

PROGETTO

GALILEI

DapaGliflozin: whAt eLse In the worLd of EVIdences?

GLIFLOZINE: LA METFORMINA
DEL III MILLENNIO



BOLOGNA

STAR HOTELS EXCELSIOR

18 giugno 2024

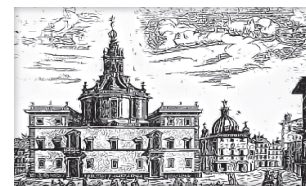
SGLT2i: subito insieme alla metformina,
subito dopo la metformina, e comunque
prima di ogni altro farmaco?

Raffaella Buzzetti

Dipartimento di Medicina Sperimentale



SAPIENZA
UNIVERSITÀ DI ROMA



UMBERTO I
POLICLINICO DI ROMA



Diapositiva preparata da RAFFAELLA BUZZETTI e ceduta alla Società Italiana di Diabetologia.
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Disclosures

La Prof.ssa Raffaella Buzzetti dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Novo Nordisk
- Eli Lilly
- Abbott
- Atrazeneca
- Vertex
- Guidotti

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.).

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- 1. Guidelines indications
- 1. Primary prevention data
- 1. Before metformin/before other drugs?

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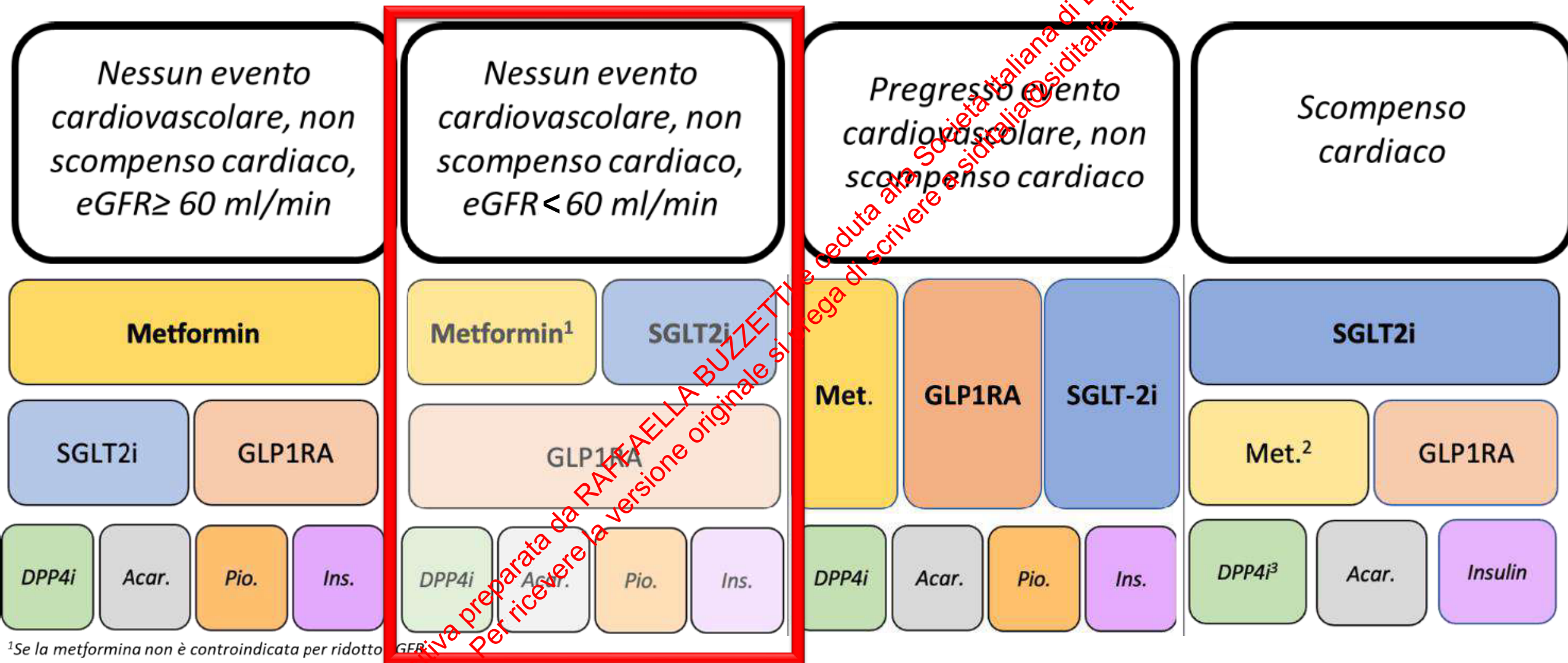
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linee guida SID/AMD 2023



¹Se la metformina non è controindicata per ridotto eGFR.

²Se la metformina non è controindicata per ridotta funzione cardiaca.

³Eccetto 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 sulfanilurre e alinidi

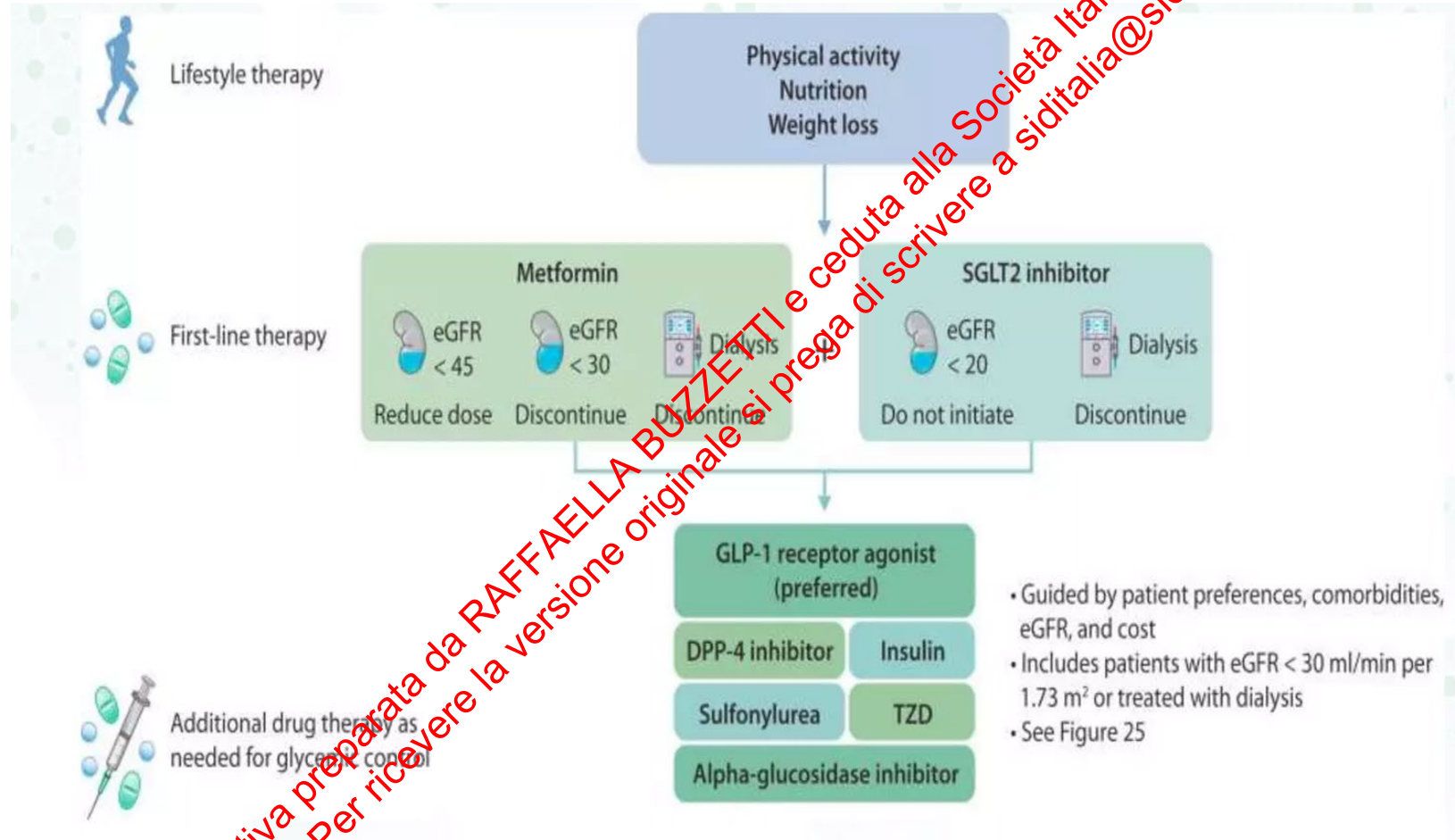
Linee Guida KDIGO

Diabetes with CKD



Linee Guida KDIGO

Treatment algorithm for selecting glucose-lowering drugs for patients with T2D and CKD



Renal outcomes with SGLT2i

ORIGINAL ARTICLE

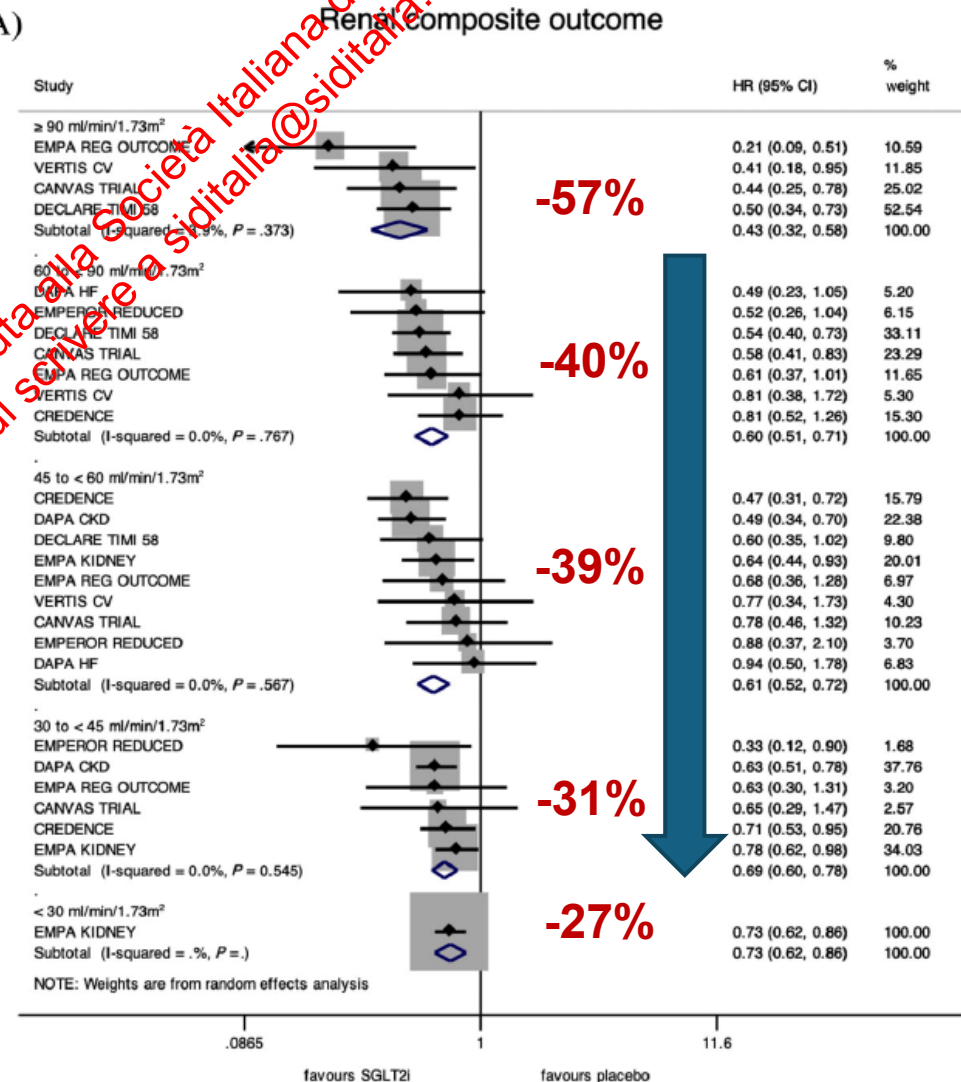
Impact of baseline kidney function on the effects of sodium-glucose co-transporter-2 inhibitors on kidney and heart failure outcomes: A systematic review and meta-analysis of randomized controlled trials

Ernesto Maddaloni MD¹ | Ilaria Cavallari MD² | Ylenia La Porta MD² |
Alessandro Appetecchia MD² | Luca D'Onofrio MD¹ | Francesco Grigioni MD²
Raffaella Buzzetti MD¹ | Rury R. Holman MD³

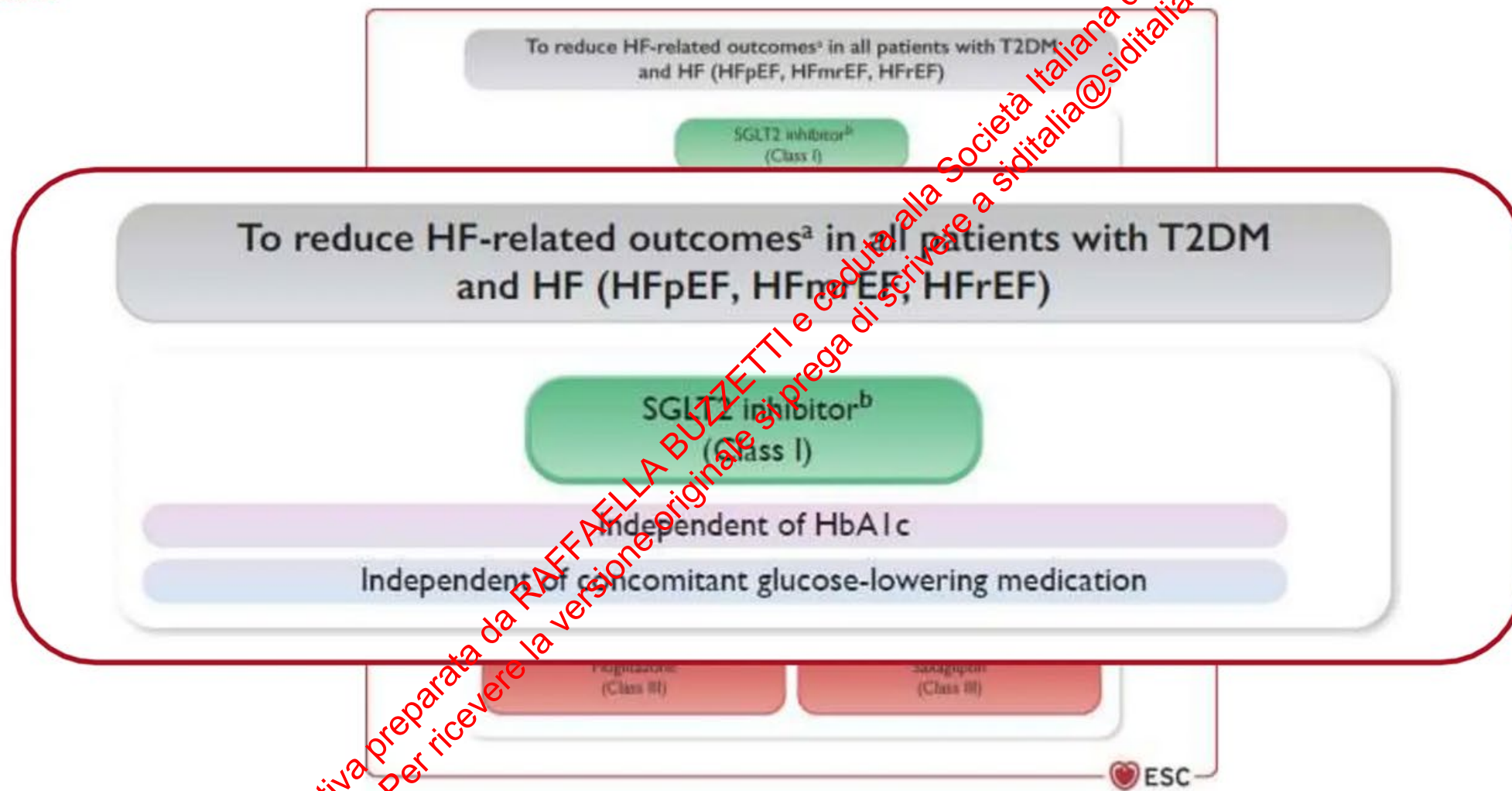
- ✓ SGLT2i reduces the risk of renal outcomes across all eGFR categories
- ✓ Higher benefit if SGLT2i is started with higher eGFR

W

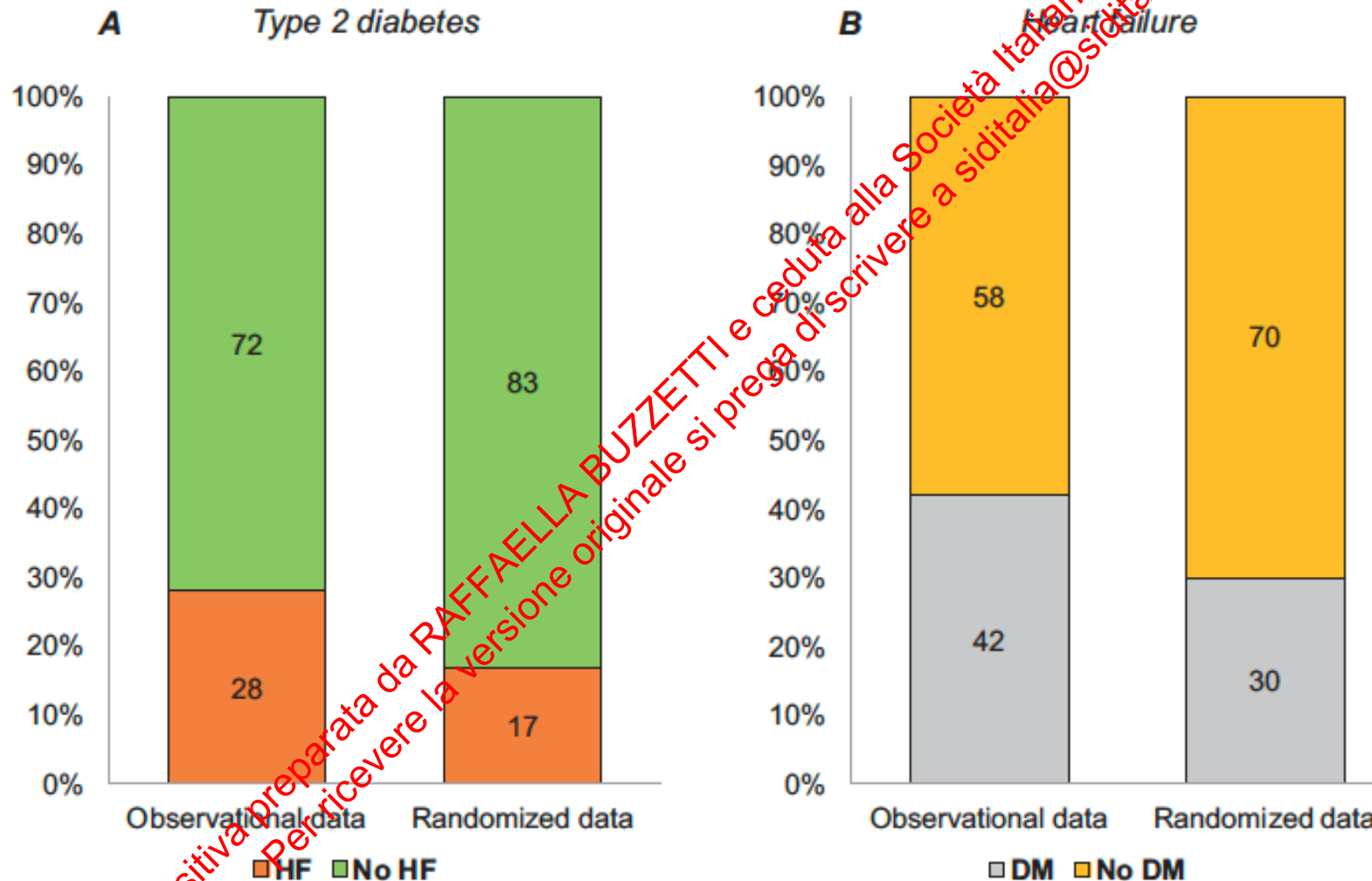
(A)



Glucose-lowering treatment of patients with heart failure and type 2 diabetes



Heart failure in diabetes



Revised recommendations (2)

2019	Class	Level	2023	Class	Level
ASCVD risk reduction by glucose-lowering medications in diabetes					
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce CV events.	I	A	SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
			In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk $\geq 10\%$, treatment with a SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C

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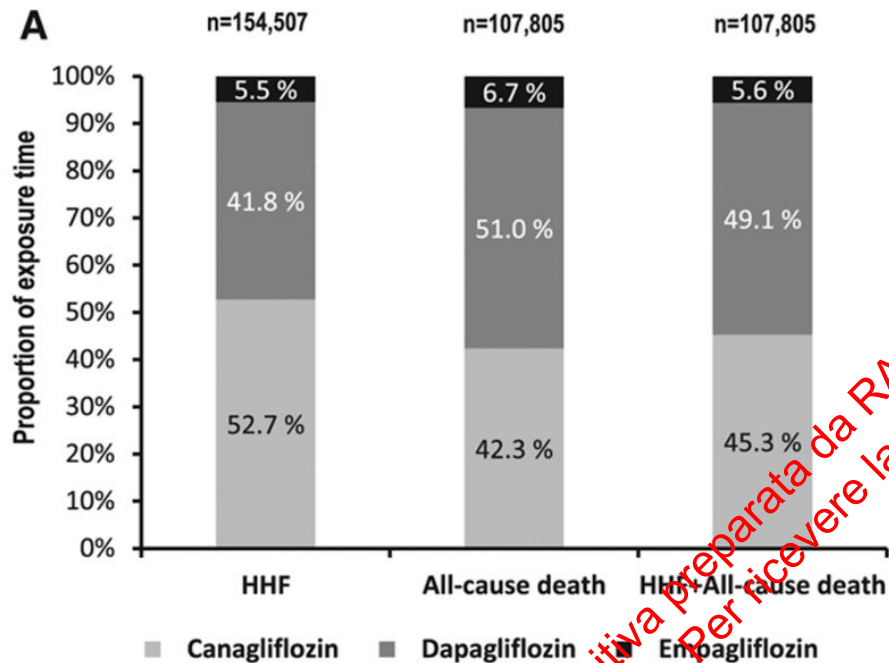
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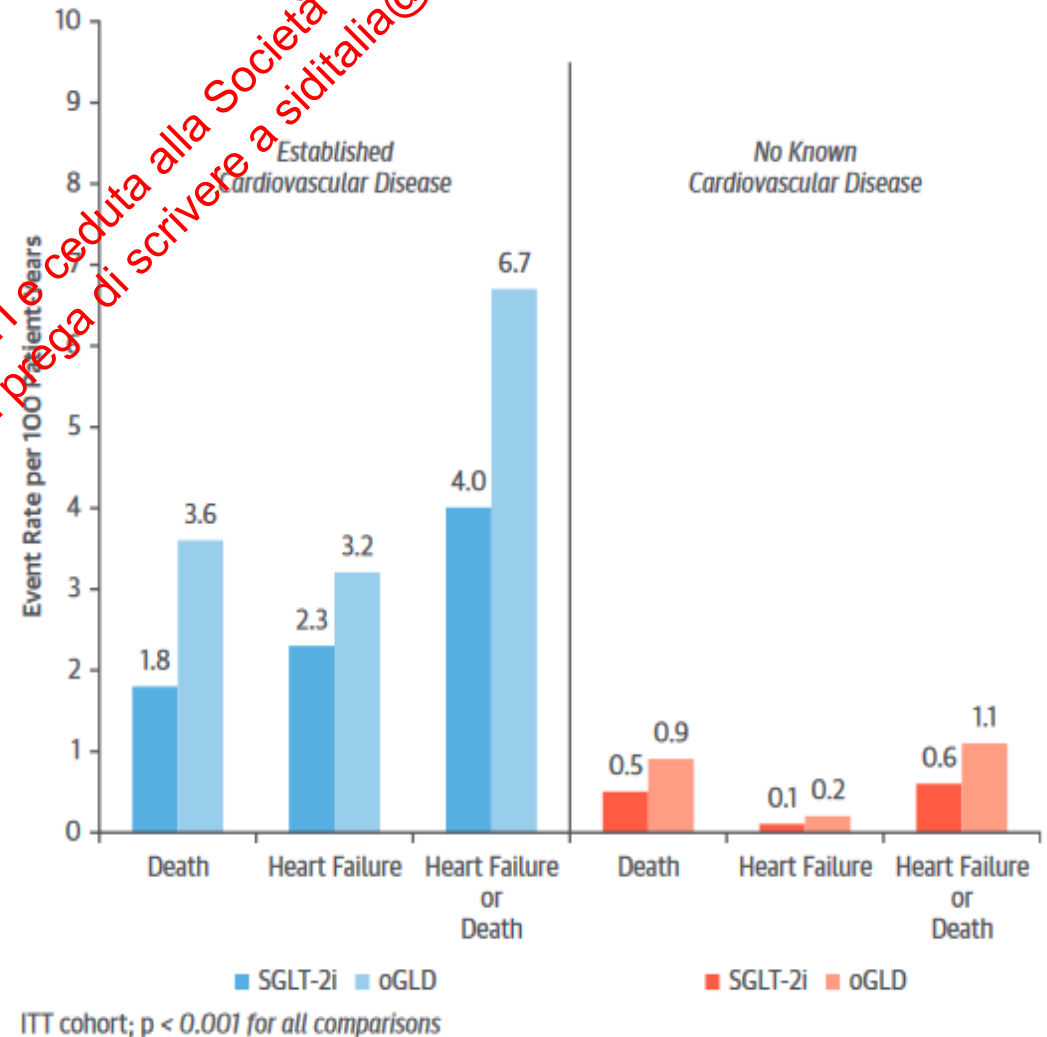
ORIGINAL RESEARCH ARTICLE

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)



Population: Patients with T2D who were newly started on either SGLT-2i or oGLDs



By 51% death
By 46% HHF or death



Real-World: CVD-REAL 3

Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study

Prof Hiddo J L Heerspink, PhD • Prof Avraham Karasik, MD • Marcus Thuresson, PhD • Cheli Melzer-Cohen, MSc • Prof Gabriel Chodick, PhD • Kamlesh Khunti, FMedSci • et al. [Show all authors](#)

THE LANCET
Diabetes & Endocrinology

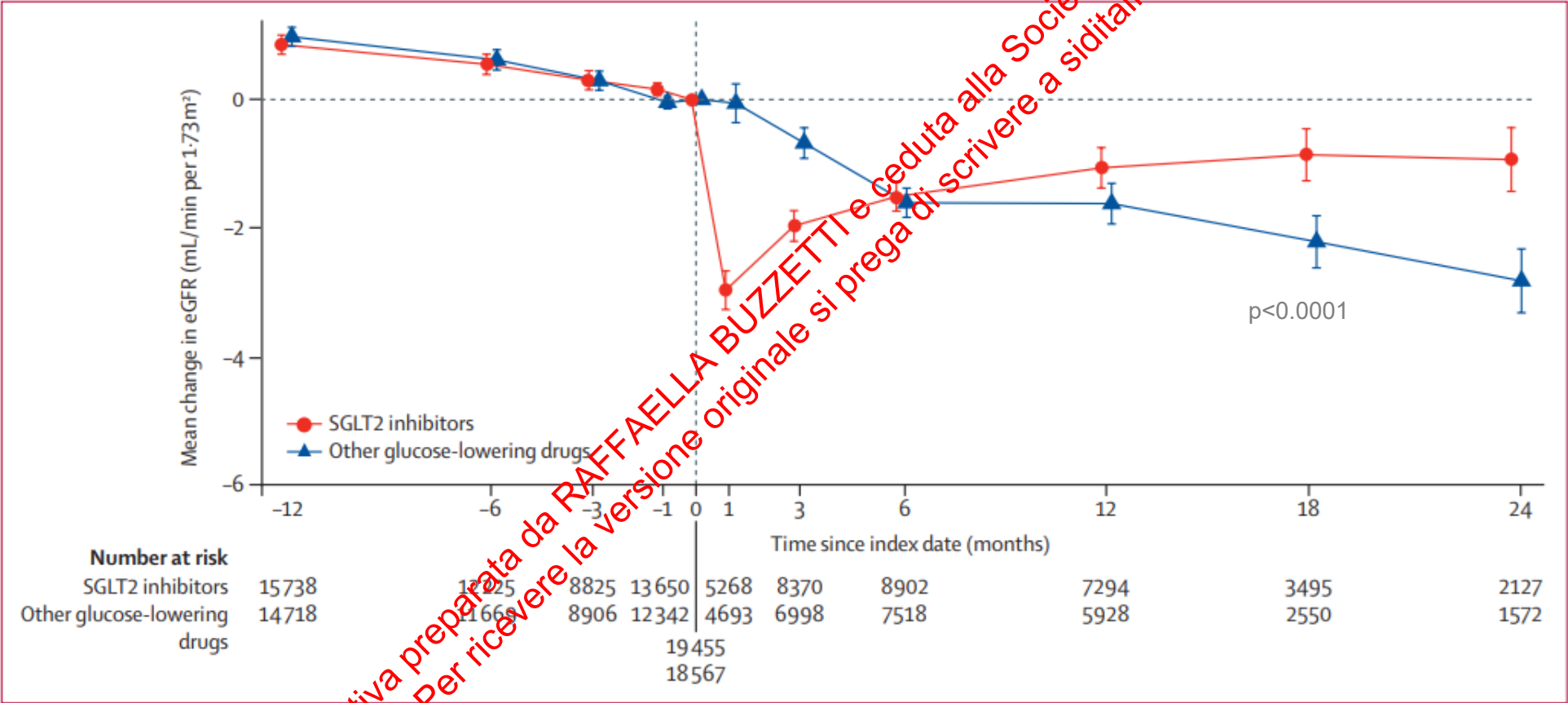
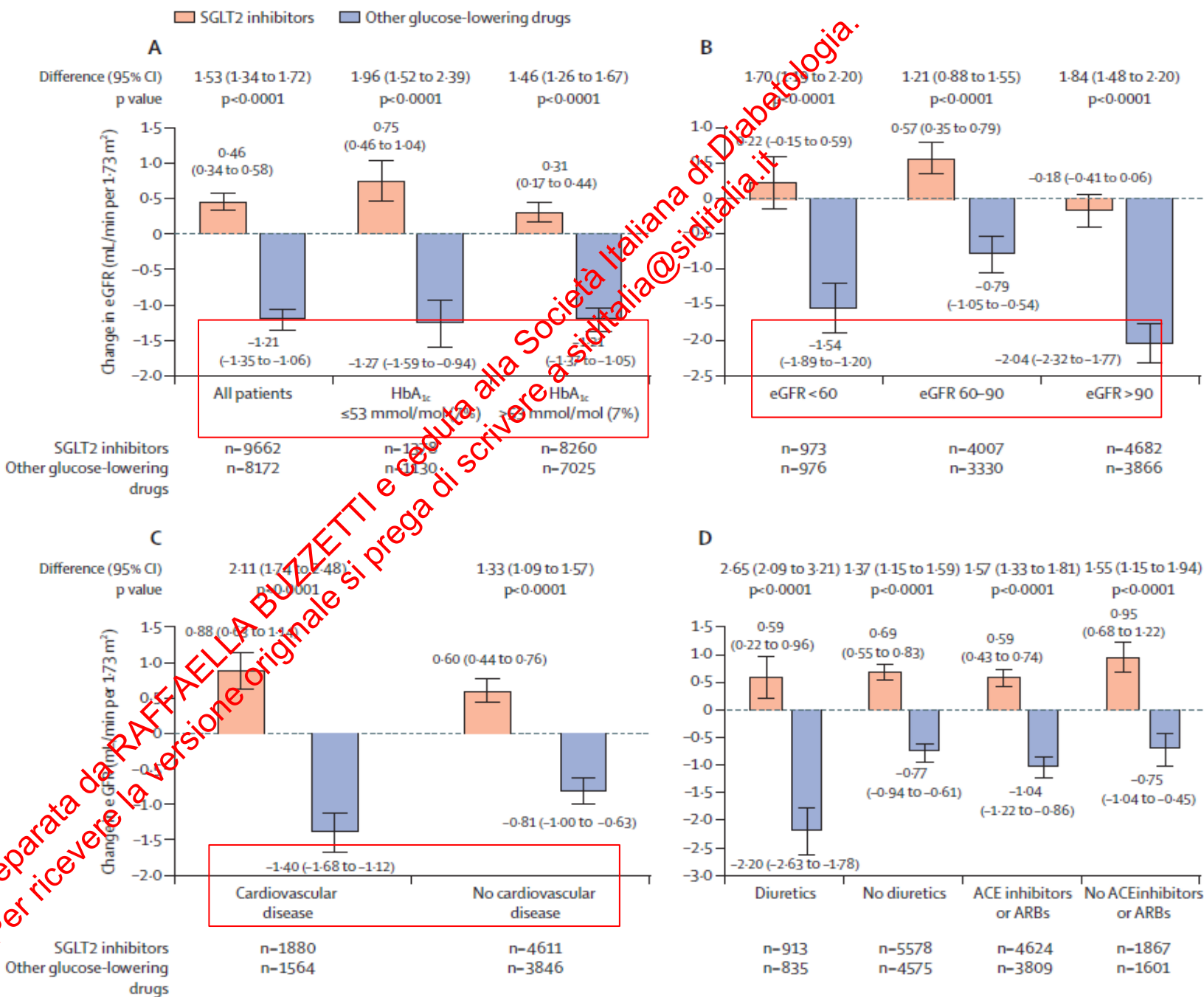


Figure 2: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other glucose-lowering drugs (on treatment)

Population: patients with type 2 diabetes with or without chronic kidney disease

Heerspink HJL, et al. Lancet Diabetes Endocrinol. 2020.

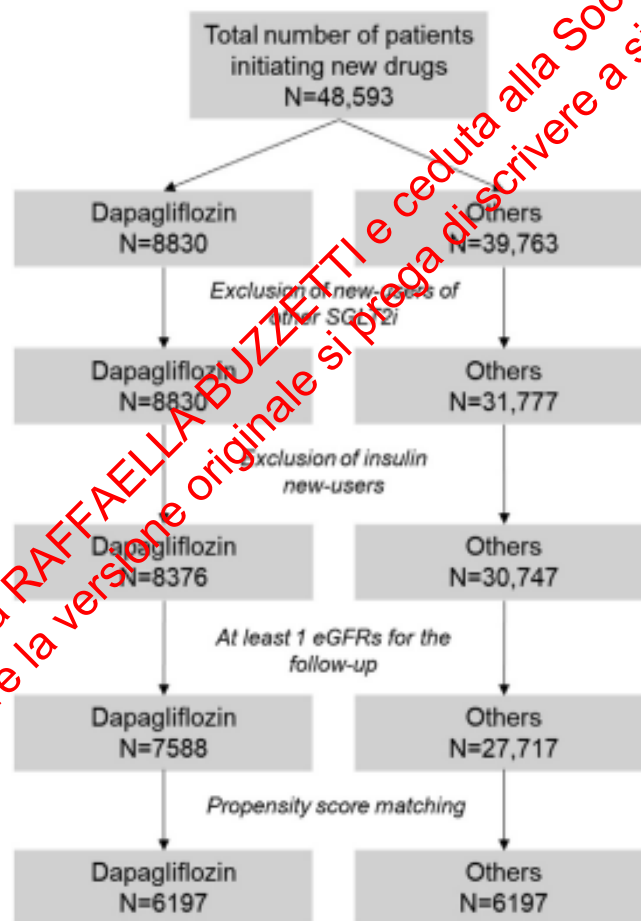
Real-World: CVD-REAL 3



Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk

Real-World: **DARWIN-RENAL (2024)**

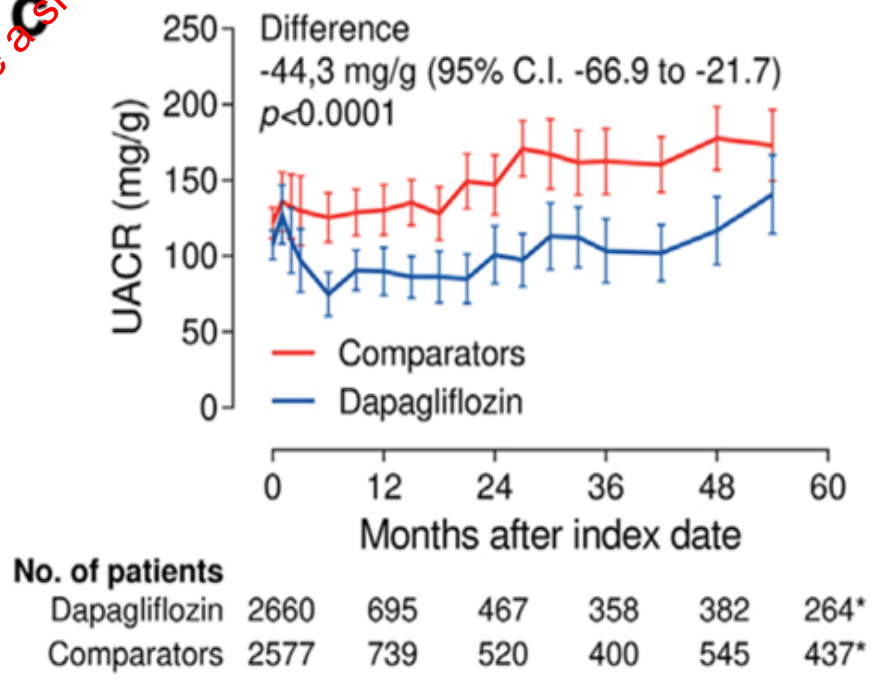
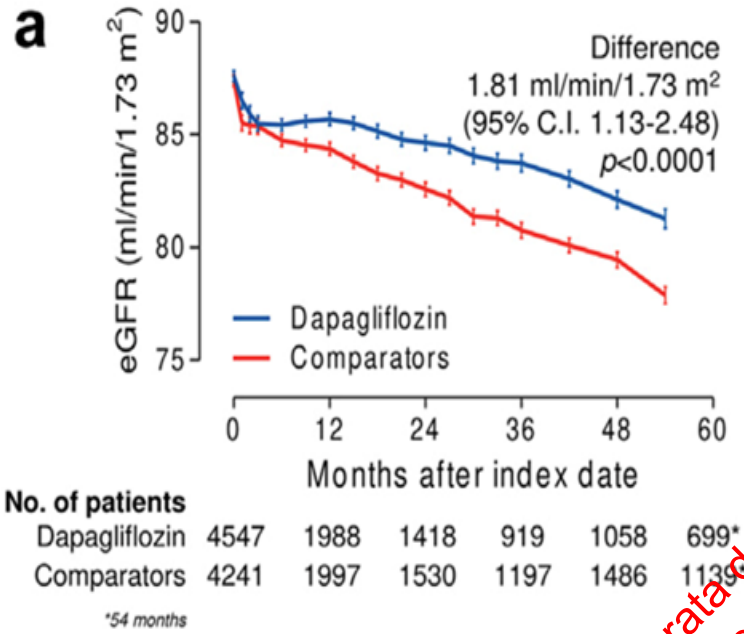
Gian Paolo Fadini,^{a,b,f,*} Enrico Longato,^{c,f} Mario Luca Morieri,^a Stefano Del Prato,^d Angelo Avogaro,^a and Anna Solini,^e
DARWIN-Renal Study Investigators



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Long-term benefits of dapagliflozin on renal outcomes of type 2 diabetes under routine care: a comparative effectiveness study on propensity score matched cohorts at low renal risk

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SGLT2i / Metformin : who's first?

Sodium-glucose cotransporter 2 inhibitor versus metformin as first-line therapy in patients with type 2 diabetes mellitus: a multi-institution database study

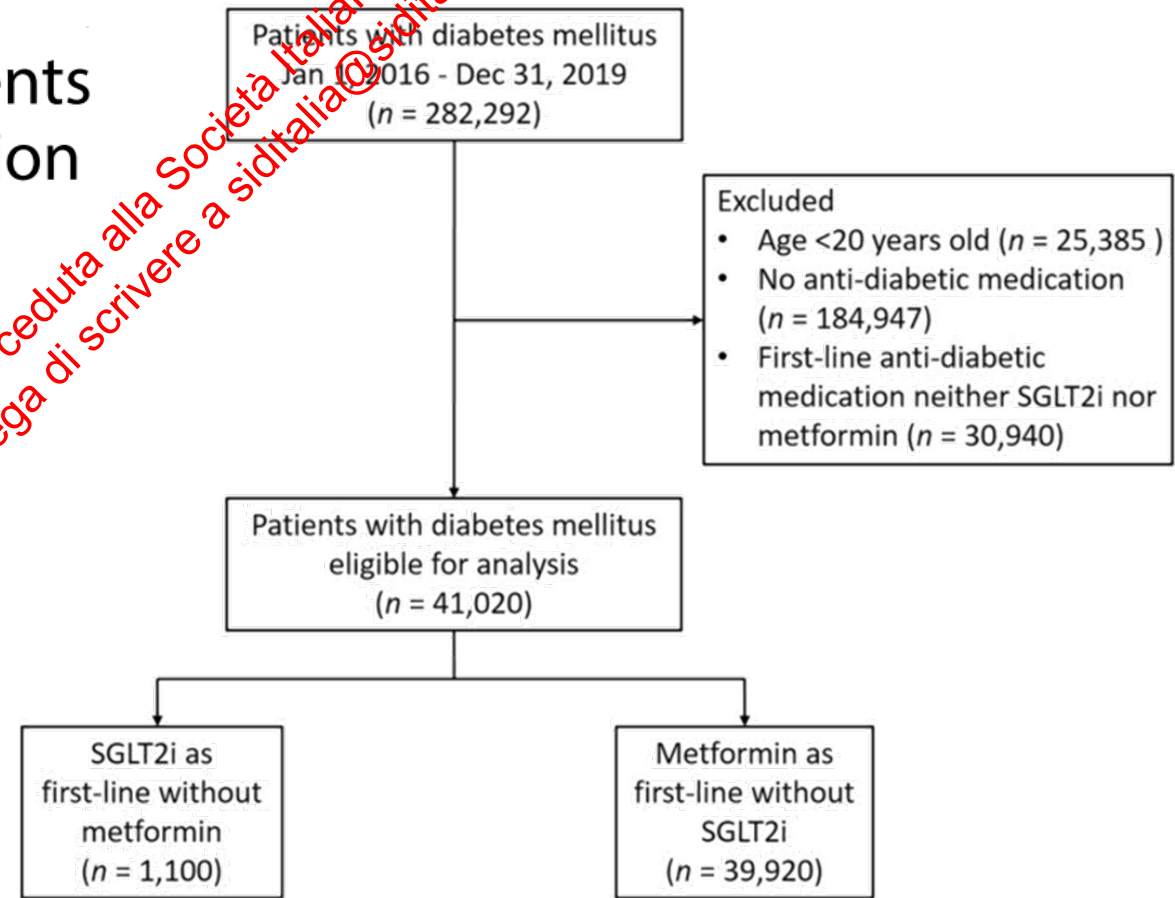
Tien-Hsing Chen¹, Yan-Rong Li², Shao-Wei Chen³, Yu-Sheng Lin⁴, Chi-Chin Sun⁵, Dong-Yi Chen⁶, Chun-Tai Mao¹, Michael Wu⁷, Chih-Hsiang Chang⁸, Pao-Hsien Chu⁶ and Victor Chien-Chia Wu^{6*} 

Cardiovascular Diabetology

Retrospective cohort study

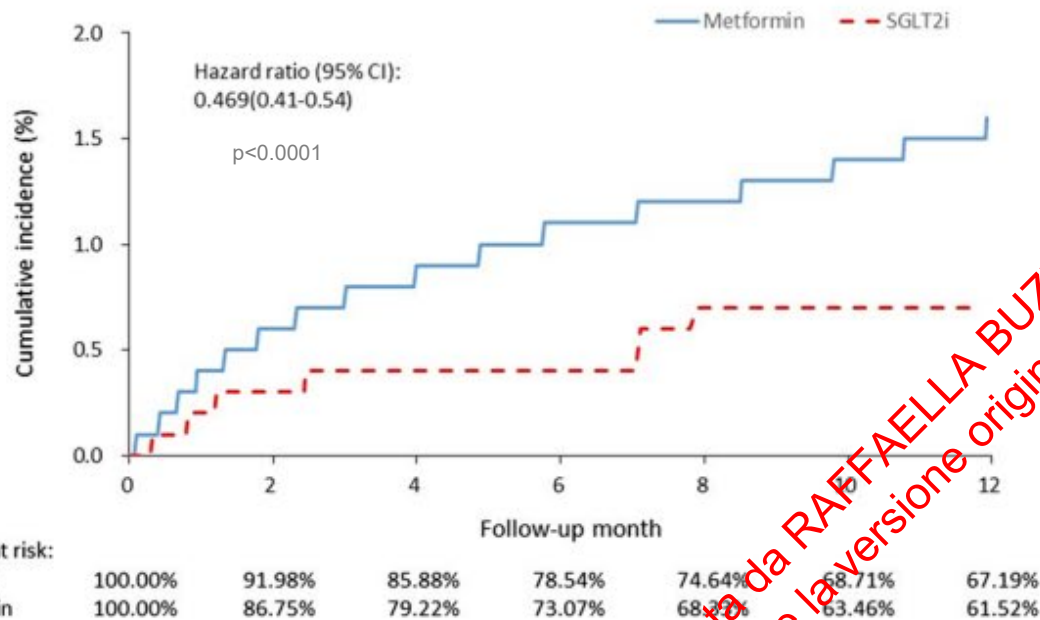
Primary outcomes: heart failure hospitalization, acute coronary syndrome, ischemic stroke, and all-cause mortality

Fig. 1

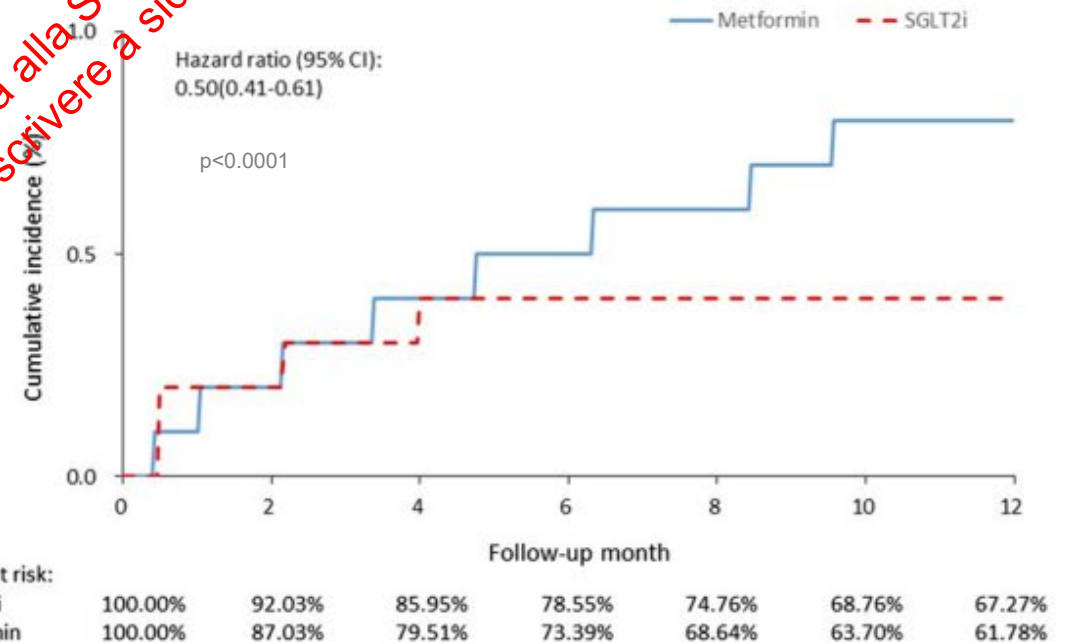


SGLT2i / Metformin : who's first?

a Heart failure hospitalization



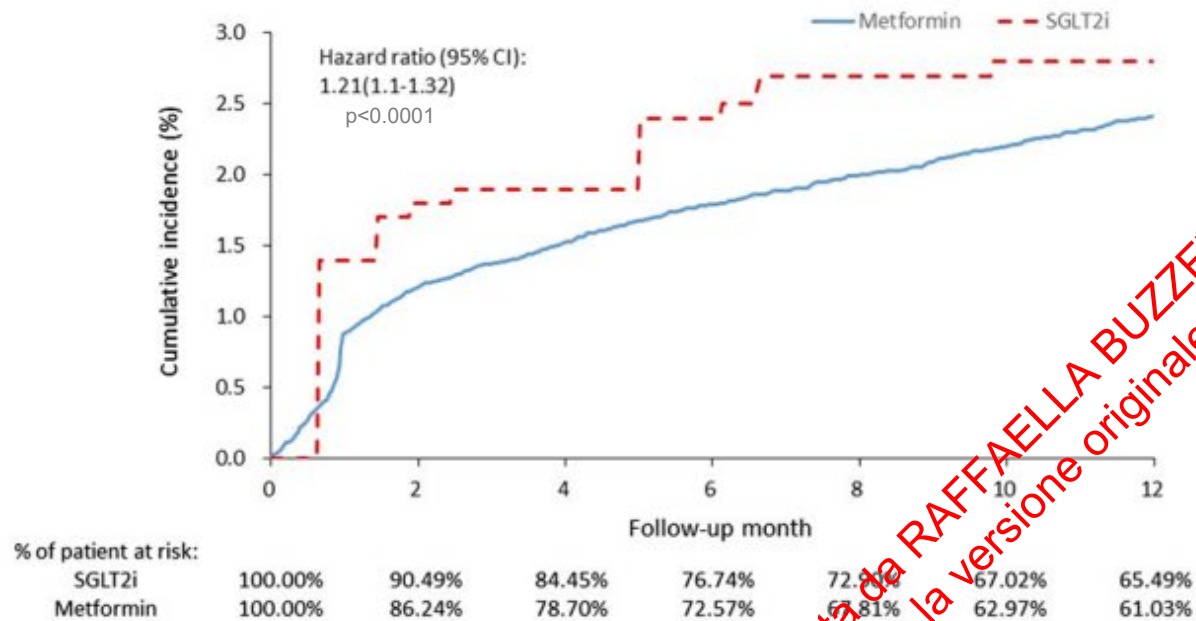
b Acute coronary syndrome



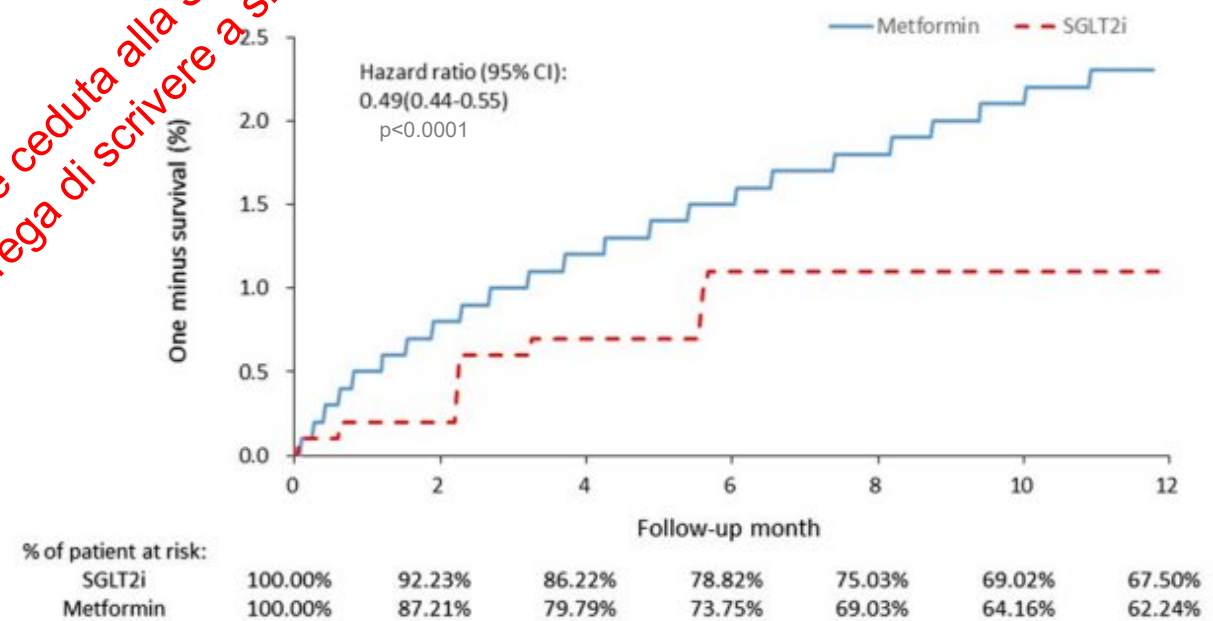
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SGLT2i / Metformin : who's first?

c Ischemic stroke



d All-cause mortality



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SGLT2i / Metformin : coexistence?

Article

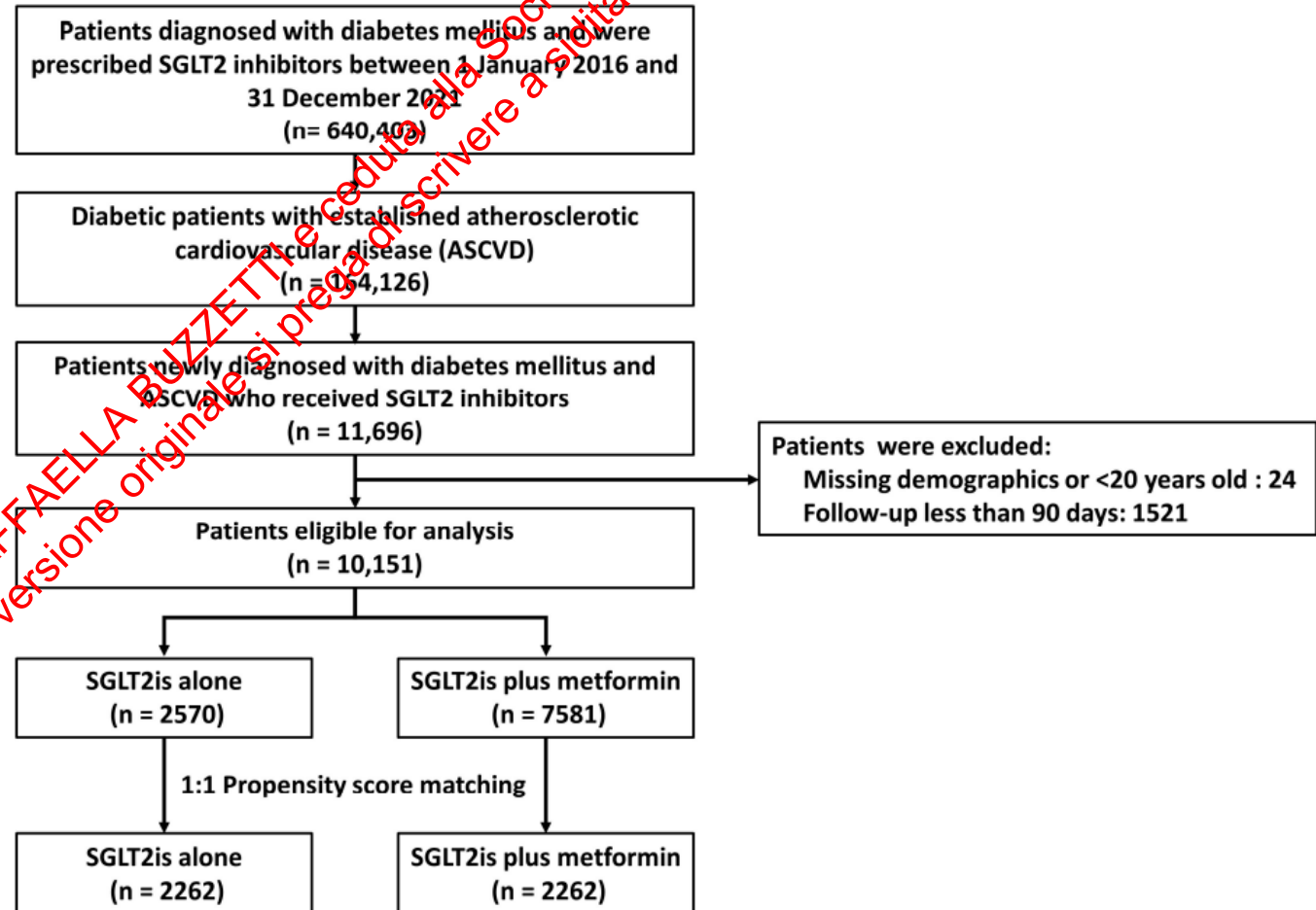
Effects of SGLT2 Inhibitors with and without Metformin in High-Risk, Treatment-Naïve Patients with Diabetes

Chen-Yu Huang¹ and Jen-Kuang Lee^{2,3,4,5,6,*}

Retrospective cohort study

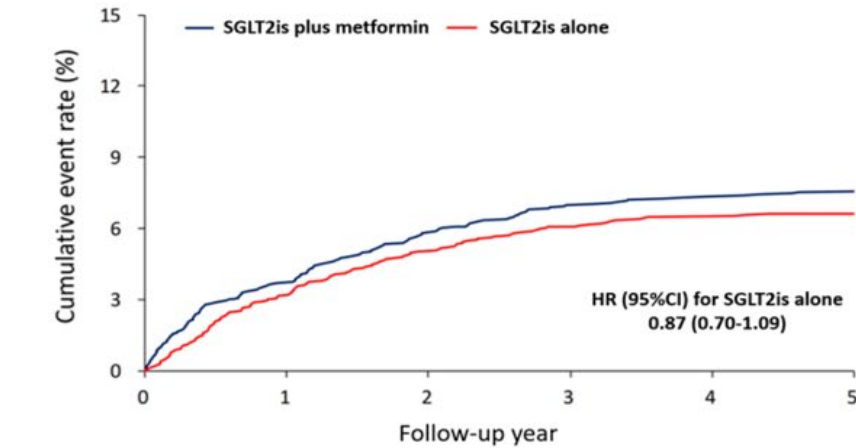
Primary outcome: major adverse cardiovascular events (MACEs)

Secondary outcomes: cardiovascular death, hospitalization for heart failure, and renal outcomes.



SGLT2i / Metformin : coexistence?

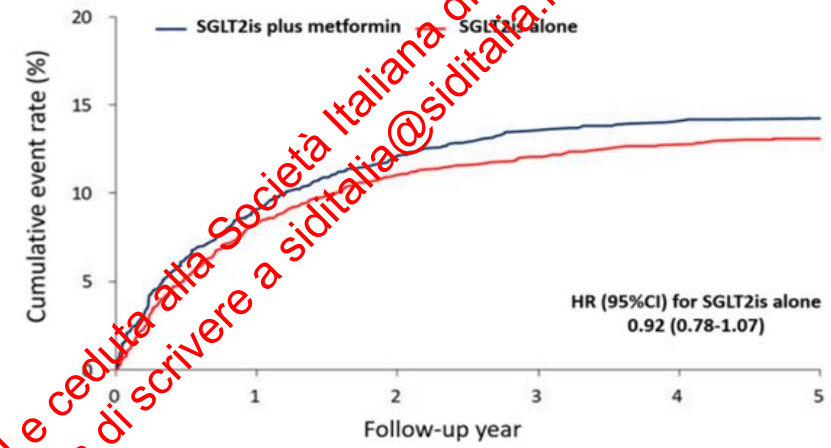
MACEs



Number of patients at risk:						
SGLT2i alone	2262	1491	817	458	203	45
Plus metformin	2262	1482	813	440	186	

(A)

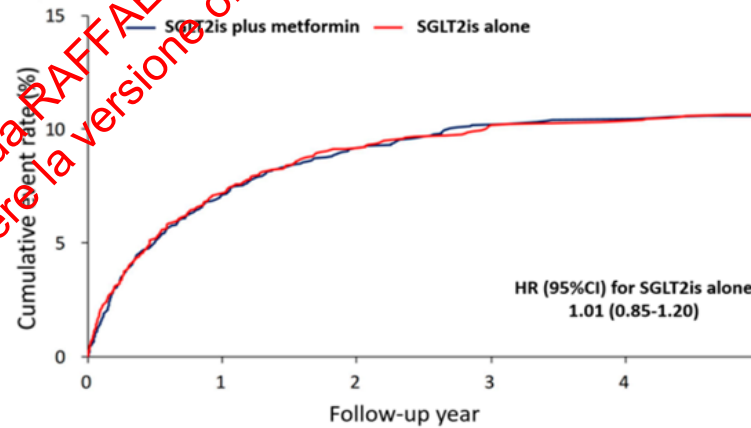
Newly diagnosed CKD



Number of patients at risk:						
SGLT2i alone	2262	1395	740	395	162	37
Plus metformin	2262	1374	736	381	153	53

(B)

Cardiovascular death and HHF



Number of patients at risk:						
SGLT2i alone	2262	1433	796	445	200	46
Plus metformin	2262	1429	793	435	188	60

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SGLT2i / Metformin : upcoming trials

Is an SGLT2i better than metformin as first line in T2D?

23rd August 2022

RECRUITING ⓘ

SGLT2 Inhibitors As First Line Therapy to Prevent Renal Decline in Type 2 Diabetes (START)

ClinicalTrials.gov ID ⓘ NCT05345327

Sponsor ⓘ The George Institute

Information provided by ⓘ The George Institute (Responsible Party)

Last Update Posted ⓘ 2023-08-24

Brief Summary

The aim of the trial is to evaluate the effects of the SGLT2 inhibitor, dapagliflozin, compared to metformin on annual decline in eGFR when used as first line therapy in people with Type 2 Diabetes.

Detailed Description

This study is a randomised, double blinded, community-based clinical trial and will be undertaken in primary care sites across Victoria, New South Wales and Queensland, Australia. Following a 4-week active run-in period, eligible participants will be randomised to either dapagliflozin 10mg daily, or metformin XR 2000mg daily in a 1:1 ratio.

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Conclusions

SGLT2

- safe in use
- effective as antidiabetic
- useful in prevention of complications

→ Why not as first line treatment?

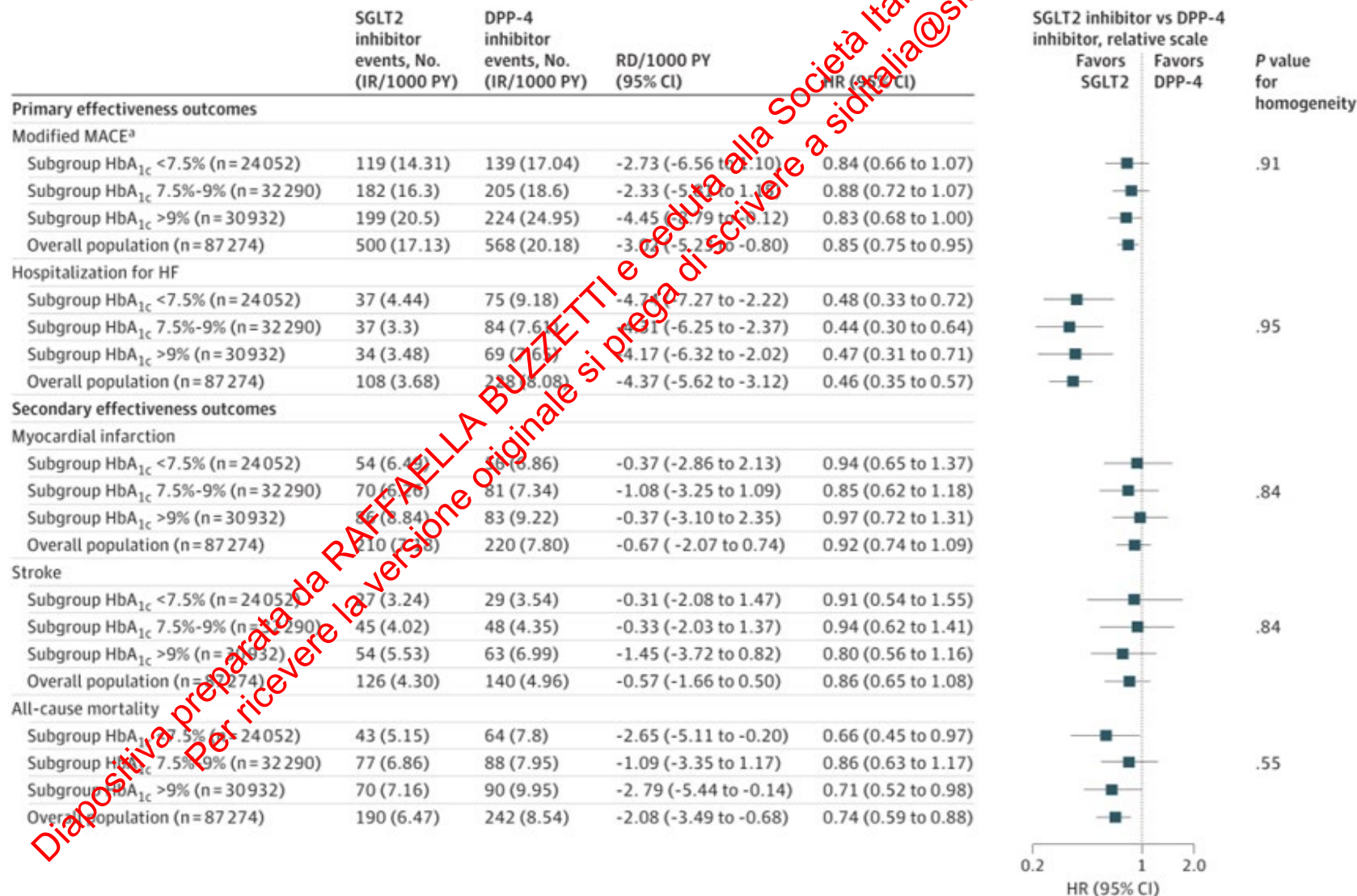
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Grazie a Francesco De Vita.....

From: **Comparing Effectiveness and Safety of SGLT2 Inhibitors vs DPP-4 Inhibitors in Patients With Type 2 Diabetes and Varying Baseline HbA_{1c} Levels**

JAMA Intern Med. 2023;183(3):242-254. doi:10.1001/jamainternmed.2022.6664



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Comparative effectiveness of SGLT2i versus GLP1-RA on cardiovascular outcomes in routine clinical practice

Edouard L. Fu^{a,b,*,1}, Catherine M. Clase^c, Roemer J. Janse^a, Bengt Lindholm^d, Friedo W. Dekker^a, Meg J. Jardine^e, Juan-Jesus Carrero^b

Adults who newly started SGLT2i or GLP1-RA therapy in Stockholm, Sweden, during 2013–2019.

Primary outcome: major adverse cardiovascular events (MACE), a composite of cardiovascular (CV) death, myocardial infarction and stroke.

Secondary outcomes: individual MACE components and hospitalization for heart failure

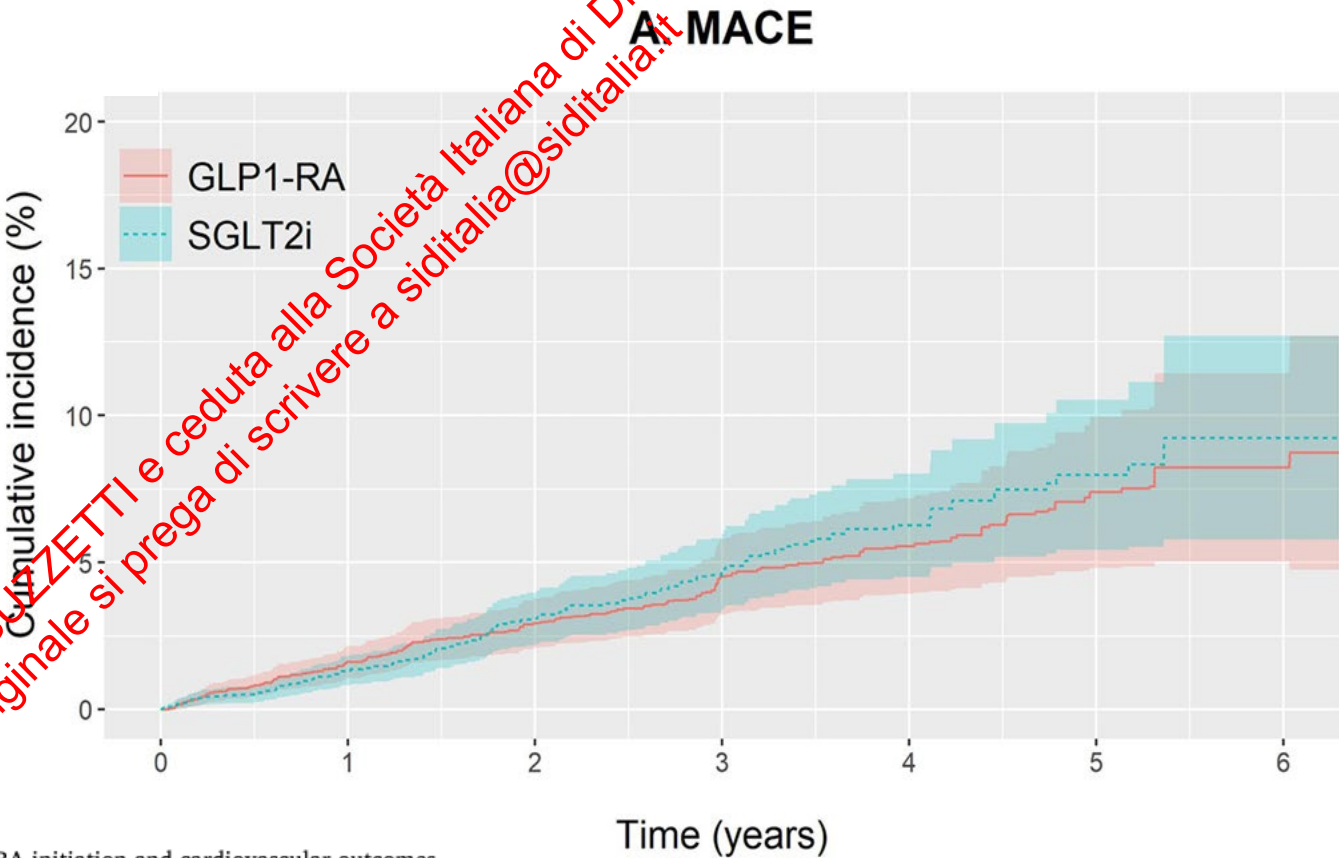


Table 2
Number of events, incidence rates and adjusted hazard ratios for the association between SGLT2i vs. GLP1-RA initiation and cardiovascular outcomes.

Outcome	SGLT2 inhibitors		GLP1-RA		Adjusted Hazard Ratio (95% CI) [†]
	Events*	Events per 1000 person years*	Events*	Events per 1000 person years*	
Primary outcome					
MACE	155	16.4 (13.9–19.2)	211	14.1 (12.3–16.1)	1.04 (0.83–1.31)
Secondary outcomes					
HF hospitalization	74	7.7 (6.1–9.7)	143	9.5 (8–11.2)	0.80 (0.59–1.09)
Cardiovascular death	31	3.2 (2.2–4.6)	51	3.4 (2.5–4.4)	0.95 (0.58–1.55)
Myocardial infarction	81	8.5 (6.7–10.6)	119	7.9 (6.6–9.5)	0.91 (0.67–1.24)
Ischemic stroke	61	6.4 (4.9–8.2)	49	3.2 (2.4–4.3)	1.71 (1.14–2.59)

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Ischemic stroke

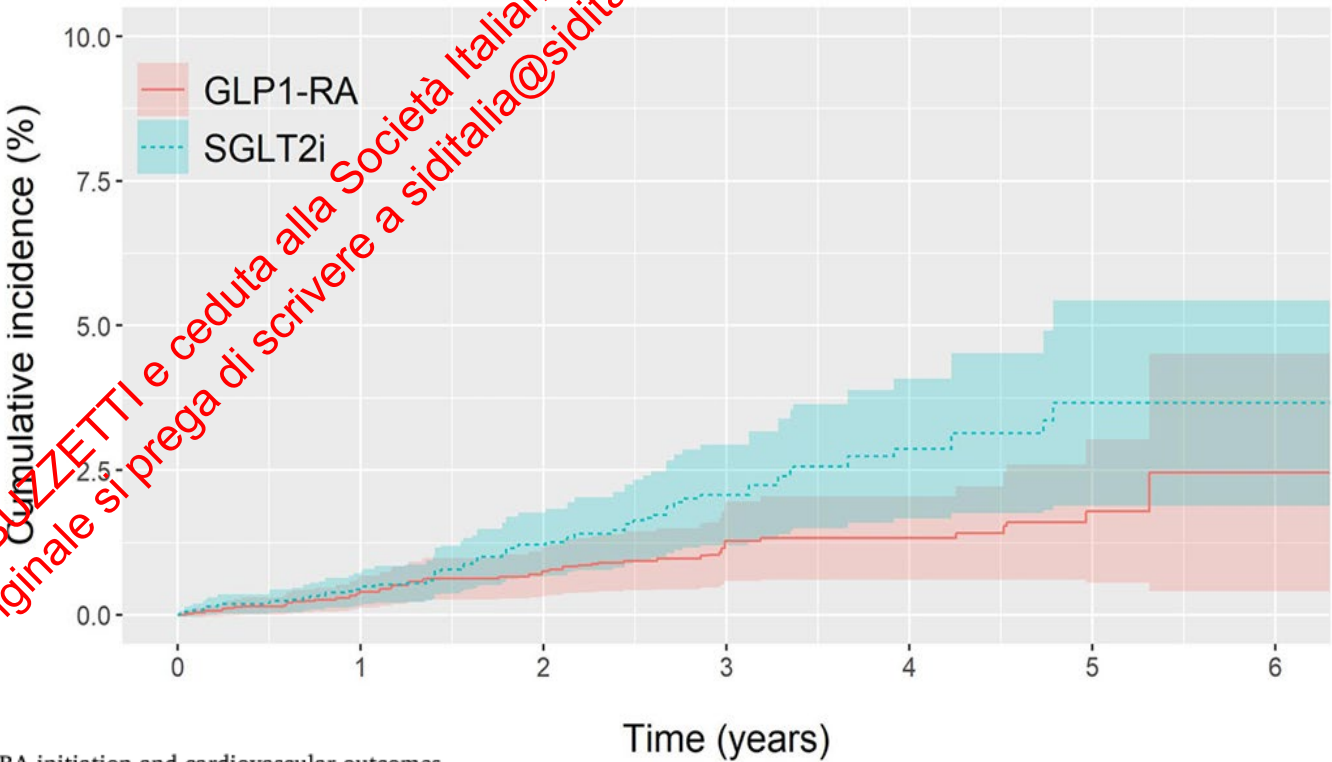


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Meta-analyses of cardiorenal effects exerted by GLP-1RA and SGLT-2 inhibitors in patients with or without T2D

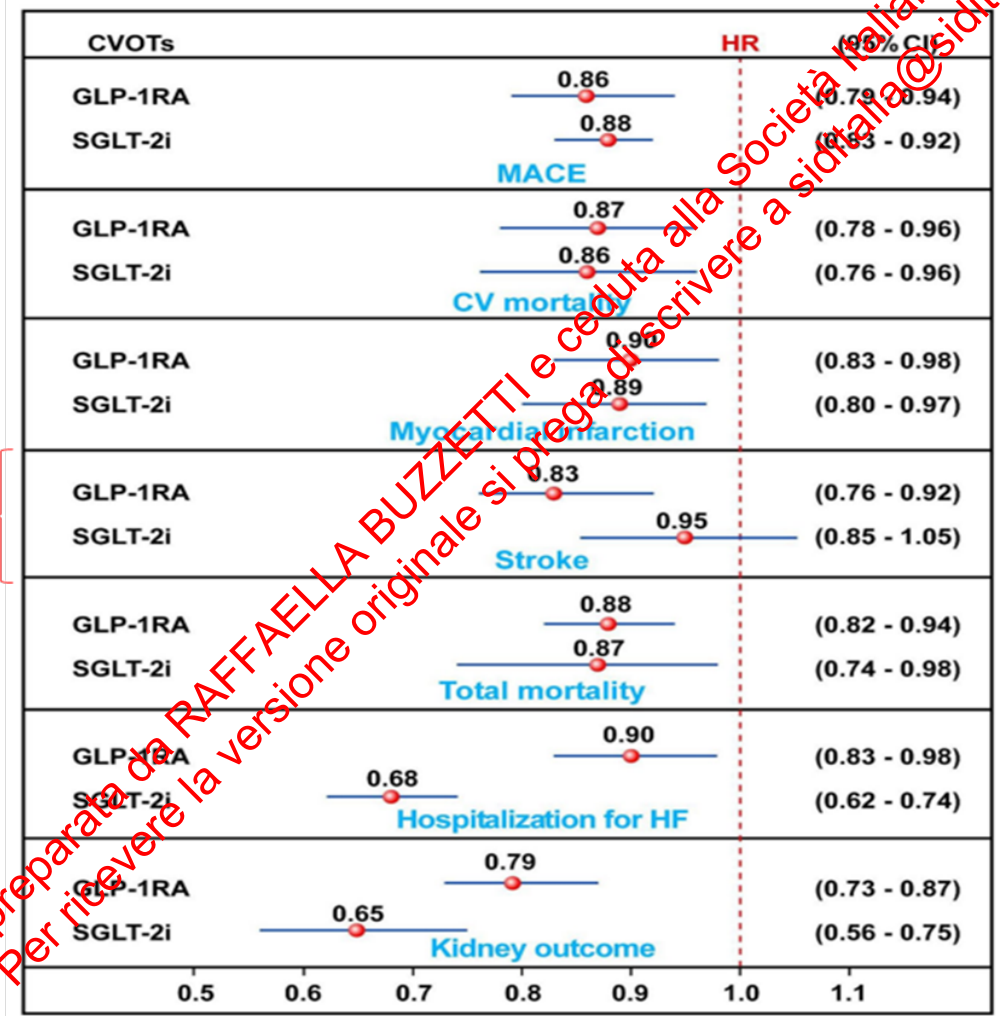
GLP-1 receptor agonists vs. SGLT-2 inhibitors: the gap seems to be leveling off

Dario Giugliano^{1,2*}, Lorenzo Scappaticcio^{1,2}, Miriam Longo¹, Giuseppe Bellastella^{1,2} and Katherine Esposito^{2,3}

GLP1RA > SGLT2



SGLT2 > GLP1RA



SGLT2 = GLP1RA



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