Diagnostic pathways and novel treatment options in HFpEF

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed

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Definition of heart failure

Diagnostic pathways and novel treatment options in HFpEF

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2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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European Heart Journal (2016) **37**, 2129-2200 - doi:10.1093/eurheartj/ehw 128

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Definition of heart failure

With preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		**HFrEF**	**HFmrEF**	**HFpEF**
CRITERIA	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.).	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.).

European Heart Journal (2016) **37**, 2129-2200 - doi:10.1093/eurheartj/ehw 128

Diagnosis of Heart Failure with preserved Ejection Fraction (HFpEF)

Diagnostic pathways and novel treatment options in HFpEF

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HFpEF

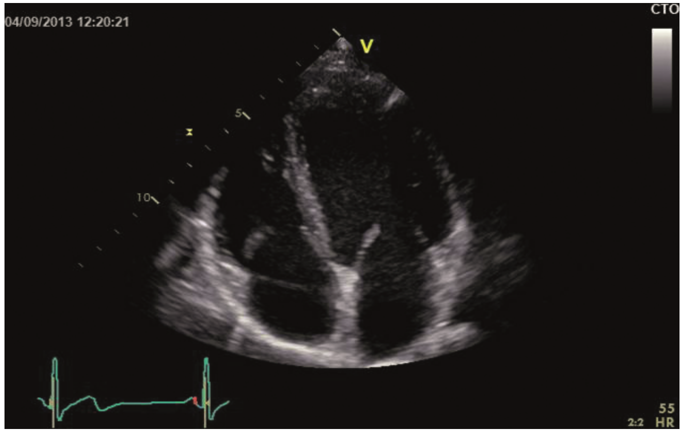
- Patients with HFpEF are a heterogenous group with various underlying aetiologies and pathophysiological abnormalities
- Diagnosis of HFpEF remains challenging
- LVEF is normal and signs and symptoms of HF are often non-specific and do not discriminate well between HF and other clinical conditions
- Diagnosis of HFpEF requires the following conditions to be fulfilled:
  - Presence of symptoms and/or signs of HF
  - Preserved EF (LVEF ≥ 50% or 40-49% for HFmrEF)
  - Elevated levels of NPs (BNP > 35 pg/ml and/or NT-ProBNP > 125 pg/ml
  - Objective evidence of other cardiac functional and structural alterations underlying HF

Eur Heart J 2016; 37:2129-2200

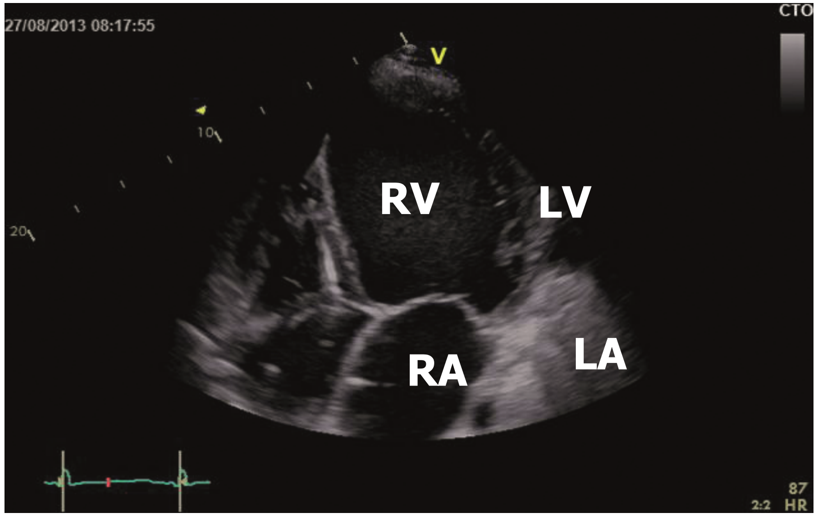
Symptoms and signs typical of heart failure

Symptoms	Signs
Typical	**More spécific**
• Breathlessness • Orthopnoea • Paroxysmal nocturnal dyspnoea • Reduced exercise tolerance • Fatigue, tiredness, increased time to recover after exercise • Ankle swelling	• Elevated jugular venous pressure • Hepatojugular reflux • Third heart sound (gallop rhythm) • Laterally displaced apical impulse
Less typical	**Less specific**
• Nocturnal cough • Wheezing • Bloated feeling • Loss of appetite • Confusion (especially in the elderly) • Depression • Palpitations • Dizziness • Syncope • Bendopnea	• Weight gain (>2 kg/week) • Weight loss (in advanced HF) • Tissue wasting (cachexia) • Cardiac murmur • Peripheral oedema (ankle, sacral, scrotal) • Pulmonary crepitations • Reduced air entry and dullness to percussion at lung bases (pleural effusion) • Tachycardia • Irregular pulse • Tachypnoea • Cheyne Stokes respiration • Hepatomegaly • Ascites • Cold extremities • Oliguria • Narrow pulse pressure

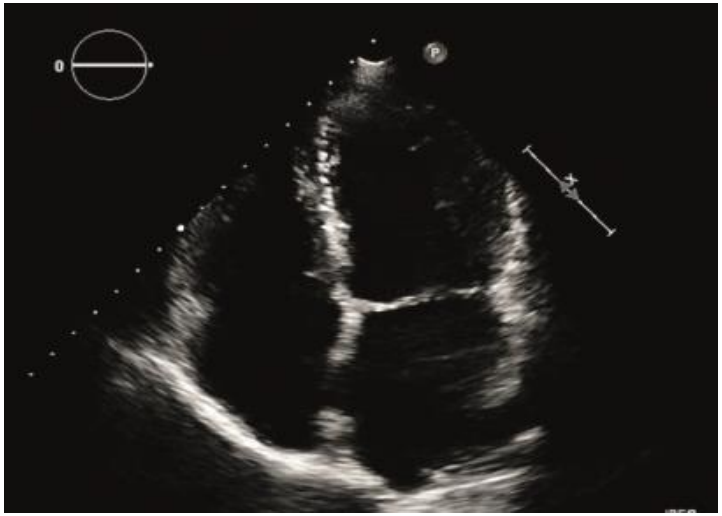
Heart Failure - Echocardiography



Normal heart



Dilatation of left chamber with impaired LV function - systolic impairment



Patient with diastolic impairment. Left atrium is enlarged

HFrEF **2012 ESC GL 2012** **HFpEF**

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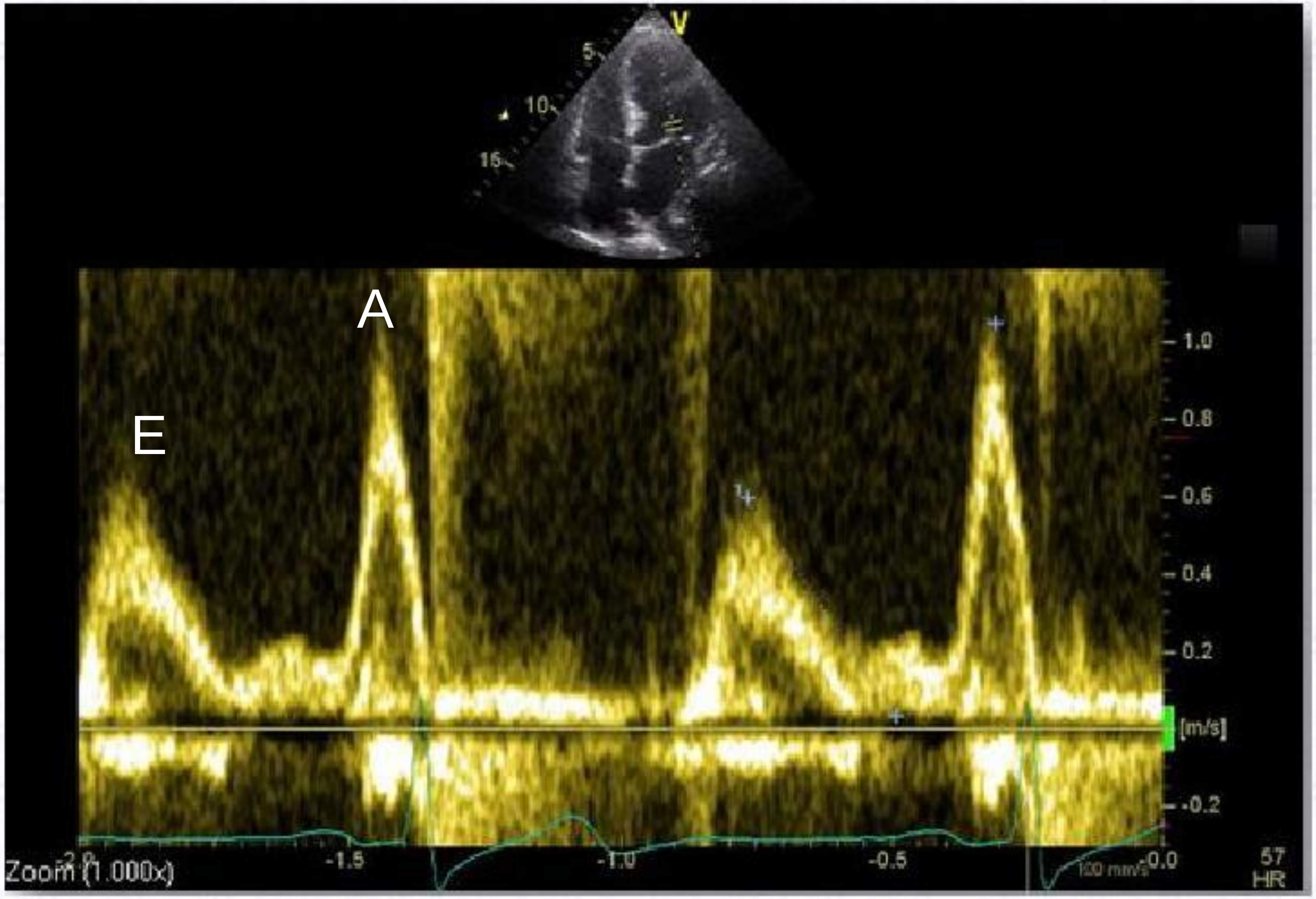
Functional or Structural Cardiac abnormalities related to HF-PEF

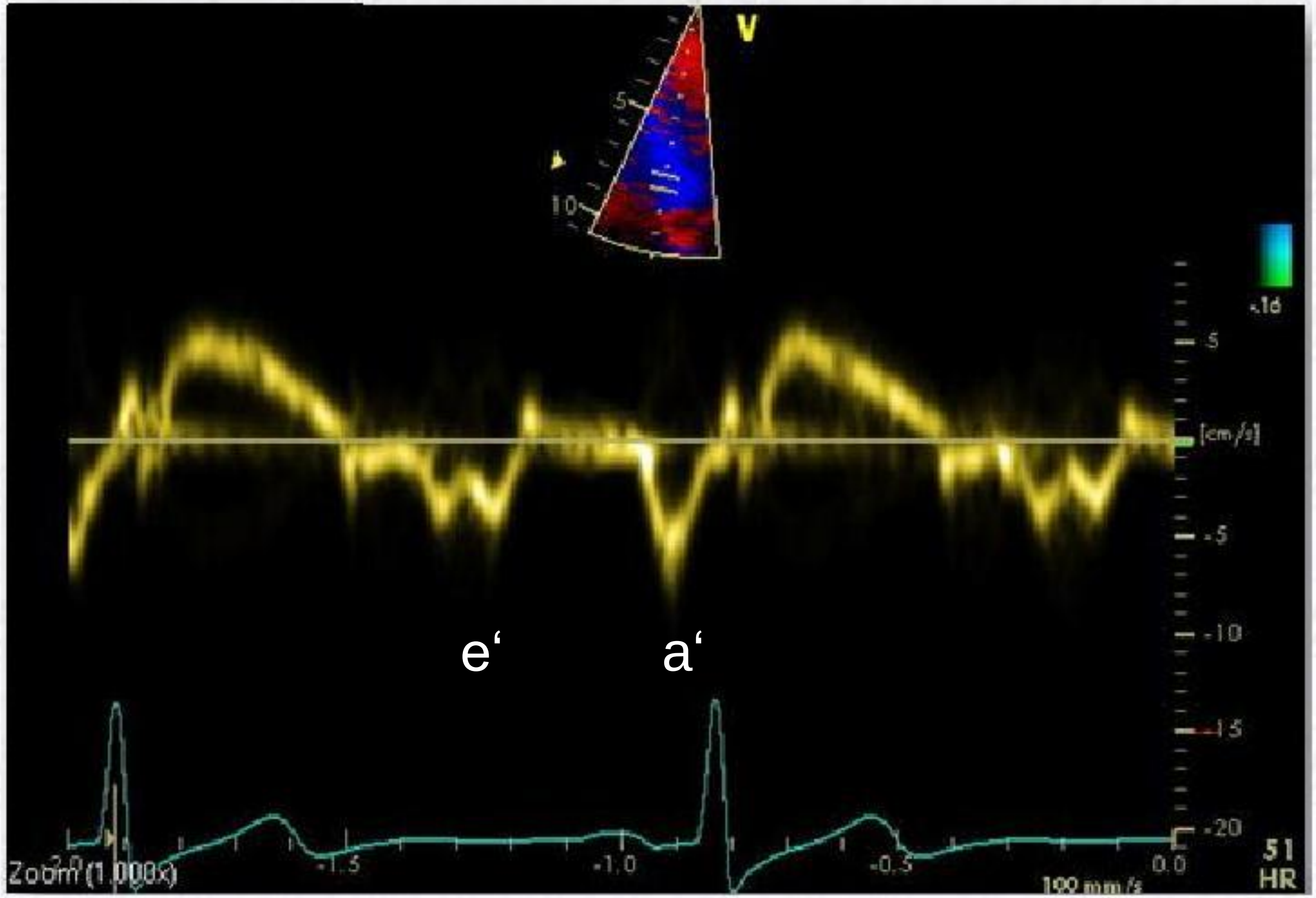
- Abnormalities of the mitral inflow pattern, tissue velocities (e'), or the E/e' ratio (Indicate degree of LV filling dysfunction and estimate filling pressures).
- Left atrial volume index: increased (volume >34 mL/m^2) Increased LV filling pressure (past or present) or mitral valve disease.
- LV mass index: increased: >95 g/m^2 in women and >115 g/m^2 in men.

European Heart Journal (2012) 33, 1787–1847
European Journal of Heart Failure (2012) 14, 803–869

Mitral Inflow Pattern

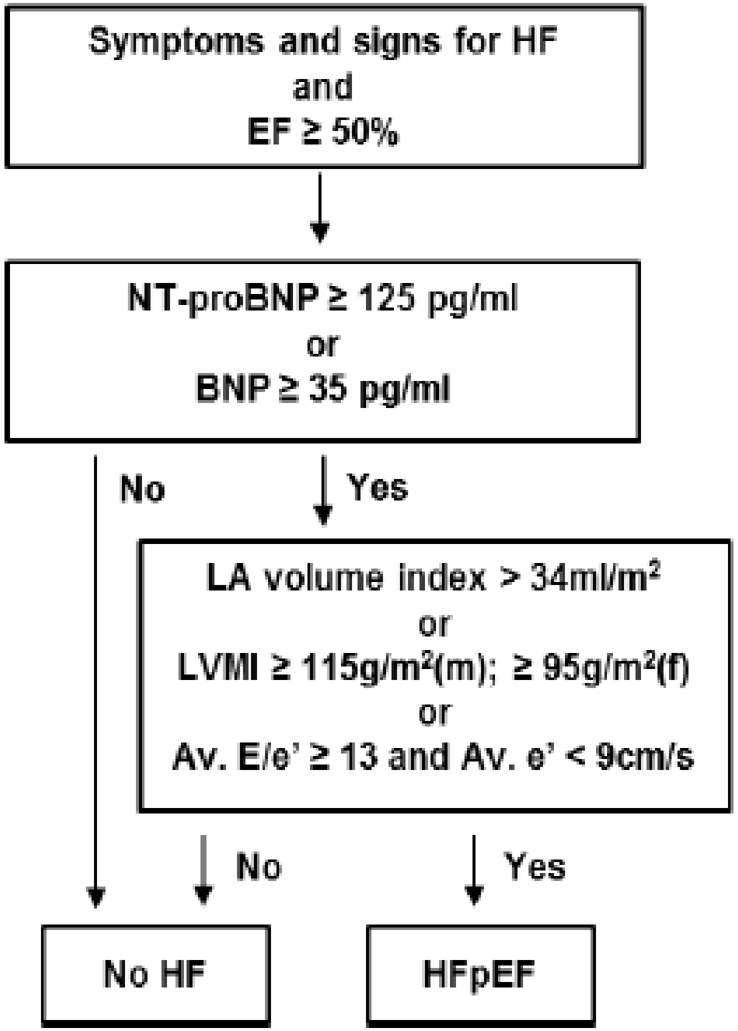


Tissue Doppler Imaging



European Heart Journal (2012) 33, 1787–1847
European Journal of Heart Failure (2012) 14, 803–869

ESC 2016 algorithm for HFpEF diagnosis



H_2FPEF Diagnostic Score

- Consecutive patients with unexplained dyspnea referred for hemodynamic exercise testing 2006-2016 to Mayo Clinic
- Gold standard HFpEF diagnosis: PCWP ≥ 15 mmHg at rest or ≥ 25 mm Hg during exercise
- Scoring system developed to distinguish HFpEF from non-cardiac dyspnea in 414 patients (64% HFpEF)

	OR (95% CI)	β Estimate	*P* Value
Multivariable model (AICc, 393.72; AUC, 0.854; *P*<0.0001)			
Atrial fibrillation	4.59 (1.84–13.22)	1.52	0.0007
Body mass index >30 kg/m²	2.90 (1.68–5.09)	1.07	0.0001
Age >60 y	2.12 (1.12–3.82)	0.75	0.01
Treatment with ≥2 antihypertensives	1.78 (1.04–3.02)	0.58	0.03
E/e′ ratio >9	1.87 (1.07–3.26)	0.63	0.03
Pulmonary artery systolic pressure >35 mm Hg	1.74 (0.92–3.35)	0.55	0.09
Diabetes mellitus or prediabetes	1.67 (0.97–2.87)	0.51	0.06
LA volume index >30 mL/m²	1.59 (0.88–2.88)	0.47	0.1
Chronic kidney disease stage 3 or greater	1.46 (0.66–3.30)	0.37	0.4
NT-proBNP >275 pg/mL	1.26 (0.66–2.41)	0.23	0.5

Reddy YNV et al. Circulation 2016;138:861-870

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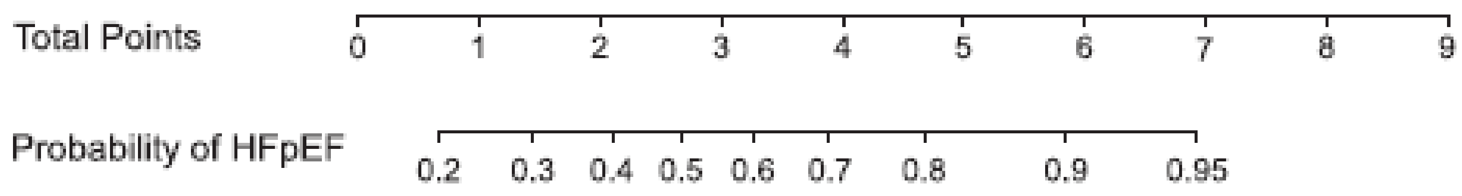
H_2FPEF Diagnostic score

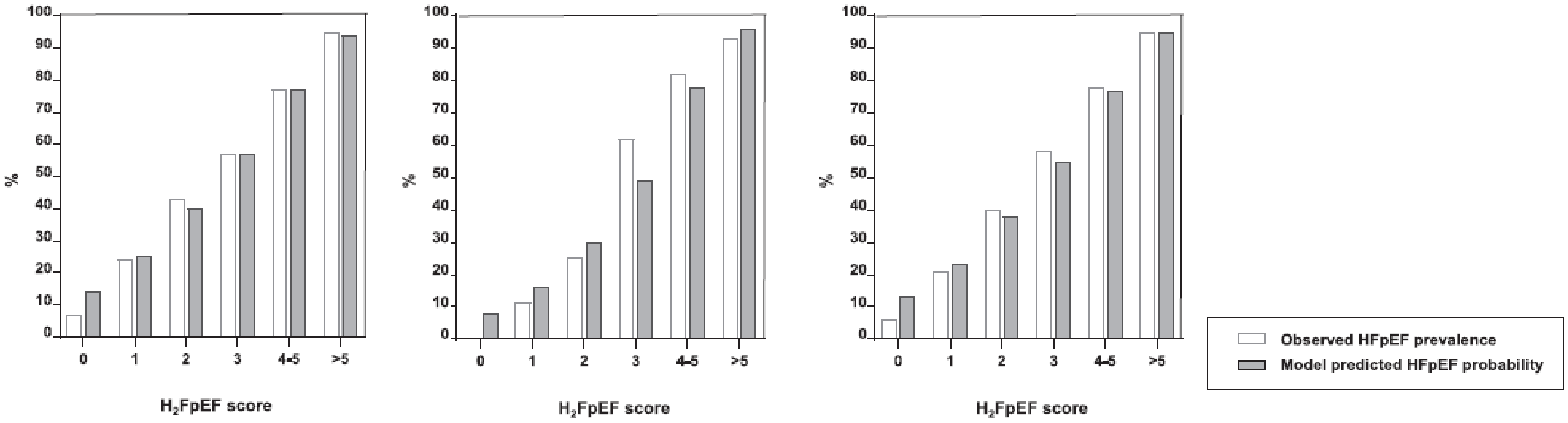
	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
	H_2FPEF score		Sum (0-9)



Reddy YNV et al. Circulation 2016;138:861-870

H_2FPEF Diagnostic score Calibration & Validation

Derivation	Validation	Overall



N	41	34	46	58	115	120

N	9	9	12	13	22	27

N	50	43	58	71	134	150

- Validated in a separate test cohort of 100 patients (61% HFpEF)
- Strong discrimination of HFpEF from controls (AUC 0,84, 95% CI:0.80-0.88)
- Better discriminated HFpEF from controls compared to 2016 ESC Guidelines (AUC + 0.169) or 2007 ESC criteria (+0.173; both $p<0.001$)

Reddy YNV et al. Circulation 2016;138:861-870

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ESC HFA-PEFF Score

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7cm/s* or lateral e' < 10cm/s* *or* Average E/e' ≥ 15	LAVI > 34 ml/m² + *or* LVMI ≥ 149/122 g/m² (m/w) and RWT > 0.42 #	NT-proBNP > 220 pg/ml *or* BNP > 80 pg/ml	NT-proBNP > 660 pg/ml *or* BNP > 240 pg/ml
Minor	Average E/e' 9 - 14 *or* TR velocity > 2.8 m/s *or* GLS < 16%	LAVI 29-34 ml/m² *or* LVMI > 115/95 g/m² (m/w) *or* RWT > 0.42 *or* LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml *or* BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml *or* BNP 105-240 pg/ml

Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2–4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Pieske B et al. Presented at ESC HF Congress Vienna 2018

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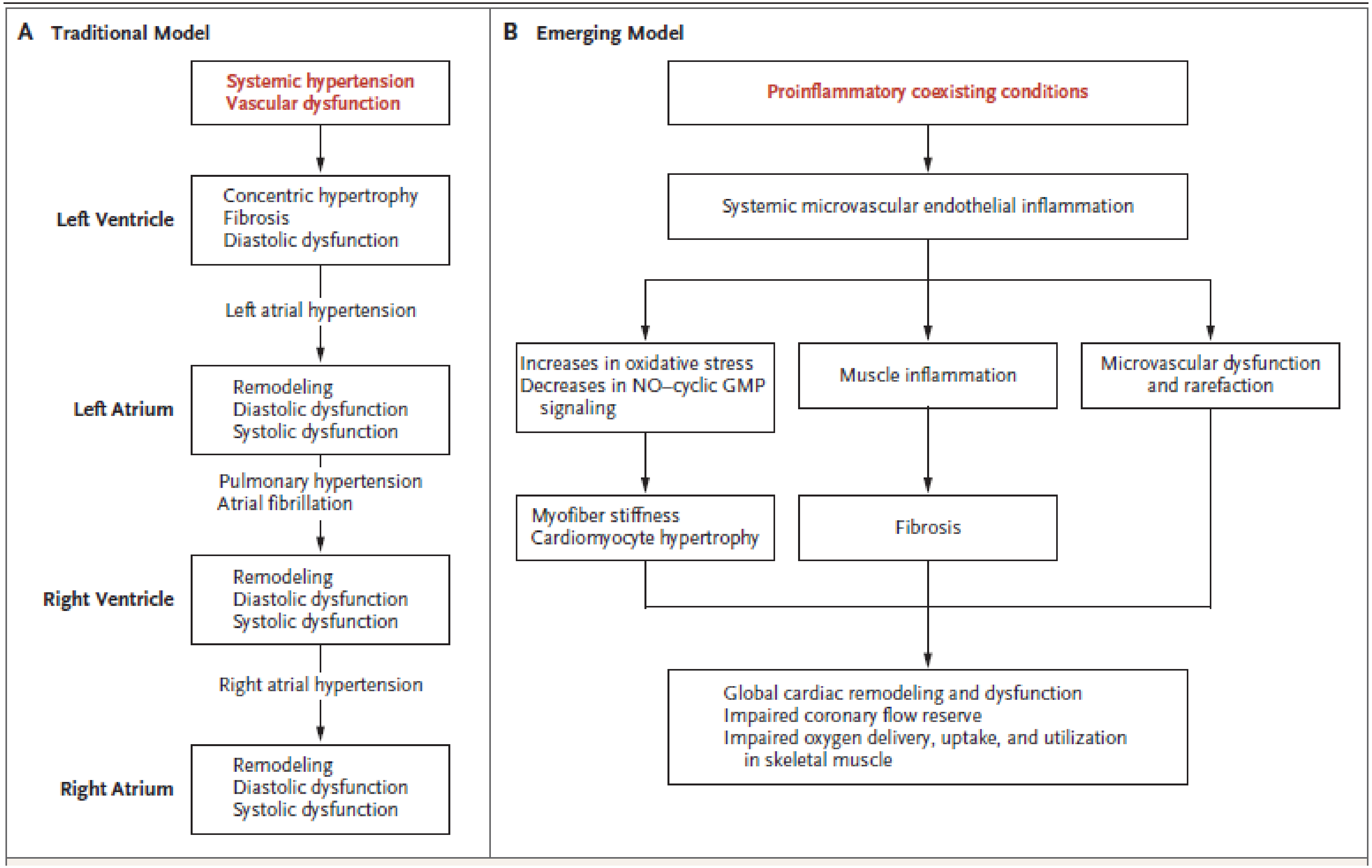
Pathophysiological model of HFpEF



Redfield MM. Heart Failure with preserved Ejection Fraction. NEJM 2016;375:1868-1877 (Review)

Drug Treatment for Heart Failure with preserved Ejection Fraction (HFpEF)

Diagnostic pathways and novel treatment options in HFpEF

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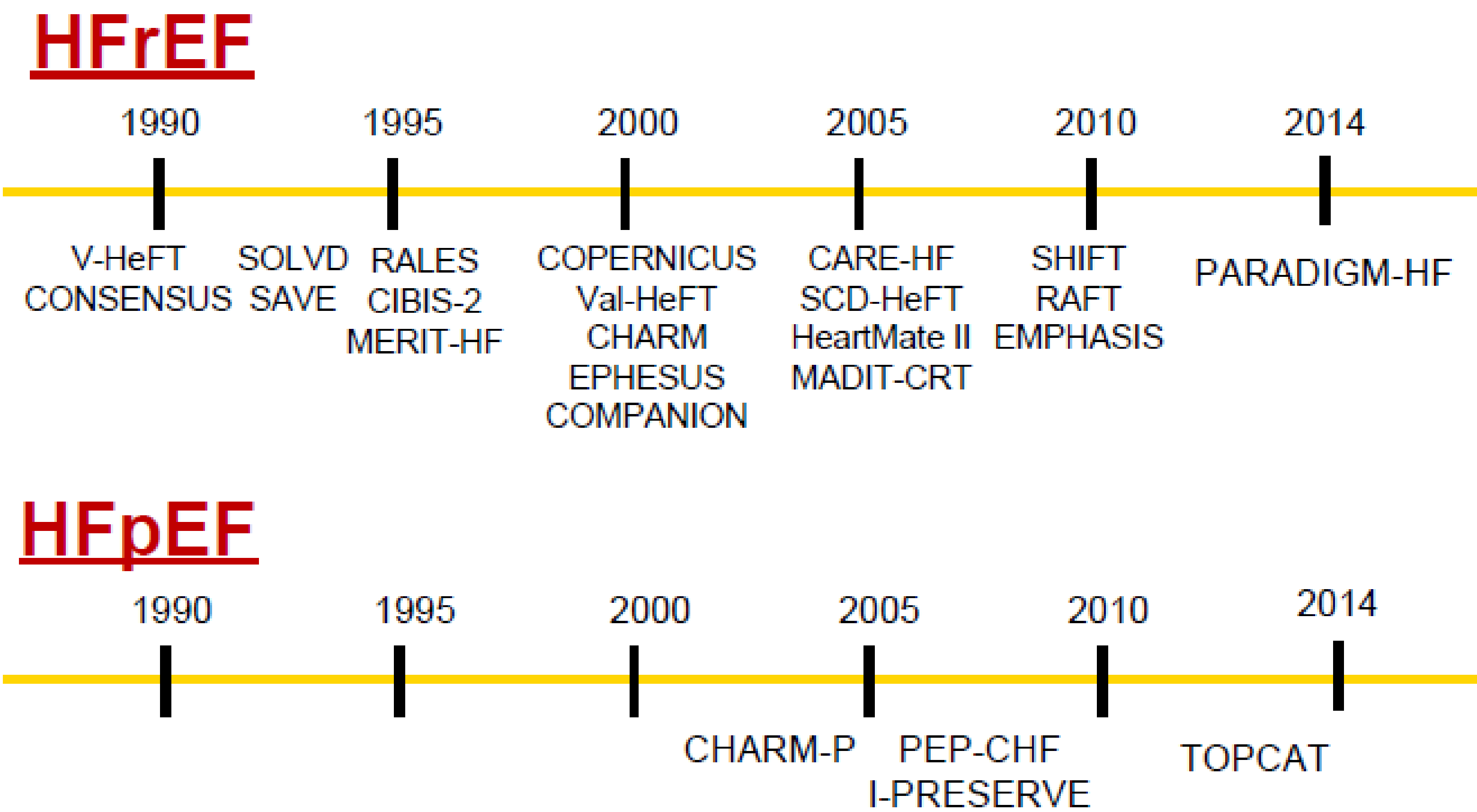
Landmark Heart Failure RCTs

Landmark Heart Failure RCTs



Solomon DS. Presented at ESC Congress Munich 2018

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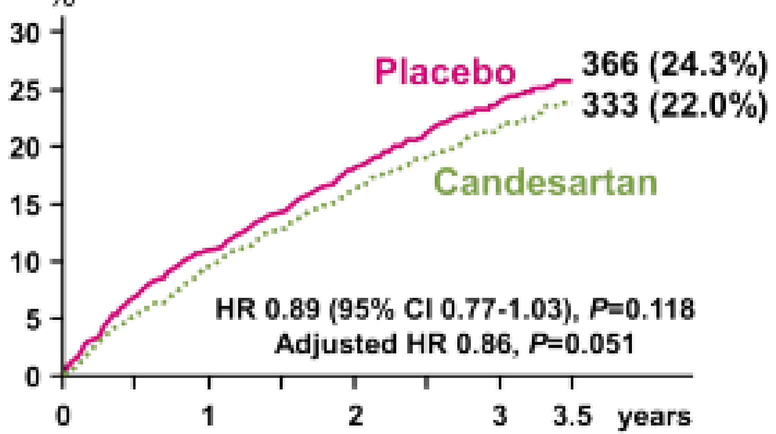
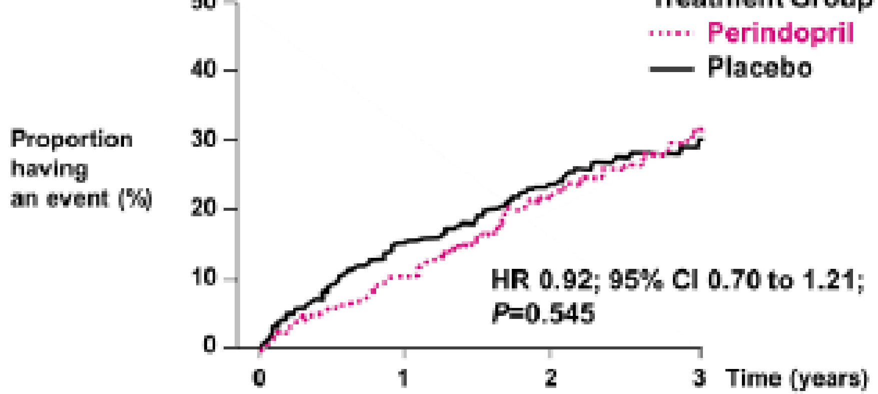
Outcome Trials in HFpEF

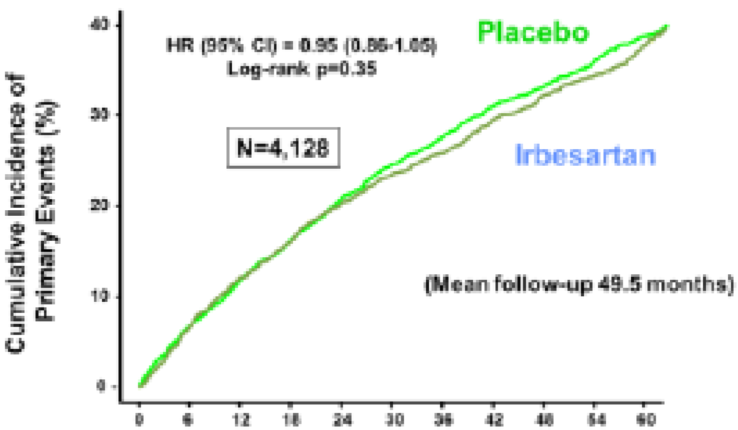
CHARM-Preserved



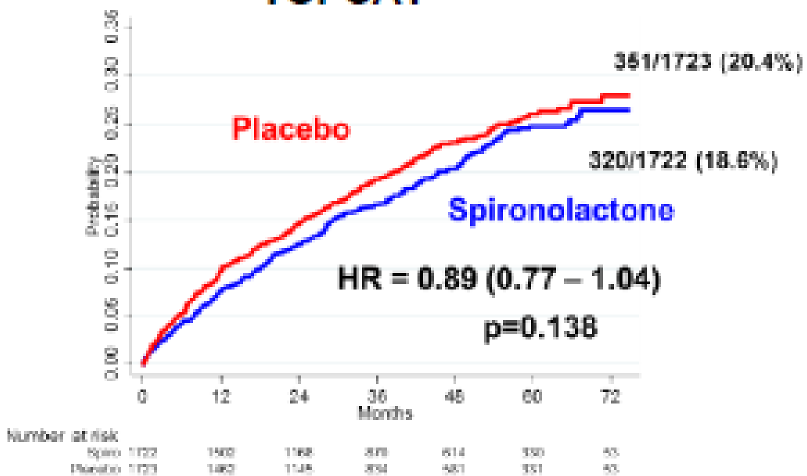
PEP-CHF



I-PRESERVE



TOPCAT



Solomon DS. Presented at ESC Congress Munich 2018

Pharmacologic Therapy for HFpEF: What not to do

- Negative trials for available therapies

Solomon DS. Presented at ESC Congress Munich 2018

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No support for Sildenafil in HFpEF

ONLINE FIRST

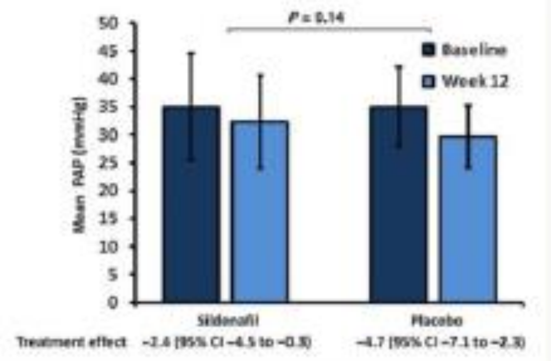
Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction
A Randomized Clinical Trial

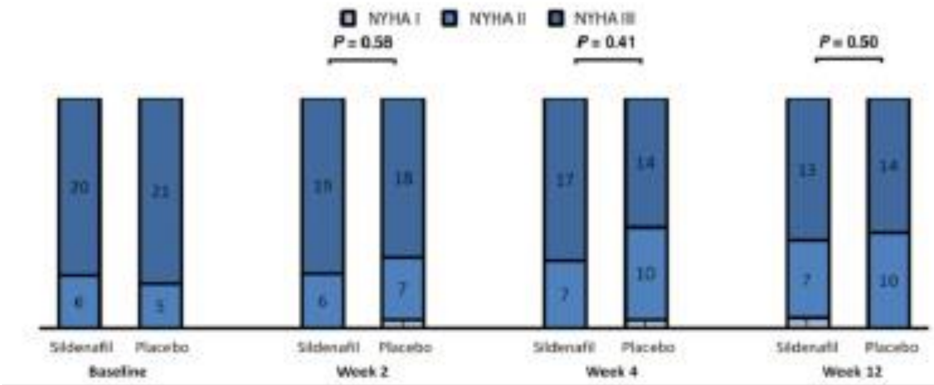
Table 3. Primary, Secondary, and Safety End Points

	Placebo		Sildenafil		
	No. of Patients	Variable	No. of Patients	Variable	*P* Value
Primary end point					
Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min	94	−0.20 (−0.70 to 1.00)	91	−0.2 (−1.70 to 1.11)	.90
Secondary end points					
Clinical rank score, mean[a]	94	95.8	95	94.2	.85
Change in 6-minute walk distance at 24 wk, median (IQR), m	95	15.0 (−26.0 to 45.0)	99	5.0 (−37.0 to 55.0)	.92
Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min	98	0.03 (−1.10 to 0.67)	97	0.01 (−1.35 to 1.25)	.98
Change in 6-minute walk distance at 12 wk, median (IQR), m	96	18.0 (−14.5 to 48.0)	99	10.0 (−25.0 to 39.0)	.12
Components of clinical rank score at 24 wk					
Death, No. (%)[b]	103	0	113	3 (3)	.25
Hospitalization for cardiovascular or renal cause, No. (%)	103	13 (13)	113	15 (13)	.89
Change in MLHFQ, median (IQR)	91	−8 (−21 to 5)	91	−8 (−19 to 0)	.44
Safety end points, No. (%)					
Adverse events	103	78 (76)	113	90 (80)	.49
Serious adverse events	103	16 (16)	113	25 (22)	.22
Change in left ventricular structure by CMRI at 24 wk					
Left ventricular mass by CMRI, g	47	0.6 (−5.7 to 7.9)	49	−1.5 (−5.9 to 7.1)	.93
Left ventricular end-diastolic volume by CMRI, mL	47	−4.3 (−15.5 to 8.1)	49	3.7 (−4.9 to 14.0)	.13
Change in diastolic function parameters at 24 wk					
Medial e', m/s	83	0.00 (−0.01 to 0.01)	77	0.00 (−0.01 to 0.01)	.89
E/e'	80	−1.6 (−4.7 to 2.2)	75	0.2 (−2.4 to 3.1)	.16
PA systolic pressure, mm Hg	55	−2 (−5 to 8)	45	2 (−5 to 7)	.94
Change in core laboratory biomarkers at 24 wk					
Creatinine, mg/dL	94	0.01 (−0.10 to 0.08)	94	0.05 (−0.04 to 0.15)	.047
Cystatin C, mg/L	99	0.01 (−0.08 to 0.11)	99	0.06 (−0.04 to 0.16)	.01
NT-proBNP, pg/mL	94	−23 (−198 to 139)	95	15 (−90 to 272)	.03
Endothelin-1, pg/mL	98	−0.01 (−0.46 to 0.47)	98	0.38 (−0.10 to 0.97)	.046
Aldosterone, ng/dL	95	0 (−7.0 to 4.8)	95	−1.1 (−7.7 to 3.0)	.85
NT-procollagen III, μg/L	93	−0.03 (−1.49 to 1.54)	95	0.67 (−1.17 to 1.40)	.77

Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial

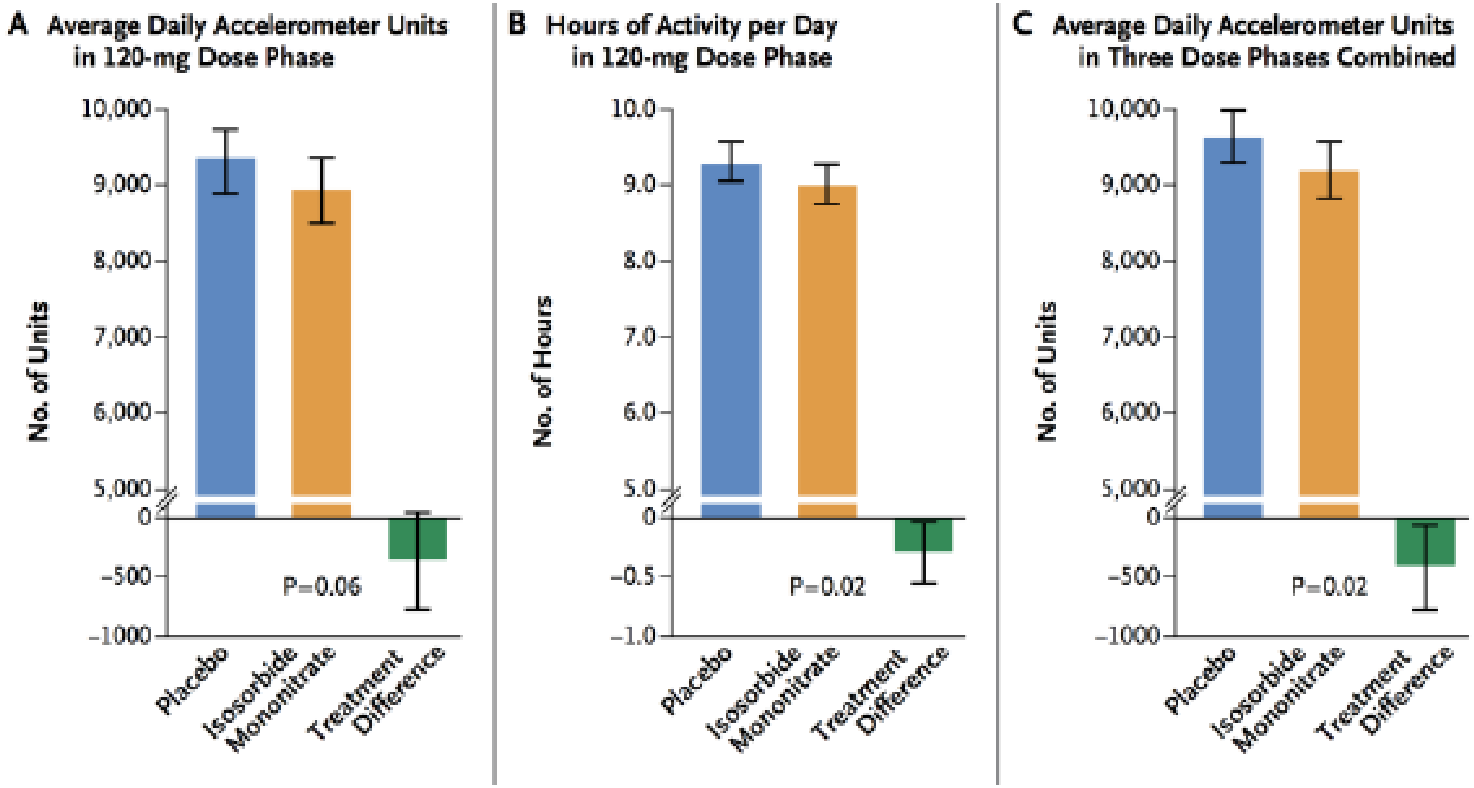
Elke S. Hoendermis[1*], Licette C.Y. Liu[1], Yoran M. Hummel[1], Peter van der Meer[1], Rudolf A. de Boer[1], Rolf M.F. Berger[2], Dirk J. van Veldhuisen[1], and Adriaan A. Voors[1]





NEAT-HFpEF: No Difference in Primary or Secondary Endpoints
(including 6 min walk, QoL, NT-pro BNP)

Isosorbide Mononitrate with dose up-titration (30 to 120 mg/day over 4 weeks) vs. placebo in crossover design



Solomon DS. Presented at ESC Congress Munich 2018

EDIFY: No improvement in any of co-primary endpoints with ivabradine

- 179 pts NYHA Class II/III, in SR, with HR ≥ 70 bpm
- NT-proBNP of ≥ 220 og/ml (BNP ≥ 80 pg/ml) and left ventricular ejection fraction of ≥ 45%
- Ivabardine (or palcebo) was titrated to 7.5 mg bid
- Pts. were followed for 8 months: Echo-Doppler E/e ratio, 6 MWT, plasma proNT-proBNP

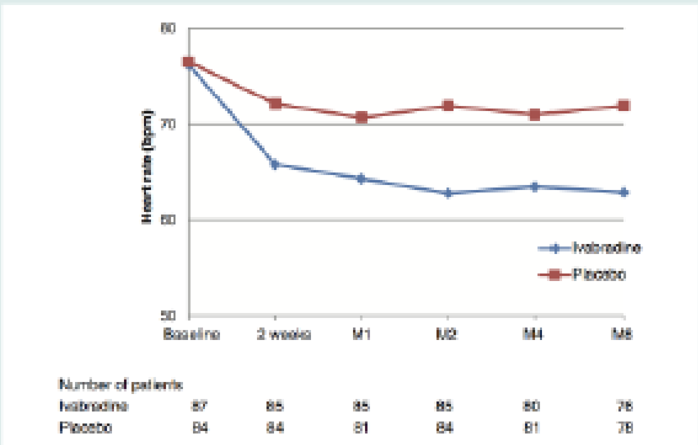


Figure 3 Mean heart rate during the study by treatment group. M1, month 1; M2, month 2; M4, month 4; M8, month 8.

Table 2 Co-primary endpoints at baseline and change over the 8-month treatment period

	Baseline		Change (last post-baseline value from baseline)		Between-group estimate[a]
	Median	Q1–Q3	Median	Q1–Q3	
E/e′					
Ivabradine ($n = 84$)	12.6	9.7–16.2	0.970	−0.8 to 2.9	1.4 (0.3–2.5) $P = 0.135$
Placebo ($n = 83$)	12.9	10.1–16.0	−0.590	−2.2 to 1.4	
6MWT, m					
Ivabradine ($n = 84$)	323.0	243.5–375.0	0.0	−28.5 to 35.0	−3.8 (−19.1 to 11.6) $P = 0.882$
Placebo ($n = 84$)	321.0	256.5–368.0	11.0	−15.5 to 40.0	
NT-proBNP, pg/mL					
Ivabradine ($n = 83$)	385.0	263.0–738.0	19.0	−98.0 to 199.0	[b]
Placebo ($n = 82$)	343.0	238.0–631.0	16.5	−134.0 to 126.0	

Solomon DS. Presented at ESC Congress Munich 2018

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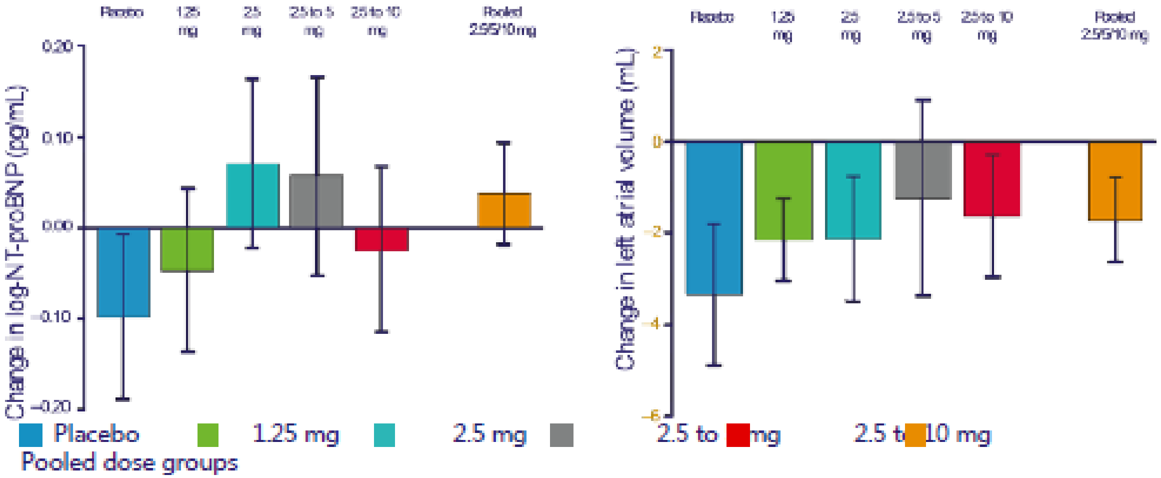
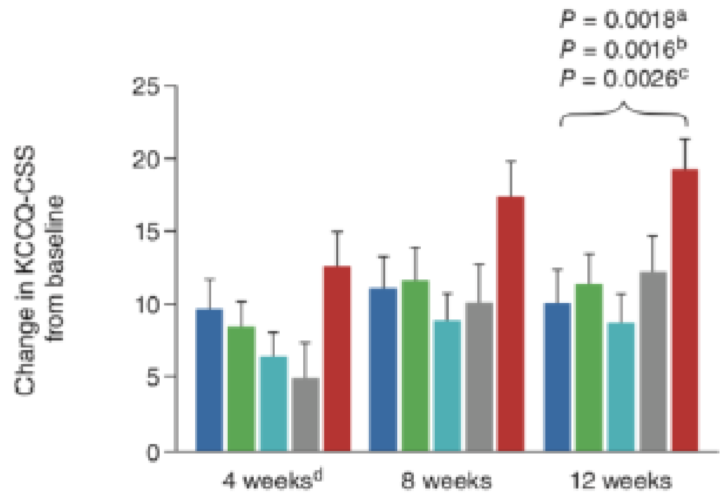
Vericiguat in HFpEF: SOCRATES-Preserved

Primary endpoint: Log-NT-pro BNP and LAV



Pieske et al. EHJ 2017



Fillippatos et al. EJHF 2017

- Stimulation of Guanylyl cyclase (sGC): NO mediated GTP⇨cGMP
- No reduction inLog-NT-proBNP or in LAV at 12 weeks compared with placebo
- Secondary QoL endpoint showed significant benefit at highest doses

Solomon DS. Presented at ESC Congress Munich 2018

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HFpEF

2012 ESC Guidelines

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF.

2016 ESC Guidelines

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF.

HFpEF is extremly Comorbid

Table 1. Characteristics of Patients.*

Characteristic	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
Mean LVEF — %	25.9	62.4	<0.001
Age — yr	71.8 ± 12	75.4 ± 11.5]	<0.001
Male sex — no. (%)	983 (62.6)	302 (34.3)	<0.001
Peptic ulcer disease — no. (%)	94 (6.0)	74 (8.4)	0.02
Hepatitis or cirrhosis — no. (%)	20 (1.3)	16 (1.8)	0.28
Dementia — no. (%)	76 (4.8)	49 (5.6)	0.43
Hemoglobin <10 g/dl — no. (%)	155 (9.9)	186 (21.1)	<0.001
Mean systolic blood pressure — mm Hg	146	156	<0.001
Mean respiratory rate — breaths/min	26	26	0.17
Serum sodium <136 mmol/liter — no. (%)	362 (23.1)	209 (23.8)	0.70
Serum creatinine >150 mmol/liter — no. (%)	296 (18.9)	195 (22.2)	0.95
Dialysis — no. (%)	18 (1.1)	9 (1.0)	0.78

	HFrEF	HFpEF	P-value
Age	71.8 ± 12	75.4 ± 11.5	< 0.001
Hypertension	49.2%	55.1%	0.005
Atrial Fibrillation	23.6%	31.8%	< 0.001
COPD	13.2%	17.7%	0.002
Anemia	9.9%	21.1%	< 0.001

Bhatia et al. NEJM 2006

Solomon DS. Presented at ESC Congress Munich 2018

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Recommendation for treatment of patients with HFpEF and HFmrEF

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Eur Heart J 2016; 37:2129-22000

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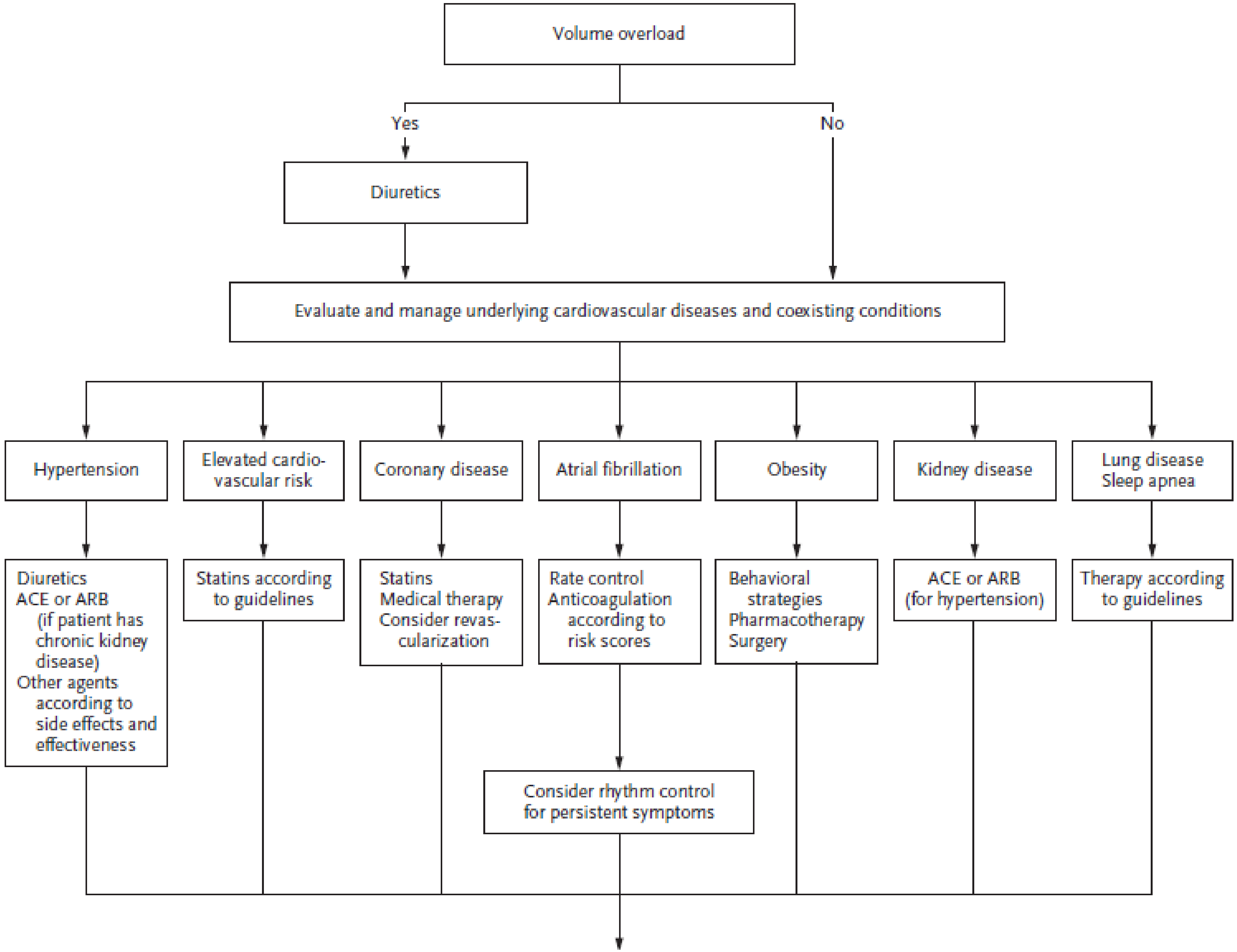
Treatment algorithm for HFpEF (1)

Decongestion

Treat Comorbidities
(most say treat according to guidelines]

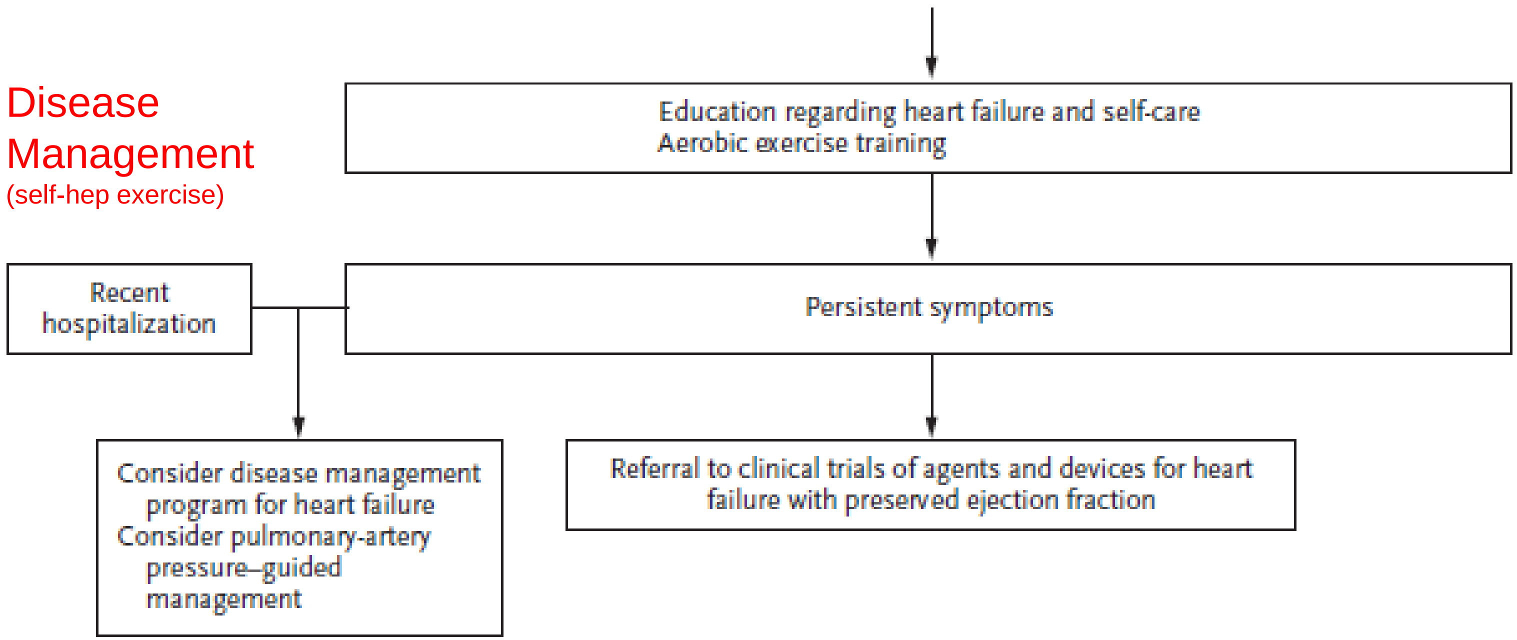


Redfield MM. Heart Failure with preserved Ejection Fraction. NEJM 2016;375:1868-1877 (Review)

MÜNCHEN KLINIK

Treatment algorithm for HFpEF (2)

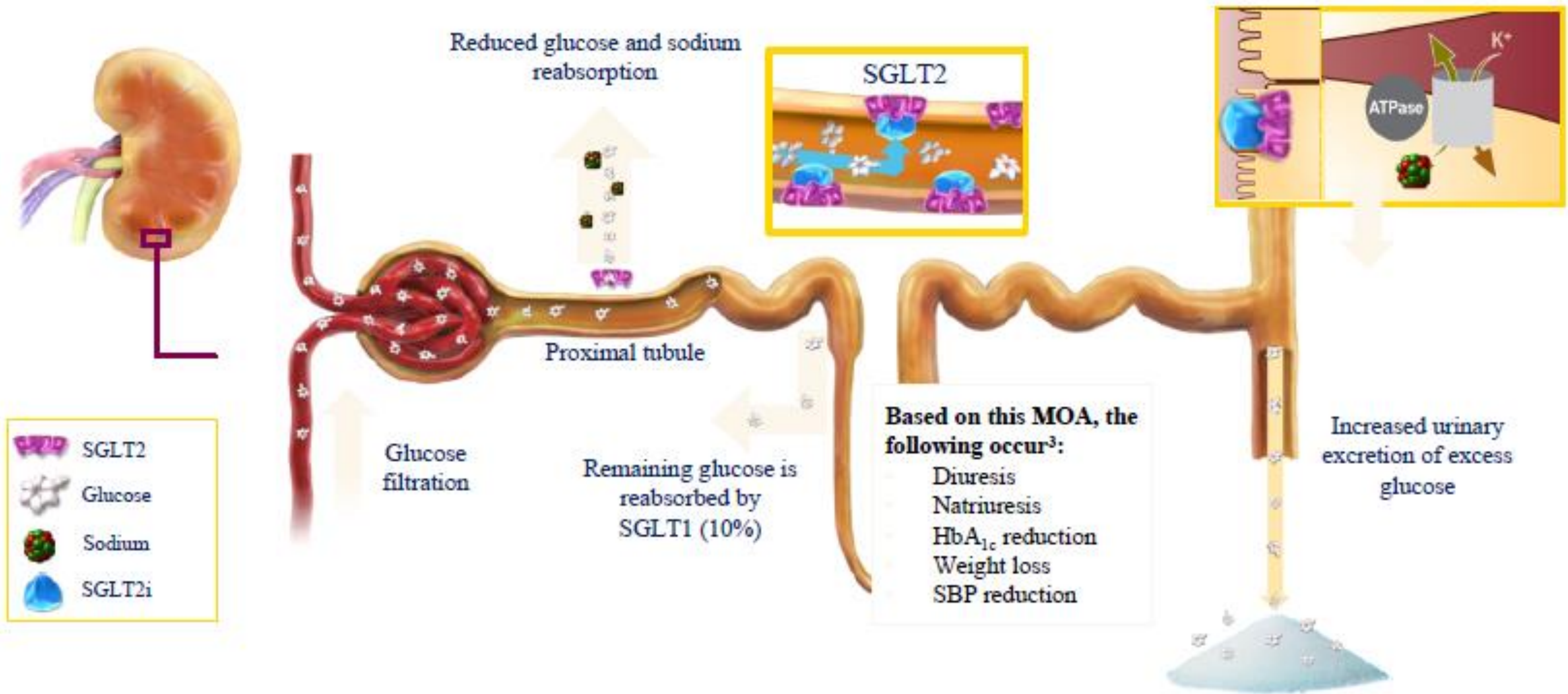
Disease
Management
(self-hep exercise)



Redfield MM. Heart Failure with preserved Ejection Fraction. NEJM 2016;375:1868-1877 (Review)

New Therapies Being Tested

SGLT2 Inhibitors block SGLT2 and reduce Glucose and Na⁺-Reabsorption



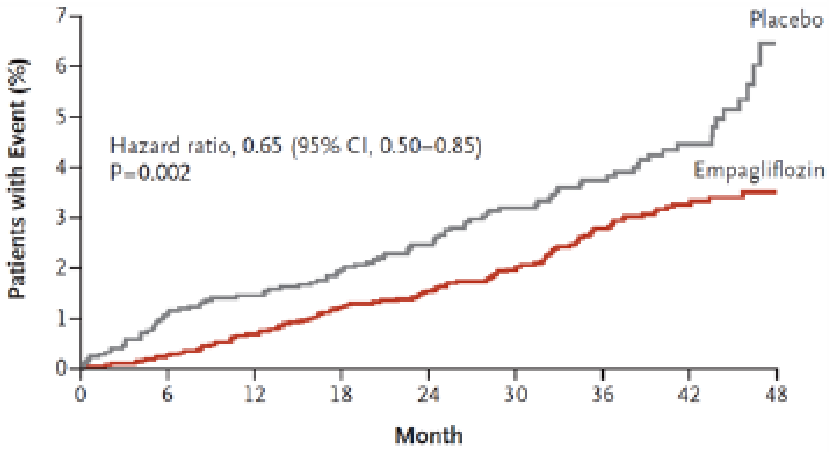
Solomon DS. Presented at ESC Congress Munich 2018

Hospitalization for Heart Failure

EMPA-REG: ARR 1.4%

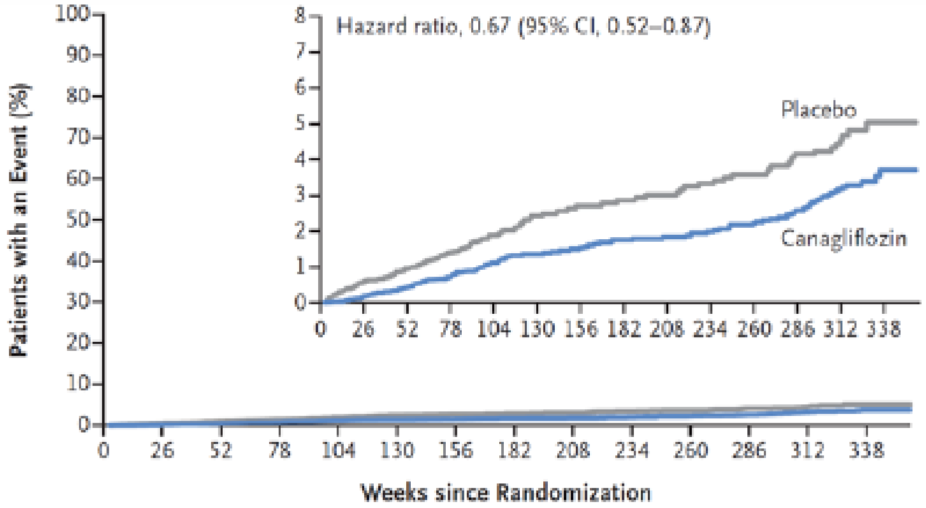
- Impact of SGLT2-inhibitor on hospitalization
- Side by side comparison of the effect of empagliflozin (EMPA-REG OUTCOME) and canagliflozin (CANVAS) on cumulative incidence of hopitalization in heart failure

EMPA-REG



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

CANVAS



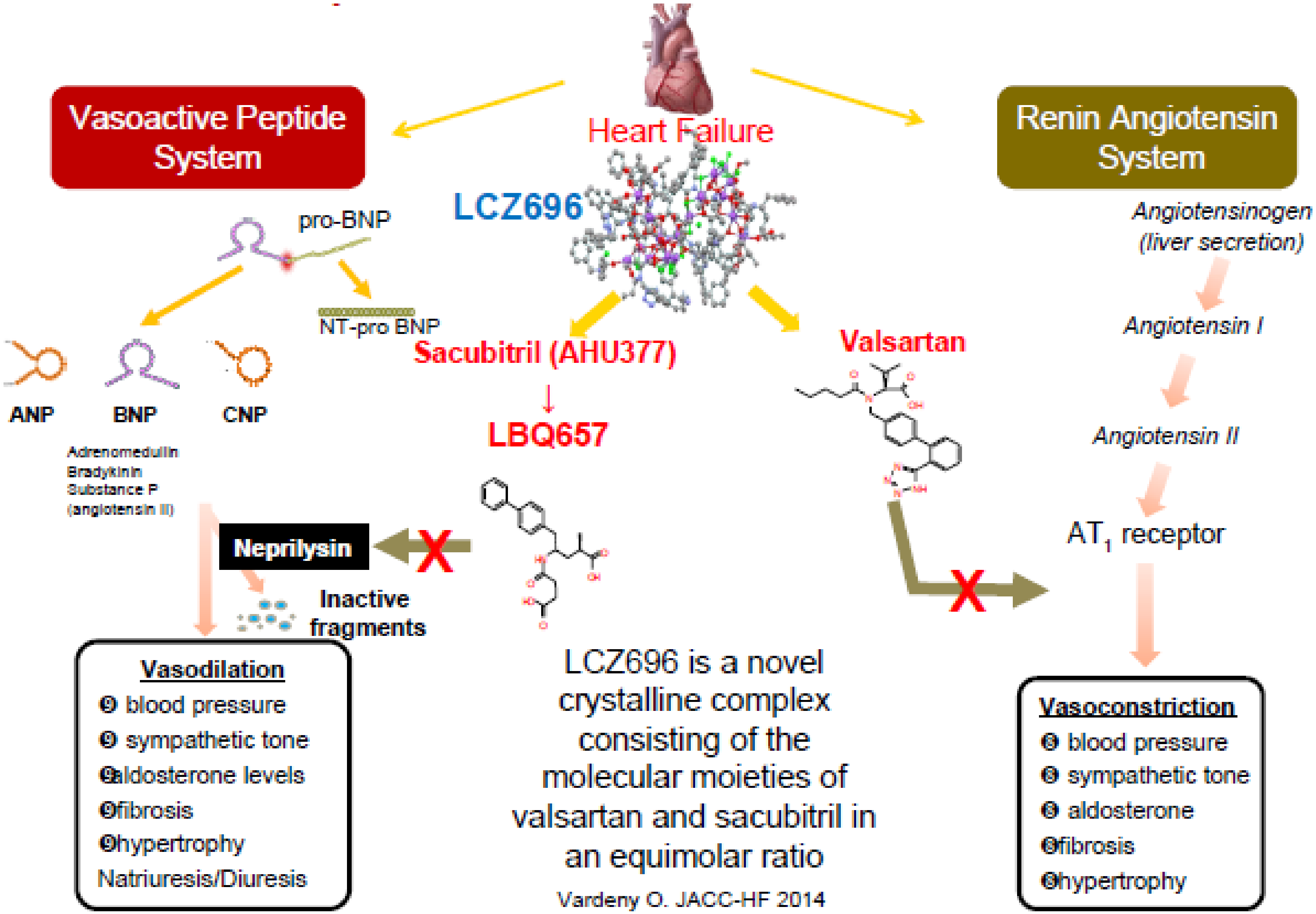
No. at Risk														
Placebo	4347	4267	4198	4123	3011	1667	1274	1256	1236	1210	1180	1158	829	233
Canagliflozin	5795	5732	5653	5564	4437	3059	2643	2610	2572	2540	2498	2451	1782	490

Zinman B et al. *N Engl J Med* 2015;373:2117-28; Neal B, et al. N Engl J Med. 2017; Epub ahead of print.

Solomon DS. Presented at ESC Congress Munich 2018

MÜNCHEN KLINIK

LCZ696 – Angiotensin Receptor Neprilysin Inhibitor -simultaneously inhibits NEP and RAS



Solomon DS. Presented at ESC Congress Munich 2018

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PARAGONHF

Target patient population: ~4,800 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

Randomization 1:1

Double-blind treatment period

Active run-in period

Screening

Valsartan 80 mg BID*

LCZ696 100 mg BID

LCZ696 200 mg BID

Valsartan 160 mg BID

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

up to 2 weeks

3–8 weeks

~240 weeks

Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

Steering Cmt: S. Solomon, co-Chair, J. McMurray, Co-Chair, I. Anand, F. Zannad, A. Maggioni, M. Packer, M. Zile, B. Pieske, J. Rouleau, M. Redfield, C. Lam, D. Van Veldhuisen, F. Martinez, J. Ge, H. Krum, M. Pfeffer

Solomon DS. Presented at ESC Congress Munich 2018

Device treatment for Heart Failure with preserved Ejection Fraction (HFpEF)

Diagnostic pathways and novel treatment options in HFpEF

EMB 2019

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Devices for HFpEF

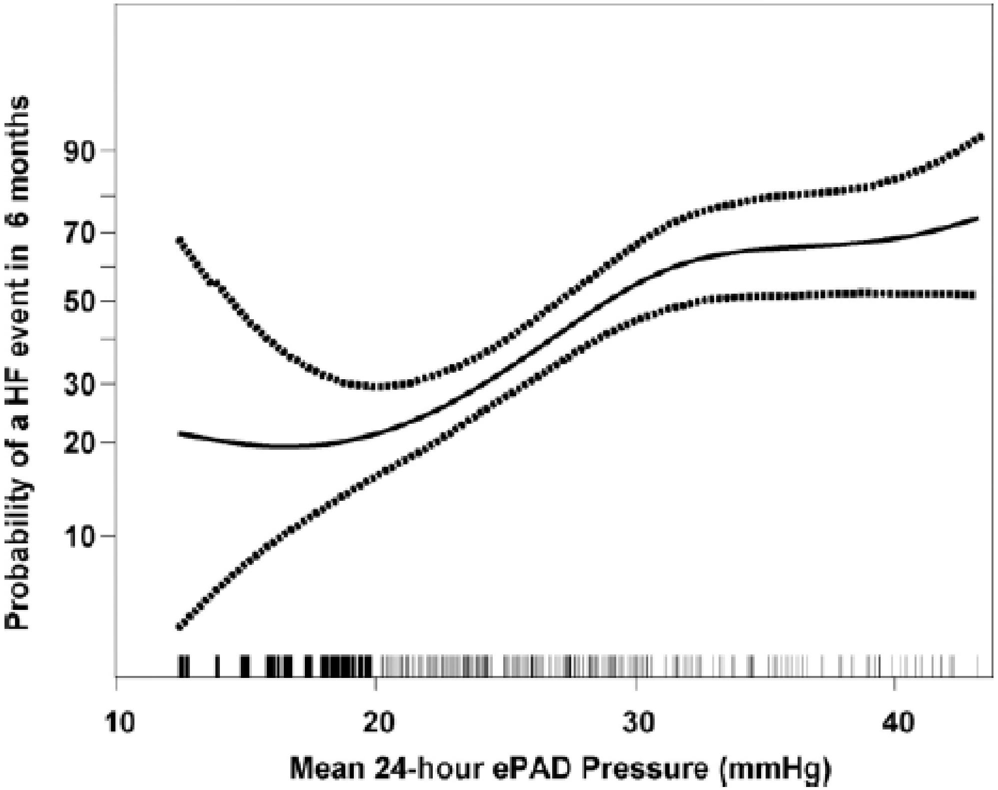
- Implantable Hemodynamic Monitors
- Interatrial Shunt Devices
- Cardiac Contractility Modulation (CCM)
- Baroreflex Activation Therapy
- Self-Expanding Elastic Devices
- Others

Pressure-Guided Heart Failure Therapy

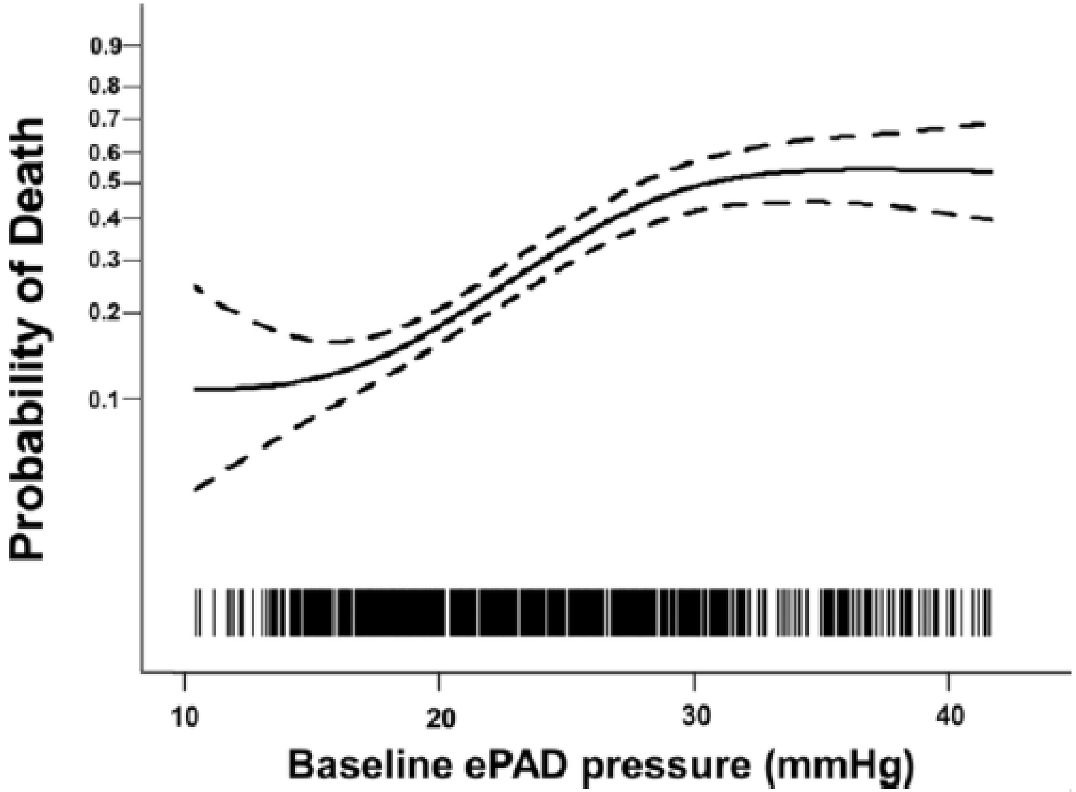
- Elevated intracardiac and pulmonary artery pressures are associated with increased morbidity and mortality, regardless of LV ejection fraction
- Lowering intra-cardiac and pulmonary artery pressures improves clinical outcomes in both HFrEF and HFpEF patients
- In HFpEF patients, PA-pressure guided therapy reduces the risk of hospitalizations by ≥ 50%

Abraham WT. Presented at ESC Congress Munich 2018

Chronic Ambulatory Intracardiac Pressures and Future HF Events and Mortality



Stevenson LW et al. Circ Heart Fail 2010



Zile MR et al. Circ Heart Fail 2017

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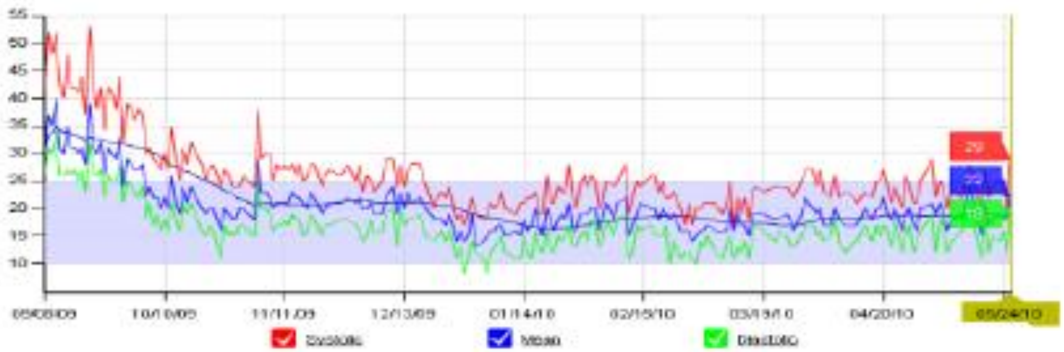
Pulmonary Artery Pressure Monitoring System

Catheter-based delivery system

MEMS-based pressure sensor

Home electronics

PA Measurement database



CardioMEMS (Abbott)

Abraham WT. Presented at ESC Congress Munich 2018

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Randomized CHAMPION Clinical trial: Reduction in Clinical Events over Full Duration

	Treatment (n=270)	Control (n=280)	Absolute Reduction	Relative Reduction HR (CI)	p-value
Heart Failure Hospitalizations	182	279	97	0.67 (0.55 – 0.80)	<0.0001
Death or Heart Failure Hospitalizations	232	343	111	0.69 (0.59 – 0.82)	<0.0001
All Cause Hospitalizations	554	672	118	0.84 (0.75 – 0.95)	0.0032
Death or All Cause Hospitalizations	604	736	132	0.84 (0.76 – 0.94)	0.0017

Abraham WT. Presented at ESC Congress Munich 2018

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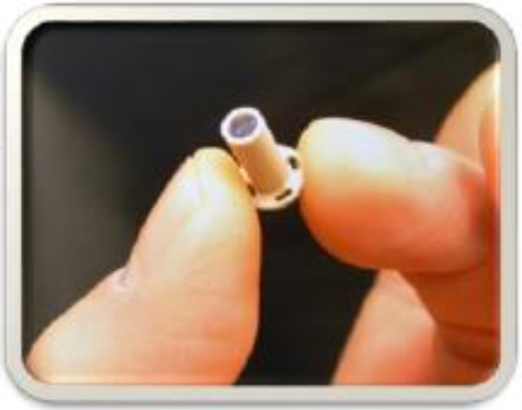
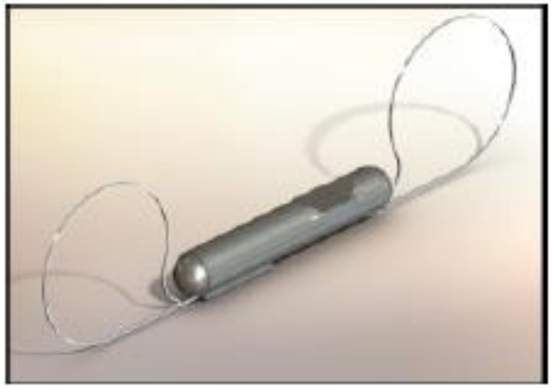
More Pressure Monitors to Come



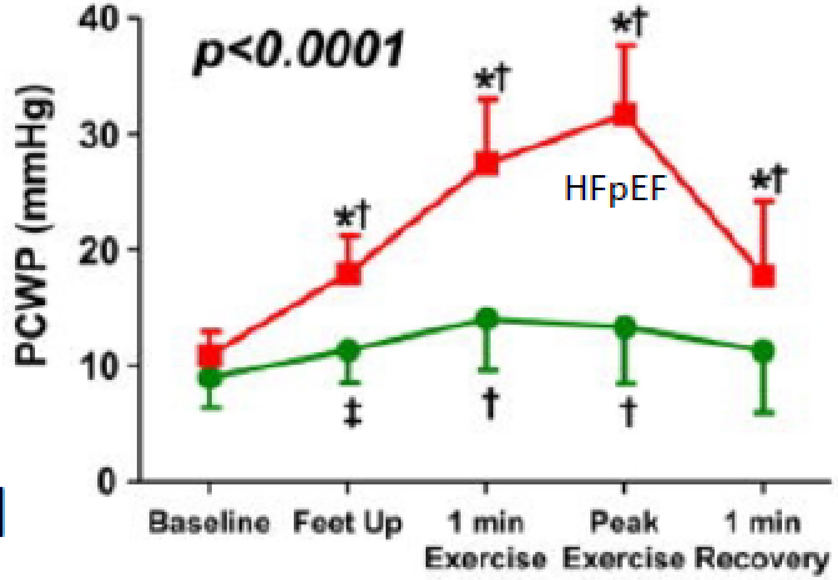


Abraham WT, Perl L J Am Coll Cardiol 2017, Abraham WT. Presented at ESC Congress Munich 2018

MÜNCHEN KLINIK

Elevated LAP during Exercise in HFpEF

- HFpEF (LVEF ≥ 50%) and HFmrEF (LVEF 40-49%):
  - Increasing in prevalence
  - High morbidity/mortality
  - No proven effective therapies
  - Heterogeneous syndromes
  - **Common pathophysiologic thread** ⇧*LA pressure at rest and with exercise*



Borlaug BA, et al. *Circ Heart Fail* 2010

Why does Interatrial Shunt Therapy make sense?

- Creation of a small inter-atrial shunt could reduce LAP and limit LAP increase during HF exacerbations and during exercise

- Patients with mitral valve stenosis and an atrial septal defect (ASD) have fewer symptoms than patients with an intact septum[1]

- Closure of ASDs in patients with unrecognized left ventricular dyfunction results in elevated LAP and pulmonary edema[2]

[1] Lutembacher R. Arch Mal Coeur 1916
[2] Ewert P et al. Catheter Cardiovasc Interv 2001

Abraham WT. Presented at ESC Congress Munich 2018

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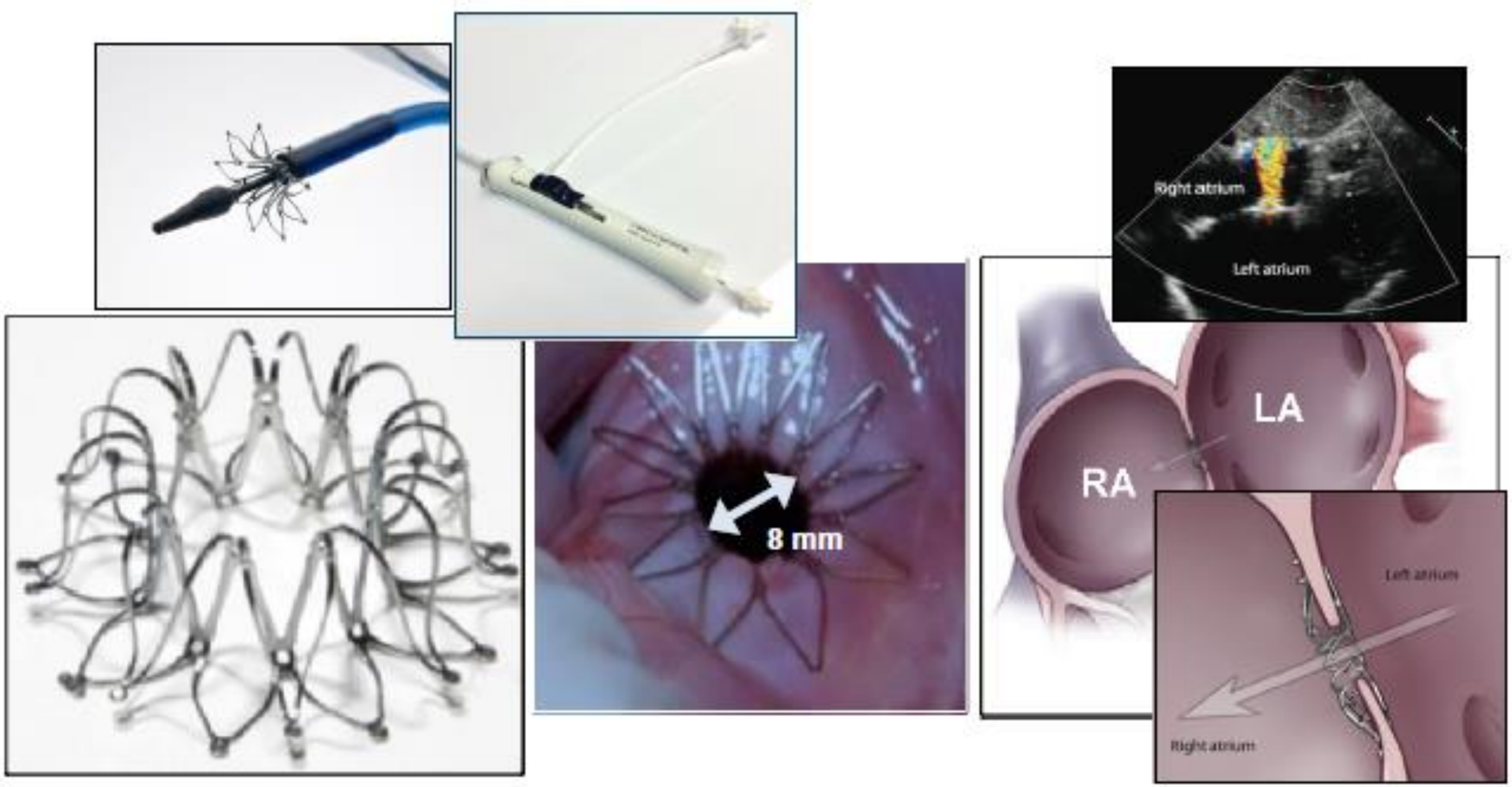
InterAtrial Shunt Device (IADS®)



IASD proposed mode of action: dynamic LA decompression by shunting blood from LA → RA + systemic veins, at rest and particularly during exercise

Feldmann T … Shah SJ. Circ Heart Fail 2016 Jul;9(7) NCT02600234
Feldman T. Presented at ESC Congress Munich 2018

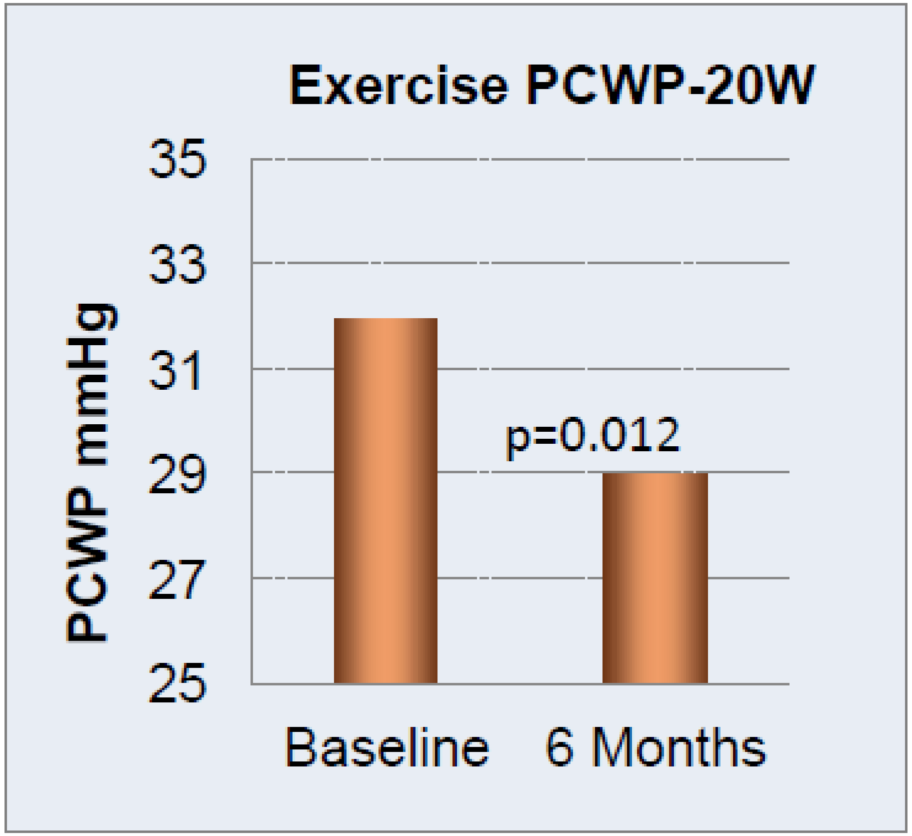
MÜNCHEN KLINIK

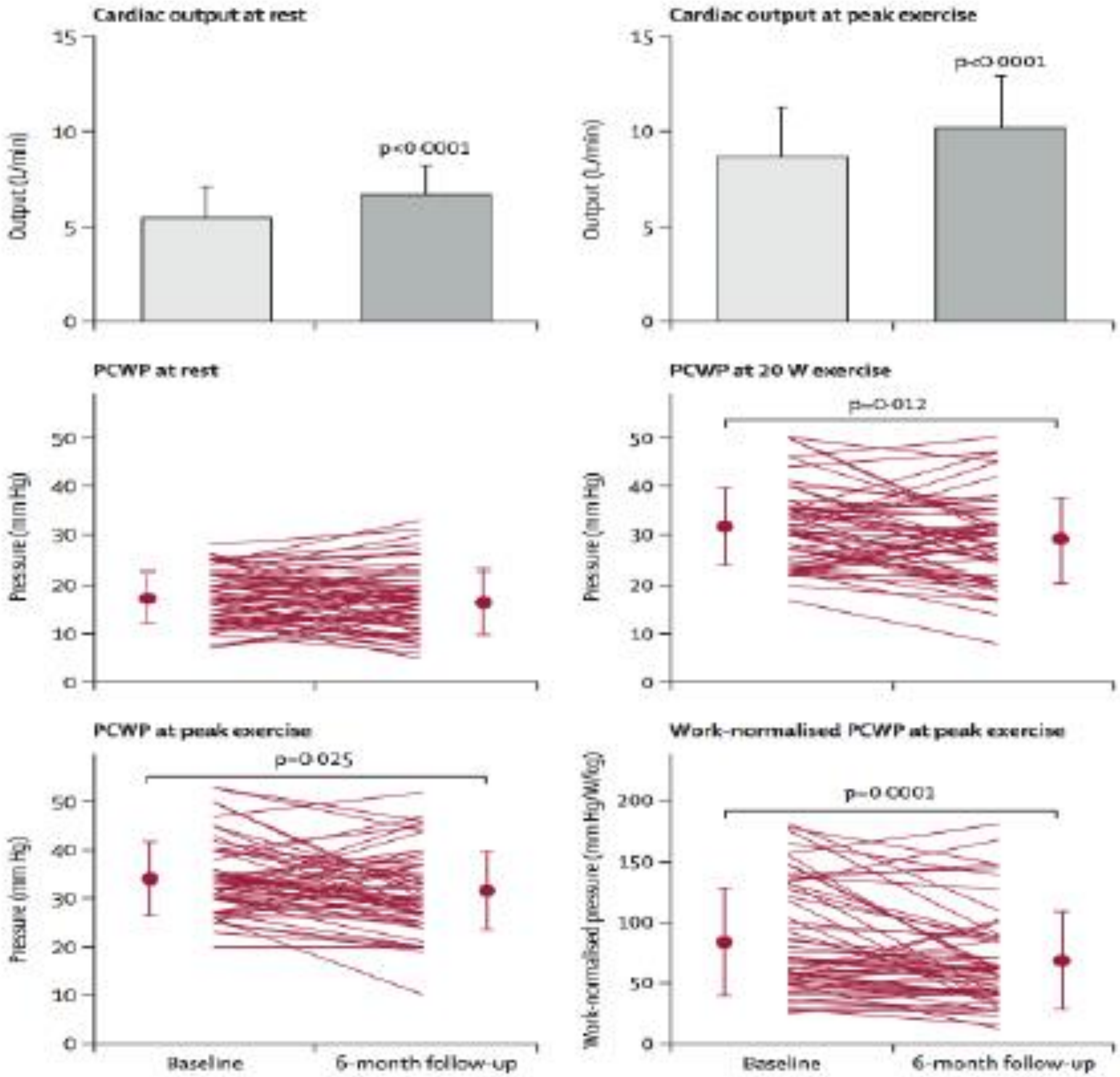
REDUCE LAP-HF I RCT

- Prospective, non-randomized study
- Symptomatic HF (n064)
- Preserved EF (>40%)
- Elvated PCWP at rest (> 15 mmHg) or during exercise (> 25 mm Hg)
- Monitored by independant DSMB and CEC
- Assessed by independant Core-Laboratories
  - Echo
  - Hemodynamics
- Three Year Follow-up

Hasenfuß G et al. Lancet 2016

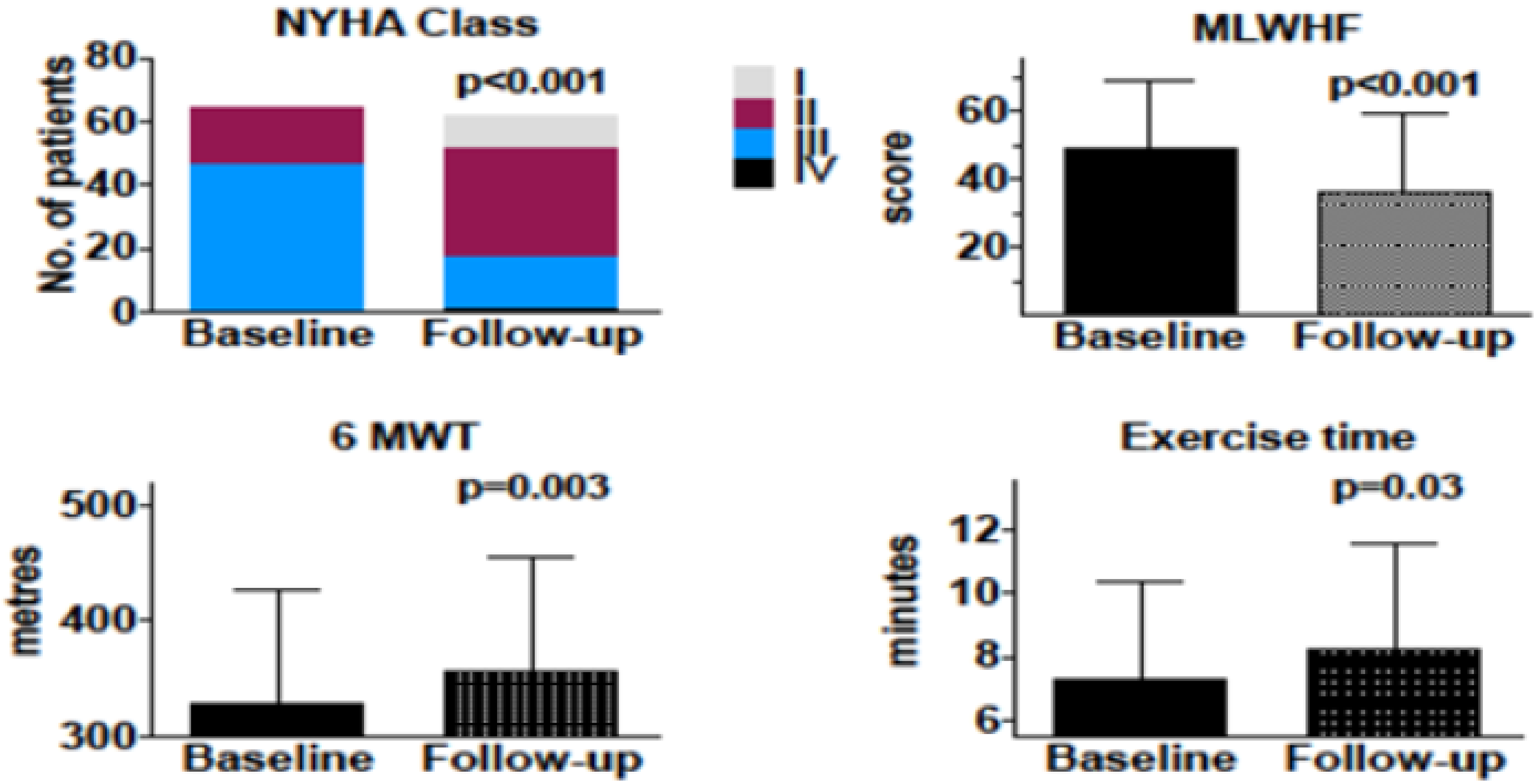
REDUCE LAP-HF I RCT - Results





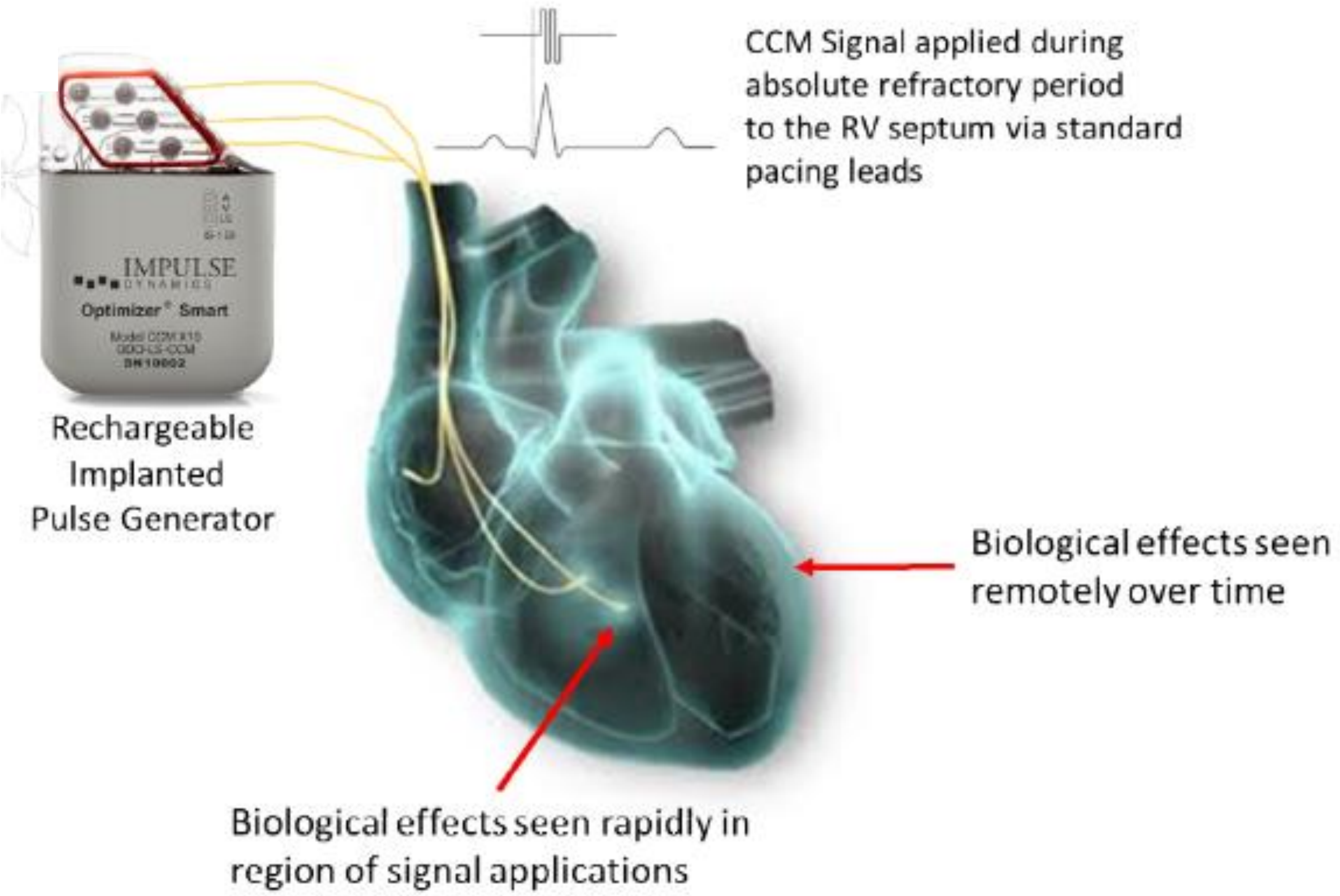
Hasenfuß G et al. Lancet 2016

REDUCE LAP-HF I RCT - Results



Hasenfuß G et al. Lancet 2016

Cardiac Contractility Modulation (CCM)

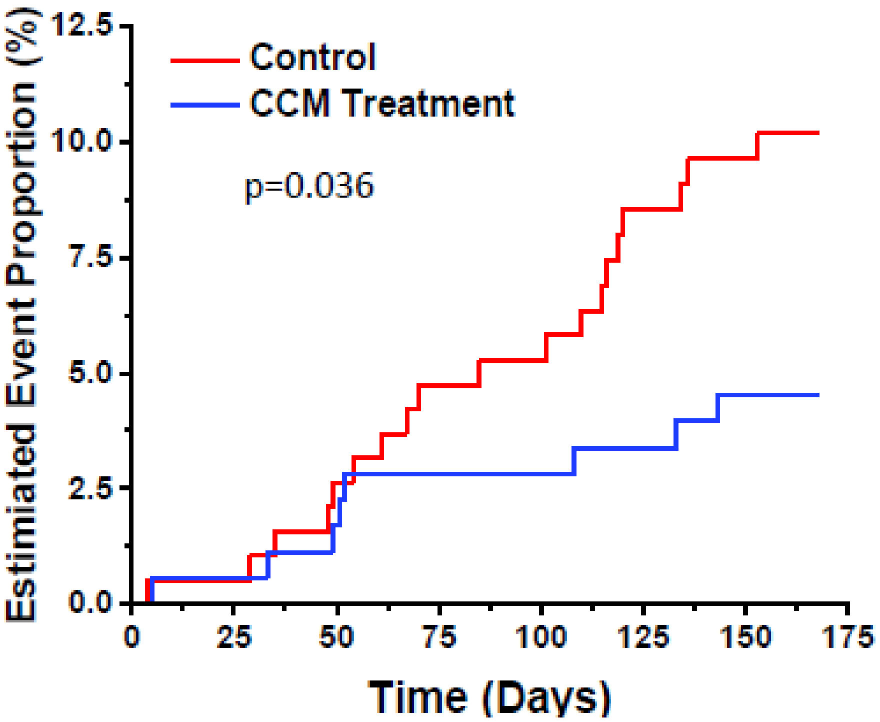


- Delivered by an IPG
- Rechargeable Battery
- 1 Atrial Lead (sensing)
- 2 RV Septal Leads (sensing + CCM delivery)
- Signals effect the biology of failing myocardium (genes, proteins, and phosphorylation) that improve function

mk MÜNCHEN KLINIK

Cardiac Contractility Modulation (CCM)

FIX-HF-5 + FIX-HF-5C:
Cardiovascular Death + HF Hospitalizations



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HFpEF
Take home message

- HFpEF is alive and accounts for about half of heart failure
- Diagnosis of HFpEF is challenging
- Clinical diagnosis remains key
- Probability scores (e.g. H2FPEF, ESC HFA-PEFF) may assist in diagnosis/determination of which symptomatic patient needs further testing
- Contribution factors makes HFpEF more likely: age, AFib, hypertension , increased LA volume
- Drug treatment is limited, but there are promising potential therapies being tested
- Device treatment has recently been shown as a potential new option

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Thank you

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KLINIK

Zwischentitel oder Agendapunkt mit/ohne Nummerierung

Hier kann optional ein ergänzender Text stehen

MÜNCHEN KLINIK

Hier steht die Überschrift der Seite
Masterlayout: Inhalt

Hier steht der Text in Arial 14 Punkt mit 0,95 Zeilenabstand. Der Absatzabstand 14 Punkt, was einer Leerzeile entspricht.

- Die Aufzählungszeichen sind ein Punkt aus den Standard-Aufzählungszeichen von PowerPoint.

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Eine Zwischenüberschrift wird (manuell)
in der Arial bold und in mük-Petrol abgesetzt.

- Für Aufzählungen ohne Absatzabstand
- nutzen Sie bitte die Funktion
- “Listenebene” erhöhen”

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➔ **Fazit-Box: Optional, Stand und Größe ist variabel.**

Erste Textebene

- Zweite Textebene mit Aufzählungs-zeichen

Dritte Textebene ohne Aufzählungs-zeichen und eingerücktem Text

Quellenangabe (optional) in 10 Punkt

MÜNCHEN KLINIK

Hier steht die Überschrift der Seite
Masterlayout: Inhalt // 2 Textfelder

Hier steht der Text in Arial 14 Punkt mit 0,95 Zeilenabstand. Der Absatzabstand 14 Punkt, was einer Leerzeile entspricht.

- Die Aufzählungszeichen sind ein Punkt aus den Standard-Aufzählungszeichen von PowerPoint.

Zwischenüberschrift in der Arial bold und in mük-Petrol

- Für Aufzählungen ohne Absatzabstand
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- Die Aufzählungszeichen sind ein Punkt aus den Standard-Aufzählungszeichen von PowerPoint.

Zwischenüberschrift in der Arial bold und in mük-Petrol

- Für Aufzählungen ohne Absatzabstand
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➔ **Fazit-Box: Optional, Stand und Größe ist variabel.**

Erste Textebene

- Zweite Textebene mit Aufzählungs-zeichen

Dritte Textebene ohne Aufzählungs-zeichen und eingerücktem Text

Quellenangabe (optional) in 10 Punkt

MÜNCHEN KLINIK

Hier steht die Überschrift der Seite
Masterlayout: Inhalt // 3 Textfelder

**Zwischenüberschrift
in der Arial bold
und in mük-Petrol**

Hier steht der Text in Arial 14 Punkt mit 0,95 Zeilen-abstand. Der Absatzabstand 14 Punkt.

- Die Aufzählungszeichen sind ein Punkt.

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**Zwischenüberschrift in
der Arial bold
und in mük-Petrol**

- Für Aufzählungen
- ohne Absatzabstand
- nutzen Sie bitte
- die Funktion
- “Listenebene” erhöhen”

**Zwischenüberschrift
in der Arial bold
und in mük-Petrol**

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**Zwischenüberschrift in
der Arial bold
und in mük-Petrol**

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**Zwischenüberschrift
in der Arial bold
und in mük-Petrol**

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**Zwischenüberschrift in
der Arial bold
und in mük-Petrol**

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- nutzen Sie bitte
- die Funktion
- “Listenebene” erhöhen”

➔ **Fazit-Box: Optional, Stand und Größe ist variabel.**

Erste Textebene

- Zweite Textebene mit Aufzählungs-zeichen

Dritte Textebene ohne Aufzählungs-zeichen und eingerücktem Text

Quellenangabe (optional) in 10 Punkt

MÜNCHEN KLINIK

Hier steht die Überschrift der Seite
Masterlayout: Inhalt // 4 Textfelder + OL

Overline (Hintergrundfarbe variabel)

- Hier steht der Text in Arial 14 Punkt mit 0,95 Zeilenabstand.
- Der Absatzabstand ist hier auf 7 Punkt reduziert.
- Lorem ipsum dolor sit amet, consetetur sadipscing elitr

Overline (Hintergrundfarbe variabel)

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- Der Absatzabstand ist hier auf 7 Punkt reduziert.
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Overline (Hintergrundfarbe variabel)

- Hier steht der Text in Arial 14 Punkt mit 0,95 Zeilenabstand.
- Der Absatzabstand ist hier auf 7 Punkt reduziert.
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Overline (Hintergrundfarbe variabel)

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- Der Absatzabstand ist hier auf 7 Punkt reduziert.
- Lorem ipsum dolor sit amet, consetetur sadipscing elitr

→ Hinweis:

- Dieses Masterlayout kann auch mit „nur“ 2 Textfeldern verwendet werden.
- Textboxen bitte einfach löschen

Quellenangabe (optional) in 10 Punkt

MÜNCHEN KLINIK

Hier steht die Überschrift der Seite
Masterlayout: Inhalt // 3 Textfelder mit Pfeil (Ablauf)

Overline

- Hier steht der Text in Arial 14 Punkt mit 0,95 Zeilenabstand.
- Der Absatzabstand ist hier auf 7 Punkt reduziert.
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Overline

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➔ Fazit-Box: Optional, Stand und Größe ist variabel.

Erste Textebene

- Zweite Textebene mit Aufzählungs-zeichen

Dritte Textebene ohne Aufzählungs-zeichen und eingerücktem Text

Quellenangabe (optional) in 10 Punkt

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Musterseite mit Textfeldern
Entscheidungsbedarf

		Ja	Nein
1	Beschreibung	X	
2	Beschreibung		X
3	Beschreibung		
4	Beschreibung		
5	Beschreibung		
6	Beschreibung		
7	Beschreibung		

MÜNCHEN
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Musterseite mit Textfeldern
Ausblick / nächste Schritte

- Beschreibung
- Beschreibung
- Beschreibung
- Beschreibung
- Beschreibung
- Beschreibung
- Beschreibung

Fazit-Box: Optional, Stand und Größe ist variabel.

Musterseite mit Tabelle
Festlegung der nächsten Schritte

	Beschreibung		Verantworlich	Frist
1	Lorem ipsum dolor sit amet, sed diam nonumy eirmoder conser. Lorem ipsum dolor sit amet	→	Vorname Nachname	00.00.2018
2	Lorem ipsum dolor sit amet, sed diam nonumy eirmoder conser. Lorem ipsum dolor sit amet	→	Vorname Nachname	00.00.2018
3	Lorem ipsum dolor sit amet, sed diam nonumy eirmoder conser. Lorem ipsum dolor sit amet	→	Vorname Nachname	00.00.2018
4	Lorem ipsum dolor sit amet, sed diam nonumy eirmoder conser. Lorem ipsum dolor sit amet	→	Vorname Nachname	00.00.2018
5	Lorem ipsum dolor sit amet, sed diam nonumy eirmoder conser. Lorem ipsum dolor sit amet	→	Vorname Nachname	00.00.2018
6	Lorem ipsum dolor sit amet, sed diam nonumy eirmoder conser. Lorem ipsum dolor sit amet	→	Vorname Nachname	00.00.2018
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Quellenangabe (optional) in 10 Punkt

Musterseite mit Diagrammen

Lorem ispum

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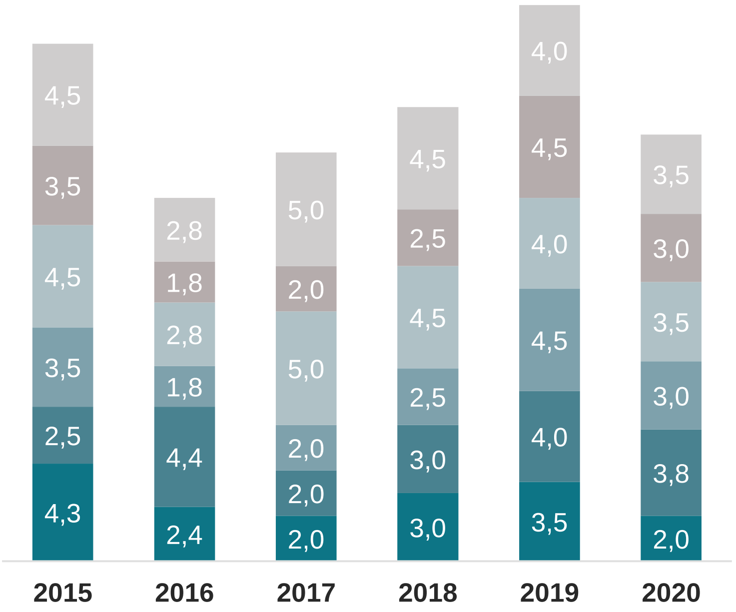

Lorem ispum

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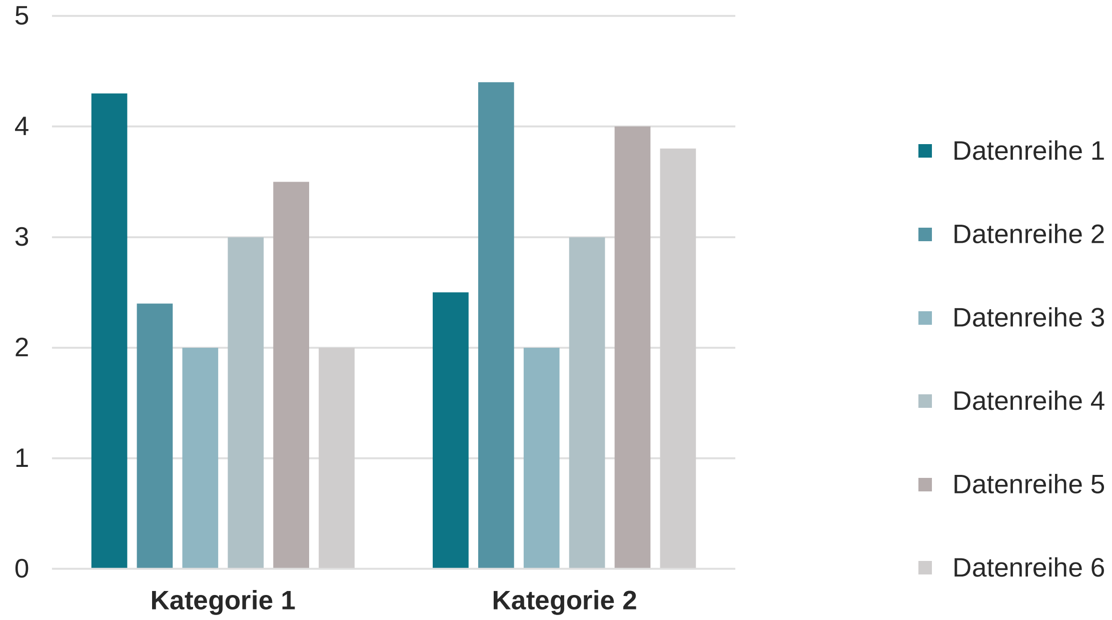

Quellenangabe (optional) in 10 Punkt

Musterseite mit Diagrammen

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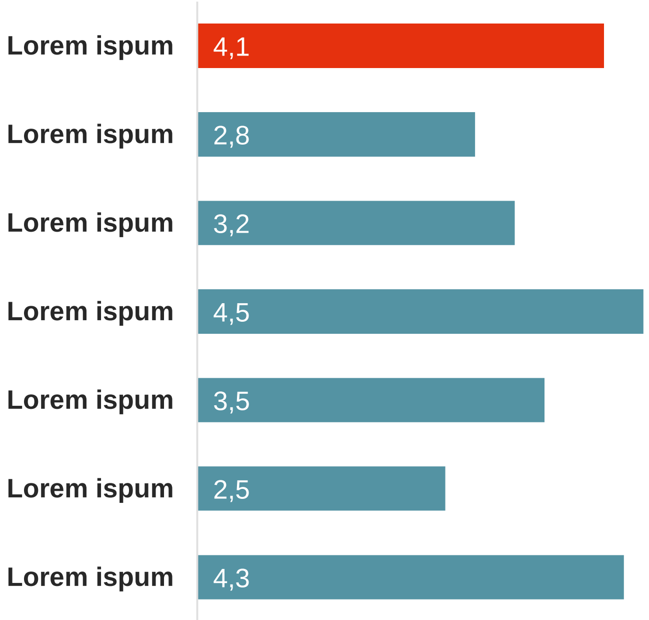

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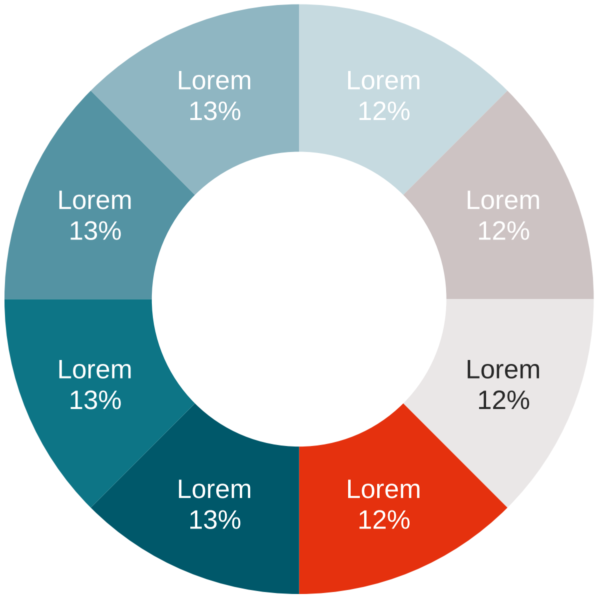

➔ **Fazit-Box: Optional, Stand und Größe ist variabel.**

Erste Textebene

- Zweite Textebene

Dritte Textebene

Quellenangabe (optional) in 10 Punkt