Heart failure randomized clinical trials: how we changed standard of care.

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Disclosures:
Honoraria/Consultancy: Amgen, Astrazeneca, Novartis, Pfizer, Servier, Vifor
Research grants: Amgen, Servier
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
Diuretics to relieve symptoms/signs of congestion

+ ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

Yes

ADD ivabradine

No

No

No
**Beta-blockade in heart failure**

Slow introduction of efficient therapy

- 1975
- First report (Waagstein et al)
- 1979
- Indication improved survival (Swedberg et al)

- 1993
- Confirmed in large clinical trials
- to
- Carvedilol, bisoprolol and metoprolol

- 1999
ACC/AHA Guidelines for the Management of CHF 1995

ACC/AHA TASK FORCE REPORT

Guidelines for the Evaluation and Management of Heart Failure
Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure)

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ACC/AHA Guidelines 1995

• “use of beta-blockers for the treatment of chronic heart failure remains investigational, but the official status of beta-blockers may change as recent data are reviewed. Hence, physicians might consider the use of a beta-blocker in selected patients with chronic heart failure.”
**US Carvedilol Programme**

Survival

- **Carvedilol** (n=696)
- **Placebo** (n=398)

Risk reduction = 65%

$p < 0.001$

Days

- 0
- 50
- 100
- 150
- 200
- 250
- 300
- 350
- 400

**Risk reduction = 65%**


**COPERNICUS:**

Survival

- **Carvedilol**
- **Placebo**

Risk reduction = 35%

$p = 0.00013$

Months

- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21

**Risk reduction = 35%**

Packer et al (2001)

**CIBIS-II**

Survival

- **Bisoprolol**
- **Placebo**

Risk reduction = 34%

$p < 0.0001$

Time after inclusion (days)

- 0
- 200
- 400
- 600
- 800

**Risk reduction = 34%**

CIBIS-II Investigators (1999)

**MERIT-HF**

Mortality (%)

- **Placebo**
- **Metoprolol CR/XL**

Risk reduction = 34%

$p = 0.0062$

Months of follow-up

- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21

The MERIT-HF Study Group (1999)
Meta-analysis of 22 beta-blocker studies in CHF

Brophy et al Ann Int Med 2001
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

Yes

ADD ivabradine

No

No
Renin-angiotensin in aldosterone system

- Angiotensinogen
  - Renin
  - Angiotensin I
  - Angiotensin II
  - ACE
  - Bradykinin
  - Inactive Fragments
  - Bradykinin

- Aldosterone
  - AT₁
  - AT₂

- Benefits:
  - Vasodilation
  - Antiproliferation (kinins)
  - Vasoconstriction
  - Cell growth
  - Na/H₂O retention
  - Sympathetic activation

Cough, Angioedema
Benefits?
Classes of RAAS-inhibitors

Givertz, M Circ. 2001
• 253 patients in NYHA class IV
• Randomized to placebo/enalapril
• From first patient to end of study 20 month
• 118 deaths

CONSENSUS

Swedberg et al NEJM 1987
Neuroendocrine Activation and Mortality

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

Modified from Swedberg et al 1990

P<0.01

Modified from Swedberg et al 1990
EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*

Mean dose enalapril 16.6 mg
RR 0.84; (CI 0.74-0.95) p=0.007

Worsening HF

<table>
<thead>
<tr>
<th>Placebo 1284</th>
<th>1159</th>
<th>1085</th>
<th>1005</th>
<th>939</th>
<th>819</th>
<th>669</th>
<th>487</th>
<th>299</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril 1285</td>
<td>1195</td>
<td>1127</td>
<td>1069</td>
<td>1010</td>
<td>891</td>
<td>697</td>
<td>526</td>
<td>333</td>
</tr>
</tbody>
</table>

P = 0.0045
ACE-inhibitor Trials in Heart Failure/LV-dysfunction
Mortality

• Randomized large (>1000 patients), long-term (1 year) trials
• ACEI vs. placebo
• 12763 patients in 4 trials

SAVE, AIRE, TRACE

SOLVD

Total

0.74
0.87
0.80

Flather et al Lancet 2000
Classes of RAAS-inhibitors
5010 pts in NYHA class II (61.7%), III (36.2%) or IV (3.1%).
Mean EF 27% and mean age 62 years
Background: ACEI 92.3%, Beta-blocker 35.5%

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>Placebo</th>
<th>Valsartan</th>
<th>RR (C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>N=2511</td>
<td>N=2499</td>
<td>1.02</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>484 (19.4%)</td>
<td>(495(19.7%)</td>
<td>(0.9-1.15)</td>
<td></td>
</tr>
<tr>
<td>Mortality and all cause hosp.</td>
<td>801 (32.1%)</td>
<td>723(28.8%)</td>
<td>0.87</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>(0.79-0.96)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cohn et al NEJM 2002
• All Cause Mortality in the Val-HeFT Trial

![Graph showing the probability of survival over time after randomization for Valsartan and Placebo treatments. The graph indicates a downward trend with time, with the Valsartan line slightly above the Placebo line. The probability of survival is plotted on the y-axis, and time after randomization is plotted on the x-axis. The graph includes a note that P = 0.8 and n = 5010.](image_url)
3 component trials (N=7601) comparing candesartan to placebo in patients with symptomatic heart failure.

**CHARM Programme**

- **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 for each trial: CV death or CHF hospitalization

Primary outcome for Overall Programme: All-cause death
CHARM: Primary endpoint

- **Overall**
  - Placebo: 886 (23.3%)
  - Candesartan: 945 (24.9%)
  - HR 0.91 (CI 95% 0.83-1.00), p=0.055
  - adjusted HR 0.90 (CI 95% 0.82–0.99), p=0.032

- **Added**
  - Placebo: 483 (37.9%)
  - Candesartan: 538 (42.3%)
  - HR 0.85 (CI 95% 0.75-0.96), p=0.011
  - adjusted HR 0.85 (CI 95% 0.75–0.96), p=0.010

- **Alternative**
  - Placebo: 334 (33.0%)
  - Candesartan: 406 (40.0%)
  - HR 0.77 (CI 95% 0.67-0.89), p=0.0004
  - adjusted HR 0.70 (CI 95% 0.60–0.81), p<0.0001

- **Preserved**
  - Placebo: 333 (22.0%)
  - Candesartan: 366 (24.3%)
  - HR 0.89 (CI 95% 0.77-1.03), p=0.118
  - adjusted HR 0.86 (CI 95% 0.74–1.0) p=0.051
CHARM-Overall: All-cause death

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Candesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 years</td>
<td>3803</td>
<td>3796</td>
</tr>
<tr>
<td>1 year</td>
<td>3563</td>
<td>3464</td>
</tr>
<tr>
<td>2 years</td>
<td>3271</td>
<td>3170</td>
</tr>
<tr>
<td>3 years</td>
<td>2215</td>
<td>2157</td>
</tr>
<tr>
<td>3.5 years</td>
<td>761</td>
<td>743</td>
</tr>
</tbody>
</table>

HR 0.91 (95% CI 0.83-1.00), p=0.055
Adjusted HR 0.90, p=0.032

Candesartan: 945 (24.9%)
Placebo: 886 (23.3%)

P<0.001
HR 0.70
P<0.001
HR 0.82

Pfeffer et al Lancet 2003
CHARM - Low EF trials
All-cause death

Number at risk
Candesartan: 2289, 2105, 1894, 1382, 580
Placebo: 2287, 2023, 1811, 1333, 548

All cause death (%)
Placebo: 708 (31.0%)
Candesartan: 642 (28.0%)

Hazard ratio 0.88 (95% CI 0.79 – 0.98), p=0.018

Young et al Circ 2004
Improving survival in CHF
1 year mortality

SOLVD-T (1991)
RRR 21%

CIBIS-2 (1999)
RRR 33%

CHARM-Added (2003)
(β blocker subgroup)
RRR 30%
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

Yes

ADD ivabradine

No

No
ACC/AHA Guidelines 1995

• “trials support the use of ACE inhibitors in all patients with symptomatic heart failure, unless the inhibitors are contraindicated or not tolerated.”
Classes of RAAS-inhibitors

Givertz, M Circ. 2001
RALES
Randomized ALdactone Evaluation Study

- 1663 pts HF (NYHA III or IV, EF <35%)

- spironolactone vs. placebo

- Endpoint:
  - Total mortality

30% risk reduction

Pitt et al NEJM 1999
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*
Inclusion Criteria

- **Inclusion**
  - > 55 years of age
  - **NYHA functional class II**
  - Ejection fraction < 30% (or, if between 30% and 35%, QRS >130 msec)
  - Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated).
  - within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, BNP > 250 pg/ml or Nt-pro-BNP > 500 pg/ml (males) or 750 pg/ml (females)].

- **Exclusion**
  - Serum potassium > 5.0 mmol/L
  - eGFR < 30 ml/min/1.73 m²
  - Need for a potassium-sparing diuretic
  - Any other significant comorbid condition.
Primary Endpoint Cardiovascular Death or Hospitalization for HF -37%

HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001

No. at Risk
Placebo 1373
Eplerenone 1364

Years from Randomization
0 1 2 3
848 925 512 562 199 232
## Safety

(Investigator reported events)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone (N=1360)</th>
<th>Placebo (N=1373)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>979 (72)</td>
<td>1007 (73.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hyperkalemia – n (%)</td>
<td>109 (8)</td>
<td>50 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypokalemia – n (%)</td>
<td>16 (1.2)</td>
<td>30 (2.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Renal failure – n (%)</td>
<td>39 (2.9)</td>
<td>42 (3.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypotension – n (%)</td>
<td>46 (3.4)</td>
<td>37 (2.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Gynecomastia and other breast disorders – n (%)</td>
<td>10 (0.7)</td>
<td>14 (1.0)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Diuretics to relieve symptoms/signs of congestion\(^{a}\)

+  

ACE inhibitor (or ARB if not tolerated)\(^{b}\)

\[\text{ADD a beta-blocker}^{b}\]

\[\text{Still NYHA class II–IV?}\]

\[\text{Yes}\]

\[\text{ADD a MR antagonist}^{b,d}\]

\[\text{No}^{c}\]

\(\text{McMurray et al EHJ 2012}\)
Relative risk of primary composite endpoint in the placebo group divided by quintiles of heart rate

**Primary composite endpoint**

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 - &lt;72</td>
<td>1.00</td>
</tr>
<tr>
<td>72 - &lt;75</td>
<td>1.15</td>
</tr>
<tr>
<td>75 - &lt;80</td>
<td>1.33</td>
</tr>
<tr>
<td>80 - &lt;87</td>
<td>1.80</td>
</tr>
<tr>
<td>≥ 87</td>
<td>2.34</td>
</tr>
</tbody>
</table>

**HF hospitalisation**

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 - &lt;72</td>
<td>1.00</td>
</tr>
<tr>
<td>72 - &lt;75</td>
<td>1.55</td>
</tr>
<tr>
<td>75 - &lt;80</td>
<td>1.85</td>
</tr>
<tr>
<td>80 - &lt;87</td>
<td>2.20</td>
</tr>
<tr>
<td>≥ 87</td>
<td>2.99</td>
</tr>
</tbody>
</table>

**CV death**

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>1.85</td>
</tr>
</tbody>
</table>

**Death from HF**

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td>3.40</td>
</tr>
<tr>
<td></td>
<td>3.56</td>
</tr>
</tbody>
</table>
Beta-blocker dose and heart rate reduction in chronic HF patients

23 trials in 19,209 HF patients with beta-blocker (mean EF=17%-36%)

Results of 13 univariable meta-regressions evaluating the effect of individual covariates on mortality benefits of beta-blockers in heart failure

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th>Trials, n</th>
<th>Patients, n</th>
<th>Ratio of Relative Risks (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of men</td>
<td>21</td>
<td>18,773</td>
<td>0.93 (0.79–1.10) per 10% increment</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean age</td>
<td>21</td>
<td>18,773</td>
<td>1.04 (0.86–1.24) per decade</td>
<td>0.69</td>
</tr>
<tr>
<td>Percentage with an ischemic cause</td>
<td>21</td>
<td>18,773</td>
<td>0.99 (0.86–1.14) per 20% increment</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean baseline LVEF</td>
<td>20</td>
<td>18,392</td>
<td>1.04 (0.92–1.18) per 5% increment</td>
<td>0.54</td>
</tr>
<tr>
<td>Percentage with NYHA class III or IV symptoms</td>
<td>21</td>
<td>18,773</td>
<td>1.00 (0.96–1.05) per 10% increment</td>
<td>0.84</td>
</tr>
<tr>
<td>Percentage with atrial fibrillation</td>
<td>8</td>
<td>8915</td>
<td>1.00 (0.91–1.09) per 5% increment</td>
<td>0.95</td>
</tr>
<tr>
<td>Percentage of digoxin use</td>
<td>19</td>
<td>18,336</td>
<td>1.01 (0.96–1.06) per 10% increment</td>
<td>0.64</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>19</td>
<td>17,981</td>
<td>1.07 (0.88–1.32) per 5 beats/min</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart rate reduction*</td>
<td>17</td>
<td>17,831</td>
<td>0.82 (0.71–0.94) per 5 beats/min</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>β-Blocker dose</strong></td>
<td>17</td>
<td>17,660</td>
<td>1.02 (0.93–1.10) per increment</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean Baseline SBP</td>
<td>17</td>
<td>17,516</td>
<td>1.00 (0.73–1.35) per 20 mm Hg</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean SBP reduction</td>
<td>10</td>
<td>5,462</td>
<td>1.02 (0.87–1.20) per 2 mm Hg</td>
<td>0.78</td>
</tr>
<tr>
<td>Agent</td>
<td>21</td>
<td>18,773</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>–</td>
<td>–</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>–</td>
<td>–</td>
<td>1.05 (0.82–1.35) per 20 mm Hg</td>
<td>0.68</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>–</td>
<td>–</td>
<td>1.03 (0.77–1.38) per 20 mm Hg</td>
<td>0.85</td>
</tr>
<tr>
<td>Atenolol</td>
<td>–</td>
<td>–</td>
<td>0.89 (0.29–2.76) per 10% increment</td>
<td>0.83</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>–</td>
<td>–</td>
<td>1.36 (1.09–1.69) per 20 mm Hg</td>
<td>0.009</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>–</td>
<td>–</td>
<td>1.30 (0.99–1.71) per 20 mm Hg</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Ivabradine: pure heart rate reduction

If inhibition reduces the diastolic depolarization slope, thereby lowering heart rate.

Ivabradine

Ivabradine inhibition reduces the diastolic depolarization slope, thereby lowering heart rate.

Inclusion criteria

- ≥18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF ≤35%)
- Heart rate ≥70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤12 months

Chronic HF background treatment

Mean ivabradine dose: 6.4 mg bid at 1 month
6.5 mg bid at 1 year

Primary composite endpoint
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR (95% CI), 0.82 (0.75–0.90),

\[ p < 0.0001 \]

Placebo - 18%

Ivabradine

Effect of ivabradine in prespecified subgroups

- **Age**
  - <65 years
  - ≥65 years

- **Sex**
  - Male
  - Female

- **Beta-blockers**
  - No
  - Yes

- **Aetiology of heart failure**
  - Non-ischaemic
  - Ischaemic

- **NYHA class**
  - NYHA class II
  - NYHA class III or IV

- **Diabetes**
  - No
  - Yes

- **Hypertension**
  - No
  - Yes

- **Baseline heart rate**
  - <77 bpm
  - ≥77 bpm

Test for interaction

\[ p = 0.029 \]

**Hazard ratio**

- Favours ivabradine
- Favours placebo

- A cut-off of ≥75 bpm was chosen by the EMA for the approval of ivabradine in chronic heart failure
- 64% of the patients enrolled in SHIFT had a heart rate ≥ 75 bpm
### Effect of ivabradine on major outcomes in patients with HR ≥75 bpm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td>0.76</td>
<td>0.68-0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.83</td>
<td>0.71-0.97</td>
<td>0.0166</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>0.70</td>
<td>0.61-0.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from HF</td>
<td>0.61</td>
<td>0.46-0.81</td>
<td>0.0006</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.83</td>
<td>0.72-0.96</td>
<td>0.0109</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>0.82</td>
<td>0.75-0.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiovascular hospitalization</td>
<td>0.79</td>
<td>0.71-0.88</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

Yes

ADD ivabradine
Summary

- Over the last 40 years, treatment of chronic heart failure has improved dramatically.
- A series of randomized, controlled trials have led to a change in standard of care.
- Further improvements should hopefully replace old by new therapies more than adding them.