27ème CONGRÈS DU CNCH
Présentiel et digital

Prise en charge de l'insuffisance cardiaque : quelles nouveautés ?

Traitement médicamenteux : mise au point et recommandations

Dr Nataliya Hrynchyshyn
Cardiologue

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

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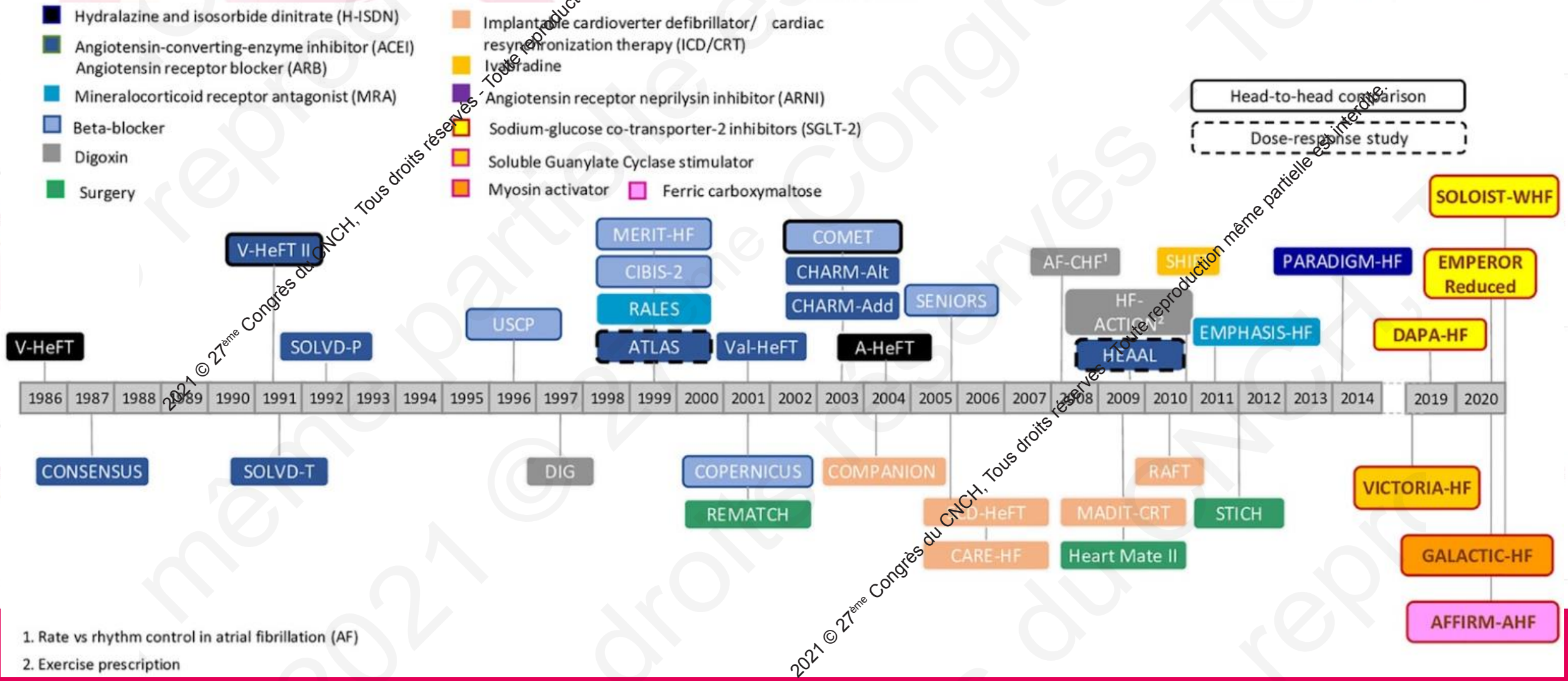
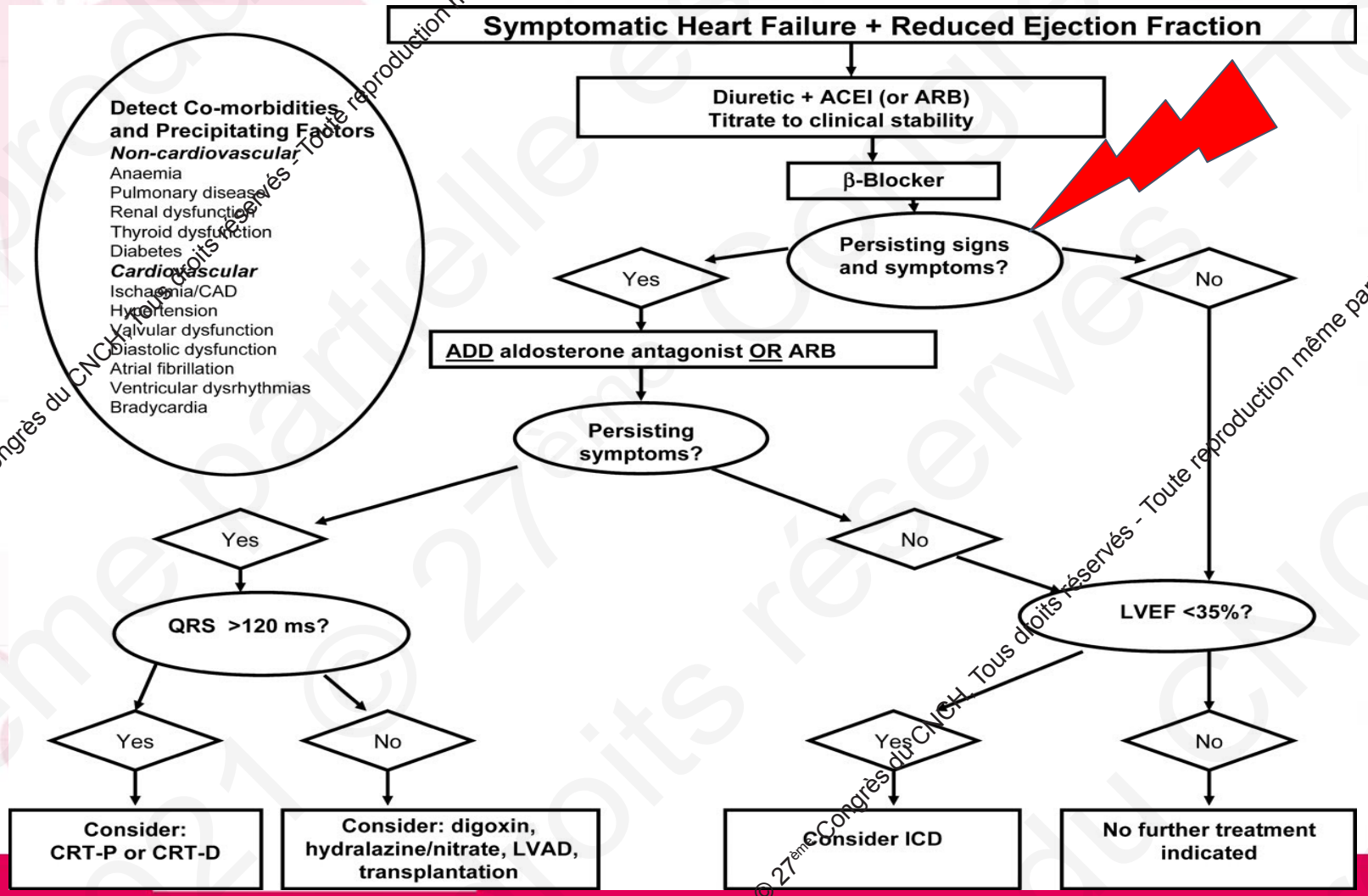
Évolution de traitement d'IC



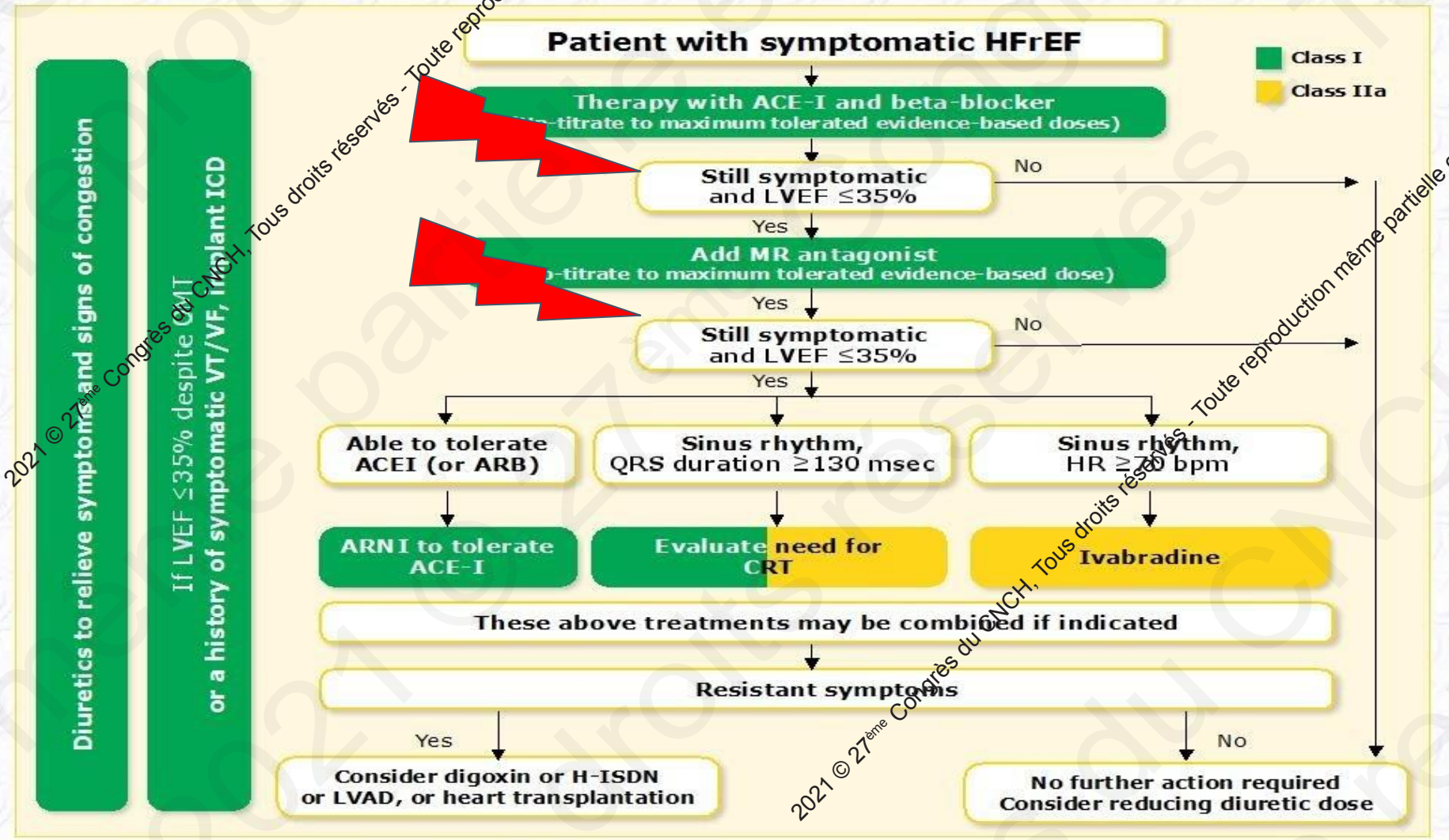
1. Rate vs rhythm control in atrial fibrillation (AF)
2. Exercise prescription

Recommendations ESC 2008

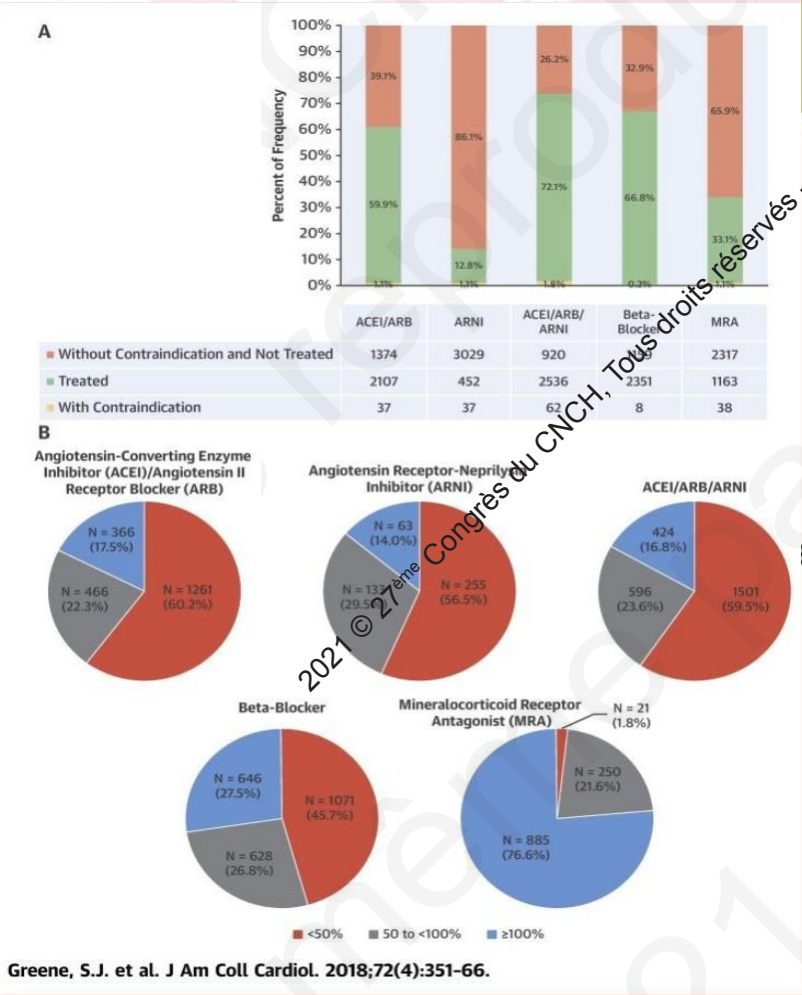


Recommendations ESC 2016

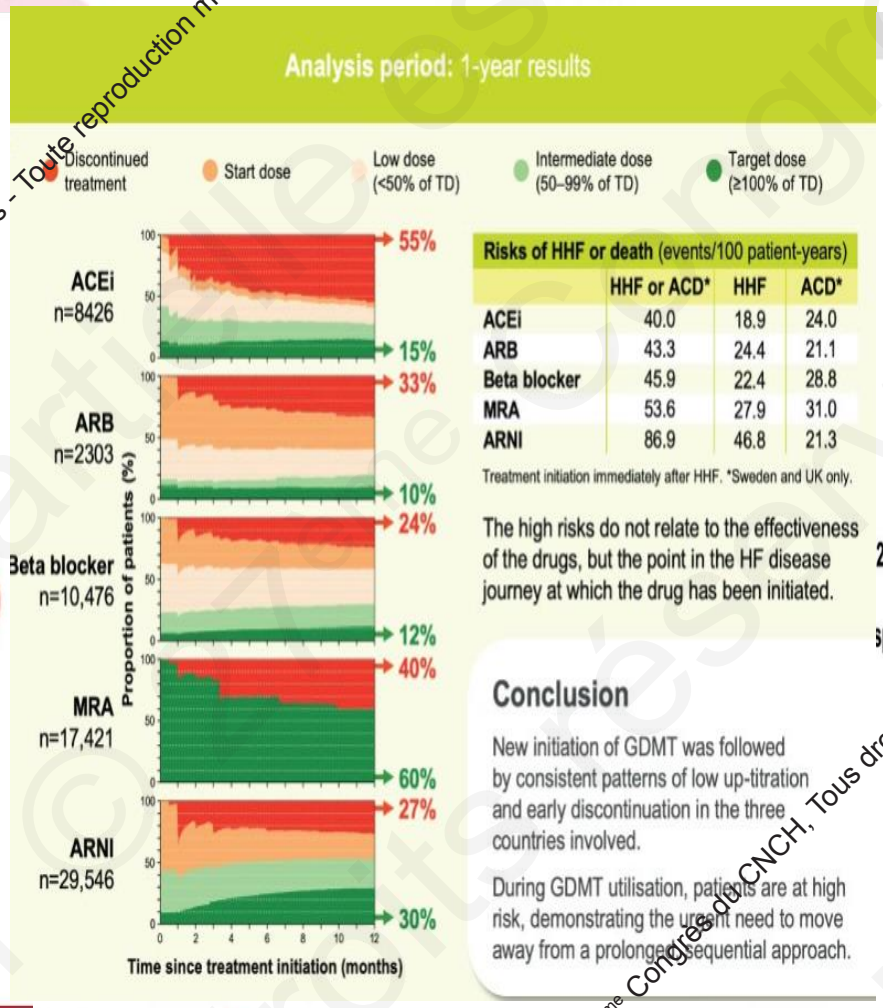
Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction

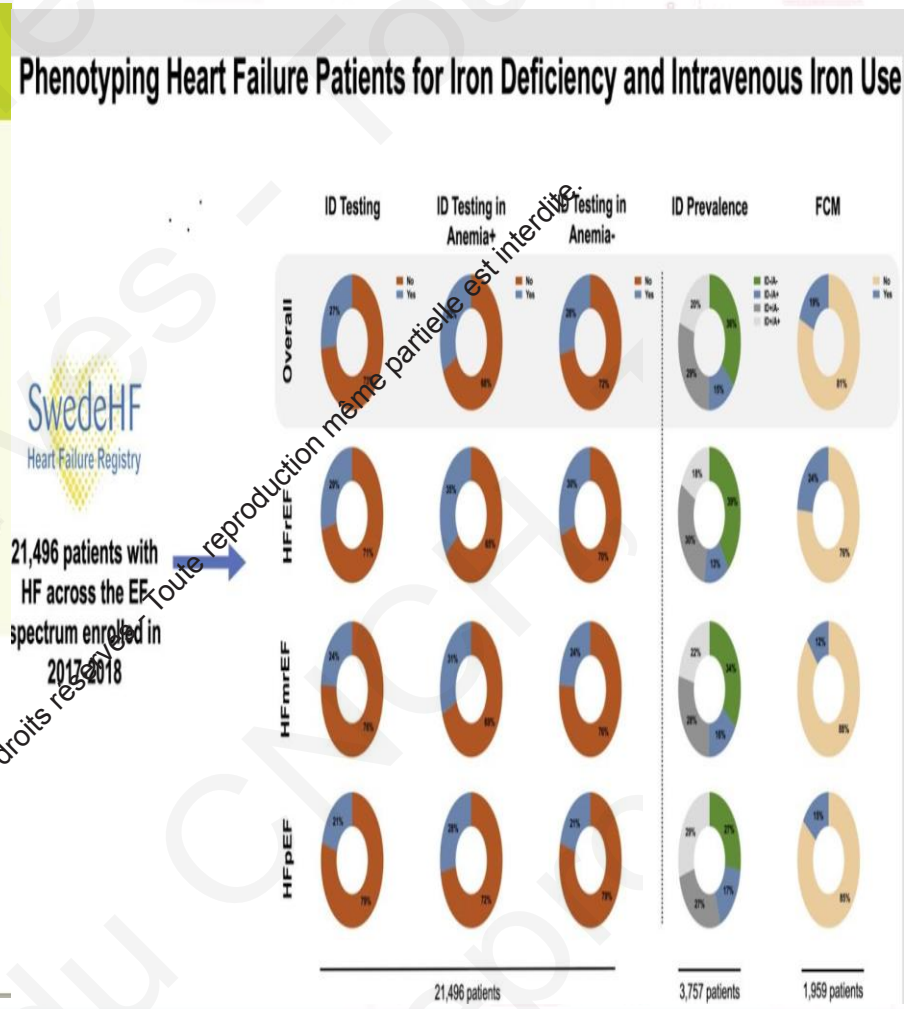


Optimisation insuffisante de traitement d'IC

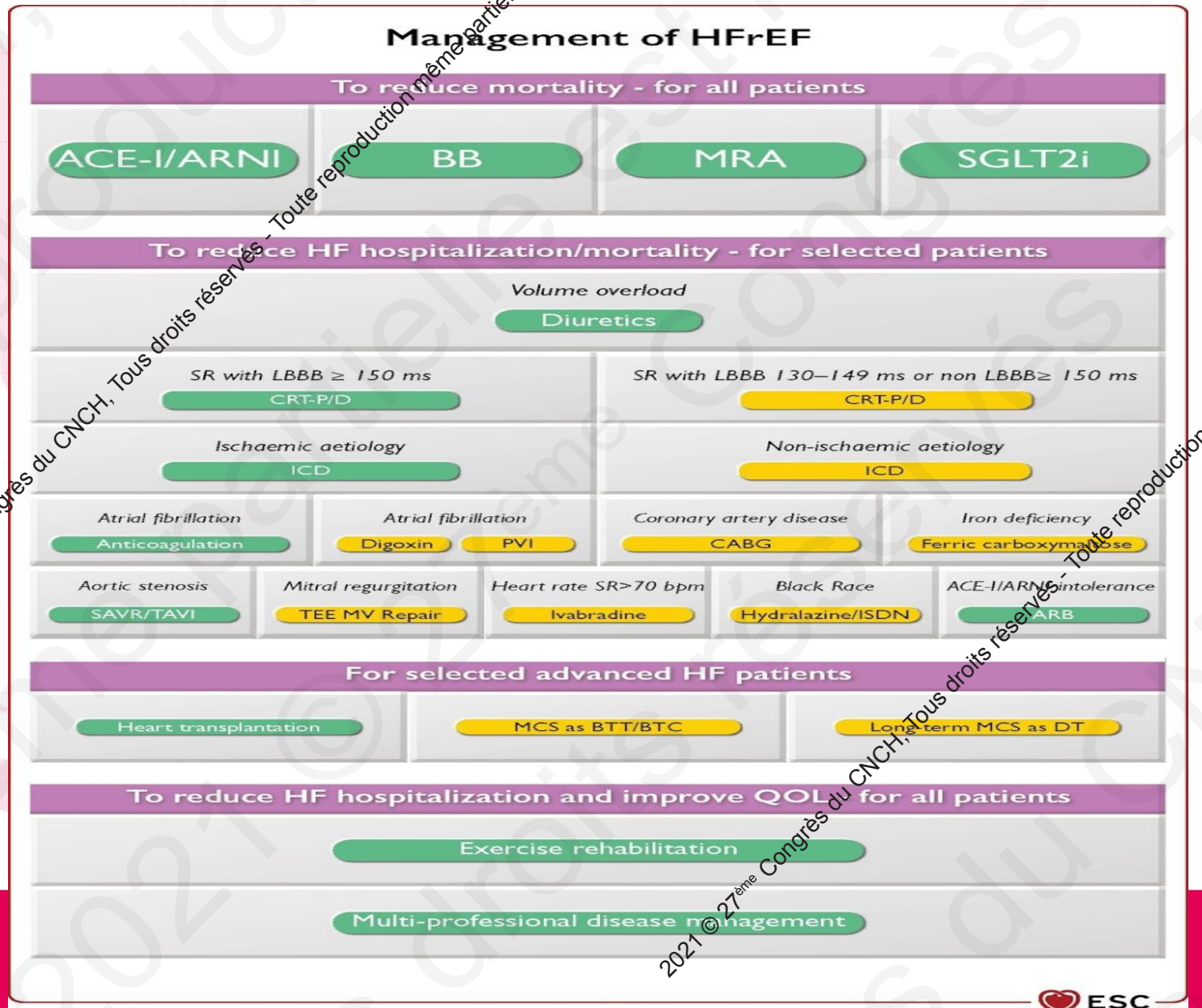


Greene, S.J. et al. J Am Coll Cardiol. 2018;72(4):351-66.





Recommendations ESC 2021



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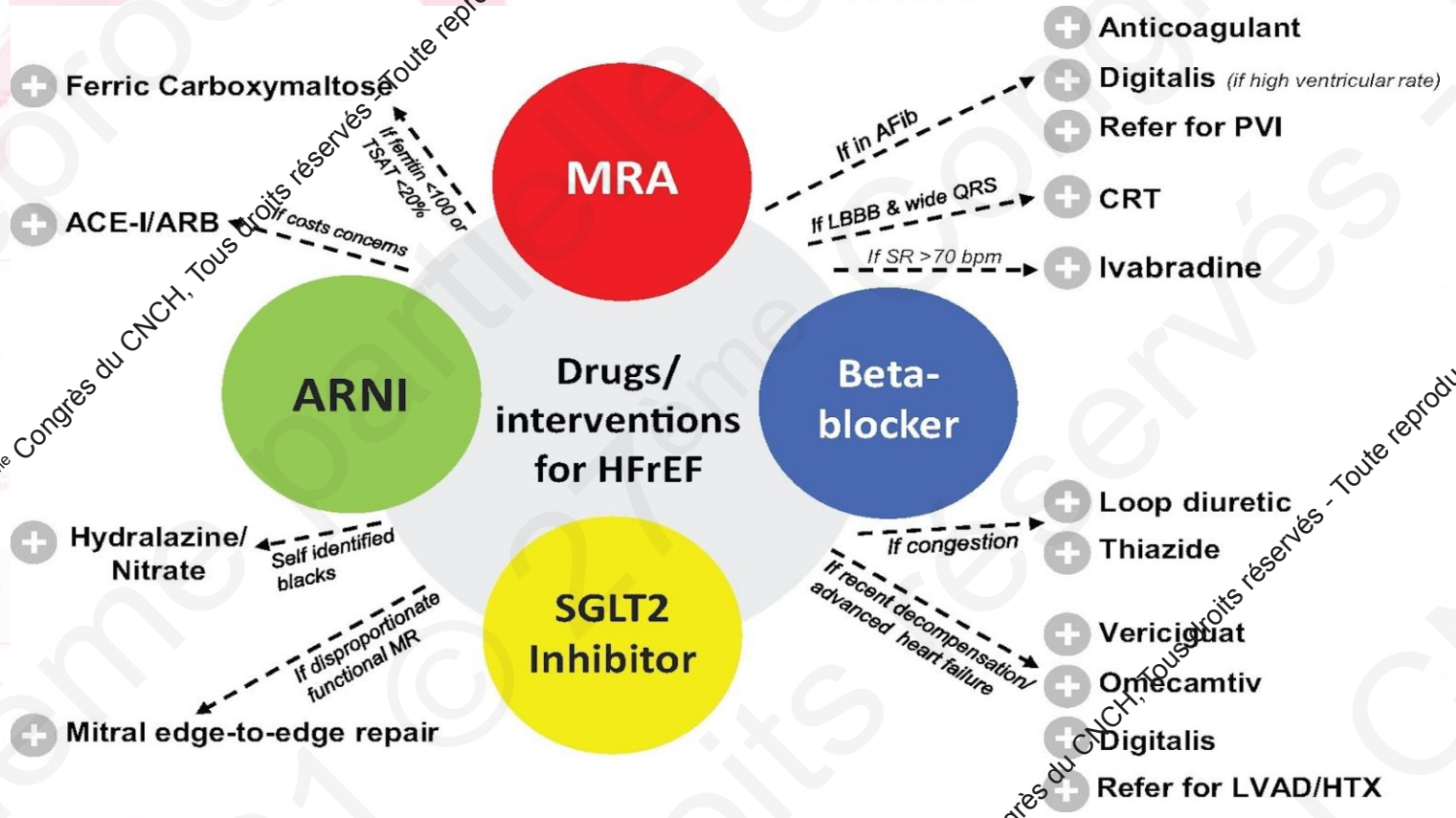
LES 4 FANTASTIQUES

ESC European Society of Cardiology



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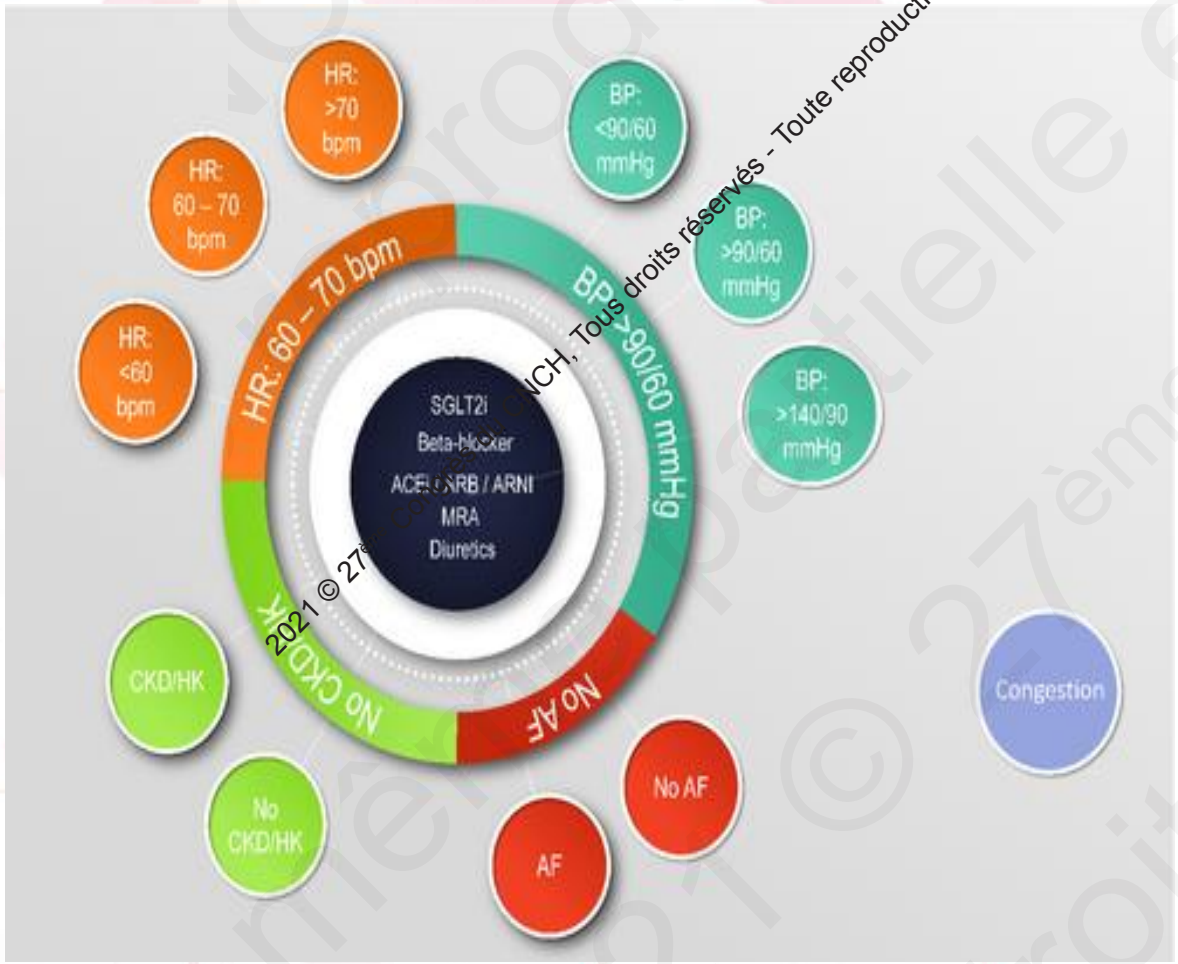
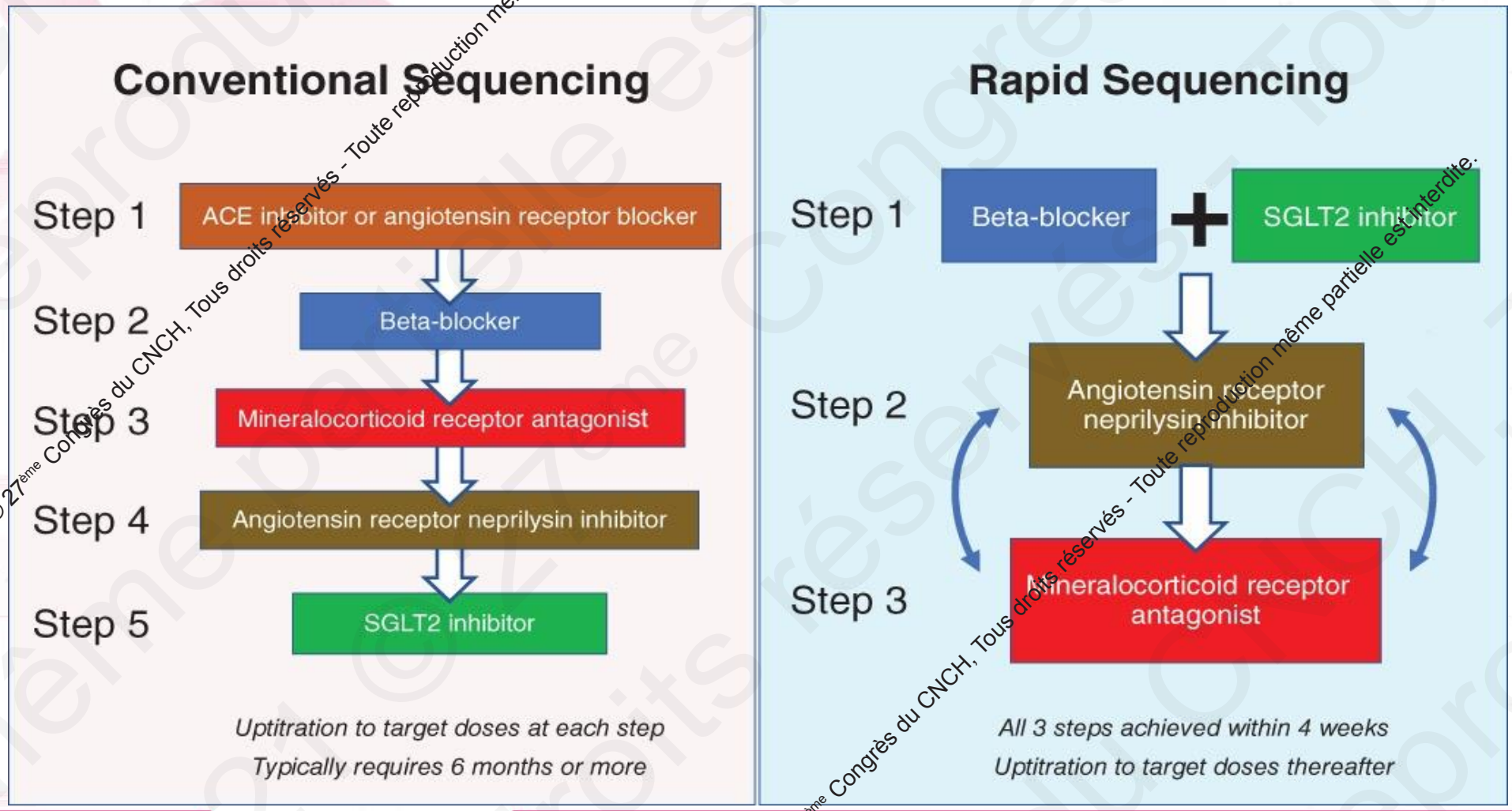
Adapter le traitement selon profil de patient



Rosano, Europeans Journal of Heart Failure, 2021

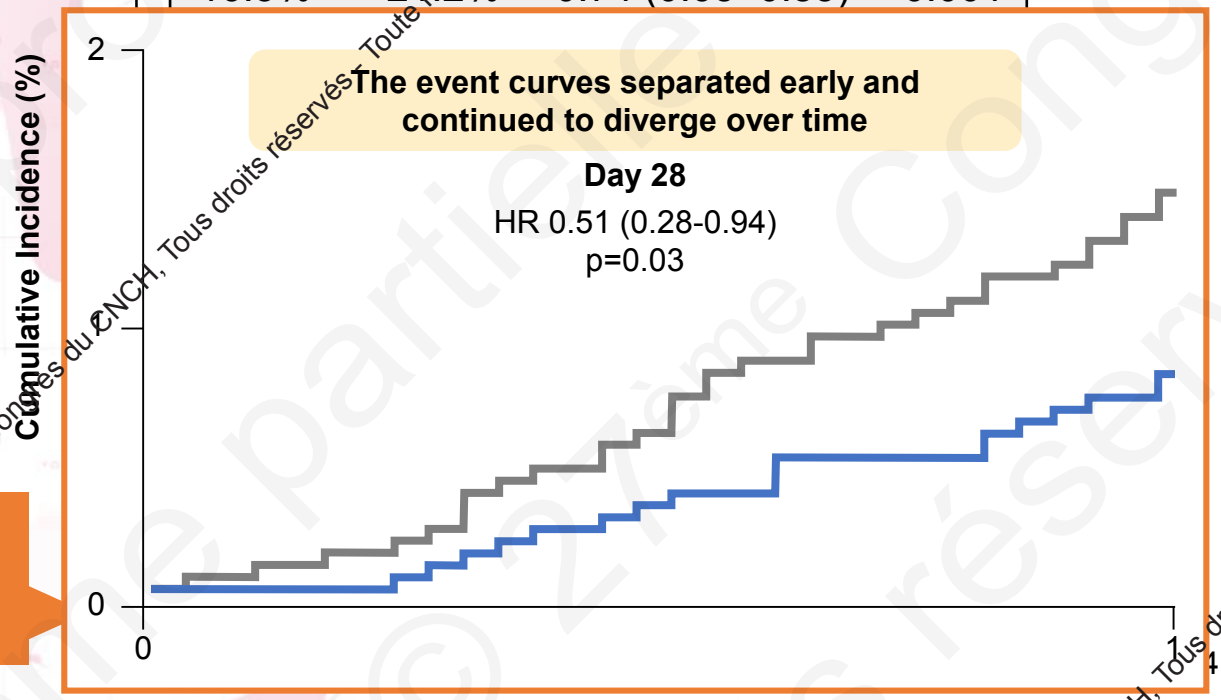
Optimisation rapide



Packer et al, Eur J of Heart Fail, 2021

Primary Endpoint: CV Death or hHF or an Urgent HF Visit[1,2]

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



Primary endpoint was statistically significant as early as Day 28

26% RRR

4.9% ARR

NNT=21

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

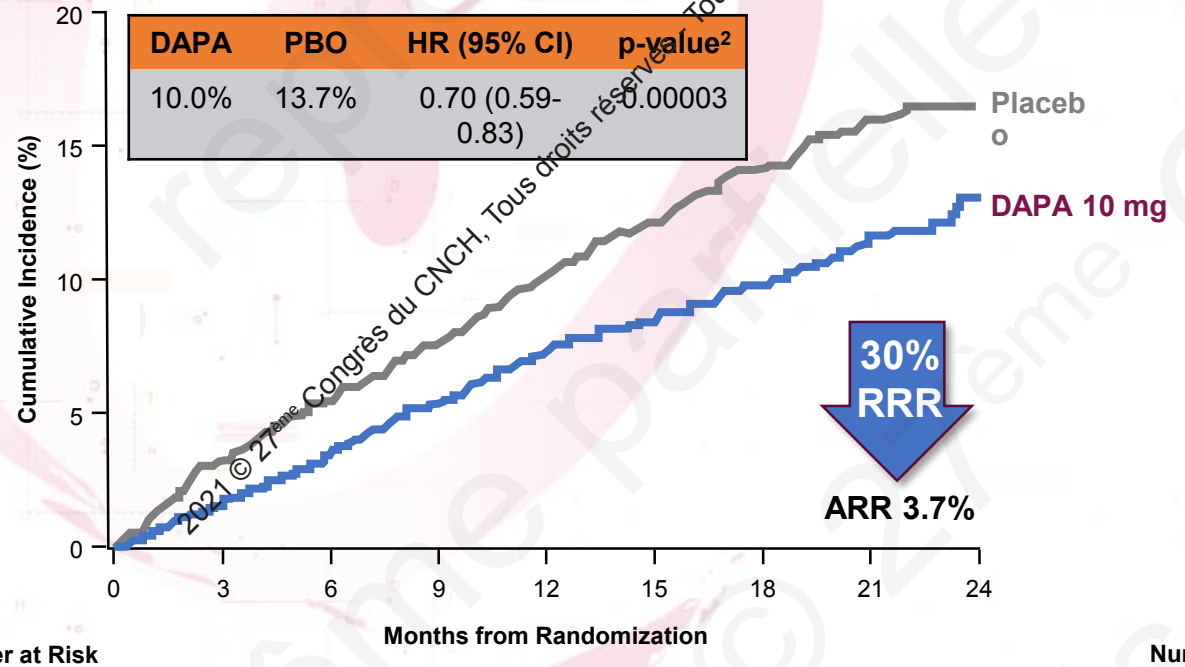
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Berg DD et al. *JAMA Cardiol*. 2021;6:499-507.

Components of the Primary Endpoint[1,2]

Worsening HF Event[a]

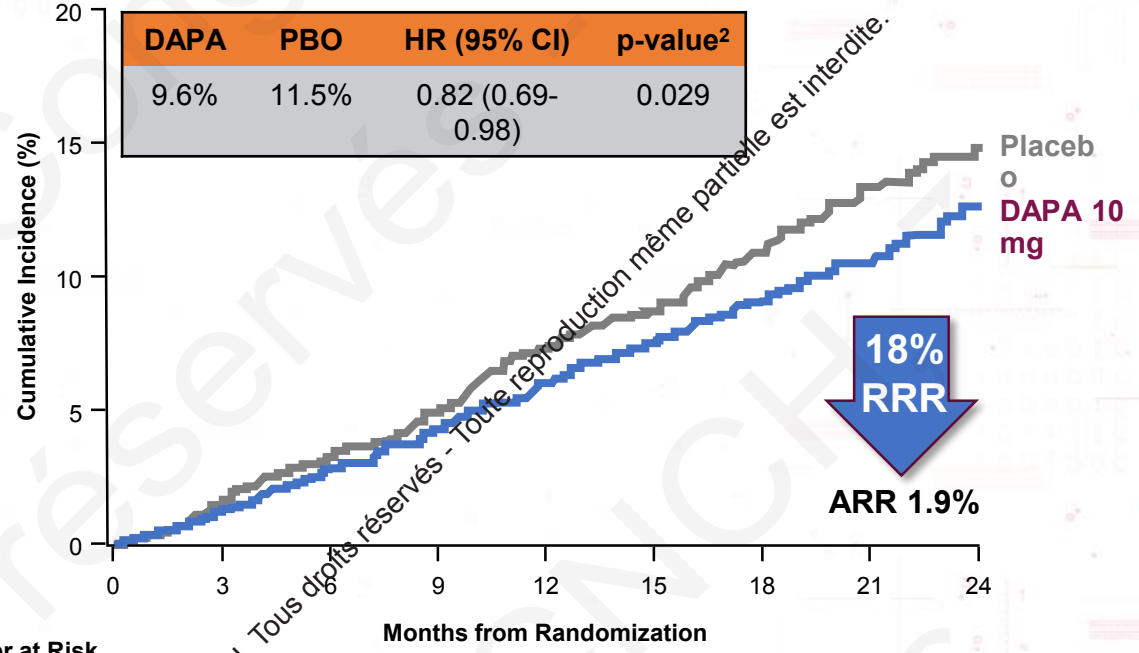
DAPA	PBO	HR (95% CI)	p-value[2]
10.0%	13.7%	0.70 (0.59-0.83)	0.00003



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

DAPA	PBO	HR (95% CI)	p-value[2]
9.6%	11.5%	0.82 (0.69-0.98)	0.029



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

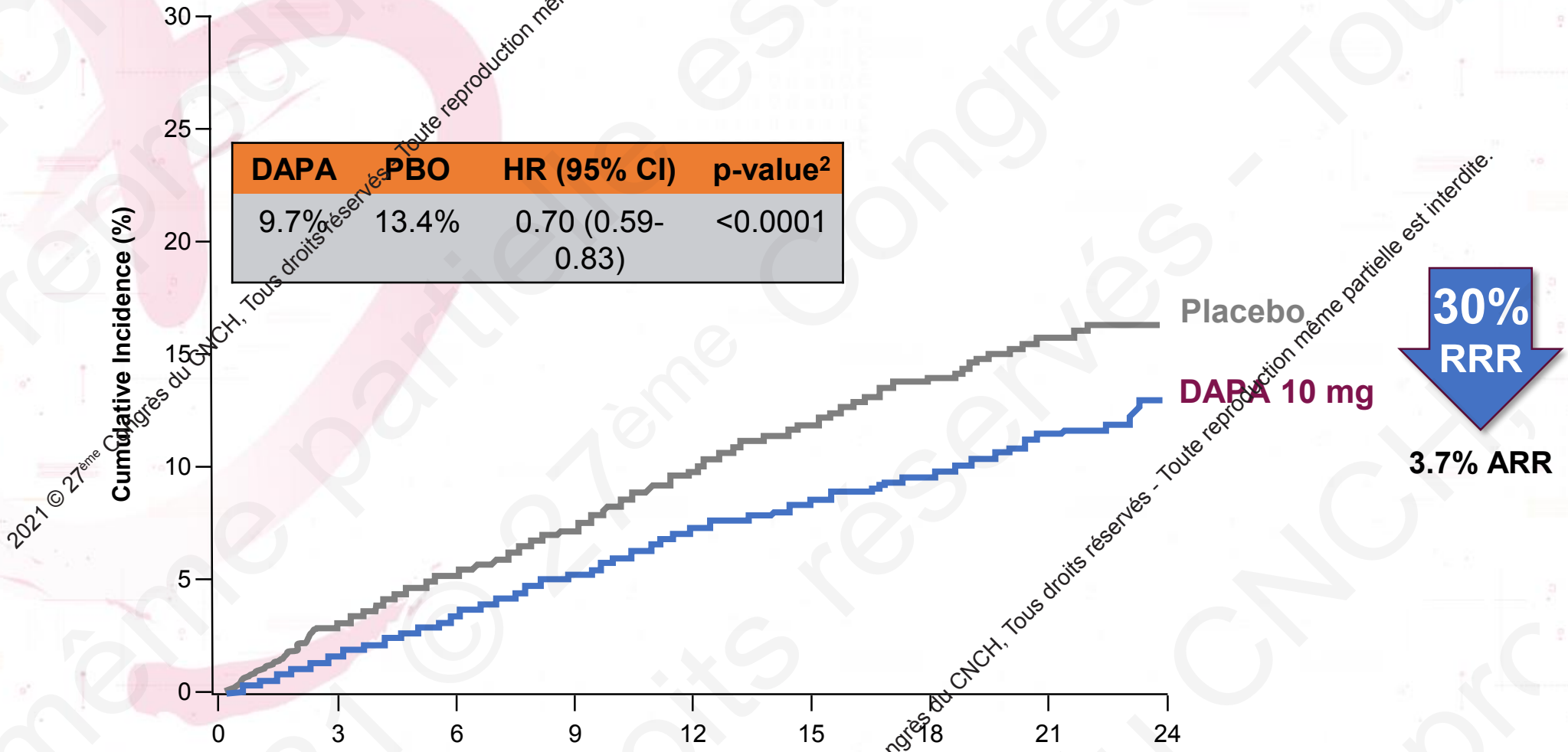
[a]Worsening HF includes hHF or urgent HF visit.

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.

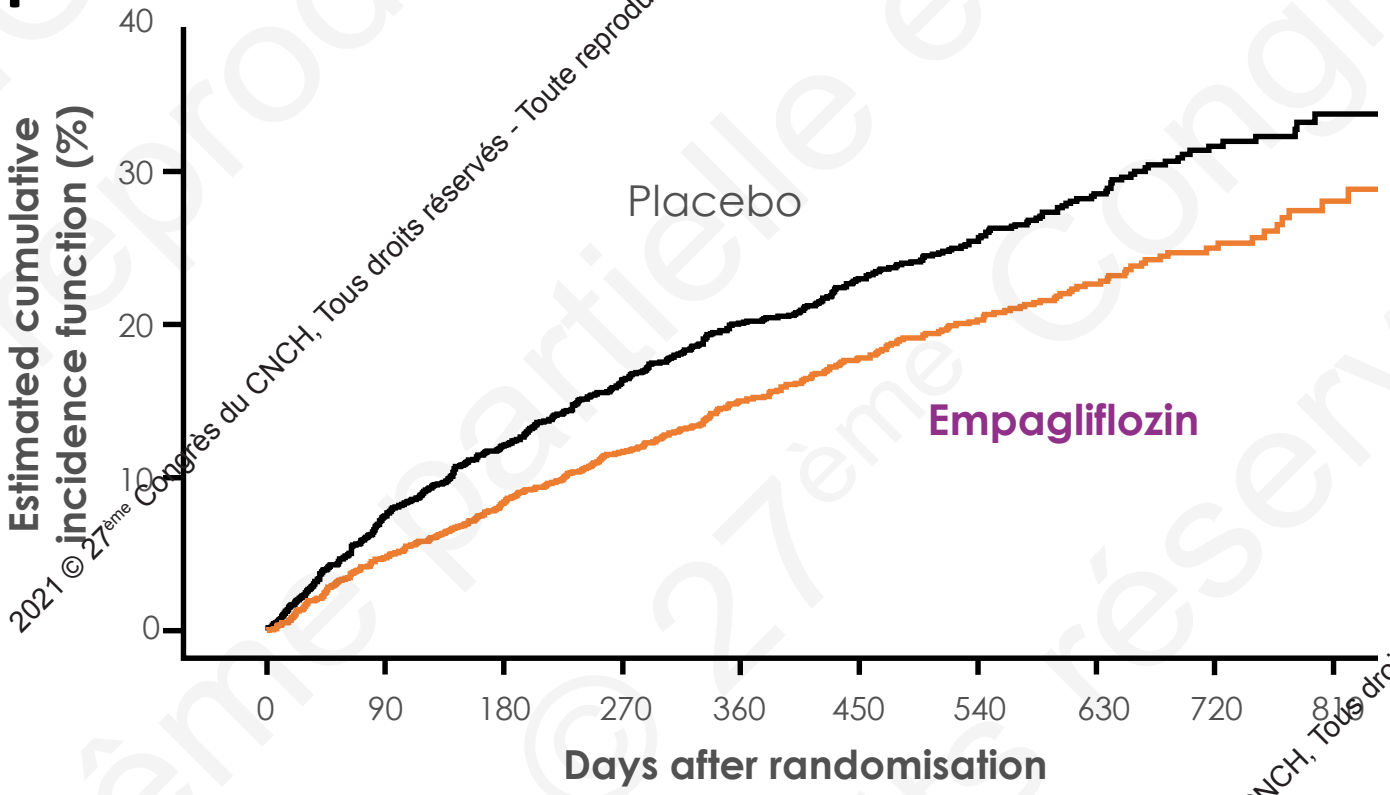
Hospitalization for Heart Failure (hHF)[1]

DAPA	PBO	HR (95% CI)	p-value[2]
9.7%	13.4%	0.70 (0.59-0.83)	<0.0001



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

Primary endpoint: First adjudicated CV death or hospitalisation for heart failure



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%

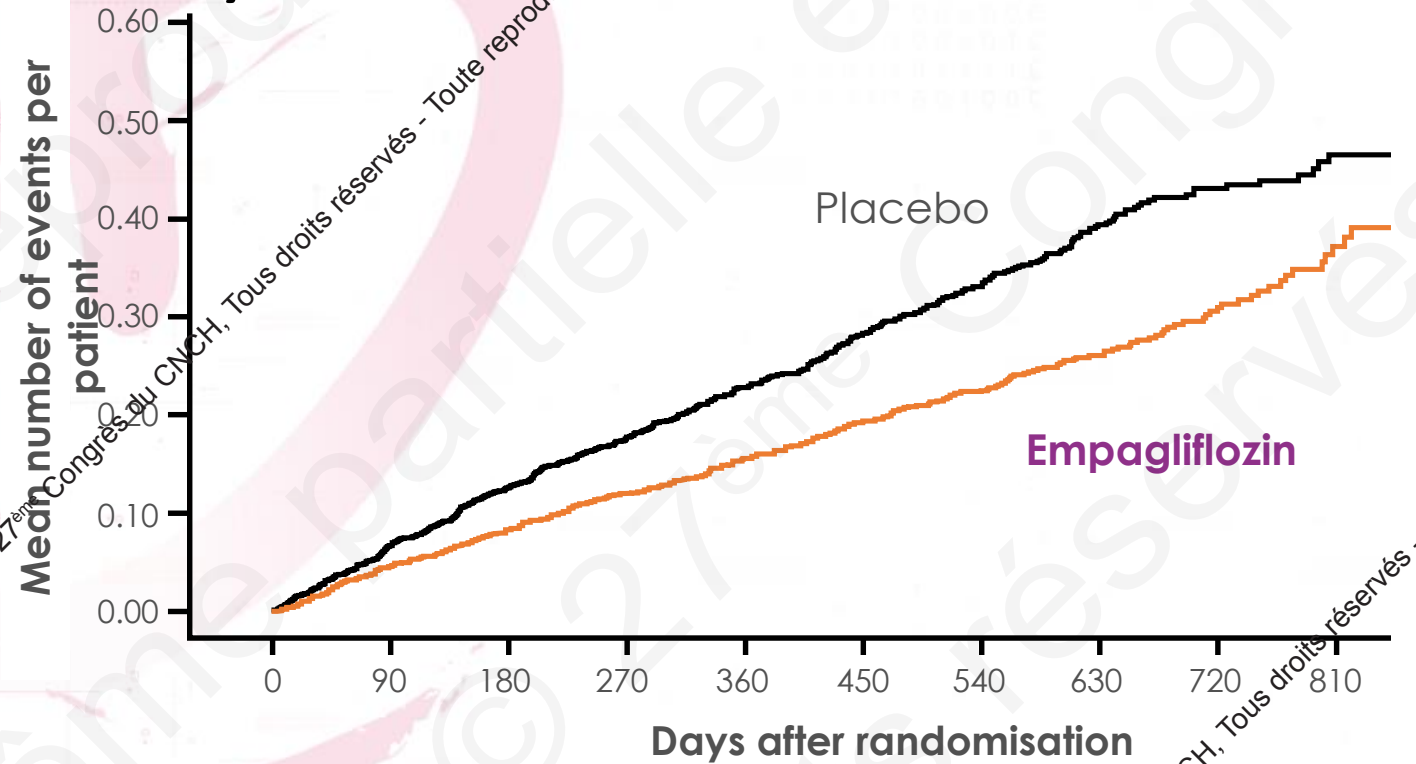
NNT = 19

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

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment
CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ARR, absolute risk reduction; RRR, relative risk reduction. NNT: Number needed to treat
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

Key secondary: Adjudicated total hospitalisations for heart failure (first and recurrent)



Patients at risk

Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

RRR 30%

HR 0.70
(95% CI 0.58, 0.85)
p<0.001

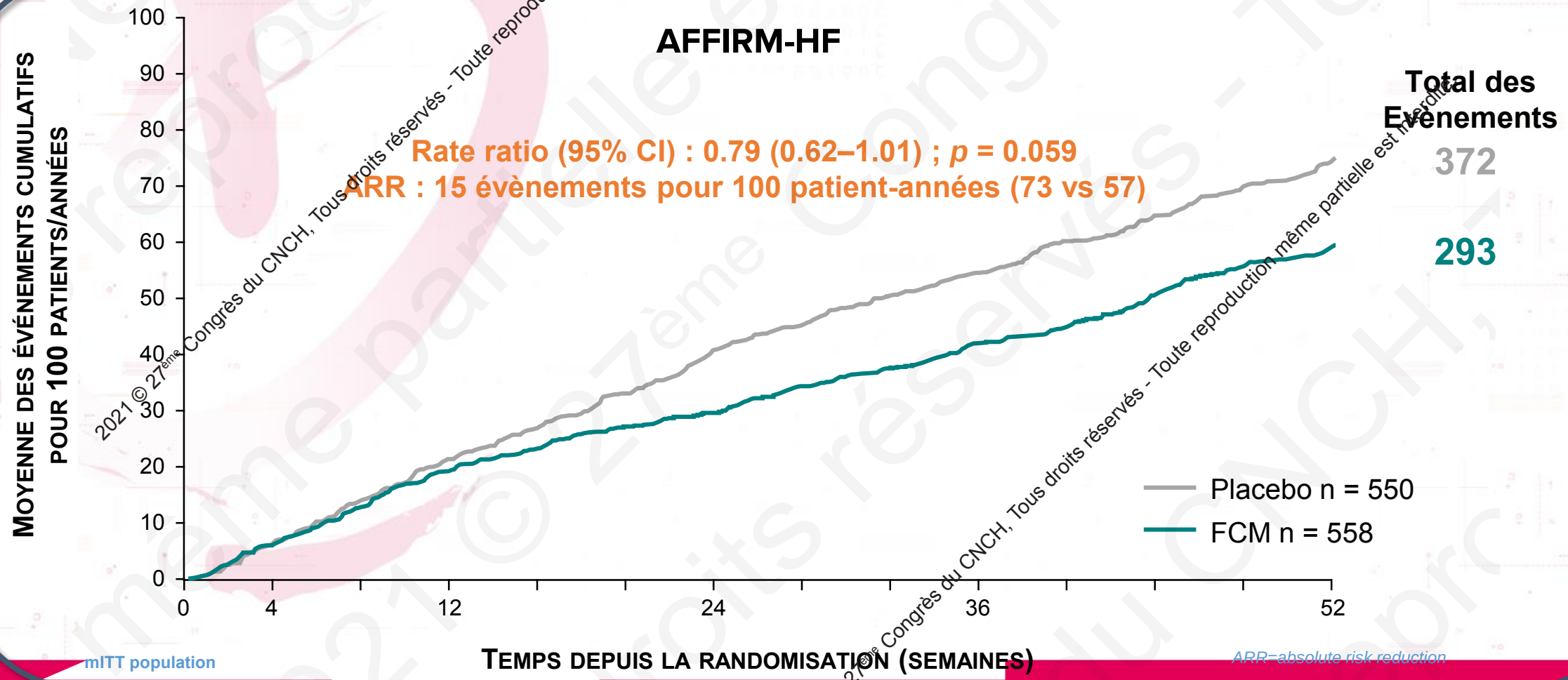
Emagliflozin: 388 events
Placebo: 553 events

Analysis of first and recurrent HHF accounting for CV death as terminal event using a joint frailty model. Model includes covariates age, baseline eGFR, treatment, region, baseline diabetes status, sex, and baseline LVEF, estimated dependence between adjudicated HHF and adjudicated CV death, and variance of frailty. CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction

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

RÉSULTATS – CRITÈRE PRIMAIRE

HOSPITALISATIONS TOTALES POUR IC ET DÉCÈS CV



mITT population

ARR=absolute risk reduction

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

CONCLUSIONS – AFFIRM-AHF

- Chez les patients avec une **carence en fer**, **stabilisés après un épisode de décompensation d'IC**, **avec une FEVG < 50%**, le traitement par FCM (versus placebo), prescrit avant la sortie de l'hôpital, entraine à 52S :

  - ✔ **Une réduction de risque de survenue du critère composite d'hospitalisations pour IC et décès CV de 21%** (p = 0,059) à la **limite de la significativité** et sans effet apparent sur les décés CV (Critère primaire)
  - ✔ Le résultat du critère primaire est essentiellement impacté par la **réduction des hospitalisations pour insuffisance cardiaque de 26% (p = 0,0013)**
  - ✔ **Une réduction de 20% du risque de survenue de la première hospitalisation pour insuffisance cardiaque ou décès CV** (p = 0,030)

- **80% des patients n'ont eu recours qu'à 1 ou 2 administrations de FCM** durant l'étude

- L'analyse de sensibilité pré-spécifiée Covid avant le gel des données révèle une différence en faveur du FCM sur les critères primaires et secondaires

- Tolérance : comparable entre FCM et placebo

La supplémentation par le FCM chez des patients en CM, avec une FEVG < 50%, stabilisés après un épisode d'IC aigue, réduit le risque de ré-hospitalisations pour IC

ESC 2021 guidelines: other drugs recommended or to be considered in selected patients with HFrEF

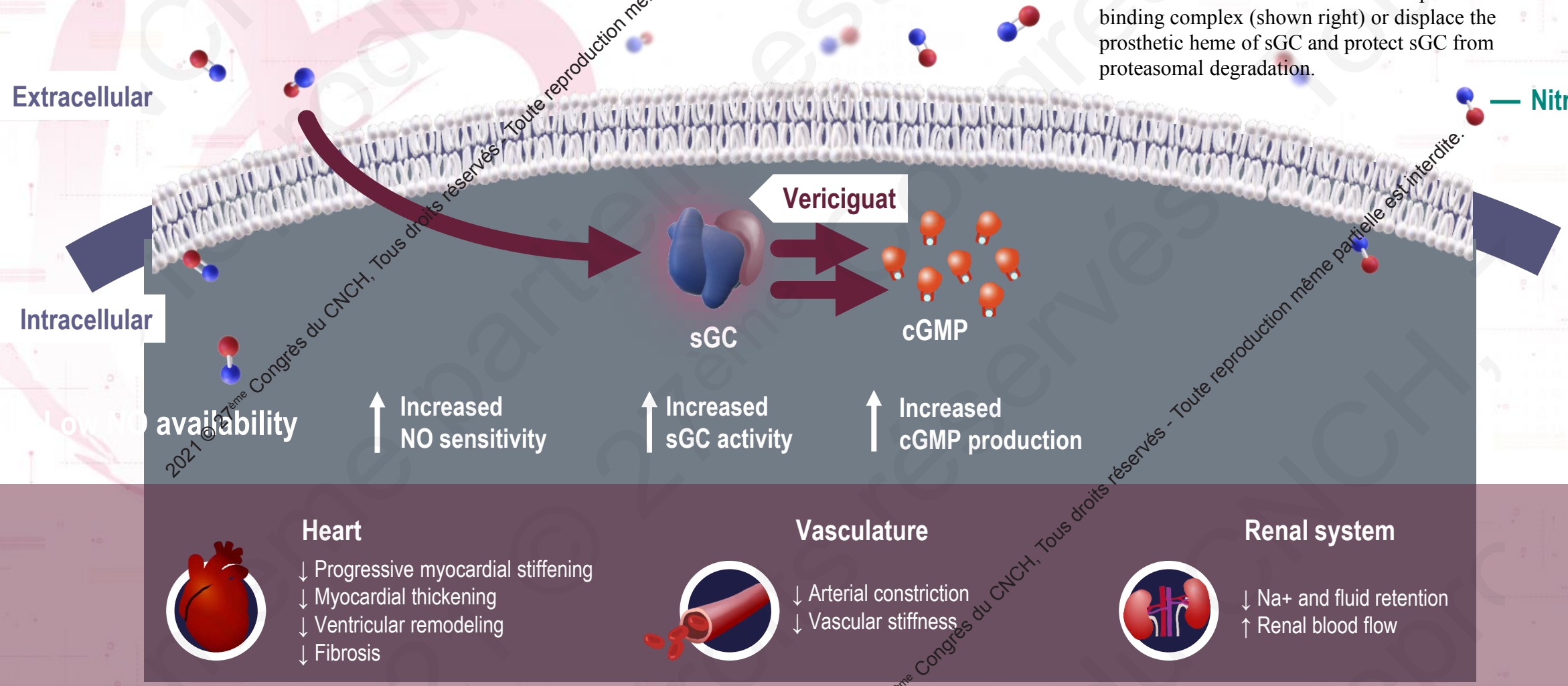
Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate any of an ACE-I, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death.[143]	IIb	B
Digoxin		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).[144]	IIb	B
I_f-channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.[139]	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.[140]	IIa	C
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.[141]	IIb	B
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.[142]	IIa	B

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

sGC Stimulation Targets an Untapped Pathway That May Lead to the Development and Progression of HF[1–8]

Stimulators of sGC stabilize the nitrosyl–heme complex

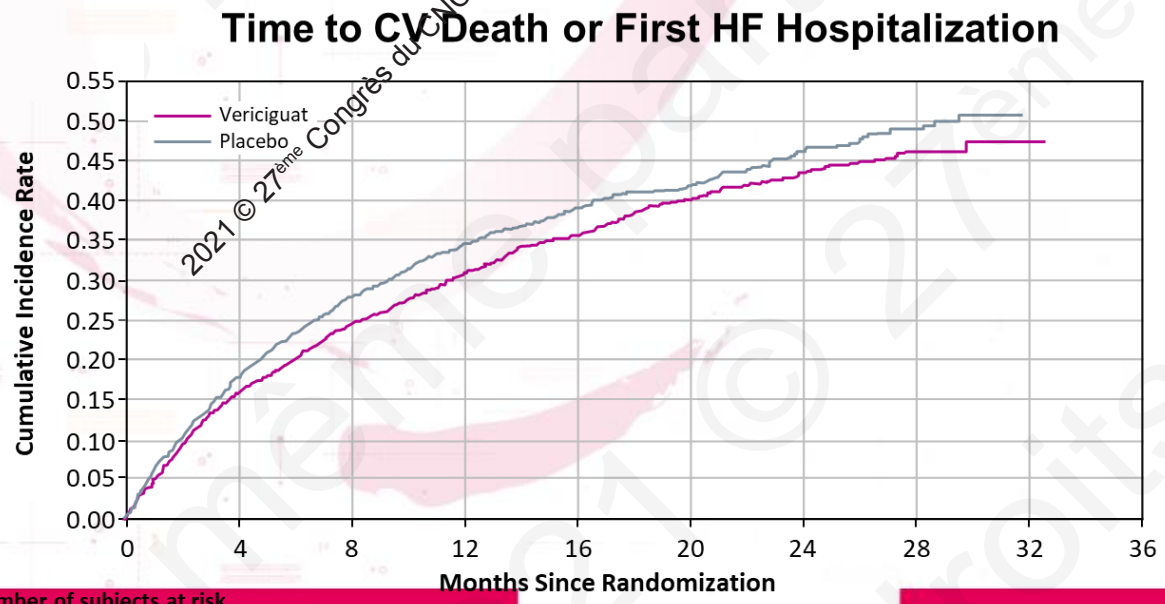
Activators of sGC bind to the unoccupied heme-binding complex (shown right) or displace the prosthetic heme of sGC and protect sGC from proteasomal degradation.



1. Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123. 2. Mann DL et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Elsevier/Saunders; 2015. 3. Boerrigter G et al. *Handb Exp Pharmacol*. 2009;191:485. 4. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225. 5. Felker G & Mann D. *Heart Failure: A Companion to Braunwald's Heart Disease*. Elsevier; 2020. 6. Armstrong PW et al. *JACC Heart Fail*. 2018;6:96; 7. Follmann M et al. *J Med Chem* 2017;60:5146; 8. Mathar I et al. *Circulation*. 2018;138:A15553.

Vericiguat significantly reduced the risk of the primary composite end point of HFH or CV death[1]

	Vericiguat (N=2,526)			Placebo (N=2,524)			Treatment Comparison	
	n	(%)	Annual %[a]	n	(%)	Annual %[a]	HR (95% CI)[b]	*P* Value[c]
Primary composite outcome and components								
HFH[d] or CV death	897	(35.5)	33.6	972	(38.5)	37.8	0.90 (0.82, 0.98)	0.02
HFH[d]	691	(27.4)		747	(29.6)			
CV death[e]	206	(8.2)		225	(8.9)			



HR: 0.90 (95% CI: 0.82-0.98)
***P*=0.02**
ARR: 4.2% per year
Annual NNT: 24†

Median treatment duration for primary endpoint and FU : 10.8 mo

†Calculations:
ARR= 37.8-33.6= 4.2
Annual NNT = 100/4.2 = 24

For patients with multiple events, only the first event contributing to the composite endpoint is counted in the table. [a]Total patients with an event per 100 patient-years at risk. [b]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race). [c]From log-rank test stratified by the stratification factors defined by region and race. [d]Time to first event. [e]Deaths included in the primary and secondary composiite outcomes were not preceded by a hospitalization for HF. N = number of subjects in ITT population. n = number of patients with an event. Based on data up to the primary completion date (18 June 2019).

1. Armstrong PW, et al. Vericiguat in patients with heart failure with reduced ejection fraction. *N Engl J Med*. DOI: 10.1056/NEJMoa1915928.

DIFFERENCES BETWEEN PARADIGM-HF, DAPA-HF, EMPEROR-REDUCED, GALACTIC-HF AND VICTORIA (2)

Baseline characteristics*	PARADIGM HF (N=8399)[1–4] sacubitril/valsartan	DAPA-HF (N=4744)[5,6] Dapagliflozin	EMPEROR-Reduced (N=3730)[7] empagliflozin	GALACTIC-HF (N=8256)[8] omecamtiv mecarbil	VICTORIA (N=5050)[9] vericiguat
Median NT-proBNP, pg/ml	1608	1437	1907	2001	2816
Mean LVEF, % (% ≤ 30%)	29.5 ± 6.2	31.1 ± 6.8	27.5 ± 6.0 (73%)	26.6 ± 6.3	28.9 ± 8.3 (86%<40%)
NYHA class III or IV	25%	32%	25%	47%	41%
HFH <6 months ago	31%	16%	NR#	NR	84%
eGFR, ml/min/1.73 m²	68 (mean)	66 (mean)	62 (mean)	59 (median‡)	62 (mean)
eGFR <60 ml/min/1.73 m²	37%	41%	48%	52%	53%§
Median follow up (months)	27	18.2	16	21.8	10.8
Control arm : **Primary endpoint** events/ 100 PY	13.2	15.6	21.0	26.3	37.8
First HFH events/ 100 PY	7.5	9.8	8.1	10.8	13.9
CV death events/ 100 PY	7.7	7.9	15.5	19.1	23.1

*Some values in table were derived from different patient n-numbers than shown due to data availability. #In the EMPEROR-Reduced study, HFH was reported in ≤12 months (31%). ‡In the GALACTIC-HF study, median eGFR (IQR) values are reported for the omecamtiv mecarbil and placebo arms. §eGFR ≤60 ml/min/1.73 m²; ‡Secondary endpoint value.

eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalisation; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PY, patient years.

1. McMurray JJV et al. *Eur J Heart Fail.* 2014;16:817–825; 2. Solomon SD et al. *JACC Heart Failure.* 2016;4:816–822; 3. McMurray JJV et al. *N Engl J Med.* 2014;371:993–1004; 4. Butler J et al. *Circulation.* 2020;142:717–719; 5. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402–1411; 6. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 7. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 8. Teerlink JR et al. *N Engl J Med.* 2020; doi: 10.1056/NEJMoa2025797; 9. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

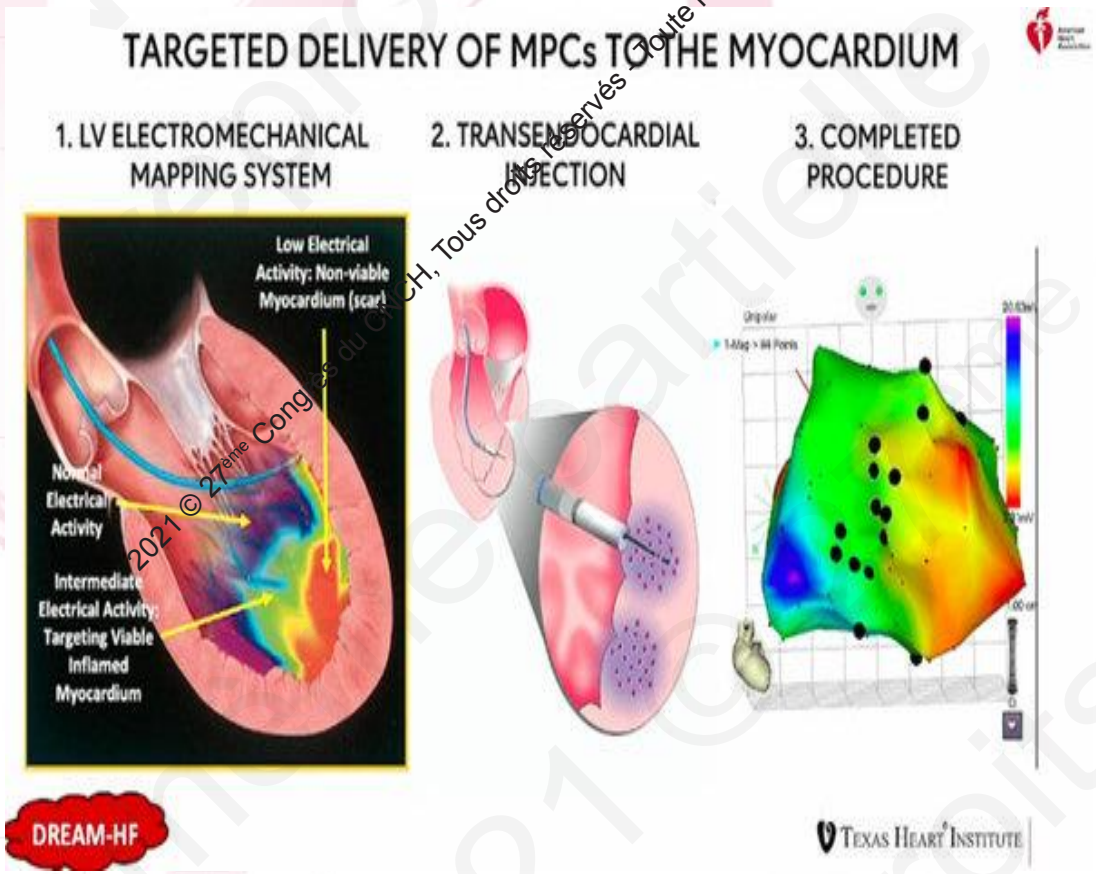
Conclusions

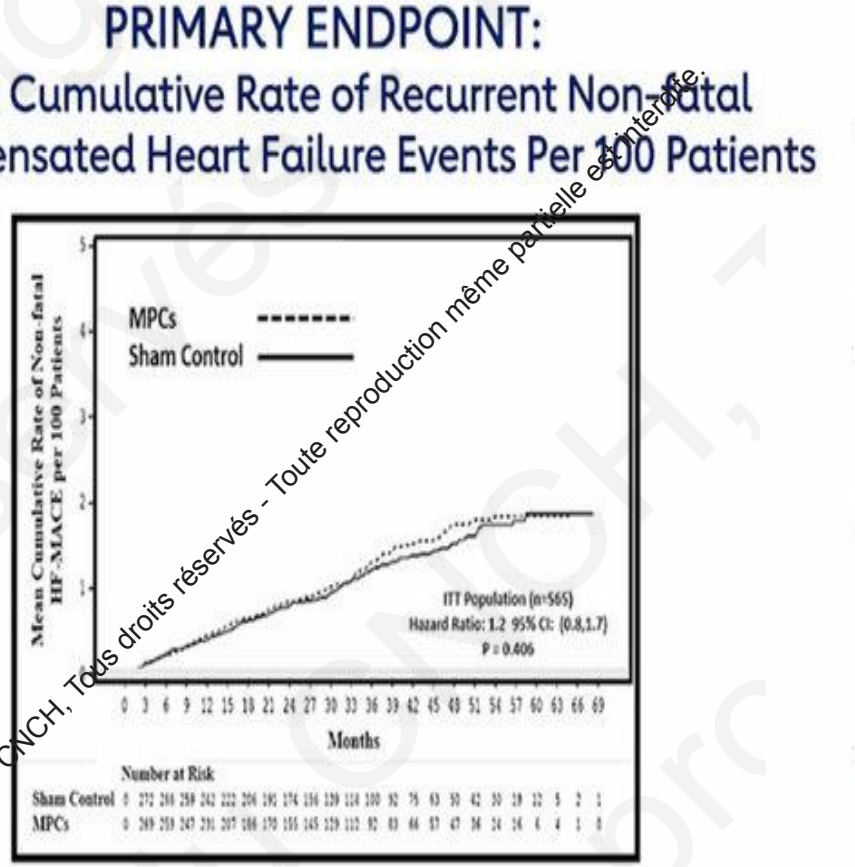
- Vericiguat engages a **new therapeutic target** by enhancing the cyclic GMP pathway directly
- Vericiguat achieved clinically **meaningful absolute primary event reduction of 4.2** / 100 patient-yrs. in the presence of guideline based care
- Vericiguat **is the first and only therapy to be recommended by the ESC for patients following a worsening HF event**
- Vericiguat has an excellent safety profile:
  - **No excessive reduction in blood pressure** even in patients who are predisposed to BP decreases (e.g. older patients, those with lower baseline SBP and those receiving concurrent ARNi)[2]
  - **No impact on renal function**[3]
- Vericiguat is **a once-daily** medicine, **easy to titrate**, generally **safe and well tolerated**, without the need for monitoring renal function or electrolytes,
- **The beneficial effect of vericiguat vs placebo is consistent** even in high-risk groups such as those with **AF**, with **low baseline SBP**, **with poor renal function**, or with **hyperK+** [2–4]
- Vericiguat may be considered on top of 4 pilars drugs after a new worsening event or if symptoms remain

AF, atrial fibrillation; ARNi, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; cTnT, cardiac troponin; European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide SBP, systolic blood pressure

1. Metra M. ESC-HF. 2021. Oral; 2. Lam CSP *et al.* ESC-HF. 2021. Oral; 3. Voors AA *et al*. *Eur J Heart Fail.* 2021; doi: 10.1002/ejhf.2221; 4. Ponikowski P *et al.* ESC-HF. 2021. Oral; 5. Ezekowitz JA *et al.* ESC-HF 2021. Oral; 6. DeFilippi CR *et al.* ESC-HF. 2021. Oral.

Thérapie cellulaire: étude DREAM-HF

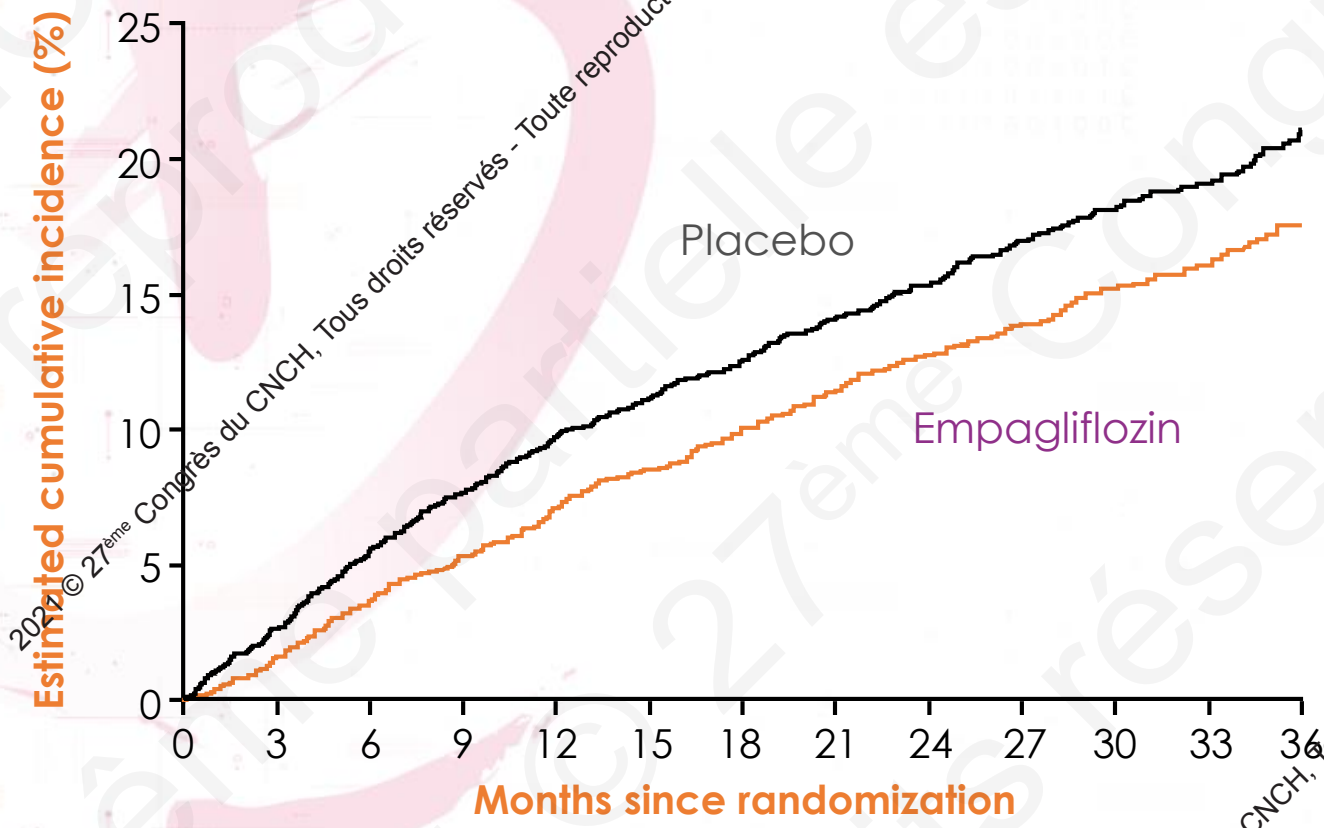




ICFEP

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

Empagliflozin demonstrated a clinically meaningful 21% RRR in the composite primary endpoint of CV death or HHF



Patients at risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	581	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1000	709	402

RRR 21%

ARR 3.3%

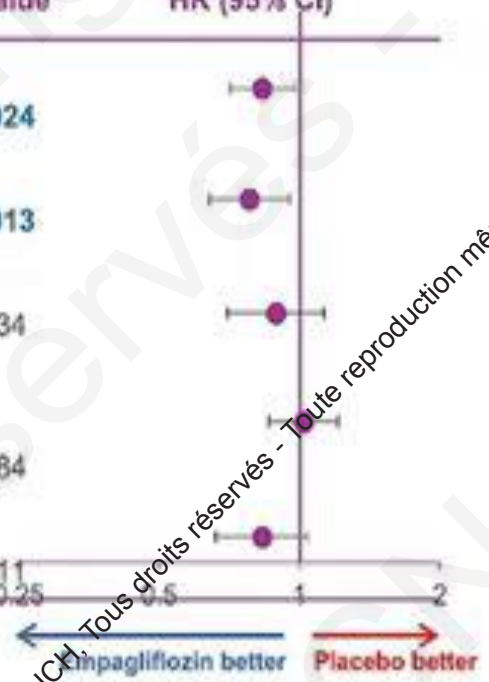
NNT*=31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

EMPEROR-PRESERVED: FE VG >50%

Endpoint	Events		Events/100 patient-years				HR (95% CI)
	Placebo (n=2,003)	Empagliflozin (n=2,002)	Placebo	Empagliflozin	HR (95% CI)	P-value	
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	



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