Understanding and Development of New Therapies for Heart Failure
- Lessons from Recent Clinical Trials -
Clinical trials

- Evidence-based medicine, clinical practice
- Impact upon
  - Understanding pathophysiology
  - Changing clinical practice through clarifying risk/benefit of intervention
- Cons
  - Cannot address all questions
  - “Art of medicine” not studied
  - Trial patients not like real-world patients
  - Long duration, expensive, …
100 Large-scale Clinical Trials over 20 yrs

- ACE inhibitors
- Beta blockers
- Angiotensin receptor blockers (ARB’s)
- CCB’s, vasodilators, inotropes
- Anti-arrhythmic agents
- Device strategies like ICD, RCT
- Surgical intervention, immunomodulation, anticoagulation, exercise
VHeft - 1

PROBABILITY OF DEATH

Placebo (273)  
Prazosin (183)  
Hz + ISDN (186)

MONTHS

N Engl J Med 1986;314:1547
ACEI in Severe Heart Failure

CONSENSUS

PROBABILITY OF DEATH

ACEI in Mild to Moderate Heart Failure

n = 2589
CHF
- NYHA II-III
- EF < 35

SOLVD (Treatment)  
*N Engl J M 1991;325:293*

p = 0.0036

% MORTALITY

Months

Enalapril n=1285

Placebo n=1284

n = 2589
CHF
- NYHA II-III
- EF < 35
ACEI In Asymptomatic LV Dysfunction

ACEI

In Asymptomatic LV Dysfunction

% MORTALITY

n = 4228
No CHF symptoms
EF < 35

SOLVD (Prevention)

p = 0.30

Placebo
n=2117

Enalapril
n=2111

n = 4228
No CHF symptoms
EF < 35

SOLVD (Prevention)

p = 0.30

Placebo
n=2117

Enalapril
n=2111

Months

0 6 12 18 24 30 36 42 48

0 10 20 30 40 50

Enalapril
n=2111

Placebo
n=2117

p = 0.30
SAVE
Radionuclide EF ≤ 40%

AI RE
Clinical and/or radiographic signs of HF

TRACE
Echocardiographic EF ≤ 35%

All-Cause Mortality

Probability of Event

Years

ACE-I 2995
Placebo 2971

ACE-I 702/2995 (23.4%)
Placebo: 866/2971 (29.1%)

OR: 0.74 (0.66–0.83)

β blockers in CHF – All-cause Mortality

US Carvedilol Study

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

Risk reduction = 65%


US Carvedilol Study

- Survival
- Days
- Risk reduction = 65%
- P < 0.001

CIBIS-II

- Bisoprolol
- Placebo

Risk reduction = 34%

P < 0.0001

CIBIS-II Investigators (1999)

CIBIS-II

- Time after inclusion (days)

MERIT-HF

- Metoprolol CR/XL
- Placebo

Risk reduction = 34%

P = 0.0062

The MERIT-HF Study Group (1999)
ARB’s in heart failure

• ELITE, ELITE-II
  – Losartan vs. captopril in old patients
  – similar primary end point

• RESOLVED
  – candesartan
Spironolactone - RALES

n=1,663, NYHA III-IV, EF ≤ 35%, 24months, Spironolactone 25-50 mg

Probability of Survival

Neurohormonal & cytokine adjustment

Myocardial injury

Cardiac function

Acute (adaptive)

Activation of SAS, RAAS, Endothelin, AVP, Inflammatory cytokines, Oxidative stress

Chronic (maladaptive)
Hypertrophy, Remodeling, Apoptosis
Established guideline from past clinical trials

- **ACE inhibitors** in all patients with LV systolic dysfunction who can tolerate them
- **ARB’s** in ACE inhibitor intolerant patients with LV systolic dysfunction
- **Beta blockers** in stable patients with mild to moderate symptoms without significant congestion
- **Aldosterone antagonists** in moderate to severe HF
Recent clinical trials impacting HF therapy

• **Beta blockers**
• **Angiotensin-aldosterone antagonists**
  – Angiotensin receptor blockers
  – Aldosterone antagonist
• **Other medical therapeutics**
  – NEP inhibitor
  – Anticytokines
  – Antiarrhythmic agent
  – t-type CCB’s
• **Device**
  – ICD
  – RCT
COMET

Cardiovascular and Non-Cardiovascular Death

CV death hazard ratio 0.80
95% CI 0.70-0.90, P=.0004

Non-CV death hazard ratio 1.08
95% CI 0.77-1.50, P=.6592

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Time (Years)</th>
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<tbody>
<tr>
<td>Metoprolol</td>
<td>1518</td>
</tr>
<tr>
<td></td>
<td>1359</td>
</tr>
<tr>
<td></td>
<td>1234</td>
</tr>
<tr>
<td></td>
<td>1105</td>
</tr>
<tr>
<td></td>
<td>933</td>
</tr>
<tr>
<td></td>
<td>352</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>1511</td>
</tr>
<tr>
<td></td>
<td>1366</td>
</tr>
<tr>
<td></td>
<td>1258</td>
</tr>
<tr>
<td></td>
<td>1154</td>
</tr>
<tr>
<td></td>
<td>1002</td>
</tr>
<tr>
<td></td>
<td>382</td>
</tr>
</tbody>
</table>
Effects of Different $\beta$ Blocking Agents

- Bisoprolol
- Metoprolol
- Carvedilol

Cofactors

Cardiac cell toxicity
COPERNICUS

All-cause mortality

Placebo

Carvedilol

% Survival

P = 0.00013
35% risk reduction

Packer et al. NEJM 2001
Recent beta blocker trials

- **COMET**, carvedilol vs. metoprolol
  - carvedilol is better

- **COPERNICUS**, carvedilol in severe (class III B & IV) HF
  - 35% mortality reduction

- **CAPRICORN**, carvedilol in post-MI HF (EF<40%)
  - 23% reduction in all-cause mortality risk reduction

- **BEST**, bucindolol
  - Only non-statistically insignificant reduction in mortality and morbidity

- **MOXCON**, moxonidine, centrally acting beta blocker
  - Increased mortality
Recent Angiotensin-Aldosterone Antagonist Trials

- **Angiotensin receptor blockers**
  - OPTIMAAL: losartan in post-MI LV dysfunction
  - Valsartan: Val-HeFT, VALIANT
  - Candesartan: CHARM programme

- **Aldosterone antagonist**
  - Eplerenone: EPHESUS
Val-HeFT: Valsartan vs. Placebo

n=5,010, NYHA II-IV, EF ≤ 40%, 23 months

Conventional Tx (including ACE inhibitors) + Valsartan 160mg bid

Probability of Survival (%)

- Valsartan (n=2,511)
- Placebo (n=2,499)

Probability of Event-free Survival (%)

- Valsartan (n=2,511)
- Placebo (n=2,499)

13.3% Risk Reduction

Add Valsartan

- 27.5% Hospitalization, Improvement of EF, NYHA class, Sx and Signs

P=0.80

P=0.009

Val-HeFT: Valsartan vs. Placebo

n=5,010, NYHA II-IV, EF ≤ 40%, 23 months

Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening HF, IV Inotropes or Vasodilators)

Combined End Point
- ACEi +, β-blocker - 3034
- ACEi +, β-blocker + 1610
- ACEi -, β-blocker - 226
- ACEi -, β-blocker + 140

Death
- ACEi +, β-blocker - 3034
- ACEi +, β-blocker + 1610
- ACEi -, β-blocker - 226
- ACEi -, β-blocker + 140

RR, 95% CI

CV Death, MI, or HF by Treatment

Valsartan vs. Captopril: HR = 0.96; P = 0.198
Valsartan + Captopril vs. Captopril: HR = 0.97; P = 0.369

Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

CHARM Programme

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

- **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 hospitalisation

Pfeffer et al, Lancet 2003
CHARM-Alternative
Primary outcome, CV death or CHF hospitalisation

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

Granger et al, Lancet 2003
CHARM-Added
Primary outcome, CV death or CHF hospitalisation

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

McMurray et al, Lancet 2003
CHARM-Preserved
Primary outcome, CV death or CHF hospitalisation

HR 0.89 (95% CI 0.77-1.03), p=0.118
Adjusted HR 0.86, p=0.051

Yusuf et al, Lancet 2003
ARB’s in Heart Failure
esp. valsartan & candesartan

• Alternative in patients who are intolerant to ACE inhibitors

• Added to standard therapy

• Avoid using with both ACE inhibitor and beta blockers, esp. valsartan
### EPHESUS Results: Eplerenone vs. Placebo in Addition to Standard Therapy for Heart Failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Reduction vs. Placebo</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Deaths</td>
<td>15%</td>
<td>0.75-0.96</td>
<td>0.008</td>
</tr>
<tr>
<td>Deaths from CV Causes</td>
<td>17%</td>
<td>0.72-0.94</td>
<td>0.005</td>
</tr>
<tr>
<td>CV Mortality or CV Hospitalization</td>
<td>17%</td>
<td>0.79-0.95</td>
<td>0.002</td>
</tr>
<tr>
<td>Death from any Cause</td>
<td>17%</td>
<td>0.86-0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>Sudden Death from CV</td>
<td>17%</td>
<td>0.64-0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Sudden Cardiac Death and Baseline EF &lt;30%</td>
<td>33%</td>
<td>0.50-0.91</td>
<td>0.009</td>
</tr>
</tbody>
</table>

CI = Confidence Interval; CV = Cardiovascular; EF = Ejection Fraction

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Eplerenone can be added to standard therapy in post-MI patients.
Recent clinical trials
– other medical therapeutics -

• NEP inhibitor
  – omapatrilat (OVERTURE)

• Anticytokines
  – Endothelin antagonists: bosentan, enrasentan
  – TNF-alpha antagonist: etanercept, infliximab

• Antiarrhythmic agent
  – Dofetilide

• Calcium channel blockers
  – Mibefradil – increased mortality by 11%
TNF in heart failure

Circulating Levels of TNF

Effect of Etanercept on LV Structure and Function

- LV Ejection Fraction (%)
- LV End Systolic Volume (ml)
- LV Mass (gm)

- Placebo
- 5 mg/m² Etanercept
- 12 mg/m² Etanercept

*p < 0.05

Survival

- < 25 percentile
- 25-50 percentile
- 50-75 percentile
- > 75 percentile

p = 0.01

Weeks
Recent clinical trials using device

- ICD
  - MADIT-II, SCD-HeFT

- RCT(Resynchronization therapy) or bi-ventricular pacing
  - MIRACLE, COMPANION
**MIRACLE**

Trial Design: MIRACLE was a double-blind, randomized trial of cardiac resynchronization (n=228) vs control (n=225) for 6 months in patients with moderate-to-severe heart failure and an intraventricular conduction delay. The primary endpoints were New York Heart Association functional class, quality of life, and the distance walked in 6 minutes at 6 month follow-up.

<table>
<thead>
<tr>
<th>Improvement by ≥1 NYHA Class</th>
<th>Distance walked in 6 Minutes</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.001</td>
<td>p=0.005</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

**Results**

- Cardiac resynchronization therapy (CRT) was associated with improvements in all 3 primary endpoints compared with placebo (NYHA class, quality of life and walking distance; Figure)
- Device implantation unsuccessful in 8% of patients
- Secondary endpoints also improved with CRT: time on the treadmill during exercise testing (+81 vs +19 sec, p=0.001); peak oxygen consumption (+1.1 vs +0.2 ml/kg/min, p=0.009); ejection fraction (+4.6% vs -0.2%, p<0.001); QRS duration (-20 vs 0 msec, p<0.001) and need for hospital admission (8% vs 15%, p=0.02)
- Death or worsening heart failure requiring hospitalization ↓ in CRT arm (28% vs 44%; p=0.03)

**Conclusions**

- Among patients with chronic heart failure and ventricular dysynchrony, biventricular pacing was associated with improved functional class, increased 6-minute walk distance and maximal oxygen uptake, and improved quality of life
- Longer follow-up and larger trials of CRT pending


[www.cardiosource.com](http://www.cardiosource.com)
Clinical Consequences of Ventricular Dysynchrony

- Abnormal Interventricular Septal Wall Motion
- Reduced dP/dt
- Reduced Diastolic Filling Times
- Prolonged MR Duration

Proposed Mechanisms of Cardiac Resynchronization

Improved Contraction Pattern
- Improves Interventricular Synchrony
- Reduces Paradoxic Septal Wall Motion
- Improves LV Regional Wall Motion
- Lowers End-Systolic Volumes
- Improves LV dP/dt
COMPANION

- Pharmacological therapy plus
  - CRT mortality 23.7 %
  - CRT + ICD mortality 43.4 %

**CRT**: Cardiac Resynchronization Therapy
**ICD**: Implantable cardioverter defibrillator
Treatment of Heart Failure

Stage A
- Risk control

Stage B
- ACEI
- Beta blockers
- ICD in proper Pt

Stage C
- ACEI, BB
- Diuretics, Digoxin
- ARB's, aldosterone Antagonist
- Consider ICD+CRT

Stage D
- Inotropes
- Specialized therapy
- Transplantation
- Mechanical assist

Secondary prevention
Modification of physical activity
Lessons from Recent HF Clinical Trials

- Mortality and morbidity of HF is still high.

- Beta blockers
  - Carvedilol seems better than metoprolol
  - Added benefit with carvedilol even in post-MI and severe HF

- ARB’s is valuable as an alternative to ACEI intolerant patients or can be added to standard therapy.

- CRT (bi-ventricular pacing) coupled with ICD is superior to medical therapy alone in selected HF population.

- More aggressive blockade of neurohormonal or cytokine activation is not necessarily beneficial.
Saturation of Benefit with Incremental Neurohormonal Blockade in Chronic Heart Failure

Aldosterone antagonists

1975 2002

Time (Years)

Event Rate

Placebo
ACE Inhibitors
β-Blockers except Bucindolol
Bucindolol
Omapatrilat
Etanercept
Moxonidine
Endothelin Antagonists
Angiotensin Receptor Antagonist

VAL-HeFT
CHARM
Potential Therapeutic Target Beyond Neurohormonal Activation

- CRT
- ICD

- Wall Stress
- Myocardial Metabolism
- Ischemia
- Arrhythmias
- Anemia
- Renal Insufficiency
- Sleep Disorders