Treatment of heart failure: past, present and future

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Treatment of low LVEF CHF
NYHA class III-IV: Moderate-severe symptoms

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II • Mild</th>
<th>Class III • Moderate</th>
<th>Class IV • Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Mild symptoms - occasional swelling</td>
<td>Noticeable limitations in ability to exercise or participate in mildly strenuous activities</td>
<td>Unable to do any physical activity without discomfort</td>
</tr>
<tr>
<td>Can perform ordinary activities without any limitations</td>
<td>Somewhat limited in ability to exercise or do other strenuous activities</td>
<td>Comfortable only at rest</td>
<td>Some HF symptoms at rest</td>
</tr>
</tbody>
</table>
CONSENSUS
Co-operative North Scandinavian Survival Trial

253 patients, NYHA class IV only (no LVEF entry requirement). Furosemide 98% (mean dose 205mg), digoxin 93% and spironolactone 53% (mean dose 80mg). Mean follow-up 6.3 months.

Mortality reduced from 44% to 26%
RRR 40% P=0.002

Swedberg et al NEJM 1987
RALES
Randomized ALdactone Evaluation Study

1663 patients, NYHA class III-IV, LVEF ≤0.35. ACE-i 95%, digoxin 73% and beta blockers 10.5%. Mean follow-up 24 months.

30% relative risk reduction in mortality P<0.001

Pitt et al. NEJM 1999
2289 patients, NYHA class III-IV, LVEF ≤0.25. ACE-i/ARB 97%, digoxin 66% and spironolactone 20%. Mean follow-up 10.4 months

Death from all causes
35 % risk reduction

Death or hosp. from all causes
24 % risk reduction

Packer et al NEJM 2001
Biventricular/multi-site pacing or “cardiac resynchronization” therapy
CRT for severe HF: two pivotal trials

COMPANION
CV death or CV hospitalization

CARE-HF
Death or CV hospitalization

Event free survival (%)

Days

Cleland et al. NEJM 2005
Cumulative benefit of poly-pharmacy (and CRT) in severe HF
Ventricular assist devices
HeartMate II trial

200 patients, ineligible for transplantation. Randomized 2:1 continuous- vs. pulsatile-flow device. Mean age 64 years and mean LVEF 17%.
Evidence-based treatment of systolic heart failure

NYHA class II-III: Mild-moderate symptoms

- Class I: No symptoms. Can perform ordinary activities without any limitations.
- Class II: Mild symptoms. Occasional swelling.
- Class III: Noticeable limitations in ability to exercise or do other strenuous activities. Can participate in mildly strenuous activities.
- Class IV: Unable to do any physical activity without discomfort. Some HF symptoms at rest.
Pharmacotherapy
SOLVD Treatment Trial
Studies of Left Ventricular Dysfunction

2569 patients, NYHA class II-IV, LVEF ≤0.35. Diuretic 85%, digoxin 67%. Followed for a mean of 41 months

Cumulative mortality (%) vs. years

Relative risk reduction = 16%

p=0.0036

SOLVD Investigators NEJM 1991
2647 patients, NYHA class III/IV, LVEF ≤0.35. Diuretic 99%, digoxin 52%, ACEi 96%. Followed for a mean of 1.3 years.

CIBIS 2
Cardiac Insufficiency Bisoprolol Study 2

34% Reduction in Deaths

Survival

Time after inclusion (days)

Lancet January 1999
MERIT HF
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure

3991 patients, NYHA class II-IV, LVEF ≤0.40. Diuretic 91%, digoxin 64%, ACEi/ARB 96%. Followed for a mean of 12 months

34% Reduction in Deaths

Lancet June 1999
2128 patients ≥70 yrs with prior HF hospitalization or LVEF ≤0.35
Followed for a mean of 21 months

SENIOERS
Study of the Effects of Nebivolol Intervention on Outcomes
and Rehospitalisation in Seniors with Heart Failure

Beta-blockers are the most evidence-based therapy in heart failure

**MERIT-HF**

- Placebo vs. Metoprolol CR/XL
- $P=0.0062$, Risk reduction = 34%

**CIBIS-2**

- Placebo vs. Bisoprolol
- $P=0.0001$, Risk reduction = 34%

**COPERNICUS**

- Placebo vs. Carvedilol
- $P=0.00013$, Risk reduction = 35%

**SENIORS**

- Placebo vs. Nebivolol
- $P=0.214$, Risk reduction = 12%
The stunning success of ACE inhibitors and beta blockers in mild-moderate HF

- SOLVD-T 1991: Diuretic/digoxin 15.7%
- CIBIS 2 1999: Diuretic/digoxin ACE inhib. 12.4%, Diuretic/digoxin ACE inhib. 13.2%, Diuretic/digoxin ACE inhib. Beta-blocker 8.8%
The cornerstone of therapy

ACE inhibitor (or ARB)
Beta-blocker
Can we do even better?

Adding to an ACE inhibitor:

• Angiotensin receptor blocker?
• Sinus node inhibitor?
• Aldosterone antagonist?
CHARM-Added
Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity

2548 patients, NYHA class II-IV, LVEF ≤0.40. Diuretic 90%, digoxin 59%, ACEi 100%; β-blocker 56%, spironolactone 17%. Followed a median of 41 months.

![Graph showing the proportion with cardiovascular death or hospital admission for CHF over time, indicating lower rates for Candesartan compared to Placebo.](Image)

**Placebo**
- Hazard ratio 0.85
- 95% CI 0.75–0.96, p=0.011
- Adjusted hazard ratio 0.85, p=0.010

**Candesartan**

_McMurray et al Lancet 2003_
Sinus node inhibition

\( I_f \) current inhibition with ivabradine
SHIFT
Systolic Heart failure treatment with the If inhibitor ivabradine Trial

6558 patients, NYHA class II-IV, LVEF ≤0.35, HF hosp. within 1 year, sinus rhythm, HR ≥70/min. Diuretic 84%, digoxin 22%, ACEi 79%/ARB 14%, β-blocker 90%, aldo. antagonist 60%. Followed for a median of 23 months

![Graph showing the comparison between Placebo (937 events) and Ivabradine (793 events) with a log-rank test p-value of 0.82 (95% CI 0.75-0.90), p<0.0001.](image)
SHIFT: Components of primary endpoint

**Cardiovascular death**

- Placebo (491 events)
- Ivabradine (449 events)

HR 0.91 (95% CI 0.80–1.03), p=0.128

**HF hospitalization**

- Placebo (672 events)
- Ivabradine (514 events)

HR 0.74 (95% CI 0.66–0.83), p<0.0001

Months of follow-up
### SHIFT: The problem in interpretation

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily dosage of β blocker (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>90.2</td>
<td>89.5</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>66.8</td>
<td>71.2</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Patients at target dose of β blocker</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Patients at ≥ 50% target dose of β blocker</td>
<td>56%</td>
<td>56%</td>
</tr>
</tbody>
</table>
What effect will SHIFT have on clinical practice?

**Ivabradine in heart failure—no paradigm SHIFT...yet**

Wisely and slowly, they stumble that run fast

*William Shakespeare (Romeo and Juliet, Act II, Scene iii)*

In *The Lancet* today, investigators provide support for Shakespeare’s admonishment, in two articles from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT). The investigators randomised baseline heart rates (<77 beats per min). Ivabradine was well tolerated with relatively few, although statistically significant, mechanism-related adverse events, such as bradycardia, atrial fibrillation, and visual disturbances. The accompanying analyses from the second SHIFT report showed a proportional relation between baseline heart rate and subsequent outcomes in the placebo-

*John Teerlink*
Is aldosterone antagonism beneficial in mild HF?
The missing piece of the aldosterone-antagonist jigsaw

LVSD and HF/diabetes after AMI
Mild HF symptoms (NYHA class II)
Severe HF symptoms (NYHA class III/IV)

EPHESUS EMPHASIS-HF RALES
EMPHASIS-HF
Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure

2737 patients, ≥55 years, NYHA class II, with CV hospitalization within 6 months (or elevated BNP/NT pro BNP) and LVEF ≤0.30 (or ≤0.35 if QRS duration >130msec. Followed for a median of 21 months

Hazard ratio, 0.63 (95% CI, 0.54–0.74)
P<0.001

Zannad, McMurray et al NEJM 2011
## EMPHASIS-HF: Other outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.76 (0.62-0.93)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.76 (0.61-0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>All-cause death or HF hospitalization</td>
<td>0.65 (0.55-0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause death or all-cause hospitalization</td>
<td>0.75 (0.66-0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.58 (0.47-0.70)</td>
<td>&lt;0.001</td>
</tr>
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Devices
SCD-HeFT
Sudden Cardiac Death in Heart Failure Trial

2521 patients with LVEF ≤0.35 and NYHA class II-III HF
Followed for a median of 45.5 months

Mortality rate

- Placebo
- Amiodarone, p=0.53
- ICD therapy, p=0.007

Can we do even better than optimal medical therapy and an ICD?

Adding CRT to OMT and an ICD:

• MADIT-CRT
• RAFT
MADIT-CRT
Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

1820 patients with LVEF ≤0.30, NYHA class I-II HF, sinus rhythm and QRS duration ≥120 ms. Followed for a median of 2.4 yr (stopped early). Randomized 3:2 CRT+ICD vs ICD.

HR 0.66 (0.52–0.84)

P<0.001
## MADIT-CRT: components of primary endpoint

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<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or heart failure</td>
<td>0.66 (0.52-0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure only</td>
<td>0.59 (0.47-0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death at any time</td>
<td>1.00 (0.69-1.44)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
1798 patients with LVEF ≤0.30, NYHA class II-III HF, sinus rhythm and QRS duration ≥120 ms. Followed for median of 3.3 yr. Primary outcome death or HF hospitalization.
## RAFT: Secondary outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>0.75 (0.62-0.91)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>0.76 (0.60-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.68 (0.56-0.83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MADIT-CRT and RAFT: Sub-group analyses

- Both trials showed an interaction between sex, QRS duration and QRS morphology and effect of CRT
- More benefit in: women (vs. men), QRS ≥150 msec (vs. <150 msec) and LBBB (vs. RBBB)
What’s in the pipeline?

- Chronic HF with low LVEF
- Chronic HF with preserved LVEF (HF-PEF)
- Acute HF

Focus on ongoing large-scale mortality/morbidity outcome studies
Can we beat an ACE inhibitor?

ATMOSPHERE: design overview

Primary outcome: CV death or heart failure hospitalization
(event driven: 2162 patients)

- **Open-label run-in**
  - Enalapril
  - Enalapril + aliskiren

- **Randomization**
  - Enalapril 10 mg twice daily (n=2,200)
  - Aliskiren 300 mg once daily (n=2,200)
  - Aliskiren 300mg/enalapril 20 mg Daily (n=2,200)

- **Double-blind**
  - ~48 weeks (event driven)
LCZ 696: an Angiotensin Receptor Neprilysin inhibitor (ARNi)

Molecular complex of:

- An ARB - valsartan
- A NEP/neprilysin inhibitor – AHU 377

NEP inhibition blocks breakdown of natriuretic peptides and augments plasma concentrations
A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction.

**Primary objectives**
- Evaluate if LCZ696 is superior in delaying time to first occurrence of either CV mortality or HF hospitalization in CHF pts (NYHA Class II – IV) with reduced ejection fraction.

**Secondary objectives**
- All cause mortality
- Renal progression (eGFR change)
- Clinical summary score (assessed by KCCQ)

**Patient population**
- 7980 patients with CHF NYHA class II – IV and reduced ejection fraction (LVEF < 40%)
- BNP>150 pg/ml (NTproBNP > 600 pg/ml) or BNP > 100 pg/ml (NTproBNP > 400 pg/ml) and hospitalization within the last 12 months
Treating anaemia in HF with an ESP (darbepoetin)?
Hypothesis: Darbepoetin will improve outcomes in patients with HF and anaemia

Population: 3400 patients with LVEF ≤0.35 and NYHA class III-IV HF/class II and CV admission/ER visit within 12 months

Anaemia: Hb ≥9.0 g/dL and ≤12.0 g/dL

Intervention: Darbepoietin sc vs placebo; target Hb 13.0-14.5 g/dL

Primary endpoint: Death or HF hospitalisation

Status: Started summer 2006
WARCEF: HF and the risk of stroke
Hypothesis: Which of two commonly used treatments warfarin or aspirin is better for preventing death and stroke in patients with low LVEF?

Population: ~2860 patients NYHA I-IV with LVEF ≤35% and not in AF

Intervention: Aspirin 325mg or warfarin (INR 2.5-3.0)

Primary endpoint: Death or stroke

Status: Recruitment started October 2002/estimated study completion 2012
New CRT trials
**Patients**
NYHA Class I-III, with advanced AV block, not currently indicated for CRT, LVEF ≤ 45%

**Objective**
Assess whether biventricular pacing (BiV) will limit the clinical progression of heart failure when compared with atrial synchronous RV pacing

**Primary endpoint**
Composite of mortality, morbidity & cardiac function

**Size & Locations**
Up to 1,636 patients in up to 65 centers in North America

**Study period**
Variable; Up to two interim analyses planned

**Status**
Enrolling

**Sponsor**
Medtronic
Hypothesis: is CRT beneficial in patients with a narrow QRS with echo dyssynchrony?

Population: 2330 patients with LVEF ≤0.35 and LVEDD ≥55mm. NYHA class III-IV. Indication for ICD. QRS duration <130 ms. Optimal drug therapy.

Echo dyssynchrony: TDI intra-LV dyssynchrony (opposing wall delay of ≥ 80 ms in the 4-C or apical LA view. Speckle-tracking radial strain septal-posterior wall delay ≥ 130 ms.

Intervention: CRT-D on vs. CRT-D off

Primary endpoint: Death or HF hospitalisation

Status: Started summer 2008
We still do not have evidence-based treatment
Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist
Hypothesis: Spironolactone will reduce morbidity and mortality in mild HF and preserved LV function

Population: 4500 patients >50 yrs with NYHA II HF (and admission or elevated BNP), EF ≥45%

Intervention: Spironolactone (15-45 mg) vs placebo

Primary endpoint: CV death, RCA, HF hospitalisation

Status: Recruitment started 2008; slow; expected completion uncertain
Acute heart failure

- Ultrafiltration: Aquapheresis
- Bilevel or continuous positive airway pressure: Preload reduction
- Nitrates, nitroprusside, dobutamine: Arterial vasodilation
- Dobutamine, dopamine, milrinone: Increased inotropy
- Nitrates, morphine: Venodilation
- Furosemide: Natriuresis
Cardiac myosin activator: omecamptiv Mecarbil

Cardiac Myosin Activation: A Potential Therapeutic Approach for Systolic Heart Failure


Online Science March 2011

Chemically Tuned Myosin Motors

Leslie A. Leinwand and Richard L. Moss
Randomization

**Acute HF**
LVEF<40%
BNP >400pg/mL
SBP≥110mmHg
~1,800 patients

- **Aliskiren 150 mg**
- **Aliskiren 300 mg**
- **Placebo**
- **Conventional therapy**

- **Primary outcome: CV death or HF hospitalization at 6 months (381 events)**

- In-hospital entry and initiation
  - 2 weeks
  - ~15 months (event-driven)*

*Except concomitant use of an ACEI and ARB

*Follow-up at Week 2, Month 1, 2 and 3, with on-going assessments every 3 months thereafter
Surgery
Surgical Treatment for Ischemic Heart Failure (STICH)
STICH: coronary revascularization results

Premiering ACC
New Orleans
April 2011
“Regenerative medicine”: stem cell therapy
Not discussed because of time

- **Other positive treatment trials:** e.g. DIG (digoxin); HF-ACTION (exercise); GISSI-HF (PUFA); A-HeFT (H-ISDN); ASCEND-HF (nesiritide in acute HF)

- **Important neutral treatment trials:** e.g. CORONA, GISSI-HF (both rosuvastatin); I-PRESERVE (irbesartan in HF-PEF); AF-CHF (rate vs. rhythm control); PROTECT (rolofylline - renal function); STICH (LV remodeling surgery).

- **Important negative treatment trials:** e.g. ANDROMEDA (dronedarone)

- **Monitoring trials:** – BNP/NT-pro BNP; remote monitoring; implanted monitors (CHAMPION)
Summary: heart failure clinical trial milestones

- **1987** ACE inhibitors, severe HF (CONSENSUS)

- **1991** ACE inhibitor mild/mod HF (SOLVD)

- **1999** Aldosterone antagonist severe HF (RALES)

- **1999-2001** Beta blockers mild-severe HF (CIBIS-2, MERIT-HF, COPERNICUS)

- **2001-2003** ARBs mild/mod HF (Val-HeFT, CHARM)

- **2004/5** CRT severe HF (COMPANION, CARE-HF)

- **2005** ICD (SCD-HeFT)

- **2009** HeartMate II (LVAD)

- **2009** HF-ACTION (exercise)

- **2010** $I_f$ current inhib. (SHIFT)

- **2010** CRT mild/mod HF (MADIT-CRT, RAFT)

- **2010** Aldo. Antag. mild/ mod HF (EMPHASIS-HF)
Treatment algorithm for patients with symptomatic heart failure (NYHA functional class II – IV) and a reduced left ventricular ejection fraction (LVEF ≤35%)

1. **ACE-I (or ARB if not tolerated)**
   - ADD Beta-blocker
   - Still NYHA Class II-IV?
     - yes
     - no

2. **ADD aldosterone antagonist (or ARB if not tolerated)**
   - Still NYHA Class II-IV?
     - yes
     - no

3. **LVEF ≤35%?**
   - yes
   - no

4. **QRS duration ≥150 msec?**
   - yes
   - Consider CRT-P/CRT-D
   - no
   - Consider ICD

5. **Still NYHA Class II-IV?**
   - yes
   - no

6. **No further specific treatment. Continue in disease management programme.**

7. **Consider ivabradine if: sinus rhythm/HR ≥70 bpm/LVEF ≤35%**
   - Digoxin
   - Hydralazine/nitrate

8. **IF NYHA class IV: consider LVAD, transplantation.**