LA FORZA DELLA PRECOCITÀ
NELLA PROTEZIONE CARDIORENALE
NEL DIABETE DI TIPO 2:
dalla teoria alla pratica clinica

BOLOGNA STARHOTELS EXCELSIOR 2/3 DICEMBRE 2025

SESSIONE FRONTALE

Moderatori: Raffaella Buzzetti, Gloria Formoso

Overview Scientifica

SGLT2i nella pratica clinica: Effetto nefroprotettivo delle gliflozine

Gian Paolo Fadini

Università di Padova

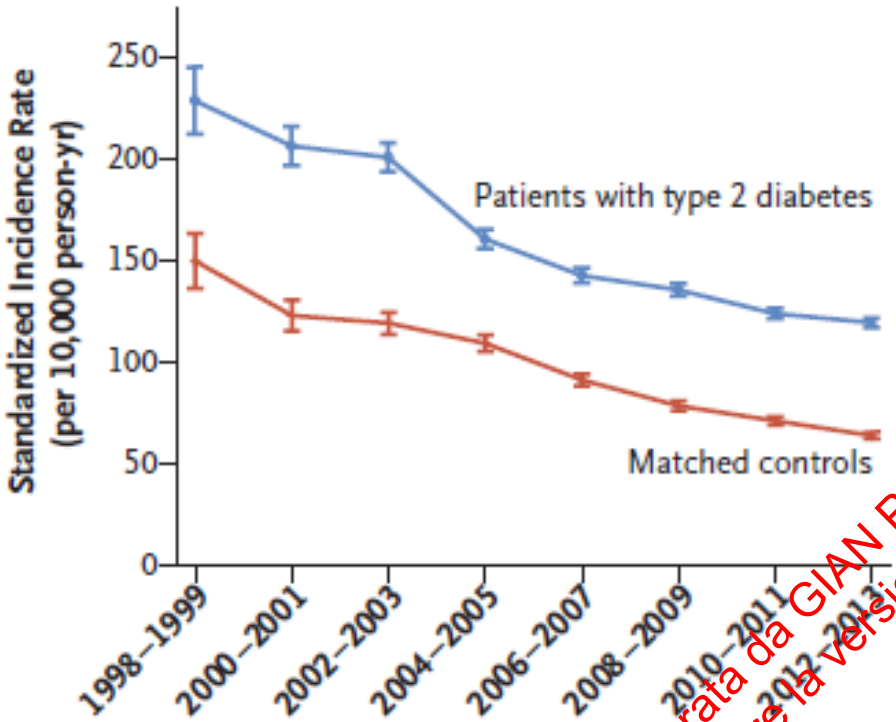
Dichiarazione di interessi

- Il Prof. GIAN PAOLO FADINI dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:
- - Astrazeneca
- - Boehringer
- - Lilly
- - Guidotti
- - Novo Nordisk
- - Sanofi

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.)

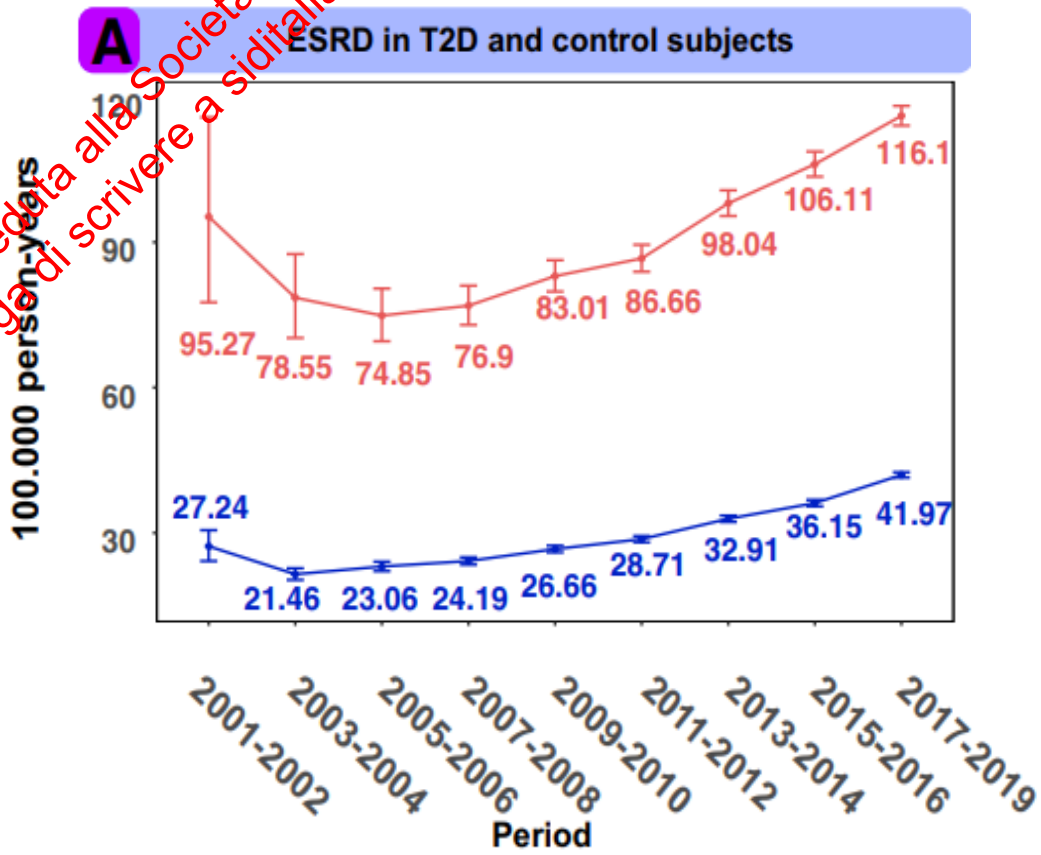
Secular trends in cardio-renal disease

Death from cardiovascular disease



Rawshani, NEJM 2017

Diabetic Kidney Disease



Halmien, Diabetes care Oct 2022

CKD primary prevention

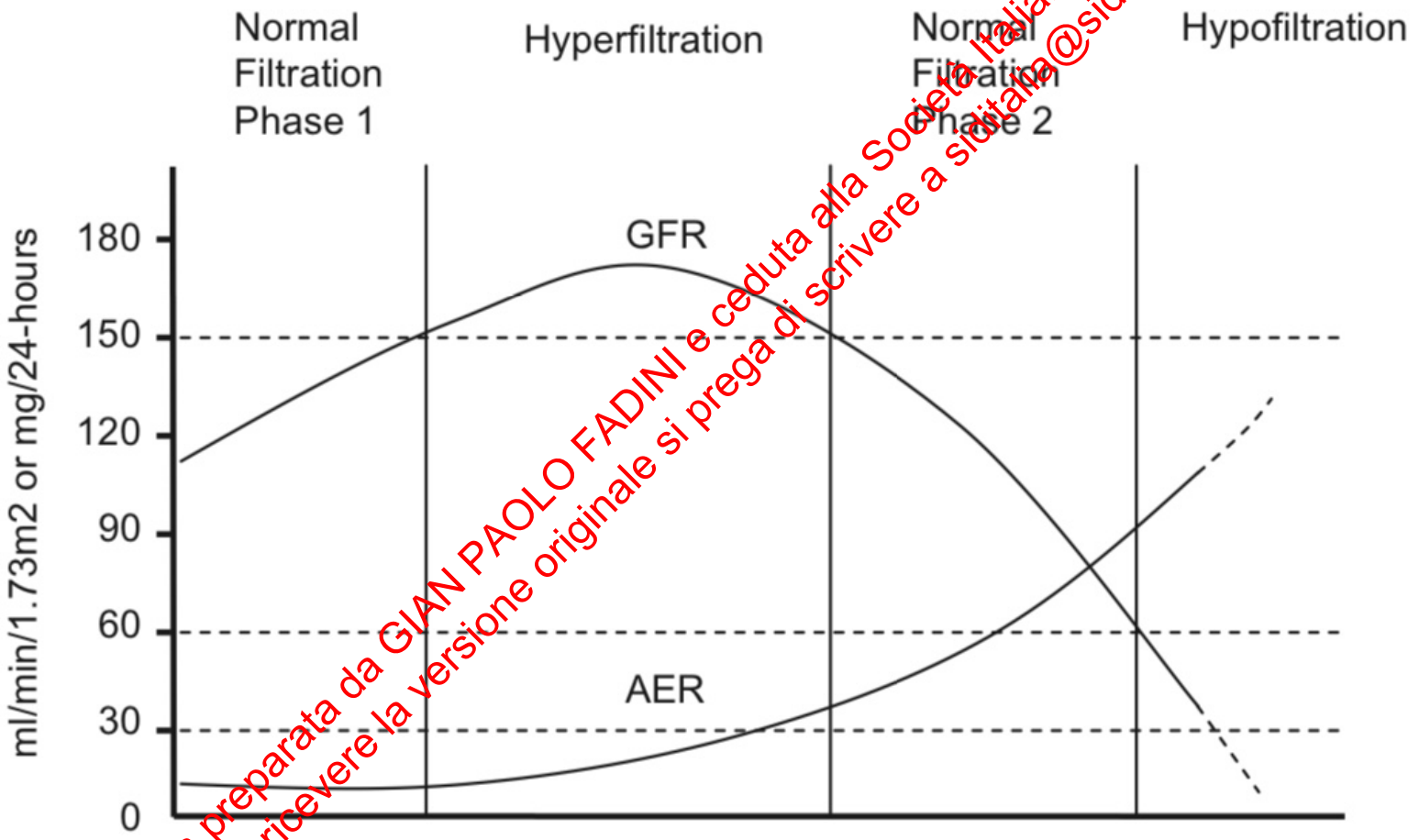
Table 1 | **Approach to preventive strategies in CKD**

Approach	Main goal	Additional targets	Alarming signs	Risk factors to target	Interventions
Primary prevention	Avert kidney disease	Manage risk factors for kidney disease; educate on primordial prevention	Glomerular hyperfiltration	Diabetes; hypertension; obesity; solitary kidney; genetic risks; other risk factors	Support lifestyle modifications with moderate physical activity; provide dietary advice including avoidance of high sodium and excessive protein intake; prevent and manage obesity; improve glycaemic and blood pressure control; identify genetic risk factors; ensure adequate hydration
Secondary prevention	Identify early disease	Slow CKD progression; prolong kidney health	Emerging or worsening albuminuria; declining eGFR	Proteinuria; poorly controlled hypertension; poor glycaemic control; high protein intake	Manage proteinuria; encourage low-sodium and low-protein diet; encourage more plant-based sources for dietary protein; identify and offer effective pharmacotherapy; individualize therapy; identify and manage additional CKD risk factors; explore integrative and alternative approaches
Tertiary prevention	Avoid kidney failure	Delay dialysis transition; preserve the remaining kidney function	Worsening uraemic signs and symptoms	AKI events and AKI risk factors; worsening cardiac function (cardiorenal syndrome)	Manage uraemic symptoms and comorbidities; manage fluid and sodium retention; manage cardiovascular risk factors; explore novel kidney preservative and supportive therapies

Primary prevention is to avert emergence of [illegible] chronic kidney disease (CKD), secondary prevention aims to identify CKD as early as possible and tertiary prevention strives to avoid end-stage kidney disease, also known as kidney failure. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

NATURE REVIEWS NEPHROLOGY, 16(3); 2020

Glomerular hyperfiltration



NEPHROLOGY DIALYSIS TRANSPLANTATION, VOLUME 27, ISSUE 5; MAY 2012

Diabetes Care
American Diabetes Association

Glomerular Hyperfiltration Predicts Kidney Function Decline and Mortality in Type 1 and Type 2 Diabetes: A 21-Year Longitudinal Study

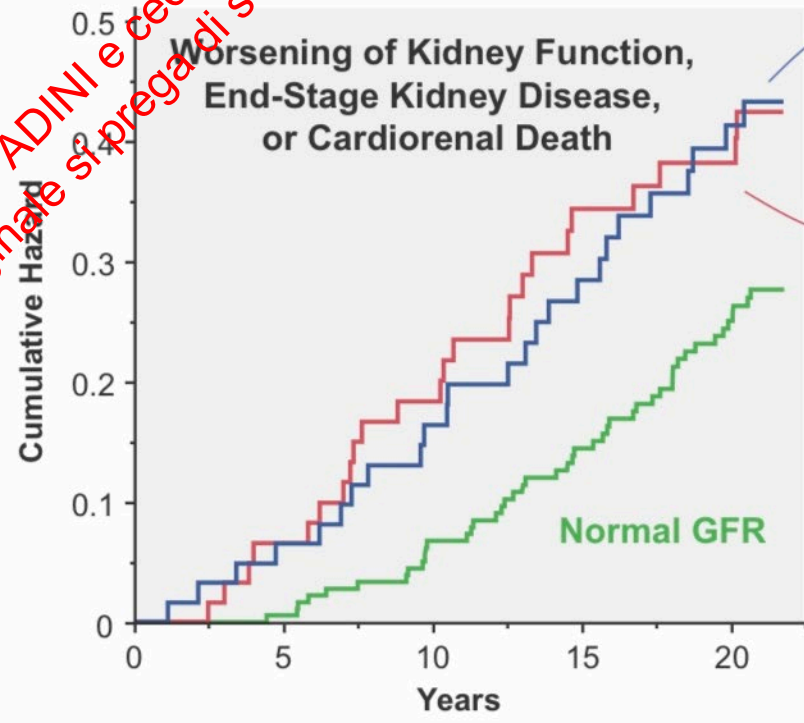
Diego Moriconi, Luca Sacchetta, Martina Chiriacò, Lorenzo Nesti, Giovanna Forotti, Andrea Natali, Anna Solini and Domenico Tricò

Diabetes Care 2023;46(4):845–853 | https://doi.org/10.2337/dc22-2003

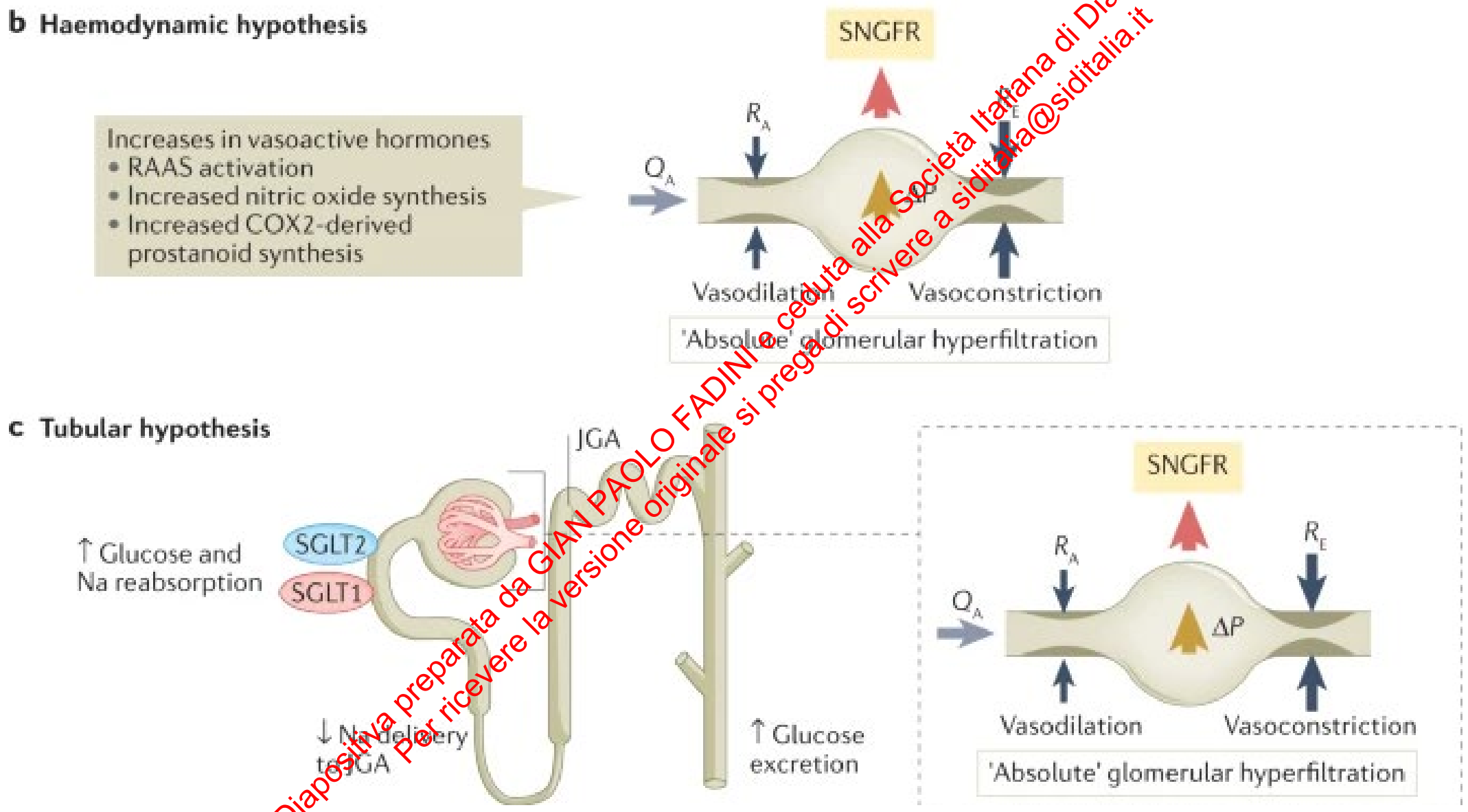
Glomerular hyperfiltration, similar to hypofiltration, increased the combined risk of worsening kidney function and mortality from cardiovascular or renal causes in diabetes

PROGNOSTIC ROLE OF GLOMERULAR HYPERFILTRATION

In 314 patients with type 1 or type 2 diabetes followed up for 21 years, glomerular filtration rate (GFR) was measured at baseline by dynamic renal scintigraphy



The origin of glomerular hyperfiltration



Nature Reviews Nephrology 2022;18:435–451

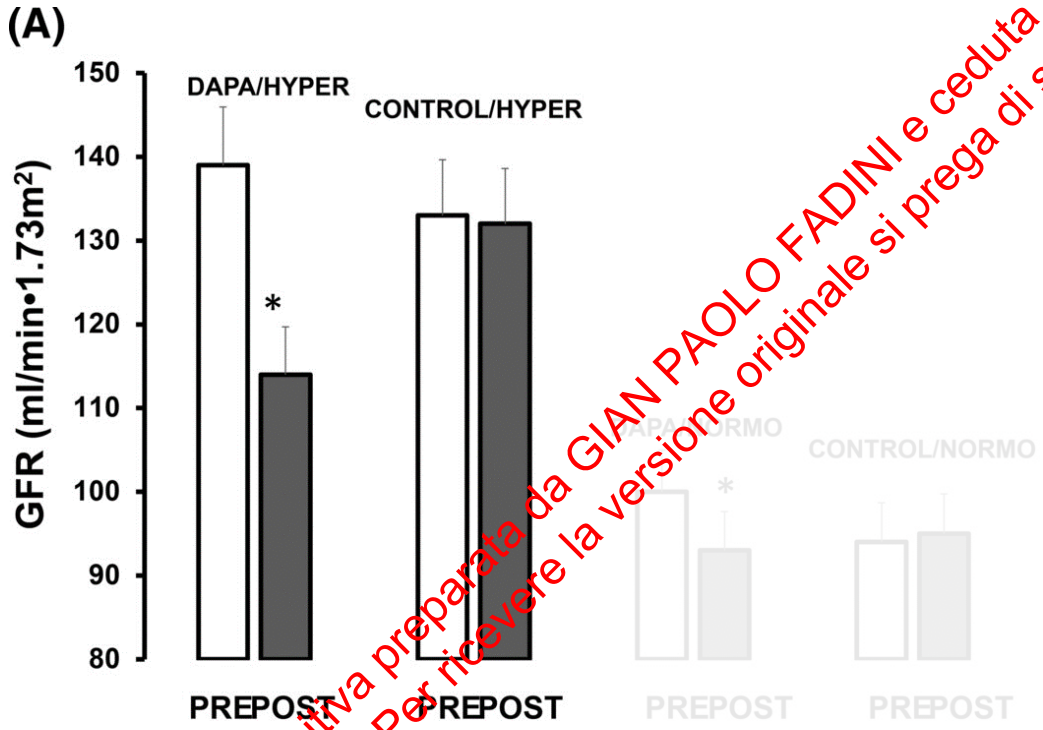
Dapagliflozin in hyperfiltering T2D

A randomized controlled trial

60 T2D pts w/wo hyperfiltration were randomized to

- Dapagliflozin
- Metformin / Glipizide

For 4 months, to achieve similar HbA1c improvement (from 8.5% to 7.0%)



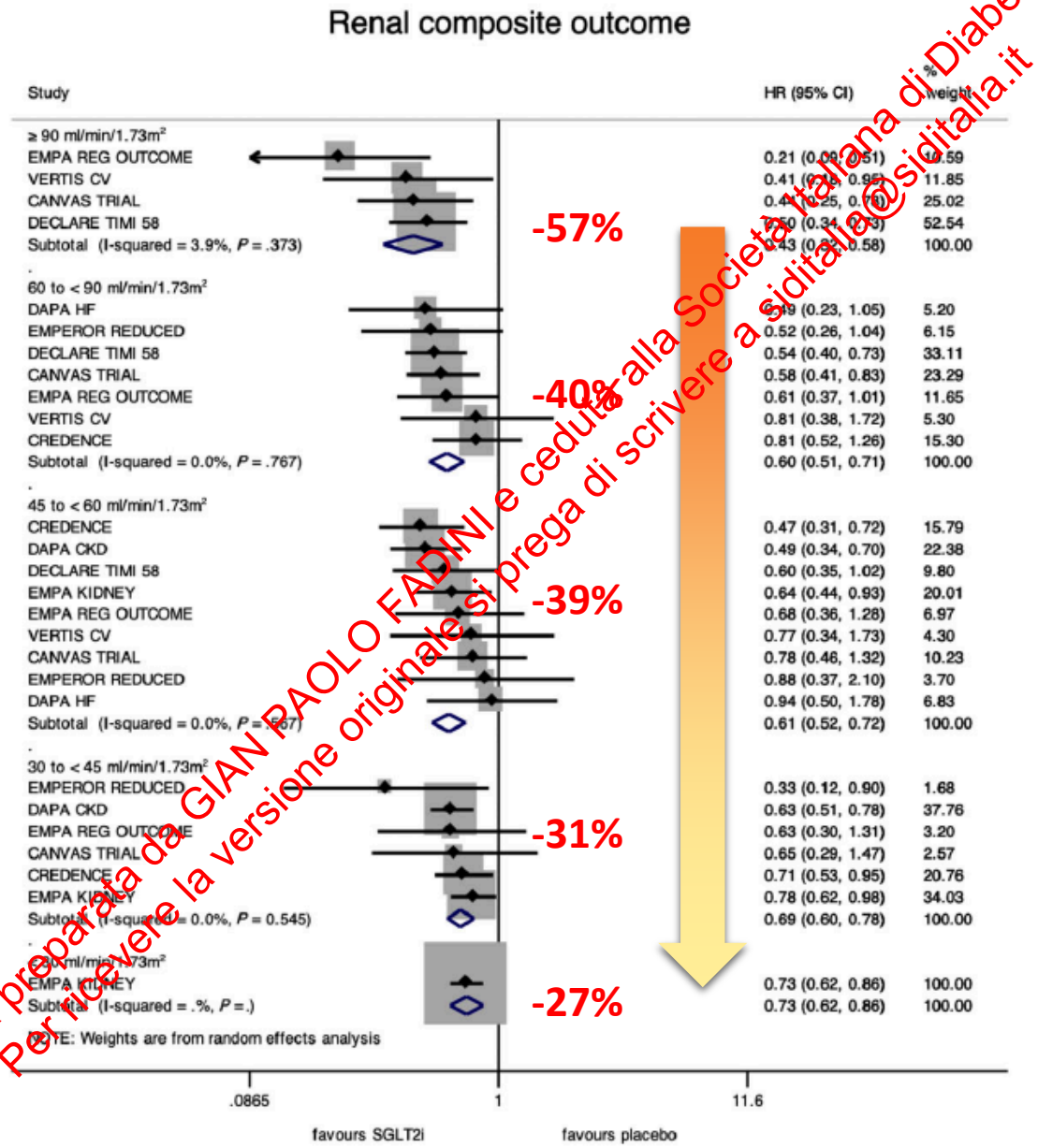
+ Decreased

- filtration fraction
- renal vascular resistance

Diabetes Obes Metab. 2025 Feb;27(2):944-952.

- ✓ Dapagliflozin counters one of the key mechanisms driving DKD progression

Risk of adverse kidney outcomes with SGLT2i by baseline eGFR

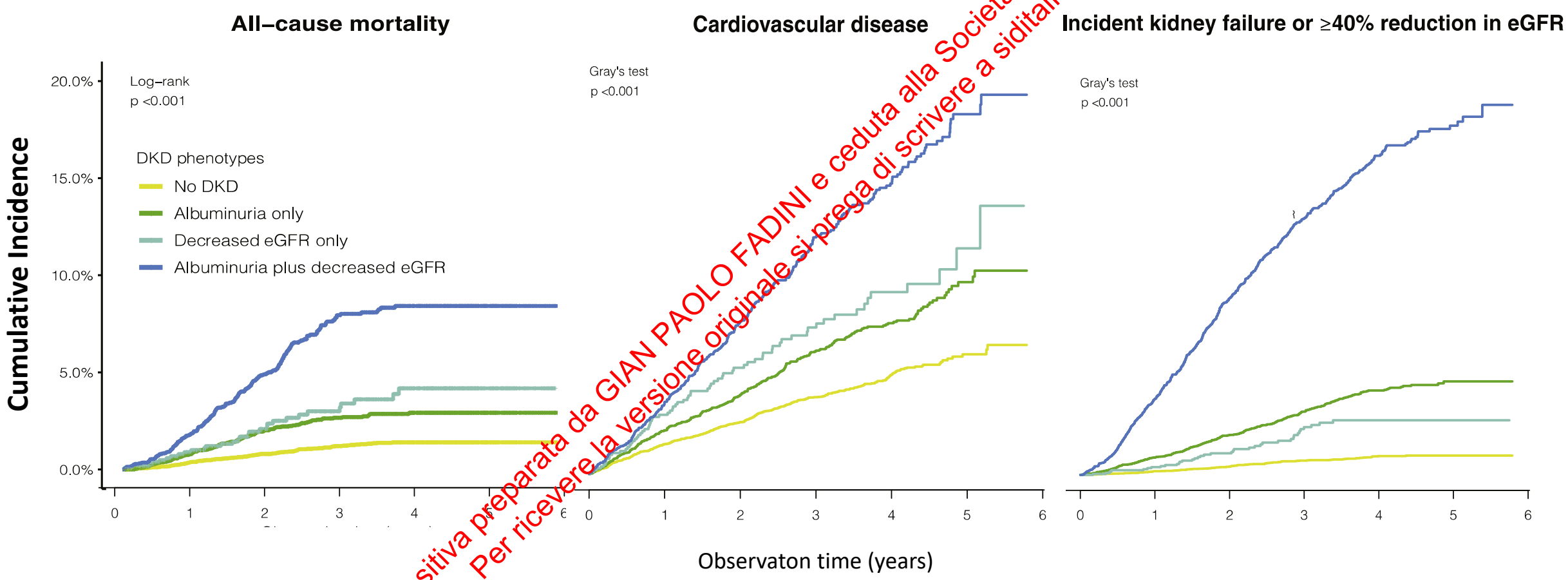


Diabetes Obes Metab. 2023 May;25(5):1341-1350

- ✓ Dapagliflozin counters one of the key mechanisms driving DKD progression
- ✓ Early initiation of SGLT2i (primary prevention) grants the best relative risk reduction of adverse kidney outcomes

The presence of albuminuria worsens all outcomes

- **19,025 Chinese adults with T2D**
- **9,312 with eGFR>30: low GFR only (11%), albuminuria only (59%), low GFR+albuminuria (30%)**

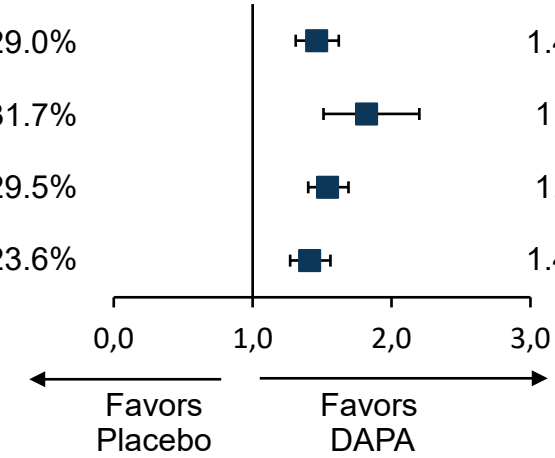


Hong Kong Diabetes Biobank Study Group, AJKD 2022

Effects of dapagliflozin on albuminuria

DECLARE-TIMI

	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	Cox p-value
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate		
Endpoints						
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.6)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	175/575 (30.4)	31.7%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.00%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<0.0001



Mosenzon O et al, Diabetes Care, 2021

- ✓ Dapagliflozin counters one of the key mechanisms driving DKD progression
- ✓ Early initiation of SGLT2i (primary prevention) grants the best relative risk reduction of adverse kidney outcomes
- ✓ Dapagliflozin is potently active against progression of albuminuria

Early use of dapagliflozin under routine care

DARWIN-Renal study

Objective

Demonstrate the long-term efficacy of dapagliflozin on multiple renal outcomes and albuminuria in patients with type 2 diabetes and low renal risk

Study design

Multicenter retrospective comparative study of efficacy, conducted by the Italian Society of Diabetology in 50 centers specialized in diabetes care in Italy.

Data Collected

From January 2015 to September 2022, clinical data were extracted from electronic medical records

Enrolled population

- Patients started on dapagliflozin
- Patients started on any other glucose-lowering medication (GLM)

The comparator drugs included: metformin (5.8%), DPP-4 inhibitors (40%), GLP-1 receptor agonists (22.3%), sulfonylureas/glinides (16.1%), pioglitazone (8%), and acarbose (4%)

Fadini et al. The Lancet Regional Health –Europe 2024

Early use of dapagliflozin under routine care

DARWIN-Renal study

Key patient characteristics

Matched cohorts n=6197 / group

Largely a primary renal prevention population
6% CKD
15% albuminuria

Age	61 years
Sex	61% males
Diabetes duration	10 years
BMI	31 kg/m^2
Systolic blood pressure	137 mm Hg
Diastolic blood pressure	79 mm Hg
Fasting glucose	169 mg/dl
HbA1c	8.2%
eGFR	**87.5 ml/min/1,73 m^2**
CKD	**6.4%**
Micro-/macroalbuminuria	**15%**
Microangiopathy	34%
Macroangiopathy	30%

Background therapy

Metformin	84%
Basal insulin	29%
Bolus insulin	9%
Sulphonylurea	10%
GLP-1RA	3.2%
Pioglitazone	2.4%
DPP-4i	1.7%

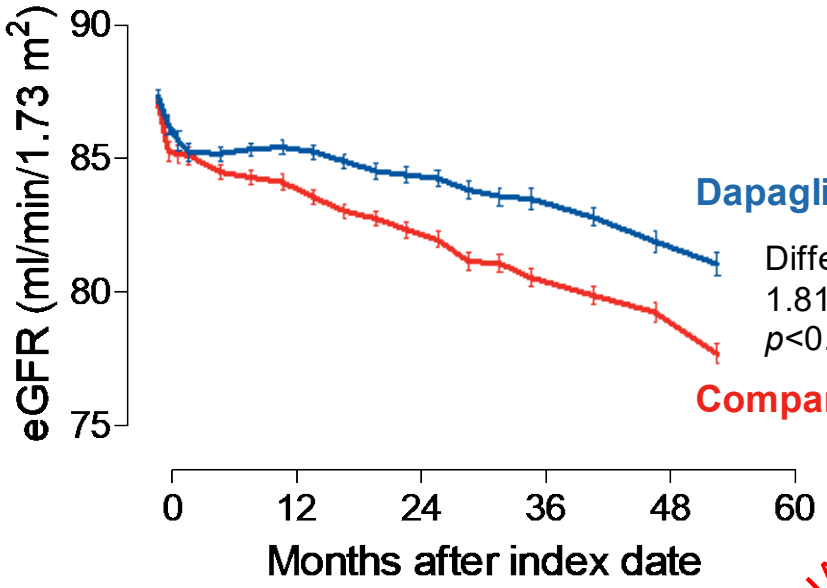
Comparators

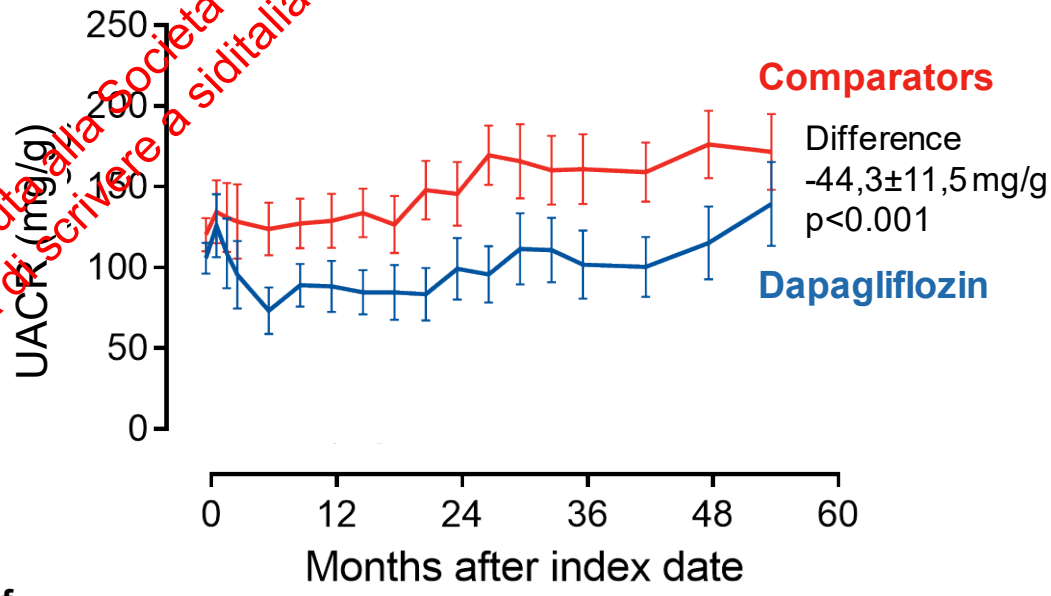
DPP-4i	38.9%
GLP-1RA	31.0%
Sulphonylureas	16.2%
Pioglitazone	7.0%
Metformin	5.1%
Acarbose	3.9%

Fadini et al. The Lancet Regional Health –Europe 2024

Early use of dapagliflozin under routine care

DARWIN-Renal study





*54

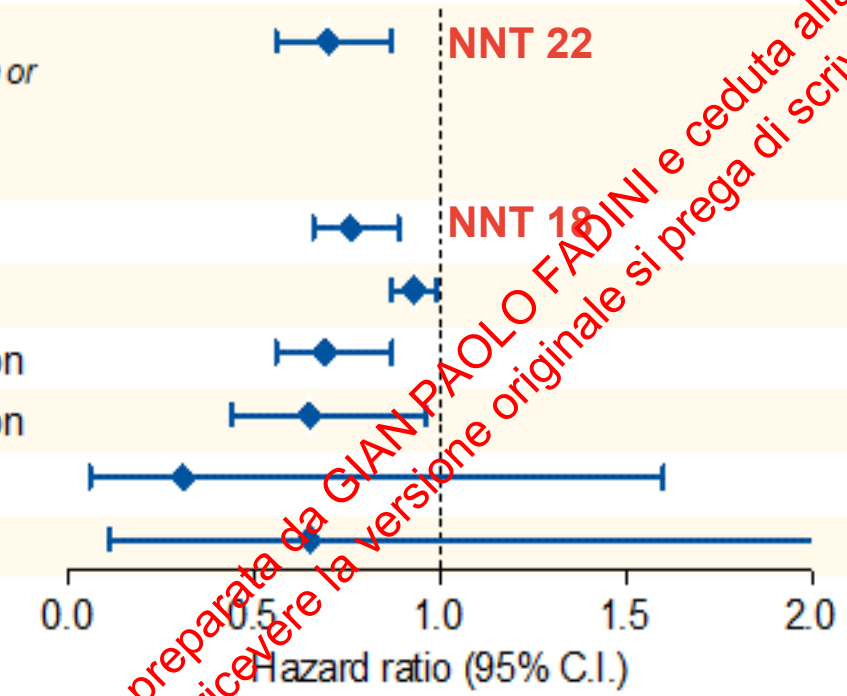
Fadini et al. The Lancet Regional Health –Europe 2024

Early use of dapagliflozin under routine care

DARWIN-Renal study

A) Dapagliflozin

Endpoint	Crude rates / 1000 PYE Dapagl.	Controls	Adjusted hazard ratio (95% C.I.)	p-value
Composite renal *Sustained >40% eGFR reduction or End-stage kidney disease or Dialysis*	16.3	25.5	0.70 (0.56 - 0.87)	0.002
New-onset CKD	28.3	39.4	0.76 (0.66 - 0.89)	<0.001
Worsening CKD class	237.5	250.4	0.93 (0.87 - 0.99)	0.037
Sustained >40% eGFR reduction	16.2	25.5	0.69 (0.56 - 0.87)	0.002
Sustained >57% eGFR reduction	4.9	8.5	0.65 (0.44 - 0.96)	0.035
End-stage kidney disease	0.2	0.9	0.32 (0.06 - 1.63)	0.169
Dialysis	0.2	0.3	0.65 (0.11 - 3.70)	0.658



Fadini et al. The Lancet Regional Health –Europe 2024

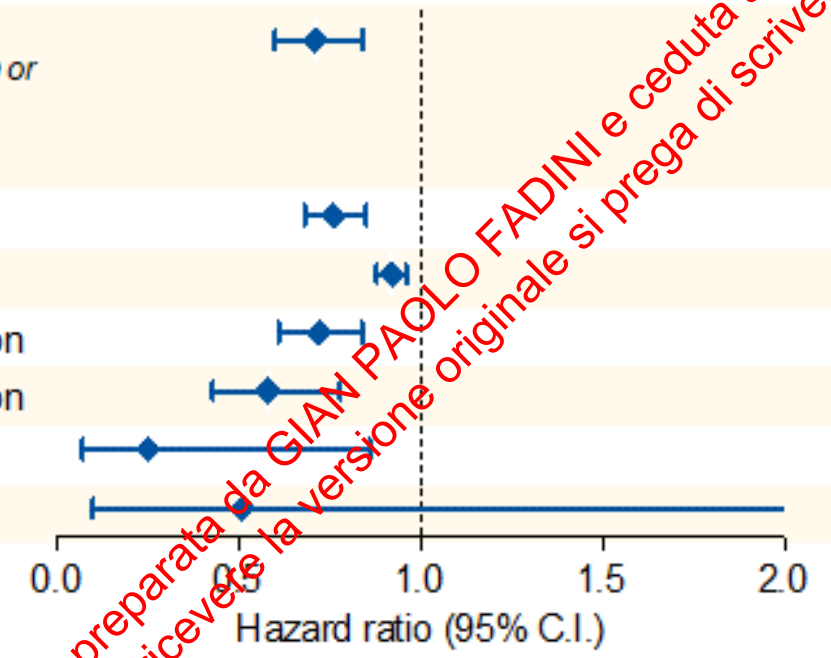
Early use of SGLT2i under routine care

DARWIN-Renal study

10,918 new users of SGLT2i* vs 10,918 new users of comparators

B) All SGLT2 inhibitors

Endpoint	Crude rates / 1000 PYE SGLT2i	Crude rates / 1000 PYE Controls	Adjusted hazard ratio (95% C.I.)	p-value
Composite renal *Sustained >40% eGFR reduction or End-stage kidney disease or Dialysis*	16.4	25.2	0.71 (0.60 - 0.84)	<0.001
New-onset CKD	28.4	39.6	0.76 (0.68 - 0.85)	<0.001
Worsening CKD class	237.0	254.1	0.92 (0.88 - 0.96)	<0.001
Sustained >40% eGFR reduction	16.5	25.2	0.72 (0.61 - 0.84)	<0.001
Sustained >57% eGFR reduction	4.4	8.5	0.58 (0.43 - 0.78)	<0.001
End-stage kidney disease	0.2	0.9	0.25 (0.07 - 0.86)	0.042
Dialysis	0.1	0.2	0.51 (0.10 - 2.55)	0.436



*dapagliflozin 53.1%; empagliflozin 38.7%; canagliflozin 8.0%; ertugliflozin 0.1%.

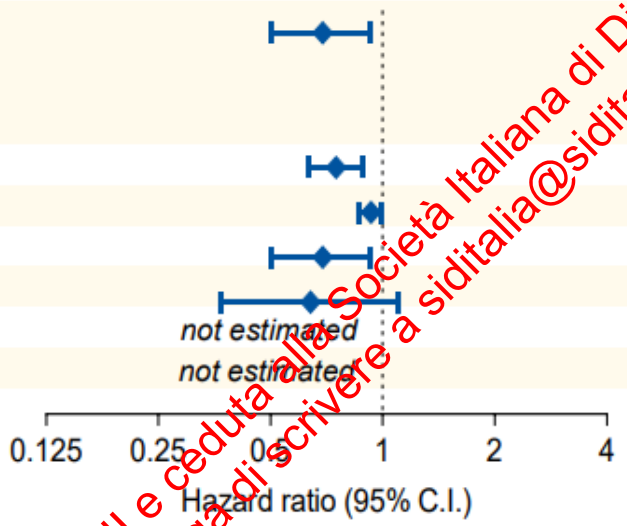
- ✓ Dapagliflozin counters one of the key mechanisms driving DKD progression
- ✓ Early initiation of SGLT2i (primary prevention) grants the best relative risk reduction of adverse kidney outcomes
- ✓ Dapagliflozin is potently active against progression of albuminuria
- ✓ In people with T2D and low renal risk, dapagliflozin reduced eGFR loss and UACR increase, projected to reduce rates of ESKD

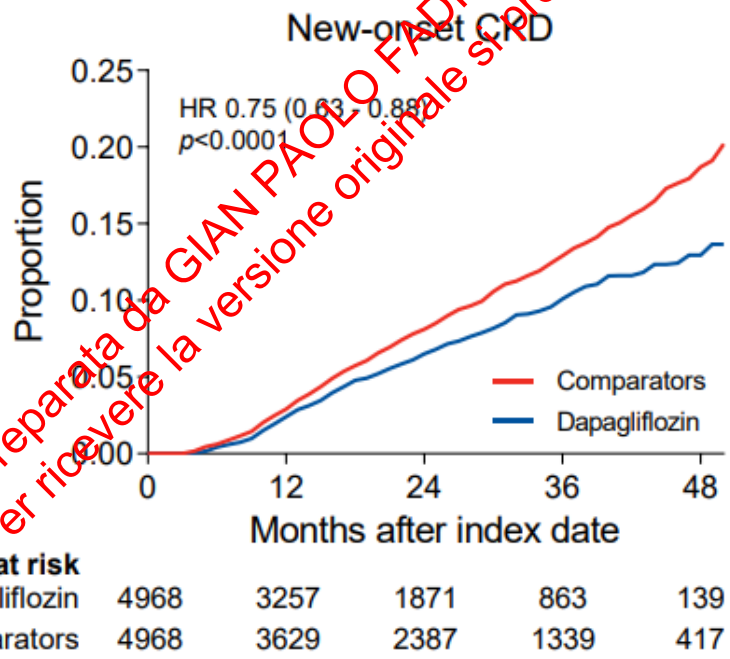
Primary prevention cohort

5000 pts / group
Baseline eGFR 90 ml/min
Baseline UACR 10 mg/g

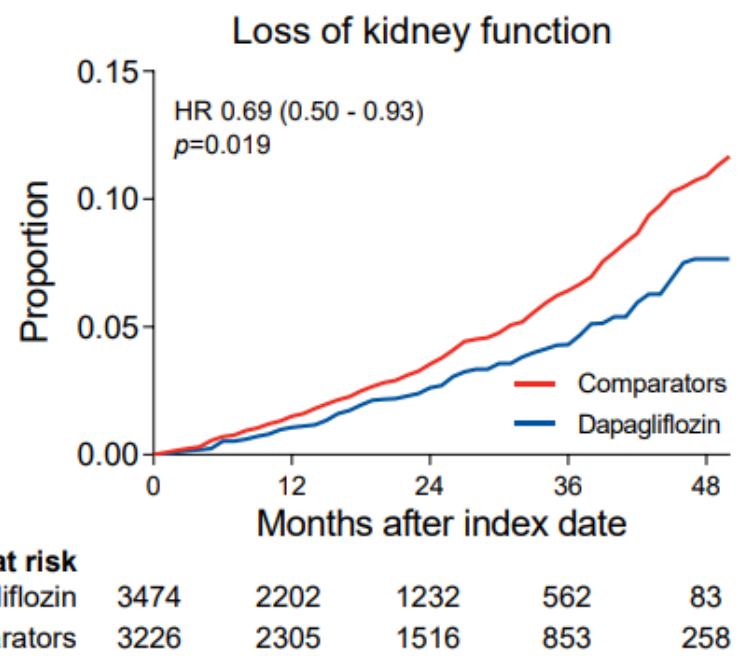
0% CKD
All eGFR >60 ml/min
UACR <30 mg/g

Endpoint	Crude rates / 1000 PYE Dapagl.	Controls	Adjusted hazard ratio (95% C.I.)	p-value
Composite renal *Sustained >40% eGFR reduction or End-stage kidney disease or Dialysis*	12.0	19.3	0.69 (0.50 - 0.93)	0.018
New-onset CKD	26.4	37.5	0.75 (0.63 - 0.88)	<0.0001
Worsening CKD class	235.9	250.2	0.93 (0.86 - 0.99)	0.030
Sustained >40% eGFR reduction	12.0	19.3	0.69 (0.50 - 0.93)	0.019
Sustained >57% eGFR reduction	3.5	6.4	0.64 (0.37 - 1.10)	0.113
End-stage kidney disease	*not estimated*			
Dialysis	*not estimated*			





No. at risk					
Dapagliflozin	4968	3257	1871	863	139
Comparators	4968	3629	2387	1339	417



No. at risk					
Dapagliflozin	3474	2202	1232	562	83
Comparators	3226	2305	1516	853	258

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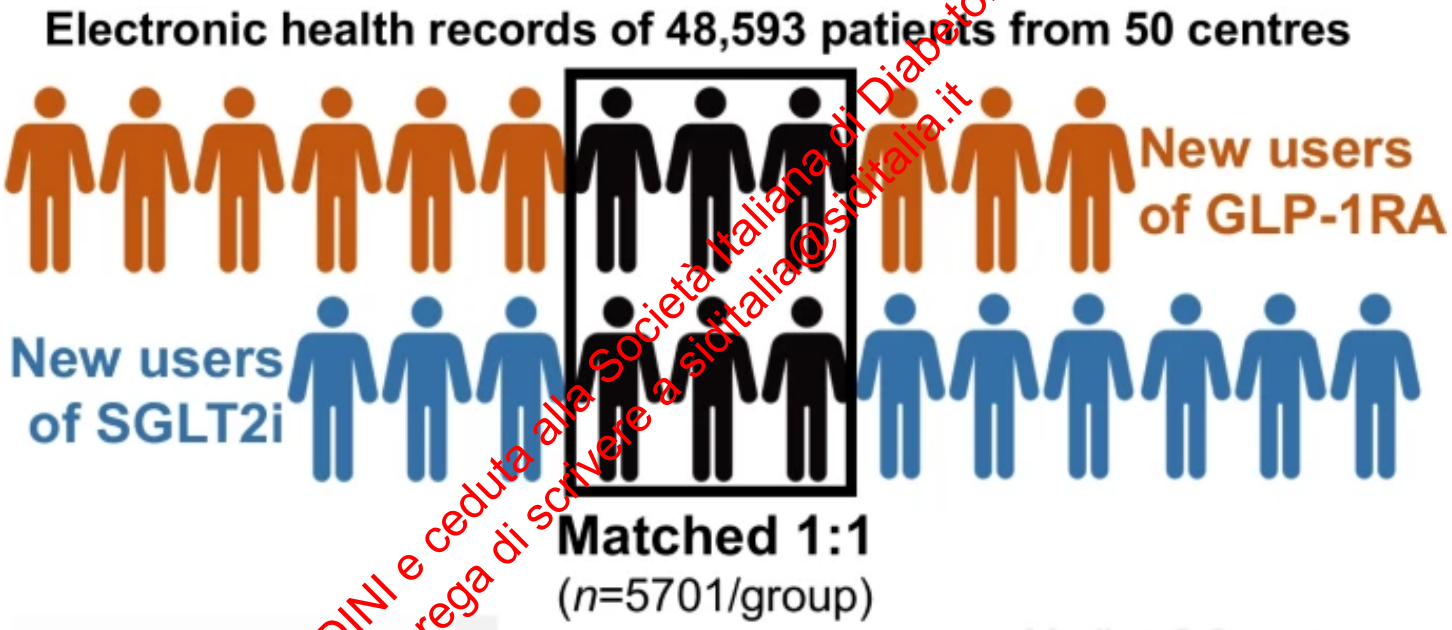
- ✓ In people with T2D and low renal risk, dapagliflozin reduced eGFR loss and UACR increase, projected to reduce rates of ESKD
- ✓ In primary prevention, dapagliflozin prevented new-onset CKD

SGLT2i *vs* GLP-1RA

5701 pts / group
Age 61
Baseline eGFR 87 ml/min

9% eGFR <60 ml/min
15% UACR >30 mg/g



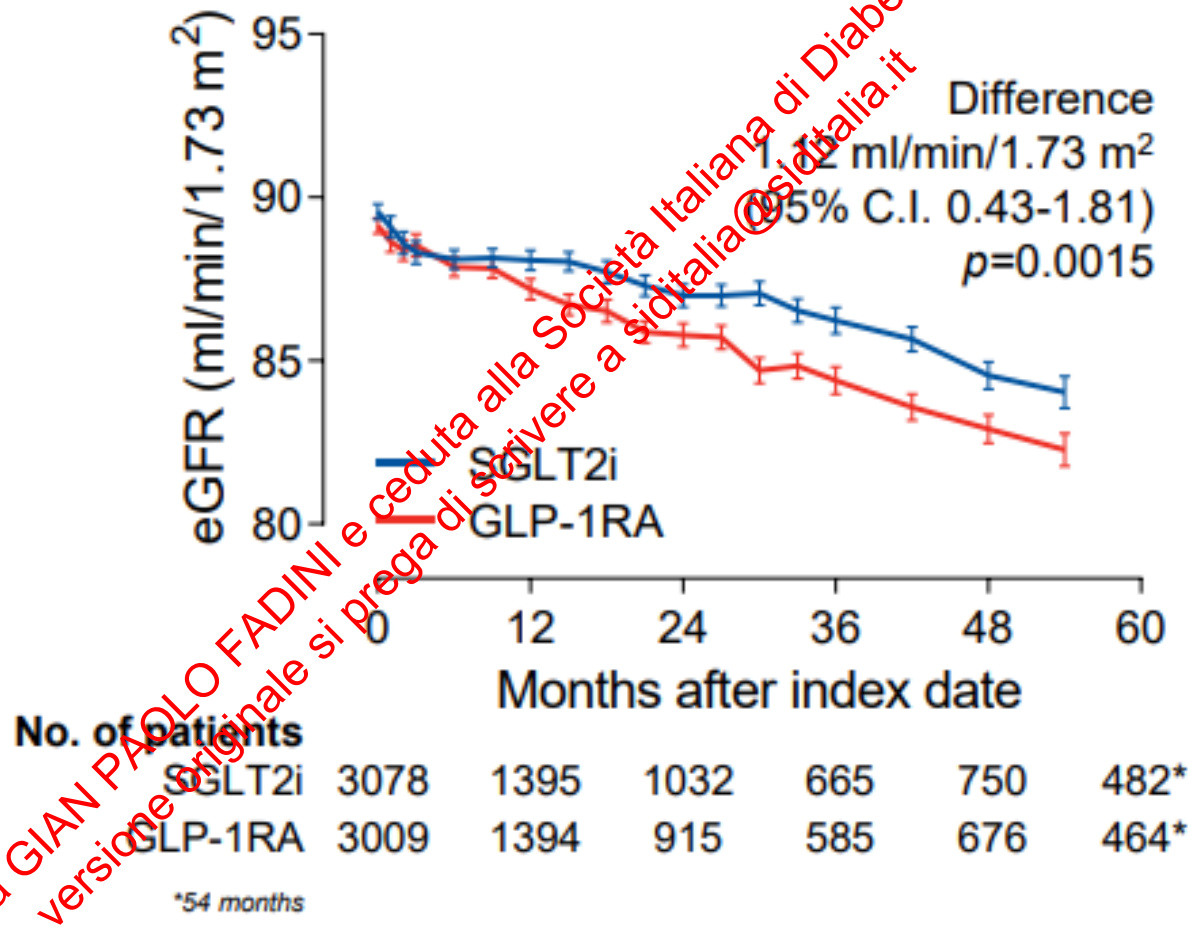
Diabetologia. 2024 Nov;67(11):2585-2597

SGLT2i *vs* GLP-1RA

Primary prevention

4430 pts / group
Age 60
Baseline eGFR 90 ml/min

0% eGFR <60 ml/min
0% UACR >30 mg/g



Diabetologia. 2024 Nov;67(11):2585-2597.

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- ✓ In primary prevention, dapagliflozin prevented new-onset CKD
- ✓ SGLT2i grant better preservation of kidney function vs GLP-1RA, even in primary renal prevention

Early use of SGLT2i under routine care

In combination therapy with GLP-1RA

Rationale

- SGLT2i and GLP-1RA have potentials for protecting from adverse kidney outcomes in people with T2D
- Many patients with T2D receive the combination in clinical practice
- The combination is supposed to have additional protective effects compard with either drug class alone
- The best sequencing of SGLT2i and GLP-1RA for kidney protection is not known

Objective

- Compare kidney outcomes in people with T2D who received the combination therapy starting with SGLT2i (SG group) or the GLP-1RA group (GS group).

Exposure: SG vs GS sequence

Primary outcome measure: change in eGFR over time

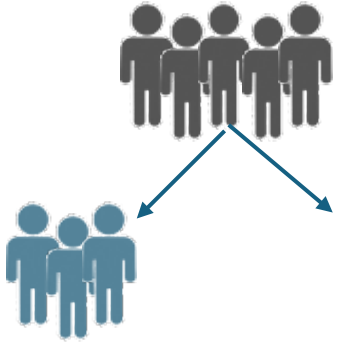
Secondary outcome measures: change in UACR, HbA1c, body weight

submitted

Early use of SGLT2i under routine care

In combination therapy with GLP-1RA

People with T2D on both SGLT2i and GLP-1RA



GS (GLP-1RA first)

SG (SGLT2i first)

Inverse probability of treatment weighting

Age 69 y

29% females

Duration 15 y

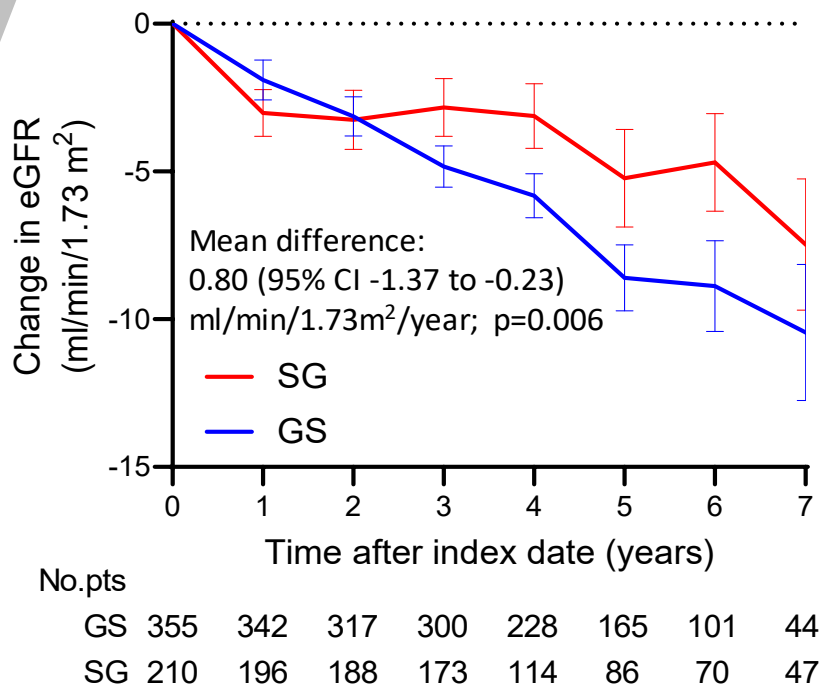
BMI 31 kg/m^2

HBA1c 8.4%

eGFR 80 ml/min

HbA1c Weight UACR

Similar effect on HbA1c, weight and UACR, but better eGFR preservation in SG vs GS



No.pts

GS	355	342	317	300	228	165	101	44
SG	210	196	188	173	114	86	70	47

Under review

SGLT2i as foundational therapy for preventing CKD in T2D

- ✓ Dapagliflozin counters one of the key mechanisms driving DKD progression
- ✓ Early initiation of SGLT2i (primary prevention) grants the best relative risk reduction of adverse kidney outcomes
- ✓ Dapagliflozin is potently active against progression of albuminuria
- ✓ In people with T2D and low renal risk, dapagliflozin reduced eGFR loss and UACR increase, projected to reduce rates of ESKD
- ✓ In primary prevention, dapagliflozin prevented new-onset CKD
- ✓ SGLT2i grant better preservation of kidney function vs GLP-1RA, even in primary renal prevention
- ✓ Early SGLT2i use confers better renal protection even when GLP-1RA intensification is subsequently required