Heart Failure Pharmacology

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Objectives

• Participant will understand the pathophysiology of heart failure
• Participant will be able to identify current guideline driven therapies for heart failure
• Participant will be able to understand the risks an benefits of the current pharmacological therapies for treatment of heart failure
Disclosures

I have no disclosures related to this presentation.
General HF

• “...a clinical syndrome manifested by breathlessness and fatigue at rest or during exertion with accompanying structural and/or functional myocardial disease.” ¹

• CHRONIC DISEASE
Common Types of Heart Failure

- Idiopathic
- Ischemic
- Hypertensive
- Peripartum
- Valvular- rheumatic
- Infiltrative- amyloid
- Infectious- myocarditis
- Metabolic- mitochondrial
- Auto-immune- lupus
- Tachy-induced- AF
- Chemotherapy- Herceptin
- Radiation
- Alcohol/drugs
- Inflammatory- sarcoid
- Obesity
- Muscular dystrophies
- Familial
General HF

• An estimated 5.1 million Americans >20yo have HF²
• In 2010- 1.023 million discharges for HF²
• In 2010- 1.801 million physician office visits with a primary diagnosis of HF²
• Projections show that by 2030, the total cost of HF will increase almost 120% to $70 billion from the 2013 estimated total cost of $32 billion²

Stages in the development of HF and recommended therapy by stage.

NYHA Functional Class

- **I** - no physical limitations. Ordinary activities do not cause undue shortness of breath or fatigue

- **II** - slight limitation of physical activity. Comfortable at rest, but ordinary activities will cause symptoms

- **III** - marked limitation of physical activity. Comfortable at rest, but less than ordinary activity will cause symptoms

- **IV** - severe limitation of physical activity. Symptoms at rest and with any activity
HFrEF vs. HFpEF

• HFrEF—“systolic heart failure”
  – LVEF ≤ 40%

• HFpEF—“diastolic heart failure”
  – LVEF ≥ 50%

• Treatments are different
HFrEF

- Focus on neurohormonal blockade
- Goal is to improve EF, improve functional class, and keep decongested

- Beta Blocker
- ACEi/ARB
- Aldosterone Antagonist
- Hydralazine and Nitrate (in African Americans)
- Diuretics prn
FIGURE 86.1. Depicted are the factors in cardiogenic shock perpetuating continued left ventricular (LV) dysfunction and progressive deterioration in cardiac output (CO). As CO falls, renal blood flow is reduced, which thus activates the renin-angiotensin-aldosterone system. Angiotensin II (AII) directly results in vasoconstriction and indirectly increases blood volume by enhancing aldosterone release. Hypotension resulting from a further fall in CO activates the central nervous system release of antidiuretic hormone (ADH). Inactivation of baroreceptors enhances sympathetic tone and vasoconstriction. As CO, renal blood flow, and hypotension remain reduced, preload and afterload continue to increase, and this leads to further LV dysfunction. ↑, increased; ↓, decreased; SVR, systemic vascular resistance.
**FIGURE 85.6.** The renin-angiotensin-aldosterone system in heart failure. AVP, arginine vasopressin; CNS, central nervous system; NE, norepinephrine.
72yo AA female

- Recently DCd from hospital after first episode/initial diagnosis of decompensated HF (EF15%)– 10 day LOS, diuresed 25lbs! 7 days later...
- VS: 137/86, HR 75, Wt 255lbs (same as at DC)
- PE: Euvolumic, feeling better, FC III
- Labs today: wnl
- DC meds
  - Lisinopril 5mg, once daily
  - Furosemide 40mg, twice daily
  - Spironolactone 12.5mg, once daily
72yo AA female

• What should we do with her medications?
• Should we add anything?
• What do we need to know before we can safely add a new medication?
• DC meds
  — Lisinopril 5mg, once daily
  — Furosemide 40mg, twice daily
  — Spironolactone 12.5mg, once daily
72yo AA female

- Add a BetaBlocker
  - Which one?
    - Metoprolol succinate, carvedilol (short acting, or CR)
  - What dose?

### Initial and Target Doses for Beta-Blocker Therapy in Heart Failure

<table>
<thead>
<tr>
<th>Beta-Blocker</th>
<th>Starting Dose</th>
<th>Target Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
<td>( \beta_1 )-Selective blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inconvenient dosage forms for initial dose titration</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bid</td>
<td>25 mg bid (( \leq 85 ) kg)</td>
<td>( \beta )-Nonselective blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg bid (( &gt;85 ) kg)</td>
<td></td>
</tr>
<tr>
<td>Carvedilol phosphate, extended</td>
<td>10 mg daily</td>
<td>80 mg daily(^2)</td>
<td>( \alpha )-Blocking properties</td>
</tr>
<tr>
<td>release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate, extended</td>
<td>12.5-25 mg daily</td>
<td>200 mg daily</td>
<td>( \beta_1 )-Selective blocker</td>
</tr>
<tr>
<td>release</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\text{From ACCF/AHA Guidelines.}\)

\(^{2}\text{Equivalent to carvedilol immediate release 25 mg twice daily}\)
Beta-Blockers (BB)

- Coreg, coreg CR, metoprolol succinate (*NOT* tartrate)
- Decrease sympathetic stimulation
- Reverses and protects the heart from adverse remodeling
- Side effects: hypotension, bradycardia, fluid overload
- DO NOT START OR INCREASE BB DURING ACUTE EXACERBATION
Medication titration and BP in systolic HF

• START LOW AND GO SLOW!
• Try not to make too many changes at once
• Many different approaches
• The lower the better → without adverse effects. Don’t be afraid of the numbers!
  – Symptomatic hypotension
  – End organ perfusion
  – Falls in the elderly
72yo AA female

• Comes back to the office for follow up 2 weeks later
• HPI: “a little more tired and SOB”
• VS: 136/84, HR 70, Wt: 260lbs (+5lbs), warm extremities
• PE: 1+ BLE edema, noticeably SOB when laying back
• Labs: renal function and K normal
72yo AA female

• What is going on?
  — Explore etiologies

• Current meds:
  — Lisinopril 5mg, once daily
  — Furosemide 40mg, twice daily
  — Spironolactone 12.5mg, once daily
  — Coreg 3.125mg, twice daily
72yo AA female

• Most likely some additional fluid related to initiation of BB—don’t need to stop it just yet

• Increase diuretics—try increasing loop diuretic first
Diuretics

- Loop diuretics - furosemide, torsemide, bumetanide
- Thiazide-like diuretics - hydrochlorothiazide, metolazone
- Can be used separately – have a synergistic benefit when used together
- Need to monitor renal function, potassium, and s/s dehydration

- Can we do anything else for her?
72yo AA female

- Increase ACE

### Dosing of ACE Inhibitors in Heart Failure

<table>
<thead>
<tr>
<th>ACEI</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<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>Fosinopril</td>
<td>5-10 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg daily</td>
<td>20-40 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8-16 mg daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg bid</td>
<td>20 mg bid</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
</tr>
</tbody>
</table>

*From ACCF/AHA Guidelines.*
Angiotensin Converting Enzyme Inhibitors (ACEI)

• Captopril, enalapril, lisinopril, quinapril, ramipril, fosinopril
• Vasodilator → decreases workload on the heart
• Side effects - cough, renal dysfunction, angioedema, hyperkalemia, hypotension
Angiotensin Receptor Blockers (ARB)

• Losartan, candesartan, valsartan
• Vasodilator $\rightarrow$ decreases workload on the heart
• Side effects- renal dysfunction, angioedema, hyperkalemia, hypotension

• ALWAYS CHECK LABS WITHIN ONE WEEK OF CHANGING ACE/ARB OR DIURETIC DOSE
FIGURE 85.6. The renin-angiotensin-aldosterone system in heart failure. AVP, arginine vasopressin; CNS, central nervous system; NE, norepinephrine.
72yo AA female

• Returns two weeks later for follow up
• HPI: “feeling better” “still SOB going upstairs”
• VS: BP 126/78, HR 76, Wt 253 (-7lbs)
• PE: wnl
• Labs: creat up 5% from previous, K 4.0
  —Monitor trends
72yo AA female

• What do we do?
• Current meds
  — Lisinopril 10mg, once daily
  — Furosemide 60mg, twice daily
  — Spironolactone 12.5mg, once daily
  — Coreg 3.125mg, twice daily
72yo AA female

- Increase coreg again to 6.25mg, twice daily
- Can consider increase in aldactone to 25mg, once daily as well

<table>
<thead>
<tr>
<th>Aldosterone antagonist</th>
<th>Initial daily dose</th>
<th>Target daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spironolactone</strong></td>
<td>12.5 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td><strong>Eplerenone</strong></td>
<td>25 mg once daily</td>
<td>50 mg once daily</td>
</tr>
</tbody>
</table>
Aldosterone Antagonists (AA)

- Spironolactone, eplerenone
- Reduces Na retention at the kidney
- Blocks the harmful effects of aldosterone on the myocardium- hypertrophy
- Side effects: renal dysfunction and ↑K

- CHECK LABS FREQUENTLY
FIGURE 85.6. The renin-angiotensin-aldosterone system in heart failure. AVP, arginine vasopressin; CNS, central nervous system; NE, norepinephrine.
72yo AA female

- Fast forward 2mos. She has been doing well…
  - VSS, BP avg 110/60

- Current meds:
  - Lisinopril 40mg, once daily
  - Furosemide 40mg, twice daily
  - Spironolactone 25mg, once daily
  - Coreg 50mg, twice daily (>85kg)

- Looks pretty good—anything else we should do?
72yo AA female

• Seeing as she is AA, we should also add hydralazine and isordil

• BP is under decent control, but as long as there is some room there, we should add these medications

• Often an under-utilized beneficial therapy in this population
Isosorbide and Hydralazine

- Isordil, hydralazine

- Vasodilator → decreases workload on the heart

- Indicated for those who cannot tolerate ACE/ARB- renal dysfunction, and AA with systolic heart failure

- Monitor for low BP; headaches common, lupus like reaction with hydralazine
72yo AA female

• We repeat the echo 3 mos later
• EF 55%

• SHE IS CURED!

  —Stop the meds, right? She doesn’t need them any more.
  —NO!!!
Digoxin

• Increases myocardial contractility
• Reduces HR- can aid in rate control for afib
• Need to monitor for toxicity
  –Vision changes, lethargy, arrhythmias, N/V, anorexia
• Lower doses for CKD
• Can be added for HFrEF after other therapies are optimized
# Medication Benefits in Systolic Heart Failure

<table>
<thead>
<tr>
<th>Medication</th>
<th>Improves Survival</th>
<th>Reduces Hospitalizations</th>
<th>Improves Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
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<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Diuretics</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Isosorbide dinitrate and hydralazine</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Digoxin</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Not everyone is perfect!
58yo Caucasian male

- PMH: Chronic right sided HF and diastolic dysfunction, liver cirrhosis, monthly paracentesis, CKD (baseline creat~ 2.9), HTN, DM, leg ulcers, PVD, chronic AF, COPD on home O₂

- DCd from the hospital 2 days ago, LOS 20days for ADHF: required dialysis for a couple of days, IV lasix gtt for diuresis, complicated by Cdiff
58yo Caucasian male

• First visit- looks ok-- trace edema, SOB at his baseline, seems to be taking meds correctly
• VS: 100/64, 95bpm, Wt 200lbs (+2 from DC)
• DC meds (abbreviated)
  – Cardizem CR 240 mg
  – Coumadin 4mg daily
  – Lasix 80mg BID (has been on lasix for 15yrs)
  – Toprol 200mg once daily
58yo Caucasian male

- Visit 3 days later- increased edema, increased SOB (though comfortable at rest), and wt is up 4lbs
- What now?
- Increase lasix to 100mg BID
- Visit one week later- Wt up another 4lbs
- What now?!?
58yo Caucasian male

- Change to torsemide or add a thiazide-type diuretic

- Torsemide is more bioavailable than furosemide and the pt may have built a tolerance to furosemide

- A thiazide diuretic will augment the diuresis of the loop diuretic

- Keep an eye on renal function and K- replace if needed
45 yo Caucasian male

- Presents to the Emergency Department with SOB and increasing lower extremity edema over the last month

- PMH: “My doctor told me my blood pressure was high once…(gasp)… but that’s all. I haven’t seen him in about 7 years.”

- VS: 190/88, HR 87, SpO2 94%, T 36.9°C, Wt 280lbs, Ht 5’10”
45 yo Caucasian male

• Current medications: none

• Physical exam
  – General: overweight, SOB at rest
  – Resp: bibasilar crackles, otherwise clear
  – Cardiac: RRR, normal S1, S2, no murmurs
  – Neck: JVD near to angle of jaw at 90d
  – Abd: soft, round, obese, no organomegaly
  – Ext: bilateral lower ext edema, 2+, to mid thighs
45 yo Caucasian male

- Labs (abbreviated)
  - Na 130
  - K 3.9
  - BUN 10
  - Creat 1.0
  - H/H 13/37
  - BNP 347
- Cardiac enzymes- wnl

- CXR- pulmonary vascular congestion
- Limited echocardiogram- Left ventricular hypertrophy, EF 55%, stage III diastolic dysfunction
45 yo Caucasian male

- Heart Failure with Preserved Left Ventricular Ejection Fraction, aka Diastolic dysfunction

- Most likely cause in his case is long-standing, uncontrolled hypertension
ACC/AHA Guidelines for HF with Preserved LVEF

Class I

• 1. Systolic and diastolic blood pressure should be controlled in patients with HFpEF in accordance with published clinical practice guidelines to prevent morbidity. *(Level of Evidence: B)*

• 2. Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF. *(Level of Evidence: C)*
45 yo Caucasian male

• Medications...
  – Antihypertensive(s)- my preference would be ACE/ARB (check on renal function and K first), candesartan showed a significant decrease in HF related hospitalization

  – Diuretics- IV lasix to start, oral loop diuretic later, and thiazide prn should he need it
IV Inotropes

- Continuous infusion for palliation and/or bridge to advanced therapies
  - Dobutamine
    - Directly stimulates beta receptors
    - Vasodilator
  - Milrinone
    - Blocks cAMP resulting in increased cardiac inotropy and vasodilation
- Both can be arrhythmogenic
- Life expectancy is about 6mos after initiation
Other Common Medications of the HF patient

• Anti-platelet-
  – Aspirin, plavix

• Anticoagulation-
  – Vitamin K antagonist- warfarin
  – Direct thrombin inhibitors

• Anti-arrhythmic medications- not many well tolerated
  – Amioderone, tikosyn
OTC Medications to AVOID in HF

• NSAIDs
  – Ibuprofen (Advil®), naproxen (Aleve®)

• Decongestants
  – Pseudoephendrine (Sudafed®)

• Supplements/Herbals
  – We really don’t know enough about them!
Prescription Medications to AVOID in Heart Failure Patients

• Calcium channel blockers (in HFrEF)- diltiazem, verapamil
  —Amlodipine and felodipine are the exceptions

• Thiazolidinediones (TZDs)- rosiglitazone, pioglitazone

• Many antiarrhythmic
Bottom Line

• Systolic HF
  – BB, ACE/ARB, and aldosterone antagonist
  – Nitrates and hydralazine
  – Digoxin
  – Diuretics if needed

• Diastolic HF
  – Control BP, arrhythmias
  – Diuretics if needed
Stages in the development of HF and recommended therapy by stage.

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

Reduced Mortality and Readmissions by ~20%
References

Cleveland Clinic

Every life deserves world class care.