Нови молекули в лечението на хроничната сърдечна недостатъчност

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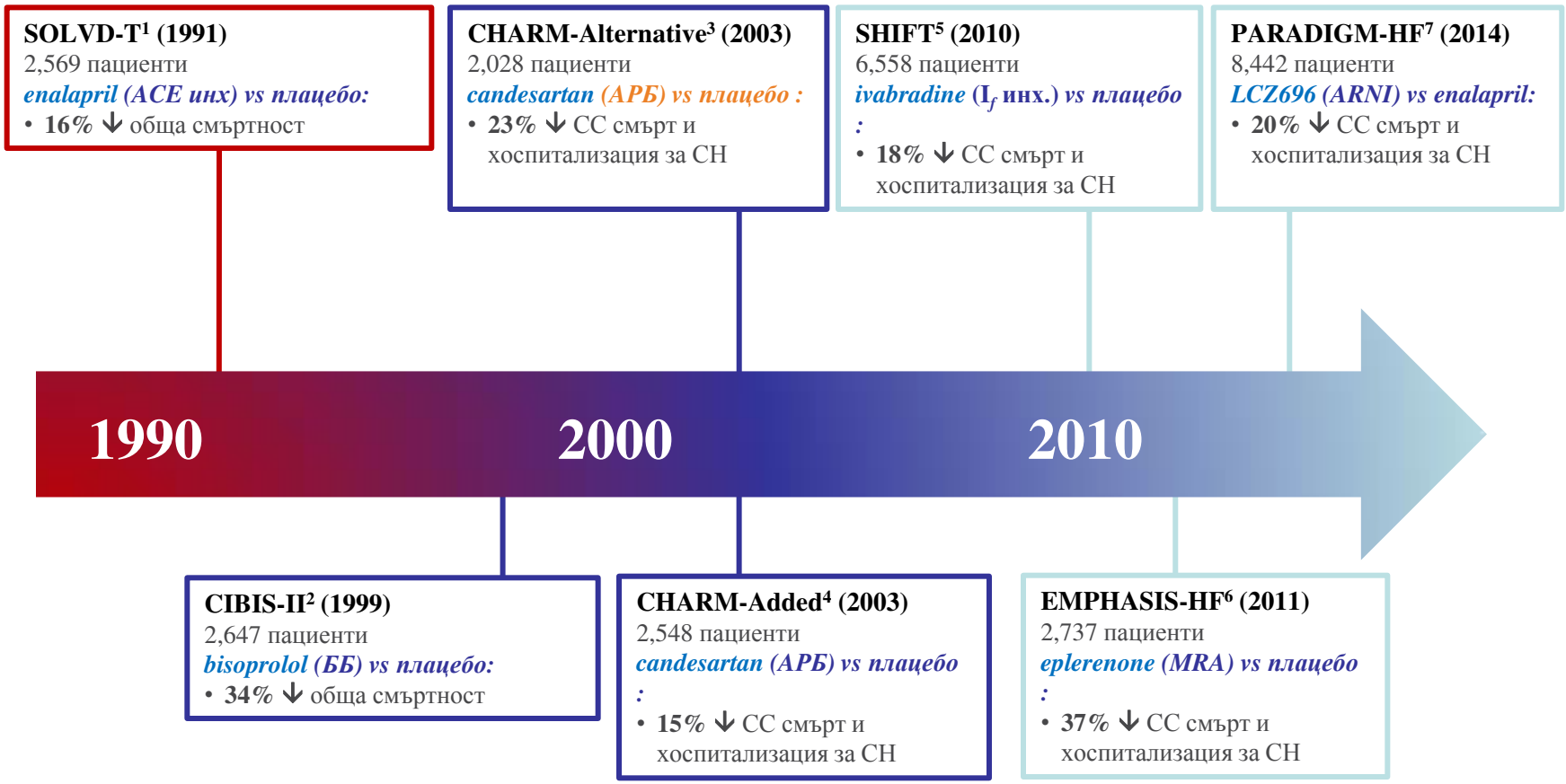
REMARKS ON ANGINA PECTORIS.

BY JOHN WARREN, M. D.

IN our inquiries into any particular subject of Medicine, our labours will generally be shortened and directed to their proper objects, by a knowledge of preceding discoveries.

Значими проучвания в областта на HFrEF



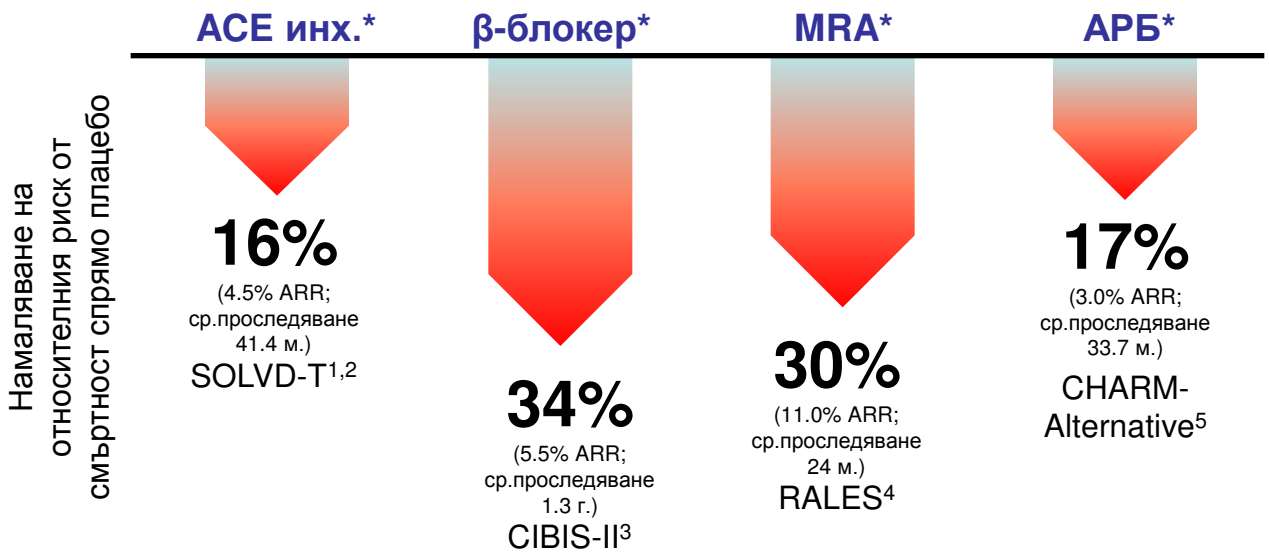
Percentages are relative risk reductions vs comparator

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor neprilysin inhibitor; BB=beta blocker; CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist. See notes for definitions of study names

1. SOLVD Investigators. N Engl J Med 1991;325:293–302
2. CIBIS-II Investigators. Lancet 1999;353:9–13; 3. Granger et al. Lancet 2003;362:772–6
4. McMurray et al. Lancet 2003;362:767–771; 5. Swedberg et al. Lancet 2010;376:875–85
6. Zannad et al. N Engl J Med 2011;364:11–21; 7. McMurray et al. N Engl J Med 2014;371:993–1004

Смъртността от СН с намалена ФИ остава висока въпреки въвеждането на нови терапии, които удължават преживяемостта

- Преживяемостта при хронична СН се подобрява с появата на нови лечения[1]



- Въпреки това смъртността остава висока:

  ~50% от пациентите със СН умират в рамките на 5 г. от диагнозата[6–8]

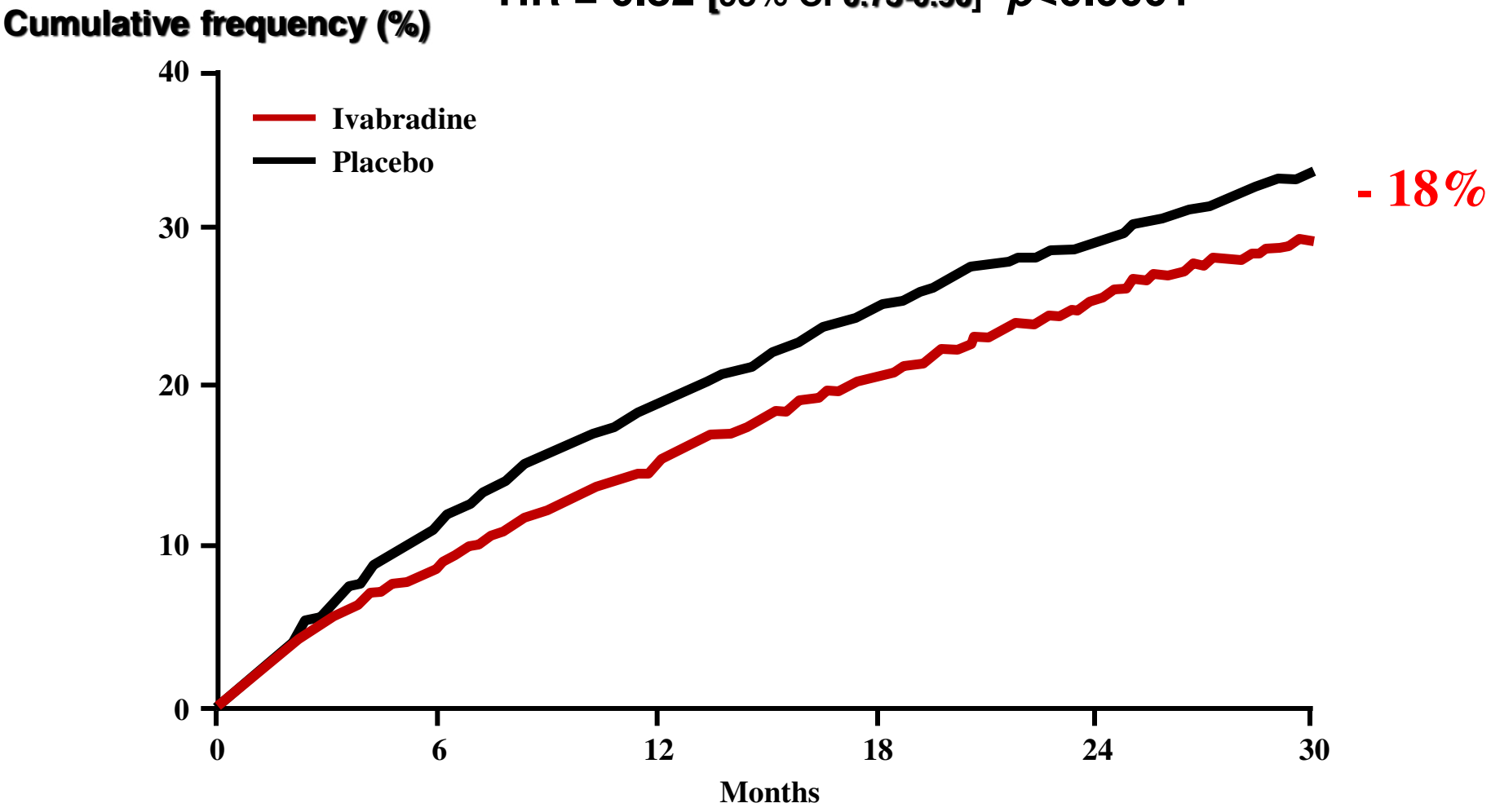
*на фона на стандартна терапия (с изкл.на CHARM-Alternative, където основната терапия с ACEI е изключена). Популацията варира м/у проучванията, поради което не могат да се правят директни сравнения за намаляването на относителния риск. SOLVD, CIBIS-II и RALES са включвали пациенти с ФИ≤35%, а CHARM-Alternative – с ФИ ≤40%

1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302; 3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17;–50; 5. Granger et al. Lancet 2003;362:772–6; 6. Go et al. Circulation 2014;129:e28-e292; 7. Yancy et al. Circulation 2013;128:e240–327; 8. Levy et al. N Engl J Med 2002;347:1397–402

CC смърт/хоспитализации за CH

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

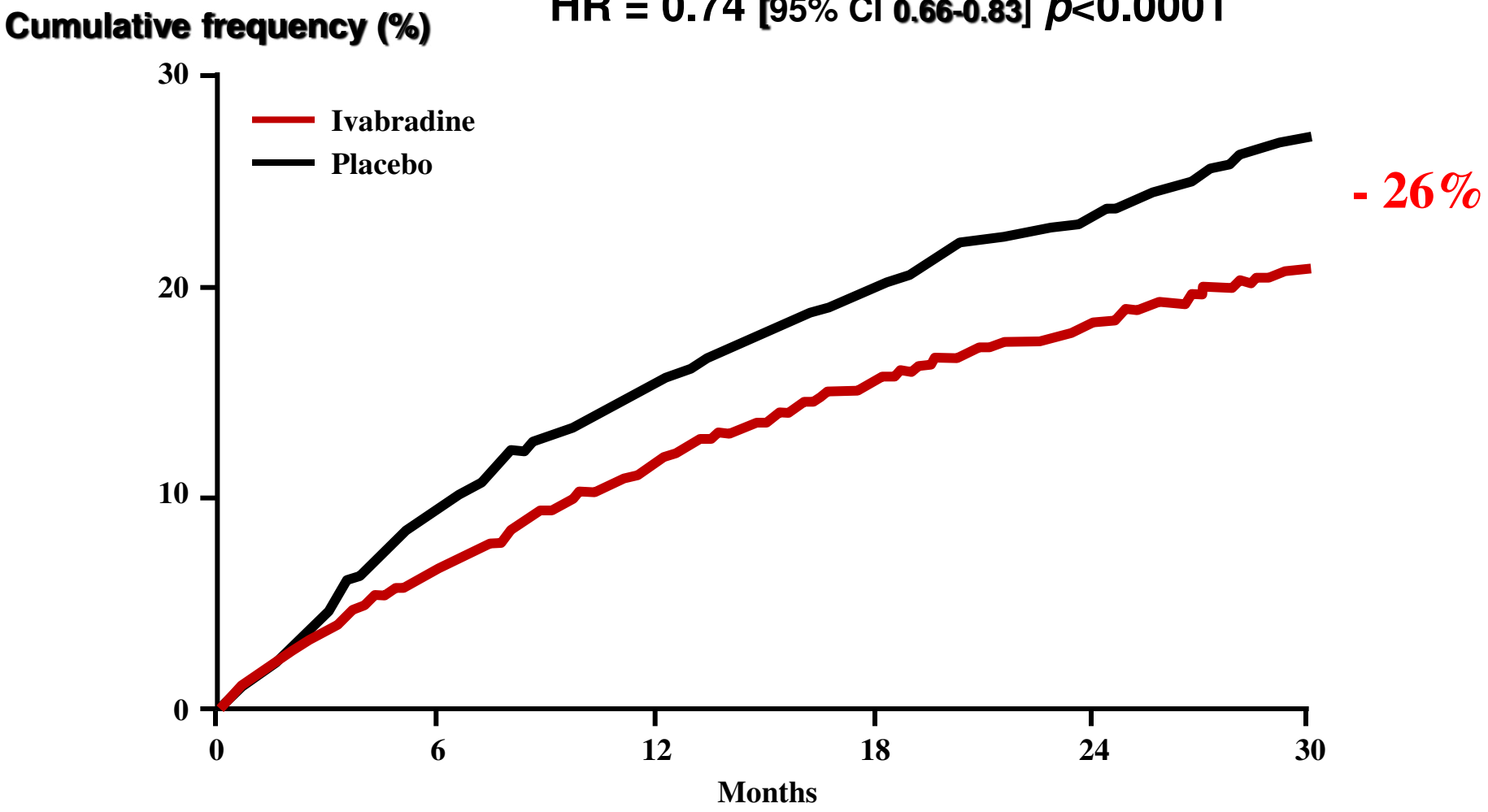
HR = 0.82 [95% CI 0.75-0.90] $p<0.0001$



хоспитализации за СН

Ivabradine n=514 (9.4%PY) Placebo n=672 (12.7%PY)

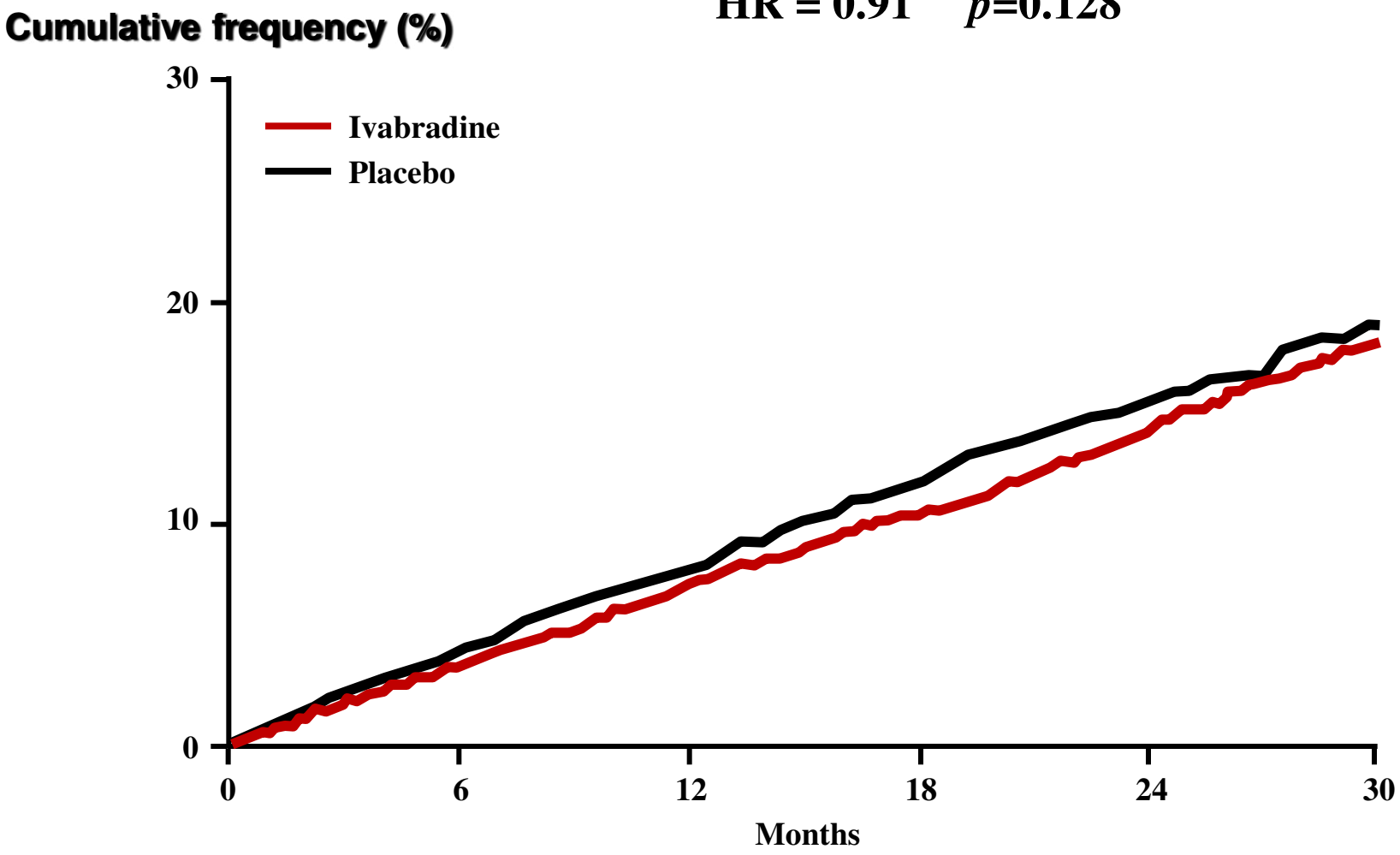
HR = 0.74 [95% CI 0.66-0.83] p<0.0001

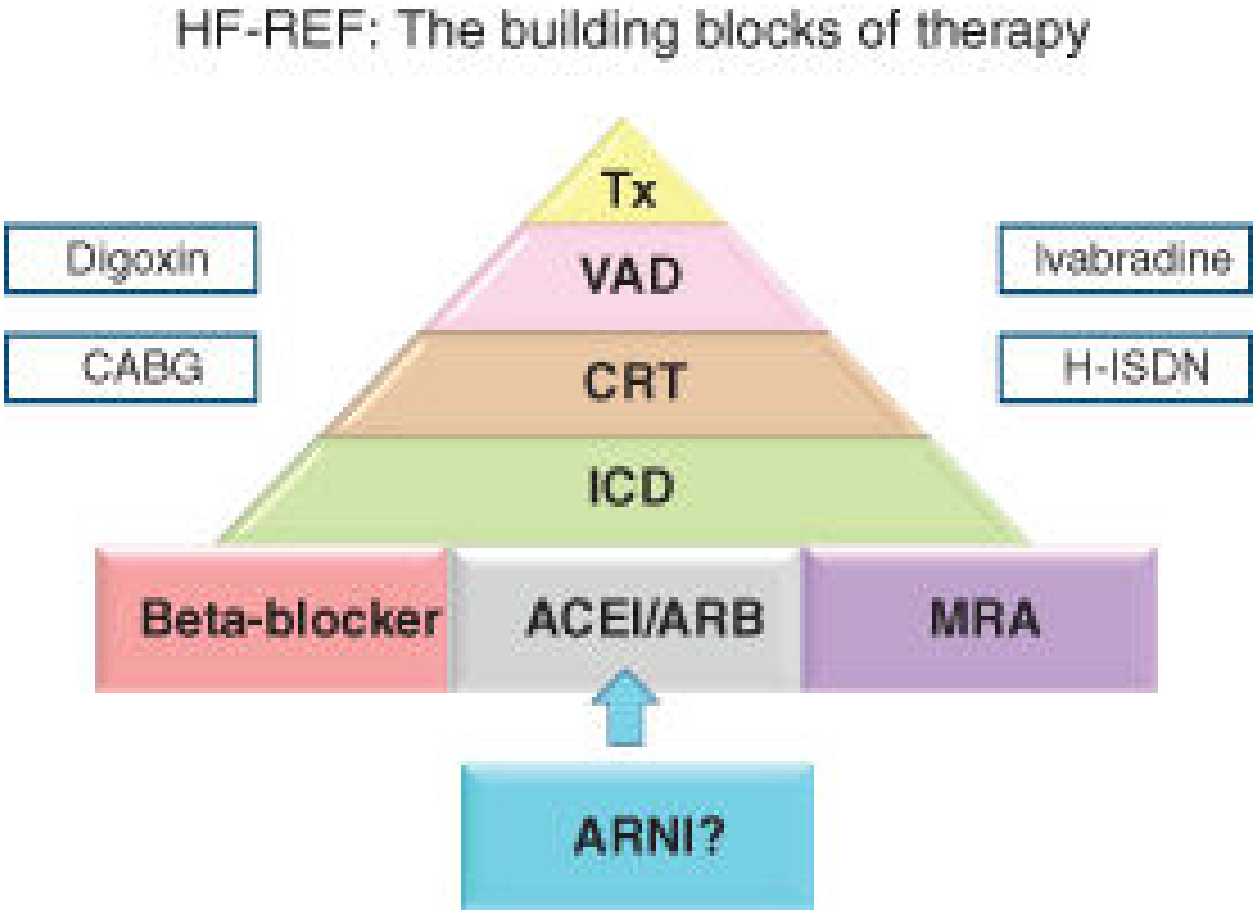


CC смърт

Ivabradine n=449 (7.5%PY) Placebo n=491 (8.3%PY)

HR = 0.91 p=0.128





European Journal of Heart Failure
Volume 17, Issue 3, pages 242-247, 9 MAR 2015 DOI: 10.1002/ejhf.250
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.250/full#ejhf250-fig-0004

Лечението на СН със запазена изтласна фракция (HF pEF) изисква нов терапевтичен подход

- Различният отговор към терапията, при лечение на HFpEF и HFrEF предполага, че това са две различни като етиология и прогресия заболявания, и изисква различен и специфичен терапевтичен подход[1]
  - Много терапии, доказали ползи при лечение на HFrEF се свързват с намаление на ЛК дилатация; тези терапии са недостатъчно ефективни при лечение на HFpEF, където ЛК дилатация не е водещо патофизиологично нарушение[2]

HFrEF[3]

- Множество, рандомизирани и контролирани, двойно-слепи клинични проучвания
- Избор на терапия, базиран на дългосрочни данни за СС ползи
- Общ консенсус за лечение сред кардиологичната общност
- RCTs са потвърдени с данни от реалната клинична практика
- Медицина-базирана на доказателствата

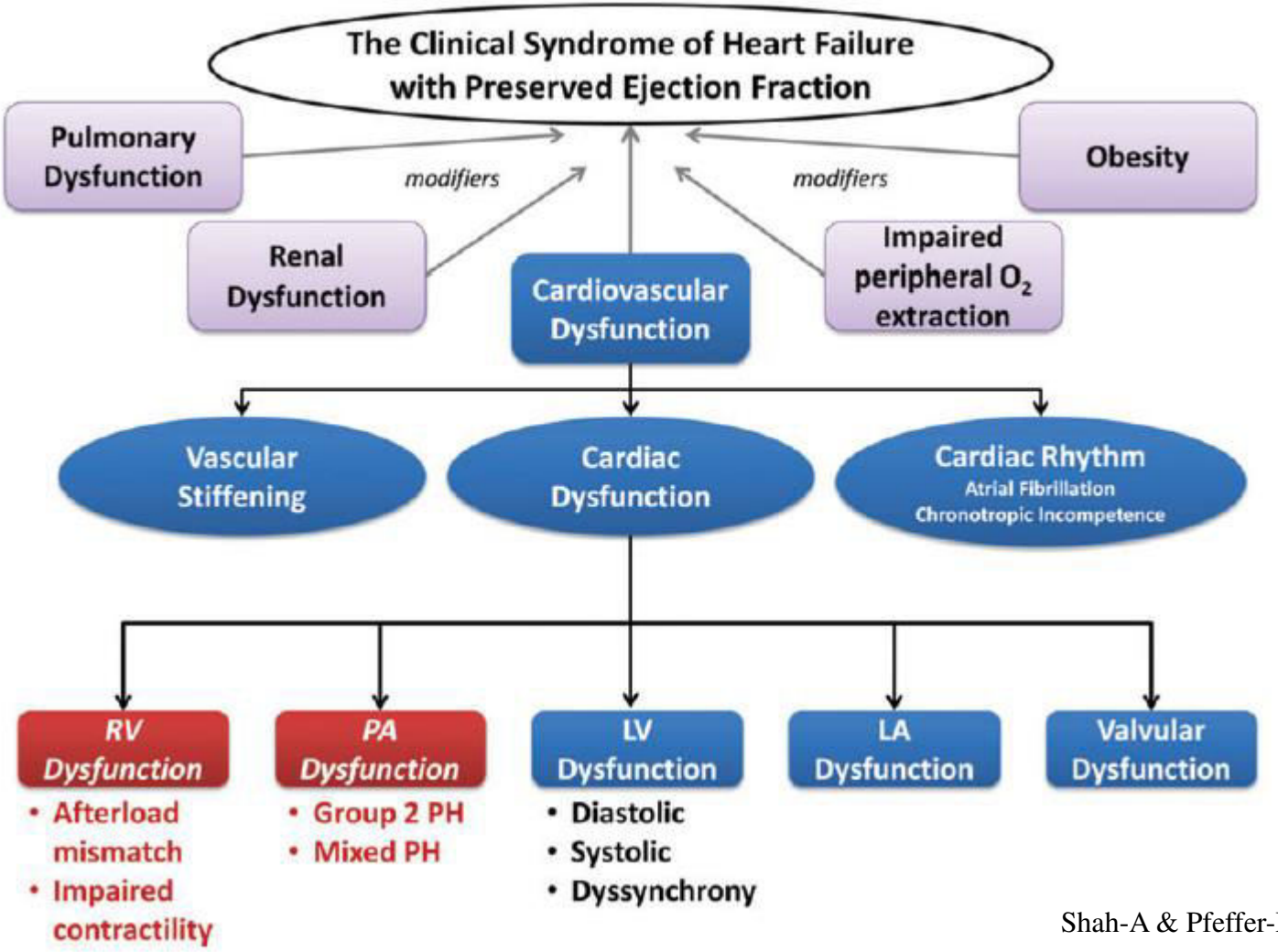
HFpEF[3,4]

- Предимно механистични проучвания и малки клинични изпитвания
- Терапевтични стратегии, основани на лечение на симптоми и съпътстващи заболявания
- Ограничен консенсус за лечение сред кардиологичната общност
- Няма консистентност на данните от рандомизирани контролирани проучвания и данни от обсервационните проучвания

HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction, LV=left ventricle

1. Paulus et al. Eur Heart J 2007;28:2539–50
2. Iwano & Little. J Cardiol. 2013;62:1-3
3. McMurray et al. Eur Heart J 2012;33:1787–847
4. Blanche et al. Swiss Med Wkly 2010;140:66–72

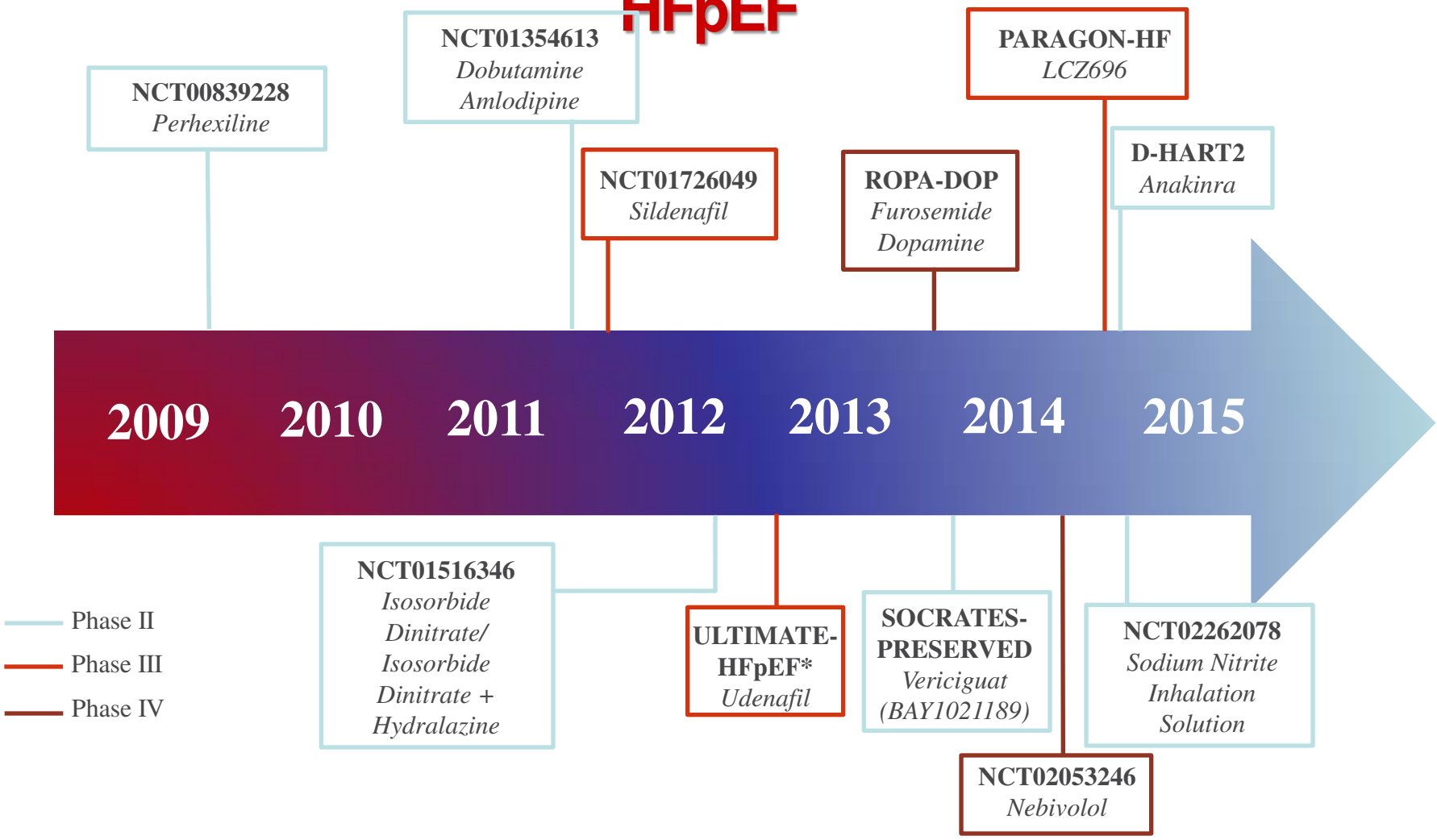
Сърдечно-съдови механизми, участващи в развитието на СН със запазена фракция на изтласкване (HFpEF)



Shah-A & Pfeffer-M, JACC 2014

LA, left atrial; LV, left ventricular; PH, pulmonary hypertension; Mixed, PH resulting from elevated pulmonary artery wedge pressure and elevated pulmonary vascular resistance; RA, right arial; RV, right ventricular

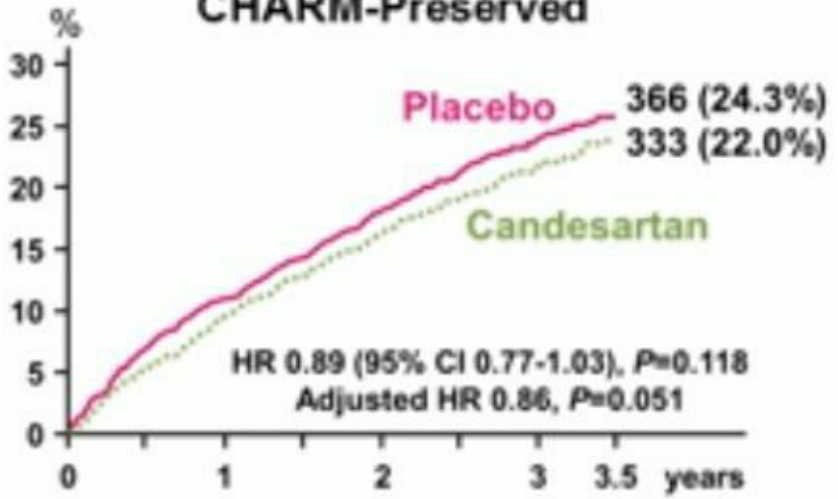
Има няколко текущи проучвания за приложението на нови терапии за лечение на HFpEF



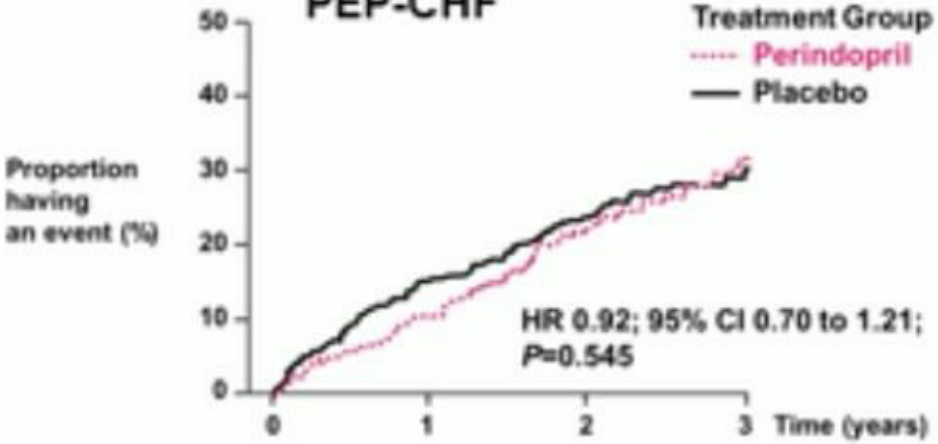
Recruiting studies organized according to start date of trial. *The ULTIMATE-HFpEF trial has since terminated.
D-HART2=Diastolic Heart failure Anakinra Response Trial 2; HFpEF=heart failure with preserved ejection fraction; PARAGON-HF=Prospective comparison of ARNI with Arb Global Outcomes in heart failure with preserved ejectioN fraction; ROPA-DOP= Randomized Evaluation of HFpEF Patients With Acute Heart Failure and Dopamine; SOCRATES-PRESERVED= SOluble guanylate Cyclase stimulatoR in heArT failurE Study; ULTIMATE-HFpEF= Udenafil Therapy to Improve Symptomatology, Exercise Tolerance and Hemodynamics in Patients With HFpEF

Information obtained from: http://clinicaltrials.gov/ct2/results?term=HFpEF&recr=Open&cond=%22Heart+Failure%22&pg=1 Last accessed Nov 27 2014

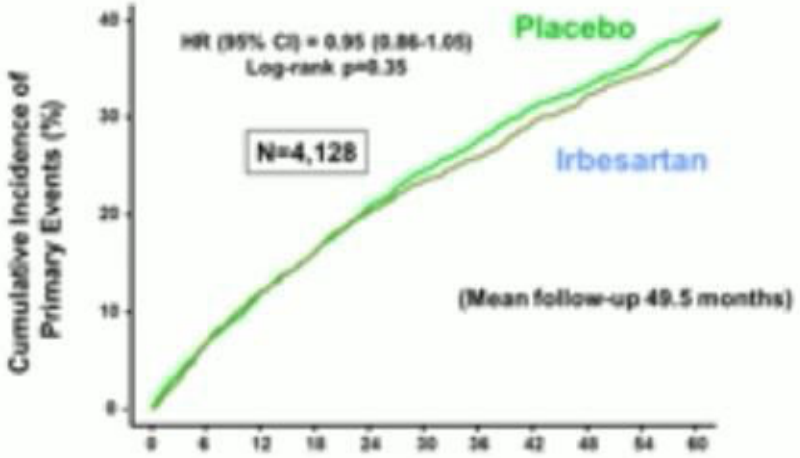
CHARM-Preserved



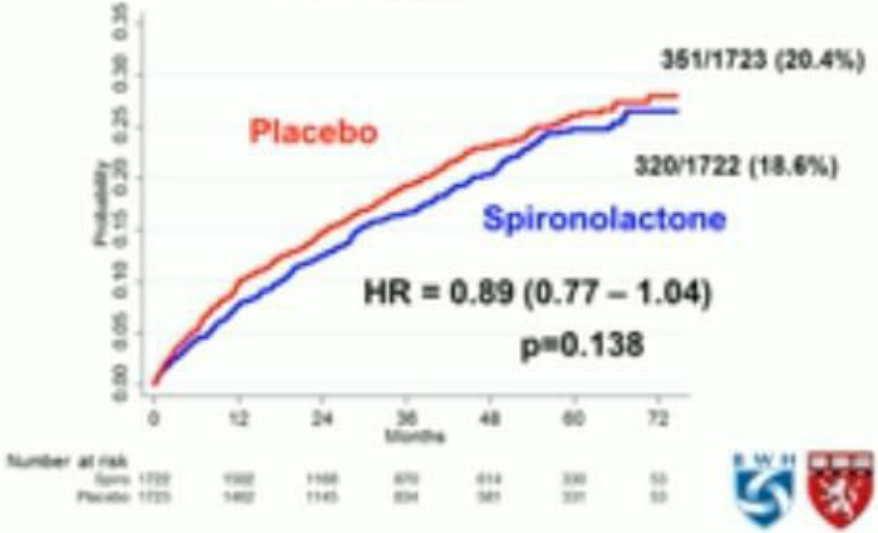
PEP-CHF



I-PRESERVE



TOPCAT



The NEW ENGLAND JOURNAL OF MEDICINE

ESTABLISHED ... VOL. 370 NO. 15

Spironolactone ... jection Fraction

Bertram Pitt, M.D., Marc A ... M.D., Inder S. Anand, M.D.
Brian Claggett, Ph. ... H., Rafael Diaz, M.D.,
Jerome L. Fleg, M.D., Ivan ... hristopher T. Kenwood, M.S.
Eldrin F. Lewis, M.D., M.P ... Shaburishvili, M.D., Ph.D.,
Sanjiv J. Shah, M ... Song Yang, Ph.D.,

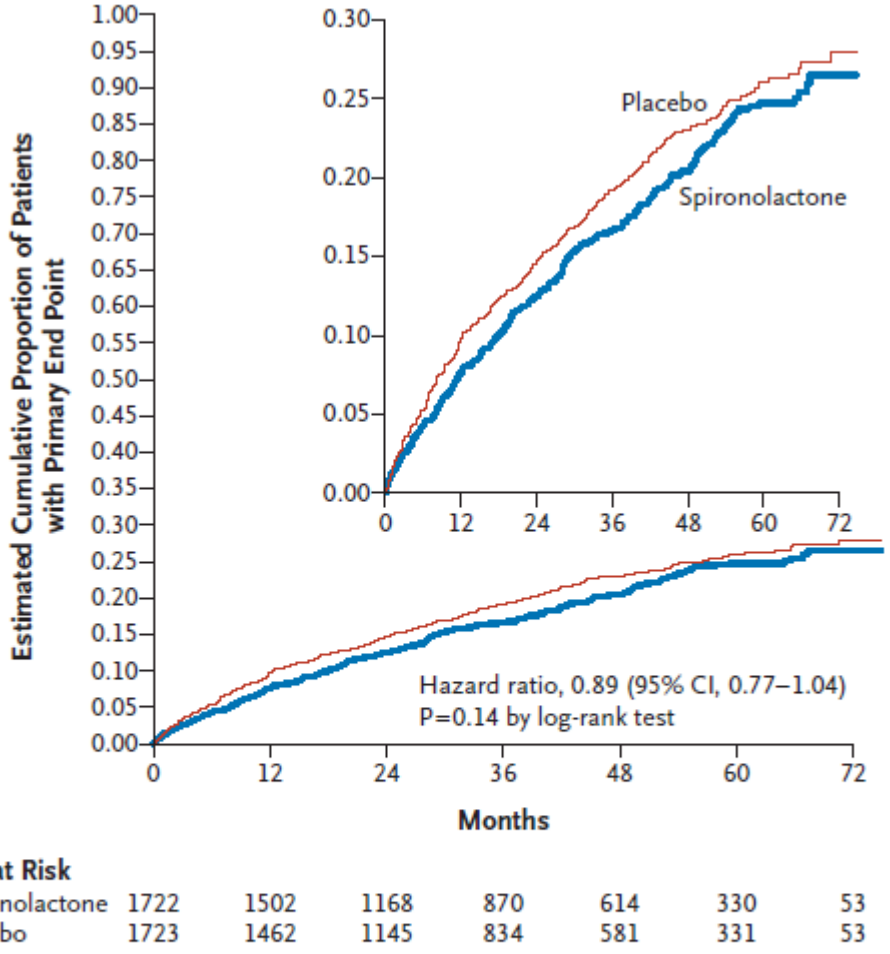
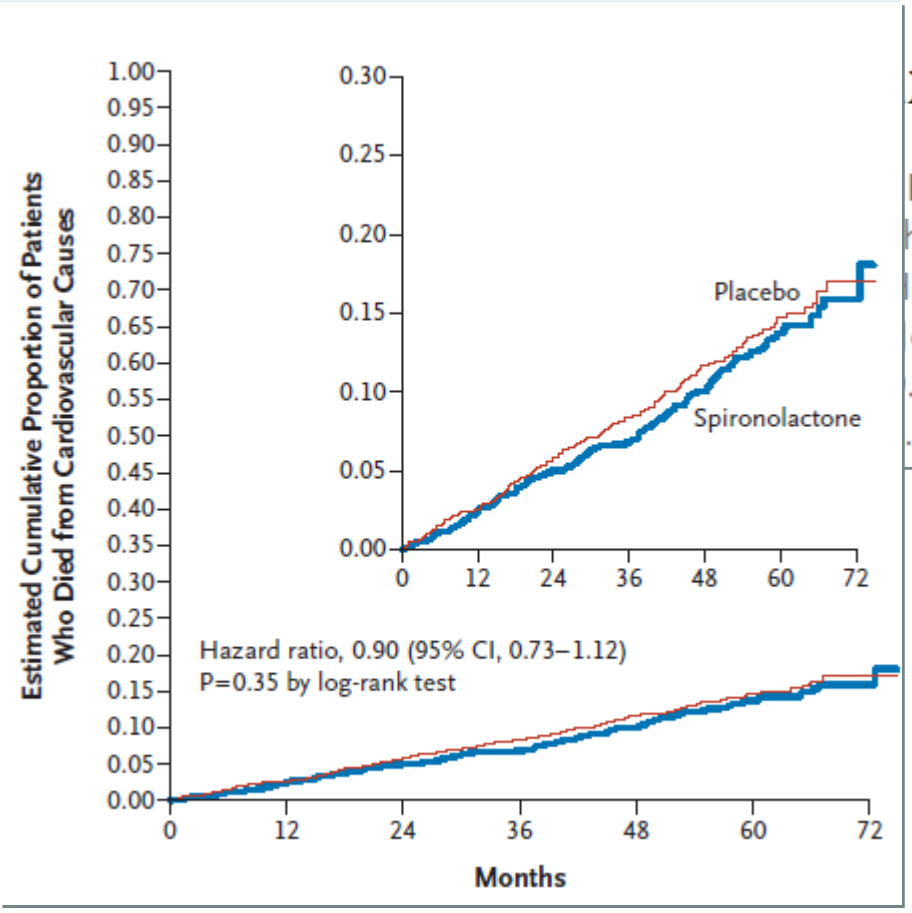


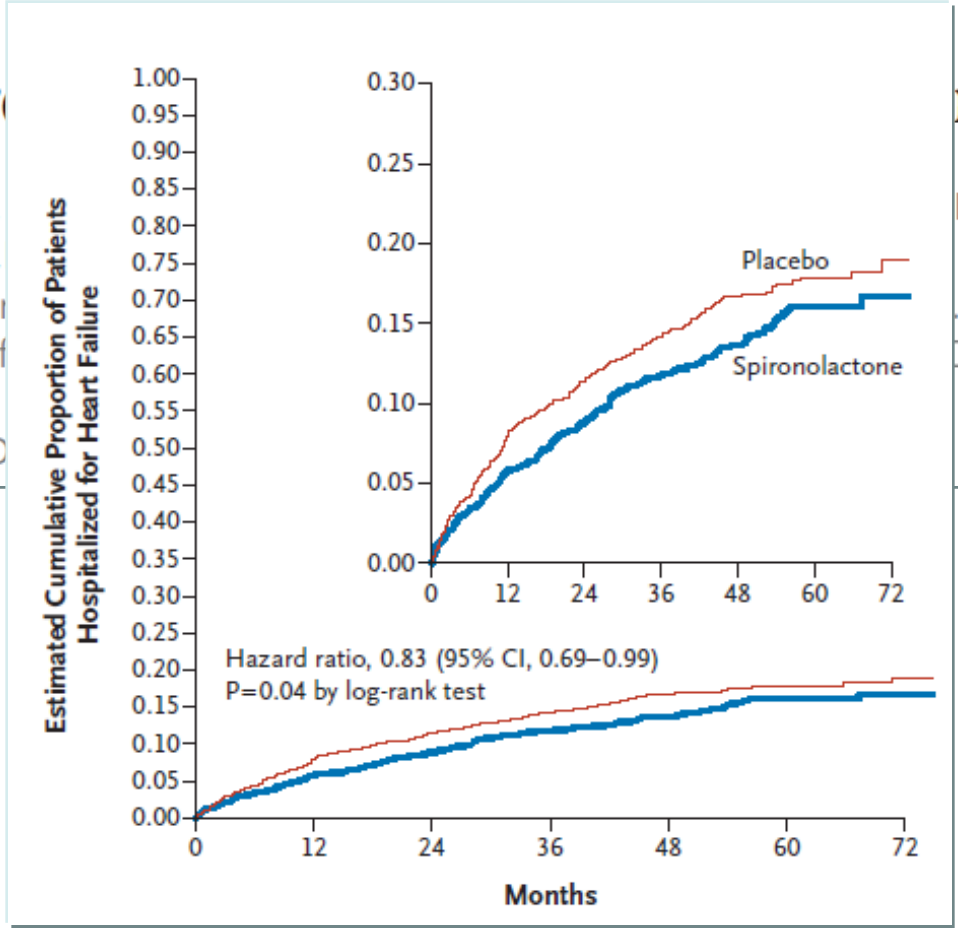
Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

The NEW ENGLAND JOURNAL of MEDICINE

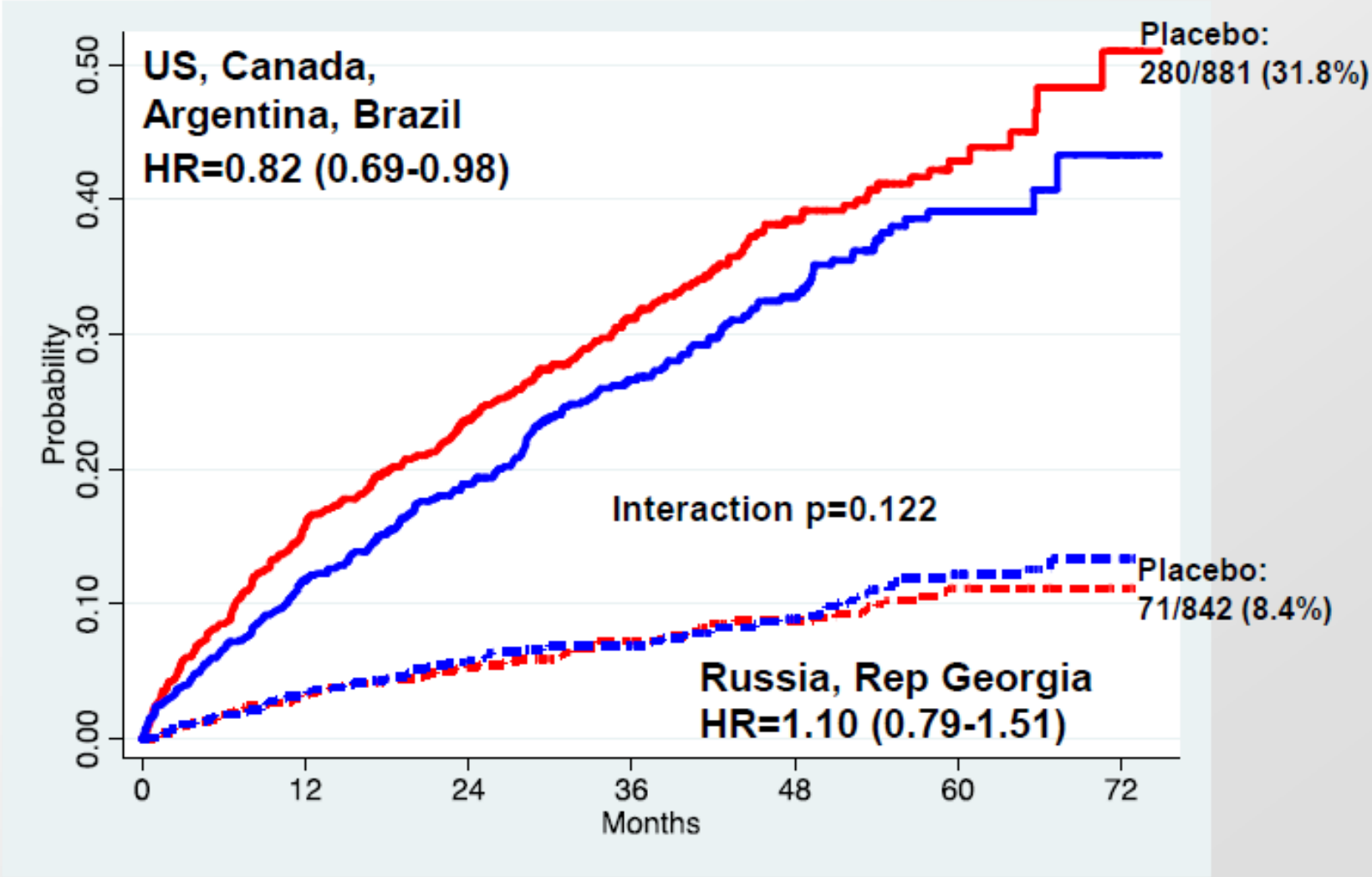
ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

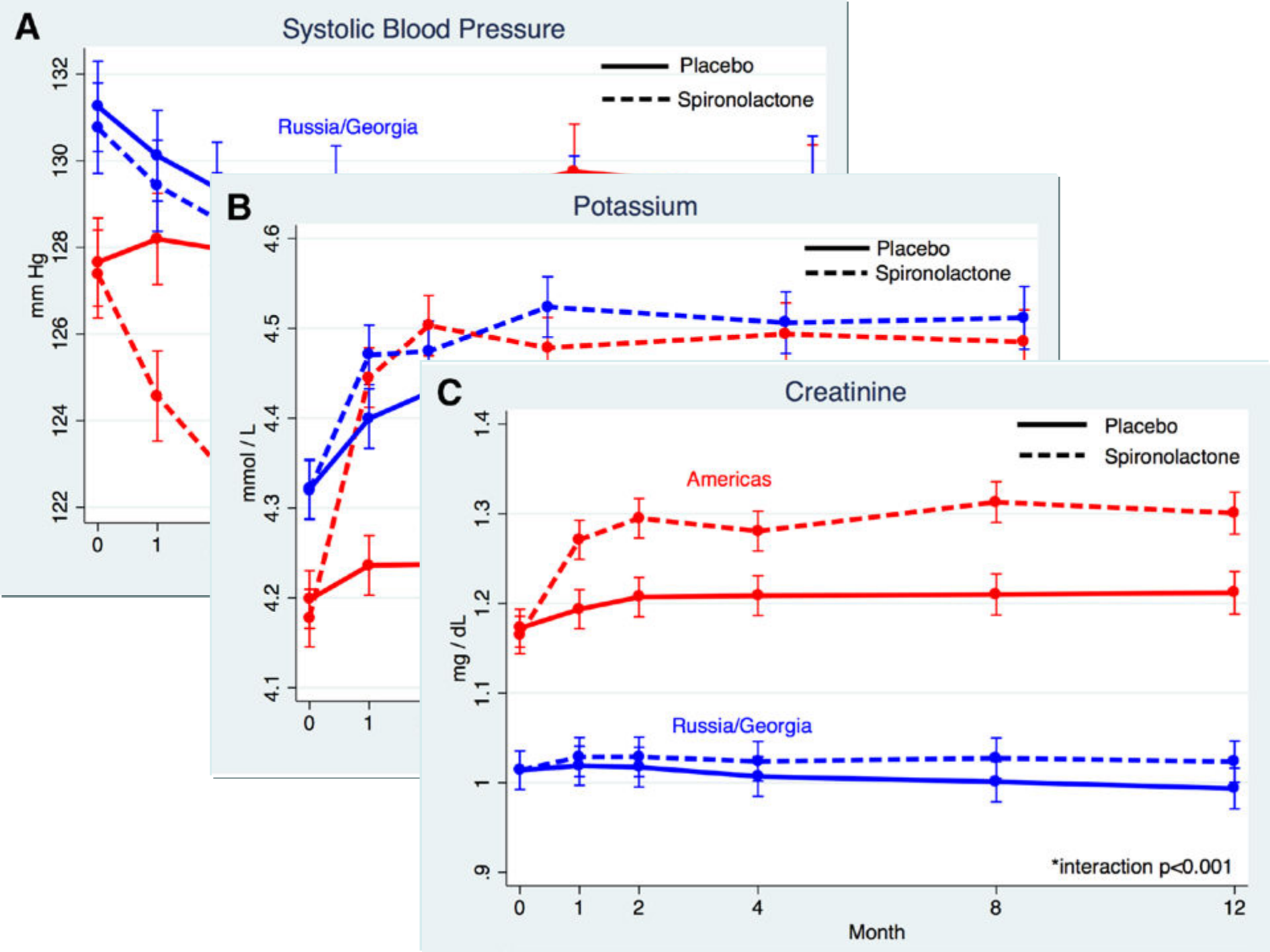




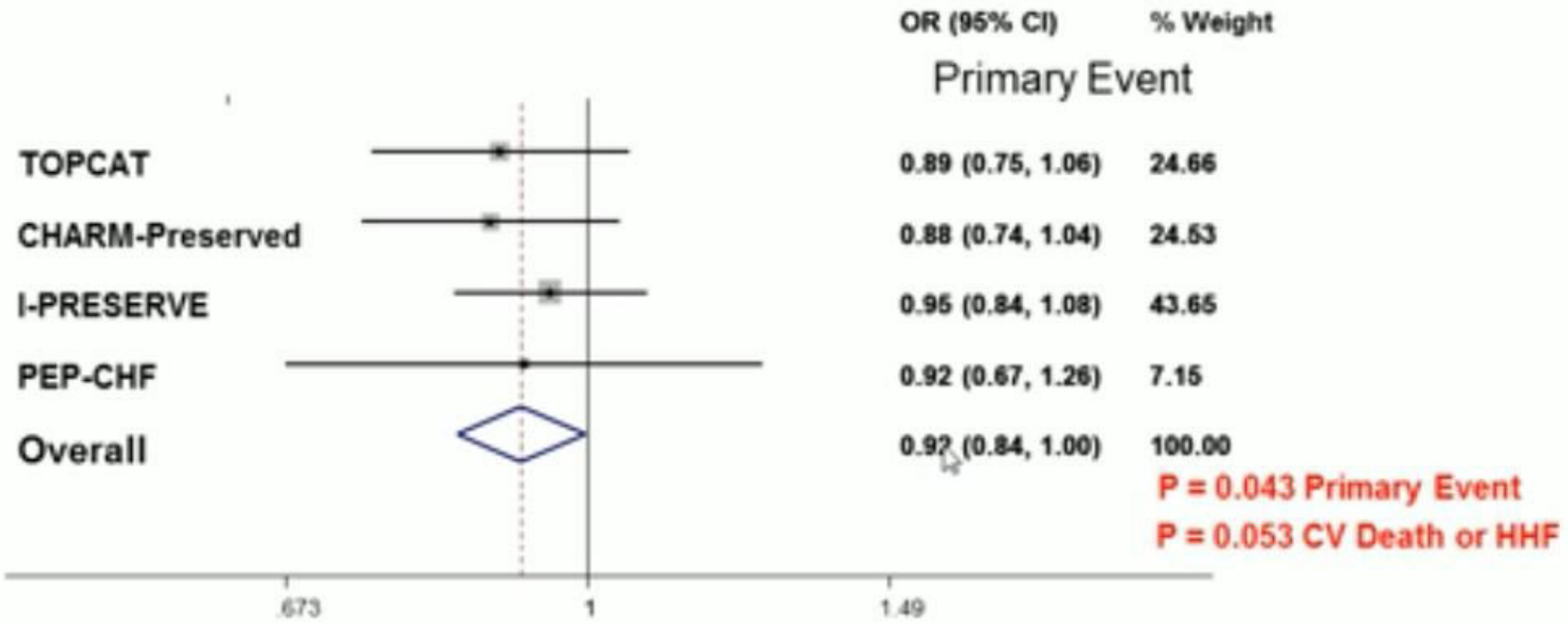
Exploratory (post-hoc): Placebo vs. Spiro by region

TOPCAT
Funded by the NHLBI



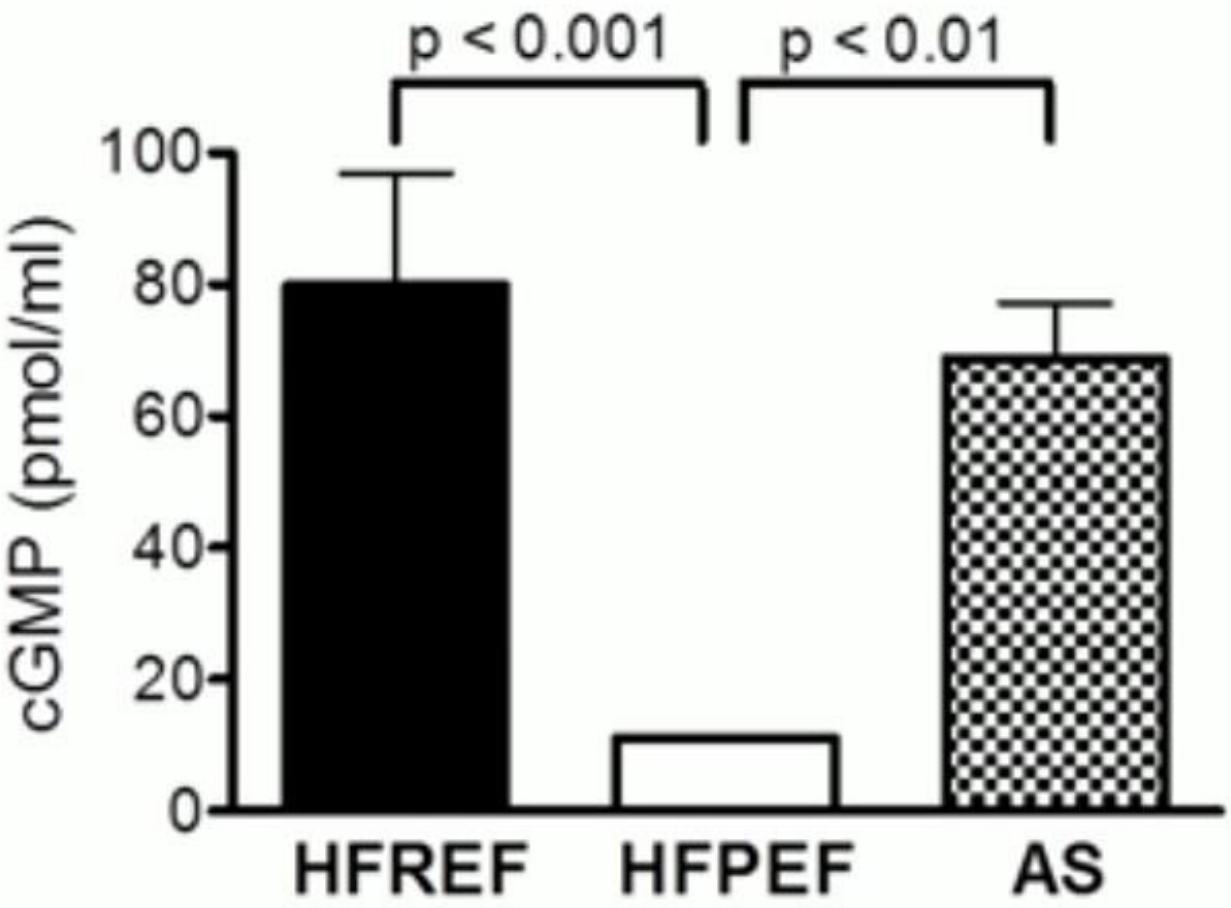

A
Systolic Blood Pressure
Placebo
Spironolactone
Russia/Georgia
mm Hg
132
130
128
126
124
122
0
1
B
Potassium
Placebo
Spironolactone
mmol / L
4.6
4.5
4.4
4.3
4.2
4.1
0
1
C
Creatinine
Placebo
Spironolactone
Americas
Russia/Georgia
mg / dL
1.4
1.3
1.2
1.1
1
.9
*interaction p<0.001
0
1
2
4
8
12
Month

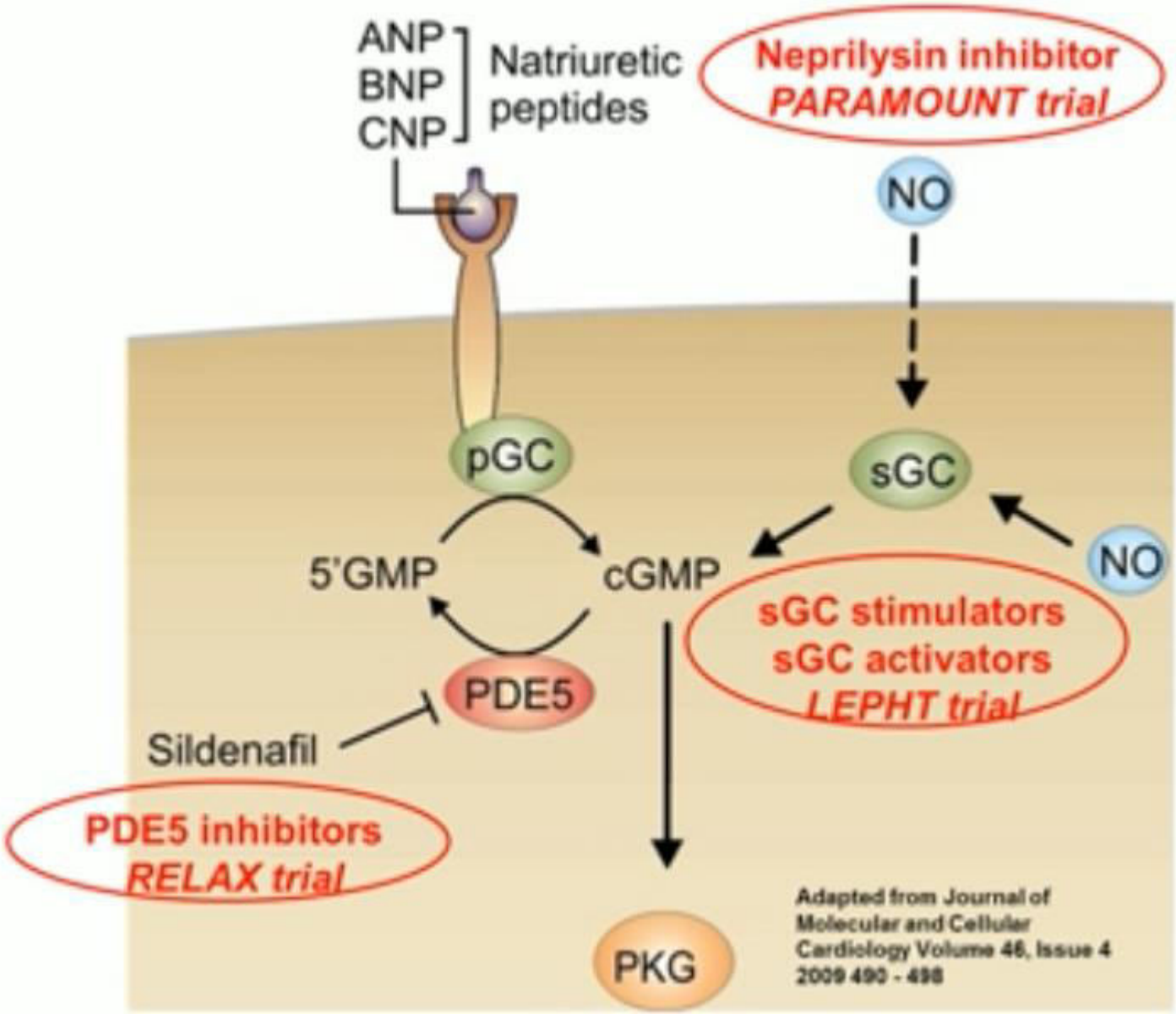
RAAS при HFpEF



Therapy	Trial(s)	Phase II	Phase III
Spironolactone	ALDO-DHF	Completed – ½ primary endpoints positive	
Spironolactone	TOPCAT		Completed (n = 3400) Primary Endpoint Negative (with caveats)
Sildenafil	RELAX	Completed - Neutral	
Vericiguat	SOCRATES-Preserved	Ongoing	
LCZ696	PARAMOUNT	Completed – Positive	
LCZ696	PARAGON-HF		Ongoing (n=4300)
Atriotomy Device	CEMark Trial	Early	
Inorganic Nitrates	NEAT Trial	Finished Enrollment	

Миокарден cGMP при HFpEF

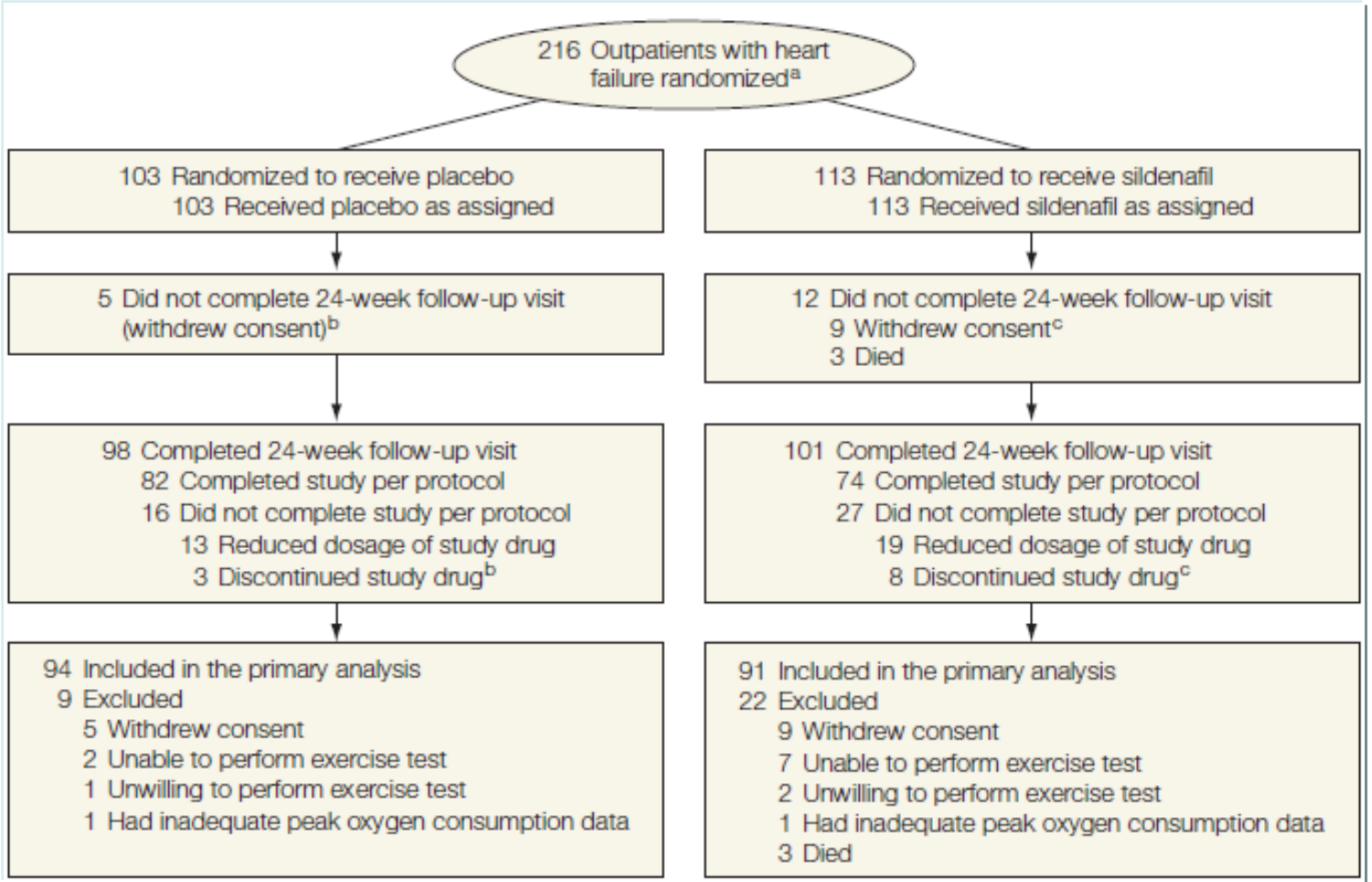



ANP
BNP
CNP
Natriuretic peptides
Neprilysin inhibitor
PARAMOUNT trial
NO
pGC
sGC
5'GMP
cGMP
NO
sGC stimulators
sGC activators
LEPHT trial
PDE5
Sildenafil
PDE5 inhibitors
RELAX trial
PKG
Adapted from Journal of Molecular and Cellular Cardiology Volume 46, Issue 4 2009 490 - 498

ONLINE FIRST

Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial



Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial

Table 3. Primary, Secondary, and Safety End Points

	Placebo		Sildenafil		
	No. of Patients	Variable	No. of Patients	Variable	*P* Value
Primary end point					
Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min	94	−0.20 (−0.70 to 1.00)	91	−0.2 (−1.70 to 1.11)	.90
Secondary end points					
Clinical rank score, mean[a]	94	95.8	95	94.2	.85
Change in 6-minute walk distance at 24 wk, median (IQR), m	95	15.0 (−26.0 to 45.0)	90	5.0 (−37.0 to 55.0)	.92
Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min	96	0.03 (−1.10 to 0.67)	97	0.01 (−1.35 to 1.25)	.98
Change in 6-minute walk distance at 12 wk, median (IQR), m	96	18.0 (−14.5 to 48.0)	99	10.0 (−25.0 to 36.0)	.13
Components of clinical rank score at 24 wk					
Death, No. (%)[b]	103	0	113	3 (3)	.25
Hospitalization for cardiovascular or renal cause, No. (%)	103	13 (13)	113	15 (13)	.89
Change in MLHFQ, median (IQR)	91	−8 (−21 to 5)	91	−8 (−19 to 0)	.44
Safety end points, No. (%)					
Adverse events	103	78 (76)	113	90 (80)	.49
Serious adverse events	103	16 (16)	113	25 (22)	.22

Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial

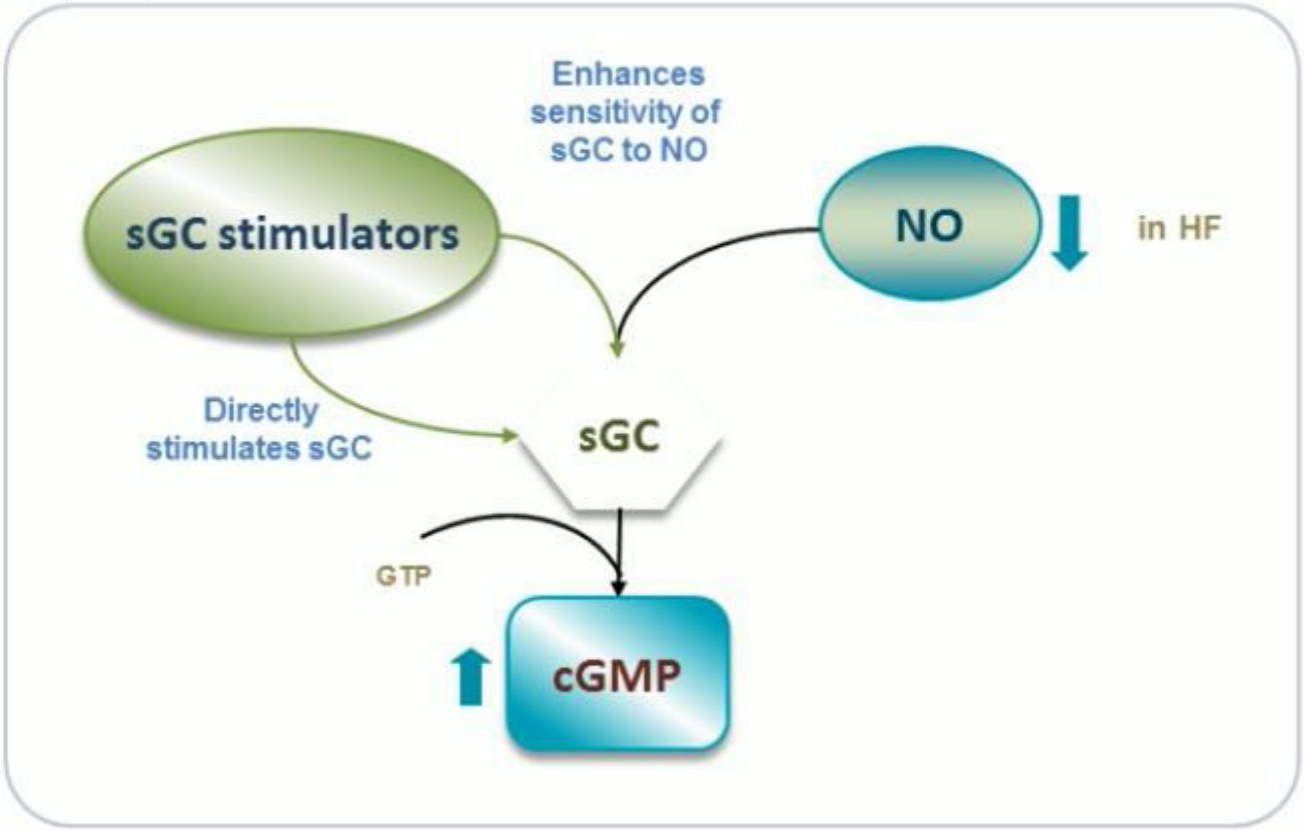
Table 4. Additional Prespecified End Points

	Placebo		Sildenafil		
	No. of Patients	Median (IQR)	No. of Patients	Median (IQR)	*P* Value
Change in left ventricular structure by CMRI at 24 wk					
Left ventricular mass by CMRI, g	47	0.6 (−5.7 to 7.9)	49	−1.5 (−5.9 to 7.1)	.93
Left ventricular end-diastolic volume by CMRI, mL	47	−4.3 (−15.5 to 8.1)	49	3.7 (−4.9 to 14.5)	.13
Change in diastolic function parameters at 24 wk					
Medial e', m/s	83	0.00 (−0.01 to 0.01)	77	0.00 (−0.01 to 0.01)	.88
E/e'	80	−1.6 (−4.7 to 2.2)	75	0.2 (−2.4 to 3.1)	.16
PA systolic pressure, mm Hg	58	−2 (−8 to 8)	45	2 (−5 to 7)	.94
Change in vascular function by CMRI at 24 wk					
Arterial elastance, mm Hg/mL	45	0.03 (−0.14 to 0.23)	47	−0.08 (−0.41 to 0.12)	.02
Systemic vascular resistance, wood units	45	0.13 (−0.15 to 0.43)	47	−0.04 (−0.38 to 0.21)	.09
Aortic distensibility, 10^{-3} mm Hg^{-1}	31	0.13 (−0.17 to 0.42)	29	0.18 (−0.12 to 0.67)	.38
Change in core laboratory biomarkers at 24 wk					
Creatinine, mg/dL	94	0.01 (−0.10 to 0.09)	94	0.05 (−0.04 to 0.15)	.047
Cystatin C, mg/L	95	0.01 (−0.08 to 0.11)	95	0.05 (−0.04 to 0.16)	.01
NT-proBNP, pg/mL	94	−23 (−198 to 139)	95	15 (−90 to 372)	.03
Endothelin-1, pg/mL	95	−0.01 (−0.48 to 0.47)	95	0.38 (−0.10 to 0.97)	.046
Aldosterone, ng/dL	95	0 (−7.0 to 4.8)	95	−1.1 (−7.7 to 3.0)	.85
NT-procollagen III, μg/L	93	−0.03 (−1.49 to 1.54)	95	0.07 (−1.17 to 1.42)	.77
Uric acid, mg/dL	94	−0.1 (−0.7 to 0.7)	94	0.3 (−0.4 to 1.4)	.02

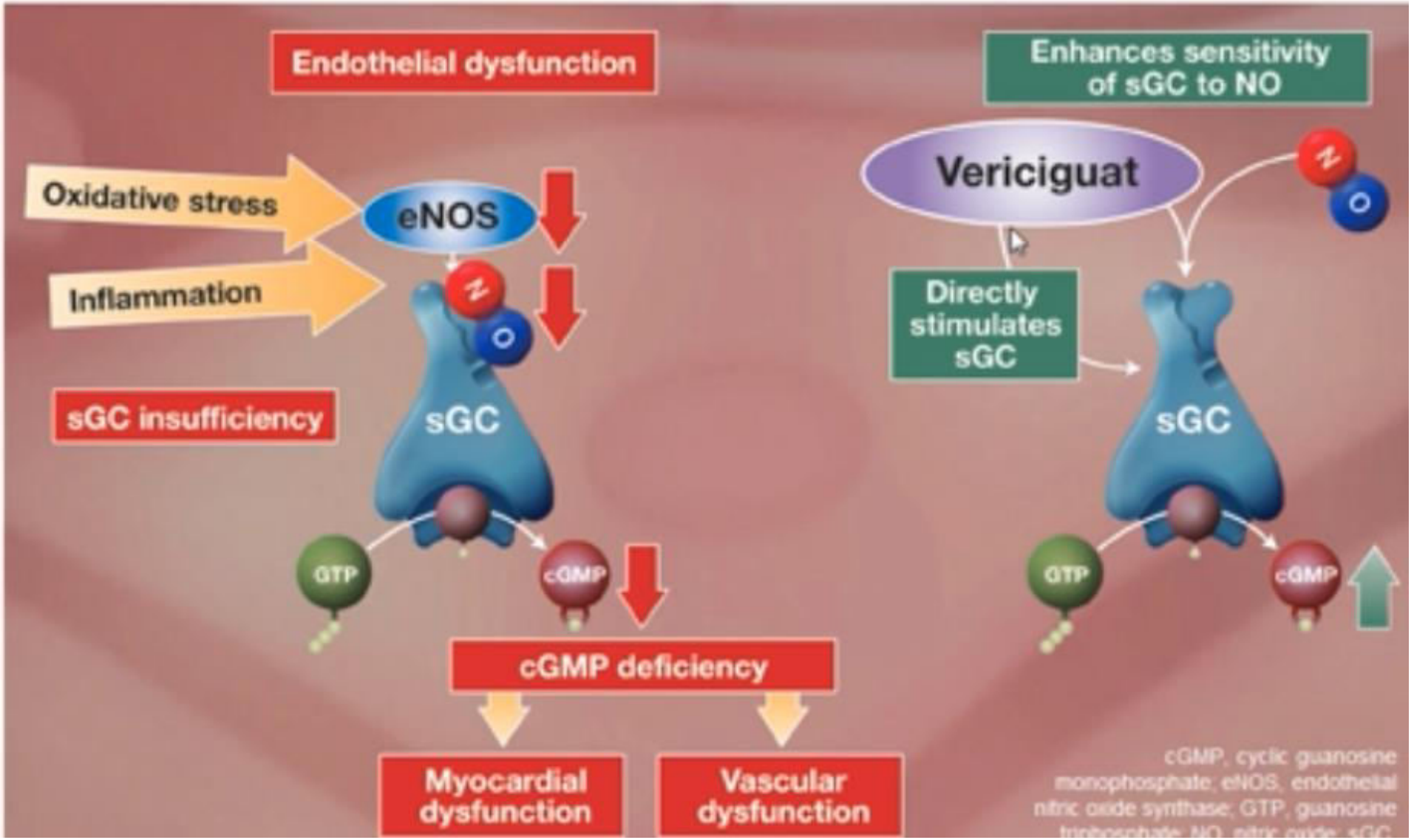
Стимулатори на разтворимата GC за перорална употреба

Riociguat:

- Targets soluble guanylate cyclase (sGC)
- Increases cGMP production independently of NO
- Activity unaffected by depleted NO levels*



*) Grimminger et al. Eur Respir J 2009;33:785–792


Endothelial dysfunction
Oxidative stress
Inflammation
eNOS
N
O
sGC insufficiency
sGC
GTP
cGMP
cGMP deficiency
Myocardial dysfunction
Vascular dysfunction
Enhances sensitivity of sGC to NO
Vericiguat
Directly stimulates sGC
sGC
GTP
cGMP
cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine

Soluble Guanylate Cyclase stimulator Heart Failure Studies: The SOCRATES Program

	SOCRATES-REDUCED	SOCRATES-PRESERVED
Design	2 randomized parallel-group, placebo-controlled, double-blind, dose finding phase IIb studies of 4 dose regimens of the oral sGC stimulator vericiguat over 12 weeks	
Inclusion Criteria	Worsening chronic heart failure requiring hospitalization (or IV diuretic for HF) with initiation after clinical stabilization	
	LVEF <45%	LVEF ≥45% Left atrial (LA) enlargement
Primary Outcome	NT-proBNP at 12 weeks	NT-proBNP / LA vol. at 12 weeks (split α: each $p<0.025$)
Enrollment	410 patients in 5 arms	470 patients in 5 arms
Study status	FPFV Nov 29, 2013	FPFV Nov 6, 2013
CT.gov ID	NCT01951625	NCT01951638

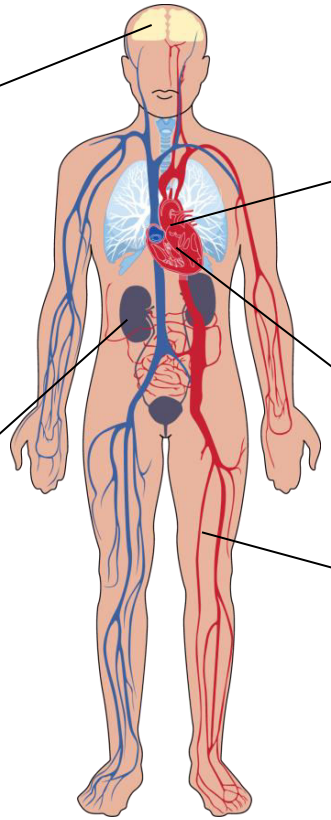
Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction (NEAT)Trial

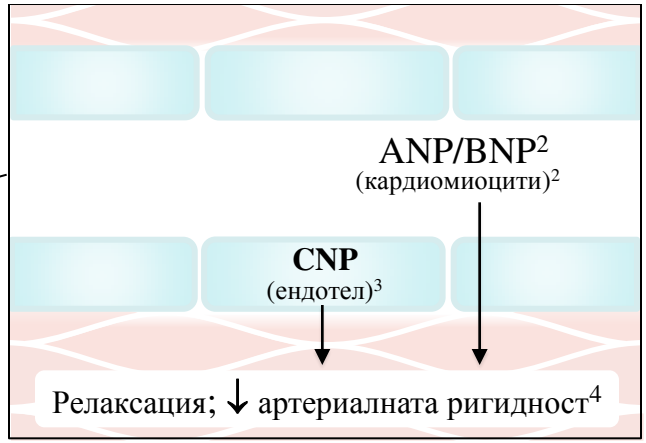
- **Patients: HFpEF Patients, > 50 years, LVEF >= 50% Plus one of following:**
  - Previous hospitalization for heart failure (HF)
  - elevated filling pressures at rest (LVEDP≥15 or PCWP≥20) or with exercise (PCWP≥25) or
  - Elevated NT-proBNP (> 400 pg/ml) or BNP (> 200 pg/ml) or
  - Echo evidence of diastolic dysfunction
  - ^ LV Mass, RWT, PWT
- **Therapy: Isosorbide Mononitrate vs. Placebo**
- **Primary Endpoint: Improvement in Physical Activity by Accelerometry at 6 and 12 weeks**
- **Secondary Endpoints: Change in NT-proBNP, 6 minute walk, Improvement in daily activity, QOL etc.**

Потенциални полезни ефекти на NP при CH

Ефекти на ANP и BNP, освободени в сърцето и бъбреците и CNP в съдовете[1]

↓ Симпатикусов тонус[2]
↓ Вазопресин[2]
↓ Понижен прием на сол и вода[2]





↓ Хипертрофия[2,5–7]
↓ Фибробластна пролиферация[4,8,9]

↑ Na^+/H_2O диуреза[2]
↓ Алдостерон[2]
↓ Ренин[2]

Вазодилатация[2,3,4]
↓ Периферно съдово съпротивление[4]
↓ Пулмо-артериално налягане[4]
↓ Пулмо-капилярно налягане[4]
↓ Налягане в дясното предсърдие[4]

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; HF=heart failure

1. Forssmann et al. Arch Histol Cytol 1989;52 Suppl:293–315; 2. Levin et al. N Engl J Med 1998;339;321–8; 3. Lumsden et al. Curr Pharm Des 2010;16:4080–8; 4. Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9; 5. Gardner et al. Hypertension 2007;49:419–26; 6. Tokudome et al. Circulation 2008;117;2329–39; 7. Horio et al. Endocrinology 2003;144:2279–84; 8. D'Souza et al. Pharmacol Ther 2004 ;101:113–29; 9. Cao & Gardner. Hypertension 1995;25:227–34;

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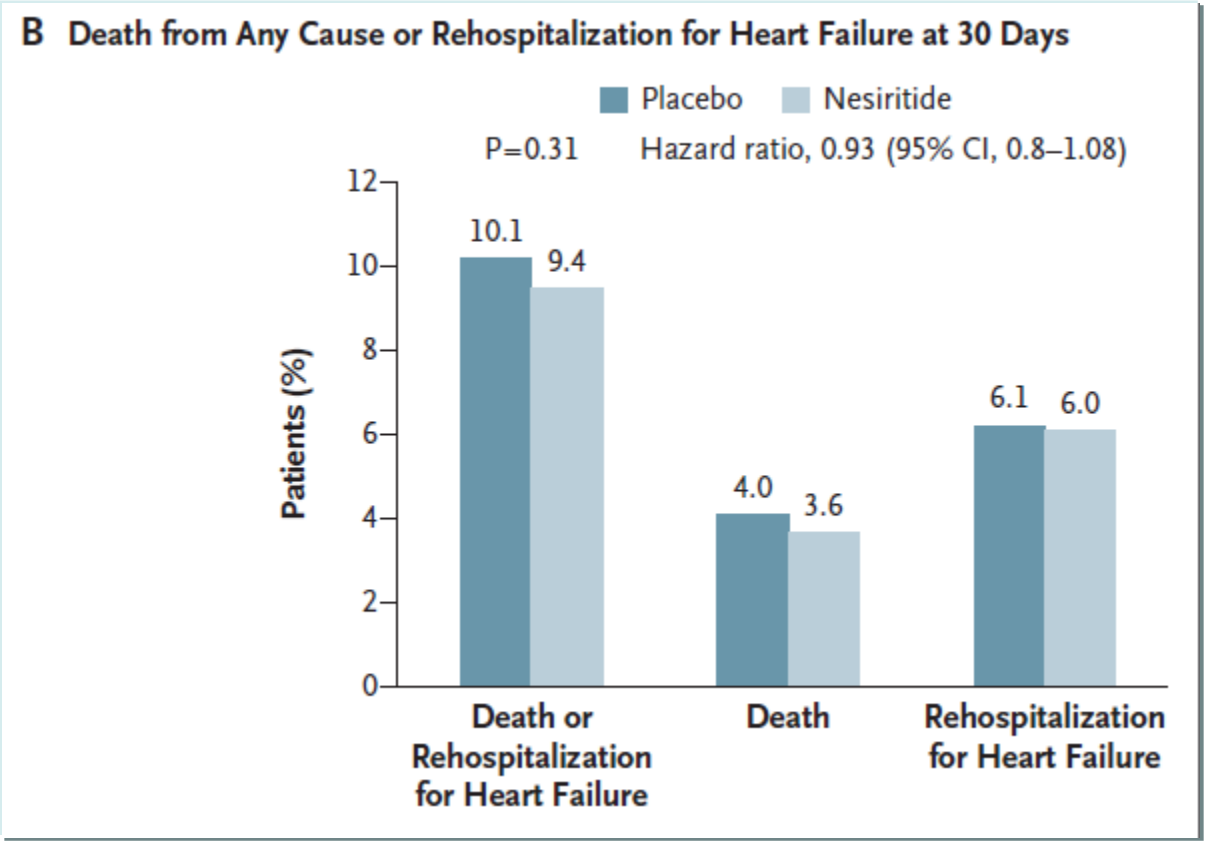
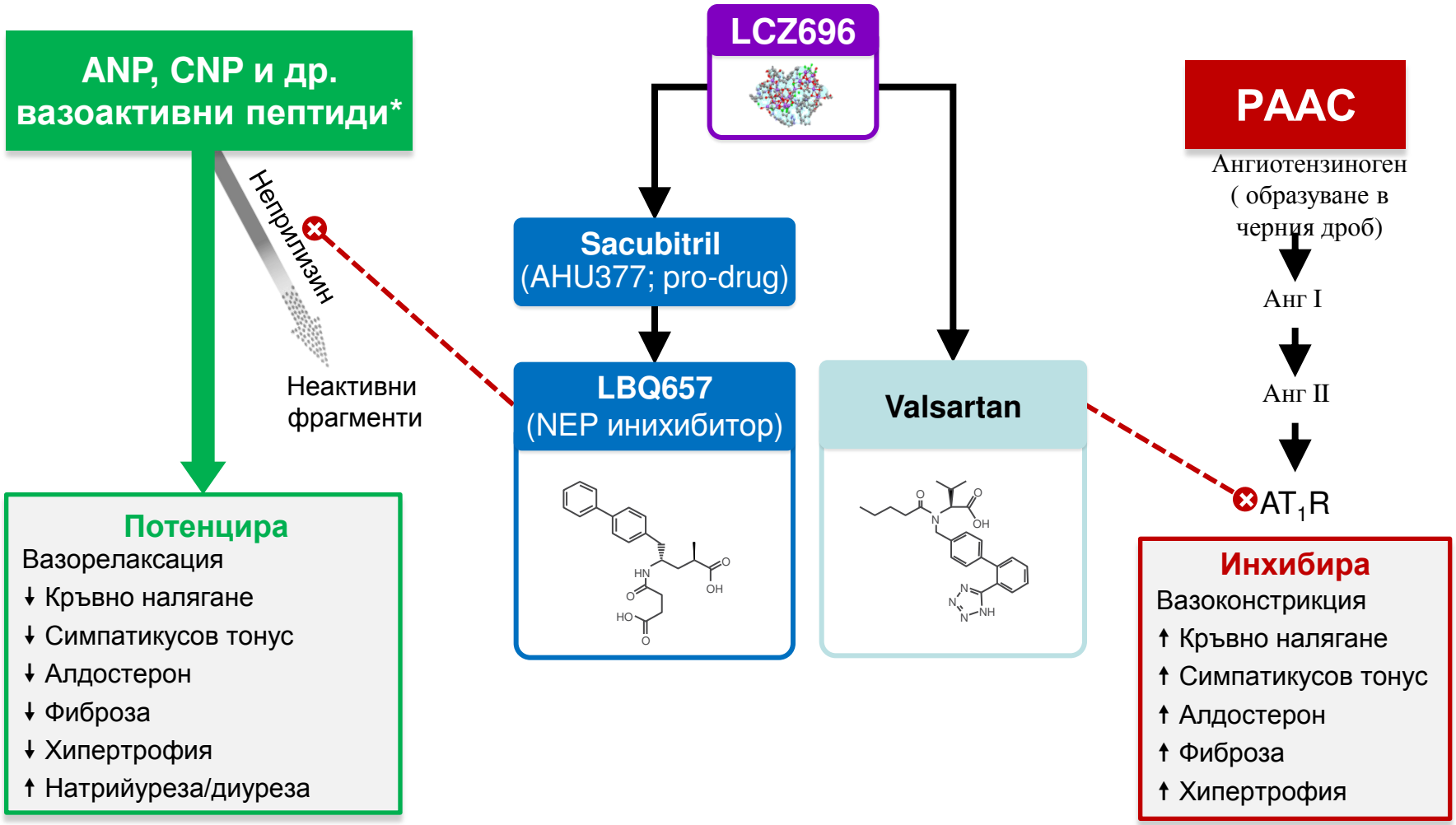
ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure



LCZ696 инхибира NEP (чрез LBQ657) и блокира AT1R (чрез valsartan)



*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP
Ang=angiotensin; ANP=atrial natriuretic peptide; AT_1=angiotensin II type 1; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; NEP=neprilysin; RAAS=renin angiotensin aldosterone system

Levin et al. N Engl J Med 1998;339:321–8;
Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Schrier & Abraham N Engl J Med 2009;341:577–85;
Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;
Feng et al. Tetrahedron Letters 2012;53:275–6

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

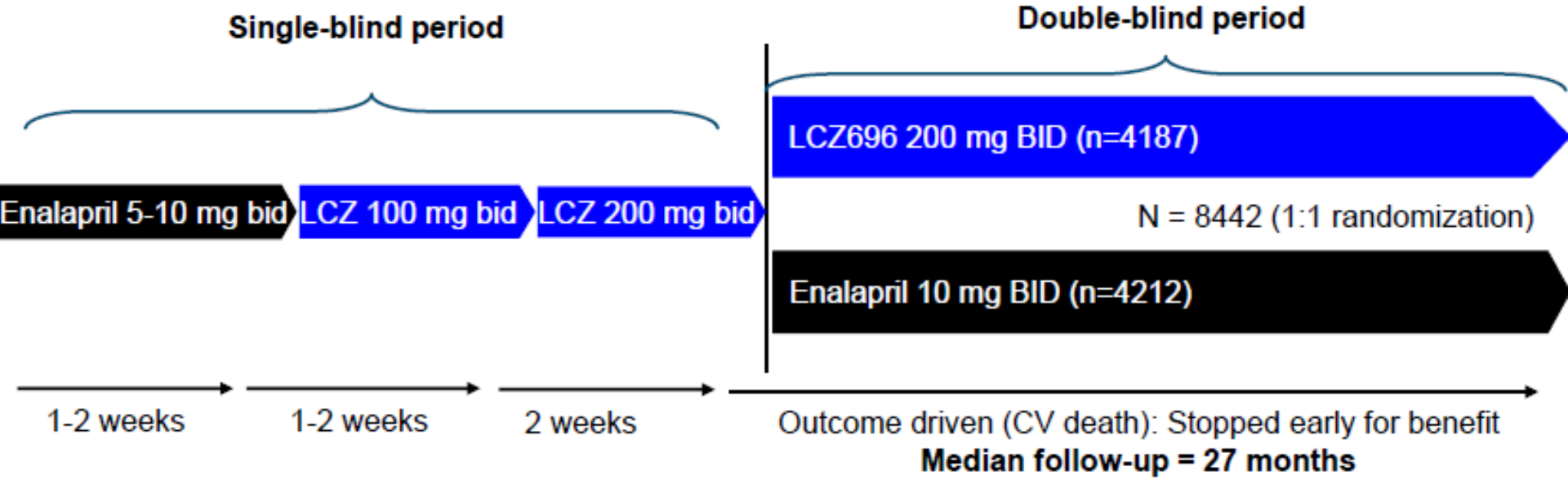
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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*

PARADIGM-HF

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

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.40 (amended to ≤0.35).
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within12 mo. BNP ≥100 pg/ml (NTpro-BNP ≥400 pg/ml)
- Background RAS blocker therapy equivalent to enalapril ≥10 mg/d
- Beta-blocker and MRA as recommended by guidelines
- SBP ≥100 mmHg run-in/ ≥95 mmHg at randomization
- eGFR ≥30 ml/min/1.73m^2 /no decrease >25% (amended to 35%)
- Potassium ≤5.2 mmol/l run-in/ ≤5.2 mmol/l at randomization



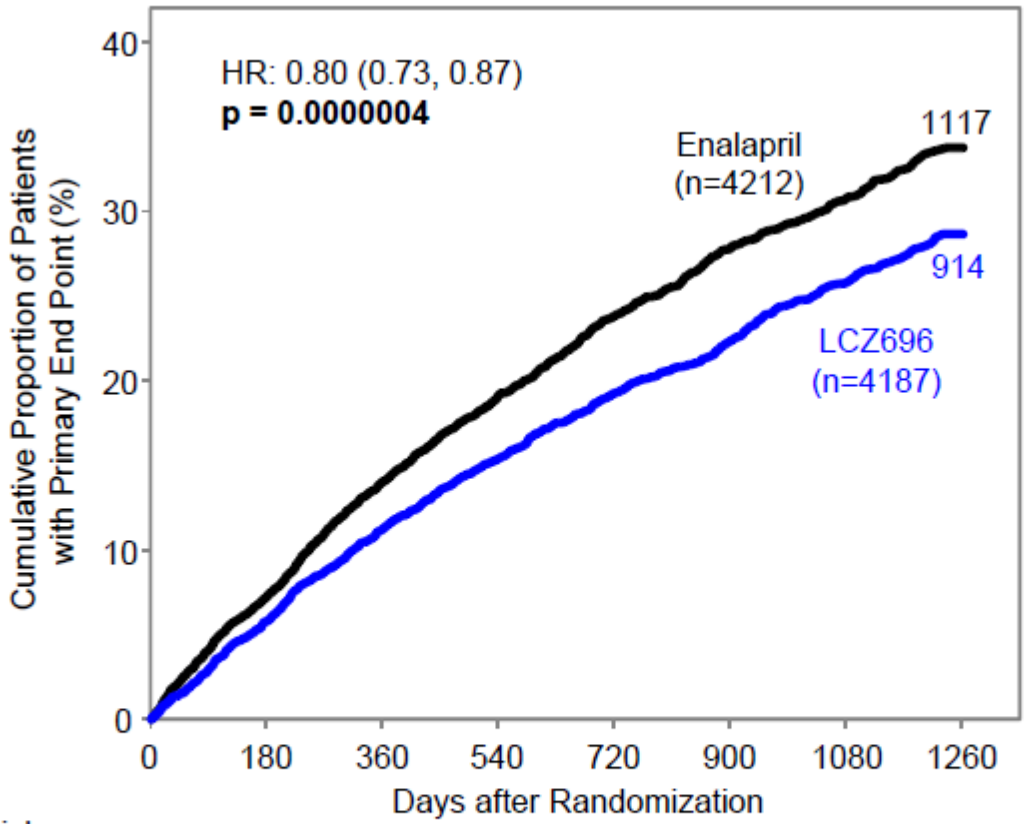
Prior ACEi/ARB use discontinued

Trial	N	Target dose, mg	Mean daily dose, mg
CONSENSUS (1987)*	127	20 bid	18.4
SOLVD-T (1991)†	1284	10 bid	16.6
SOLVD-P (1992)	2111	10 bid	16.7
V-HeFT II (1991)	403	10 bid	15.0
OVERTURE (2002)	2884	10 bid	17.7
CARMEN (2004)	190 E only 191 E+Carv	10 bid 10 bid	16.8 14.9
CIBIS-3 (2005)	190 E first 191 Bisop first	10 bid 10 bid	17.2 15.8
PARADIGM-HF	4212	10 bid	18.9

*† N.B. active run-in; 49% reached target dose.*22% reached target dose*

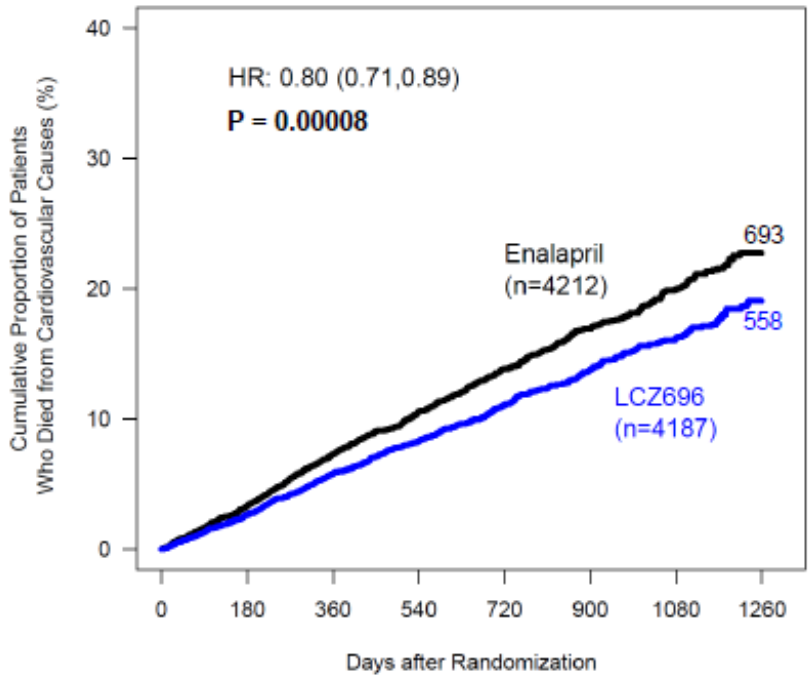
	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
CRT	7.0%	6.7%
ICD	15%	15%

CC смърт/хоспитализации за CH

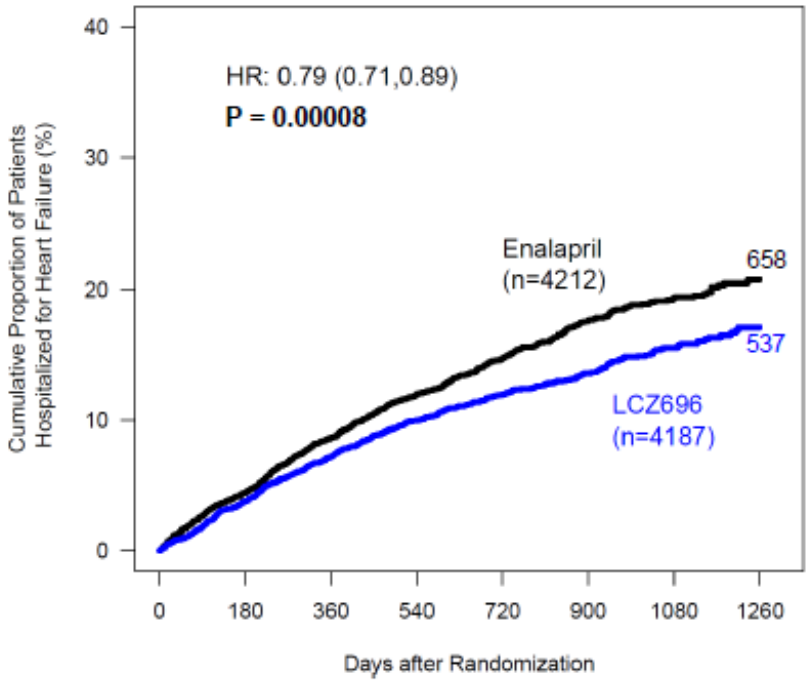


At risk								
Enalapril:	4212	3883	3579	2922	2123	1488	853	236
LCZ696:	4187	3922	3663	3018	2257	1544	896	249

Death from CV causes
20% risk reduction

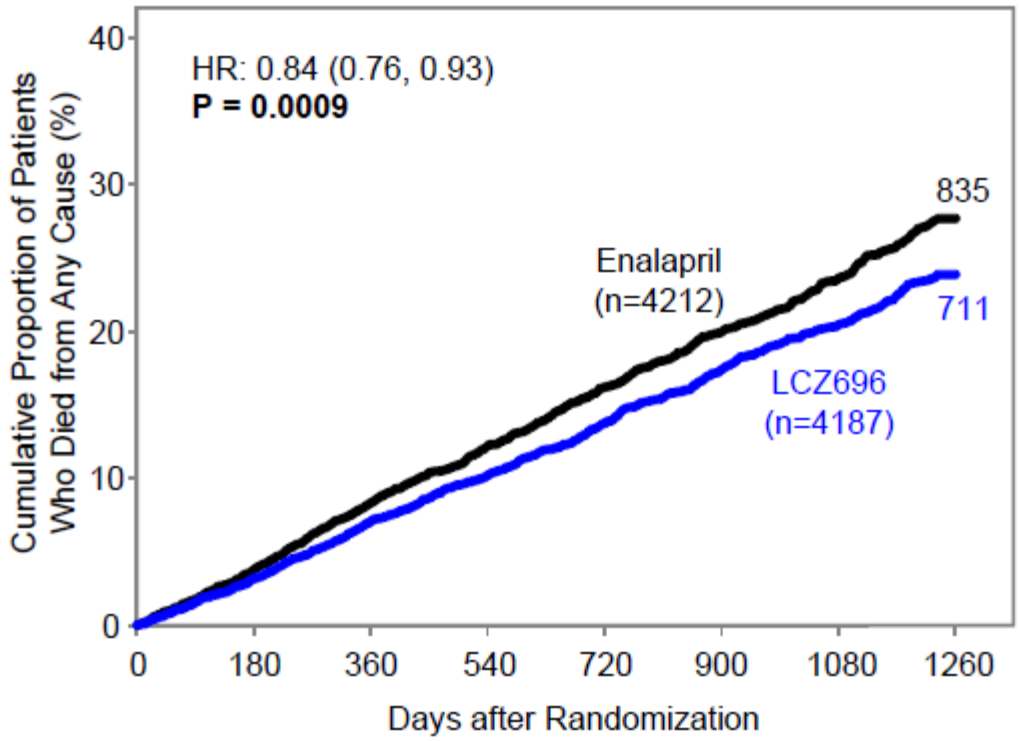


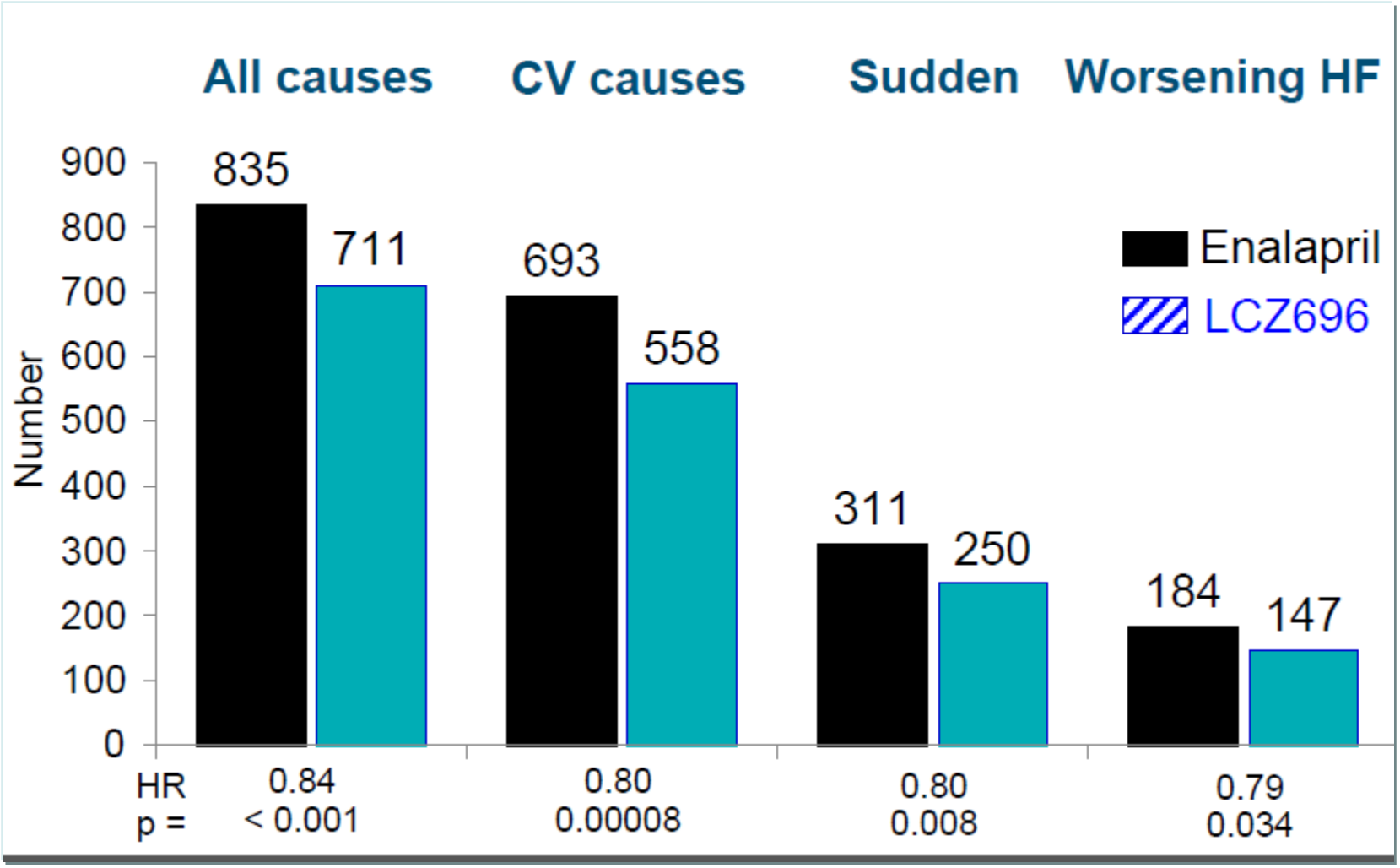
HF hospitalization
21% risk reduction



McMurray, Packer et al NEJM 2014

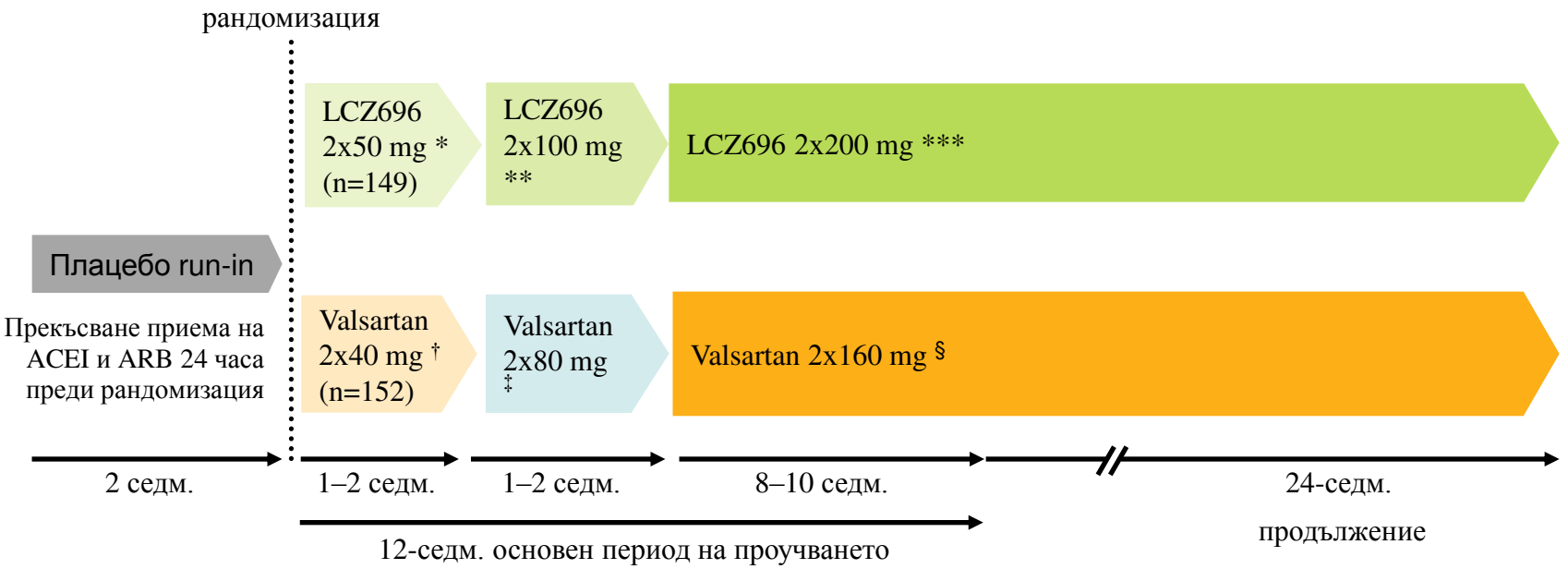
Death from any cause
16% risk reduction




All causes
CV causes
Sudden
Worsening HF
Number
900
800
700
600
500
400
300
200
100
0
835
711
693
558
311
250
184
147
Enalapril
LCZ696
HR
p =
0.84
< 0.001
0.80
0.00008
0.80
0.008
0.79
0.034

PARAMOUNT: дизайн на проучването

- 12-седмично, рандомизирано, двойно-сляпо, мултицентрово, паралелно-групово, активно контролирано проучване за оценка ефективността и безопасността на LCZ696 2x200 mg дневно спрямо valsartan 2x160 mg при пациенти с ХСН и запазена ФИ (≥45%), последван от 24-седм. период на допълнително наблюдение
- 685 пациента, 65 центъра, 13 страни са скринирани в PARAMOUNT, от които 308 са рандомизирани в изпитването



*100 mg TDD; **200 mg TDD; ***400 mg TDD; †80 mg TDD; ‡160 mg TDD; §320 mg TDD-

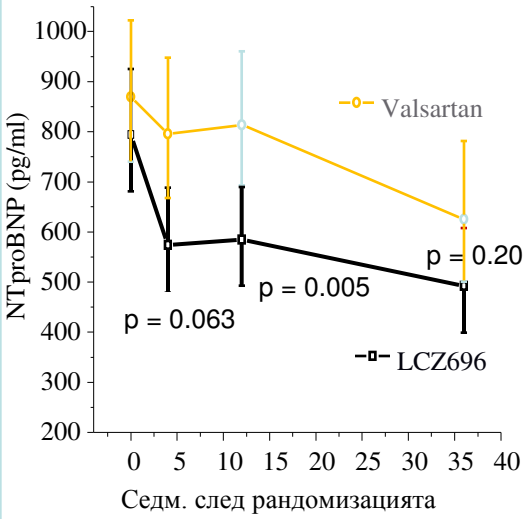
Solomon et al. Lancet 2012;380:1387–95

LCZ696 in HFpEF
PARAMOUNT Phase II results

- По-голяма редукция на NT-proBNP с LCZ696 на12 седм. спрямо valsartan (23%, p=0.005); тази промяна се запазва до 36 седм. но не запазва статистическа значимост (15%, p=0.20).
- По-голямо намаление на размера на LA на 36 седм. с LCZ696 (LAV : p=.0009; LAVI: p=.0026; LAD=.01).
- Повече пациенти с подобрение в класа по NYHA с LCZ696 (p=0.05)

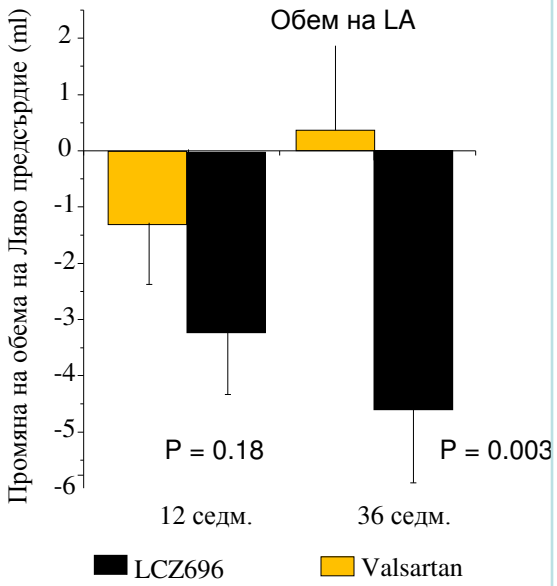
Намаление на NT-proBNP

1° крайна цел: NT-proBNP
(23% намаление на 12 седм.)



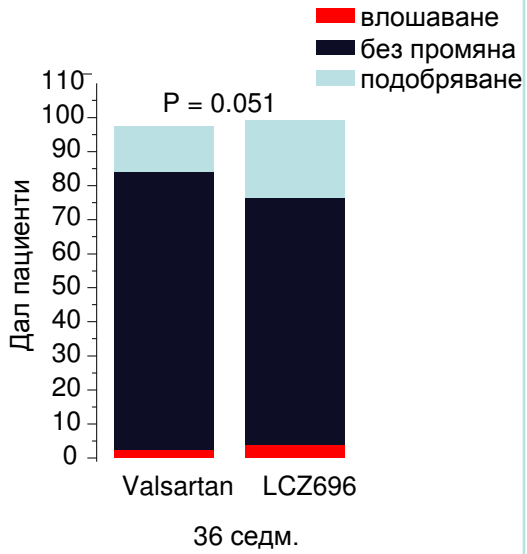
Намаление на ремоделирането на LA

2° крайна цел: размер на LA
(7% намаление на 36 седм.)



Промяна на NYHA клас

2° крайна цел: NYHA
(9% подобрение на 36седм.)



NYHA: New York Heart Association Classification

Solomon et al. LANCET 2012;380:1387–95.

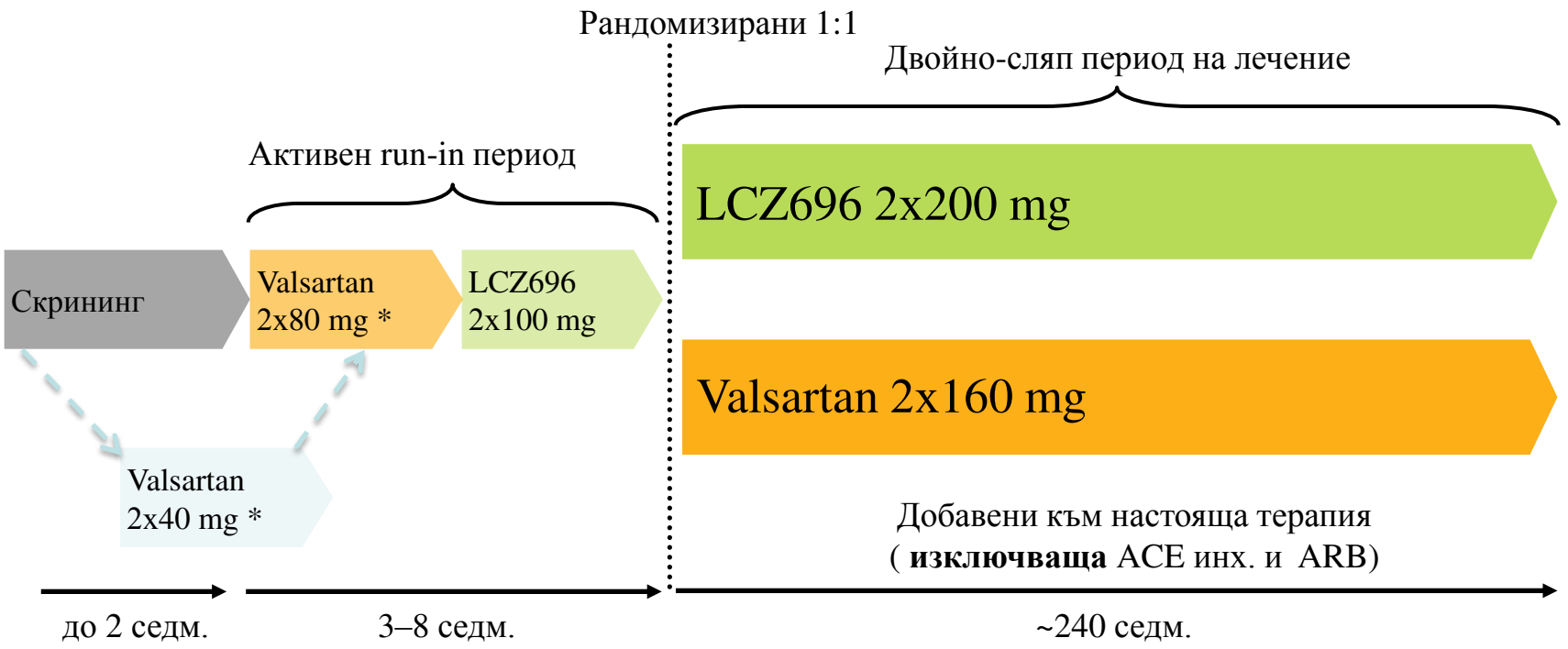
The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

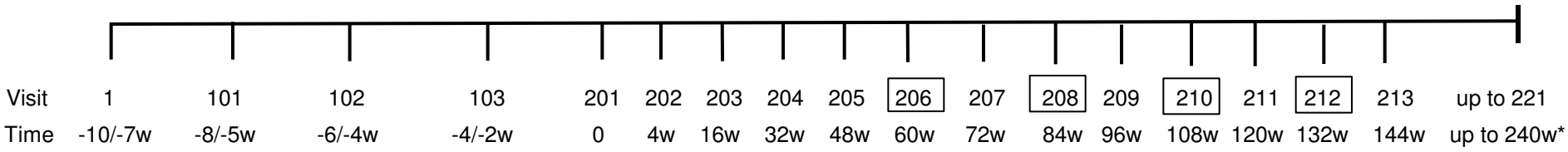
*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**

ventricular pressures and wall stress. These findings suggest that LCZ696 could have favourable effects in patients with this disorder, and that further testing of the drug in this patient population might be warranted.

PARAGON-HF- дизай на проучването:

~4,300 пациенти със CH (NYHA клас II–IV) и LVEF ≥45%





*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1.

☐ Indicates telephone visit contact visit

Първична крайна цел : СС смърт и хоспитализации за CH (първа и последващи) (очаквани~1,721 събития)

Key inclusion criteria:

- Age ≥55 years; LVEF ≥45%
- Symptoms of HF requiring treatment with diuretic(s) for ≥30 days prior to study entry
- Current symptomatic HF (NYHA class II–IV)
- Structural heart disease (LAE and/or LVH)

AND either

- HF hospitalization* within 9 months prior to study entry and Elevated NT-proBNP (>200 for NSR or > 600 for AF)

OR

- Elevated NT-proBNP (>300 pg/mL for patients with SR or >900 pg/mL for patients with AF)

CABG=coronary artery bypass graft; LAE=left atrial enlargement; LVEF=left ventricular ejection fraction; SBP=systolic blood pressure

Key exclusion criteria:

- History of LVEF <45%
- MI, CABG or any event within the 6 months prior to study entry that may have reduced LVEF
- Current acute decompensated HF
- K > 5.2 mmol/L; eGFR < 30 L/min/1.73m^2
- SBP < 110mm Hg or > 180mm Hg. If SBP. *if SBP >150 mmHg and <180 mmHg, the patient should be receiving ≥3 antihypertensive drugs
- Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity. Specifically, patients with the following are excluded:
  - severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (i.e., requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) or
  - Hemoglobin (Hgb) <10 g/dl, **or**
  - body mass index (BMI) >40 kg/m^2

Time to move on from 'time-to-first': should all events be included in the analysis of clinical trials?

Stefan D. Anker[1,2*] and John J.V. McMurray[3]

[1]Applied Cachexia Research, Department of Cardiology, Charité, Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany; [2]Centre for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; and [3]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

Повтарящите хоспитализации за СН по-точно отразяват тежестта на заболяването (HFpEF)

Table I Number of events in 'time-to-first event' analysis and 'recurrent events' analysis of heart failure trials

Trial	Time-to-first-event (CV death or HF hospitalization): CV death as % of primary outcome (*n*/*n* = *N*)	Recurrent events (all CV deaths and all HF hospitalizations): CV death as % of all events (*n*/*n* = *N*)
CHARM-Added	316/705 = 1021 (31.0%)	649/1443 = 2092 (31.0%)
CHARM-Alternative	237/503 = 740 (32.0%)	471/1053 = 1524 (30.9%)
EMPHASIS-HF	188/417 = 605 (31.1%)	332/702 = 1034 (32.1%)
SHIFT	544/1186 = 1730 (31.4%)	940/2113 = 3053 (30.7%)
I-PRESERVE	392/661 = 1053 (37.2%)	613/1176 = 1789 (34.3%)
CHARM-Preserved	190/509 = 699 (27.2%)	340/968 = 1308 (26.0%)

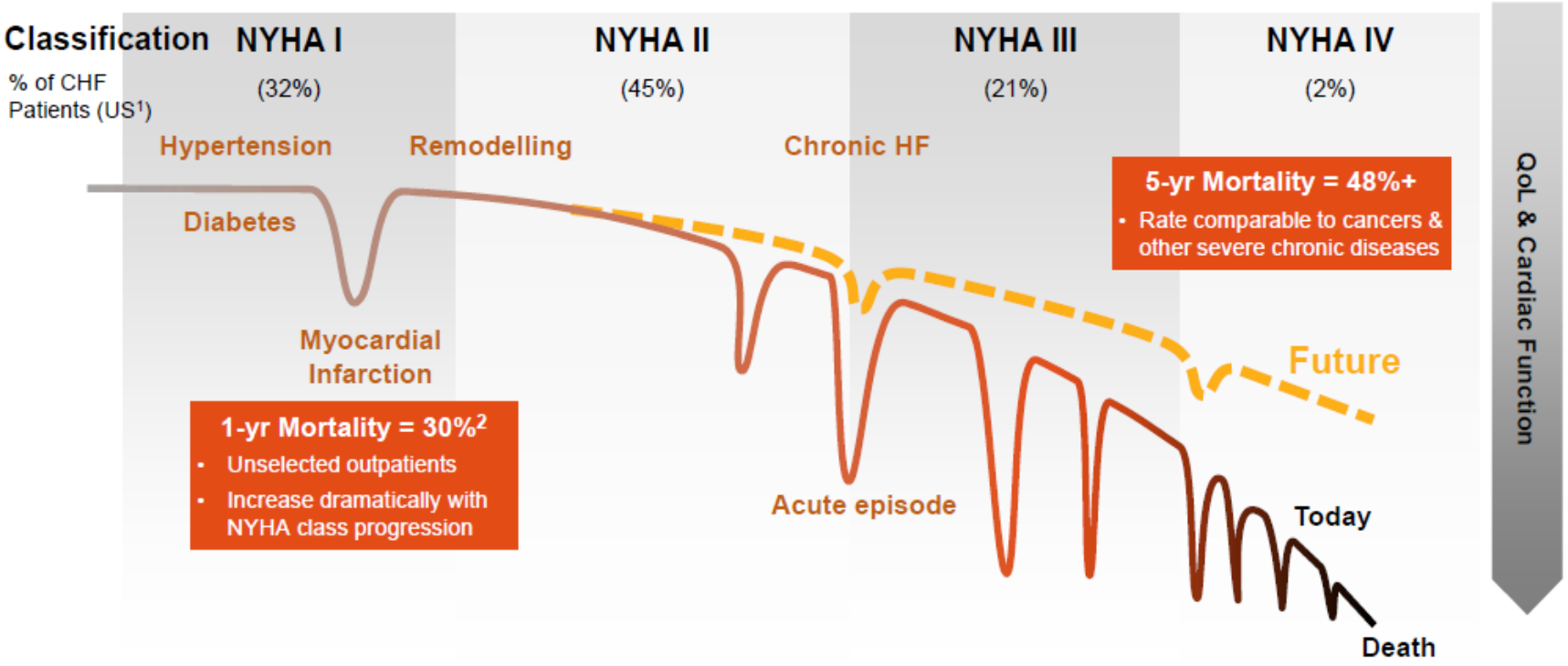
n/*n*, CV death/HF hospitalization; *N*, CV death or HF hospitalization (time-to-first event) or total number of CV deaths plus total number of HF hospitalizations (recurrent events). CV, cardiovascular; HF, heart failure.

European Heart Journal 2012:33(22):2764-5.

Хронична сърдечна недостатъчност

„*Низходяща негативна по ход спирала*“

- **От СН страдат около 2% от възрастното население.**
- **Честотатта на СН се увеличава с възрастта (> 10% над 65 години).**
- **Смъртността от СН остава много висока – 30% през 1-ата година от диагнозата до 50% на 5-та година.**
- **65% от пациентите със СН имат средно годишно ≥2 хоспитализации**



PRAISE, COPERNICUS, US Carvedilol, MERIT-HF, Val-HeFT, SOLVD-T
Chen J, et al. *JAMA*. 2011;306(15):1669; Muntwyler J et al. *Eur Heart J*. 2002;23:1861-6.
Note: 1-yr mortality / readmission in AHF patients 40%; Dickstein K et al. *Eur Heart J*. 2008;29:2388-442.

European Heart Journal (2015) **36**, 410–412
doi:10.1093/eurheartj/ehu501

LCZ696: too good to be true?

Robert M. Califf*

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Heart failure: a state of "neurohumoral imbalance"

Vasoconstrictor/ anti-natriuretic /pro-mitotic mediators

Vasodilator/ natriuretic/ anti-mitotic mediators

A paradigm shift: from "neuro-humoral inhibition" to "neuro-humoral modulation"

Vasoconstrictor/ anti-natriuretic /pro-mitotic mediators

Vasodilator/ natriuretic/ anti-mitotic mediators

Нови молекули в лечението на хроничната сърдечна недостатъчност

- Лечението на HFpEF остава емпирично към настоящия момент
  - Редукция на застоя – диуретик
  - Лечение на исхемията
  - Контрол на АН
  - Контрол на камерната честота при перманентно ПМ
  - Задържане на синусов ритъм
- Липса на доказана дефинитивна терапия
- Обещаващи фаза II и III проучвания