Bad Waltersdorf 15.02.2017

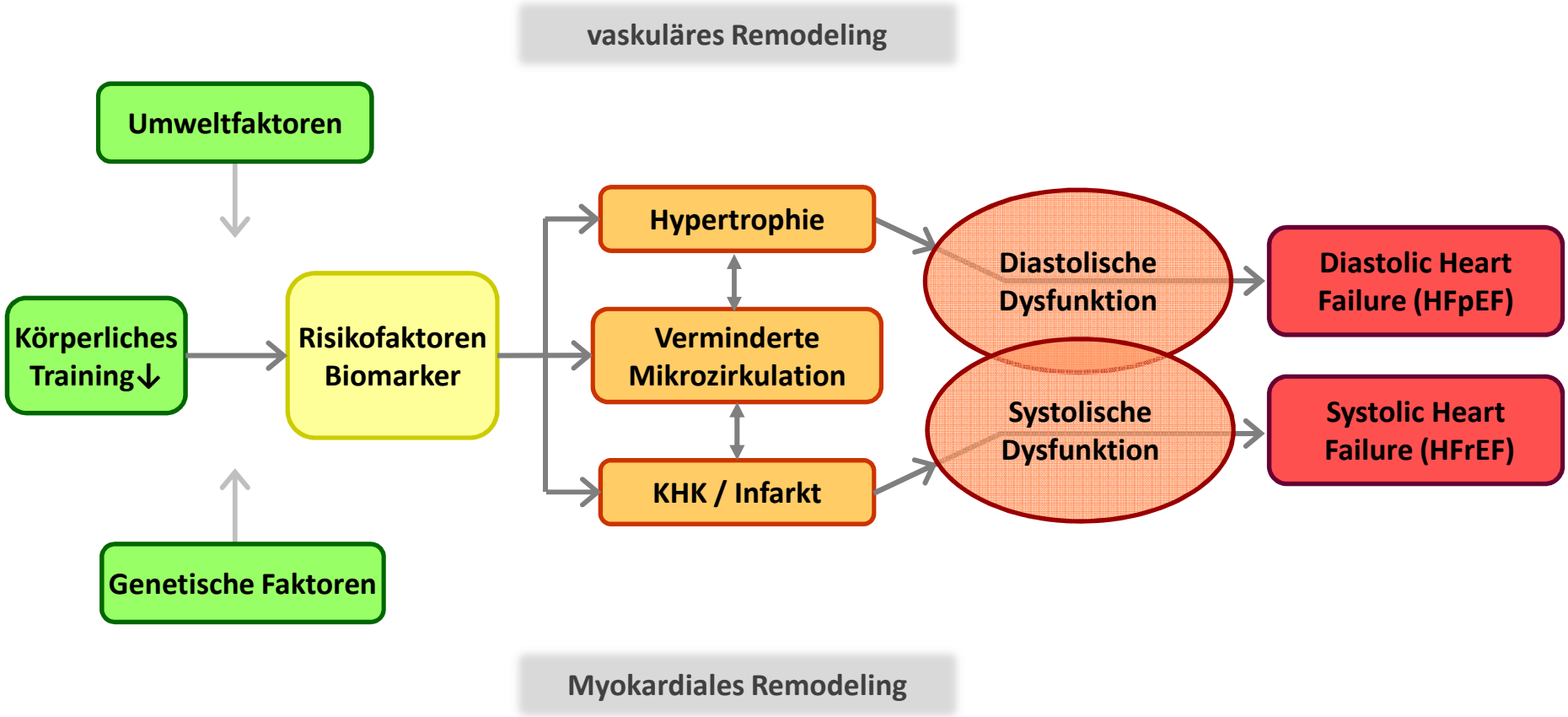
Neue Wege in der Therapie der Herzinsuffizienz

Assoz. Prof. PD Dr. Dirk von Lewinski

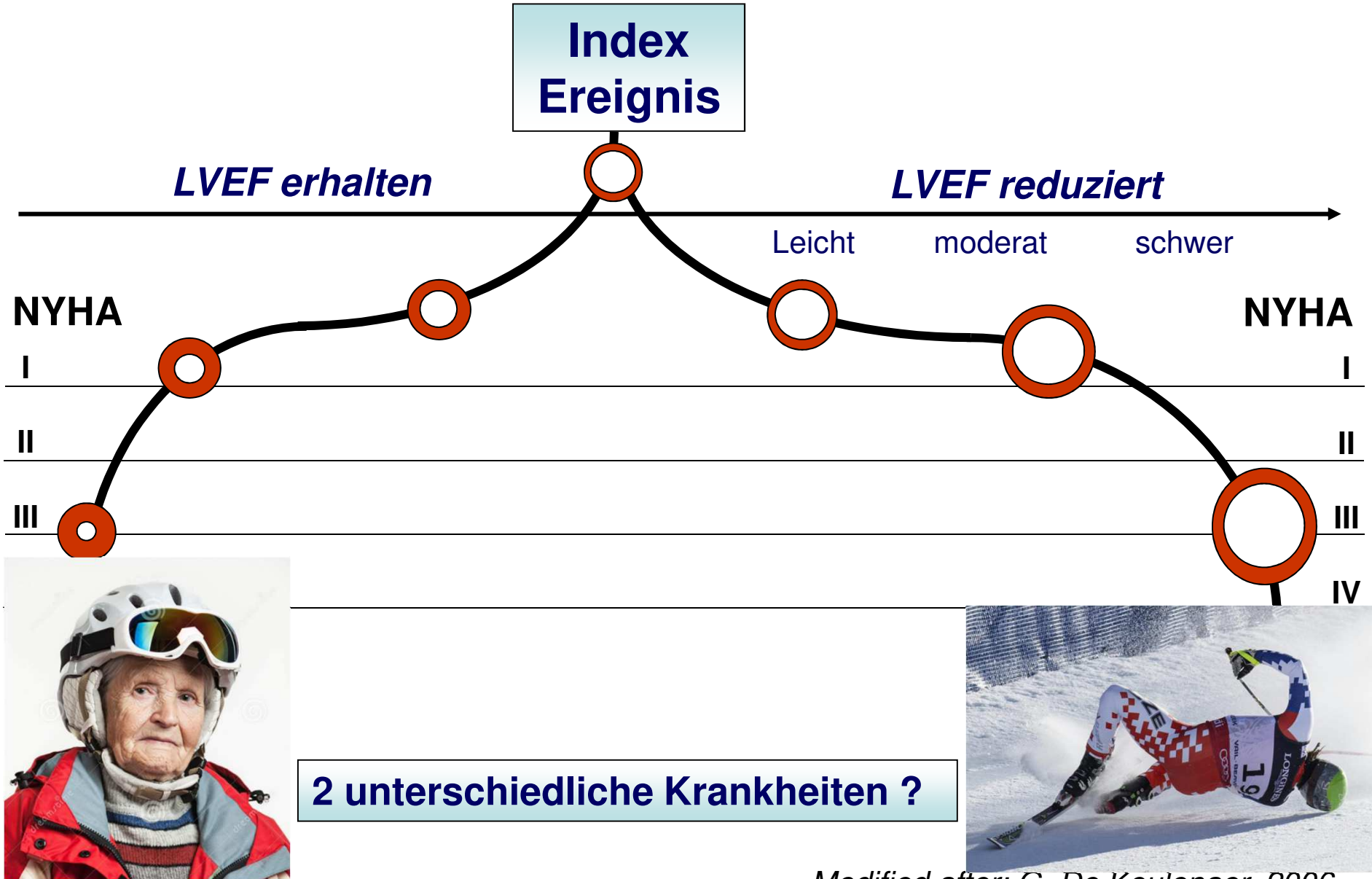
Abteilung für Kardiologie

Medizinische Universität Graz

Das Kardiovaskuläre Kontinuum

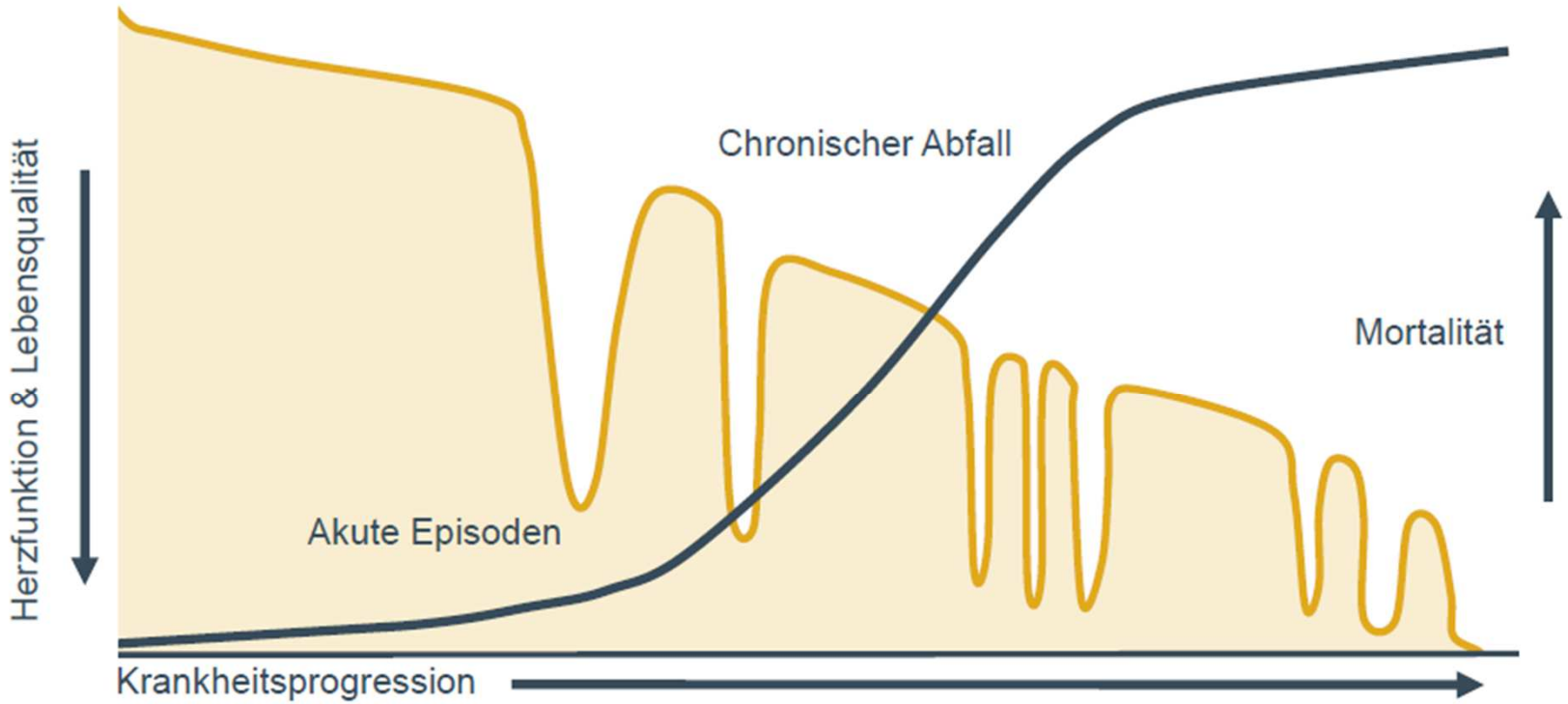


Pathophysiologie



Modified after: G. De Keulenaer, 2006

Herzinsuffizienz - Prognose

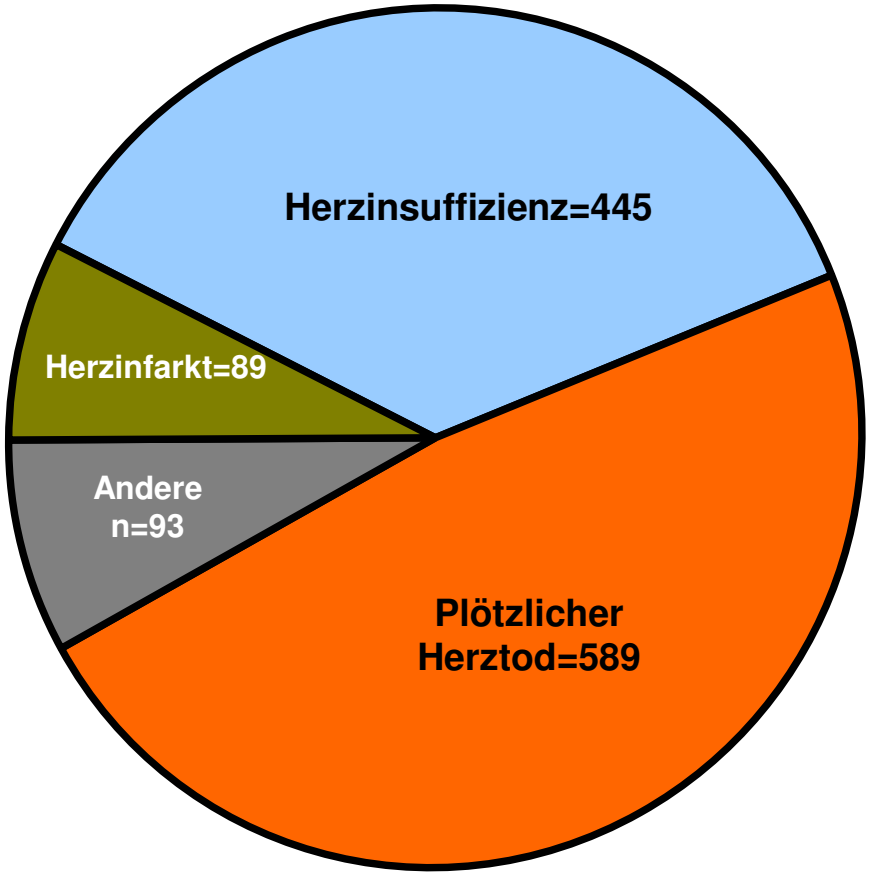


Gheorghiade et al., Am J Cardiol 2005; 96:11G–17G

Mortalität

ATLAS-Studie: 3164 Patienten, NYHA II-IV, EF 22.6 %,

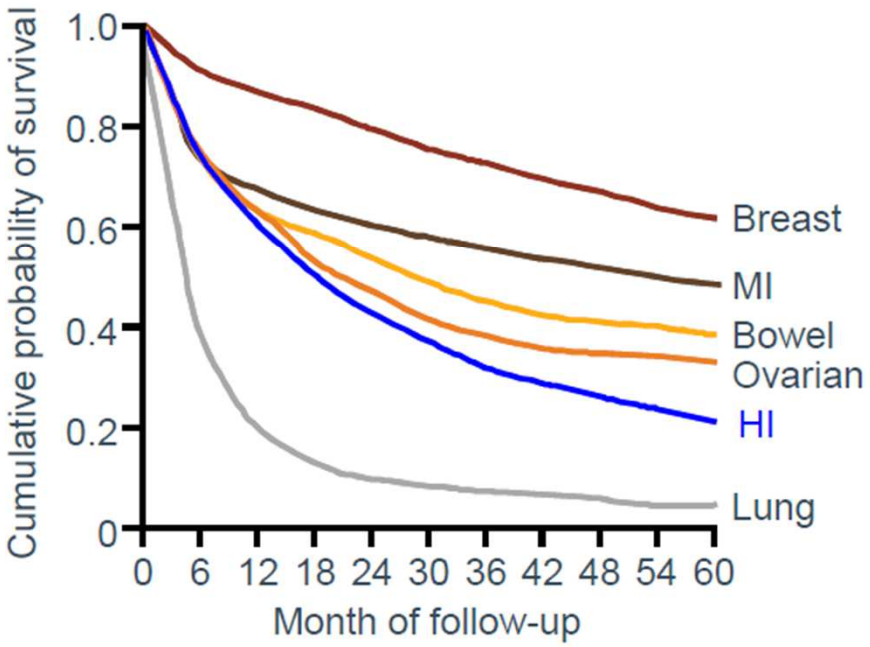
Lisinopril 2.5-5 vs. 32.5-35 mg



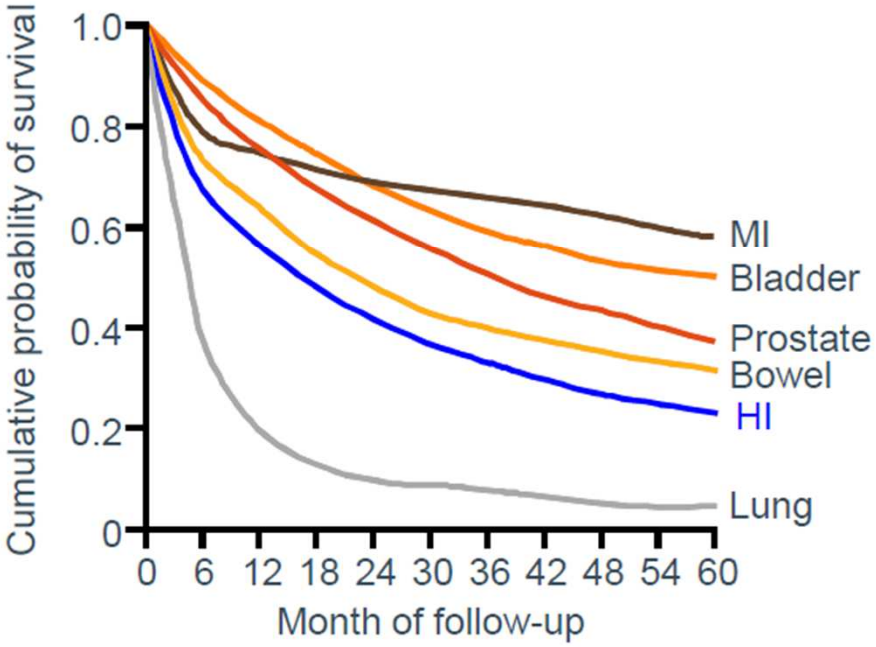
Poole-Wilson PA et al., Heart 2003; 89:42-48

Prognose

Frauen

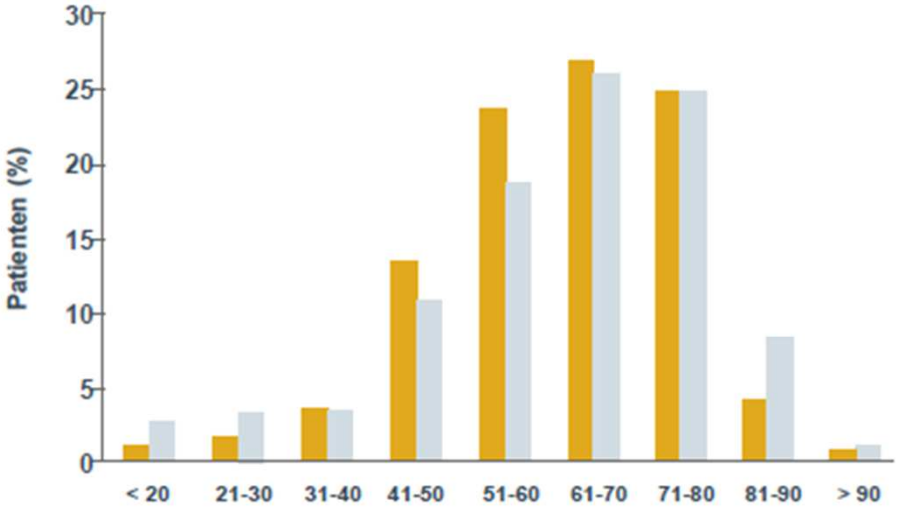


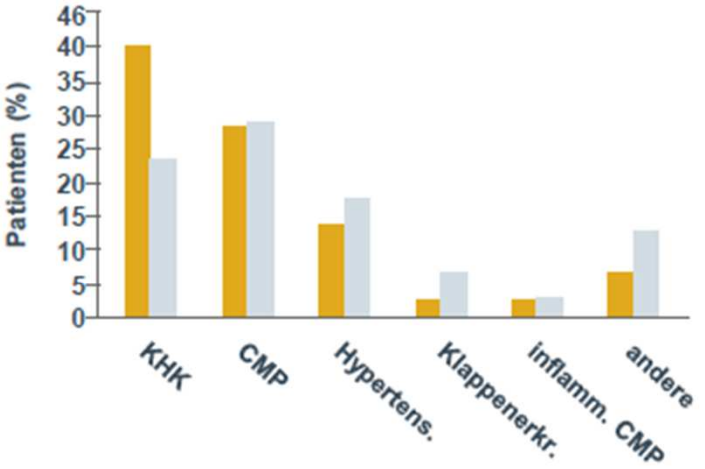
Männer

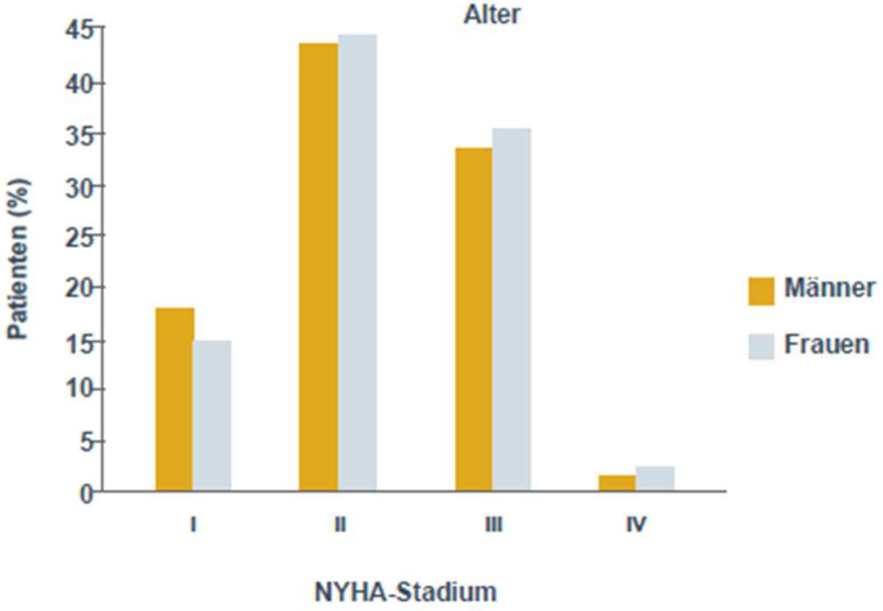


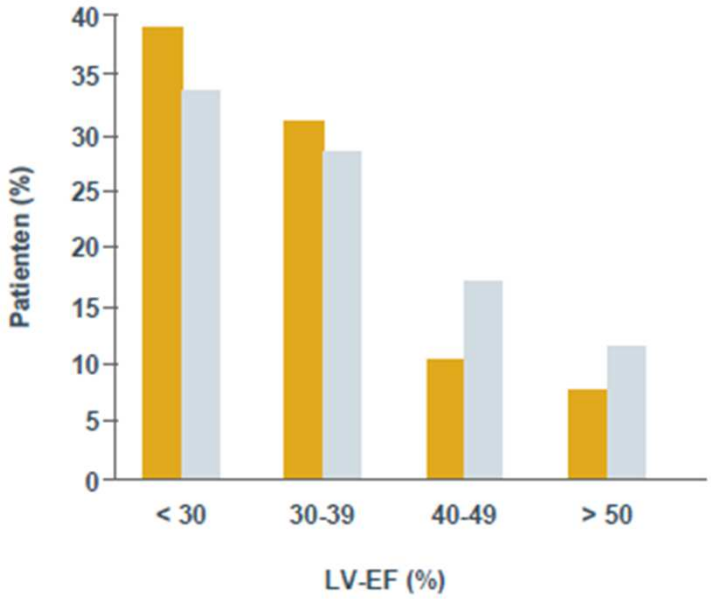
Stewart et al., Eur J Heart Fail 2001; 3:315–322

Epidemiologie – Österreich









Pölzl G et al. Herzinsuffizienz-Register- (HIR-) Austria 2006–2009: Erfahrungen und Konsequenzen. J KARDIOL 2010; 17 (3–4); 85–92

Herzinsuffizienz 1952

Hypertonie	Keine Medikation
Herzinfarkt	Keine CCU, Mortalität 30%
Rheumatische CMP "Senile" CMP Luetische Aortenklappen	Wichtige Ursachen
Idiopathische dilatative CMP Diastolische Herzinsuffizienz	Nicht bekannt

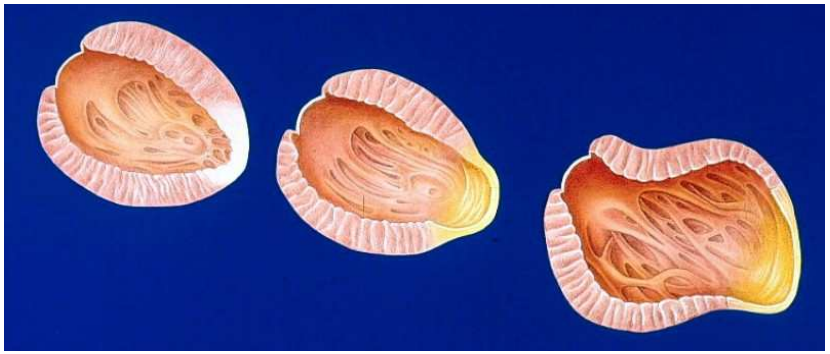
Strenge Bettruhe, Sedierung, O_2

Diät:	red. Kalorien, Na^+ 200-400 mg/Tag
Digitalis:	fast alle
Diuretika:	organische Quecksilberpräparate
Andere:	Venektomie; rotierende Lagerung

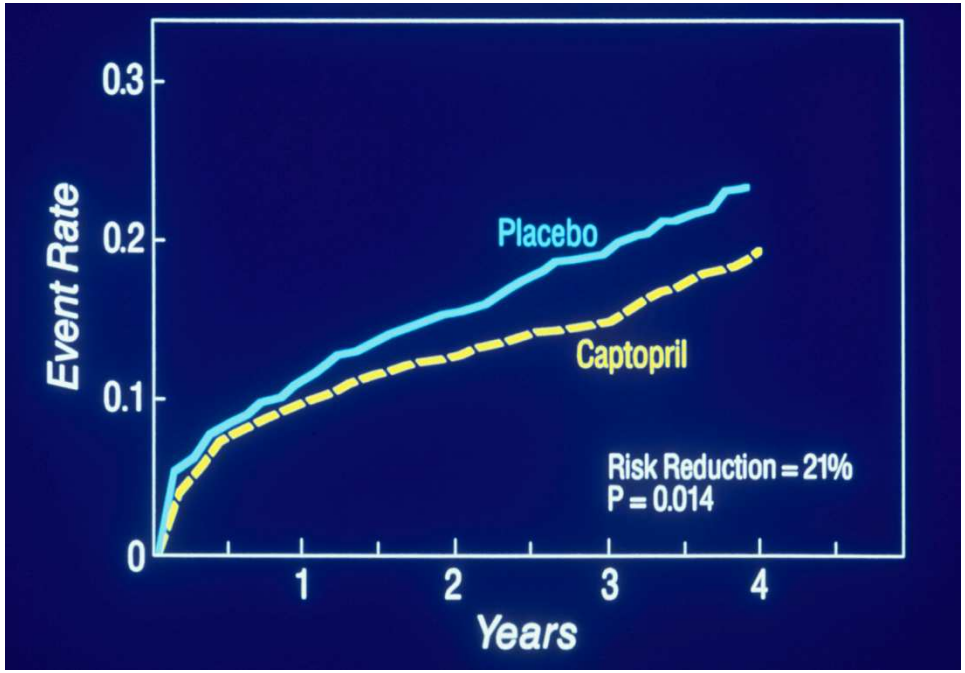
Herzinsuffizienz Therapie

„godfathers“ of heart failure
Pfeffer and Braunwald

President´s Dinner,
Jahrestagung ÖKG
25.5.2013, Salzburg



Pfeffer and Braunwald
Circulation 1990



SAVE trial, Pfeffer, Braunwald et al
NEJM 1992

Leitlinie der ESC von Mai 2016

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

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

- **85 Seiten**
- **659 Zitate**

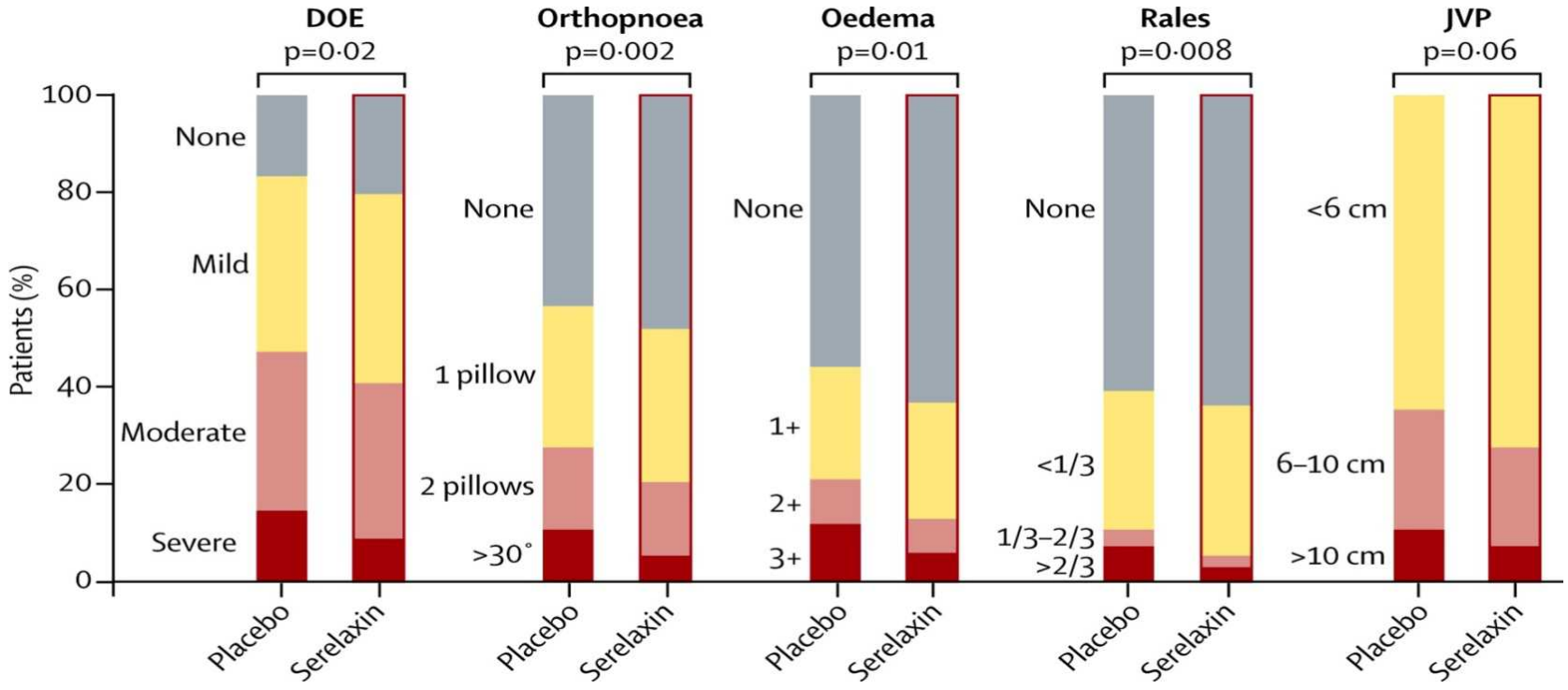
- **Akute Herzinsuffizienz**
- **Neue Unterscheidung in HFrEF, HFmrEF und HFpEF**
- **Erstmalig Bewertung ARNI**
- **Neues Flußdiagramm Therapie**

Studien mit Inotropika

Studie	Inotropikum	Ergebnis
Enoximon	Enoximon	Erhöhte Mortalität
PROMISE	Milrinon	Erhöhte Mortalität
PROFILE	Flosequinan	Erhöhte Mortalität
OPTIME-CHF	Milrinon	Erhöhte Mortalität
VEST I	Vesnarinon	Erhöhte Mortalität
VEST II	Vesarinon	Erhöhte Mortalität
PICO	Pimobendan	Erhöhte Mortalität
PRIME 2	Ibopamin	Erhöhte Mortalität
PROTECT	Rolofyllin	Neutral
ASCEND	Nesiritide	Neutral
SURVIVE	Levosimendan	Neutral
Revive	Levosimendan	Neutral
DIG	Digoxin	Neutral

Pharmakotherapie AHF

RELAX-AHF 1161 Patienten mit AHF, Therapie mit Serelaxin (rekombinates humanes Relaxin-2a)
Primärer Endpunkt war Dyspnoe

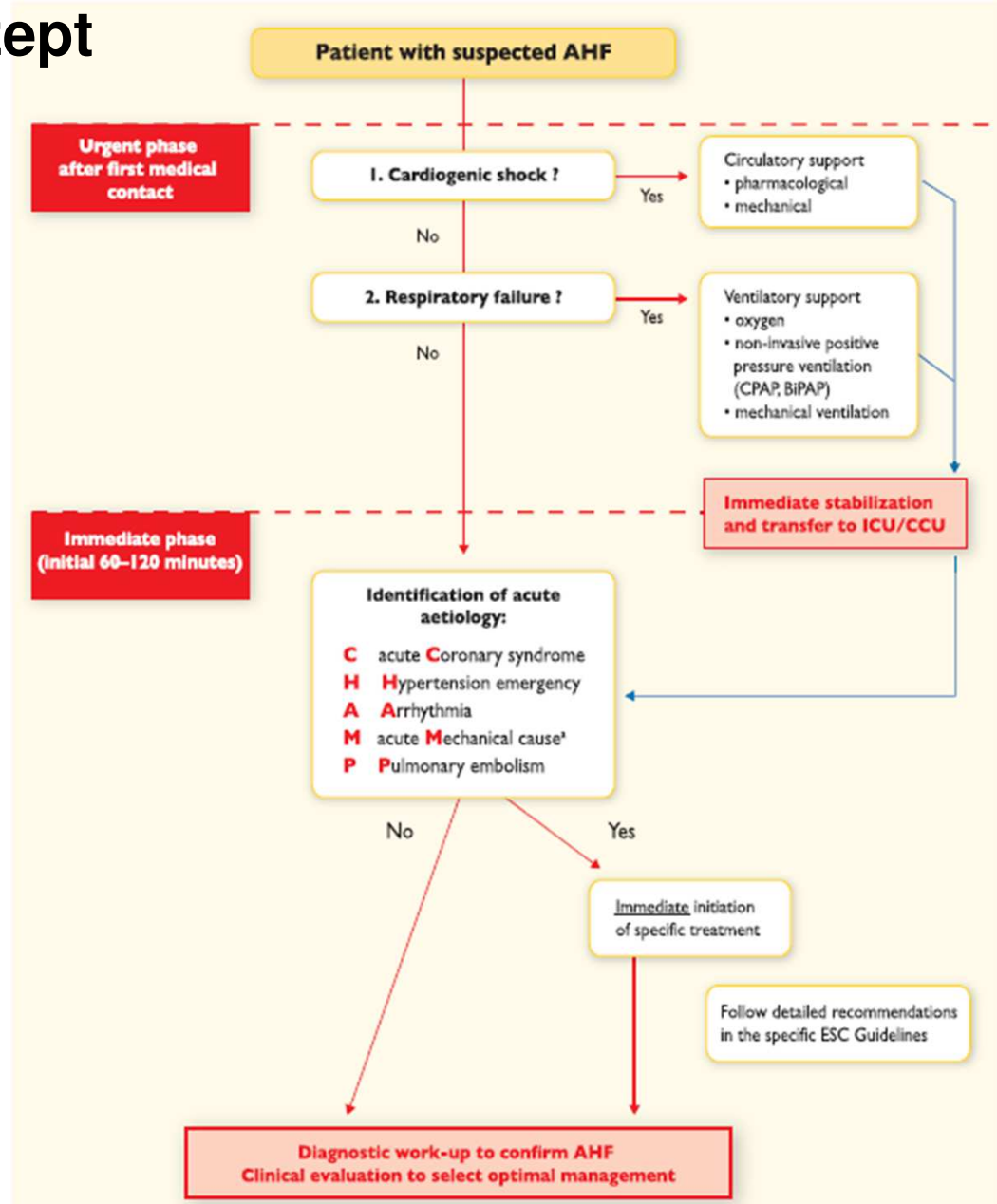


Serelaxin reduzierte die180d- Mortalität: HR 0,63, 95% CI 0,42–0.93; p=0,019)

The Lancet Volume 381, (2013) 29 - 39

Neue ESC guideline Mai 2016

„time to therapy“ Konzept analog zu ACS



ESC guideline 2016

European Heart Journal
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- **85 Seiten**
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- **Akute Herzinsuffizienz**
- **Unterteilung in HFrEF, HFmrEF und HFpEF**
- **ARNI erstmals empfohlen**
- **Neuer flow chart**

Leitlinie der ESC von Mai 2016 - HFmrEF

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).

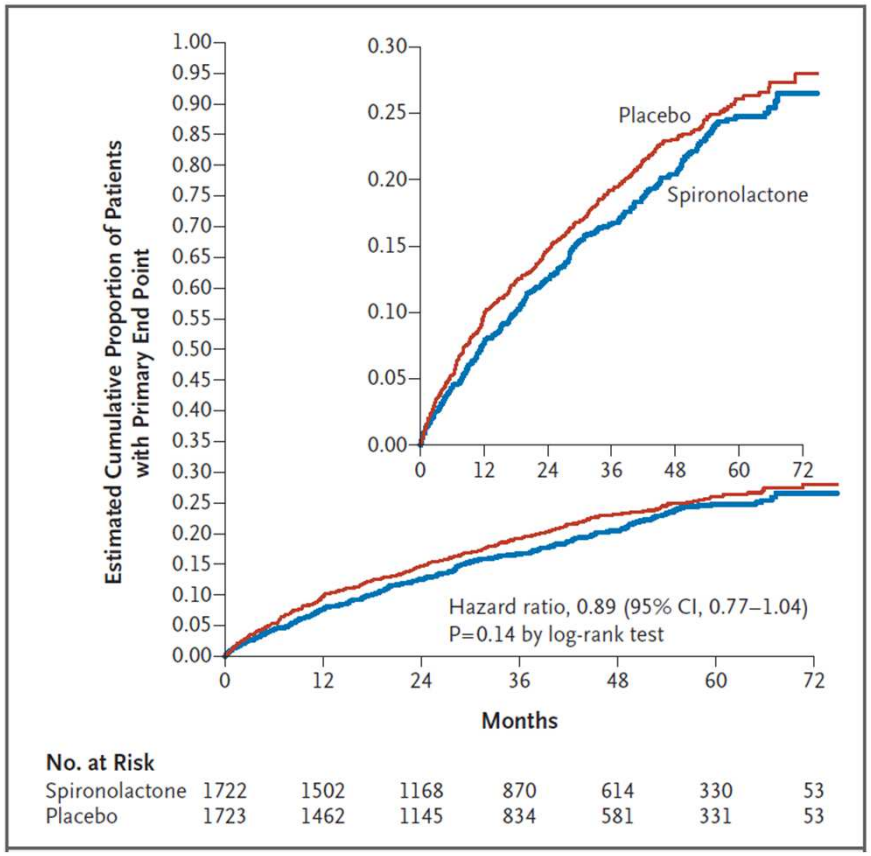
Die Klassifizierung von HFmrEF als eigenständige Gruppe soll insbesondere die Forschung in dem Bereich stimulieren nach den bislang sehr enttäuschenden Ergebnissen zu HFpEF

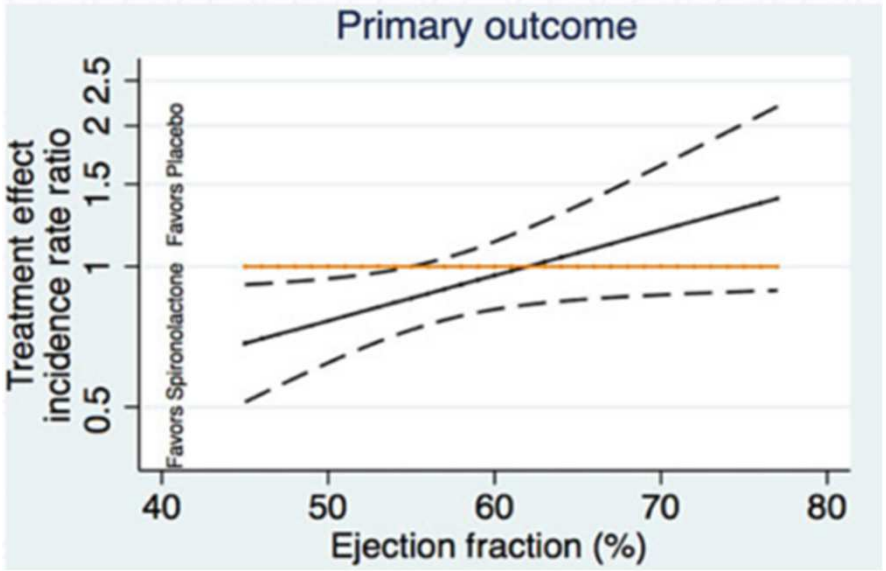
Patienten mit **HFmrEF** haben in aller Regel nur geringe systolische Dysfunktion aber zusätzlich:

- diastolische Dysfunktion
- relevante strukturelle Herzerkrankung (LVH, LA-Dilatation)
- erhöhtes (ntpro-)BNP

HEFpEF Aldosteronantagonisten

TOPCAT 3454 Patienten, EF > 45%
Spironolakton 15-45mg vs. Placebo
Primärer Endpunkt: KV-Tod und CMP-Hospitalisierung





„HFmrEF greater treatment effect than HFpEF“

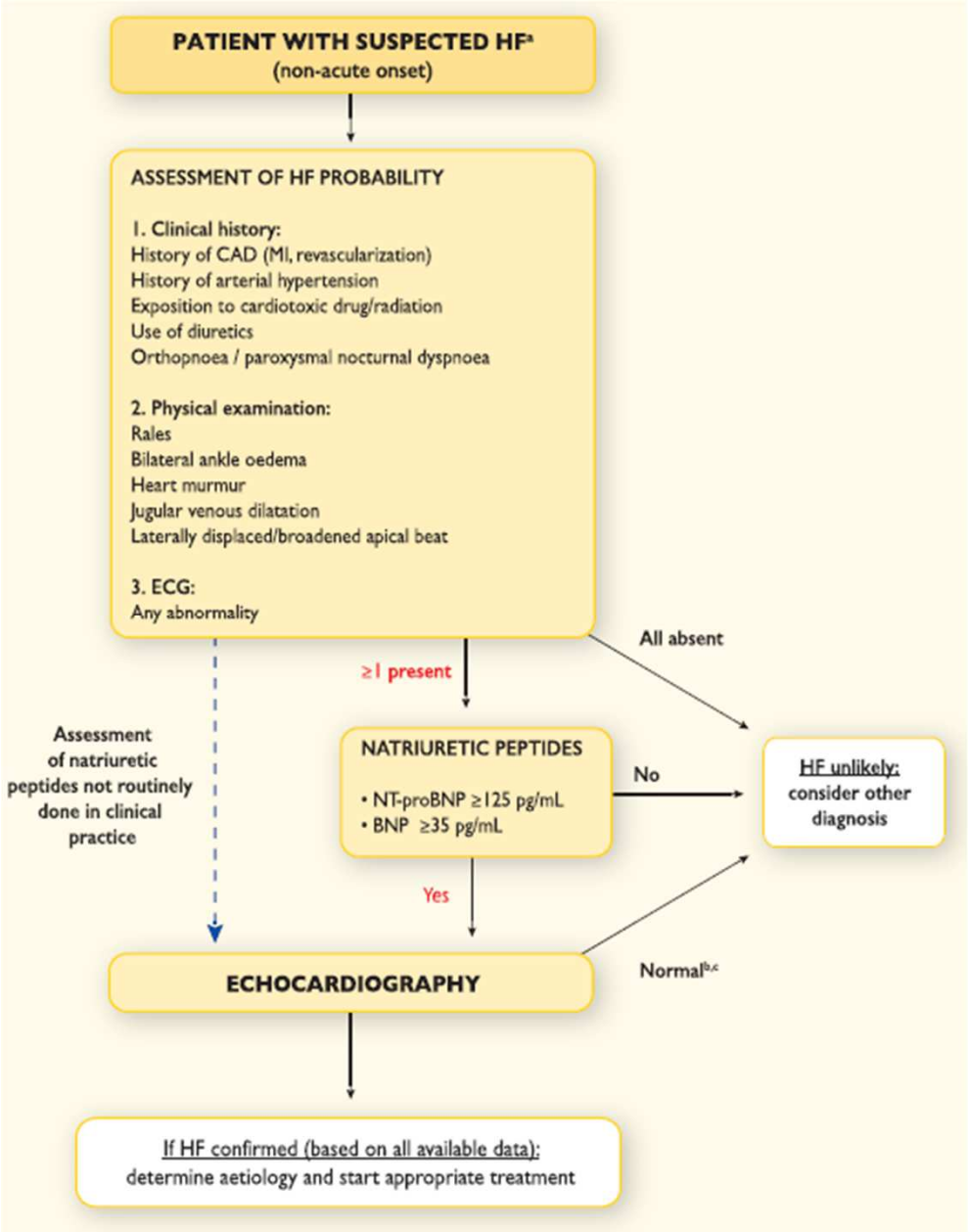
Pitt B et al., NEJM 2014; 370:1383-92

Leitlinie der ESC von Mai 2016 - Diagnose

- **Identifizierung** der zugrunde liegenden Erkrankung
- zumeist myokardial
- aber auch Klappen-, Perikard- und Endokarderkrankungen sowie Rhythmusstörungen in Betracht ziehen
- Die Identifizierung ist entscheidend für die Therapieplanung

Symptoms	Signs
Typical	**More specific**
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

Leitlinie der ESC von Mai 2016

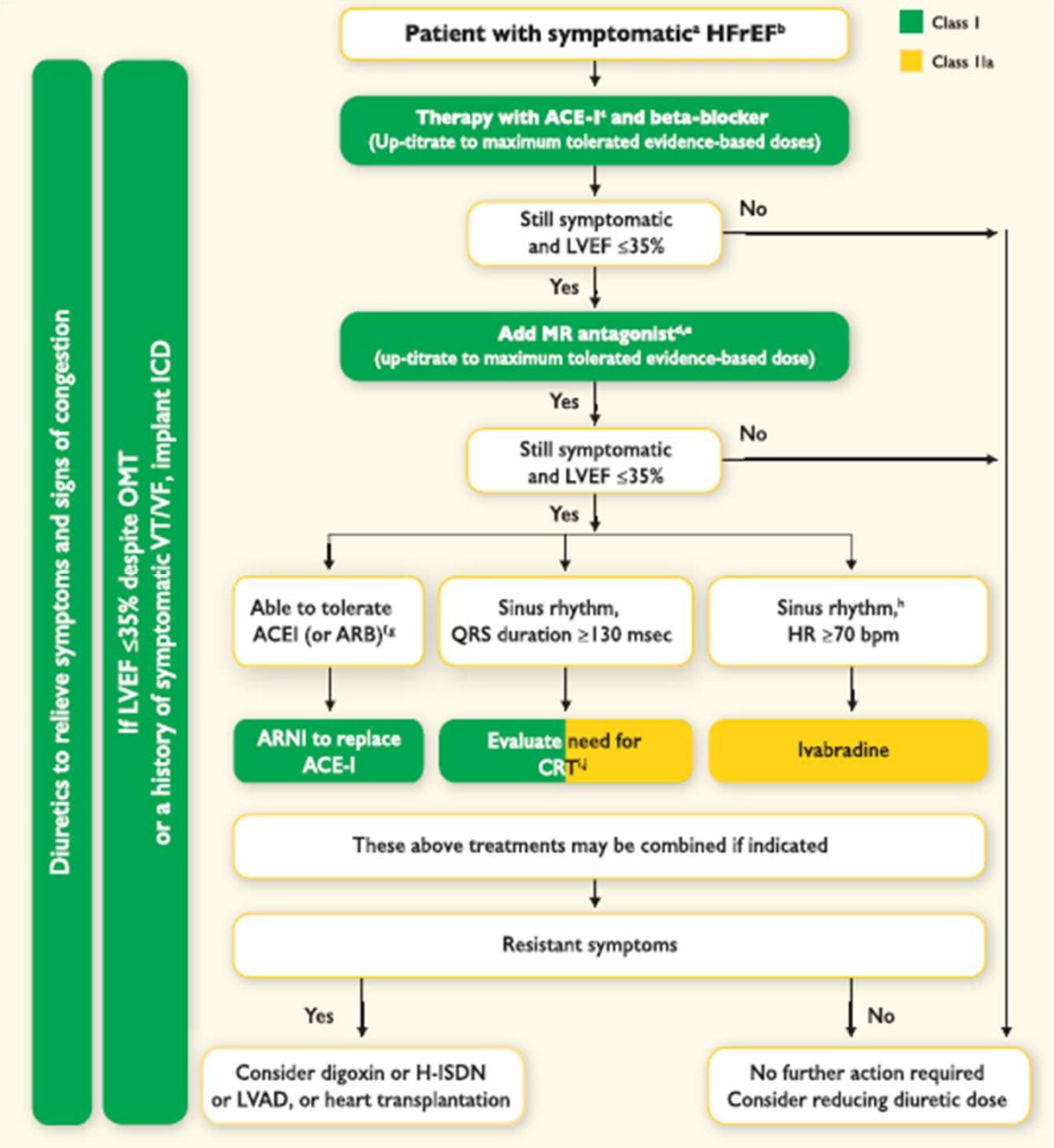


- EKG zum rule out
  aber sehr unspezifisch
- Rö-Thorax unspezifisch
- Blutabnahme mit BB, Na, K, GFR, Bili, AST, ALT, gGT, glukose (HbA1c), TSH, Ferritin
- USKG als wichtigste Untersuchung
  auch Lungenschall wegen Stauung und V. cava wegen Volumenstatus (IIb/C)

Leitlinie der ESC von Mai 2016

- EF soll nach Simpson gemessen werden, bei schlechter Bildqualität mit Kontrastmittel
- Keine Bestimmung mehr im M-mode (z.B. Teichholz)
- HFpEF Kriterien:
  - LAVI >34 mL/m^2, LVMI ≥115 g/m^2 (M) / ≥95g/m^2 (F)
  - E/e' ≥13, Ø e' septal & lateral <9cm/s
  - (Strain oder TRINS velocity)
- Optimal: Stressecho am Liegeergometer
- Erschwerte Diagnostik bei Vorhofflimmern beachten

Leitlinie der ESC von Mai 2016



Maximale Auftitrierung

QRS 130ms (statt 120ms) für CRT

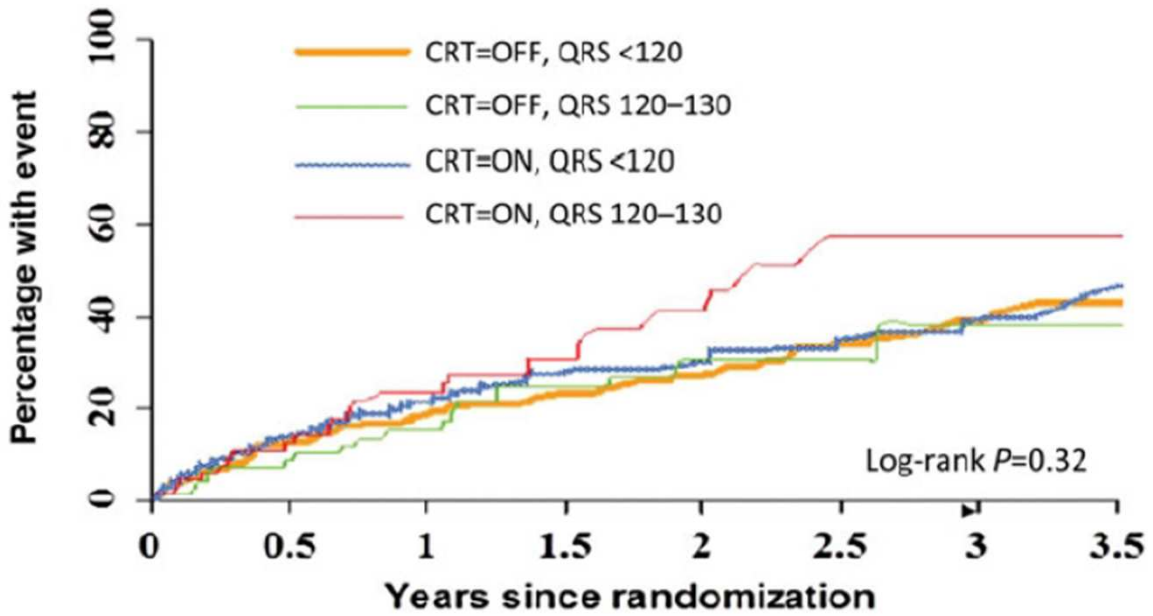
ARNI

Diuretikareduktion erwägen

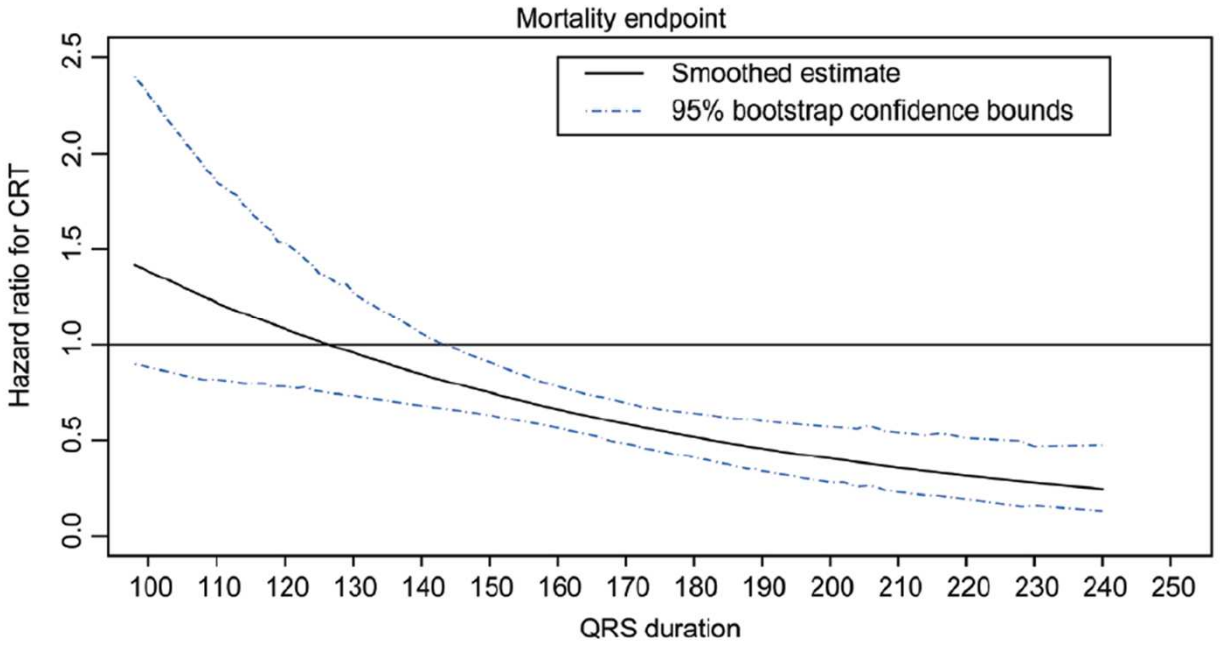
„However, it is now recognized that preventing HF hospitalisation and improving functional capacity are important benefits to be considered if a mortality excess is ruled out.“

Leitlinie der ESC von Mai 2016

Euro-CRT
800 Patienten,
CRT an/aus
Zunahme der
Ereignisse bei
QRS 120-130ms
und CRT **an**

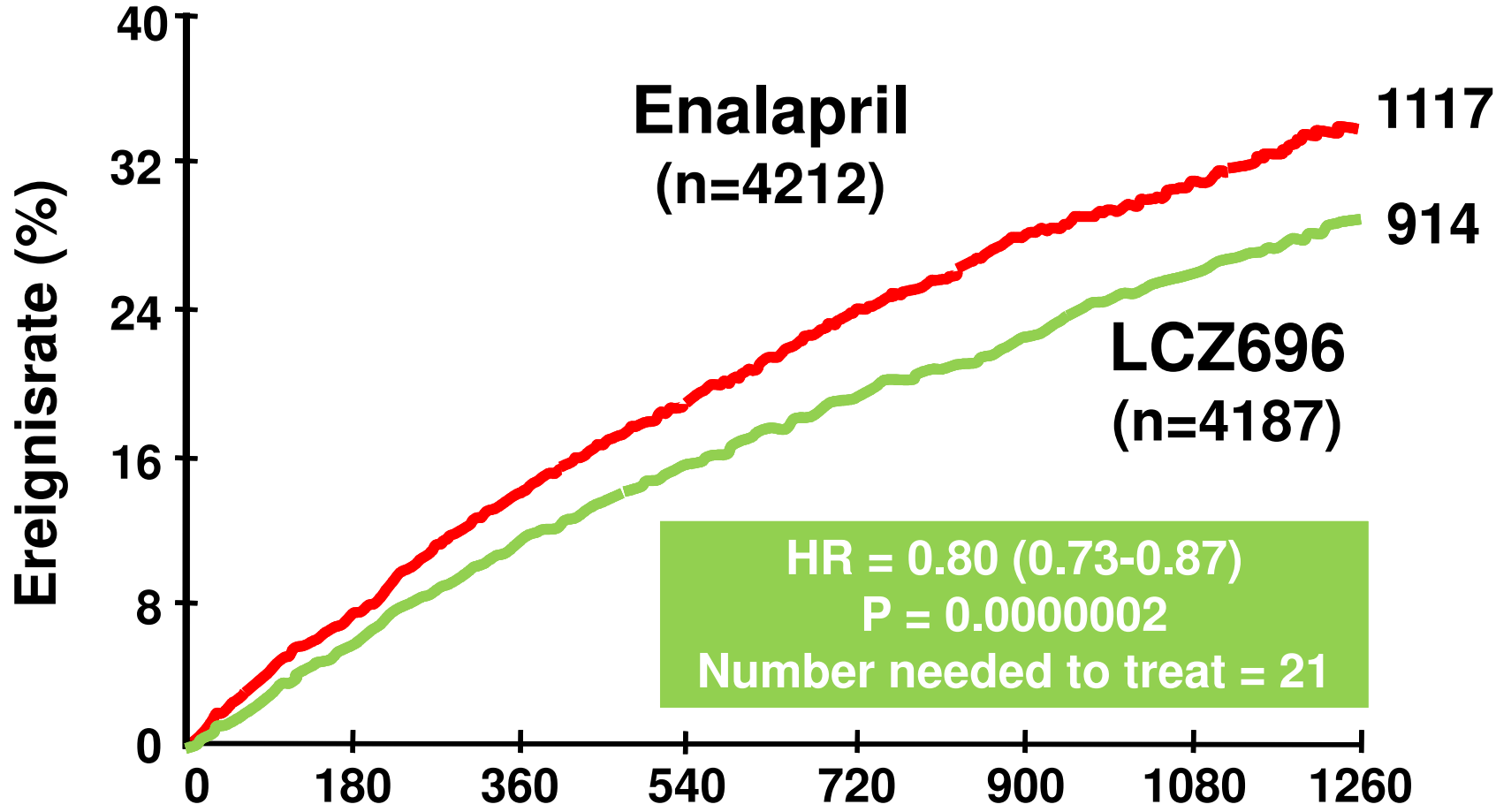


QRS „Sweet spot“
Analyse EHJ
Cleland et al 2013



ARNI (Entresto) –AT II und Neprilysin-Inhibitor

PARADIGM; Primärer Endpunkt (CV-Tod oder HF-Hospitalisierung)



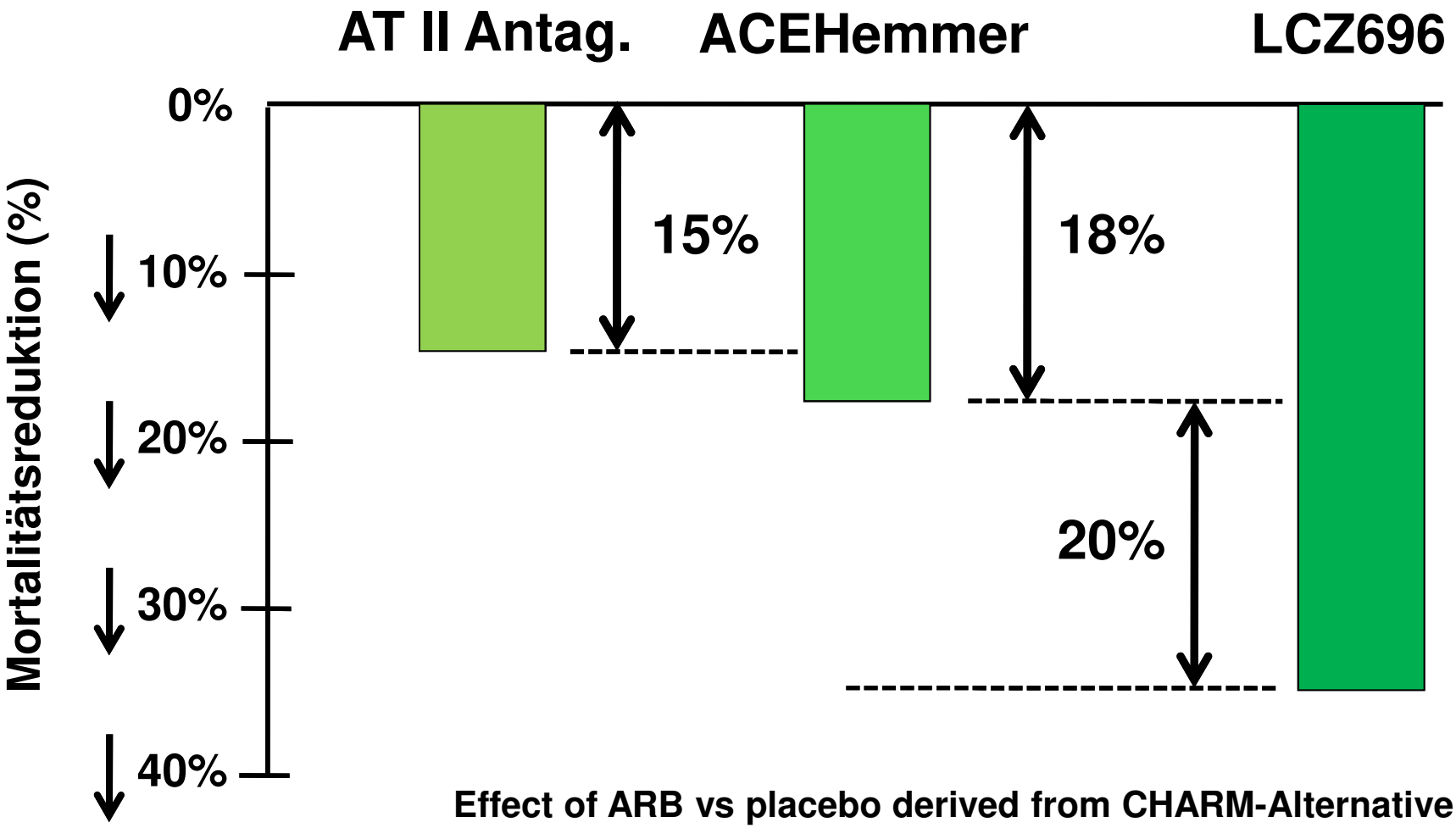
Patients at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

ARNI (Entresto) - Nebenwirkungen

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospektiv festgelegte Nebenwirkungen			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Studienabbruch wg. Nebenwirkung	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioödem			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

ARNI (Entresto)

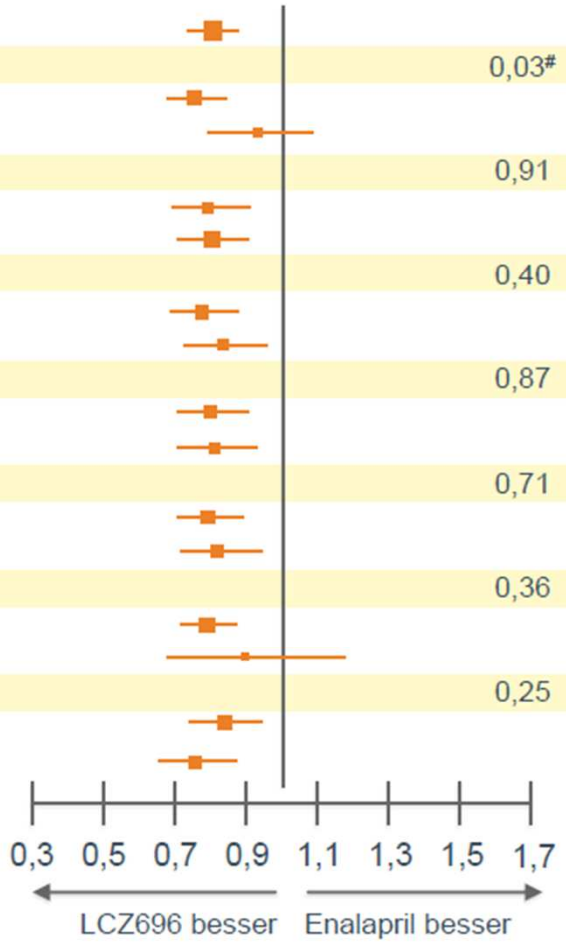
Vergleich zu ACE-Hemmer und AT-II Antag.



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

ENTRESTO (LCZ696)

Subgruppe, n Patienten	**LCZ696**	**Enalapril**	**P-Wert für Wechselwirkung**
Alle Patienten	4187	4212	
NYHA-Klasse			0,03#
I oder II	3178	3130	
III oder IV	1002	1076	
Geschätzte GFR			0,91
<60 ml/min/1,73 m²	1541	1520	
≥ 60 ml/min/1,73 m²	2646	2692	
Diabetes			0,40
Nein	2736	2756	
Ja	1451	1456	
Systolischer Blutdruck			0,87
≤ Median	2298	2299	
> Median	1889	1913	
Auswurffraktion			0,71
≤ Median	2239	2275	
> Median	1948	1936	
Auswurffraktion			0,36
≤ 35 %	3715	3722	
> 35 %	472	489	
Vorhofflimmern			0,25
Nein	2670	2638	
Ja	1517	1574	



#Eine nominal sign. Interaktion von NYHA-Klasse bei Randomisierung und Behandlungseffekt auf den primären Endpunkt (P=0,03, nicht adjustiert für Mehrfachvergleiche) wurde für die Interaktion von NYHA-Klasse und Behandlungseffekt auf die CV-bedingte Mortalität nicht beobachtet (P=0,76)

*Die Größe der Quadrate entspricht der Anzahl der Patienten in jeder Subgruppe.

McMurray et al., N Engl J Med 2014; 371(11):993–1004

ARNI (Entresto) - Amyloid

43 Probanden; 14 Tage

Entresto 400mg/d vs. Placebo

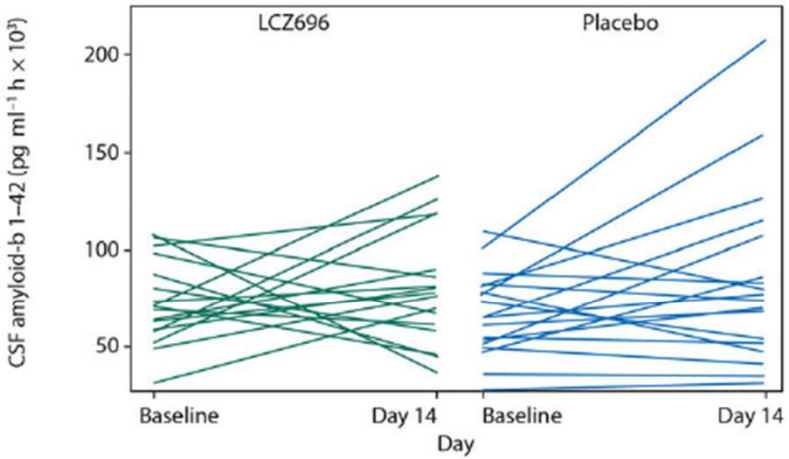
British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 878–890 878

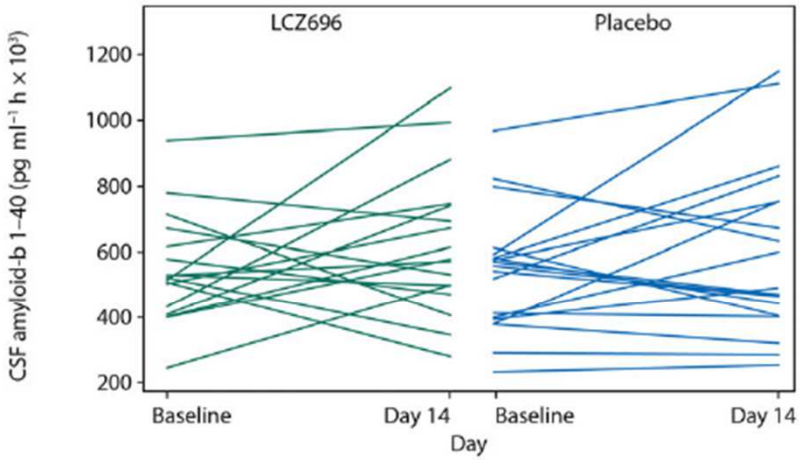
PHARMACODYNAMICS

The effect of LCZ696 (sacubitril/valsartan) on amyloid-β concentrations in cerebrospinal fluid in healthy subjects

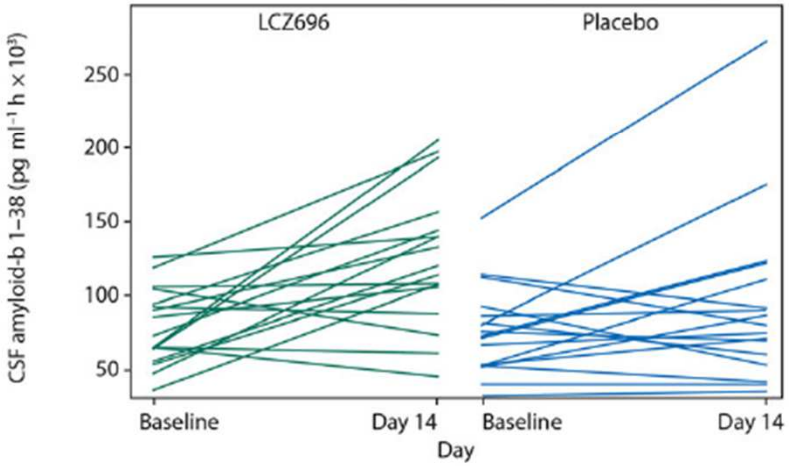
A Amyloid-β 1–42, CSF



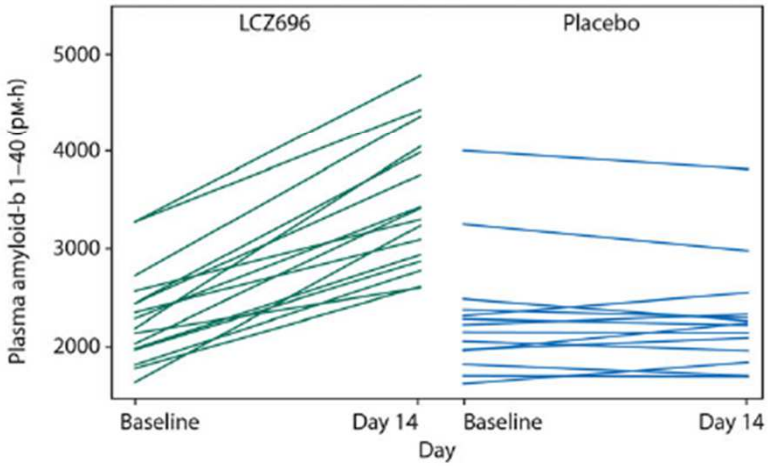
B Amyloid-β 1–40, CSF



C Amyloid-β 1–38, CSF



D Amyloid-β 1–40, plasma



Herzinsuffizienz und Diabetes – Therapie

PARADIGM, 8399 Patienten
LCZ699 vs. Enalapril

Inhibition von Angiotensin + Neprilysin versus Enalapril bei Herzinsuffizienz

(Paradigm)

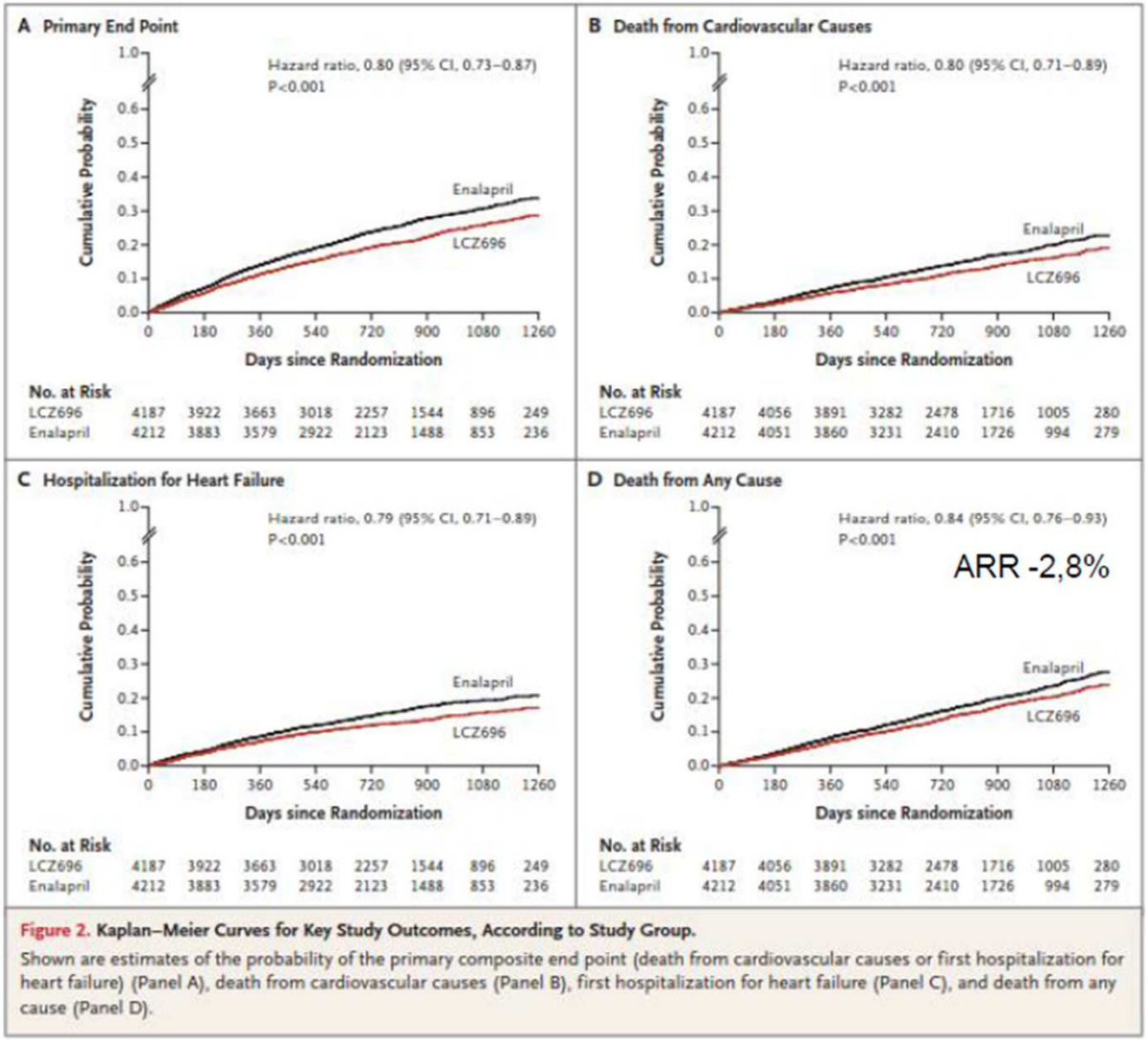
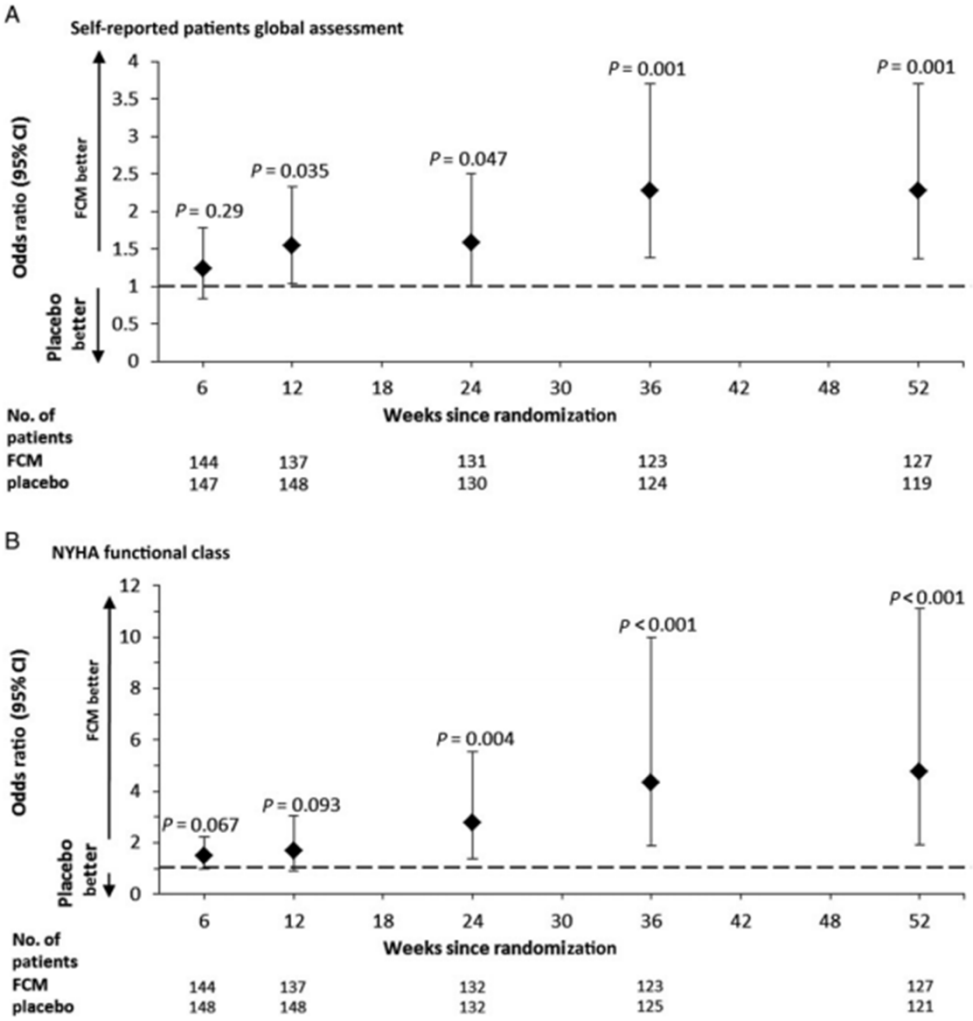


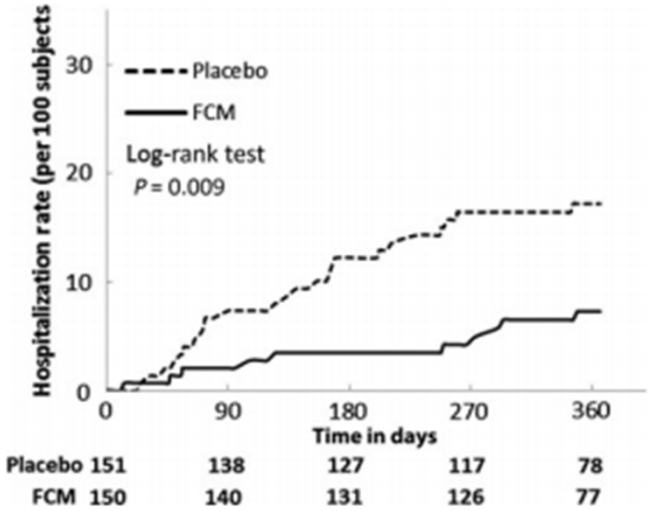
Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

Ca. 30% Diabetes
Kein unterschied
in der Effizienz

Eisensubstitution mit Eisencarboxymaltose

CONFIRM HF Studie (2014); 304 Patienten; EF < 45%; Ferritin < 100µg/l (300µg/l); Follow up 52 Wochen





Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A

Ponikowski et al., Eur Heart J, 31Aug2014

Herzinsuffizienz – welche Medikamente nicht

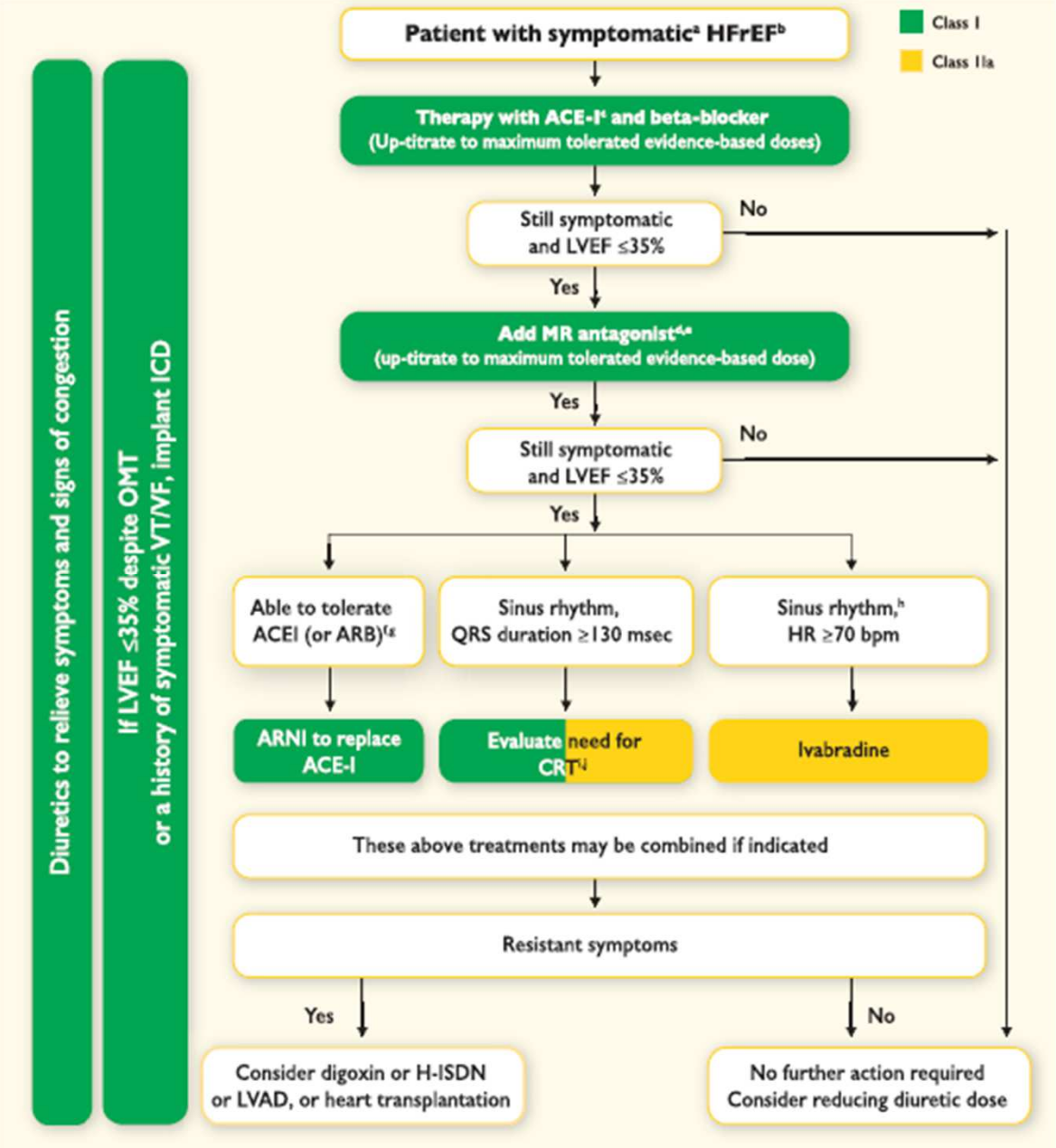
Ohne gesicherten Nutzen sind:

- Statine (Rosuvastatin)
  - CORONA (subgroup): 5011 Patienten mit EF<40% und iCMP kein Nutzen
  - GISSI-HF: 4574 Patienten, EF<40% oder Hospitalisierung im letzten Jahr - kein Nutzen
- Renininhibitoren (Aliskiren) – ASTRONAUT – kein Nutzen
- OAK – kein Nutzen ggü. Placebo oder ASS (NOAK Studien laufen)
- Omega-3-Fettsäuren, nur wenn EPA- und DHA-Gehalt > 85%

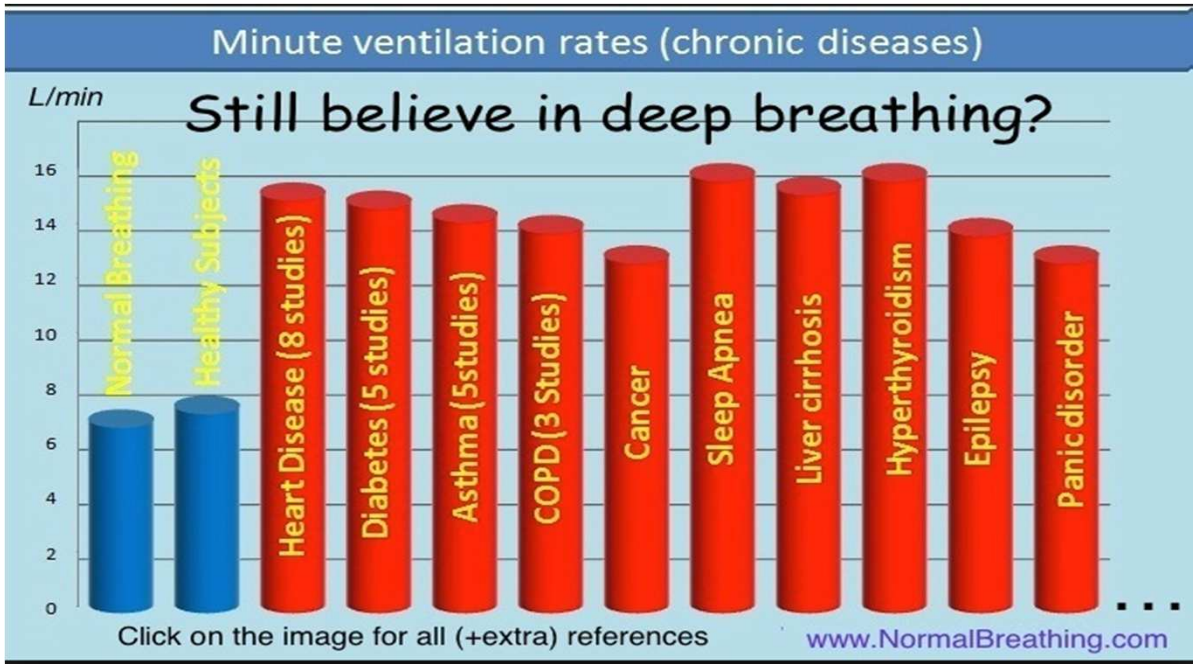
Vermutlich schädlich:

- Glitazone (Substanzunabhängig?) – CMP Verschlechterung?
- CCB (außer Amlodipin und Felodipin) - CMP Verschlechterung?
- NSAR und COX2-Inhib. – Volumenretention - CMP Verschlechterung?
- ARB oder Aliskiren bei ACE-Hemmer plus Aldosteronhemmer
- Monoxidin (erhöhte Mortalität bei HFrEF)
- α-Blocker (Verschlechterung HFrEF)
- adaptive Servoventilation

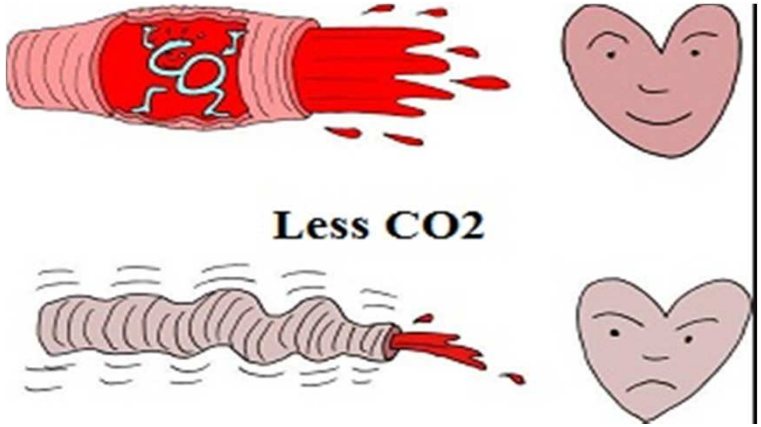
ESC guideline 2016

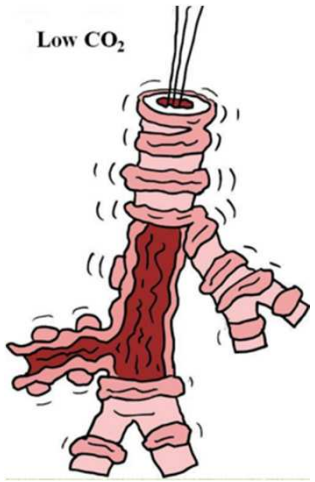


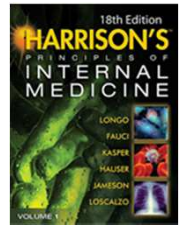
Why do heart failure patients have Dyspnea?



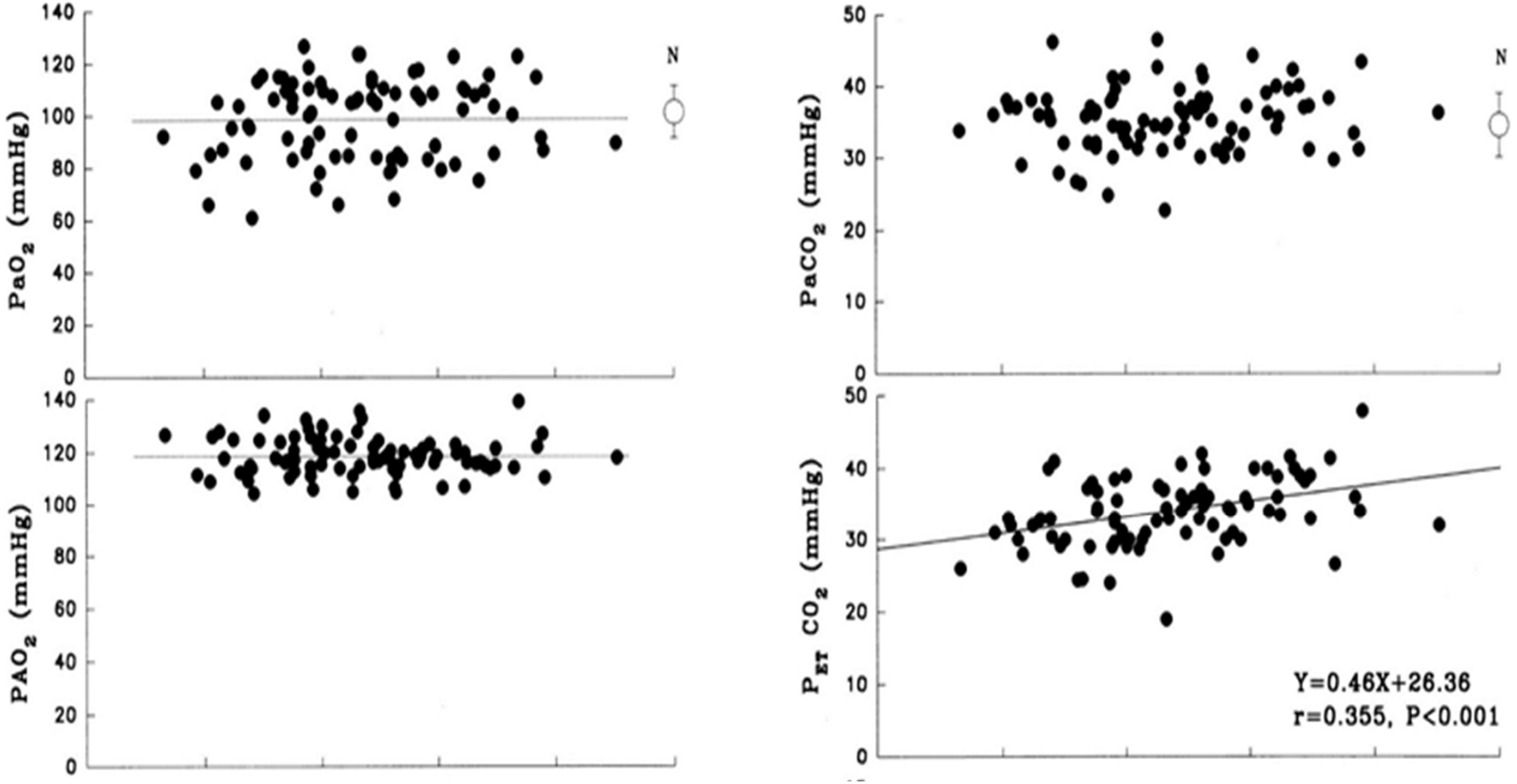
Respiratory failure is usually classified to be hypoxemic or hypercarbic







Why do heart failure patients have Dyspnea?



Why do heart failure patients have Dyspnea?

Heart failure is a physiological state in which cardiac output is insufficient to meet the needs of the body and lungs.

Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

Jean-Claude Tardif[1]*, Eileen O'Meara[1], Michel Komajda[2], Michael Böhm[3], Jeffrey S. Borer[4], Ian Ford[5], Luigi Tavazzi[6], and Karl Swedberg[7], on behalf of the SHIFT Investigators

diogram was 16.1 months (IQR, 13–19.9). Mean dosage of ivabradine during the substudy was 6.0 ± 1.6 mg bid. Heart rate was reduced by 14.7 ± 11.4 bpm in the ivabradine group to 63.5 ± 9.5 bpm at 8 months vs. by 5.8 ± 10.8 bpm to 72.2 ± 12.4 bpm with placebo.

Table 3 Echocardiographic parameters at baseline, 8 months, and their changes in the substudy

Variable	Ivabradine				Placebo				Treatment effect	
	n	Baseline	8 months	Change	*n*	Baseline	8 months	Change	E (SE), 95% CI	*P*-value
Primary endpoint										
LVESVI (mL/m^2)	208	65.2 ± 29.1	58.2 ± 28.3	−7.0 ± 16.3	203	63.6 ± 30.1	62.8 ± 28.7	−0.9 ± 17.1	−5.8 (1.6), −8.8 to −2.7	<0.001
Secondary endpoints										
LVESV (mL)	208	123.8 ± 55.6	110.8 ± 54.6	−13.0 ± 31.6	203	122.2 ± 59.8	120.9 ± 56.4	−1.3 ± 32.8	−11.2 (3.0), −17.1 to −5.4	<0.001
LVEDVI (mL/m^2)	204	93.9 ± 32.8	85.9 ± 30.9	−7.9 ± 18.9	199	90.8 ± 33.1	89.0 ± 31.6	−1.8 ± 19.0	−5.5 (1.8), −8.9 to −2.0	0.002
LVEDV (mL)	204	178.4 ± 63.4	163.7 ± 60.6	−14.7 ± 36.4	199	174.7 ± 67.6	171.7 ± 63.8	−2.9 ± 36.8	−10.9 (3.4), −17.6 to −4.2	0.001
LVEF (%)	204	32.3 ± 9.1	34.7 ± 10.2	2.4 ± 7.7	199	31.6 ± 9.3	31.5 ± 10.0	−0.1 ± 8.0	2.7 (0.8), 1.3 to 4.2	<0.001

78.4 x (0.323x178.4) = 4.52

78.8 x (0.316x174.7) = 4.35

78.4-14.7 x (0.347x163.7) = 3.62

78.8-5.8 x (0.315x171.7) = 3.95

Dyspnea and J-receptors

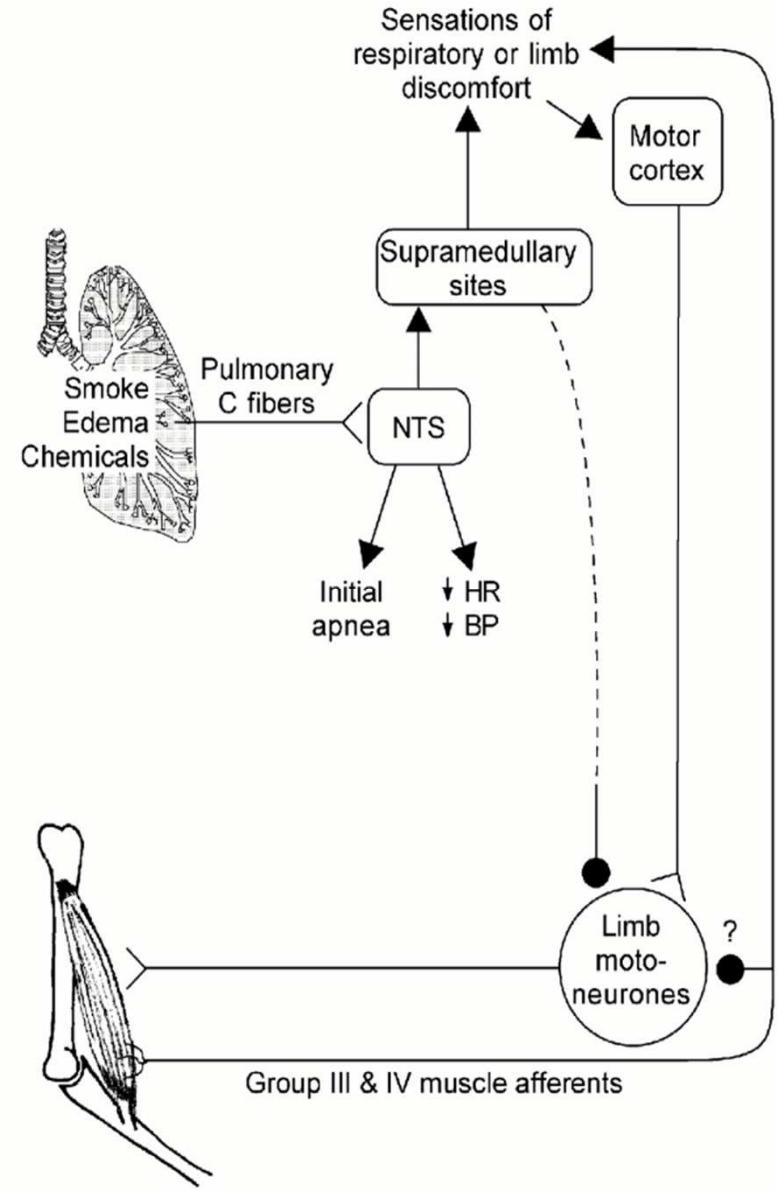
J-receptors are known since 1985

(J = juxtacapillary)

They respond to increased blood flow and pressure (PCWP), local edema and chemicals

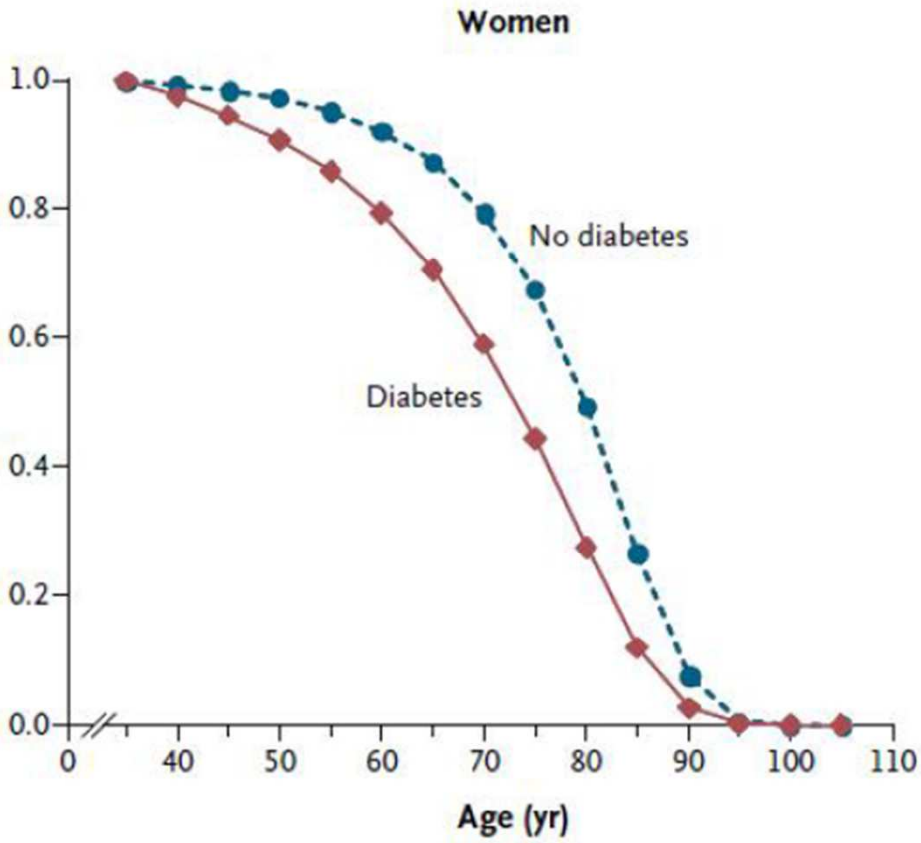
J-receptors can be pharmacologically activated by lobeline

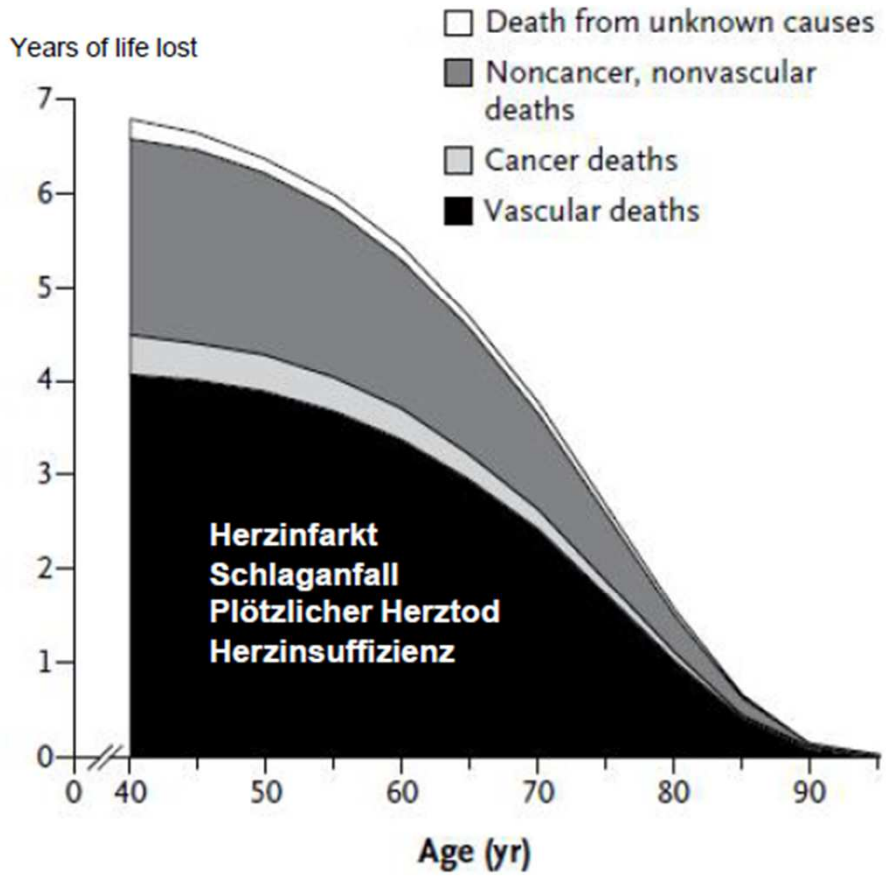
Rapidly adapting receptors (RAR) cause increase in respiratory rate



Herzinsuffizienz und Diabetes - Prognose

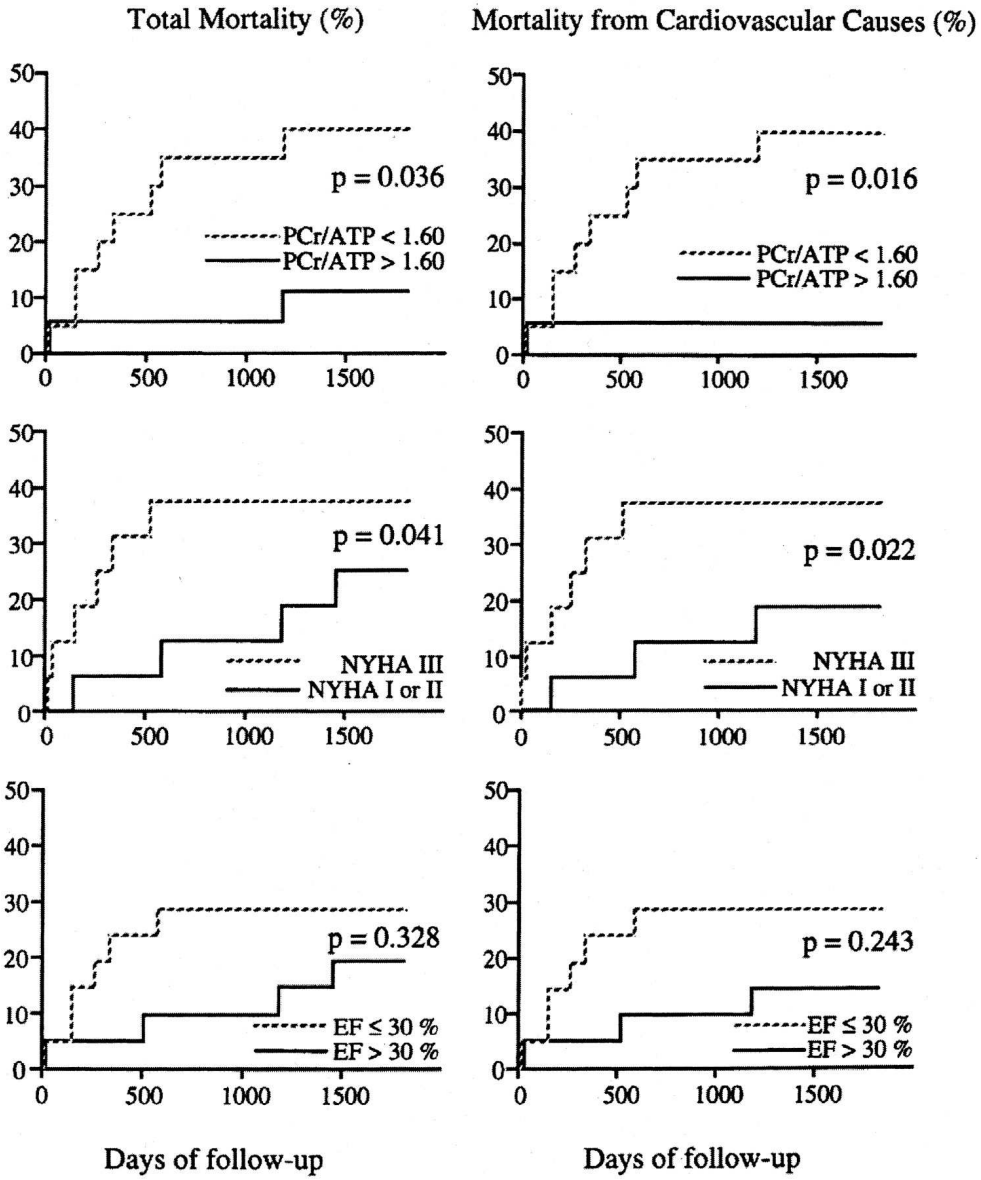
820900 Patienten, insg. 12,3 Mio. Patientenjahre und 123205 Todesfälle





The Emerging risk factor Collaboration. N Engl J Med 2011;364:829-41.

Herzinsuffizienz und Metabolismus



Joanne S. Ingwall, and Robert G. Weiss Circulation Research. 2004;95:135-145

gesund

Fettsäure —PPARα↑→ PCr

Glukose → ATP

gestresst

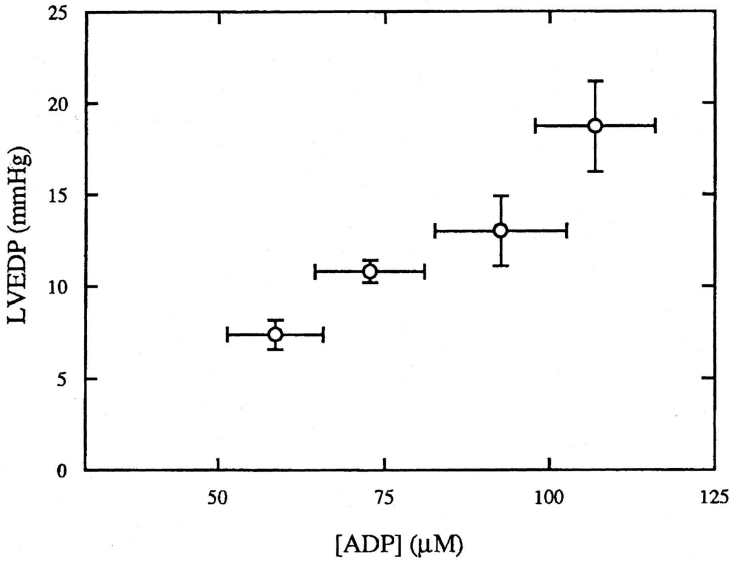
Fettsäure —PPARα↓→ PCr

Glukose → ATP

insuffizient

Fettsäure —PPARα↓→ PCr

Glukose → ATP



Herzinsuffizienz und Diabetes - Inzidenz

17076 Patienten, gematchte Gruppen, Follow up von 72 Monaten

Herzinsuffizienz pro 1000 Personen Jahre nach Altersgruppe

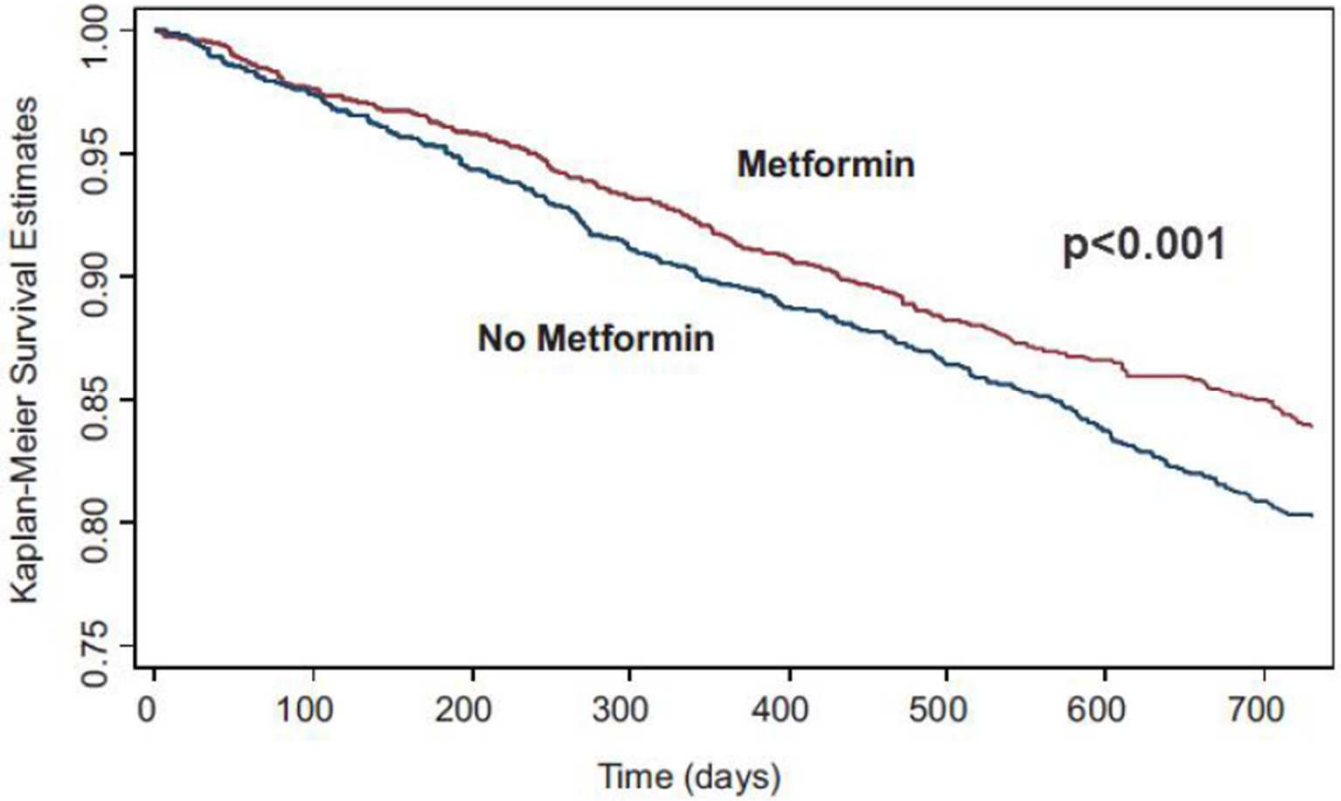
Age	Diabetic patients	Nondiabetic patients	Rate ratio	95% CI
<45 years	4.5	0.4	11.0	5.6–21.8
45–54 years	11.9	1.4	8.6	6.4–11.4
55–64 years	23.6	5.0	4.7	3.9–5.8
65–74 years	38.7	13.7	2.8	2.4–3.3
75–84 years	63.9	34.7	1.8	1.6–2.2
85–94 years	97.8	78.8	1.2	0.8–1.8
95+ years	59.5	110.4	0.5	0.1–2.2
All	30.9	12.4	2.5	2.3–2.7

Bertoni A et al. Diabetes Care 27: 1879-1884 (2004)

Herzinsuffizienz und Diabetes – Therapie

Cohortenstudie 6185 Patienten (USA) mit Herzinsuffizienz und Diabetes

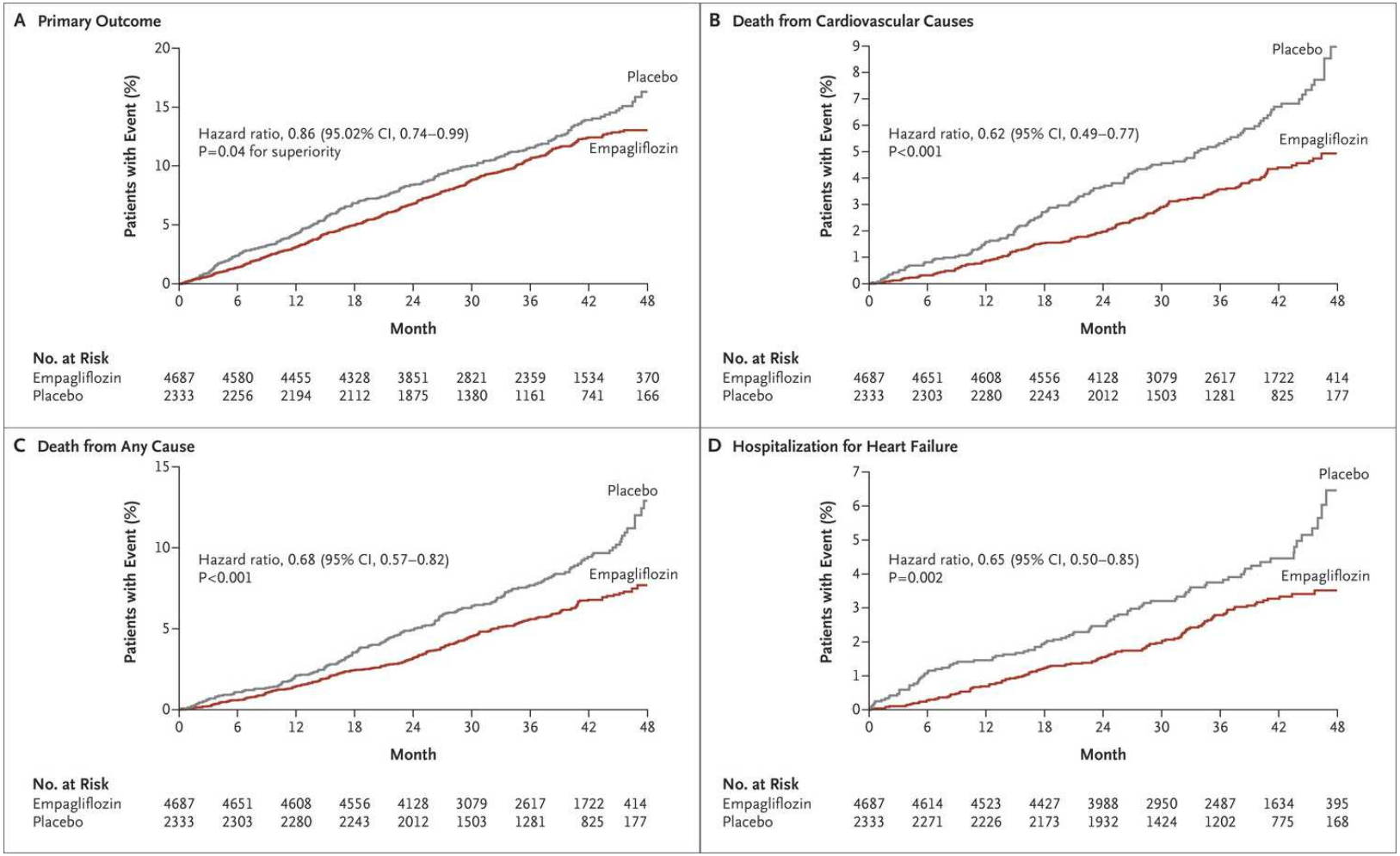
Metformin Use and Mortality in Ambulatory Patients With Diabetes and Heart Failure



Aguilar D et al. Circ Heart Fail. 2011;4:53-58

Antidiabetics and cardiovascular risk

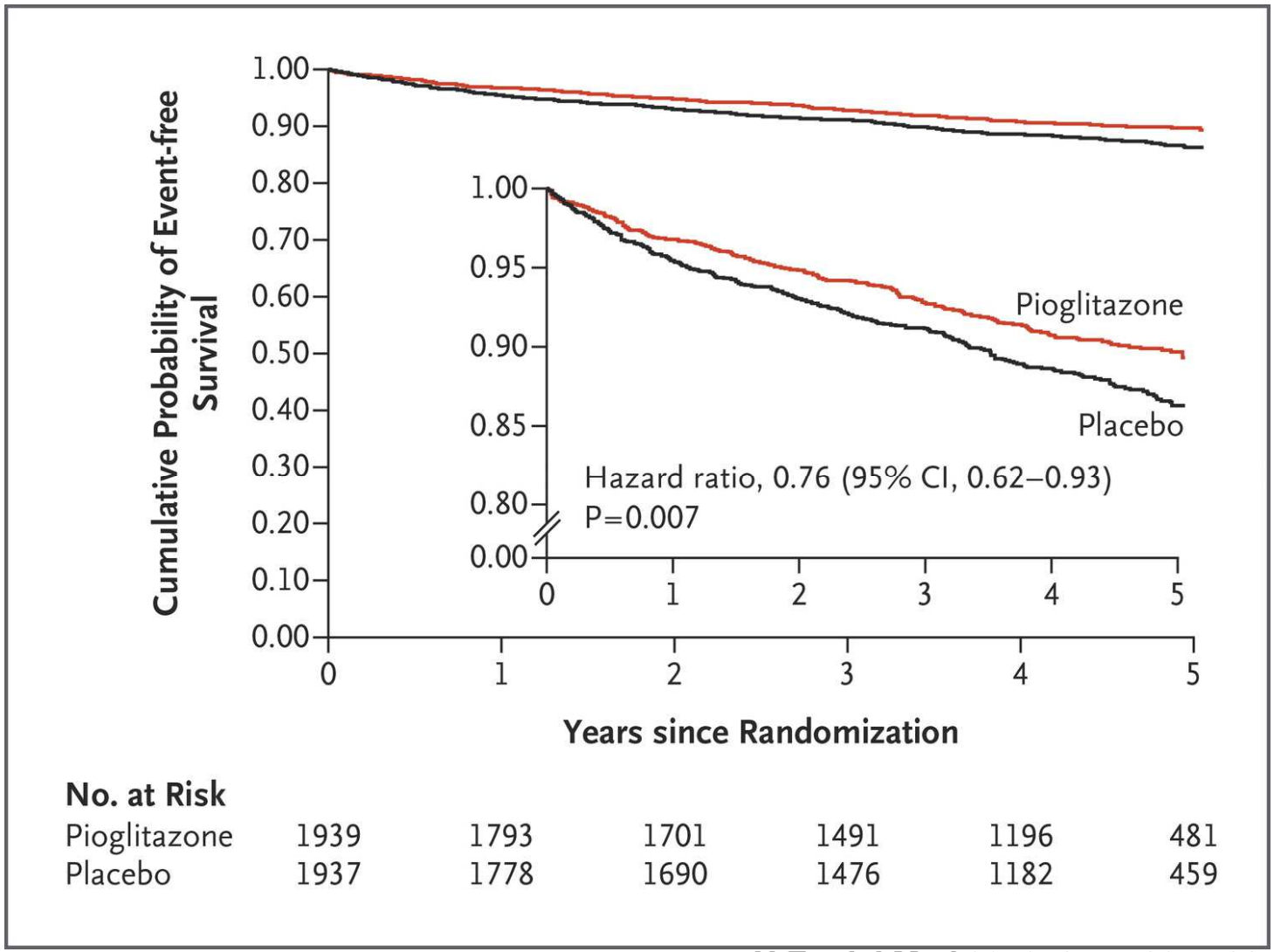
EMPA-REG outcome: Empagliflozin bei Diabetes mit hohem KV Risiko 7020 Patienten, Empagliflozin 10mg, vs. 25 mg vs. placebo



N Engl J Med 2015; 373:2117-2128

Antidiabetics and cardiovascular risk

IRIS: Pioglitazon bei Nicht-Diabetikern (aber Insulin-resistent) nach Schlaganfall/TIA - 3876 Patienten, Zieldosis Pioglitazon 45mg/d



No. at Risk						
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

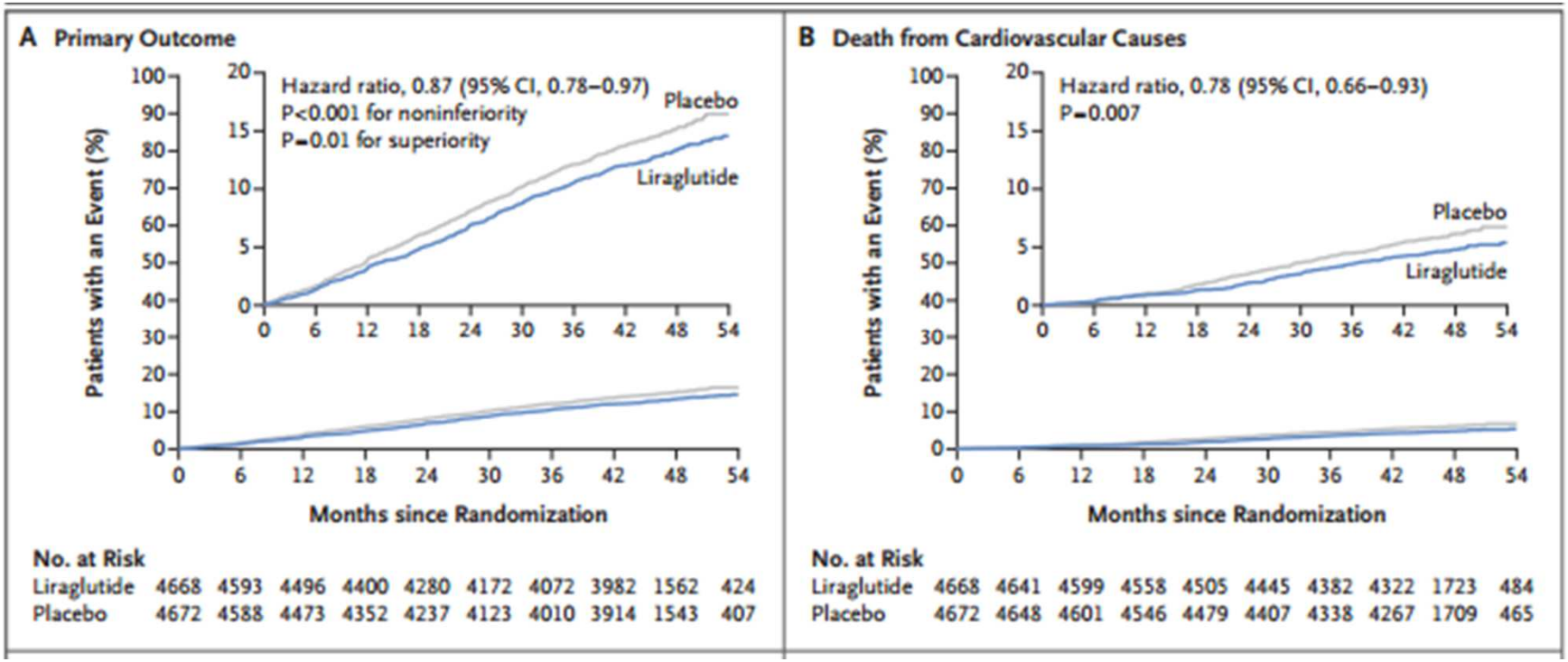
N Engl J Med 2016; 374:1321-1331 April 7, 2016

Antidiabetics and cardiovascular risk

The NEW ENGLAND JOURNAL of MEDICINE
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

LEADER
Liraglutide bei Diabetikern
Mit hohem KV Risiko
(5 Jahre follow-up)
9340 Patienten,
Zieldosis 0.6-1.8mg/d

Adverse event leading to permanent discontinuation of trial regimen			
Any adverse event	444 (9.5)	339 (7.3)	<0.001
Serious adverse event	192 (4.1)	245 (5.2)	0.01
Severe adverse event	164 (3.5)	188 (4.0)	0.20
Nausea	77 (1.6)	18 (0.4)	<0.001
Vomiting	31 (0.7)	2 (<0.1)	<0.001
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level‡	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002



SERVE-HF (Herzinsuffizienz)

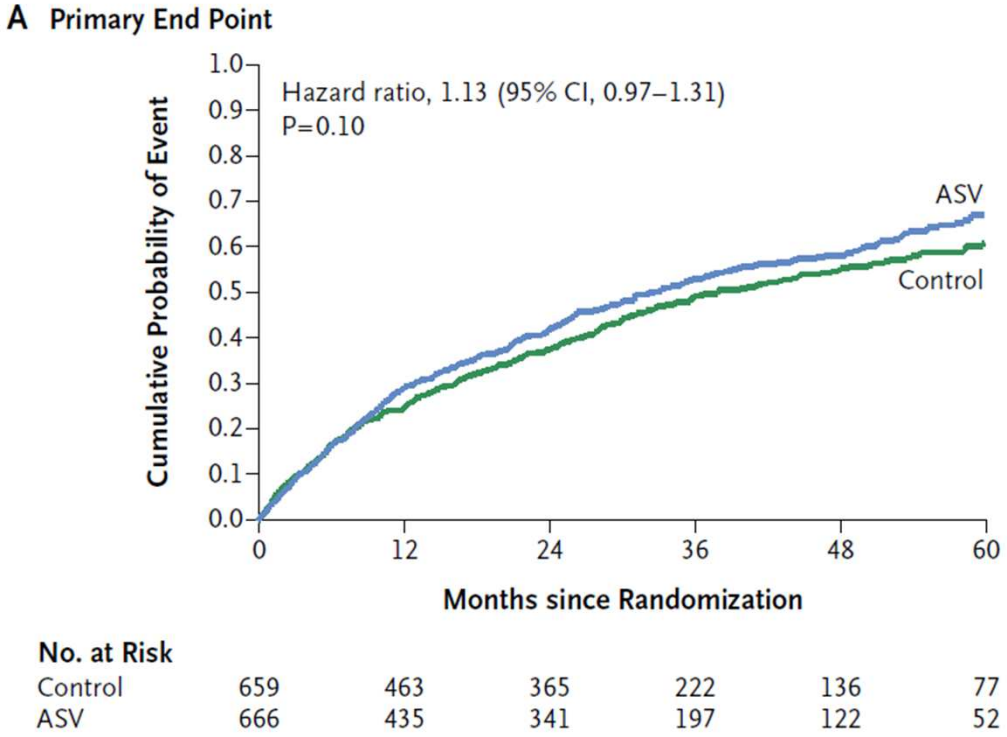
SERVE-HF
1325 Patienten mit einer LVEF < 45% Apnoe/Hypopnoe Index von > 15/h
(vorwiegende zentralen Episoden)

Eine zentrale Schlafapnoe ist bei Patienten mit Herzinsuffizienz mit einer schlechten Prognose und Mortalität assoziiert.

Die Therapie reduzierte zentrale Apnoeereignisse 25.2 vs. 3.2-4.0/h nach 24mo

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 17, 2015 VOL. 373 NO. 12

Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure



Tod, lebensrettender KV-Eingriff, ungeplante Hospitalisierung wegen CMP

Kasuistik 1

- Patient, geb. 1937
- Belastungsdyspnoe NYHA II-(III)
- iCMP, EF 30%
- St.p. ICD/CRT 2011
- Paroxysmales VHFlimmern, Niereninsuffizienz (GFR 55)
- NIDDM (ED 1998; HbA1c 7,8)
- Schlafapnoesyndrom, Leichtkettenmyelom
- Medikation: Blopress 8mg 1-0-1, Concor 5mg 0-1-0,
  Aquaphoril 20mg 1-0-0, Lasix 40mg 2-1-0,
  Sedacoron 200mg 1-0-0, OAK (Marcumar)
  Sortis 10mg 0-0-1, Metformin 500mg 1-0-1
- Status: 168cm, 80kg; 110/75mmHg; ~70/min,
- HT leise, arrhythmisch, Unterschenkelödeme

Kasuistik 1


NYHA class
I or II 3178 3130 0.03 0.76
III or IV 1002 1076
Estimated GFR 0.91 0.73
<60 ml/min/1.73 m² 1541 1520
≥60 ml/min/1.73 m² 2646 2692
Diabetes 0.40 0.05
No 2736 2756
Yes 1451 1456
Systolic blood pressure 0.87 0.62
≤Median 2298 2299
>Median 1889 1913
Ejection fraction 0.71 0.80
≤Median 2239 2275
>Median 1948 1936
Ejection fraction 0.36 0.36
≤35% 3715 3722
>35% 472 489
Atrial fibrillation 0.25 1.00
No 2670 2638
Yes 1517 1574
NT-proBNP 0.16 0.33
≤Median 2079 2116
>Median 2103 2087
Hypertension 0.87 0.14
No 1218 1241
Yes 2969 2971
Prior use of ACE inhibitor 0.09 0.06
No 921 946
Yes 3266 3266
Prior use of aldosterone antagonist 0.10 0.32
No 1916 1812
Yes 2271 2400
Prior hospitalization for heart failure 0.10 0.19
No 1580 1545
Yes 2607 2667
Time since diagnosis of heart failure 0.27 0.21
≤1 yr 1275 1248
>1 to 5 yr 1621 1611
>5 yr 1291 1353
0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7
LCZ696 Better
Enalapril Better
0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7
LCZ696 Better
Enalapril Better

„The best physician for a patient with HF would be one with ***excellent training, extensive experience, and superb judgment*** with regard to all aspects of the disease.

He or she ***would not necessarily follow guidelines slavishly***."

J.N. Cohn, Circ Heart Fail 2008;1:87-88