Società Medico Chirurgica di Ferrara dal 1846

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Terapia medica dell'obesità e rene

Dr. Riccardo Spaggiari

Azienda Ospedaliero-Universitaria di Ferrara

Dichiarazione conflitti di interesse

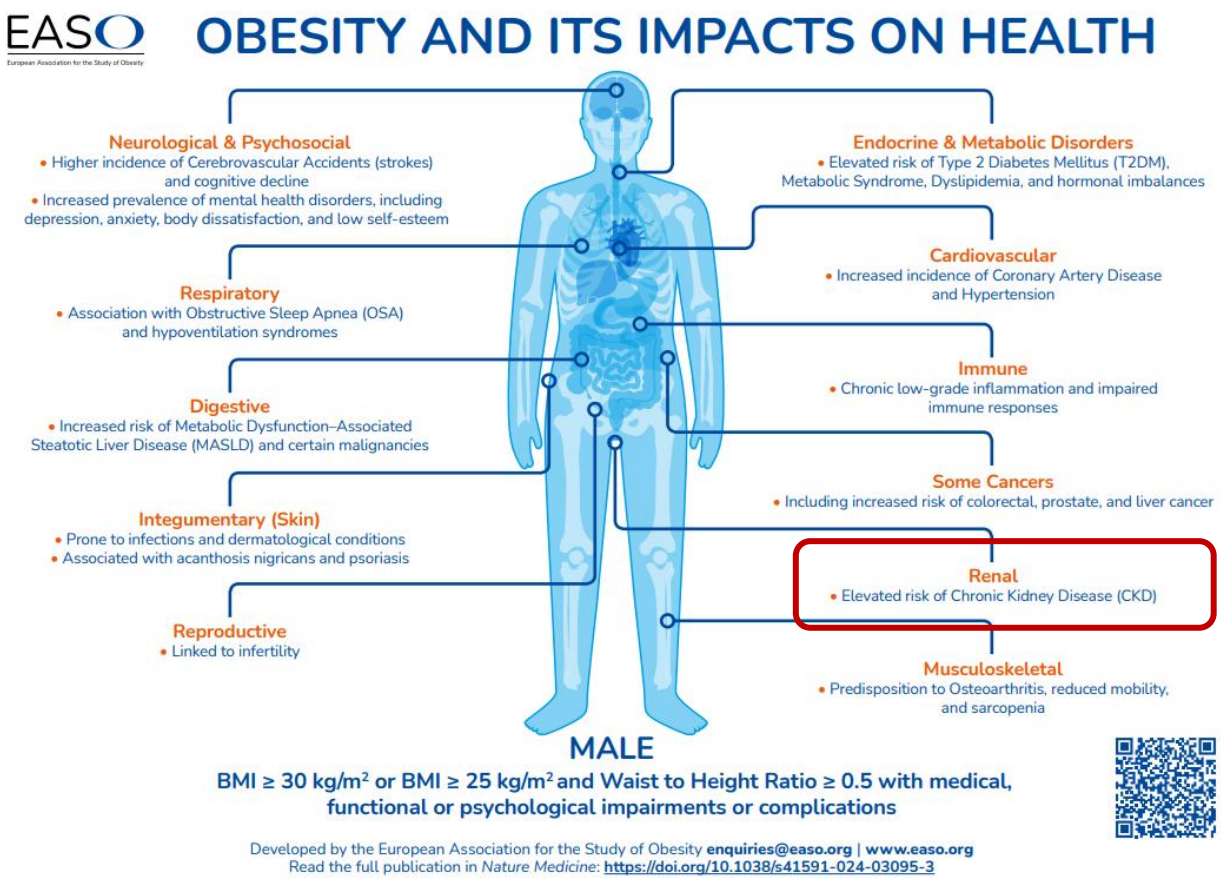
Il sottoscritto

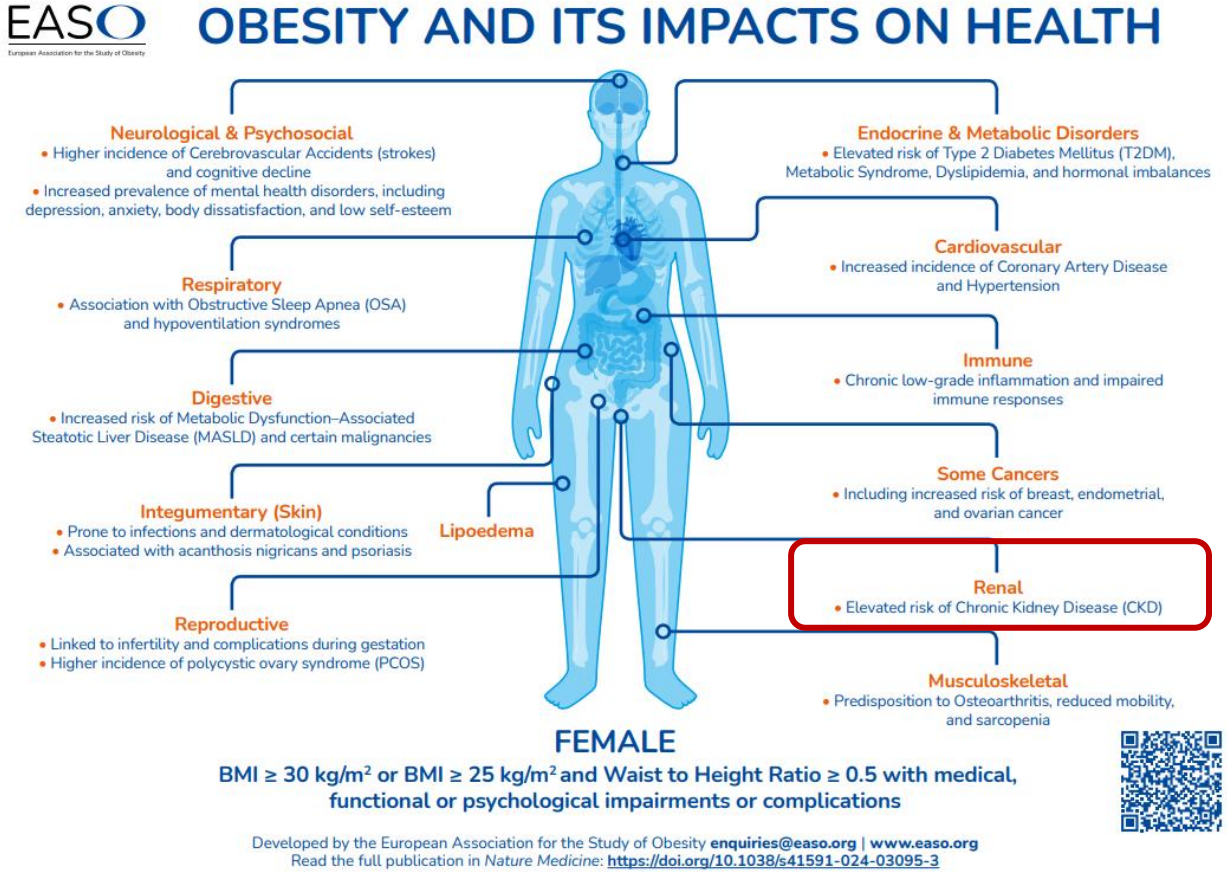
ai sensi dell’art. 76, comma 4 dell’Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

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

- Novo Nordisk (Sub-Investigator, senza compenso)
- Eli Lilly and Company (Sub-Investigator, senza compenso)
- Daiichi-Sankyo (Sub-Investigator, senza compenso)
- Fondazione Menarini (rimborso spese per partecipazione a evento scientifico)

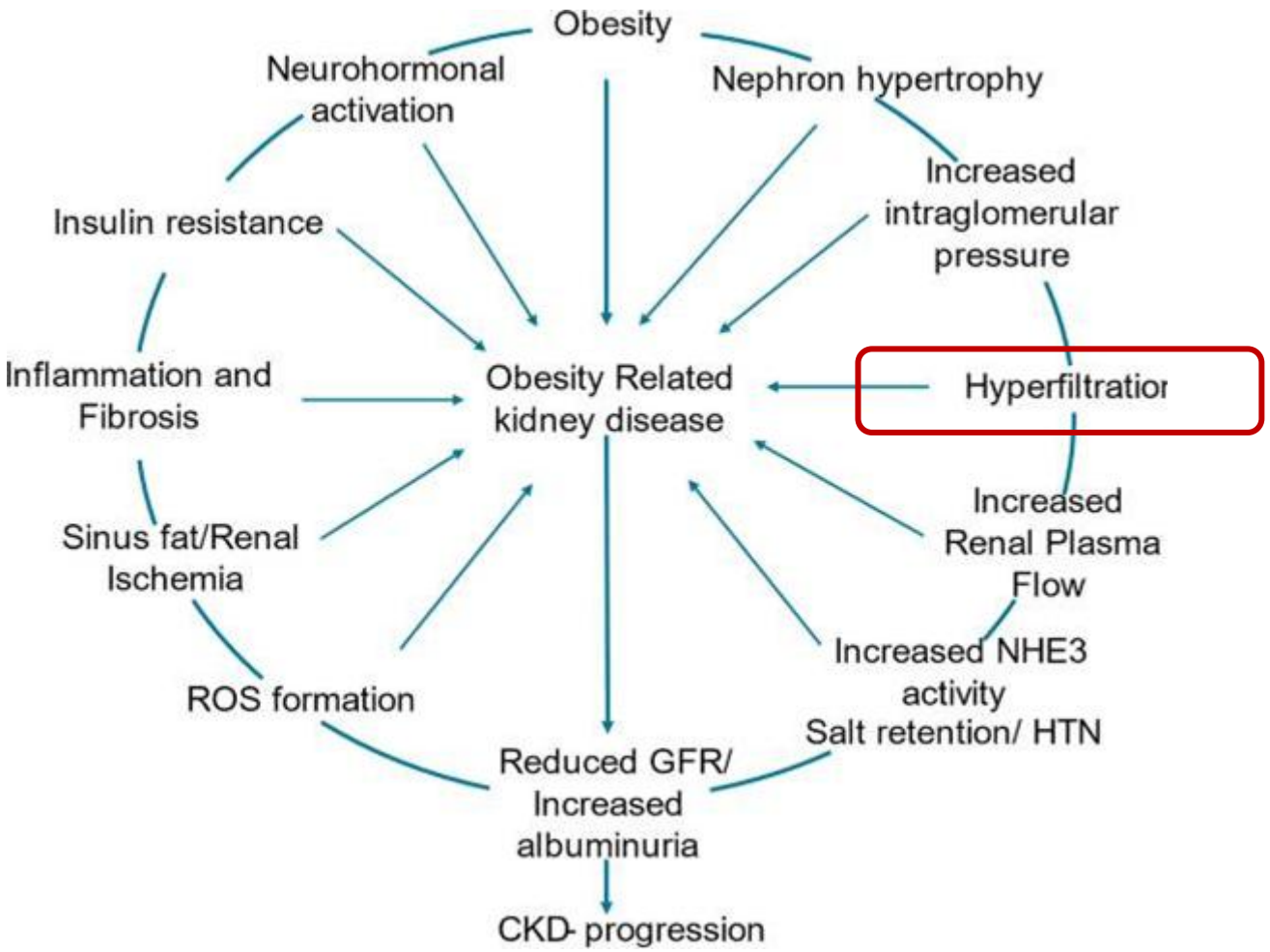
Obesità: una malattia sistemica





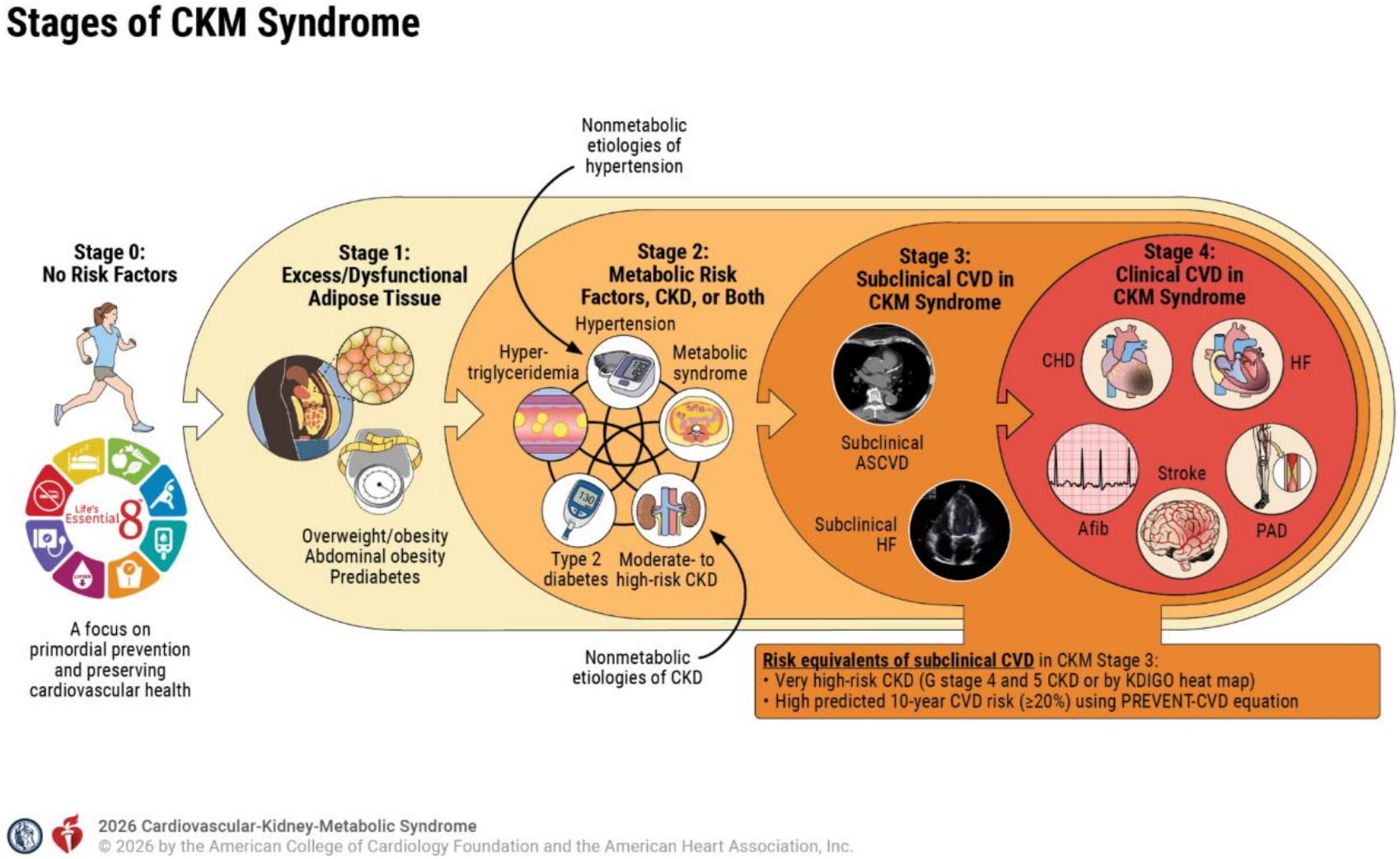
Obesità come fattore di progressione dell'IRC

Obesity-related glomerulopathy



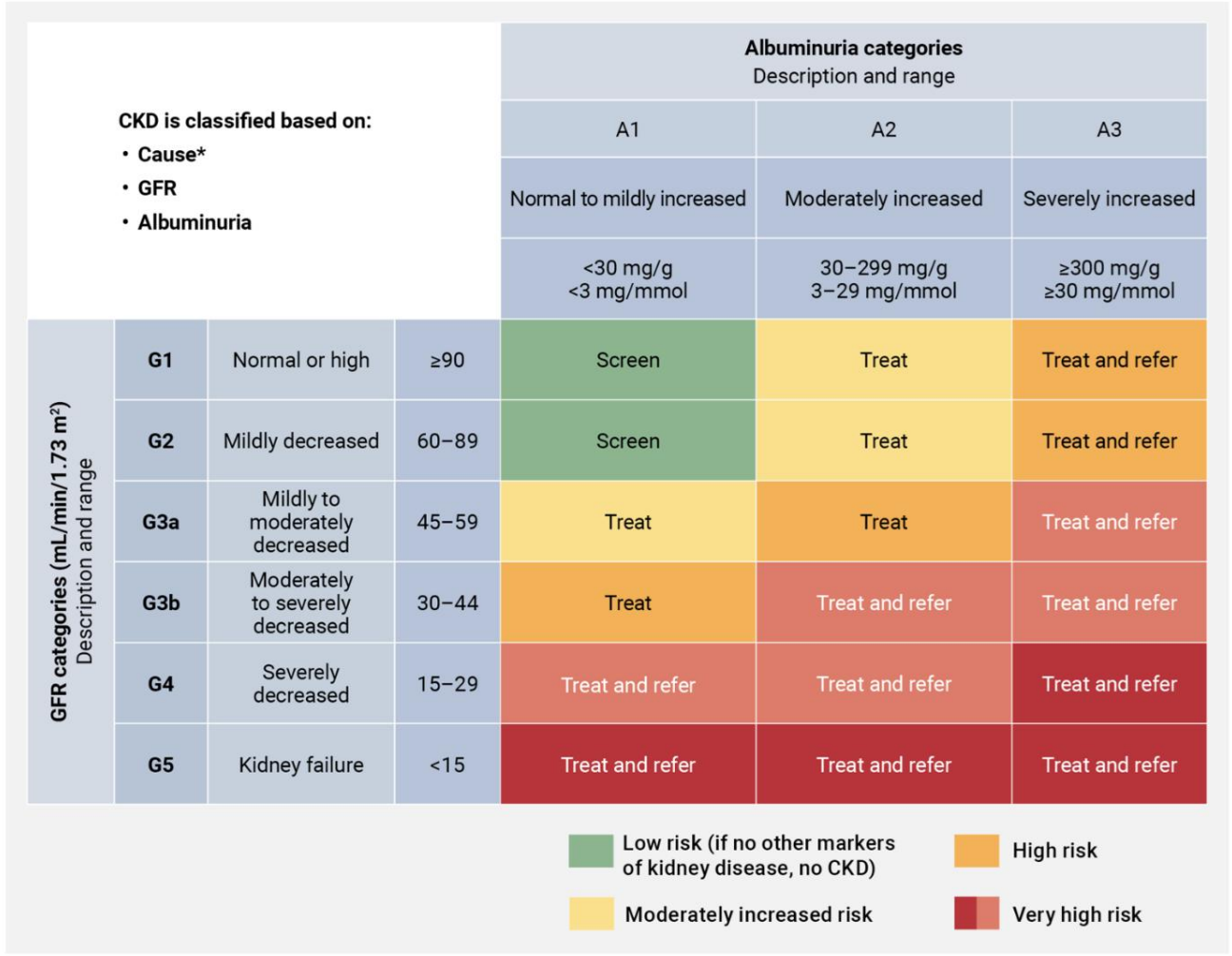
Dada A et al. Curr Res Physiol. 2025 Oct 31;8:100172.

La sindrome cardio-nefro-metabolica (CKM)



Ndumele CE et al. J Am Coll Cardiol. 2026 Jun 9;87(22S):e1889-e2007.

Classificare la disfunzione renale



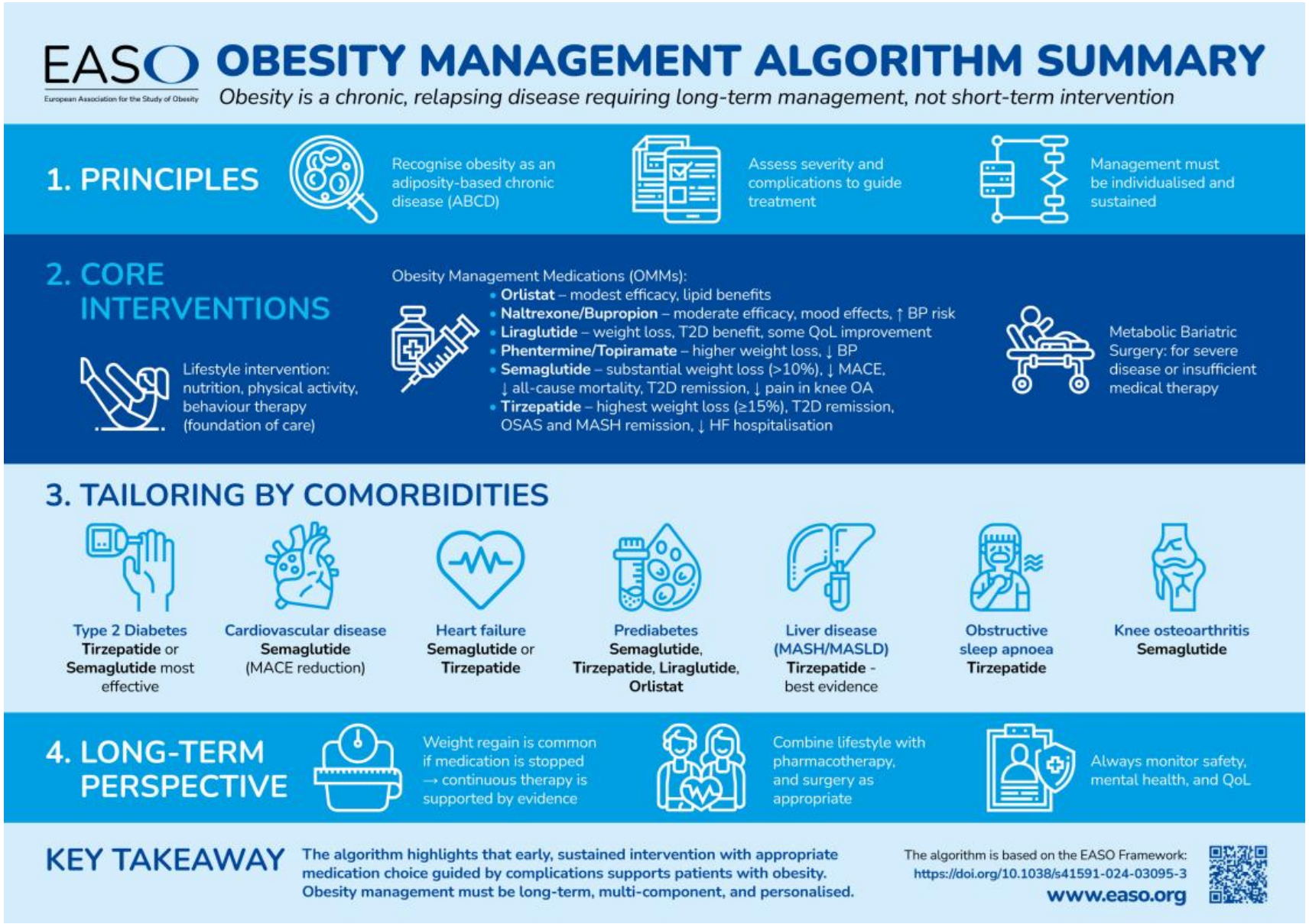
CKD is classified based on: • Cause* • GFR • Albuminuria				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen	Treat	Treat and refer
	G2	Mildly decreased	60–89	Screen	Treat	Treat and refer
	G3a	Mildly to moderately decreased	45–59	Treat	Treat	Treat and refer
	G3b	Moderately to severely decreased	30–44	Treat	Treat and refer	Treat and refer
	G4	Severely decreased	15–29	Treat and refer	Treat and refer	Treat and refer
	G5	Kidney failure	<15	Treat and refer	Treat and refer	Treat and refer

Low risk (if no other markers of kidney disease, no CKD)
High risk
Moderately increased risk
Very high risk

2026 Cardiovascular-Kidney-Metabolic Syndrome
© 2026 by the American College of Cardiology Foundation and the American Heart Association, Inc.

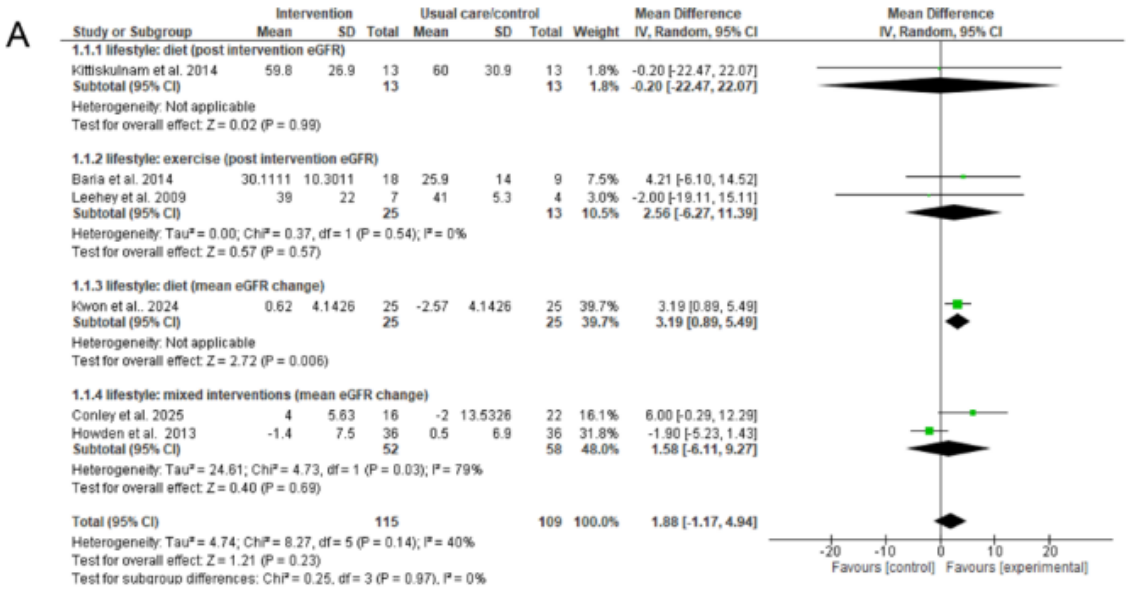
Ndumele CE et al. J Am Coll Cardiol. 2026 Jun 9;87(22S):e1889-e2007.

Trattamento di obesità e sovrappeso

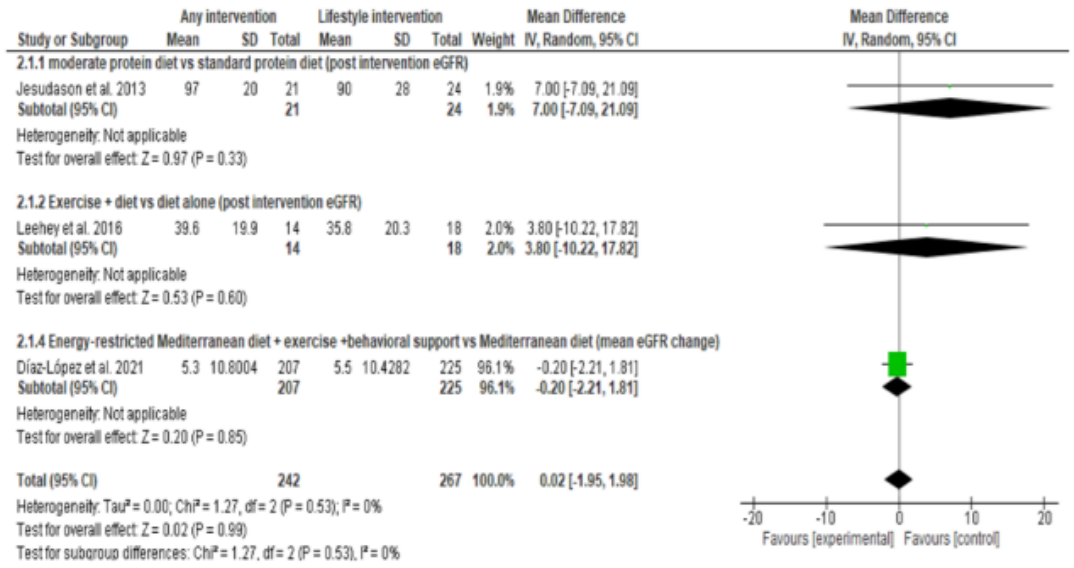


Effetto del calo di peso su rene

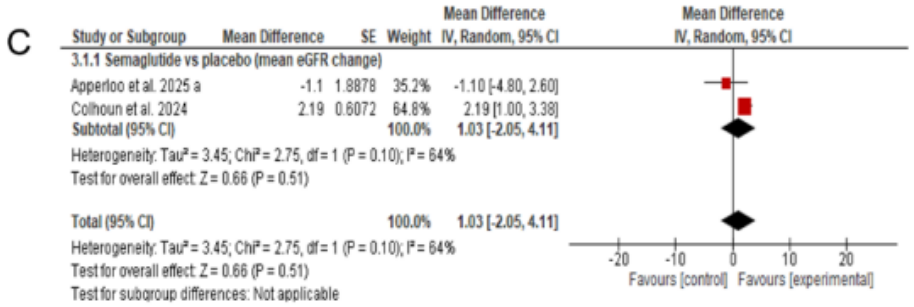
A



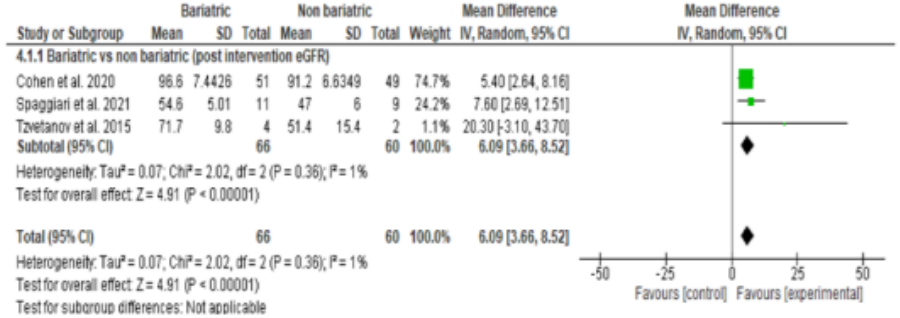
B



C



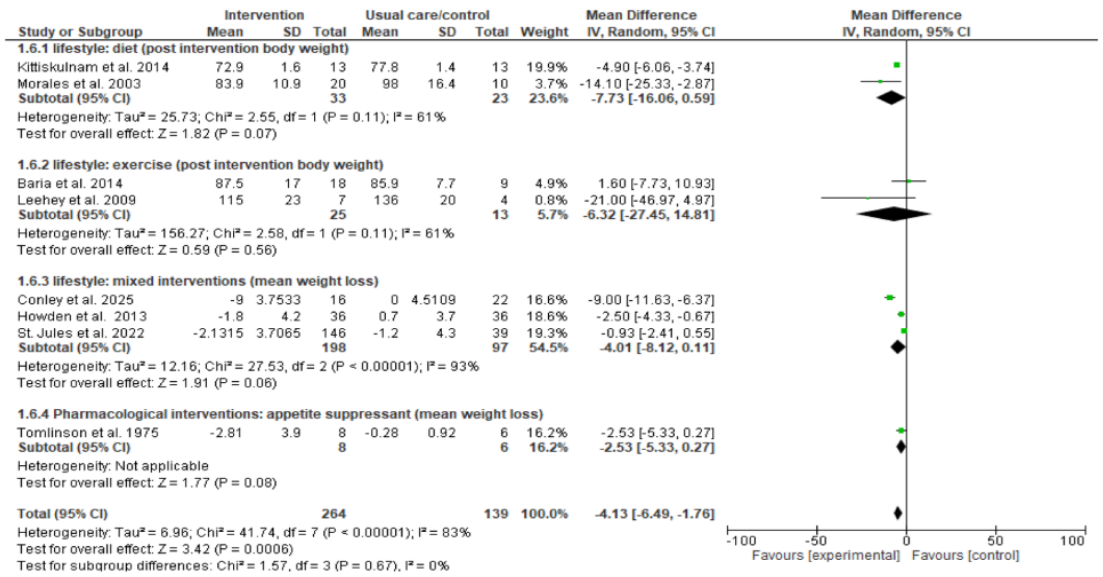
D



Stamatiou A et al. Diabetes Obes Metab. 2026 Sep;28(9):8266-8276.

Effetto del calo di peso su rene

A



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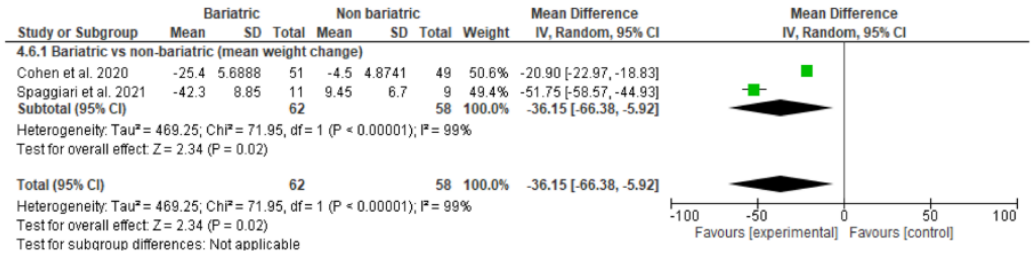
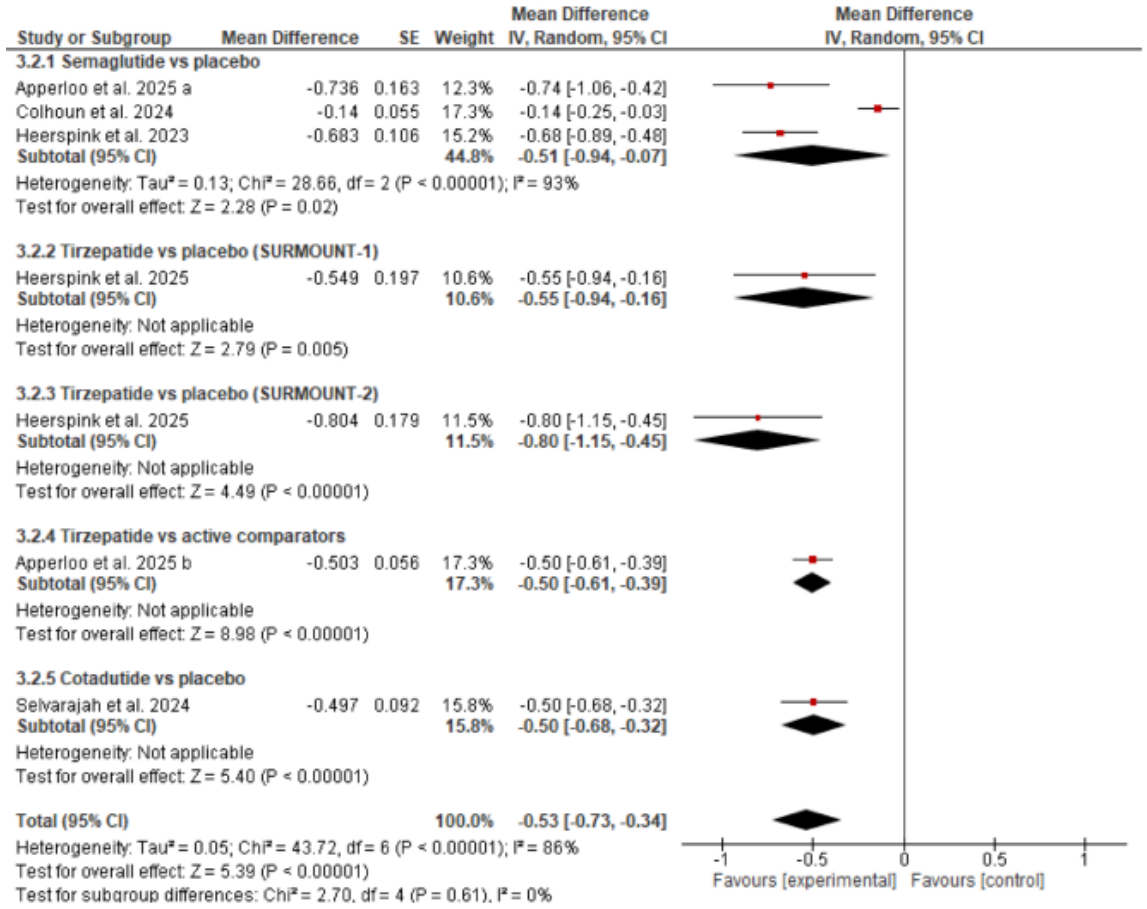


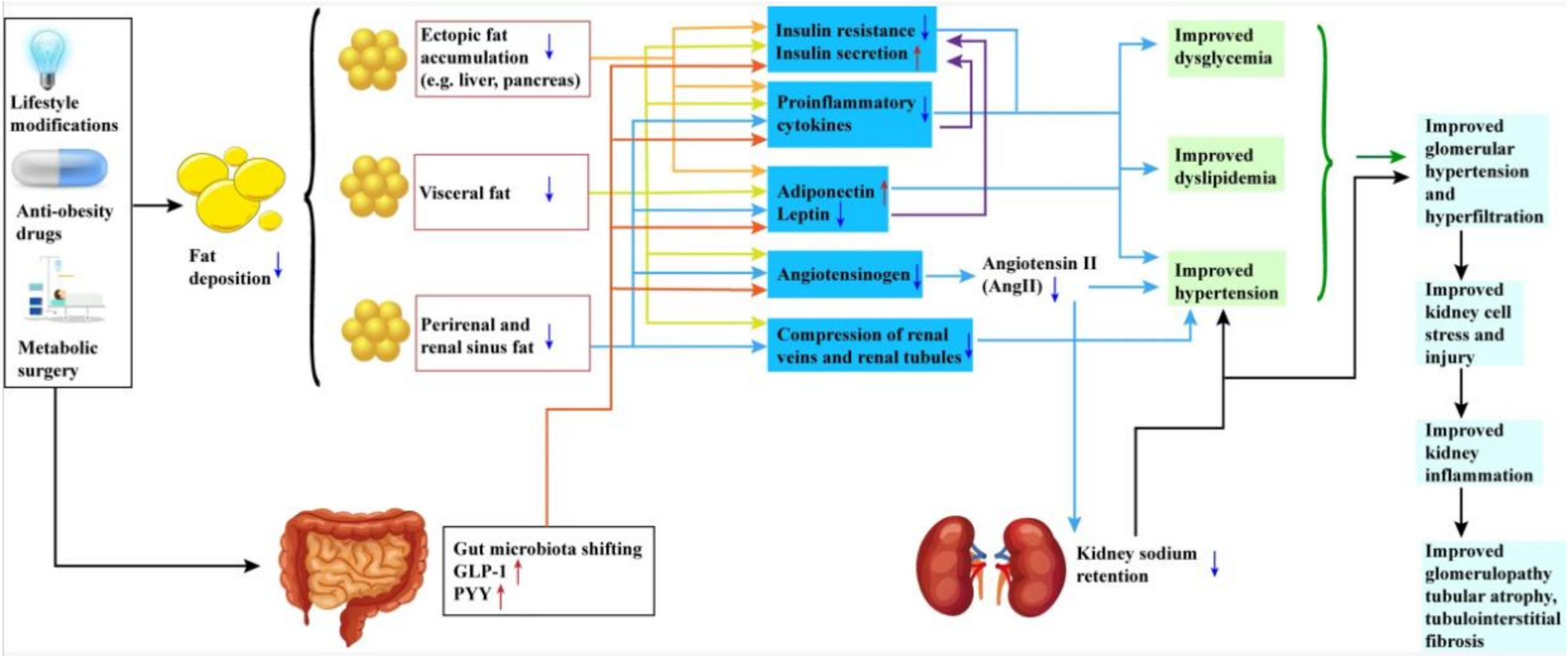
Calo ponderale



Riduzione dell'albuminuria

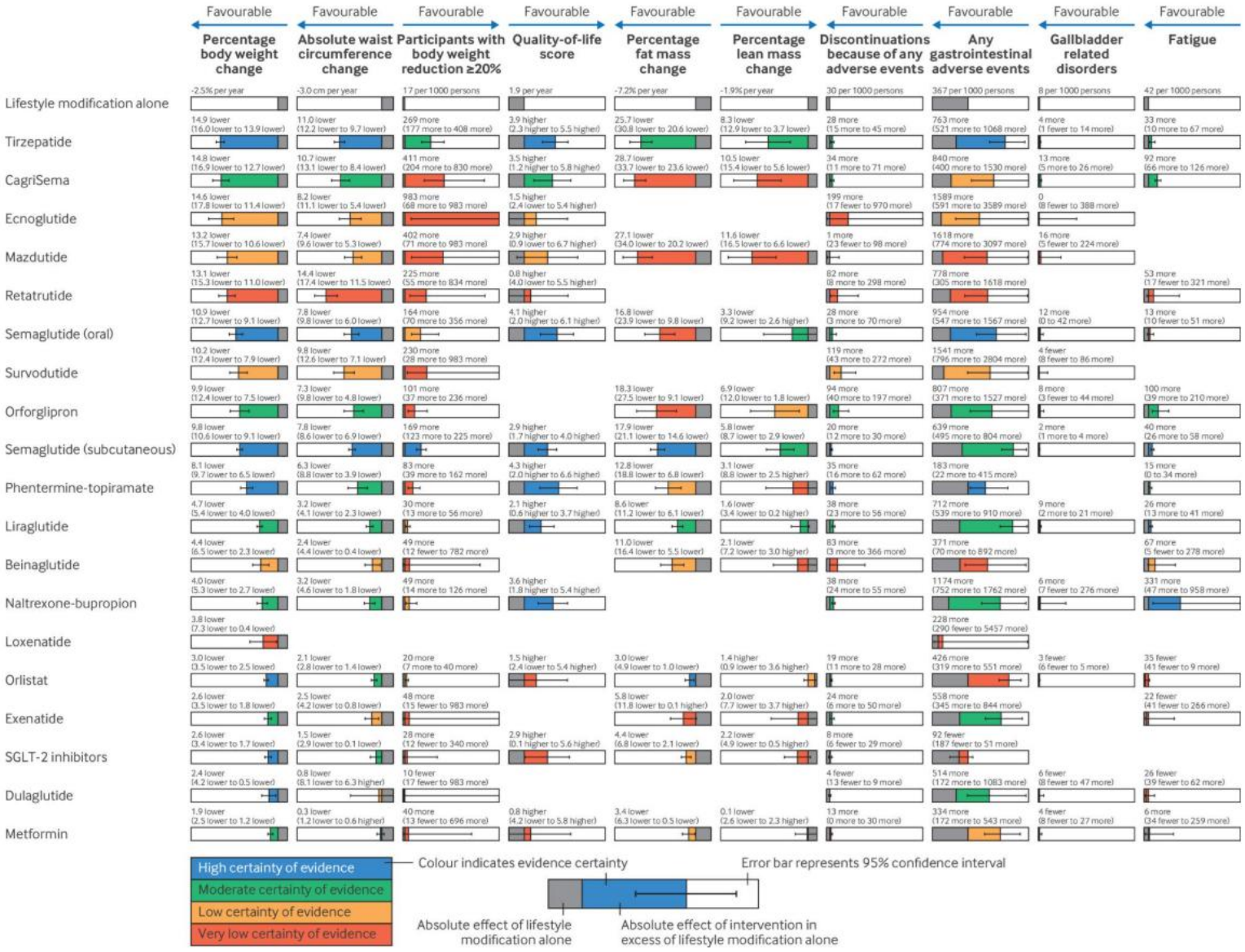
Stamatiou A et al. Diabetes Obes Metab. 2026 Sep;28(9):8266-8276.

Possibili benefici renali del calo ponderale



Gong X et al. Front Endocrinol (Lausanne). 2024 Jan 31;15:1320627.

Nuove frontiere nel trattamento farmacologico del paziente obeso



Nong K et al. BMJ. 2026 Jul 8;394:e372161.

I «vecchi» farmaci: effetto sul rene

CASE REPORT

Orlistat-induced oxalate nephropathy: an under-recognised cause of chronic kidney disease

Laurence Richard Solomon,[1] Andrew Christopher Nixon,[1] Leanne Ogden,[1] Beena Nair[2]

Naltrexone-Bupropione escreto dal rene e da rimodulare in caso di insufficienza renale moderato-severa

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Renal Outcomes in Type 2 Diabetes

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D.,
Kirstine Brown-Frandsen, M.D., Steven P. Marso, M.D.,
Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D.,
Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee and Investigators*

Solomon LR et al. BMJ Case Rep. 2017 Nov 12;2017:bcr2016218623
Mann JFE et al. N Engl J Med. 2017 Aug 31;377(9):839-848.

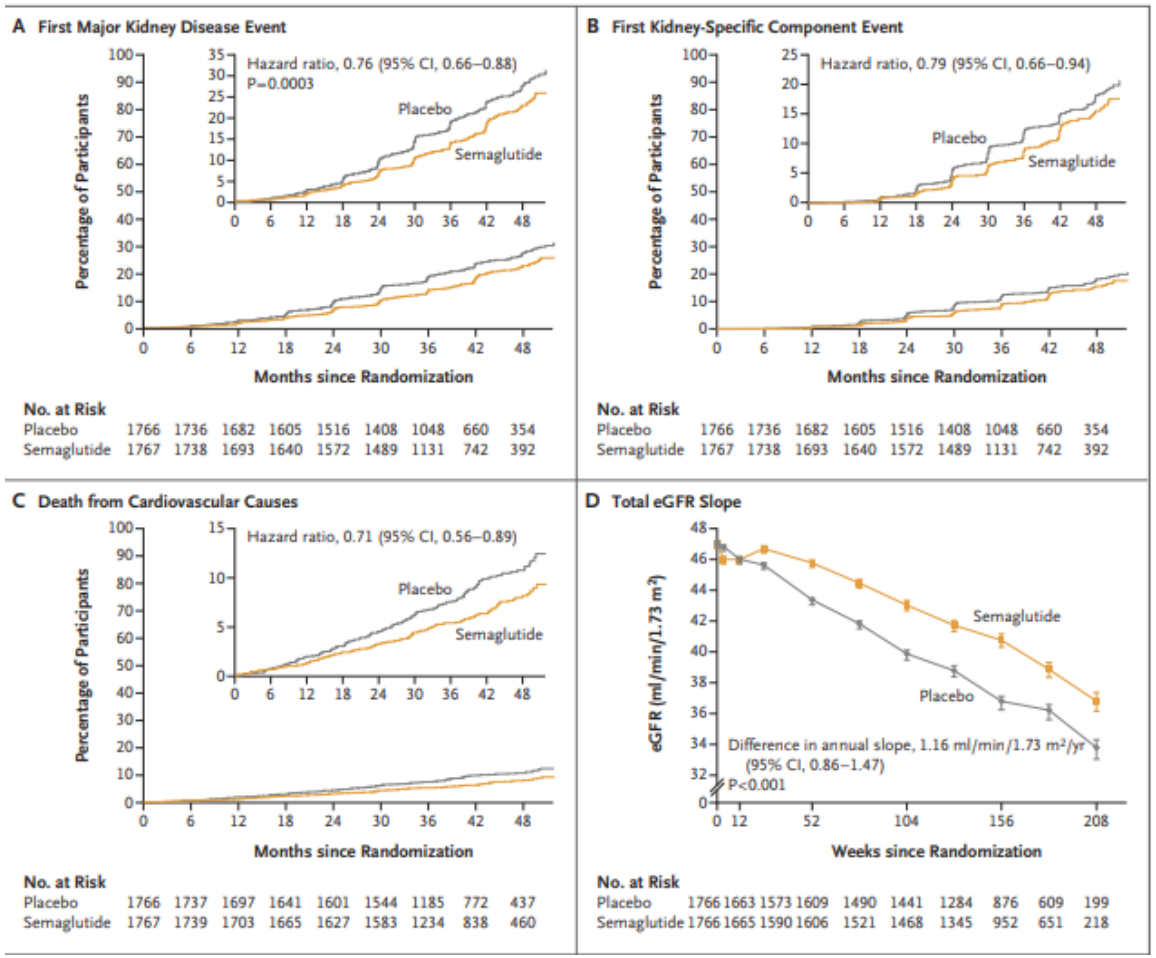
Effetto di GLP1-RA su funzione renale

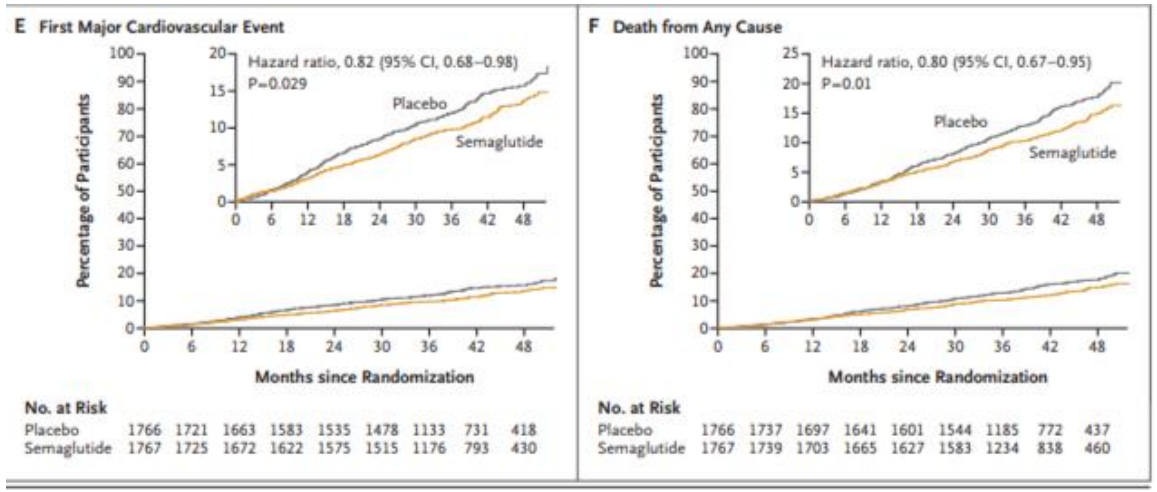
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*





Perkovic V et al. N Engl J Med. 2024 Jul 11;391(2):109-121.

Effetto di GLP1-RA su funzione renale

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

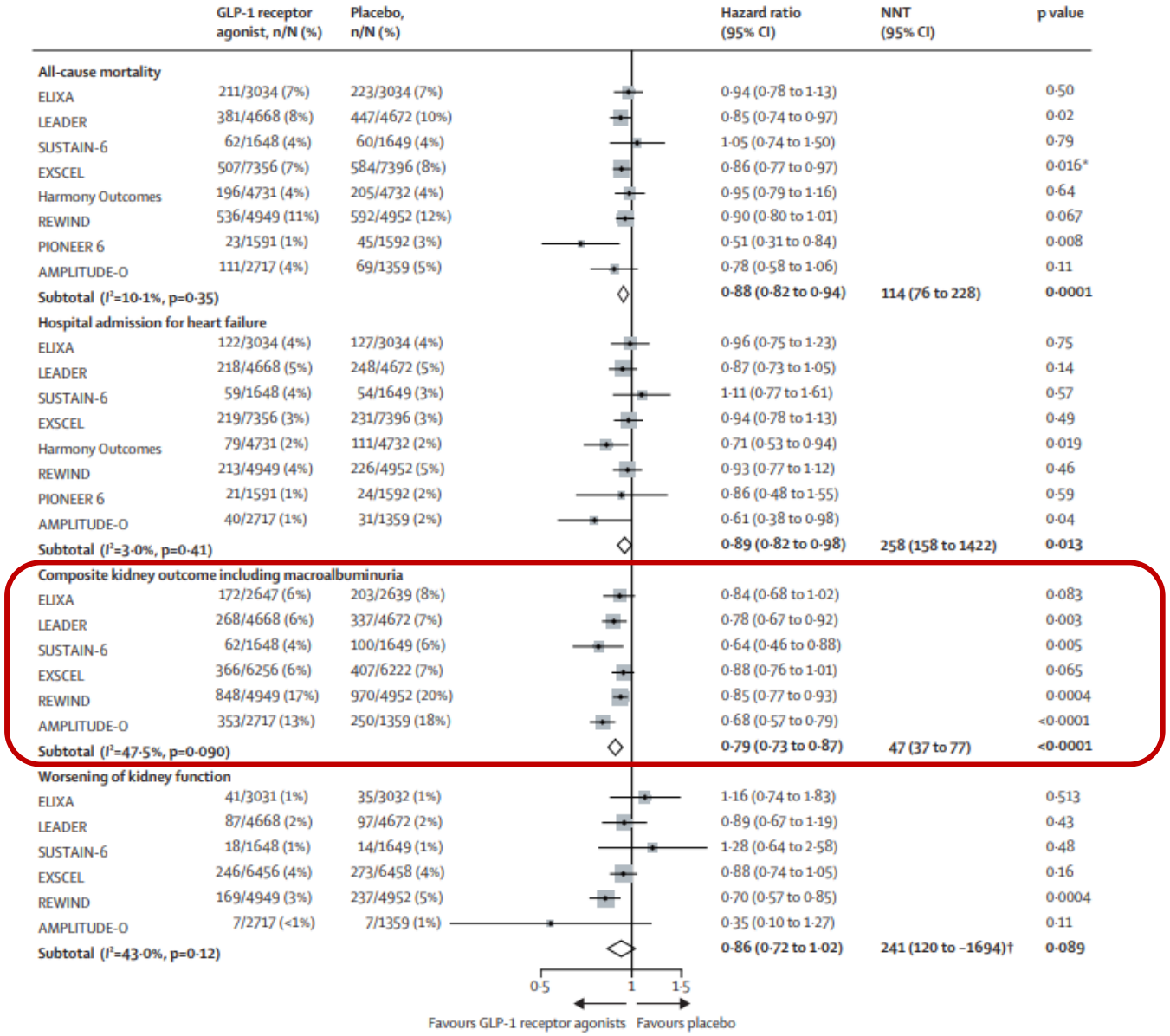
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

Lincoff AM et al. N Engl J Med. 2023 Dec 14;389(24):2221-2232.

Effetto di GLP1-RA su funzione renale



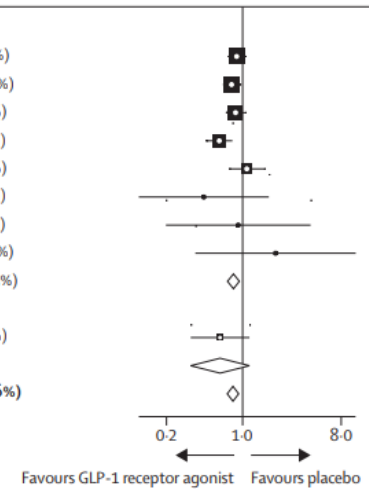
Sattar N et al. Lancet Diabetes Endocrinol. 2021 Oct;9(10):653-662.

Effetto di GLP1-RA su funzione renale

A Composite kidney outcome

	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)	Weight (%)
With diabetes				
EXSCEL[40]	246/6459 (3·8%)	273/6466 (4·2%)	0·88 (0·74–1·05)	25·22%
FLOW[26]	218/1767 (12·3%)	260/1766 (14·7%)	0·79 (0·66–0·94)	24·94%
LEADER[24,33]	184/4668 (3·9%)	212/4672 (4·5%)	0·86 (0·70–1·05)	21·36%
REWIND[23,35]	84/4949 (1·7%)	136/4952 (2·7%)	0·61 (0·46–0·80)	14·08%
SUSTAIN-6[25,41]	58/1648 (3·5%)	57/1649 (3·5%)	1·09 (0·75–1·58)	8·94%
ELIXA[37]	3/2702 (0·1%)	7/2793 (0·3%)	0·44 (0·11–1·73)	0·77%
AMPLITUDE-O[39]	9/2717 (0·3%)	3/1359 (0·2%)	0·91 (0·20–4·19)	0·62%
Harmony Outcomes[38]	4/4731 (0·1%)	2/4732 (<0·1%)	2·00 (0·37–10·87)	0·51%
Subtotal	806/29 441 (2·7%)	950/28 389 (3·3%)	0·82 (0·73–0·93)	
Without diabetes				
SELECT[27,42]	17/8803 (0·2%)	27/8801 (0·3%)	0·62 (0·33–1·15)	3·56%
			0·62 (0·33–1·15)	
Overall	**823/38 244 (2·2%)**	**977/37 190 (2·6%)**	**0·81 (0·72–0·92)**	

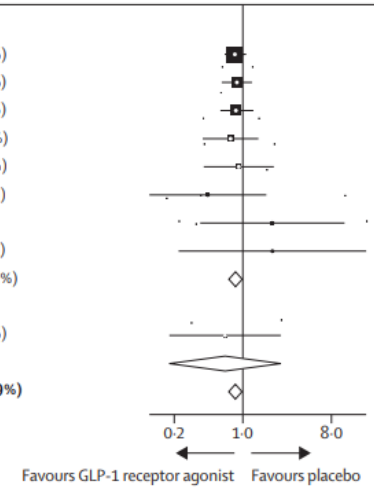
With diabetes p<0·001, I^2=26·41%
Without diabetes p=0·13
Overall p<0·001, I^2=23·11%
Heterogeneity by diabetes status p=0·38



B Kidney failure

With diabetes				
FLOW[26]	142/1767 (8·0%)	165/1766 (9·3%)	0·83 (0·66–1·04)	48·99%
LEADER[24,33]	56/4668 (1·2%)	64/4672 (1·4%)	0·87 (0·61–1·24)	19·28%
EXSCEL[40]	55/6259 (0·9%)	65/6230 (1·0%)	0·85 (0·59–1·22)	18·39%
REWIND[23,35]	16/4949 (0·3%)	21/4952 (0·4%)	0·75 (0·39–1·44)	5·69%
SUSTAIN-6[25,41]	11/1648 (0·7%)	12/1649 (0·7%)	0·91 (0·40–2·07)	3·59%
ELIXA[37]	3/2702 (0·1%)	7/2793 (0·3%)	0·44 (0·11–1·73)	1·29%
Harmony Outcomes[38]	4/4731 (0·1%)	2/4732 (0%)	2·00 (0·37–10·87)	0·85%
AMPLITUDE-O[39]	4/2717 (0·1%)	1/1359 (0·1%)	2·00 (0·22–18·06)	0·50%
Subtotal	291/29 441 (1·0%)	337/28 389 (1·2%)	0·84 (0·72–0·99)	
Without diabetes				
SELECT[27,42]	4/8803 (<0·1%)	6/8801 (0·1%)	0·66 (0·18–2·44)	1·42%
			0·66 (0·18–2·44)	
Overall	**295/38 244 (0·8%)**	**343/37 190 (0·9%)**	**0·84 (0·72–0·98)**	

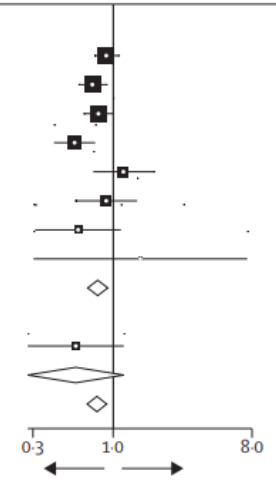
With diabetes p=0·03, I^2=0%
Without diabetes p=0·53
Overall p=0·03, I^2=0%
Heterogeneity by diabetes status p=0·72



C Worsening of kidney function

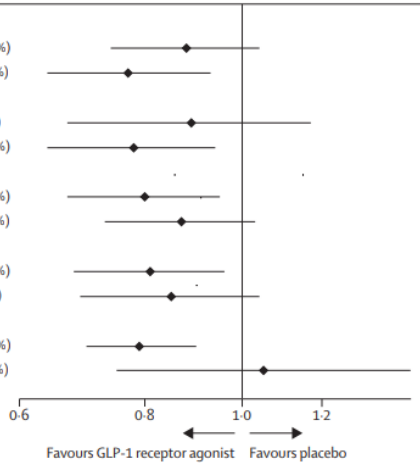
With diabetes				
EXSCEL[40]	239/6259 (3·8%)	266/6466 (4·1%)	0·90 (0·75–1·07)	22·42%
FLOW[26]	165/1767 (9·3%)	213/1766 (12·1%)	0·73 (0·59–0·90)	20·17%
LEADER[24,33]	149/4668 (3·2%)	184/4672 (3·9%)	0·80 (0·64–0·99)	19·21%
REWIND[23,35]	61/4949 (1·2%)	108/4952 (2·2%)	0·56 (0·41–0·76)	13·47%
ELIXA[25,46]	41/3031 (1·4%)	35/3032 (1·2%)	1·16 (0·74–1·83)	8·03%
SUSTAIN-6[25,41]	33/1648 (2·0%)	40/1649 (2·4%)	0·90 (0·57–1·43)	7·70%
PIONEER 6[34]	15/1591 (0·9%)	25/1592 (1·6%)	0·59 (0·31–1·12)	4·50%
AMPLITUDE-O[39]	6/2717 (0·2%)	2/1359 (0·1%)	1·50 (0·30–7·45)	0·82%
Subtotal	709/26 630 (2·7%)	873/25 488 (3·3%)	0·79 (0·68–0·92)	
Without diabetes				3·68%
SELECT[27,42]	12/8724 (0·1%)	21/8742 (0·2%)	0·57 (0·28–1·17)	
			0·57 (0·28–1·17)	
Overall	**721/35 354 (2%)**	**894/34 230 (2·6%)**	**0·78 (0·68–0·91)**	

With diabetes p<0·001, I^2=42·66%
Without diabetes p=0·13
Overall p<0·001, I^2=39%
Heterogeneity by diabetes status p=0·38



A Composite kidney outcome

	Trials (n)	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)	I^2 (%)	$p_{interaction}$
Participants with cardiovascular disease						
≥80%	6	275/25 269 (1·1%)	308/24 006 (1·3%)	0·88 (0·74–1·04)	0%	0·30
<80%	3	548/12 975 (4·2%)	669/13 184 (5·1%)	0·77 (0·64–0·93)	60·7%	
Participants with chronic kidney disease						
≥25%	3	285/6132 (4·6%)	320/4774 (6·7%)	0·89 (0·67–1·17)	37·8%	0·45
<25%	6	538/32 112 (1·7%)	657/32 416 (2·0%)	0·78 (0·64–0·94)	41·4%	
Type of GLP-1 receptor agonist						
Human GLP-1	6	565/26 566 (2·1%)	694/26 572 (2·6%)	0·80 (0·67–0·95)	42·9%	0·48
Exendin-4	3	258/11 678 (2·2%)	283/10 618 (2·7%)	0·87 (0·73–1·03)	0%	
Frequency of administration						
Once per week	7	636/30 874 (2·1%)	758/29 725 (2·6%)	0·81 (0·68–0·96)	42·7%	0·71
Once per day	2	187/7370 (2·5%)	219/7465 (2·9%)	0·85 (0·69–1·04)	0%	
Duration of follow-up						
≥3 years	5	749/26 446 (2·8%)	908/26 657 (3·4%)	0·79 (0·70–0·90)	30·4%	0·13
<3 years	4	74/11 798 (0·6%)	69/10 533 (0·7%)	1·05 (0·75–1·47)	0%	



Badve SV et al. Lancet Diabetes Endocrinol. 2025 Jan;13(1):15-28.

Effetto di GLP1-RA su funzione renale

Systemic

↓ body weight
↓ food intake/reward
↑ early satiety
↑ energy expenditure

↓ blood pressure

↓ dysglycaemia
↓ insulin resistance → ↓ hyperinsulinaemia
↓ dyslipidaemia

Heart/vasculature

↑ endothelial function
↓ inflammation and remodelling in vasculature and myocardium

↓ atherosclerosis → ↓ renal vascular disease
↓ heart failure → ↓ cardiorenal syndrome

Adipose tissue

↓ visceral fat depots adjacent to/within kidney:
- Peri-renal fat
- Renal sinus fat

Changes in adipocytokine secretion, e.g.:
- ↓ circulating leptin → ↓ blood pressure
- ↑ circulating adiponectin → podocyte differentiation

Kidney

Clinical studies:

↑ natriuresis
- Inhibition of Na^+-H^+ antiporter (NHE3) in proximal tubule
- ↓ intraglomerular pressure via activation of tubuloglomerular feedback

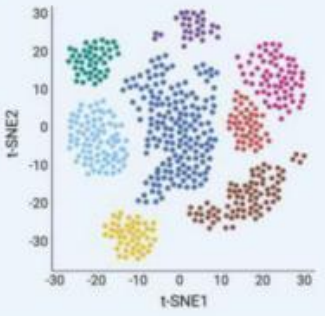
↓ albuminuria → ↓ tubular injury and CKD progression
- Secondary/post-hoc analyses of CVOTs in T2DM and overweight/obesity (multiple GLP-1RAs)
- FLOW RCT with primary kidney outcome (semaglutide)

Preclinical studies:

↑ cAMP/PKA signalling
↓ intra-renal RAAS activation
↓ renal hypoxia/ischaemia-reperfusion injury
↓ kidney glucotoxicity/lipotoxicity
↑ nutrient utilisation, e.g. ↑ FAO
↓ oxidative stress and inflammation, e.g.
↓ RAGE pathway and ↓ ferroptosis

→ ↓ glomerulosclerosis
→ ↓ interstitial fibrosis

Direct nephroprotective effects in multiple kidney cell types by scRNA-seq, some independent of glycaemia



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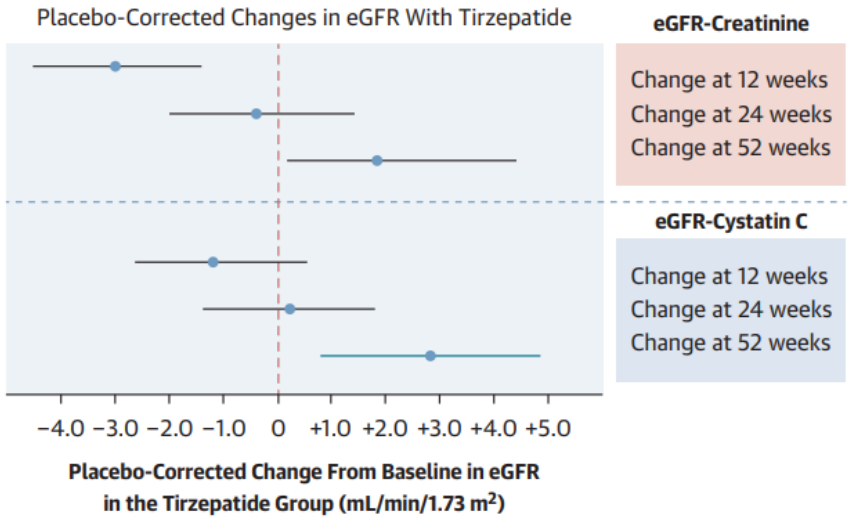
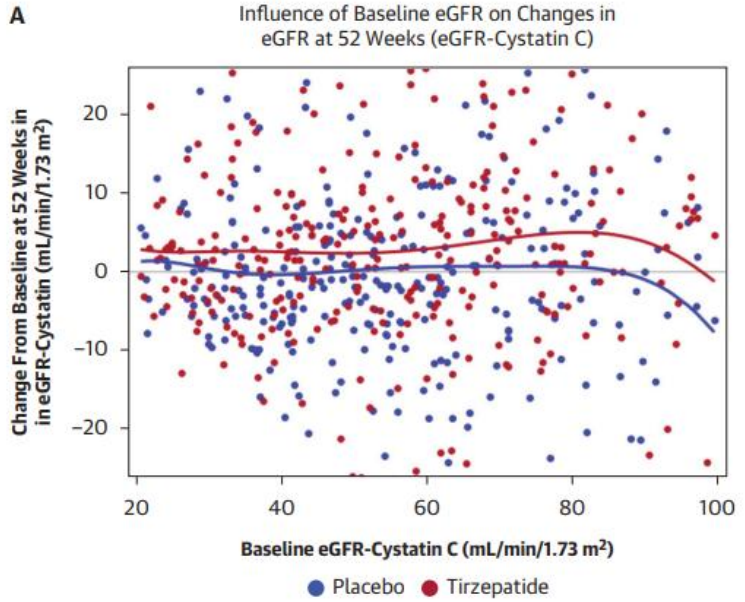
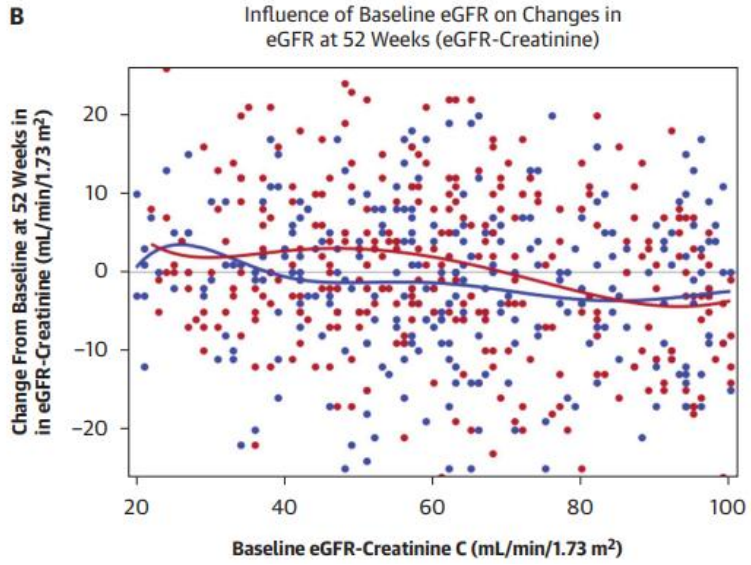
Poliagonisti e rene (GLP1/GIP)







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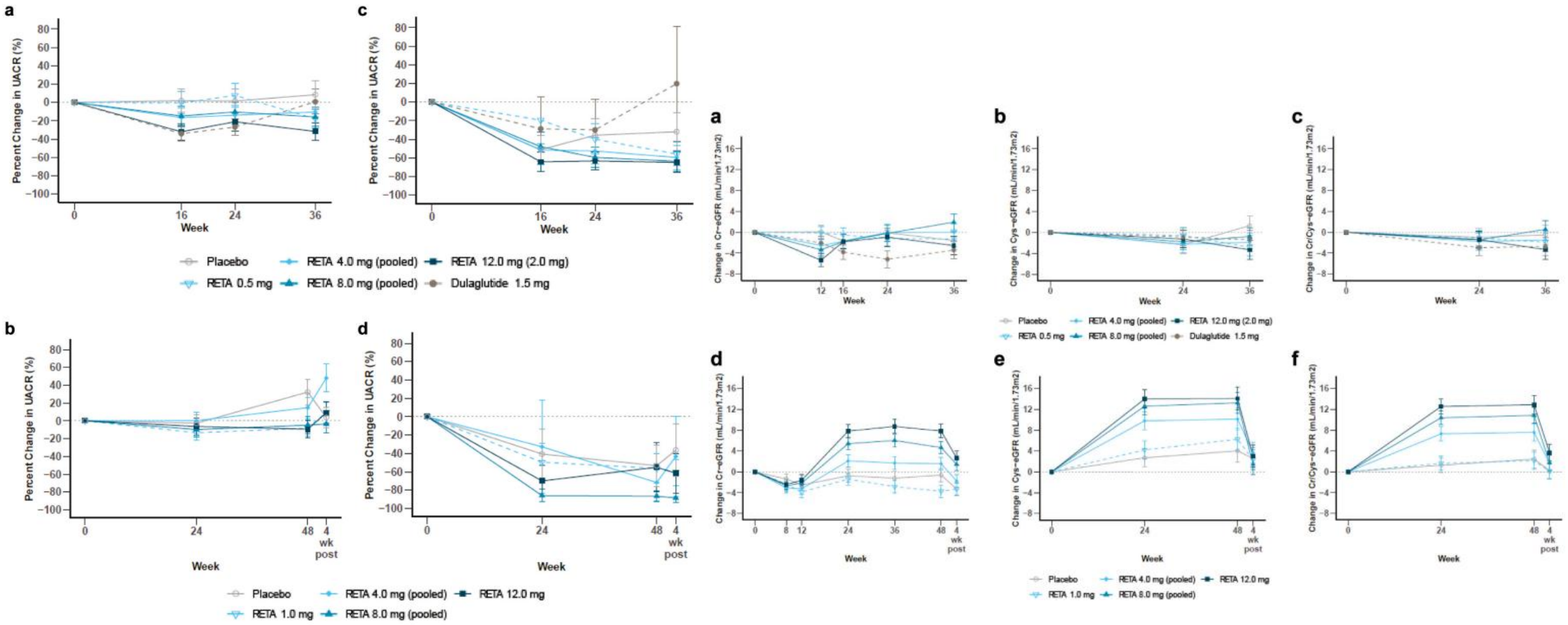
Poliagonisti e rene (GIP/GLP1/Glucagon)



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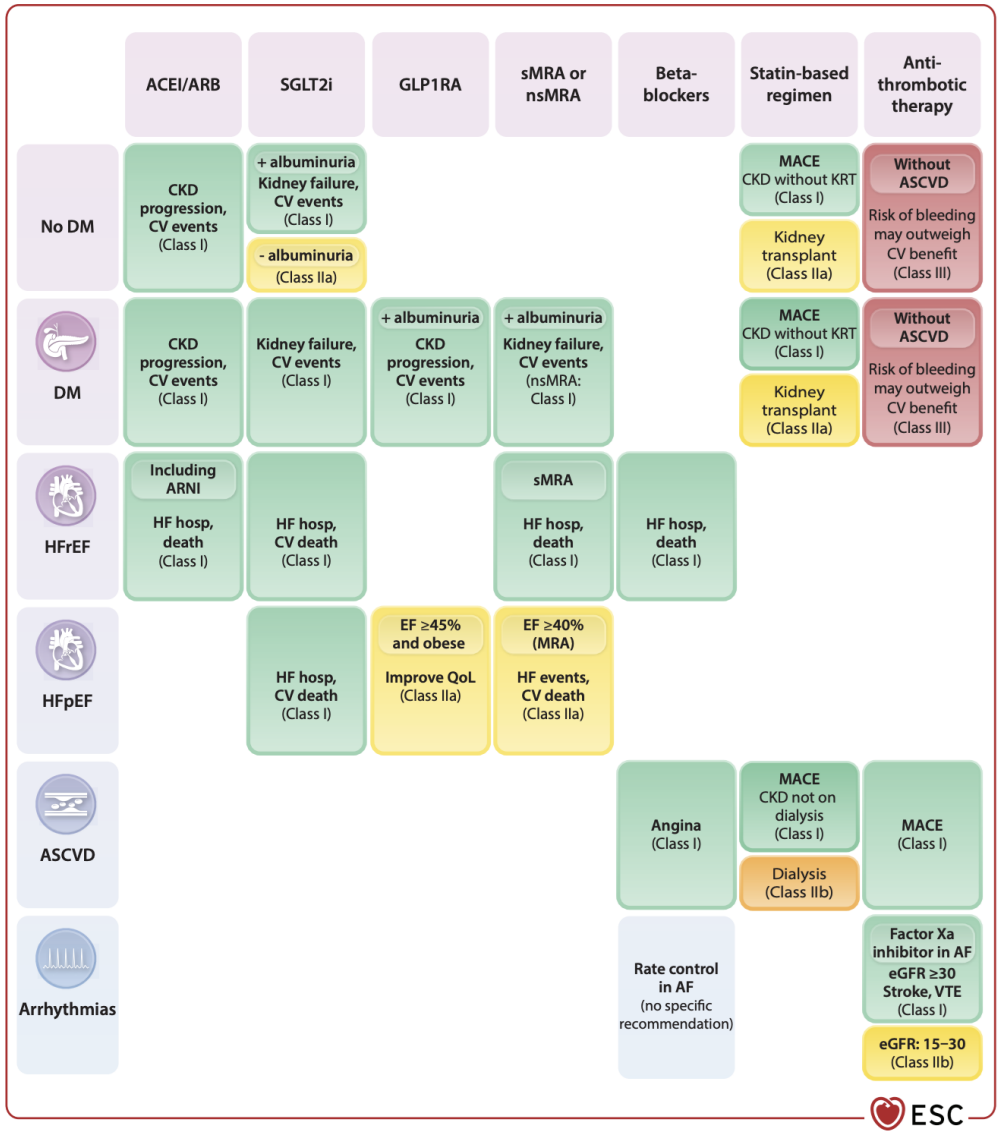

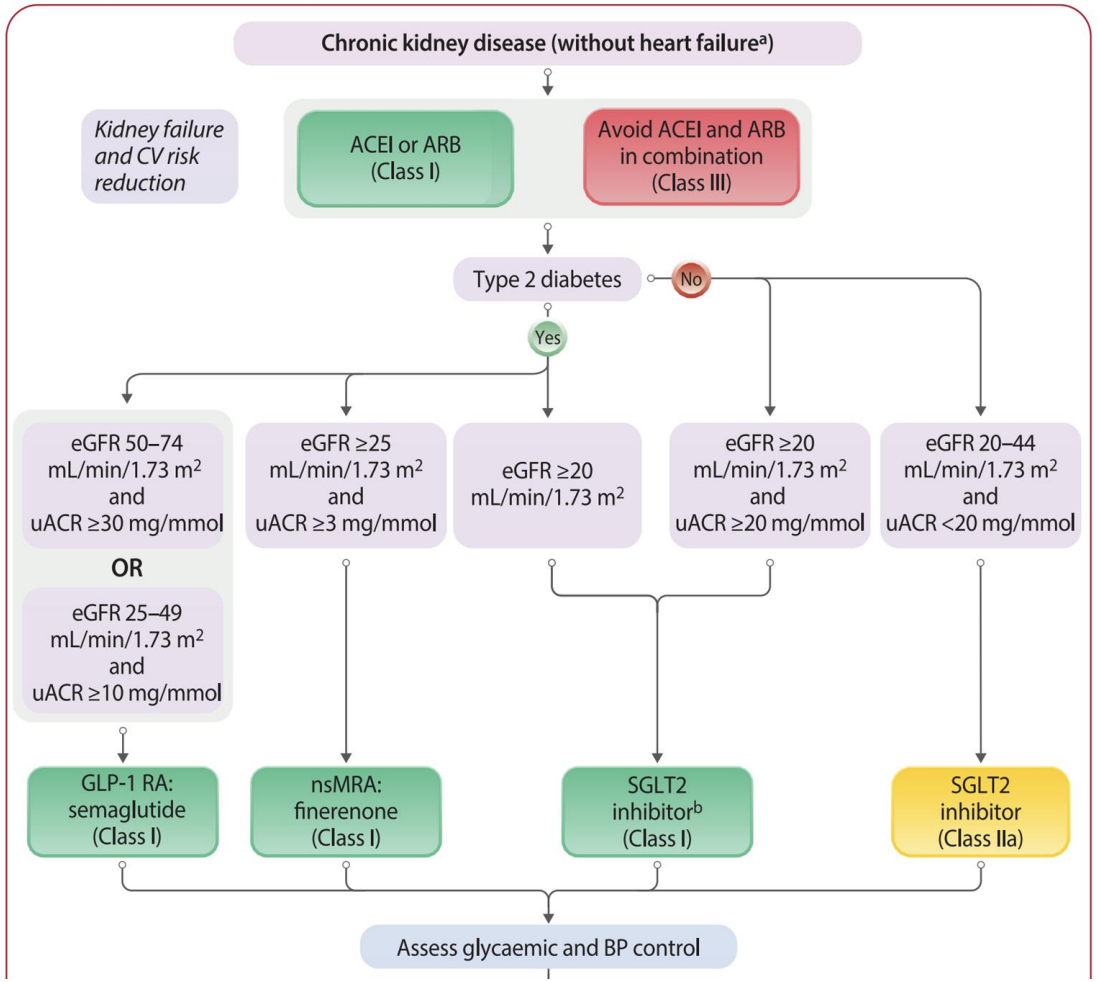

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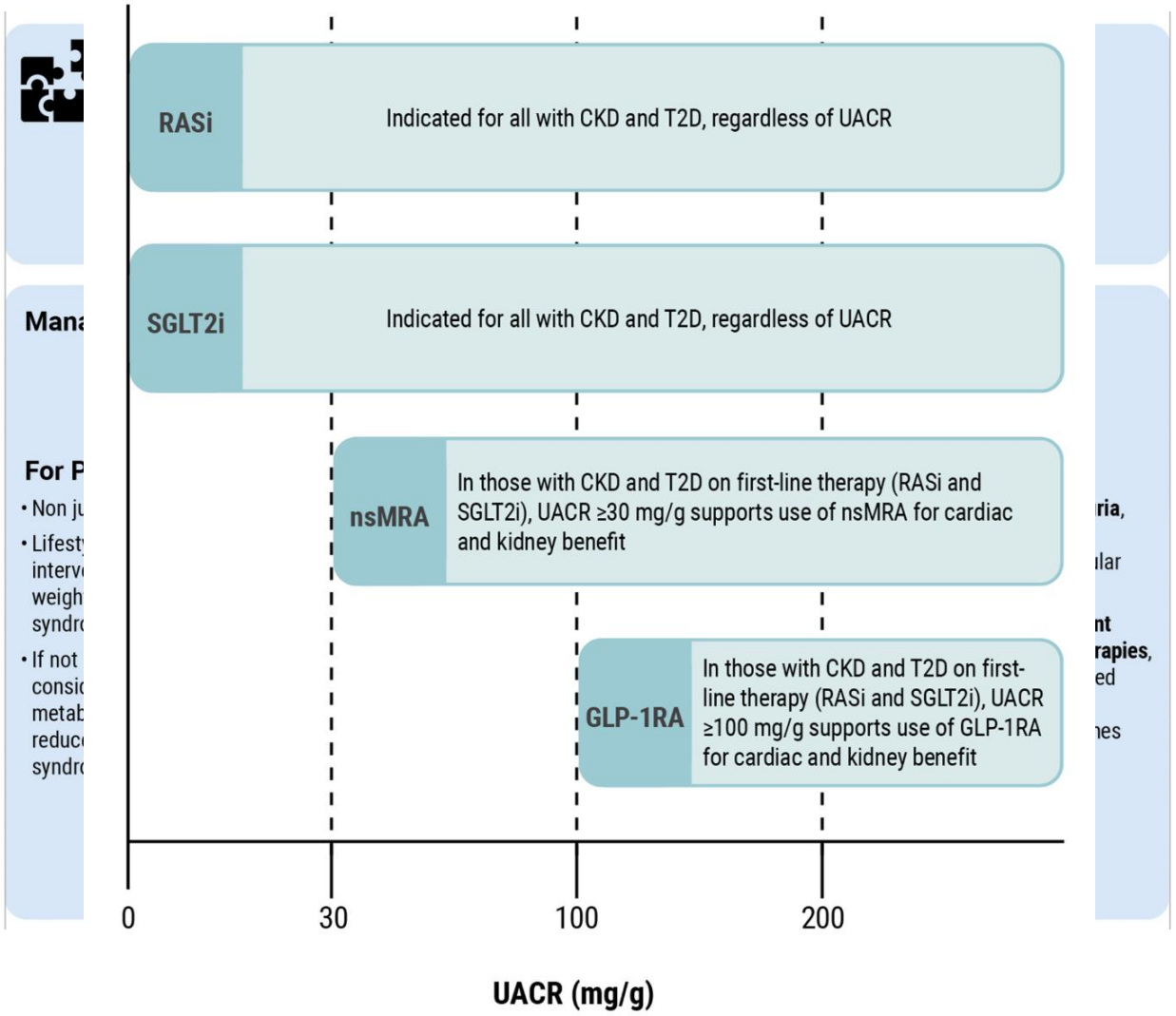
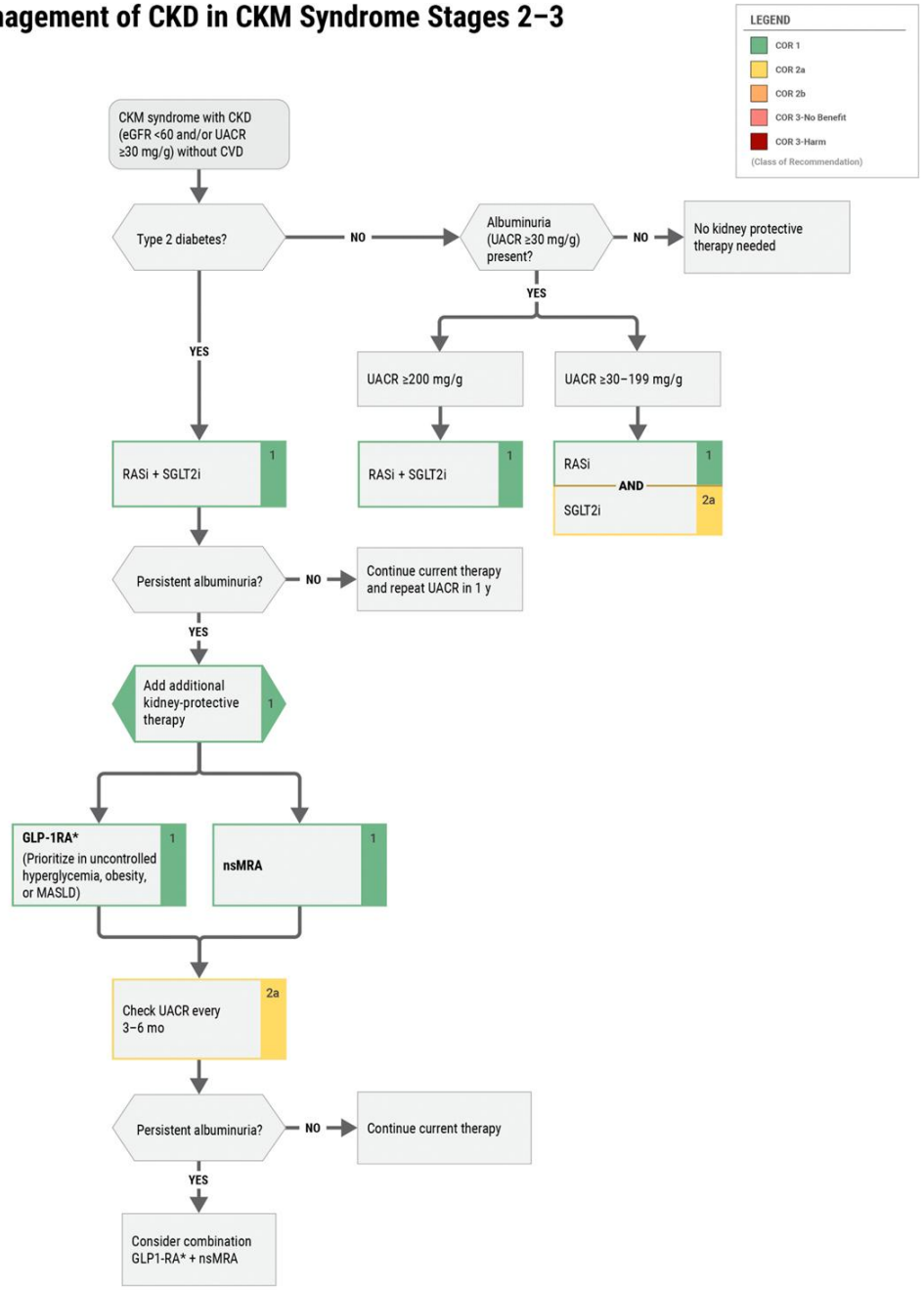
Linee guida 2026 AHA/ACC/ADA/ANS





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Conclusioni

L’obesità è una malattia cronica con complicanze multiorgano, compresa la **disfunzione renale**

Il **calo ponderale** determina potenziali benefici sulla funzione renale

Le nuove farmacoterapie (**incretinomimetici**) determinano cali ponderali significativi e benefici sulla disfunzione renale, specie in presenza di marcata albuminuria

Recenti linee guida europee ed americane consigliano utilizzo di diversi farmaci, tra cui **RASi, SGLT2i e anche nsMRA e GLP-1RA in presenza di albuminuria**, nei pazienti con IRC e obesità/rischio cardiovascolare

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