Review of Heart Failure Disease Management

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Disclosure

• Speakers bureau
  – None
• Advisory Board
  – Medtronic
• Funded research to our program
  – Medtronic, Guidant, ACORN, Resmed
  – Novartis, Fujisawa, Roche, celladon etc...
  – Thoratec
  – Heartware
Today’s Agenda

• Background
  – We will be discussing SYSTOLIC heart failure: HFrEF
  – 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
From: Patient Selection for Ventricular Assist Devices: A Moving Target


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 7 oz 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

Cardiomyopathy evaluate for reversibility

- When to perform endomyocardial biopsy

Yegle 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

EVEREST
tolvaptan vasopressin antagonist

Protect
Rolofylline: Adenosine antagonist

TRIDENT-1
tonapofylline-adenosine antag

Pre-RELAX-AHF
Relaxin: vasodilator

And Hijacked from Dr. Ken Margulies and then further modified

Carvedilol Dose-Response Trial (MOCHA): Effect on Ejection Fraction and Morbidity

Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up duration 6 months; placebo (n=84), carvedilol (n=261). Adapted from Bristow et al, 1996.

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

Presented at HFSA 10/2015

### 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 *despite ACEI or ARB and beta-blockade* dysfunction

- Remember to add Aldactone
- Don’t forget about digoxin
- evaluate for CRT/ICD
- Disease management: food/volume diary
- consider hydralazine-nitrate
- consider combination diuretics or loop with different bioavailability
  - Metolzone, diuryl
  - turosemide or bumetanide
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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
Survival After HF Hospitalizations

Median Survival Years

- No CKD: 1 hosp (11,110), 2 hosp (3264), 3 hosp (5472), 4 hosp (4098)
- With CKD: 1 hosp (11,110), 2 hosp (3264), 3 hosp (5472), 4 hosp (4098)
- Age 75-85: 1 hosp (11,110), 2 hosp (3264), 3 hosp (5472), 4 hosp (4098)
- Age > 85: 1 hosp (11,110), 2 hosp (3264), 3 hosp (5472), 4 hosp (4098)

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

Days

0% 5% 10% 15% 20% 25% 30% 35% 40% 45%

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

Duration of Follow-up (Mo)

Cumulative Survival (%)

Circulation 1991;83:778-786

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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

Analysis of Recurrent Cardiovascular Events and Mortality

Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease phase 2 survival curve for all-cause mortality in high-dose recombinant adeno-associated viral vector (AAV) containing human sarcolemmal reticulum Ca2+ ATPase2a (SERCA2a) gene (AAV1/SERCA2a) group versus placebo.

@ 3 years decrease in:
MI
Worsening HF
HF-related hospitalization
VAD/OHT/Death
Results carried out at 3 years

N=39 patients received IC adeno associated sarcoplasmic reticulum CA2 ATPase v placebo
N=459, increase QOL, increased smwt, decreased Symptoms and trend to increased time to first rehospitalization

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

**Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure**

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

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

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
Main reasons for not achieving beta-blocker target dose, %

<table>
<thead>
<tr>
<th>Reason</th>
<th>Ivabradine n=2099</th>
<th>Placebo n=2126</th>
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<tbody>
<tr>
<td>Hypotension</td>
<td>44</td>
<td>45</td>
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<tr>
<td>Fatigue</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>12</td>
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<tr>
<td>Bradycardia</td>
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Main reasons for not prescribing beta-blocker, %

<table>
<thead>
<tr>
<th>Reason</th>
<th>Ivabradine n=344</th>
<th>Placebo n=341</th>
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<tr>
<td>COPD</td>
<td>37</td>
<td>32</td>
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<tr>
<td>Hypotension</td>
<td>17</td>
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<td>Asthma</td>
<td>10</td>
<td>11</td>
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<tr>
<td>Cardiac decomp.</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
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Background beta-blocker treatment


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

With 70% of the patients on 7.5 mg of ivabradine daily and avg HR 74 (ivabradine gp) vs 64 (placebo)

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 event 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

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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>
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<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (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, rapid/irregular heartbeat (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, rapid/irregular heartbeat (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, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.</td>
</tr>
</tbody>
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INTERMACS Registry: Patient Profiles

- Profile 1: "Crushing and buzzing" - critical cardiogenic shock
- Profile 2: "Progressive decline" - inotropic dependence with continued deterioration
- Profile 3: "Low but inotrope dependent" - describes clinical stability on mild-to-moderate doses of intravenous inotropes
- Profile 4: "Recurrent advanced heart failure" - "recurrent" rather than "refractory" decompensation
- Profile 5: "Exertion intolerant" - describes patients who are comfortable at rest but are exercise intolerant
- Profile 6: "Exertion limited" - a patient who is able to do some mild activity, but fatigue results within a few minutes (usually means physical exercise)
- Profile 7: "Advanced NYHA III" - describes patients who are clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent

NYHA

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INTERMACS

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</thead>
</table>
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

Futile Implants

Too Late

Successful Implants

1-Year Survival 53 – 94%

1-Year Survival 6%

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**
- Prevent CHF Progression
- And Death

**Hemodynamic Agents**
- 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 serelaxin groups. Ongoing RELAX-AHF2: approximately 6800 patients

Metra JACC 2013: 61;196-206
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

P=0.03

Purpurexide

Torsamide

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

The DOSE Trial Felker NEJM 2011
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 (S) 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)
  - Neseritide 8% (5 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

**Braunwald Panel conclusions**
- Conduct a large (several thousand subjects) trial of clinical outcomes to assess further benefits and risks of neseritide 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

Clinical Trial: Methods and Design

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

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

Digoxin: improved QOL
Dobutamine: beta agonist
Milrinone: PDE inhibitor
CLR325 trial: more to come

Hasenfuss & Teerlink EJH 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
Heart Failure Studies

• Observations
  – Failed myocyte
    • Down regulation of β 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
  – CUPID Study
  – STOP-HF Study

• Planned
  – Short duration of HF
  – Reversible insult
  • Surprise
    WH: 50%, 1 y
    CJ: 55%
    TJ: 35-40%, 2 1/2
    LD: 60%
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/DT
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
Impella 2.5, CP 5.0
FULL SUPPORT

Increase Myocardial demand:
Tandem heart
ECMO
Shock with Acute MI

Meta analysis

LVAD: Impella 2.5 vs IABP

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

Figure 2 Meta-analysis showing the mean difference in haemodynamic parameters 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.

Permanent Mechanical Circulatory Support

1990’s 2000 2010 and Beyond
Take away points

- **Congestion** is a target of therapy as well as a marker of outcome
  - If patient remains congested despite OMM, they are at high risk for poor outcome without aggressive intervention
  - **IV diuretics**: Continuous infusion is no better than bolus, but also not harmful
  - **Combination diuretics** are safe but require 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
      – Tandom 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!!