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Insuffisance cardiaque et SGLT2 i : quoi de neuf ?

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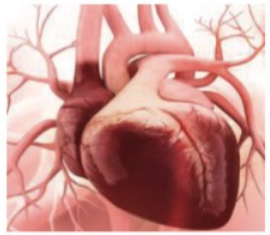
Ce que nous savions

Effets des iSGLT2 sur la sécurité cardiovasculaire



	MACE	Décès CV	hIC	Décès CV + hIC	Mortalité globale
EMPA-REG OUTCOME	**0,86** (0,74-0,99)	**0,62** (0,49-0,77)	**0,65** (0,50-0,85)	**0,66** (0,55-0,79)	**0,68** (0,57-0,82)
CANVAS	**0,86** (0,75-0,97)	**0,87** (0,72-1,06)	**0,67** (0,52-0,87)	**0,78** (0,67-0,91)	**0,87** (0,74-1,01)
DECLARE-TIMI 58	**0,93** (0,84-1,03)	**0,98** (0,82-1,17)	**0,73** (0,61-0,88)	**0,83** (0,73-0,95)	**0,93** (0,82-1,04)
VERTIS-CV	**0,97** (0,85-1,11)	**0,92** (0,77-1,11)	**0,70** (0,54-0,90)	**0,88** (0,75-1,03)	**0,93** (0,80-1,08)

Qui ? Tout patient IC à FE reduite

Quand ? Dès le diagnostic.

2019

DAPA-HF TRIAL

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

AMERICAN COLLEGE of CARDIOLOGY

Randomized, parallel group, placebo-controlled trial

Objective: To evaluate dapagliflozin (a sodium-glucose cotransporter 2 [SGLT2] inhibitor) compared with placebo among patients with heart failure and a reduced ejection fraction (HFrEF).

4,744 patients

Inclusion criteria: patients with symptomatic HF; LVEF ≤40% NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/ml; if atrial fibrillation/flutter ≥900 pg/ml)

Dapagliflozin 10 mg daily (n = 2,373)		Placebo (n = 2,371)
	PRIMARY OUTCOME	
16.3	Cardiovascular death, hospitalization for HF, or urgent HF visit% HR 0.74; 95% CI 0.65-0.85, P< 0.001	21.2
	SECONDARY OUTCOME	
9.6	Cardiovascular death % HR 0.82; 95% CI 0.69 to 0.98	11.5
1.2	Worsening of renal function % HR 0.71; 95% CI 0.44 to 1.16	1.6

Conclusion: Dapagliflozin vs. placebo was associated with a reduction in cardiovascular deaths and HF events

McMurray JJV, Solomon SD, Inzucchi SE, et al., for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*, 2019; [EPub Ahead of Print].

Management of HFrEF

To reduce mortality - for all patients

ACE-I/ARNI | BB | MRA | SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload: Diuretics

SR with LBBB ≥ 150 ms: CRT-P/D	*SR with LBBB 130–149 ms or non LBBB≥ 150 ms*: CRT-P/D
Ischaemic aetiology: ICD	*Non-ischaemic aetiology*: ICD
Atrial fibrillation: Anticoagulation	*Atrial fibrillation*: Digoxin, PVI
Coronary artery disease: CABG	*Iron deficiency*: Ferric carboxymaltose
Aortic stenosis: SAVR/TAVI	*Mitral regurgitation*: TEE MV Repair
Heart rate SR>70 bpm: Ivabradine	*Black Race*: Hydralazine/ISDN
ACE-I/ARNI intolerance: ARB	

For selected advanced HF patients

Heart transplantation | MCS as BTT/BTC | Long-term MCS as DT

To reduce HF hospitalization and improve QOL - for all patients

Exercise rehabilitation

Multi-professional disease management

www.escardio.org/guidelines

2020

EMPEROR-REDUCED

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

AMERICAN COLLEGE of CARDIOLOGY

Double-blind, parallel-group, placebo-controlled trial

Objective: To evaluate the use of empagliflozin in patients with chronic heart failure and a reduced ejection fraction with or without diabetes.

3730 patients

Inclusion criteria: Adults (≥18 years of age) with or without diabetes who had chronic heart failure (functional class II, III, or IV) with a left ventricular ejection fraction of 40% or less on excellent baseline GDMT.

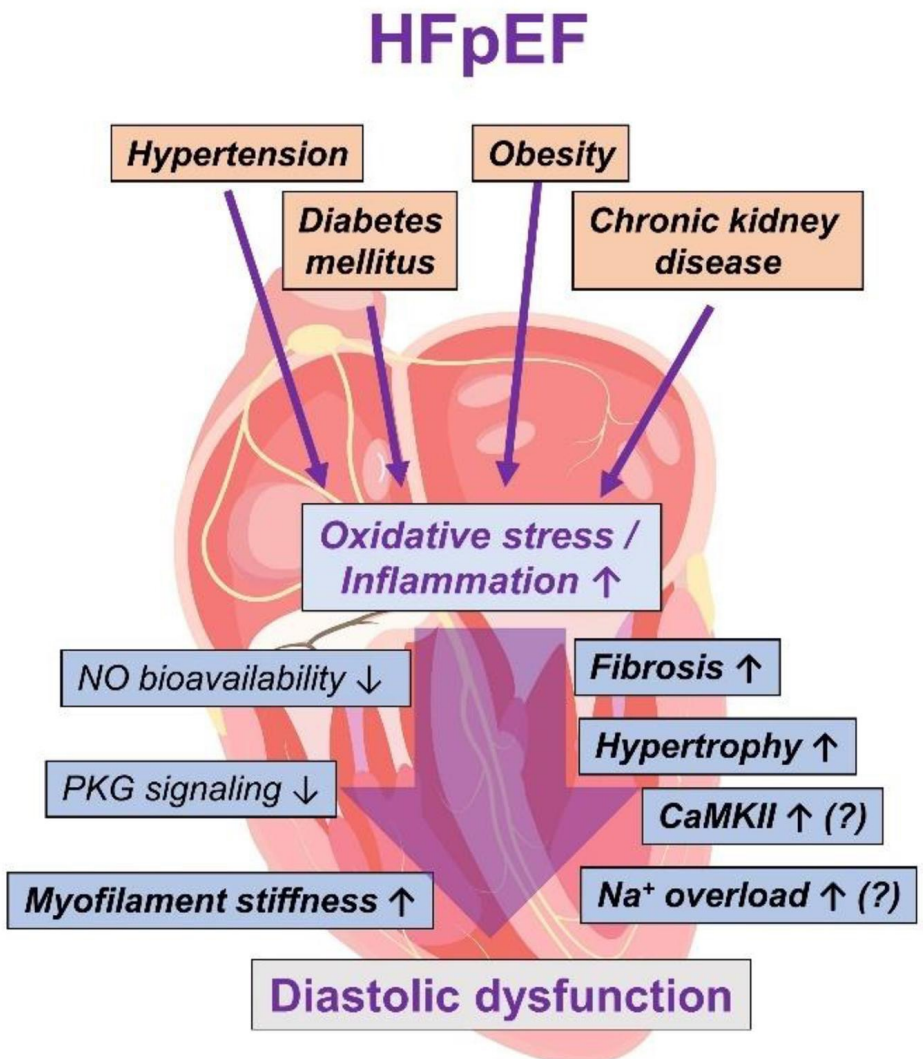
empagliflozin (N=1863)		placebo (N=1867)
	PRIMARY OUTCOME	
19.4	Cardiovascular death or hospitalization for heart failure % HR 0.75; 95% CI, 0.65 to 0.86; P<0.001	24.7
	SECONDARY OUTCOME	
388	Total no. of hospitalizations for heart failure (N) HR 0.70; 95% CI, 0.58 to 0.85; P<0.001	553
-0.55	Mean change in eGFR per year HR 1.73 ; 95% CI, 1.10 to 2.37; P<0.001	-2.28

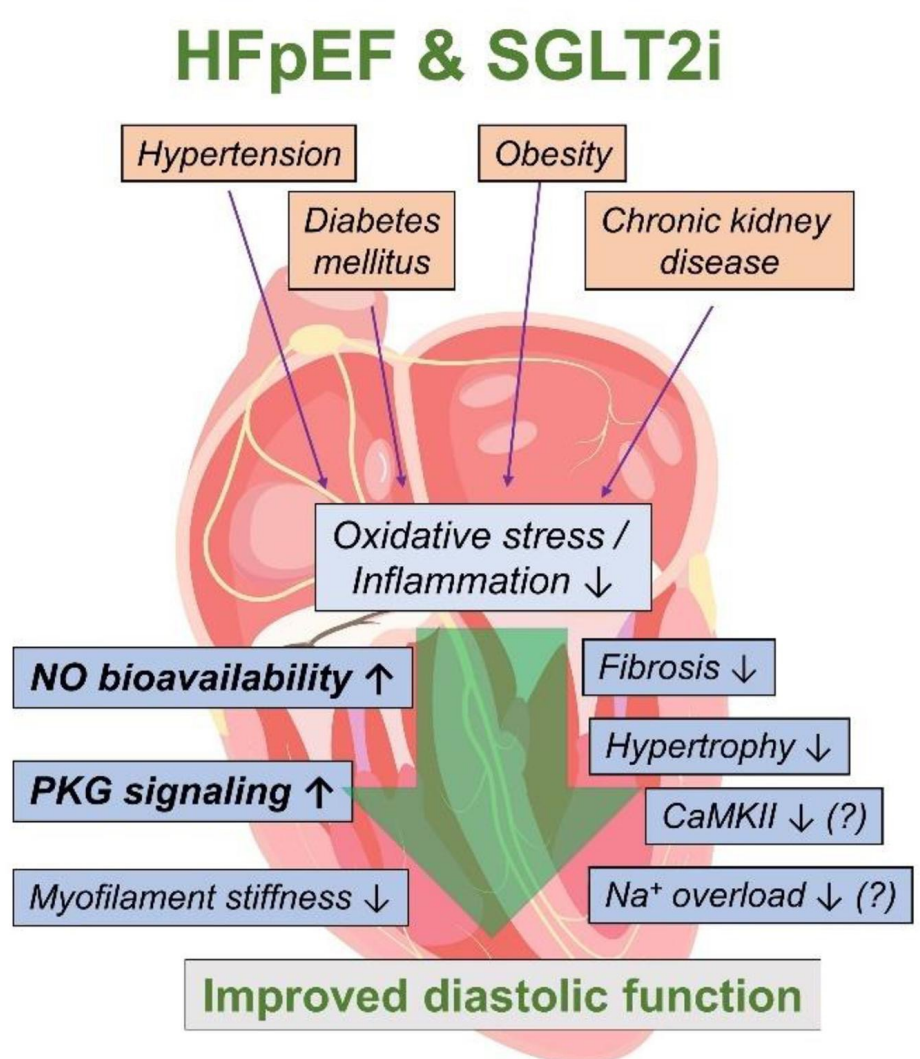
Conclusion: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.

Packer M, Anker SD, Butler J, et al., for the EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020;Aug 29:[Epub ahead of print].

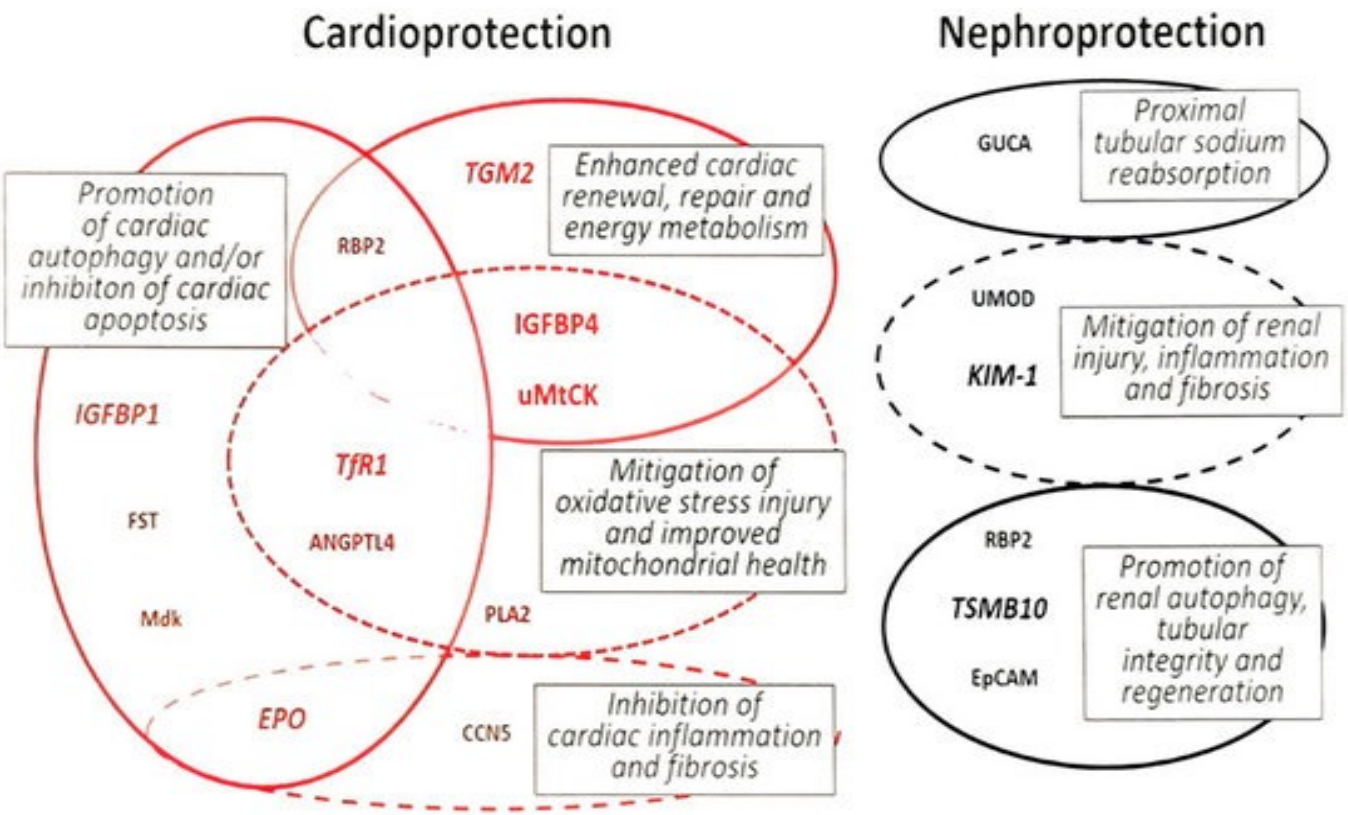
Ce que nous avons appris

Comment ça marche ?





Comment ça marche ?



Ce que nous avons appris

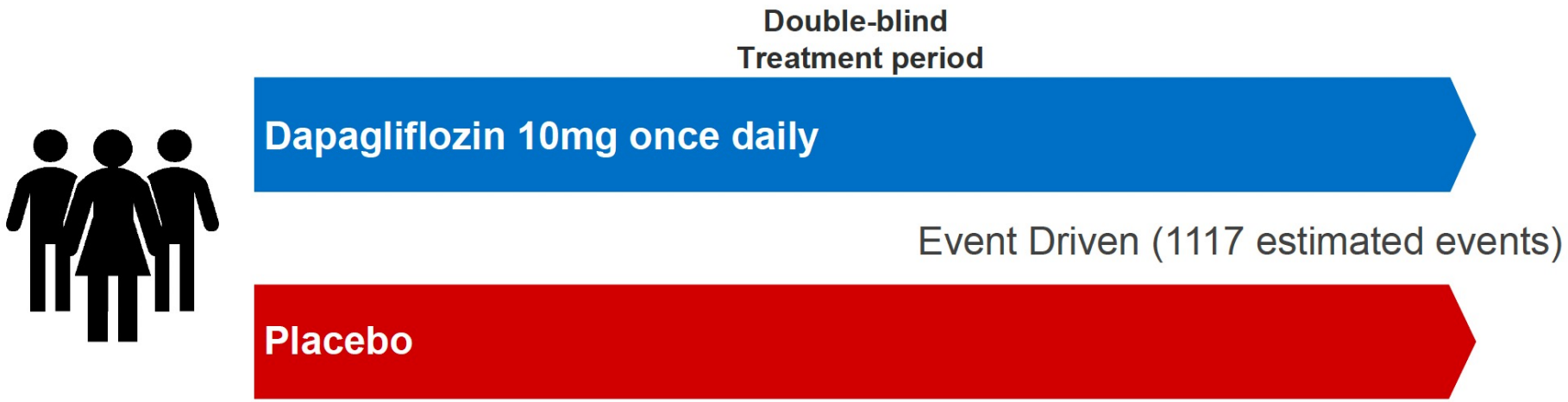
DELIVER Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure and mildly reduced or preserved ejection fraction

DELIVER

Eligibility Criteria

- Age ≥ 40 years
- NYHA class II-IV
- LVEF > 40% (including prior LVEF ≤ 40%)
- Structural Heart Disease (LVH or LA Enlargement)
- Elevated Natriuretic Peptides (> 300 pg/ml or 600 pg/ml in AFF)
- Either Ambulatory or Hospitalized for Heart Failure



Solomon et al. Eur J Heart Fail 2021

Endpoints and Analysis Plan

Dual Primary Endpoints – Full Population and Patients with LVEF < 60%

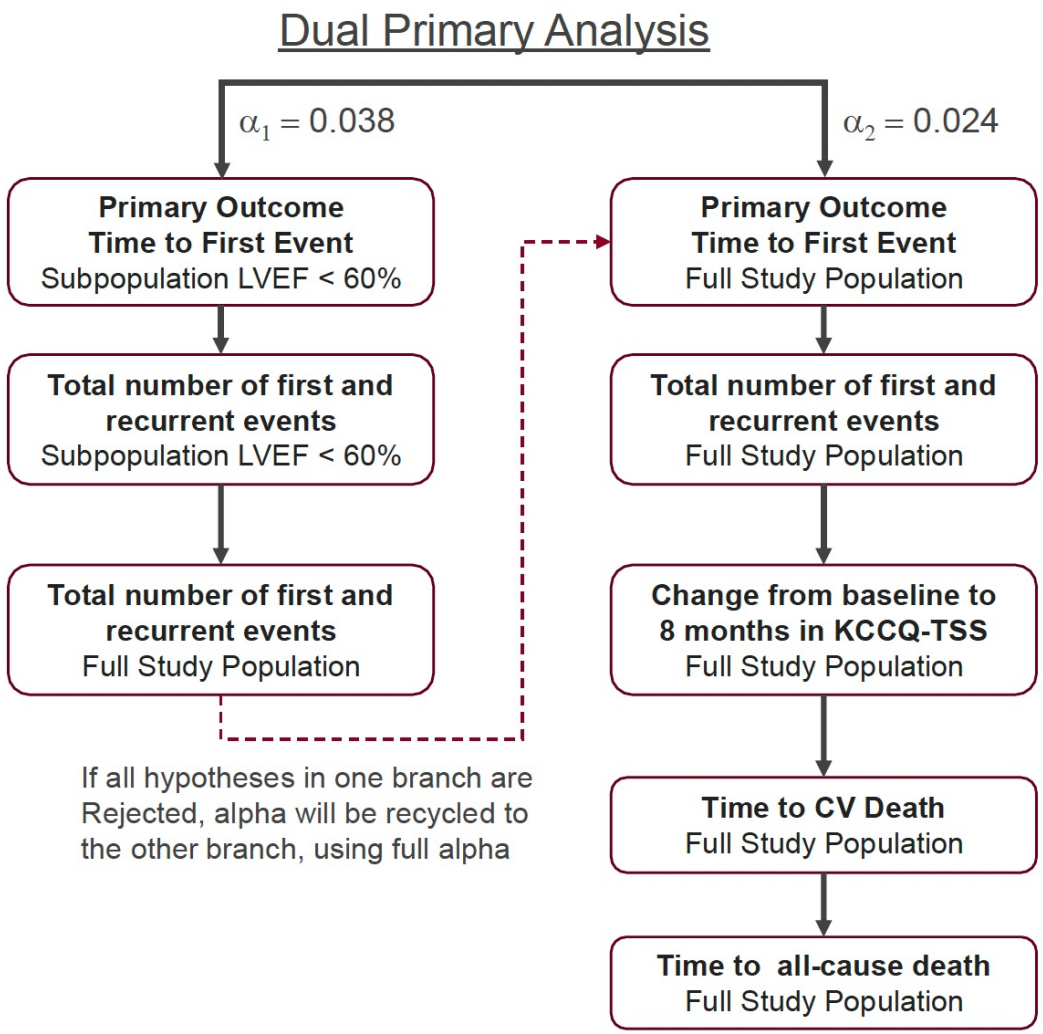
Primary Endpoint

Time to first Composite of

- CV death or
- Worsening Heart Failure (HF Hospitalization or Urgent HF Visit)

Secondary Endpoints

- Total HF Events + CV Death (both populations)
- Change in KCCQ TSS at 8 months (full)
- CV Death (full)
- All-Cause Death (full)



DELIVER Baseline Characteristics

Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132
Age (years)	71.8 ± 9.6	71.5 ± 9.5
Female Sex	43.6%	44.2%
Baseline LVEF (%)	54.0 ± 8.6	54.3 ± 8.9
LVEF < 60%	70.3%	69.3%
HF with Improved EF (Prior LVEF ≤ 40%)	18.3%	18.5%
Race		
White	70.7%	71.0%
Black	2.6%	2.5%
Asian	20.1%	20.6%
Other	6.6%	5.9%
Geographic Region		
Europe and Saudi Arabia	47.7%	48.2%
Asia	19.4%	19.8%
Latin America	19.2%	18.5%
North America	13.7%	13.5%
NYHA Class at Baseline		
II	73.9%	76.6%
III/IV	26.1%	23.4%
KCCQ Total Symptom Score	70 ± 23	70 ± 22

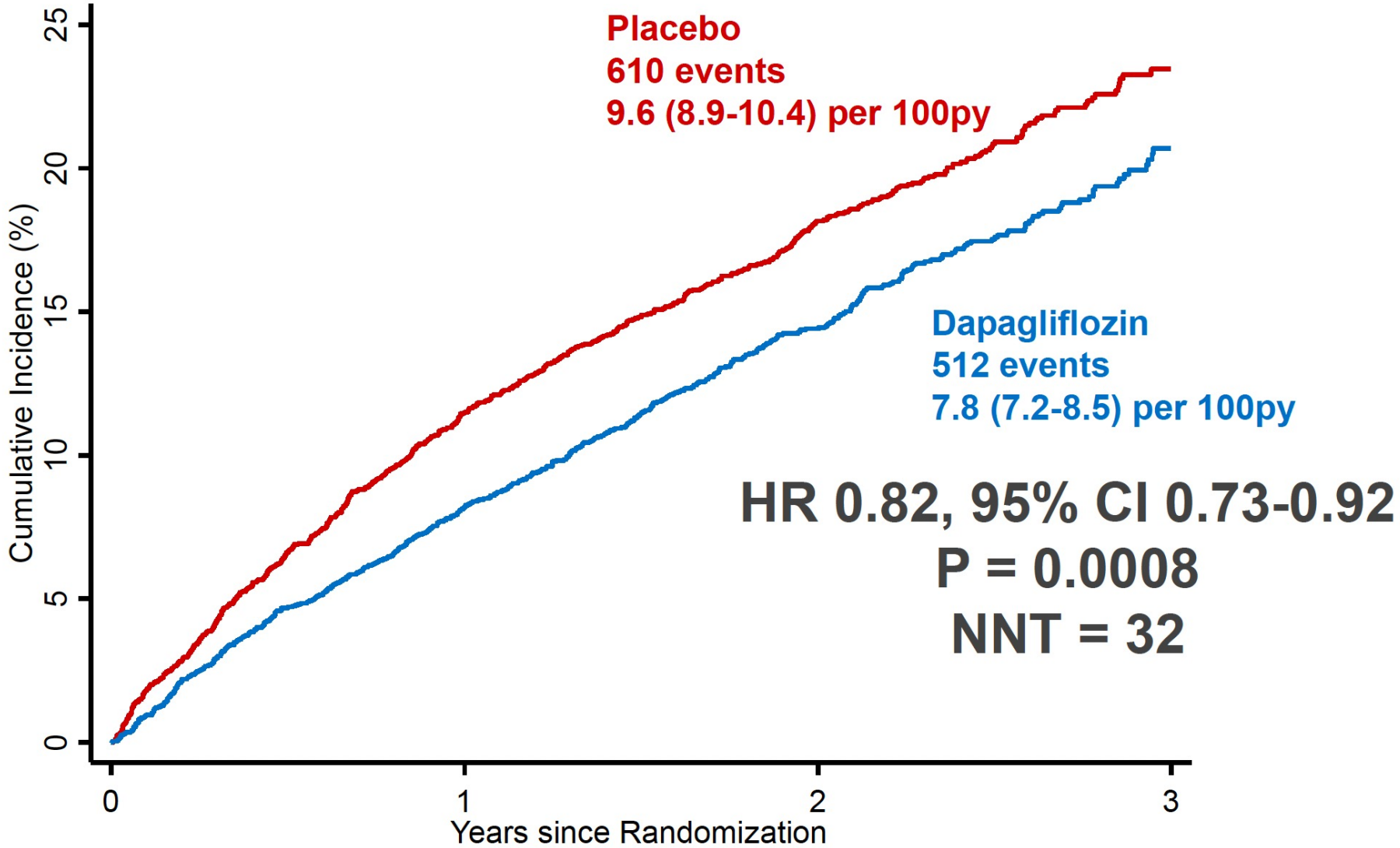
DELIVER Baseline Characteristics (2)

Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132
NT-proBNP when no AFF (ECG) (pg/ml)	729 [472, 1299]	704 [467, 1265]
NT-proBNP in AFF (ECG) (pg/ml)	1408 [956, 2256]	1387 [966, 2180]
Prior HF Hospitalization	40.6%	40.5%
Atrial Fibrillation/Flutter at Enrollment	42.4%	42.1%
Type 2 Diabetes	44.7%	44.9%
eGFR (mL/min/1.73m^2)	61.2 ± 19.0	60.9 ± 19.3
eGFR < 60 mL/min/1.73m^2	48.4%	49.6%
Medications		
Loop diuretics	76.7%	76.9%
Angiotensin converting enzyme inhibitors (ACEi)	36.5%	36.7%
Angiotensin receptor blocker (ARB)	36.2%	36.4%
Sacubitril-valsartan	5.3%	4.3%
β-blocker	82.8%	82.5%
Mineralocorticoid receptor antagonist (MRA)	42.8%	42.4%

Primary Endpoint: CV Death or Worsening HF

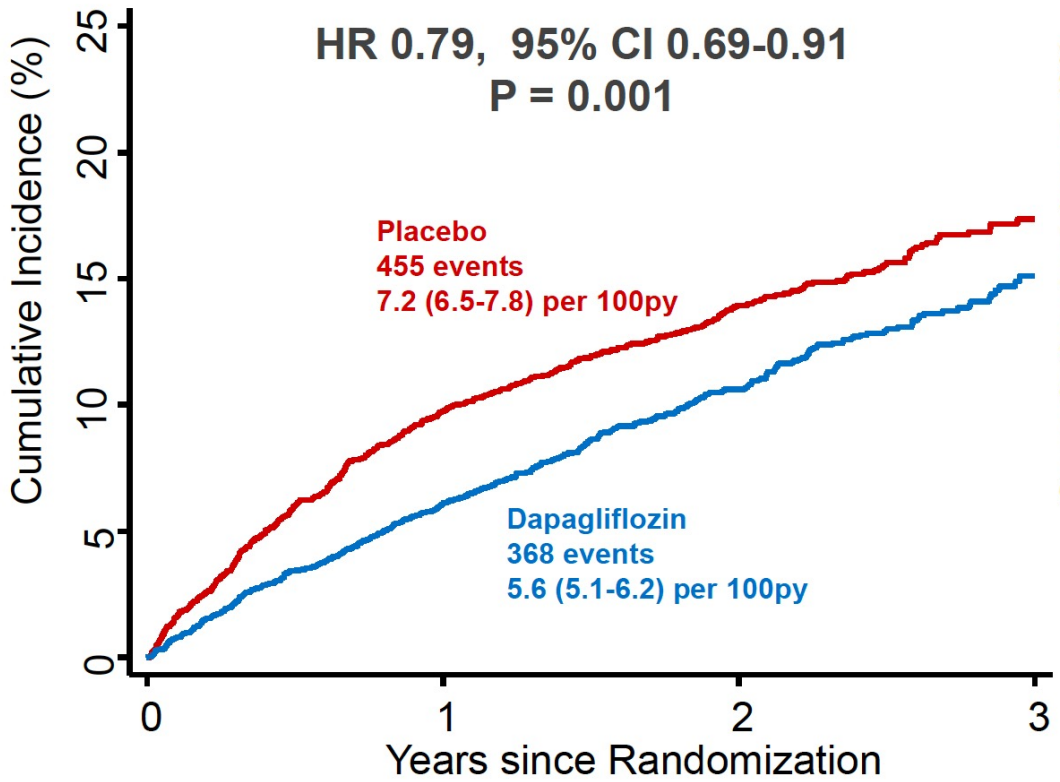
Full Population



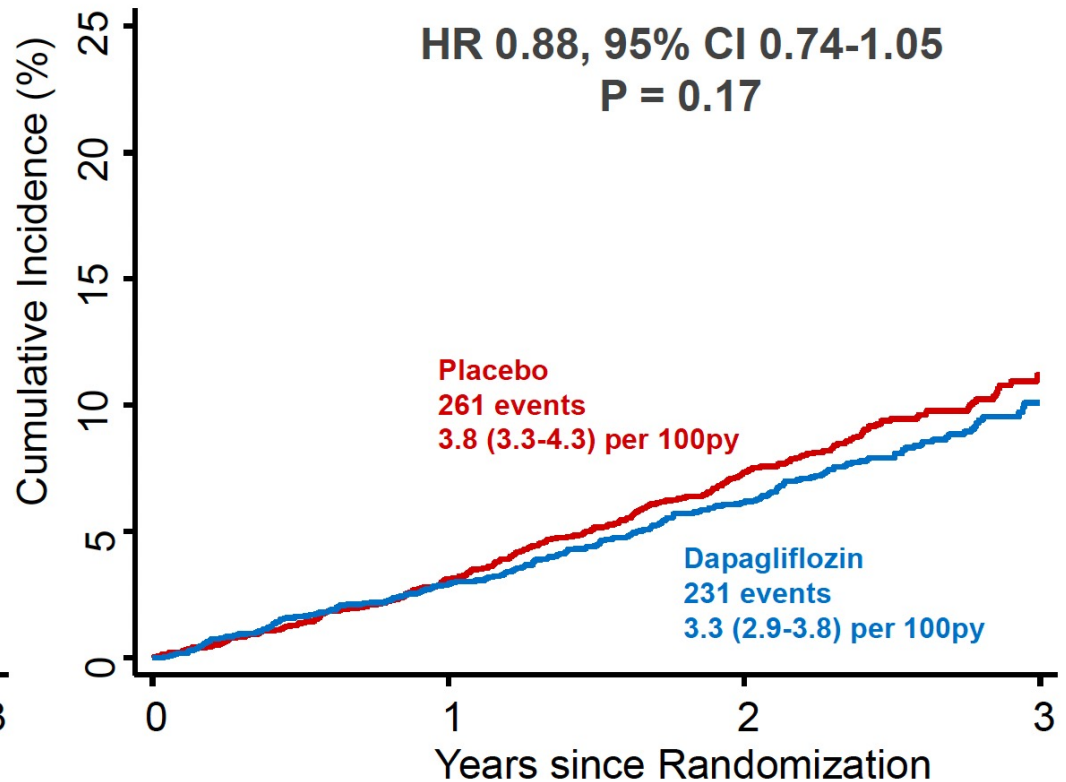
Components of Primary Endpoint

Full Population

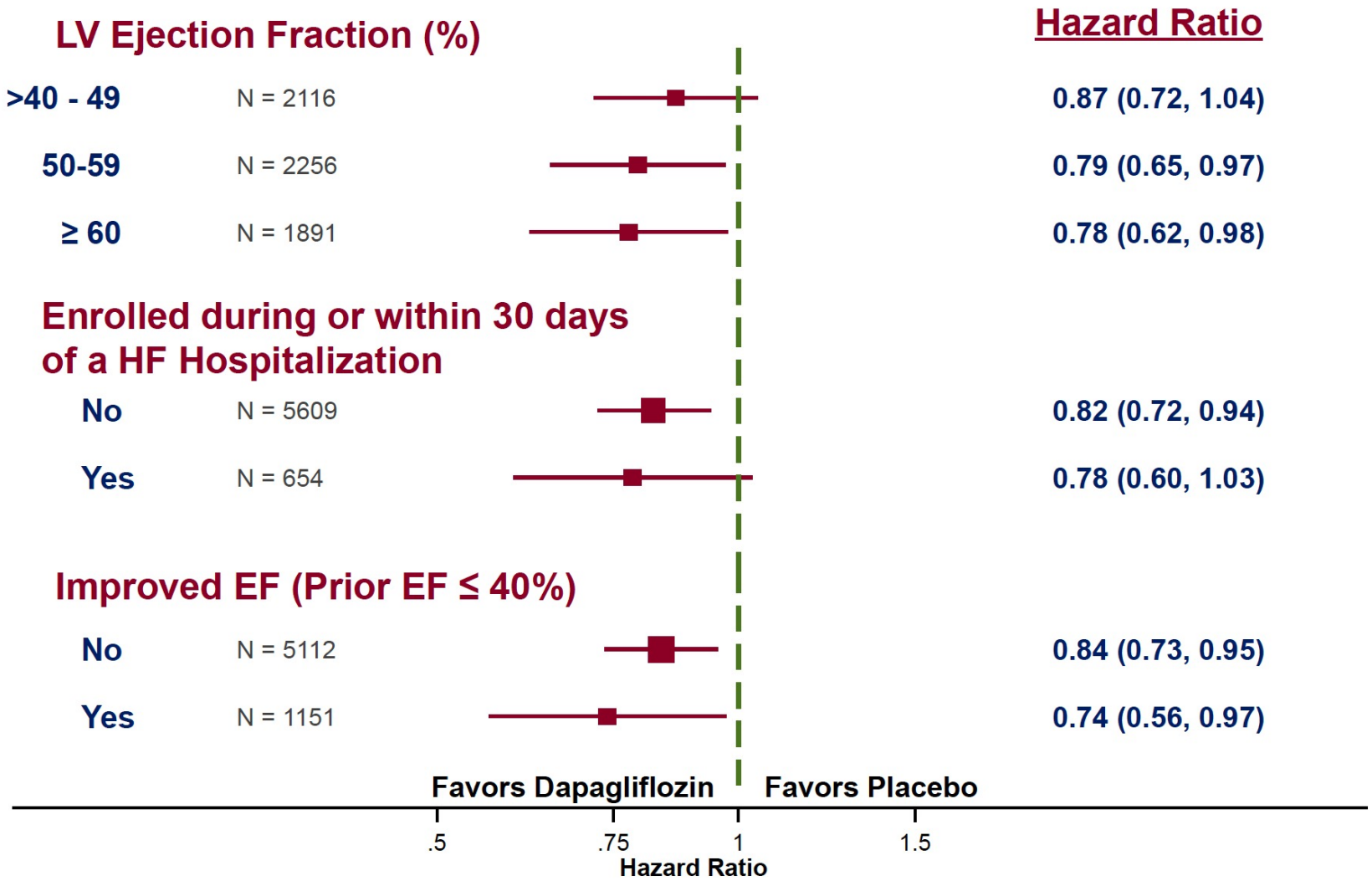
Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



Cardiovascular Death



Primary Endpoint in Prespecified Subgroups



60% is the new 40% or not ….

Peu importe la FE …

Adverse Events*

AE data collection of Serious Adverse Events, Adverse Events leading to treatment discontinuation and other selected adverse events

	Dapagliflozin* n=3126	Placebo* n=3127
Any SAE (including death)	1361 (43.5%)	1423 (45.5%)
Any AE leading to treatment discontinuation	182 (5.8%)	181 (5.8%)
Any AE leading to treatment interruption	436 (13.9%)	494 (15.8%)
Any amputation	19 (0.6%)	25 (0.8%)
Any definite or probable diabetic ketoacidosis	2 (0.1%)	0 (0.0%)
Any major hypoglycemic event	6 (0.2%)	7 (0.2%)
Events related to volume depletion	42 (1.3%)	32 (1.0%)
Renal Events	73 (2.3%)	79 (2.5%)

*On treatment (in patients receiving at least one dose and up to 30 days following last dose of IP)

Pooled analysis of DAPA-HF and DELIVER

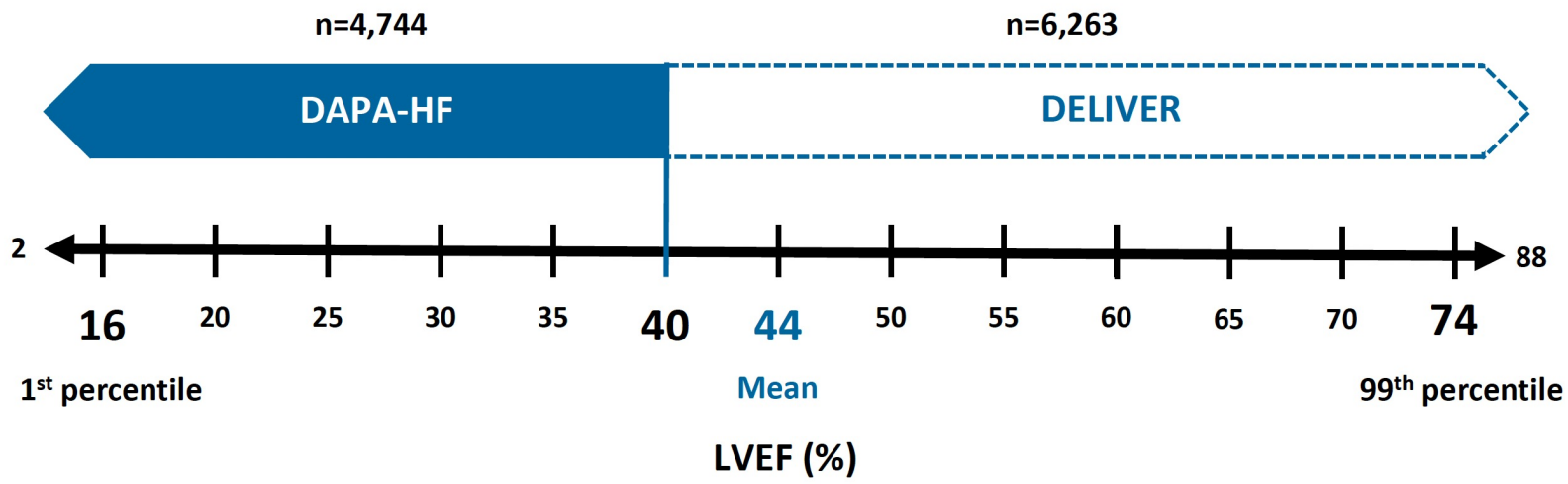
Pardeep S Jhund
BHF Glasgow Cardiovascular Research Centre, University of Glasgow
& Queen Elizabeth University Hospital, Glasgow

DAPA-HF and DELIVER pooled dataset

Dapagliflozin 10mg once daily vs placebo

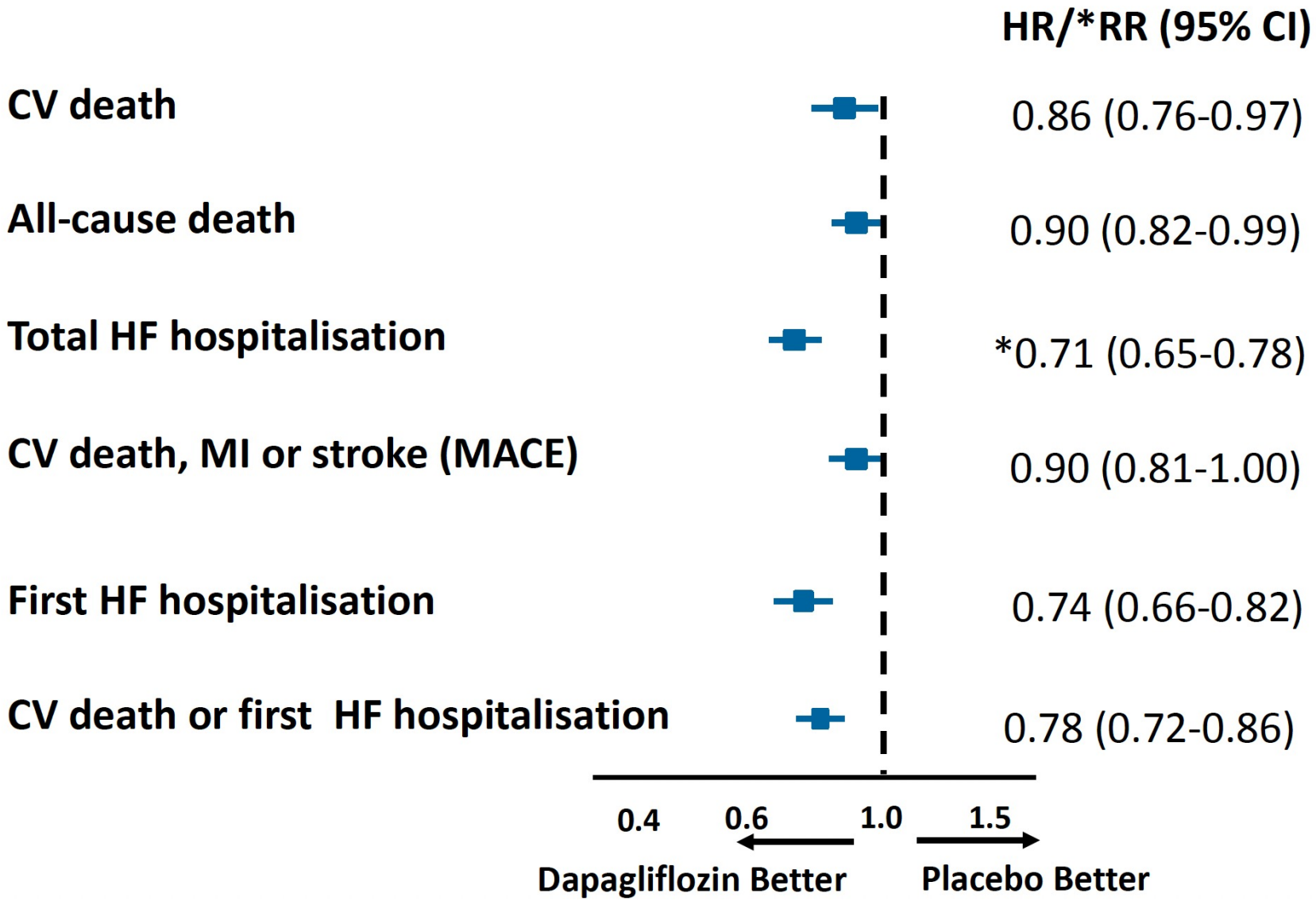
Median follow-up = 22 (IQR 17-30) months

Pooled dataset n=11,007

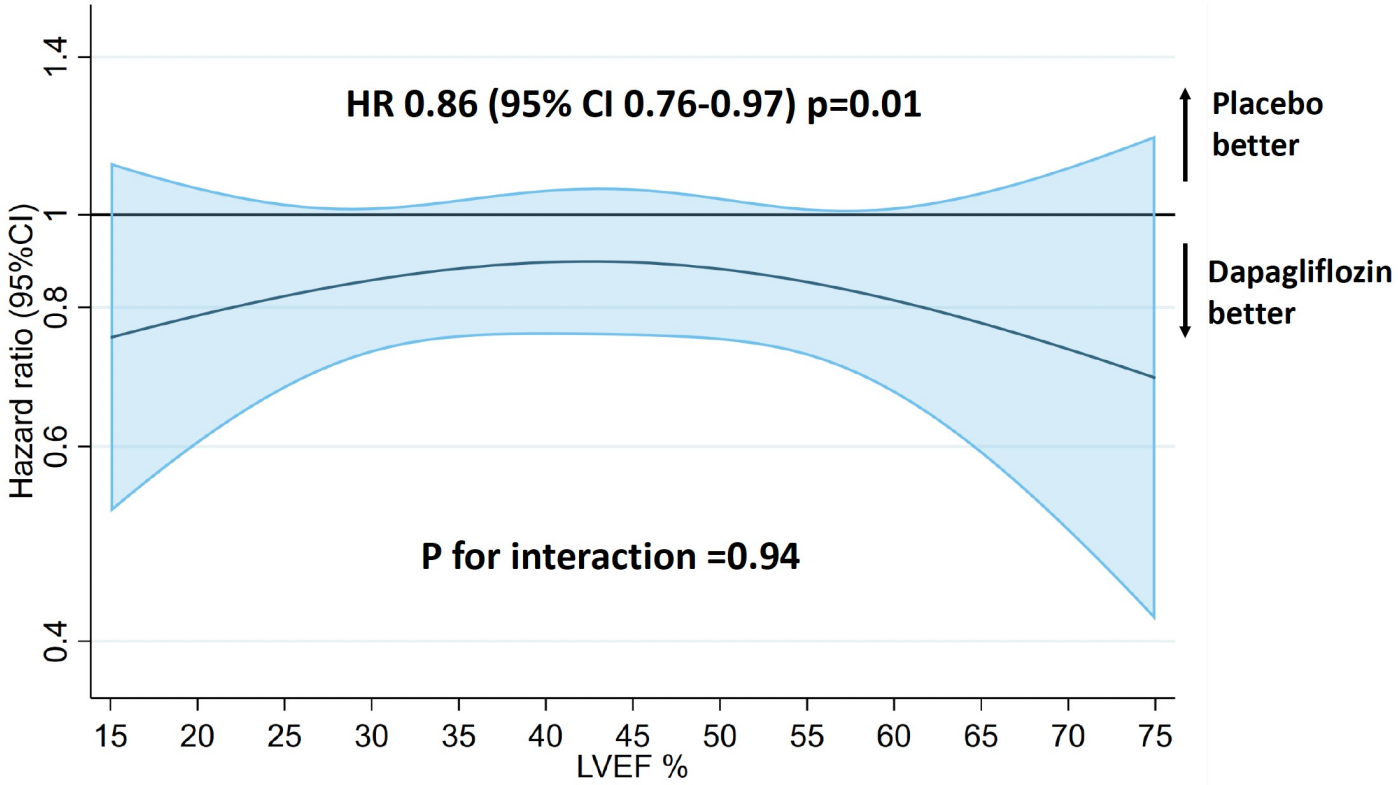


McMurray JJV et al Eur J Heart Fail. 2019;21:665-675 and Solomon SD et al Eur J Heart Fail 2021;23:1217-1225

DAPA-HF & DELIVER pooled: Outcome hierarchy



DAPA-HF & DELIVER pooled: Cardiovascular death



Ce que nous devrions faire

EMPEROR-Preserved trial #ESCCongress

Effect of empagliflozin on CV death and heart failure hospitalisations in patients with heart failure with a preserved ejection fraction, with and without diabetes

Conclusion

Empagliflozin reduces the risk of a composite of CV death or hospitalisation for heart failure (HF) in patients with HF and a preserved ejection fraction (HFpEF) with or without diabetes.

Background

The EMPEROR-Reduced trial previously showed that the SGLT2 inhibitor empagliflozin reduced the risk of CV death or hospitalisation for HF in patients with HF and a reduced ejection fraction.

Study objectives

EMPEROR-Preserved evaluated the effects of SGLT2 inhibition in HFpEF patients with and without diabetes.

Who and what?

622 centres · 23 countries

5,988

symptomatic HFpEF patients
(left ventricular ejection fracion >40%)

randomised 1:1

Empagliflozin · Placebo

On top of all appropriate treatments
for HFpEF and co-morbidities

Primary endpoint

Median follow-up ▸ 26 months

Composite of CV death or
hospitalisation for HF

Empagliflozin 13.8%

Placebo 17.1%

6.9 vs 8.7 events per 100 patient-years

HR: 0.79; 95% CI: 0.69–0.90; *p=0.0003*)

Secondary outcomes

Hospitalisations for HF
(including first and recurrent events)

Empagliflozin < Placebo

HR: 0.73; 95% CI: 0.61–0.88; *p<0.001*)

Rate of decline in glomerular filtration
rate (eGFR) during study treatment

-1.25 Empagliflozin

-2.62 Placebo

ml/min/1.73 m²/year

p<0.0001

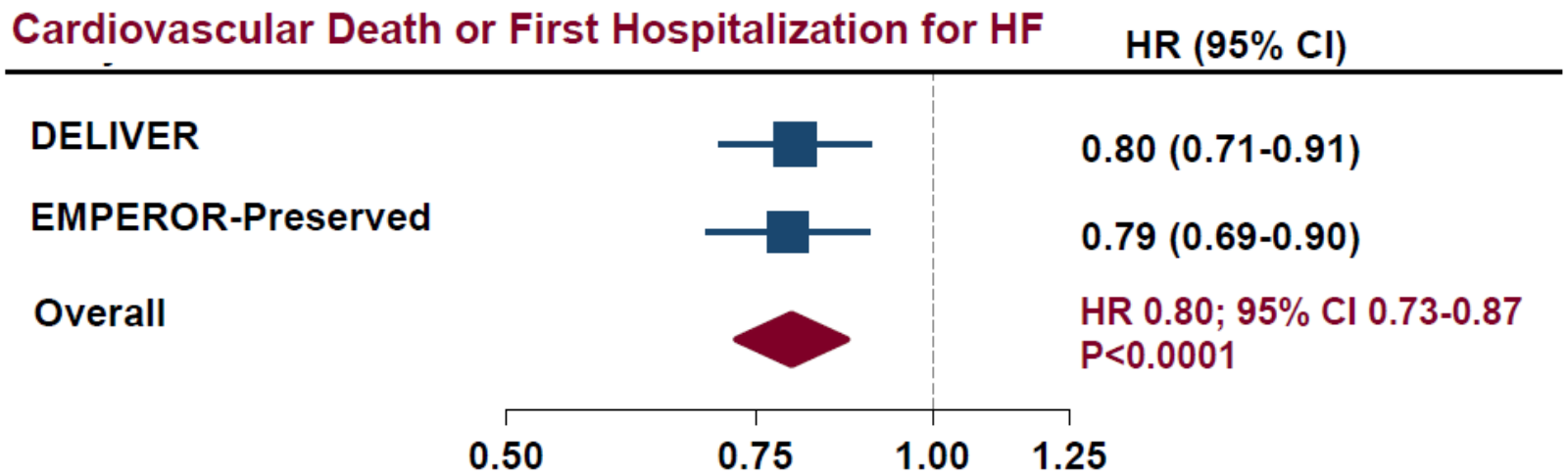
Serious adverse events

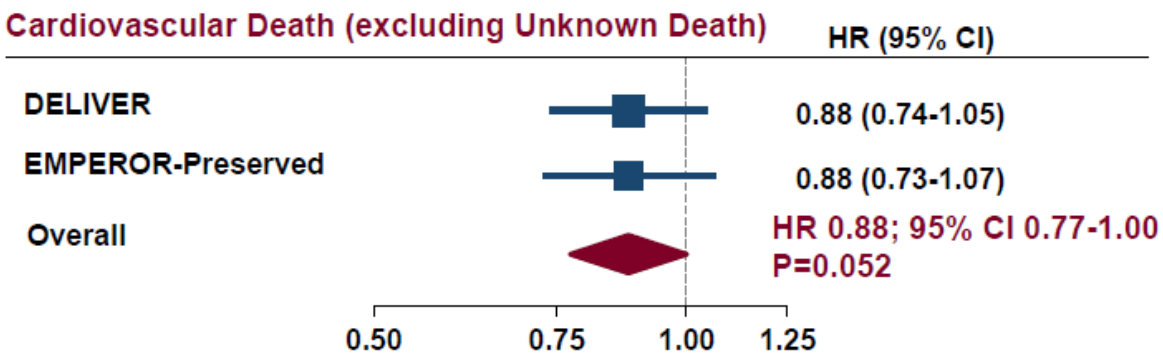
Empagliflozin 47.9%

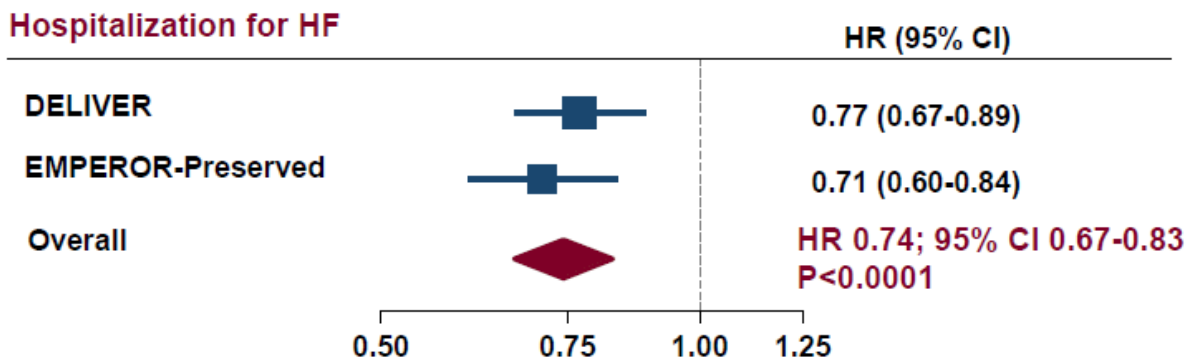
Placebo 51.6%

DELIVER and EMPEROR-Preserved Meta-Analysis:

↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components

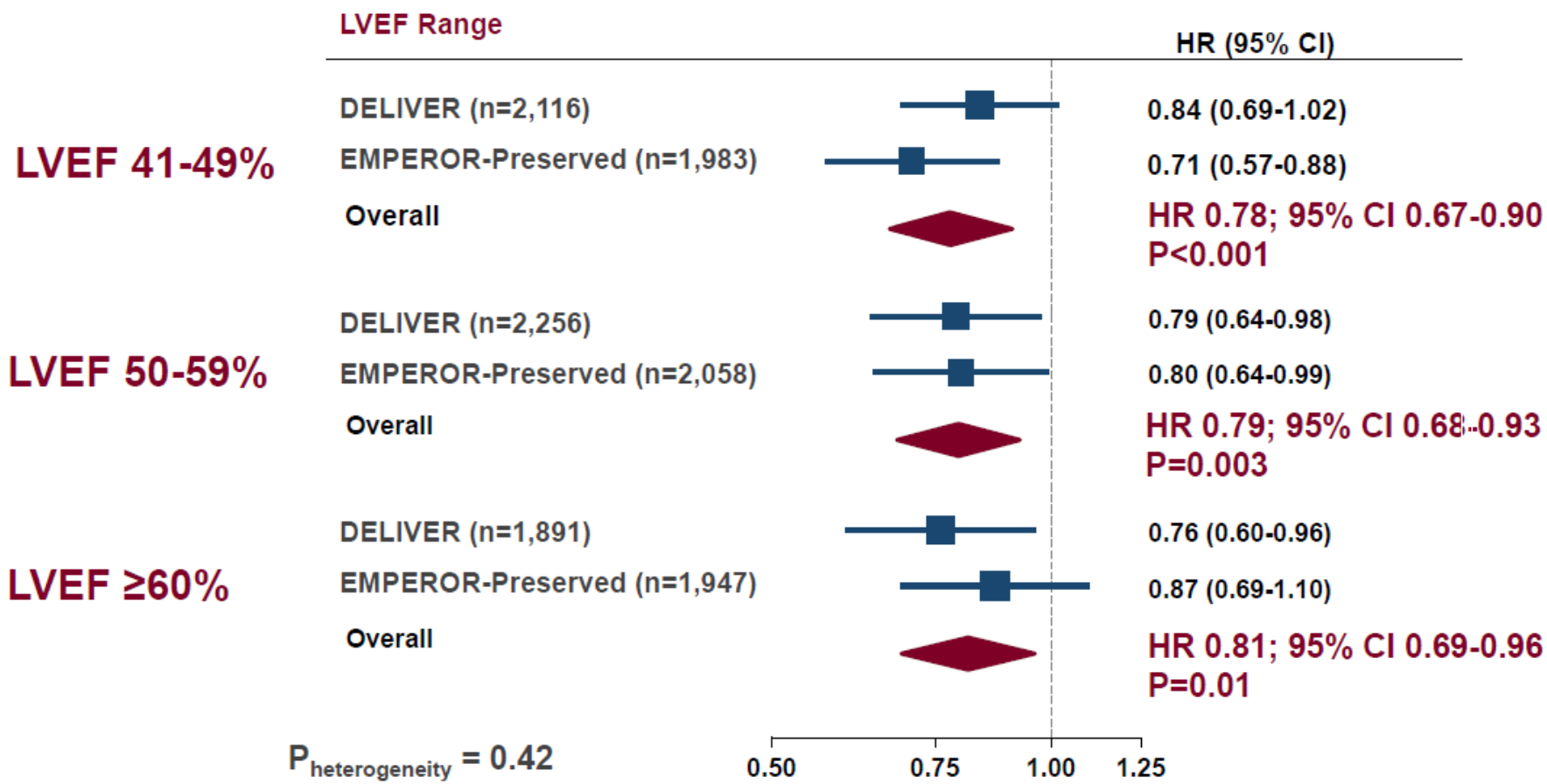






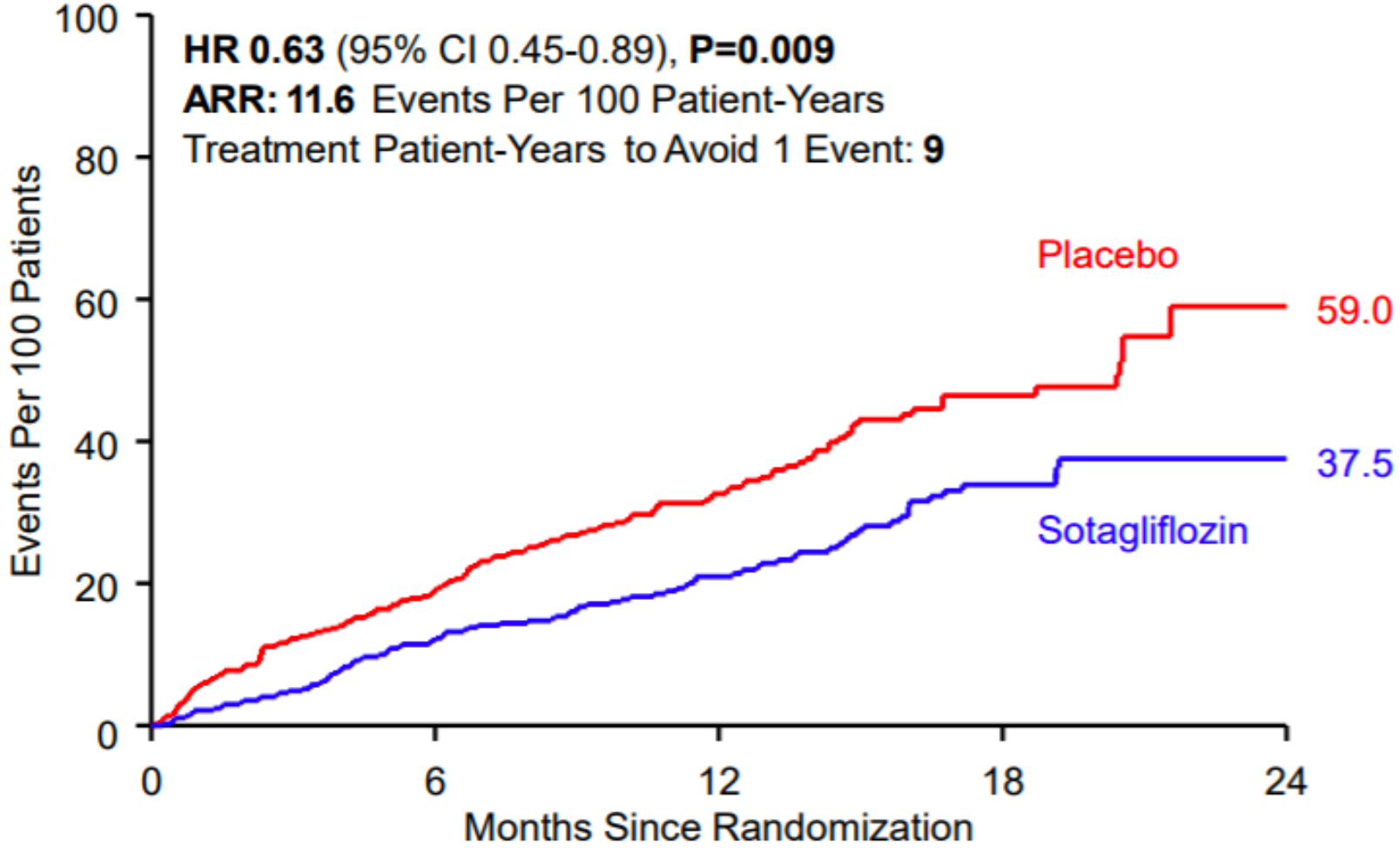
$P_{heterogeneity}$ >0.40 for all endpoints

DELIVER and EMPEROR-Preserved Meta-Analysis:
Consistent Reductions in Primary Endpoint across LVEF Range, including among LVEF ≥60%



Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 739 Patients with HFpEF (≥50%)

SOLOIST
SCORED



For this analysis, patients from SCORED needed to have a history of HF within 2 years.

Bhatt DL. ACC 2021, virtual.

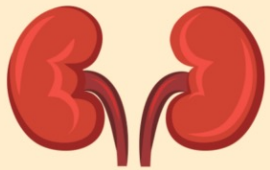
SOLOIST - WHF TRIAL

Bhatt DL et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-128.

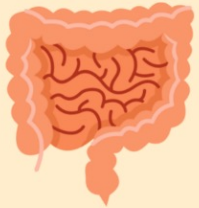
SOTAGLIFLOZIN

inhibits

SGLT-2 → increases urinary glucose excretion



SGLT-1 → delays intestinal glucose absorption



QUESTION

In patients with diabetes and recently worsening HF, does SOTAGLIFLOZIN:
↓ CV mortality?
↓ HF urgent visits?
↓ HF hospitalizations?

INCLUSION

18 - 85 yo patients with diabetes hospitalized for signs or symptoms of HF and treatment with IV diuretics

1222 patients

TOTAL NO. OF EVENTS (RATE PER 100 PATIENT YEARS)

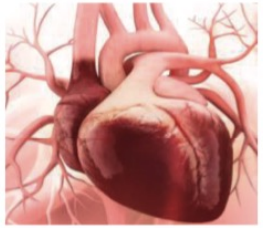
	PRIMARY OUTCOME: HF urgent visits + HF hospitalizations + CV Death	SECONDARY OUTCOME: HF urgent visits + HF hospitalizations	SECONDARY OUTCOME: CV Death
Sotagliflozin n=608	245 (51)	194 (40)	51 (11)
	HR 0.67 95% CI 0.52-0.85 p<0.001	HR 0.64 95% CI 0.49-0.83 p<0.001	HR 0.84 95% CI 0.58-1.22 p=0.36
Placebo n=614	355 (76)	297 (64)	58 (13)

CONCLUSION

In patients with diabetes with worsening HF, sotagliflozin significantly decreased CV deaths, HF urgent visits, and HF hospitalizations

Created by @TDonisan | @CardioNerdsJC

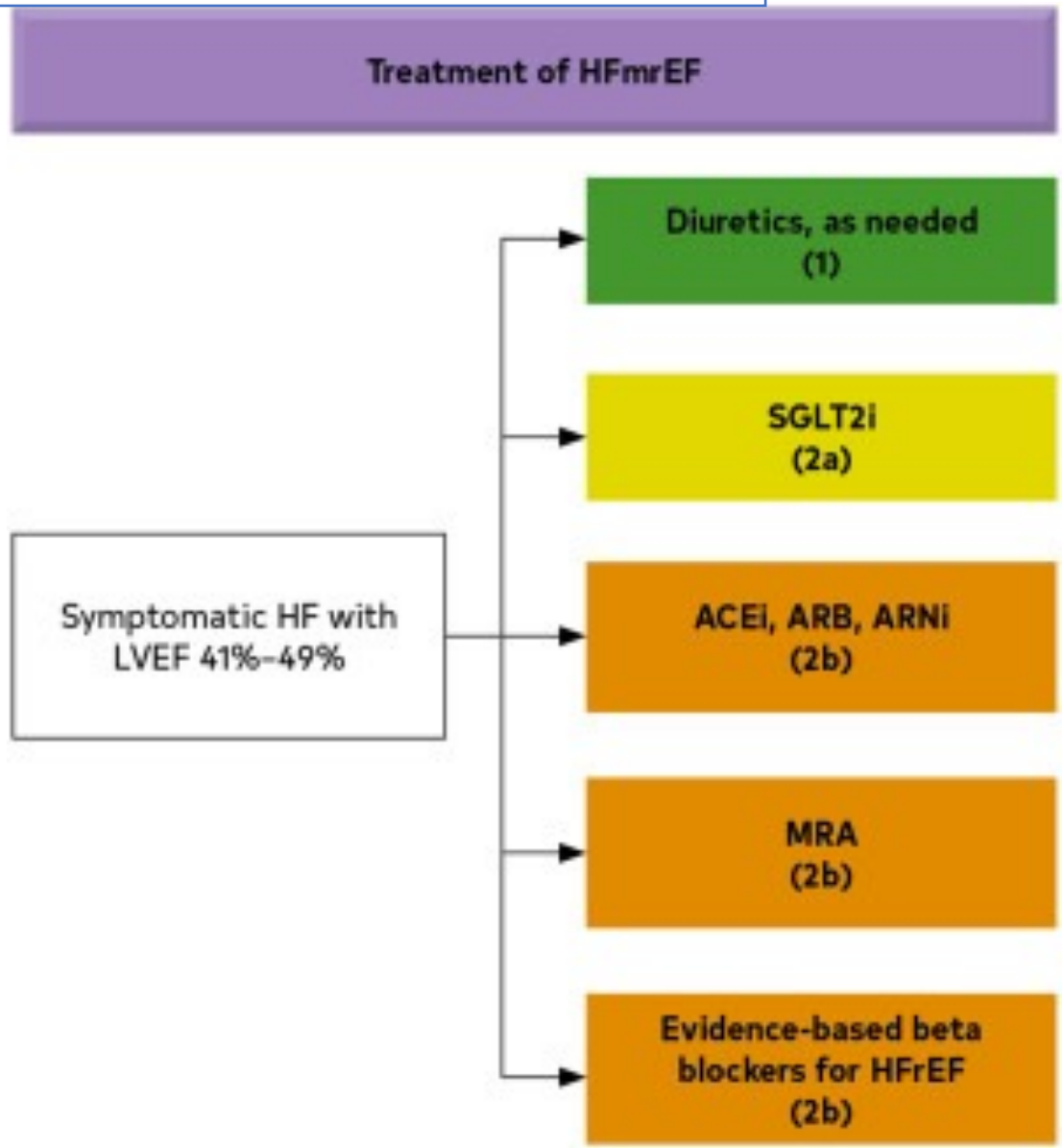
Effets des iSGLT2 sur l'insuffisance cardiaque

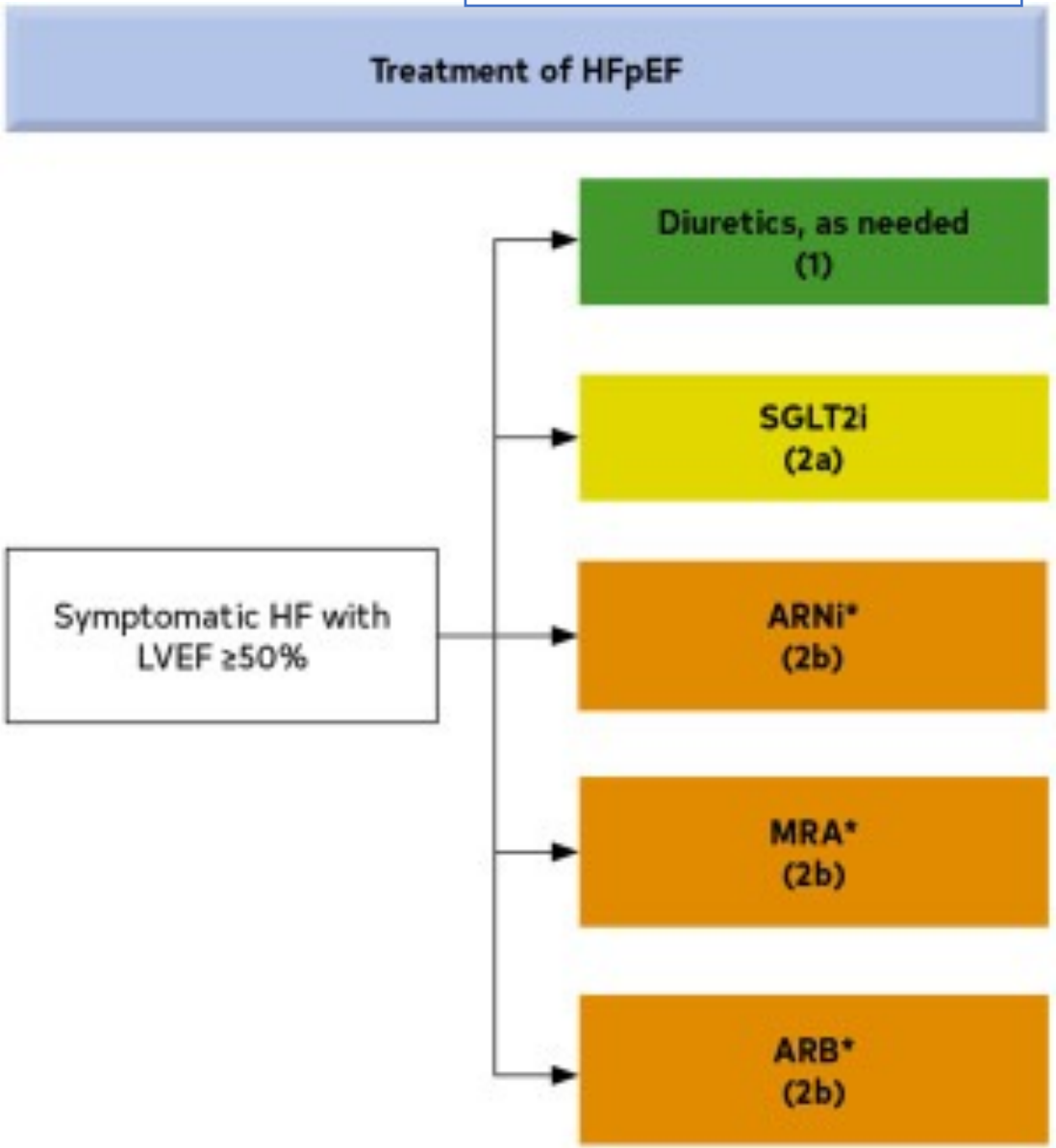


	FEVG	Décès CV	hIC	Décès CV + hIC	Mortalité globale
DAPA-HF	< 50 %	**0,82** (0,69-0,98)	**0,70** (0,59-0,83)	**0,75** (0,65-0,85)	**0,83** (0,71-0,97)
EMPEROR-REDUCED	< 50 %	**0,92** (0,75-1,12)	**0,69** (0,59-0,81)	**0,75** (0,65-0,86)	**0,92** (0,77-1,10)
EMPEROR-PRESERVED	> 40 %	**0,91** (0,76-1,09)	**0,71** (0,60-0,83)	**0,79** (0,69-0,90)	**1,00** (0,87-1,15)
DELIVER	> 40 %	ND	ND	Significatif (*)	ND

Qui ? Tout patient IC, quelque soit sa FE.

Quand ? Dès le diagnostic.





2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Conclusions

Les iSGLT2 ont vu leurs indications s'élargir dans les recommandations internationales au vu des résultats favorables des essais cliniques

Ils avaient déjà montré une réduction d'environ 30 % des hospitalisations pour insuffisance cardiaque (hIC) chez les patients diabétiques de type 2 à haut risque CV

Ils ont aussi montré une réduction des hIC et de la mortalité CV chez les patients (avec ou sans diabète) avec insuffisance cardiaque à fraction d'éjection réduite (ICFER)

Cet effet positif a été confirmé récemment chez des patients avec fraction d'éjection modérément altérée (ICFEI) ou préservée (ICFEP)

Ces effets favorables sont retrouvés quelle que soit la fonction rénale jusqu'à un débit de filtration glomérulaire de 25 à 30 ml/ min/1,73 m2