Nouveautés dans le traitement de l'Insuffisance cardiaque chronique:

Richard Isnard

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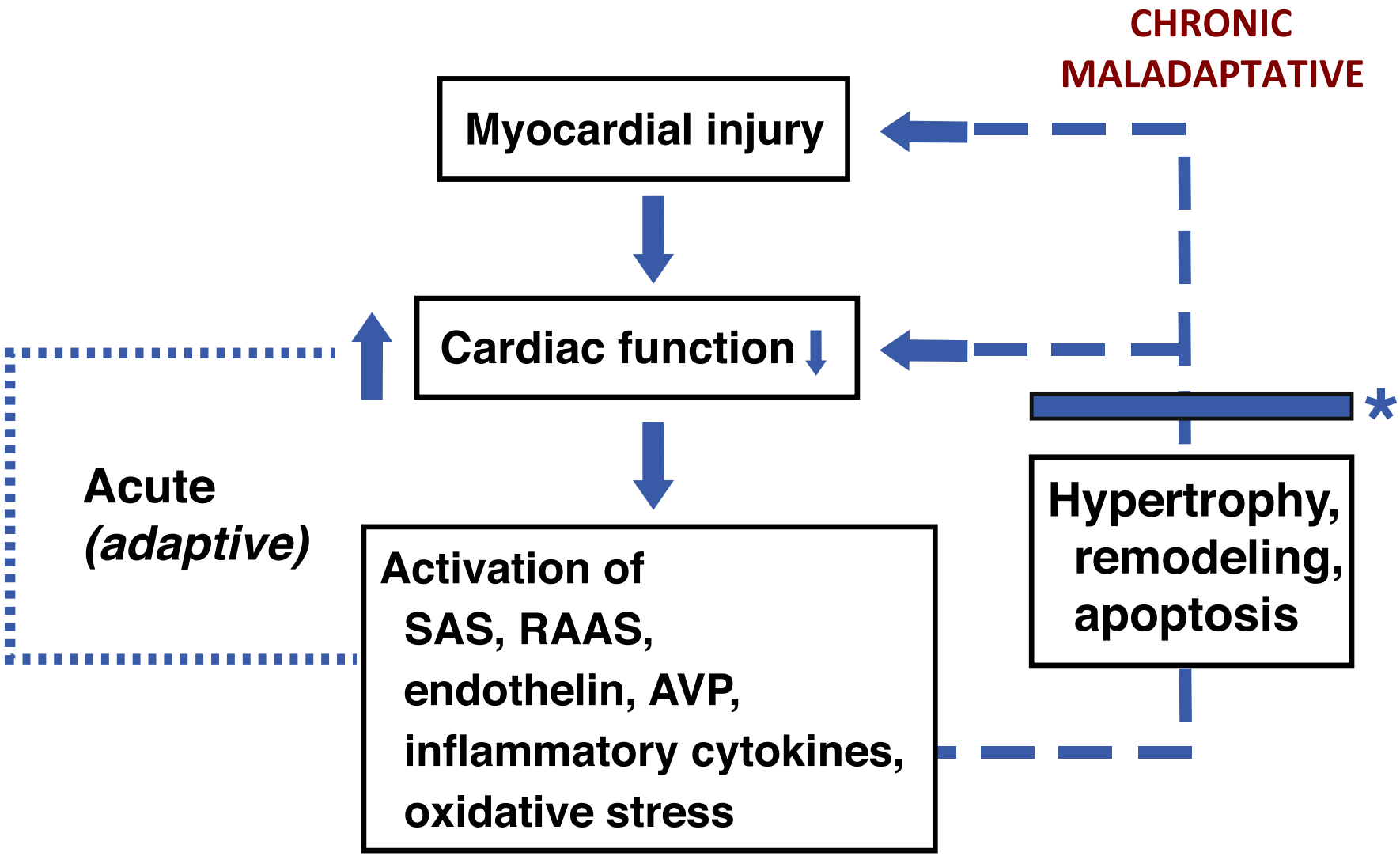
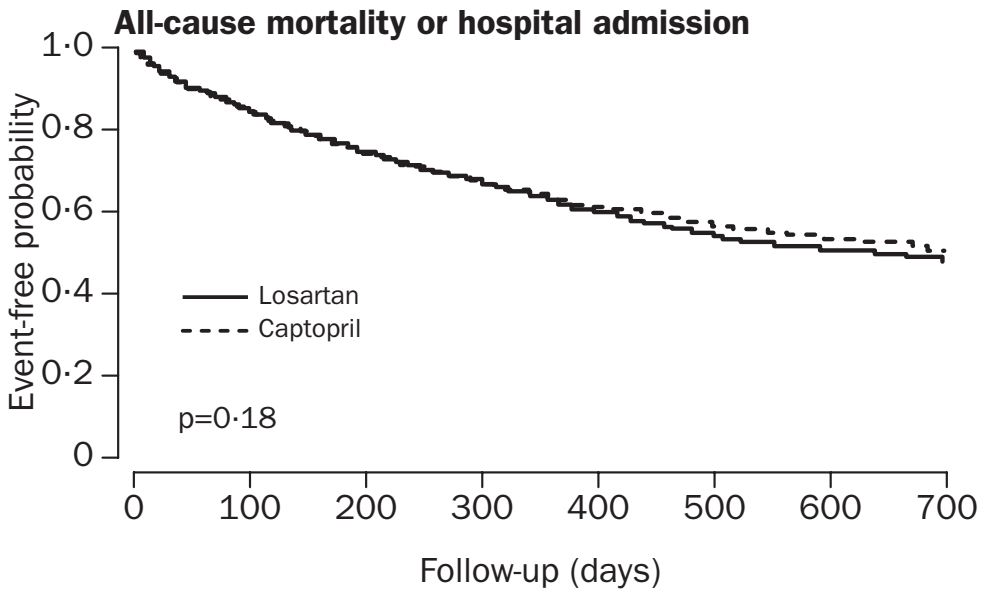
UPMC
SORBONNE UNIVERSITÉS



Braunwald, JACC Heart Failure 2013

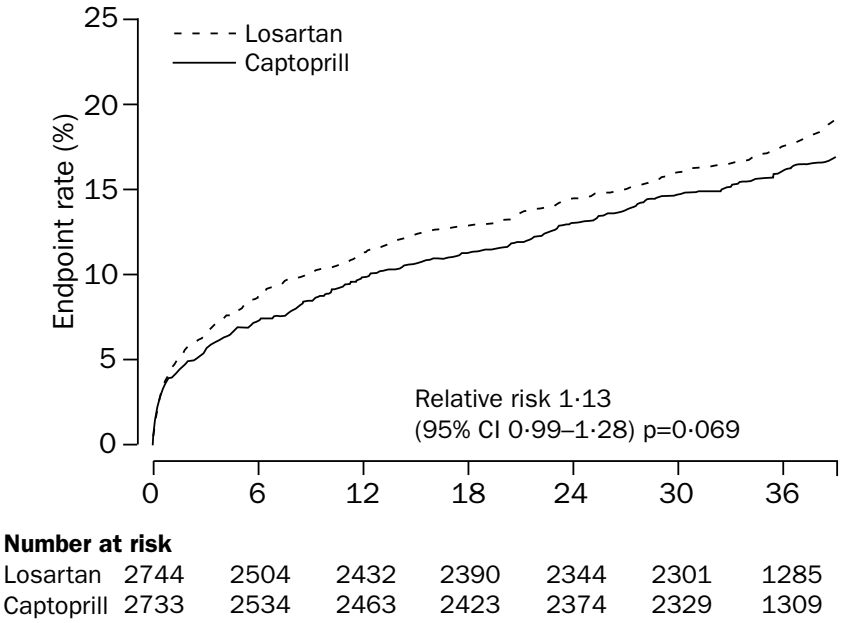
ARA2 versus IEC

Insuffisance cardiaque Chronique à FE basse



ELITE 2, Lancet 2000

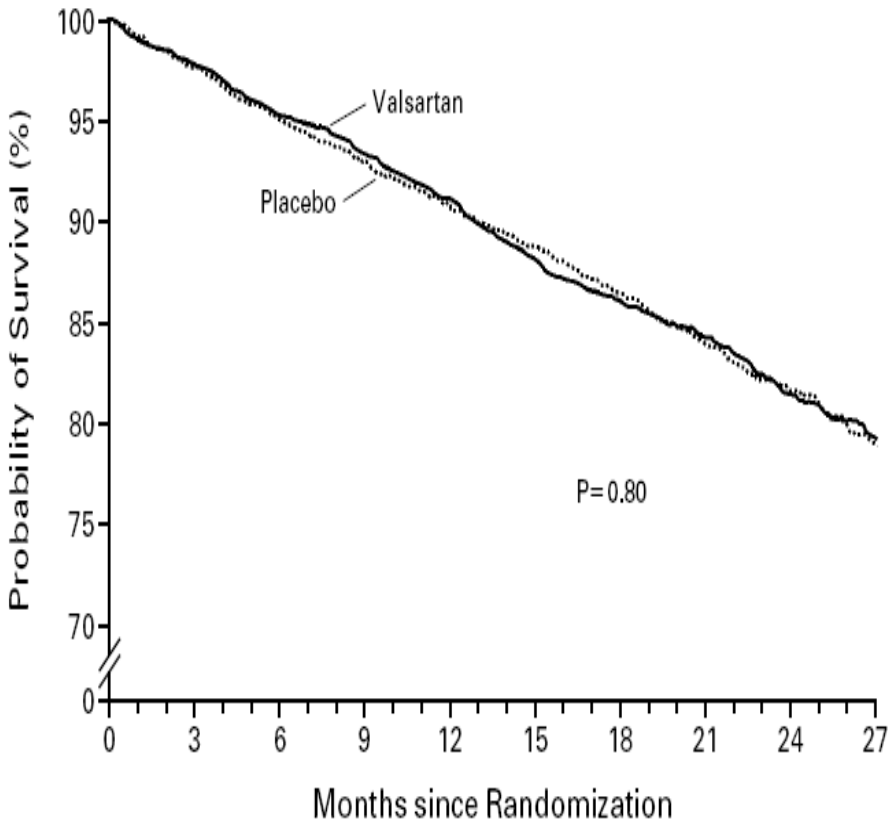
Infarctus avec FE basse ou insuffisance cardiaque



OPTIMAAL, Lancet 2003

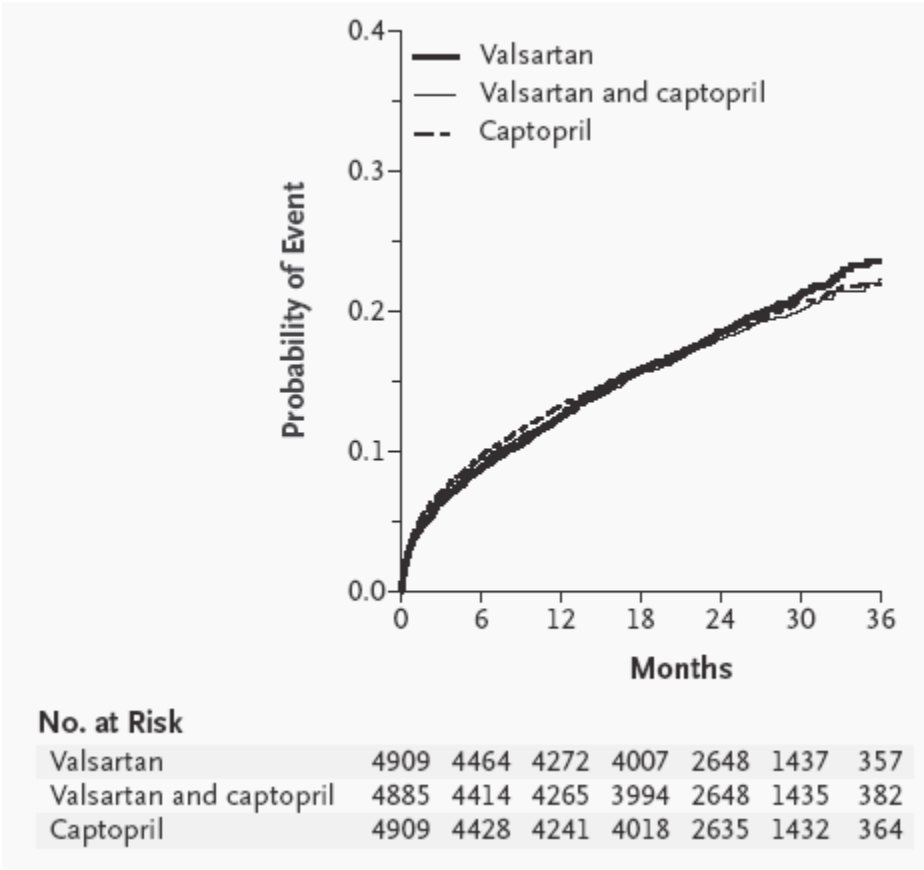
Association IEC – ARA2

Insuffisance cardiaque Chronique à FE basse



VAL-HEFT, NEJM 2001

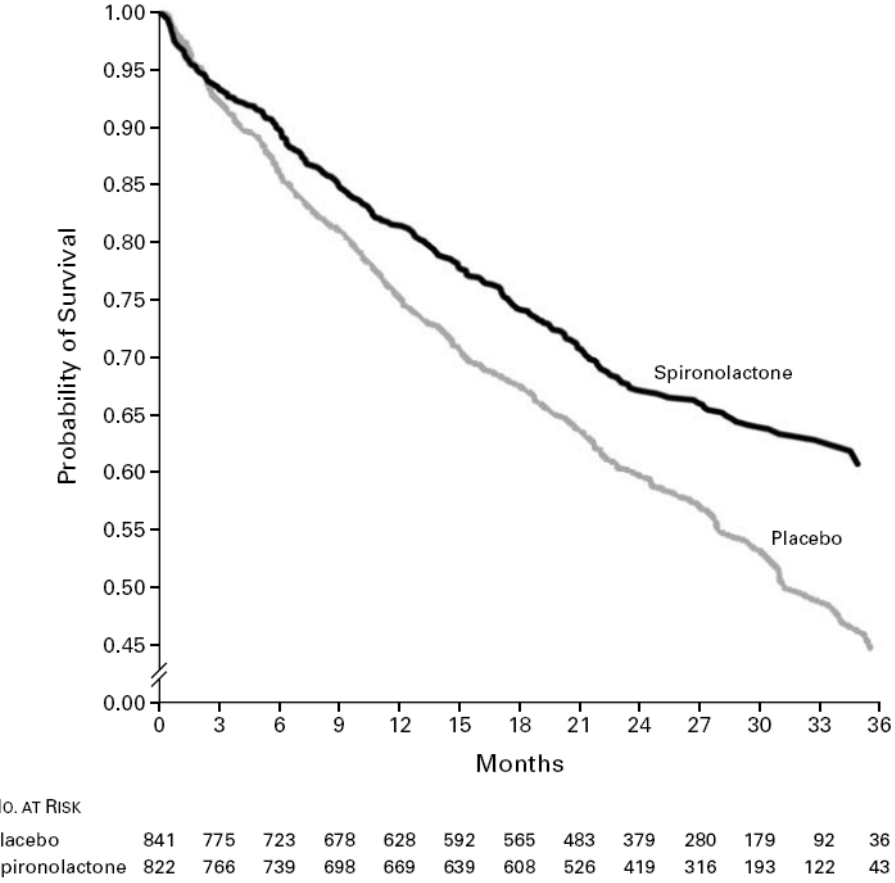
Infarctus avec FE basse ou insuffisance cardiaque



VALIANT, NEJM 2003

Association antialdostérone- IEC

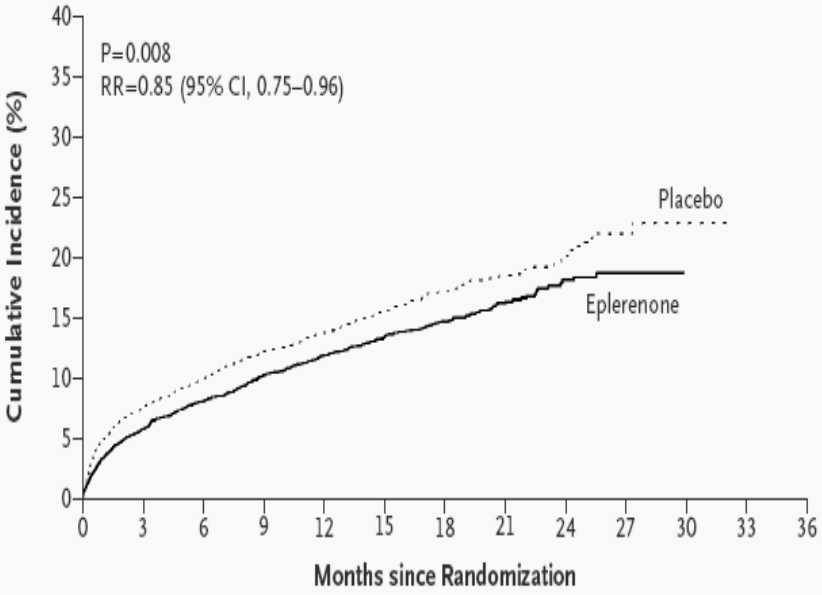
Insuffisance cardiaque chronique grave avec FE basse



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

RALES, NEJM 1999

Infarctus avec FE basse ou insuffisance cardiaque



No. at Risk													
Placebo	3313	3064	2983	2830	2418	1801	1213	709	323	99	2	0	0
Eplerenone	3319	3125	3044	2896	2463	1857	1260	728	336	110	0	0	0

EPHESUS, NEJM 2003

The NEW ENGLAND JOURNAL of MEDICINE

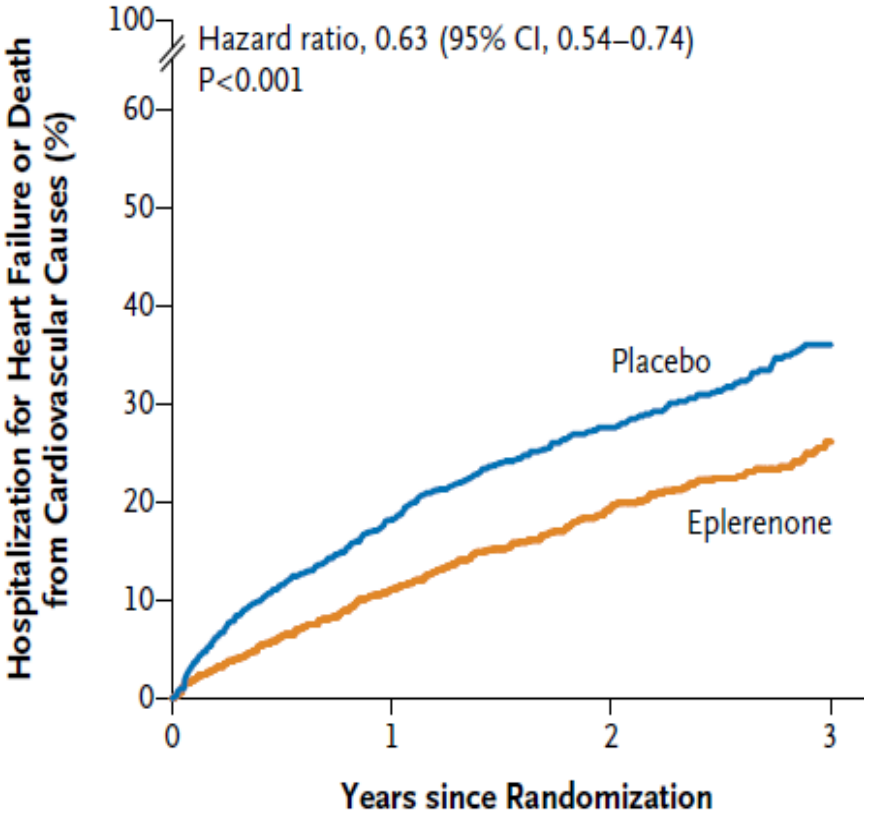
ORIGINAL ARTICLE

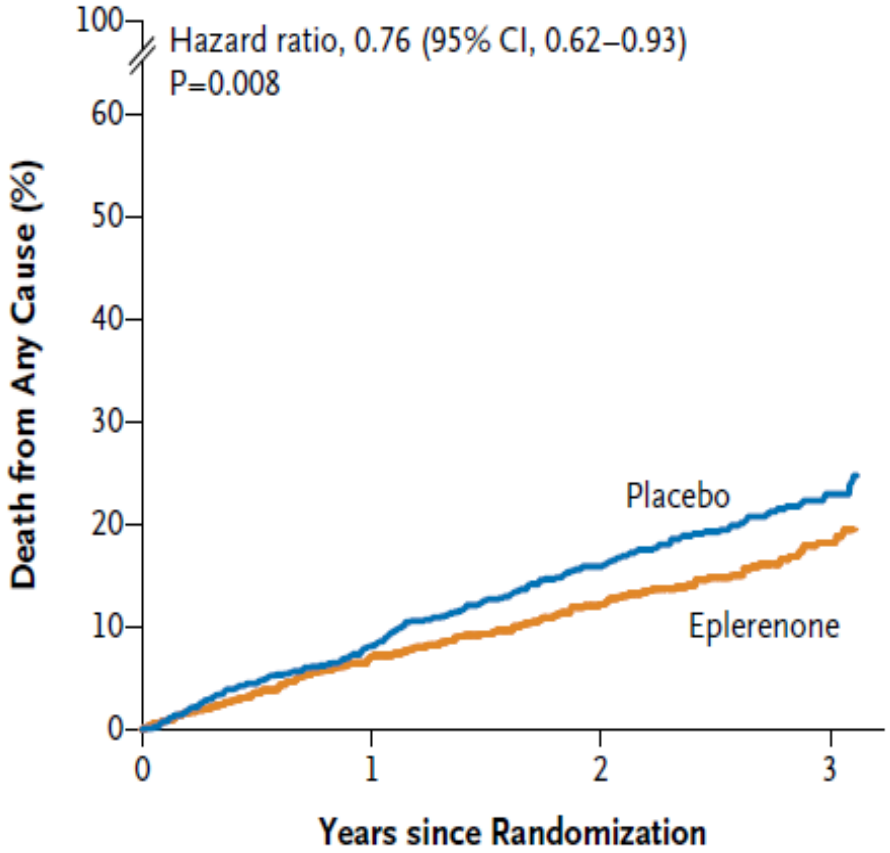
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

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

Zannad, N Engl J Med 2010

Emphasis Main Results

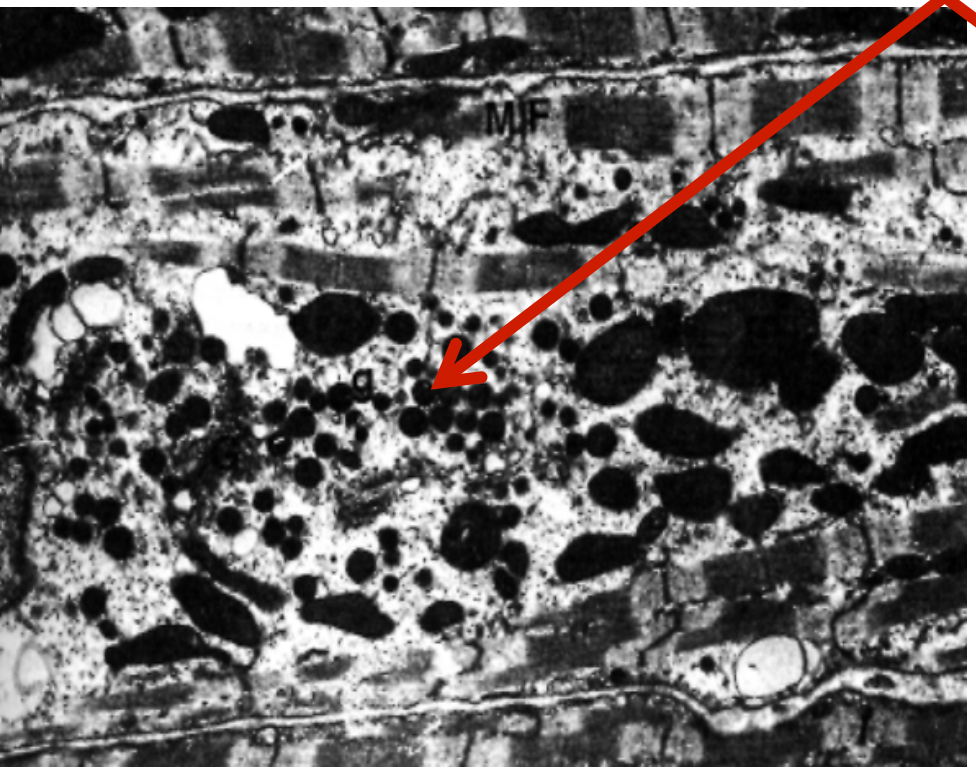




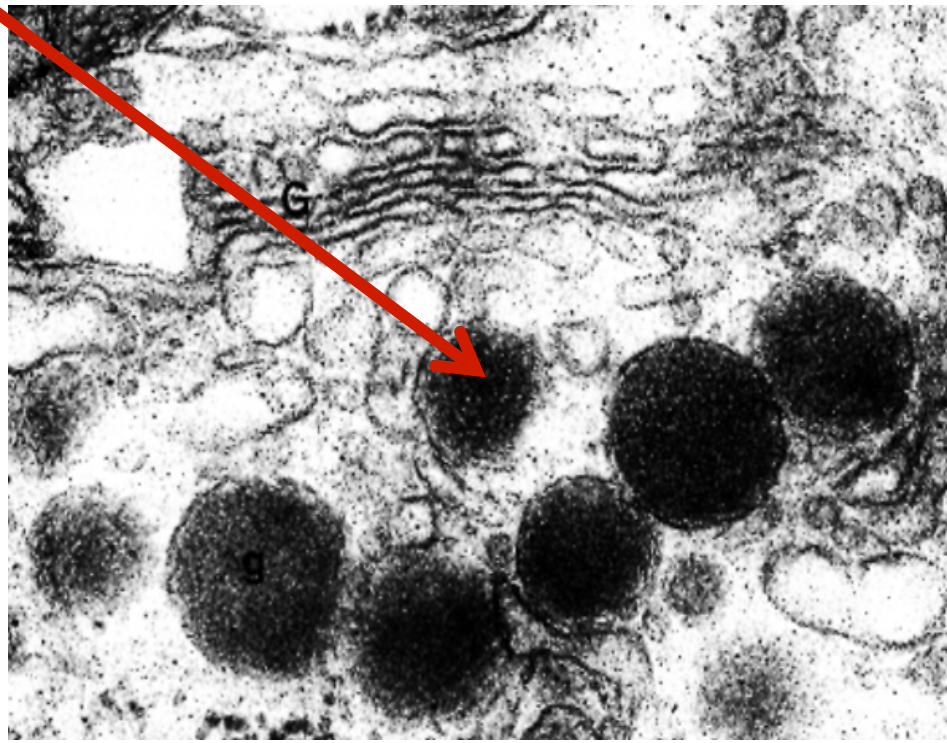
Zannad, N Engl J Med 2010

Natriuretic peptides: a success story

secretion granules



x 4700



x 82 000

Rats atrial myocytes (PY Hatt)

Life Sciences, Vol. 28, pp. 89-94 Pergamon Press
Printed in the U.S.A.

Vol. 28, No. 1, 1981

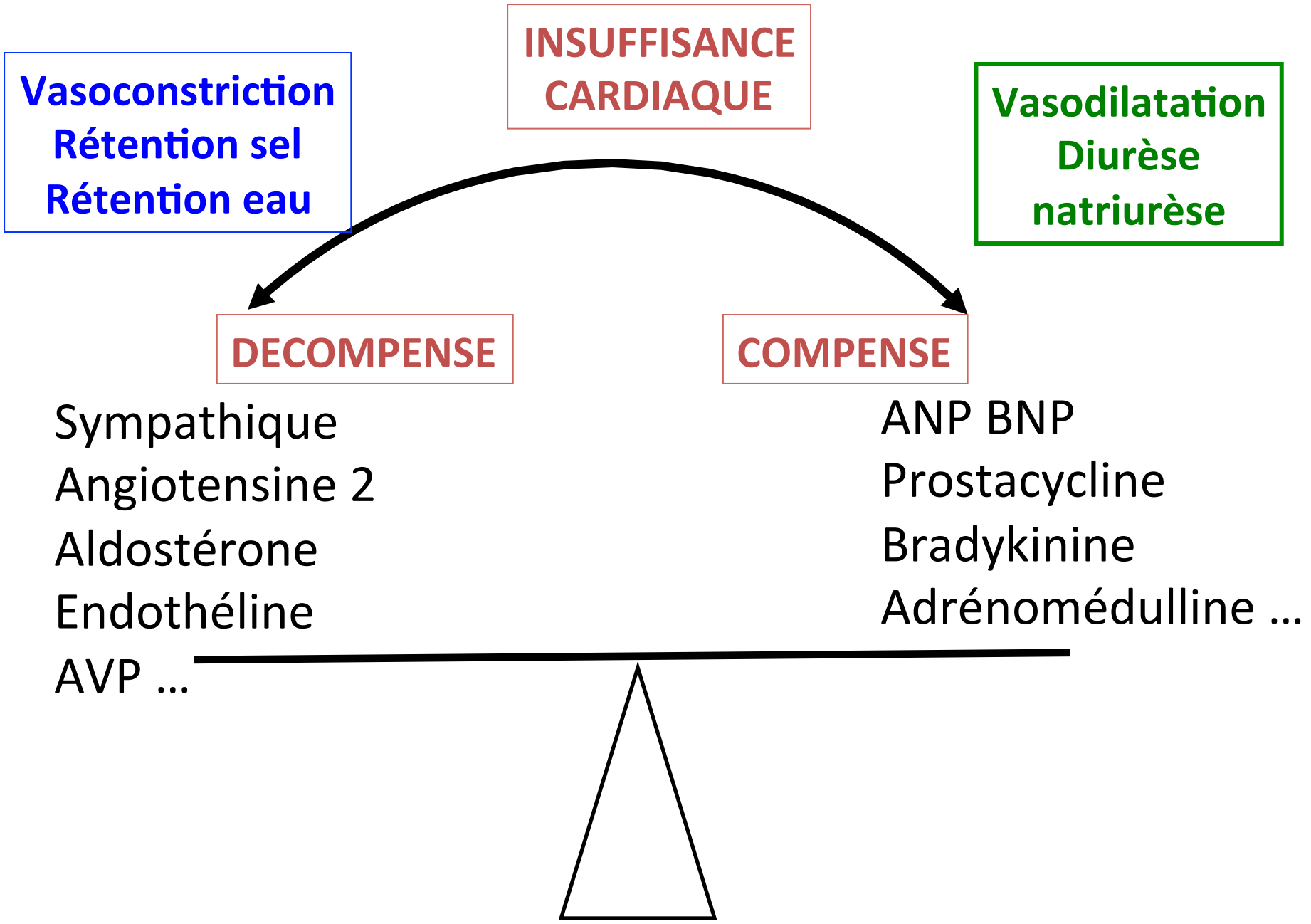
A RAPID AND POTENT NATRIURETIC RESPONSE TO INTRAVENOUS INJECTION OF ATRIAL MYOCARDIAL EXTRACT IN RATS

A. J. de Bold, H. B. Borenstein, A. T. Veress, H. Sonnenberg

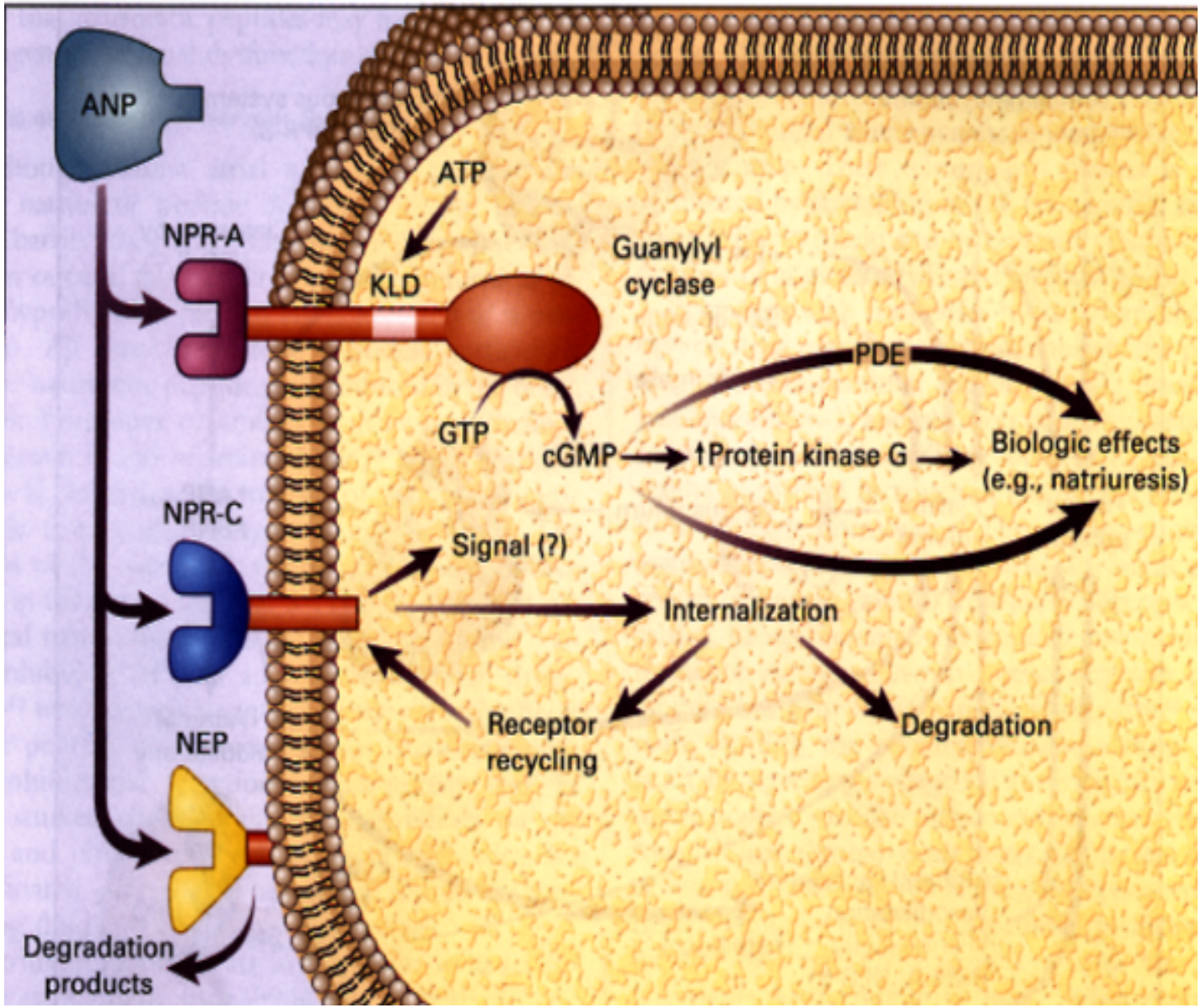
Dept. of Pathology, Queen's University, Kingston, Ont. and
Dept. of Physiology, University of Toronto, Toronto, Ont.

(Received in final form October 21, 1980)

Impact Factor = 2.53


INSUFFISANCE CARDIAQUE
Vasoconstriction
Rétention sel
Rétention eau
Vasodilatation
Diurèse
natriurèse
DECOMPENSE
COMPENSE
Sympathique
Angiotensine 2
Aldostérone
Endothéline
AVP …
ANP BNP
Prostacycline
Bradykinine
Adrénomédulline …

Voies de dégradation des peptides natriurétiques



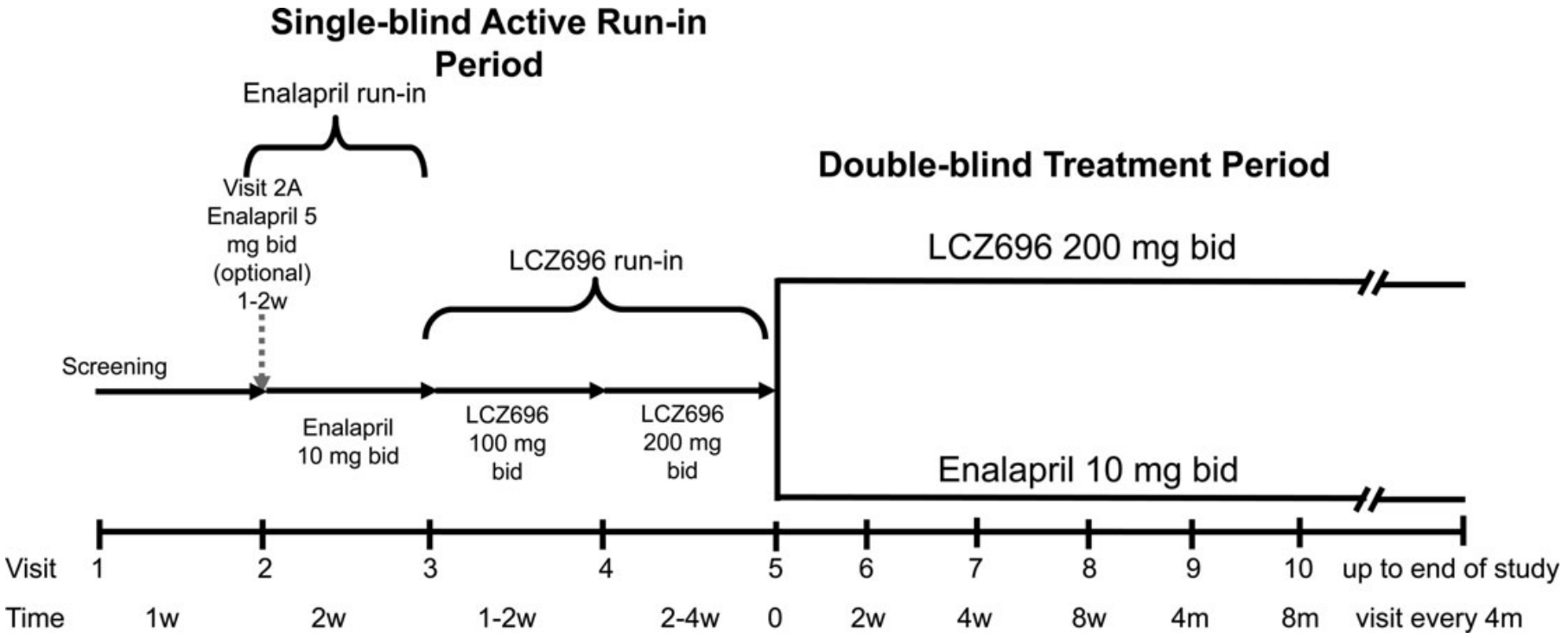
PARADIGM-HF

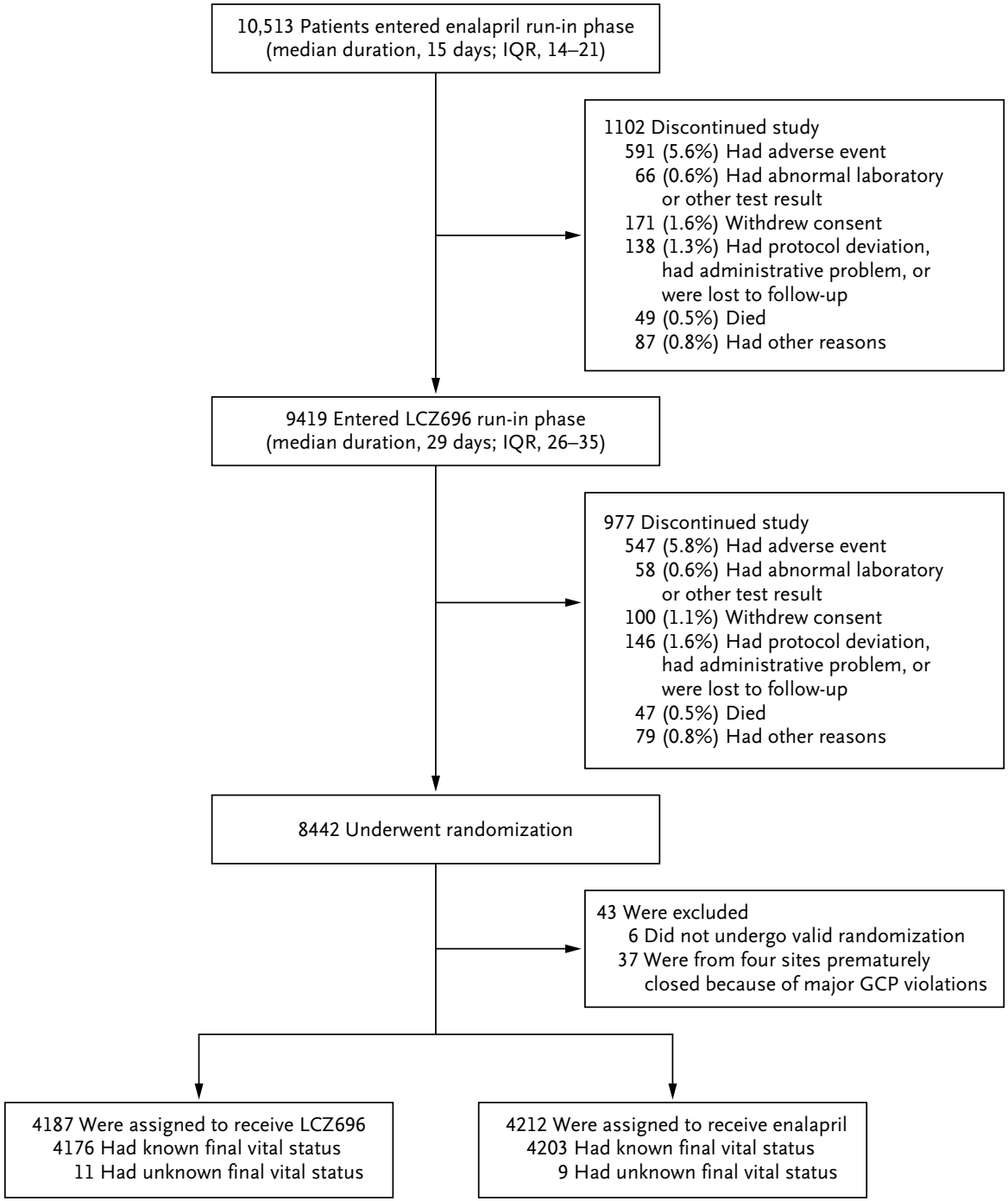
The NEW ENGLAND JOURNAL of MEDICINE

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*


Single-blind Active Run-in Period
Enalapril run-in
Visit 2A
Enalapril 5 mg bid (optional)
1-2w
Double-blind Treatment Period
LCZ696 200 mg bid
LCZ696 run-in
Screening
Enalapril 10 mg bid
LCZ696 100 mg bid
LCZ696 200 mg bid
Enalapril 10 mg bid
Visit 1 2 3 4 5 6 7 8 9 10 up to end of study
Time 1w 2w 1-2w 2-4w 0 2w 4w 8w 4m 8m visit every 4m


10,513 Patients entered enalapril run-in phase
(median duration, 15 days; IQR, 14–21)
1102 Discontinued study
591 (5.6%) Had adverse event
66 (0.6%) Had abnormal laboratory or other test result
171 (1.6%) Withdrew consent
138 (1.3%) Had protocol deviation, had administrative problem, or were lost to follow-up
49 (0.5%) Died
87 (0.8%) Had other reasons
9419 Entered LCZ696 run-in phase
(median duration, 29 days; IQR, 26–35)
977 Discontinued study
547 (5.8%) Had adverse event
58 (0.6%) Had abnormal laboratory or other test result
100 (1.1%) Withdrew consent
146 (1.6%) Had protocol deviation, had administrative problem, or were lost to follow-up
47 (0.5%) Died
79 (0.8%) Had other reasons
8442 Underwent randomization
43 Were excluded
6 Did not undergo valid randomization
37 Were from four sites prematurely closed because of major GCP violations
4187 Were assigned to receive LCZ696
4176 Had known final vital status
11 Had unknown final vital status
4212 Were assigned to receive enalapril
4203 Had known final vital status
9 Had unknown final vital status

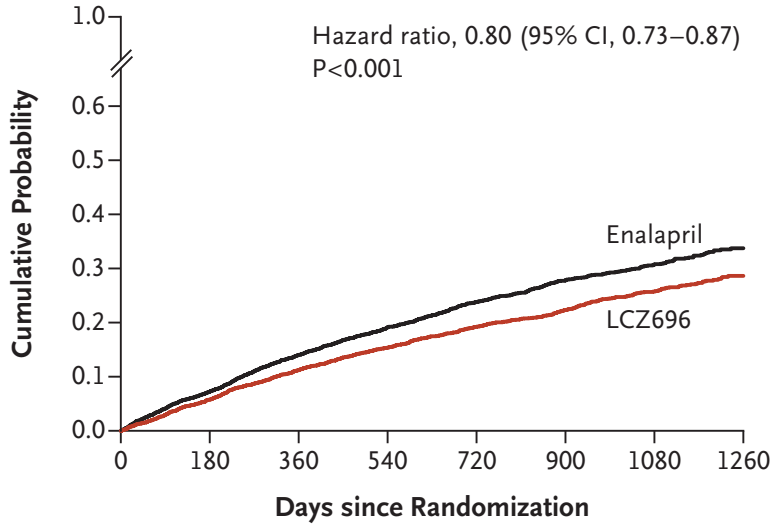
Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	213 (5.1)	215 (5.1)
Asian	759 (18.1)	750 (17.8)
Other	452 (10.8)	466 (11.1)
Systolic blood pressure — mm Hg	122±15	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)

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
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)
Missing data	7 (0.2)	6 (0.1)
Medical history — no. (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Pretrial use of ARB‖	929 (22.2)	963 (22.9)

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
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)

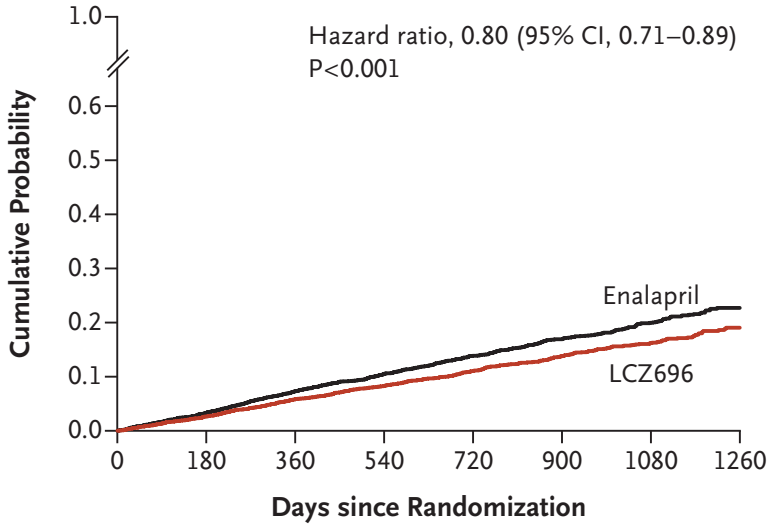
Arrêt de l’étude après un suivi de 27 mois

A Primary End Point



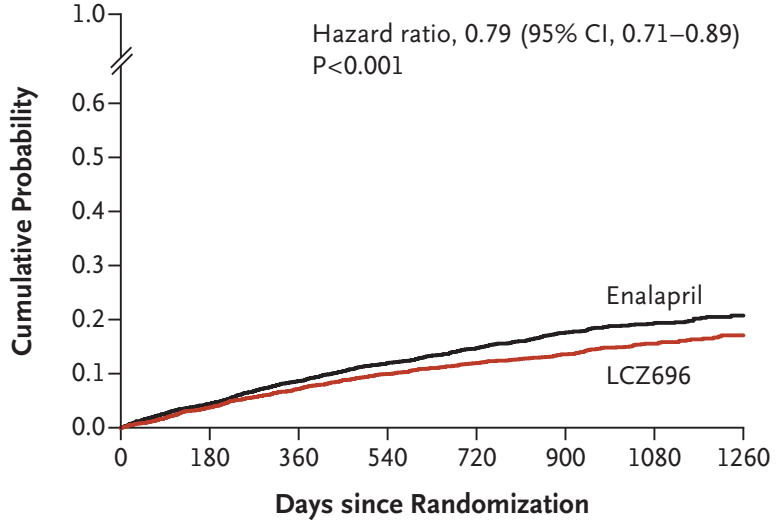
No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

B Death from Cardiovascular Causes



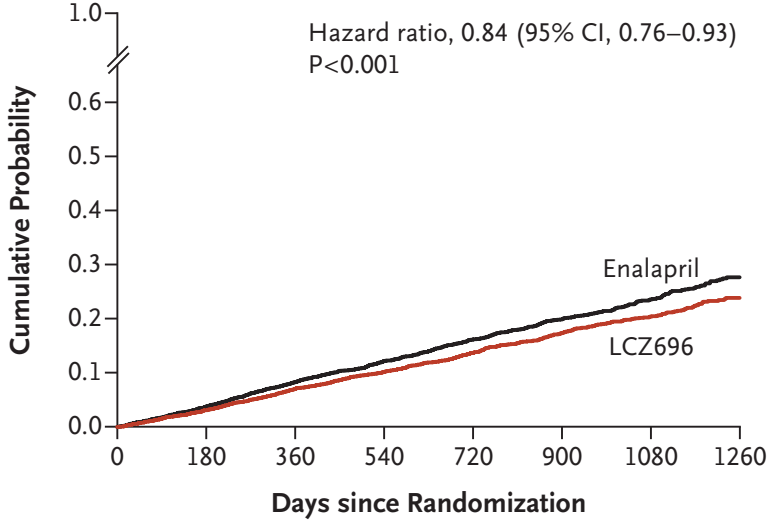
No. at Risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

C Hospitalization for Heart Failure



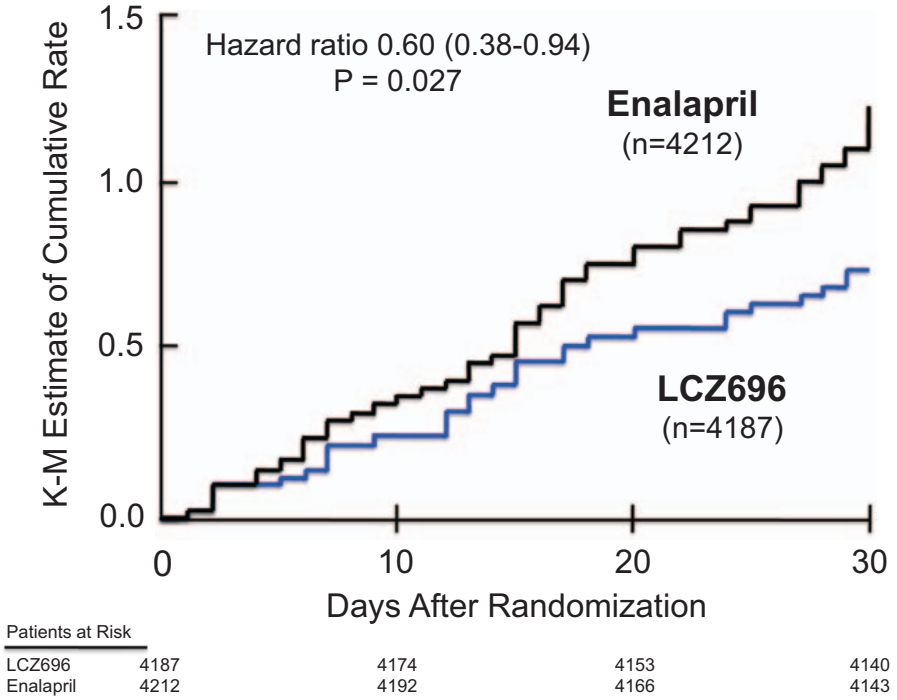
No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

D Death from Any Cause



No. at Risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

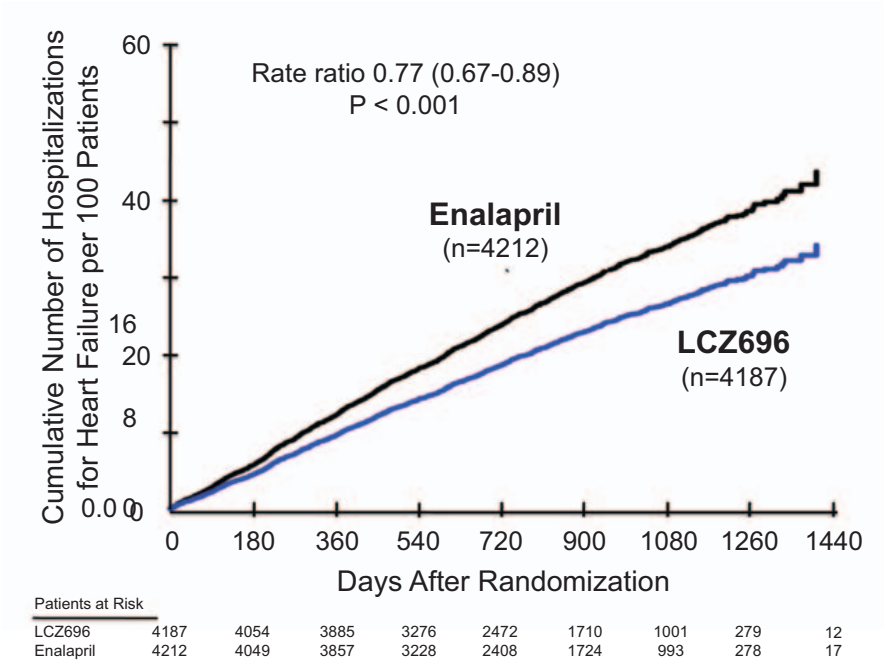
Time to 1st hosp (30 days)



Patients at Risk

LCZ696	4187	4174	4153	4140
Enalapril	4212	4192	4166	4143

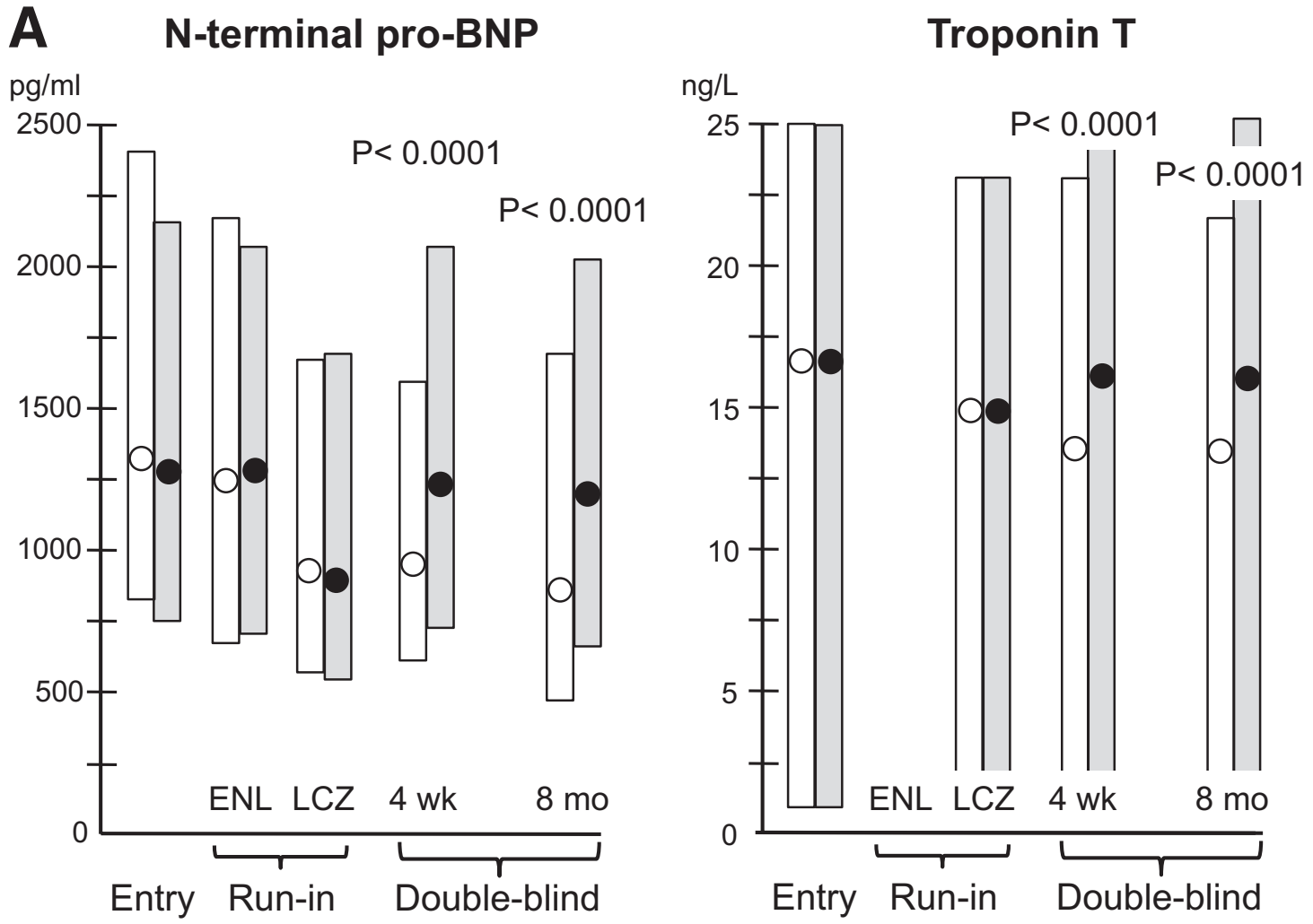
Total number of hospitalisations



Patients at Risk

LCZ696	4187	4054	3885	3276	2472	1710	1001	279	12
Enalapril	4212	4049	3857	3228	2408	1724	993	278	17

Packer, Circulation 2014



Packer, Circulation 2014

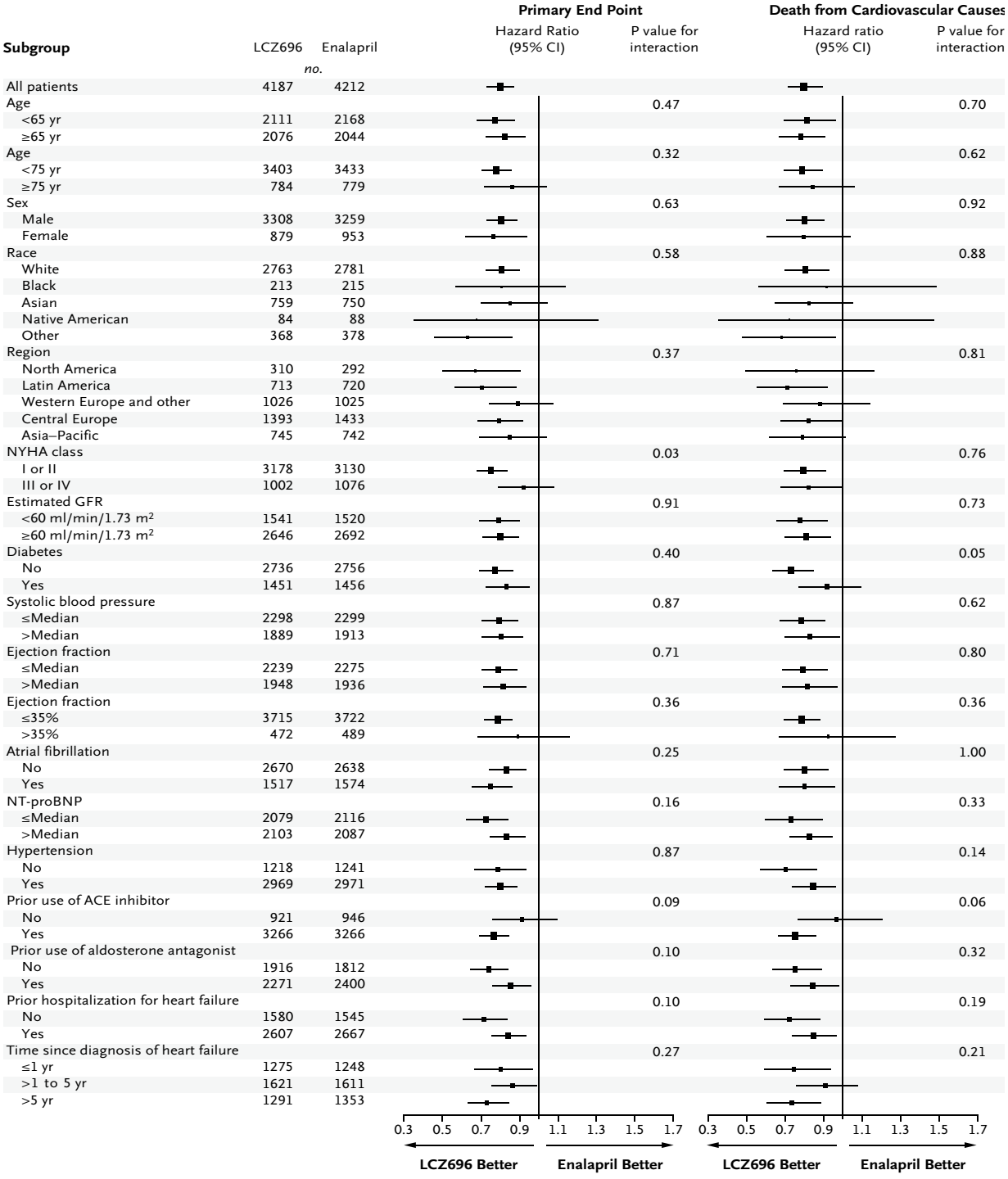
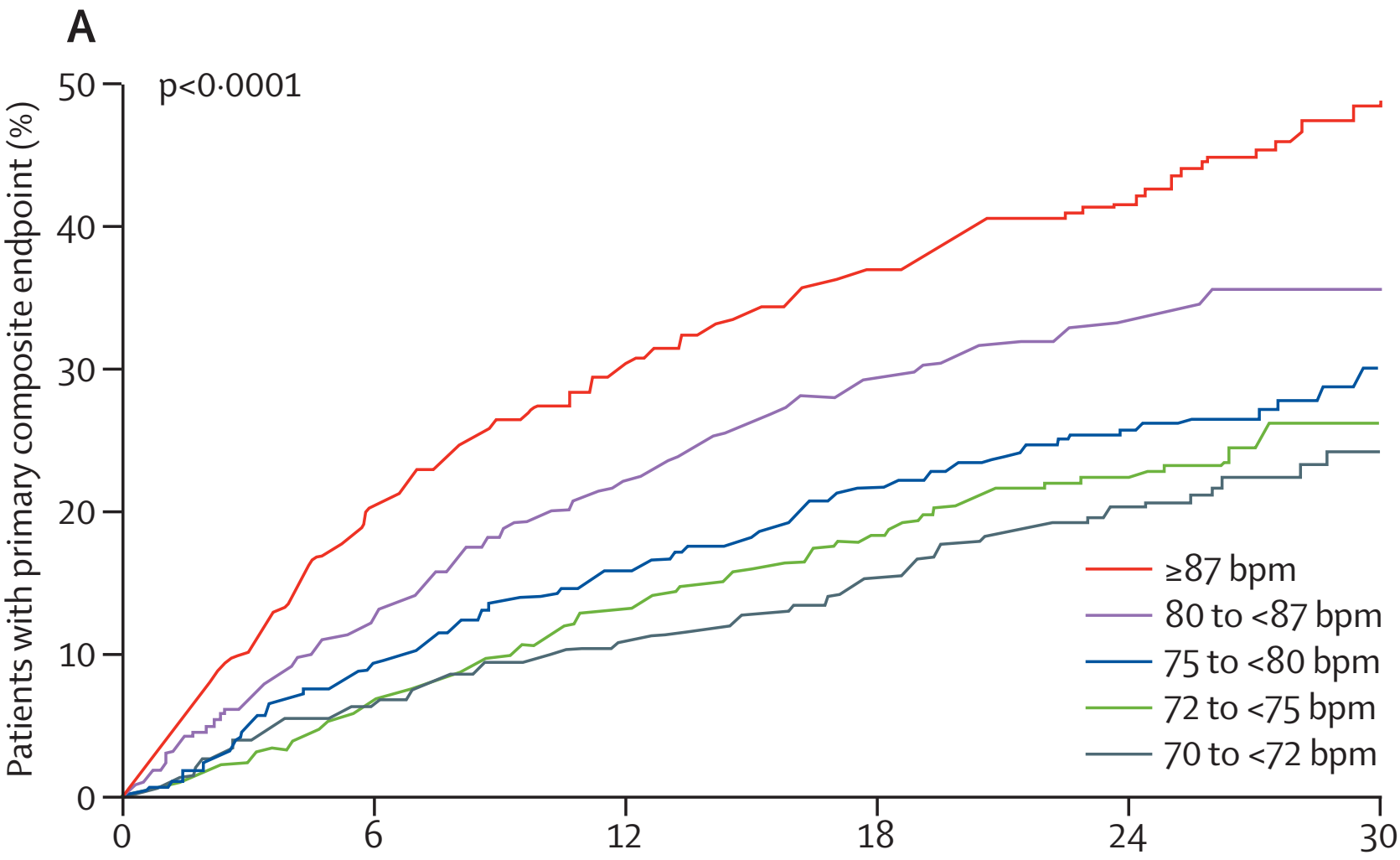

Primary End Point
Death from Cardiovascular Causes
Subgroup
LCZ696
Enalapril
no.
Hazard Ratio (95% CI)
P value for interaction
Hazard ratio (95% CI)
P value for interaction
All patients 4187 4212
Age 0.47 0.70
<65 yr 2111 2168
≥65 yr 2076 2044
Age 0.32 0.62
<75 yr 3403 3433
≥75 yr 784 779
Sex 0.63 0.92
Male 3308 3259
Female 879 953
Race 0.58 0.88
White 2763 2781
Black 213 215
Asian 759 750
Native American 84 88
Other 368 378
Region 0.37 0.81
North America 310 292
Latin America 713 720
Western Europe and other 1026 1025
Central Europe 1393 1433
Asia–Pacific 745 742
NYHA class 0.03 0.76
I or II 3178 3130
III or IV 1002 1076
Estimated GFR 0.91 0.73
<60 ml/min/1.73 m2 1541 1520
≥60 ml/min/1.73 m2 2646 2692
Diabetes 0.40 0.05
No 2736 2756
Yes 1451 1456
Systolic blood pressure 0.87 0.62
≤Median 2298 2299
>Median 1889 1913
Ejection fraction 0.71 0.80
≤Median 2239 2275
>Median 1948 1936
Ejection fraction 0.36 0.36
≤35% 3715 3722
>35% 472 489
Atrial fibrillation 0.25 1.00
No 2670 2638
Yes 1517 1574
NT-proBNP 0.16 0.33
≤Median 2079 2116
>Median 2103 2087
Hypertension 0.87 0.14
No 1218 1241
Yes 2969 2971
Prior use of ACE inhibitor 0.09 0.06
No 921 946
Yes 3266 3266
Prior use of aldosterone antagonist 0.10 0.32
No 1916 1812
Yes 2271 2400
Prior hospitalization for heart failure 0.10 0.19
No 1580 1545
Yes 2607 2667
Time since diagnosis of heart failure 0.27 0.21
≤1 yr 1275 1248
>1 to 5 yr 1621 1611
>5 yr 1291 1353
0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7
LCZ696 Better
Enalapril Better
0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7
LCZ696 Better
Enalapril Better

Table 3. Adverse Events during Randomized Treatment.*

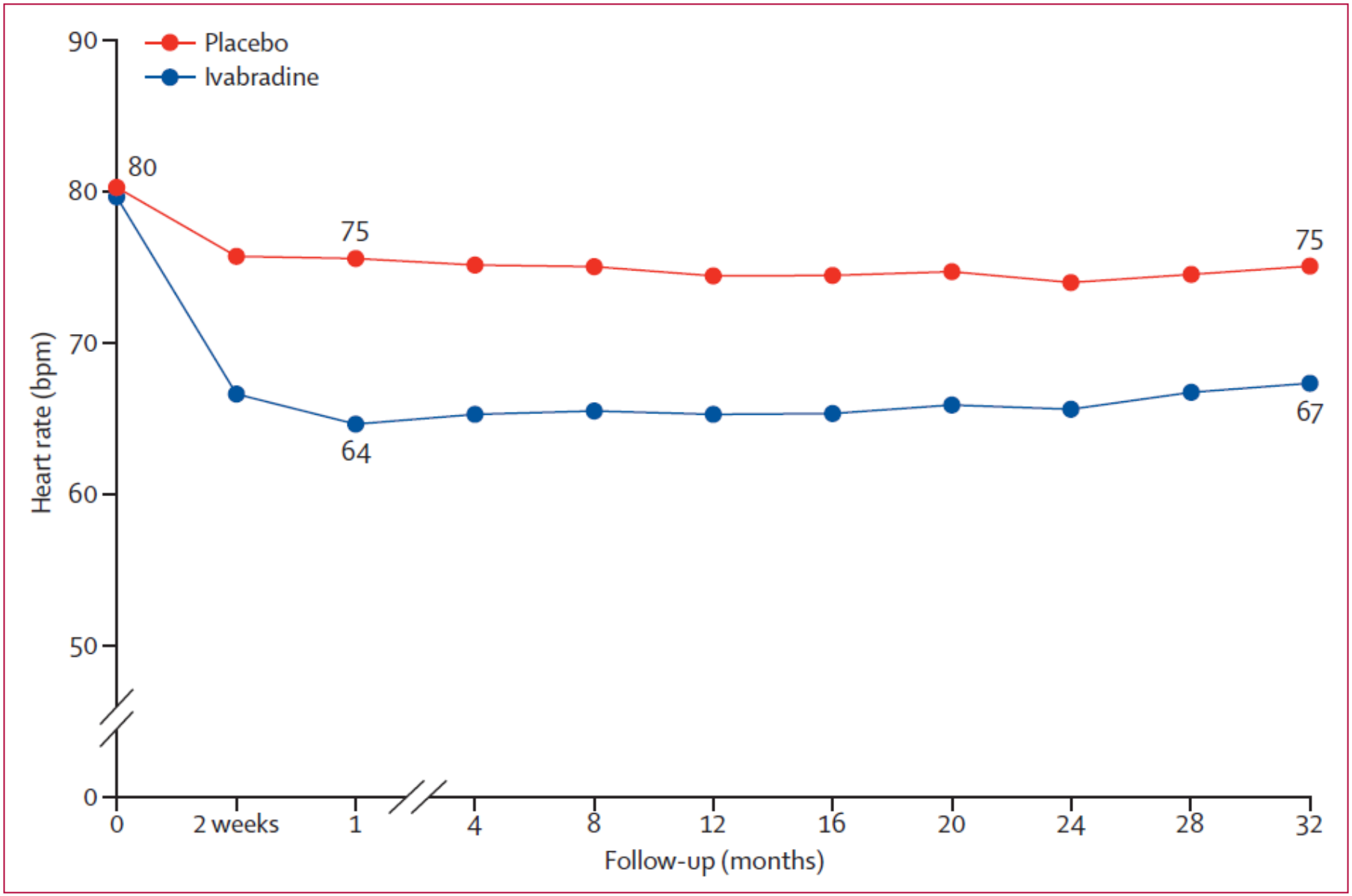
Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

Rôle de la fréquence cardiaque

Heart rate as a risk factor in CHF

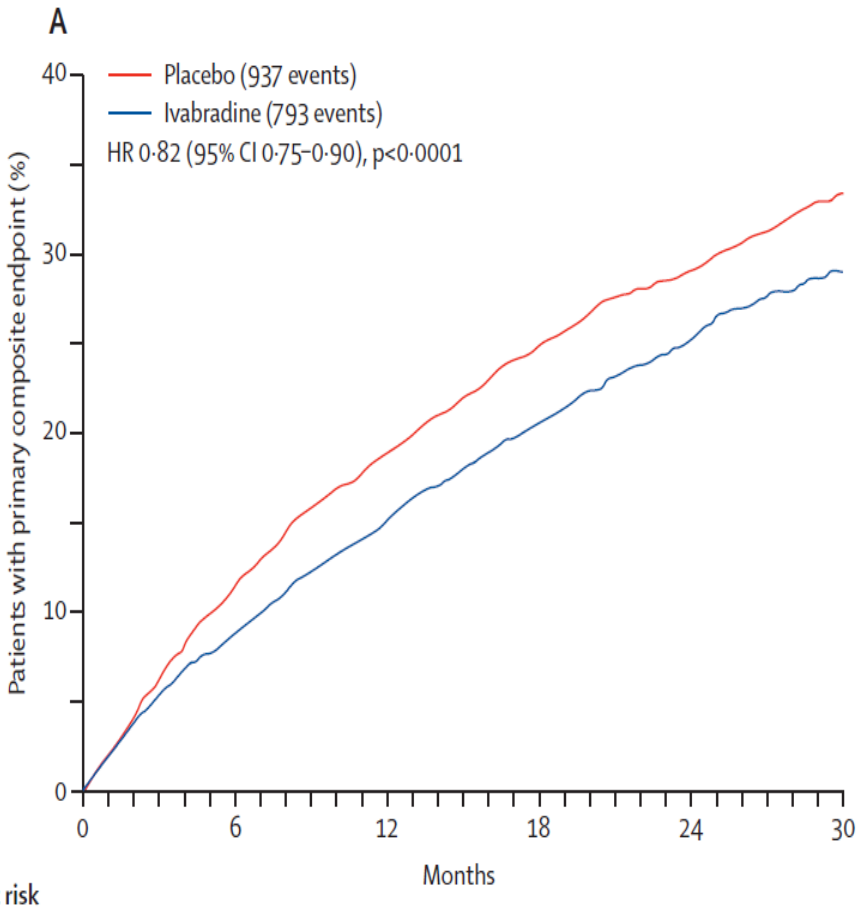


Boehm, Lancet 2010

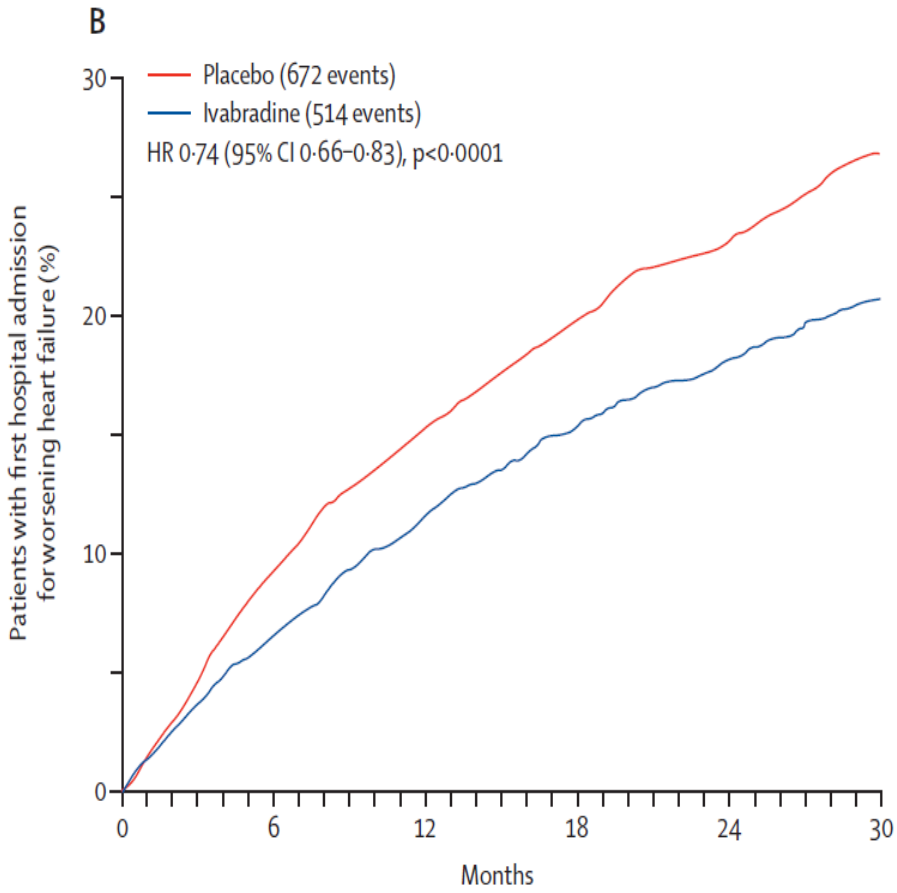


Swedberg, Lancet 2010

Décès ou Hosp IC



Hosp IC



Swedberg, Lancet 2010

Archives of Cardiovascular Disease (2014) **107**, 563—571

GUIDELINES

Diagnosis and treatment of iron deficiency in patients with heart failure: Expert position paper from French cardiologists

Diagnostic et traitement de la carence martiale chez les patients insuffisants cardiaques : le point de vue d'experts cardiologues français

Randomized placebo-controlled studies						
Toblli et al. (2007) [7]	40	Iron deficiency and anaemia	NYHA class II—IV; ejection fraction $\leq 35\%$	Iron sucrose	6 months	Reduction in NT-proBNP ($P < 0.01$) and CRP ($P < 0.01$); improvement in LVEF, NYHA functional class, exercise capacity, renal function and quality of life (all $P < 0.01$)
Okonko et al. (2008) (FERRIC-HF study) [6]	35	Iron deficiency with and without anaemia	NYHA class II—III	Iron sucrose (928 ± 219 mg)	18 weeks	Increase in pVO_2/kg ($P = 0.01$); improvement in NYHA functional class ($P = 0.007$) and patient global assessment ($P = 0.002$)
Anker et al. (2009) (FAIR-HF study) [4]	459	Iron deficiency with or without anaemia	NYHA class II—III	Ferric carboxymaltose (1850 ± 433 mg)	24 weeks	Improvement in patient global assessment and NYHA functional class (primary criteria; $P < 0.001$); improvement in 6-minute walk distance and quality of life ($P < 0.001$); similar effect in patients with or without anaemia

European Heart Journal (2015) **36**, 657–668
doi:10.1093/eurheartj/ehu385

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

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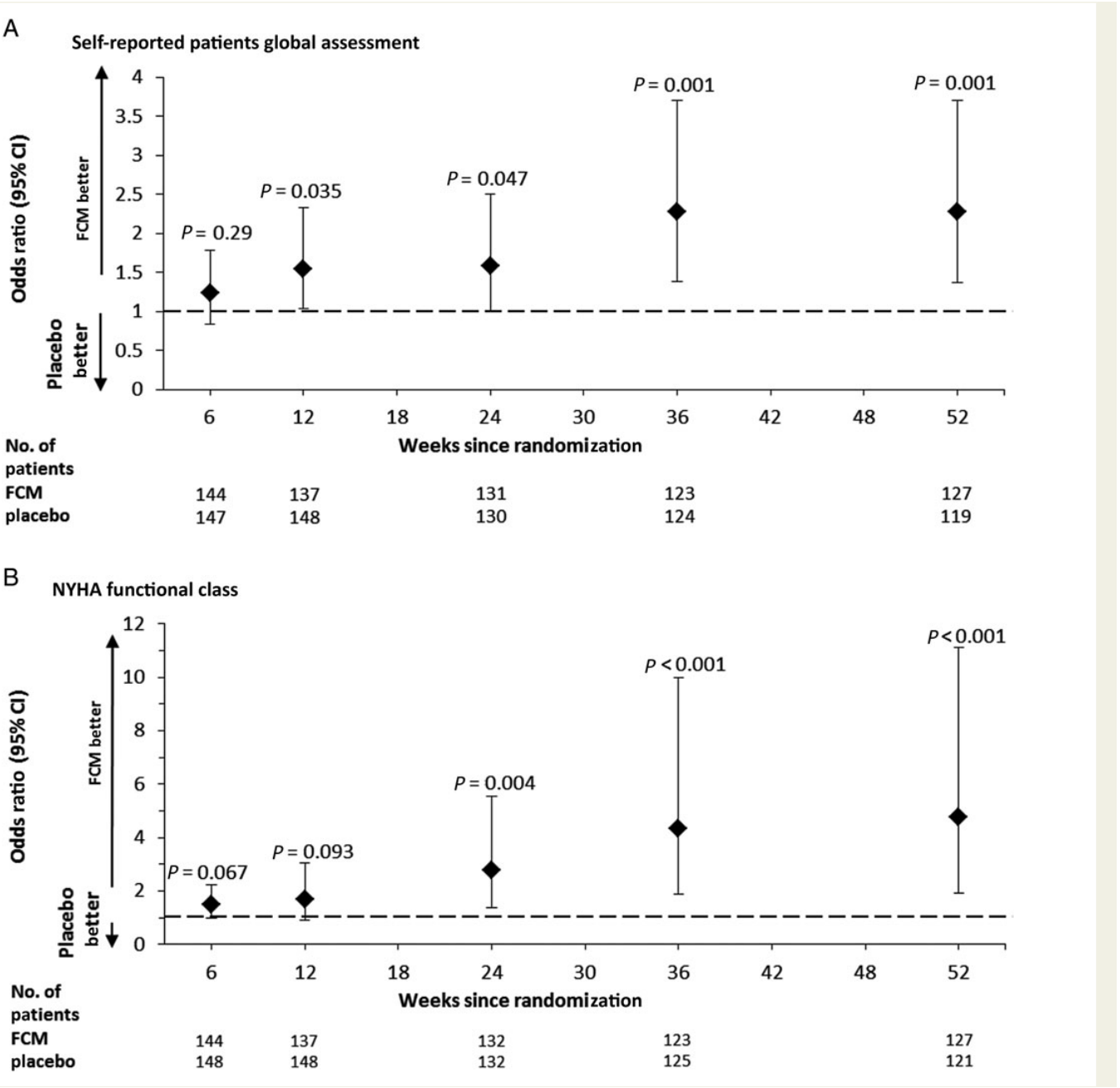
Ferritine < 100 ng/ml ou si entre 100 et 300 ng/ml, saturation transferrine < 20 %



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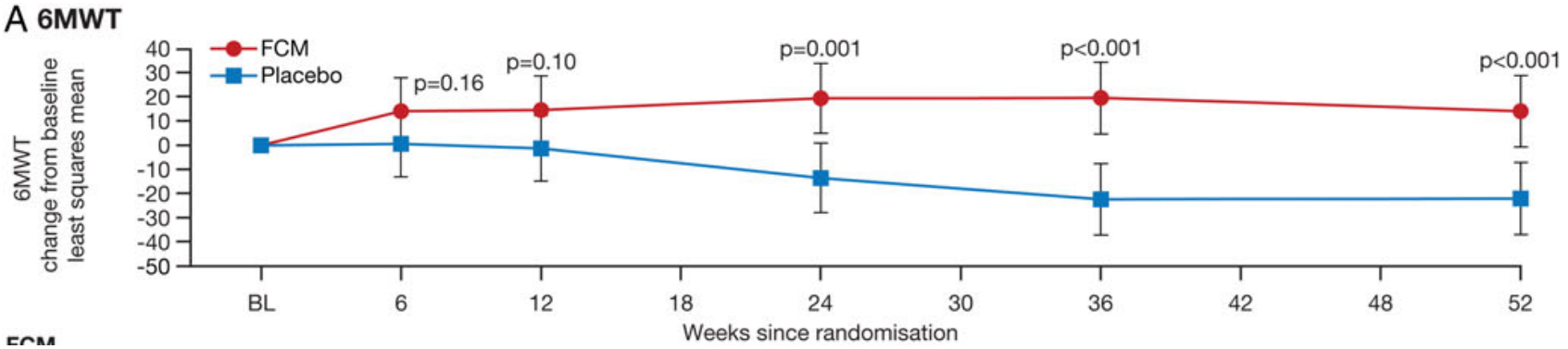

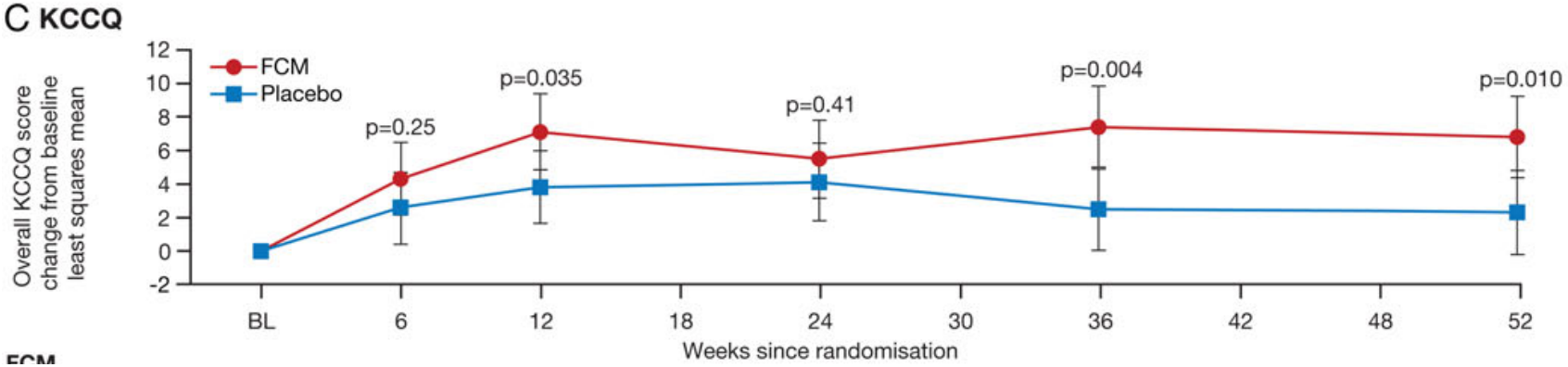

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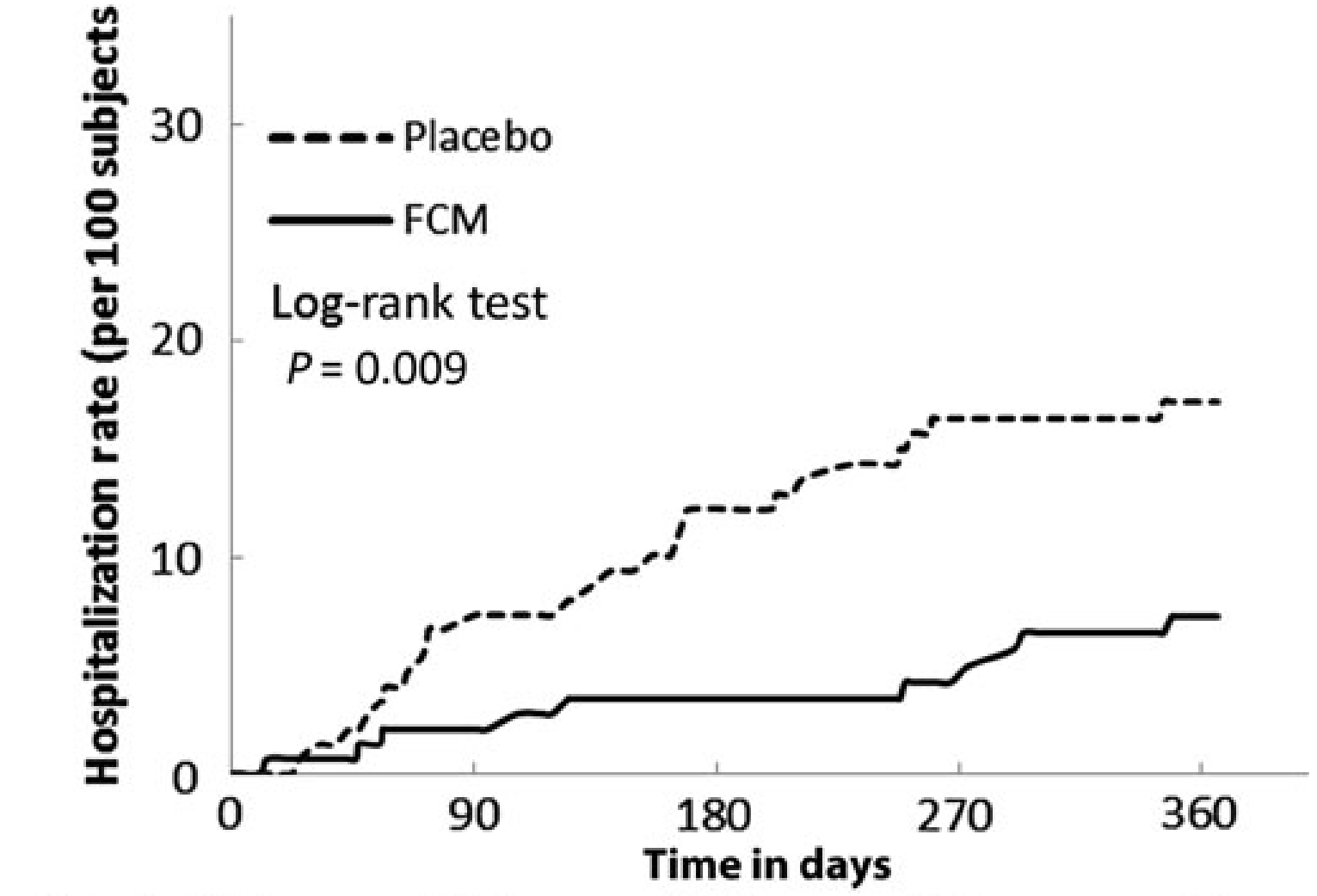

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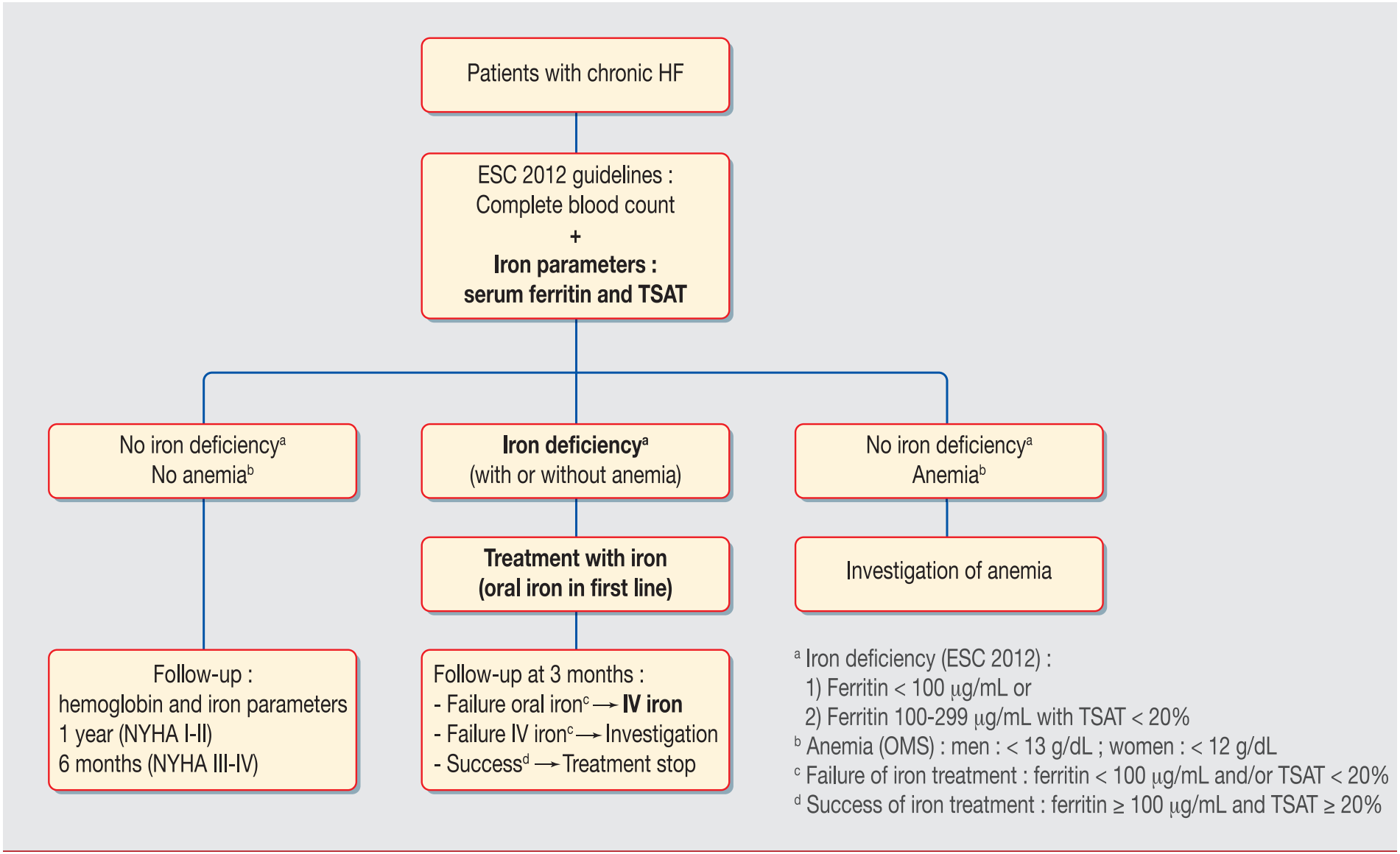

Patients with chronic HF
ESC 2012 guidelines :
Complete blood count
+
Iron parameters :
serum ferritin and TSAT
No iron deficiency[a]
No anemia[b]
Iron deficiency[a]
(with or without anemia)
No iron deficiency[a]
Anemia[b]
Treatment with iron
(oral iron in first line)
Investigation of anemia
Follow-up :
hemoglobin and iron parameters
1 year (NYHA I-II)
6 months (NYHA III-IV)
Follow-up at 3 months :
- Failure oral iron[c] → IV iron
- Failure IV iron[c] → Investigation
- Success[d] → Treatment stop
[a] Iron deficiency (ESC 2012) :
1) Ferritin < 100 µg/mL or
2) Ferritin 100-299 µg/mL with TSAT < 20%
[b] Anemia (OMS) : men : < 13 g/dL ; women : < 12 g/dL
[c] Failure of iron treatment : ferritin < 100 µg/mL and/or TSAT < 20%
[d] Success of iron treatment : ferritin ≥ 100 µg/mL and TSAT ≥ 20%

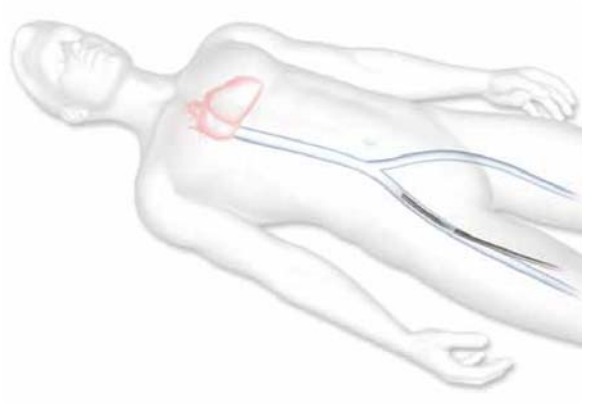
Les échecs dans l'IC à FE basse

- Les inotropes (Essential, Atomic)
- Les vasodilatateurs purs: flosequinan (Profile)
- Inhibiteurs de la rénine (aliskiren) (Astronaut)
- Omapatrilat (Overture)
- Les anti-endothélines: bosentan (Reach)
- Les anti TNF (recover, renaissance)
- Les statines (corona)
- L'EPO (Red-HF)

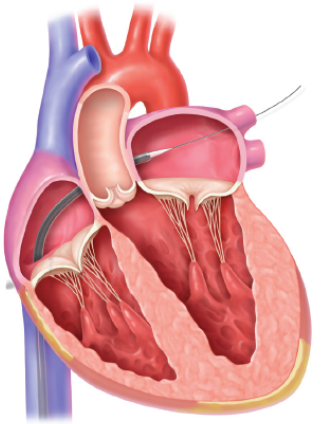
MITRACLIP

Procedural Overview

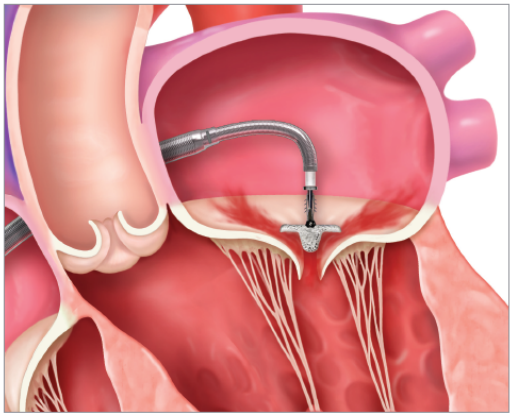
Patient and System Preparation

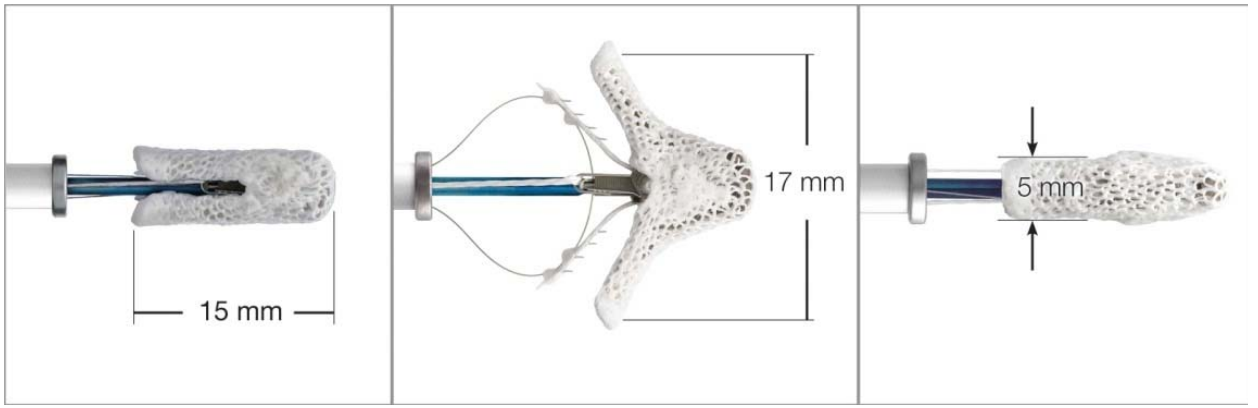


Transseptal Crossing and Guide Insertion

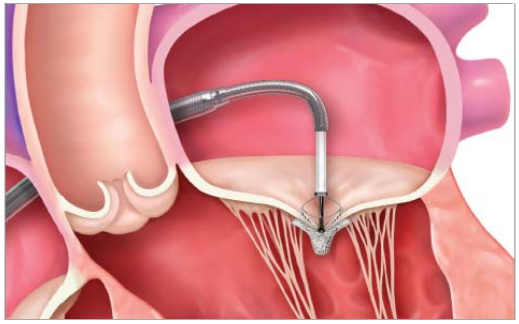


Clip Delivery System Insertion and Steering in the Left Atrium

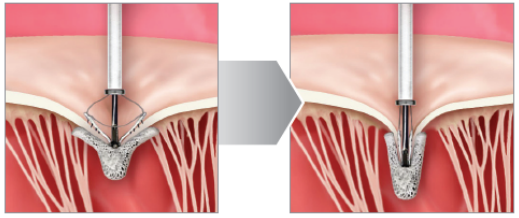




Advancing into Left Ventricle and Leaflet Grasping



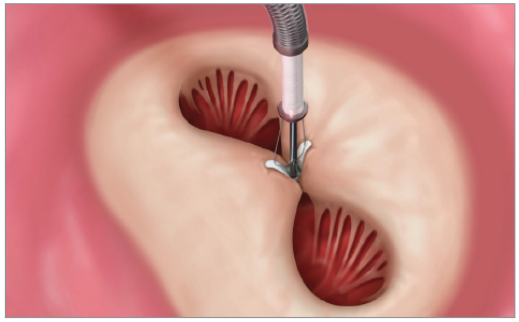
After the Clip is aligned over the regurgitant jet in the left atrium, the System is then advanced into the left ventricle to begin the grasping procedure. Leaflet grasping is done by slowly retracting the System back towards the left atrium to allow the leaflets to come to rest on the Clip Arms and then dropping the Grippers.



Clip Arms closed to 120º

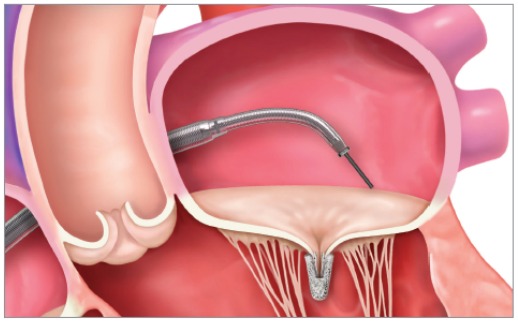
Clip Arms closed to 20º

Leaflet Insertion Assessment and Hemodynamic Measurements

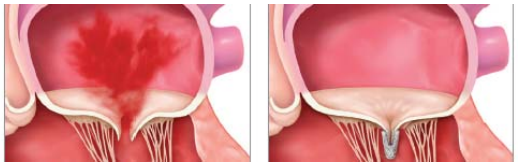


Prior to Clip closure and deployment, a leaflet insertion and hemodynamic assessment must be performed. The leaflet insertion assessment ensures both leaflets are fully inserted and secure into the Clip. In addition, the MR reduction and pressure gradients are assessed to ensure regurgitation reduction without stenosis.

Deployment and System Removal



Once the assessments are positive, the Clip can be fully closed and deployed in a multistep process. The physician may also decide to place a second Clip to optimize MR reduction. The System is removed by releasing deflections on the catheter and slowly removing from the patient. Groin management and continued medical therapy are recommended per the institution's guidelines.



IC à FE préservée

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Spironolactone for Heart Failure with Preserved Ejection Fraction

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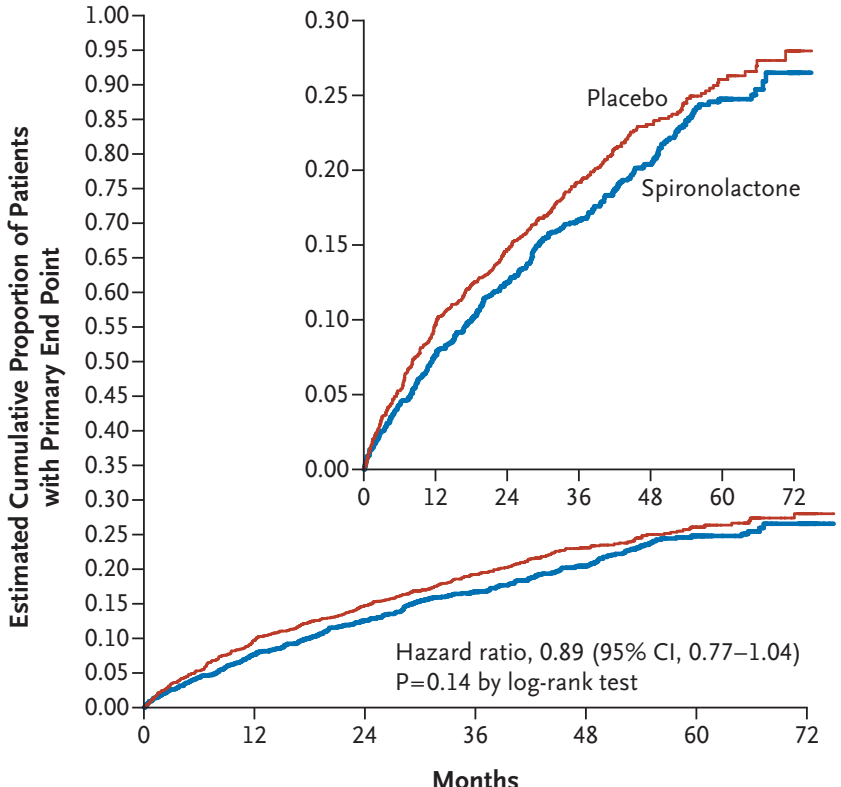
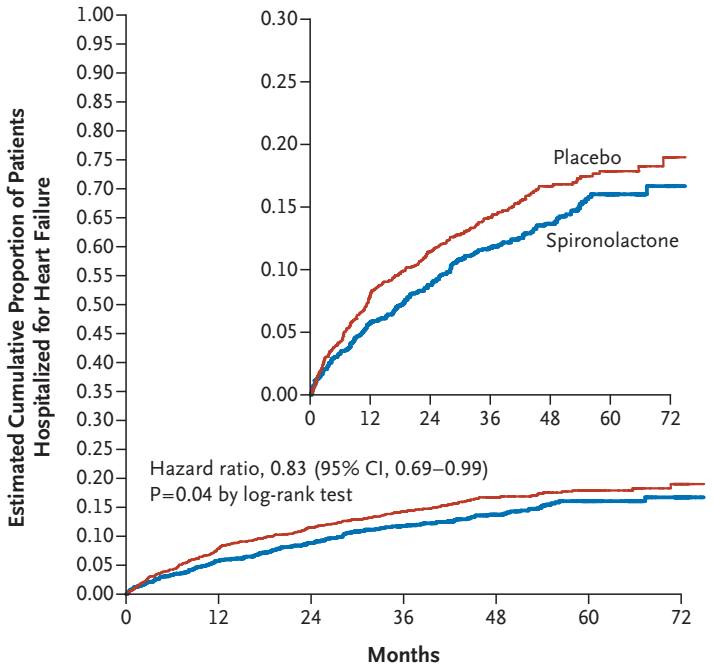
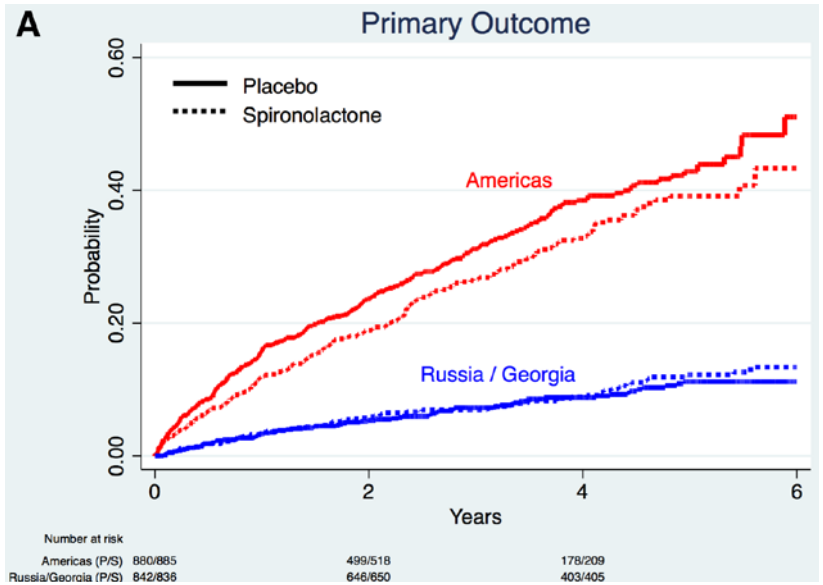
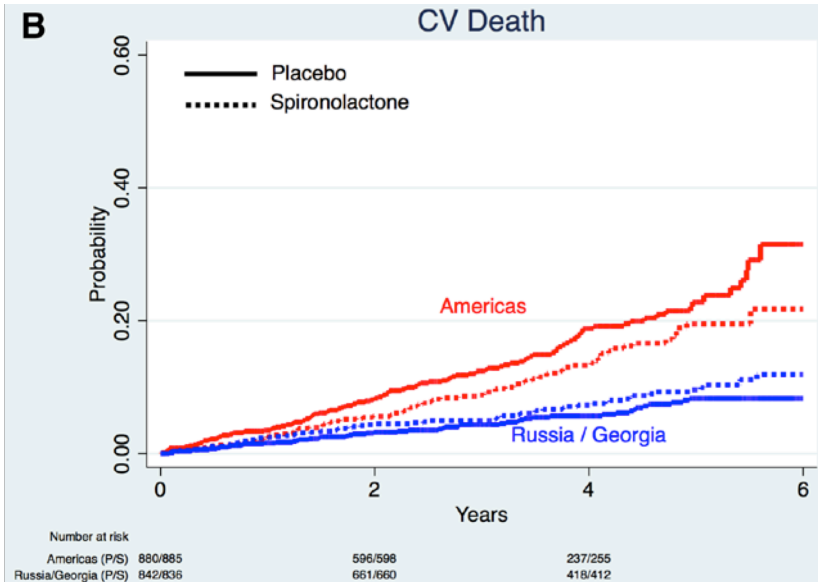
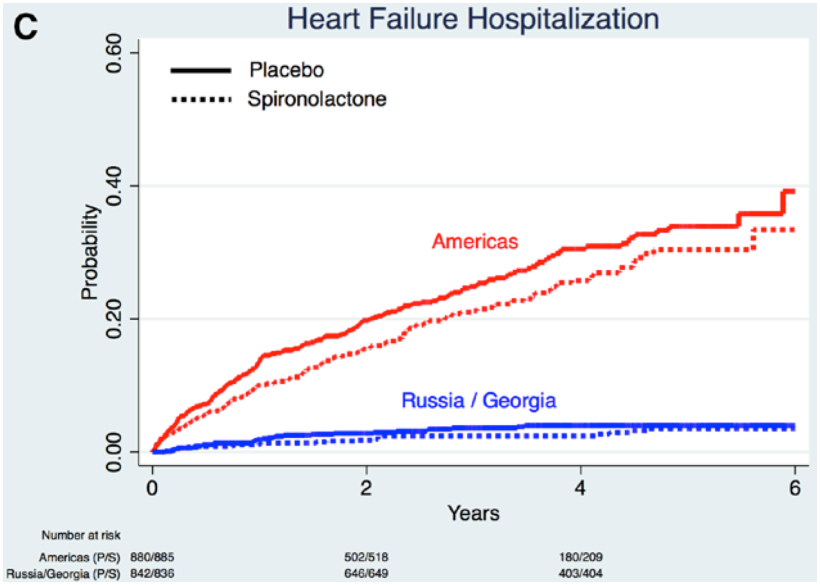




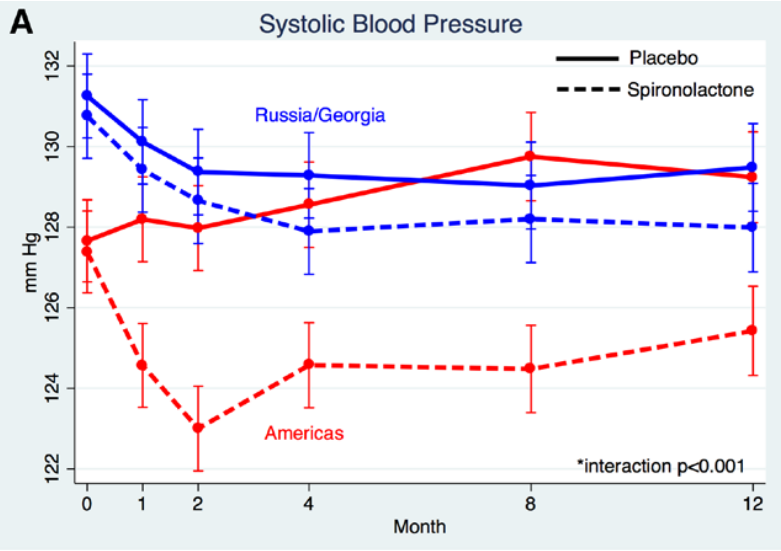
Variations régionales

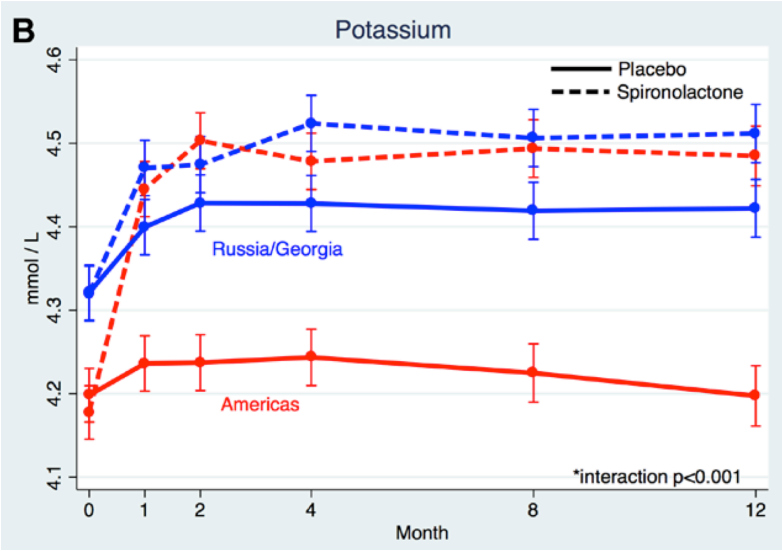


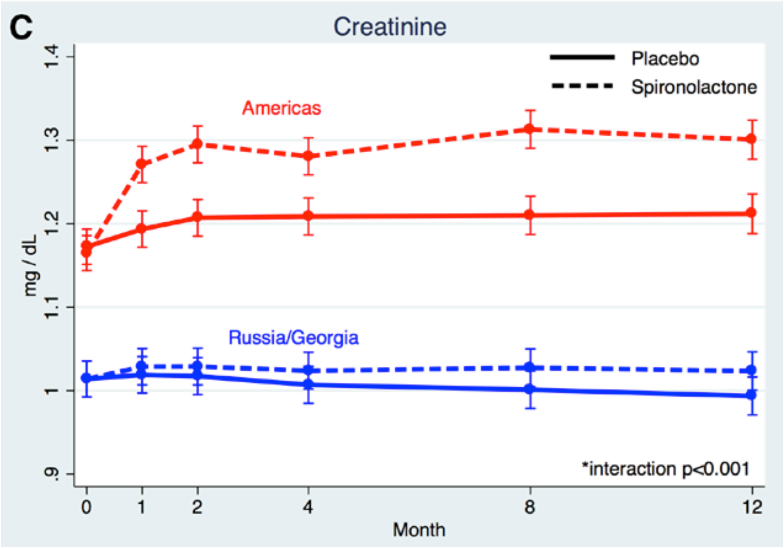




Autres effets







Month 8 Reported Daily Dose, mg	Americas, n (%)		Russia/Georgia, n (%)		*P*, Treatment-Region Interaction
	Spironolactone (n=866)	Placebo (n=846)	Spironolactone (n=823)	Placebo (n=830)	
0	212 (24.5)	160 (18.9)	59 (7.2)	61 (7.3)	
15	194 (22.4)	105 (12.4)	83 (10.1)	38 (4.6)	
30	319 (36.8)	386 (45.6)	570 (69.3)	597 (71.9)	
45	141 (16.3)	195 (23.0)	111 (13.5)	134 (16.1)	
Average dose, mg	21.7	25.9	28.4	29.5	0.001