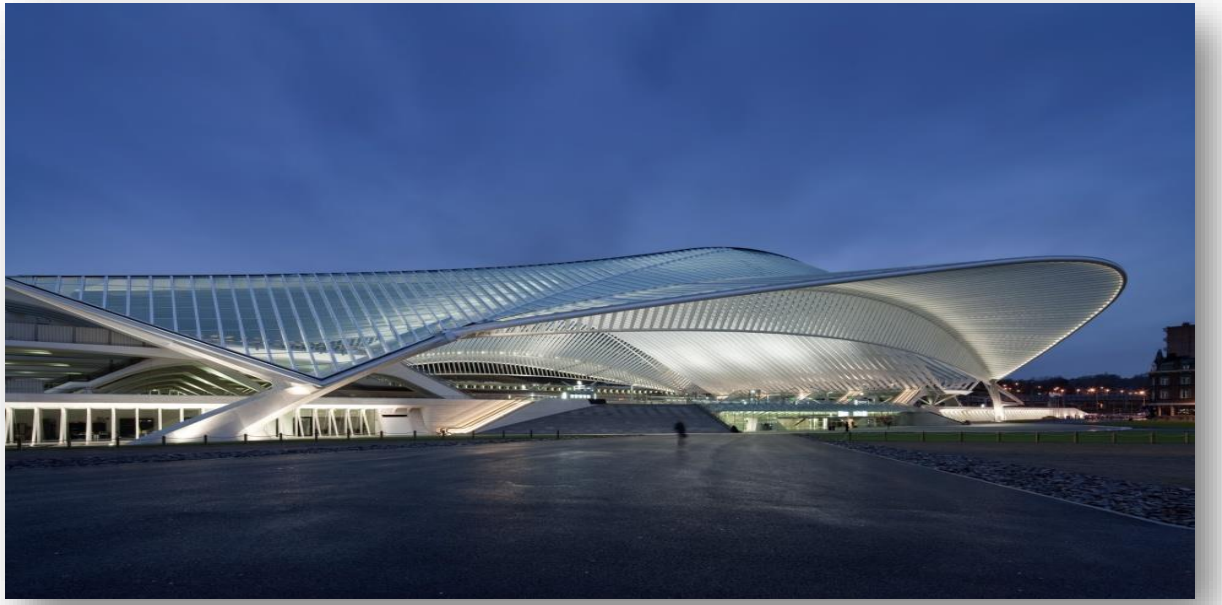
La révolution des Inhibiteurs du SGLT2 pour les patients cardiaques



Dr Pierre Troisfontaines
Service de Cardiologie

Dr Pierre Troisfontaines

- Cardiologue & Chef de Service de Cardiologie au C.H.R. de la Citadelle (Liège)
- Responsable du Centre de l'Insuffisance cardiaque du C.H.R. de la Citadelle depuis 2005.

- Membre de la Société Belge de Cardiologie.

- Past-Président du Belgian Working Group on Heart Failure and Cardiac Function.
- Membre de la Heart Failure Association (HFA-ESC).
- Membre du Heart Failure Policy Network.

- Vice-président de l'ASBL, « Mon Cœur Entre Parenthèses ».

BWGHF
Belgian Working Group on Heart Failure

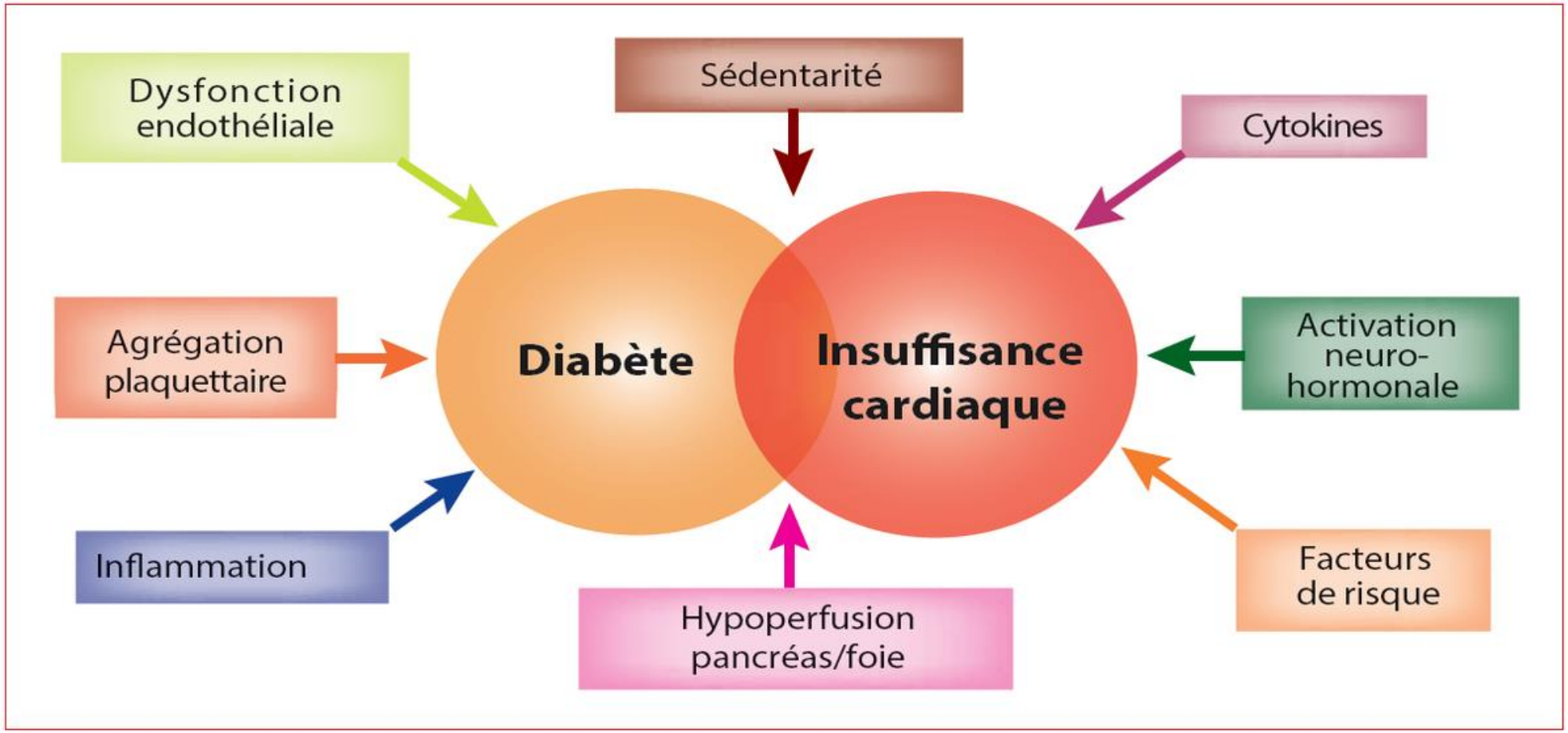
CHR Liège
CITADELLE CHATEAU ROUGE SAINTE ROSALIE
VOTRE SANTÉ, NOTRE MÉTIER

Diabète & insuffisance cardiaque

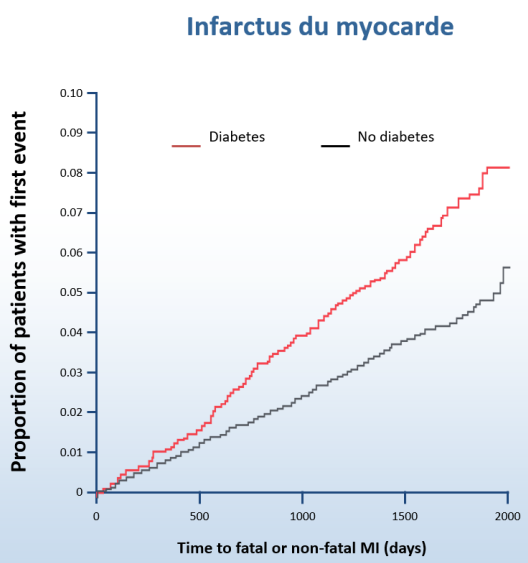
L'association diabète et insuffisance cardiaque est fréquente

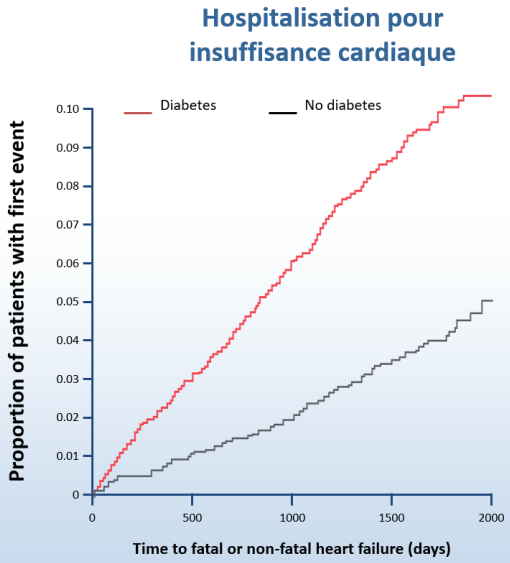
30 à 40 % des patients inclus dans des études dans l'IC sont **diabétiques**

Risque de survenue d'une insuffisance cardiaque augmente d'~ **15-20 % pour + 1 % HBa1c.**



Le diabète accélère la survenue d'un premier événement CV



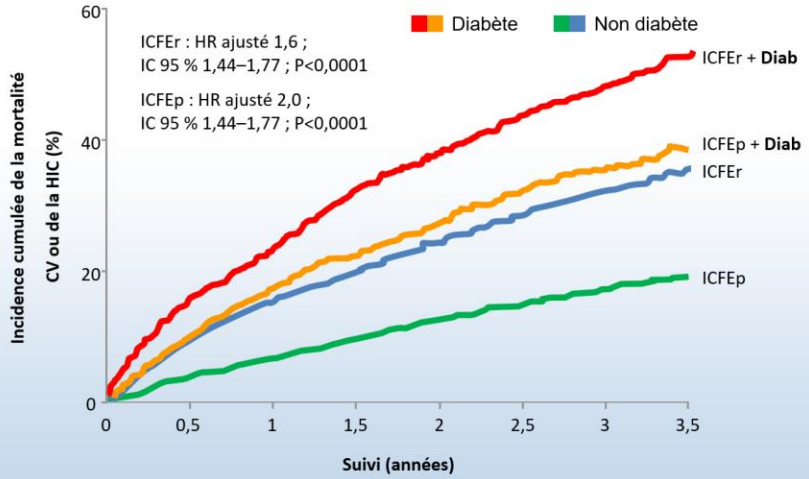


McMurray JJV *et al. Lancet Diabetes Endocrinol* 2014;2:843

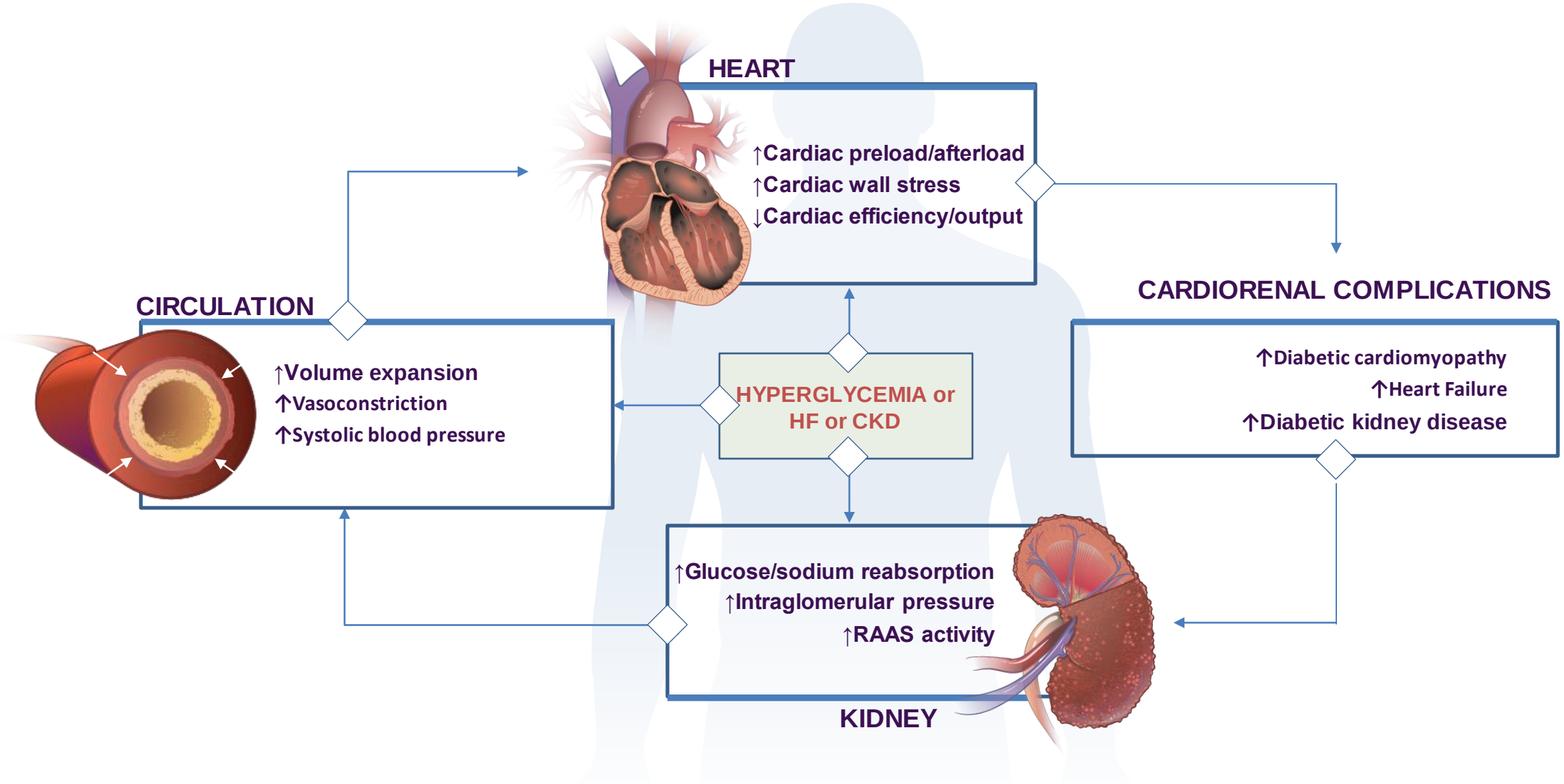
Diabète & insuffisance cardiaque: Les liaisons dangereuses

Le risque de décès ou l'hospitalisation pour insuffisance cardiaque est supérieur chez les patients atteints de DT2

Augmentation du risque d'hospitalisation ou de décès due à une ICFEr par rapport à une ICFEp

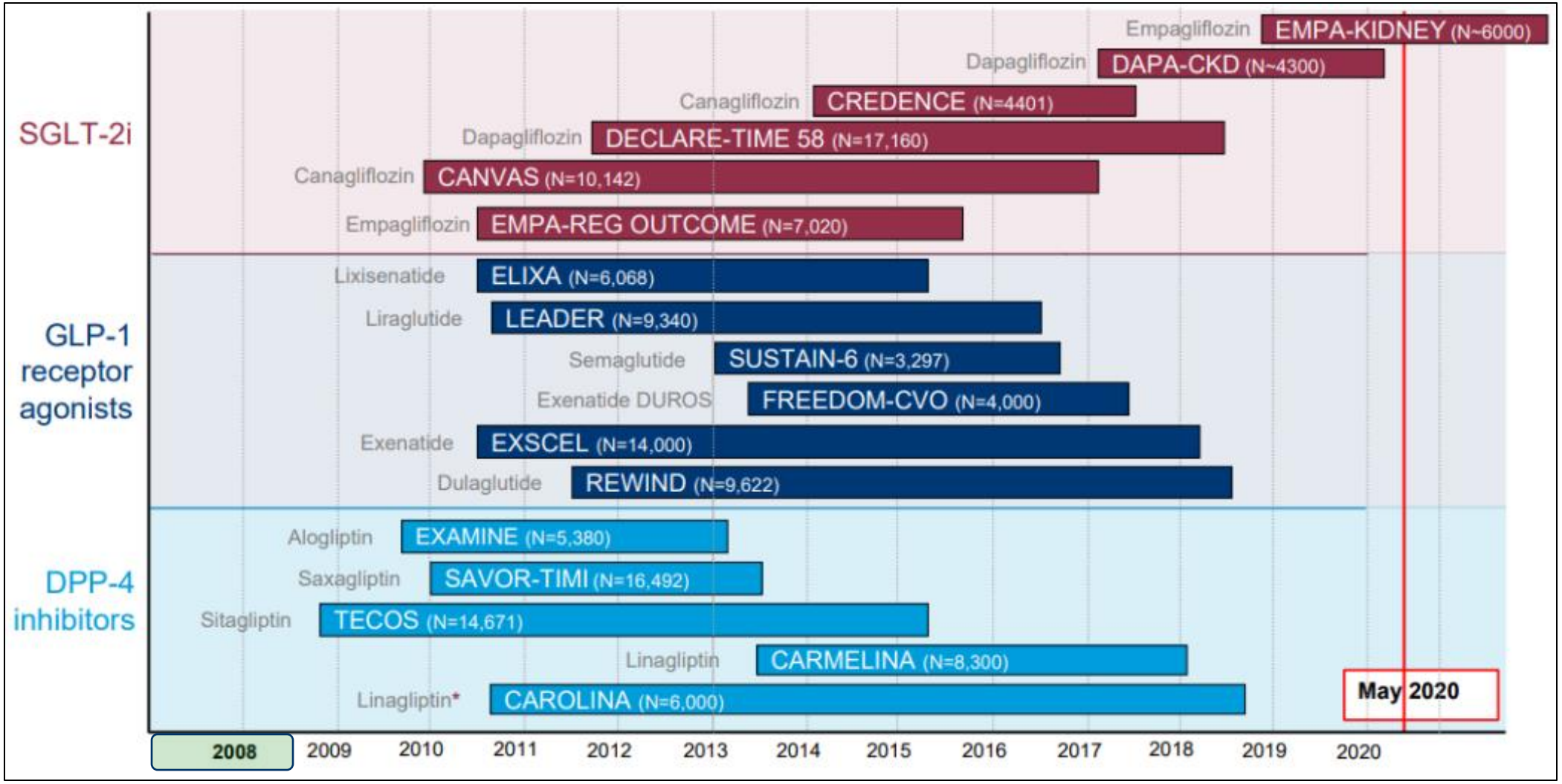


Interaction physio-pathologique entre le rein et le cœur



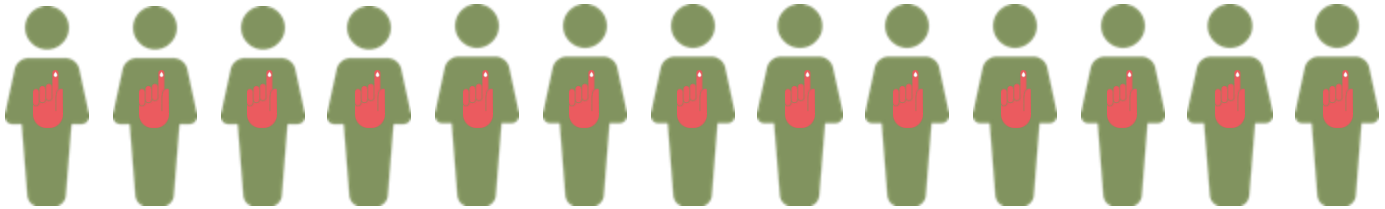
1. Muralidaran Y, et al. *J Diabetes Metab.* 2015, 6:10. 2. Sattar N, et al. *Diabetologia*. 2016;59(7):1333-1339. 3. Wanner C, *Am J Cardiol*. 2017;120(1S):S59-S67. 4. Sattar N, et al. *Circulation*. 2018;138:7–9. 5. Mazidi M, et al. *J Am Heart Assoc.* 2017;6(6):e004007.

CV outcome trials with novel anti-diabetic treatments



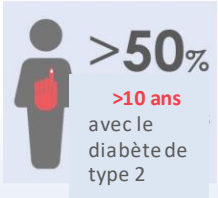
Hiddo L. Heerspink ; ESC 2021

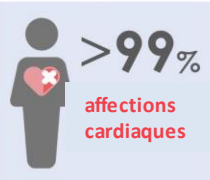
EMPA-REG OUTCOME® :
Une étude majeure pour les patients DT2

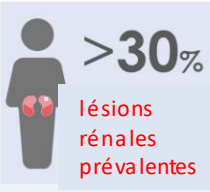


Randomisation

7 020 patients diabétiques de type 2







Placebo

Empagliflozine
10 mg

Empagliflozine
25 mg

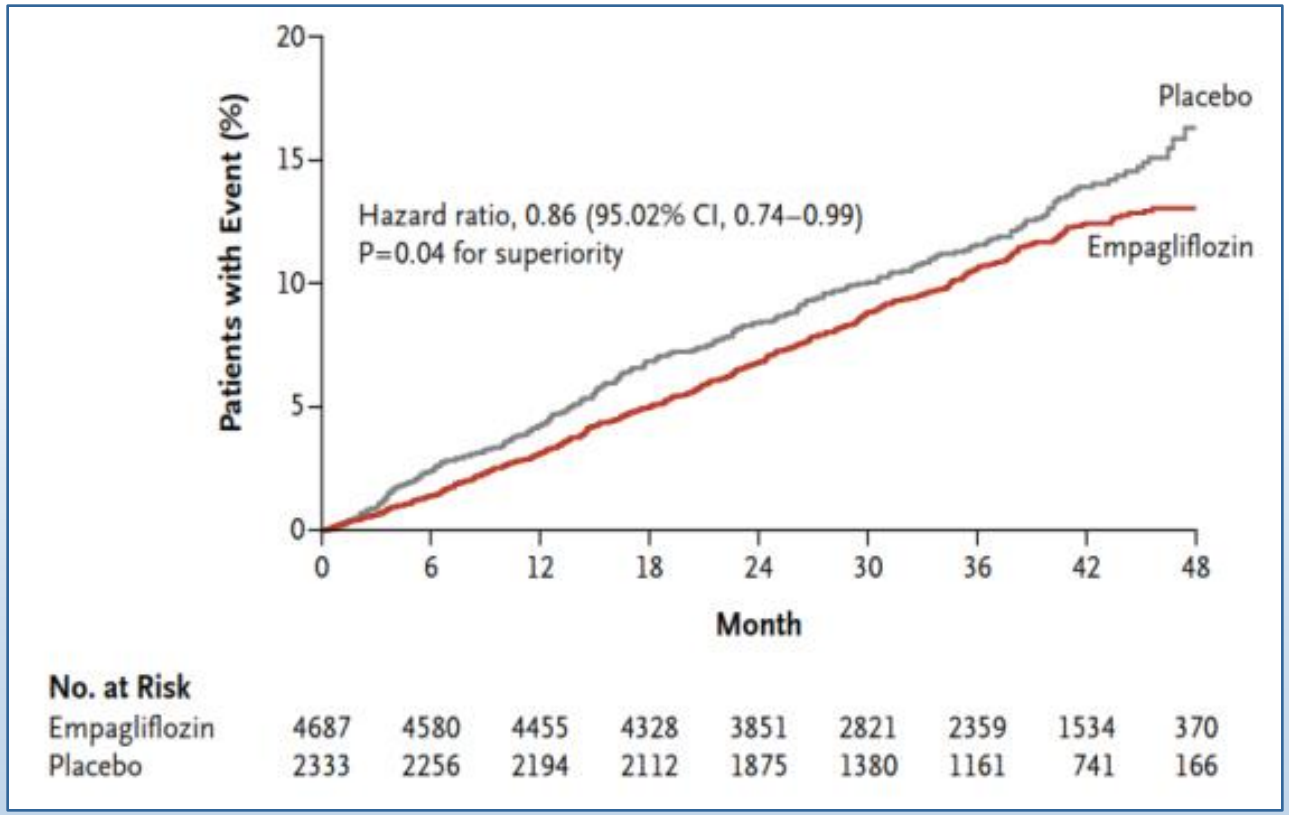
En ajout au traitement standard

Usage d'un hypotenseur	Usage de statine	Usage d'AAS
95 %	77 %	83 %

Zinman B. et al., N Engl J Med, 2015: 373(22):2117-28

Empagliflozine réduit le taux d'événements CV majeurs

Critère principal d'évaluation = décès CV, IM non fatal, AVC non fatal



14% RRR

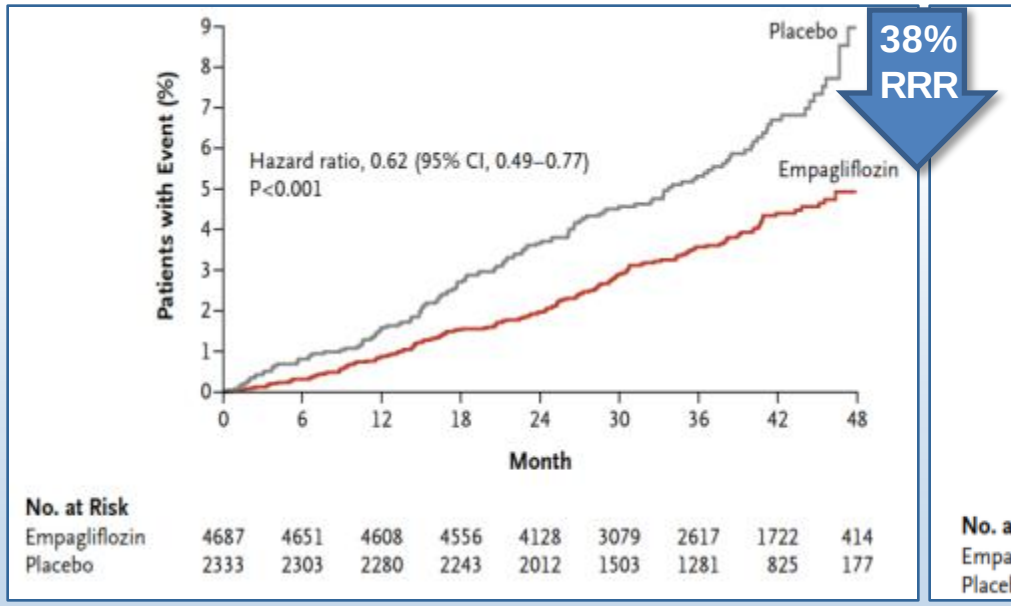
Empagliflozine* a réduit le risque de décès CV, d'IM non fatal ou d'AVC non fatal de 14 %

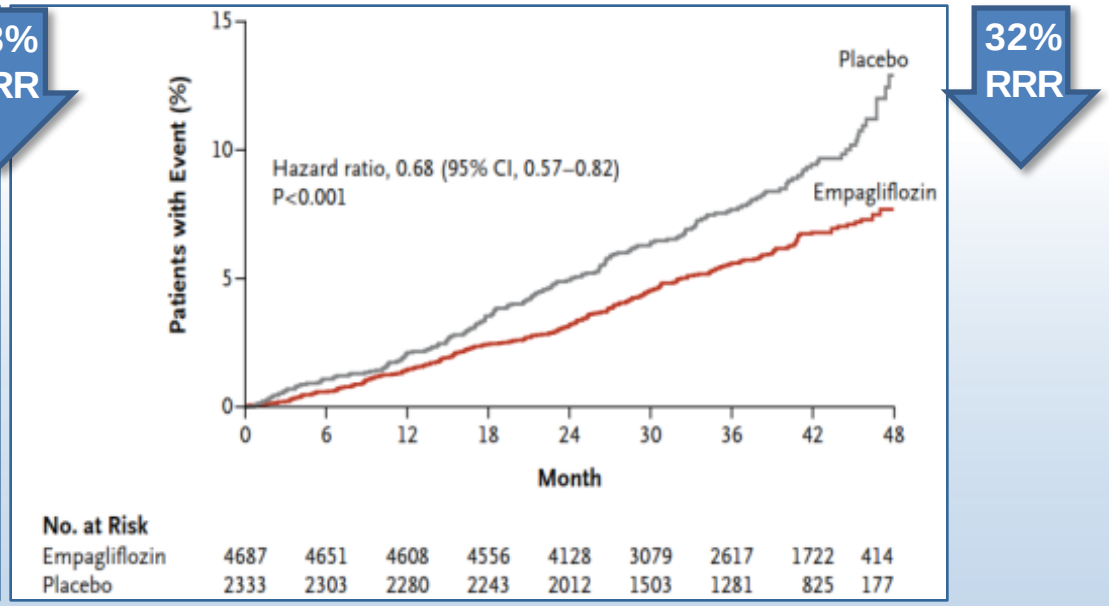
*En traitement d'appoint. Résultat obtenu en groupant les patients sous empagliflozine 10mg et empagliflozine 25mg
CV, cardiovasculaire; IM, infarctus du myocarde; AVC, accident vasculaire cérébral
Zinman B, et al. N Engl J Med 2015;373:2117–2128.

Empagliflozine réduit le taux de mortalité CV et de mortalité totale

Décès dû à des causes CV
-38 % de RRR avec l'empagliflozine

Mortalité totale
-32 % de RRR avec l'empagliflozine

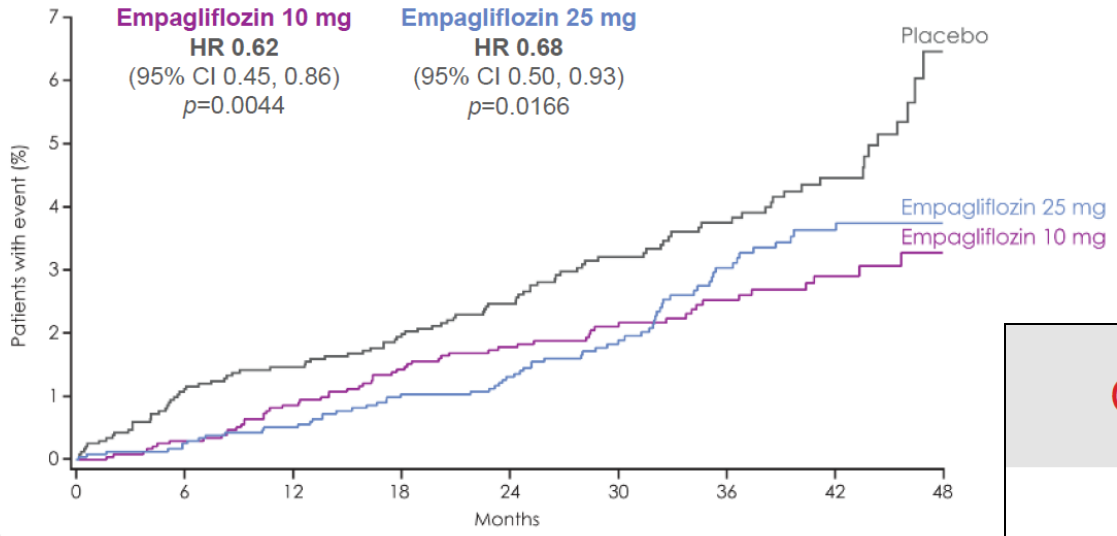




Empagliflozine* a réduit la mortalité CV de 38 % et a amélioré la survie en réduisant la mortalité totale de 32 %

* En traitement d'appoint
Zinman B, et al. N Engl J Med 2015;373:2117–2128

Hospitalisation for heart failure



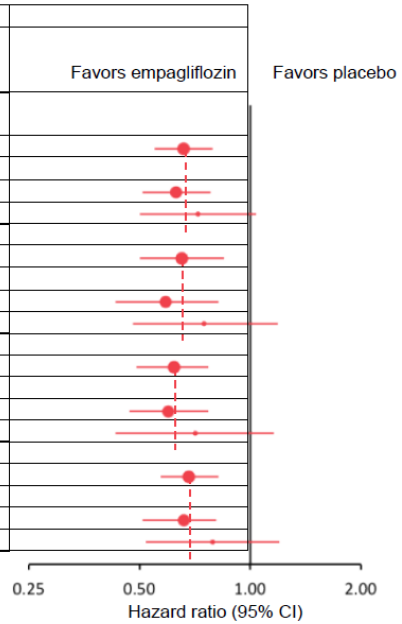
No. of patients									
Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

29

Cumulative incidence function. HR, hazard ratio

Outcomes in patients with and without heart failure

	Empagliflozin			Placebo		
	No. of patients with event/ no. of patients	%		No. of patients with event/ no. of patients	%	Hazard ratio (95% CI)
Heart failure hospitalization or cardiovascular death						
All patients	265/4687	5.7		198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline						
No	190/4225	4.5		149/2089	7.1	0.63 (0.51–0.78)
Yes	**75/462**	**16.2**		**49/244**	**20.1**	**0.72 (0.50–1.04)**
Hospitalization for heart failure						
All patients	126/4687	2.7		95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline						
No	78/4225	1.8		65/2089	3.1	0.59 (0.43–0.82)
Yes	**48/462**	**10.4**		**30/244**	**12.3**	**0.75 (0.48–1.19)**
Cardiovascular death						
All patients						
Heart failure at baseline	172/4687	3.7		137/2333	5.9	0.62 (0.49–0.77)
No	134/4225	3.2		110/2089	5.3	0.60 (0.47–0.77)
Yes	**38/462**	**8.2**		**27/244**	**11.1**	**0.71 (0.43–1.16)**
All-cause mortality						
All patients	269/4687	5.7		194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline						
No	213/4225	5.0		159/2089	7.6	0.66 (0.54–0.81)
Yes	**56/462**	**12.1**		**35/244**	**14.3**	**0.79 (0.52–1.20)**



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

Trois études cardio-vasculaires concernant des SGLT2i

Études	EMPA-REG OUTCOME [7]	CANVAS [8]	DECLARE-TIMI 58 [9]
Suivi médian (années)	3,1	3,6	4,2
Patients (n) iSGLT2 *versus* placebo	4 687 *versus* 2 333 (7020 pts)	5 795 *versus* 4 247 (10,142 pts)	8 582 *versus* 8 578 (17,160 pts)
Prévention CV secondaire *versus* primaire (%)	> 99 *versus* < 1	65 *versus* 35	40 *versus* 60
HbA_{1c} moyenne (%)	8,1	8,2	8,3
Inhibiteur de SGLT2	Empagliflozine 10 ou 25 mg	Canagliflozine 100-300 mg	Dapagliflozine 10 mg
Critère primaire composite CV	MACE 3 points 0,86 [0,74–0,99] $p < 0,001$	MACE 3 points 0,86 [0,75-0,97] $p = 0,02$	MACE 3 points 0,93 [0,84-1,03] $p = 0,17$ ---------- Autre critère primaire CV pré-spécifié (mortalité CV ou hospitalisation pour IC) 0,83 [0,73-0,95] $p = 0,005$
IDM	0,87 [0,70–1,09] $p = 0,23$	0,85 [0,69-1,05] p = NT	0,89 [0,77-1,01] p = NT
AVC	1,18 [0,89–1,56] $p = 0,26$	0,87 [0,69-1,09] p = NT	1,01 [0,84-1,21] p = NT
Mortalité CV	0,62 [0,49–0,77] $p < 0,001$	0,87 [0,72-1,06] p = NT	0,98 [0,82-1,17] p = NT
Mortalité globale	0,68 [0,57–0,82] $p < 0,001$	0,87 [0,74-1,01] $p = 0,24$	0,93 [0,82-1,04] p = NT
Hospitalisation pour IC	0,65 [0,50–0,85] $p = 0,002$	0,78 [0,67-0,91] p = NT (a)	0,73 [0,61-0,88] p = NT
Critère composite rénal	0,61 (b) [0,53-0,70] $p < 0,001$	0,60 (c) [0,47-0,77] $p < 0,001$	0,53 (d) [0,43-0,66] p = NT

2015

EMPA-REG OUTCOME®

2016

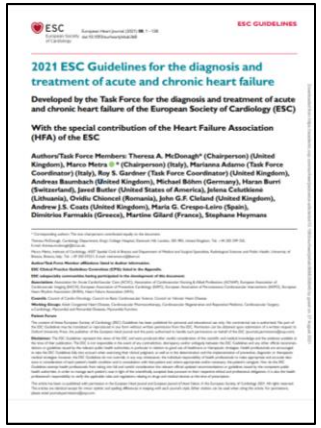
CANVAS Program

2018

DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG Dapagliflozin Effect on Cardiovascular Events

Médecine des maladies Métaboliques - Mars 2019 - Vol. 13 - N°2

Nouvelle Classification de l'IC selon FEvg


ESC GUIDELINES

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

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

		HFrEF	HFmrEF	HFpEF
Types d'IC		ICFEr		ICFEp
Critères	1	Symptômes ± signes cliniques d'IC		
	2	FEVG < 40 %	FEVG 40-49 %	FEVG ≥ 50 %
	3	-	1. Taux de peptides natriurétiques élevés : BNP ≥ 35 pg/mL ou NT-proBNP ≥ 125 pg/mL 2. Au moins un des facteurs additionnels : a. une anomalie structurelle cardiaque : HVG, dilatation OG (> 34 mL/m²) ; b. une dysfonction diastolique : E/e' ≥ 13 ou e' < 9 cm/s.	

1. Chronic heart failure (CHF), when patients have an established diagnosis of HF or who have a more gradual onset of symptoms
2. Acute heart failure (AHF) when presenting acutely

McDonagh T, et al. Eur Heart J 2021;00:1-128

CITADELLE CHATEAU ROUGE SAINTE ROSALIE
VOTRE SANTÉ, NOTRE MÉTIER

ESC European Society of Cardiology

Etudes randomisées sur les inh-SGLT2 dans l'insuffisance cardiaque

	EMPEROR-Preserved[1]	EMPEROR-Reduced[2]	Dapa-HF[3]	SOLOIST-WHF[4,5]
Sample size	4126	2850*	4500	4000[4] (6667 ?)[5]
Key inclusion criteria	• Chronic HF† • Elevated NT-proBNP • eGFR ≥20 ml/min/1.73 m²		• Symptomatic HFrEF† • Elevated NT-proBNP • eGFR ≥30 ml/min/1.73 m²	• Type 2 diabetes • Chronic HF • Elevated NT-proBNP • Hospital admission for worsening HF and haemodynamically stable
	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)	
Primary endpoint	• Time to first event of adjudicated CV death or adjudicated HHF		• Time to first occurrence of CV death, HHF or urgent HF visit	• Time to first event of CV death or HHF (both EF<50% and II)
Key secondary endpoints	• Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence of sustained reduction of eGFR • Change from baseline in KCCQ		• Total number of CV death or HHF • All-cause mortality • Composite of ≥50% sustained eGFR decline, ESRD or renal death • Change from baseline in KCCQ	• Total number of CV death, HHF or urgent HF visit • Composite of ≥50% sustained eGFR decline, chronic dialysis, renal transplant or sustained eGFR <15 ml/min/1.73 m²
Start date	March 2017	March 2017	February 2017	June 2018
Expected completion date	June 2020	June 2020	December 2019	January 2021

Dapagliflozin in Patients with Chronic HFrEF With or Without T2D

DAPAHF

4744 patients

- ≥18 years of age
- *With or without T2D*
- Diagnosis of symptomatic HFrEF (NYHA class II-IV) for ≥ 2 months
- LVEF ≤40% within last 12 months
- Elevated NT-proBNP
- eGFR ≥30 mL/min/1.73 m^2
- Stable SoC HFrEF treatment

1:1 Double-blind

Dapagliflozin 10 mg + standard of care[a]

Placebo + standard of care[a]

Visit 1 (enrollment) Day -14 | Visit 2 (randomization) Day 0 | Visit 3 Day 14 | Visit 4 Day 60 | Visit 5 Day 120 | Visit 6, etc. Every 120 days

Target primary endpoint events: 844[1]
Median follow-up: 18.2 months[2]
Completion: July 2019[3]

Primary Endpoint

- **Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit**

Secondary Endpoints

- **Time to first occurrence of either of the components of the composite: CV death or hHF**
- **Total number of (first and recurrent) hHF and CV death**
- **Change from baseline measured at 8 months in the total symptom score of the KCCQ**
- **Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD[b] or renal death**
- **Time to death from any cause**

[a]Patients were treated according to regional standard of care for HF. Dose reduction or discontinuation of standard of care therapy was discouraged unless all other measures failed. Changes in standard of care medications was at the discretion of the investigator; [b]Defined as sustained eGFR <15 mL/min/1.73m^2, chronic dialysis treatment, or receiving a renal transplant.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray JJV et al. *N Engl J Med.* 2019; 381:1995-2008; 3. Study NCT03036124. ClinicalTrials.gov website; 4. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402-1411.

DAPACARE The Largest SGLT2i Development Program[a] Worldwide[1-4]

DAPAHF First and Largest SGLT2i HFrEF Trial to Successfully Improve Outcomes and Symptoms[2,5]

DAPA-HF Overview[5]

N=4744

- 45% T2D
- 55% No T2D

1:1 Double-blind

- DAPA 10 mg n=2373
- Placebo n=2371

Inclusion Criteria: ≥18 years with or without T2D, LVEF ≤40%, NYHA class II-IV, elevated NT-proBNP, eGFR ≥30 mL/min/1.73 m^2, stable SoC HFrEF treatment

Significant Reduction in Composite of CV Death or Worsening HF[5,b]

26% RRR

HR 0.74 (0.65-0.85)

p<0.001

NNT=21

- **CV Death[6]**: 18% RRR, p=0.029
- **hHF[6]**: 30% RRR, p=0.00003 [Includes urgent HF visits]

Consistent Benefit Across a Broad and Representative Population

- T2D/No T2D[7]
- Background HF therapy[8]
- Diuretic use and dose[9]
- Baseline LVEF[10]
- NT-proBNP[11]
- eGFR[12]

Risk of both **first and recurrent hHF events**[13]

Reduction in **all-cause mortality** (p=0.022[c])[6]

HF symptom improvement more common and deterioration less common[14]

Significantly reduced risk of CV death or worsening HF[b] **as early as**[15] Day 28

DAPA-HF Safety[5,7]

DAPA was well-tolerated in patients with and without T2D

Adverse events rarely led to discontinuation of treatment

No events of major hypoglycemia or DKA in patients without T2D

DAPA is the only SGLT2i approved for HFrEF[16,17]

Proven benefit highlighted in an **HFA-ESC Position Paper**[18]

Heart Failure Characteristics

DAPAHF

Characteristic	Dapagliflozin 10 mg (n=2373)	Placebo (n=2371)
NYHA functional classification, n (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
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, n (%)		
Ischemic	1316 (55.5)	1358 (57.3)
Non-ischemic	857 (36.1)	830 (35.0)
Unknown	200 (8.4)	183 (7.7)

IQR = interquartile range; NT-pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.

Medical History

DAPAHF

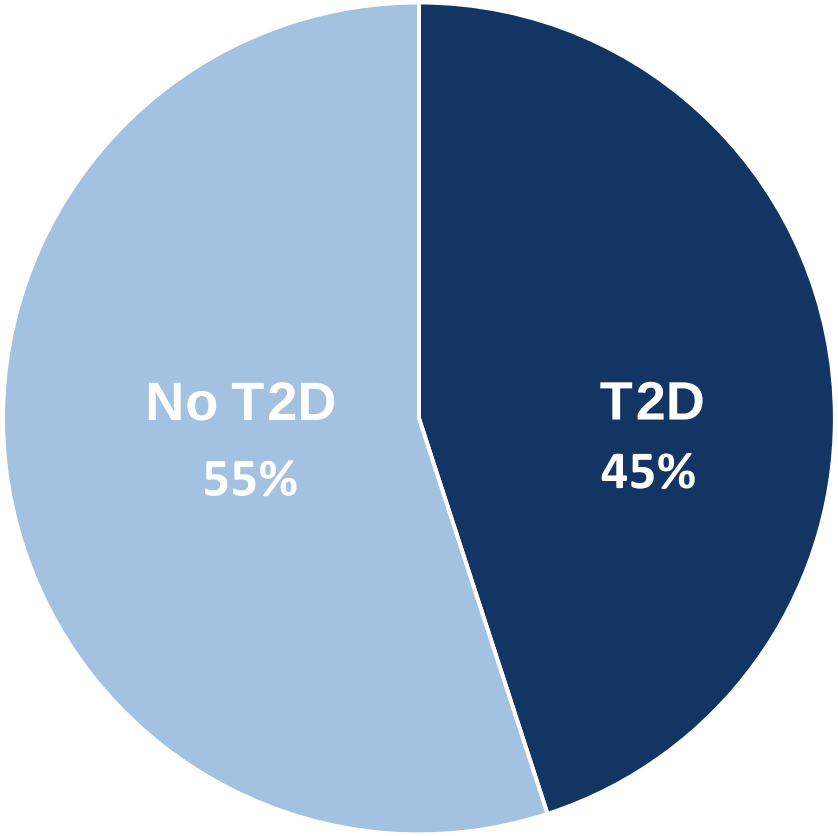
Characteristic	Dapagliflozin 10 mg (n=2373)	Placebo (n=2371)
Hospitalization for heart failure, n (%)	1124 (47.4)	1127 (47.5)
Atrial fibrillation, n (%)	916 (38.6)	902 (38.0)
Diabetes mellitus[a], n (%)	993 **(41.8)**	990 **(41.8)**
Estimated GFR, mL/min/1.73 m^2	66.0 ± 19.6	65.5 ± 19.3
Estimated GFR 30-60 mL/min/1.73 m^2, n/total N (%)	962/2372 (40.6)	964/2371 (40.7)
Device therapy, n (%)		
Implantable cardioverter-defibrillator[b]	622 (26.2)	620 (26.1)
Cardiac-resynchronization therapy[c]	190 (8.0)	164 (6.9)

[a]Includes 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2); [b]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator; [c]Cardiac-resynchronization therapy with or without a defibrillator.

GFR = glomerular filtration rate; HbA1c = glycated hemoglobin.

McMurray JJV et al. Article and online protocol. *N Engl J Med*. 2019;381:1995-2008.

Majority of Patients in DAPA-HF Did **Not** Have Type 2 Diabetes



N=4744

No T2D (n=2605)

- Normal HbA1c (HbA1c <5.7% at Visits 1 and 2): n=839; 17.7%
- Prediabetes (HbA1c ≥5.7-<6.5% at Visit 1 or 2): n=1748; 36.8%
- HbA1c single measurement <5.7% or not available: n=18; 0.4%

T2D (n=2139)

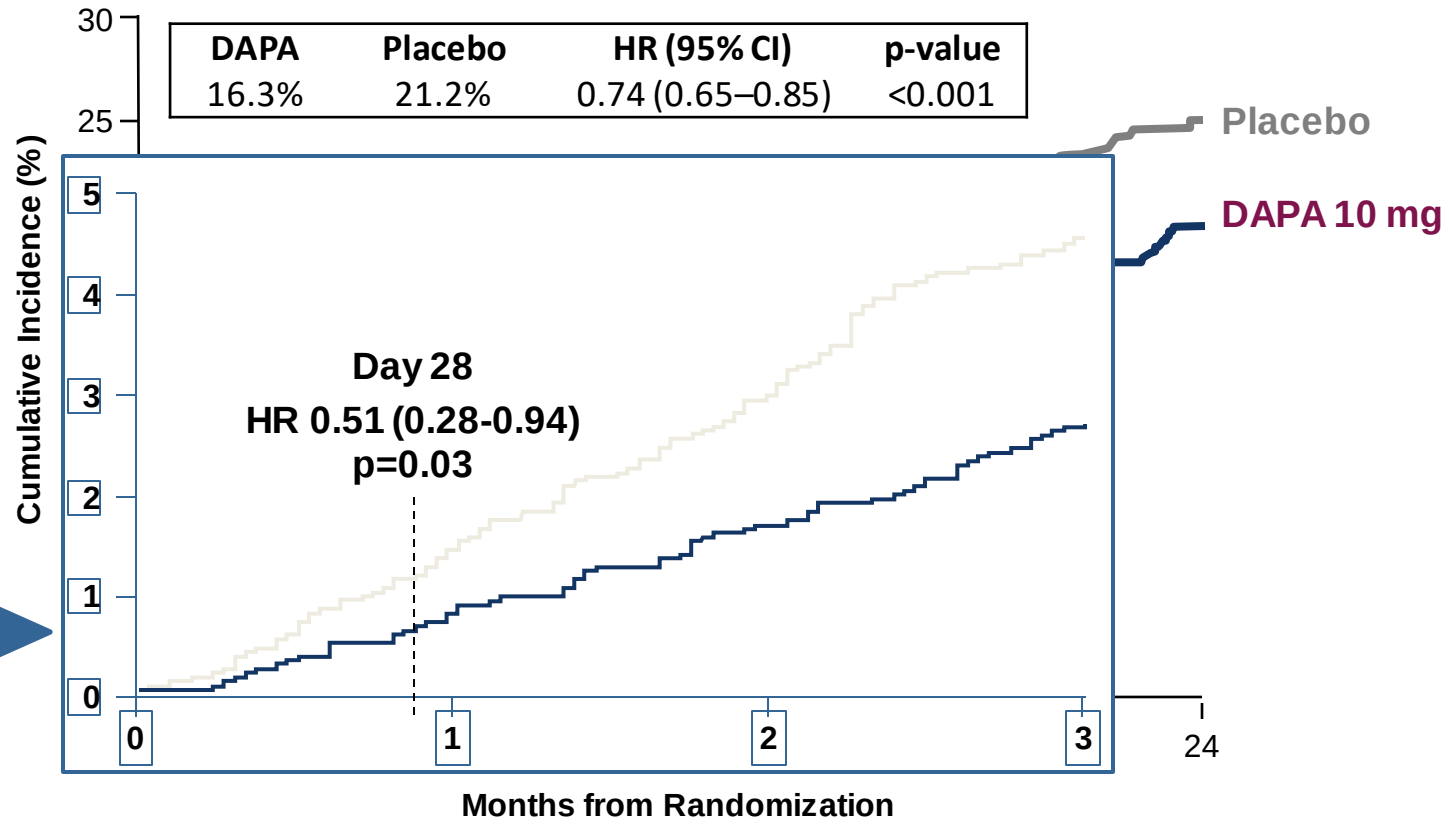
- Pre-existing diagnosis of T2D: n=1983; 41.8%
- Previously undiagnosed T2D (HbA1c ≥6.5% at Visits 1 and 2): n=156; 3.3%

HbA1c = glycated hemoglobin; T2D = type 2 diabetes.

Petrie MC et al. *JAMA*. 2020;323:1353-1368.

Primary Endpoint: CV Death or hHF or an Urgent HF Visit

DAPA	Placebo	HR (95% CI)	p-value
16.3%	21.2%	0.74 (0.65–0.85)	<0.001



26% RRR

4.9% ARR

NNT=21

Primary endpoint was statistically significant as early as Day 28

Number at Risk

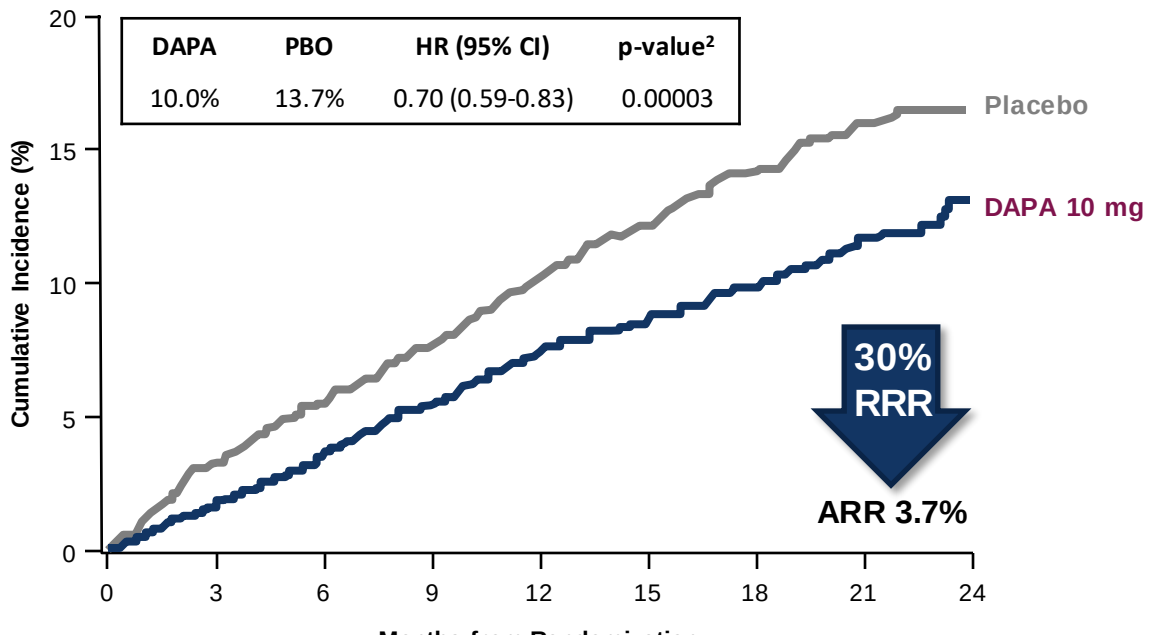
DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

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.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

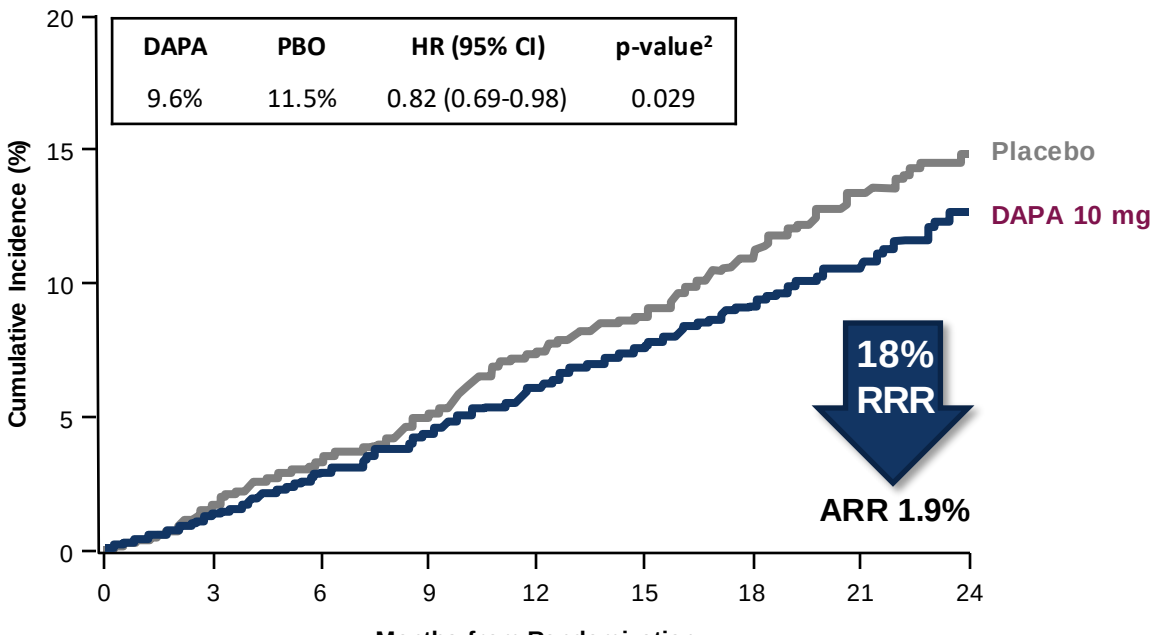
Components of the Primary Endpoint

Worsening HF Event[a]



Number at Risk									
DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

CV Death



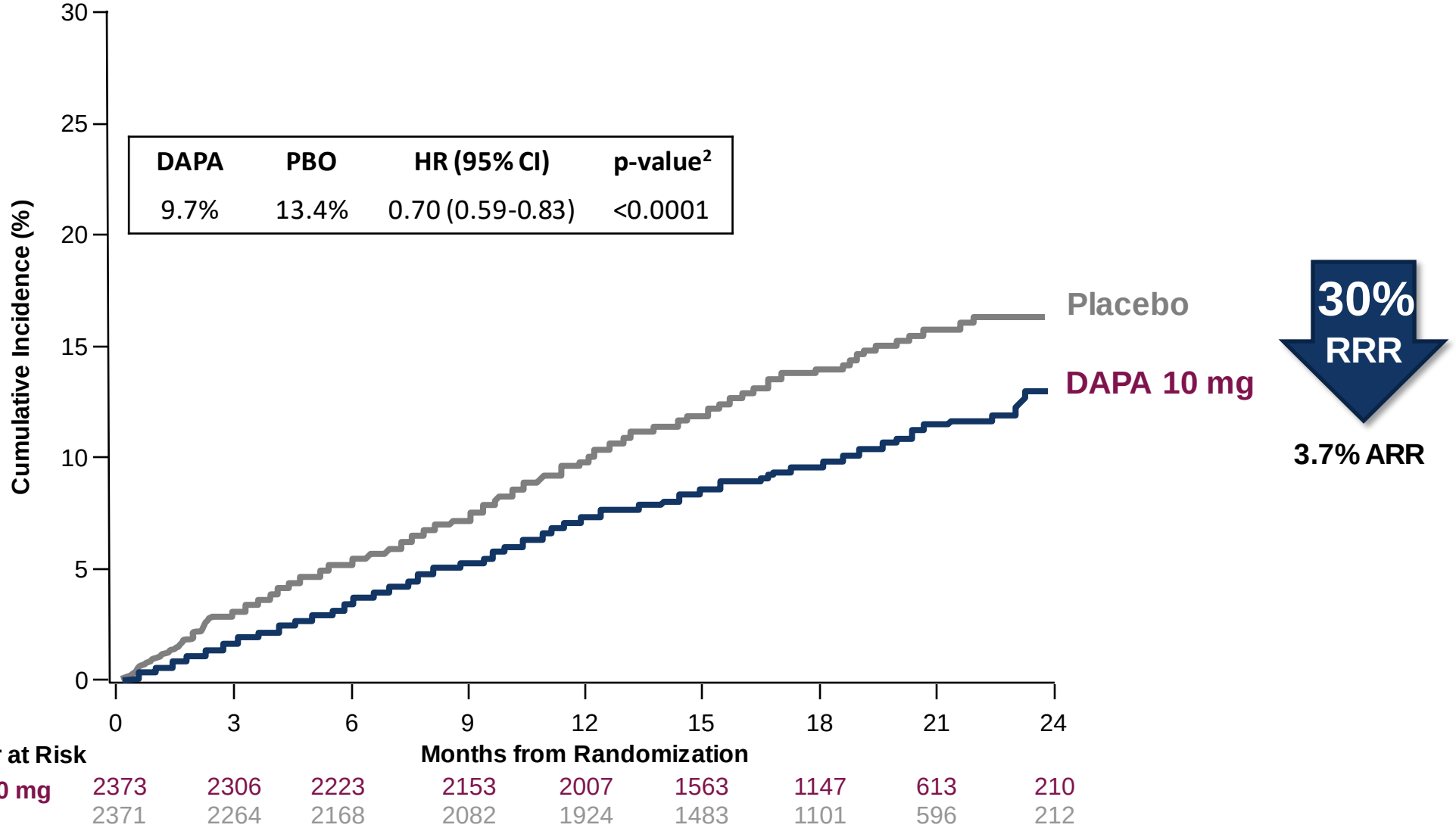
Number at Risk									
DAPA 10 mg	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

[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; PBO = placebo; RRR = relative risk reduction.

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.

Hospitalization for Heart Failure (hHF)

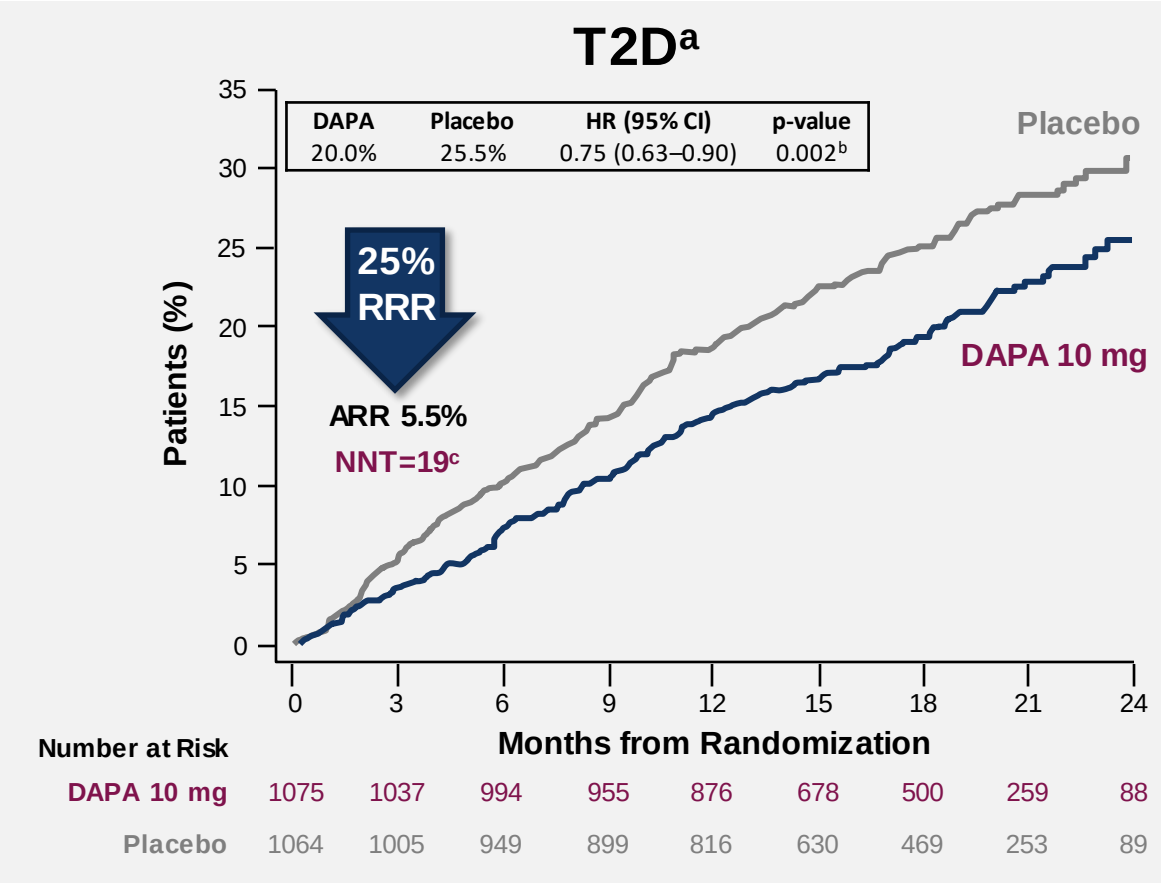


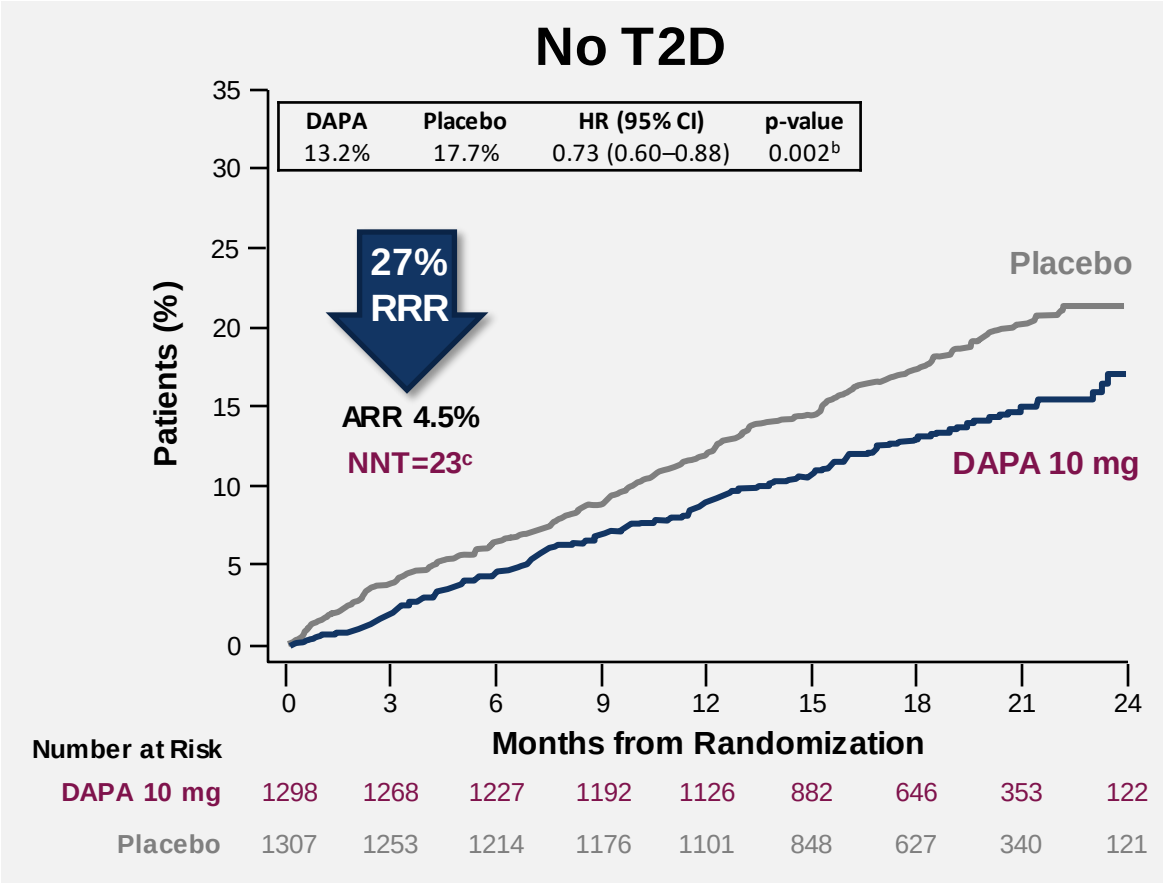
ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; PBO = placebo; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Docherty KF et al. *Circulation.* 2020;142:1623-1632.

Primary Outcome: CV Death, hHF, or Urgent HF Visit by Diabetes Status[1]

Dapagliflozin significantly reduced the primary endpoint, regardless of diabetes status



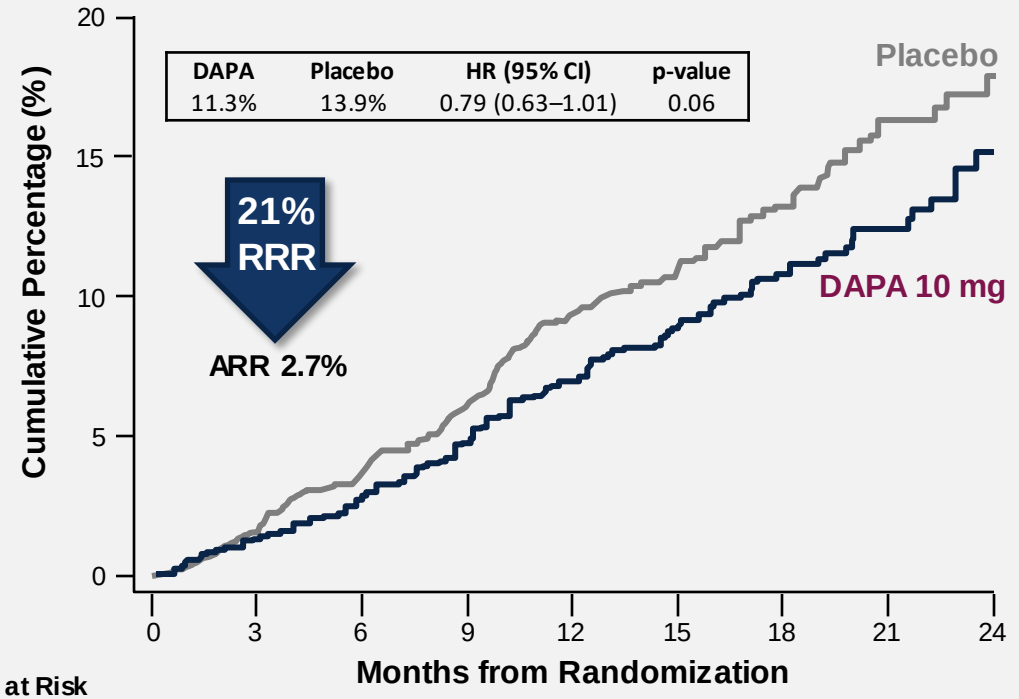


Interaction p-value=0.80[d]

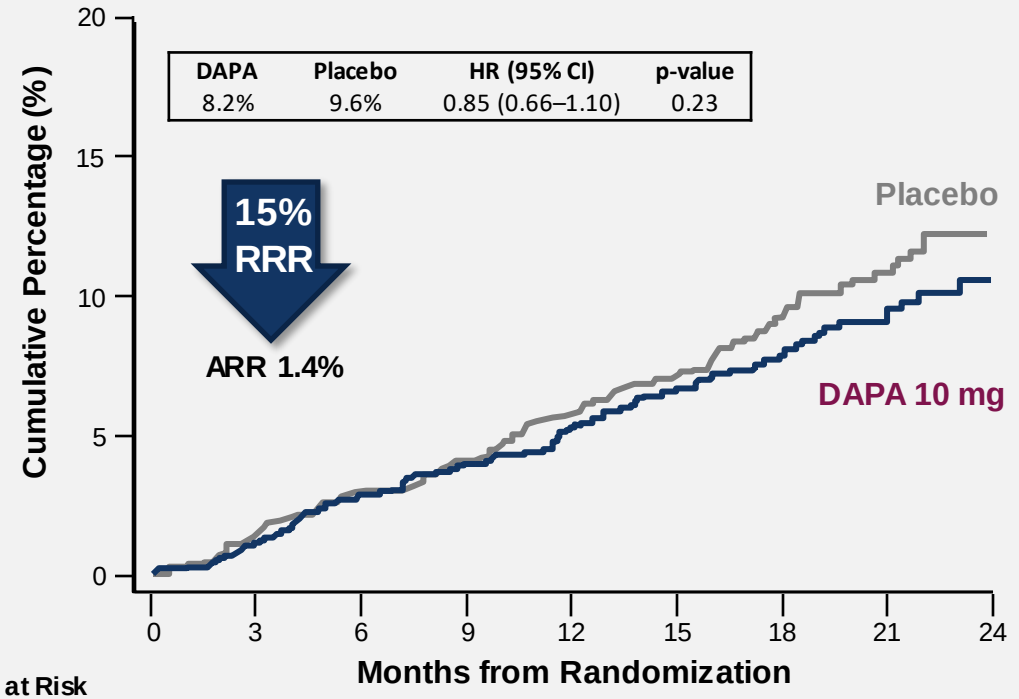
[a]Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2); [b]Nominal p-value; [c]NNT = 1/ARR; [d]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

1. Petrie MC et al. *JAMA*. 2020;323:1353-1368; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

CV Death by Diabetes Status[1]



Number at Risk									
DAPA 10 mg	1075	1060	1041	1015	951	739	552	295	104
Placebo	1064	1044	1019	985	910	717	534	286	102



Number at Risk									
DAPA 10 mg	1298	1279	1252	1233	1176	925	690	376	128
Placebo	1307	1286	1260	1245	1181	919	685	378	132

Interaction p-value=0.70[b]

[a]Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2); [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

1. Petrie MC et al. *JAMA*. 2020;323:1353-1368; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

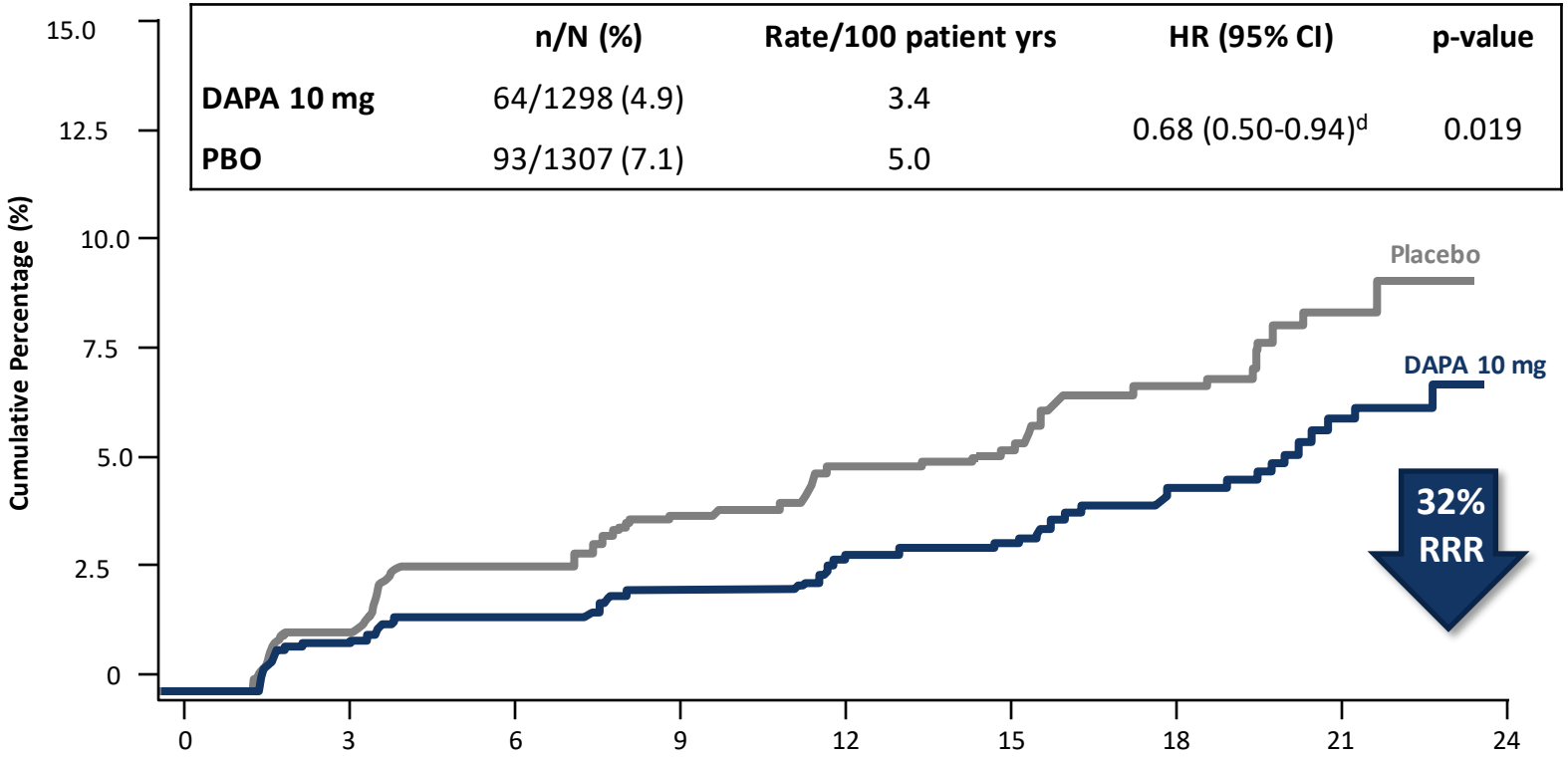
Dapagliflozin Reduced the Incidence of New Onset T2DM[a] in the Population without T2DM at Baseline

New Onset T2DM[a]: 157/2605 (6.0%)

HbA1c 5.7-6.4%[b] at baseline: 95.5%

HbA1c 6.0-6.4%[c] at baseline: 86.6%

	n/N (%)	Rate/100 patient yrs	HR (95% CI)	p-value
DAPA 10 mg	64/1298 (4.9)	3.4	0.68 (0.50-0.94)[d]	0.019
PBO	93/1307 (7.1)	5.0		

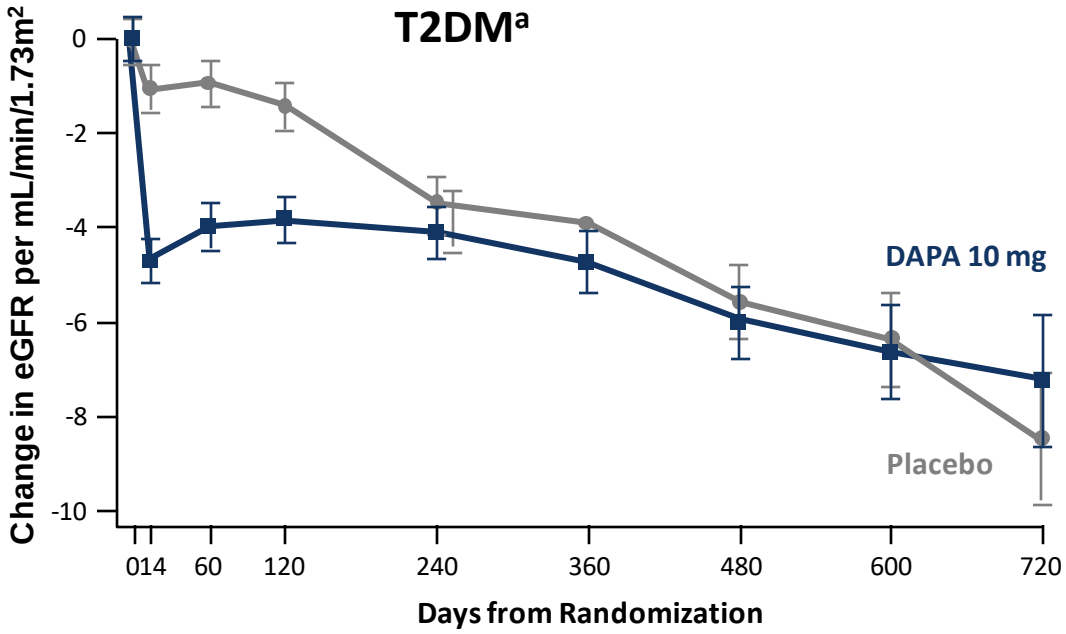


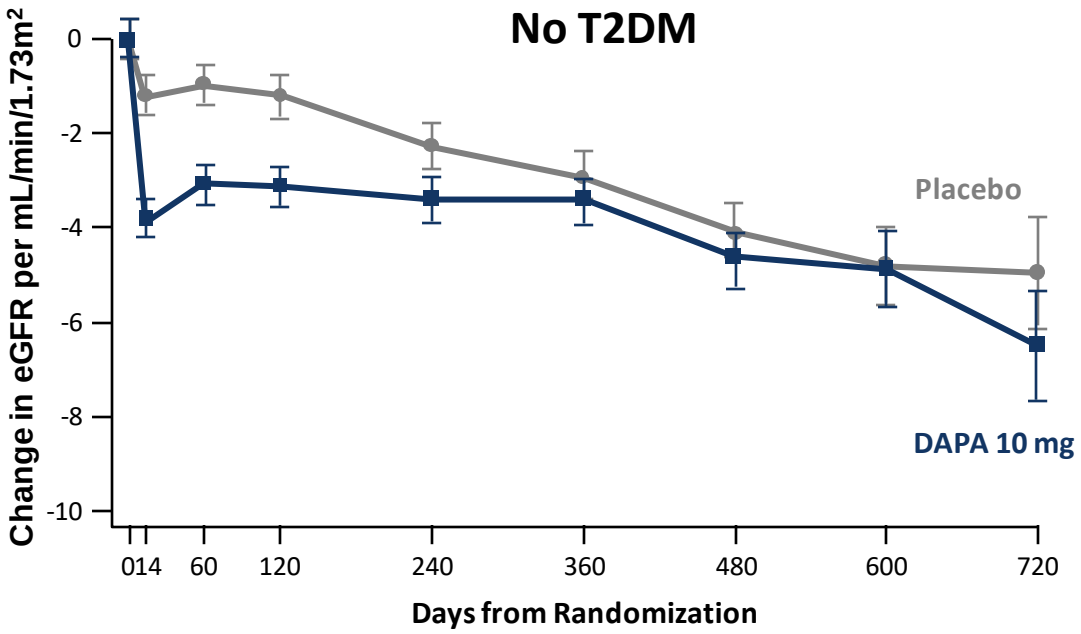
Number at Risk									
DAPA 10 mg	1298	1266	1233	1208	1147	895	666	366	123
Placebo	1307	1268	1225	1198	1127	874	642	358	125

[a]Defined as an HbA1c ≥6.5% on 2 consecutive visits OR a diagnosis of T2D made by the patient's personal physician and prescribed a glucose lowering medication; [b]Definition of prediabetes per ADA; [c]Definition of prediabetes per International Expert Committee; [d]HR using the Fine & Gray model, accounting for competing risk of mortality, 0.69 (95% CI, 0.50-0.95). ADA = American Diabetes Association; ARR = absolute risk reduction; DAPA = dapagliflozin; HbA1c = glycated hemoglobin; HR = hazard ratio; PBO = placebo; RRR = relative risk reduction; T2D = type 2 diabetes; yrs = years.

Inzucchi SE, et al. *Diabetes Care.* 2021; **44**:586-594.

Dapagliflozin Significantly Attenuated eGFR Decline After 14 Days in Patients With and Without T2DM[1]





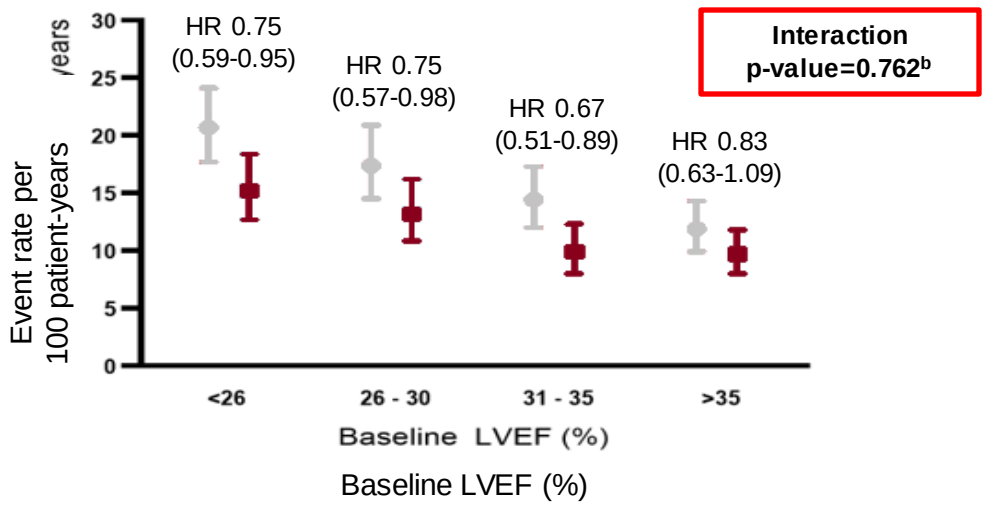
	Acute (Day 0-14)		Chronic (Day 14-720)	
	Slope[b] (95% CI)	p-value[c]	Slope[b] (95% CI)	p-value[c]
DAPA	-122.26 (-134.82 to -109.69)	<0.001	-1.29 (-1.78 to -0.80)	<0.001
Placebo	-26.00 (-38.70 to -13.31)		-3.56 (-4.06 to -3.06)	

	Acute (Day 0-14)		Chronic (Day 14-720)	
	Slope[b] (95% CI)	p-value[c]	Slope[b] (95% CI)	p-value[c]
DAPA	-98.61 (-110.09 to -87.12)	<0.001	-2.05 (-2.36 to -1.75)	<0.001
Placebo	-30.47 (-41.85 to -19.08)		-3.11 (-3.42 to -2.80)	

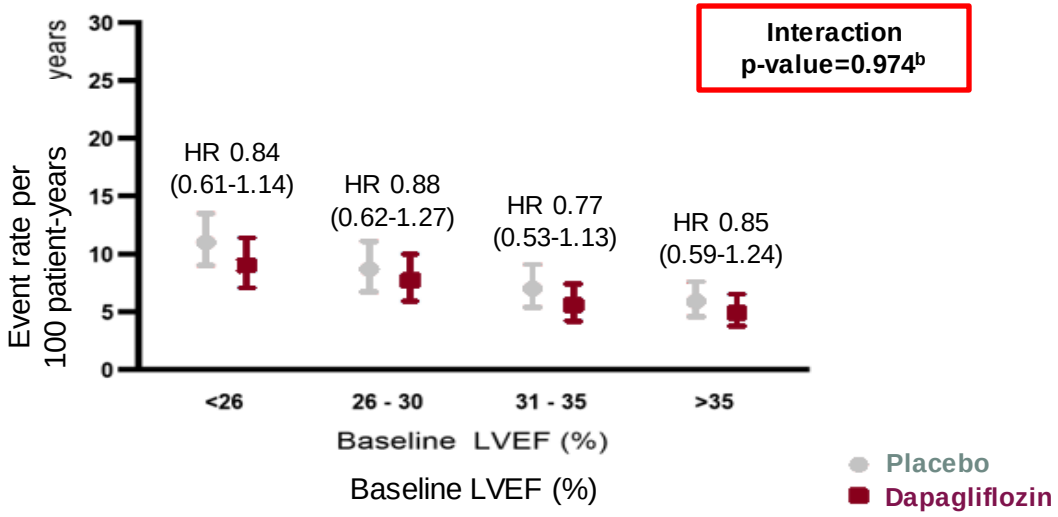
[a] Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2)[2]; [b]Change in eGFR per year; [c]Difference in slopes. DAPA = dapagliflo
eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; T2D = type 2 diabetes. Jundh PS et al. *Circulation*. 2021; **143**:298-309.

Benefit of Dapagliflozin Was Consistent Regardless of Baseline LVEF Category

CV death or worsening HF[a]

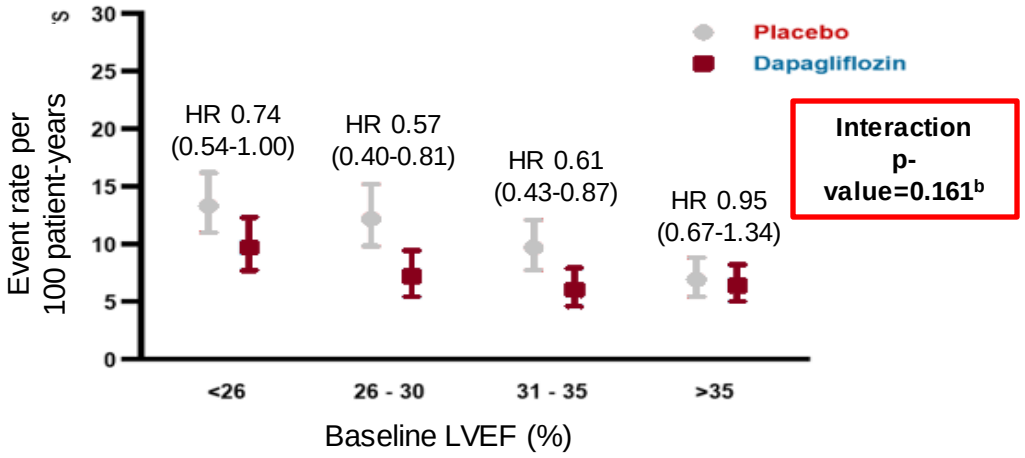


CV death

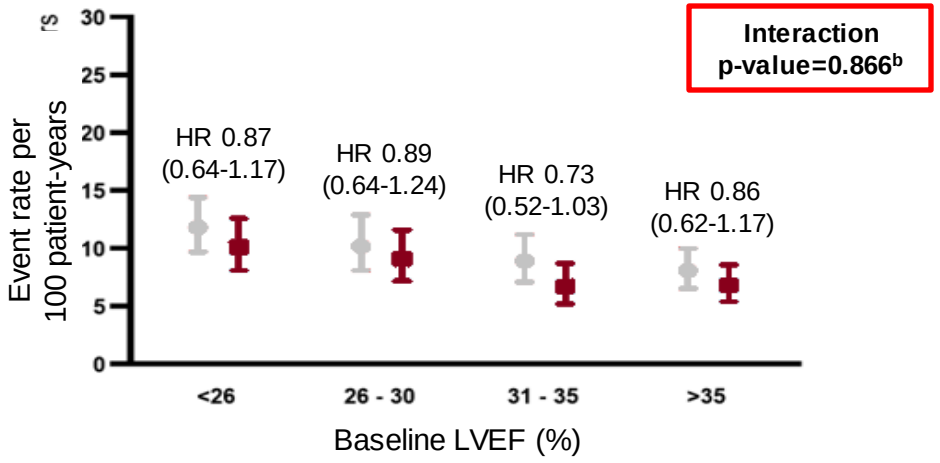


Placebo
Dapagliflozin

Worsening HF[a]



All-cause death



[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]

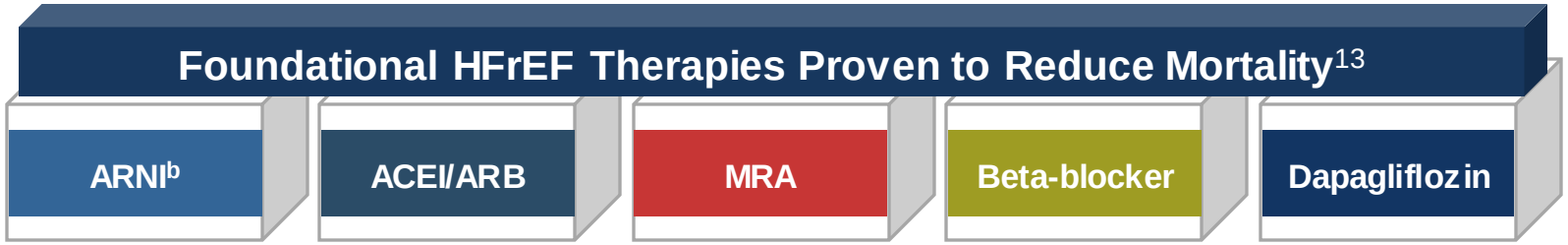
1. Dewan P et al. Article and supplementary appendix. *Eur J Heart Fail*. 2020;22:1247-1258; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

DAPA-HF Summary

- Dapagliflozin provided a statistically-significant and clinically meaningful **reduction in the composite of CV death or worsening HF events**[a] and **improvement in HF symptoms**, when compared to placebo in patients with HFrEF, both with and without T2D.[1,2]
  - **Consistent benefit** in the primary endpoint across the broad range of patients with HFrEF including:

T2D/No T2D[3]	Baseline LVEF[6]
Background HF therapy[4]	Baseline NT-proBNP[7]
Diuretic use and dose[5]	eGFR[8]

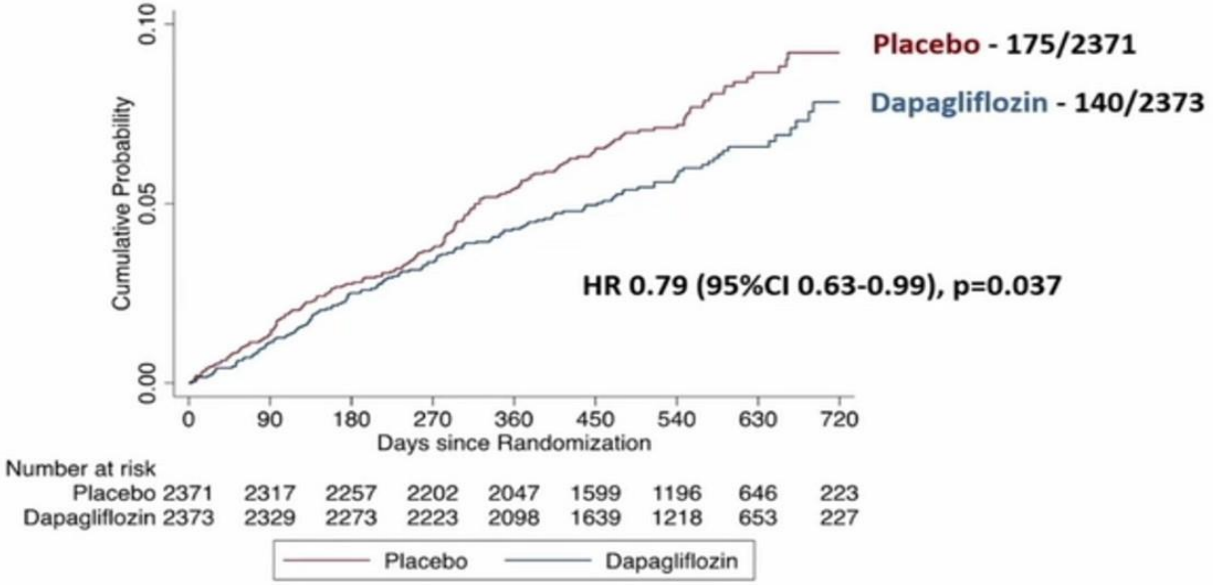
- Dapagliflozin is the **first SGLT2 inhibitor** to demonstrate a significant and clinically meaningful **reduction in both the CV death and worsening HF[a] components of the primary composite endpoint** as well as a **reduction in all-cause mortality**.[2,9,10]
- The **safety findings** of DAPA-HF, **in patients with and without T2D, were consistent** with the well-established safety profile of dapagliflozin and the rate of treatment discontinuation was low.[1-3]
- Dapagliflozin is one of the **SGLT2 inhibitor approved for HFrEF**.[11,12]



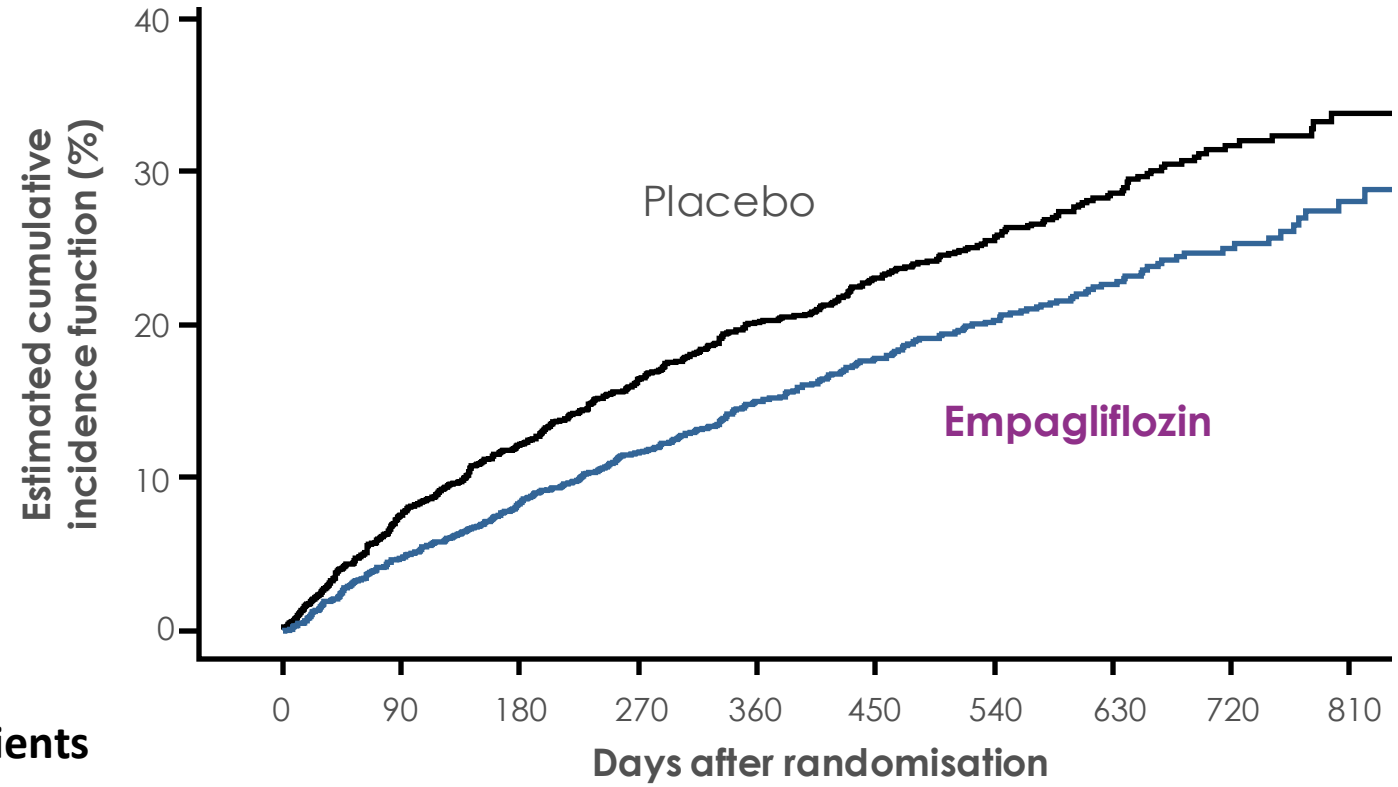
DAPA-HF : la dapagliflozine prévient arythmies ventriculaires, arrêts cardiaques ressuscités et morts subites dans l'insuffisance cardiaque à FEVG altérée

- James Curtain (Glasgow, Royaume-Uni et Irlande du Nord) : *"DAPA-HF"*.
- **Cette étude complémentaire sur base de DAPA-HF a étudié les effets de la prise quotidienne de 10 mg de dapagliflozine sur les évènements rythmiques chez ces patients.**
- Le traitement par dapagliflozine diminue la survenue du critère de jugement principal rythmique de 21 % IC 95 % (0.63-0.99) p = 0.037 (**Figure 1**).

Ventricular arrhythmia, resuscitated cardiac arrest or sudden death



EMPEROR-Reduced: Empaglifozin Significantly Reduced Risk of CV Death or HF Worsening on top of SoC



2850 Patients

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

RRR 25%

ARR 5.2%

NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

Empagliflozin:
361 patients with event
Rate: 15.8/100 patient-years
Placebo:
462 patients with event
Rate: 21.0/100 patient-years

Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

DAPA HF

Primary outcome and components of primary outcome

Worsening HF* or CV death

26% RRR
p<0.001
16.1% vs 20.9%
HR = 0.75 (0.65-0.85)

HHF

30% RRR
NR†
9.7% vs 13.4%
HR = 0.70 (0.59-0.83)

CV death

18% RRR
NR†
9.6% vs 11.5%
HR = 0.82 (0.59-0.83)

Secondary outcomes

HHF or CV death

25% RRR
p<0.001
16.1% vs 20.9%
HR = 0.75 (0.65-0.85)

Total HHF and CV death events

25% RRR
p<0.001
567 vs 742
HR = 0.75 (0.65-0.88)

Total Death

17% RRR
NR†
11.6% vs 13.9%
HR = 0.83 (0.71-0.97)

*Unplanned HHF or urgent visit resulting in intravenous therapy for HF; †*p*-value not reported in publication McMurray J et al. *N Engl J Med* 2019;381:1995hospitalisation

EMPEROR HEART FAILURE STUDIES

Primary outcome and components of primary outcome

HFF or CV death

25% RRR
p<0.001
19.4% vs 24.7%
HR = 0.75 (0.65-0.86)

HHF

31% RRR
13.2% vs 18.3%
HR = 0.69 (0.59-0.81)

CV death

8% RRR
10% vs 10.8%
HR = 0.92 (0.75-1.12)

Secondary outcomes

First and recurrent HFF

30% RRR
p<0.001
338 vs 553
HR = 0.75 (0.65-0.88)

Renal Event
eGFR

1.73ml/min/1.73m²
p<0.001
-0.55 vs -2.28

Prespecific analyses

Renal Event
chronic dialysis or renal transplantation or a profound, sustained reduction in the estimated GFR)

50% RRR
1.6% vs 3.1%
HR = 0.50 (0.32-0.77)

Total Death

8% RRR
13.4% vs 14.2%
HR = 0.92 (0.77-1.10)

DAPA-HF and EMPEROR-Reduced Study Designs

	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)
		• 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 ≥30 mL/min/1.73 m²** • 55% without T2D	• **eGFR ≥20 mL/min/1.73 m²** • ~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

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. *N Engl J Med*. 2020;383:1413-1424.

DAPA-HF and EMPEROR-Reduced Patient Populations

	DAPA-HF[1,2]	EMPEROR-Reduced[3,a]
HF characteristics	• NYHA functional Class II: 68% • Mean KCCQ: 68 • Mean LVEF: 31% • Median NT-proBNP: 1437 pg/mL • Prior hHF: 47%	• NYHA functional Class II: 75% • Mean KCCQ: NR • **Mean LVEF: 27%** • **Median NT-proBNP: 1926 pg/mL** • Prior hHF (≤12 months): 31%
History & co-morbidity	• Without T2D: 55% • Median BMI: 27 kg/m^2 • Prior MI/Coronary Revascularization:44% MI, 34% PCI and 17% CABG • Hx of HTN/Stroke: 74%/10% • **Mean eGFR: 66 mL/min/1.73 m^2**	• Without T2D: 50% • Median BMI: 28 kg/m^2 • Prior MI/Coronary Revascularization: NR • Hx of HTN/Stroke: 72%/NR • **Mean eGFR: 62 mL/min/1.73 m^2**

Background therapy	• ACEI/ARB/ARNI: 94%
	  • ACEI/ARB: 83%
	  • ARNI: 11%
	• Beta-blocker: 96%
	• MRA: 71%
	• Diuretics: 93%
	• Digoxin: 19%
	• CRT: 7%
	• ICD: 26%
		• ACEI/ARB/ARNI: 90%
		  • ACEI/ARB: 69%
		  • ARNI: 21%
		• Beta-blocker: 95%
		• MRA: 73%
		• Diuretics: NR
		• Digoxin: NR
		• CRT: 12%
		• ICD: 32%

1. McMurray JJV et al. *Eur J Heart Fail*. 2019;21:1402-1411; 2. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 3. Packer M et al. *N Engl J Med*. 2020; 383:1413-1424.

Select Outcomes from the DAPA-HF and EMPEROR-Reduced Trials

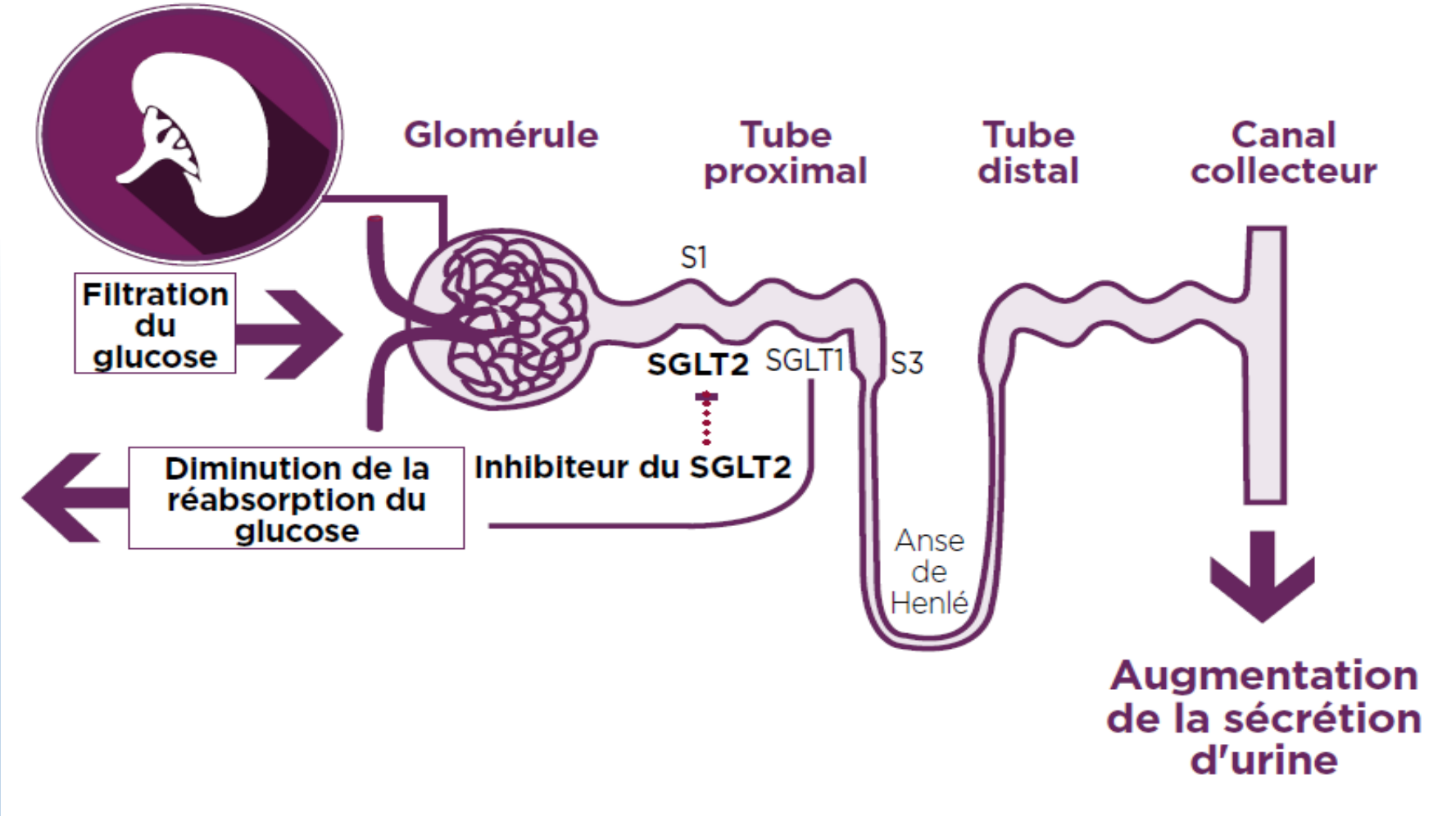
DAPA-HF[1,2,3] (N=4744)	Outcome	EMPEROR-Reduced[4] (N=3730)
	Composite of hHF/CV death (primary outcome)	
0.74 (0.65-0.85)[a]	HR (95% CI)	0.75 (0.65-0.86)
DAPA 11.6 vs. PBO 15.6	Rate per 100 patient-years	EMPA 15.8 vs. PBO 21.0
<0.001	p-value	<0.001
	Hospitalization for HF	
0.70 (0.59-0.83)	HR (95% CI)	0.69 (0.59-0.81)
DAPA 6.9 vs. PBO 9.8	Rate per 100 patient-years	EMPA 10.7 vs. PBO 15.5
<0.0001	p-value	NR
	CV death	
0.82 (0.69-0.98)	HR (95% CI)	0.92 (0.75-1.12)
DAPA 6.5 vs. PBO 7.9	Rate per 100 patient-years	EMPA 7.6 vs. PBO 8.1
0.029	p-value	NS
	All-cause death	
0.83 (0.71-0.97)	HR (95% CI)	0.92 (0.77-1.10)
DAPA 7.9 vs. PBO 9.5	Rate per 100 patient-years	EMPA 10.1 vs. PBO 10.7
0.022[b]	p-value	NS

This chart does not imply comparable or superior efficacy/safety profiles. Each study was placebo-controlled and no direct comparisons to the other SGLT2 inhibitor were included. Please refer to study publications for additional information.

[a]Also includes urgent HF visit; [b]Nominal p-value.

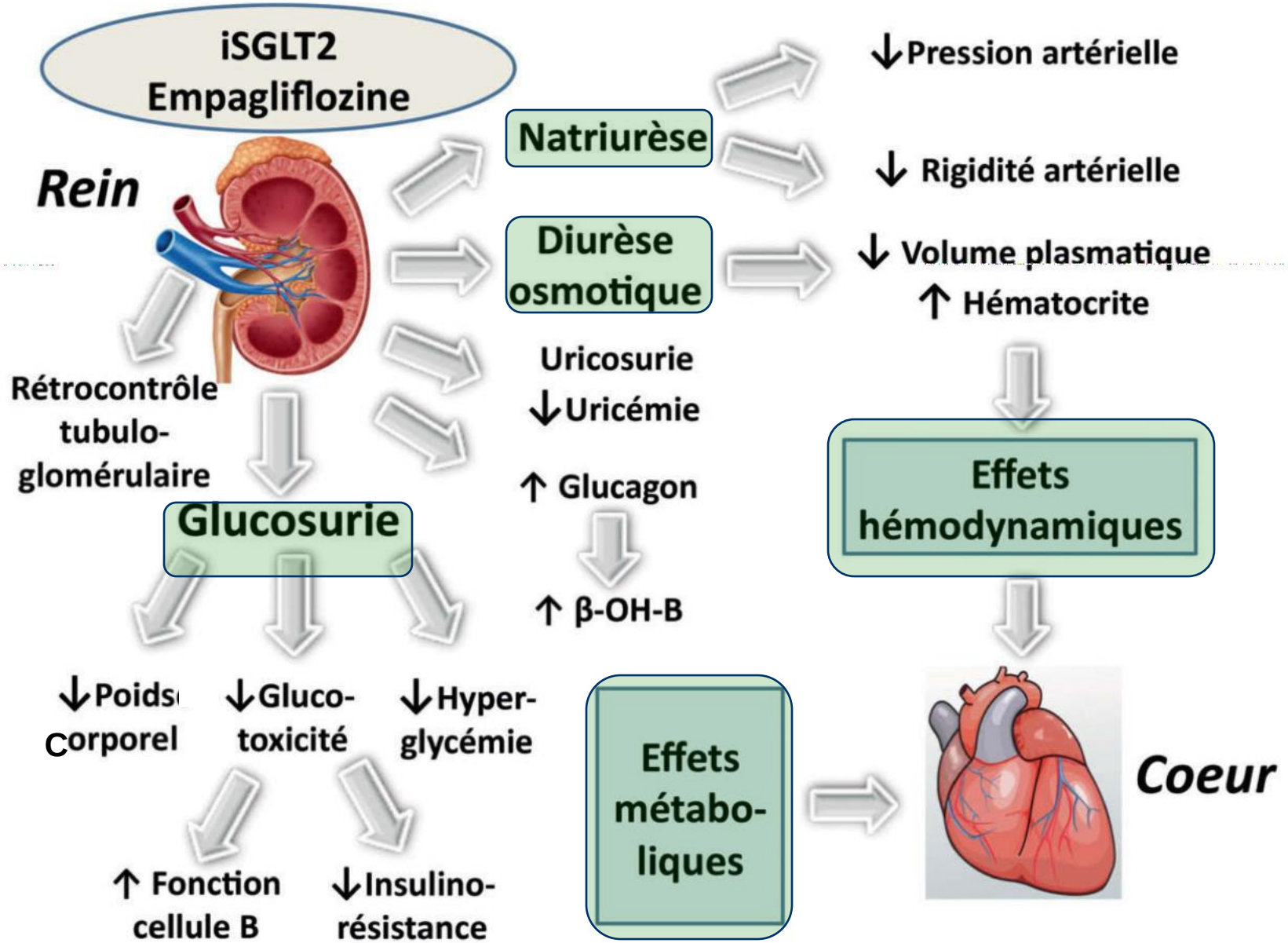
1. McMurray JJV et al. *N Engl J Med.* 2019;318;1995-2008; 2. Ponikowski P et al. Presented at: ACC Annual Scientific Sessions with WCC Virtual Meeting; March 28-30, 2020; 3. McMurray J. Presented at ESC Congress; August 31-September 4, 2019; Paris, France; 4. Packer M et al. *N Engl J Med.* 2020; 383:1413-1424.

Mode d'action des inhibiteurs du SGLT2



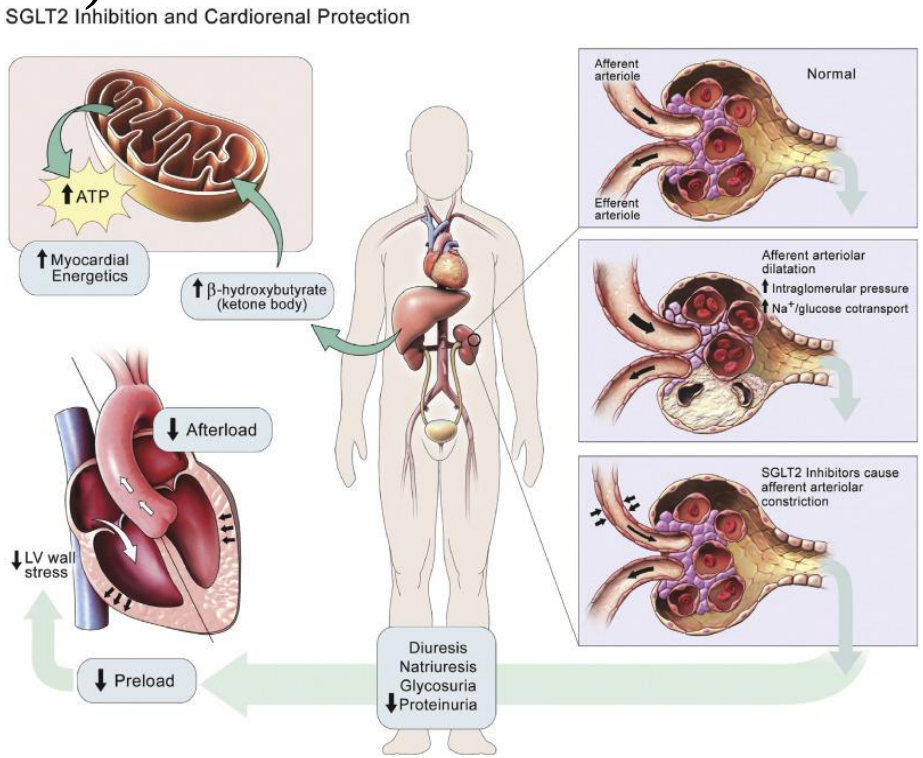
Basé sur Chao E et al, Nature Reviews Drug Discovery 9, 551-559

Effets bénéfiques des inhibiteurs des SGLT2



Inhr SGLT2: Protection CV

1. Réduction de l'activation du RAAS (protection cardio-vasculaire)
2. Réduction du volume plasmatique / extravasculaire (cardio-protection)
3. Amélioration du métabolisme énergétique du cœur (cardio-protection)
4. Amélioration du contrôle du diabète (endocrino-protection)
5. Réduction de poids (80 kcal / jour - 1 kg)
6. Réduction de la PA (3 mmHg sys)
7. Réduction de l'athérosclérose
(↓ HbA1c, ↑ sécrétion d'acide urinique)
8. Diurèse osmotique
9. Réduction de la congestion (<10% ↓ NT-proBNP)
10. Réduction de l'hypertension intra-glomérulaire
(néphro-protection)?



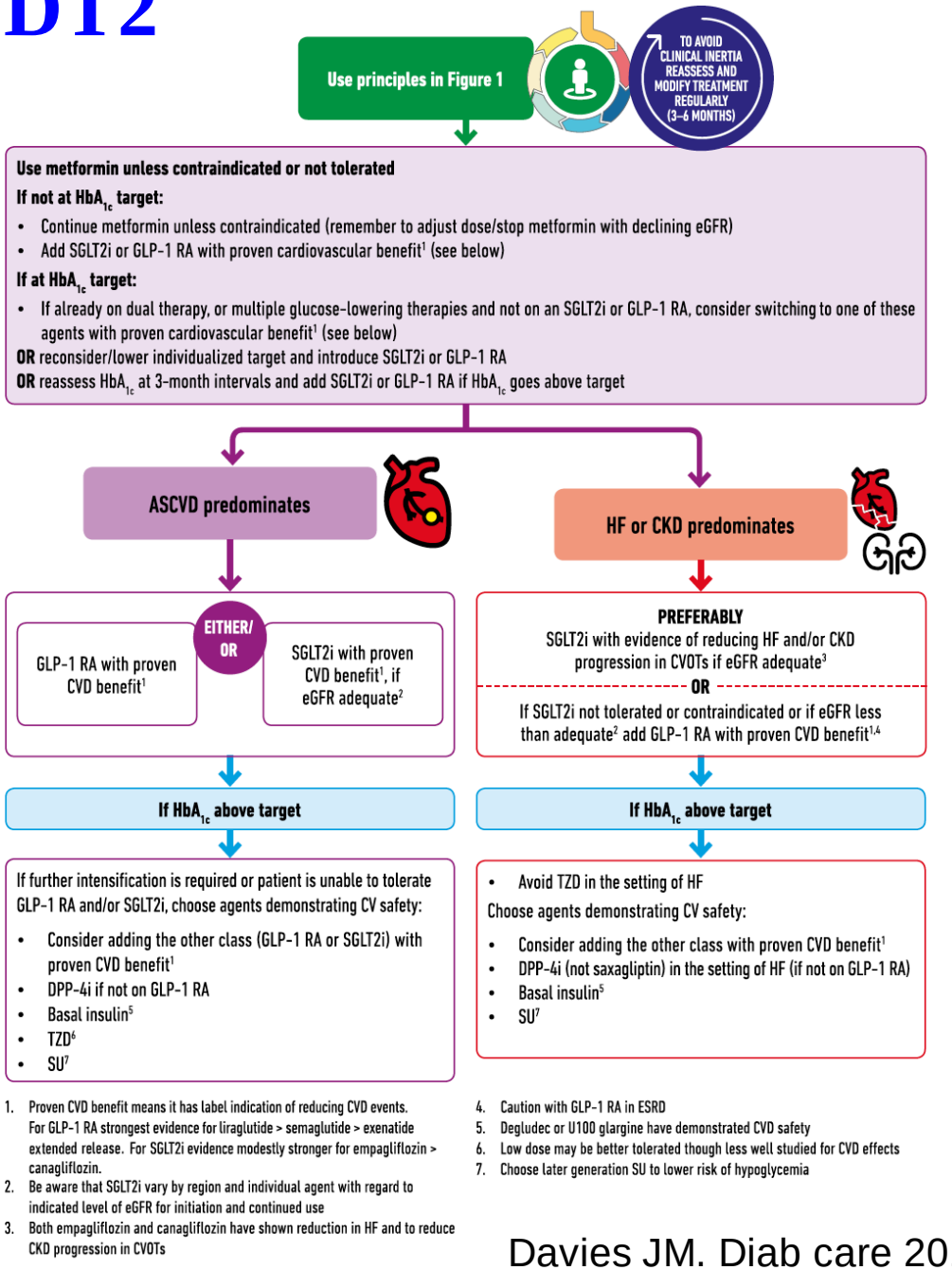
Verbrugge F, Mullens W, et al. Cur Cardiovasc Risk Rep 2015
Verbrugge F, Mullens W, et al. Circ Heart Fail Rep 2017

Consensus 2018 ADA/EASD dans le DT2

Après metformine en première intention : Privilégier les médicaments qui ont fait leur preuve en termes de prévention cardiovasculaire et rénale.

Insuffisance cardiaque ou maladie rénale

Deux classes thérapeutiques indiquées avec un ordre hiérarchique
1/ I-SGLT2
2/ AR-GLP1

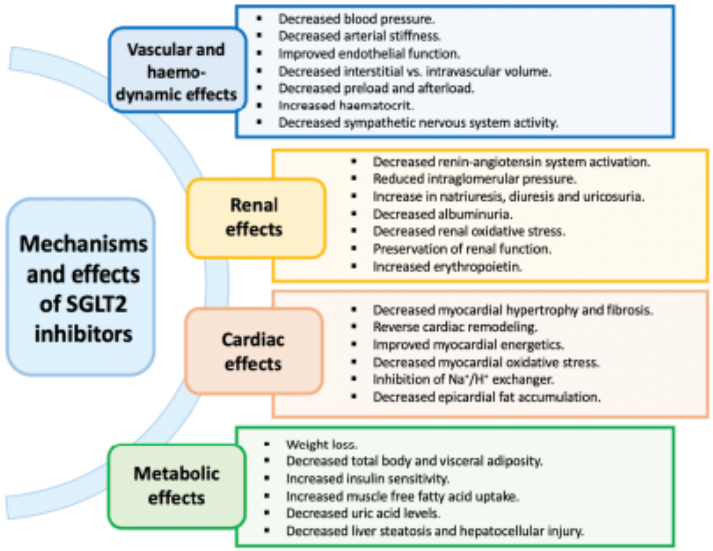


Davies JM. Diab care 2018

ESC European Society of Cardiology
European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1954
POSITION PAPER

Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. The position paper of the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1,2*†], Gabriele Fragasso[3], Mark Petrie[4], Wilfried Mullens[5,6], Roberto Ferrari[7], Thomas Thum[8], Johann Bauersachs[9], Stefan D. Anker[10,11], Robin Ray[12], Yuksel Çavuşoğlu[13], Marija Polovina[1,14], Marco Metra[15], Giuseppe Ambrosio[16], Krishna Prasad[17], Jelena Seferović[1,18], Pardeep S. Jhund[19], Giuseppe Dattilo[20], Jelena Čelutkiene[21], Massimo Piepoli[22], Brenda Moura[23], Ovidiu Chioncel[24,25], Tuvia Ben Gal[26], Stefan Heymans[27], Rudolf A. de Boer[28], Tiny Jaarsma[29], Loreena Hill[30], Yuri Lopatin[31], Alexander R. Lyon[32], Piotr Ponikowski[33], Mitja Lainščak[34,35], Ewa Jankowska[33], Christian Mueller[36], Francesco Cosentino[37], Lars Lund[38], Gerasimos S. Filippatos[39], Frank Ruschitzka[40], Andrew J.S. Coats[41], and Giuseppe M.C. Rosano[42†]

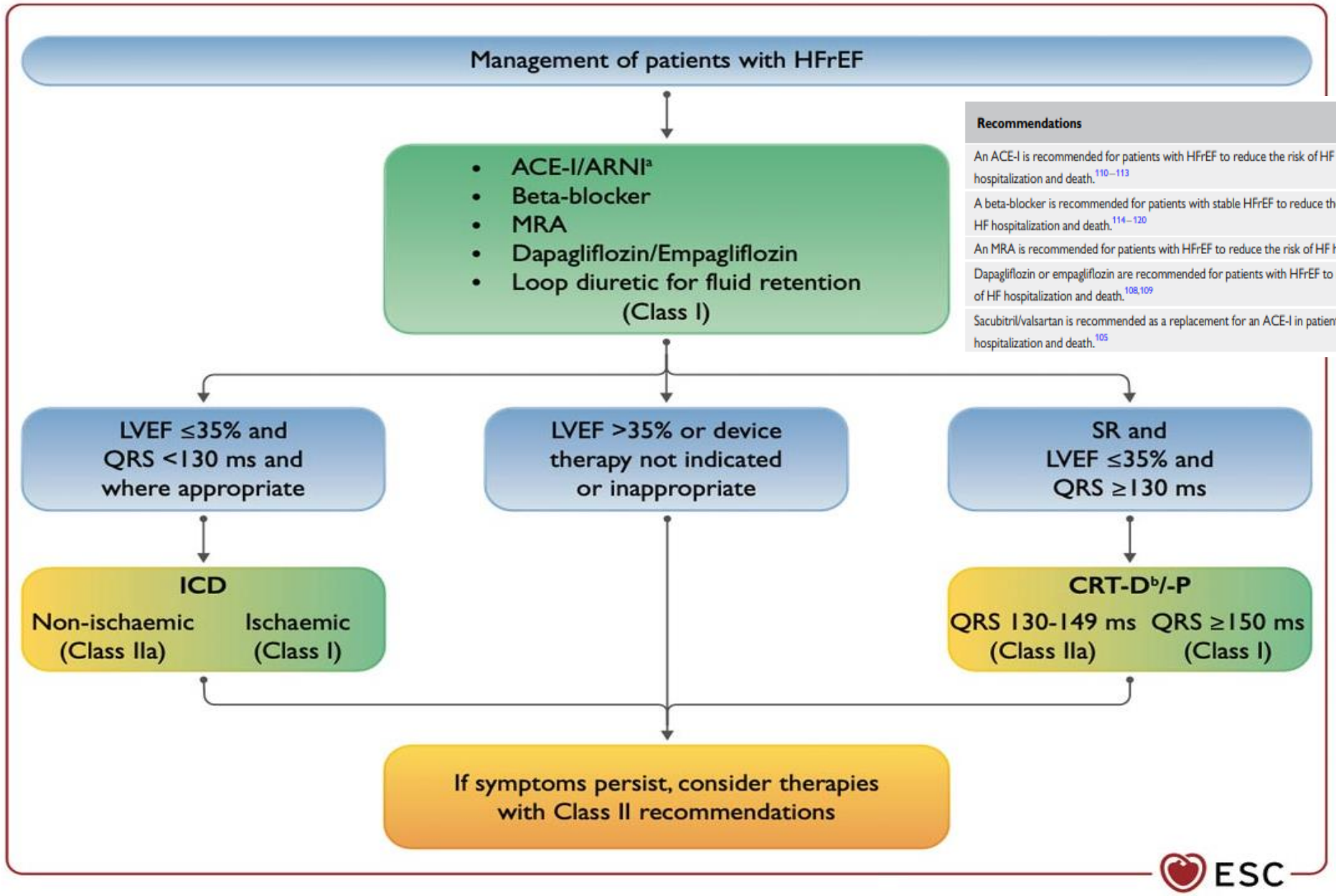


- Canagliflozin, Dapagliflozin, or Empagliflozin are all effective for the prevention of HF hospitalization in patients with T2DM and established CV disease or at high CV risk, and this is consistent with a class effect of SGLT2 inhibitors.

- **Dapagliflozin** or **empagliflozin** are recommended to reduce the combined risk of heart failure hospitalization and CV death in patients with heart failure and reduced ejection fraction, with or without T2DM.

Seferovic P et al. Eur J Heart Fail 2020; 22:1984-1986
Seferovic P et al. Eur J Heart Fail 2020; 22:1495-1503

2021 ESC Guidelines for HFrEF



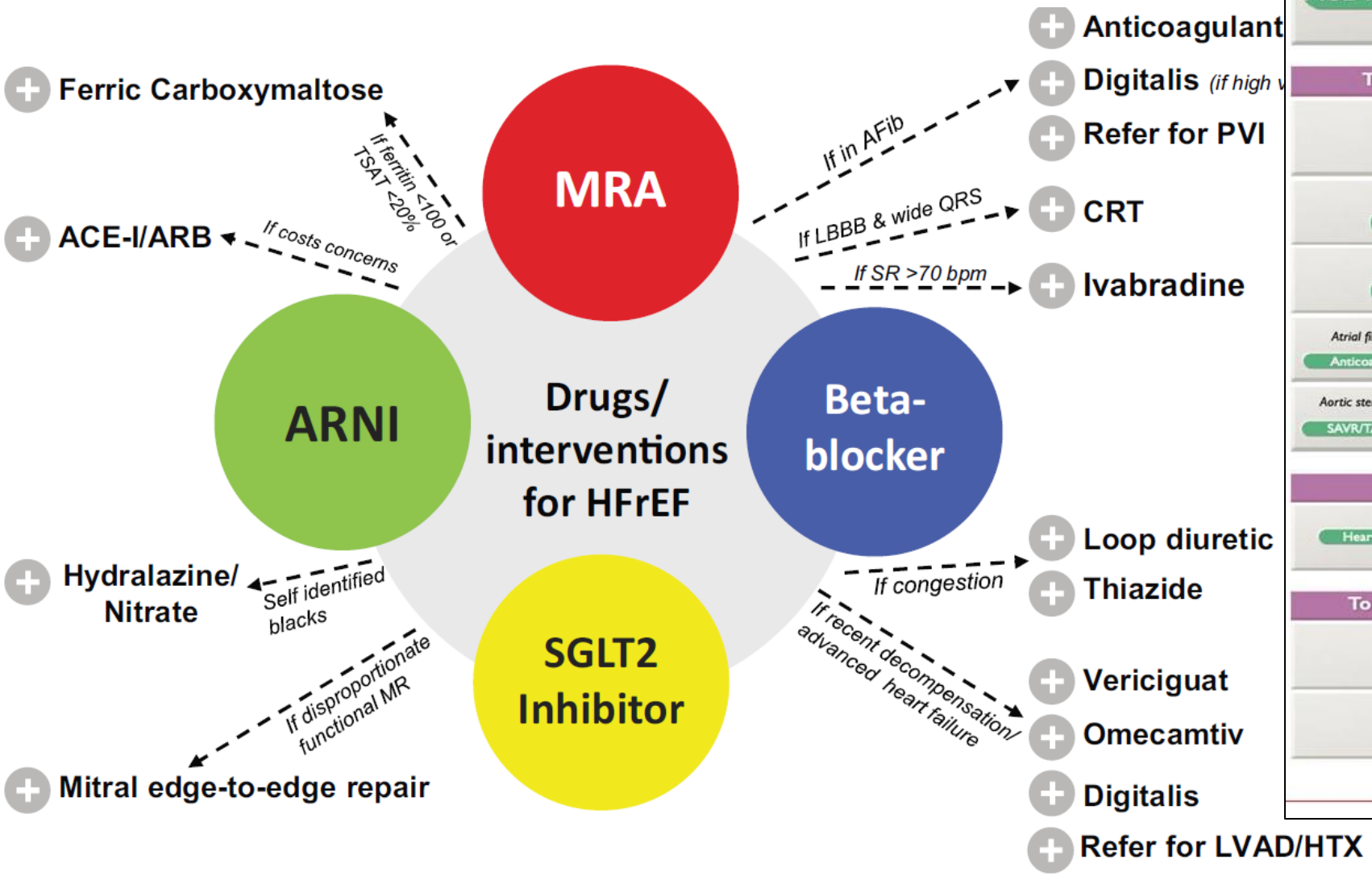
Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients 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

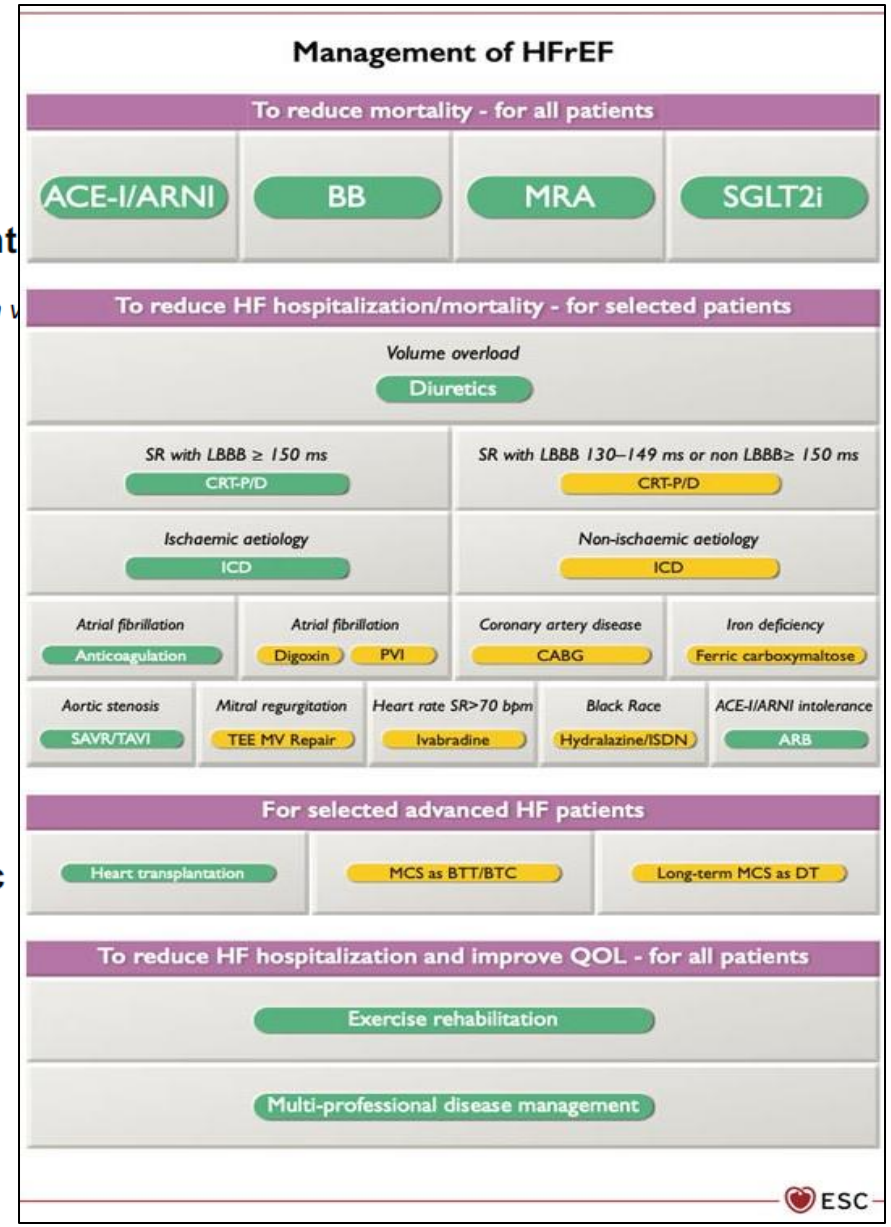
European Heart Journal 2021

Heart failure drug treatment: the fantastic four

Johann Bauersachs *

Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany





Bauersachs J. *Eur Heart J.* 2021. doi:10.1093.eurheartj.ehaa1012
Maddox TM, et al. *J Am Coll Cardiol.* 2021. doi:10.1016/j.jacc.2020.11.022

Remboursement dans l'IC

La spécialité pharmaceutique à base de FORXIGA (dapagliflozine) est remboursée si elle est utilisée chez les bénéficiaires adultes pour le traitement de l'insuffisance cardiaque chronique symptomatique à fraction d'éjection réduite, en complément à un traitement standard.
La spécialité est remboursée si au début du traitement avec la spécialité pharmaceutique à base de dapagliflozine les conditions cumulatives suivantes sont remplies:

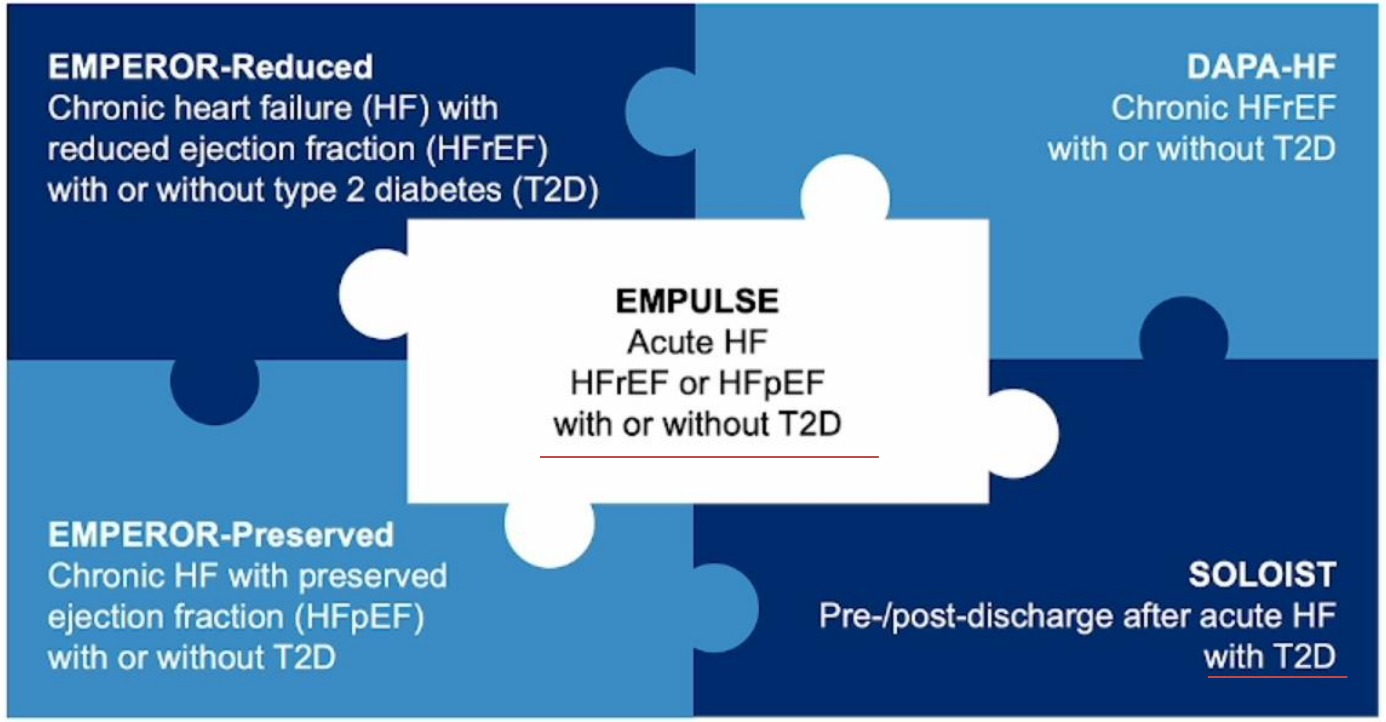
1. **L'état du bénéficiaire correspond à:**
   une classe NYHA (New York Heart Association) II;
   Ou une classe NYHA III;
   Ou une classe NYHA IV;
2. **Le bénéficiaire ne souffre pas de diabète de type 1**
3. **Fraction d'éjection ventriculaire gauche < = 40% (objectivée par échocardiographie)**

b) Le nombre de conditionnements remboursables tiendra compte d'une posologie maximale de 10 mg (dapagliflozine) par jour.

JARDIANCE® (Empaglifozine) sera remboursé pour le traitement des adultes souffrant d'insuffisance cardiaque chronique symptomatique avec fraction d'éjection réduite (ICFEr)[1] à partir du 1er juin 2022.

Efficacy and Safety of Empagliflozin in Hospitalized Heart Failure Patients: Main Results From the EMPULSE Trial

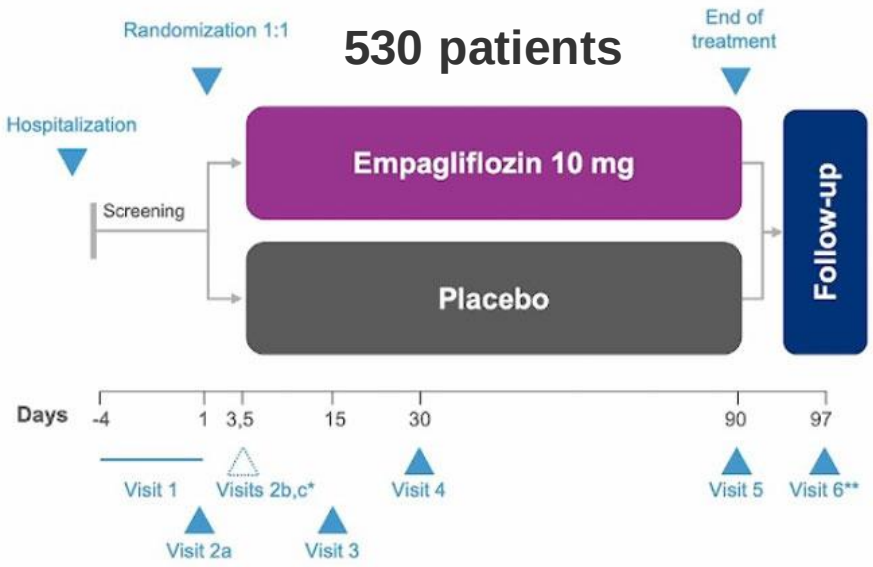
EMPULSE: the missing link



Empagliflozin in patients hospitalized for acute heart failure: the EMPULSE trial

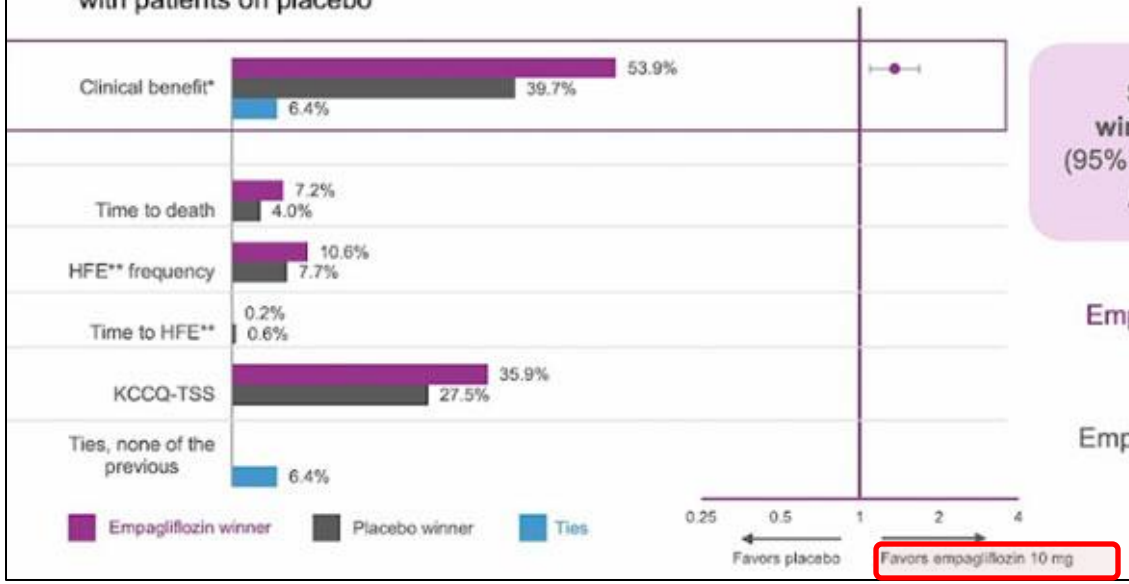
Adriaan A. Voors,[1] Christiane E. Angermann,[2] John. R. Teerlink,[3] Sean P. Collins,[4] Mikhail Kosiborod,[5] Jan Biegus,[6] João Pedro Ferreira,[7] Michael E. Nassif,[8] Mitchell A. Psotka,[9] Jasper Tromp,[10] Martina Brueckmann,[11] Jon P. Blatchford,[12] Afshin Salsali,[13] Piotr Ponikowski,[6] for the EMPULSE Trial Investigators

[1]University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; [2]Comprehensive Heart Failure Centre, University & University Hospital of Würzburg, Würzburg, Germany; [3]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, USA; [4]Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, USA; [5]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, USA and the George Institute for Global Health and the University of New South Wales, Sydney, NSW, Australia; [6]Institute of Heart Diseases, Medical University, Wroclaw, Poland; [7]Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France; and Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal; [8]Saint Luke's Mid America Heart Institute and the University of Missouri, Kansas City, USA; [9]Inova Heart and Vascular Institute, Falls Church, USA; [10]Saw Swee Hock School of Public Health, National University of Singapore, Singapore; [11]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [12]Elderbrook Solutions GmbH on behalf of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [13]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA



Primary endpoint

- Patients treated with empagliflozin were 36% more likely to experience a clinical benefit* compared with patients on placebo

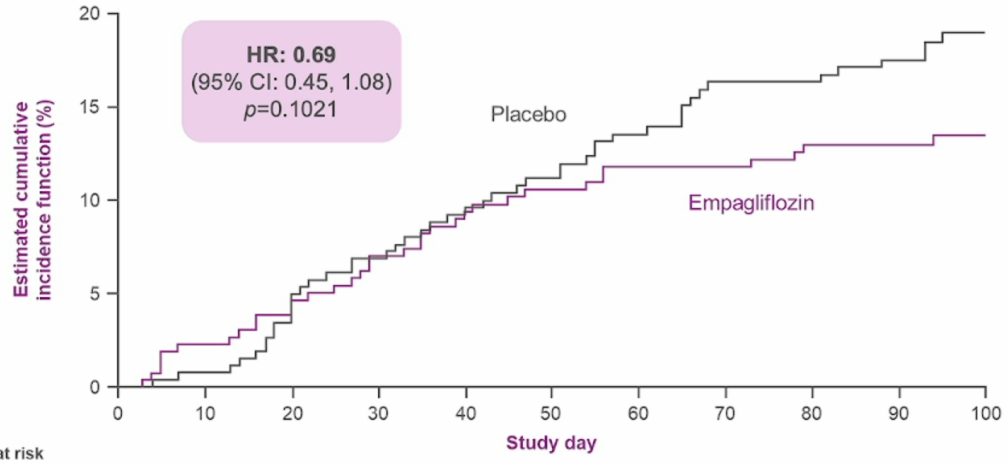


Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Death:
Empagliflozin: 4.2%
Placebo: 8.3%

HF event:
Empagliflozin 10.6%
Placebo 14.7%

Time to cardiovascular death or first HFE*

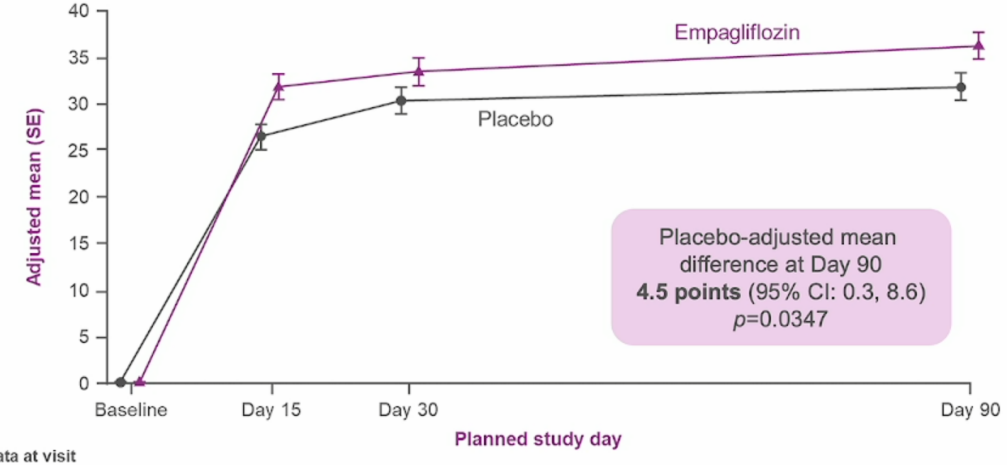


Patients at risk											
Placebo	265	261	249	236	228	221	213	206	205	200	67
Empagliflozin	265	252	243	234	228	223	220	220	216	211	64

DREAM-HF

*HFE includes hospitalizations for heart failure, urgent heart failure visits, and unplanned outpatient visits. CI, confidence interval; HFE, heart failure event; HR, hazard ratio.

Secondary endpoint: change in KCCQ-TSS at Day 90



Placebo-adjusted mean difference at Day 90
4.5 points (95% CI: 0.3, 8.6)
p=0.0347

No. with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

DREAM-HF

CI, confidence interval; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score.

Quid de l'HFpEF ?

EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (NCT03057951)

PRESERVED-HF: Dapagliflozin Effect on Symptoms and Biomarkers in patients with HFpEF (NCT03030235)

Empagliflozin (10 mg)

EMPEROR-Preserved – empagliflozin versus placebo

- **Goal: 5720 patients**
- **Estimated completion: 2020**

Dapagliflozin (10 mg)

DELIVER – dapagliflozin versus placebo

- **Goal: 4700 patients**
- **Estimated completion: 2021**

EMPEROR-Preserved: EMPagliflozin outcomE tRial in Patients With chrOnic HFpEF

5250 patients
≥ 18 years, with chronic HFpEF
(NYHA class II to IV, LVEF >40%)

→ R 1:1 Double -blind

→ Placebo

→ Empagliflozin 10 mg

All other HF medications per treating physician

Estimated completion:
November 2020

Primary endpoint:
- Time to first event of: CV death **or** HHF

Secondary endpoints:
- Occurrence of adjudicated HHF
- Change from baseline in eGFR
- Time to occurrence of sustained reduction in eGFR
- Time to occurrence of all cause mortality
- Time to onset of T2D
- Change from baseline in KCCQ

ClinicalTrials.gov. NCT03057951.

EMPEROR-Preserved - Une révolution !

Premier traitement efficace de l'insuffisance cardiaque à FEVG préservée

EMPEROR-Preserved – Study Design

Phase III, randomized, double-blind, placebo-controlled trial

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Population: T2DM & non-T2DM, aged ≥18 years, chronic HF (NYHA class II–IV), eGFR ≥20 and raised NT-BNP (>300 pg/mL in SR & >900 pg/mL in AF)

EMPEROR-Preserved
LVEF >40%

5988 patients

Patients with structural heart disease* or HHF within 12 months of screening

*Left atrial enlargement or LV hypertrophy

Empagliflozin 10 mg once daily + standard of care

Placebo once daily + standard of care

Median follow-up 26 months

Randomization stratified by baseline LVEF ≥50% vs 41–49%

COMPOSITE PRIMARY ENDPOINT
Time to first event of adjudicated cardiovascular death or adjudicated HHF

SECONDARY ENDPOINTS
- First and recurrent adjudicated HF hospitalization events
- Slope of change in eGFR (CKD-EPI)

DREAM-HF

5988 patients avec insuffisance cardiaque
FEVG > 40%, avec ou sans diabète.
Suivi de 26 mois

ESC Congress 2021

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

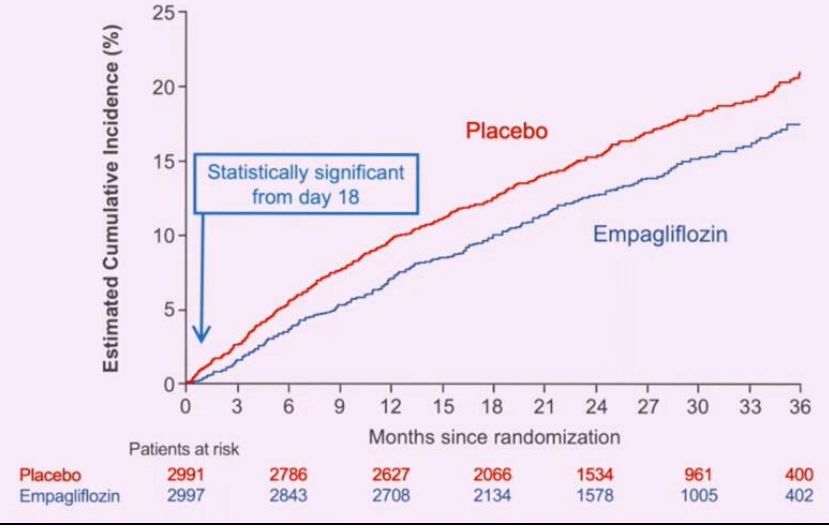
21% ↓ in risk
P = 0.0003

First Secondary Endpoint
Total (first and recurrent) heart failure hospitalizations

27% ↓ in risk
P = 0.0009

Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

P < 0.0001
Difference: 1.36 mL/min/1.73 m² per year



HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

RRR 21%

NNT=31
During a median trial period of 26 months.

Empagliflozin in Heart Failure With a Preserved Ejection Fraction ≥50% Results From the EMPEROR-Preserved Clinical Trial

Stefan D. Anker, MD, PhD

EMPEROR-Preserved – Study Design

Phase III, randomized, double-blind, placebo-controlled trial

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Population: T2DM & non-T2DM, aged ≥18 years, chronic HF (NYHA class II–IV), eGFR ≥20 and raised NT-BNP (>300 pg/mL in SR & >900 pg/mL in AF)

EMPEROR-Preserved
LVEF >40%

5988 patients

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*Left atrial enlargement or LV hypertrophy

Empagliflozin 10 mg once daily + standard of care

Placebo once daily + standard of care

Median follow-up 26 months

Randomization stratified by baseline LVEF ≥50% vs 41–49%

COMPOSITE PRIMARY ENDPOINT
Time to first event of adjudicated cardiovascular death or adjudicated HHF

SECONDARY ENDPOINTS
- First and recurrent adjudicated HF hospitalization events
- Slope of change in eGFR (CKD-EPI)

DREAM-HF

Objectives of This Analysis

- **Summarize the effects of empagliflozin in HF patients with preserved LVEF of ≥50% (i.e. HFpEF) observed in the EMPEROR-Preserved trial**

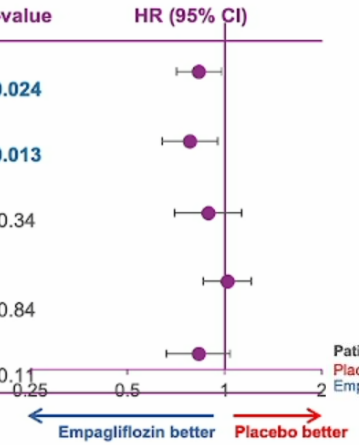
→ This are the patients with "True" HFpEF (according to recent HF guidelines)

- Contrast the results observed in patients with HFpEF with the results in HF patients with mildly reduced LVEF of 41–49% (i.e. HFmrEF)
- Compare the results observed in patients with HFpEF (LVEF ≥50%) in EMPEROR-Preserved with the results of other relevant trials

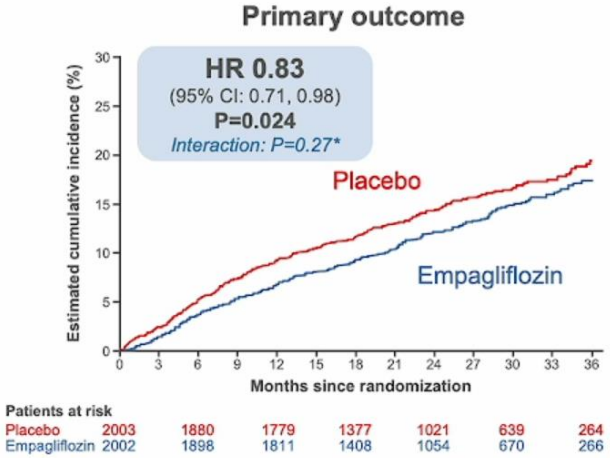
	HFpEF (≥50%) (n=4,005)	HFmrEF (41–49%) (n=1,983)	P-value
Age, years (±SD)	72.8 ± 9.2	70.1 ± 9.7	<0.001
Women, n (%)	2019 (50)	657 (33)	<0.001
Diabetes, n (%)	1913 (48)	1025 (52)	0.004
Ischaemic HF, n (%)	1134 (28)	983 (50)	<0.001
NYHA functional class II, n (%)	3255 (81)	1628 (82)	0.58
NT-proBNP (median, IQR), pg/mL	946 (482, 1677)	1025 (550, 1882)	<0.001
Atrial fibrillation or flutter, n (%)	2224 (56)	911 (46)	<0.001
Baseline eGFR (mL/min/1.73 m^2)	59.4 ± 19.5	63.0 ± 20.3	<0.001
Co-medications of interest, n (%)			
ACE inhibitors/ARBs/ARNi	3149 (79)	1690 (85)	0.001
Beta blocker	3375 (84)	1792 (90)	<0.001
MRA	1320 (33)	924 (47)	<0.001
Diuretics	3246 (81)	1563 (79)	0.041

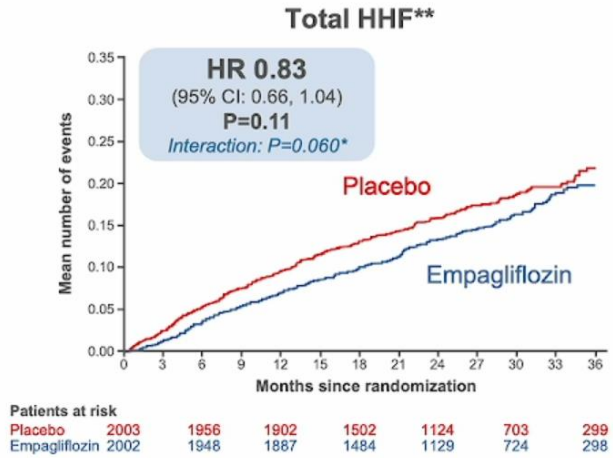
Effect of Empagliflozin vs Placebo: Primary and Secondary Outcomes – LVEF ≥50%

Endpoint	Events		Events/100 patient-years		HR (95% CI)	P-value
	Placebo (n=2,003)	Empagliflozin (n=2,002)	Placebo	Empagliflozin		
Primary endpoint						
LVEF ≥50%	318	270	8.0	6.7	**0.83** (0.71, 0.98)	**0.024**
First HHF						
LVEF ≥50%	226	182	5.7	4.5	**0.78** (0.64, 0.95)	**0.013**
CV death						
LVEF ≥50%	144	126	3.4	3.0	0.89 (0.70, 1.13)	0.34
All-cause mortality						
LVEF ≥50%	260	259	6.1	6.1	1.02 (0.86, 1.21)	0.84
Total HHF*						
LVEF ≥50%	332	285	7.9	6.8	0.83 (0.66, 1.04)	0.11



Effect of Empagliflozin vs Placebo: Outcomes in Patients with LVEF ≥50%



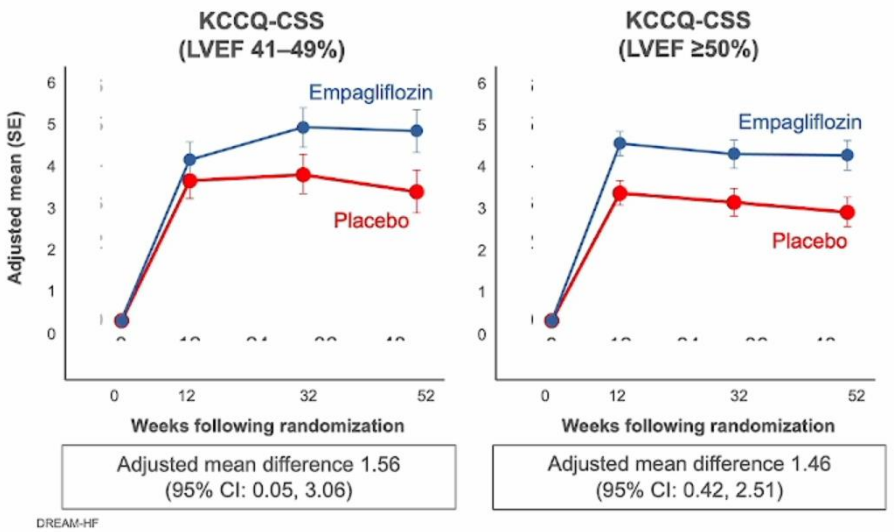


Results for key endpoints in the subgroup of patients with HFpEF (i.e. LVEF ≥50%)

	Primary Endpoint Composite of cardiovascular death or heart failure hospitalization	**17% ↓ in risk** **P = 0.024**
	Hospitalisation for HF First heart failure hospitalization	**22% ↓ in risk** **P = 0.013**
	QoL KCCQ-CSS	**P = 0.006** Difference vs Placebo: 1.46 points improvement
	Kidney Function Slope of decline in glomerular filtration rate over time	**P < 0.0001** Difference vs Placebo: 1.24 mL/min/1.73 m^2 per year

DREAM-HF

Treatment Effect on KCCQ-CSS by LVEF Category



Change from baseline (SE) at Week 52

LVEF 41–49%

Empagliflozin: 4.86 ± 0.54
Placebo: 3.30 ± 0.55
P-value = 0.043

LVEF ≥50%

Empagliflozin: 4.24 ± 0.38
Placebo: 2.78 ± 0.38
P-value = 0.006

P-interaction value = 0.92

- In the EMPEROR-Preserved trial, empagliflozin significantly improved the composite endpoint of a first event of CV death or hospitalization for HF in patients with LVEF ≥50% by 17%.
- Improvements were also observed in health-related QoL, measures of kidney function and symptom status.
- This is the first large-scale study to document meaningful and significant improvements associated with drug therapy in patients with True HFpEF.

DELIVER

Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure

~6100 Patients

- ≥40 years of age
- Diagnosis of symptomatic HF (NYHA functional Class II-IV) and typical signs/symptoms of HF ≥6 weeks before enrollment with at least intermittent need for diuretic treatment
- LVEF >40% and evidence of structural heart disease within 12 months of enrollment
- Elevated NT-proBNP levels
- Both ambulatory and hospitalized patients off IV HF therapy for 24 hours may be enrolled

1:1 randomization

Dapagliflozin 10 mg + standard of care

Placebo + standard of care

Primary Endpoint

- Time to first occurrence of any components of the composite: CV death, hHF, urgent HF visit

Secondary Endpoints

- Total number of (first and recurrent) hospitalizations for HF and CV death
- Change from baseline in the total symptom score of the KCCQ at 8 months
- Proportion of patients with worsened NYHA class from baseline to 8 months
- Time to the occurrence of death from any cause

Estimated Completion: November 2021

CV = cardiovascular; HF = heart failure; hHF = hospitalization for heart failure; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal proB-type natriuretic peptide; NYHA = New York Heart Association.

Study NCT03619213. ClinicalTrials.gov website.

DELIVER and EMPEROR-Preserved Study Designs

	DELIVER[1]	EMPEROR-Preserved[2,3]
Interventions	Dapagliflozin 10 mg daily or placebo (1:1)	Empagliflozin 10 mg daily or placebo (1:1)
Patient population	• Patients ≥40 years of age with symptomatic NYHA Class II-IV HF and a medical history of symptoms/signs of HF present ≥6 weeks before enrollment with at least intermittent need for diuretics • Elevated NT-proBNP levels • LVEF >40% (HFpEF) • Evidence of structural heart disease documented within the last 12 months • eGFR[a] ≥25 mL/min/1.73m^2	• Patients ≥18 years of age (Japan: ≥20 years of age) with NYHA Class II-IV HF • Elevated NT-proBNP levels • LVEF >40% (HFpEF) • Structural heart disease within 6 months or hHF within 12 months • eGFR[a] ≥20 mL/min/1.73m^2 • Stable dose of diuretics, if prescribed
Sample size	~6100	5988 (actual)
Study duration	33 months	38 months
Primary outcome	Time to first occurrence of any component of the composite: • CV death • hHF • an urgent HF visit	Time to first occurrence of any component of the composite: • CV death • hHF
Secondary outcomes	• Total first and recurrent hHF and CV death • Change from baseline in KCCQ at 8 months • Proportion of patients with worsened NYHA Class from baseline to 8 months • Time to all-cause mortality	• Occurrence of first and recurrent hHF • eGFR[a] slope of change from baseline • Time to first occurrence of sustained reduction of eGFR, chronic dialysis, or renal transplant • Time to first hHF • Time to CV death • Time to all-cause mortality • Time to diabetes onset • Change from baseline in KCCQ at 52 weeks • Occurrence of all-cause hospitalization
Background Therapy	• Stable SoC treatment	• Stable SoC treatment
Status	2021	2021

[a]Based on the Chronic Kidney Disease-Epidemiology Collaboration Equation.

1. Study NCT03619213. ClinicalTrials.gov website; 2. Study NCT03057951. ClinicalTrials.gov website; 3. Anker SD et al. *Eur J Heart Fail*. 2019;21:1279-1287.

En conclusion :

Le diabète et les maladies cardio-vasculaires ont des liaisons dangereuses

Inhr-SGLT2 est classé comme un traitements du diabète de type 2 MAIS…

- Effets métaboliques, hémodynamiques, vasculaires,..
- I-SGLT2 : prévention et traitement de l'insuffisance cardiaque et protection rénale
- Protection très précoce
- Protection indépendante de la glycémie, poids, PA..
- Bénéfices additifs aux traitements standards dans HFrEF & HFpEF
- Importance de de la prise en charge multidisciplinaire

Merci de votre attention

CITADELLE CHATEAU ROUGE SAINTE ROSALIE

VOTRE SANTÉ, NOTRE MÉTIER