Empagliflozin: What's New – What's Hot

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Disclosures

- Advisory Boards: AstraZeneca; Eli Lilly; Novo Nordisk; Roche Diabetes Care, Sanofi
- Consultant: Boehringer Ingelheim; Lifescan; Merck Sharp & Dohme; Sanofi, AstraZeneca, Medimmune, Roche Diabetes Care, Sanofi, Medtronic
- Research Support: Eli Lilly, Roche Diabetes Care

SGLT-2i and Cardiovascular Benefit

1. SGLT-2i in specific populations: HFrEF, HFpEF, non-diabetic, elderly
2. SGLT-2i in special settings: inpatient care, telemedicine
3. New insight on mechanism of action

SGLT-2i and Renal Benefit

New Benefits of SGLT-2i

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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

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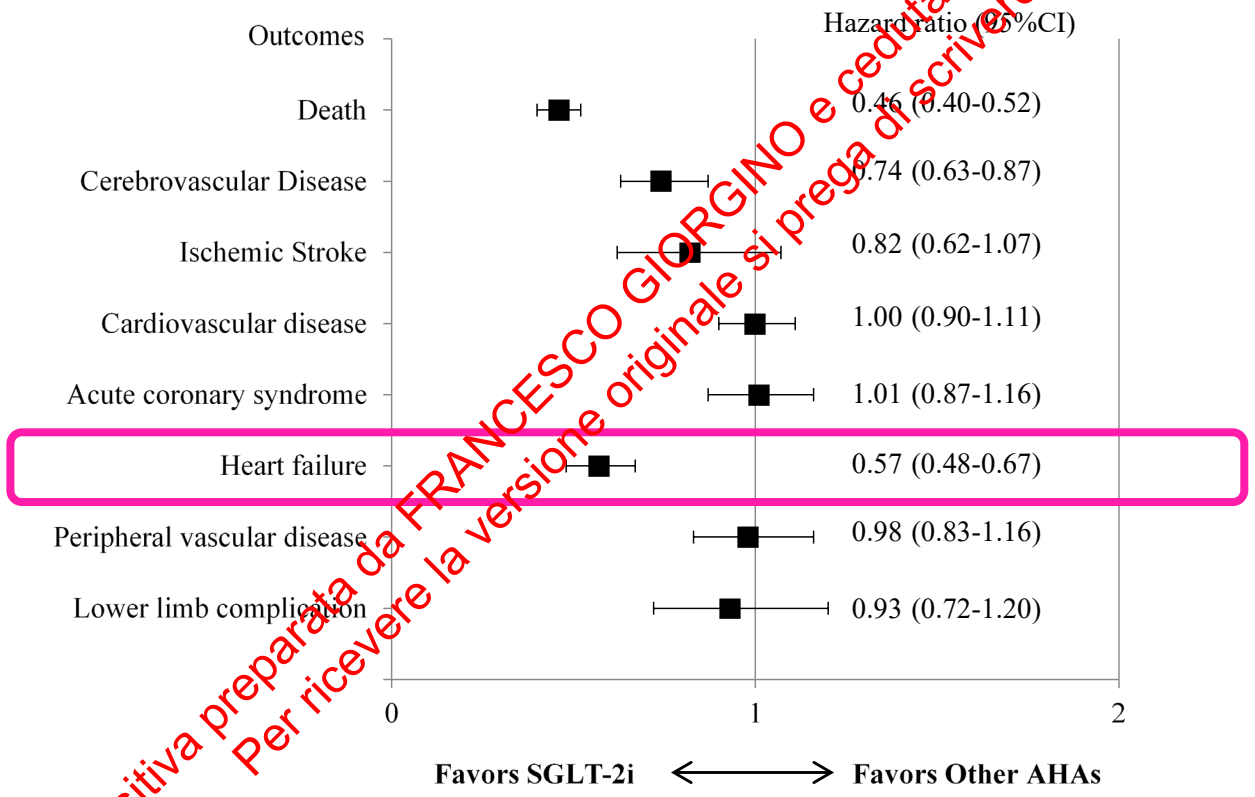
Pooled Risk of Death and Clinical Events in Matched Populations According to Treatment Status in the Lombardy and Apulia Regions, from 2010 to 2018

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



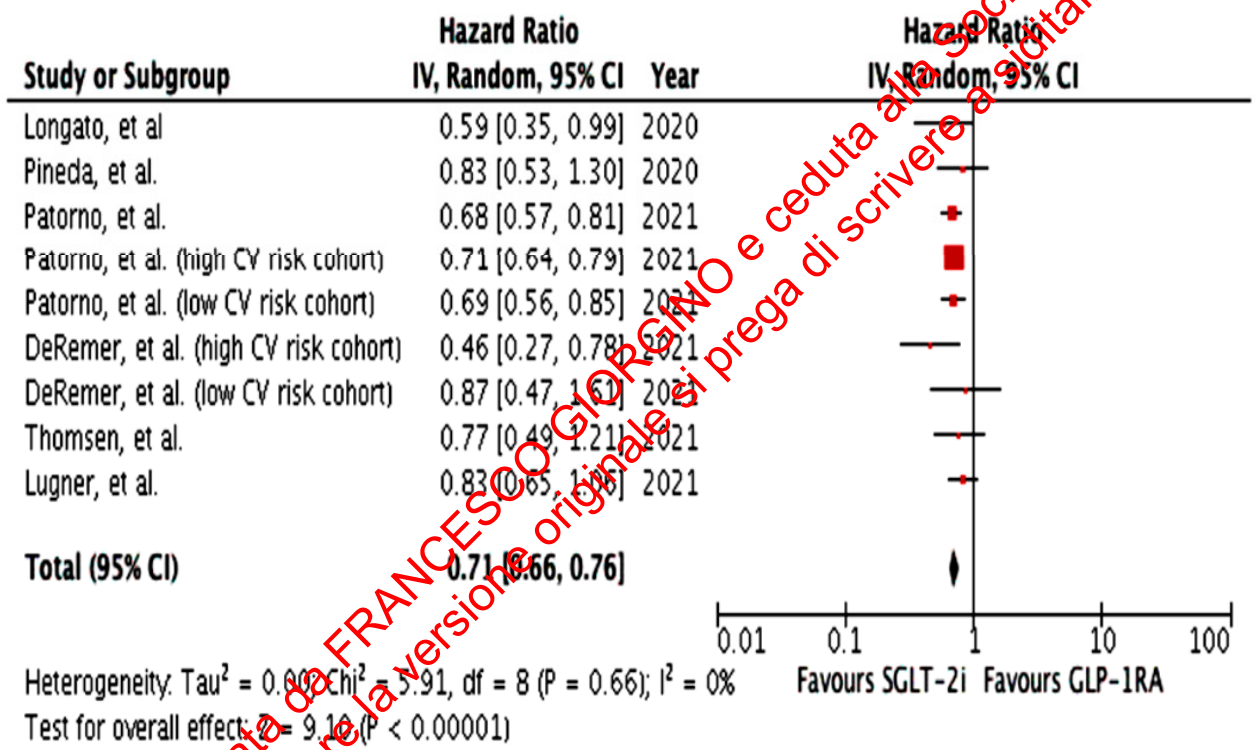
SGLT-2i

A, Apulia; L, Lombardy

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

Effects of SGLT-2i vs. GLP-1RA on hHF in Real-World Studies

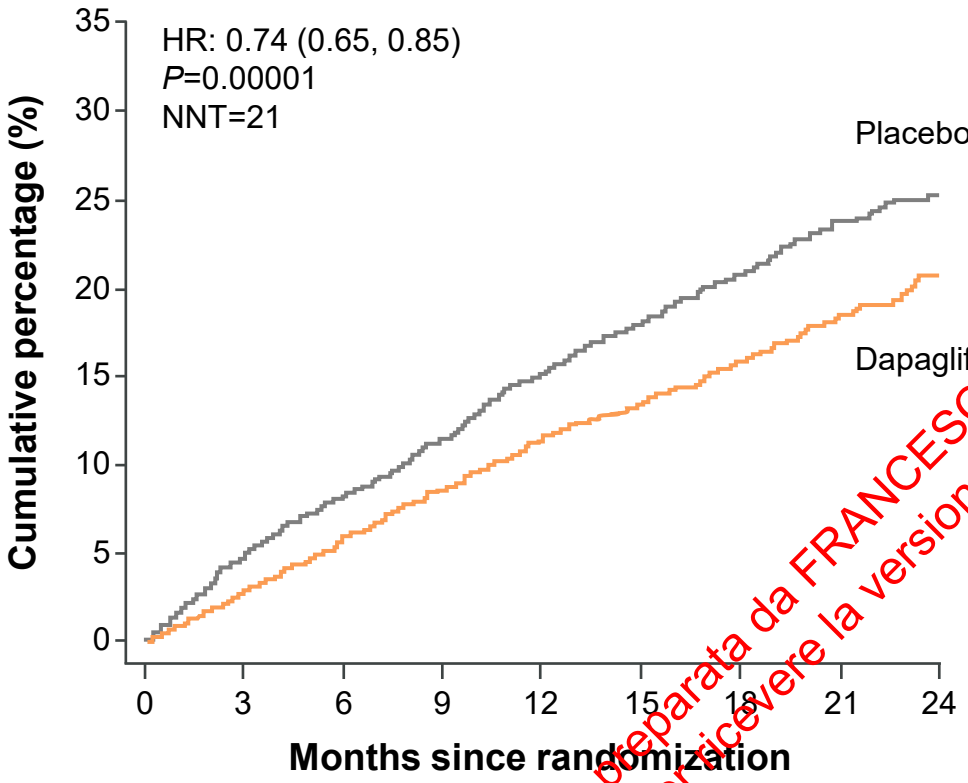
Hospitalization for Heart Failure



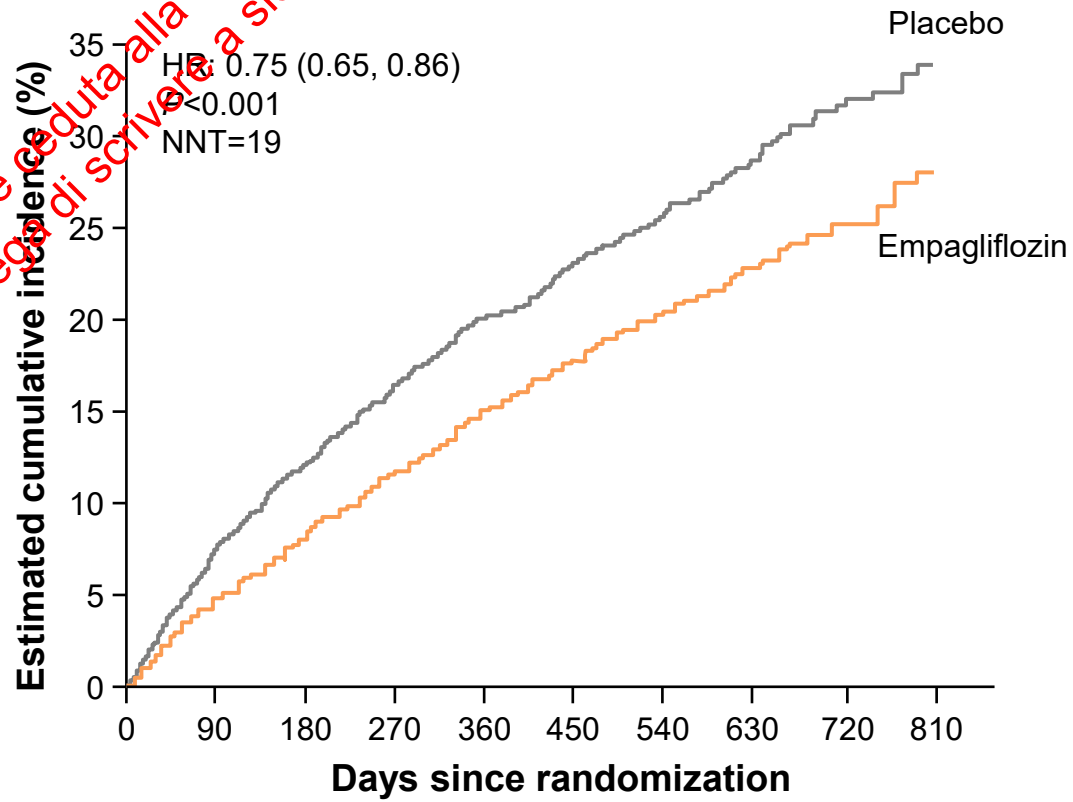
Caruso I et al, *Metabolites*, 2022

The DAPA-HF and EMPEROR-Reduced Trials Demonstrated the Positive Effects of SGLT2 Inhibition on HF Outcomes in HFrEF

DAPA-HF primary composite:
CV death / HF hospitalization / urgent HF visit[1]



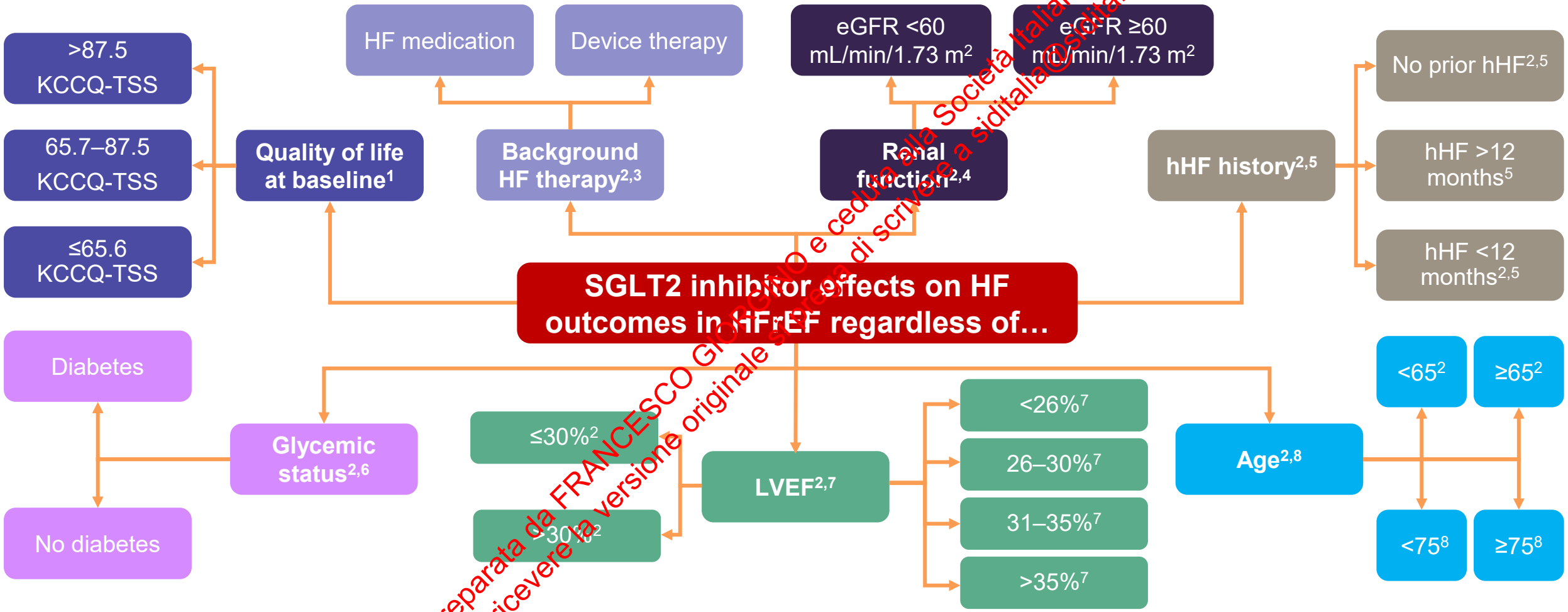
EMPEROR-Reduced primary composite:
CV death / HF hospitalization[2]



CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2; NNT, number needed to treat

1. McMurray JJV, et al. *N Engl J Med* 2019;381:1995–2008; 2. Packer M, et al. *N Engl J Med* 2019;381:1995–2008

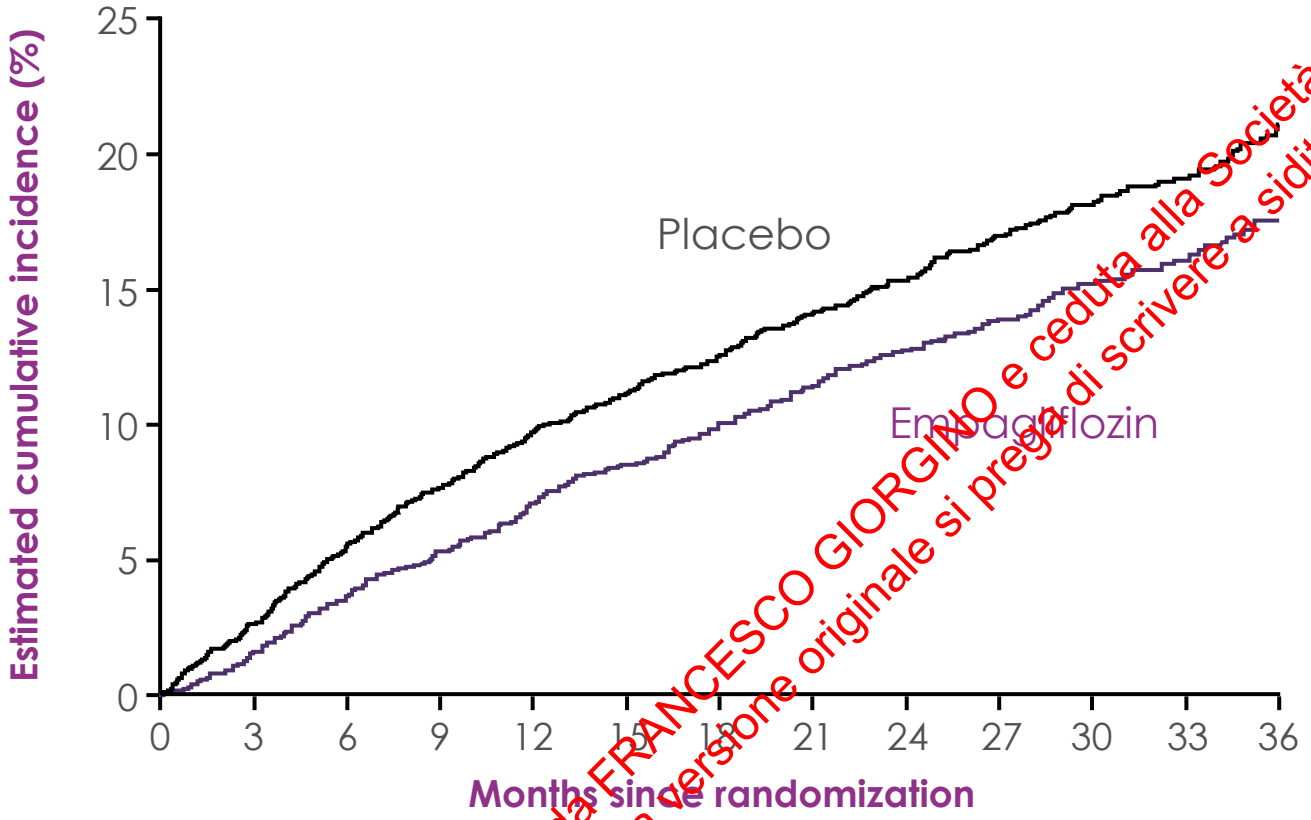
DAPA-HF and EMPEROR-Reduced Showed Consistent Effects on Primary Outcomes Across a Range of Patient Groups



eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalized heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide

1. Kosiborod M, et al. Presented at American Heart Association Scientific Sessions; November 16th–18th, 2019; Philadelphia, PA, USA; 2. Packer M, et al. *N Engl J Med* 2020 [Epub ahead of print]; 3. Docherty KF, et al. *Eur Heart J* 2020;41:2379–2392; 4. Solomon SD, et al. Presented at American Society of Nephrology Kidney Week 2019; November 5th–10th, 2019; Washington, DC, USA; 5. Sabatine MS. Presented at America Heart Association Scientific Sessions; November 16th–18th, 2019; Philadelphia, PA, USA; 6. McMurray J. Presented at America Heart Association Scientific Sessions; November 16th–18th, 2019; Philadelphia, PA, USA; 7. Solomon SD. Presented at America Heart Association Scientific Sessions; November 16th–18th, 2019; Philadelphia, USA; 8. Martinez FA, et al. *Circulation* 2020;141:100–111

EMPEROR-Preserved: Clinically Meaningful 21% RRR in the Composite Primary Endpoint of CV Death or HHF



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2781	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

NNT*=31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.

Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

EMPEROR-Preserved: Empagliflozin Improves CV Outcomes in HFpEF Irrespective of Diabetes Status at Baseline

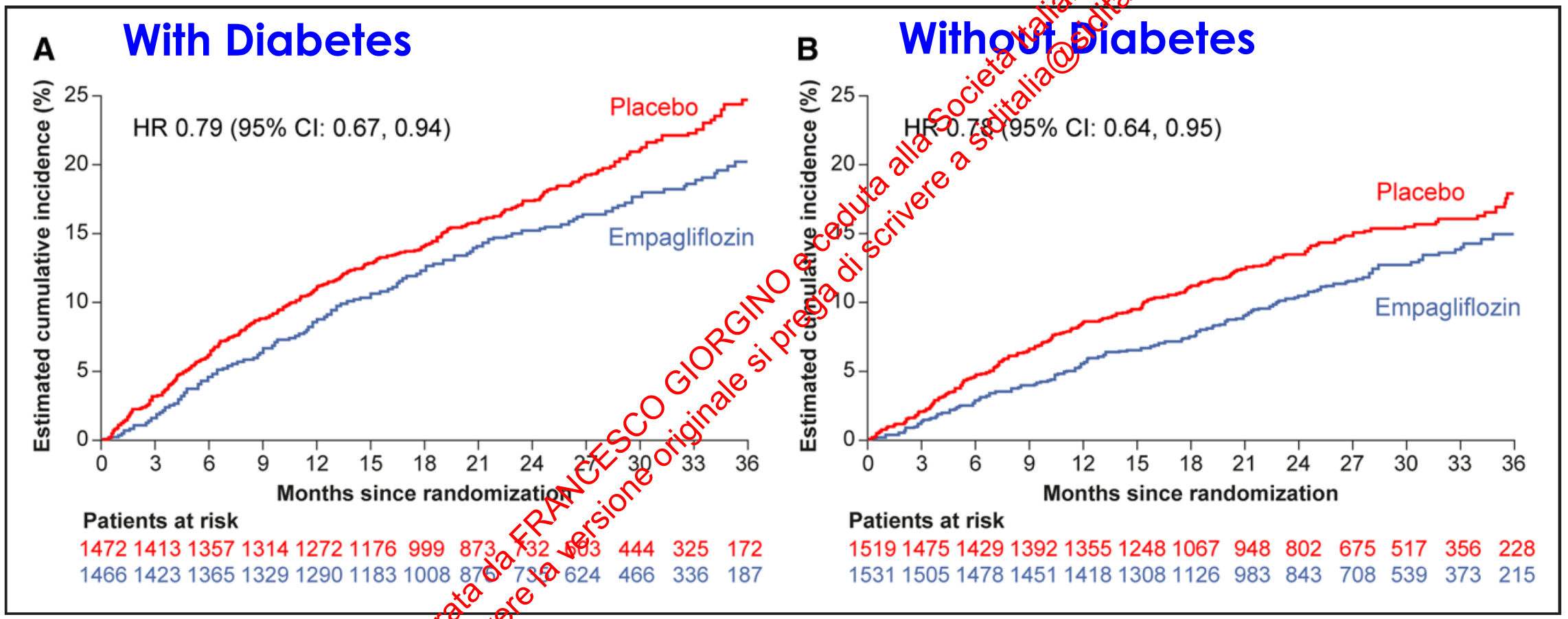
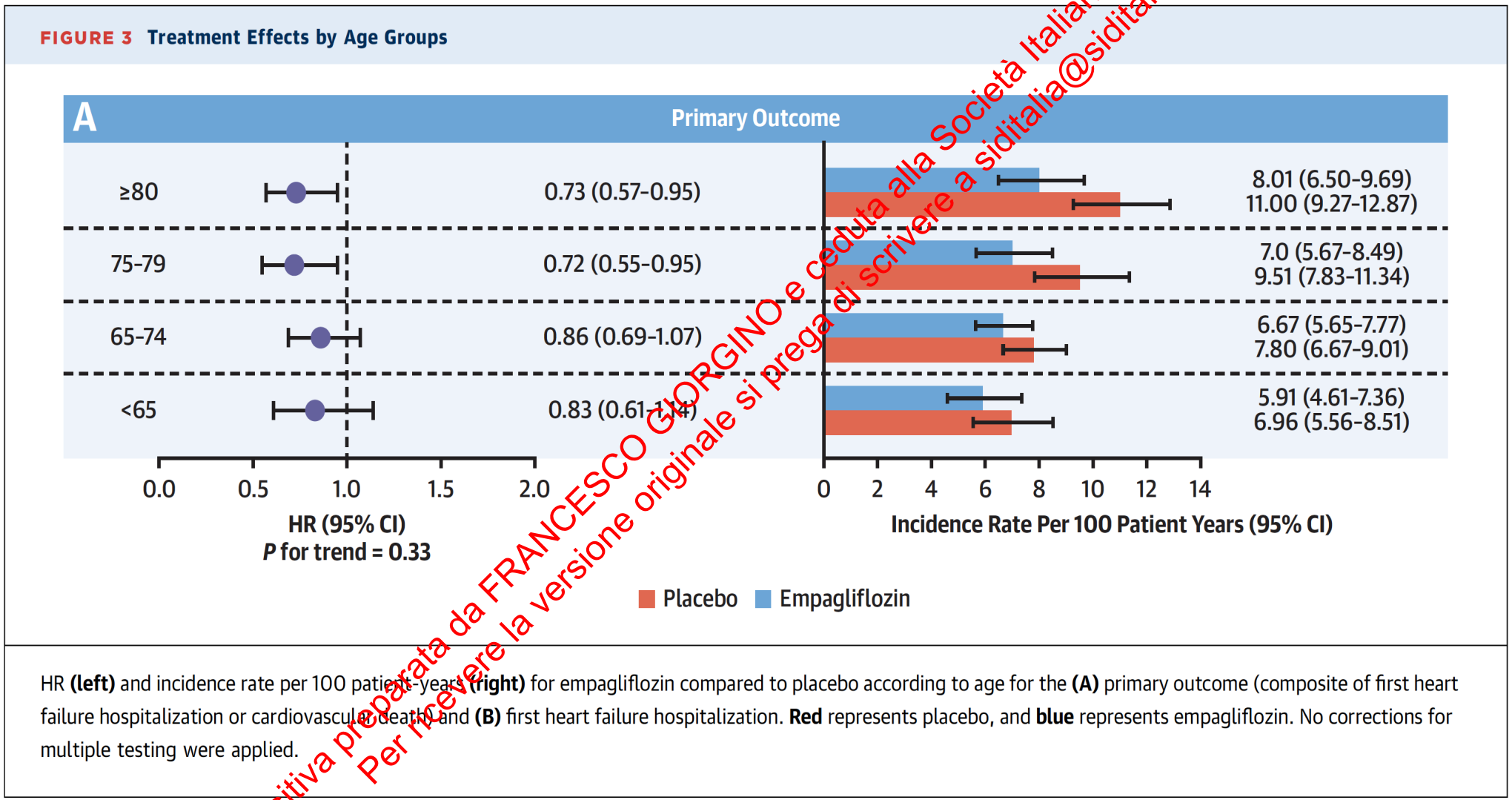


Figure 2. Effect of empagliflozin vs placebo on the primary end point of cardiovascular death or first hospitalization for heart failure in patients with and without diabetes.

Effect of empagliflozin vs placebo on the primary end point of cardiovascular death or first hospitalization for heart failure in (**A**) patients with diabetes at baseline and (**B**) patients without diabetes. HR indicates hazard ratio.

Filippatos G et al, *Circulation* 2022

EMPEROR-Preserved: Empagliflozin Improves CV Outcomes in HFpEF Irrespective of Age



HR **(left)** and incidence rate per 100 patient-years **(right)** for empagliflozin compared to placebo according to age for the **(A)** primary outcome (composite of first heart failure hospitalization or cardiovascular death) and **(B)** first heart failure hospitalization. **Red** represents placebo, and **blue** represents empagliflozin. No corrections for multiple testing were applied.

Böhm M et al, *J Am Coll Cardiol* 2022

SGLT-2i and Cardiovascular Benefit

1. SGLT-2i in specific populations: HFrEF, HFpEF, non-diabetic, elderly
2. SGLT-2i in special settings: in-patient care, telemedicine
3. New insight on mechanism of action

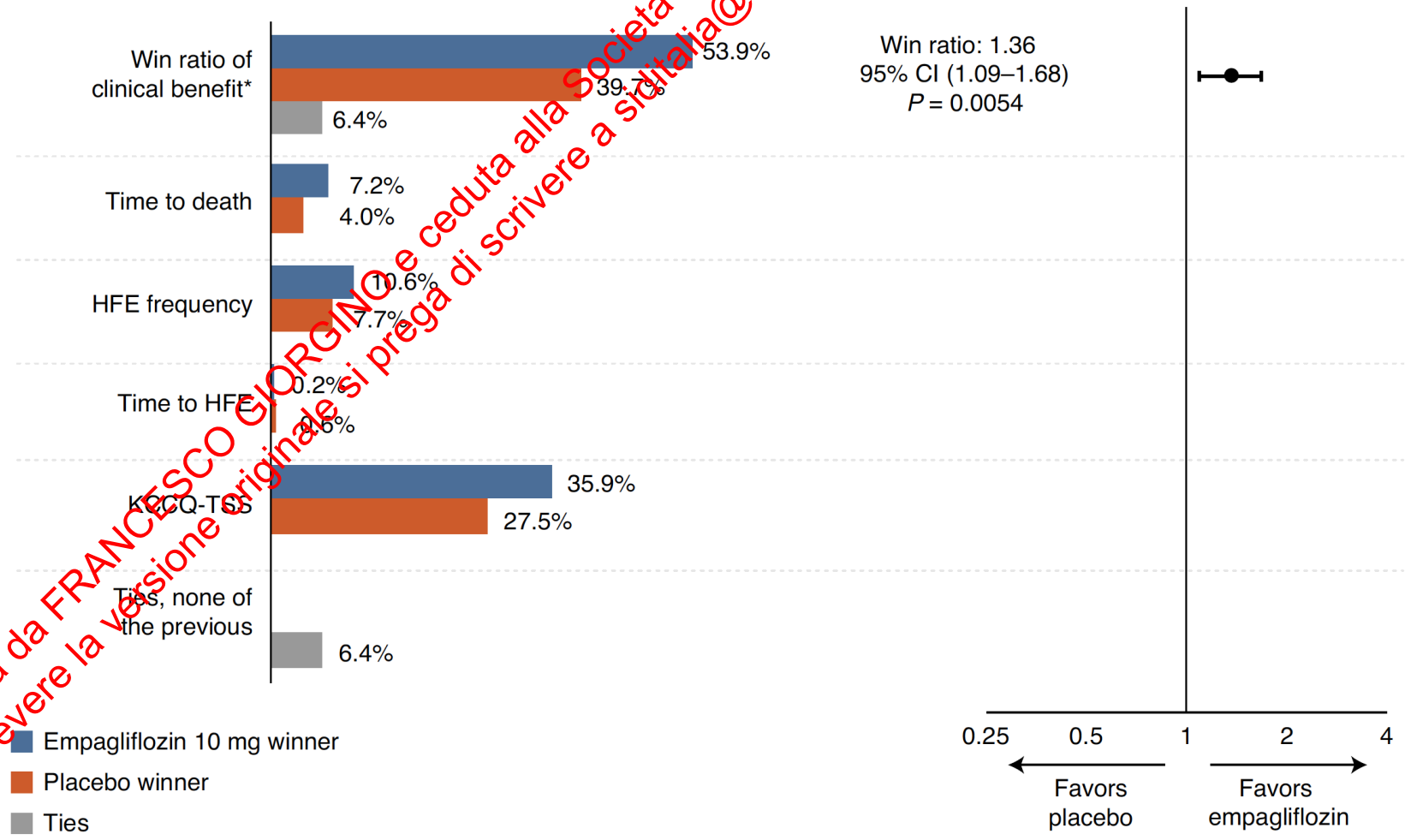
SGLT-2i and Renal Benefit

New Benefits of SGLT-2i

Effect of Empagliflozin in Patients Hospitalized for Acute HF

The EMPULSE Trial

- 530 patients with **acute** *de novo* or decompensated **HF**
- **HFrEF** and **HFpEF**
- Randomized **1:1 empagliflozin 10 mg vs placebo** when **clinically stable** (median time post hospital admission 3 days)
- Follow-up: **90 days**
- **Primary hierarchical composite outcome**: all-cause death + number of HFEs + time to first HFE + ≥5 points difference in KCCQ-TSS



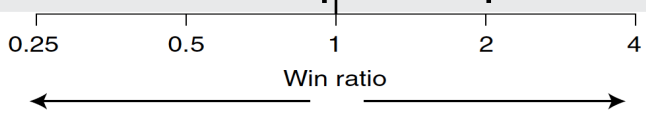
HF, heart failure; HFE, heart failure event; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score

Voors AA et al, *Nat Med* 2022

Effect of Empagliflozin in Patients Hospitalized for Acute HF

The EMPULSE Trial

Subgroup	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *P* value
	Number of patients			
All patients	265	265	1.36 (1.09–1.68)	
Heart failure status				0.7590
De novo	88	87	1.29 (0.89–1.89)	
Decompensated chronic	177	178	1.39 (1.07–1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07–2.02)	
Non-diabetic	141	149	1.30 (0.97–1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01–1.90)	
≥70 years	149	136	1.43 (1.06–1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06–1.81)	
Female	86	93	1.27 (0.88–1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34–1.30)	
Europe	168	171	1.59 (1.20–2.09)	
North America	66	69	1.32 (0.87–2.00)	
Baseline NT-proBNP (pg ml^{-1})				0.7904
<Median	125	130	1.36 (0.99–1.85)	
≥Median	130	126	1.44 (1.06–1.96)	
Baseline eGFR (CKD-EPI)				0.7562
≥60 ml min^{-1} 1.73 m^{-2}	88	106	1.48 (1.04–2.13)	
<60 ml min^{-1} 1.73 m^{-2}	161	145	1.38 (1.04–1.83)	
Atrial fibrillation or flutter at baseline				0.1129
No	123	133	1.68 (1.22–2.32)	
Yes	142	132	1.18 (0.88–1.59)	
Baseline LVEF (%)				0.9008
HFrEF (LVEF ≤40%)	182	172	1.35 (1.04–1.75)	
HFpEF (LVEF >40%)	76	93	1.39 (0.95–2.03)	



HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

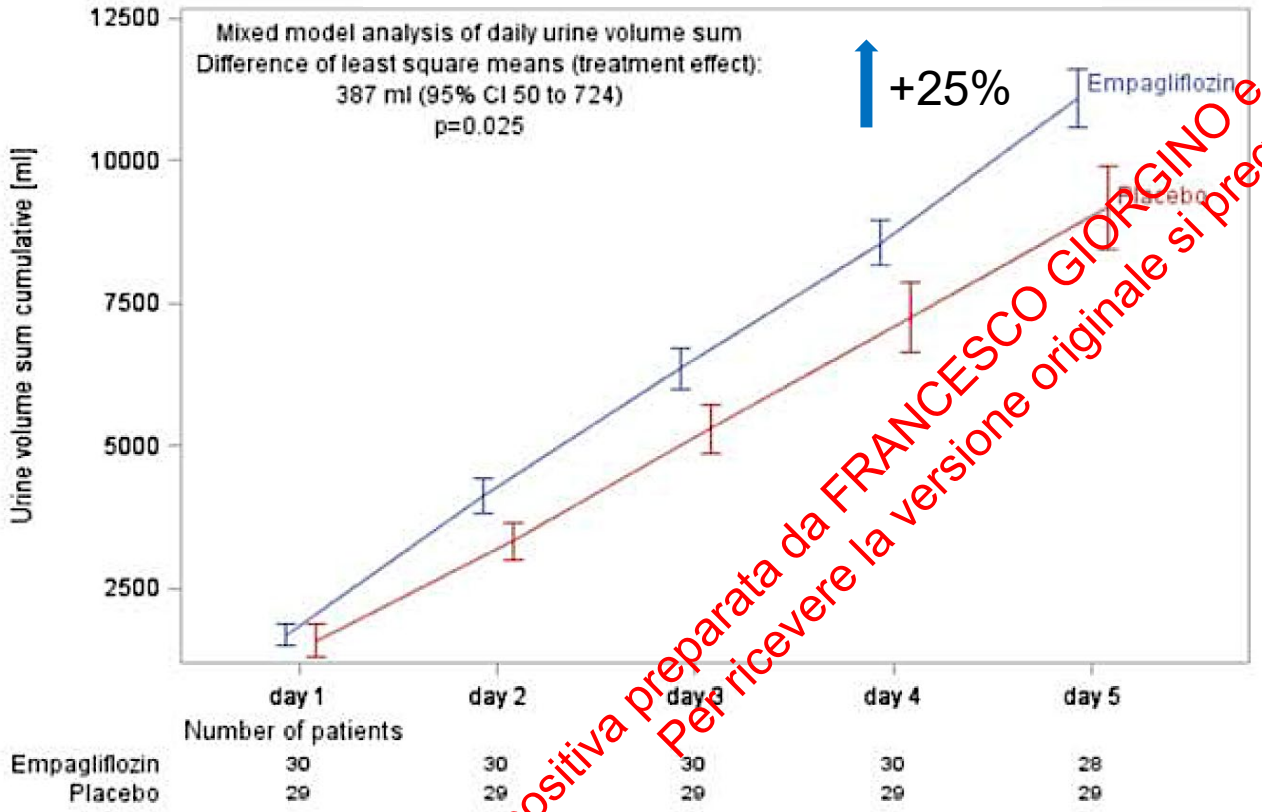
Voors AA et al, *Nat Med* 2022

Effect of Early Empagliflozin Initiation in Acute Decompensated HF

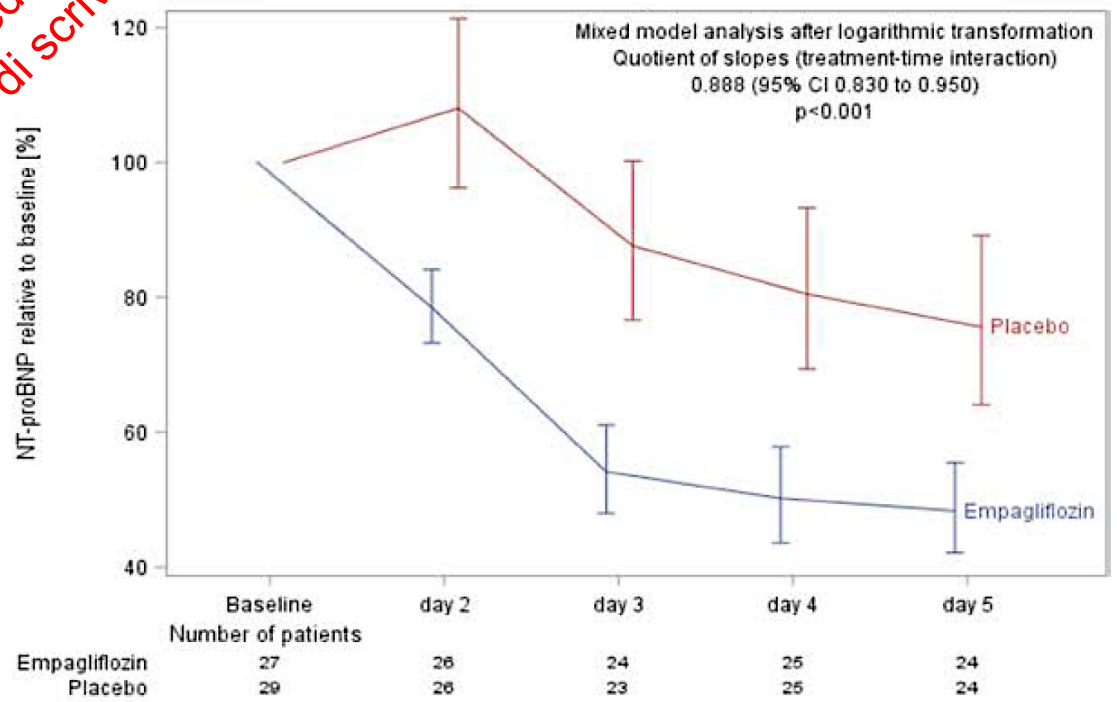
The EMPAG-HF Trial

- 60 patients with **acute decompensated HF**
- Randomized **1:1 empagliflozin 25 mg vs placebo within 12 hours of hospitalization**
- Follow-up: **5 days (with a 30 days extension)**
- Primary composite outcome: **cumulative urine volume in 5 days**

Cumulative Urine Volume



Dynamics in NT-proBNP



Schulze PC et al, *Circulation* 2022

HF, heart failure

Effect of Early Empagliflozin Initiation in Acute Decompensated HF

The EMPAG-HF Trial

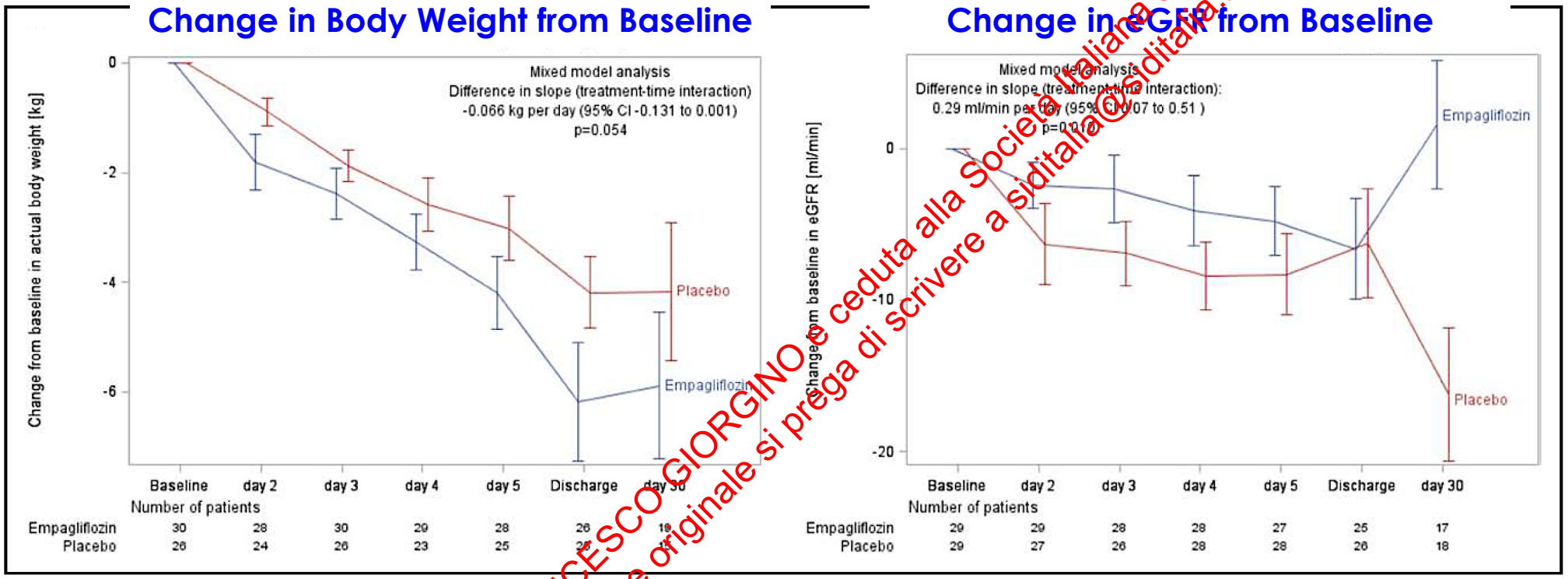


Figure 3. Secondary outcomes with extended 30-day follow-up.

A, Change in body weight from baseline in both groups. **B**, Dynamics in estimated glomerular filtration rate (eGFR) as change from baseline in both groups. Error bars represent SEM.

Outcomes	Empagliflozin	Placebo	Estimation of group difference* (95% CI)
Cumulative dose of diuretics (in milligrams furosemide equivalent)	313±194.6	351.4±220.7	−38.4 (−176.7 to 70.0)
Diuretic efficiency (mL/mg furosemide equivalent)	8.3 (−32.9 to 58.8)	−25.9 (−80.3 to 16.8)	43.7 (0.1 to 93)

Schulze PC et al, *Circulation* 2022

Effect of Early Empagliflozin Initiation in Acute Decompensated HF

The EMPAG-HF Trial

Table 4. Safety Events

Event	Empagliflozin	Placebo
Worsening heart failure	1 (3.3)	4 (13.8)
Worsening renal function (increase in serum creatinine ≥26.5 µmol/L [0.3 mg/dL])	3/26 (11.5)	9/28 (32.1)
Worsening liver function	0	0
Change in coagulation status at day 5	1/23 (4.3)	2/25 (8)
Urinary tract infection	1 (3.3)	4 (13.8)
Stroke or transient ischemic attack	1 (11.1)	0
30-day mortality	1 (3.3)	2 (6.9)

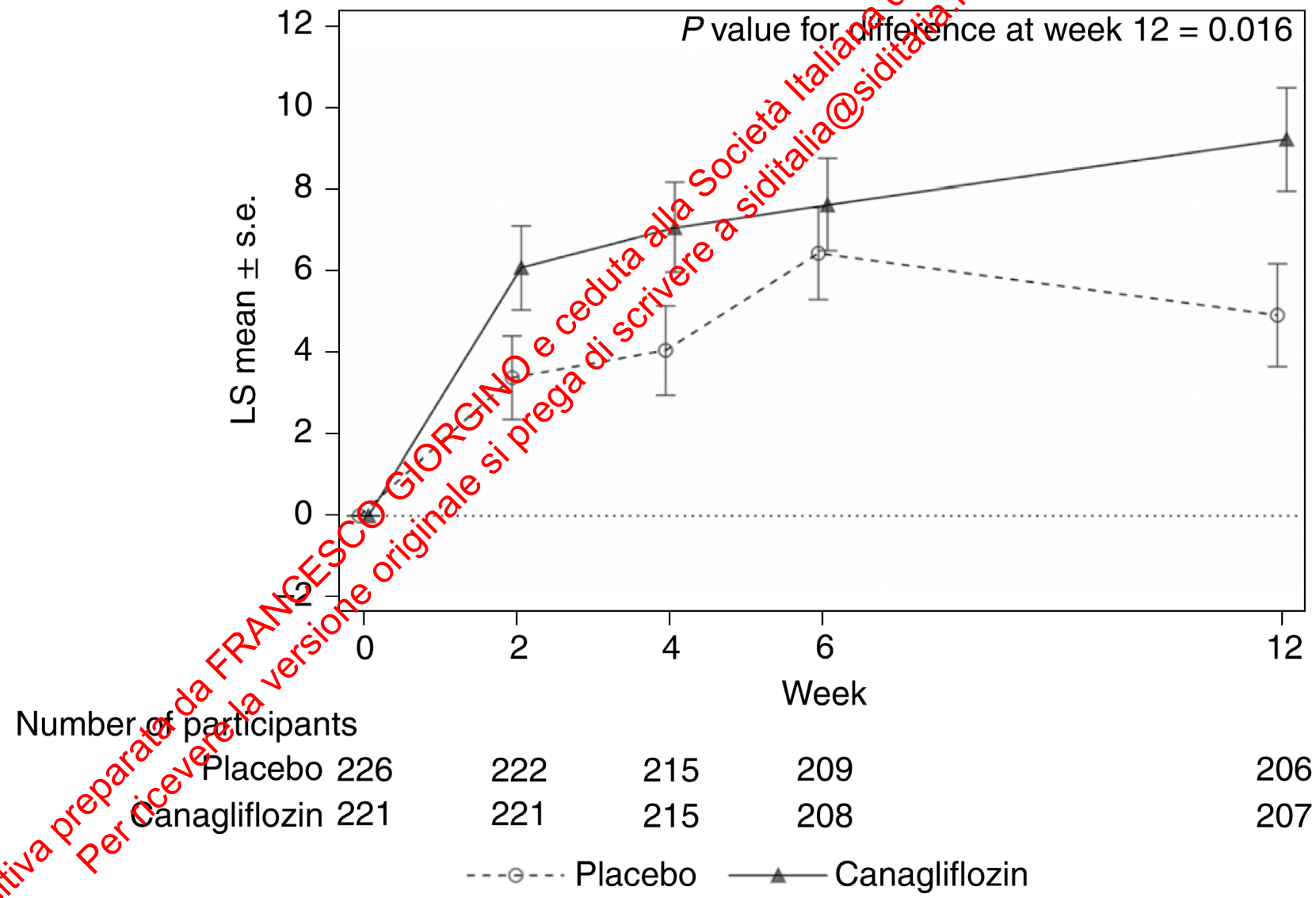
All data are expressed as n/total N (%).

Schulze PC et al, *Circulation* 2022

Canagliflozin Improves KCCQ Total Symptoms Score in Telemedicine

The CHIEF-HF Trial

Randomized, double-blind trial, without in-person interactions between doctor and patient: direct engagement of patients through a study website, electronic informed consent, direct home delivery of study medication, completion of the primary endpoint by a mobile application and a Fitbit to monitor activity



Spertus JA et al., *Nat Med* 2022

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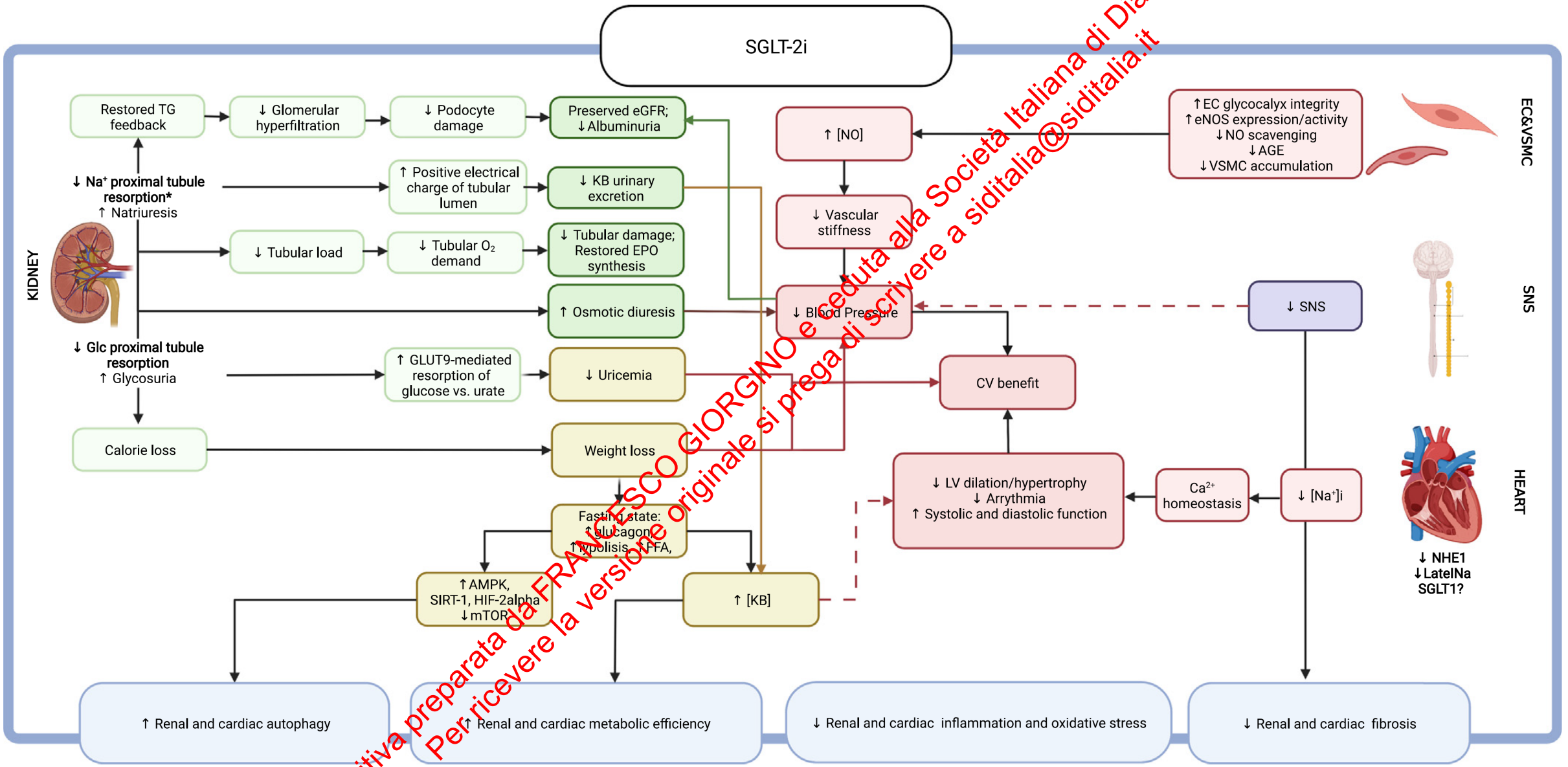
New Benefits of SGLT-2i

SGLT-2 Inhibitors as Cardio-Renal Protective Agents



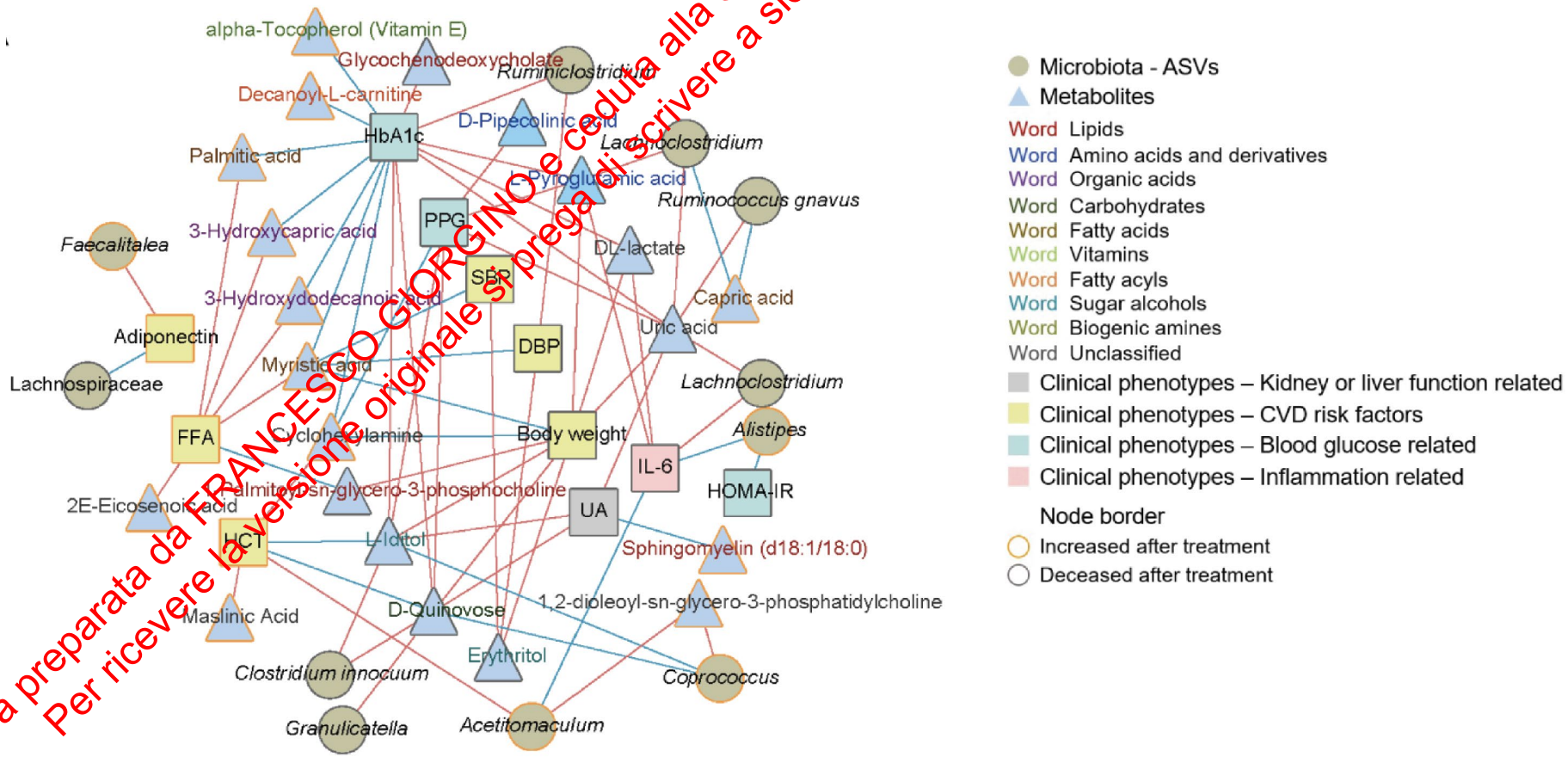
*Mediated by both SGLT-2 and NHE3 inhibition

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

Empagliflozin-mediated Benefits on the Cardiovascular Risk Profile Are Associated With Changes in Gut Microbiota and Plasma Metabolites

- 76 patients with **CV risk factors**
- Randomized, open-label: Empagliflozin 10 mg (n=40) vs Metformin 1700 mg/die (n=38)
- Follow-up: **3 months**
- Outcomes: **changes in clinical parameters related to glucose metabolism and CV risk, gut microbioma, plasma metabolites**

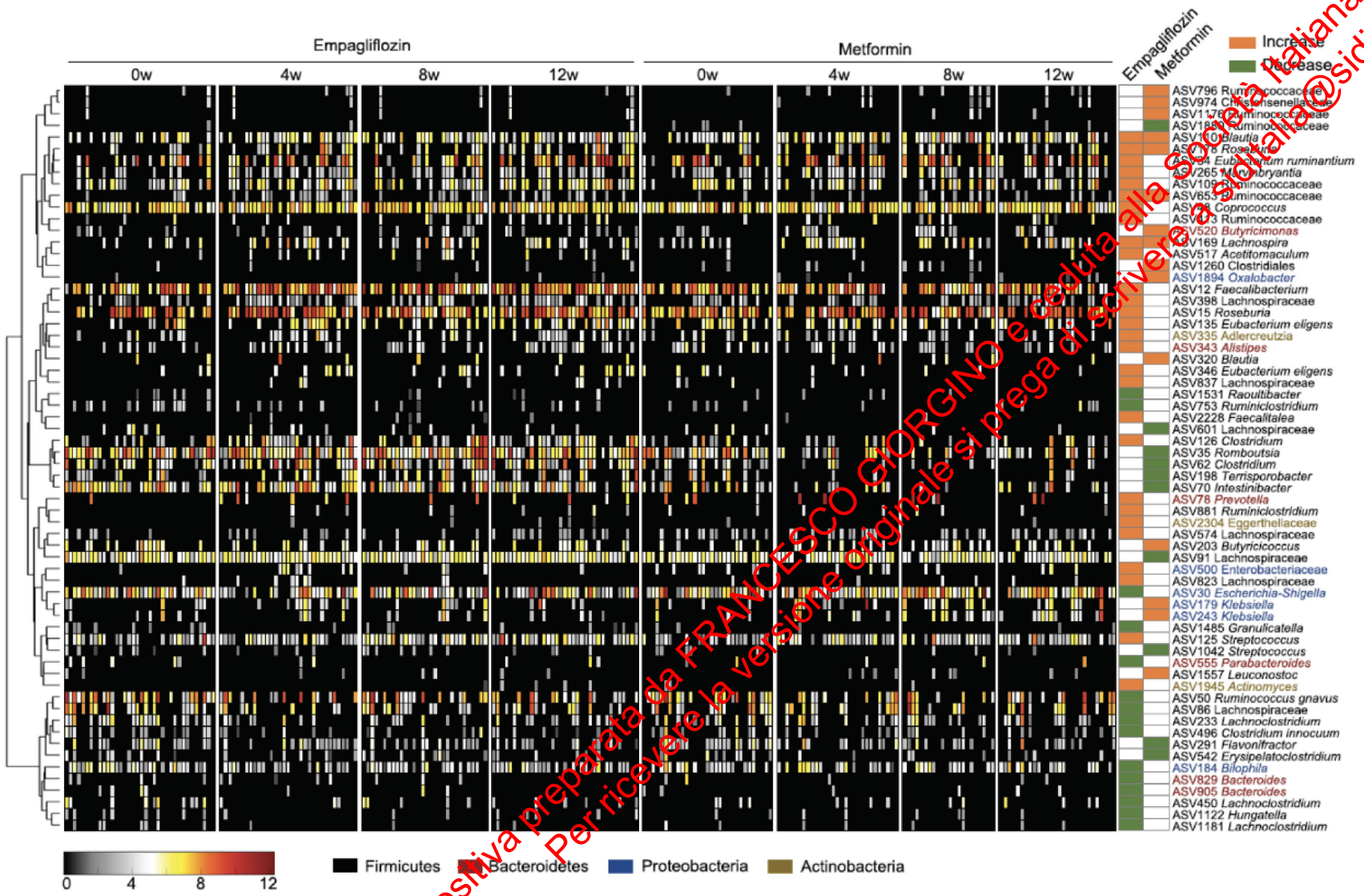
- ↑**Sphingomyelin**: prevent gut bacteria-derived LPS translocation reducing inflammation
- ↓**Glycochenodeoxycholate acid**: may reduce insulin-resistance and hepatic steatosis
- ↓**Uric acid**: may reduce risk of hypertension, HF, CV and all cause-death



Red connections - positive correlation (FDR < 0.05); blue connections - negative correlations (FDR < 0.05).
ASVs, amplicon sequence variants; CV; cardiovascular; LPS, lipopolysaccharide; DBP, diastolic blood pressure; FFA, free fatty acid; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6; PPG, postprandial plasma glucose; SBP, systolic blood pressure; UA, uric acid.

Deng X et al, *J Clin Endocrinol Metab* 2022

Empagliflozin-mediated Benefits on the Cardiovascular Risk Profile Are Associated With Changes in Gut Microbiota and Plasma Metabolites



- **↑SCFA-producing bacteria (e.g. Roseburia, Faecalibacterium)**:
  - ↑ Glycaemic control
  - ↓ Inflammation
  - ↓ Tumorigenesis
  - ↓ Oxidative stress
- **↓Gram negative harmful bacteria (e.g. Escherichia-Shigella)**:
  - ↑ Inflammation
  - ↑ Gut barrier disruption

SCFA, short chain fatty acids

Deng X et al, *J Clin Endocrinol Metab* 2022

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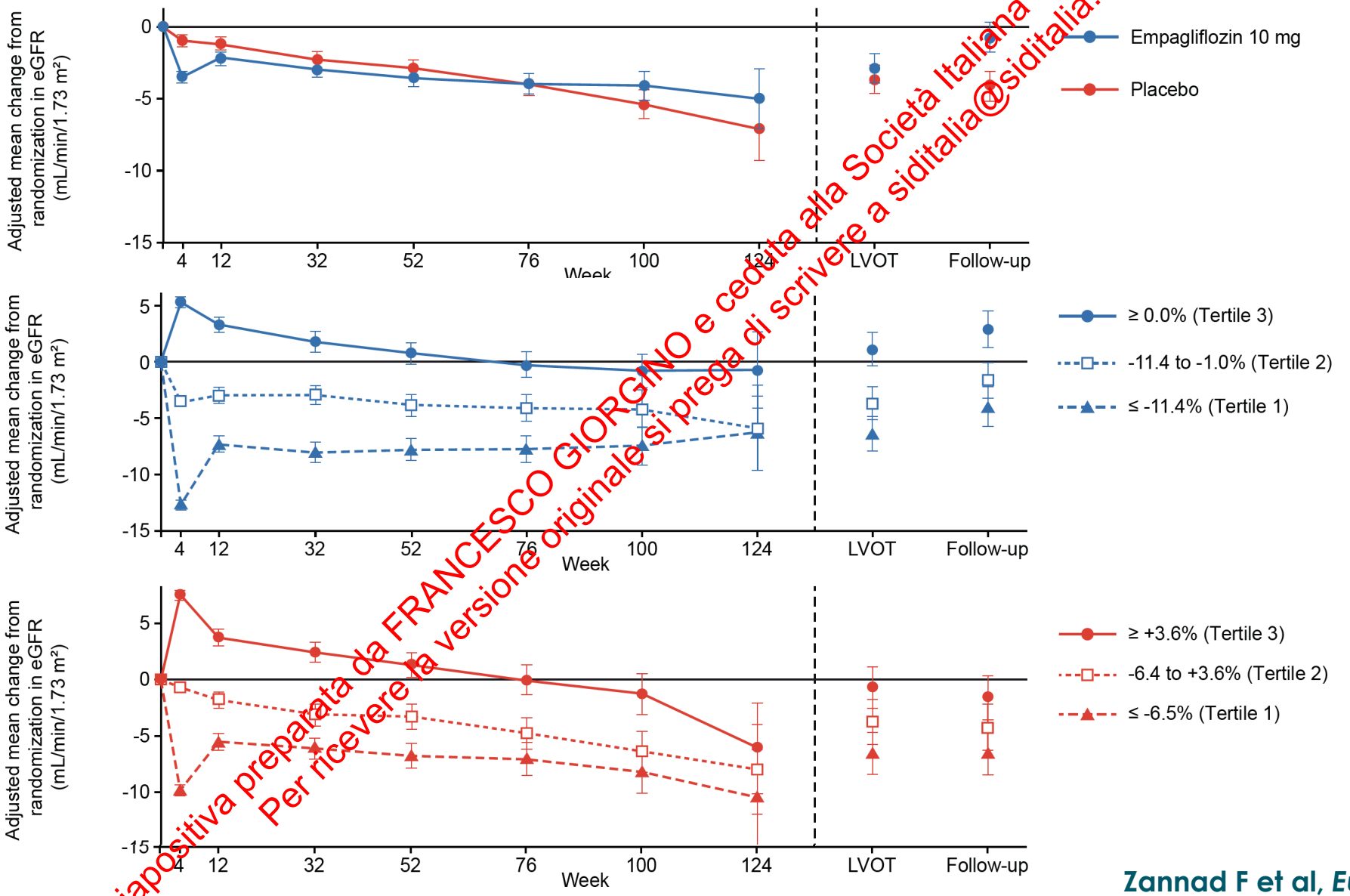
1. Implications of the early eGFR “dip” with SGLT-2i treatment
2. Additional renal benefits
3. New associations

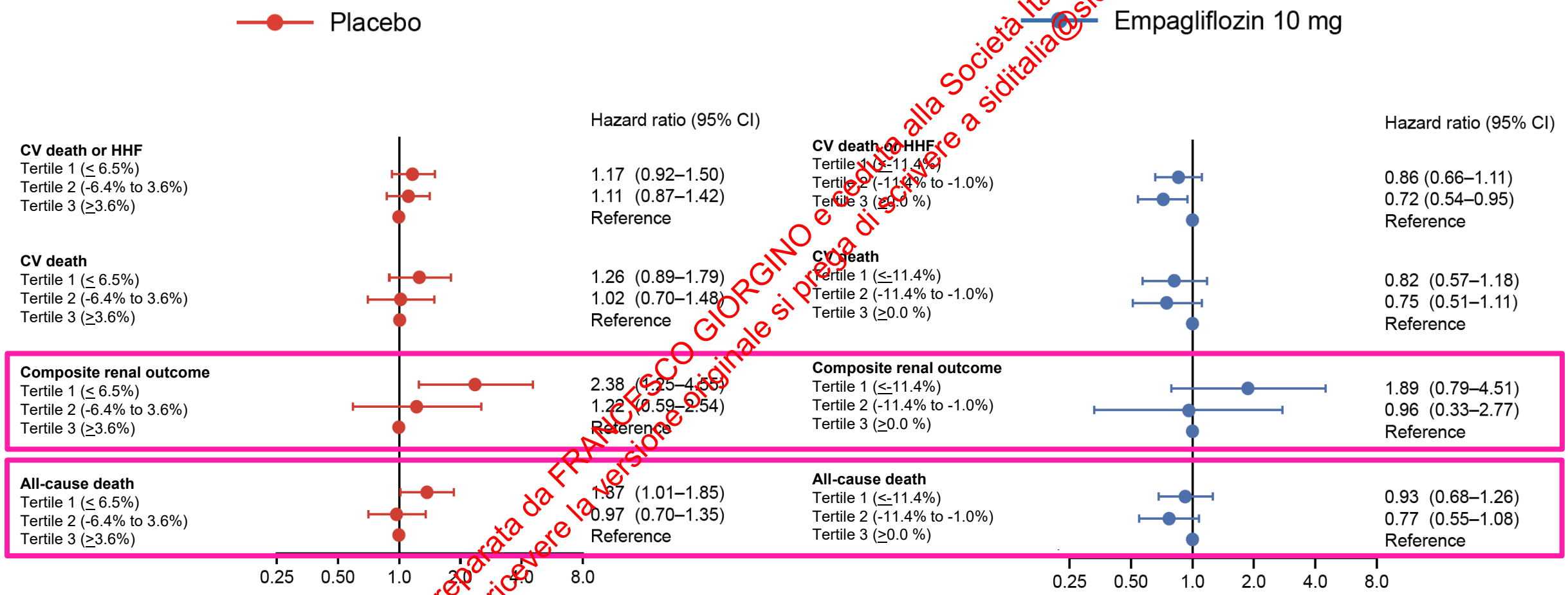
New Benefits of SGLT-2i

Early eGFR Changes in EMPEROR-Reduced and Risk of Worsening Kidney Function and All-Cause Mortality in Empagliflozin vs. Placebo



Zannad F et al, *Eur J Heart Fail* 2022

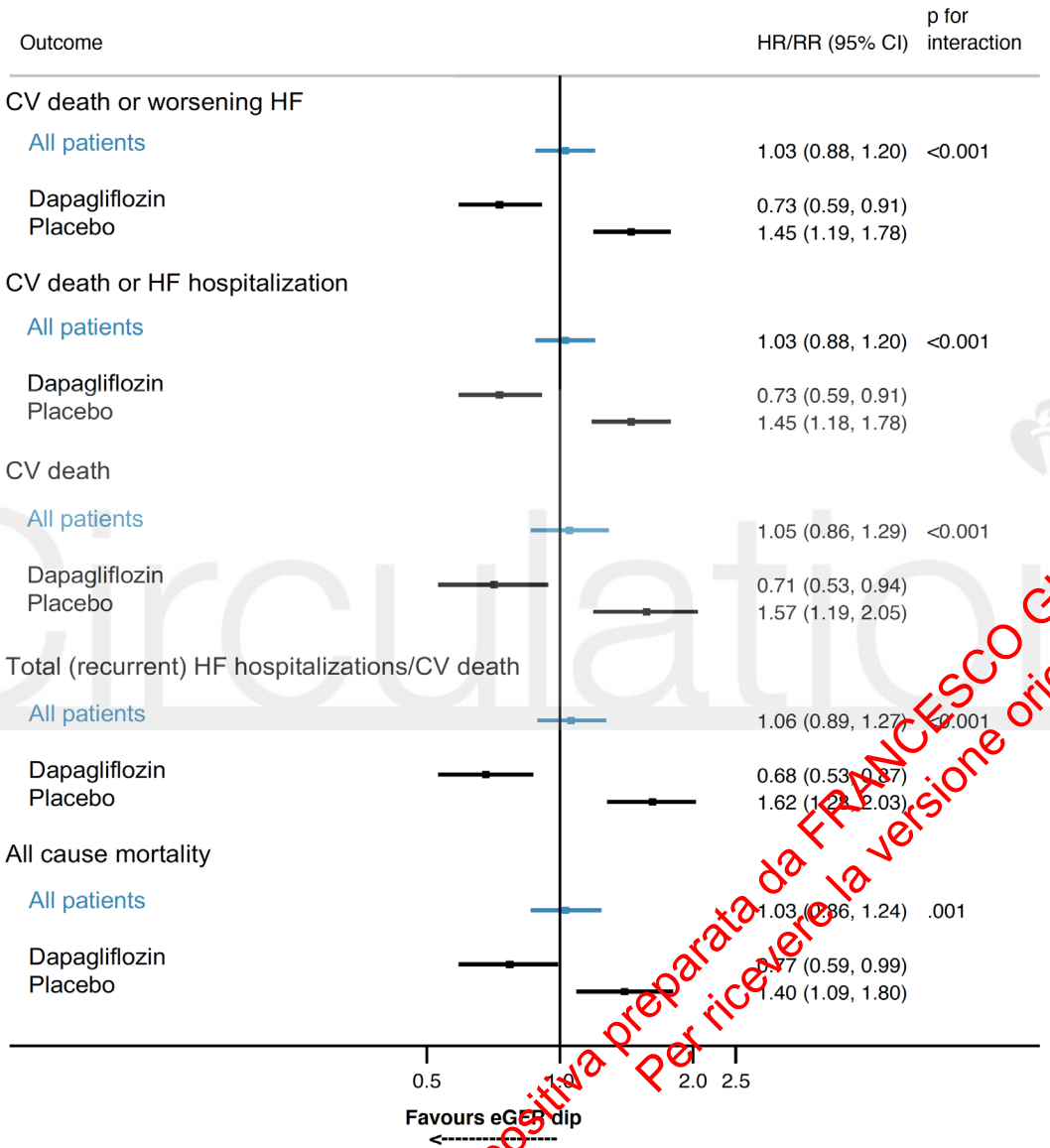
Early eGFR Changes in EMPEROR-Reduced and Risk of Worsening Kidney Function and All-Cause Mortality in Empagliflozin vs. Placebo

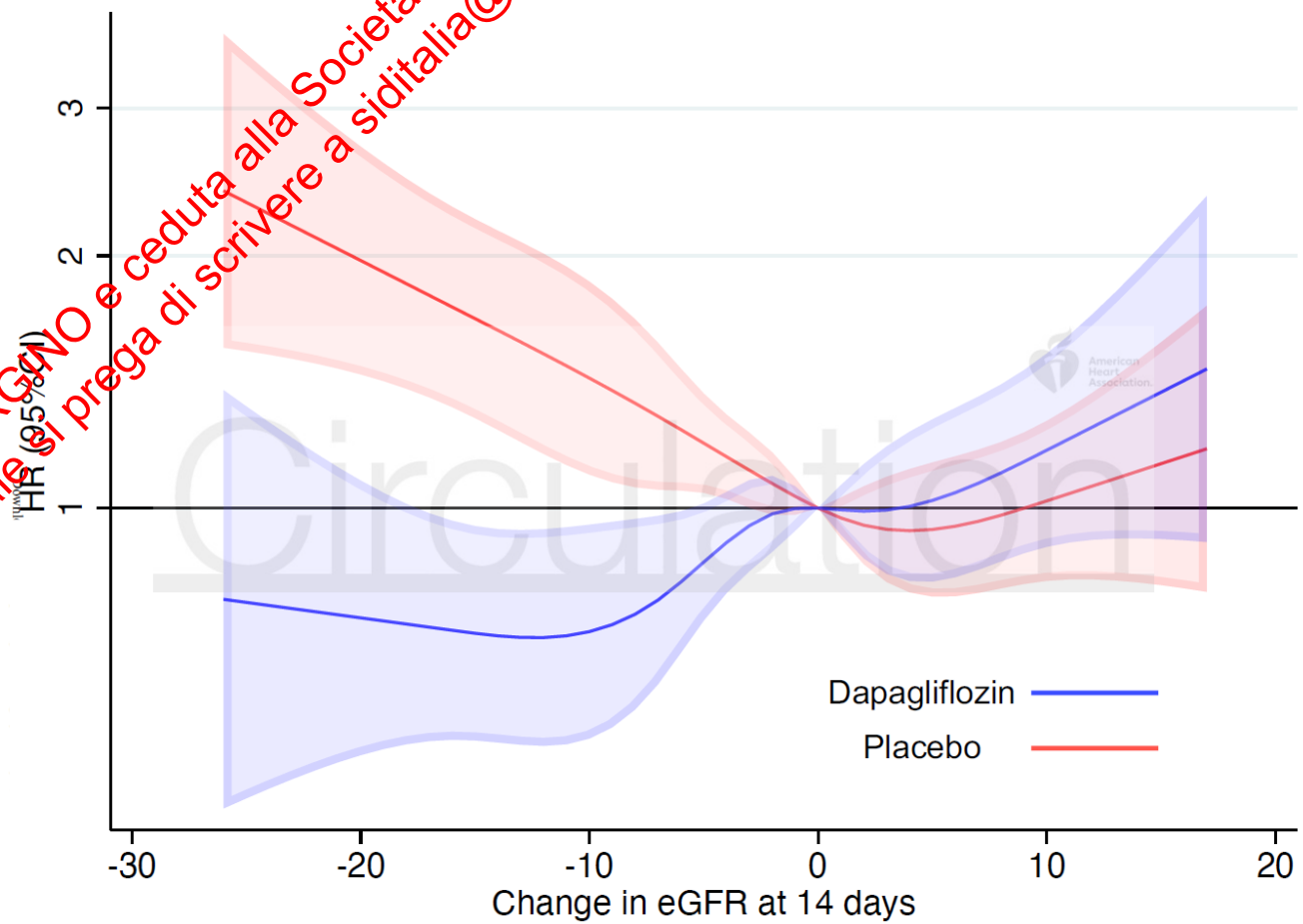


CV, cardiovascular; HHF, hospitalization for heart failure

modified from **Zannad F et al, *Eur J Heart Fail* 2022**

Early eGFR Decline in DAPA-HF is Associated with Better CV Outcomes in Patients on Dapagliflozin vs. Placebo





CV, cardiovascular; HF, heart failure

Adamson C et al, *Circulation* 2022

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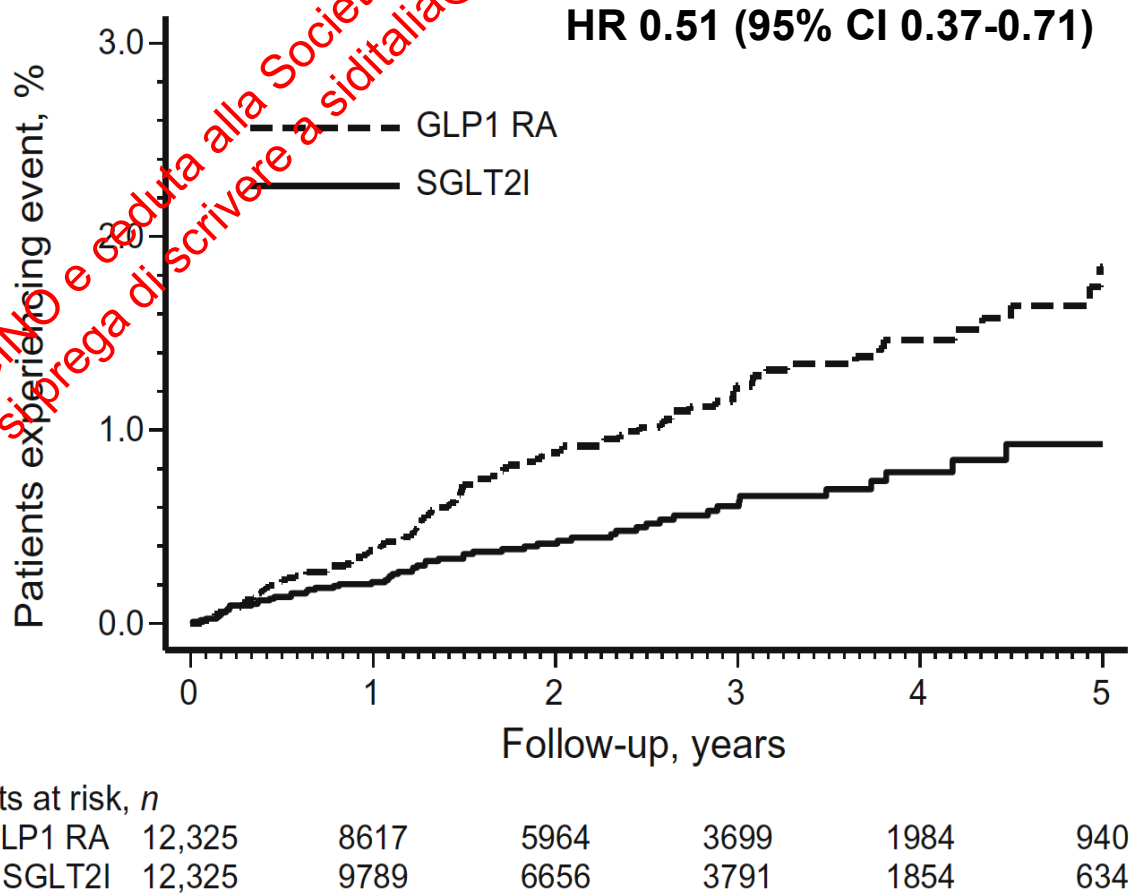
New Benefits of SGLT-2i

SGLT-2i May Reduce the Risk of Nephrolithiasis

- Nationwide, active-comparator new-user cohort study
- 12 325 matched SGLT-2i and GLP-1RA new users
- Median follow-up: 2 years

	SGLT2I	GLP1 RA
Sensitivity analysis with recurrent nephrolithiasis as outcome		
Patients, *n*	731	731
Events (*n*)	54	74
Person time, years	1485	1386
Rate per 1000 person-years (95% CI)	36.4 (27.8, 47.5)	53.4 (42.5, 67.0)
Rate difference per 1000 person-years (95% CI)	−17.0 (−32.6, −1.3)	
HR (95% CI)	0.68 (0.48, 0.97)	



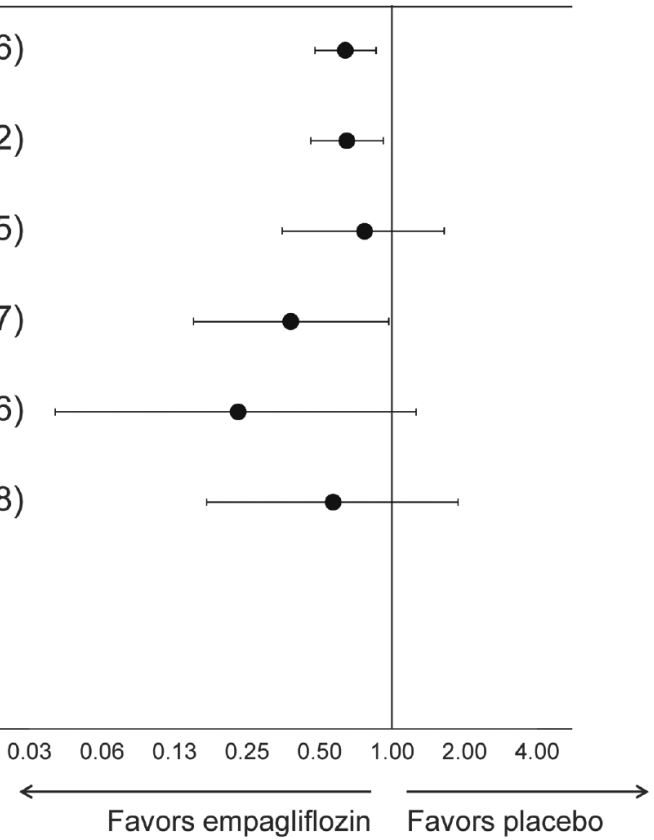
SGLT-2i, sodium-glucose transporter-2 inhibitors; GLP-1RA, GLP-1 receptor agonists

Kristensen KB et al, *Diabetologia* 2021

SGLT-2i May Reduce the Risk of Nephrolithiasis

Pooled data from 15 081 type 2 diabetic patients randomized to empagliflozin or placebo in 20 phase I-IV trials

	Empagliflozin		Placebo		Incidence rate ratio (95% CI)
	n with events/ N analyzed	Rate/ 100pt-yrs (95% CI)	n with events/ N analyzed	Rate/ 100pt-yrs (95% CI)	
Urinary tract lithiasis (all preferred terms)	104/10177	0.63 (0.51, 0.76)	79/4904	1.01 (0.80, 1.25)	0.64 (0.48, 0.86)
Nephrolithiasis	75/10177	0.45 (0.36, 0.57)	57/4904	0.72 (0.55, 0.94)	0.65 (0.46, 0.92)
Renal colic	16/10177	0.10 (0.05, 0.16)	10/4904	0.13 (0.06, 0.23)	0.77 (0.35, 1.65)
Ureterolithiasis	8/10177	0.05 (0.02, 0.09)	10/4904	0.13 (0.06, 0.23)	0.38 (0.15, 0.97)
Calculus bladder	2/10177	0.01 (0.00, 0.04)	4/4904	0.05 (0.01, 0.13)	0.23 (0.04, 1.26)
Calculus urinary	6/10177	0.04 (0.01, 0.08)	5/4904	0.06 (0.02, 0.15)	0.57 (0.17, 1.88)
Calculus urethral	1/10177	0.01 (0.00, 0.03)	0/4904		-
Nephrocalcinosis	2/10177	0.01 (0.00, 0.04)	0/4904		-



Balasubramanian P et al., *J Clin Endocrinol Metab* 2022

SGLT-2i and Cardiovascular Benefit

1. SGLT-2i in specific populations: HFrEF, HFpEF, non-diabetic, elderly
2. SGLT-2i in special settings: in-patient care, telemedicine
3. New insight on mechanism of action

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New Benefits of SGLT-2i

Design of the COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using an UACR Endpoint study (CONFIDENCE)

Background

Both finerenone (nonsteroidal MRA) and empagliflozin (SGLT2i) can reduce kidney and cardiovascular events in people with CKD and T2D.

CONFIDENCE (NCT05254002) investigates whether dual therapy with finerenone and empagliflozin is superior to either agent alone in reducing albuminuria.

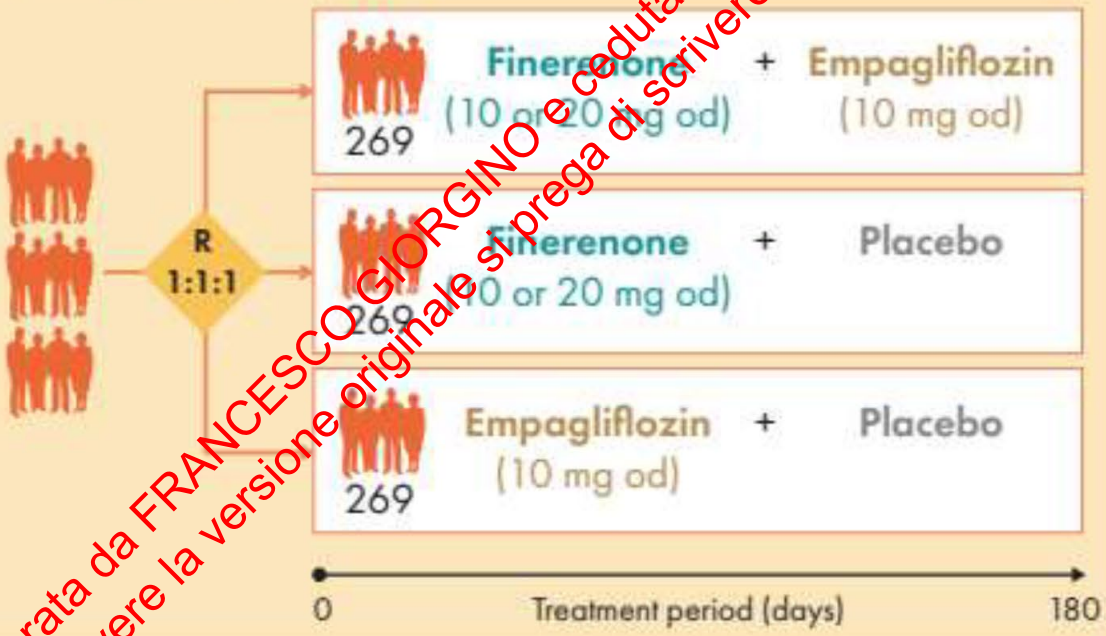
Participants

- 807 participants
- 125 centres
- 13 countries

✓
- ≥ 18 years
- T2D, CKD stage 2–3
- UACR ≥ 300 to < 5000 mg/g

✗
- T1D
- Serum K^+ > 4.8 mmol/L
- Treatment with SGLT1/2i or MRA

Treatment arms



Primary outcomes

Relative change in UACR from baseline to 180 days in:

Dual therapy vs. Finerenone

Dual therapy vs. Empagliflozin

Conclusion

Should an additive effect be shown, early and efficient intervention with dual finerenone and SGLT2i therapy could slow disease progression and provide long-term benefits for people with CKD and T2D.

Green JB, *Nephrol Dial Transplant* 2022

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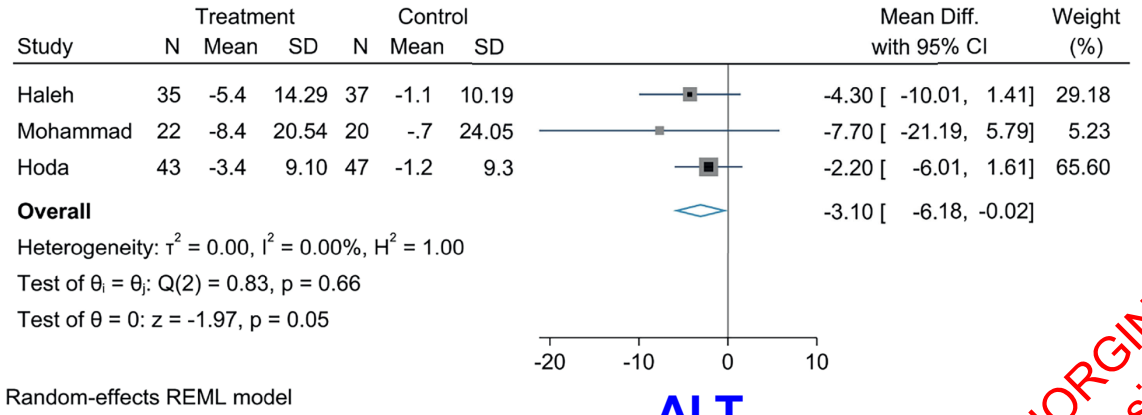
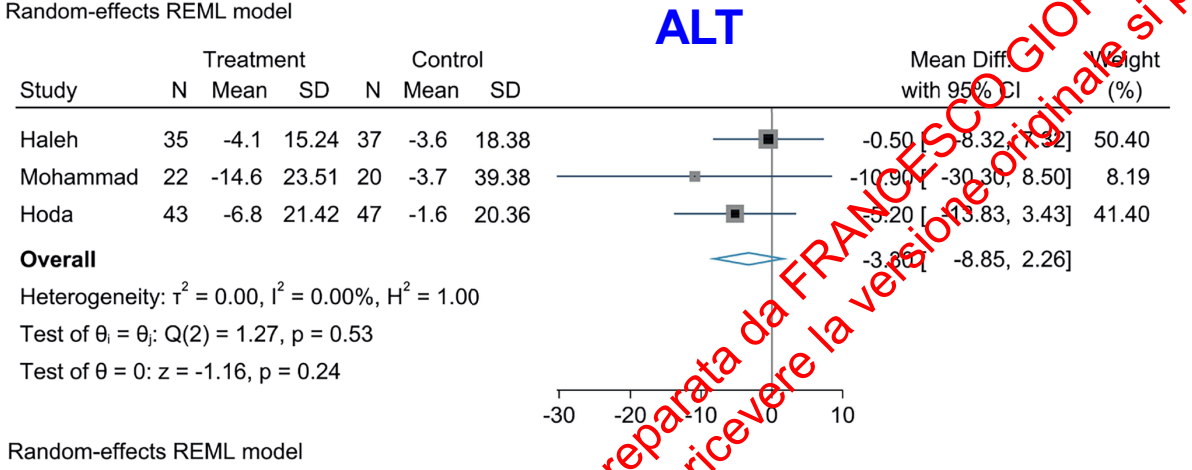
Efficacy of Empagliflozin on NAFLD: a Meta-Analysis

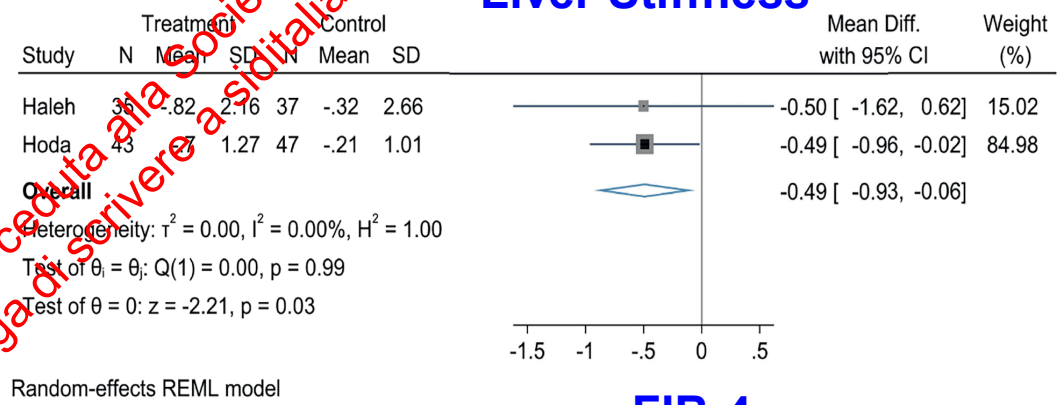
AST



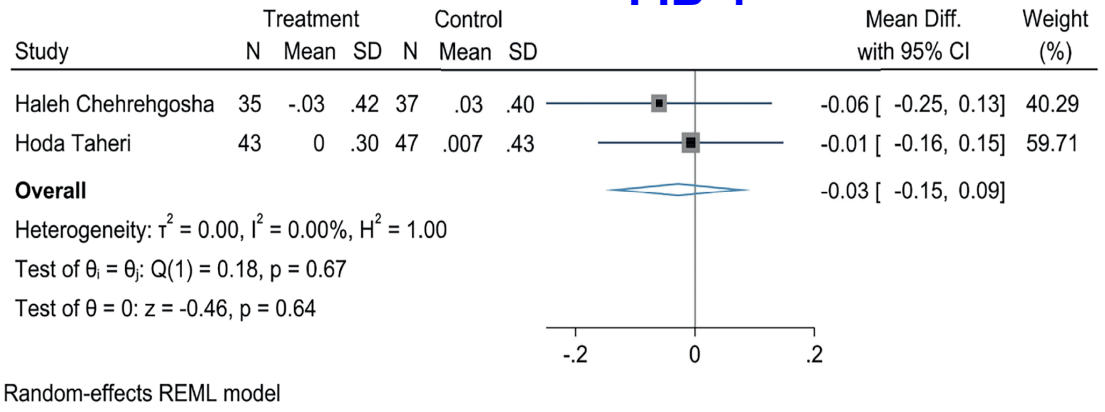
ALT



Liver Stiffness



FIB-4

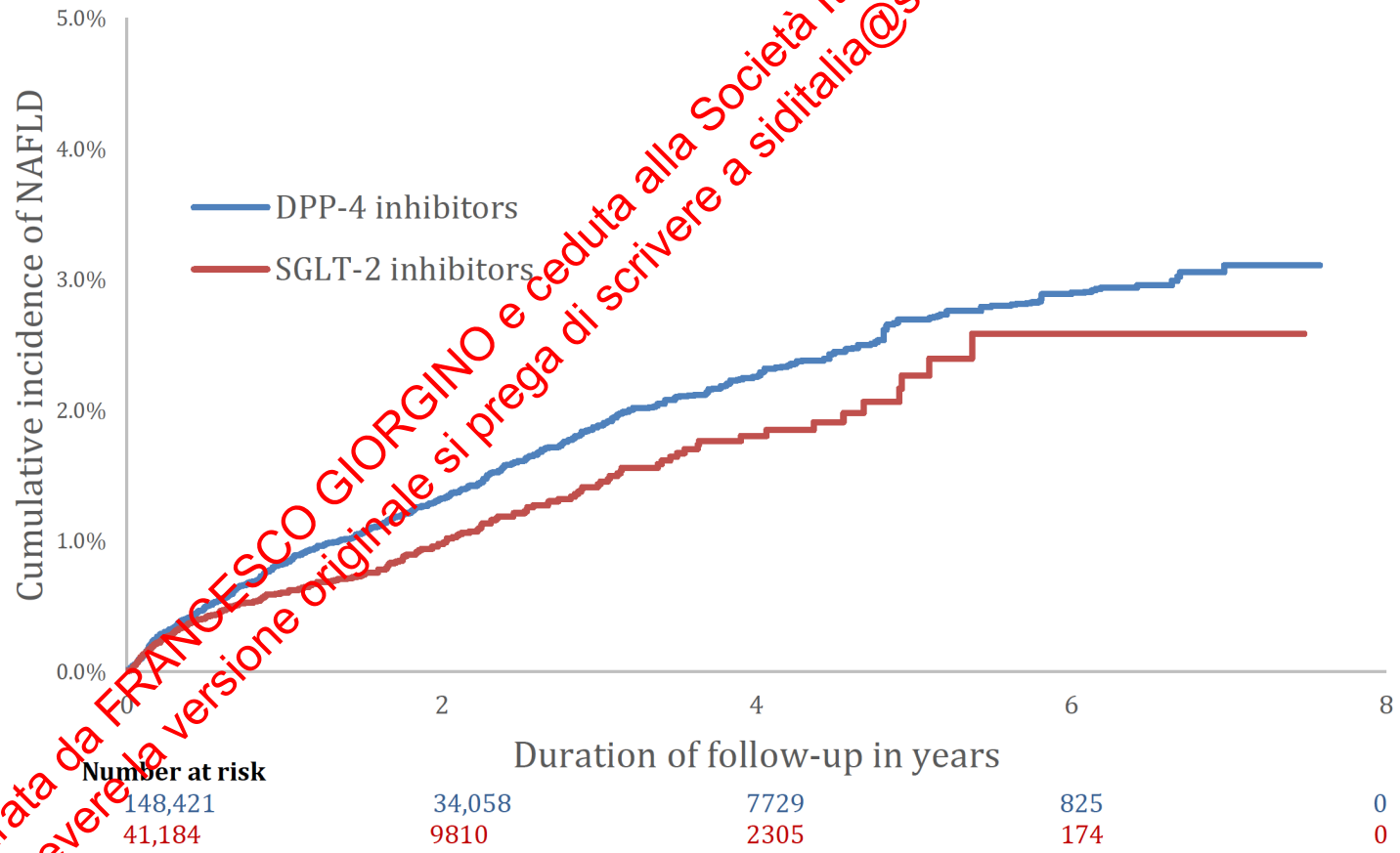


FIB-4, fibrosis-4 index; NAFLD, non-alcoholic fatty liver disease

Zhang Y et al, *Front Endocrinol* 2022

Treatment with SGLT-2i vs. DPP-4i is Associated with Reduced Incidence of NAFLD

- UK Clinical Practice Research Datalink
- 41184 and 148421 new users of SGLT-2i and DPP-4i
- SGLT-2i were associated with a decreased risk of NAFLD (HR 0.78, 95% CI 0.68-0.89)



Pradhan R et al, *Diabetes Care* 2022

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Empagliflozin Mitigates Peripheral Diabetic Neuropathy through a Glucose-Independent AMPK-Mediated Signaling

- 112 rats were allocated into 4 groups: control, STZ-induced diabetes, STZ-induced diabetes + EMPA, STZ-induced diabetes + EMPA + AMPK inhibitor dorsomorphin (15 days of treatment)
- **Diabetic Peripheral Neuropathy** was elicited by single intraperitoneal injections of freshly prepared STZ and nicotinamide

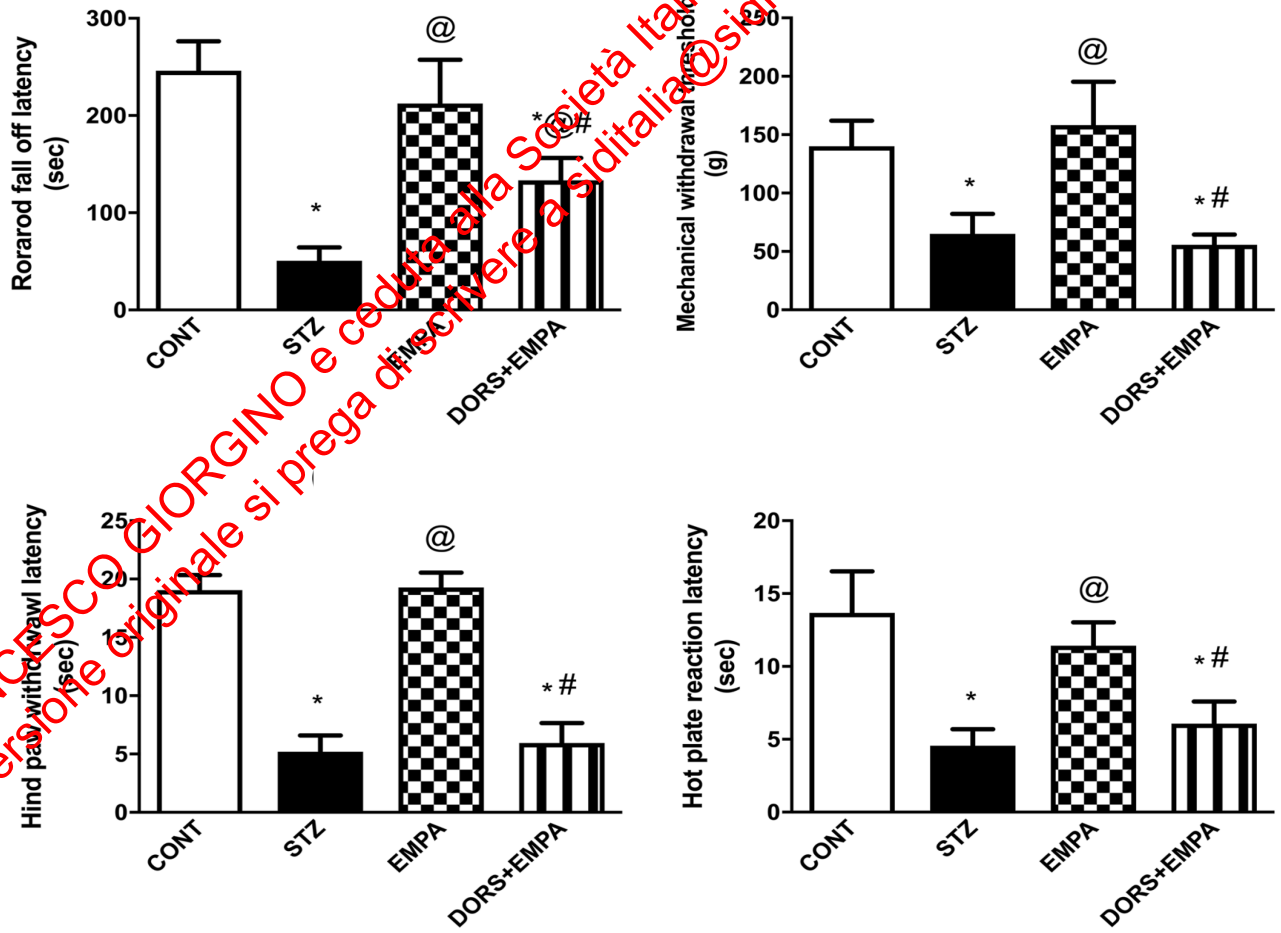
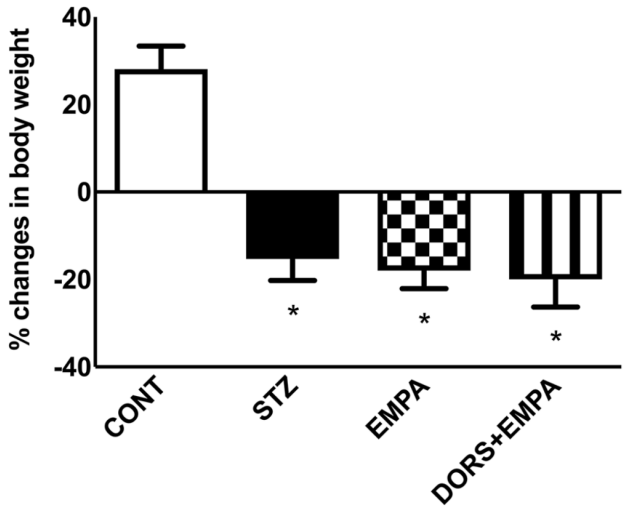


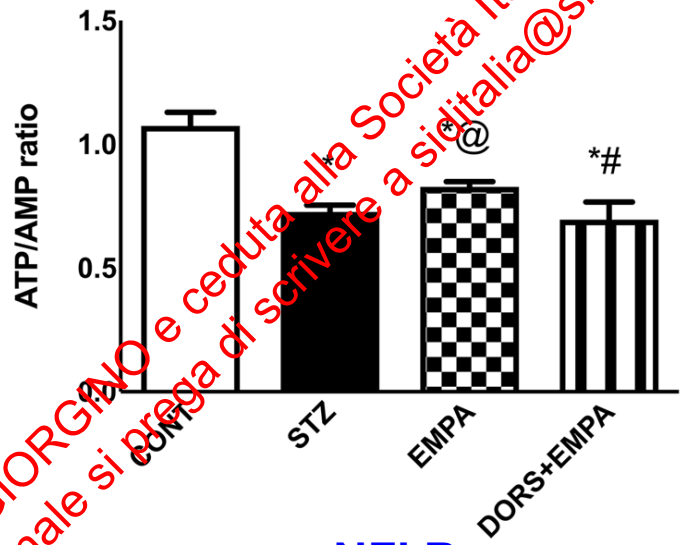
Fig. 3 Effect of EMPA on motor and sensory performance in STZ-induced DPN in rats. Panels represent: (**a**) rotarod fall-off latency, (**b**) Randell-Selitto mechanical withdrawal threshold, (**c**) cold allodynia hind paw withdrawal latency, and (**d**) hot plate reaction latency. Every bar with a vertical line displays the mean ± SD (n = 8-10). (*) vs CONT, (@) vs STZ, (#) vs EMPA; $P < 0.05$. CONT: control; DPN: diabetic peripheral neuropathy; DORS: dorsomorphin; EMPA: empagliflozin; STZ: streptozotocin

Abdelkader NF et al, *Arch Pharm Res* 2022

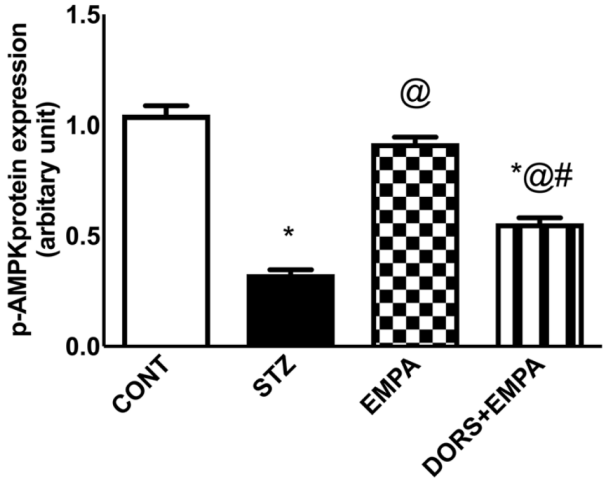
Empagliflozin Mitigates Peripheral Diabetic Neuropathy through a Glucose-Independent AMPK-Mediated Signaling

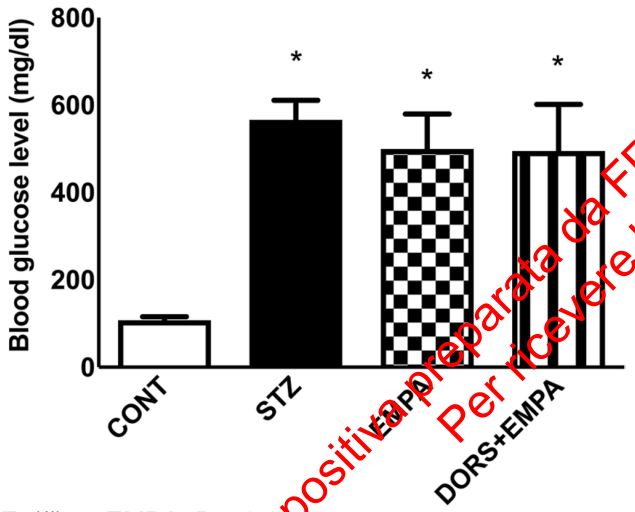


↑ATP/AMP ratio

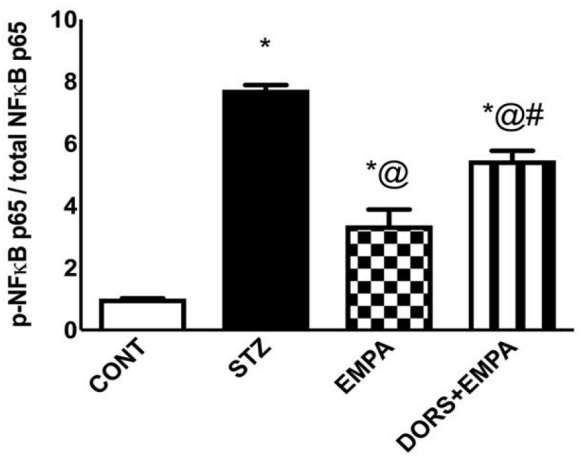


↑ph-AMPK

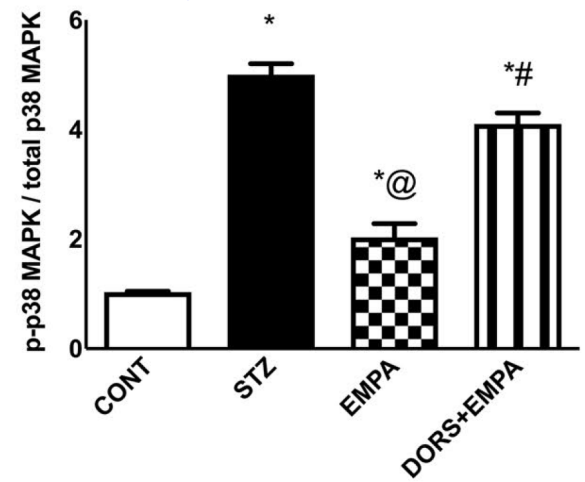




↓NFkB



↓ph-38 MAPK



(*) vs CONT, (@) vs STZ, (#) vs EMPA; P < 0.05

CONT: control; DPN: diabetic peripheral neuropathy; DORS: dorsomorphin; EMPA: empagliflozin; STZ: streptozotocin; ph-, phospho

Abdelkader NF, *Arch Pharm Res* 2022

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Neuroprotective Effect of SGLT-2 Inhibitors

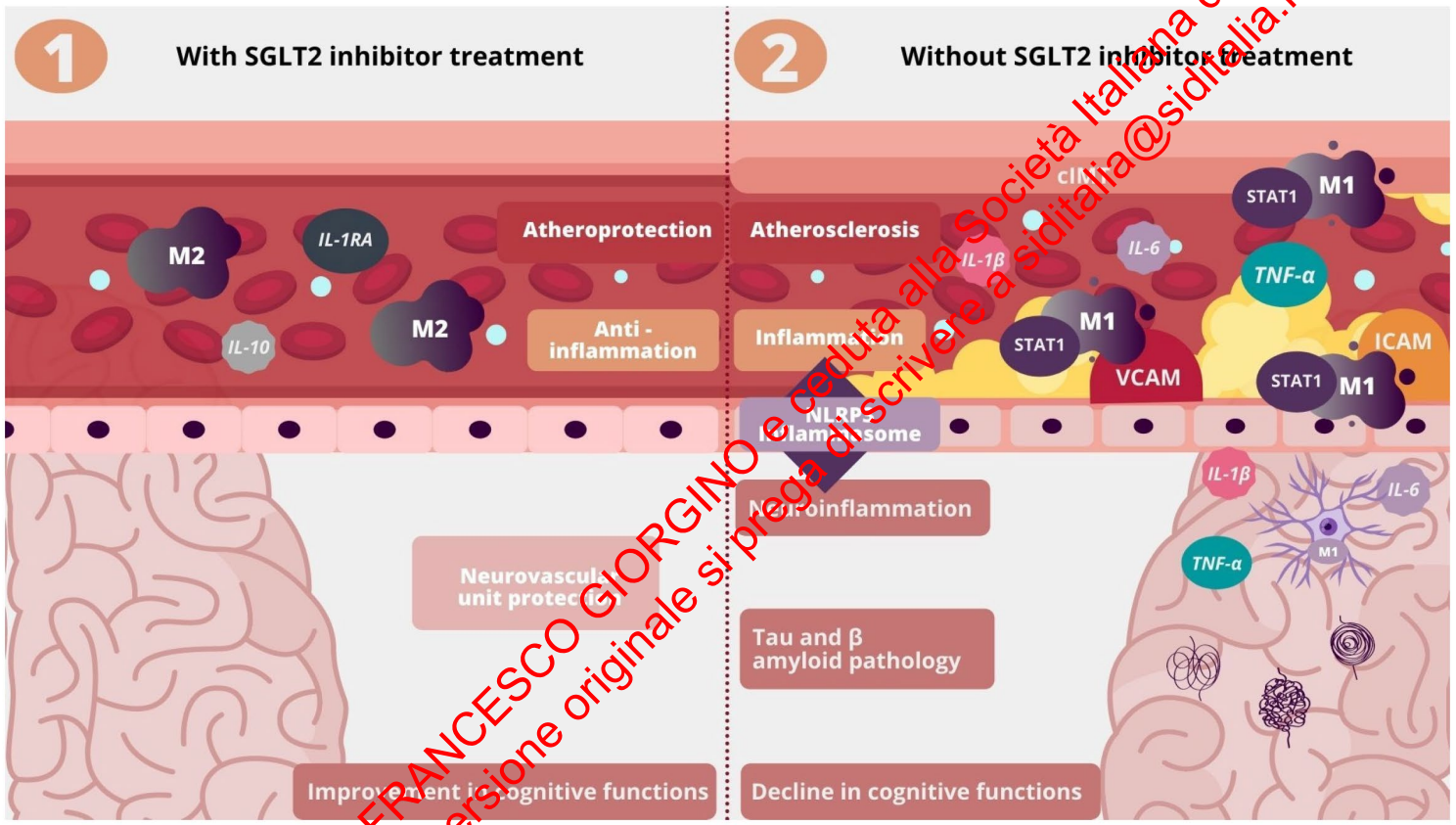

Figure 2. Influence of SGLT2 inhibitors on inflammation, atherosclerosis, and neuroinflammation. IL-1RA—Interleukin 1 Receptor Agonist, cIMT—carotid intima-media thickness, STAT1—Signal transducer and activator of transcription 1, VCAM—Vascular Cell Adhesion Molecule; ICAM-Intracellular Adhesion Molecule.

Pawlos A et al., *Molecules* 2022

J Alzheimers Dis. 2022;87(2):635-642. doi: 10.3233/JAD-215678.

Association Between Use of Sodium–Glucose Co-Transporter–2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal Study of Patients with Type 2 Diabetes

Serena Low [1 2 3], Kiat Sern Goh [4], Tze Pin Ng [5], Angela Moh [2], Su Fen Ang [2], Jiexun Wang [2], Keven Ang [2], Wern Ee Tang [6], Ziliang Lim [6], Tavintharan Subramaniam [1], Chee Fang Sum [1], Su Chi Lim [1 2 3 7]

Results: There were 138 patients (29.0%) on SGLT2i, including 84 (17.7%) for < 3 years and 54 (11.3%) for ≥3 years. SGLT2i use was positively associated with RBANS total score increase in language (coefficient 0.60; 95% CI 0.10–1.11; p = 0.019) in unadjusted analysis. This positive association persisted in fully adjusted model (coefficient 0.74; 95% CI 0.12 to 1.36; p = 0.019). SGLT2i use for ≥3 years was positively associated with RBANS score increase globally and in language domain in fully adjusted analysis with coefficients 0.54 (95% CI 0.13 to 0.95; p = 0.010) and 1.12 (95% CI 0.27 to 1.97; p = 0.010) respectively.

Conclusion: Our findings revealed a previously unobserved association between ≥3 years SGLT2i use and improved cognitive scores globally and in language domain and executive function. Future studies should investigate the role of SGLT2i in ameliorating cognitive decline.

Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction

Pasquale Mone,[1,2,3] Angela Lombardi,[1] Jessica Gambardella,[1,4] Antonella Pansini,[2] Gaetano Macina,[2] Maria Morgante,[2] Salvatore Frullone,[2] and Gaetano Santulli[1,4,5]

Diabetes Care 2022;45:1247–1251 | https://doi.org/10.2337/dc21-2434

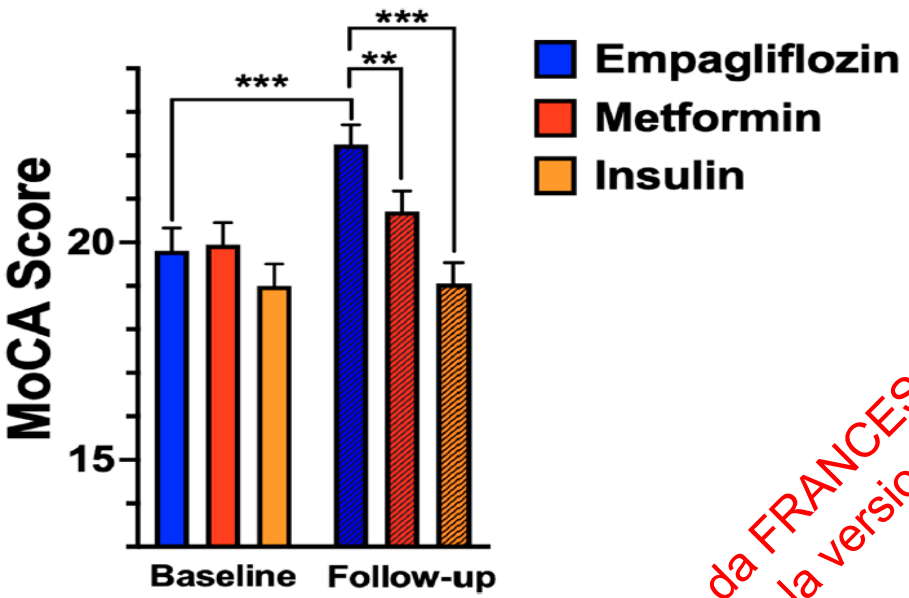

Figure 1—MoCA score in the empagliflozin, metformin, and insulin groups evaluated at baseline and follow-up. Data are means ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$.

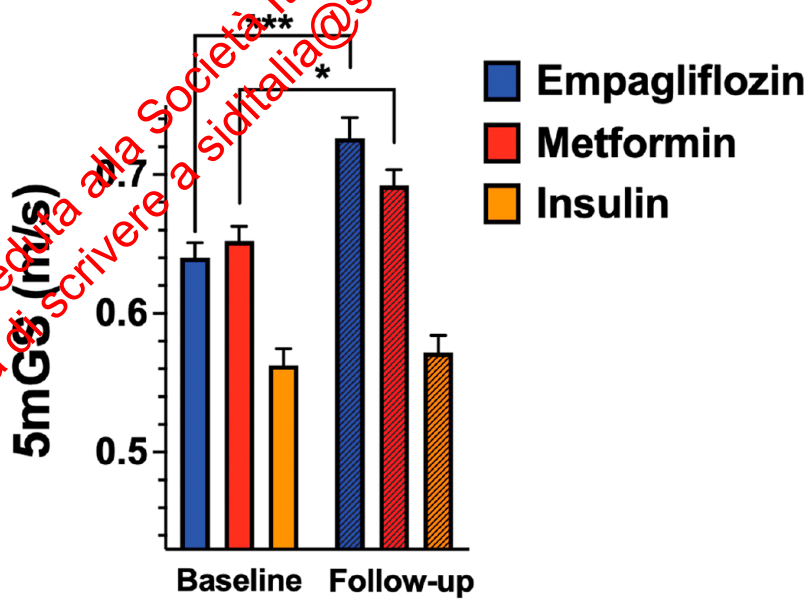

Figure 2—The 5mGS in the empagliflozin, metformin, and insulin groups measured at baseline and follow-up. Data are means ± SD. $^{*}P < 0.05$, $^{***}P < 0.001$.

- 162 frail older adults with HFpEF and diabetes
- at baseline and after 1 month, Montreal Cognitive Assessment scores and assessment of physical performance by the 5-m gait speed test

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