and Stroke Statistical Update
Left Ventricular Dysfunction

- **Systolic:** Impaired contractility/ejection
  - Approximately two-thirds of heart failure patients have systolic dysfunction\(^1\)

- **Diastolic:** Impaired filling/relaxation

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Lilly, L. Pathophysiology of Heart Disease. Second Edition p 200
ATLAS: High-dose ACE-I reduces adverse outcomes in heart failure

- Death: -8% reduction, $P = .07$
- CV mortality: -10% reduction
- Death/all hospitalizations: -12% reduction, $P = .002$
- CV hospitalizations: -16% reduction, $P = .05$
- HF hospitalizations: -24% reduction, $P = .002$

Relative Doses of ACEI

- Captoprili 50 mg TID
- Enalapril 20 mg BID
- Lisinopril 40 mg qd
- Ramipril 10 mg qd
Blockade of RAAS

Angiotensinogen (Liver)

- Angiotensin I
- Angiotensin II

\[ \text{Angiotensinogen} \rightarrow \text{Angiotensin I} \rightarrow \text{Angiotensin II} \]

\[ \text{Angiotensin I} \rightarrow \text{Angiotensin II} \]

\[ \text{Angiotensin II} \rightarrow \text{AT}_1 \text{ receptor} \rightarrow \text{vasodilation and cough} \]

\[ \text{AT}_1 \text{ receptor} \rightarrow \text{inactive peptides} \]

\[ \text{Bradykinin} \rightarrow \text{vasodilation and cough} \]

\[ \text{ACE Inhibitor} \rightarrow \text{inactive peptides} \]

\[ \text{ARB} \rightarrow \text{AT}_1 \text{ receptor blocker} \]

\[ \text{AT}_1 \text{ receptor} \rightarrow \text{vasodilation and cough} \]

\[ \text{AT}_2 \text{ receptor} \]

Vasodilation and cough

Bradykinin

Inactive peptides

ACE Inhibitor

ARB

AT$_1$ receptor blocker
CHARM-Alternative: ACEI intolerant Patients
Primary outcome CV death or CHF hospitalisation

Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up 6 months; placebo (n=84), carvedilol (n=261).

MOCHA* Multicenter Oral Carvedilol Heart Failure Assessment.

Mortality†

- Placebo
- 0.25 mg bid
- 12.5 mg bid
- 25 mg bid

Ejection Fraction

- Placebo
- 0.25 mg bid
- 12.5 mg bid
- 25 mg bid

**P<.005 vs placebo.
§P<.0001 vs placebo.

†Mortality was not a planned end point in this study.

Target Doses of Beta Blockers

- Carvedilol 25 mg BID
- Metoprolol Succinate 150 mg qd
- Coreg CR 80 mg qd
Randomized Aldactone Evaluation Study (RALES)

Inclusion Criteria
NYHA Class 3 or 4
LVEF < 35%
Cr < 2.5
K < 5.0


Probability of Survival

Spironolactone
Placebo

$P < 0.0002$

RR 27% lower
EMPHASIS-HF: Eplerenone in NYHA II

Hazard ratio, 0.63 (95% CI, 0.54–0.74)
P<0.001

Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P=0.008

Hazard ratio, 0.77 (95% CI, 0.67–0.88)
P<0.001

Hazard ratio, 0.58 (95% CI, 0.47–0.70)
P<0.001

Zannad F et al. NEJM 2010.
Hyperkalemia Secondary to Spironolactone for Heart Failure

Admission Rate For Hyperkalemia

Mortality from Hyperkalemia

AHeFT: Overall Survival

- NYHA III and IV
- Full medical therapy
- AA only

PARADIGM-HF: Sacubitril/Valsartan

A Primary End Point
Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P < 0.001

Cumulative Probability

No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

B Death from Cardiovascular Causes
Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P < 0.001

Cumulative Probability

No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

C Hospitalization for Heart Failure
Hazard ratio, 0.79 (95% CI, 0.71–0.89)
P < 0.001

Cumulative Probability

No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

D Death from Any Cause
Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P < 0.001

Cumulative Probability

No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

## PARADIGM-HF: Sacubitril/Valsartan

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LCZ696 No.</th>
<th>Enalapril No.</th>
<th>Primary End Point Hazard Ratio (95% CI)</th>
<th>P-value for interaction</th>
<th>Death from Cardiovascular Causes Hazard Ratio (95% CI)</th>
<th>P-value for interaction</th>
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<td>Time since diagnosis of heart failure</td>
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<td>≤1 yr</td>
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<td>&gt;1 to 5 yr</td>
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<td>&gt;5 yr</td>
<td>1291</td>
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</table>
Ivabradine: CV death or HF Hospitalization

Ivabradine: Hospitalization for HF

Ivabradine: CV death

Achieving Cardiac Resynchronization

Mechanical Goal: Atrially-synchronized biventricular pacing
CRT Improves Submaximal Exercise

CRT Control

Baseline (meters)

291 ± 101
305 ± 85

Change from Baseline (meters)

Distance Walked in 6 Minutes

P=0.004
P=0.003
P=0.005

Follow-up Period (Month)

0 1 3 6

Abraham W et al. NEJM 2002;346:1845-1853.
Patient Activity Improved Over Time in Patients with CRT

• 56 InSync III patients monitored minutes of daily patient activity
• 7-day means were compared from 1st week after implant at 2 weeks, 1 month, and 3 months.

CRT Improves Cardiac Function and Structure

Absolute Change in LVEF

Change in MR Jet Area

Change in LVEDD

Paired median change from baseline at 6 months. Error bars are 95% CI.

Baseline (%)  |  Baseline (cm²)  |  Baseline (mm)
--- | --- | ---
22 ± 6  | 7.2 ± 4.9  | 69 ± 10
22 ± 6  | 7.6 ± 6.4  | 70 ± 10

Indications for the Cardiac Resynchronization-ICD System

A CRT-ICD system is indicated for the reduction of HF symptoms in patients that meet the following criteria:

- Moderate to severe heart failure (NYHA Class II-IV)
- QRS $\geq 120$ msec (although substantially greater efficacy if $>150$ msec)
- LV ejection fraction $\leq 35$
- Symptomatic despite maximized medical therapy
# 2 Year Mortality with CRT/CRT-D in NYHA Class IV Patients

**TABLE 3. Mode of Death at 2 Years**

<table>
<thead>
<tr>
<th>Mode of Death</th>
<th>OPT (n/N=55/253)</th>
<th>CRT (n/N=79/538)</th>
<th>CRT-D (n/N=83/512)</th>
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</thead>
<tbody>
<tr>
<td><strong>All death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>29 (62)</td>
<td>34 (45)</td>
<td>34 (55)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>46 (26)</td>
<td>92 (23)</td>
<td>68 (20)</td>
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<tr>
<td><strong>HF</strong></td>
<td></td>
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<tr>
<td>NYHA class IV</td>
<td>14 (29)</td>
<td>17 (26)</td>
<td>21 (41)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>18 (10)</td>
<td>34 (10)</td>
<td>29 (8)</td>
</tr>
<tr>
<td><strong>Sudden cardiac death</strong></td>
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<td></td>
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<tr>
<td>NYHA class IV</td>
<td>8 (25)</td>
<td>11 (16)</td>
<td>4 (9)</td>
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<tr>
<td>NYHA class III</td>
<td>10 (5)</td>
<td>36 (9)</td>
<td>13 (5)</td>
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<td><strong>Other</strong></td>
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<tr>
<td>NYHA class IV</td>
<td>7 (28)</td>
<td>6 (12)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>18 (14)</td>
<td>22 (6)</td>
<td>26 (8)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).
### TABLE 4. Functional Capacity in NYHA Class IV Patients: Change From Baseline to 6 Months

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number</th>
<th>Median (Q1, Q3)</th>
<th>% Improved</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>6-Minute walk</strong></td>
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<tr>
<td>CRT/CRT-D</td>
<td>69</td>
<td>45.6 (-15.2, 106.4)</td>
<td>...</td>
<td>0.55</td>
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<tr>
<td>OPT</td>
<td>12</td>
<td>45.6 (-22.3, 60.9)</td>
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<td><strong>Quality of life</strong></td>
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<td>CRT/CRT-D</td>
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<td>-25.0 (-44.0, -8.0)</td>
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<td>52</td>
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Q Indicates quartile.
RAFT: CRT-D in NYHA Class II

HEART TRANSPLANTS
Kaplan-Meier Survival
(Transplants: January 1982 - June 2010)

Half-life = 10 years
Conditional half-life = 13 years

N = 96,273

Survival (%)

Years

Mechanical Circulatory Support
HeartMate II Improvements in BTT Survival from Clinical Trial to Commercial Use

P < 0.001 log-rank test

John, Naka, Smedira et al Ann Thor Surgery 2011
MCS Prior to Cardiac Transplantation

Year of Transplant

% of Patients


ECMO VAD+ECMO TAH LVAD+RVAD RVAD LVAD

JHLT in press, 2016
ENDURANCE Trial: DT Survival

Kaplan-Meier Survival
Overall HVAD Compared to Control

Log rank P value = 0.170

HVAD (n=296)
Control (n=149)

Presented by Pagani F. et al. ISHLT 2015, Nice, France
COMPANION: Secondary Endpoint of All-Cause Mortality

CRT vs. OPT: RR = 24%, p=0.060 (Critical boundary=0.014)
CRT-D vs. OPT: RR = 36%, p=0.003 (Critical boundary=0.022)

12-month Event Rates
OPT: 19%
CRT: 15% (AR=4%)
CRT-D: 12% (AR=7%)

Days from Randomization

% of Patients Event-Free

OPT
CRT
CRT-D

HR 0.76 (CI: 0.58-1.01)
HR 0.64 (CI: 0.48-0.86)
HeartMate III: Full MagLev™ Technology

**Key Design Features: Large and Consistent Gaps**

- HeartMate III secondary flow paths are \(~0.5 \text{ mm}\) along the side, and \(~1.0 \text{ mm}\) pump above and below the rotor.
  - Conversely, hydrodynamic bearings are typically operated with much smaller gaps, \(0.05 \text{ of a millimeter}\) or so.
- HeartMate III pump surfaces are flat and flow is undisturbed, wedging surfaces and other features required for hydrodynamic bearings are not required.
### Comparison of Blood Flow Pathway Sizes

Using a Red Blood Cell for Scale

<table>
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<tr>
<th></th>
<th>Gap Size</th>
<th># of Red Blood Cells</th>
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<td>Full MagLev</td>
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<td>Hydrodynamic Bearing</td>
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</table>

**Note:** The use of a red blood cell as a measuring unit is for illustration purposes and is not meant to imply actual blood flow quantities during operation.

Stacked RBCs

at least 20X larger blood flow paths
Artificial Pulse Overview

- The HM III with full magnetic levitation and wide gaps is intrinsically capable of very sharp speed changes, enabling an “artificial pulse” feature that has so far in pre-clinical studies proved to contribute negligible hemolysis and require low incremental power consumption.

- While unproven, augmenting the pulsatility that is generally diminished in rotary pump patients may have benefit for some patients or in certain circumstances, perhaps in part addressing adverse events such as; aortic insufficiency, bleeding and thrombogenesis.
Primary End Point Analysis (ITT)

Survival at 6 months free of disabling stroke or reoperation to replace or remove the pump

Non-inferiority Analysis
Absolute difference +9.4% (95% LCB -2.1%), P<0.0001

Superiority Analysis
HR 0.55, (95% CI 0.32-0.95), P=0.037

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LCB, lower confidence boundary, HR, hazard ratio, and CI, confidence interval
40 yo male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min Lisinopril 5 mg qd and Toprol XL 150 mg qd.

Next step should be:

a) Add aldactone 25 mg qd  
b) Add digoxin 0.125 mg qd  
c) Refer for CRT-D  
d) Increase Lisinopril to 10 mg qd  
e) Add corlanor
40 yo male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min Lisinopril 5 mg qd and Toprol XL 150 mg qd.

Next step should be:
a) Add aldactone 25 mg qd
b) Add digoxin 0.125 mg qd
c) Refer for CRT-D
d) Increase Lisinopril to 10 mg qd
e) Add corlanor
40 yo AA male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min Lisinopril 40 mg qd and Toprol XL 150 mg qd.

Next step should be:

a) Add aldactone 25 mg qd
b) Add digoxin 0.125 mg qd
c) Refer for CRT-D
d) Add hydralazine/nitrates
e) Add corlanor
Audience Response Question

40 yo AA male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min
Lisinopril 40 mg qd and Toprol XL 150 mg qd.

Next step should be:
a) Add aldactone 25 mg qd
b) Add digoxin 0.125 mg qd
c) Refer for CRT-D
d) Add hydralazine/nitrates
e) Add corlanor
40 yo white male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min. QRS duration 170 msec. Lisinopril 40 mg qd, Toprol XL 150 mg qd, aldactone 25 mg qd.

Next step should be:

a) Refer for CRT-D
b) Add hydralazine/nitrates
c) Add corlanor (ivabradine)
d) Add entresto (sacubitril/valsartan)
e) Change to Lisinopril to entresto (sacubitril/valsartan)
Audience Response Question

40 yo white male with NIDM and Class III heart failure. Creatinine 1.0 and K 4.1. LVEF 30%. HR 90/min. QRS duration 170 msec. Lisinopril 40 mg qd, Toprol XL 150 mg qd, aldactone 25 mg qd.

Next step should be:

a) Refer for CRT-D
b) Add hydralazine/nitrates
c) Add corlanor (ivabradine)
d) Add entresto (sacubitril/valsartan)
e) Change to Lisinopril to entresto (sacubitril/valsartan)
Conclusions

- ACEI/ARB/beta blocker doses should be maximized
- Aldosterone receptor antagonist for symptomatic patients
- Hydralazine/nitrates for symptomatic African Americans
- Consider Entresto (Sacubitril/Valsartan) as an alternative to ACEI/ARB in symptomatic LV systolic dysfunction
- Consider Corlanor (Ivabradine) in symptomatic patients with elevated HR
- CRT-D in patients who remain symptomatic, particularly NYHA Class II and III, and have prolonged QRS duration
- CRT of questionable benefit in NYHA Class IV patients
- MCS improves quality of life and functional capacity with a trade off of adverse events