Advances in Heart Failure Therapy

Joyce W. Wald, DO, FACC
Associate Professor of Clinical Medicine
Heart Failure/Transplant Program
Associate Medical Director, MCS Program
Director, Practice Development
University of Pennsylvania

Disclosure

• **Speakers bureau**
  – None

• **Advisory Board**
  – Medtronic

• **Funded research to our program**
  – Medtronic, Guidant, ACORN, Resmed
  – Novartis, Fujisawa, Roche, celladon etc…
  – Thoratec (now Abott)
  – Heartware (now Medtronic)
Today’s Agenda

• Background
  – We will be discussing SYSTOLIC heart failure: HFrEF
  – Evaluation for reversible causes

• Chronic systolic heart failure
  – Current therapies
  – How to tell a patient is failing despite treatment
  – New Therapies
    • Medical
    • Device
    • Clinical trials

• Acute systolic heart failure
  – Current and new therapies
  – Heart transplant and mechanical circulatory support
From: Patient Selection for Ventricular Assist Devices: A Moving Target


Current Estimate of the Number of Advanced HF Patients
This represents approximate number of potential VAD candidates.

Figure Legend:
Current Estimate of the Number of Advanced HF Patients
This represents approximate number of potential VAD candidates.
Etiology of Cardiomyopathy

- Abnormal loading conditions
  - Valvular disease
  - Hypertension
  - Shunts
- Toxins
  - Chemotherapeutics
  - Cobalt/heavy metal
  - Alcohol
- Genetic
  - familial
  - Muscular dystrophies
  - Mitochondrial disorders
  - Hypertrophic
  - ARVD
- Insults
  - Ischemia
  - Tachycardia
  - High PVC burden
  - Viral
  - Thyroid disease
- Unclear etiology
  - Peripartum
  - Idiopathic
  - HIV
- Infiltrative
  - Hemachromatosis
  - Sarcoidosis
  - amyloid

Cardiomyopathy evaluate for reversibility

- Alcohol intake?
  - In persons who consumed 70 g of ethanol (or the equivalent of 7oz of whiskey, 20 oz of wine, or 72 oz of beer [ie, six 12-oz cans]) per day for 20 years, 36% had an abnormal ejection fraction.
- Tachycardia mediated
- Asynchrony
  - PVC-induced (> 10%)
  - BBB
  - RV pacing
- Ischemia
- Valvular disease
- Consider RV biopsy

Simantirakis E. Arrhythmia-induced cardiomyopathies: the riddle of the chicken or the egg still unanswered? *Eur Space*. Nov 2011
Cardiomyopathy evaluate for reversibility

- When to perform endomyocardial biopsy

Think about myocarditis with arrhythmias, + troponin

Lymphocytic myocarditis

Giant Cell Myocarditis

Yeglee N et al Value of MRI in patients with a clinical suspicion of acute myocarditis EUR RAD 2007;17:2211
Gotsman & Keren Fulminant lymphocytic myocarditis vs giant cell myocarditis. ESCARDIO.org Oct 2008
**Cardiomyopathy**
evaluate for reversibility

- When to perform endomyocardial biopsy

Think Sarcoid with CHB, arrhythmias

Kandolin R et al. Circ Arrhythm Electrophysiol 2011;4:303-309

---

**Therapy For Chronic Systolic Heart Failure**

Diminishing Returns with Vasodilators & Neurohumoral Antagonists in HF

- Placebo
- Hydralazine
- ACE-I
- 1st Gen β-blockers (Metoprolol)
- 2nd Gen β-blockers (Carvedilol)
- ARBs & Aldo Antagonists
- NEP+ACE Inhibitors
- TNFα Antagonists
- Endothelin Antagonists

Event Rate

1980 1990 2000 2010

And Hijacked from Dr. Ken Margulies and then further modified

- EVEREST
  Tolvaptan vassspressin antagonist
- Protect
  Rolofylline: Adenosine antagonist
- TRIDENT-1
  Tonapofylline-adenosine antag
- Pre-RELAX-AHF
  Relaxin:vasodilator
Carvedilol Dose-Response Trial (MOCHA): Effect on Ejection Fraction and Morbidity

Changes in LVEF

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean change in LVEF (EF units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>6.25 mg bid</td>
<td>0.5</td>
</tr>
<tr>
<td>12.5 mg bid</td>
<td>1.0</td>
</tr>
<tr>
<td>25 mg bid</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Cardiovascular hospitalizations

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean number/subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.1</td>
</tr>
<tr>
<td>6.25 mg bid</td>
<td>0.2</td>
</tr>
<tr>
<td>12.5 mg bid</td>
<td>0.3</td>
</tr>
<tr>
<td>25 mg bid</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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

Adapted from Bristow et al, 1996.

*P<.05 vs placebo

BB Dose Matters: almost 20 years later!!!!!

Presented at HFSA 10/2015

<table>
<thead>
<tr>
<th>BB dose (carvedilol equivalent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low = &lt;25 mg daily</td>
</tr>
<tr>
<td>Hi = ≥25 mg daily</td>
</tr>
</tbody>
</table>

Baseline Heart Rate

<table>
<thead>
<tr>
<th>Low = &lt;70 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi = ≥70 bpm</td>
</tr>
</tbody>
</table>

LH - low dose, high HR
13% higher risk of bad outcome: All cause death, all cause hosp
The beneficial effect is beyond the HR effect, even if HR is already low

Aldosterone Inhibitors

**RALES Trial**
- 1663 NYHA III-IV
- 25 mg Aldactone vs Placebo
  - 30% reduction in death*
    - Progressive HF
    - SCD
  - 35% reduction in hospitalization
  - Significant improvement in NYHA functional class

*Pitt et al. NEJM 1999;341:709*

**EPHESUS Trial**
- 6632 pts 3-14 d after AMI, EF < 40%
  - And sign of HF
  - Or DM with or without signs of HF
- 50 mgQD Eplerenone vs placebo
  - Significant reduction in:
    - Death 14% v 17%
    - CVd/hosp 27% v 30%
    - SCD 4.9% vs 6%

*Pitt NEJM 2003;348:1309*

**EMPHASIS Trial**
N= 2737 with mild HF EF ≤ 35%
Improvement with Epleranone

*Zannad NEJM 2011;364:11*

Take Away Points

- **ACE-Inhibitors** are still first line therapy
- **ARBs** is as effective if ACE intolerant, the addition of ARB to ACE therapy may be done without harm, maybe some benefit, but close watch of potassium and renal function
- **Beta Blockers**: dose matters, try and achieve target doses, even at the cost of vasodilator dose
- We are using **aldosterone inhibitors** earlier, they are becoming also part of the mainstay of therapy
  - Caveat: compliance, Scr ≤ 2.5 and K ≤ 5
The Frequent Flyer

Non Compliant

Undertreated

The Truly Medically Refractory

Under educated

U can Never win

Solutions To Common Problems

Inotropes MCS Transplant

The keys:
Know WHO to intervene on
Know WHAT to intervene with

Solutions to common problems:
continued symptomatic LV dysfunction despite ACEI or ARB and beta-blockade

- Is BB dose at target?
- Remember to add Aldactone
- Don’t forget about digoxin
- evaluate for CRT/ICD
- Reevaluate for reversible causes
- Disease management: food/volume diary
- consider hydralazine-nitrate
- consider combination diuretics or loop with different bioavailability
  - Metolazone, diuryl
  - turosemide or bumetanide
Today’s Agenda

• Background
  – We will be discussing SYSTOLIC heart failure: HFrEF
  – Evaluation for reversible causes
• Chronic systolic heart failure
  – Current therapies
  – How to tell a patient is failing
  – New Therapies
    • Medical
    • Device
    • Clinical trials
• Acute systolic heart failure
  – Current and new therapies
  – Heart transplant and mechanical circulatory support

This patient is slipping!!!! Consider advanced therapies!!!!

• Intolerance of beta-blockers
• Intolerance of ACEi/ARBs
• Recurrent hospitalizations
• Need for inotropes
• Hyponatremia
• Progressive renal insufficiency
• Increasing diuretic need
• Living in a smaller and smaller space

Despite compliance with background therapy and diet
If you can’t get a patient to be compliant, advanced therapies is NOT the answer
Mortality Risk By Decreasing Quartiles of LVEF and GFR


Diuretics and Mortality – PRAISE1

*Levy ESC HF 2003*

Figure 2 -KM Survival - Daily Diuretic Dose mg/kg

\[ p < 0.0001 \]
Survival After HF Hospitalizations

Setoguchi et al Am Heart J 2007

Circulatory-renal limitations to ACEI use.

Kittleson et al. JACC 2003;41:2029
**BNP Concentration for the Prediction of Clinical Events**

*Death or Heart Failure Hospitalization*

- BNP > 480 pg/ml
- BNP 230-480 pg/ml
- BNP < 230 pg/ml

N = 325


---

**The Prognostic Value of Maximal Oxygen Consumption**

- VO₂ > 14 ml/Kg/min
- VO₂ ≤ 14 ml/Kg/min (listed)*
- VO₂ ≤ 14 ml/Kg/min (not listed)*

* p<0.005 for VO₂ ≤ 14 vs > 14

*Circulation 1991:83:778-786*
Today’s Agenda

• Background
  – We will be discussing SYSTOLIC heart failure: HFrEF
  – Evaluation for reversible causes

• Chronic systolic heart failure
  – Current therapies
  – How to tell a patient is failing
  – New Therapies
    • Medical
    • Device
    • Clinical trials

• Acute systolic heart failure
  – Current and new therapies
  – Heart transplant and mechanical circulatory support

What’s new in Chronic HF Therapy?

• NECTAR-HF
  – Chronic vagal stimulation

• CUPID
  – Intracoronary infusion of SRCA 2a

• CONFIRM-HF
  – Iron therapy symptomatic anemic HF patients

• PARADIGM-HF
  – Angiotensin receptor-neprilysin inhibitor-LCZ696

• SHIFT
  – Ivabradine
Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApY foR Heart Failure randomized controlled trial

N=96 2:1 randomization
6 month follow up
Although no change in LV end syst diam
Significantly improved quality of life
Need larger trials

Clinical/Translational Research

Long-Term Effects of AAV1/SERCA2a Gene Transfer in Patients With Severe Heart Failure

N=39 patients received IC adeno associated sarcoplasmic reticulum CA2 ATPase v placebo

- @ 3 years decrease in:
  - MI
  - Worsening HF
  - HF-related hospitalization
  - VAD/OHT/Death
- Results carried out ot 3 years
Ferritin < 100 ug/L or transferrin sat was < 20%.

N=459, increase QOL, increased smwt, decreased Symptoms and trend to increased time to first rehospitalization

**Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency**

Stefan D. Anker, M.D.
Gerasimos Filip, M.D.
Kenneth Dickstein, M.D.
Thomas F. Lüscher, M.D.
Joanna Niepgowska, M.D.
Barbara von Eise, M.D.
Philip A. Poole-Wilson, M.D.

Iron therapy for the treatment of iron deficiency in chronic heart failure: intravenous or oral?

Thomas McDougall† and Alan C. Mackay‡

N = 8442 NYHA II, IV HF
EF < 40% LCZ696 200 mg BID vs enalapril 10 mg bid.

FDA approval but await long term OC.

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides to Balance Maladaptive Mechanisms in Heart Failure


N = 8442 NYHA II-IV HF
EF ≤ 40% LCZ696 200 mg BID vs enalapril 10 mg bid.

LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

FDA approval but await long term OC.
Ivabradine selectively inhibits the sinus node thereby decreasing myocardial oxygen demand without effecting inotropy or blood pressure.

Swedberg Lancet 2010;376:875

Inclusion Criteria Background Tx

- >18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF ≤35%)
- Heart rate >70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure <12 months
Background beta-blocker treatment

<table>
<thead>
<tr>
<th>Main reasons for not prescribing beta-blocker, %</th>
<th>Main reasons for not achieving beta-blocker target dose, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine n=344</td>
<td>Ivabradine n=2099</td>
</tr>
<tr>
<td>Placebo n=341</td>
<td>Placebo n=2126</td>
</tr>
<tr>
<td>COPD</td>
<td>Hypotension</td>
</tr>
<tr>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>32</td>
<td>45</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Fatigue</td>
</tr>
<tr>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>Asthma</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Cardiac decomp.</td>
<td>Dizziness</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>


Mean heart rate reduction

70% of patients on ivabradine 7.5 mg bid

Conclusion

Ivabradine significantly reduces major risks associated with heart failure (f/u up to 23 months):

- 18\% reduction in CV death or hospital admission for worsening HF
- 26\% reduction in death from heart failure
- 26\% reduction in hospital admission for worsening heart failure

Benefits are apparent early (within 3 months), are consistent in predefined subgroups, and have been demonstrated on top of recommended therapy.

Treatment is well tolerated.


FDA

- On April 15, 2015 the FDA approved Ivabradine in the US
  - “To reduce the risk of heart failure hospitalization”
  - LVEF less than 35\%
  - Heart rate above 70 on maximally tolerated beta blockade
Take Away Points

Vagal nerve stimulation did not improve markers of remodeling, but did improve symptoms, more to come

- **IV iron** is beneficial in symptomatic HF patients, stay tuned for PO iron
- Intracoronary infusion of AAV1/SERCA2a in patients with advanced heart failure, positive signals of cardiovascular events which persist for years.
  - No safety concerns were noted during the 3-year follow-up.
  - Larger scale CUPID 2 was negative:
    - ?correct carrier AAV1 VS AAV9
    - ?correct molecule to effect cell function? S100A1

Take away points (cont’d)

- **LCZ696**: angiotensin-neprilysin inhibitor reveals significant reduction in cardiovascular events compared to ACE-I
  - Now FDA approved
- **Ivabradine**: SA node inhibitor leads to a significant reduction in morbidity and mortality in patients with systolic HF
  - Heart rate above 70 on maximally tolerated beta blockade
Today’s Agenda

• Background
  – Evaluation for reversible causes
  – How to tell a patient is failing

• Chronic systolic heart failure
  – Current therapies
  – New Therapies
    • Medical
    • Device
    • Clinical trials

• Acute systolic heart failure
  – Current and new therapies
  – Heart transplant and mechanical circulatory support

Severe Heart Failure
Recognizing the “Walking Wounded”

• Underperfused
  – Walk in, drive in, fly in
  – Obvious
    • Malignant arrhythmias
    • Low BP
  – Less Obvious (3T’s)
    • End organ underperfusion despite a normal BP
      – Talk: lethargic, breathless at the end of a sentence
      – Touch: cool, pulses are low, lips/ears turn blue when they lay back for exam
      – Testing:
        • Lactate
        • Tbil/LFTs
        • Scr/BUN
New York Heart Association (NYHA) Classification of Heart Failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath (dyspnea).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or shortness of breath (dyspnea).</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or shortness of breath (dyspnea).</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of fatigue, palpitation or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.</td>
</tr>
</tbody>
</table>

INTERMACS Registry: Patient Profiles

**INTERMACS Registry for Mechanical Circulatory Support**

- **Profile 1**: “Advancing Decompensation”
  - describes patients who are in rapid deterioration

- **Profile 2**: “Progression of Failure”
  - describes clinical progression of functional, hemodynamic and laboratory decompensation

- **Profile 3**: “Stable but Inotropic Dependent”
  - describes patients who are stable on inotropic support

- **Profile 4**: “Recurrent Advanced Heart Failure”
  - describes patients who are in decompensation

- **Profile 5**: “Sustained Improvement”
  - describes patients who are improving after initial failure

- **Profile 6**: “Sustained Inhibition”
  - describes patients who are in stable condition

- **Profile 7**: “Advanced NYHA III”
  - describes patients who are in advanced NYHA III

The Right Time for VAD Implantation

**Key to Survival After Mechanical Circulatory Support**

Operative Risk Death

Worsening of nutritional state, end-organ and RH function

Successful Implants

1-Year Survival 53 – 94%

Futile Implants

1-Year Survival 6%

Too Late

Deaths related to pt selection not device malfunction
Acute Decompensated heart failure vs SHOCK

- **ADHF:::** congestion, possibly low output, quickly responsive to medical intervention
  - Medical therapy
- **SHOCK:::** unstable hemodynamics, end organ underperfusion
  - Device therapy
    - Ischemic shock AMI
    - Hemodynamic shock
    - Arrhythmic shock

**Goals of Therapy:**

Chronic Versus Acute HF

- **Long-Term Goals**
  - Ventricular Remodeling
  - Vascular Remodeling

- **Short-Term Goals**
  - Increased PCWP
  - Decreased CO

- Neurohormonal Antagonists
- Hemodynamic Agents

- Prevent CHF Progression And Death
- Relief of Symptoms Stabilization of Organ Function

PCWP = pulmonary capillary wedge pressure.
RELAX-AHF and Pre RELAX-AHF Trials

N=1395

Concl: N=1395 decreased 180 day mortality, markers of end organ damage (scr, transaminases) and markers of decongestion (BNP) were improved in the seralaxin groups. Ongoing RELAX-AHF2: appro 6800 pts; completed 1/26/17; ClinicalTrials.gov Identifier:NCT01870778

Metra JACC 2013: 61;196-206

More About Congestion

The CHAMPION Trial Abraham LANCET 2011

PCWP after tailored therapy
Predicted outcomes

LWS AJC 1990

Protocol: if PAP pressures elevated:
first: increase diuretics
second: increase vasodilators

Target Pressures:
sPAP: 15-35
dPAP: 8-20
mPAP: 10-25
TO: Cardiology Faculty, Fellows and Advanced Practitioners
FROM: Scott Manaker, MD, Ph.D.
DATE: October 23, 2015
RE: CardioMEMS

As you may know, CardioMEMS is an implantable hemodynamic monitoring device that allows remote monitoring of hemodynamic data in patients with heart failure. This monitoring is distinct from, and not reportable as, monitoring the patient’s fluid status via daily impedance measurements taken by an implantable CRT-D or ICD device (eg, Optivol - reported with CPT 93297 and 93299 for the professional and technical components, respectively). **Currently, coverage for remote monitoring of CardioMEMS is being deemed investigational and experimental by Medicare, despite FDA approval of the device.**

CardioMEMS remote monitoring cannot be reported at this time with any specific CPT procedure code. In the near future, this may change with services reportable for patients enrolled in a clinical trial. Please feel free to contact Carol Pohlig BSN, RN, CPC (carol.pohlig@uphs.upenn.edu or 215-614-0240) for additional questions or concerns involving billing and coding of this or other remote cardiac monitoring services. Thank you for your attention to this matter.

**Congestion: what’s new with diuresis?**

Murray AJM 2001

Ferreira EJIM 2014

Combination of Loop Diuretics With Thiazide-Type Diuretics in Heart Failure

Jacob C. Jumper, MD,* Tracy A. DeWalt, RD, PatriciaD. BCPN,* Adrian F. Hernandes, MD†‡

may be more effective, but use with caution: must watch Na, Potassium and magnesium!
Congestion: what’s new with diuresis?

The DOSE Trial Felker NEJM 2011

Trend towards more weight loss in the high dose strategy and decreased DOE, it was at the cost of trend towards higher Scr (that did not last) out to 60 days. Also, the low dose group did require an increase in dose

Neseritide

- **V-MAC Trial** 489 pts (IV)
  - Placebo v IV NTG vs Nes 0.01
  - Efficacious in lowering PCWP, PAP & sx

- **Efficacy Trial** 127 pts (RHC)
  - Placebo v 0.015 Nes v 0.03 Nes [X 6 h]
  - No diuretics
  - Significant decrease in PCWP and symptoms and increase in UO

- **Comparative Trial** 305 pts
  - Standard tx v 0.015 v 0.03 [up to 7 d]
  - Improvement in global clinical status similar to ST

- **PRECEDENT Study** 245 pts (III/IV)
  - DB (5) v 0.015 Nes v 0.03 Nes
  - DB proarrhythmic
  - Nes no increase in arrhythmias, heart rate, despite greater decrease in BP

- **Sackner-Bernstein** (meta-analyses)
  - Mortality (Circ 2005)
  - Renal failure (JAMA 2005)

- **E. Braunwald Panel’s Report**
  - June 13, 2005
  - Serum creatinine increase > 0.5 mg/dl (VMAC)
    - Control 7 % (5 days)
    - 21% (30 days)
    - Neseritide 8% (5 days)
    - 28% (30 days)
  - Mortality
    - Completed trials: trend increase in 30 d mortality
      - Approximately 1.3 HR, 30% increase
      - Confidence intervals around this ratio are wide
        - No increase in 180 day mortality
Nesiritide

Braunwald Panel conclusions

- Conduct a large (several thousand subjects) trial of clinical outcomes to assess further benefits and risks of nesiritide compared to standard therapy in acute, decompensated heart failure and severe dyspnea

- Current use
  - In hospital
  - Acutely decompensated Heart failure
  - Dyspnea at rest

- And should not be used
  - to replace diuretics
  - or as outpatient

ASCEND Trial

N= 7141 ADHF
Neseritide had no effect on renal function
Out to 30 days
Change in renal function is associated with
30 day mortality or HF rehospitalization

Van Deursen CIRC 2014;130:958

Mechanical Fluid Removal

Clinical Trial

Ultrafiltration is Associated With Fewer Rehospitalizations than Continuous Diuretic Infusion in Patients With Decompensated Heart Failure: Results From UNLOAD

Van Deursen MD, FAC, FANA., Mitchell T, Gaetzerling, MD, FACC, FANA, James, John K, Torbick, MD, FACC, FANA, and Far A, Ajour, MD, FACC.

Cardiorenal Rescue Study in Acute Decompensated Heart Failure: Rationale and Design of CARRESS-HF, for the Heart Failure Clinical Research Network

UF lead to worse renal function and no decrease in hospitalizations

Do Any Patients with Acute Decompensated Heart Failure and Acute Cardio-Renal Syndrome Benefit from Ultrafiltration?

Fig. 3. Freedom from heart failure rehospitalization. Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration (red line), intravenous (IV) bolus diuretic (green line), and IV continuous diuretic (blue line) groups.

Testani Sem in Dialysis 2014;27(3):231
Inotropic Therapy in Patients With ADHF

- Routine use not indicated in short- or long-term setting (despite low EF)
- Rather, inotropes should only be used in patients with:
  - Cardiogenic shock ie: signs of end organ underperfusion
  - Decompensated patients refractory to diuretics
  - Short-term bridge to definitive treatment such as revascularization or cardiac transplantation
  - To optimize vasodilator therapy or add BB therapy


Inotropes

- Digoxin: improved QOL
- Dobutamine: beta agonist
- Milrinone: PDE inhibitor
- CLR325 trial: more to come
- BMS study: BMS-986231

Hasenfuss & Teerlink EHJ 2011
Heart Failure Studies

- **Human Heart Tissue Protocol** (Kenneth Margulies, MD)
  - To study heart tissue specimens in human heart failure. All patients listed for transplant or VAD are asked to participate.
  - As well as non-failing hearts that are not suitable for heart transplant
    - 3 types of hearts:
      - Failed (evaluated at time of OHT)
      - Failed but rested (after LVAD support)
      - Non-failing heart
    - *Dr. Margulies has assembled the largest biorepositories of human heart samples in the world*

- **Samples**
  - Processed for study
    - With clinical data
  - Banked for future study

- **Observations**
  - Failed myocyte
    - Down regulation of B receptors
    - Deplete of SRCA 2a

- **Recovery Plan**
  - Promoting growth of new cells?
  - Improving function of existing cells?
  - VAD as a platform

K Margulies, Biorepository, University of Pennsylvania
Recovery at Penn

Study Protocol
- De novo
  - Gene therapy
  - Stem cell therapy
- LVAD platform
  - Clenbuterol
  - Stem cell
  - OMM

- Planned
  - Short duration of HF
  - Reversible insult
- Surprise

Recrudescence with non compliance

Vasodilator Therapy
Ace-inhibitors & H/I
B-Blockers

ARBs
Aldosterone Inhibitors

CRT
Inotropes CHF soln Devices
OHT VAD
Advanced Surgical Therapies:
Heart Transplant or VAD Therapy

Are they sick enough For Transplant/VAD?
Inotropes
Poor cardiac reserve
VO2 < 14
Despite OMM
Limitations are only
Cardiac
Intractable arrhythmias

Any other organs That limit life span?
Cancer
Diabetes
Lung disease
pulmonary HTN
Liver disease
Renal disease

Are they healthy Enough to undergo Surgery?
Malnourished
Too deconditioned
Liver failure
Do they have Social Support?

Relative age cut off for heart transplant is 65 yo
Age cut off for Heart Lung is 55 yo
Age cut off for heart liver or heart kidney is 60 yo

Heart Transplant vs LVAD/D T
How to Choose?

Are they sick enough For Transplant/VAD?
Inotropes
Poor cardiac reserve
VO2 < 14
Despite OMM
Limitations are only
Cardiac
Intractable arrhythmias

Age over 65
Concern for worsening co morbidities with immunosuppression
DM
Need to test compliance recent smoking recent non compliance
Need to test social support
Malignancy < 5 years (treated) with a good prognosis

BTT: bridge to transplant  DT: destination therapy  BTD: bridge to decision  BTI: intent
How to Choose a Device?
When to think about needing a device
- End organ perfusion that is not improving despite medical hemodynamic therapy
  - Intropes
  - Hypotension
- Ischemia with a large territory at risk
- Hemodynamically unstable arrhythmia

• Temporary devices
  - Crash and burn
  - Unknown
  - Reversible insult

• More permanent devices
  - BTT, DT, Recovery

Indication For Device
Determines Which Device(s) to Pull off the Shelf

• BTT: (Bridge to Transplant)
  - Any device
    - right sided support alone
    - Left sided support alone
    - Biventricular support

• DT: (Destination Therapy)
  - Left sided support only
    - REMATCH Trial: HM I > OMM
    - HM II Trial: HM II > HM I (BTT and DT)
    - MOMENTUM: HM II vs HM III (BTT and DT)

• Crash and Burn: Intermacs 1, unknown patient.
  - Temporary devices
Temporary Devices

**IABP**
- Tandem heart
- ECMO

Increase Myocardial demand:
- Tandem heart
- ECMO

**FULL SUPPORT**

**Shock with Acute MI**

Cheng EuHJ 2009
Meta analysis

![Meta-analysis table](image)

**Figure 3** Meta-analysis showing the relative risk of crude 30-day mortality with use of percutaneous left ventricular assist devices. Random effects models were used for meta-analysis. Weighted mean differences with 95% confidence intervals are presented on the right of the figure. IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

LVAD: Impella 2.5 vs IABP

**WORKS IN PROGRESS**

A Randomized Clinical Trial to Evaluate the Safety and Efficacy of a Percutaneous Left Ventricular Assist Device Versus Intra-Aortic Balloon Pumping for Treatment of Cardiogenic Shock Caused by Myocardial Infarction

Maltez Sferrazza, MD, Lilli Hintz, MD, Ina Rues, MS, Georg Struthk, MD, J Lorenzo, MD, Fagel, MD, Robert Reus, MS, MHC,_PC, Jose Dordings, MD, PhD, Alena Kramat, MD, Albert Schoning, MD
**Take away points**

**Congestion** is a target of therapy as well a marker of outcome

- If patient remains congested despite OMM, they are at high risk for poor outcome w/o aggressive intervention
- **IV diuretics**: Continuous infusion is no better than bolus, but also not harmful
- **Combination diuretics** are safe but RQ close monitoring of labs
- **Mechanical unloading (UF)** may have earlier decongestion, but no definite improvement in outcomes (conflicting results)

• **Inotropes** should not be used routinely for ADHF, however in select patients:
  - End organ under perfusion during ADHF refractory to standard therapy (vasodilators, diuresis)
  - Bridge to advanced therapy to maintain end organ function
  - Exciting new molecules to help improve myocardial performance without the cost of increasing mortality
Take away points (cont’d)

**Neseritide** is safe and effective for decongestion, renal perfusion and optimization of hemodynamics –when used correctly

- Must be able to recognize the **walking wounded**
- Outcomes are better, no matter the therapy, if patients are **recognized and referred early** for advanced therapy
- The survival for **SHOCK** is still poor
  - Even contemporary data shows a 30 d mortality of 46%
  - **Temporary devices** for the acutely ill with MOF: impella and tandem heart have proven hemodynamically superior to IABP, however in small trials, this has not translated to improved 30 day mortality.

Conclusions

**Chronic heart failure**

- Ambulatory patients on medical therapy
  - **BB therapy** is important and dose matters
  - **Aldosterone inhibitors** are becoming a mainstay of therapy
  - Consider **iron** for symptomatic HF pts who are iron deficient
  - **Ivabradine** (if HR > 70 despite OMM) improved outcomes
    - FDA approved, await launch and
  - **LCZ696**: angiotensin neprilysin inhibitor: await FDA approval
  - Targeting congestion is important to patient outcomes
    - cardiomems PA monitoring
  - Target **recovery**: besides aggressive medical therapy,
    - cell therapy, gene therapy, mechanical support

- **Acute decompensated heart failure**
  - IV diuresis bolus = continuous, high dose better
  - **Neseritide** is safe but should be used selectively
  - **Seralaxin** may have a benefit RELAX-AHF 2 is underway
Conclusions (cont’d)

• Advanced heart failure
  – End organ under perfusion or severe symptoms despite maximal therapy
  – Acutely ill, refractory to medical therapy
  • Temporary devices
    – IABP
    – Impella 2.5, CP, 5.0
    – Tandem heart, RP
    – ECMO
  • Permanent Platforms: better outcome with earlier tx
    – Heart transplant
    – Durable VADs (Mechanical Circulatory Support)
      • HM II
      • Heart ware
      • with exciting new, smaller devices on the horizon

THANK YOU!!