Les inhibiteurs SGLT2, aujourd'hui le cœur, demain les poumons ?

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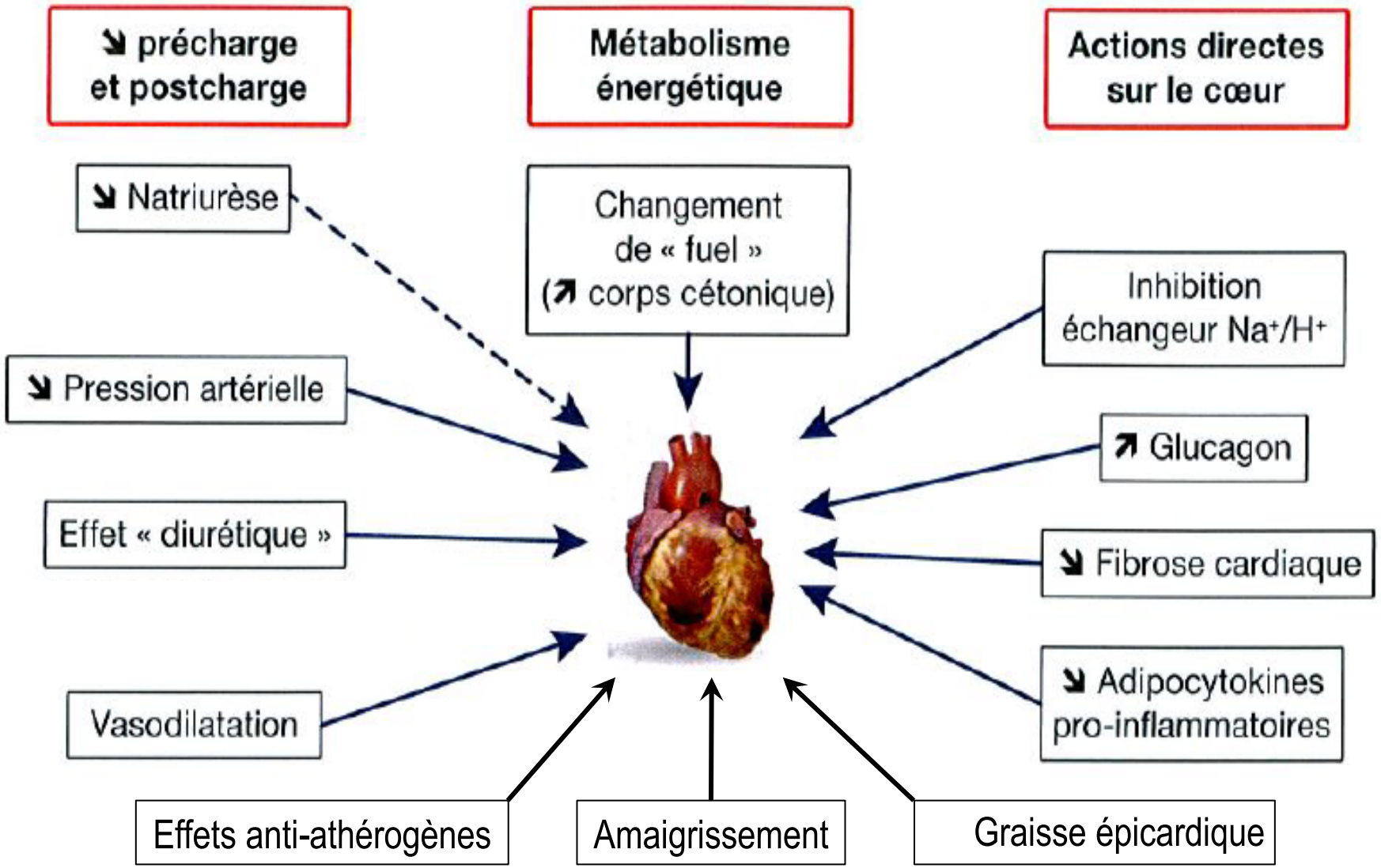
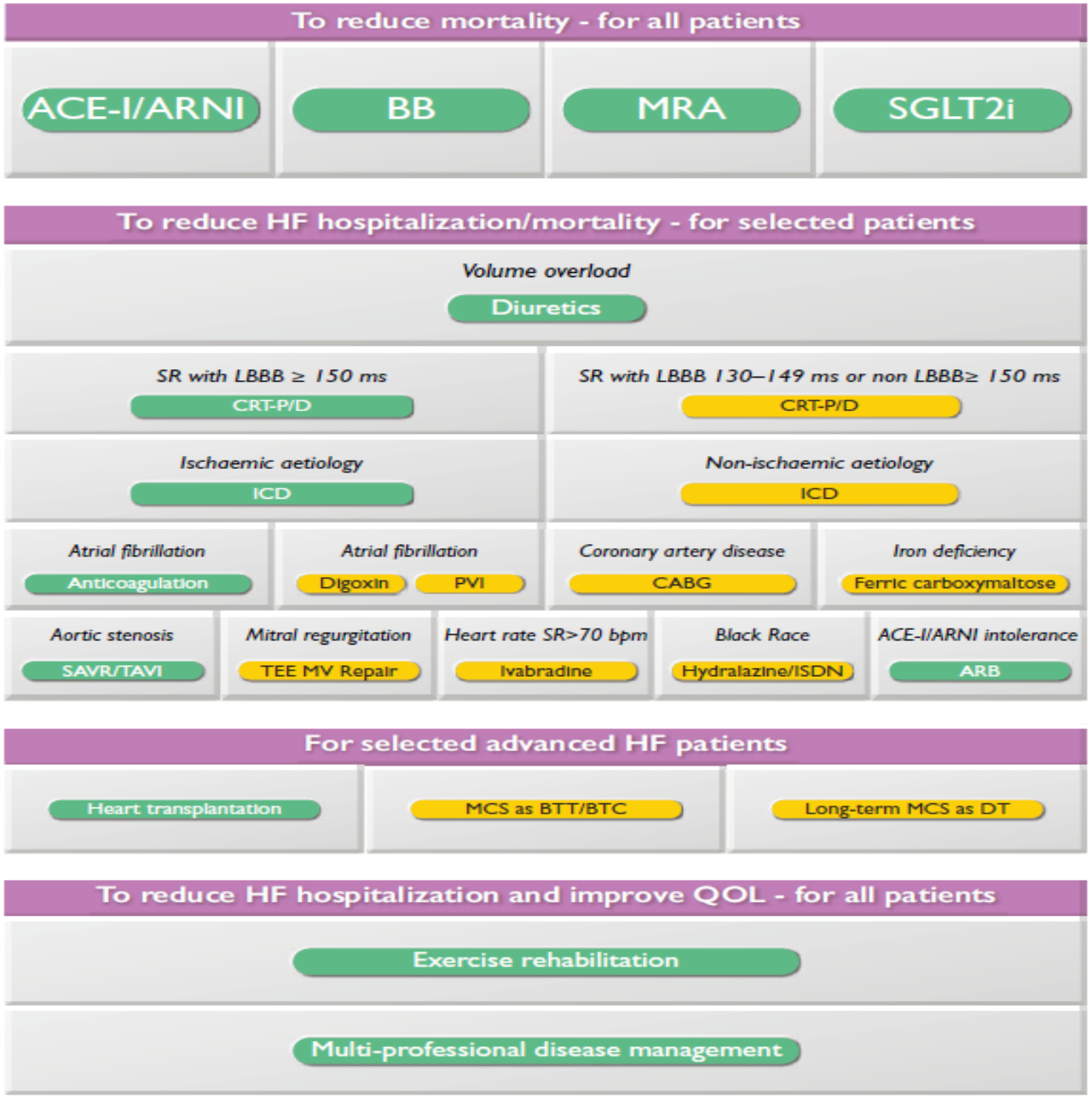
Mécanismes d'action des inhibiteurs SGLT2 dans l'insuffisance cardiaque



Algorithme du traitement de l'insuffisance cardiaque chronique à fraction d'éjection réduite (FE < 40 %) 2021



Eur Heart J 2021;42(36):3599-3726

Traitement pharmacologique de 1ère intention de l'IC à FE réduite (FE ≤ 40 %) 2021

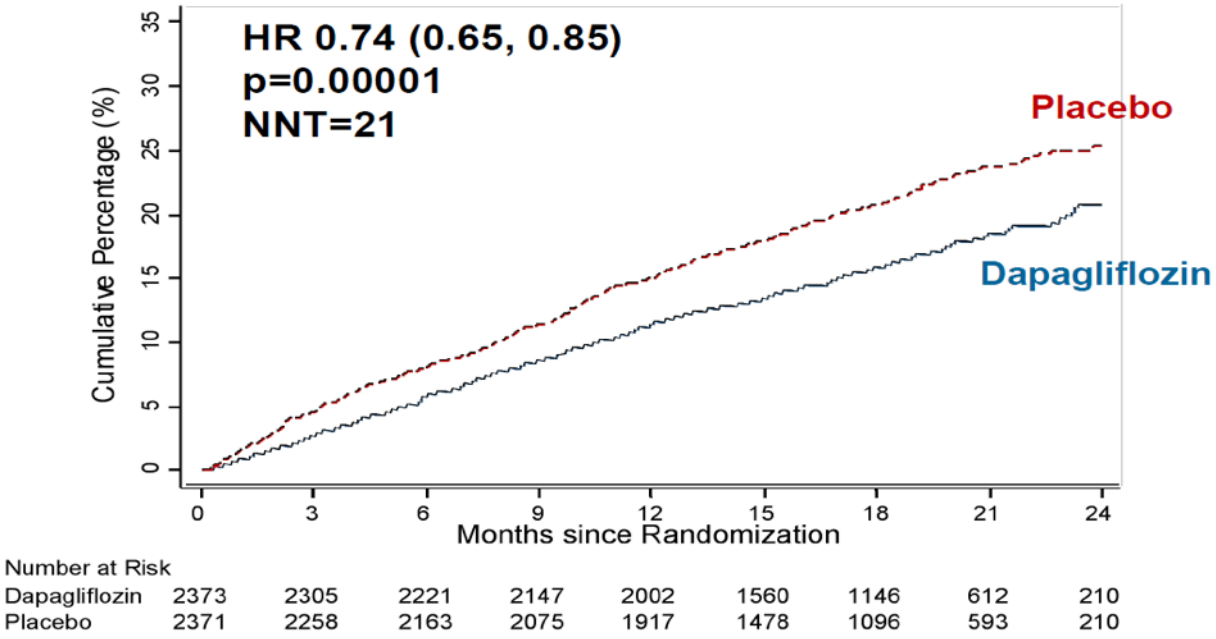
Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B
Sacubitril/valsartan may be considered in ACI-naive with HFrEF to reduce the risk of HF hospitalization and death	IIb	B

Eur Heart J 2021;42(36):3599-3726

Inhibiteurs SGLT2 dans l'insuffisance cardiaque chronique à FE réduite : 2 essais positifs

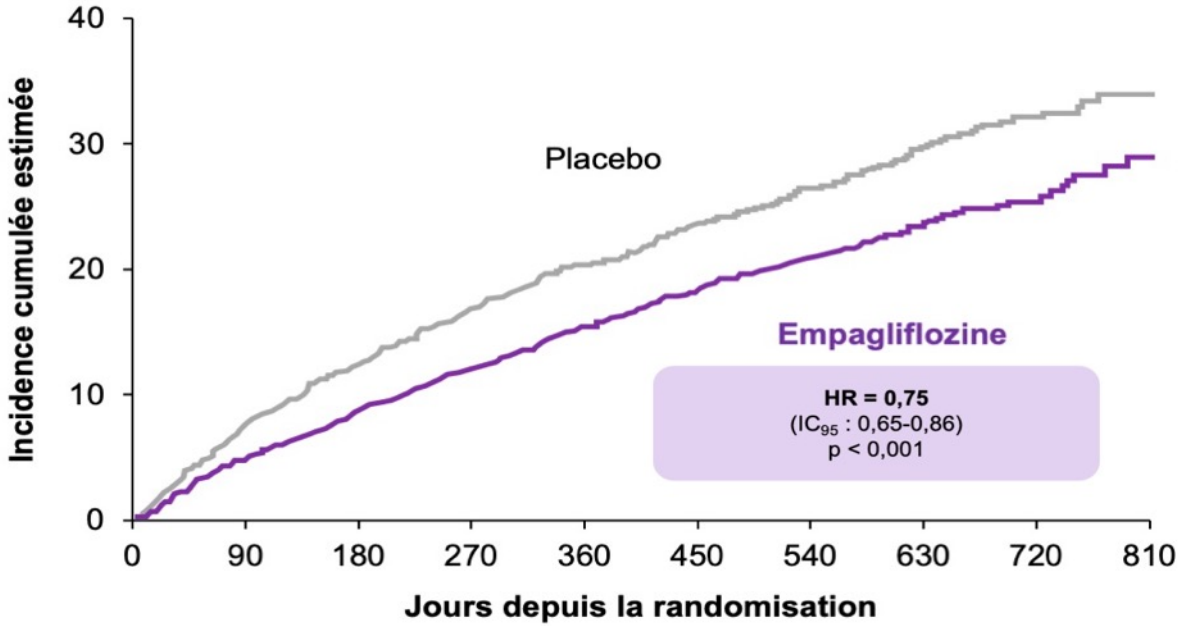
DAPA-HF[1]

CV Death/HF hospitalization/Urgent HF visit



EMPEROR-Reduced[2]

CV Death/HF hospitalization

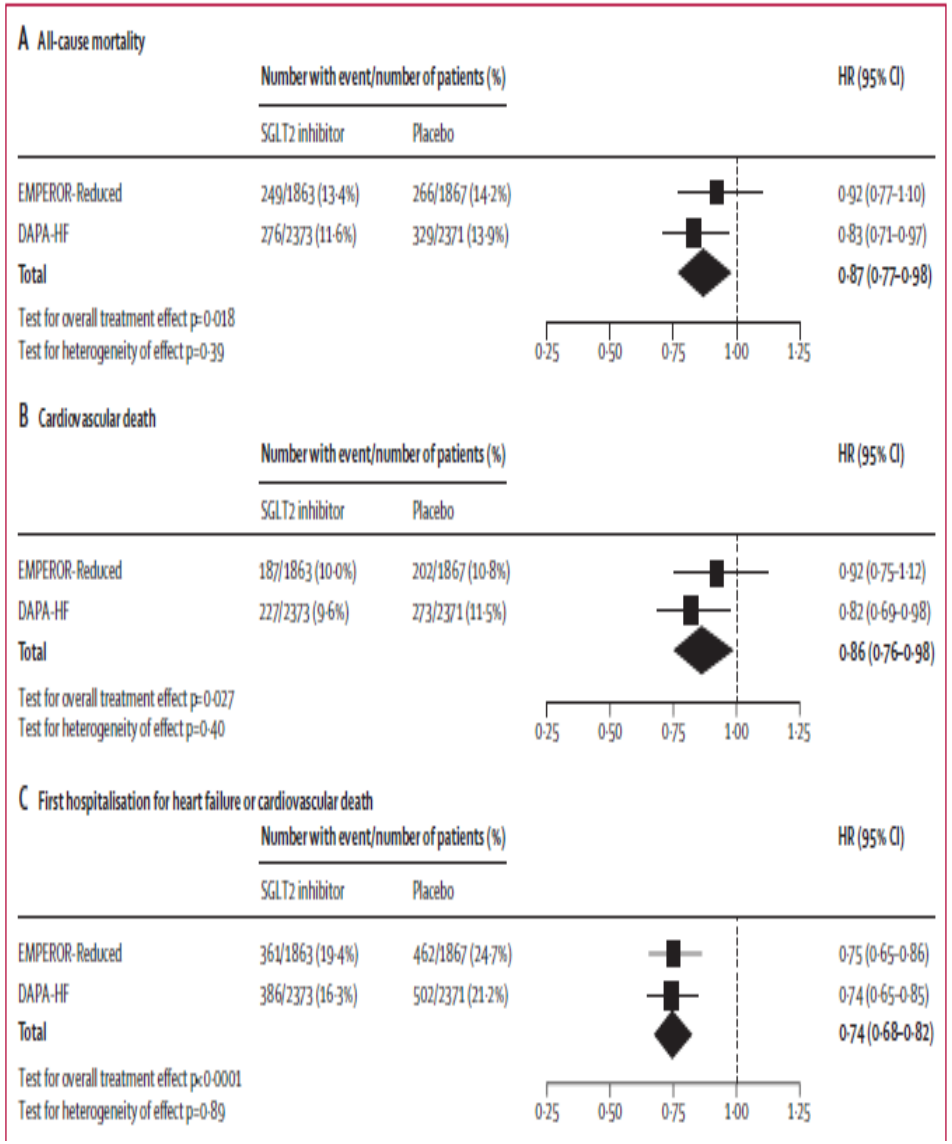


Pourcentage de patients diabétiques :

- DAPA-HF : 41,8 %
- EMPEROR-Reduced : 49,8 %

1.N Engl J Med 2019;381(21):1995-2008
2.N Engl J Med 2020;383(15):1413-1424

Méta-analyse des essais DAPA-HF et EMPEROR-Reduced : effets des gliflozines sur les décès, les hospitalisations pour décompensation cardiaque et les évènements rénaux au cours de l'ICFEr chronique

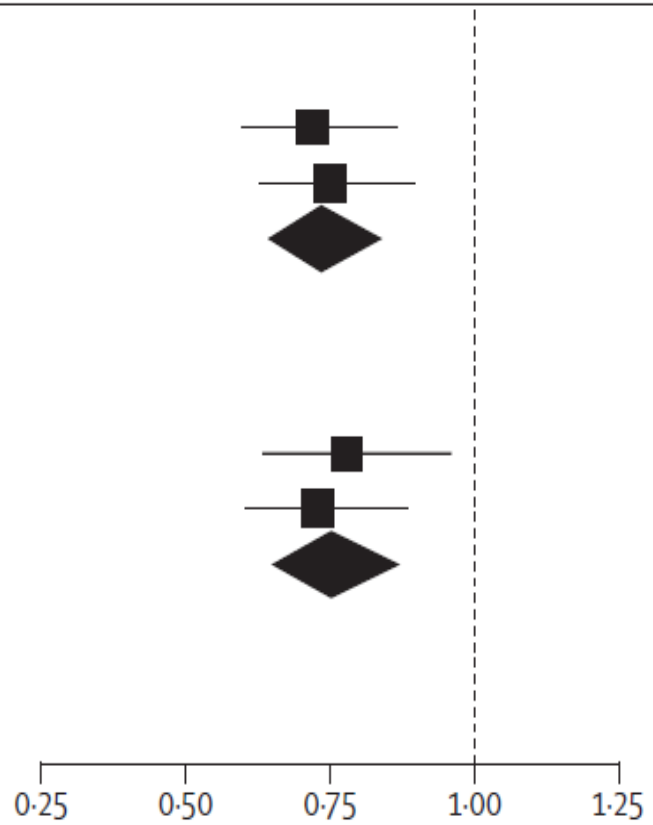


Lancet 2020; 396(10254):819-829

Méta-analyse des essais DAPA-HF et EMPEROR-Reduced : effets des gliflozines sur les décès cardiovasculaires ou la première hospitalisation pour insuffisance cardiaque en fonction du statut glycémique des patients

A Diabetes status

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
With diabetes			
EMPEROR-Reduced	200/927 (21·6%)	265/929 (28·5%)	0·72 (0·60–0·87)
DAPA-HF	215/1075 (20·0%)	271/1064 (25·5%)	0·75 (0·63–0·90)
Subtotal			**0·74 (0·65–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·76			
Without diabetes			
EMPEROR-Reduced	161/936 (17·2%)	197/938 (21·0%)	0·78 (0·64–0·97)
DAPA-HF	171/1298 (13·2%)	231/1307 (17·7%)	0·73 (0·60–0·88)
Subtotal			**0·75 (0·65–0·87)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·65			
Test for treatment by subgroup interaction p=0·81			

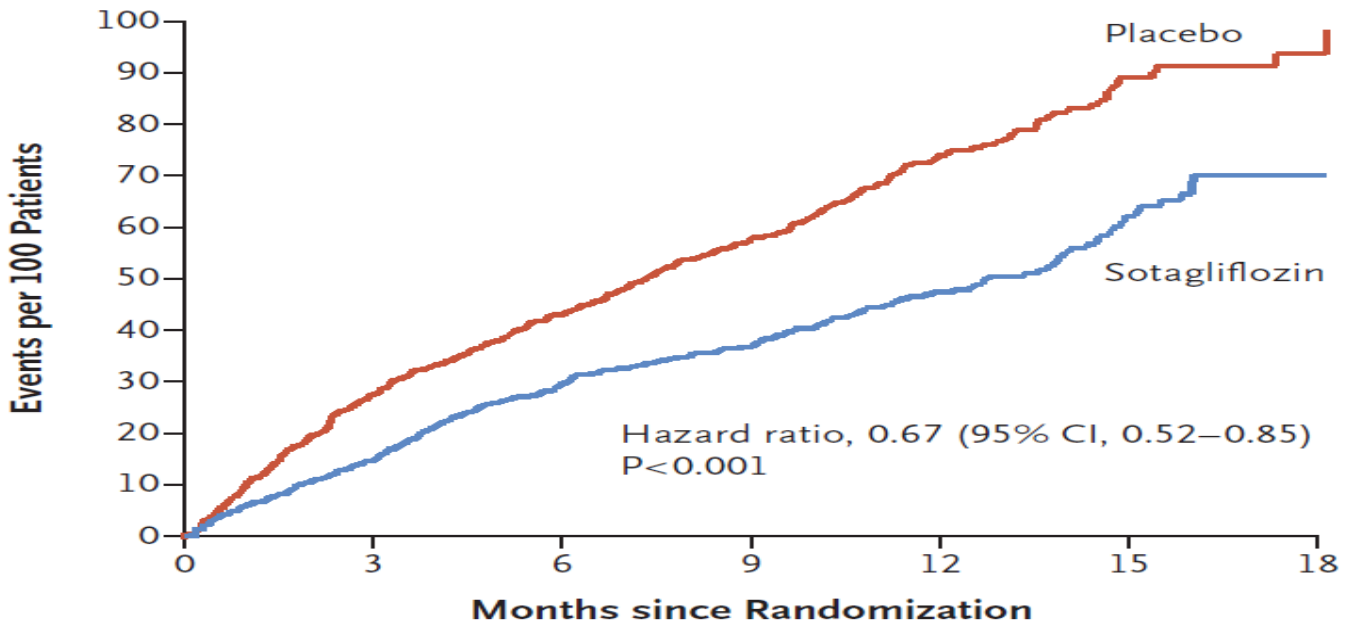


Lancet 2020; 396(10254):819-829

Inhibiteurs SGLT2 introduits au décours d'une insuffisance cardiaque aiguë

SOLOIST-WHT

CV Death/HF hospitalization/Urgent HF visit

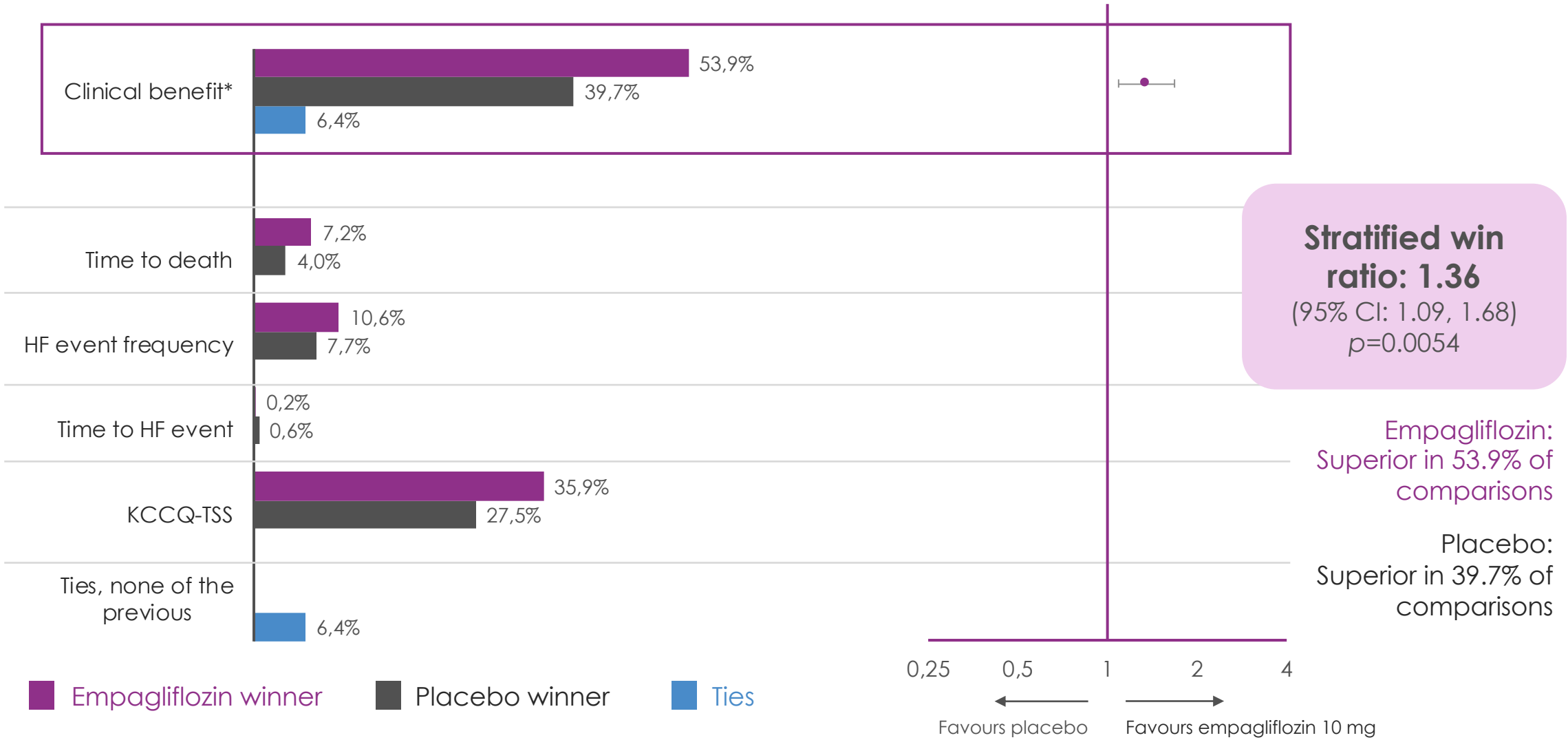


No. at Risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

Mais 100 % de patients diabétiques et étude interrompue prématurément pour défaut de financement du sponsor

N Engl J Med 2021;384:117-128

Inhibiteurs SGLT2 introduits au décours d'une insuffisance cardiaque aiguë – Etude EMPULSE



Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Empagliflozin: Superior in 53.9% of comparisons

Placebo: Superior in 39.7% of comparisons

45 % de patients diabétiques

Tromp J et al. Eur J Heart Fail. 2021;23:826. AHA presentation 14/11/2021Efficacy and Safety of Empagliflozin in Hospitalized Heart Failure Patients: Main Results From the EMPULSE Trial
Science News from Scientific Sessions 2021 - Professional Heart Daily | American Heart Association

Comment mettre en place le traitement médical de fond au décours d'une hospitalisation pour décompensation ?

Recommendations	Class
Recommendations for management of patients after HF hospitalization	
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I
It is recommended that evidence-based oral medical treatment be administered before discharge.	I
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I

Ordre d'introduction fonction de présentation clinique
Augmentation des posologies tous les 15 jours

European Heart Journal (2021)
00, 1-128 ESC GUIDELINES
doi:10.1093/eurheartj/ehab368

Effects of first line pharmacological treatments in parameters defining profiles patient

SGLT2i

Congestion	SGLT2i have diuretic effects
SBP	SGLT2i have very modest impact on BP (↓ 2 mmHg SBP)
HR	SGLT2i have no impact on HR
CKD	SGLT2i may transiently reduce GFR at introduction SGLT2i have no effect on kalemia SGLT2i improve renal prognosis SGLT2i can be used until GFR < 20 mL/min
Diabetes	SGLT2i are recommended to treat type 2 diabetes in HF patients (I, A)

European Journal of Heart Failure (2021) 23, 872–881 POSITION PAPER doi:10.1002/ejhf.2206

Treatment of diabetes in HF patients

Recommendation	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.[293–297]	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.[108,109,136]	I	A

Eur Heart J 2021;42(36):3599-3726

How to prevent adverse effects of SGLT2i ?

Relevant adverse events reported in EMPEROR-Reduced and DAPA-HF trials

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41·4%)	896 (48·1%)	846 (35·7%)	951(40·2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6·0%)	158 (6·7%)
Volume depletion	197 (10·6%)	184 (9·9%)	170 (7·2%)	153 (6·5%)
Ketoacidosis	0	0	3 (0·1%)	0
Severe hypoglycaemic events	6 (0·3%)	7 (0·4%)	4 (0·2%)	4 (0·2%)
Bone fractures	45 (2·4%)	42 (2·3%)	48 (2·0%)	47 (2·0%)
Lower limb amputation	13 (0·7%)	10 (0·5%)	13 (0·5%)	12 (0·5%)
Fournier's Gangrene	1 (0·1%)	0	0	1 (0·1%)

Lancet 2020;396:819-29

How to prevent adverse effects of SGLT2i secondary to hypoglycemia effects ?

SGLT2i increase glycosuria if glycemia > 0,8 g/L

- Adverse events secondary of hypoglycemia
  - Decrease by 50 % sulfamides/glinides dosages
  - Decrease by 30 % insulin dosage
  - Diabetologist consultation
- Adverse events secondary to ↑ ketone production
  - Only in insulinopenic patients
  - Therapeutic education
  - Stop SGLT2i before surgery, if prolonged fasting…
- Adverse events secondary to increase glycosuria : urinary and genital infections
  - Personal hygiene
  - Increase water intake when start treatment
  - Therapeutic education

Traitement pharmacologique de l'IC à FE modérément réduite (FE > 40 et < 50 %)

Définition de l'insuffisance cardiaque – Recos ESC 2021

	IC à FE réduite	IC à FE modérément réduite	IC à FE préservée
Clinique	Présence de symptômes ± signes d'IC[a]		
FE	≤ 40 %	41 – 49 % (54 ?)	≥ 50 % (55 ?)
PN		[b]	BNP en RS > 35 pg/mL en FA > 105 NT-proBNP en RS > 125 pg/mL en FA > 365
Echo		[b]	Anomalies structurelles HVG, dilatation OG (> 34 mL/m²) Anomalies fonctionnelles E/e' > 9 PAPS > 35 mmHg

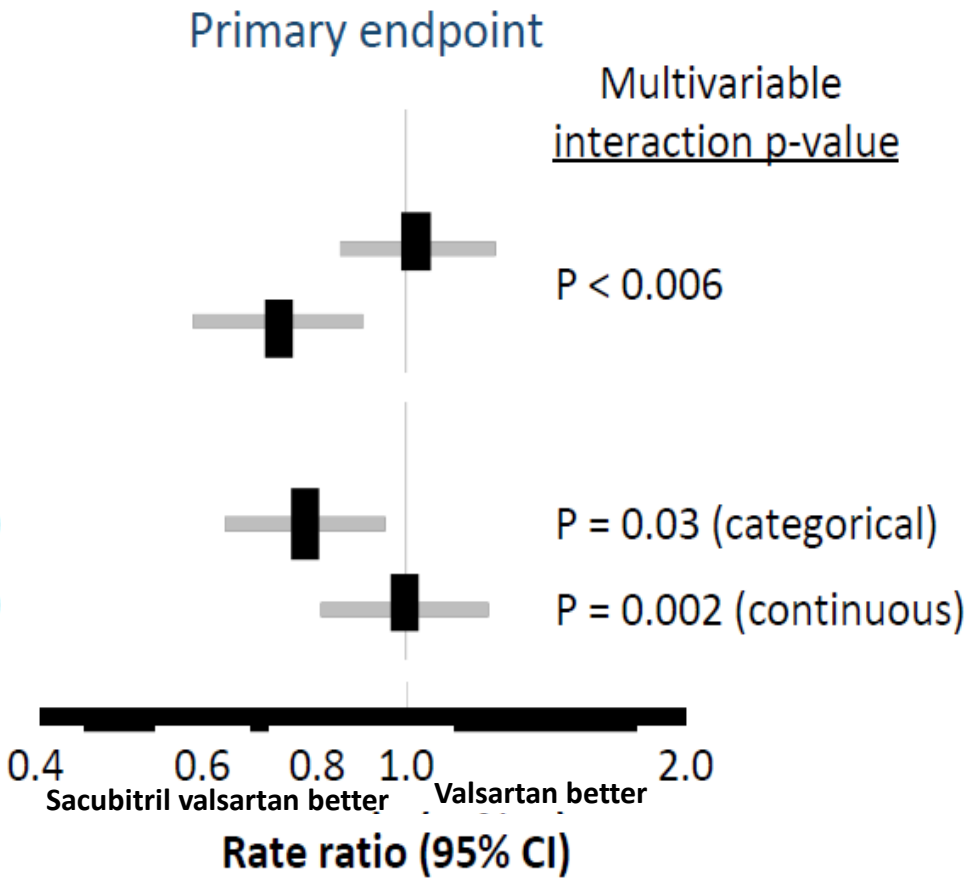
[a] Les signes peuvent ne pas être présents aux stades précoces de l'IC et chez les patients traités de manière optimale

[b] La présence d'anomalies structurales ou fonctionnelles renforce le diagnostic

Etude PARAGON-HF : analyse en sous-groupe

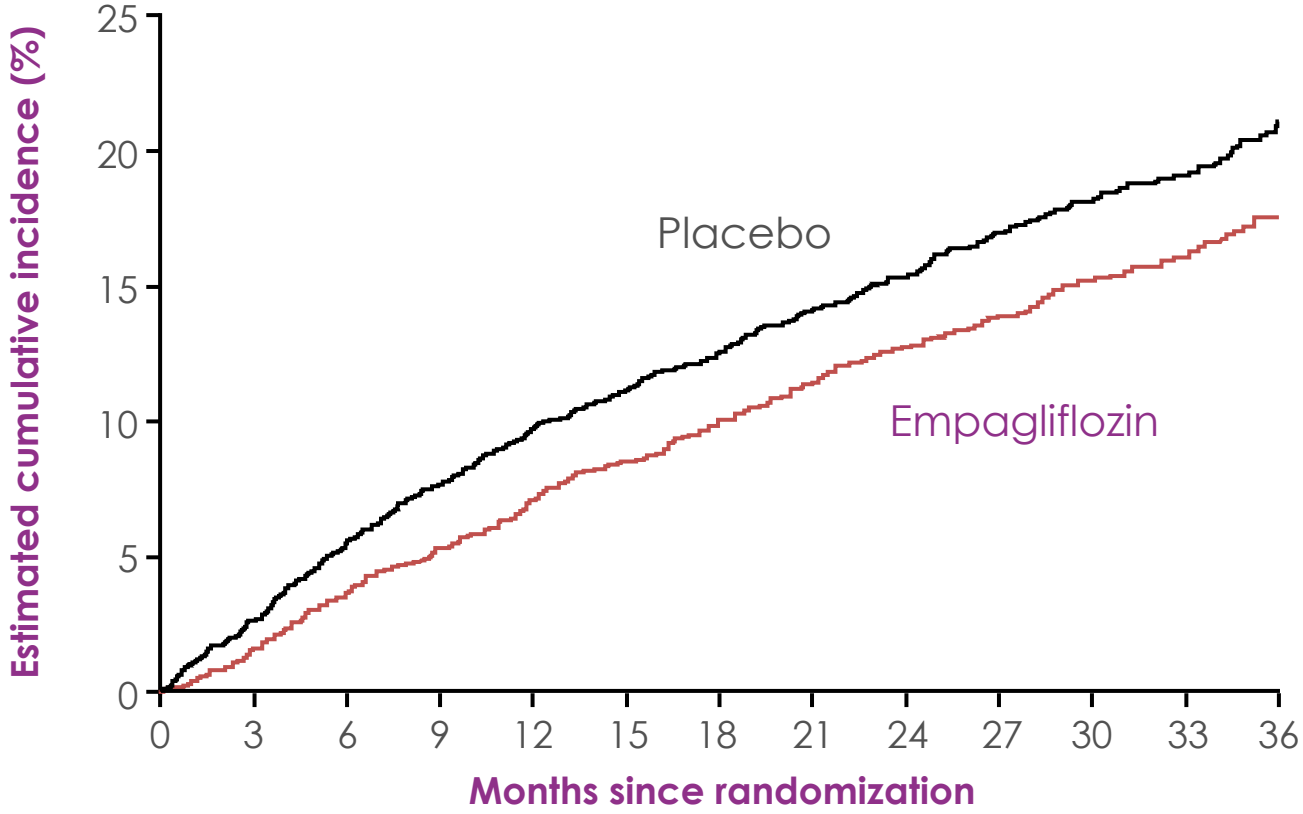
Analyse en sous-groupe en multivarié du critère primaire de l'essai PARAGON-HF selon le sexe et la valeur de la fraction d'éjection

Subgroup	No. of events/ patients	Rate ratio (95% CI)	Multivariable interaction p-value
Sex			
Male	980/2317	1.03 (0.85–1.25)	P < 0.006
Female	923/2479	0.73 (0.59–0.90)	
LVEF			
at or below median (57%)	1048/2495	0.78 (0.64–0.95)	P = 0.03 (categorical)
above median (57%)	855/2301	1.00 (0.81–1.23)	P = 0.002 (continuous)



N Engl J Med 2019 ;381(17):1609-1620,Le Journal du CCF N° 09 , 2019-N9-Journal du CCF.pdf (sfcardio.fr)

Emperor preserved-Empagliflozin demonstrated 21% RRR in the composite primary endpoint of CV death or HHF



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

NNT*=31

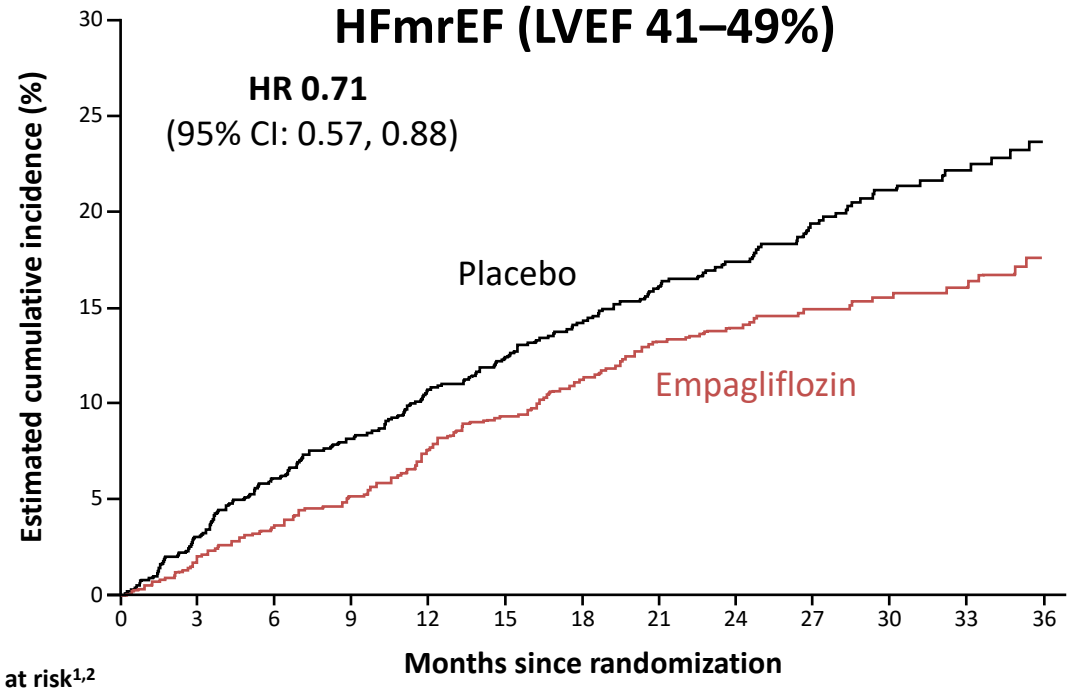
HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

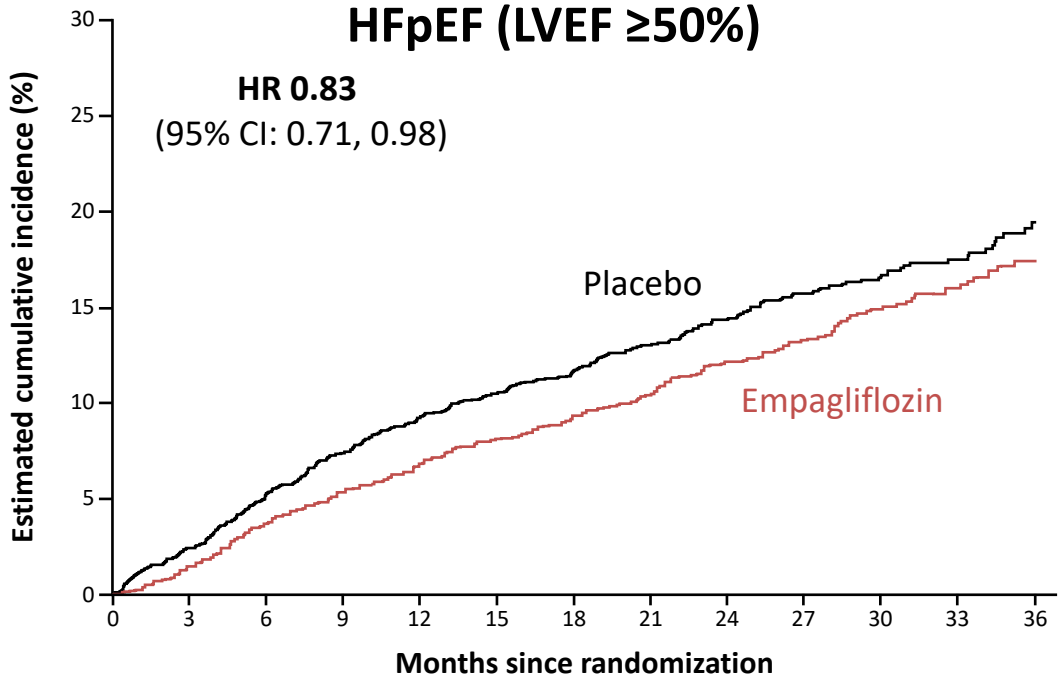
Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.
Anker S et al. N Engl J Med. 2021; DOI: 10.1056/NEJMoa2107038

EMPEROR-Preserved: Effect of empagliflozin on CV death or HHF did not significantly differ between patients with HFmrEF or HFpEF

Primary composite endpoint: Time to first event of adjudicated CV death or HHF





Patients at risk[1,2]

Placebo	998	945	906	880	848	794	689	601	513	422	322	228	136
Empagliflozin	995	968	945	927	897	834	726	625	524	450	335	246	136

Placebo	2003	1943	1880	1826	1779	1630	1377	1220	1021	856	639	453	264
Empagliflozin	2002	1960	1898	1853	1811	1657	1408	1233	1054	882	670	463	266

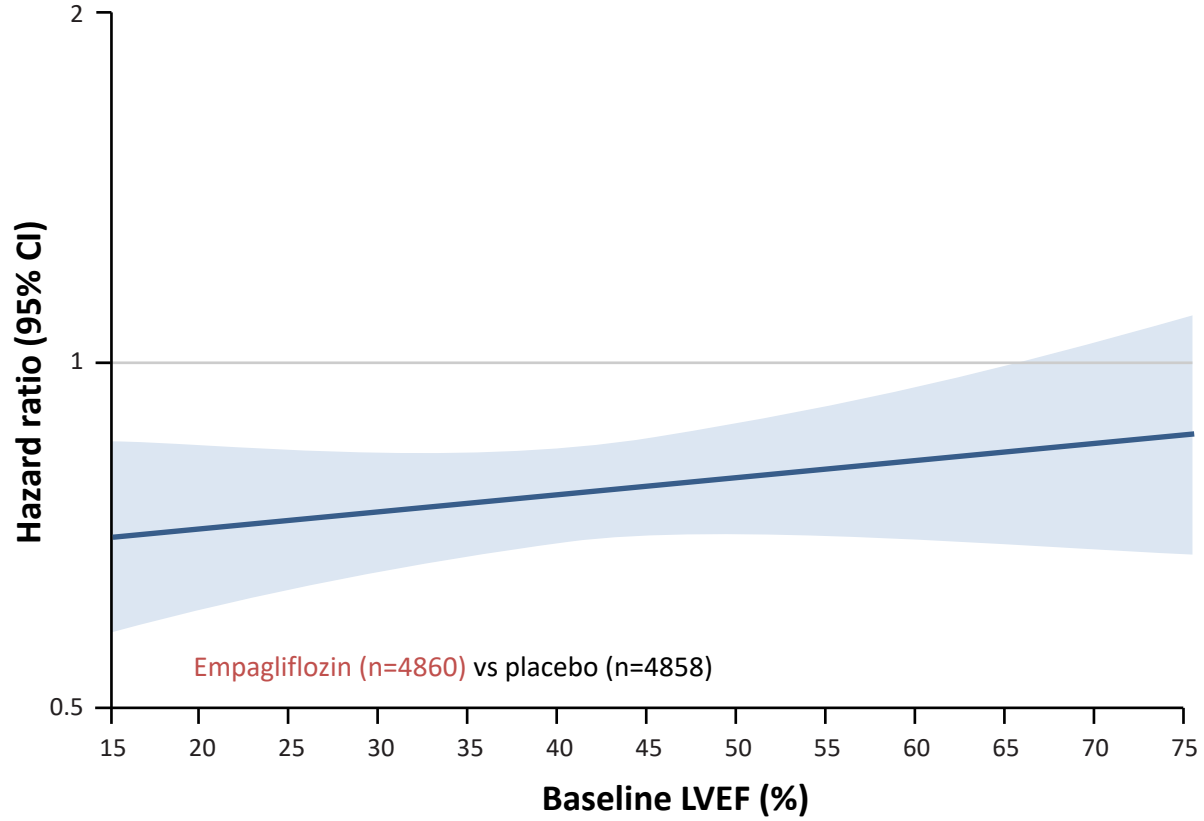
Interaction: p=0.27[2]

CI, confidence interval; CV, cardiovascular; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Javed Butler European Heart Journal (2022) 43, 416–426 https://doi.org/10.1093/eurheartj/ehab798 . Anker S *et al.* Presented at AHA 2021 Scientific Sessions, 13–15 November 2021.

EMPEROR-Pooled: LVEF, effect of empagliflozin on CV death or first HHF

Primary composite endpoint: Time to first event of adjudicated CV death or HHF



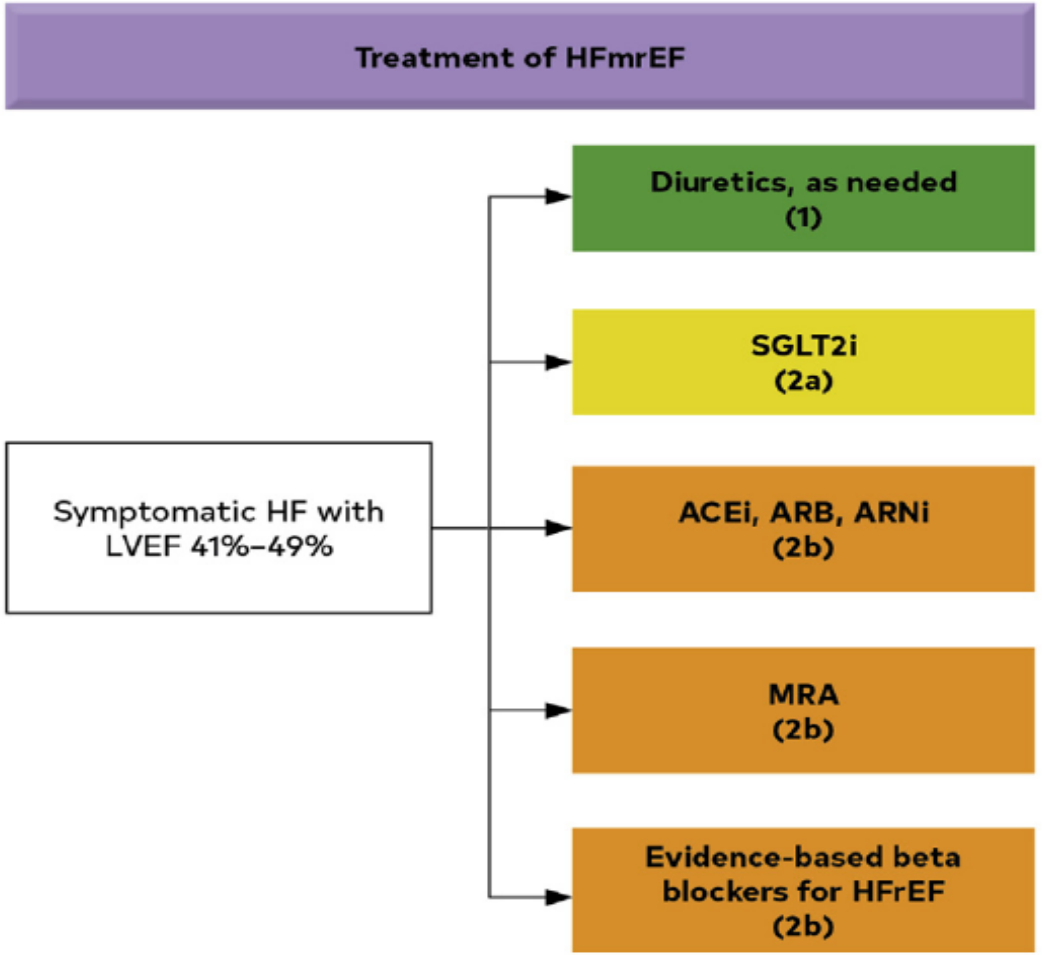
Interaction: *p*=0.30

Ejection fraction analysed as a continuous variable based on the assumption that the relationship is linear. Shaded areas represent the 95% CI.
CI, confidence interval; CV, cardiovascular; HHF, hospitalizations for heart failure; LVEF, left ventricular ejection fraction.
Javed Butler European Heart Journal (2022) 43, 416–426 https://doi.org/10.1093/eurheartj/ehab798

Conduite à tenir thérapeutique – AHA/ACC/HFSA 2022

Traitement pharmacologique de 1ère ligne dans l'ICFE modérément réduite (FE entre 41 et 49 %)

COR	LOE	RECOMMENDATIONS
2a	B-R	1. In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (33).
2b	B-NR	2. Among patients with current or previous symptomatic HFmrEF (LVEF, 41%-49%), use of evidence-based beta blockers for HFrEF, ARNi, ACEi, or ARB, and MRAs may be considered, to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum (34-41).

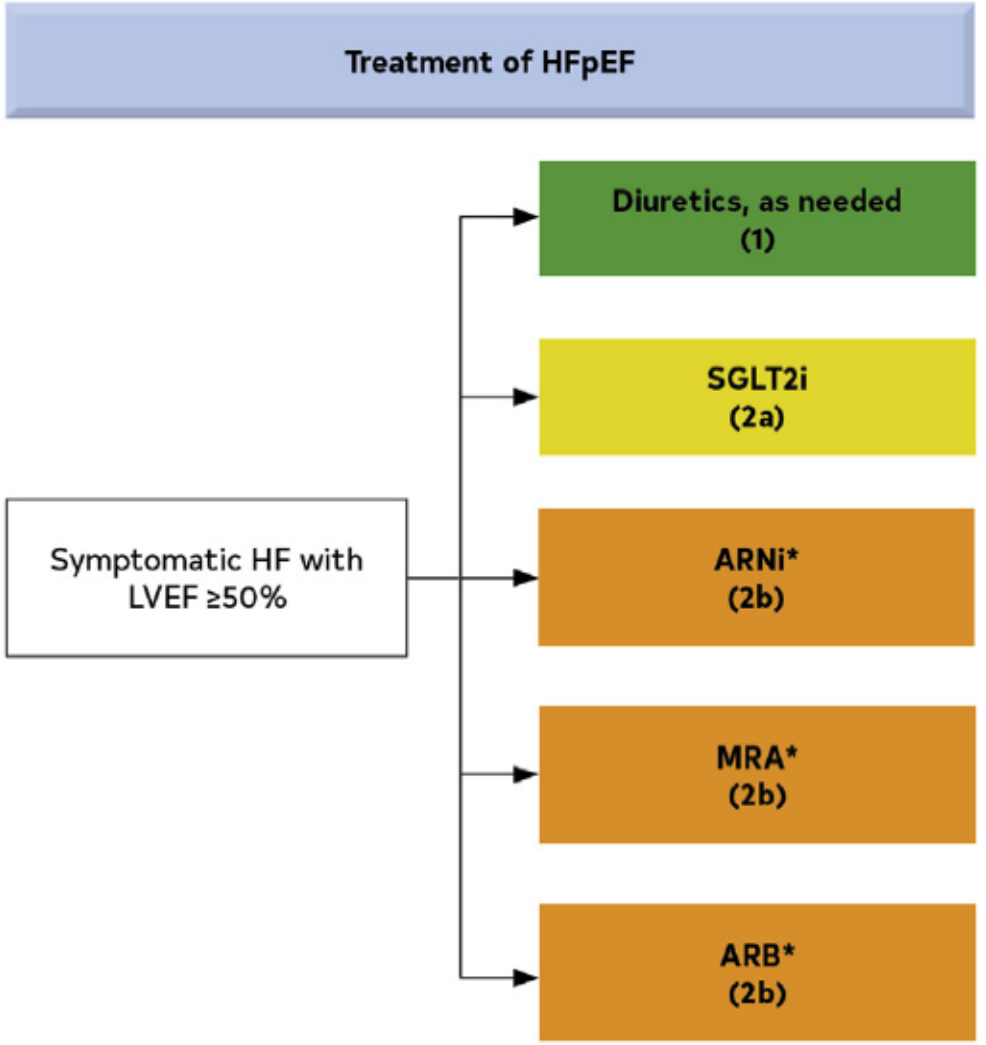


JACC 2022;79(17):1757-1780
Circulation 2022; Apr 1; doi:10,1161/CIR.0000000000001063 (Online ahead of print)

Conduite à tenir thérapeutique – AHA/ACC/HFSA 2022

Traitement pharmacologique de l'ICFEp (FE ≥ 50 %)

COR	LOE	RECOMMENDATIONS
2a	B-R	1. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (33).
2b	B-R	2. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (38,42,43).
2b	B-R	3. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (35,40).

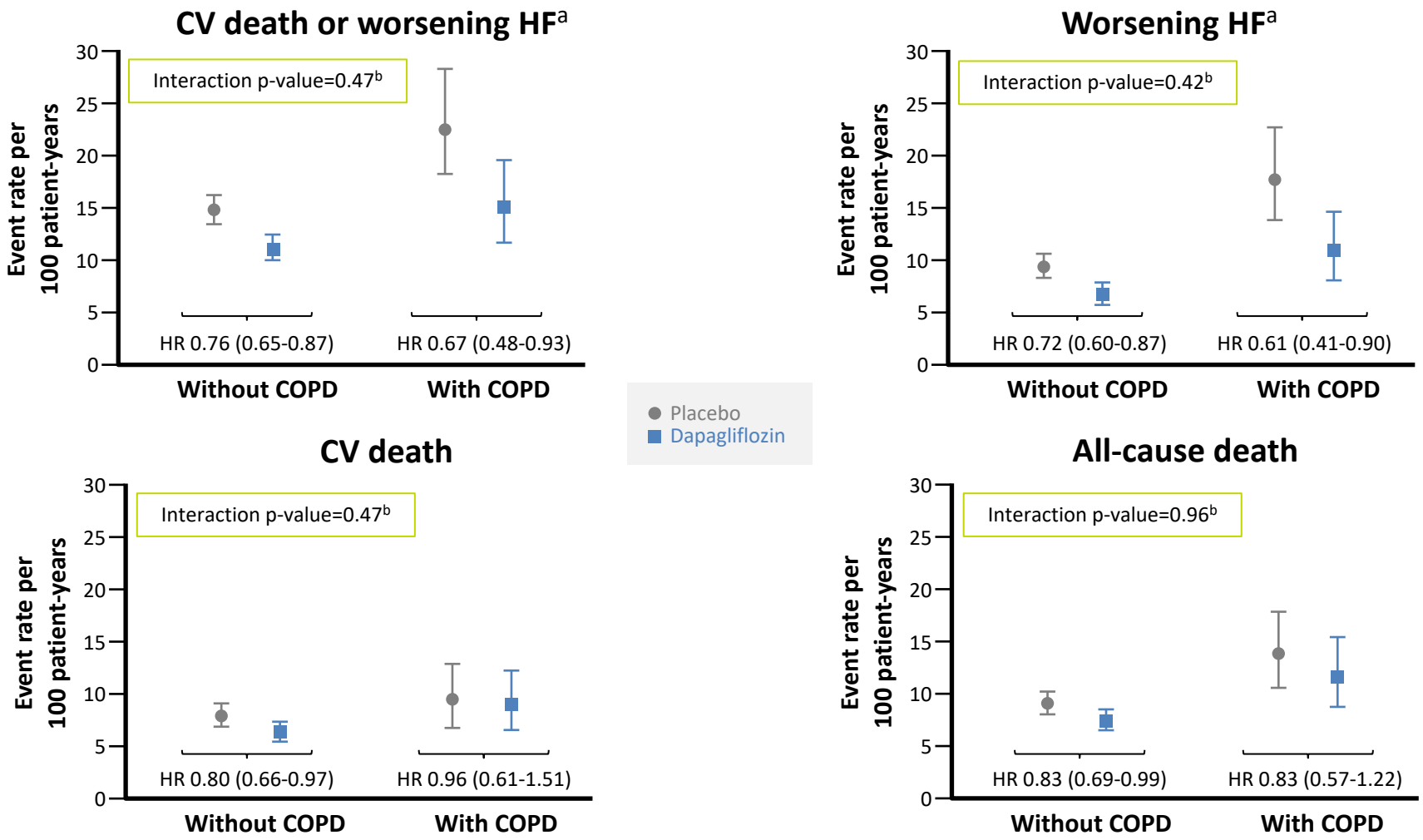


JACC 2022;79(17):1757-1780
Circulation 2022; Apr 1; doi:10,1161/CIR.0000000000001063 (Online ahead of print)

Analyse post-hoc de l'étude DAPA-HF

Benefit of Dapagliflozin was Consistent in Patients With and Without COPD

Dapagliflozin event rates consistently lower than placebo for the primary endpoint, components of the primary endpoint, and all-cause death, without any interaction based on COPD status



12.3% of the population in DAPA-HF had a history of COPD.

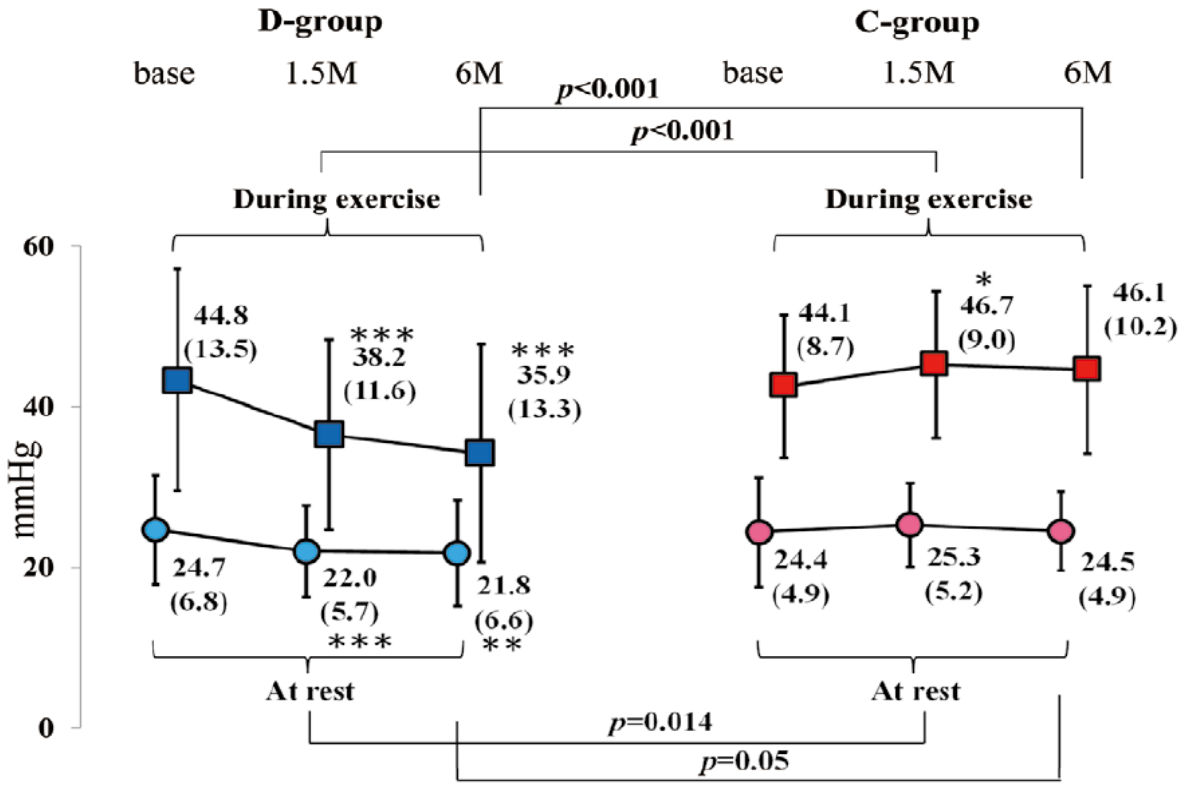
[a]Worsening HF includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

COPD = chronic obstructive pulmonary disease; CV = cardiovascular; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.

1. Dewan P et al. *Eur J Heart Fail*. 2021;23:632-643; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Effets de la dapagliflozine sur les pressions systoliques ventriculaires droites au repos ou à l'effort chez des patients diabétiques de type 2

78 pts, 5 mg/j dapagliflozine ou placebo, échocardiographie d'effort à 0, 1,5 et 6 mois



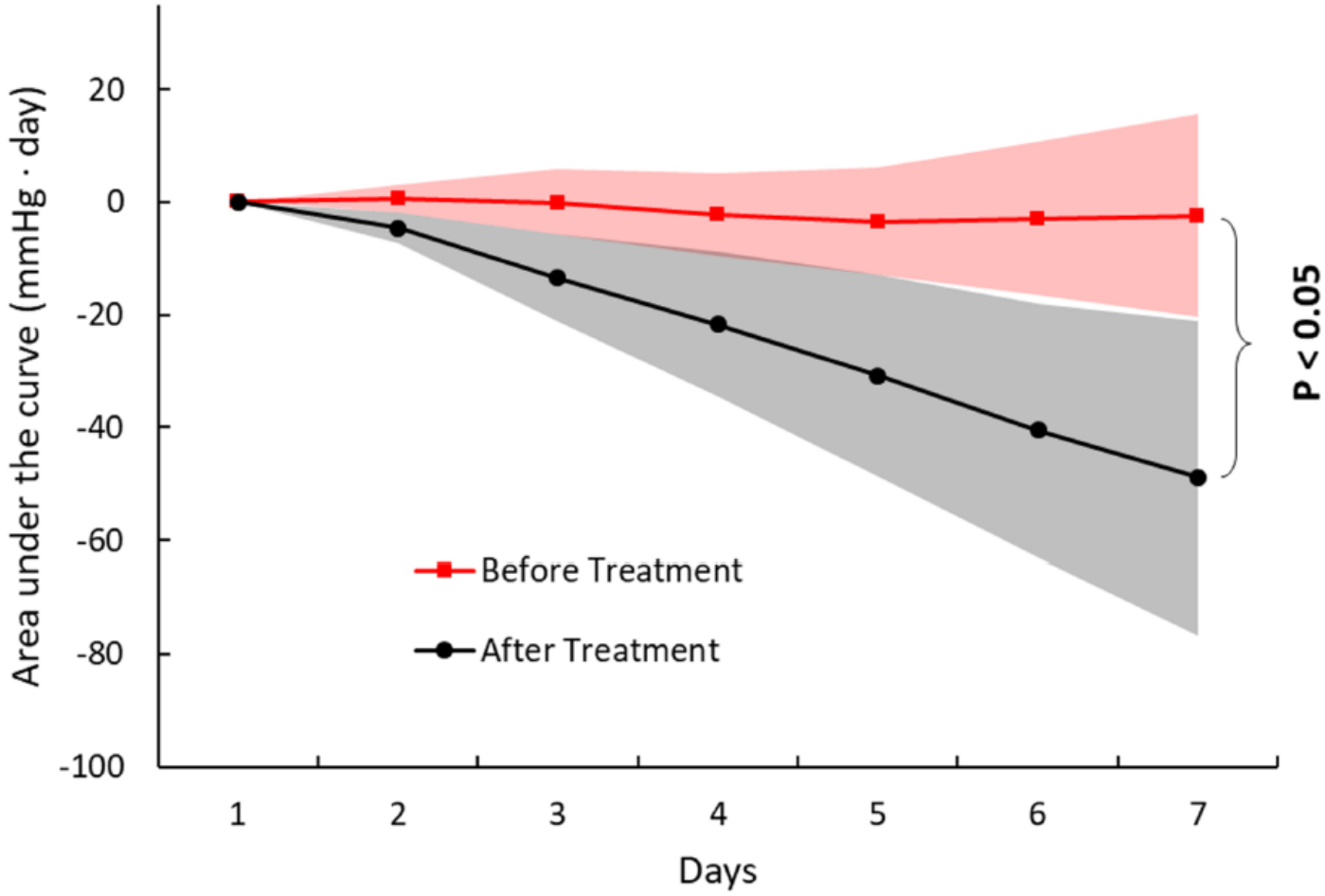
Adjusted means of change	D-group	C-group	Difference (95% CI)	*P*-value
ANCOVA	-8.7 (2.2)	1.8 (2.3)	-10.5 (-14.4, -6.6)	< 0.001
MMRM	-6.8 (1.9)	4.0 (1.9)	-10.8 (-14.6, -6.9)	< 0.001

Diminution PSVD associée significativement à réduction des pressions de remplissage VG

Kayano H *et al.* Circ J 2020;84:1807-1817

Etude pilote : effets de la dapagliflozine sur la pression artérielle pulmonaire moyenne dans l'ICFEr

Télésurveillance PAP par matériel embarqué, CardioMEMS, chez 9 patients avec ICFEr

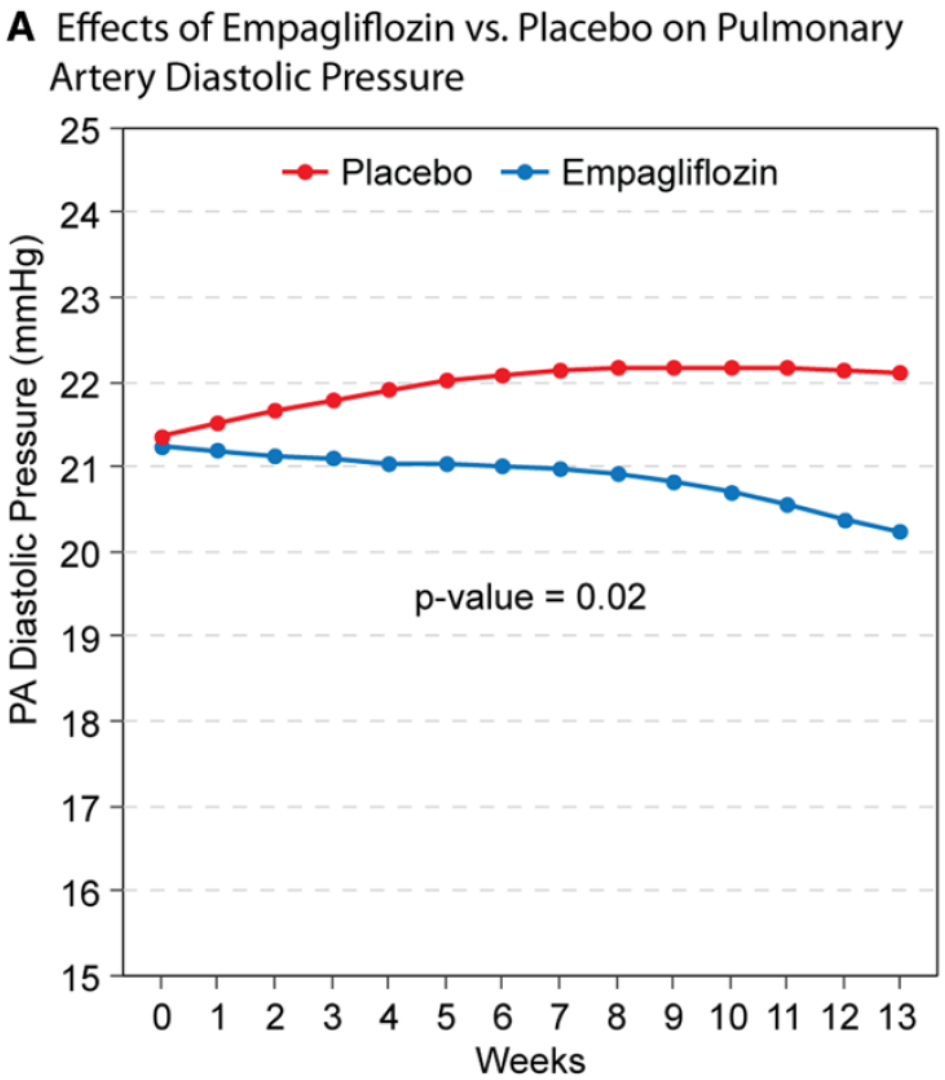


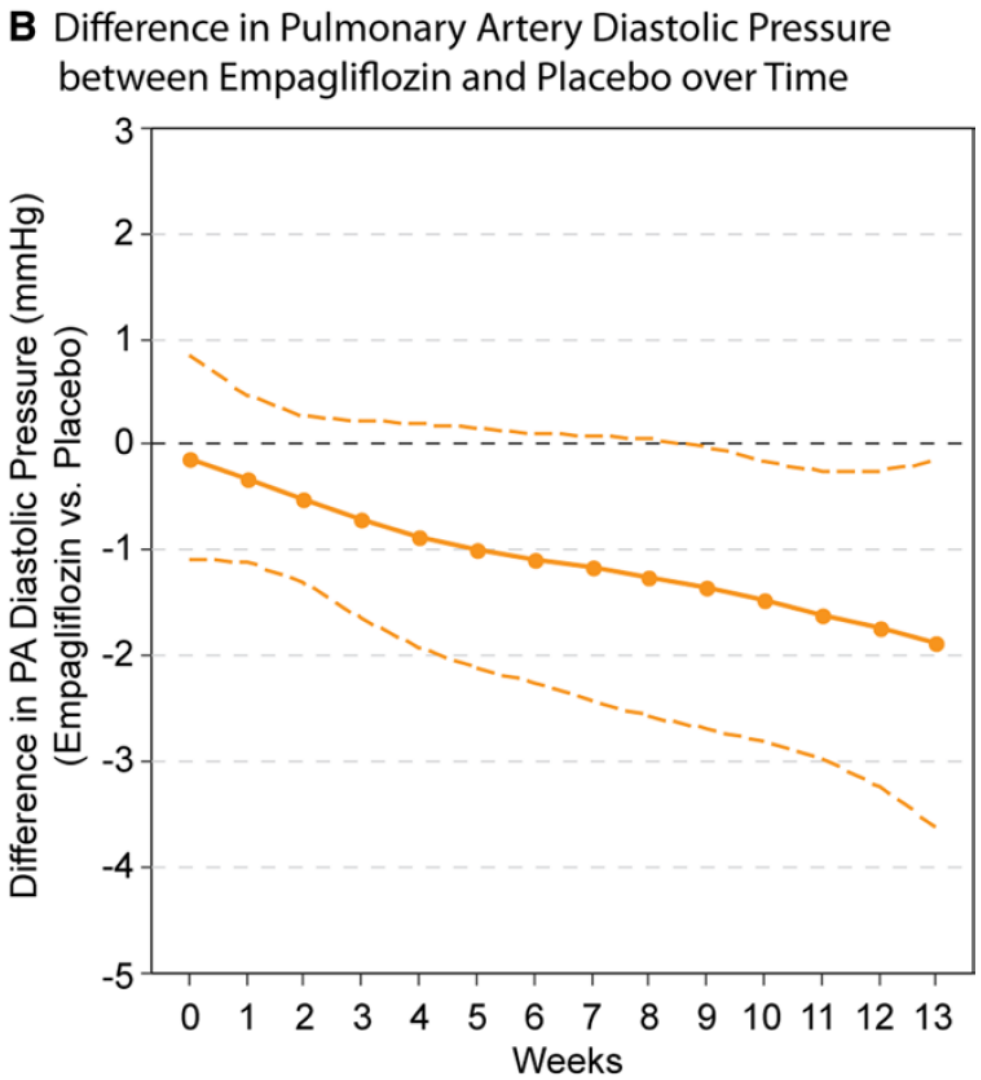
Réduction PAPM très précoce dès le 2j puis stable

Mullens W, *et al.* ESC Heart Fail 2020;7(5):2071-2073

Etude EMBRACE-HF : effets de l'empagliflozine sur la pression artérielle pulmonaire diastolique

Télésurveillance PAD par matériel embarqué spécifique, CardioMEMS, chez 65 patients avec IC

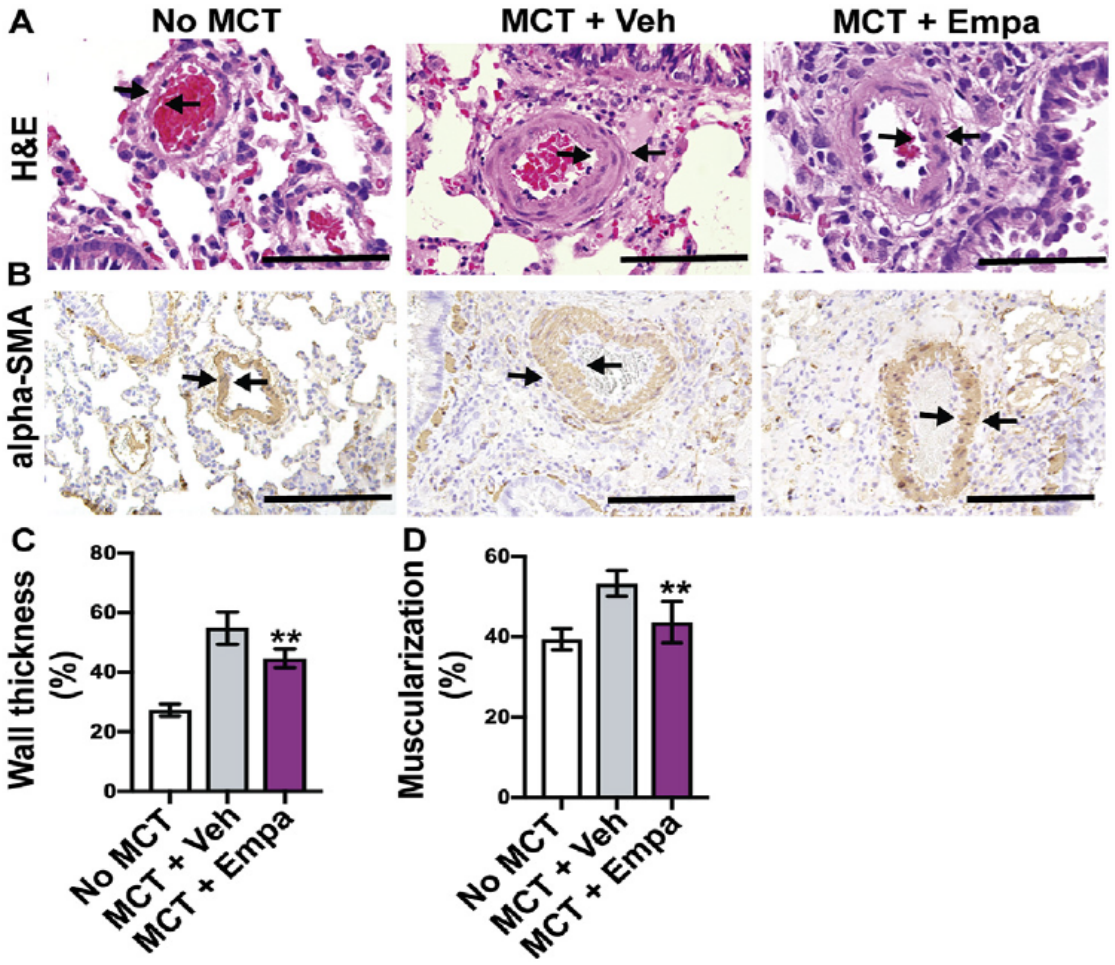




Nassif ME, *et al*. Circulation 2021;143(17):1673-1686

The SGLT2 inhibitor empagliflozin reduces mortality and prevents progression in experimental pulmonary hypertension

Empagliflozin prevented pulmonary vascular remodeling in MCT-treated rats



Diminution PAP moyenne associée à une réduction de l'hypertrophie et de la fibrose ventriculaire droite

Chowdhury B *et al.* Biochem Biophys Res Commun 2020;524(1):50-56

Mécanismes des effets des iSGLT2 sur la pression artérielle pulmonaire

- ↓ PCP par effet natriurétique et diurétique
- Effet vasodilatateur direct sur les vaisseaux pulmonaires médiés par NO
- Effet anti-remodelage ventriculaire droit

Que retenir ?

- Les inhibiteurs SGLT2 sont les premiers traitements ubiquitaires de toutes les formes d'insuffisance cardiaque à FE réduite, modérément réduite ou préservée, utiles dans les HTP du groupe 2
- Leurs actions hémodynamiques sur les pressions pulmonaires suggèrent un effet favorable dans d'autres groupes d'hypertension pulmonaire, confirmé par les travaux expérimentaux
- Une étude de preuve de concept (DAPH : Dapagliflozine in Pulmonary Arterial Hypertension) est en cours de réalisation (52 pts avec VO_2 à T0 et à 3 mois) dans l'HTP du groupe 1

ESC Guidelines 2021 - Eur Heart J 2021; 42(36):3599-3726
Ten Commandments' of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure | European Heart Journal | Oxford Academic (oup.com)
Sodium–glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction **https://doi.org/10.1002/ejhf.2397**