Universitätsklinikum ST. PÖLTEN

KARL LANDSTEINER
PRIVATUNIVERSITÄT FÜR GESUNDHEITSWISSENSCHAFTEN

HEART FAILURE ASSOCIATION OF THE ESC

EUROPEAN SOCIETY OF CARDIOLOGY®

HYPERKALIÄMIE UND HERZINSUFFIZIENZ

Priv.-Doz. Dr. Deddo Mörtl, FHFA

Arbeitsgruppe Herzinsuffizienz

der Österreichischen Kardiologischen Gesellschaft

ÖKG
Österreichische Kardiologische Gesellschaft

WAS IST HERZINSUFFIZIENZ?

Klinische Definition der Herzinsuffizienz

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- Klinisches Syndrom

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- Klinisches Syndrom
- Typische Symptome (z.B. Atemnot, Knöchelödeme, Müdigkeit)

Tabelle 1: Symptome und klinische Zeichen einer Herzinsuffizienz (HI)

Symptome
typisch
Kurzatmigkeit
Orthopnoe
Paroxysmale nächtliche Dyspnoe
Eingeschränkte körperliche Belastungsbreite
Müdigkeit, Schläfrigkeit, verlängerte Erholungsphasen nach Anstrengung
Knöchelödeme
weniger typisch
Nächtlicher Husten
Giemen
Gewichtszunahme (>2 kg/Woche)
Gewichtsverlust (bei fortgeschrittener HI)
Völlegefühl
Appetitlosigkeit
Verwirrtheit (besonders bei älteren Patienten)
Depression
Palpitationen
Synkopen

modifiziert nach ESC, 2012

Ebner, Fruhwald, Mörtl: Praxisleitfaden der AG Herzinsuffizienz 2012

Klinische Definition der Herzinsuffizienz

- Klinisches Syndrom
- Typische Symptome (z.B. Atemnot, Knöchelödeme, Müdigkeit)
- ev. mit typischen Zeichen (z.B. Halsvenenstauung, Rasselgeräusche, Ödeme)

Tabelle 1: Symptome und klinische Zeichen einer Herzinsuffizienz (HI)

Symptome	Klinische Zeichen
typisch	*spezifisch*
Kurzatmigkeit	Jugularvenenstauung
Orthopnoe	Hepatojugulärer Reflux
Paroxysmale nächtliche Dyspnoe	Herzgeräusche
Eingeschränkte körperliche Belastungsbreite	Vorhandener dritter Herzton (Galopprhythmus)
Müdigkeit, Schläfrigkeit, verlängerte Erholungsphasen nach Anstrengung	Seitlich verlagerter Herzspitzenstoß
Knöchelödeme	
weniger typisch	*weniger spezifisch*
Nächtlicher Husten	Periphere Ödeme (Knöchel, sakral, skrotal)
Giemen	Pulmonale Rasselgeräusche
Gewichtszunahme (>2 kg/Woche)	Pleuraerguss
Gewichtsverlust (bei fortgeschrittener HI)	Tachykardie
Völlegefühl	Unregelmäßiger Puls
Appetitlosigkeit	Tachypnoe (> 16/min)
Verwirrtheit (besonders bei älteren Patienten)	Hepatomegalie
Depression	Aszites
Palpitationen	Kachexie
Synkopen	

modifiziert nach ESC, 2012

Ebner, Fruhwald, Mörtl: Praxisleitfaden der AG Herzinsuffizienz 2012

Klinische Definition der Herzinsuffizienz

- Klinisches Syndrom
- Typische Symptome (z.B. Atemnot, Knöchelödeme, Müdigkeit)
- ev. mit typischen Zeichen (z.B. Halsvenenstauung, Rasselgeräusche, Ödeme)
- verursacht durch strukturelle und/oder funktionelle Herzerkrankung (die in reduziertem Herzminutenvolumen mündet und/oder erhöhten intrakardialen Füllungsdrücken in Ruhe oder auch bei Belastung).

Herzinsuffizienz Definition

HF-Typ		HFrEF	HFmrEF	HFpEF
KRITERIEN	1	Symptome ±Zeichen[a]	Symptome ±Zeichen[a]	Symptome ±Zeichen[a]
	2	LVEF < 40%	LVEF 40–49%	LVEF ≥ 50%
	3		1. erhöhte Serumkonzentrationen der natriuretischen Peptide[b] 2. mindestens 1 zusätzliches Kriterium: a. relevante strukturelle Herzerkrankung (LVH und/oder LAE) b. diastolische Dysfunktion[c]	1. erhöhte Serumkonzentrationen der natriuretischen Peptide[b] 2. mindestens 1 zusätzliches Kriterium: a. relevante strukturelle Herzerkrankung (LVH und/oder LAE) b. diastolische Dysfunktion[c]

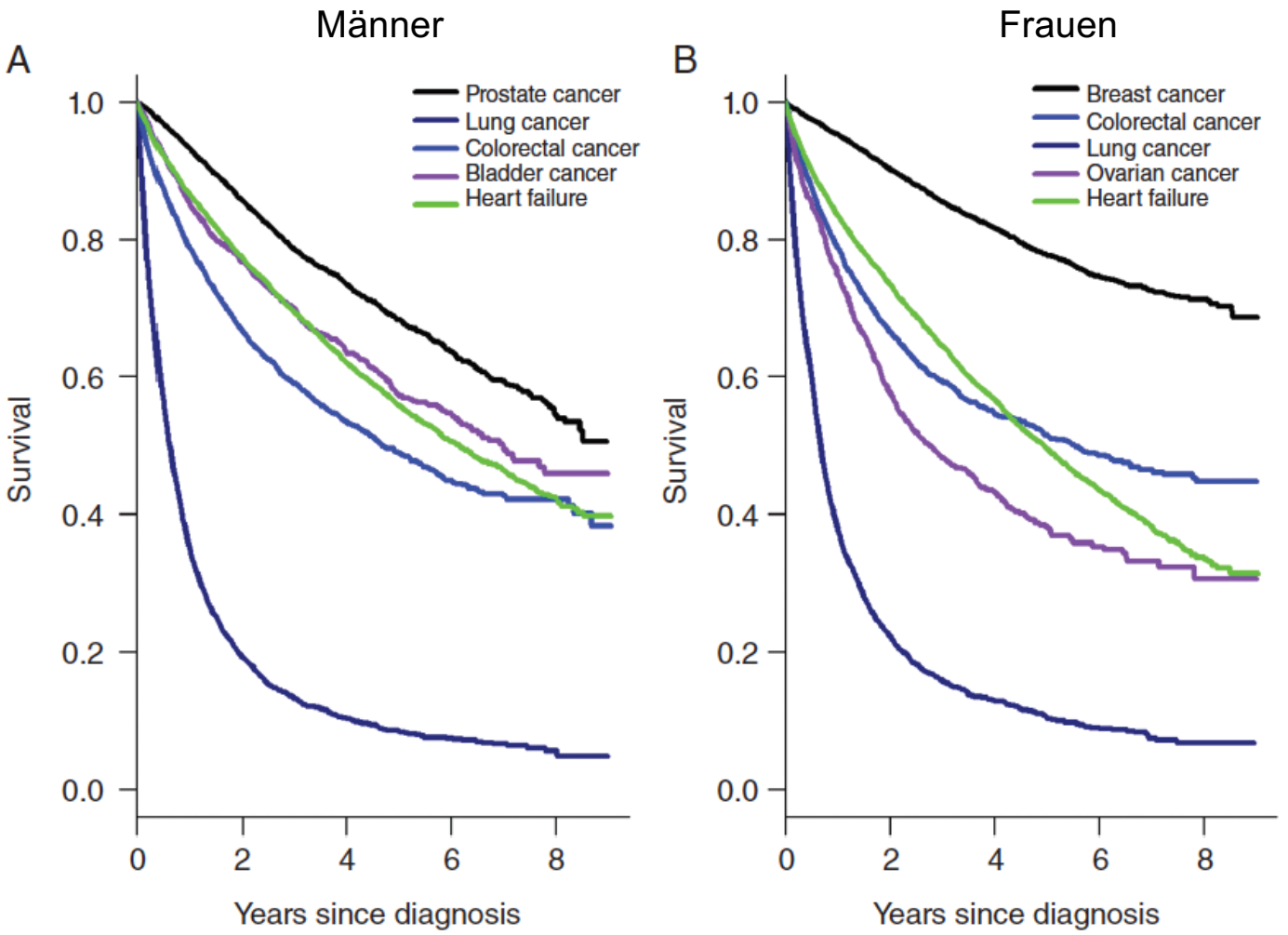
Übersetzt aus ESC HF Guidelines 2016

Herzinsuffizienz Häufigkeit

- 1-2% der erwachsenen Bevölkerung -> 70.000-140.000
- life-time risk eines 40 jährigen ist 20%, eines 55 jährigen bereits 30%.
- Die Prävalenz steigt mit zunehmendem Alter.
- lt. Statistik Austria ca 24.000 HI-Hospitalisierungen jährlich in Ö.
- HI ist die häufigste Hospitalisierungsursache bei über 65jährigen.
- Entlassungsdiagnose HI hat sich in den vergangenen 3 Dekaden verdreifacht.
- Verstärkung des Trends durch:

  Zunahme der Lebenserwartung
  des Überlebens nach Myokardinfarkt
  der Risikofaktoren (z.B. art. Hypertonie,...)

Herzinsuffizienz: Bösartiger als Krebs?



Mamas et al., EJHF 2019:19; 1095–1104

Fazit: Herzinsuffizienz ist charakterisiert durch

- Sehr hohe Patientenzahlen
- Schlechte Lebensqualität
- Einschränkung der Leistungsfähigkeit
- Hohe Hospitalisierungsraten
- Hohe Sterberaten

Behandlungsziele der Herzinsuffizienz

- Patientenzahlen
- Lebensqualität ↑
- Leistungsfähigkeit ↑
- Hospitalisierungsraten ↓
- Sterberate ↓

Behandlungsziele der Herzinsuffizienz

- Patientenzahlen
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Herzinsuffizienztherapie

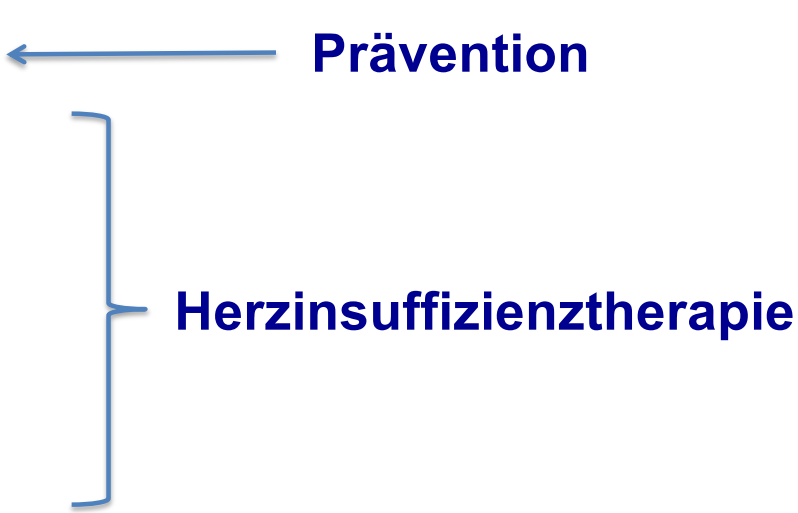
Behandlungsziele der Herzinsuffizienz

- Patientenzahlen ↓
- Lebensqualität ↑
- Leistungsfähigkeit ↑
- Hospitalisierungsraten ↓
- Sterberate ↓

} **Herzinsuffizienztherapie**

Behandlungsziele der Herzinsuffizienz

- Patientenzahlen ↓
- Lebensqualität ↑
- Leistungsfähigkeit ↑
- Hospitalisierungsraten ↓
- Sterberate ↓



WIE THERAPIERT MAN HERZINSUFFIZIENZ?

Herzinsuffizienz Definition

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Übersetzt aus ESC HF Guideines 2016

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Offiziell keine wirksame Therapie

Übersetzt aus ESC HF Guideines 2016

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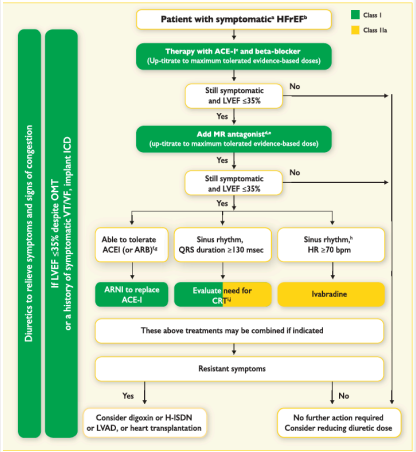
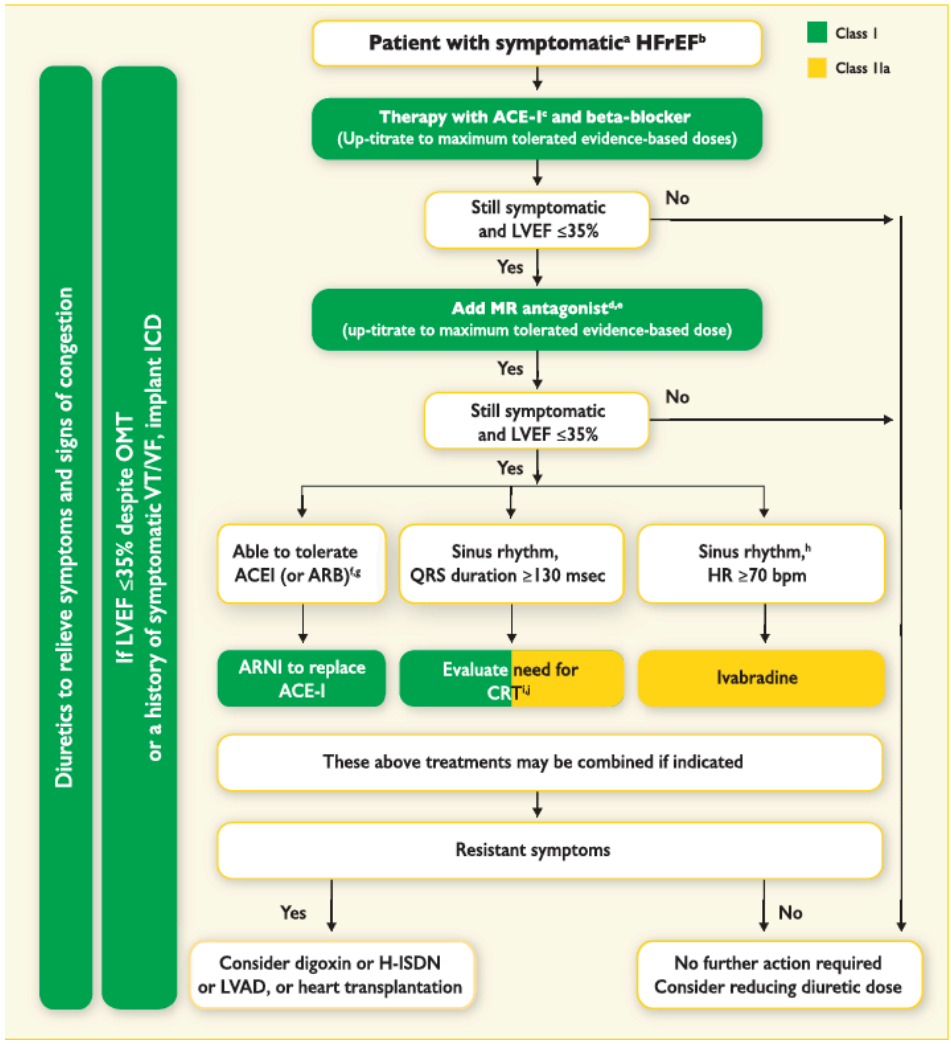
	3		1. erhöhte Serumkonzentrationen der natriuretischen Peptide[b] 2. mindestens 1 zusätzliches Kriterium: a. relevante strukturelle Herzerkrankung (LVH und/oder LAE) b. diastolische Dysfunktion[c]	1. erhöhte Serumkonzentrationen der natriuretischen Peptide[b] 2. mindestens 1 zusätzliches Kriterium: a. relevante strukturelle Herzerkrankung (LVH und/oder LAE) b. diastolische Dysfunktion[c]

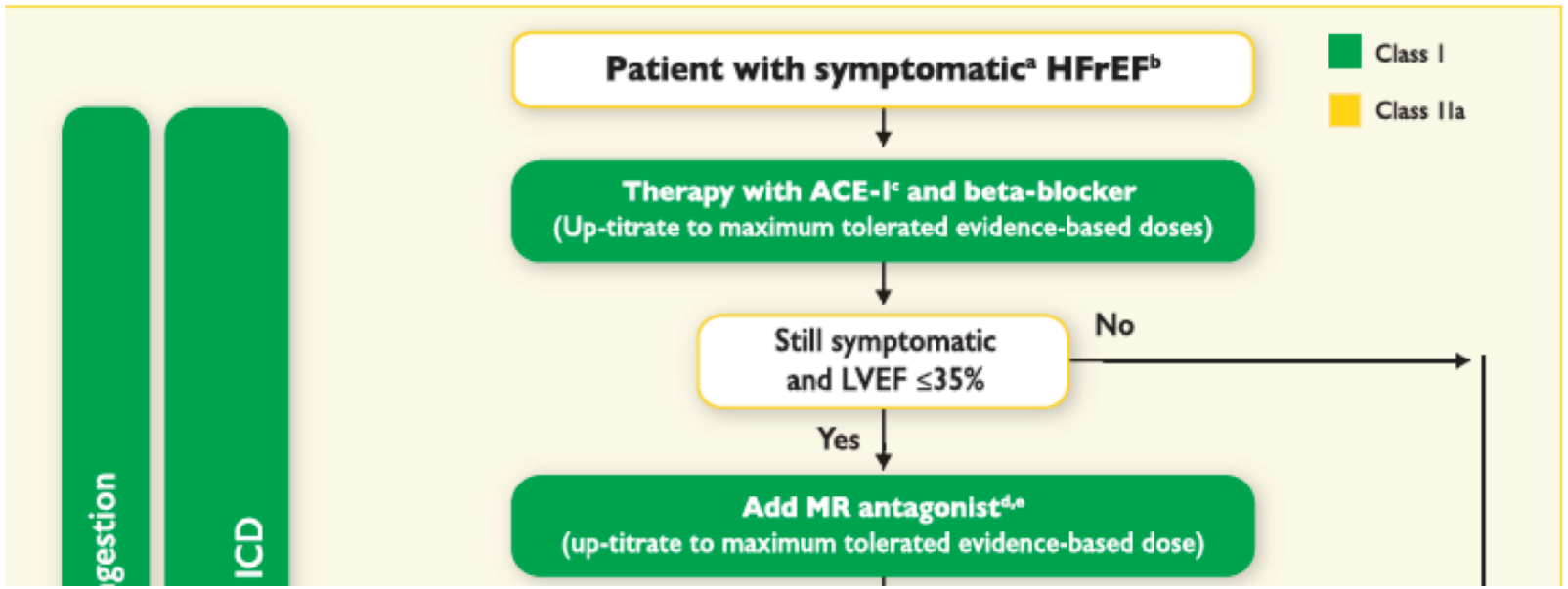
Offiziell keine wirksame Therapie

Übersetzt aus ESC HF Guideines 2016

Behandlung der HFrEF



ESC 2016


Patient with symptomatic[a] HFrEF[b]
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic
and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Class I
Class IIa
gestion
ICD

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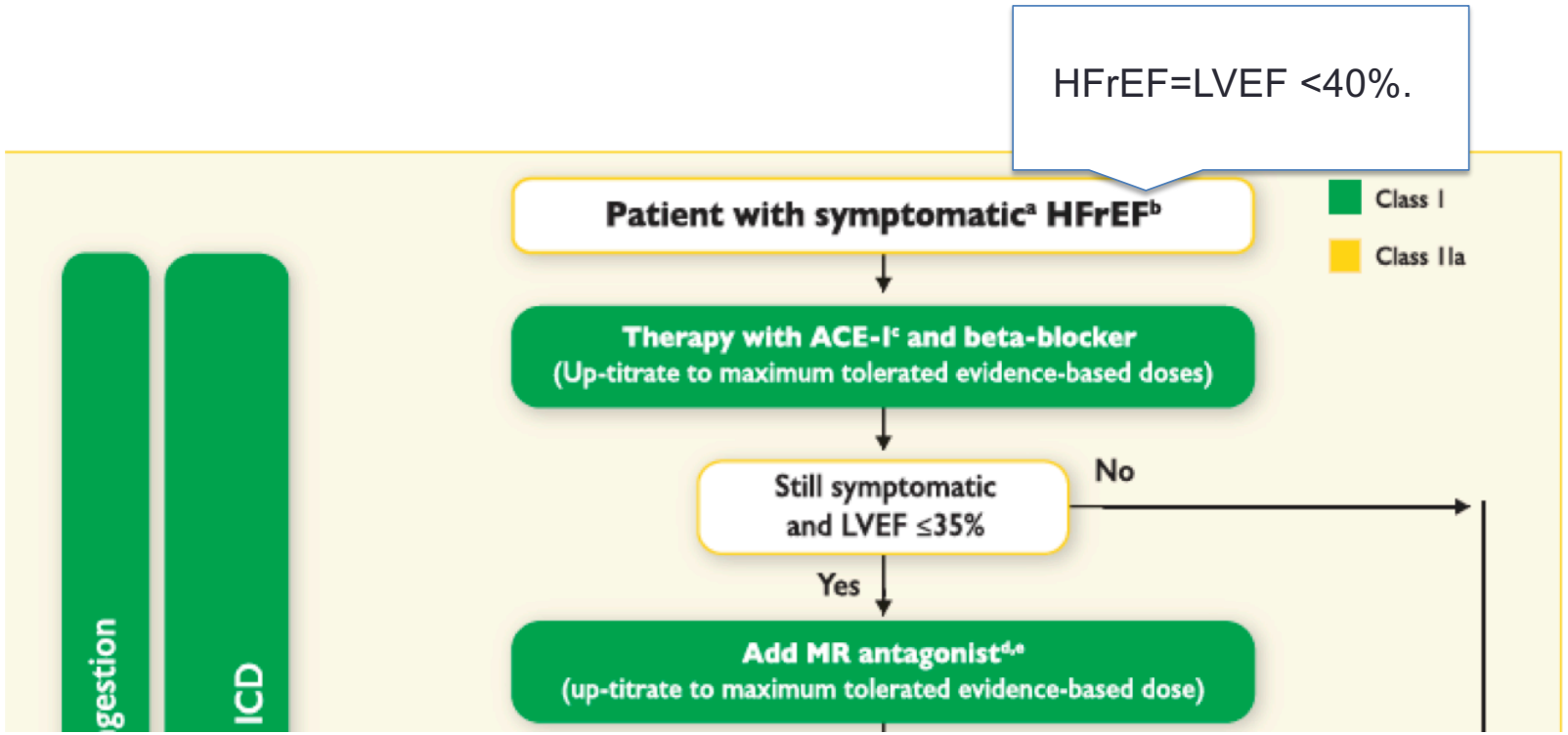
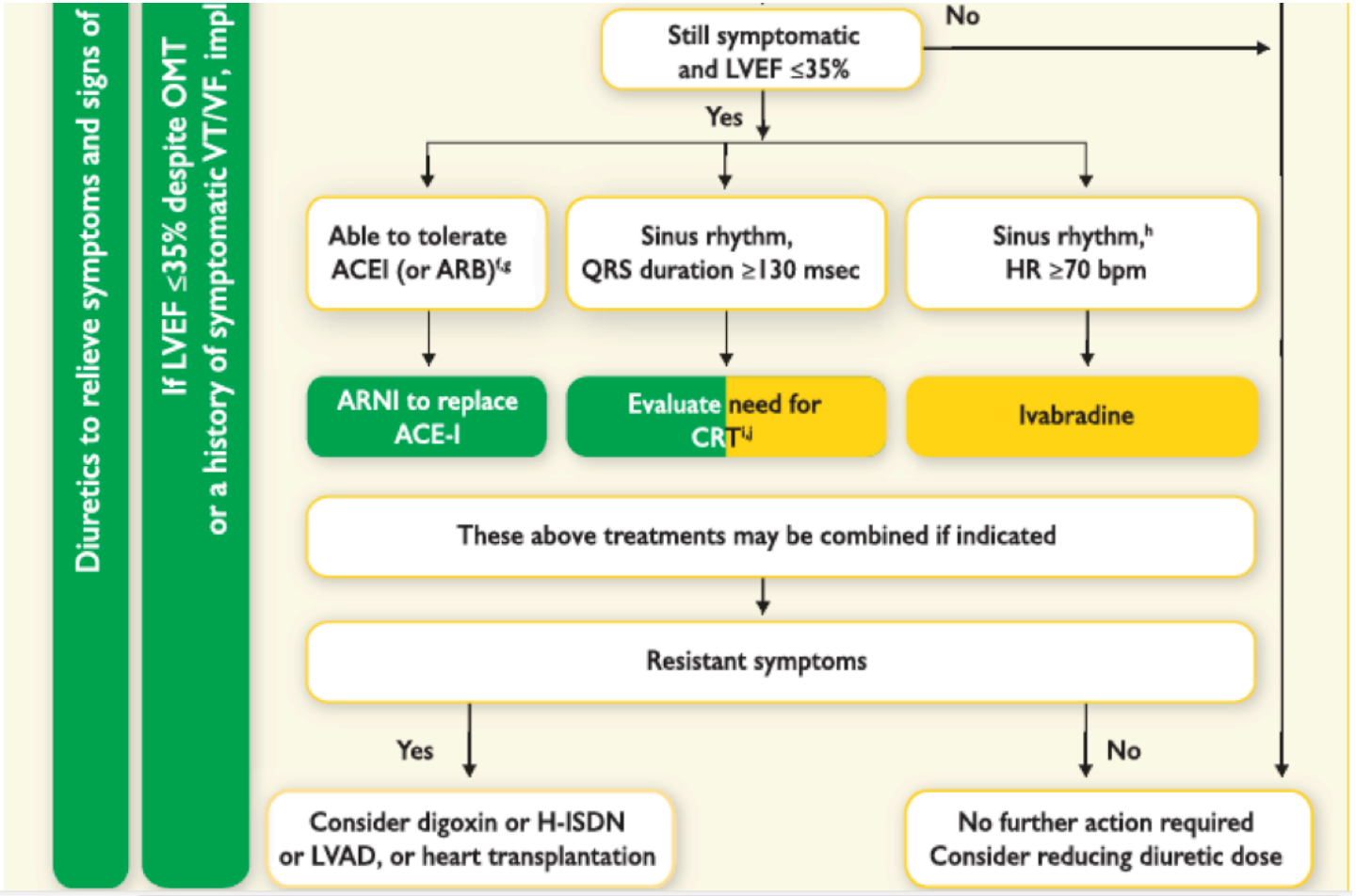
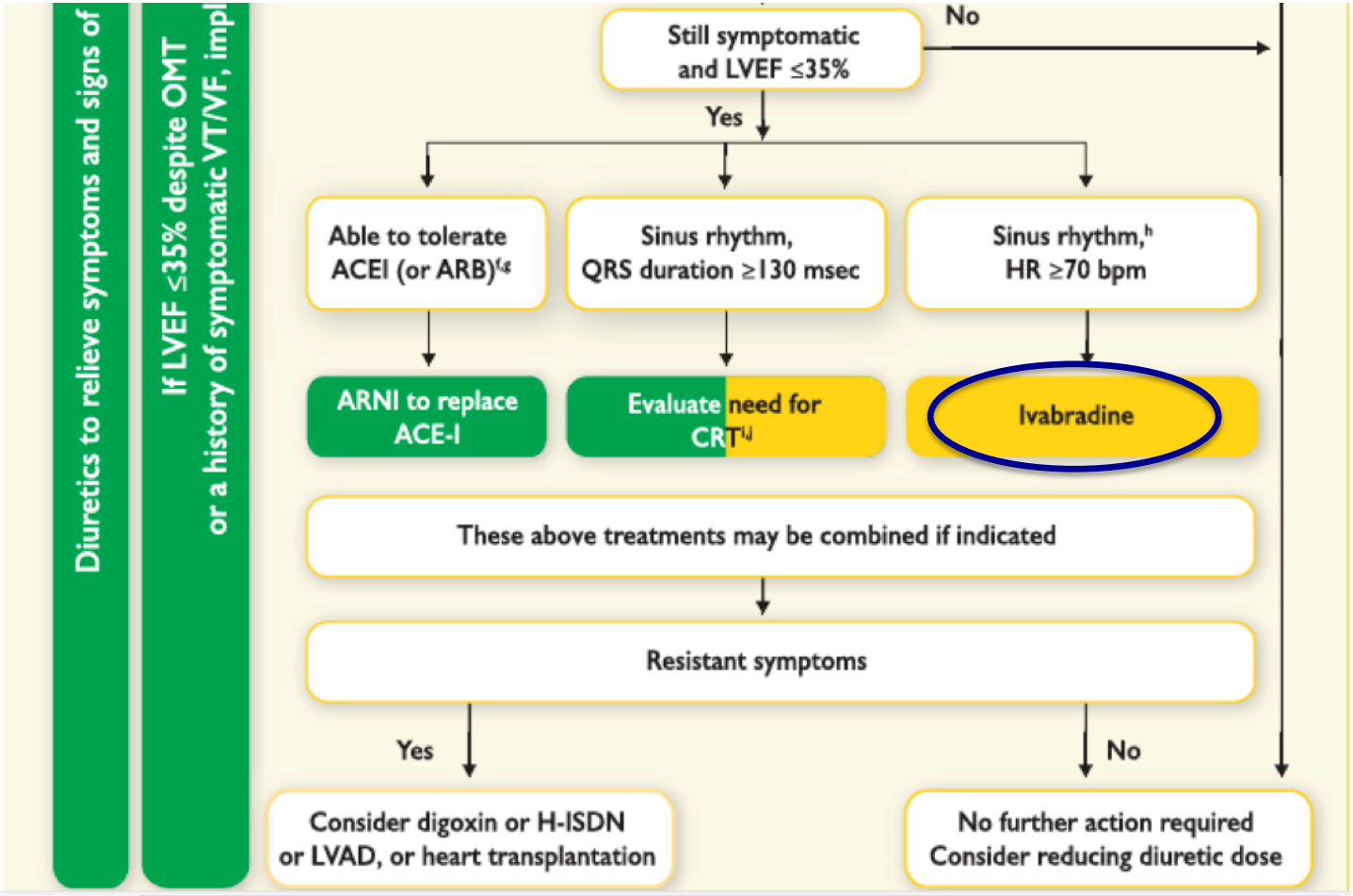
HFrEF=LVEF <40%.



ESC 2016


Diuretics to relieve symptoms and signs of
If LVEF ≤35% despite OMT
or a history of symptomatic VT/VF, impl
Still symptomatic
and LVEF ≤35%
No
Yes
Able to tolerate
ACEI (or ARB)[f,g]
Sinus rhythm,
QRS duration ≥130 msec
Sinus rhythm,[h]
HR ≥70 bpm
ARNI to replace
ACE-I
Evaluate need for
CRT[i,j]
Ivabradine
These above treatments may be combined if indicated
Resistant symptoms
Yes
No
Consider digoxin or H-ISDN
or LVAD, or heart transplantation
No further action required
Consider reducing diuretic dose

ESC 2016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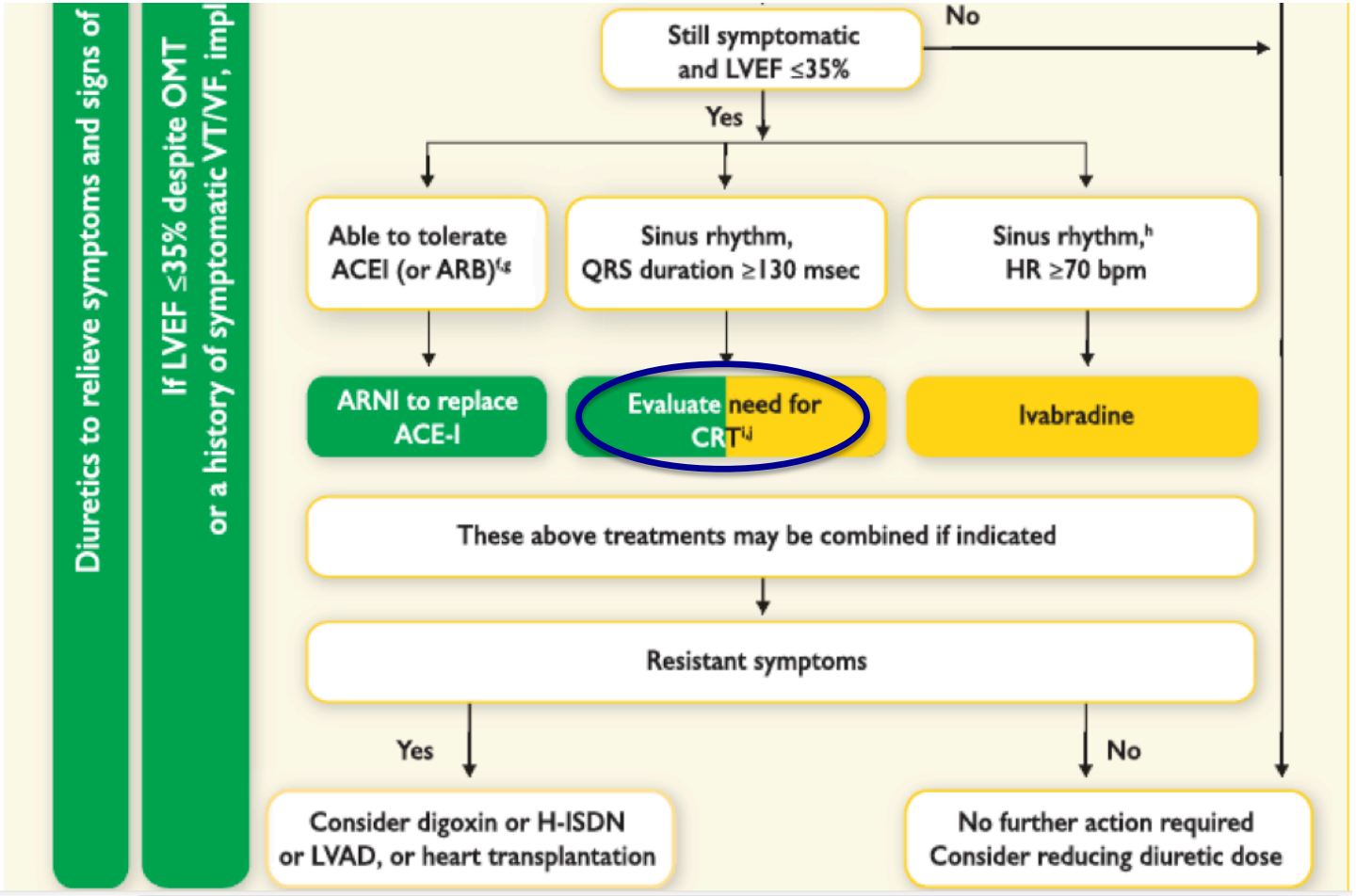
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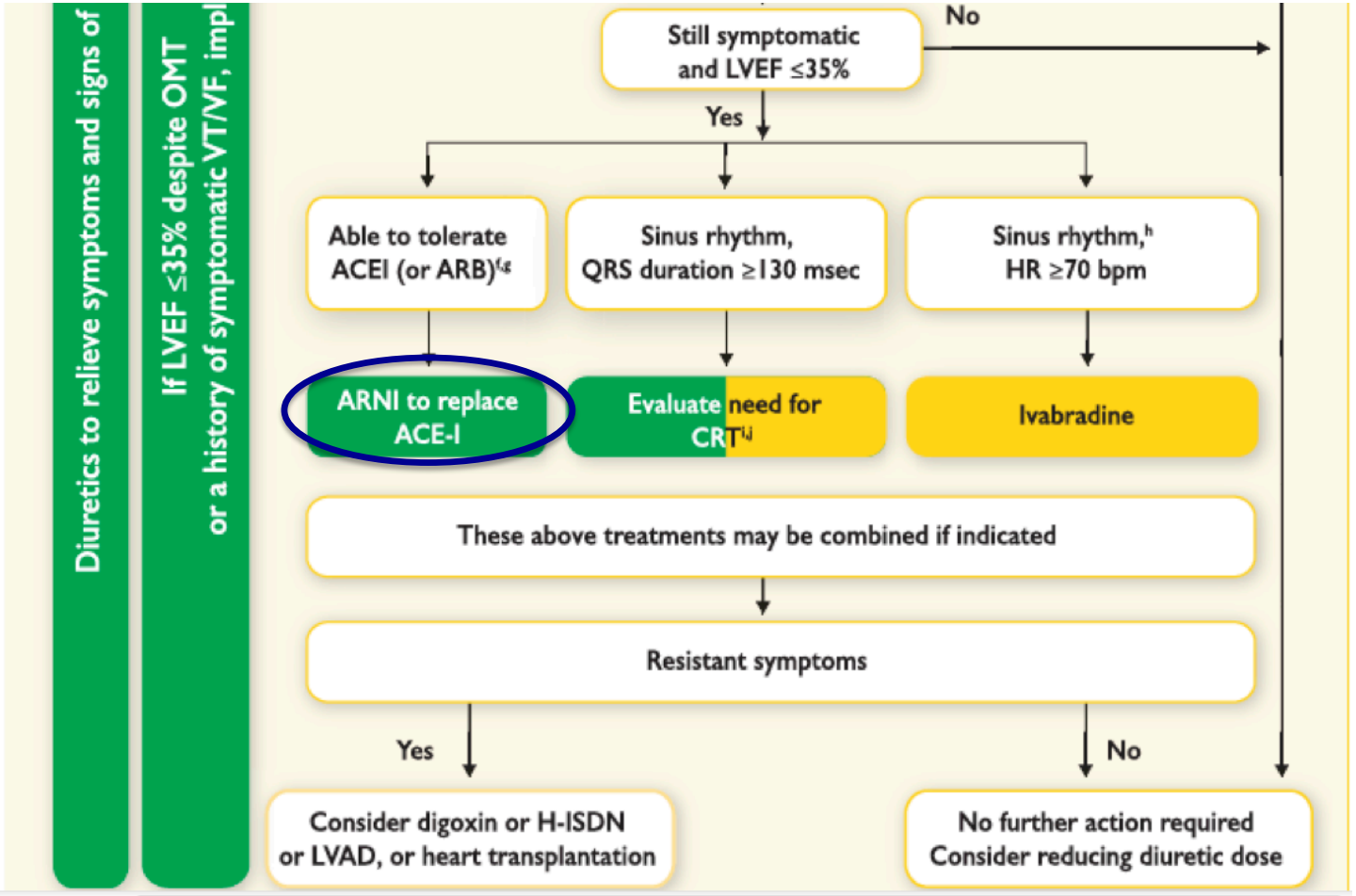
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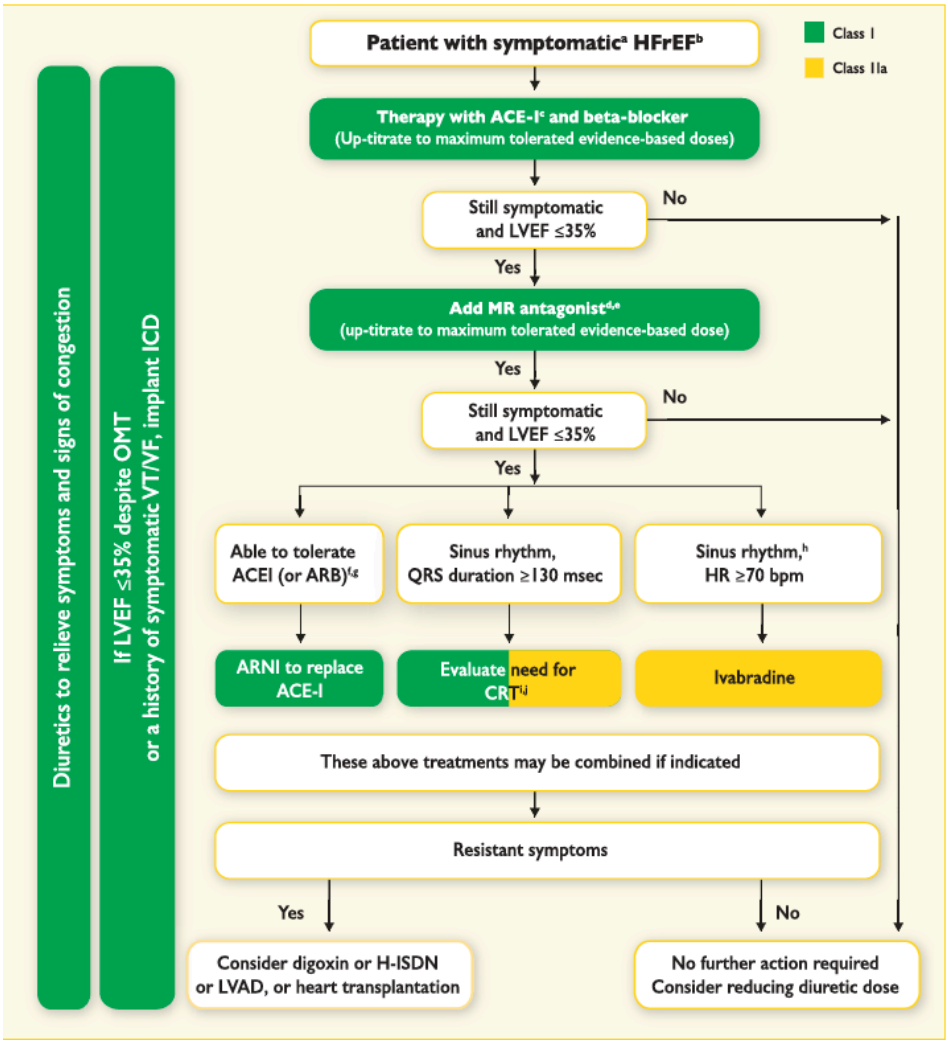
Medikamentöse Behandlung der HFrEF



	Class	Level
ACE-Hemmer	I	A
Betablocker	I	A
MRA	I	A
Sac/Val	I	B
Ivabradin	IIa	B

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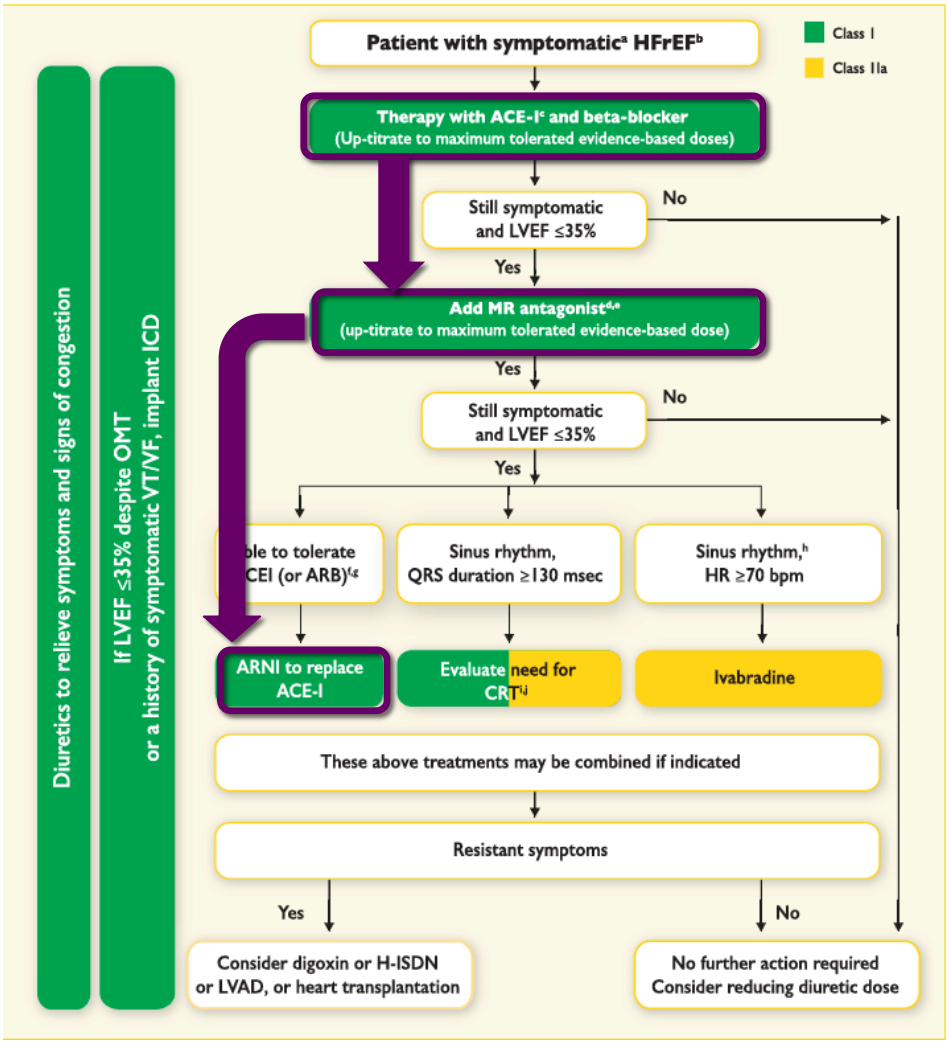
Medikamentöse Behandlung der HFrEF



	Class	Level
ACE-Hemmer	I	A
Betablocker	I	A
MRA	I	A
Sac/Val	I	B
Ivabradin	IIa	B

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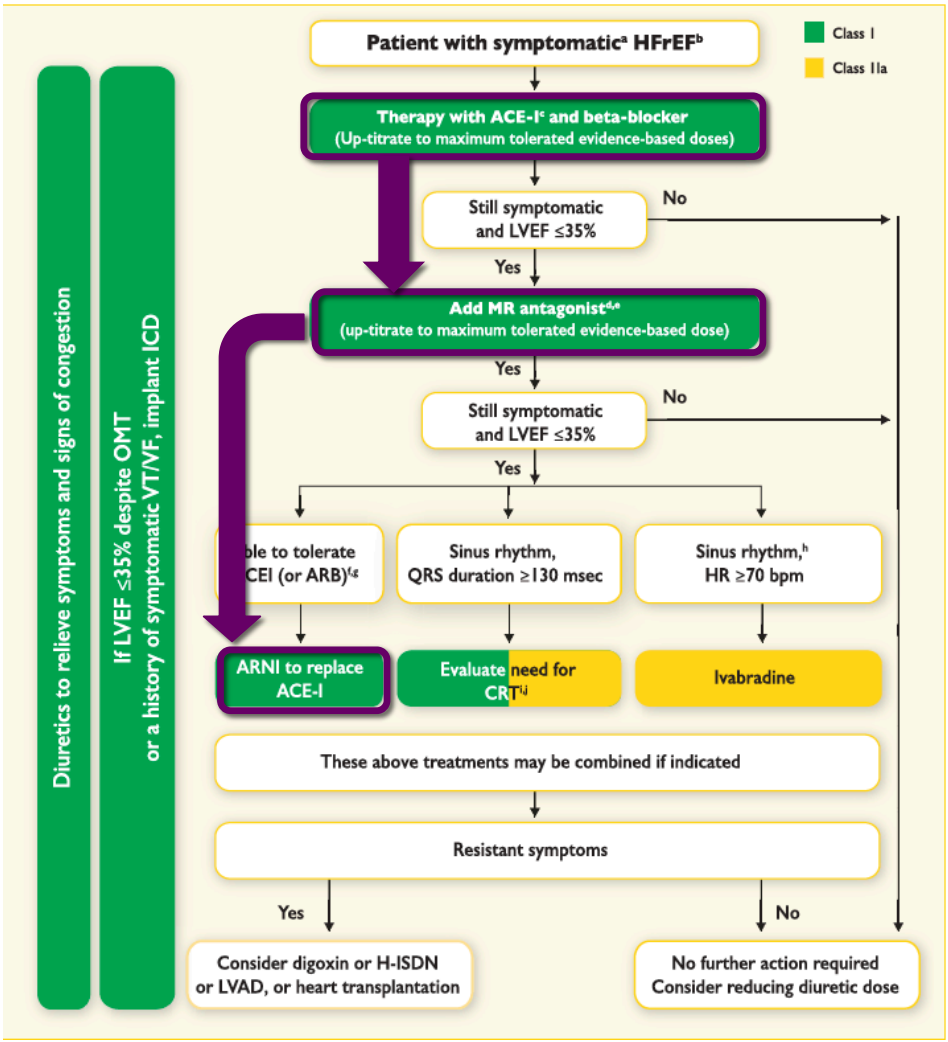
Medikamentöse Behandlung der HFrEF



	Class	Level
ACE-Hemmer	**I**	A
Betablocker	I	A
MRA	**I**	A
Sac/Val	**I**	B
Ivabradin	IIa	B

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Neurohormonale Antagonistentherapie

Substanzklasse	Mortalitätsreduktion
ACE-Hemmer: CONSENSUS 1987	27%
SOLVD 1991	16%
Betablocker: CIBIS II 1999	30-35%
COPERNICUS 2002	
MERIT-HF 1999	
Mineralocorticoidrezeptorantagonisten: RALES 1999	30%
EMPHASIS-HF 2011	24%
Sacubitril/Valsartan: PARADIGM-HF 2014	16%

Table 7.2 Evidence-based doses of disease-modifying drugs in key randomized trials in heart failure with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	20 *b.i.d.*
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 o.d.	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 o.d.
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
I*f*-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

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WOZU AUFTITRIEREN?

WOZU AUFTITRIEREN?

1) Empfehlung in Guidelines

7.2 Treatments recommended in all symptomatic patients with heart failure with reduced ejection fraction

7.2.1 Angiotensin-converting enzyme inhibitors

ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF[2,5,163–165] and are recommended unless contraindicated or not tolerated in all symptomatic patients. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS). There is evidence that in clinical practice the majority of patients receive suboptimal doses of ACEI.[166] ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death (see Section 6).

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WOZU AUFTITRIEREN?

2) Auftitrationsprotokolle in Studien

The New England
Journal of Medicine

Volume 325 AUGUST 1, 1991 Number 5

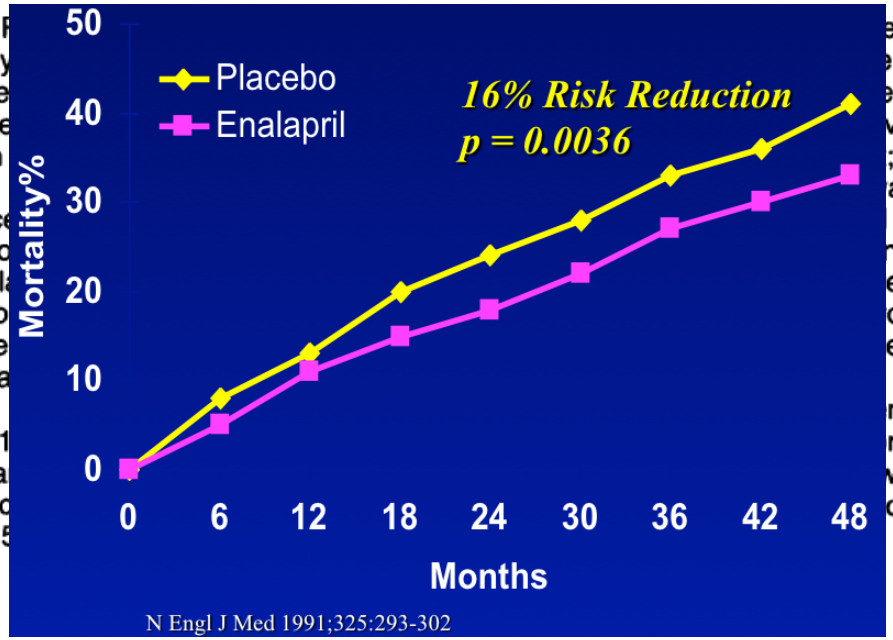
EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*

Abstract *Background.* F
failure have a high mortality
frequently. We studied the
verting–enzyme inhibitor, e
pitalization in patients with
tion fractions ≤0.35.

Methods. Patients rec
for heart failure were rando
placebo (n = 1284) or enal
to 20 mg per day in a doub
percent of the patients we
ation functional classes II a
41.4 months.

Results. There were 51
(39.7 percent), as compa
group (35.2 percent) (reduc
cent confidence interval, 5



ere observed in several
largest reduction oc-
ed to progressive heart
vs. 209 in the enalapril
; 95 percent confidence
as little apparent effect
as due to arrhythmia
nts died or were hospi-
e (736 in the placebo
oup; risk reduction, 26
erval, 18 to 34 percent;

nalapril to conventional
rtality and hospitaliza-
with chronic congestive
ctions. (N Engl J Med

Randomization and Dose Titration after Randomization

Randomization was performed with a computer-generated allocation schedule that had a block size of 16 patients stratified according to hospital. Treatment with enalapril or placebo was started at 2.5 mg or 5 mg twice daily on the basis of the patient's clinical condition and the participating physician's judgment. The dose was titrated up to a maximum of 10 mg twice daily if the patient did not have symptomatic hypotension or worsening renal function. After

SOLVD Investigators NEJM 1991; 325: 293-302

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 6, 2011 VOL. 364 NO. 1

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

ABSTRACT

BACKGROUND

Mineralocorticoid antagonists improve survival among patients with chronic, severe systolic heart failure and heart failure after myocardial infarction. We evaluated the effects of eplerenone in patients with chronic systolic heart failure and mild symptoms.

METHODS

In this randomized, double-blind trial, we randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

From INSERM, Centre d'Investigation Clinique 9501 and Unité 961, Centre Hospitalier Universitaire, and the Department of Cardiology, Nancy University, Nancy, France (F.Z.); the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Epidemiology and Preventive Medicine, Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, VIC, Australia (H.K.); the Department of Cardiology, Thorax Center, University Medical Center, Groningen, the Netherlands (D.J.V.); the De-

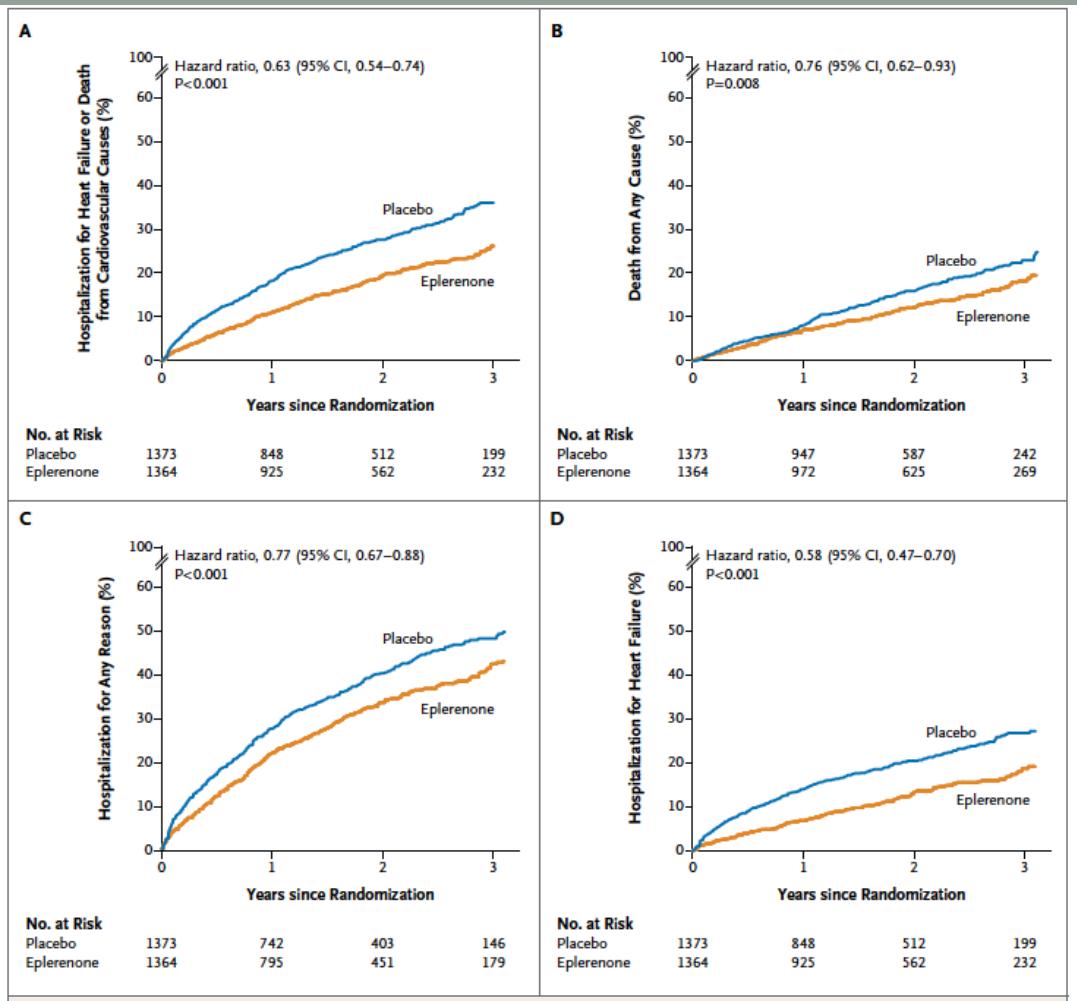


Figure 1. Cumulative Kaplan–Meier Estimates of Rates of the Primary Outcome and Other Outcomes, According to Study Group.

The hazard ratios for eplerenone versus placebo are shown for hospitalization for heart failure or death from cardiovascular causes (the primary outcome) (Panel A), death from any cause (Panel B), hospitalization for any reason (Panel C), and hospitalization for heart failure (Panel D).

Zannad NEJM 2011

STUDY PROCEDURES

We used a computerized randomization system involving concealed study-group assignments to randomly assign patients to receive eplerenone (Inspra, Pfizer) or matching placebo. Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m^2), provided the serum potassium level was no more than 5.0 mmol per liter.

Zannad NEJM 2011

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Zannad NEJM 2011

WOZU AUFTITRIEREN?

3) Dosis-abhängige Effekte der RAAS-Inhibition

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

Milton Packer, MD; Philip A. Poole-Wilson, MD; Paul W. Armstrong, MD; John G.F. Cleland, MD; John D. Horowitz, MD; Barry M. Massie, MD; Lars Rydén, MD; Kristian Thygesen, MD; Barry F. Uretsky, MD; on behalf of the ATLAS Study Group*

Background—Angiotensin-converting enzyme (ACE) inhibitors are generally prescribed by physicians in doses lower than the large doses that have been shown to reduce morbidity and mortality in patients with heart failure. It is unclear, however, if low doses and high doses of ACE inhibitors have similar benefits.

Methods and Results—We randomly assigned 3164 patients with New York Heart Association class II to IV heart failure and an ejection fraction ≤30% to double-blind treatment with either low doses (2.5 to 5.0 mg daily, n=1596) or high doses (32.5 to 35 mg daily, n=1568) of the ACE inhibitor, lisinopril, for 39 to 58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a nonsignificant 8% lower risk of death (P=0.128) but a significant 12% lower risk of death or hospitalization for any reason (P=0.002) and 24% fewer hospitalizations for heart failure (P=0.002). Dizziness and renal insufficiency was observed more frequently in the high-dose group, but the 2 groups were similar in the number of patients requiring discontinuation of the study medication.

Conclusions—These findings indicate that patients with heart failure should not generally be maintained on very low doses of an ACE inhibitor (unless these are the only doses that can be tolerated) and suggest that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be very small. (***Circulation*. 1999;100:2312-2318.**)

TABLE 2. Effect of Treatment on Major Clinical Events

	Low-Dose	High-Dose	Hazard Ratio	*P*
All-cause mortality	717 (44.9)	666 (42.5)	0.92 (0.82–1.03)	0.128
Cardiovascular mortality	641 (40.2)	583 (37.2)	0.90 (0.81–1.01)	0.073
All-cause mortality+hospitalization for any reason	1338 (83.8)	1250 (79.7)	0.88 (0.82–0.96)	0.002
All-cause mortality+hospitalization for cardiovascular reason	1182 (74.1)	1115 (71.1)	0.92 (0.84–0.99)	0.036
All-cause mortality+hospitalization for heart failure*	964 (60.4)	864 (55.1)	0.85 (0.78–0.93)	<0.001
Cardiovascular mortality+hospitalization for cardiovascular reason	1161 (72.7)	1088 (69.4)	0.91 (0.84–0.99)	0.027
Fatal and nonfatal myocardial infarction+hospitalization for unstable angina	224 (14.0)	207 (13.2)	0.92 (0.76–1.11)	0.374

Values in parentheses indicate percentage or range. *P* values determined by log-rank test. Hazard ratios represent 95% CI, except f

TABLE 3. Effect of Treatment on Number of Hospitalizations

	Low-Dose	High-Dose	Percent Reduction in High-Dose Group	*P*
Hospitalizations for any reason	4397	3819	13	0.021
Hospitalizations for cardiovascular reason	2923	2456	16	0.050
Hospitalization for heart failure	1576	1199	24	0.002
Hospitalization for ischemic events	543	432	20	0.085

P values are derived from the Wilcoxon rank sum test for between-group comparisons of the number of hospitalizations per patient.

Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

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Lancet 2009; 374: 1840–48

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See Comment page 1808

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Summary

Background Angiotensin-receptor blockers (ARBs) are effective treatments for patients with heart failure, but the relation between dose and clinical outcomes has not been explored. We compared the effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure.

Methods This double-blind trial was undertaken in 255 sites in 30 countries. 3846 patients with heart failure of New York Heart Association class II–IV, left-ventricular ejection fraction 40% or less, and intolerance to angiotensin-converting-enzyme (ACE) inhibitors were randomly assigned to losartan 150 mg (n=1927) or 50 mg daily (n=1919). Allocation was by block randomisation stratified by centre and presence or absence of β-blocker therapy, and all patients and investigators were masked to assignment. The primary endpoint was death or admission for heart failure. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00090259.

Findings Six patients in each group were excluded because of poor data quality. With 4·7-year median follow-up in each group (IQR 3·7–5·5 for losartan 150 mg; 3·4–5·5 for losartan 50 mg), 828 (43%) patients in the 150 mg group versus 889 (46%) in the 50 mg group died or were admitted for heart failure (hazard ratio [HR] 0·90, 95% CI 0·82–0·99; p=0·027). For the two primary endpoint components, 635 patients in the 150 mg group versus 665 in the 50 mg group died (HR 0·94, 95% CI 0·84–1·04; p=0·24), and 450 versus 503 patients were admitted for heart failure (0·87, 0·76–0·98; p=0·025). Renal impairment (n=454 *vs* 317), hypotension (203 *vs* 145), and hyperkalaemia (195 *vs* 131) were more common in the 150 mg group than in the 50 mg group, but these adverse events did not lead to significantly more treatment discontinuations in the 150 mg group.

Interpretation Losartan 150 mg daily reduced the rate of death or admission for heart failure in patients with heart failure, reduced left-ventricular ejection fraction, and intolerance to ACE inhibitors compared with losartan 50 mg daily. These findings show the value of up-titrating ARB doses to confer clinical benefit.

Funding Merck (USA).

HEAAL: Tod oder HI-Hospitalisierung

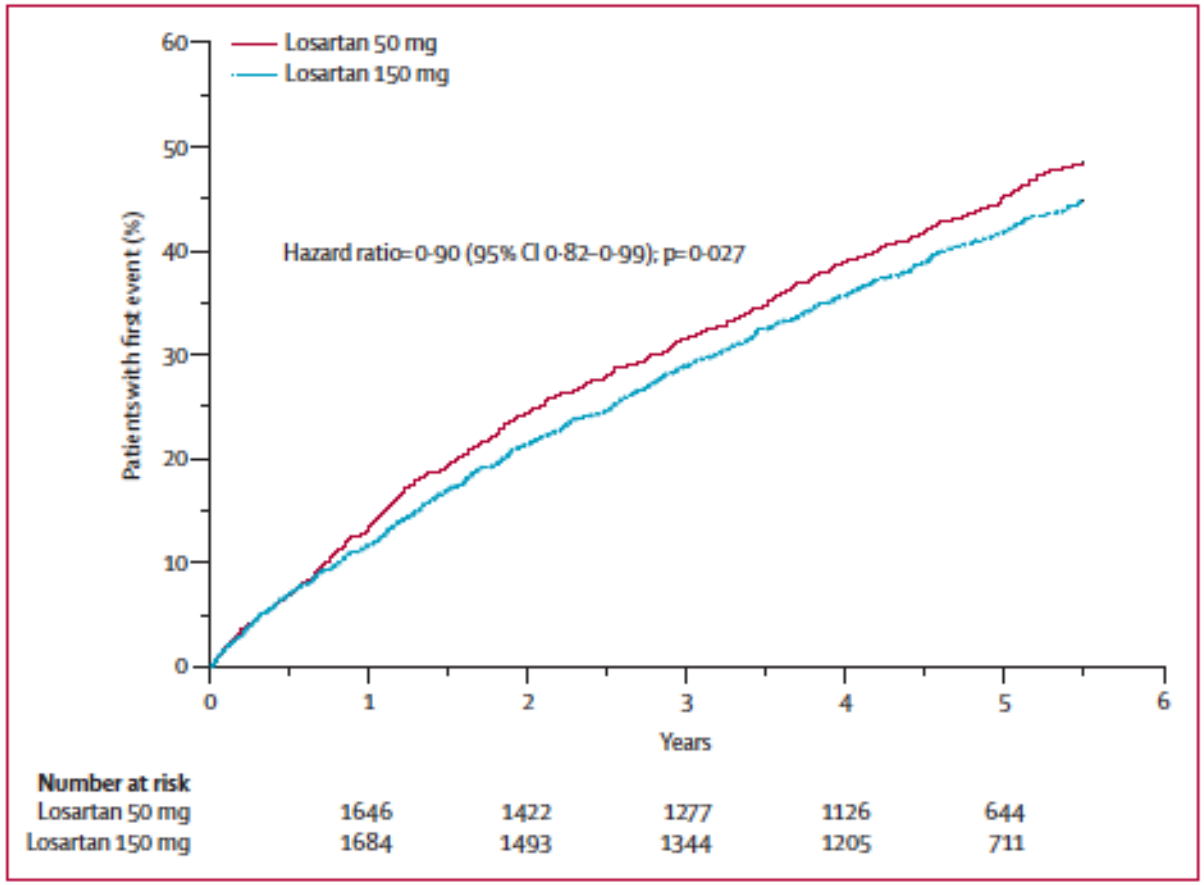

Figure 2: **Kaplan-Meier cumulative event curves for the primary composite endpoint of death or admission for heart failure**

Konstam et al. Lancet 2009; 374: 1840-48

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Heart Failure

Long-Term, Dose-Dependent Effects of Spironolactone on Left Ventricular Function and Exercise Tolerance in Patients With Chronic Heart Failure

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Verona, Italy

OBJECTIVES This study was designed to assess the effects of spironolactone (SP) on left ventricular (LV) function and exercise tolerance in patients with chronic heart failure (CHF).

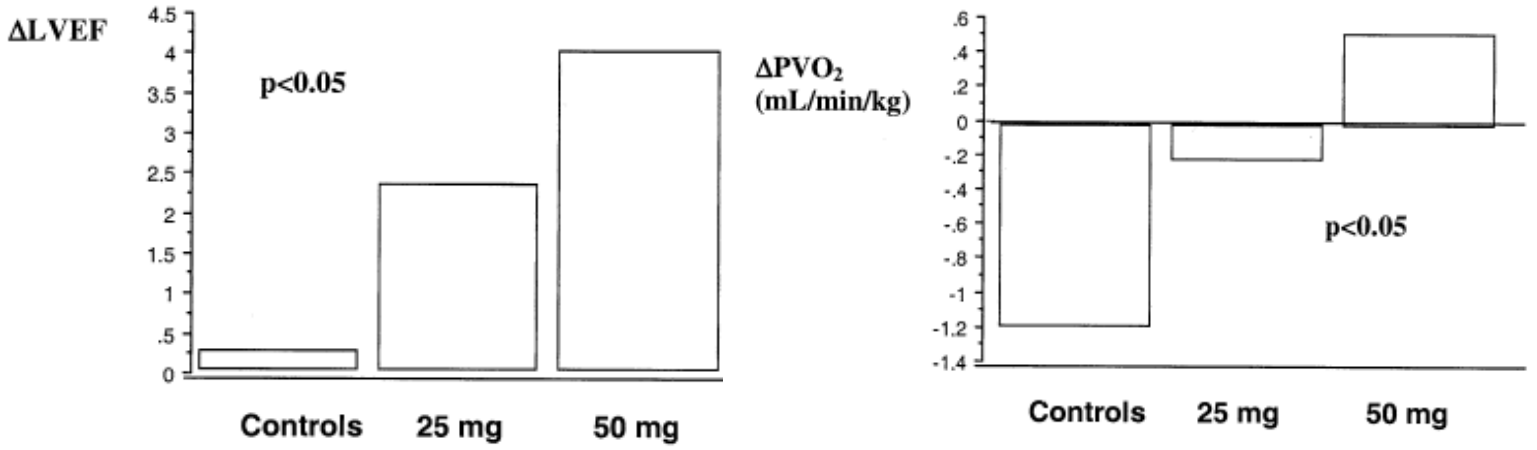
BACKGROUND In severe heart failure (HF), SP improves survival, but the underlying mechanisms are not clear.

METHODS We randomized 106 outpatients with HF to SP (12.5 to 50 mg/day) (group 1) or control (group 2). Complete echocardiography and cardiopulmonary exercise testing were performed at baseline and 12 months after randomization.

RESULTS Left ventricular end-systolic volume at baseline and at follow-up was 188 ± 94 ml and 171 ± 97 ml in group 1 and 173 ± 71 ml and 168 ± 79 ml in group 2 (treatment group-by-time interaction, $p = 0.03$). Left ventricular ejection fraction at baseline and at follow-up was 33 ± 7% and 36 ± 9% in group 1 and 34 ± 7% and 34 ± 9% in group 2 (treatment group-by-time interaction, $p = 0.02$). At baseline, 9 patients in group 1 and 3 patients in group 2 had a restrictive mitral filling pattern, a marker of severe diastolic dysfunction; at follow-up, 3 patients in group 1 and no patient in group 2 improved their pattern. No patient in group 1 and 4 patients in group 2 worsened their pattern (chi-square, $p = 0.02$). Peak oxygen consumption increased significantly in patients treated with 50 mg of SP and decreased in group 2 (17.7 ± 5.2 vs. 18.5 ± 5.9 and 19.1 ± 5.6 vs. 17.9 ± 5.3, respectively; analysis of variance, $p = 0.01$).

CONCLUSIONS Spironolactone improves LV volumes and function; furthermore, it improves exercise tolerance at the highest administered dose. Our data might explain the mortality reduction during aldosterone antagonism in patients with HF. (J Am Coll Cardiol 2002;40:304–10)

Spironolacton: dosisabhängige Effekte nach 12 Monaten



Cicoira et al., JACC 2002;40:304-10

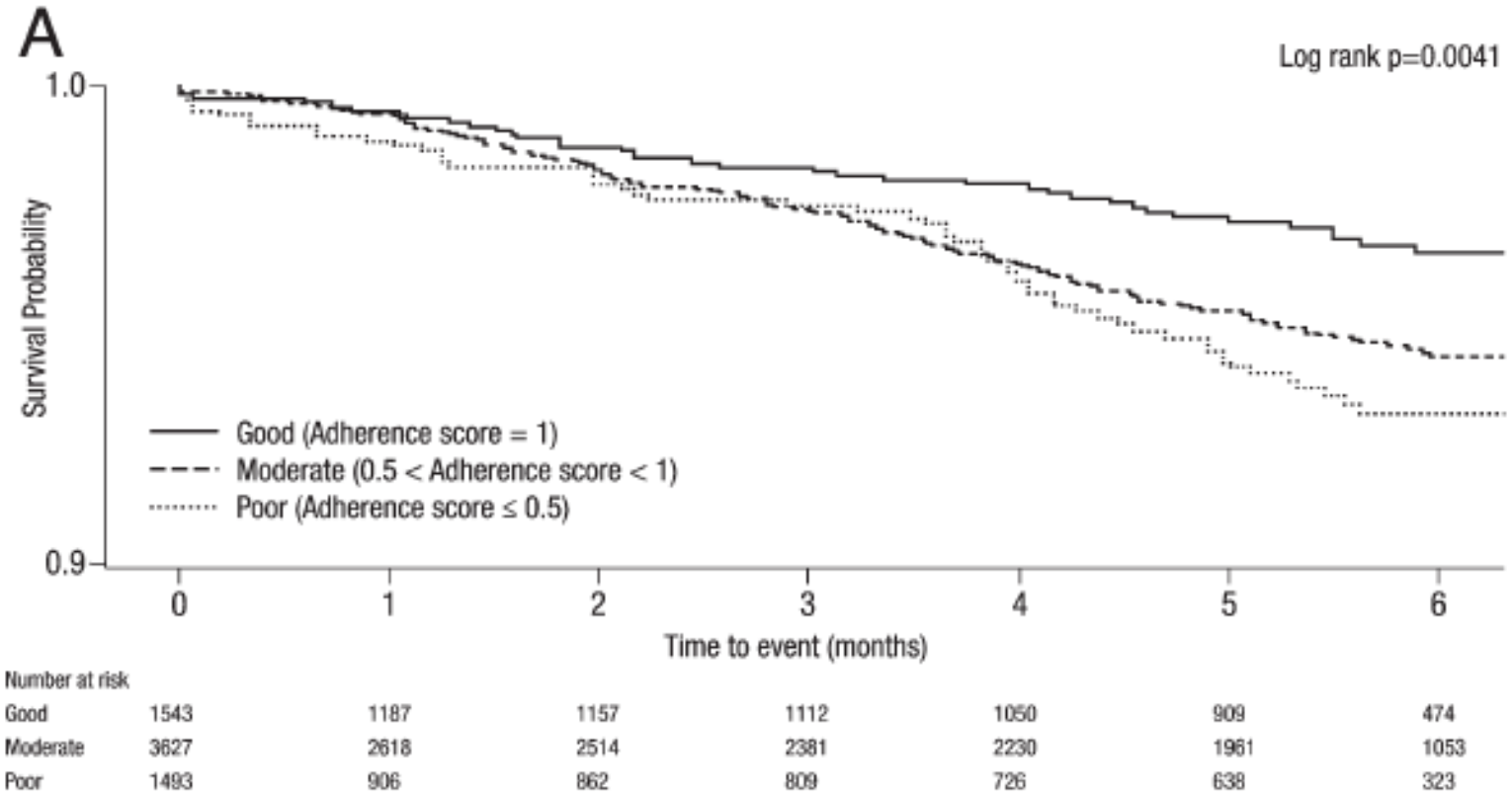
~~WIE~~ THERAPIERT MAN HERZINSUFFIZIENZ?

Table 1. Heart failure medication and adherence in men and women during the study period

	Total ($n = 36\,829$)	Men ($n = 16\,496$)	Women ($n = 20\,333$)	p-value men versus women
At least one prescription filled (%)				
ACEI/ARB	76.4	79.1	74.2	<0.001
Beta-blocker	67.7	70.6	65.4	<0.001
Aldosterone antagonists	47.2	50.0	44.9	<0.001
Diuretics	87.8	86.7	88.6	<0.001
Cardiac glycosides	26.9	24.1	29.2	<0.001
Adherence (%)				
ACEI/ARB	49.3	52.2	47.1	<0.001
Beta-blocker	40.4	42.8	38.4	<0.001
Aldosterone antagonists	16.1	17.3	15.2	<0.001
Diuretics	53.3	51.2	55.0	<0.001
Cardiac glycosides	4.3	4.0	4.6	0.006

Marzluf et al., Pharmacoepidemiology and drug safety 2015; 24: 722–730

Guideline-Adhärenz und Sterberate



Number at risk							
Good	1543	1187	1157	1112	1050	909	474
Moderate	3627	2618	2514	2381	2230	1961	1053
Poor	1493	906	862	809	726	638	323

Komajda et al, EHJ 2017; 19: 1414–1423

Dosisreduktion *(Enalapril oder Sacubitril/Valsartan)* **und Sterberate**

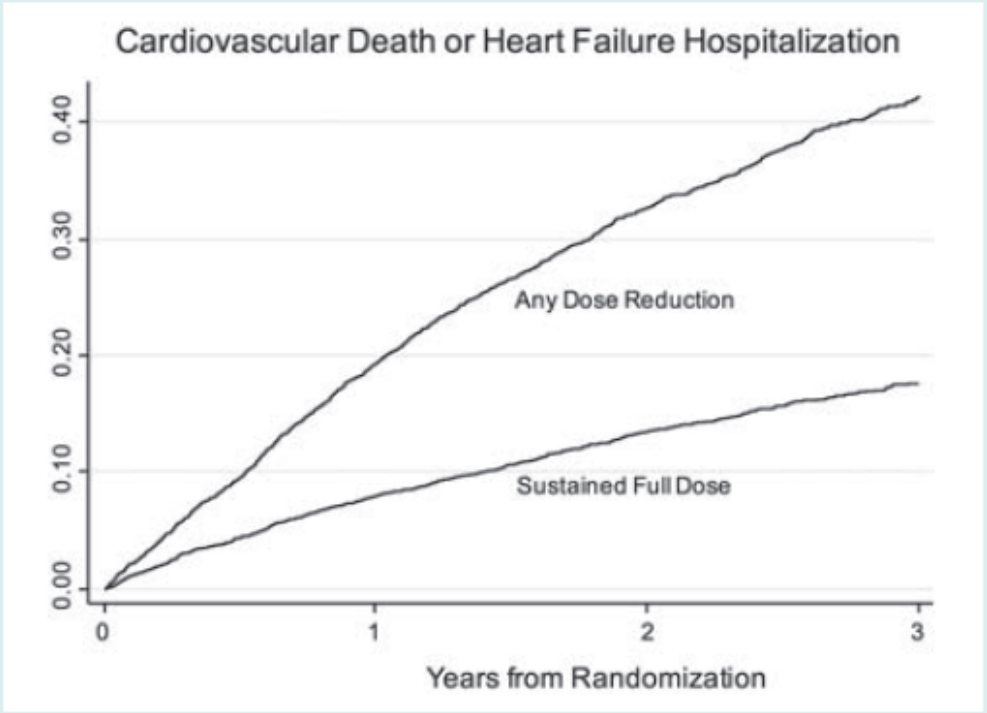
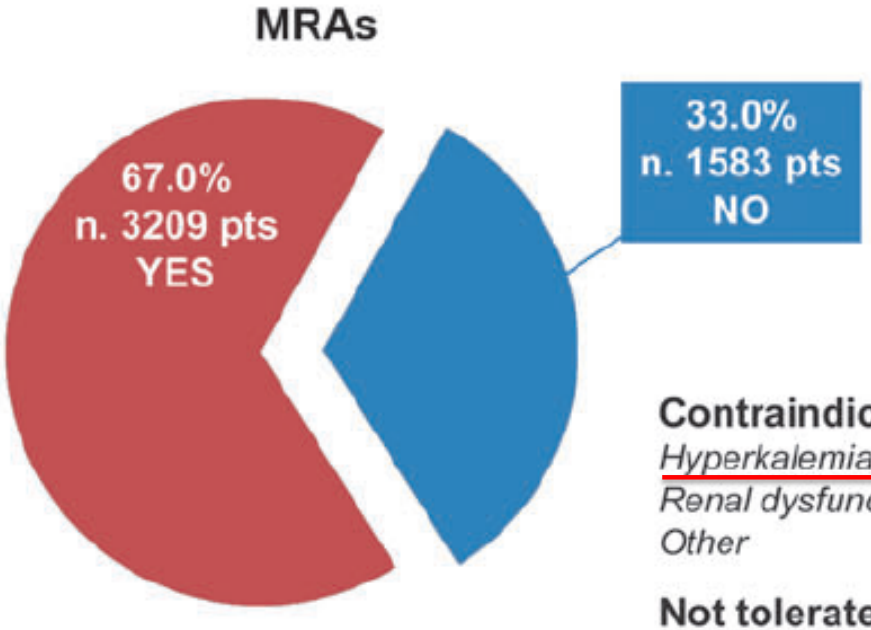


Figure 1 Kaplan–Meier curves showing primary outcome events by dose reduction status. Participants with a dose reduction had a higher risk of the primary event compared with those who remained on full study medication doses.

Vardeny et al. EJHF 2016 (PARADIGM-HF)

GRÜNDE FÜR MANGELNDE THERAPIEADHÄRENZ

ESC Heart Failure Long-Term Registry: 12 440 Patients

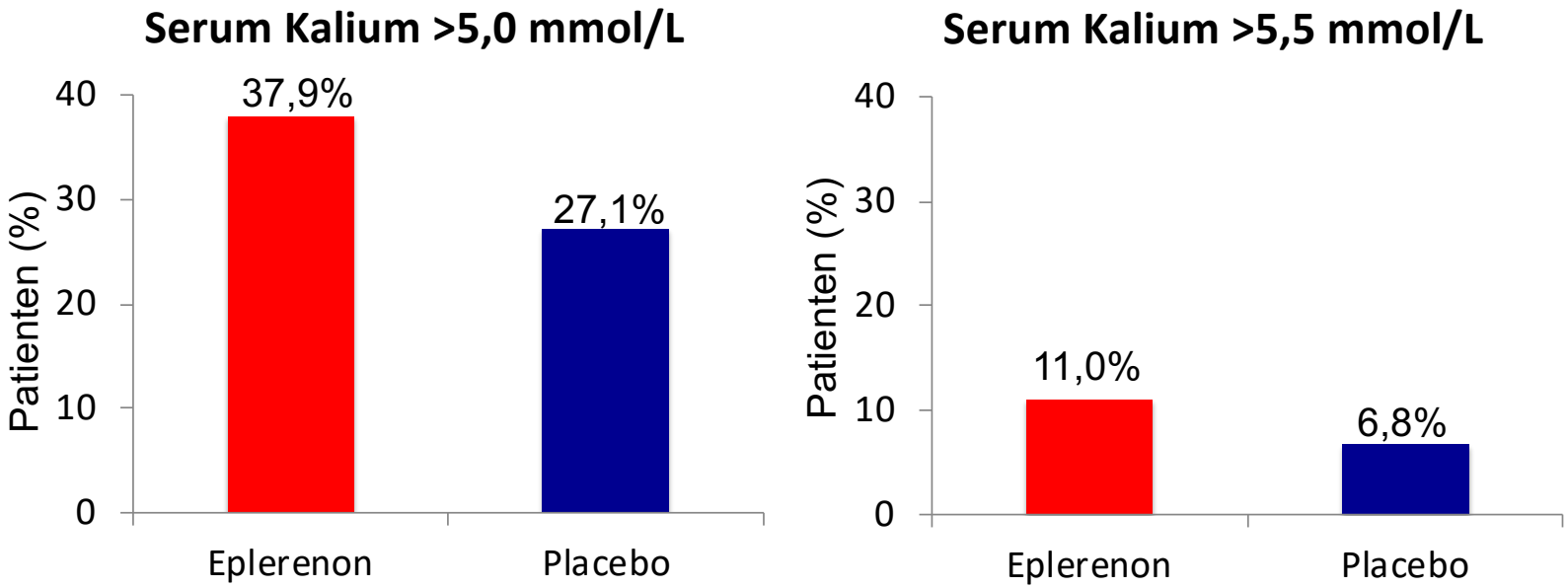


Contraindicated	**n. 268 (5.6%)**
Hyperkalemia	*n. 94 (35.1%)*
Renal dysfunction	*n. 153 (57.1%)*
Other	*n. 21 (7.8%)*
Not tolerated	**n. 147 (3.1%)**
Hyperkalemia	*n. 53 (36.1%)*
Worsening renal function	*n. 34 (23.1%)*
Gynecomastia	*n. 34 (23.1%)*
Other	*n. 26 (17.7%)*
Not indicated	**n. 908 (18.9%)**
Real undertreatment	**n. 260 (5.4%)**

MRAs=mineralcorticoid receptor antagonists

Maggioni EJHF 2013

Herzinsuffizienz: Hyperkaliämie bei MRA (EMPHASIS-HF)



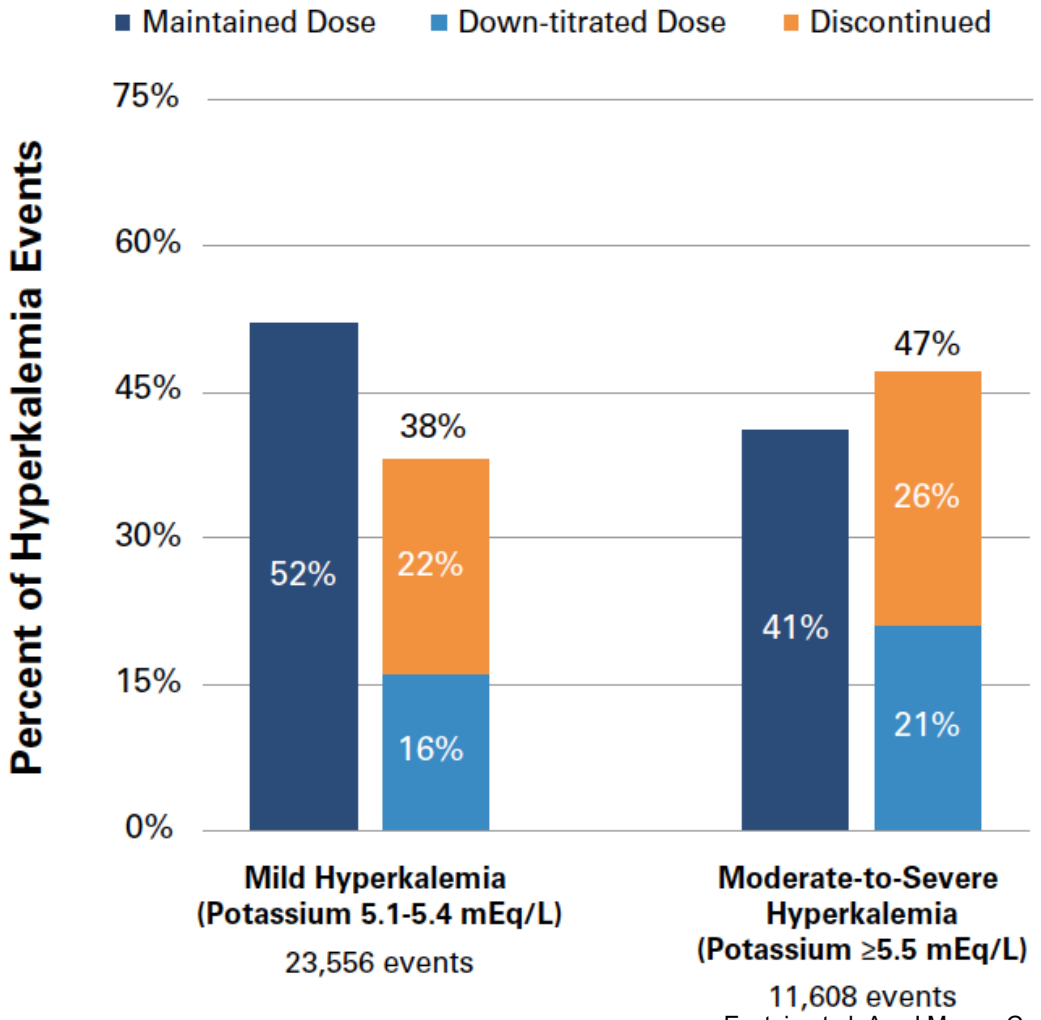
Rossignol Circulation: Heart Failure 2014: 7; 52-58.

Hyperkaliämie >6 mmol/L bei Herzinsuffizienztherapie mit MRA

Trial	Treatments	> 6,0 mmol/L
RALES[1,2]	Spironolactone vs placebo	2%
EMPHASIS-HF[3,4]	Eplerenone vs placebo	2.5%

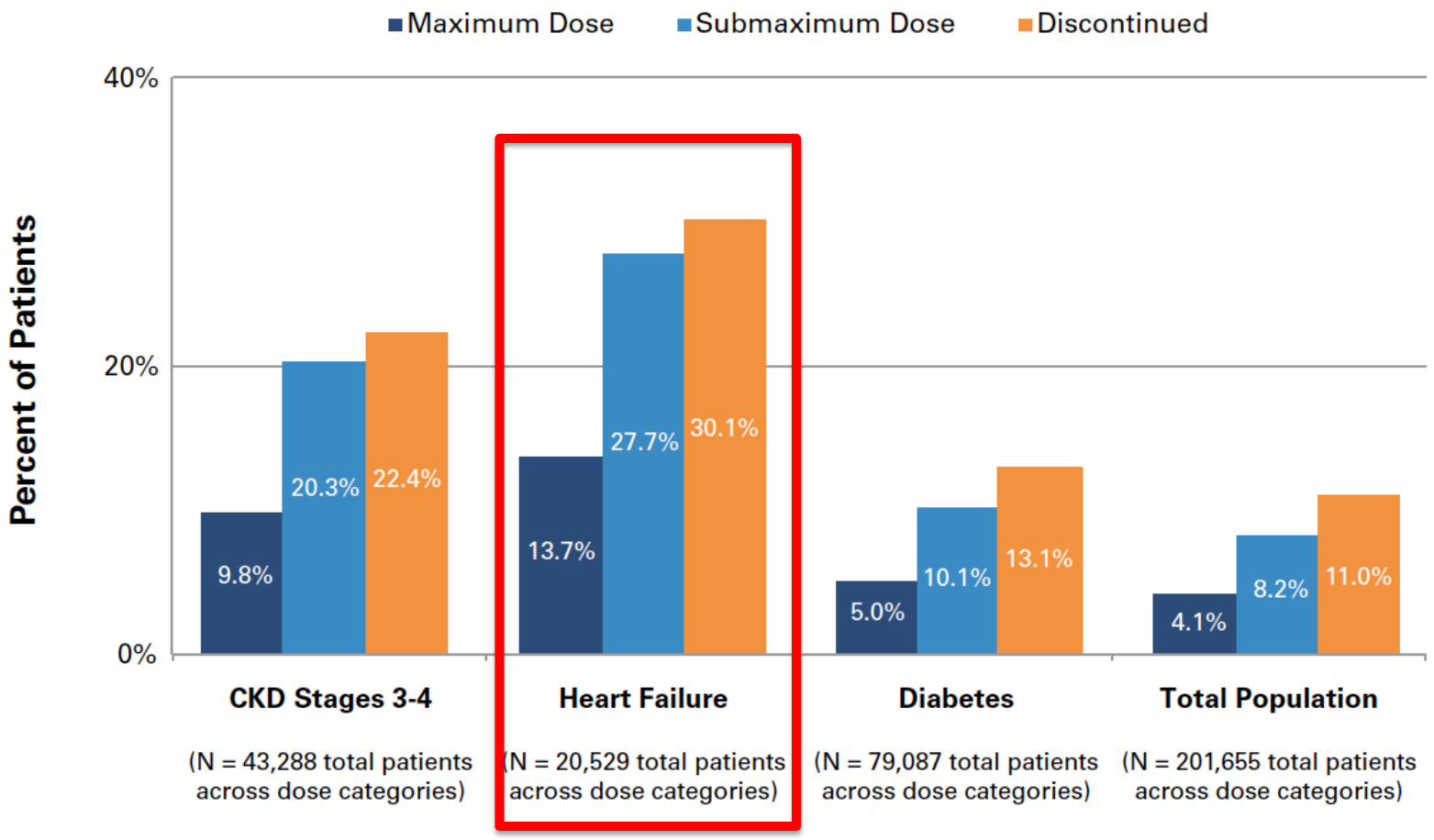
1.Pitt B, et al. N Engl J Med. 1999;341:709-717;
2. The RALES Investigators. Am J Cardiol. 1996;78:902-907;
3. Zannad F, et al. N Engl J Med. 2011;364:11-21;
4. Eschalier R, et al. J Am Coll Cardiol 2013;62:1585-1593;

Hyperkaliämie und Änderung der RAAS-I Dosis



Epstein et al. Am J Manag Care. 2015;21:S212-S220

Änderung der RAAS-I Dosis und Mortalität



Epstein et al. Am J Manag Care. 2015;21:S212-S220

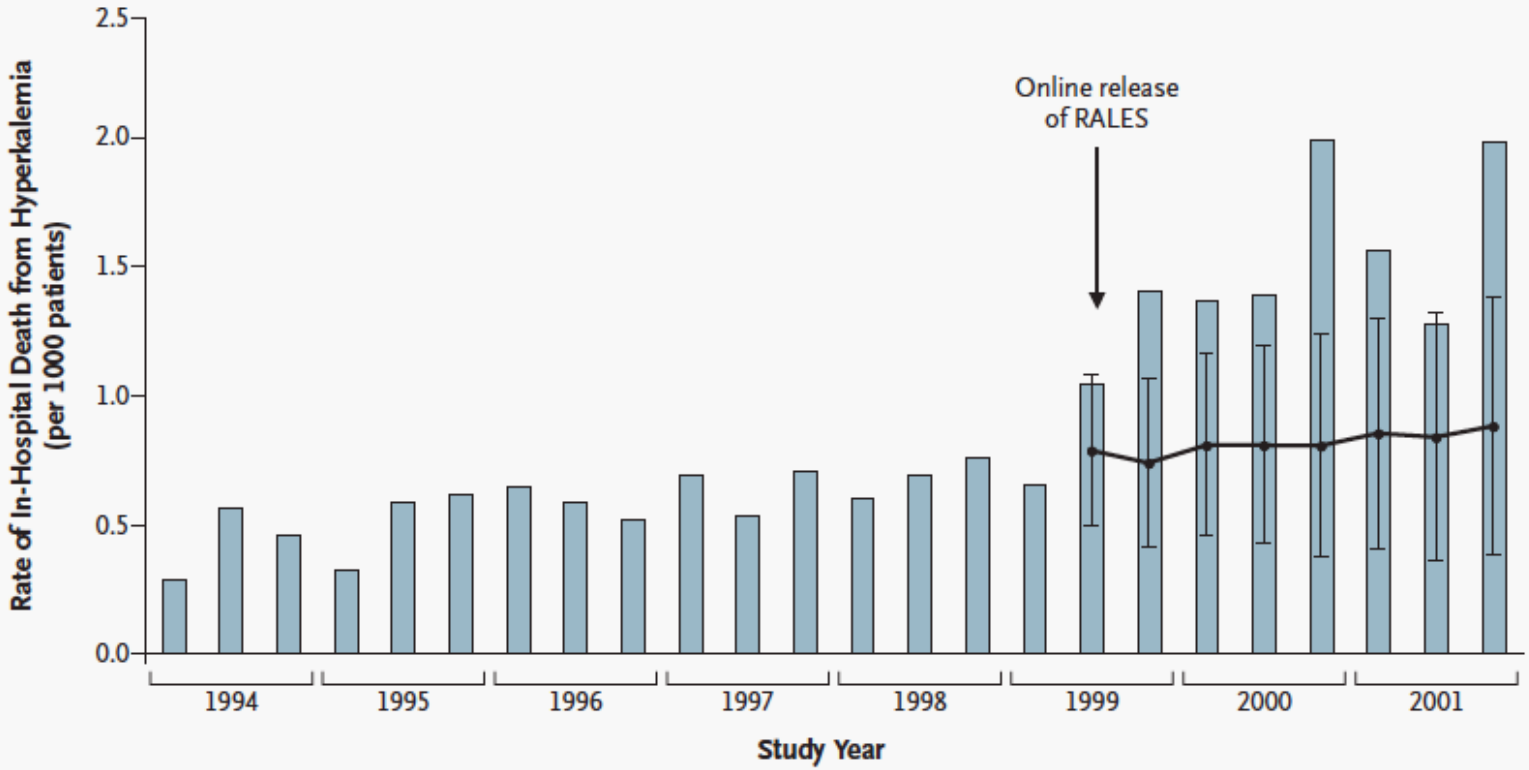


Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

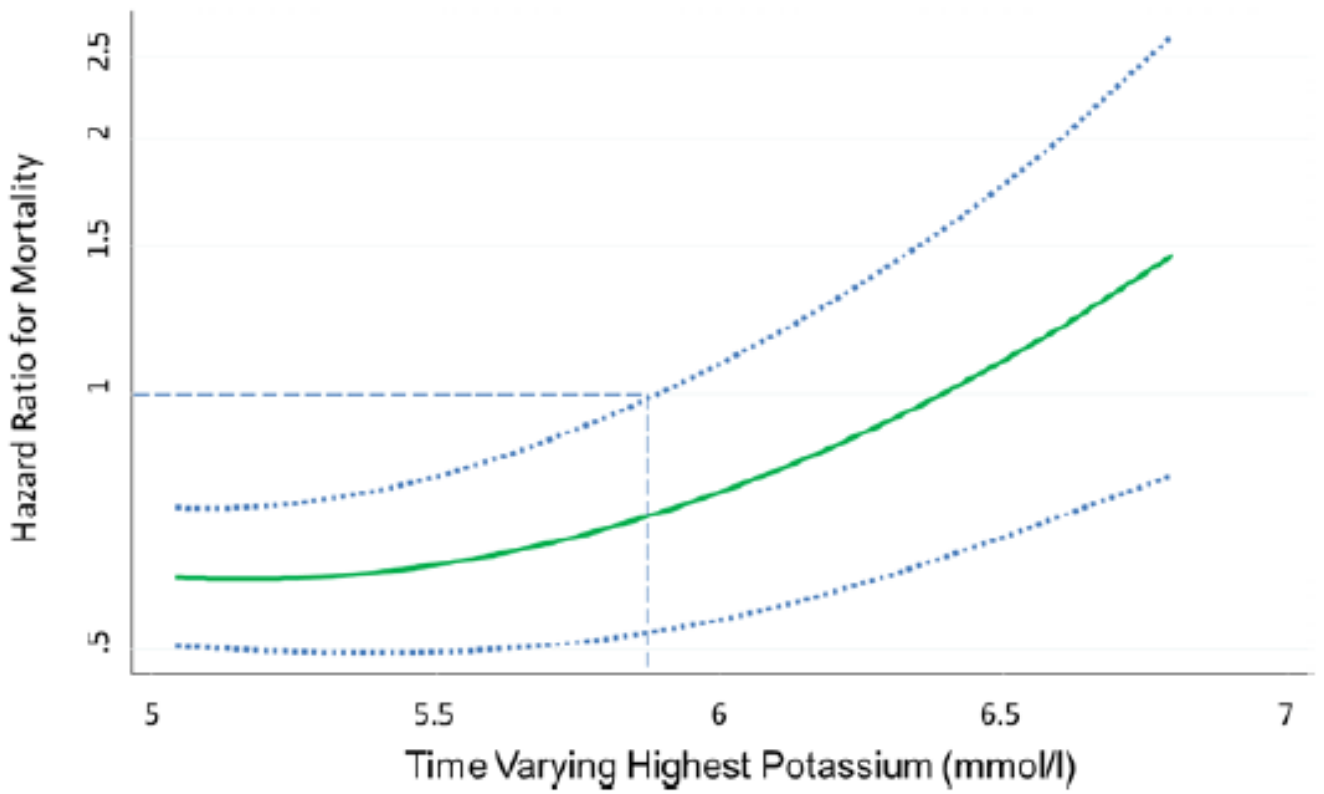
Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Juurlink NEJM 2004

WELCHER KALIUMSPIEGEL IST NOCH OK?

Was sagen die Daten?

Welches Kalium ist noch ok?



Vardeny Circ Heart Fail 2014

Welches Kalium ist noch ok?

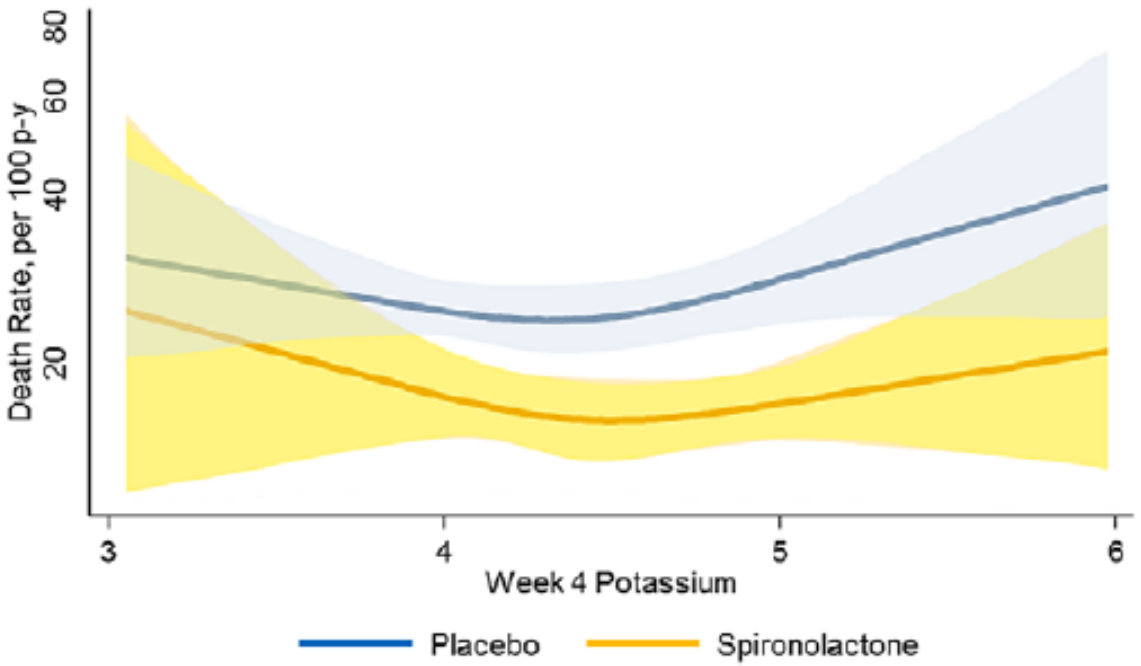


Figure 3. Rates of death after visit 2 (4 weeks) by treatment, based on serum potassium levels at visit 2. Mortality rates were higher in participants randomized to placebo when compared with those taking spironolactone at all potassium levels. $P<0.0001$ for comparison between spironolactone and placebo. Shaded areas represent 95% confidence intervals.

Vardeny Circ Heart Fail 2014

WELCHER KALIUMSPIEGEL IST NOCH OK?

Was sagen die Guidelines?

Table 3 Existing recommendations on renin angiotensin aldosterone system inhibitors use according to K^+ levels

K^+ levels	Recommendation
>6	Stop RAASi (ESC HF,[20] NICE[7])
>5.5 mEq/L	Reduce dose of/stop ACEI/ARB (K/DOQI[55–57])
5.1–5.5	K/DOQI (e): take measures to lower K^+ when initiating RAASI
>5	Do not start RAASis if >5.0 (K/DOQI,[55–57] HFSA HF,[63] NICE[7])
	Reduce dose of/stop RAASi if >5-0 (ACCF/AHA HF,[18] ESC HF,[20] K/DOQI[55–57])
	MRA not recommended if >5.0 (HFSA HF[63])
	Maintain MRA between 4.0 and 5.0 (ACA/AHA[18])
	Do not routinely offer a RAASi to people with CKD if their pre-treatment K^+ levels are >5.0 mEq/L
	A K^+ lowering agent should be started.
4.5–5	In patients not on maximal guideline-recommended target dose of RAASI therapy, it is recommended to up-titrate/start RAASi therapy and closely monitor K^+ levels.

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URSACHEN DER HYPERKALIÄMIE

Hyperkaliämie: 1) erhöhte Zufuhr

a. Potassium supplements
b. Salt substitute (e.g. DASH)
c. Fruits (bananas, melons, orange juice)
d. Alfalfa
e. Amino acids (aminocaproic acid, arginine, lysine)
f. Dandelion
g. Dried toad skin
h. Hawthorne berry
i. Horsetail
j. Liliy of the valley
k. Milkweed
l. Nettle
m. Noni juice
n. Siberian ginseng
o. Stored blood products

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Hyperkaliämie: 2) reduzierte Ausscheidung

a. Potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride)
b. Beta-blockers v.a. nicht-selektive BB
c. NSAIDs
d. Sacubitril/valsartan
e. Renin-angiotensin-aldosterone inhibitors (RAASi): ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists
f. Direct renin inhibitors (aliskiren)
g. Mannitol
h. Cyclosporine or tacrolimus
i. Pentamidine
j. Trimethoprim-sulfamethoxazole
k. Heparin
l. Digitalis
m. Calcineurin inhibitors
n. Penicillin G

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Hyperkaliämie: 2) reduzierte Ausscheidung

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j. Trimethoprim-sulfamethoxazole

k. Heparin

l. Digitalis

m. Calcineurin inhibitors

n. Penicillin G

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HYPERKALIÄMIE BEI HERZINSUFFIZIENZ: WAS NUN?

Behandlung der Hyperkalämie

Table 2 **Treatment of acute or chronic hyperkalaemia**

Promote update of K^+ into the intracellular space	Stimulate Na+/K+-ATPase: • β2-adrenergic agonists (IV, nebulized) • Insulin (IV) ± glucose • Sodium bicarbonate (if metabolic acidosis) • Combination cocktails
Cardiac membrane stabilization	• Calcium chloride or gluconate (IV) • Hypertonic saline (3–5%)
Increase K^+ elimination	• Loop diuretics (IV, oral) to increase renal K^+ excretion • Haemodialysis for removal of K^+ from blood • Cation-exchange resins (sodium polystyrene sulfonate) to enhance faecal K^+ excretion (PO, PR) • Sodium bicarbonate alkalinizes the urine and increases urinary K+ excretion • New K^+ binders: patiromer, sodium zirconium cyclosilicate
Other	• Fludrocortisone (PO) in aldosterone deficiency

IV, intravenous; PO, per os (orally); PR, per rectum; Na, sodium; K, potassium; IV, intravenous; PO, per os.

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Patients	Recommendation
Chronic or recurrent hyperkalaemia on RAASi therapy	An approved K^+-lowering agent may be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified
Chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAASi	RAASi should be optimised and an approved K^+-lowering agent may be initiated as soon as confirmed K^+ levels are >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified
K+ levels of 4.5–5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy	Initiate/up-titrate RAASi therapy and closely monitor K^+ levels. If K^+ levels rise above 5.0 mEq/L, initiate an approved K^+-lowering agent
K+ levels of >5.0–≤6.5 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy	Initiate an approved K^+-lowering agent. If levels <5.0 mEq/L are detected, up-titrate RAASi - K+ level should be closely monitored and K+ lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified
K+ levels of >5.0–≤6.5 mEq/L on maximal tolerated, guideline-recommended target dose of RAASi therapy	Treatment with a K^+ lowering agent may be initiated. K^+ level should be closely monitored and K+ lowering treatment should be maintained unless alternative treatable aetiology for hyperkalaemia is identified
K+ levels of >6.5 mEq/L on either maximal sub-maximal tolerated, guideline-recommended target dose of RAASi therapy	Discontinue/reduce RAASi. Treatment with a K^+ lowering agent may be initiated as soon as K^+ levels >5.0 mEq/l. K^+ level should be closely monitored

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Hyperkaliämie bei HI: ESC-Consensus

Kalium (mmol/L)	RAAS-I Dosis	Prozedere
4,5-5,0	**submaximal**	**Start/Steigerung RAAS-I**, engmaschige K^+ Kontrollen, **falls K^+ >5,0 -> K^+-Senker**
>5,0-6,5	**maximal**	**K^+-Senker** beginnen und beibehalten, falls keine andere reversible Ursache für Hyperkaliämie gefunden
>5,0-6,5	**submaximal**	**K^+-Senker, sobald K^+ <5,0 -> Start/Steigerung RAAS-I**, engmaschige K^+ Kontrollen, K^+-Senker beibehalten, falls keine andere reversible Ursache für Hyperkaliämie gefunden
>6,5	**maximal oder submaximal**	**RAAS-I stoppen/reduzieren, K^+-Senker** beginnen und beibehalten, falls keine andere reversible Ursache für Hyperkaliämie gefunden

Übersetzt und modifiziert - Rosano et al. EHJ- Cardiovasc Pharmacother (2018) 4, 180–188

ESC-Consensus auf den Punkt gebracht...

2 Ziele:

1. **RAAS-I steigern** - bis Zieldosis

2. **K^+ <5,5mmol/L halten** - Optimierungsmaßnahmen
   oder Kaliumsenker

WELCHE KALIUMSENKER STEHEN UNS ZUR VERFÜGUNG?

Kalium-Senker

	Natrium Polystyren-Sulfonat	Patiromer	Natrium Zirkonium Zyklosilikat
Mechanismus	Unspezifische Kationen-Bindung im Austausch gegen Na^+	K^+-Bindung im Austausch gegen Ca++	K^+-Bindung im Austausch gegen Na+ und H^+
Zeit bis Normokaliämie	Unbekannt und unbestätigt (Tage bis Wochen?)	1 Wo, 84% erreichen Zielwert in 24h, 98% in 48h	84% innerhalb 24h
Wirkungsort	Kolon	Distales Kolon	Ob. und unt. GI-Trakt?
Medikamenten-Interaktion	Antazida, Laxantien, Digitalis, Sorbit, Lithium, Thyroxin	Keine, wenn 3h Abstand	Keine?
NW	Schlechte Toleranz/Adhärenz. Darmnekrosen, Hypokaliämie, GI-NW, E-lytstörungen.	Gut toleriert. Hypomagnesiämie, leichte/mittelgradige Obstipation	Gut toleriert. Ödeme, GI-NW, Hypokaliämie
Zulassung:	US: 1958, Ö: ?	US: 2015 EU: 2017	US: 2018 EU: 2018

Kalium-Senker

	Natrium Polystyren-Sulfonat	Patiromer	Natrium Zirkonium Zyklosilikat
Mechanismus	Unspezifische Kationen-Bindung im Austausch gegen Na^+	K^+-Bindung im Austausch gegen Ca++	K^+-Bindung im Austausch gegen Na+ und H^+
Zeit bis Normokaliämie	Unbekannt und unbestätigt (Tage bis Wochen?)	1 Wo, 84% erreichen Zielwert in 24h, 98% in 48h	84% innerhalb 24h
Wirkungsort	Kolon	Distales Kolon	Ob. und unt. GI-Trakt?
Medikamenten-Interaktion	Antazida, Laxantien, Digitalis, Sorbit, Lithium, Thyroxin	Keine, wenn 3h Abstand	Keine?
NW	Schlechte Toleranz/Adhärenz. Darmnekrosen, Hypokaliämie, GI-NW, E-lytstörungen.	Gut toleriert. Hypomagnesiämie, leichte/mittelgradige Obstipation	Gut toleriert. Ödeme, GI-NW, Hypokaliämie
Zulassung:	US: 1958, Ö: ?	US: 2015 EU: 2017	US: 2018 EU: 2018

Kalium-Senker

	Natrium Polystyren-Sulfonat	Patiromer	Natrium Zirkonium Zyklosilikat
Mechanismus	Unspezifische Kationen-Bindung im Austausch gegen Na^+	K^+-Bindung im Austausch gegen Ca++	K^+-Bindung im Austausch gegen Na+ und H^+
Zeit bis Normokaliämie	Unbekannt und unbestätigt (Tage bis Wochen?)	1 Wo, 84% erreichen Zielwert in 24h, 98% in 48h	84% innerhalb 24h
Wirkungsort	Kolon	Distales Kolon	Ob. und unt. GI-Trakt?
Medikamenten-Interaktion	Antazida, Laxantien, Digitalis, Sorbit, Lithium, Thyroxin	Keine, wenn 3h Abstand	Keine?
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Zulassung:	US: 1958, Ö: ?	US: 2015 EU: 2017	US: 2018 EU: 2018

PATIROMER

Die Key Facts zuerst...

Patiromer

Veltassa 8,4 g Pulver zur Herstellung einer Suspension zum Einnehmen
Veltassa 16,8 g Pulver zur Herstellung einer Suspension zum Einnehmen
Veltassa 25,2 g Pulver zur Herstellung einer Suspension zum Einnehmen

Patiromer

Dosierung

Die empfohlene Anfangsdosis liegt bei 8,4 g Patiromer einmal täglich.

Die Tagesdosis kann je nach Serumkaliumspiegel und gewünschtem Zielbereich in wöchentlichen oder auch längeren Intervallen angepasst werden. Die Tagesdosis kann um jeweils 8,4 g erhöht oder gesenkt werden, je nachdem was zum Erreichen des Zielbereichs erforderlich ist. Die maximale Dosis beträgt 25,2 g täglich. Wenn das Serumkalium unter den gewünschten Bereich fällt, sollte die Dosis reduziert oder die Behandlung abgebrochen werden.

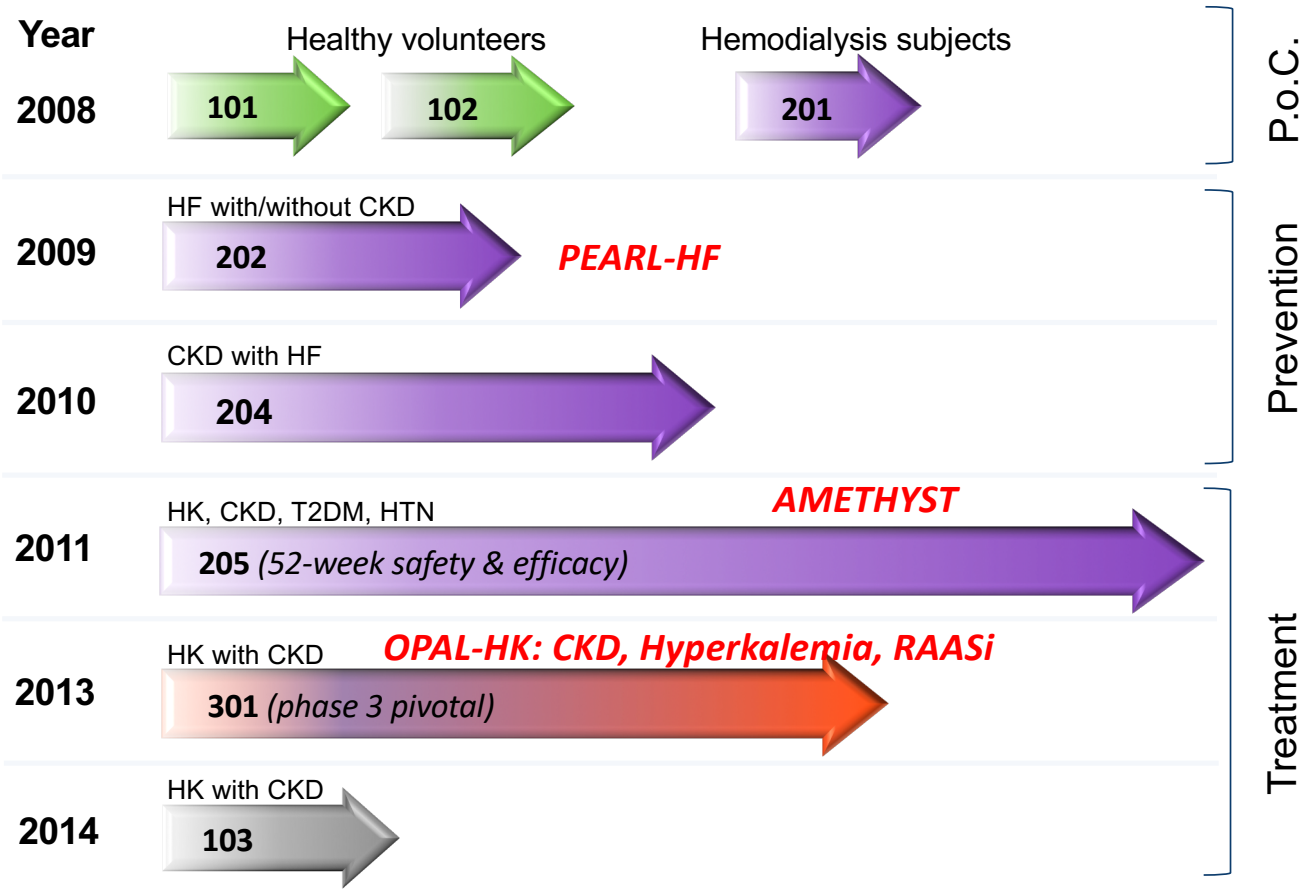
Wenn die Einnahme einer Dosis vergessen wird, sollte diese Dosis möglichst bald noch am selben Tag eingenommen werden. Die vergessene Dosis sollte nicht mit der nächsten Dosis zusammen eingenommen werden.

Die Einnahme von Veltassa sollte im Abstand von 3 Stunden zu anderen oral einzunehmenden Arzneimitteln erfolgen (siehe Abschnitt 4.5).

PATIROMER

Ein paar Studiendaten...

Patiromer Clinical Development



PATIROMER

Ein paar Studiendaten:

1) Senkt es das Kalium?

2) Ermöglicht es mehr RAAS-I bei Herzinsuffizienz?

Original Investigation

Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease

The AMETHYST-DN Randomized Clinical Trial

George L. Bakris, MD; Bertram Pitt, MD; Matthew R. Weir, MD; Mason W. Freeman, MD; Martha R. Mayo, PharmD; Dahlia Garza, MD; Yuri Stasiv, PhD; Rezi Zawadzki, DrPH; Lance Berman, MD; David A. Bushinsky, MD; for the AMETHYST-DN Investigators

IMPORTANCE Hyperkalemia is a potentially life-threatening condition predominantly seen in patients treated with renin-angiotensin-aldosterone system (RAAS) inhibitors with stage 3 or greater chronic kidney disease (CKD) who may also have diabetes, heart failure, or both.

OBJECTIVES To select starting doses for a phase 3 study and to evaluate the long-term safety and efficacy of a potassium-binding polymer, patiromer, in outpatients with hyperkalemia.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, multicenter, open-label, dose-ranging, randomized clinical trial (AMETHYST-DN), conducted at 48 sites in Europe from June 2011 to June 2013 evaluating patiromer in 306 outpatients with type 2 diabetes (estimated glomerular filtration rate, 15 to <60 mL/min/1.73 m^2 and serum potassium level >5.0 mEq/L). All patients received RAAS inhibitors prior to and during study treatment.

INTERVENTIONS Patients were stratified by baseline serum potassium level into mild or moderate hyperkalemia groups and received 1 of 3 randomized starting doses of patiromer (4.2 g [n = 74], 8.4 g [n = 74], or 12.6 g [n = 74] twice daily [mild hyperkalemia] or 8.4 g [n = 26], 12.6 g [n = 28], or 16.8 g [n = 30] twice daily [moderate hyperkalemia]). Patiromer was titrated to achieve and maintain serum potassium level 5.0 mEq/L or lower.

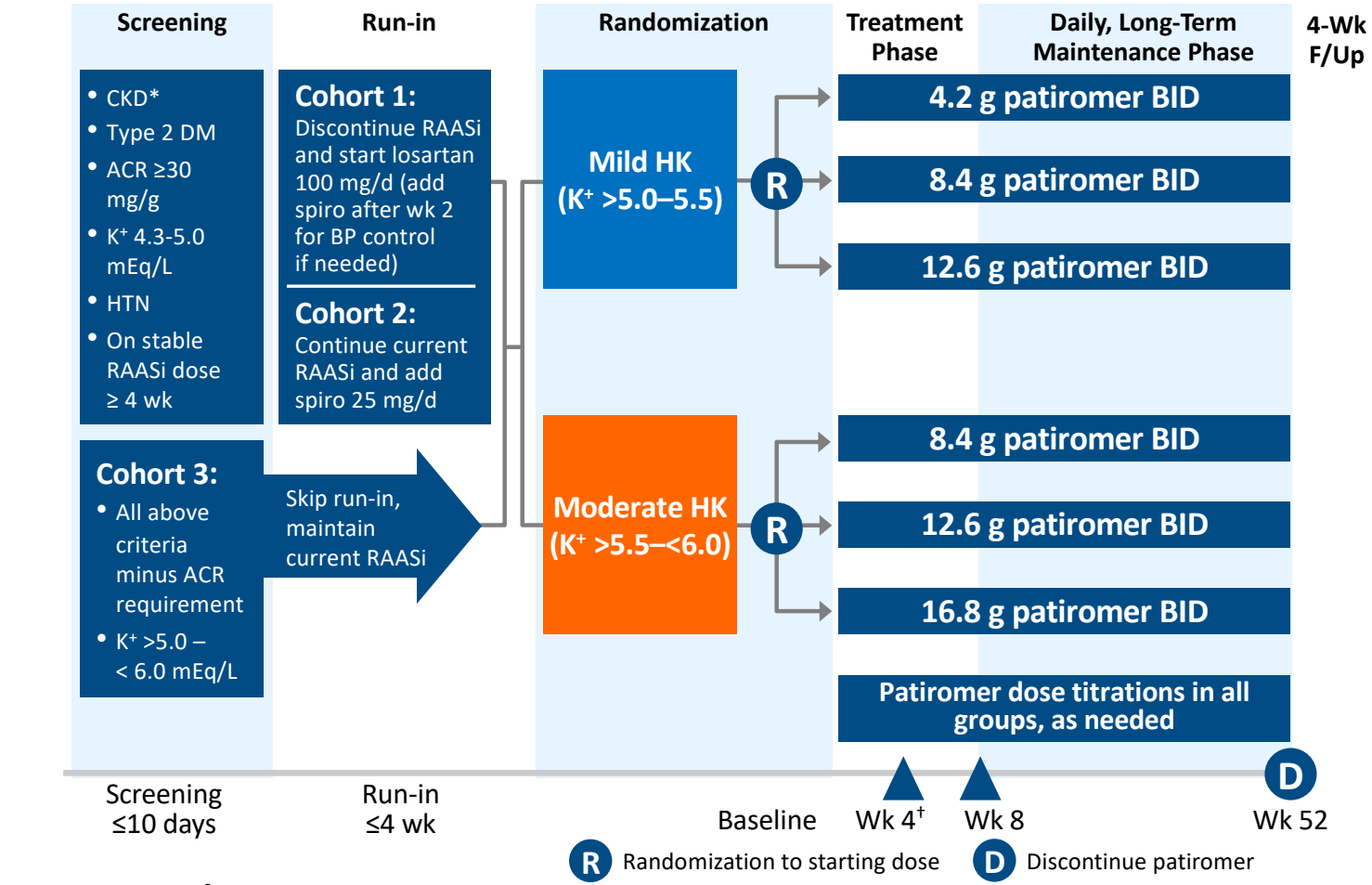
MAIN OUTCOMES AND MEASURES The primary efficacy end point was mean change in serum potassium level from baseline to week 4 or prior to initiation of dose titration. The primary safety end point was adverse events through 52 weeks. Secondary efficacy end points included mean change in serum potassium level through 52 weeks.

Editorial page 129

Supplemental content at jama.com

Bakris JAMA 2015

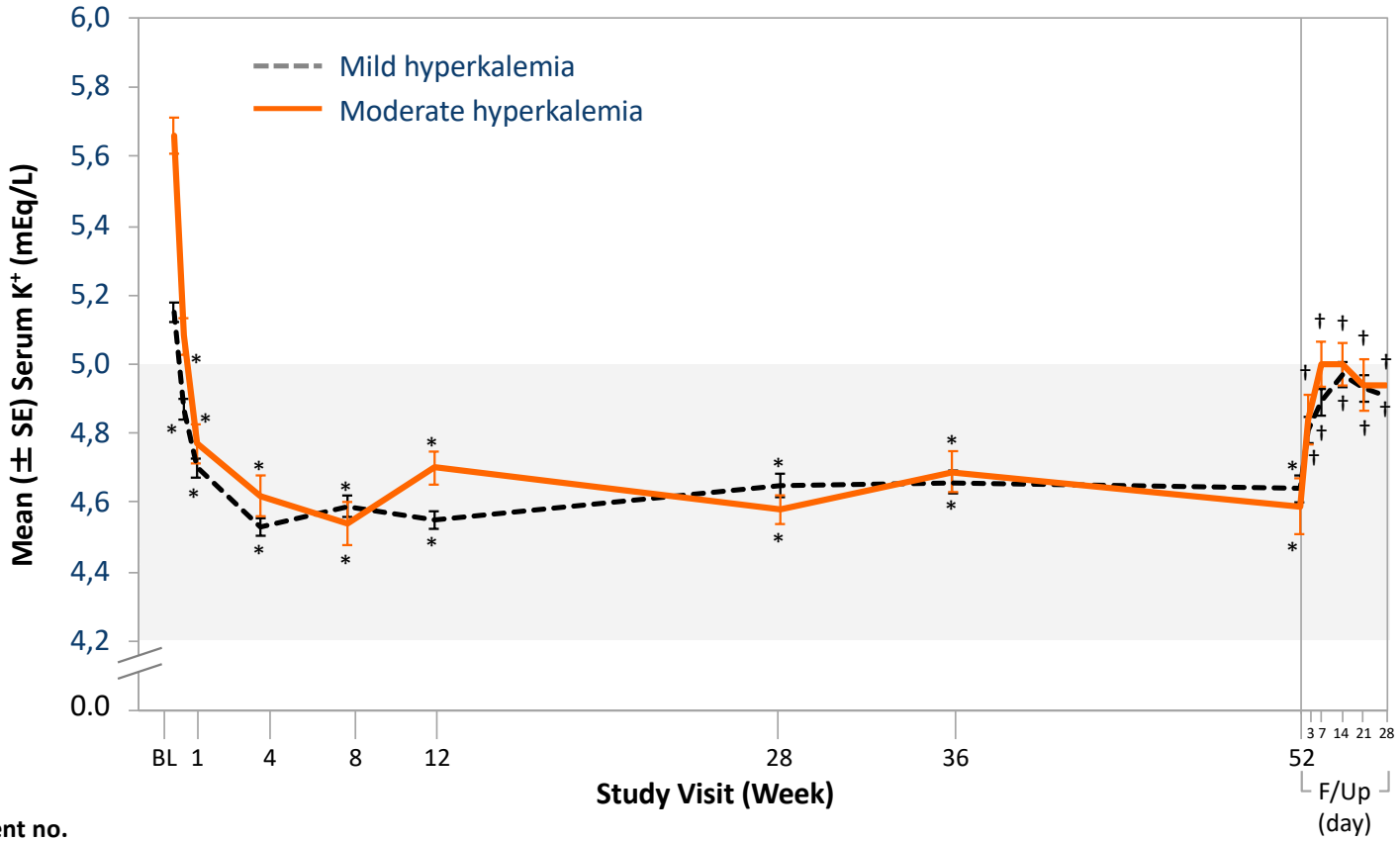
Study Design: *AMETHYST*



*eGFR 15-60 ml/min/m^2
†Primary endpoint

Bakris G., et al., ASN 2014

AMETHYST: Change in serum K+ baseline - week 52



Patient no.								
Mild HK:	218	204	199	192	175	163	156	145
Moderate HK:	83	83	73	70	65	61	53	49

All serum K^+ analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum K^+ value at baseline and therefore are not included in the analysis at this timepoint. *p<0.001 by t-test for change from baseline. †p≤0.001 by t-test for change from Week 52 (or from the last dose of patiromer received during the study). BL, baseline; F/Up, follow-up; HK, hyperkalemia.

Bakris G., et al., ASN 2014

AMETHYST: Botschaft

- Patiromer reduziert dauerhaft (52 Wochen) das Serumkalium bei Patienten mit Hyperkaliämie und chronischer Niereninsuffizienz

European Heart Journal (2011) 32, 820–828
doi:10.1093/eurheartj/ehq502

FASTTRACK CLINICAL

Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial

Bertram Pitt[1]*, Stefan D. Anker[2,3], David A. Bushinsky[4], Dalane W. Kitzman[5], Faiez Zannad[6], and I-Zu Huang[7], on behalf of the PEARL-HF Investigators

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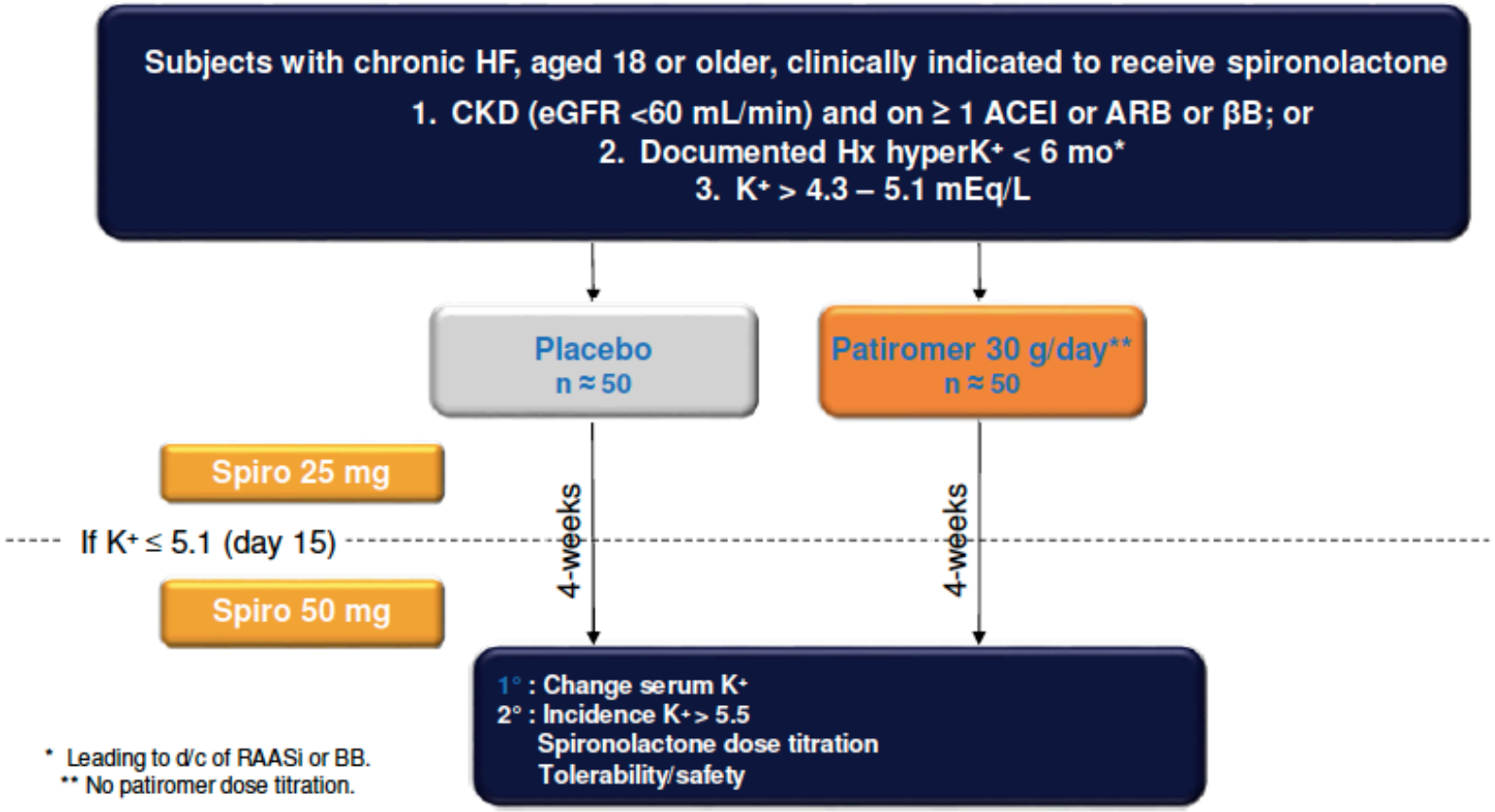
Received 10 September 2010; revised 3 December 2010; accepted 14 December 2010; online publish-ahead-of-print 5 January 2011

See page 791 for the editorial comment on this article (doi:10.1093/eurheartj/ehr058)

Aims To evaluate efficacy and safety of RLY5016 (a non-absorbed, orally administered, potassium [K^+]-binding polymer) on serum K^+ levels in patients with chronic heart failure (HF) receiving standard therapy and spironolactone.

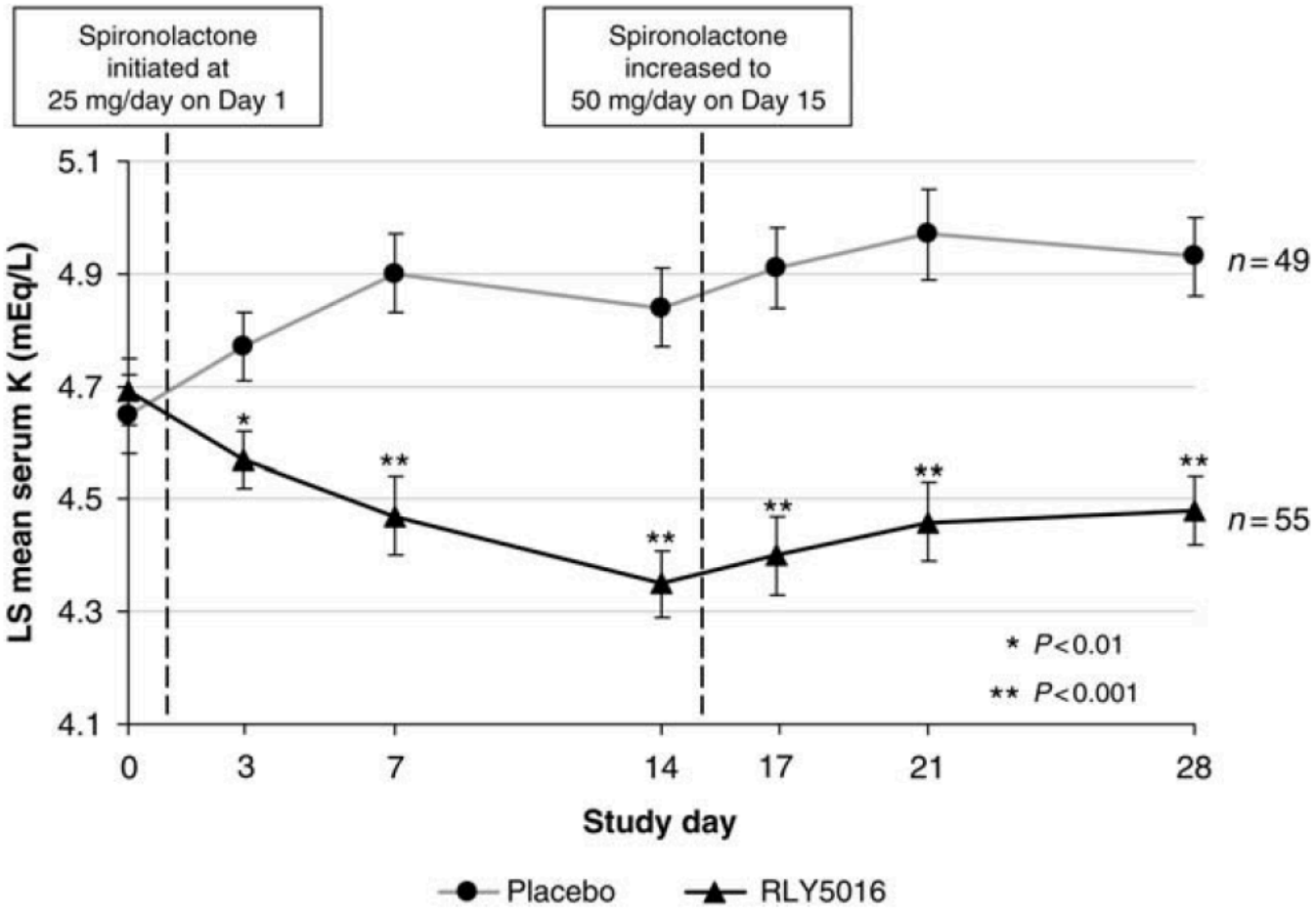
Methods and results One hundred and five patients with HF and a history of hyperkalaemia resulting in discontinuation of a renin–angiotensin–aldosterone system inhibitor/blocker and/or beta-adrenergic blocking agent or chronic kidney disease (CKD) with an estimated glomerular filtration rate of <60 mL/min were randomized to double-blind treatment with 30 g/day RLY5016 or placebo for 4 weeks. Spironolactone, initiated at 25 mg/day, was increased to 50 mg/day on Day 15 if K^+ was ≤5.1 mEq/L. Endpoints included the change from baseline in serum K^+ at the end of treatment (primary); the proportion of patients with hyperkalaemia (K^+ >5.5 mEq/L); and the proportion

PEARL-HF Study Design



Pitt EHJ 2011

PEARL-HF


Spironolactone initiated at 25 mg/day on Day 1
Spironolactone increased to 50 mg/day on Day 15
LS mean serum K (mEq/L)
5.1
4.9
4.7
4.5
4.3
4.1
0
3
7
14
17
21
28
Study day
n=49
n=55
* P<0.01
** P<0.001
Placebo
RLY5016

PEARL-HF

Table 4 Incidence of hyperkalaemia by baseline estimated glomerular filtration rate

Baseline eGFR (mL/min)	No. (%) of patients with hyperkalaemia (serum potassium > 5.5 mEq/L) at any study visit		
	RLY5016 30 g/day	Placebo	*P*-value
<60	1/15 (6.7)	5/13 (38.5)	0.041
≥60	3/40 (7.5)	7/36 (19.4)	0.125
All patients (eGFR = 81 ± 33)	4/55 (7.3)	12/49 (24.5)	0.015

PEARL-HF

Auftitration von Spironolacton auf 50mg/d

Table 2 **Summary of incidence of hyperkalaemia, hypokalaemia, hypomagnesaemia, and increase of spironolactone dose**

	No. (%) of patients		*P*-value
	RLY5016 30 g/day (*n* = 55)	Placebo (*n* = 49)	
Serum potassium >5.5 mEq/L[a]	4 (7)	12 (25)	0.015
Serum potassium <4.0 mEq/L	26 (47)	5 (10)	<0.001
Serum potassium <3.5 mEq/L	3 (6)	0 (0)	0.094
Serum magnesium <1.8 mg/dL	13 (24)	1 (2)	0.001
Spironolactone dose increased	50 (91)	36 (74)	0.019

PEARL-HF: Botschaft

Patiromer verhindert Hyperkaliämien

bei Patienten mit Herzinsuffizienz und ermöglicht die Auftitration von Spironolacton auf die Zieldosis

Zusammenfassung

- Bei HFrEF ist die **RAAS-I lebensnotwendig**
- Bis zu einem Serum-Kalium von 6,0 mmol/L scheint man bzgl. Datenlage auf der sicheren Seite zu sein – nicht aber bzgl. Fachinformationen und Guidelines
- **Neue Kaliumsenker ermöglichen die RAAS-Inhibition** ohne Hyperkaliämie-Hazard

VIELEN DANK!