TRAITEMENT MÉDICAL DE L'INSUFFISANCE CARDIAQUE

Les recommandations

P Gibelin

Nice

LES RECOMMANDATIONS ESH 2012

European Heart Journal
doi:10.1093/eurheartj/ehs104

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

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

Authors/Task Force Members: John J. V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y. H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).

Principales modifications entre 2008 et 2012

1. Une extension de l'indication des MRA

2. Nouvelle indication pour ivabradine

Traitement de base

- **Diurétique**

  Posologie minimale nécessaire pour contrôler la surcharge
- **IEC**
- **Bêta-bloquant**
- **Antagoniste des récepteurs minéralocorticoïdes**
- **Ivabradine (quand FC ≥70 bpm)**

Une confirmation

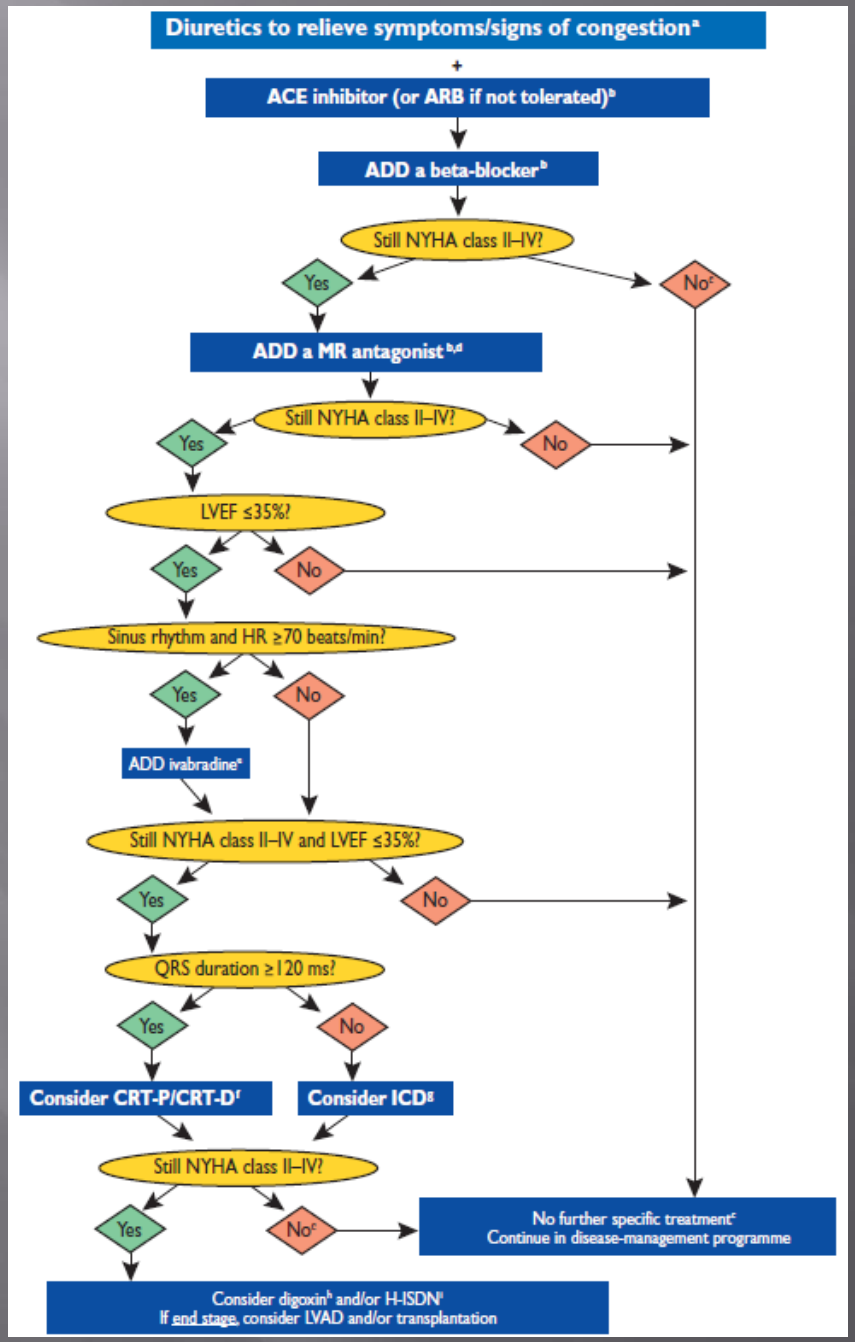
- **Place limitée pour les ARA II**

  - Toux sous IEC

  - En cas d'amélioration insuffisante, l'association IEC- AA remplace l'association IEC-ARA II

  - Association IEC-ARAII uniquement si AA mal toléré

  - Trithérapie IEC-AA-ARA II contre-indiquée


Diuretics to relieve symptoms/signs of congestion[a]
+
ACE inhibitor (or ARB if not tolerated)[b]
ADD a beta-blocker[b]
Still NYHA class II–IV?
Yes
No[c]
ADD a MR antagonist[b,d]
Still NYHA class II–IV?
Yes
No
LVEF ≤35%?
Yes
No
Sinus rhythm and HR ≥70 beats/min?
Yes
No
ADD ivabradine[e]
Still NYHA class II–IV and LVEF ≤35%?
Yes
No
QRS duration ≥120 ms?
Yes
No
Consider CRT-P/CRT-D[f]
Consider ICD[g]
Still NYHA class II–IV?
Yes
No[c]
No further specific treatment[c]
Continue in disease-management programme
Consider digoxin[h] and/or H-ISDN[i]
If end stage, consider LVAD and/or transplantation

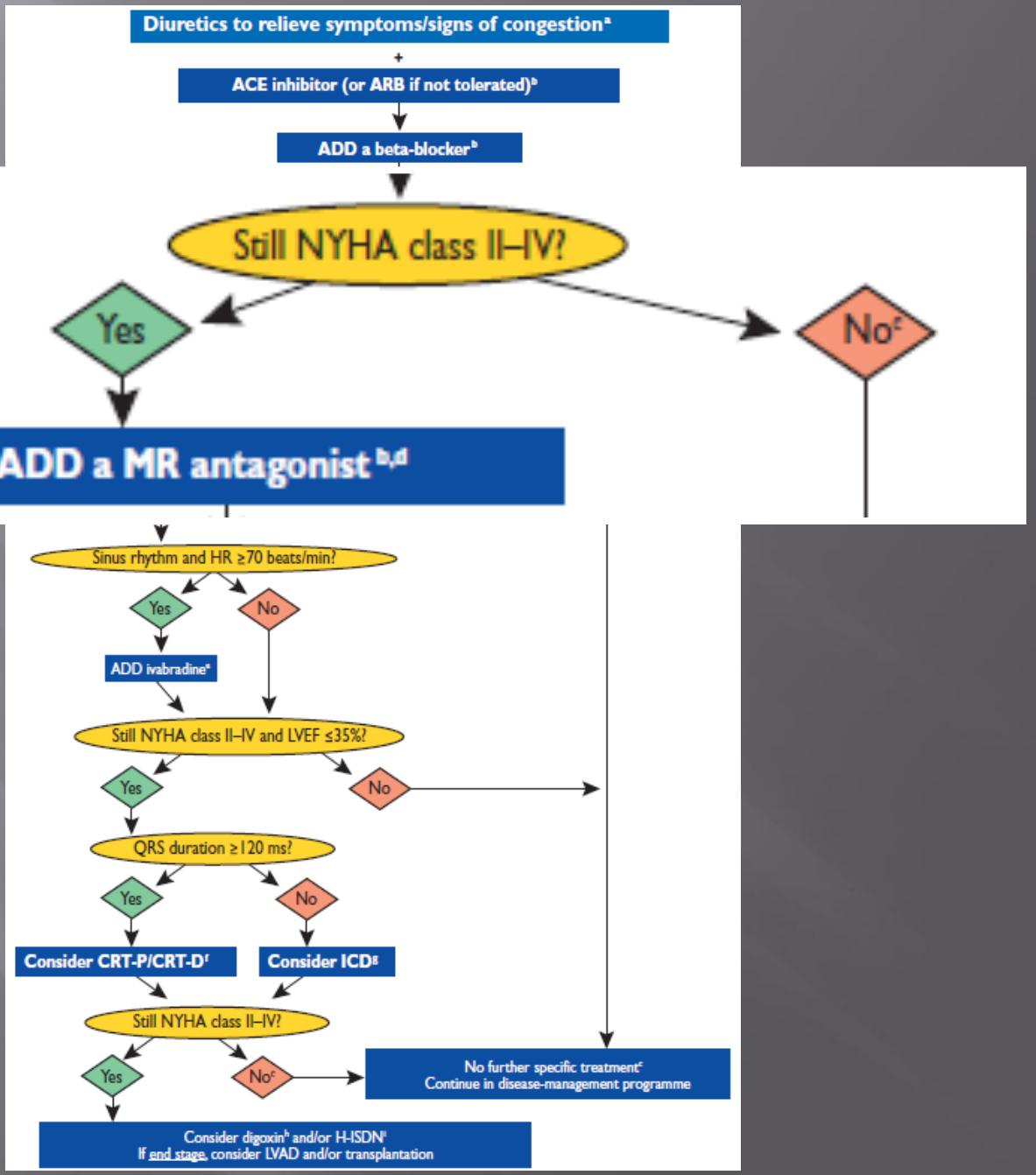
IEC / Bêta-bloquant en pratique

Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II–IV) systolic heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
An ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	87–91
A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	92–98

Table 14 Evidence-based doses of disease-modifying drugs used in key randomized trials in heart failure (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE inhibitor		
Captopril[a]	6.25 t.i.d.	50 t.i.d.
Enalapril	2.5 b.i.d.	10–20 b.i.d.
Lisinopril[a]	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
Trandolapril[a]	0.5 o.d.	4 o.d.
Beta-blocker		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25–50 b.i.d.
Metoprolol succinate (CR/XL)	12.5/25 o.d.	200 o.d.
Nebivolol[c]	1.25 o.d.	10 o.d.
ARB		
Candesartan	4 or 8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan[b,c]	50 o.d.	150 o.d.


Diuretics to relieve symptoms/signs of congestion[a]
+
ACE inhibitor (or ARB if not tolerated)[b]
ADD a beta-blocker[b]
Still NYHA class II–IV?
Yes
No[c]
ADD a MR antagonist[b,d]
Sinus rhythm and HR ≥70 beats/min?
Yes
No
ADD ivabradine[e]
Still NYHA class II–IV and LVEF ≤35%?
Yes
No
QRS duration ≥120 ms?
Yes
No
Consider CRT-P/CRT-D[f]
Consider ICD[g]
Still NYHA class II–IV?
Yes
No[c]
No further specific treatment[c]
Continue in disease-management programme
Consider digoxin[h] and/or H-ISDN[i]
If end stage, consider LVAD and/or transplantation

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*

Age > 55 years

NYHA class II

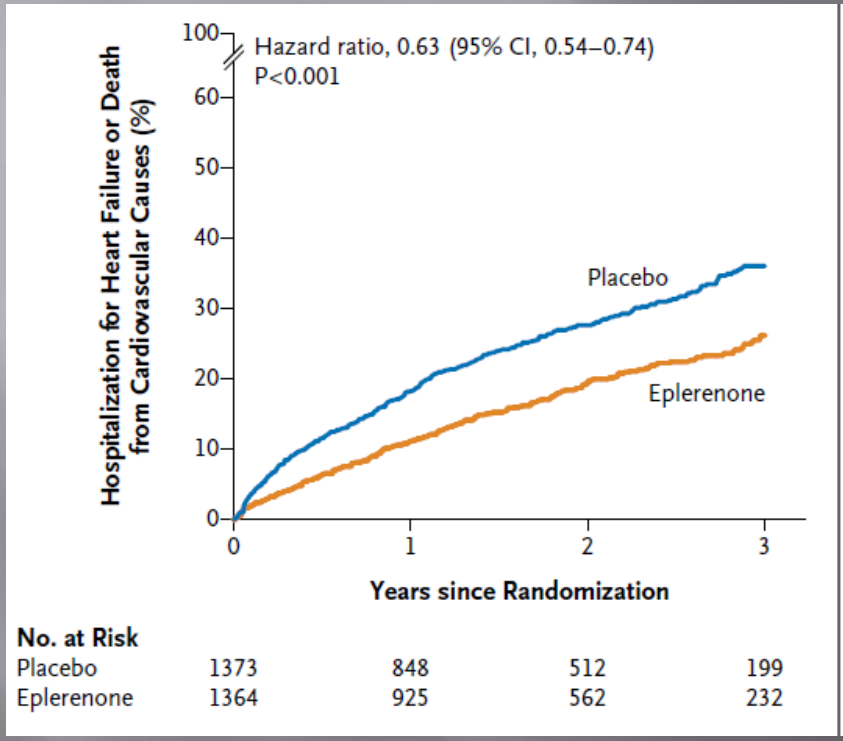
LVEF: < 30% or 30-35% with QRS > 130 ms

Exclusion: serum K level < 5 mmom/l and GFR < 30ml/mn

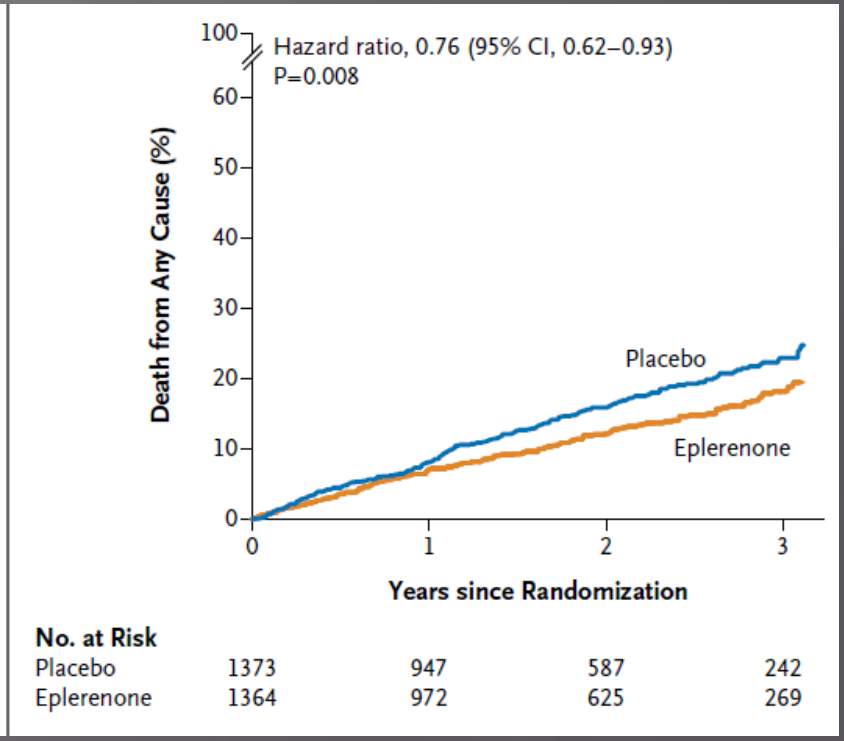
EMPHASIS-HF Trial

Characteristic	Eplerenone (N=1364)	Placebo (N=1373)
Age — yr	68.7±7.7	68.6±7.6
Female sex — no. (%)	309 (22.7)	301 (21.9)
Race — no. (%)†		
White	1127 (82.6)	1141 (83.1)
Black	37 (2.7)	30 (2.2)
Asian	158 (11.6)	158 (11.5)
Other	42 (3.1)	44 (3.2)
Heart rate — beats/min	72±12	72±13
Medication — no. (%)		
Diuretic	1150 (84.3)	1176 (85.7)
ACE inhibitor	1068 (78.3)	1057 (77.0)
ARB	262 (19.2)	267 (19.4)
ACE inhibitor, ARB, or both	1282 (94.0)	1275 (92.9)
Beta-blocker	1181 (86.6)	1193 (86.9)
Digitalis glycosides	363 (26.6)	377 (27.5)
Antiarrhythmic drug	196 (14.4)	192 (14.0)
Antithrombotic drug (antiplatelet or oral anticoagulant)	1205 (88.3)	1214 (88.4)
Lipid-lowering agent	857 (62.8)	856 (62.3)

EMPHASIS-HF Trial

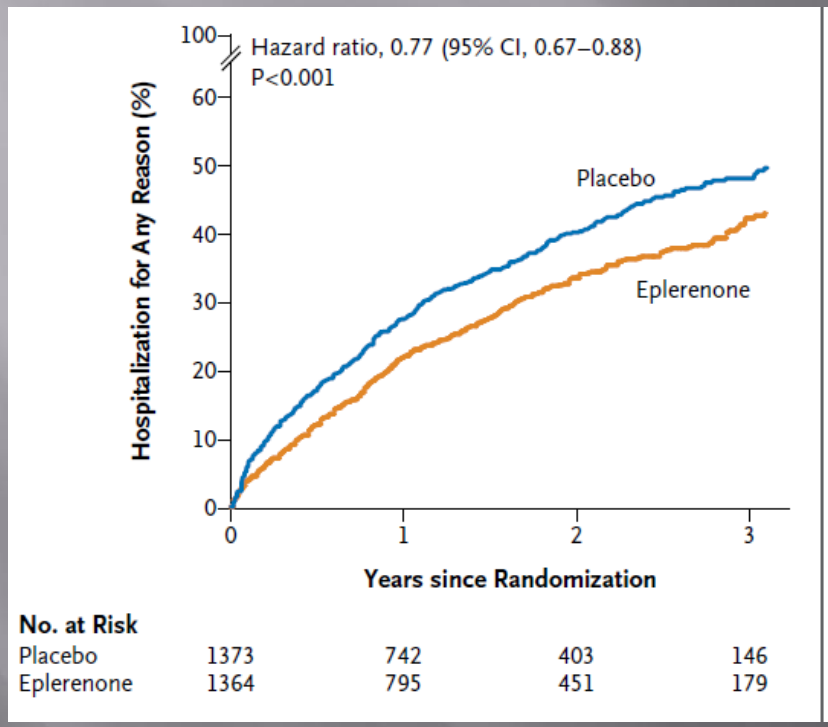


No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

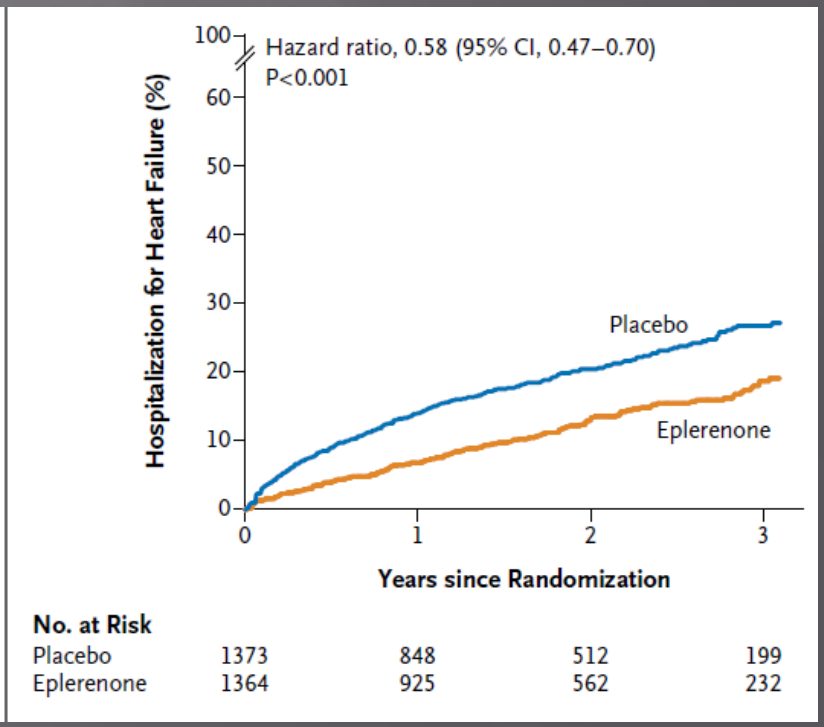


No. at Risk				
Placebo	1373	947	587	242
Eplerenone	1364	972	625	269

EMPHASIS-HF Trial



No. at Risk				
Placebo	1373	742	403	146
Eplerenone	1364	795	451	179

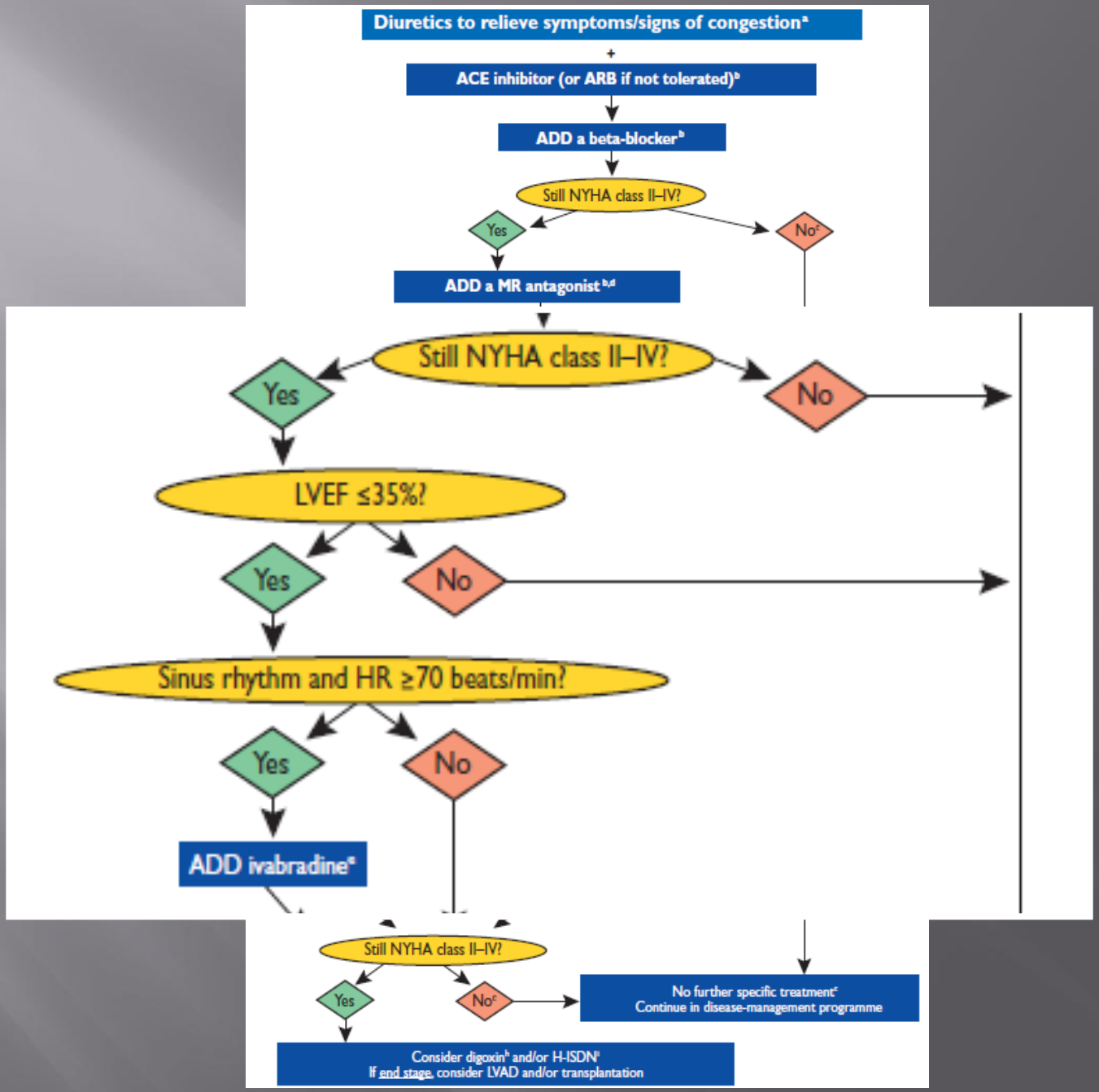


No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

Anti-aldostérone en pratique

An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death.	I	A

MRA		
Eplerenone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	25–50 o.d.

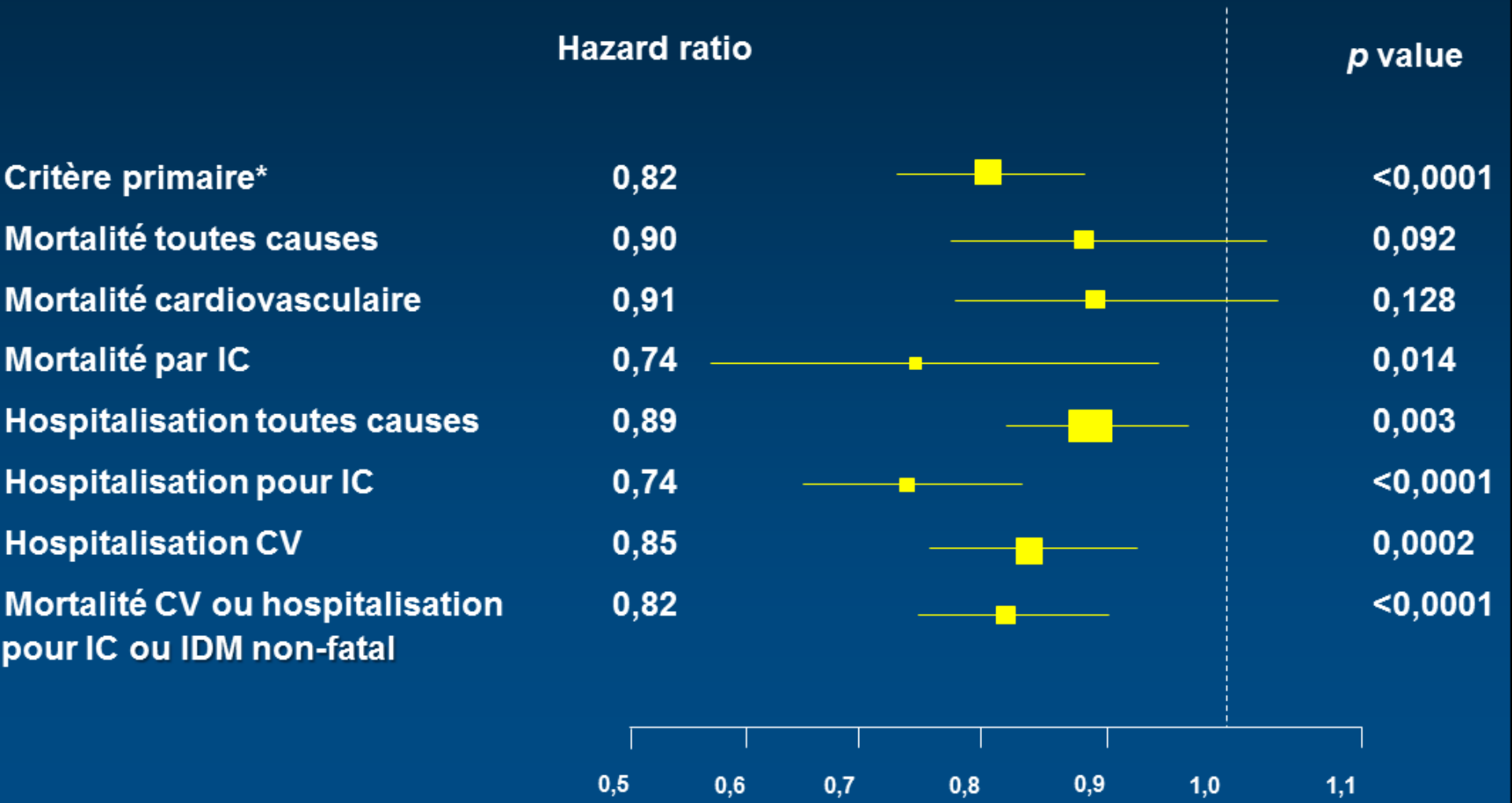

Diuretics to relieve symptoms/signs of congestion[a]
+
ACE inhibitor (or ARB if not tolerated)[b]
ADD a beta-blocker[b]
Still NYHA class II–IV?
Yes
No[c]
ADD a MR antagonist[b,d]
Still NYHA class II–IV?
Yes
No
LVEF ≤35%?
Yes
No
Sinus rhythm and HR ≥70 beats/min?
Yes
No
ADD ivabradine[e]
Still NYHA class II–IV?
Yes
No[c]
No further specific treatment[c]
Continue in disease-management programme
Consider digoxin[b] and/or H-ISDN[f]
If end stage, consider LVAD and/or transplantation

Critères d'inclusion

- ≥18 ans
- Classe II à IV à la classification NYHA
- Origine ischémique/non- ischémique
- Dysfonction systolique ventriculaire gauche (FE ≤35%)
- **Fréquence cardiaque ≥70 bpm**
- Rythme sinusal
- Hospitalisation pour aggravation d'une insuffisancec cardiaque ≤12 months documentée

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81.

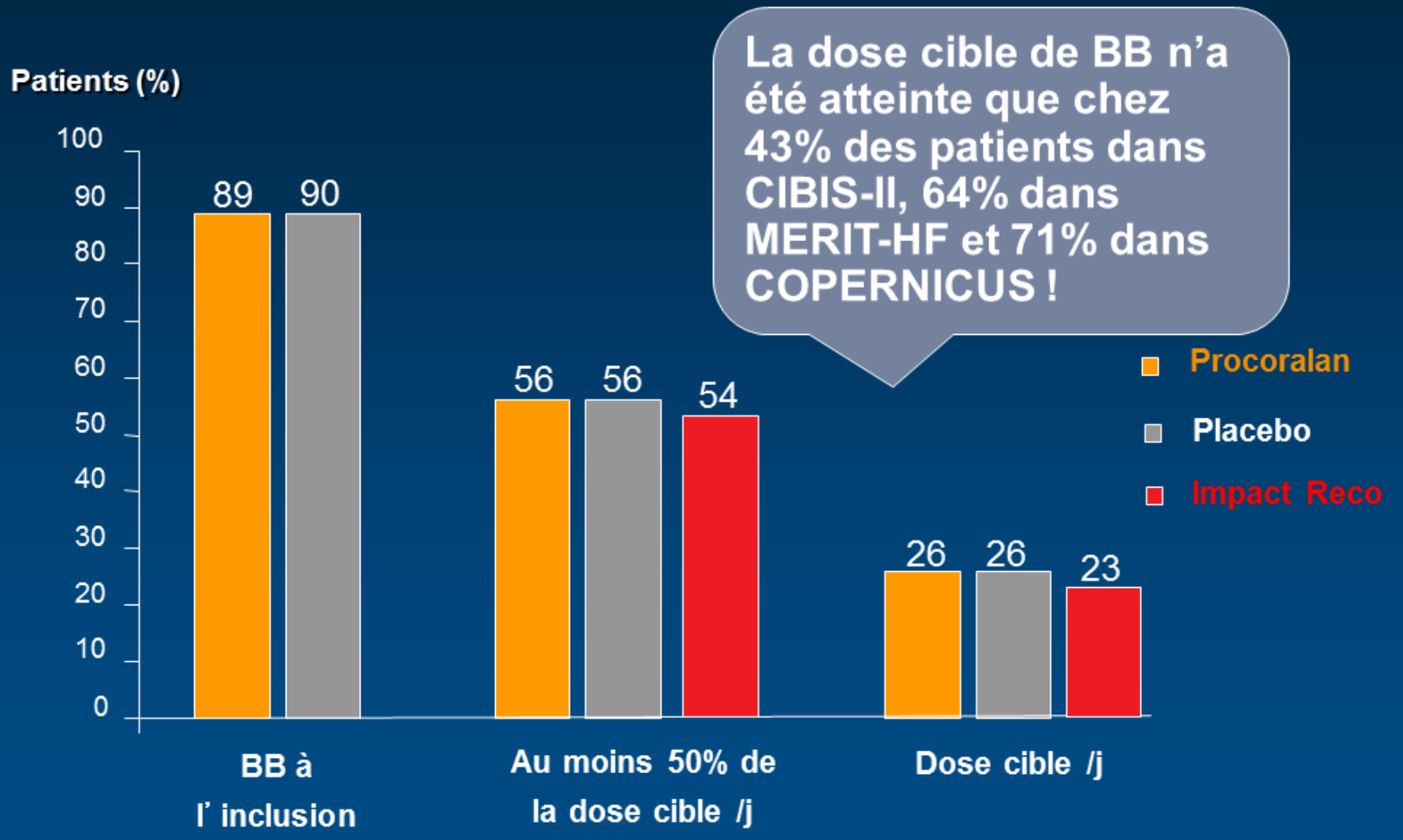
Principaux résultats de SHIFT : Effet de Procoralan sur les évènements



*Mortalité CV ou hospitalisation pour IC

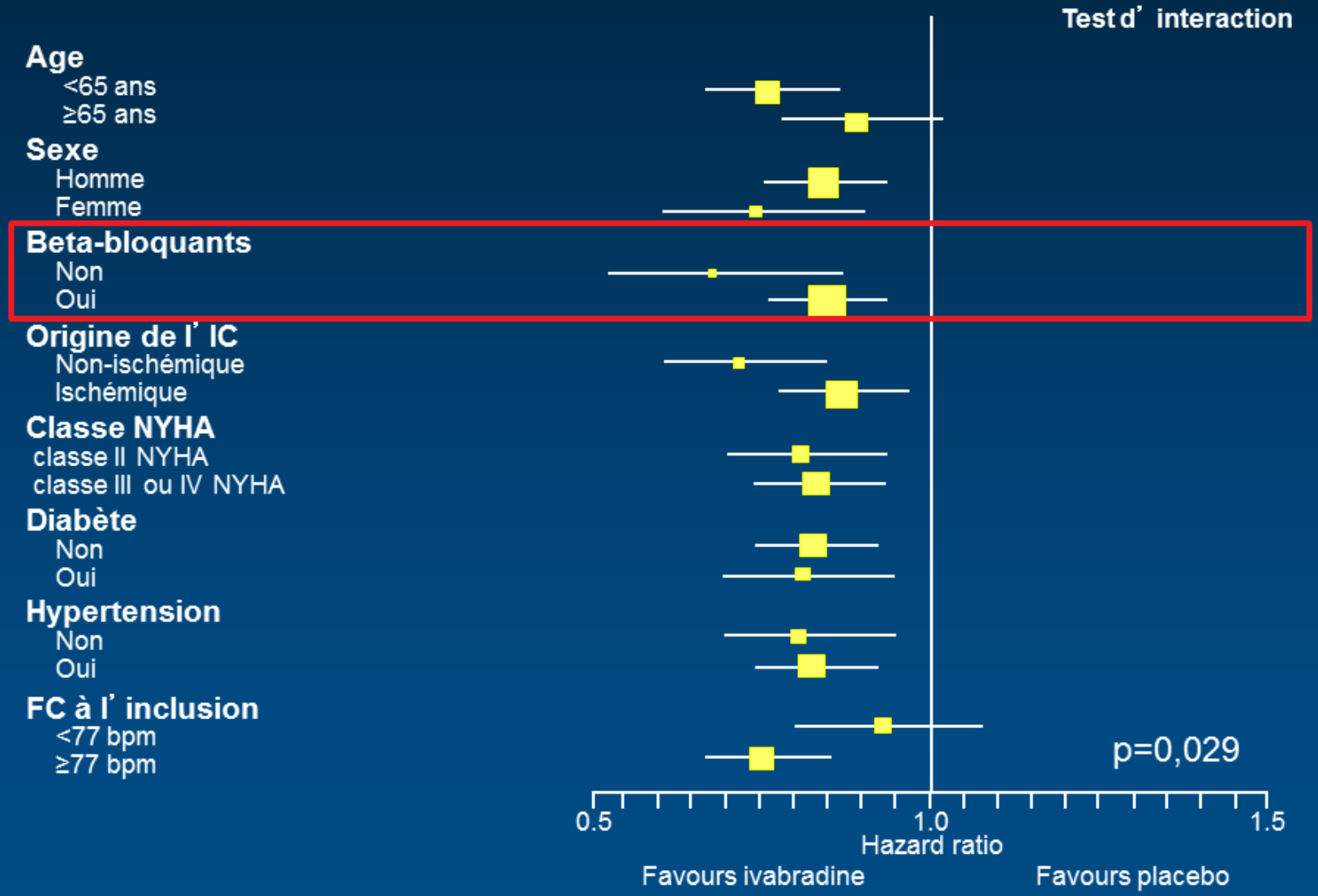
Swedberg K, et al. *Lancet*. 2010;376:875-885

Traitement par bêta bloquant optimisé



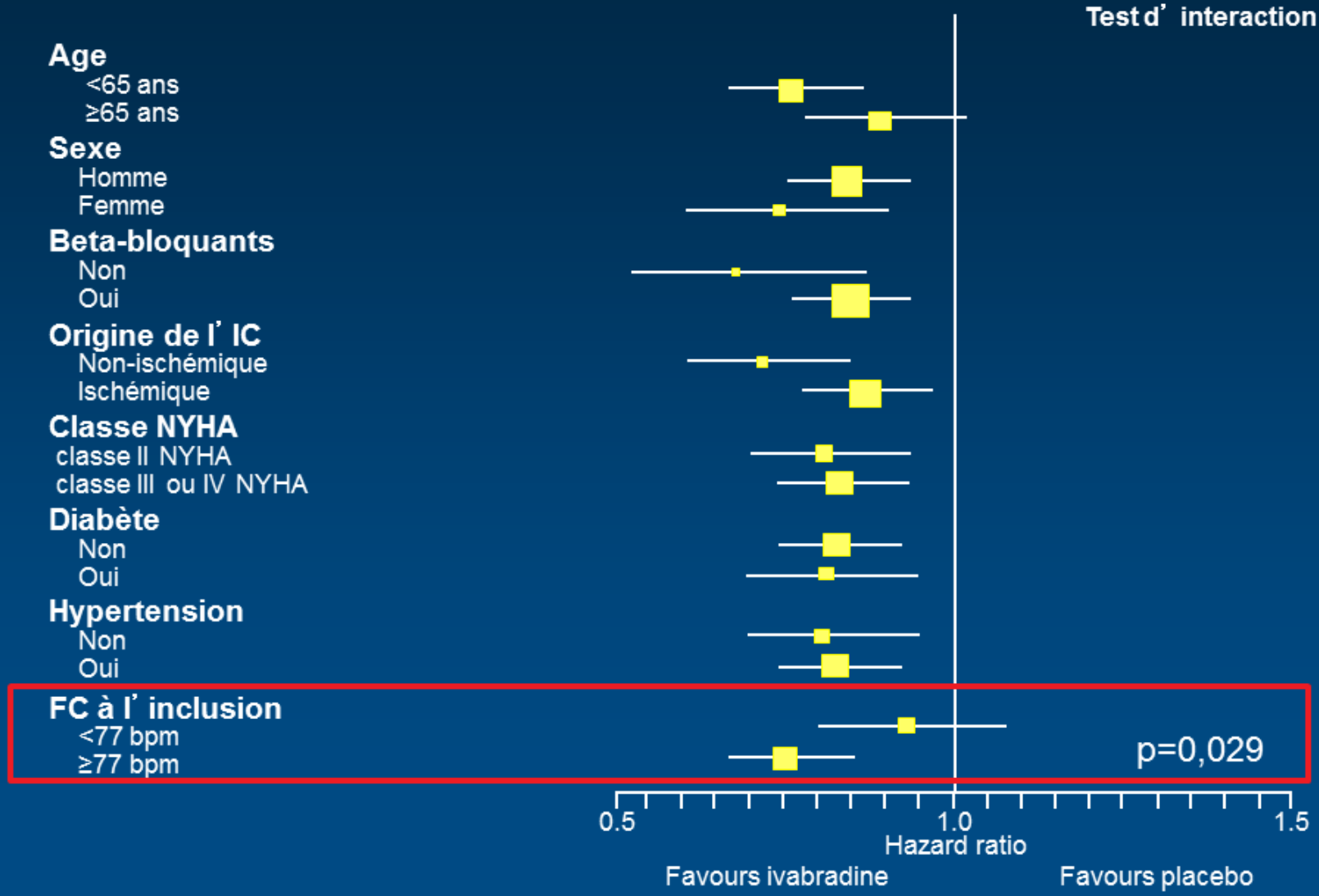
Swedberg K, et al. *Lancet.* Online 29-08-2010

Bénéfices de Procoralan sur le critère primaire quels que soient les groupes de patients



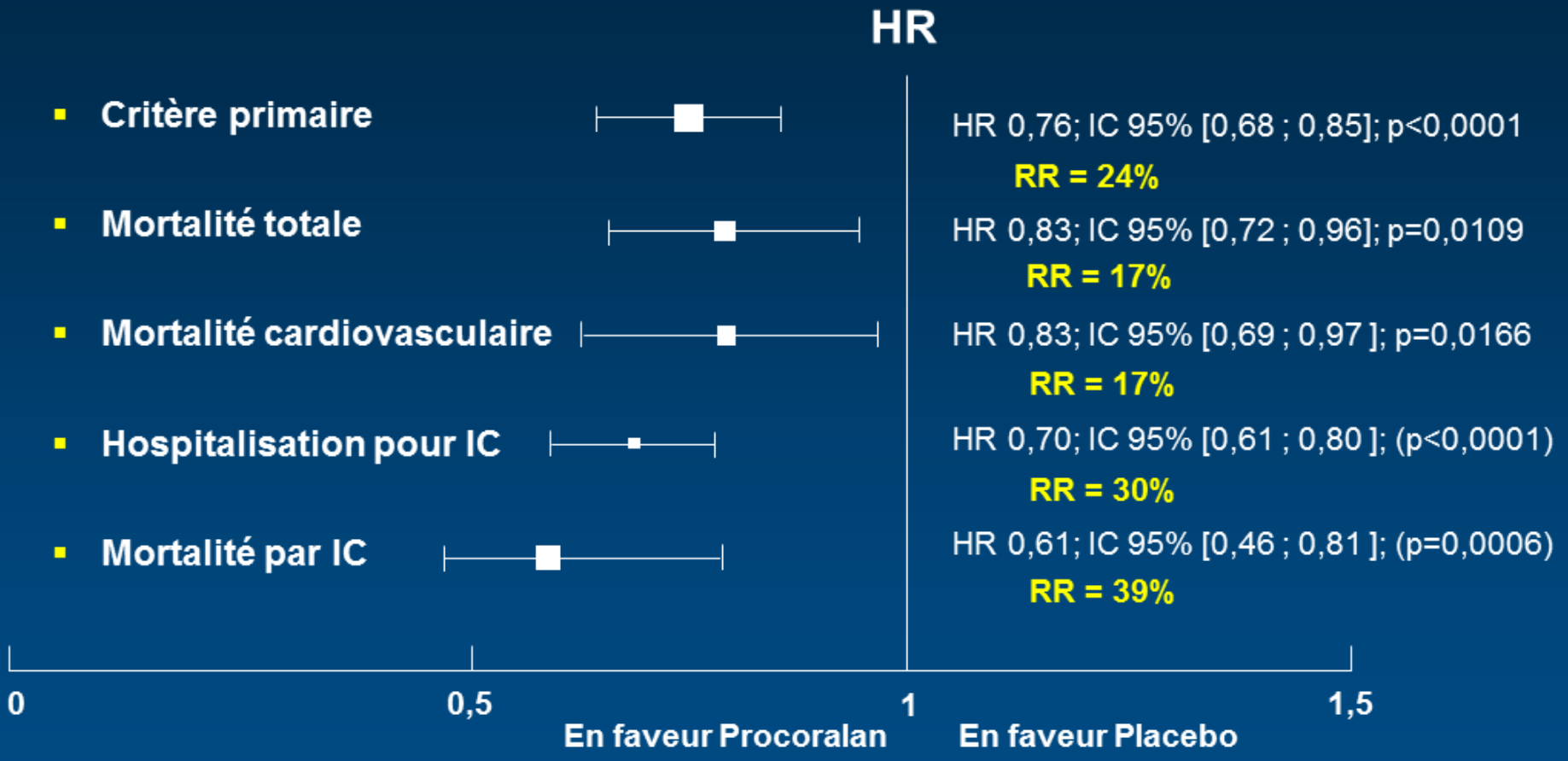
Swedberg K, et al. *Lancet* 2010; 376:875-885

Analyse par sous-groupes



Swedberg K, et al. *Lancet* 2010; 376:875-885

Effets de Procoralan sur les évènements chez les patients dont la FC ≥ 75 bpm



Critère Primaire = Mortalité CV ou hospitalisation pour IC

RR = Réduction du Risque Relatif

RCP Procoralan, EPAR

Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (NYHA class II–IV) systolic heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
Thiazolidinediones (glitazones) should not be used as they cause worsening HF and increase the risk of HF hospitalization.	III	A	131–133
Most CCBs (with the exception of amlodipine and felodipine) should not be used as they have a negative inotropic effect and can cause worsening HF.	III	B	134
NSAIDs and COX-2 inhibitors should be avoided if possible as they may cause sodium and water retention, worsening renal function and worsening HF.	III	B	135, 136
The addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor AND a mineralocorticoid antagonist is NOT recommended because of the risk of renal dysfunction and hyperkalaemia.	III	C	–

8. Pharmacological treatment of heart failure with 'preserved' ejection fraction (diastolic heart failure)

No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF (see Section 11). Two very small studies (<30 patients each) have shown that the heart rate-limiting calcium-channel blocker (CCB) verapamil may improve exercise capacity and symptoms in these patients.[137,138] Rate-limiting CCBs may also be useful for ventricular rate control in patients with AF and in the treatment of hypertension and myocardial ischaemia (which is not the case in patients with HF-REF where their negative inotropic action can be dangerous). Beta-blockers may also be used to control the ventricular rate in patients with HF-PEF and AF.

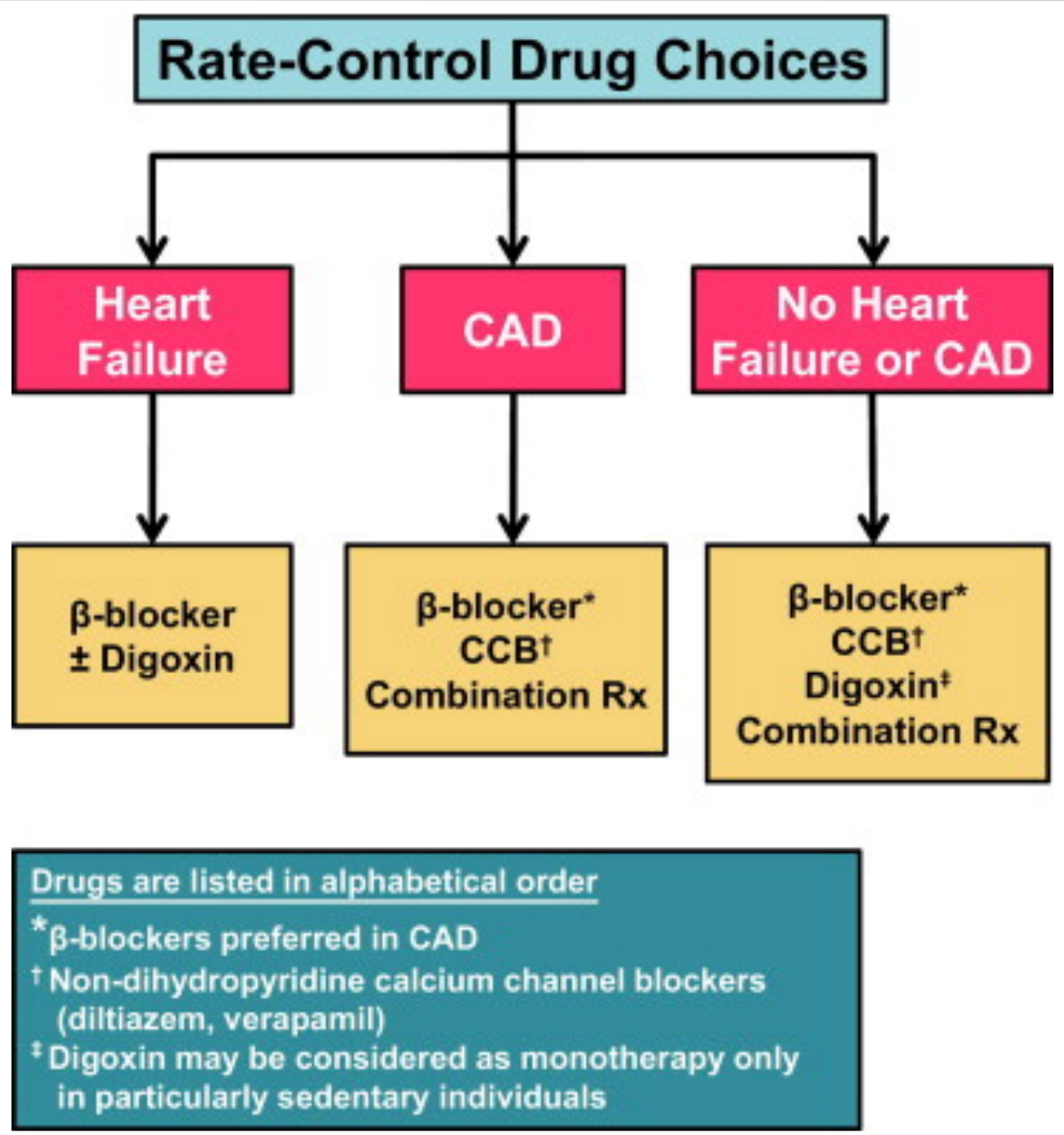
The key mortality–morbidity trials to date are:

- The 3023-patient Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial, which showed no reduction in the primary composite endpoint (cardiovascular death or HF hospitalization).[139]
- The 850-patient Perindopril for Elderly People with Chronic Heart failure trial (PEP-CHF), which showed no reduction in the primary composite endpoint of death or HF hospitalization.[140]
- The 4128 patient Irbesartan in heart failure with preserved systolic function trial (I-Preserve) which showed no reduction in the primary composite outcome of death or cardiovascular hospitalization (specifically, HF, myocardial infarction, unstable angina, arrhythmia, or stroke).[141]

FA ET IC

Contrôle de la fréquence cardiaque

Figure 3

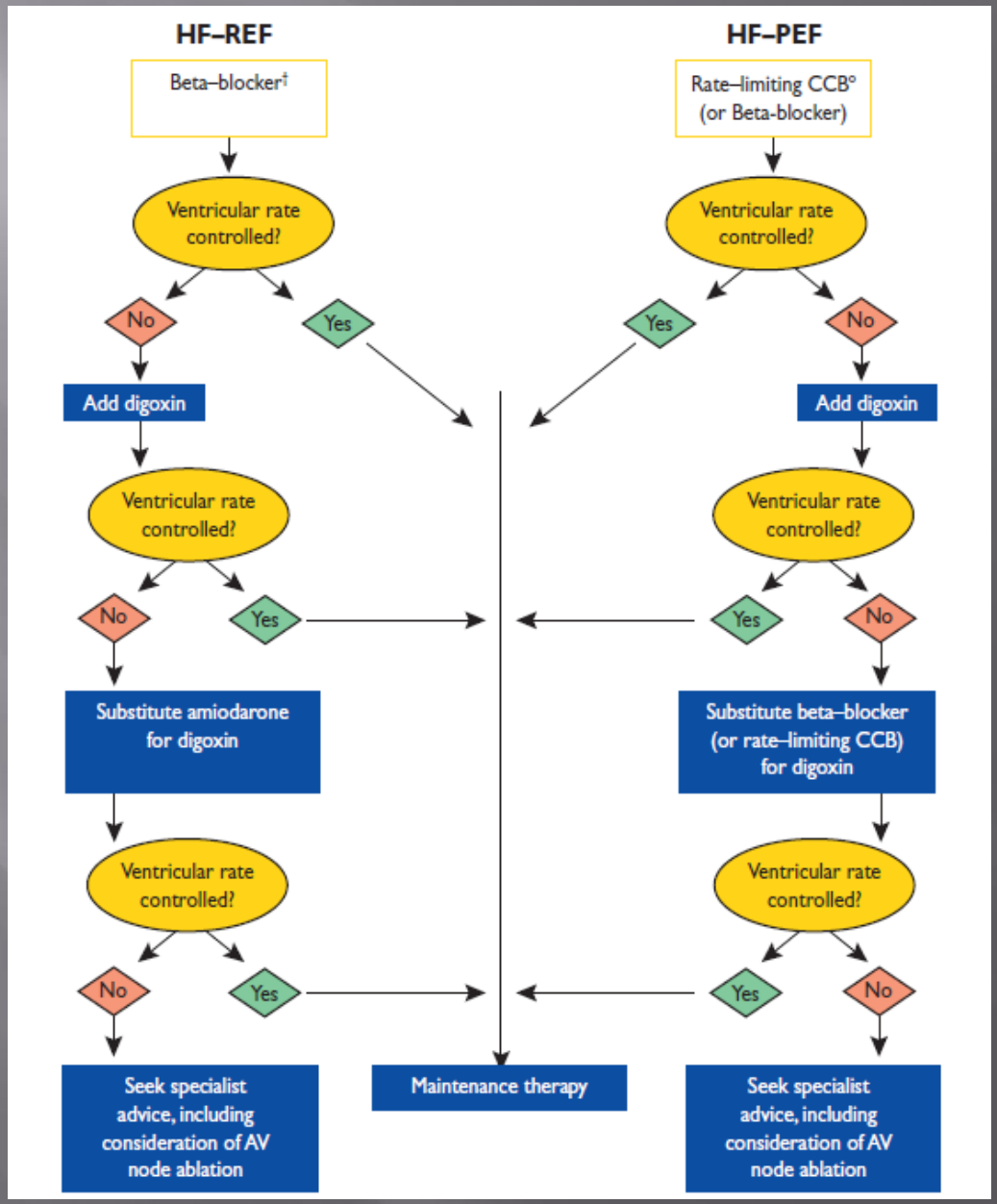


Canadian Journal of Cardiology 2012; 28:125-136

Contrôle de la fréquence

- ICFEA:
  - B bloquants préférés à la digoxine
    - Contrôle de la Fc à l'effort
    - Indiqué dans l'IC
    - Combinaison plus efficace
- ICFEP:
  - IC bradycardisants: vérapamil ou diltiazem alternative au B bloquants
  - Association avec digoxine plus efficace au repos

Controlling the ventricular rate in AF patients



Controlling the ventricular rate in AF patients

Recommendations	Class[a]	Level[b]	Ref[c]
Step 1: A beta-blocker			
A beta-blocker is recommended as the preferred first-line treatment to control the ventricular rate because of the associated benefits of this treatment (reducing the risk of hospitalization for worsening HF and reducing the risk of premature death).	I	A	92–98
Alternative Step 1 treatment			
(i) Digoxin is recommended in patients unable to tolerate a beta-blocker	I	B	113
(ii) Amiodarone may be considered in patients unable to tolerate a beta-blocker or digoxin.	IIb	C	–
(iii) AV node ablation and pacing (possibly CRT) may be considered in patients unable to tolerate any of a beta-blocker, digoxin, or amiodarone.	IIb	C	–
Step 2: Digoxin			
Digoxin is recommended as the preferred second drug, in addition to a beta-blocker, to control the ventricular rate in patients with an inadequate response to a beta-blocker.	I	B	113
Alternative Step 2 treatment			
(i) Amiodarone may be considered in addition to either a beta-blocker or digoxin (but not both) to control the ventricular rate in patients with an inadequate response and unable to tolerate the combination of both a beta-blocker and digoxin.	IIb	C	–
(ii) AV node ablation and pacing (possibly CRT) may be considered in patients with an inadequate response to two of three of a beta-blocker, digoxin and amiodarone.	IIb	C	–
No more than two of three of a beta-blocker, digoxin, and amiodarone (or any other drug suppressing cardiac conduction) should be considered because of the risk of severe bradycardia, third-degree AV block, and asystole.	IIa	C	–

Contrôle du rythme

- Pas de supériorité par rapport au contrôle de la fréquence sur la morbi-mortalité
- Réservé au patients avec une cause réversible de la FA (hyperthyroidie) ou un facteur favorisant (pneumonie)
- FA mal tolérée après traitement optimal sur la Fc et sur l'IC
- Seul l'amiodarone peut être utilisée
- ICA réduction par CCE ou amiodarone IV

AF – Rhythm control

In patients with chronic HF, a rhythm-control strategy (including pharmacological or electrical cardioversion) has not been demonstrated to be superior to a rate-control strategy in reducing mortality or morbidity.[171] This strategy is probably best reserved for patients with a reversible secondary cause of AF (e.g. hyperthyroidism) or an obvious precipitant (e.g. recent pneumonia) and in patients who cannot tolerate AF after optimization of rate control and HF therapy. Amiodarone is the only antiarrhythmic that should be used in patients with systolic HF.[172,173] The role of catheter ablation as a rhythm control strategy in HF is at present uncertain.[174,175]

Recommendations for a rhythm control-management strategy in patients with AF, symptomatic HF (NYHA functional class II–IV), and LV systolic dysfunction and no evidence of acute decompensation

Recommendations	Class[a]	Level[b]	Ref[c]
Electrical cardioversion or pharmacological cardioversion with amiodarone may be considered in patients with persisting symptoms and/or signs of HF, despite optimum pharmacological treatment and adequate control of the ventricular rate, to improve clinical/symptomatic status.	IIb	C	–
Amiodarone may be considered prior to (and following) successful electrical cardioversion to maintain sinus rhythm.	IIb	C	–
Dronedarone is not recommended because of an increased risk of hospital admissions for cardiovascular causes and an increased risk of premature death.	III	A	176, 177
Class I antiarrhythmic agents are not recommended because of an increased risk of premature death.	III	A	178

AF = atrial fibrillation; EF = ejection fraction; HF = heart failure; LV = left ventricular; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

ICA ET FA

Patients with AF and a rapid ventricular rate			
Patients should be fully anticoagulated (e.g. with i.v. heparin), if not already anticoagulated and with no contraindication to anticoagulation, as soon as AF is detected to reduce the risk of systemic arterial embolism and stroke.	I	A	184
Electrical cardioversion is recommended in patients haemodynamically compromised by AF and in whom urgent restoration of sinus rhythm is required to improve the patient's clinical condition rapidly.	I	C	–
Electrical cardioversion or pharmacological cardioversion with amiodarone should be considered in patients when a decision is made to restore sinus rhythm non-urgently ('rhythm control' strategy). This strategy should only be employed in patients with a first episode of AF of <48 h duration (or in patients with no evidence of left atrial appendage thrombus on TOE).	I	C	–
Intravenous administration of a cardiac glycoside should be considered for rapid control of the ventricular rate.	I	C	–
Dronedarone is not recommended because of safety concerns (increased risk of hospital admission for cardiovascular causes and an increased risk of premature death), particularly in patients with an EF ≤40%.	III	A	176
Class I antiarrhythmic agents are not recommended because of safety concerns (increased risk of premature death), particularly in patients with LV systolic dysfunction.	III	A	178

ETUDE PARADIGME

Angiotensin-neprilysin inhibition vs enalapril in heart failure

N engl j med sept 2014

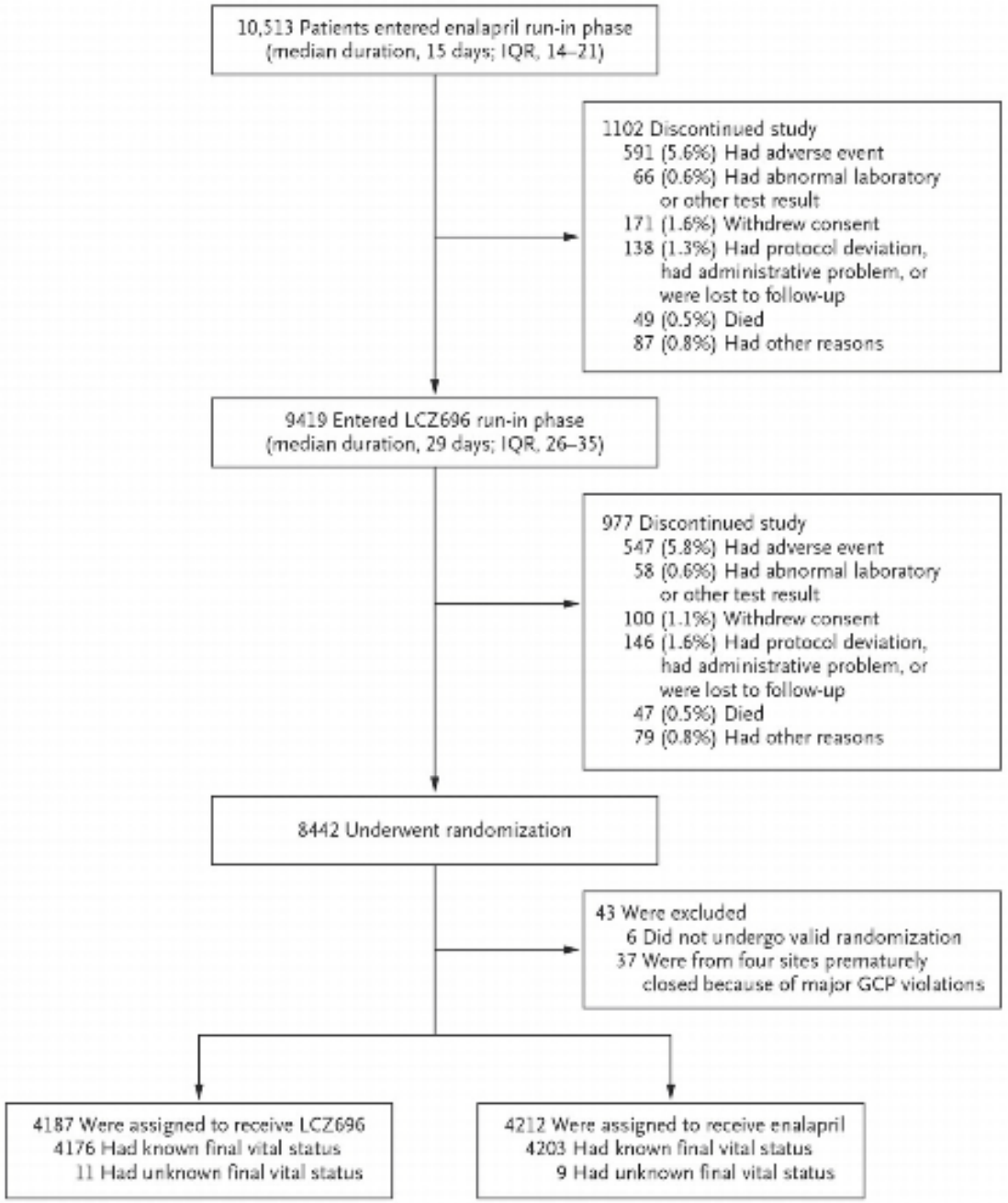

10,513 Patients entered enalapril run-in phase
(median duration, 15 days; IQR, 14–21)
1102 Discontinued study
591 (5.6%) Had adverse event
66 (0.6%) Had abnormal laboratory or other test result
171 (1.6%) Withdrew consent
138 (1.3%) Had protocol deviation, had administrative problem, or were lost to 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

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.5
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	223 (5.3)	215 (5.1)
Asian	759 (18.1)	750 (17.8)
Other	452 (10.8)	466 (11.1)
Region — no. (%)		
North America	310 (7.4)	292 (6.9)
Latin America	713 (17.0)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1453 (34.5)
Asia–Pacific	745 (17.8)	742 (17.6)
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)	2590 (61.5)
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)	1654 (886–3305)
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1069 (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	1838 (43.9)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Prerandomization ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Prerandomization ARB‖	929 (22.2)	963 (22.9)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1225 (29.3)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	625 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

* Plus–minus values are means ±SD. There were no significant differences between the two groups except for the use of digitalis ($P=0.04$) and mineralocorticoid-receptor antagonists ($P=0.01$), with values not adjusted for multiple testing. Percentages may not total 100 because of rounding. More details about the baseline characteristics are provided in Section 3 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range.

† Race or ethnic group was reported by the investigators.

‡ This category includes South Africa and Israel.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The data for New York Heart Association (NYHA) class reflect the status of patients at the time of randomization. Patients were required to have at least NYHA class II symptoms at screening.

‖ At the screening visit, 30 patients were not receiving the protocol-required treatment with an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB), and 45 patients were taking both drugs. Doses of prerandomization ACE inhibitors and ARBs are provided in the Supplementary Appendix.

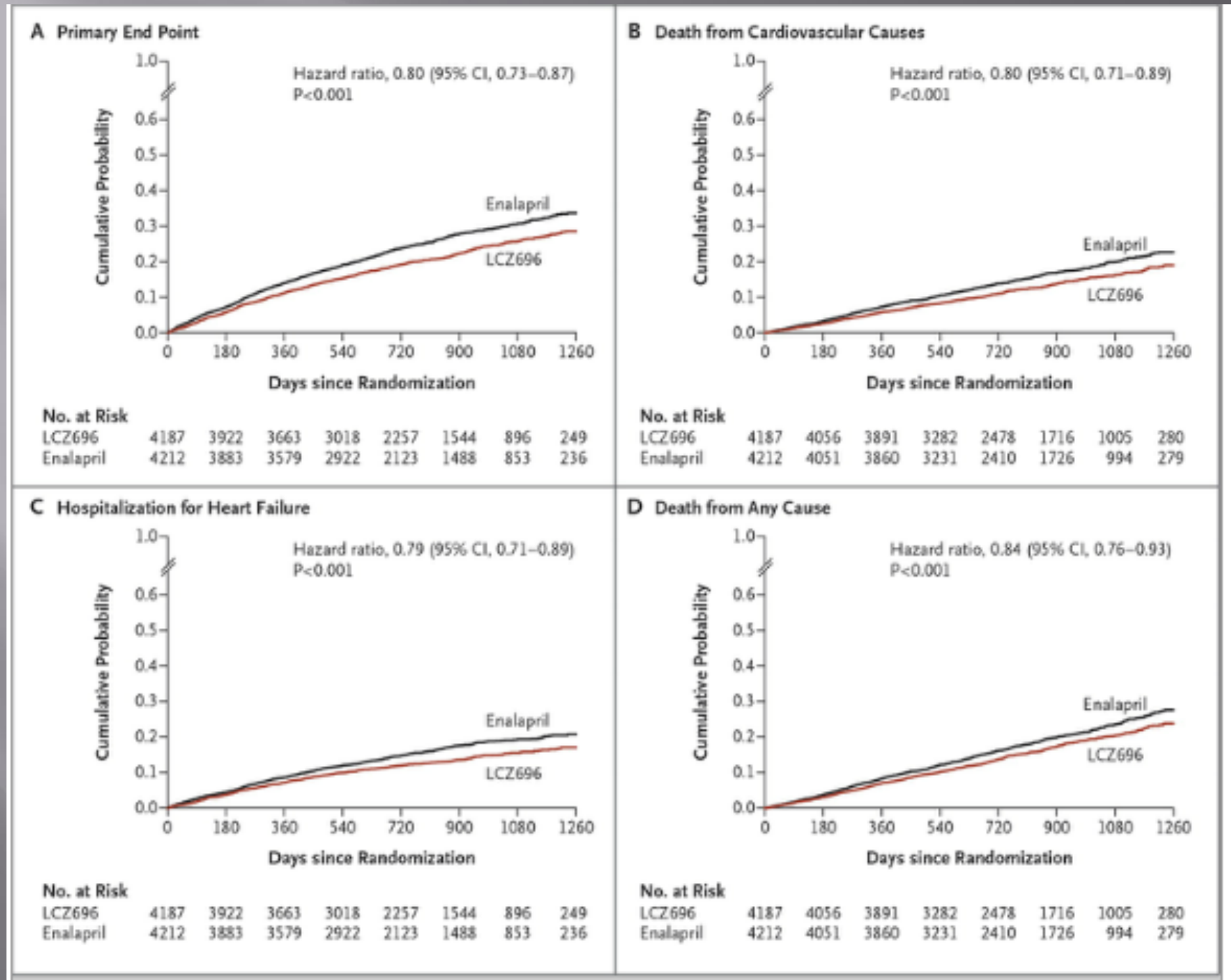

A Primary End Point
Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236
B Death from Cardiovascular Causes
Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
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
Hazard ratio, 0.79 (95% CI, 0.71–0.89)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
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
Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

Table 2. Primary and Secondary Outcomes.*

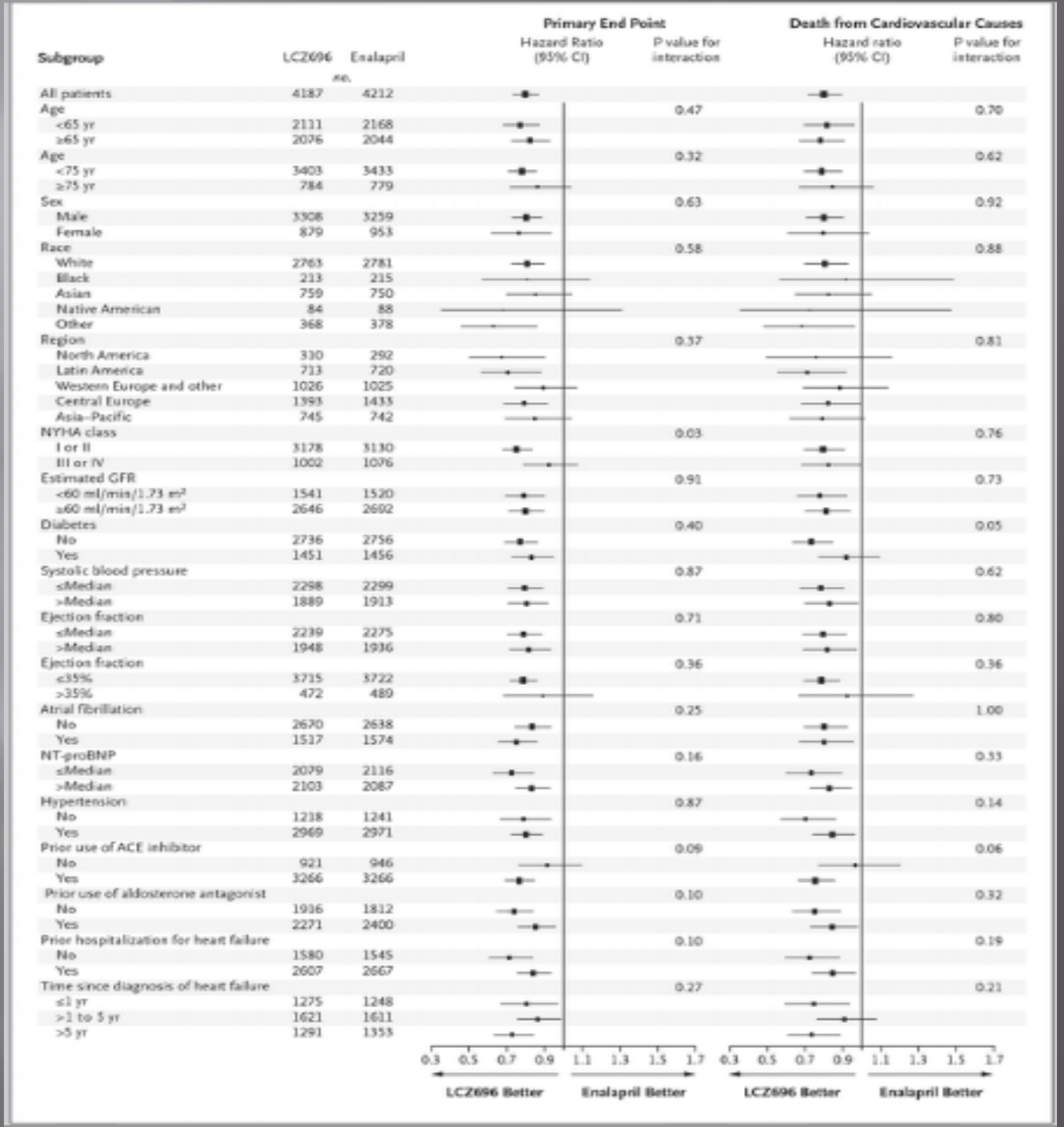
Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	–2.99±0.36	–4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.

† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.

‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.

§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m^2, to less than 60 ml per minute per 1.73 m^2.


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 1238 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 1936 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

Conclusions

- Un objectif: mettre en pratique les recommandations
- Optimisation progressive du traitement
- Surveillance clinique et biologique
- Reconsidérer le traitement à chaque suivi
- Anti-aldostérone et ivabradine reconnus
- Concilier recommandations et AMM ?
- Nouvelles recommandations pour le LCZ 696?