Malattia renale cronica nel diabete (DKD): un'evoluzione "ibrida" e le nuove strategie di trattamento

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Disclosure

La Dr.ssa **Garofolo Monia**
dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Eli-Lilly, Novo Nordisk, Bayer

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.).

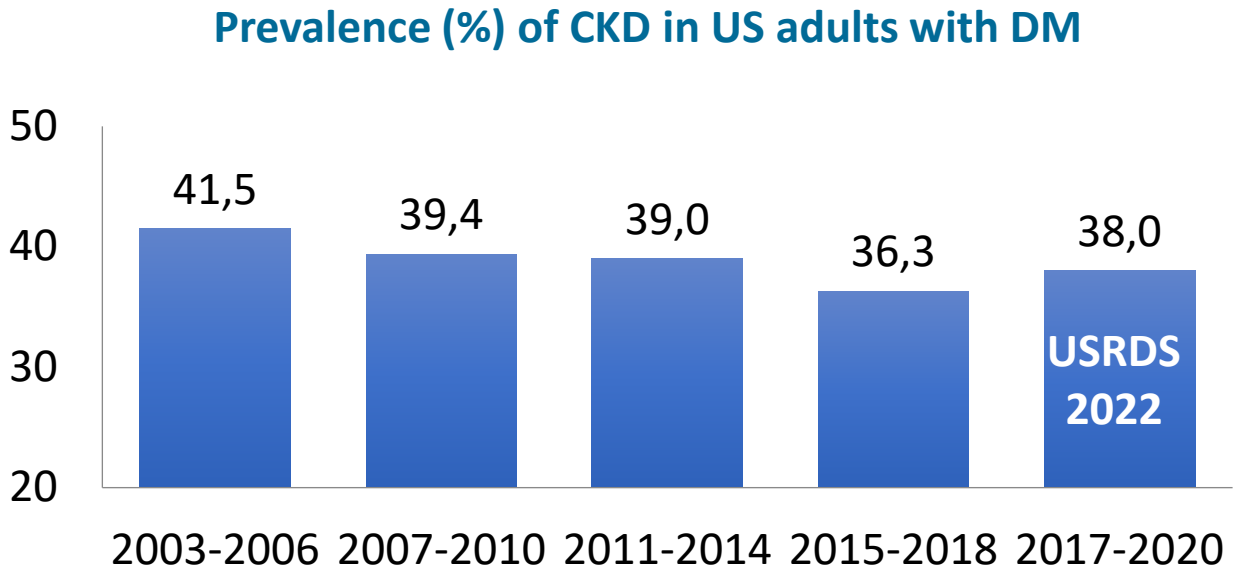
- **Epidemiologia ‘ibrida’ della DKD**

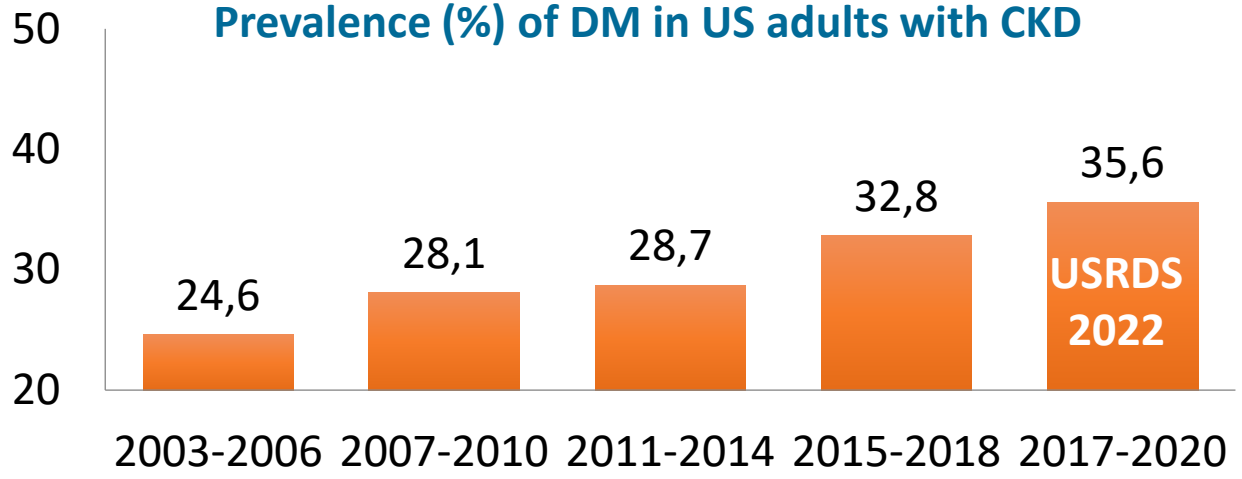
USRDS – 2021 ADR – CKD in US adults

- Il Report 2021 dell'USRDS esamina la prevalenza di CKD nel DMT2 in quattro distinti periodi di quattro anni ciascuno: dal 2003-2006 al 2015-2018.

- **La prevalenza di CKD nel DM è diminuita** progressivamente attraverso i quadrienni dal 41.5% al 36.3%.

- D'altra parte, **la prevalenza del DM tra gli individui con CKD è aumentata** dal 24.6% nel 2003-2006, al 32,8% nel 2015-2018.





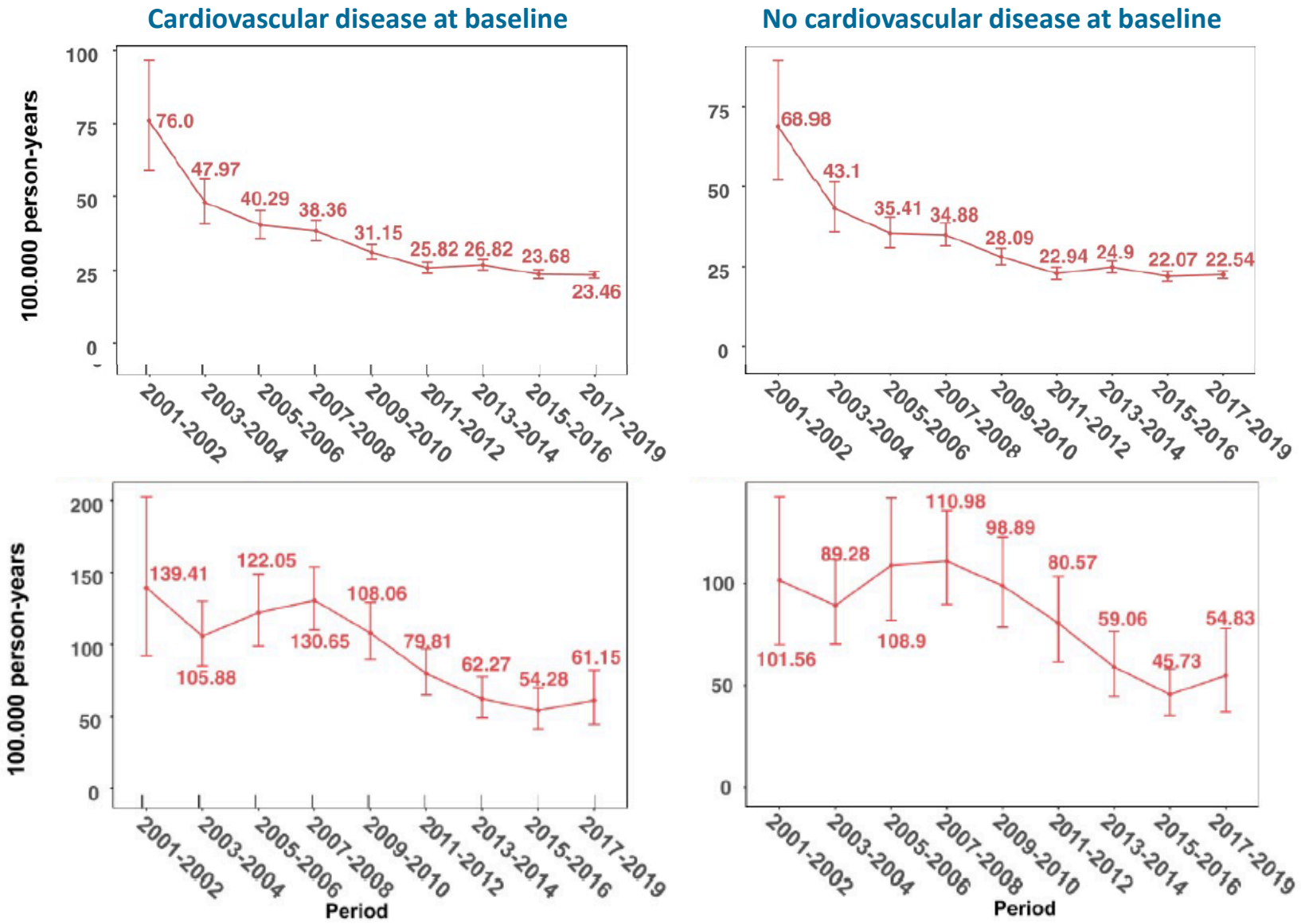
US Renal Data System 2018 Annual Data Report – 2021 Annual Data Report , AJKD 2022; 79 (suppl. 1): S1-S177; USRDS – 2022 ADR

Temporal Trends for Nephropathy and ESRD in Type 2 and Type 1 Diabetes

701,622 patients with diabetes from the Swedish National Diabetes Register and 2,738,137 control subjects

Incidence of DKD in Type 2 Diabetes

Incidence of DKD in Type 1 Diabetes



Halminen J et al. Diabetes Care 2022; 45: 2326-2335

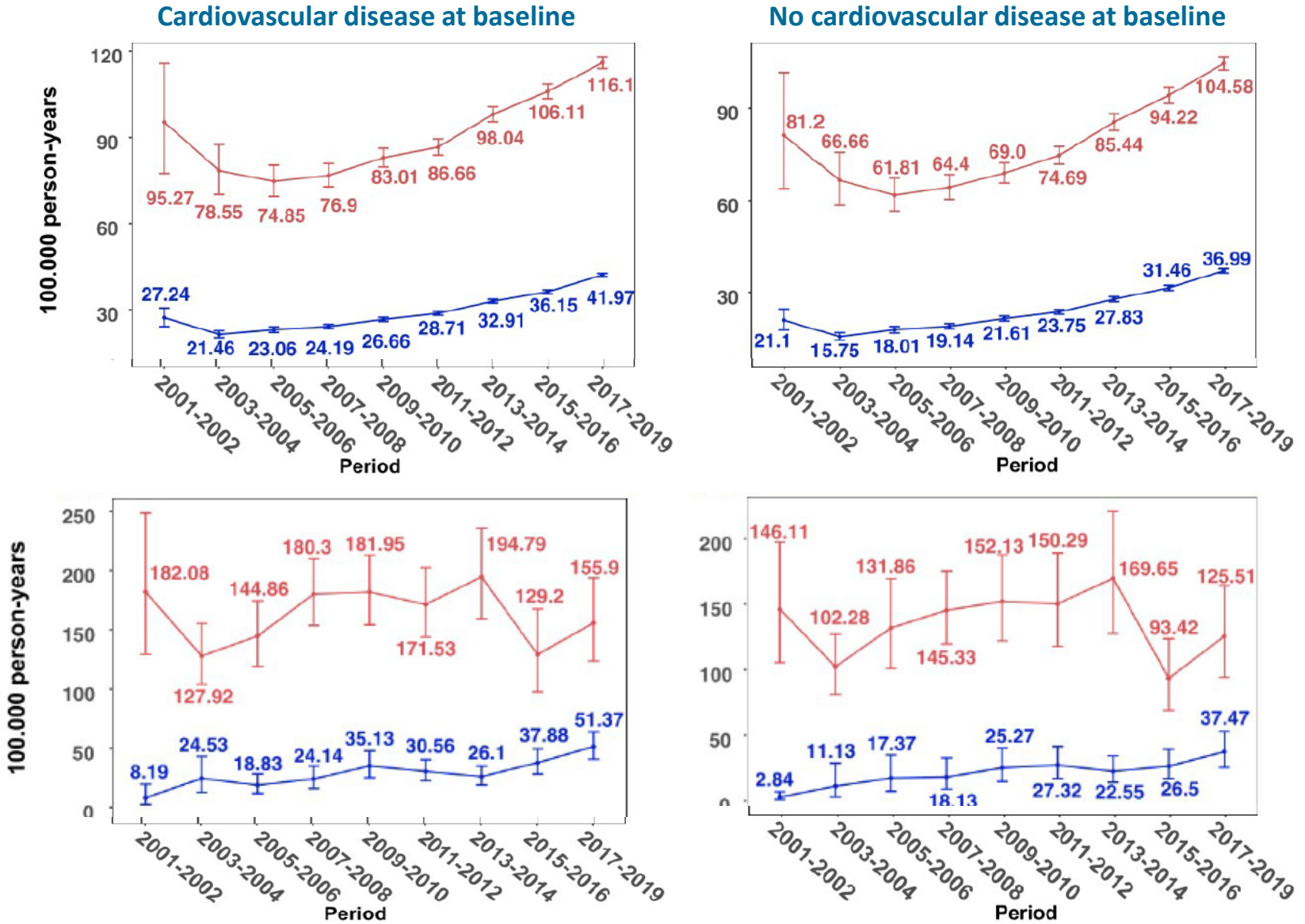
Temporal Trends for Nephropathy and ESRD in Type 2 and Type 1 Diabetes

666,899 patients with T2D from the Swedish National Diabetes Register and 2,577,579 control subjects

Incidence of ESRD in Type 2 Diabetes and Controls

DM Control

Incidence of ESRD in Type 1 Diabetes and Controls



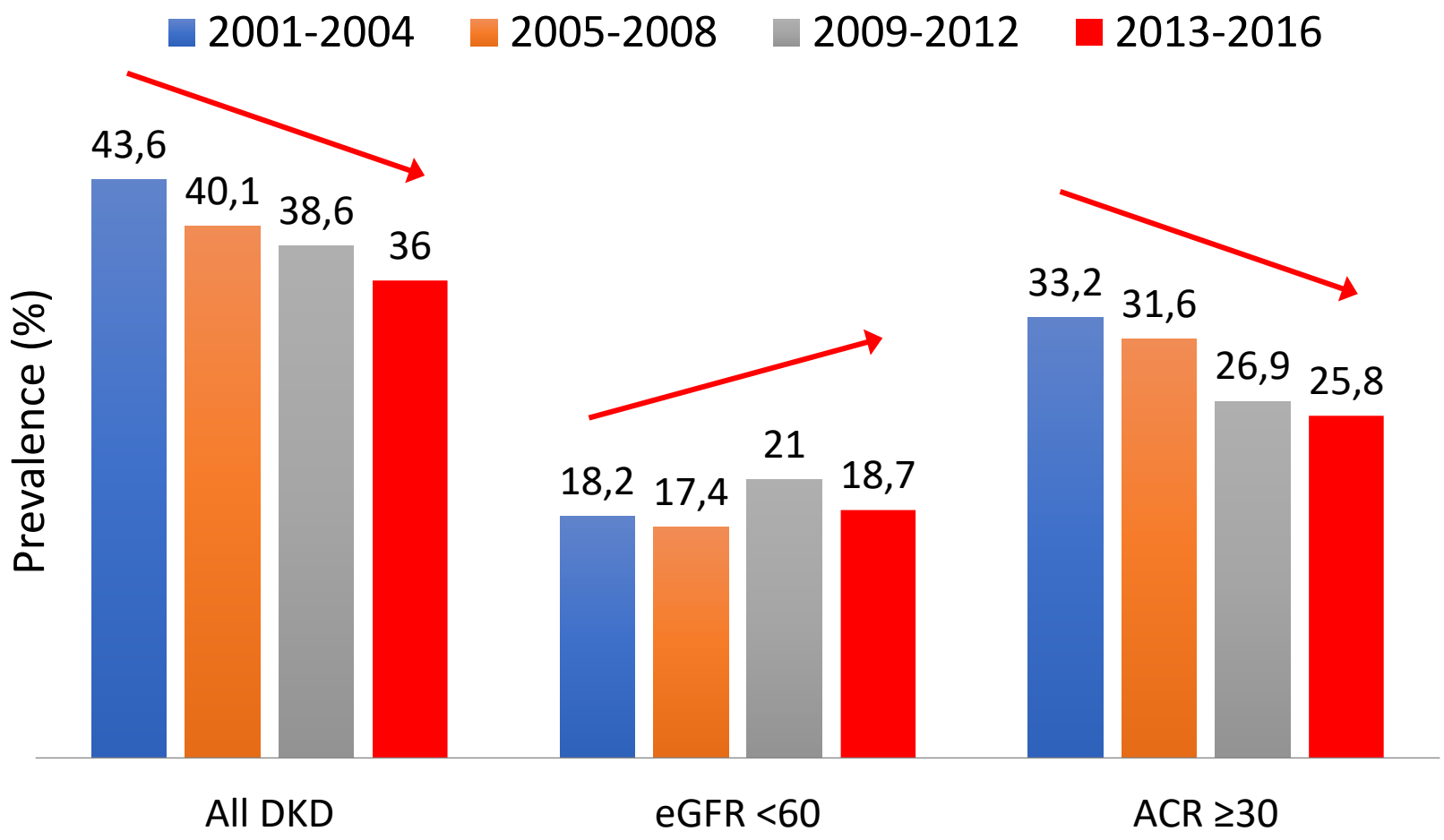
Halminen J et al. Diabetes Care 2022; 45: 2326-2335

- Epidemiologia ‘ibrida’ della DKD
- **Fenotipi ‘ibridi’ di DKD**

USRDS – 2018 ADR – CKD in US adults

Prevalence (%) of DKD in NHANES population within DM, 2001-2016

- DKD diagnosticata come eGFR <60 ml/min/1.73 m^2 e/o ACR ≥30 mg/g.
- Prevalenza di **DKD** e odd ratios (OR) si riducevano progressivamente.
- Prevalenza di **eGFR <60** e OR aumentavano (da 1.9 a 2.4).
- Prevalenza di **ACR ≥30** e OR si riducevano progressivamente (da 4.16 to 3.03).



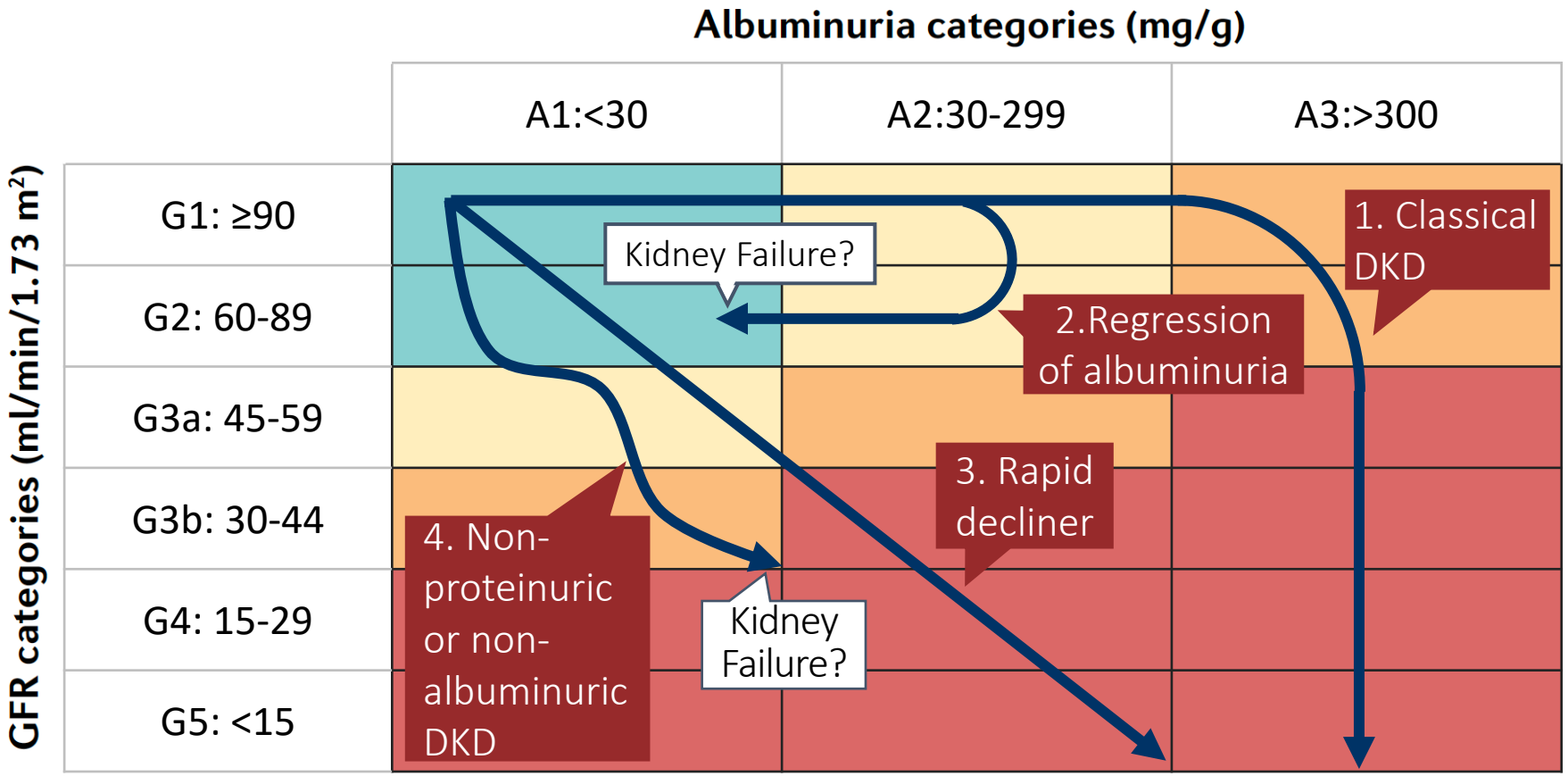
US Renal Data System - 2018 Annual Data Report – Am J Kidney Dis 2019; 73(Suppl 1): S1-S28

DKD phenotypes

- La DKD è tradizionalmente caratterizzata da una fase di iperfiltrazione, comparsa di albuminuria persistente e successiva diminuzione della velocità di filtrazione glomerulare (GFR); questa traiettoria è ampiamente riconosciuta come il **fenotipo classico di DKD** (1).

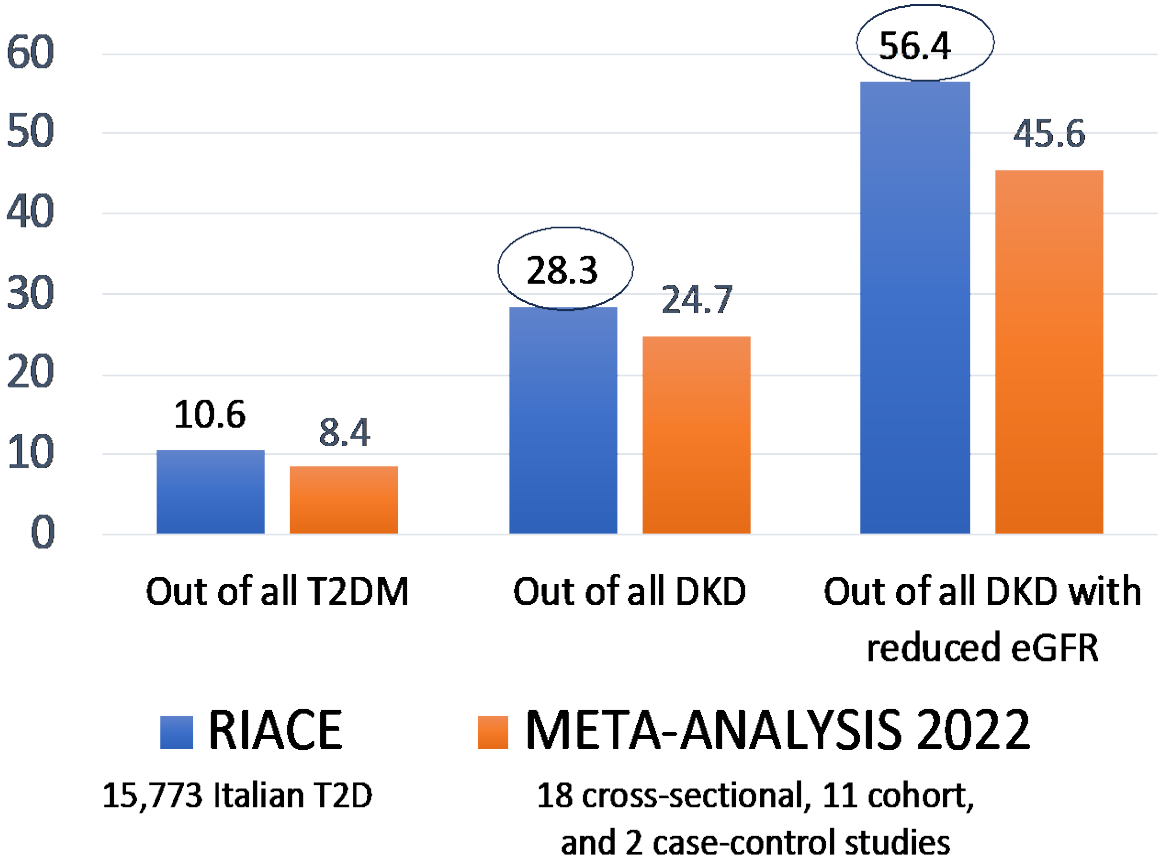
- Tuttavia, le traiettorie della funzione renale (modifiche in GFR e albuminuria nel tempo) possono differire da questo fenotipo classico.

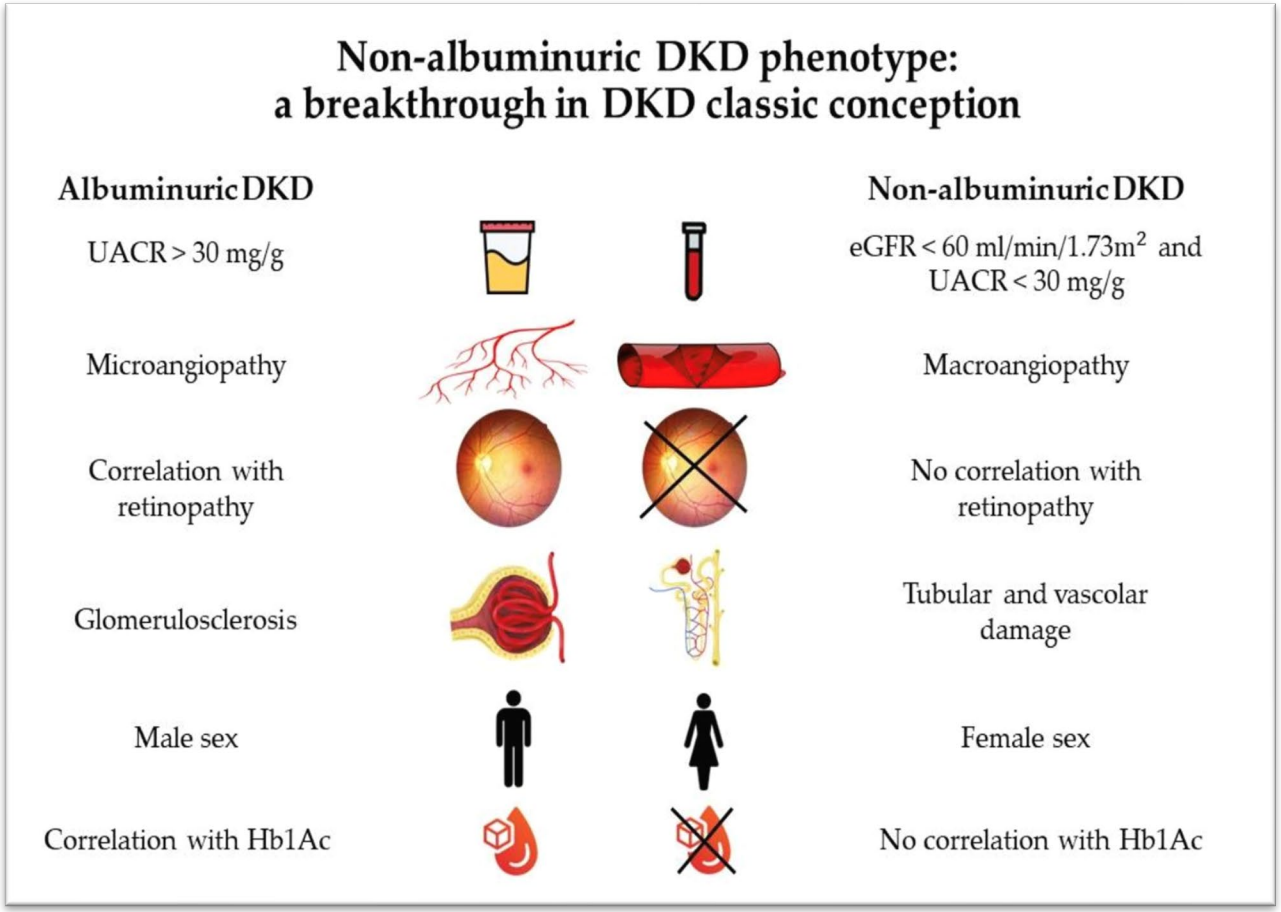
- Sono stati descritti tre fenotipi alternativi non classici di DKD, caratterizzati da:
  - Regressione dell'albuminuria (2)
  - Rapido declino di eGFR (3)
  - Riduzione di eGFR in assenza di albuminuria o proteinuria (4); il **fenotipo emergente di DKD**



Oshima M, et al.. *Nat Rev Nephrol* 2021; 17: 740-750.

Distribution and characteristics of non-albuminuric DKD phenotypes in RIACE and in the most recent meta-analysis





Penno G et al. J Hypertens. 2011; 29: 1802-9 - Shi S et al. Front Endocrinol (Lausanne) 2022; 13: 871272 - Scilletta S et al. Biomolecules. 2023 Apr 26; 13: 752

The prevalence of the Alb¯DKD phenotypes in different populations with type 1 and type 2 DM is increasing

T1DM (Alb-DKD of all DKD with reduced eGFR)

Cross-sectional studies from several countries:

FinnDiane	FINLAND	1998-2005	15.5%
Penno G. et al.	**ITALY**	**2001-2009**	**58.6%**
Pacilli A. et al.	**ITALY**	**2004-2011**	**48.9%**
Lamacchia O. et al.	**ITALY**	**2004-2011**	**51.5%**
UK National Diabetes Audit	UK	2007-2008	54.4%
Colombo M. et al.	SCOTLAND	2010-2013	59.1%

Pugliese G et al., Nutr Metab Cardiovasc Dis 2019, 29: 1127-1150 (Joint Position Statement SID-SIN)

- Epidemiologia ‘ibrida’ della DKD
- Fenotipi ‘ibridi’ di DKD
- **Prognosi ‘ibrida’ della DKD**

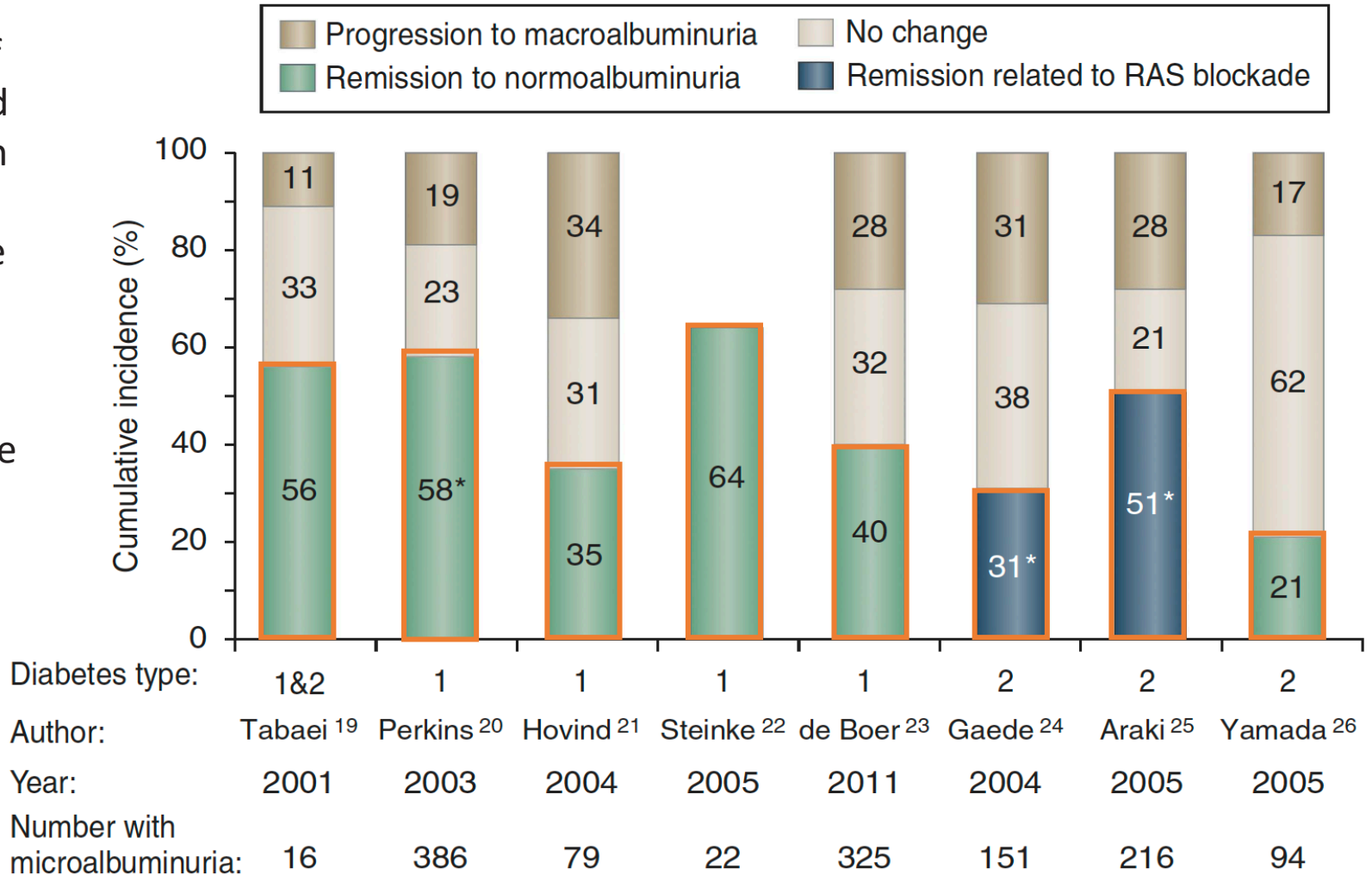
Diabetic Kidney Disease

3 gigantic risks

(1) Premature death
(2) CV disease (including HF)
(3) Kidney failure

Regression of albuminuria

- In the early 1980s, occurrence of microalbuminuria was associated with a 60-80% risk of progression to macroalbuminuria over 6-14 years, mainly in people with type 1 diabetes.
- Today, the development of microalbumiuria can no longer be viewed as a committed and irreversible stage of DKD, as spontaneous remission is common.

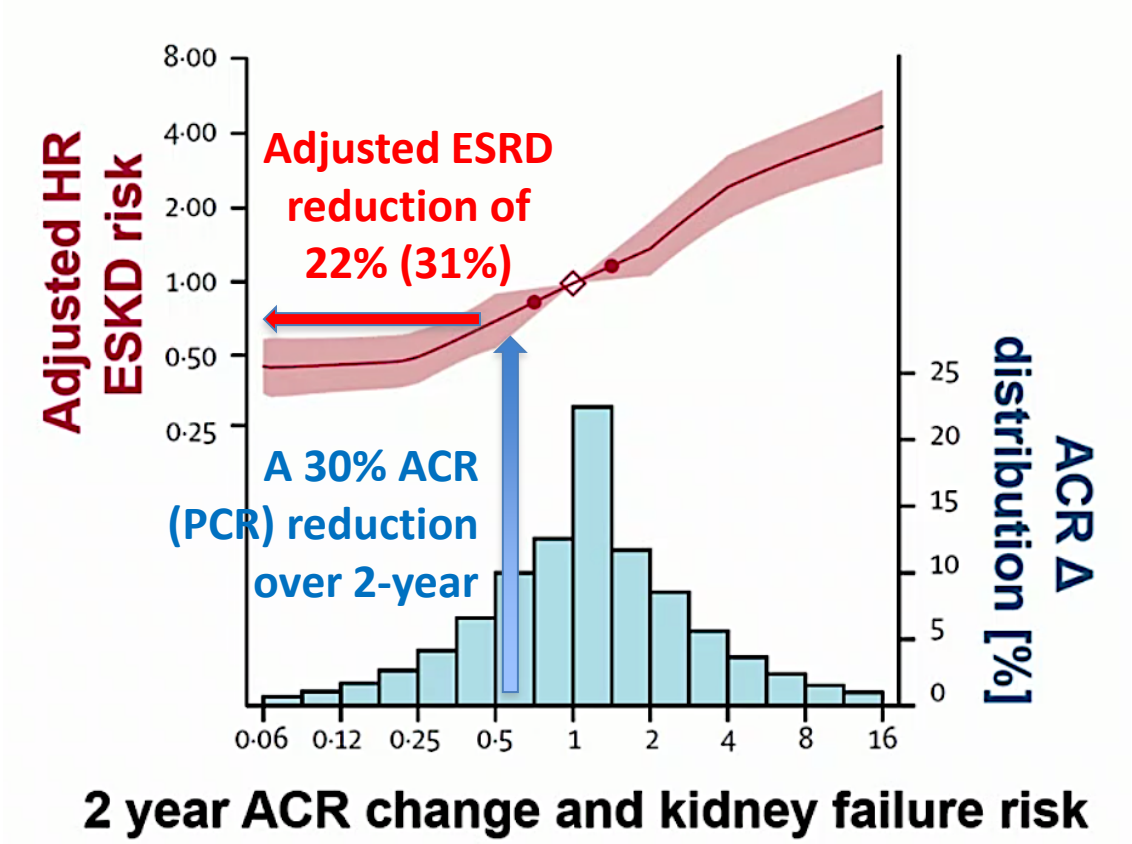


MacIsaac RJ et al. Kidney Int. 2014; 86: 50-7

Change in Albuminuria as a Surrogate Endpoint of the DKD Course

Meta-analysis of observational studies

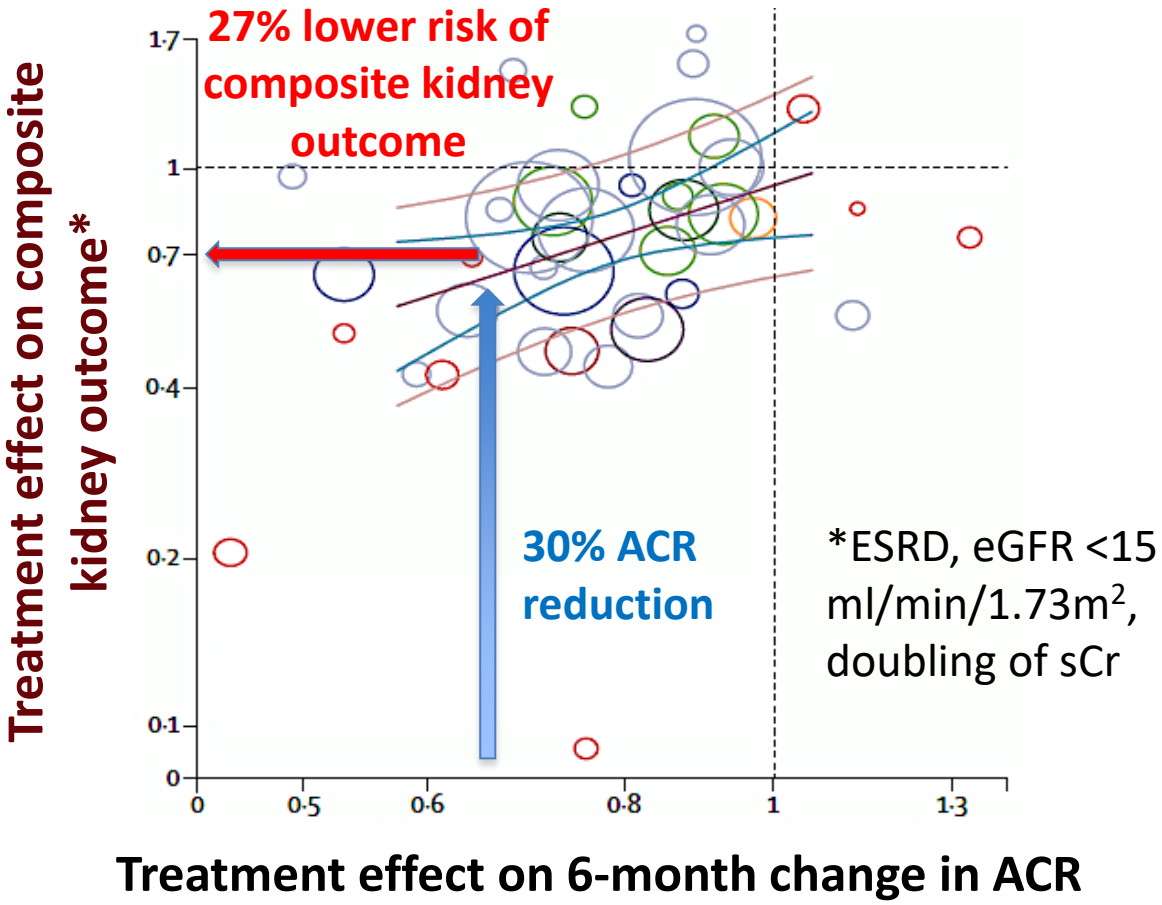
28 cohorts - 693,816 individuals (80% with DM)
7,461 ESRD events in a follow-up of 3.4 years



Coresh J et al.
Lancet Diabetes Endocrinol. 2019; 7(2): 115-127

Treatment effects in randomized interventional trials

41 studies - 29,979 individuals (71% with DM)
3,935 events (13%) in a follow-up of 3.4 years



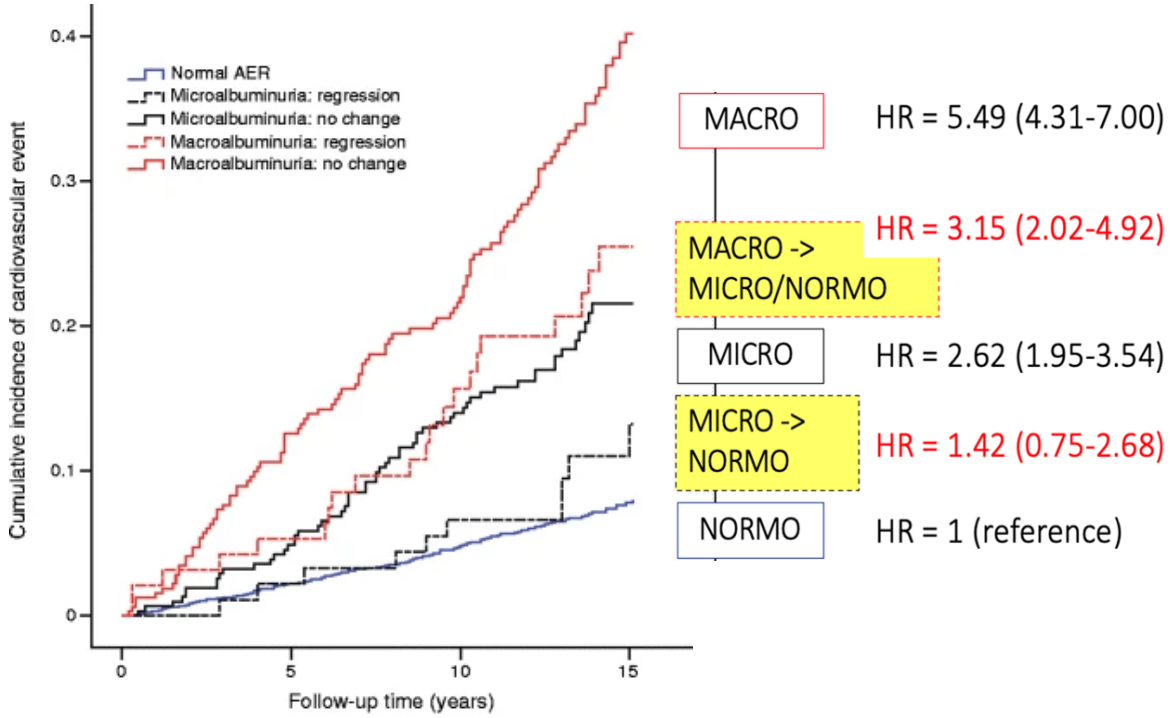
*ESRD, eGFR <15 ml/min/1.73m^2, doubling of sCr

Heerspink HJL et al.
Lancet Diabetes Endocrinol. 2019; 7(2): 128-139

The Finnish Diabetic Nephropathy Study: regression of albuminuria and its association with incident CV outcomes and mortality in T1DM

Among 3642 T1D, 102 (23.3%) individuals with prior microalbuminuria and 111 (23.4%) with prior macroalbuminuria had regressed at baseline

Incidence of cardiovascular events



MACRO — HR = 5.49 (4.31-7.00)

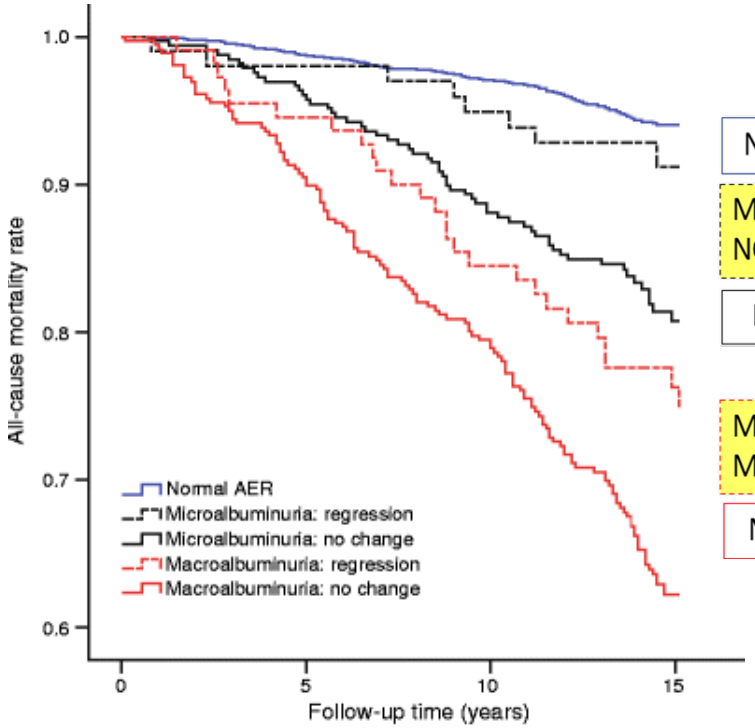
MACRO -> MICRO/NORMO — HR = 3.15 (2.02-4.92)

MICRO — HR = 2.62 (1.95-3.54)

MICRO -> NORMO — HR = 1.42 (0.75-2.68)

NORMO — HR = 1 (reference)

All-cause mortality rate



NORMO — HR = 1 (reference)

MICRO -> NORMO — HR = 1.32 (0.65-2.69)

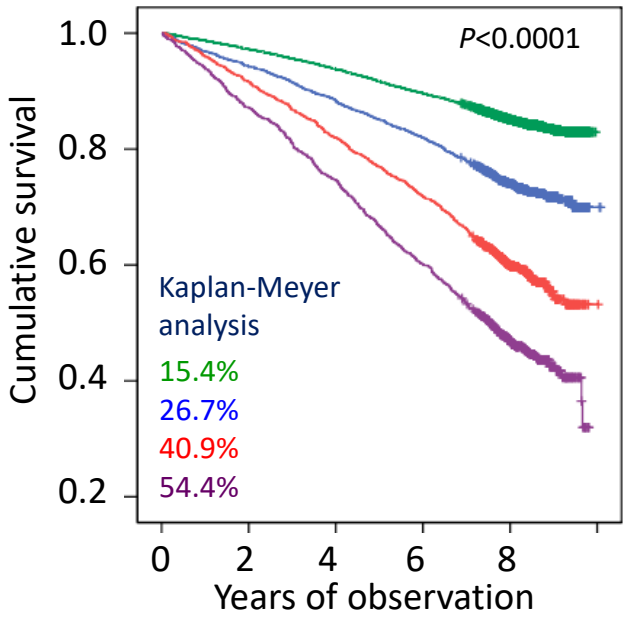
MICRO — HR = 2.87 (2.11-3.91)

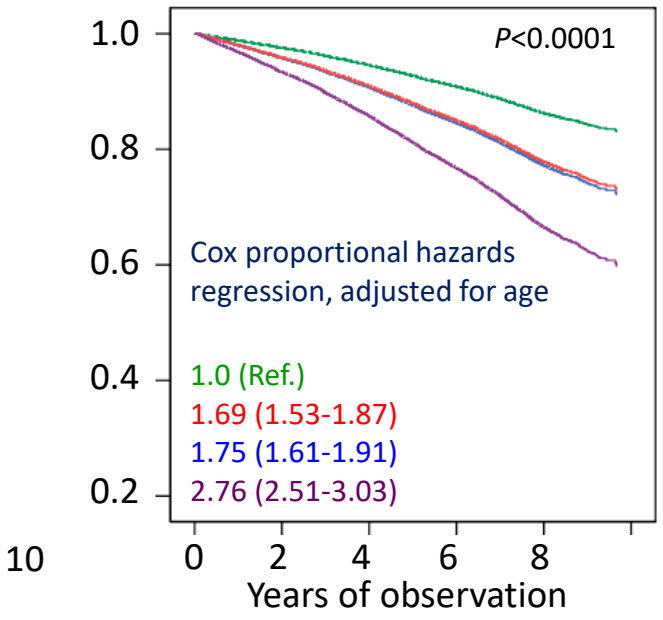
MACRO -> MICRO/NORMO — HR = 3.86 (2.55-5.83)

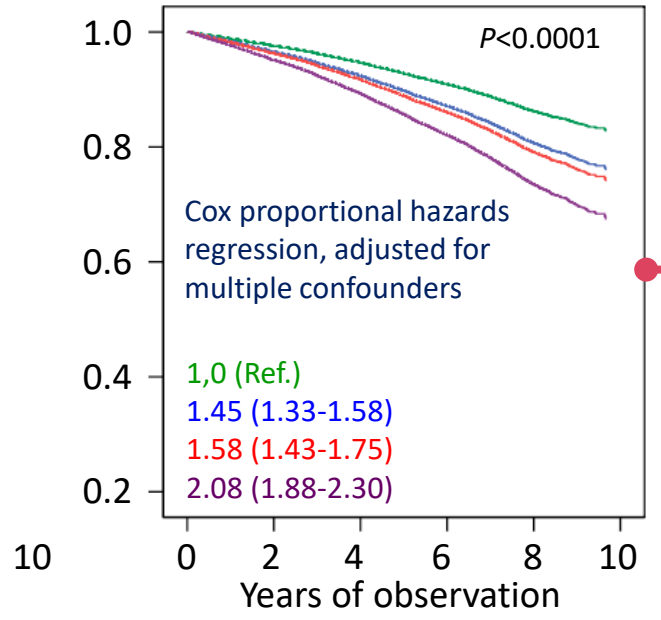
MACRO — HR = 7.22 (5.69-9.14)

Jansson F et al. Diabetologia 2018; 61: 1203-1211

RIACE (Renal Insufficiency and Cardiovascular Events): All-cause mortality







Alb⁻/eGFR⁻ — Alb⁺/eGFR⁻ — Alb⁻/eGFR⁺ — Alb⁺/eGFR⁺

KDIGO cat	A1a	A1b	A2	A3
G1	1 (Ref.)	0.94 (0.78-1.12)	1.31 (1.08-1.60)	2.19 (1.55-3.11)
G2a	0.80 (0.67-0.96)	1.05 (0.89-1.25)	1.31 (1.09-1.58)	2.48 (1.82-3.38)
G2b	1.10 (0.83-1.12)	1.06 (0.88-1.27)	1.39 (1.15-1.68)	1.71 (1.23-2.36)
G3a	1.32 (1.07-1.-62)	1.39 (1.14-1.69)	1.48 (1.22-1.80)	2.26 (1.71-3.00)
G3b	1.85 (1.40-2.44)	2.25 (1.79-2.82)	2.09 (1.69-2.59)	2.78 (2.14-3.63)
G4-5	1.61 (0.88-2.97)	2.25 (1.49-3.37)	2.79 (2.09-3.70)	4.66 (3.59-6.05)

Cox proportional hazards regression, adjusted for multiple confounders

The RIACE Study Group. Diabetologia 2018; 61: 2277-2289

Risk of Rapid Kidney Function Decline, All-Cause Mortality, and Major Cardio-vascular Events in Nonalbuminuric Chronic Kidney Disease in Type 2 Diabetes

Settings & Participants

Action to Control Cardiovascular Risk in Diabetes
ACCORD

Multicenter randomized , controlled trial

N = 10,185

Follow-up: 8.8 years

Analysis

Exposures

No diabetic kidney disease (DKD)

Decreased eGFR only

Albuminuria only

Decreased eGFR + albuminuria

- No DKD as reference group

Results

	Mortality	CVD	CKD* Progression
	HR (95% CI)		
Decreased eGFR only	**1.42** (1.14-1.78)	**1.44** (1.13-1.84)	**0.76** (0.34-1.70)
Albuminuria only	**1.82** (1.59-2.08)	**1.88** (1.63-2.16)	**1.72** (1.27-2-34)
Decreased eGFR + albuminuria	**2.38** (1.92-2.90)	**2.37** (1.89-2.97)	**4.52** (2.91-7.01)

* new or worsening nephropathy; doubling of creatinine or reaching eGFR <20 ml/min; and ESKD

CONCLUSION: All DKD phenotypes are associated with higher risk of mortality and CVD compared with no DKD. Alb-DKD is not associated with CKD progression

Buyadaa O et al. Diabetes Care 2020; 43: 122-129

Nonalbuminuric Diabetic Kidney Disease and Risk of All-Cause Mortality and CV and Kidney Outcomes in T2D: Findings From the Hong Kong Diabetes Biobank

Settings & Participants

HONG KONG DIABETES BIOBANK 香港糖尿病生物庫

Multicenter, prospective, cohort study

N = 19,025

Follow-up: 3.1 years

Analysis

Exposures

No diabetic kidney disease (DKD)

Decreased eGFR only

Albuminuria only

Decreased eGFR + albuminuria

- No DKD as reference group

Results

	Mortality	CVD	HHF	CKD* Progression
	HR (95% CI)			
Decreased eGFR only	1.59 (1.04-2.44)	1.14 (0.88-1.48)	3.08 (1.82-5.21)	2.37 (1.63-3.43)
Albuminuria only	2.00 (1.52-2.63)	1.19 (1.02-1.40)	3.14 (2.09-4.73)	3.77 (3.05-4.66)
Decreased eGFR + albuminuria	3.26 (2.43-4.38)	1.47 (1.23-1.76)	5.50 (3.63-8.34)	14.01 (11.31-17.36)

CONCLUSION: All DKD phenotypes are associated with higher risk of mortality, CVD, HHF and CKD progression compared with no DKD

*incident kidney failure or ≥40% reduction in eGFR

Jin Q et al. Am J Kidney Dis 2022; 80: 196-206

Risk of cardiovascular disease, death, and renal progression in diabetes according to albuminuria and estimated glomerular filtration rate

Settings & Participants

China Cardiometabolic Disease and Cancer Cohort (4C) Study

Nationwide, population-based, prospective cohort study

N = 36,509

Follow-up: 3.2 years

Analysis

Exposures

- No diabetic kidney disease (DKD)
- Decreased eGFR only
- Albuminuria only
- Decreased eGFR + albuminuria

• No DKD as reference group

Results

HR (95% CI)

	Mortality	CVD	CKD* Progression
Decreased eGFR only	**1.42** (1.04-1.92)	**1.42** (1.08-1.88)	**0.97** (0.60-1.57)
Albuminuria only	**1.99** (1.69-2.34)	**1.60** (1.39-1.84)	**2.08** (1.77-2.45)
Decreased eGFR + albuminuria	**3.14** (2.44-4.05)	**2.35** (1.84-2.99)	**3.72** (2.90-4.78)

*≥30% reduction in eGFR, reaching eGFR <15 ml/min, development of ESRD, or death due to CKD

CONCLUSION: Diabetes subjects with albuminuria are at higher risks of developing clinical outcomes, as well as patients with non-albuminuric DKD with age <65 years

Niu J et al. Diabetes & Metabolism 2023; 49: 101420

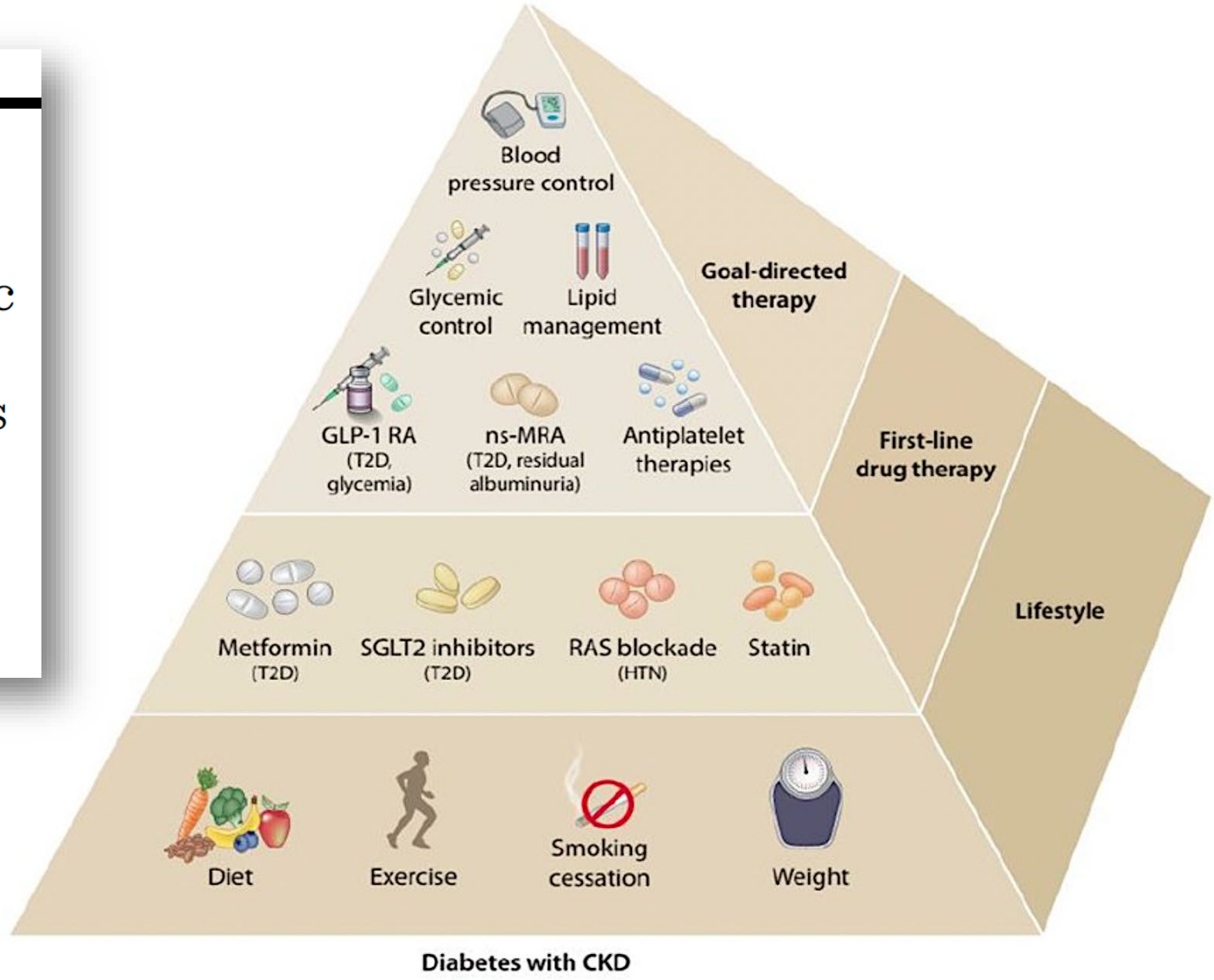
- Epidemiologia ‘ibrida’ della DKD
- Fenotipi ‘ibridi’ di DKD
- Prognosi ‘ibrida’ della DKD
- **‘Current science’ nel trattamento della DKD**

Holistic approach for improving outcomes in patients with diabetes and CKD

Diabetes Care

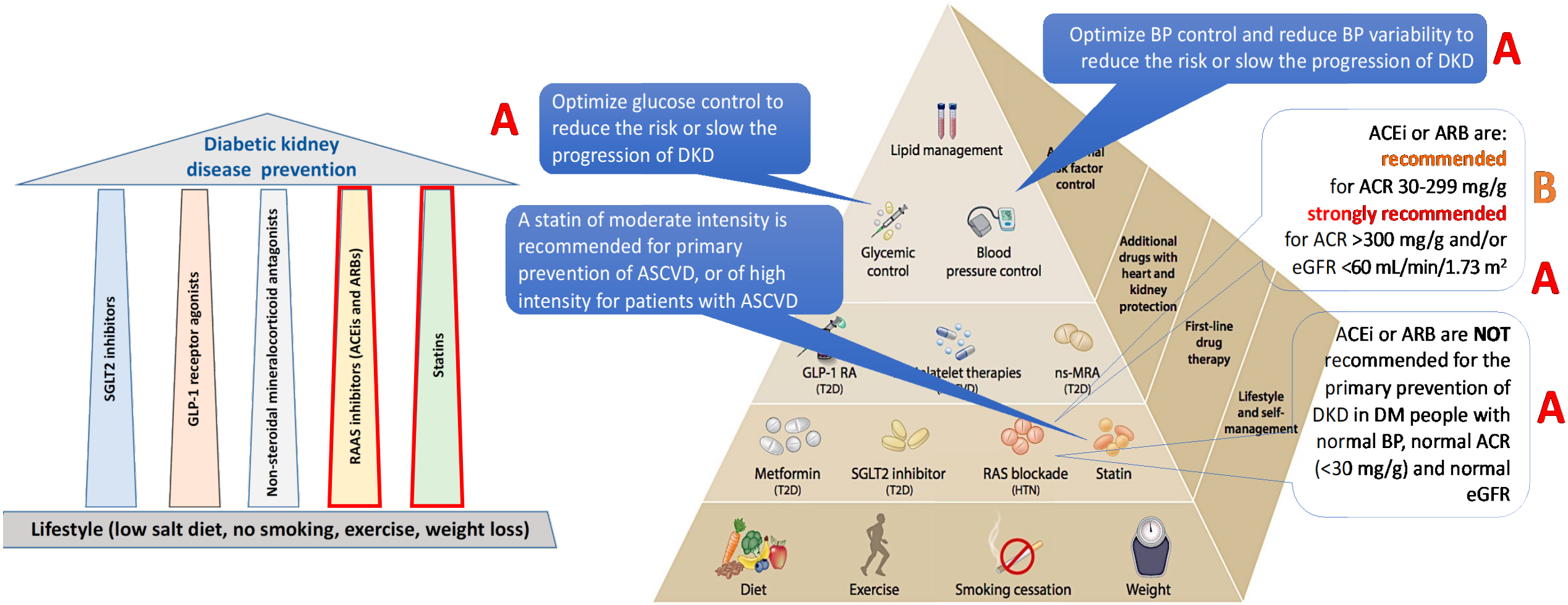
Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

https://doi.org/10.2337/dci22-0027



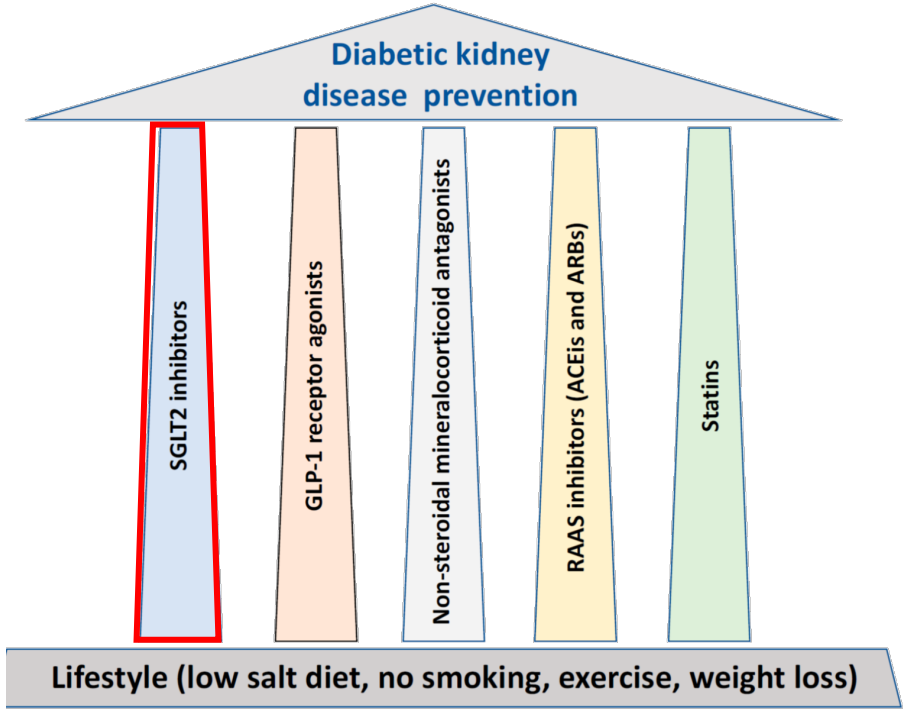
de Boer IH et al. Diabetes Care 2022; 45: 3075-3090

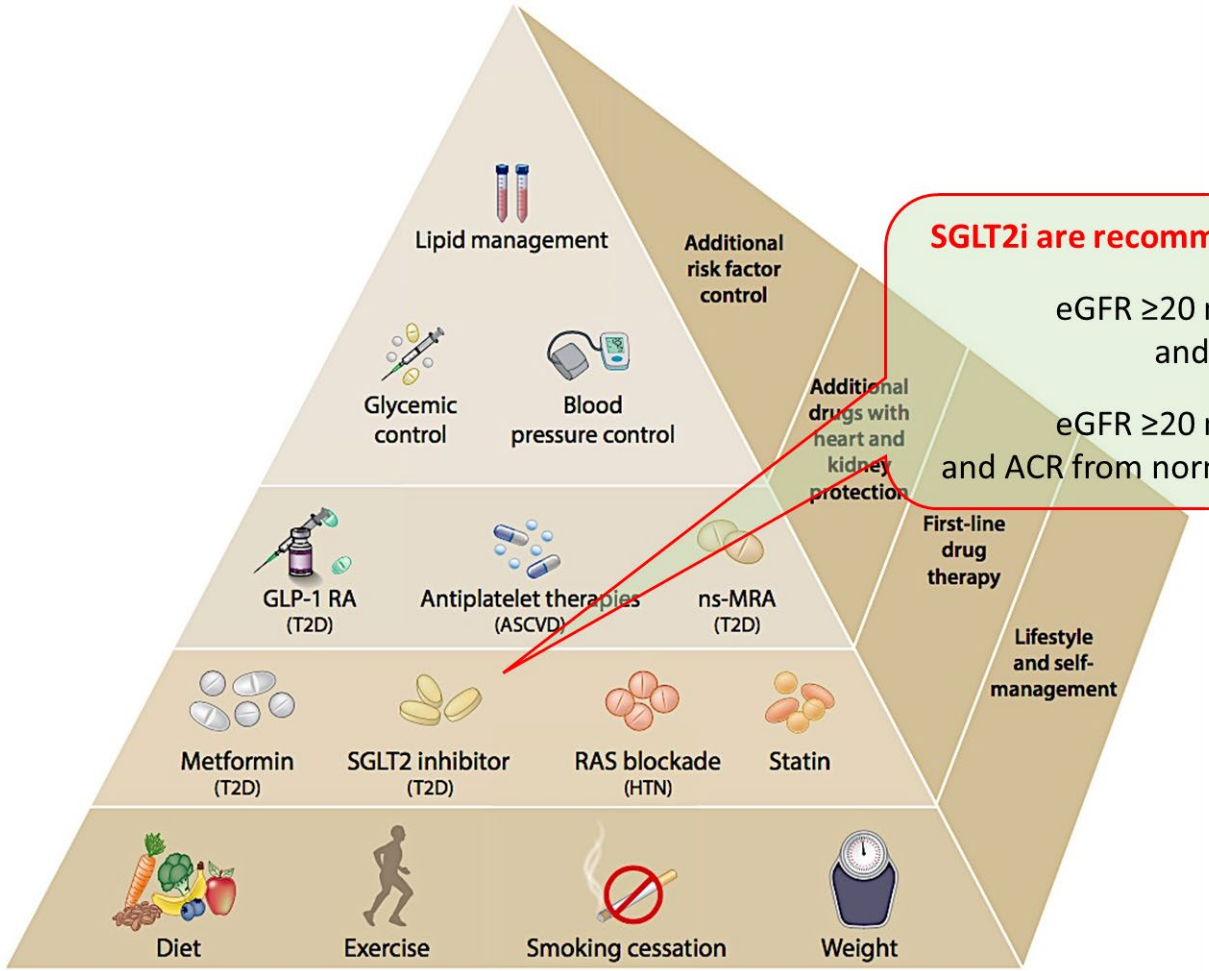
Holistic approach for improving outcomes in patients with diabetes and CKD 2022 Consensus Report by the ADA and KDIGO



Kearney J and Gnudi L. Pharmaceutics 2023, 15: 1343 - de Boer IH et al. Diabetes Care 2022; 45: 3075-3090

Holistic approach for improving outcomes in patients with diabetes and CKD 2022 Consensus Report by the ADA and KDIGO





SGLT2i are recommended for DKD:

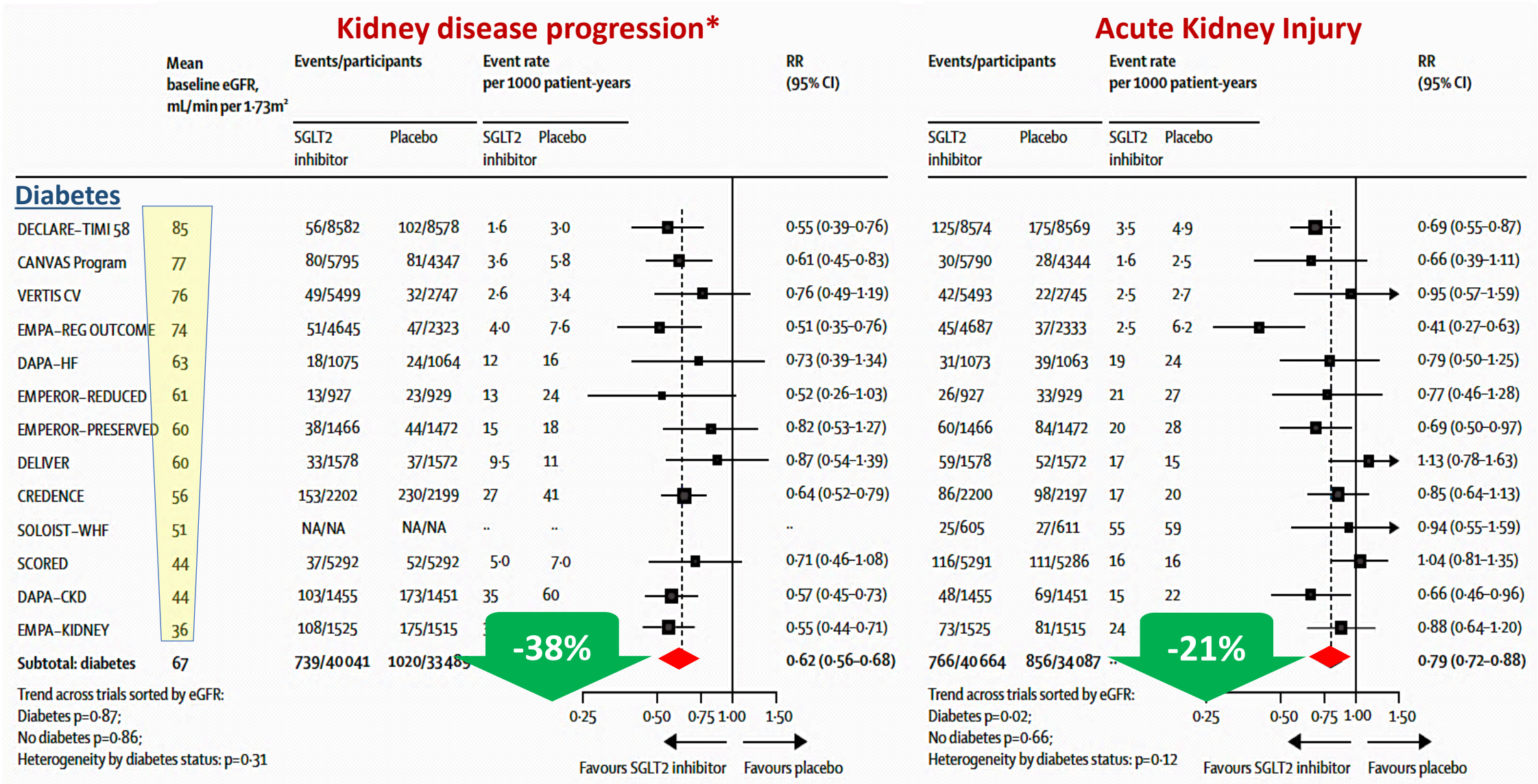
eGFR ≥20 mL/min/1.73 m^2 and ACR ≥200 mg/g — **A**

eGFR ≥20 mL/min/1.73 m^2 and ACR from normal to 200 mg/g — **B**

Kearney J and Gnudi L. Pharmaceutics 2023, 15: 1343 - de Boer IH et al. Diabetes Care 2022; 45: 3075-3090

Effect of SGLT2 inhibition on kidney disease outcomes by eGFR

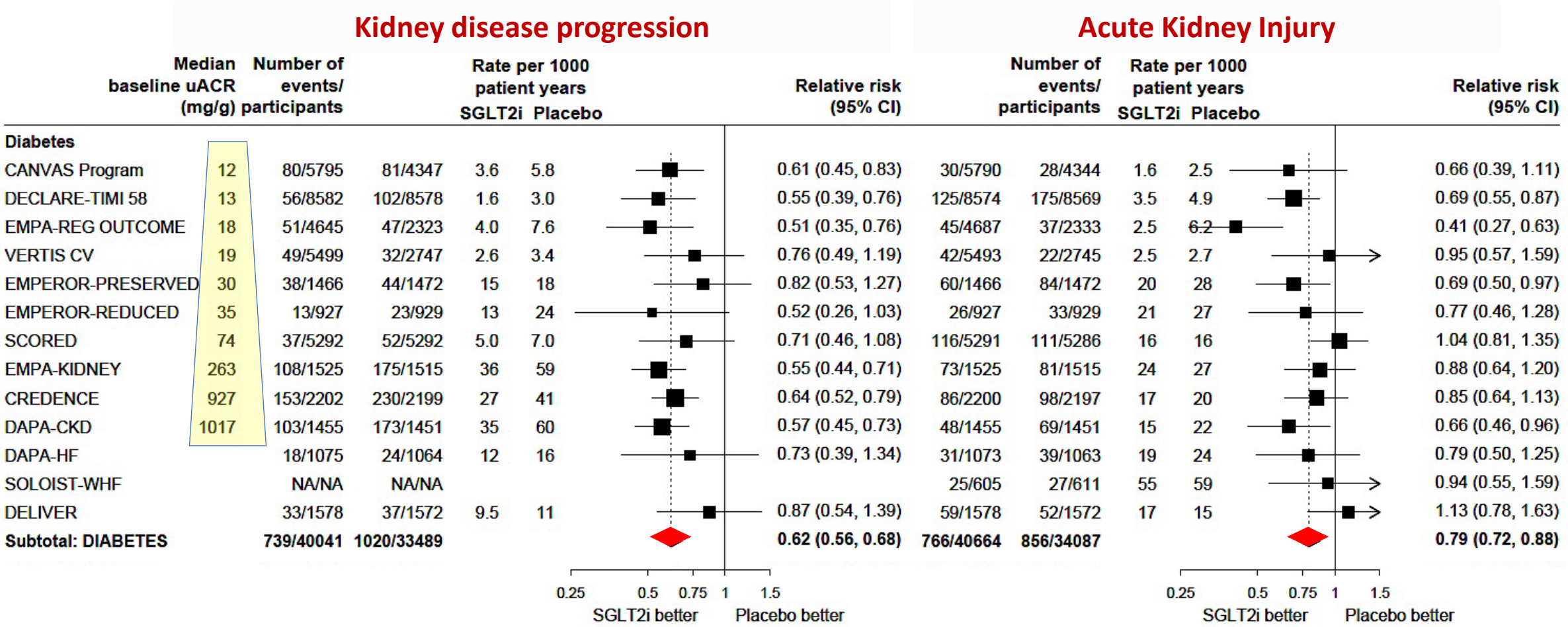
13 studies - 90,409 participants of which 74,804 [82.7%] with diabetes [>99% with T2D]



* ≥50% decrease in eGFR, eGFR <15 ml/min, ESKD, or death from kidney failure

The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Lancet 2022; 400: 1788-1801

Effect of SGLT2 inhibition on kidney disease outcomes by uACR



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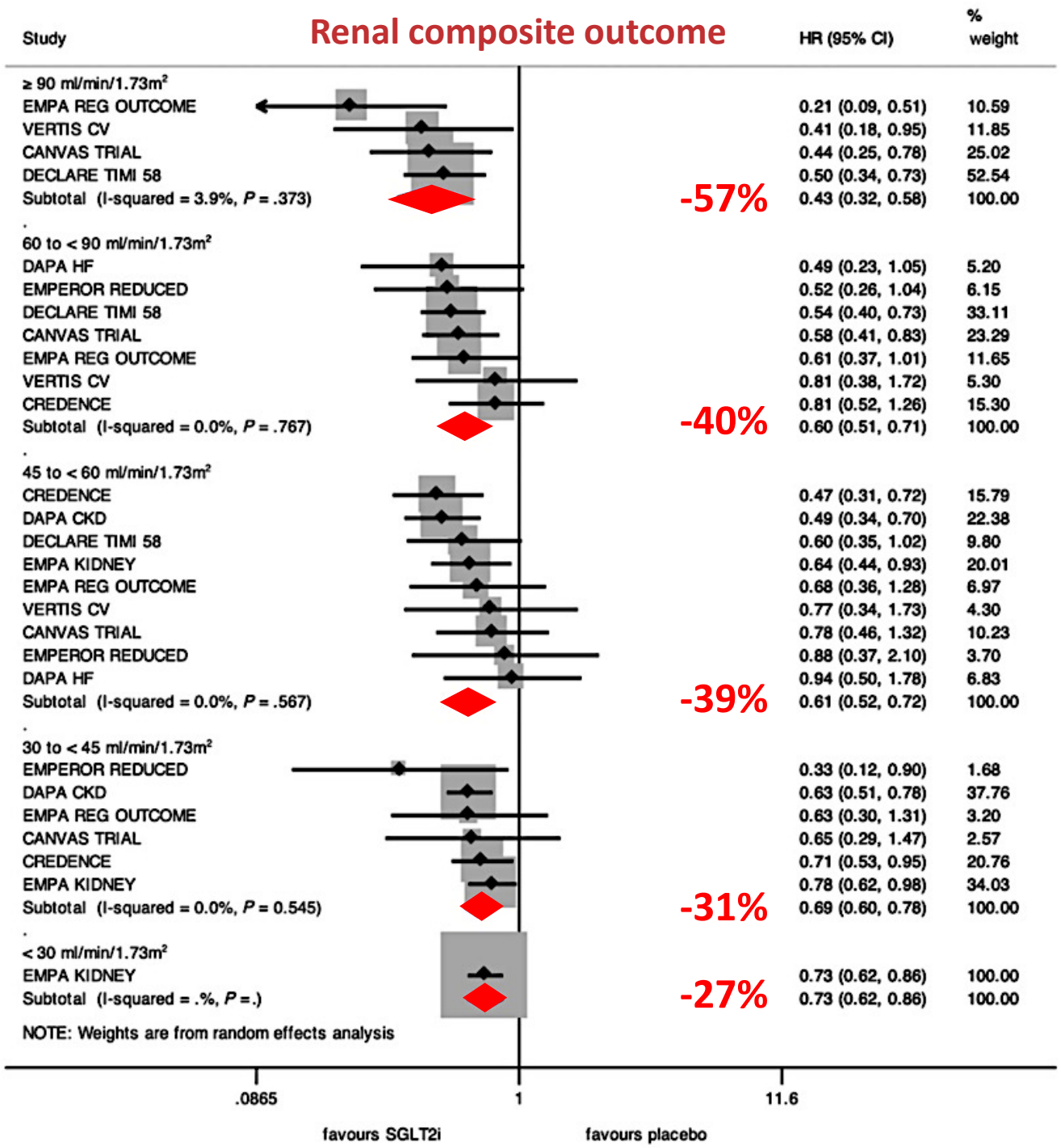
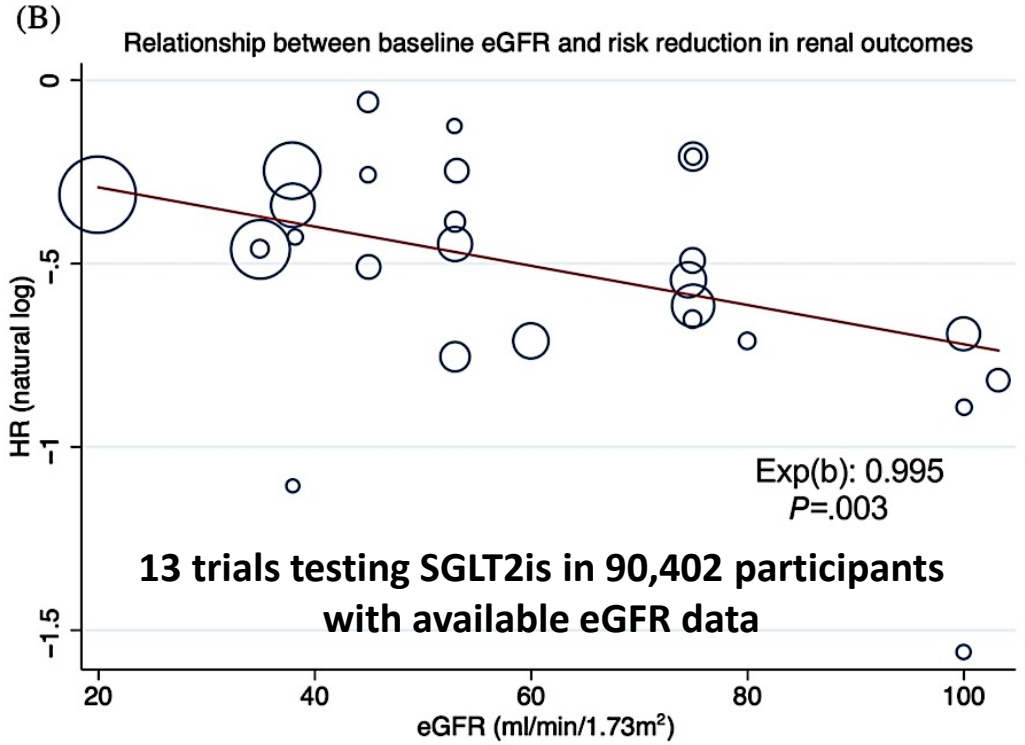


Impact of baseline kidney function on the effects of SGLT2 inhibitors on kidney and heart failure outcomes:

A systematic review and meta-analysis of randomized controlled trials



13 trials testing SGLT2is in 90,402 participants with available eGFR data

EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58

CREDENCE, DAPA-HF, DAPA-CKD, VERTIS-CV

EMPEROR-REDUCED, EMPEROR-PRESERVED

SCORED, SOLOIST-WHF, DELIVER, **EMPA-KIDNEY**

Maddaloni E et al. Diabetes Obes Metab 2023; 25: 1341-1350

Impact of baseline kidney function on the effects of SGLT2 inhibitors on kidney and heart failure outcomes:

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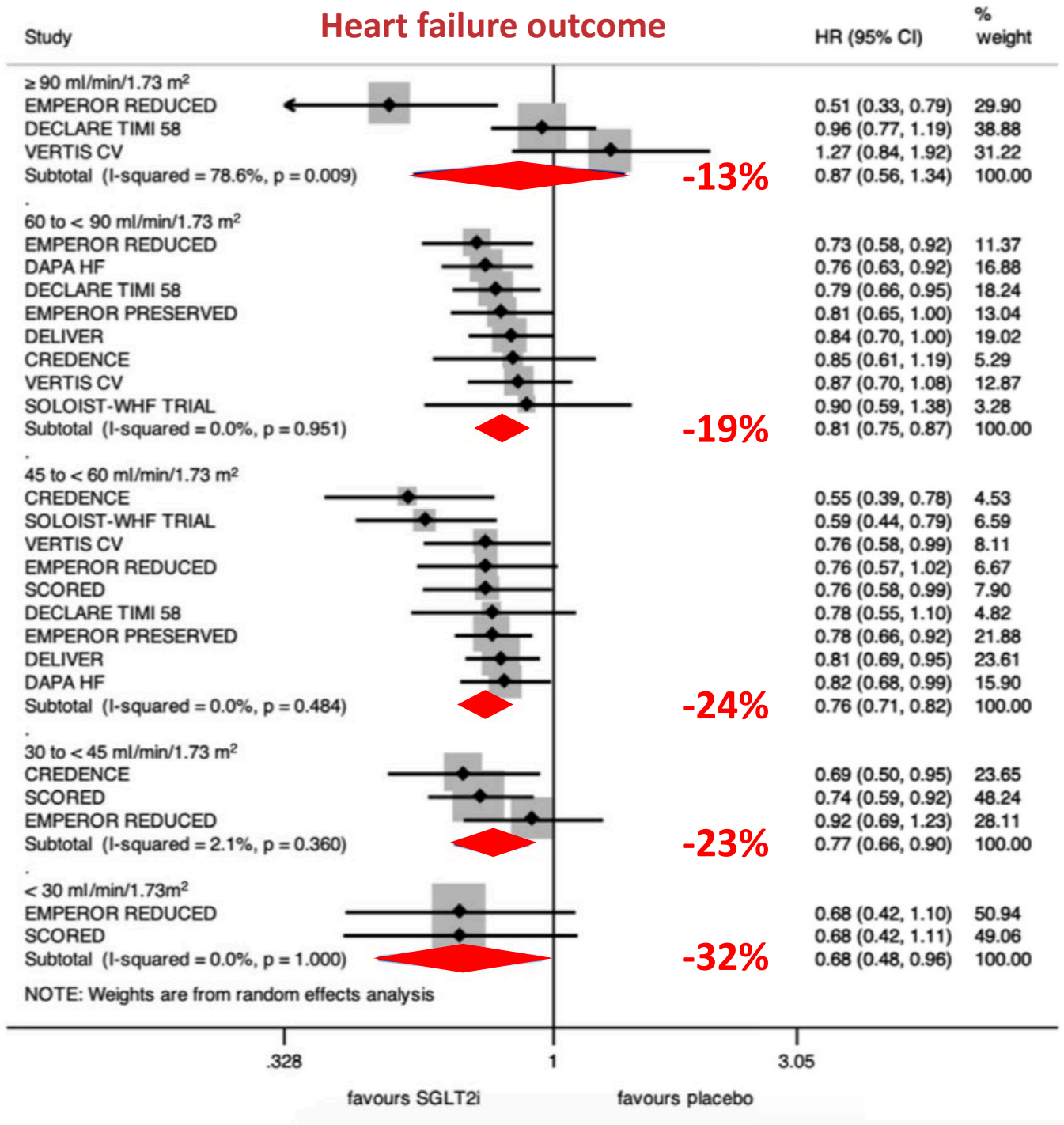
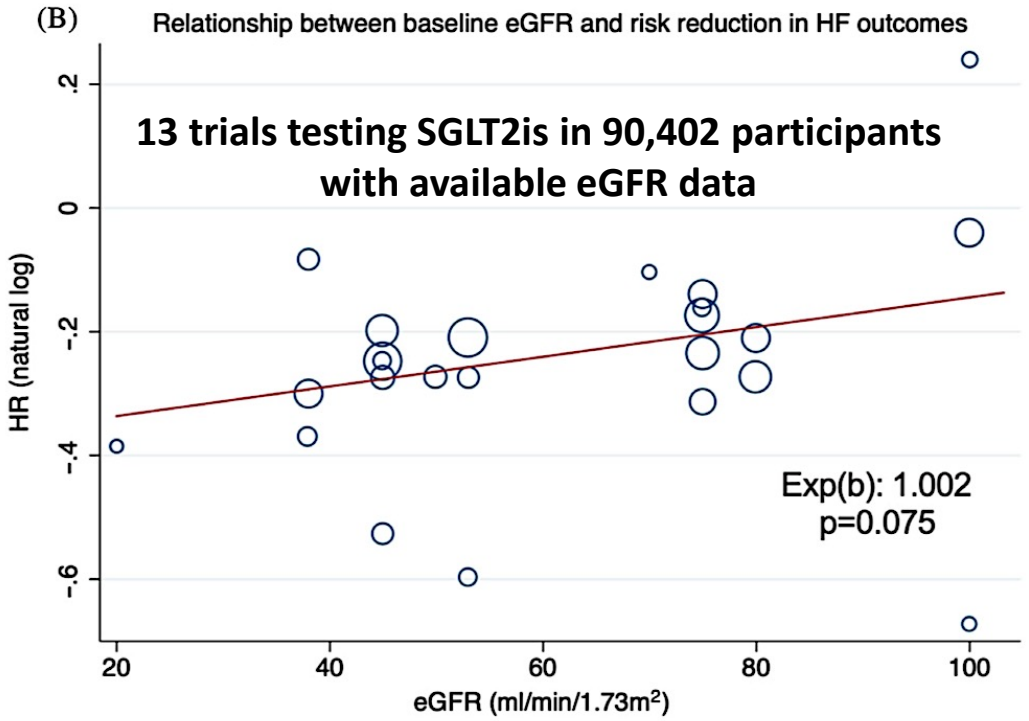




EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58

CREDENCE, DAPA-HF, DAPA-CKD, VERTIS-CV

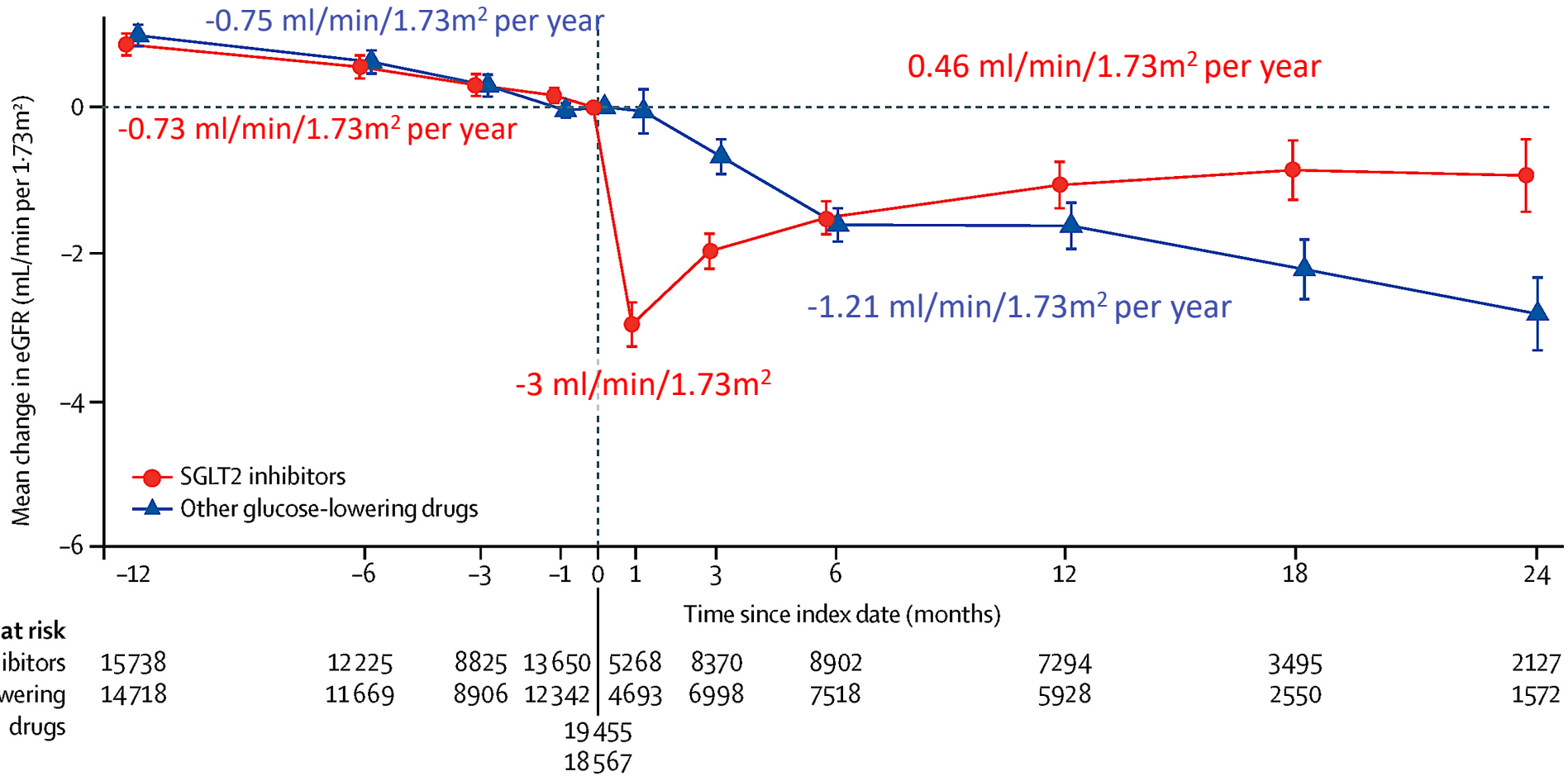
EMPEROR-REDUCED, EMPEROR-PRESERVED

SCORED, SOLOIST-WHF, DELIVER, **EMPA-KIDNEY**

Maddaloni E et al. Diabetes Obes Metab 2023; 25: 1341-1350

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

71,122 new users matched by propensity scores: SGLT2i vs other glucose-lowering drugs – mean follow-up 15 months
Mean eGFR = 90.7 ml/min/1.73m^2; 8.3% with eGFR ≤60 ml/min/1.73m^2

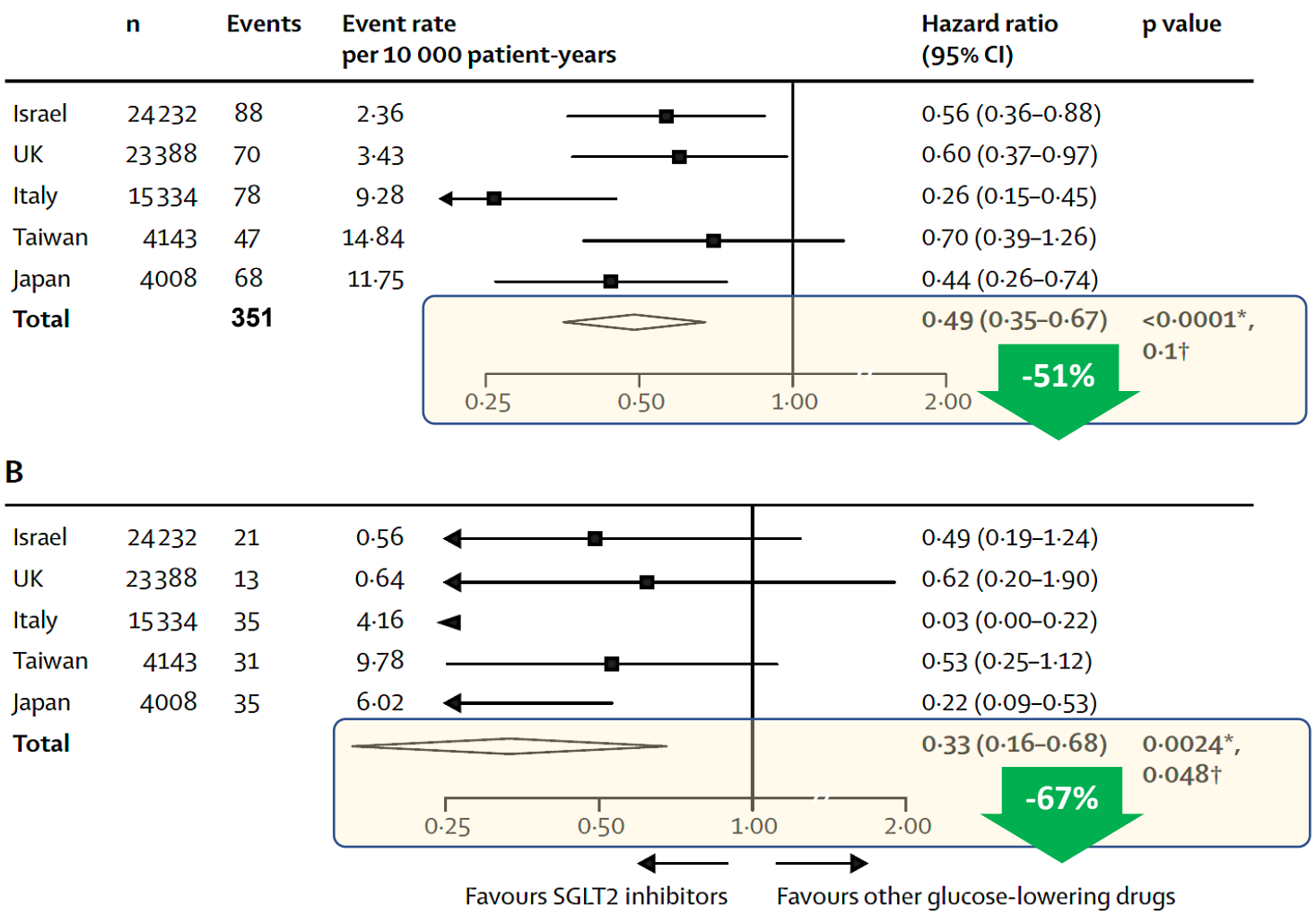


between-group difference: 1·53 mL/min per 1·73 m² per year (1·34 to 1·72; p<0·0001)

Dapagliflozin: 57.9%
Empagliflozin: 34.1%
Canagliflozin: 5.7%
Others: 2.3%

Heerspink HJL et al. Lancet Diabetes Endocrinol 2020; 8: 27-35

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

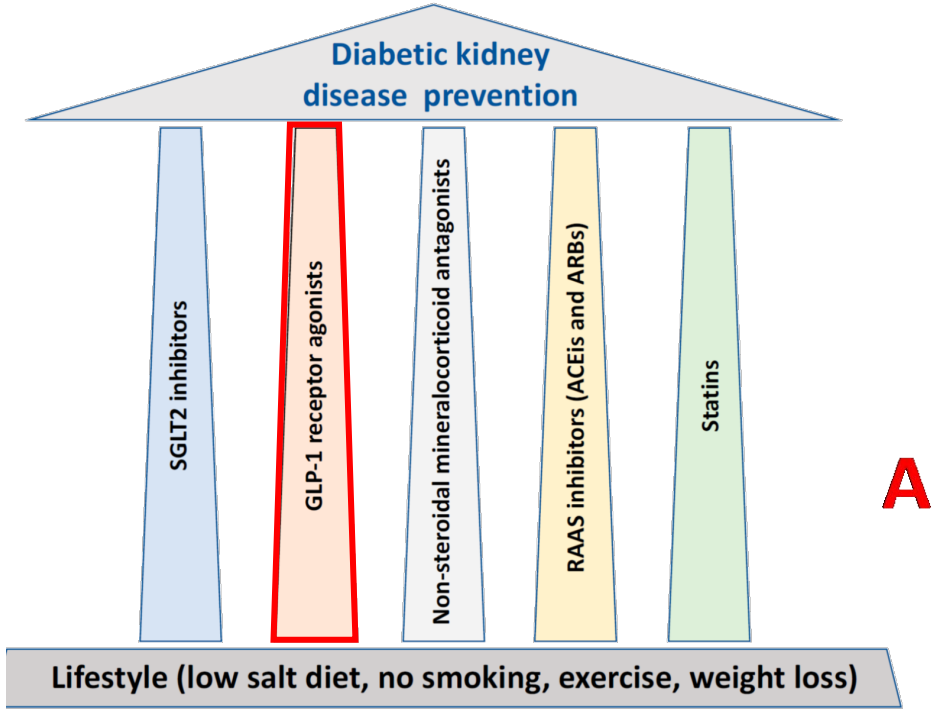


Composite of 50% decline in eGFR or ESKD

ESKD alone

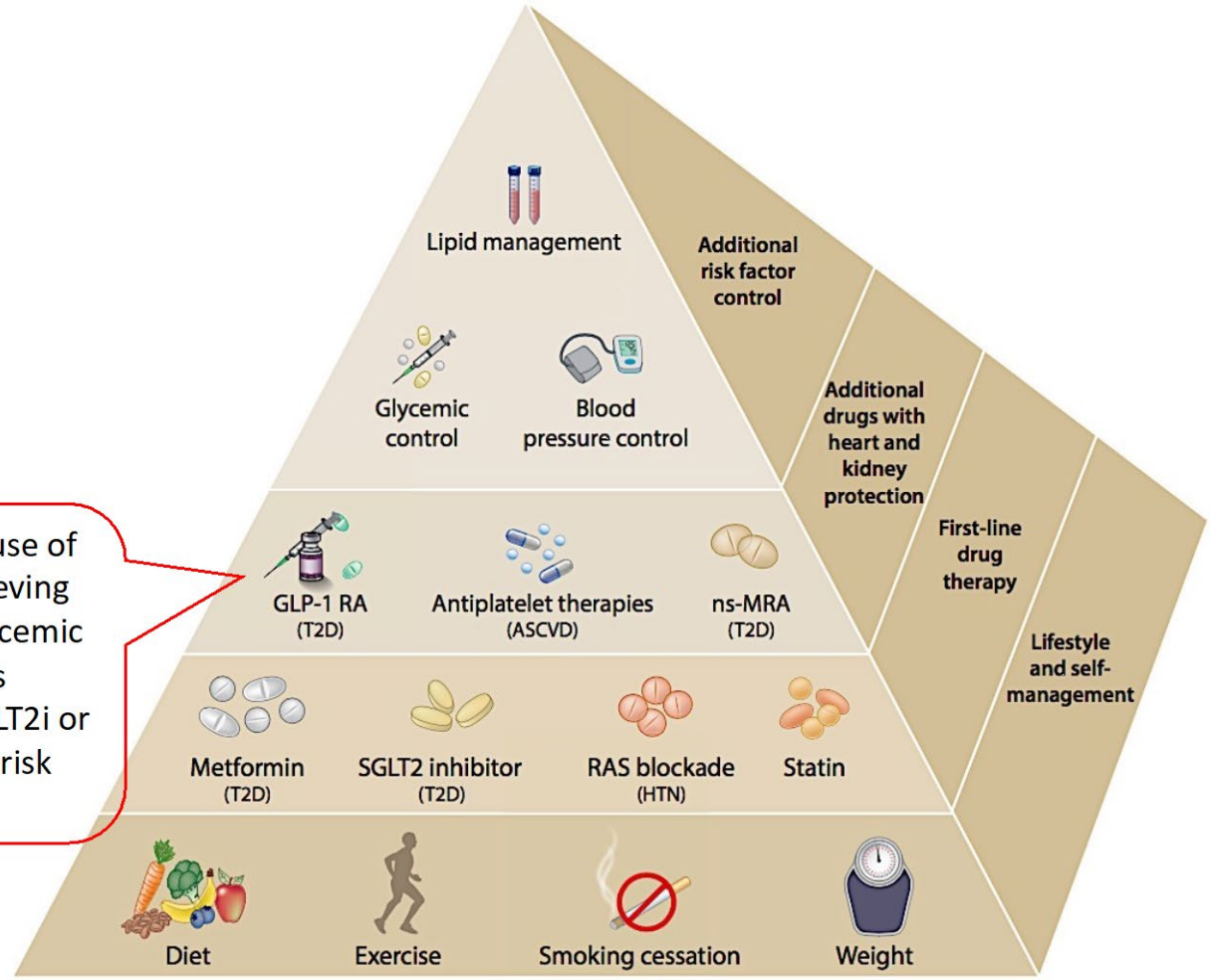
Heerspink HJL et al. Lancet Diabetes Endocrinol 2020; 8: 27-35

Holistic approach for improving outcomes in patients with diabetes and CKD 2022 Consensus Report by the ADA and KDIGO



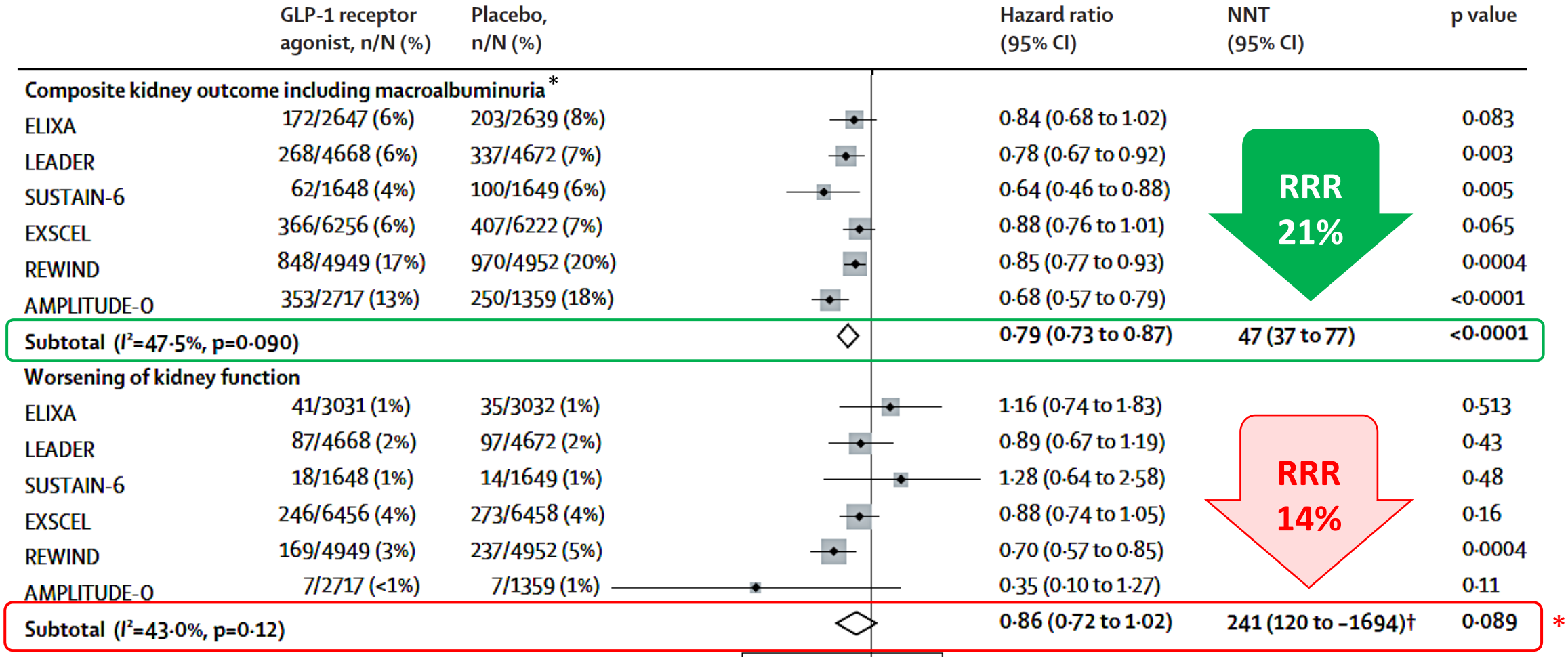
A

In DKD consider use of GLP1-RA for achieving individualized glycemic target, in subjects unable to use SGLT2i or for additional CV risk reduction



Kearney J and Gnudi L. Pharmaceutics 2023, 15: 1343 - de Boer IH et al. Diabetes Care 2022; 45: 3075-3090

Kidney outcomes with GLP-1RAs in T2D: a systematic review and meta-analysis of randomised trials (8 trials, 60.080 participants)



RRR 18%

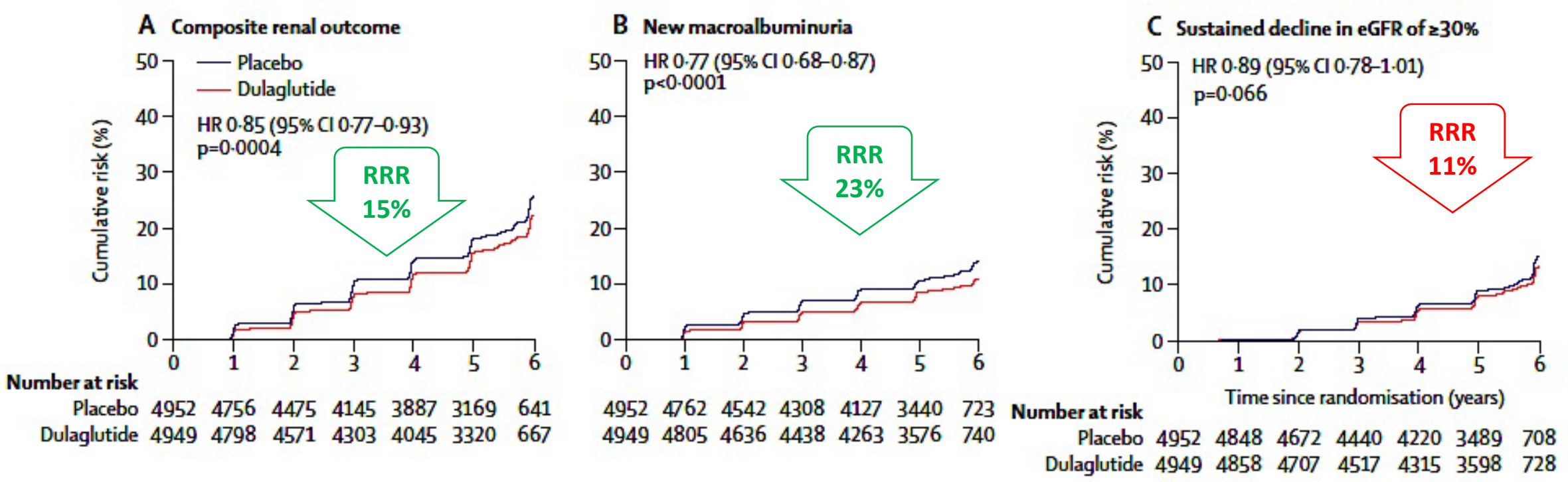
* HR 0.82 (0.69-0.98), p=0.030 with the removal of ELIXA

* development of macroalbuminuria, doubling of serum creatinine, >40% decline in eGFR, kidney replacement therapy, or death due to kidney disease. Kidney outcomes were not available for HARMONY and PIONEER-6

Sattar N et al. Lancet Diabetes Endocrinol 2021; 9: 653-662

Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomized, placebo-controlled trial

9901 subjects randomized to dulaglutide or placebo - median follow-up 5.4 years



*new macroalbuminuria (UACR >33.9 mg/mmol), a sustained decline in eGFR of 30%, or chronic renal replacement therapy

Similar effects of dulaglutide on the composite renal outcome were noted in subgroups defined by eGFR (<60 or ≥60 ml/min), baseline albuminuria, and the use of ACEi or ARB, as well as in subgroups defined by age, sex, duration of diabetes, and HbA1c.

Gerstein H et al. Lancet. 2019; 394: 131-138

Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomized, placebo-controlled trial

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Main analyses of renal effect						
Composite renal outcome	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004
Components of composite renal outcome						
New macroalbuminuria	441 (8·9%)	1·76	561 (11·3%)	2·29	0·77 (0·68–0·87)	<0·0001
Sustained decline in eGFR of ≥30%	453 (9·2%)	1·79	500 (10·1%)	2·00	0·89 (0·78–1·01)	0·066
Chronic renal replacement therapy	16 (0·3%)	0·06	21 (0·4%)	0·08	0·75 (0·39–1·44)	0·39
Serious renal adverse event*	84 (1·7%)	0·32	93 (1·9%)	0·36	0·90 (0·67–1·20)	0·46
Sensitivity analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥50%	61 (1·2%)	0·24	108 (2·2%)	0·42	0·56 (0·41–0·76)	0·0002
Composite renal outcome with this decline	496 (10·0%)	1·99	649 (13·1%)	2·66	0·74 (0·66–0·84)	<0·0001

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

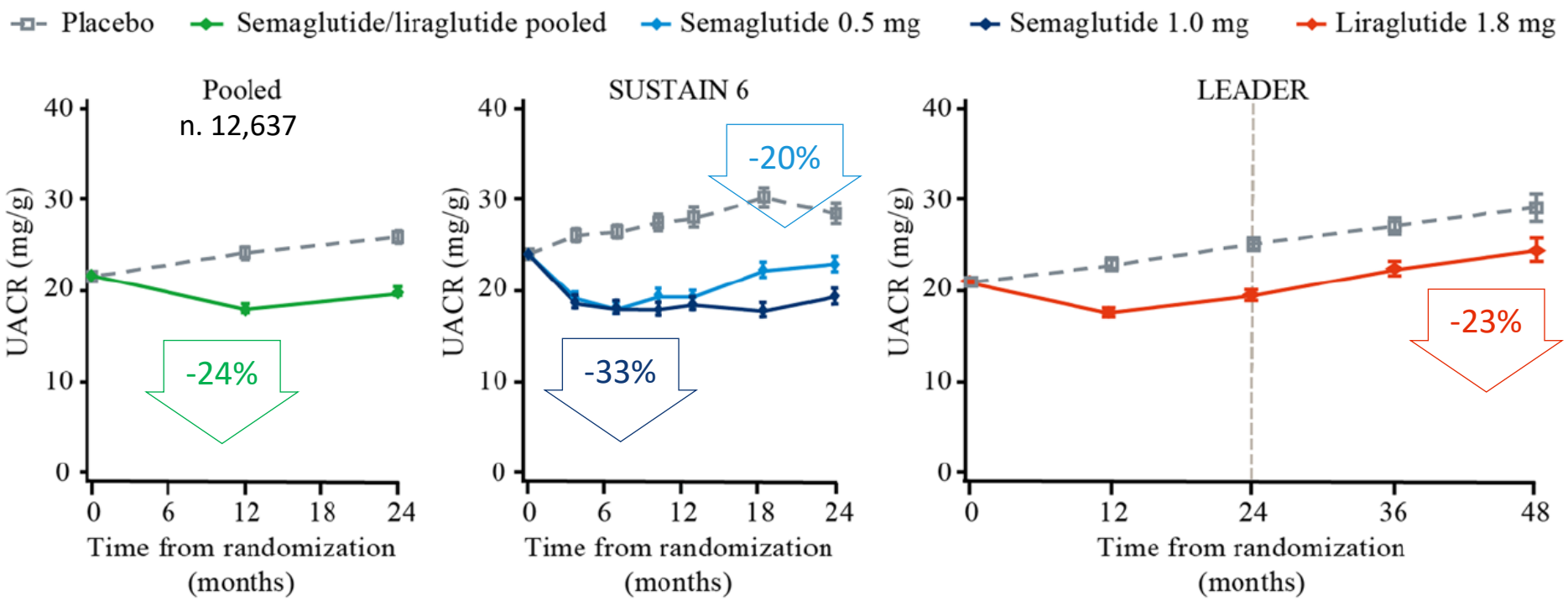
Table 2: **Effect of treatment allocation on renal outcomes**

RRR 30%

RRR 44%

Gerstein H et al. Lancet. 2019; 394: 131-138

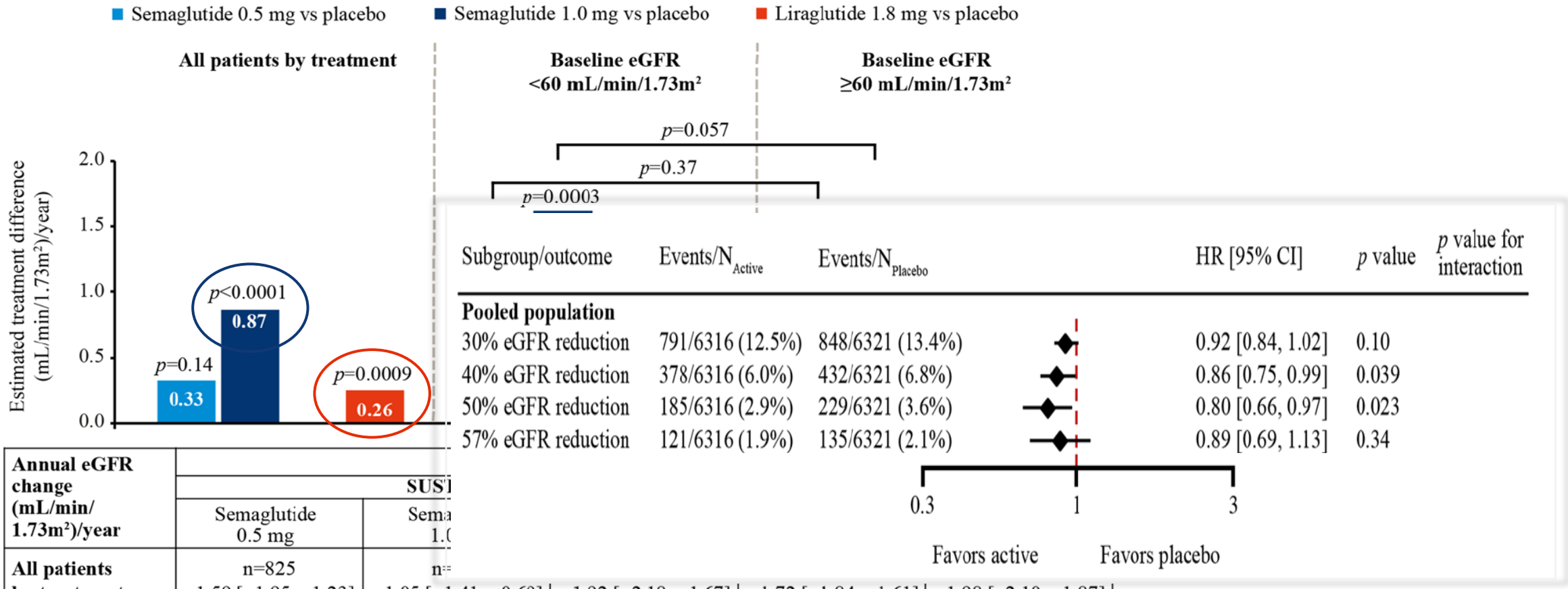
Effect of the GLP-1 RA Semaglutide and Liraglutide on Kidney Outcomes in Patients With T2D: Pooled Analysis of SUSTAIN 6 and LEADER



Estimated treatment ratio at 2 years (treatment vs placebo) [95% CI]; *p* value*			
Overall pooled trial population	**SUSTAIN 6**		**LEADER**
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Liraglutide 1.8 mg
0.76 [0.73, 0.80]; $p<0.001$	0.80 [0.72, 0.90]; $p<0.001$	0.67 [0.60, 0.76]; $p<0.001$	0.77 [0.73, 0.82]; $p<0.001$
Estimated treatment ratio at 2 years (by-treatment comparisons) [95% CI]; *p* value			
Liraglutide 1.8 mg vs semaglutide 0.5 mg	0.96 [0.85, 1.09]; $p=0.53$	Liraglutide 1.8 mg vs semaglutide 1.0 mg	1.15 [1.02, 1.31]; $p=0.024$

Shaman AM et al. Circulation. 2022;145:575–585

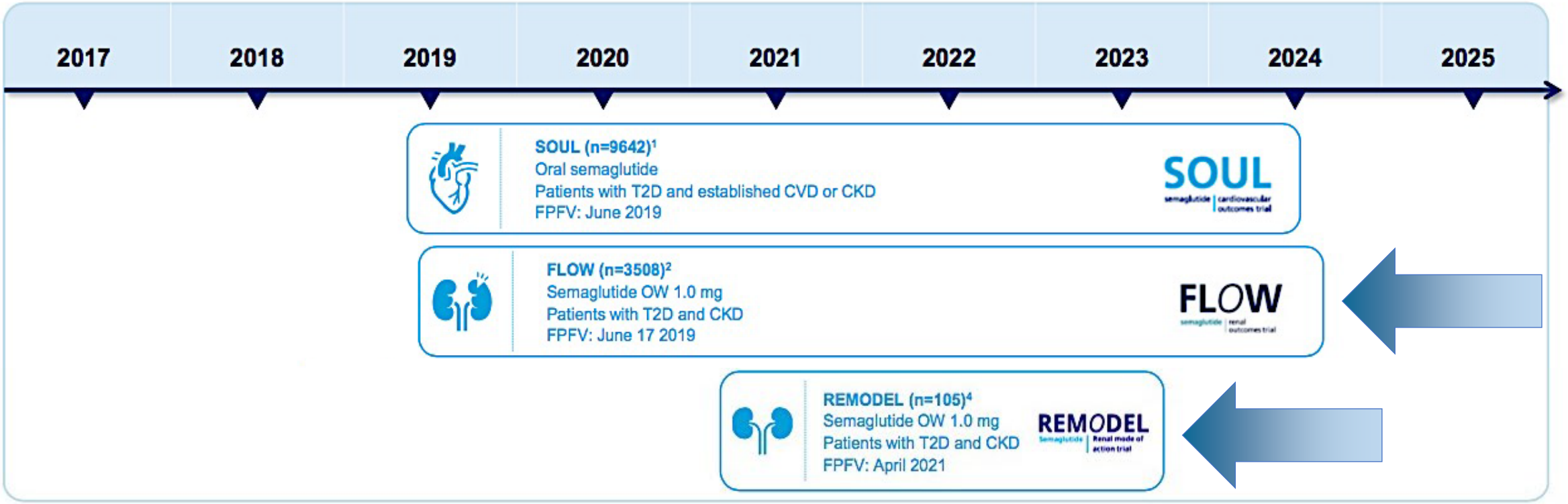
Effect of the GLP-1 RA Semaglutide and Liraglutide on Kidney Outcomes in Patients With T2D: Pooled Analysis of SUSTAIN 6 and LEADER



Annual eGFR change (mL/min/ 1.73m²)/year	SUST				
	Semaglutide 0.5 mg	Sema 1.0			
All patients by treatment	n=825 −1.59 [−1.95, −1.23]	n= −1.05 [−1.41, −0.69]	−1.92 [−2.18, −1.67]	−1.72 [−1.84, −1.61]	−1.98 [−2.10, −1.87]
<60 mL/min/ 1.73m² at baseline	n=212 −1.20 [−1.90, −0.49]	n=204 −0.25 [−0.97, 0.48]	n=427 −1.87 [−2.37, −1.36]	n=968 −1.44 [−1.68, −1.19]	n=905 −2.11 [−2.37, −1.85]
≥60 mL/min/ 1.73m² at baseline	n=613 −1.73 [−2.15, −1.32]	n=617 −1.31 [−1.72, −0.90]	n=1221 −1.94 [−2.24, −1.64]	n=3544 −1.80 [−1.92, −1.67]	n=3593 −1.95 [−2.08, −1.83]

Shaman AM et al. Circulation. 2022;145:575–585

Renal outcomes of GLP-1 RA therapy: current RCTs



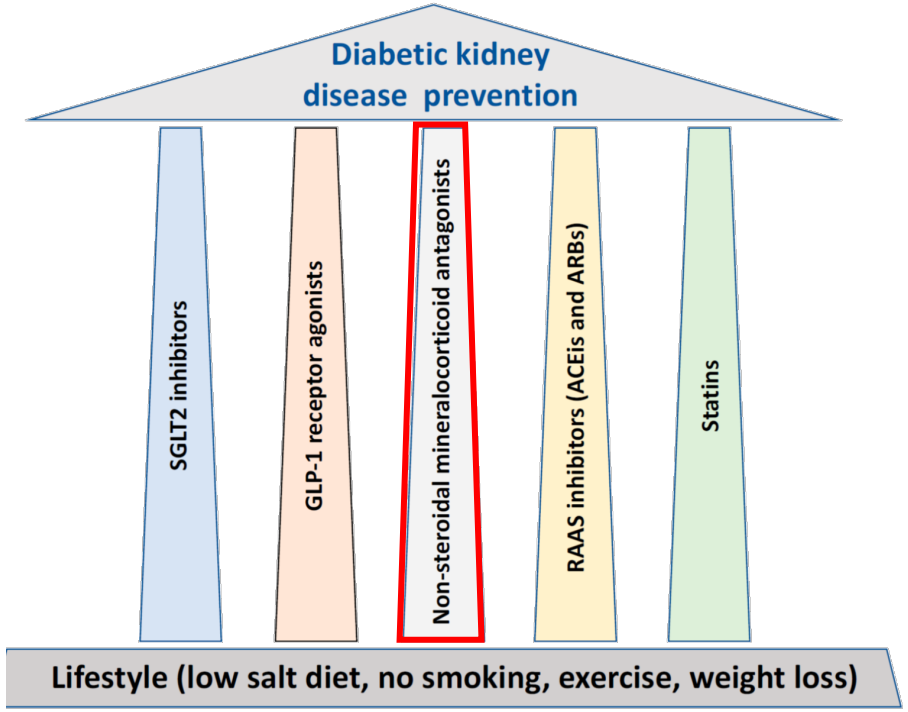
ClinicalTrials.gov NCT03914326; ClinicalTrials.gov NCT03819153; ClinicalTrials.gov NCT04865770

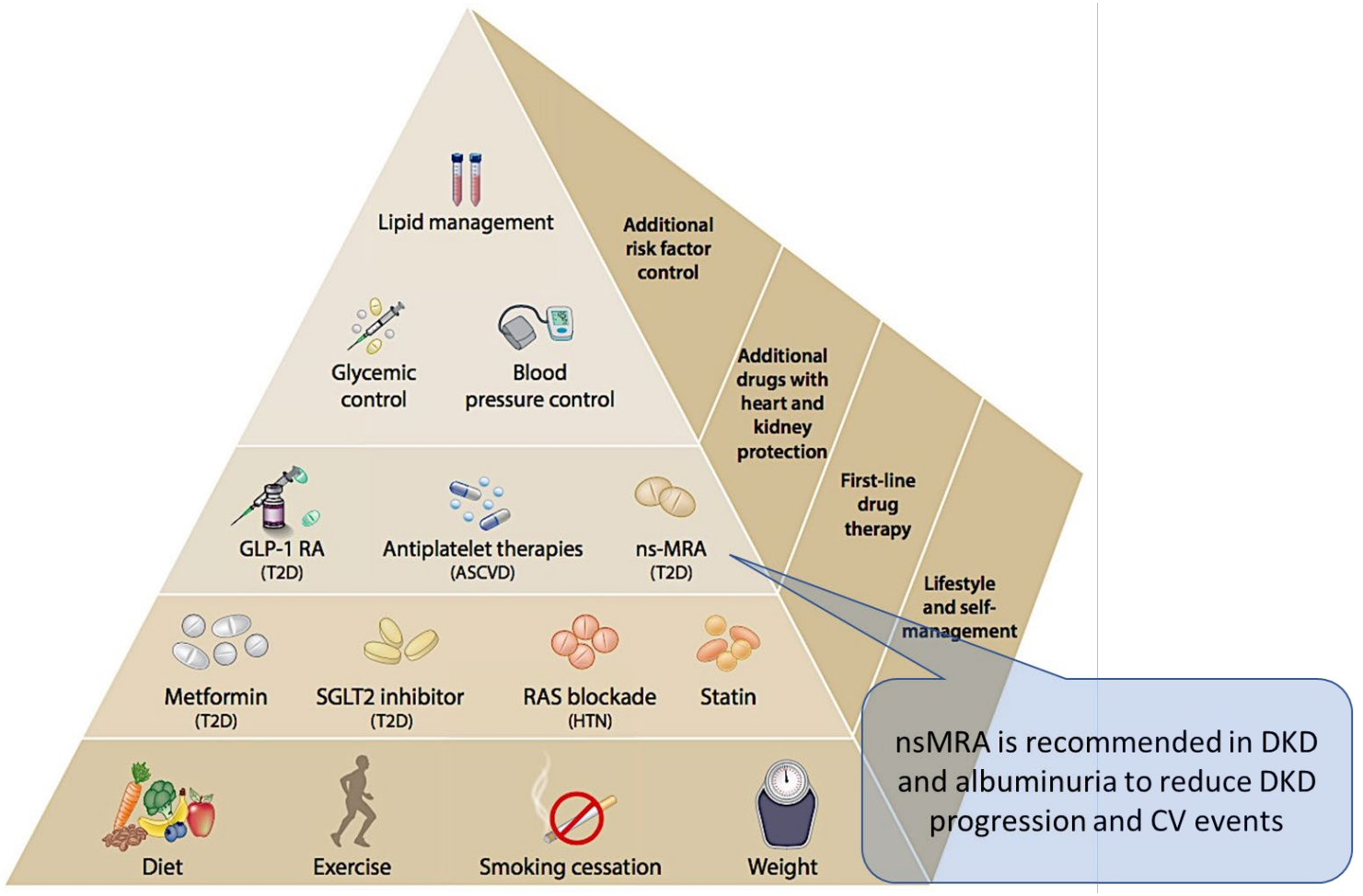
- Epidemiologia ‘ibrida’ della DKD
- Fenotipi ‘ibridi’ di DKD
- Prognosi ‘ibrida’ della DKD
- ‘Current science’ nel trattamento della DKD
- **‘Evolving science’ nel trattamento della DKD**

What will help?

- Epidemiologia ‘ibrida’ della DKD
- Fenotipi ‘ibridi’ di DKD
- Prognosi ‘ibrida’ della DKD
- ‘Current science’ nel trattamento della DKD
- **‘Evolving science’ nel trattamento della DKD**
  - **Finerenone**

Holistic approach for improving outcomes in patients with diabetes and CKD 2022 Consensus Report by the ADA and KDIGO





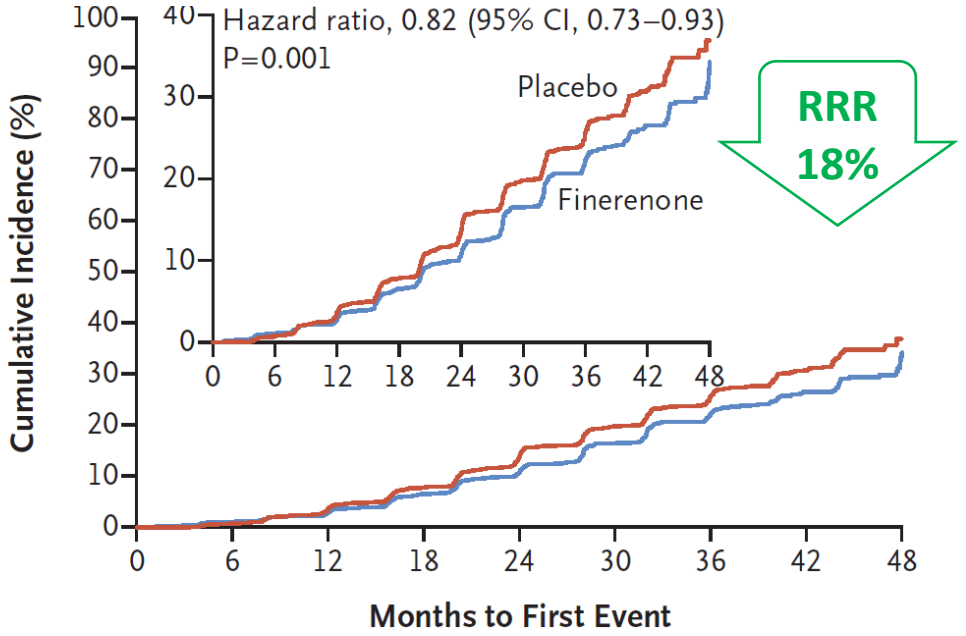
Kearney J and Gnudi L. Pharmaceutics 2023, 15: 1343 - de Boer IH et al. Diabetes Care 2022; 45: 3075-3090

Kidney outcomes with finerenone in patients with T2D and chronic kidney disease: the FIDELIO-DKD and FIGARO-DKD trials

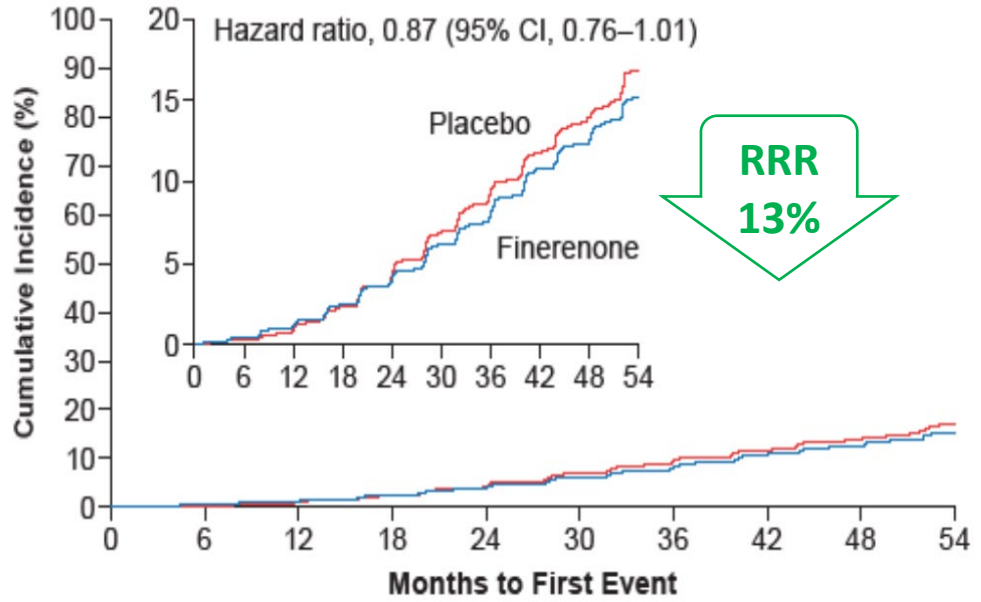
FIDELIO-DKD

Renal endpoint: time to onset of kidney failure, sustained decrease of eGFR ≥40%, or renal death

FIGARO-DKD



No. at Risk									
Placebo	2841	2724	2586	2379	1758	1248	792	453	82
Finerenone	2833	2705	2607	2397	1808	1274	787	441	83



No. at Risk										
Placebo	3666	3546	3436	3282	3096	2507	1933	1443	907	485
Finerenone	3686	3550	3445	3301	3131	2540	1940	1481	908	480

FIDELITY pooled analysis

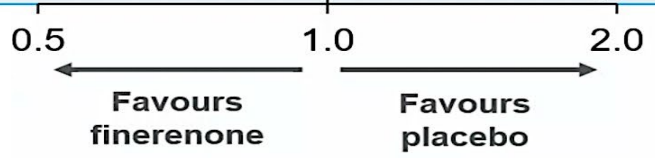
Bakris GL et al. N Engl J Med 2020;383:2219-29; Pitt B et al. N Engl J Med 2021;385:2252-63; Agarwal R et al. European Heart Journal 2022; 43: 474–484

Cardiovascular and kidney outcomes with finerenone in patients with T2D and chronic kidney disease: the FIDELITY pooled analysis

Results

	HR (95% CI)	p-value	Risk ↓
Endpoint CV composite* (NNT 46)	0.86 (0.78 – 0.95)	0.0018	14%
HHF	0.78 (0.66 – 0.92)	0.0030	22%
Kidney composite (NNT 60)	0.77 (0.67 – 0.88)	0.0002	23%
Dialysis	0.80 (0.64 – 0.99)	0.040	20%

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
≥57% eGFR composite kidney outcome	360 (5.5)	465 (7.1)	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD#	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040‡
eGFR <15 ml/min/1.73 m²¶	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026‡
≥57% decrease in eGFR from baseline¶	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	–



*cardiovascular death, non-fatal MI, non-fatal stroke, or HHF

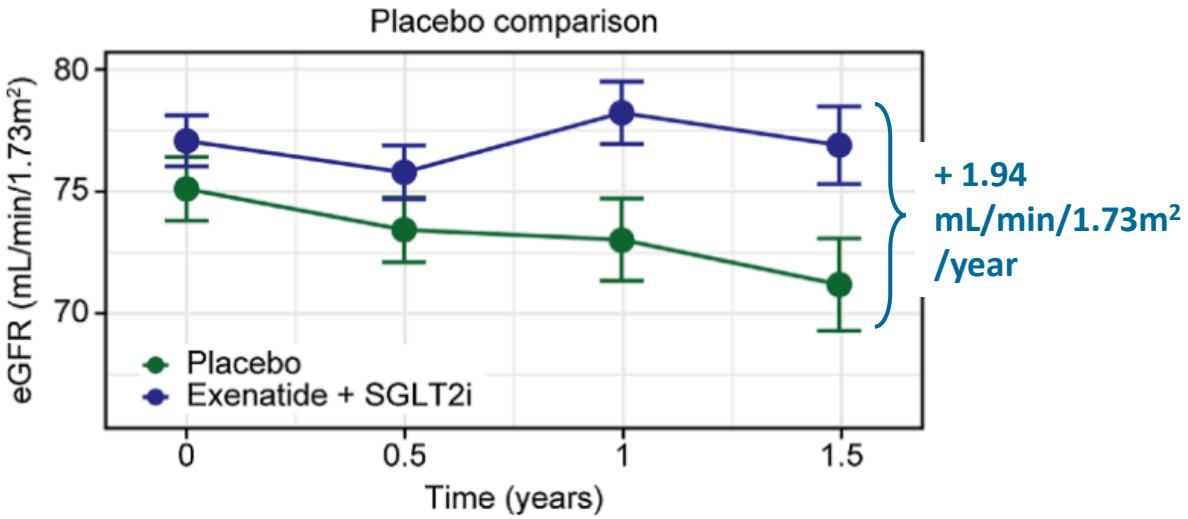
FIDELITY

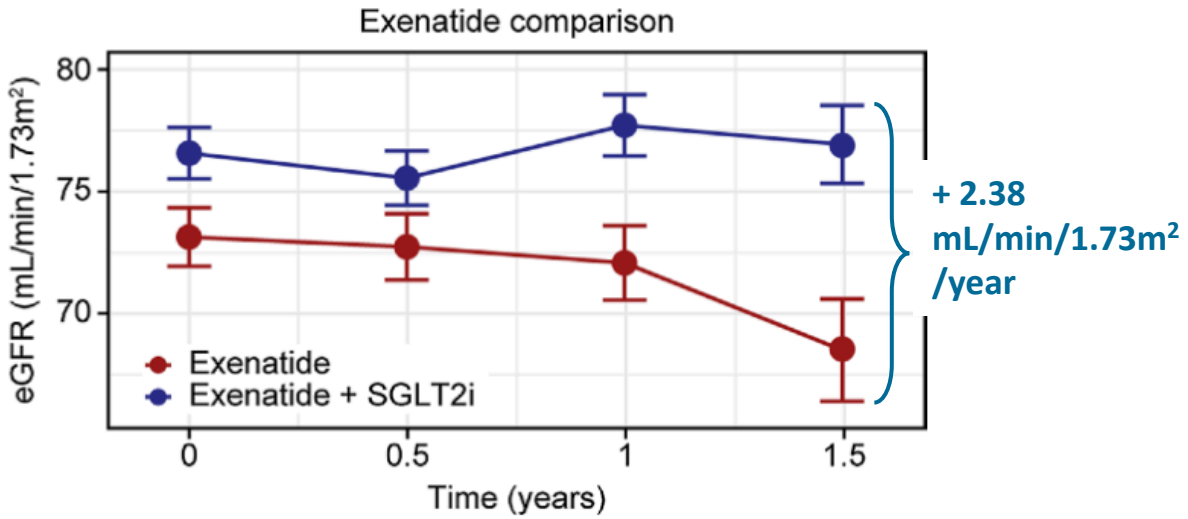
Agarwal R et al. European Heart Journal 2022; 43: 474–484

- Epidemiologia ‘ibrida’ della DKD
- Fenotipi ‘ibridi’ di DKD
- Prognosi ‘ibrida’ della DKD
- ‘Current science’ nel trattamento della DKD
- **‘Evolving science’ nel trattamento della DKD**
  - Finerenone
  - **Combinazione SGLT2i e GLP1-RA**

Effects of exenatide and open-label SGLT2 inhibitor treatment: insights from the EXSCEL trial (1)

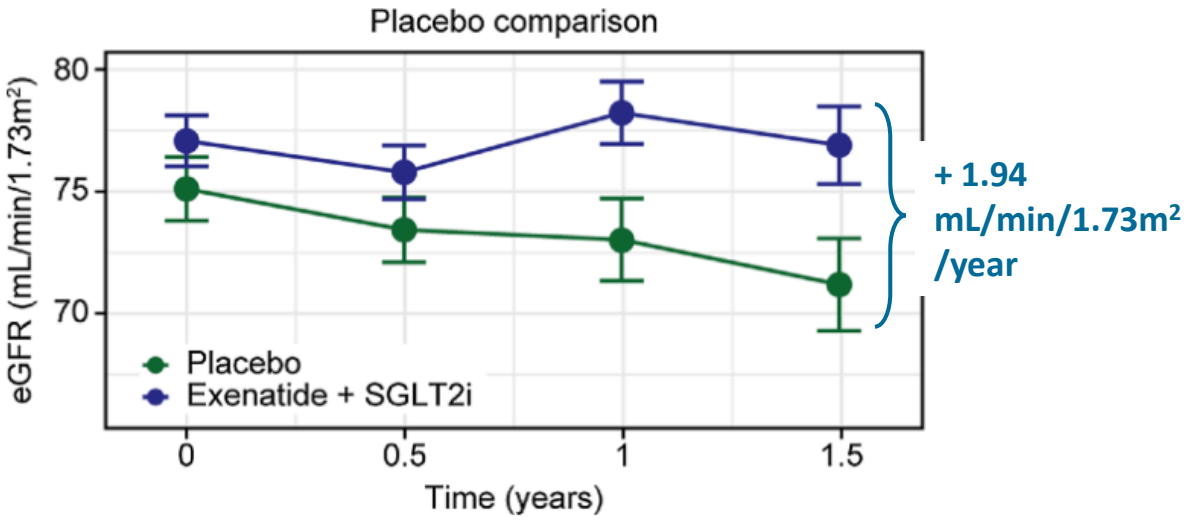
Among 645 (8.7%) EQW participants using an SGLT2i, 572 were matched in the placebo comparison and 575 in the EQW comparison

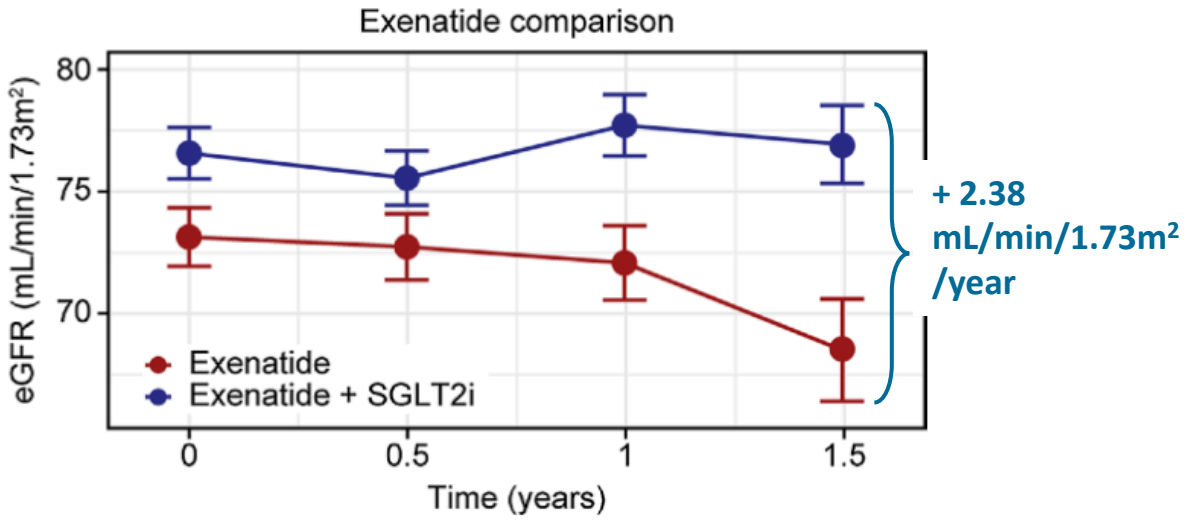




1. Clegg LE, et al., Cardiovasc Diabetol 2019; 18: 138

Effects of exenatide and open-label SGLT2 inhibitor treatment: insights from the EXSCEL trial (1)

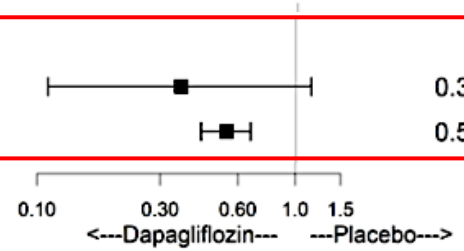




Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from DECLARE-TIMI 58 (2)

Renal specific outcome* with dapagliflozin vs. placebo by GLP-1 RA use (4.4% of the cohort)

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	p-value	p-interaction
Baseline GLP-1 receptor agonists					
Yes (n. 750)	4/397 (1.0%)	10/353 (2.8%)	0.36 (0.11, 1.15)	0.0836	0.4894
No (n. 16,410)	123/8185 (1.5%)	228/8225 (2.8%)	0.54 (0.43, 0.67)	<.0001	



***A composite of:**

- sustained decrease of ≥40% in eGFR
- ESRD
- death from renal causes

1. Clegg LE, et al., Cardiovasc Diabetol 2019; 18: 138 - 2. Cahn A et al. Diabetes Obes Metab 2021; 23: 29-38

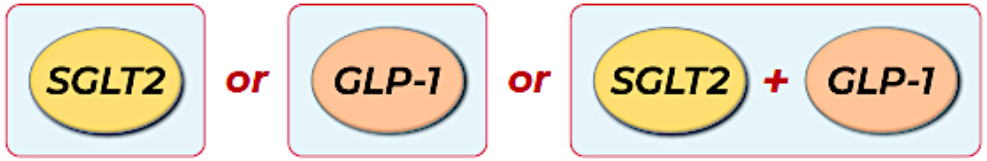
PRECIDENTD

Prevention of Cardiovascular and Diabetic Kidney Disease in Type 2 Diabetes

Is a randomized, open label, pragmatic clinical trial designed to compare rates of the total number of cardiovascular, kidney, and death events among three alternative treatments for patients with T2D and either established ASCVD or at high risk for ASCVD.

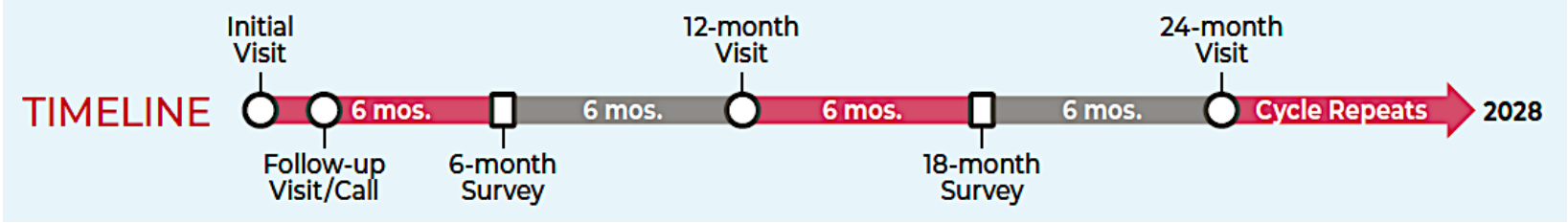
The study is randomly assigning 9,000 T2D and ASCVD or high-risk forASCVD in a 1:1:1 allocation to:

- SGLT2i: empagliflozin, dapagliflozin, or canagliflozin
- GLP-1RA: dulaglutide, liraglutide, semaglutide
- Combination of SGLT2i and GLP-1RA



Participants will be followed for the occurrence of the trial primary endpoint:

- total (first and recurrent) number of episodes of myocardial infarction, stroke, arterial revascularization, hospitalization for heart failure, development of ESKD, kidney transplantation, and mortality



Up to 5.5-year follow-up for primary outcome

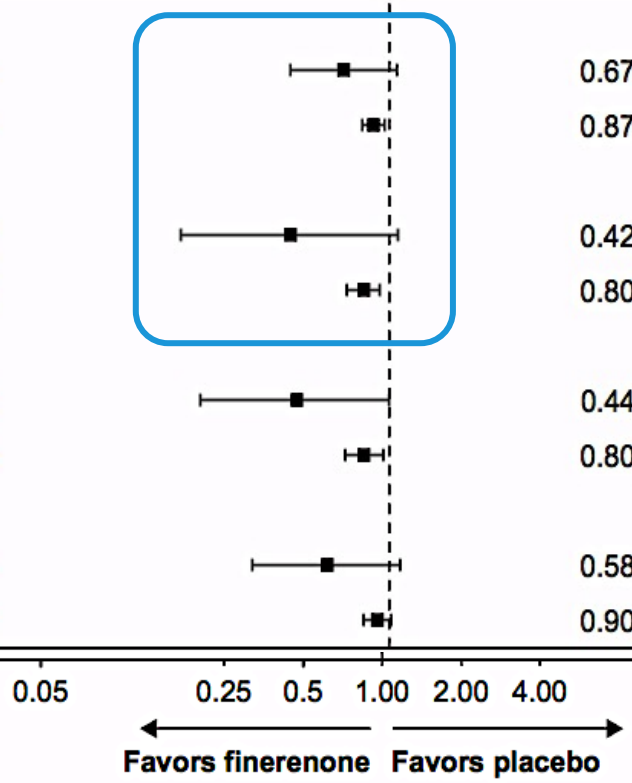
ClinicalTrials.gov Identifier: NCT05390892

- Epidemiologia ‘ibrida’ della DKD
- Fenotipi ‘ibridi’ di DKD
- Prognosi ‘ibrida’ della DKD
- ‘Current science’ nel trattamento della DKD
- **‘Evolving science’ nel trattamento della DKD**
  - Finerenone
  - Combinazione SGLT2i e GLP1-RA
  - **Combinazione Finerenone e SGLT2i/GLP1-RA**

Finerenone in Patients With CKD and T2D by SGLT2 Inhibitor Treatment: The FIDELITY Analysis

Analysis of kidney and CV composite outcomes in patients receiving or not an **SGLT2i at baseline** (n. 877, 6.7%)

	Finerenone	Placebo	Finerenone	Placebo	HR (95% CI)	$P_{interaction}$
	n/N (%)		*n* per 100 PY			
Analysis for outcomes in patients receiving/not receiving an SGLT2i at baseline						
Cardiovascular composite *						
SGLT2i at baseline	39/438 (8.9)	52/439 (11.8)	2.95	4.08	0.67 (0.42–1.07)*	0.46†
No SGLT2i at baseline	786/6,081 (12.9)	887/6,068 (14.6)	4.44	5.08	0.87 (0.79–0.96)*	
Kidney composite **						
SGLT2i at baseline	9/438 (2.1)	17/439 (3.9)	0.70	1.37	0.42 (0.16–1.08)*	0.29†
No SGLT2i at baseline	351/6,081 (5.8)	448/6,068 (7.4)	2.06	2.64	0.80 (0.69–0.92)*	
Hospitalization for heart failure						
SGLT2i at baseline	10/438 (2.3)	22/439 (5.0)	0.74	1.68	0.44 (0.19–0.99)*	0.18†
No SGLT2i at baseline	246/6,081 (4.0)	303/6,068 (5.0)	1.35	1.68	0.80 (0.68–0.95)*	
All-cause death						
SGLT2i at baseline	20/438 (4.6)	30/439 (6.8)	1.46	2.23	0.58 (0.30–1.10)*	0.24†
No SGLT2i at baseline	532/6,081 (8.7)	584/6,068 (9.6)	2.86	3.16	0.90 (0.80–1.02)*	



*cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure

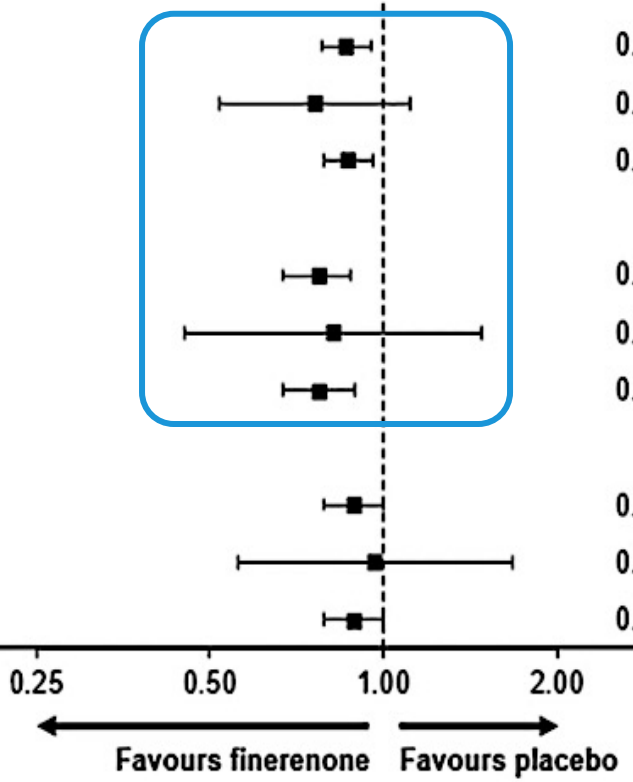
** kidney failure, a sustained decrease of ≥57% in eGFR from baseline, or renal death

Rossing P et al. Diabetes Care 2022; 45: 2991-2998

Finerenone in patients across the spectrum of CKD T2D by GLP-1 RA use (FIDELIO-DKD and FIGARO-DKD)

Of 13,026 patients, 944 (7.2%) received a **GLP-1RA at baseline**, with similar proportion in the finerenone (497/6519; 7.6%) and placebo (447/6507; 6.9%) groups

	Finerenone	Placebo	Finerenone	Placebo	Hazard ratio (95% CI)	$p_{interaction}$
	n/N (%)		n per 100 PY			
Cardiovascular composite *						
Overall	825/6519 (12.6)	939/6507 (14.4)	4.34	5.01	0.86 (0.78, 0.95)	
GLP-1RA use at baseline	58/497 (11.7)	64/447 (14.3)	3.79	4.90	0.76 (0.52, 1.11)	0.63
No GLP-1RA use at baseline	767/6022 (12.7)	875/6060 (14.4)	4.38	5.02	0.87 (0.79, 0.96)	
Kidney composite (eGFR ≥ 57%) **						
Overall	360/6519 (5.5)	465/6507 (7.1)	1.96	2.55	0.77 (0.67, 0.88)	
GLP-1RA use at baseline	22/497 (4.4)	27/447 (6.0)	1.47	2.10	0.82 (0.45, 1.48)	0.79
No GLP-1RA use at baseline	338/6022 (5.6)	438/6060 (7.2)	2.01	2.59	0.77 (0.67, 0.89)	
All-cause mortality						
Overall	552/6519 (8.5)	614/6507 (9.4)	2.76	3.10	0.89 (0.79, 1.00)	
GLP-1RA use at baseline	33/497 (6.6)	25/447 (5.6)	2.05	1.79	0.97 (0.56, 1.67)	0.41
No GLP-1RA use at baseline	519/6022 (8.6)	589/6060 (9.7)	2.83	3.20	0.89 (0.79, 1.00)	



*cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for HF

** kidney failure, a sustained decrease of ≥57% in eGFR from baseline, or renal death

Rossing P et al. Diabetes Obes Metab 2023; 25: 407-416

Design of the COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with CKD and T2D using a 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.

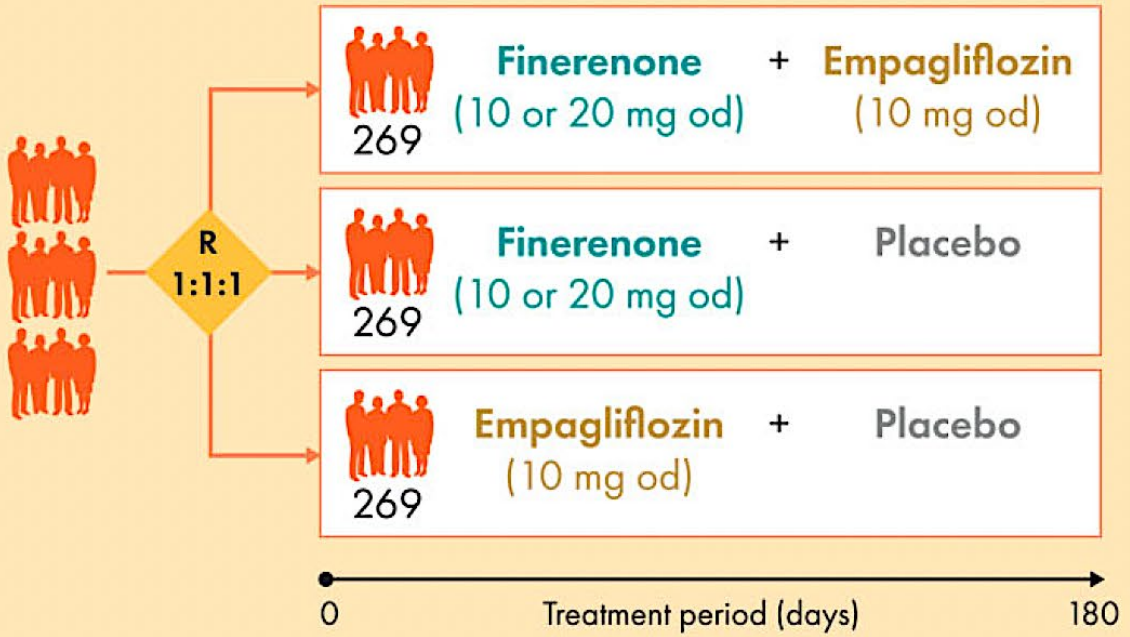
Participants

- 807 participants
- 125 centres
- 13 countries

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

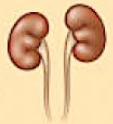
- T1D
- Serum K^+ > 4.8 mmol/L
- Treatment with SGLT1/2i or MRA

Treatment arms



Primary outcomes

Relative change in UACR from baseline to 180 days in:



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 et al. Nephrol Dial Transplant. 2023 Mar 31;38(4):894-903

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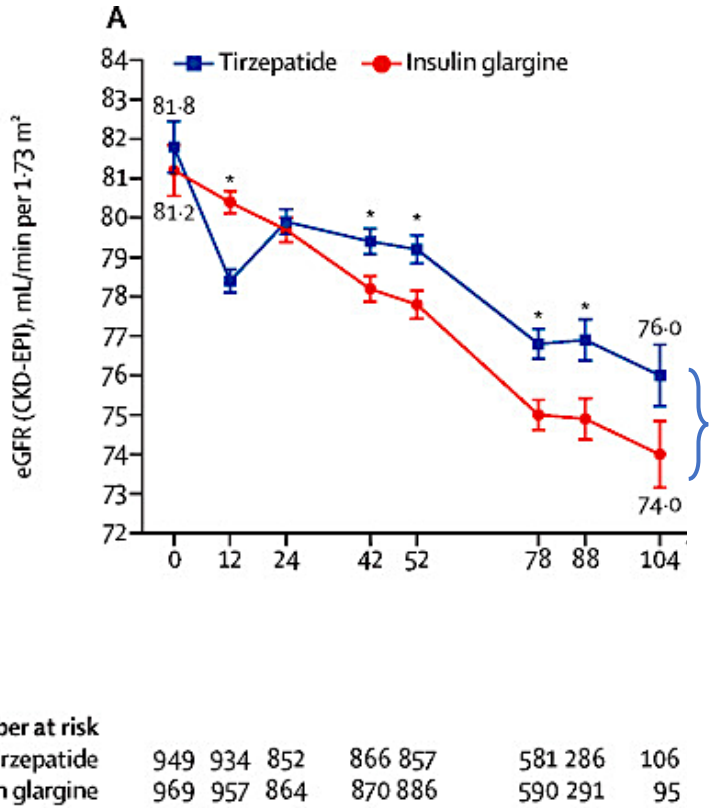
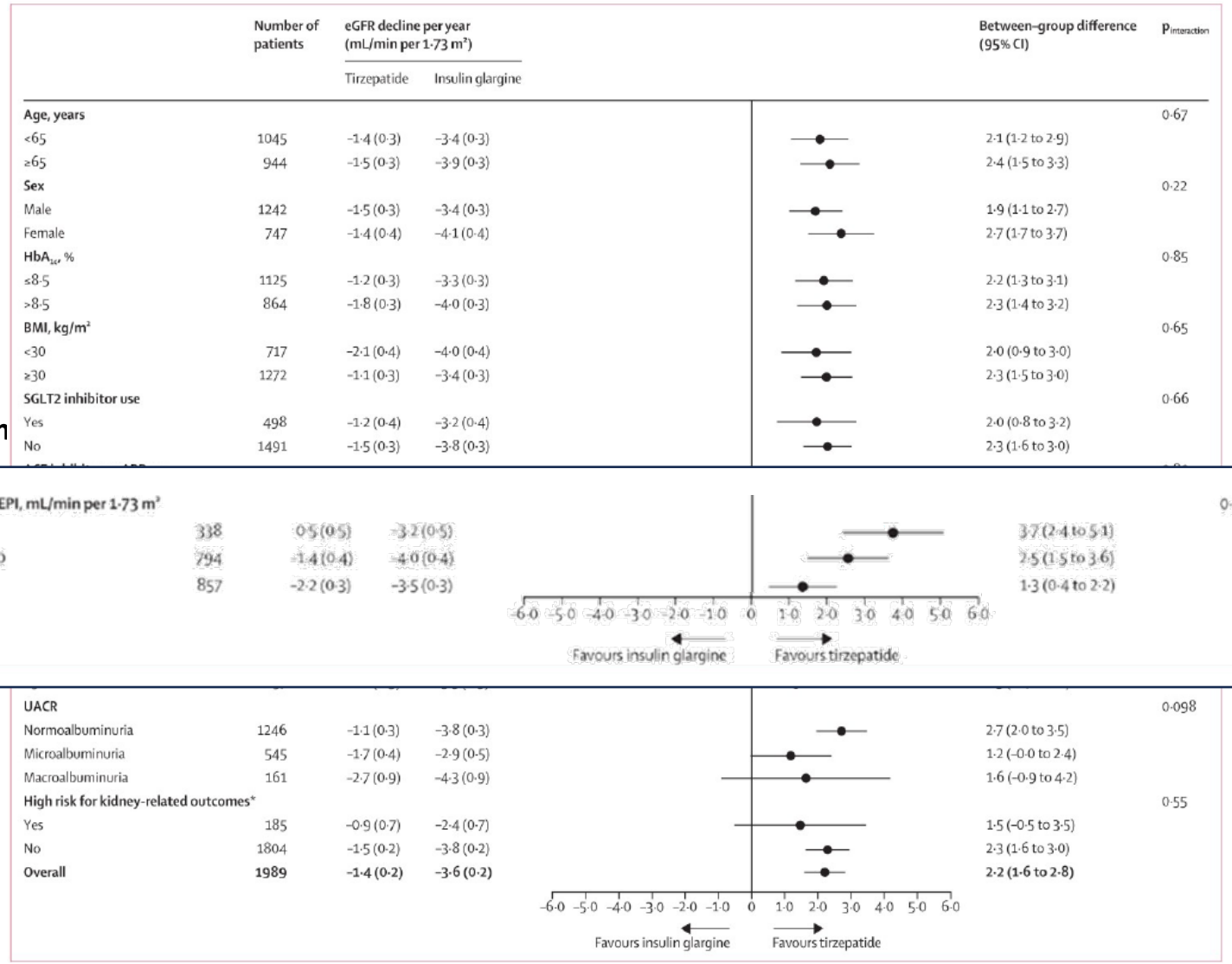
- Fenotipi ‘ibridi’ di DKD
- Prognosi ‘ibrida’ della DKD
- ‘Current science’ nel trattamento della DKD
- **‘Evolving science’ nel trattamento della DKD**
  - Finerenone
  - Combinazione SGLT2i e GLP1-RA
  - Combinazione Finerenone e SGLT2i/GLP1-RA
  - **Tirzepatide**

Effects of tirzepatide versus insulin glargine on kidney outcomes in T2D in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

1995 subjects randomly assigned to tirzepatide (995) or insulin glargine (1000) – median study duration 85 weeks



2.2 mL/m



Heerspink HJL et al. Lancet Diabetes Endocrinol 2022; 10: 774-785

Effects of tirzepatide versus insulin glargine on kidney outcomes in T2D in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

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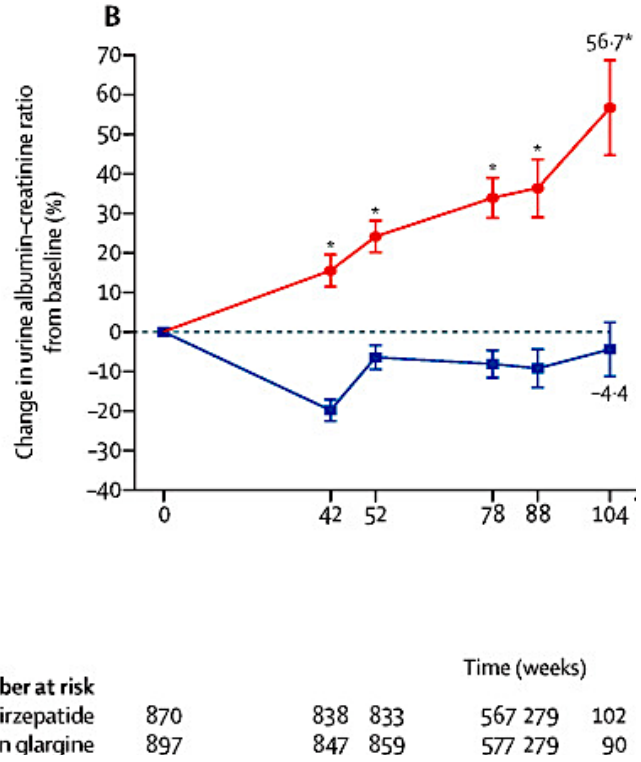
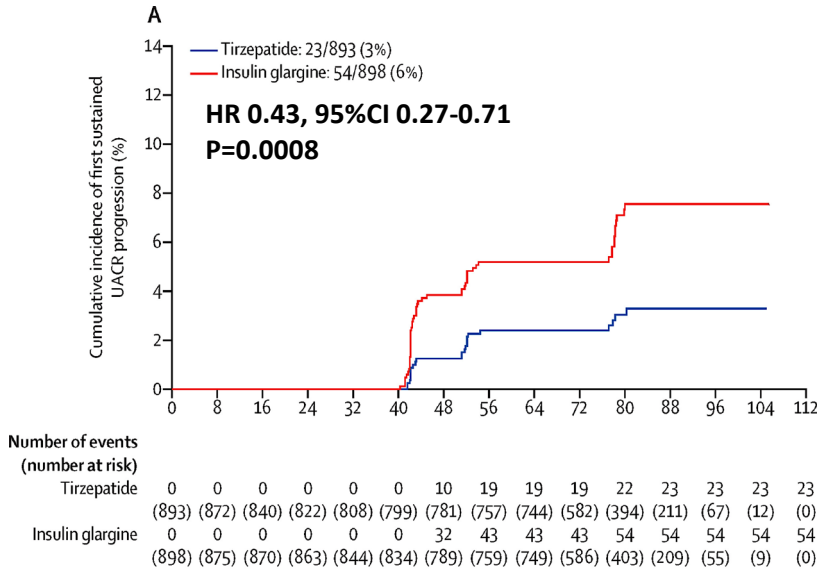
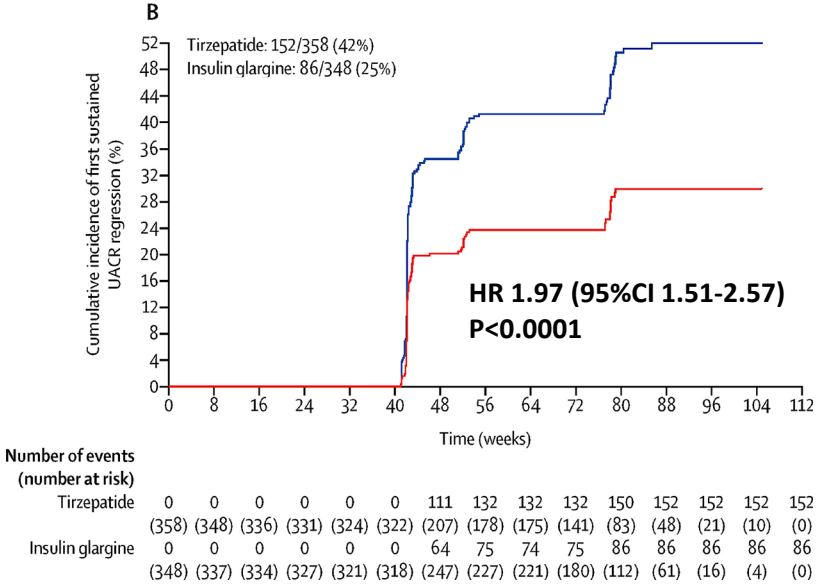


Tirzepatide significantly decreased the likelihood of progression to increasingly severe stage of ACR and significantly increased the likelihood of regression to a less severe albuminuria stage

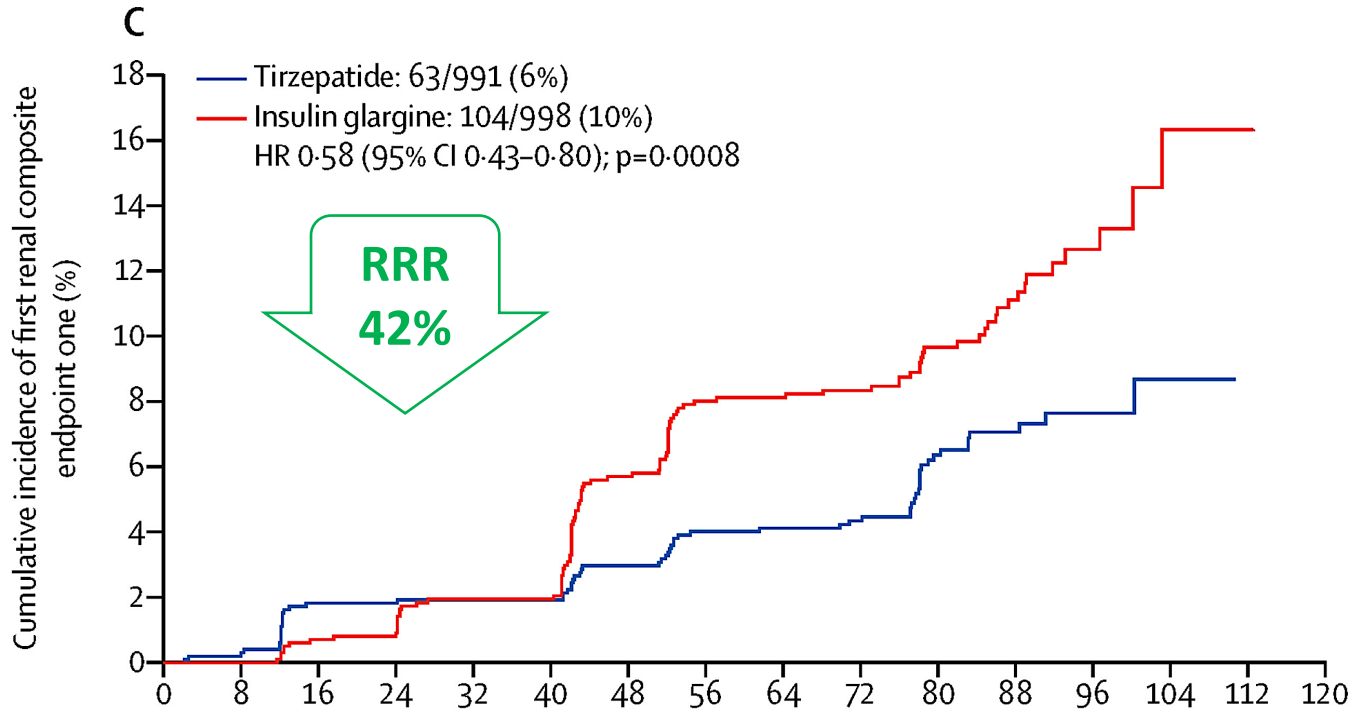




Heerspink HJL et al. Lancet Diabetes Endocrinol 2022; 10: 774-785

Effects of tirzepatide versus insulin glargine on kidney outcomes in T2D in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

Composite kidney outcome: eGFR decline >40%, death due to kidney failure, ESRD, new onset macroalbuminuria



Number of events (number at risk)																
Tirzepatide	0 (991)	3 (985)	18 (962)	18 (952)	19 (947)	19 (944)	29 (930)	39 (912)	40 (902)	42 (815)	56 (609)	60 (391)	62 (180)	63 (41)	63 (0)	63 (0)
Insulin glargine	0 (998)	0 (988)	7 (973)	9 (966)	19 (946)	19 (940)	55 (901)	77 (867)	78 (849)	80 (755)	89 (555)	96 (369)	101 (164)	104 (35)	104 (1)	104 (0)

Heerspink HJL et al. Lancet Diabetes Endocrinol 2022; 10: 774-785

Effects of tirzepatide versus insulin glargine on kidney outcomes in T2D in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

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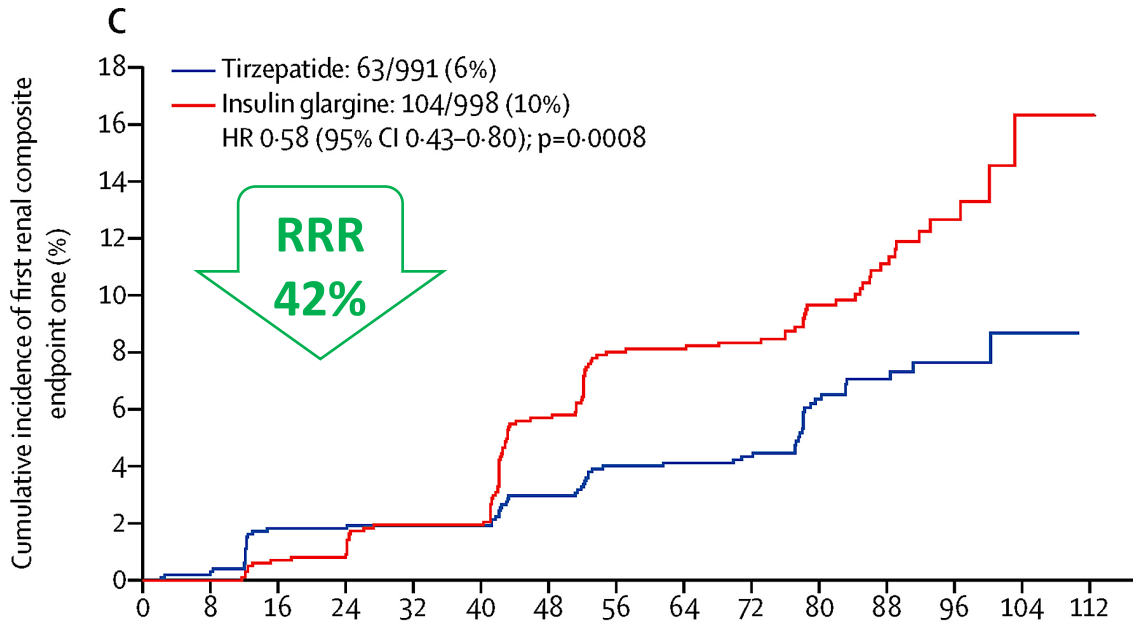

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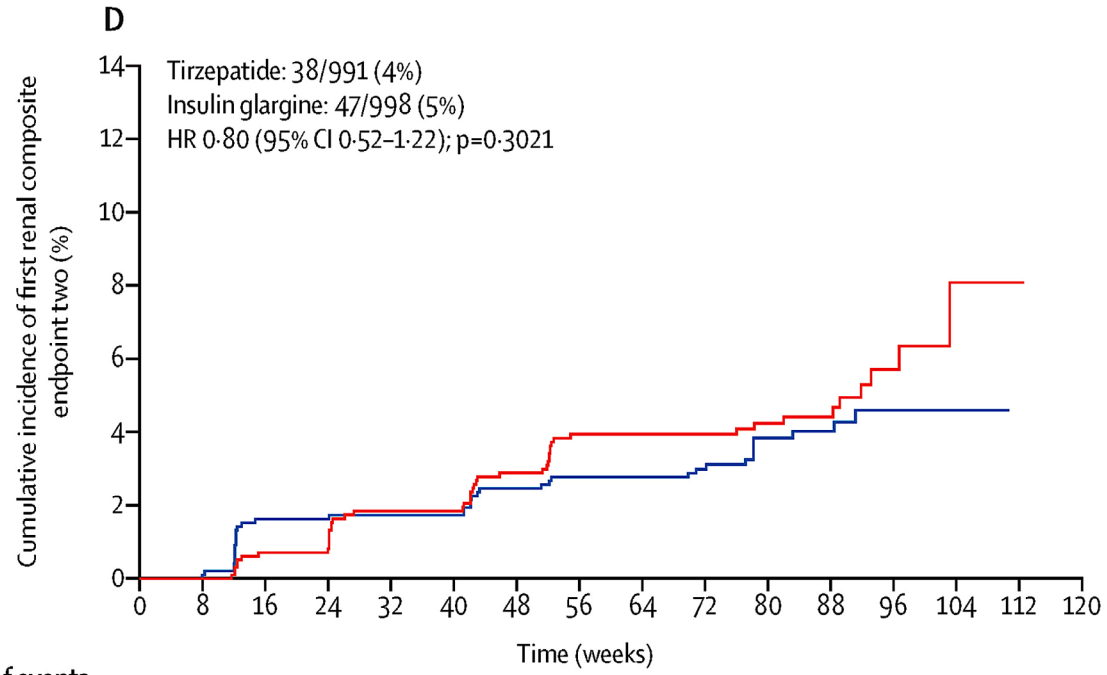
Composite kidney outcome: eGFR decline >40%, death due to kidney failure, ESRD



Number of events (number at risk)																
Tirzepatide	0 (991)	1 (987)	16 (964)	16 (954)	17 (949)	17 (946)	24 (935)	27 (924)	27 (915)	29 (825)	35 (625)	36 (405)	38 (187)	38 (43)	38 (0)	38 (0)
Insulin glargine	0 (998)	0 (988)	7 (973)	8 (967)	18 (947)	18 (941)	28 (928)	38 (906)	38 (887)	38 (789)	40 (585)	41 (392)	45 (177)	47 (40)	47 (1)	47 (0)

Heerspink HJL et al. Lancet Diabetes Endocrinol 2022; 10: 774-785

- Epidemiologia ‘ibrida’ della DKD
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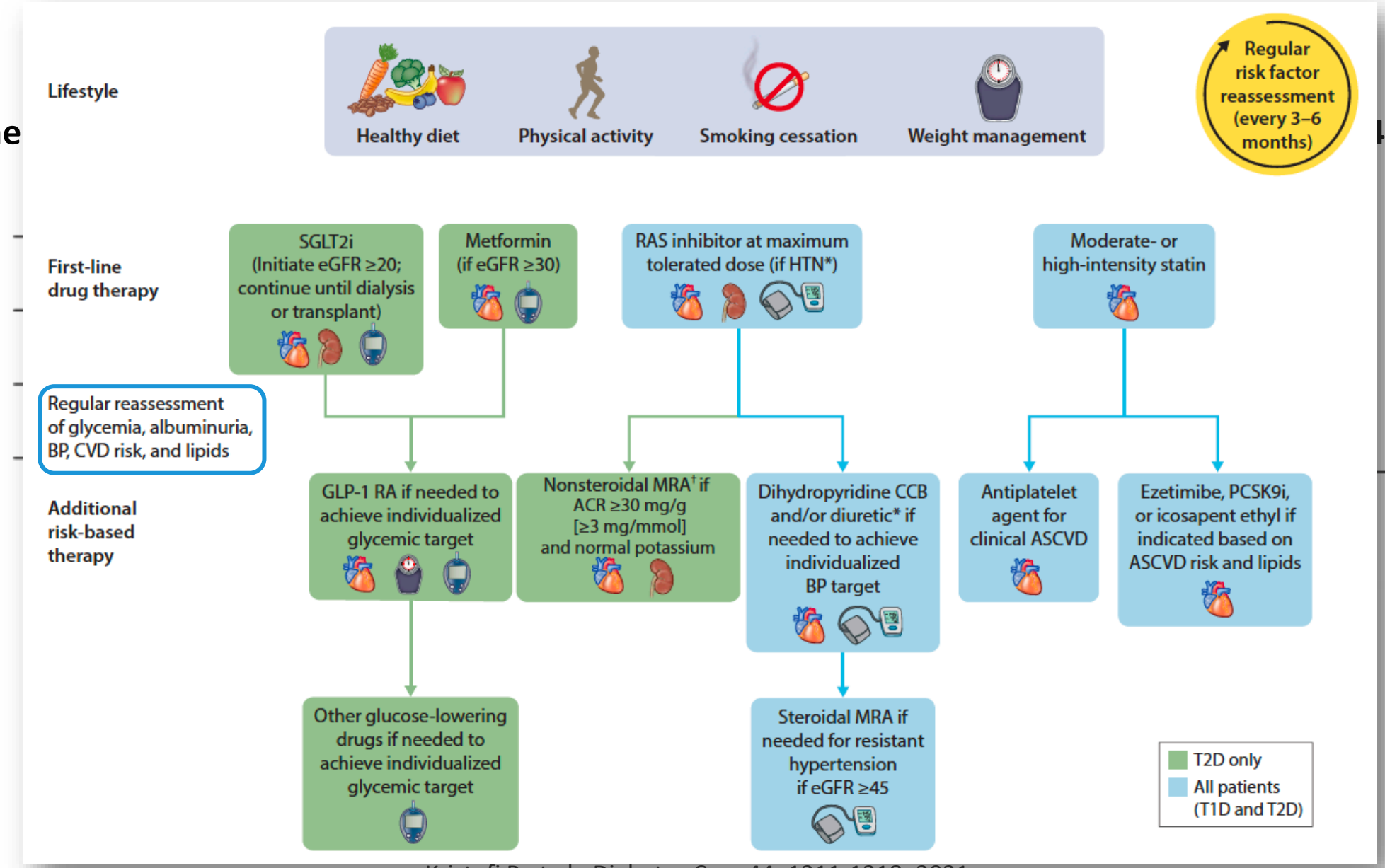
  - Tirzepatide
- **Opportunità di trattamento nel DMT1**

Translation of T2D treatments to T1D: is it an opportunity?

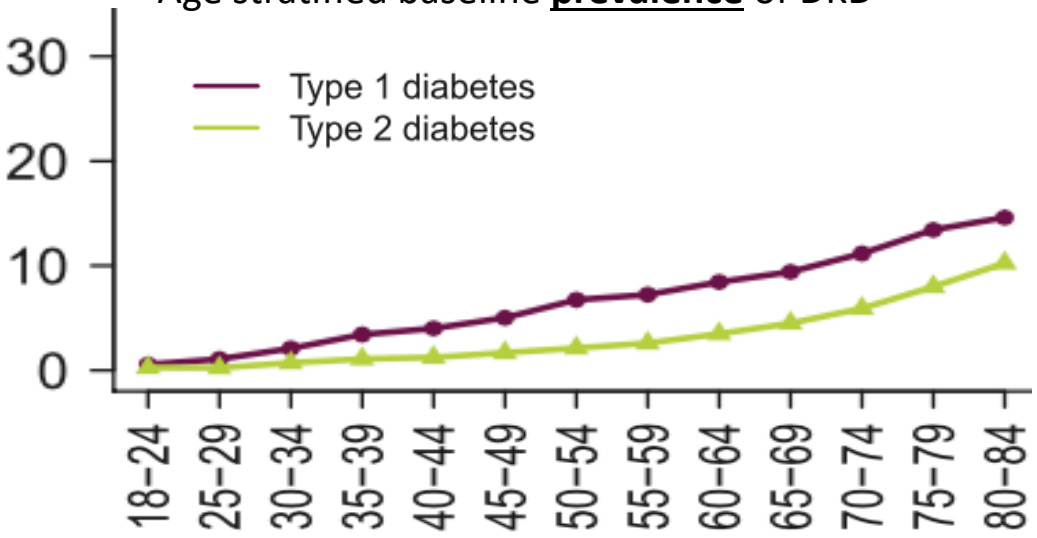


Kristofi R et al., Diabetes Care 44: 1211-1218, 2021

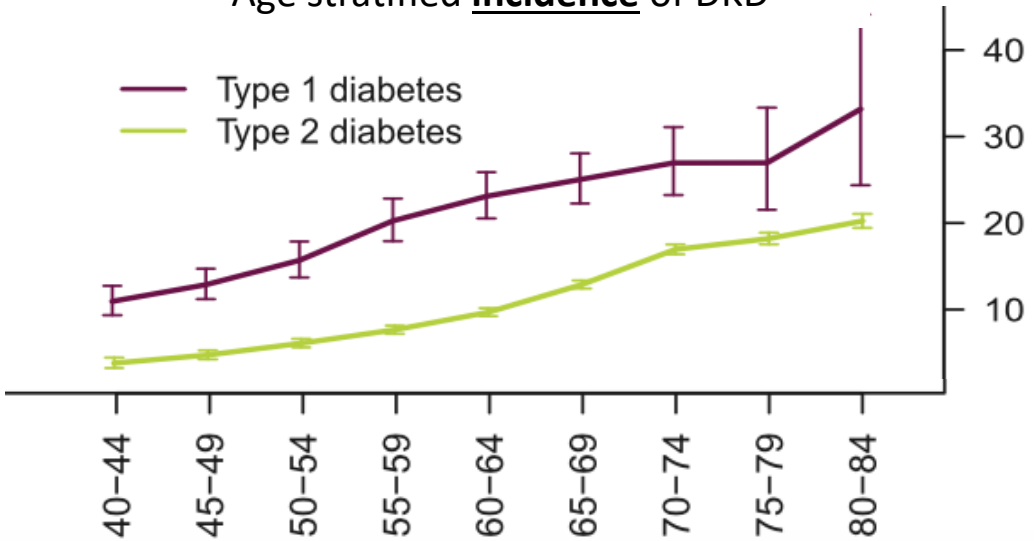
Translation of T2D treatments to T1D: is it an opportunity?

The risk of DKD may be even greater in individuals with T1D (n = 59,331) vs T2D (n = 484,241) [1]

Age stratified baseline **prevalence** of DKD



Age stratified **incidence** of DKD



Pooled analyses of three T1D trial programs [2-4]

		n.	UACR	eGFR	sBP/dBP	hematocrit	Uric acid
inTandem 1 & 2	Sotagliflozin	1575	↓ *	↓ acute dip	↓	↑	↓
EASE-2 & 3	Empagliflozin	1695	↓ *	↓ acute dip	↓	↑	↓
DEPICT-1 & 2	Dapagliflozin	1646	↓ *	↓ acute dip	↓		

** Baseline UACR ≥30 mg/g subgroup*

1. Kristofi R et al., Diabetes Care 44: 1211-1218, 2021; 2. Van Raalte DH et al., Diabetes Care 42: 1921-1929, 2019;
3. Cherney DZI et al., Clin J Am Soc Nephrol 16: 1715-1719, 2021; 4. Groop PH et al., Lancet Diabetes Endocrinol 8: 845-854, 2020

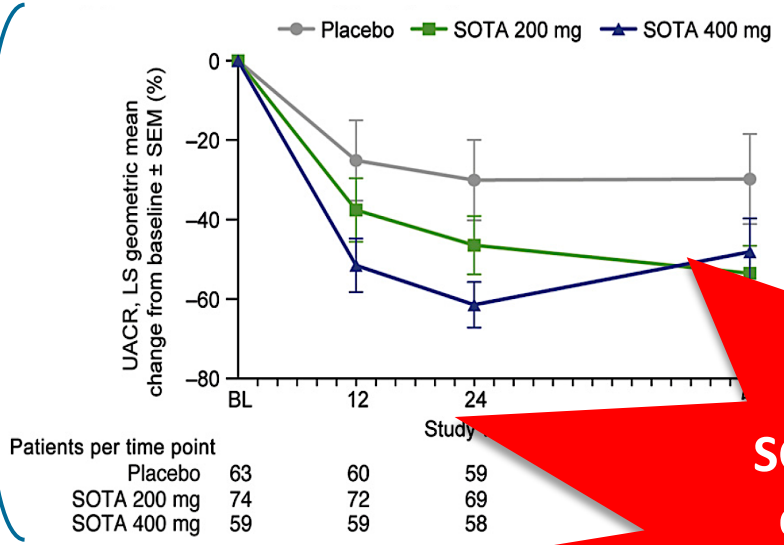
Pooled analyses of three T1D trial programs[1-3]

1575 T1D in inTandem1 and inTandem2

1705 T1D in EASE-2 and EASE-3

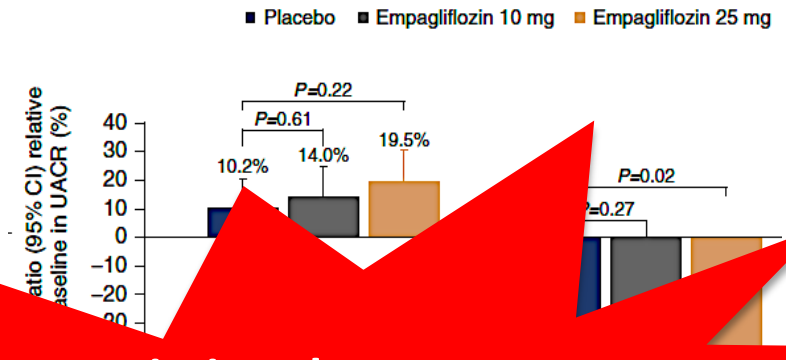
251 T1D with albuminuria in DEPICT-1 & 2

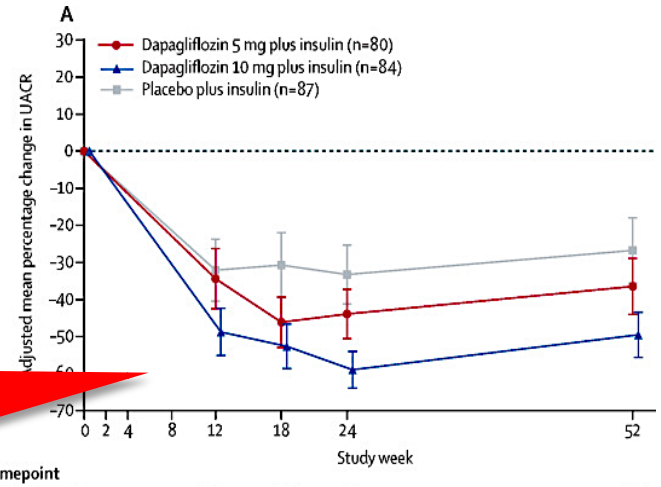
UACR



Patients per time point

Placebo	63	60	59
SOTA 200 mg	74	72	69
SOTA 400 mg	59	59	58

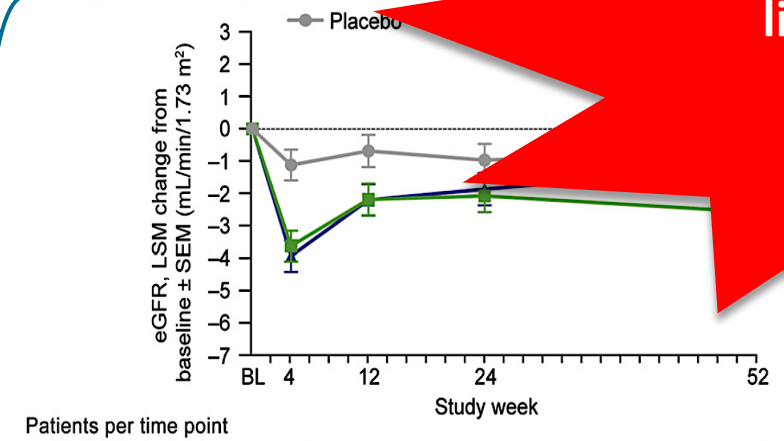




Participants per timepoint

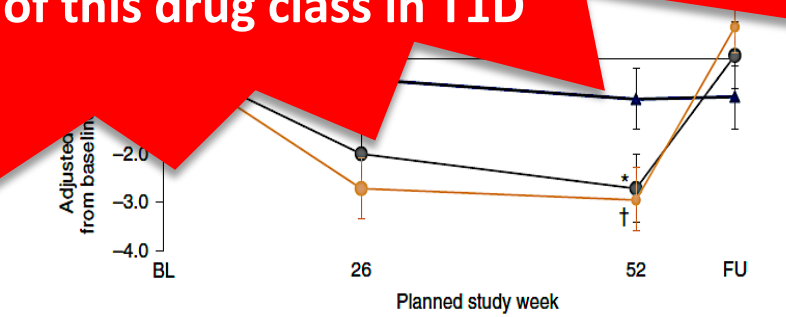
Dapagliflozin 5 mg	79	76	75	71	78
Dapagliflozin 10 mg	84	79	77	73	81
Placebo	87	83	80	79	83

eGFR



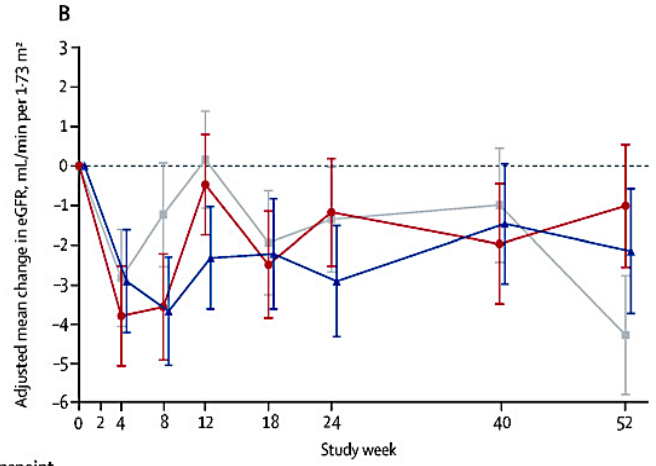
Patients per time point

Placebo	526	511	486	481	374
SOTA 200 mg	524	502	486	479	392
SOTA 400 mg	525	505	491	477	380



Participants, *n*

Placebo	241	212	192	233
Empagliflozin 2.5 mg	N/A	N/A	N/A	N/A
Empagliflozin 10 mg	243	228	203	234
Empagliflozin 25 mg	242	231	220	234



Participants per timepoint

Dapagliflozin 5 mg	80	77	76	75	76	72	64	61
Dapagliflozin 10 mg	84	80	80	80	77	73	70	63
Placebo	87	86	82	84	82	79	75	66

Associations between SGLT2i with increased risk of diabetic ketoacidosis have limited the implementation of this drug class in T1D

1. Van Raalte DH et al. Diabetes Care 2019; 42: 1921-1929

2. Cherney DZI et al. Clin J Am Soc Nephrol 2021;16: 1715-1719

3. Groop PH et al. Lancet Diabetes Endocrinol 2020;8: 845-854

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  - Tirzepatide
- Opportunità di trattamento nel DMT1
- **Conclusioni**

Take Home Messages

- La DKD è in calo, ma l'incidenza di ESRD da DKD sta probabilmente aumentando.
- I diversi fenotipi di DKD hanno eterogeneo rischio di outcome CV o renali e diversa prognosi
- Gli SGLT2i e i GLP-1 RA, insieme a ACE inibitori o ARB, sono raccomandati nella terapia della DKD
- Il trattamento con Finerenone sarà un'ulteriore opzione terapeutica, raccomandata per molti soggetti con DKD
- L'uso di questi farmaci (SGLT2i, GLP-1 RA e Finerenone) nel trattamento della DKD nel diabete tipo 1 rimane un'opportunità scarsamente esplorata e occorre uno impegno importante per ampliare le opzioni terapeutiche in questa popolazione
- Finora, non sono stati pubblicati RCT disegnati per valutare gli effetti renali della combinazione dei trattamenti con comprovati benefici cardiorenali (SGLT2i e/o GLP-1 RA e/o Finerenone) o in differenti fenotipi di DKD …
- … sebbene una sempre più precisa terapia personalizzata potrà ottimizzare la protezione renale

Grazie dell’attenzione