Pulmonary Hypertension and the Right and Left Ventricle

26 August-Munich

Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction

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Disclosure Information M Guazzi

Member of Advisory Board: Merck Sharpe, Pfizer

Speaker/Travel Fees: Bayer, Pfizer, Merck Sharpe
The Continuum of Diastolic HF: from HFpEF to PH HFpEF

**VASCULAR**
- Wall stiffening
- Abnormal vasorelaxation (impaired endoth. function, increased constriction)

**CARDIAC**
- Hypertrophy
- Fibrosis
- Impaired coronary reserve

**PULMONARY**
- Lung capillary stress failure
- Capillary/arter. remodeling

Ventricular-vascular uncoupling

HFpEF

PH HFpEF
PH due to Left Heart Disease (Group 2): Definition

Galie’ N et al 2009 – Eur Heart J

PRECAPILLARY PH
- mean PAP ≥ 25 mmHg
- PCWP < 15 mmHg
- The TPG* is increased

POSTCAPILLARY PH
- mean PAP ≥ 25 mmHg
- PCWP > 15 mmHg
- The TPG* may/may not be increased

* : TPG: mean PAP-PCWP
Symptoms
HF Dx unclear
Echo Doppler

Report from the 4° World Symposium on PH (Dana Point): working group on non-PAH-pulmonary Hypertension

Old
HTN, DM, CAD, Lipids
CRX findings of HF
LV H
Atrial enlargement
Grade II-IV diast. Dysf.
Response to diuretic
HF hospitalization

Any age
No or mild HTN
Echo no clear LVH
BNP normal
Euvolemic

DHF Likely

DHF Uncertain
Exclude other causes of PH
RHC

PH+normal EF

DHF Unlikely
Exclude other causes of PH
RHC

Young
No HTN, DM, CAD, Lipids
CRX findings of PAH
D-shaped LV
Markedly reduced DLCO
PAH associated diseases/drugs

Diagnosis of Non-Pulmonary Arterial Hypertension
Pulmonary Hypertension

Old
HTN, DM, CAD, Lipids
CRX findings of HF
LV H
Atrial enlargement
Grade II-IV diast. Dysf.
Response to diuretic
HF hospitalization

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Young
No HTN, DM, CAD, Lipids
CRX findings of PAH
D-shaped LV
Markedly reduced DLCO
PAH associated diseases/drugs

Report from the 4° World Symposium on PH (Dana Point): working group on non-PAH-pulmonary Hypertension
HFpEF, PAH....?

PASP=58 mmHg
Mean PAP=40 mmHg
PCWP=11 mmHg
TPG=34 mmHg

PASP=60 mmHg
Mean PAP=42 mmHg
PCWP=21 mmHg
TPG=25 mmHg
Spectrum of Pulmonary Hypertension: ASPIRE REGISTRY

1344 consecutive PAH and PH treatment-naive cases diagnosed between 2001-2010

157 patients with Group 2 PH

<table>
<thead>
<tr>
<th></th>
<th>HFrEF</th>
<th>HFpEF</th>
<th>Valv. Dis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP, mmHg</td>
<td>24</td>
<td>22</td>
<td>26*§</td>
</tr>
<tr>
<td>mean PAP, mmHg</td>
<td>43</td>
<td>37</td>
<td>48*</td>
</tr>
<tr>
<td>mean RAP, mmHg</td>
<td>17</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

Hurdman J et al Eur Resp J 2012;39:945-955
Emerging Concepts in PH HFpEF: The Prevalence

Darmouth Dynamic Registry

- 455 HFpEF patients studied
- mPAP determined by right heart cath.

N=239 PH
mean PAP= 34 mmHg

N=219 no PH
mean PAP= 20 mmHg

Leung CC et al. Am J Cardiol 2010;106:284-286
PH Diagnosis by Exercise Hemodynamic in HFrEF

- 55 patients with exercise dyspnoea, normal BNP assay; normal resting haemodynamics and euvolemic
- PCWP > 25 mmHg at peak exercise as main criteria for PH diagnosis

RIGHT and LEFT HEART catheterisation during supine exercise

Borlaug B et al Circ Heart Fail 2010;3:588-595
Primary Outcome: Definition of PH prevalence and severity in HFpEF due to hypertensive heart disease

Secondary Outcome: Mortality rate according to PASP

**CONTROL Group**: n=619
- LVEF > 50%
- No CV disease
- BMI < 30

**HTN without HFpEF**: n=719
- LVEF > 50%
- Hypertension
- No HF

**HTN with HFpEF**: n=244
- LVEF > 50%
- HF signs/sympt.
- no valve disease
PASP in HFpEF

Prevalence of PH (PASP ≥ 35 mmHg):
2% in CON; 8% in HTN; 83% in HFpEF

Adjusted p * < 0.05 vs CON
KM Survival Curves According to Median PASP

Lam C et al. JACC 2009;53:1119-1126

Multivariate predictors of Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Hazard Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP, mm Hg</td>
<td>136</td>
<td>1.20 per 10 mm Hg</td>
<td>0.028</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>136</td>
<td>0.98 per U</td>
<td>0.199</td>
</tr>
<tr>
<td>Left atrial volume/BSA, ml/m²</td>
<td>136</td>
<td>1.12 per 10 ml/m²</td>
<td>0.237</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>136</td>
<td>1.26 per 0.1 U</td>
<td>0.121</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>136</td>
<td>0.96 per 10 g/m²</td>
<td>0.383</td>
</tr>
</tbody>
</table>
**Clinical Characteristics of Pulmonary Hypertension in Patients With Heart Failure and Preserved Ejection Fraction**

Thenappan Thenappan, MD; Sanjiv J. Shah, MD; Mardi Gomberg-Maitland, MD, MSc; Brett Collander, MD; Ajay Vallakati, MD; Pranavkumar Shroff, MD; Stuart Rich, MD

(Circ Heart Fail. 2011;4:257-265.)

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**Adjusted p * <0.05 vs HFP EF**

**mean PAP, mmHg**

- **HFpEF**
  - **N=52**
- **PAH**
  - **N=522**
- **PH HFpEF**
  - **N=100**
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HFpEF (n=45)</th>
<th>PAH (n=522)</th>
<th>PH-HFpEF (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs</strong></td>
<td>67±11</td>
<td>48±14</td>
<td>64±13†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>26 (58)</td>
<td>400 (77)</td>
<td>82 (82)*</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>WHO functional class III and IV, n (%)</strong></td>
<td>23 (51)</td>
<td>474 (91)</td>
<td>97 (97)*</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>BSA, m²</strong></td>
<td>2.0±0.3</td>
<td>1.8±0.2</td>
<td>2.0±0.3†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>33 (77)</td>
<td>152 (29)</td>
<td>79 (79)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>12 (28)</td>
<td>44 (8)</td>
<td>37 (37)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>22 (49)</td>
<td>79 (15)</td>
<td>46 (46)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>16 (37)</td>
<td>22 (4)</td>
<td>27 (27)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Treadmill exercise capacity, Mets</strong></td>
<td>NA</td>
<td>3.8±2.1</td>
<td>2.8±1.2</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL‡</strong></td>
<td>1.1 (0.9–1.5)</td>
<td>1.0 (0.8–1.2)</td>
<td>1.1 (0.9–1.4)†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Echocardiographic variables**

<table>
<thead>
<tr>
<th></th>
<th>HFpEF (n=25)</th>
<th>PAH (n=522)</th>
<th>PH-HFpEF (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5-Inhibitors</td>
<td>0 (0)</td>
<td>16 (4)</td>
<td>4 (4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Prostacyclins</td>
<td>0 (0)</td>
<td>16 (3)</td>
<td>0 (0)</td>
<td>0.14</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>88±28</td>
<td>88±39</td>
<td>76±28</td>
<td>0.09</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>11.3±2.2</td>
<td>10±2</td>
<td>11±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interventricular septal thickness, mm</td>
<td>11.5±2.7</td>
<td>10.4±2.6</td>
<td>11.3±3.2</td>
<td>0.03</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>60±6</td>
<td>60±10</td>
<td>62±7</td>
<td>0.13</td>
</tr>
<tr>
<td>Left atrial enlargement, n (%)$</td>
<td>20 (65)</td>
<td>85 (18)</td>
<td>56 (64)†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right atrial enlargement, n (%)$</td>
<td>13 (41)</td>
<td>411 (89)</td>
<td>57 (68)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV hypertrophy, n (%)$</td>
<td>7 (22)</td>
<td>240 (57)</td>
<td>32 (45)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Right Heart Involvement in \textit{PH HFpEF}

\textbf{Right Atrial Enlargement}

\textbf{Right Ventricle Hypertrophy}

\textit{Adjusted }p^* <0.05 \textit{ vs HFpEF; }p^# <0.05 \textit{ vs PAH}

\textit{Thenappan et al. Circ HF 2011}
### Right Heart Geometry, Function and BNP in PH HFpEF

159 HFpEF with left-sided PH (elevated mPAP and PCWP)

<table>
<thead>
<tr>
<th>Variables</th>
<th>BNP &lt; 100 pg/mL</th>
<th>BNP &gt; 100 pg/mL</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>62</td>
<td>61</td>
<td>0.67</td>
</tr>
<tr>
<td>LV mass index, gr/m²</td>
<td>49</td>
<td>55</td>
<td>0.67</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>25</td>
<td>27</td>
<td>0.17</td>
</tr>
<tr>
<td>PVR, dynes/cm⁵</td>
<td>87</td>
<td>142</td>
<td>0.42</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>12</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>22</td>
<td>19</td>
<td>0.00035</td>
</tr>
<tr>
<td>RV end-diastolic area</td>
<td>12.1</td>
<td>14.6</td>
<td>0.001</td>
</tr>
<tr>
<td>RV end-systolic area</td>
<td>6.5</td>
<td>8.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Anyan VJ et al. Am J Cardiol 2012 in press
When Treating PH in HFpEF and How are Pulmonary and Cardiac Objectives Interrelated?

- Hydrostatic Pressure
- Alveolar-capillary membrane integrity
- Permeability
- Lymphatic drainage capacity

SYSTEMIC CONGESTION (JVD, edema)

RV FAILURE

↑ RV+RA PRESSURE

↑ PA PRESSURE

↑ PCWP (PULMONARY CONGESTION)

↑ LA AND LV DIASTOLIC PRESSURE

↑ LVDP+IMPAIRED VOLUME REGULATION

ABNORMAL LV RELAXATION and STIFFNESS

Alveolar Edema

Volume redistribution in pulm. vascular bed + Interstitial Edema

Mitral Regurgitation
Clinical Case

- Male, 38 years old
- First presentation at ER dept. for incoming dyspnea
- Severe hypertension (210/130 mmHg)
- $\text{PO}_2 = 92 \text{ mmhg}$
- NTproBNP = 2390 pg/ml

PASP = 54 mmHg
(RAP = 5 mmHg)

E/A = 5.0
E/E' = 15.2
**Baseline**

- E/A = 5.0
- E/E' = 15.2
- PASP = 54 mmHg (RAP = 5 mmHg)

**2-months post-therapy***

- BP: 145/85 mmHg; NT-pro BNP: 870 pg/ml
- E/A = 1.2
- E/E' = 10.0
- PASP = 51 mmHg (RAP = 5 mmHg)

***: Furosemide (50 mg), Ramipril (10 mg), Carvedilol (25 mg)
Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

A Community-Based Study

Carolyn S. P. Lam, MBBS,*† Véronique L. Roger, MD, MPH,* Richard J. Rodeheffer, MD,* Barry A. Borlaug, MD,* Felicity T. Enders, PhD,*† Margaret M. Redfield, MD*

Rochester, Minnesota; and Singapore, Singapore

PASP (Bernoulli eq.) and PCWP (11.96+0.596 x E/E1) estimated by Echo
Long-term Monitoring of Pulmonary Hemodynamics in PH HFpEF Patients

22 optimally-treated pts with stable HFpEF and moderate PH (mean PAP 37.8 mmHg)

PCWP (mmHg)  

Baseline  |  6 months  |  1-year

Pulm. Arteriolar Res. (Wood)

*: p<0.01 vs baseline

Tranpulmonary Gradient (mmHg)

*: p<0.01 vs baseline

Guazzi M et al Circulation 2011;124:164-174
Different Hemodynamic Stages in Group 2 PH

A) PASSIVE Increase in Pulmonary Pressure
   - TPG <12 mmHg; PCWP >15 mmHg
   - PAP
   - RV
   - LA
   - Atrial Pressure

B) REACTIVE Pulmonary Hypertension
   - TPG ≥12 mmHg; PCWP >15 mmHg
   - PAP
   - RV
   - LA
   - Atrial Pressure

C) OUT of PROPORTION Pulmonary Hypertension
   - TPG ≥12 mmHg; PCWP >15<25 mmHg
   - PAP
   - RV
   - LA
   - Atrial Pressure
Pathobiology of Left-Sided PH at Different Hemodynamic Stages

- **REACTIVE Pulm. Hypertension**
  - > Enlarged and thickened pulmonary venules
  - > Arterial medial hypertrophy and intimal fibrosis
  - > Interstitial edema
  - > Lymphatic vessel dilatation
  - > No evidence of plexogenic vasculopathy except for few reported cases of severe mitral stenosis exposed to severe high PVRs.*

- **OUT of PROPORTION Pulm. Hypertension**
  - > Initial or intermediate venular and arterial changes (?)

- **PASSIVE Pulm. Hypertension**
  - > ??
Lung Capillary Remodeling and Endotelial Dysfunction in Left-Sided PH: Cellular Mechanisms

- Rat model of aortic banding for 9 weeks
- In vivo lung microcirculation studies

Kerem A et al Circ Res 2010;16:1103-1116
Endothelial and vascular smooth muscle cell pathways involved in the regulation of pulmonary arterial tone and pharmacological approaches.

Guazzi M, Borlaug BA. Circulation 2012;126:975-990
## PAH Therapies in Heart Failure

<table>
<thead>
<tr>
<th>Trial/ Drug</th>
<th>No of pts/ NYHA class/ EF</th>
<th>Study duration</th>
<th>Primary END-POINT</th>
<th>Pulm. hemo. end-point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST (Epoprostenol)</td>
<td>471 / III-IV / &lt; 35%</td>
<td>26 weeks</td>
<td>Survival</td>
<td>No</td>
<td>Early term. (trend to ↑ mortality)</td>
</tr>
<tr>
<td>REACH-1 (Bosentan)</td>
<td>370 / III-IV / &lt; 35%</td>
<td>26 weeks</td>
<td>Clin. status @ 26 w</td>
<td>No</td>
<td>Early term. (safety, abn LFT)</td>
</tr>
<tr>
<td>ENABLE 1-2 (Bosentan)</td>
<td>1613 / III-IV / &lt; 35%</td>
<td>18 weeks on average (312 pts)</td>
<td>All cause Mort./HF hosp</td>
<td>No</td>
<td>Fluid ret. ↑ hosp.</td>
</tr>
<tr>
<td>HEAT (Darusentan)</td>
<td>157 / III / &lt; 35%</td>
<td>3 weeks</td>
<td>Syst. and Pulm. Hemo</td>
<td>No</td>
<td>PCWP↓, PVR↓, CI ↑, ↑ doses trend to ↑ mortality</td>
</tr>
<tr>
<td>EARTH (Darusentan)</td>
<td>642 / II-IV / &lt; 35%</td>
<td>24 weeks</td>
<td>Change in LVESV @ 24 w + functional status</td>
<td>No</td>
<td>No benefits, trend to ↑ mortality</td>
</tr>
</tbody>
</table>
# PDE5 Expression in Different Vascular Beds

## Table 1. Functions of PDEs and Cardiovascular Effects of Specific Inhibitors

<table>
<thead>
<tr>
<th>Family</th>
<th>Enzyme Main Functions</th>
<th>Selective Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heart</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contractility</td>
</tr>
<tr>
<td>PDE1</td>
<td>Regulates smooth muscle contraction, sperm function, immune cell activation, neuronal signaling</td>
<td>…</td>
</tr>
<tr>
<td>PDE2</td>
<td>Regulates aldosterone secretion, long-term memory, endothelium barrier function under inflammation</td>
<td>↑</td>
</tr>
<tr>
<td>PDE3</td>
<td>Regulates platelet aggregation, cardiac and vascular smooth muscle contractility, renin release, oocyte maturation; mediates insulin signaling (antilipotic effects)</td>
<td>↑ ↑ ↑</td>
</tr>
<tr>
<td>PDE4</td>
<td>Has a role in brain function, vascular smooth muscle proliferation, fertility, vasodilation, cardiac contractility, macrophage activation</td>
<td>↑</td>
</tr>
<tr>
<td>PDE5</td>
<td>Is a well-established regulator of vascular smooth muscle contraction especially in lung and corpus cavemosum; is involved in the control of platelet aggregation; may regulate cGMP signaling in the brain</td>
<td>↑</td>
</tr>
<tr>
<td>PDE7</td>
<td>Has a role in T-cells and other inflammatory cells activation</td>
<td></td>
</tr>
<tr>
<td>PDE8</td>
<td>May be involved in T-cell activation and sperm function</td>
<td></td>
</tr>
<tr>
<td>PDE9</td>
<td>Has been postulated to regulate the NO-&gt;GMP signaling in brain</td>
<td></td>
</tr>
<tr>
<td>PDE10</td>
<td>Is considered a regulator of cGMP in the central nervous system and may be involved in the learning and memory processes</td>
<td></td>
</tr>
<tr>
<td>PDE11</td>
<td>May play a role in sperm development and function</td>
<td></td>
</tr>
</tbody>
</table>

PDE indicates phosphodiesterase.

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Guazzi M Circ Heart Fail 2008;1:272-280
PDE-5 Inhibition: Comparison of Acute Effects with Other Pulmonary Vasodilators

### Pulmonary Vasodilatation

<table>
<thead>
<tr>
<th></th>
<th>NO (inh.)</th>
<th>PGI (i.v.)</th>
<th>Sil (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>change in PVRI (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Pulmonary Selectivity

<table>
<thead>
<tr>
<th></th>
<th>NO (inh.)</th>
<th>PGI (i.v.)</th>
<th>Sil (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>change in PVR/SVR ratio (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Intrapulmonary Selectivity

<table>
<thead>
<tr>
<th></th>
<th>NO (inh.)</th>
<th>PGI (i.v.)</th>
<th>Sil (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>change in paO₂ (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Transpulmonary cGMP Release in HF Patients with High PVR: Acute Effects of Sildenafil (40 mg)

Melenowsky V et al. JACC 2009;54:595-600
Rat model of aortic banding for 9 weeks
In vivo lung microcirculation studies

Capillary remodeling
Capillary/Arterioles Wall Thick
Capillary NO release to ACh

Sham
CHF

B
C
D

ø <150 µm
ø 150-250 µm
ø 250-1000 µm

mean vascular wall thickness (µm)

mean vascular wall thickness (µm)

mean vascular wall thickness (µm)

Sham
CHF
CHF+
Sildenafil

Baseline Acethylcholine

Sildenafil Preserves Lung Endothelial Function and Prevents Pulmonary Vascular Remodeling in a Rat Model of Diastolic Heart Failure

Jun Yin, MD, PhD*; Marian Kukucka, MD*; Julia Hoffmann, MSc; Anja Sterner-Kock, DVM, PhD; Juergen Burhenne, MD, PhD; Walter E. Haefeli, MD, PhD; Hermann Kuppe, MD, PhD; Wolfgang M. Kuebler, MD, PhD

(Circ Heart Fail. 2011;4:198-206)
RV Shape

Sham

CHF

CHF + sild

RV Systolic Function

Pulm. Acceleration Time (ms)

TAPSE (mm)

sham

CHF

CHF+sil

#esc2012 cardio.org
Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction: a Target of Phosphodiesterase-5 Inhibition in a 1-year Study

Study Hypothesis

Pre-capillary pulmonary hypertension and RV function may benefit from chronic PDE5-inhibition

- Randomized, Double-blind, placebo-controlled trial
- **Primary Outcome:** Changes in pulmonary hemodynamics (PVR, mean PAP, mean PCWP, arterial elastance) and RV function (Frank Starling, MSEJR, TAPSE) @ 6 and 12 months

44 pts with hypertensive heart disease and signs and symptoms of HF (average LVEF 60±4 %)

Guazzi M et al Circulation 2011;124:164-174
### Effects of PDE5 Inhibition on Pulmonary Hemodynamics and RV Function in PH HFrEF

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th></th>
<th>Sildenafil</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
<td>12 Months</td>
<td>Baseline</td>
<td>6 Months</td>
<td>12 Months</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
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<tr>
<td>Mean RAP (mmHg)</td>
<td>23</td>
<td>22</td>
<td>24</td>
<td>23</td>
<td>11 * §</td>
<td>9 * §</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>37</td>
<td>38</td>
<td>40</td>
<td>39</td>
<td>22 * §</td>
<td>18 * §</td>
</tr>
<tr>
<td>Mean PWP (mmHg)</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>19 * §</td>
<td>18 * §</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>14</td>
<td>15</td>
<td>18</td>
<td>16</td>
<td>3.8 * §</td>
<td>3.3 * §</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>3.3</td>
<td>3.4</td>
<td>4.0 *</td>
<td>3.9</td>
<td>1.2 * §</td>
<td>1.0 * §</td>
</tr>
<tr>
<td>Pulm. Art. Elastance (mmHg/ml)</td>
<td>0.69</td>
<td>0.73</td>
<td>0.80</td>
<td>0.75</td>
<td>0.39 * §</td>
<td>0.36 * §</td>
</tr>
<tr>
<td><strong>RV function/dimensions</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RV maximal short axis</td>
<td>5.5</td>
<td>5.7</td>
<td>5.7</td>
<td>5.6</td>
<td>5.0 * §</td>
<td>5.0 * §</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>11</td>
<td>11</td>
<td>5.7</td>
<td>5.6</td>
<td>19 * §</td>
<td>20 * §</td>
</tr>
<tr>
<td>RV MSEJR, mL/sec</td>
<td>242</td>
<td>231</td>
<td>221</td>
<td>236</td>
<td>276 * §</td>
<td>275 * §</td>
</tr>
</tbody>
</table>

Adjusted p * <0.01 vs Placebo; p § 0.01 vs Baseline
Effects of PDE5 Inhibition on RV Contractility in HFpEF

Baseline

6 months

Stroke Volume (mL. beat⁻¹)

RV End-Diastolic Pressure (mmHg)

* Placebo

* Sildenafil

Placebo

Sildenafil

#esc2012 www.escardio.org
DOC? CAN YOU WRITE ME A PRESCRIPTION FOR SOME OF THAT VIAGRA

Say No!
Wait… and
RELAX
Phosphodiesterase-5 Inhibition to Improve Functional Status and LV Mass in HFrEF (Relax Trial)

- Study Design: Randomized, placebo-controlled, double blind
- Study Population: 190 pts with HFrEF > 50%
- Primary Endpoint: Exercise capacity (VO$_2$) at 24 w.
- Secondary Outcomes: peak VO$_2$ at 12 w, 6MWT at 12 and 24 w, Composite clinical score at 24 w
- TertiaryEndpoints: change in LV mass, LV diastolic function, PASP, neuroendocrine and renal function biomarkers

190 pts

- Placebo
- Sildenafil (20 mg x 3)
- Sildenafil (60 mg x 3)

12 weeks

24 weeks

September 2008

Clinical Trials.gov Identifier: NCT00763867
PH is an evolving and meaningful clinical manifestation of *HFpEF* that appears a long way far from a complete understanding and optimal treatment.

Modulation of NO pathway by PDE5 inhibition is promising due to the strong rationale and the high pulmonary selectivity.

The expectations on future therapeutic approaches may rise if pulmonary vascular disease may definitively emerge as viable therapeutic target in these patients.