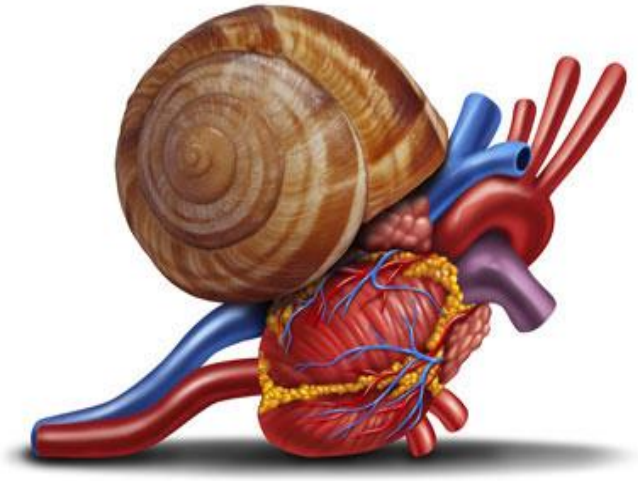


Actualités thérapeutiques médicamenteuses en insuffisance cardiaque.

Grande journée SSMG 2019
« Ce ne serait pas mon cœur, Docteur? »
Actualités en cardiologie pour le médecin généraliste.

GHdC asbl

C.H.U. de Charleroi

cndg
CLINIQUE NOTRE-DAME DE GRÂCE ASBL
GOSSELIES

5 Octobre 2019.

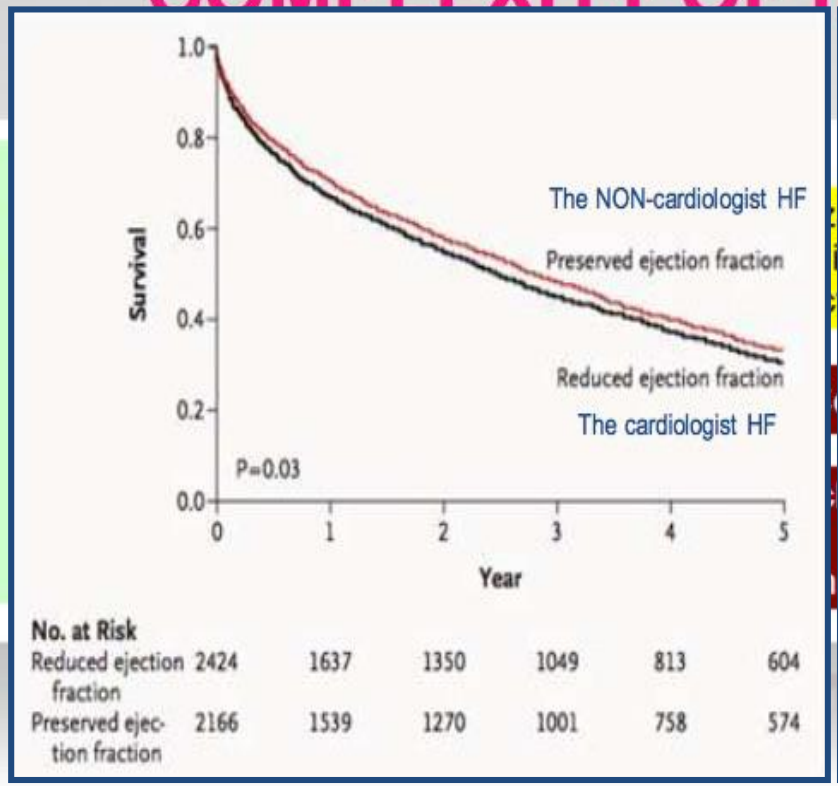
Dr F. Chenot.

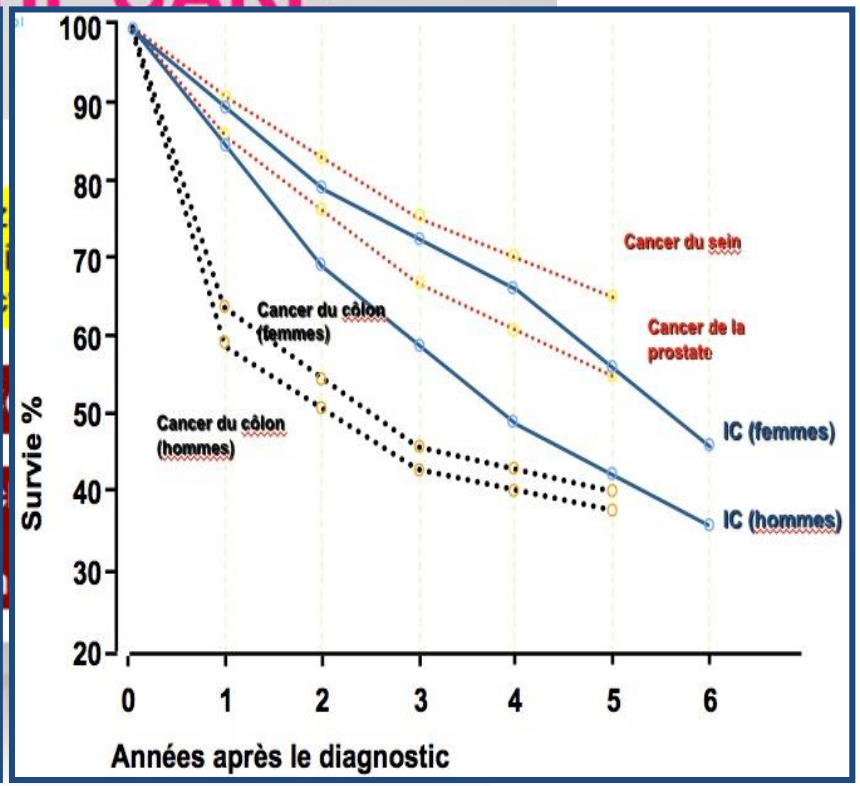
SSMG 50 ans

Les enjeux de l'insuffisance cardiaque.

National data

COMPLEXITY OF HF CARE

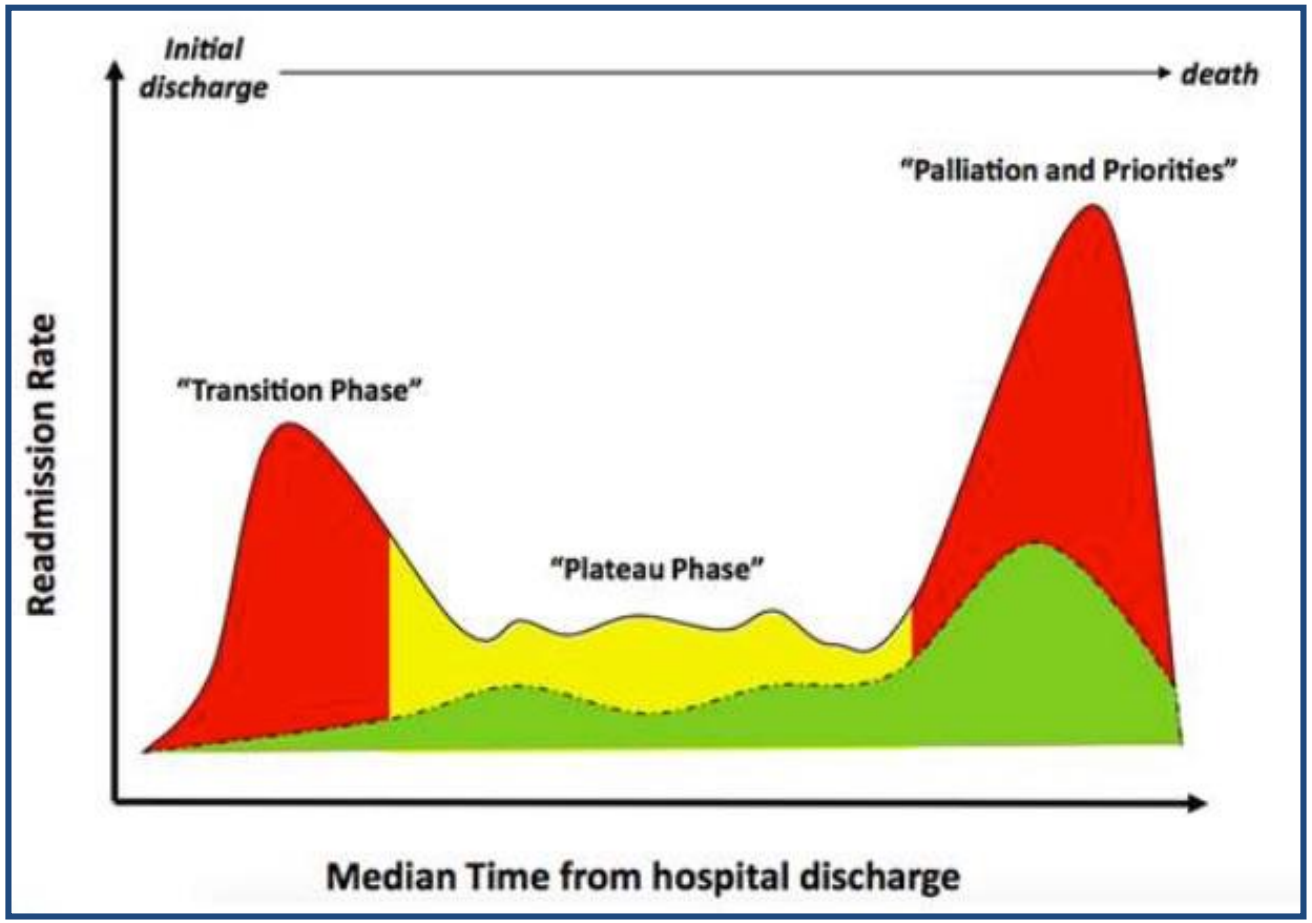




Journées francophones de l'insuffisance cardiaque
Lille, septembre 2018

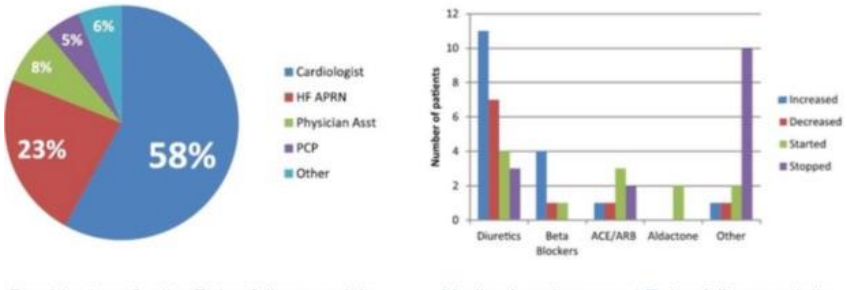
Bhatia et al. NEJM 2006;355:251-9

Risque de réadmission précoce.



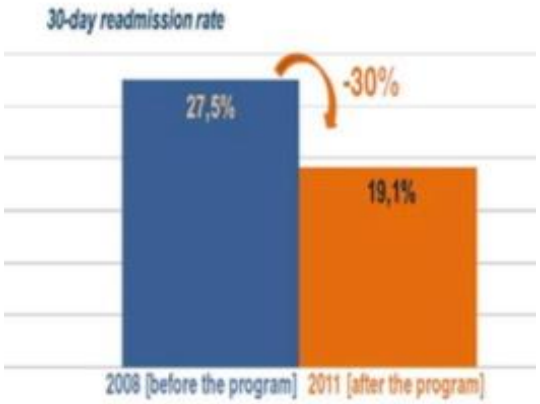
Desai A, Stevenson L , Circ 2012;126:501-506

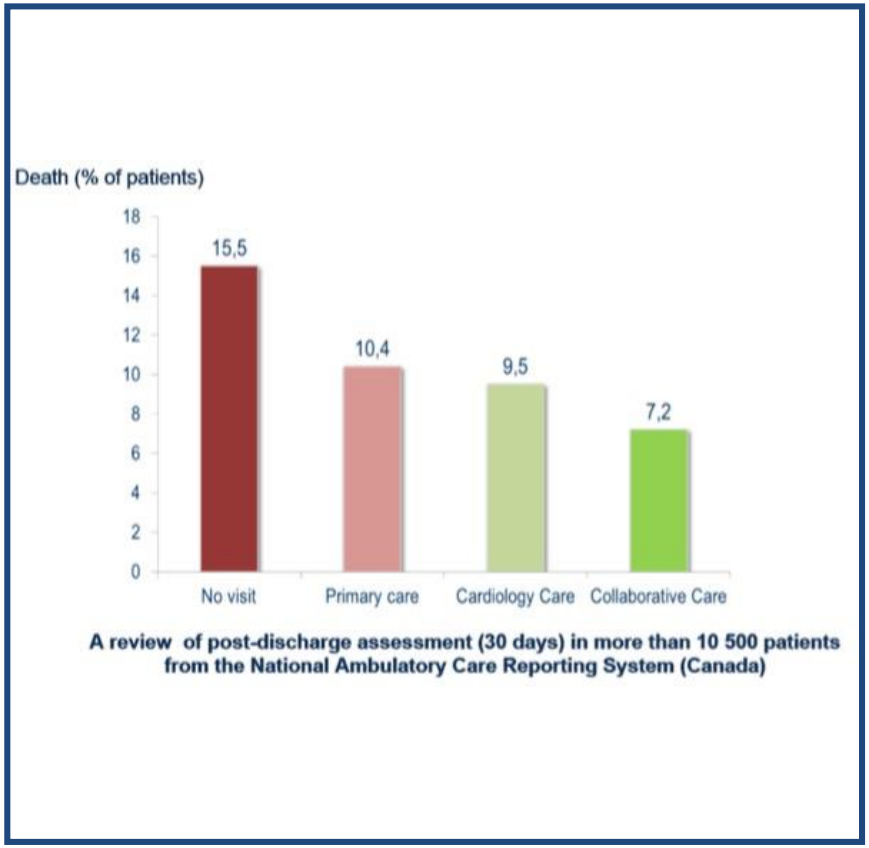
Réévaluation précoce.



Provider type for the 7-day follow-up visit

Medication changes at 7-day follow-up visits





Ryan J et al. Am J Med. 2013;126(11):989-994

Metra M, et al. Circulation. 2010;122:1782-1785

Insuffisance cardiaque en 2019.

Actualités médicamenteuses.

Guidelines 2016.

Comorbidités.

Guidelines

2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

Definition of heart failure

With preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

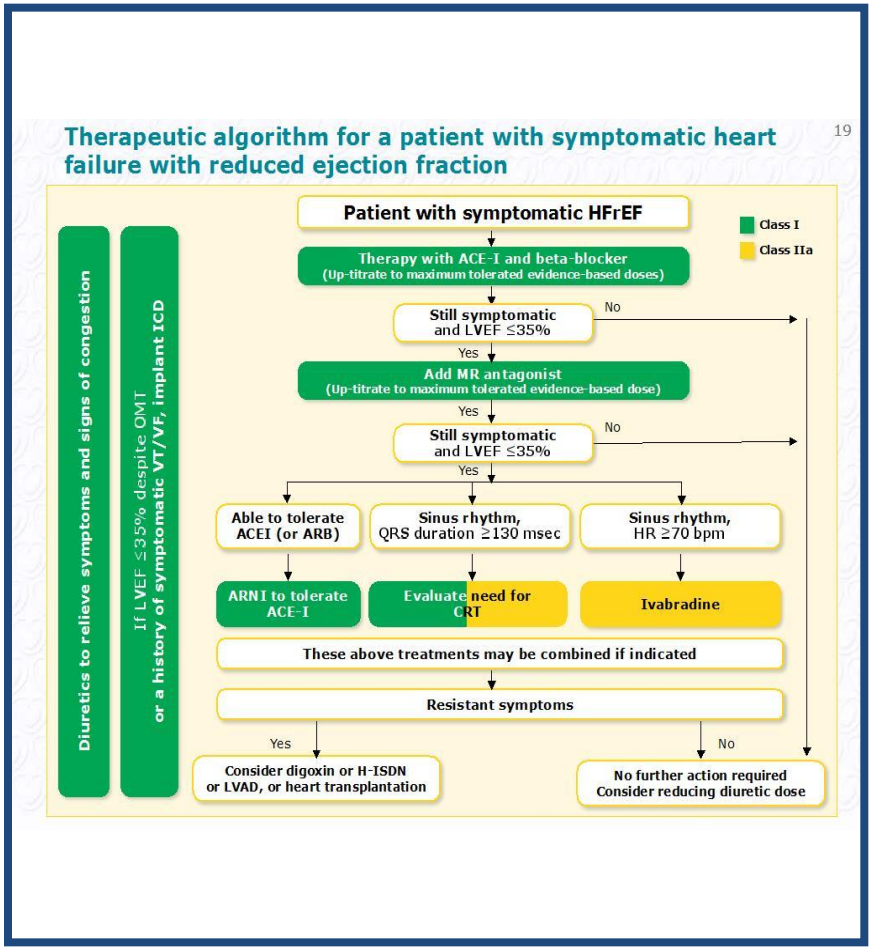
Type of HF		HFrEF	HFmrEF	PFpEF
CRITERIA	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1.Elevated levels of natriuretic peptides. 2.At least one additional criterion: a.relevant structural heart disease (LVF and/or LAE); b.diastolic dysfunction (for details see Section 4.3.2.).	1.Elevated levels of natriuretic peptides. 2.At least one additional criterion: a.relevant structural heart disease (LVF and/or LAE); b.diastolic dysfunction (for details see Section 4.3.2.).

European Heart Journal (2016) **37**, 2129-2200 - doi:10.1093/eurheartj/ehw 128

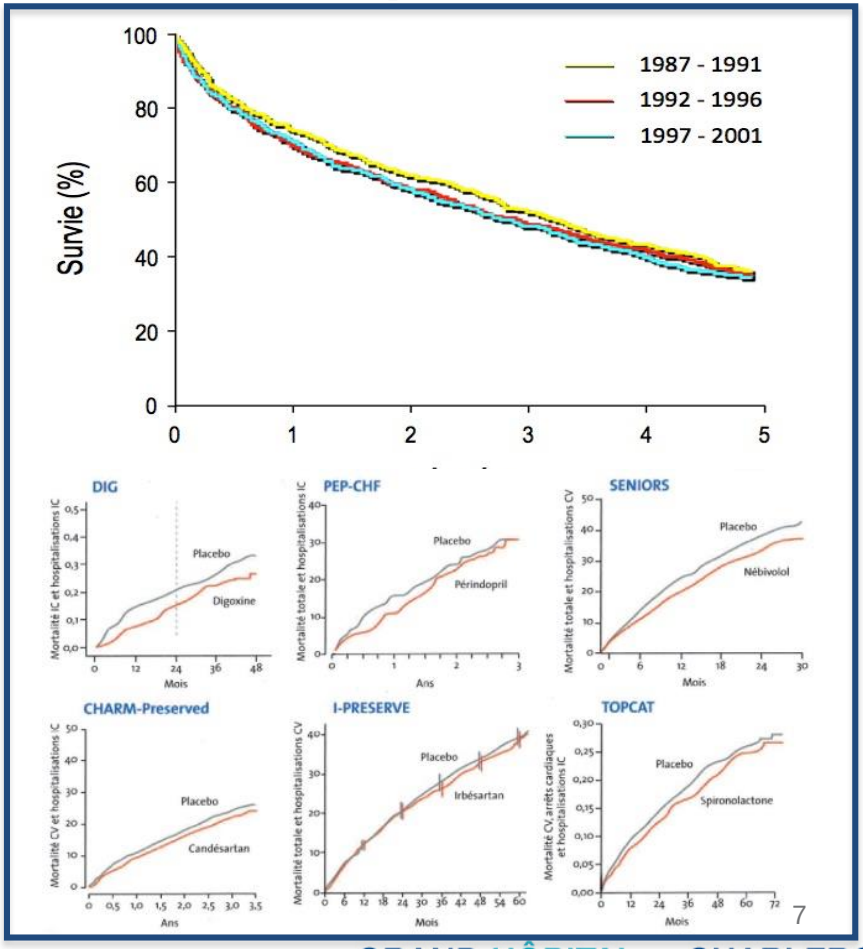
Guidelines: traitement

2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

HFrEF



HFpEF

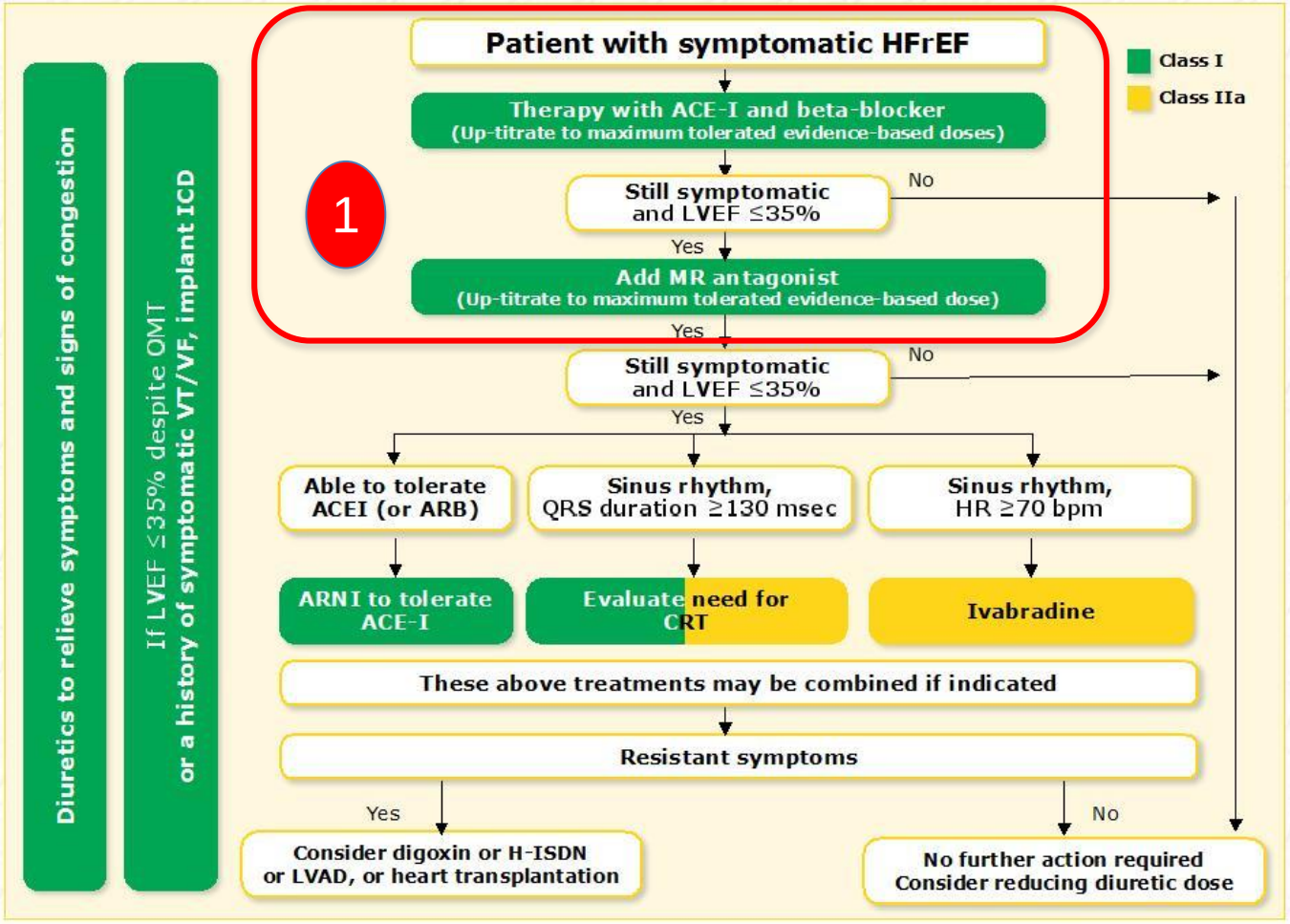


Guidelines

2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,

Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction

19



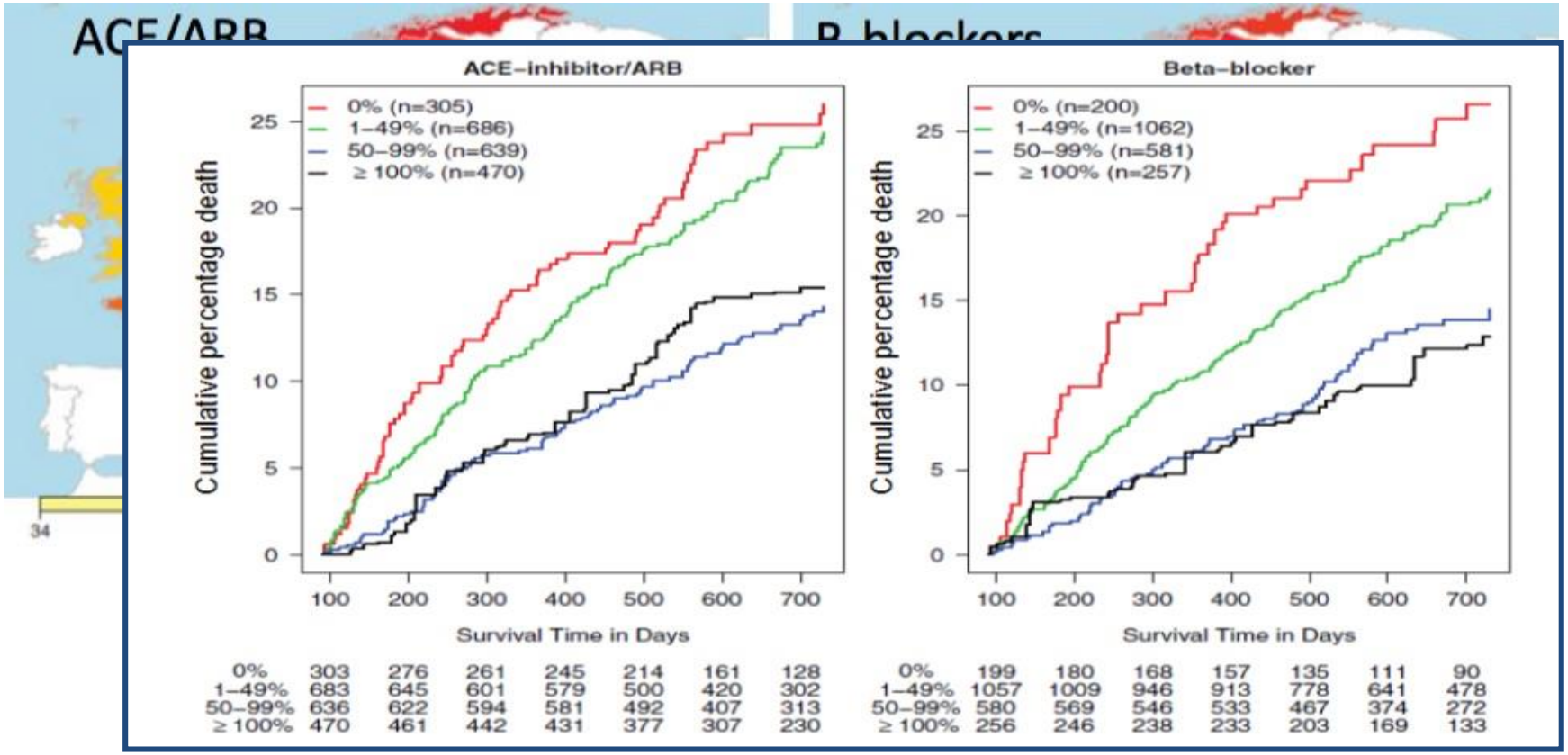
Titration et adhérence…

Recommendations	Class [a]	Level [b]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

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

Biostat

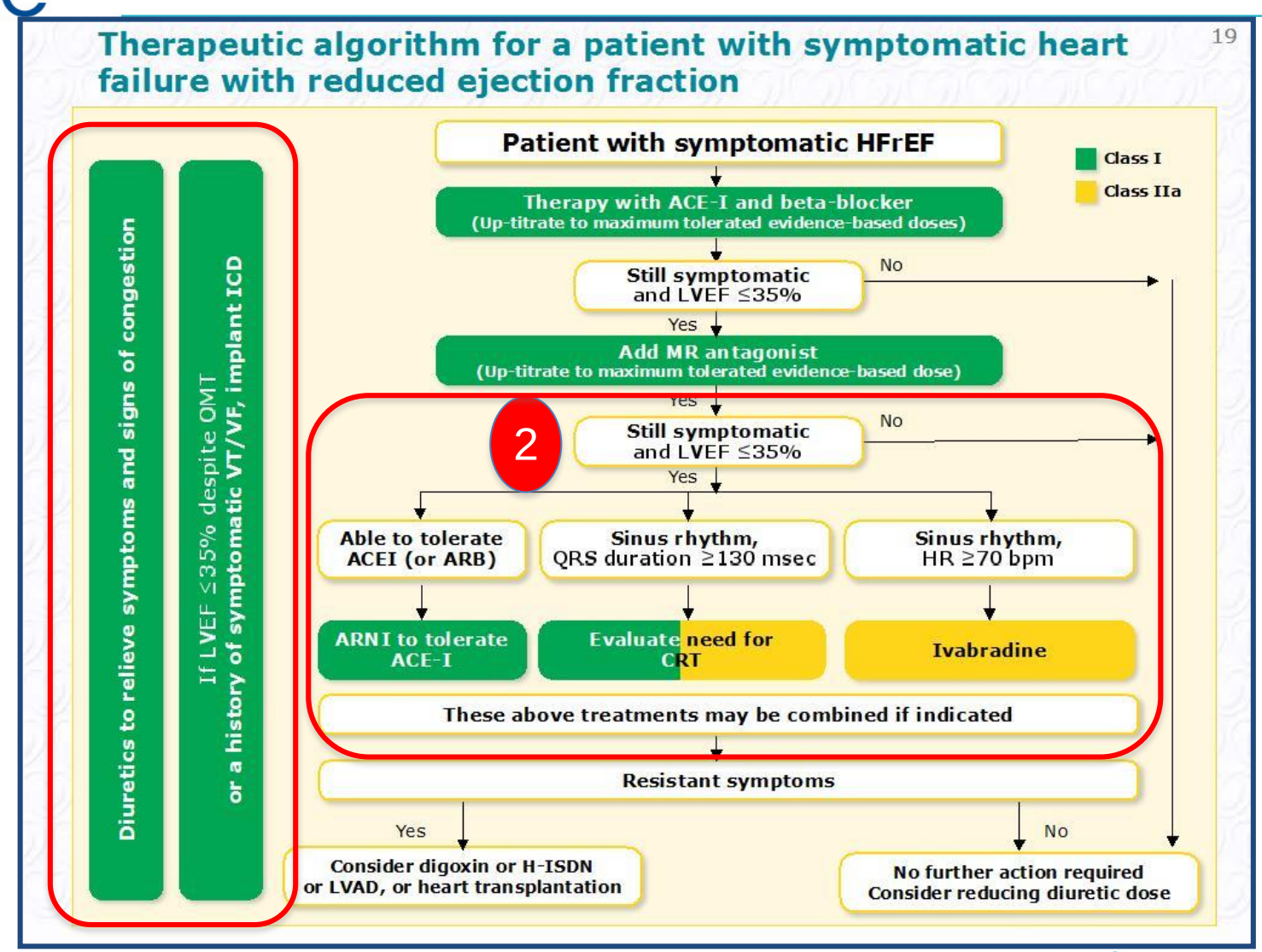
2516 HFrEF pts ,11 pays ESC.



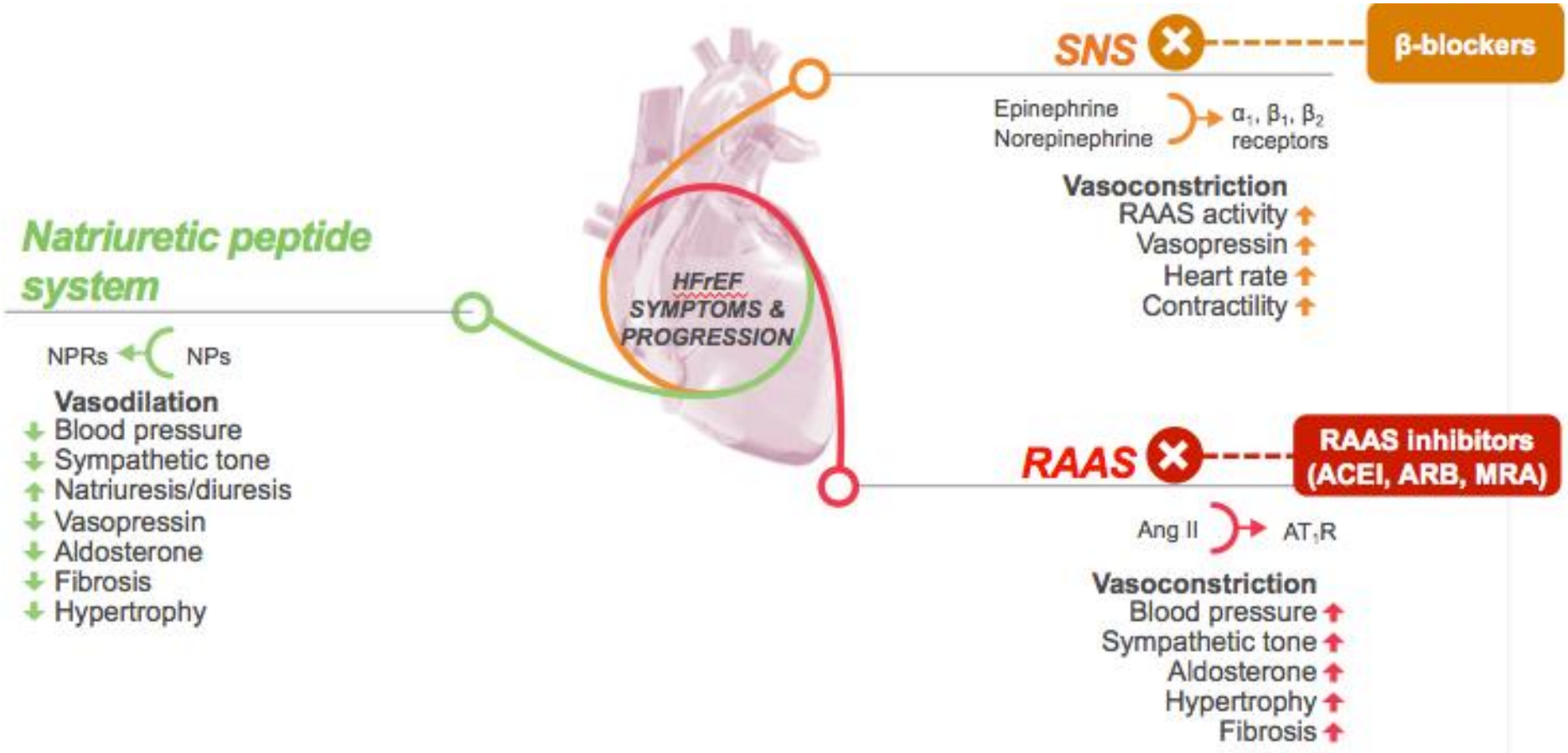
Ouwerkerk M et al. Eur Heart J. 2017;38(24):1883–1890

Guidelines

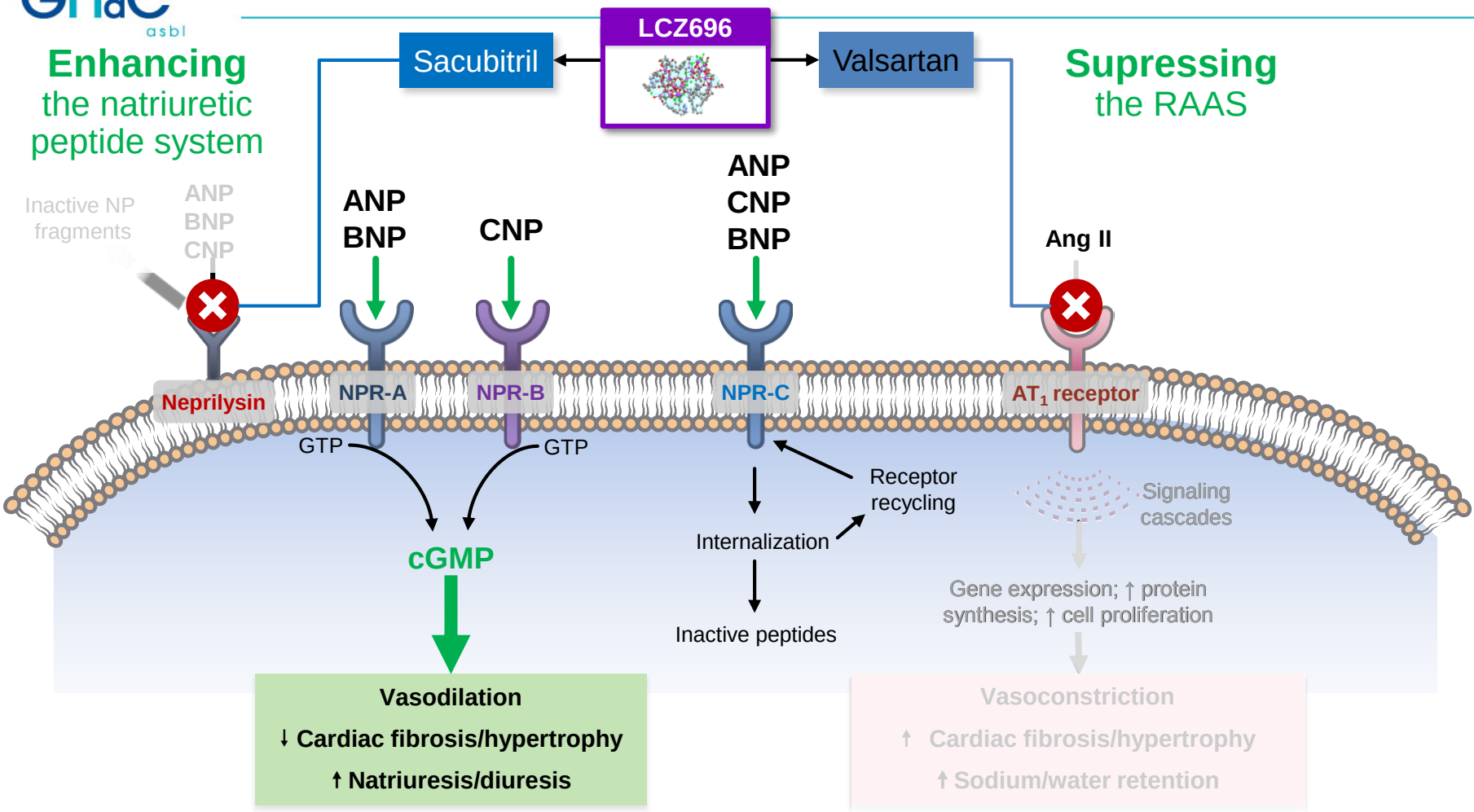
2016 ESC Guidelines for heart failure; European Heart Journal 20 May 2016,



ARNI (sacubitril-valsartan, Entresto®)



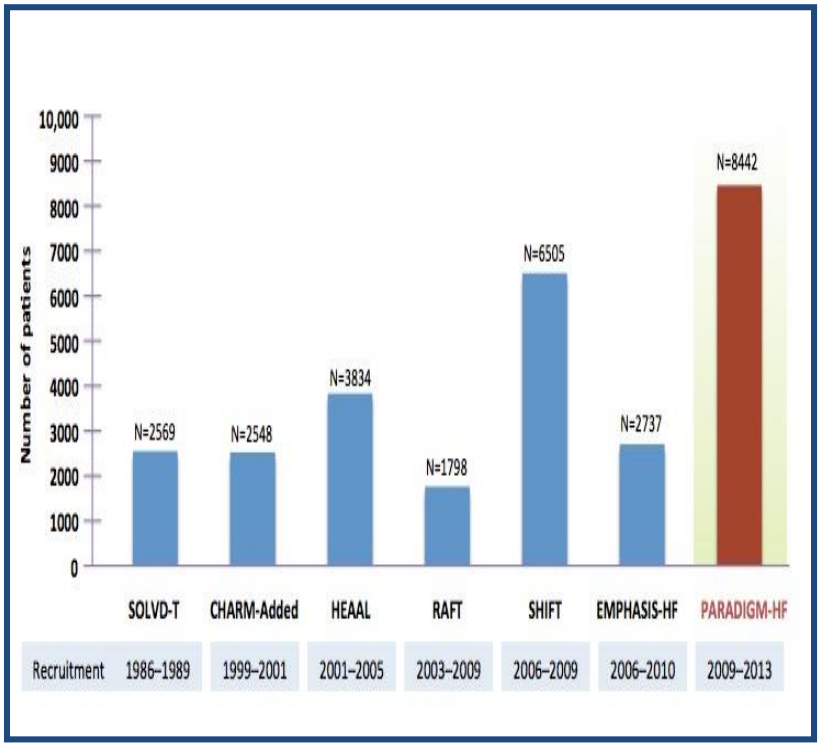
ARNI (sacubitril-valsartan, Entresto®)

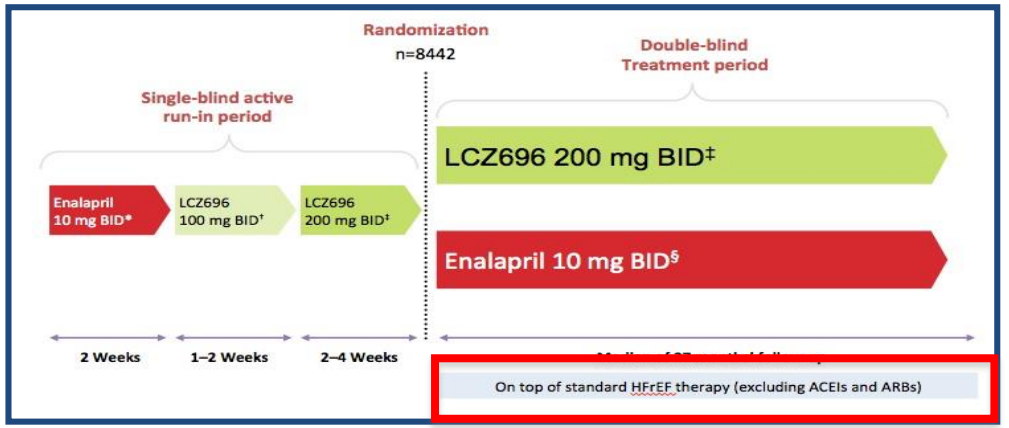


Levin et al. New Engl J Med 1998;339:321–8; Gardner et al. Hypertension 2007;49:419–26;
Molkentin. J Clin Invest 2003;111:1275–77; Nishikimi et al. Cardiovasc Res 2006;69:318–28;
Guo et al. Cell Res 2001;11:165–80; Von Lueder et al. Circ Heart Fail 2013;6:594–605;
Yin et al. Int J Biochem Cell 2003;35:780–3; Mehta and Griendling. Am J Physiol Cell Physiol 2007;292:C82–97; Langenickel and Dole. Drug Discov Today: Ther Strategies 2012;9:e131–e137

PARADIGM-HF

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





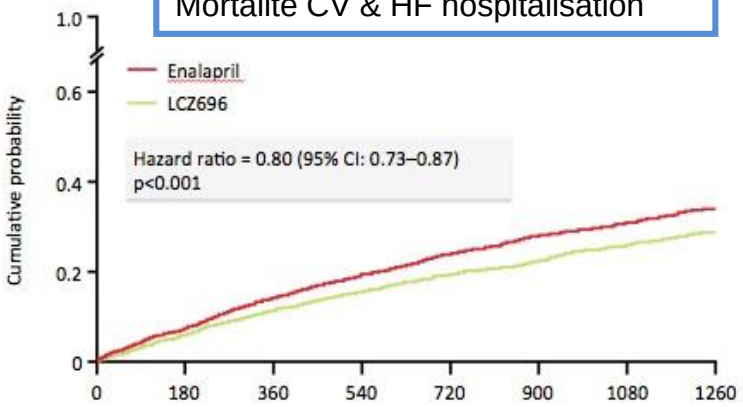
Characteristic*	LCZ696 (n=4187)	Enalapril (n=4212)
Age, years	63.8 ± 11.5	63.8 ± 11.3
Women, n (%)	879 (21.0)	953 (22.6)
Ischemic cardiomyopathy, n (%)	2506 (59.9)	2530 (60.1)
LV ejection fraction, %	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class, n (%)		
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
SBP, mmHg	122 ± 15	121 ± 15
Heart rate, beats/min	72 ± 12	73 ± 12
NT pro-BNP, pg/mL (IQR)	1631 (885–3154)	1594 (886–3305)
BNP, pg/mL (IQR)	255 (155–474)	251 (153–465)
History of diabetes, n (%)	1451 (34.7)	1456 (34.6)
Treatments at randomization, n (%)		
Diuretics	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
β-blockers	3899 (93.1)	3912 (92.9
Mineralocorticoid antagonists	2271 (54.2)	2400 (57.0)
ICD	623 (14.9)	620 (14.7)
CRT	292 (7.0)	282 (6.7)

McMurray et al. Eur J Heart Fail. 2014;16:817–25

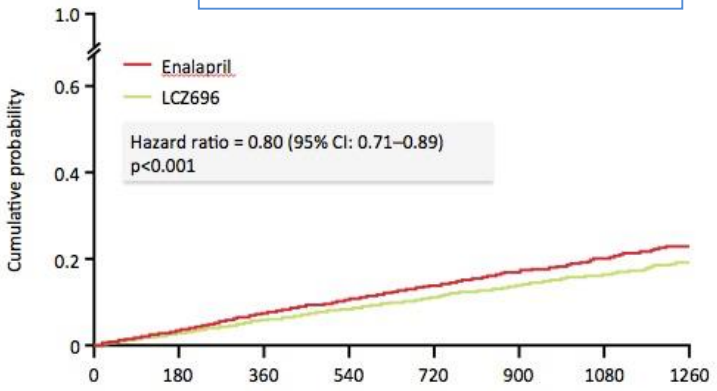
PARADIGM-HF

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

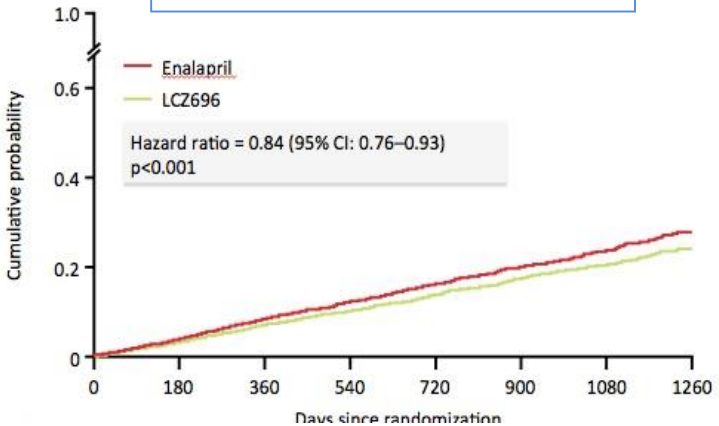
Mortalité CV & HF hospitalisation



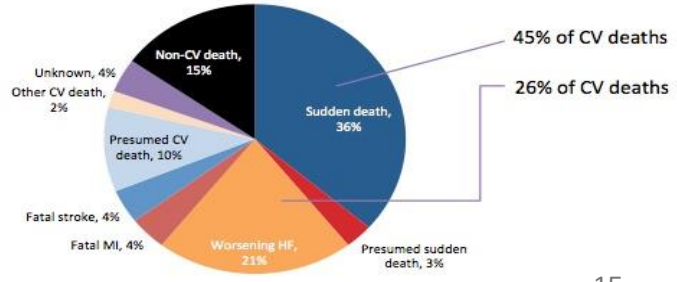
Mortalité CV



Mortalité Totale



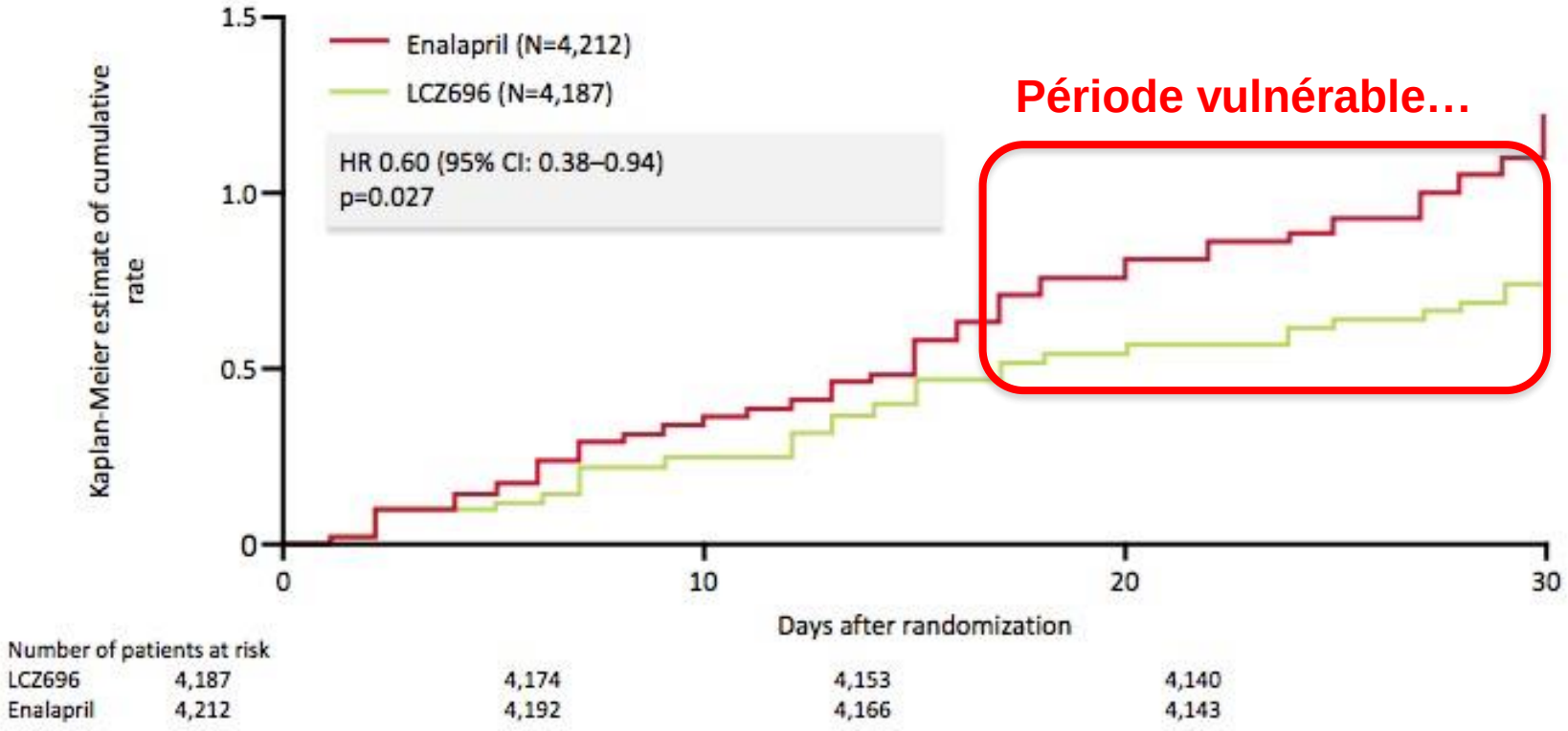
In the PARADIGM-HF trial, CV causes accounted for 81% of all deaths



McMurray et al. Eur J Heart Fail. 2014;16:817–25

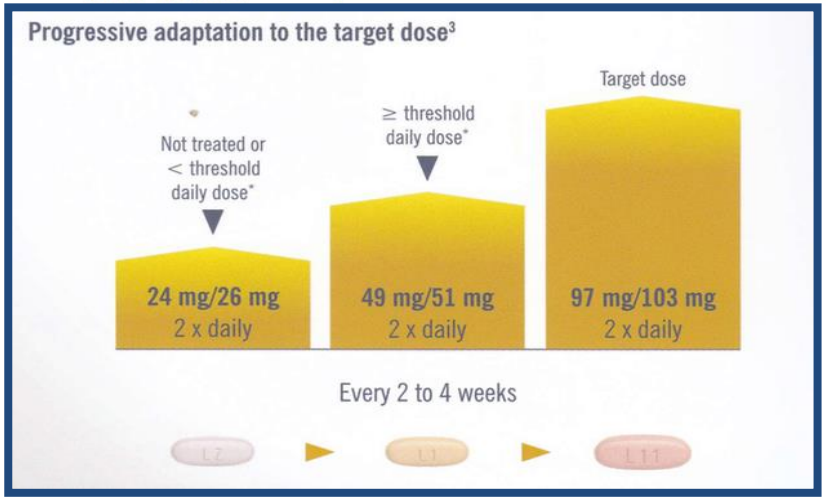
PARADIGM-HF

réduction précoce des réadmissions HF.



McMurray et al. Eur J Heart Fail. 2014;16:817–25

Entresto en pratique…



Dosage thresholds of ACEis and ARBs, commonly used for treatment of symptomatic Chronic Heart Failure with reduced ejection fraction, for ENTRESTO® treatment initiation[16]

Treatment	Threshold daily dose*
ACEis	
Captopril[4]	100 mg
Cilazapril[5]	2.5 mg
Enalapril[6]	10 mg
Fosinopril[7]	20 mg
Lisinopril[8]	10 mg
Perindopril[9] (Coversyl)[10]	4mg (5mg)
Quinapril[11]	20 mg
Ramipril[12]	5 mg
ARBs	
Candesartan[13]	16 mg
Losartan[14]	50 mg
Valsartan[15]	160 mg

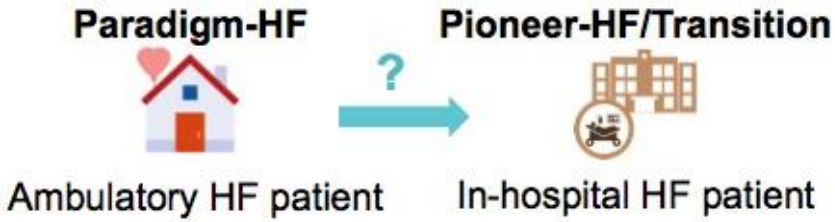
- **Critères de Remboursement :**
  - **Inititation** par un Cardiologue ou un interniste.
    - NYHA II-IV
    - LVEF ≤ 35%
    - OMT sous IECA/ARB
  - **Titration libre**!
- **Quel suivi pratique?**
  - Profil TA!
  - Titration/3-4 semaines, bio J+10. (Fonction rénale, ionogramme)
  - **NT proBNP**

Diminution de la dose en fonction du profil de tolérance:

- hypotension symptomatique / inférieure à 95 mmHg,
- Hyperkaliémie >5,4mmol/l
- Dégradation de la fonction rénale.
  - Légère (DFGe 60-90 ml/min/1.73m2) : DI 100 mg 2x/J.
  - Modérée (DFGe 30-60 ml/min/1.73m2) : DI 50 mg 2x/J
  - Sévère (DFGe <30 ml/min/1.73m2) : DI 50 mg 2x/J, précautions.
  - IRT : pas recommandé.

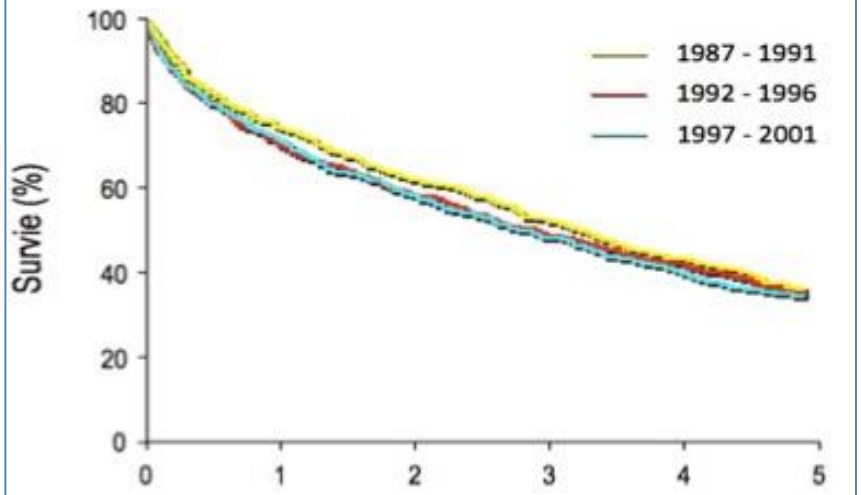
Au-delà de PARADIGM-HF?

R/ Intrahospitalier?



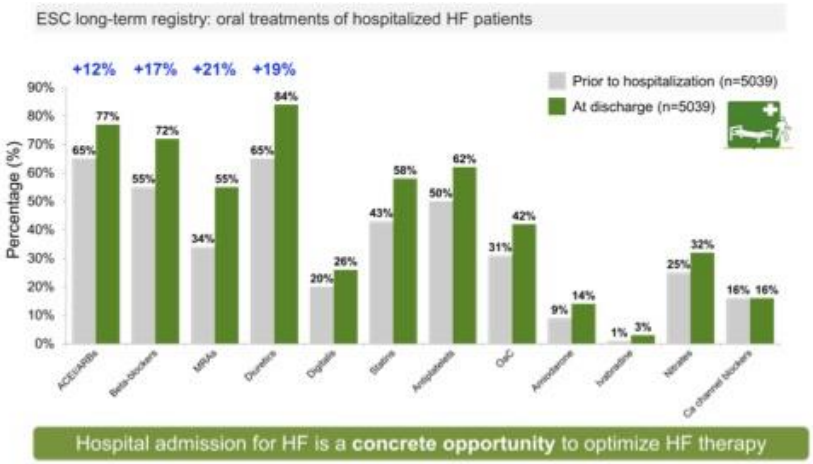
PIONNEER-HF
TRANSITION

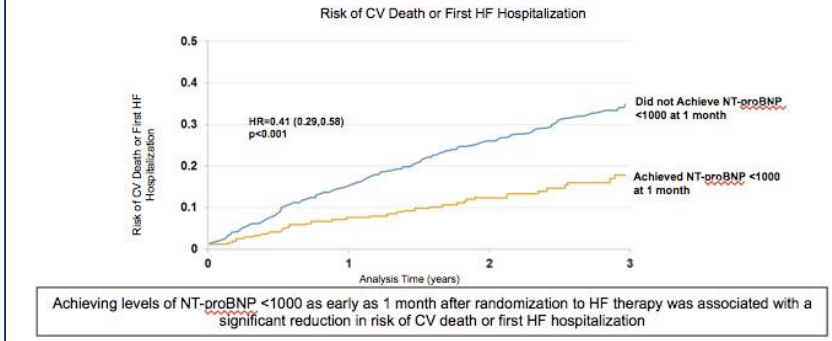
HFpEF?



PARAGON-HF

Administration intrahospitalière?



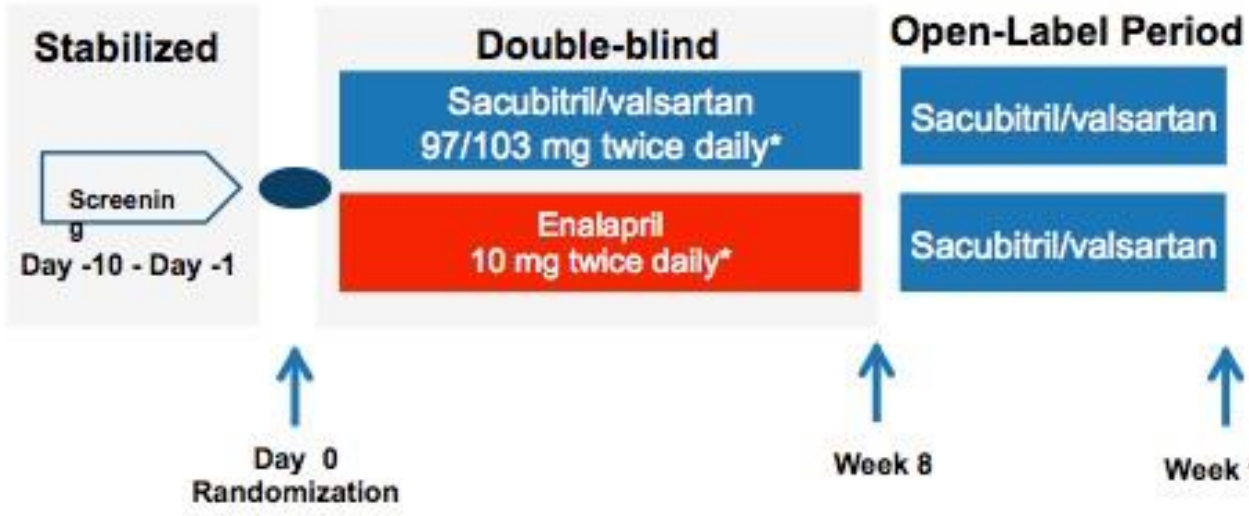


Maggioni et al. Eur J Heart Fail 2013;15,1173–84

Zile MR, et al. J Am Coll Cardiol. 2016;68(22):2425–2436.

PIONEER HF

Comparison of sacubitril/valsartan vs. Enalapril on effect of **NT-pro-BNP** in patients stabilized from an acute heart failure episode



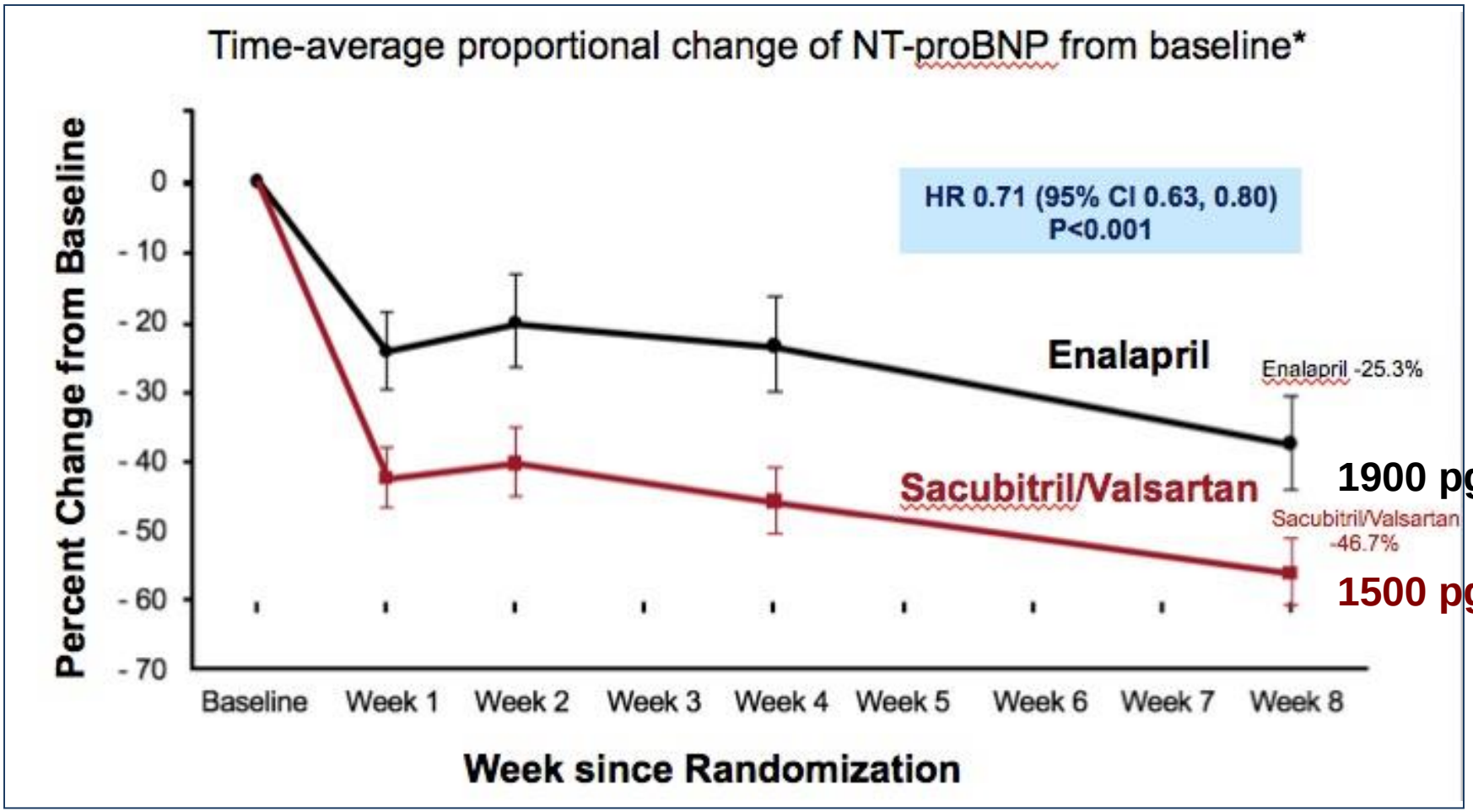
At the end of Week 8 study treatment, patients in the enalapril group were switched to sacubitril/valsartan and all patients remained on sacubitril/valsartan for the 4-week open-label period

PIONEER HF

	Sacubitril/Valsartan (n=440)	Enalapril (n=441)
Age (years)	61 (50.5, 71)	63 (54, 72)
Women (%)	25.7	30.2
Black (%)	35.9	35.8
Prior HF diagnosis (%)	67.7	63.0
LVEF, median (25th, 75th)	0.24 (0.18, 0.30)	0.25 (0.20, 0.30)
Systolic pressure, median (25th, 75th) mm Hg	118 (110, 133)	118 (109, 132)
NT-proBNP median (25th, 75th) pg/mL at randomization	2883 (1610, 5403)	2536 (1363, 4917)
ACEi/ARB therapy (%)	47.3	48.5
Beta-adrenergic blockers (%)	59.6	59.6
NYHA class (%)		
NYHA I	0.9	1.1
NYHA II	22.7	27.7
NYHA III	64.3	61.0
NYHA IV	8.9	8.2

Velazquez E, Morrow D, DeVore, A, et al., N EnglJ Med. 2018

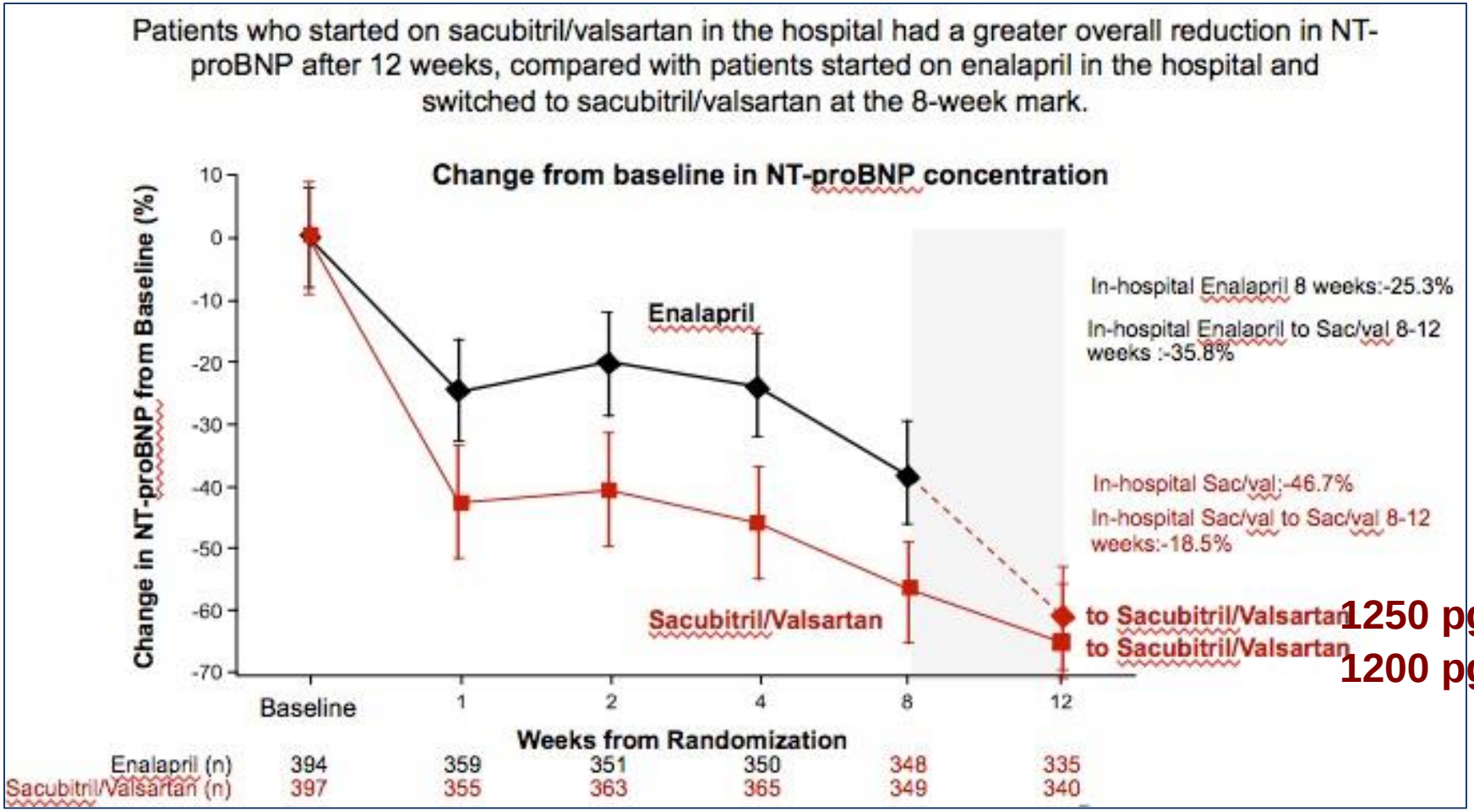
PIONEER HF



Velazquez E, Morrow D, DeVore, A, et al., N EnglJ Med. 2018

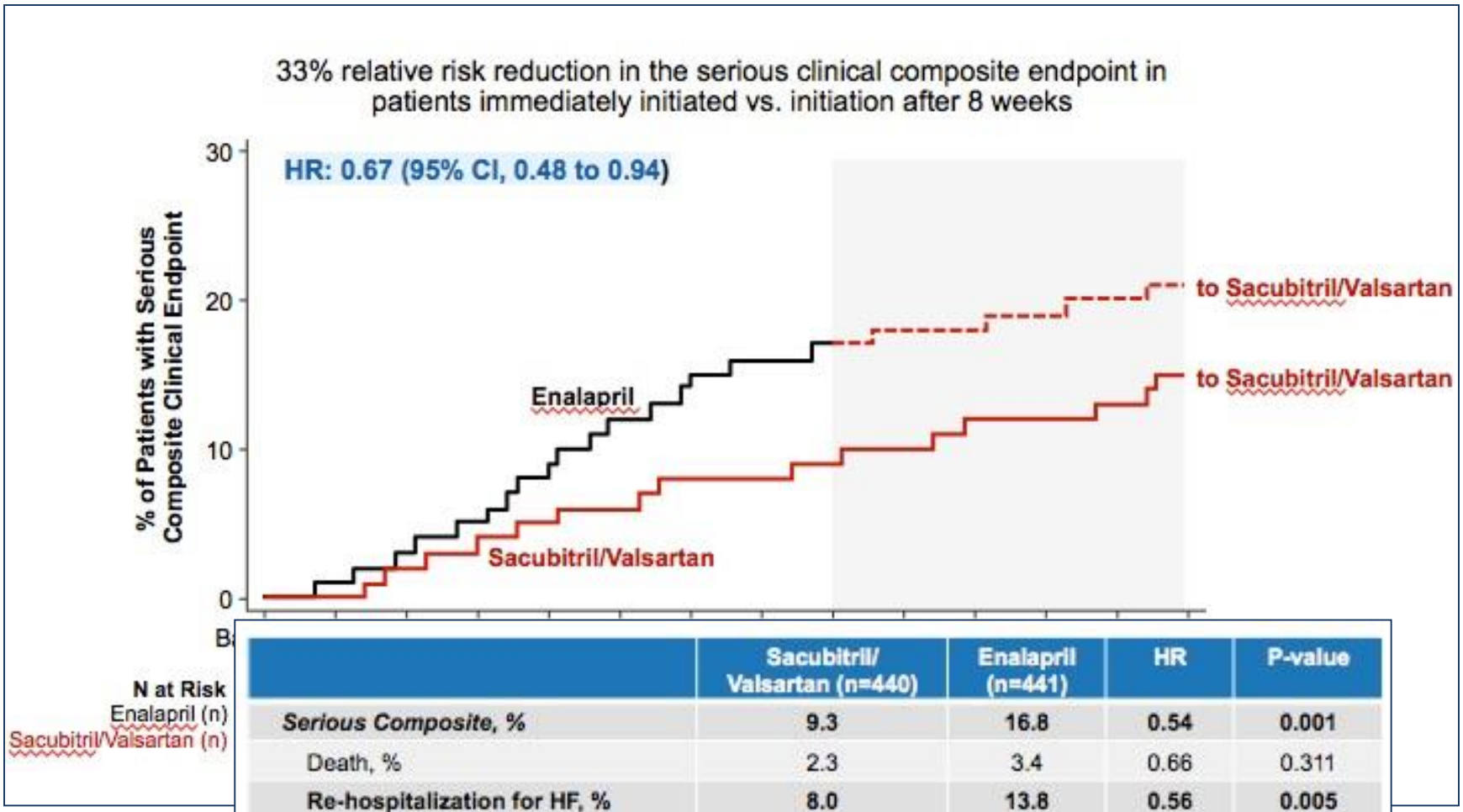
PIONEER HF: open label

Patients who started on sacubitril/valsartan in the hospital had a greater overall reduction in NT-proBNP after 12 weeks, compared with patients started on enalapril in the hospital and switched to sacubitril/valsartan at the 8-week mark.



Velazquez E, Morrow D, DeVore, A, et al., N EnglJ Med. 2018

Serious Clinical Composite Events: Death, Hospitalization for HF, LVAD or listing for cardiac transplant

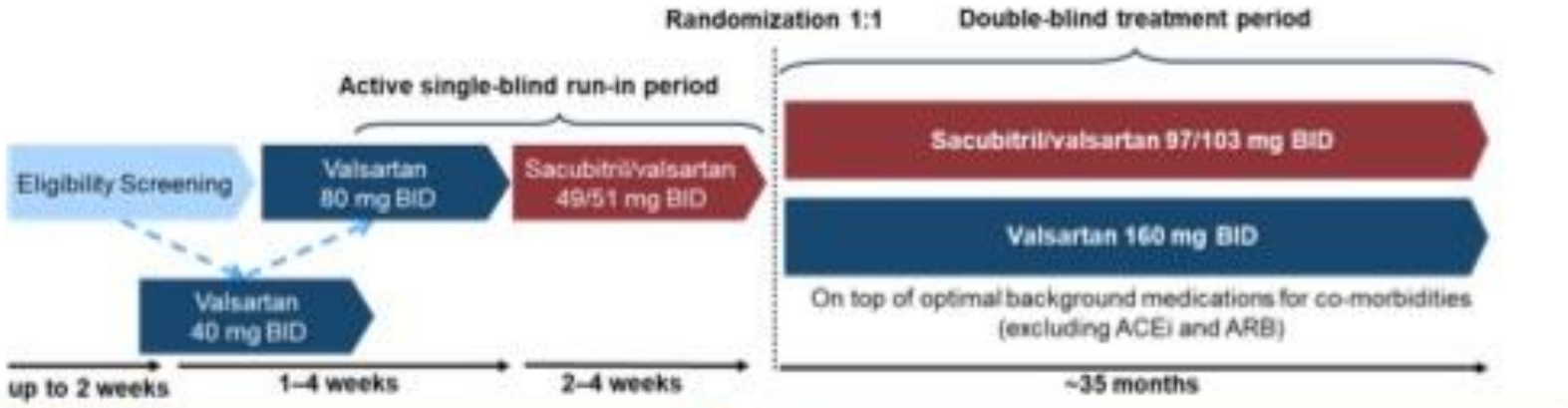


	Sacubitril/ Valsartan (n=440)	Enalapril (n=441)	HR	P-value
Serious Composite, %	**9.3**	**16.8**	**0.54**	**0.001**
Death, %	2.3	3.4	0.66	0.311
Re-hospitalization for HF, %	**8.0**	**13.8**	**0.56**	**0.005**
Requirement of LVAD, %	0.2	0.2	0.99	0.999
Cardiac Transplant, %	0	0	-	-

PARAGON HF.

Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction.

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death



Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

Solomon SD, et al. JACC-Heart Fail 2017; 5(7):471-482.

PARAGON HF : « HFpEF »

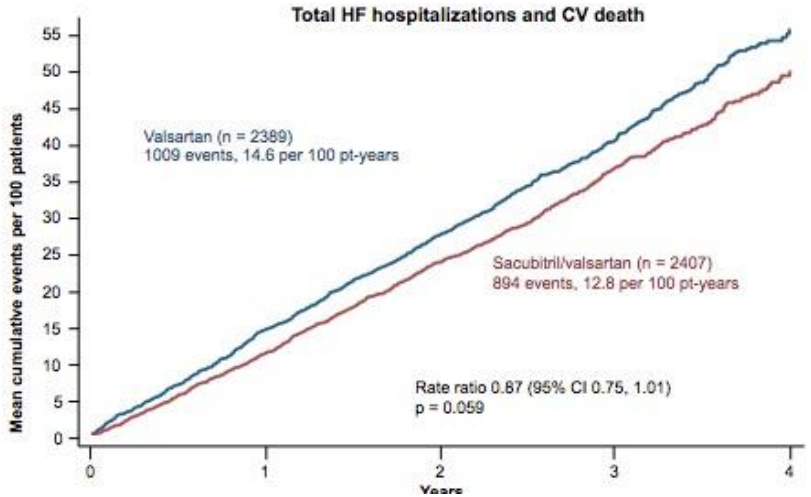
Key inclusion criteria	Key exclusion criteria
✓ ≥ 50 years of age and LVEF ≥ 45% within 6 months prior to screening ✓ Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s) for at least 30 days prior to enrollment ✓ Structural heart disease (LAE or LVH by echocardiography) within 6 months prior to screening ✓ Patients with at least one of the following ➢ HF hospitalization within 9 months prior to screening and NT-proBNP >200 pg/mL for patients without AF or >600 pg/mL for patients with AF* OR ➢ No recent HF hospitalization: NT-proBNP >300 pg/mL for patients without AF or >900 pg/mL for patients with AF*	✓ Any prior measurement of LVEF < 40% ✓ Current acute decompensated heart failure ✓ MI, CABG or any event within the 6 months prior to screening that could have reduced the LVEF (unless LVEF confirmed as ≥ 45%) ✓ Requirement for treatment with two or more of the following: ACEi, ARB or renin inhibitor ✓ SBP < 110 or ≥ 180mm Hg (or > 150mm Hg if patient not taking 3 or more antihypertensive medications) ✓ Serum potassium >5.2 mmol/L at screening, or >5.4 mmol/L at the end of each run-in period ✓ eGFR <30 mL/min/1.73m^2 at screening, OR at the end of each run-in period eGFR <25 mL/min/1.73m^2 or eGFR reduction of >35% compared to that at screening

PARAGON HF

		Sacubitril/valsartan N=2,407	Valsartan N=2,389
Age (years) – mean (SD)		72.7 (8.3)	72.8 (8.5)
Sex – n (%)	Male	1166 (48.4)	1151 (48.2)
	Female	1241 (51.6)	1238 (51.8)
Race – n (%)	Caucasian	82%	81%
	Black	2.2%	2.1%
	Asian	12%	13%
Region – n (%)	North America*	12%	11%
	Latin America	7.9%	7.5%
	Western Europe	29%	29%
	Central Europe	36%	36%
	Asia/Pacific/other**	16%	16%
Baseline LVEF – median [IQR]		57 [51,62]	57 [50,63]
Baseline NT-proBNP (pg/mL) – median (IQR) – Sinus rhythm		583 [370, 1046]	611 [389, 1072]
Baseline NT-proBNP (pg/mL) – median (IQR) – Atrial fibrillation		1633 [1191, 2388]	1536 [1153, 2212]

Solomon et al.NEJM 2019; epub ahead of print. Doi:10.1056/NEJMoa1908655

PARAGON HF

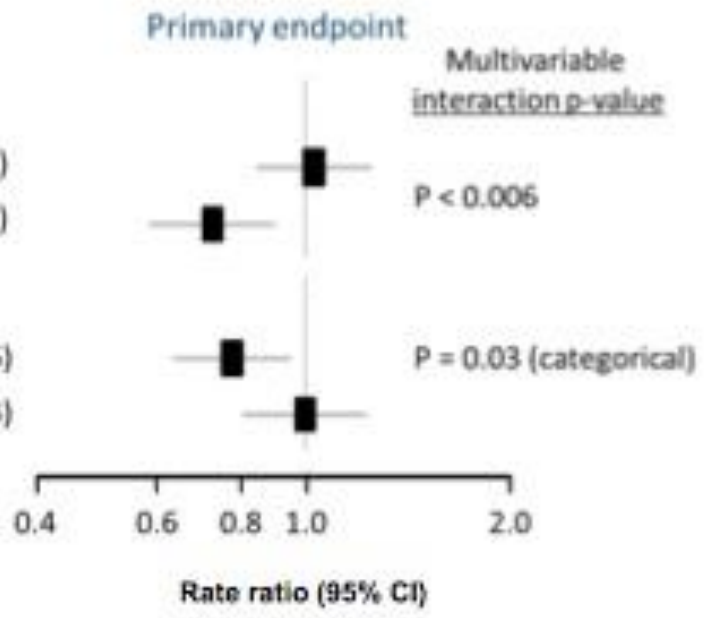


	Sacubitril/valsartan (n = 2407)	Valsartan (n = 2389)	Rate ratio	p-value
Primary endpoint				
Total (first and recurrent) hospitalizations for heart failure or death from cardiovascular causes (total number of events)*	894 (37.1) 12.8 per 100-patient years	1009 (42.2) 14.6 per 100-patient years	0.87 (0.75, 1.01)	0.059
Components				
Total hospitalizations for worsening of HF, n (%)	690 (28.7)	797 (33.4)	0.85 (0.72, 1.00)	0.056†
Death from CV causes, n (%)	204 (8.5%)	212 (8.9%)	0.95 (0.79, 1.16)	0.62†

Solomon et al.NEJM 2019; epub ahead of print. Doi:10.1056/NEJMoa1908655

PARAGON HF
Prespecified subgroups.

Subgroup	No. of events/ patients	Rate ratio (95% CI)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
LVEF		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)



Solomon et al.NEJM 2019; epub ahead of print. Doi:10.1056/NEJMoa1908655

Synthèse Entresto 2019

1. Patient ambulant HFrEF (Cl. I)
2. Administration précoce intrahospitalière:
   - Réduction (précoce et soutenue) de 30% du NTproBNP à 8 semaines VS enalapril.
   - Sécure (même chez les pts naïfs RAASi)
   - +/- 50% pt atteignent de la dose cible.
3. HFpEF:
   - Presque …
   - Particulièrement chez la femme et FE 50-57%.
   - Traitement « taille unique » ou « sur mesure » ? …
   - Suggère probable bénéfique dans HFmrEF

Insuffisance cardiaque en 2019.

Actualités thérapeutiques.

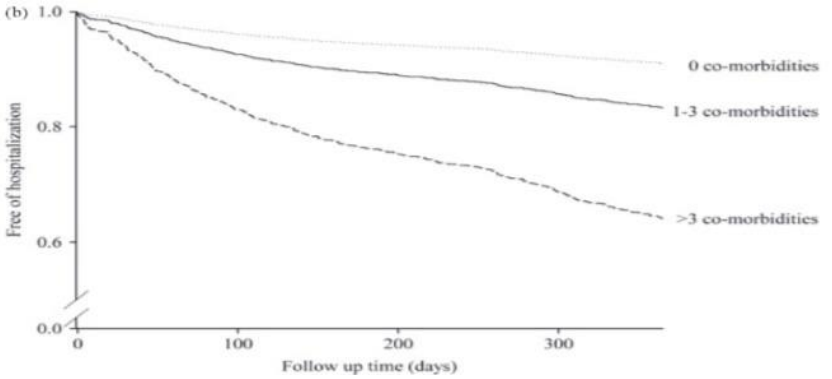
Guidelines 2016.

Comorbidités.

Comorbidités

Prévalence des comorbidités

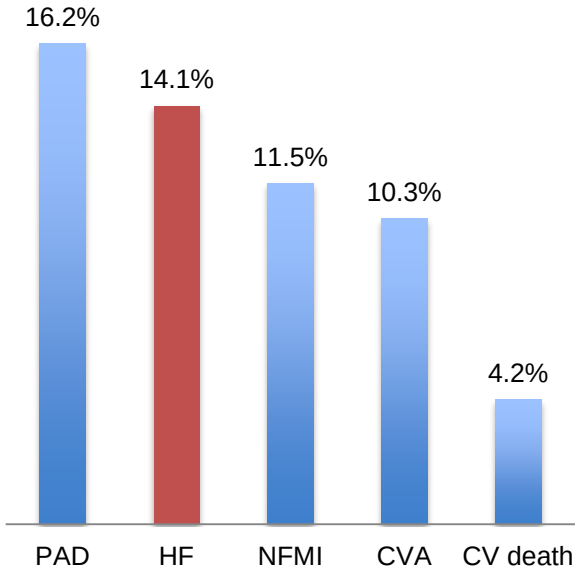
	HFrEF (LVEF <40%)	HFpEF (LVEF ≥40%)	*P*-value
Chronic kidney disease	541 (41)	383 (39)	0.381
Anaemia	349 (28)	306 (30)	0.130
Diabetes	470 (30)	343 (28)	0.191
COPD	255 (16)	173 (14)	0.101
Stroke	166 (11)	129 (10)	0.892
Sleep apnoea	69 (4)	49 (4)	0.578
Hypothyroidism	152 (10)	96 (8)	0.062
Hyperthyroidism	54 (4)	32 (3)	



Van Deursen VM, et al. Eur J Heart Fail 2014

Liaisons dangereuses…

% évènement « vasculaire »



Shah AD et al, Lancet Diabetes Endocrinol. 2015; 3:105-113.

Mortalité annuelle X 10 !

Mortality rate among >65 y T2DM patients (with or without HF) in 1994 over 60 months[1]

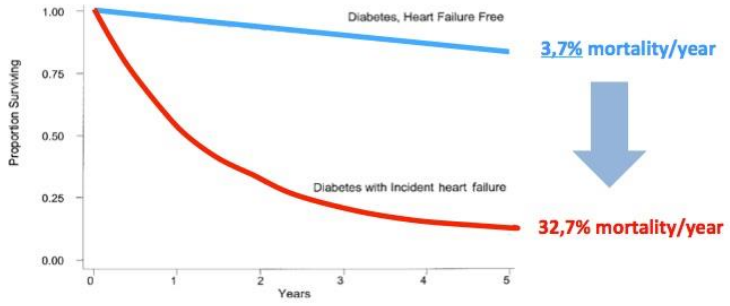
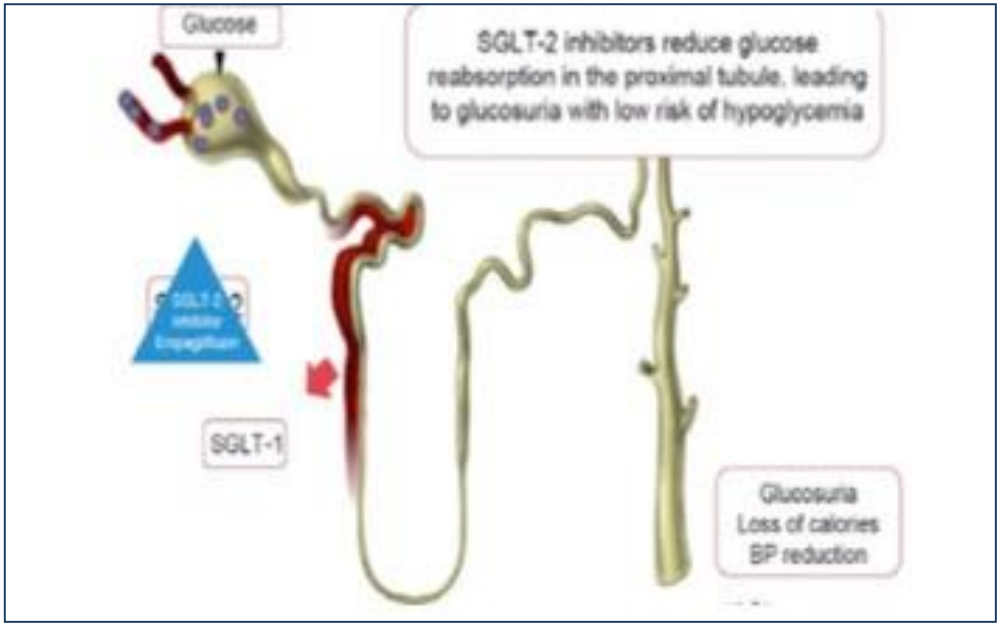
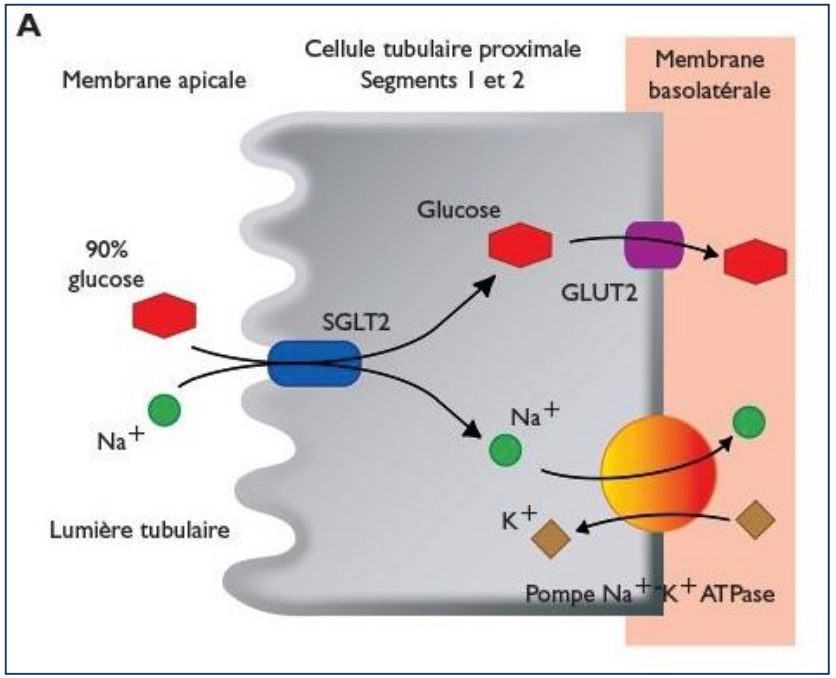


Figure 1—*Five-year Kaplan-Meier survival estimates for 115,803 adults age ≥65 years in fee-for-service Medicare with diabetes by incident heart failure status.*

Bertoni AG et al, Diabetes Care 2004; 27 (3): 699-703

Inhibiteurs du co-transporteur sodium-glucose type 2 (SGLT-2i).

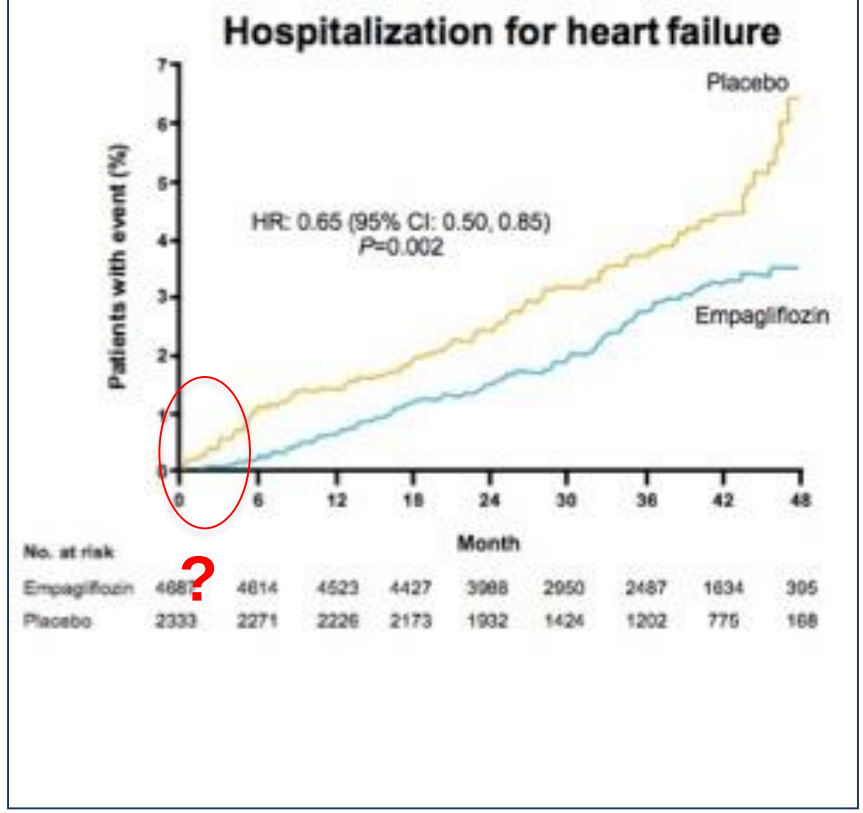




EMPA-REG OUTCOME.

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Outcome	Patients with event / analyzed		Hazard ratio	95% CI	*P* value
	Empagliflozin	Placebo			
3-point MACE[a]	490/4687	282/2333	0.86	0.74, 0.99	0.04
CV death	172/4687	137/2333	0.62	0.49, 0.77	<0.001
Nonfatal MI[b]	213/4687	121/2333	0.87	0.70, 1.09	0.22
Nonfatal stroke	150/4687	60/2333	1.24	0.92, 1.67	0.16
Hospitalization for heart failure	126/4687	95/2333	0.65	0.50, 0.85	0.002



Zinman B et al. N Engl J Med. 2015;373:2117–2128.

Guidelines ESC 2016.

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class	Level	Ref
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B	149, 156–158

Empagliflozin should be considered in patients with T2D in order to **delay the onset of heart failure and prolong life**

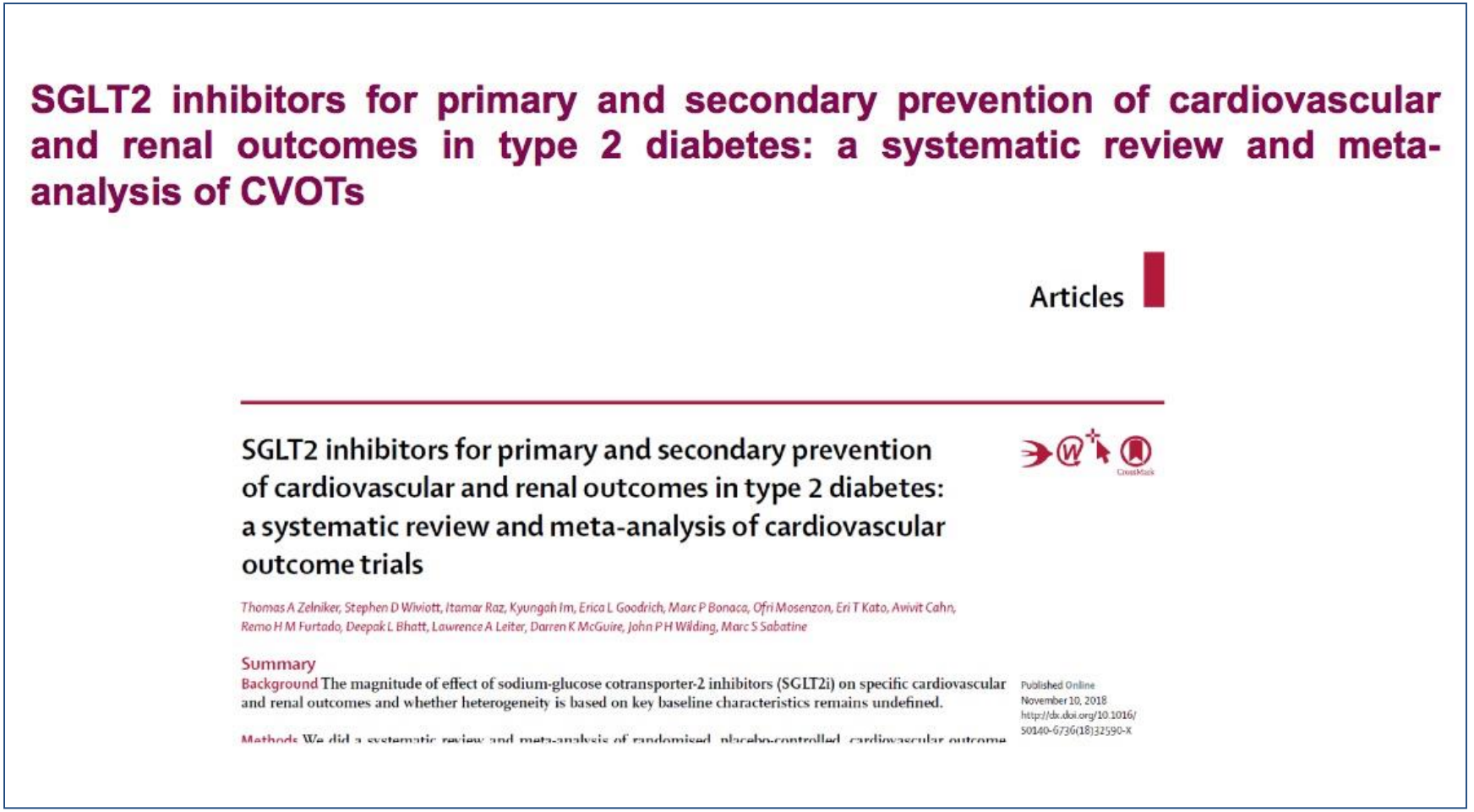
Class IIa

Level B

Ponikowski P et al. Eur Heart J 2016;37:2129

Meta-analyse.

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of CVOTs



Articles

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Summary

Background The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined.

Methods We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome

Published Online November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X

Zelniker et al. **Lancet. 2019 Aug 17;394(10198):560-561**

Meta-analyse.

Jardiance® *Invokana®* *Forxiga®*

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

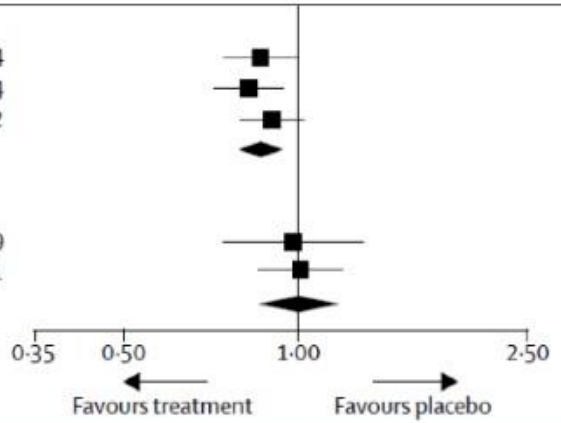
Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

Zelniker et al. ***Lancet. 2019 Aug 17;394(10198):560-561***

Meta-analyse: MACE

MACE stratifiés par la présence de maladie AS établie.

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**

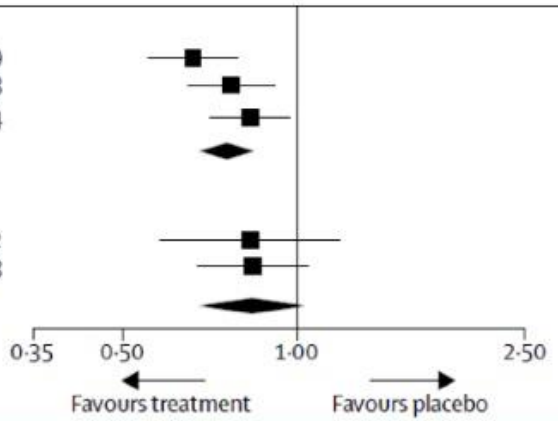


Zelniker et al. ***Lancet. 2019 Aug 17;394(10198):560-561***

Meta-analyse.

Hospitalisations IC / mortalité CV stratifiées par la présence de maladie AS établie

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**

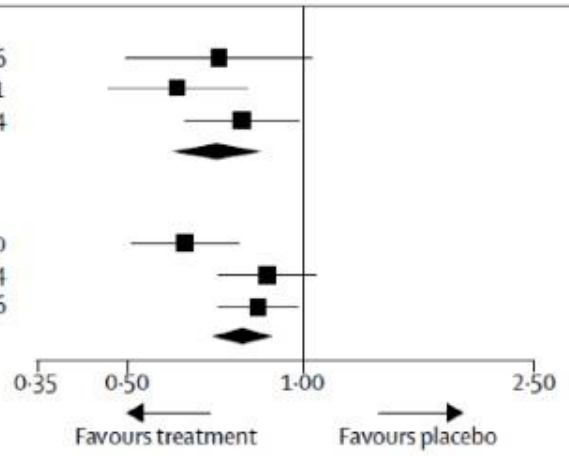


Zelniker et al. ***Lancet. 2019 Aug 17;394(10198):560-561***

Meta-analyse.

Hospitalisations IC / mortalité CV stratifiées par la présence d'insuffisance cardiaque.

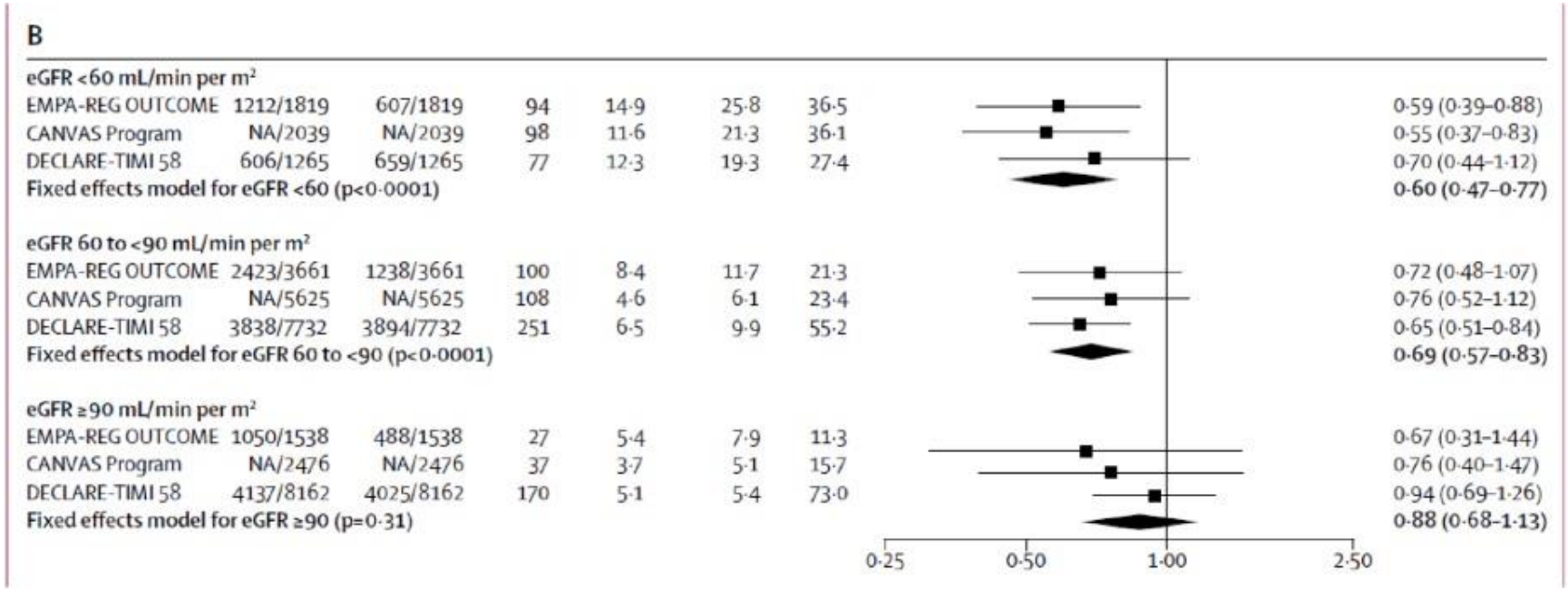
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462/706	244/706	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803/1461	658/1461	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852/1724	872/1724	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225/6314	2089/6314	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992/8681	3689/8681	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730/15 436	7706/15 436	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**



Zelniker et al. ***Lancet. 2019 Aug 17;394(10198):560-561***

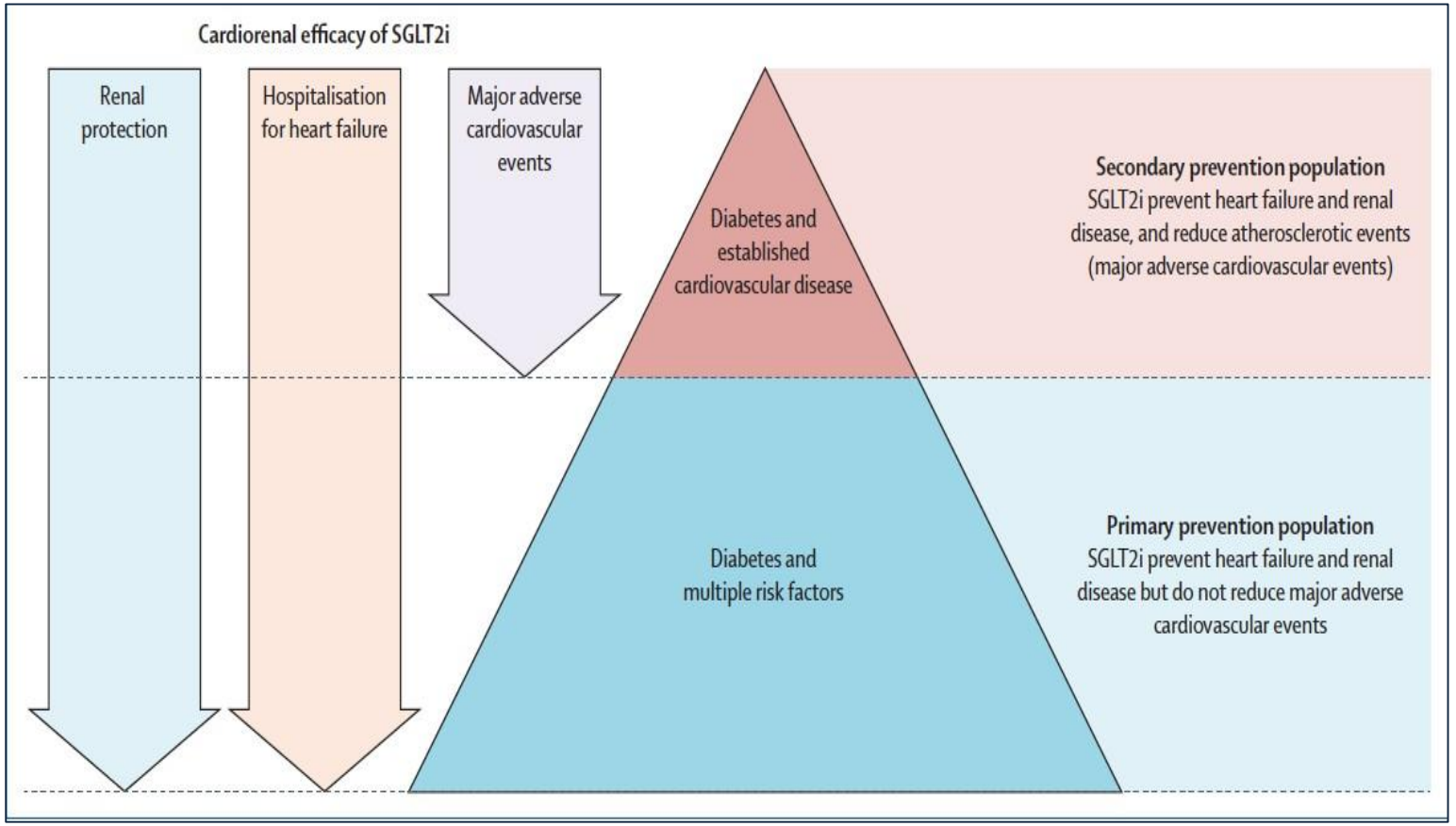
Meta-analyse.

Hospitalisations IC stratifiées par eGFR



Zelniker et al. ***Lancet. 2019 Aug 17;394(10198):560-561***

Meta-analyse.



Zelniker et al. ***Lancet. 2019 Aug 17;394(10198):560-561***

D'un PARADIGM à un autre?

- Effet protecteur « de classe ».
- Mécanisme?
- Réduction importante des (premières) hospitalisations pour IC / mortalité CV:
  - Indépendamment de
    - IC pré-existante.
    - Prévention primaire et secondaire.
  - Surtout lors de baisse du DFG (remboursement?).

… utilisable chez le patient IC non-diabétique???

SGLT2-i chez les IC (non-diabétiques)?

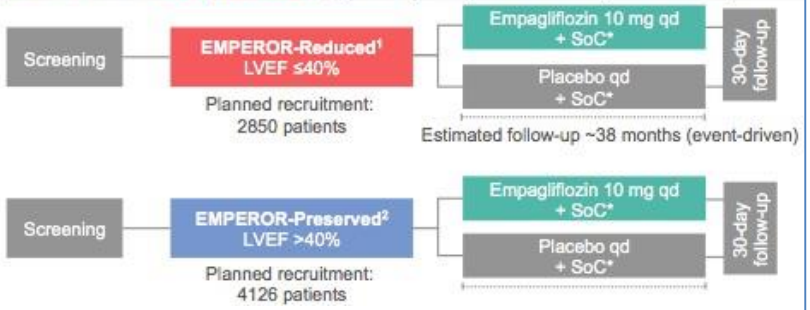
Emperor

Reduced & Preserved.

Phase III randomised double-blind placebo-controlled studies

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with **reduced**[1] or **preserved**[2] **ejection fraction**

Population: T2D **and** non-T2D, age ≥18 years, chronic HF (NYHA II–IV)



DAPA-HF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Lju, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, and A.-M. Langkilde, for the DAPA-HF Trial Co

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

N Engl J Med. 2019 Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print]

DAPA-HF

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Age — yr	66.2±11.0	66.5±10.8
Female sex — no. (%)	564 (23.8)	545 (23.0)
Body-mass index†	28.2±6.0	28.1±5.9
Race — no. (%)‡		
White	1662 (70.0)	1671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region — no. (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1094 (46.1)	1060 (44.7)
Asia–Pacific	543 (22.9)	553 (23.3)
NYHA functional classification — no. (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate — beats/min	71.5±11.6	71.5±11.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3
Left ventricular ejection fraction — %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)
Principal cause of heart failure — no. (%)		
Ischemic	1316 (55.5)	1358 (57.3)
Nonischemic	857 (36.1)	830 (35.0)
Unknown	200 (8.4)	183 (7.7)
Medical history — no. (%)		
Hospitalization for heart failure	1124 (47.4)	1127 (47.5)
Atrial fibrillation	916 (38.6)	902 (38.0)
Diabetes mellitus§	993 (41.8)	990 (41.8)
Estimated GFR		
Mean — ml/min/1.73 m^2	66.0±19.6	65.5±19.3
Rate of <60 ml/min/1.73 m^2 — no./total no. (%)	962/2372 (40.6)	964/2371 (40.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	622 (26.2)	620 (26.1)
Cardiac resynchronization therapy‖	190 (8.0)	164 (6.9)

Table 1. (Continued.)

Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Heart failure medication — no. (%)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril–valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)
Digitalis	445 (18.8)	442 (18.6)
Glucose-lowering medication — no./total no. (%)**		
Biguanide	504/993 (50.8)	512/990 (51.7)
Sulfonylurea	228/993 (23.0)	210/990 (21.2)
DPP-4 inhibitor	161/993 (16.2)	149/990 (15.1)
GLP-1 receptor agonist	11/993 (1.1)	10/990 (1.0)
Insulin	274/993 (27.6)	266/990 (26.9)

N Engl J Med. 2019 Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print]

DAPA-HF

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)	*events/100 patient-yr*	Placebo (N=2371)	*events/100 patient-yr*	Hazard or Rate Ratio or Difference (95% CI)	P Value
Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%)¶	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Death from any cause — no. (%)	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)	NA
Safety outcomes						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA

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DAPA-HF

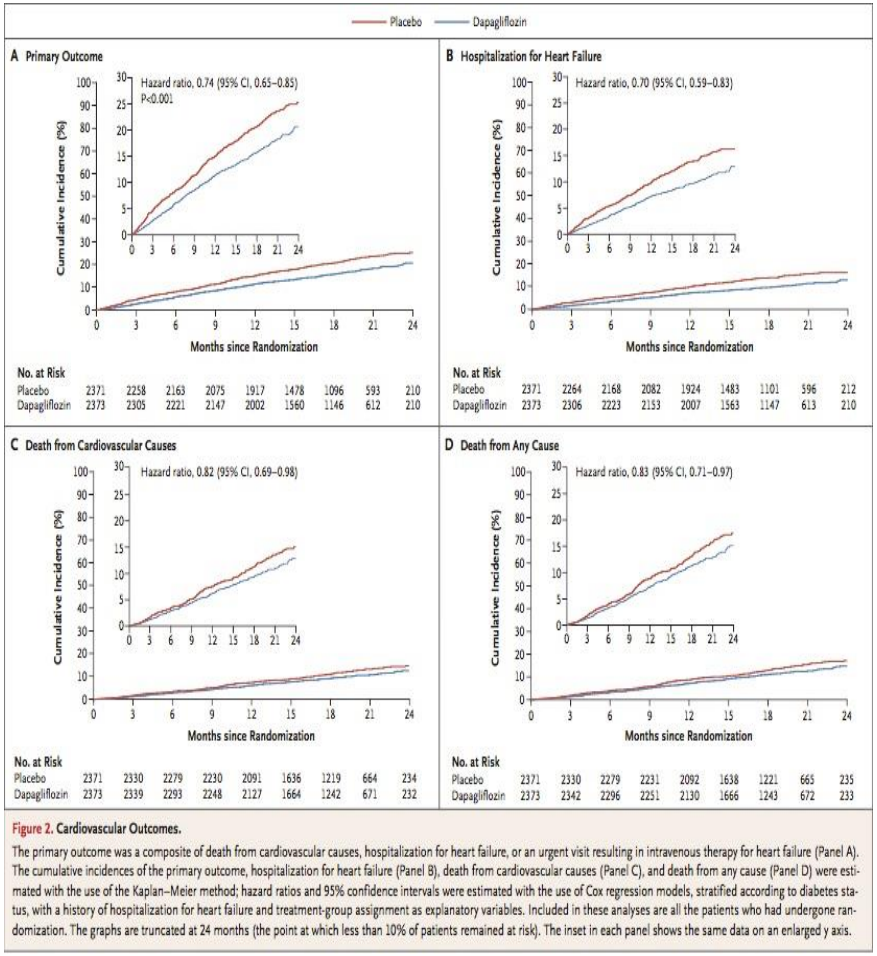

Figure 2. Cardiovascular Outcomes.

The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure (Panel A). The cumulative incidences of the primary outcome, hospitalization for heart failure (Panel B), death from cardiovascular causes (Panel C), and death from any cause (Panel D) were estimated with the use of the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables. Included in these analyses are all the patients who had undergone randomization. The graphs are truncated at 24 months (the point at which less than 10% of patients remained at risk). The inset in each panel shows the same data on an enlarged y axis.

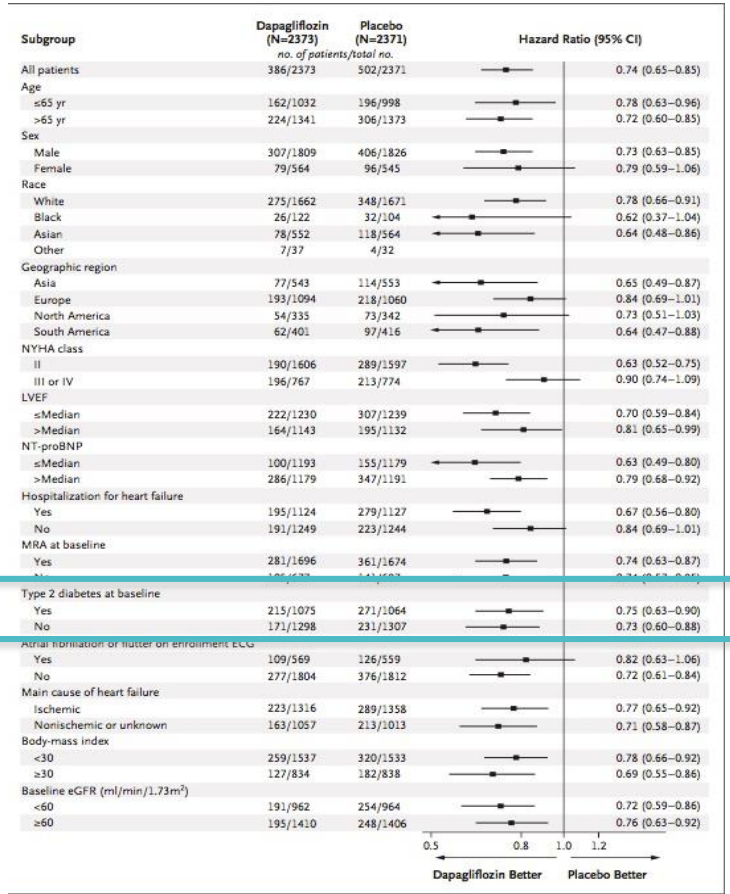

Figure 3. Primary Composite Outcome, According to Prespecified Subgroup.

Shown is the primary outcome of the trial — a composite of hospitalization for heart failure, an urgent visit resulting in intravenous therapy for heart failure, or death from cardiovascular causes — according to subgroups that were prespecified in the protocol. Race was reported by the investigators. The body-mass index is the weight in kilograms divided by the square of the height in meters. ECG denotes electrocardiography, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

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Actualités thérapeutiques 2019 en insuffisance cardiaque.

Conclusions.

THMs

1. Fréquent, tue, coûte cher.
2. Appliquer les guidelines!

   Traitement bien codifié mais *sous-utilisé*!
3. Penser aux comorbidités… et les traiter!
4. Encadrer et ***éduquer*** le malade.
5. Vers de nouveaux traitements (HFpEF?) / de nouveaux concepts.

Merci de votre attention!