

Behandlung der systolischen Herzinsuffizienz



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ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

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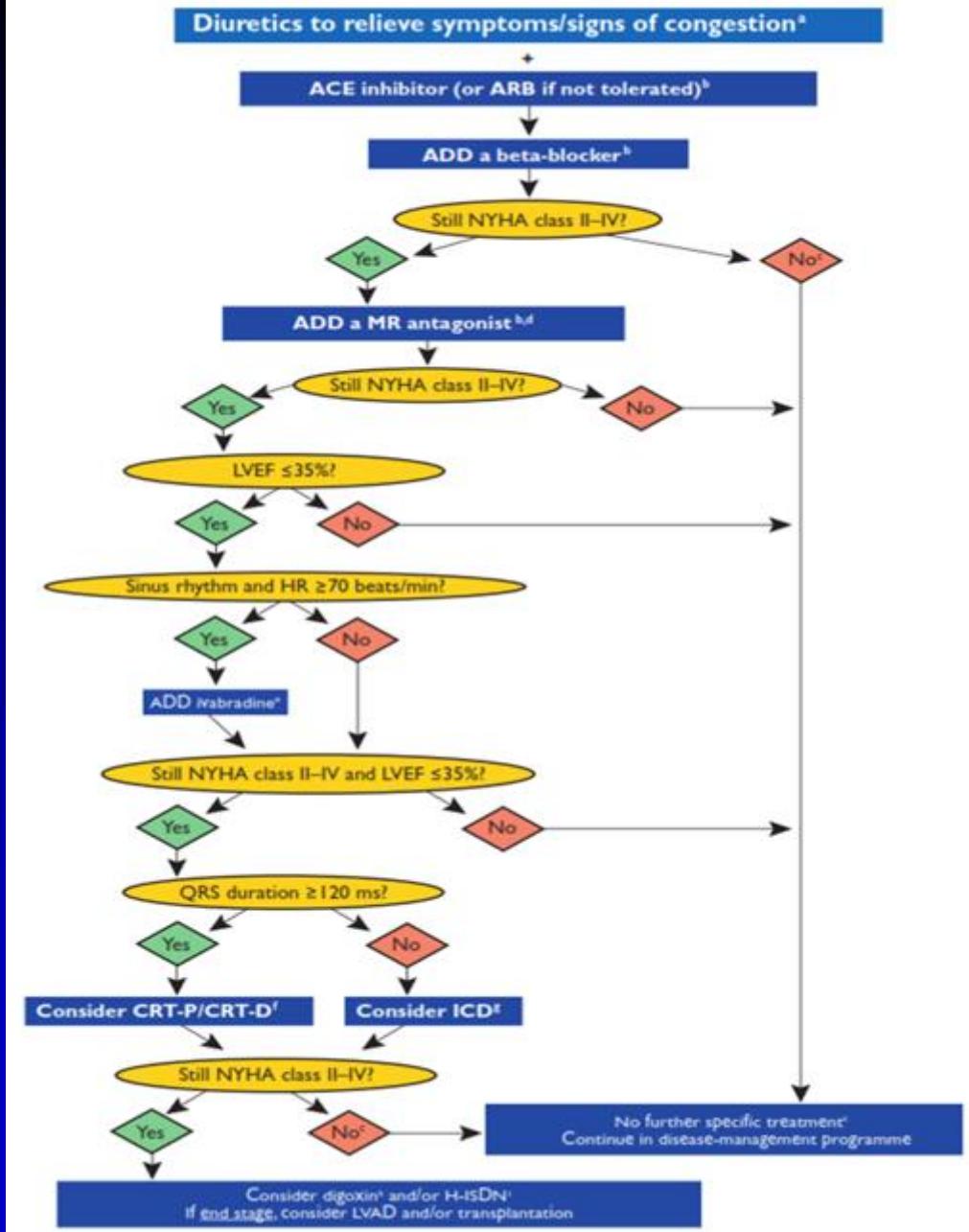
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

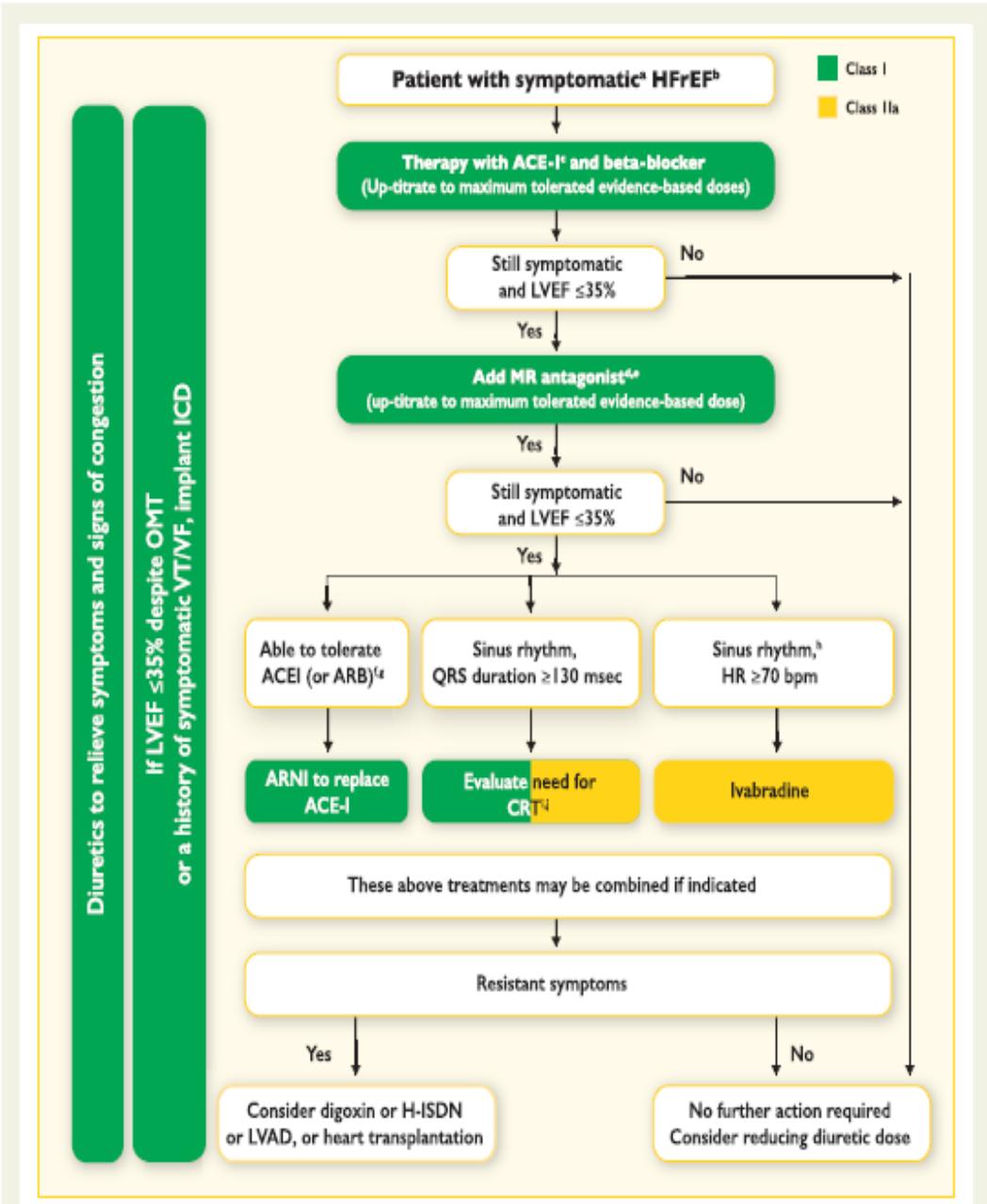
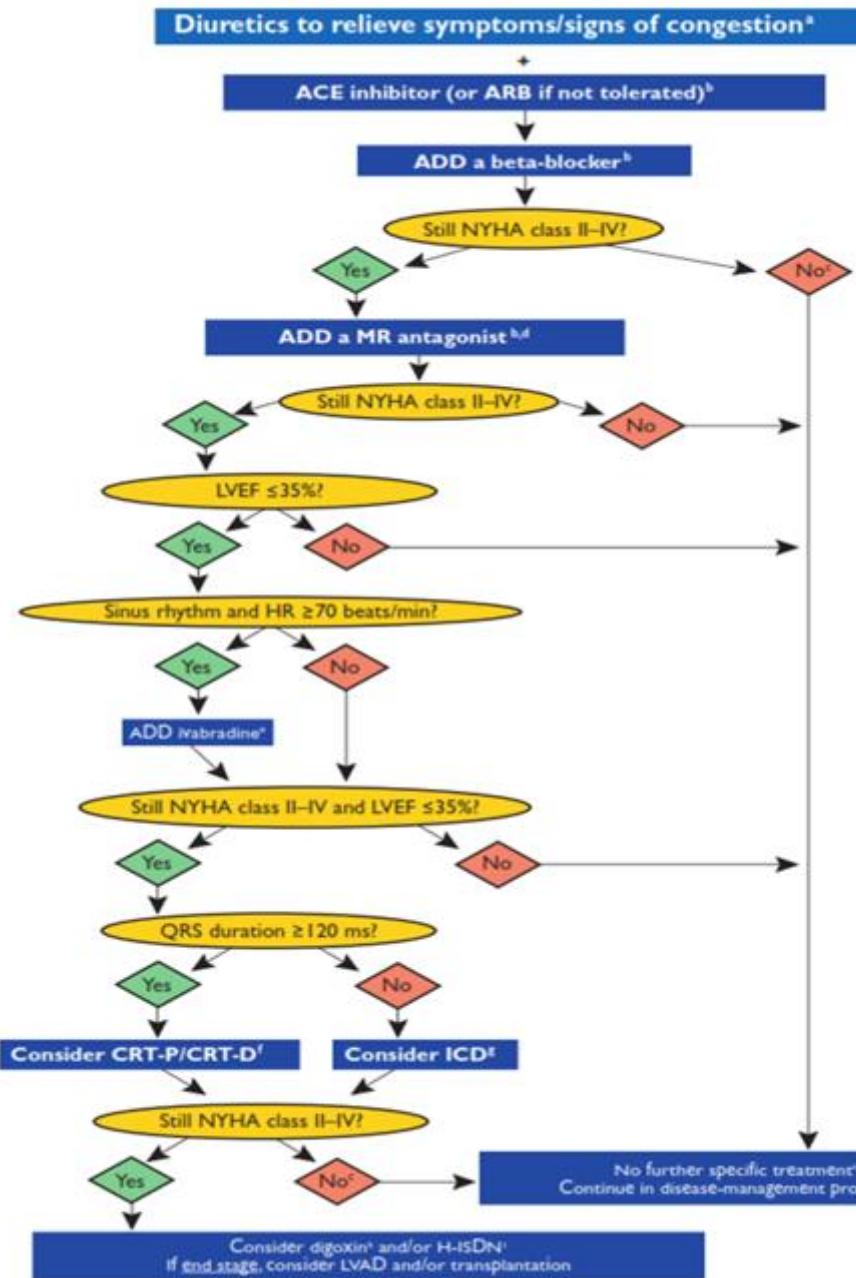
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

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

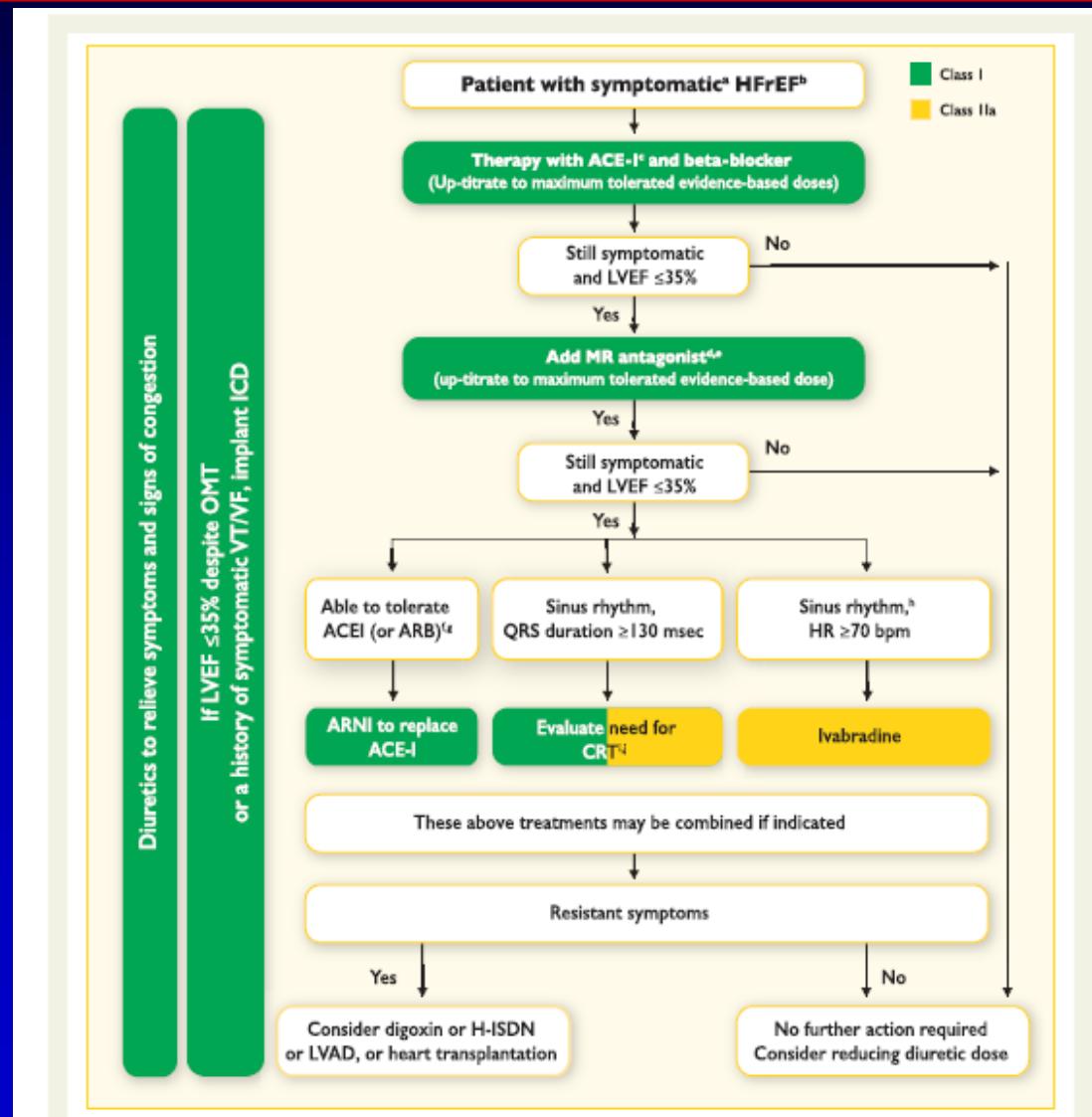
Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

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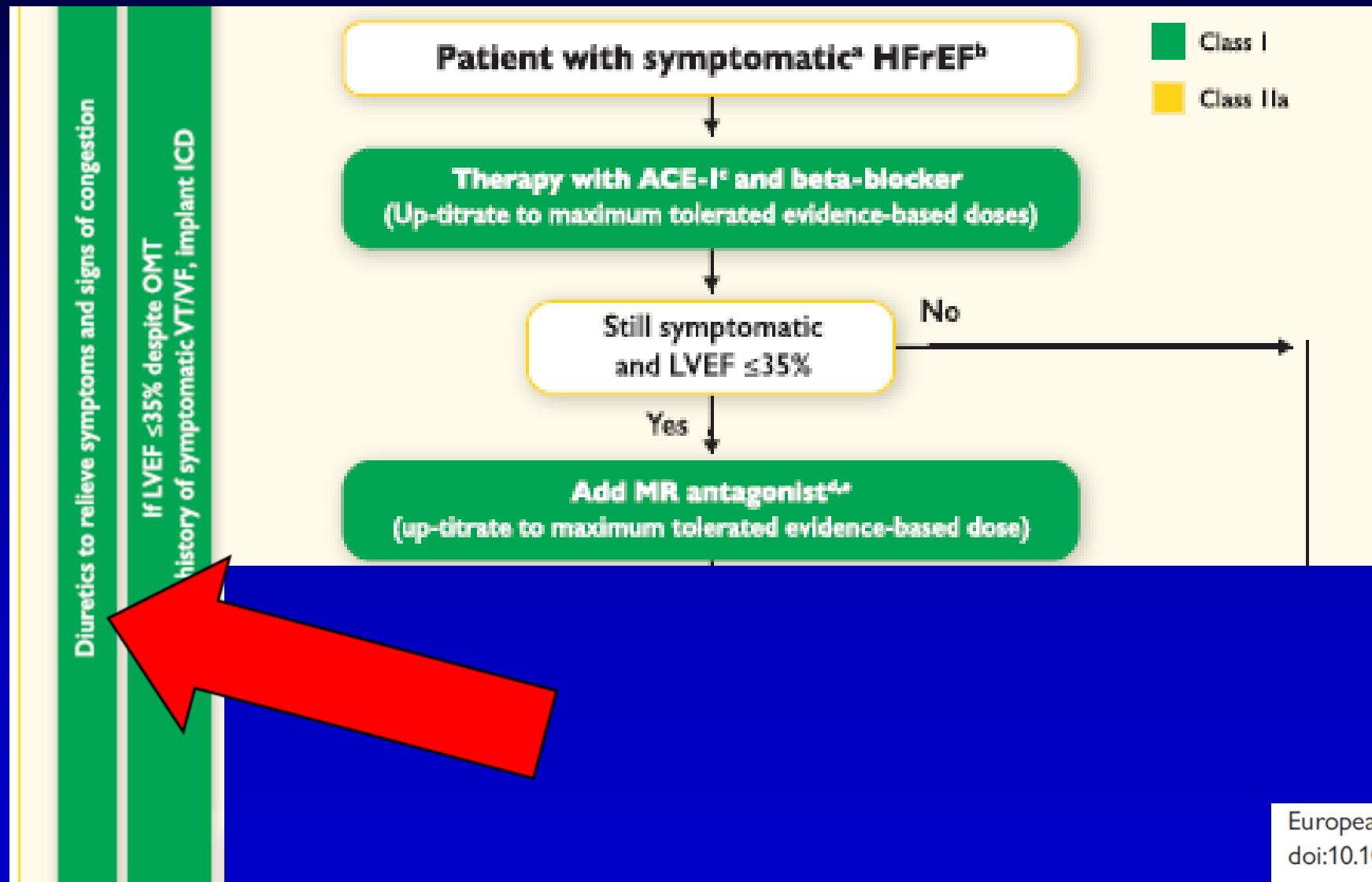




2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



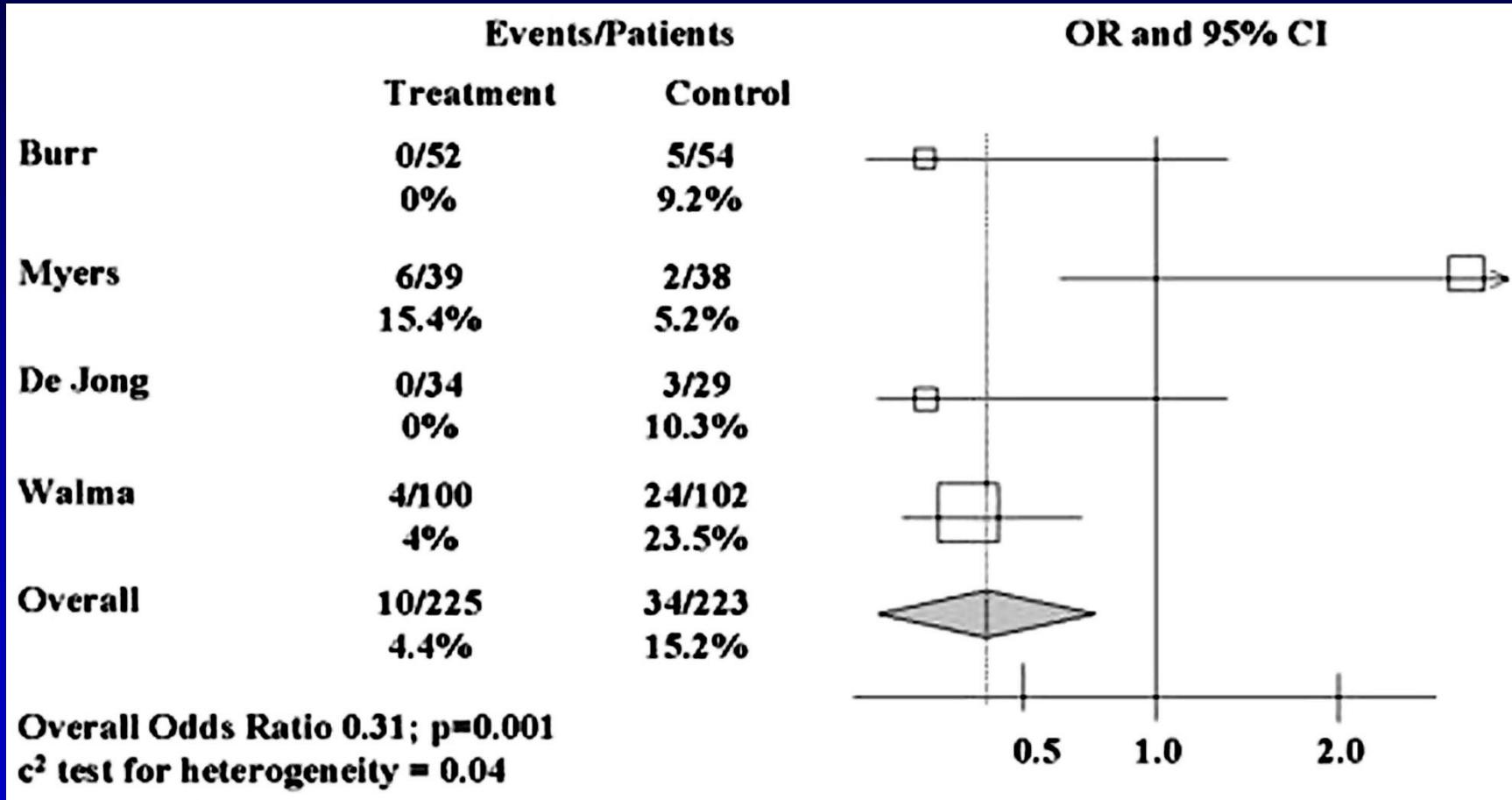
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials



R. Faris*, M. Flather, H. Purcell, M. Henein, P. Poole-Wilson, A. Coats



Withdrawal in Patients on ACE-Inhibitors

(Cross over)

A

14 Pts.

- Captopril (3x25 mg)
- Furosemide (40 mg)
- + Amiloride (5 mg)

3 Months
stable

Captopril

10 Pts.
(stable)

4 Pts.

Pulmonary Edema
(11d, 33d, 8d, 16d)

B

14 Pts.

- Furosemide (40 mg)
- + Amiloride (5 mg)

→

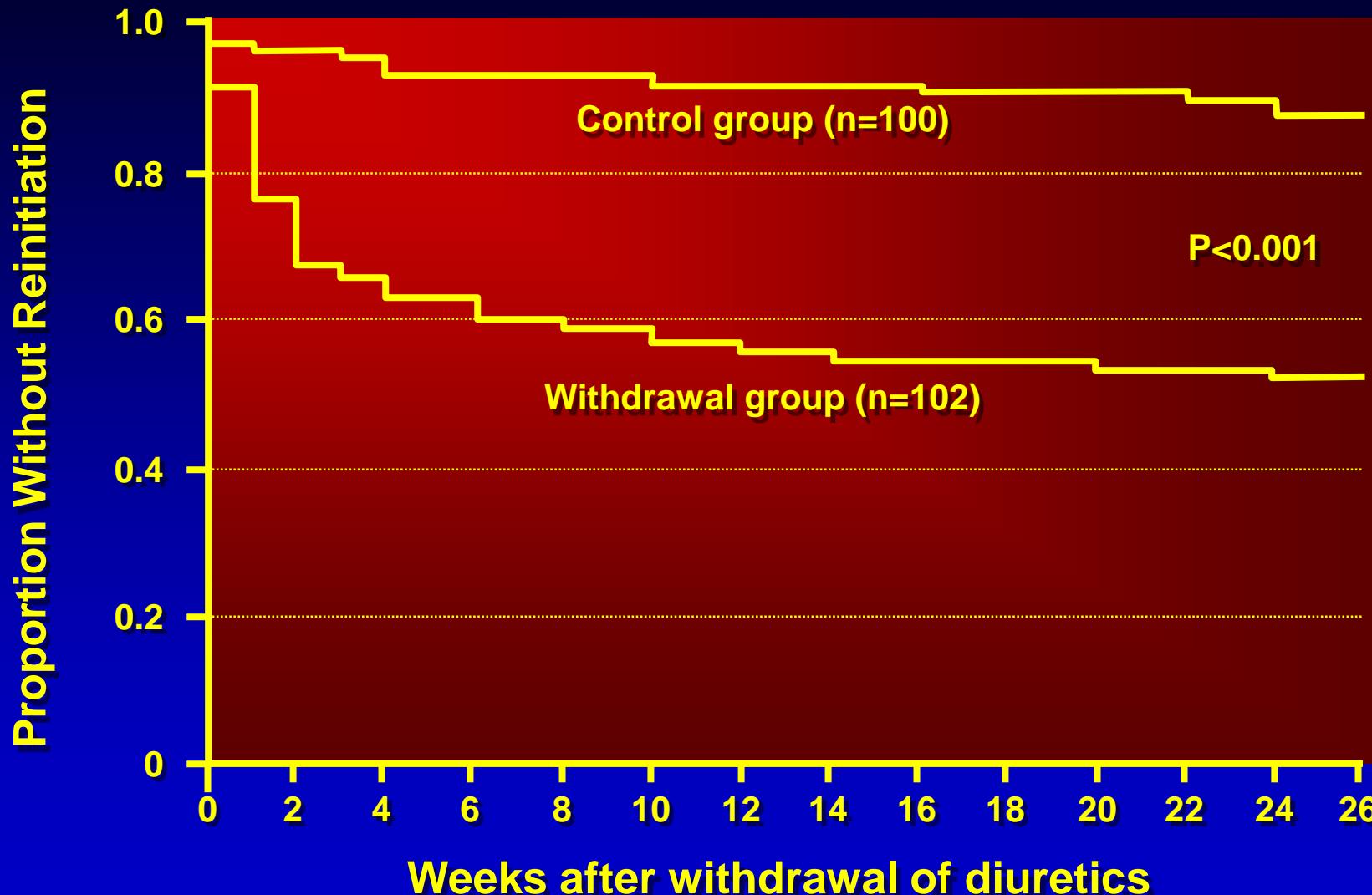
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↓

No Withdrawals

14 Pts.
(stable)

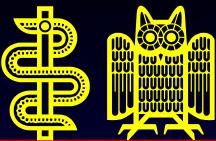
Withdrawal of Diuretic in Older Individuals without Ouvert CHF



Walma et al, BMJ 315 (1997): 464-468

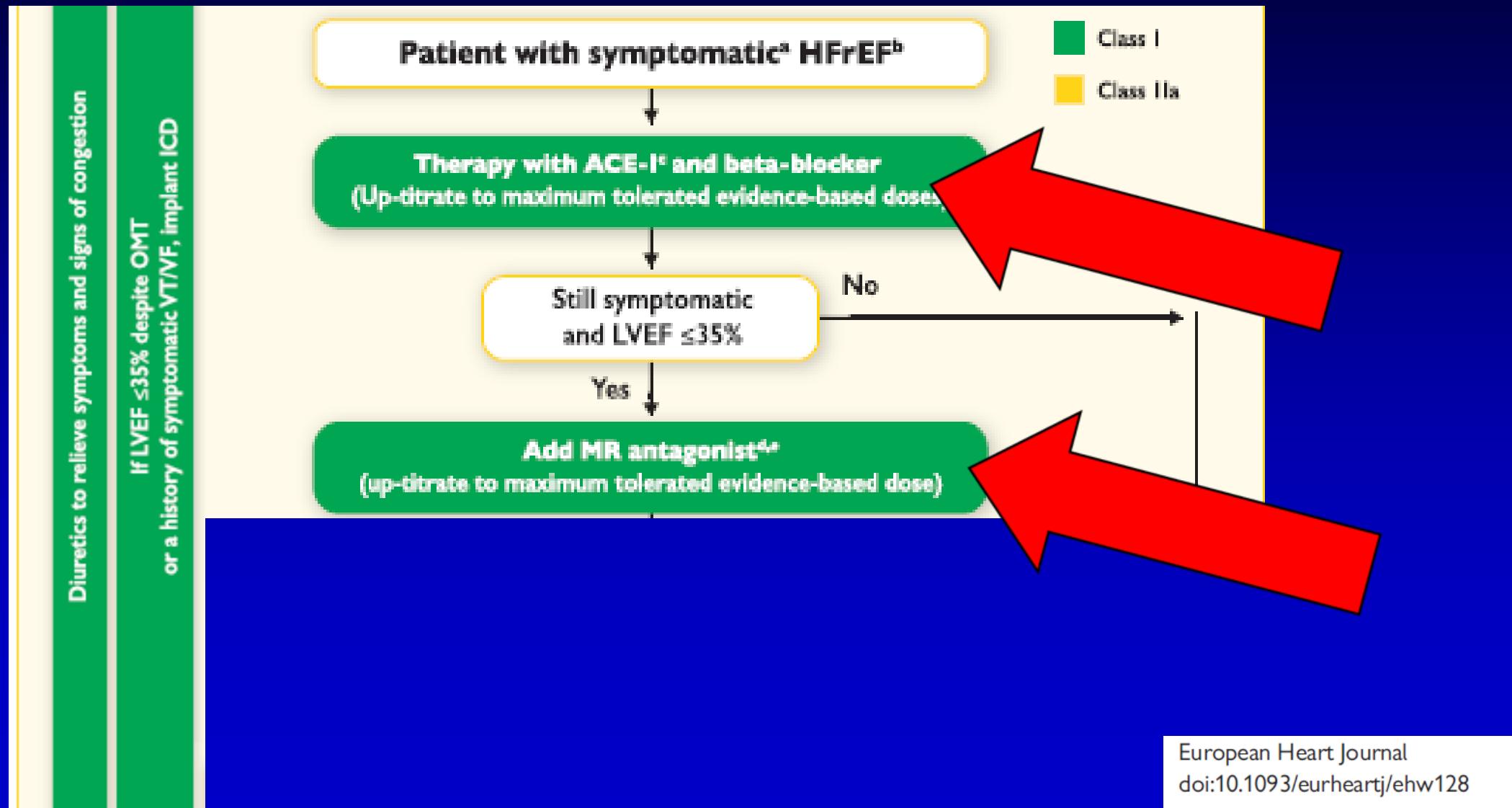
AS-af-0102

Withdrawal of Diuretics in Older Individuals without Ouvert CHF



Criterion	Withdrawal group (n=102)	Control group (n=100)	Risk difference (%) (95% CI)
All	50	13	36 (22 to 50)
Heart Failure	25	4	21 (11 to 31)
Hypertension	9	5	4 (-3 to 11)
Subjective shortness of breath	6	0	6 (1 to 11)
Non-cardiac ankle oedema	4	1	3 (-1 to 8)
Miscellaneous clinical conditions	3	1	2 (-2 to 6)
Other	3	2	1 (-3 to 5)

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



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

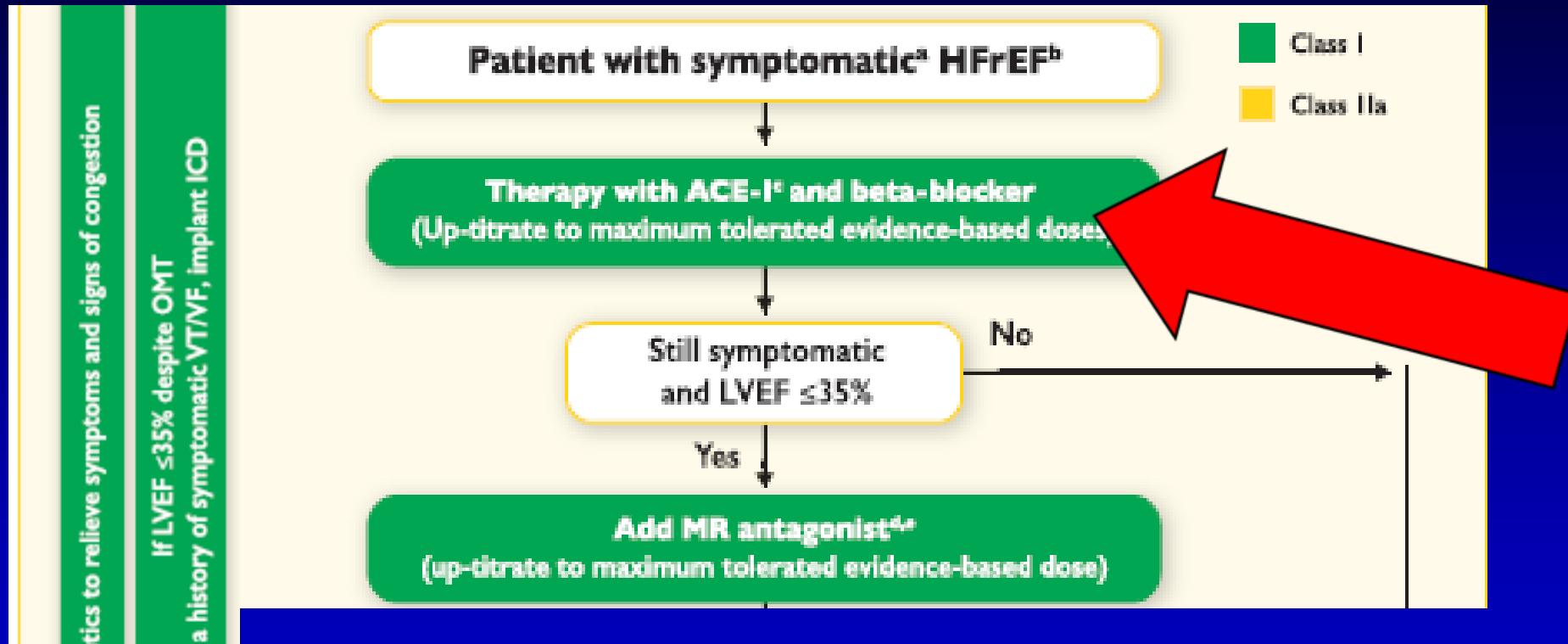
Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class ^a	Level ^b	Ref ^c
An ACE-I ^d is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163 –165
A beta-blocker is recommended, in addition an ACE-I ^d , for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167– 173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I ^d and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

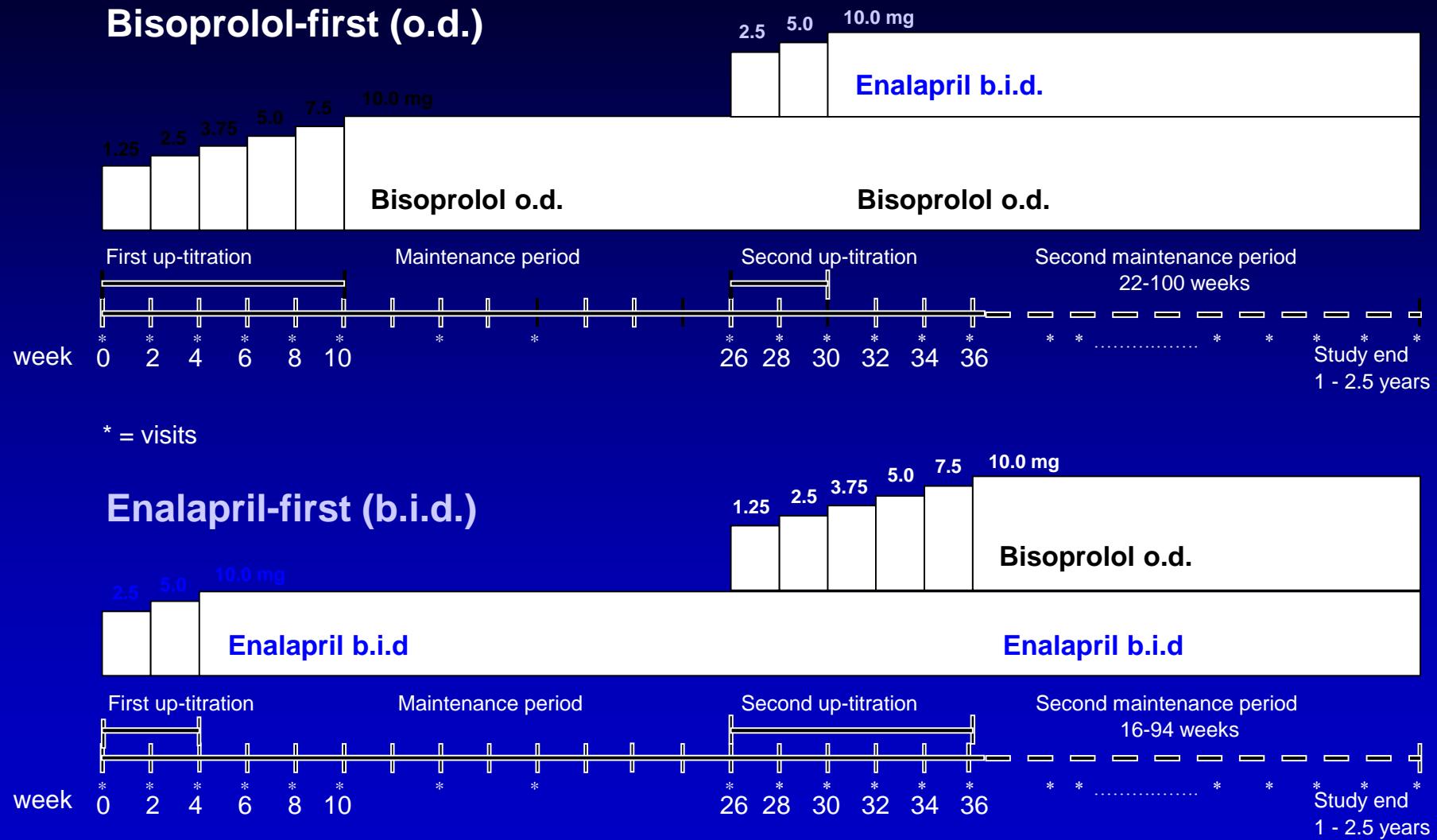
Not new!



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

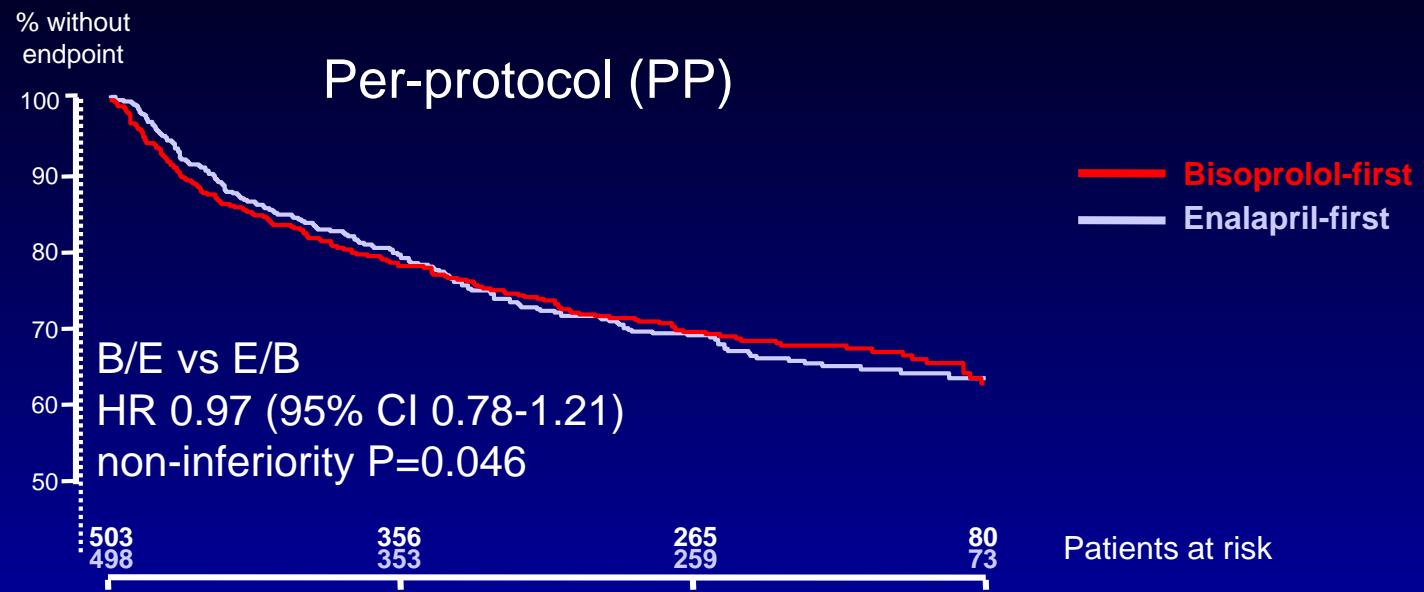


Study design – CIBIS III

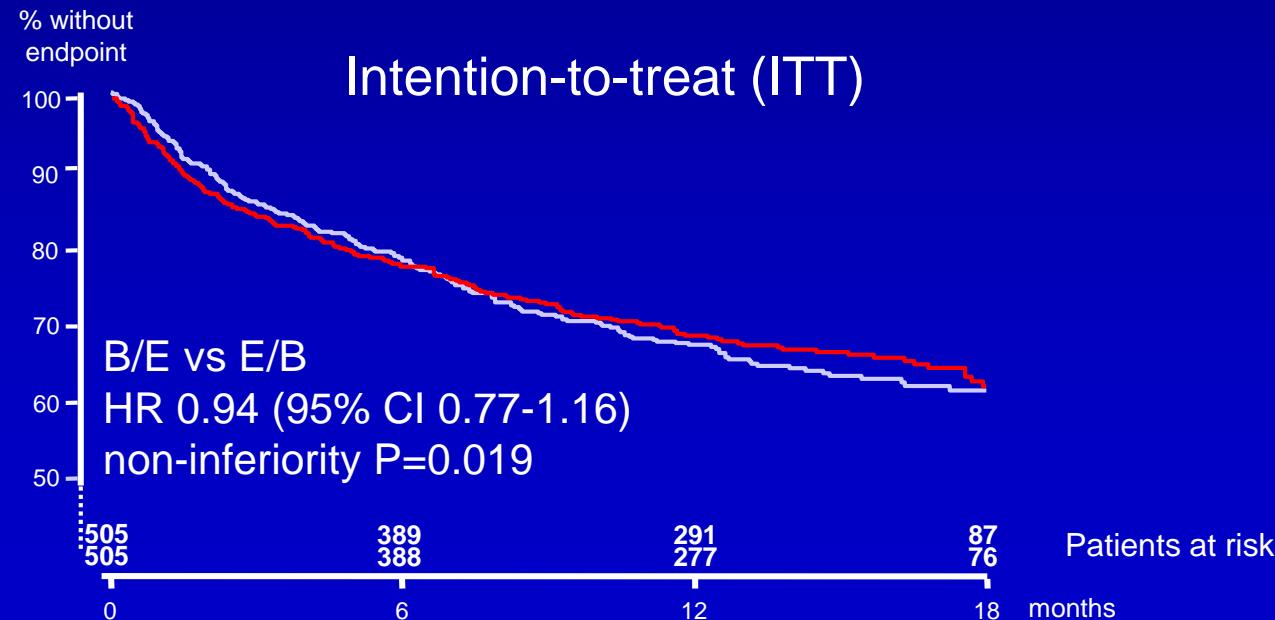


Primary endpoint – CIBIS III

Mean follow-up
1.25 years

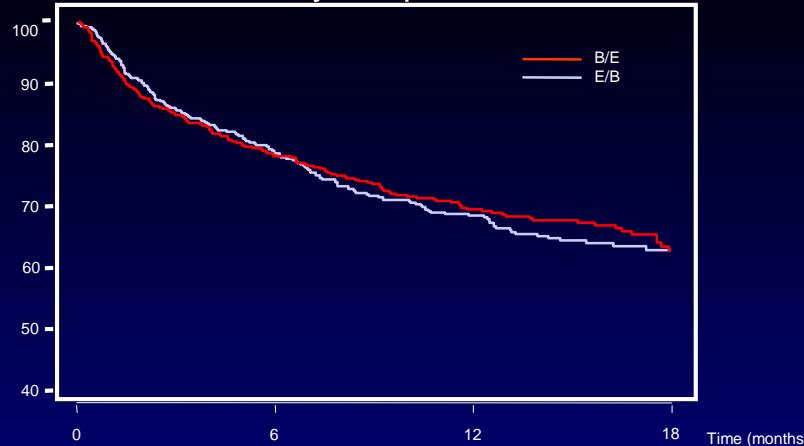


For non-inferiority
 $P<0.025$ denotes
statistical significance
(unilateral test)

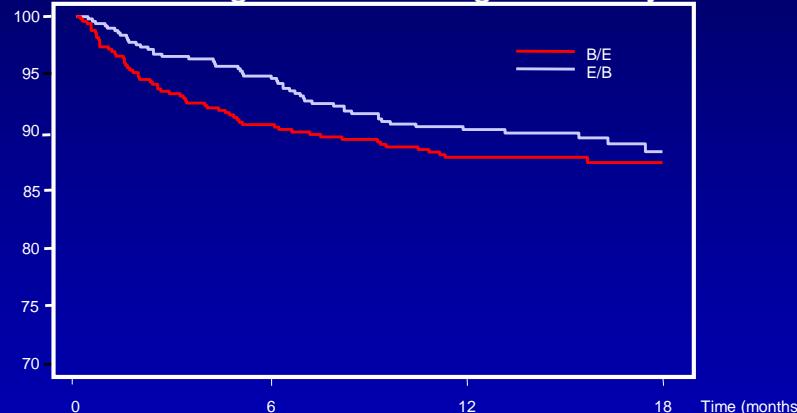


Food for Thoughts – CIBIS III

% event-free Primary endpoint PP



Worsening of CHF throughout study



All cause mortality at end of monotherapy phase

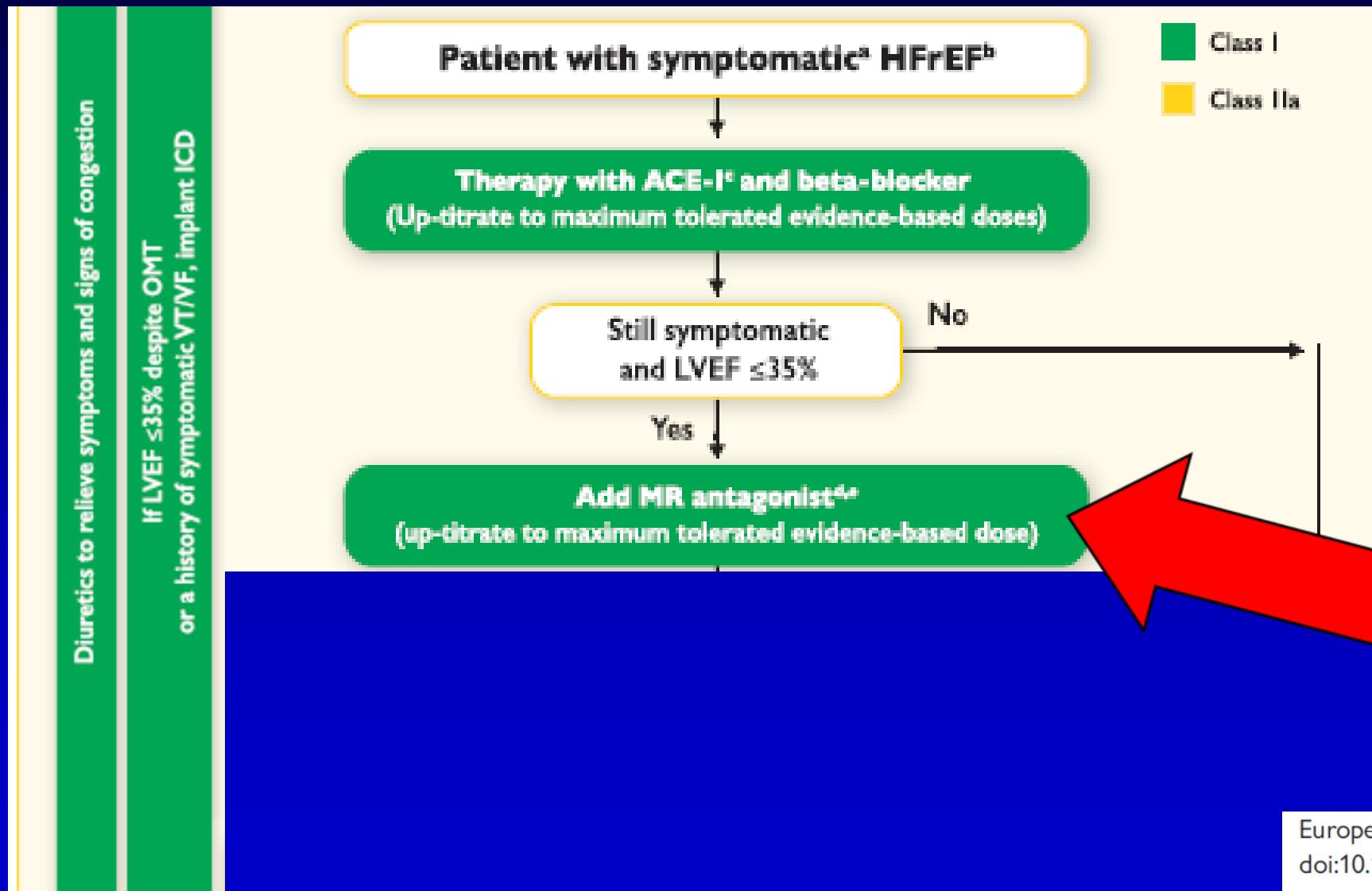


Bisoprolol-first achieved clinically comparable survival and all-cause hospitalization compared with enalapril-first.

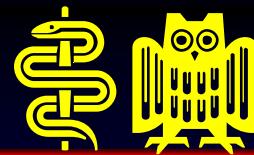
Bisoprolol-first was associated with a trend towards increased worsening of CHF in the early phase of treatment.

Bisoprolol-first showed a trend towards improved survival during the early study phase (which was maintained during combined therapy).

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



Protection by a Steroid-Spirolactone Against Certain Types of Cardiac Necroses.* (25782)



HANS SELYE

Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada,

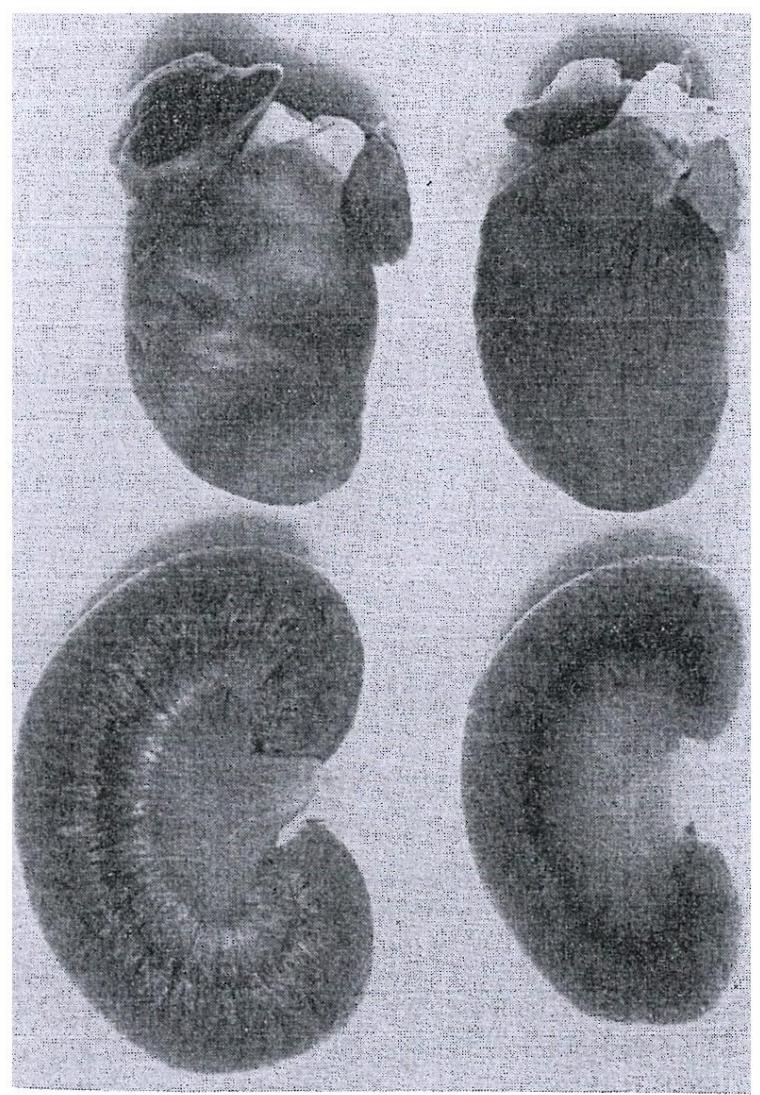
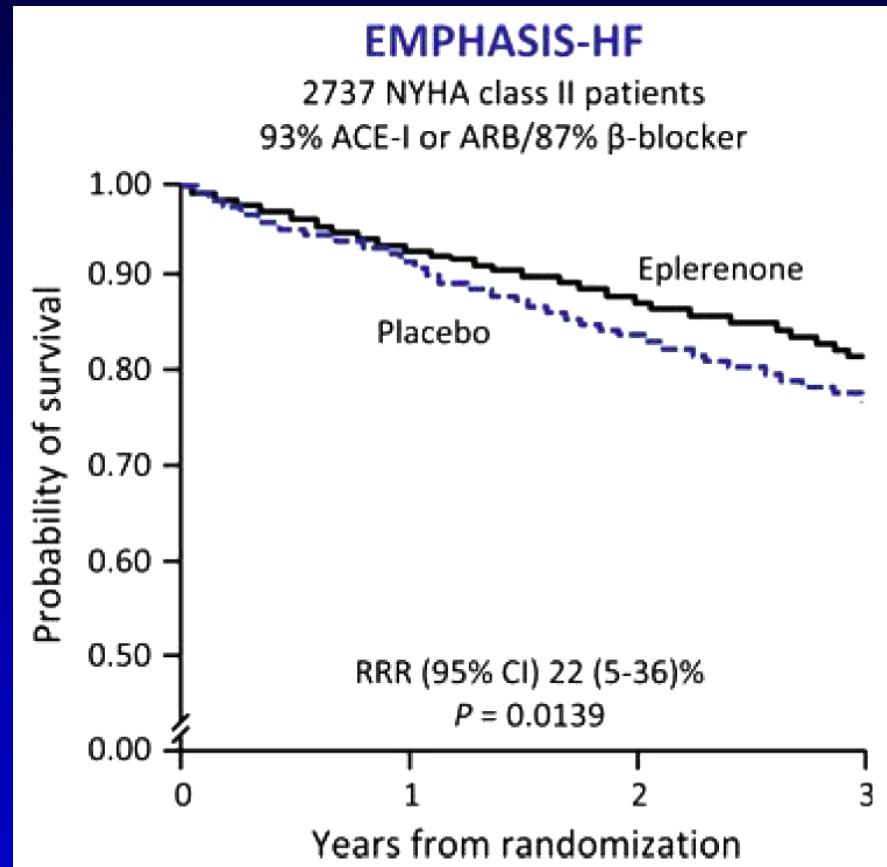
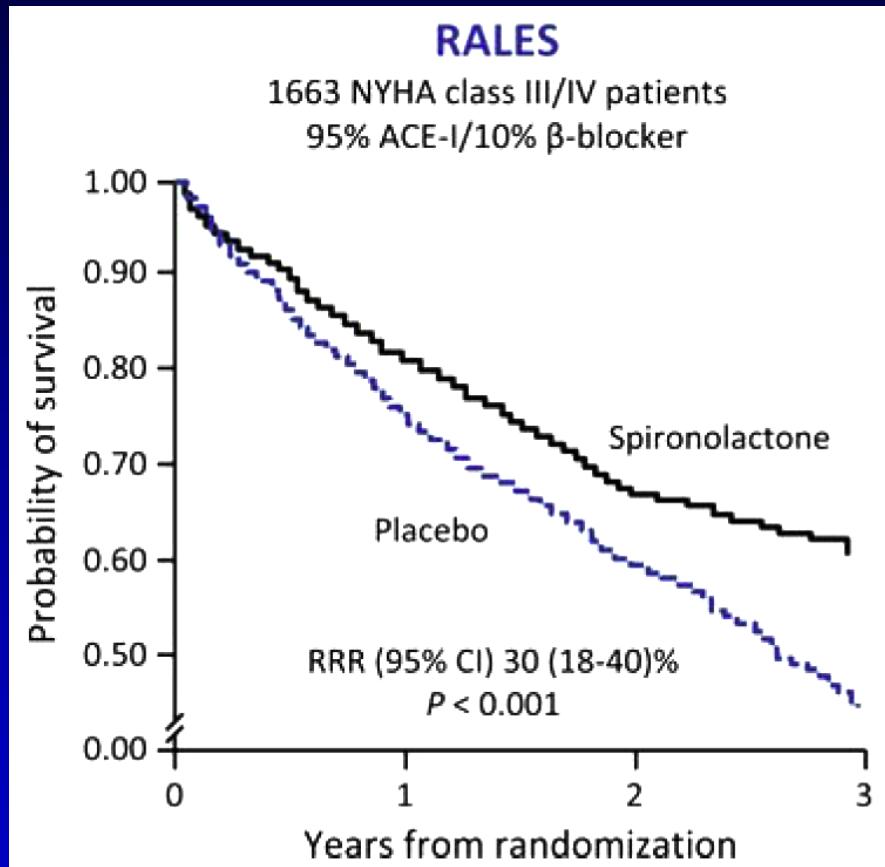


FIG. 1. Typical multiple myocardial necroses and extensive nephrocalcinosis—particularly at cortico-medullary junction line—in a rat (Group 1 of first experiment) in which F-COL + Na₂HPO₄ was administered (left). Compare with the apparently normal organs of a rat (Group 2 of first experiment) treated with SC-9420 in addition to F-COL + Na₂HPO₄.

Aldosterone Receptor Blocker in Severe (left) and Moderate (right) Heart Failure



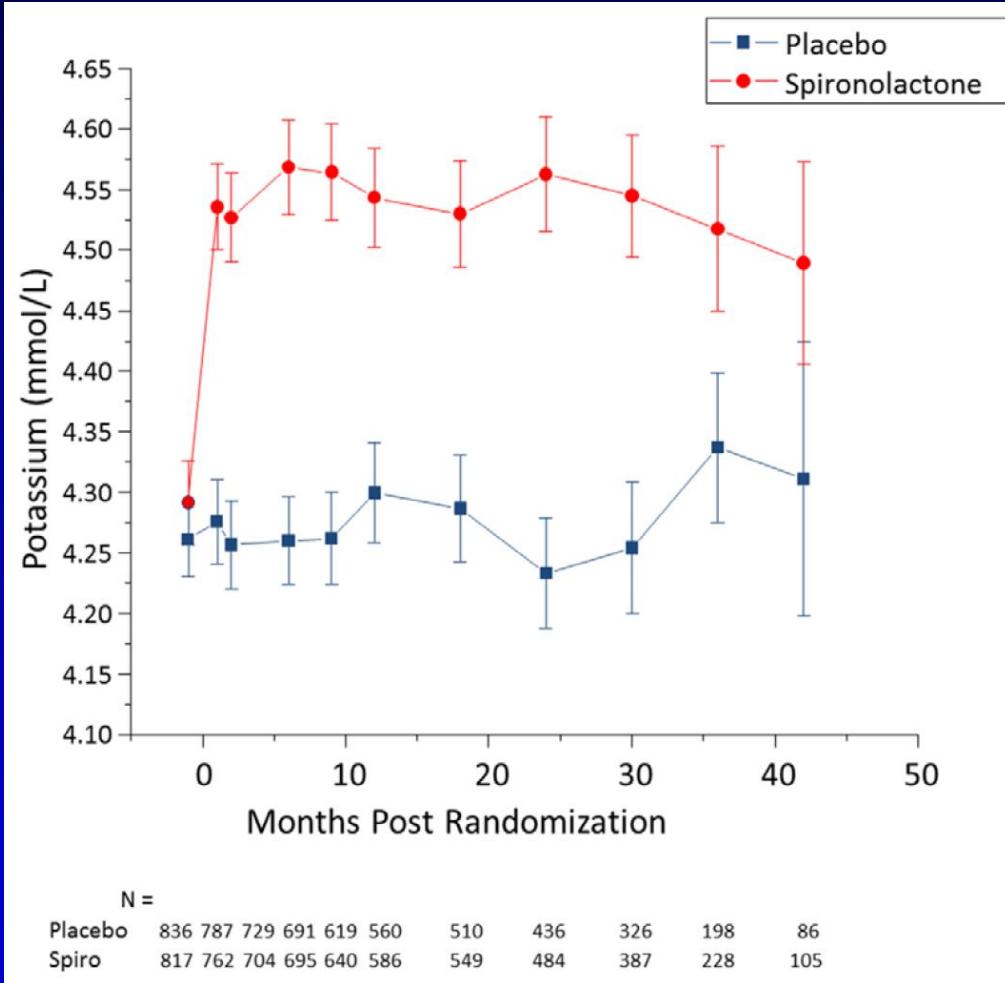
Pitt et al,
N Engl J Med 341 (1999); 709-717

Zannad et al,
N Engl J Med 364 (2011); 11-21



Incidence, Predictors, and Outcomes Related to Hypo- and Hyperkalemia in Patients With Severe Heart Failure Treated With a Mineralocorticoid Receptor Antagonist

Orly Vardeny, PharmD, MS; Brian Claggett, PhD; Inder Anand, MD;
Patrick Rossignol, MD, PhD; Akshay S. Desai, MD, MPH; Faiez Zannad, MD, PhD;
Bertram Pitt, MD; Scott D. Solomon, MD;
for the Randomized Aldactone Evaluation Study (RALES) Investigators



Consistency of Laboratory Monitoring During Initiation of Mineralocorticoid Receptor Antagonist Therapy in Patients With Heart Failure



Observed Laboratory Testing of Potassium and Creatinine Levels Among Patients Initiating Mineralocorticoid Receptor Antagonist Therapy for Heart Failure

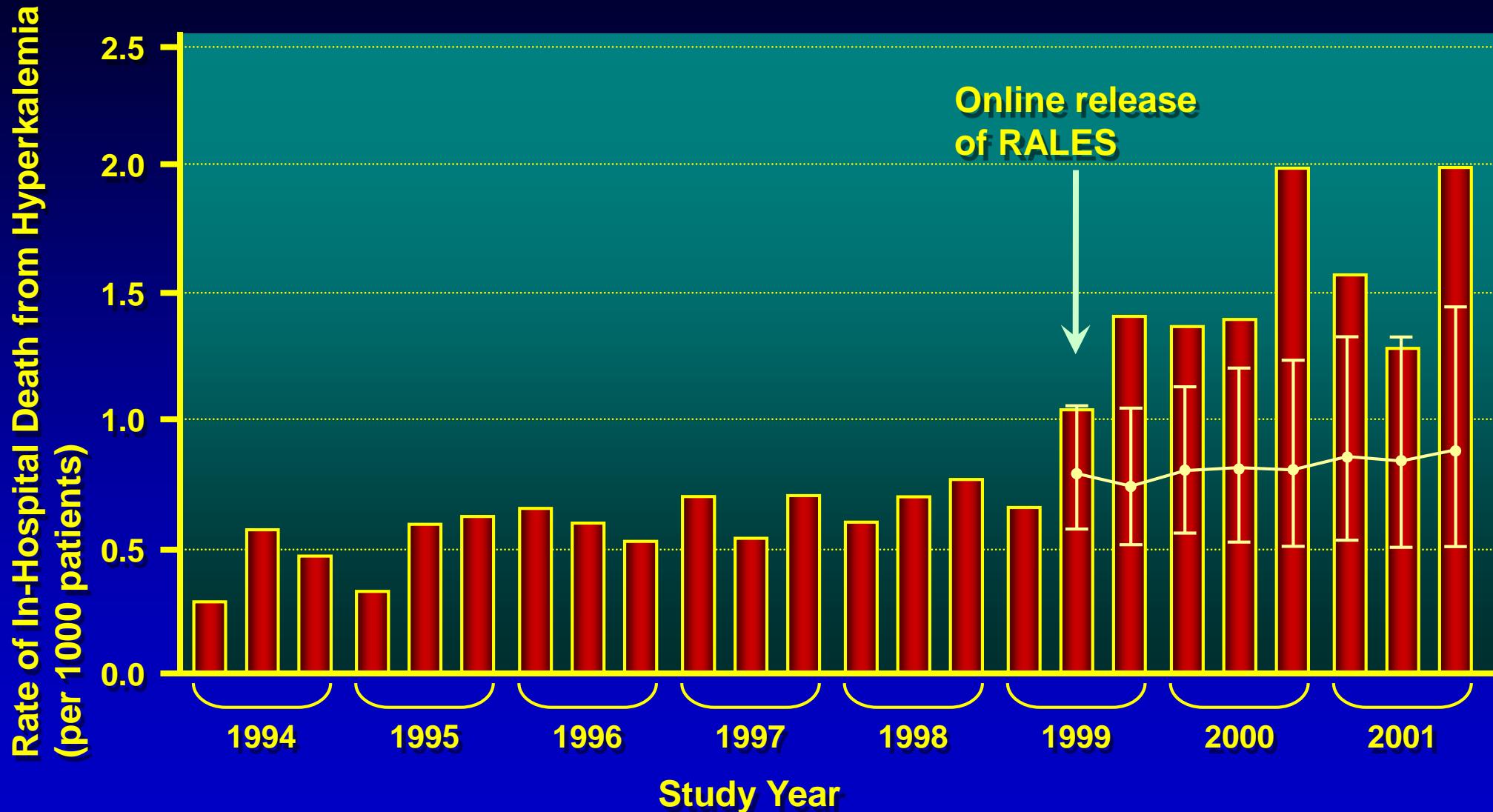
	No. (%) of Patients (N = 10 443)
Preinitiation testing (120 d before drug initiation)	
Appropriate ^a	9564 (91.6)
None	879 (8.4)
Early postinitiation testing (1-10 d after drug initiation)	
Appropriate ^b	1384 (13.3)
Any	4661 (44.6)
None	5782 (55.4)
Extended postinitiation testing (11-90 d after drug initiation)	
Appropriate ^c	3122 (29.9)
Any	8115 (77.7)
None	2328 (22.3)
Received all appropriate testing	756 (7.2)
No preinitiation or postinitiation testing	280 (2.7)

^a Defined by the presence of at least 1 laboratory claim (or hospitalization) within 120 days before drug initiation.

^b Defined by the presence of 2 laboratory claims (or hospitalizations or 1 laboratory claim plus hospital discharge within 3 days before initial outpatient prescription fill) within 10 days after drug initiation.

^c Defined by the presence of 3 laboratory claims (or hospitalizations) within 11 to 90 days after drug initiation.

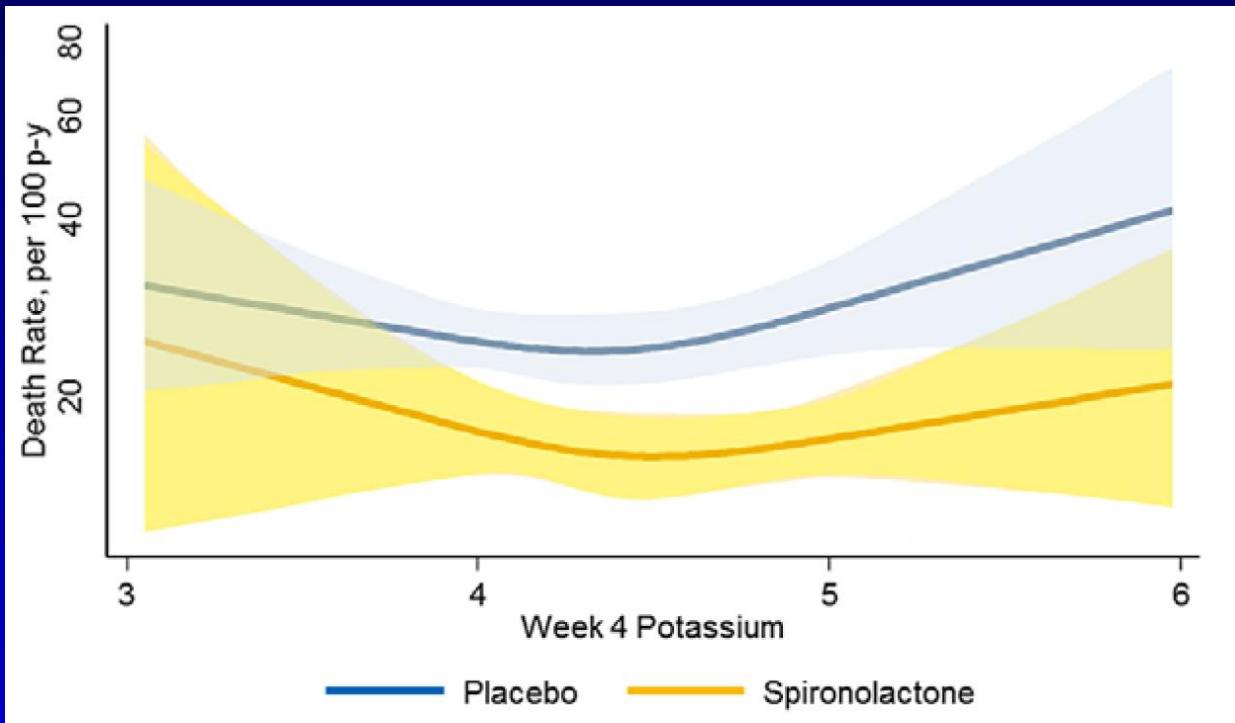
Hospitalizations due to Hyperkalemia after RALES





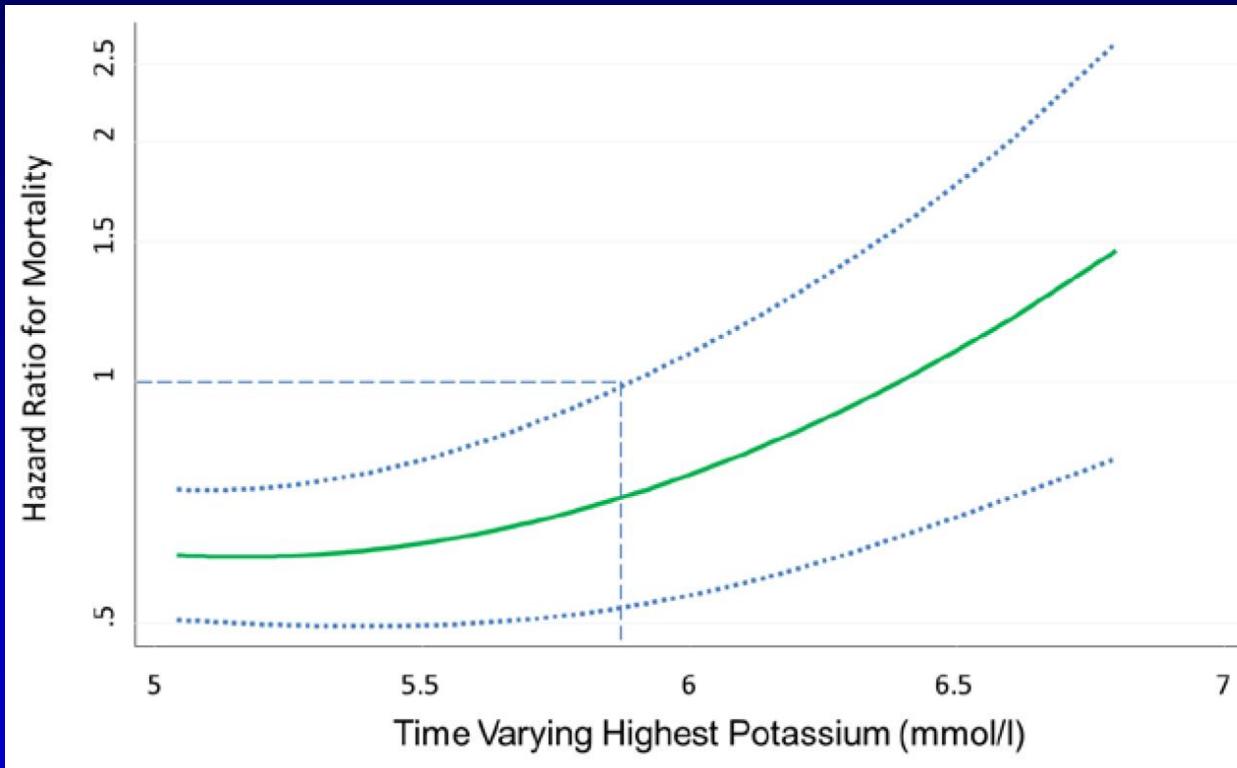
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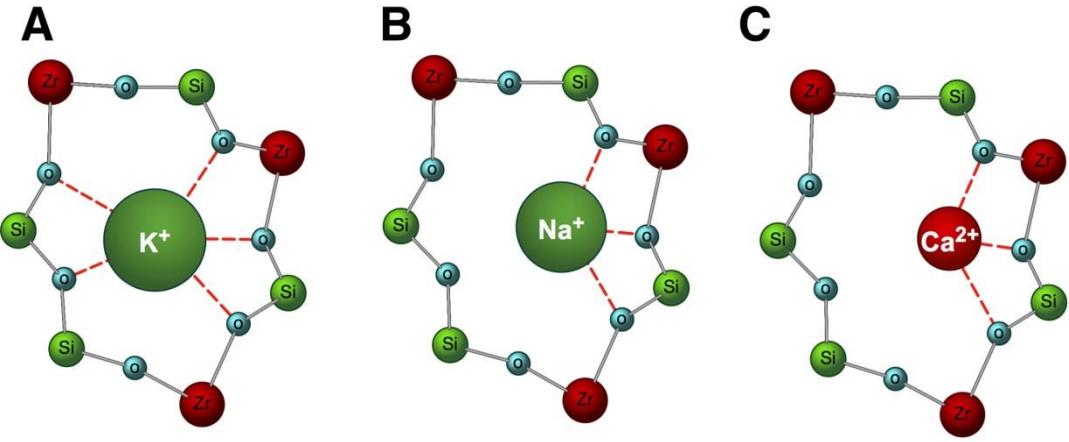
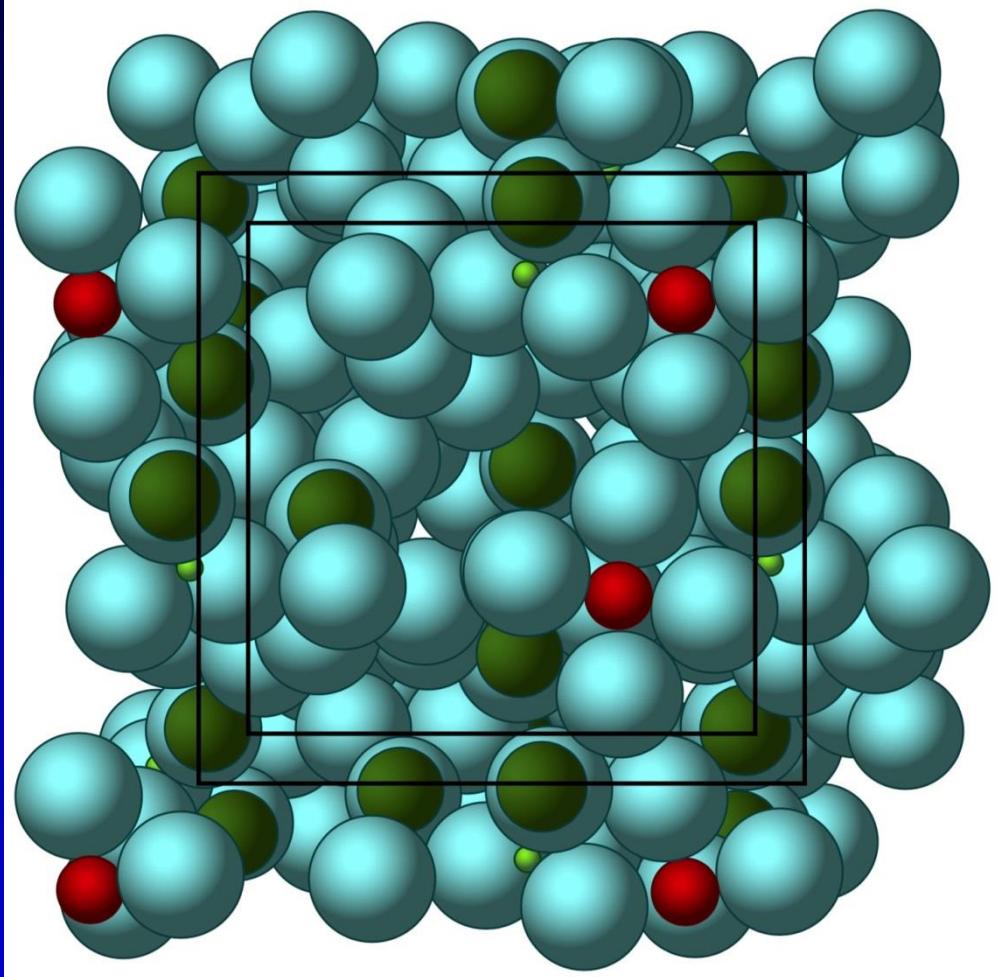


New Potassium Binders for the Treatment of Hyperkalemia

Current Data and Opportunities for the Future



Bertram Pitt, George L. Bakris



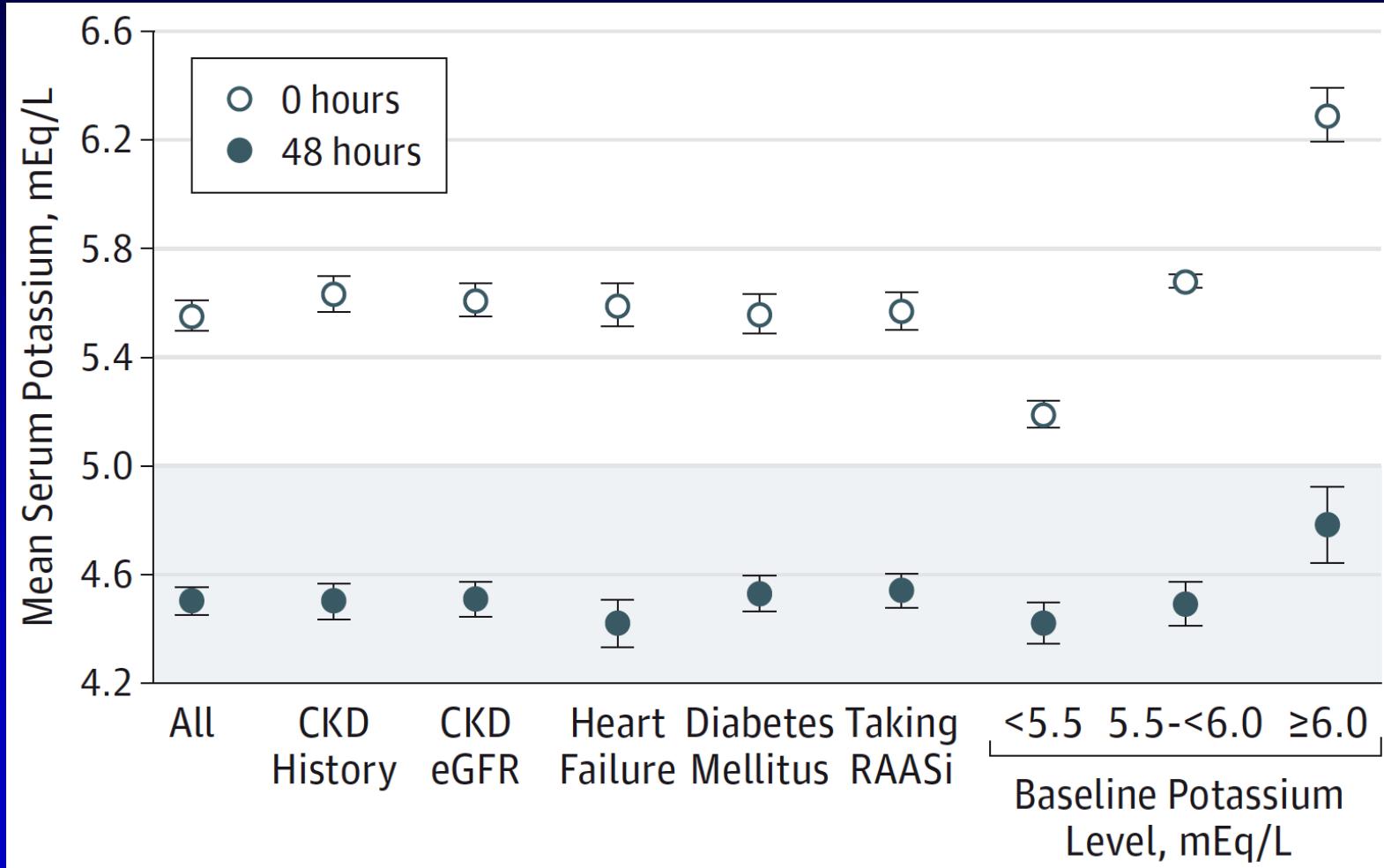
Structure of ZS-9. Pore detail with potassium ion (A), sodium ion (B), and calcium ion (C). Blue spheres indicates oxygen atoms; green spheres, silicon atoms; and red spheres, zirconium atoms.

Reprinted from Stavros *et al*, *PLoS One* 9 (2014) e114686 with permission of the publisher. Copyright © 2014, the Authors.



Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia The HARMONIZE Randomized Clinical Trial

Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD



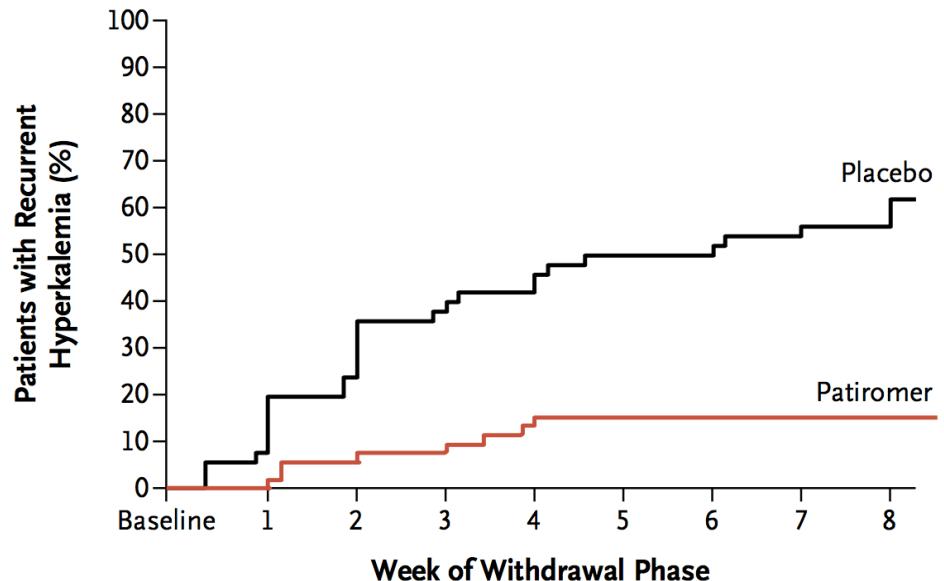


Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

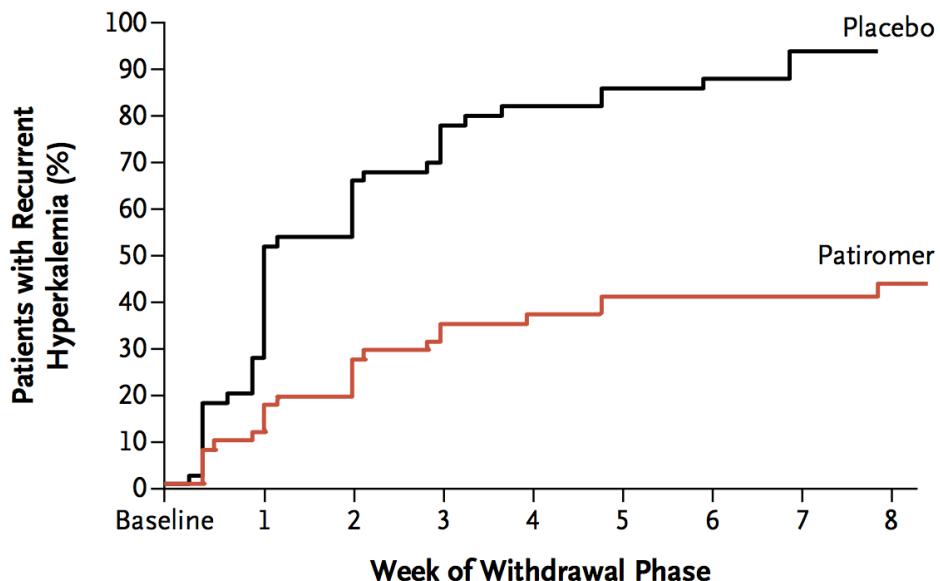
Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wlettes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

Time to First Recurrence of Hyperkalemia during the Randomized Withdrawal Phase

A Time to First Serum Potassium Level ≥ 5.5 mmol/liter



B Time to First Serum Potassium Level ≥ 5.1 mmol/liter



No. at Risk

Placebo	52	46	38	31	29	25	25	23	15
Patiromer	55	53	49	48	45	43	42	42	32

No. at Risk

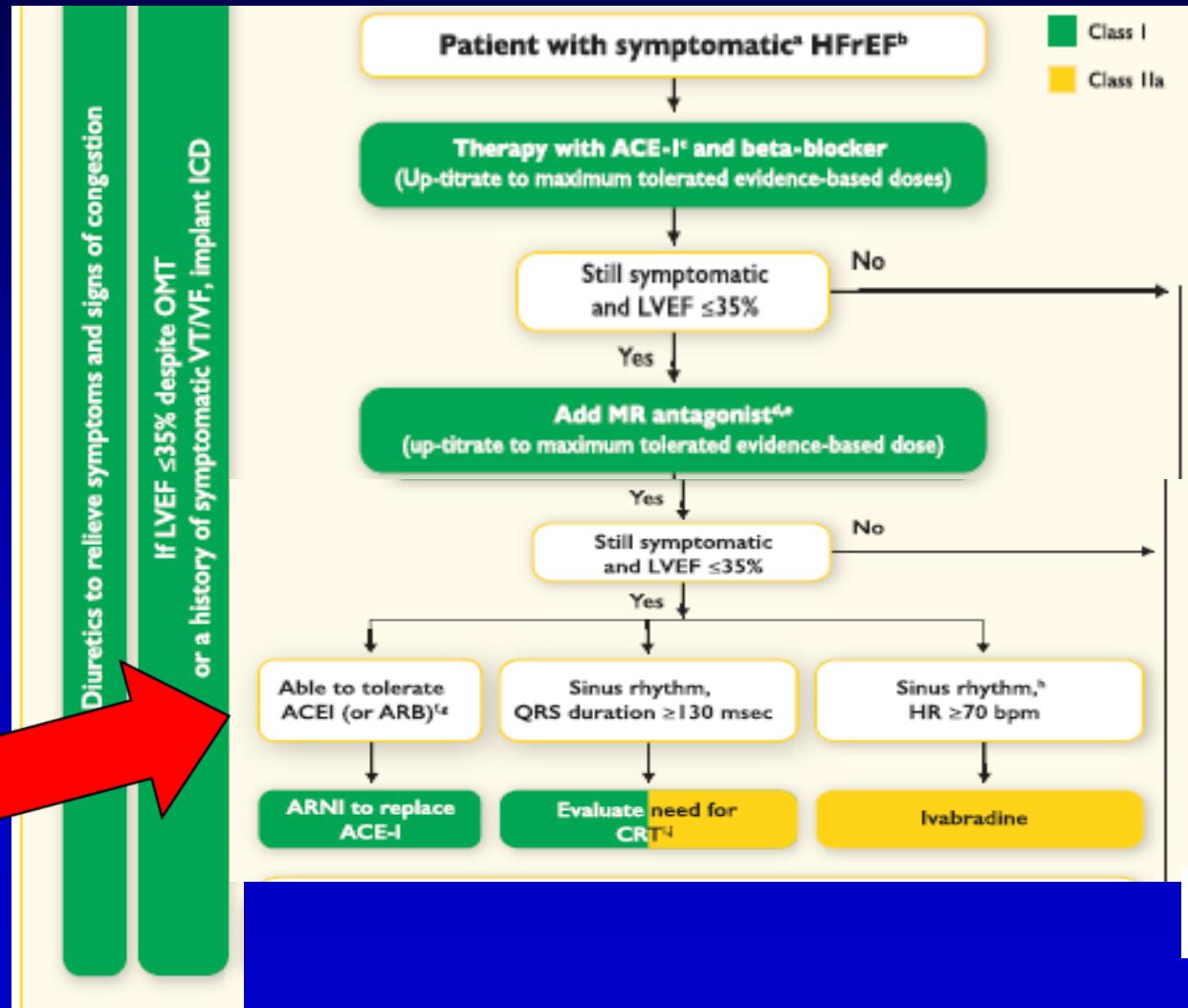
Placebo	52	37	24	16	10	8	8	7	1
Patiromer	55	47	42	36	34	30	29	29	23

What do we need?

- Randomised, prospektive Study
- GFR 15-45 ml/min
- Spironolactone plus Patiromir vs Standardtherapie
- planned



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

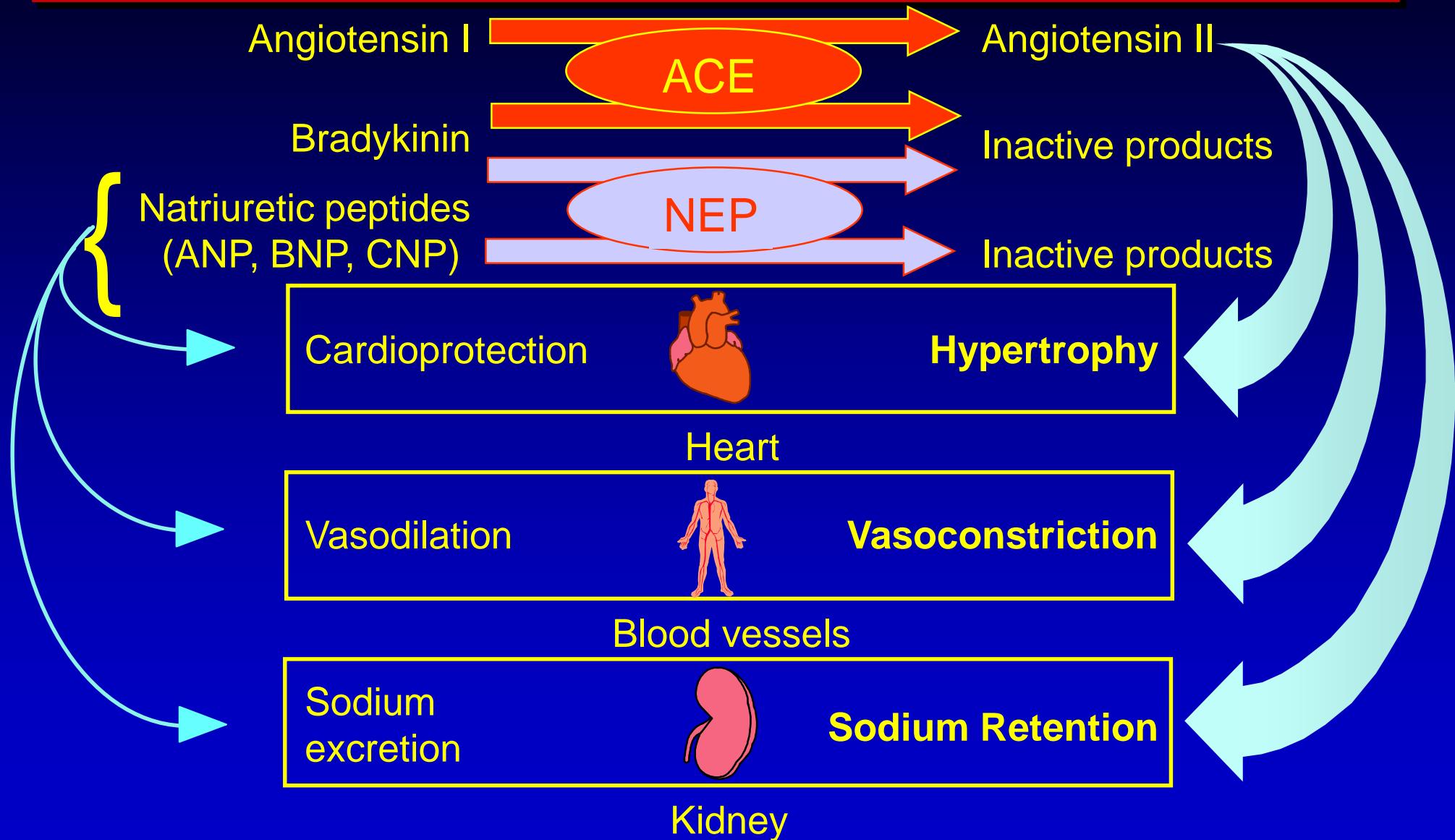


Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI



COR	LOE	Recommendations
I	ARNI: B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).
	See Online Data Supplements 1 and 18.	

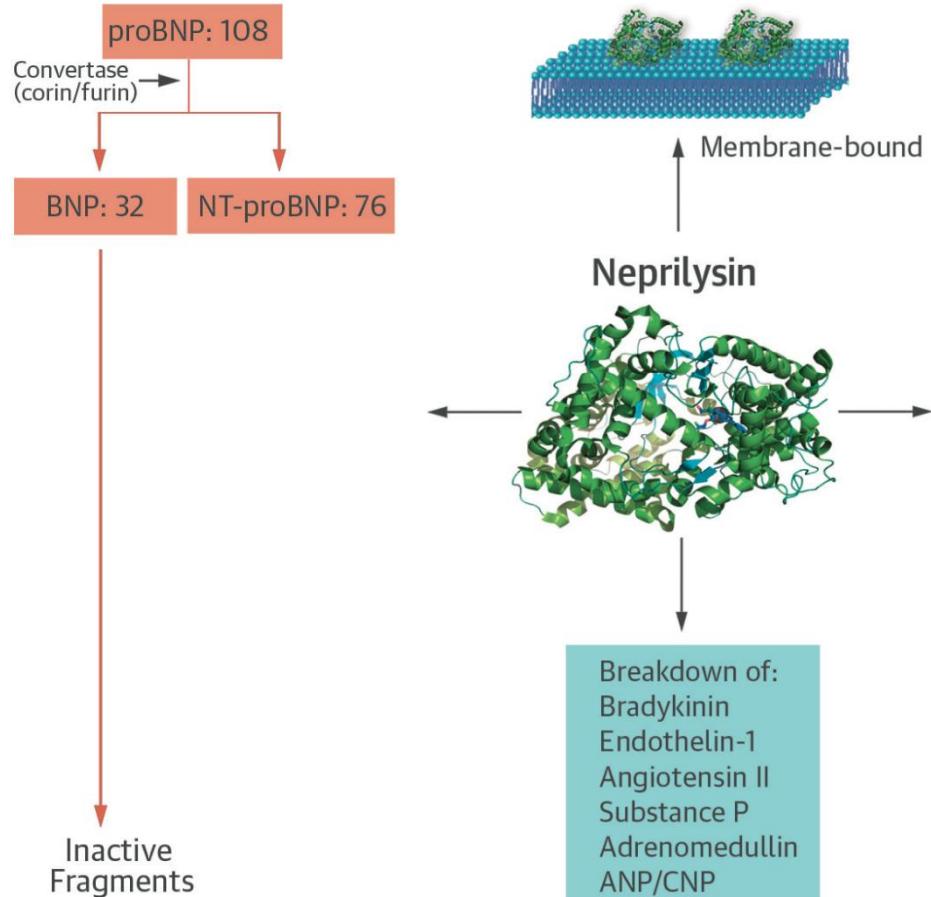
Regulation of Natriuretic Peptides, Bradykinin and Angiotensin II





Soluble Neprilysin Is Predictive of Cardiovascular Death and Heart Failure Hospitalization in Heart Failure Patients

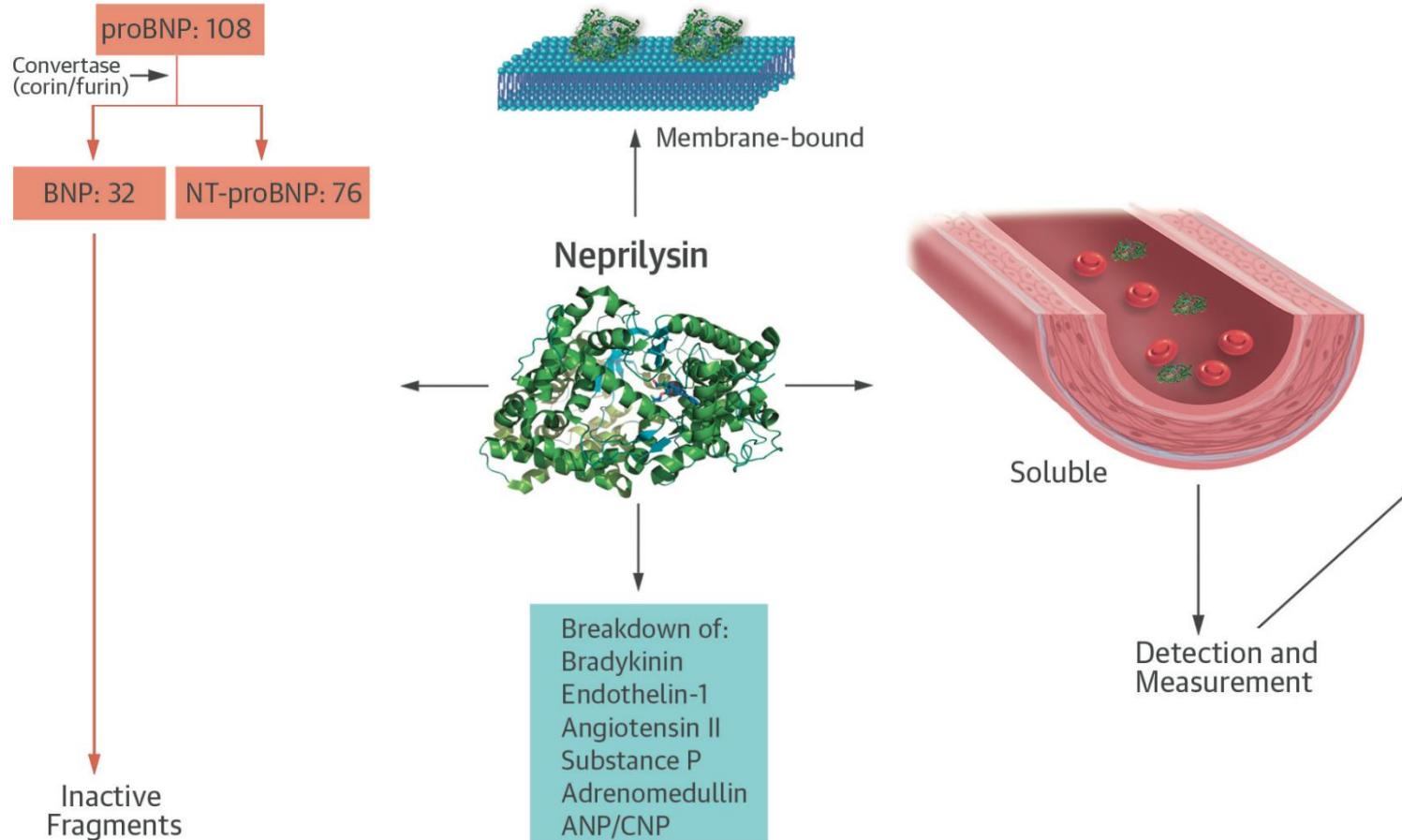
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Mar Domingo, MD, PhD,* Elisabet Zamora, MD, PhD,*‡ Agustín Urrutia, MD, PhD,*‡ Josep Lupón, MD, PhD*‡





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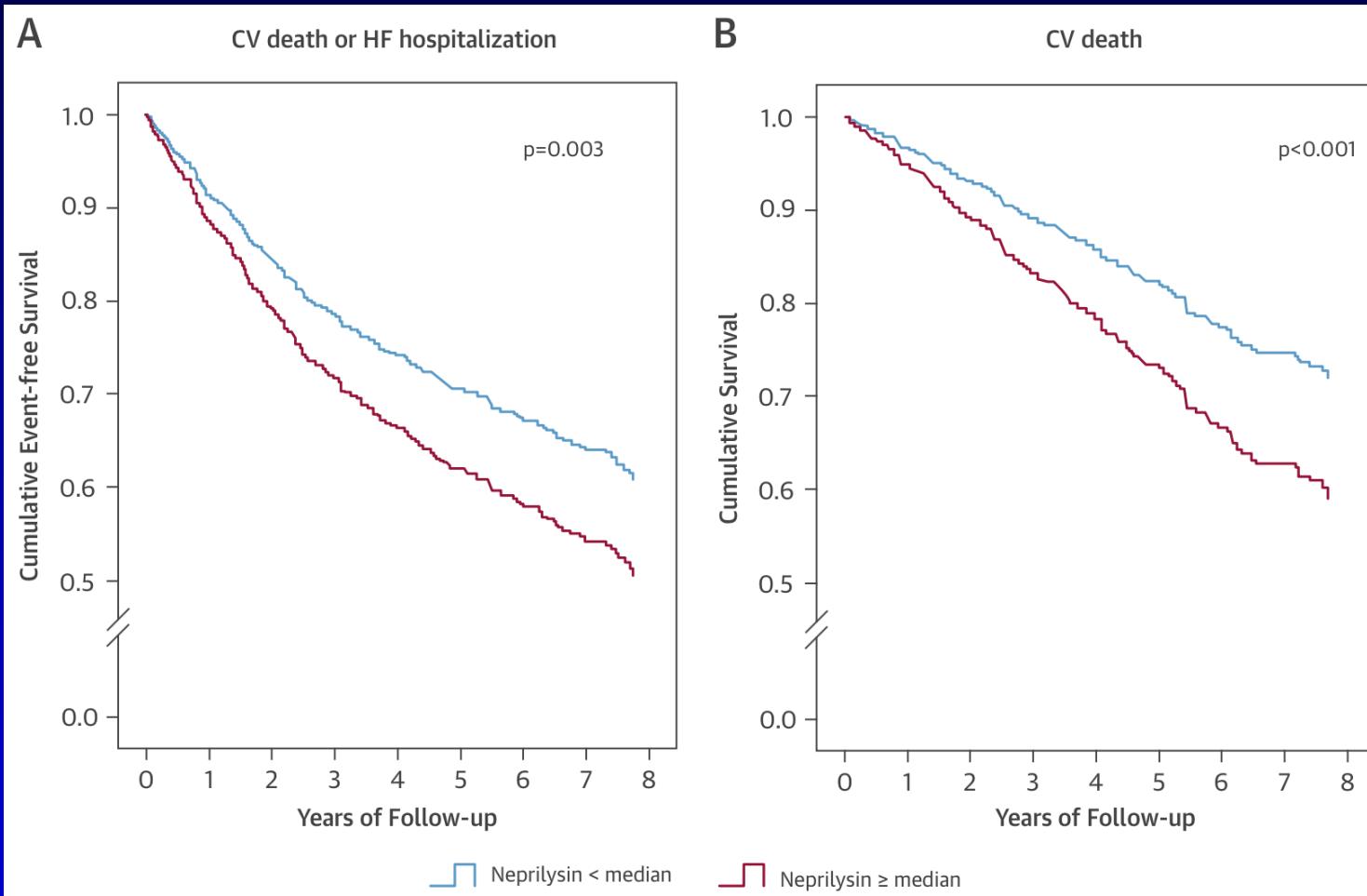
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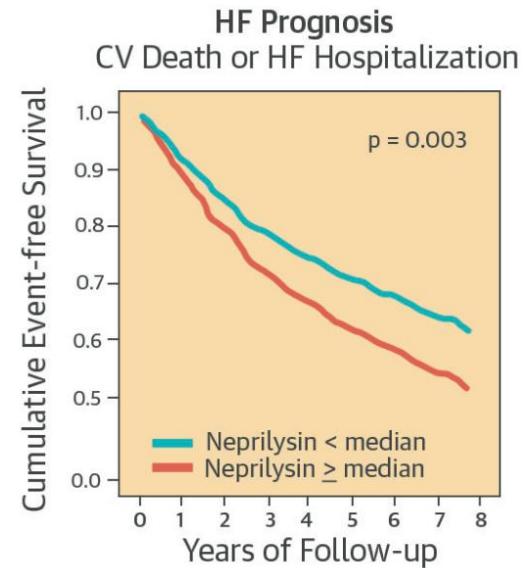
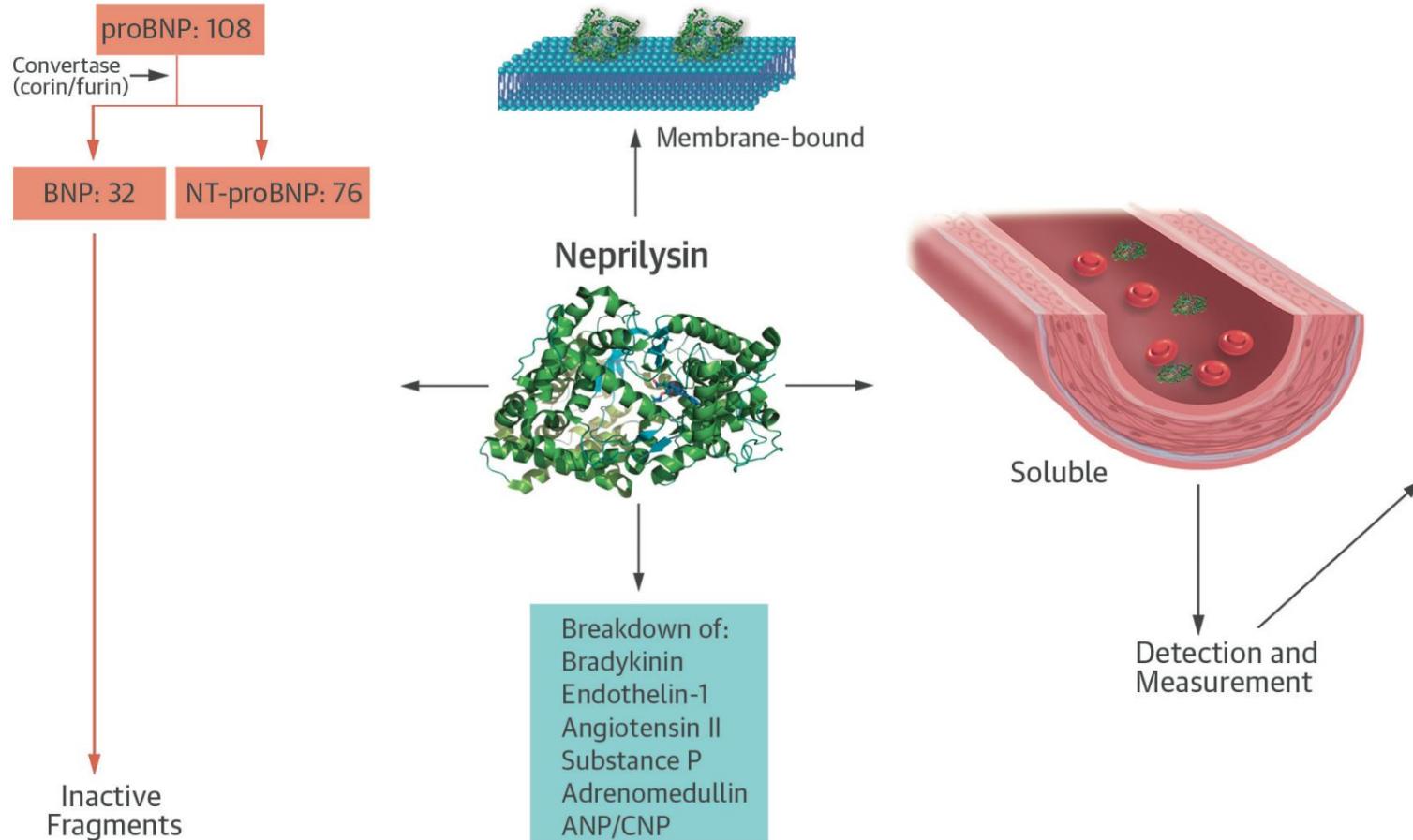
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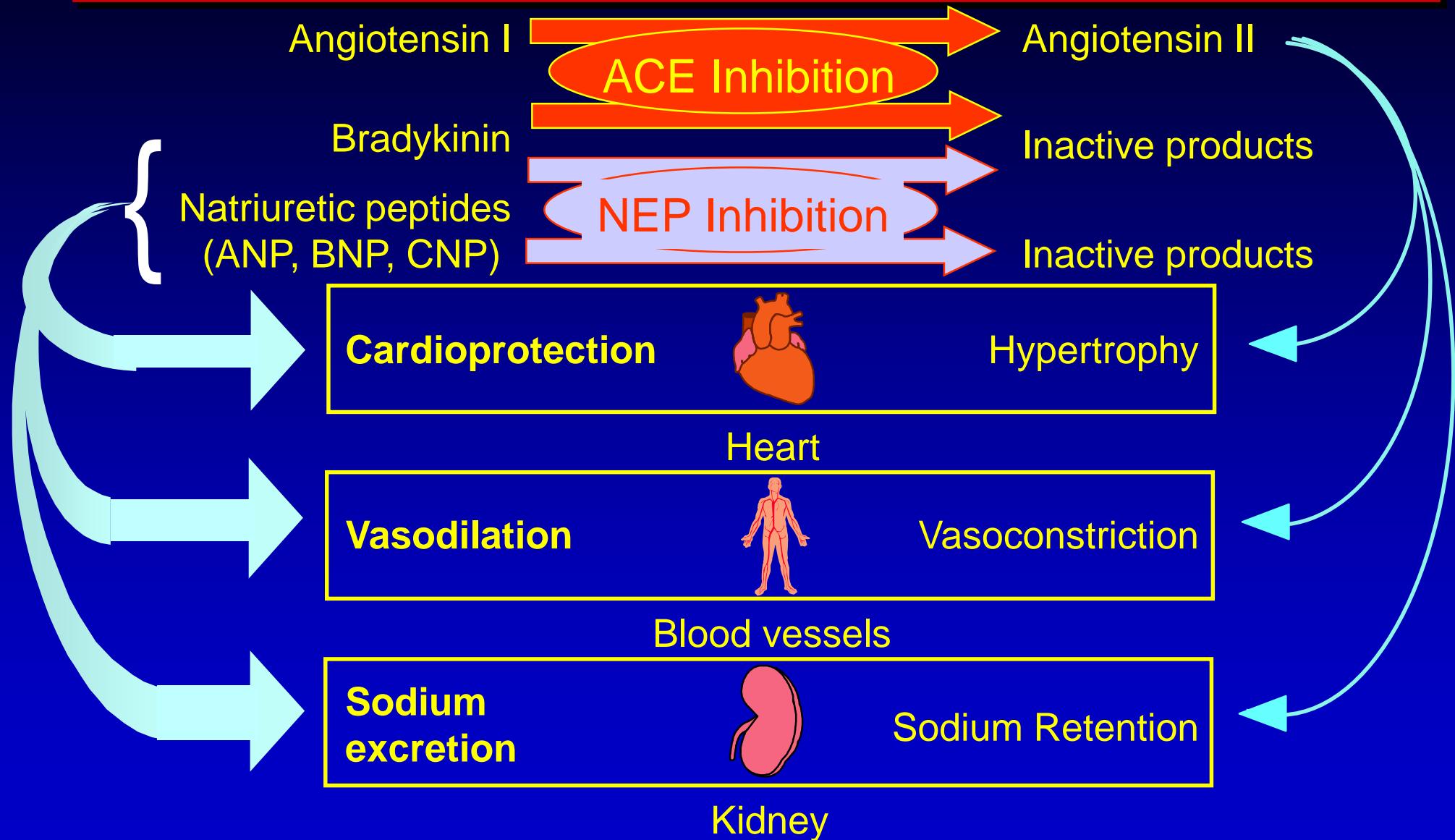


Soluble Neprilysin Is Predictive of Cardiovascular Death and Heart Failure Hospitalization in Heart Failure Patients

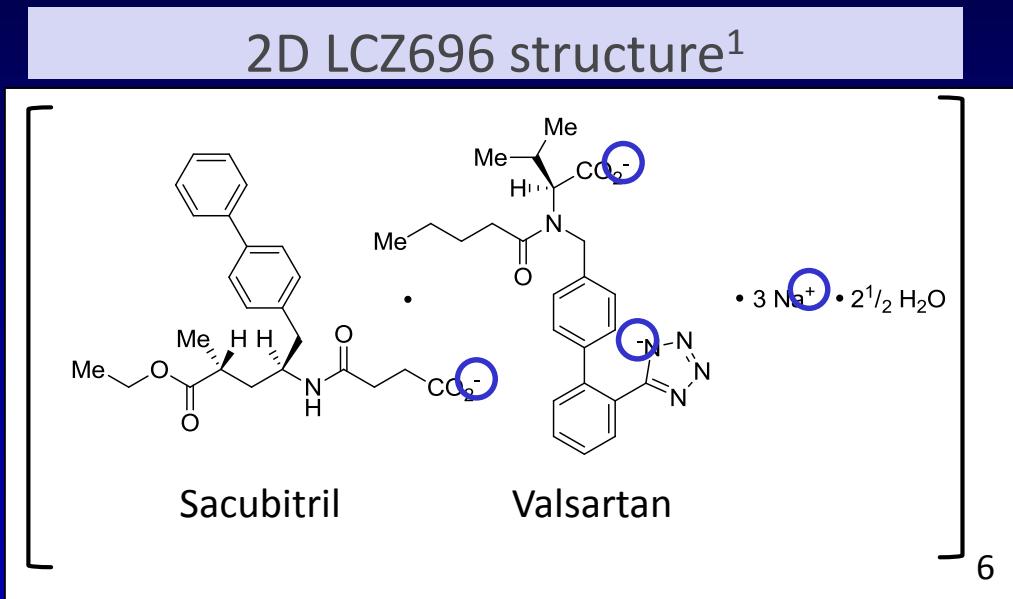
Antoni Bayés-Genís, MD, PhD,*† Jaume Barallat, MD, ‡§ Amparo Galán, MD, PhD, ‡‡ Marta de Antonio, MD, PhD,*† Mar Domingo, MD, PhD,* Elisabet Zamora, MD, PhD,*† Agustín Urrutia, MD, PhD,*† Josep Lupón, MD, PhD*†



Concept of ARNIs : Pharmacologic Actions



LCZ696 is a salt complex



- LCZ696 comprises the anionic forms of sacubitril and valsartan, sodium cations and water²
- Its smallest crystal structure unit consists of:²
 - 6 sacubitril and 6 valsartan molecules in anionic form
 - 18 sodium cations
 - 15 water molecules

- LCZ696 is available in three doses:³
 - 50 mg (24 mg sacubitril / 26 mg valsartan)
 - 100 mg (49 mg sacubitril / 51 mg valsartan)
 - 200 mg (97 mg sacubitril / 103 mg valsartan)

1. Novartis Data on File: LCZ696 Investigator's Brochure Edition 16, 25 March 2015;

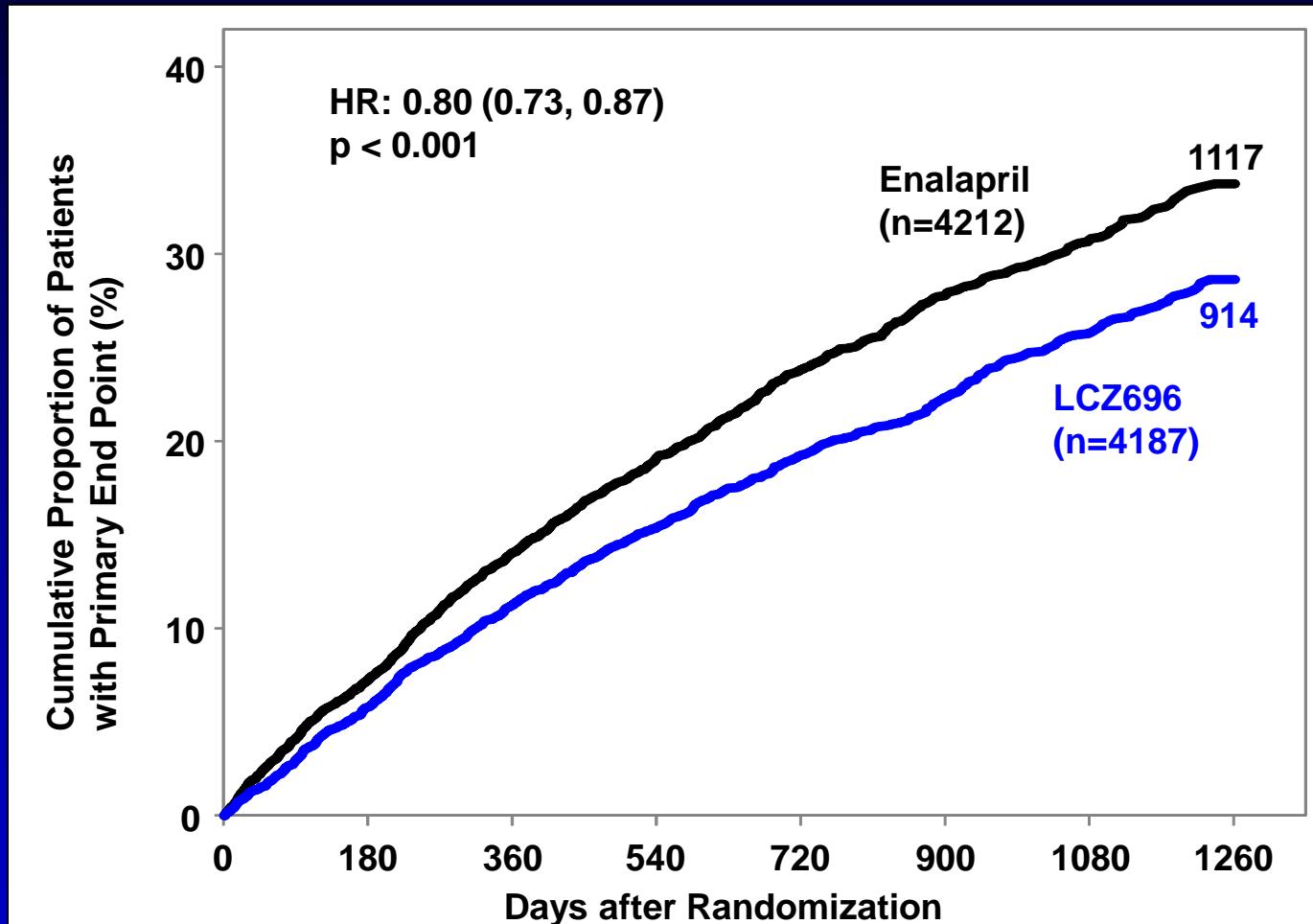
2. Feng et al. Tetrahedron Lett 2012;53:275-6;

3. Novartis Data on File: Entresto Product Information, Version 1.0, 2015

<http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf>; Last Accessed 21 August 2015

PARADIGM-HF: Primary outcome

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial



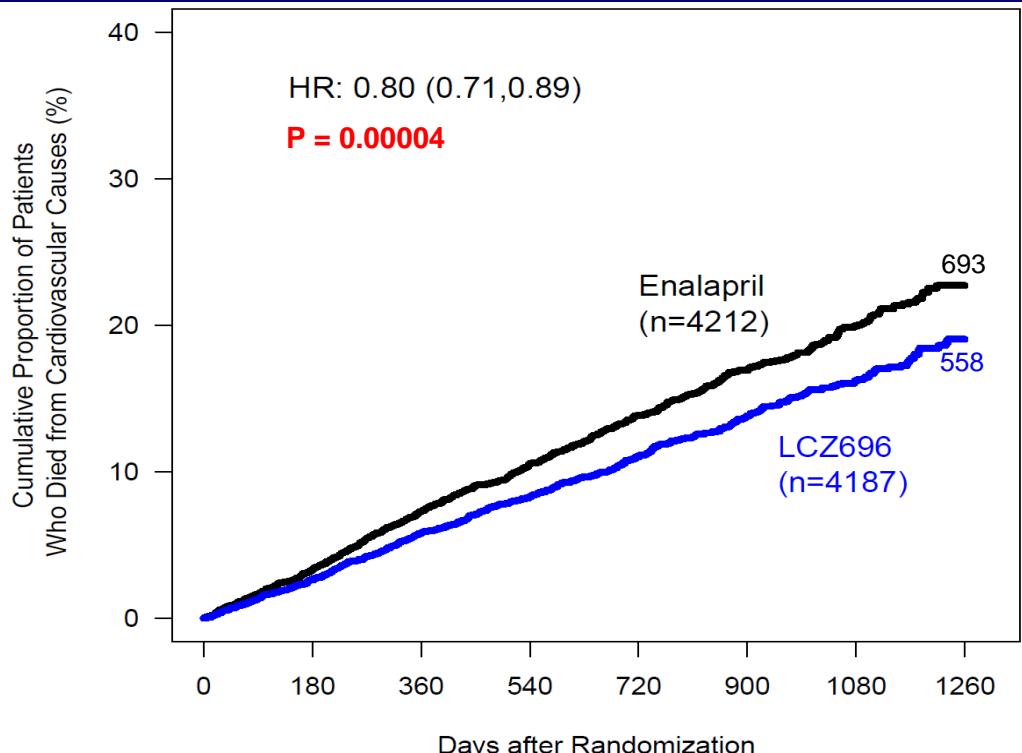
At risk

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

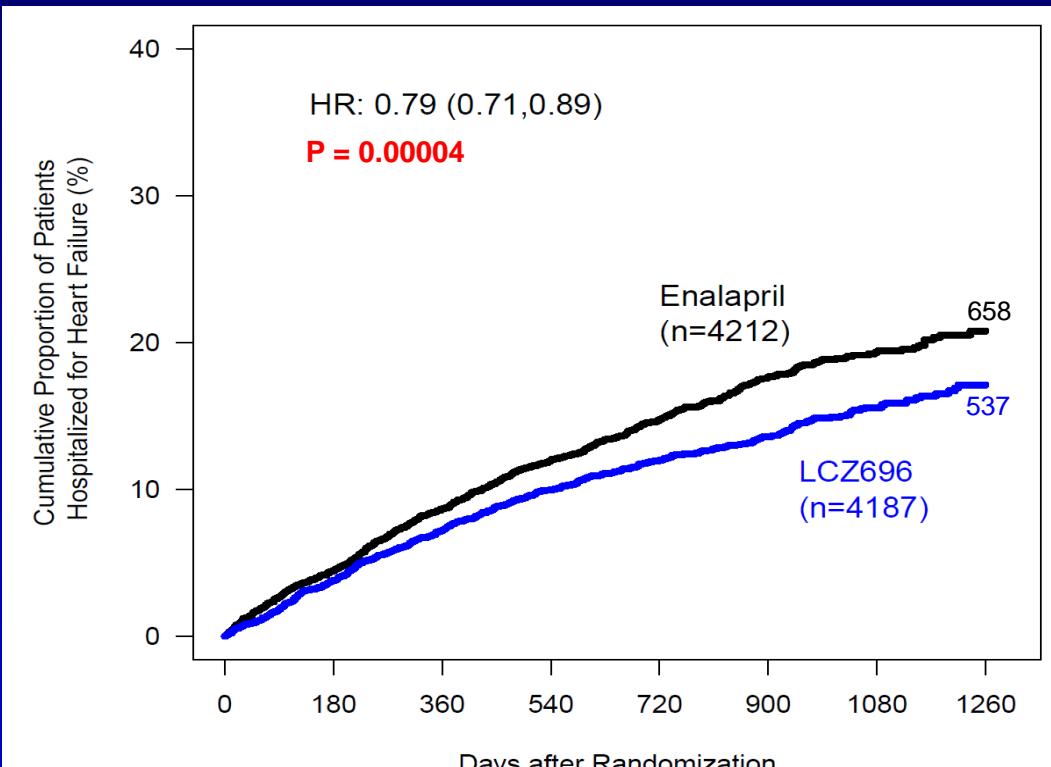
PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

**Death from CV causes
20% risk reduction**



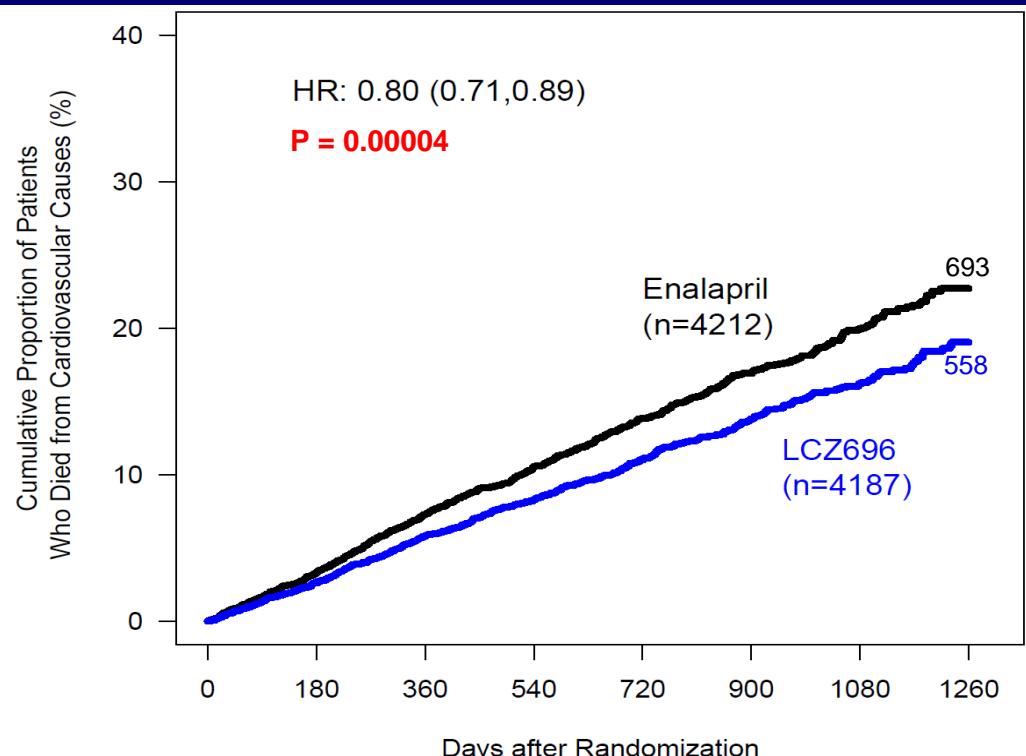
**HF hospitalization
21% risk reduction**



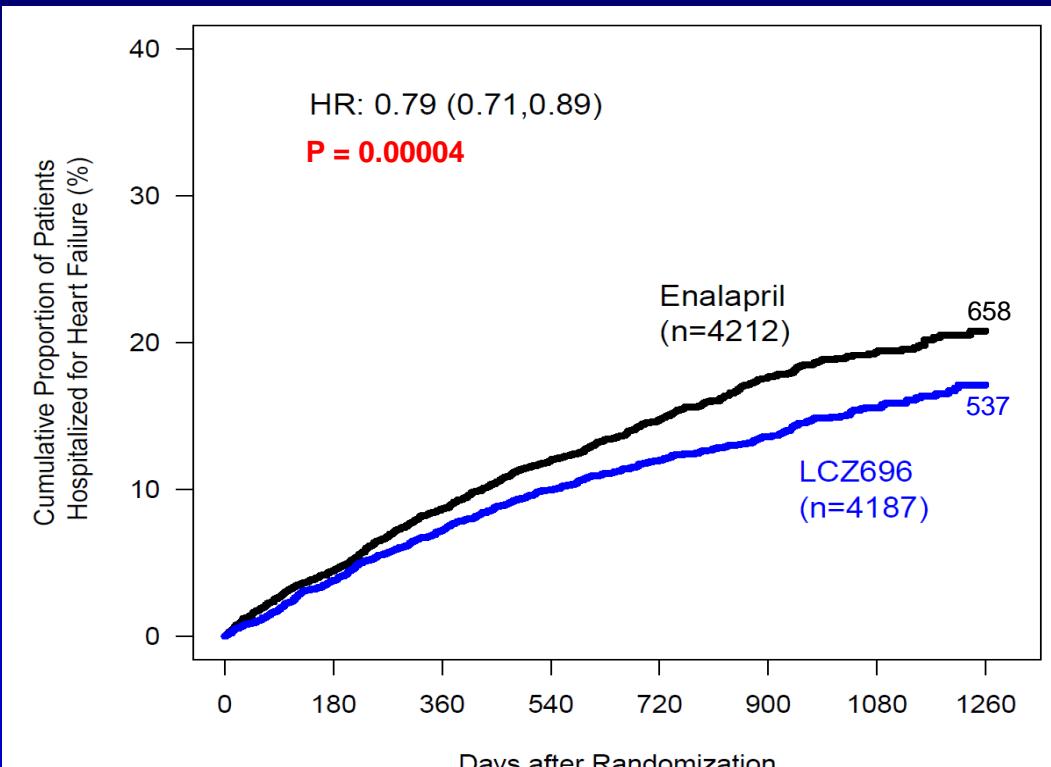
PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

**Death from CV causes
20% risk reduction**

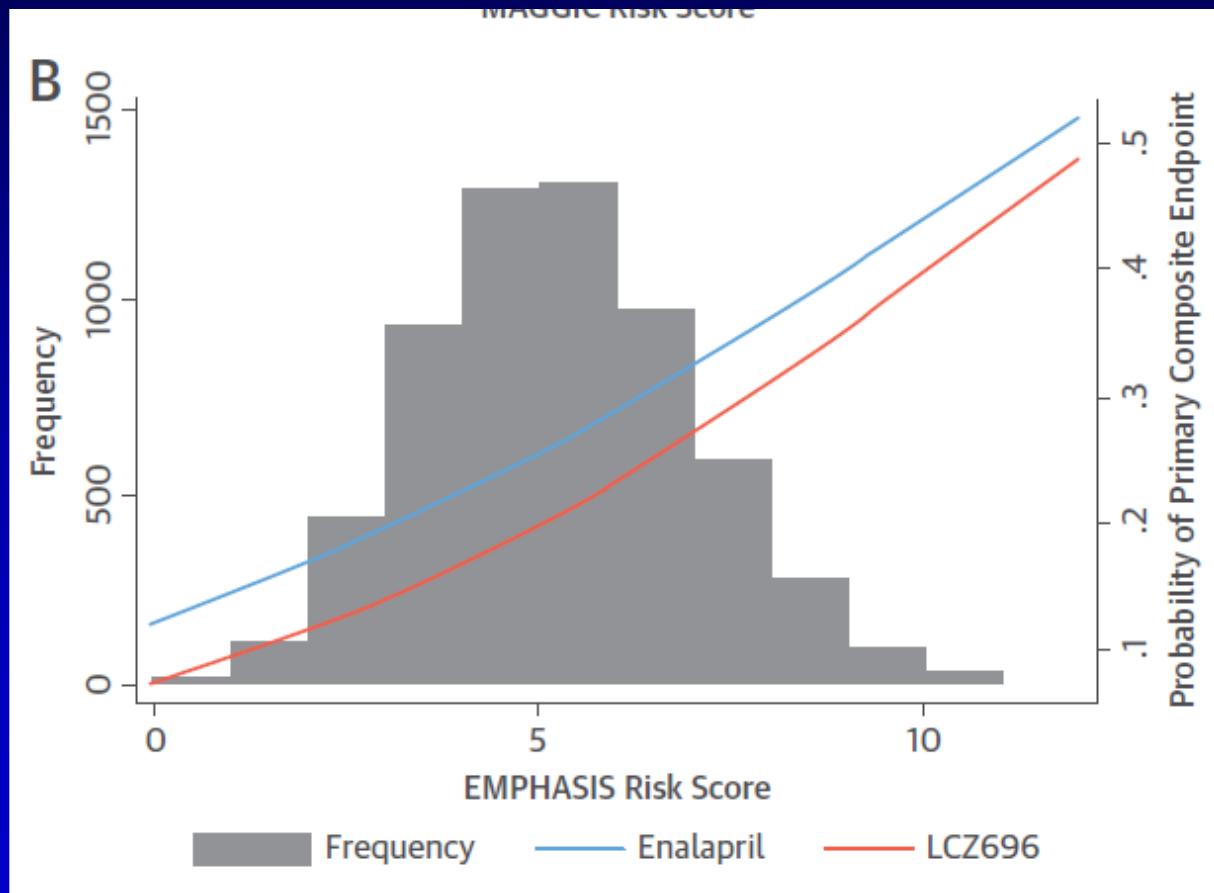


**HF hospitalization
21% risk reduction**

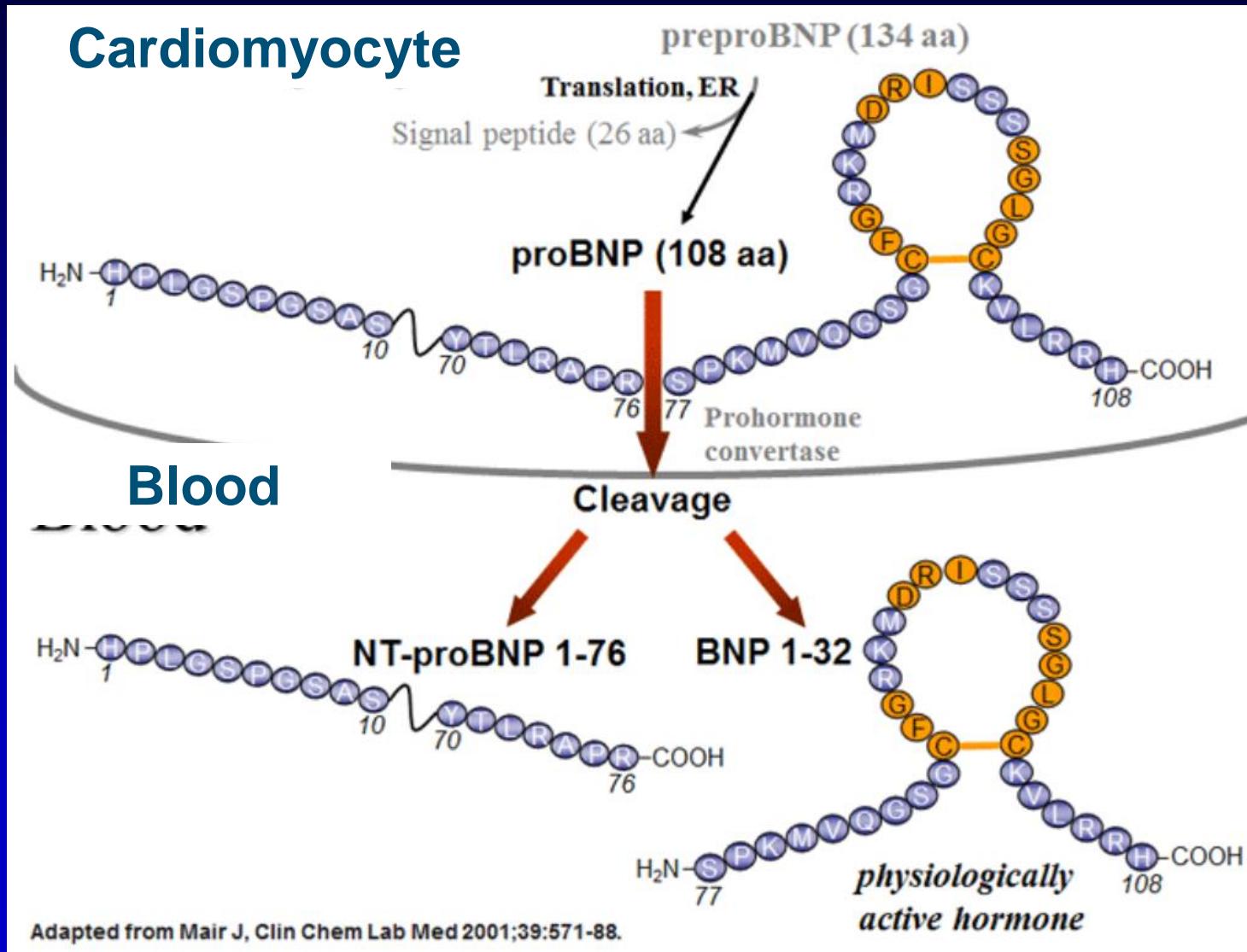


Comparing LCZ696 With Enalapril According to Baseline Risk Using the MAGGIC and EMPHASIS-HF Risk Scores

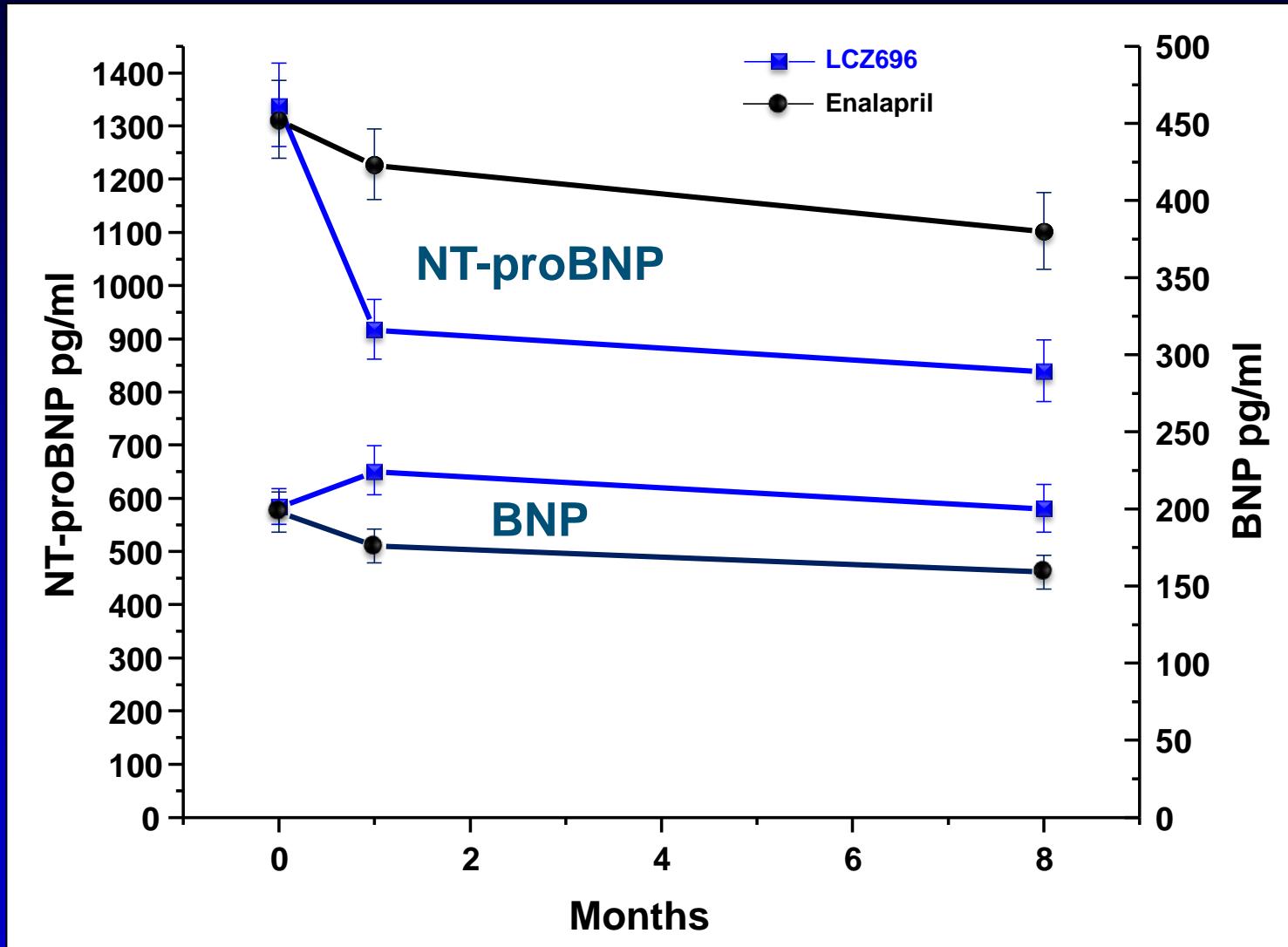
An Analysis of Mortality and Morbidity in PARADIGM-HF



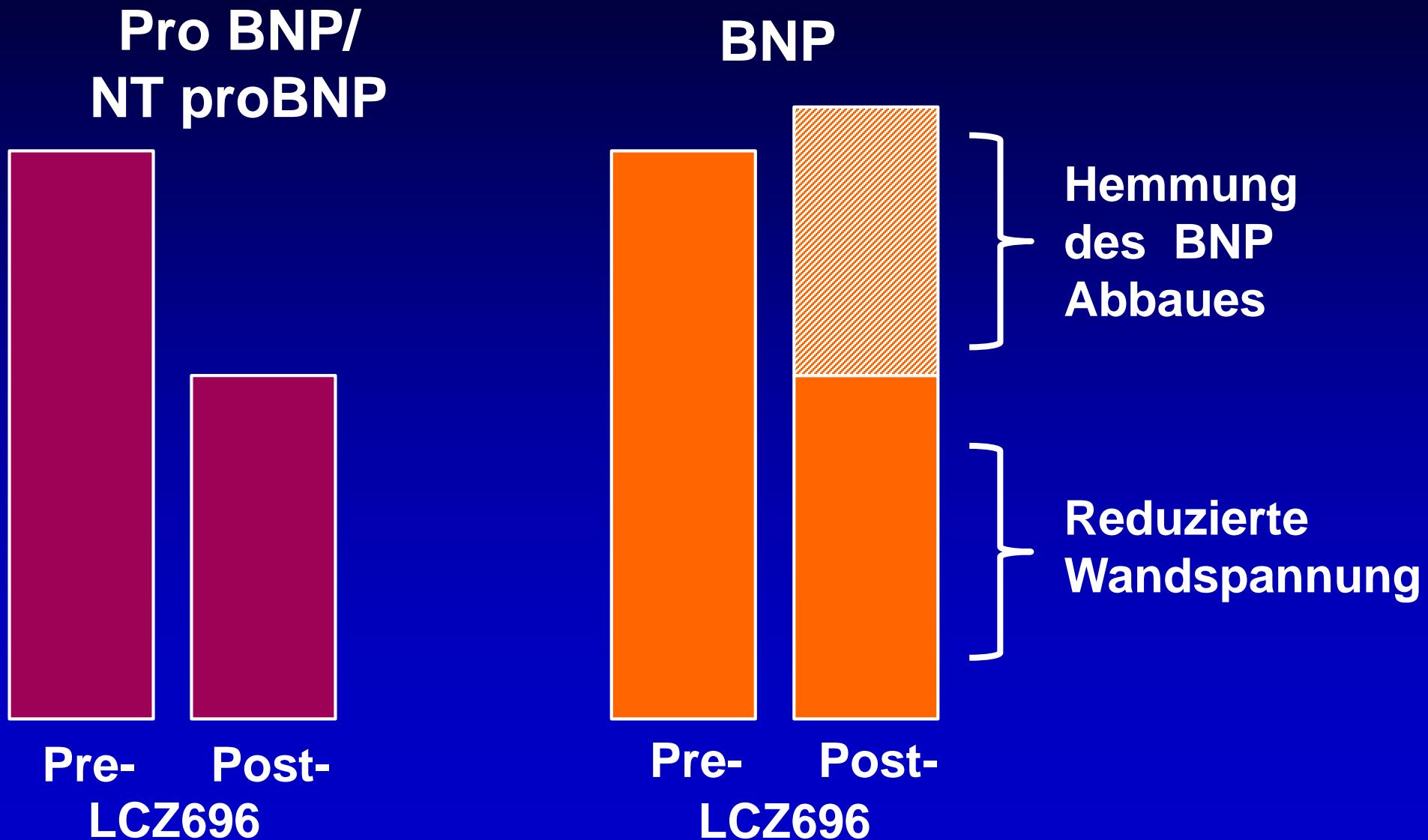
What to do with Markers: NT pro BNP and BNP



PARADIGM-HF: NT-proBNP and BNP



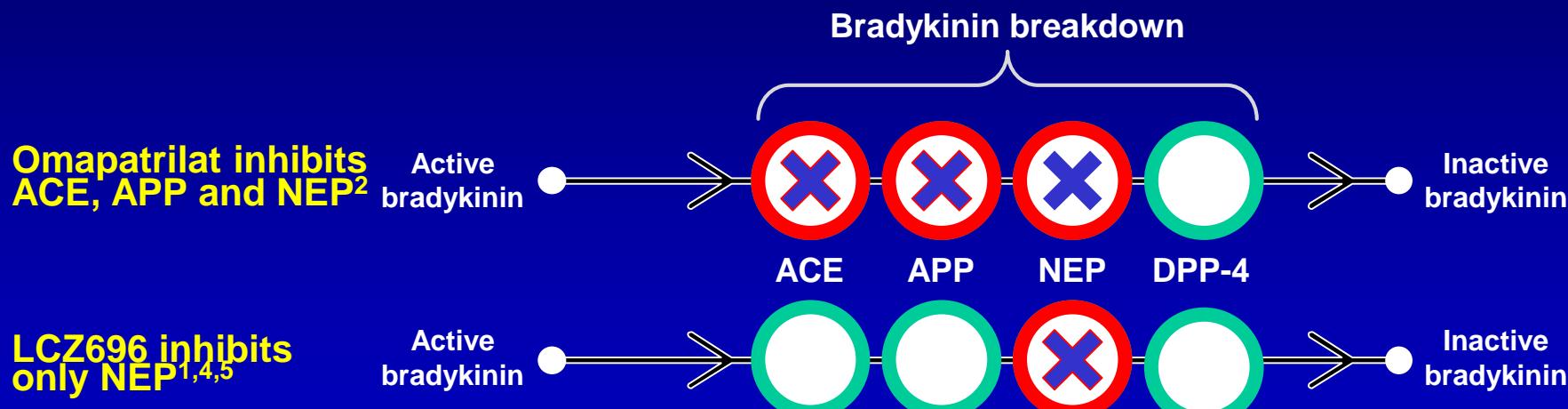
NT pro BNP and BNP Änderungen with LCZ696 (*schematisch*)



How to Switch from an ACE Inhibitor? Angioedema?

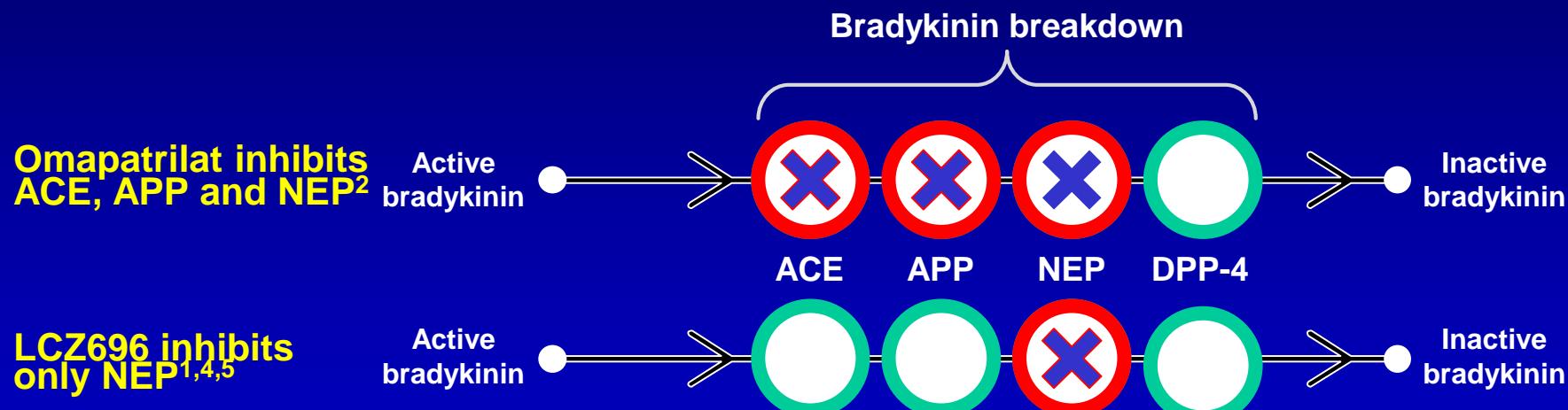
LCZ696 actively inhibits Neprilysin and the AT₁ receptor, thus enabling alternative degradation pathways for bradykinin

- Bradykinin is a substrate of Neprilysin and other vasoconstrictors (ACE, APP, DPP-4) – its elevation has been associated with cough and angioedema^{2,3}
- Omapatrilat inhibits three enzymes (ACE, APP, NEP) involved in the breakdown of bradykinin, which is likely to be responsible for the development of angioedema²



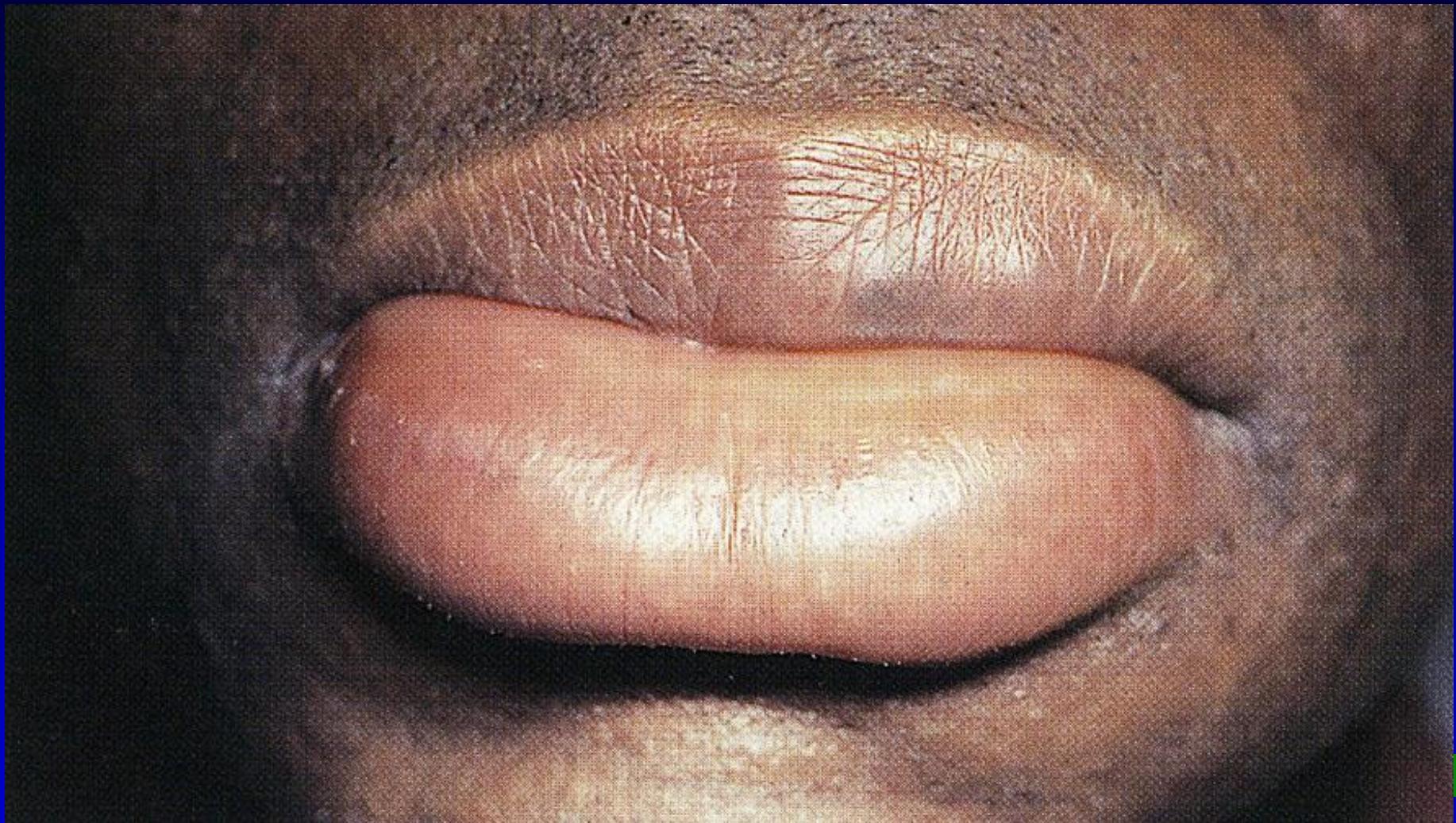
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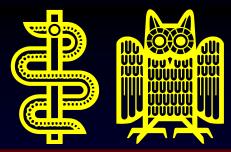
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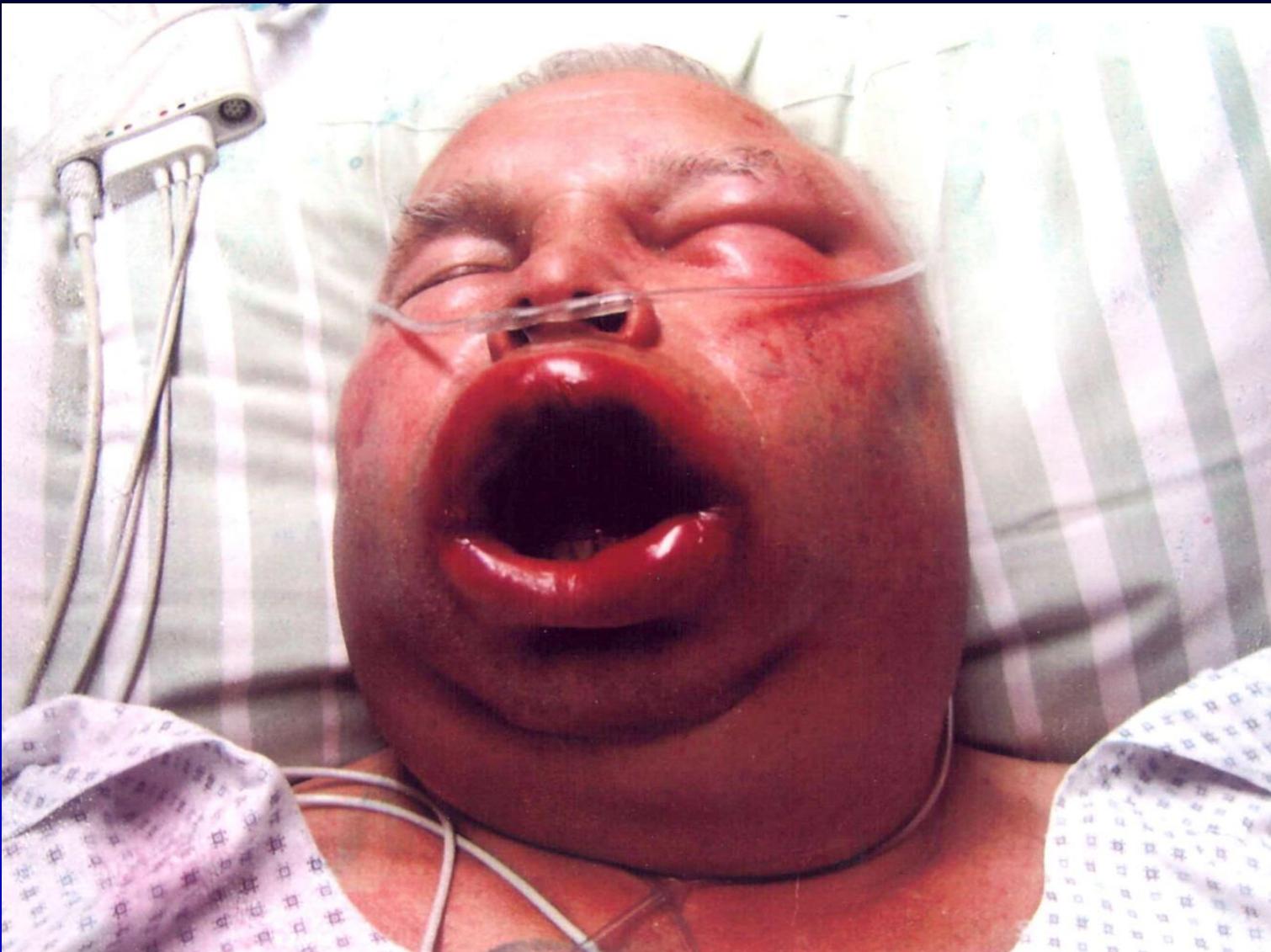
Take Care of Wash Out, ie at least 36 hours!

ACE-NEP Inhibition: Omapatrilat





Quincke-Ödem



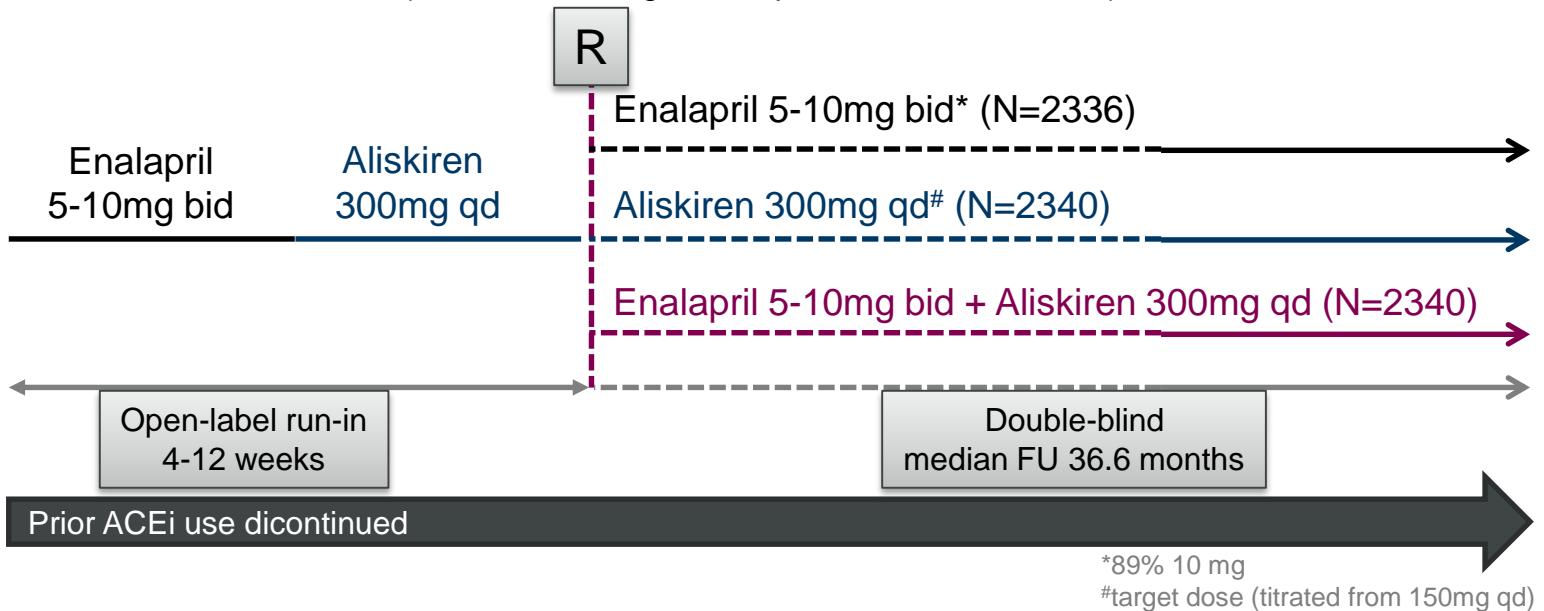
What do we need?

- PARAGON: LCZ in HFPEF
- Single application
- Resistant hypertension. Impaired renal function

ATMOSPHERE

Methods

Primary outcome: CV death or heart failure hospitalization
(event driven: target 2318 patients, 2369 occurred)



In reducing the risk of the primary composite outcome of cardiovascular death or heart failure hospitalization ...

Superiority hypotheses

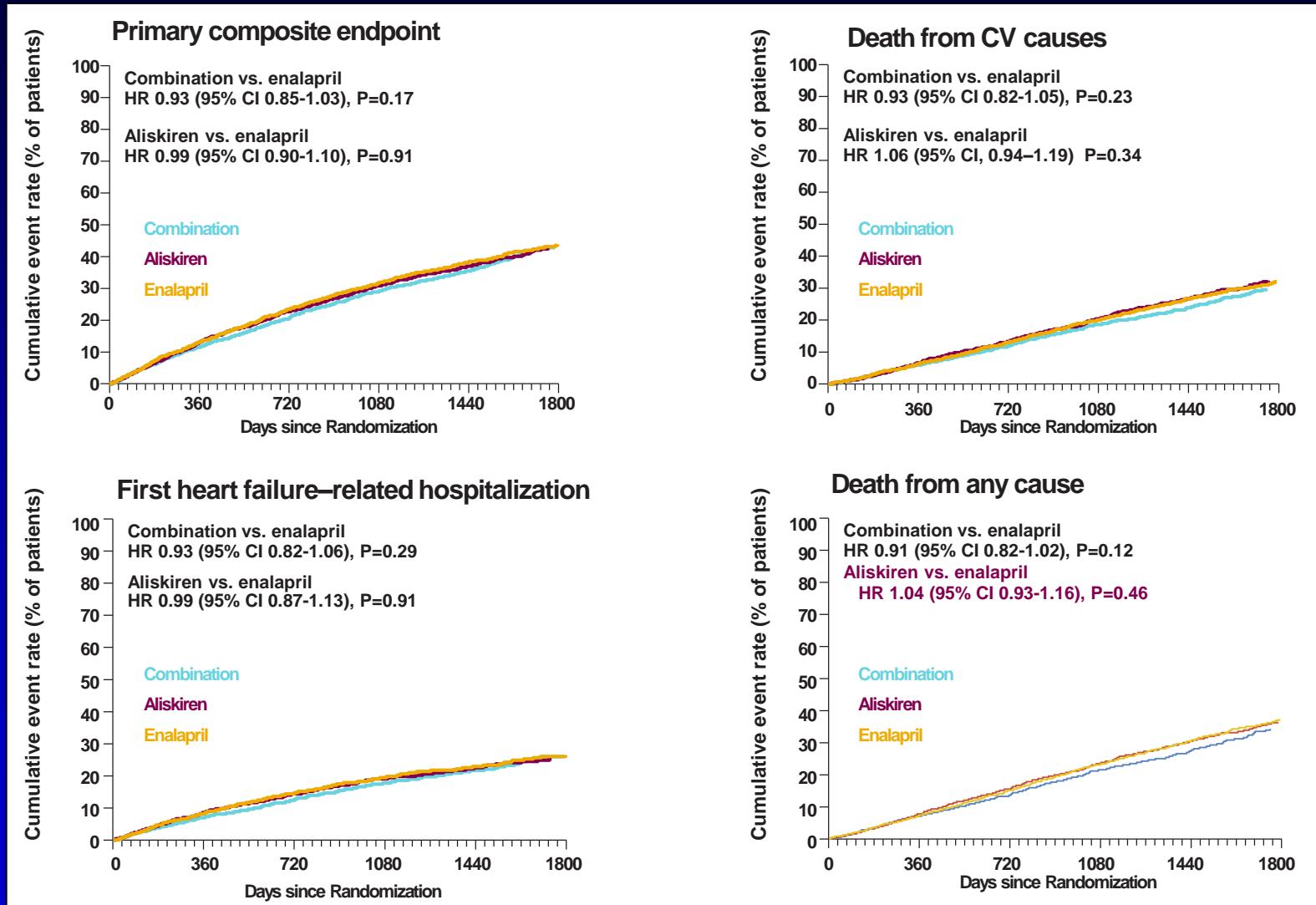
- Aliskiren added to enalapril is superior to enalapril
- Aliskiren monotherapy is superior to enalapril

Non-inferiority hypotheses

- Aliskiren monotherapy is non-inferior to enalapril

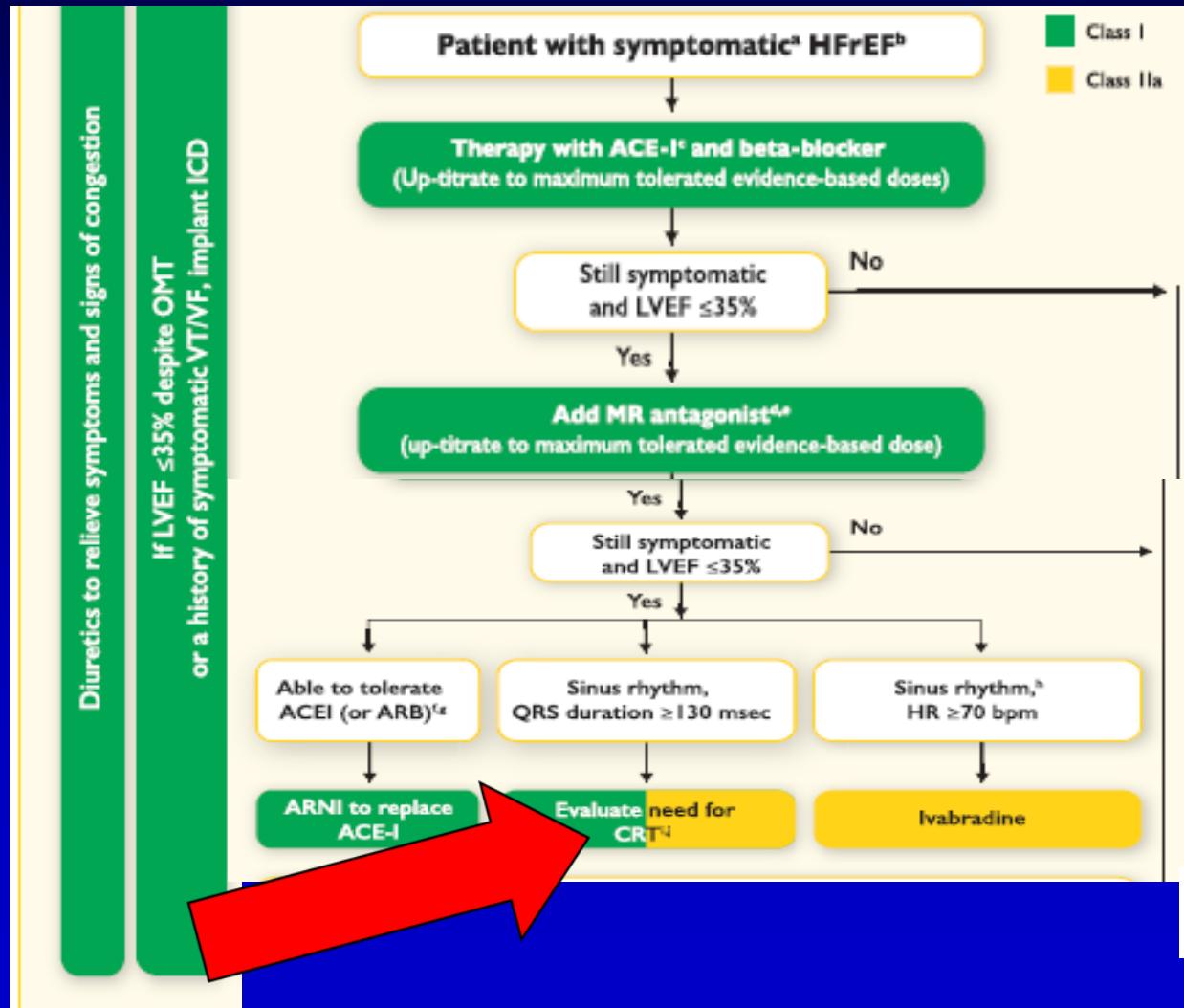
ATMOSPHERE

Results – superiority hypothesis





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





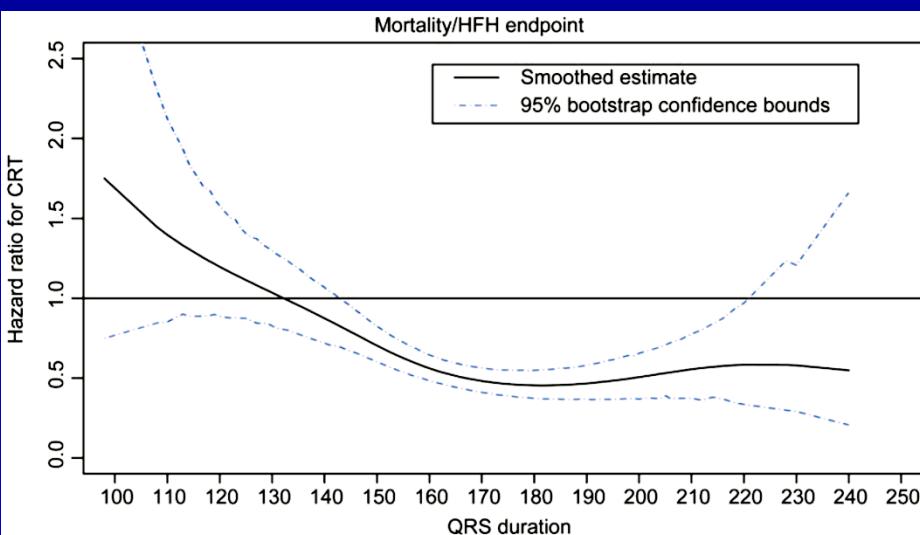
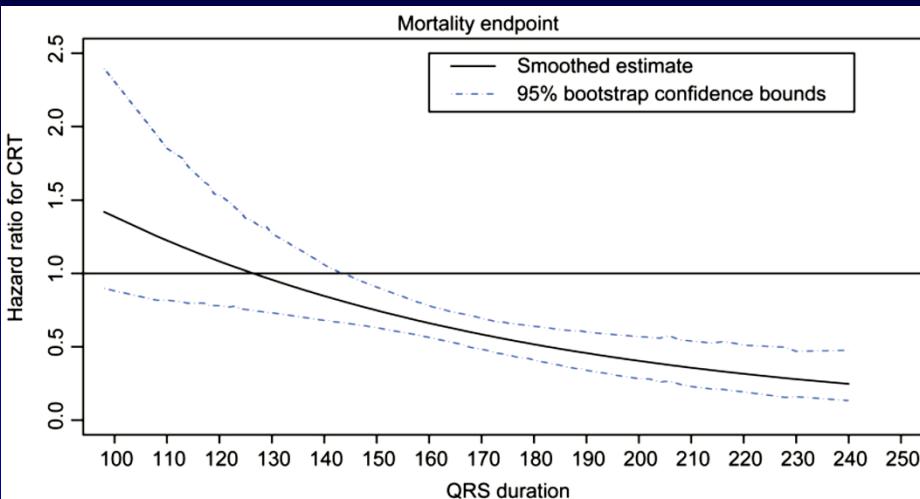
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

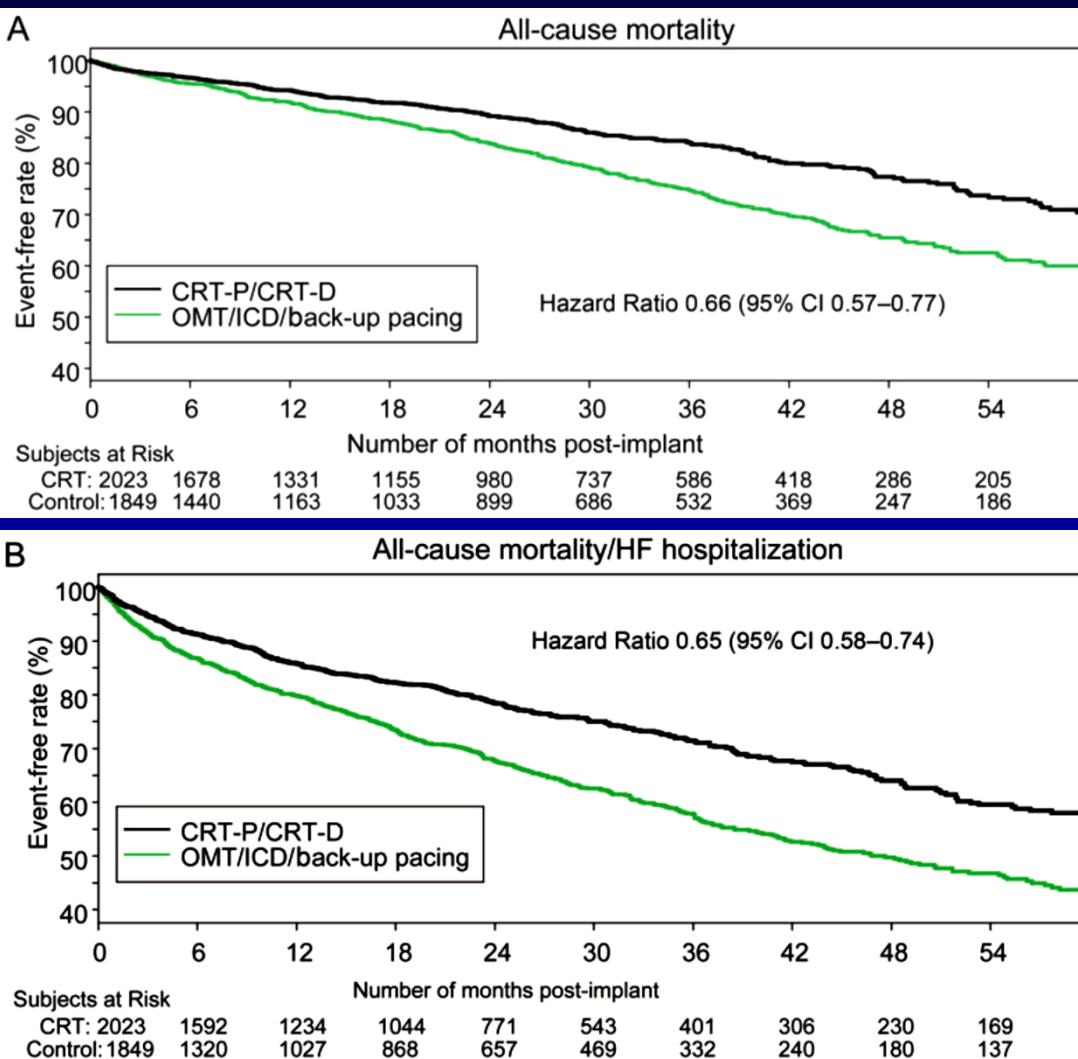
Recommendations	Class ^a	Level ^b	Ref ^c
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 msec and LBBB QRS morphology and with LVEF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 150 msec and non-LBBB QRS morphology and with LVEF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF $\leq 35\%$ despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF $\leq 35\%$ in NYHA Class III–IV ^d despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥ 130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285



An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure

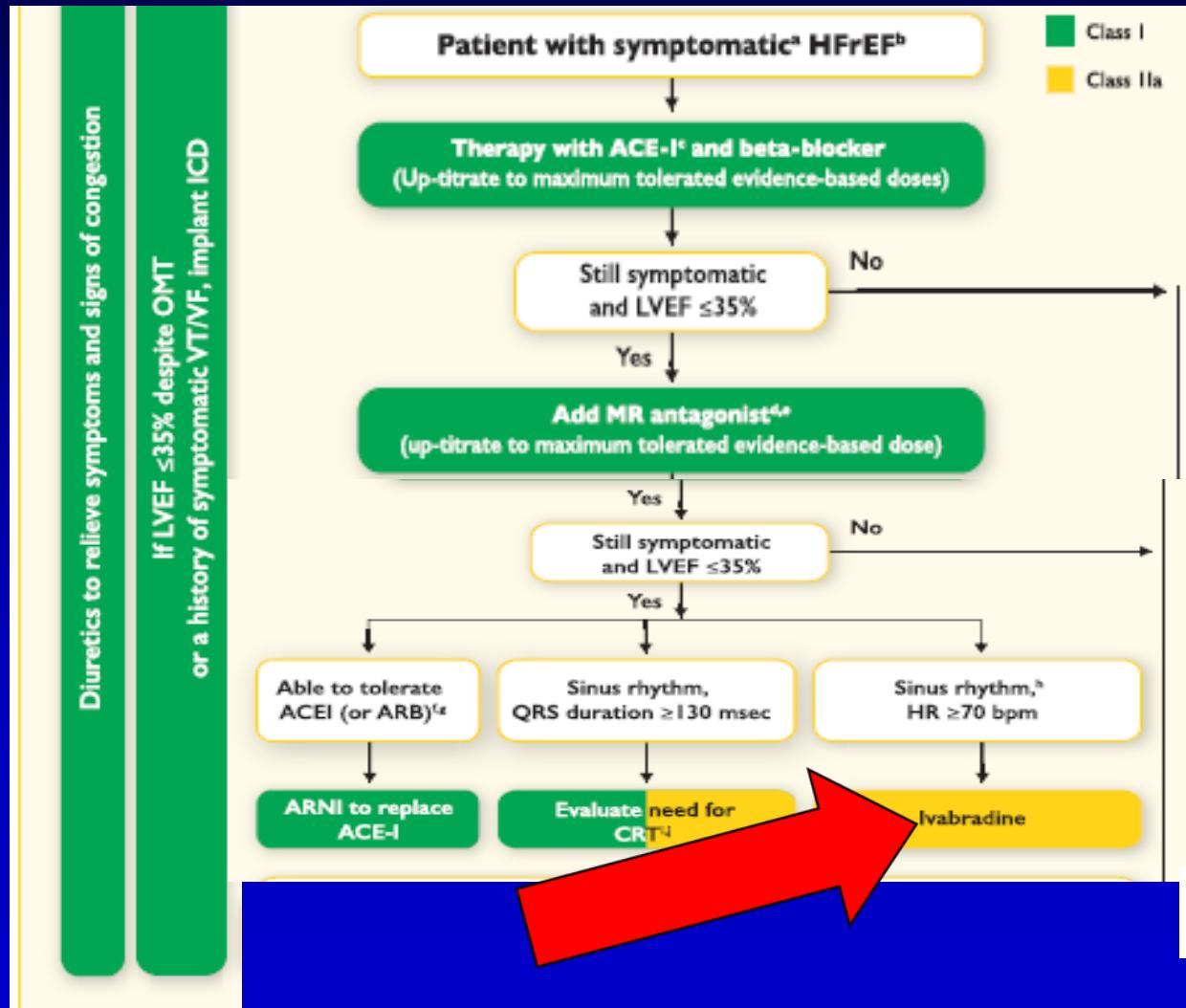


An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure



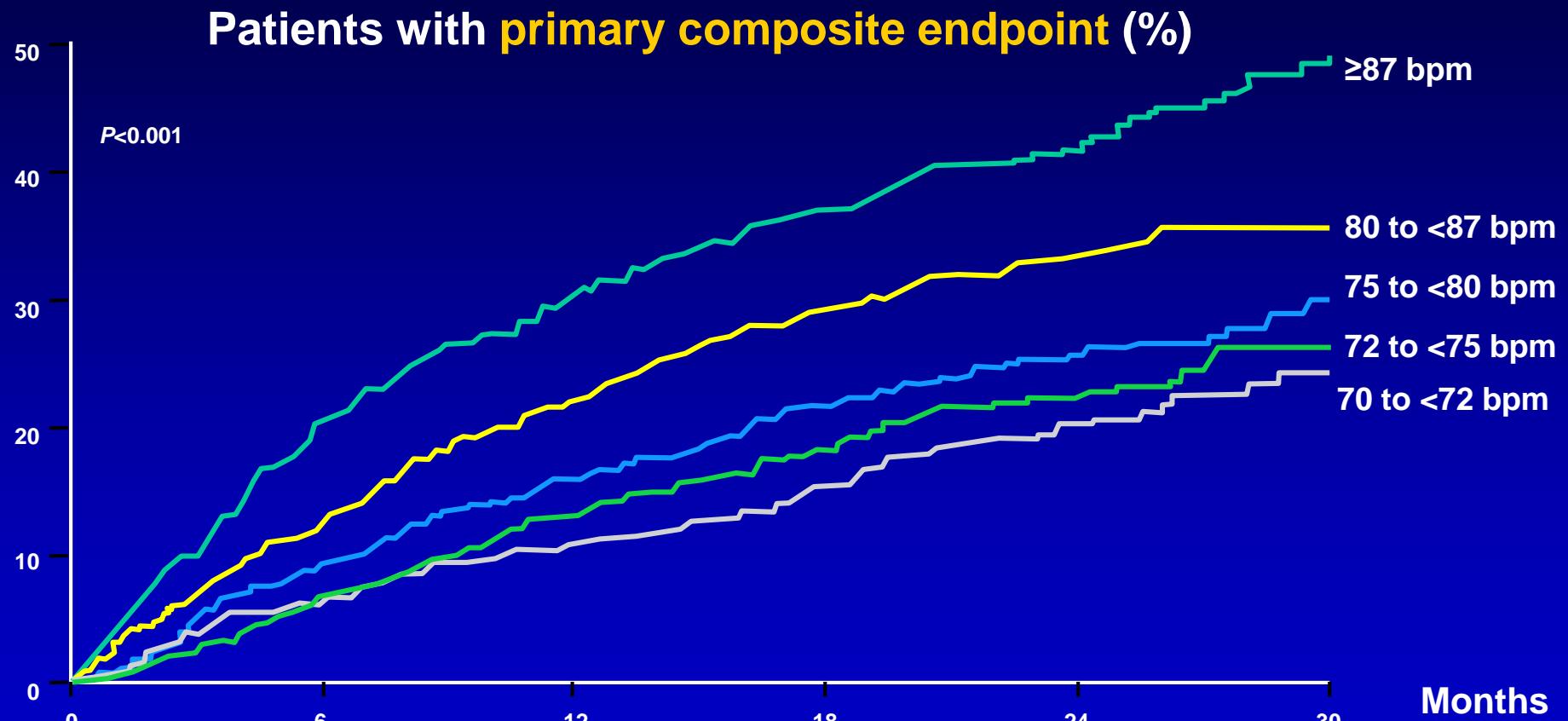


2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



Baseline heart rate is a predictor of endpoints on placebo

Stable CHF, SR > 70 bpm



Primary composite endpoint: risk increases by 2.9% per 1-bpm increase, and by 15.6% per 5-bpm increase

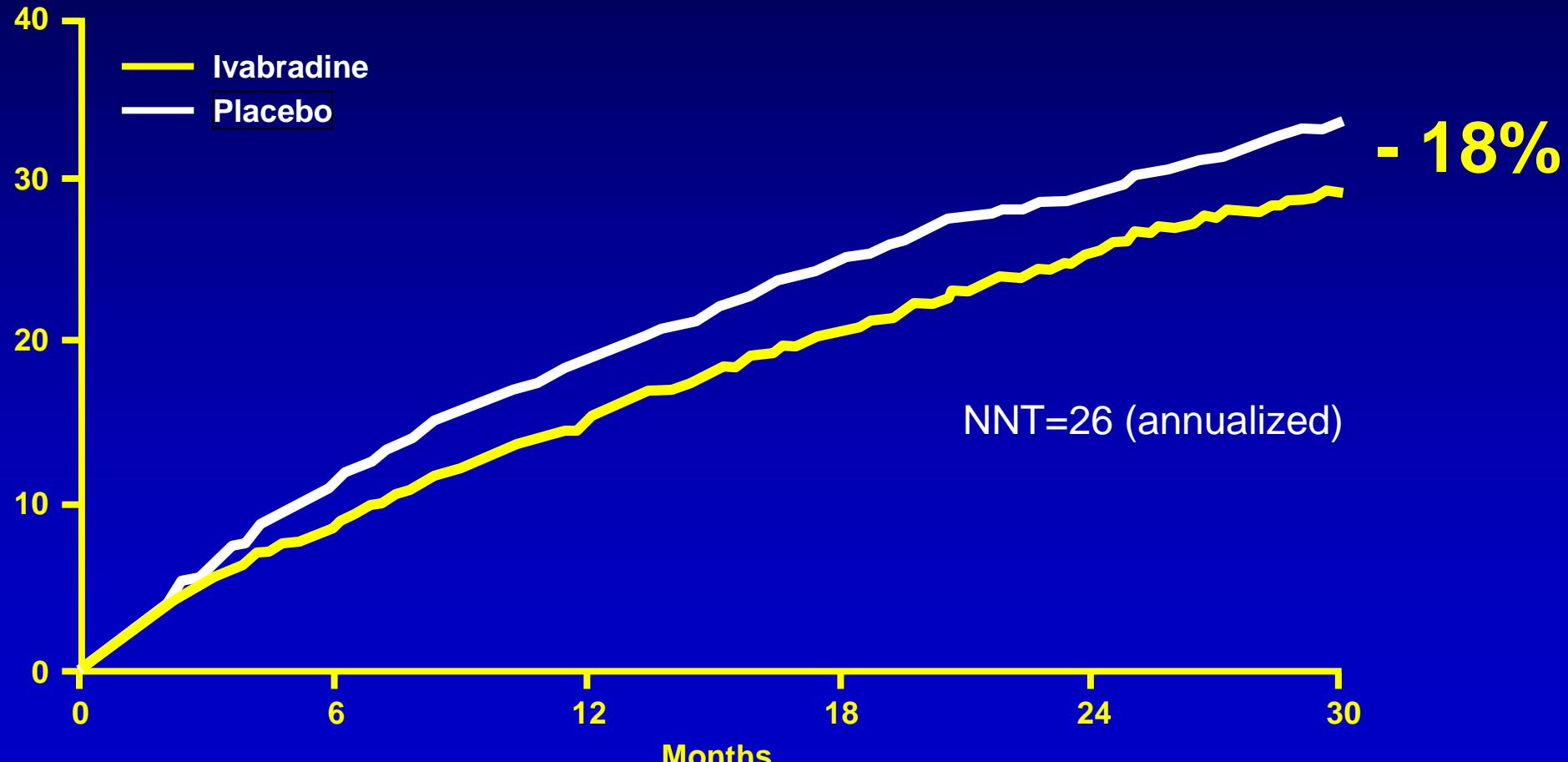
Primary composite endpoint

NYHA II-IV, SR > 70 bpm

Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

HR = 0.82 $p<0.0001$

Cumulative frequency (%)



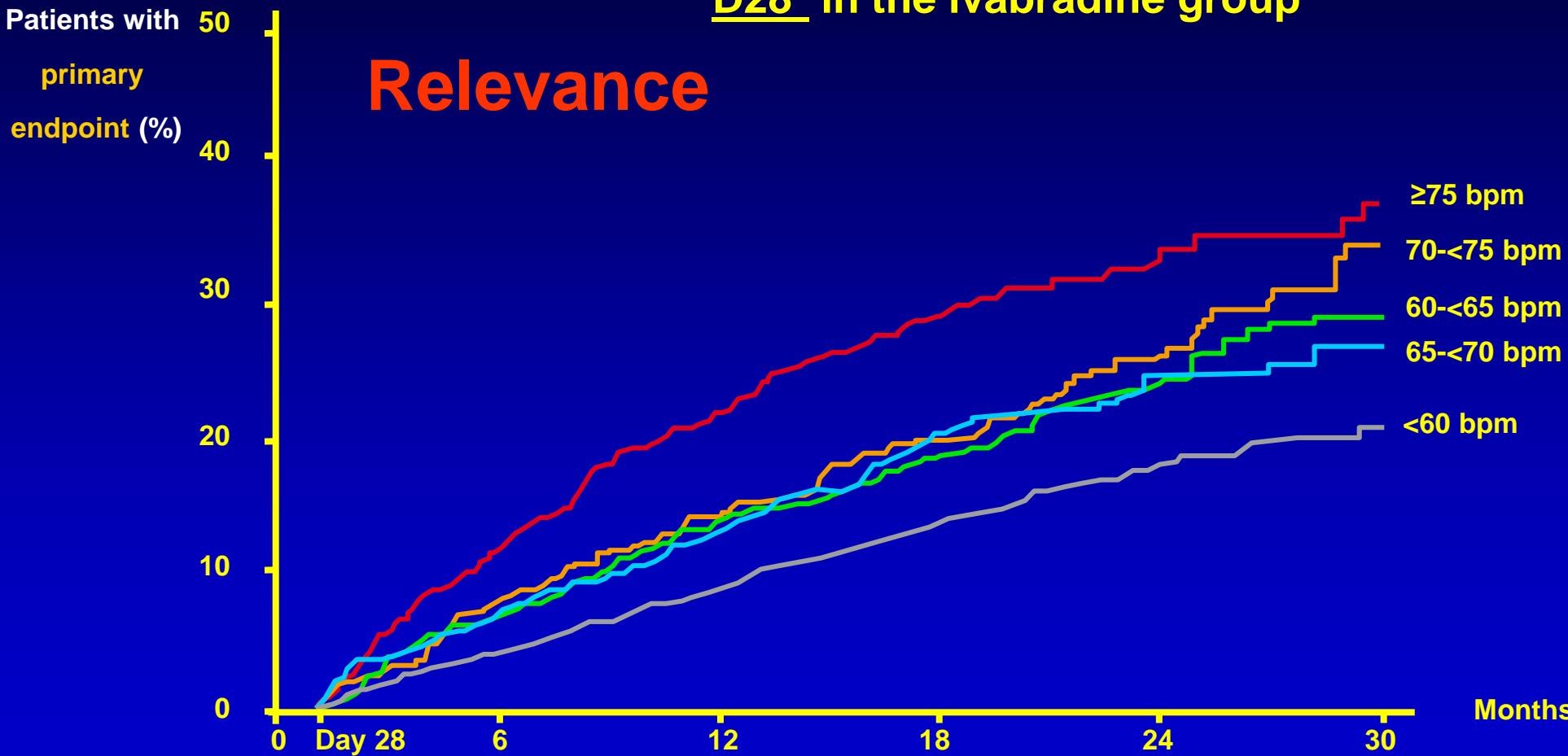
Swedberg et al, Lancet 376 (2010): 875-885

Effect of ivabradine on outcomes

Endpoints	Hazard ratio	95% CI	p value
Primary composite endpoint	0.82	[0.75;0.90]	p<0.0001
CV death	0.91	[0.80;1.03]	p=0.128
Hospitalization for HF	0.74	[0.66;0.83]	p<0.0001
All-cause death	0.90	[0.80;1.02]	p=0.092
Death from HF	0.74	[0.58;0.94]	p=0.014
Hospitalization for any cause	0.89	[0.82;0.96]	p=0.003
Hospitalization for CV reason	0.85	[0.78;0.92]	p=0.0002

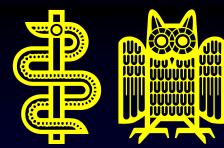
Achieved Heart Rate at Day 28

Primary composite endpoint according to heart rate achieved at D28* in the ivabradine group





Comorbidities in Chronic Heart Failure



Detect Co-morbidities and Precipitating Factors

Non-cardiovascular

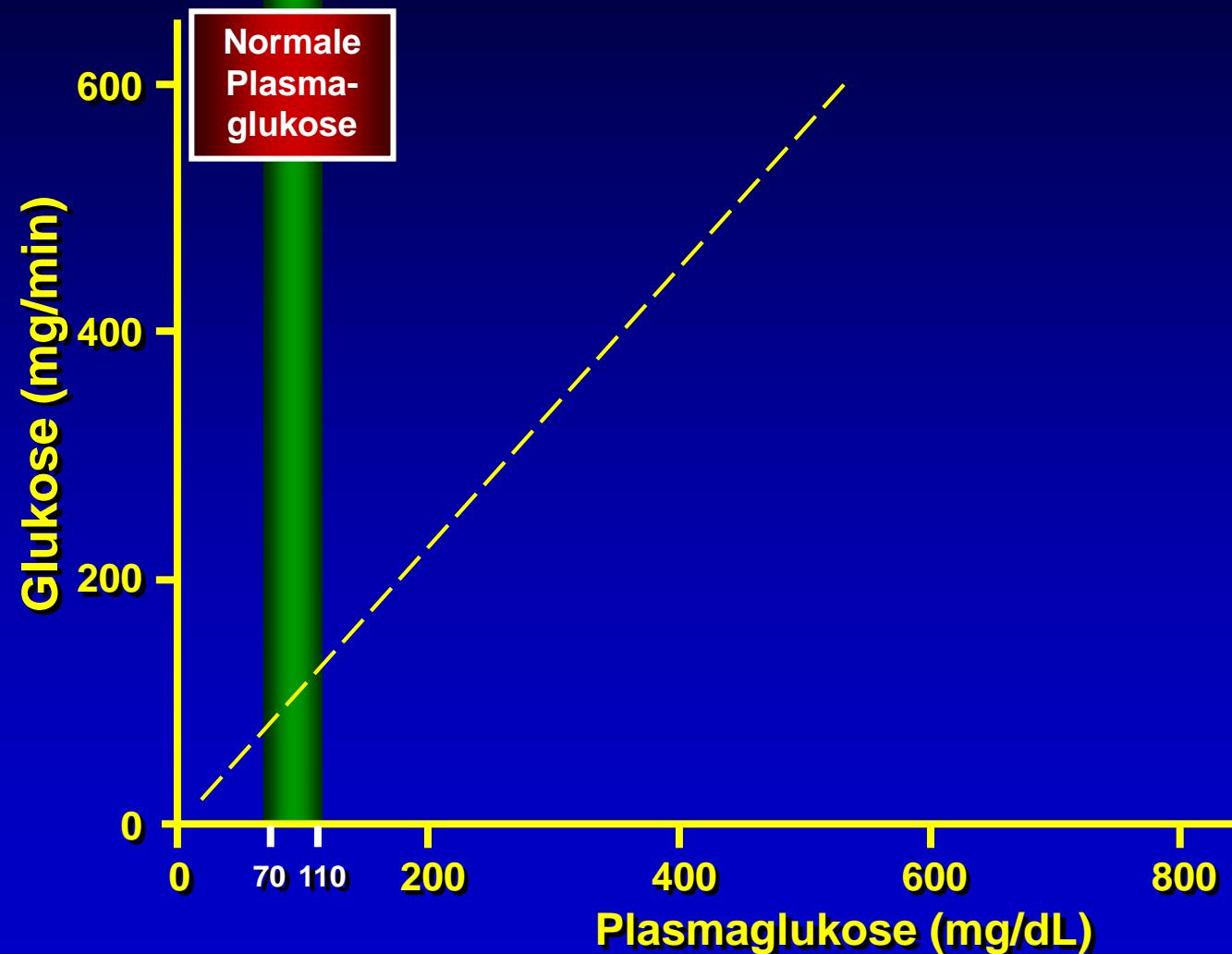
- Anaemia
- Pulmonary disease
- Renal dysfunction
- Thyroid dysfunction
- Diabetes

Cardiovascular

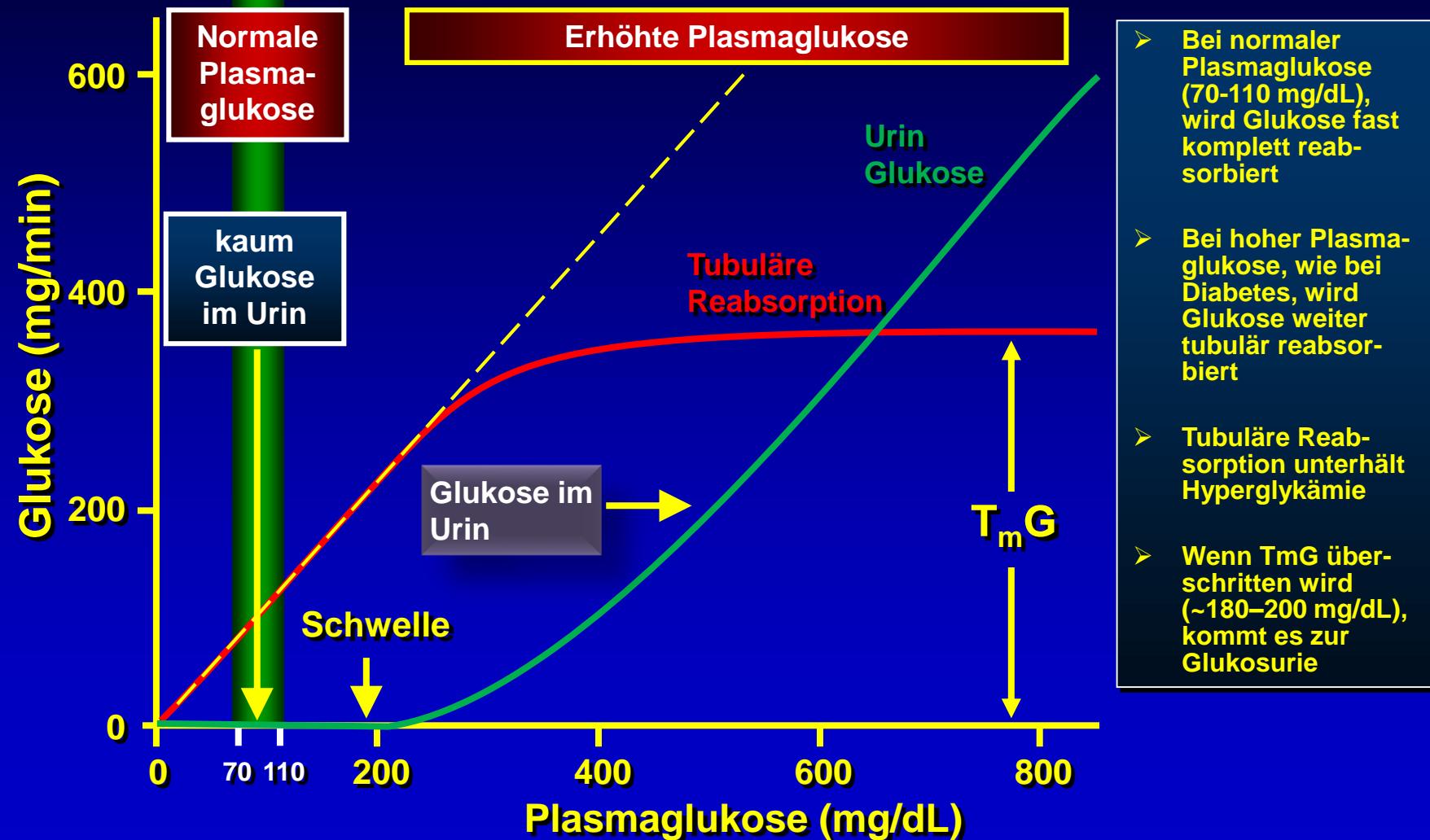
- Ischemia / CAD
- Hypertension
- Valvular dysfunction
- Diastolic dysfunction
- Atrial fibrillation
- Ventricular dysrhythmias
- Bradycardia

Diabetes

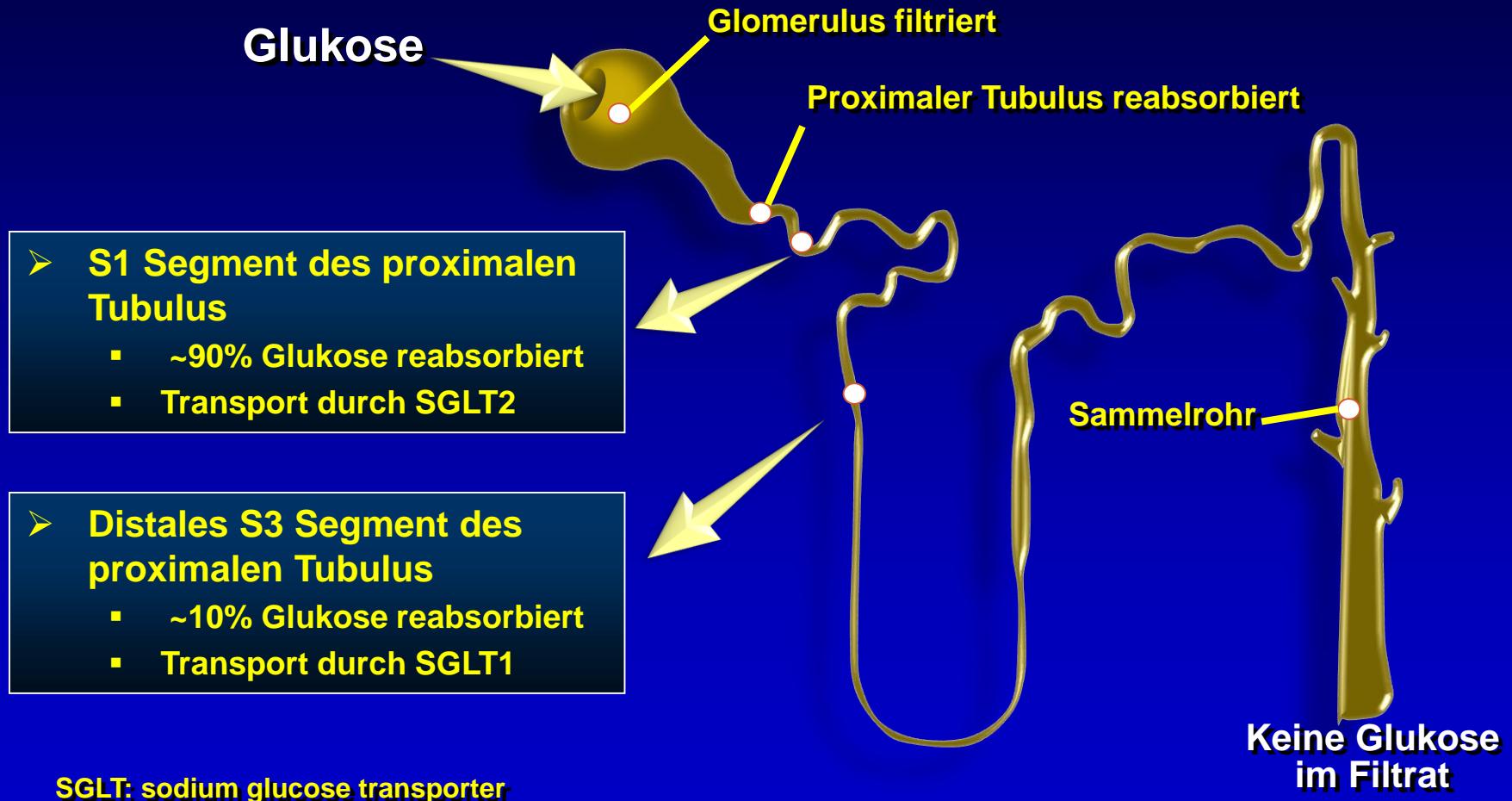
Fast die gesamte filtrierte Glukose wird beim Gesunden reabsorbiert



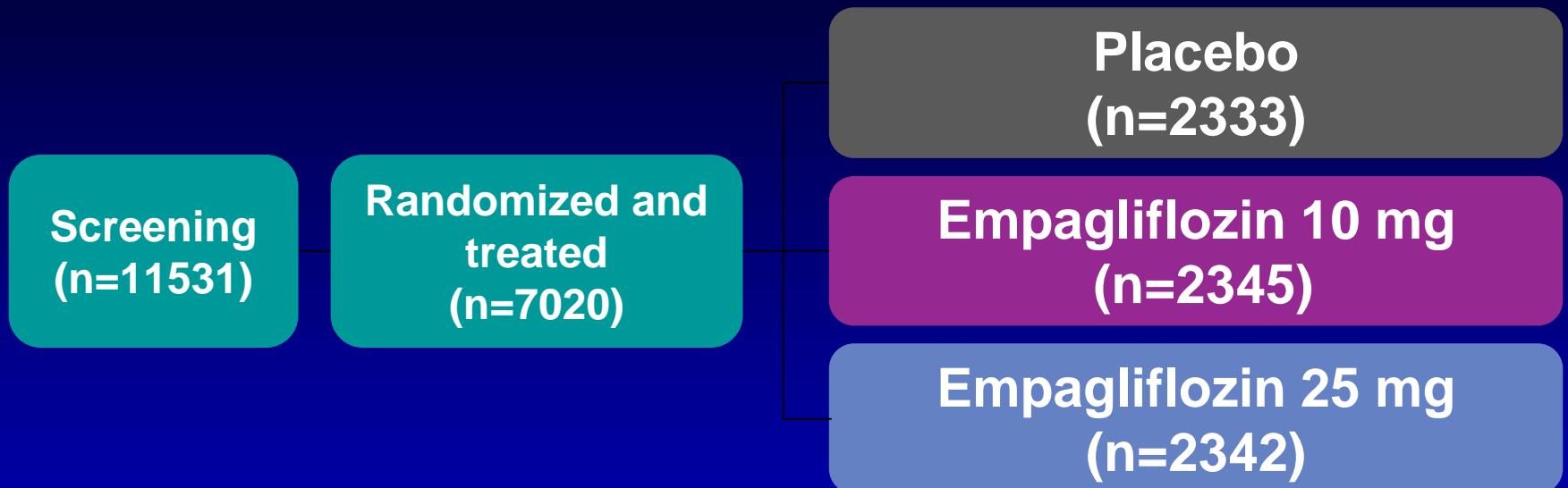
Fast die gesamte filtrierte Glukose wird beim Gesunden reabsorbiert



Glukose- Reabsorption findet im proximalen Tubulus statt



EMPA-REG OUTCOME[®]: Trial design



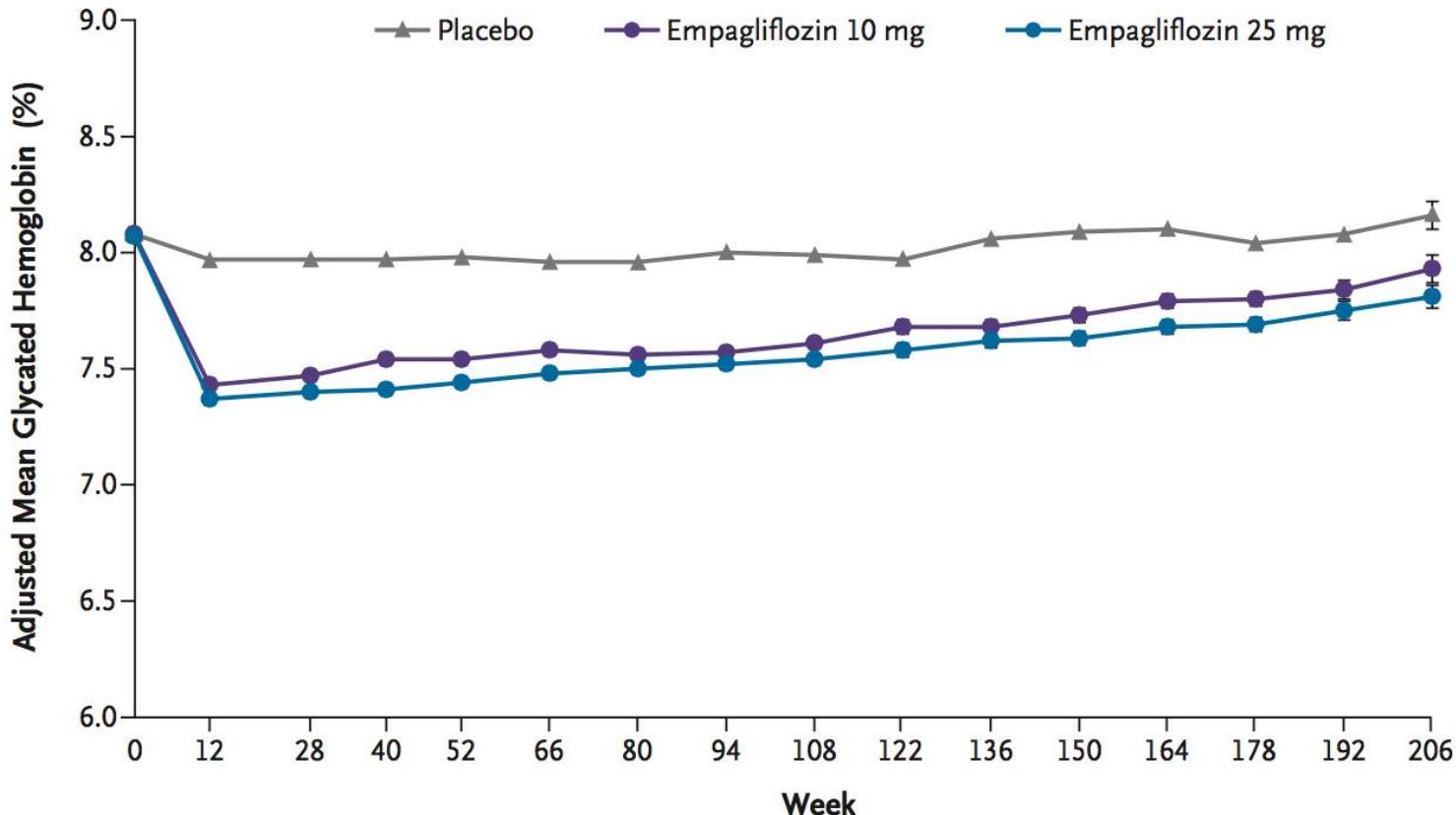
- Study medication was given in addition to standard of care
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event
- 97.0% of patients completed the study and final vital status was available for 99.2% of patients

Zinman B et al. N Engl J Med 2015 DOI: 10.1056/NEJMoa1504720.



Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
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and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators



No. at Risk

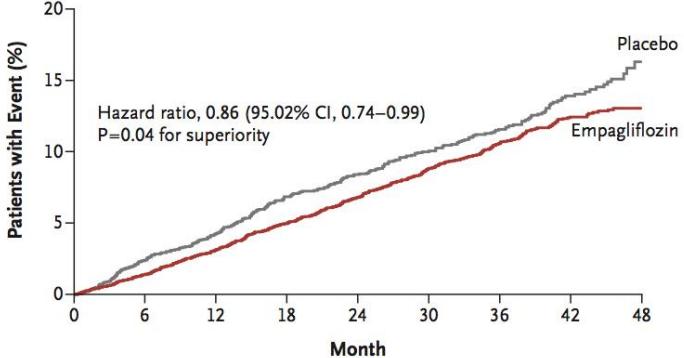
	0	12	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

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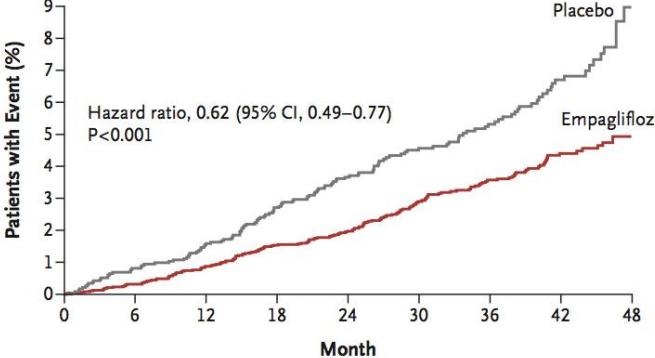
A Primary Outcome



No. at Risk
Empagliflozin
Placebo

4687	4580	4455	4328	3851	2821	2359	1534	370
2333	2256	2194	2112	1875	1380	1161	741	166

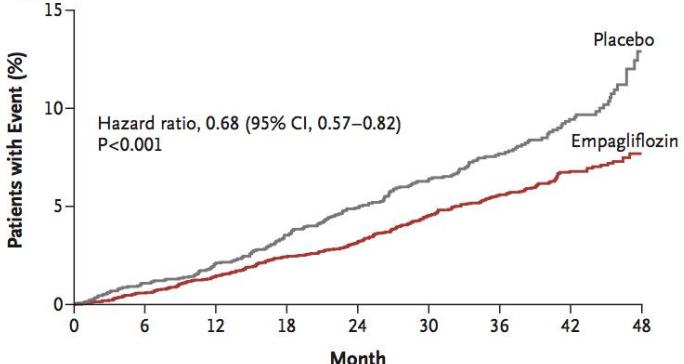
B Death from Cardiovascular Causes



No. at Risk
Empagliflozin
Placebo

4687	4651	4608	4556	4128	3079	2617	1722	414
2333	2303	2280	2243	2012	1503	1281	825	177

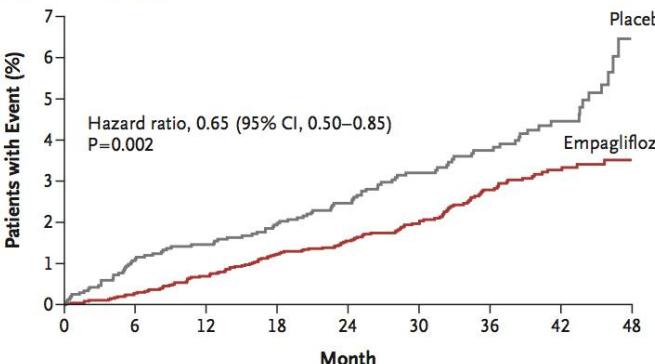
C Death from Any Cause



No. at Risk
Empagliflozin
Placebo

4687	4651	4608	4556	4128	3079	2617	1722	414
2333	2303	2280	2243	2012	1503	1281	825	177

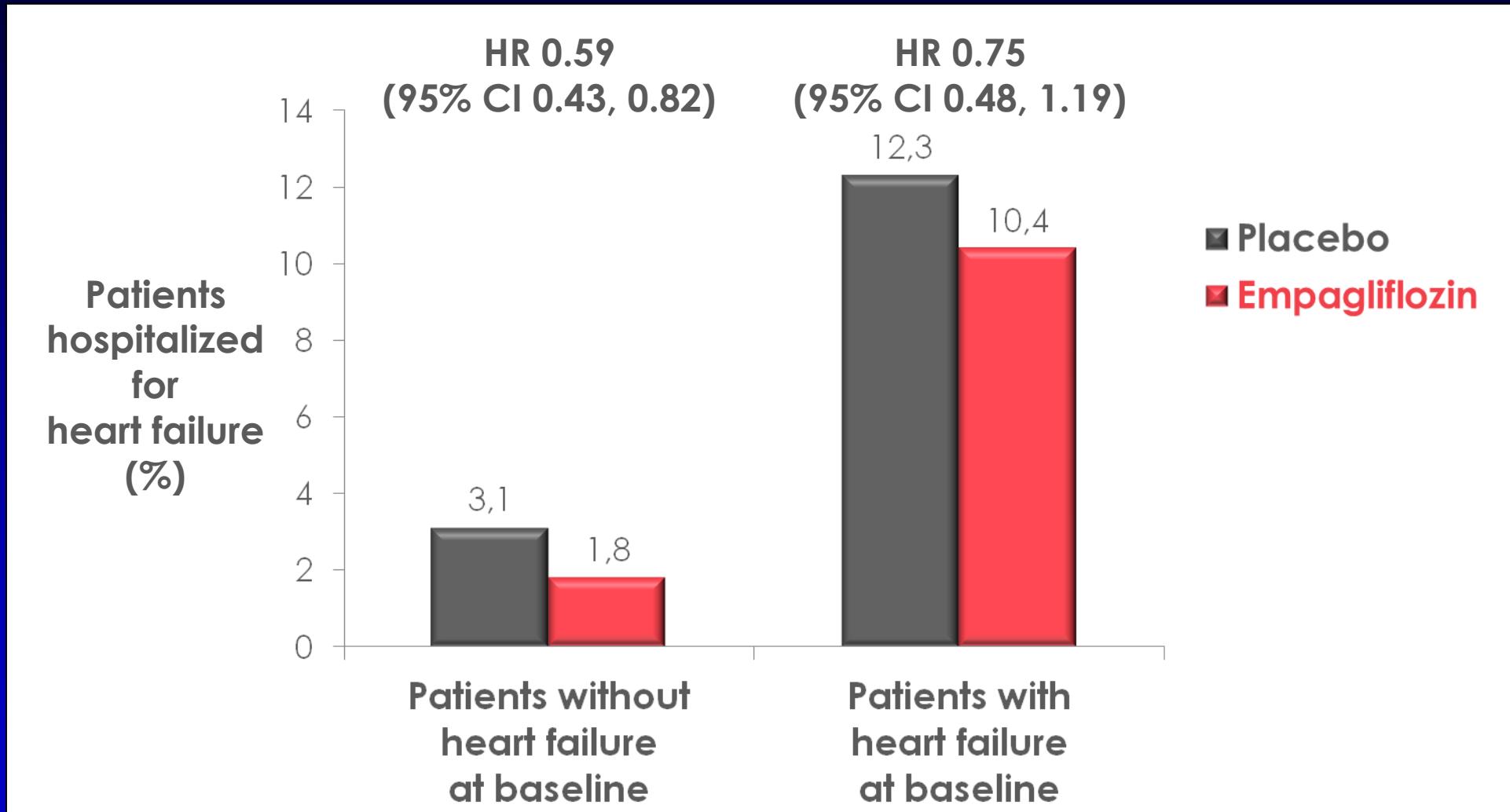
D Hospitalization for Heart Failure



No. at Risk
Empagliflozin
Placebo

4687	4614	4523	4427	3988	2950	2487	1634	395
2333	2271	2226	2173	1932	1424	1202	775	168

Hospitalization for heart failure in patients with vs without heart failure at baseline



Cox regression analysis.

HR, hazard ratio; CI, confidence interval.

Zinman et al, N Engl J Med (Suppl.) [doi: 10.1056/NEJMoa1504720]

Diabetes

Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.

IIa

C

440,441

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

Diabetes

Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.

IIa

C

440 ,441

Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.

IIa

B

130

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

Diabetes

Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.

IIa

C

440, 441

Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.

IIa

B

130

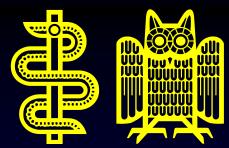
Diabetes

Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.

III

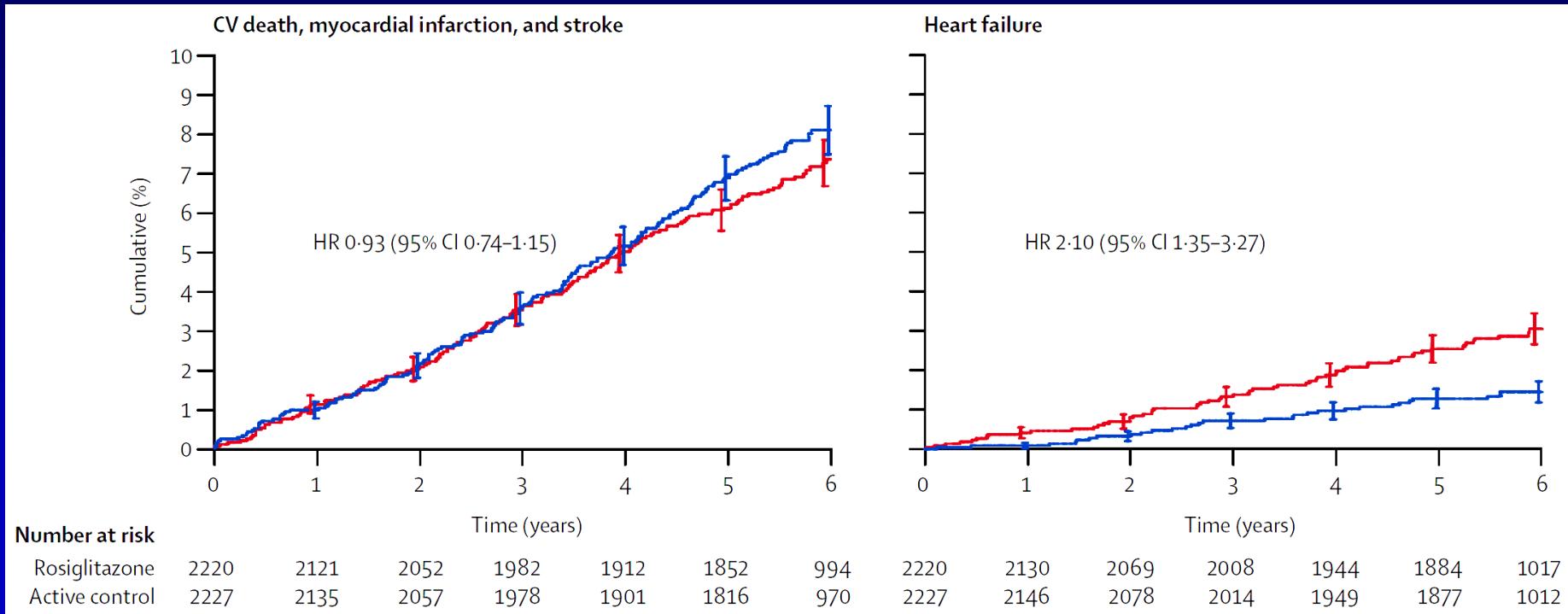
A

209, 210

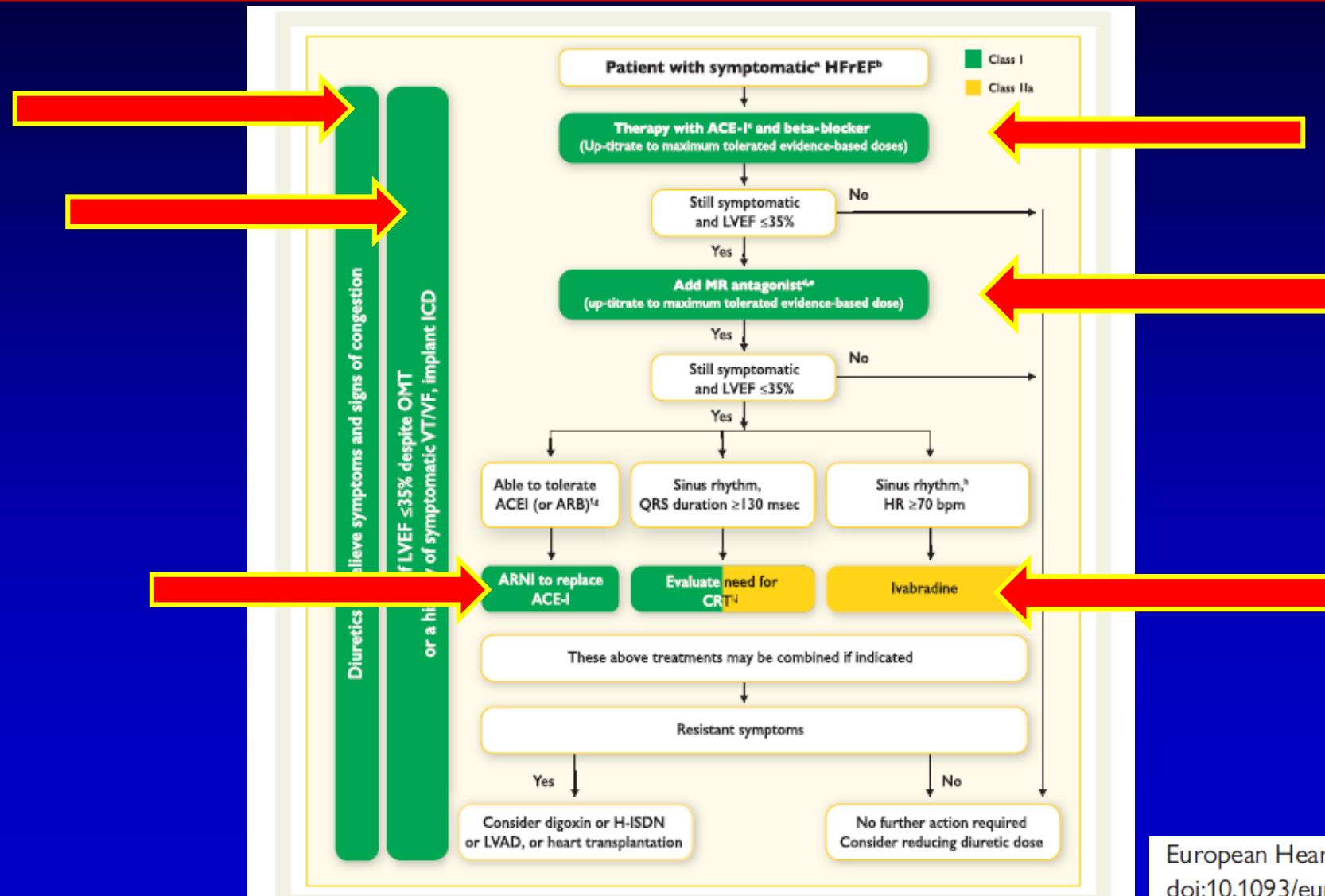


Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Philip D Home, Stuart J Pocock, Henning Beck-Nielsen, Paula S Curtis, Ramon Gomis, Markolf Hanefeld, Nigel P Jones, Michel Komajda, John JV McMurray, for the RECORD Study Team*



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



Leitlinien

Sind lesenswert!



**Guide-
lines**



... sollten nur auch gelesen werden!

Thank you
for your attention!



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