Effetti degli SGLT2-i: oltre la glicosuria

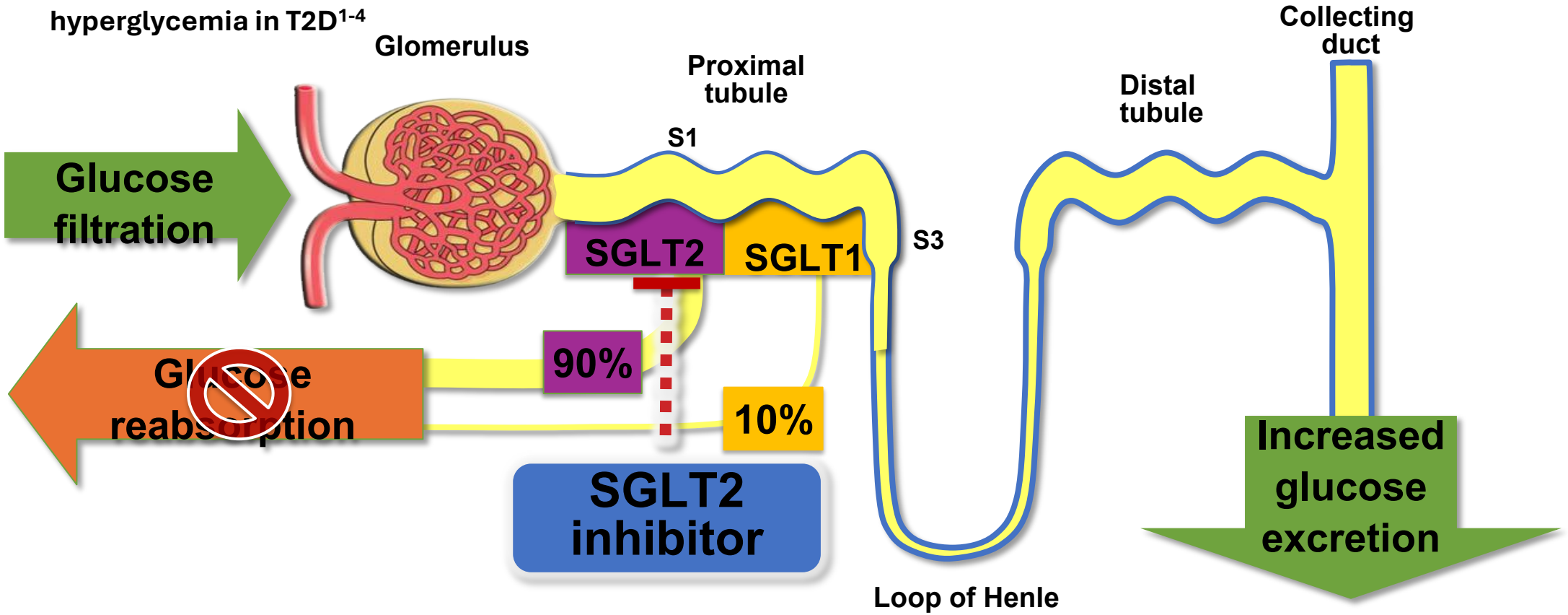
Maria Perticone

La sottoscritta Prof.ssa Maria Perticone dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

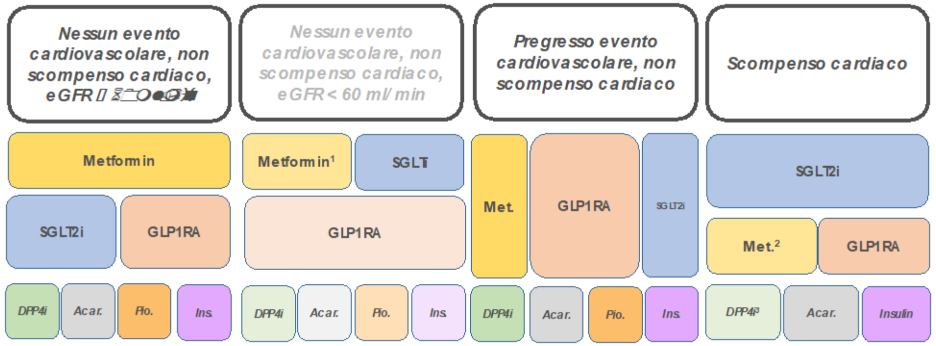
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Background - MoA

Sodium-glucose transporter 2 inhibitors (SGLT2) inhibitors were initially developed and approved to reduce hyperglycemia in T2D[1-4]



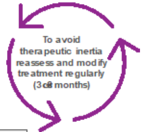
Standard of care AMD/SID 2023



[1]Se la metformina non è controindicata per ridotto eGFR.
[2]Se la metformina non è controindicata per ridotta funzione cardiaca.
[3]Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.
La raccomandazione sui pazienti con eGFR <60 ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfaniluree e glinidi

Linee guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)

ADA 2023 Standards of Medical Care includes several treatment options for patients with T2D and comorbidities or high risk



Use of glucose-lowering medications in the management of T2D

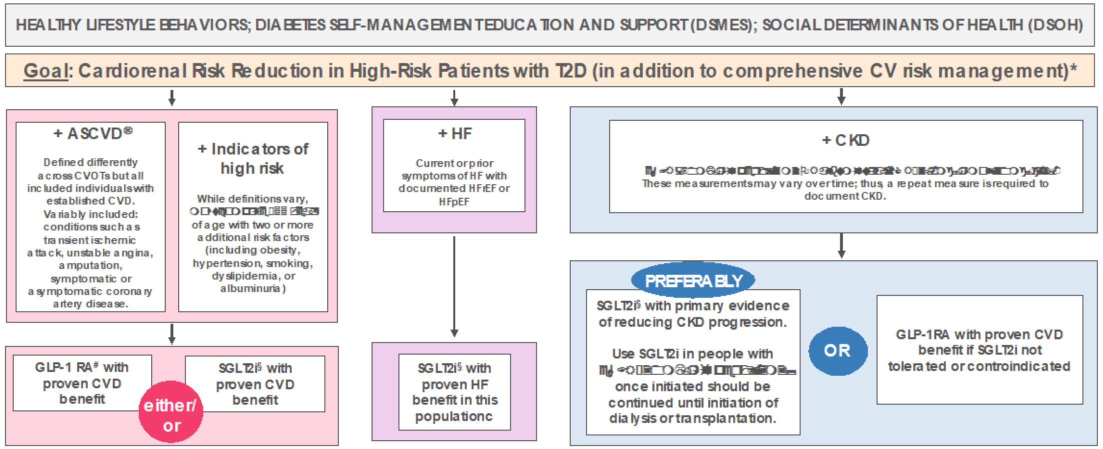
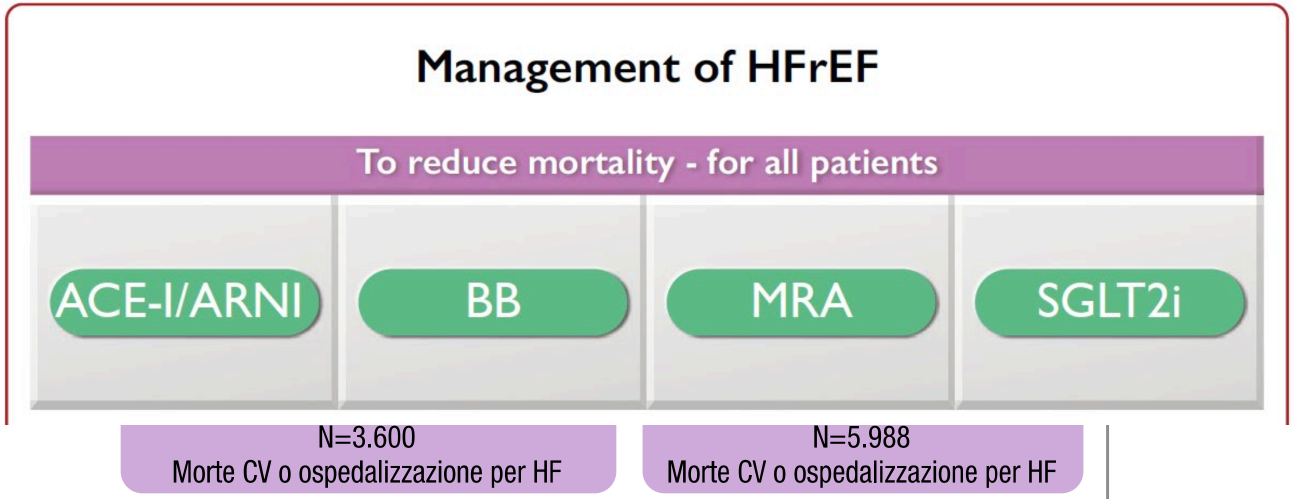


Figure adapted from the American Diabetes Association. Diabetes Care 2023;46:S1.
There are additional recommendations if HbA1c remains above target or if further cardiorenal risk reduction is needed; for full recommendations please refer to the reference.
*In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.
† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. For details, please refer to the reference.
# For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.
§ For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD.

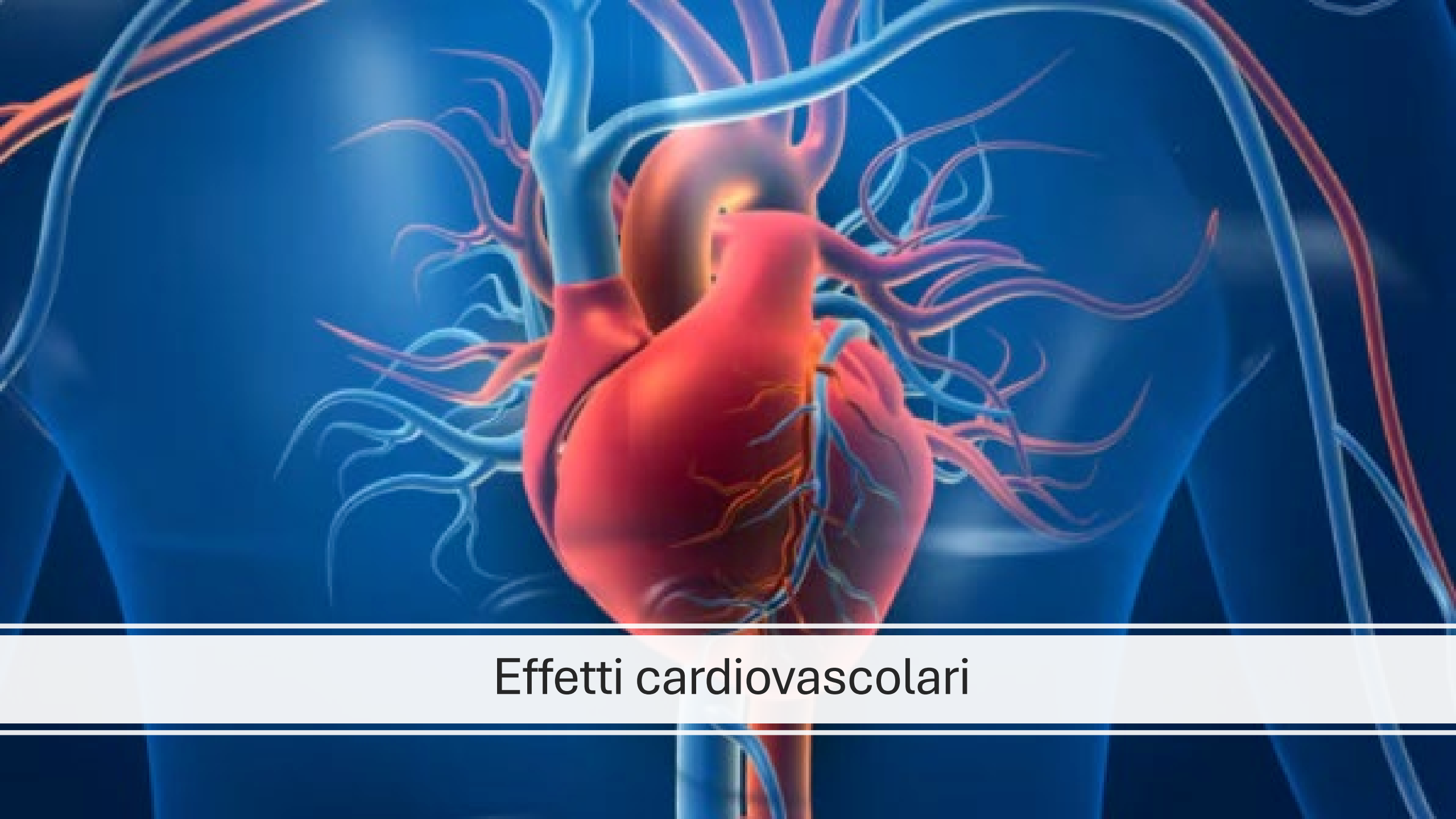
The 2022 KDIGO and 2023 ESC guidelines recommend SGLT2 inhibitors for their CV and kidney benefits for the treatment of people with CKD[1,2]



"We le<GmmeFd Ke: KFg **people with T2D, CKD,** and an **eGFR ≥2 ml/min per 1.73 m²** with an **SGLT2 inhibitor** 1/)."*†

"A **SGLT2 inhibitor** (canagliflozin, empagliflozin, or dapagliflozin) is **recommended in patients with T2D and CKD** with an **eGFR ≥20 ml/min/1.73 m²** to reduce the risk of CVD and kidney failure(1A)."*‡

For agent-spe<ifi< le<GmmeFd: KGFs, µD: se lefel KGKe n: Fu: <Kulel sVples<li; iFg iFfGln: KGF; †WiKAiF e: <Al e<GmmeFd: KGF, Ke strength of the recommendation is indicated as Level 1 or Level 2, and the quality of the supporting evidence is shown as A, B, C, or D. For this recommendation: (1A): Level 1, strong recommendation; A, high quality of evidence; ‡WiKAiF e: <Al e<GmmeFd: KGF, Ke sKeFgKA Gf Ke le<GmmeFd: KGF is iFdi<: Ked : s 0 D ss I, II IIa, IIb) or III, and the quality of the supporting evidence is shown as A, B, or C. For this recommendation: (1A): Level 1, Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; A, Data derived from multiple randomized clinical trials or meta-analyses.



Effetti cardiovascolari

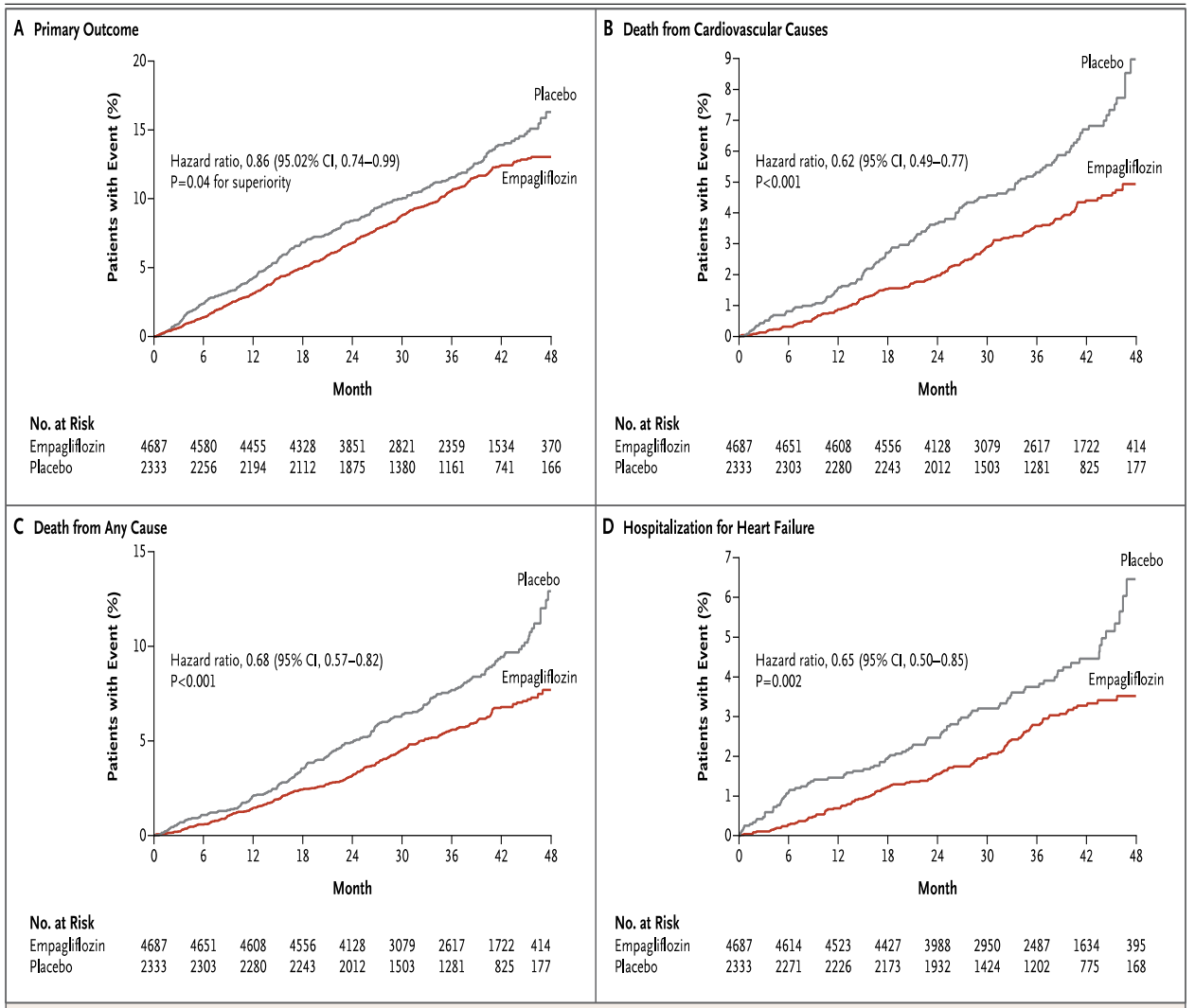


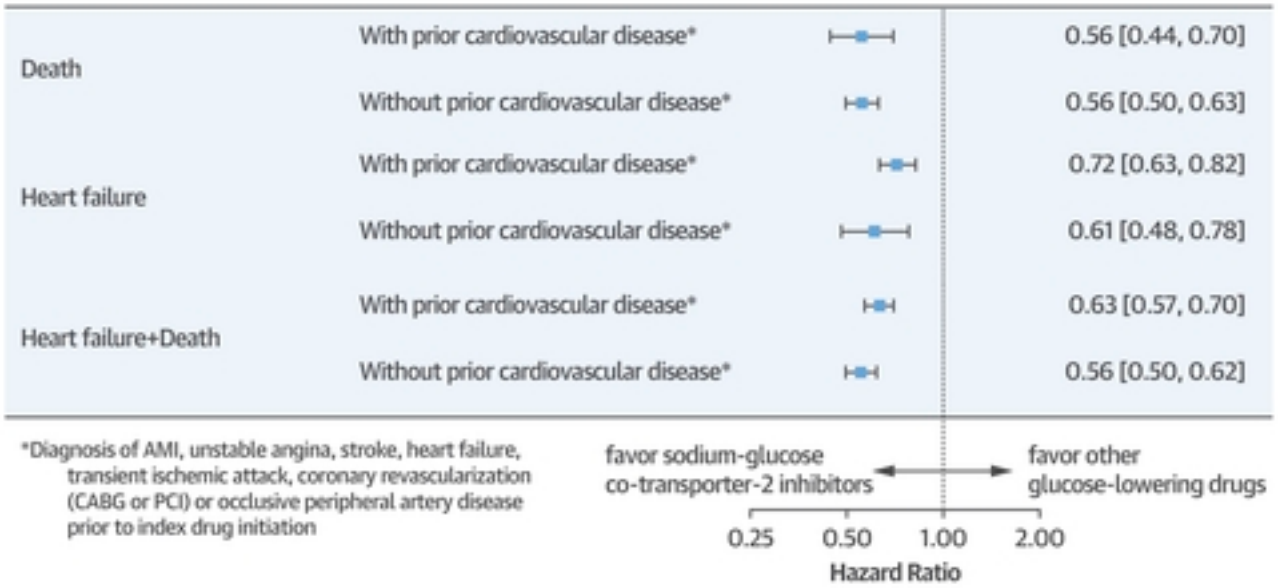
Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

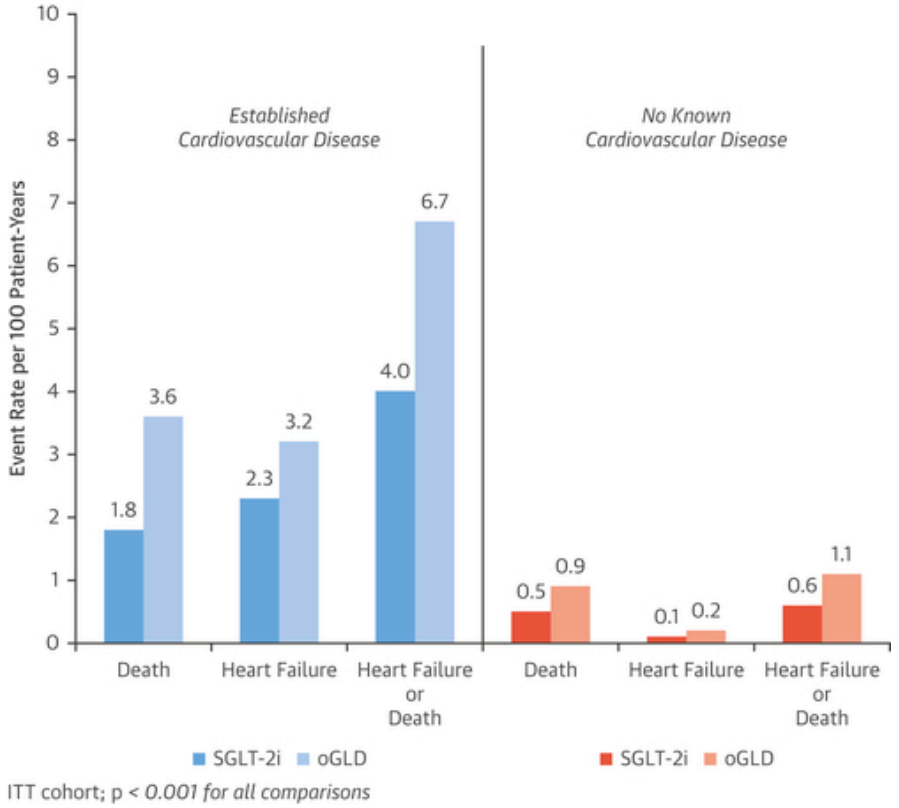
	EMPA-REG OUTCOME (Empagliflozin)	**CANVAS program** (Canagliflozin)	**DECLARE-TIMI58** (Dapagliflozin)	**VERTIS-CV** (Ertugliflozin)
3P-MACE non-inferiority				
3P-MACE Superiority	**HR 0.86 [CI: 0.74 - 0.99] RRR: 14 %**	**HR 0.86 [CI: 0.75 - 0.97] RRR: 14 %**	HR 0.93 [CI: 0.84 - 1.03]	Not tested for superiority
CV death or hHF	**HR: 0.66* [CI: 0.55 – 0.79] RRR: 34 %**	**HR 0.72 [CI: 0.55 - 0.94] RRR: 28 %**	**HR 0.83 [CI: 0.73 - 0.95] RRR: 17 %**	HR 0.88 [CI: 0.75 – 1.03]
CV death	**HR: 0.62* [CI: 0.49 - 0.77] RRR: 38 %**	HR 0.87 [CI: 0.72 -1.06]	HR 0.98 [CI: 0.82 - 1.17]	HR 0.92 [CI: 0.77 - 1.11]
HHF	**HR: 0.65* [CI: 0.50 - 0.85] RRR: 35 %**	**HR 0.67 [CI: 0.52 - 0.87] RRR: 33 %**	**HR 0.73 [CI: 0.61 – 0.88] RRR: 27 %**	**HR 0.70 [CI: 0.54 – 0.90] RRR: 30 %**
Renal Composite (most comparable)	**HR: 0.54 [CI: 0.40 – 0.75] RRR: 36 %**	**HR 0.59* [CI: 0.44 - 0.79] RRR: 41 %**	**HR 0.53 [CI: 0.43 – 0.66] RRR: 47 %**	HR 0.81 [CI: 0.63 – 01.04] Did not include Albuminuria
All-Cause mortality	**HR: 0.68* [CI: 0.57 – 0.82] RRR: 32 %**	HR 0.87 [CI: 0.74 - 1.01]	HR 0.93 [CI: 0.82 – 1.04]	N/A

CVD-REAL

CENTRAL ILLUSTRATION: Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease



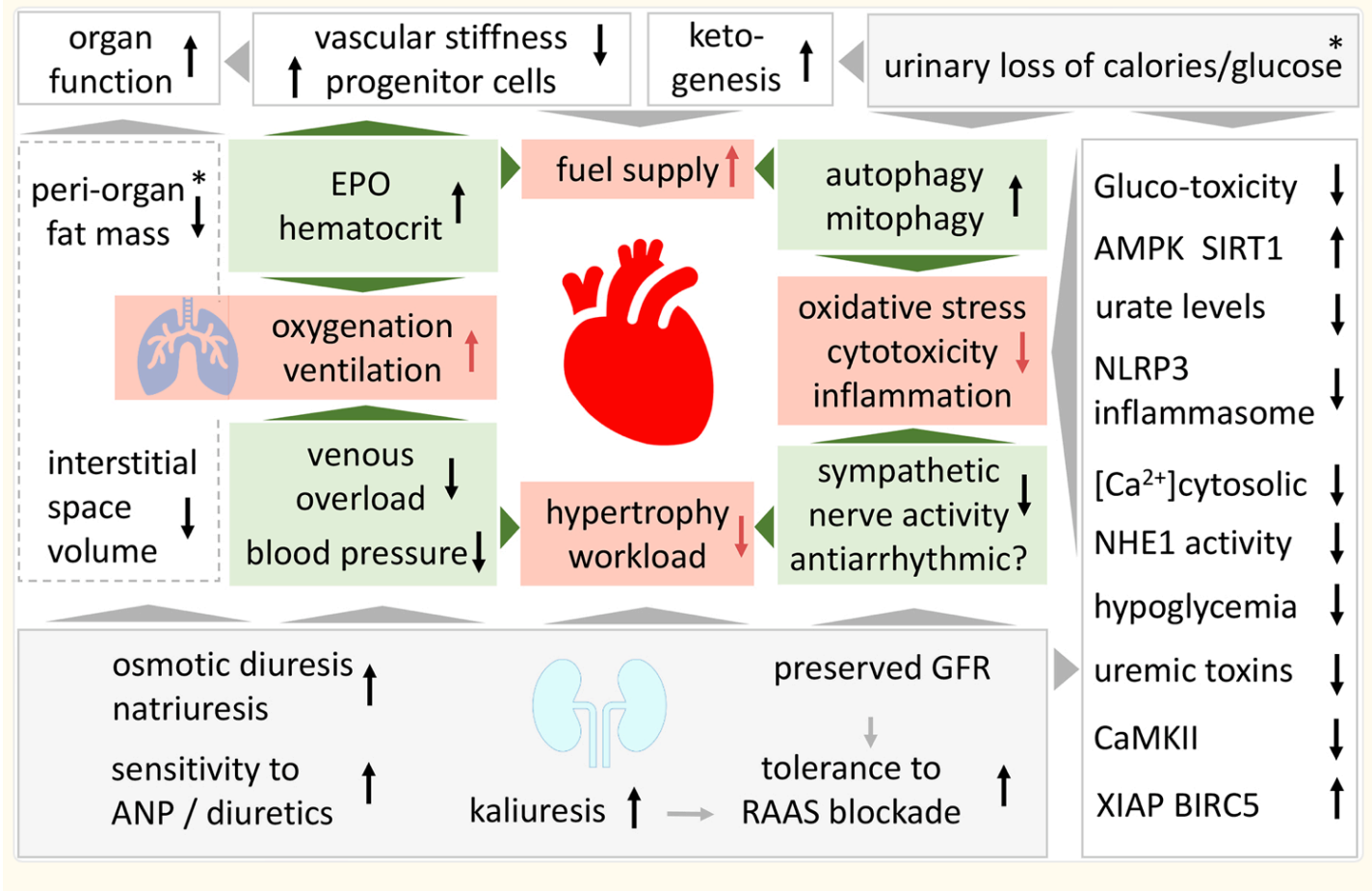
Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497-506.



ITT cohort; p < *0.001 for all comparisons*

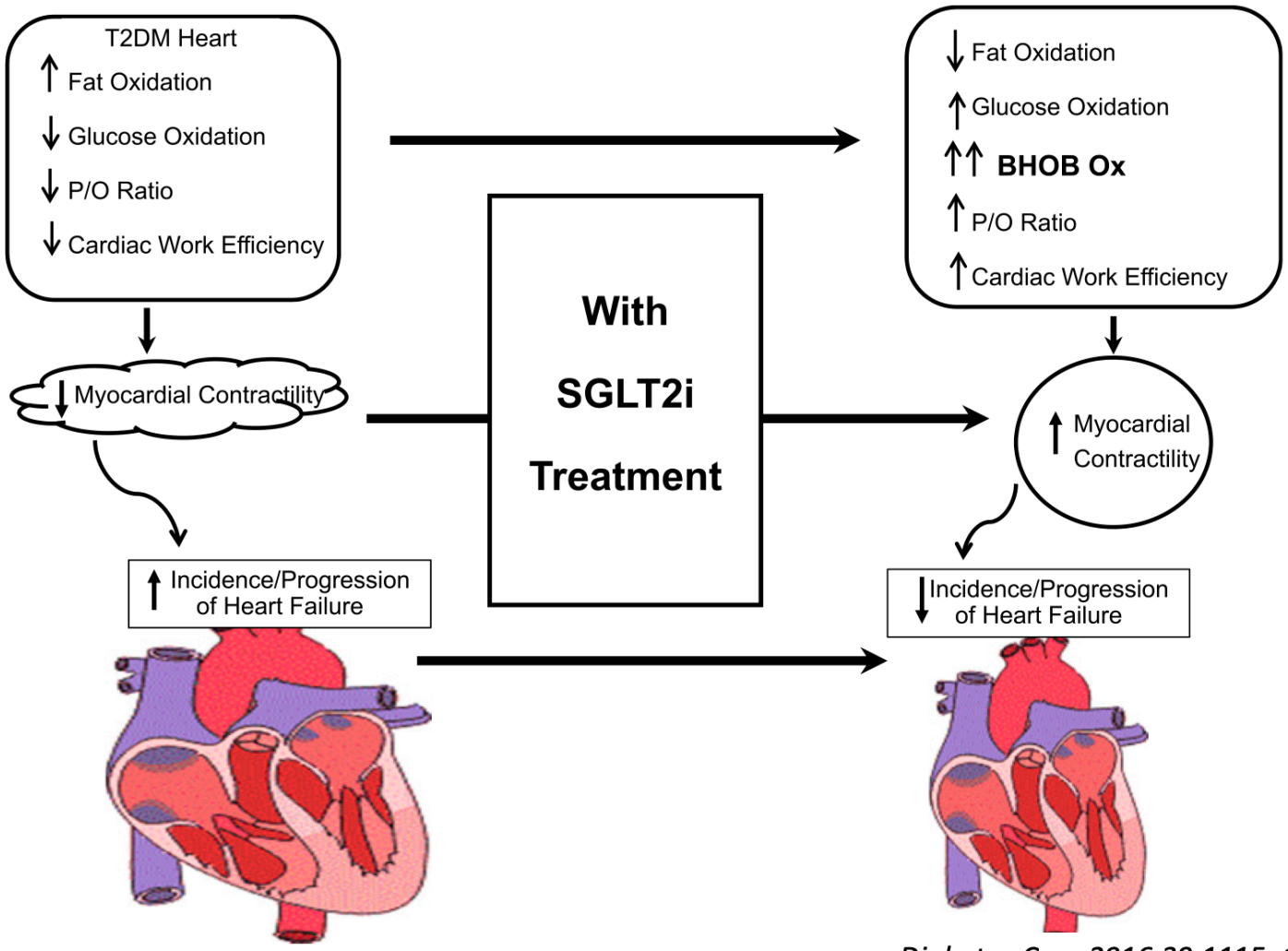
Matthew A. Cavender et al. *JACC* 2018; 71:2497-2506.

Potenziali effetti cardioprotettivi degli SGLT2-i



Annu Rev Physiol. 2021 February 10; 83: 503–528. doi:10.1146/annurev-physiol-031620-095920.

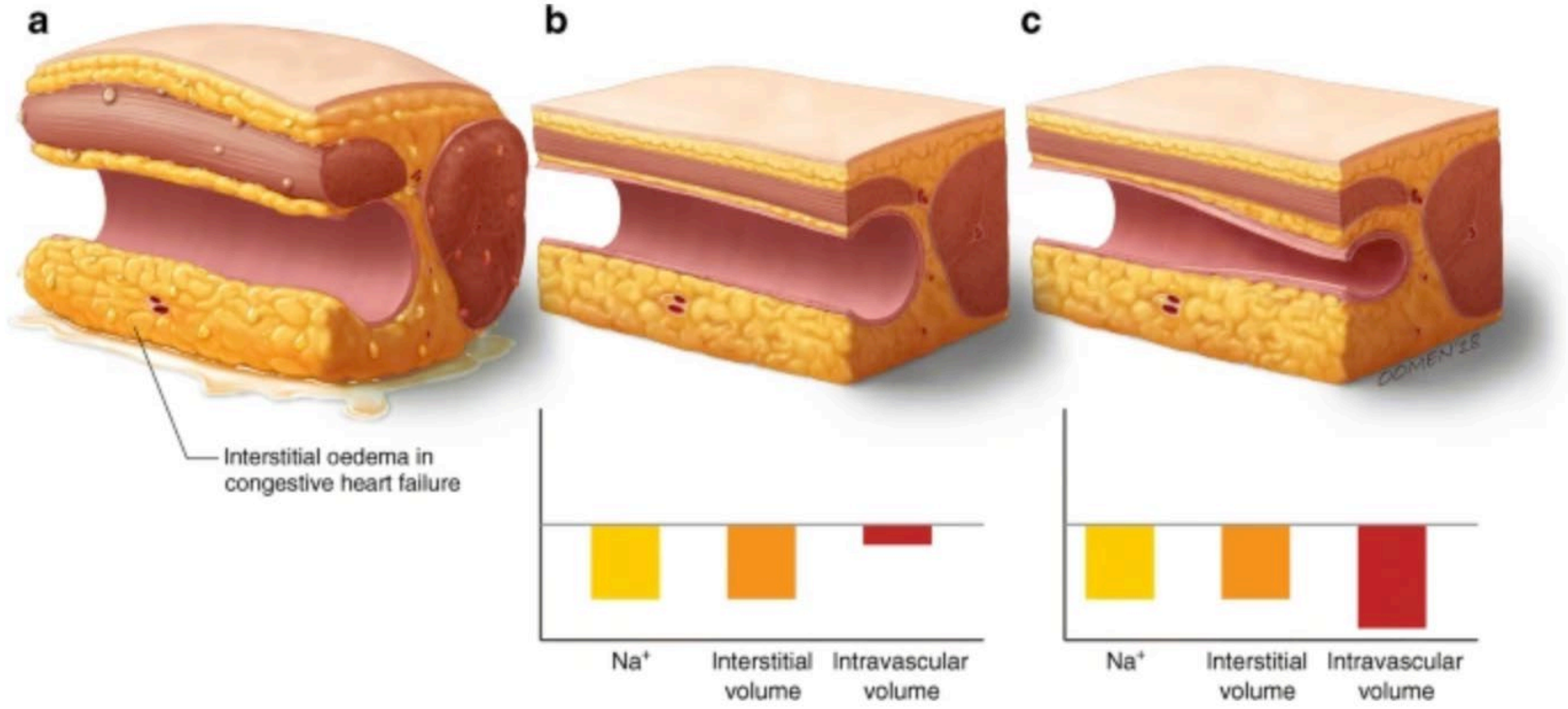
Shift in fuel energetics hypothesis



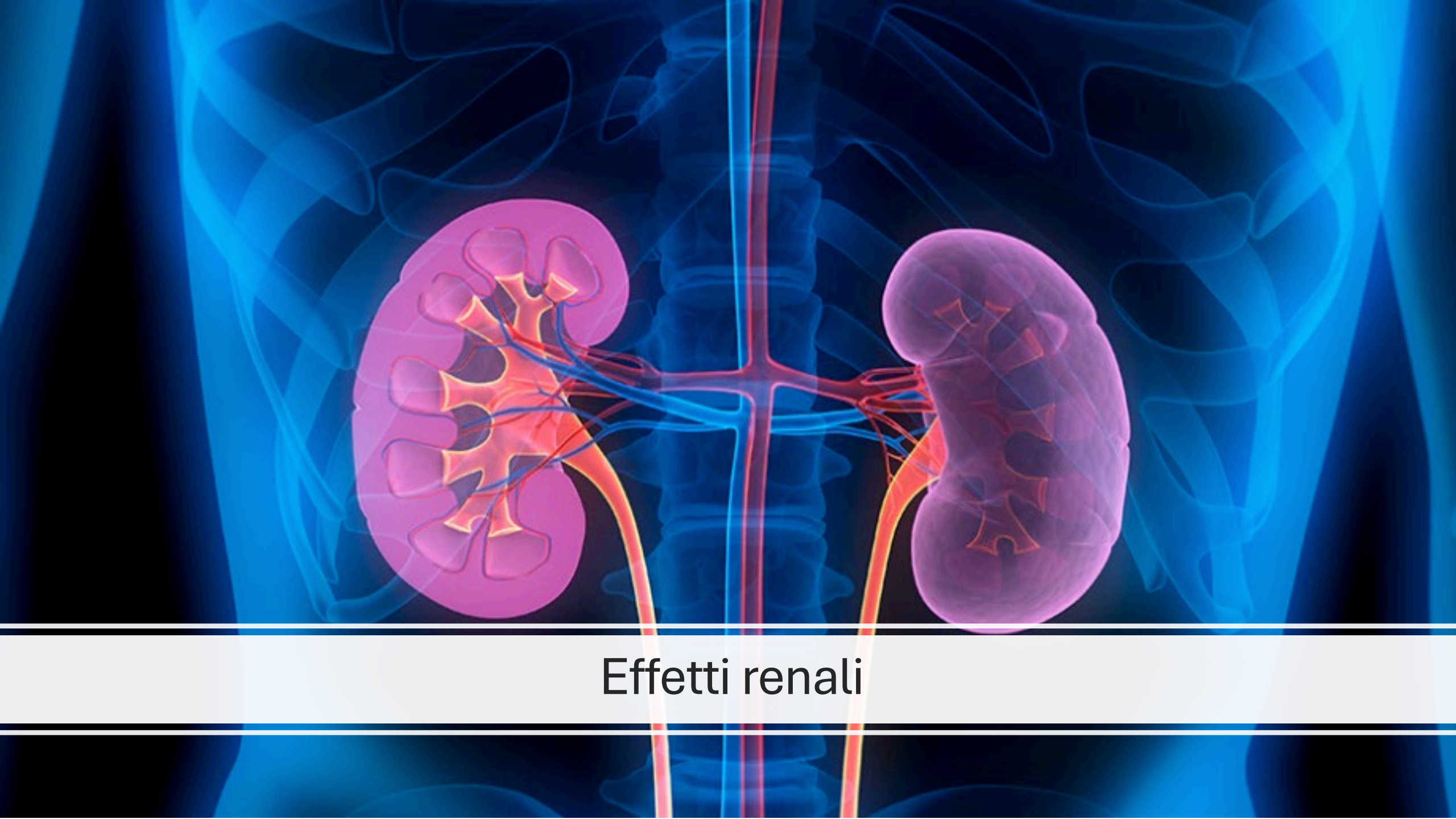
Diabetes Care 2016;39:1115–1122 | DOI: 10.2337/dc16-0542

Gli SGLT2-i NON agiscono allo stesso modo dei diuretici dell'ansa!

Fig. 4

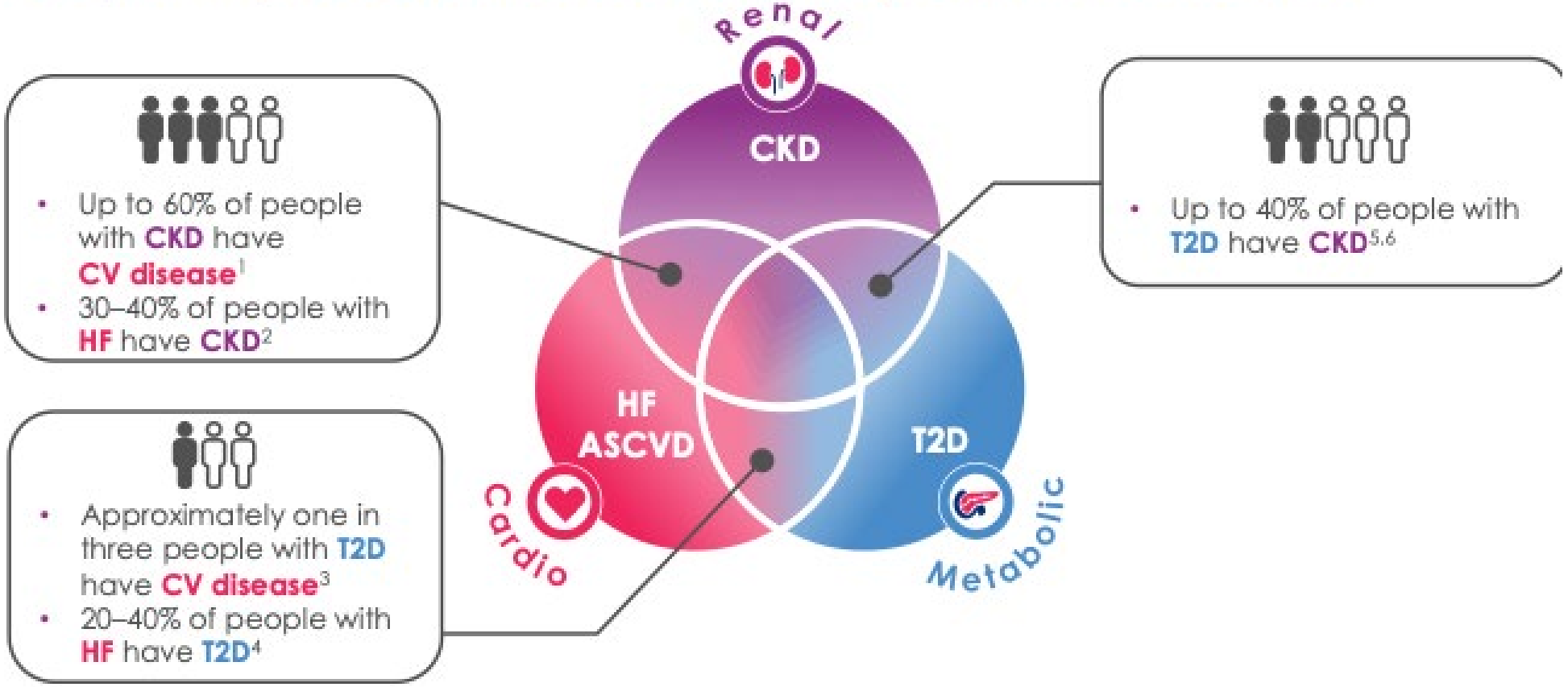


Diabetologia (2018) 61:2108–2117



Effetti renali

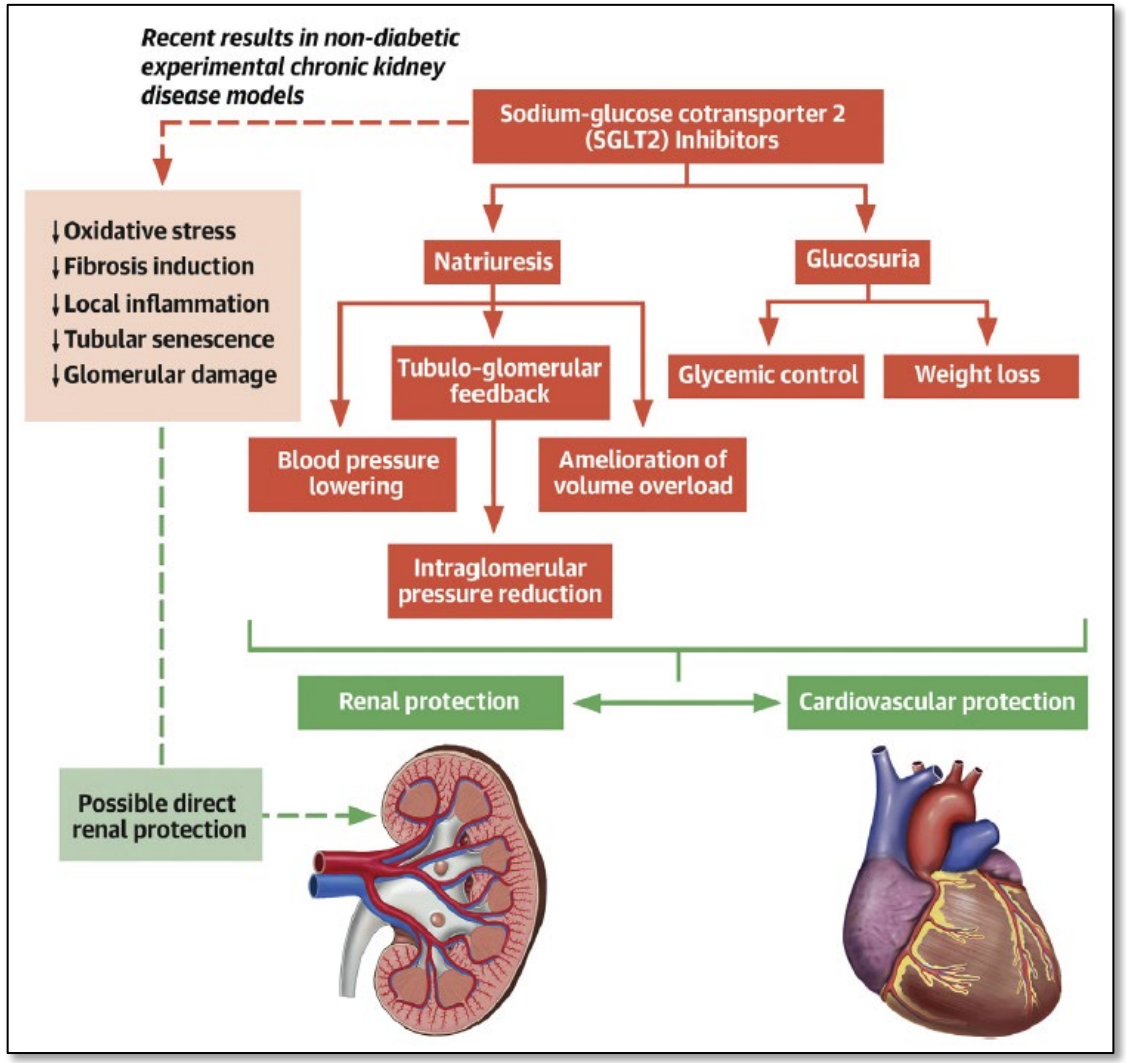
Cardiovascular, renal and metabolic conditions frequently coexist because they are interrelated



ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; T2D, type 2 diabetes

1. Lovre D *et al. Endocrinol Metab Clin North Am* 2018;47:237; 2. Ahmed A *et al. Heart Fail Clin* 2008;4:387; 3. Einarson TR *et al. Cardiovasc Diabetol* 2018;17:83; 4. Thomas MC *et al. Curr Cardiol Rev* 2016;12:249; 5. Alkabbani M *et al. JAMA* 2016;316:602; 6. International Diabetes Foundation. Diabetes Atlas 9th Edition. http://www.diabetesatlas.org (accessed Mar 2023)

Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview



The protective effects of SGLT2i on the kidney are believed to be mediated by several hemodynamic and nonhemodynamic mechanisms. The improvements of cardiac function by SGLT2i may contribute to their favorable effects on the kidneys halting the “vicious cardiorenal circle”.

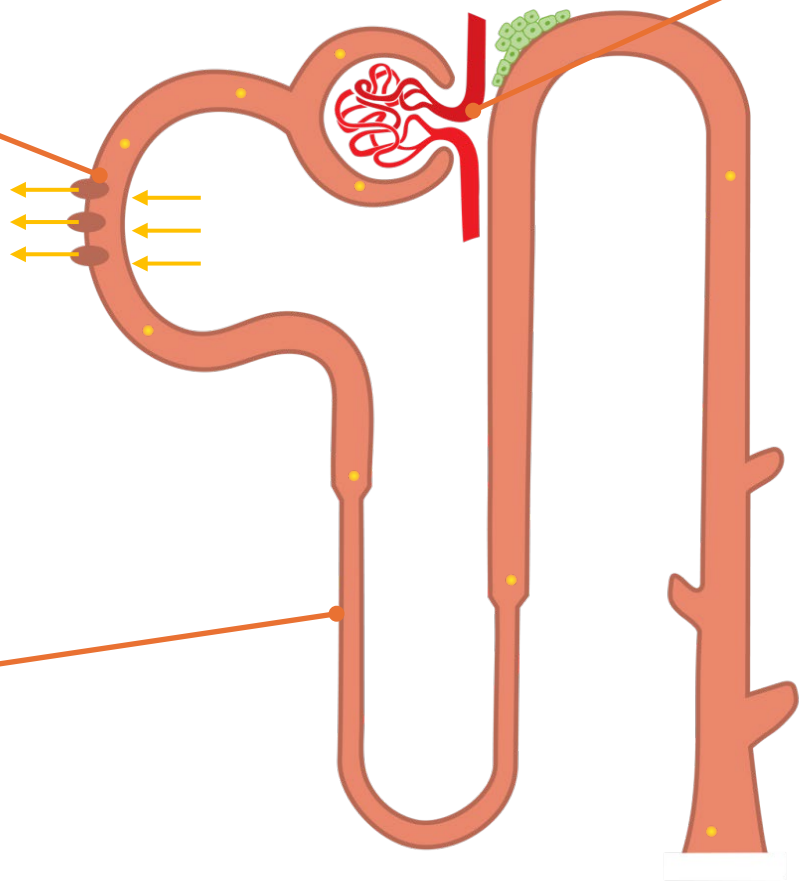
SGLT2i, Sodium-glucose cotransporter 2 inhibitors

Zelniker TA et al. *J Am Coll Cardiol*. 2020 Feb 4;75(4):422-43

Kidney protective effects of SGLT2 inhibitors could be mediated by different mechanisms

Reduction in sodium and glucose reabsorption induced by SGLT2 inhibitors reduces tubular workload and could **ameliorate renal hypoxia**, resulting in **improvements in tubular cell structural integrity** and possibly function[1]

SGLT2 inhibitors have beneficial effects on **anti-inflammatory**, **anti-oxidant** and **anti-fibrotic** markers[1]



SGLT2 inhibitors increase distal sodium delivery, thereby activating **tubuloglomerular feedback** and reducing hyperfiltration[1]

This leads to:

- Decreased intraglomerular pressure[2,3]
- Decreased proteinuria[3]

- SGLT2 inhibitors reduce **body weight** and **fat mass** along with improvement of endothelial function[4]

1. Dekkers CCJ et al. Curr Diab Rep 2018;18:27; 2. Thomas MC et al. Diabetologia 2018;61:2098; 3. Heerspink HJL et al. Kidney Int 2018;94:26; 4. Sugyama S et al. Intern Med 2018;57:2147

Prognosis of CKD by eGFR and albuminuria categories[2]

- Low risk*
- Moderately increased risk
- High risk
- Very high risk

eGFR category range (mL/min/1.73m²)			Albuminuria stage, description and range (mg/g)		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30	30–300	>300
G1	≥90				
G2	60–89				
G3a	45–59				
G3b	30–44				
G4	15–29				
G5	<15				

EMPA-KIDNEY population[1]
Patients with or without
<90 mL/min/1.73m² and
or
mL/min/1.73m²

CREDENCE population[3]
Patients with T2D and CKD
mL/min/1.73m² **and**
UACR >300 mg/g

DAPA-CKD population[4]
Patients with or without T2D
and eGFR ≥25 to <75
mL/min/1.73m² **and** UACR

The KDIGO 2024 CKD guideline recommends the use of SGLT2 inhibitors in people with CKD across the cardio, renal and metabolic spectrum[1]

Recommendations indicate SGLT2 inhibitors* to treat:

CKD and **T2D**

Patients with **T2D, CKD and an eGFR ≥20 ml/min/1.73 m²** (1A)

CKD and **HF†**

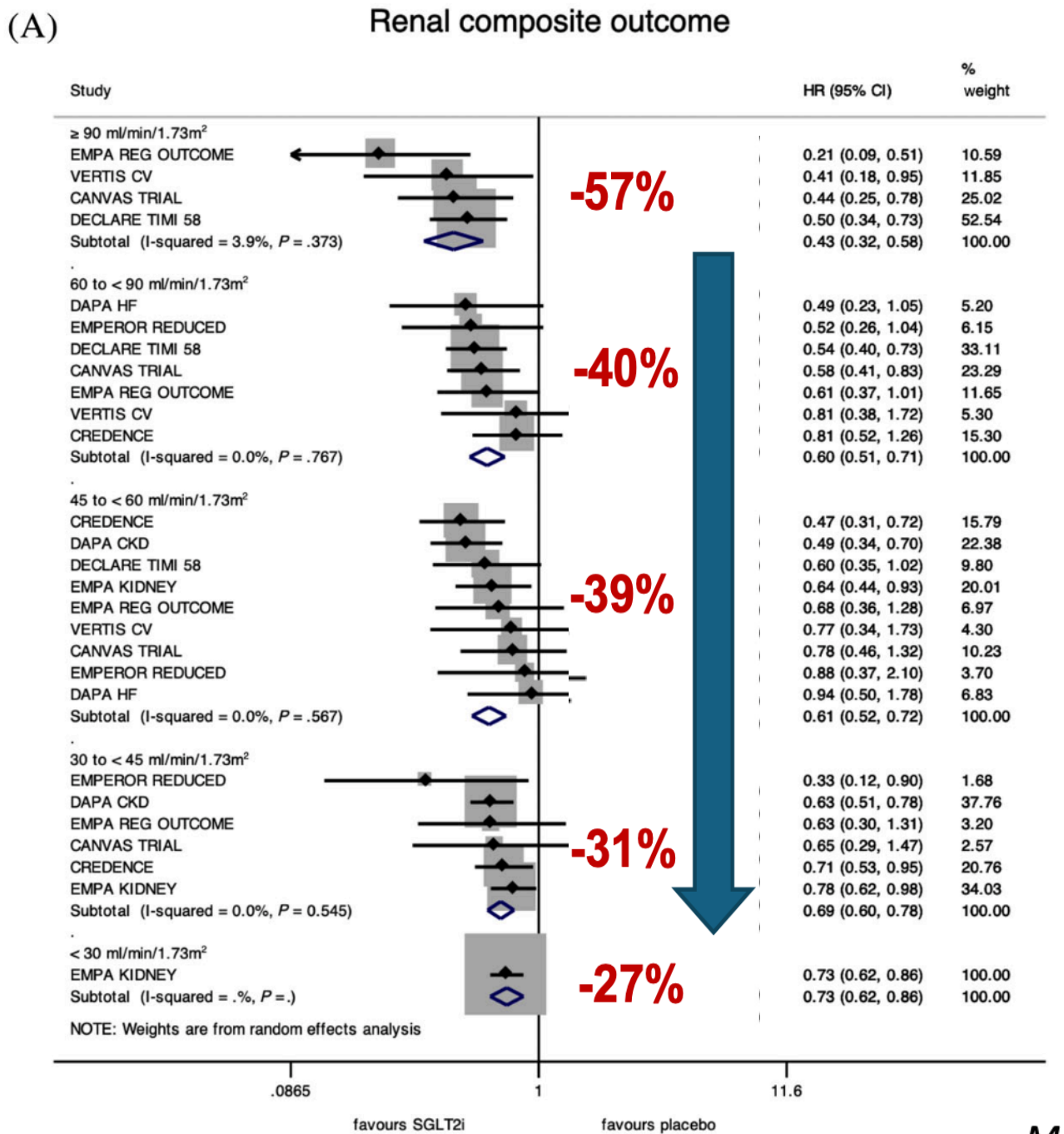
Adults with **CKD and HF irrespective** of level of **albuminuria** (1A)

CKD

Adults with **CKD with an eGFR ≥20 ml/min/1.73 m² with UACR ≥200 mg/g (≥20 mg/mmol)** (1A)

Adults with **eGFR 20 to 45 ml/min/1.73 m² with UACR <200 mg/g (<20 mg/mmol)** (2B)

(A)



Maddaloni E et al., DOM, 2023

Altri effetti extraglicemici degli SGLT2-i

biomedicines

MDPI

Article

Effect of SGLT2-Inhibitors on Polygraphic Parameters in Elderly Patients Affected by Heart Failure, Type 2 Diabetes Mellitus, and Sleep Apnea

Giuseppe Armentaro [1,†], Corrado Pelaia [1,†], Valentino Condoleo [1], Giandomenico Severini [1], Giulia Crudo [1], Mario De Marco [1], Carlo Alberto Pastura [1], Valeria Tallarico [2], Rita Pezzella [3], Domenico Aiello [4], Sofia Miceli [1], Raffaele Maio [1], Gianluigi Savarese [5], Giuseppe M. C. Rosano [6,7,‡] and Angela Sciacqua [1,*,‡]

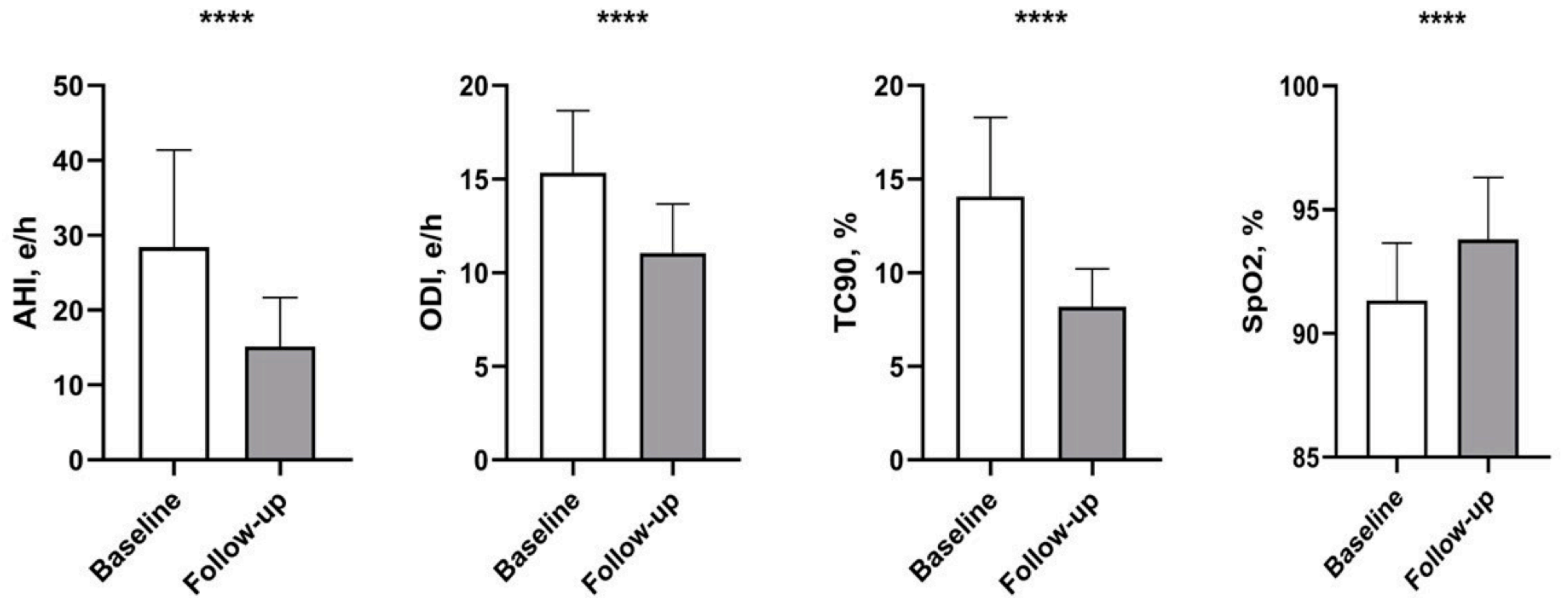
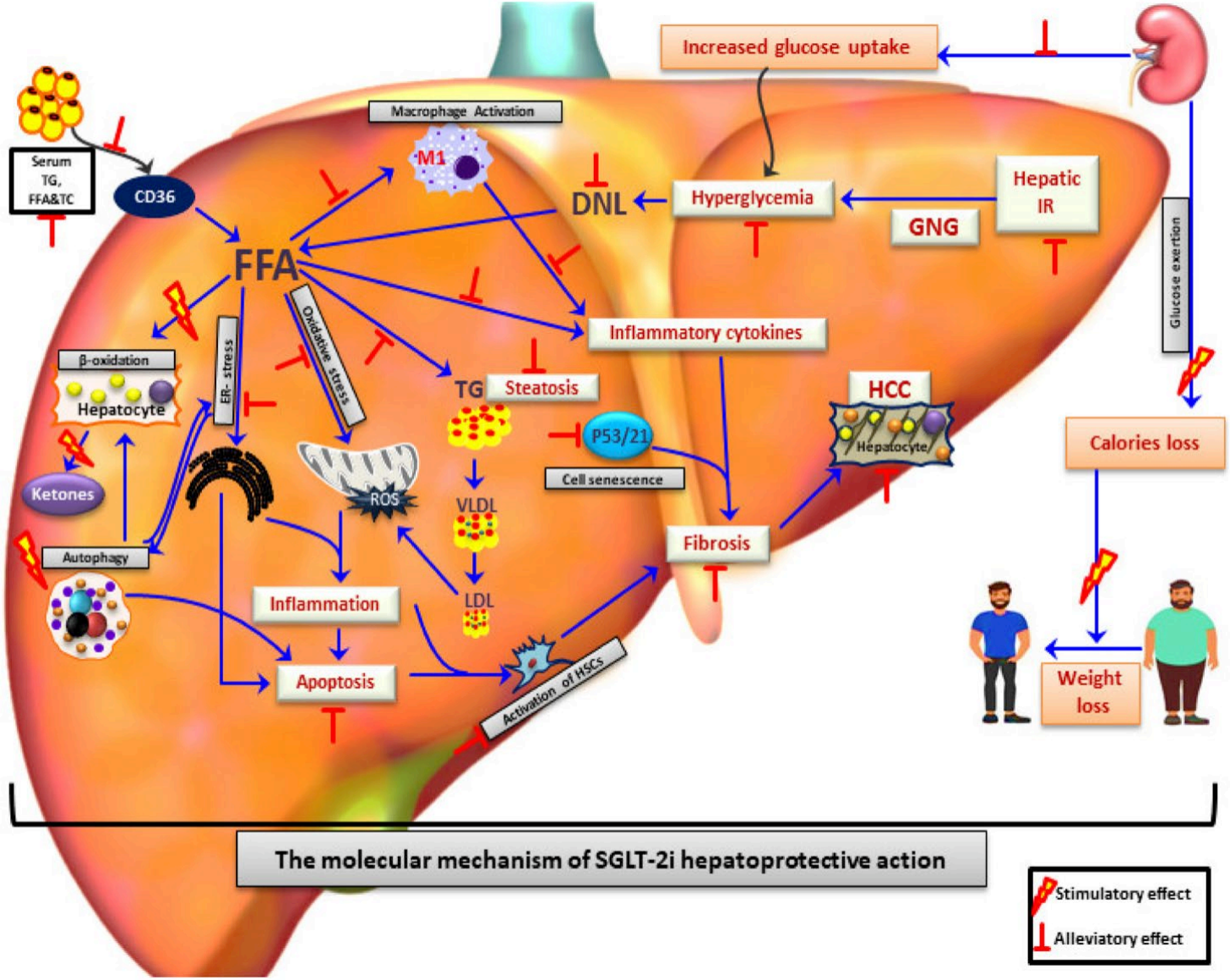
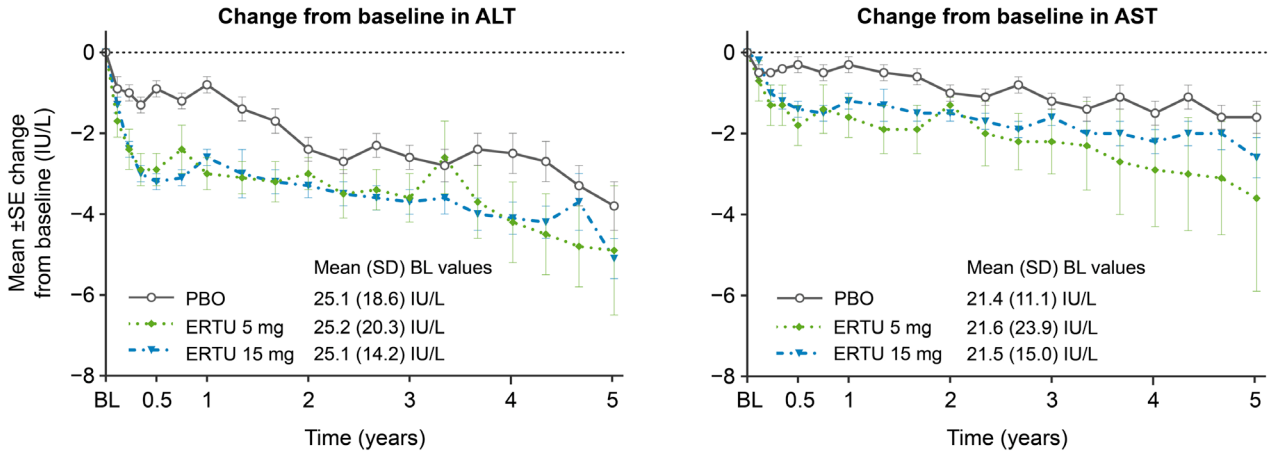
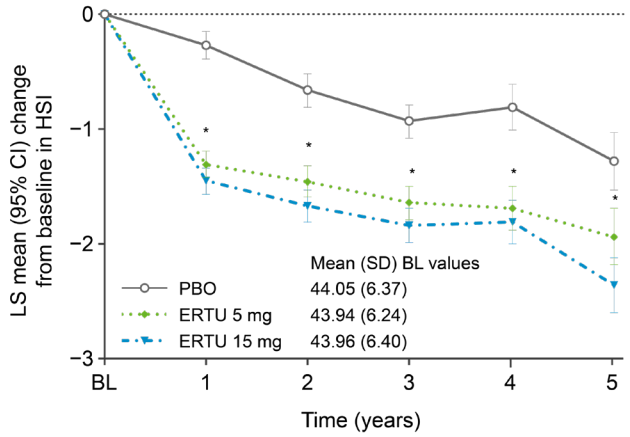


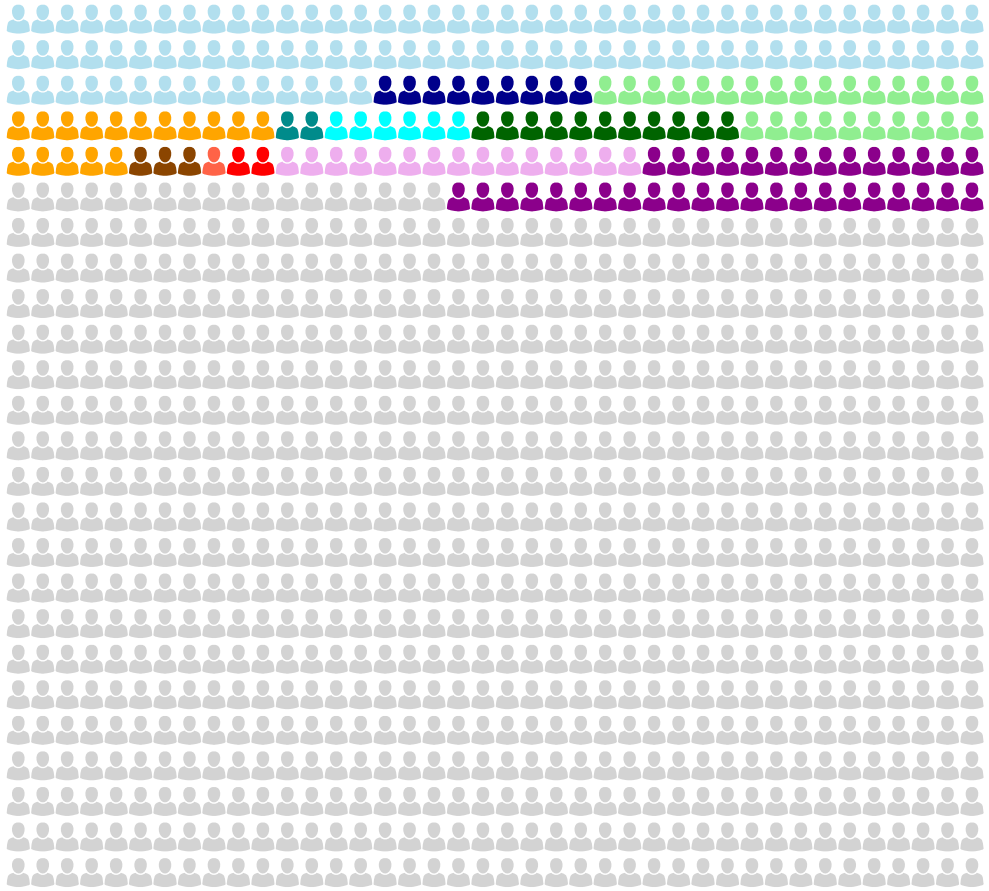
Figure 1. Baseline to follow-up change in polygraphic parameters in patients treated with SGLT2i. Data are mean ± SD. **** $p < 0.0001$ vs. baseline.


Increased glucose uptake
Macrophage Activation
M1
Serum TG, FFA&TC
CD36
DNL
Hyperglycemia
Hepatic IR
GNG
Glucose exertion
FFA
Inflammatory cytokines
β-oxidation
Hepatocyte
ER- stress
Oxidative stress
TG
Steatosis
HCC
Hepatocyte
P53/21
Cell senescence
Calories loss
Ketones
ROS
VLDL
Autophagy
Fibrosis
Inflammation
LDL
Apoptosis
Activation of HSCs
Weight loss
The molecular mechanism of SGLT-2i hepatoprotective action
Stimulatory effect
Alleviatory effect

VERTIS CV


Change from baseline in ALT
Mean ±SE change from baseline (IU/L)
0
−2
−4
−6
−8
BL
0.5
1
2
3
4
5
Time (years)
Mean (SD) BL values
PBO 25.1 (18.6) IU/L
ERTU 5 mg 25.2 (20.3) IU/L
ERTU 15 mg 25.1 (14.2) IU/L
Change from baseline in AST
Mean (SD) BL values
PBO 21.4 (11.1) IU/L
ERTU 5 mg 21.6 (23.9) IU/L
ERTU 15 mg 21.5 (15.0) IU/L


LS mean (95% CI) change from baseline in HSI
0
−1
−2
−3
BL
1
2
3
4
5
Time (years)
*
Mean (SD) BL values
PBO 44.05 (6.37)
ERTU 5 mg 43.94 (6.24)
ERTU 15 mg 43.96 (6.40)



95/1000 MACE_underTTT; 9/1000 Prevented_MACE; 26/1000 HHF_underTTT; 11/1000 Prevented_HHF; 6/1000 ESRD_c_underTTT; 2/1000 Prevented_ESRD_c; 16/1000 Amp_Spont; 3/1000 Induced_Amp ; 1/1000 Keto_Spont; 2/1000 Induced_Keto; 15/1000 Gen_Spont; 36/1000 Induced_Gen; 778/1000 No event

For each 1000 individuals treated over 3.5 years SGLT2-i are expected, on average, to:

- **decrease the number of deaths from 70 to 61**
- **prevent 9 MACE, 11 HHF and 2 ESRD**
- **induce 2 DKA and 36 genital infections**

778 are expected to avoid all investigated outcomes

Diabetologia (2022) 65:2000–2010

To be continued