Practical Pearls in Optimizing Heart Failure Guideline Directed Therapy in Outpatient Care

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Disclosures

- None
Case Discussion

- MF presented at age 50
  - Shortness of breath on exertion
  - No chest pain
  - RBBB with occasional PVCs

- Social History
  - Born in El Salvador and moved to US 1979
  - Worked as a housekeeper
  - No tobacco, alcohol or drugs
  - Married with 3 children

- Family History
  - Father had CAD
  - Mother had dyslipidemia
Case Discussion

- Seen in the ER
- New diagnosis of HF
- Refused admission
- Started on diuretic and instructed to f/u with PCP
Heart Failure Impact

- 5.7 million Americans have HF, with >8 million by 2030\(^1\)
- Cost each year is \sim\$31 billion, increasing to \sim\$70 billion by 2030\(^1\)
- 1 in 9 death certificates mention HF\(^1\)
- Over 65,000 people die from HF yearly\(^1\)
- Average 5-year mortality is \sim50\%\(^1\)
- Readmission rates within 30 days are 20-25\%\(^2\)

Heart Failure

- “A common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.”¹

- HFrEF: LVEF ≤ 40%
- HFrEF: LVEF > 40%

Etiologies of Heart Failure/Basic Screening

- CAD
- HTN
- Tachycardia (ie: Afib)
- Valvular
- Restrictive: amyloid, sarcoid
- Thyroid
- Drugs and alcohol
- Postpartum

- Chemotherapy
- Anemia
- Diabetes
- Chagas
- Takotsubo
- Idiopathic
ACC/AHA Stages of HF and NYHA Functional Classification of HF

<table>
<thead>
<tr>
<th>ACC/AHA HF stage</th>
<th>NYHA functional class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without HF</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current HF symptoms</td>
<td>II Symp. with moderate exertion</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions</td>
<td>III Symp. with minimal exertion</td>
</tr>
<tr>
<td></td>
<td>IV Symptomatic at rest</td>
</tr>
</tbody>
</table>

Symptoms of Heart Failure

- Shortness of breath
- Swelling of feet & legs
- Chronic lack of energy
- Difficulty sleeping at night due to breathing problems
- Swollen or tender abdomen with loss of appetite
- Cough with frothy sputum
- Increased urination at night
- Confusion and/or impaired memory
Pathophysiology

Myocardial Injury \(\rightarrow\) Fall in LV Performance

**NEUROHORMONAL ACTIVATION:**
Renin Angiotensin II-Aldosterone Axis
System, Sympathetic Nervous System
Endothelin, TNF, Norepinephrine

Myocardial Toxicity

Remodeling and Progressive worsening of LV function

Mortality and Morbidity

Peripheral vasoconstriction
Hemodynamic alterations

Heart Failure Symptoms:
dyspnea, fatigue, edema

BNP (B-type natriuretic peptide)
Case Discussion

- **Echo:** LVEF 15-20%. Dilated left ventricle with severe global hypokinesis. Left atrial enlargement. Moderate MR and TR.

- **Positive Chagas Serologies**

- **LHC:** Clean coronary arteries.
  - LVED = 28 mmHg (normal range 3-12)
Chagas Disease

- Carlos Chagas- Brazilian physician, focused on malaria
- Discovered a Trypanosome organism
- Named it in honor of his mentor, Oswaldo Cruz (Trypansoma Cruzi)
- Endemic in Mexico, Central and South America
- Majority of transmissions are vector-borne (>80%)
Chagas Infection

**Acute Disease**
- Viral syndrome: low-grade fevers, body aches, headache, fatigue
- Can last up to several weeks and is usually not recognized.
- Rarely, patients can develop acute myocarditis and heart failure with mortality of 5%.
- 90% cure rate with treatment, but rarely diagnosed and usually enter next stage of disease.

**Indeterminate Stage**
- After the acute illness, patients enter into a chronic carrier state in which there are no symptoms.
- This phase can last between 10-20 years.
- The parasite is dormant in tissue and is usually not detectable in the blood.
- About 40-50% of patients will eventually progress to develop clinically evident disease.
Chagas Disease: Chronic Manifestations

- The *most common complication* of chronic Chagas disease is *cardiac*.
  - The earliest manifestation is conduction abnormalities on EKG, i.e. RBBB, LAFB, LPFB
  - This is then followed by slow progressive enlargement in heart size
  - Finally, there is the development of symptoms of overt heart failure and sudden death from arrhythmia
  - At this final stage, the disease becomes irreversible and treatment with antiparasitic therapy does not alter the disease course
Chagas in the US

- Believed to be primarily a disease of Latin America and not clinically relevant in the US
- “Disease of the poor”

Testing:
- The commercially available test in the community is the TESA
- Confirmatory testing is done through the CDC

Treatment:
- Only 2 agents to treat: nifurtimox and benznidazole—chemo-like drugs
- Amiodarone
Chagas in Primary Care

- Screening Latin American Immigrants for Chagas
  - Unexplained cardiomyopathy
  - Unexplained ventricular arrhythmias, tachy or brady arrhythmias
  - Apical aneurysm
- Maintain long-term follow-up to monitor for disease progression
- Referral to Chagas treatment center
Olive View-UCLA Medical Center

- 1st National Center of Excellence for the evaluation and treatment of Chagas Disease
- Collaborative approach with the Red Cross and the Centers for Disease Control (CDC)

Questions or Referrals

Olive View-UCLA Medical Center
Salvador Hernandez, Chagas Clinic Coordinator
Phone: 818-364-4287
Email: salherandez@dhs.lacounty.gov or Chagas@dhs.lacounty.gov
Website: www.chagas21.wix.com/chagasla
<table>
<thead>
<tr>
<th>Class</th>
<th>Trial</th>
<th>Drug</th>
<th>Main Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi</td>
<td>CONSENSUS</td>
<td>Enalapril v. placebo</td>
<td>40% ↓ all-cause mortality; ↓CHF progression</td>
</tr>
<tr>
<td></td>
<td>SOLVD</td>
<td>Enalapril v. placebo</td>
<td>16% ↓ mortality (mild-mod HF)</td>
</tr>
<tr>
<td></td>
<td>Val-HeFT II</td>
<td>Enalapril vs. hydral + ISDN</td>
<td>ACEi better</td>
</tr>
<tr>
<td>ARB</td>
<td>CHARM</td>
<td>Candesartan v. placebo (added to ACEi, BB)</td>
<td>↓CV mortality; ↓HF hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Val-HeFT</td>
<td>Candesartan added to standard therapy</td>
<td>No benefit; improved symptoms</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>COMET</td>
<td>IR MTP v. Coreg</td>
<td>Coreg superior in ↓all-cause mortality</td>
</tr>
<tr>
<td></td>
<td>COPERNICUS</td>
<td>Coreg v. placebo</td>
<td>24% ↓ risk of death or hospitalization</td>
</tr>
<tr>
<td></td>
<td>MERIT-HF</td>
<td>MTP XL v. placebo</td>
<td>39% ↓mortality</td>
</tr>
<tr>
<td></td>
<td>CIBIS-II</td>
<td>Bisoprolol v. placebo</td>
<td>Sig ↓all-cause mortality, all-cause hosp., sudden death</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>RALES</td>
<td>Spironolactone v. placebo</td>
<td>30% ↓mortality &amp; symptoms</td>
</tr>
<tr>
<td></td>
<td>EMPHASIS-HF</td>
<td>Eplerenone v. placebo</td>
<td>37% ↓CV death or HF hospitalization</td>
</tr>
<tr>
<td>Digoxin</td>
<td>DIG</td>
<td>Digoxin</td>
<td>↓hospitalizations but not mortality</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>A-HeFT</td>
<td>Hydralazine + ISDN</td>
<td>↓mortality in AA</td>
</tr>
</tbody>
</table>
Case Discussion

- Current meds:
  - Furosemide 40 mg daily

- Vitals: HR 78  BP 132/68

- Labs: K=3.6, Creat=1.2
Loop Diuretics

- Used first when patients are volume overloaded
- Relieve signs and symptoms of hypervolemia
- Dosing determined by response
- Careful monitoring of potassium and renal function
- Maintenance dose to prevent recurrent fluid retention
## Loop Diuretics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Max Total Daily Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 to 1 mg daily or bid</td>
<td>10 mg</td>
<td>4 to 6 hours</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 to 40 mg daily or bid</td>
<td>600 mg</td>
<td>6 to 8 hours</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20 mg daily</td>
<td>200 mg</td>
<td>12 to 16 hours</td>
</tr>
<tr>
<td><strong>Thiazide Diuretics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5 to 25 mg daily</td>
<td>100 mg</td>
<td>24 to 72 hours</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 mg daily or bid</td>
<td>200 mg</td>
<td>6 to 12 hours</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 mg daily</td>
<td>20 mg</td>
<td>12 to 24 hours</td>
</tr>
</tbody>
</table>
Which medication would you like to start first?

- Carvedilol 3.125 mg BID
- Hydralazine 12.5 mg TID
- Lisinopril 10 mg daily
- Spironolactone 25 mg daily
ACEi or Beta Blocker First?

- Clinical trials used ACEi first
- ACEi provide rapid hemodynamic benefit and will not exacerbate HF
- Beta blocker effects are delayed and there may be a transient worsening of cardiac function with initiation
- Start low dose ACEi and increase to moderate dose
- Initiate BB if not in HF and titrate
- Titrate together to goal doses
Angiotensin Converting Enzyme Inhibitor (ACEi)

- Mortality reduction of 20-25% seen in multiple trials
- Death plus hospitalization reduced 30-35%
- Usually started during optimization of diuretics
- Increase dose every 1-2 weeks to reach goal doses
- Monitor serum potassium and renal function
Angiotensin Receptor Blockers (ARBs)

- Reasonable alternative with intolerance to ACEi (cough)
- Alternative to those already taking ARB (i.e., for HTN)
- NOT used: h/o adverse reactions (i.e., angioedema, hyperkalemia or renal insufficiency)
- Routine combination of ACEi with ARB NOT recommended
### ACEi/ARB doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEi:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg bid</td>
<td>10-20 mg bid</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg daily</td>
<td>20-40 mg daily</td>
</tr>
<tr>
<td><strong>ARBs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg daily</td>
<td>50-150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg daily</td>
<td>160 mg bid</td>
</tr>
</tbody>
</table>
ACEi and ARBs

ACE inhibitors
- ACE inhibitors are recommended for all patients with HF/EF

ARBs
- ARBs are recommended in patients with HFrEF who are ACE inhibitor intolerant
- ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HFrEF
- Addition of an ARB may be considered in persistently symptomatic patients with HF/EF on GDMT
- Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful
Case Discussion

- Lisinopril 10 mg daily started

- Patient seen in f/u 2 weeks later:
  - HR 88 BP 132/68
  - K+ 4.2 Creat 1.28

- Still with peripheral edema and DOE
What’s the next step?

- Increase Lisinopril?
- Start beta blocker?
- Add aldosterone antagonist?
Titrate ACEi

- Increase further afterload reduction
- Could also increase Lasix at the same time but will need close monitoring of renal function and potassium

- Dose increased to 20 mg daily, then to 40 mg daily after 2 weeks
- F/u labs: K+ 4.9 Cr 1.78
Creatinine Bump

- Initial increase in creatinine after starting ACE is expected (<10 to 20%)
- ARF: increase in serum creatinine of:
  - >0.5 mg/dL if initial was <2 mg/dL OR
  - >1 mg/dL if initial was >2 mg/dL
- Either stop or decrease dose to prior acceptable dose
- Repeat labs within 1 week
- ACEi increase in creatinine usually improves in 2-3 days
Start Beta Blocker

- Used with no or minimal fluid retention
- Risk of transient worsening of symptoms or increase in symptoms for up to 10 weeks before improvement
- Double dose at 2 week intervals
- BB lead to increases in LVEF
- BB may be more effective in reducing cardiac death due to anti-ischemic properties
## Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bid</td>
<td>25-50 mg bid</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>Metoprolol Succinate (Toprol XL)</td>
<td>12.5 to 25 mg daily</td>
<td>200 mg daily</td>
</tr>
<tr>
<td><strong>Metoprolol Tartate</strong></td>
<td>12.5 mg bid</td>
<td>200 mg bid</td>
</tr>
</tbody>
</table>
Case Discussion

- Titrated ACEi and beta blocker
- Vitals: HR 68  BP 103/62
- Labs: K+ 4.6  Cr 1.45
- JVP 8-10, no peripheral edema
- Symptoms: DOE at 1 block and with ADLs
Next step?

- Start spironolactone 12.5 mg daily
- Increase Lasix to 40 mg bid
- Start hydralazine + nitrate
- Digoxin 0.125 mg daily
Mineralcorticoid Receptor Antagonist (MRA)

- Used only in patients with K+ <5.0 and creatinine <2.0 in women or <2.5 in men
- LVEF ≤35% and NYHA FC II-IV
- Monitor renal function and potassium
- Endocrine side effects
<table>
<thead>
<tr>
<th>MRAs</th>
<th>Initial Dose (if K+ &lt;5)</th>
<th>Maintenance Dose (if K+ &lt;5)</th>
</tr>
</thead>
</table>
| **Spironolactone:**  
eGFR ≥50 | 12.5 to 25 mg daily | 25 mg daily |
| eGFR 30 - 49 | 12.5 mg daily or every other day | 12.5 to 25 mg daily |
| **Eplerenone:**  
eGFR ≥50 | 25 mg daily | 50 mg daily |
| eGFR 30 - 49 | 25 mg every other day | 25 mg daily |
Hyperkalemia

- Start low dose ACEi, ARB, MRA
- Monitor labs one week after initiating or increasing dose
- Decrease dose of last increased drug if $K^+ \leq 5.5$
- Stop one agent if $K^+ > 5.5$

- Low-potassium diet; avoid $K^+$ containing salt substitutes
- Avoid NSAIDs
Optimized on ACEi, BB and aldosterone antagonist....now what?

- Patient continues to be a NYHA FC III despite GDMT
- Euvolemic

Consider:
  - Digoxin
  - Addition of hydralazine + nitrate (especially in Blacks)
  - Change from ACEi to neprilysin inhibitor/ARB
  - Add ivabradine
**Digoxin**

- DIG trial: reduction in hospitalizations but no benefit in overall mortality
- Although, survival improved with serum digoxin levels between 0.5 - 0.8 ng/mL and worsened with ≥1.2
- Can improve symptoms (ie: fatigue, dyspnea and exercise tolerance)
- Usual dose is 0.125 mg daily
Hydralazine + nitrate

- Persistent NYHA FC II - IV, LVEF ≤40% and on GDMT
- Evidence is stronger in Blacks (A-HEFT)
- In place of ACEi or ARB in those intolerant
- Provides symptomatic and mortality benefit
- Starting dose is hydralazine 25 mg tid and isosorbide dinitrate 20 mg tid
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine + isosorbide dinitrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BiDil (Fixed Dose)</td>
<td>37.5 mg/20 mg tid</td>
<td>75 mg/40 mg tid</td>
</tr>
<tr>
<td>Hydralazine + isordil</td>
<td>25-50 mg/20-30 mg tid to qid</td>
<td>300 mg/120 mg in divided doses</td>
</tr>
<tr>
<td>Hydralazine + isosorbide mononitrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine + imdur</td>
<td>25 mg tid + 30 mg daily</td>
<td>100 mg tid + 30 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg bid + 30 mg daily</td>
</tr>
</tbody>
</table>
Entresto: sacubitril-valsartan neprilysin inhibitor-ARB (ARNI)

- Neprilysin inhibitor prevents degradation of vasoactive peptides and increases levels of the peptides
- ARB blocks vasoconstrictive effects
- PARADIGM-HF: superior to enalapril
- Reduced relative risk of:
  - CV death or first HF hospitalization
  - All cause mortality
- Used in place of ACEi and ARBs
- Careful monitoring for angioedema, hyperkalemia, renal function, hypotension
PARADIGM-HF Trial

A. Primary End Point

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001

B. Death from Cardiovascular Causes

Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P<0.001

C. Hospitalization for Heart Failure

Hazard ratio, 0.79 (95% CI, 0.71–0.89)
P<0.001

D. Death from Any Cause

Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P<0.001
Corlanor: ivabradine

- LVEF ≤35%
- SR with resting HR ≥70 bpm
- On max tolerated beta blocker OR contraindication to beta blocker
- SHIFT trial: Reduces risk of hospitalization
Other Medications

Anticoagulation
- Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*
- The selection of an anticoagulant agent should be individualized
- Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke*
- Anticoagulation is not recommended in patients with chronic HF/EF without AF, a prior thromboembolic event, or a cardioembolic source

Statins
- Statins are not beneficial as adjunctive therapy when prescribed solely for HF

Omega-3 fatty acids
- Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HF/EF or HFpEF patients

Other drugs
- Nutritional supplements as treatment for HF are not recommended in HF/EF
- Hormonal therapies other than to correct deficiencies are not recommended in HF/EF
- Drugs known to adversely affect the clinical status of patients with HF/EF are potentially harmful and should be avoided or withdrawn
- Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation

Calcium channel blockers
- Calcium channel-blocking drugs are not recommended as routine treatment in HF/EF
Medication management as outpatient

- Start low and go slow!
- Certain patients (ie: elderly, CKD) may need more frequent visits and lab monitoring
- Monitor vitals, especially orthostatics
- Monitor renal function and electrolytes with every initiation and dose change
- Symptoms of fatigue and weakness occur w/dose increases
- Discourage self decreasing or discontinuation of meds
- Can temporarily decrease doses during acute noncardiac illnesses
- Education of patient and family about benefits of drug therapy
Outpatient Management

- Medication Teaching & Reconciliation
- Fluid Restriction
- Salt Restriction
- Daily Weight Log
- Signs and Symptoms to report
- Activity and Exercise
- Self Management skills
- Clinic follow-up and notification

- Barriers: SES, transportation, work, education level

Event-free survival defined as time to first hospitalization or death
Event-free survival defined as time to first hospitalization or death


Fonarow G C et al. J Am Heart Assoc 2012;1:16-26
Case Discussion

- She continued to decline despite GDMT
- Presented with worsening CHF symptoms: dyspnea on minimal exertion, orthopnea, pedal edema. Lasix increased.
- Persistently fluid overloaded
- Needing frequent hospitalizations
- Having arrhythmias
- BNP 2017
- NYHA Class III-IV
Natural Course of the disease
Summary: Optimizing Outpatient Heart Failure Therapy

- Use loop diuretics at adequate dose to relieve congestion
- ACEi + beta blockers for all with LVEF ≤40%
- ARBs for ACEi intolerant patients
- Use agents with demonstrated efficacy in clinical trials, titrate to maximally tolerated dose
- Aldosterone antagonists are the preferred “third” agent
- Hydralazine + nitrate may be useful for select populations
- Digoxin may still be useful, caution with dose
- ARNI is new agent that may replace ACEi and ARB
- Ivabradine may be useful in decreasing hospitalizations
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Lead Nurse Practitioner
Advanced Heart Disease Program
Comprehensive Transplant Center
Los Angeles, California

Faculty Disclosure: NONE
Stages & Treatment of HF

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Using cardiotoxins
  - With family history of cardiomyopathy

**THERAPY**
- **Goals**
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- **Drugs**
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- **Goals**
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- **Drugs**
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients:
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- **Goals**
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- **Strategies**
  - Identification of comorbidities
  - Diuresis to relieve symptoms of congestion
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
  - Revascularization or valvular surgery as appropriate

**Heart Failure**

- **Goals**
  - Control symptoms
  - Patient education
  - Prevent hospitalization
  - Prevent mortality
- **Drugs for routine use**
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- **Drugs for use in selected patients**
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
  - In selected patients:
    - CRT
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE D**
Refractory HF

- Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- **Goals**
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
  - Prevent mortality
- **Drugs**
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - ICD
  - Revascularization or valvular surgery as appropriate

- **Options**
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

**Refactory Symptoms of HF at rest, despite GDMT**

- **Goals**
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
  - Prevent mortality
- **Drugs**
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - ICD
  - Revascularization or valvular surgery as appropriate

- **Options**
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation
HF Stages Treatment Options

Stage A: High risk with no symptoms

Stage B: Structural heart disease, no symptoms

Stage C: Structural disease, previous or current symptoms

Stage D: Refractory symptoms requiring special intervention

End Stage HF

Hospice

VAD, transplantation

- Cardiac resynchronization if bundle-branch block present
- Aldosterone antagonist, nesiritide
- Consider multidisciplinary team
- Revascularization, mitral-valve surgery
- Dietary sodium restriction, diuretics, and digoxin
- ACE inhibitors and beta-blockers in all patients
- ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
- Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
- Risk-factor reduction, patient and family education

HF Clinical Trajectory

Clinical Events and Findings Useful for Identifying Patients With Advanced HF

<table>
<thead>
<tr>
<th>Event/finding</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated (≥2) hospitalizations or ED visits for HF in the past year</td>
<td></td>
</tr>
<tr>
<td>Progressive deterioration in renal function (e.g., rise in BUN and creatinine)</td>
<td></td>
</tr>
<tr>
<td>Weight loss without other cause (e.g., cardiac cachexia)</td>
<td></td>
</tr>
<tr>
<td>Intolerance to ACE inhibitors due to hypotension and/or worsening renal function</td>
<td></td>
</tr>
<tr>
<td>Intolerance to beta blockers due to worsening HF or hypotension</td>
<td></td>
</tr>
<tr>
<td>Frequent systolic blood pressure &lt;90 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Persistent dyspnea with dressing or bathing requiring rest</td>
<td></td>
</tr>
<tr>
<td>Inability to walk 1 block on the level ground due to dyspnea or fatigue</td>
<td></td>
</tr>
<tr>
<td>Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose &gt;160 mg/d and/or use of supplemental metolazone therapy</td>
<td></td>
</tr>
<tr>
<td>Progressive decline in serum sodium, usually to &lt;133 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Frequent ICD shocks</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Russell et al. Congest Heart Fail. 2008;14:316-21.
# Causes for ↑Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Noncardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Heart failure, including RV syndromes</td>
<td></td>
</tr>
<tr>
<td>- Acute coronary syndrome</td>
<td></td>
</tr>
<tr>
<td>- Heart muscle disease, including LVH</td>
<td></td>
</tr>
<tr>
<td>- Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>- Pericardial disease</td>
<td></td>
</tr>
<tr>
<td>- Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>- Myocarditis</td>
<td></td>
</tr>
<tr>
<td>- Cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>- Cardioversion</td>
<td></td>
</tr>
<tr>
<td>- Advancing age</td>
<td></td>
</tr>
<tr>
<td>- Anemia</td>
<td></td>
</tr>
<tr>
<td>- Renal failure</td>
<td></td>
</tr>
<tr>
<td>- Pulmonary causes: obstructive sleep apnea, severe pneumonia, pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>- Critical illness</td>
<td></td>
</tr>
<tr>
<td>- Bacterial sepsis</td>
<td></td>
</tr>
<tr>
<td>- Severe burns</td>
<td></td>
</tr>
<tr>
<td>- Toxic-metabolic insults, including cancer chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>
Novel HF Devices

The CardioMEMS™ HF System

A tool for comprehensive care, this device is the first and only device proven to improve quality of life. It also improves free from device limitations by 37%² in hospitalization through the systematic monitoring of medications.
Implantable Devices

Implantable Cardioverter Defibrillator (ICD)
- EF < 35%
- 40 days post MI
- NYHA II-III
- Life expectancy 1 year

Cardiac Resynchronization Therapy (CRT-D or CRT) or Biventricular Implantable Cardioverter Defibrillator (BiVICD)
- EF < 35%
- QRS ≥ 150 msec
- NYHA III-IV on optimal medical therapy
- Recent evidence showed benefits in Class II HF
Devices: How are they different?

ICD

BiV-ICD
Treatment Options

OR

&
Patients With Refractory End-Stage Heart Failure (Stage D)

♥ Severe heart disease despite adequate medical therapy.
- Unacceptable QOL
- Unacceptable risk of cardiac death
- No other reasonable surgical options
- Intractable Angina
- Refractory Heart Failure
- Uncontrolled Ventricular arrhythmias

♥ General eligibility – absence of any non-cardiac condition which would limit life expectancy

**Referral for cardiac transplantation in potentially eligible patients is recommended**
Treatment Options for AHD

- 300,000 Class IIIb/IV
  - ~50,000 potential VAD candidates for DT
  - ~100,000 Heart Tx candidates
  - ~150,000 Non-Tx/VAD

- 2,100 Heart transplants/yr
- ~97,000 waiting medical Rx
- ~10,000 MCS*
  - 8,000 LVADs
Case Discussion: Diagnostic

Transthoracic Echo

- LV diast diam: 5.7 cm
- LV syst diam: 4.9 cm
- LVEF: 15-20%
- PA pressure: 40-45

- CPX: Exercised 8 mins.
  - VO2 max 19.1 ml/kg/min
  - NYHA functional class II

Transthoracic Echo

- LV diast diam: 6.6 cm
- LV syst diam: 5.4 cm
- LVEF: 15-20%
- PA pressure: 30

- Dual Chamber ICD
Case Discussion: Disease Progression

Readmitted with:
- VERY SEVERE systolic heart failure decompensation
- BP 73/49, HR 84, O2 sat 99%, JVP 13-15
- BNP 5,000, Troponin 0.07, EF 15%
- Crackles right lung base
- Soft II/VI systolic murmur
- Pulsatile liver
- NYHA Class IV

RHC Hemodynamics:
- RAP: 21/22/19
- RV: 48/10/15
- PAP: 48/26
- PCWP: 29
- CO: 3.91
- CI: 1.56
The Evaluation Process

Three Questions

❤️ Is the heart sick enough?
❤️ Is the rest of the body well enough?
❤️ Is there enough social & financial support?

Two Goals

❤️ Improve survival and quality of life
❤️ Optimize use of the donor organ
Specific Contraindications

- Active infection
- Recent malignancy
- Severe IDDM with EOD
- Severe PVD
- CVA
- Irreversible lung disease
- Acute PE and/or infarct
- Irreversible renal dysfunction
- Irreversible liver dz
- Severe PHTN unresponsive to med Rx
- Morbid obesity BMI > 35
- Age greater than 70 (relative contraindication)
- High risk for non-compliance
- Recent smoking, alcohol, or drug history
- Inadequate social support
Pre-Transplant Evaluation

**Screening Tests**
- Full History and Physical
- Echocardiogram
- CPX
- Right Heart Cath
- LHC
- PFTs, 24 hour urine, colonoscopy, vascular dental clearance, pap, mammo, lab tests, serologies

**Psychosocial Eval**
- Caregiver plan
- Financial Clearance
- Substance Abuse
- Relocation needs
- Emotional/Mental health: Depression, Anxiety Psychosis
- Behavioral Health: Compliance, Motivation
Patient Selection & Treatment

### Congestion at Rest

<table>
<thead>
<tr>
<th>Low Perfusion at Rest</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and Dry</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PCW normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(compensated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold and Dry</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PCW low/normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI decreased</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Cold and Wet          | -  |     |
| PCW elevated          |    |     |
| CI decreased          |    |     |

### Inotropic Drugs
- Dobutamine
- Milrinone
- Calcium Sensitizers

### Natriuretic Peptides
- Nesiritide
- Nitroprusside
- Nitroglycerin

### Vasodilators
- Nitroprusside
- Nitroglycerin

R. Bourge, UAB Cardiology (adapted from L. Stevenson)
Stevenson LW. *Eur J Heart Failure* 1999;1:251-257
IV Inotropic infusions in Stage D

❤ May be used until definitive therapy until resolution of acute precipitating problem (Class 1: LOE C)

❤ Reasonable “bridge therapy” in patient refractory to GDMT, device therapy but eligible for OHT or MCS (Class IIa: LOE B)

❤ Short term use is reasonable in compromised hospitalized patients to preserve perfusion and end-organ performance (Class IIb: LOE B)

❤ Long term use may considered as palliative Rx for symptom management (Class IIb: LOE B)

❤ Long term use without specific indication other palliative care, is potentially harmful (Class III: LOE B)
Waiting for an OHT

- **Status 1A**
  - PA catheter + two drips
  - VAD < 30 days
  - IABP or ventilator
  - Exceptions

- **Status 1B**
  - One inotrope
  - VAD > 30 days

- **Status 2**
  - Everyone else

**Longer wait time**
- Larger body size
- Blood type O
- Time on list
Orthotopic Heart Transplantation

Figure 1: The donor heart’s left atrium is sewn onto the recipient’s left atrium.
NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
ADULT HEART TRANSPLANTS
Kaplan-Meier Survival by Era

1982-1992 vs. 1993-2002: p < 0.0001
1982-1992 vs. 2003-6/2010: p < 0.0001
1993-2002 vs. 2003-6/2010: p < 0.0001


(Transplants: January 1982 - June 2010)
Cross-Sectional Analysis of Functional Status of Surviving Recipients

(Follow-ups: January 2000 – June 2011)
### Case Discussion: Chagas Monitoring

**Table 1: Strategy for pretransplant screening and posttransplant management of TC infection in heart transplant recipients**

**Before heart transplantation**
- Screen all patients with idiopathic dilated cardiomyopathy born in a Chagas disease endemic country for TC infection
- Perform serological testing using two serological assays with different formats and TC antigen preparations

**After heart transplantation**
- Examine cardiac explant by microscopy for presence of TC amastigotes and myocarditis
- Examine paraffin blocks of explanted tissue by (1) IHC for TC and (2) tissue PCR for TC
- Perform serial clinical evaluation for signs/symptoms of allograft dysfunction and arrhythmia (including ECG and 2D echocardiogram)
- Perform serial laboratory evaluation using (1) microscopy of blood buffy coat with attention to TC organisms, (2) EMB with attention to the presence of TC amastigotes and (3) whole blood PCR testing for TC at CDC per schedule:
  - Posttransplant months 1 and 2: Weekly
  - Posttransplant months 3–6: Every 2 weeks
  - Posttransplant months 6–12: Monthly
  - Posttransplant months 13–24: Every 3 months
  - Posttransplant months 25 and greater: Every 6 months

TC, *Trypanosoma cruzi*; IHC, immunohistochemistry; PCR, polymerase chain reaction; ECG, electrocardiogram; 2D, two-dimensional; EMB, endomyocardial biopsy; CDC, Centers for Disease Control and Prevention.
Treatment for Chagas Reactivation

• CDC and Infectious Disease Collaboration
• Benznidazole therapy initiated
• Tailored Immunosuppression:
  - Discontinued mycophenolate mofetil.
  - Azathioprine initiated. Steroid weaning.
• Chagas reactivation is common post transplant (65%) and is associated with high mortality
• Serologic testing for early detection and treatment is necessary to prevent adverse outcomes
• Psychosocial and religious considerations

---

**Table 1. Frequency of Adverse Effects Associated with Benznidazole and Nifurtimox in Adults.**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifurtimox</td>
<td></td>
</tr>
<tr>
<td>Anorexia and weight loss</td>
<td>50–75%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15–50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15–26</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>12–40</td>
</tr>
<tr>
<td>Headache</td>
<td>13–70</td>
</tr>
<tr>
<td>Dizziness or vertigo</td>
<td>12–33</td>
</tr>
<tr>
<td>Mood changes</td>
<td>10–49</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10–54</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13–30</td>
</tr>
<tr>
<td>Peripheral neuropathy†</td>
<td>2–5</td>
</tr>
<tr>
<td>Decreased short-term memory</td>
<td>6–14</td>
</tr>
<tr>
<td>Leukopenia‡</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Early discontinuation because of side effects</td>
<td>6–40</td>
</tr>
</tbody>
</table>

**Benznidazole**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic dermatitis§</td>
<td>29–50%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0–30</td>
</tr>
<tr>
<td>Peripheral neuropathy†</td>
<td>0–30</td>
</tr>
<tr>
<td>Anorexia and weight loss</td>
<td>5–40</td>
</tr>
<tr>
<td>Nausea, vomiting, or both</td>
<td>0–5</td>
</tr>
<tr>
<td>Leukopenia‡</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia‡</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Early discontinuation because of side effects</td>
<td>7–13</td>
</tr>
</tbody>
</table>

† This dose-dependent side effect, which usually occurs late in the course of treatment, requires discontinuation of the drug. The condition is reversible but may require months to resolve.
‡ This side effect requires discontinuation of the drug.
§ This side effect is not dose-dependent. The drug should be discontinued if allergic dermatitis is severe, exfoliative, or associated with fever. The Stevens–Johnson syndrome has been reported.

* Data are from Wegner and Rohwedder, Coura et al., and Jackson et al.
* Data are from Viotti et al., Coura et al., Pinazo et al., and Pérez-Molina et al.
Left Ventricular Assist Device HeartMate® II

- Continuous Axial Flow.
- Non-pulsatile.
- 3-10 liters/min.
- Quiet, small.
- Easy to implant.
- Reduces surgical morbidity.
- Smaller driveline.
- Low thromboembolic rate
- Extended durability.

1st successful implant 2003
Survival for Destination LVAD

LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE


Rose et al. NEJM 2001;345:1435-43
Pneumatic VADs

Advantages:
- Easy to implant
- Uni-Bi VAD config.
- Wide range of patient size (BMI)
- Thrombus visible

Anterior abdominal wall

RVAD  LVAD  Exit Site
Candidates for TAH

❤️ Irreversible severe biventricular failure.
❤️ Larger patients requiring high CO.
❤️ Cardiogenic shock with end-organ dysfunction.
❤️ Unique anatomic issues.
❤️ Refractory VT.
❤️ Heart transplant pts with severe CAD or refractory rejection.

NOT Candidates for TAH

❤️ BSA < 1.7 meters $^2$, < 10 cm b/w sternum & $10^{th}$ ant vertebral body/chest CT
❤️ Ineligible for OHT
❤️ Inability to anticoagulate.
❤️ Irreversible end-organ dysfunction.
❤️ Non-cardiac problem limiting survival.
❤️ Inability informed consent.
Advances in TAH Technology

- Implantable pulsatile (pneumatic)
- Low cardioembolic and infection rate
- Flow: 10 liters/min with physiologic response

Current console/driver
(450 lbs) “Big Blue” In hospital only

Companion driver (30 lbs)

Freedom driver (12 lbs)
Palliative Care Exists on a Continuum

Old Paradigm

Curative care

Palliative Care

New Paradigm

Prolonging life

Relieving symptoms

TIME
<table>
<thead>
<tr>
<th>Site</th>
<th>All*</th>
<th>Heart Failure^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>50%</td>
<td>35%</td>
</tr>
<tr>
<td>Nursing home</td>
<td>23%</td>
<td>34%</td>
</tr>
<tr>
<td>Home</td>
<td>23%</td>
<td>31%</td>
</tr>
<tr>
<td>Hospice</td>
<td>39%</td>
<td>12%</td>
</tr>
</tbody>
</table>

^Teno et al. *JAMA* 2004;291:88-93
CASE DISCUSSION
Future Directions

- Novel Biomarkers
- Increase use of Novel agents
- Stem cell
- Genotyping, Pharmacogenetics
- Better organ preservation
- Smaller MCS devices, portable smaller battery packs
Summary

- Primary Prevention or early diagnosis
- GDMT improves QOL and survival
- Early Referral to Tertiary Center or Disease Management Programs
- Appropriate patient selection
- Nurse Practitioners play pivotal roles across the continuum of HF disease progression.
Thank You

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