DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUFFORSCHUNG E.V.

Kompetenznetz Herzinsuffizienz

Herz Zentrum Göttingen

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Herzzentrum der Georg-August-University Göttingen

Klinik für Kardiologie und Pneumologie

Therapieansätze der diastolischen Herzinsuffizienz „Lifestyle“ Veränderungen oder Medikamente? Rolle von Schlafapnoe, Übergewicht, Vorhofflimmern

Kloster Eberbach, 29. Juni 2016

Conflict of Interest - Disclosure

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

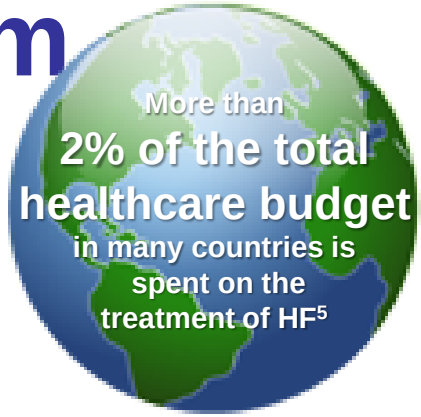
Affiliation/Financial Relationship	Company
1. Honoraria for lectures	Bayer, Berlin Chemie, Boehringer Ingelheim, CVRx, Medtronic, Novartis, Pfizer, Servier
2. Honoraria for advisory board activities	Boehringer Ingelheim, Novartis
3. Participation in clinical trials	Bayer, Boston Scientific, Celladon, CVRx, Johnson &Johnson, Medtronic, Novartis, Pfizer, Servier
4. Research funding	BMBF (Kompetenznetz Herzinsuffizienz und DZHK), European Union (Horizon 2020) and Boehringer Ingelheim

Gliederung

1. **Formen der Herzinsuffizienz und Prognose**

2. Therapien der Herzinsuffizienz mit erhaltener Ejektionsfraktion

Heart failure imposes a significant economic burden on the healthcare system



GLOBAL ECONOMIC BURDEN OF HF EXCEEDS
US$ 45 billion[1–4]

70% OF THE COST OF HF IS
DUE TO HOSPITALIZATIONS[5]

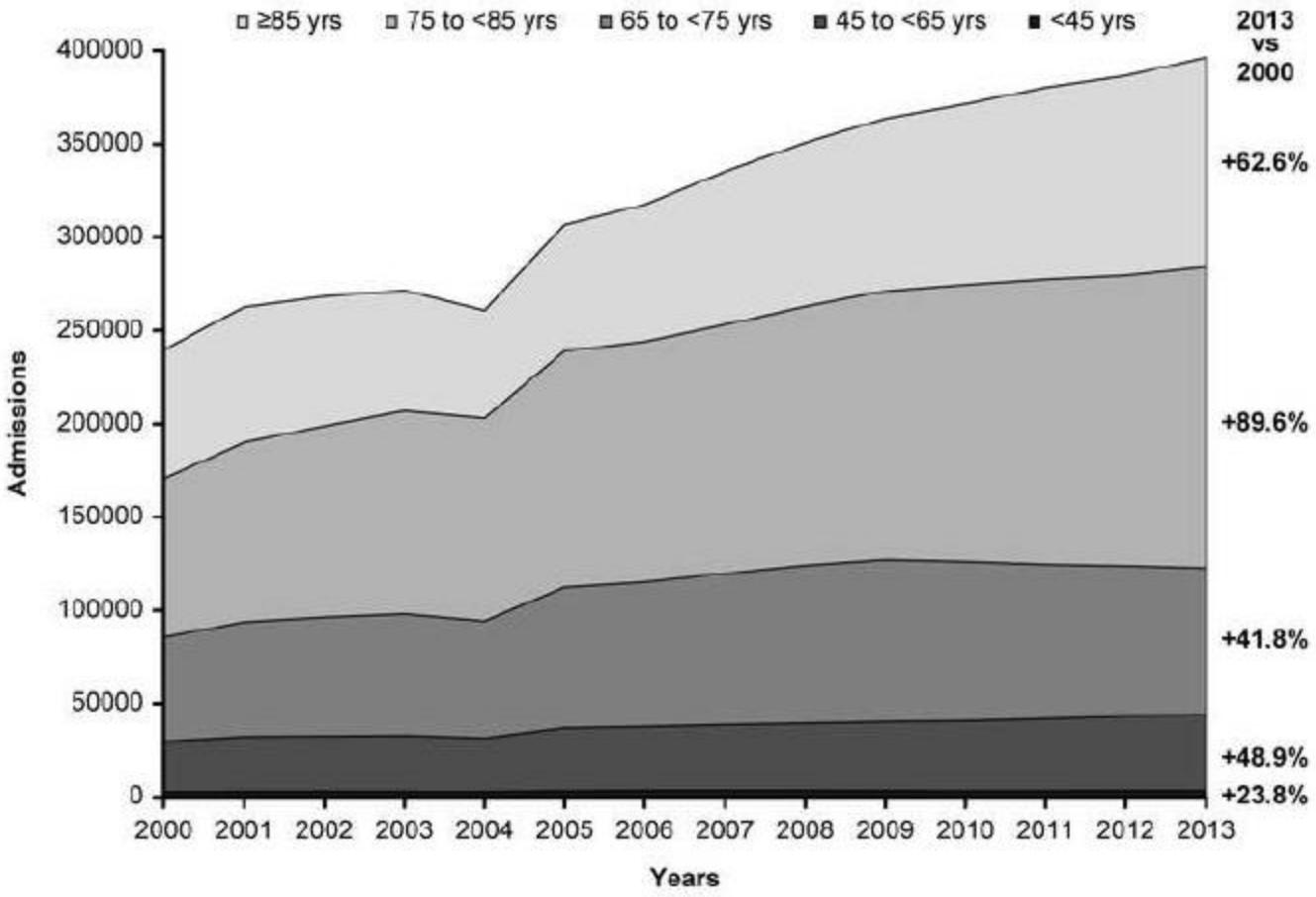
~**10%** OF THE COST OF HF IS
DUE TO PHARMACOLOGICAL TREATMENT[6]

8–9% **COST SAVING** COULD POTENTIALLY BE ACHIEVED WITH THERAPY THAT
REDUCES LENGTH OF HOSPITAL STAY BY ONE DAY‡[7]

HF=heart failure; ‡Data from semi-Markov cost-effectiveness model based on a hypothetical acute HF therapy that reduces UK hospital length of stay by 1 day;

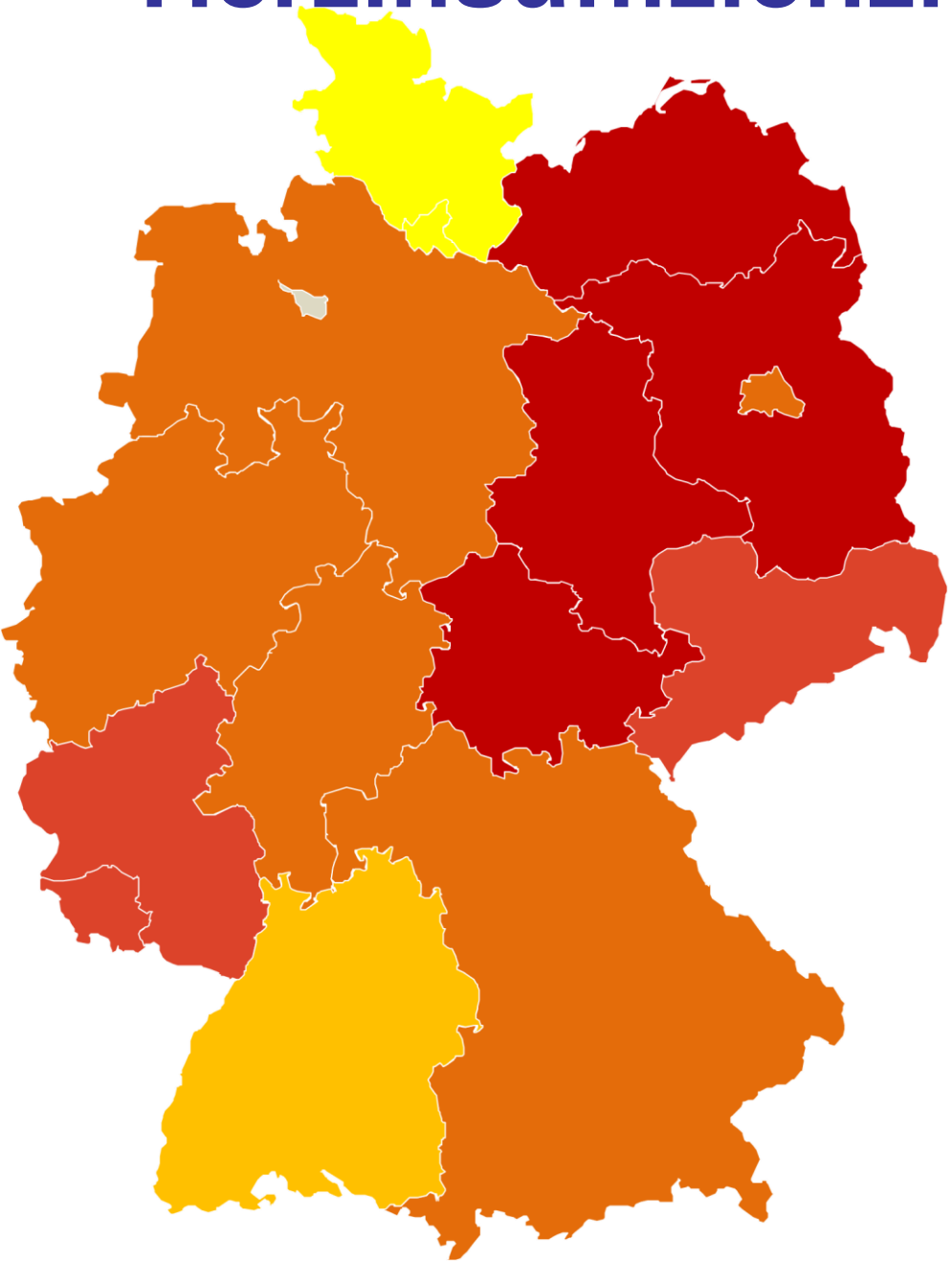
1. Lloyd-Jones et al. Circulation 2010;121:e46–e215; 2. Neumann et al. Dtsch Arztebl Int. 2009;106:269–75;
3. Berry et al. Eur J Heart Fail 2001;3:283–91; 4. Stewart et al. Eur J Heart Fail 2002;4:361–71; 5. Dickstein et al. Eur Heart J 2008;29:2388–442;
6. Hunt et al. J Am Coll Cardiol 2009;53:e1–90; 7. Lalla et al. Presented at the World Congress of Cardiology (WCC), Dubai, UAE, 18–21 April 2012

Krankenhausaufnahmen in Deutschland wegen Herzinsuffizienz



Christ M, …, Wachter R, et al. Eur J Heart Fail 2016)

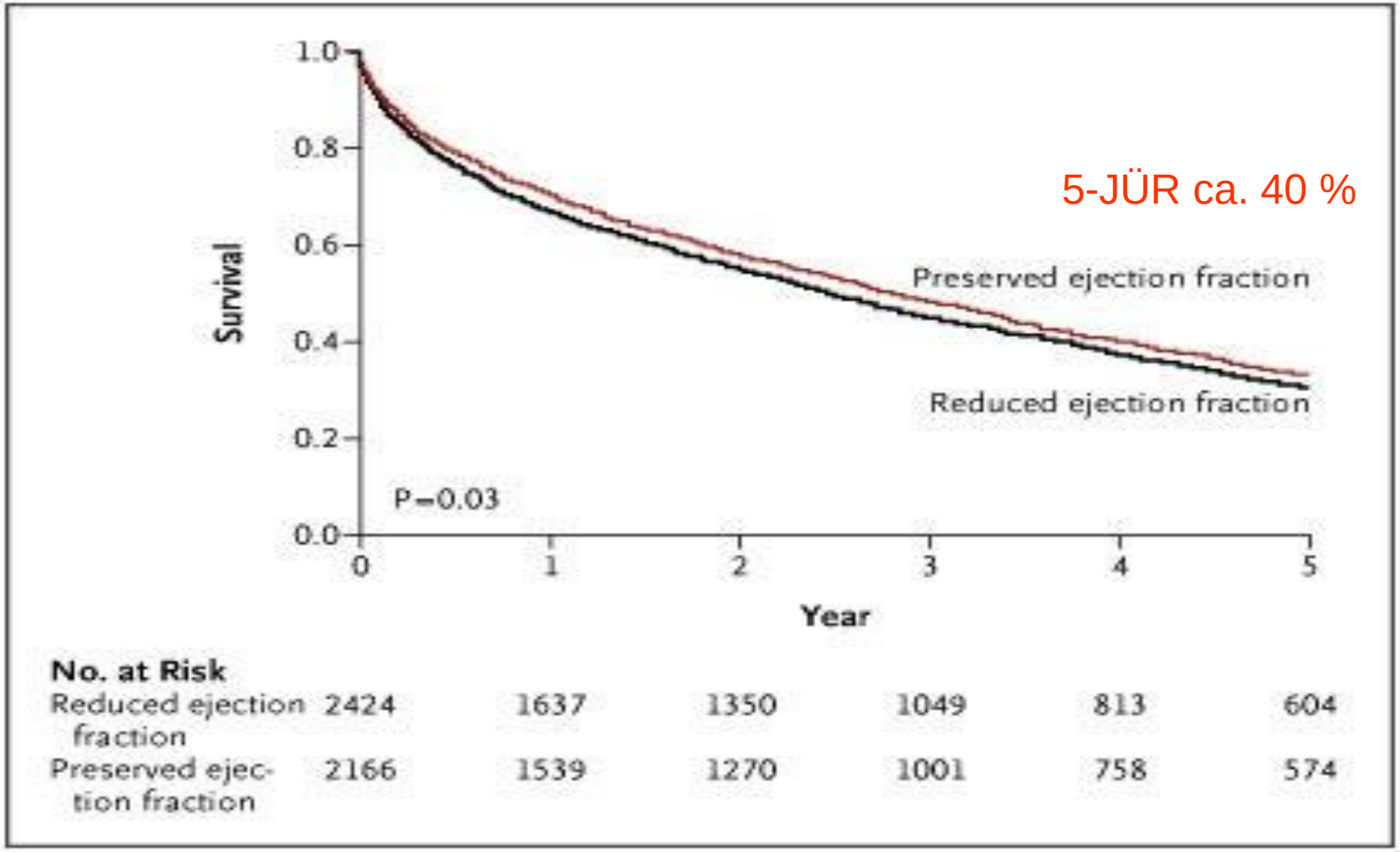
Herzinsuffizienzhospitalisation D



Pro 100,000

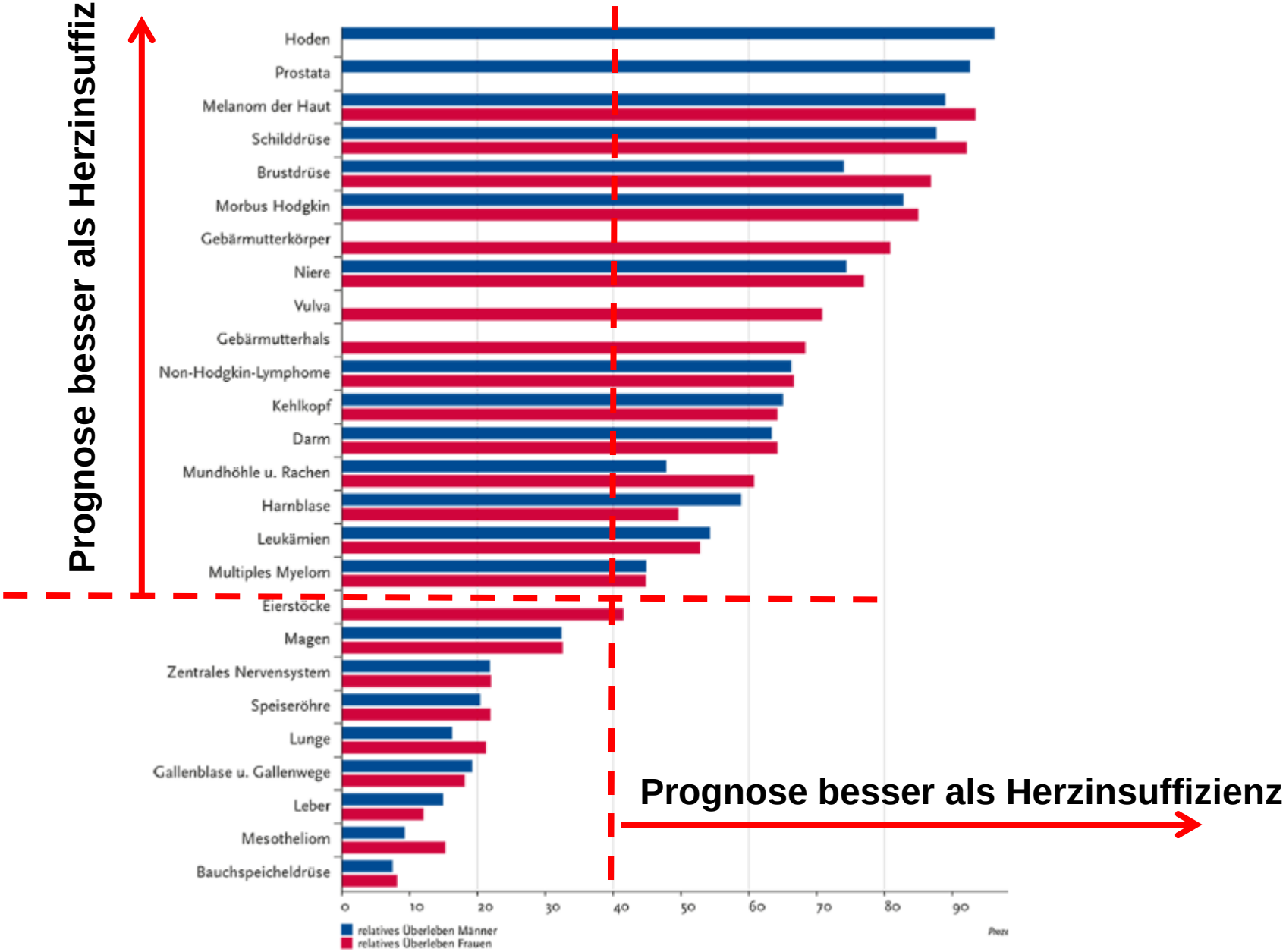
- Weniger als 257
- 257 bis 272
- 273 bis 305
- 306 bis 352
- 353 bis 409
- 410 und mehr

Überlebenskurve der Herzinsuffizienz: nach Hospitalisierung wegen HI



Owan et al., NEJM 2006

Relatives Überleben

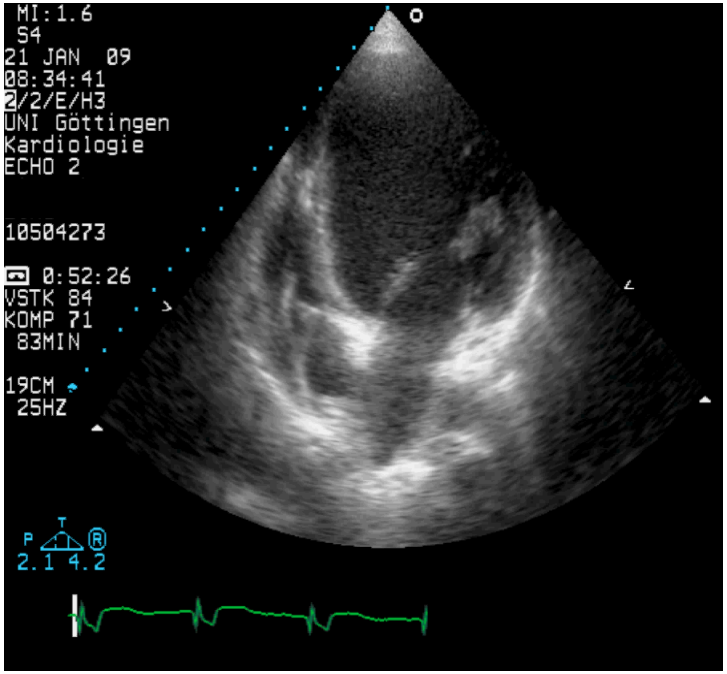


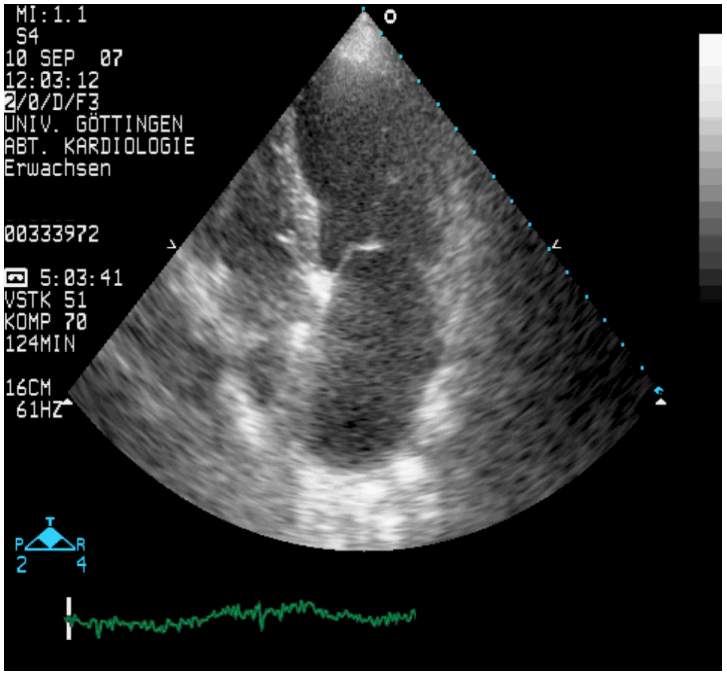
RKI, Periodenanalyse 2009-2010

Formen der Herzinsuffizienz

HFrEF = SHF
Heart failure with reduced EF

HFpEF = DHF
Heart failure with preserved EF





Eine neue Form der Herzschwäche (HFmrEF)

Neuerung

Table 3.1 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[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 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).	1. Elevated levels of natriuretic peptides[b]; 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).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL

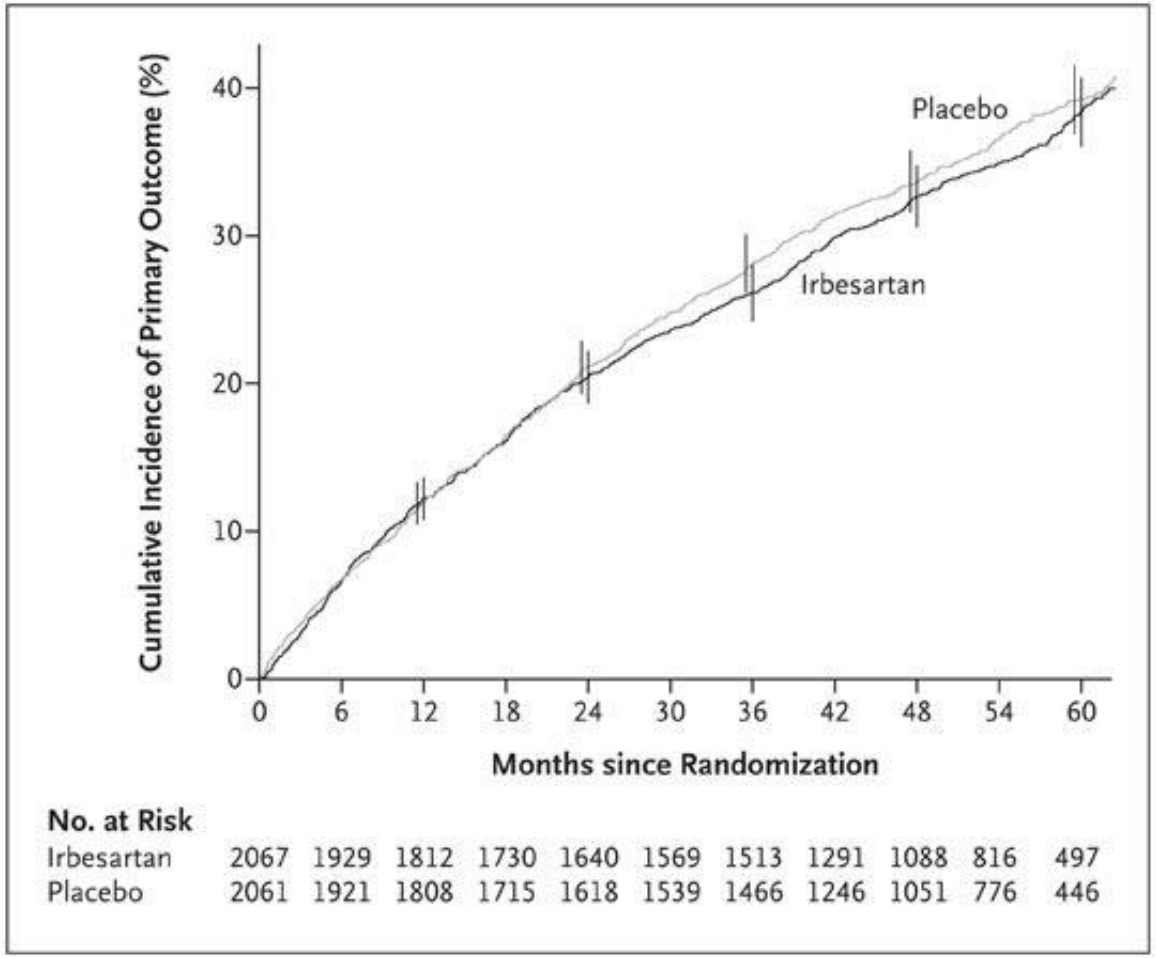
Ponikowski et al., EHJ 2016

Gliederung

1. Formen der Herzinsuffizienz und Prognose

2. **Therapien der Herzinsuffizienz mit erhaltener Ejektionsfraktion**

Irbesartan bei diastolischer Herzinsuffizienz (I-Preserve)



p=0.35

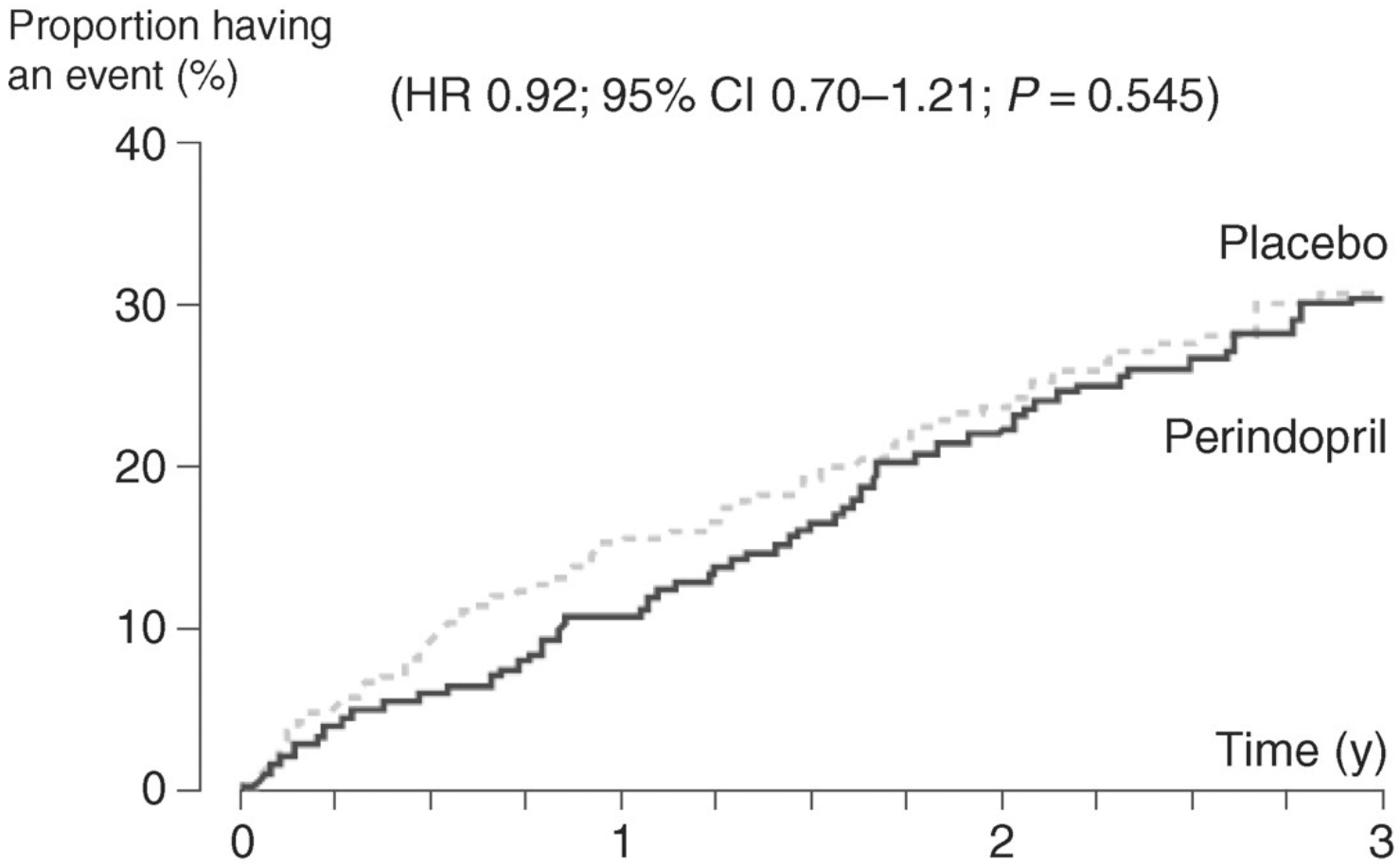
Primärer Endpunkt: Tod, kardiovask. Hospitalisation

Massie et al., NEJM 2008

ACE inhibitors in the elderly

PEP-CHF Study: Perindopril (4mg) vs. Placebo in 850 patients (>70Jahre); F.U. 2.1 years

Primary EP: Time until death or heart failure hospitalization

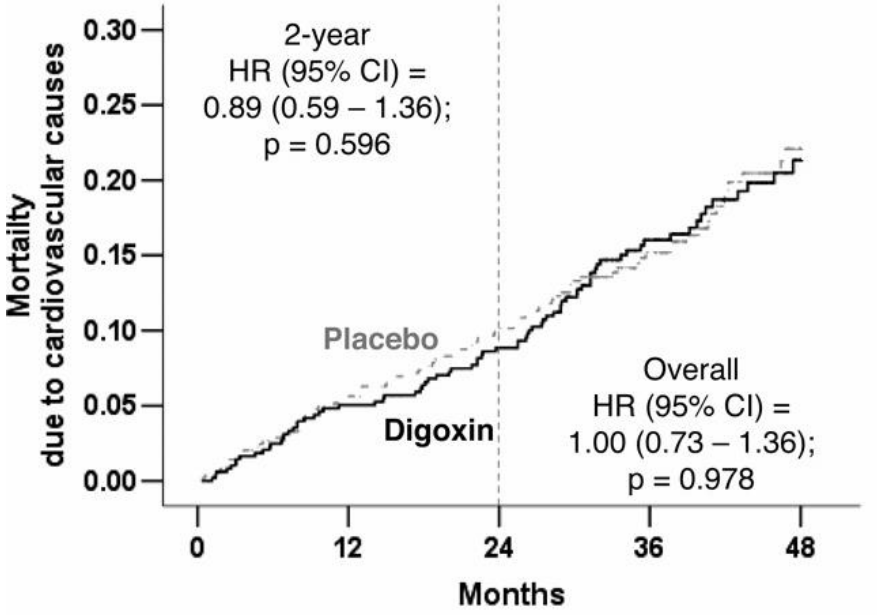


Cleland et al., Eur Heart J 2006

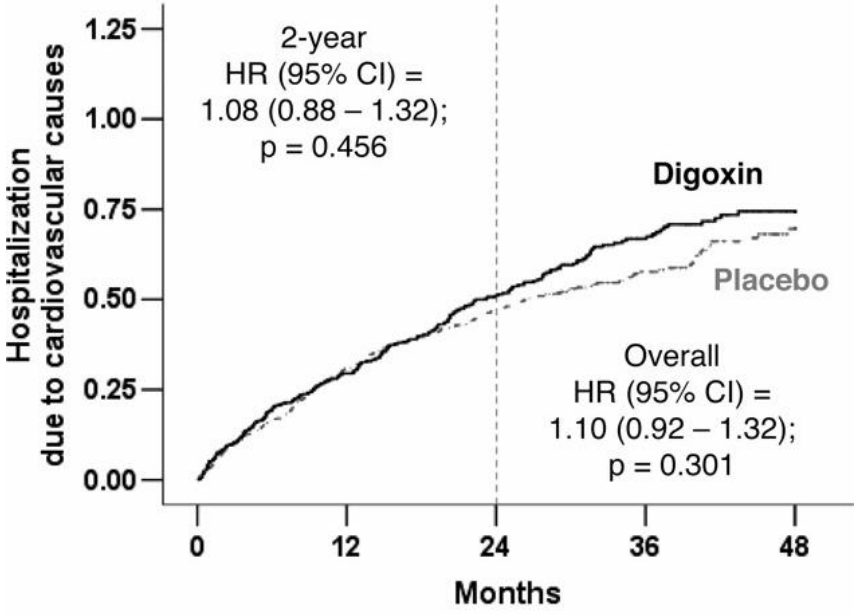
Digitalis in diastolic heart failure ?

DIG-Trial: 988 heart failure patients, EF>45% with SR. Digoxin vs. Placebo, 37 months F.U.

Cardiovascular mortality

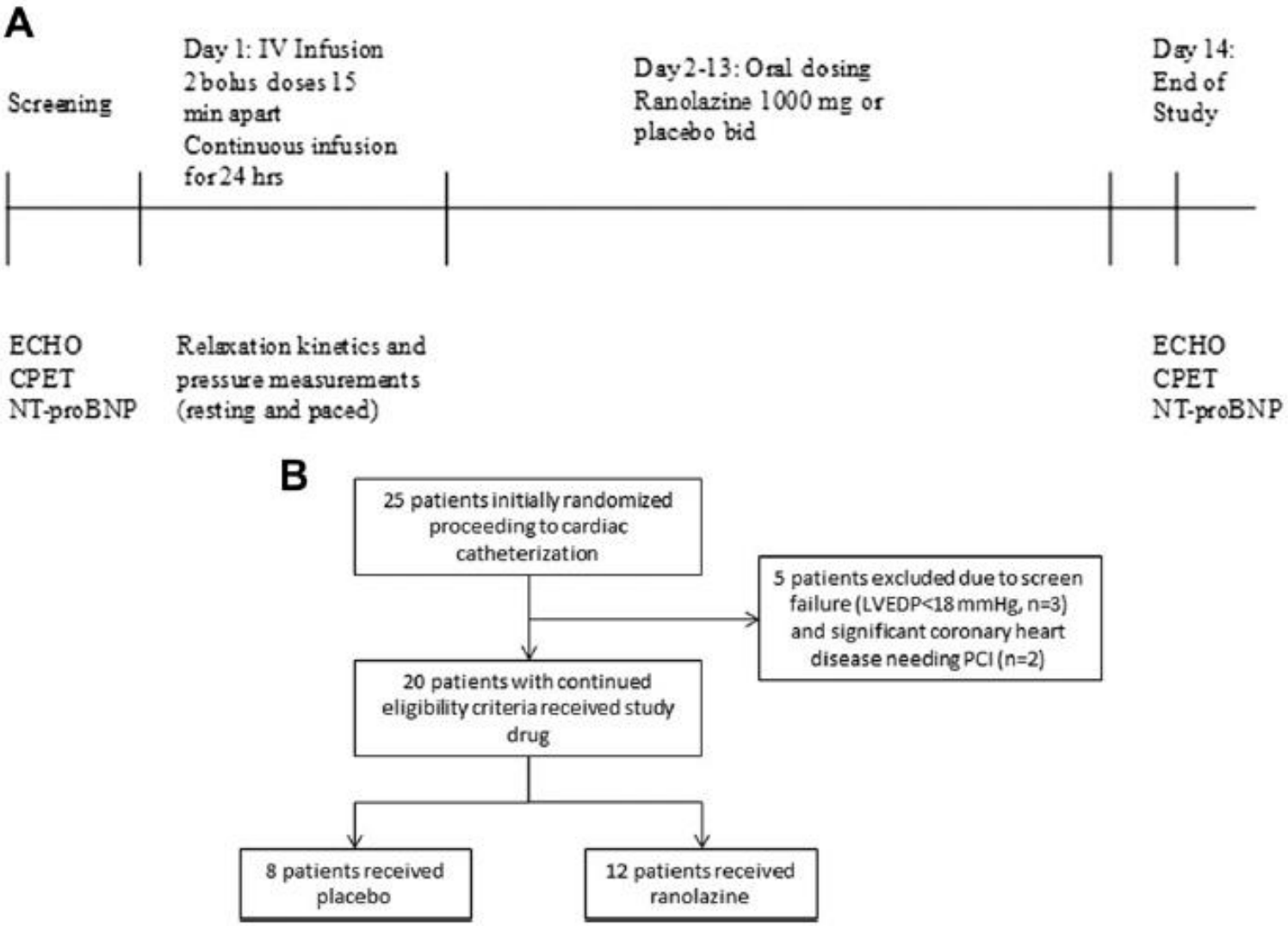


Cardiovascular hospitalisation



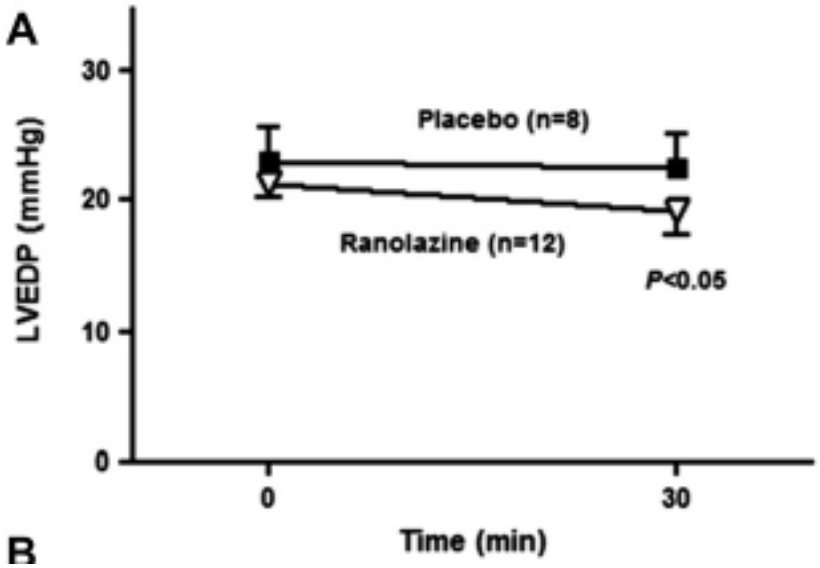
Ahmed et al., Circulation 2006; 114(5)

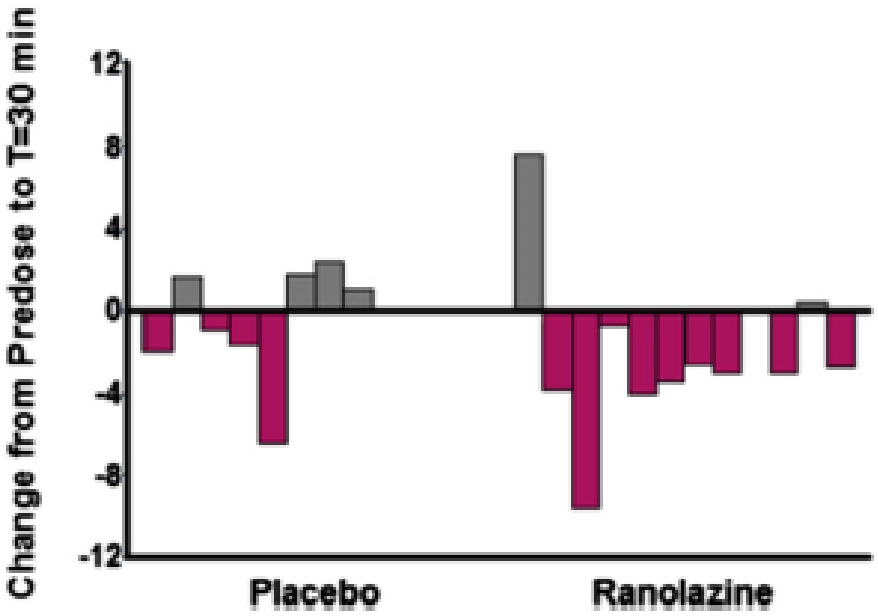
Rali-DHF: Pilotstudie mit Ranolazin



Maier LS et al., JACC HF 2013

Rali-DHF: Veränderung LVEDP





Maier LS et al., JACC HF 2013

HFpEF: Aldosteronrezeptor Blockade?

Aldo-DHF

(Aldosterone receptor blockade in diastolic heart failure)

422 Patienten mit HFpEF

Prospektive Placebo-kontrollierte randomisierte Studie

Spironolacton 25 mg vs. Placebo für 12 Monate

Primäre Endpunkte:

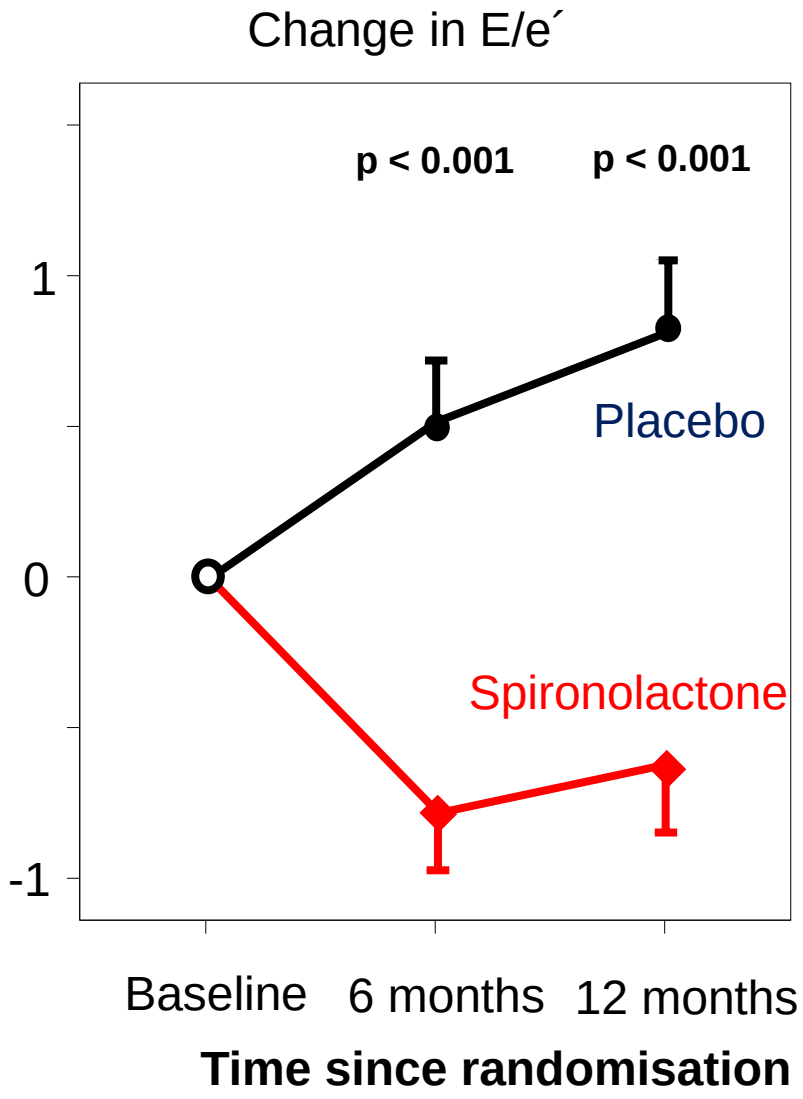
1. **peak Sauerstoffaufnahme (Spiroergometrie, peak VO_2)**
2. **Diastolische Funktion (Echo, E/E´)**

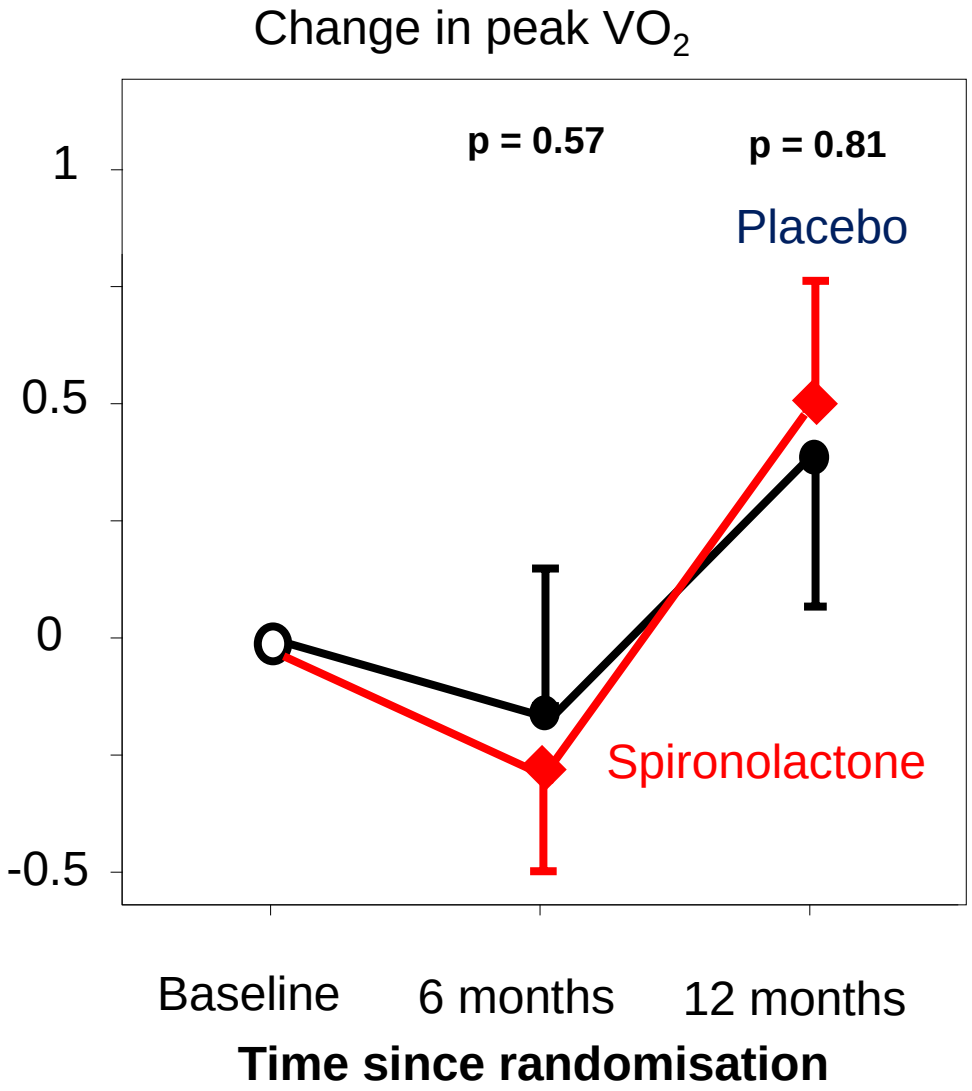
Bundesministerium für Bildung und Forschung

Kompetenznetz Herzinsuffizienz

Edelmann et al. Eur J Heart Faill 2010

Primary endpoints





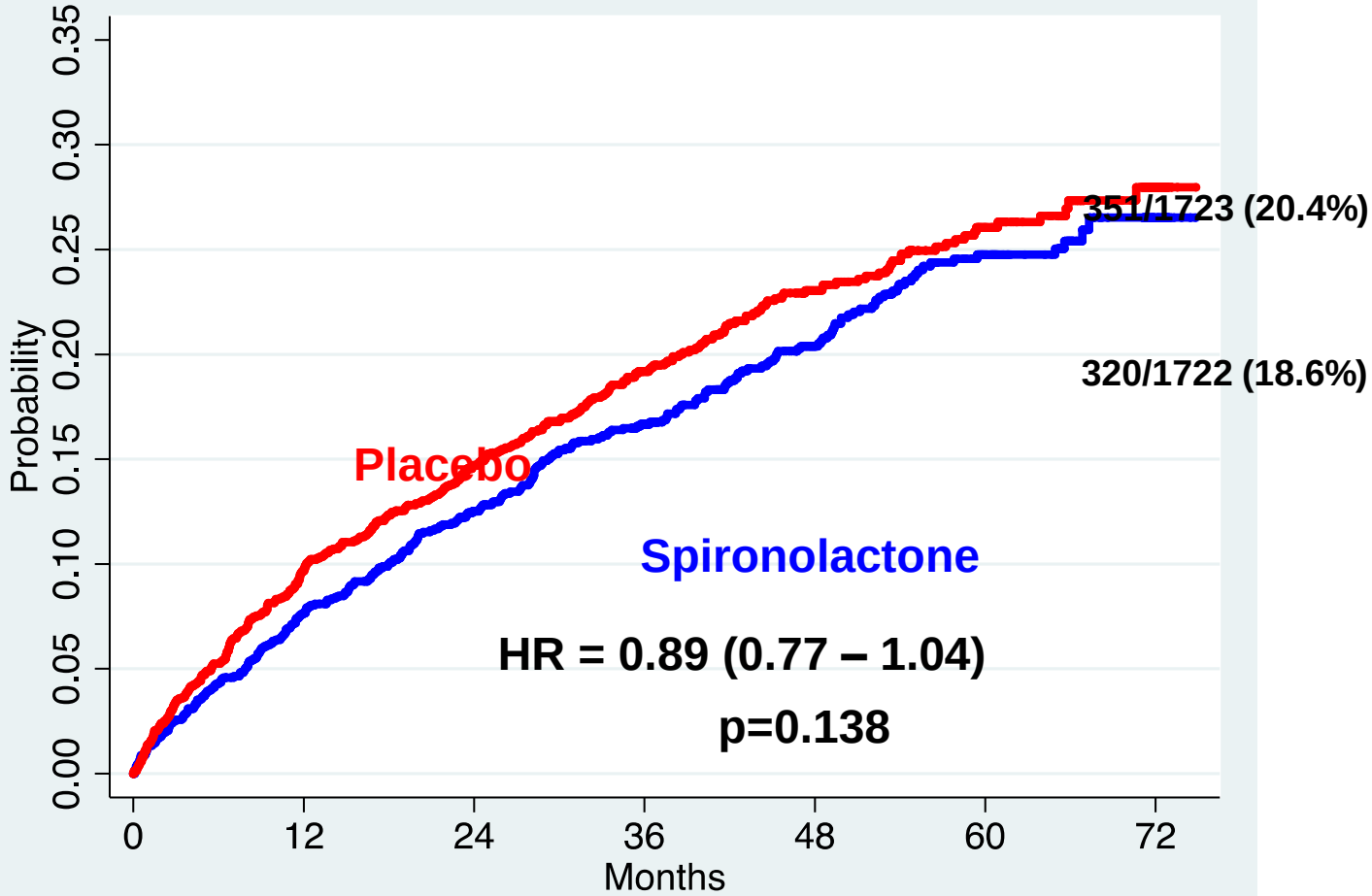
Edelmann F, Wachter R (equally contributed), JAMA 2013

Treatment **O**f **P**reserved **C**ardiac Function Heart Failure with an **A**ldosterone an**T**agonist **(TOPCAT)**

- Objective
  - To determine if spironolactone reduces the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for heart failure, compared with placebo, in adults with HF-Preserved EF.
- Inclusions:
  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  - Hospitalization within the past year for management of heart failure, or
  - Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- Major Exclusions:
  eGFR<30 mL/min/1.7m^2, serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Rationale and design: (A. Desai, Am Heart J 2011)

1° Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



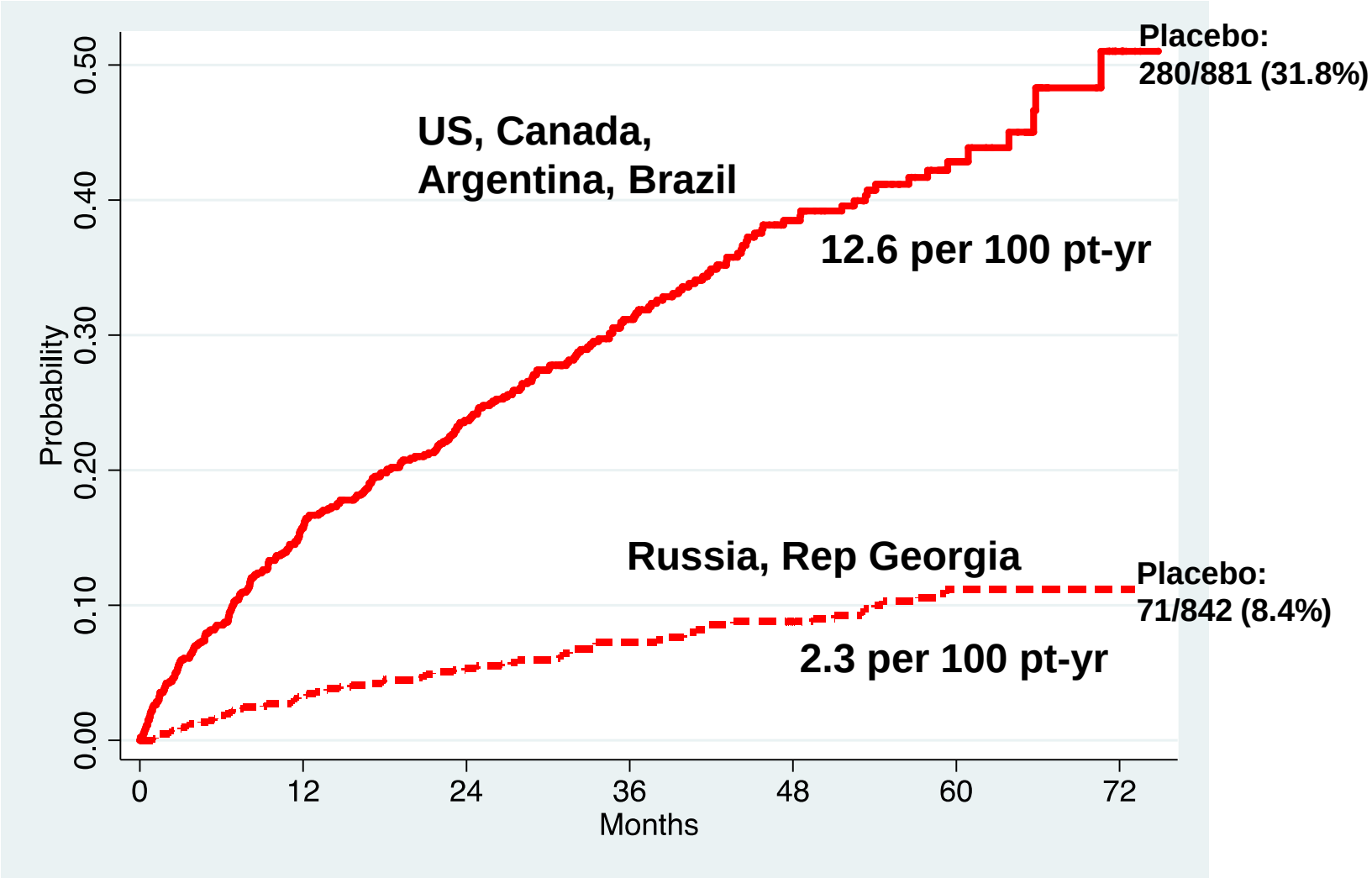
Number at risk

Spiro	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

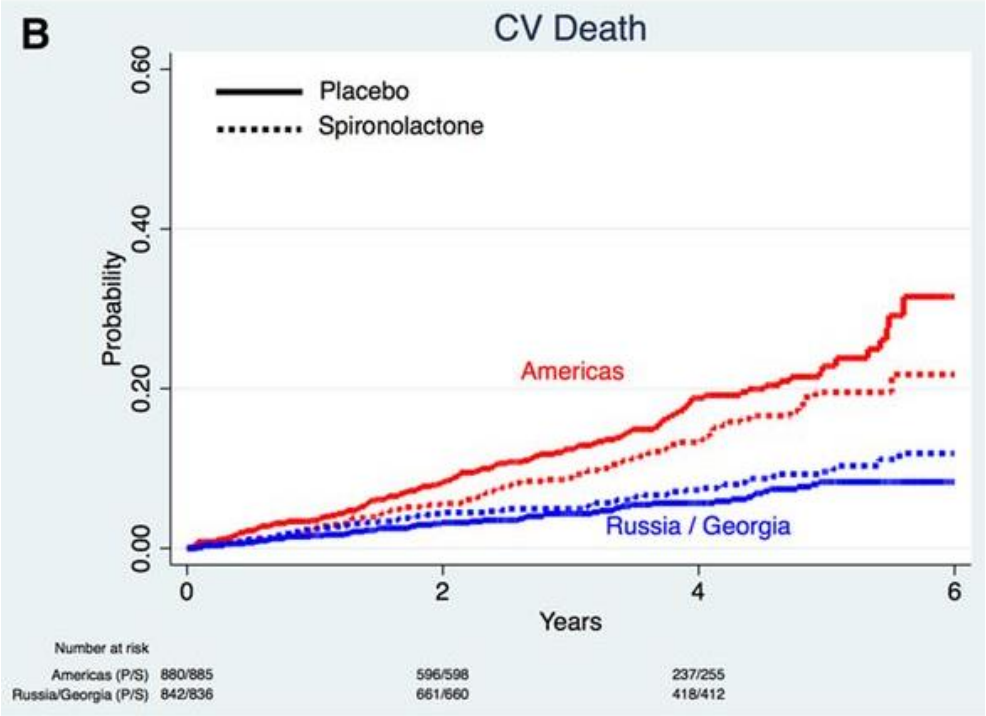
Pitt B, et al., NEJM 2014

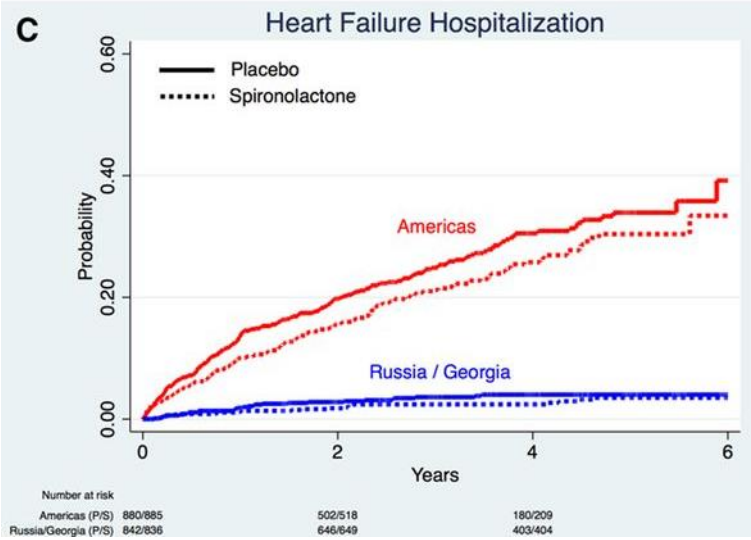
Placebo Rates:

Primary Outcome, by region



Prognose nach Region in TOPCAT

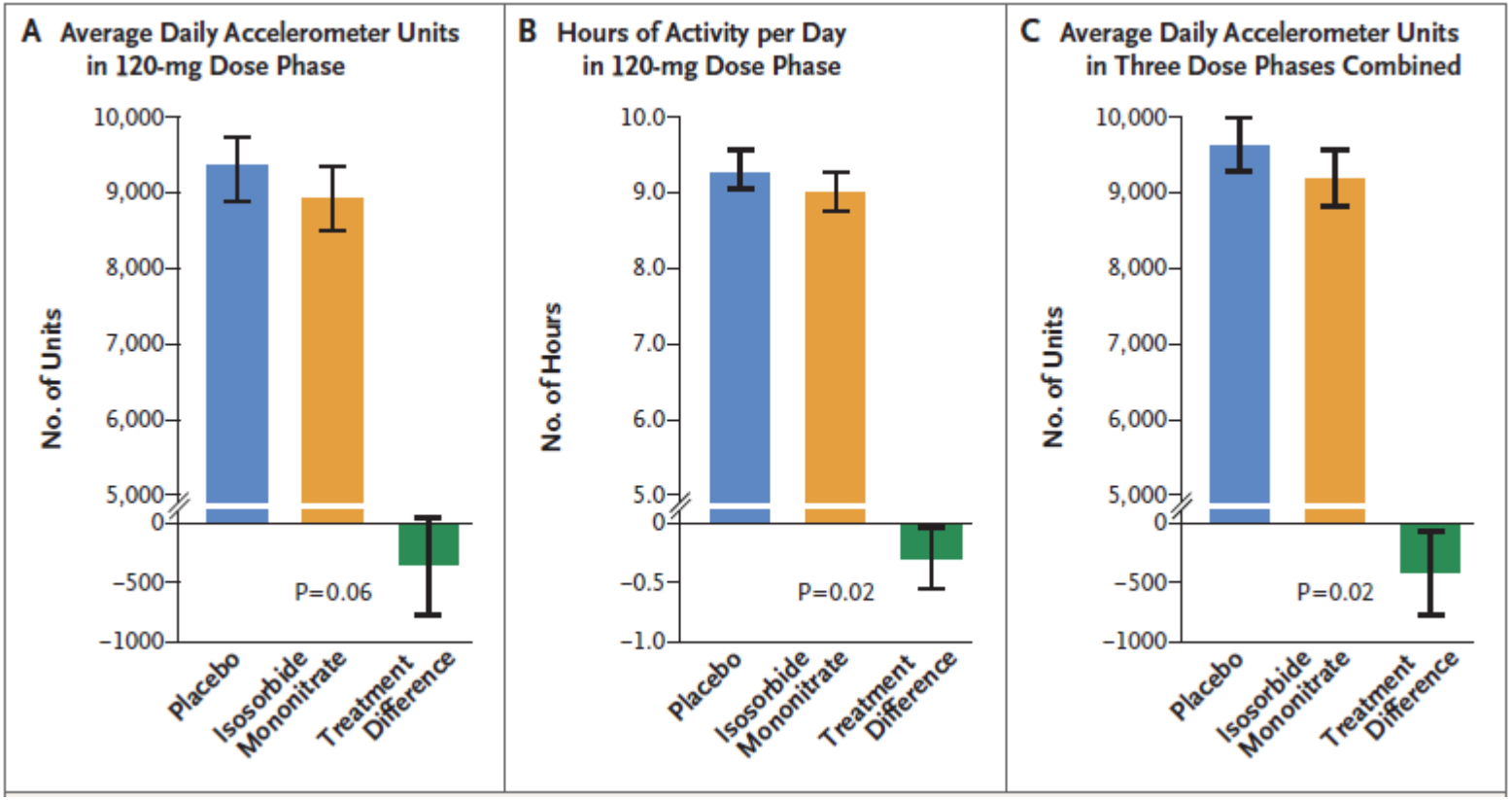




Pfeffer et al. Circulation. 2015;131:34-42

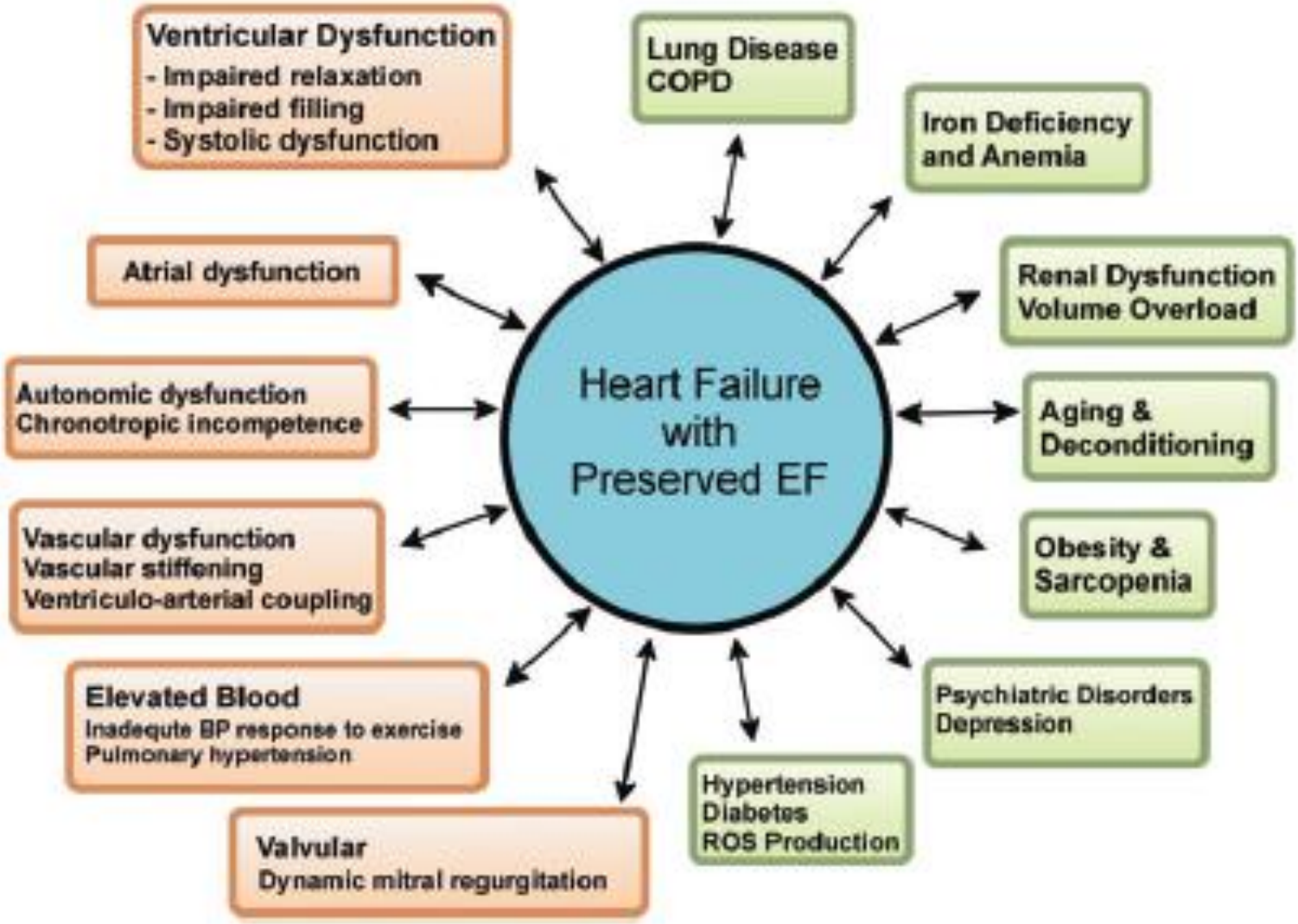
Isosorbidmononitrat in HFpEF

N = 110, doppel-blind, cross-over, 69 Jahre, 57 % Frauen



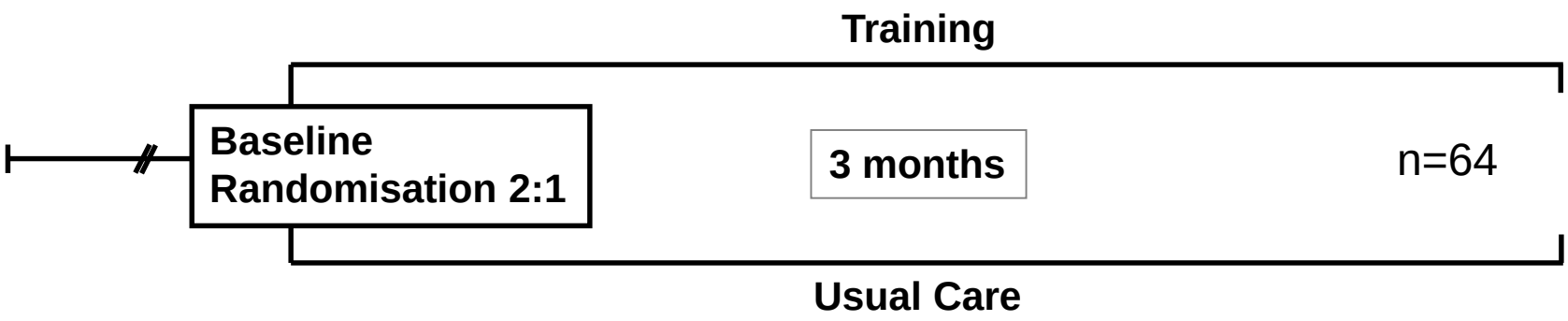
Redfield MM, et al., NEJM 2015

Pathophysiologie und Comorbiditäten bei HFpEF



Senni et al. Eur J Heart F 2014

Exercise Training: Ex-DHF-P

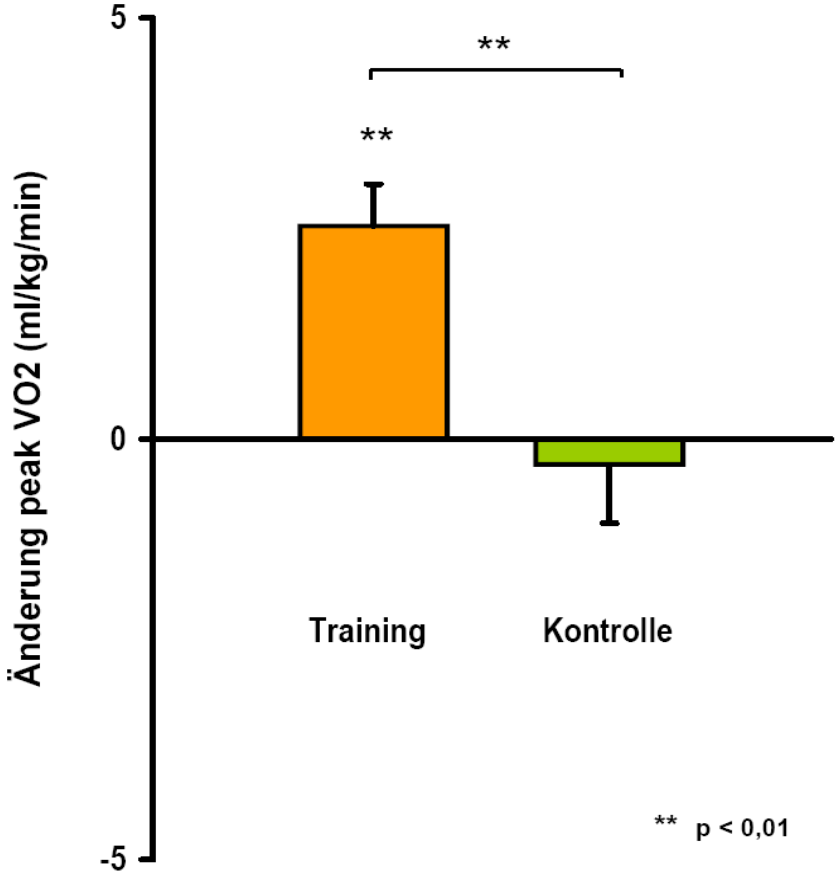


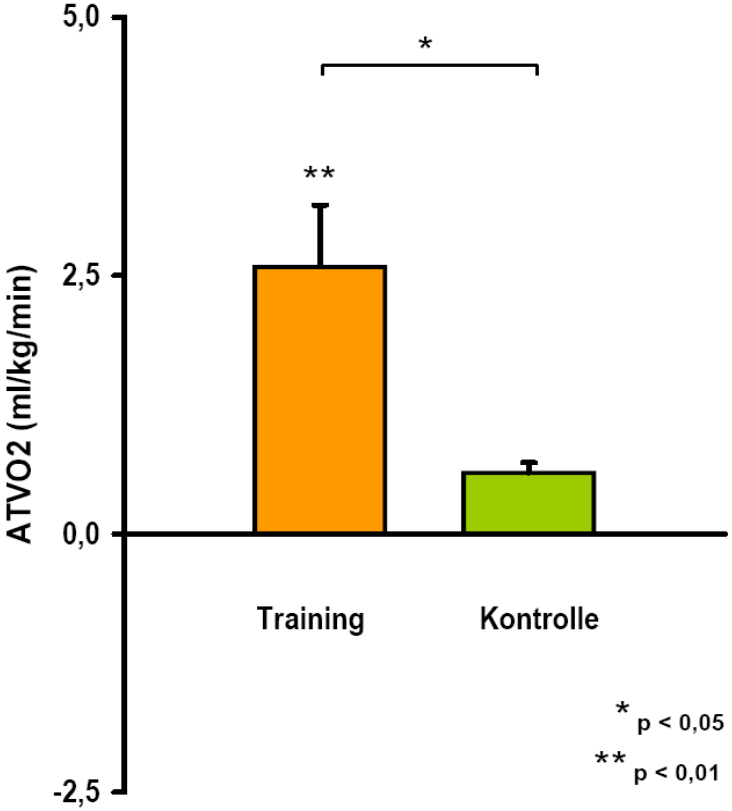
Resistance training		**60% 1-RM** **1 x 15**	**60% 1-RM** **2 x 15**
Endurance training	**50-60% peak VO_2** **10-20min**	**60-70% peak VO_2** **20-35min**	**65-70% peak VO_2** **30-35min**
	2x/ week	**3x/ week**	**3x/ week**

Edelmann F et al., JACC 2011

Ex-DHF-P: Primärer Endpunkt

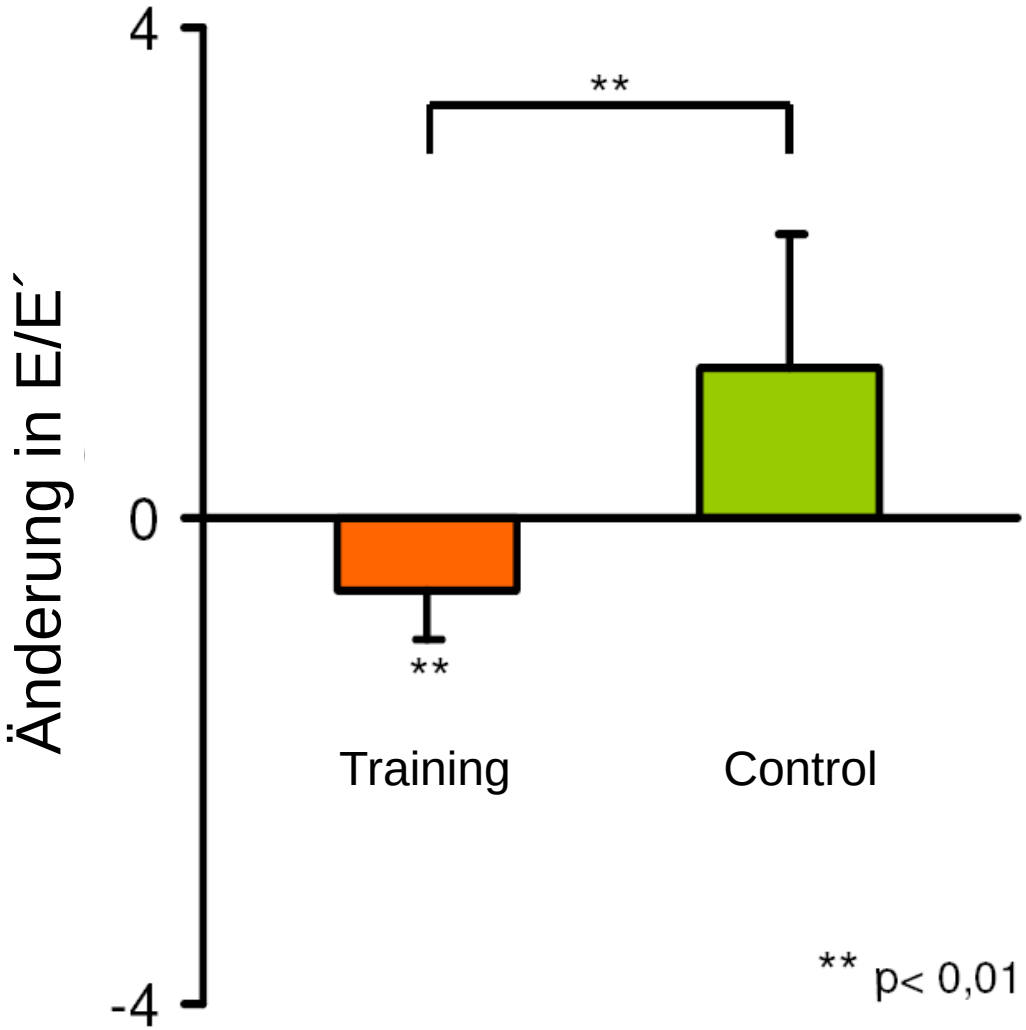
Spiroergometry





Edelmann F, …., Wachter R, et al., JACC 2011

Diastolische Funktion: E/É



Edelmann F, …, Wachter R, et al., JACC 2011

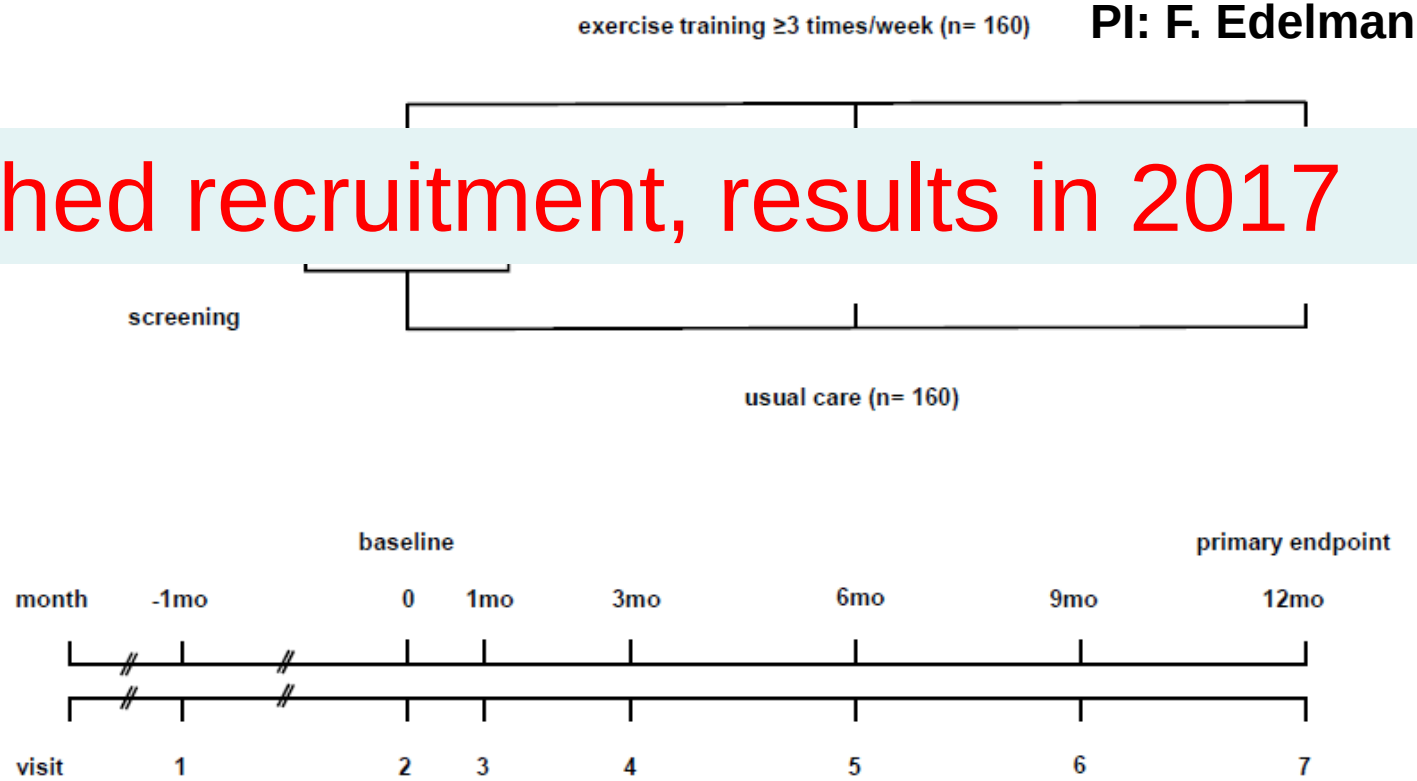
Exercise Training: Ex-DHF Trial

multi-center, prospective, randomised, controlled, parallel group study to assess the effects of exercise training in n=320 patients with HFpEF (composite outcome score)

PI: F. Edelmann

Flow

Finished recruitment, results in 2017

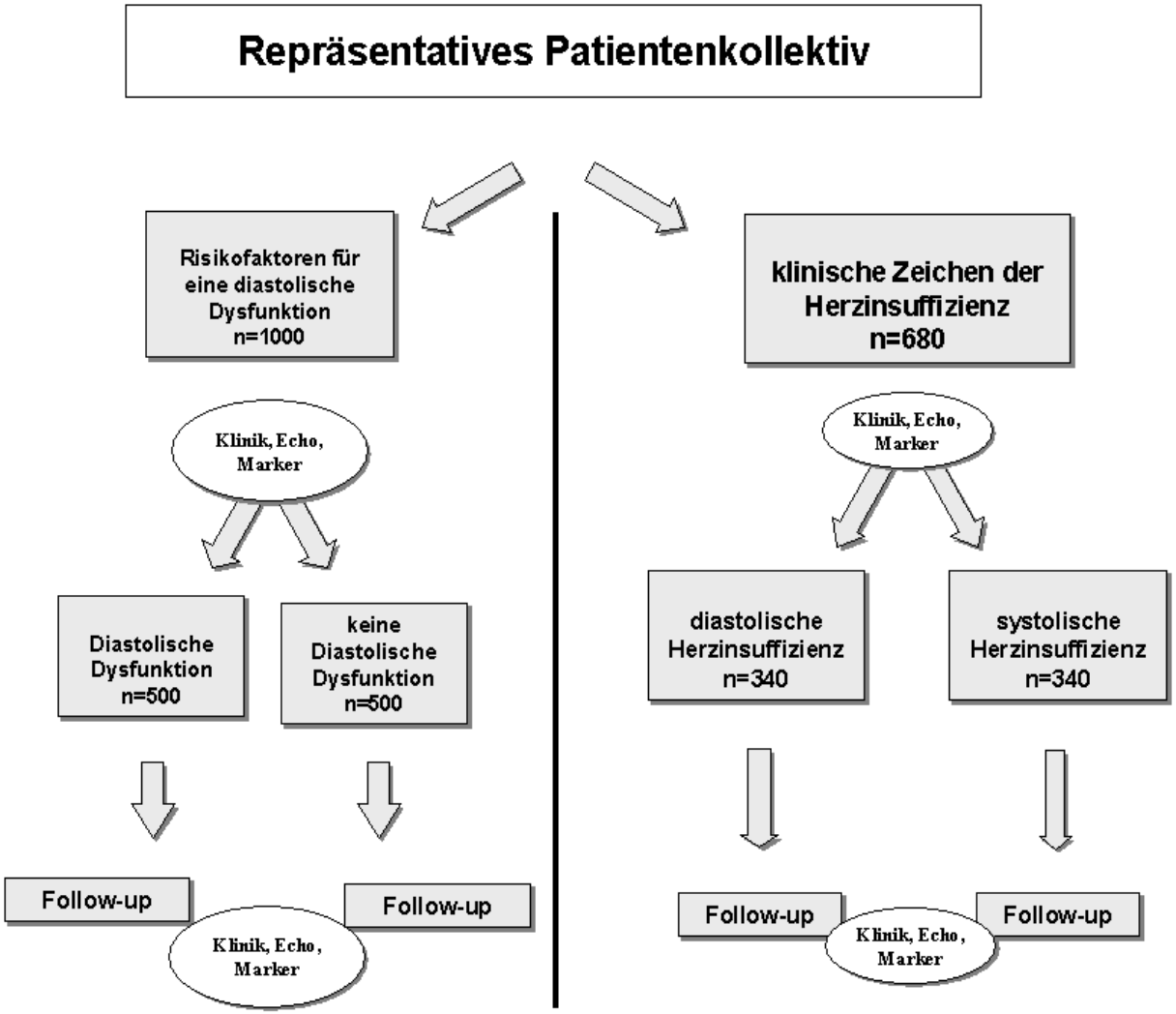


(http://www.controlled-trials.com/ ISRCTN86879094)

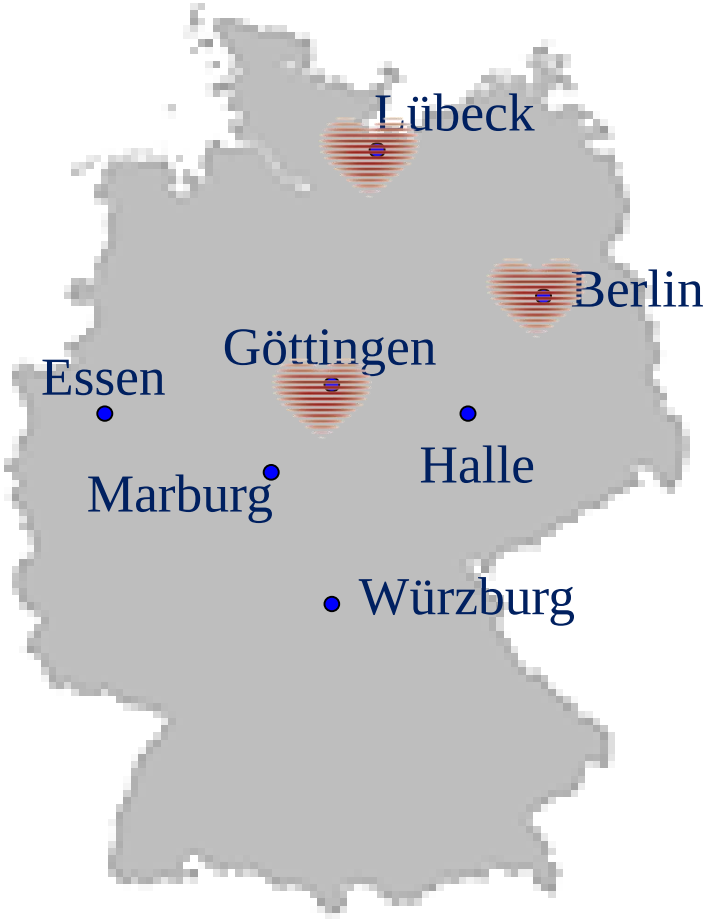
Deutsche Forschungsgemeinschaft

Kompetenznetz Herzinsuffizienz

Diastolische Dysfunktion – Diast-CHF



Partner/Standorte des TP 7



DZHK Standort

Einteilung der diastolischen Funktion

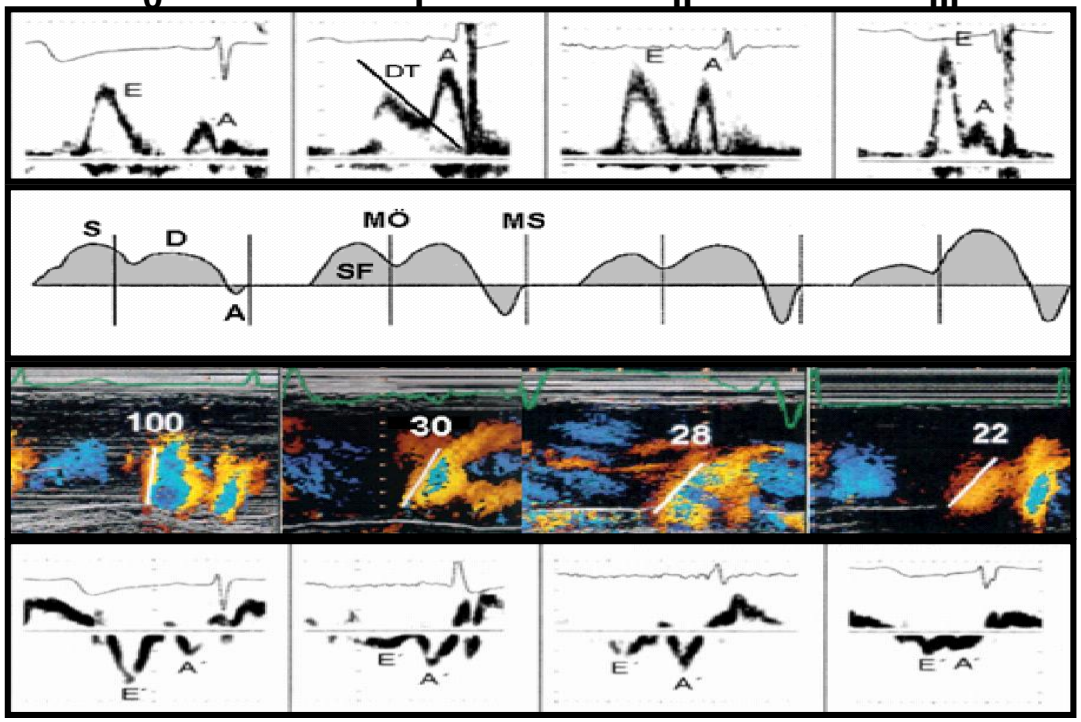
	Normal 0	Impaired Relaxation I	Pseudo-Normal II	Restrictive III

a) Transmitral Doppler LV inflow velocity

b) Pulmonary vein Doppler velocity

c) Colour-Doppler M-mode

d) Doppler Tissue Imaging (mitral annulus)

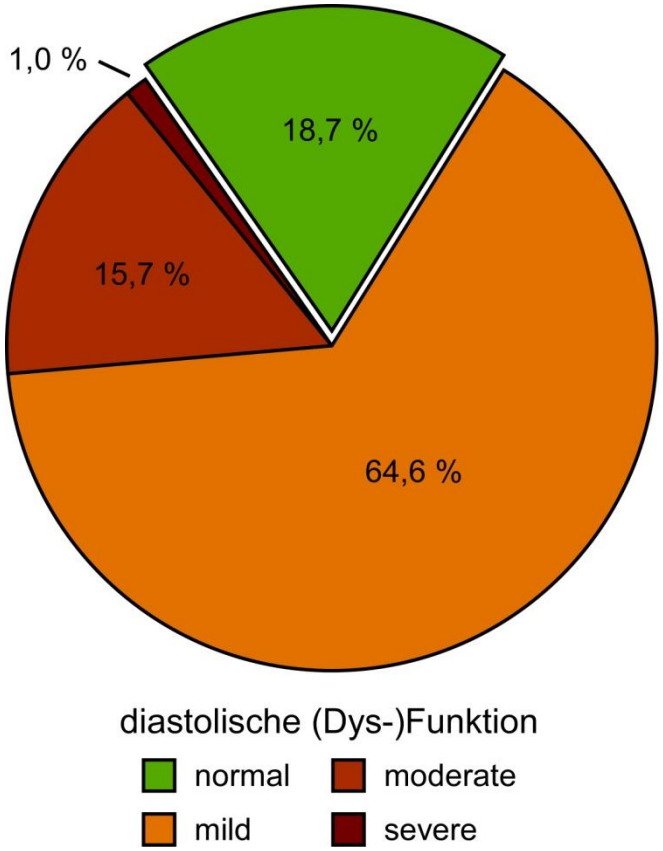


LV-Relaxation	Normal	Impaired	Impaired	Impaired
LV-Compliance	Normal	Normal - ↓	↓↓	↓↓↓
LA-Pressure	Normal	Normal - ↑	↑↑	↑↑↑

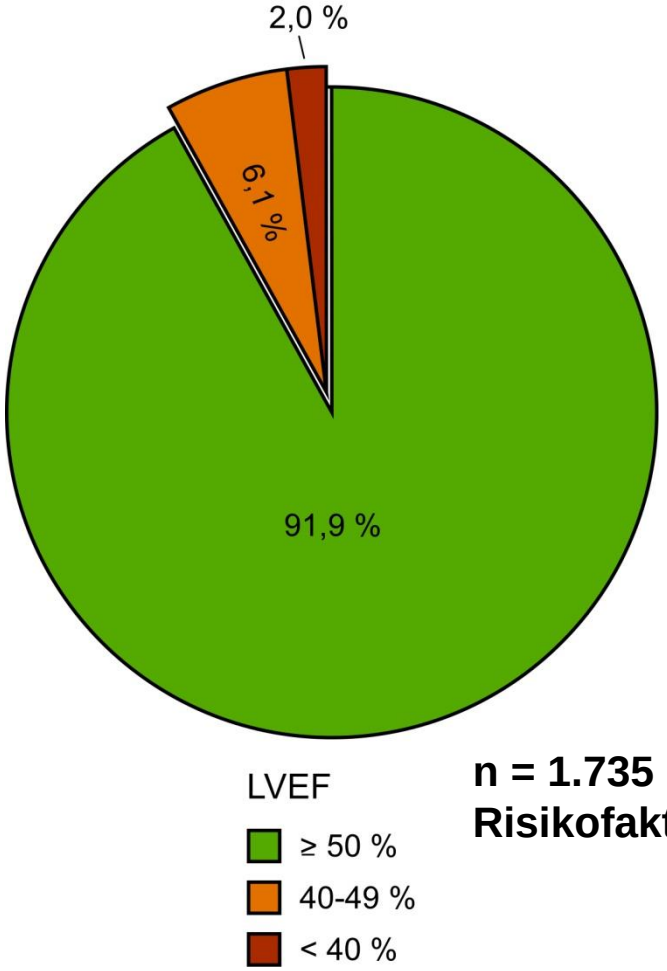
Prävalenz der LV-Dysfunktion
(n=1.735 ambulante hausärztliche Patienten mit Risikofaktoren

Kompetenznetz Herzinsuffizienz

Diastolische Dysfunktion



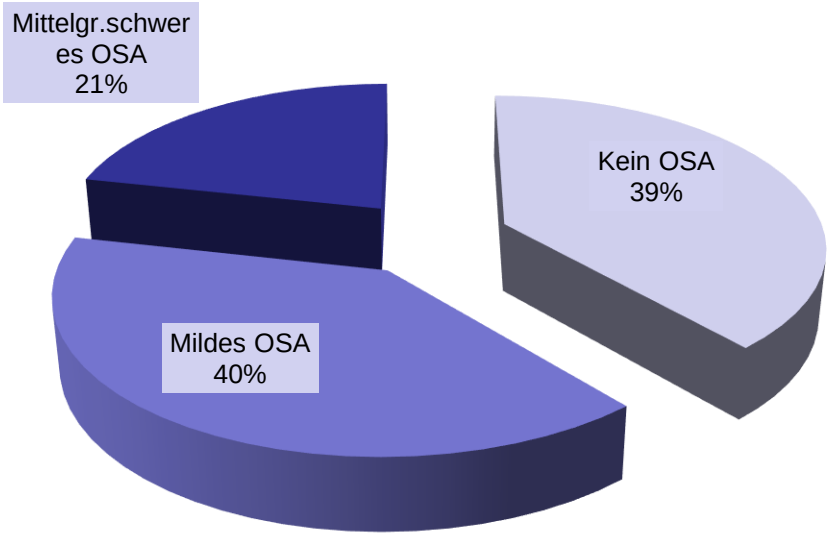
Systolische Dysfunktion

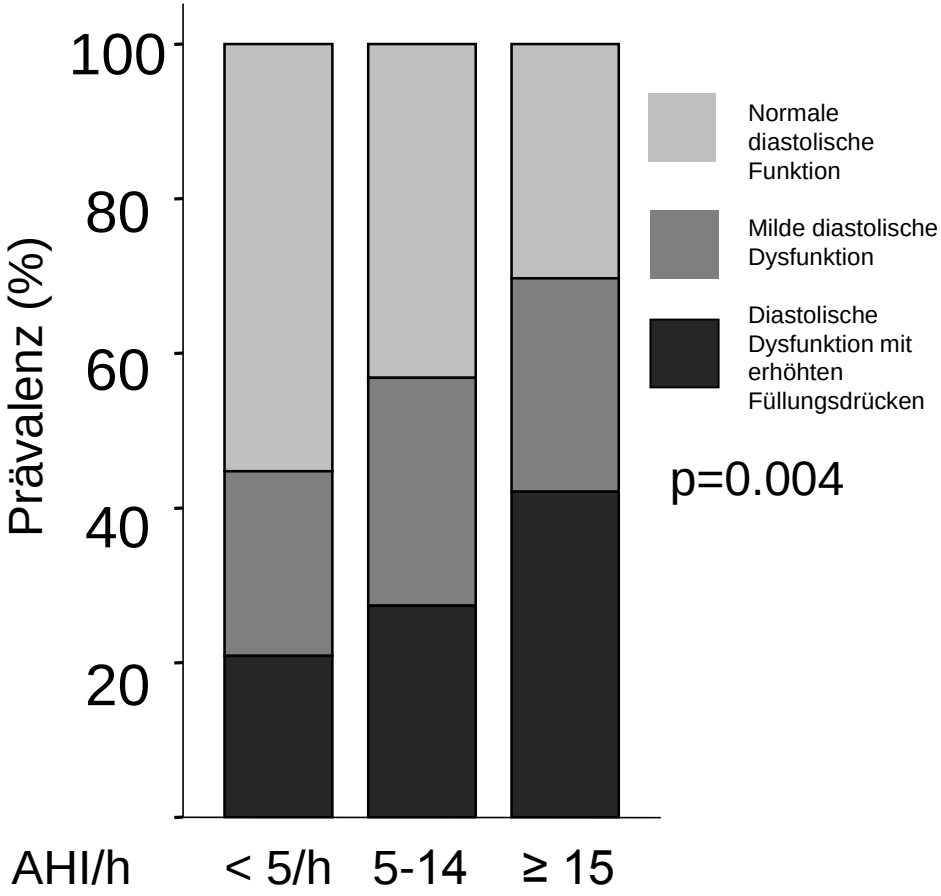


n = 1.735 Patienten mit Risikofaktoren

Obstruktive Schlafapnoe (OSA) und diastolische Funktion

Prävalenz des OSA (n=378)

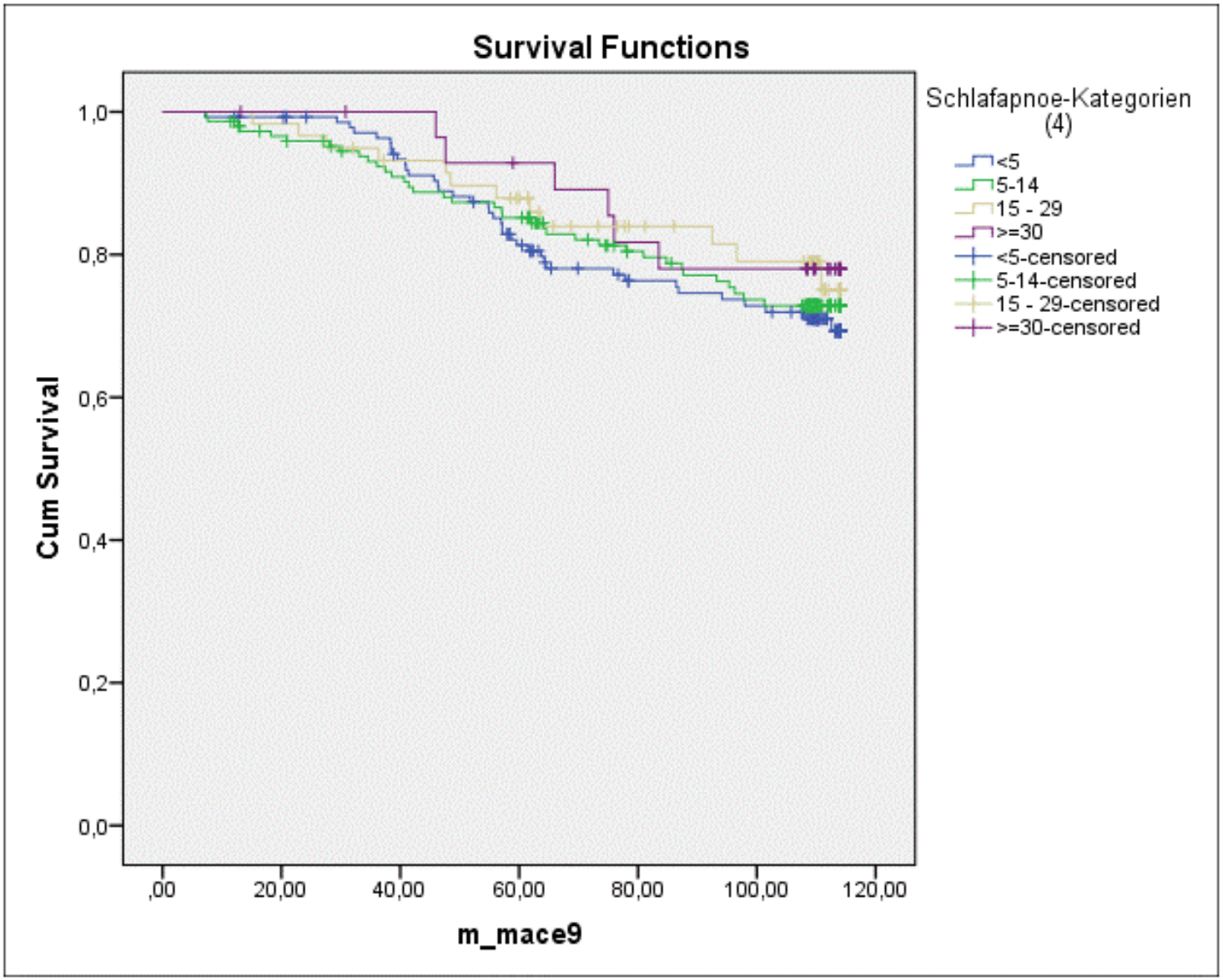




Wachter et al., Eur Respir J 2013

Kein Einfluss des Schlafapnoesyndroms auf die Langzeitprognose!

Überleben



Therapie des Übergewichtes

Research

Original Investigation

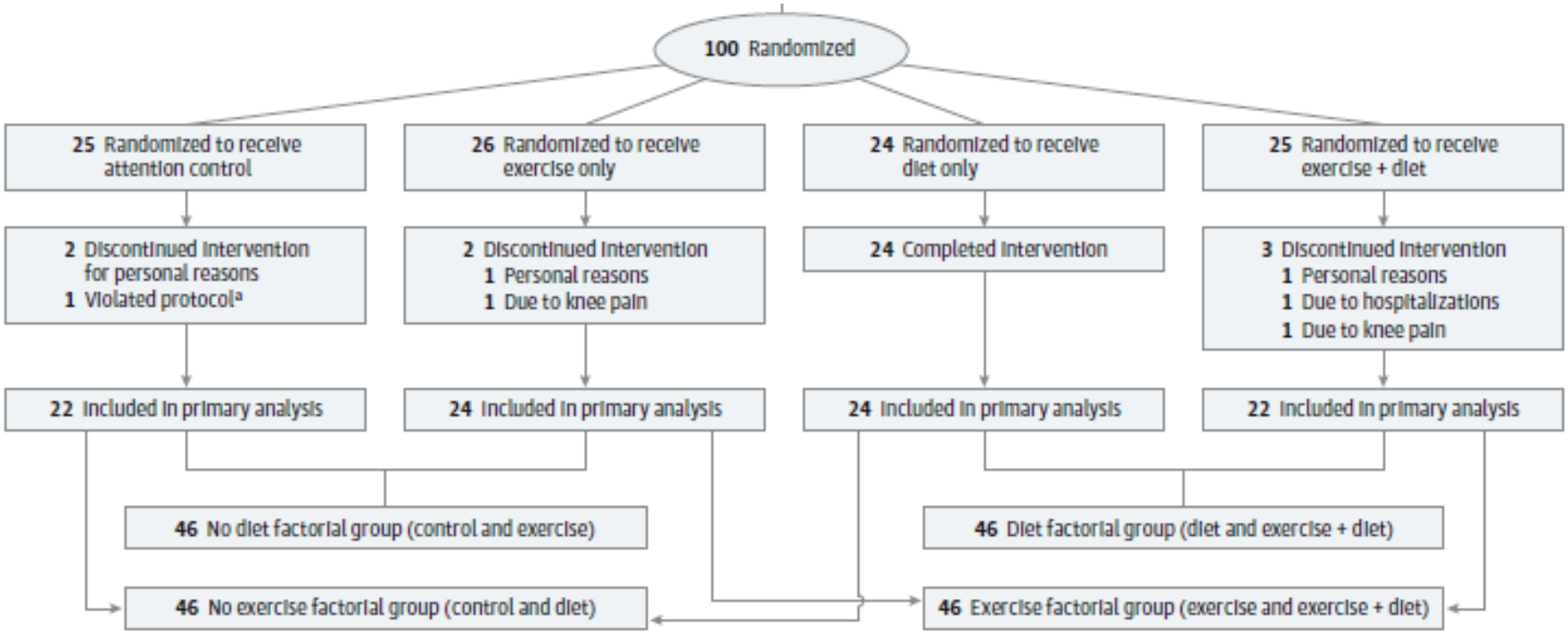
Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction

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

Kitzman D et al., JAMA 2016

2x2 faktorielles Studiendesign



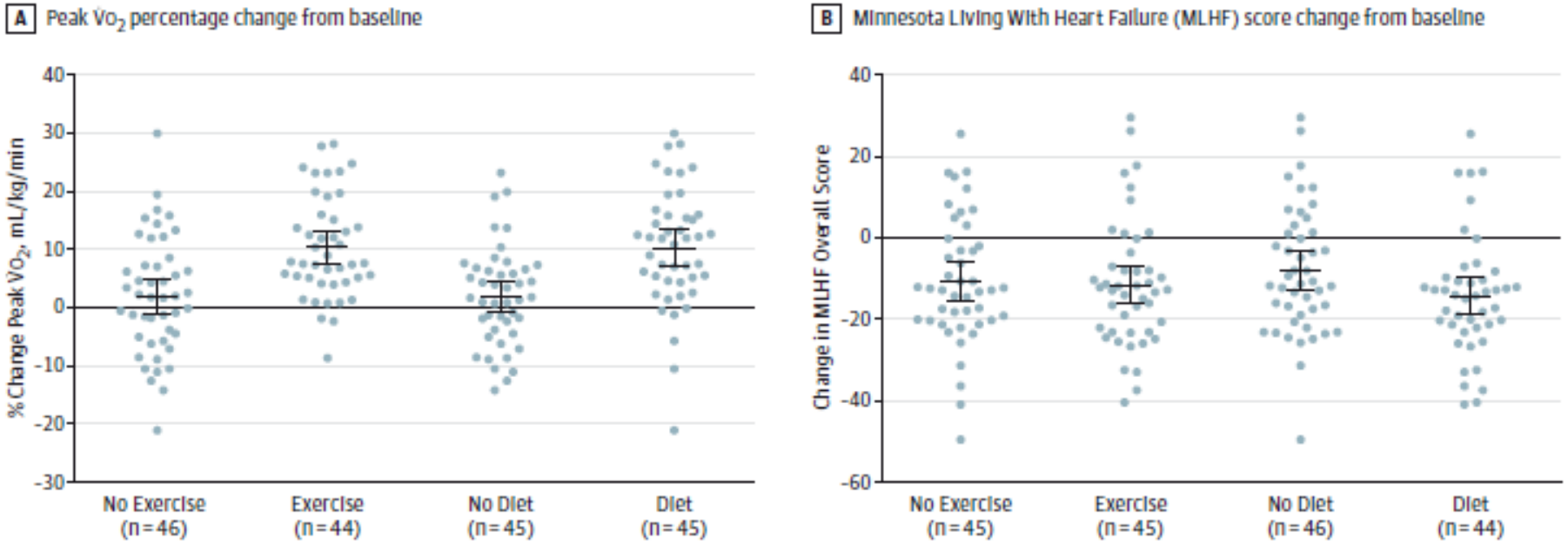
Kitzman D et al., JAMA 2016

Basischarakteristika

Characteristic	Factorial Group, mean (SD)			
	Exercise (n = 51)	No Exercise (n = 49)	Diet (n = 49)	No Diet (n = 51)
Demographic and Weight Characteristics, Mean (SD)				
Age, y	66.9 (5.5)	66.0 (4.8)	66.4 (5.0)	66.6 (5.4)
Women, No. (%)	41 (80)	40 (82)	40 (82)	41 (80)
White, No. (%)	28 (55)	27 (55)	24 (49)	31 (61)
Body weight, kg	109 (21)	102 (13)	105 (17)	106 (19)
Body surface area, m^2	2.12 (0.22)	2.06 (0.15)	2.09 (0.19)	2.09 (0.19)
BMI	40.3 (7.1)	38.4 (4.8)	39.0 (5.0)	39.7 (7.1)
Body fat, %	45 (6)	46 (7)	45 (6)	45 (7)

Kitzman D et al., JAMA 2016

Coprimäre Endpunkte



Kitzman D et al., JAMA 2016

Vorhofflimmern und Herzinsuffizienz

Epidemiology and Prevention

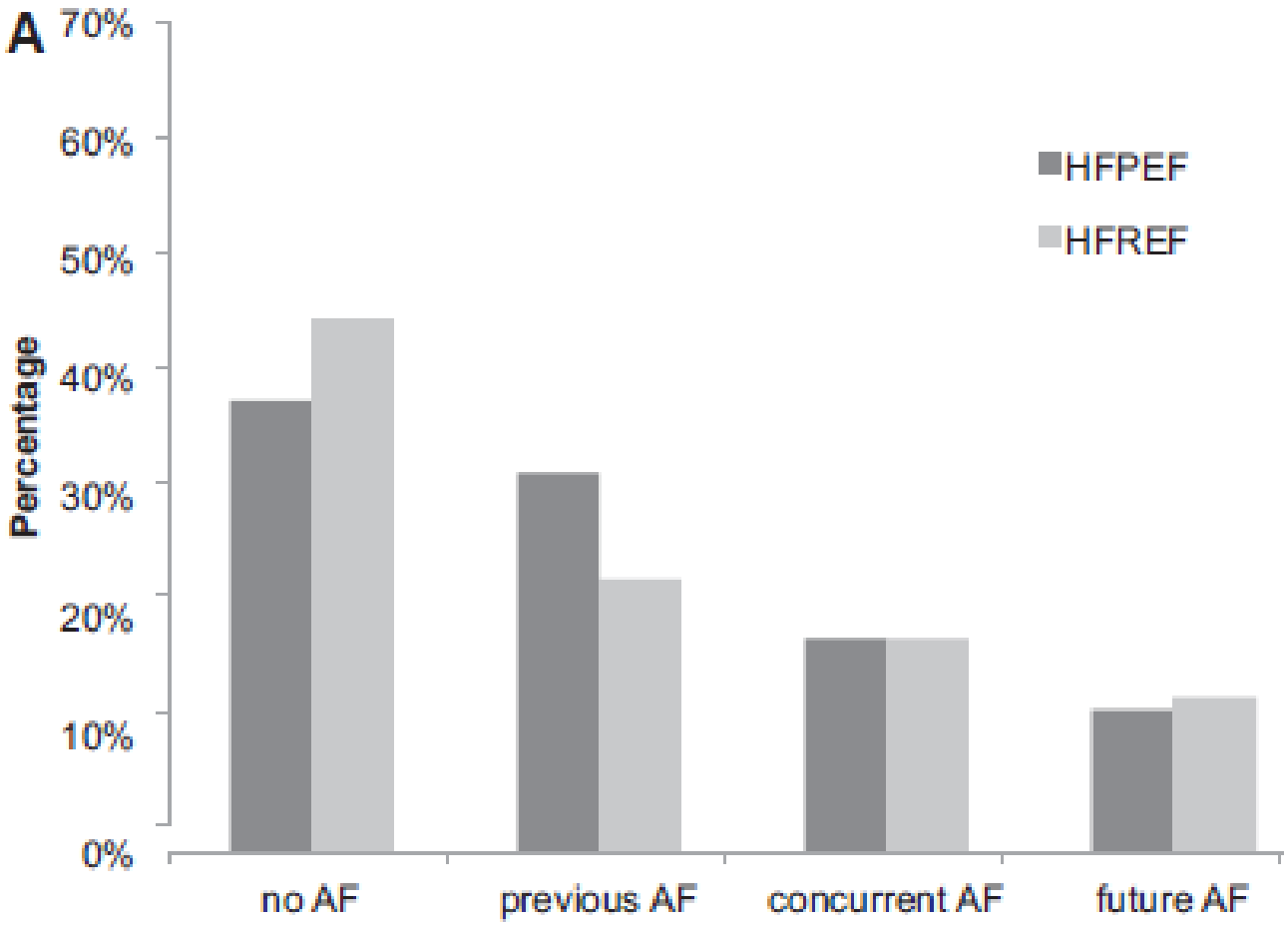
Atrial Fibrillation Begets Heart Failure and Vice Versa

Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction

Rajalakshmi Santhanakrishnan, MBBS; Na Wang, MA; Martin G. Larson, SD; Jared W. Magnani, MD, MSc; David D. McManus, MD; Steven A. Lubitz, MD, MPH; Patrick T. Ellinor, MD, PhD; Susan Cheng, MD; Ramachandran S. Vasan, MD; Douglas S. Lee, MD, PhD; Thomas J. Wang, MD; Daniel Levy, MD; Emelia J. Benjamin, MD, ScM; Jennifer E. Ho, MD

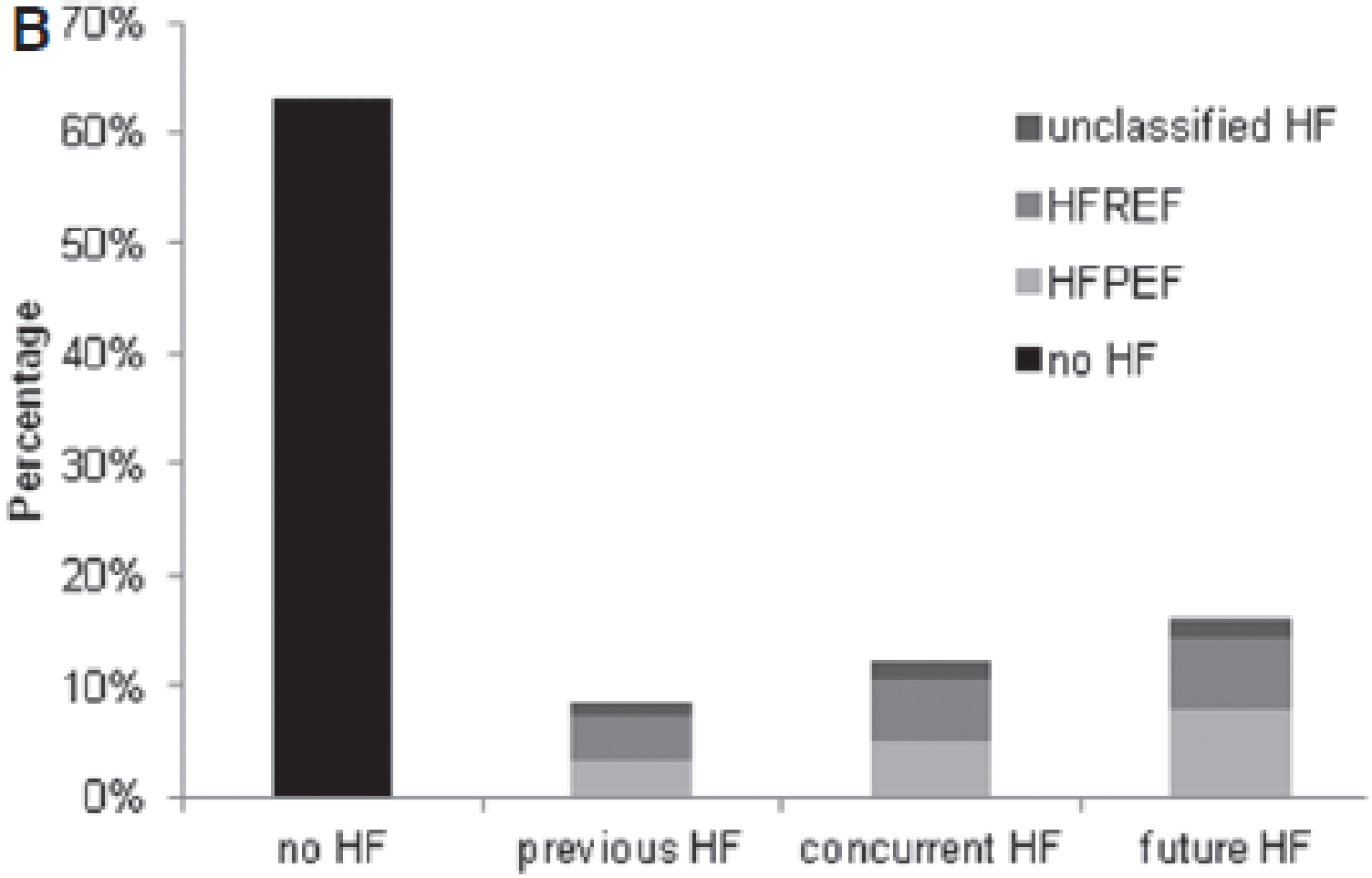
Santhanakrishnan et al., Circulation 2016

57 % der Herzinsuffizienzpatienten haben Vorhofflimmern



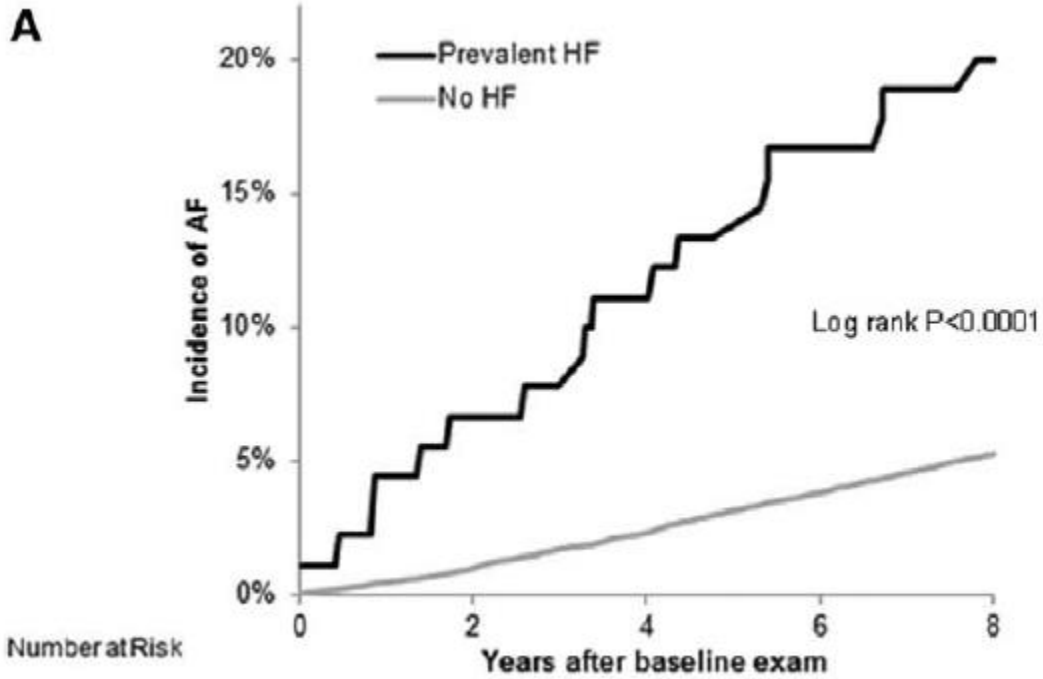
Santhanakrishnan et al., Circulation 2016

37 % der Vorhofflimmerpatienten haben eine Herzinsuffizienz



Santhanakrishnan et al., Circulation 2016

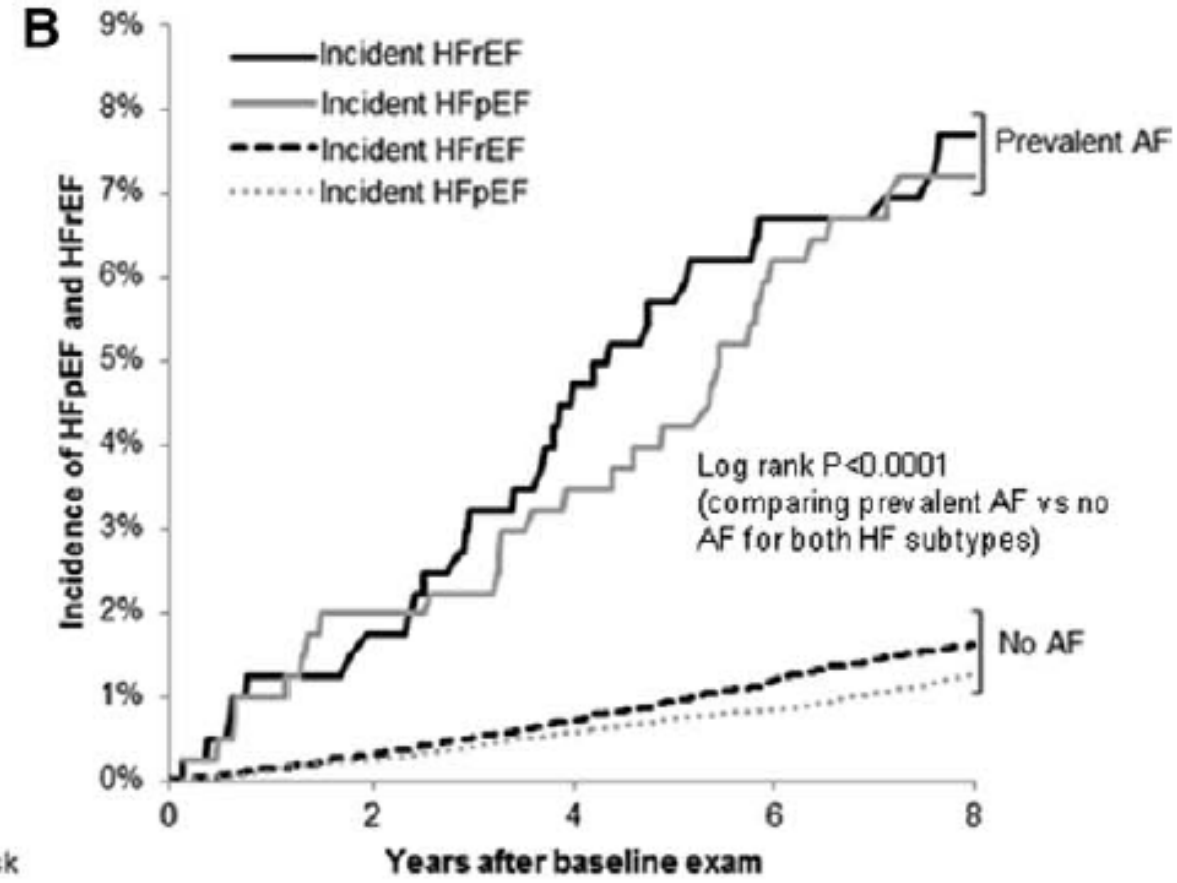
Herzinsuffizienz erhöht das Auftreten von Vorhofflimmern



Number at Risk					
Prevalent HF	90	64	51	34	25
No HF	14774	14395	13847	13237	12613

Santhanakrishnan et al., Circulation 2016

Vorhofflimmern erhöht das Auftreten von HFpEF und HFrEF



Number at Risk					
Prevalent AF	403	354	293	247	209
No AF	14800	14478	14004	13477	12934

Santhanakrishnan et al., Circulation 2016

Zusammenfassung

Aktueller Stand:
Schlechte Prognose bei HFrEF and HFpEF, 5-JÜR 40 %, schlechter als viele Krebserkrankungen

Therapien bei HFrEF:
Nitrate schaden!
Aldosteronantagonismus für die richtigen Patienten?
Körperliches Training?

Comorbiditäten:
OSA: verschlechtert diastolische Funktion, Einfluss auf Langzeitprognose fraglich. Therapiestudien zu OSA bei HFpEF fehlen.

Übergewicht: Therapie ab BMI > 35, dann ist kalorische Restriktion ähnlich gut wie körperliches Training

Vorhofflimmern: Häufig koinzident mit Herzinsuffizienz, beide Erkrankungen begünstigen sich gegenseitig.
Therapiestudien fehlen.