Optimisation de la prise en charge de l'insuffisance cardiaque

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Déclaration de liens d'intérêt

Au cours des quatre dernières années, **j'ai eu une affiliation ou des intérêts** (financiers ou de nature non-pécuniaire) avec la ou les société(s) suivante(s) :

Nom de la Société	Type d'affiliation	Période
ASTRAZENECA	expert	2019-22
PFIZER	expert	2019-22
BAYER	expert	2019-22
BOERINGHER	expert	2019-22

Mme GM 78 ans

- Hospitalisée pour fatigue, essoufflement, faiblesse des jambes

- ATCD :
  - ATL IVA en 2020, obésité (BMI à 28 kg/m²), I Rénale avec DFG 38 ml/min/m²
  - Dyslipidémie, HTA
- TTT : Sacubitril/Valsartan 24/26 mg, Bisoprolol 2,5 mg, Aspirine 75 Mg, Simvastatine 40 mg

- TA 95/60 mmHg, NYHA 3
- ECG rythme sinusal avec FC 65 BPM
- NTproBNP 1825 ng/ml
- ETT : FEVG 30%, OG dilatée

Cas fictif

Est-ce que vous introduisez un iSGLT2 ?

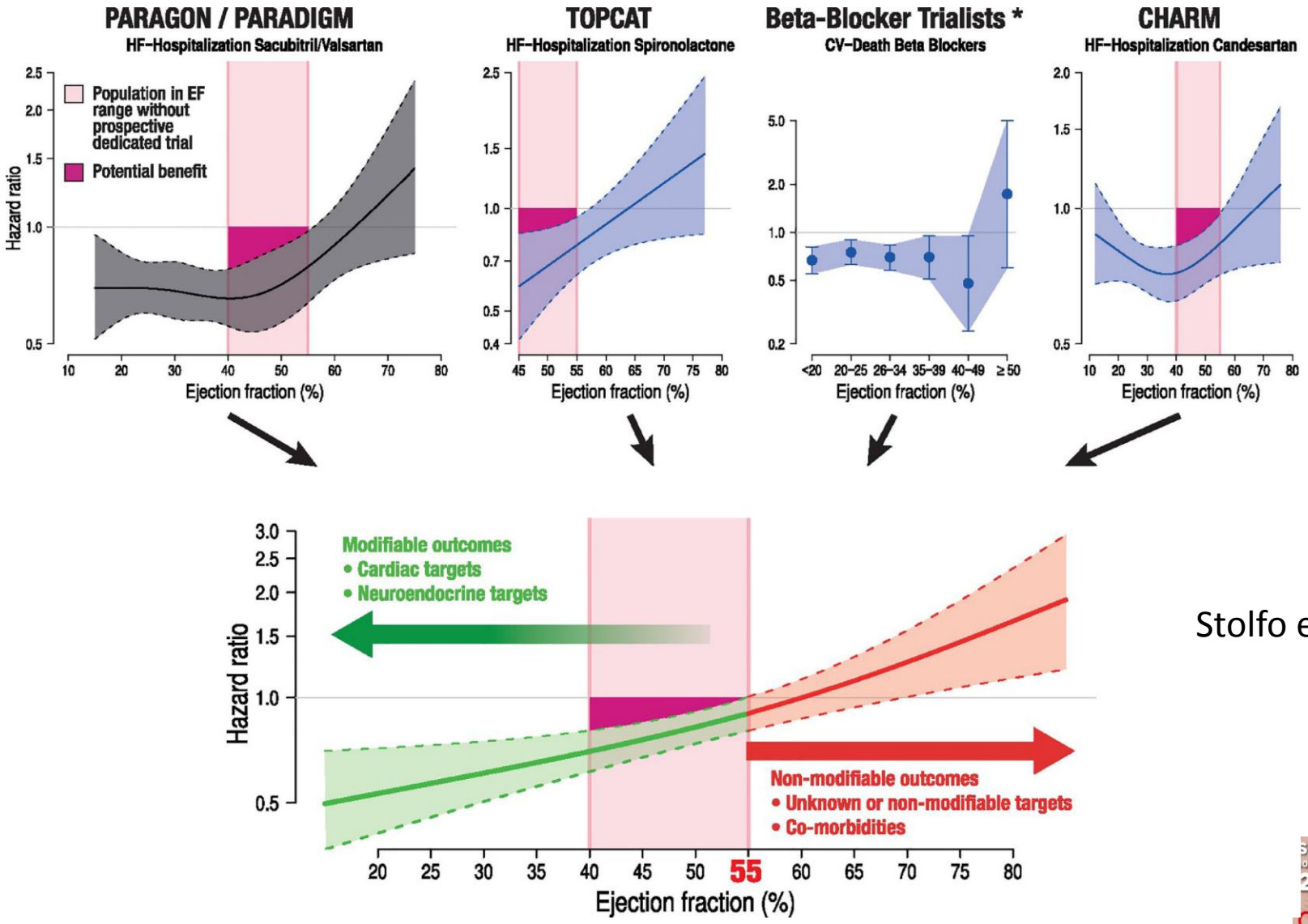
A- Oui

B- Oui après stabilisation des signes congestifs

C- Non, on attend une nouvelle évaluation FEVG

D- Non, on ajoute des MRA

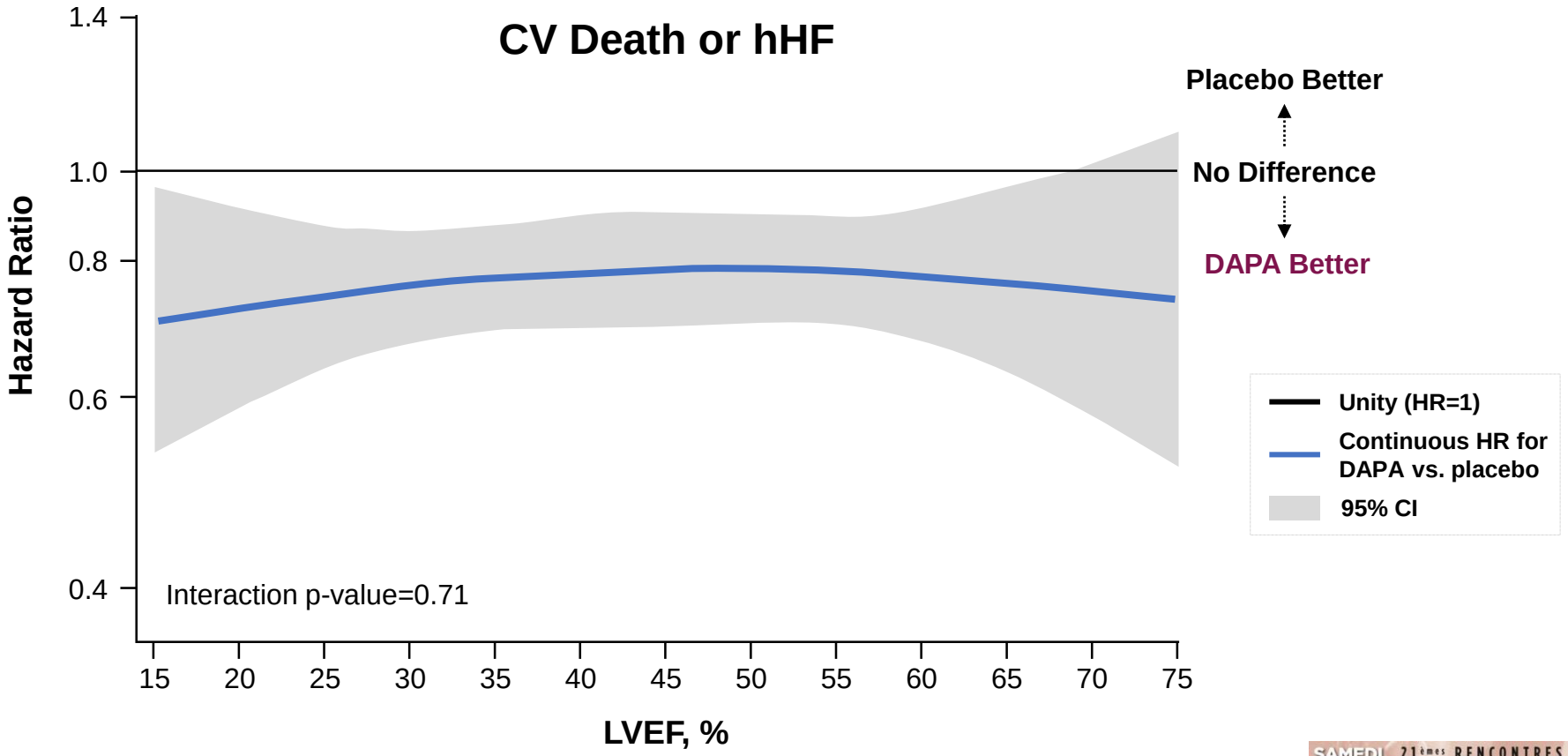
E- Je ne sais pas



Stolfo et al, EJIM 2022

Pooled DAPA-HF + DELIVER

DAPAHF — Pre-specified patient-level pooled analysis — DELIVER

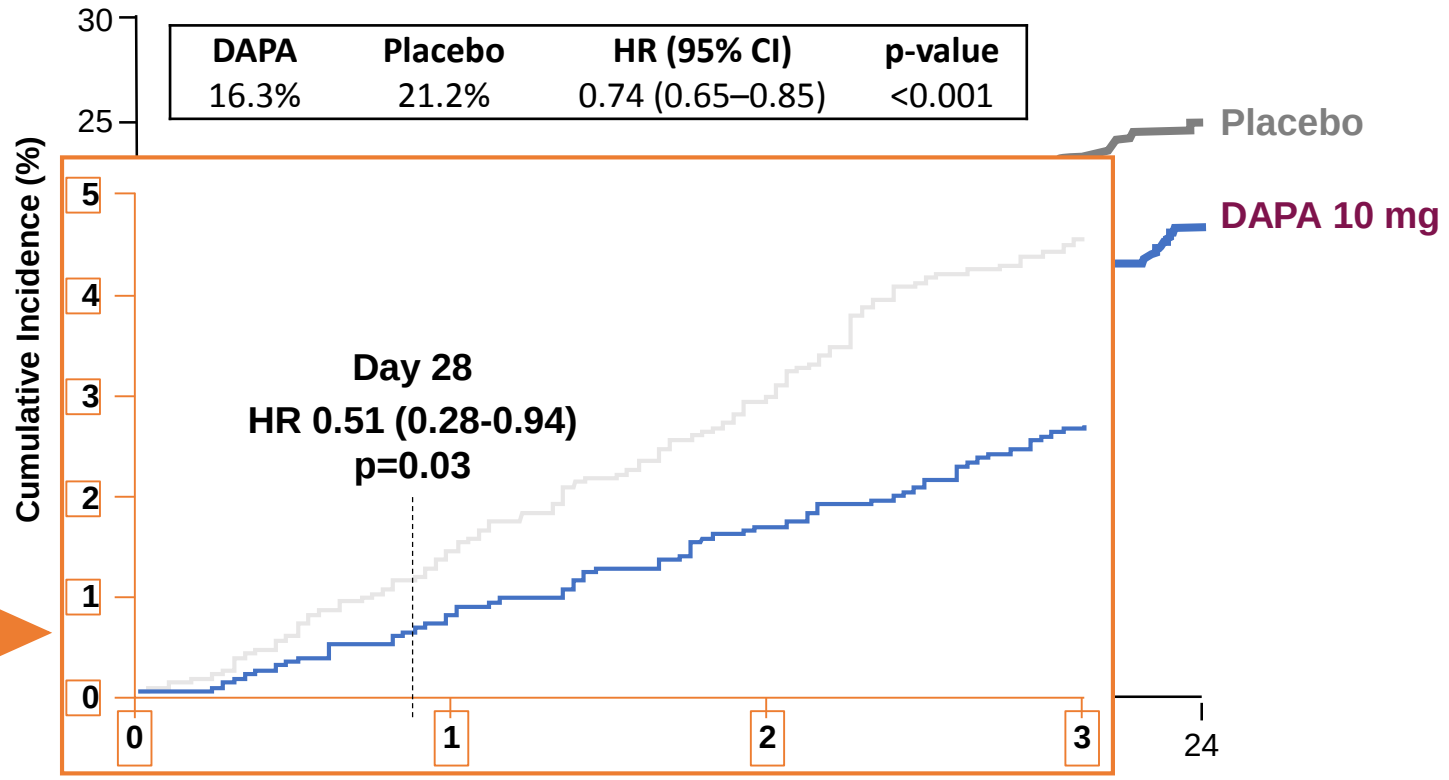


CV = cardiovascular; DAPA = dapagliflozin; hHF = heart failure hospitalization; HR= hazard ratio; LVEF = left ventricular ejection fraction.

Jhund PS et al. Online ahead of print. *Nat Med*. 2022.

Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

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



26% RRR

4.9% ARR

NNT=21

Statistically significant benefit seen as early as Day 28

Number at Risk

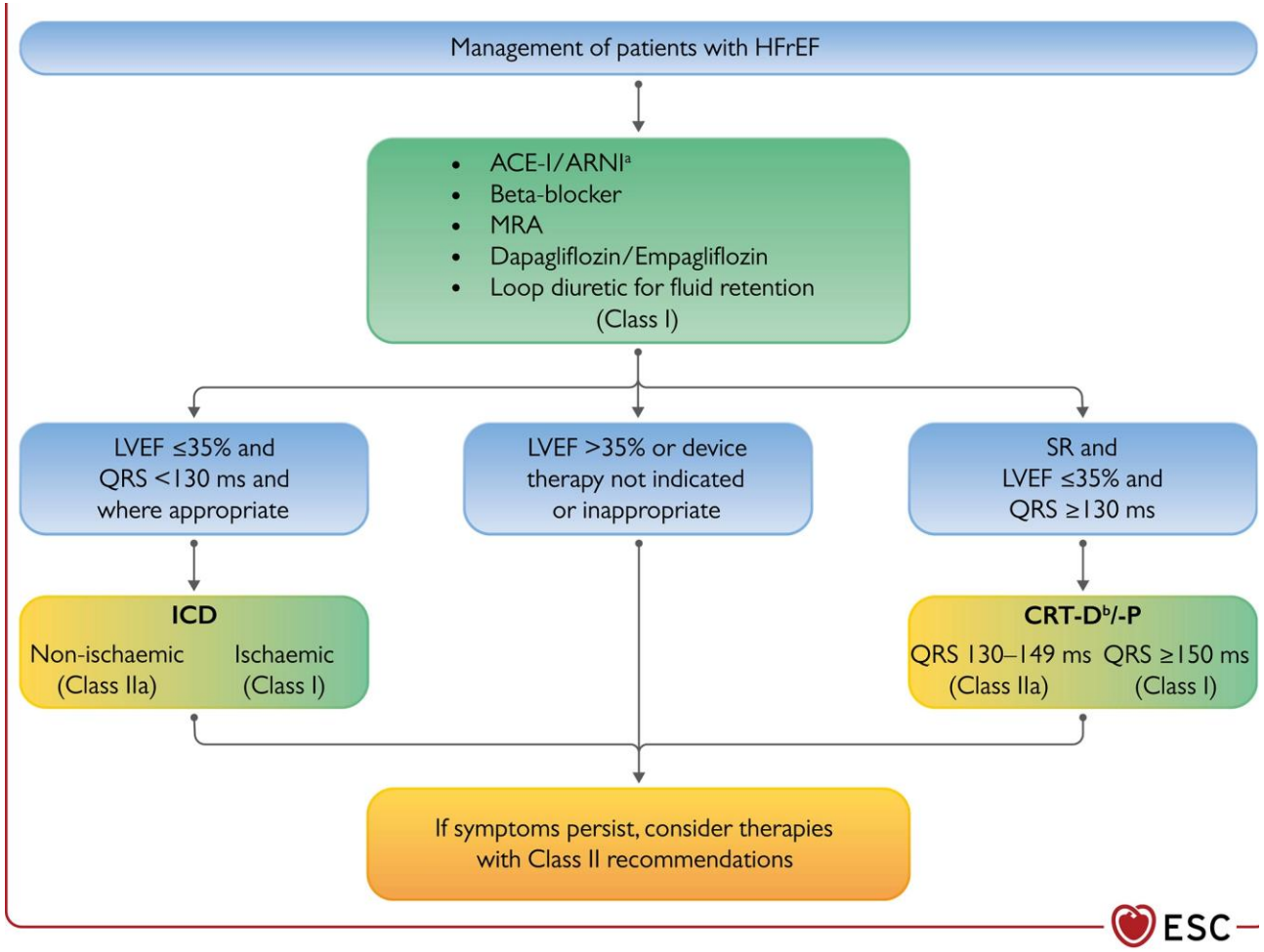
DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

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.

Peut-on initier le traitement rapidement ?

HFrEF



ACC/AHA

7.7. Preserved EF (HFpEF)

7.7.1. HF With Preserved Ejection Fraction

Recommendations for HF With Preserved Ejection Fraction* Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

*See Section 7.2, "Diuretics and Decongestion Strategies in Patients with HF," and Section 10.2, "Management of Atrial Fibrillation (AF) in HF" for recommendations for use of diuretics and management of AF in HF.

Sur quel éléments pouvez-vous argumenter l'intérêt d'instaurer <u>un iSGLT2</u> ?

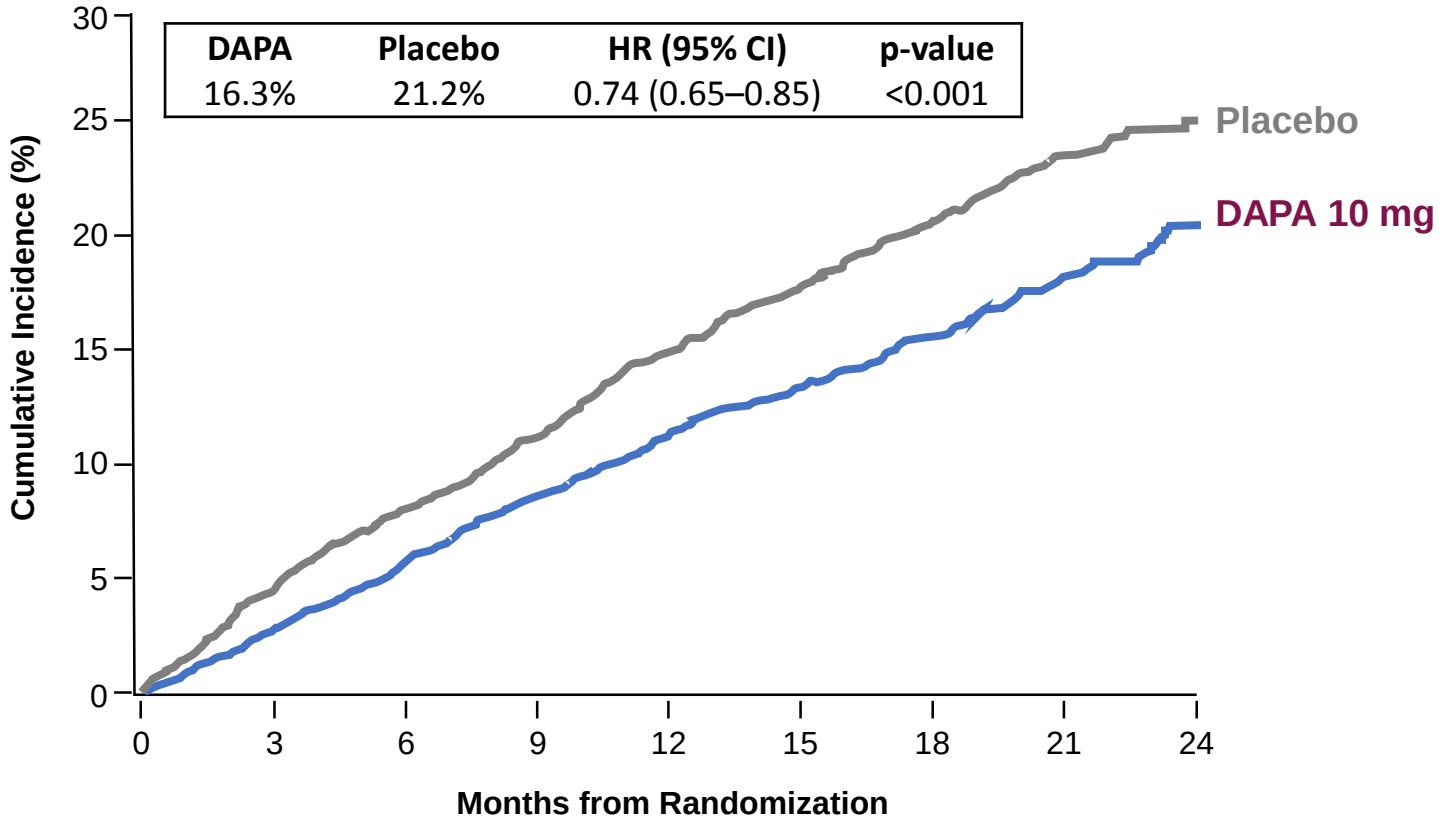
A- il diminue la mortalité

B- il diminue le risque d'hospitalisation

C- il améliore la qualité de vie

D- Il y a peu d'effet secondaires

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



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4.9% ARR

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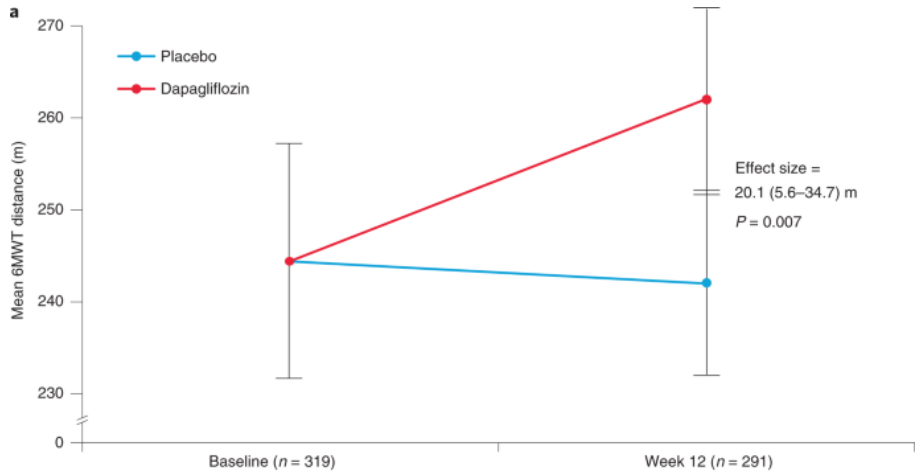
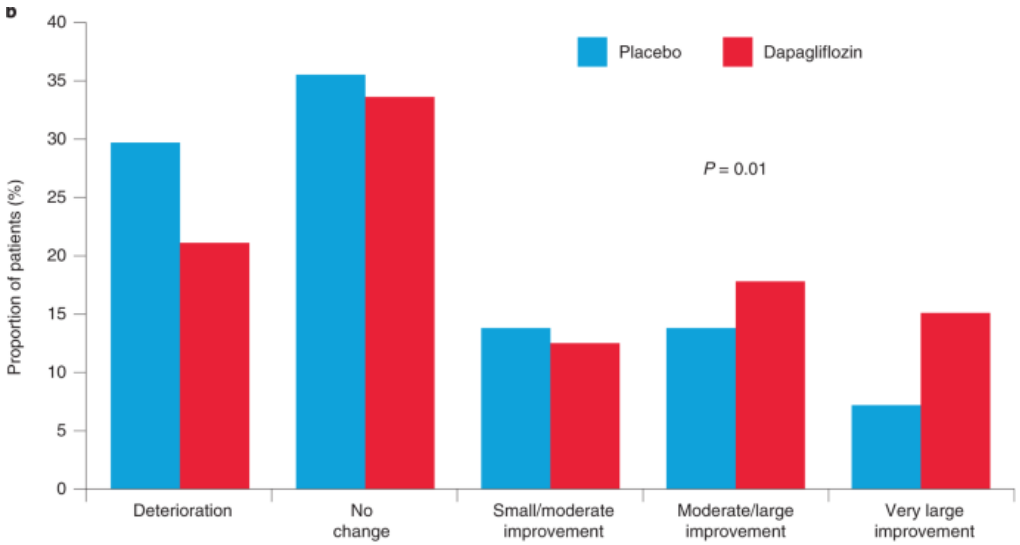
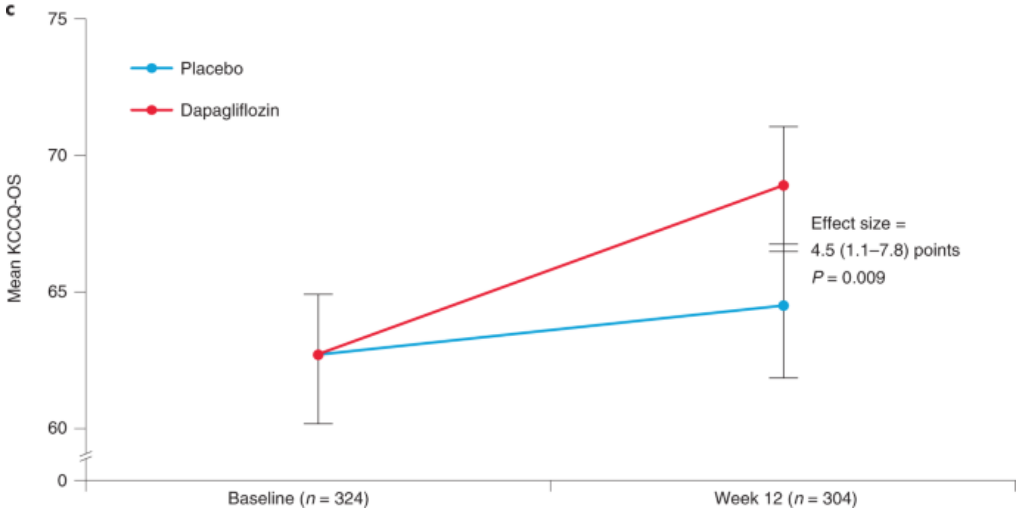
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

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.

Qualité de vie







Nassif et al. Nature medecine 2021. **27**, 1954–1960

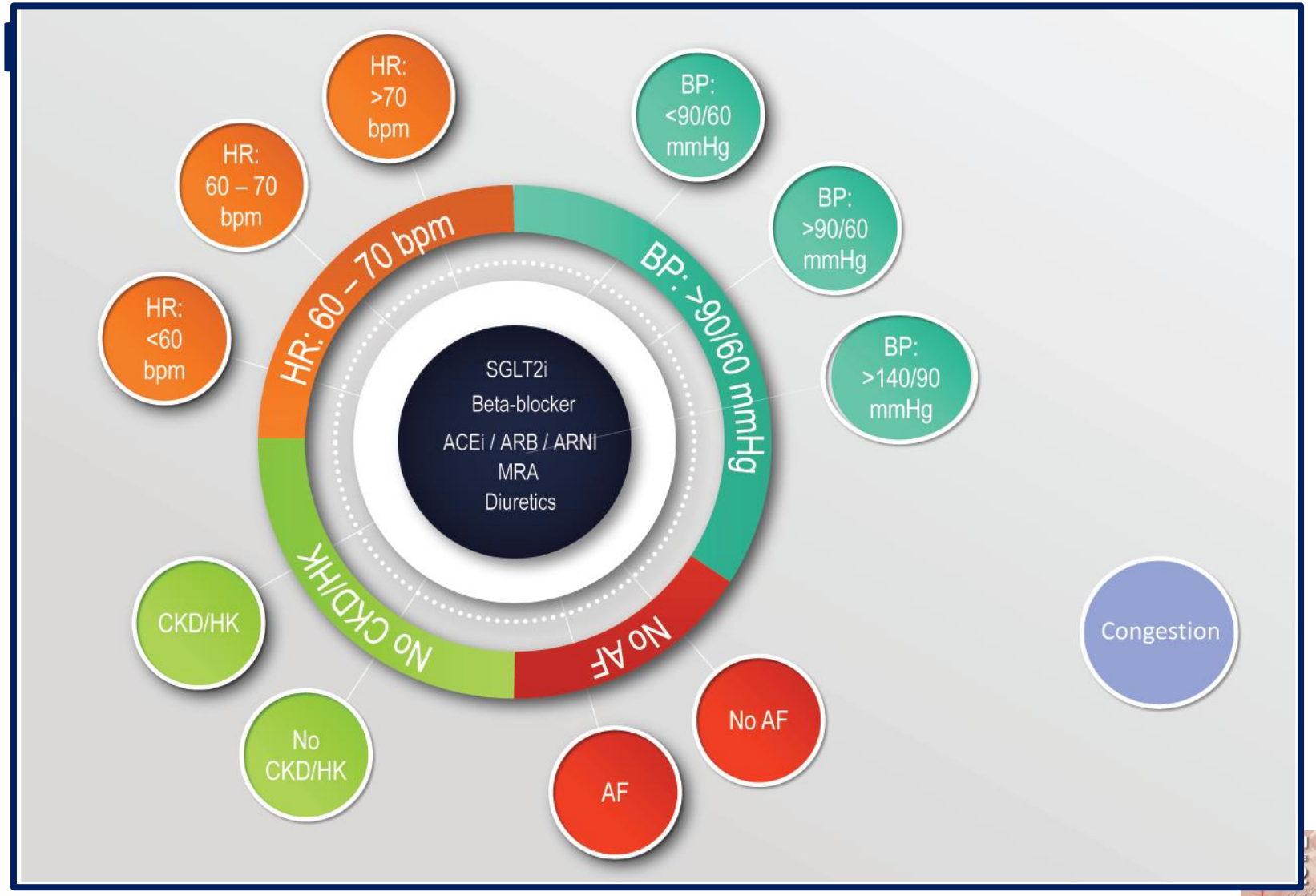
Tolérance : de l'étude DAPA-HF sont consistants avec le profil de tolerance bien établi de la dapagliflozine

Event, n (%)	Dapagliflozin10 mg (n=2368)	Placebo (n=2368)	p-value
AE leading to treatment discontinuation[1]	111 (4.7)	116 (4.9)	0.79
AE of interest[1]			
Volume depletion[b]	178 (7.5)	162 (6.8)	0.40
Renal AE[c]	153 (6.5)	170 (7.2)	0.36
Fracture	49 (2.1)	50 (2.1)	1.00
Amputation	13 (0.5)	12 (0.5)	1.00
Major hypoglycemia[d]	4 (0.2)	4 (0.2)	-
Diabetic ketoacidosis[e]	3 (0.1)	0 (0)	-
Additional AEs			
Fournier's gangrene[1]	0 (0)	1 (<0.1)	-
Genital infection[2]			
Serious	0	1 (0.0)	-
Leading to treatment discontinuation	7 (0.3)	0	-
Urinary tract infection[2]			
Serious	14 (0.6)	17 (0.7)	-
Leading to treatment discontinuation	5 (0.2)	5 (0.2)	-

[a]Safety population included all patients who had undergone randomization and received at least one dose of dapagliflozin or placebo. [b]Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23; [c]Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009. Serious adverse events of acute kidney injury were reported in 23 dapagliflozin patients (1.0%) and 46 placebo patients (1.9%). [d]Defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline. [e]All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline and were adjudicated as definite or probable.

1. McMurray JJV et al. Article and supplementary material. *N Engl J Med*. 2019; 381:1995-2008; 2. In House Data, AstraZeneca Pharmaceuticals LP. Clinical study report D1699C00001.

2021 ESC/HFA Consensus Recommends Starting SGLT2 Inhibitors as a Component of Foundational Therapy for All



[a]In patients with predominant chronic coronary syndrome, BP threshold is 120/80 mmHg.
Rosano GMC et al. *Eur J Heart Fail.* 2021;23:872-881.

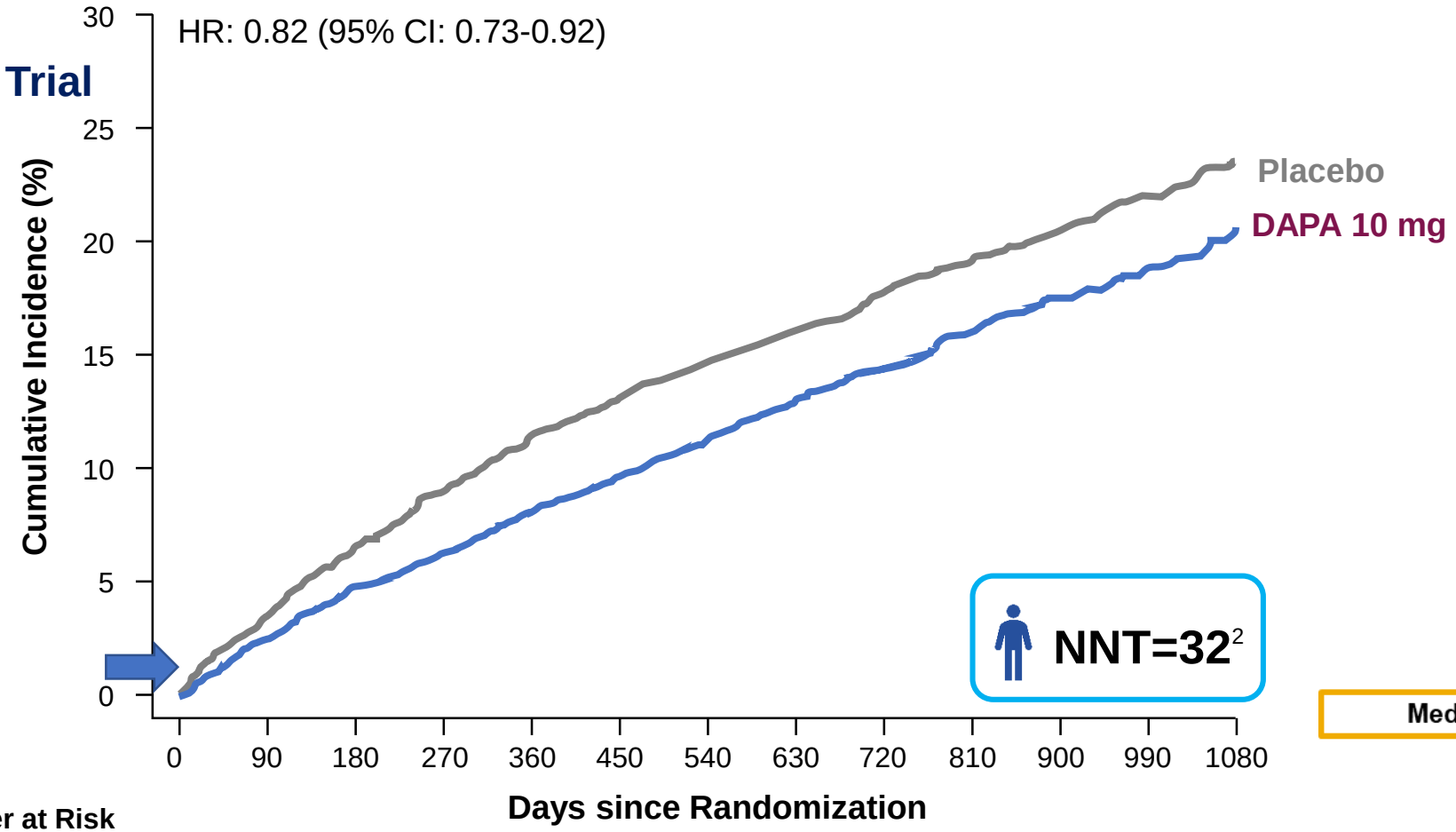
Mme GM 78 ans

- L'état de notre patiente s'améliore
- Elle sort et vous la revoyez en consultation quelques semaines plus tard
- Son état est meilleur, et le NTproBNP est à 500 pg/ml
- ETT : FEVG 50%, OG dilatée, PAPs à 50 mmHg, VD non dilaté

- → Modifiez vous son traitement ? Dans quel sens ?

Primary Composite of CV Death, hHF or Urgent HF Visit

DELIVER Trial



18 % RRR

3.1% ARR
p=0.0008[2]

Median follow-up: 2.3 years

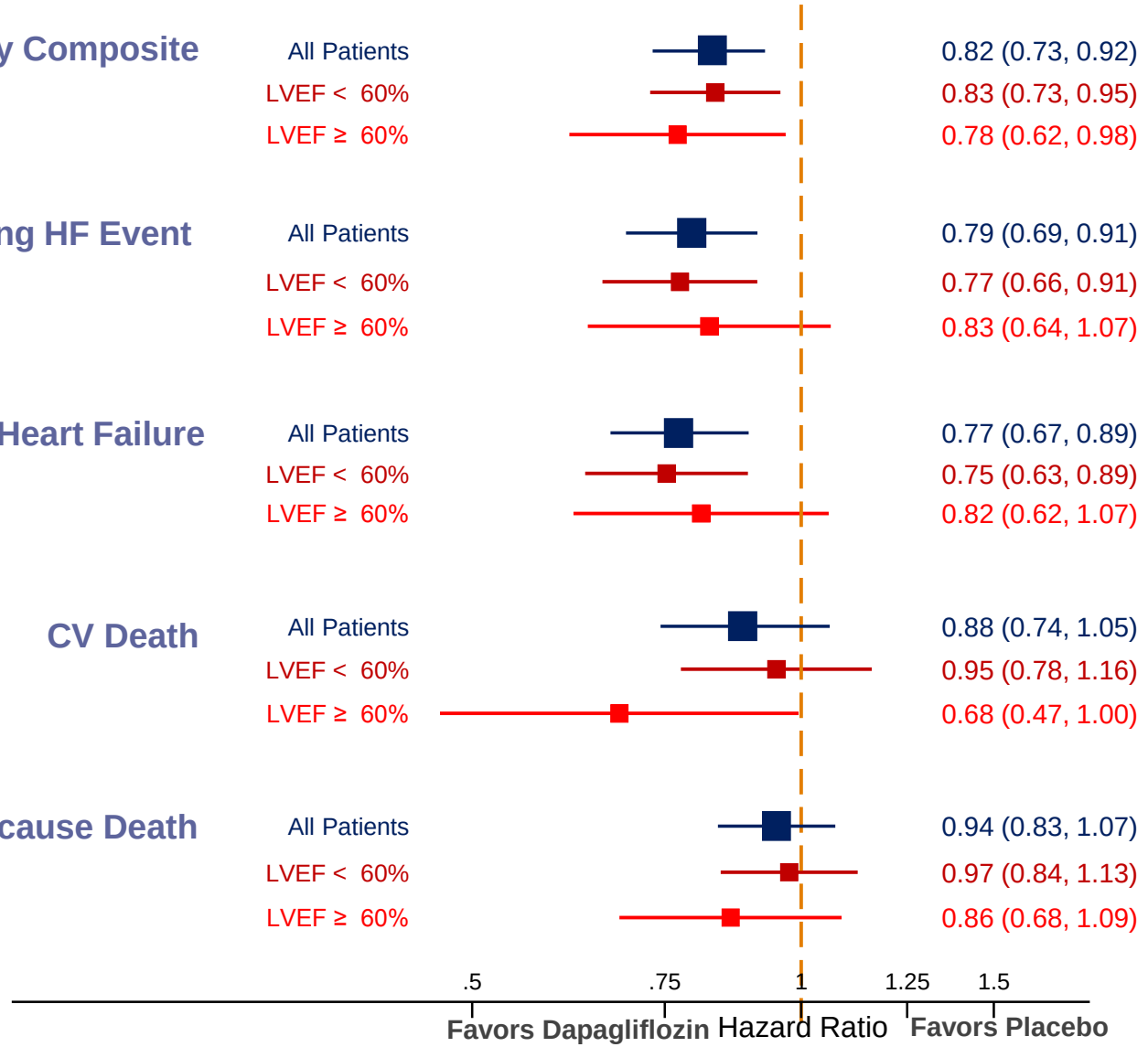
Number at Risk

DAPA 10 mg	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

Endpoints



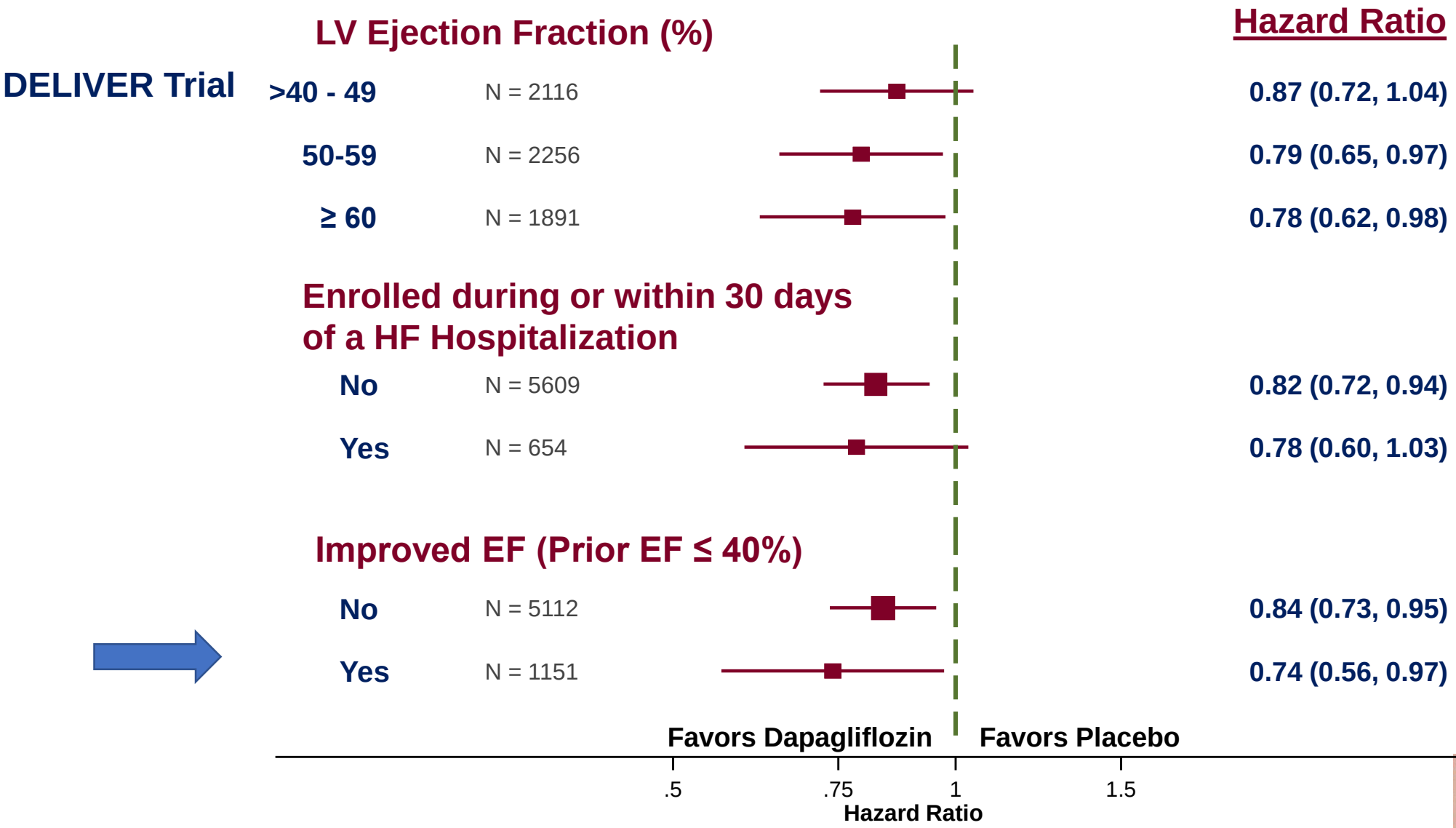
All Patients N = 6263

LVEF < 60% N = 4372 (70%)

LVEF ≥ 60% N = 1891 (30%)

Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

Et en fonction de la FE ?



Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

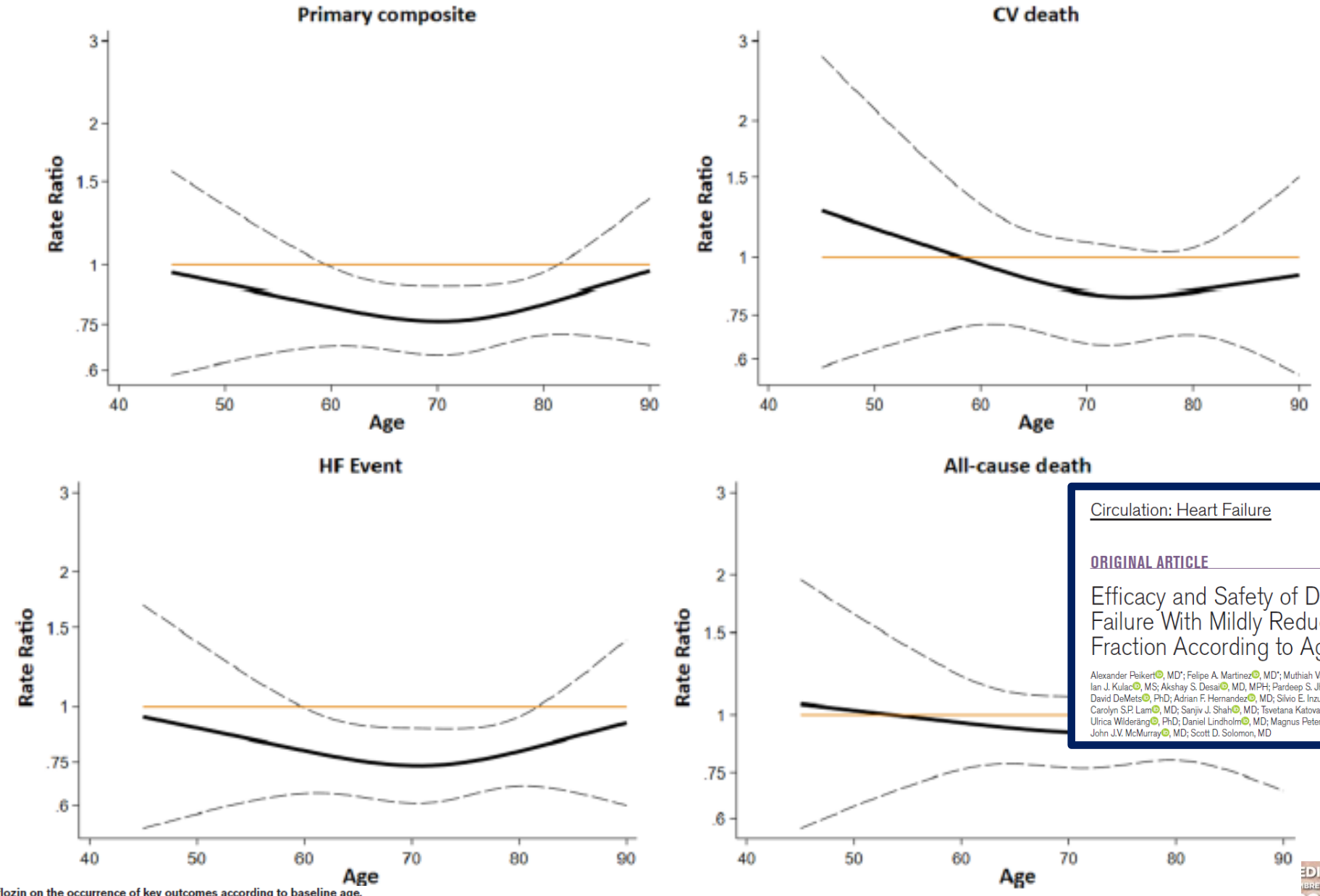


Figure 2. **Effect of dapagliflozin on the occurrence of key outcomes according to baseline age.**
Treatment effect of dapagliflozin, compared with placebo, on the primary composite outcome (first occurrence cardiovascular [CV] death, heart failure [HF] hospitalization, or urgent HF visit), CV death, heart failure events, including its components HF hospitalization and urgent HF visit, and all-cause death across a range of baseline age. Estimated rate ratios and 95% CIs were obtained from Poisson regression models with baseline age expressed via restricted cubic spline.

Circulation: Heart Failure

ORIGINAL ARTICLE

Efficacy and Safety of Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial

Alexander Peikert, MD*; Felipe A. Martinez, MD*; Muthiah Vaduganathan, MD, MPH*; Brian L. Claggett, PhD; Ian J. Kulac, MS; Akshay S. Desai, MD, MPH; Pardeep S. Jhund, MBChB, MSc, PhD; Rudolf A. de Boer, MD; David DeMets, PhD; Adrian F. Hernandez, MD; Silvio E. Inzucchi, MD; Mikhail N. Kosiborod, MD; Carolyn S.P. Lam, MD; Sanjiv J. Shah, MD; Tsvetana Katova, MD; Béla Merkely, MD; Orly Vardeny, PharmD, MS; Ulrica Wilderäng, PhD; Daniel Lindholm, MD; Magnus Petersson, MD; Anna Maria Langkilde, MD; John J.V. McMurray, MD; Scott D. Solomon, MD

Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

Pression artérielle et Kaliémie ?

Sous-analyse de DAPA HF

TABLE 3 Changes in Repeated Measurements by Randomized Treatment in Patients Taking and Not Taking MRA

	Patients Not on MRA		Patients on MRA		
	Placebo (n = 697)	Dapagliflozin (n = 677)	Placebo (n = 1,674)	Dapagliflozin (n = 1,696)	p Value for Interaction
Systolic blood pressure, mm Hg					
Change from baseline at 8 months	−2.20 ± 16.90	−3.46 ± 15.78	0.37 ± 14.48	−1.29 ± 14.51	
Difference*	−1.00 (−2.72 to 0.72); p = 0.254		−1.58 (−2.59 to −0.58); p = 0.002		0.88
Creatinine, mg/dl					
Change from baseline at 8 months	0.04 ± 0.26	0.08 ± 0.24	0.04 ± 0.24	0.06 ± 0.24	
Difference*	0.03 (0.01 to 0.06); p = 0.021		0.02 (−0.003 to 0.03); p = 0.103		0.32
Potassium, mmol/l					
Change from baseline at 8 months	0.08 ± 0.52	0.11 ± 0.49	0.1 ± 0.53	0.06 ± 0.54	
Difference*	0.03 (−0.03 to 0.08); p = 0.349		−0.03 (−0.07 to 0.002); p = 0.064		0.60
NT-proBNP, pg/ml					
Change from baseline at 8 months	406 ± 2,949	−286 ± 2,071	−25 ± 2,934	−159 ± 2,503	
Difference*	−690 (−1,121 to −259); p = 0.002		−140 (−662 to 383); p = 0.60		0.55
Weight, kg					
Change from baseline at 8 months	−0.26 ± 4.09	−0.94 ± 3.80	0.24 ± 4.08	−0.86 ± 3.89	
Difference*	−0.67 (−1.11 to −0.23); p = 0.003		−0.98 (−1.28 to −0.68); p < 0.001		0.84
Hematocrit, %					
Change from baseline at 8 months	−0.26 ± 3.83	2.42 ± 3.55	−0.16 ± 3.8	2.27 ± 4.04	
Difference*	2.61 (2.21 to 3.00); p < 0.001		2.42 (2.15 to 2.68); p < 0.001		0.53
Glycated hemoglobin,† %					
Change from baseline at 8 months	0.10 ± 1.28	−0.17 ± 1.22	0.04 ± 1.30	−0.21 ± 1.08	
Difference*	−0.30 (−0.50 to −0.10); p = 0.003		−0.24 (−0.37 to −0.11); p < 0.001		0.43

*Difference between placebo and dapagliflozin at 8 months with 95% confidence interval. †Glycated hemoglobin values are listed only for the patients with medical history of diabetes (n = 1,983).

Abbreviations as in Table 1.

Shen et al. JACC HF 2021;9:254–64

Fonction rénale ?

eGFR indicates estimated glomerular filtration rate; HF, heart failure; and HR, hazard ratio.

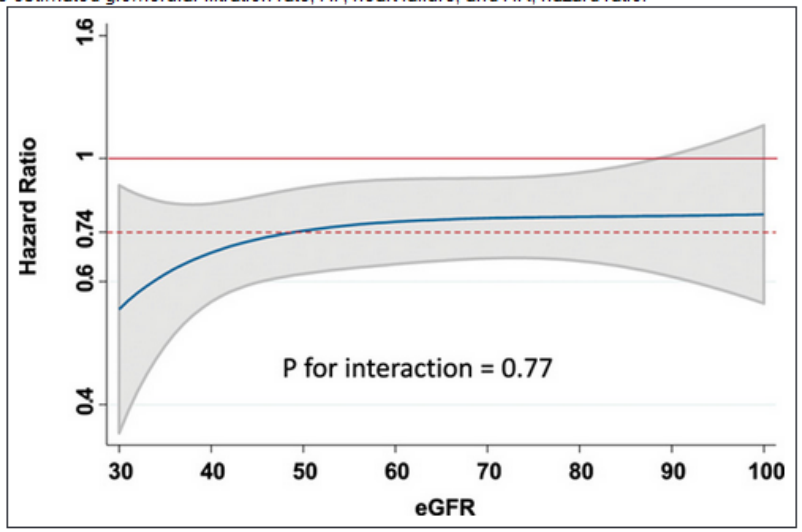
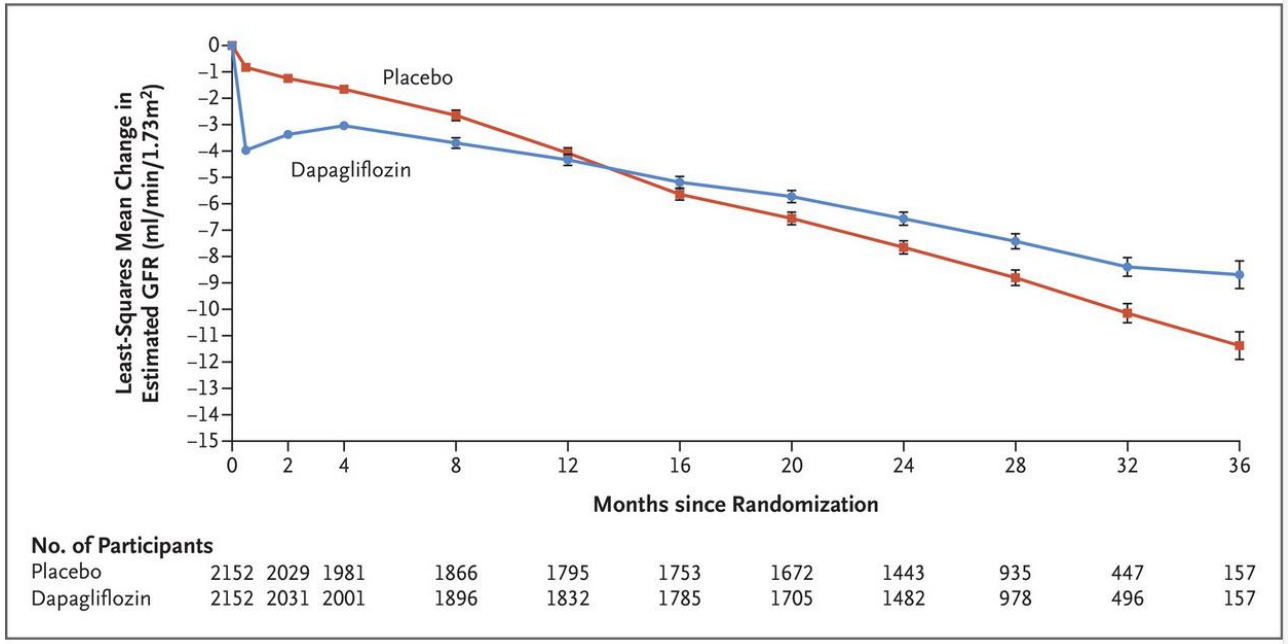


Figure 1. Effect of dapagliflozin on the primary outcome by eGFR at baseline. The blue line represents continuous hazard ratio, and the gray area represents the 95% CI with the overall hazard ratio for the effect of dapagliflozin on the primary outcome given by the dashed red line. eGFR indicates estimated glomerular filtration rate.

DAPA-HF

DAPA CKD : Circulation. 2021;143:438–448



Change from Baseline in Estimated GFR

Heerspink et al. NEJM. 2020; 383:1436-1446

DELIVER Trial
Tolérance

Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Variable	Dapagliflozin (N=3131)		Placebo (N=3132)		Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
	values	*events/ 100 patient-yr*	*values*	*events/ 100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths‡	815	11.8	1057	15.3	0.77 (0.67–0.89)	<0.001
Change in KCCQ total symptom score at mo 8§	—	—	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ total symptom score at mo 8 among survivors	—	—	—	—	2.4 (1.5–3.4)	NA
Death from any cause — no. (%)	497 (15.9)	7.2	526 (16.8)	7.6	0.94 (0.83–1.07)	NA
Safety outcomes — no./total no. (%)¶						
Any serious adverse event	1361/3126 (43.5)	—	1423/3127 (45.5)	—	—	—
Any adverse event that led to discontinuation of dapagliflozin or placebo	182/3126 (5.8)	—	181/3127 (5.8)	—	—	—
Any adverse event that led to interruption of dapagliflozin or placebo	436/3126 (13.9)	—	494/3127 (15.8)	—	—	—
Any amputation	19/3126 (0.6)	—	25/3127 (0.8)	—	—	—
Any adverse event that potentially placed a patient at risk for a lower-limb amputation	188/3126 (6.0)	—	199/3127 (6.4)	—	—	—
Any definite or probable diabetic ketoacidosis	2/3126 (0.1)	—	0	—	—	—
Any major hypoglycemic event‖	6/3126 (0.2)	—	7/3127 (0.2)	—	—	—
Any serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo that was suggestive of volume depletion	42/3126 (1.3)	—	32/3127 (1.0)	—	—	—
Any renal serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo	73/3126 (2.3)	—	79/3127 (2.5)	—	—	—
Fournier's gangrene	0	—	0	—	—	—

* All treatment effects are shown as hazard ratios, except for the total number of hospitalizations for heart failure and cardiovascular deaths, which is reported as a rate ratio, and the change in Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score at month 8, which is reported as a win ratio. The total symptom scores on the KCCQ range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy.

† Cardiovascular death was also a prespecified secondary outcome.

‡ Worsening heart failure events were defined as hospitalization for heart failure or an urgent visit for heart failure. The total number of worsening heart failure events included first and recurrent events.

§ The results of the assessment of the KCCQ total symptom score in a sensitivity analysis in which data were not censored after March 11, 2020, were similar to those shown (win ratio, 1.11; 95% CI, 1.05 to 1.18).

¶ A total of 10 patients (5 in the dapagliflozin group and 5 in the placebo group) were excluded from the safety analyses because they did not receive any dose of dapagliflozin or placebo. Safety outcomes were events with an onset date on or after the date of the first dose and up to and including 30 days after the last dose of dapagliflozin or placebo.

‖ Major hypoglycemic events are defined in the Supplementary Methods section in the Supplementary Appendix.

Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

Faut-il adapter la dose de diurétique ?

102 patients were included (73.4±11.7 years, 57.8% men). FEVG was 44.9%±14.7%

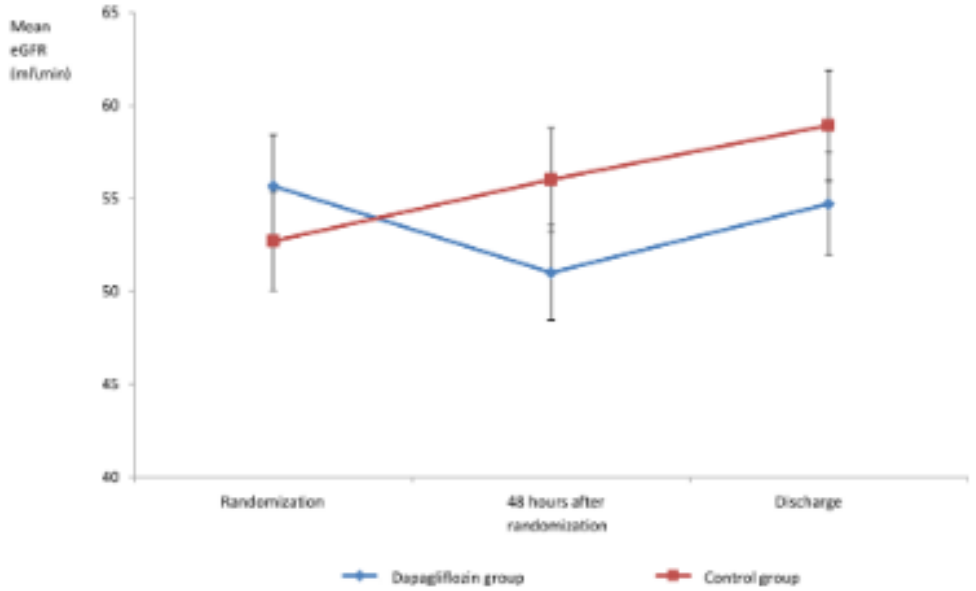


Figure 3 The use of dapagliflozin was not associated with a significant deterioration of renal function from randomisation to discharge. eGFR, estimated glomerular filtration rate.

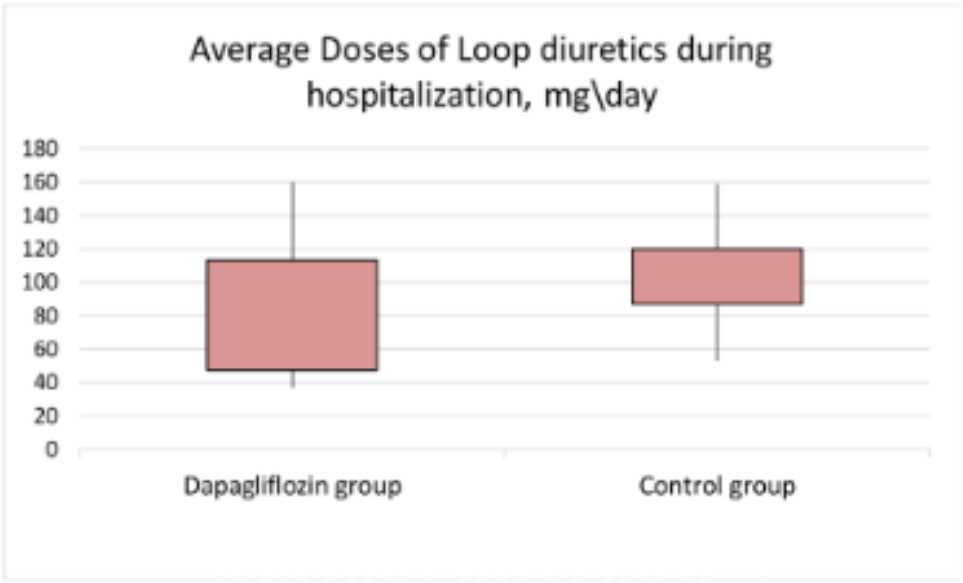


Figure 4 The use of dapagliflozin was associated with lower doses of loop diuretics (p=0.001).

Charaya K, et al. Open Heart 2022;9:e001936.

Conclusion

L'optimistion de la prise en charge est dynamique
Et aussi quodifiée
Dapagliflozine en pratique

- Très efficace sur morbi-mortalité
- Efficace sur la QOL
- Très bien toléré
- Ne pas attendre pour instaurer le traitement

Les données de l'étude DELIVER sont en cours d'évaluation par les autorités de santé.

MERCI POUR VOTRE PARTICIPATION