I-SGLT2: QUEL(S) MECANISME(S) D'ACTION ?

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Université Paris Cité

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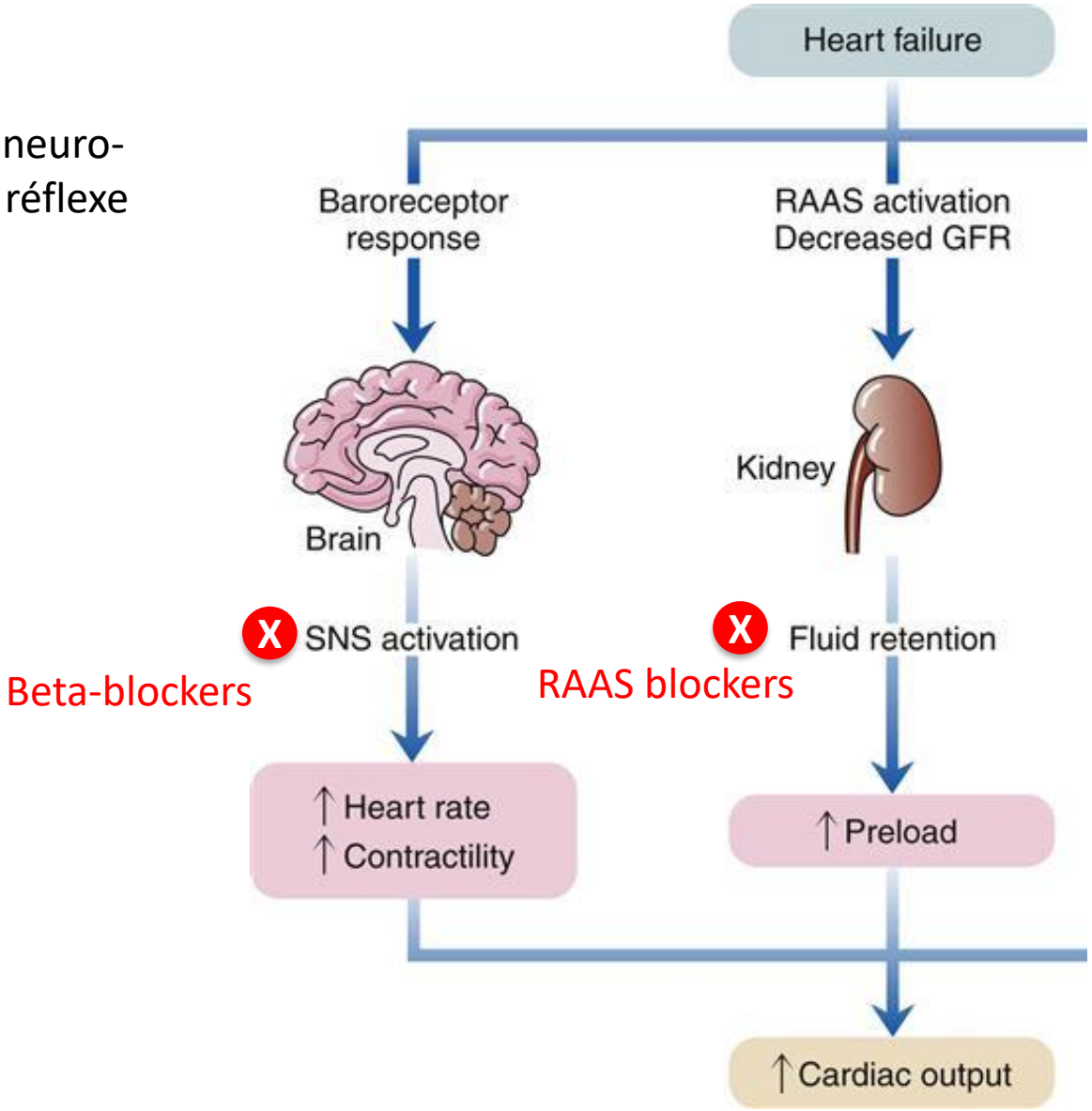
Patents :
"GDF3 as a biomarker and biotarget in post-ischemic cardiac remodeling"
"Use of alpha-V integrin (CD51) inhibitors for the treatment of cardiac fibrosis"
"Methods for improving relaxation of striated myocytes"

Scientific Advisor: 4DCell (Montreuil, France); Kimialys (Paris, France)

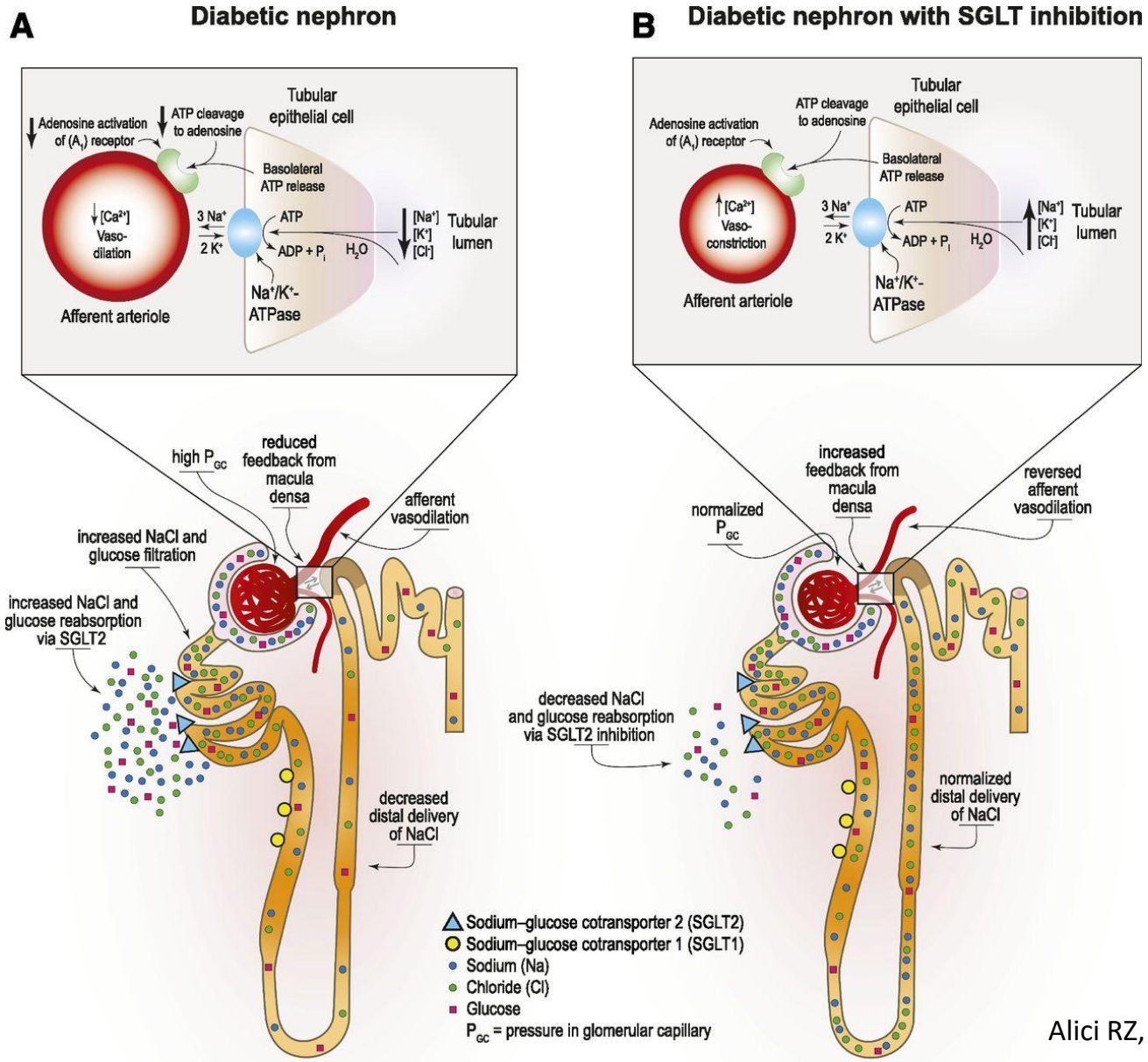
AVANT & APRES LES SGLT2i

➔ Bloquer l'activation neuro-hormonale réflexe



➔ Autres approches ?

Mode d'action primaire des inhibiteurs de SGLT2



➔ A target to primarily reduce glucose reabsorption

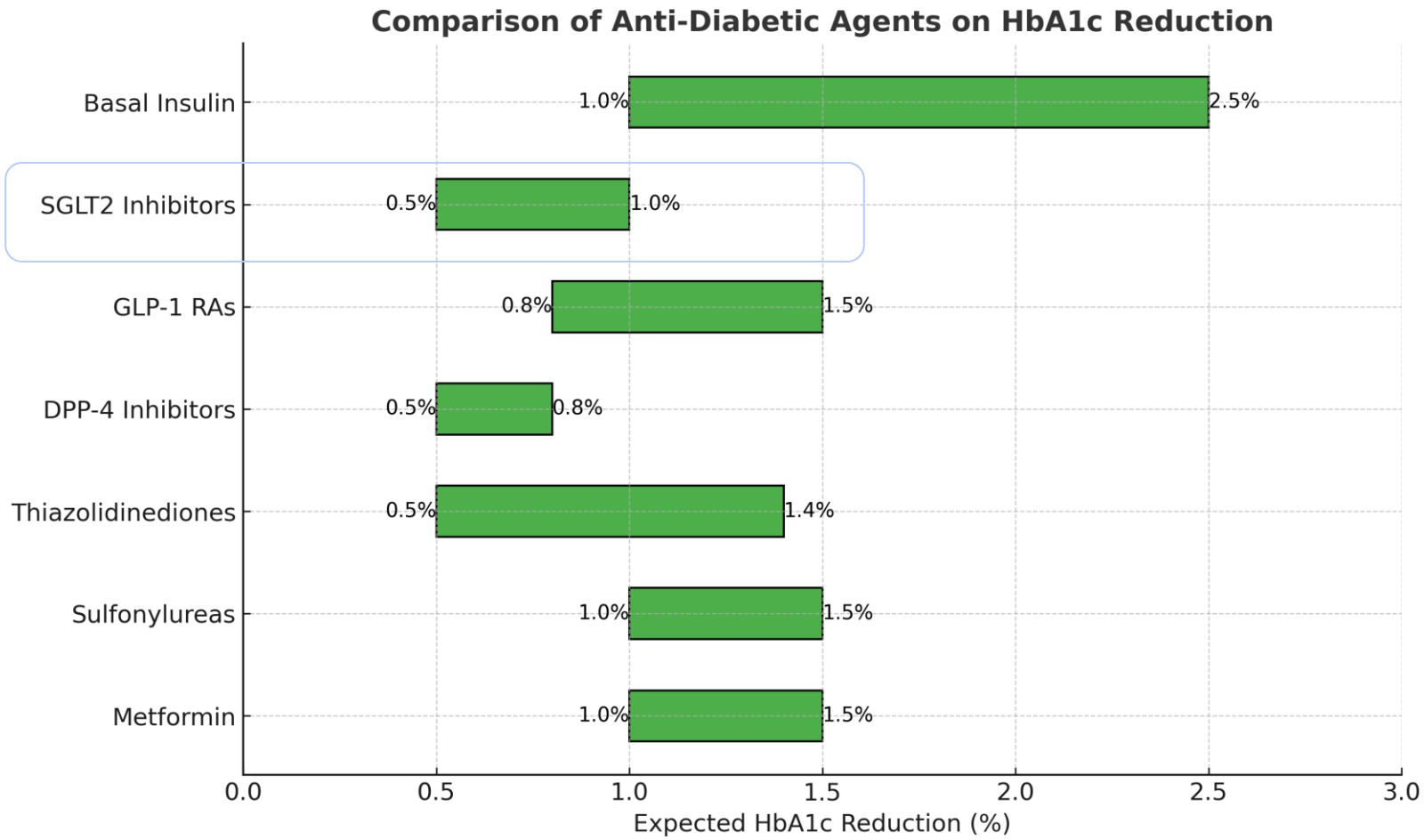
Dapaglifozin
Empaglifozin
Canaglifozin
Sotaglifozin

Alici RZ, Diabetes, 2019;68:248-57

SGLT2i et traitement du diabète ?

Table 1. SGLT-2 inhibitors approved for the treatment of T2DM

Agent	Year Approved	Starting Dose
Canagliflozin	2013	100 mg QD
Dapagliflozin	2014	5 mg QD
Empagliflozin	2014	10 mg QD



L'échec des glitazones

Thiazolinediones : agonistes PPAR-gamma = augmente la sensibilité à l'insuline des tissus périphériques

Effet sur l'HBa1c : 1 +- 0.3%

Juillet 2007, Nissen et al. NEJM

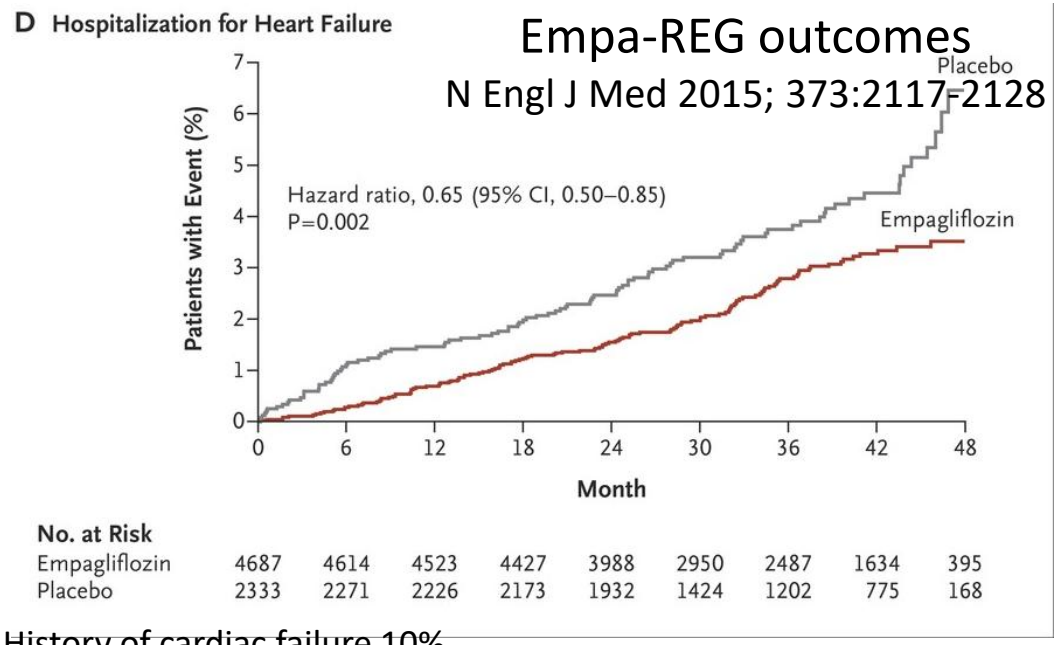
Table 1. Odds Ratios for Cardiovascular Events According to 2007 Meta-Analysis of 42 Trials and 2010 Meta-Analysis of 52 Trials.

Outcome	2007 Analysis (42 trials, 14,237 patients)	2010 Analysis (52 trials, 16,995 patients)
	odds ratio (95% confidence interval)	
Major adverse cardiovascular event	1.2 (0.8–1.9)	1.4 (0.9–2.2)
Death from cardiovascular causes	1.7 (0.7–5.0)	1.5 (0.6–3.8)
Myocardial infarction	1.5 (0.9–2.7)	1.8 (1.0–3.3)
Stroke	0.6 (0.2–1.2)	0.9 (0.4–1.8)
Death from any cause	1.7 (0.8–4.0)	1.4 (0.7–2.7)
Serious myocardial ischemia	1.4 (1.0–2.1)	1.5 (1.1–2.0)
Total myocardial ischemia	1.4 (1.1–1.8)	1.3 (1.1–1.7)
Congestive heart failure	—	1.9 (1.3–2.9)

Glifozine et risque d'insuffisance cardiaque chez le diabétique

Empa-REG outcomes

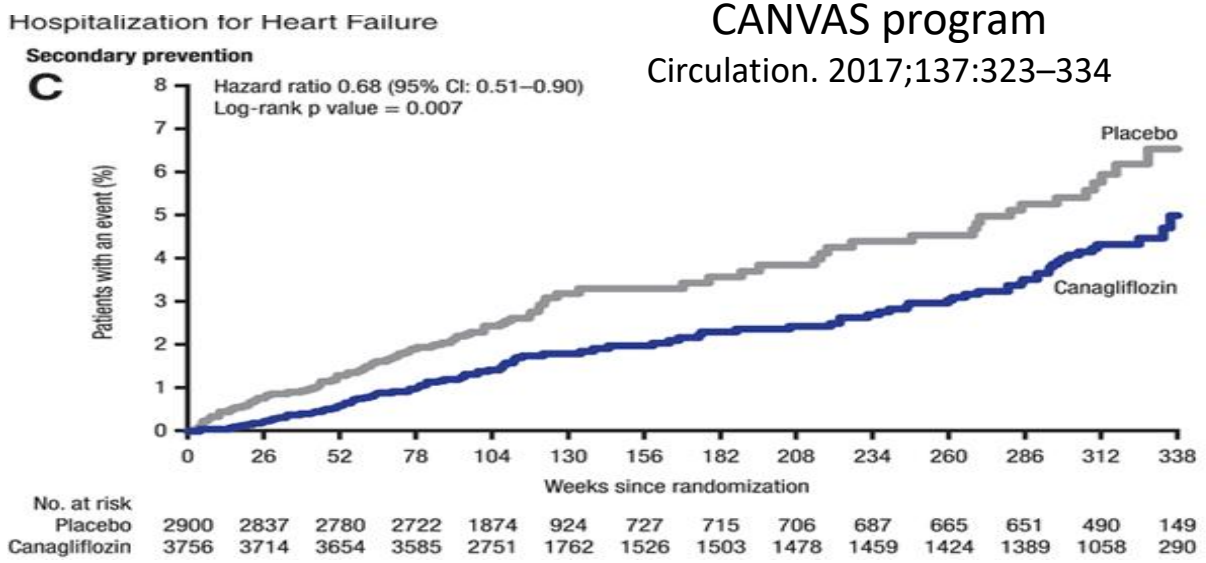
N Engl J Med 2015; 373:2117-2128



History of cardiac failure 10%

CANVAS program

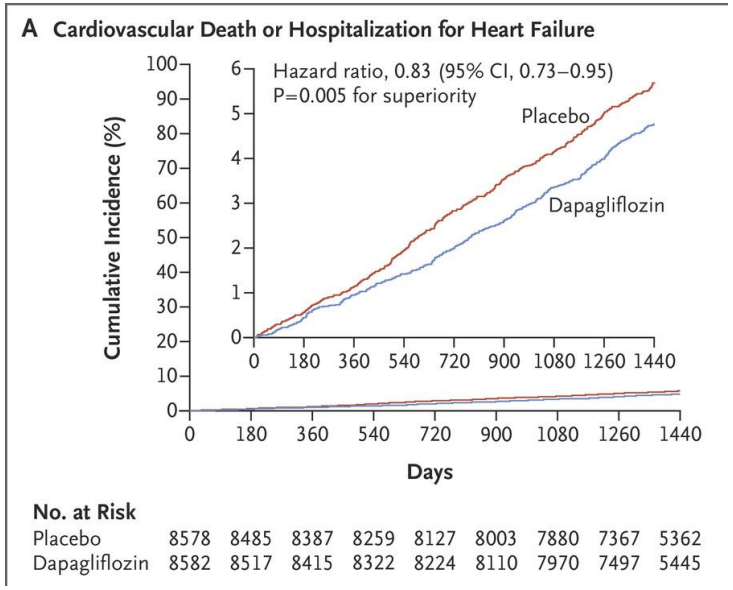
Circulation. 2017;137:323–334



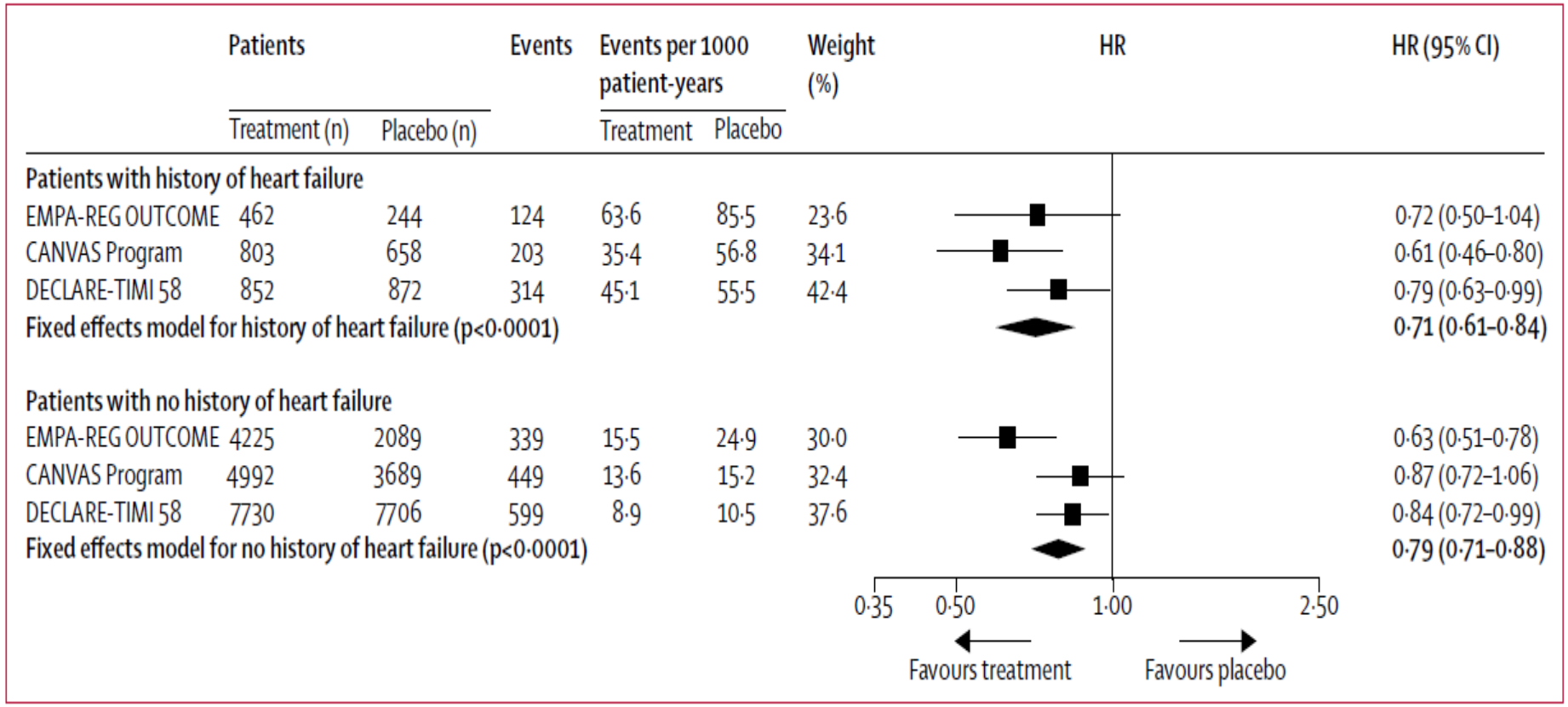
History of cardiac failure 7% (primary) to 17% (secondary)

DECLARE Timi 58

N Engl J Med 2019; 380:347-357



Méta-analyse des essais des inhibiteurs SGLT2 sur les décès cardiovasculaires et les hospitalisations pour insuffisance cardiaque chez les patients diabétiques



Les iSGLT2 sont recommandés chez les patients diabétiques de type 2 insuffisants cardiaques pour diminuer le risque d'hospitalisation pour insuffisance cardiaque sauf contre-indication (classe I, niveau A)

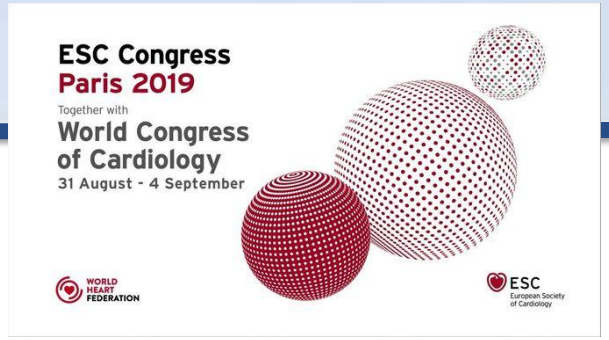
Eur Heart J 2020;41(2):255-323
Lancet 2019;393:31-39

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod,
F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm



Paris Cardiovascular research Center
PARCC
H E G P

➔ Add-on therapy
➔ 55% sans DNID

4744 patients

- ≥18 years of age
- With or without T2D
- Diagnosis of symptomatic HFrEF (NYHA class II-IV) for ≥ 2 months
- LVEF ≤40% within last 12 months
- Elevated NT-proBNP
- eGFR ≥30 mL/min/1.73 m²
- Stable SoC HFrEF treatment

1:1
Double-blind

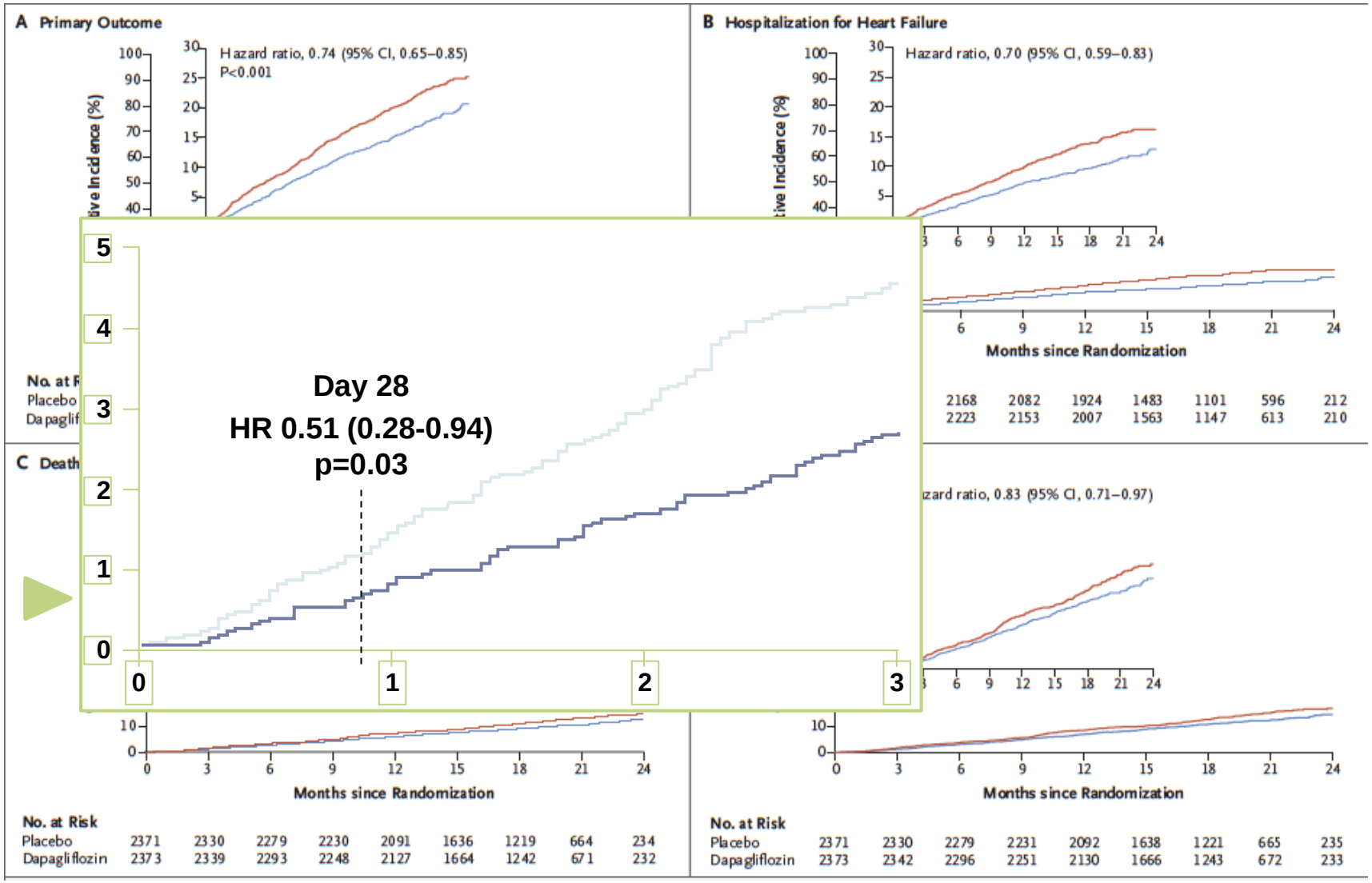
Dapagliflozin 10 mg + standard of care[a]

Placebo + standard of care[a]

Visit 1 (enrollment) Day -14	Visit 2 (randomization) Day 0	Visit 3 Day 14	Visit 4 Day 60	Visit 5 Day 120	Visit 6, etc. Every 120 days

Median follow-up: 18.2 months

Multiples bénéfices

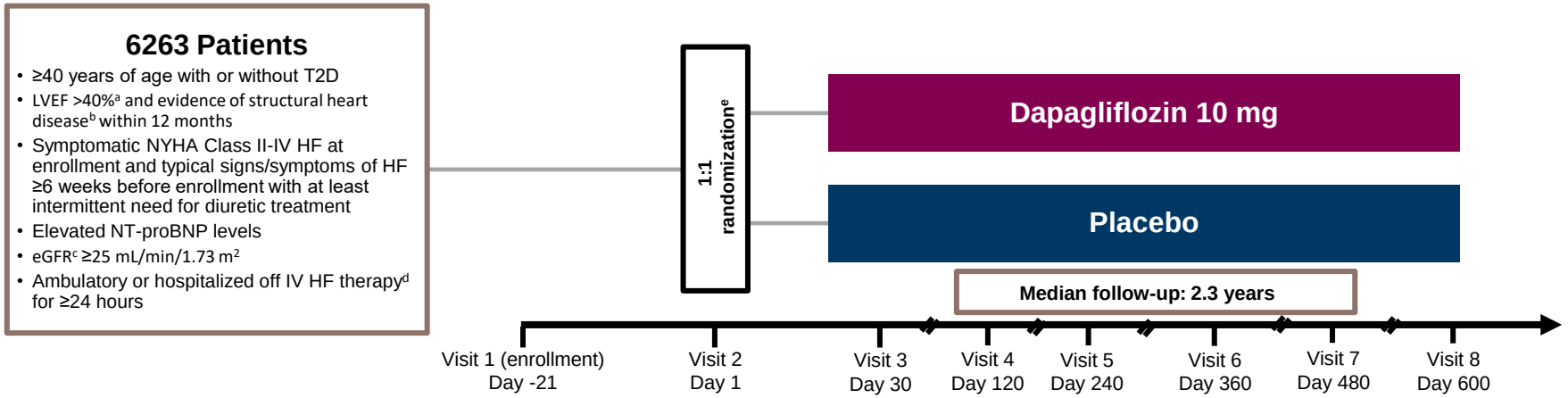


McMurray JJ NEJM 2019

SGLT2i and HF with mildly reduced or preserved LVEF

DELIVER

DELIVER



Primary Endpoint

- Time to first occurrence of any component of the composite of CV death or worsening HF events (hHF or urgent HF visit)
  - Full patient population
  - Patients with LVEF <60%

Secondary Endpoints

- Total number of HF events (first and recurrent) and CV deaths in the full patient population and in patients with LVEF <60%
- Change from baseline in KCCQ-TSS at 8 months
- Time to occurrence of CV death
- Time to occurrence of death from any cause

[d]Including diuretics; [e]Stratified by T2D status (established diagnosis/HbA1c ≥6.5% at enrollment).

1. Solomon SD et al. *Eur J Heart Fail.* 2021;23(7):1217-1225; 2. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 3. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

Le seul traitement efficace pour l'ICFEP

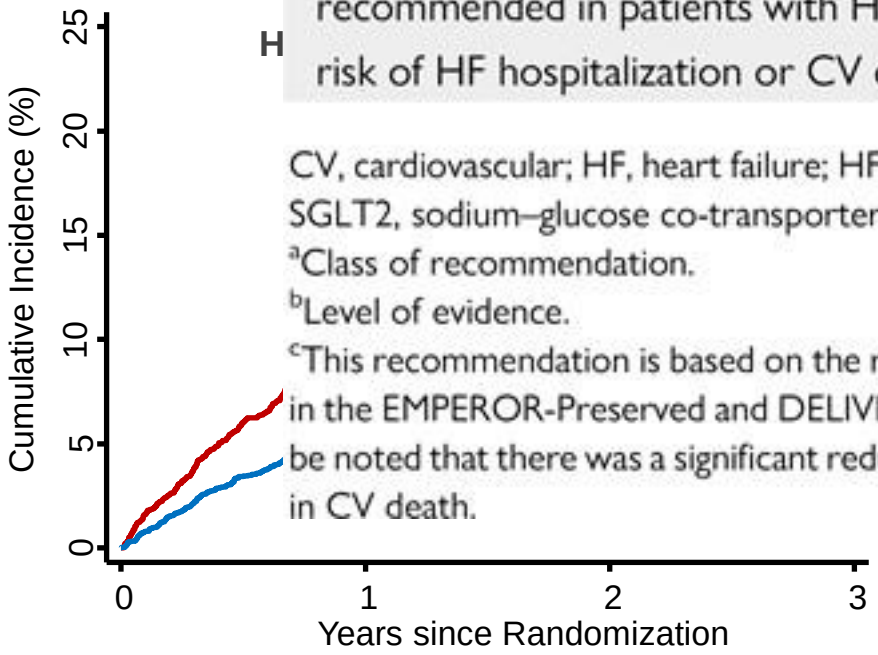
(HF H

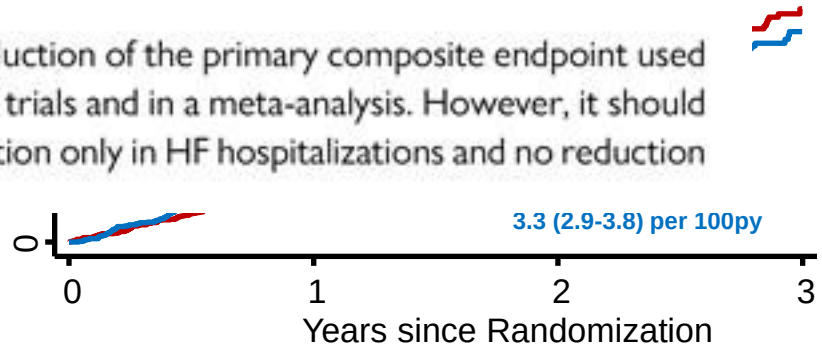
H

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

© ESC 2023

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

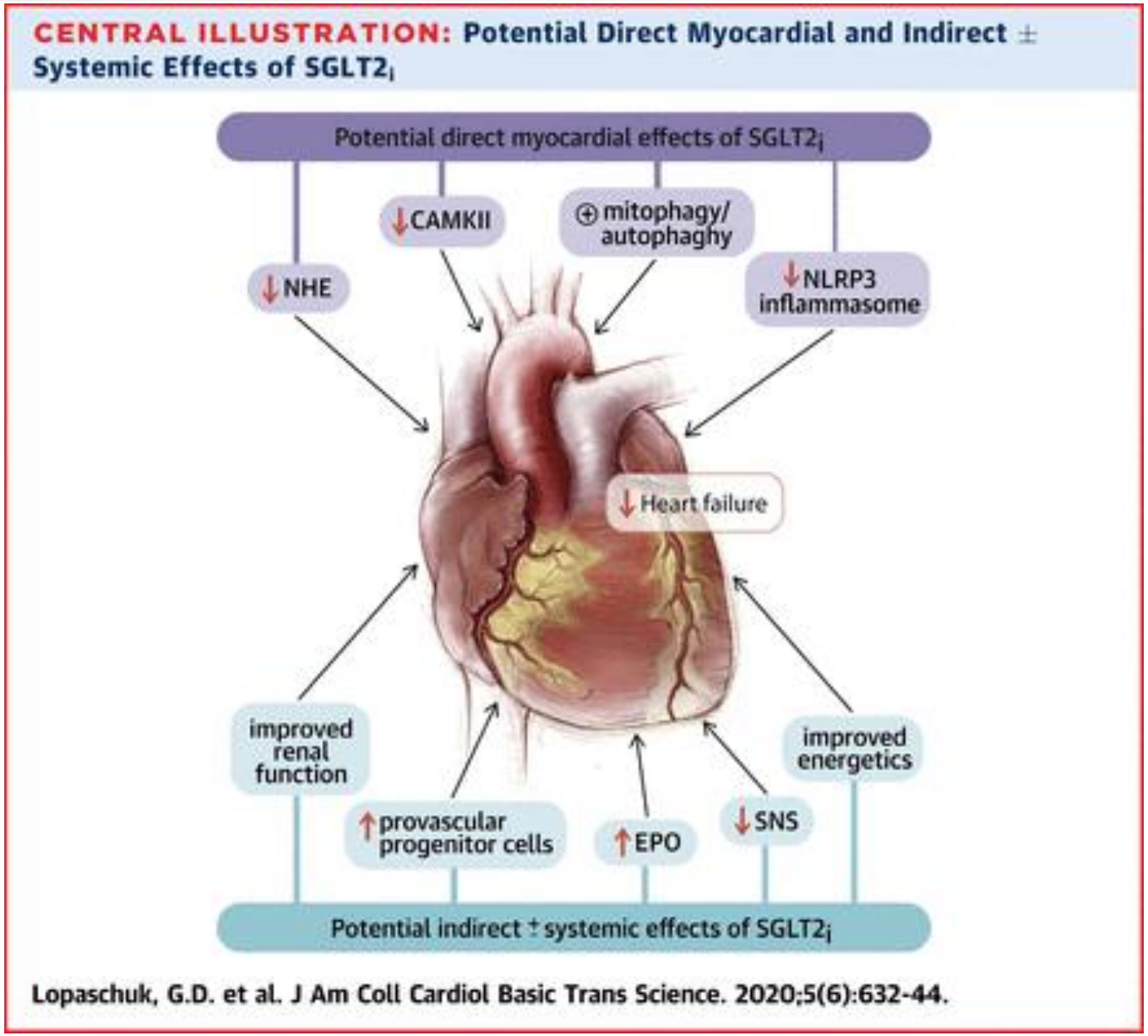




2019 : Gli…quoi ?

2023 : La première classe thérapeutique indiquée dans toutes les formes d'insuffisance cardiaque

Effets myocardiques directs et indirects des SGLT2i

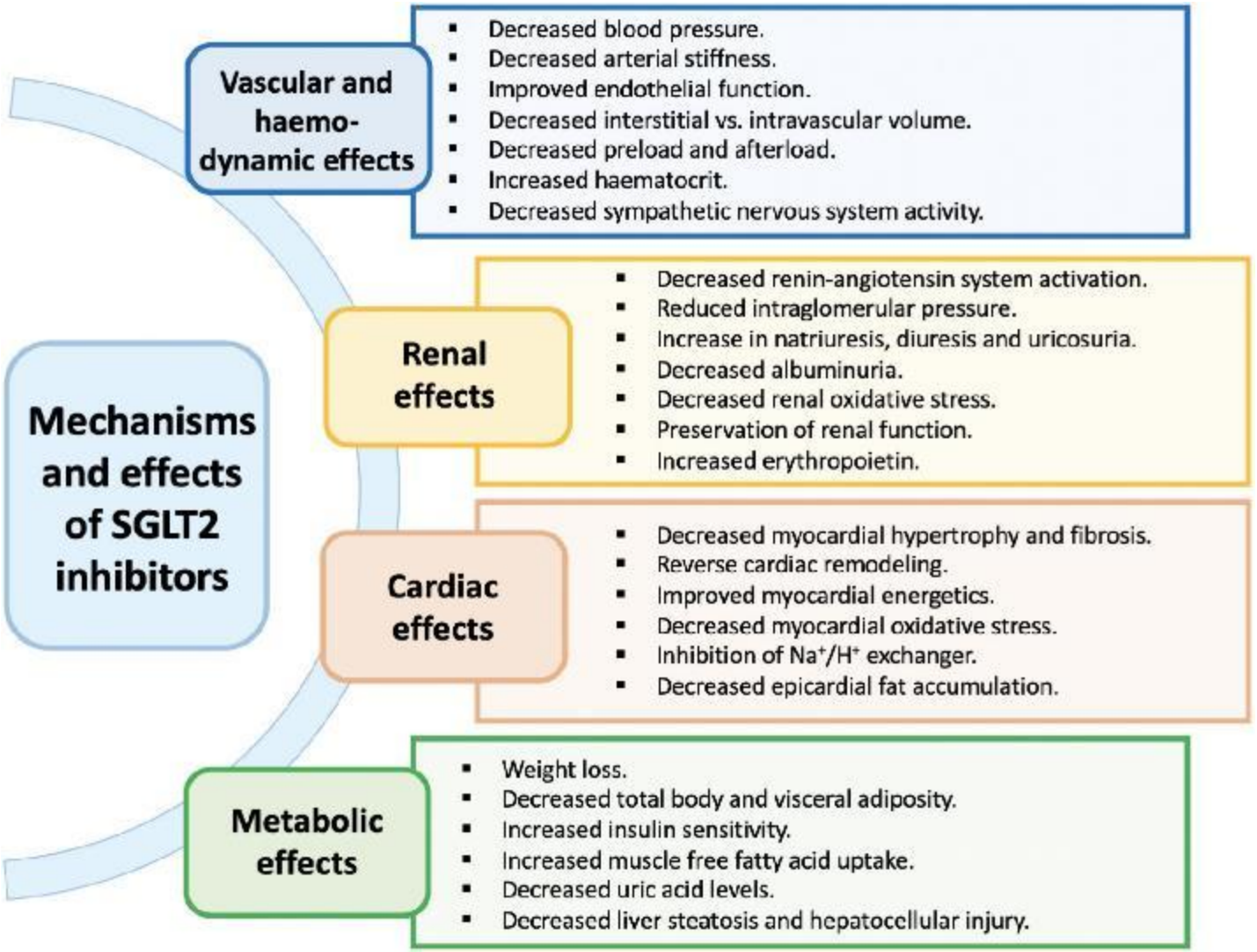


➔ Action directe sur le myocarde / cardiomyocytes

Hypothèses	+++
Data	- - -

➔ Amélioration des conditions de pré et post-charge, sur un lien cardio-rénal

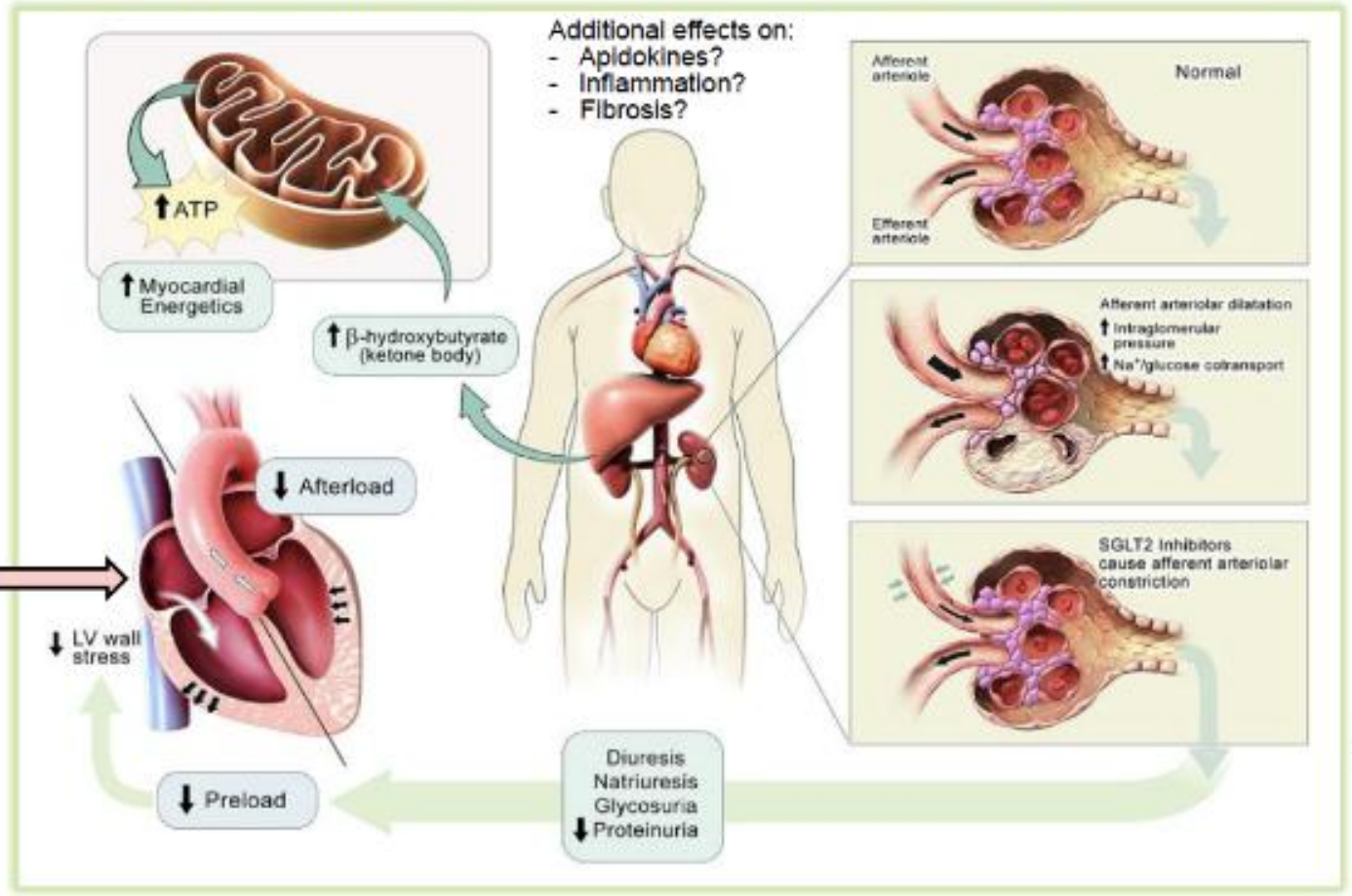
Effets myocardiques directs et indirects des SGLT2i



Hypothèses	+++
Data	- - -

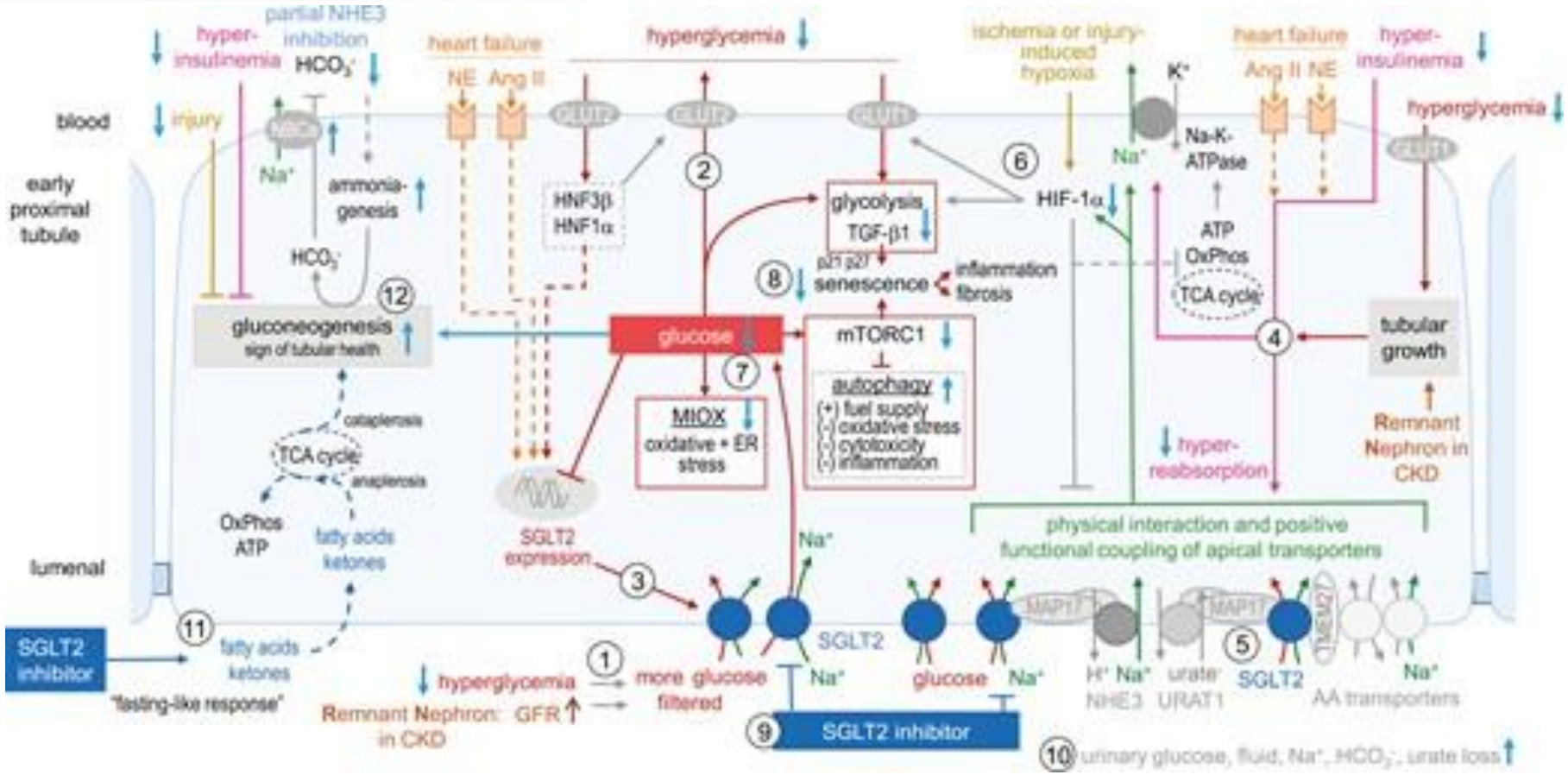
Un effet Métabolo-diurétique ?

"The metabolodiuretic promise of SGLT2 inhibition: The search for the sweet spot in heart failure"



Adapted from Verma, McMurray & Cherney JAMA Cardiol. 2017; 2:939-940

SGLT2i and natriuresis ?



Glycosuria-driven natriuresis and osmotic diuresis
Initial fluid loss (1-2 Kgs) in the initial 2 weeks after initiation
Then stabilizes

This effect is increased in heart failure patients ?

Vallon V. Am J Hypertension, 2024

SGLT2i and interstitial volume ?

Congestive heart failure

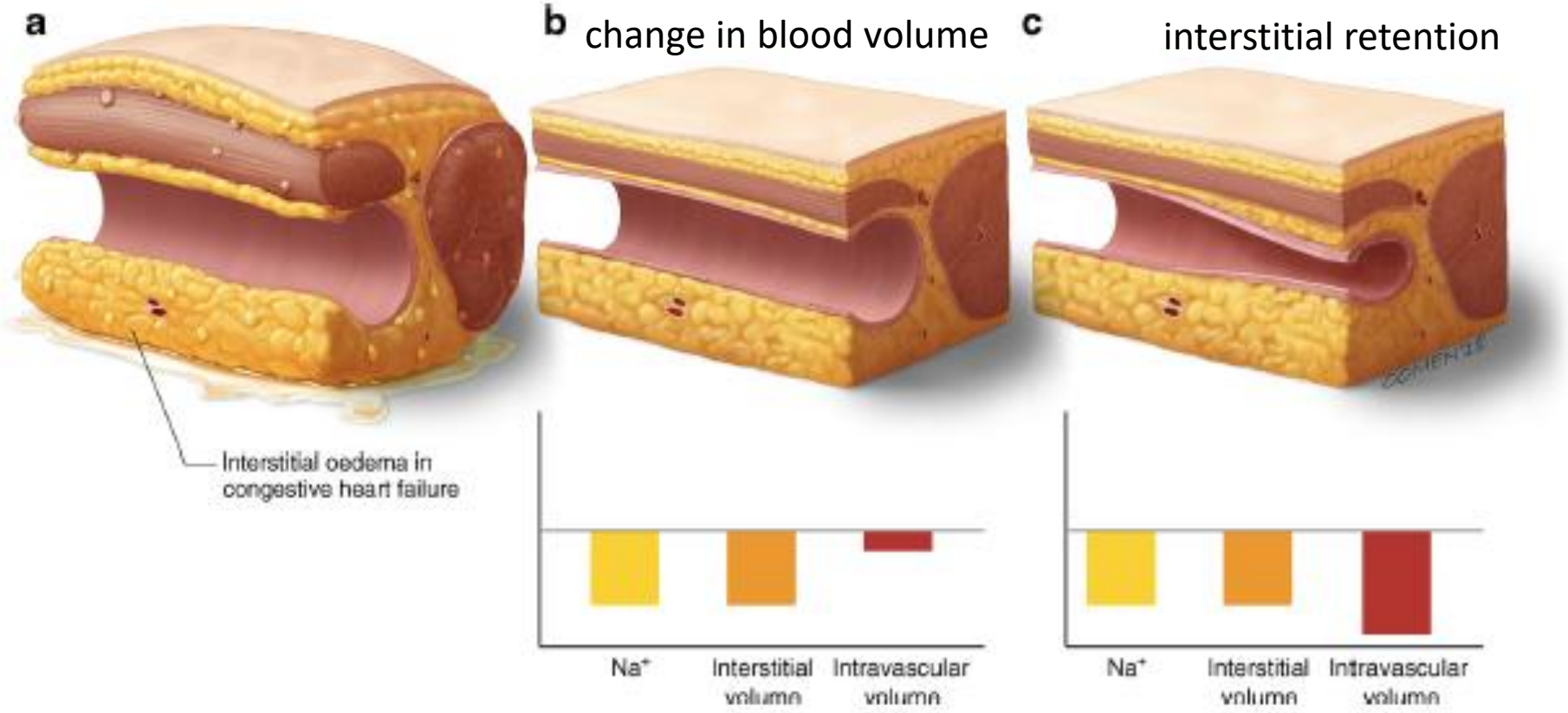
Interstitial oedema ++

SGLT2 inhibitors

Reduce intersitial volume with minimal change in blood volume

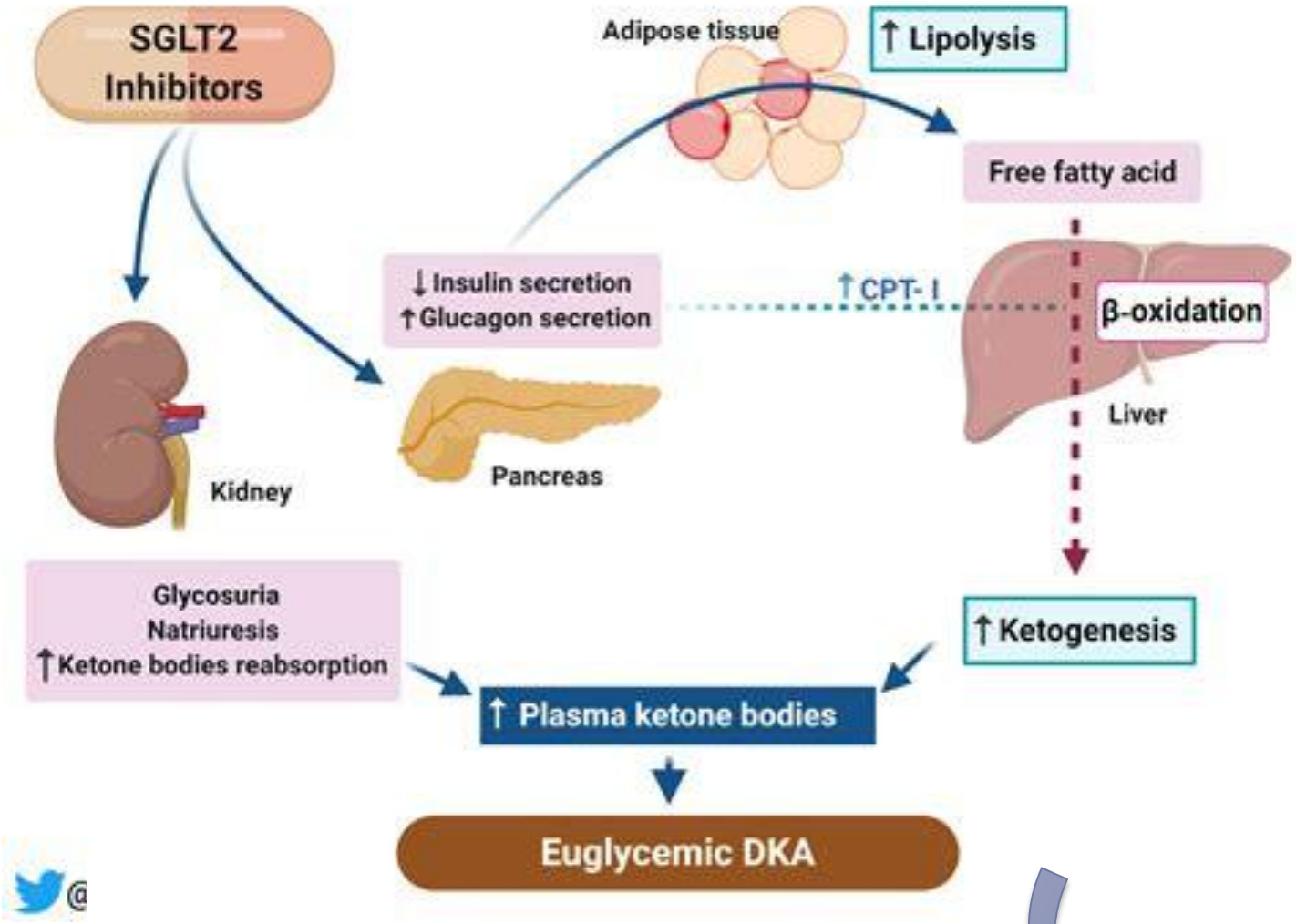
Loop diuretics

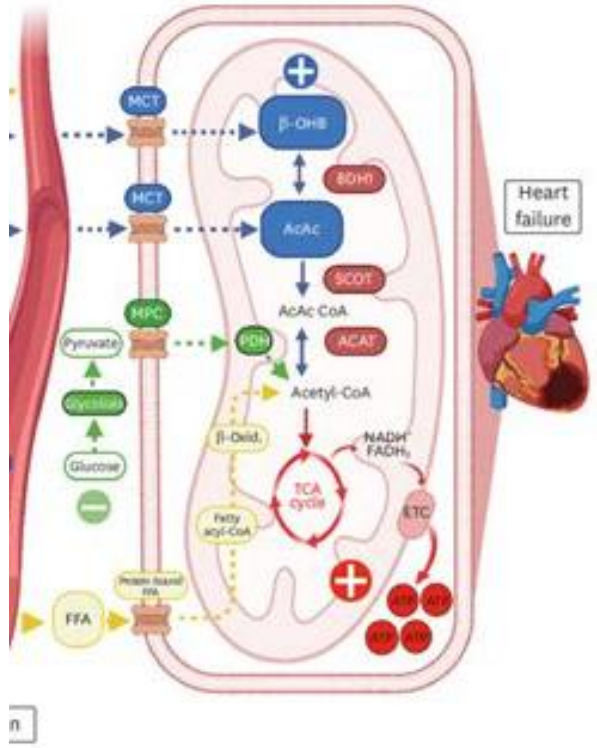
Reduce intravascular blood volume and interstitial retention



> SGLT2i will in turn limit the aberrant reflex neurohormonal stimulation that occurs in the setting of intravascular depletion ?

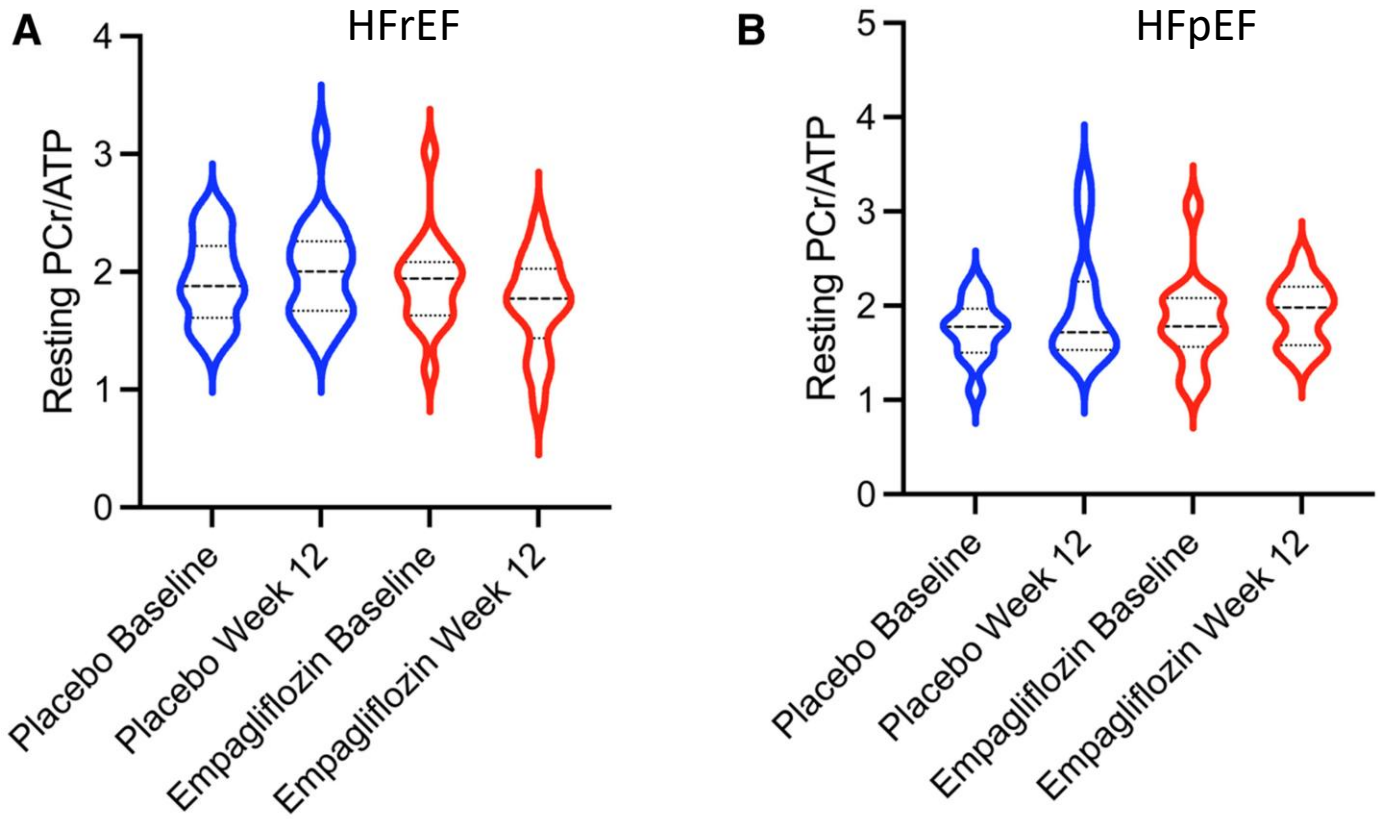
SGLT2i and ketone bodies : the fastin—like response





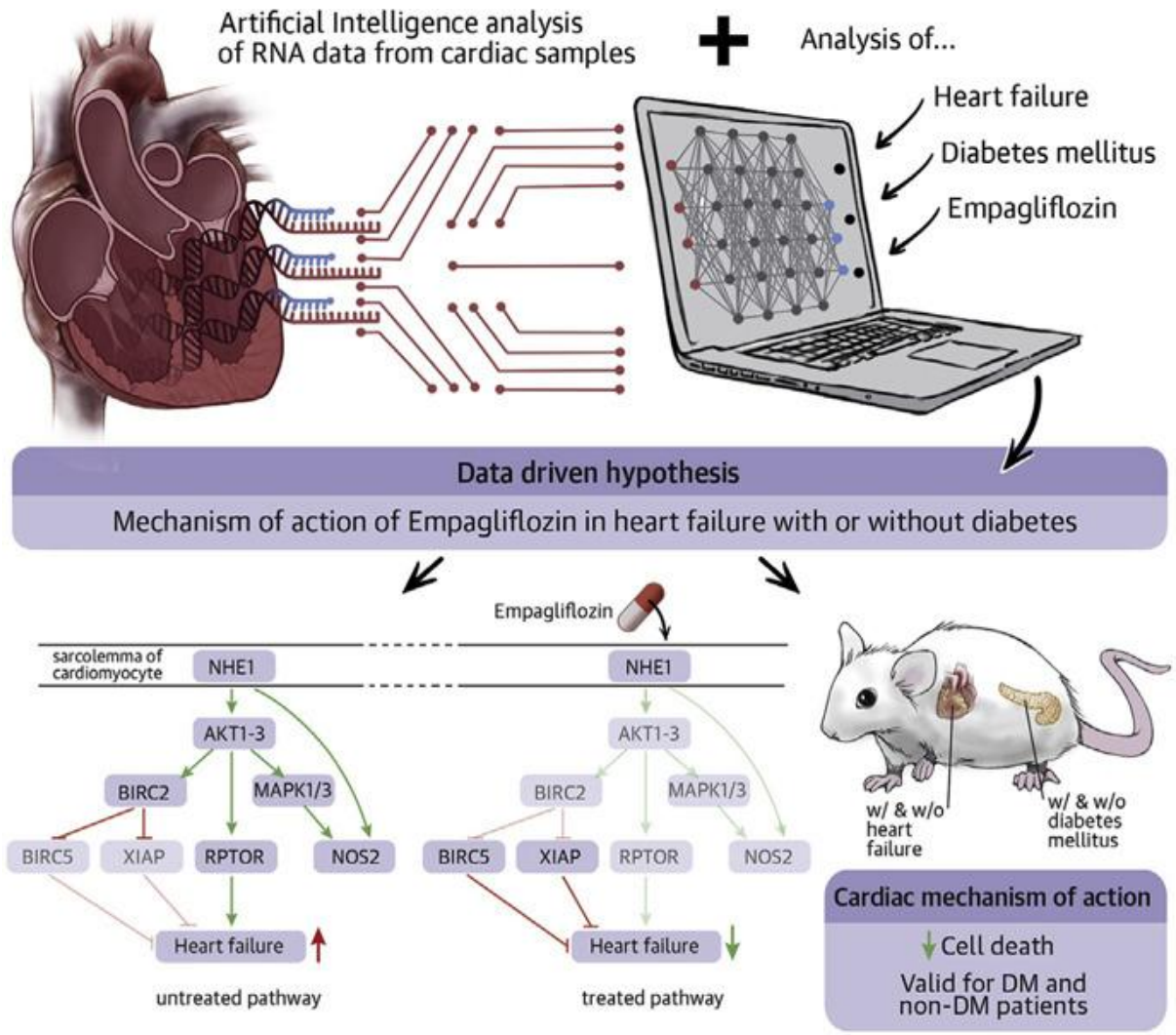
No impact on cardiac energy metabolism in patients

EMPA-VISION (Assessment of Cardiac Energy Metabolism, Function and Physiology in Patients With Heart Failure Taking Empagliflozin)
Double-blind, placebo controlled, randomised study ; N=72 HFpEF and HFrEF patients
Primary endpoint: cardiac phosphocreatine:ATP ratio (PCr/ATP) from baseline to week 12, determined by phosphorus magnetic resonance spectroscopy at rest and during peak dobutamine stress



Hundertmark M. et al, Circulation 2023 (22): 1654-69

SGLT2-independent effects of SGLT2i ? Look at NHE1



Iborra-Egea, O. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(7):831-40.

SGLT2 is not expressed in cardiomyocytes

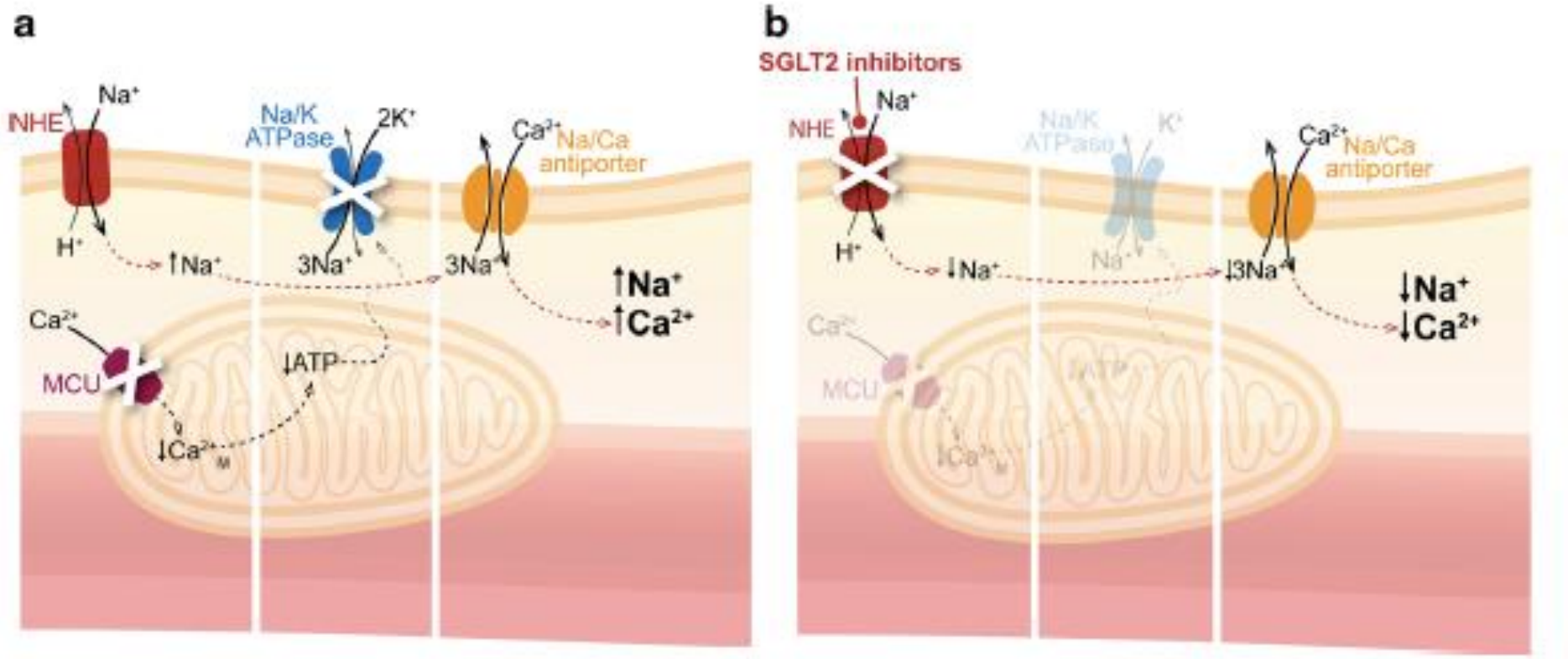
NHE1: sodium – hydrogen exchanger 1

SGLT2i and indirect calcium regulation ?

➔ Direct inhibitory effect on the cardiac sodium – hydrogen exchanger (NHE)

Heart Failure

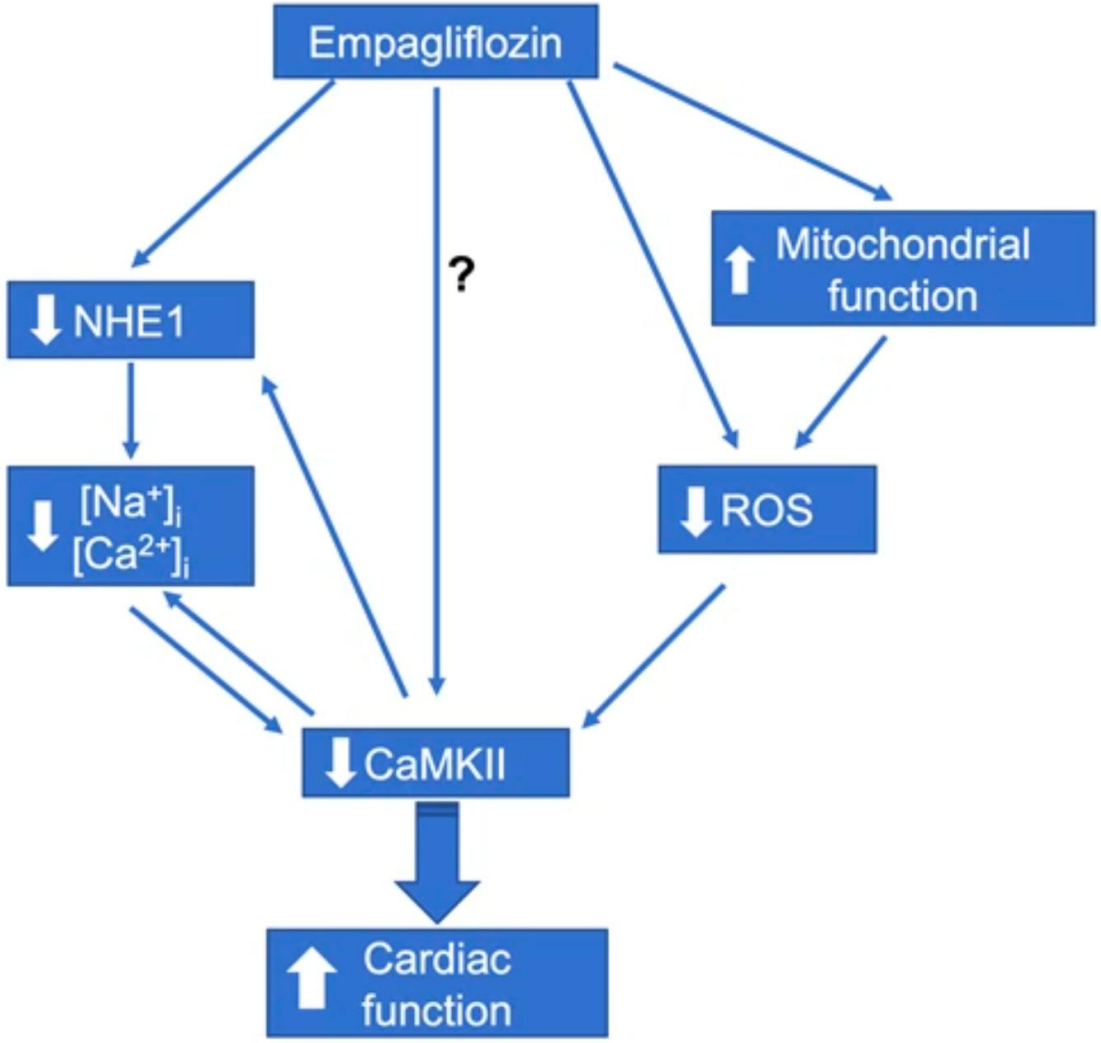
Heart Failure + glifozine



➔ Diastolic calcium levels will be reduced

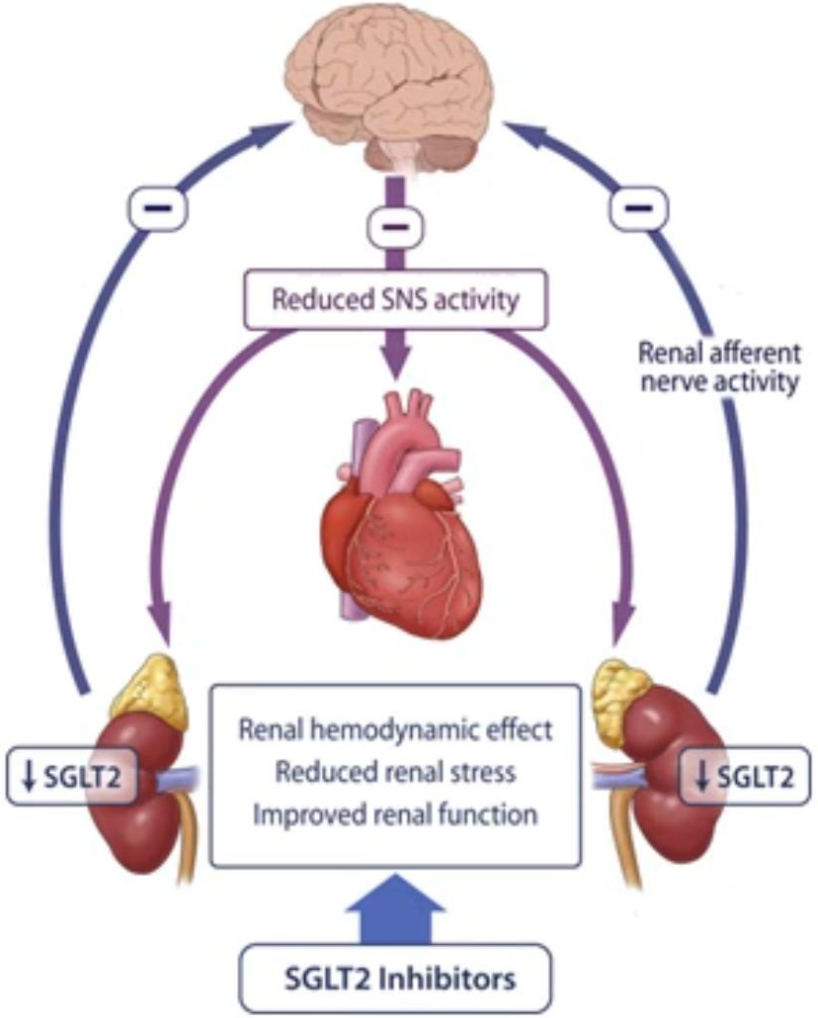
SGLT2i and CAMKII activity

- Upregulation of CAMKII in heart failure with reduced DF, HCM, diabetic heart failure
- Indirect inhibition of CAMKII hyper-activity by SGLT2i
- Reduction of deleterious effect including myocyte apoptosis



Trum et al. Biochim Biophys Acta Mol Basis Dis 2020

SGLT2i and the sympathetic system ?



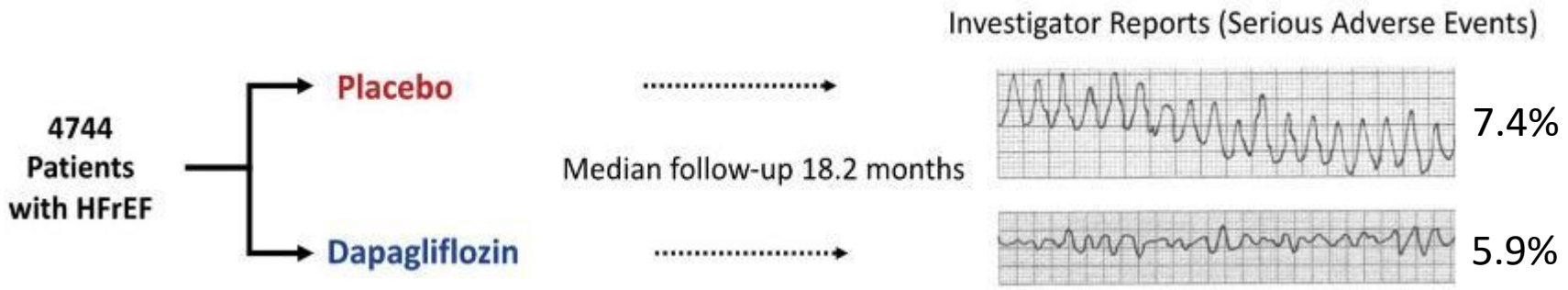
SGLT2i have sympathoinhibitory effects

Could be linked to a reduction in renal stress with resultant inhibition of the renal afferent sympathetic activation

SGLT2i > Kidney > heart ?

Sano et al. 2019 JACC BTS
Verma et al. 2018

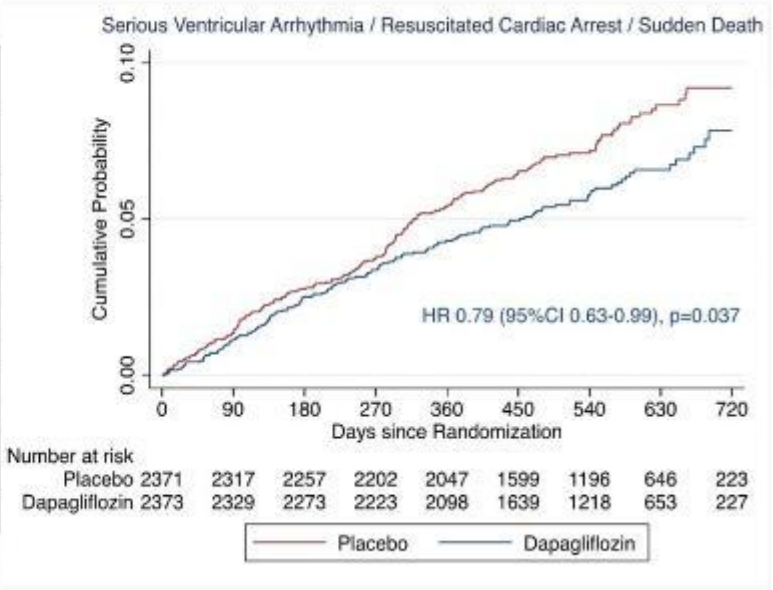
Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF



Backward stepwise logistic regression multivariable model to predict any serious ventricular arrhythmia, resuscitated cardiac arrest or sudden death

Predictor Variable*	Odds Ratio (95% CI)	p Value**	χ2
Log-transformed NT-proBNP (per 1 unit increase)	1.54 (1.34 – 1.77)	<0.001	36.0
Previous Ventricular Arrhythmia	1.93 (1.41 – 2.64)	<0.001	16.8
LVEF (per 5% increase)	0.86 (0.78 – 0.94)	0.001	11.9
Systolic BP (per 10mmHg)	0.88 (0.81 – 0.96)	0.004	8.1
Previous MI	1.42 (1.11– 1.82)	0.005	7.8
Sex- male	1.53 (1.10 – 2.12)	0.012	6.3
BMI (per 1 kg/m^2 increase)	1.03 (1.00 – 1.05)	0.020	5.4
Sodium (per 1 mmol/L increase)	0.96 (0.92 – 0.99)	0.039	4.3
Non-white race	0.85 (0.72 – 0.99)	0.038	4.3
Dapagliflozin	0.80 (0.63 – 1.02)	0.067	3.4
Cardiac Resynchronization Therapy	0.64 (0.39 – 1.04)	0.070	3.3
Previous HF hospitalization	0.99 (0.78 – 1.27)	0.985	0.0

*Randomized treatment and history of heart failure hospitalization were fixed factors in the model. **The p-value threshold was set at p<0.1



Eur Heart J, Volume 42, Issue 36, 21 September 2021, Pages 3727–3738, https://doi.org/10.1093/eurheartj/ehab560

SGLT2i and other direct cardiac effects

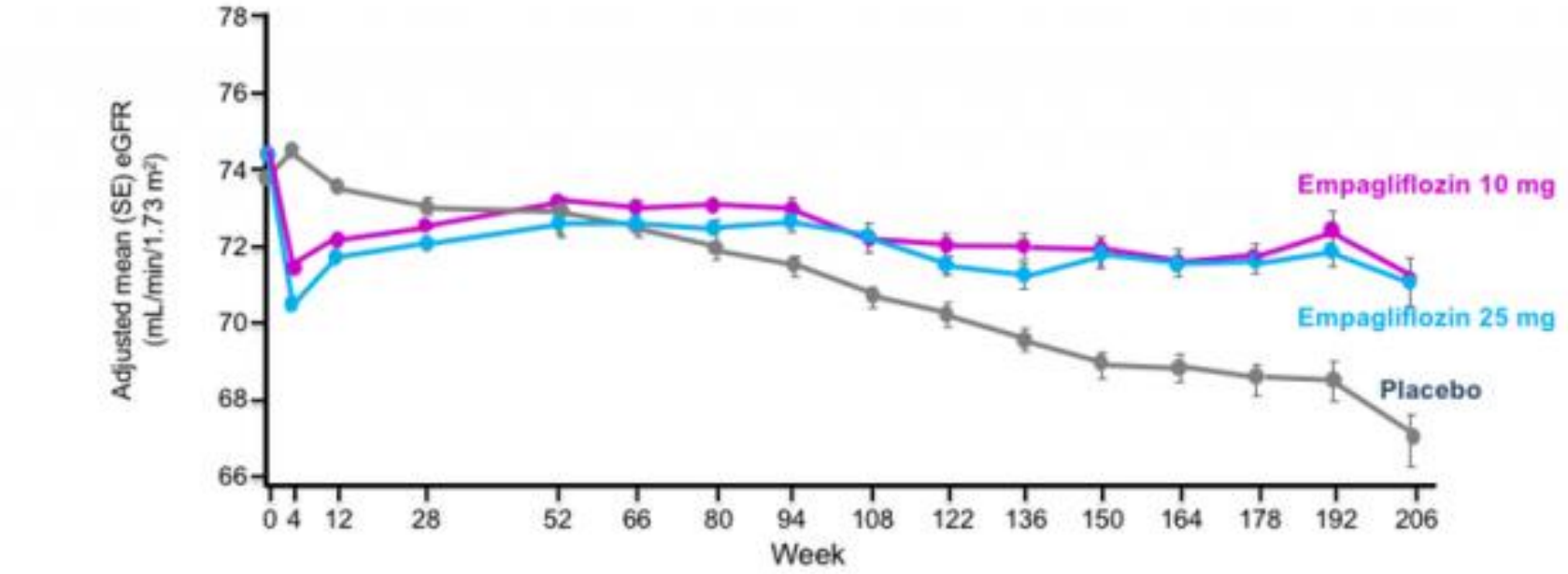
- Reduction in low-grade inflammation : systemic reduction in inflammasome (through inhibition of NLRP3)

- Improved bioenergetics with easier use of ketones by cardiomyocytes
  ➔ improvement in the metabolic switch sugar : fatty acids to produce ATP

- Improved mitochondrial function and reduced ROS

And if it was the kidney ?

eGFR over time

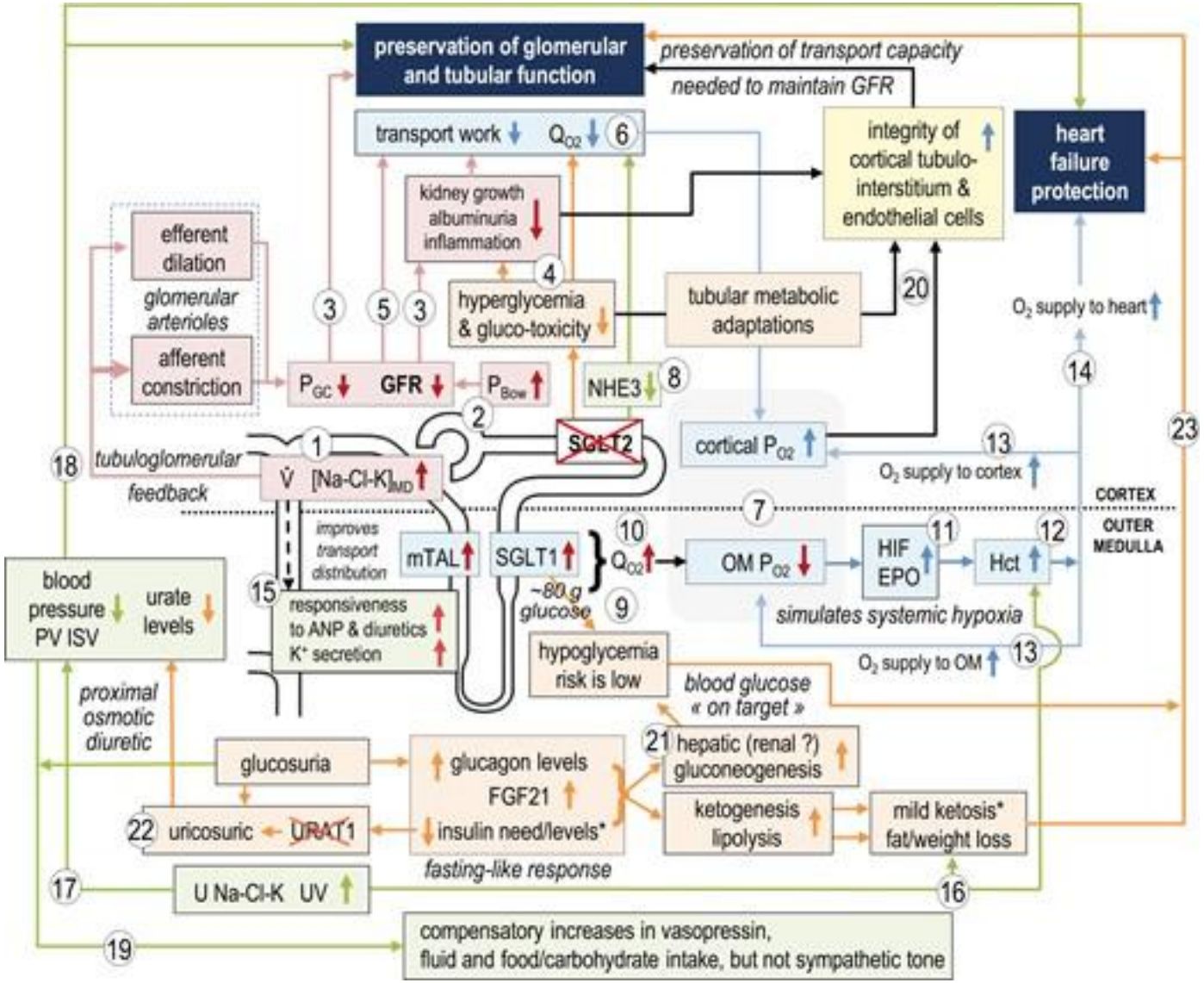


Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448	171
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513	193
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524	216

Mixed model repeated measures analysis in the treated set (OC-AD)

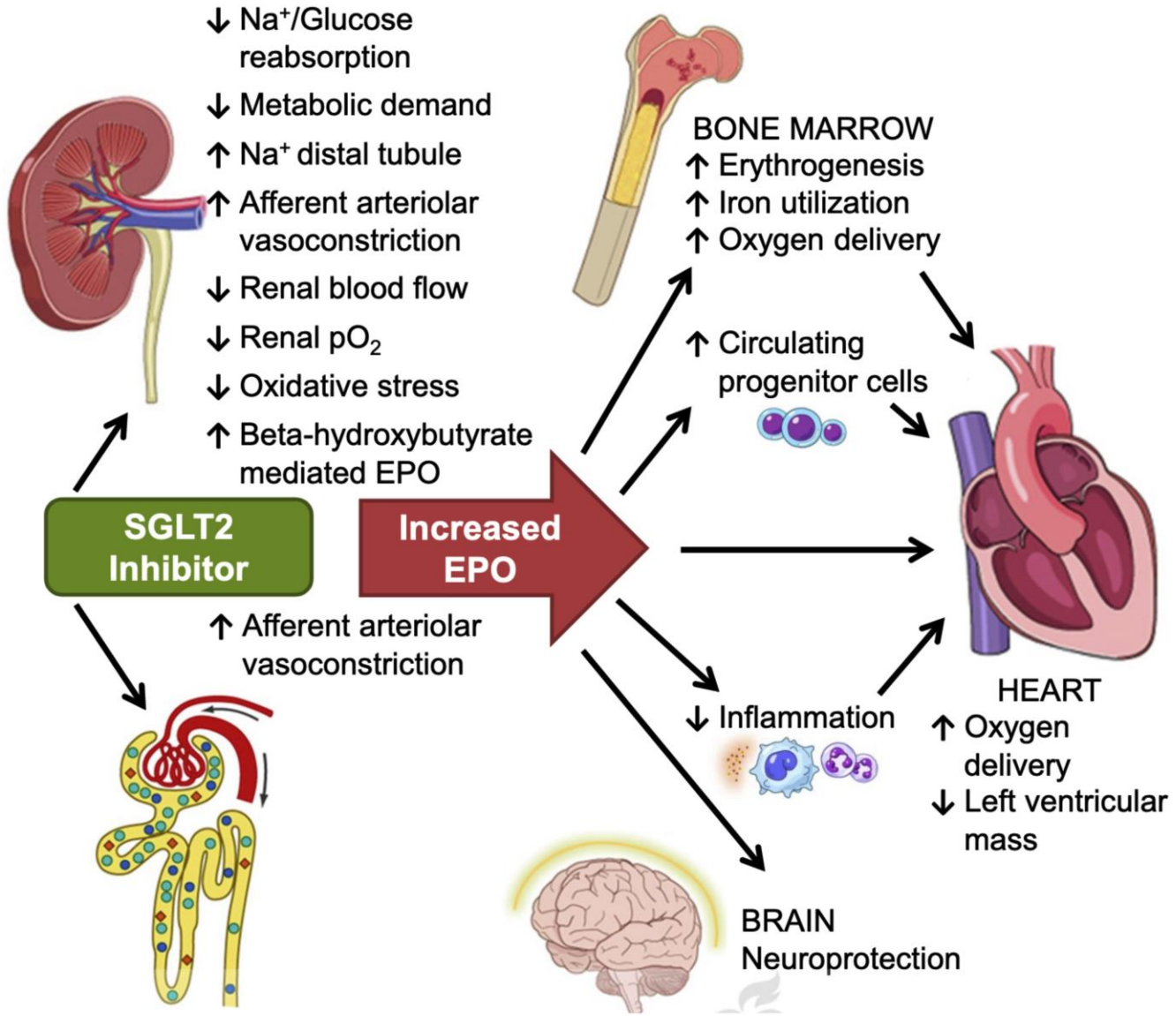
EMPA-REG Outcome

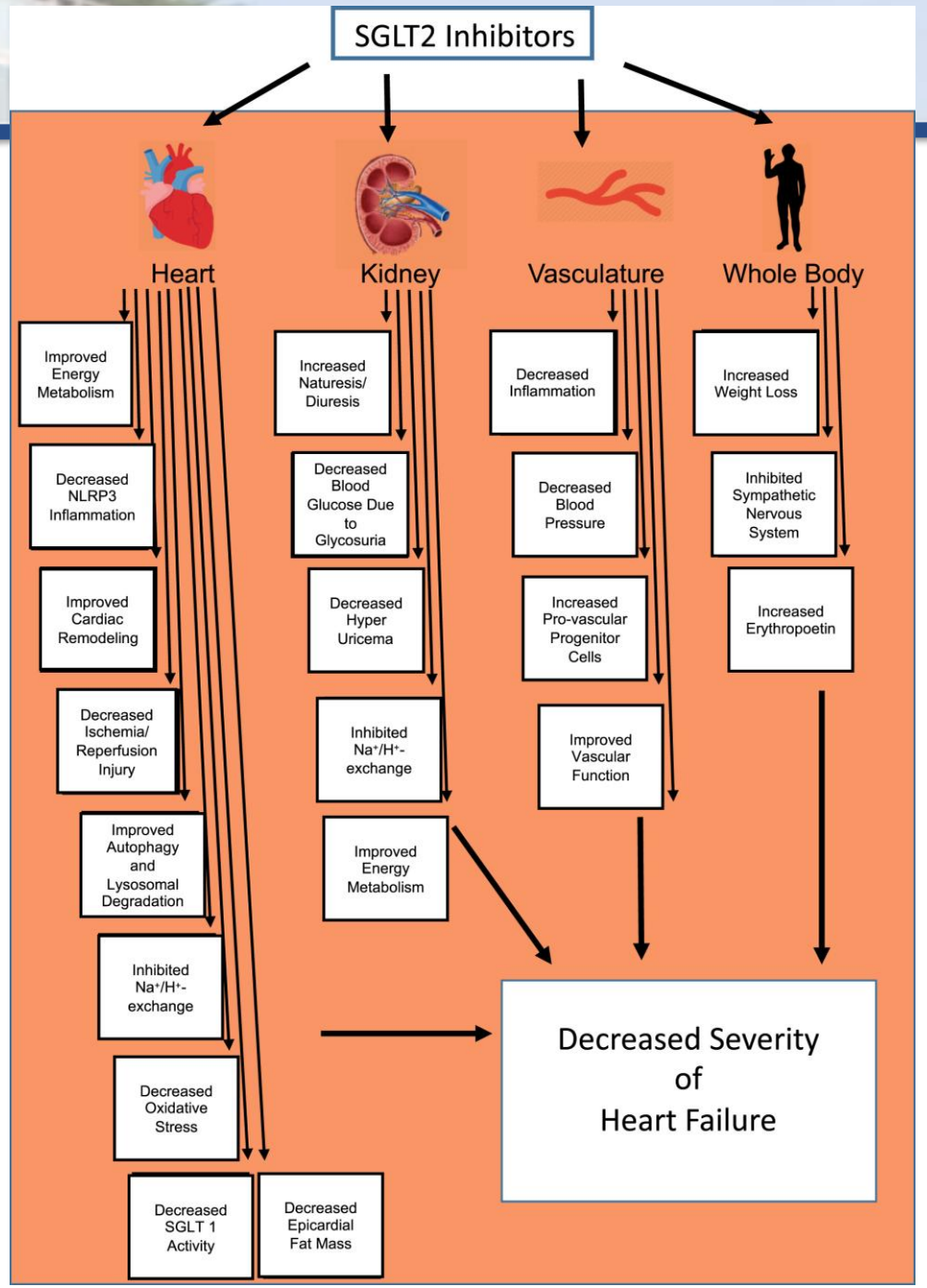
The nephroprotective effects of SGLT2i



Vallon V. Am J Hypertension, 2024

And if it was the kidney ?




SGLT2 Inhibitors
Heart
Kidney
Vasculature
Whole Body
Improved Energy Metabolism
Decreased NLRP3 Inflammation
Improved Cardiac Remodeling
Decreased Ischemia/ Reperfusion Injury
Improved Autophagy and Lysosomal Degradation
Inhibited Na+/H+- exchange
Decreased Oxidative Stress
Decreased SGLT 1 Activity
Decreased Epicardial Fat Mass
Increased Naturesis/ Diuresis
Decreased Blood Glucose Due to Glycosuria
Decreased Hyper Uricema
Inhibited Na+/H+- exchange
Improved Energy Metabolism
Decreased Inflammation
Decreased Blood Pressure
Increased Pro-vascular Progenitor Cells
Improved Vascular Function
Increased Weight Loss
Inhibited Sympathetic Nervous System
Increased Erythropoetin
Decreased Severity of Heart Failure

En conclusion

- Après de nombreuses années où la pharmacologie de l'insuffisance cardiaque à fraction d'éjection réduite était centrée sur le blocage de l'activation des systèmes neuro-hormonaux, de nouvelles cibles thérapeutiques plus « cardio-centrées » sont maintenant disponibles

- Les inhibiteurs de SGLT2 vont s'imposer comme une nouvelle classe majeure du traitement de l'insuffisance cardiaque systolique

- L'élargissement de l'arsenal thérapeutique va poser la question du positionnement de chaque molécule et de leur combinaison

- L'insuffisance cardiaque à fraction d'éjection préservée n'est plus orpheline en termes de traitements ➔ iSGLT2

Thank you for your attention

Clinical Investigations Center, Hôpital Européen Georges Pompidou
& Team 7 Paris Cardiovascular Research Center