Advanced heart failure: Medical management - old and new

John McMurray
BHF Cardiovascular Research Centre
University of Glasgow
What do we know?

There are known knowns; these are things we know that we know.

There are known unknowns; that is to say there are things that we now know we don't know.

But there are also unknown unknowns – there are things we do not know, we don't know.

*United States Secretary of Defence, Donald Rumsfeld*
What’s in the pipeline?

Focus on ongoing large-scale mortality/morbidity outcome studies – mainly in systolic heart failure
**ACE inhibitors**

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>SOLVD-Treatment</th>
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<tbody>
<tr>
<td>I</td>
<td>II</td>
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**CONSENSUS**
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

Mortality %

Placebo
Enalapril

p=0.001
Is there a better way to block the RAAS?

DRI, direct renin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; K⁺ potassium ion; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone (corticotropin); BK, bradykinin; AT₁R, angiotensin II type 1 receptor; MR, mineralcorticoid receptor.
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)

Double-blind

Aliskiren 300mg/enalapril

20 mg Daily (n=2,200)

4-8 weeks

~48 weeks (event driven)
Mineralocorticoid antagonists (MRAs)

EMPHASIS-HF

NYHA Class

RALES

I II III IV
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 $P<0.001$
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:** ~3,500 patients, ≥50 yrs with symptomatic HF, EF ≥45% and elevated BNP (≥100 pg/mL)/NT proBNP (≥360 pg/mL) or HF hospitalization within 12 months

• **Intervention:** Spironolactone (30 mg) vs placebo

• **Primary endpoint:** CV death, RCA, HF hospitalisation

• **Status:** Currently planned to report AHA November 2013
Is there a better way to block the RAAS?

DRI, direct renin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; K⁺ potassium ion; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone (corticotropin); BK, bradykinin; AT₁R, angiotensin II type 1 receptor; MR, mineralcorticoid receptor.
Potential advantage of non-steroidal MRAs

- More selective for the mineralocorticoid receptor
- Greater affinity for the mineralocorticoid receptor
- Differential tissue activity: cardiac > renal; reduce risk of hyperkalaemia
- Some have residual L-type calcium channel blocking activity
Non-steroidal MRAs: more selective for cardiac/vascular than renal tissue?
Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease

Bertram Pitt¹*, Gerasimos Filippatos², Mihai Gheorghiade³, Lars Kober⁴, Henry Krum⁵, Piotr Ponikowski⁶, Christina Nowack⁷, Peter Kolkhof⁸, So-Young Kim⁹, and Faiez Zannad¹⁰

- Patients with HF-REF and mild/moderate CKD (Part A/B)
- 4 weeks treatment; 15/60 patients per group
- Placebo vs. spironolactone vs. BAY 94-8862 (3/4 doses/regimens)
Beta-blockers

NYHA Class

I  II  III  IV

USCP, MERIT-HF, CIBIS 2

COPERNICUS
Beta-blockers are the most evidence-based therapy in heart failure.
2128 patients ≥70 yrs with prior HF hospitalization or LVEF ≤0.35
Followed for a mean of 21 months

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.
SHIFT: Subgroups (NYHA class II vs. III/IV)

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>Ivabradine group (n=3169)</th>
<th>Placebo group (n=3334)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class II</td>
<td>300 (18.9%)</td>
<td>356 (22.5%)</td>
<td>0.81 (0.69-0.94)</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>493 (29.8%)</td>
<td>580 (34.5%)</td>
<td>0.83 (0.74-0.94)</td>
</tr>
</tbody>
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Swedberg et al Lancet 2010
Digatalis glycosides
DIG versus SHIFT

CV death or HF hospitalisation

DIG

SHIFT

Castagno et al Eur Heart J 2012
## DIG versus SHIFT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DIG (RRR %)</th>
<th>SHIFT (RRR%)</th>
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<tbody>
<tr>
<td>Heart failure hospitalization</td>
<td>-28%</td>
<td>-26%</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>-13%</td>
<td>-15%</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>-8%</td>
<td>-11%</td>
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PDE V inhibitors
PDE V inhibitors

- **Sildenafil**: HF-REF also HF-PEF – RELAX
- **Udenafil**: ULTIMATE-HF and ULTIMATE-HFpEF
- **Tadalafil**: PITCH-HF - n=2100, LVEF < 40% and PHT)

**pitch**

Phosphodiesterase Type 5 inhibition with Tadalafil changes outcomes in Heart Failure (pitch-HF)
Neurohumoral modulation vs. neurohumoral inhibition

- Vasoconstrictor, anti-natriuretic, growth-promoting mediators
- Vasodilator, natriuretic, growth-inhibiting mediators
Natriuretic peptides: How the heart protects itself

• The heart is an endocrine organ
• It secretes A and B type natriuretic peptides into the circulation where they act on the blood vessels, kidneys, adrenal glands, brain etc
• These peptides protect the heart from volume and pressure overload
Natriuretic peptides: Physiological actions

- Sympathetic outflow
- Neuroendocrine function
- AVP
- Corticotropin
- Salt appetite
- Water intake
- Blood pressure
- Plasma volume
- Venous return
- ADH
- Peripheral vasculature
  - Vasodilatation
  - Permeability
- haematocrit
- (NPR-A, NPR-B)
- Central nervous system
  - CNP
  - (NPR-A, NPR-B)
- Clearance by
  - NPR-C
  - NEP
- ANP
- BNP
- Adrenal aldosterone
- Kidney
  - GFR
  - U$_{NaV}$
  - UV
  - Renin
  - URO
  - (NPR-A)
A new approach?

ARNi

Angiotensin Receptor Neprilysin inhibitor
LCZ 696

Molecular complex of:

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

Outcomes driven (estimated mean f/u = 30-32 months)

Prior ACEi/ARB use discontinued

~7,600 patients enrolled as of 21/11/12
Two important developments

- Replacing rather than adding drugs
- Treating co-morbidity rather than heart failure *per se*
Treating anaemia in HF

Treating anaemia in HF with an ESP?
**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:** Closing 2012.
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†


CONFIRM-HF: Placebo vs. FC; n=300; 6MWT
EFFECT-HF: Control; n=160; peak VO₂
Acute heart failure

- **Ultrafiltration:**
  - *Aqua/natriuresis*

- **Bilevel or continuous positive airway pressure:**
  - *Preload reduction*

- **Dobutamine,**
  - *Dopamine,*
  - *Milrinone:*
  - *Increased inotropy*

- **Nitrates,**
  - *Nitroprusside,*
  - *Dobutamine:*
  - *Arterial vasodilation*

- **Nitrates,**
  - *Morphine:*
  - *Venodilation*

- **Furosemide:**
  - *Natriuresis*
Acute Heart Failure (1 symptom AND 1 sign) <24 hours after admission (n=308)

2x2 factorial randomization

Low Dose (1 x oral) Q12 IV bolus
Low Dose (1 x oral) Continuous infusion
High Dose (2.5 x oral) Q12 IV bolus
High Dose (2.5 x oral) Continuous infusion

48 hours

1) Change to oral diuretics
2) continue current strategy
3) 50% increase in dose

72 hours

Co-primary endpoints

60 days

Clinical endpoints

Diuretics: DOSE study design

Clinical endpoints

• Efficacy: PGA (VAS)
• Safety: Change in Cr
DOSE: Patient Global Assessment (VAS AUC) - Low vs. high dose diuretic

Low VAS AUC, mean (SD) = 4171 (1436)
High VAS AUC, mean (SD) = 4430 (1401)  
P=0.06
## DOSE: Secondary endpoints - Low vs. high dose diuretic

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea VAS AUC at 72 hours</td>
<td>4478</td>
<td>4668</td>
<td>0.041</td>
</tr>
<tr>
<td>Free from congestion at 72 hrs</td>
<td>11%</td>
<td>18%</td>
<td>0.091</td>
</tr>
<tr>
<td>Change in weight at 72 hrs</td>
<td>-6.1 lbs</td>
<td>-8.7 lbs</td>
<td>0.011</td>
</tr>
<tr>
<td>Net volume loss at 72 hrs</td>
<td>3575 mL</td>
<td>4899 mL</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NTproBNP at 72 hrs (pg/mL)</td>
<td>-1194</td>
<td>-1882</td>
<td>0.06</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>37%</td>
<td>40%</td>
<td>0.56</td>
</tr>
<tr>
<td>Cr increase &gt; 0.3 mg/dL over 72 hrs</td>
<td>14%</td>
<td>23%</td>
<td>0.041</td>
</tr>
<tr>
<td>Length of stay, days (median)</td>
<td>6</td>
<td>5</td>
<td>0.55</td>
</tr>
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</table>
Acute Heart Failure Trials

Milrinone
Tolvaptan
Tezosentan
Levosimendan
Adenosine antagonists
Nesiritide

REST IN PEACE
Relaxin: RELAX-AHF

Relaxin

- Anti-oxidant/
  Anti-apoptotic

- Anti-proliferative/
  Anti-inflammatory

Vasodilator
RELAX-AHF: All-cause mortality

1161 patients, hospitalised for acute HF, diuretic treatment, still dyspnoeic at rest/minimal exertion, pulmonary congestion on CXR, elevated BNP/NT proBNP, renal dysfunction, SBP >125 mm Hg, randomised within 16 hr.

Teerlink et al Lancet 2012
New (designer) natriuretic peptides

CD-NP synthetic chimeric peptide
Ularitide/urodilatin

ANP

BNP

CNP

Uro
Omecamtiv mecarbil (CK-1827452/AMG423): A selective cardiac myosin activator

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

Fady I. Malik,1* James J. Hartman,1 Kathleen A. Elias,1 Bradley P. Morgan Katjuša Brejc,1 Robert L. Anderson,1 Sandra H. Sueoka,1 Kenneth H. Lee Roman Sakowicz,1 Ramesh Baliga,1 David R. Cox,2 Marc Garard,1 Guiller Raja Kawas,1 Erica Kraynack,2 David Lenzi,1 Pu Ping Lu,1 Alexander Muc Xiangping Qian,1 Daniel W. Pierce,1 Maria Pokrovskii,1 Ion Suehiro,1 Sh Todd Tochimoto,1 Corey Valdez,1 Wen Yue Wang,1 Tatsuo Katori,2 David / You-Tang Shen,1,5 Stephen F. Vatner,3,4 David J. Morgans1

To the rescue of the failing heart

Heart failure is characterized by weakened contractions of heart muscle. A drug that directly activates the key force-generating molecule in this muscle may be a valuable tool to strengthen the failing heart.

DONALD M. BERS & SAMANTHA P. HARRIS

Heart failure affects tens of millions of people worldwide, with patients’ prognosis often being a bleak five-year survival from the time of diagnosis1. Patients

ORGANELLE, the sarcoplasmic reticulum, releases calcium ions (Ca2+) into the cytoplasm of the heart-muscle cells in a synchronized manner (Fig. 1). The Ca2+ activates myofilaments — organized structures in the cytoplasm composed of interdigitating filaments of

Chemically Tuned Myosin Motors

Leslie A. Leinwand1 and Richard L. Moss3

PERSPECTIVES

SCIENCE VOL 331 18 MARCH 2011

TRANSLATIONAL MEDICINE

NATURE | VOL 473 | 5 MAY 2011

MEDICINE
How does omecamtiv mecarbil work?

The actin-myosin cycle

Omecamtiv mecarbil increases the number of independent force generators (myosin heads) interacting with the actin filament

"More hands pulling on the rope"

Malik FI, et al. Science 2011
Randomization

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

**Aliskiren 300 mg**
- Aliskiren 150 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
Putting it all together
Treatment options for patients with chronic symptomatic systolic heart failure (NYHA class II-IV)
2012
Small steps or a giant leap?
Looking ahead
Gene therapy using an adenovirus vector
Calcium Up-Regulation by Percutaneous Administration of Gene therapy In Cardiac Disease (CUPID Trial)

**Trans-catheter (coronary) delivery of AAV1/SERCA2a**

- **Cardiac Contraction**
  - Intracellular Ca\(^{2+}\) increased, binds troponin C and starts contractile machinery

- **Relaxation**
  - Intracellular Ca\(^{2+}\) declines via re-uptake into SR

- **SERCA2a** removes 70\% of the intracellular calcium from the intracellular space in humans

- **SERCA2a activity** reduced in heart failure
Can we replace the dead muscle/scar tissue with new myocytes?
“Regenerative medicine”: stem cell therapy

Cardiomyocyte proliferation

Cardiac regeneration

Terminal differentiation
Low proliferation capacity

Inflammation
Hostile microenvironment

Cardiac regeneration

Inadequate proliferation and differentiation
Inadequate chemotaxis

Insufficient numbers of available stem cells
Loss of stem-cell function with age

Bone-marrow stem-cell mobilization

Resident cardiac stem cells
Crystal ball gazing

"The telephone has too many shortcomings to be seriously considered as a means of communication."
Western Union internal memo, 1876

"I think there is a world market for maybe five computers."
Thomas Watson, chairman of IBM, 1949

"We don't like their sound and guitar music is on the way out."
Decca records rejects the Beatles, 1962