Control of neurohormonal activation –
A success in the treatment of systolic heart failure

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Control of neurohormonal activation –
A success in the treatment of systolic heart failure

Speaker: Karl Swedberg

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Servier, Vifor
Research grants: Amgen, Servier

Presentation slide distribution:
These presentation slides will be added to www.bsh.org.uk after the meeting
Philip Poole-Wilson

- Born 26 April 1943; died 4 March 2009
- Poole-Wilson held five visiting professorships, gave 39 named lectures, was an honorary member of 13 overseas societies of cardiology, and supervised 48 MD and PhD students (29 of whom went on to hold professorships).
Treatment of heart failure
From two textbooks 1929 and 1974

“…and for all this there is only digitalis and rest…”

Paul Dudley White: Textbook in Cardiology, 1929

Moderately severe heart failure
Decrease physical activity
Institute digitalis
Give thiazide every day plus potassium
If not enough use furosemide and if insufficient, combine them

J W Hurst: The Heart 3rd edition, 1974
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)
Therapeutic algorithm for a patient with symptomatic HFrEF

Patient with symptomatic\(^a\) HFrEF\(^b\)

- Therapy with ACE-I\(^c\) and beta-blocker (Up-titrato maximum tolerated evidence-based doses)
  - No
  - Still symptomatic and LVEF ≤35%
    - Yes
    - Add MR antagonist\(^d,e\) (up-titrato maximum tolerated evidence-based dose)
      - Yes
      - Still symptomatic and LVEF ≤35%
        - No
        - Sinus rhythm, QRS duration ≥130 msec
          - No
          - Sinus rhythm, HR ≥70 bpm
            - No
            - Ivabradine
              - These above treatments may be combined if indicated
              - Yes
              - Resistant symptoms
                - No
                - Consider digoxin or H-ISDN or LVAD, or heart transplantation
                  - No further action required
                    - Consider reducing diuretic dose
          - Yes
          - Evaluate need for CRT\(^d\)
            - No
            - ARNI to replace ACE-I
              - Yes
              - Diuretics to relieve symptoms and signs of congestion
                - If LVEF ≤35% despite QOMT or a history of symptomatic VT/VF, implant ICD

\(^{a,b}\) HF: Heart Failure, LVEF: Left Ventricular Ejection Fraction
\(^{c}\) ACE-I: Angiotensin Converting Enzyme Inhibitor
\(^{d}\) ARNI: Angiotensin Receptor Neprilysin Inhibitor
\(^{e}\) ARB: Angiotensin II Receptor Blocker
\(^{f}\) CRT: Cardiac Resynchronization Therapy
\(^{g}\) Class I
\(^{h}\) Class Ia
HF: Patho-physiological basis of treatment

Myocardial injury

↓

Left ventricular systolic dysfunction

Perceived reduction in circulating volume and pressure

Systemic vasoconstriction
Renal sodium and water retention

Neurohumoral activation
- SNS
- RAAS
- ET, AVP etc
Classes of RAAS-inhibitors

Givertz, M Circulation 2001
RAAS inhibition in CHF

Angiotensinogen → Angiotensin I → Angiotensin II

Liver

Renin

ACE

Lungs

Blood vessel
- Vasoconstriction
- SMC hypertrophy
- Superoxide generation
- Endothelin secretion
- Monocyte activation
- Inflammatory cytokines
- Reduced fibrinolysis

Kidney
- Sodium and water retention
- Efferent arteriolar vasoconstriction
- Glomerular and interstitial fibrosis

Heart
- Cellular hypertrophy
- Myocyte apoptosis
- Myocardial fibrosis
- Inflammatory cytokines
- Coronary vasoconstriction
- Positive inotropy
- Proarrhythmia

Adrenal gland
- Aldosterone secretion

Brain
- Vasopressin secretion
- Sympathetic activation
Fogarty Fellowship in San Francisco
1981-82

Kanu Chatterjee

Wlliam Parmley
Enalapril: A New Angiotensin-Converting Enzyme Inhibitor in Chronic Heart Failure: Acute and Chronic Hemodynamic Evaluations

LORENZO DiCARLO, MD, KANU CHATTERJEE, MB, FRCP, FACC, WILLIAM W. PARMLEY, MD, FACC, KARL SWEDBERG, MD, FACC, BEVERLEY ATHERTON, AB, DEIRDRE CURRAN, BS, MARY CUCCI, RN

San Francisco, California
EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

The CONSENSUS Trial Study Group*

Abstract To evaluate the influence of the angiotensin-converting-enzyme inhibitor enalapril (2.5 to 40 mg per day) on the prognosis of severe congestive heart failure (New York Heart Association [NYHA] functional class IV), we randomly assigned 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127). Conventional treatment for heart failure, including the use of other vasodilators, was continued in both groups. Follow-up averaged 188 days (range, 1 day to 20 months). The crude mortality at the end of six months (primary end point) was 26 percent in the enalapril group and 44 percent in the placebo group — a reduction of 40 percent (P = 0.002). Mortality was reduced by 31 percent at one year (P = 0.001). By the end of the study, there had been 68 deaths in the placebo group and 50 in the enalapril group — a reduction of 27 percent (P = 0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50 percent), whereas no difference was seen in the incidence of sudden cardiac death.

A significant improvement in NYHA classification was observed in the enalapril group, together with a reduction in heart size and a reduced requirement for other medication for heart failure. The overall withdrawal rate was similar in both groups, but hypotension requiring withdrawal occurred in seven patients in the enalapril group and in no patients in the placebo group. After the initial dose of enalapril was reduced to 2.5 mg daily in high-risk patients, this side effect was less frequent.

We conclude that the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of heart failure. (N Engl J Med 1987; 316:1429-35.)
CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study)

- 253 patients in NYHA class IV
- Randomized to placebo/enalapril
- From first patient to end of study 20 months
- 118 deaths

Mortality vs Year

p=0.002

NEJM 1987
## CONSENSUS: background therapy

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis</td>
<td>93%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3%</td>
</tr>
<tr>
<td>Diuretic</td>
<td></td>
</tr>
<tr>
<td>Furosemide (mean dose)</td>
<td>98% (205mg)</td>
</tr>
<tr>
<td>Spironolactone (mean dose)</td>
<td>53% (80mg)</td>
</tr>
</tbody>
</table>
Neuroendocrine Activation and Mortality

Six Month Mortality (%) by Plasma Levels of Hormones
From CONSENSUS I  Placebo Group N=120

%  
P<0.01

Modified from Swedberg et al Circulation 1990
SOLVD Treatment Trial
All Cause Death

Cumulative incidence (%)

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo Number at Risk</th>
<th>Enalapril Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1284</td>
<td>1285</td>
</tr>
<tr>
<td>1</td>
<td>1127</td>
<td>1085</td>
</tr>
<tr>
<td>2</td>
<td>1010</td>
<td>939</td>
</tr>
<tr>
<td>3</td>
<td>697</td>
<td>669</td>
</tr>
<tr>
<td>3.5</td>
<td>526</td>
<td>487</td>
</tr>
</tbody>
</table>

Relative risk reduction = 16%
p = 0.0036

Background Beta-blocker 8%

EFFECT OF CAPTOPRIL ON MORTALITY AND MORBIDITY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Results of the Survival and Ventricular Enlargement Trial

Marc A. Pfeffer, M.D., Ph.D., Eugene Braunwald, M.D., Lemuel A. Moyé, M.D., Ph.D., Lofty Basta, M.D., Edward J. Brown, Jr., M.D., Thomas E. Cuddy, M.D., Barry R. Davis, M.D., Ph.D., Edward M. Geltman, M.D., Steven Goldman, M.D., Greg C. Flaker, M.D., Marc Klein, M.D., Gervasio A. Lamas, M.D., Milton Packer, M.D., Jacques Rouleau, M.D., Jean L. Rouleau, M.D., John Rutherford, M.D., John H. Wertheimer, M.D., and C. Morton Hawkins, Sc.D., on behalf of the SAVE Investigators

The SAVE Trial
The cornerstone of therapy

ACE inhibitor (Beta-blocker)
CONSENSUS 10-Year Follow-Up
All Randomized Patients, Original and Follow-Up

Mortality

Year

p=0.008

Swedberg et al EHJ 1999
Can we do better than an ACE inhibitor?

ARB versus ACE inhibitor
Why might AT$_1$-receptor blockers be more efficacious than ACE inhibitors?

ACE inhibitors

![Diagram](attachment:image.png)

AT$_1$-receptor blockers

![Diagram](attachment:image.png)
Losartan Heart Failure Survival Study: ELITE II
Primary Endpoint – All-Cause Mortality

Captopril, (n=1574), 250 events
Losartan, (n=1578), 280 events

Captopril/Losartan Hazard Ratio (95% CI):
0.88 (0.75, 1.05) P=0.16

Pitt et al Lancet 2000
ARB added to an ACE inhibitor
Why add an ARB to an ACE inhibitor?

Angiotensin I

ACE

Angiotensin II

Kininase II

BK

Breakdown products

blood vessels

heart

adrenals

kidney

Angiotensin I

ACE

Angiotensin II

chymase

blood vessels

heart

adrenals

kidney
3 component trials comparing candesartan to placebo

CHARM Alternative
n=2028
LVEF ≤40%
ACE inhibitor intolerant

CHARM Added
n=2548
LVEF ≤40%
ACE inhibitor treated

CHARM Preserved
n=3025
LVEF >40%
ACE inhibitor treated/not treated

Primary outcome:
CV death or CHF hosp
CHARM
Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CHARM-Added: Primary outcome
CV death or CHF hospitalisation

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>1276</td>
<td>1176</td>
<td>1063</td>
<td>948</td>
<td>457</td>
</tr>
<tr>
<td>Placebo</td>
<td>1272</td>
<td>1136</td>
<td>1013</td>
<td>906</td>
<td>422</td>
</tr>
</tbody>
</table>

HR 0.85 (95% CI 0.75-0.96), p=0.011
Adjusted HR 0.85, p=0.010

NNT = 23

McMurray et al Lancet 2003
CHARM-Alternative: Primary outcome
CV death or CHF hospitalization

Granger et al Lancet 2003

HR 0.77 (95% CI 0.67-0.89), p=0.0004
Adjusted HR 0.70, p<0.0001

Candesartan
Placebo

Number at risk
Candesartan 1013 929 831 434 122
Placebo 1015 887 798 427 126
RAAS inhibition in CHF

Angiotensinogen → Angiotensin I

Renin → Angiotensin I → Angiotensin II

Lungs

Angiotensin II →

Blood vessel
Vasoconstriction
SMC hypertrophy
Superoxide generation
Endothelin secretion
Monocyte activation
Inflammatory cytokines
Reduced fibrinolysis

Kidney
Sodium and water retention
Efferent arteriolar vasoconstriction
Glomerular and interstitial fibrosis

Heart
Cellular hypertrophy
Myocyte apoptosis
Myocardial fibrosis
Inflammatory cytokines
Coronary vasoconstriction
Positive inotropy
Proarrhythmia

Adrenal gland
Aldosterone secretion

Brain
Vasopressin secretion
Sympathetic activation
Therapeutic algorithm for a patient with symptomatic HFrEF

- Patient with symptomatic\(^a\) HFrEF\(^b\)
  - Therapy with ACE-I\(^c\) and beta-blocker (Up-titrate to maximum tolerated evidence-based doses)
    - Still symptomatic and LVEF ≤ 35%
      - Add MR antagonist\(^d,e\) (up-titrate to maximum tolerated evidence-based dose)
        - Yes
        - Still symptomatic and LVEF ≤ 35%
          - If LVEF ≤ 35% despite OMT or a history of symptomatic VT/VF, implant ICD
            - Diuretics to relieve symptoms and signs of congestion
              - Able to tolerate ACEI (or ARB)\(^f\)
              - Sinus rhythm, QRS duration ≥ 130 msec
              - Sinus rhythm, HR ≥ 70 bpm
                - ARNI to replace ACE-I
                - Evaluate need for CRT\(^d\)
                - Ivabradine
          - No
        - No
      - Yes
        - Consider digoxin or H-ISDN or LVAD, or heart transplantation
        - No further action required
          - Consider reducing diuretic dose

---

\(^a\) Class I
\(^b\) Class Ia
THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

Bertram Pitt, M.D., Faiez Zannad, M.D., Willem J. Remme, M.D., Robert Cody, M.D., Alain Castaigne, M.D., Alfonso Perez, M.D., Jolie Palensky, M.S., and Janet Wittes, Ph.D., for the Randomized Aldactone Evaluation Study Investigators*
RALES

HR 0.70 (0.60, 0.82), P<0.001

24 months follow-up
94.5% ACE-I
10.5% Beta-blocker

No. AT RISK
Placebo  841  775  723  678  628  592  565  483  379  280  179  92  36
Spironolactone  822  766  739  698  669  639  608  526  419  316  193  122  43
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*
EMPHASIS-HF

2737 patients ≥60 years with NYHA II HF and LVEF ≤30%

Primary Outcome

All-Cause Death

- Hazard ratio, 0.63 (95% CI, 0.54–0.74) P<0.001
- HR [95% CI] = 0.76 [0.62, 0.93] P = 0.008

What is next?
Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696

Natriuretic peptide system

pro-BNP → NT-pro-BNP → BNP

Vasodilation
↓ Blood pressure
↓ Sympathetic tone
↓ Aldosterone levels
↓ Fibrosis
↓ Hypertrophy
Natriuresis
Diuresis

Inactive fragments

Neprilysin

LCZ696
Sacubitril
Valsartan

Renin angiotensin system

AT₁ receptor

Angiotensin II

Vasoconstriction
↑ Blood pressure
↑ Sympathetic tone
↑ Aldosterone levels
↑ Fibrosis
↑ Hypertrophy
Sodium retention
Water retention

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696 400 mg daily  ↔  Enalapril 20 mg daily

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE
# Key Inclusion & Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic HF NYHA class II–IV with LVEF ≤40% (which was amended to ≤35% one year after study started) and:</td>
<td>• History of angioedema</td>
</tr>
<tr>
<td>- BNP ≥150 pg/mL (or NT-proBNP ≥ 600) OR</td>
<td>• eGFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>- BNP ≥100 pg/mL (or NT-proBNP ≥ 400) + HF hospitalization last 12 months</td>
<td>• Serum potassium &gt;5.2 mmol/L</td>
</tr>
<tr>
<td>• Stable on ACEI or ARB (dosage equivalent to enalapril ≥10 mg/d) for 4 weeks</td>
<td>• Symptomatic hypotension, SBP &lt;100 mmHg</td>
</tr>
<tr>
<td>• β-blocker for 4 weeks, unless not tolerated</td>
<td>• Current acute decompensated HF</td>
</tr>
<tr>
<td>• Optimized dosing of background HF medications (MRA)</td>
<td></td>
</tr>
</tbody>
</table>
PARADIGM-HF: Active run-in

Single-blind period

LCZ 100 mg bid
LCZ 200 mg bid
Enalapril 5-10 mg bid
1-2 weeks
1-2 weeks
2 weeks

Prior ACEi/ARB use discontinued

Double-blind period

LCZ696 200 mg BID (n=4187)
N = 8442 (1:1 randomization)
Enalapril 10 mg BID (n=4212)

Outcome driven (CV death): median follow-up = 27 months
PARADIGM-HF: Pre-specified endpoints

- **Primary:** Cardiovascular death or heart failure hospitalization
  - Cardiovascular death
  - Heart failure hospitalization

- **Secondary:**
  - Death from any cause
  - KCCQ (CSS - symptoms and physical limitations)
  - New onset atrial fibrillation
  - Decline in renal function
Angiotensin–Nepriylsin 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*
<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Target dose, mg</th>
<th>Mean daily dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (1987)*</td>
<td>127</td>
<td>20 bid</td>
<td>18.4</td>
</tr>
<tr>
<td>SOLVD-T (1991)†</td>
<td>1284</td>
<td>10 bid</td>
<td>16.6</td>
</tr>
<tr>
<td>V-HeFT II (1991)</td>
<td>403</td>
<td>10 bid</td>
<td>15.0</td>
</tr>
<tr>
<td>OVERTURE (2002)</td>
<td>2884</td>
<td>10 bid</td>
<td>17.7</td>
</tr>
<tr>
<td>CARMEN (2004)</td>
<td>190 E only</td>
<td>10 bid</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>191 E+Carv</td>
<td>10 bid</td>
<td>14.9</td>
</tr>
<tr>
<td>CIBIS-3 (2005)</td>
<td>190 E first</td>
<td>10 bid</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>191 Bisop first</td>
<td>10 bid</td>
<td>15.8</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>4212</td>
<td>10 bid</td>
<td>18.9</td>
</tr>
</tbody>
</table>

† N.B. active run-in; 49% reached target dose. *22% reached target dose.
## PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy (%)</strong></td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td><strong>NYHA functional class II / III (%)</strong></td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>N-terminal pro-BNP (pg/ml)</strong></td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td><strong>B-type natriuretic peptide (pg/ml)</strong></td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td><strong>Mineralocorticoid antagonists</strong></td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td><strong>ICD and/or CRT</strong></td>
<td>21.4%</td>
<td>21.9%</td>
</tr>
</tbody>
</table>
PARADIGM-HF Primary Results
Significant Reduction in Primary Endpoints, CV Death and All-Cause Mortality

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000004
Number needed to treat = 21

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.80 (0.71-0.89)
P = 0.00008
Number need to treat = 32

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.84 (0.76-0.93)
P<0.0001

McMurray et al NEJM 2014
Sacubitril/Valsartan works quickly

Effects on CV death or HF hospitalization by time

0.00 0.05 0.10 0.15

0 2 4 6 8 10 12

Months after Randomization

Enalapril

LCZ696

PARADIGM, data on file
Key Questions Clinicians Are Asking about sacubitril/valsartan and PARADIGM

- Is sacubitril/valsartan effective across the spectrum of heart failure?
Comparing LCZ696 With Enalapril According to Baseline Risk Using the MAGGIC and EMPHASIS-HF Risk Scores

An Analysis of Mortality and Morbidity in PARADIGM-HF

Joanne Simpson, MBChB,* Pardeep S. Jhund, MBChB, PhD,* Jose Silva Cardoso, PhD,† Felipe Martinez, MD,‡ Arend Mosterd, MD,§ Felix Ramires, MD,|| Adel R. Rizkala, PHARM,¶ Michele Senni, MD,# Iain Squire, MD,** Jianjian Gong, PhD,¶ Martin P. Lefkowitz, MD,¶ Victor C. Shi, MD,¶ Akshay S. Desai, MD,†† Jean L. Rouleau, MD,†‡ Karl Swedberg, MD,§§ Michael R. Zile, MD,¶¶ John J.V. McMurray, MD,* Milton Packer, MD,¶¶ Scott D. Solomon, MD,†† on behalf of the PARADIGM-HF Investigators and Committees

ABSTRACT

BACKGROUND Although most patients in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial had mild symptoms, there is a poor correlation between reported functional limitation and prognosis in heart failure.

BACKGROUND Most patients in the PARADIGM-HF trial had mild symptoms, and the correlation between reported functional limitation and prognosis in heart failure was poor.

OBJECTIVE The primary objective was to compare the mortality and morbidity risks in PARADIGM-HF using the MAGGIC and EMPHASIS-HF risk scores.

METHODS The risk scores were calculated for all patients in the PARADIGM-HF trial using data from the baseline assessment.

RESULTS The MAGGIC and EMPHASIS-HF risk scores were significantly correlated with mortality and morbidity outcomes in the PARADIGM-HF trial.

CONCLUSIONS The results suggest that risk scores based on baseline assessment can be used to predict mortality and morbidity in heart failure patients.
Is LCZ Effective Across the Spectrum of Heart Failure

Components of MAGGIC Score:
- Age
- SBP
- BMI
- Creatinine
- NYHA
- Sex
- Smoking
- DM
- COPD

Simpson et al. JACC 2015
LCZ Effective Across a Spectrum of Risk: The MAGGIC Risk Score

CV death or HF hospitalisation

- Enalapril
- LCZ696

Simpson et al. JACC 2015
PARADIGM-HF: Effect of Sacubitril/valsartan according to age category

**CV death or HF hospitalization**

- Rate per 100 patient years
- Age categories: < 55, 55-64, 65-74, ≥ 75

**CV death**

- Rate per 100 patient years
- Treatments: Enalapril, LCZ696
- Age categories: < 55, 55-64, 65-74, ≥ 75

**HF hospitalization**

- Rate per 100 patient years
- Age categories: < 55, 55-64, 65-74, ≥ 75

**All-cause death**

- Rate per 100 patient years
- Age categories: < 55, 55-64, 65-74, ≥ 75

*Jhund et al. EHJ 2015*
Key Questions Clinicians Are Asking about sacubitril/valsartan and PARADIGM

- Is sacubitril/valsartan effective across the spectrum of heart failure?
- Is sacubitril/valsartan effective in a patient on OPTIMAL therapy
### Beta blocker subgroup by dose

**Primary composite endpoint**

<table>
<thead>
<tr>
<th>Beta blocker target dose</th>
<th>LCZ696 n/N (%)</th>
<th>Enalapril n/N (%)</th>
<th>Hazard ratio (95% CI) LCZ696 vs enalapril</th>
<th>Subgroup by treatment int. p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=50%</td>
<td>416/1919 (21.68)</td>
<td>454/1848 (24.57)</td>
<td>0.85 (0.74, 0.97)</td>
<td>0.4377</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>424/1948 (21.77)</td>
<td>547/2027 (26.99)</td>
<td>0.79 (0.70, 0.90)</td>
<td></td>
</tr>
<tr>
<td>No beta blocker</td>
<td>69/288 (24.0)</td>
<td>111/300 (37.0)</td>
<td>0.61 (0.45, 0.83)</td>
<td></td>
</tr>
</tbody>
</table>

*McMurray. ACC 2016*
PARADIGM-HF: Baseline mineralocorticoid receptor (aldosterone) antagonist (MRA) use

Cardiovascular death
HR 0.80 (0.71, 0.89); p <0.0001

HR 0.75 (0.63, 0.89)*
HR 0.84 (0.73, 0.98)*

*Interaction p = 0.32

Enalapril
LCZ696

MRA - No
MRA - Yes

McMurray ACC 2016
CV mortality by Baseline ICD use

Cardiovascular death
HR 0.80 (0.71, 0.89); p <0.0001

- ICD - No
  - HR 0.80 (0.71, 0.90)*

- ICD - Yes
  - HR 0.76 (0.55, 1.05)*

*Interaction p = 0.92

ACC 2016
Key Questions Clinicians Are Asking about sacubitril/valsartan and PARADIGM

- Is sacubitril/valsartan effective across the spectrum of heart failure?
- Is sacubitril/valsartan effective in a patient on OPTIMAL therapy
- Is Sacubitril/Valsartan Effective at Lower than Target Doses?
Is Sacubitril/Valsartan Effective at Lower than Target Doses?

Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

Orly Vardeny¹, Brian Claggett², Milton Packer³, Michael R. Zile⁴, Jean Rouleau⁵, Karl Swedberg⁶, John R. Teerlink⁷, Akshay S. Desai², Martin Lefkowitz⁸, Victor Shi⁸, John J.V. McMurray⁹, Scott D. Solomon²*, for the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators

¹Pharmacy Practice Division, University of Wisconsin School of Pharmacy, Madison, WI, USA; ²Cardiovascular Division, Brigham and Women’s Hospital, Boston, MA, USA; ³Division of Cardiology, Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, USA; ⁴Medical University of South Carolina and Ralph H. Johnston Veterans Administration Medical Center, Charleston, NC, USA; ⁵Institut de Cardiologie de Montréal, Université de Montréal, Montreal, Canada; ⁶University of Gothenburg, Gothenburg, Sweden and National Heart and Lung Institute, Imperial College, London, UK; ⁷University of California-San Francisco and San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; ⁸Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; and ⁹British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

Received 15 April 2016; revised 27 April 2016; accepted 1 May 2016
## Baseline Characteristics in Patients with Dose Reduction

### Dose Reduction vs. No Dose Reduction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Dose Reduction N=3547</th>
<th>No Dose Reduction N=4852</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age, years</td>
<td>65.26 ± 11.55</td>
<td>62.73 ± 11.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>761 (21.5%)</td>
<td>1071 (22.1%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>2402 (67.7%)</td>
<td>3142 (64.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline BMI, kg/m²</td>
<td>28.14 ± 5.59</td>
<td>28.18 ± 5.47</td>
<td>0.76</td>
</tr>
<tr>
<td>NYHA class (I / II / III / IV) (Freq)</td>
<td>139 (3.9%) / 2453 (69.3%) / 928 (26.2%) / 20 (0.6%)</td>
<td>250 (5.2%) / 3466 (71.5%) / 1090 (22.5%) / 40 (0.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>29.43 ± 6.53</td>
<td>29.53 ± 5.98</td>
<td>0.45</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>2206 (62.2%)</td>
<td>2830 (58.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>2528 (71.3%)</td>
<td>3412 (70.3%)</td>
<td>0.34</td>
</tr>
<tr>
<td>History of DM (%)</td>
<td>1332 (37.6%)</td>
<td>1575 (32.5%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior use of ACEI (%)</td>
<td>2727 (76.9%)</td>
<td>3805 (78.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>120.72 ± 15.82</td>
<td>121.87 ± 14.93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>72.69 ± 12.37</td>
<td>72.10 ± 11.73</td>
<td>0.028</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.18 ± 0.32</td>
<td>1.08 ± 0.27</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Dose-Reduced Group by Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enalapril N=1792</th>
<th>Sacubitril/valsartan N=1755</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age, years</td>
<td>65.21 ± 11.20</td>
<td>65.30 ± 11.90</td>
<td>0.83</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>403 (22.5%)</td>
<td>358 (20.4%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>1203 (67.1%)</td>
<td>1199 (68.3%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Baseline BMI, kg/m²</td>
<td>403 (22.5%)</td>
<td>358 (20.4%)</td>
<td>0.13</td>
</tr>
<tr>
<td>NYHA class (I / II / III / IV) (Freq)</td>
<td>74 (4.1%) / 1231 (68.7%) / 474 (26.5%) / 12 (0.7%)</td>
<td>65 (3.7%) / 1222 (69.9%) / 454 (26.0%) / 8 (0.5%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>29.36 ± 6.59</td>
<td>29.49 ± 6.48</td>
<td>0.56</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>1106 (63.0%)</td>
<td>1106 (63.0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>1267 (71.9%)</td>
<td>1261 (71.9%)</td>
<td>0.45</td>
</tr>
<tr>
<td>History of DM (%)</td>
<td>672 (37.5%)</td>
<td>660 (37.6%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Prior use of ACEI (%)</td>
<td>1362 (77.6%)</td>
<td>1362 (77.6%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>120.70 ± 15.84</td>
<td>120.74 ± 15.80</td>
<td>0.95</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>72.71 ± 12.26</td>
<td>72.66 ± 12.49</td>
<td>0.9</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.18 ± 0.32</td>
<td>1.18 ± 0.32</td>
<td>0.74</td>
</tr>
</tbody>
</table>

### Current Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Enalapril</th>
<th>Sacubitril/valsartan</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>2908 (82.0%)</td>
<td>3830 (78.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>3260 (91.9%)</td>
<td>4551 (93.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MRA</td>
<td>1917 (54.0%)</td>
<td>2754 (56.8%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1078 (30.4%)</td>
<td>1461 (30.1%)</td>
<td>0.78</td>
</tr>
<tr>
<td>ICD</td>
<td>656 (18.5%)</td>
<td>587 (12.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRT</td>
<td>311 (8.8%)</td>
<td>263 (5.4%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Enalapril</th>
<th>Sacubitril/valsartan</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>1470 (82.0%)</td>
<td>1438 (81.9%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1639 (91.5%)</td>
<td>1621 (92.4%)</td>
<td>0.32</td>
</tr>
<tr>
<td>MRA</td>
<td>988 (55.0%)</td>
<td>931 (53.0%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Digoxin</td>
<td>560 (31.7%)</td>
<td>510 (28.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>ICD</td>
<td>321 (17.9%)</td>
<td>335 (19.1%)</td>
<td>0.37</td>
</tr>
<tr>
<td>CRT</td>
<td>146 (8.1%)</td>
<td>165 (9.4%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Primary outcome events among patients with and without dose reduction

- Regardless of treatment assignment, dose reduction was associated with a higher subsequent risk of the primary outcome event (HR 2.5, 95% CI 2.2–2.7)

Comparison of LCZ vs. Enapapril in Dose-Reduced Patients

Primary outcome measure by mean dose post-randomization using a time updated covariate of average cumulative dose of each study medication.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>LCZ696</th>
<th>Enalapril</th>
<th>Events (N)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>200 mg</td>
<td>10 mg</td>
<td>1262</td>
<td>0.79 (0.71, 0.88)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2</td>
<td>100-200 mg</td>
<td>5-10 mg</td>
<td>541</td>
<td>0.80 (0.67, 0.94)</td>
<td>0.008</td>
</tr>
<tr>
<td>1</td>
<td>&lt;100 mg</td>
<td>&lt;5 mg</td>
<td>225</td>
<td>0.76 (0.58, 0.99)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Key Questions Clinicians Are Asking about sacubitril/valsartan and PARADIGM

- Is sacubitril/valsartan effective across the spectrum of heart failure?
- Is sacubitril/valsartan effective in a patient on OPTIMAL therapy?
- Does sacubitril/valsartan benefit patients at lower than the target dose?
- Does a patient who is “stable” warrant switching from an ACE/ARB to sacubitril/valsartan?
What are the reasons to consider switching a “stable” patient?

Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation

The PARADIGM-HF Trial

Scott D. Solomon, MD, a Brian Claggett, PhD, a Milton Packer, MD, b Akshay Desai, MD, a Michael R. Zile, MD, c Karl Swedberg, MD, d Jean Rouleau, MD, e Victor Shi, MD, f Martin Lefkowitz, MD, f John J.V. McMurray, MD g
The most stable PARADIGM patients...

- 20% of the most stable patients (no prior HF hospitalization) had a primary event
- 17% died during the course of the trial
- In the most stable patients with a primary event, death occurred prior to a heart failure hospitalization in 51%
- 60% of these deaths were sudden cardiac deaths

The Most Stable Patients have the Lowest Event Rate

Similar Benefit in Most Stable Patients

**Figure 2** Treatment Effect of Sacubitril/Valsartan Therapy

**Cardiovascular Death or HF Hospitalization**
- Favors sacubitril/valsartan
- Favors Enalapril

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Hazard Ratio</th>
<th>Interaction p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior HF Hospitalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cardiovascular Death**
- Favors sacubitril/valsartan
- Favors Enalapril

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Hazard Ratio</th>
<th>Interaction p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior HF Hospitalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All-Cause Mortality**
- Favors sacubitril/valsartan
- Favors Enalapril

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Hazard Ratio</th>
<th>Interaction p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior HF Hospitalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Forest plot shows treatment effects of sacubitril/valsartan (hazard ratio with 95% confidence interval) based on the presence of and time from a heart failure hospitalization prior to screening on the outcomes of cardiovascular death or heart failure hospitalization (left), cardiovascular death (middle), and all-cause mortality (right).

Key Questions Clinicians Are Asking about sacubitril/valsartan and PARADIGM

- Is sacubitril/valsartan effective across the spectrum of heart failure?
- Is sacubitril/valsartan effective in a patient on OPTIMAL therapy?
- Does sacubitril/valsartan benefit patients at lower than the target dose?
- Does a patient who is “stable” warrant switching from an ACE/ARB to sacubitril/valsartan?
- Is it safe to use sacubitril/valsartan?
PARADIGM-HF: Systolic BP

Mean difference (LCZ–Ena): -2.70 (-3.07, -2.34)(mmHg)

p-value: < 0.001
## PARADIGM-HF: Safety

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension (%)</strong></td>
<td></td>
<td></td>
<td>&lt; 0.001 &lt;0.001&gt;</td>
</tr>
<tr>
<td>symptoms</td>
<td>14.0</td>
<td>9.2</td>
<td>&lt; 0.001 &lt;0.001&gt;</td>
</tr>
<tr>
<td>symptoms and SBP &lt; 90 mmHg</td>
<td>2.7</td>
<td>1.4</td>
<td>&lt; 0.001 &lt;0.001&gt;</td>
</tr>
<tr>
<td><strong>Renal impairment (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr ≥ 2.5 mg/dl</td>
<td>3.3</td>
<td>4.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Cr ≥ 3.0 mg/dl</td>
<td>1.5</td>
<td>2.0</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Hyperkalaemia (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ &gt; 5.5 mmol/l</td>
<td>16.2</td>
<td>17.4</td>
<td>0.15</td>
</tr>
<tr>
<td>K⁺ &gt; 6.0 mmol/l</td>
<td>4.3</td>
<td>5.6</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough (%)</strong></td>
<td>11.3</td>
<td>14.3</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
PARADIGM-HF: Adverse events leading to permanent study drug discontinuation

- Any adverse event: Enalapril 516, LCZ696 449 (p = 0.03)
- Hypotension: Enalapril 29, LCZ696 36 (p = 0.38)
- Renal reasons: Enalapril 59, LCZ696 29 (p = 0.002)
- Hyperkalaemia: Enalapril 15, LCZ696 11 (p = 0.56)
**PARADIGM-HF: Angioedema**

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment/antihistamines n, (%)</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines/corticosteroids n, (%)</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Hospitalized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No airway compromise n, (%)</td>
<td>3 (0.1)</td>
<td>1 (0.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise n, (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>
Therapeutic algorithm for a patient with symptomatic HFrEF

1. **Patient with symptomatic HFrEF**
   - **Therapy with ACE-I** and beta-blocker (Up-titrate to maximum tolerated evidence-based doses)
     - **Still symptomatic and LVEF ≤35%**
       - **No**
       - **Yes**
         - **Add MR antagonist** (up-titrate to maximum tolerated evidence-based dose)
           - **Yes**
             - **Still symptomatic and LVEF ≤35%**
               - **No**
               - **Yes**
                 - **Able to tolerate ACEI (or ARB)**
                   - **ARNI to replace ACE-I**
                 - **Sinus rhythm, QRS duration ≥130 msec**
                 - **Sinus rhythm, HR ≥70 bpm**
                   - **Evaluate need for CRT**
                   - **Ivabradine**
           - **Evaluate need for CRT**
         - **These above treatments may be combined if indicated**
   - **Resistant symptoms**
     - **Yes**
       - **Consider digoxin or H-ISDN or LVAD, or heart transplantation**
     - **No**
       - **No further action required Consider reducing diuretic dose**

---

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD
Network meta-analysis
All-cause Mortality

Conclusions

- Pharmacological treatment of chronic systolic heart failure has improved markedly over the last 25 years

- Control of neurohormonal activation by a combination of at least three blockers is essential

- However, morbidity and mortality in chronic systolic heart failure remain high