Les inhibiteurs de iSGLT2 en transplantation
L'approche du greffeur cardiaque

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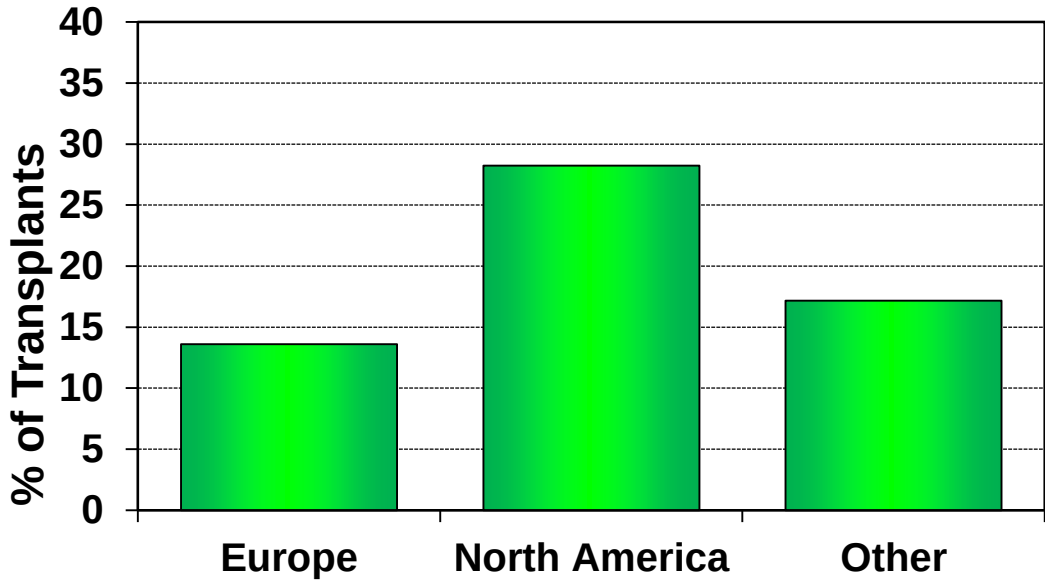
Gliflozines : Diabète et greffé coeur

✓ Diabète pré greffe cœur

18-26% patients (30-35% de cardiopathie ischémiques)



JHLT. 2019; 38(10): 1015-1066

✓ NODAT 20-30% (21% étude de registre de 2022)
Incidence en baisse

Newman JD et al, Heart Lung Transplant 2022;41:1537–1546

✓ Recommandées dans la prise en charge du diabète du greffé par sociétés savantes

Velleca A, Guidelines ISHLT J Heart Lung Transplant. 2023 ;42:e1-e141.

Table 4
Studies on heart transplant recipients: association of SGLT2 inhibitors and efficacy and safety outcomes.

	Reduced mortality	Effect on kidney efficacy endpoints	Effect on cardiovascular efficacy endpoints	Change in HbA1c (% as median **)	Change in weight (kg as mean [median **])	Discontinuation due to adverse event; Rationale (#)	AKI; No. of events (%)	DKA; No. of events (%)	UTI; No. of events (%)	Genital infection; No. of events (%)
Cehic et al. 2019 ($n = 101$)	NR	NR	NR	↓ 0.6 in SGLT2 inhibitor group **	↓ 2 in SGLT2 inhibitor group **	AKI (1)	1 (4.5%) in SGLT2 inhibitor group	0	0 in SGLT2 inhibitor group	0 in SGLT2 inhibitor group
Sammour et al. 2021 ($n = 21$)	NR	NR	NR	↓ 0.9 **	↓ 12.4	0	NR	0	NR	0

** value reported as median; HbA1c = hemoglobin A1c; AKI = acute kidney injury; DKA = diabetic ketoacidosis; UTI = urinary tract infection; NR = not reported; kidney and cardiovascular efficacy endpoints as defined in Methods.

Lin Y. Transplant. Rev. 2023, *37*, 100729.

Cehic MG, Transplant Direct. 2019 ;5(5):e450.

Sammour Y, J Heart Lung Transplant. 2021;40:426-429

La relation glycosurie sous iSGLT2/ eGFR est très linéaire.

Chez les patients diabétiques de type 2 l'efficacité glycémique des gliflozines est corrélée au DFG

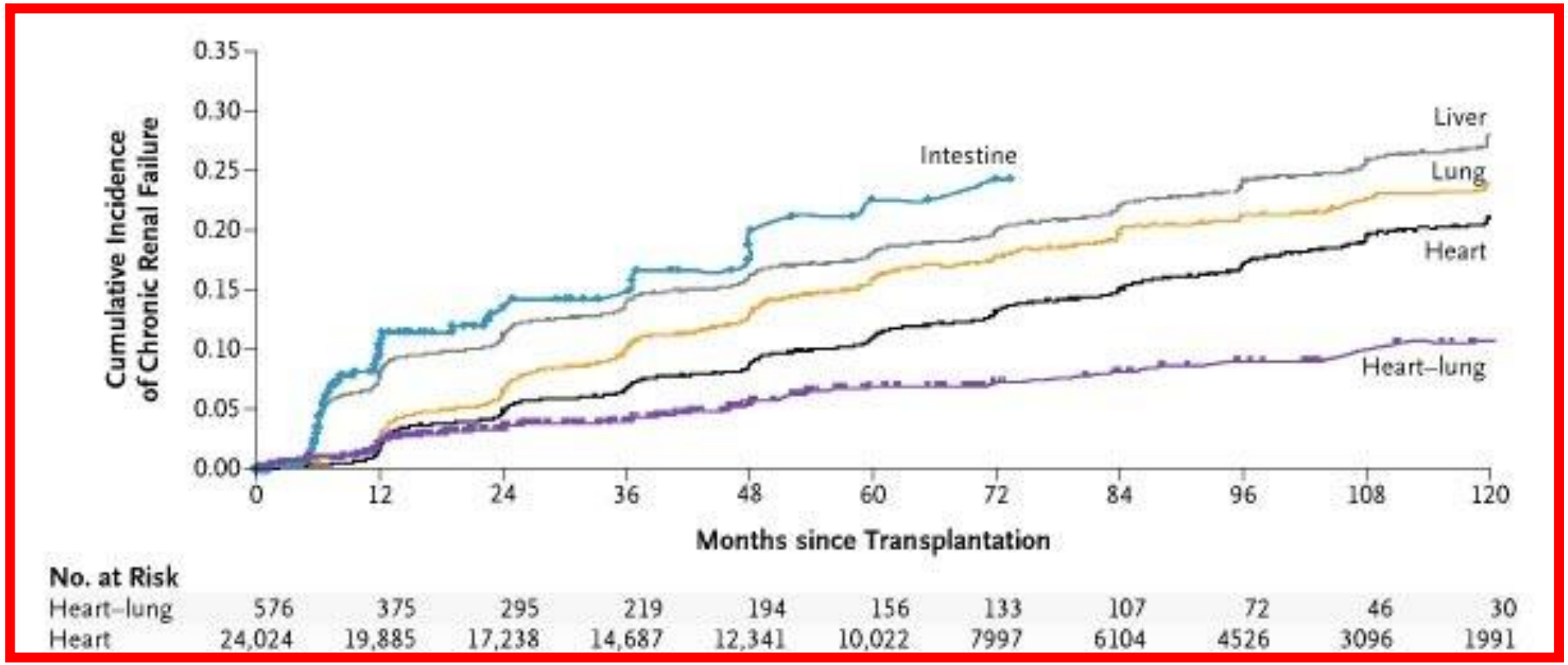
Dapagliflozine : efficacité réduite lorsque le débit de filtration glomérulaire (DFG) est < 45 mL/min et est vraisemblablement absente chez les patients atteints d'insuffisance rénale sévère. Un seul dosage 10mg.

Empagliflozine:

Diabète de type 2 [b] Patients présentant un diabète de type 2 et une pathologie cardiovasculaire avérée	≥ 60	Commencer par 10 mg d'empagliflozine.
		Chez les patients qui tolèrent 10 mg d'empagliflozine et nécessitent un meilleur contrôle glycémique, la dose peut être augmentée à 25 mg d'empagliflozine.
	45 à < 60 effet correct	Commencer par 10 mg d'empagliflozine.[b]
		Continuer avec 10 mg d'empagliflozine chez les patients déjà sous Jardiance.
	30 à < 45[b] effet modeste	Commencer par 10 mg d'empagliflozine.
		Continuer avec 10 mg d'empagliflozine chez les patients déjà sous Jardiance.
	< 30	L'empagliflozine n'est pas recommandée.

Velleca A, Guidelines ISHLT J Heart Lung Transplant. 2023 ;42(5):e1-e141.

Gliflozines : Insuffisance rénale et greffé coeur



No. at Risk											
Heart–lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991

Ojo AO, N Engl J Med. 2003;349:931-40

Incidence de la dysfonction rénale chronique*, données ISHLT 2019

6,7%, 15,7% et 22,3% à respectivement 1, 5 et 10 ans de greffe cardiaque

**créatinine > 221 umol/L, la dialyse chronique ou la transplantation rénale*

Gliflozines : Dysfonction cardiaque et Greffé coeur

Cause of Death	0-30 Days (N=6,871)	31 Days - 1 Year (N=5,980)	>1-3 Years (N=4,211)	>3-5 Years (N=3,630)	>5-10 Years (N=9,441)	>10-15 Years (N=7,108)	>15 Years (N=5,695)
Cardiac Allograft Vasculopathy	83 (1.2%)	190 (3.2%)	456 (10.8%)	449 (12.4%)	1,153 (12.2%)	859 (12.1%)	598 (10.5%)
Acute Rejection	268 (3.9%)	474 (7.9%)	412 (9.8%)	171 (4.7%)	176 (1.9%)	67 (0.9%)	29 (0.5%)
Graft Failure	2,716 (39.5%)	1,052 (17.6%)	1,112 (26.4%)	884 (24.4%)	1,838 (19.5%)	1,231 (17.3%)	944 (16.6%)

Mortalité registre ISHLT 2019 : 01/1995 – 06/ 2018

J Heart Lung Transplant 2019; 38: 1015-1066

	Graft failure (*n*=178)	Controls (*n*=369)	*P*-value
Recipients			
Age, years	54.8 ± 11.5	54.5 ± 11.3	0.787
Body mass index, kg/m^2	26.6 ± 3.9	25.5 ± 3.9	0.005
Women	16.9%	16.3%	0.861
Year of transplantation			0.001
1991–1998	50.6%	33.9%	
1999–2006	32.6%	39.3%	
2007–2014	16.9%	26.8%	

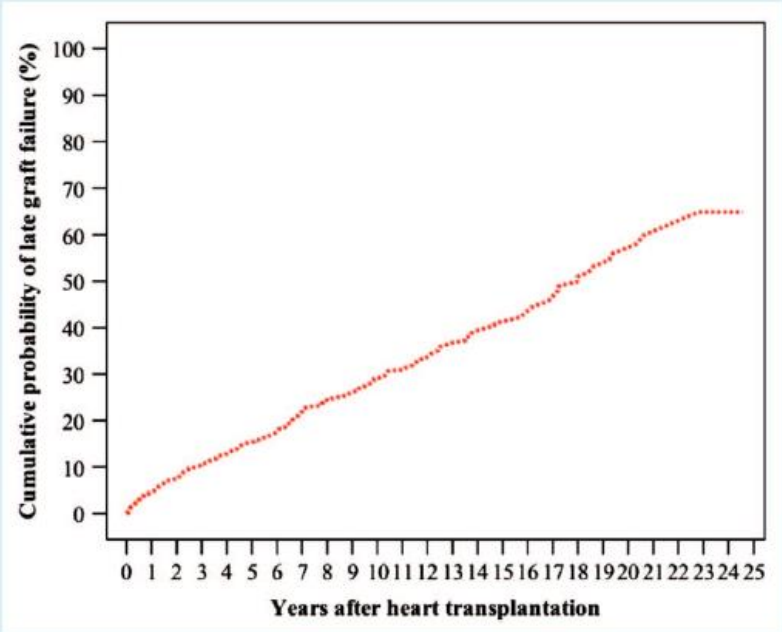


Figure 1 Cumulative probability of hospitalization due to new-onset, symptomatic late graft failure among 547 first, single-organ, heart transplant recipients who survived the early postoperative period: Kaplan–Meier analysis.

Lopez-Sainz A European Journal of Heart Failure 2018; 20:385-394

Table 3 **Clinical characteristics of 178 cardiac transplant recipients at the time of their first hospitalization due to new-onset late graft failure**

Medical history	
Age, years	61.4 ± 12.1
Time since transplantation, years	6.9 ± 5.5
Length of hospital stay, days	13.8 ± 12.5
Diabetes mellitus	33.1%
Hypertension	56.2%
History of graft rejection	65.7%
History CMV infection	22.5%
History of malignancy	12.9%
Echocardiography	
LVEDD, mm	48.1 ± 6.8
LVEDD ≥55 mm	15.2%
Left ventricular hypertrophy	30.3%
Restrictive physiology	56.2%
LVEF	51.9 ± 15.3
LVEF groups	
<40%	19.1%
40–49%	20.8%
≥50%	60.1%

Graft rejection	
Not assessed	11.2%
Cellular rejection	
0R	43.8%
1R	21.3%
2R	17.4%
3R	6.2%
Antibody-mediated rejection	
p-AMR 0	69.7%
p-AMR 1	17.5%
p-AMR 2	1.7%
Cardiac allograft vasculopathy	
Not assessed	5.6%
CAV 0 (absent)	43.8%
CAV 1	1.7%
CAV 2	3.9%
CAV 3	38.8%
Detected at necropsy	6.2%

ICFER et iSGLT2: 2 grandes études. 4è pilier du TTT de L'ICFEr ESC 2021-23

Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A

European Heart Journal (2023) 44, 3627–3639

McMurray N N Engl J Med. 2019; 21:665-75

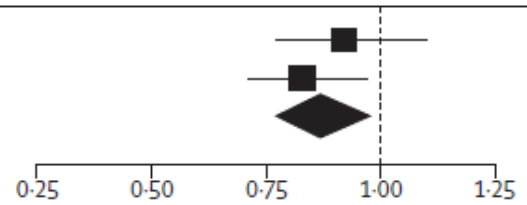
Packer M N Engl J Med. 2020;383(15):1413-1424

	EMPEROR-Reduced **		DAPA-HF *	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76.5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)

*McMurray N et al. Engl J Med. 2019; 21:665-75
**Packer M et al. N Engl J Med. 2020;383(15):1413-1424
Zannad F et al. Lancet. 2020;396:819-829.

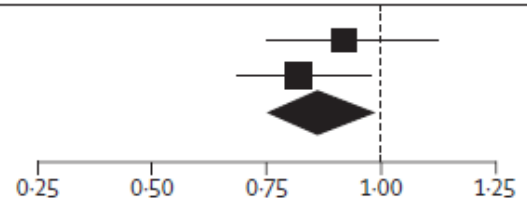
A All-cause mortality

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	249/1863 (13·4%)	266/1867 (14·2%)	0·92 (0·77–1·10)
DAPA-HF	276/2373 (11·6%)	329/2371 (13·9%)	0·83 (0·71–0·97)
Total			**0·87 (0·77–0·98)**
Test for overall treatment effect p=0·018			
Test for heterogeneity of effect p=0·39			



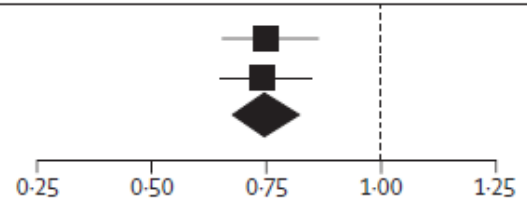
B Cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	187/1863 (10·0%)	202/1867 (10·8%)	0·92 (0·75–1·12)
DAPA-HF	227/2373 (9·6%)	273/2371 (11·5%)	0·82 (0·69–0·98)
Total			**0·86 (0·76–0·98)**
Test for overall treatment effect p=0·027			
Test for heterogeneity of effect p=0·40			



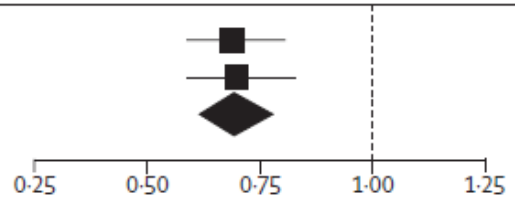
C First hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
DAPA-HF	386/2373 (16·3%)	502/2371 (21·2%)	0·74 (0·65–0·85)
Total			**0·74 (0·68–0·82)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·89			



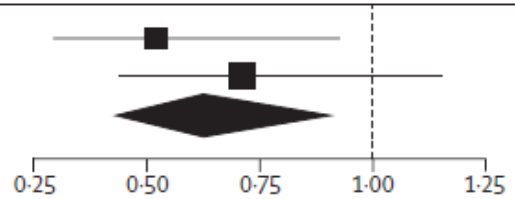
D First hospitalisation for heart failure

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	246/1863 (13·2%)	342/1867 (18·3%)	0·69 (0·59–0·81)
DAPA-HF	231/2373 (9·7%)	318/2371 (13·4%)	0·70 (0·59–0·83)
Total			**0·69 (0·62–0·78)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·90			



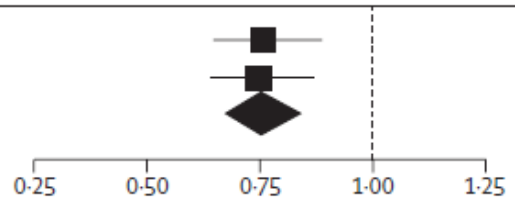
E First kidney outcome composite

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			**0·62 (0·43–0·90)**
Test for overall treatment effect p=0·013			
Test for heterogeneity of effect p=0·42			



F All (first and recurrent) hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		RR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	575/1863 (30·9%)	753/1867 (40·3%)	0·76 (0·65–0·89)
DAPA-HF	567/2373 (23·9%)	742/2371 (31·3%)	0·75 (0·65–0·88)
Total			**0·75 (0·68–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·91			



Critère primaire et sous groupe

- Diabète, sexe, utilisation ARNI, eGFR, BMI= pas de différence
- NYHA II> III ou IV, efficacité race noire, asiatique > race blanche

Effets indésirables

	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%)

Data are n(%). Definitions of medical concepts describing adverse events of interest were not exactly similar between the two trials. The absolute numbers of events cannot be compared across the two trials because of different definitions and observation periods. For EMPEROR-Reduced, we show here adverse events up to 7 days after discontinuation of study medication, and for lower limb amputations up to the end of the trial. For DAPA-HF, we show here on-treatment analysis set for all adverse events, except for lower limb amputation shown on and off treatment. See appendix (p 4) for additional details on adverse event definitions.

Table 2: **Relevant adverse events reported in the two trials**

Pas d'étude spécifique chez le transplanté = extrapolation

EMPA-HTx en cours

Table 1 Study end points

Change from baseline	Method of assessment
Primary ▶ Glycaemia	Change of HbA1c and/or fructosamine
Key secondary ▶ Cardiac interstitial fibrosis ▶ Renal function ▶ Development of diabetes	Change of left ventricular interstitial fibrosis and mass as assessed by CMR Mean change in eGFR HbA1c ≥6.5%, and/or FPG ≥7.0 mmol/L; or clinically diagnosed by treating physician

Table 2 Inclusion and exclusion criteria

Inclusion criteria	▶ Men and women over 18 years of age ▶ Cardiac transplant recipients recruited within 6–8 weeks from the date of cardiac transplant ▶ Free from major rejection at enrolment ▶ Baseline eGFR >30 mL/min/1.73 m^2 ▶ Willingness to give written informed consent and willingness to participate to and comply with the study

Raven LM, *et al. BMJ Open* 2023;13:e069641

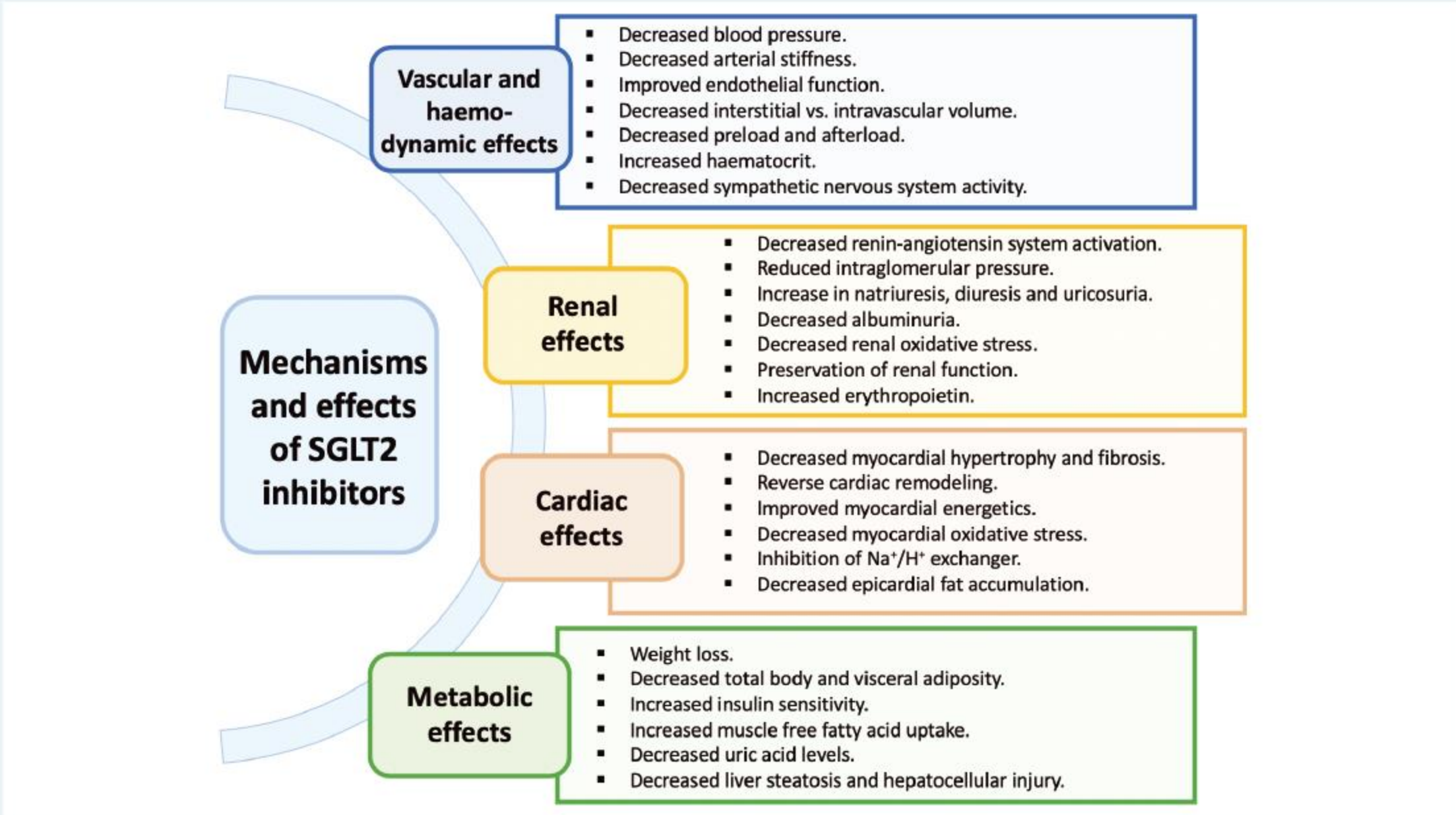
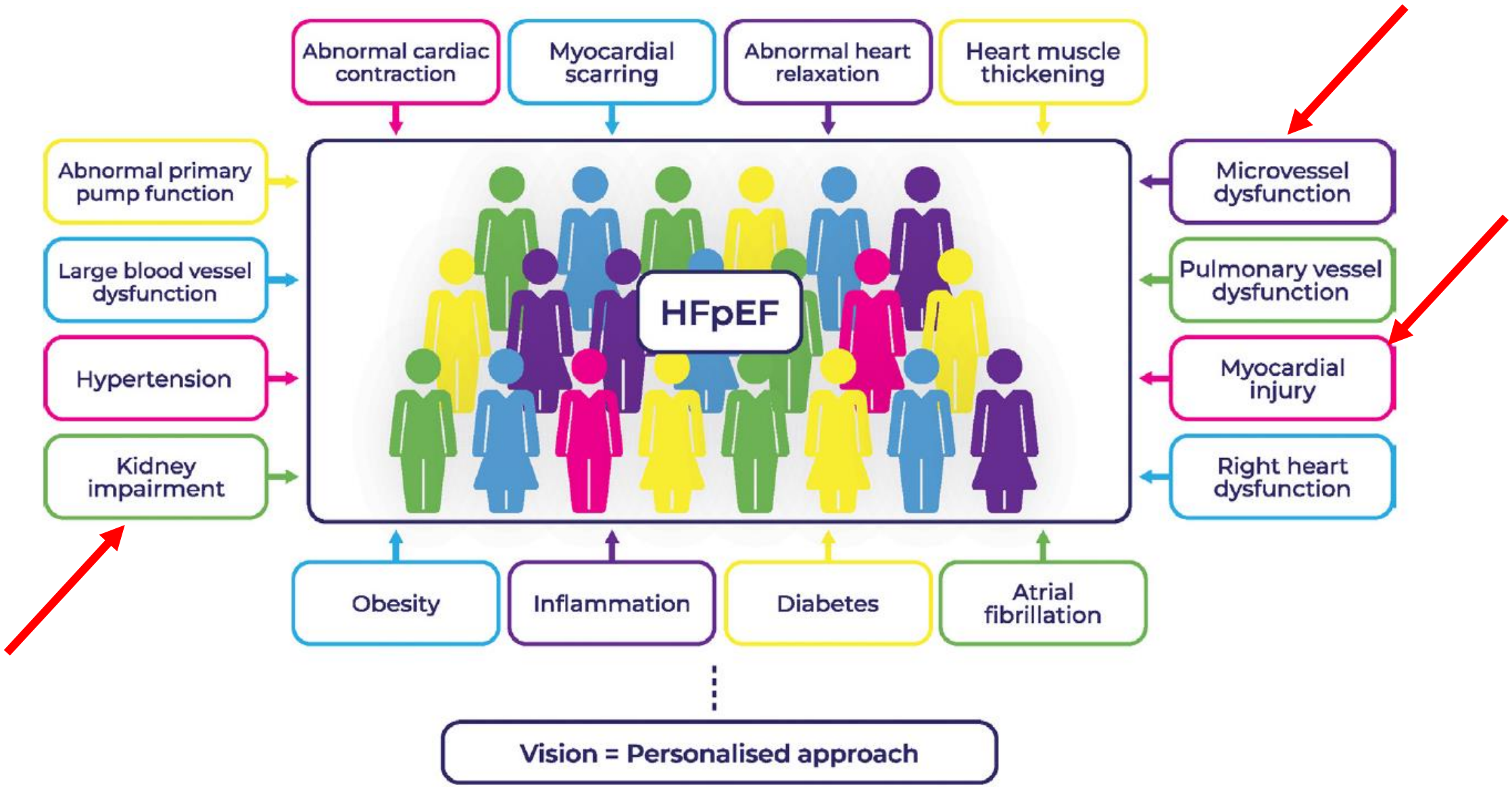
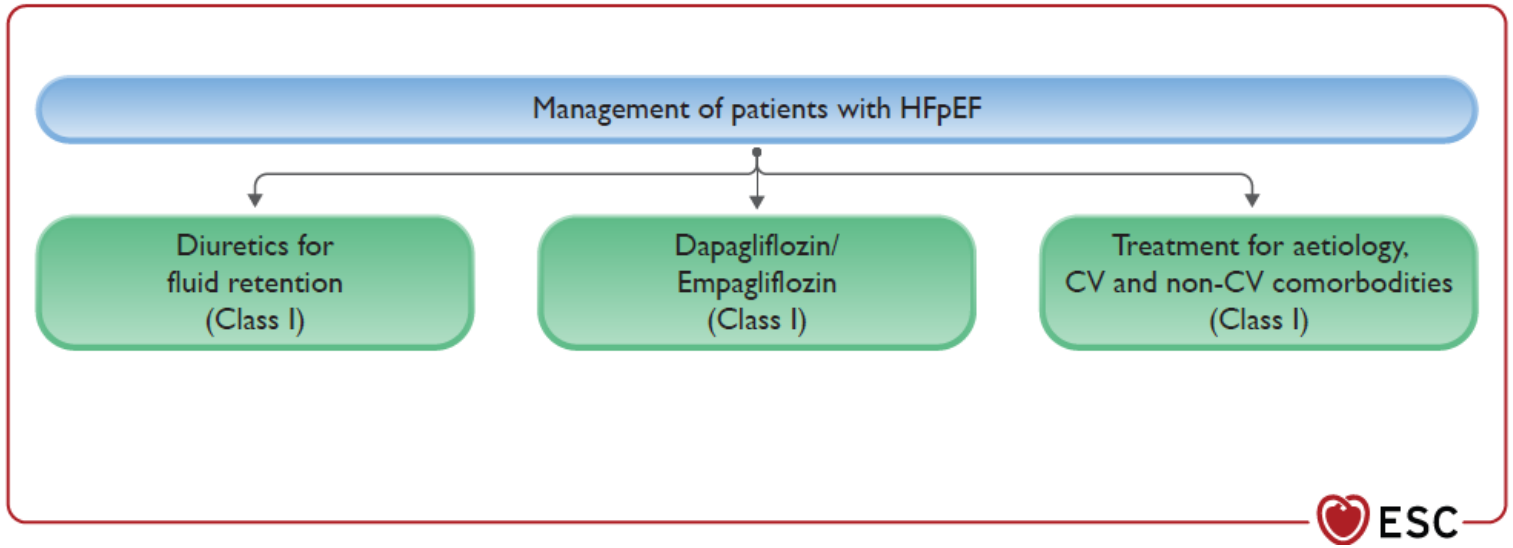


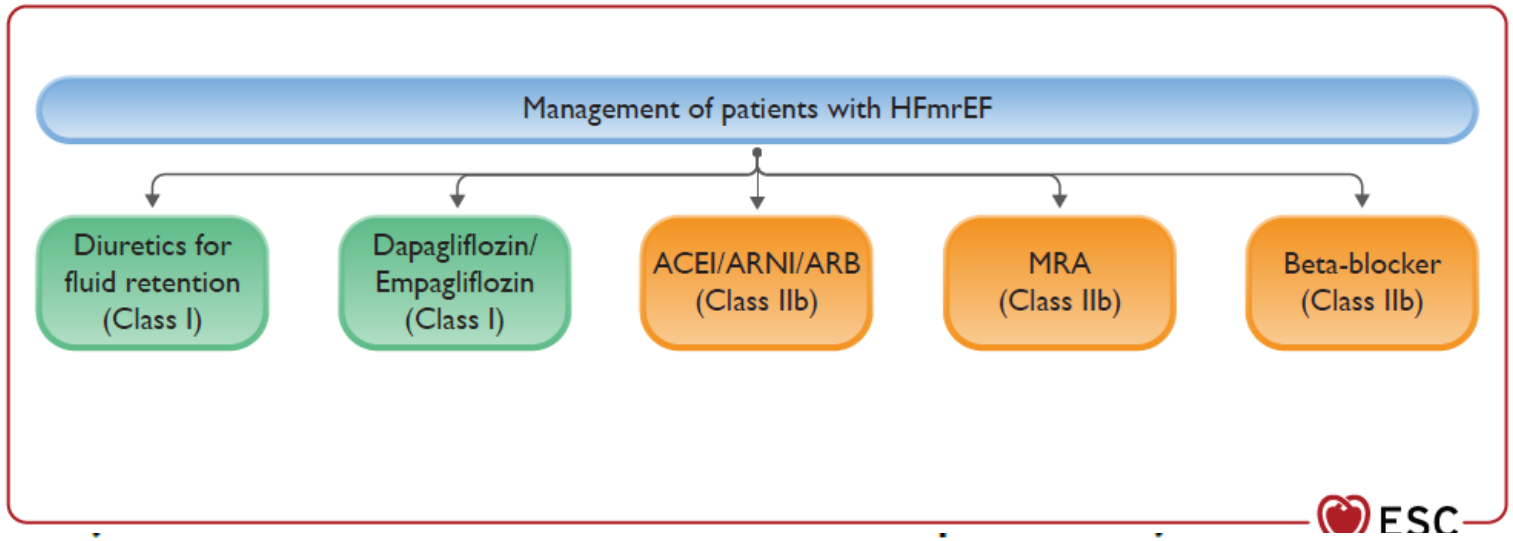
Figure 1 Proposed biological mechanisms and effects of sodium–glucose co-transporter 2 (SGLT2) inhibitors.

Séferovic et al. Eur J of Heart Fail 2020;22:1495-503

ICFEp et ICFEmr= majorité des transplantés







Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Eur Heart J 2023;44:3627-3639

Méta-analyse : 12 251 pts symptomatiques, hospitalisés ou ambulatoires, IC à FEVG ≥ 40%

	DELIVER (n=6263)	EMPEROR-Preserved (n=5988)
(Continued from previous pa		
Baseline characteristics		
Mean age, years	71·7 (9·6)	71·9 (9·6)
Sex		
Women	2747 (43·9%)	2676 (44·7%)
Men	3516 (56·1%)	3312 (55·3%)
NYHA functional class		
II	4713 (75·3)	4883 (81·5%)
III–IV	1549 (24·7)	1101 (18·4)
Mean LVEF, %	54·2% (8·8)	54·3% (8·8)
Median NT-proBNP, pg/mL	1011 (623–1751)	974 (499–1731)
Mean eGFR, mL/min/1·73 m²	61·0 (19·1)	60·6 (19·9)
Diabetes	2806 (44·8%)	2938 (49·1%)
History of heart failure hospitalisation	2539 (40·5%)	1369 (22·9%)†

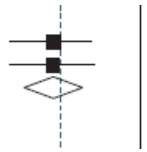
Caractéristiques	Greffons cardiaques greffés en 2022	
	n	%
Age		
0-17 ans	17	4,1
18-29 ans	64	15,6
30-55 ans	224	54,5
56-65 ans	81	19,7
>=66 ans	25	6,1
(m ± ds, ans)	44,6	15,2
Sexe		
Masculin	246	59,9
Féminin	165	40,1

Donneurs en 2022 ABM

Vaduganathan M,lancet. 2022;400:757-767.
Anker SD et al. N Engl J Med. 2021;385(16):1451-61.
Solomon SD et al. N Engl J Med. 2022;387(12):1089-1098

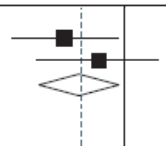
Cardiovascular death or heart failure hospitalisation

	Number with event/ number of patients (%)		Hazard ratio (95% CI)
	SGLT2 inhibitors	Placebo	
HFrEF			
DAPA-HF	382/2373 (16·1%)	495/2371 (20·9%)	0·75 (0·65–0·85)
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
Subtotal			0·75 (0·68–0·83)
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=1·00			



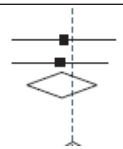
Cardiovascular death

HFrEF			
DAPA-HF	227/2373 (9·6%)	273/2371 (11·5%)	0·82 (0·69–0·98)
EMPEROR-Reduced	187/1863 (10·0%)	202/1867 (10·8%)	0·92 (0·75–1·12)
Subtotal			0·86 (0·76–0·98)
Test for overall treatment effect p=0·027			
Test for heterogeneity of effect p=0·40			



Heart failure hospitalisation

HFrEF			
DAPA-HF	231/2373 (9·7%)	318/2371 (13·4%)	0·70 (0·59–0·83)
EMPEROR-Reduced	246/1863 (13·2%)	342/1867 (18·3%)	0·69 (0·59–0·81)
Subtotal			0·69 (0·62–0·78)
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·90			



	DELIVER		EMPEROR-Preserved	
	Dapagliflozin (n=3126)	Placebo (n=3127)	Empagliflozin (n=2996)	Placebo (n=2989)
Any serious adverse event	1361 (43·5%)	1423 (45·5%)	1436 (47·9%)	1543 (51·6%)
Amputation	19 (0·6%)	25 (0·8 %)	16 (0·5%)	23 (0·8%)
Diabetic ketoacidosis	2 (0·1%)	0 (0·0 %)	4 (0·1%)	5 (0·2%)
Hypoglycaemia	6 (0·2 %)	7 (0·2 %)	73 (2·4%)	78 (2·6%)
Renal	73 (2·3 %)	79 (2·5 %)	363 (12·1%)	384 (12·8%)

En conclusion, Gliflozines chez le transplanté cardiaque

- ✓ Innocuité surtout sur la base des données de greffe rénale

- ✓ Efficacité:

Diabète : quelques études, recommandations ISHLT

Insuffisance rénale: par extrapolation, nombreux candidats en Tx cardiaque

Insuffisance cardiaque et mortalité cardio vasculaire: par extrapolation

mais le transplanté cardiaque insuffisant cardiaque= modèle ICFEp
Idem pour le transplanté rénal