QUELLES NOUVEAUTES DANS LE TRAITEMENT DE L'INSUFFISANCE CARDIAQUE ?

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Risk Factors and Heart failure: Molecular and Clinical Investigations

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Table 1: Classes of Recommendations		
Classes of Recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Je te recommande de le faire ….

Car le niveau de preuve ….

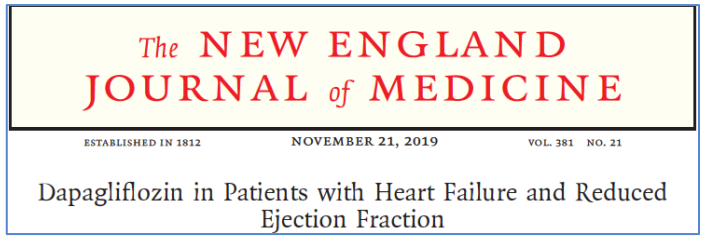
Table 2: Level of Evidence	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

La saga des SGLT 2 i

Quelle année

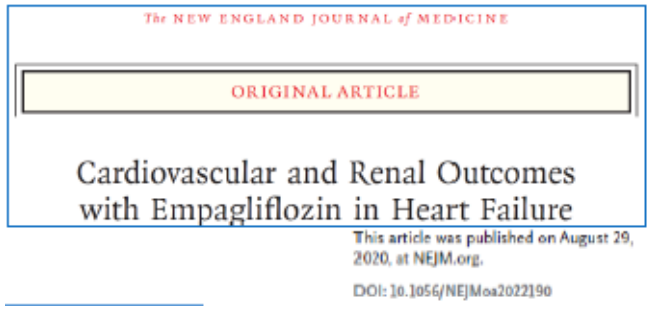
SGLT2-I in heart failure ± diabetes

	DAPAGLIFOZ E	EMPAGLIFOZINE	SOTAGLIFOZINE
	ESC2019	*ESC2020*	
HF-rEF	**DAPA-HF**	**EMPEROR-Reduced**	
HF-pEF	DELIVER (Declare-Timi 58)	EMPEROR-Preserved	(SCORED)
PostMI with rEF	DAPA-MI	EMPACT-MI	
Acute /worsening HF	DICTATE-AHF	EMPULSE	**SOLOIST-WHF**
Exercise ability		EMEPRIAL	


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

This article was published on August 29, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2022190

DAPA-HF and EMPEROR-Reduced

Phase III randomised double-blind placebo-controlled trials

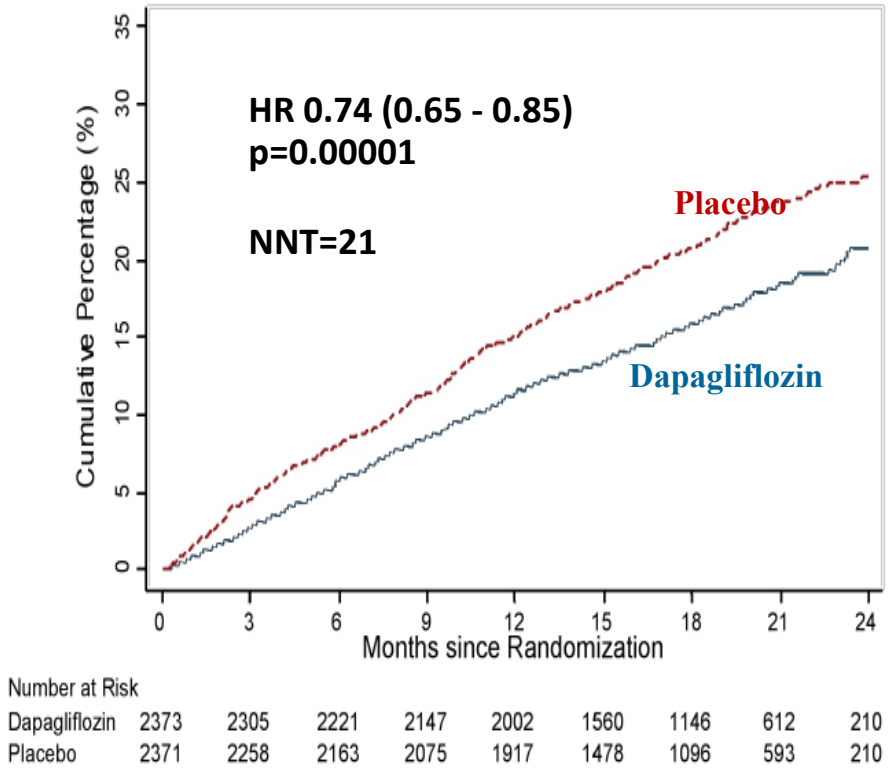
Chronic symptomatic HF with LVEF ≤ 40% and elevated NTproBNP levels

WITH OR WITHOUT DIABETES

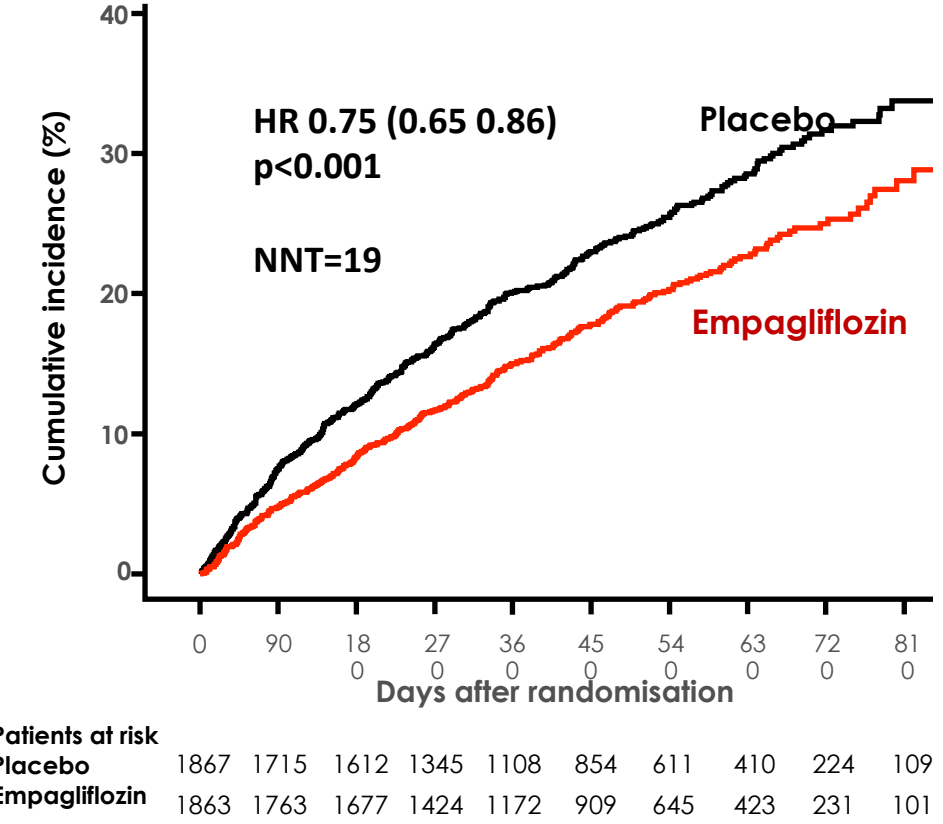
	DAPA-HF	EMPEROR-reduced
Intervention/control	Dapagliflozin 10 mg vs. placebo	Empagliflozin 10 mg vs. placebo
Number of included pts	N = 4744	N = 3730
Diabetes	45%	50%
Follow-up time	Median 18.2 months	Median 15.7 months
Primary outcome	Time to first CV death or hospitalisation for HF or urgent HF visit	Time to first CV death or hospitalisation for HF
Key secondary endpoints	Time to first CV death or hospitalisation for HF	- Total hospitalisations for heart failure - eGFR slope

DAPA-HF and EMPEROR-Reduced

Primary composite outcome



McMurray JJ et al. NEJM 2019



Packer M et al. NEJM 2020

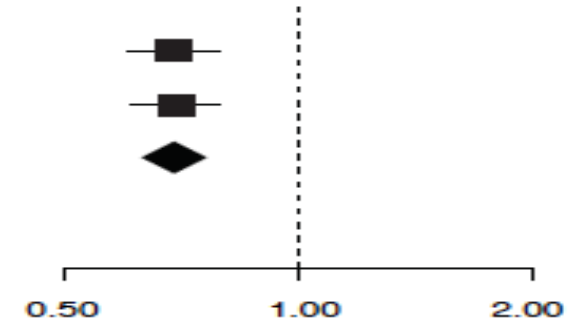
DAPA-HF and EMPEROR-Reduced

Components of the primary outcome

First HHF

	SGLT2i n with event/N analysed (%)	Placebo n with event/N analysed (%)	HR (95% CI)
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)

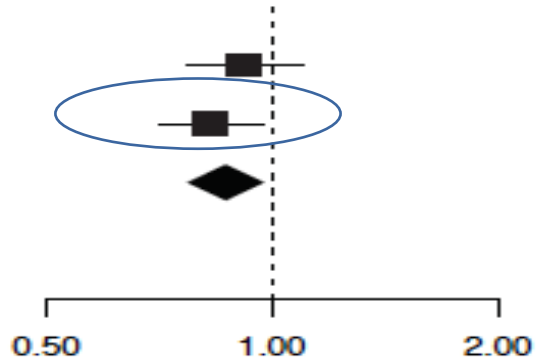
Test for overall treatment effect, p<0.0001
Test for heterogeneity of effect, p=0.90



CV death

	SGLT2i n with event/N analysed (%)	Placebo n with event/N analysed (%)	HR (95% CI)
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



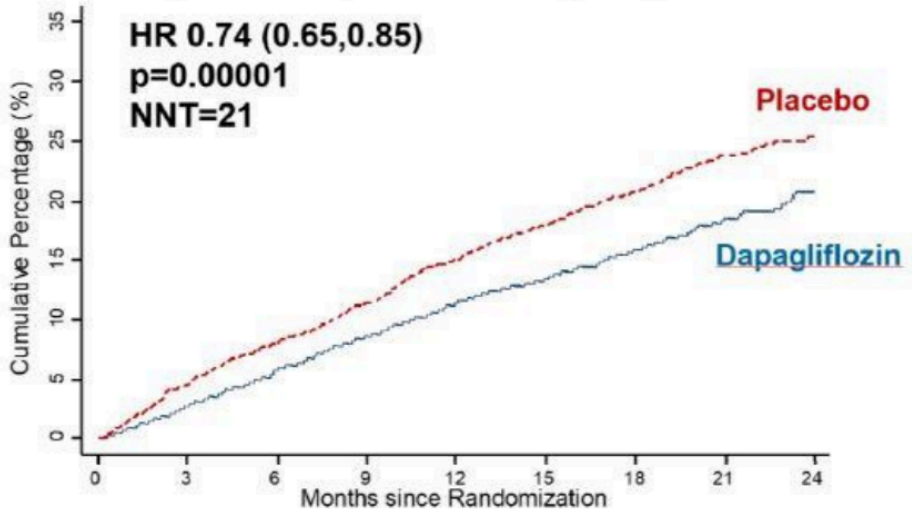
Zannad F et al. Lancet 2020

DAPA - HF

Results

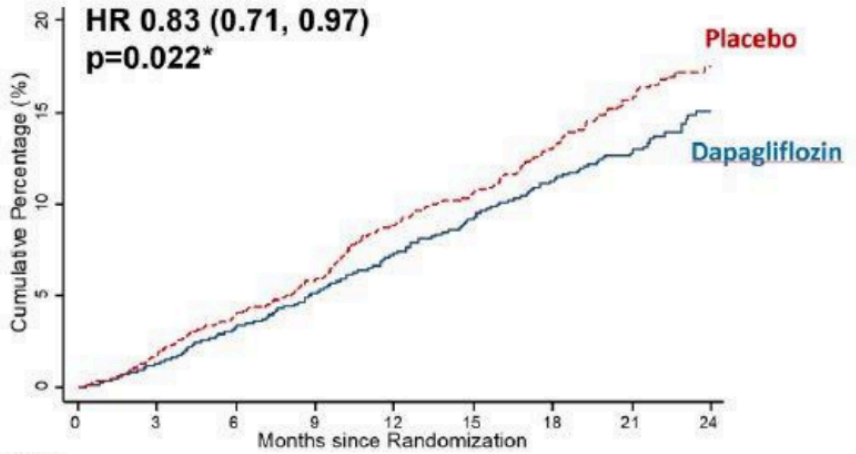
Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



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

All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

Kansas City Cardiomyopathy Questionnaire (KCCQ)

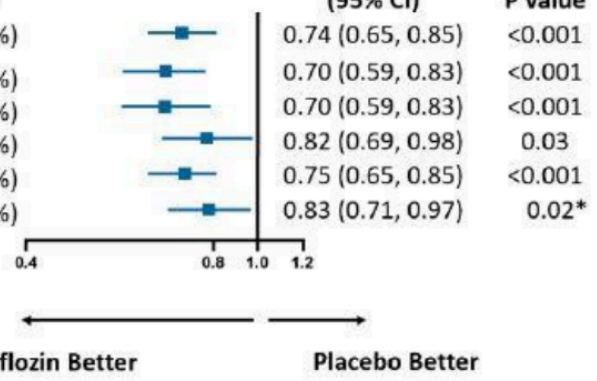
Total Symptom Score: Proportion with ≥5 point change from baseline to 8 months*

Treatment	Dapagliflozin	Placebo	Odds ratio (95% CI)
≥5 point improvement	58%	51%	1.15 (1.08,1.23) P<0.001
≥5 point deterioration	25%	33%	0.84 (0.78,0.90) P<0.001

*Taking account of death

Summary of worsening HF events and death

Outcome	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)	P value
CV death, HF hospitalization or urgent HF visit	386 (16.3%)	502 (21.2%)	0.74 (0.65, 0.85)	<0.001
HF hospitalization or urgent HF visit	237 (10.0%)	326 (13.7%)	0.70 (0.59, 0.83)	<0.001
HF hospitalization	231 (9.7%)	318 (13.4%)	0.70 (0.59, 0.83)	<0.001
CV death	227 (9.6%)	273 (11.5%)	0.82 (0.69, 0.98)	0.03
CV death or HF hospitalization	382 (16.1%)	495 (20.9%)	0.75 (0.65, 0.85)	<0.001
Death from any cause	276 (11.6%)	329 (13.9%)	0.83 (0.71, 0.97)	0.02*



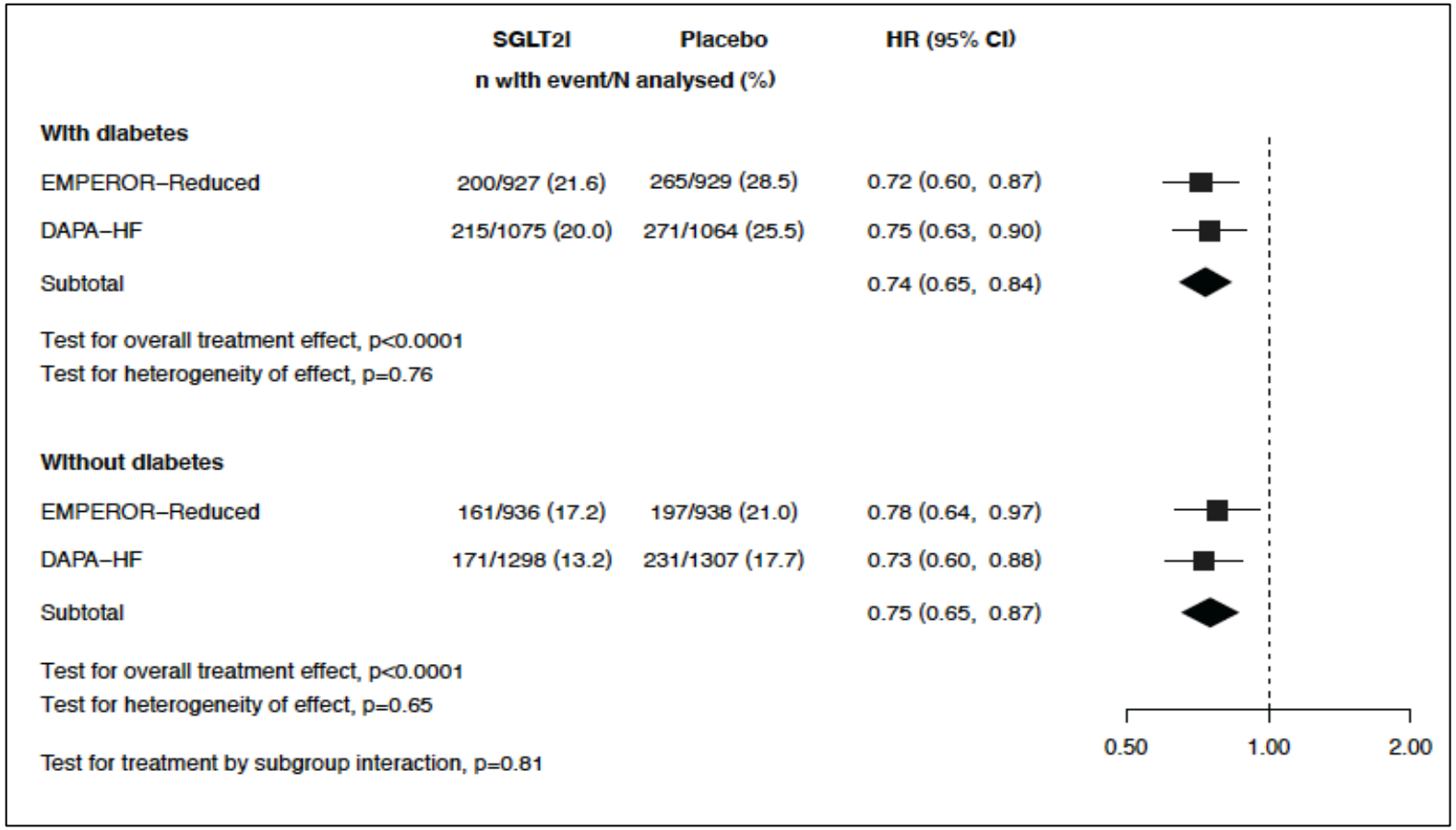
DAPA-HF and EMPEROR-Reduced

No increase in adverse events

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	**Placebo**	**Dapagliflozin**	**Placebo**
Serious AEs	41.4%	48.1%	35.7%	40.2%
Any renal AE	9.4%	10.3%	6.0%	6.7%
Volume depletion	10.6%	9.9%	7.2%	6.5%
Ketoacidosis	0	0	0.1%	0
Severe hypoglycaemic events	0.3%	0.4%	0.2%	0.2
Bone fractures	2.4%	2.3%	2.0%	2.0%
Lower limb amputation	0.7%	0.5%	0.5%	0.5%

DAPA-HF and EMPEROR-Reduced

Benefical whatever diabetes status



Zannad F et al. Lancet 2020

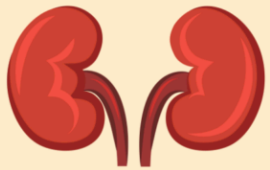
SOLOIST - WHF TRIAL

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

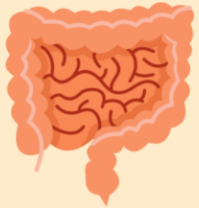
SOTAGLIFLOZIN

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

2020

EMPEROR-REDUCED

Cardiovas
with Em

Double-blind,

Objective: To e
with chronic he
with or without

3730
patients

Inclusio
without
tional cl
fraction

empagliflozi
(N=1863)

2019

DAPA-HF TRIAL

Dapagli
Failure a

Randomized

Objective: To
cotransporte
placebo amo
reduced ejec

2020

SOLOIST-WHF TRIAL

Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?

DAPA-CKD

21 Countries
286 Centers

≥18 yo

eGFR ≥ 25 to ≤ 75ml/min

UACR ≥ 200 to ≤ 5000mg/g

Max tolerated dose of ACEi/ARB

With and without T2DM

Mean Age 62y, 67% ♂
eGFR 43ml/min
UACR 950mg/g
ACEi/ARB 97%
With T2DM 68%

MEAN FOLLOW-UP: 2.4 YEARS

10 mg
DAPAGLIFLOZIN
+STANDARD CARE
N=2152

N=4304

P
PLACEBO
+STANDARD CARE
N=2152

Sustained ≥ 50% decline in GFR, ESKD, Renal or CV Death	Sustained ≥ 50% decline in GFR, ESKD, Renal Death	CV Death or hHF	All-cause Mortality
HR 0.61 (95% CI 0.51-0.72) p=0.000000018 NNT=19	HR 0.56 (0.45-0.68) p=0.000000018	HR 0.71 (0.55-0.92) p=0.0089	HR 0.69 (0.53-0.88) p=0.0035

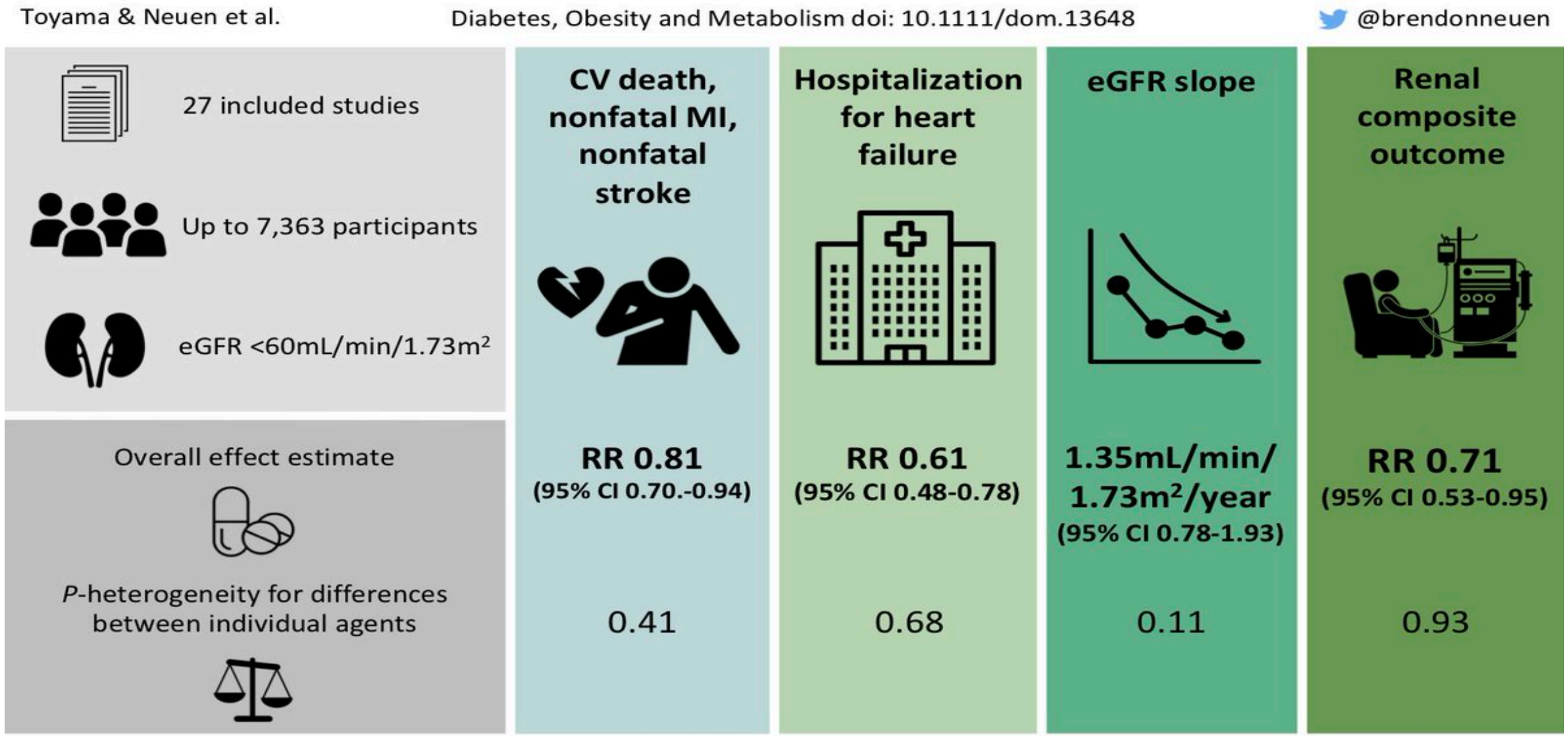
Results are consistent with patients with and without T2DM
% of patients who discontinued the drug or who experienced SAE was similar in both groups
DKA, 2 in placebo group vs none in Dapagliflozin group
No DKA or severe hypoglycemia in patients without T2DM

CONCLUSION: Dapagliflozin significantly reduces the risk of kidney failure, CV death or hospitalization for HF and all-cause mortality in patients with CKD with and without T2DM compared to placebo. Dapagliflozin was well-tolerated, in keeping with its established safety profile.

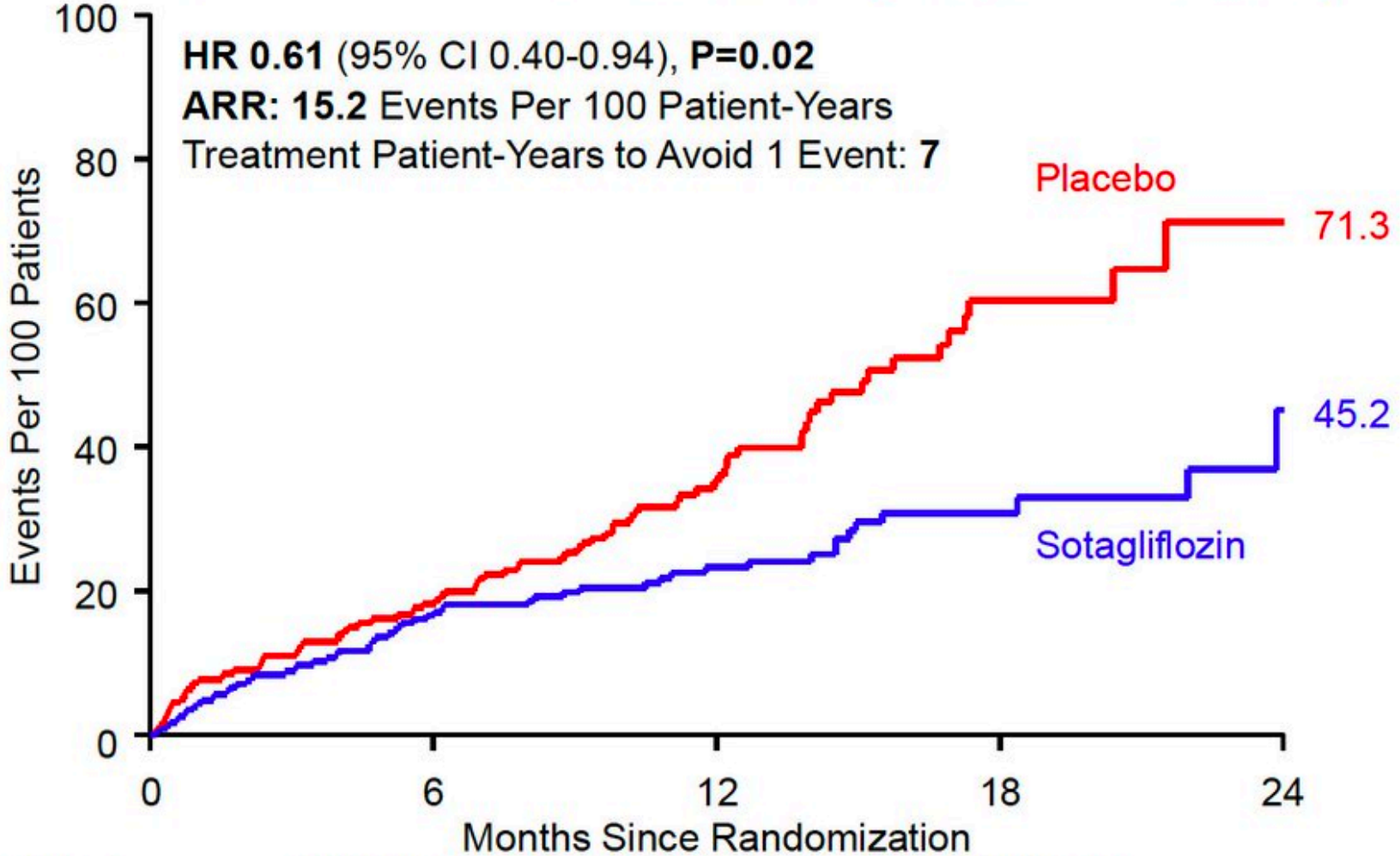
DAPA-CKD
presented by Professor Heerspink at the ESC Congress August 30, 2020

Visual Abstract by: Ana Naidas, MD

Les SGLT2 i sont des medicaments de:
l'IC à FE altérée et de l'IRC chez le diabetique et le non diabetique
donc des Médicaments du Cardiologue



Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 456 Patients with HFmrEF (40% - <50%)*

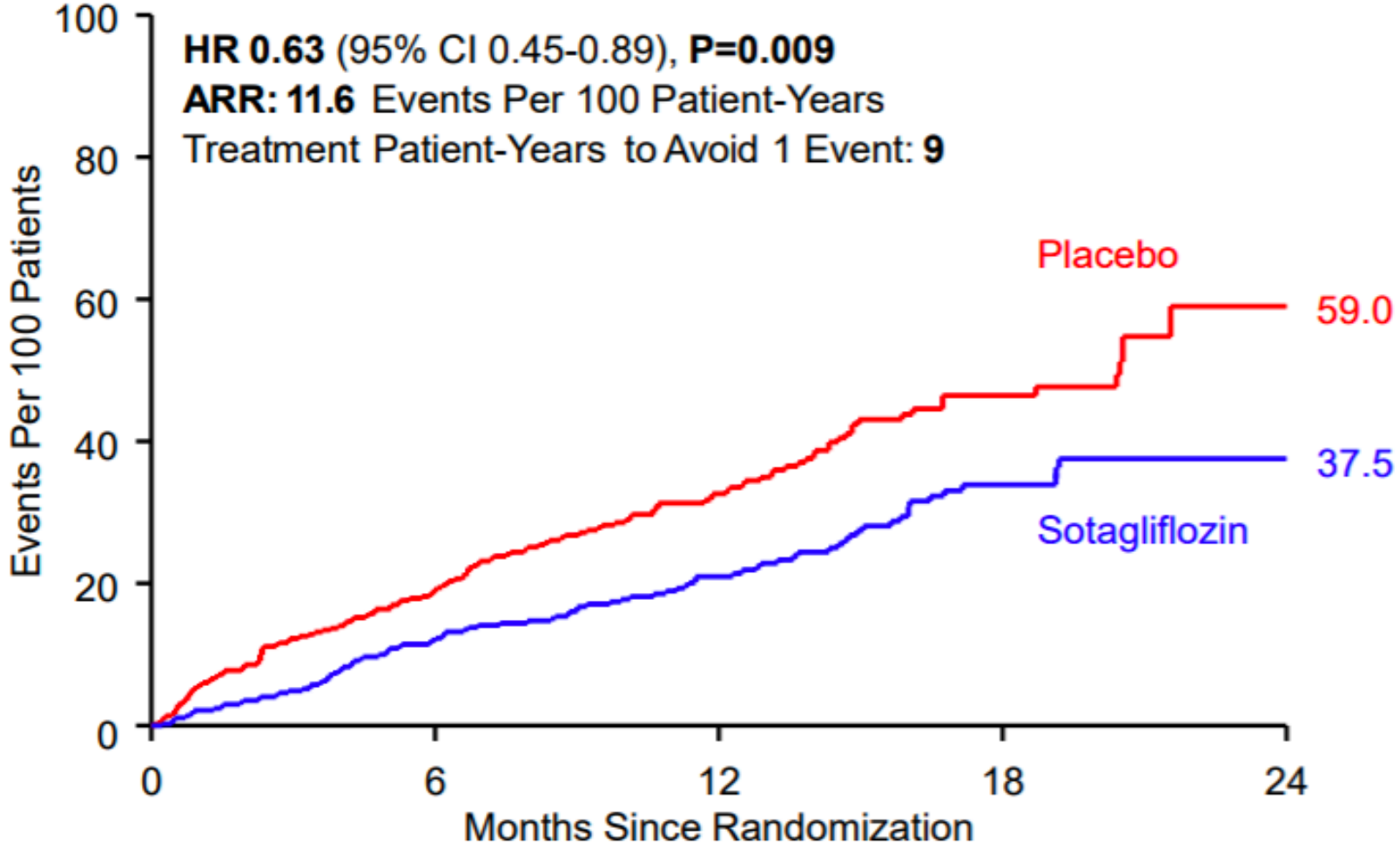


t DL. ACC 2021, virtual.

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

*post hoc

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



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

Bhatt DL. ACC 2021, virtual.

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%

What is new (1)

Recommendations for the diagnosis of HF	Class
Right heart catheterization should be considered in patients where HF is thought to be due to constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease, and high output states.	IIa
Right heart catheterization may be considered in selected patients with HFpEF to confirm the diagnosis.	IIb
Recommendations for treatment of chronic HF – *HFrEF*	**Class**
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I
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.	IIb

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Fer et IC

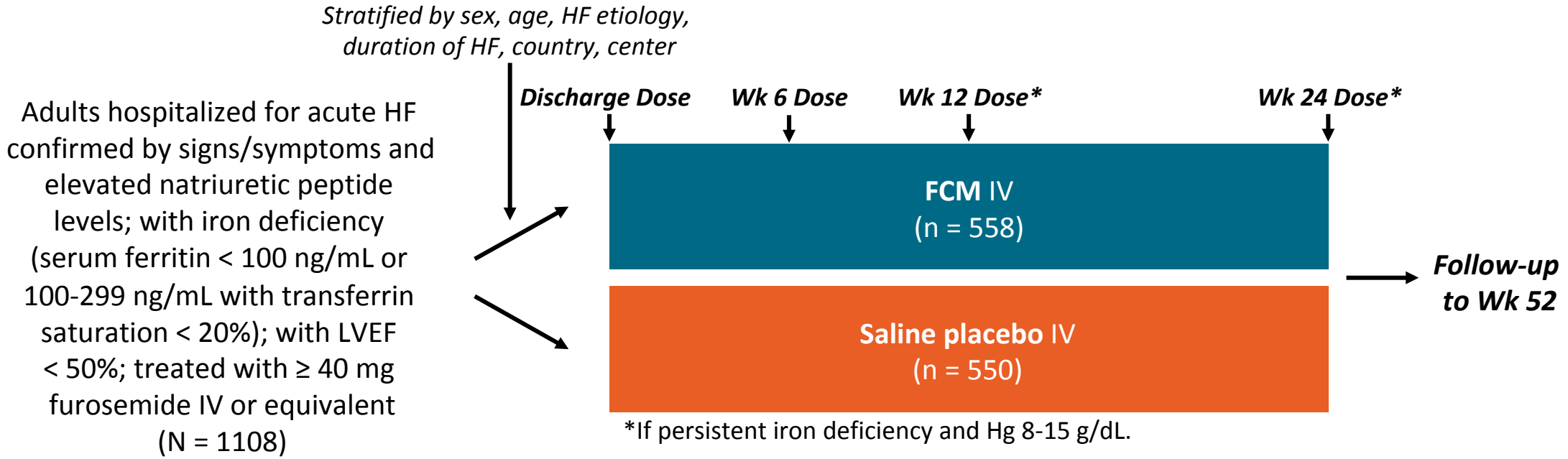
Ce que l'on savait

- Iron deficiency observed in ~ 50% of patients with heart failure[1]
  - Associated with increased risk of death, exercise intolerance, and impaired quality of life[1-3]
- Treatment with IV ferric carboxymaltose associated with greater exercise capacity, improved symptoms, and better quality of life in iron-deficient, ambulatory patients with heart failure[4]
- Unknown whether FCM is beneficial in iron-deficient patients with stabilized acute heart failure[5]
- AFFIRM-HF trial compared cardiovascular outcomes and safety with FCM vs placebo at discharge in iron-deficient patients with stabilized acute heart failure[5,6]

1. Klip. Am Heart J. 2013;165:575. 2. Jankowska. J Card Fail. 2011;17:899. 3. Enjuanes. Int J Cardiol. 2014;174:268.
4. Anker. NEJM. 2009;361:2436. 5. Ponikowski. AHA 2020. Abstr LBS.02. 6. Ponikowski. Lancet. 2020;[Epub].

Ce que l'on a fait : AFFIRM-AHF

- International, randomized, double-blind phase IV trial



- Primary composite endpoint: total HF hospitalizations and CV death up to Wk 52
- Secondary endpoints (all up to Wk 52): composite of total CV hospitalizations and CV death; CV death; total HF hospitalizations; time to first HF hospitalization or CV death; days lost due to HF hospitalizations or CV death

Ponikowski. Lancet. 2020;[Epub]. NCT02937454.

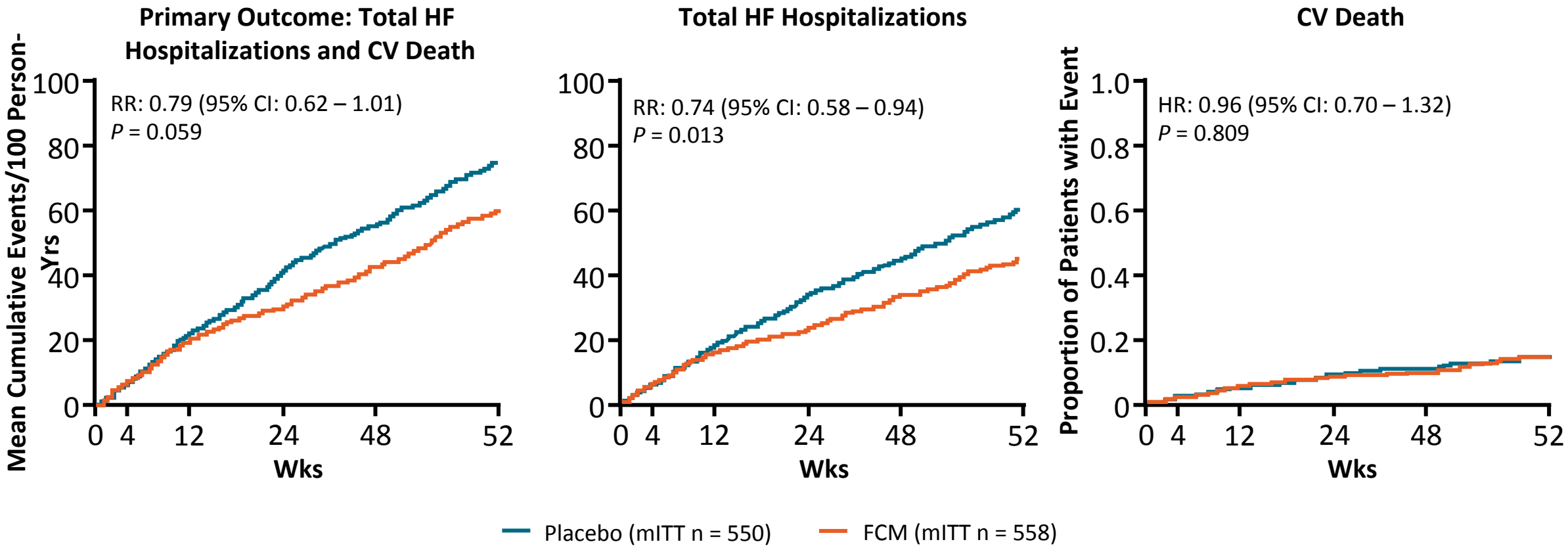
AFFIRM-AHF: Baseline Characteristics

Characteristic	FCM (n = 558)	Placebo (n = 550)
Mean age, yrs (SD)	71.2 (10.8)	70.9 (11.1)
Female, n (%)	244 (44)	250 (45)
Mean systolic BP, mm Hg (SD)	119.8 (15.2)	119.7 (15.6)
NYHA class III/IV, n (%)	272 (49)/16 (3)	277 (50)/22 (4)
Mean LVEF, % (SD)	32.6 (9.6)	32.7 (10.0)
Ischemic etiology, n (%)	265 (47)	257 (47)
HF newly diagnosed at index hospitalization, n (%)	153 (27)	165 (30)
Comorbidities, n (%)		
▪ Atrial fibrillation/flutter	314 (56)	305 (55)
▪ Diabetes	227 (41)	243 (44)
▪ CKD	222 (40)	227 (41)

Laboratory Data	FCM (n = 558)	Placebo (n = 550)
Median NT-proBNP, pg/mL (IQR)	4743 (2781-8128)	4684 (2785-8695)
Median BNP, pg/mL (IQR)	1068 (802-1715)	1204 (803-1955)
Mean Hg, g/dL (SD)	12.3 (1.6)	12.1 (1.6)
▪ Anemia, n (%)	292 (52)	312 (57)
Mean ferritin, ng/mL (SD)	83.9 (62.2)	88.5 (68.6)
▪ Ferritin < 100 ng/mL, n (%)	408 (73)	380 (69)
Mean TSAT, % (SD)	15.2 (8.3)	14.2 (7.5)
▪ TSAT < 20%, n (%)	457 (82)	469 (85)
eGFR < 60 mL/min/1.73 m^2, n (%)	292 (52)	288 (52)

Ponikowski. Lancet. 2020;[Epub].

Ce que nous avons appris : AFFIRM-AHF



Ponikowski. Lancet. 2020;[Epub].

Ce que nous avons appris : AFFIRM-AHF - Conclusions

- In iron-deficient patients with stabilized acute HF, FCM at discharge did not significantly improve primary composite outcome of total HF hospitalizations and CV death vs placebo
  - FCM significantly decreased total HF hospitalizations, time to first HF hospitalization or CV death, but not risk of CV death
- Prespecified COVID-19 sensitivity analyses found significant improvement in first HF hospitalization or CV death (21% reduction; *P* = .023)
- FCM treatment well tolerated with similar safety profiles in both arms

Ponikowski. AHA 2020. Abstr LBS.02. Ponikowski. Lancet. 2020;[Epub].

Recommendations for anaemia and iron deficiency in patients with heart failure

Recommendations	Class	Level
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.	IIa	B

HF = heart failure; LVEF = left ventricular ejection fraction; QOL= quality of life; TSAT = transferrin saturation.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

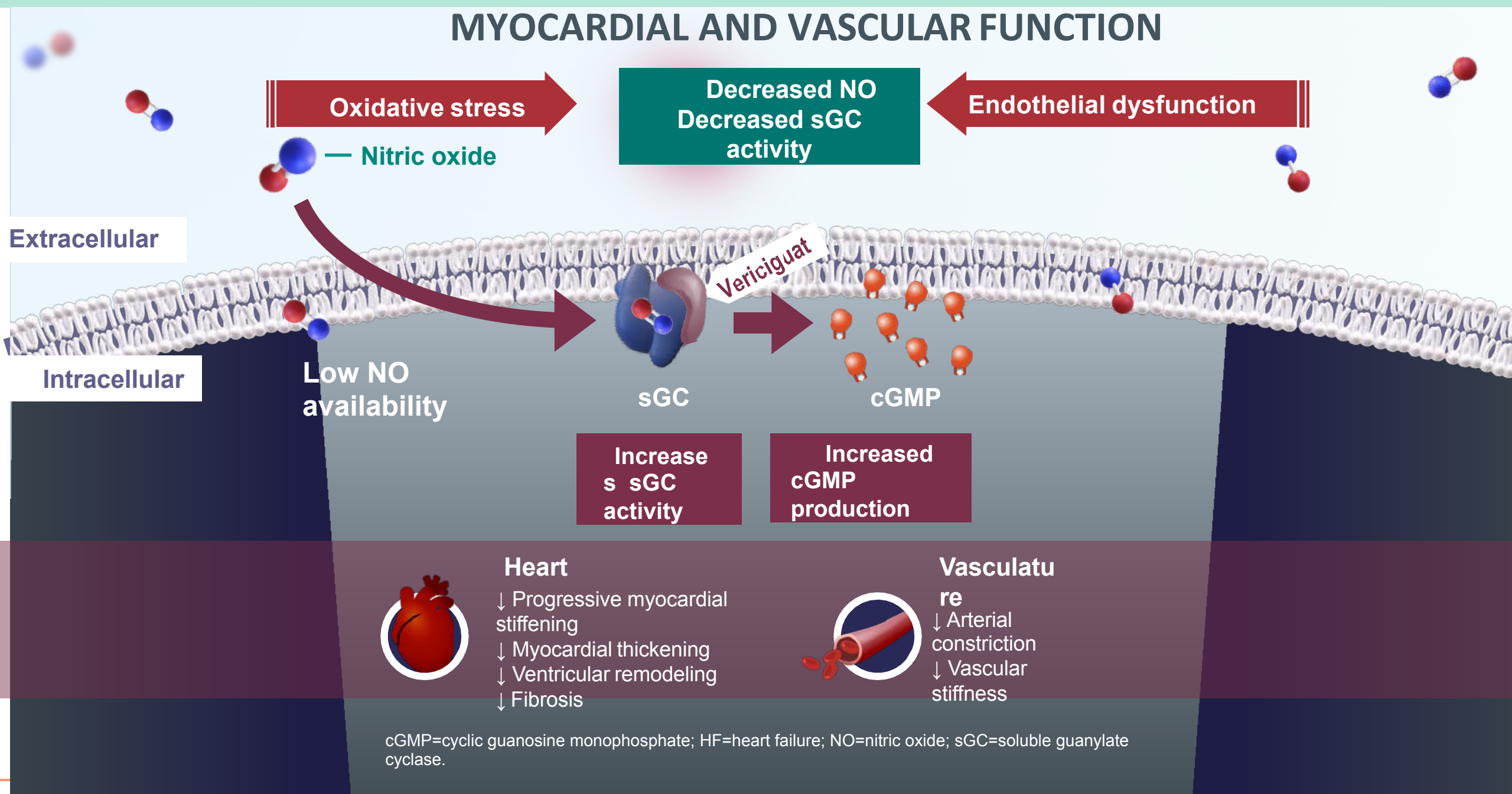
Vericiguat et IC

Ce que l'on savait / ce que l'on a fait : VICTORIA

- Despite optimal guideline-based treatment, patients with chronic heart failure (HF) have a substantial risk of death or HF hospitalization after a recent worsening HF event
- One such treatment option—based on phase IIb findings*—is the novel sGC stimulator vericiguat which directly enhances the cyclic GMP pathway
- In VICTORIA, we assessed the efficacy and safety of vericiguat in patients with reduced ejection fraction (EF) and chronic HF with a recent worsening HF event

*JAMA. 2015;314:2251-62.

VERICIGUAT INCREASES sGC ACTIVITY TO IMPROVE MYOCARDIAL AND VASCULAR FUNCTION



cGMP=cyclic guanosine monophosphate; HF=heart failure; NO=nitric oxide; sGC=soluble guanylate cyclase.

2020

VICTORIA TRIAL

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Phase 3, randomized, double-blind, placebo-controlled

Objective: To evaluate vericiguat compared with placebo among patients with HFrEF. Vericiguat increases soluble guanylate cyclase activity. By stimulating cyclic GMP, this may improve myocardial and vascular function.

5050 patients

Inclusion criteria: CHF patients; NYHA II-IV, LVEF <45%, on GDMT, recent HF hospitalization or IV diuretic use, elevated NT-proBNP ≥1000 pg/ml and clinically stable (SBP ≥100 mm Hg)

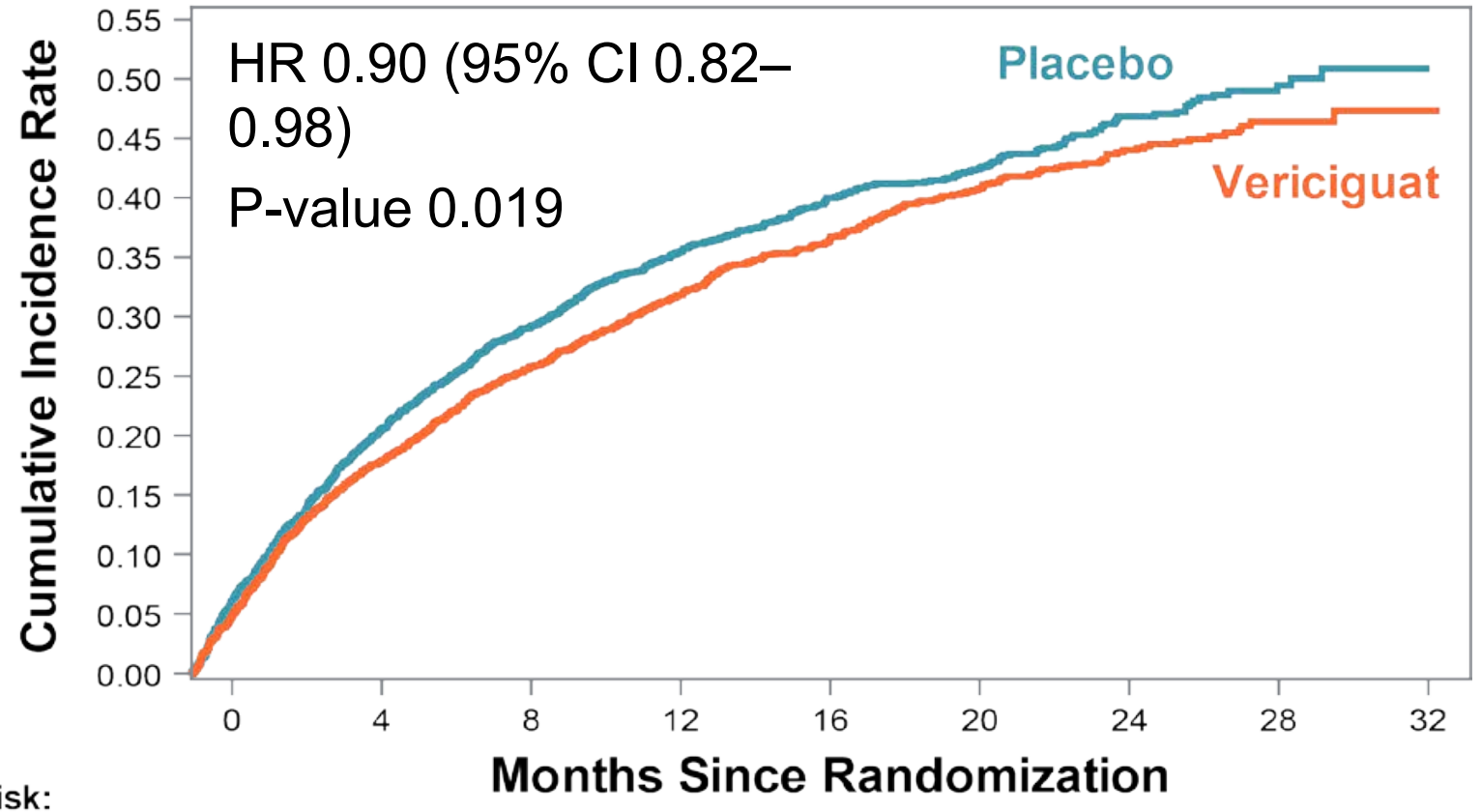
vericiguat (n = 2,526)

VS

placebo (n = 2,524)

Ce que nous avons appris : VICTORIA

Primary Composite Endpoint: CV Death or First HF Hospitalization



Safety & Tolerability

- Symptomatic hypotension and syncope tended to be more common with vericiguat
- More anemia developed with vericiguat (7.6%) than placebo (5.7%)
- Serious adverse events were similar: vericiguat (32.8%), placebo (34.8%)
- No adverse effects of vericiguat on either electrolytes or renal function
- At 12 months, 10 mg target dose achieved: vericiguat (89.2%), placebo (91.4%)

Ce que nous devrions faire : VICTORIA

- Vericiguat was significantly more effective than placebo in reducing:
  - The composite endpoint of CV death or HF hospitalization (primary endpoint)
  - HF hospitalization (first and recurrent)
- Heterogeneity in NT-proBNP quartile subgroups is the subject of ongoing investigation
- Vericiguat titrated to 10mg was generally safe and well tolerated
- Could be used in high risk HF patient with low e GFR before discharge, caution hypotension !
- Les nitrés modernes

Other pharmacological treatments indicated in selected patients with NYHA class II-IV heart failure with reduced ejection fraction (LVEF ≤40%) (3)

Recommendations	Class	Level
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.	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.	IIa	B
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.	IIb	B

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Omecamtiv et IC

Ce que l’on savait

- Les Inotropes améliorent les symptômes mais pas la Survie

- Problème des Calcitropes
  - Xamoterol, milrinone, enoximone, Flosequinan, Pimobendan, Ibopamine, Vesnarinone

- Espoir avorté avec les sensibilisants au calcium
- Espoir relancé avec les myotropes :
- Omecamtiv mecarbil: petite molecule activateur de la myosine, intérêt ?

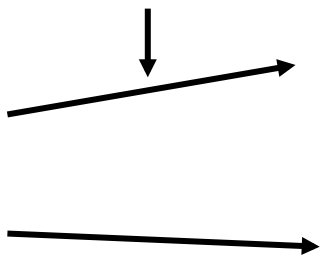
1. Teerlink. Lancet. 2016;388:2895. 2. Teerlink. JACC Heart Failure 2020;8:329. 3. Teerlink. AHA 2020. Abstr LBS.01. 4. Teerlink. NEJM. 2020;[Epub].

Ce que nous avons fait : GALACTIC-HF

- Randomized, double-blind, placebo-controlled, event-driven phase III trial

Adult (18-85 yrs of age) in/outpatients with symptomatic, chronic heart failure; LVEF ≤ 35%; BNP ≥ 125 pg/mL or NT-proBNP ≥ 400 pg/mL; receiving standard HF therapies (N = 8256)

Stratified by region, inpatient vs outpatient



Omecamtiv mecarbil* + SoC (n = 4120)

Placebo + SoC (n = 4112)

Median study exposure: 21.8 mos

*Starting dose 25 mg PO BID; adjusted to 25, 37.5 or 50 mg PO BID based on pharmacokinetic assessment at Wks 2 and 6

- Primary composite endpoint: time to first heart failure event or CV death (whichever occurs first)
- Secondary endpoints: time to CV death, change in KCCQ Total Symptom Score from baseline to Wk 24, time to first HF hospitalization, time to all-cause death

Teerlink. AHA 2020. Abstr LBS.01.

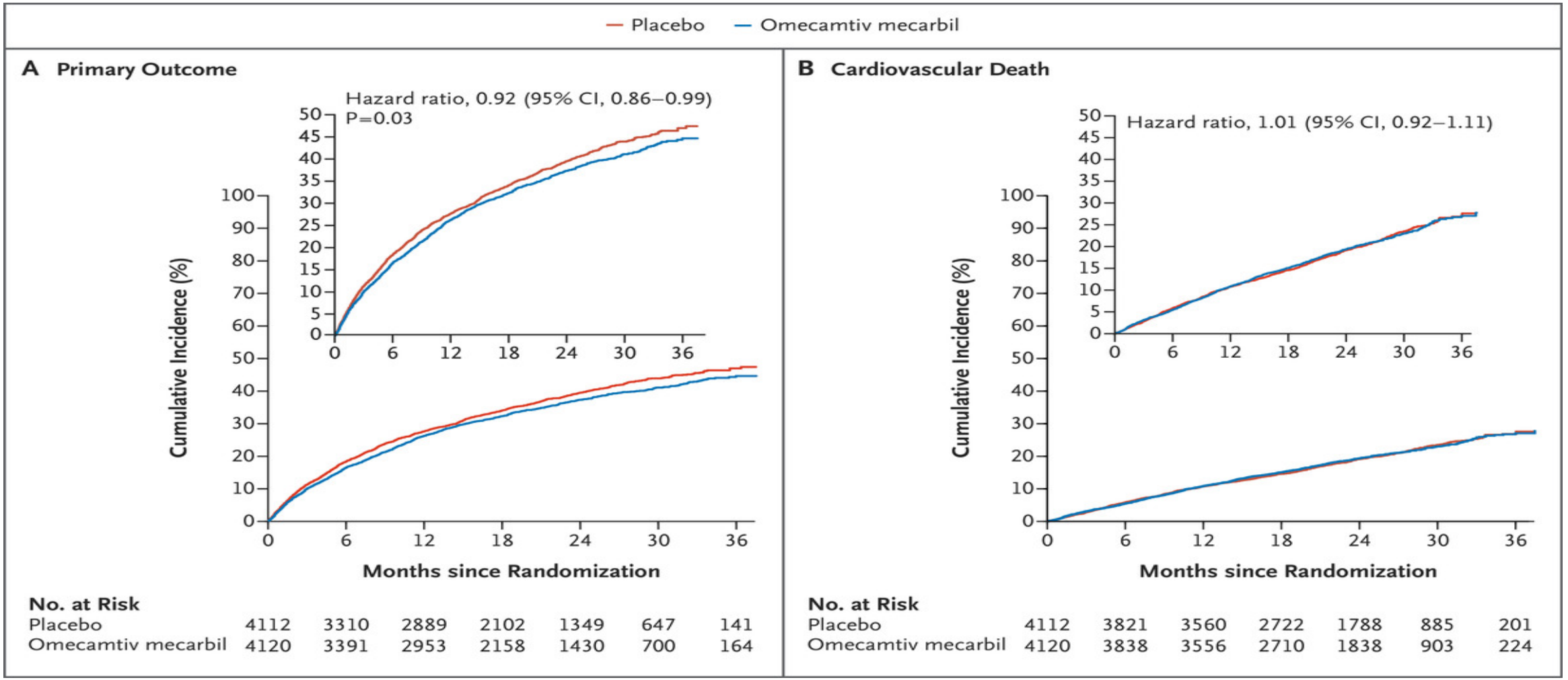
Ce que nous avons fait : GALACTIC-HF

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Omecamtiv Mecarbil (N = 4120)	Placebo (N = 4112)
Age — yr	64.5±11.3	64.5±11.4
Female sex — no. (%)	875 (21.2)	874 (21.3)
Race or ethnic group — no. (%)†		
White	3196 (77.6)	3201 (77.8)
Asian	355 (8.6)	355 (8.6)
Black	285 (6.9)	277 (6.7)
Other	284 (6.9)	279 (6.8)
Geographic region — no. (%)		
Eastern Europe or Russia	1344 (32.6)	1337 (32.5)
Western Europe, South Africa, or Australasia	961 (23.3)	960 (23.3)
Latin America	787 (19.1)	787 (19.1)
United States or Canada	693 (16.8)	693 (16.9)
Asia	335 (8.1)	335 (8.1)
Inpatient setting — no. (%)	1044 (25.3)	1040 (25.3)
Clinical features		
Atrial fibrillation or flutter — no. (%)	1146 (27.8)	1099 (26.7)
Type 2 diabetes mellitus — no. (%)	1652 (40.1)	1657 (40.3)
Ischemic heart failure — no. (%)	2193 (53.2)	2222 (54.0)
Left ventricular ejection fraction — %	26.6±6.3	26.5±6.3
NYHA classification — no. (%)		
II	2195 (53.3)	2173 (52.8)
III	1801 (43.7)	1815 (44.1)
IV	124 (3.0)	124 (3.0)
Median total symptom score on KCCQ (IQR)‡	68.8 (49.0–87.5)	68.8 (49.0–87.5)
Outpatient	74.0 (54.2–90.6)	75.0 (56.3–91.7)
Inpatient	54.2 (34.4–72.9)	52.1 (31.3–69.8)
Systolic blood pressure — mm Hg	116.3±15.4	116.6±15.3
Heart rate — beats/min	72.4±12.2	72.3±12.1
Median NT-proBNP (IQR) — pg/ml	1977 (980–4061)	2025 (1000–4105)
Median cardiac troponin I (IQR) — ng/liter	27 (12–52)	27 (13–52)
Median eGFR (IQR) — ml/min/1.73m^2	58.8 (44.3–74.3)	58.7 (43.8–73.7)
Heart-failure therapy — no. (%)		
ACE inhibitor, ARB, or ARN inhibitor	3583 (87.0)	3576 (87.0)
ARN inhibitor	819 (19.9)	782 (19.0)
Beta-blocker	3881 (94.2)	3883 (94.4)
Mineralocorticoid-receptor antagonist	3199 (77.6)	3198 (77.8)
SGLT2 inhibitor	104 (2.5)	114 (2.8)
Cardiac-resynchronization therapy	592 (14.4)	566 (13.8)
Implantable cardioverter–defibrillator	1326 (32.2)	1288 (31.3)

JR Teerlink et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2025797

Ce que nous avons appris : GALACTIC-HF



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Ce que nous avons appris : GALACTIC-HF

Outcome	HR (95% CI)	*P* Value
Time to first HF event or CV death (primary outcome)	0.99 (0.86-0.99)	.025
▪ Subgroup with baseline LVEF ≤ 28%	0.84 (0.77-0.92)	$P_{interaction}$ = .003
▪ Subgroup with baseline LVEF > 28%	1.04 (0.94-1.16)	
Time to first HF event	0.93 (0.86-1.00)	.06
Time to CV death	1.01 (0.92-1.11)	.86

- Consistent benefit in primary composite outcome seen with omecamtiv mecarbil across preplanned subgroups, except by baseline LVEF
- KCCQ symptom score change from BL to Wk 24 with omecamtiv mecarbil did not reach multiplicity controlled significance threshold of *P* = .002 (joint test *P* = .028)

Teerlink. AHA 2020. Abstr LBS.01. Teerlink. NEJM. 2020;[Epub].

Ce que nous avons appris : GALACTIC-HF

Adverse Event, %	Omecamtiv Mecarbil (n = 4110)	Placebo (n = 4101)	Relative Risk (95% CI)
Any serious AE	57.7	59.4	0.97 (0.94-1.01)
Drug discontinuation due to AE	9.0	9.3	0.97 (0.85-1.11)
Specific AEs of interest			
▪ Ventricular tachyarrhythmias	7.1	7.4	0.95 (0.82-1.11)
▪ Torsade de pointes/QT prolongation	4.3	4.8	0.90 (0.74-1.10)
▪ Serious AE of ventricular arrhythmia requiring treatment	2.9	3.1	0.93 (0.73-1.20)
Adjudicated major cardiac ischemic events	4.9	4.6	1.06 (0.87-1.29)
▪ Myocardial infarction	3.0	2.9	
▪ Hospitalized for unstable angina	0.6	0.3	
▪ Coronary revascularization	2.8	2.9	
Adjudicated strokes	1.8	2.7	0.68 (0.51-0.91)

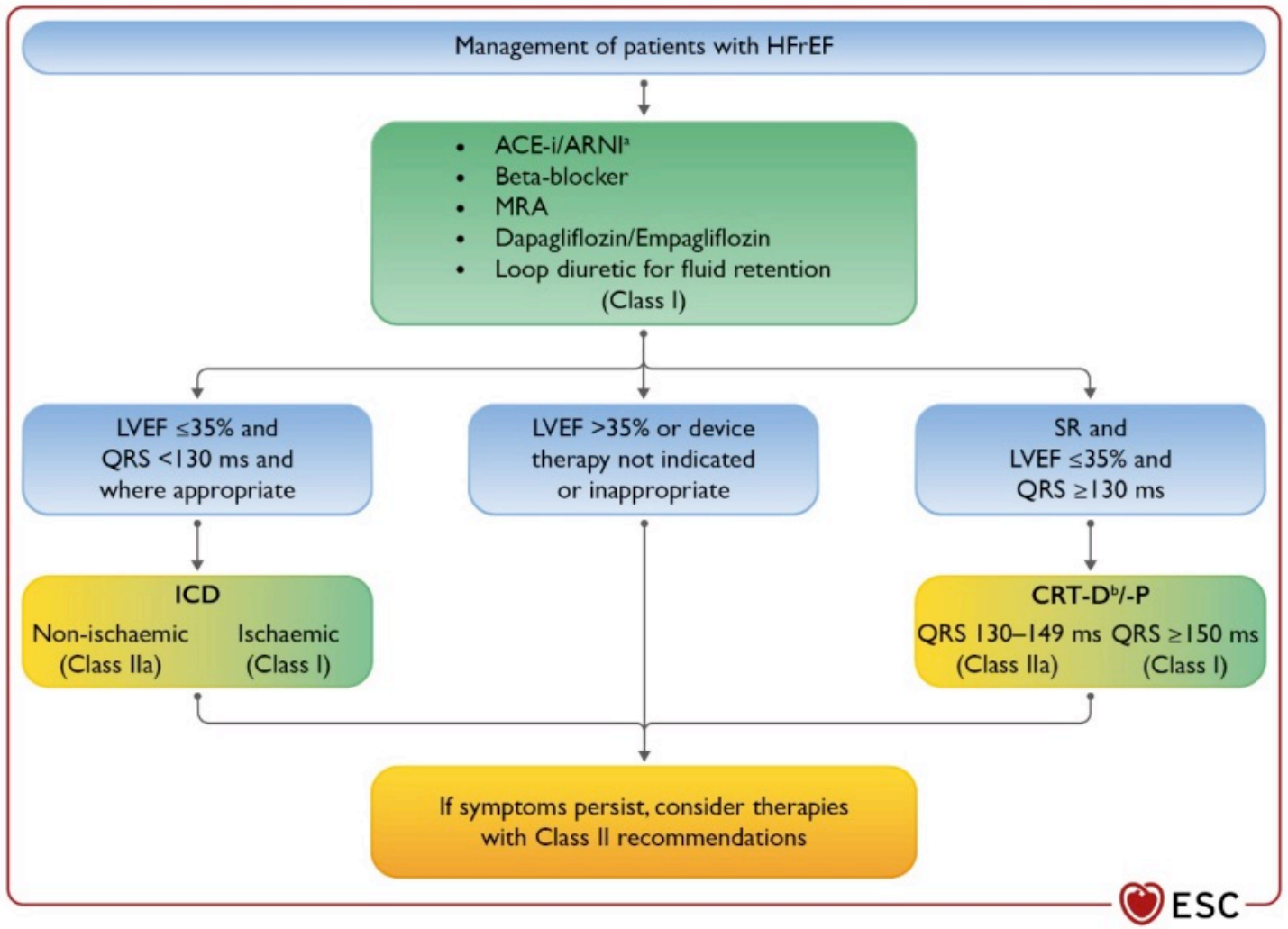
- No significant effect on systolic blood pressure, potassium homeostasis, or renal function

Teerlink. AHA 2020. Abstr LBS.01. Teerlink. NEJM. 2020;[Epub].

Ce que nous devrions faire après GALACTIC-HF

- La prise en charge :
- BB + ARNi / ARA2 + ARM+ SGLT 2 i
- Traitement de cinquieme intention omecamtiv?
  - La digoxine de 2020 sans effet hypotenseur, chez les sujets en stade 3 avec FE basse démarré tôt chez les patients décompensés
  - Le médicament de la performance?

Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction



ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm.
[a]As a replacement for ACE-I.
[b]Where appropriate. Class I=green. Class IIa=Yellow.

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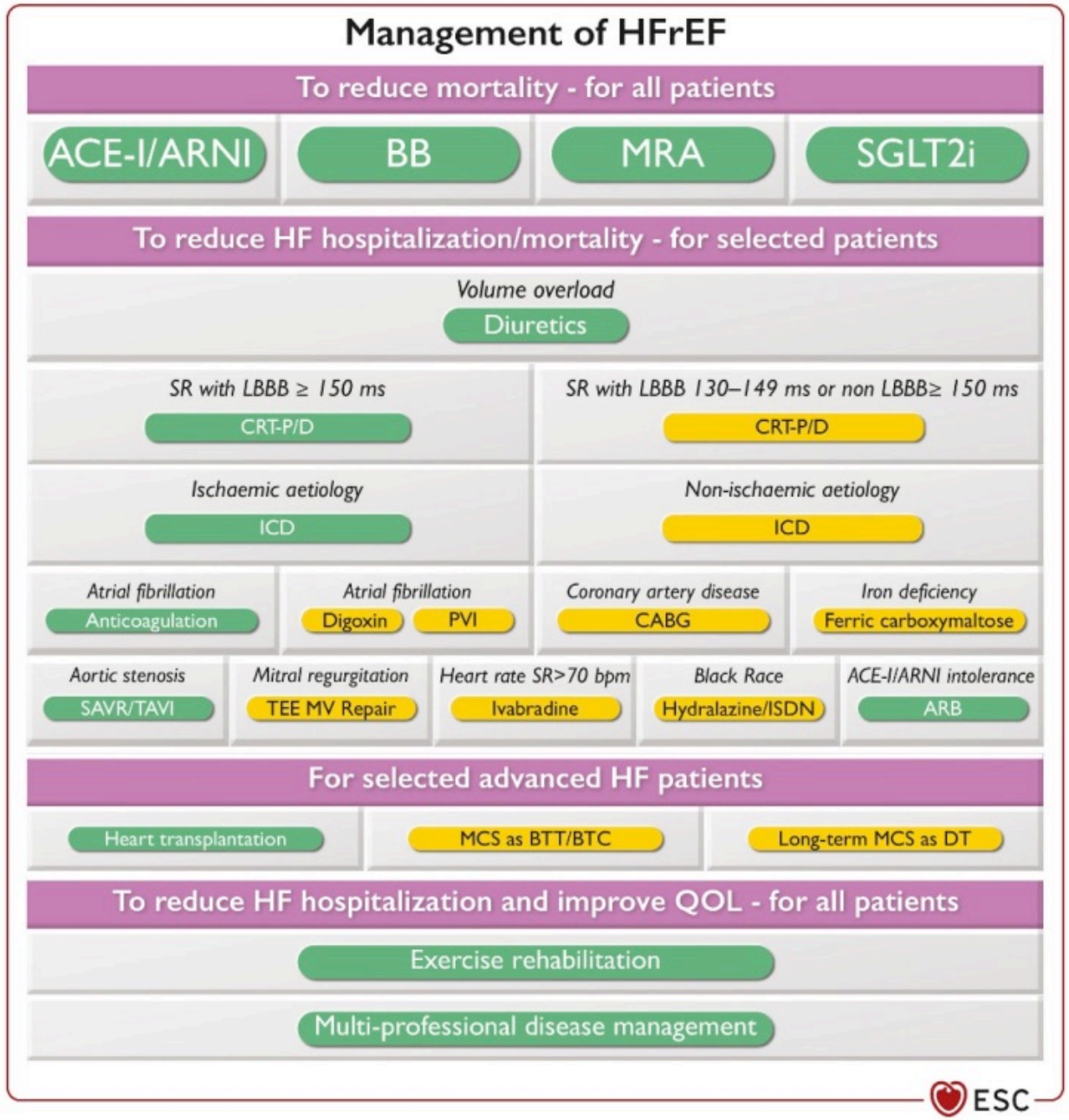


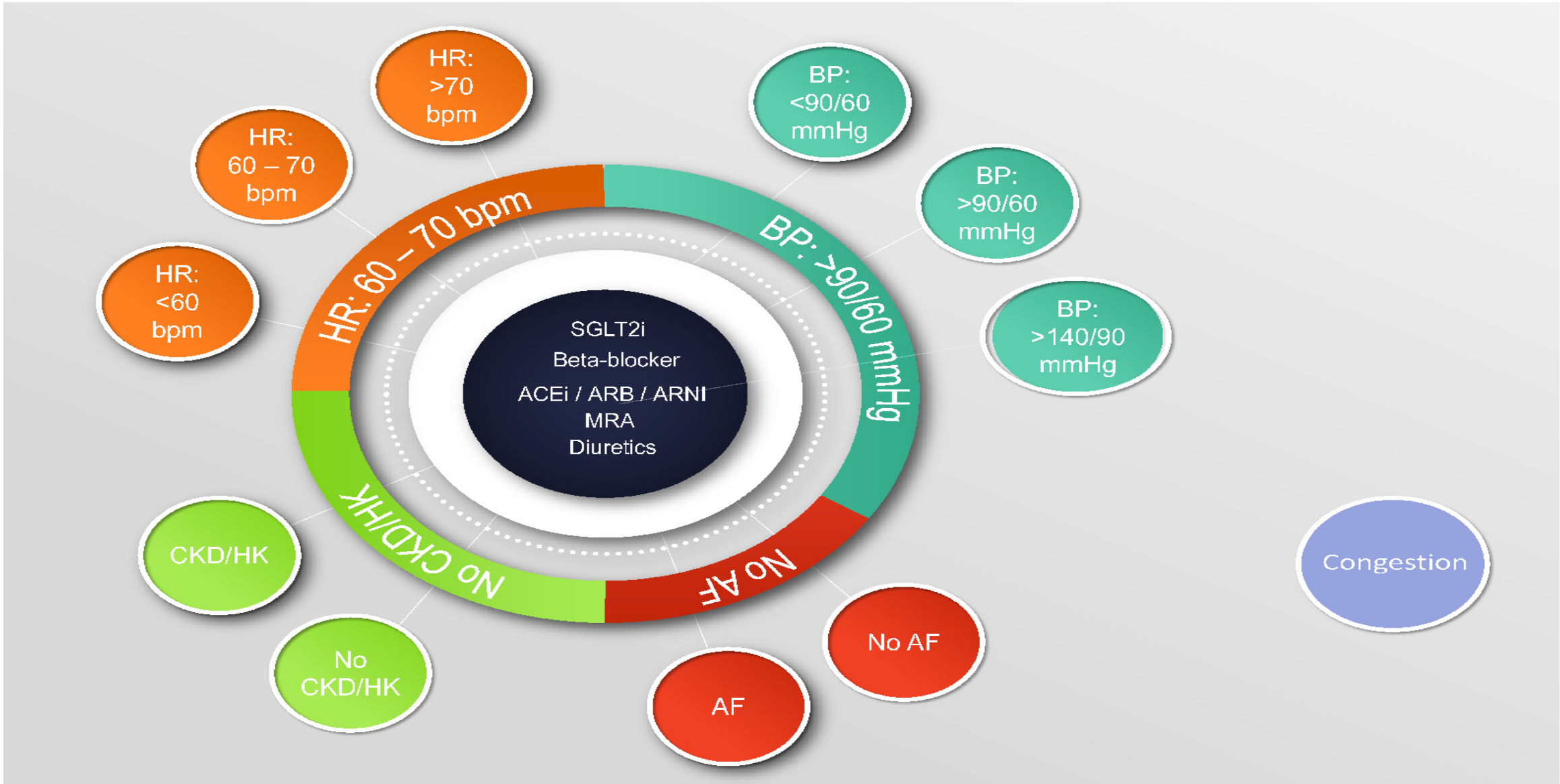
Strategic phenotypic overview of the management of heart failure with reduced ejection fraction

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; b.p.m. = beats per minute; BTC = bridge to candidacy; BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DT = destination therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = left bundle branch block; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; PVI = pulmonary vein isolation; QOL = quality of life; SAVR = surgical aortic valve replacement; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SR = sinus rhythm; TAVI = transcatheter aortic valve replacement; TEE = transcatheter edge to edge. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa (see Table 1 for further details on classes of recommendation).
The Figure showsmanagement options with Class I and IIa recommendations. See the specific Tables for those with Class IIb recommendations.

www.escardio.org/guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology



Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

European Journal of Heart Failure, First published: 01 May 2021, DOI: (10.1002/ejhf.2206)

L’ordonnance de l’IC de 2021….

- Un BB
- ARNi (nouveau bloqueur du SRA)
- MRA (nouveau MRA Finerenone)
- SGLT2 (nouveau diuretique)
- Vericiguat (nouveau nitré)
- Omecamtiv (nouvelle digoxine)