Rencontres d'Endocrinologie

D'un agent anti-diabétique à un traitement cardio-vasculaire et rénal : l'incroyable histoire des inhibiteurs des SGLT2 : state of the art

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Il était une fois.

EMPA-REG OUTCOME®

Patients with T2D and established CV disease

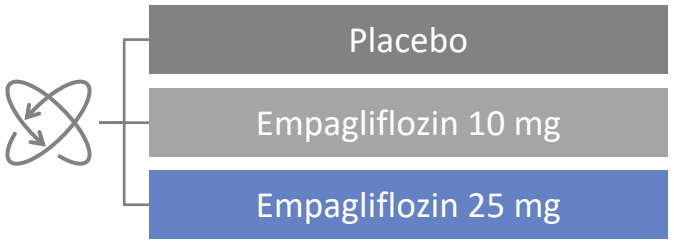
42 countries

7020 patients

CV disease was defined as ≥1 of the following:

- CAD
- PAD
- History of MI
- History of stroke

Empagliflozin or placebo given on top of standard of care



3.1 years median observation time

Primary endpoint: 3P-MACE

Pre-specified primary endpoint components:

- CV death
- Non-fatal MI
- Non-fatal stroke

Other pre-specified outcomes

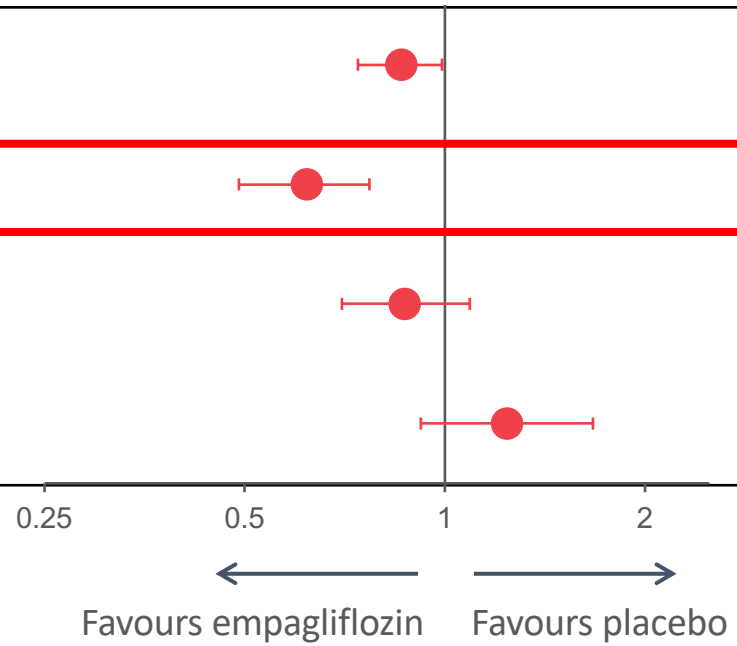
- Hospitalisation for heart failure
- All-cause mortality

%	Placebo (n=2333)	Pooled empagliflozin (n=4867)
Heart failure* ***(not an inclusion criterion)***	**10.5**	**9.9**

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

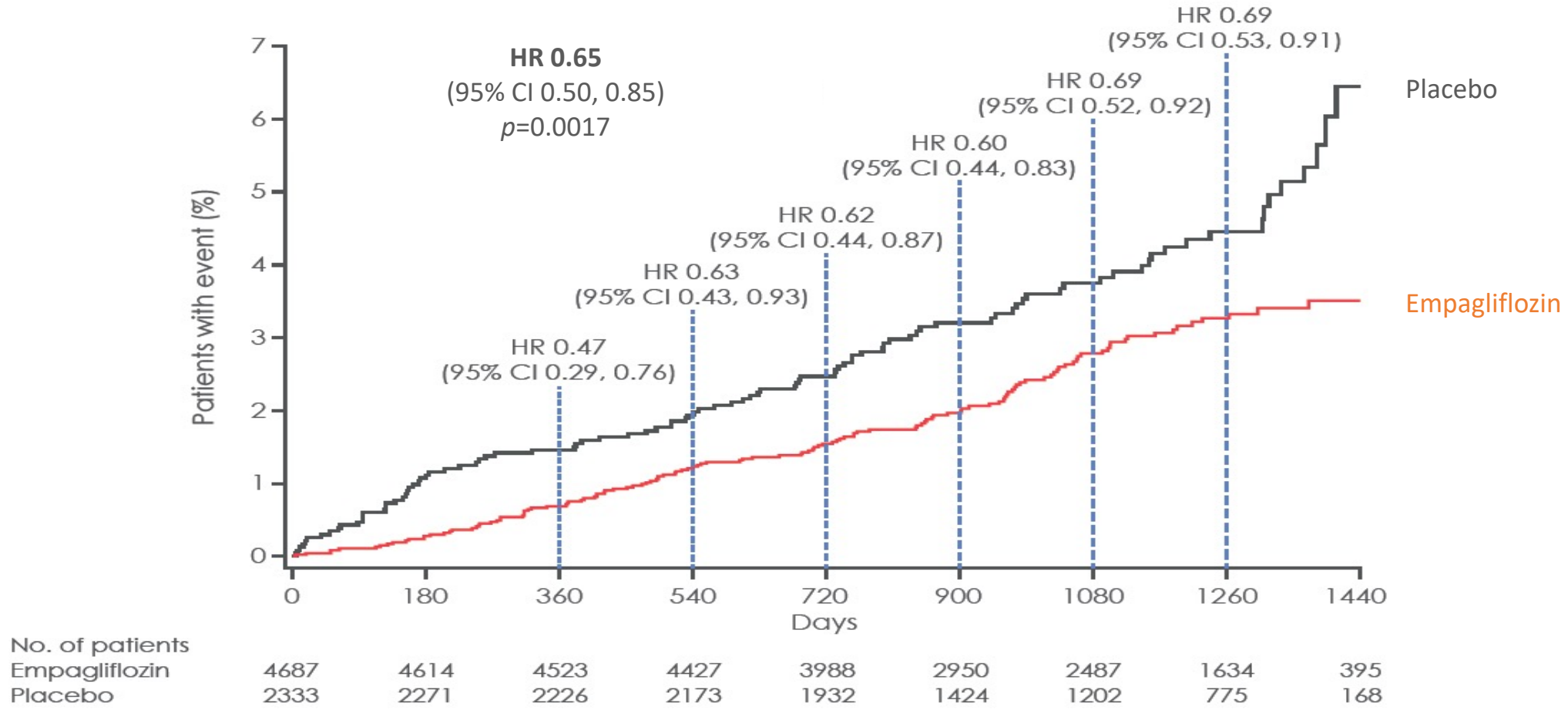
Diminution de la mortalité CV ?

	n with event/N analysed (%)			
	Empagliflozin	Placebo	HR (95% CI)	*p*-value
3P-MACE	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74, 0.99)*	0.04*
CV death	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	<0.001
Non-fatal MI	213/4687 (4.5)	121/2333 (5.2)	0.87 (0.70, 1.09)	0.22
Non-fatal stroke	150/4687 (3.2)	60/2333 (2.6)	1.24 (0.92, 1.67)	0.16



Zinman *B et al. N Engl J Med* 2015;373:2117 & supplementary appendix

Diminution du risqué d'hospitalisation pour IC



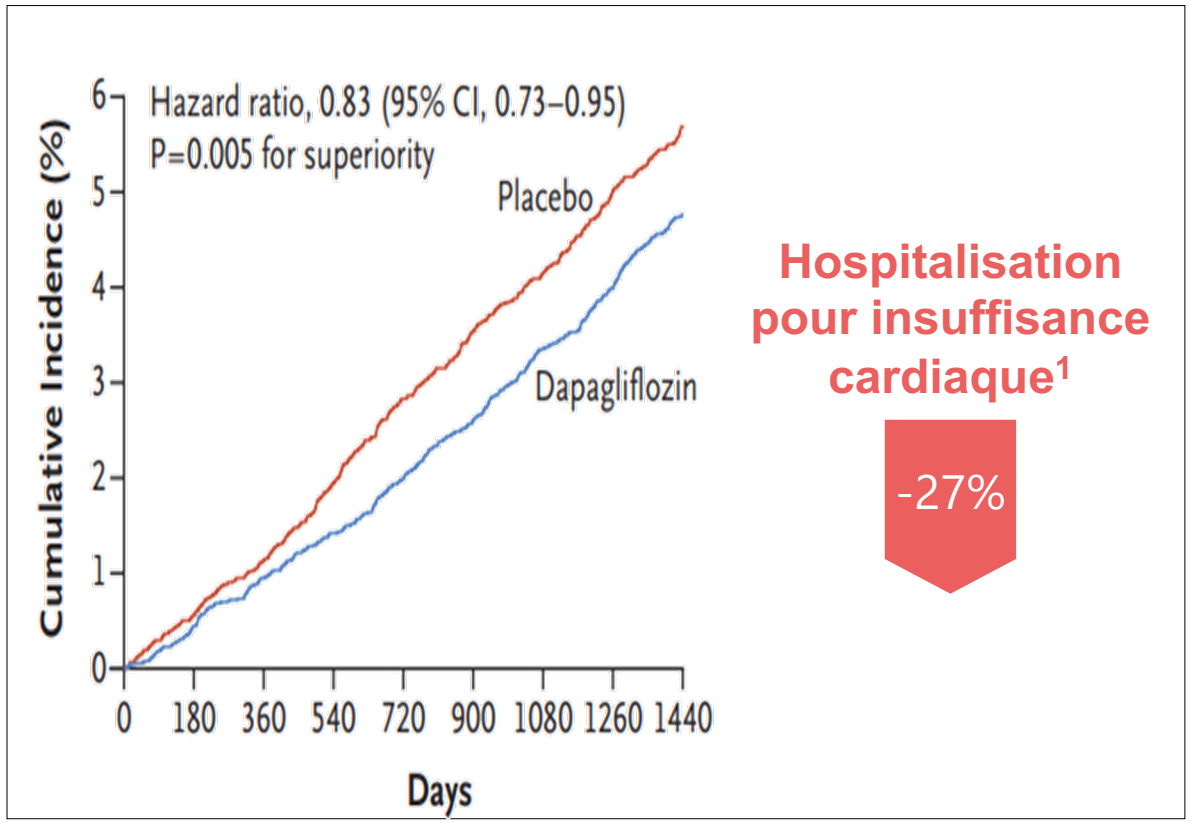
van de Borne P *et al. ESC-HF* 2016; poster P2231

Même histoire pour la dapagliflozine

DECLARE

Prévention primaire !

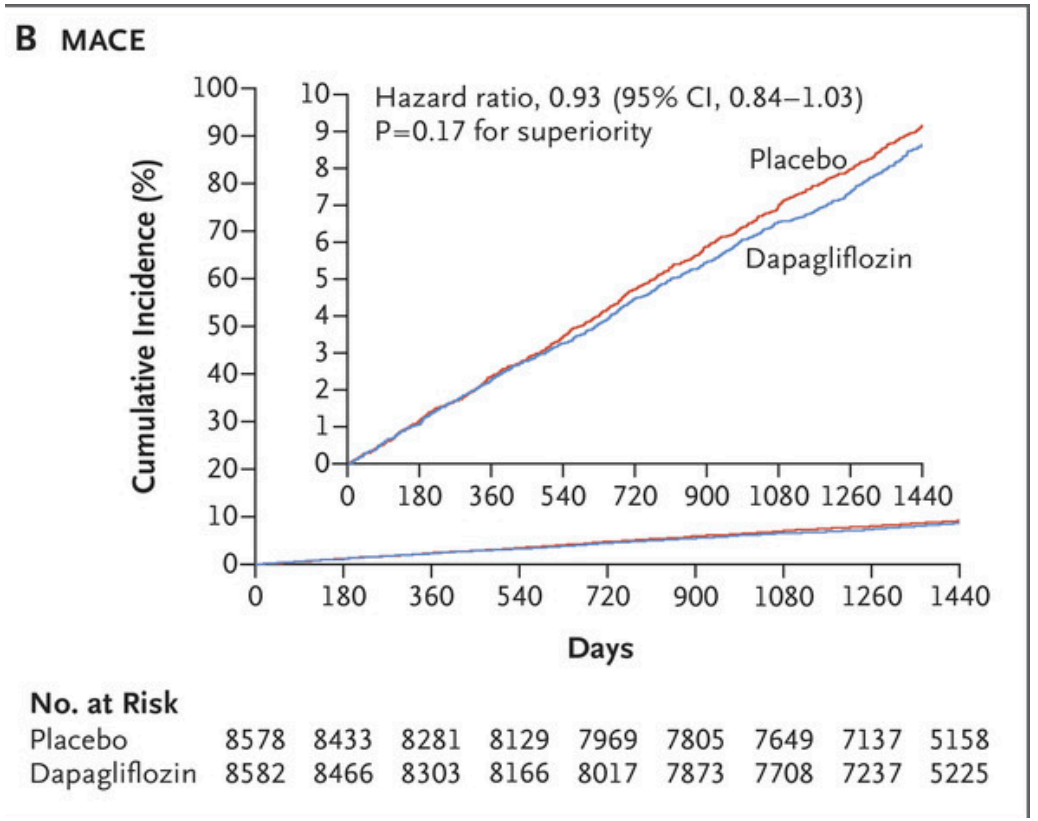
Hospitalisation pour insuffisance cardiaque



Hospitalisation pour insuffisance cardiaque[1]

-27%

Evénements Cardiovasculaires majeurs



Wiviott et al. Am Heart J 2018; 200:83-89.

Diabète et Insuffisance cardiaque , que demander de pire?

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

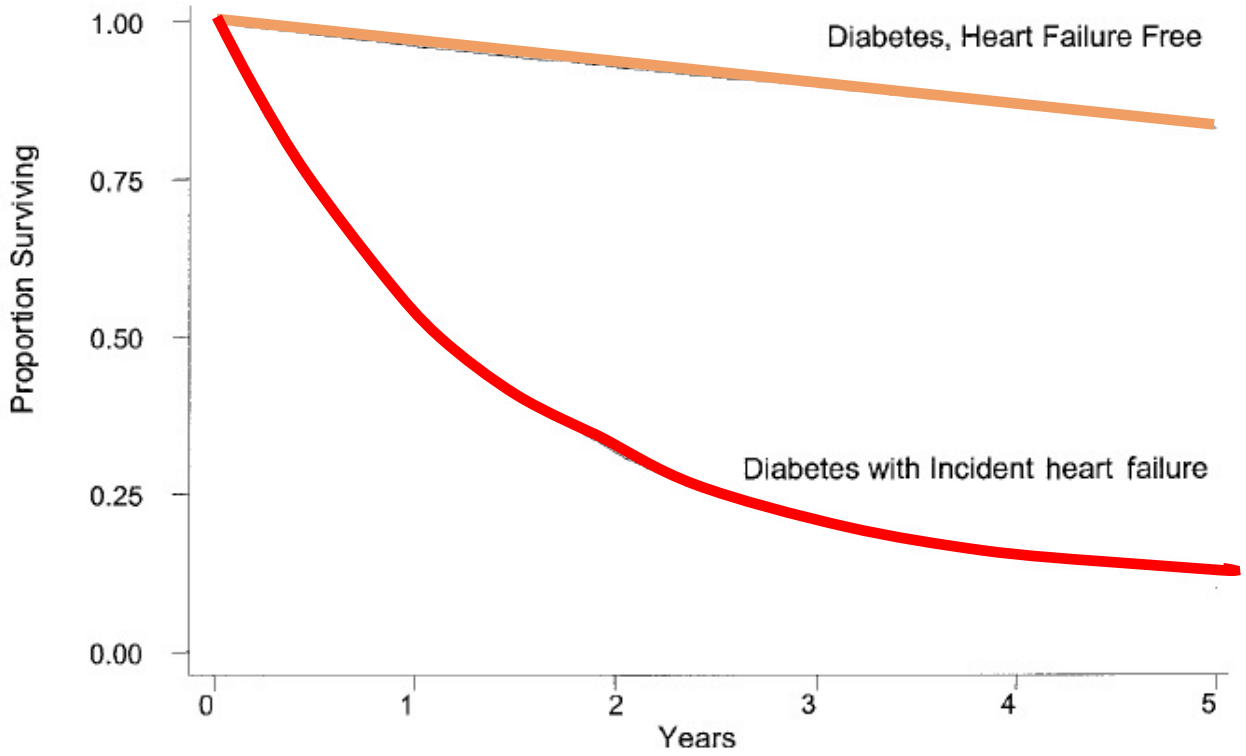


Figure 1—*Five-year Kaplan-Meier survival estimates for 115,803 adults age ≥65 years in fee-for-service Medicare with diabetes by incident heart failure status.*

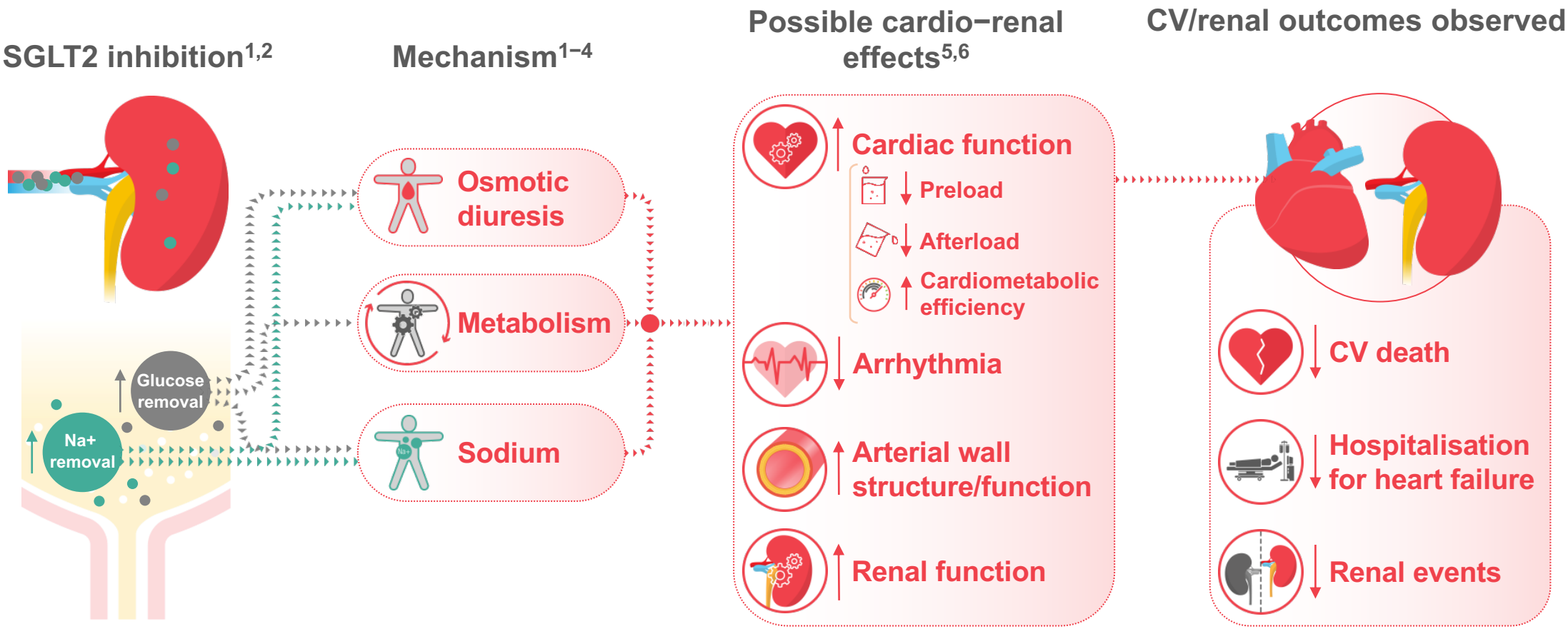
3,7% mortality/year

32,7% mortality/year

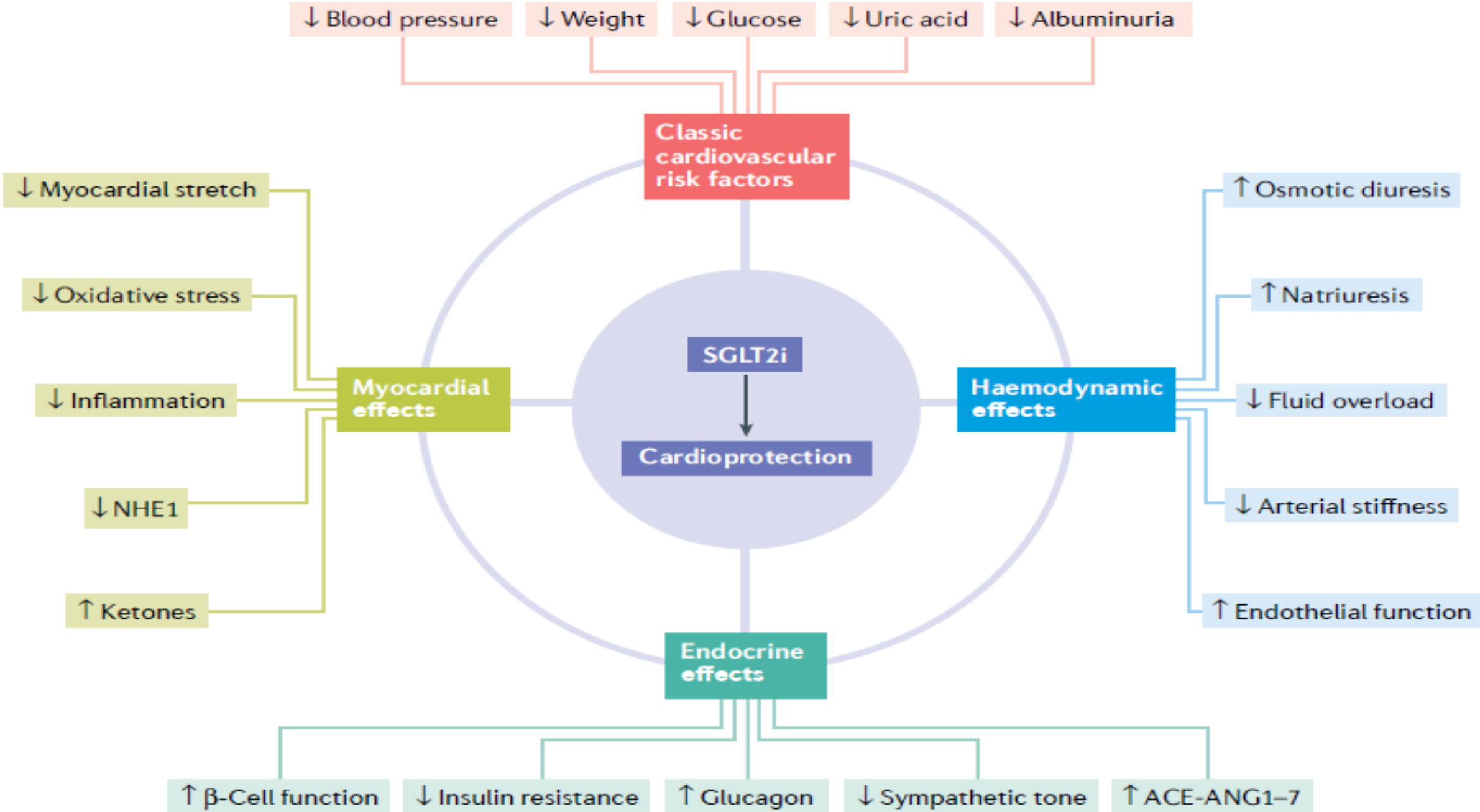
hHF = hospitalization for HF, DM = Diabetes Mellitus

1. Bertoni A. Diabetes Care 2004; 27:699-703. American cohort study (n=151 738) in elderly diabetic patients developing HF.
2. Vaur L. Diabetes Care 2003;26:855–860. DIABHYCAR study : Diabetics who developed HF had a 12-fold higher annual mortality than those not developing HF (36.4 vs. 3.2%)

Quels mécanismes ?



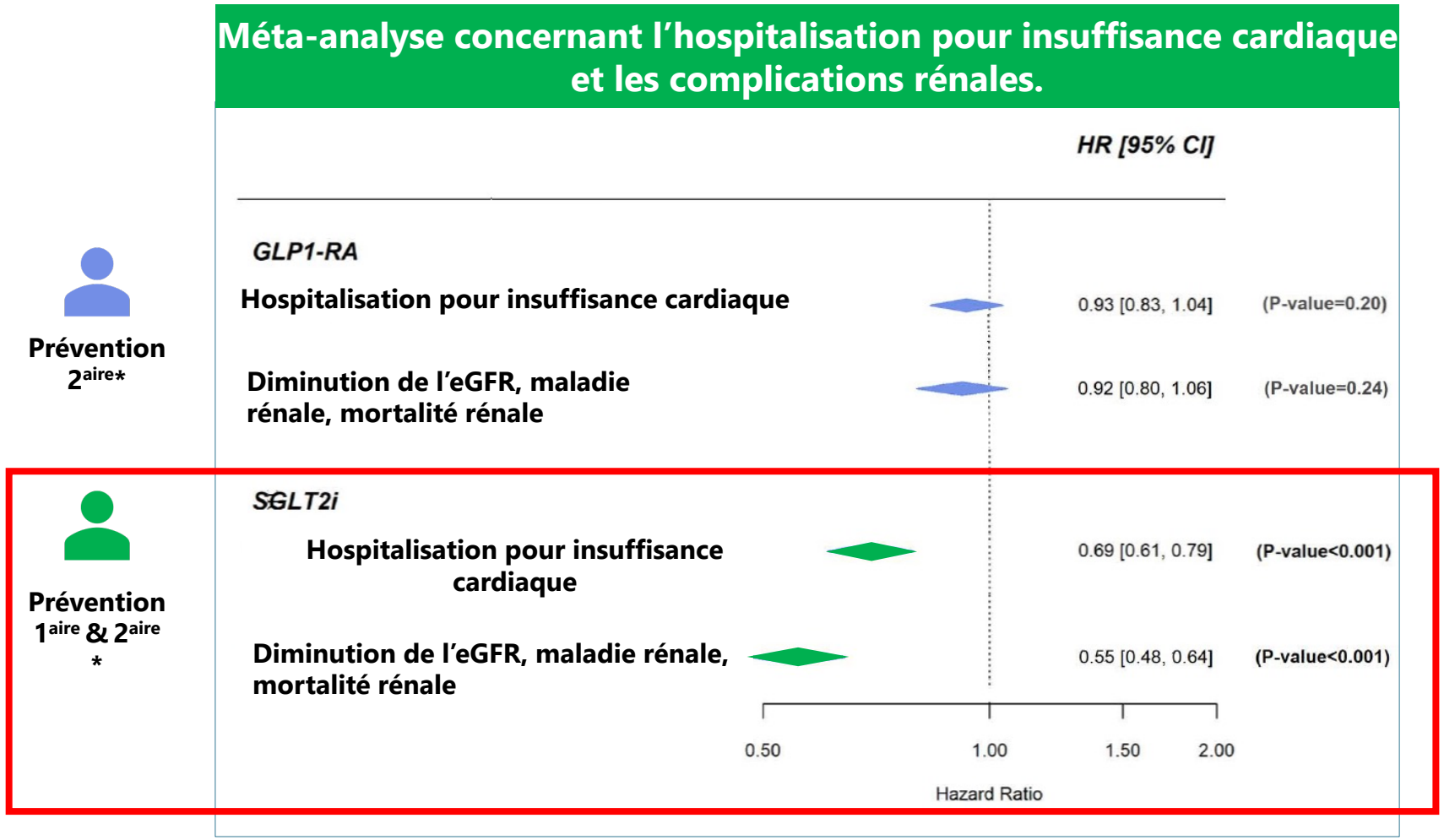
1. Heise T *et al. Diabetes Obes Metab* 2013;15:613; 2. Heise T *et al. Clin Ther* 2016;38:2265; 3. Ferrannini G *et al. Diabetes Care* 2015;38:1730; 4. Briand F *et al. Diabetes* 2016;65:2032; 5. Heerspink HJ *et al. Circulation* 2016;134:752; 6. Inzucchi S *et al. Diab Vasc Dis Res* 2015;12:90; 7. Zinman B *et al. N Engl J Med* 2015;373:2117; 8. Wanner C *et al. N Engl J Med* 2016;375:323



Scheen, Nat Rev Endocrinol. 2020 Oct;16(10):556-577.

iSGLT2 & AR-GLP1: IC et néphropathie

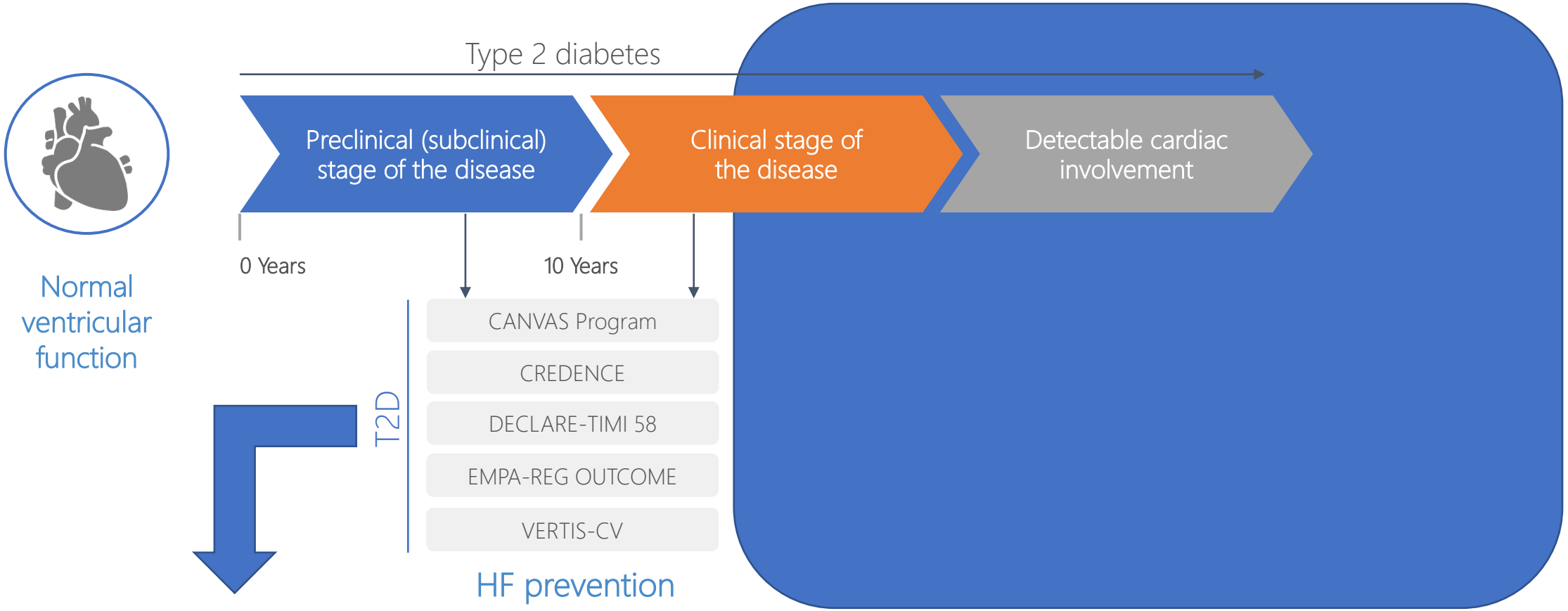
Méta-analyse concernant l'hospitalisation pour insuffisance cardiaque et les complications rénales.



*** Études GLP1-RA: ELIXA, LEADER, SUSTAIN-6, EXSCEL**
*** Études SGLT2i: DECLARE-TIMI58, CANVAS programm, EMPA-REG OUTCOME**

RA of GLP-1, receptor agonist of glucagon-like peptide-1; SGLT2-i, sodium-glucose linked transporter 2 inhibitor;
Zelniker et al Circulation 2019;139(17):2022-2031

Prévention de l'insuffisance cardiaque

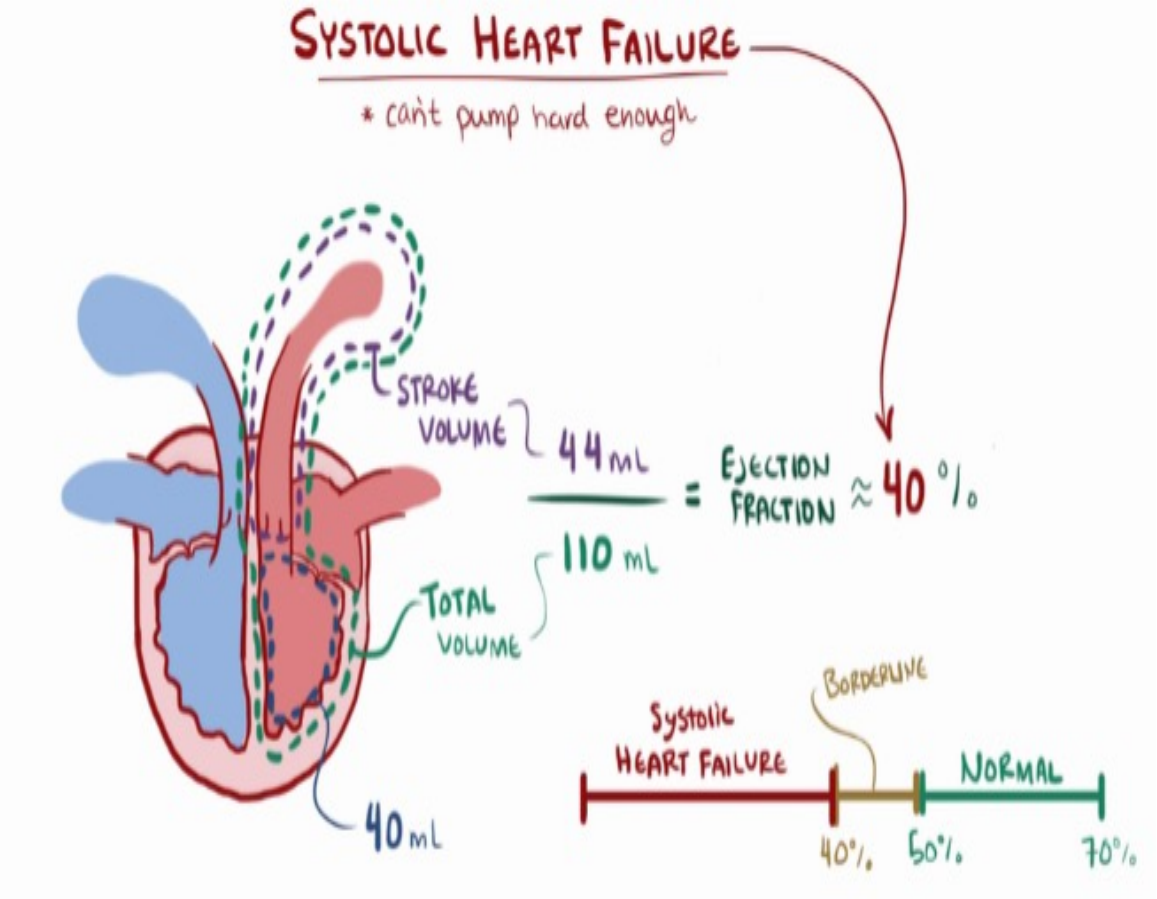


SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B

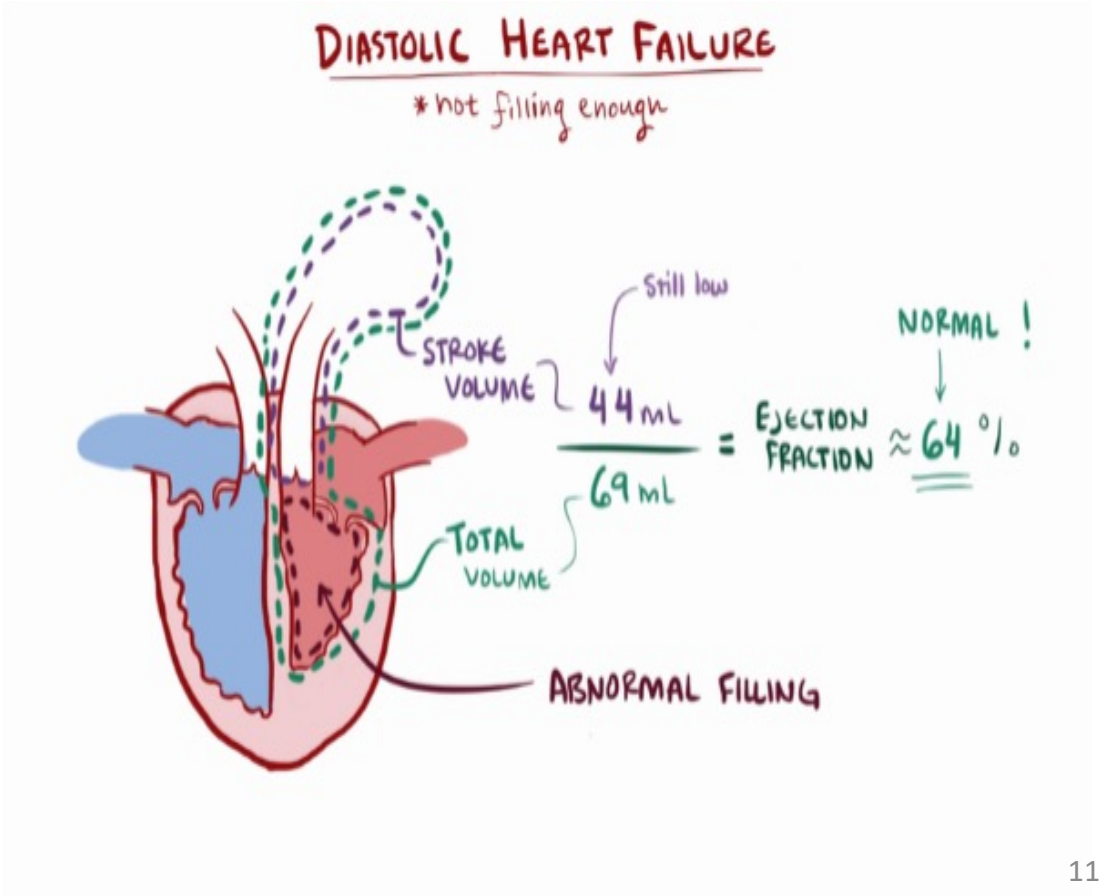
SGLT2, sodium-glucose co-transporter-2
Adapted from Bhatt DL *et al. Cell Metab*. 2019;30:847

De quoi parle-ton?

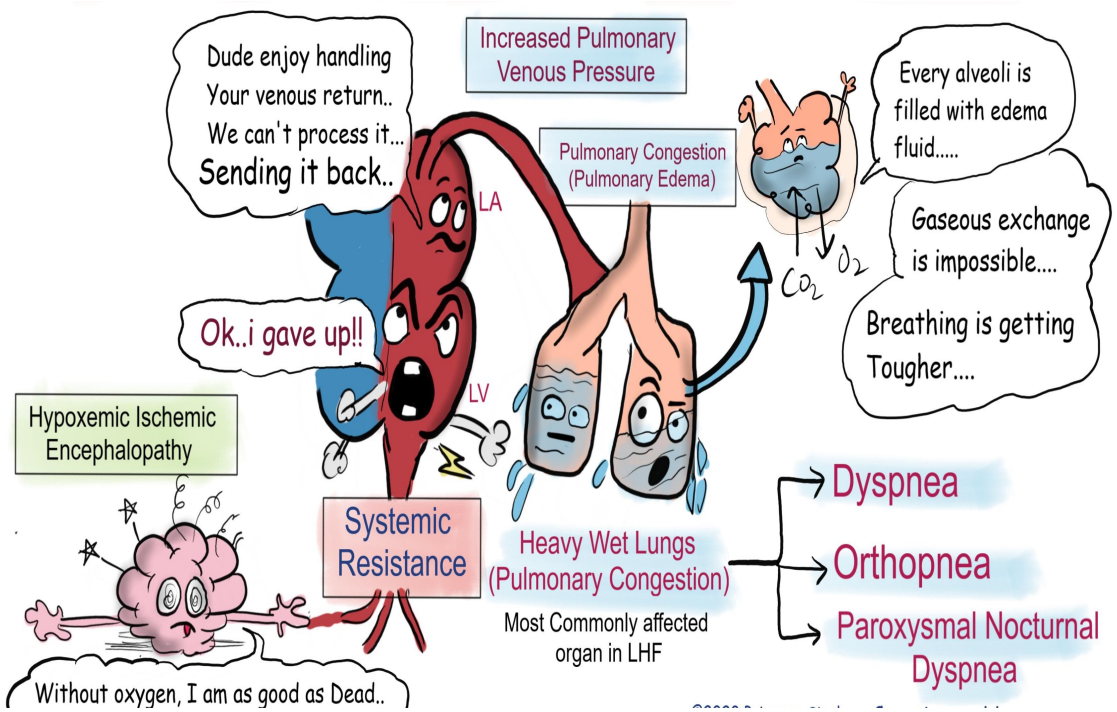
Insuffisance cardiaque à fonction altérée, HFrEF (systolique).

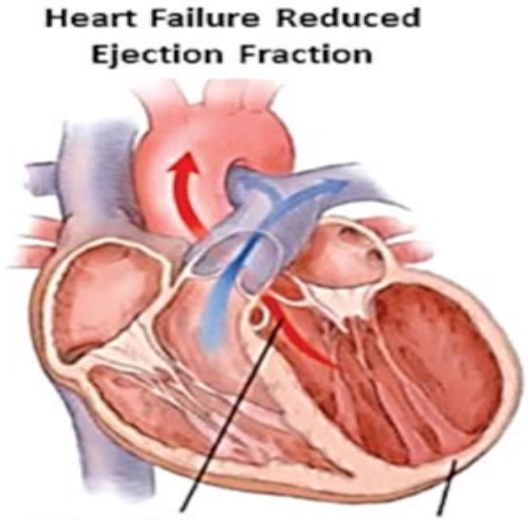


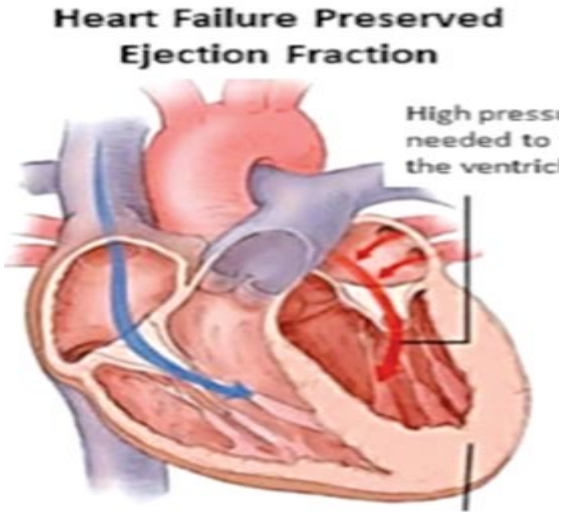
Insuffisance cardiaque à fonction conservée, HFpEF (diastolique).

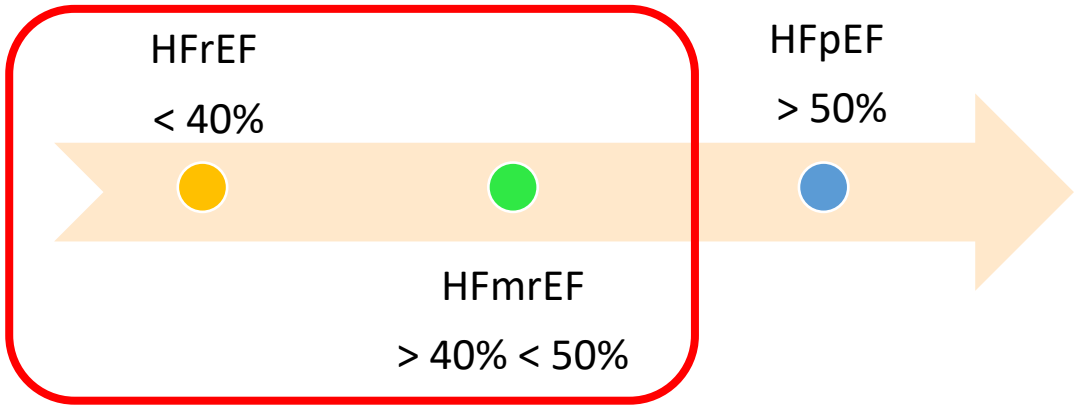


HF(m)rEF vs HFpEF









Caractéristiques des études

	DAPA-HF[1]	EMPEROR-Reduced[2,3,4]
Interventions	Dapagliflozin 10 mg daily or placebo (1:1)	Empagliflozin 10 mg daily or placebo (1:1)

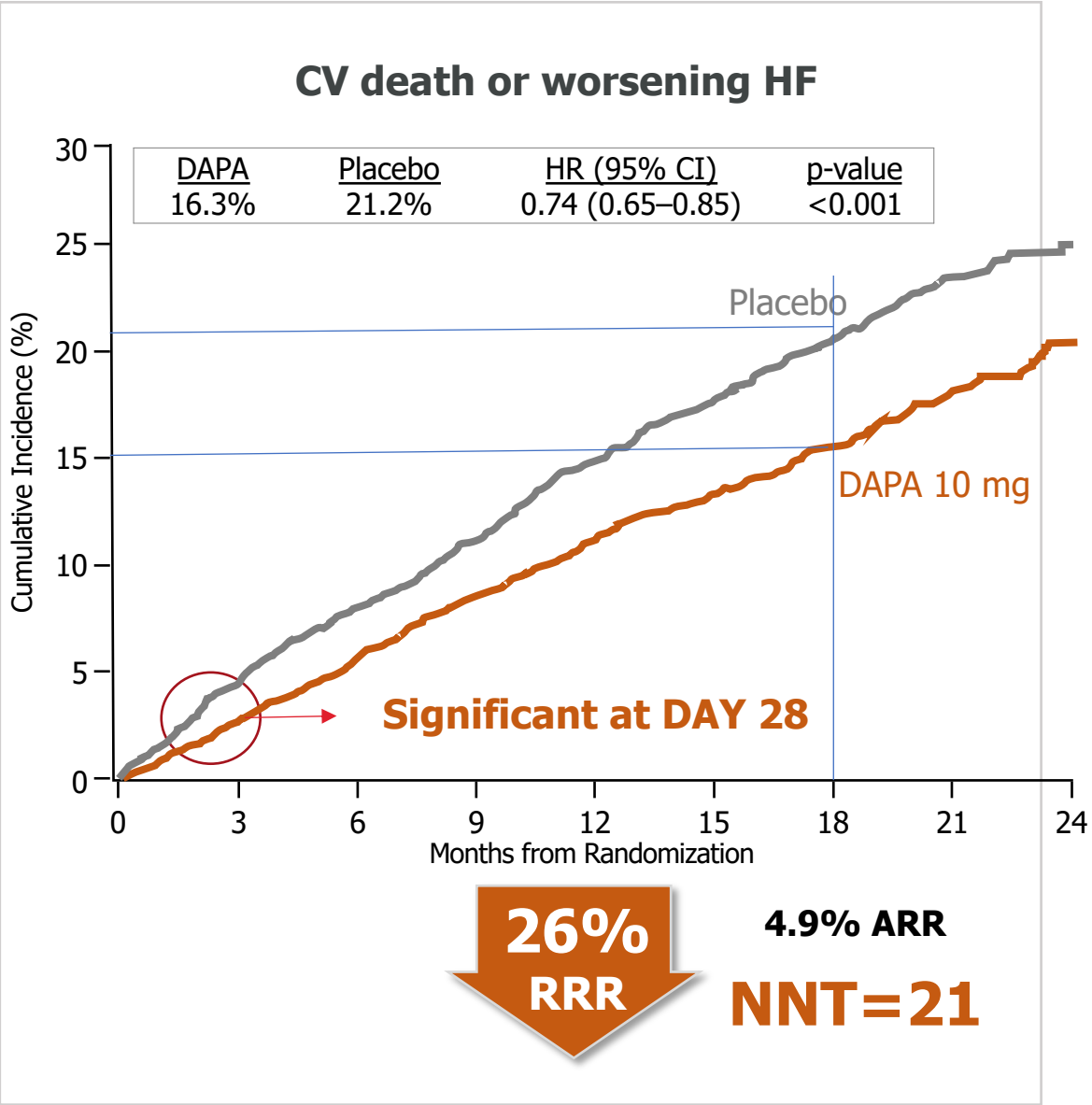
Key inclusion criteria	• Patients ≥18 years of age
	• NYHA Class II-IV HFrEF (LVEF ≤40%)
	• Elevated NT-proBNP at enrollment (Visit 1)
	  • NT-proBNP ≥600 pg/mL or
	  • NT-proBNP ≥400 pg/mL if hHF within previous 12 months or
	  • NT-proBNP ≥900 pg/mL if concomitant AF/AFL (irrespective of hHF hx)
	• eGFR ≥30 mL/min/1.73 m^2
	• 55% without T2D
		• Patients ≥18 years of age (Japan: ≥20 years of age)
		• NYHA Class II-IV HFrEF (LVEF ≤40%)
		• Elevated NT-proBNP
		  • LVEF ≤30%: ≥600 pg/mL (≥1200 pg/mL if concomitant AF)
		  • LVEF ≥31% to ≤35%: ≥1000 pg/mL (≥2000 pg/mL if concomitant AF)
		  • LVEF ≥36% to ≤40%: ≥2500 pg/mL (≥5000 pg/mL if concomitant AF)
		  • hHF ≤12 months: ≥600 pg/mL (≥1200 pg/mL if concomitant AF)
		• eGFR ≥20 mL/min/1.73 m^2
		• ~50% without T2D

Key exclusion criteria	• MI, UA, stroke, TIA, or CV procedure/surgery in previous 12 weeks • Acute decompensated HF • SBP <95 mm Hg or symptomatic hypotension • T1D • Recent treatment/intolerance to SGLT2 inhibitor	• MI, CABG, other major CV surgery, stroke, or TIA in previous 90 days • Acute decompensated HF • SBP ≥180 or <100 mm Hg or symptomatic hypotension • Recent treatment/intolerance to SGLT2 inhibitor
Sample size	N=4744	N=3730
Median follow-up	18.2 months	16 months

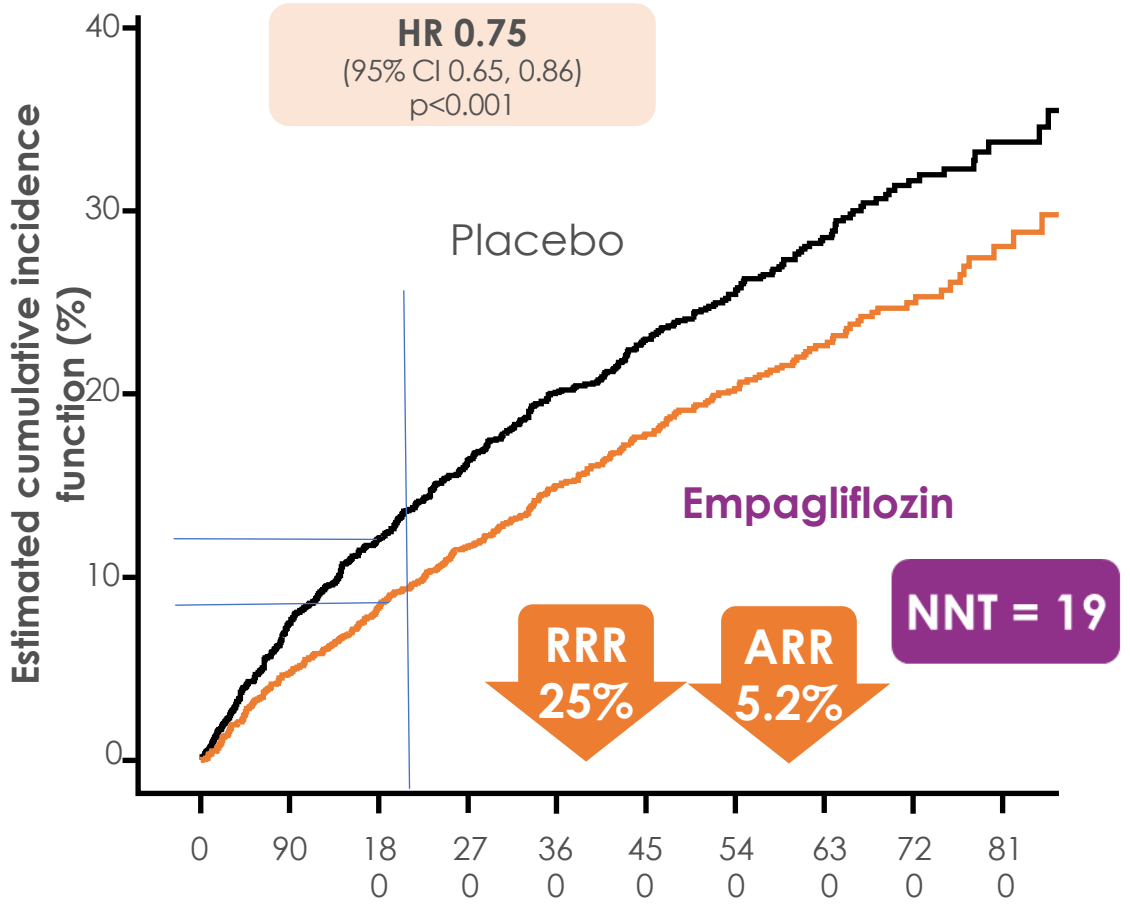
A direct comparison of the trials cannot be made due to different design and population included in the trial. No head to head comparison is available.

AF = atrial fibrillation; AFL = atrial flutter; CABG = coronary artery bypass graft surgery; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; hx = history; MI = myocardial infarction; NT-proBNP = N-terminal proB-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter; T1D = type 1 diabetes; T2D = type 2 diabetes; TIA = transient ischemic attack; UA = unstable angina. 1. McMurray JJV et al. Article and study protocol. N Engl J Med. 2019;381:1995-2008; 2. Study NCT03057977. ClinicalTrials.gov website; 3. Packer M et al. Eur J Heart Fail. 2019;21:1270-1278; 4. Packer M et al. Online ahead of print. N Engl J Med. 2020.

DAPA-HF



EMPEROR-Reduced



Patients at risk

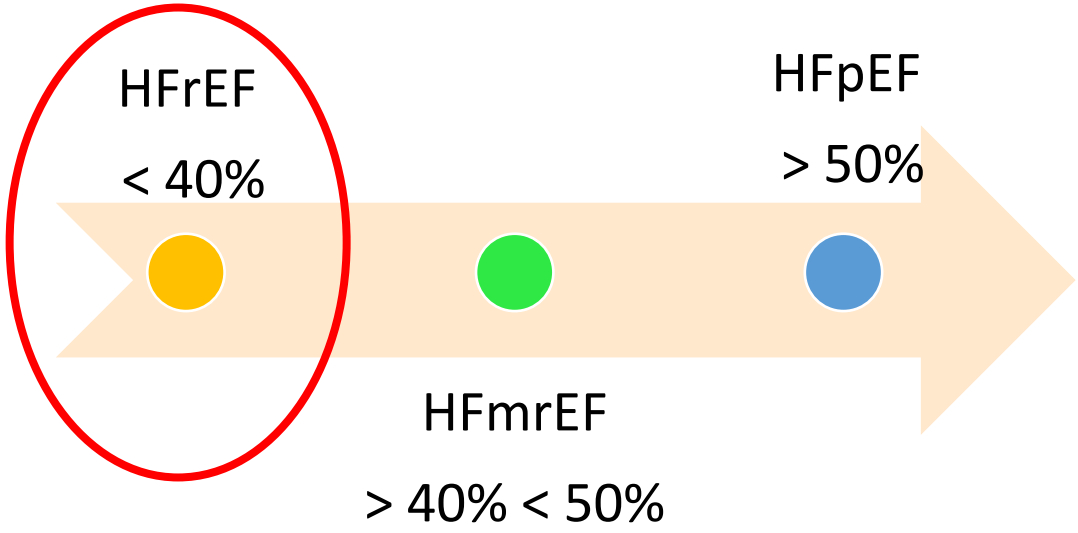
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

[a]Worsening HF includes hHF or urgent HF visit.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction; SoC: standard of Care

1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008; 2. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France

Insuffisance cardiaque à fonction réduite, HFrEF (systolique).



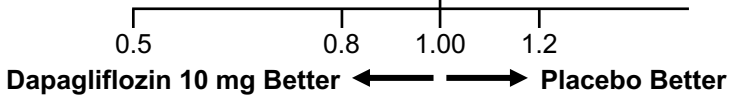
Etude	Molécule	Composite endpoint	Mortalité CV	Hospitalisation IC
EMPEROR-Reduced Trial	Empagliflozine	0,75 (0,65-0,86)	0,92 (0,75-1,12)	0,69 (0,59-0,81)
DAPA-HF trial	Dapagliflozine	0,74 (0,65-0,85)	0,82 (0,69-0,98)	0,70(0,59-0,83)

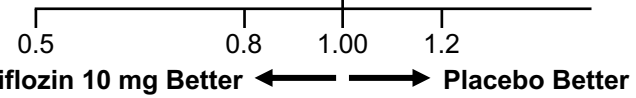
DOI: 10.1056/NEJMoa2022190
DOI: 10.1056/NEJMoa1911303

Analyses de sous groupes (DAPA-HF)

Characteristics	DAPA 10 mg n/N	PBO n/N	HR (95% CI)
Overall effect	386/2373	502/2371	0.74 (0.65-0.85)
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63-0.90)
No	171/1298	231/1307	0.73 (0.60-0.88)
Baseline eGFR, mL/min/1.73 m²			
<60	191/962	254/964	0.72 (0.59-0.86)
≥60	195/1410	248/1406	0.76 (0.63-0.92)
MRA at baseline			
Yes	281/1696	361/1674	0.74 (0.63-0.87)
No	105/677	141/697	0.74 (0.57-0.95)

Characteristics	DAPA 10 mg n/N	PBO n/N	HR (95% CI)
NYHA class			
II	190/1606	289/1597	0.63 (0.52-0.75)
III or IV	196/767	213/774	0.90 (0.74-1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59-0.84)
>Median	164/1143	195/1132	0.81 (0.65-0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49-0.80)
>Median	286/1179	347/1191	0.79 (0.68-0.92)
Atrial fibrillation or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63-1.06)
No	277/1804	376/1812	0.72 (0.61-0.84)





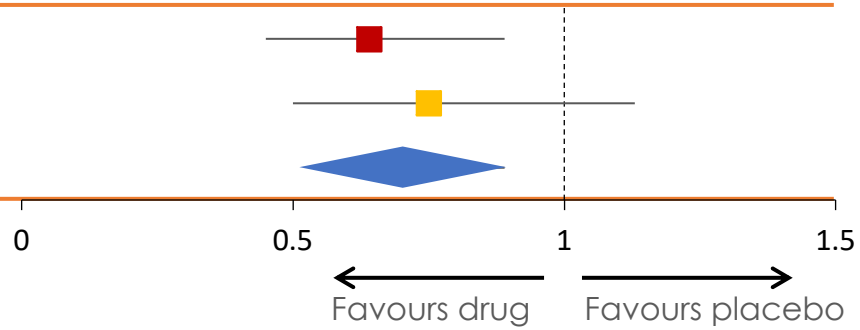
A selection of subgroups is presented above. All subgroup analyses shown were pre-specified other than ARNI (sacubitril/valsartan) at baseline.
[a]Defined as history of T2D or HbA1c ≥6.5% at both enrollment and randomization visits.
DAPA = dapagliflozin; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HR = hazard ratio; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PBO= placebo; T2D = type 2 diabetes.
1. McMurray JJV et al. N Engl J Med. 2019;381:1995-2008; 2. Solomon SD et al. Online ahead of print. J Am Coll Cardiol HF. 2020.

Meta-analysis of DAPA-HF and EMPEROR-Reduced

Résultats indépendants de la présence d'ARNi ou pas !

Receiving ARNI

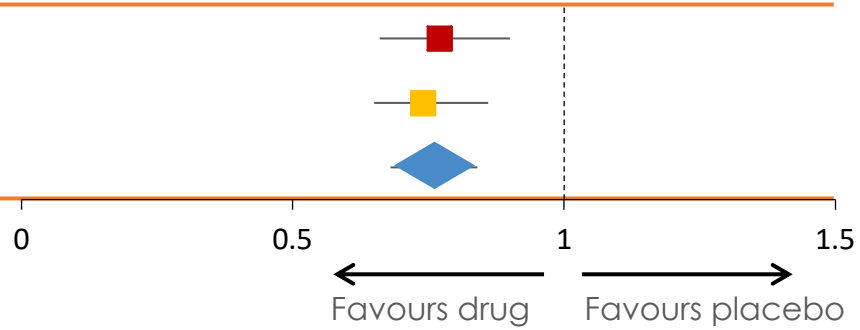
Trial	SGLT2i, n/N (%)	Placebo, n/N (%)	HR (95% CI)	HR (95% CI)
EMPEROR-Reduced	51/340 (15.0)	93/387 (24.0)	0.64 (0.45, 0.89)	
DAPA-HF	41/250 (16.4)	56/258 (21.2)	0.75 (0.50, 1.13)	
Total			0.68 (0.53, 0.89)	



Test for overall treatment effect, $p<0.0043$
Test for heterogeneity of effect, $p=0.56$

Not receiving ARNI

Trial	SGLT2i, n/N (%)	Placebo, n/N (%)	HR (95% CI)	HR (95% CI)
EMPEROR-Reduced	310/1523 (20.4)	369/1480 (24.9)	0.77 (0.66, 0.90)	
DAPA-HF	345/2123 (16.3)	446/2113 (21.1)	0.74 (0.65, 0.86)	
Total			0.75 (0.68, 0.84)	



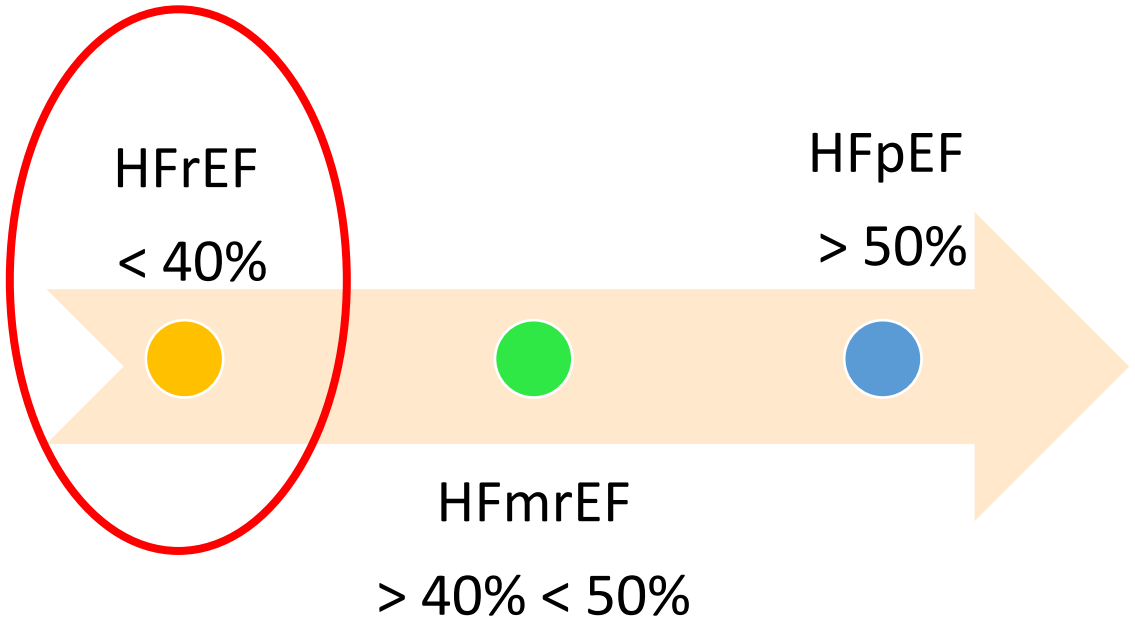
Test for overall treatment effect, $p=0.0001$
Test for heterogeneity of effect, $p=0.71$
Test for treatment subgroup interaction p=0.50

Zannad F et al. Lancet Aug.2020, doi.org/10.1016/ S0140-6736(20)31824-9

ESC European Society of Cardiology
European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

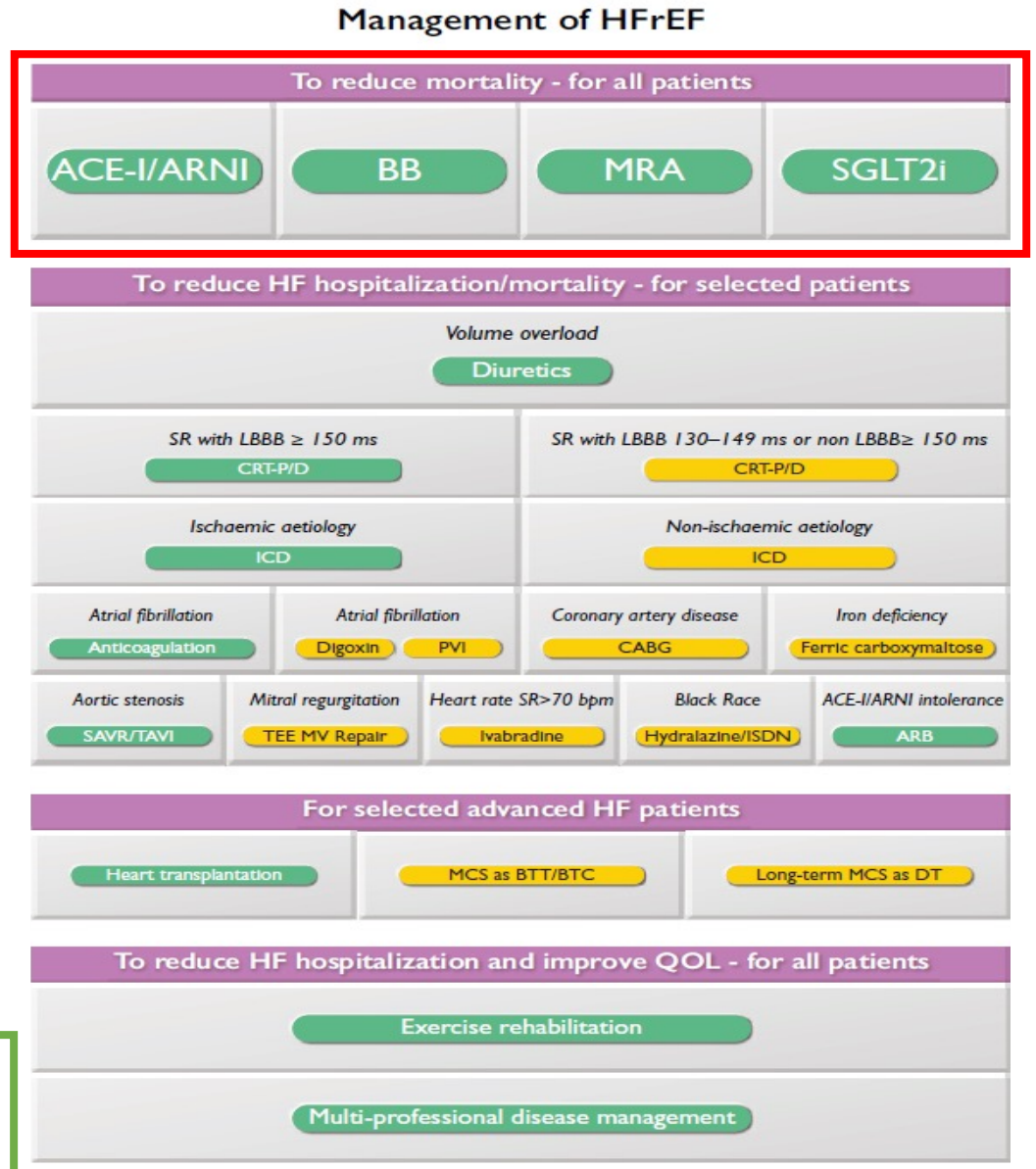
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Insuffisance cardiaque à fonction altérée, HFrEF (systolique).

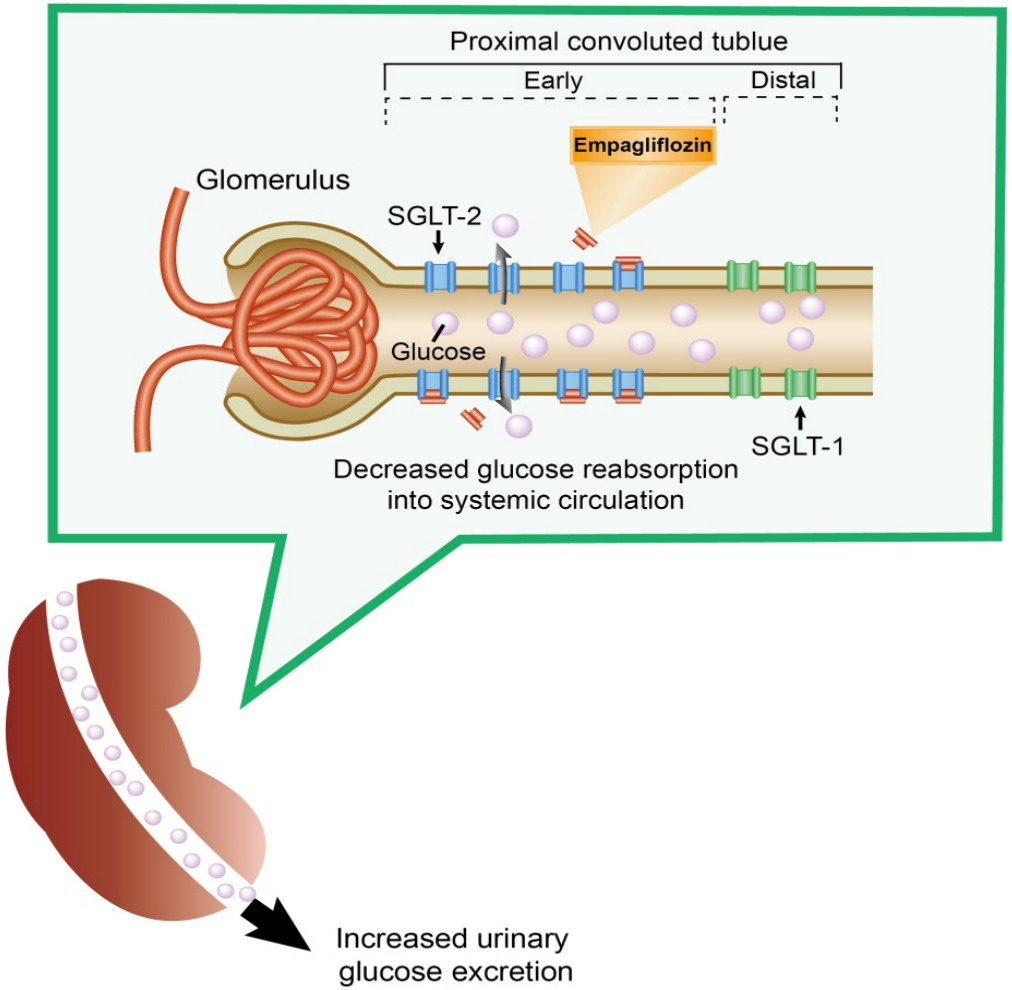


CLASSE IA

Remboursé dans l'indication



Et ensuite ?



V HFrEF

? HFmrEF

? HFpEF

Etudes dans l'HFpEF, vraiment ?

EMPEROR-Preserved
LVEF >40%

5988 patients

Empagliflozin 10 mg OD

Placebo

Median follow-up 26.2 months

COMPOSITE PRIMARY ENDPOINT

- **Time to first event of adjudicated CV death or adjudicated HHF**

CONFIRMATORY KEY SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF**
- **Slope of change in eGFR (CKD-EPI) from baseline**

DELIVER

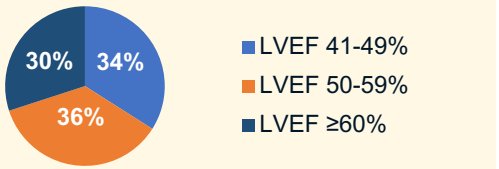
6263 Patients

- ≥40 years of age with or without T2D
- LVEF >40%[a] and evidence of structural heart disease[b] within 12 months
- Symptomatic NYHA Class II-IV HF at enrollment and typical signs/symptoms of HF ≥6 weeks before enrollment with at least intermittent need for diuretic treatment
- Elevated NT-proBNP levels
- eGFR[c] ≥25 mL/min/1.73 m²
- Ambulatory or hospitalized off IV HF therapy[d] for ≥24 hours

1:1 randomization[e]

Dapagliflozin 10 mg

Placebo



- Mean LVEF: **54%**
- Patients with prior LVEF ≤40%[3]: **~18%**

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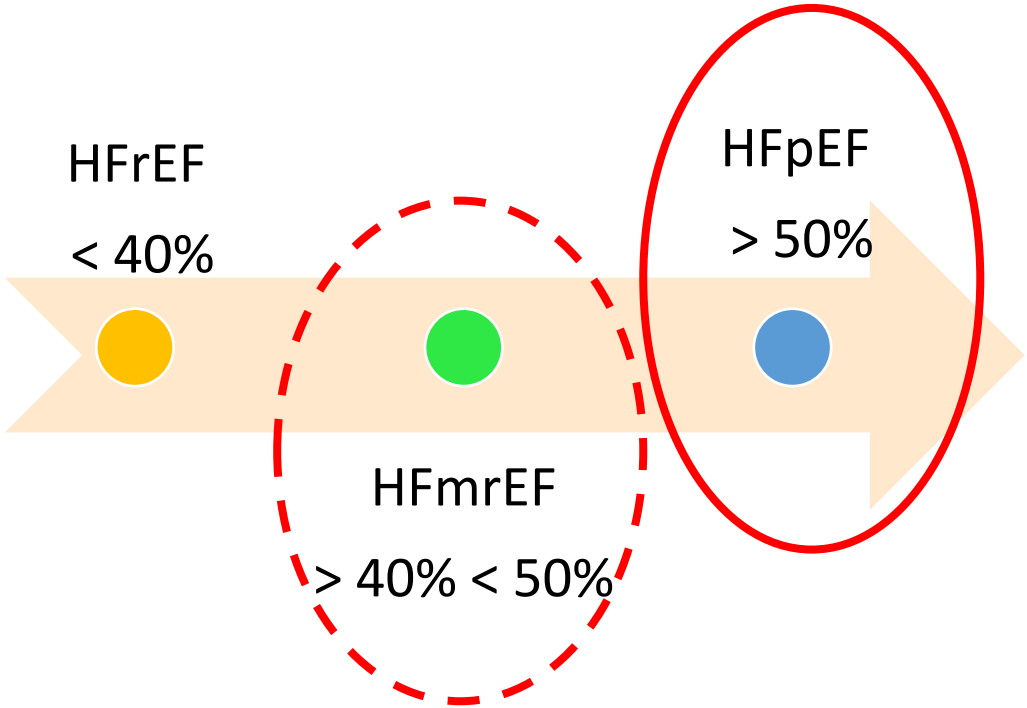
Anker S *et al. N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2107038
Solomon SD et al. *Eur J Heart Fail.* 2021;23(7):1217-1225;

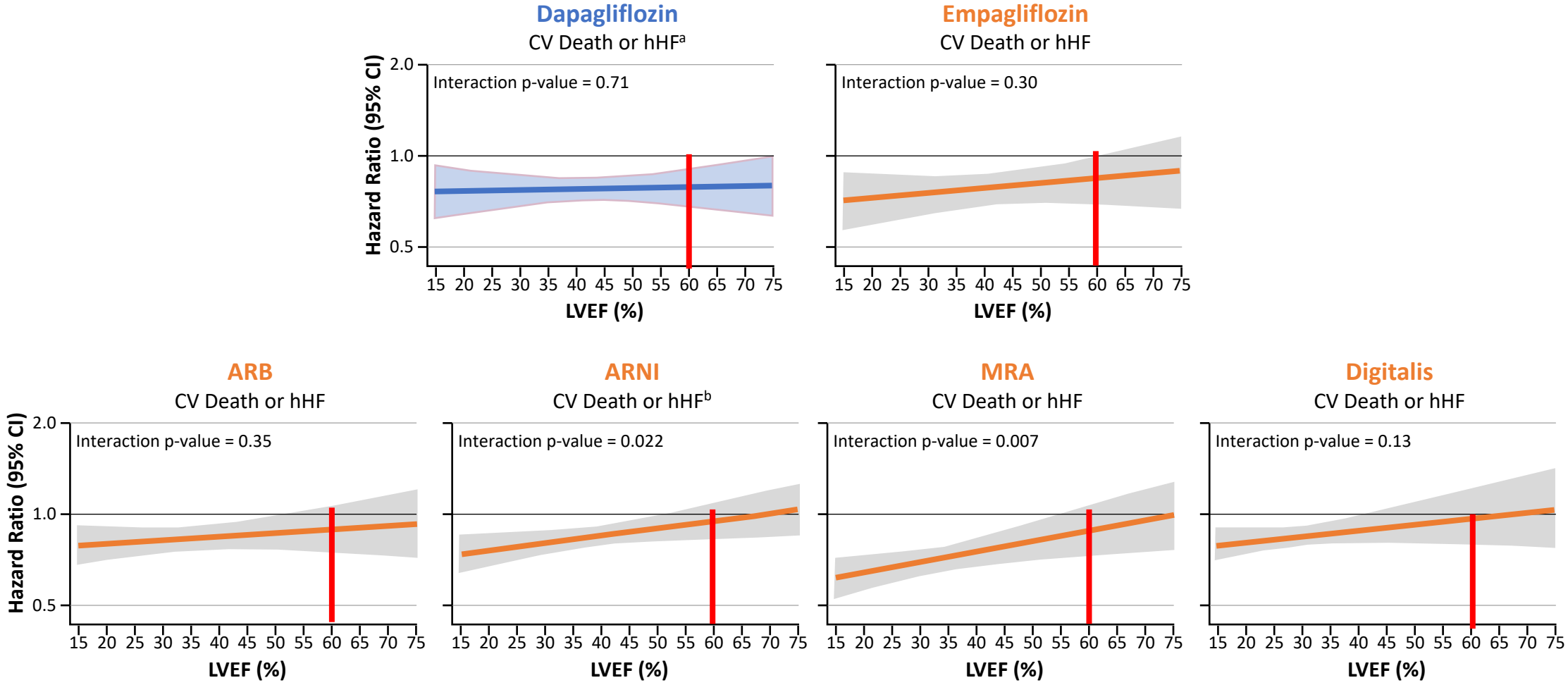
Insuffisance cardiaque à fonction conservée, HFp(m)EF (diastolique).



Etude	Molécule	Composite endpoint	Mortalité CV	Hospitalisation IC
EMPEROR-Preserved Trial	Empagliflozine	0,79 (0,69-0,90)	0,91 (0,76-1,09)	0,71(0,60-0,83)
Deliver trial	Dapagliflozine	0,82 (0,73-0,92)	0,88 (0,74-1,05)	0,79(0,69-0,91)

DOI: 10.1056/NEJMoa2107038
DOI: 10.1056/NEJMoa2206286

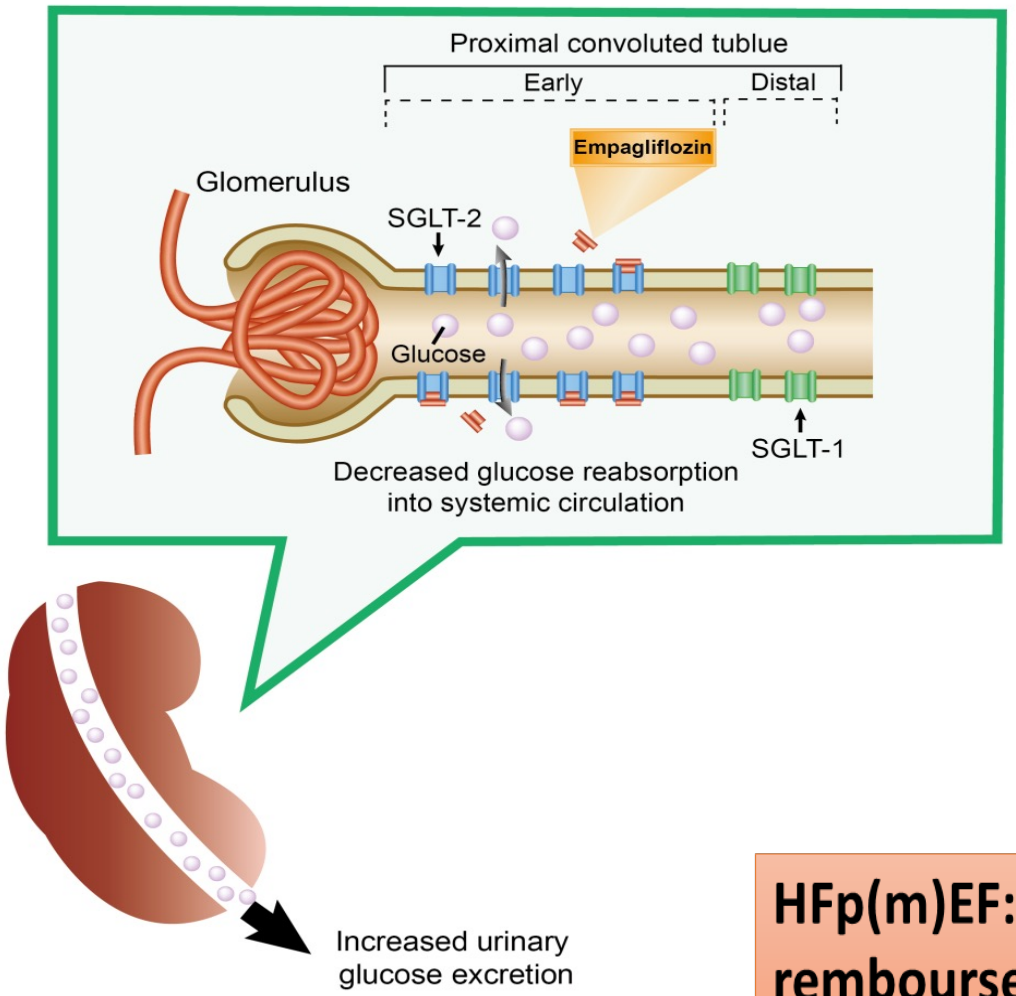
Efficacité des traitements selon la FEVG.



[a]Data utilizing linear modelling to ensure consistency across trials; [b]All data is in comparison to placebo, except for ARNI which is in comparison to enalapril or valsartan.

1. Kondo T et al. *Eur Heart J.* 2022;43(5):427-429; 2.

Fin de l'histoire ?



V HFrEF

V HFmrEF

?V HFpEF

HFp(m)EF: indications USA 2022 Classe IIA , pas de remboursement actuellement

Indication rénale

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

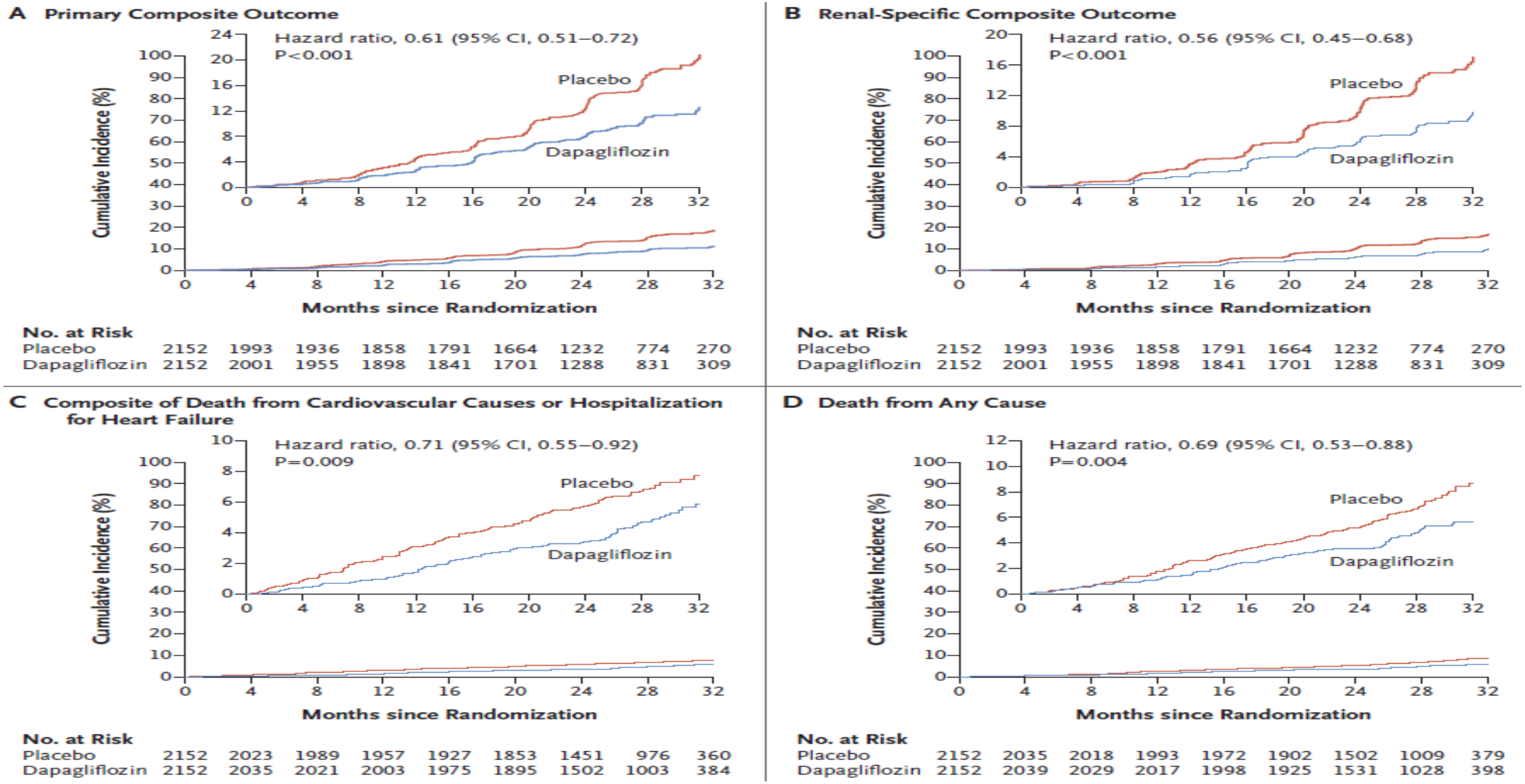
Population	
GFR moyenne	43 ml/min
GFR < 30 ml/min	13 %
Diabète II	67 %
Insuffisance cardiaque	10 %
IEC/Sartan	98 %

End point primaire composite:

- Diminution de 50 % de la GFR
- Insuffisance rénale terminale
- Mortalité d'origine rénale
- Mortalité d'origine cardio-vasculaire

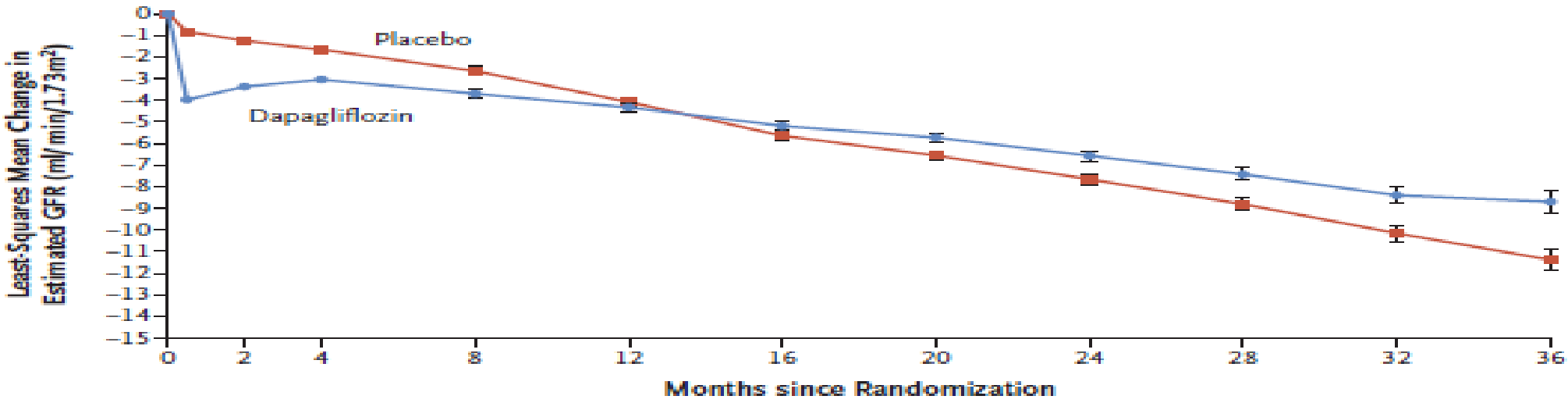
N Engl J Med 2020;383:1436-46.
DOI: 10.1056/NEJMoa2024816

DAPA-CKD Résultats



DAPA-CKD Résultats

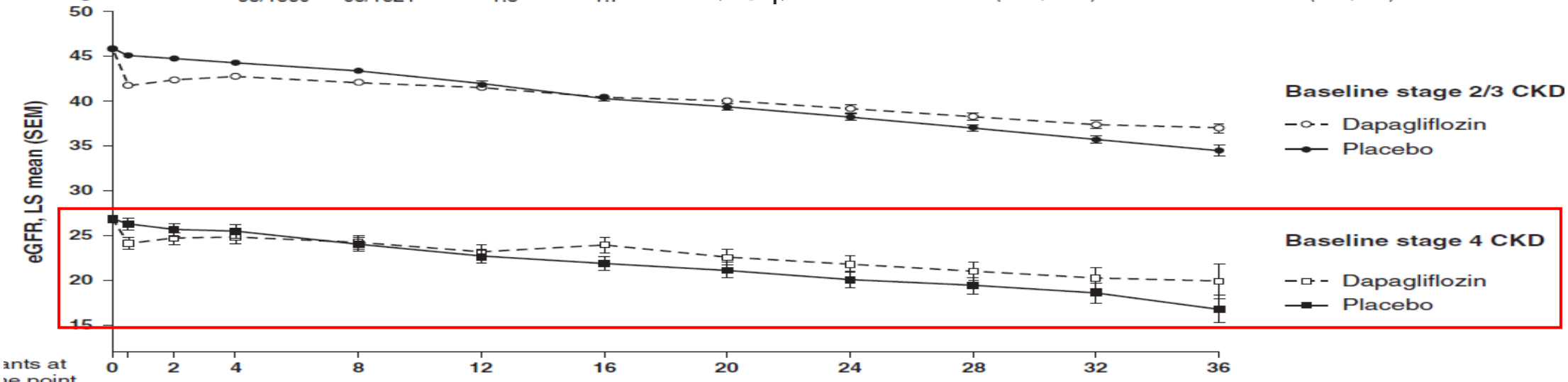
Type 2 diabetes				
Yes	152/1455	229/1451		0.64 (0.52–0.79)
No	45/697	83/701		0.50 (0.35–0.72)
Estimated GFR				
<45 ml/min/1.73 m^2	152/1272	217/1250		0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902		0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio				
≤1000	44/1104	84/1121		0.54 (0.37–0.77)
>1000	153/1048	228/1031		0.62 (0.50–0.76)



Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease

JASN 32: 2352–2361, 2021. doi: https://doi.org/10.1681/ASN.2021020167

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard Ratio (95% CI)	*P* Value for Interaction	Absolute Risk Difference, % (95% CI)	*P* Value for Interaction
Primary end point: eGFR decline ≥50%, ESKD, or kidney or CV death								
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)		5.3 (3.4, 7.3)	
Stage 4 CKD	59/293	87/331	11.1	14.9	0.73 (0.53, 1.02)	0.22	6.1 (-0.5, 12.7)	0.72
Stage 2/3 CKD	138/1859	225/1821	3.7	6.2	0.58 (0.47, 0.71)		4.9 (3.0, 6.9)	
ESKD								
Overall	109/2152	161/2152	2.5	3.8	0.64 (0.50, 0.82)		2.4 (1.0, 3.9)	
Stage 4 CKD	49/293	72/331	9.2	12.4	0.72 (0.50, 1.04)	0.64	5.0 (-1.1, 11.2)	0.24
Stage 2/3 CKD	60/1859	89/1821	1.6	2.4	0.64 (0.46, 0.89)		1.7 (0.4, 2.9)	
Kidney or CV death								
Overall	67/2152	86/2152	1.4	1.9	0.78 (0.56, 1.07)		0.9 (-0.2, 2.0)	
Stage 4 CKD	14/293	18/331	2.3	2.6	0.89 (0.44, 1.79)	0.74	0.7 (-2.8, 4.1)	0.90
Stage 2/3 CKD	53/1859	68/1821	1.3	1.7	0.76 (0.53, 1.09)		0.9 (-0.3, 2.0)	



Résumé: les Gliflozines

- ont un effet protecteur sur la survenue d'insuffisance cardiaque chez les patients diabétiques.
- sont recommandées en classe IA chez tous les patients porteurs d'une insuffisance cardiaque à fonction altérée (HFrEF).
- ont démontré un effet intéressant (diminution des hospitalisations) dans les autres phénotypes d'insuffisance cardiaque.
- ont démontré un effet néphroprotecteur significatif avec une sécurité d'utilisation satisfaisante.

Je vous remercie pour votre attention.