HFpEF in the Future: New Diagnostic Techniques and Treatments in the Pipeline

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Disclosures

• Dr. Solomon has received research support from Novartis, Daichi-Sankyo, Amgen, Boston Scientific, Forest, Biogen, the National Heart Lung and Blood Institute, NIDDK, NCI, and has consulted for Novartis and Sanofi-Aventis
It’s tough to make predictions, especially about the future.

Yogi Berra
## The Current State of Heart Failure Therapy

<table>
<thead>
<tr>
<th>Systolic Heart Failure</th>
<th>Diastolic/PSF Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple randomized controlled double-blind clinical trials</td>
<td>• Mechanistic studies and small, non-definitive trials</td>
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<tr>
<td>• Therapies based on outcomes</td>
<td>• Empiric symptom-based therapy</td>
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<tr>
<td>• General HF community consensus</td>
<td>• Limited consensus</td>
</tr>
<tr>
<td>• The randomized controlled trial has even refuted previous held “dictum”</td>
<td>• Disconnect between randomized trials and observational data</td>
</tr>
<tr>
<td>• Evidenced-based medicine</td>
<td>• Anectode-based medicine</td>
</tr>
</tbody>
</table>
Challenges to Finding Effective Treatments in Diastolic/PSF Heart Failure

- Lack of appreciation
- Lack of agreement
- Marked heterogeneity
- Difficult diagnosis
- Lack of noninvasive methods
- Opposing mechanisms
- Theoretic benefits don’t always translate to outcomes
Two Potential Reasons why the trials have Not been successful

• Wrong Patients

• Wrong Therapies
Diagnosis of HFpEF

- Diagnosis of “Heart Failure” in HFpEF
- Echocardiographic Diagnosis in HFpEF
- Stress Testing in HFpEF
- Novel Methods to Assess Cardiac Function in HFpEF
- Biomarkers beyond BNP
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BNP Important in Prognosis:
Should we make this a critical component of the diagnosis?

Most New HFpEF Trials are requiring elevated BNP/NT-proBNP for Entry!

Cleland et al. NEJM Letter 2007
BNP Caveats

• False positives
  • BNP increases with age
  • BNP higher in women than in men
  • BNP higher in atrial fibrillation

• False negatives
  • Obesity decreases BNP levels
  • Intermittent or rapid increases in pressures
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Use of Echocardiography in HFpEF

1. Establish that LV systolic function is normal

2. Exclude other possible causes of the patients’ symptoms and signs

3. Evaluate diastolic function
The GOLD Standard for Assessment of Diastolic Function
Traditional Doppler Approaches to Diastolic Function
Standard Doppler can be Diagnostically Misleading and Response to Therapy can be Impossible to Interpret

<table>
<thead>
<tr>
<th>Diastolic Function</th>
<th>Normal</th>
<th>Mild Dysfunction</th>
<th>Moderate Dysfunction</th>
<th>Severe Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Impaired Relaxation</td>
<td>Pseudo-Normal</td>
<td>Restrictive Pattern</td>
</tr>
<tr>
<td>Mitral Inflow</td>
<td>120</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0</td>
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</tbody>
</table>

E: Early Diastolic Filling
A: Atrial Filling

Worsening of Diastolic Function
Doppler Tissue Imaging Measures
Myocardial Relaxation Velocity

E' = 17 cm/s
DTI more immune to changes in Preload

<table>
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<th>Diastolic Function</th>
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<td>E</td>
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<tr>
<td>0</td>
<td>A</td>
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<td></td>
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<tr>
<td>DTI</td>
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<td>Sm</td>
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<tr>
<td>[m/s]</td>
<td></td>
<td>Em</td>
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<td></td>
<td>Am</td>
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<td></td>
<td></td>
<td>Time (msec)</td>
<td></td>
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</tbody>
</table>
Is E/E’ an accurate measure of filling pressure?

- E’ inversely related to Tau, E/E’ surrogate for filling pressure
- Mitral inflow velocity (E wave) is a measure of the LA > LV pressure gradient and is thus dependent on left atrial pressure AND ventricular relaxation.
- Dividing the E wave by E’, itself a measure of ventricular relaxation, thus yields an estimate of LA pressure (which is itself related to LV EDP)

\[
\text{PCWP} = 1.24 \left( \frac{E}{Em} \right) + 1.9 \\
\text{LAP} \uparrow = \frac{E}{Em} \geq 15
\]
Recalibrating the Barometer
Is It Time to Take a Critical Look at Noninvasive Approaches to Measuring Filling Pressures?

Scott D. Solomon, MD; Lynne W. Stevenson, MD

Circulation. 2009
Pulmonary Hypertension May be a Critical Component of HFpEF

\[ p < 0.001 \]

Lam C.S. et al
J Am Coll Cardiol. 2009;53:1119-26
**Prognostic impact of PH in HFpEF**

![Graph showing survival over years with PASP values](image)

- **PASP < 48 mmHg**
  - Survival: 1.0, 0.8, 0.6, 0.4, 0.2
  - Number remaining: 98, 86, 80, 44

- **PASP ≥ 48 mmHg**
  - Survival: 1.0, 0.8, 0.6, 0.4, 0.2
  - Number remaining: 105, 78, 67, 38

*p = 0.002*
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Elderly HFPEF Patients Have Severe Exercise Intolerance

‡ p ≤ 0.001 vs healthy age-matched normal subjects

Kitzman et al, JAMA 2002
Exercise Capacity Correlates with LV-stiffness

27 patients with DHF, 12 patients with no DHF (according to end-diastolic pressure volume relationship): Cardiopulmonary exercise testing + PV measurements by conductance catheter method
In patients with diastolic dysfunction, the abnormal relaxation prevents augmentation of relaxation as heart rate increases during exercise.

Quantifying the response of diastolic functional indices to dynamic exercise is therefore a way to assess diastolic functional reserve in patients with exertional dyspnea and normal resting ventricular systolic and diastolic function.
Stress Testing in HFrEF

- Rule out ischemia
- Heart rate reserve (unmask chronotropic incompetence)
- Unmask abnormalities of diastolic function that are less obvious at rest
- Unmask reactive pulmonary hypertension
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Normal Strain and Torsion

Rotation as viewed from apex

Clockwise

Counter-clockwise

Contraction

Systole

Diastole

Apical

Basal

Time

Notomi et al. Circulation March, 2005
The Pathophysiology of Heart Failure With Normal Ejection Fraction

Exercise Echocardiography Reveals Complex Abnormalities of Both Systolic and Diastolic Ventricular Function Involving Torsion, Untwist, and Longitudinal Motion

Yu Ting Tan, MBBS,* Frauke Wenzelburger, MD,† Eveline Lee, MBCHB,‡ Grant Heatlie, MBBS, PhD,† Francisco Leyva, MD,* Kiran Patel, MBBS, PhD,* Michael Frenneaux, MD,* John E. Sanderson, MD*

- Comprehensive assessment of 39 women with HFpEF and 27 age-matched controls with rest and exercise echocardiography.
- At rest, systolic longitudinal and radial strain, systolic mitral annular velocities, and apical rotation were lower in patients, and all failed to rise normally with exercise.
- In diastole, patients had reduced and delayed untwisting, reduced LV section at rest and with exercise, and higher EDP.
- Mitral annular systolic and diastolic velocities, systolic rotation and diastolic untwist on exercise correlated with peak VO2 max.
LV Untwisting Reflects IVPG

y = -0.44x + 0.87
r = 0.72

Notomi et al. Circ 2006; 113: 2524-2533
Systolic torsion and diastolic untwisting are significantly increased in patients with mild diastolic dysfunction.

In patients with advanced diastolic dysfunction with increased filling pressure, they are normalized or reduced.

Park et al. JASE 2008

Not Yet Ready for Prime Time!
Insights into HFpEF Mechanics

• Despite normal ejection fraction, systolic contractile function in HFpEF is not normal
• S’, longitudinal strain, strain rate and rotational mechanics are all abnormal
• These measures are not ready to be used in diagnosis yet, but stay tuned
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ST2 is a member of the interleukin-1 receptor family; the ligand for ST2 was recently identified to be IL-33.

IL-33 is a fibroblast product, induced by cellular stretch.

Provides protection against myocardial fibrosis and hypertrophy in the context of pressure overload.

The effects of IL-33 may be blunted or blocked by high concentrations of ST2 or by knocking out the ST2 gene.
Galectin-3 is a marker of fibrosis that may be important both for prognosis and as a marker of response to therapy.
Diagnosics in HFpEF: Summary

- Flow-based Doppler methods (E/A), DT unreliable
- E/E’ good at extremes, but may be less useful at the margins
- Pulmonary pressures may be essential component
- Strain and torsion worth watching as potential diagnostic measures – still lacking reliable outcomes data
- Biomarkers other than BNP may point to increased wall stress and fibrosis and may prove useful for both diagnosis, prognosis and response to therapy
- We need larger studies to confirm the relationship between measured abnormalities and outcomes
Future of Diagnosis in HFpEF

- Enormous heterogeneity in this “disorder”
- Diagnosis of a Disease or Phenotyping a Syndrome?
202 Trials of Diastolic HF or HFpEF

Clinicaltrials.gov
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>
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<tr>
<td></td>
<td>ACE inhibitors</td>
<td>Hydrochlorothiazide, 12.5–25 mg</td>
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<tr>
<td></td>
<td>Angiotensin II–receptor blockers</td>
<td>Enalapril, 2.5–40 mg</td>
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<td></td>
<td></td>
<td>Lisinopril, 10–40 mg</td>
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<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</td>
<td>Cardioversion of atrial fibrillation</td>
<td>Atenolol, 12.5–100 mg</td>
</tr>
<tr>
<td>and prevent tachycardia</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, 120–540 mg</td>
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<tr>
<td></td>
<td>Radiofrequency ablation modification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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>
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<tr>
<td></td>
<td>Calcium-channel blockers</td>
<td>Atenolol, 12.5–100 mg</td>
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<tr>
<td></td>
<td>Coronary-artery bypass surgery,</td>
<td>Metoprolol, 25–100 mg</td>
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<tr>
<td></td>
<td>percutaneous coronary intervention</td>
<td>Diltiazem, 120–540 mg</td>
</tr>
<tr>
<td></td>
<td>Control hypertension</td>
<td>Verapamil, 120–360 mg</td>
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<tr>
<td></td>
<td>Anthypertensive agents</td>
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<tr>
<td></td>
<td>Chlorthalidone, 12.5–25 mg</td>
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<tr>
<td></td>
<td>Hydrochlorothiazide, 12.5–20 mg</td>
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<td></td>
<td>Atenolol, 12.5–100 mg</td>
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<td></td>
<td>Metoprolol, 12.5–200 mg</td>
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<td></td>
<td>Amiodipine, 2.5–10 mg</td>
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<td></td>
<td>Felodipine, 2.5–20 mg</td>
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<td>Candesartan, 4–32 mg</td>
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<td></td>
<td>Losartan, 50–100 mg</td>
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<tr>
<td>Measures with Theoretical Benefit in</td>
<td>ACE inhibitors</td>
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<tr>
<td>Diastolic Heart Failure</td>
<td></td>
<td>Enalapril, 2.5–40 mg</td>
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<tr>
<td></td>
<td>Angiotensin-receptor blockers</td>
<td>Lisinopril, 10–40 mg</td>
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<tr>
<td></td>
<td>Spironolactone</td>
<td>Ramipril, 5–20 mg</td>
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<td></td>
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<td>Captopril, 25–150 mg</td>
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<td></td>
<td></td>
<td>Candesartan, 4–32 mg</td>
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<td></td>
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<td>Losartan, 50–100 mg</td>
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</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 physiologic 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 anthypertensive 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.
Pathophysiologic Approaches to Diastolic Heart Failure

**Cardiac Physiology**
- Improve diastolic relaxation
- Slow HR > improve filling
- Improve myocardial oxygen supply/demand balance
- Reduce congestion

**Renal Function**
- Improve Na and H\textsubscript{2}O handling

**Peripheral Physiology**
- Lower BP – decrease “afterload”
- Improve conduit vessel function

**Pulmonary Function**
- Pulmonary Vasodilator?

**Cardiac Structure**
- Regression of cardiac hypertrophy
- Reduce fibrosis
Pharmacologic Rx for HFpEF

**ACE/ARB**
- PEP-CHF
- CHARM-Preserved
- I-PRESERVE

**Aldosterone Antagonists**
- TOPCAT
- Aldo-DHF
- Beta-Blockers
- Seniors (±)
- CHINESE

**ARNI**
- PARAMOUNT

**PDE-5**
- RELAX

**AGE-Breaker**
- Alegebnium
### SENIORS: Death or CV Hospitalization by Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Nebivolol</th>
<th>Placebo</th>
<th>Favors Nebivolol</th>
<th>Favors Placebo</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>LVEF, n (%)</strong></td>
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<tr>
<td>≤35%</td>
<td>219 (21.7)</td>
<td>249 (25.1)</td>
<td></td>
<td></td>
<td>0.42*</td>
</tr>
<tr>
<td>&gt;35%</td>
<td>110 (17.6)</td>
<td>125 (21.9)</td>
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<td></td>
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<tr>
<td><strong>Sex, n (%)</strong></td>
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</tr>
<tr>
<td>Male</td>
<td>231 (23.5)</td>
<td>250 (25.2)</td>
<td></td>
<td></td>
<td>0.11*</td>
</tr>
<tr>
<td>Female</td>
<td>101 (15.5)</td>
<td>125 (21.8)</td>
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<tr>
<td><strong>Age, n (%)</strong></td>
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<tr>
<td>&lt;75 y</td>
<td>148 (16.6)</td>
<td>176 (21.4)</td>
<td></td>
<td></td>
<td>0.51*</td>
</tr>
<tr>
<td>≥75 y</td>
<td>184 (24.6)</td>
<td>199 (26.7)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>332 (31.1)</td>
<td>375 (35.3)</td>
<td></td>
<td></td>
<td>0.039†</td>
</tr>
</tbody>
</table>

Multicentre, prospective, randomized, open-label, blinded endpoint (PROBE) trial. N = 1200

Randomized to either β-blocker (metoprolol succinate) or control

Primary endpoint is a composite of hospitalization for heart failure and cardiovascular death

Secondary endpoints: cardiovascular death, heart failure mortality or hospitalization, all-cause mortality, change in New York Heart Association class, change in left ventricular ejection fraction, increase in NT-proBNP (by 50% of the value at randomization), β-blocker tolerance, and premature termination of β-blocker therapy due to adverse events

Follow-up period minimum of 2 years
A.G.E.s Stimulate Multiple Inflammatory and Metabolic Pathways

Receptors

Macrophages
Epithelial
Mesangial
Endothelium

Stimulation of Inflammatory & Metabolic Pathways

Multispecific AGE-receptors

RAGE
AGE R-1
AGE R-2
AGE R-3 (Galectin 3)
MSRA

Sources: Adapted from Raj, AJKD, 2000
Aronson, D and Rayfield, E, Cardiovascular Diabetology 2002

Cytokines
(TNFα, IL-1, IL-6)

Extracellular Matrix Production
(CTGF, TGFβ)

Metabolic Pathway Activation
(PKCα)

Growth Factors
(TGFβ, CTGF, PDGF, VEGF, IGF-1)

Adhesion Molecules
(VCAM-1, ICAM)

Gene Expression
(NFκ β, ERK, 1, 2, JNK)

Oxidative Stress
(NADPH Oxidase)
Short-Term Dosing With Alagebrium Restores Flexibility In The Left Ventricle In Aged Dogs

Male mongrel dogs. ALT-711: 1 mg/kg, oral, 4 weeks
Adapted from Asif et al, PNAS 2000
23 Patients with Diastolic HF
Open Label Alagebrium for 16 Weeks

Baseline

- LV Mass (MRI)
  - 125 ± 35

- Annular E (TDI)
  - 7.3 ± 1.2

Treatment

- LV Mass (MRI)
  - 119 ± 34, p=0.036

- Annular E (TDI)
  - 8.4 ± 1.7, p=0.045

Little, J Card Failure 2005
LCZ696: first in class, Angiotensin Receptor Neprilysin Inhibitor (ARNI) rapidly converted to NEPi and valsartan

- LCZ696 is a novel, dual-acting agent which delivers concomitant neprilysin inhibition and angiotensin (AT1) receptor blockade (ARB)
- Ingestion of LCZ696 results in systemic exposure of the neprilysin inhibitor (NEPi) pro-drug AHU377 (which is further metabolized to LBQ657) and valsartan (AT-1 receptor blocker)

**Highly selective NEP inhibitor:**
- IC\textsubscript{50} for human NEP = 7.3 nM
- ACE > 100 μM
- APP > 1 mM
**PARAMOUNT: Therapeutic Validation Study (CLCZ696B2214)**

**Design**
- 12 wks, randomized, double-blind, active controlled study evaluating LCZ 200 mg bid compared to valsartan 160 mg bid followed by 6 month extension
- LCZ 696 and valsartan will be progressively up-titrated to the target doses

**Population**
- Approximately 300 pts with chronic HF (NYHA class II-IV), LVEF ≥ 45%, and elevated NT-proBNP > 400 pg/ml

**Primary objective**
- NT-proBNP reduction from baseline at 12 weeks (core study) with 6 month extension

**Secondary objectives**
- HF symptoms and QoL – Kansas City Cardiomyopathy Questionnaire & global assessment
- Echocardiographic parameters of diastolic function, cardiac filling pressures (LVDP using E/E’ as surrogate) and PASP
- Evaluate the effects on BNP, ANP, and cGMP as well as collagen markers (PIIP and TMP)
- Renal function and safety and tolerability
- Arterial stiffness (PWV, AI, central BPs) in sub-population

**Sample size**
- 80% power to detect a 25% reduction in NT-proBNP vs comparator
Improvement in Measures of Structure and Function with Sildenafil in HFpEF

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>1 Year</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>E' – placebo (cm/s) n=22</td>
<td>4.8 ± 0.8</td>
<td>4.7 ± 0.8</td>
<td>4.7 ± 0.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>E' Sildenafil (cm/s) n=23</td>
<td>4.6 ± 0.8</td>
<td>5.2 ± 0.8</td>
<td>5.2 ± 0.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>E/E' Placebo n=22</td>
<td>13.0 ± 5</td>
<td>13.9 ± 4</td>
<td>13.8 ± 5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>E/E' Sildenafil n=23</td>
<td>13.1 ± 5</td>
<td>9.8 ± 5</td>
<td>9.4 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

Guazzi et al. Circ HF 2011
Study Design: Randomized (1:1), double-blind, placebo controlled treatment study

Intervention: PDE-5 inhibition with sildenafil (20 mg tid for 12 weeks followed by 60 mg tid for 12 weeks) or placebo for 24 weeks

Study population: 190 patients with a clinical diagnosis of HF and normal EF (50%) enrolled over a planned 3.25 year enrollment period.

Primary outcome: The primary endpoint will be exercise capacity as assessed by the change in peak peak VO2 at 24 weeks of double blinded therapy compared to the baseline peak VO2.

Secondary outcomes:
1. Change in a composite score reflective of clinical status after 24 weeks of double-blinded treatment with PDE-5 inhibitor or placebo.
2. Change in submaximal exercise capacity at 12 and 24 weeks as assessed by 6 minute walk test
3. Change in peak VO2 at 12 weeks
Myocardial Fibrosis in Hypertension and CHF: The Aldosterone Hypothesis

Aldosterone promotes myocardial fibrosis, enhances ventricular stiffness, and worsens diastolic function.

Hypertension potentiates diastolic dysfunction by enhancing myocyte hypertrophy and interstitial fibrosis.

Aldosterone receptor antagonists may have a therapeutic role.

TOPCAT: Trial Design

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

**PLUS ONE OF THE FOLLOWING:**
- HF HOSPITALIZATION WITHIN 12 MONTHS
- BNP $\geq$ 100 PG/ML
- N-TERMINAL PRO-BNP $\geq$ 360 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=3500

Week 0

Week 4

~ 3.25 yrs
**Ongoing: Aldo-DHF**

**Aldosterone Receptor Blockade in Diastolic Heart Failure**

*Funded by BMBF/DLR (Clinical Trial Program)*

- Double-blind, randomised, placebo-controlled, parallel group
- 420 patients
  - 1:1 spironolactone 25 mg vs. Placebo, Follow-up 18 months

≥ 50 years with heart failure ≥NYHA II
LV EF ≥50%
Echocardiographic evidence of diastolic dysfunction ≥ ASE °I
Peak VO2 <20 ml/min/kg

**Primary Endpoints:**
1. Change in maximum exercise capacity (peak VO2) on spiroergometry at 12 months compared to baseline
2. Change in E/é as indicator of diastolic function at 12 months compared to baseline

ISRCTN94726526 (www.controlled-trials.com)
Efficacy of Treating Anemia in Heart Failure With a Normal Ejection Fraction (HFNEF) on Ventricular Function, Exercise Capacity and Health Status

- **NCT00286182**, Funded by NIH (NIA)
- **Study Design**: Treatment, Randomized, Single-Blind, Placebo Control, Expanded Access Assignment, Safety/Efficacy Study
- **Intervention**: Epoetin alfa versus placebo
- **Primary Outcomes**: Left Ventricular End Diastolic Volume (by Three Dimensional Echocardiography)
- **Secondary Outcomes**: Peak Oxygen Consumption by Cardiopulmonary Exercise Testing; 6-minute walk duration; Health Status (Kansas City Cardiomyopathy Questionnaire); Left ventricular structure (volumes and mass) and function (stroke volume, cardiac output); Hospitalization
- **Expected Total Enrollment**: 60
The Baroreflex as a Therapeutic Target in Hypertension and Heart Failure

Carotid Baroreceptor Stimulation

Brain

Autonomic Nervous System
Inhibited sympathetic activity and enhanced parasympathetic activity

Heart

Vessels

Kidneys

\( \downarrow \) HR

\( \uparrow \) Vasodilation

\( \downarrow \) Stiffness

\( \uparrow \) Diuresis

\( \downarrow \) Renin secretion

Reduced excessive blood pressure
Reduced afterload, wave reflections and augmentation
Reduced myocardial work and oxygen consumption
Reduced neurohormonal stimulus
Increased venous capacitance
Sustainable Reduction of SBP over 4 years

7. The response is sustainable
8. The response has a large magnitude
Reduction in Left Ventricular Mass Index at 3 and 12 Months

* Based on current ASE guidelines and classifications

Bisognano et al, J Clinical Hypertension 2009
HOPE4HF Trial

• Randomized open-label study of Rheos baroreflex activation therapy system in patients with HF, EF >= 40%, elevated BP, elevated BNP

• N = 540

• Primary outcome: CV Death or HF Event

• Secondary Outcomes: LV Mass, QOL
Effect of Exercise Training on Exercise Capacity in Elderly Patients with HFPEF

Kitzman et al, Circulation HF, 2010 In Press

p < 0.0001
Ex-DHF Pilot Study
Prospective, randomised, controlled, multicenter trial in patients with mild DHF

Inclusion criteria:
Age ≥ 45, NHHA II-III, preserved EF, echo signs of DDys, at least 1 RF

Screening for eligibility (n=71)

Randomisation 2:1

Training (n= 46)
Supervised, facility based endurance / resistance training (32 sessions)

3 months follow up

Controls (n= 21)
Usual care / activity alone

3 months follow up

Primary endpoint: change in peak VO₂
Secondary endpoints: echocardiographic parameters, exercise capacity, QOL, serum biomarkers

Edelmann, Pieske et al. unpublished
Effect of Exercise Training on Measures of Diastolic Function

C Echo: E/é

D LAVI

Edelmann F… Pieske B. Unpublished
Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation

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Summary

• One size may not fit all in HFpEF (which may explain why trials have failed)
• As we get better at “phenotyping” in HFpEF, we should aim for more “directed” therapies
• There are potential roles for pharmacologic therapy, device therapy, and lifestyle intervention
The Future of HFpEF

“The future ain’t what it used to be”
Yogi Berra

“The future is much like the present, only longer”
Dan Quisenberry

“The future will be better tomorrow”
Dan Quayle