Heart Failure with “Preserved” Ejection Fraction:
A trialists perspective on why are we having so much trouble finding a therapy

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DISCLOSURES

• Dr. Solomon has received research Support from Abbott, Amgen, Boston Scientific, Daichi-Sankyo, Novartis, NHLBI, NCI, and has consulted for Novartis, Abbott
Additional Disclosure

Agnostic
I don't know & you don't either
Distribution of EF in Hospitalized Patients With Heart Failure

OPTIMIZE-HF Registry, N=41,267

Similar Signs and Symptoms in Patients with HFpEF and HFrEF in CHARM

- Edema
- Orthopnea
- PND
- Rest dyspnea
- S₃
- Crackles
- JVP >6 cm
- Cardiomegaly

CHARM Investigators
Heart Failure: Population Trends

Discordant Trends in HF Prevalence

- Preserved ejection fraction: $r = 0.81$, $P < 0.001$
- Reduced ejection fraction: $r = -0.33$, $P = 0.23$

Proportion of HF-PEF is increasing...

$P = 0.92$, $P < 0.001$

Owan TE, et al. NEJM 2006; 355:251-9
Diastolic Heart Failure

Gerard P. Aurigemma, M.D., and William H. Gaasch, M.D.

Table 2. Management Principles for Patients with Diastolic Heart Failure.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Treatment*</th>
<th>Daily Dose of Medication†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce the congestive state</td>
<td>Salt restriction</td>
<td>&lt;2 g of sodium per day</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>Furosemide, 10–120 mg</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td>Hydrochlorothiazide, 12.5–25 mg</td>
</tr>
<tr>
<td></td>
<td>Angiotensin II-receptor blockers</td>
<td>Enalapril, 2.5–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lisinopril, 10–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candesartan, 4–32 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan, 25–100 mg</td>
</tr>
<tr>
<td>Maintain atrial contraction and prevent tachycardia</td>
<td>Cardioversion of atrial fibrillation</td>
<td>Atenolol, 12.5–100 mg</td>
</tr>
<tr>
<td></td>
<td>Sequential atrioventricular pacing</td>
<td>Metoprolol, 25–100 mg</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>Verapamil, 120–360 mg</td>
</tr>
<tr>
<td></td>
<td>Calcium-channel blockers</td>
<td>Diltiazem, 120–140 mg</td>
</tr>
<tr>
<td></td>
<td>Radiofrequency ablation modification of atrioventricular node and pacing</td>
<td></td>
</tr>
<tr>
<td>Treat and prevent myocardial ischemia</td>
<td>Nitrates</td>
<td>Isosorbide dinitrate, 30–180 mg</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
<td>Isosorbide mononitrate, 30–90 mg</td>
</tr>
<tr>
<td></td>
<td>Calcium-channel blockers</td>
<td>Atenolol, 12.5–100 mg</td>
</tr>
<tr>
<td></td>
<td>Coronary-artery bypass surgery, percutaneous coronary intervention</td>
<td>Metoprolol, 12.5–200 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine, 2.5–10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Felodipine, 2.5–20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enalapril, 2.5–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lisinopril, 10–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candesartan, 4–32 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan, 50–100 mg</td>
</tr>
<tr>
<td>Control hypertension</td>
<td>Antihypertensive agents</td>
<td>Chlorthalidone, 12.5–25 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrochlorothiazide, 12.5–10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atenolol, 12.5–100 mg</td>
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<tr>
<td></td>
<td></td>
<td>Metoprolol, 12.5–200 mg</td>
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<td></td>
<td>Amlodipine, 2.5–10 mg</td>
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<td></td>
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<td></td>
<td>Enalapril, 2.5–40 mg</td>
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<td></td>
<td>Lisinopril, 10–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candesartan, 4–32 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan, 50–100 mg</td>
</tr>
<tr>
<td>Measures with Theoretical Benefit in Diastolic Heart Failure</td>
<td>ACE inhibitors</td>
<td>Enalapril, 2.5–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lisinopril, 10–40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramipril, 5–20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Captopril, 25–150 mg</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-receptor blockers</td>
<td>Candesartan, 4–32 mg</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>Losartan, 50–100 mg</td>
</tr>
</tbody>
</table>

* Treatments listed for the first four goals are those generally used in clinical practice. Angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers, and spironolactone inhibit the renin-angiotensin-aldosterone system and thus have a theoretical benefit, but more data are required to show that they reduce the risk of heart failure.

† The list of medications is not comprehensive but, rather, includes examples that are in common clinical use or have been included in studies of pathophysiologic mechanisms in diastolic dysfunction or heart failure or were included in larger trials that generally were not designed to assess outcomes in diastolic heart failure. Candesartan is the only agent studied in a randomized, controlled trial involving patients with diastolic heart failure. A more exhaustive list of antihypertensive agents can be found in the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.
No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.

Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF.

Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF (see Section
CHARM-Preserved
CV Death or HF Hospitalization

Placebo
366 (24.3%)
333 (22.0%)

Candesartan

HR 0.89 (95% CI 0.77-1.03), \( P=0.118 \)
Adjusted HR 0.86, \( P=0.051 \)
PEP-CHF: Primary End-point During Follow-up

I-PRESERVE: Primary Endpoint
Death or protocol specified CV hospitalization

Cumulative Incidence of Primary Events (%)

HR (95% CI) = 0.95 (0.86-1.05)
Log-rank p=0.35

N=4,128

(Mean follow-up 49.5 months)

No. at Risk
Irbesartan 2067 1929 1812 1730 1640 1569 1513 1291 1088 816 497
Placebo 2061 1921 1808 1715 1618 1539 1466 1246 1051 776 446
HFpEF

- Prevalent Disease
- High morbidity and cost to society
- No specific therapy beyond symptom reduction that is recommended or approved
# The Current State of Heart Failure Therapy

<table>
<thead>
<tr>
<th>Heart Failure with Reduced Ejection Fraction</th>
<th>Heart Failure with Preserved Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Robust Animal Models</td>
<td>• Poor Animal Models</td>
</tr>
<tr>
<td>• Pathophysiologic Understanding</td>
<td>• Limited Pathophysiologic Understanding</td>
</tr>
<tr>
<td>• Targeted Drug Therapy</td>
<td>• Few Targeted Treatments</td>
</tr>
<tr>
<td>• Multiple randomized controlled</td>
<td>• Mechanistic studies, small non-</td>
</tr>
<tr>
<td>double-blind clinical trials</td>
<td>definitive trials</td>
</tr>
<tr>
<td>• Therapies based on outcomes</td>
<td>• Empiric symptom-based therapy</td>
</tr>
<tr>
<td>• ACE/ARB/ALDO, Beta Blockers</td>
<td>• Limited consensus</td>
</tr>
<tr>
<td>• General HF community consensus</td>
<td>• Anectode-based medicine</td>
</tr>
<tr>
<td>• The randomized controlled trial</td>
<td></td>
</tr>
<tr>
<td>has even refuted previous held</td>
<td></td>
</tr>
<tr>
<td>“dictum”</td>
<td></td>
</tr>
<tr>
<td>• Evidenced-based medicine</td>
<td></td>
</tr>
</tbody>
</table>
Challenges to Finding Effective Treatments in HFpEF

- Lack of appreciation
- Lack of agreement
- Marked heterogeneity
- No consensus on diagnosis
- Conflicting mechanisms proposed
- Theoretic benefits have not translated to outcomes
- (we can’t even agree on a name)
Possible Reasons why the trials have Not been successful

- Wrong Concepts
- Wrong Patients
- Wrong Endpoints
- Trial Problems
- There is no Disease
- Wrong Therapies
Wrong Concepts

• Targeted therapy generally requires some understanding of the disease process
• Enormous debate over molecular, cellular and pathophysiological basis of HFpEF
• These have predominantly focused on diastolic function
Is Diastolic Dysfunction Responsible for HF-PEF?

Stiffness constant $\beta$:
- Controls: $0.01 \pm 0.01$
- DHF: $0.03 \pm 0.01^{**}$

Zile et al., NEJM, 350 (19): 1953
Some potential mechanisms of diastolic dysfunction in HFpEF

Dysfunctional Calcium handling

Abnormalities in spring-like Titin protein

Increased extracellular fibrosis, reduced ventricular compliance & shift in the PV relationship
The GOLD Standard for Assessment of Diastolic Function
The GOLD Standard for Assessment of Diastolic Function
Traditional Doppler Approaches to Diastolic Function
Three Phases of Diastolic Function

Worsening of Diastolic Function
Doppler Tissue Imaging Measures Myocardial Relaxation Velocity

Diastolic Dysfunction is EXTREMELY prevalent

| Table 1. Prevalence of Systolic and Diastolic Dysfunction According to Age and Sex* |
|------------------------|----------------|----------------|----------------|----------------|----------------|
|                        | No. (%) of Patients Affected |                |                |                |                |
|                        | Age Group, y                | 45-54          | 55-64          | 65-74          | 75+            | Overall        |
|                        | Variables                   |                |                |                |                |
|                        | Diastolic Dysfunction       |                |                |                |                |
|                         | Mild                        |                |                |                |                |
|                         | All                         | 27 (4.8)       | 72 (13.2)      | 149 (34.2)     | 123 (52.8)     | 371 (20.8)     |
|                         | Men                         | 20 (7.2)       | 43 (16.0)      | 76 (37.2)      | 49 (57.0)      | 188 (22.5)     |
|                         | Women                       | 7 (2.4)        | 29 (10.4)      | 73 (31.6)      | 74 (50.3)      | 183 (19.4)     |
|                         | Moderate                    |                |                |                |                |
|                         | All                         | 8 (1.4)        | 33 (6.0)       | 43 (9.9)       | 34 (14.6)      | 118 (6.6)      |
|                         | Men                         | 5 (1.8)        | 19 (7.1)       | 17 (8.3)       | 15 (17.4)      | 56 (6.7)       |
|                         | Women                       | 3 (1.0)        | 14 (5.0)       | 26 (11.3)      | 19 (12.9)      | 62 (6.6)       |
|                         | Severe                      |                |                |                |                |
|                         | All                         | 0 (0)          | 2 (0.4)        | 3 (0.7)        | 8 (3.4)        | 13 (0.7)       |
|                         | Men                         | 0 (0)          | 0 (0)          | 2 (1.0)        | 3 (3.5)        | 5 (0.6)        |
|                         | Women                       | 0 (0)          | 2 (0.7)        | 1 (0.4)        | 5 (3.4)        | 8 (0.8)        |

Systolic Dysfunction

Redfield et al. JAMA 2003
Diastolic Dysfunction is EXTREMELY prevalent

50% of patients with hypertension have evidence of diastolic dysfunction

<table>
<thead>
<tr>
<th>Table 1. Prevalence of Systolic and Diastolic Dysfunction According to Age and Sex*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Diastolic Dysfunction</td>
</tr>
<tr>
<td>Mild All</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Moderate All</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Severe All</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
</tbody>
</table>

Redfield et al. JAMA 2003
High Prevalence of Diastolic Dysfunction Regardless of Clinical Status

Shah A. et al. AHA 2012
Is Systolic Function actually “Preserved” in HFpEF?
Myocardial Strain Measured by 2D-speckle Tracking Echocardiography

Speckle tracking analyzes the motion of the coherent “speckle” to assess myocardial deformation.

\[
\text{Strain} = \frac{(L - L_0)}{L_0} \times 100 \, [\%]
\]
Speckle Tracking to assess Global Longitudinal Strain
<table>
<thead>
<tr>
<th>Normal</th>
<th>LVEF</th>
<th>65%</th>
</tr>
</thead>
<tbody>
<tr>
<td>E’ Lateral (cm/s)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>E/E’</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Longitudinal Strain</td>
<td>-21.5%</td>
<td></td>
</tr>
<tr>
<td>S’ Lateral (cm/s)</td>
<td>11.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HFpEF Patient</th>
<th>LVEF</th>
<th>63%</th>
</tr>
</thead>
<tbody>
<tr>
<td>E’ Lateral (cm/s)</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>E/E’</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Longitudinal Strain</td>
<td>-13.6%</td>
<td></td>
</tr>
<tr>
<td>S’ Lateral (cm/s)</td>
<td>6.1</td>
<td></td>
</tr>
</tbody>
</table>
Myocardial Strain in Normals, HTN, HFpEF and HFrEF

### Normal (n=43)
- Longitudinal Strain: 13.8 ± 3.8
- Circumferential Strain: 7.6 ± 1.2
- E’ (cm/s) (lateral): 13.8 ± 3.8
- E/E’: < 8

### HTN (n=166)
- Longitudinal Strain: 7.6 ± 1.2
- Circumferential Strain: 7.5 ± 2.6
- E’ (cm/s) (lateral): 7.6 ± 1.2
- E/E’: 8.8 ± 2.3

### HFpEF (n=200)
- Longitudinal Strain: 7.5 ± 2.6
- Circumferential Strain: 7.3 ± 3.2
- E’ (cm/s) (lateral): 7.5 ± 2.6
- E/E’: 12.7 ± 7.4

### HFrEF (n=1077)
- Longitudinal Strain: 7.3 ± 3.2
- Circumferential Strain: 7.3 ± 3.2
- E’ (cm/s) (lateral): 7.3 ± 3.2
- E/E’: 14.8 ± 10.4
Wrong Concepts

- Diastolic dysfunction is extremely prevalent – unlikely that diastolic dysfunction alone can be responsible
- Patients with HFpEF have abnormalities of systolic function despite normal ejection fraction
Wrong Patients

To test a therapy we need to identify patients who

a) have the disease your are trying to treat

b) Are at risk for “outcomes”
If we want to treat this disease we have to be able to diagnose it. To diagnose HFpEF you need two things:

- Heart Failure
- “Preserved” Ejection Fraction

* Neither of these is as simple as you might think.
Diagnosis of Heart Failure

• Signs
• Symptoms
• Exclusions
  • Other causes of signs and sx
Key Questions in the Diagnosis of HFpEF

• Can we use the same criteria to diagnose heart failure in HFpEF as in HFrEF?
• How certain are we of the diagnosis of HF?
• Are we able to identify patients who are at risk for HF hospitalization or Mortality?
NEJM Says This is a Mortal Disease!

Mortality 29% first year!
12%/yr subsequently

Mortality 22% first year!
Lower Event Rates in HF-pEF in Clinical Trials

CV Death or HF Hospitalization Rate (per 100-pts yrs)

Ejection Fraction (%)

CHARM

I-PRESERVE

Mortality 4-6% per year!
Influence of History of HF Hospitalization on Outcome

**Preserved LVEF**

- **HR 1.95 (1.6, 2.4)**

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>946</td>
<td>917</td>
<td>892</td>
<td>860</td>
<td>832</td>
<td>802</td>
<td>553</td>
<td>135</td>
</tr>
<tr>
<td>Yes</td>
<td>2077</td>
<td>1913</td>
<td>1802</td>
<td>1720</td>
<td>1625</td>
<td>1550</td>
<td>1044</td>
<td>300</td>
</tr>
</tbody>
</table>

**Months**

- Prior HF hosp
- No prior HF hosp

*Lancet 2003; 362: 777-81*
Event Rate after a HF Hospitalization

Time to Death/HF Hosp

Time to Death/HF Hosp after a Hospitalization

CHARM - unpublished
Rate of Death or HF Hospitalization AFTER Discharge from a HF Hospitalization

Time After Hospitalization for HF

- 0-30 days
- 30-60 days
- 60-90 days
- 90-180 days
- 6 mo
- 12 mo
- 24 mo
- > 24 mos

Rate of Death or HF Hospitalization (per 100-patient years)

- Low EF
- Preserved EF
NT-ProBNP and Prognosis in HF-PEF

Cleland et al. NEJM 2007
I-Preserve
Outcomes by Baseline NT-proBNP Quartiles

**All-cause Mortality**
- NT-pro BNP (pg/mL):< 133, 134 - 338, 339 - 963, > 964
- Percent Mortality: 7.9%, 13.8%, 19.2%, 40.8%

**Primary Endpoint**
- NT-pro BNP (pg/mL):< 133, 134 - 338, 339 - 963, > 964
- Primary Composite Endpoint (%): 16.4%, 27.6%, 40.4%, 59.0%

**Hospitalization for HF and HF Deaths**
- NT-pro BNP (pg/mL):< 133, 134 - 338, 339 - 963, > 964
- Percent Mortality: 5.2%, 12.6%, 19.2%, 31.7%

Anand et al. Circulation HF 2011
What is the Appropriate Cutoff in HFpEF?

10%  20%  30%  40%  50%  60%  70%  80%

Low Ejection Fraction  CHARM  TOPCAT, I-Preserve  ASE “normal”  Preserved Ejection Fraction
Wrong Endpoints

Or wrong analysis
Time to First Event
CV Death or HF Hospitalization

Placebo
- 366 (24.3%)

Candesartan
- 333 (22.0%)

HR 0.89 (95% CI 0.77-1.03), P=0.118
Adjustment HR 0.86, P=0.051

CHARM Investigators
HF Hospitalizations in CHARM-Preserved
The patient journey is not reflected in current trials which frequently mask all but the first event.

- Each HF hospitalization heralds a substantial worsening of the long term prognosis, and effect that appears additive with recurrent hospitalizations.
- This suggests that the patient journey is important and can portend outcomes. It is therefore important to clinicians and patients.
Investigator-Reported HF Hospitalizations
CHARM Preserved

Placebo  Candesartan

$P=0.015^\dagger$

$P=0.013^\ddagger$

† Chi Square Test.
‡ Wilcoxon Rank Sum Test based on number of hospitalizations/follow-up time.
Statistical methodologies that Employ Recurrent Event Analysis May offer greater power in HFpEF

Method of LJ Wei, PhD
TRIAL PROBLEMS: The Retrospectsoscope
PEP-CHF: Primary End-point During Follow-up

90% on study therapy at 1 yr
< 40% on study therapy by study end

Proportion having an event (%)

Treatment Group
- Perindopril
- Placebo

HR 0.92; 95% CI 0.70 to 1.21; P=0.545

Patients at risks
- Perindopril: 424, 374, 184, 70
- Placebo: 426, 356, 186, 69

Cleland et al. World Congress of Cardiology 2006; September 3, 2006; Barcelona, Spain.
PEP-CHF Primary End-point at One Year

Time to first occurrence of total mortality or HF Hospitalisation

Proportion having an event (%)

HR 0.69; 95% CI 0.47 to 1.01; \( P=0.055 \)
Relative risk reduction: -31%

Patients at risks

<table>
<thead>
<tr>
<th>Perindopril</th>
<th>424</th>
<th>408</th>
<th>399</th>
<th>390</th>
<th>374</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>426</td>
<td>405</td>
<td>387</td>
<td>374</td>
<td>356</td>
</tr>
</tbody>
</table>

Cleland et al. World Congress of Cardiology 2006; September 3, 2006; Barcelona, Spain.
Trial Problems

• Drop outs (patients go off study drug)
• Drop ins (patients go on other therapies, maybe imbalanced)
• Particular types of adverse events might plague most of these therapies (hyperkalemia, hypotension, renal dysfunction)
THERE IS NO DISEASE

IS THIS JUST A COLLECTION OF COMORBIDITIES?

Editorial

Can Brain Natriuretic Peptide Be Used to Guide the Management of Patients With Heart Failure and a Preserved Ejection Fraction? The Wrong Way to Identify New Treatments for a Nonexistent Disease

Milton Packer, MD
Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community

Carolyn S.P. Lam, MBBS, MRCP; Asya Lyass, PhD; Elisabeth Kraigher-Krainer, MD; Joseph M. Massaro, PhD; Douglas S. Lee, MD, PhD; Jennifer E. Ho, MD; Daniel Levy, MD; Margaret M. Redfield, MD; Burkert M. Pieske, MD, PhD; Emelia J. Benjamin, MD, ScM; Ramachandran S. Vasan, MD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio (95% CI)*</th>
<th>P value*</th>
<th>Cut-off percentile</th>
<th>Cut-off value</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>1.21 (1.01–1.45)</td>
<td>0.036</td>
<td>&gt;75th percentile</td>
<td>&gt; 1.05 mg/dl</td>
<td>1</td>
</tr>
<tr>
<td>FEV1:FVC ratio</td>
<td>1.21 (1.02–1.43)</td>
<td>0.029</td>
<td>&lt;25th percentile</td>
<td>&lt; 91% predicted</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin concentration</td>
<td>1.24 (1.09–1.40)</td>
<td>&lt;0.001</td>
<td>&lt;25th percentile</td>
<td>&lt; 13 g/dl</td>
<td>1</td>
</tr>
</tbody>
</table>

Cumulative Incidence

- Score ≥ 2
- Score = 1
- Score = 0

$P = 0.026$
Wrong Therapies

- Multiple mechanisms likely at play in this disease make for difficulty in identifying a targeted therapy
- Focus on similar therapies as in HFrEF (i.e., RAAS inhibitors, vasodilators) may be flawed
OUTCOMES TRIALS in HFpEF

Tested Minimally
• Calcium Blockers
• Beta-Blockers (SENIORS)
• ACE Inhibitors

Tested Suboptimally
• ACE Inhibitors (PEP-CHF)

Testing Currently
• Aldosterone Antagonists (TOPCAT)

In Testing
• ARNI

Tested Equivocally
• ARBs (CHARM-Preserved, I-Preserve)

Tested Poorly
• Sildenafil (RELAX)

Not in Testing
• Renin Inhibitor
• AGE Breaker
• Ranolazine
• Devices ±
Aldo-DHF Study Design

Multicenter, randomised, placebo-controlled double-blind, two-armed parallel-group study

Equally ranked co-primary endpoints: Change in diastolic function (E/é) and maximal exercise capacity (peak VO$_2$) after 12 months for spironolactone compared to placebo.

Secondary endpoints: Changes in other echocardiographic measures of cardiac function and structure; Changes in other measures of exercise capacity; Neuroendocrine activation; HF symptoms; Quality of life; Safety and tolerability of study medication.
ALDO-DHF: Primary endpoints

**E/e′**
- Placebo: 12.8±4.4 to 13.6±4.3
- Spironolactone: 12.7±3.6 to 12.1±3.7

**Peak VO2**
- Placebo: Baseline
- Spironolactone: Baseline

*Pieske et al. ESC 2012*
TOPCAT: Trial Design

- AGE \( \geq 50 \text{YRS} \)
- EF \( \geq 45\% \text{ WITHIN 6 MONTHS} \)
- HEART FAILURE SYMPTOMS AND SIGNS
- CONTROLLED SYSTOLIC BP (< 140 mm Hg)*
- SERUM K\(^+\) \( \leq 5.0 \text{ MMOL/L} \)

PLUS ONE OF THE FOLLOWING:
- HF HOSPITALIZATION WITHIN 12 MONTHS
- BNP \( \geq 100 \text{ PG/ML} \)
- N-TERMINAL PRO-BNP \( \geq 360 \text{ PG/ML} \)

RANDOMIZE

PLACEBO
15 MG

SPIRONOLACTONE
15 MG

DOSE TITRATION (TARGET 30 MG)
* Optional Titration to 45 mg at 4 mos

COMPOSITE PRIMARY ENDPOINT
CV death, Aborted cardiac arrest, Hospitalization for management of HF

N = 3400

Week 0
Week 4
\(~ 3.25 \text{ yrs}\)
RELAX: PDE-5 inhibition in HF-PEF

216 Outpatients with heart failure randomized

- 103 Randomized to receive placebo
  - 103 Received placebo as assigned
  - 5 Did not complete 24-week follow-up visit (withdrew consent)
  - 98 Completed 24-week follow-up visit
    - 82 Completed study per protocol
    - 16 Did not complete study per protocol
    - 13 Reduced dosage of study drug
    - 3 Discontinued study drug
  - 94 Included in the primary analysis
    - 9 Excluded
      - 5 Withdrew consent
      - 2 Unable to perform exercise test
      - 1 Unwilling to perform exercise test
      - 1 Had inadequate peak oxygen consumption data

- 113 Randomized to receive sildenafil
  - 113 Received sildenafil as assigned
  - 12 Did not complete 24-week follow-up visit
    - 9 Withdrew consent
    - 3 Died
  - 101 Completed 24-week follow-up visit
    - 74 Completed study per protocol
    - 27 Did not complete study per protocol
    - 19 Reduced dosage of study drug
    - 8 Discontinued study drug
  - 91 Included in the primary analysis
    - 22 Excluded
      - 9 Withdrew consent
      - 7 Unable to perform exercise test
      - 2 Unwilling to perform exercise test
      - 1 Had inadequate peak oxygen consumption data
      - 3 Died
### RELAX Endpoints

#### Table 3. Primary, Secondary, and Safety End Points

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>Sildenafil</th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Variable</td>
<td>No. of Patients</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min</td>
<td>94</td>
<td>-0.20 (-0.70 to 1.00)</td>
<td>91</td>
<td>-0.2 (-1.70 to 1.11)</td>
<td>.90</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical rank score, mean^a</td>
<td>94</td>
<td>95.8</td>
<td>95</td>
<td>94.2</td>
<td>.85</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
<td>95</td>
<td>15.0 (-26.0 to 45.0)</td>
<td>90</td>
<td>5.0 (-37.0 to 55.0)</td>
<td>.92</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min</td>
<td>96</td>
<td>0.03 (-1.10 to 0.67)</td>
<td>97</td>
<td>0.01 (-1.35 to 1.25)</td>
<td>.98</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
<td>96</td>
<td>18.0 (-14.5 to 48.0)</td>
<td>99</td>
<td>10.0 (-25.0 to 36.0)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Components of clinical rank score at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, No. (%)^b</td>
<td>103</td>
<td>0</td>
<td>113</td>
<td>3 (3)</td>
<td>.25</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular or renal cause, No. (%)</td>
<td>103</td>
<td>13 (13)</td>
<td>113</td>
<td>15 (13)</td>
<td>.89</td>
</tr>
<tr>
<td>Change in MLHFQ, median (IQR)</td>
<td>91</td>
<td>-8 (-21 to 5)</td>
<td>91</td>
<td>-8 (-19 to 0)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>Safety end points, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>103</td>
<td>78 (76)</td>
<td>113</td>
<td>90 (80)</td>
<td>.49</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>103</td>
<td>16 (16)</td>
<td>113</td>
<td>25 (22)</td>
<td>.22</td>
</tr>
<tr>
<td><strong>Change in left ventricular structure by CMRI at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular mass by CMRI, g</td>
<td>47</td>
<td>0.6 (-5.7 to 7.9)</td>
<td>49</td>
<td>-1.5 (-5.9 to 7.1)</td>
<td>.93</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume by CMRI, mL</td>
<td>47</td>
<td>-4.3 (-15.5 to 8.1)</td>
<td>49</td>
<td>3.7 (-4.9 to 14.5)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Change in diastolic function parameters at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial e', m/s</td>
<td>83</td>
<td>0.00 (-0.01 to 0.01)</td>
<td>77</td>
<td>0.00 (-0.01 to 0.01)</td>
<td>.88</td>
</tr>
<tr>
<td>E/e'</td>
<td>80</td>
<td>-1.6 (-4.7 to 2.2)</td>
<td>75</td>
<td>0.2 (-2.4 to 3.1)</td>
<td>.16</td>
</tr>
<tr>
<td>PA systolic pressure, mm Hg</td>
<td>58</td>
<td>-2 (-8 to 8)</td>
<td>45</td>
<td>2 (-5 to 7)</td>
<td>.94</td>
</tr>
<tr>
<td><strong>Change in core laboratory biomarkers at 24 wk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>94</td>
<td>0.01 (-0.10 to 0.09)</td>
<td>94</td>
<td>0.05 (-0.04 to 0.15)</td>
<td>.047</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>95</td>
<td>0.01 (-0.08 to 0.11)</td>
<td>95</td>
<td>0.05 (-0.04 to 0.16)</td>
<td>.01</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>94</td>
<td>-23 (-198 to 139)</td>
<td>95</td>
<td>15 (-90 to 372)</td>
<td>.03</td>
</tr>
<tr>
<td>Endothelin-1, pg/mL</td>
<td>95</td>
<td>-0.01 (-0.48 to 0.47)</td>
<td>95</td>
<td>0.33 (-0.10 to 0.97)</td>
<td>.046</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>95</td>
<td>0 (-7.0 to 4.8)</td>
<td>95</td>
<td>-1.1 (-7.7 to 3.0)</td>
<td>.85</td>
</tr>
<tr>
<td>NT-procollagen III, μg/L</td>
<td>93</td>
<td>-0.03 (-1.49 to 1.54)</td>
<td>95</td>
<td>0.07 (-1.17 to 1.42)</td>
<td>.77</td>
</tr>
</tbody>
</table>
LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

Natriuretic Peptide System

- pro-BNP
- BNP
- NT-pro BNP
- Neprilysin
- Inactive fragments
- Vasodilation: ↓ blood pressure, ↓ sympathetic tone, ↓ aldosterone levels, ↓ fibrosis, ↓ hypertrophy
- Natriuresis/Diuresis

Heart Failure

- LCZ696
- AHU377
- Valsartan
- LBQ657

Renin Angiotensin System

- Angiotensinogen (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor

- Vasoconstriction: ↑ blood pressure, ↑ sympathetic tone, ↑ aldosterone, ↑ fibrosis, ↑ hypertrophy
**PARAMOUNT: Study Design**

301 patients randomized

**Primary objective**
NT pro-BNP reduction from baseline at 12 weeks

**Secondary objectives**
- Echocardiographic measures of diastolic function, left atrial size, LV size and function, PASP
- HF symptoms, Clinical composite assessment and Quality of life (KCCQ)
- Safety and tolerability

![Study Design Diagram]

Baseline randomization visit and visit at end of 12 weeks of core study

Clinicaltrials.gov NCT00887588  
Solomon et al. ESC Hotline 2012  
Lancet 2012
PARAMOUNT Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PARAMOUNT (HFpEF)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=232</td>
<td>N=50</td>
</tr>
<tr>
<td>Age, y</td>
<td>71±9</td>
<td>60±8</td>
</tr>
<tr>
<td>Female, %</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>BMI</td>
<td>29.6 (25.9, 33.6)</td>
<td>25.2±4.9</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>eGFR &lt; 60, %</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Prior HF hospitalization, %</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>59±7</td>
<td>60±5</td>
</tr>
<tr>
<td>LVEDVI, ml/m²</td>
<td>58.3 (50.5, 67.7)</td>
<td>49.9 (42.5, 54.2)</td>
</tr>
<tr>
<td>LVESVI, ml/m²</td>
<td>23.3 (19.2, 29.5)</td>
<td>18.9 (16.4, 21.5)</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>74 (63.3, 90.7)</td>
<td>66.2 (54, 76)</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>16.1±7.0</td>
<td>5.7±2.3</td>
</tr>
<tr>
<td>E' lateral</td>
<td>7.5±2.7</td>
<td>11.8±2.7</td>
</tr>
<tr>
<td>LAVI, ml/m²</td>
<td>36±13</td>
<td>25±2.8</td>
</tr>
<tr>
<td>NT-pro BNP, pg/ml</td>
<td>894 (526, 1456.5)</td>
<td>-</td>
</tr>
</tbody>
</table>
Key Secondary Endpoints

Left Atrial Volume

- Change in Left Atrial Volume (ml)
  - Valsartan
  - LCZ696
  - P = 0.18
  - P = 0.003

- No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks

NYHA Class

- Percent of Patients
  - LCZ696
  - Valsartan
  - Week 12
  - Week 36
  - P = 0.11
  - P = 0.05

Solomon et al. ESC Hotline 2012
Lancet 2012
PARAGON-HF

**Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejection fraction**

| Design | ▪ Double-blind period: Randomized to LCZ696 200 mg bid vs. valsartan 160 mg bid  
  ▪ 2 years 9 months enrollment; estimated 2 years follow-up |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>▪ Composite endpoint of CV death and total (first and recurrent) HF hospitalization</td>
</tr>
</tbody>
</table>
| Secondary Endpoints | ▪ Composite endpoint of CV death, total HF hospitalization, total stroke, and total MI  
  ▪ NYHA classification at 8 months  
  ▪ Time to new onset AF in patients with no history of AF and with sinus rhythm on ECG at V1  
  ▪ All-cause mortality |
| Current major inclusion criteria | ▪ ≥55 years of age, male or female, and LVEF ≥ 45%  
  ▪ Current symptomatic HF (NYHA Class II-IV)  
  ▪ Symptoms of HF ≥30 days prior to Visit 1  
  ▪ Treatment with diuretic(s) within 30 days prior to V1  
  ▪ Structural heart disease (LAE or LVH)  
  ▪ HF hospitalization within 9 months OR Visit 1 elevated NT-proBNP (>300 pg/mL for patients in sinus rhythm or >900 pg/mL for patients with AF at Visit 1) |
| Sample size | ▪ 4300 subjects |
| Leadership | ▪ Chairs: S.Solomon, J. McMurray; Executive Cmt: I.Anand, A. Maggioni, F. Zannad  
  ▪ Steering cmt: M.Packer, M.Zile, B. Pieske, M.Redfield, J.Rouleau, M.Pfeffer, D. Van Veldhuisen, F. Martinez |

Beginning Q4 2013 – Investigators Wanted!
Exercise Training in HF-PEF

64 subjects randomized 2:1 to supervised exercise training (endurance+resistance) vs. usual care x 3 months, primary endpoint = change in peak VO2
Conclusions

- HFpEF – broad heterogeneous clinical syndrome and not a disease
- Terminology descriptive – doesn’t imply etiology or pathophysiology
- Extreme heterogeneity has hindered ability to find a therapy
- We need to better characterize the heterogeneity and then target therapies - One size may NOT fit all in HFpEF
- We need to learn from our mistakes as we design new trials
- HFpEF continues to be worth studying!
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell