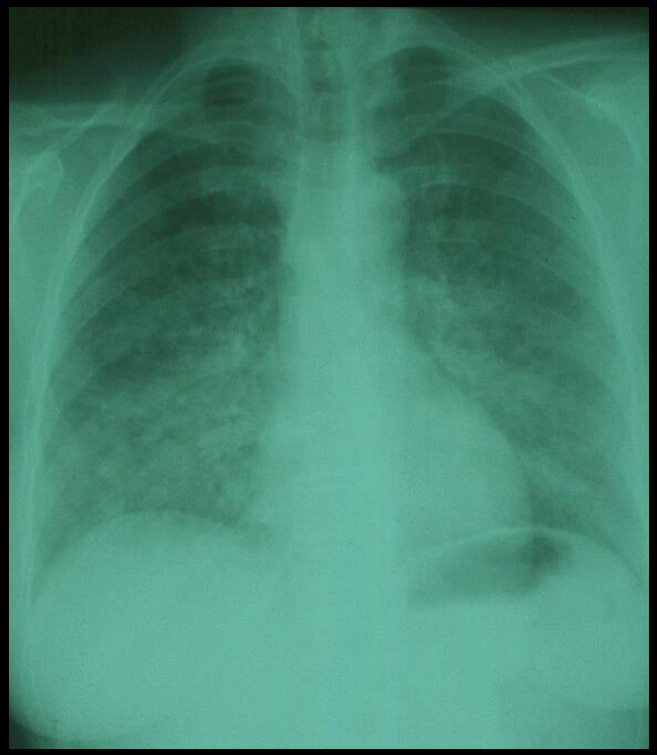
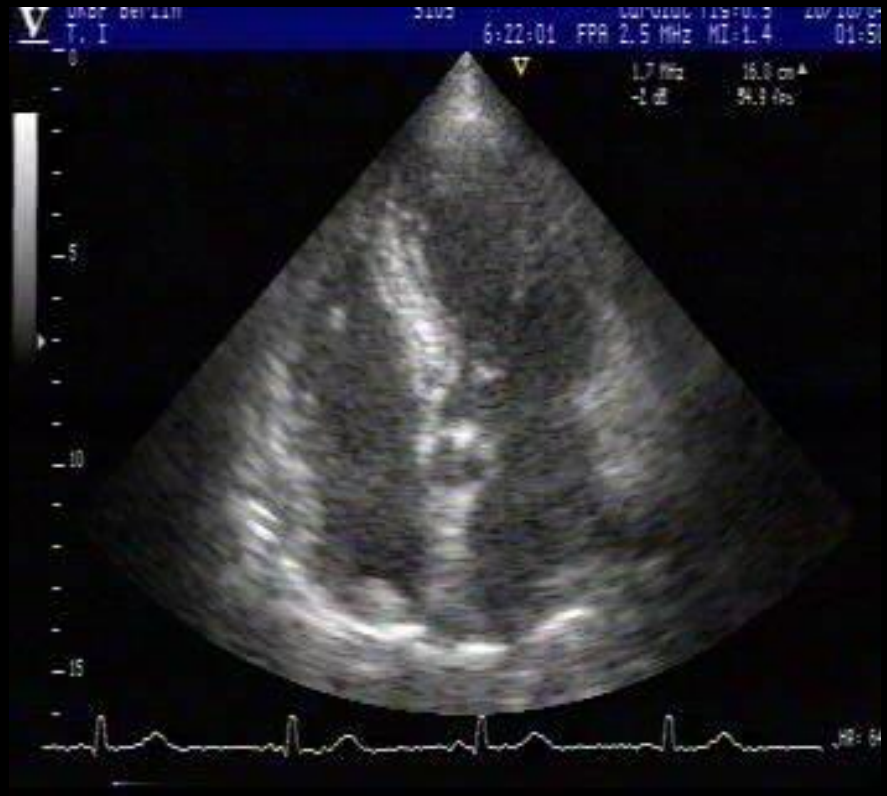
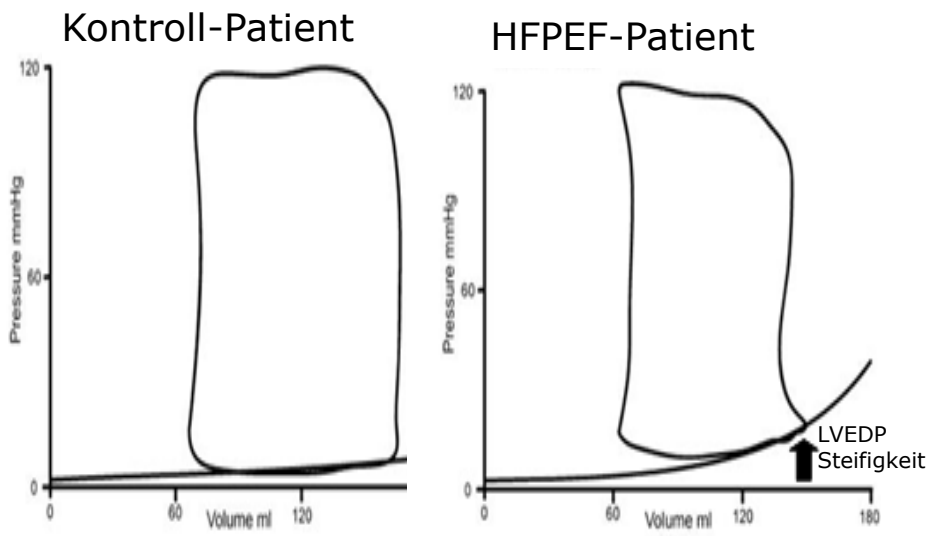
Die Diastolische Herzinsuffizienz: Auf der Suche nach einer einheitlichen Definition und wirksamen Therapie

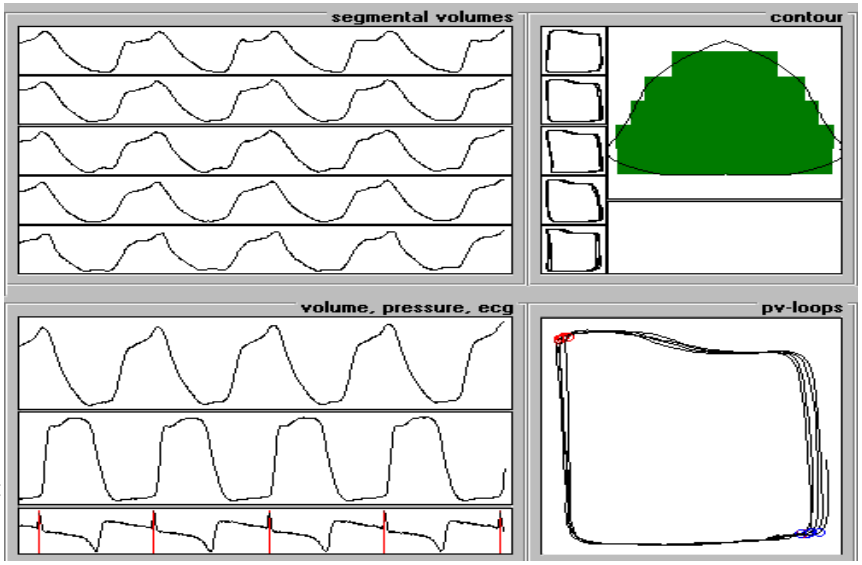


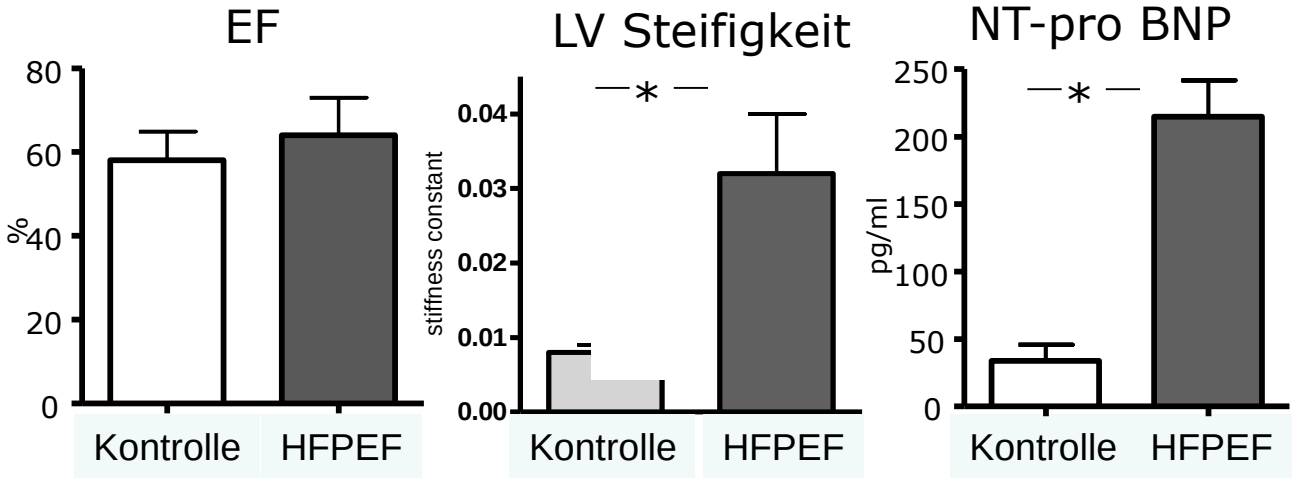


Prof. Dr. med. C. Tschöpe
Charite – Campus Virchow Klinikum
Berlin

Hämodynamische Charakterisierung von Patienten mit Herzinsuffizienzsymptomen trotz erhaltener Ejektionsfraktion





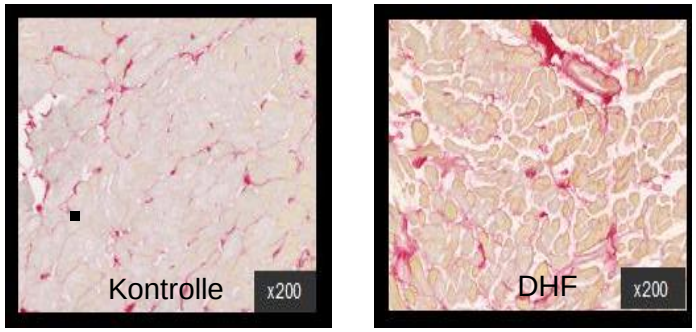


*n =70/ Gruppe, *P<0.05

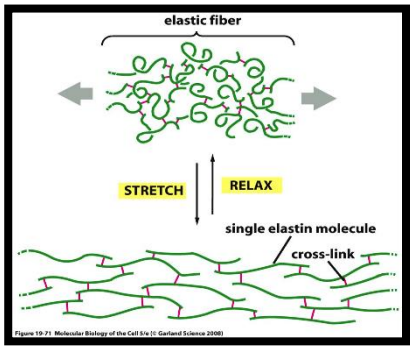
Kasner, Tschöpe et al, Circulation 2007
Westermann, Tschöpe et al, Circulation 2008

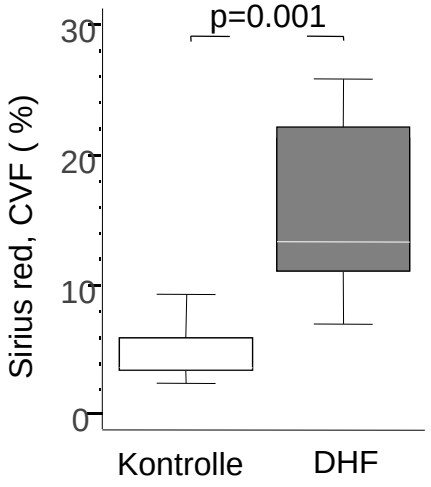
Korrelation: LV Steifigkeit und LV Kollagenindex bei Patienten mit diastolischer Herzinsuffizienz

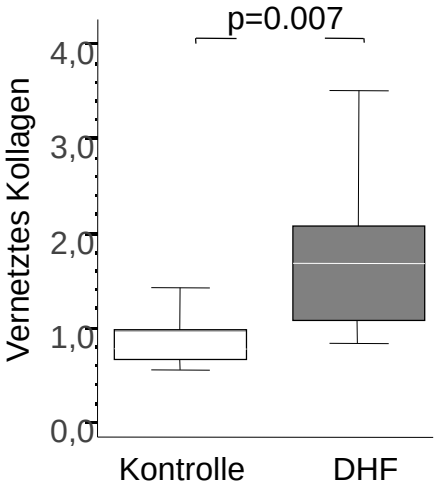
Änderung in Quantität



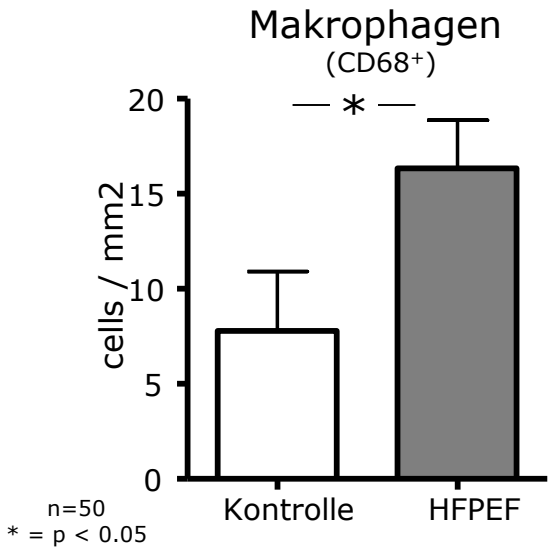
Änderung in Qualität

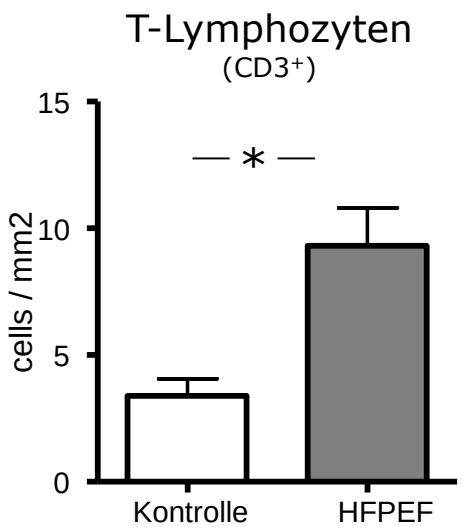




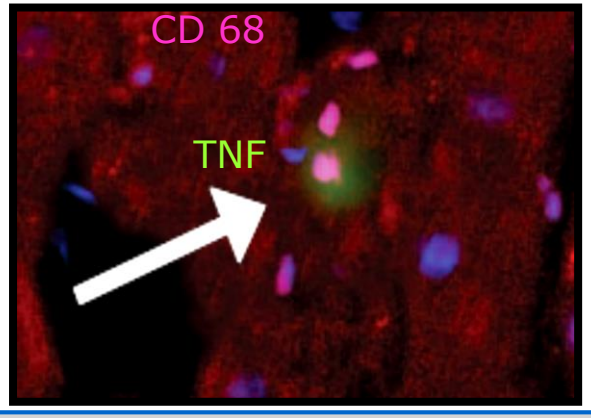


Entzündungsnachweis in endomyokardialen Biopsien von Patienten mit diastolischer Herzinsuffizienz

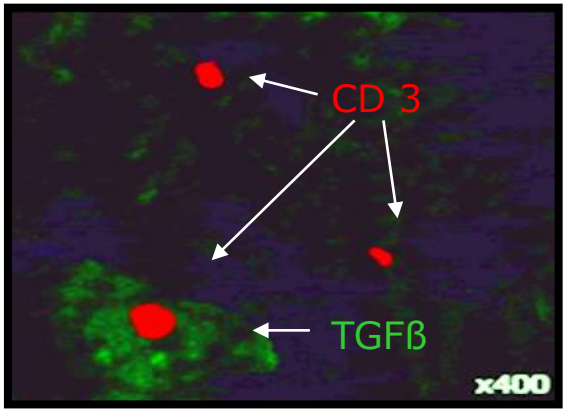




Kolokalization von
TNF- α / CD 68 Zellen

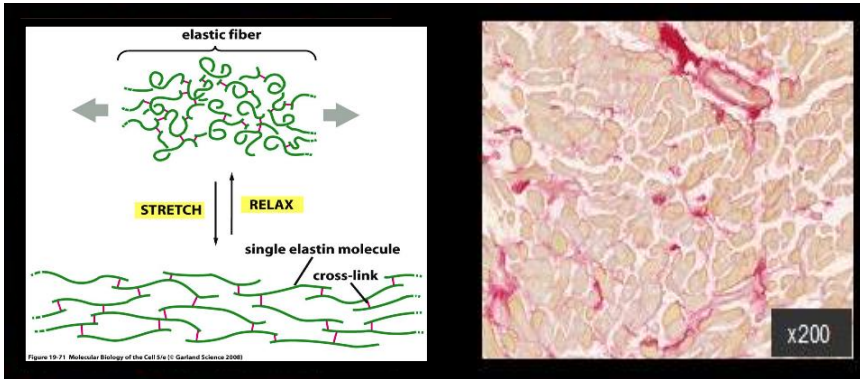


Kolokalization von
TGF-β / CD 3 Zellen

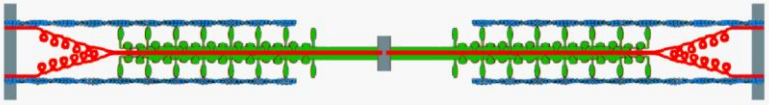


Mechanismen
erhöhte passive LV Steifigkeit

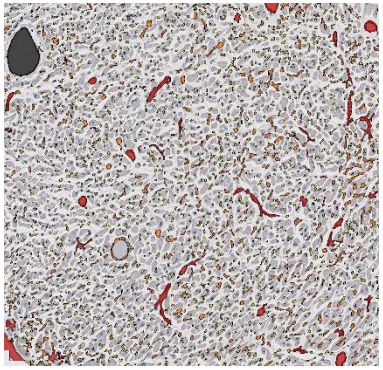
Matrix

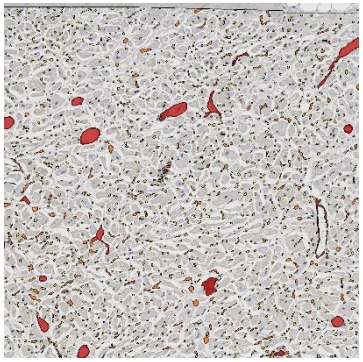


Myozyt



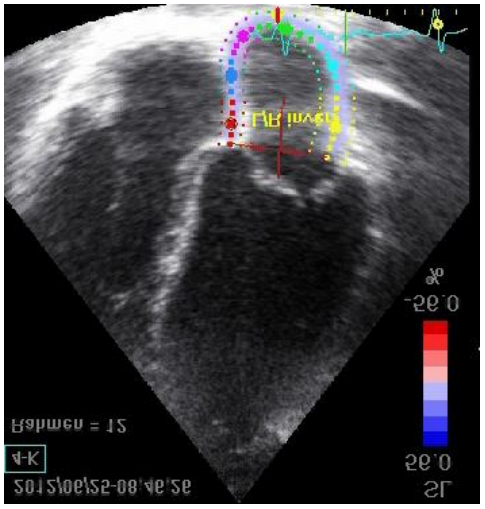
Endothelium

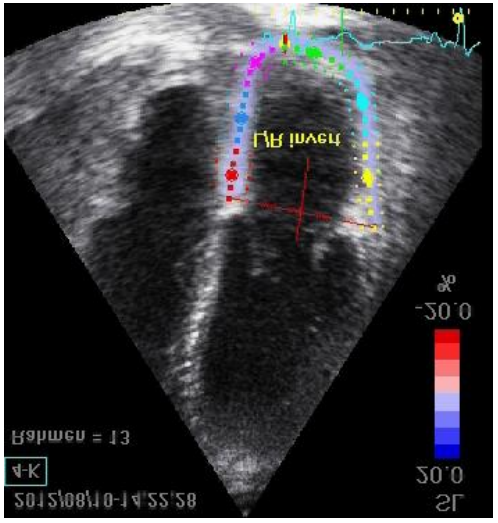




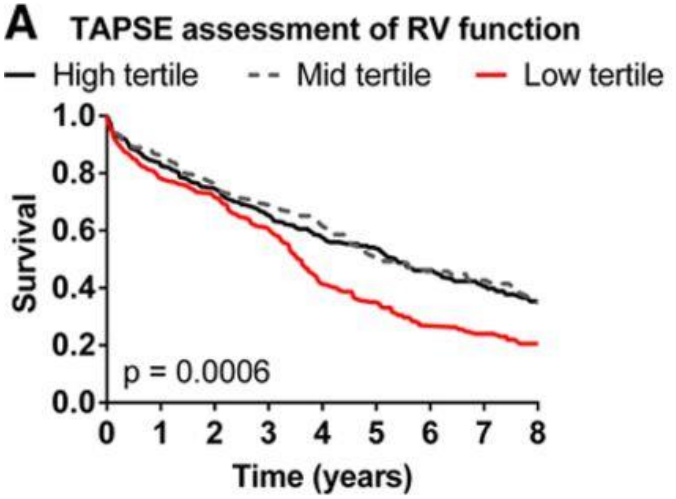
Gefässrarifizierung

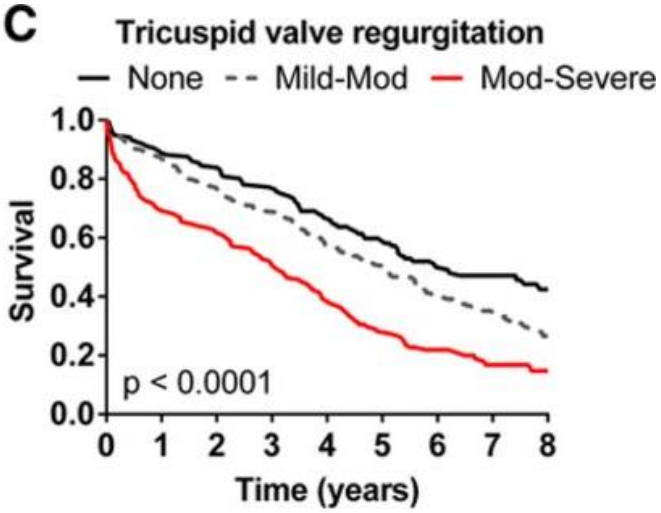
Vorhoffunktion



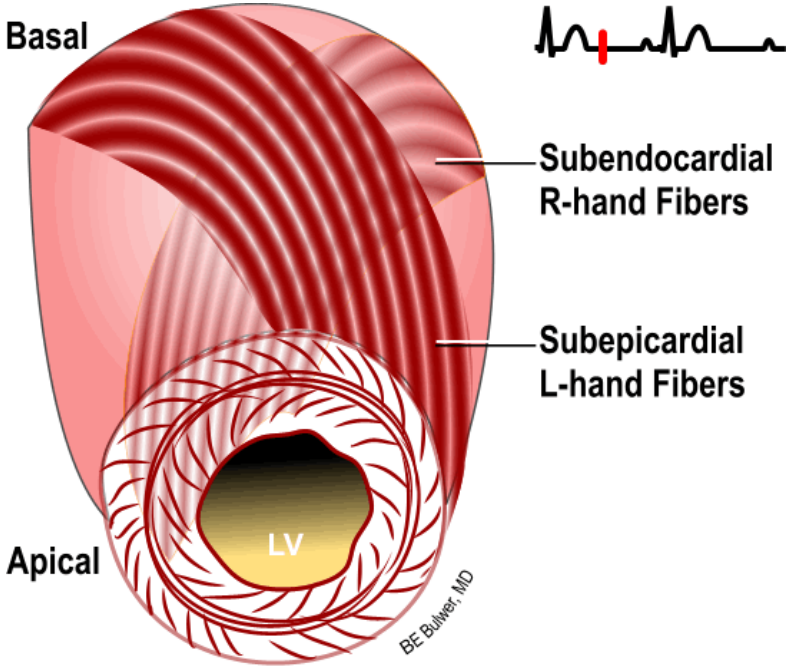


RV-Funktion

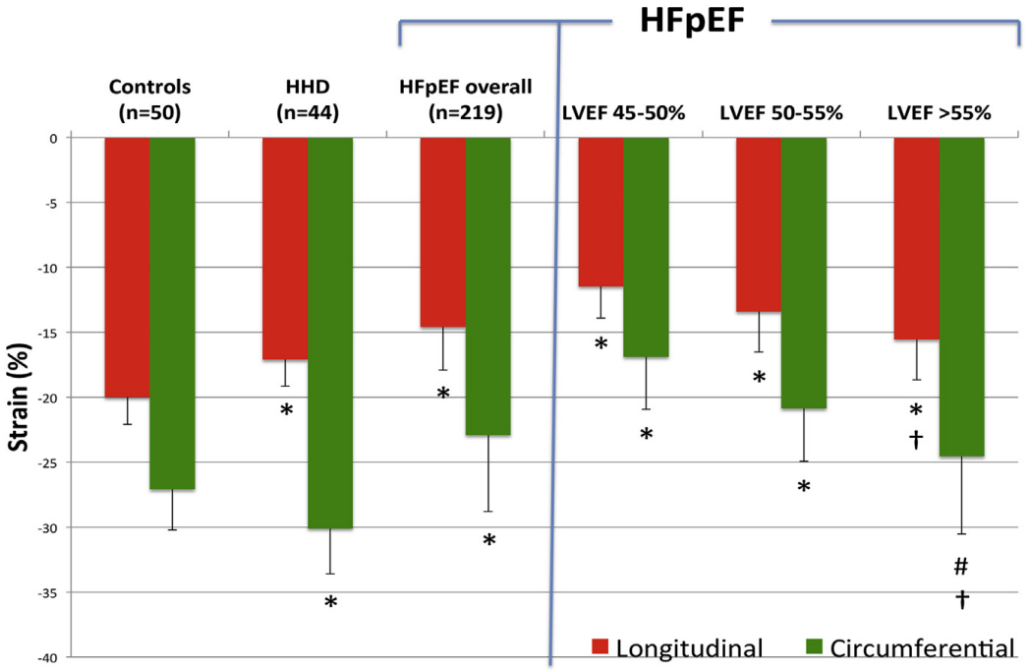




“Diastolische Herzinsuffizienz” bedeutet nicht normale systolische Funktion

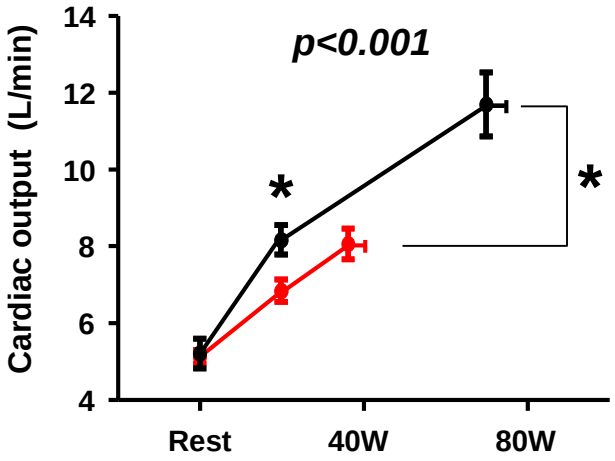


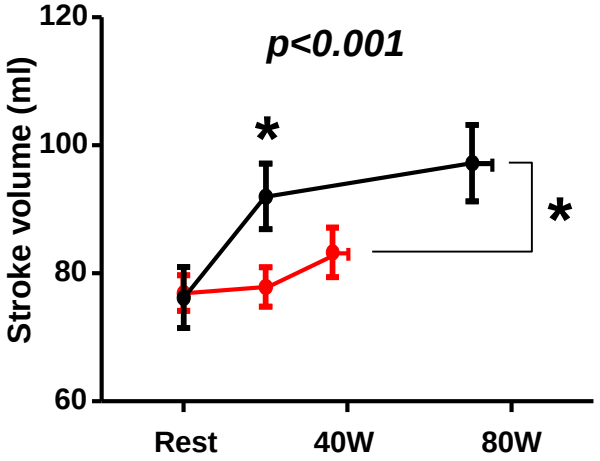
Longitudinal and circumferential Systolic Strain in HFpEF vs. HHD

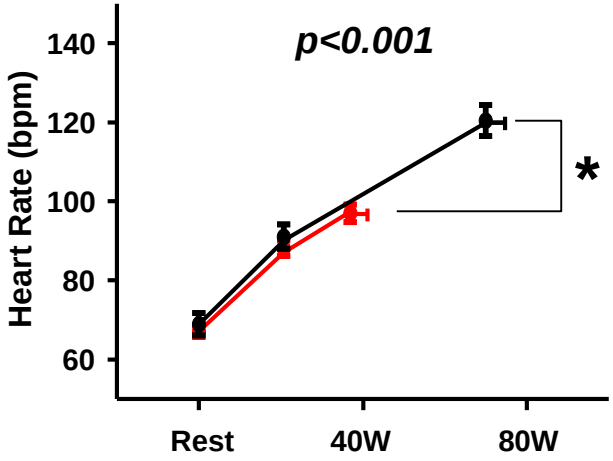


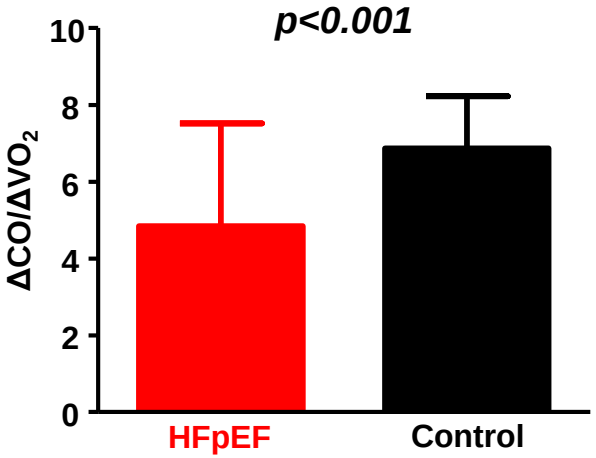
Kraigher-Krainer et al., JACC 2014

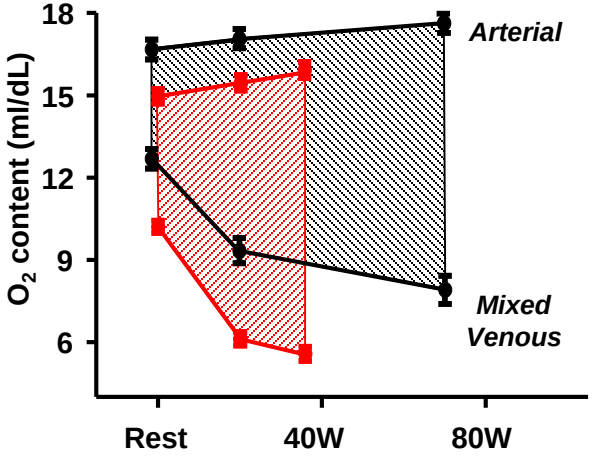
Hämodynamische Konsequenzen unter Belastung









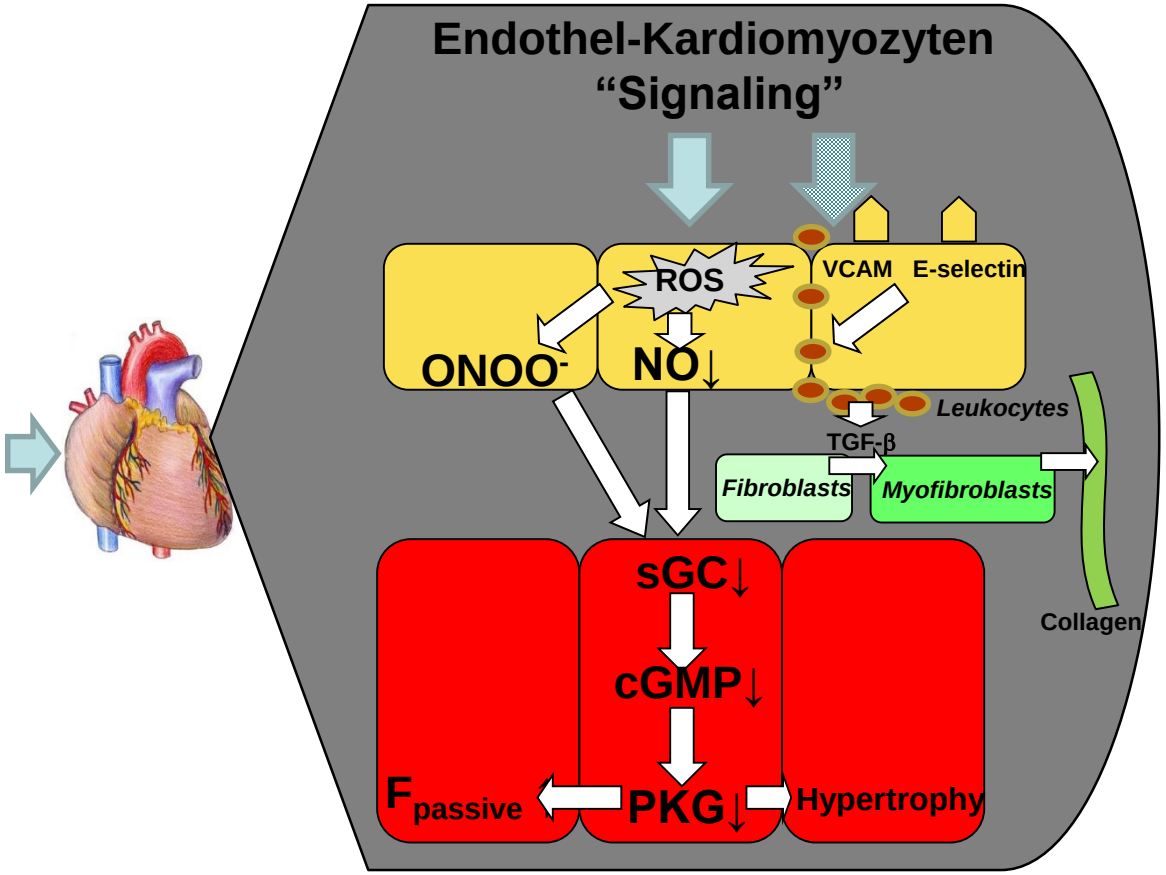


— *"DHF"* — *Control*

Borlaug et al. *Eur Heart J* 2016

Von DHF zu einem heterogenem Syndrom: Herzinsuffizienz mit erhaltener EF

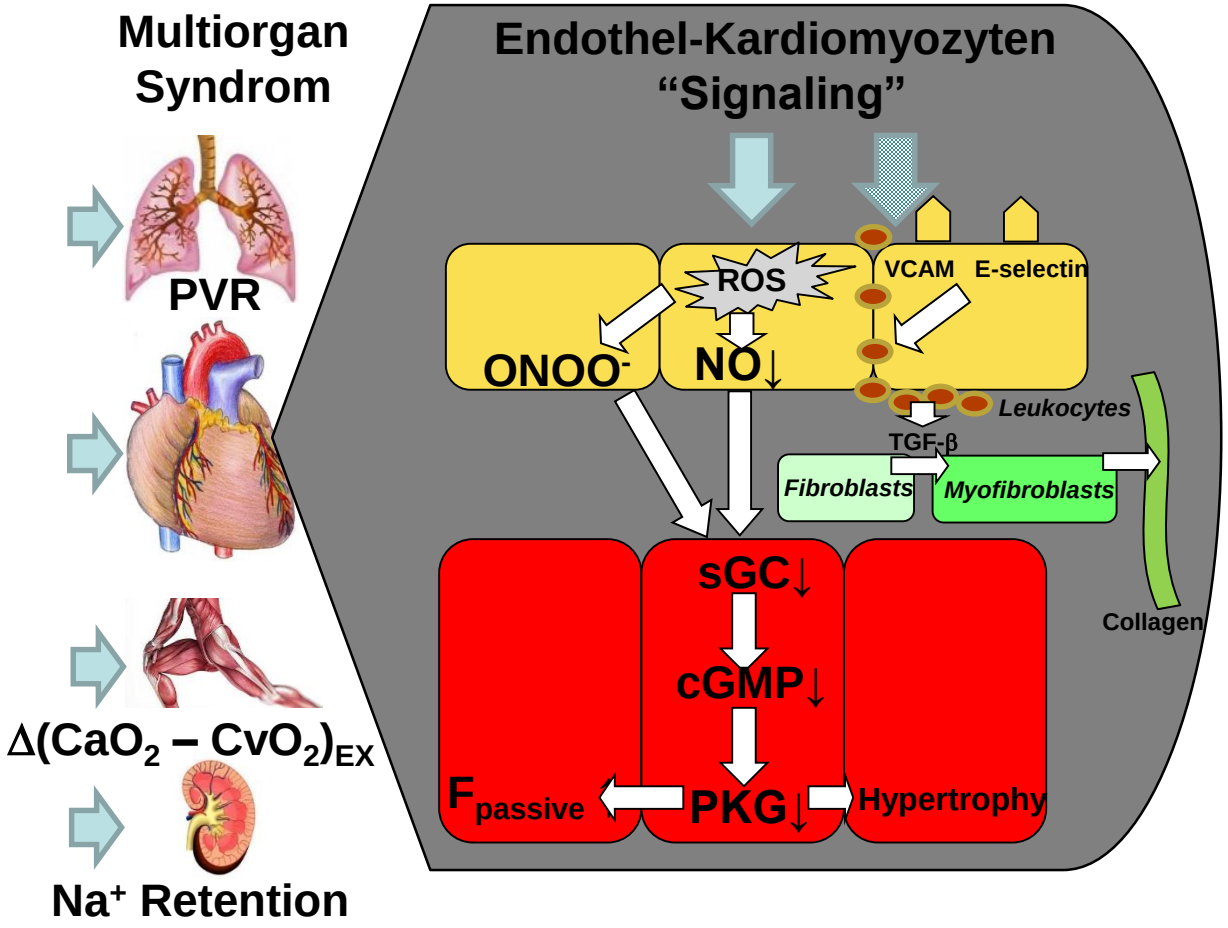
“HFpEF”



Paulus Tschöpe JACC 2013
Paulus Heerenbeck JACC 2015

Von DHF zu einem heterogenem Syndrom: Herzinsuffizienz mit erhaltener EF

“HFpEF”

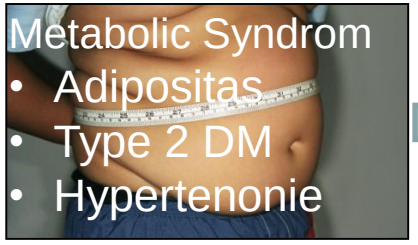


Paulus Tschöpe JACC 2013
Paulus Heerenbeck JACC 2015

Von DHF zu einem heterogenem Syndrom: Herzinsuffizienz mit erhaltener EF

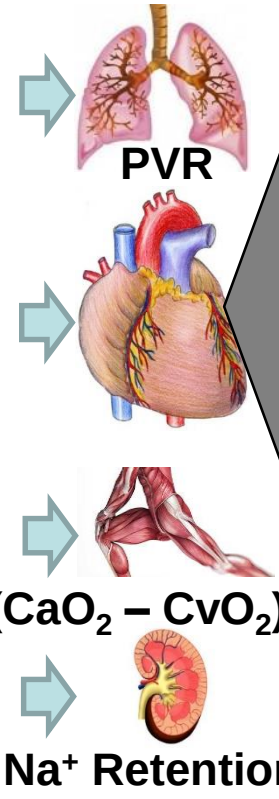
"HFpEF"

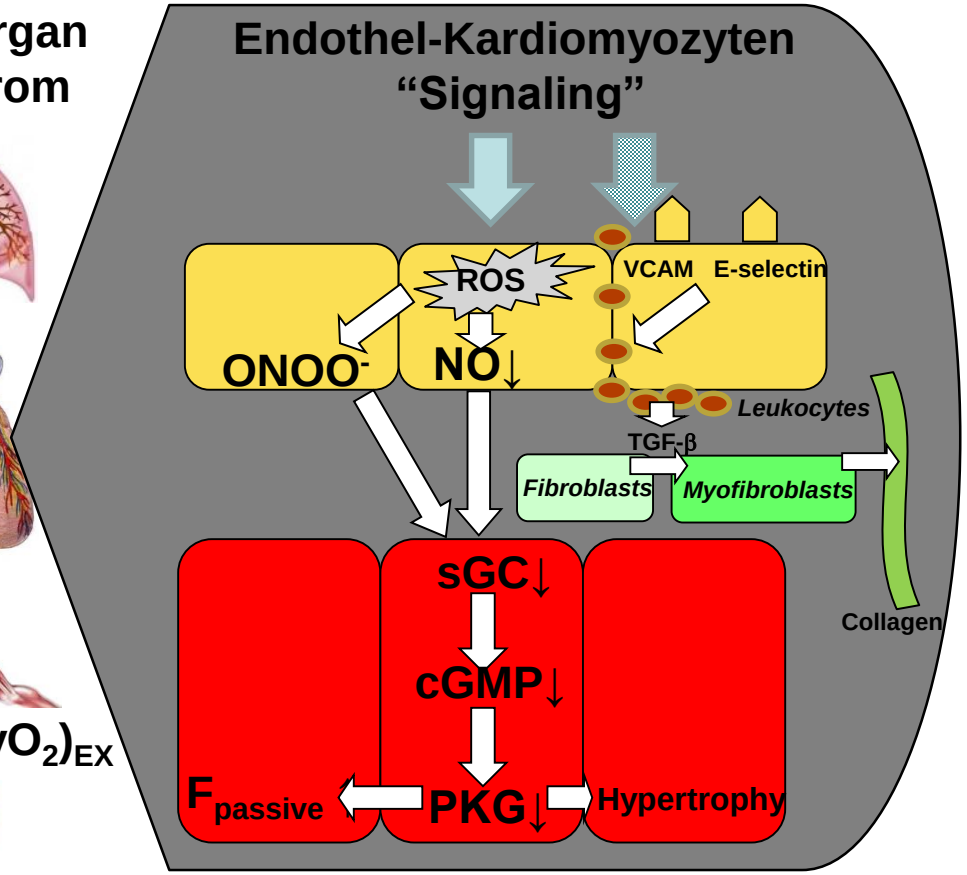
Komorbiditäten



Systemische Inflammation

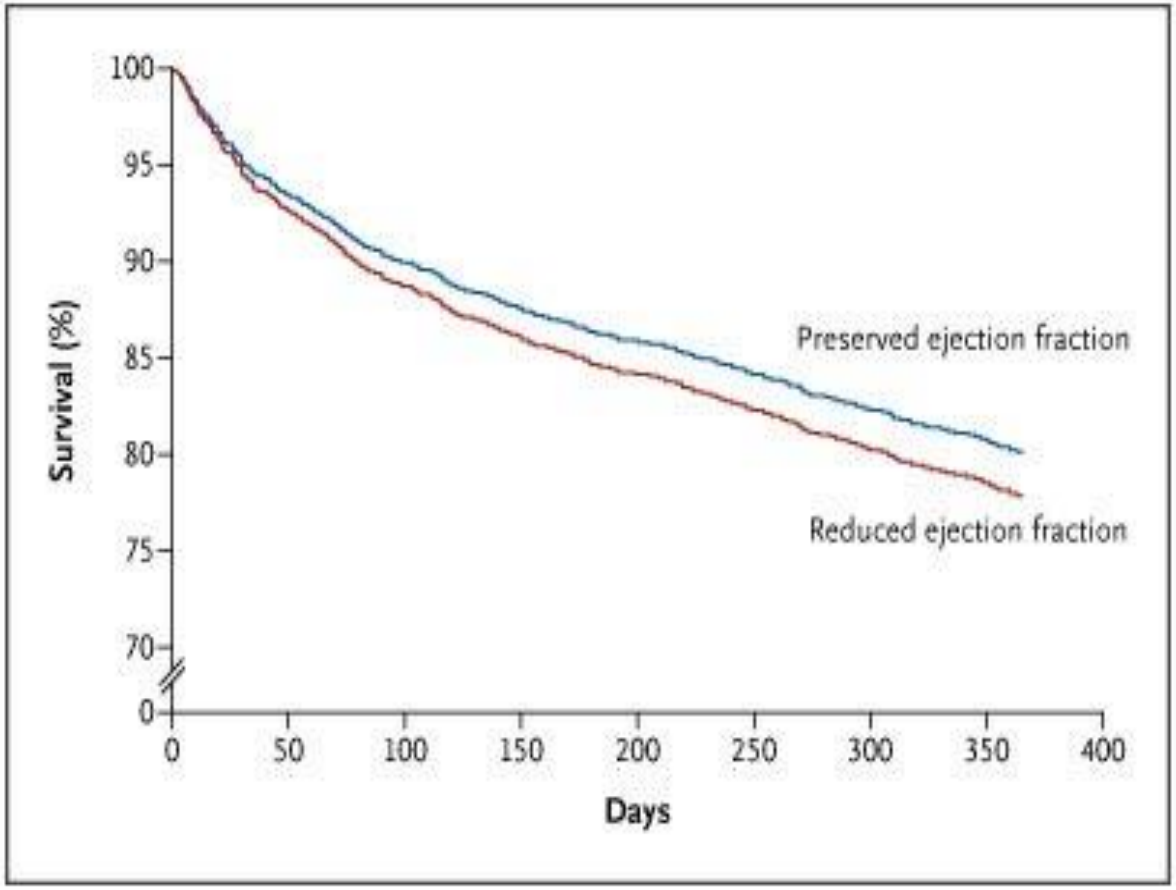
Multiorgan Syndrom





Paulus Tschöpe JACC 2013
Paulus Heerenbeck JACC 2015

Überlebensraten von Patienten mit Herzinsuffzienz und reduzierter versus erhaltener Auswurffraktion 1 Jahr nach Krankenhaus-Aufnahme



Bhatia R et al. N Engl J Med 2006;355:260-269

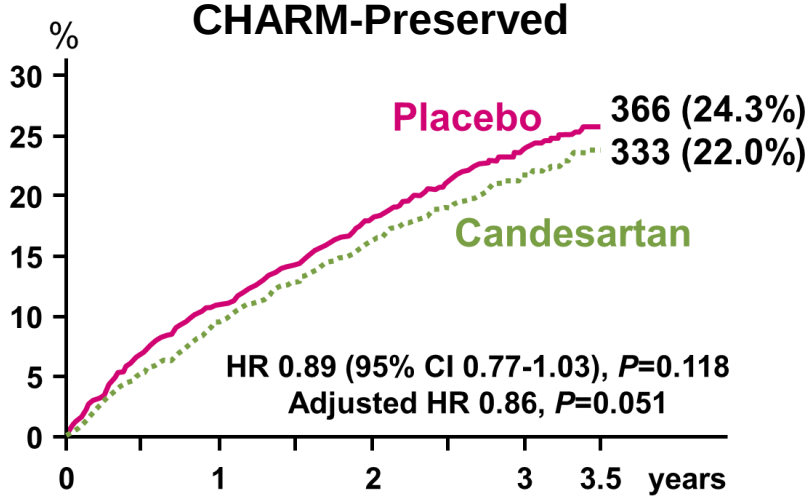
Therapie:

Etablierte Konzepte übertragen?

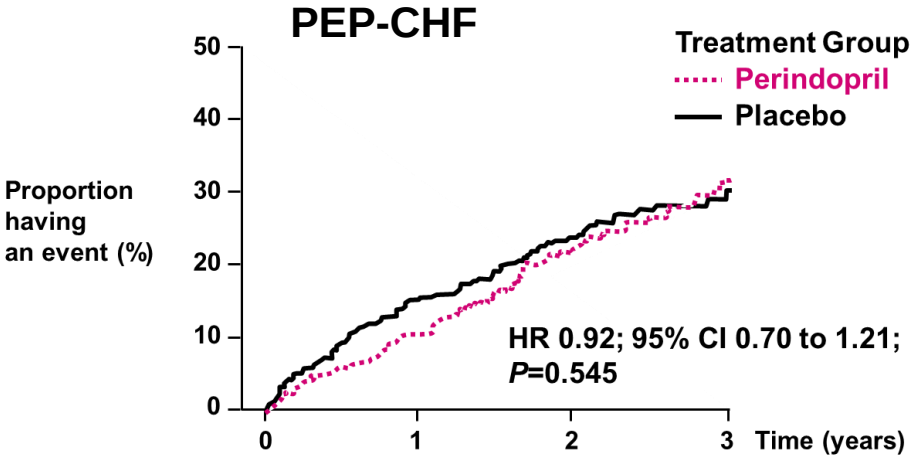
„One fits all?“

Outcome-Studien bei HFpEF

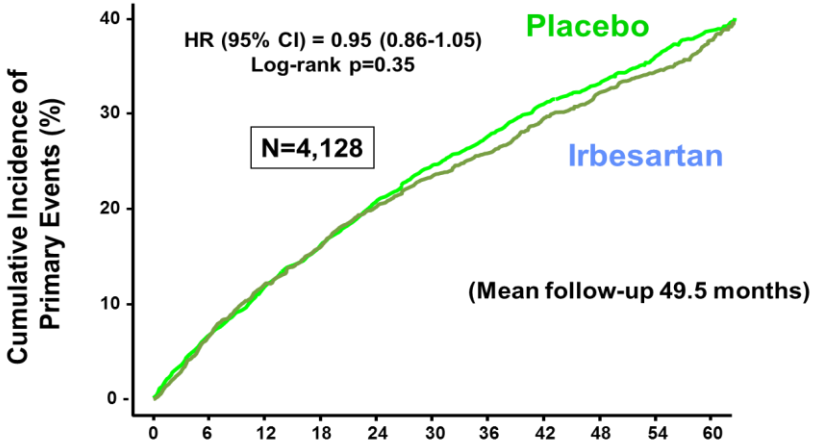
CHARM-Preserved



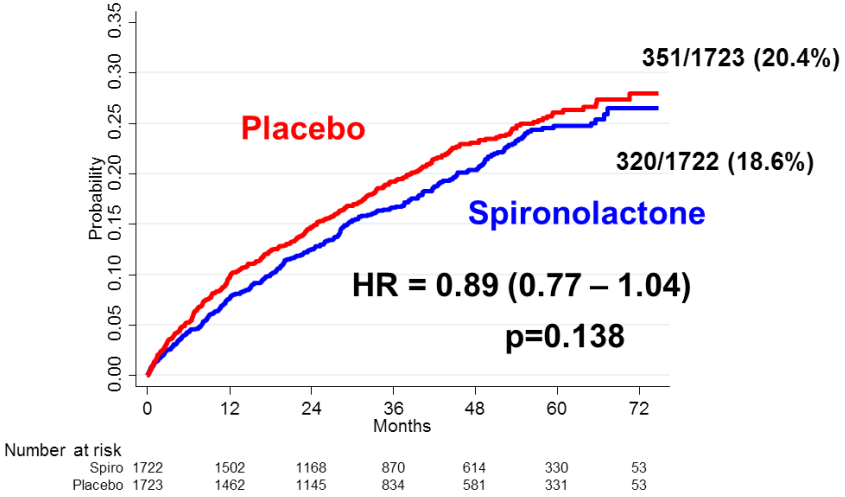
PEP-CHF



I-PRESERVE

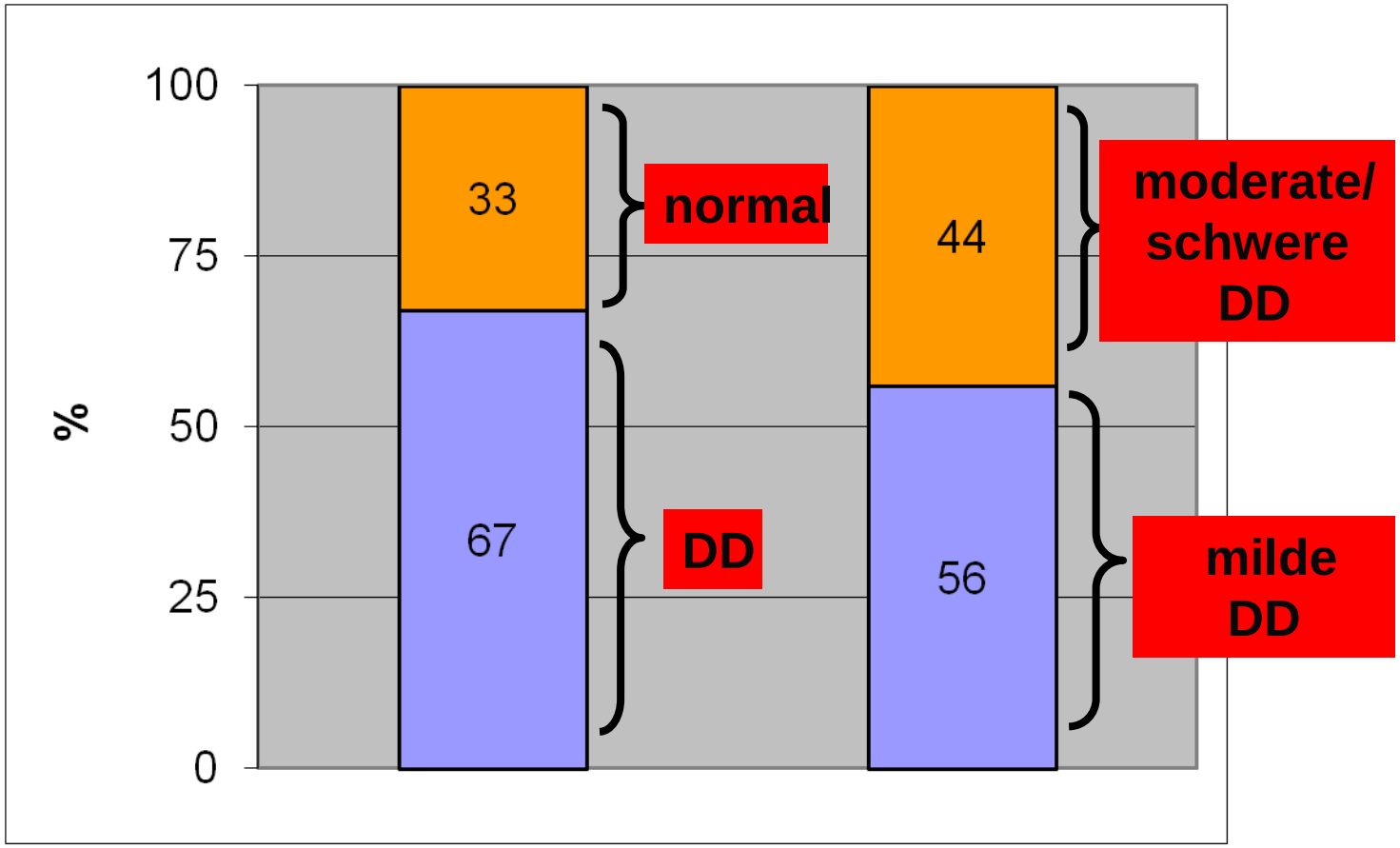


TOPCAT



Wer hatte eine bedeutsame diastolische Dysfunktion in CHARM-PRESERVED ?

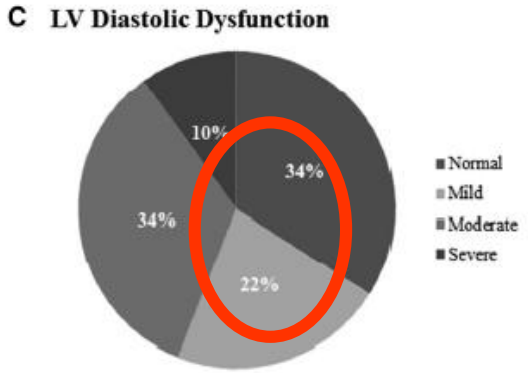
(CHARMES-Substudy)



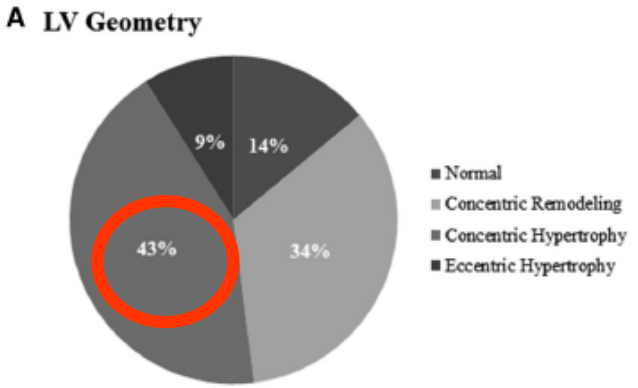
Nach Persson et al , JACC 2007

Echosubstudie in TOPCAT

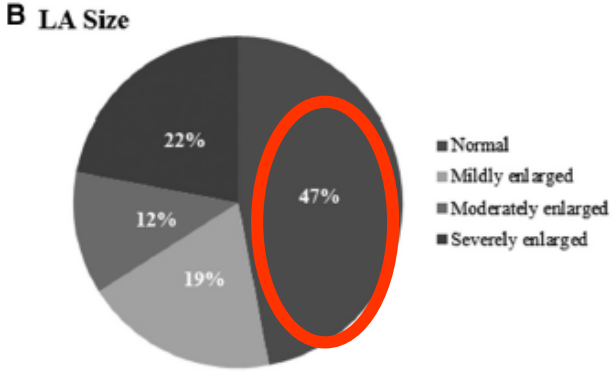
~ 56%
normale diastolische Funktion



43% kein strukturelles LV Remodeling



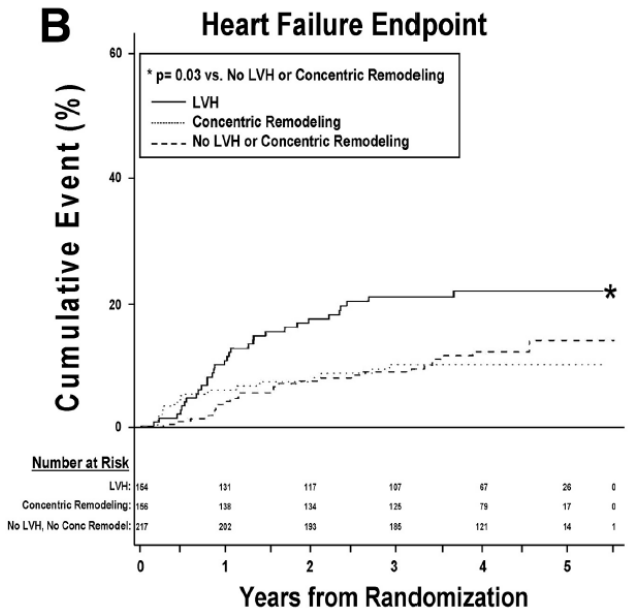
47% normale Vorhofgrösse



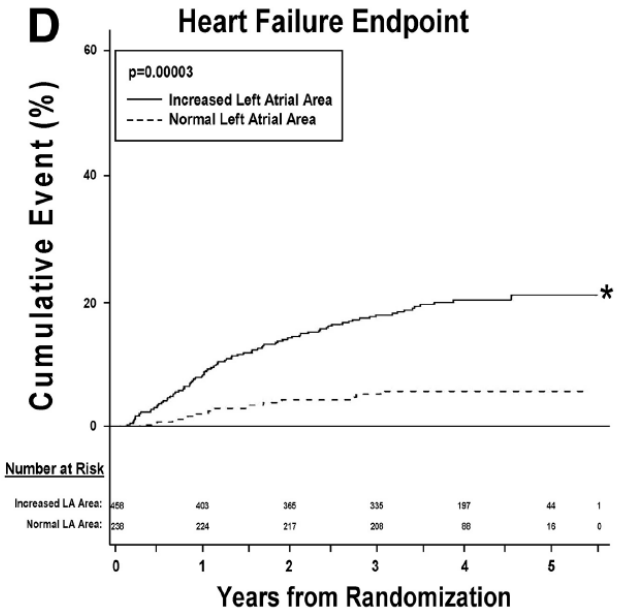
Remodeling und Prognose

I-Preserve Echo Substudy:
Objective evidence of remodeling/diastolic dysfunction = more heart failure endpoints!

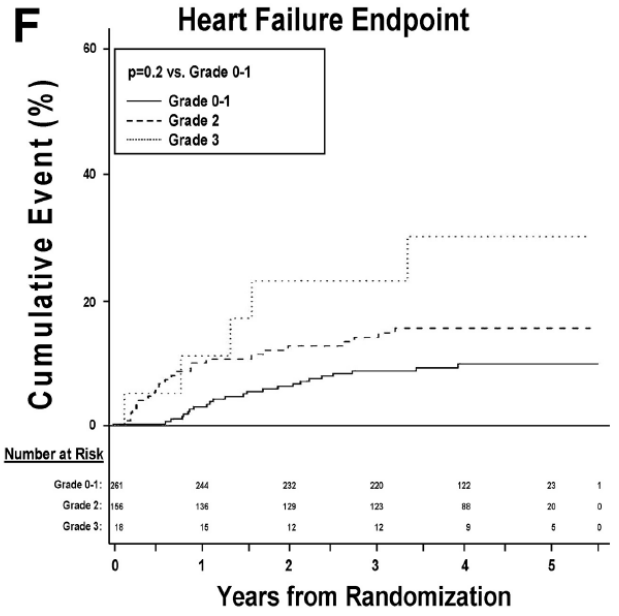
LV Hypertrophie



LA Dilatation



Diastolische Dysfunktion



Zile et al.; Circulation 2011

Multifaktorielle kardiale Ätiologien bei HFPEF

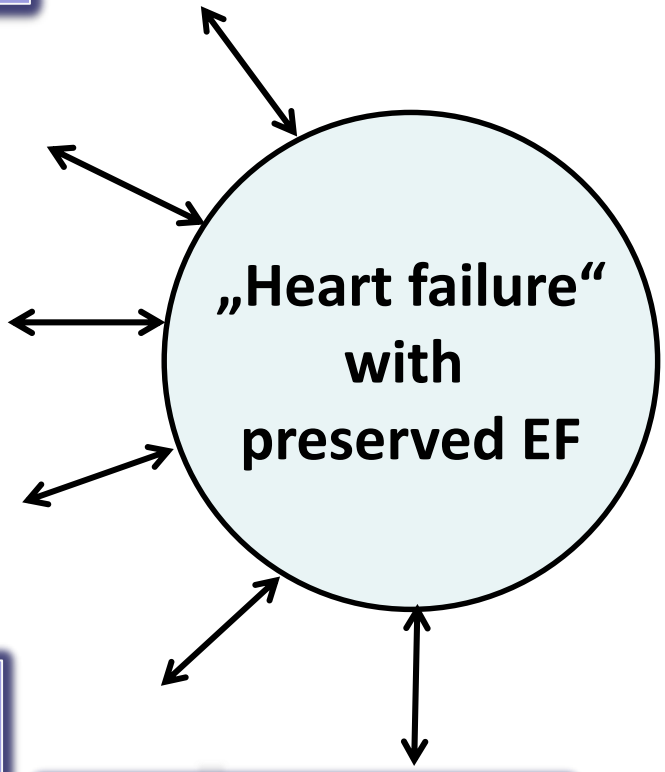
Ventricular Dysfunction
- Impaired relaxation
- Impaired filling
- Systolic Dysfunction

Atrial dysfunction

Autonomic dysfunction
Chronotropic incompetence

Vascular dysfunction
Vascular stiffening
Ventriculo-arterial coupling

Elevated blood pressure
Inadequate BP response to exercise
Pulmonary hypertension



Valvular disease
Dynamic mitral regurgitation

Klinische Definition Diagnostik

Diagnostische Kriterien für HFpEF

1 **Zeichen und/oder Symptome der CHF**

und

HFPEF = mehr Patienten, aber wenig spezifisch

HFPEF mit DHF = weniger Patienten, mehr spezifisch

und

3 **Abnormale Relaxation, Füllung, Steifigkeit**

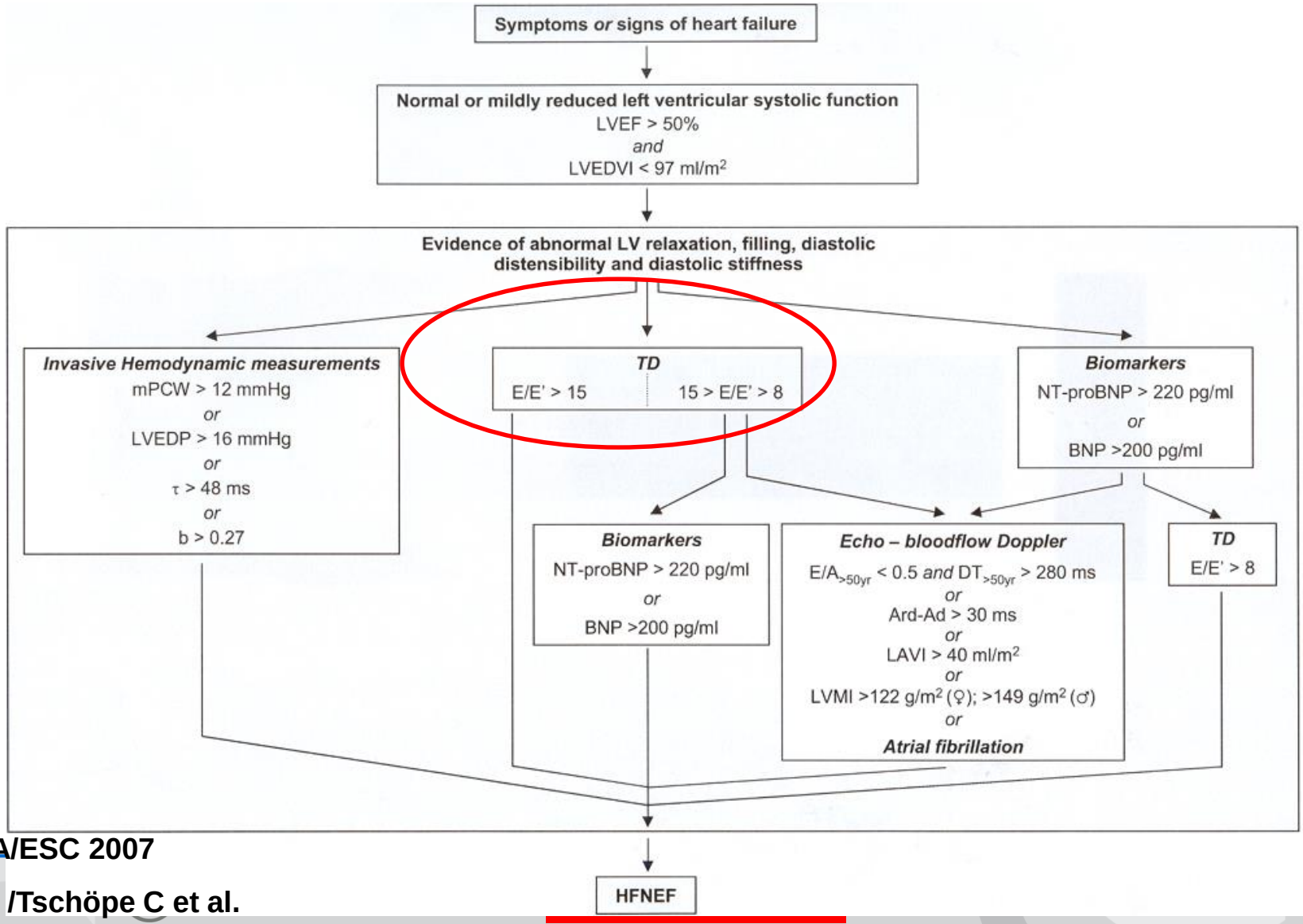
HFPEF

HFPEF mit DD

Paulus, Tschöpe ... et al for the Heart Failure and Echocardiography Associations of the ESC; Eur Heart J April 2007

Patric C. Tschöpe

Diastolische Dyfunktion in HFpEF



HFA/ESC 2007

Paulus W /Tschöpe C et al.

„Filling Index“

E/E´

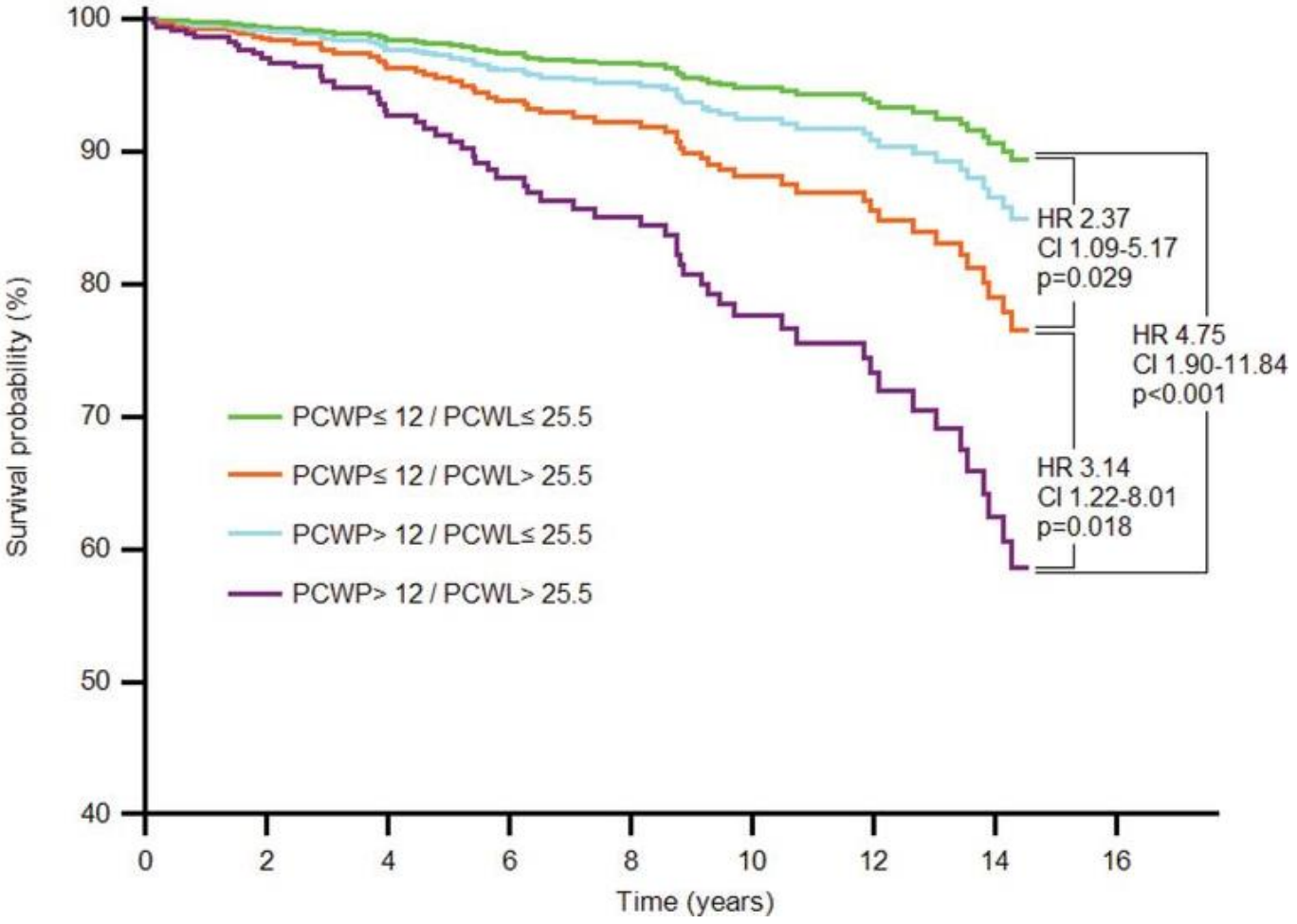
no HFPEF **< 8** **?** **> 15** **HFPEF**

E/A and DT
Pulmonal Venen Doppler
BNP
LAVI / Strain
LAVI > > 26 ml/m2 *

*> 40 ml/m2 sufficient evidence for diastolic dysfunction

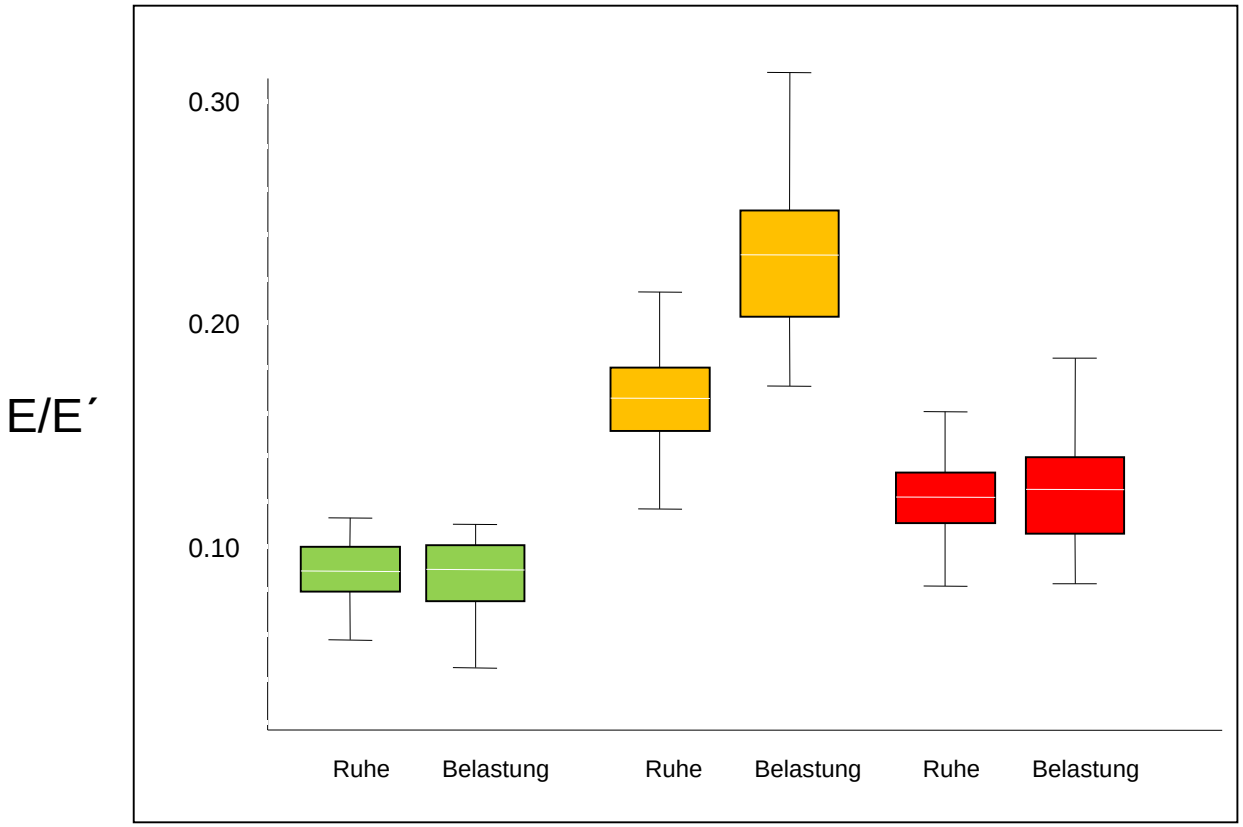
Paulus, Tschöpe ... et al for the Heart Failure and Echocardiography Associations of the ESC; Eur Heart J April 2007

Rechtsherzkathetermessungen unter Belastung und Prognose bei HFpEF

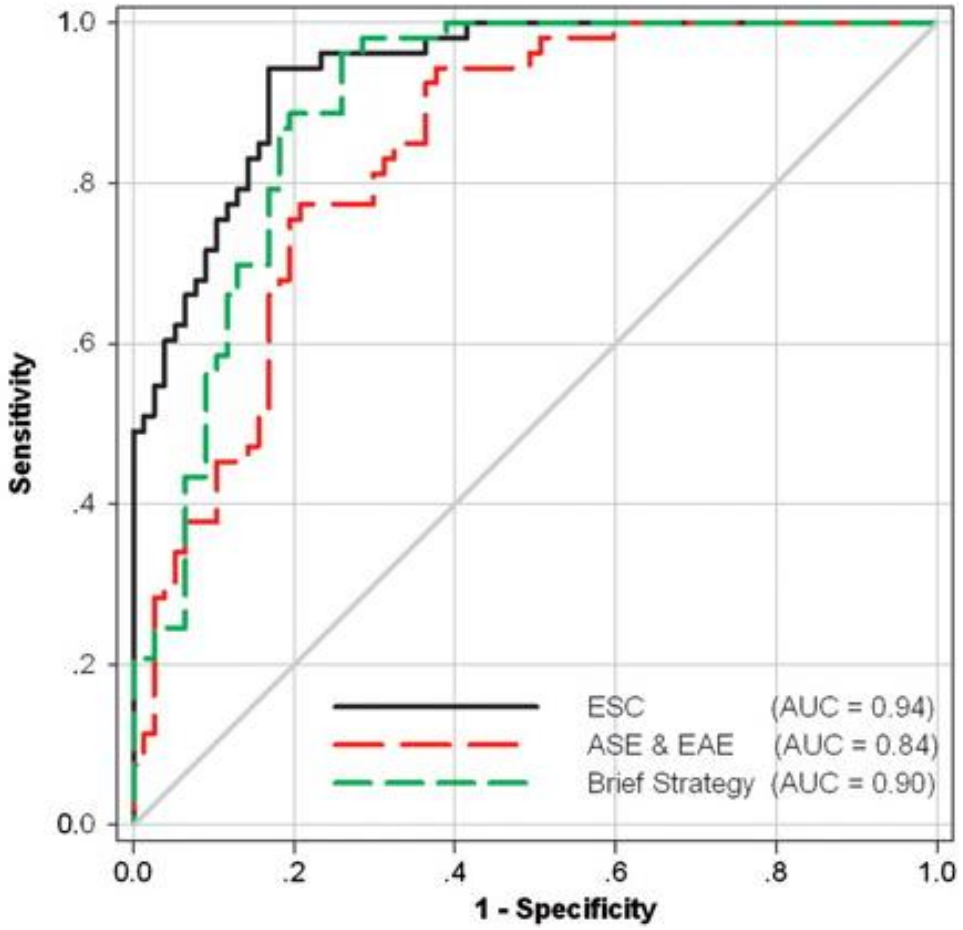


Dorfs S et al., Eur Heart J., 2014, 3103-12

Rolle der Belastungs 3D Echokardiographie



Validierung der ESC Empfehlungen



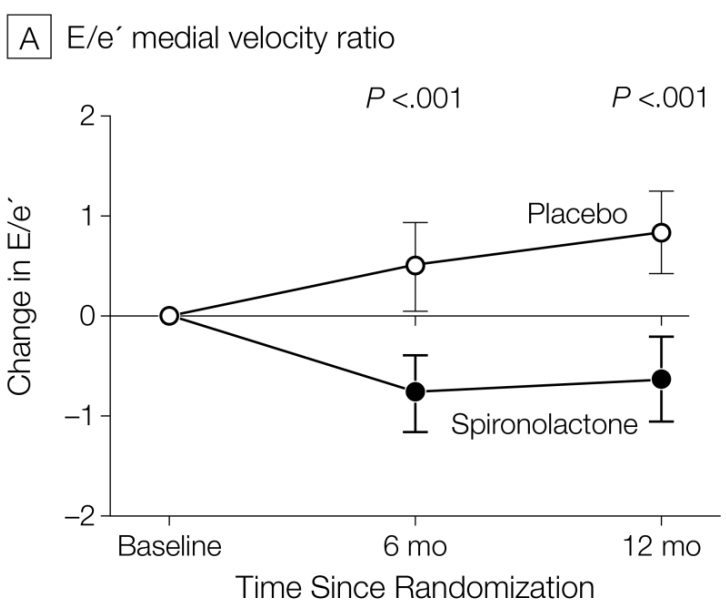
Aber bis heute in keinem Outcome Trail angewandt

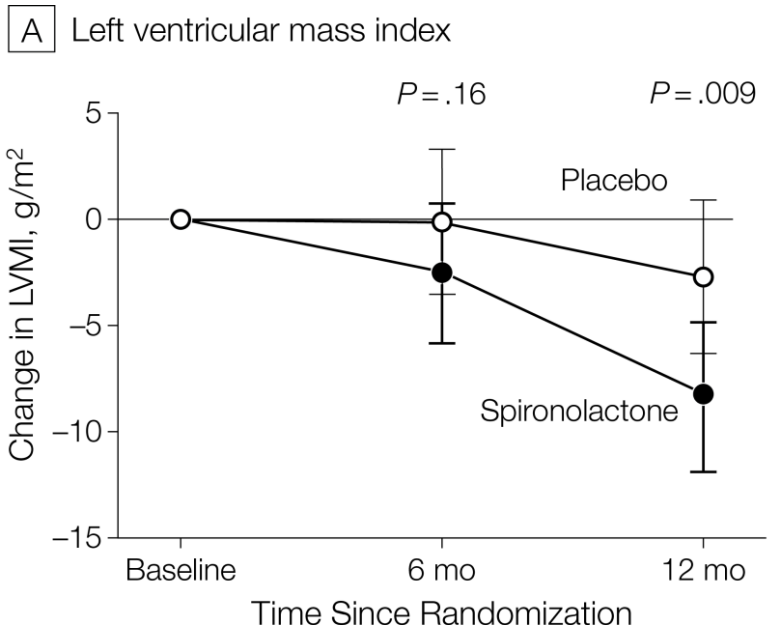
Ausnahme:
Phase II:
- ALDO-DHF
- Paramount

Shuai X et al. Eur J Heart Fail 2011

ALDO-DHF

Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction: The Aldo-DHF Randomized Controlled Trial

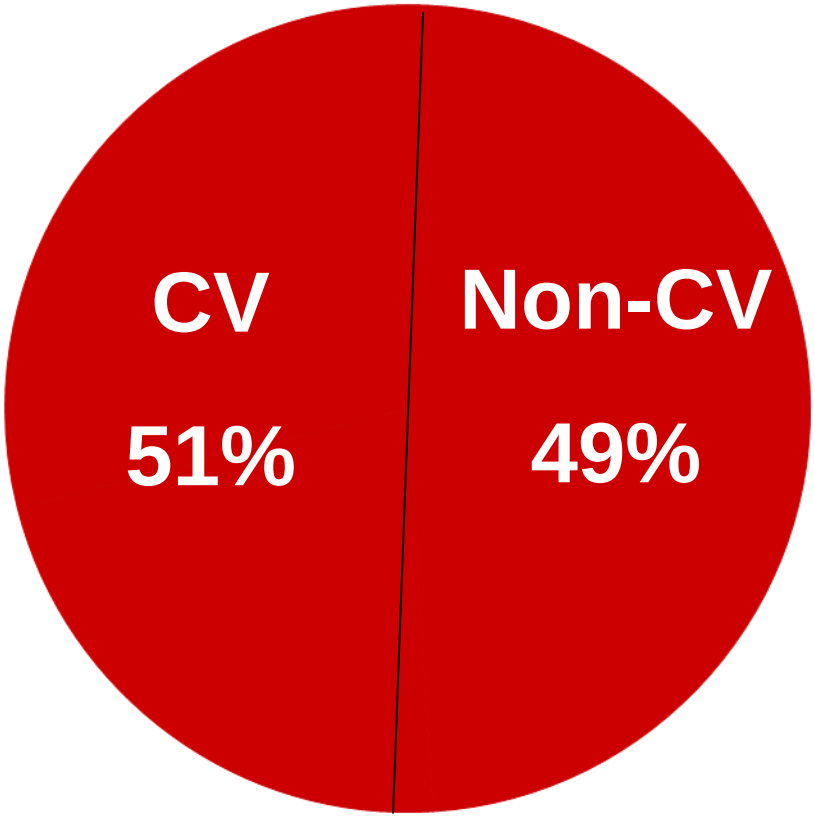




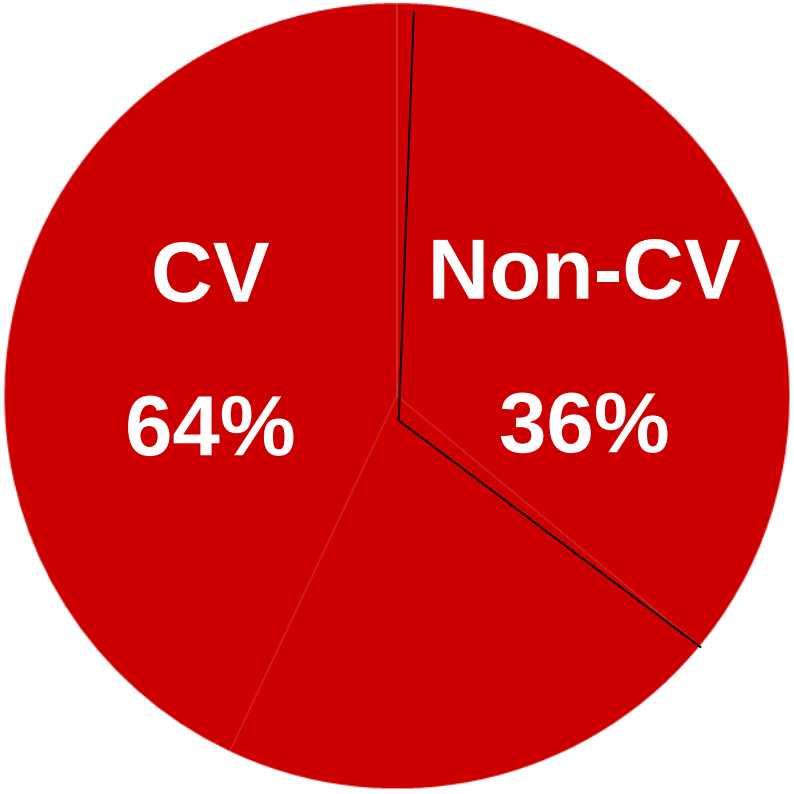
Kein Effekt auf Lebensqualität

Edelmann et al, JAMA 2013

Rolle der Komorbiditäten bei HFpEF

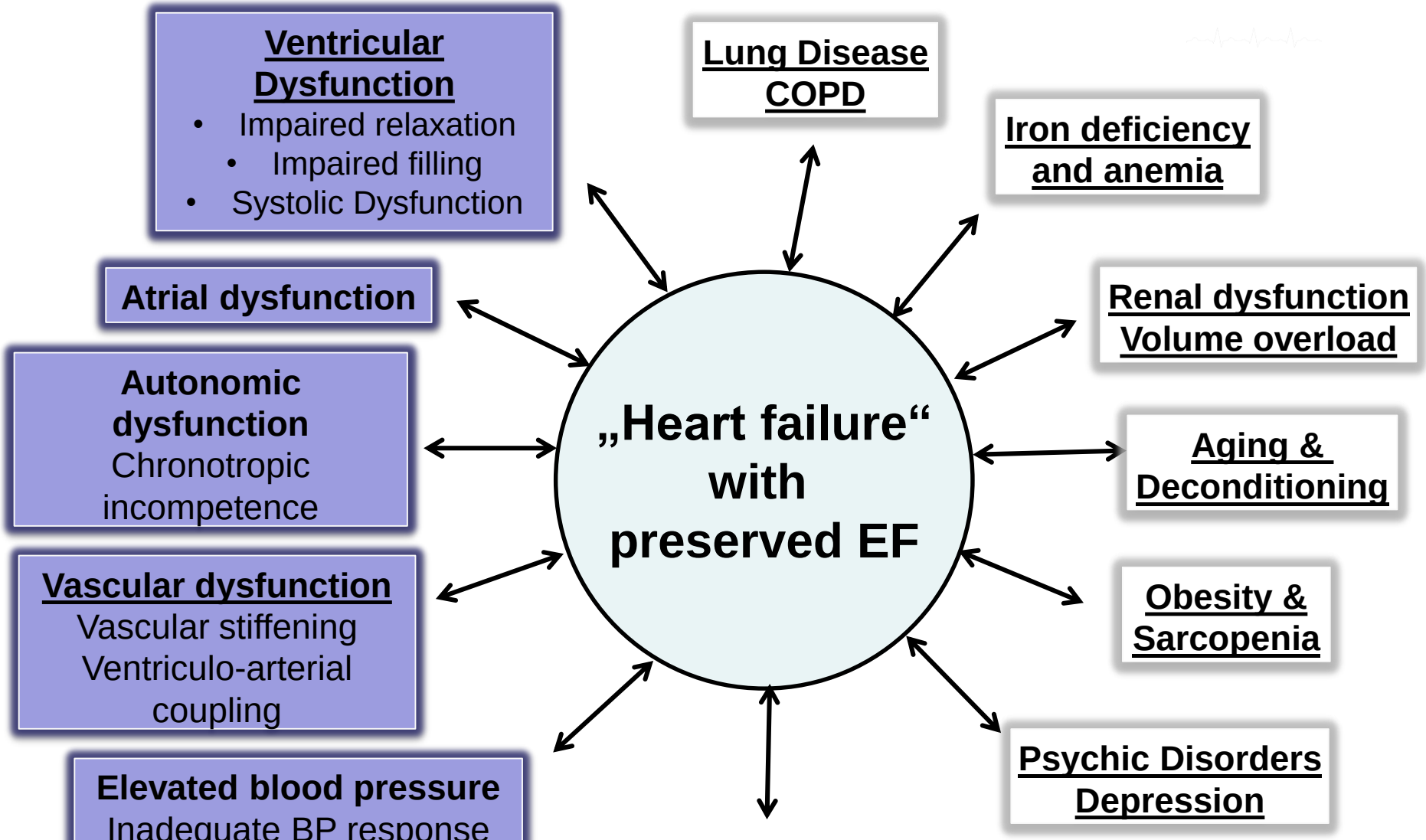


HFpEF



HFrEF

Henkle DM, Circ-HF 2008


Ventricular Dysfunction
• Impaired relaxation
• Impaired filling
• Systolic Dysfunction
Lung Disease COPD
Iron deficiency and anemia
Atrial dysfunction
Renal dysfunction Volume overload
Autonomic dysfunction
Chronotropic incompetence
„Heart failure“ with preserved EF
Aging & Deconditioning
Vascular dysfunction
Vascular stiffening
Ventriculo-arterial coupling
Obesity & Sarcopenia
Psychic Disorders Depression
Elevated blood pressure
Inadequate BP response to exercise
Pulmonary hypertension
Valvular disease
Dynamic mitral regurgitation

64,140 Registrations
2000 – 2011
64 of 77 hospitals
84 of 1,011 primary care clinics
→ *validity / generalizability*
43 relevant co-variates
→ *reliability*

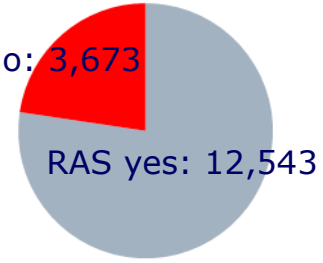
The Swedish Heart Failure Registry

→ 22,349 Re-registrations

41,791 Unique patients

→ 25,575 EF < 40%
EF unknown
ACEi or ARB unknown

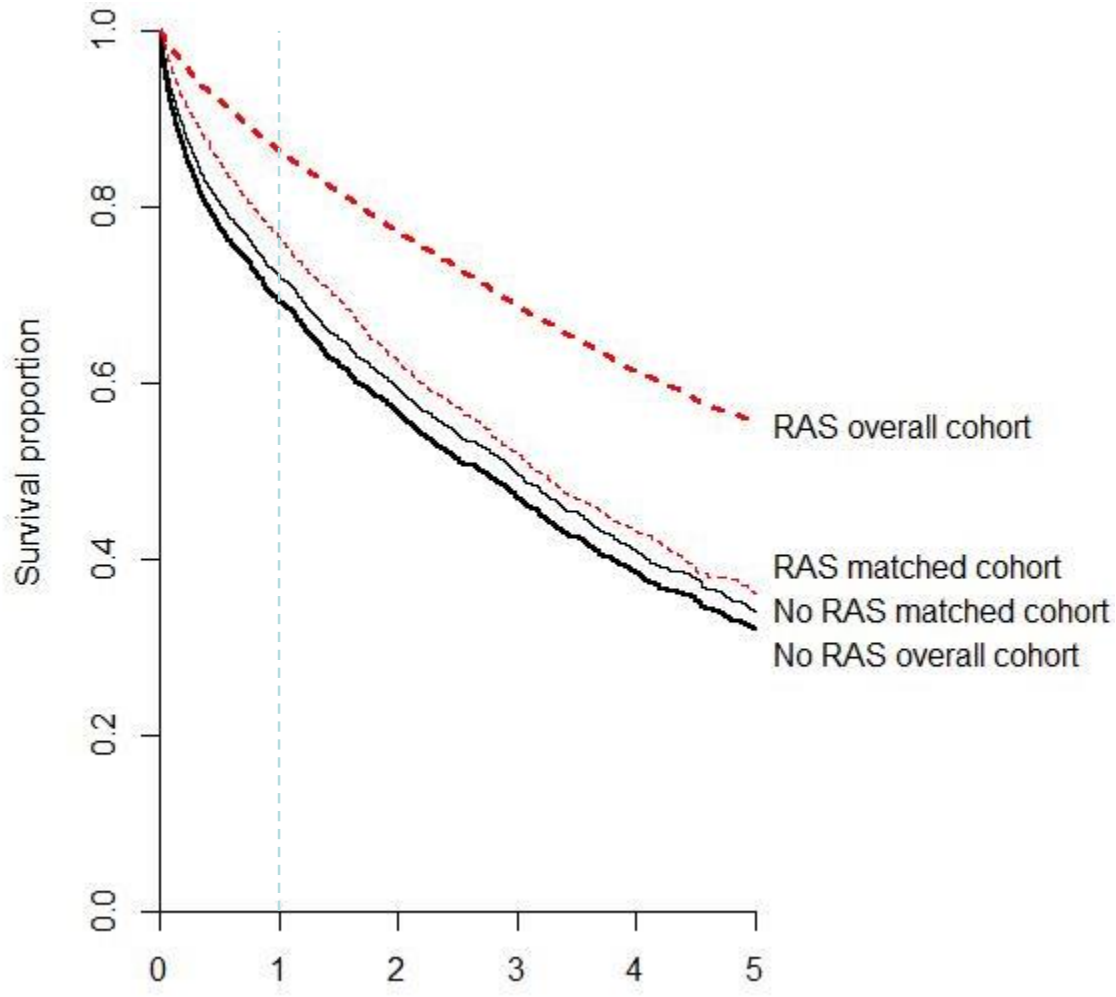
16,216 EF **≥ 40%**



- Propensity score
- Matching 1:1 based on propensity score and age

6,658 Matched population

RAS-Antagonisten reduzieren HFpEF Mortalität in ”the real life”



1-year survival

86%

77%

72%

69%

Un-adjusted HR: 0.48, p < 0.001

Matched HR: 0.91, p = 0.008

Studien vs Register

The Swedish Heart Failure Registry: older, sicker, more ”real-life”

	CHARM-Preserved Candesartan	PEP-CHF Perindopril	I-PRESERVE Irbesartan	Owan / Bhatia	Matched cohort ACEi / ARB
Age	67	75	72	74 / 75	**79**
Creatinine, µmol/L , mL/min	-	95-97	88	141 / -	**Clearance 52-53**
NT-proBNP, ng/L	-	335-453	320-360	-	**4,577-5,192**
Treatment change	-	26% cross-over	34% stopped 40% hade ACEi	NA	**Unknown**
Primary end-point	CV death or HF hospitalization	Death or HF hospitalization	Death or CV hospitalization	Death	**Death**
Endpoint at 1 yr	~8%	~10%	~12%	29% / 22%	**23% vs. 28%**
Significant benefit	↓ HF hospitalization	↓ HF hospitalization at 1 year	None	NA	↓ **Mortality**
Reference	Yusuf, Lancet 2003	Cleland, EHJ 2006	Massie, NEJM 2008	Owan, NEJM 2006 Bhatia, NEJM 2006	

Einteilung von HFpEF Patienten nach klinischen Kriterien

Pheno-Mapping

Pheno-group 1

- *N=128*
- Younger
- Moderate diastolic dysfunction
- Normal BNP

Pheno-group 2

- *N=120*
- Obese
- Diabetic
- Obstructive sleep apnea
- Worst LV relaxation

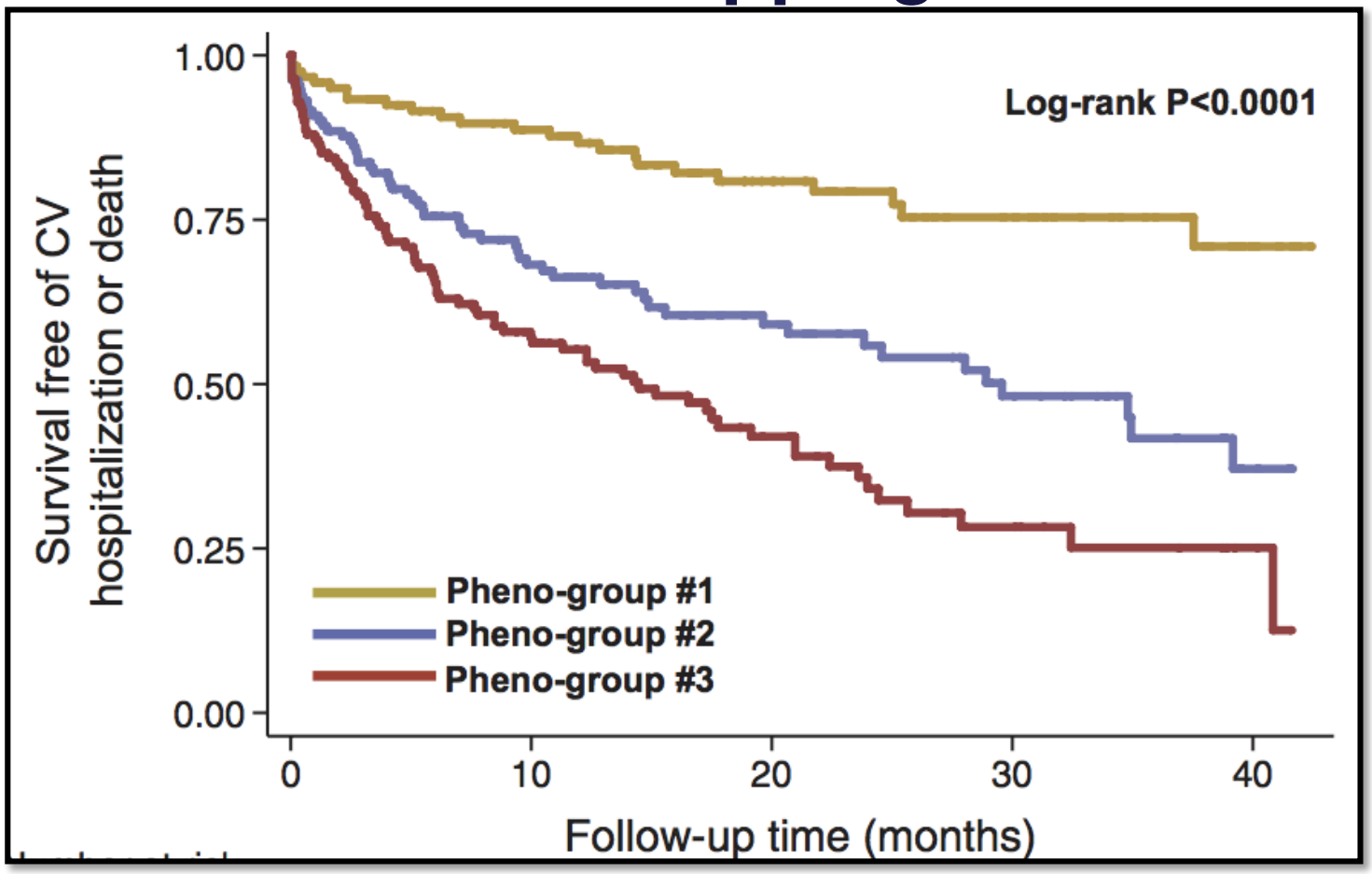
Pheno-group 3

- *N=149*
- Older
- Chronic kidney disease
- Pulmonary hypertension
- RV dysfunction

Shah SJ, et al. Circulation 2015

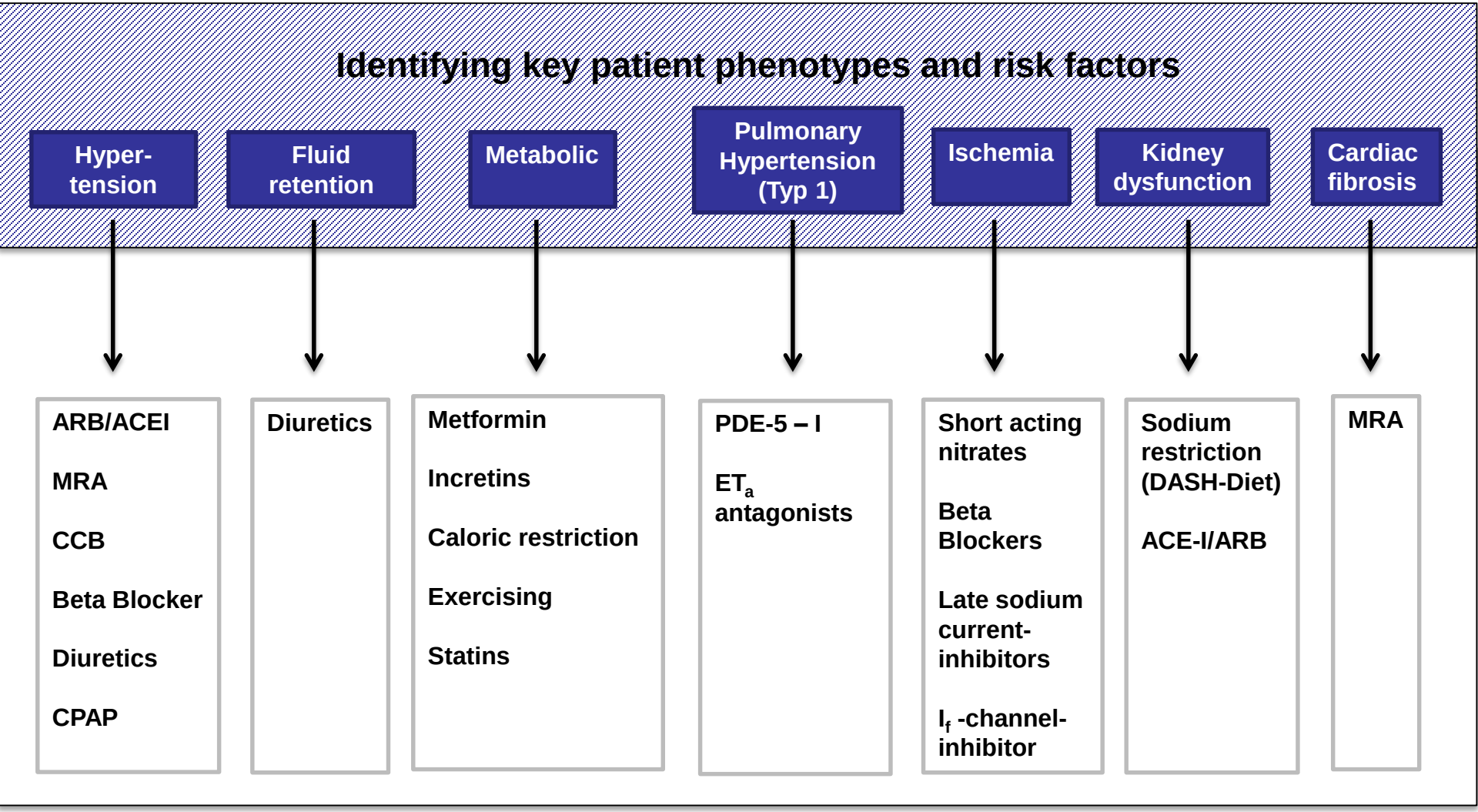
Eintteilung von HFpEF Patienten nach klinischen Kriterien

Pheno-Mapping



Shah SJ, et al. Circulation 2015

Therapeutisches Management nach Symptomen und Risikofaktoren bei HFpEF



Tschöpe et al CRC 2017 in press

Spezifische Therapie Evidence Ia

Diagnosesicherung nach der Leitlinie … et al. 2007 Eur Heart J

Kausale medikamentöse Therapie der …eiten:

-> …tes , Adipositas, Ischämie, KHK, Klappen

Evidenced based therapy

Mögl- Therapie Optionen

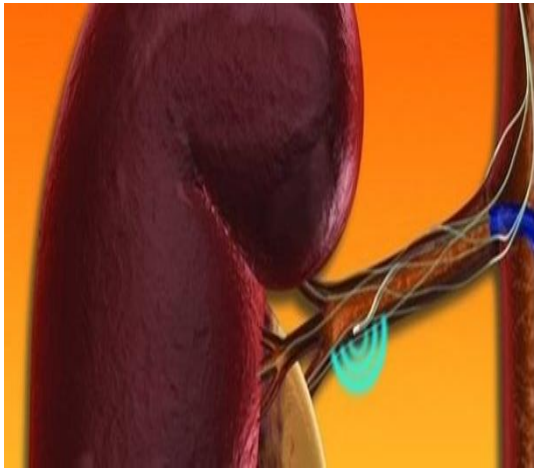
LVH	**Congestion**	**Tachykardie**	**Ischämie**
(LVMI >122 g/m2 (♀); >149 g/m2 (♂)) **LAVI** (>40 mL/m2)	(Lungenstau/Ödem, E/E´> 15)	(HF > 71/min and Ausschluss neg. Chronotropic) **Vorhofflim…**	
•**RAS Inhibition** **Aldo-Antagonismus** • Calcium Blocker	…ka	•**Beta-Blocker** •Calcium Blocker	• Nitrate Spray • Ranolazin • Ivabradin (HF > 75) ?

No good evidence yet

Device Therapie bei HFpEF?

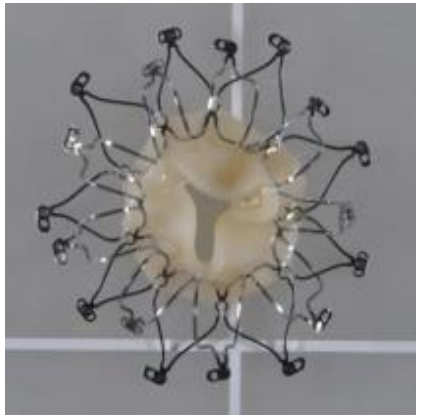
Devices bei der Therapie von HFpEF

Renale Denervierung



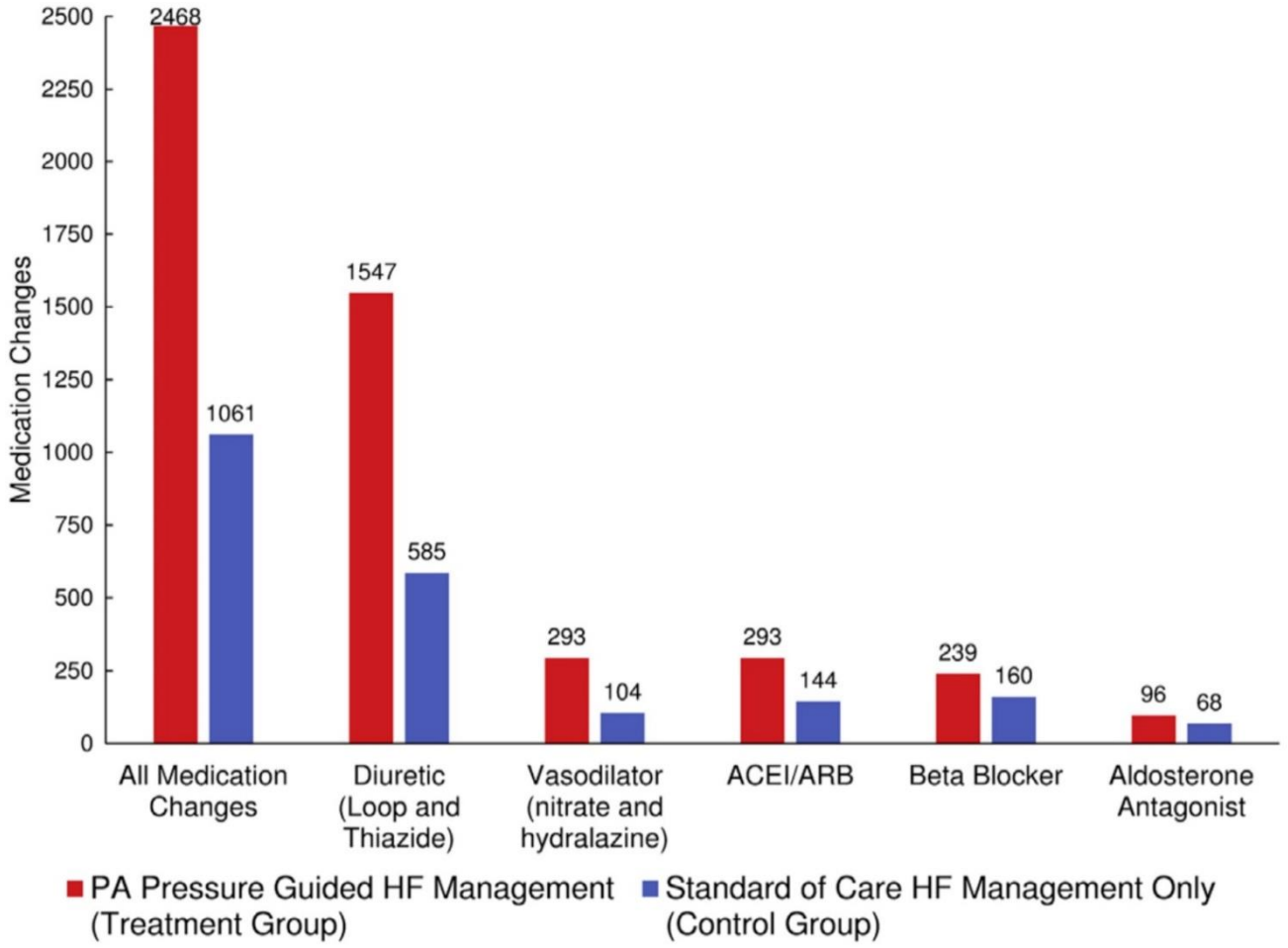
CCM

Druck-sensor



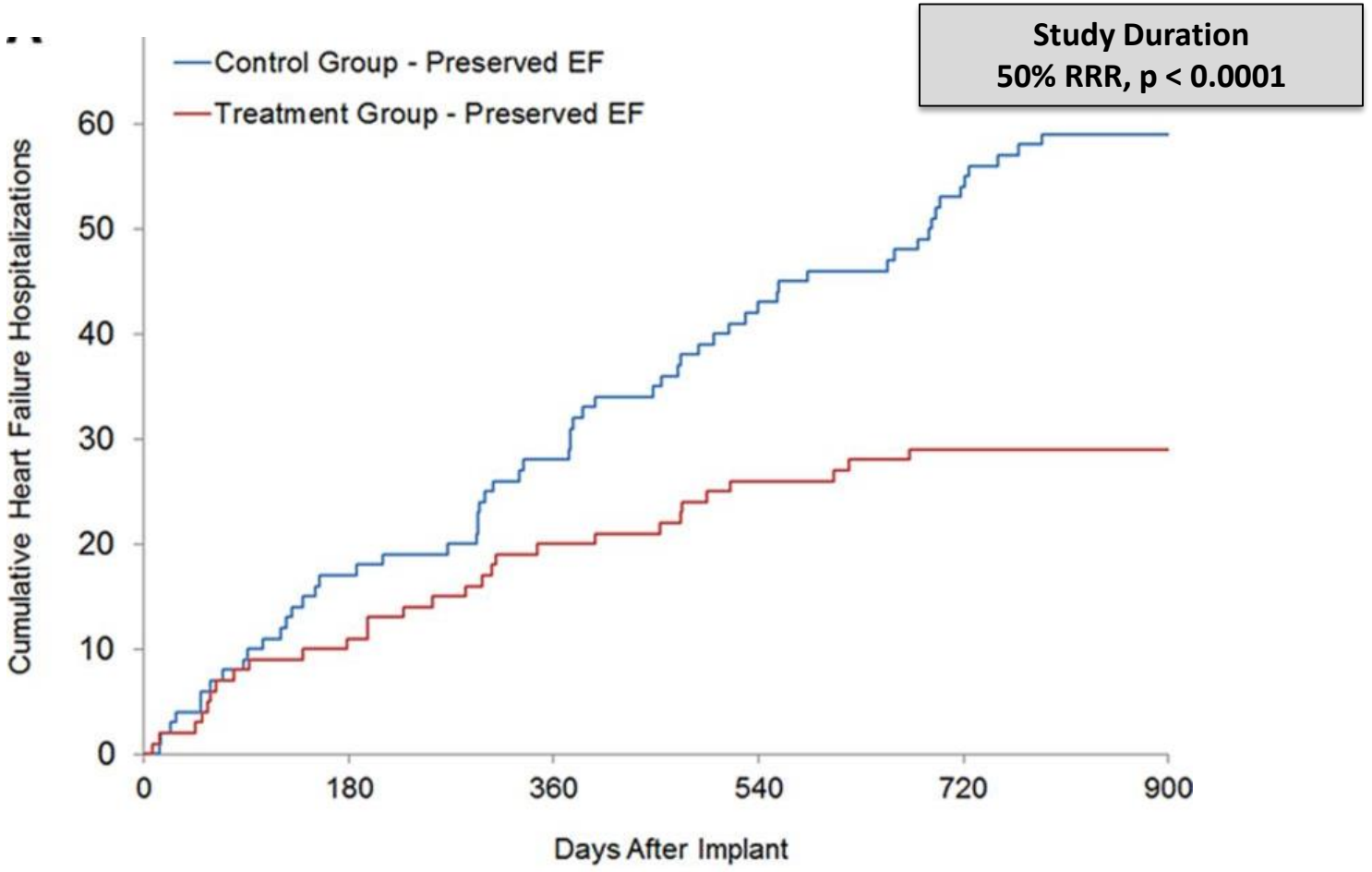
Ventile

Drucksensor: Cardiomems
Anpassungen der Medikamente



Costanzo et al, JACC Heart Failure 4 (2016): 333-344

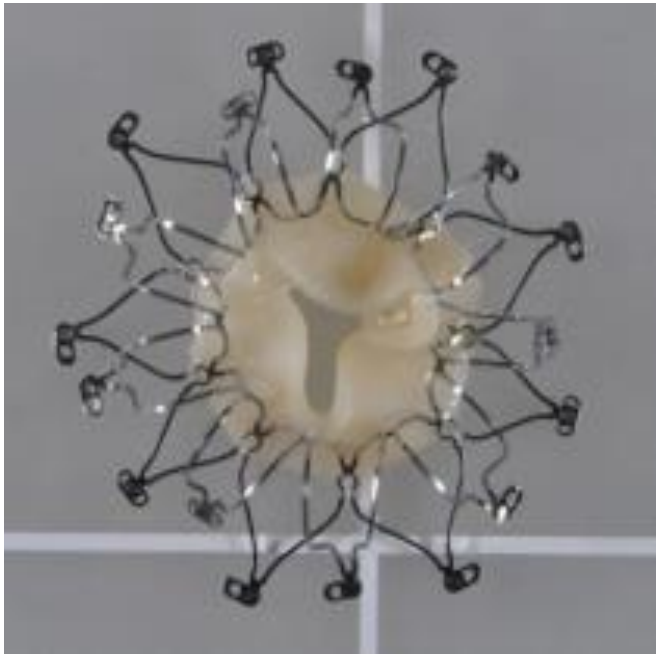
Drucksensor: CardioMEMS
Reduktion der Hospitalisierungsrate bei HFpEF

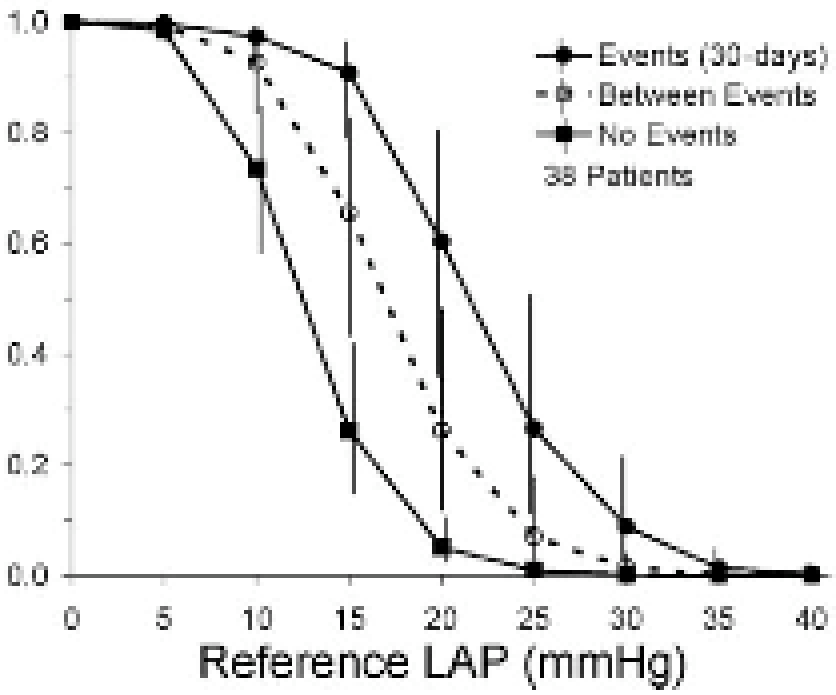


Adamson PB, et al: Circ Fail 2014;7:935-944

Devices bei der Therapie der HFpEF

Ventile



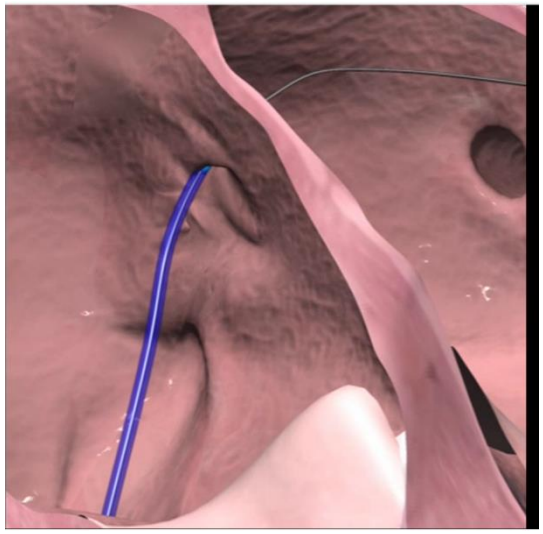


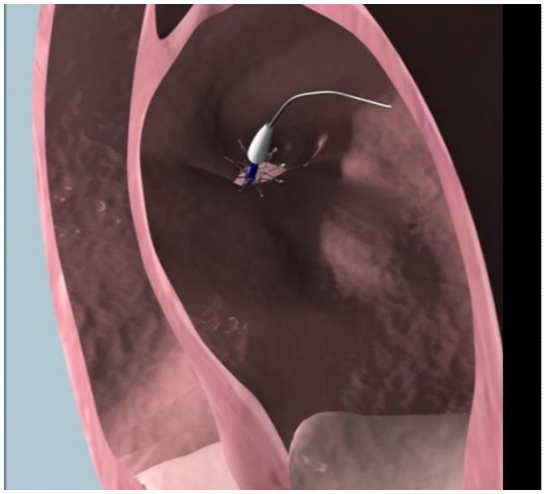
Patients admitted had an average LAp of 23 mm Hg

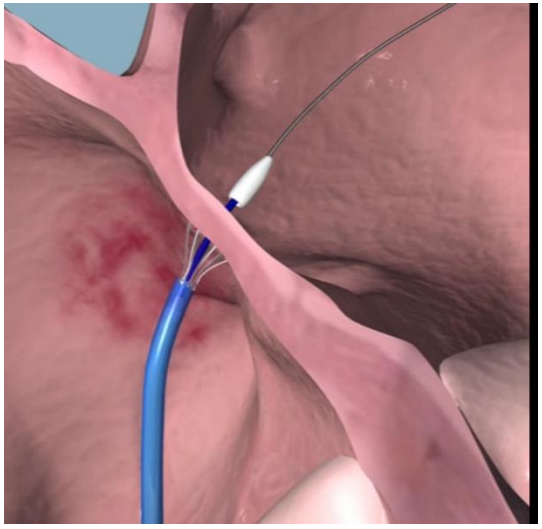
Rule of thumb:

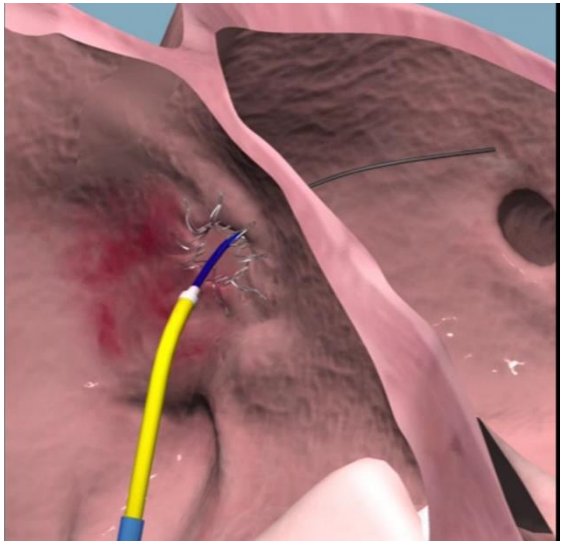
- **LAp<18 = good**
- **LAp 18-24 = b'line**
- **Lap > 24 = trouble**

Devices bei der Therapie der HFpEF

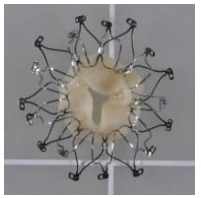




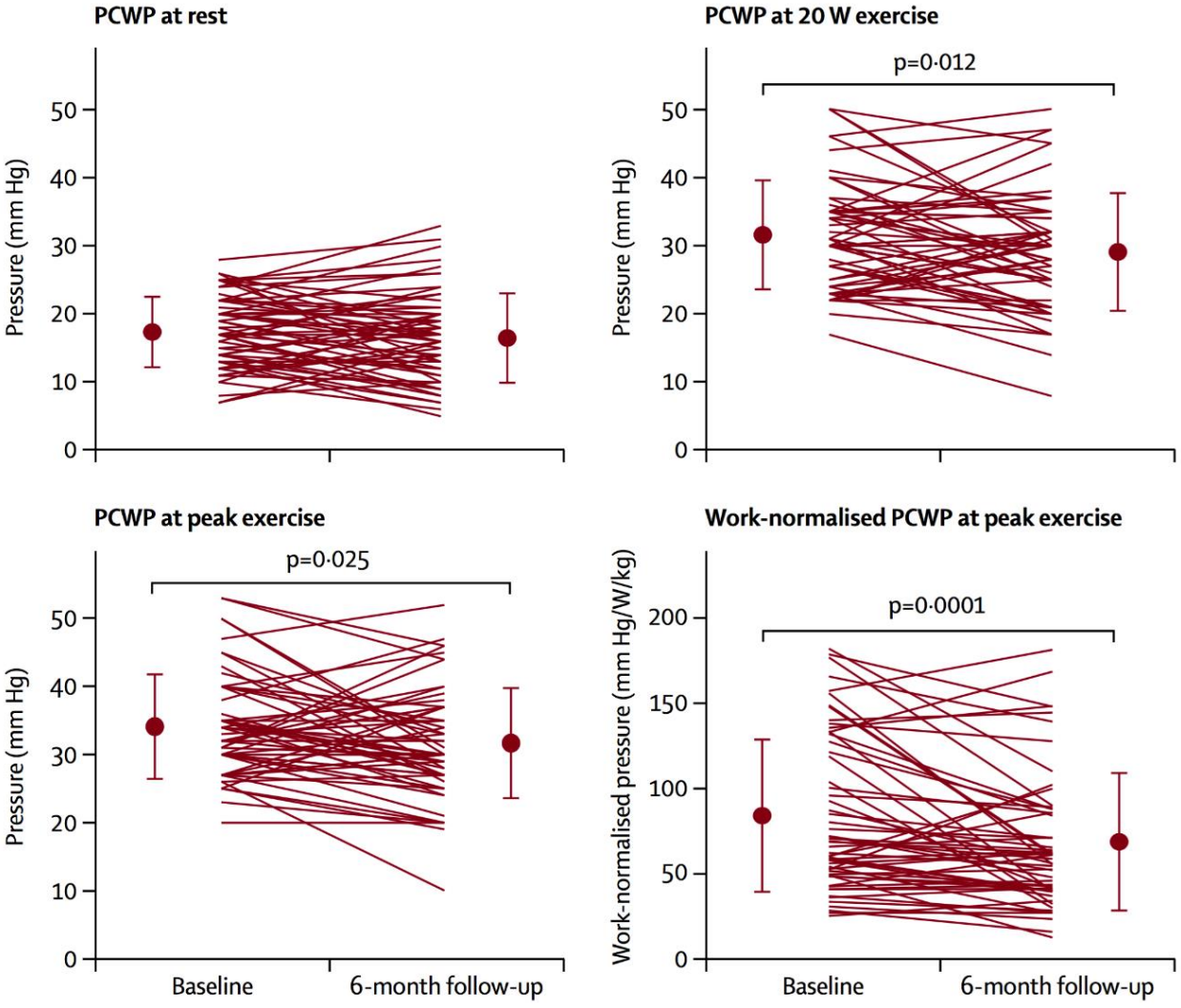




A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial



*Gerd Hasenfuß, Chris Hayward, Dan Burkhoff, Frank E Silvestry, Scott McKenzie, Finn Gustafsson, Filip Malek, Jan Van der Heyden, Irene Lang, Mark C Petrie, John G F Cleland, Martin Leon, David M Kaye, on behalf of the REDUCE LAP-HF study investigators**

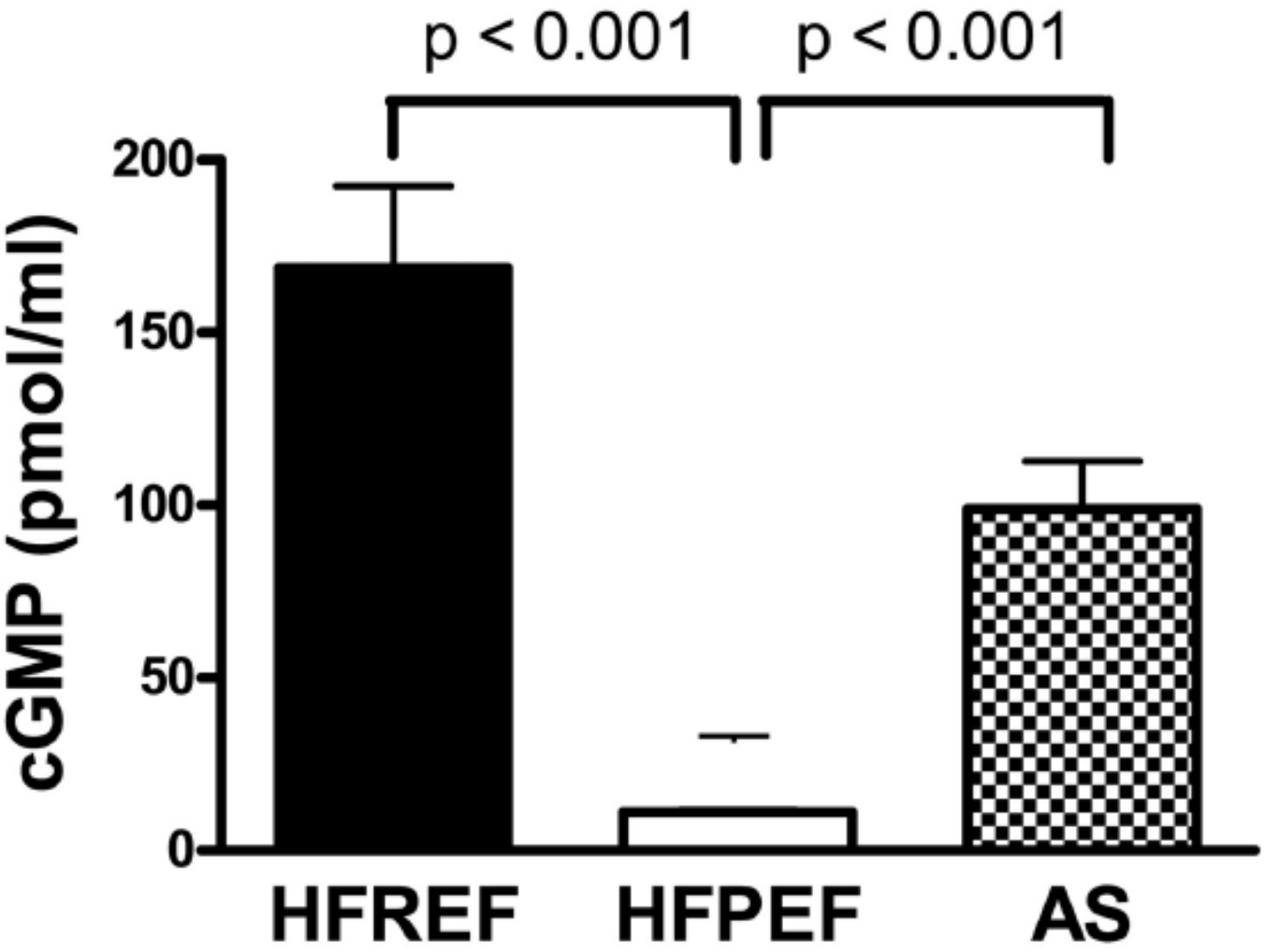


Prof. C. Tschöpe

Hasenfuß et al, Lancet 387 (2016): 1298-1304

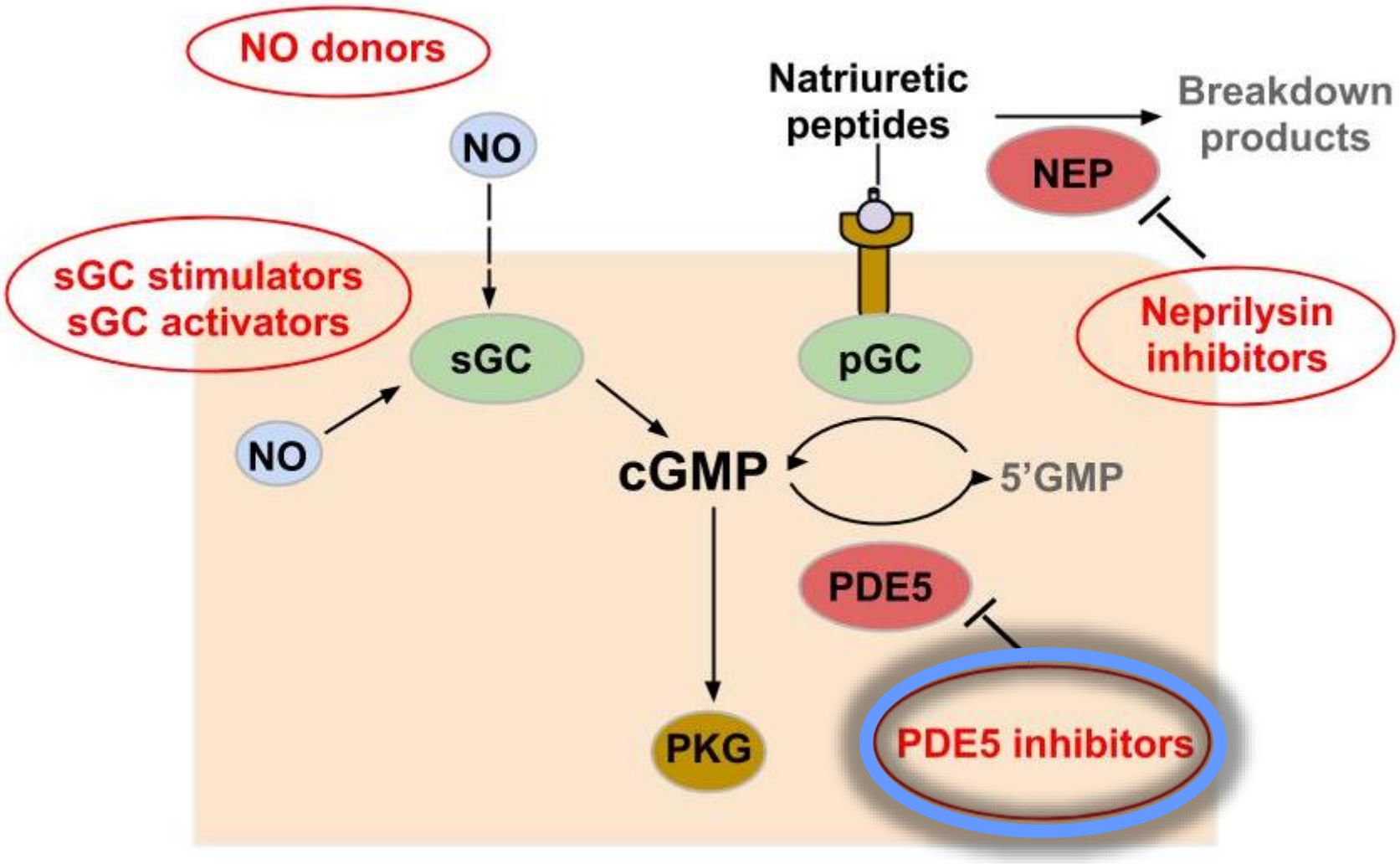
Neue Konzepte

Unterschiede im NO-cGMP Signalweg



Van Heerebeek Circulation 2012

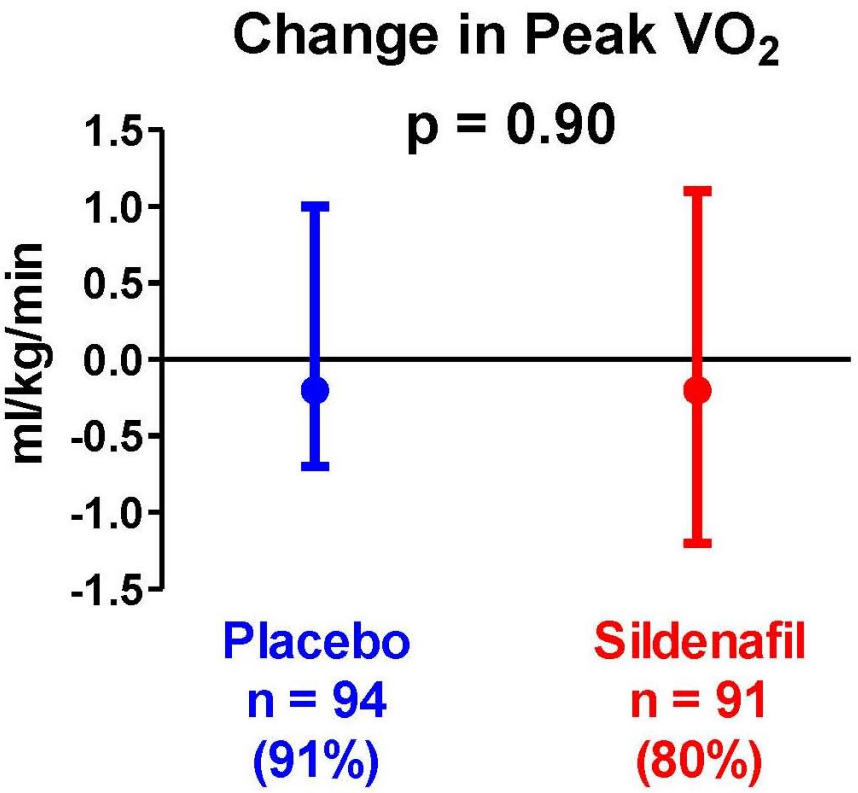
Wie kann man cGMP aktivieren?



Komajda and Lam Eur Heart J 2014

RELAX Studie
Sildenafil bei postkapillärer PH und HFpEF

Primary Endpoint

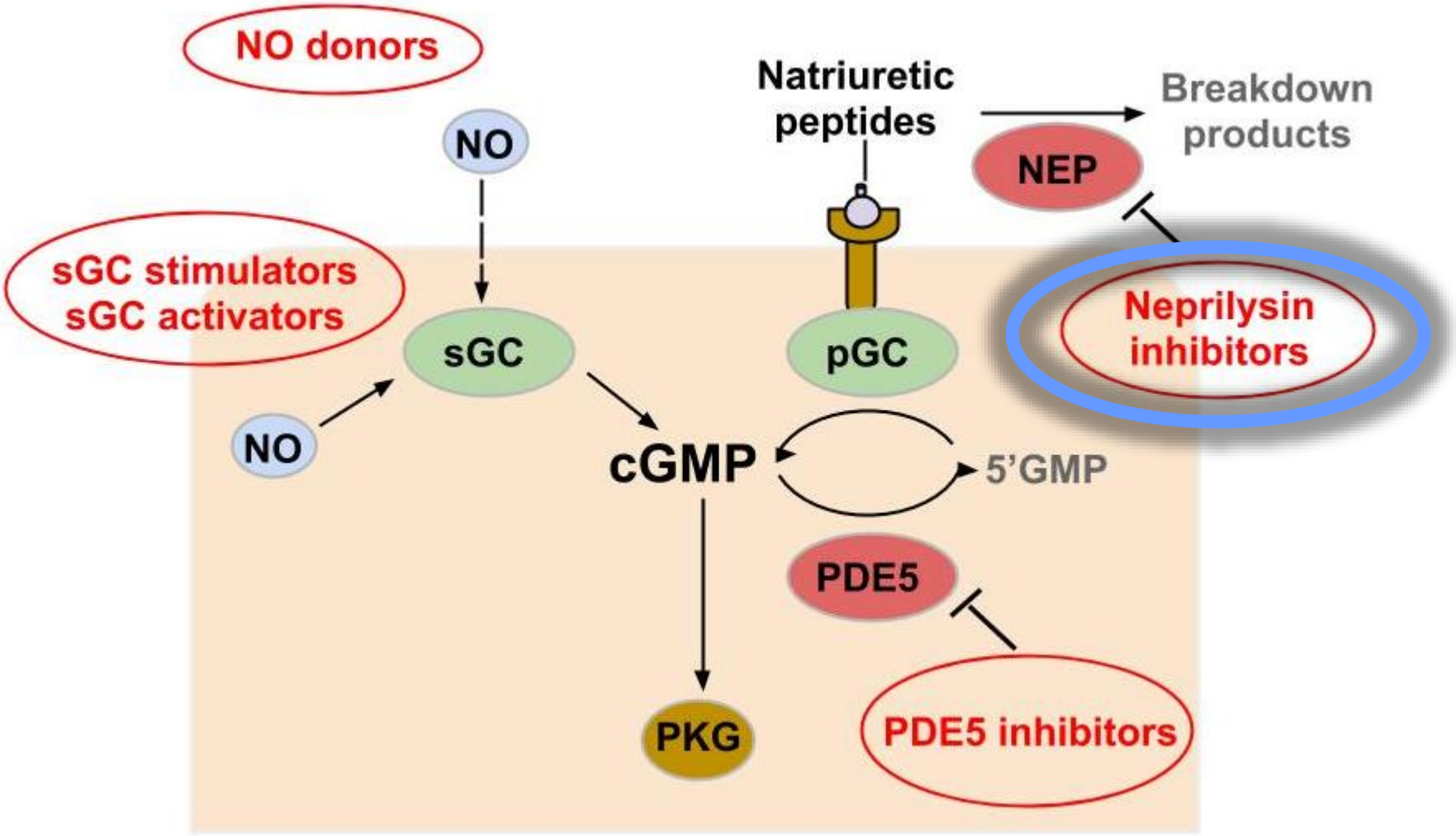


Sensitivity analyses for missing data

Multiple imputation: p = 0.98; LOCF: p = 0.98

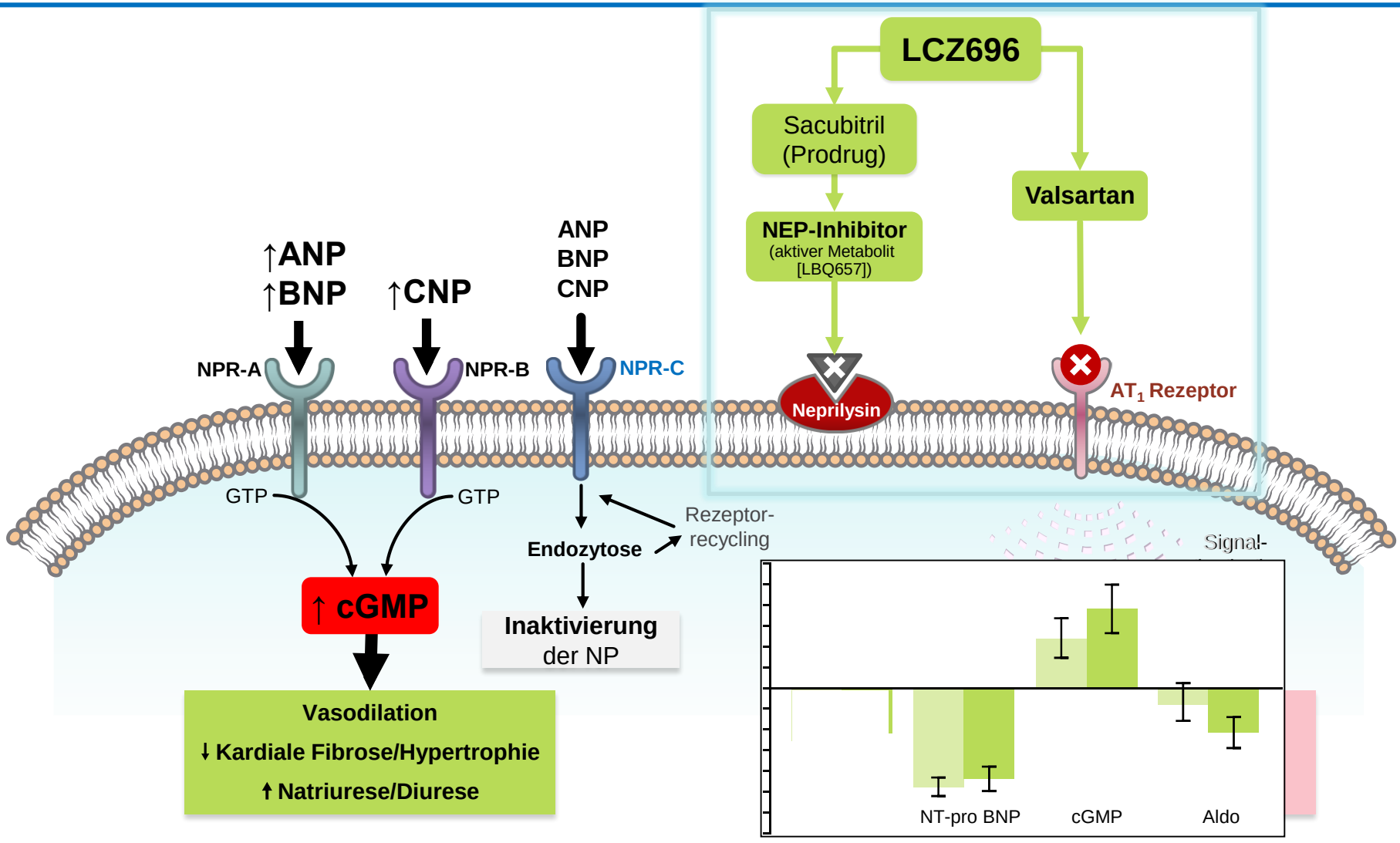
Data are median and IQR

Wie kann man cGMP aktivieren?



Komajda and Lam Eur Heart J 2014

NEP-Inhibtion impliziert auch eine cGMP Stimulation



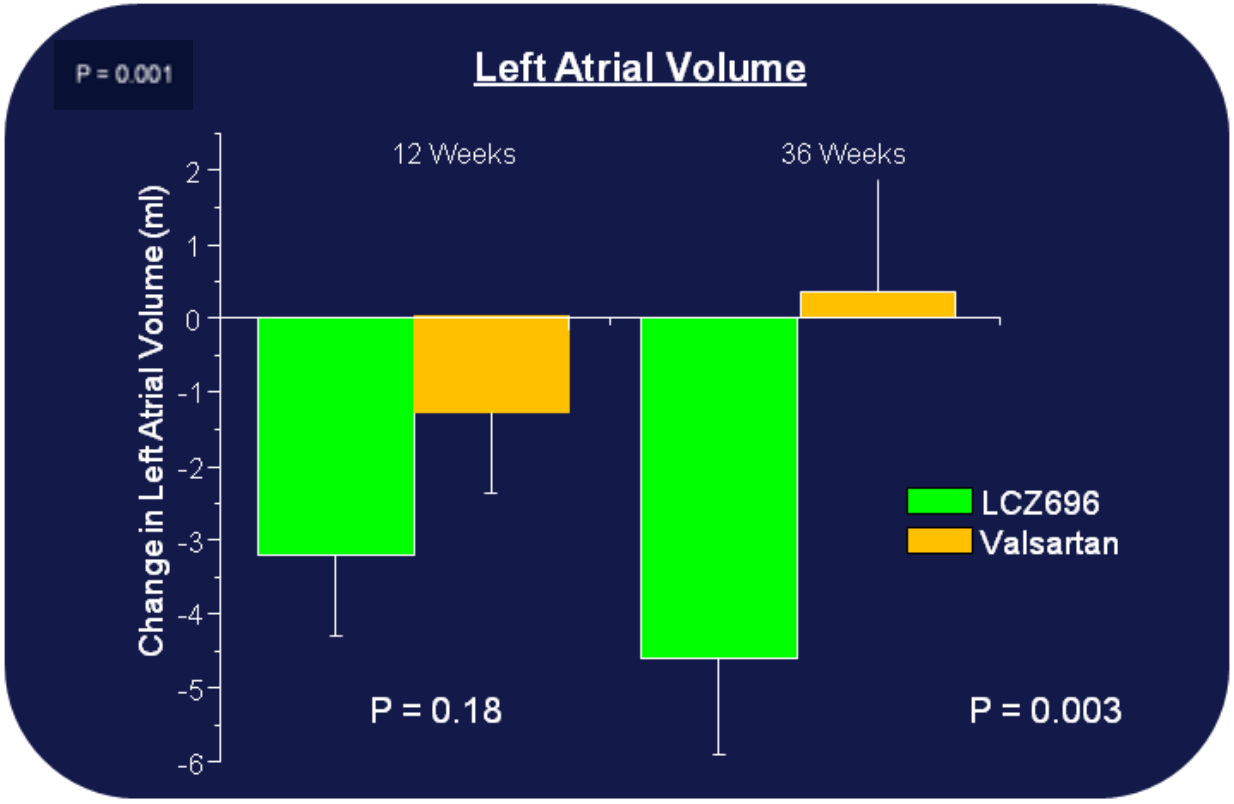
Prof. C. Tschöpe

Levin et al. N Engl J Med 1998; Gardner et al. Hypertension 2007; Molkentin. J Clin Invest 2003;

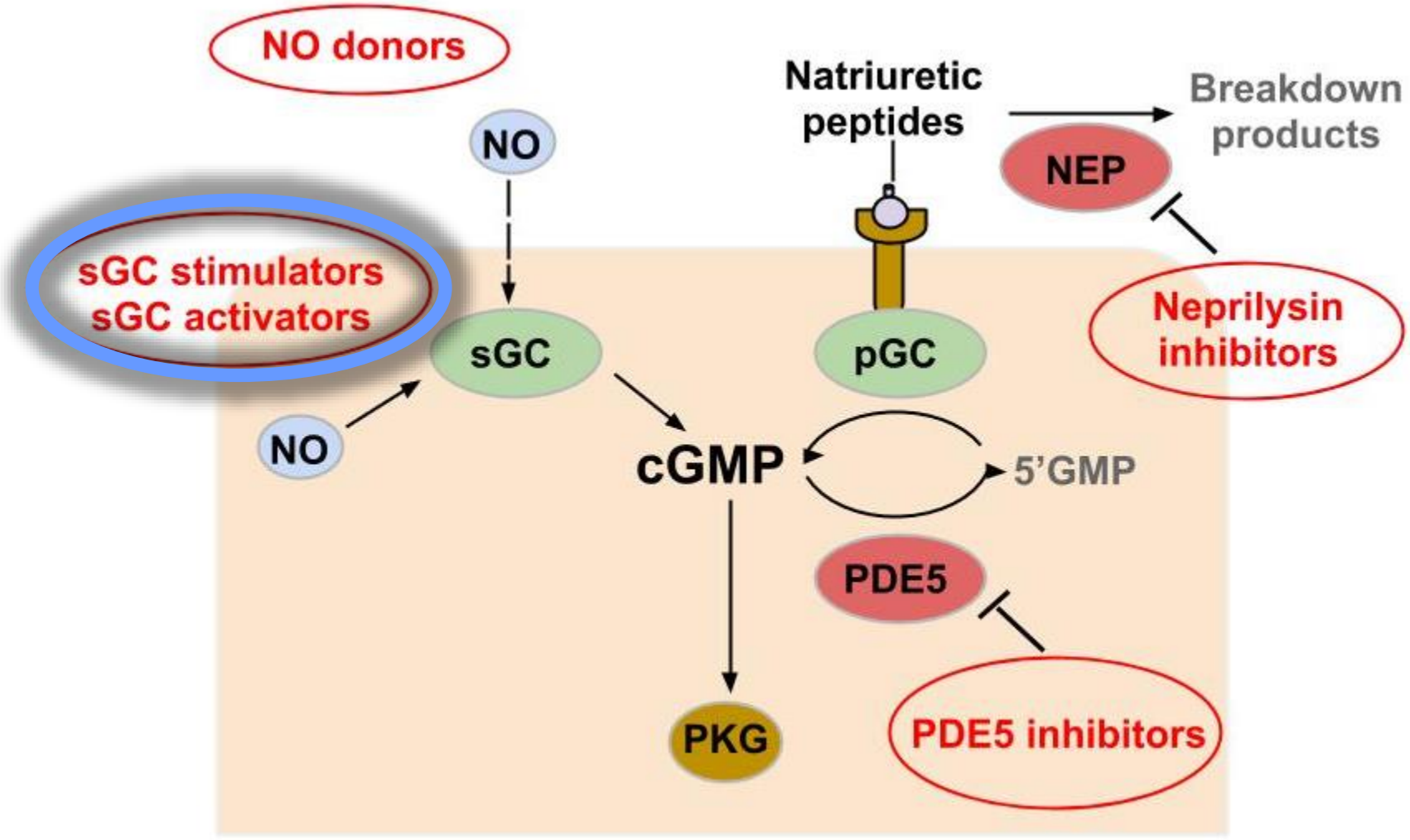
Paramount

Effekt von Valsartan und NEP- Inhibtion

Change in
Left Atrial Volume (mm)

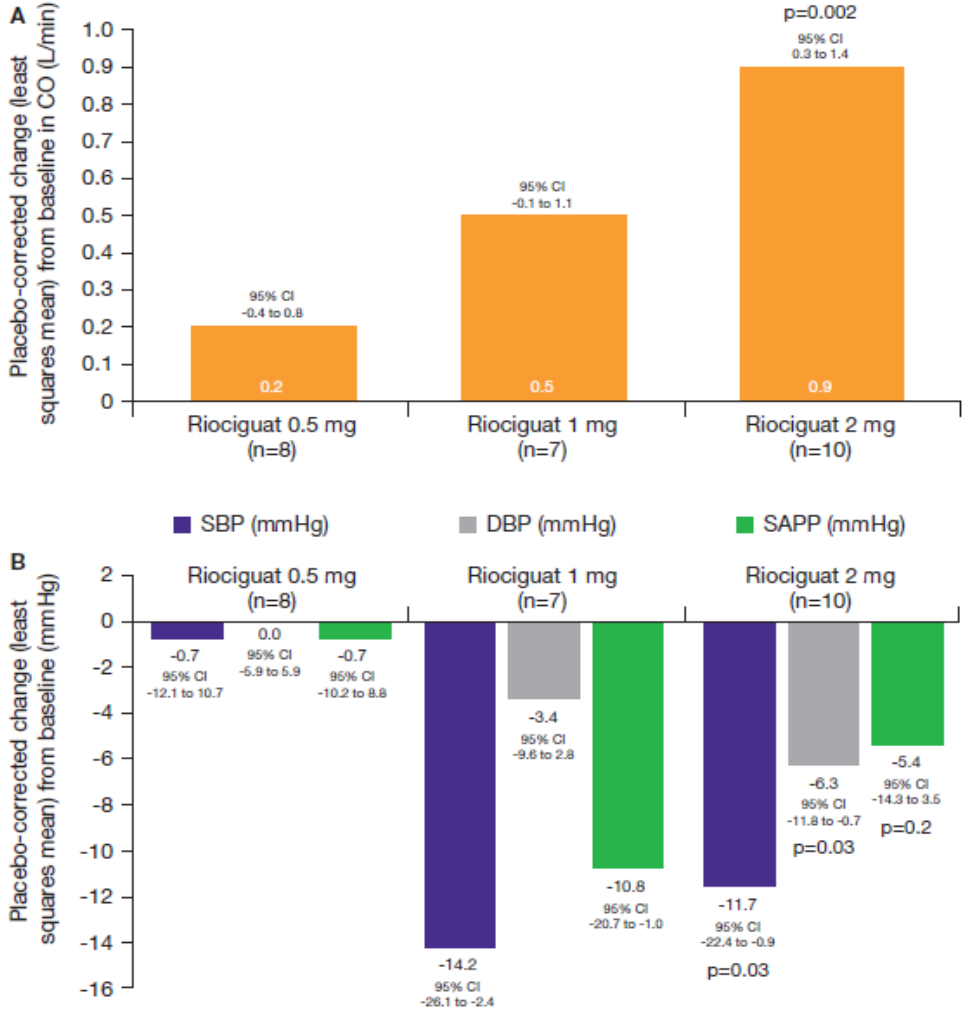


Wie kann man cGMP aktivieren?



Komajda and Lam Eur Heart J 2014

Riociguat
in HFpEF mit pulmonaler Hypertonie

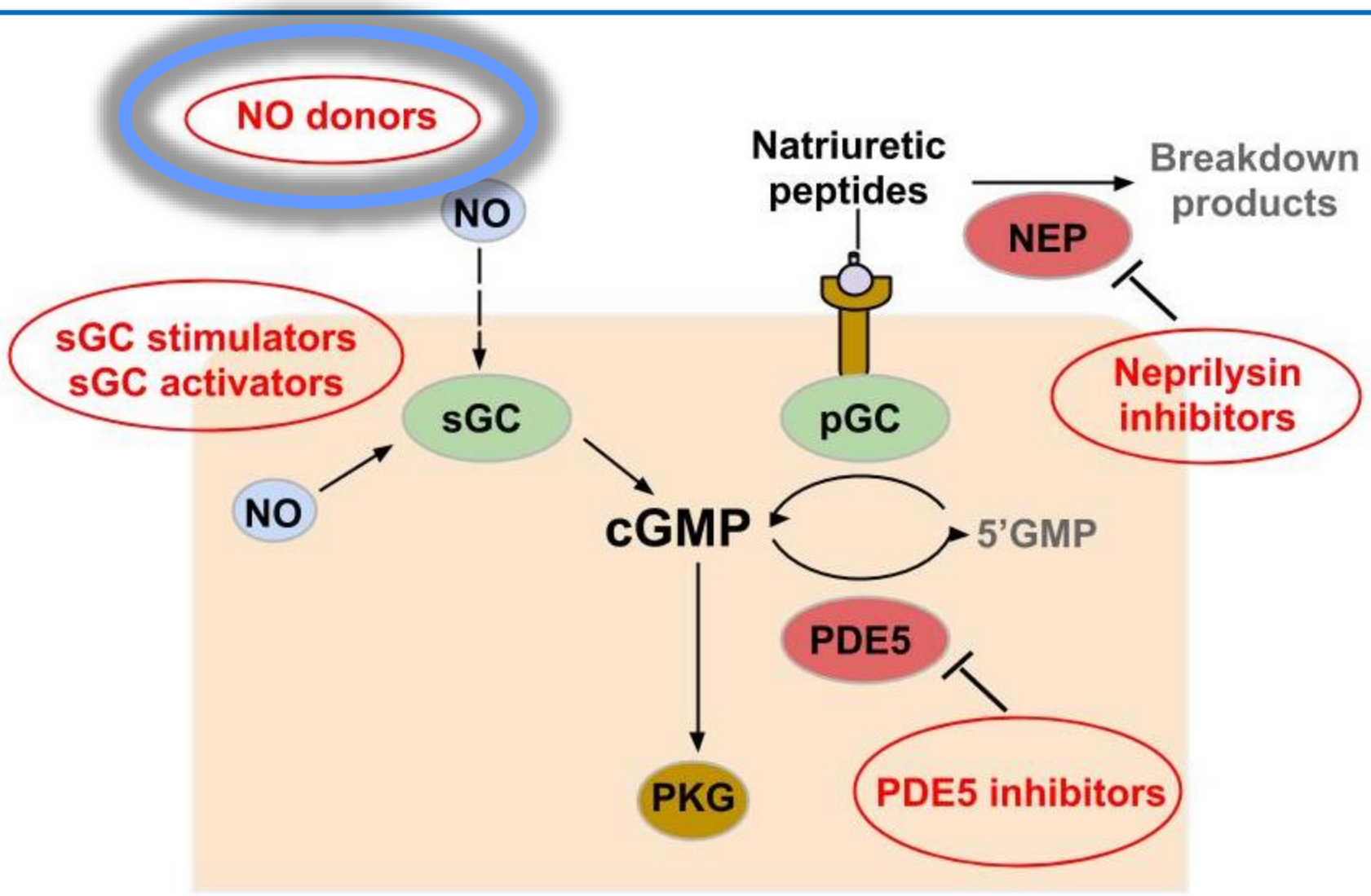


Cardiac output
(Swan Ganz)

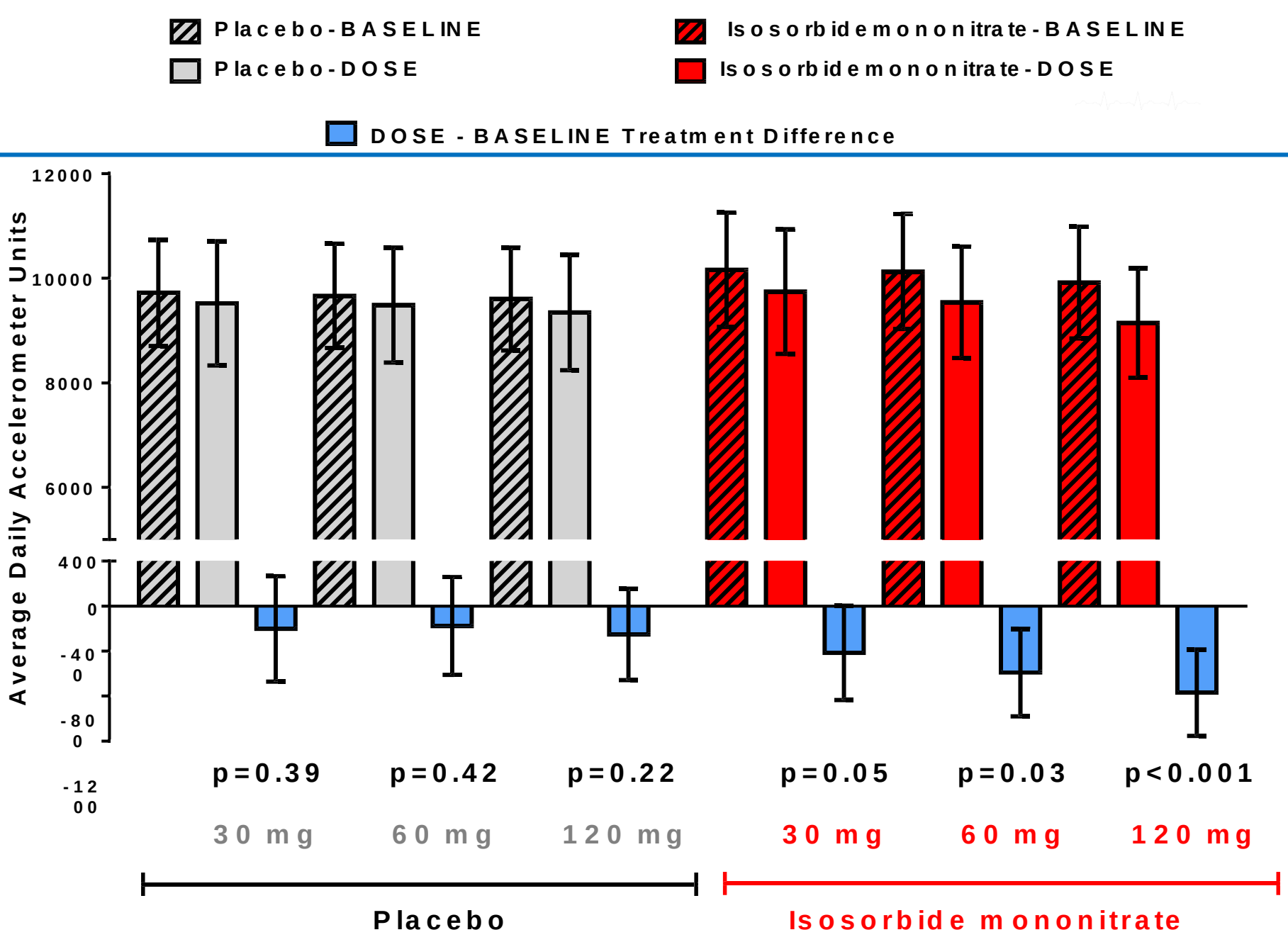
Blutdruck

DILATE study, Bonderman et al., presented at ESC 2013

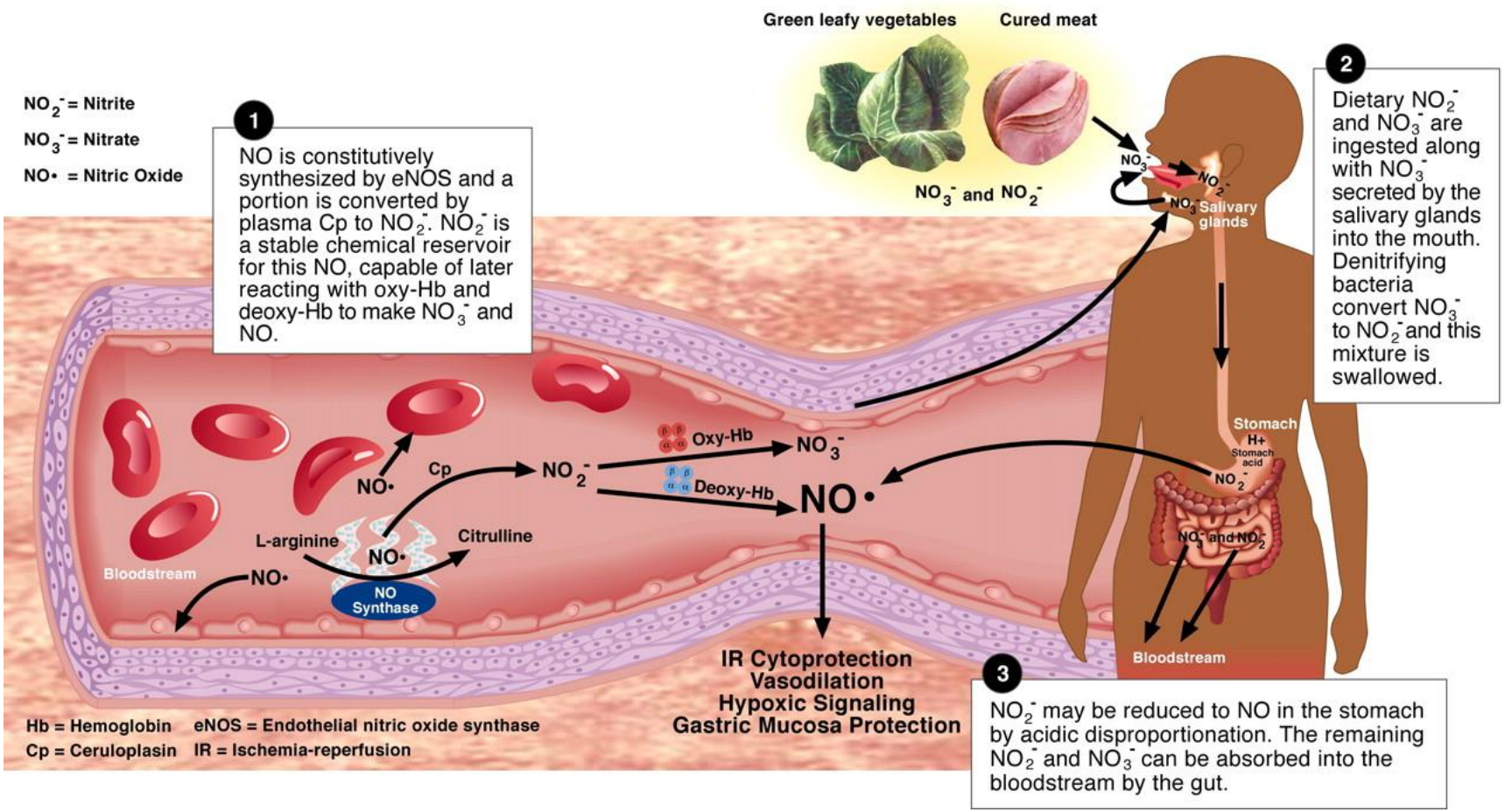
Wie kann man cGMP aktivieren?



Komajda and Lam Eur Heart J 2014


Placebo-BASELINE
Placebo-DOSE
Isosorbidemononitrate-BASELINE
Isosorbidemononitrate-DOSE
DOSE - BASELINE Treatment Difference
Average Daily Accelerometer Units
12000
10000
8000
6000
400
0
-400
-800
-1200
p=0.39
p=0.42
p=0.22
p=0.05
p=0.03
p<0.001
30 mg
60 mg
120 mg
30 mg
60 mg
120 mg
Placebo
Isosorbide mononitrate

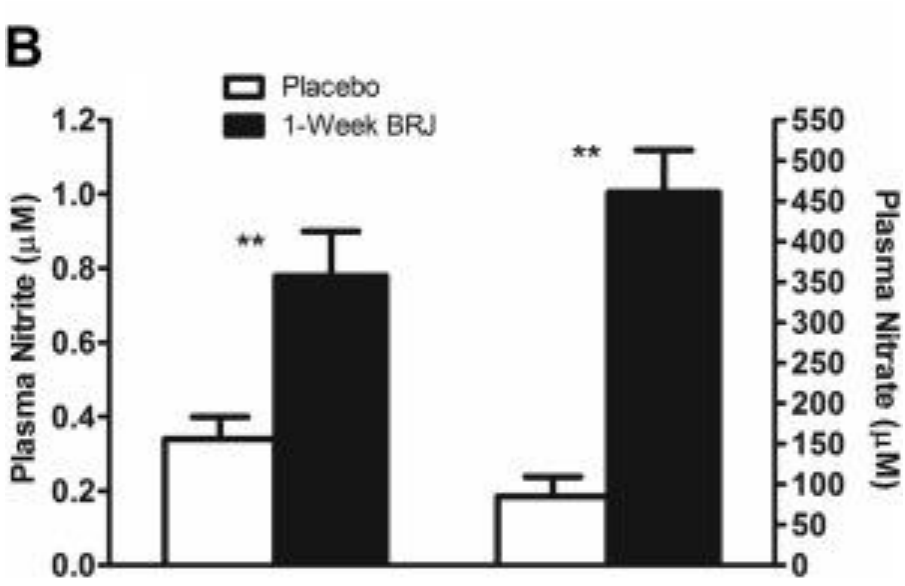
Anorganische Nitrate

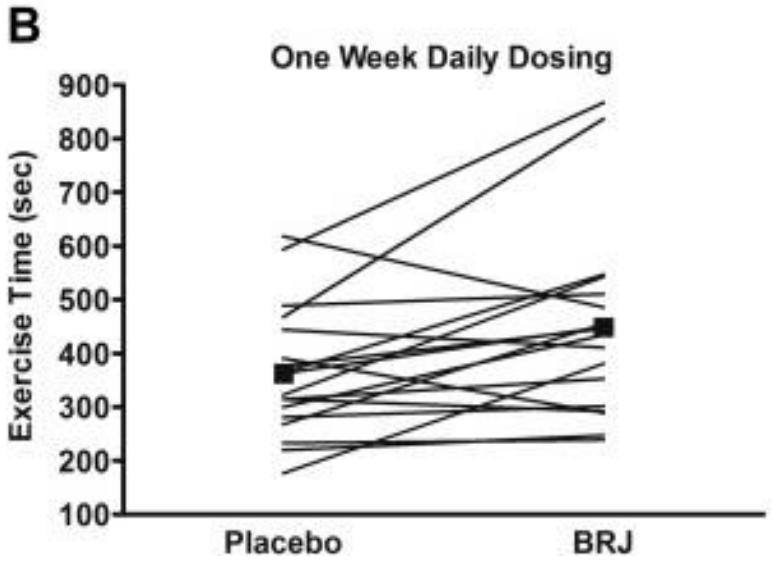


Prof. C. Tschöpe

Cameron Dezfulian et al. Cardiovasc Res 2007;75:327-338

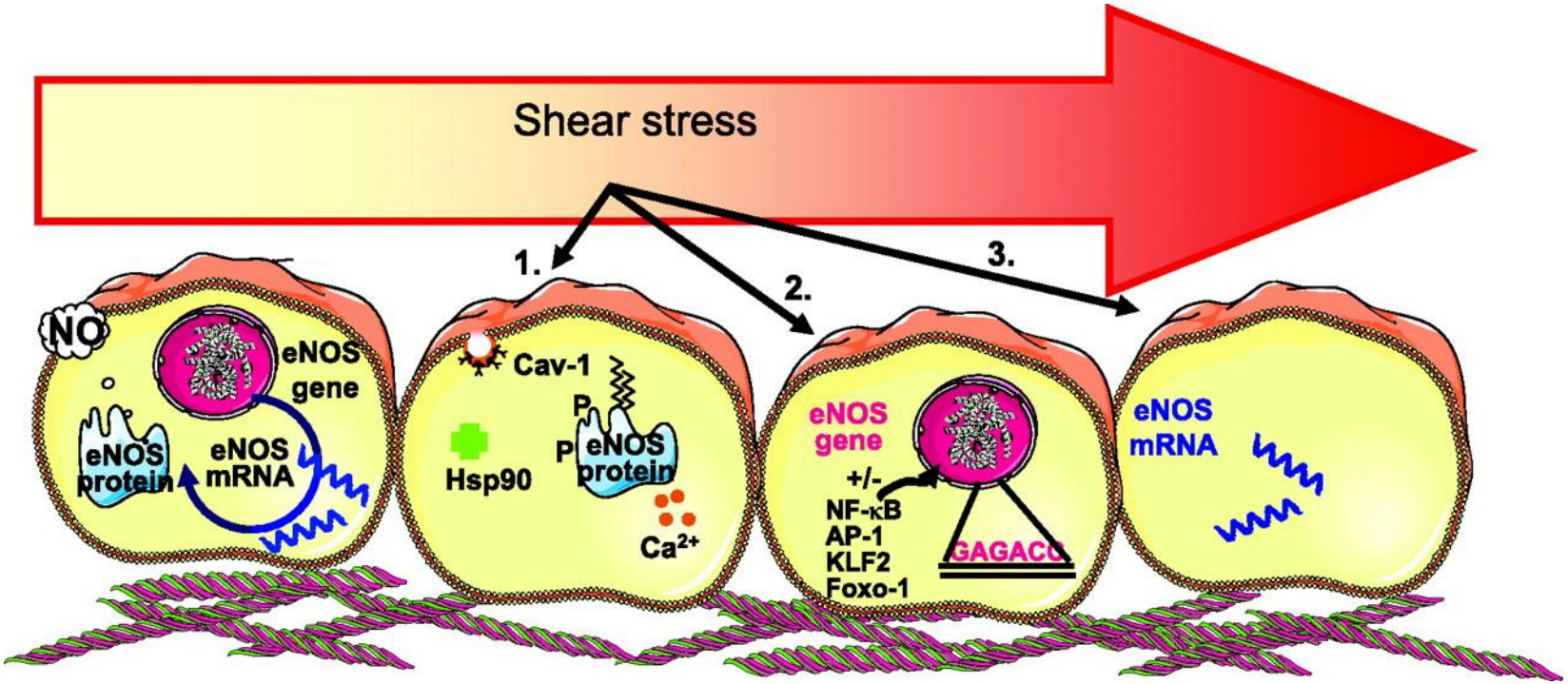
Plasma Nitrit und Nitrat nach 7 tägiger Rote Beete Saft Einnahme bei älteren HFpEF





Eggebeen J et al, JACC 2016

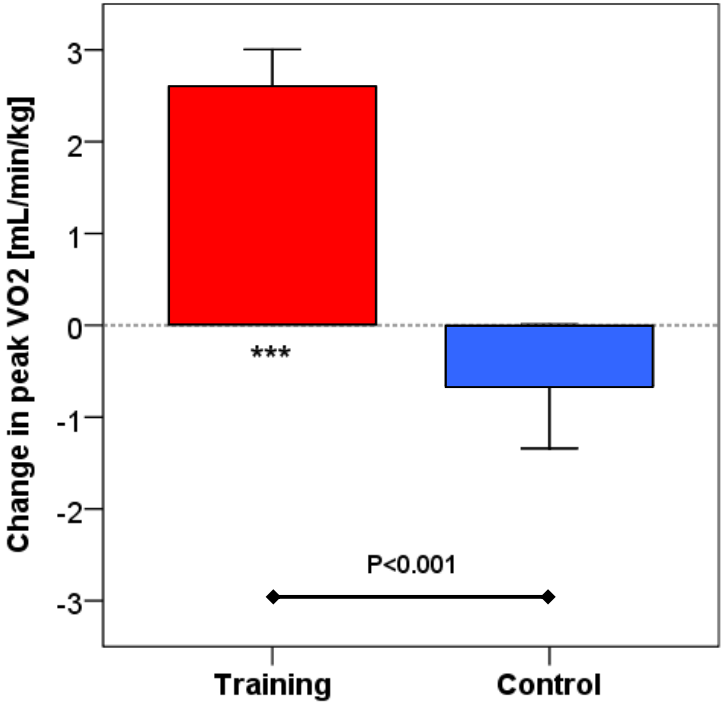
Shear Stress und Sport in HFpEF

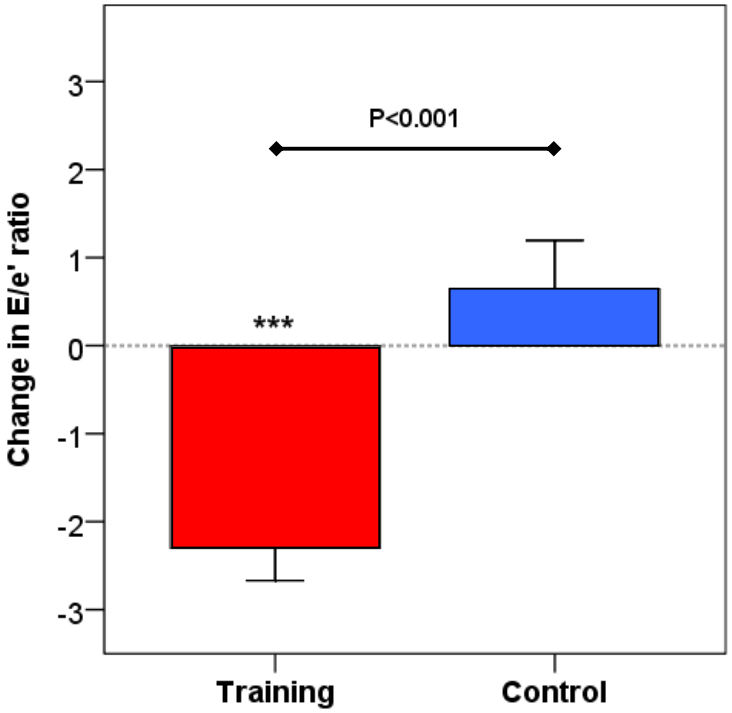


Prof. C. Tschöpe

J.-L. Balligand et al. Physiol Rev 2009;89:481-534

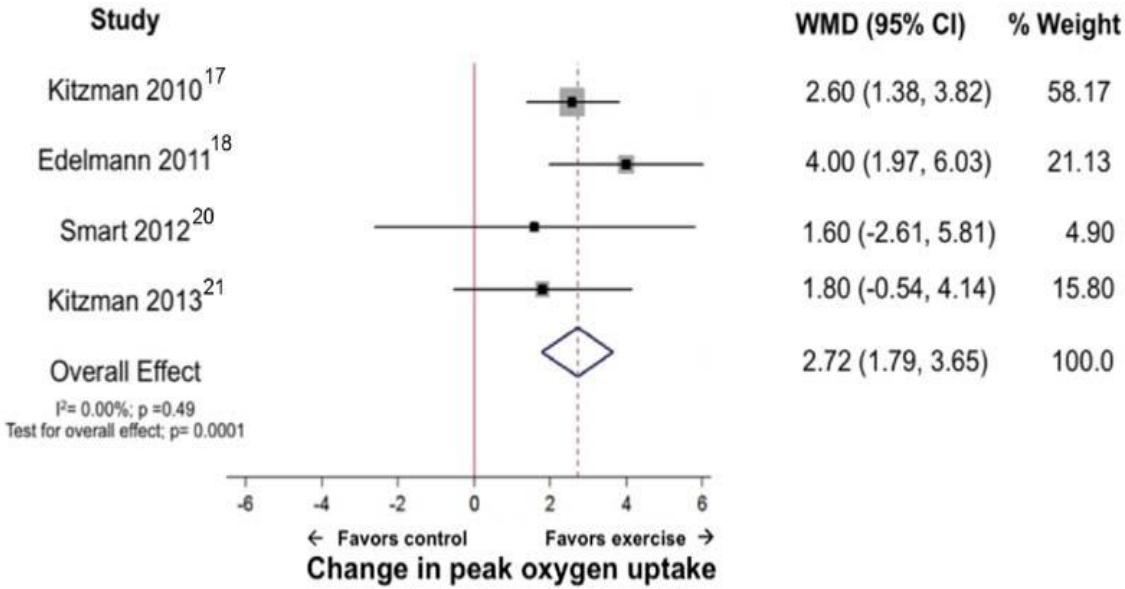
Sport bei HFpEF
Ex-DHF-P study

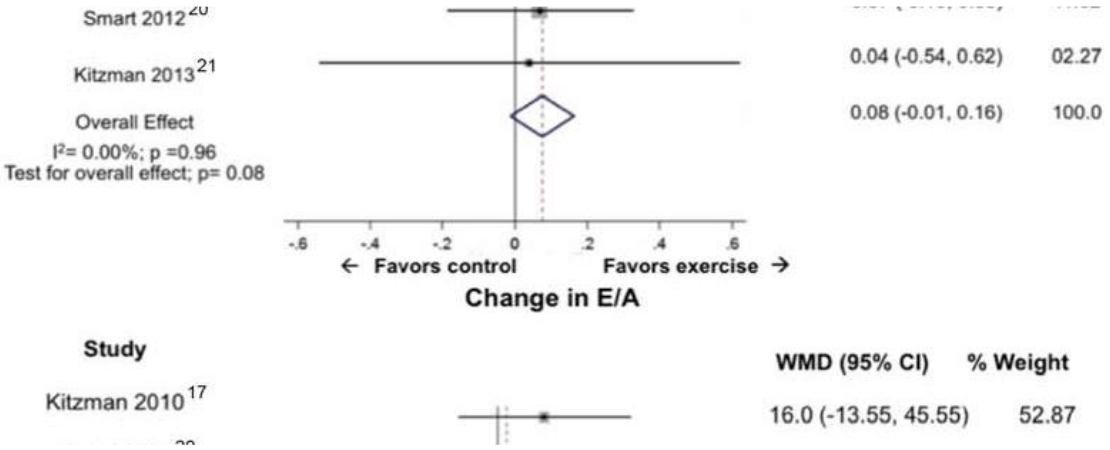




Edelmann at al JACC 2011

Effekt von Sport auf die kardiorespiratorische Fitness bei HFpEF





Pandey A, et al. Circ HF 2015

Zusammenfassung

- **50% der Pat. mit Herzinsuffizienzsymptomen haben eine erhaltene EF -. > Erhöhte Hospitalisierungs- und Mortalitätsrate**
- **Ätiologie : Hypertoniker, Diabetiker, KHK-Patienten, Ältere**
- **Heterogenes Syndrom – Achtung Komorbiditäten**
- **Diagnostik : Echokardiographie (E´/E) + BNP/LA-Grösse*/Stress Teste**
- **Therapie : in Abhängigkeit der Grundkrankheit**
  - » **RAAS Hemmstoff(e) inkl. Aldo-Block. + Diuretikum**
  - » **Beta Blocker (cave)** (Tachykard?, cave bei neg. Chronotropie)
  - » **Eventuell Ranolazin bei Ischämie / Nitrate Spray (cave)**
  - » **Sport**
  - » **Cardiomems/Shunt Systeme**
  - » **Zukunft: cGMP – Targeting: LCZ 696 - „Rote Beete“**