Two Drugs, a Girl, and a Pizza Place

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Disclosures

- Speaker’s Bureau
  - Novartis

Bao Bao – The Girl
Overview

• Heart failure pathophysiology
  • Hemodynamic model
  • Treatments
  • Neurohormonal model
  • Treatments

Bei Bei
Heart Failure

• End stage of many possible diseases
  • Treatments should target underlying cause
  • General measures to treat any kind of heart failure

• Chronic and progressive
Hemodynamic Model

Initially heart failure was thought of as a primarily hemodynamic disorder.

“A complex clinical syndrome where patients present with symptoms (i.e. dyspnea, fatigue, fluid retention) that result from any structural or functional impairment of ventricular filling or ejection of blood”
Treatments

- Treatments directed toward reversing the hemodynamic derangements
  - Diuretics (furosemide) → Alleviate congestion
  - Inotropes (dobutamine, milrinone, digoxin) → Improve contractility
  - Pure vasodilators (hydralazine, nipride) → Afterload reduction

- Treatments based on this model alleviate symptoms, but do not necessarily change the disease course

- Heart failure progresses even when the hemodynamics are treated and the primary cause is treated
Heart Rate and Heart Failure Outcomes

- Elevated resting heart rate >70 is associated with higher mortality in heart failure patient
  - Observational data

- Elevated sinus rate can be due adrenergic overactivation
  - Beta-blockers used to treat this, but over beta-blockade can cause adverse effects even when HR is normal or high
    - Hypotension, fatigue could be due to negative inotropic effects or BP lowering effects
Ivabradine Blocks the $I_f$ Channel

Corlanor® (ivabradine) Prescribing Information, Amgen.
SHIFT Trial

• Ivabradine vs. Placebo
  • Randomized, multicenter, controlled, blinded
    • N=6558
    • NYHA Class II-IV
    • LVEF ≤ 35%
    • Patients had to be on maximally tolerated dose of BB
    • Resting HR >70 on two occasions
    • Sinus rhythm
    • Hypotensive patients excluded SBP <90
Study Results

CV Death or HF Hospitalization

18% Relative Risk Reduction
• Driven by hospitalization

Patients with primary composite endpoint (%) vs Months

Placebo (937 events) vs Ivabradine (793 events)

HR 0.82 (95% CI 0.75-0.90), p<0.0001

Number at risk
Placebo group 3264 2868 2489 2061 1089 439
Ivabradine group 3241 2928 2600 2173 1191 447
Ivabradine Key points

- Patients must be in sinus rhythm
- Maximum BB dose before initiation
- Avoid in patients with BP 90/50
  - Could be HR dependent
- Increases the risk of atrial fibrillation
Neurohormonal Model

• Heart failure causes significant morbidity even when the hemodynamics are closely monitored and derangements are treated.

• Heart failure triggers endogenous neurohormonal mechanisms that persist even after the initial injury is over.

• These mechanisms can exacerbate the hemodynamic abnormalities and likely injure the myocardium as well.
Neurohormonal Model

- Heart failure triggers endogenous neurohormonal mechanisms that persist even after the initial injury is over.
- These mechanisms can exacerbate the hemodynamic abnormalities.
- However, the neurohormonal activation may have other deleterious effects other than the hemodynamic abnormalities.
Neurohormonal Model

- Renin-Angiotensin System $\uparrow$
  - ADH/Vasopressin $\uparrow$
  - Aldosterone $\uparrow$

- Sympathetic nervous system $\uparrow$

- INSULT

- Cardiac Output $\downarrow$
  - BP $\downarrow$

- Systemic Blood Pressure $\uparrow$

- Contractility $\uparrow$
  - Heart Rate $\uparrow$
Neurohormonal Model

Sympathetic nervous system $\uparrow$

$\uparrow$ SVR

Cardiac Output $\downarrow$

Renin-Angiotensin System $\uparrow$

- ADH/Vasopressin $\uparrow$
- Aldosterone $\uparrow$

Ventricular Mass $\uparrow$
- Myocyte hypertrophy
- Dilation
- Increased wall stress

Increase in intracardiac pressures

Contractility $\uparrow$

Heart Rate $\uparrow$
RAAS - Aldosterone

Liver

Angiotensinogen → Angiotensin I → Angiotensin II

Surface of pulmonary and renal endothelium: ACE

Lungs

Kidney

Tubular Na⁺, Cl⁻ reabsorption and K⁺ excretion. H₂O retention

Adrenal gland: cortex

Aldosterone secretion

Arteriolar vasoconstriction. Increase in blood pressure

ADH secretion

Pituitary gland: posterior lobe

Collecting duct: H₂O absorption

Decrease in renal perfusion (juxtaglomerular apparatus)

Na⁺ K⁺ Cl⁻ H₂O⁻

Sympathetic activity
Natriuretic Peptides

- Released naturally in decompensated heart failure
- Effects are beneficial in decompensated heart failure
- **Nesiritide** is recombinant BNP given IV
  - Decreases PCWP increases cardiac index
  - Associated with worsening renal function

ASCEND-HF Trial
Cornerstone of Therapy

- ACE inhibitors (SOLVD, CONSENSUS trials)
- Beta blockers (CIBIS II, MERIT-HF, COMET)
- ARB (CHARM, VAL-HeFT)
- MRA (RALES, EPHESUS, EMPHASIS)
- All of these trials show mortality benefit against placebo
Neprilysin

- Neprilysin is a neutral endopeptidase
  - Degrades of several vasoactive peptides including the natriuretic peptides and bradykinin
  - Degrades angiotensin II
Neprilysin

BNP

Bradykinin

Ang I → Ang II

ACE

Ang II

+ → Inactive Metabolites

+ → +
Neprilysin

- BNP
  - ↑BNP – Natriuresis, diuresis..
- Bradykinin
  - ↑Bradykinin – Angioedema
- Angiotensin II
  - ↑Angiotensin II → Vasoconstriction
Neprilysin

↑↑↑ Bradykinin

↑↑ Bradykinin

↓ Angiotensin II → Vasodilation

↑↑↑ Bradykinin → Angioedema

↑ BNP → Natriuresis, diuresis...

ACE

Ang I

+↑ Ang II

↑↑↑ Bradykinin

BNP
Entresto™

- Entresto rationale
  - Combine angiotensin receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril) for added effect
  - Capitalize on the beneficial effects of neprilysin inhibition
  - Counteract the effects of increased angiotensin II
Neprilysin Inhibition + ARB

Neprilysin

BNP

↑BNP – Natriuresis, diuresis…

Bradykinin

Bradykinin – Angioedema

Ang I → Ang II

↑Vasodilation

ACE
PARADIGM-HF

- Entresto (LCZ696) vs. Enalapril
  - ACE I chosen over ARB because ACE I still the first-line recommendation
  - Randomized, multicenter, controlled, blinded
    - N=8442
    - NYHA Class II-IV
    - LVEF ≤ 40%
    - Patients had to be able to tolerate ACE I or ARB during a run-in period before randomization
    - GFR <30 excluded
PARADIGM-HF

**Primary End Point**

CV Death or HF Hospitalization

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

**ARR=4.7%**

**RRR=20%**

**NNT=21**

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>LCZ 696</td>
<td>4187 3922 3663 3018 2257 1544 896 249</td>
</tr>
<tr>
<td>Enalapril</td>
<td>4212 3883 3579 2922 2123 1488 853 236</td>
</tr>
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Entresto™

Key points in use

- Entresto is used **INSTEAD OF** ACE I or ARB.
- If used to replace an ACE I, a 36 hour washout period is needed without ACE I or Entresto.
- Same renal function and potassium monitoring as you would do with initiation of ACE I or ARB.
- Cannot use if pregnant.
- Angioedema incidence was higher in the Entresto group (0.5% vs. 0.2%).
  - No deaths from angioedema in the trial.
Summary

• Heart failure continues to be a source of morbidity and mortality for millions of Americans

• Direct treatment for hemodynamic abnormalities improves symptoms, but not overall survival

• Addressing the neurohormonal derangements in HF patients has been effective in patients with reduced ejection fraction at improving symptoms and reducing hospitalizations and mortality
The End