Gianfranco Sinagra, MD, FESC

ASUITS- Università degli Studi di Trieste
gianfranco.sinagra@asuits.sanita.fvg.it

Conflitti di interesse

Novartis, Boehringer, Boston,
Menarini, Servier

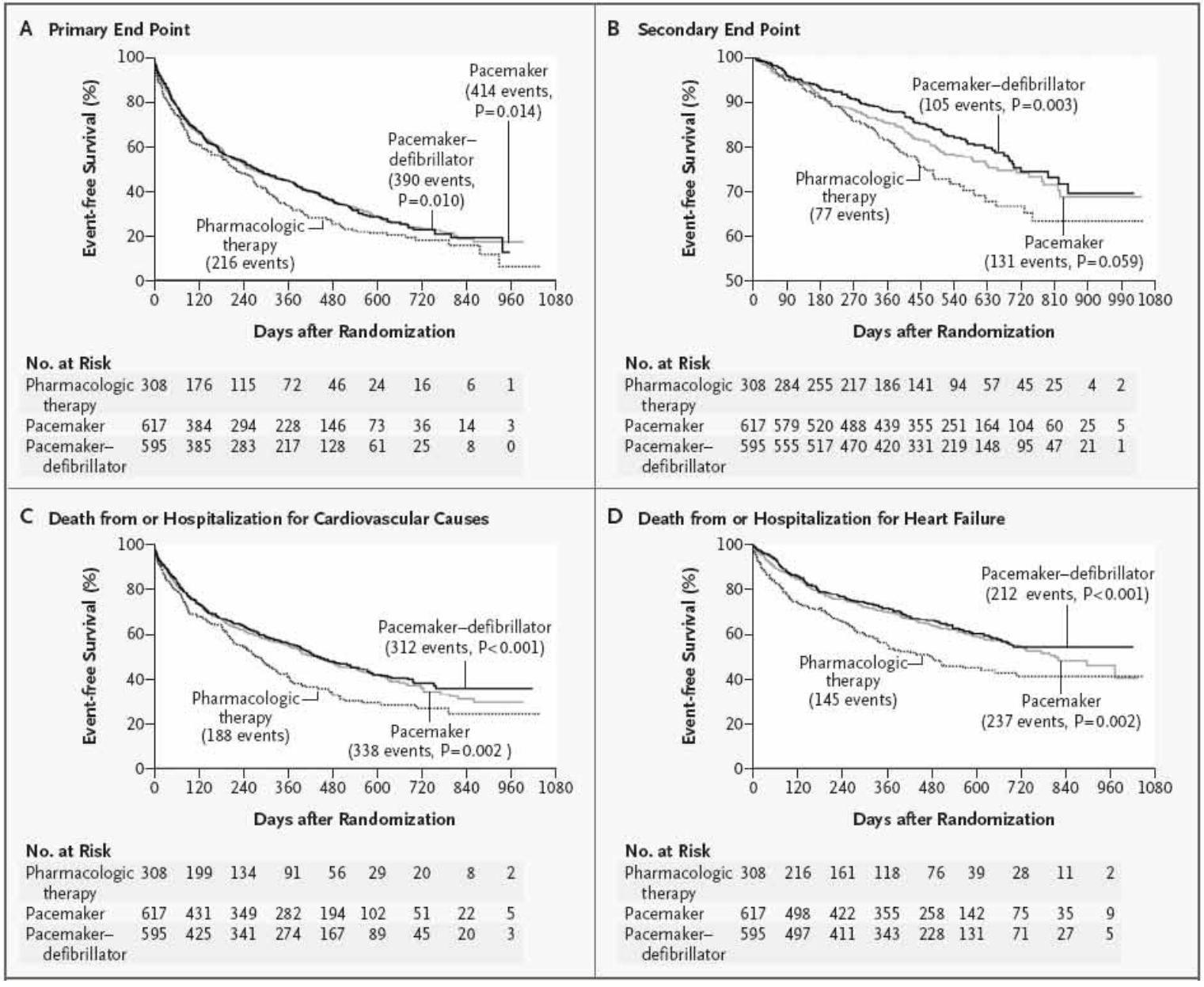
HF: Objectives of Pharmacological Treatment

1. Prognosis	Reduce mortality
2. Morbidity	Relieve symptoms and signs
	Improve quality of life
	Eliminate oedema and fluid retention
	Increase exercise capacity
	Reduce fatigue and breathlessness
	Reduce need for hospitalization
	Provide for end of life care
3. Prevention	Occurrence of myocardial damage
	Progression of myocardial damage
	Remodelling of the myocardium
	Reoccurrence of symptoms and fluid accumulation
	Hospitalization

Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure

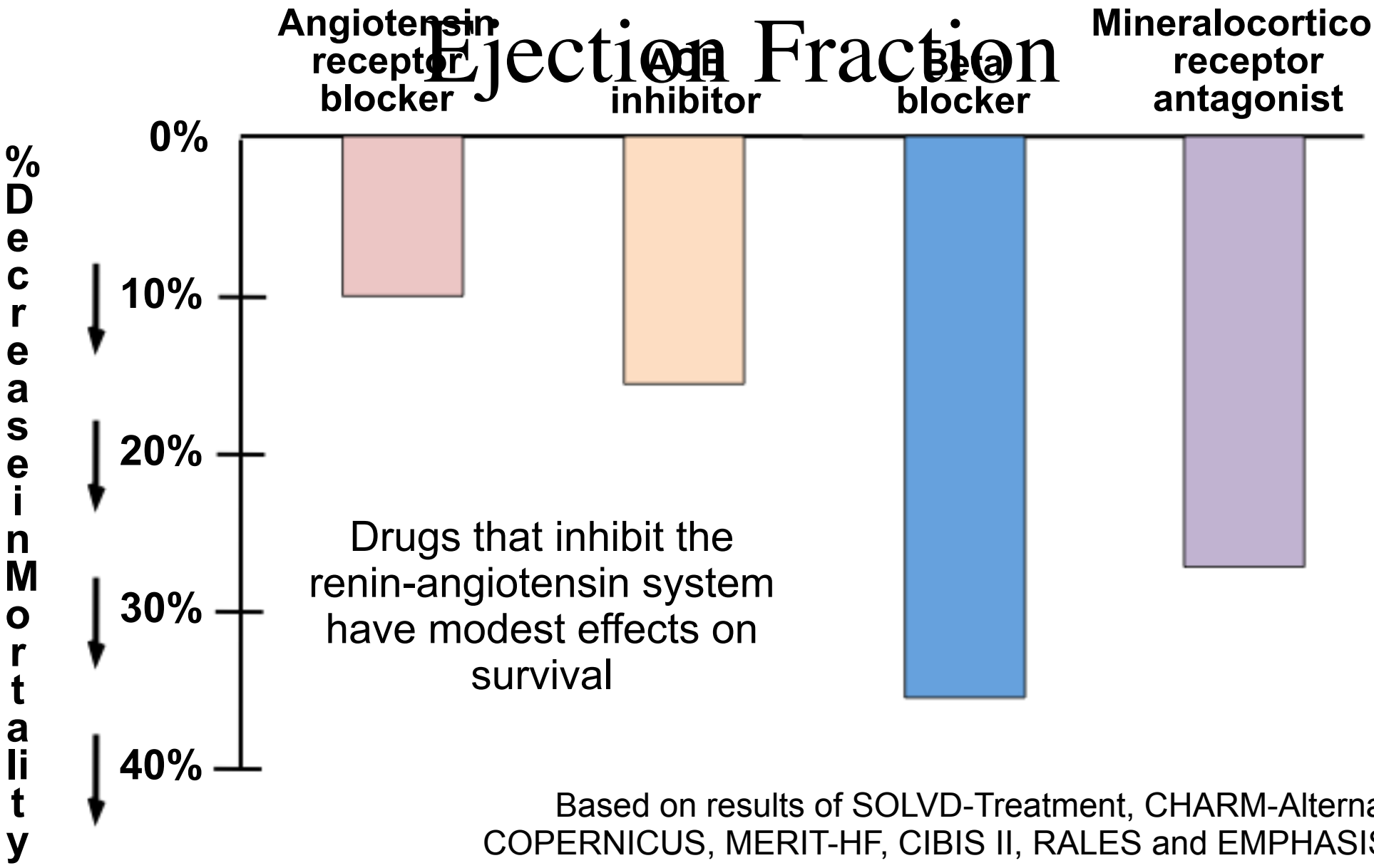
Michael R. Bristow, M.D., Leslie A. Saxon, M.D., John Boehmer, M.D., Steven Krueger, M.D., David A. Kass, M.D., Teresa De Marco, M.D., Peter Carson, M.D., Lorenzo DiCarlo, M.D., David DeMets, Ph.D., Bill G. White, Ph.D., Dale W. DeVries, B.A., and Arthur M. Feldman, M.D., Ph.D., for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators*

The NEW ENGLAND JOURNAL of MEDICINE



N = 1520 pts,
NYHA III-IV,
FEVsin<25%
QRS interval of
at least 120 msec

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction



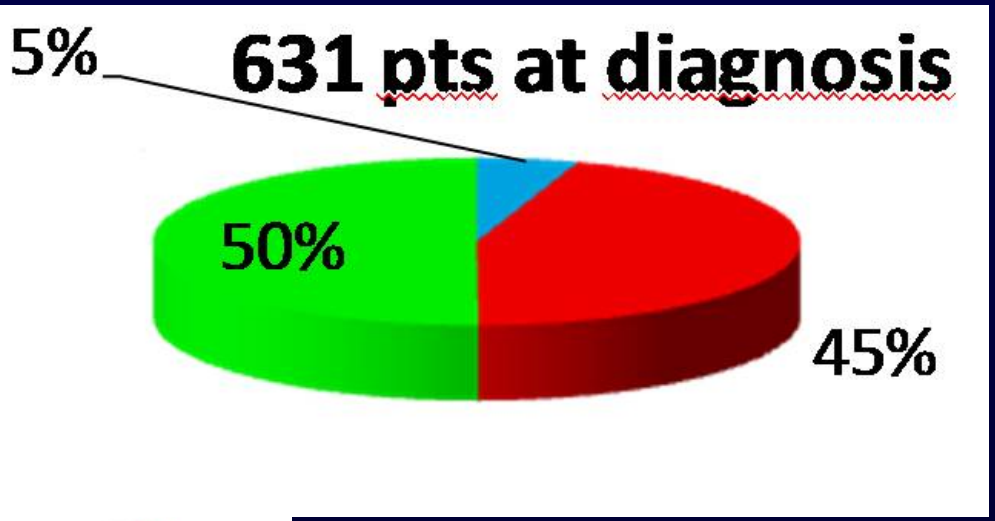
Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

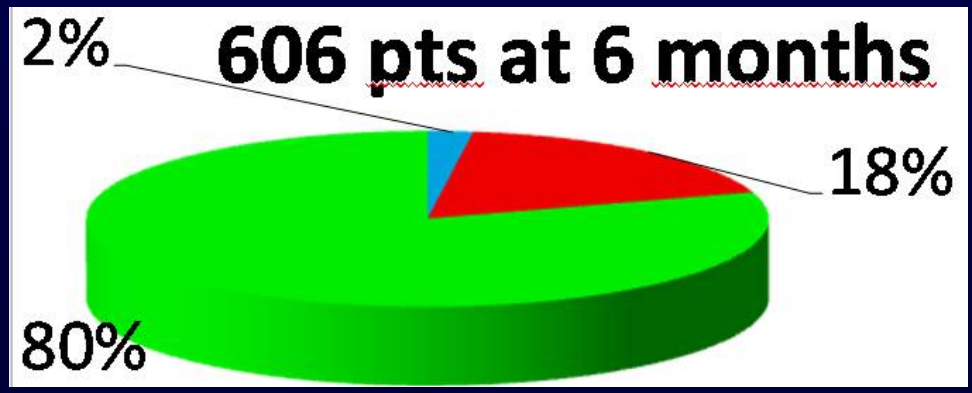
How Can Optimization of Medical Treatment Avoid Unnecessary Implantable Cardioverter-Defibrillator Implantations in Patients With Idiopathic Dilated Cardiomyopathy Presenting With "SCD-HeFT Criteria?"

Massimo Zecchin, MD[a,*], Marco Merlo, MD[a], Alberto Pivetta, MD[a], Giulia Barbati, PhD[b], Cristina Lutman, MD[a], Dario Gregori, PhD[b], Laura Vitali Serdoz, MD[a], Stefano Bardari, MD[a], Silvia Magnani, MD[a], Andrea Di Lenarda, MD[c], Alessandro Proclemer, MD[d], and Gianfranco Sinagra, MD[a]

THE TRIESTE CARDIOMYOPATHIES REGISTRY 1988-2006; DCM N=631 PTS; LVEF 30±10%

EF<35 NYHA IV | EF <35 NHYA II-III | NYHA I and/or EF>35





Ospedali Riuniti di Trieste

Zecchin M, Sinagra G et al
Am J Cardiol 2012;109:729-35

Simplistic Assumptions

- All HFs are the same;
- Pathophysiology of HF is always the same
- HF and SD incidence remain the same for each patient throughout natural history of the disease
- Pharmacokinetics and pharmacodynamics is the same for each patient
- Clinical Trial Dose is always appropriate

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

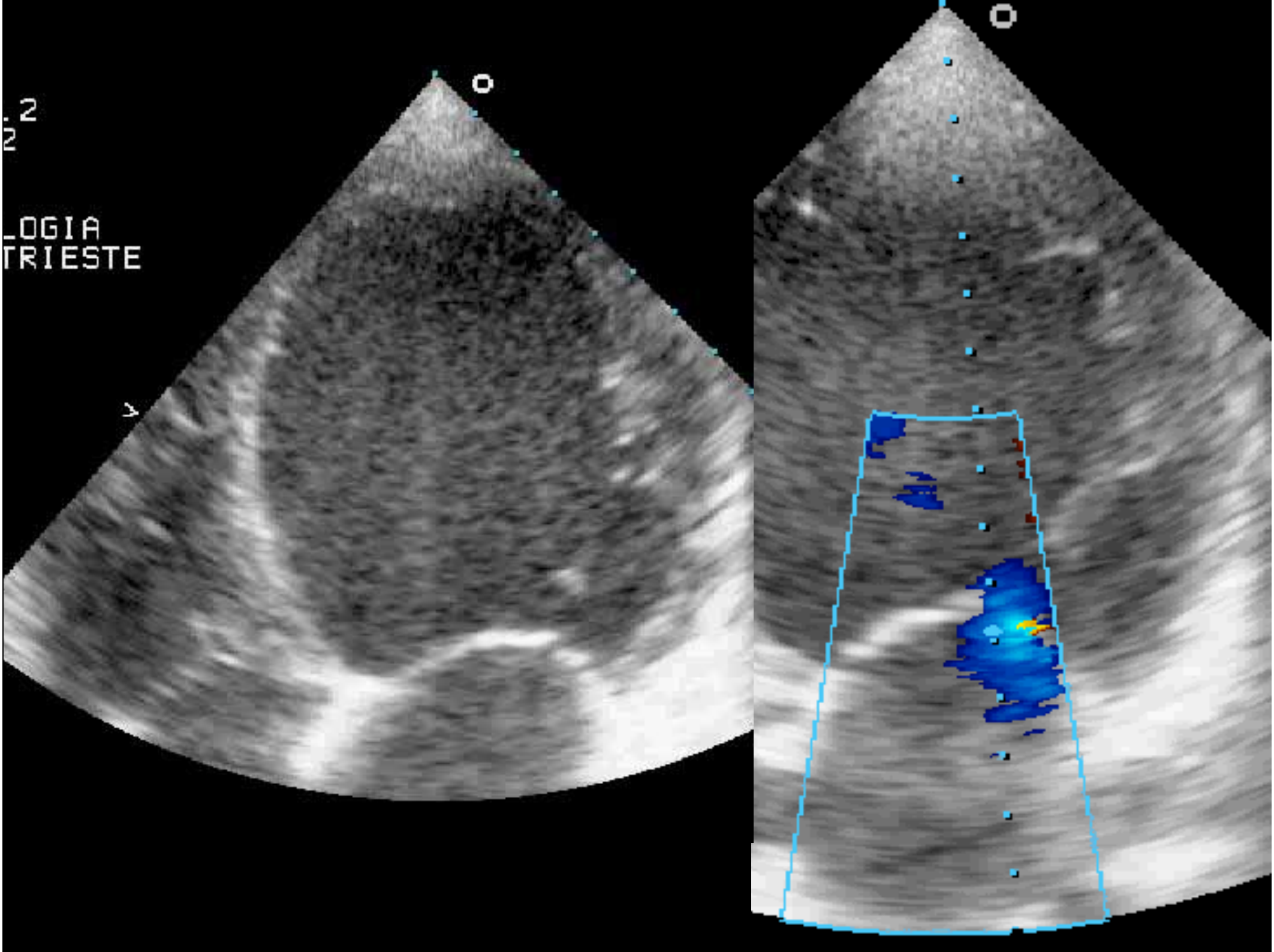
ESC GUIDELINES

EUROPEAN SOCIETY OF CARDIOLOGY®

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).

Published 20 May 2016

doi:10.1093/eurheartj/ehw128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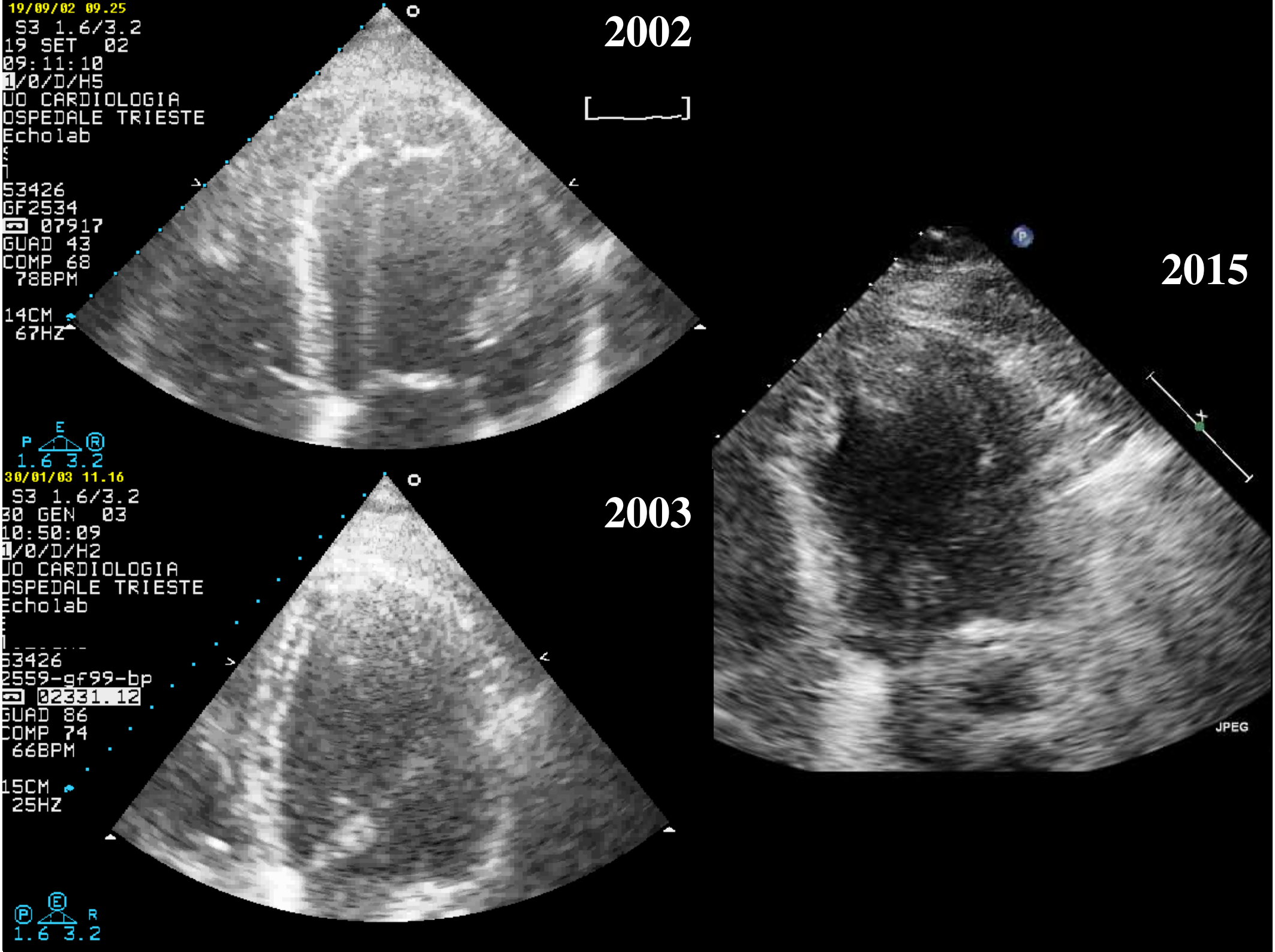
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S3 1.6/3.2
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1/0/D/H5
UO CARDIOLOGIA
OSPEDALE TRIESTE
Echolab
53426
GF2534
07917
GUAD 43
COMP 68
78BPM
14CM
67HZ
2002
P E R
1.6 3.2
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S3 1.6/3.2
30 GEN 03
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Echolab
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2015
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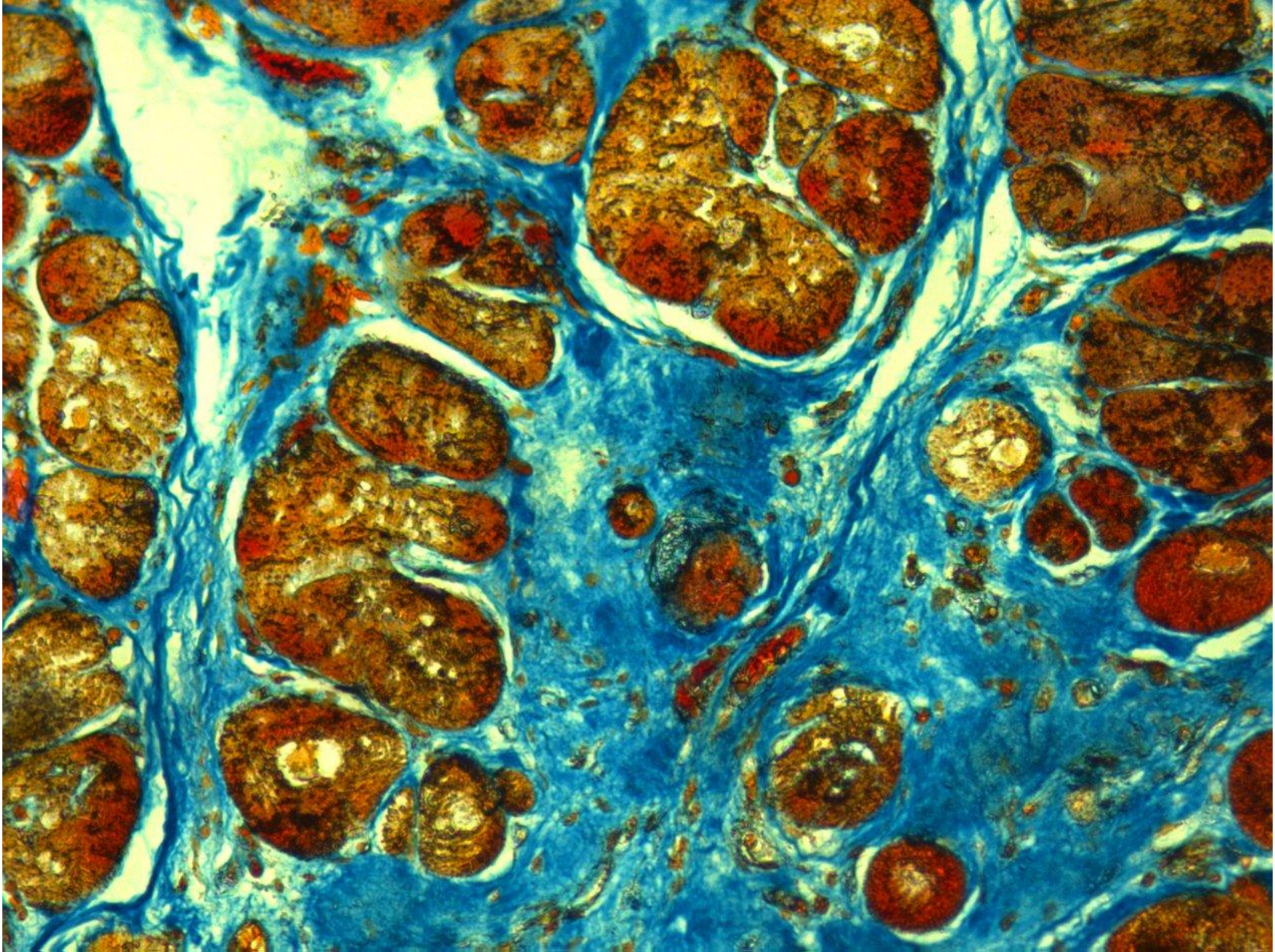
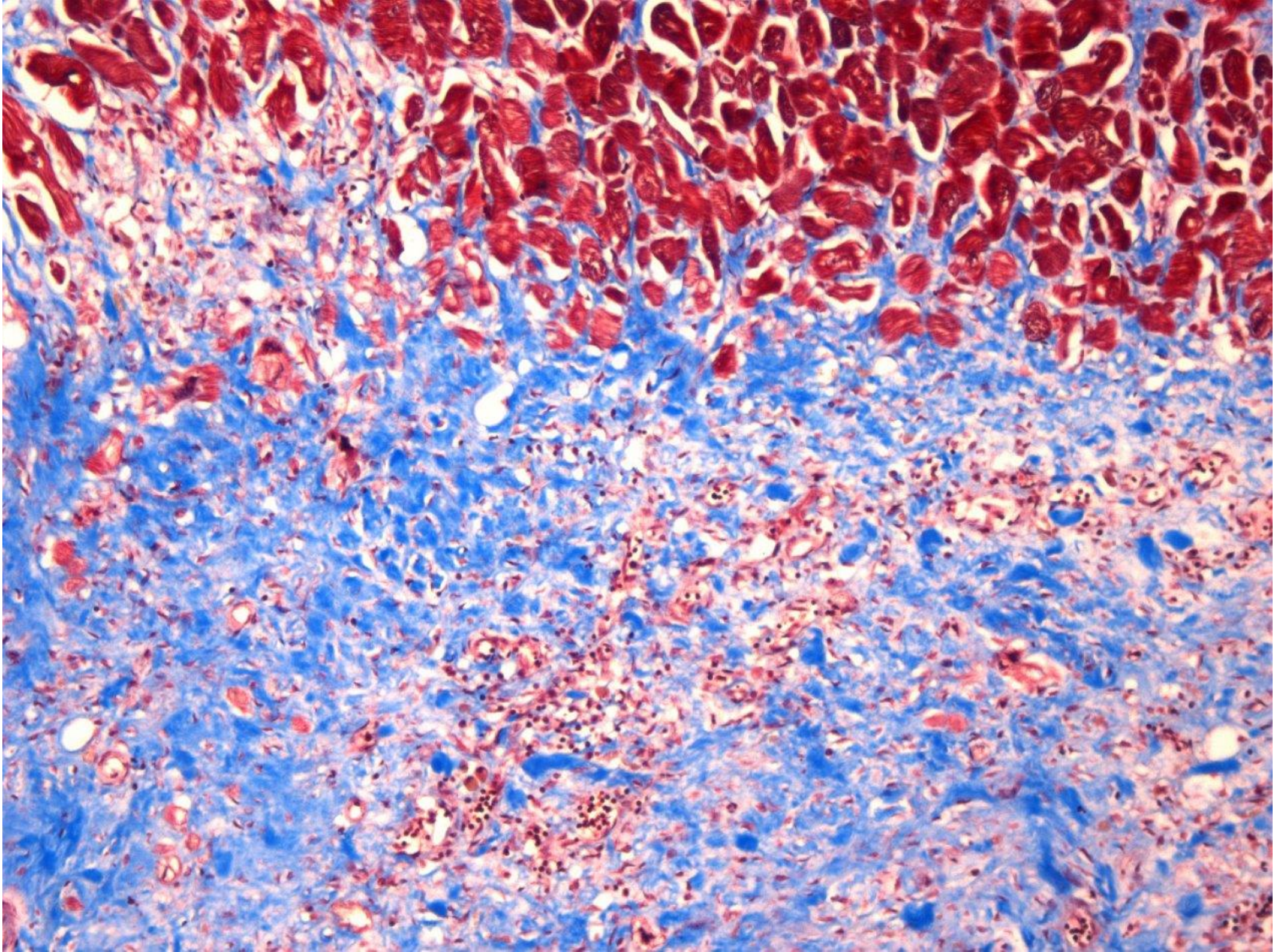
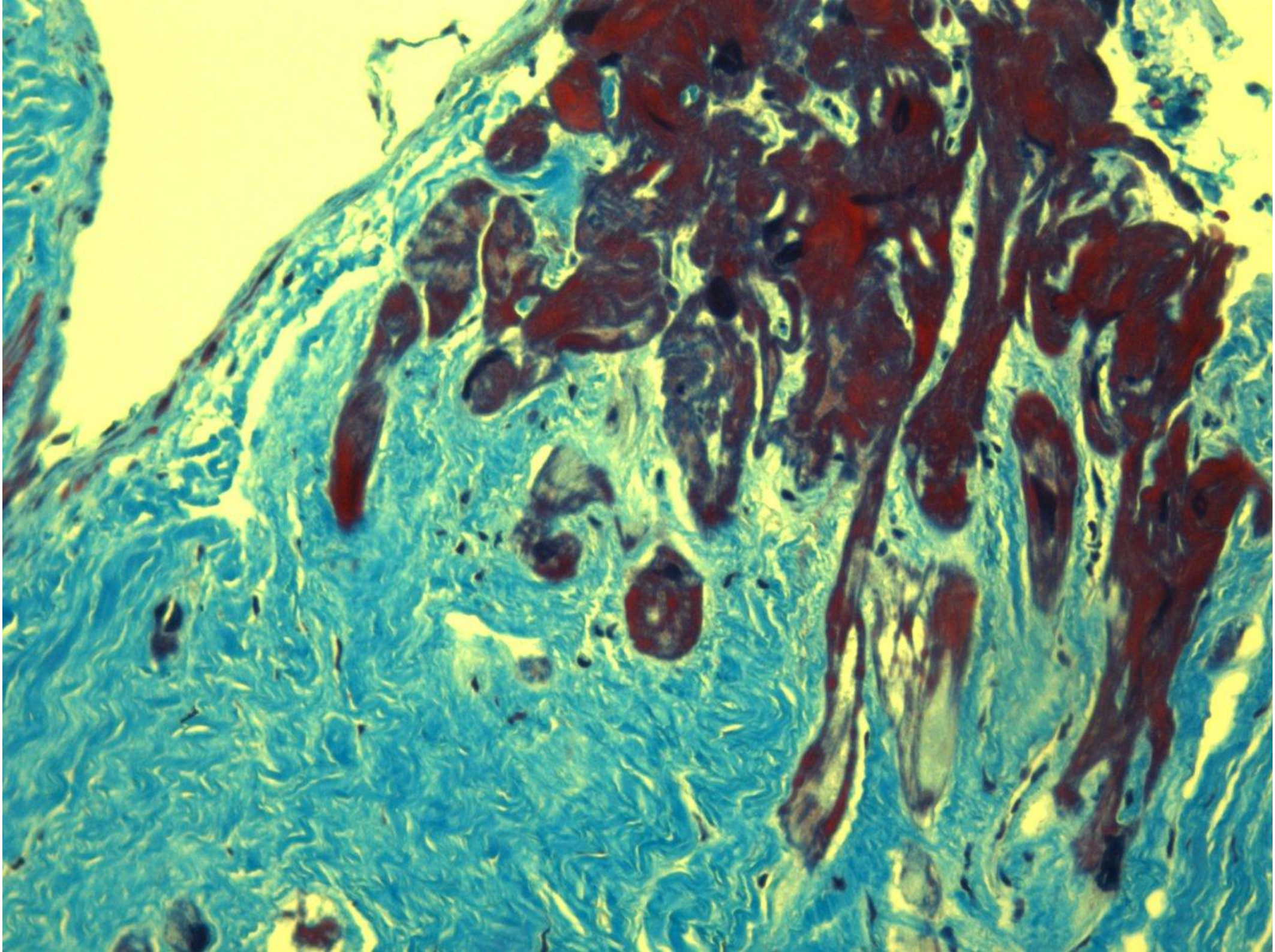






LVRR in DCM – PROGNOSTIC ROLE

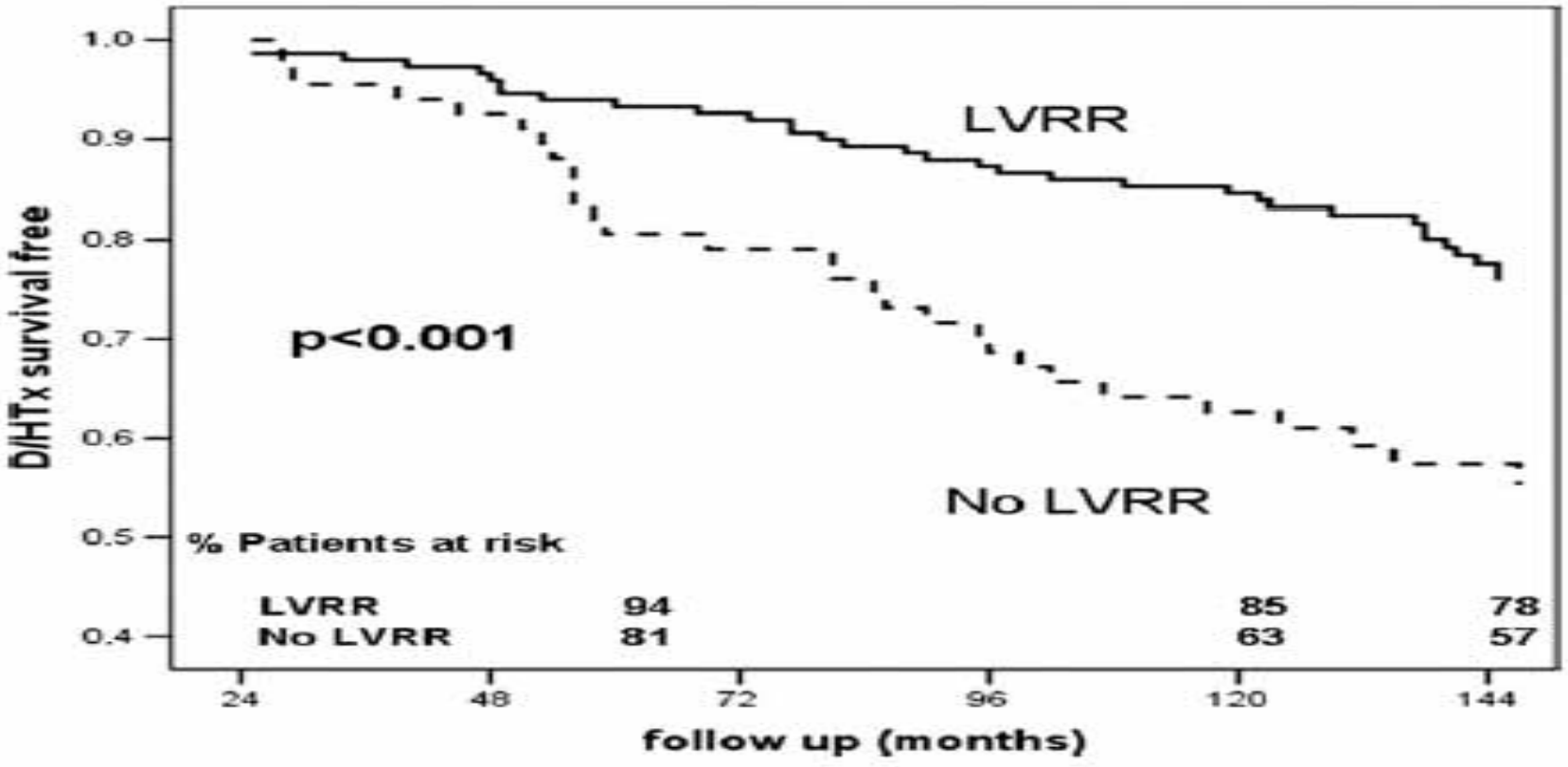
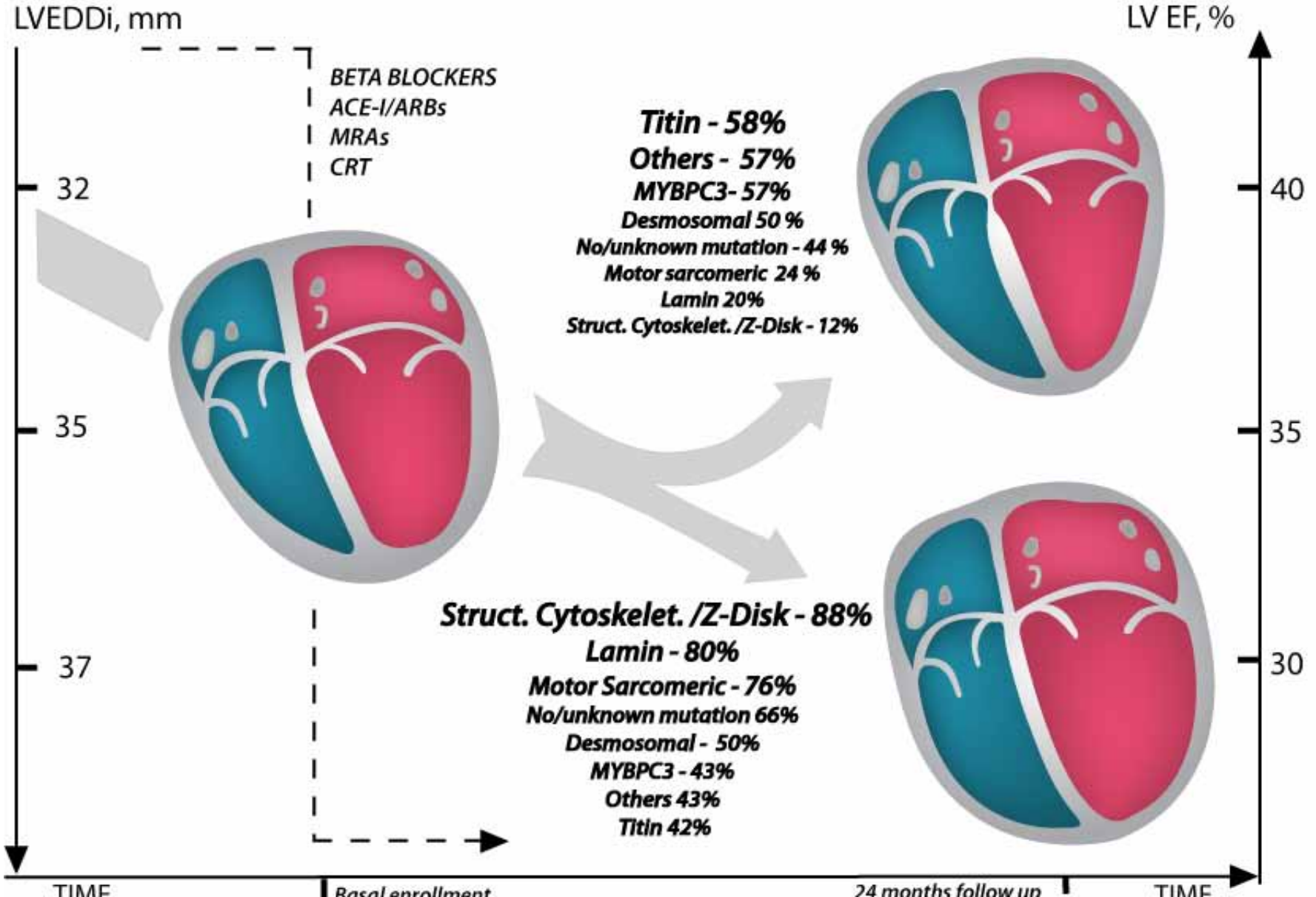


Figure 2 **Long-Term Prognostic Impact of LVRR in Idiopathic Dilated Cardiomyopathy Patients**

Comparison of long-term heart transplantation (HTx)-free survival curves between left ventricular reverse remodeling (LVRR) and non-LVRR patient subgroups. Note that the starting time point is 24 months (range 9 to 36 months). D = death.

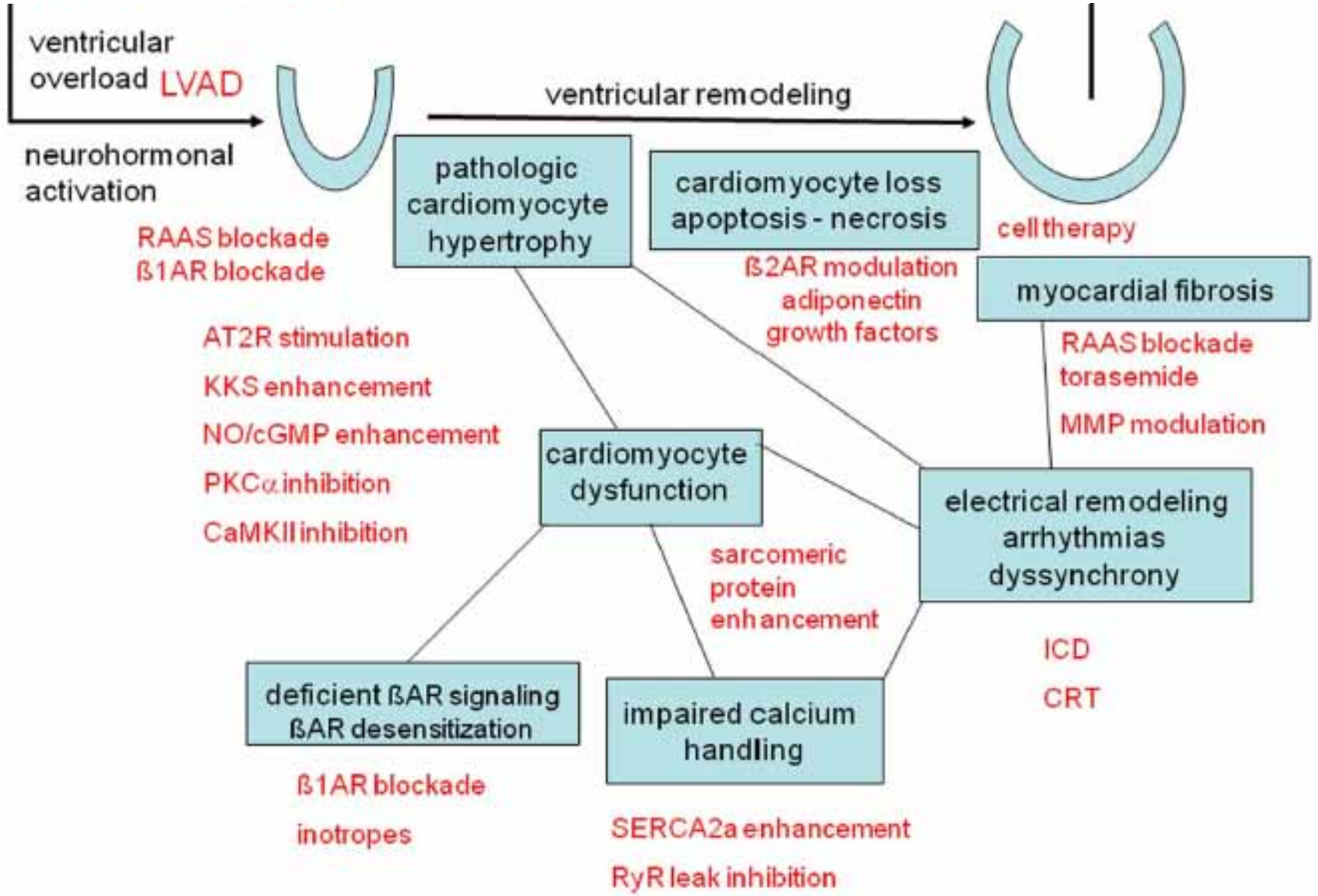
Merlo M, Sinagra G, et al. J Am Coll Cardiol,2011;57:1468-76

Genotype-Phenotype Correlations: Association between Mutation Status and Left Ventricular Reverse Remodeling in Idiopathic Dilated Cardiomyopathy. *(Heart 2017, accepted)*

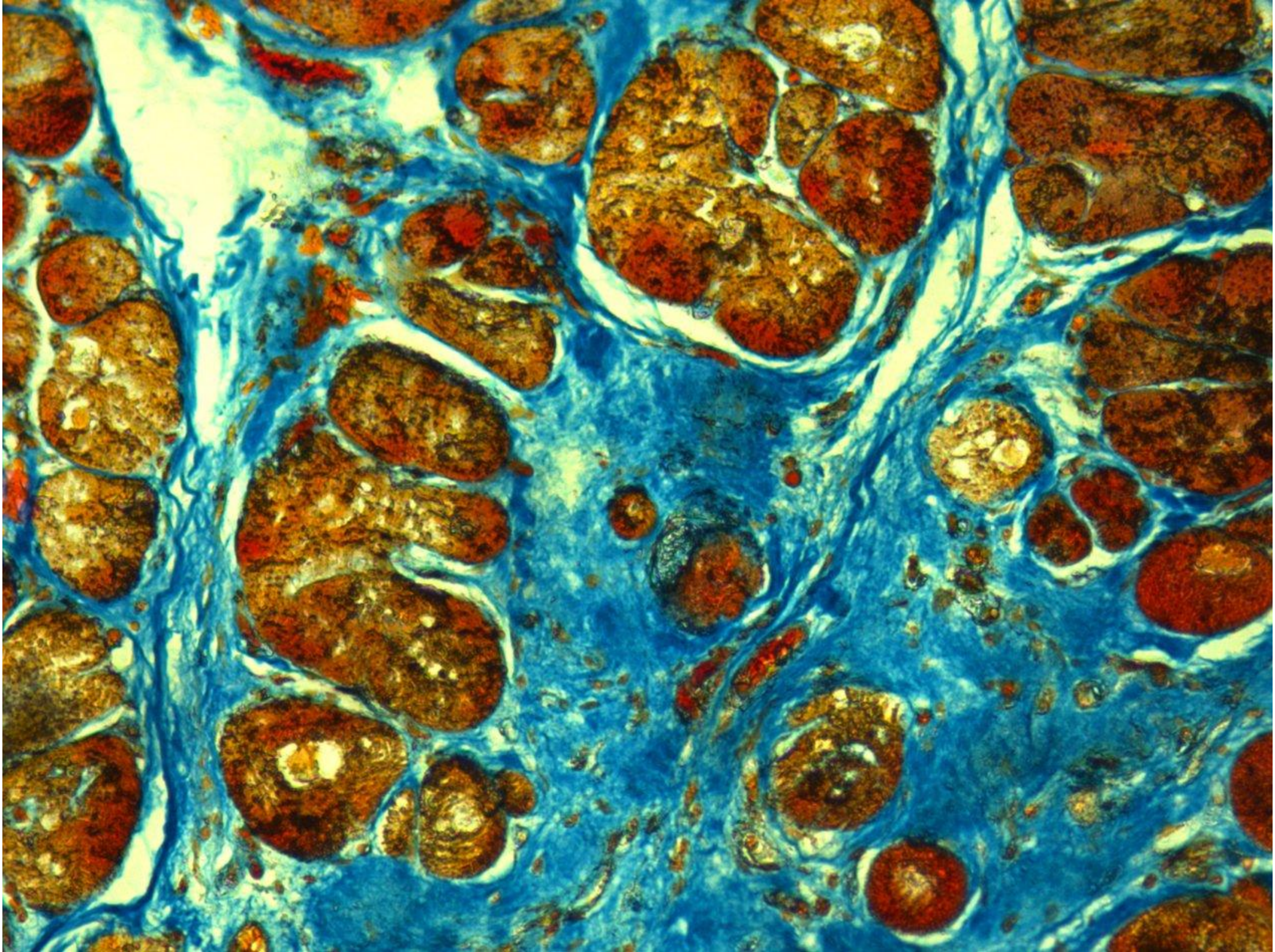


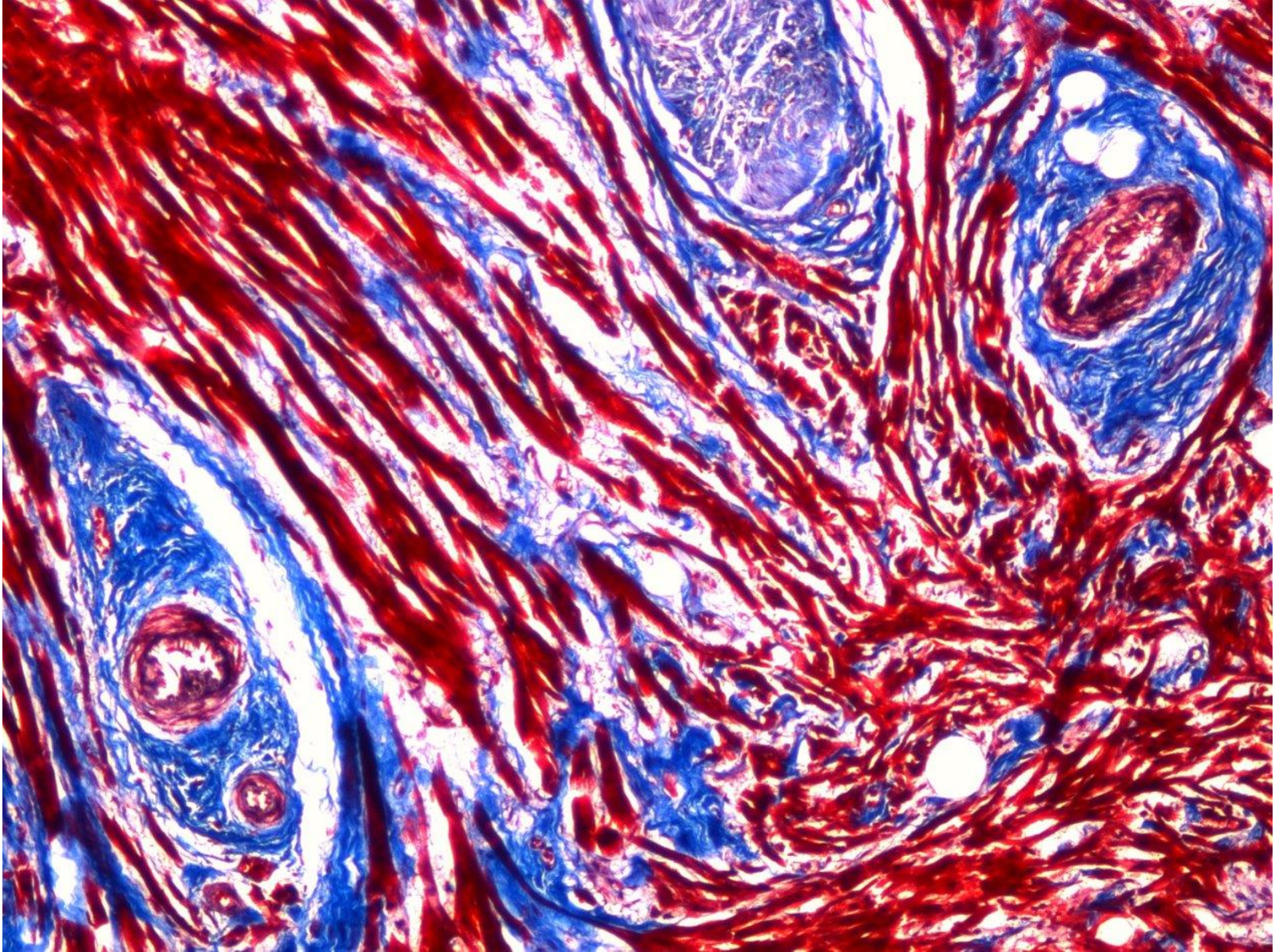
Molecular targets of current and prospective heart failure therapies

Elie R Chemaly, Roger J Hajjar, Larissa Lipskaia

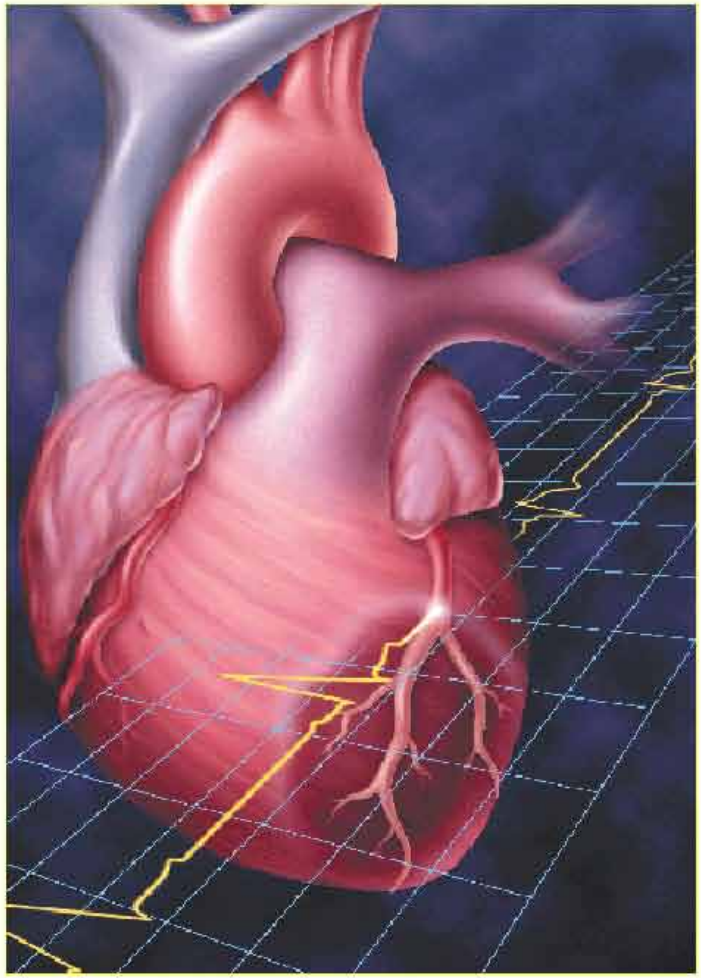


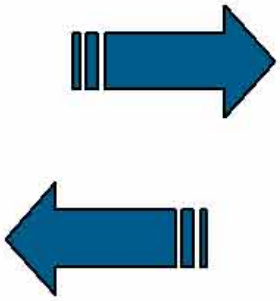
Chemaly ER, *et al. Heart* 2013;**99**:992–1003. doi:10.1136/heartjnl-2012-302970





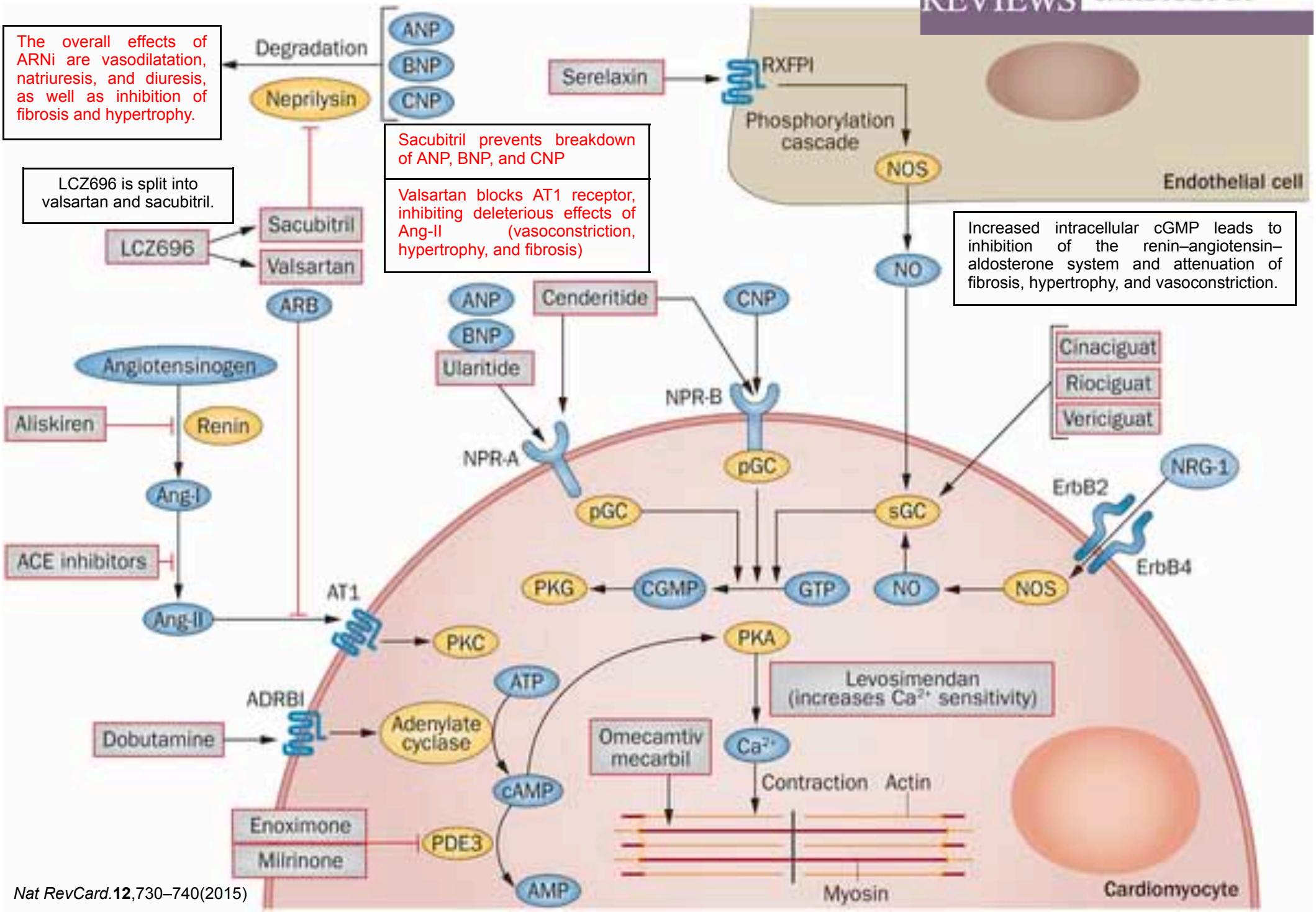
CHF and CKD





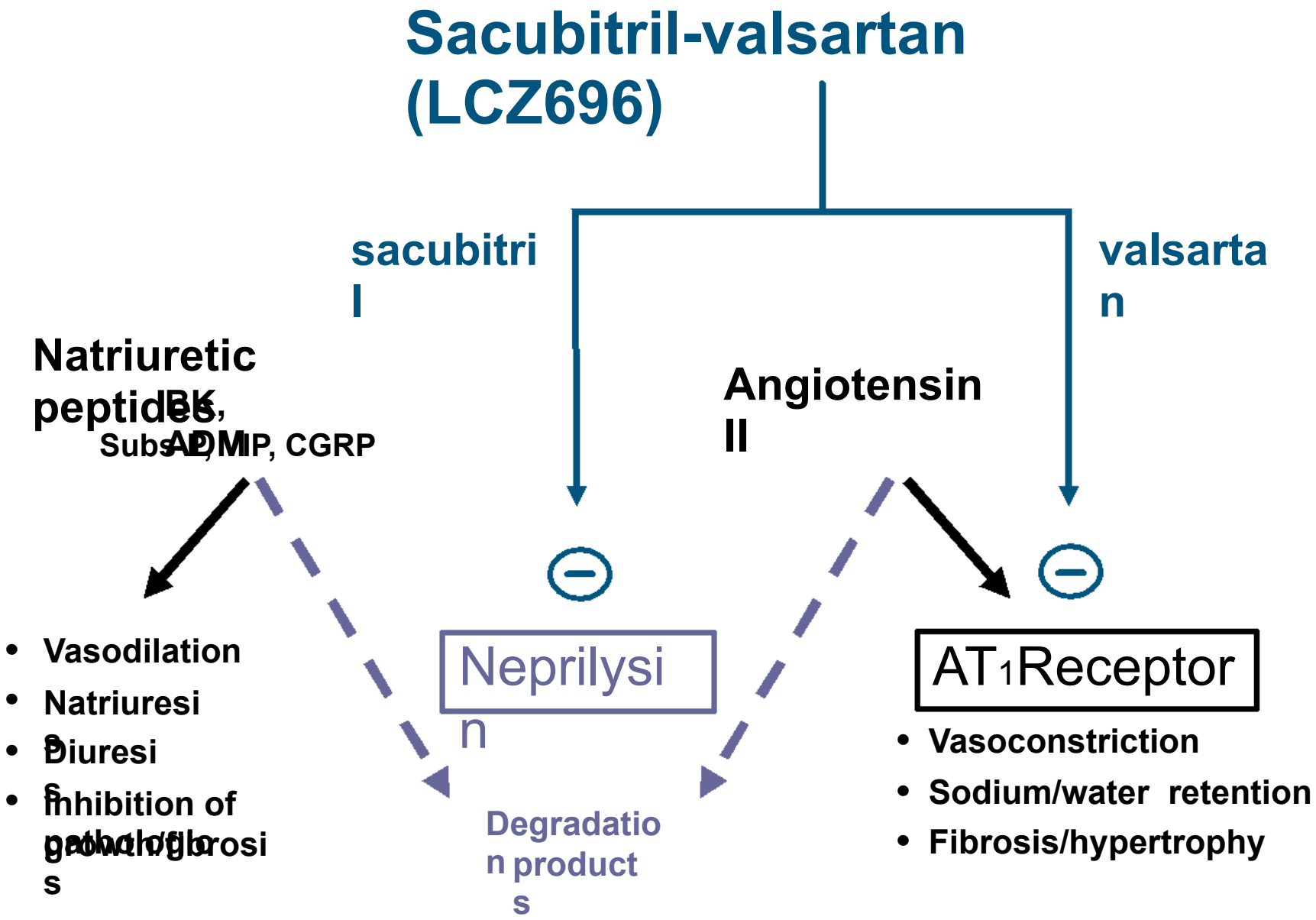
New medical therapies for heart failure

nature REVIEWS CARDIOLOGY



*Nat RevCard.***12**,730–740(2015)

Angiotensin Receptor Neprilysin Inhibition (ARNI)

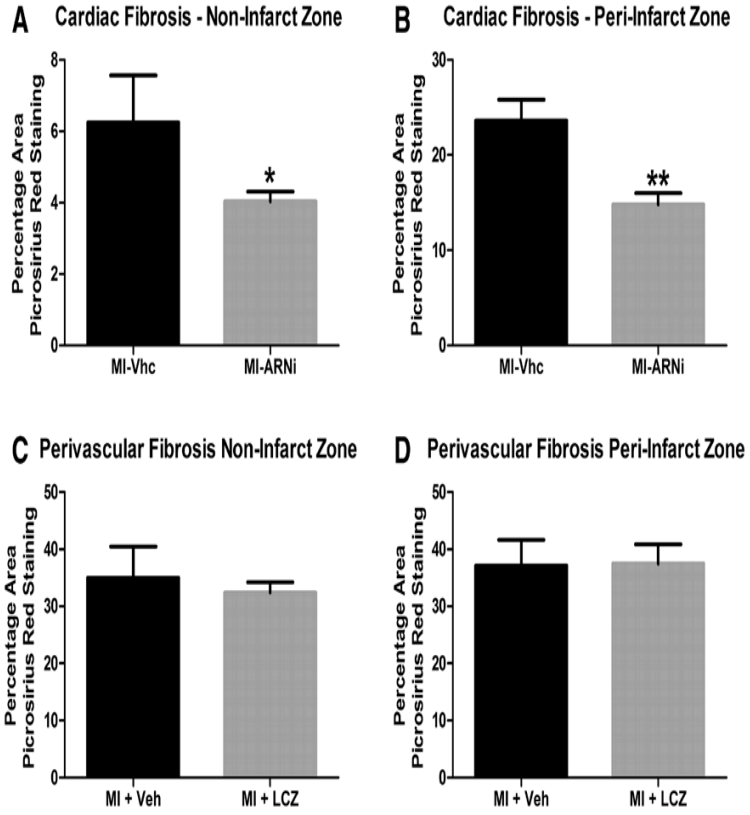


McMurray Eur J Heart Fail. 2015;17:242-

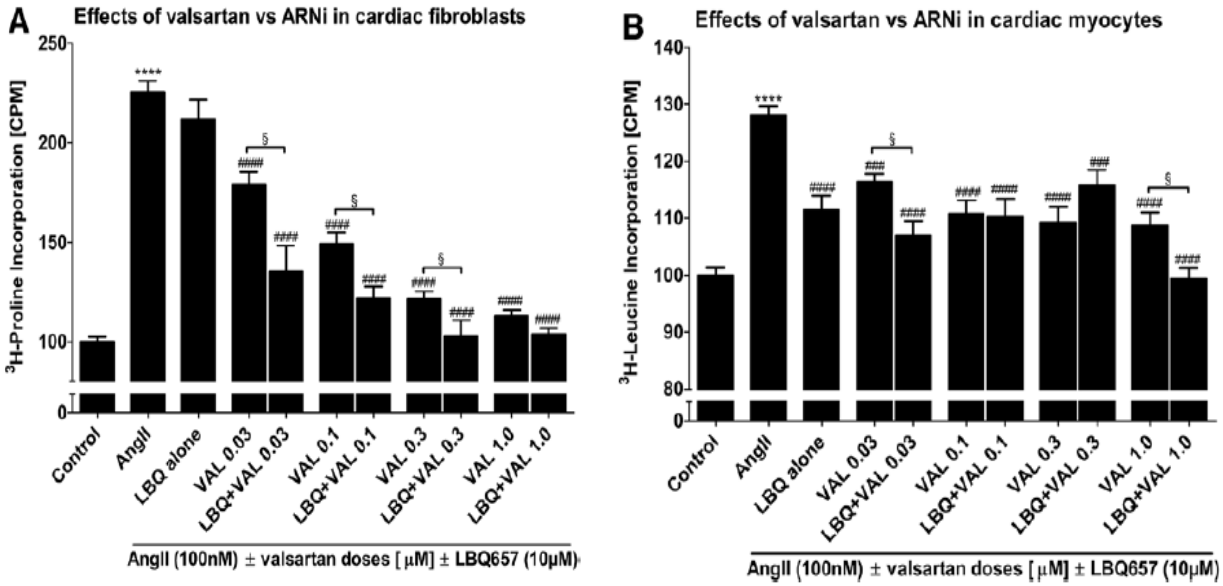
Angiotensin Receptor Neprilysin Inhibitor LCZ696 Attenuates Cardiac Remodeling and Dysfunction After Myocardial Infarction by Reducing Cardiac Fibrosis and Hypertrophy

Thomas G. von Lueder, MD, PhD*; Bing H. Wang, PhD*; Andrew R. Kompa, PhD; Li Huang, BSc; Randy Webb, PhD; Pierre Jordaan, PhD; Dan Atar, MD, PhD; Henry Krum, MBBS, PhD

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION



Effects of chronic administration of LCZ696 on cardiac fibrosis after myocardial infarction.



Effects of angiotensin receptor neprilysin inhibitor (ARNi) compared with stand-alone angiotensin receptor blocker (ARB) on cellular cardiac fibrosis and hypertrophy.

In summary, we have shown that the ARNi LCZ696 attenuated cardiac remodeling and dysfunction after experimental MI and inhibited cardiac fibrosis and cardiac hypertrophy in vivo after MI, as well as in vitro beyond that achieved by stand-alone ARB. Our data may offer novel mechanistic insight into the benefits observed with LCZ696 in clinical studies. The present findings suggest

Circ Heart Fail. 2015;8:71-78.

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

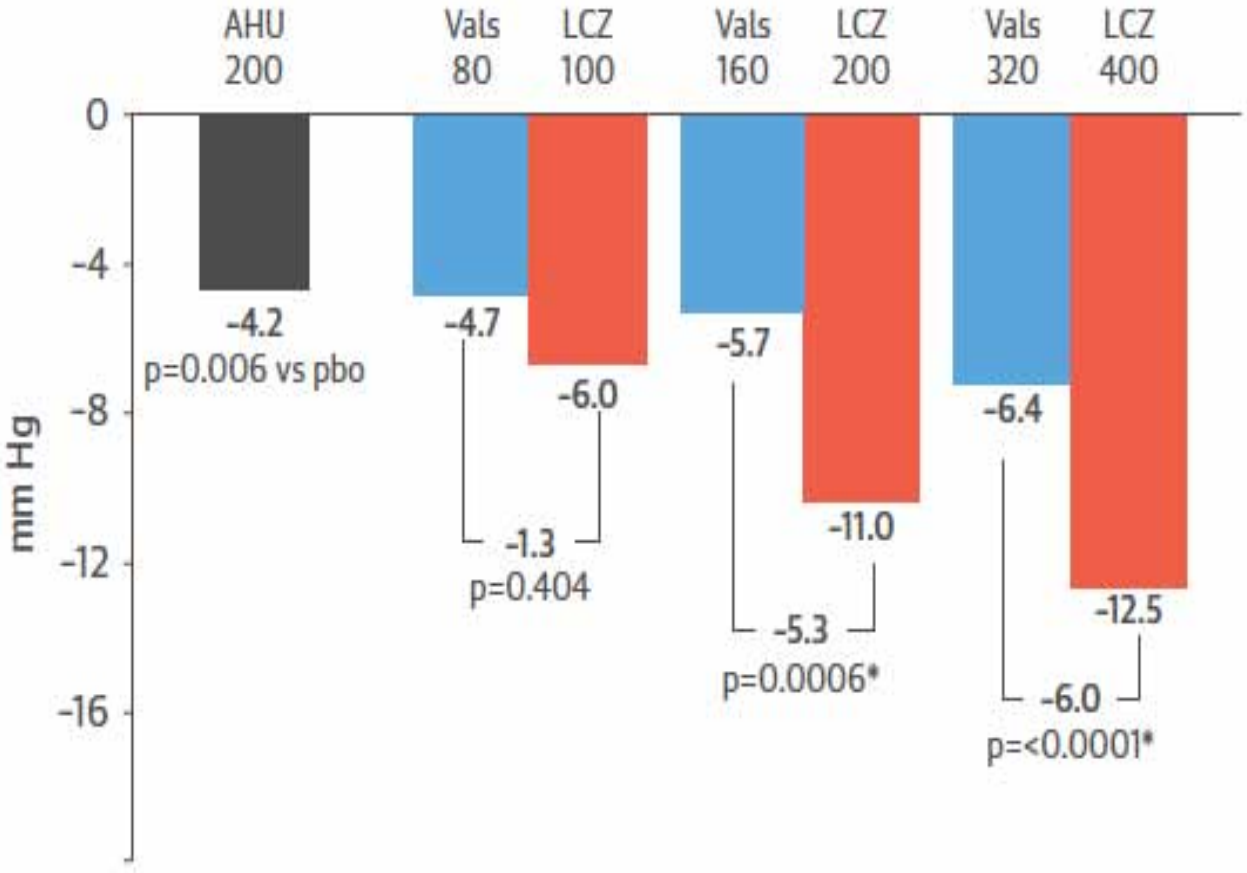
The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure

Eugene Braunwald, MD*

JACC

Complementary Blood Pressure Lowering with NEP inhibition and ARB

Mean Sitting Systolic BP Reduction: Placebo-subtracted



Placebo effect = -7.72 mmHg

n = 154 to 172 /group

Valsartan LCZ 696 AHU 377

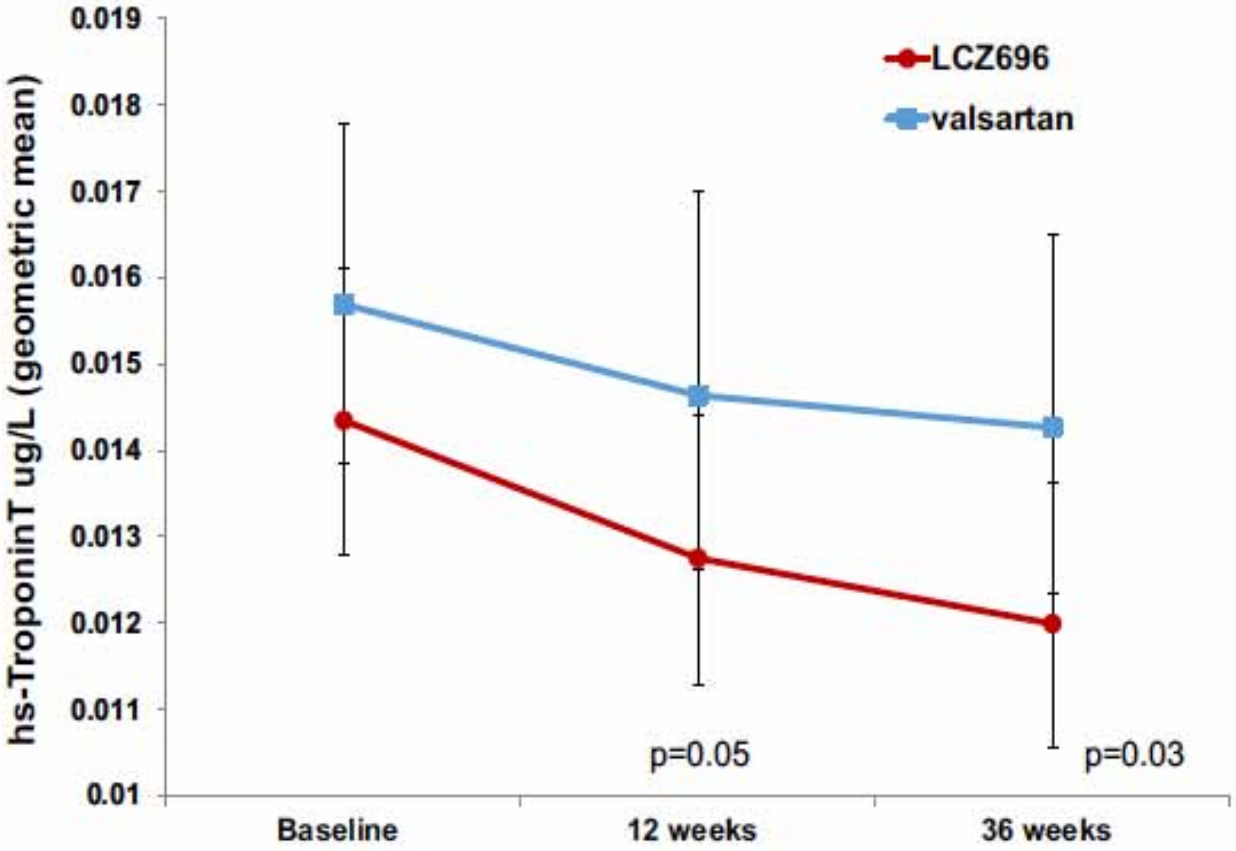
BP reduction in patients with moderate hypertension with AHU 377 (sacubitril), the prodrug for the NEPi LBQ657, and also with various doses of valsartan and LCZ696. Doses of the latter 2 drugs provided comparable degrees of angiotensin receptor blockade.

"If I have seen further, it is by standing on the shoulders of giants."

—Isaac Newton, 1676

Elevation in High-Sensitivity Troponin T in Heart Failure and Preserved Ejection Fraction and Influence of Treatment With the Angiotensin Receptor Neprilysin Inhibitor LCZ696

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION



High-sensitivity troponin T (hs-TnT) levels by treatment group

N-terminal pro-brain natriuretic peptide. Decreases in hs-TnT with LCZ696 in parallel with improvement in N-terminal pro-brain natriuretic peptide and left atrial size suggest that the angiotensin receptor neprilysin inhibitor LCZ696 may reduce this measure of myocardial injury in heart failure with preserved ejection fraction.

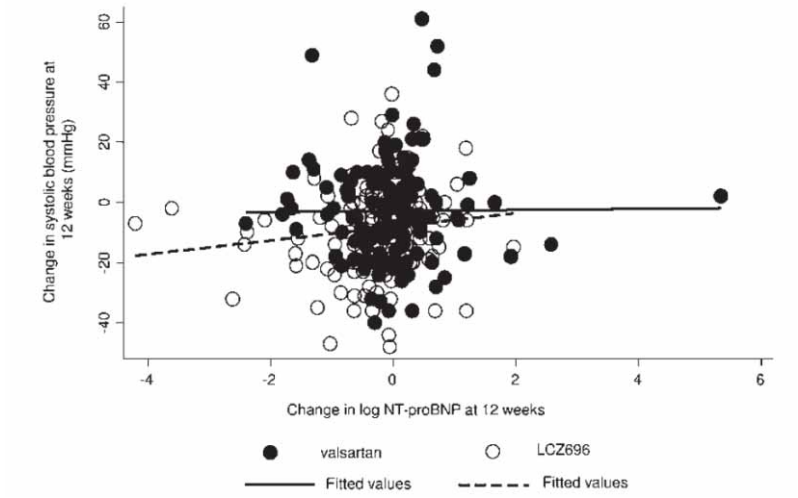
(*Circ Heart Fail*. 2014;7:953-959.)

Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial

EUROPEAN SOCIETY OF CARDIOLOGY®

Change in left atrial diameter, left atrial volume and estimated glomerular filtration rate (eGFR) according to treatment and change in systolic blood pressure at 36weeks

	Tertile 1, $n = 89$ (−50 to −12 mmHg) Change (95%CI)	Tertile 2, $n = 83$ (−11 to −2 mmHg) Change (95%CI)	Tertile 3, $n = 78$ (3–62 mmHg) Change (95%CI)	Overall	
				P LCZ696 vs. valsartan (adjusted for change in SBP at 36 weeks)	*P* for interaction
Left atrial diameter					
LCZ696	−0.15(−0.25 to −0.06)	−0.12(−0.23 to −0.01)	−0.19(−0.32 to −0.05)	0.03	0.91
Valsartan	−0.04(−0.14 to −0.06)	−0.07(−0.16 to −0.02)	−0.11(−0.22 to −0.01)		
Left atrial indexed volume					
LCZ696	−2.65 (−4.71 to −0.59)	−1.77 (−4.87 to −1.34)	−3.74 (−7.18 to −0.29)	0.01	0.61
Valsartan	−0.28(−3.54 to −2.98)	0.22 (−2.69 to −3.14)	0.80(−2.53 to 4.13)		
eGFR					
LCZ696	−3.83(−6.99 to −0.67)	−1.28(−6.26 to −3.70)	1.86(−3.02 to −6.74)	0.002	0.69
Valsartan	−9.09(−12.78 to −5.41)	−3.03(−7.16 to −1.11)	−4.28(−7.34 to −1.23)		



Correlation between change in systolic blood pressure at 12weeks and change in *N*-terminal pro-brain natriuretic peptide (NT-proBNP) at 12weeks according to randomized treatment, LCZ696 (open circles, dashed line), valsartan (closed circles, solid line).

European Journal of Heart Failure (2014) **16**, 671–677

The NEW ENGLAND JOURNAL of MEDICINE

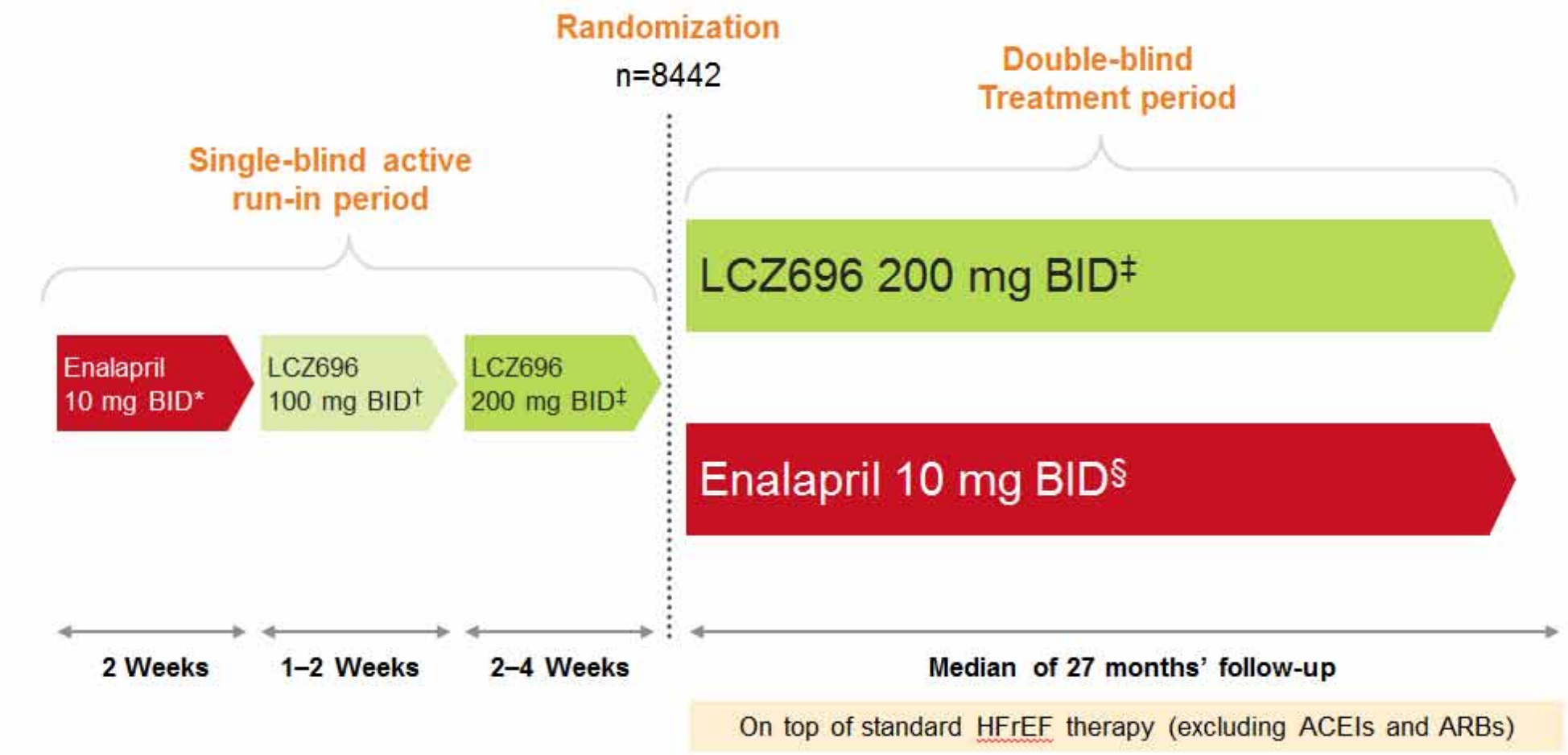
ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

PARADIGM-HF: Study Design



"This study was designed to provide evidence to support the replacement of ACE inhibitors or ARBs with LCZ696 in the management of chronic heart failure".

*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail. 2014;16:817–25; McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

PARADIGM-HF: key inclusion and exclusion criteria

Key inclusion criteria:

- Males and females aged ≥18 years
- **Chronic HF NYHA class II–IV with LVEF ≤40%* and**
  - **BNP ≥150 pg/mL (NT-proBNP ≥600 pg/mL) OR**
  - **BNP ≥100 pg/mL (NT-proBNP ≥400 pg/mL) and a hospitalization for HF within the last 12 months**
- Stable on an ACEI or an ARB (dosage equivalent to enalapril ≥10 mg/day) for at least 4 weeks
- Treatment with a stable dosage of a β-blocker for at least 4 weeks, unless otherwise contraindicated or not tolerated
- Optimized dosing of background HF medications and use of aldosterone antagonists, where indicated

Key exclusion criteria:

- History of angioedema
- **eGFR <30 mL/min/1.73m2 at screening**, end of enalapril run-in or randomization, or a >35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- **Serum potassium >5.2 mmol/L** at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the LCZ696 run-in
- Requirement for treatment with both ACEI and ARBs
- Symptomatic hypotension, **SBP <100 mmHg** at screening, OR SBP <95 mmHg at end of enalapril run-in or at randomization
- **Current acute decompensated HF**
- History of severe pulmonary disease

*The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment

McMurray, et al. N Engl J Med 2014; 10.1056/NEJMoa1409077.

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Systolic blood pressure — mm Hg	122±15	121±15
Heart rate — beats/min	72±12	73±12
Body-mass index§	28.1±5.5	28.2±5.5
Serum creatinine — mg/dl	1.13±0.3	1.12±0.3
Clinical features of heart failure		
Ischemic cardiomyopathy — no. (%)	2506 (59.9)	2530 (60.1)
Left ventricular ejection fraction — %	29.6±6.1	29.4±6.3
Median B-type natriuretic peptide (IQR) — pg/ml	255 (155–474)	251 (153–465)
Median N-terminal pro–B-type natriuretic peptide (IQR) — pg/ml	1631 (885–3154)	1594 (886–3305)
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
IV	33 (0.8)	27 (0.6)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

Mc Murray J. Et al N Engl J Med 2014;371:993-

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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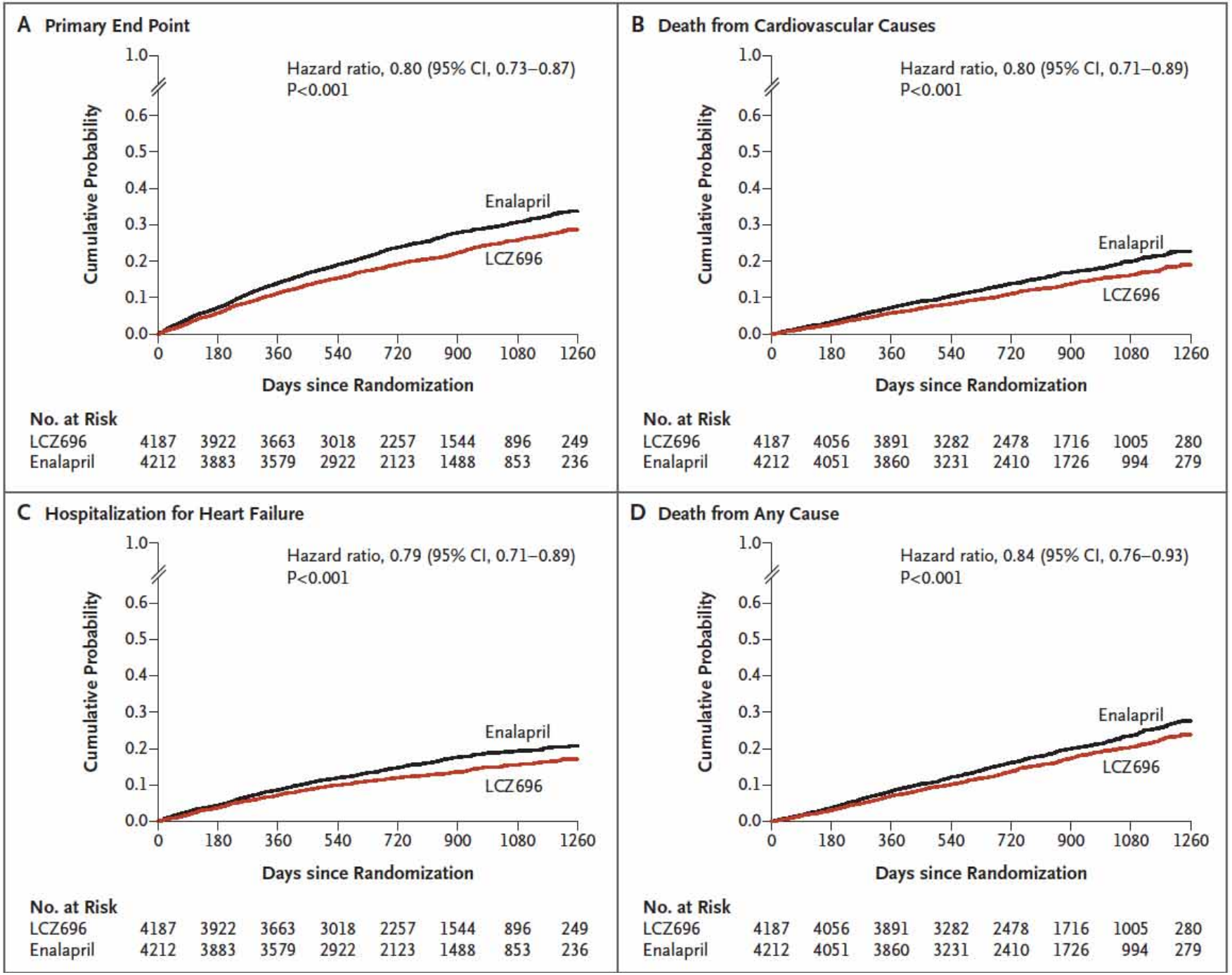


Mc Murray J. Et al N Engl J Med 2014;371:993-

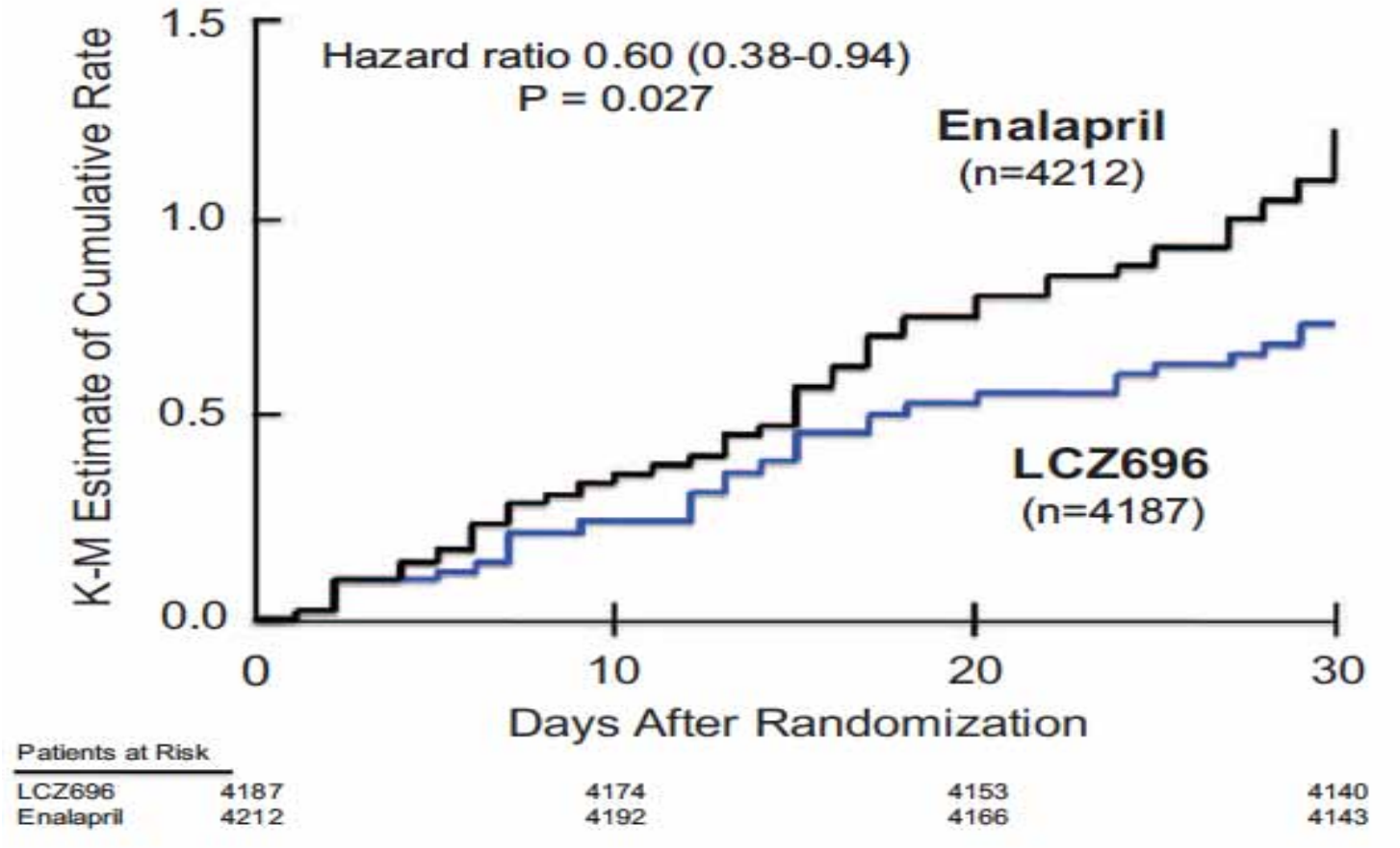
Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

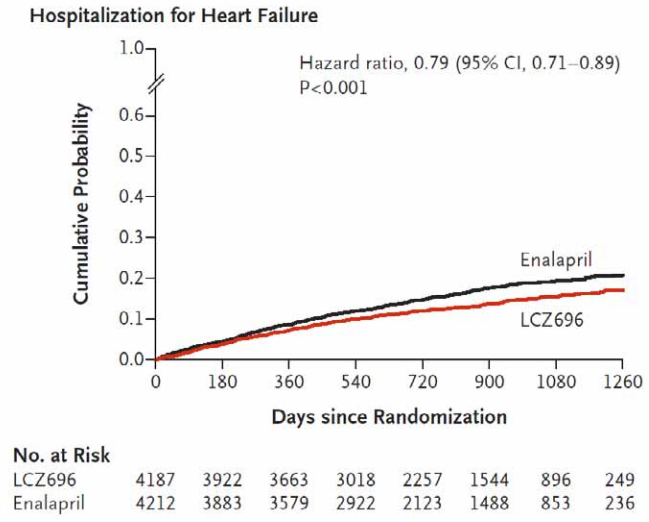
Circulation

Circulation.2015;131:54–61

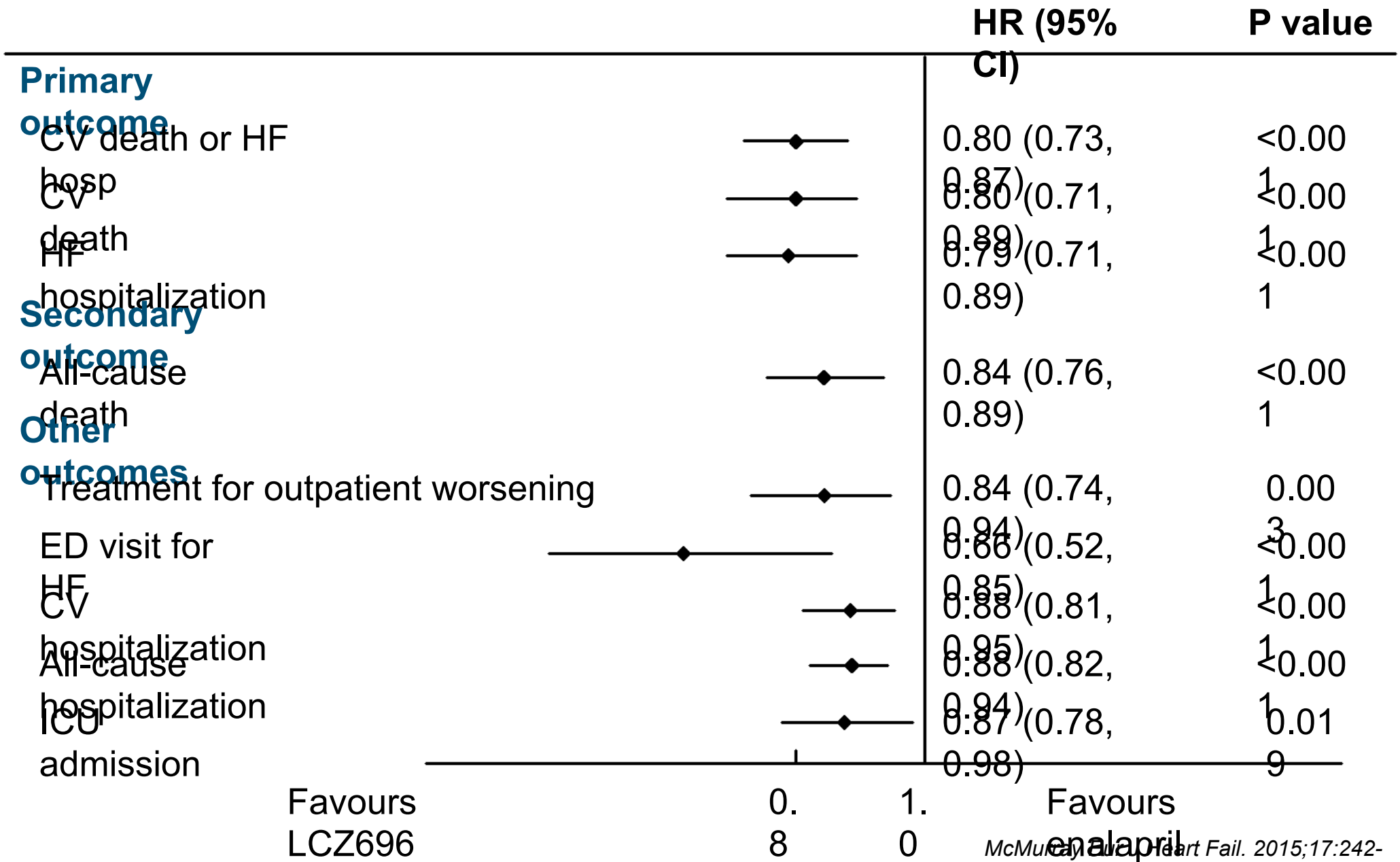
Angiotensin-neprilysin inhibition prevents the clinical progression of surviving patients with heart failure more effectively than angiotensin-converting enzyme inhibition.

Kaplan–Meier curve for the time to first hospitalization for heart failure during first 30 days after randomization





PARADIGM-HF: Summary of primary, secondary and exploratory outcomes

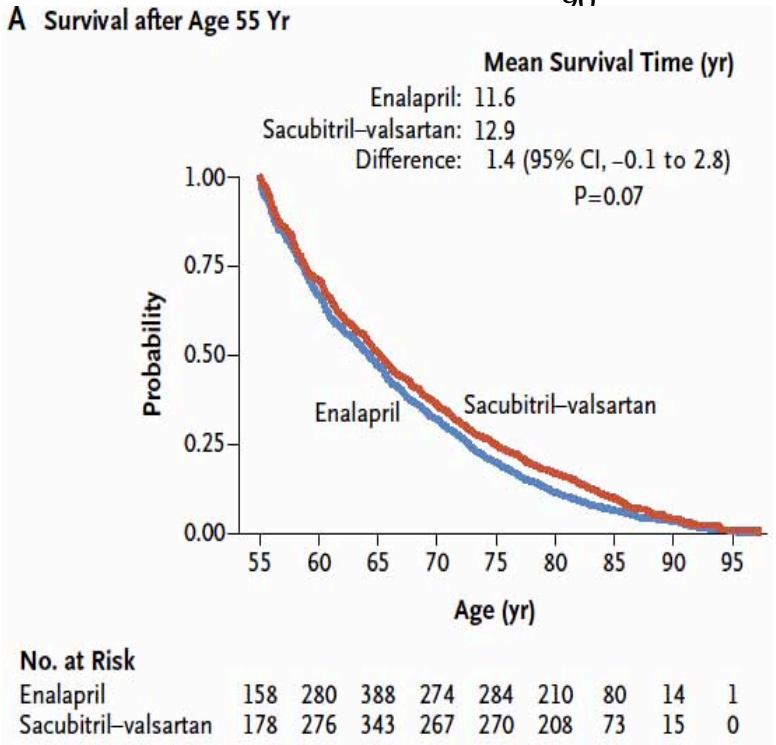


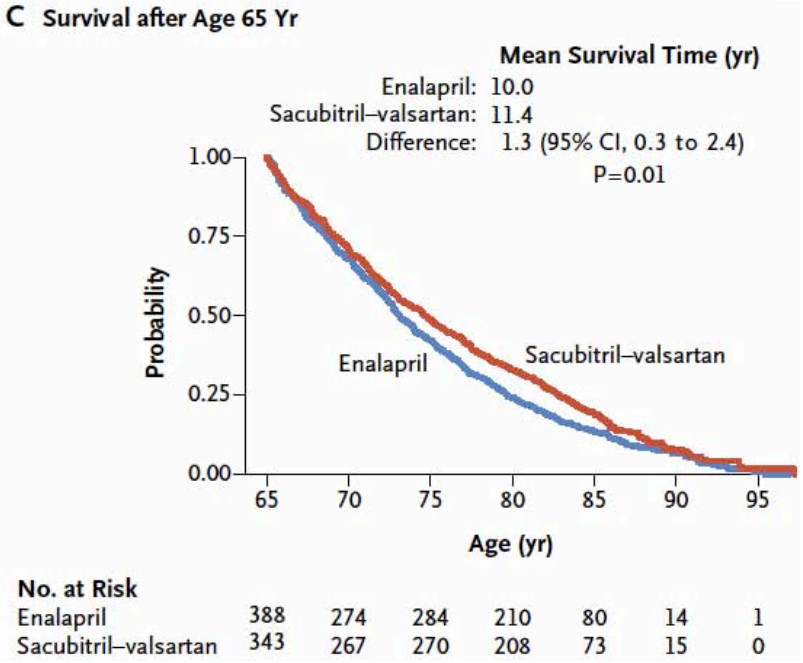
McMurray JJ. Eur J Heart Fail. 2015;17:242-

Estimating the Long-Term Treatment Benefits of Sacubitril–Valsartan

N Engl J Med. 2015 Dec 3;373(23):2289-90

The NEW ENGLAND JOURNAL of MEDICINE

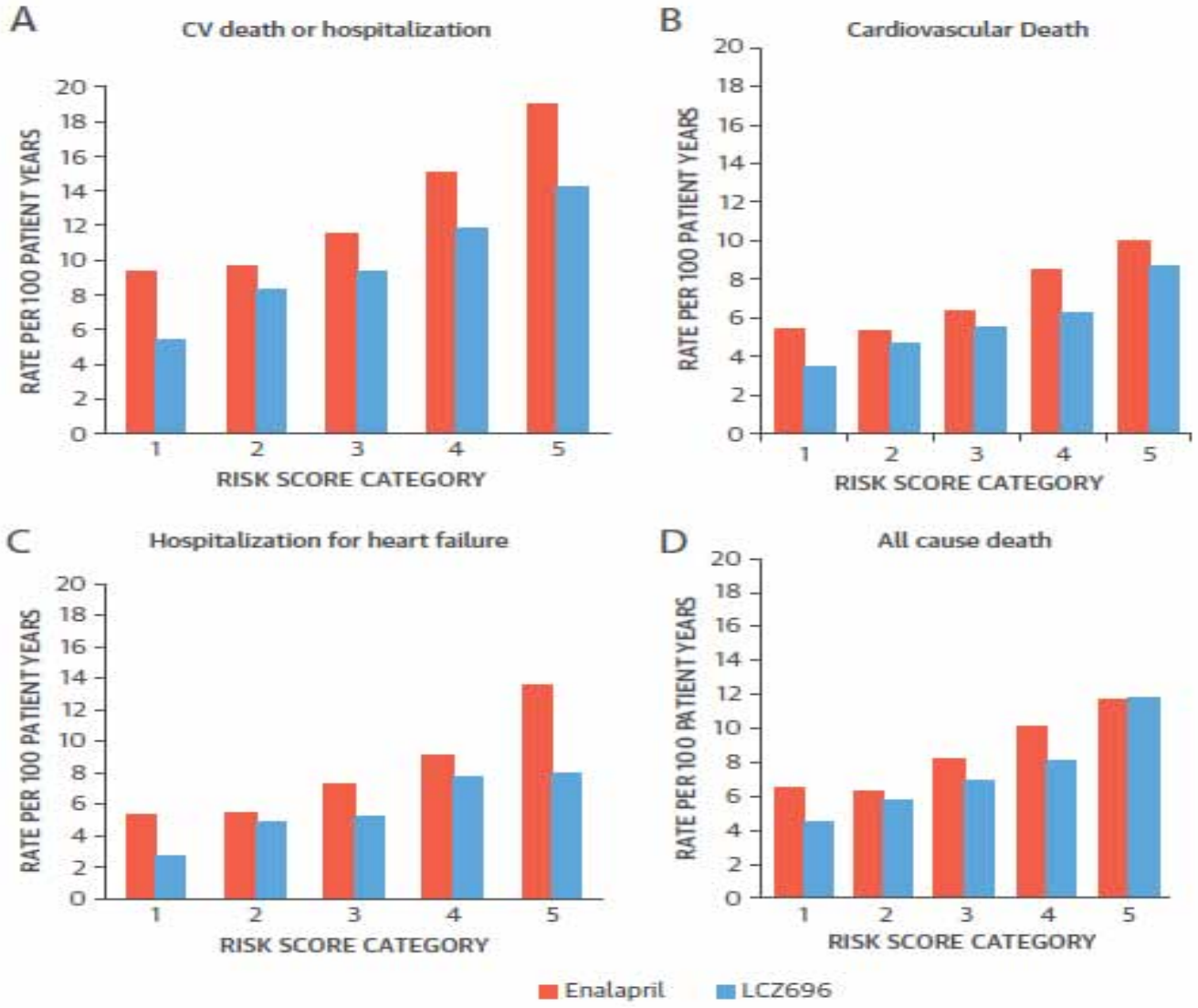




Assuming that the protective effects of LCZ 696 remain consistent with long-term use, treatment with LCZ 696 would result in a <u>projected benefit of 1 to 2 years of increased life expectancy and survival free from heart failure</u> for patients such as those in the PARADIGM-HF trial.

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

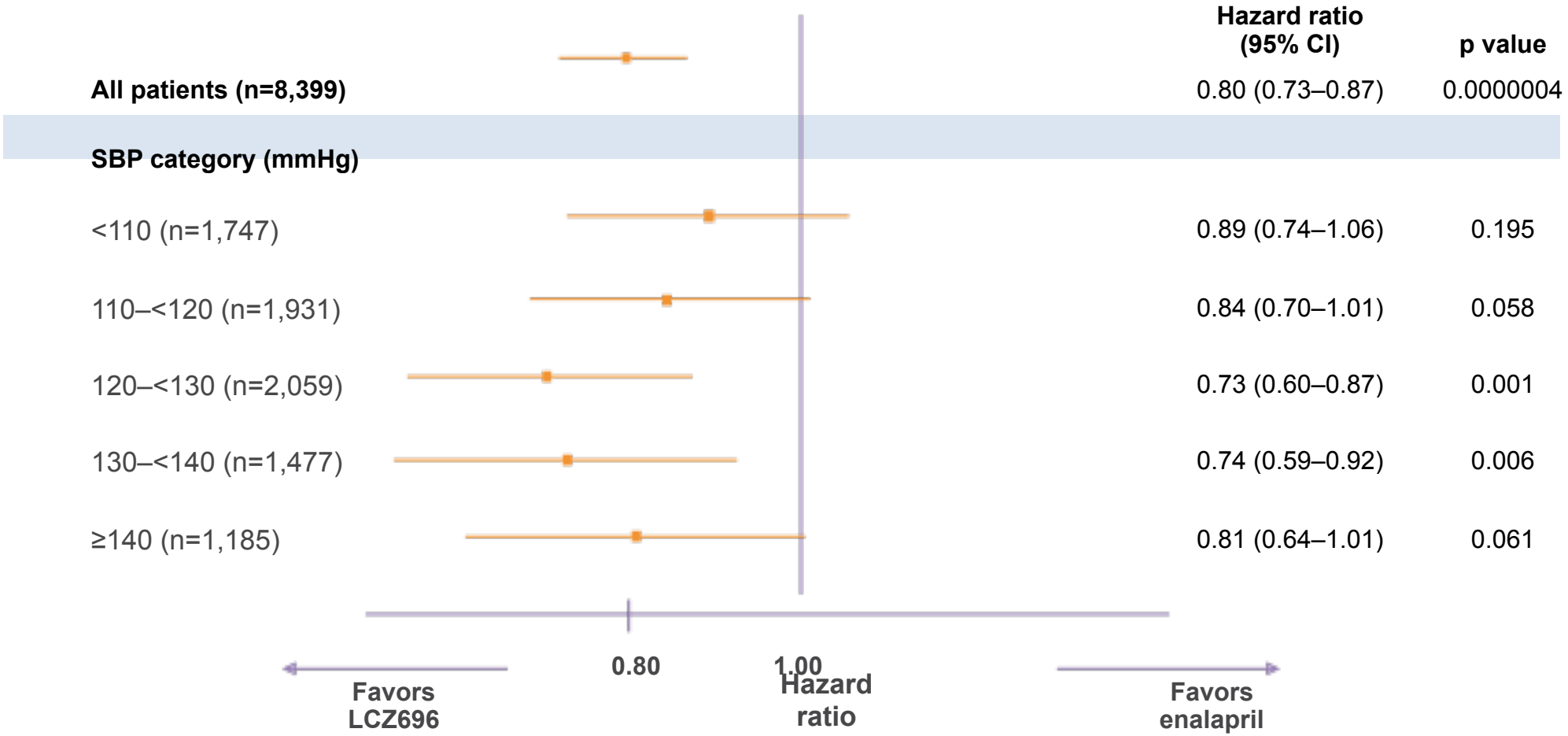


CONCLUSIONS Although most PARADIGM-HF patients had mild symptoms, many were at high risk for adverse outcomes and obtained a large absolute benefit from LCZ696, compared with enalapril, over a relatively short treatment period. LCZ696's benefit was consistent across the spectrum of risk. (PARADIGM-HF trial [Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure]; NCT01035255)

J Am Coll Cardiol 2015;66:2059–71

PARADIGM-HF: baseline SBP did not influence the treatment effect of LCZ696 compared with enalapril

- The reduction in the primary outcome (CV death or first hospitalization for HFrEF) for LCZ696 compared with enalapril was consistent across SBP categories (p=0.67 for treatment by SBP category interaction)



CI=confidence interval; CV=cardiovascular; HFrEF=heart failure with reduced ejection fraction; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; SBP=systolic blood pressure

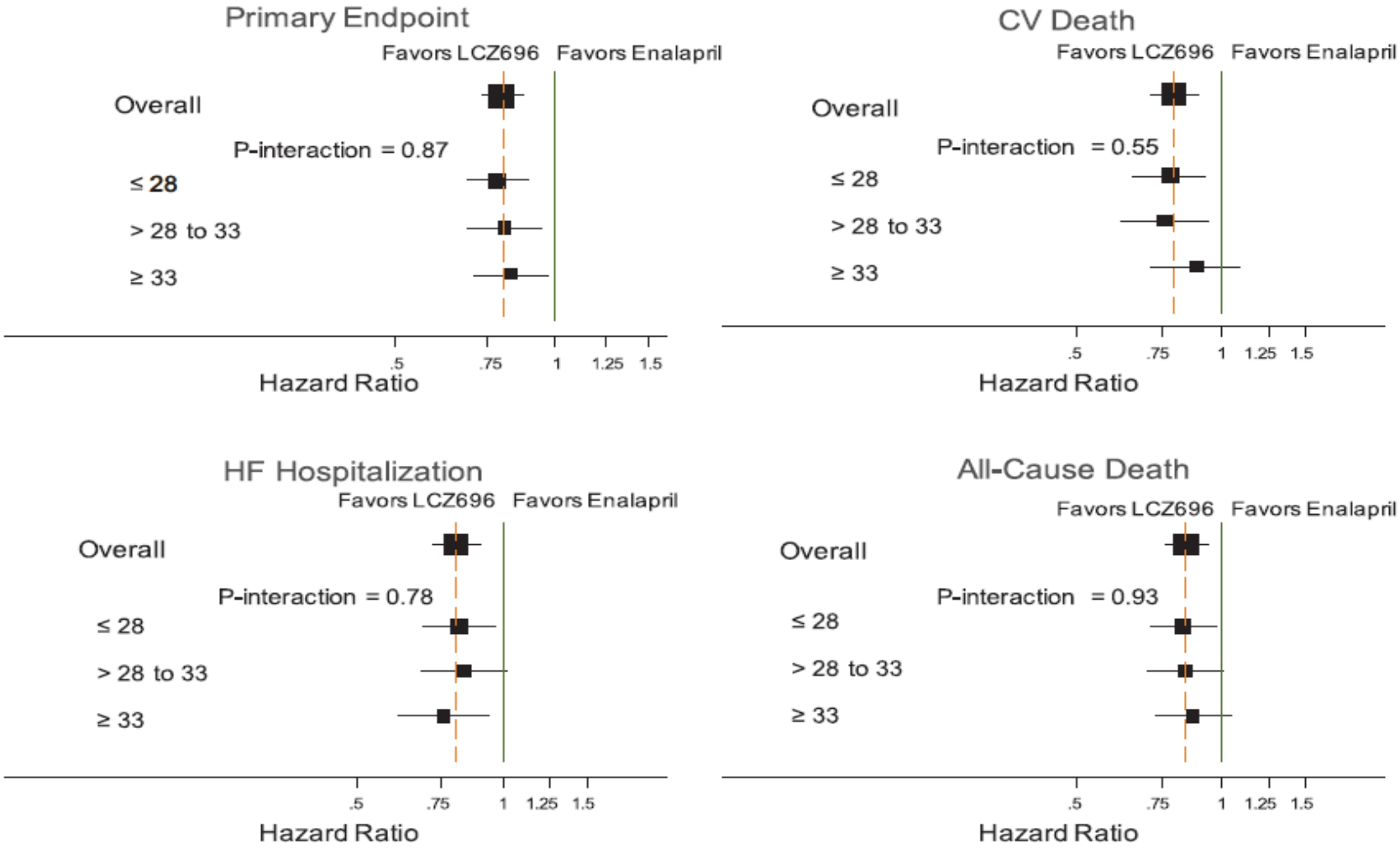
Bohm et al. Eur J Heart Fail 2015;17(Suppl 1):393 (Abstract P1794 and poster)

Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial

Circulation
Heart Failure
Circ Heart Fail. 2016;9:e002744.

Treatment effect of LCZ696 by tertile of left ventricular ejection fraction for all outcomes



Conclusions—In patients with HF and reduced EF enrolled in PARADIGM-HF, LVEF was a significant and independent predictor of all outcomes. Sacubitril/valsartan was effective at reducing cardiovascular death and HF hospitalization throughout the LVEF spectrum.

Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction

Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Table 3. Treatment Effects of LCZ696 (Sacubitril/Valsartan) According to History of Diabetes Mellitus and Glycemic Status

	Overall	Normoglycemia	Pre–Diabetes Mellitus	Undiagnosed Diabetes Mellitus	Diabetes Mellitus	*P* Values for Interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
HF hospitalization or cardiovascular death	0.80 (0.73–0.87)	0.68 (0.56–0.83)	0.76 (0.63–0.91)	0.97 (0.77–1.22)	0.87 (0.77–0.98)	0.13
Cardiovascular death	0.80 (0.71–0.89)	0.62 (0.48–0.80)	0.76 (0.61–0.96)	0.86 (0.65–1.15)	0.92 (0.77–1.09)	0.09
HF hospitalization	0.80 (0.71–0.89)	0.85 (0.65–1.12)	0.73 (0.57–0.93)	0.88 (0.65–1.20)	0.79 (0.67–0.94)	0.78
All-cause mortality	0.84 (0.76–0.93)	0.68 (0.55–0.85)	0.77 (0.63–0.95)	0.91 (0.69–1.18)	0.97 (0.83–1.14)	0.06
Significant worsening in KCCQ clinical score (≥5) at 8 mo†	0.83(0.76–0.92)‡	0.73 (0.60–0.89)‡	0.86 (0.71–1.04)‡	0.93 (0.71–1.21)‡	0.86 (0.74–1.01)‡	0.14

In each of the 3 predefined glycemia categories, LCZ696 reduced the occurrence of the primary composite outcome compared with enalapril.
No significant interaction between glycemia category and treatment (P=0.14).

Circ Heart Fail. 2016;9:e002560.

Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients

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Table 2 Baseline characteristics according to cause of death

Characteristic	Death due to HF (*N* = 331)	Sudden Death (*N* = 561)	Other CV death[a] (*N* = 359)	Non-CV Death (*N* = 295)	*P* (all categories)
Age (years)	65.9 ± 12.5	63.1 ± 12.0	66.6 ± 11.7	68.1 ± 11.8	<0.001
Creatinine (mg/dL)	1.26 ± 0.36	1.14 ± 0.30	1.18 ± 0.31	1.19 ± 0.32	<0.001
Clinical features of HF					
Ischaemic CMP	176 (53.2%)	368 (65.6%)	245 (68.2%)	193 (65.4%)	<0.001
LVEF (%)	27.6 ± 6.9	28.9 ± 6.5	29.3 ± 6.7	30.0 ± 6.8	<0.001
Median BNP (IQR)	459 [270, 914]	370 [201, 695]	391 [211, 752]	293 [172, 571]	<0.001
Median NT-pro-BNP (IQR)	3377 [1713, 6512]	2402 [1251, 5076]	2542 [1159, 5832]	1941 [1085, 4114]	<0.001
NYHA class					0.21
I	7 (2.1%)	23 (4.1%)	14 (3.9%)	9 (3.1%)	
II	214 (64.7%)	354 (63.1%)	223 (62.1%)	212 (71.9%)	
III	107 (32.3%)	177 (31.6%)	120 (33.4%)	72 (24.4%)	
IV	3 (0.9%)	7 (1.2%)	2 (0.6%)	2 (0.7%)	
Medical history					
Hospitalization for HF	237 (71.6%)	362 (64.5%)	241 (67.1%)	189 (64.1%)	0.13
MI	144 (43.5%)	276 (49.2%)	167 (46.5%)	133 (45.1%)	0.38
Treatment at randomization					
β-Blocker	297 (89.7%)	507 (90.4%)	325 (90.5%)	271 (91.9%)	0.83
MRA	196 (59.2%)	311 (55.4%)	197 (54.9%)	135 (45.8%)	0.007
ICD	70 (21.1%)	36 (6.4%)	45 (12.5%)	51 (17.3%)	<0.001
CRT	34 (10.3%)	20 (3.6%)	18 (5.0%)	28 (9.5%)	<0.001

European Heart Journal (2015) **36**, 1990–1997

Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients

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Table 3 Adjudicated causes of death and rates of death by cause according to treatment assignment, PARADIGM-HF (*N* = 8399)

	LCZ			Enalapril			HR (95% CI) *P*-value LCZ vs. Enalapril
	N	% of patients	% of deaths	*N*	% of patients	% of deaths	
Total deaths	711	17.0	100	835	19.8	100	0.84 (0.76, 0.93) $P = 0.001$
Cardiovascular death	558	13.3	78.5	693	16.5	83.0	0.80 (0.72, 0.89) $P < 0.001$
Sudden death	250	6.0	35.2	311	7.4	37.2	0.80 (0.68, 0.94) $P = 0.008$
Last contact <1 h	167	4.0	23.5	213	5.1	25.5	0.78 (0.64–0.95) $P = 0.015$
1–24 h	83	2.0	11.7	98	2.3	11.7	0.84 (0.63–1.13) $P = 0.26$
Worsening heart failure	147	3.5	20.7	184	4.4	22.0	0.79 (0.64, 0.98) $P = 0.034$
Other cardiovascular	161	3.8	22.6	198	4.7	23.7	0.81 (0.66–1.00) $P = 0.045$
Fatal MI	24	0.6	3.4	33	0.8	4.0	0.73 (0.43, 1.23) $P = 0.24$
Fatal stroke	30	0.7	4.2	34	0.8	4.1	0.88 (0.54, 1.44) $P = 0.62$
Presumed sudden death	26	0.6	3.7	23	0.5	2.8	1.12 (0.64, 1.96) $P = 0.69$
Presumed cardiovascular death	67	1.6	9.4	95	2.3	11.4	0.70 (0.51, 0.95) $P = 0.024$
Non-cardiovascular death	120	2.9	16.9	109	2.6	13.1	1.09 (0.84, 1.41) $P = 0.53$

doi:10.1093/eurheartj/ehv186

Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients

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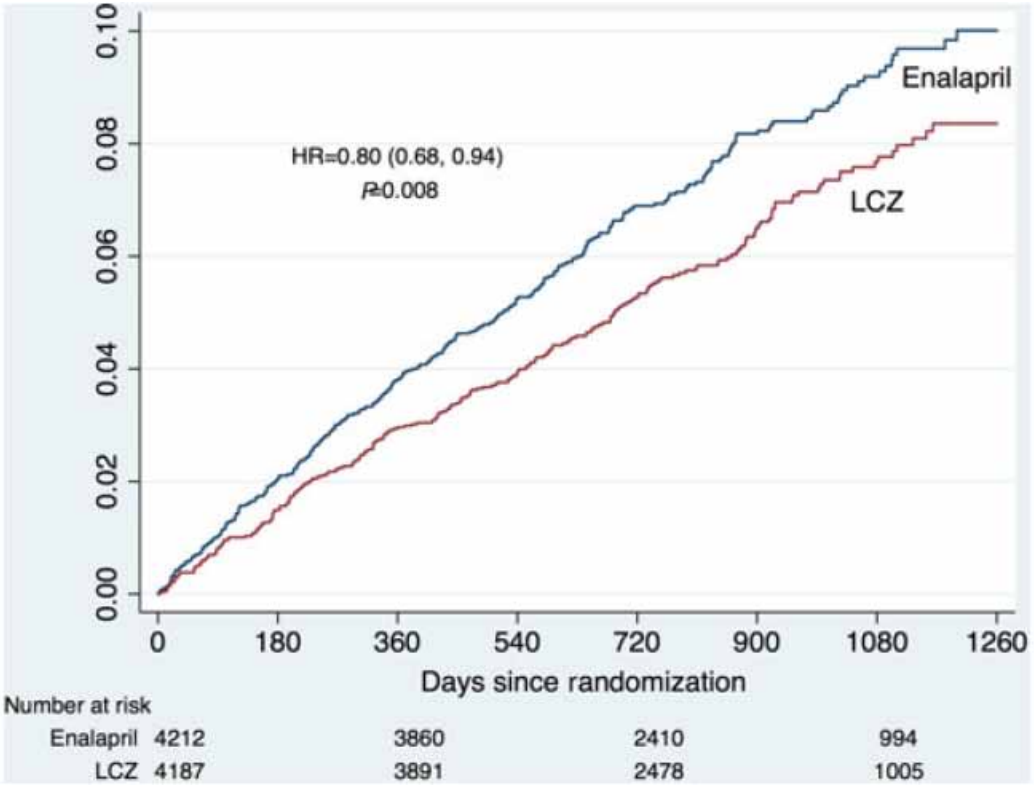
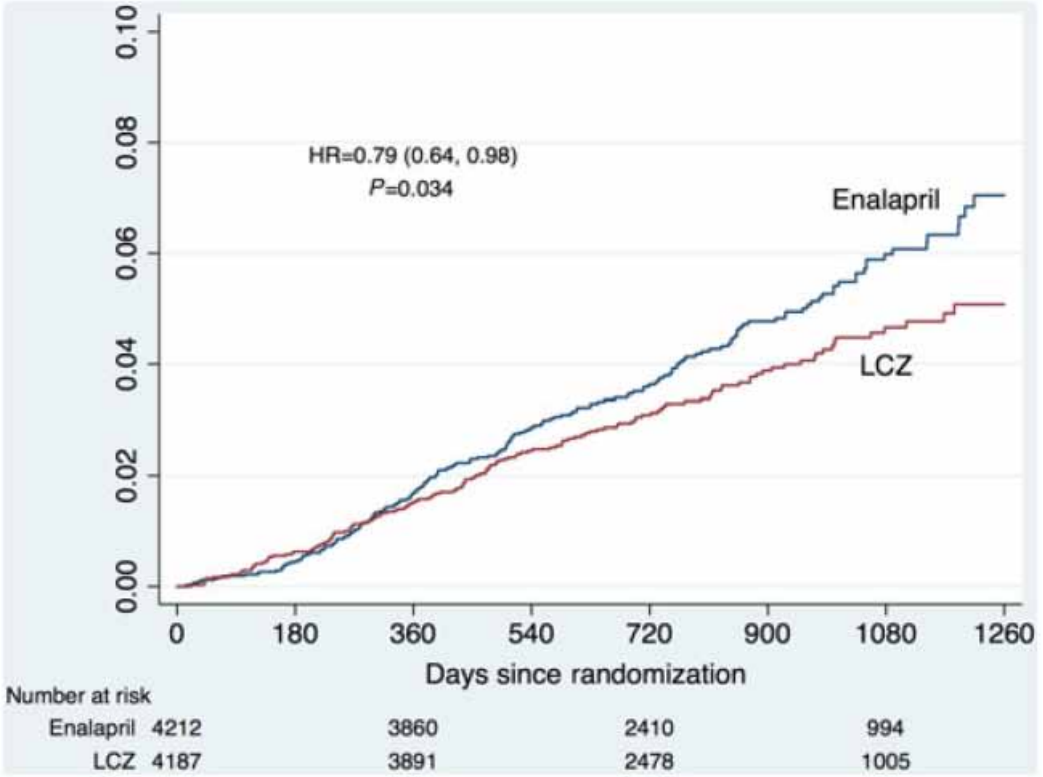
Sudden death

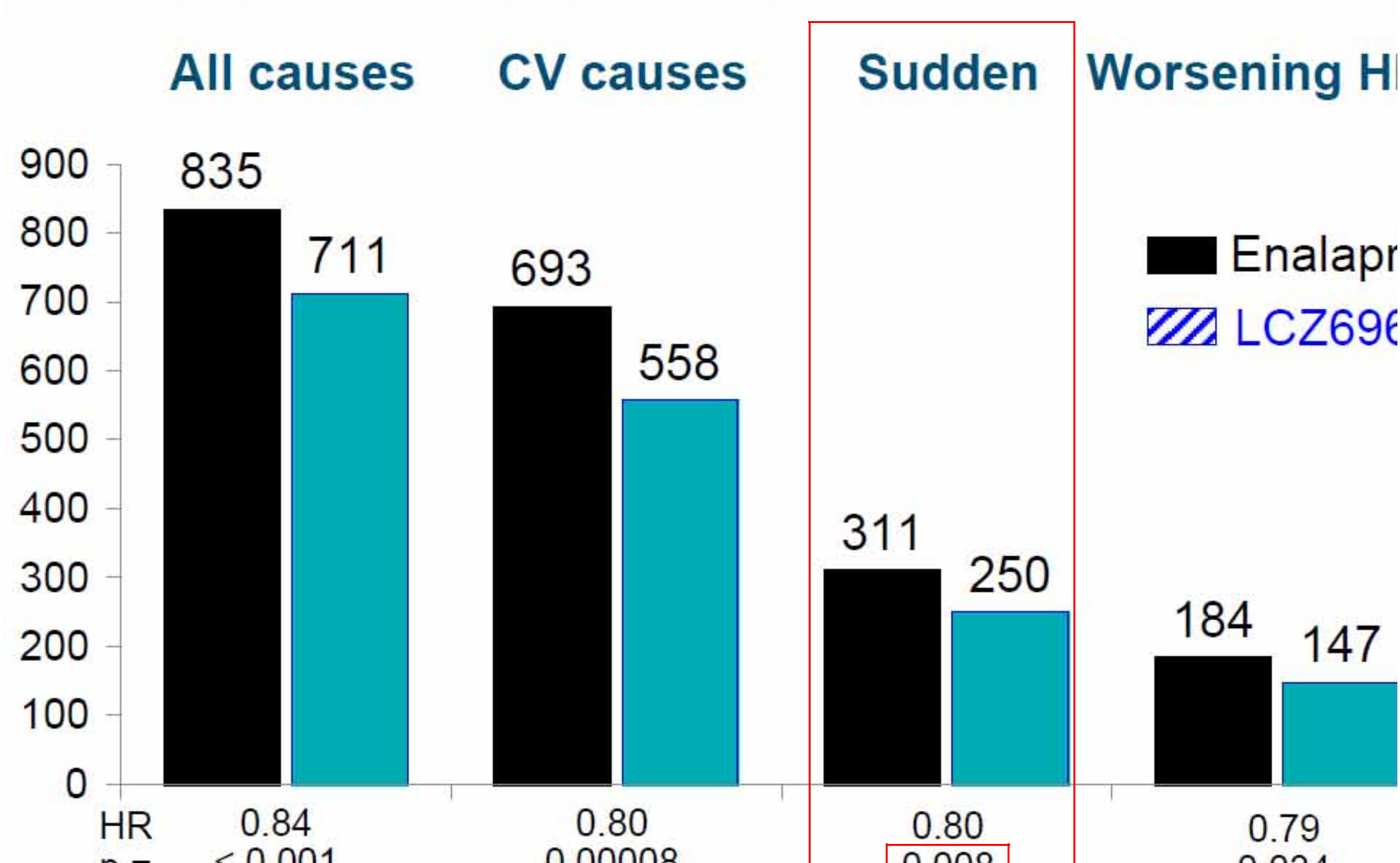


Worsening HF

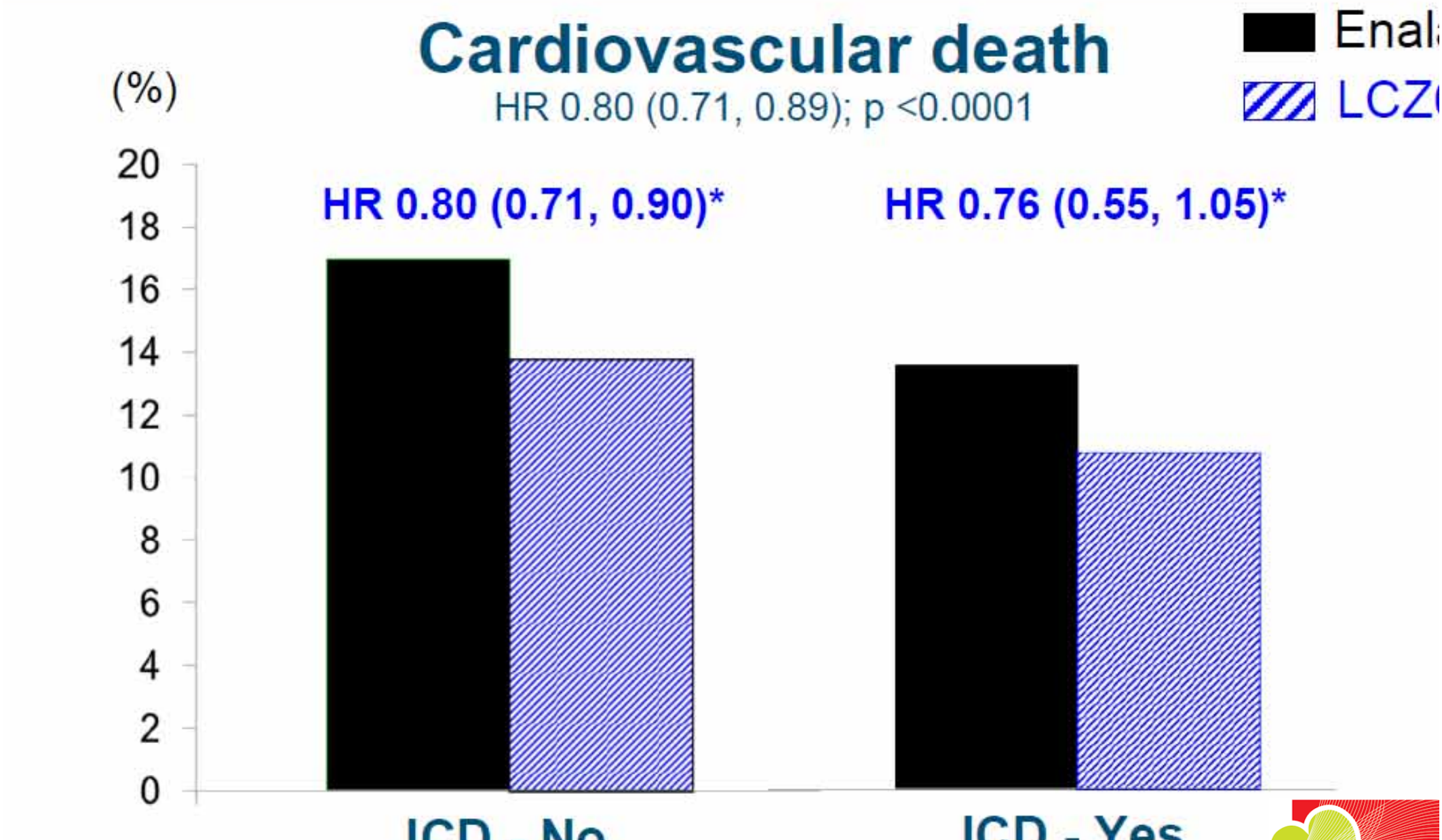


European Heart Journal (2015) **36**, 1990–1997

PARADIGM-HF: cause/ mode of death



PARADIGM-HF: Baseline ICD/CRT-D use *(post hoc analysis)*

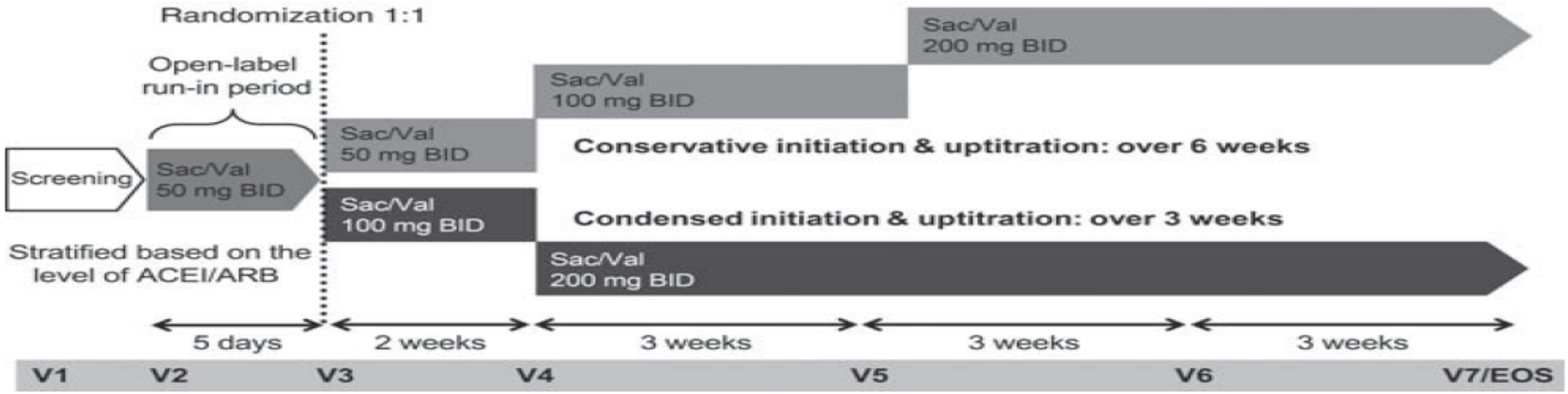


PARADIGM-HF: Pre-specified safety endpoints

	LCZ696 (n=4187)	Enalapril (n=4212)	P value
Hypotension (%)			
symptom	14.2	9.2	<0.001
symptoms and SBP <90mmHg	2.0	1.4	<0.001
Renal impairment (%)			
Cr ≥2.5mg/dl	3.4	4.8	0.001
Cr >3.0mg/dl	1.5	2.0	0.07
Hyperkalaemia (%)			
K^+ >5.5mmol/l	16.3	17.6	0.001
K^+ >6.0mmol/l	4.2	5.6	<0.001
Cough (%)	11.3	14.3	<0.001
Angioedema: not hospitalised			
No treatment/antihistamines n, (%)	10 (0.2)	5 (0.1)	0.31
Catecholamines/corticosteroids n, (%)	6 (0.1)	4 (0.1)	0.75
Angioedema: hospitalised			
No airway compromise n, (%)	3 (0.1)	1 (0.0)	0.62
Airway compromise n, (%)	0 (0.0)	0 (0.0)	1 -

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

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens

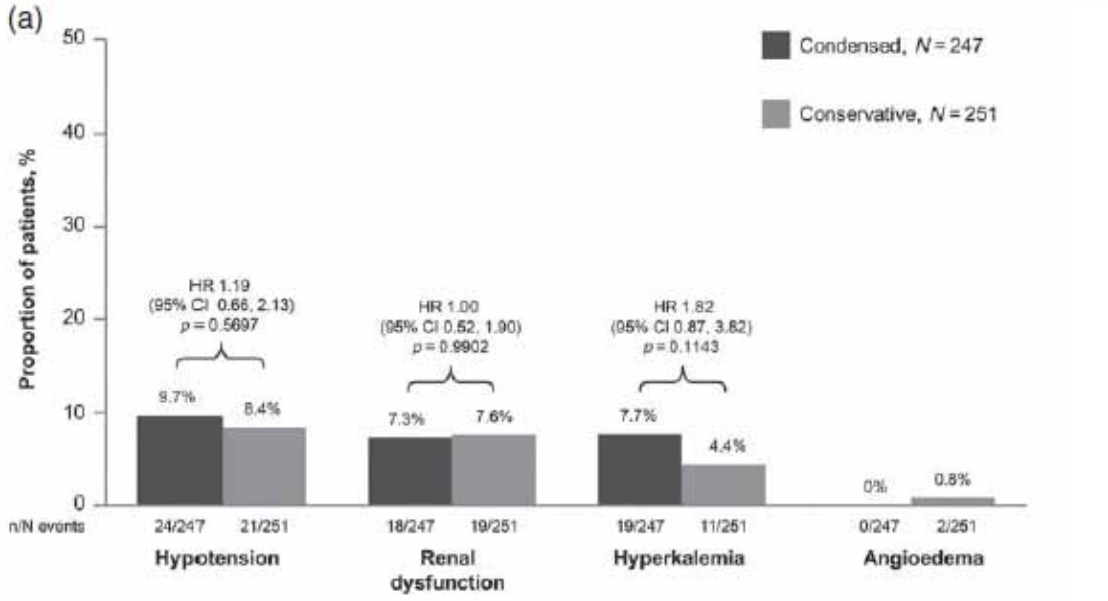


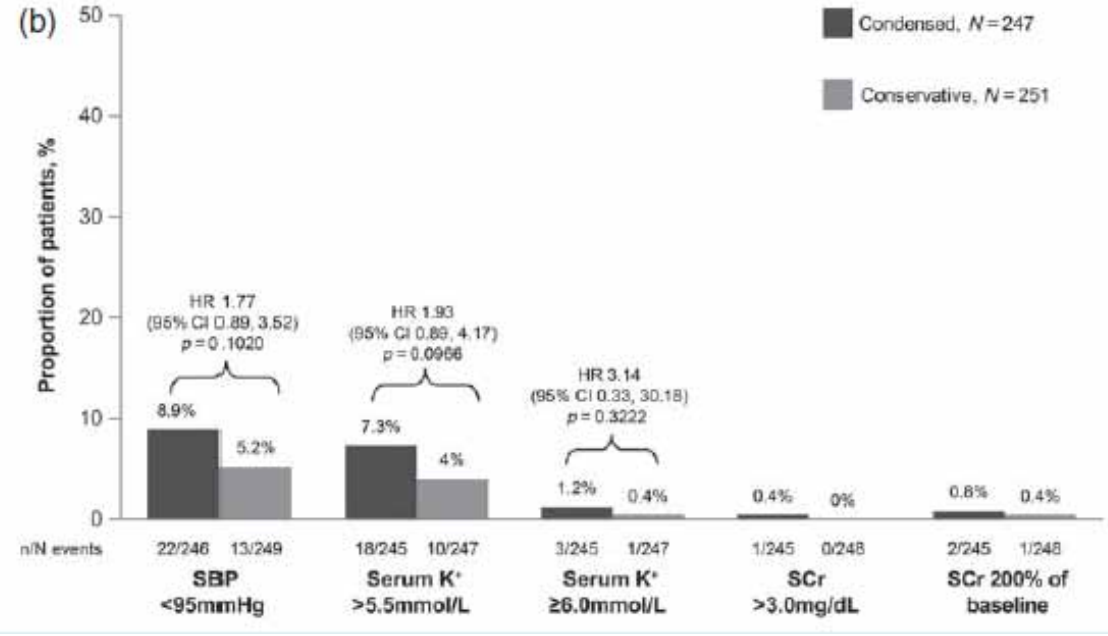
Conclusions Initiation/uptitration of sacubitril/valsartan from 50 to 200 mg twice daily over 3 or 6 weeks had a tolerability profile in line with other HF treatments. More gradual initiation/uptitration maximized attainment of target dose in the low-dose ACEI/ARB group.

Senni et al

European Journal of Heart Failure (2016)

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens





Senni et al

European Journal of Heart Failure (2016)

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

7.3.2. Pharmacological Treatment for Stage C HF With Reduced Ejection Fraction: Recommendations

7.3.2.10. Renin-Angiotensin System Inhibition With Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker or ARNI: Recommendations

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOE**	**Recommendations**
I	ACE: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)* (9-14), OR ARBs *(Level of Evidence: A)* (15-18), OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.
I	ARNI: B-R	In patients with chronic symptomatic HF*r*EF 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).

Yancy et al. 10.1016/j.jacc.2016.05.011

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

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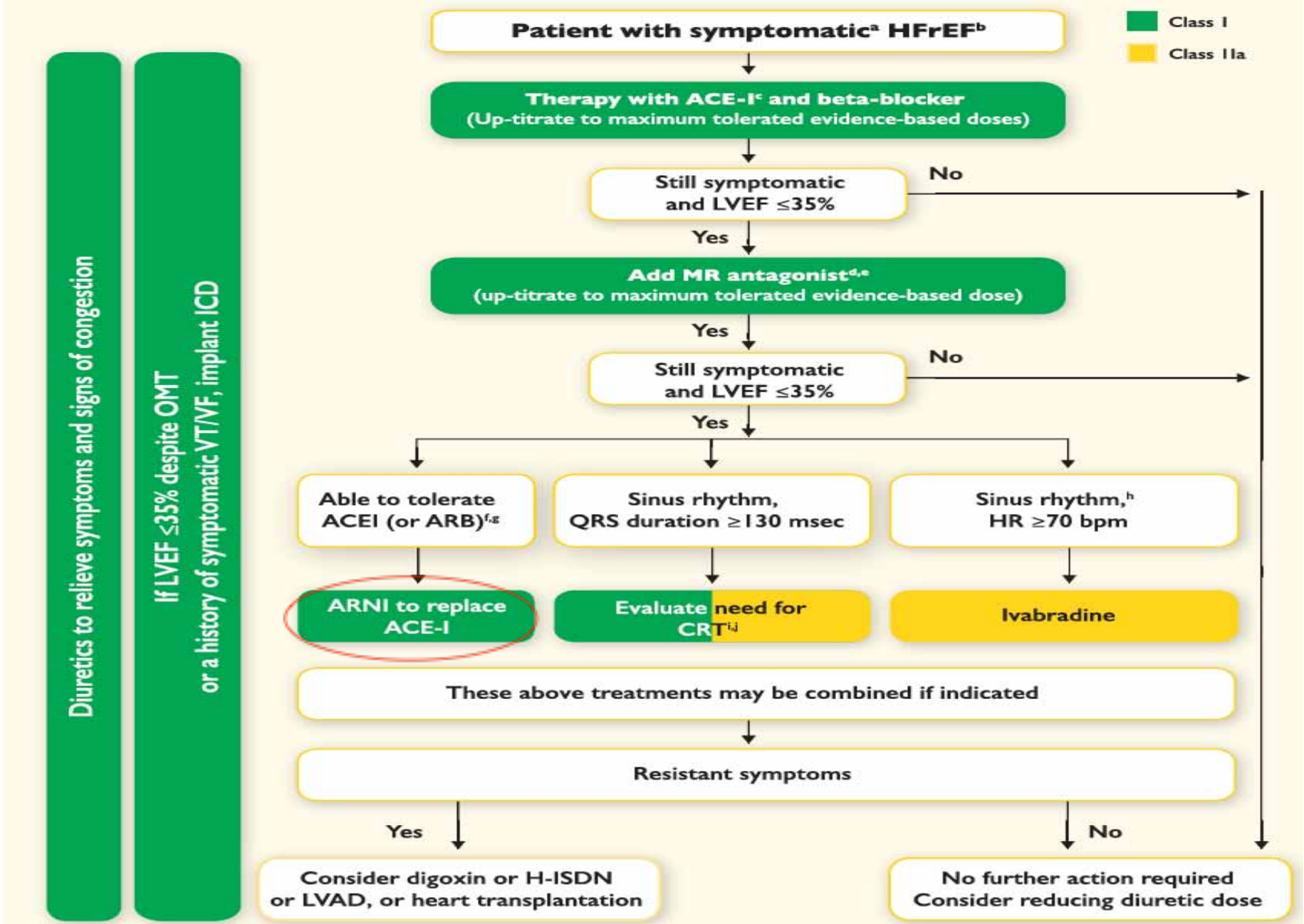
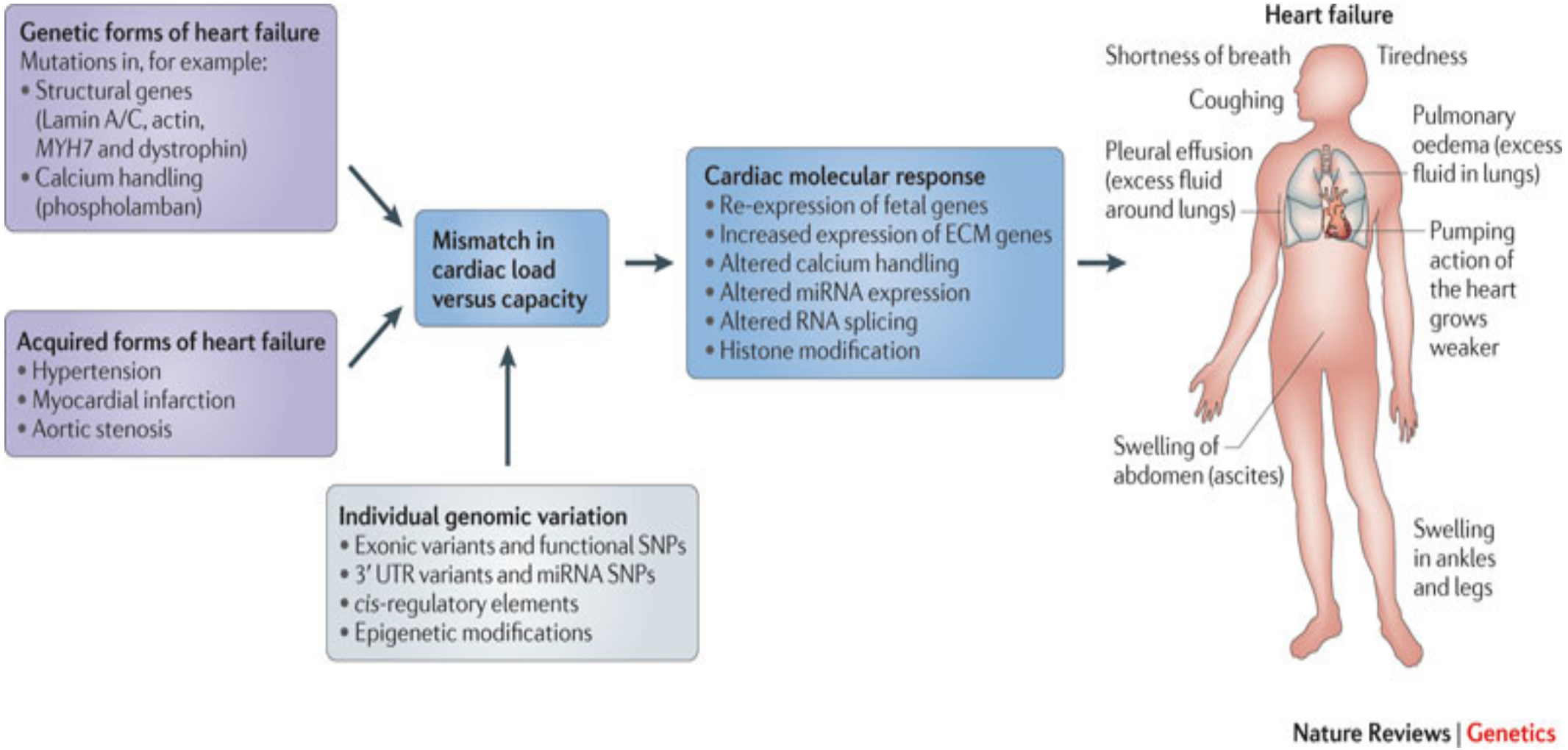
ESC GUIDELINES



Heart failure: advances through genomics

nature REVIEWS GENETICS

Esther E. Creemers, Arthur A. Wilde and Yigal M. Pinto



Nature Reviews Genetics 2011. **12**, 357-362