Neurohormonal blockade in Heart Failure

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DISCLOSURES

• NO DISCLOSURES
• JACK OF ALL TRADE CARDIOLOGIST WITH SOME RESEARCH INTEREST
Natural History of HF

Survival (%)

LV Dysfunction and Symptoms

Annual Mortality

Mechanism of Death
- Sudden death: 40%
- Worsened HF: 40%
- Other: 20%

Progression

Asymptomatic
- <5%
Mild
- 10%
Moderate
- 20%–30%
Severe
- 30%–80%
Conceptual CHF models: CHF as a neurohormonal disorder

- Chronic neurohormonal activation
  - Increased retention of sodium and water
    - Edema
  - Coronary and systemic vasoconstriction
    - Pulmonary congestion
    - Increased myocardial oxygen demand; reduced myocardial oxygen supply
      - Cardiac myocyte dysfunction and necrosis
      - Progressive impairment of cardiac structure and function
        - Disease progression
        - Decreased survival
  - Toxic effects of angiotensin II and catecholamines
    - Oxidative stress
      - Cytokines

Cardiac myocyte apoptosis
Ventricular remodelling mechanism based on experimental data.
Neurohormonal Activation in Heart Failure

- Myocardial Injury (CAD, HTN, CMP)
- LV Dysfunction
  - Increase wall stress
- Activation of RAS and SNS
- LV Remodeling and progressive LV Dysfunction
- Fibrosis, apoptosis, hypertrophy cellular/molecular alterations, myotoxicity
- Peripheral vasoconstriction
  - Hemodynamic alterations
- Morbidity/Mortality
  - Arrhythmias
  - Pump Failure
- Heart Failure Symptoms
  - Dyspnea
  - Fatigue, Edema
  - Chest Congestion
Neurohormonal Imbalance in Decompensated Heart Failure

Endothelin
Aldosterone
Angiotensin II
Vasopressin
Norepinephrine

ANP
BNP
NO
Bradykinin
Prostacyclin

vasoconstriction
vasodilation

ANP=atrial natriuretic peptide; BNP=endogenous B-type natriuretic peptide; NO=nitric oxide

NEUROHORMONAL ACTIVATION

- Norepinephrine
- Angiotensin II
- Endothelin
- Cytokines

Hypertrophy, apoptosis, ischemia, arrhythmias, remodeling, fibrosis
TREATMENT OBJECTIVES

↑ Survival
↓ Morbidity
↑ Exercise capacity
↑ Quality of life
↓ Neurohormonal changes
↓ Progression of CHF
↓ Symptoms
Evolution of Drug Therapies for CHF

- **18th Century**: Digitalis
- **19th Century**: Weak diuretics, Thiazides and furosemide
- **1960s**: Vasodilators
- **1970s-1980s**: ACE inhibitors
- **1980s**: IV inotropics
- **1990s**: Beta-blockers
  - Potential role for Angiotensin II antagonists
  - Aldosterone antagonists
Blockade of RAS

LOCAL ANG II SYNTHESIS IS INDEPENDENT OF ACE

- ANGIOTENSININOGEN (LIVER)
- RENIN INHIBITOR
- BRADYKININ
- PEPTIDES
- ACE INHIBITOR
- ANGIOTENSIN I
- CHYMASE
- ANGIOTENSIN II
- AT1 RECEPTOR BLOCKER
- AT1
- AT2
Effects of Angiotensin II via AT$_1$ receptors

- Vasoconstriction
- Hypertrophy
- Inotrope +
- Chronotrope +
- Hypertrophy (HVG)
- Fibrosis
- ↑ sodium and water retention
- Vasoconstriction of afferent and efferent arterioles
- Stimulation thirst center
- Vasopressin release
- Sympathetic activation
- Aldosterone secretion
- ↑ Catecholamines secretion

Bauer and Reams *Arch Intern Med* 1995;155:1361-1368
OPTIMISING ACEI DOSAGE

- Increase ACE

<table>
<thead>
<tr>
<th>ACEI</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
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<tr>
<td>Enalapril</td>
<td>2.5 mg bid</td>
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<tr>
<td>Fosinopril</td>
<td>5-10 mg daily</td>
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<tr>
<td>Lisinopril</td>
<td>2.5-5 mg daily</td>
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<td>Perindopril</td>
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<td>Quinapril</td>
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<td>Trandolapril</td>
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<td>4 mg daily</td>
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</table>

1From ACCF/AHA Guidelines.
Angiotensin-Converting Inhibitors

- Decrease conversion of angiotensin I-II
- Improve survival
- Decrease rate of hospitalization
- Improve symptoms
- Inhibit neurohormonal activation
- Reverse remodeling
- Decrease incidence of SCD?
ARB in Heart Failure
(meta-analysis)

• 17 Trials, 12,469pts (JACC Feb 2002)
• No superiority of ARBs in reducing all-cause mortality or hospitalizations for heart failure
• Poss. benefit with combination ace inhibition
• Beneficial for pts intolerant to ace inhibition
The Case for β-Blockade in Heart Failure

Neurohormonal activation underlies disease progression and provides basis for treatment selection

Weight of data for β-blockade equals or exceeds that of ACE inhibitors

β-Blockade is added to ACE inhibitors for more complete neurohormonal blockade
Effects of Beta-Blockade on Mortality

- **US Carvedilol Program** *(p<0.001)*: ↓ 65% *
- **CIBIS-II Trial** *(p<0.001)*: ↓ 32% †
- **MERIT-HF** *(p≈ 0.00015)*: ↓ ≈ 35% ‡

Effect of Carvedilol on Left Ventricular Ejection Fraction

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

Mulitcenter Oral Carvedilol Heart Failure Assessment


$P<.001$ vs placebo.
Not all \(\beta\)-blockers Work

BEST

Xamoterol Study Group


Lancet 1990;336:1-6
ALDOSTERONE INHIBITORS

Spironolactone

Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)

- Retention Na$^+$
- Retention H$_2$O
- Excretion K$^+$
- Excretion Mg$^{2+}$

ALDOSTERONE

→ Edema
→ Arrhythmias

Collagen deposition
- myocardium
- vessels

Fibrosis
EPHESUS
Total Mortality

Placebo + standard care (n=3313)
INSPIRA + standard care (n=3319)

RR=0.85 (95% CI, 0.75 to 0.96)
P=.008

No. at Risk
Placebo  3313  3064  2983  2830  2418  1801  1213  709  323  99
INSPIRA  3319  3125  3044  2896  2463  1857  1260  728  336  110

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

ACEI/ARB: 71.1%
Beta-blocker: 36.6%
ACEI/ARB and beta-blocker: 29.3%
Loop diuretic: 79.6%
SARA (spironolactone): 15.9%
Digoxin: 24.4%

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin II receptor blocker
SARA = selective aldosterone receptor antagonist
DIGOXIN NEUROHORMONAL EFFECTS

- ↓ Plasma Noradrenaline
- ↓ Peripheral nervous system activity
- ↓ RAAS activity
- ↑ Vagal tone
- Normalizes arterial baroreceptors
DIGOXIN

- No new data since DIG trial
  - Effect on symptoms:
    - improved symptoms
    - improved functional capacity
  - Effect on mortality
    - not better than placebo

- Recommendation: for symptomatic patients with CHF secondary to LV dysfunction

N Engl J Med 1997;336:525-533
Neurohormones well studied in heart failure.

Norepinephrine
Epinephrine
Renin Anigotensin Aldosteron
Kallikrein – kinin system

Endothelin
Vasopressin
Neuropeptide Y
Vasoactive intestinal Peptides
Nitric Oxide
Natriuretic peptides
Calcitonin gene-related peptide
Growth hormone
Cortisol
Cytokines
Neurokinin A
Substance P
What Hasn’t Worked?

**Vasopeptidase inhibition**

- **OVERTURE:** 5770 patients with FC II – IV symptoms randomized to enalapril vs omapatrilat (an inhibitor of both ACE and neutral endopeptidase). No difference in survival.

**Endothelin receptor antagonists**

- **ENABLE I/II:** low-dose bosentan (a non-selective endothelin receptor antagonist) vs placebo in patients with FC III – IV symptoms and LVEF ≤ 35%. No benefit but early worsening of heart failure early after bosentan initiation
- **EARTH:** Darusentan four doses vs placebo in 642 patients with chronic heart failure. Well tolerated but no difference in LV ESV, symptoms, or outcome
What Hasn’t Worked?

**TNF α antagonism**

- **RENEWAL**: etanercept (TNFα receptor antagonist) in 2048 patients with FC II – IV symptoms and LVEF ≤ 30%. No effect on survival or HF hospitalization.
- **ATTACH**: two doses of infliximab (an anti-TNFα monoclonal antibody) in 150 patients with FC III – IV symptoms and LVEF ≤ 35%. No effect on clinical status but increase in hospitalization in the high dose group.

**Central sympathetic inhibition**

- **MOXCON**: moxonidine SR vs placebo in 4533 patients with FC II – IV HF. Study stopped due to an early increase in deaths and adverse events with moxonidine.
Neprilysin (NEP) is responsible for natriuretic peptide degradation.

Metabolism of ANP and other peptide hormones by NEP:

- ProEndothelin → Endothelin → Degradation
- ANP → NPR-C
- NPR-A → Guanylate Cyclase → GMP → cGMP

NEP regulates:
- Diuresis
- Natriuresis
- Vasodilation
- Antiproliferative/antihypertrophic

Ang II, Bradykinin, Andrenomedullin.
A Comparison of Angiotensin Receptor-Nephrilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

![Graph showing Kaplan-Meier estimates of cumulative rates for Enalapril and LCZ696.]

**Enalapril**
(n=4212)

**LCZ696**
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk

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<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
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Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

- Effect of ARB vs placebo derived from CHARM-Alternative trial
- Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
- Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Summarising

• Neurohormonal activation is an important driver of heart failure progression
• The current treatment paradigm for heart failure revolve around the central theory of Neurohormal antagonism
• Have we reached a ceiling in Neurohormonal Inhibition, Possibly not
## Medication Benefits in Systolic Heart Failure

<table>
<thead>
<tr>
<th>Medication</th>
<th>Improves Survival</th>
<th>Reduces Hospitalizations</th>
<th>Improves Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
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<tr>
<td>Angiotensin receptor blocker</td>
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<td>Beta-blocker</td>
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<tr>
<td>Digoxin</td>
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Thank you