Evidenze e meccanismi di nefroprotezione delle glifozine

Roberto Pontremoli

Università degli Studi e IRCCS Ospedale
Policlinico San Martino - Genova

Il sottoscritto Roberto PONTREMOLI

ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara che

negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario

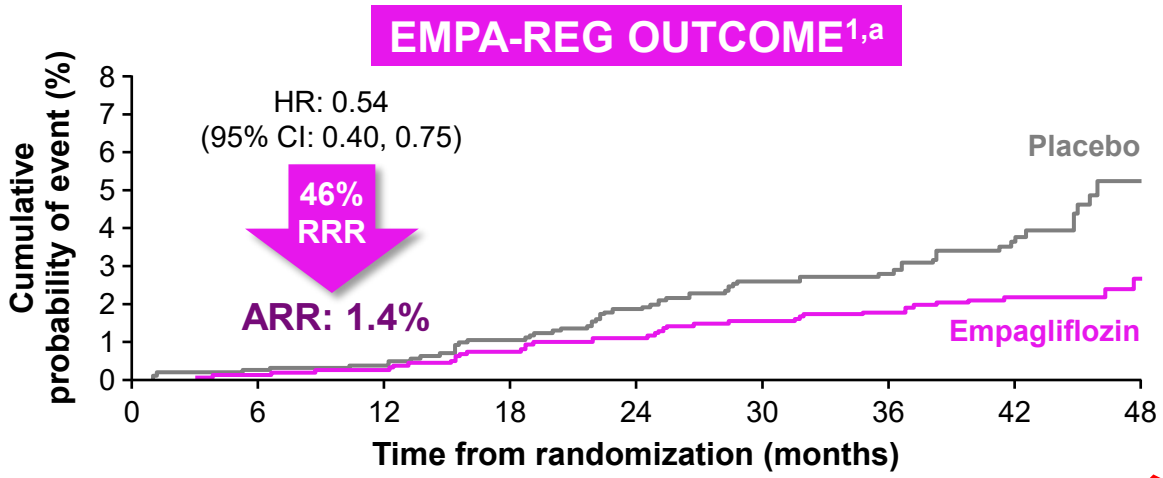
- ASTRAZENECA
- BOEHRINGER-INGELHEIM
- LILLY
- GUIDOTTI
- MENARINI
- BAYER
- ALFA-SIGMA
- NOVONORDISK

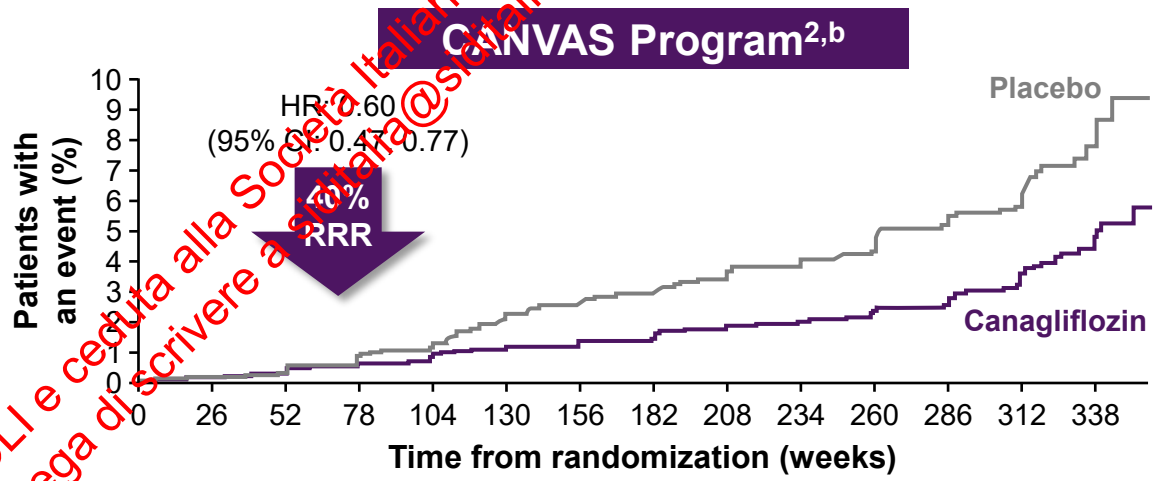
Domande Aperte

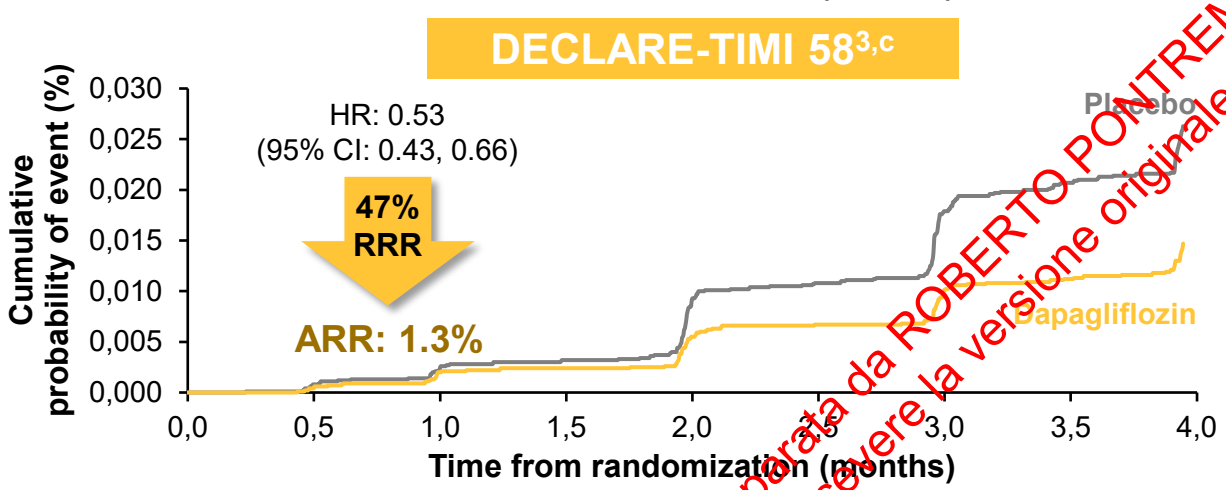
- **Quale tipologia di paziente (fenotipo di presentazione) si giova maggiormente della terapia con SGLT2i?**

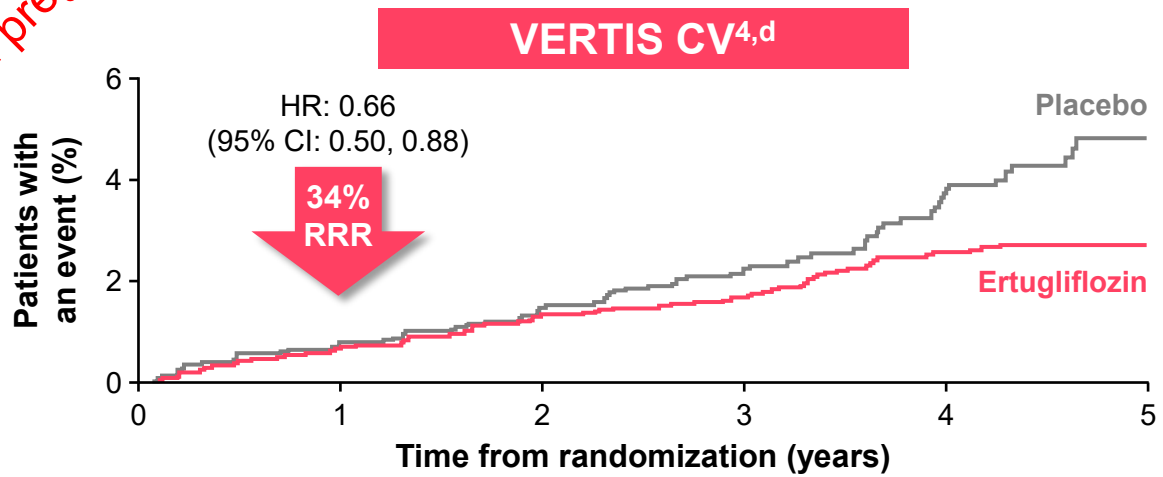
- **Quale ritieni sia il meccanismo predominante alla base dell'effetto nefroprotettivo degli SGLT2i? e perche?**

SGLT2 inhibitors in CVOTs consistently reduced the risk of kidney composite endpoints compared with placebo









1. Wanner C, et al. *N Engl J Med* 2016;375:323–334; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657; 3. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617;
4. Cherney DZI, et al. *Diabetologia* 2021;64:1256–1267

Domanda

- ***Qual è l'entità della nefroprotezione attribuibile all'impiego di SGLT2i?***
    1. ***10-15%***
    2. ***20%***
    3. ***30-45%***
    4. ***Simile a quella ottenibile con ACEis e ARBS***

Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

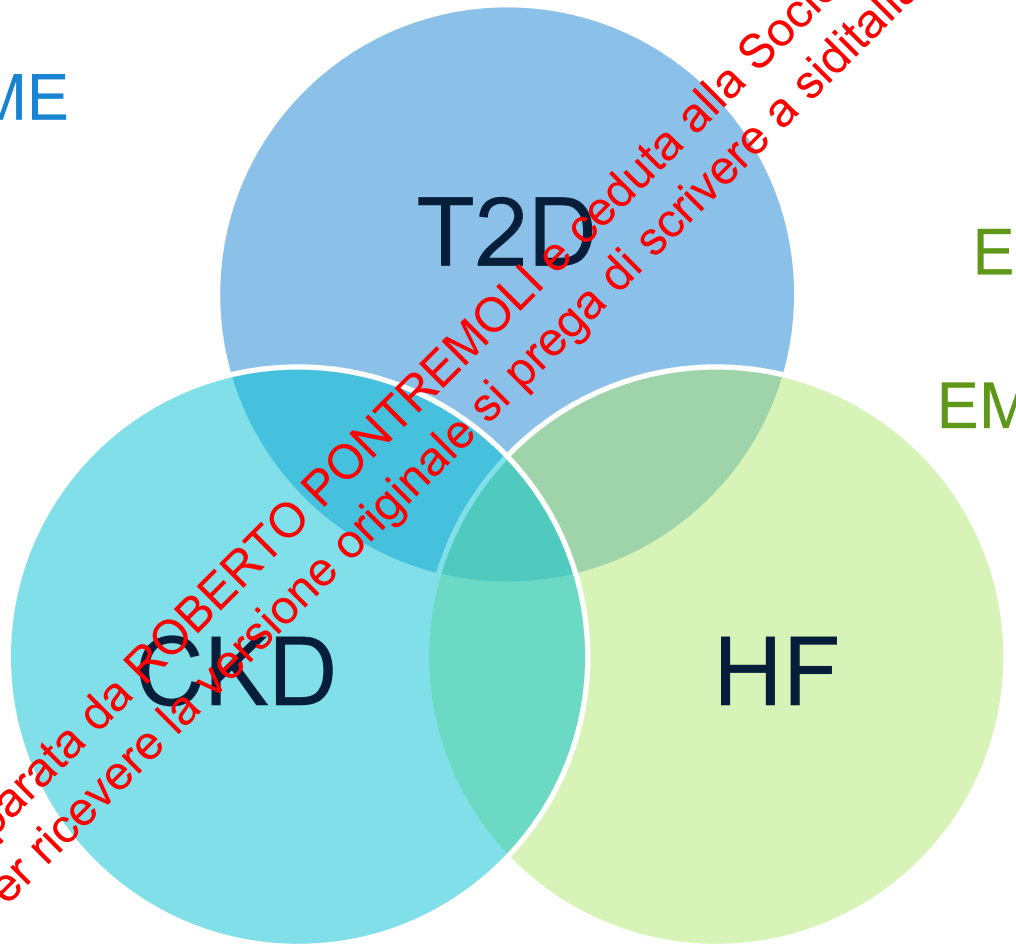
	Kidney composite outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	0.55 (0.41, 0.73)
CANVAS Program[2]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	0.60 (0.47, 0.77)
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2 and/or end-stage renal disease and/or renal death	0.53 (0.43, 0.66)
VERTIS CV*	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	0.66 (0.50, 0.88)

*Pre-specified exploratory, intention-to-treat analysis set, 95.0% CI. CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio. [1]Post-hoc exploratory, Perkovic V et al. Nephrol Dial Transplant (2019) 1–9; [2]Pre-specified exploratory, Neal B et al. N Engl J Med 2017;377:644-657; [3]Pre-specified secondary, Wiviott SD et al. N Engl J Med 2019;380:347-357

Large clinical trials of SGLT-2 inhibitors

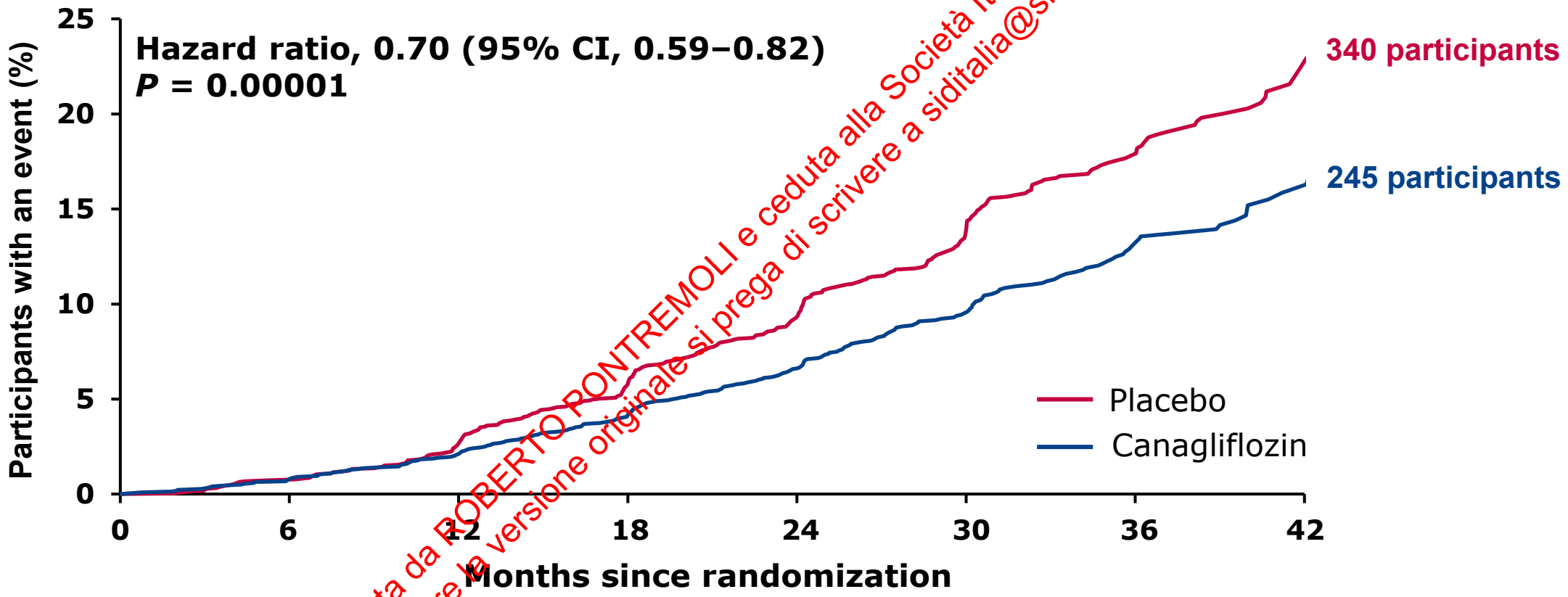
EMPA-REG OUTCOME
CANVAS
DECLARE-TIMI 58
VERTIS-CV

CREDENCE
DAPA-CKD
SCORED
EMPA-Kidney



DAPA-HF
EMPEROR-Reduced
SOLOIST
EMPEROR-Preserved
DELIVER

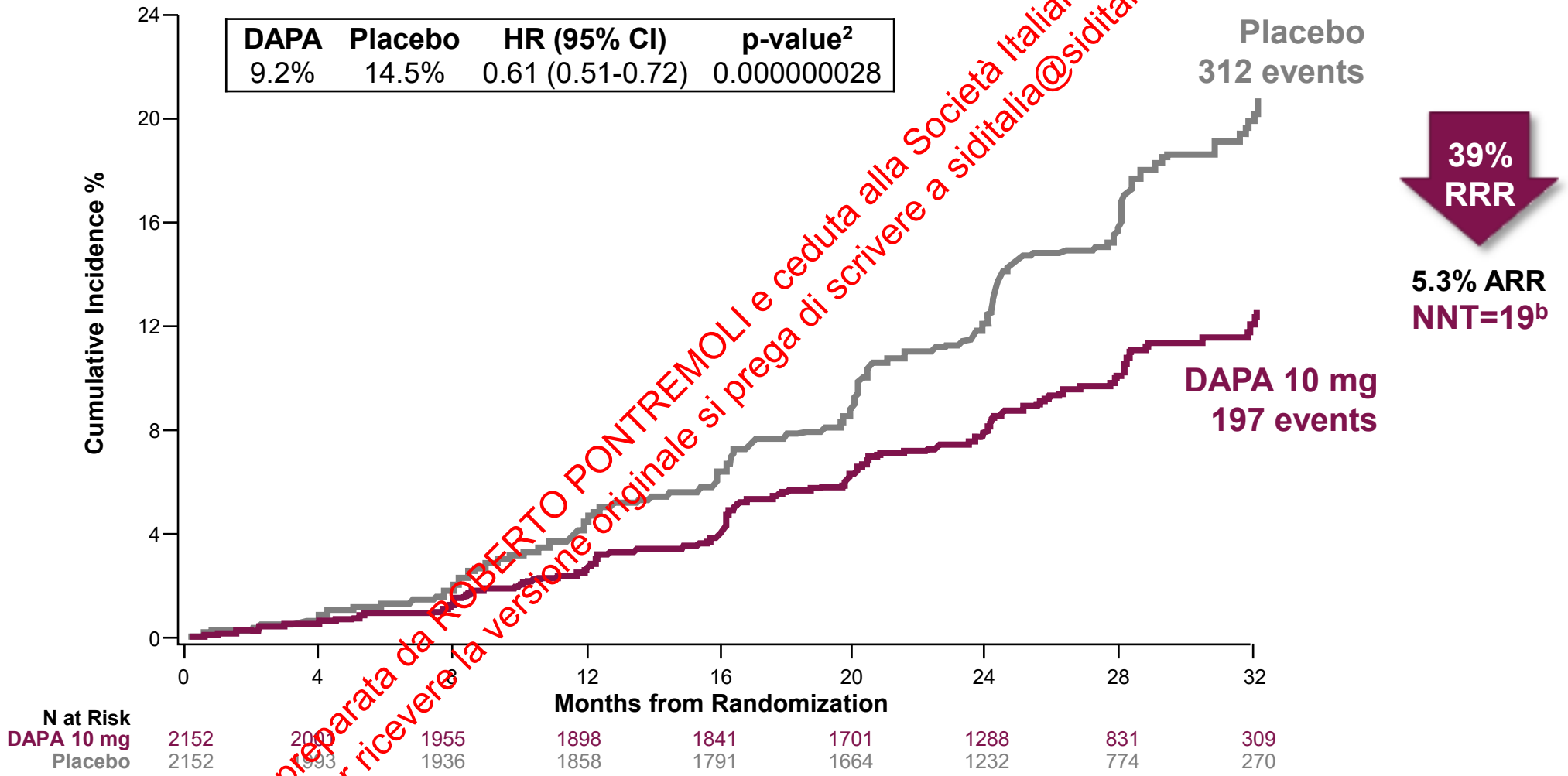
CREDENCE - Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306

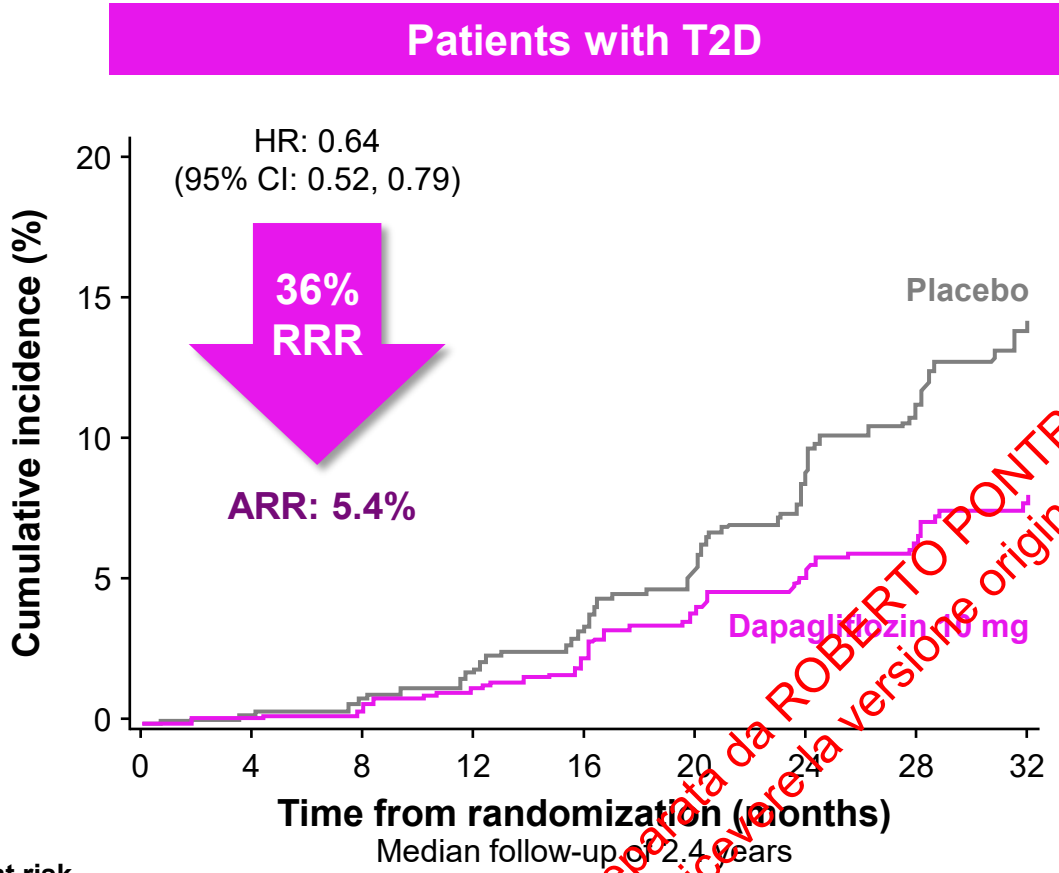
DAPA-CKD - Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death



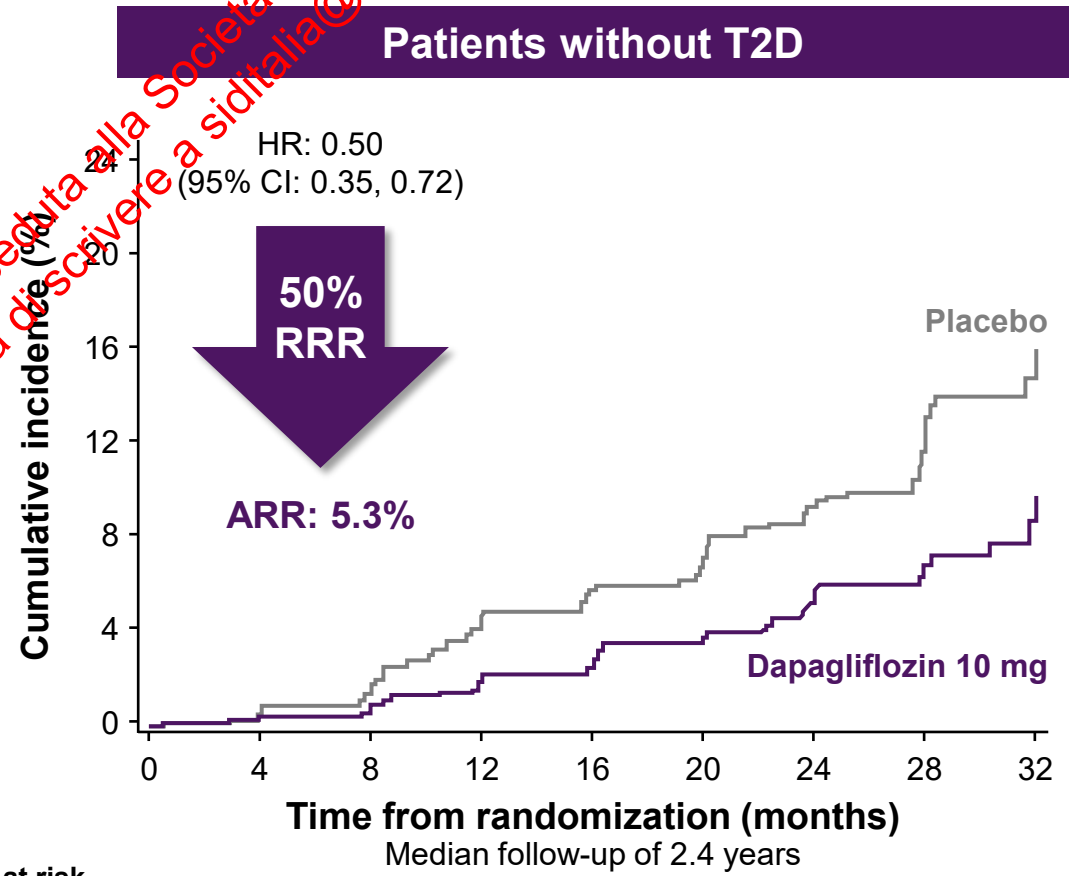
Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446

In DAPA-CKD, the effect of dapagliflozin on the risk of the primary endpoint was consistent in patients with and without T2D

The effect of dapagliflozin on the primary composite outcome[a] compared with placebo, stratified by diabetes status



No. at risk									
Dapagliflozin	1455	1383	1349	1307	1202	1155	910	580	215
Placebo	1451	1360	1321	1275	1224	1130	868	545	190



No. at risk									
Dapagliflozin	697	618	606	591	579	546	378	251	94
Placebo	701	633	615	583	567	534	364	229	80

Wheeler DC, et al. Lancet Diabetes Endocrinol 2021;9:22–31

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND

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METHODS

We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

RESULTS

A total of 6609 patients underwent randomization. During a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.

CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

The members of the writing committee (W.G. Herrington, N. Staplin, C. Wanner, J.B. Green, S.J. Hauske, J.R. Emberson, D. Preiss, P. Judge, K.J. Mayne, S.Y.A. Ng, E. Sammons, D. Zhu, M. Hill, W. Stevens, K. Wallendszus, S. Brenner, A.K. Cheung, Z.-H. Liu, J. Li, L.S. Hooi, W. Liu, T. Kadowaki, M. Nangaku, A. Levin, D. Cherney, A.P. Maggioni, R. Pontremoli, R. Deo, S. Goto, X. Rossello, K.R. Tuttle, D. Steubl, M. Petrini, D. Massey, J. Eilbracht, M. Brueckmann, M.J. Landray, C. Baigent, and R. Haynes) assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the writing committee are listed in the Appendix. Dr. Herrington can be contacted at cco.empakidney@ndph.ox.ac.uk or at the EMPA-KIDNEY Central Coordinating Office, Richard Doll Building, Old Road Campus, Roosevelt Dr., Oxford OX3 7LF, United Kingdom.

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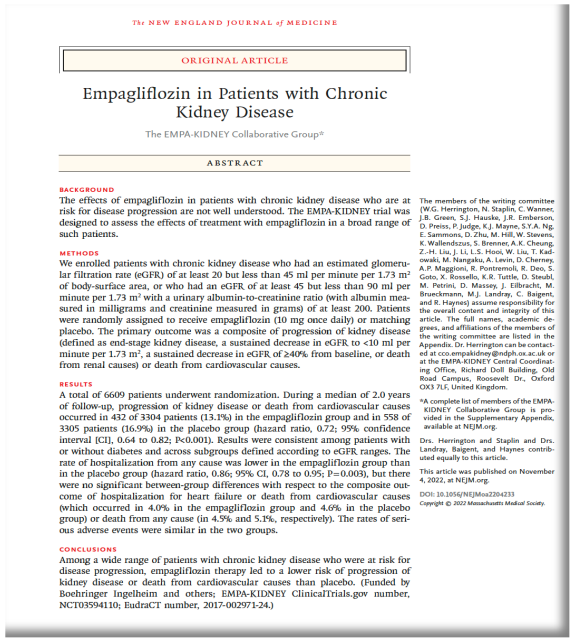

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HR 0.72
(0.64-0.80)
P<0.001
RR 28%

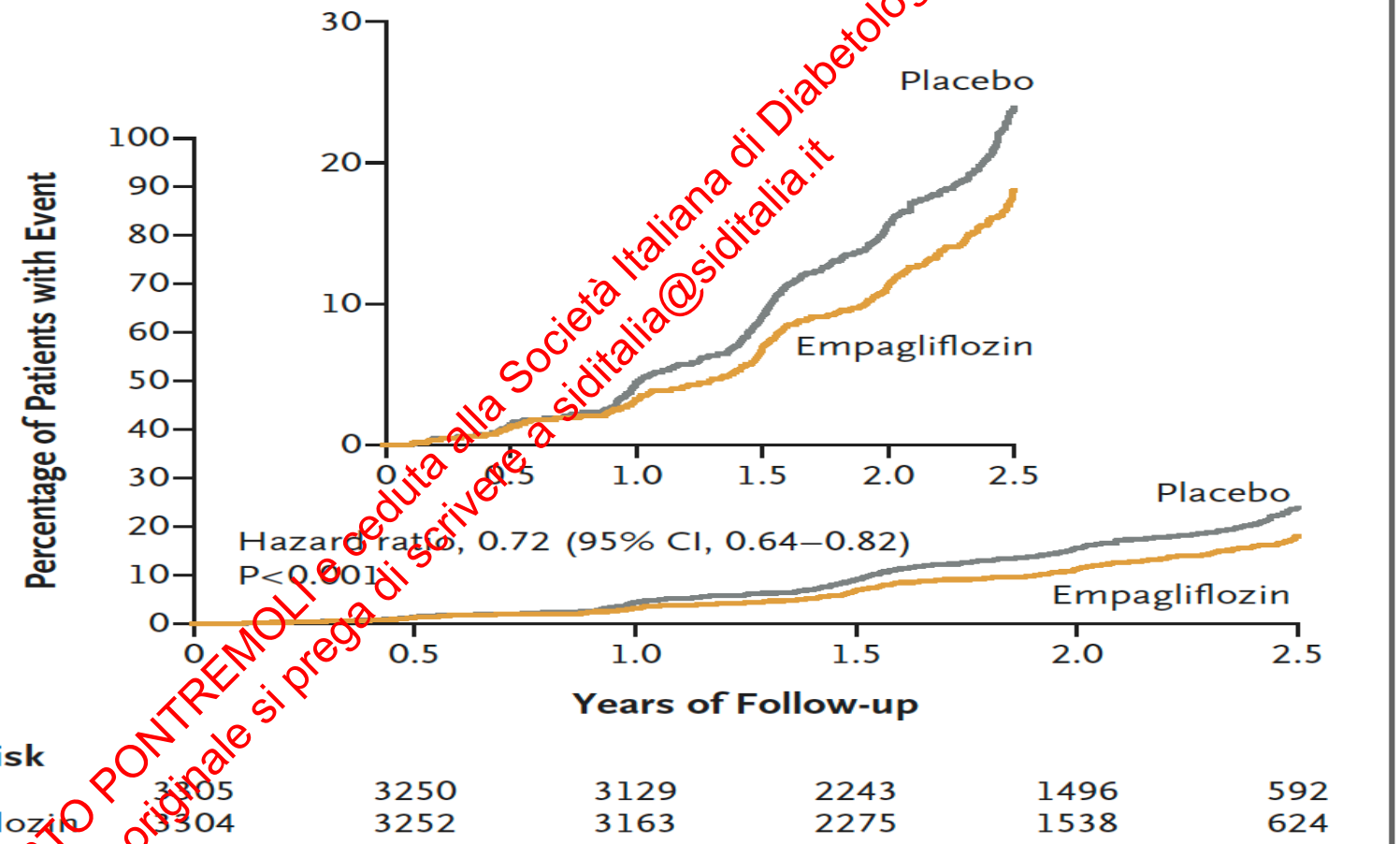
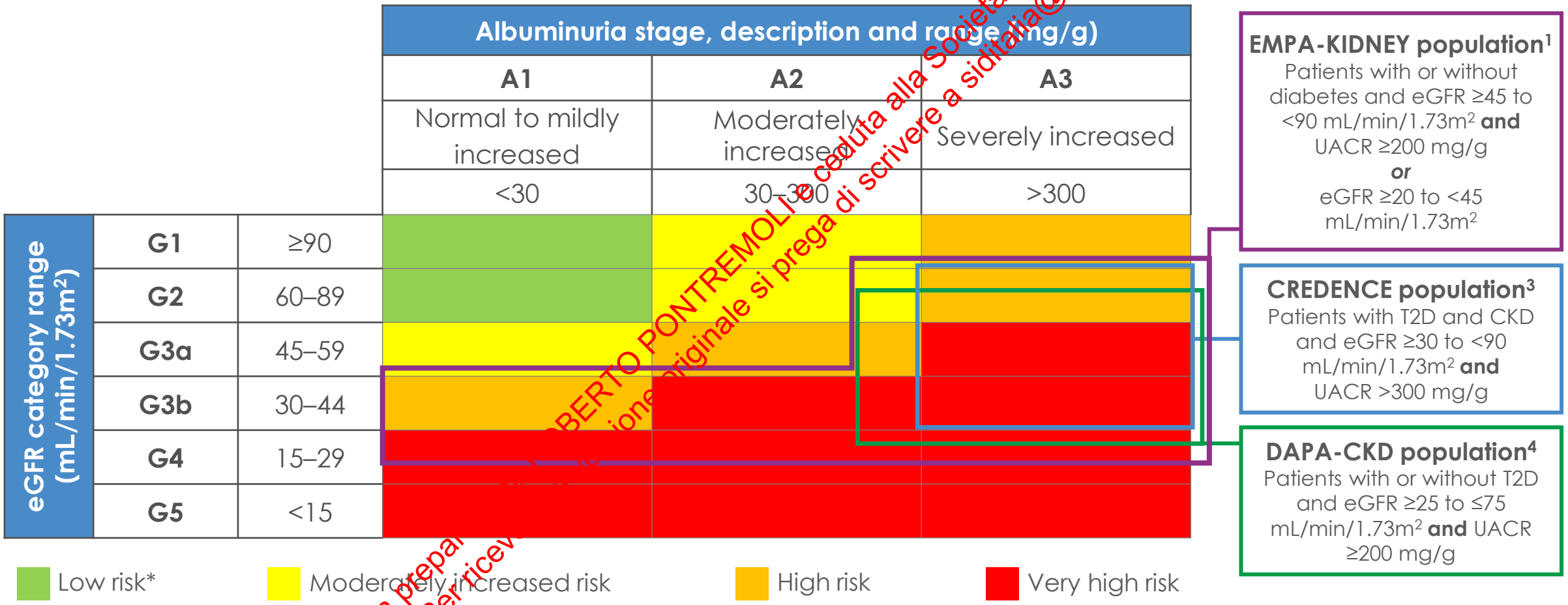


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Shown are the results of the primary composite outcome of progression of kidney disease or death from cardiovascular causes. Over a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 patients (13.1%) in the empagliflozin group and in 558 patients (16.9%) in the placebo group, representing 42 fewer primary-outcome events per 1000 patients in the empagliflozin group than in the placebo group over 2 years. The inset shows the same data on an enlarged y axis.

EMPA-KIDNEY enrolled a CKD population with a broad range of eGFR, with and without albuminuria[1]

Prognosis of CKD by eGFR and albuminuria categories[2]

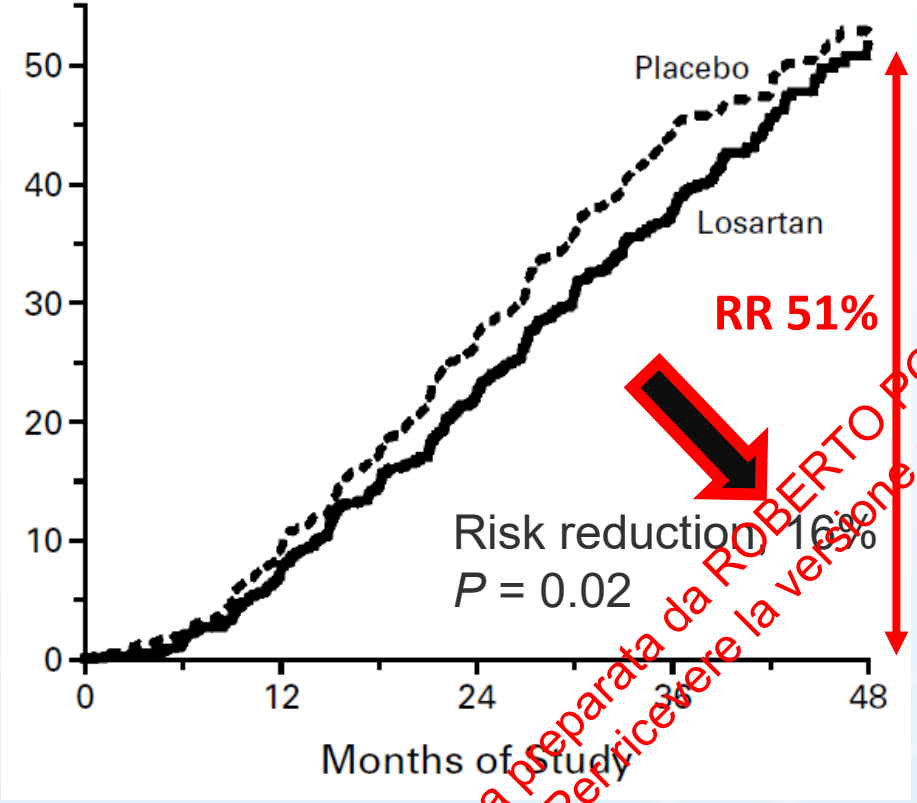


*If no other markers of kidney disease, no CKD.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; T2D, type 2 diabetes.
1. The EMPA-KIDNEY Collaborative Group. [Published online ahead of print March 3 2022]. *Nephrol Dial Transplant*. 2022. DOI:10.1093/ndt/gfac054 2. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1–150. 3. Perkovic V, *et al. N Engl J Med*. 2019; 380:2295-2306 4. Wheeler DC, *et al. Nephrol Dial Transplant* 2020;35:1700.

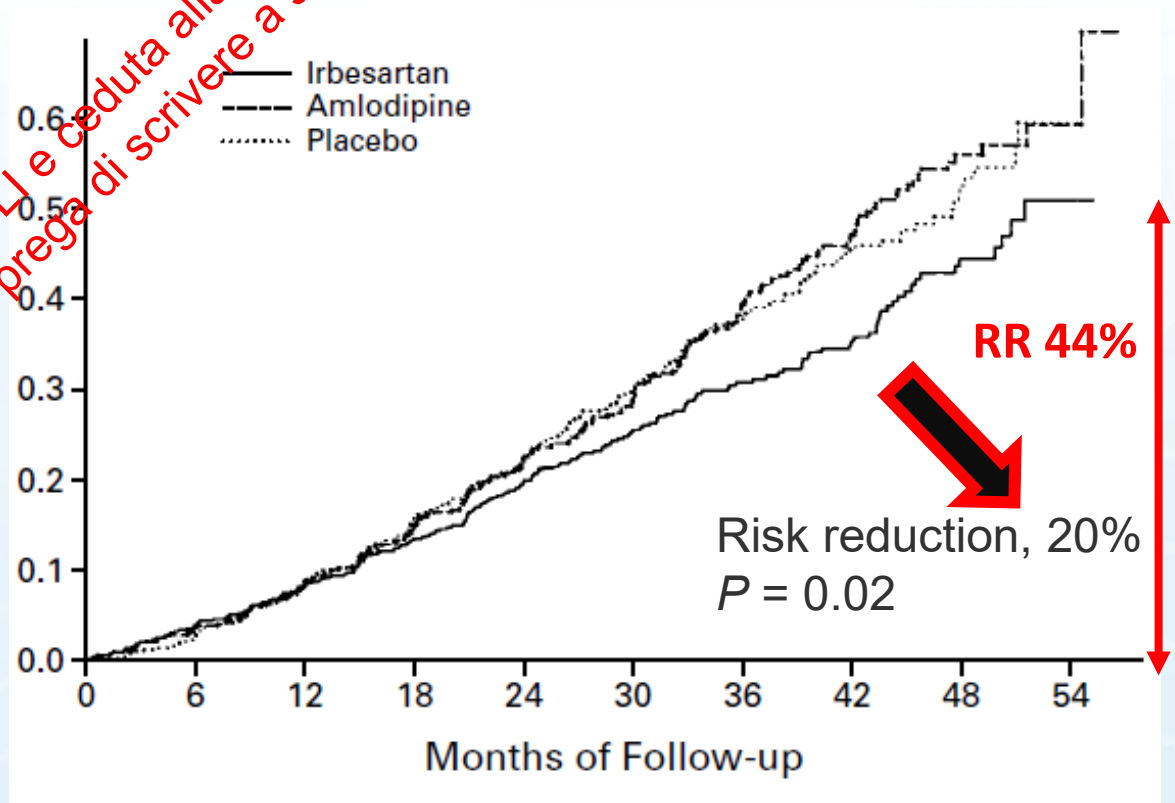
The residual risk in RAASi treated DKD patients: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

RENAAL



IDNT

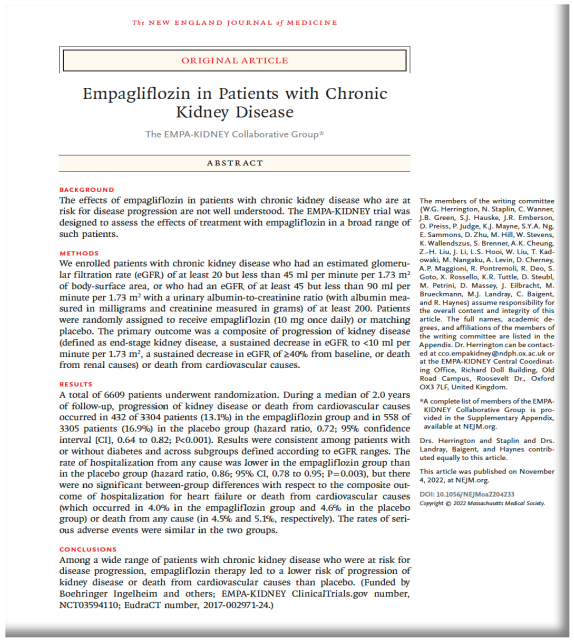


RENAAL Brenner BM et al. N Engl J Med 2001;
IDNT Lewis EJ et al. N Engl J Med 2001

Domanda

- ***L'efficacia (nefroprotezione) degli SGLT2i varia in base al rischio renale del paziente:***

1. ***si***
2. ***No***



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Benefit independent of diabetes status, eGFR at baseline

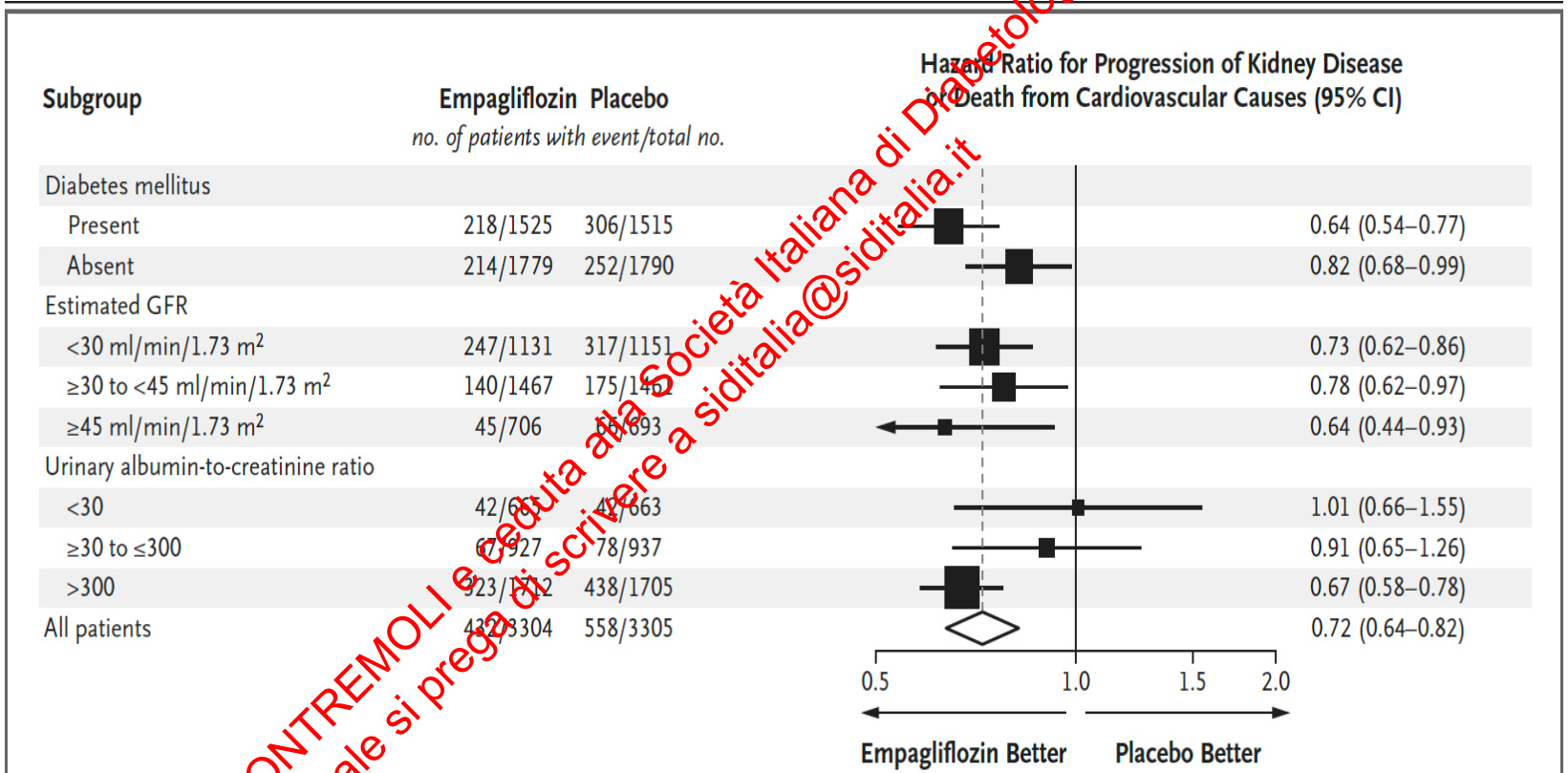

Figure 2. Primary Outcome in Key Prespecified Subgroups.

Shown are the hazard ratios for the primary outcome in key prespecified subgroups defined according to baseline characteristics. Hazard ratios and confidence intervals were estimated with the use of Cox proportional-hazards regression models, with adjustment for age, sex, history of diabetes, estimated glomerular filtration rate (GFR), urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams), and geographic region. The area of each box is proportional to the inverse of the variance of the log hazard ratios. The arrow indicates that the boundary of the 95% confidence interval is outside the graphed area. The diamond represents the result of the primary analysis, with the width of the diamond indicating the 95% confidence interval. The dashed line indicates the hazard ratio in the overall population.

Is albuminuria a prerequisite for DKD ?

	Patients n.	DM %	Follow-up years	Renal impairment	Non-albuminuric renal impairment
UKPDS *Diabetes 55: 1832-1839, 2006*	4,006	100	15	28%	67% (51%)
DCCT/EDIC *Diabetes Care 33: 1536-1543, 2010*	1,439	100 (type 1)	19	6.2%	24%
AMD Annals **Diabetes Metab Res Rev 2017 *in press***	**20,464**	100 (T1DM)	19	23.5%	**49%**

MacIsaac RJ et al., *Diabetes Care 27: 195-200, 2004*	301	100	---	36%	39%
Kramer HJ et al., NHANES III *JAMA 289: 3273-3277, 2003*	1,197	100	---	13%	36%
Thomas MC et al., NEFRON *Diabetes Care 32: 1497-1502, 2009*	3,893	100	---	23%	55%
Ninomiya T et al., ADVANCE *J Am Soc Nephrol 20: 1813-1821, 2009*	10,640	100	---	19%	62%
Bakris GL et al., ACCOMPLISH *Lancet 375: 1173-1181, 2010*	11,482	60	---	9.5%	47%
Tube SW et al., ONTARGET/ TRASCEND *Circulation 123: 1098-1107, 2011*	23,422	37	---	24%	68%
Drury PL et al., FIELD *Diabetologia 54: 32-43, 2011*	9,765	100	---	5.3%	59%
RIACE Study Group, RIACE *J Hypertens 29: 1802-1809, 2011*	15,773	100	---	18.8%	57%
AMD ANNALS **NDT 2015**	**116,777**	**100**	**---**	**21%**	**48%**

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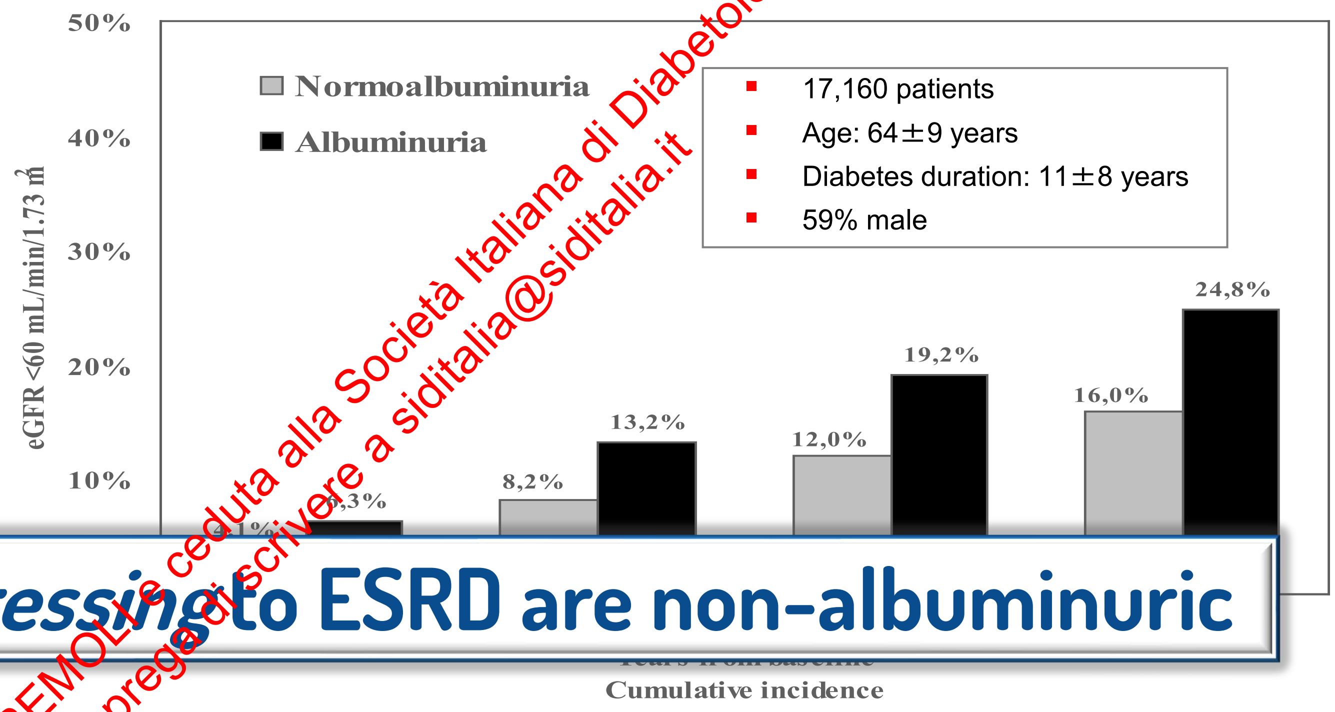
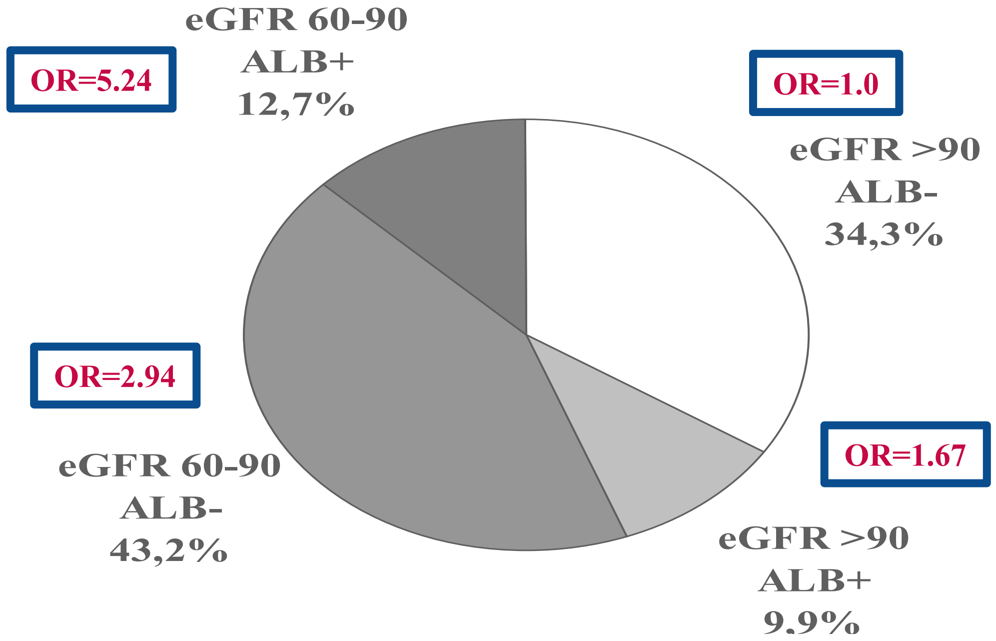
Association of kidney disease measures with risk of renal function worsening in patients with hypertension and type 2 diabetes

Francesca Viazzi [a,*], Pamela Piscitelli [b], Carlo Giorda [c], Antonio Ceriello [d,e], Stefano Genovese [e], Giuseppina T. Russo [f], Paola Fioretto [g], Pietro Guida [h], Salvatore De Cosmo [b], Roberto Pontremoli [a], the AMD-Annals Study Group

2 out of 3 pts with DKD *progressing* to ESRD are non-albuminuric





developing stage 3 CKD. The presence of albuminuria entails a greater renal risk at any given GFR value. However, due to a greater occurrence of the non-albuminuric phenotype at baseline, progression to CKD stage 3 is more likely to be observed in patients without albuminuria.

Domanda

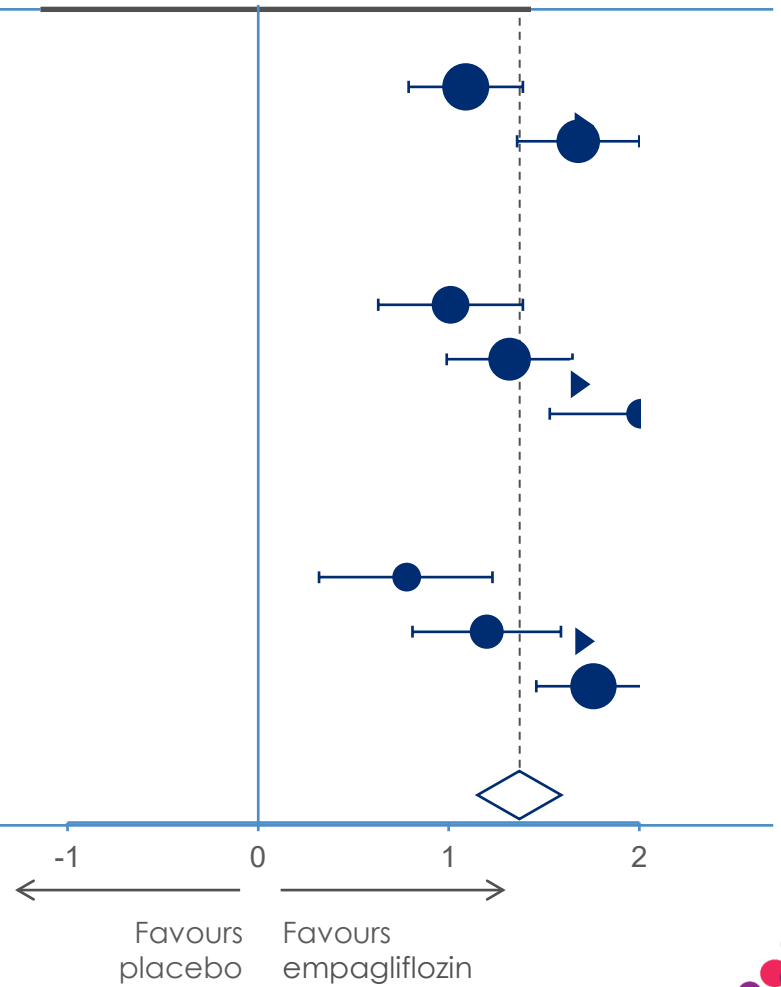
- ***Nei pazienti con normale escrezione urinaria di albumina il beneficio del trattamemento coi SGLT2i è irrilevante:***

    1. ***Si, il principale beneficio deriva dalla riduzione dell'albuminuria***

    2. ***No, gli SGLT2i dovrebbero comunque essere impiegati***

Annual rate of change in eGFR by key subgroups – Chronic slope

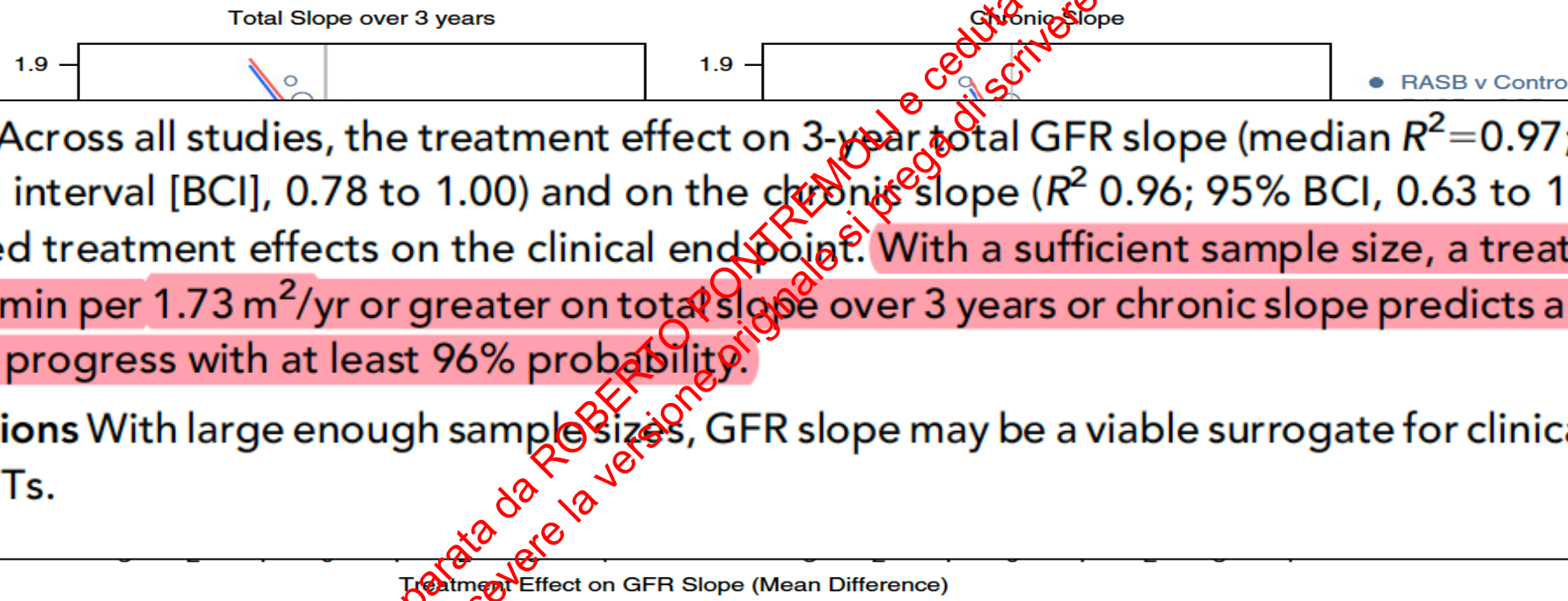
Subgroup	Empagliflozin	Placebo	Absolute difference (95% CI)
	Annual rate of change in eGFR, ml/min/1.73m², mean (SE)		
Diabetes			
No	-1.66 (0.11)	-2.75 (0.11)	1.09 (0.79, 1.39)
Yes	-1.05 (0.12)	-2.73 (0.12)	1.68 (1.36, 2.00)
eGFR, ml/min/1.73m²			
<30	-1.84 (0.14)	-2.85 (0.14)	1.01 (0.63, 1.39)
≥30 to <45	-1.18 (0.12)	-2.50 (0.12)	1.32 (0.99, 1.65)
≥45	-1.58 (0.17)	-3.60 (0.17)	2.01 (1.53, 2.49)
UACR, mg/g			
A1 (<30) normal to mildly increased	-0.11 (0.17)	-0.89 (0.16)	0.78 (0.32, 1.23)
A2 (≥30 to ≤300) moderately increased	-0.49 (0.14)	-1.69 (0.14)	1.20 (0.81, 1.59)
A3 (>300) severely increased	-2.35 (0.14)	-4.11 (0.11)	1.76 (1.46, 2.05)
All participants	**-1.37 (0.08)**	**-2.75 (0.08)**	**1.37 (1.16, 1.59)**



Mean annual rates of change in eGFR from 4 months to the final follow-up visit ('chronic slopes') by treatment allocation were estimated using shared parameter models.
eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.
The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2022; DOI: 10.1056/NEJMoa2204233

GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-Analysis of Treatment Effects of Randomized Controlled Trials

Lesley A. Inker,[1] Hiddo J. L. Heerspink,[2] Hocine Tighiouart,[3,4] Andrew S. Levey,[1] Josef Coresh,[5] Ron T. Gansevoort,[6] Andrew L. Simon,[1] Jianxin Ying,[7] Gerald J. Beck,[8] Christoph Wanner,[9] Jürgen Floege,[10] Philip Kam-Tao Li,[11] Vlado Perkovic,[12] Edward F. Vonesh,[13] and Tom Greene[7]



Results Across all studies, the treatment effect on 3-year total GFR slope (median R^2=0.97; 95% Bayesian credible interval [BCI], 0.78 to 1.00) and on the chronic slope (R^2 0.96; 95% BCI, 0.63 to 1.00) accurately predicted treatment effects on the clinical end point. With a sufficient sample size, a treatment effect of 0.75 ml/min per 1.73 m^2/yr or greater on total slope over 3 years or chronic slope predicts a clinical benefit on CKD progress with at least 96% probability.

Conclusions With large enough sample sizes, GFR slope may be a viable surrogate for clinical end points in CKD RCTs.

JASN 30: 1735–1745, 2019. doi: https://doi.org/10.1681/ASN.2019010007

Domanda

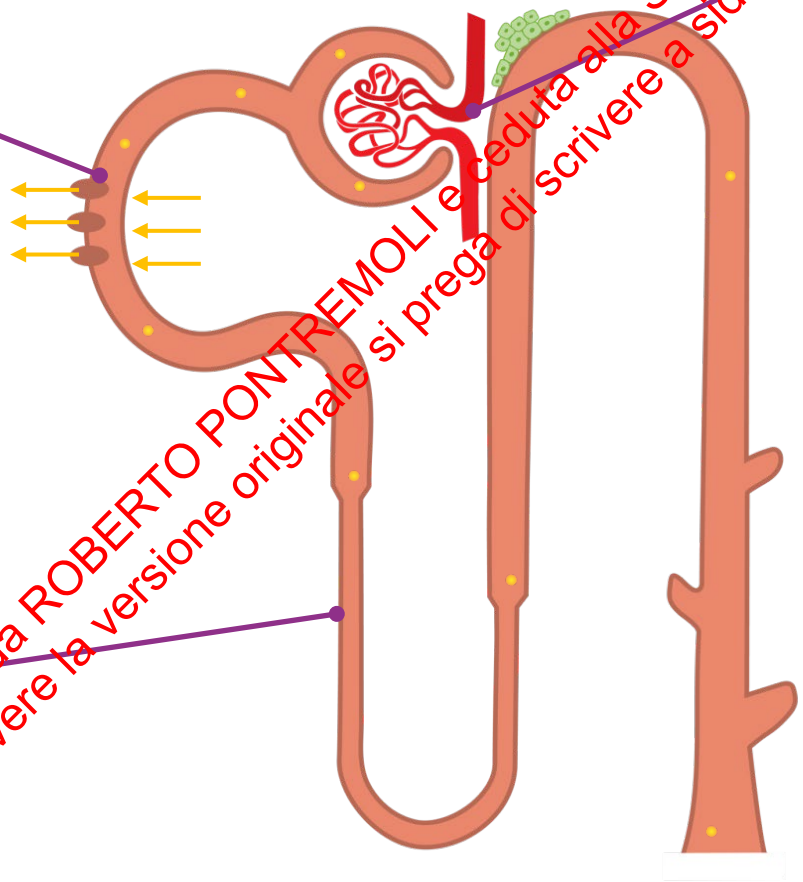
- ***Quale è il principale meccanismo fisiopatologico di nefroprotezione degli SGLT2i?***

1. ***Miglioramento dell'emodinamica glomerulare (TGF)***
2. ***Protezione dal danno tubulare (molteplici meccanismi)***
3. ***Induzione di bilancio idrico negativo***

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]



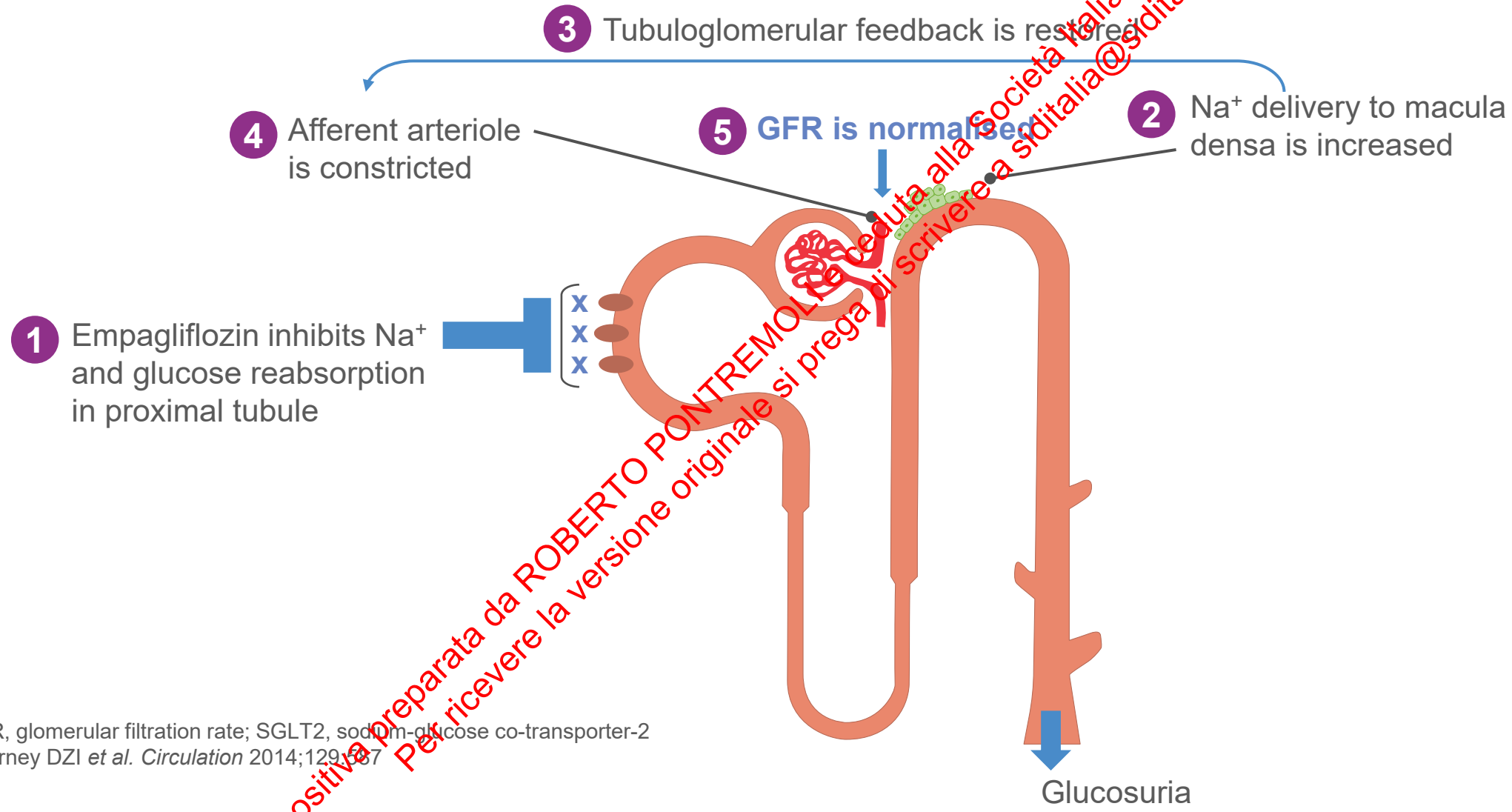
SGLT2 inhibitors increase distal sodium delivery, thereby activating **tubuloglomerular feedback** and reducing hyperfiltration[1]

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]

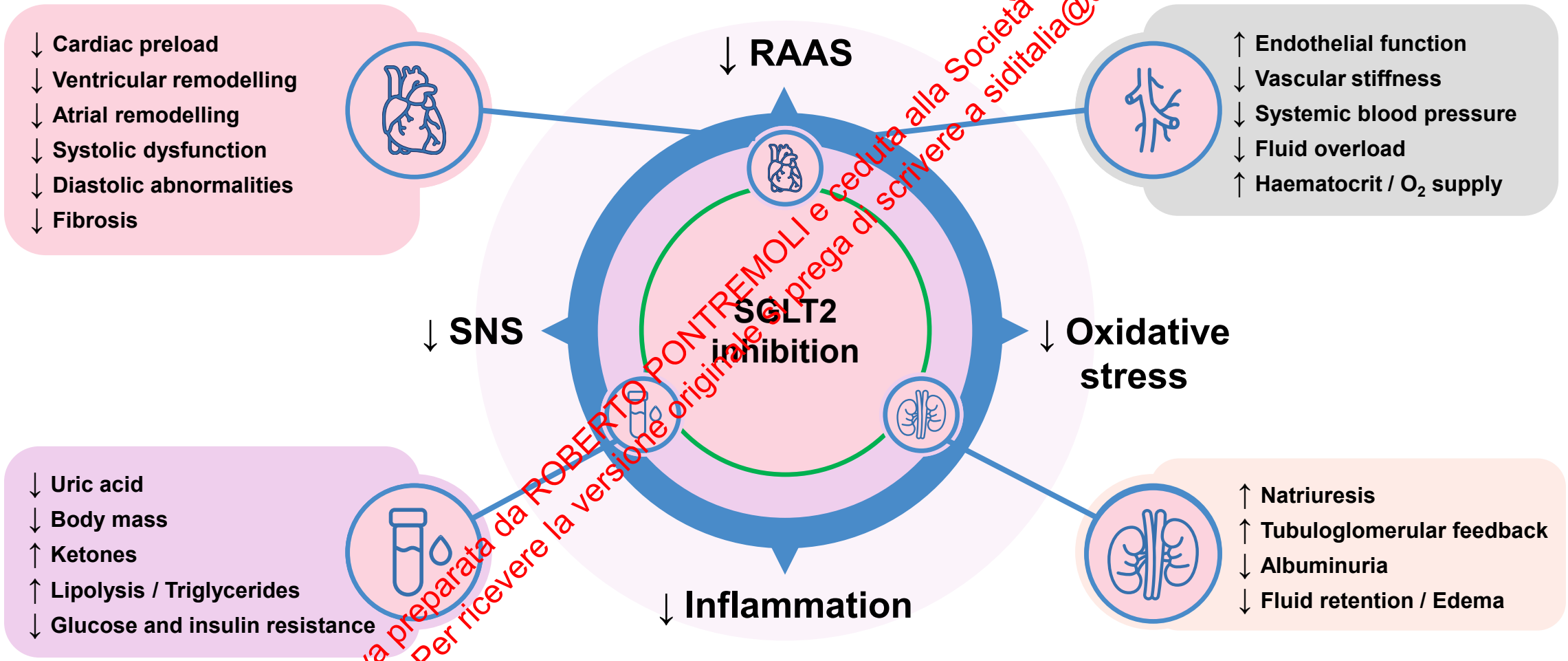
1. Dekkers CCJ et al. Curr Diab Rep 2018;18:27; 2. Thomas MC et al. Diabetologia 2018;61:2098; 3. Heerspink HJL et al. Kidney Int 2018;94:26; 4. Sugyama S et al. Intern Med 2018;57:2147

SGLT2 inhibition activates tubuloglomerular feedback, reducing intraglomerular pressure



GFR, glomerular filtration rate; SGLT2, sodium-glucose co-transporter-2
Cherney DZI *et al. Circulation* 2014;129:587

Direct and indirect actions of SGLT2 inhibitors are likely to produce CRM benefits[1–5]



ATP, adenosine triphosphate; CRM, cardiovascular, renal and metabolic; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1. Givens RC, Schulze PC. Molecular changes in heart failure. In: Eisen H, ed. Heart Failure: A Comprehensive Guide to Pathophysiology and Clinical Care. London: Springer Verlag; 2017:1–26. 2. Ronco C et al. J Am Coll Cardiol. 2008;52:1527. 3. Santos-Ferreira D et al. Cardiology. 2020;145:311–20. 4. Cowie M, Fisher M. Nat Rev Cardiol. 2020;17:761–72. 5. Scheen AJ. Nat Rev Endocrinol. 2020;16:556–77.

Visual Abstract

Effects of Empagliflozin on Fluid Overload, Weight and Blood Pressure in Chronic Kidney Disease

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

EMPA-KIDNEY trial (n=6609)
Bioimpedance substudy (n=660)

Fresenius **Body Composition Monitor (BCM)** bioimpedance spectroscopy device: three-compartment model

BCM at randomization, 2 & 18 months
Weight & blood pressure at every visit

Mixed model repeated measures analysis:

OUTCOMES
Primary: Study average "Fluid Overload"
(excess extracellular water in lean and/or adipose tissue)
Secondary: **"Fluid Overload" by time**

Tertiary assessments: subgroup effects on "Fluid Overload"; **extra- & intracellular water**; BCM-derived **fat & lean tissue indices**; **weight & blood pressure** in the substudy population

OUTCOMES

PRIMARY

"Fluid Overload"
(excess extracellular water)
-0.24 (-0.38, -0.11) L

SECONDARY

Effects were sustained over time:

2 months	18 months
-0.23 L (-0.37, -0.08)	-0.26 L (-0.46, -0.06)

TERTIARY

Weight
-0.7 kg
(-1.3, -0.1)

Systolic BP
-3.3 mmHg
(-5.5, -1.2)

Diastolic BP
-0.2 mmHg
(-1.4, 1.0)

TERTIARY

Effects on "Fluid Overload" were consistent across subgroups:
Sex, diabetes, eGFR, NTpro-BNP, baseline fluid status or diuretic use.

Significant ↓ total body water:

Total body water
-0.82 L
(-1.24, -0.40)

Extracellular
-0.49 L (-0.69, -0.30)
Intracellular
-0.30 L (-0.57, -0.03)

No significant effect on adiposity:

Fat tissue index
-0.07 kg/m²
(-0.35, 0.20)

Lean tissue index
-0.14 kg/m²
(-0.39, 0.10)

Results are between-group difference (95% CI): empagliflozin – placebo. Negative differences favour empagliflozin.
eGFR = estimated glomerular filtration rate; NTpro-BNP = N-terminal-pro B-type natriuretic peptide; BP = blood pressure.

Conclusion

In a broad range of patients with CKD, empagliflozin resulted in a sustained reduction in bioimpedance-derived estimates of body water, with no statistically significant effect on fat mass.

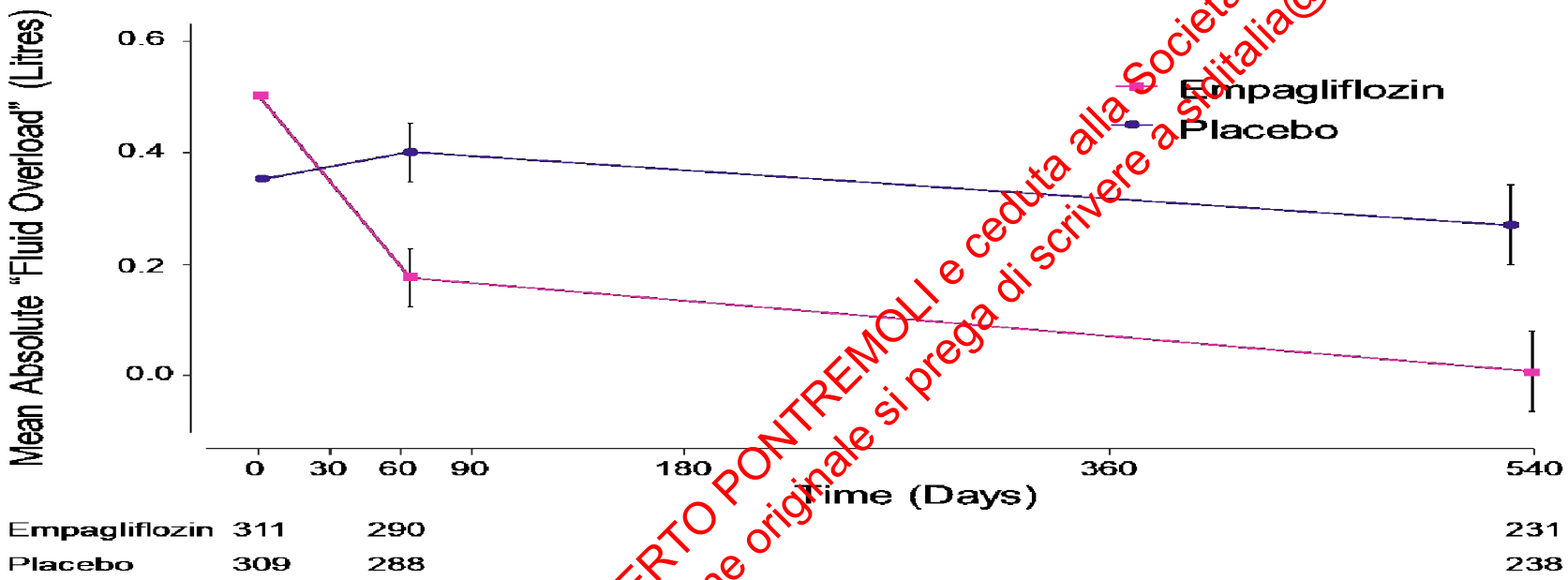
doi: 10.1681/ASN.

Effects of Empagliflozin on Fluid Overload, Weight and Blood Pressure in Chronic Kidney Disease: the EMPA-KIDNEY Bioimpedance Substudy

The EMPA-KIDNEY Bioimpedance Substudy Group,
on behalf of the EMPA-KIDNEY Collaborative Group

JASN 2023, *in press*

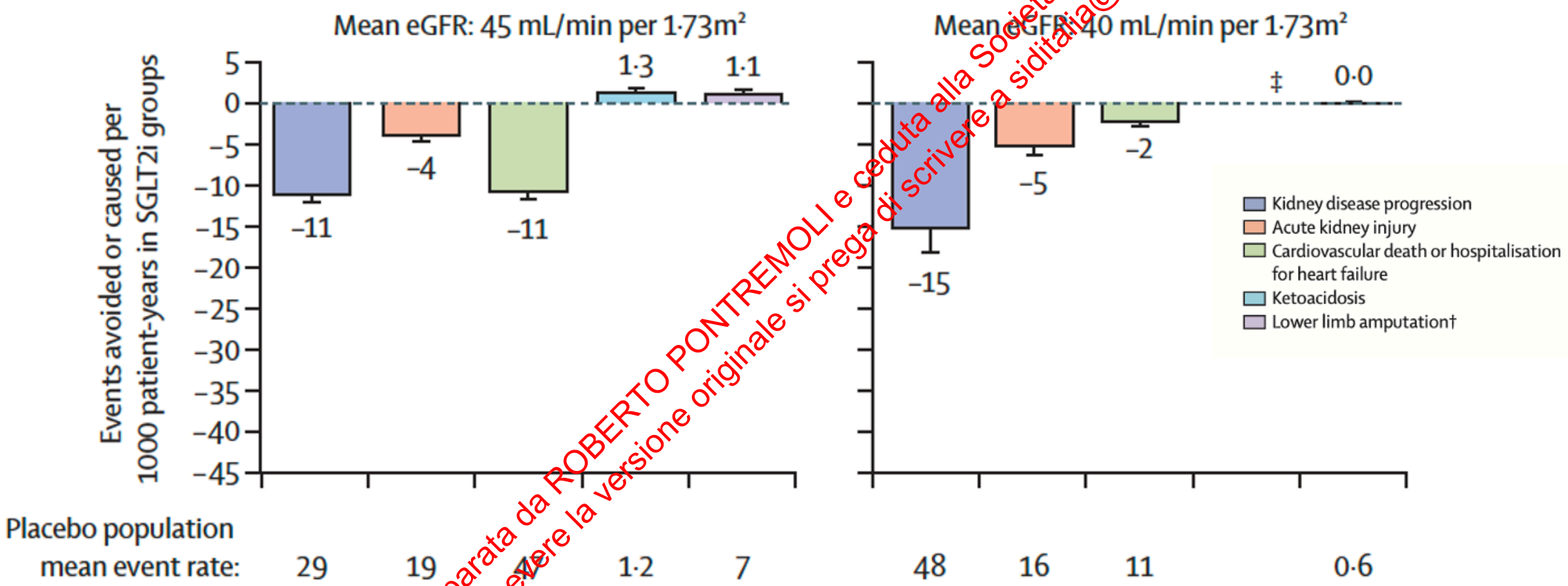
Figure 1: Effects of empagliflozin on mean bioimpedance-derived absolute "Fluid Overload" by time



	Empagliflozin Mean (SE)	Placebo Mean (SE)	Absolute Difference (95% CI)
Study average	0.10±0.05 L	0.34±0.05 L	-0.24 (-0.38, -0.11) L

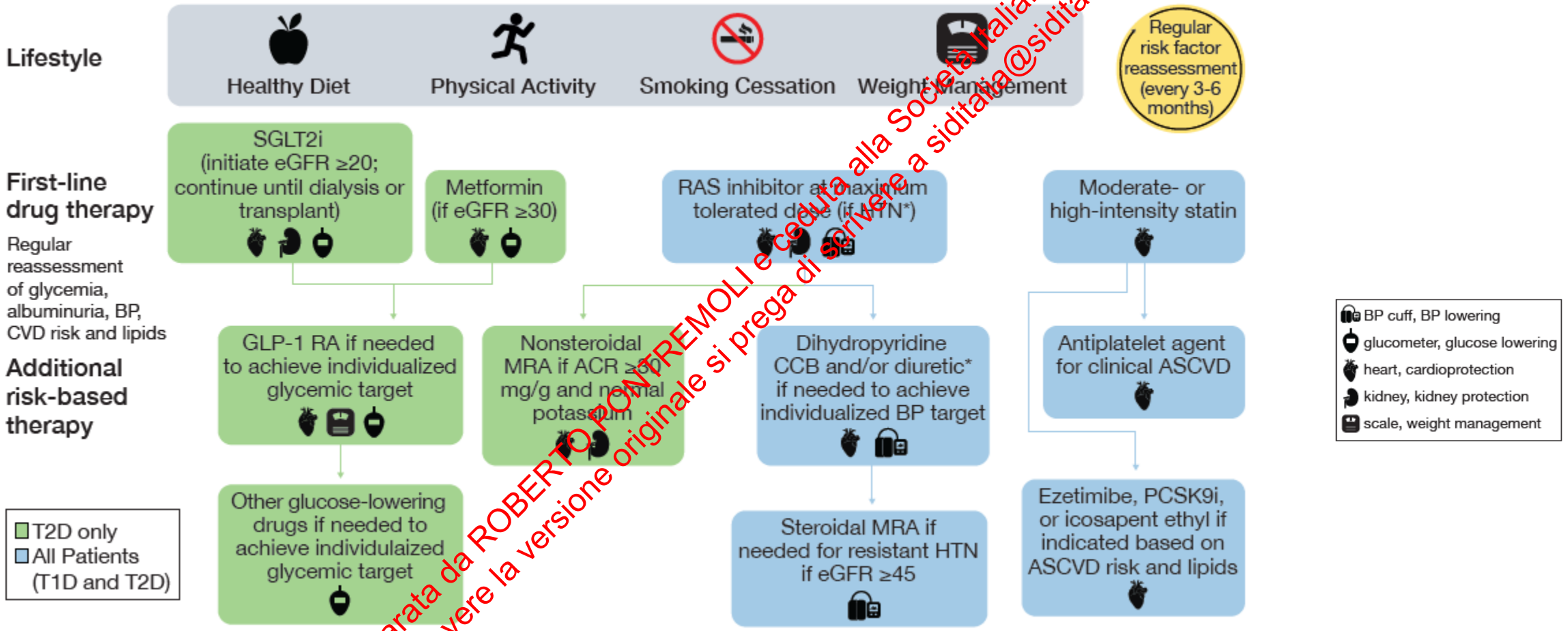
The treatment group-specific estimated marginal mean (and standard error) absolute "Fluid Overload" extracted from the mixed model repeated measures model is plotted at the median follow-up day in each time window. Analyses are adjusted for baseline absolute "Fluid Overload", age, sex, diabetes, eGFR and uACR. Participants with included measurements at each time point are shown beneath the x axis; analyses excluded 40 consenting participants with no valid follow-up measurements (3 deaths before first follow-up measurement, 28 with no measurement performed and 9 excluded due to inadequate data quality). Study averages are shown in the table (see Table 2 for differences in time windows separately). There was no significant interaction between treatment allocation and time (p=0.11).

Benefits and harms of SGLT2i in patients with CKD



The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium, Lancet nov 5 2022*

2022 KDIGO Approach for Improving Outcomes in People With Diabetes and CKD



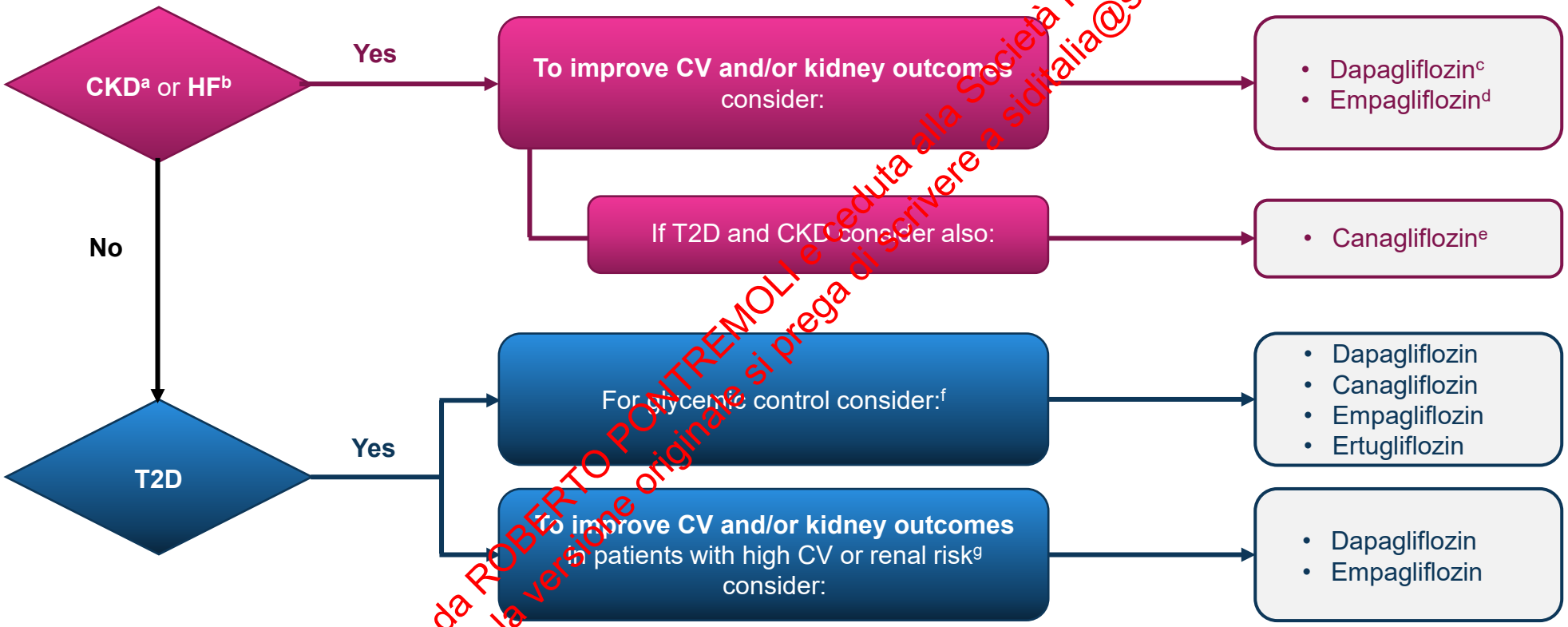
Note: eGFR is presented in units of mL/min/1.73 m^2.

*Maximum tolerated ACEi or ARB should be first-line therapy for HTN when albuminuria is present. Otherwise, dihydropyridine CCB or diuretic can also be considered; all three classes are often needed to attain BP targets.

ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin-creatinine ratio; ARB = angiotensin II receptor blocker; ADA = American Diabetes Association: ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid-receptor antagonist; PCSK9i= proprotein convertase subtilisin/kexin type 9 inhibitor; RAS = renin-angiotensin system; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes.

Rossing P et al. *Kidney Int.* 2022;102(5):990-999.

2023 ERA Consensus Paper: Algorithm for Selection of SGLT2i in Patients With CKD, HF, or T2D



[a]eGFR <60 mL/min/1.73 m^2 or UACR >30 mg/g; [b]With reduced or preserved ejection fraction; [c]Start if eGFR ≥25 mL/min/1.73 m^2 and continue until start of KRT; [d]Start if eGFR ≥20 mL/min/1.73 m^2; [e]Start if eGFR ≥30 mL/min/1.73 m^2 and continue until start of KRT; [f]While all 4 drugs may be used for glycemic control with eGFR ≥45 mL/min/1.73 m^2, an SGLT2i that has improved outcomes in CKD randomized controlled trials would be preferable if eGFR is 45-60 mL/min/1.73 m^2; [g]Established atherosclerotic CV disease (coronary, peripheral vascular, or cerebral arterial disease).

Mark PB et al. Online ahead of print. *Nephrology Dial Transplant*. 2023;gfad112.

Expanding the therapy options for diabetic kidney disease

YEAR IN REVIEW
NATURE REVIEWS | NEPHROLOGY

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