La Terapia con SGLT2-i
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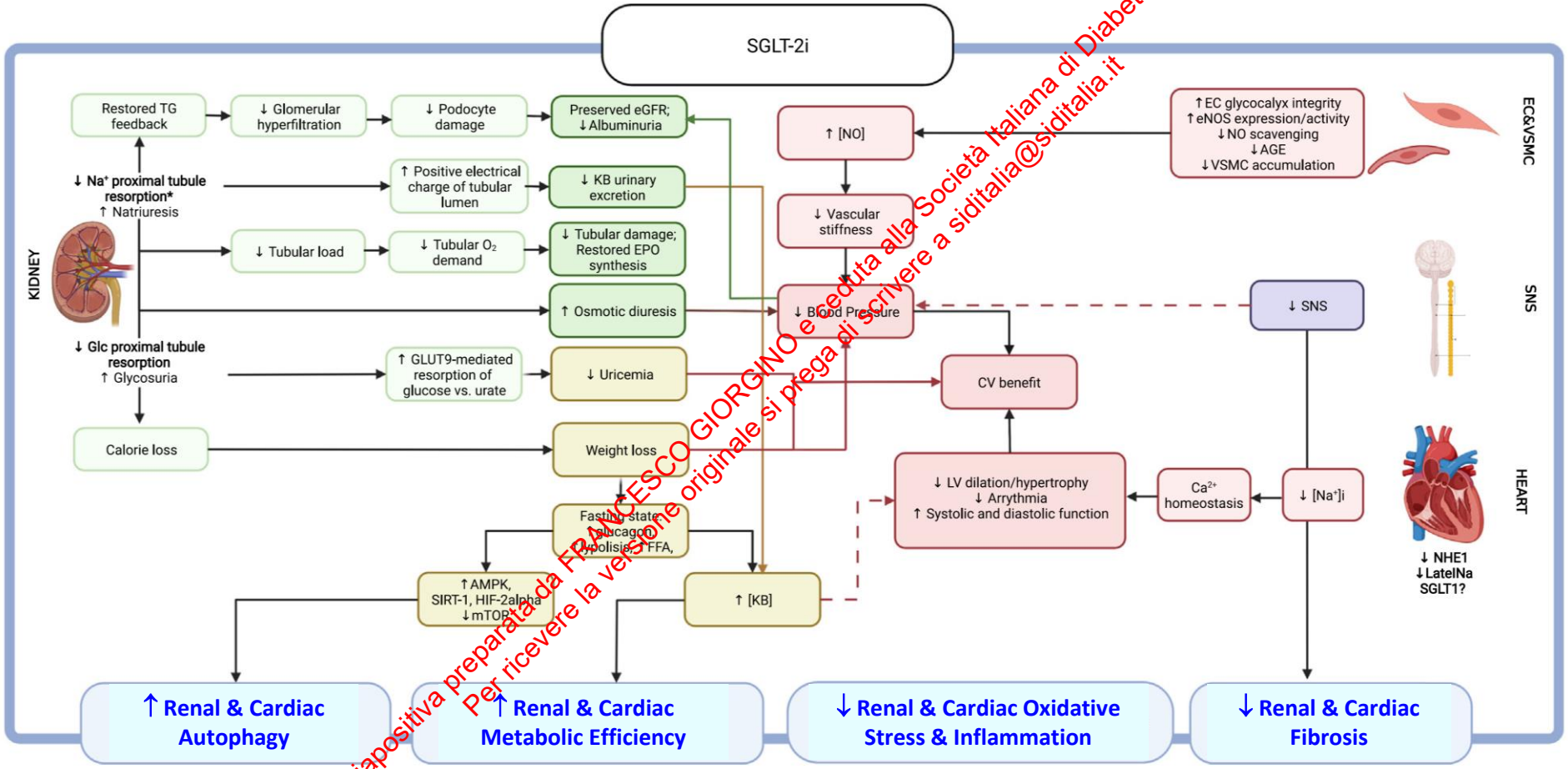
Disclosures

- **Advisory Boards**: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medimmune, Medtronic, NovoNordisk, Roche Diabetes Care, Sanofi
- **Other Boards**: European Association for the Study of Diabetes (EASD)/European Foundation for the Study of Diabetes (EFSD)
- **Consultant**: Eli Lilly, NovoNordisk
- **Lectures, presentations, or educational events**: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medtronic, NovoNordisk, Roche Diabetes Care, Sanofi
- **Research Support**: Eli Lilly, Roche Diabetes Care
- **Receipt of Medical Writing or Support for Statistical Analysis**: AstraZeneca, Eli Lilly, NovoNordisk, Roche Diabetes Care, Sanofi

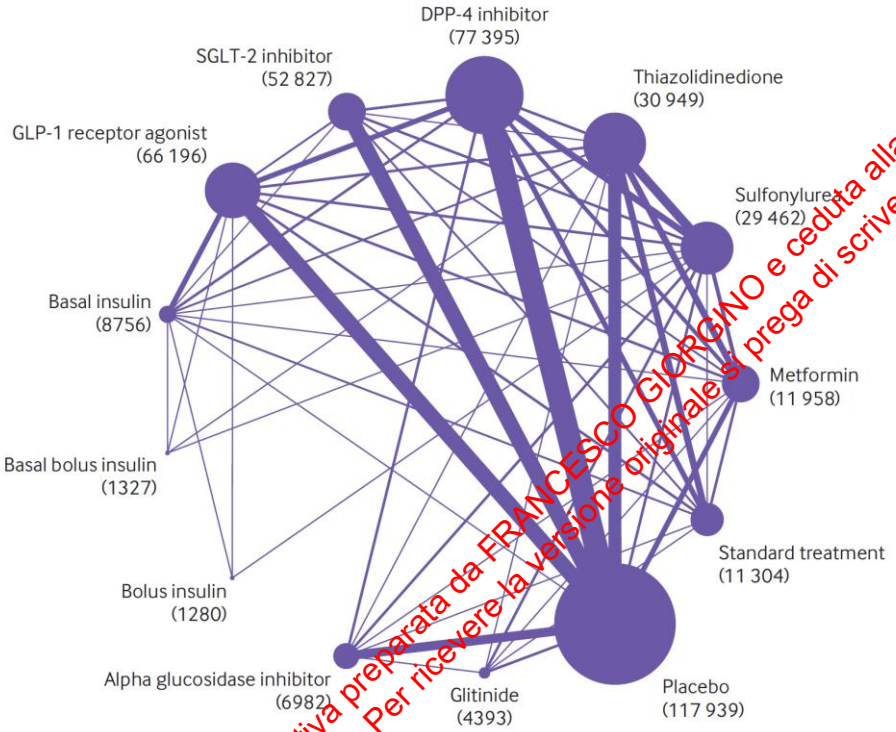
SGLT-2 Inhibitors as Cardio-renal Protective Agents



*Mediated by both SGLT-2 and NHE3 inhibition

Caruso I, Giorgino F. *Metabolism*. 2022 Feb;127:154937

SGLT-2 Inhibitors and GLP-1 RA for Type 2 Diabetes: Systematic Review and Network Meta-analysis of Randomised Controlled Trials



Varying levels of cardiovascular and kidney disease risk

1. ***very low*** **risk: no CV risk factors**
2. ***low*** **risk: ≥ 3 CV risk factors**
3. ***moderate*** **risk: CVD**
4. ***high*** **risk: CKD**
5. ***very high*** **risk: CVD and CKD**

Palmer SC et al, *BMJ* 2021

SGLT-2i vs. Placebo

Table 1 | Summary of anticipated absolute differences comparing sodium-glucose cotransporter-2 inhibitor treatment with placebo treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Diabetic ketoacidosis	Genital infection	Body weight
Very low	3 fewer (4 fewer to 2 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	4 fewer (6 fewer to 1 fewer) ⊕⊕⊕	0 more (3 fewer to 4 more) ⊕⊕⊕	1 fewer (1 fewer to 0) ⊕⊕⊕	2 fewer (4 fewer to 1 fewer) ⊕⊕⊕			
Low	10 fewer (15 fewer to 6 fewer) ⊕⊕⊕⊕	7 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	7 fewer (12 fewer to 2 fewer) ⊕⊕⊕⊕	1 more (6 fewer to 8 more) ⊕⊕⊕⊕	3 fewer (4 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (11 fewer to 7 fewer) ⊕⊕⊕⊕			
Moderate	18 fewer (25 fewer to 10 fewer) ⊕⊕⊕⊕	12 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (21 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (11 fewer to 13 more) ⊕⊕⊕⊕	6 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	23 fewer (28 fewer to 17 fewer) ⊕⊕⊕⊕	0 (1 fewer to 2 more) ⊕⊕⊕	143 more (119 more to 170 more) ⊕⊕⊕⊕	1.92 kg lower (2.23 lower to 1.62 lower) over 6 months ⊕⊕
High	26 fewer (36 fewer to 14 fewer) ⊕⊕⊕⊕	16 fewer (25 fewer to 8 fewer) ⊕⊕⊕⊕	14 fewer (23 fewer to 3 fewer) ⊕⊕⊕⊕	2 more (12 fewer to 15 more) ⊕⊕⊕⊕	25 fewer (37 fewer to 9 fewer) ⊕⊕⊕⊕	29 fewer (36 fewer to 22 fewer) ⊕⊕⊕⊕			
Very high	40 fewer (56 fewer to 21 fewer) ⊕⊕⊕⊕	24 fewer (36 fewer to 12 fewer) ⊕⊕⊕⊕	21 fewer (34 fewer to 5 fewer) ⊕⊕⊕⊕	2 more (17 fewer to 21 more) ⊕⊕⊕⊕	38 fewer (58 fewer to 14 fewer) ⊕⊕⊕⊕	58 fewer (73 fewer to 44 fewer) ⊕⊕⊕⊕			

*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

Palmer SC et al, *BMJ* 2021

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ORIGINAL ARTICLE

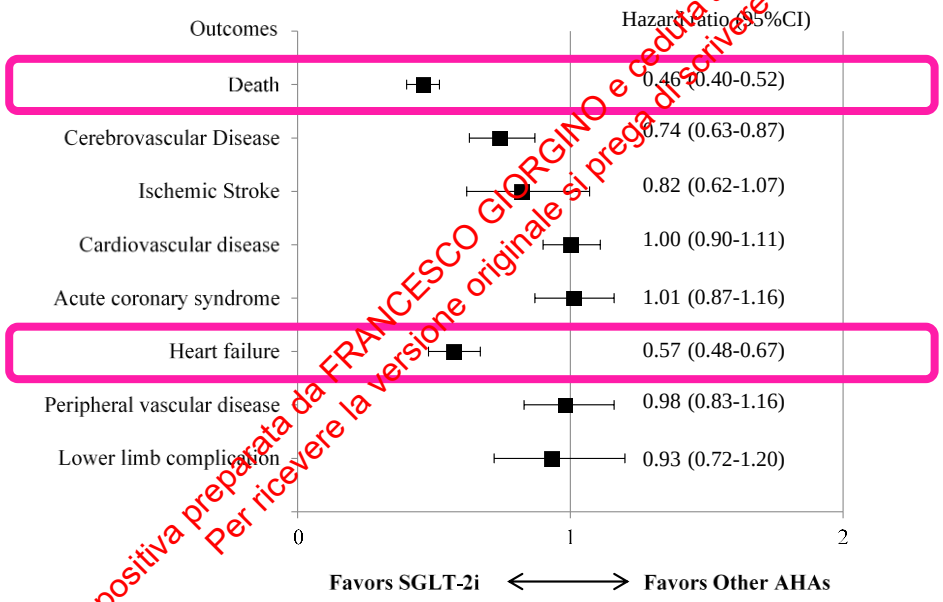
WILEY

Lower risk of death and cardiovascular events in patients with diabetes initiating glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors: A real-world study in two Italian cohorts

Marta Baviera PharmD[1] | Stefano Genovese MD[2] | Vito Lepore MD[3,4] | Pierluca Colacioppo MSc[1] | Fabio Robusto MD[3] | Mauro Tettamanti MSc[5] | Antonio D'Ettorre MSc[3] | Fausto Avanzini MD[1] | Ida Fortino MSc[6] | Antonio Nicolucci MD[3] | Maria C. Roncaglioni MSc[1] | Francesco Giorgino MD[7]

Pooled Risk of Death and Clinical Events in Matched Populations According to Treatment Status in the Lombardy and Apulia Regions, from 2010 to 2018

L SGLT-2i (N=11,683) Other AHAs (N=11,683)
A SGLT-2i (N=6,046) Other AHAs (N=6,046)



SGLT-2i

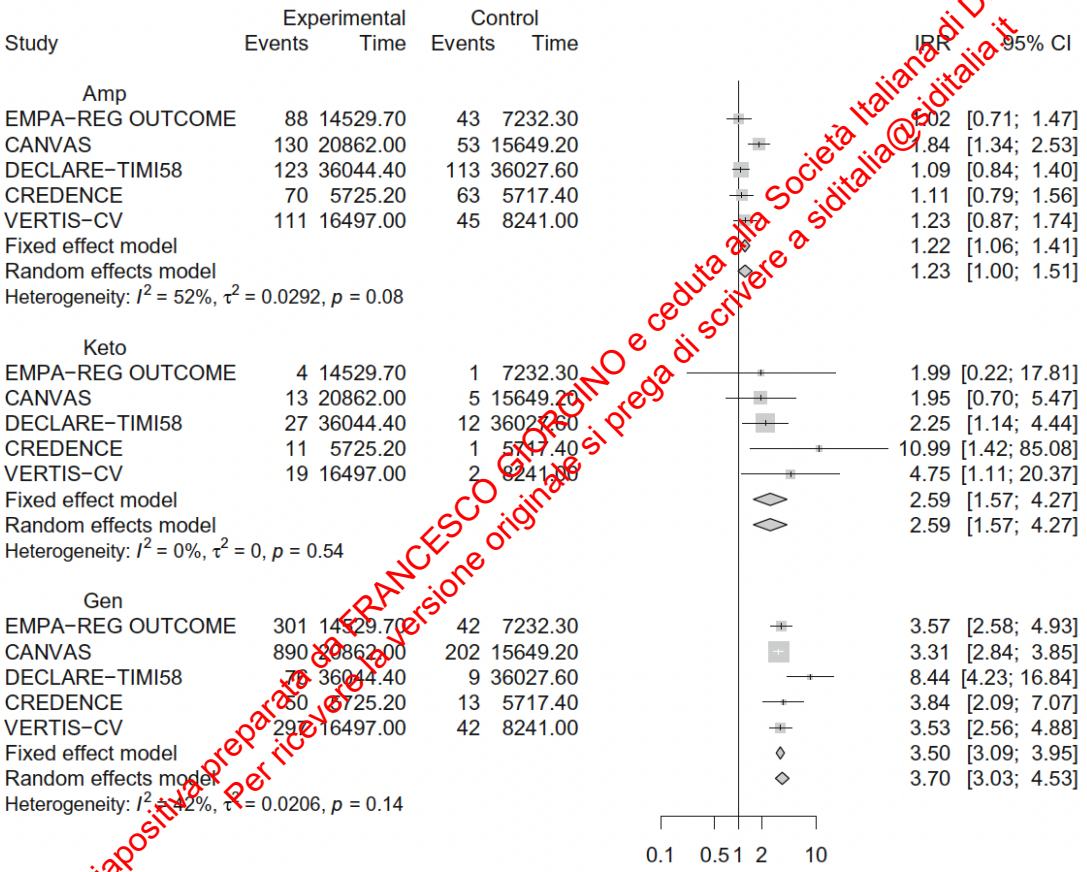
A, Apulia; L, Lombardy

Baviera M, et al., *Diabetes Obes Metab* 2021

SGLT2 inhibitors

Scheen AJ, *Exp Opinion Drug Safety* 2019

Risk and Benefits of SGLT-2i Users



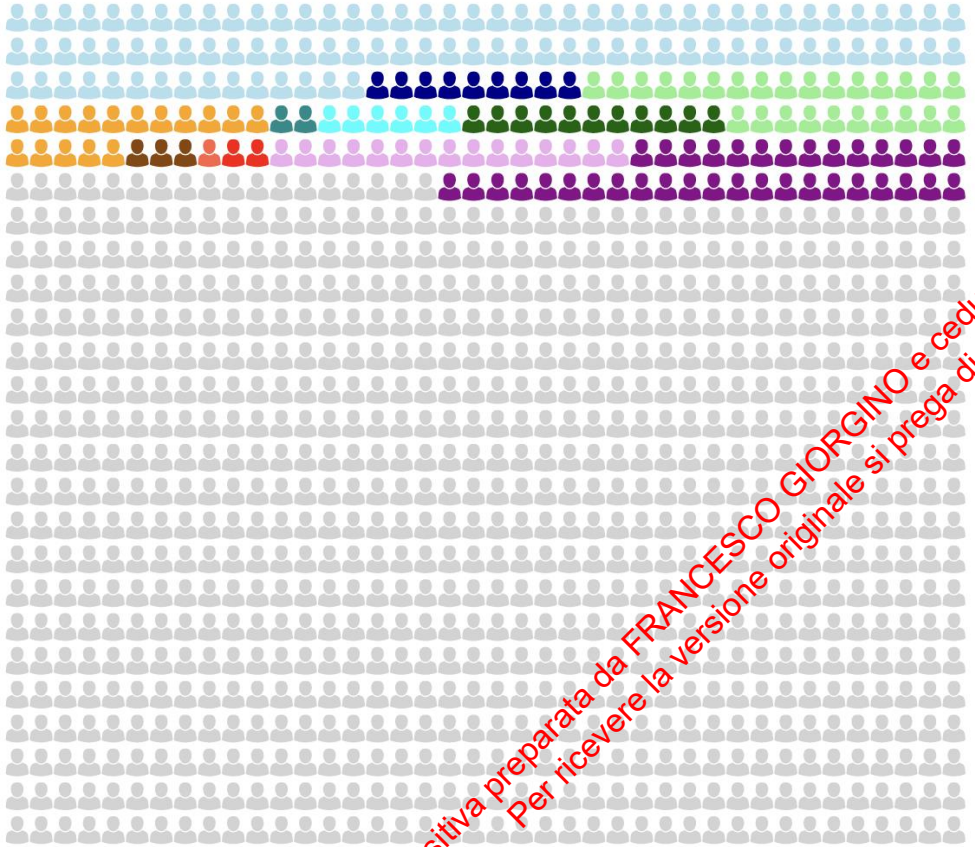
Amputations

DKA

Genital infections

Marilly E et al, *Diabetologia* 2022

Risk and Benefits of SGLT-2i Users



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 **1000** individuals treated over 3.5 years, SGLT2i are expected, on average, to:

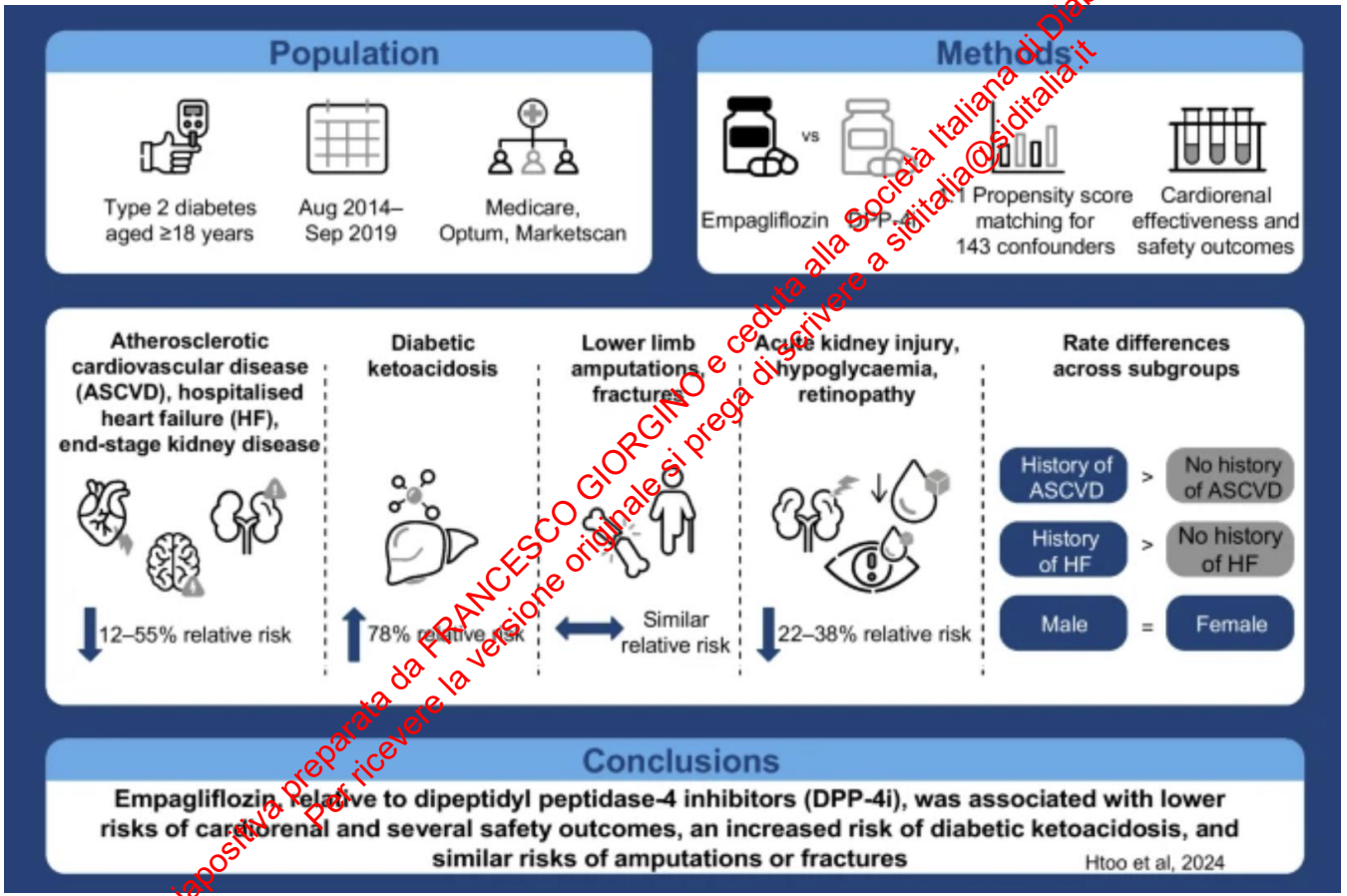
- **decrease the number of deaths from 70 to 61**
- **prevent 9 MACE, 11 HHF and 2 ESRD**
- **induce 2 DKA, 36 genital infections**

- **778** individuals are expected to avoid all investigated outcomes

Amp, aputations; Keto/DKA, diabetic ketoacidosis; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; ESRD, end stage renal disease

Marilly E et al, *Diabetologia* 2022

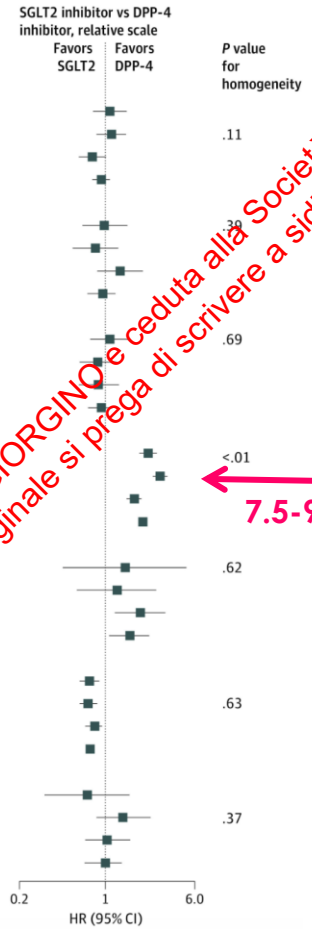
Real-World Effectiveness and Safety of Empagliflozin: the EMPRISE Study



Htoo PT et al, *Diabetologia* 2024

Safety of SGLT-2i According to Baseline HbA1c Levels

	SGLT2 inhibitor events, No. (IR/1000 PY)	DPP-4 inhibitor events, No. (IR/1000 PY)	RD/1000 PY (95% CI)	HR (95% CI)
Hypovolemia				
Subgroup HbA_{1c} <7.5% (n = 24052)	75 (9.03)	67 (8.21)	0.82 (-2.02 to 3.65)	1.10 (0.79 to 1.53)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	101 (9.04)	89 (8.07)	0.97 (-1.46 to 3.40)	1.13 (0.85 to 1.50)
Subgroup HbA_{1c} >9% (n = 30932)	81 (8.33)	101 (11.24)	-2.92 (-5.76 to 0.07)	0.76 (0.57 to 1.02)
Overall population (n = 87274)	257 (8.80)	258 (9.12)	-0.23 (-1.77 to 1.32)	0.93 (0.76 to 1.09)
Nonvertebral fractures				
Subgroup HbA_{1c} <7.5% (n = 24052)	38 (4.57)	38 (4.64)	-0.08 (-2.15 to 1.99)	0.98 (0.63 to 1.54)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	35 (3.12)	42 (3.8)	-0.68 (-2.23 to 0.87)	0.82 (0.52 to 1.28)
Subgroup HbA_{1c} >9% (n = 30932)	43 (4.41)	30 (3.33)	1.08 (-0.69 to 2.86)	1.35 (0.84 to 2.15)
Overall population (n = 87274)	116 (3.96)	110 (3.89)	0.04 (-0.97 to 1.06)	0.96 (0.69 to 1.23)
Falls				
Subgroup HbA_{1c} <7.5% (n = 24052)	49 (5.88)	44 (5.39)	0.49 (-1.80 to 2.79)	1.10 (0.73 to 1.65)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	49 (4.37)	56 (5.07)	-0.70 (-2.50 to 1.11)	0.86 (0.59 to 1.26)
Subgroup HbA_{1c} >9% (n = 30932)	44 (4.51)	47 (5.21)	-0.70 (-2.70 to 1.30)	0.88 (0.58 to 1.32)
Overall population (n = 87274)	142 (4.85)	147 (5.21)	-0.40 (-1.56 to 0.76)	0.92 (0.70 to 1.14)
Genital infections				
Subgroup HbA_{1c} <7.5% (n = 24052)	469 (58.22)	196 (24.27)	33.96 (27.69 to 40.23)	2.41 (2.04 to 2.85)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	738 (68.5)	243 (22.28)	46.22 (40.54 to 51.90)	3.10 (2.68 to 3.58)
Subgroup HbA_{1c} >9% (n = 30932)	640 (68.04)	341 (38.38)	29.66 (23.00 to 36.32)	1.82 (1.60 to 2.08)
Overall population (n = 87274)	1847 (65.41)	780 (27.99)	37.53 (33.98 to 41.09)	2.17 (1.98 to 2.36)
Diabetic ketoacidosis				
Subgroup HbA_{1c} <7.5% (n = 24052)	6 (0.72)	4 (0.49)	0.23 (-0.52 to 0.98)	1.49 (0.42 to 5.26)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	13 (1.16)	10 (0.9)	0.25 (-0.59 to 1.10)	1.37 (0.65 to 2.89)
Subgroup HbA_{1c} >9% (n = 30932)	47 (4.81)	22 (2.43)	2.38 (0.67 to 4.09)	2.06 (1.62 to 3.42)
Overall population (n = 87274)	66 (2.25)	36 (1.27)	0.45 (-0.09 to 0.99)	1.61 (1.06 to 2.43)
Acute kidney injury				
Subgroup HbA_{1c} <7.5% (n = 24052)	162 (19.55)	220 (27.22)	-7.68 (-12.3[illegible] to -2.99)	0.72 (0.59 to 0.89)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	211 (18.92)	295 (27.03)	-8.11 (-12.12 to -4.11)	0.70 (0.59 to 0.84)
Subgroup HbA_{1c} >9% (n = 30932)	225 (23.25)	268 (30.05)	-6.8[illegible] (-11.51 to -2.09)	0.79 (0.66 to 0.94)
Overall population (n = 87274)	598 (20.54)	783 (28.05)	-7.50 (-10.[illegible] to -5.04)	0.73 (0.66 to 0.81)
Lower-limb amputation				
Subgroup HbA_{1c} <7.5% (n = 24052)	9 (1.08)	13 (1.59)	-0.[illegible] (-1.62 to 0.60)	0.69 (0.29 to 1.61)
Subgroup HbA_{1c} 7.5%-9% (n = 32290)	32 (2.85)	22 (1.[illegible])	0.86 (-0.43 to 2.15)	1.44 (0.84 to 2.48)
Subgroup HbA_{1c} >9% (n = 30932)	37 (3.78)	36 (3.62)	0.16 (-1.57 to 1.90)	1.05 (0.66 to 1.68)
Overall population (n = 87274)	78 (2.56)	68 (2.46)	0.09 (-0.67 to 0.85)	1.02 (0.66 to 1.38)



Hypovolemia

Non-vertebral fractures

Falls

Genital infections

7.5-9.0%

DKA

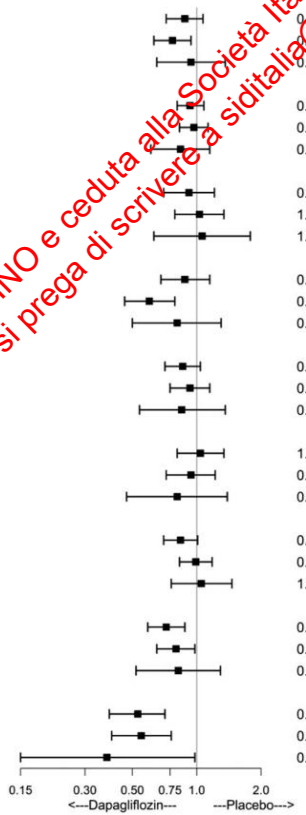
Acute kidney injury

Lower-limb amputations

D'Andrea E et al, *JAMA Intern Med*, 2023

Cardiovascular and Renal Efficacy of SGLT-2i Was Consistent Regardless of Age: Analysis from the DECLARE-TIMI 58

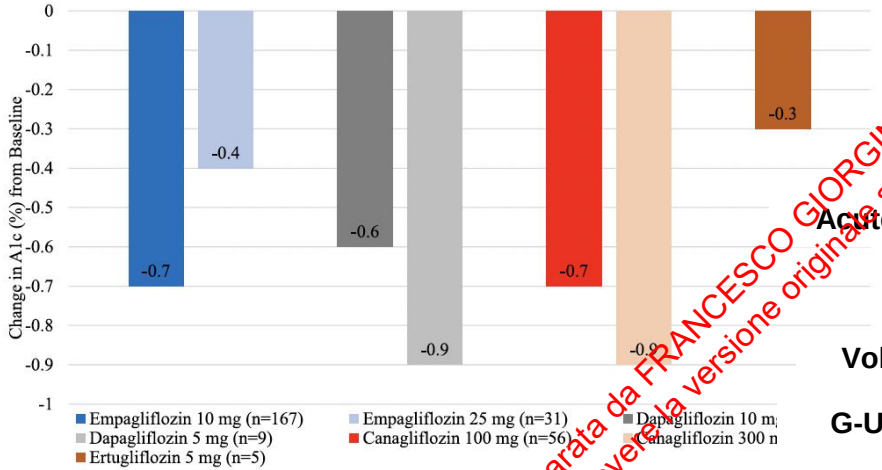
	Dapagliflozin		Placebo				
	n/N (%)	Rates per 1000 person- years	n/N (%)	Rates per 1000 person- years	Hazard ratio (95% CI)	p value	p interaction
CVD / HHF							
< 65 years	189/4631 (4.1%)	10.2	211/4622 (4.6%)	11.6	0.83 (0.72, 1.07)	0.1902	0.5277
65-< 75 years	176/3413 (5.2%)	12.8	225/3398 (6.6%)	16.7	0.77 (0.63, 0.94)	0.0099	
≥ 75 years	52/538 (9.7%)	25.2	60/558 (10.8%)	28.2	0.94 (0.65, 1.36)	0.7330	
MACE							
< 65 years	366/4631 (7.9%)	20.3	385/4622 (8.3%)	21.5	0.93 (0.81, 1.08)	0.3478	0.7352
65-< 75 years	323/3413 (9.5%)	24.2	332/3398 (9.8%)	25.2	0.97 (0.83, 1.13)	0.6509	
≥ 75 years	67/538 (12.5%)	33.2	86/558 (15.4%)	41.4	0.84 (0.61, 1.15)	0.2722	
CVD							
< 65 years	102/4631 (2.2%)	5.4	109/4622 (2.4%)	5.8	0.92 (0.70, 1.21)	0.5460	0.7953
65-< 75 years	115/3413 (3.4%)	8.2	111/3398 (3.3%)	8.0	1.03 (0.79, 1.34)	0.8238	
≥ 75 years	28/538 (5.2%)	13.1	29/558 (5.2%)	12.9	1.06 (0.63, 1.78)	0.8315	
HHF							
< 65 years	102/4631 (2.2%)	5.5	113/4622 (2.4%)	6.2	0.88 (0.68, 1.15)	0.3624	0.1402
65-< 75 years	81/3413 (2.4%)	5.9	133/3398 (3.9%)	9.9	0.60 (0.46, 0.79)	0.0003	
≥ 75 years	29/538 (5.4%)	14.1	40/558 (7.2%)	19.4	0.81 (0.50, 1.30)	0.3768	
Myocardial infarction							
< 65 years	199/4631 (4.3%)	11.0	227/4622 (4.9%)	12.6	0.86 (0.71, 1.04)	0.1205	0.8621
65-< 75 years	162/3413 (4.7%)	12.0	173/3398 (5.1%)	13.1	0.93 (0.75, 1.15)	0.5139	
≥ 75 years	32/538 (5.9%)	15.7	41/558 (7.3%)	19.3	0.85 (0.54, 1.36)	0.5020	
Any stroke							
< 65 years	126/4631 (2.7%)	6.9	119/4622 (2.6%)	6.5	1.04 (0.81, 1.34)	0.7483	0.6388
65-< 75 years	106/3413 (3.1%)	7.8	115/3398 (3.4%)	8.4	0.94 (0.72, 1.22)	0.6223	
≥ 75 years	23/538 (4.3%)	11.2	31/558 (5.6%)	14.6	0.81 (0.47, 1.39)	0.4475	
Death from any cause							
< 65 years	212/4631 (4.6%)	11.3	245/4622 (5.4%)	13.2	0.84 (0.70, 1.01)	0.0706	0.3537
65-< 75 years	246/3413 (7.2%)	17.5	248/3398 (7.3%)	17.9	0.99 (0.83, 1.18)	0.8692	
≥ 75 years	71/538 (13.2%)	33.3	74/558 (13.3%)	33.0	1.05 (0.76, 1.46)	0.7483	
Cardiorenal composite outcome							
< 65 years	167/4631 (3.6%)	9.0	226/4622 (4.9%)	12.3	0.72 (0.59, 0.88)	0.0015	0.7299
65-< 75 years	169/3413 (4.9%)	12.3	210/3398 (6.2%)	15.5	0.80 (0.65, 0.98)	0.0289	
≥ 75 years	34/538 (6.2%)	16.2	44/558 (7.9%)	20.3	0.82 (0.52, 1.29)	0.3928	
Renal-specific composite outcome							
< 65 years	65/4631 (1.4%)	3.5	121/4622 (2.6%)	6.6	0.53 (0.39, 0.71)	<.0001	0.8293
65-< 75 years	56/3413 (1.6%)	4.1	101/3398 (3%)	7.5	0.55 (0.40, 0.76)	0.0003	
≥ 75 years	6/538 (1.1%)	2.9	16/558 (2.9%)	7.4	0.38 (0.15, 0.98)	0.0452	



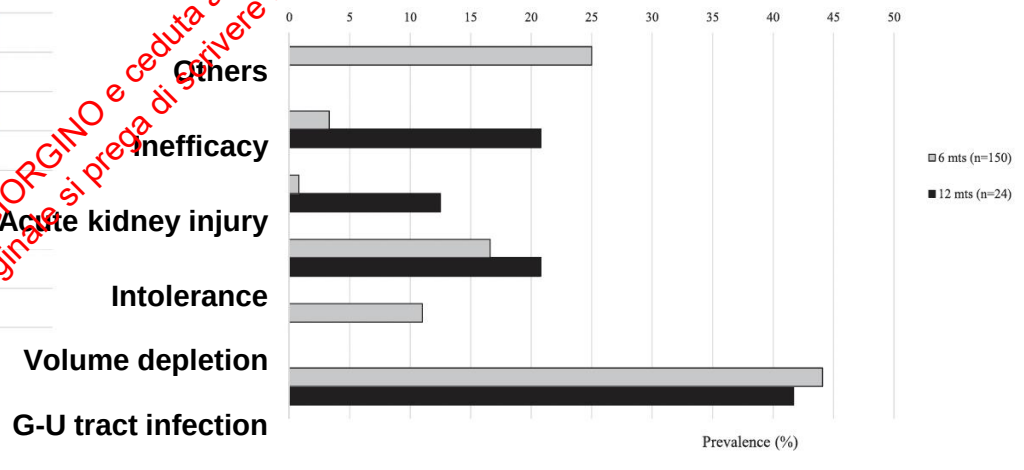
A, *Diabetes Care* 2019

SGLT-2i are Effective and Safe in Elderly Patients: The SOLD Study

- 6 outpatient clinics, 739 patients >70 years
- 17% >80 years
- Data were collected at baseline, at 6 and 12 months of follow-up



Change in HbA1c vs baseline



Causes of treatment discontinuation

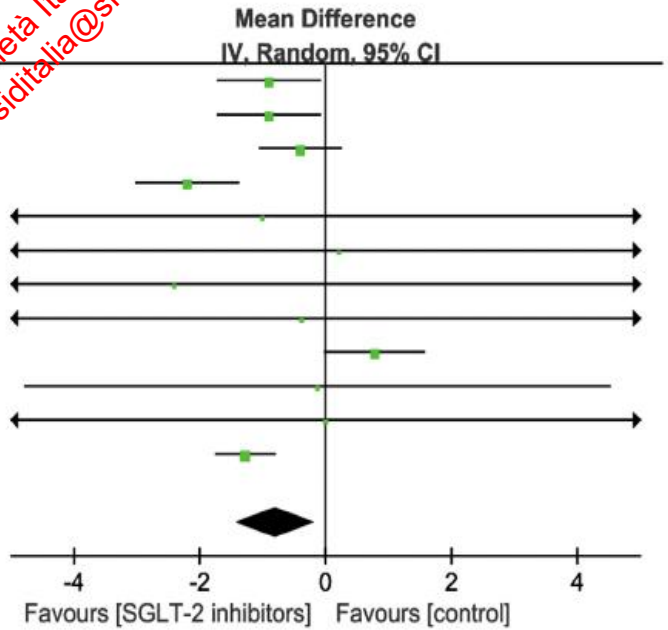
Lunati ME et al, *Pharmacol Res* 2022

SGLT-2i and Sarcopenia in Type 2 Diabetes

- 12 studies, 1,101 participants
- DXA to evaluate lean mass

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Blonde (2016)	-1.2	2.53	71	-0.3	2.58	74	14.8%	-0.90 [-1.73, -0.07]
Bode (2013)	-1.2	2.32	60	-0.3	2.12	50	14.9%	-0.90 [-1.73, -0.07]
Bolinder (2014)	-1.3	2.07	69	-0.9	1.93	71	16.4%	-0.40 [-1.06, 0.26]
Cefalu (2013)	-1.1	2.49	69	1.1	2.47	68	14.9%	-2.20 [-3.03, -1.37]
Han (2020)	-0.7	16.64	29	0.3	9.95	15	0.6%	-1.00 [-8.88, 6.88]
Horibe (2022)	-0.17	12.95	26	-0.38	10.04	24	0.9%	0.21 [-6.19, 6.61]
Hoshika (2021)	-0.37	13.46	22	2.04	13.41	29	0.7%	-2.41 [-9.86, 5.04]
Inoue (2019)	-0.61	10.65	22	-0.23	10.34	24	1.0%	-0.38 [-6.46, 5.70]
McCrimmon (2020)	-1.48	2.66	90	-2.26	2.81	88	15.1%	0.78 [-0.02, 1.58]
Nakaguchi (2020)	-0.64	10.02	31	-0.51	8.51	30	1.0%	-0.13 [-4.79, 4.53]
Sugiyama (2017)	-0.5	9.26	28	-0.5	11.12	22	1.1%	0.00 [-5.78, 5.78]
Wolf (2021)	-0.35	1.11	44	0.93	1.21	45	17.9%	-1.28 [-1.76, -0.80]
Total (95% CI)			**561**			**540**	**100.0%**	**-0.80 [-1.43, -0.16]**

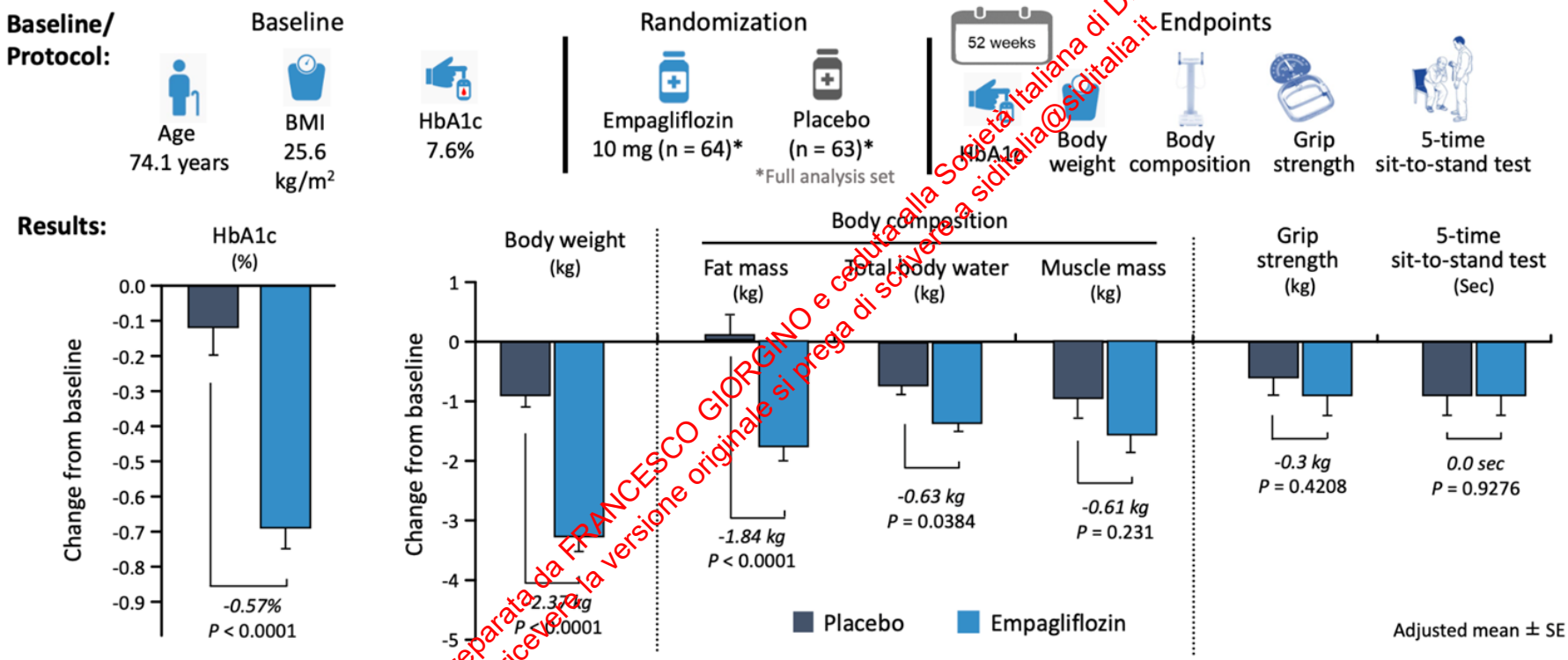
Heterogeneity: Tau² = 0.52; Chi² = 31.22, df = 11 (P = 0.001); I² = 65%
Test for overall effect: Z = 2.47 (P = 0.01)



the negative influence on muscle mass paralleled the reduction in FM and BW, and the consequent increased risk of sarcopenia warrants high attention, especially in patients already predisposed to physical frailty

Zhang S et al, *Front Endocrinol* 2023

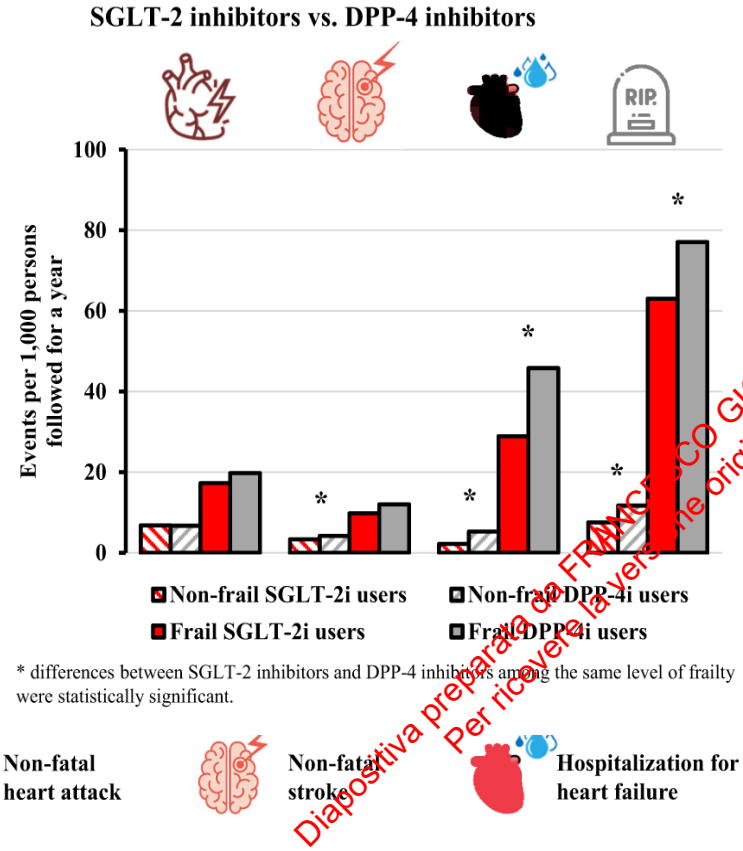
SGLT-2i and Sarcopenia in Elderly Patients (EMPA-ELDERLY)



- **Empagliflozin significantly improved HbA1c and was well tolerated in elderly patients with type 2 diabetes.**
- **No new concerns including sarcopenia or muscle weakness were observed for empagliflozin treatment.**

Yabe D et al, *Diabetes Obes Metab* 2023

CV Safety of SGLT-2i in Elderly Patients

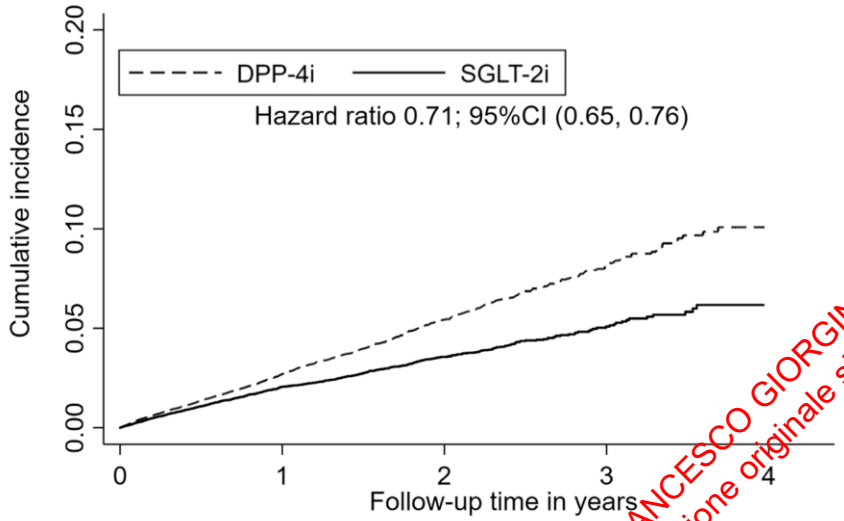


- Patients aged > 65 years initiating DPP-4i or SGLT-2i
- 1:1 propensity score matched cohorts
- Stratification according to frailty using a validated claims-based frailty index (0-1)

- SGLT-2i safely improved cardiovascular outcomes, with the **largest benefits among frail people**

Kutz A et al, *Diabetes Care* 2023

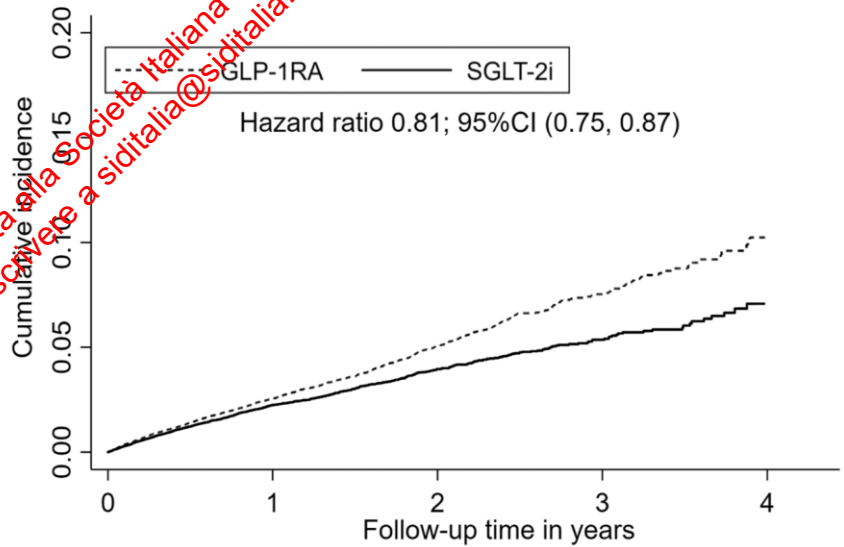
SGLT-2i Initiation is Associated with a Lower Risk of AKI Compared to DPP4i and GLP-1RA in Elderly Patients



Number at risk

DPP-4i	68130	18632	6427	1557	161
SGLT-2i	68130	17265	6181	1589	161

Figure 1A. Kaplan-Meier plots for cumulative incidence of AKI hospitalization in 1:1 propensity score matched SGLT-2i versus DPP-4i cohort.
Abbreviations: AKI, acute kidney injury; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; DPP-4i, dipeptidyl peptidase 4 inhibitors; CI, confidence interval.



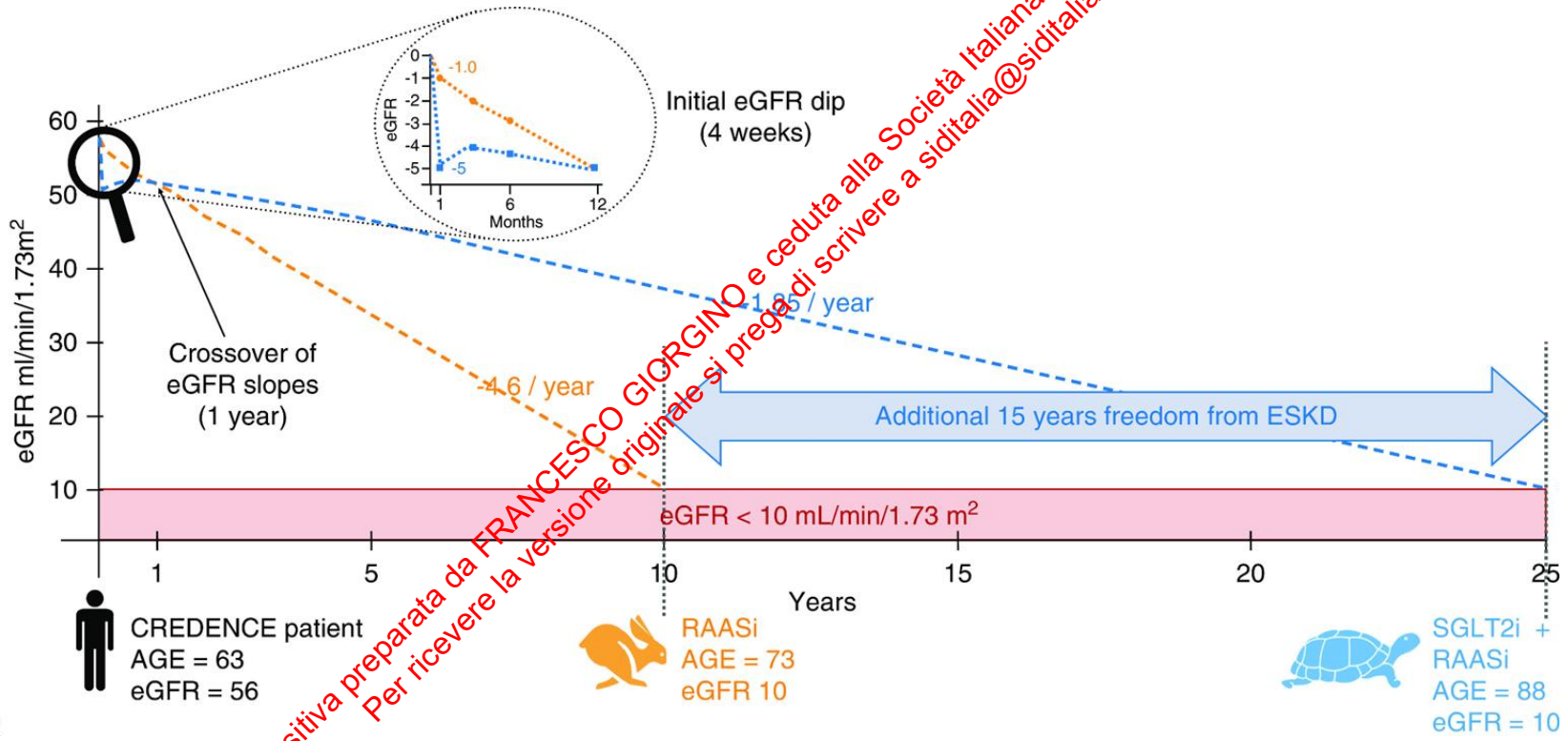
Number at risk

GLP-1RA	71477	16539	5463	1468	172
SGLT-2i	71477	18581	6651	2035	276

Figure 1B. Kaplan-Meier plots for cumulative incidence of AKI hospitalization in 1:1 propensity score matched SGLT-2i versus GLP-1RA cohort.
Abbreviations: AKI, acute kidney injury; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonist; CI, confidence interval.

Zhuo M et al, *Am J Kidney Dis* 2022

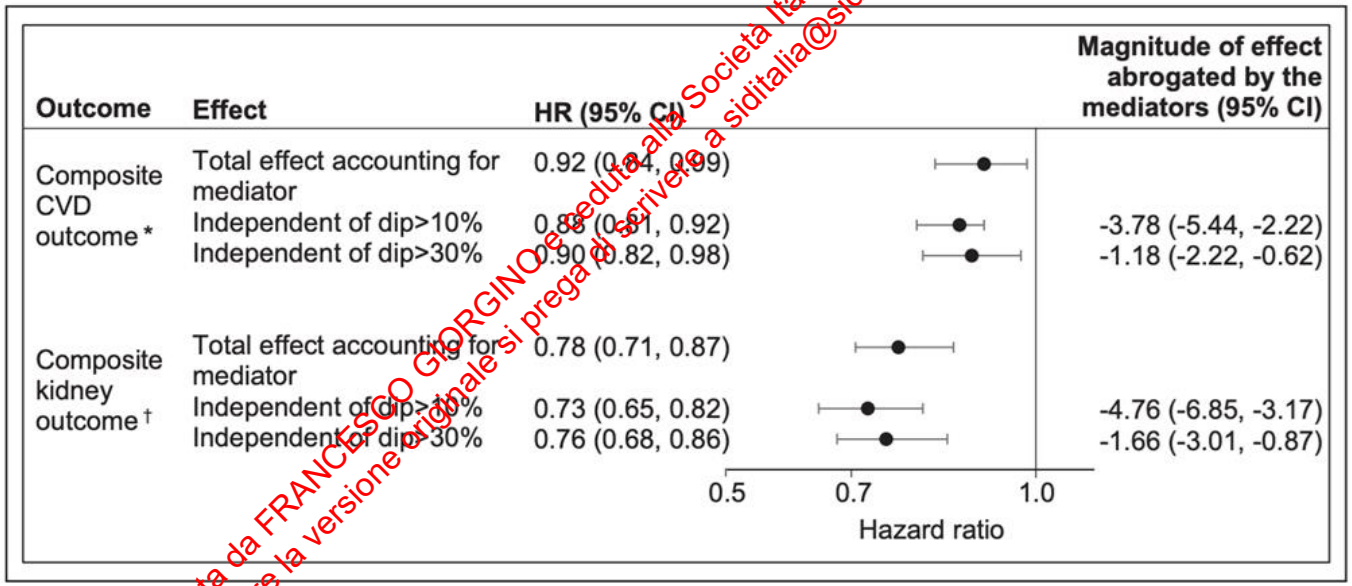
eGFR Decline after SGLT2 Inhibitor Initiation



Alejandro Y et al, *Kidney360* 2021

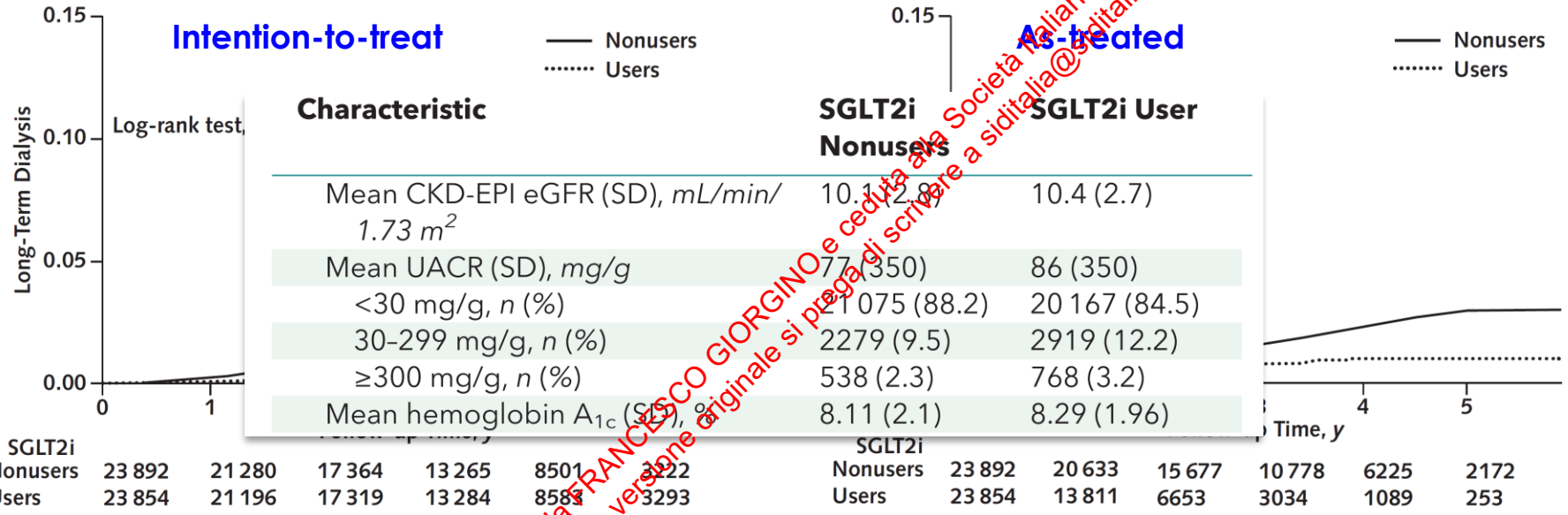
The *eGFR Dip* Does Not Influence the Effectiveness of SGLT-2i on Cardiovascular and Kidney Outcomes

SGLT2i users
(n= 36, 638) VS other antihyperglycemics
(n= 209,025)



Heerspink et al, *Clin J Am Soc Nephrol* 2021

Cumulative Incidence of Long-term Dialysis in SGLT-2i Users and Nonusers in Patients with T2D and stage 5 CKD



Characteristic	SGLT2i Nonusers	SGLT2i User
Mean CKD-EPI eGFR (SD), *mL/min/1.73 m²*	10.1 (2.8)	10.4 (2.7)
Mean UACR (SD), *mg/g*	77 (350)	86 (350)
<30 mg/g, *n* (%)	21 075 (88.2)	20 167 (84.5)
30–299 mg/g, *n* (%)	2279 (9.5)	2919 (12.2)
≥300 mg/g, *n* (%)	538 (2.3)	768 (3.2)
Mean hemoglobin A_{1c} (SD), %	8.11 (2.1)	8.29 (1.96)

CKD = chronic kidney disease; SGLT2i = sodium-glucose cotransporter-2 inhibitor; T2D = type 2 diabetes.

CKD = chronic kidney disease; SGLT2i = sodium-glucose cotransporter-2 inhibitor; T2D = type 2 diabetes.

Yen F-S et al, *Ann Intern Med* 2024

SGLT-2 Inhibitor Use in CKD

	Question	Summary of answer
Initiation	1. When should a patient taking a RAS inhibitor for the treatment of CKD initiate an SGLT2 inhibitor?	• SGLT2 inhibitors should be initiated alongside a RAS inhibitor in any patient for whom they are indicated • SGLT2 inhibitors should be initiated regardless of whether a maximum tolerated dose of RAS inhibitor has been achieved
	2. How concerned should I be about an initial eGFR decline when initiating SGLT2 inhibitor therapy?	• An initial eGFR decline is to be expected, is transient, and is not associated with any change in the beneficial effects of SGLT2 inhibitors • SGLT2 inhibitors should not be withdrawn because of an initial eGFR decline alone
	3. Should patients at lower risk of progression still initiate SGLT2 inhibitor therapy?	• The benefits of SGLT2 inhibitors extend beyond renoprotection • Initiation of an SGLT2 inhibitor should be considered regardless of risk of CKD progression
	4. Should SGLT2 inhibitors be initiated in elderly patients?	• Elderly patients are still likely to substantially benefit from SGLT2 inhibitors • SGLT2 inhibitors have shown strongly favorable risk–benefit profiles across the spectrum of frailty
Prescriber	5. Who should prescribe an SGLT2 inhibitor?	• The first person in the multidisciplinary team to identify a patient who will benefit from SGLT2 inhibitor treatment should initiate therapy and communicate with other team members
Safety	6. What is the safety profile of SGLT2 inhibitors?	• SGLT2 inhibitors are well tolerated and associated with minimal adverse effects • Counsel patients on the elevated risk of T2DM-associated DKA and genital mycotic infections associated with SGLT2 inhibitors
	7. When should SGLT2 inhibitors be stopped or withheld?	• Withhold SGLT2 inhibitors during periods of prolonged fasting, surgery, or critical illness and reinitiate therapy promptly when a patient has recovered
	8. Which patients should not be prescribed an SGLT2 inhibitor?	• Carefully evaluate risks and benefits when considering prescribing SGLT2 inhibitors to patients with type 1 diabetes, polycystic kidney disease, a history of DKA or severe urinary tract infections, UACR >5000 mg/g, or to those on intensive immunosuppressive therapies

Madero M et al, Kidney *Med* 2024

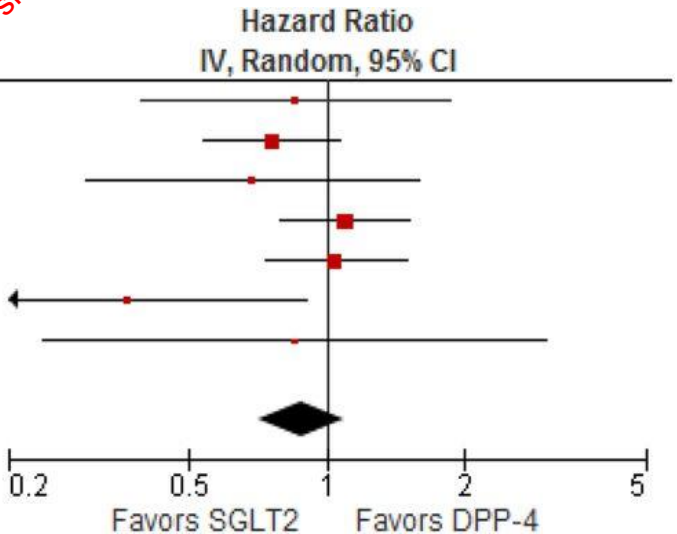
Risk of Below-knee Amputations: SGLT2i vs DPP4i

- 207,817 SGLT2i vs 207,817 DPP4i initiators
- UK e Canada claim databases
- Mean follow-up: 11 months

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Alberta	-0.1592	0.4002	6.8%	0.85 [0.39, 1.87]
British Columbia	-0.2765	0.1743	26.4%	0.76 [0.54, 1.07]
Manitoba	-0.3747	0.4314	6.0%	0.69 [0.30, 1.60]
Ontario	0.0962	0.1668	28.0%	1.10 [0.79, 1.53]
Quebec	0.0446	0.1829	24.8%	1.05 [0.73, 1.50]
Saskatchewan	-1.0106	0.4636	5.2%	0.36 [0.15, 0.90]
CPRD	-0.1621	0.6505	2.7%	0.85 [0.24, 3.04]
Total (95% CI)			**100.0%**	**0.88 [0.71, 1.09]**

Heterogeneity: Tau² = 0.01; Chi² = 7.32, df = 6 (P = 0.29); I² = 18%

Test for overall effect: Z = 1.15 (P = 0.25)



HR (95% CI) of below-knee amputation associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use among patients with type 2 diabetes. Nova Scotia was not included in this analysis because where were fewer than five events in one of the two exposure groups. IV, inverse variance.

Yu OHY et al, *Diabetes Care* 2020

Risk of Lower Limb Amputations: SGLT2i vs SU

- 13,736 SGLT2i vs 12,851 DPP4i initiators
- Data from the National Health Danish Service (2013-2018)
- Median follow-up: 1.6 years

Table 3 Risk of LLA in current SGLT2-I use compared to current SU use, stratified by concomitant antihypertensive use, and history of peripheral arterial disease

	Number of LLAs (N = 564)	IR (/1000 PY	Age/sex adjusted HR (95%CI)	Fully adjusted HR (95%CI)	p-value Wald test
Current SU use	54	2.14	Reference		
Current SGLT2-I use	36	2.30	1.24 (0.81–1.91)	1.10 (0.71–1.70)[a]	
By concomitant antihypertensive use in the previous 3 months					
Diuretics					
Yes	13	2.41	1.32 (0.66–2.25)	0.98 (0.53–1.81)[b]	0.60
No	23	2.24	1.25 (0.76–2.06)	1.17 (0.71–1.94)[b]	
Drugs acting on RAAS					
Yes	24	2.84	1.44 (0.88–2.35)	1.23 (0.75–2.02)[c]	0.35
No	12	1.67	0.97 (0.52–1.83)	0.88 (0.47–1.67)[c]	
By history of PAD					
Yes	11	17.57	7.21 (3.75–13.86)	2.24 (1.15–4.36)[d]	0.01
No	25	1.67	0.91 (0.56–1.47)	0.92 (0.56–1.49)[d]	

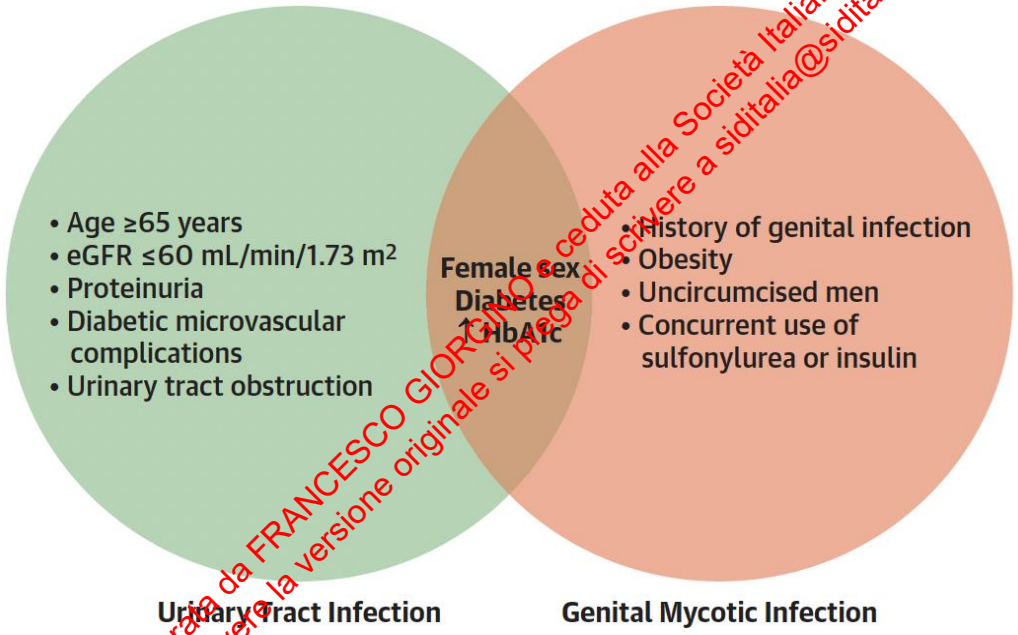
LLA lower limb amputation, *IR* incidence rate, *PY* person-years, *HR* hazard ratio, *CI* confidence interval, *NIGLD* non-insulin glucose lowering drug, *SU* sulfonylurea, *DPP4-I* dipeptidyl peptidase-4 inhibitor, *SGLT2-I* sodium-glucose co-transporter-2 inhibitor, *RAAS* renin–angiotensin–aldosterone system, *PAD* peripheral arterial disease

SU, sulphonylurea

Werkman NCC et al, *Cardiovasc Diabetol* 2023

Risk Factors for SGLT-2i Associated Genitourinary Infections

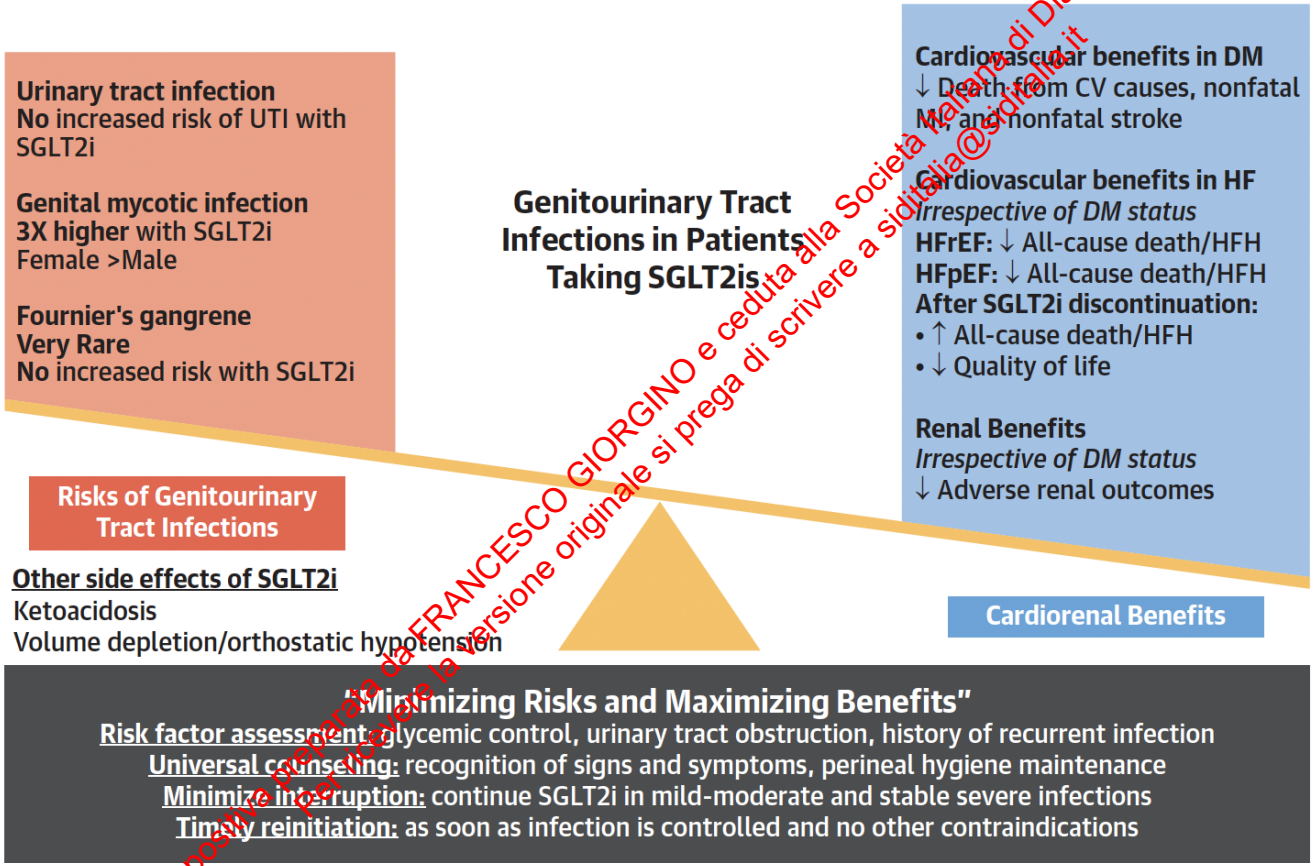
FIGURE 2 Risk Factors for SGLT2 Inhibitor-Associated GU Infections



Recognition of risk factors for sodium-glucose cotransporter 2 (SGLT2) inhibitor-associated genitourinary tract (GU) infections is essential in the prevention of GU infections before and during SGLT2 inhibitor therapy. Modifiable risk factors such as glycemic control should be corrected or optimized. eGFR = estimated glomerular filtration rate.

Kittipibul V et al, *J Am Coll Cardiol* 2024

Genitourinary Infections in SGLT-2i Users



Kittipibul V et al, *J Am Coll Cardiol* 2024

SGLT-2i Therapy

True barriers

Genital infections

DKA / Type 1 diabetes

False barriers

Elderly / Frailty / Sarcopenia (*)

Volume depletion (*)

Urinary infections

↓ GFR / Acute kidney injury

Lower-limb amputations (*)

Non-vertebral fractures

(*) caution should be observed

The long-term effects of dapagliflozin in chronic kidney disease: a time-to-event analysis

To extrapolate the outcome-based clinical benefits of treatment with dapagliflozin in patients with chronic kidney disease

Methods

Combine patient-level data from clinical trials of dapagliflozin treatment

Higher-risk	Lower-risk
DAPA-CKD trial	DECLARE-TIMI 58 trial
Whole trial population	CKD subpopulation
CKD 2–4	Early CKD
Elevated albuminuria	Low albuminuria

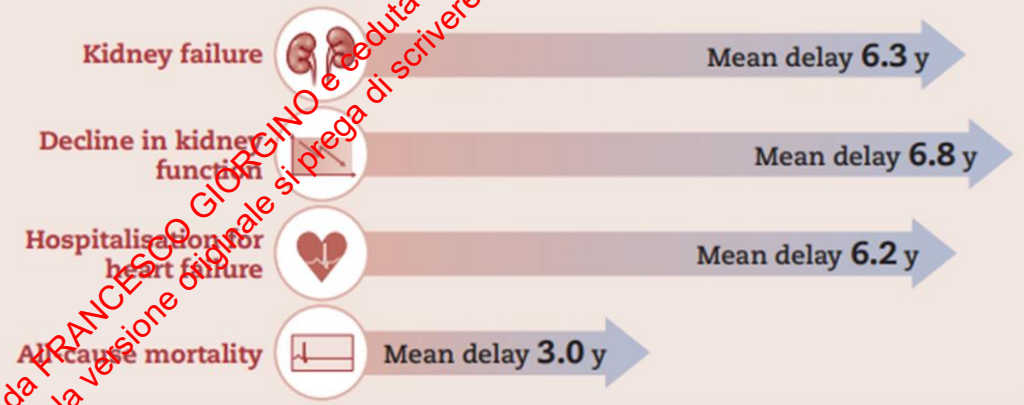
Pooled population with CKD

↓

Calculate mean time to event for clinical endpoints extrapolated across patient lifetime

Results

Treatment of a pooled (mixed higher and lower CKD risk) population with dapagliflozin over a lifetime time horizon was estimated to delay the onset of adverse clinical events



McEwan, P. *et al.*
NDT (2024)
@NDTSocial

Treatment with dapagliflozin over a lifetime time horizon may considerably delay the time to major adverse cardio-renal outcomes and improve life expectancy

McEwan P et al, *NDT* 2024