Heart Failure with Preserved Ejection Fraction: Is there Hope for New Therapies?

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Professor, Duke-NUS Graduate Medical School Singapore
Senior Consultant, National Heart Centre Singapore
## Disclosure potential conflicts of interest

<table>
<thead>
<tr>
<th>Research contracts:</th>
<th>Boston Scientific, Bayer, Thermofisher, Medtronic, and Vifor Pharma</th>
</tr>
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<tr>
<td>Consulting:</td>
<td>Bayer, Novartis, Takeda, Merck, Astra Zeneca, Janssen Research &amp; Development, LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, Roche, and Amgen</td>
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<tr>
<td>Employment in industry:</td>
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</tr>
<tr>
<td>Stockholder of a healthcare company:</td>
<td>-</td>
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<tr>
<td>Owner of a healthcare company:</td>
<td>-</td>
</tr>
</tbody>
</table>
“No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.”
ESC Guidelines 2016

“No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.”

Is there hope?

5 mechanisms → therapies
LV diastolic dysfunction & left atrial hypertension
LV diastolic dysfunction

Population-based age-, sex-, body size- adjusted

![Graph showing indexed end-diastolic volume versus end-diastolic pressure for different conditions.](Lam Circulation 2007)
Left atrium

LA remodeling and dysfunction in HTN

[Bar charts showing LA volumes and emptying fraction for different conditions: Maximal, Diastasis, Minimal, Total, Passive, Active. Asterisks indicate statistical significance.]
REDUCE-LAP HF I (Phase 2)

Control group: Baseline vs. 1-month PCWP

IASD group: Baseline vs. 1-month PCWP

*P<0.05
**P<0.01
Pulmonary hypertension & RV dysfunction
Pulmonary Hypertension

High prevalence & prognostic impact of PH in HFpEF suggest an important pathophysiologic role

CHAMPION

A

Cumulative Heart Failure Hospitalizations

Control Group - Preserved EF

Treatment Group - Preserved EF

Days After Implant

Philip B. Adamson et al. Circ Heart Fail. 2014
RV-PA coupling

**TAPSE**

Composite endpoint all-cause mortality & HF hospitalization

- **TAPSE ≥ 1.4cm**
- **TAPSE < 1.4cm**

\[ p = 0.019 \]

**TAPSE/PASP**

Composite endpoint all-cause mortality & HF hospitalization

- **TAPSE/PASP > 0.48**
- **TAPSE/PASP ≤ 0.48**

\[ p < 0.001 \]
RV dysfunction & mortality

A

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight, %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke</td>
<td>1.16 (1.00-1.34)</td>
<td>48.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Mohammed</td>
<td>1.28 (1.10-1.47)</td>
<td>42.9</td>
<td>0.0004</td>
</tr>
<tr>
<td>Pellicori</td>
<td>2.01 (1.47-2.70)</td>
<td>8.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pooled</td>
<td>1.26 (1.16-1.38)</td>
<td>100.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HR (95% CI) per 5mm↓ TAPSE

B

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight, %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke</td>
<td>1.13 (1.01-1.25)</td>
<td>47.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Melenovsky</td>
<td>1.87 (1.40-1.98)</td>
<td>17.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>Shah</td>
<td>1.01 (0.92-1.12)</td>
<td>35.3</td>
<td>NS</td>
</tr>
<tr>
<td>Pooled</td>
<td>1.15 (1.08-1.23)</td>
<td>100.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HR (95% CI) per 5%↓ FAC

Gorter Eur J Heart Fail 2016
β-agonists in HFpEF/PH

![Graphs showing changes in pulmonary arterial pressures and other hemodynamic parameters in controls and HFpEF patients with and without drug intervention.](image-url)
Plasma volume expansion
Obese HFpEF

$r = 0.56$  
$P < 0.0001$

Group $p = 0.002$  
Interaction $p = 0.5$

$P_{interaction} = 0.007$  
Obese HFpEF  
$r = 0.22$, $p = 0.03$

$P_{interaction} = 0.008$  
Obese HFpEF  
$r = 0.27$, $p = 0.006$

$P_{interaction} = 0.008$  
Non-obese HFpEF  
$r = -0.17$, $p = 0.09$

$P_{interaction} = 0.008$  
Non-obese HFpEF  
$r = -0.11$, $p = 0.3$
Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial

Dalane W. Kitzman, MD; Peter Brubaker, PhD; Timothy Morgan, PhD; Mark Haykowsky, PhD; Gregory Hundley, MD; William E. Kraus, MD; Joel Eggebeen, MS; Barbara J. Nicklas, PhD
Role for SGLT2i?

SGLT2, sodium-glucose co-transporter-2


Empagliflozin is not indicated for the treatment of heart failure or renal disease; empagliflozin is not indicated in all countries for CV risk reduction.

The pathways shown represent not yet proven hypotheses and may not apply to individual patients.

The effects shown for renal function is based on the long-term results of empagliflozin versus placebo in EMPA-REG OUTCOME.

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SGLT2 inhibition

Glucose removal

Na+ removal

Osmotic diuresis

Metabolism

Sodium

Possible cardio-renal effects

Cardiac function

Preload

Afterload

Cardiometabolic efficiency

Arrhythmia

Arterial wall structure/function

Renal function

Renal events

CV death

Hospitalisation for heart failure

CV/renal outcomes observed in EMPA-REG OUTCOME
**EMPEROR-Reduced and EMPEROR-Preserved heart failure outcome trials**

**Phase III randomised double-blind placebo-controlled studies**

**Aim:** To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with reduced\(^1\) or preserved\(^2\) ejection fraction

**Population:** T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)

---

**EMPEROR-Reduced\(^1\)**
- LVEF ≤40%
- Planned recruitment: 2850 patients
- Empagliflozin 10 mg qd + SoC*
- Placebo qd + SoC*
- Estimated follow-up ~38 months (event-driven)

**EMPEROR-Preserved\(^2\)**
- LVEF >40%
- Planned recruitment: 4126 patients
- Empagliflozin 10 mg qd + SoC*
- Placebo qd + SoC*
- Estimated follow-up ~38 months (event-driven)

*Guideline-directed medical therapy
HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SoC, standard of care
1. ClinicalTrials.gov NCT03057977; 2. ClinicalTrials.gov NCT03057951
Asian vs White HF

Singapore Asians vs Swedish whites

Bank, … Lam. JACC HF 2016
Comorbidity clusters in ASIAN-HF

**Elderly/AF**
- Characteristics: Eldest with AF and high rates of previous stroke
- More often HFpEF
- Concentric remodeling

**Metabolic**
- Characteristics: High prevalence of obesity, hypertension and diabetes
- More often HFpEF
- Concentric remodeling

**Young**
- Characteristics: Few comorbidities
- More often HFrEF
- Eccentric hypertrophy
- Best outcomes
- Best effect of medication

**Ischemic**
- Characteristics: Male patients with CAD and ischemic etiology of HF
- More often HFrEF
- Eccentric hypertrophy
- 2nd worst outcomes

**Lean Diabetic**
- Characteristics: Most often diabetic with low BMI.
- More often HFpEF
- Concentric hypertrophy
- Worst outcomes and quality of life

Tromp Submitted 2017
Systemic inflammation & endothelial dysfunction
EDITORIAL COMMENT

Endothelial Dysfunction

A Pathophysiologic Factor in Heart Failure With Preserved Ejection Fraction*

Carolyn S. P. Lam, MBBS, MS,†
Dirk L. Brutsaert, MD, PhD‡

Singapore; and Antwerp, Belgium
Endothelial dysfunction: Highly prevalent in HFpEF

Prevalence of endothelial dysfunction (RHI<2.0):
- 0% in controls, 28% in HTN, 42% in HFpEF

Borlaug JACC 2010
Endothelial dysfunction: Prognostic impact in HFpEF

Akiyama JACC 2012
Comorbidities

Microvascular inflammation
Endothelial activation

↓NO & other factors

EndMT

Collagen

Cardiomyocyte

↓cGMP
ΔTitin phosphorylation
Microvascular ischemia
Concentric LV remodeling

HFrEF

Endothelial cell

Collagen

Cardiomyocyte

Direct myocardial injury
Cell necrosis & apoptosis
Eccentric LV remodeling

Neuroendocrine activation

HFrEF

Adapted from: Paulus and Tschope J Am Coll Cardiol 2013;62:263-71

Lam and Lund Heart 2016;
Cardiac inflammation & fibrosis in human HFpEF

HFpEF (n=20) and controls (n=8) studied with conductance catheter and endomyocardial biopsy

Positive correlation between cardiac collagen, inflammatory cells, and diastolic dysfunction suggests a direct influence of inflammation on fibrosis triggering diastolic dysfunction

Role of TGFβ1 in transdifferentiation of fibroblasts to myofibroblasts, ↑collagen synthesis
Interleukin-1 blockade in HFpEF: D-HART Pilot Trial

Cross-over RCT in 12 HFpEF with plasma CRP > 2 mg/l
Microvascular endothelial activation & oxidative stress in HFpEF

Franssen JACC HF 2015
Cardiomyocyte stiffness & low myocardial cGMP-PKG activity

Franssen JACC HF 2015
Van Heerebeek Circulation 2012
Targeting Endothelial Signalling Pathways

Endothelial cell

LAMINAR SHEAR FORCES

Serelaxin

relaxin-2

pro-NRG-1

NRG-1 like substances
GGF-2 & EGF-binding domain

NRG-1

ErbB2

ErbB4

Kinase

Kinase

sGC stimulators
sGC activators

sGC

NO donors

NO

NOS-3

NEP inhibitors
LCZ696

Breakdown products
NEP

Natriuretic peptides

Neseritide Ularitide

Cardiomyocyte/smooth muscle cell

5’GMP

pGC

cGMP

PDE5

PKG

PDE5 inhibitors

Lim, Lam, Segers, Brutsaert, De Keulenaer Eur Heart H 2015
Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

A Average Daily Accelerometer Units in 120-mg Dose Phase

B Hours of Activity per Day in 120-mg Dose Phase

C Average Daily Accelerometer Units in Three Dose Phases Combined

- Placebo
- Isosorbide Mononitrate
- Treatment Difference

P-values indicated at the bottom of each bar chart.
Sodium Nitrite Improves Exercise Hemodynamics and Ventricular Performance in Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD, Katlyn E. Koepp, BS, Vojtech Melenovsky, MD, PhD
One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction

Joel Eggebeen, MS,a Daniel B. Kim-Shapiro, PhD,b,c Mark Haykowsky, PhD,d Timothy M. Morgan, PhD,e Swati Basu, PhD,b,c Peter Brubaker, PhD,c,f Jack Rejeski, PhD,c,f Dalane W. Kitzman, MDa,c

![Graph showing the effect of beetroot juice on plasma nitrite and exercise time.](image)
Targeting Endothelial Signalling Pathways

NRG-1 like substances (GGF-2 & EGF-binding domain)

LAMINAR SHEAR FORCES

pro-NRG-1

Serelaxin

NOS-3

NO donors

NEP inhibitors (LCZ696)

Breakdown products

Natriuretic peptides

Neseritide Ularitide

NRG-1

ErbB2

ErbB4

Kinase

sGC stimulators

sGC activators

AKT

ERK

NOS-3

NO

cGMP

5’GMP

PKG

PDE5

PDE5 inhibitors

Cardiomyocyte/smooth muscle cell

Lim, Lam, Segers, Brutsaert, De Keulenaer Eur Heart J 2015
Reduction in NT-proBNP from baseline to Week 12 was significantly greater with LCZ696 (200 mg BID) compared with valsartan (160 mg BID) (p=0.005).

<table>
<thead>
<tr>
<th>NT-proBNP (geometric mean)</th>
<th>LCZ696 (n=134)</th>
<th>Valsartan (n=132)</th>
<th>LCZ696 vs valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, pg/mL (95% CI)</td>
<td>783 (670, 914)</td>
<td>862 (733, 1,012)</td>
<td>0.77* (0.64, 0.92) p=0.005</td>
</tr>
<tr>
<td>Week 12, pg/mL (95% CI)</td>
<td>605 (512, 714)</td>
<td>835 (710, 981)</td>
<td></td>
</tr>
</tbody>
</table>

*0.77=ratio of the change from baseline treatment effect between LCZ696 and valsartan. LCZ696 reduced NT-proBNP 23% more than valsartan with a p value of 0.005.

Solomon et al. Lancet 2012;380:1387–95
# 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  
<table>
<thead>
<tr>
<th></th>
<th>2 years 9 months enrollment; estimated 2 years follow-up</th>
</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 pts 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  
|            | C. Lam, J. Ge |
Targeting Endothelial Signalling Pathways

**endothelial cell**

- Serelaxin
- Laminar shear forces
  - pro-NRG-1
  - NRG-1 like substances (GGF-2 & EGF-binding domain)
- NO donors
- NEP inhibitors (LCZ696, Natriuretic peptides, Nesiritide, Ularitide)

**Cardiomyocyte/smooth muscle cell**

- NRG-1
  - ErbB2, ErbB4
  - Kinase
  - NRG-1
  - sGC stimulators, sGC activators
- NOS-3
- AKT, ERK
- NO
- cGMP
- pGC
- 5'GMP
- PKG
- PDE5
- PDE5 inhibitors
SOCRATES-Preserved
Primary endpoints
No effect on log NT-proBNP or LAV at 12 weeks vs placebo

Data are mean ± standard error for the per-protocol analysis set

Presented by B. Pieske at HF Congress 2016
SOCRATES-Preserved
Pre-specified exploratory endpoint: Patient-reported health status

Change from baseline in KCCQ clinical summary score

Change from week 4 in KCCQ clinical summary score at week 12

Minimum Clinically Important Difference = 5 points

Data are mean ± standard error for the full analysis set excluding those subjects with incorrectly assigned doses

Presented by B. Pieske at HF Congress 2016
Systemic & myocardial signaling in HFpEF

Comorbidities
- Metabolic syndrome
  - Obesity
  - Type 2 DM
  - Hypertension
- Renal insufficiency

CRP, IL1RL1, GDF15

Systemic inflammation

Multiorgan involvement

Endothelium-cardiomyocyte signaling

ONOO⁻, ROS, NO, VCAM, E-selectin

Leukocytes

Fibroblasts

Myofibroblasts

Collagen

Cardiomyocytes

\[ \Delta(A-V_{O_2})_{EX} \]

\[ \text{Na}^+ \text{ retention} \]

\[ \text{sGC} \]

\[ \text{cGMP} \]

\[ \text{F}_{\text{passive}} \]

\[ \text{PKG} \]

Hypertrophy

Ex-DHF-P

A

Change in peak VO2 [mL/min/kg]

Training  Control

*** P<0.001

C

Change in E/e' ratio

Training  Control

*** P<0.001

D

Change in left atrial volume index [mL/m²]

Training  Control

*** P<0.001
Targeting Endothelial Signalling Pathways

**endothelial cell**

- **Serelaxin**
- **NOS-3**
- **NO donors**
- **NEP inhibitors**
- **LCZ696**
- **Breakdown products**
- **NGF-1 like substances**
- **EGF-binding domain**
- **LAMINAR SHEAR FORCES**
- **pro-NRG-1**
- **NRG-1**
- **ErbB2**
- **ErbB4**
- **sGC stimulators**
- **sGC activators**
- **AKT**
- **ERK**
- **NOS-3**
- **cGMP**
- **PKG**
- **PDE5**
- **5’GMP**
- **PDE5 inhibitors**

Lim, Lam, Segers, Brutsaert, De Keulenaer Eur Heart H 2015
Sildenafil in HFpEF-PH: Guazzi

Guazzi et al., Circulation 2011
Sildenafil in HFpEF (regardless of PH): RELAX

Table 3. Primary, Secondary, and Safety End Points

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min</td>
<td>94 94</td>
<td>−0.20 (−0.70 to 1.00) 95</td>
<td>−0.2 (−1.70 to 1.11) 90</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical rank score, mean</td>
<td>94</td>
<td>95</td>
<td>94 95</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 24 wk, median (IQR), m</td>
<td>95</td>
<td>90</td>
<td>15.0 (−26.0 to 45.0) 5.0 (−37.0 to 55.0)</td>
</tr>
<tr>
<td>Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min</td>
<td>96</td>
<td>97</td>
<td>0.03 (−1.10 to 0.67) 0.01 (−1.35 to 1.25)</td>
</tr>
<tr>
<td>Change in 6-minute walk distance at 12 wk, median (IQR), m</td>
<td>96</td>
<td>99</td>
<td>18.0 (−14.5 to 48.0) 10.0 (−25.0 to 36.0)</td>
</tr>
<tr>
<td>Components of clinical rank score at 24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, No. (%)</td>
<td>103</td>
<td>113</td>
<td>0 3 (3)</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular or renal cause, No. (%)</td>
<td>103</td>
<td>113</td>
<td>13 (13) 15 (13)</td>
</tr>
<tr>
<td>Change in MLHFQ, median (IQR)</td>
<td>91</td>
<td>91</td>
<td>−8 (−21 to 5) −8 (−19 to 0)</td>
</tr>
<tr>
<td>Safety end points, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>103</td>
<td>113</td>
<td>78 (76) 90 (80)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>103</td>
<td>113</td>
<td>16 (16) 25 (22)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

a A mean value of 95 in each group is expected under the null hypothesis of no treatment effect.

b Site investigator identified causes of death were sudden death (n=1), progressive cardiorenal failure (n=1), and noncardiovascular (n=1).
Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial

![Graph showing mean PAP (mmHg) for Sildenafil and Placebo at Baseline and Week 12.]

- Sildenafil: Treatment effect $-2.4$ (95% CI $-4.5$ to $-0.3$)
- Placebo: Treatment effect $-4.7$ (95% CI $-7.1$ to $-2.3$)
PAH vs. PH in Heart Failure: Spectrum of Phenotypes and Therapeutic Consequences

**Severity of PH**
- **DPG**
- **PVR**

**Cpc-PH**
- Severe PH
- RV Function ↓
- Perhaps
  - Guazzi 2011
  - COMPERA 2015

**Ipc-PH**
- Moderate PH
- Normal RV Function
- No
  - Hoendermis
  - EHJ 2015

**No PH Therapy**
- RELAX (JAMA 2013)
- NEAT (NEJM 2015)

**Targeted PAH Therapy**
- "pure"
- "typical"
- "atypical"

**PAH**
- "pure" "typical" "atypical"

**HF**
- No PH
- Normal RV Function

Numerous PAH RCTs
- AMBITION Ex-PAS
Comorbidities

Endothelial cell

Microvascular inflammation

Endothelial activation

↓NO & other factors

EndMT

Collagen

Cardiomyocyte

↓cGMP

ΔTitin phosphorylation

Microvascular ischemia

Concentric LV remodeling

HFpEF

HFrEF

Endothelial cell

Collagen

Cardiomyocyte

Direct myocardial injury

Cell necrosis & apoptosis

Eccentric LV remodeling

Neuroendocrine activation

Adapted from: Paulus and Tschope J Am Coll Cardiol 2013;62:263-71
Microvascular rarefaction

HFpEF (n=124) & controls (n=104 non-cardiac death, no HF) from Olmsted County who underwent autopsy

![Graph showing MVD (vessels per mm²) and % Fibrosis for Control and HFpEF groups.](image)

*Mohammad Circulation 2015*
Microvascular ischemia

Van Empel et al. JAMA 2014
Potential cardiometabolic targets in HFpEF
Fibrosis & Titin changes
Passive myocardial stiffness, titin & collagen in HTN+HFpEF
TOPCAT

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)

Russia, Rep Georgia
HR=1.10 (0.79-1.51)
Targeting lysyl oxidase-like 2

- **LOXL2** expression and distribution in **Control** and **HFpEF** groups.

- **Cross-linked collagen** levels in relation to **LVEDP**, **LOXL2 area fraction**.

- **Correlation** between **COL1A** expression and **Echocardiographic E/E' ratio**.

- **Fibrosis** percentage in various treatment conditions.

- **Schematic** representation of the signaling pathways involved in the study.

Titin

Increasing titin’s compliance via inhibition of the splicing factor RBM20 (triggered by raloxifene)
HFpEF: Hope for new therapies

Mechanisms to therapies

- LV diastolic dysfunction & LA hypertension
- Pulmonary hypertension & RV dysfunction
- Plasma volume overload
- Systemic endothelial inflammation
- Fibrosis & titin changes
Thank you

Circulation on the Run
PODCAST SERIES