Meeting Nazionale ITACARE-P 2025

La Cardiologia Riabilitativa e Preventiva come snodo fondamentale della cura della persona con cardiopatia

CENTRO CONGRESSI FRENTANI
Roma, 21-22 novembre 2025

Oltre il controllo glicemico: opportunità terapeutiche di SGLT2 e GLP1-RA nel paziente iperteso e diabetico

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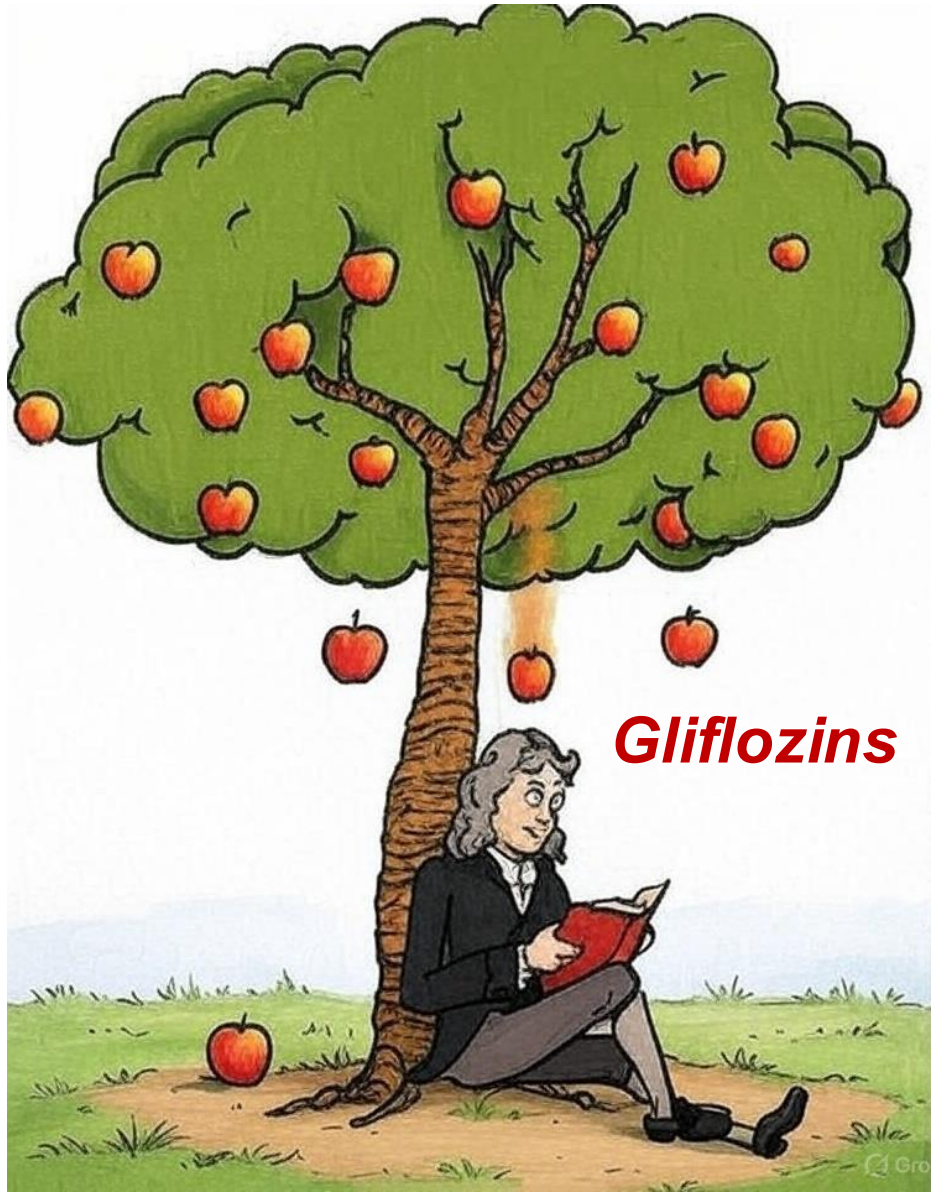
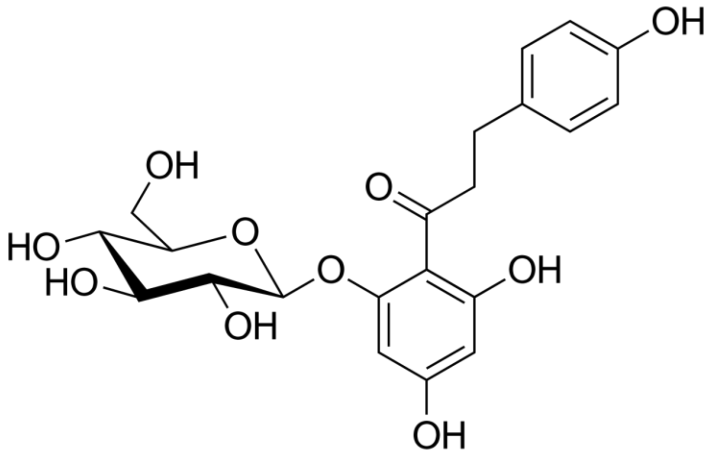
ITACARE-P
ITALIAN ALLIANCE FOR CARDIOVASCULAR REHABILITATION AND PREVENTION

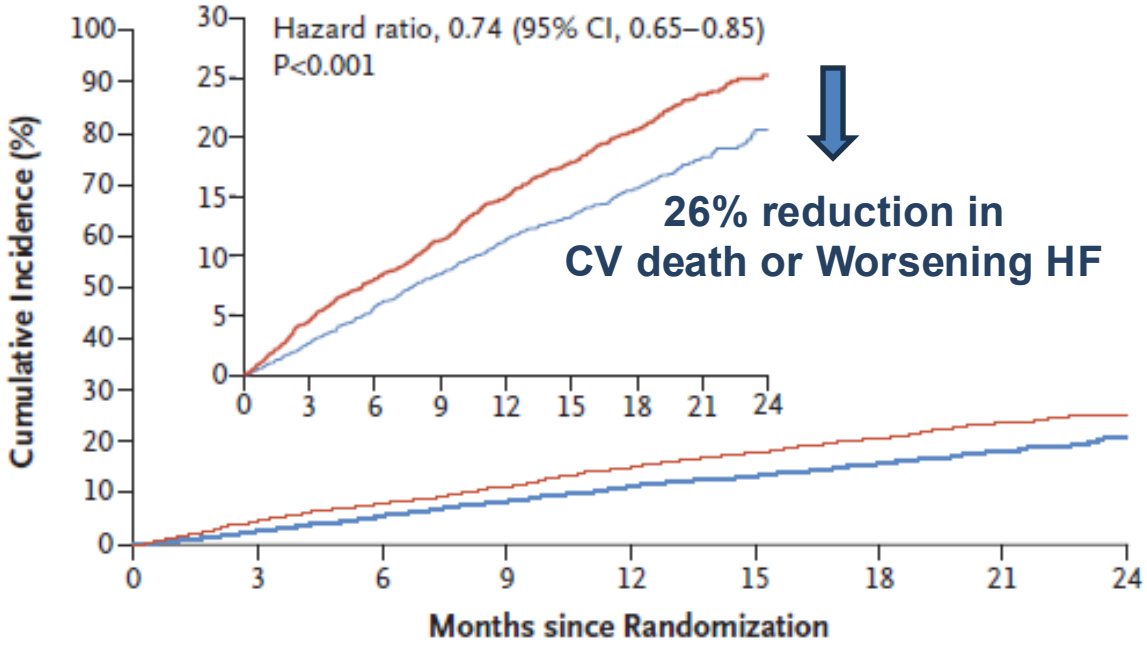




Phlorizin

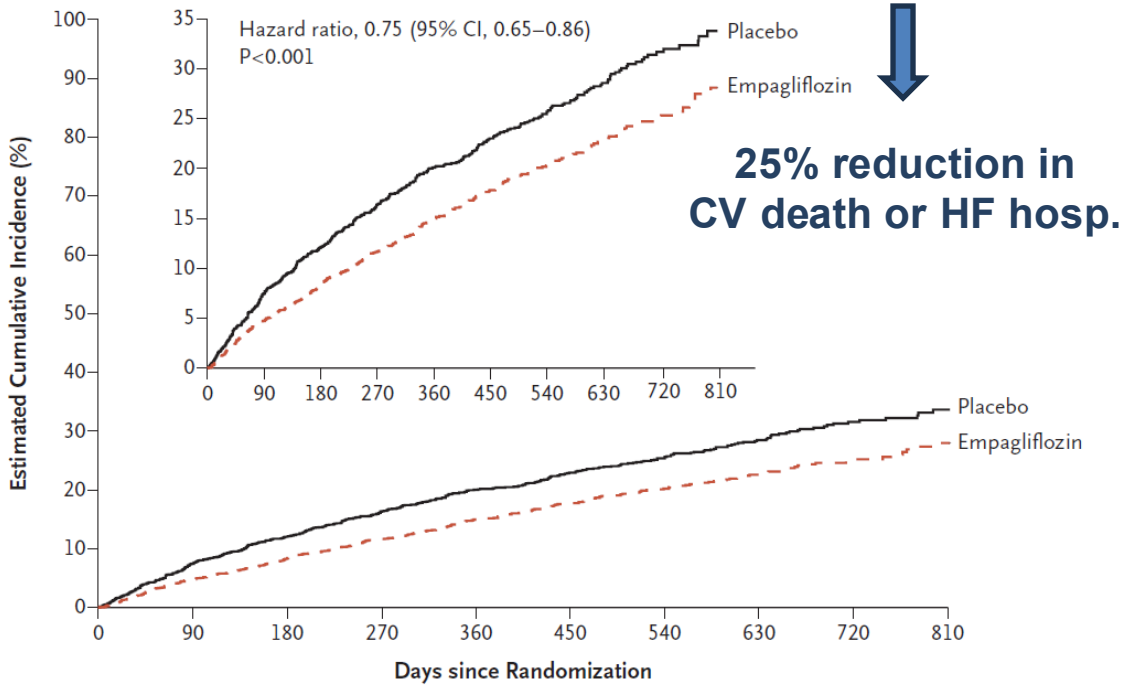
SGLT2i revolution (HFrEF)

DAPA-HF



No. at Risk									
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

EMPEROR Reduced



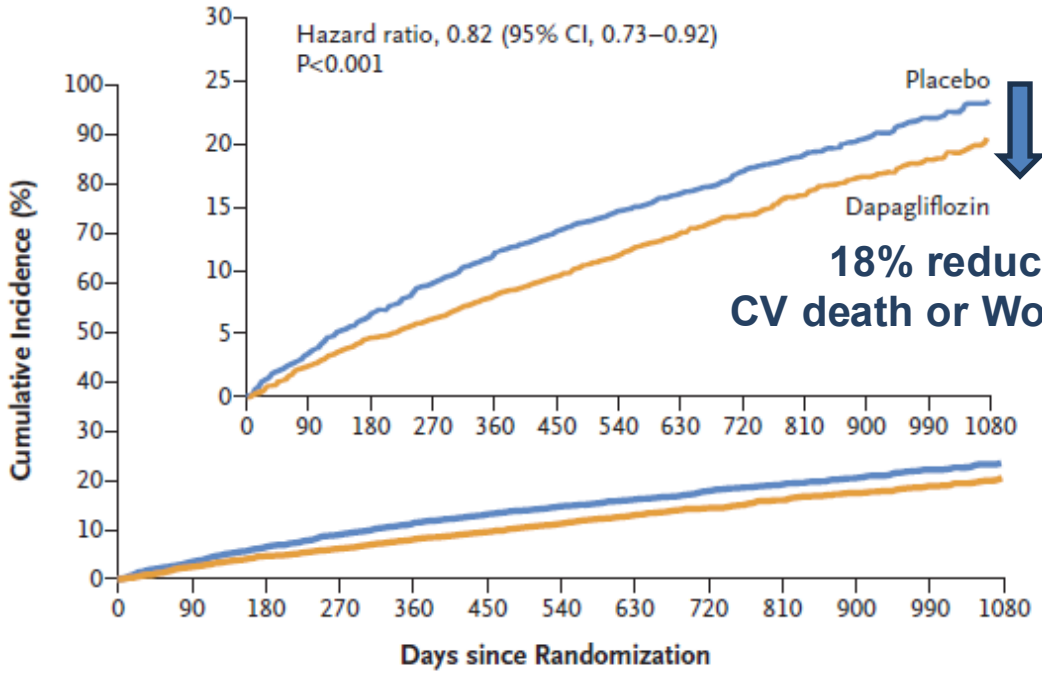
at Risk										
ebo	1867	1715	1612	1345	1108	854	611	410	224	109
agliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

McMurray et al., *N Engl J Med*, 2019

Packer et al., *N Engl J Med*, 2020

SGLT2i revolution (HFpEF)

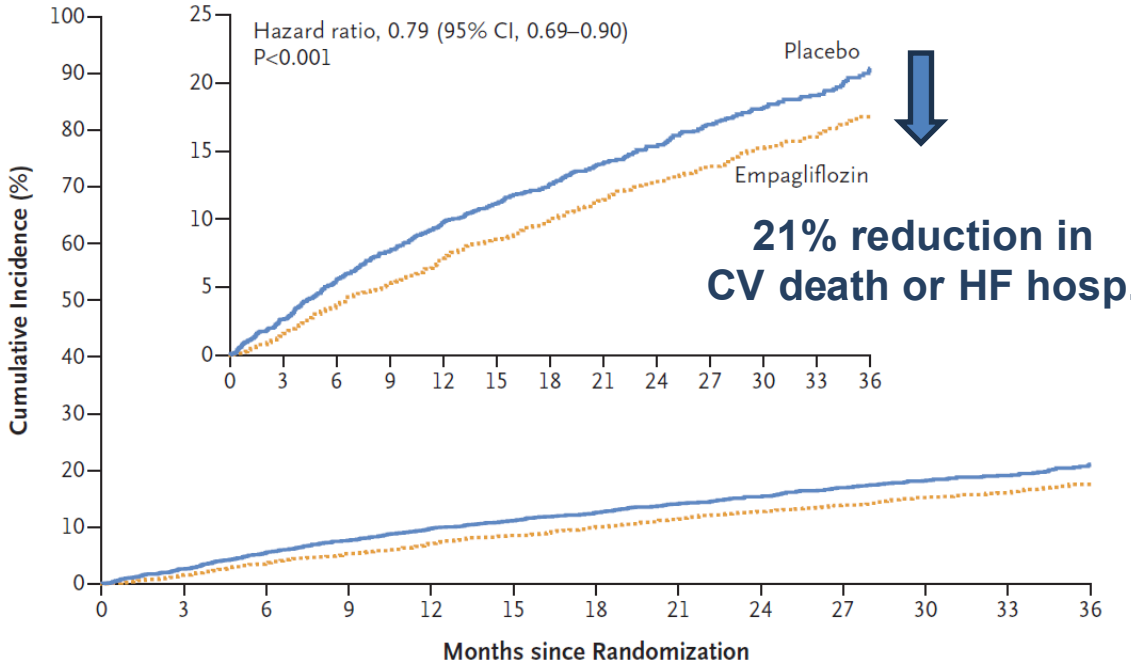
DELIVER



18% reduction in CV death or Worsening HF

No. at Risk													
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

EMPEROR Preserved



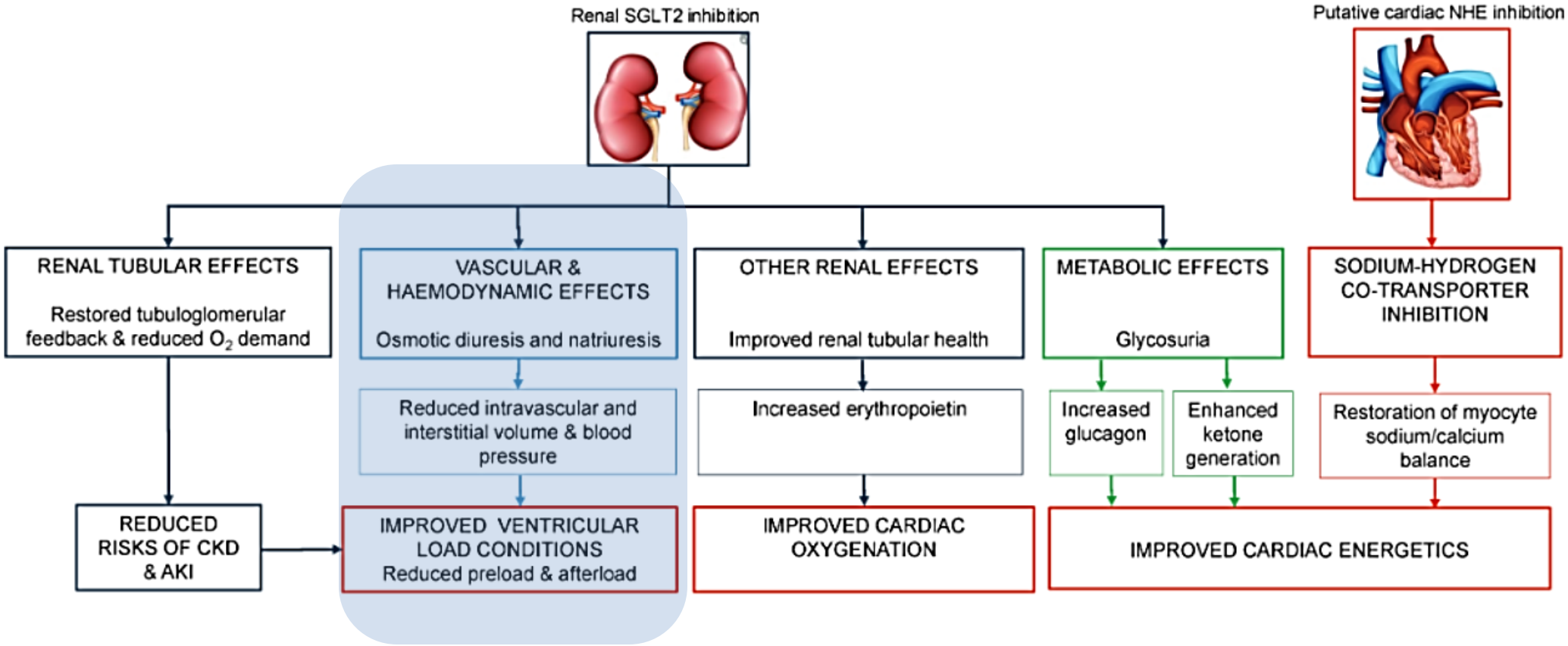
21% reduction in CV death or HF hosp.

No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Solomon et al., *N Engl J Med*, 2022

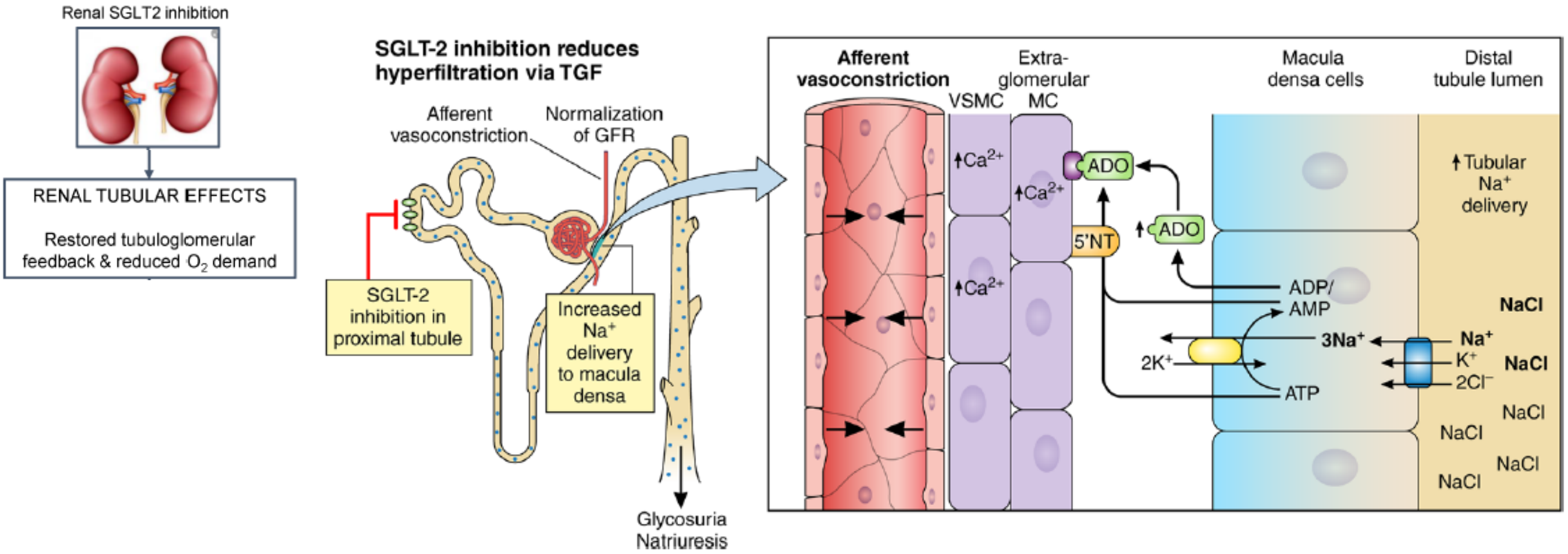
Anker et al., *N Engl J Med*, 2021

Nephroprotective effects of SGLT2i

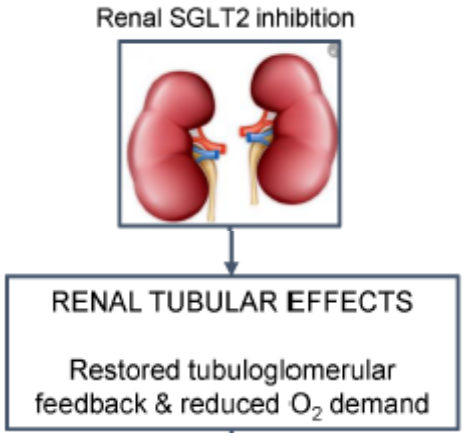


Herrington et al., *Eur J Heart Fail*, 2021

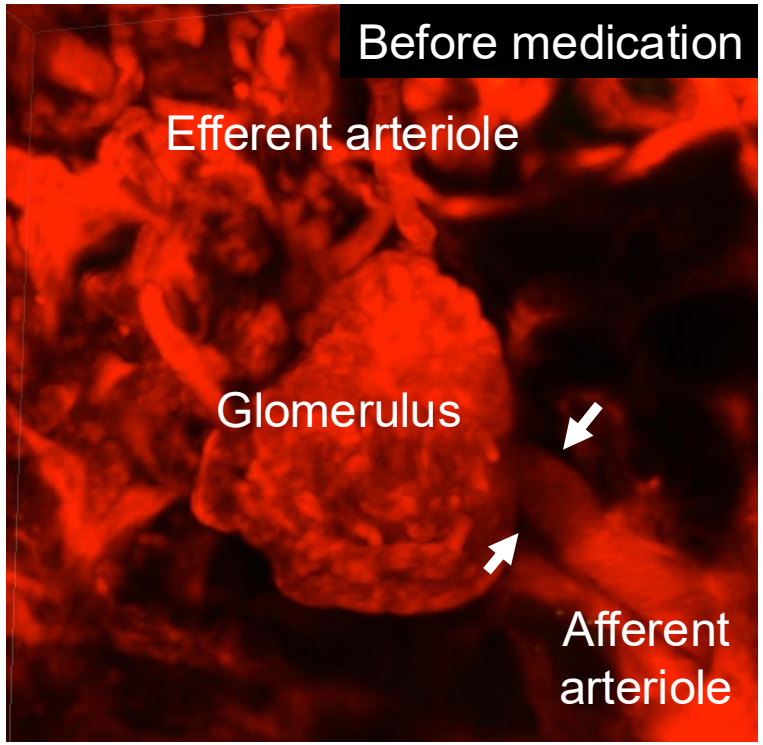
SGLT2i: renal tubular effects

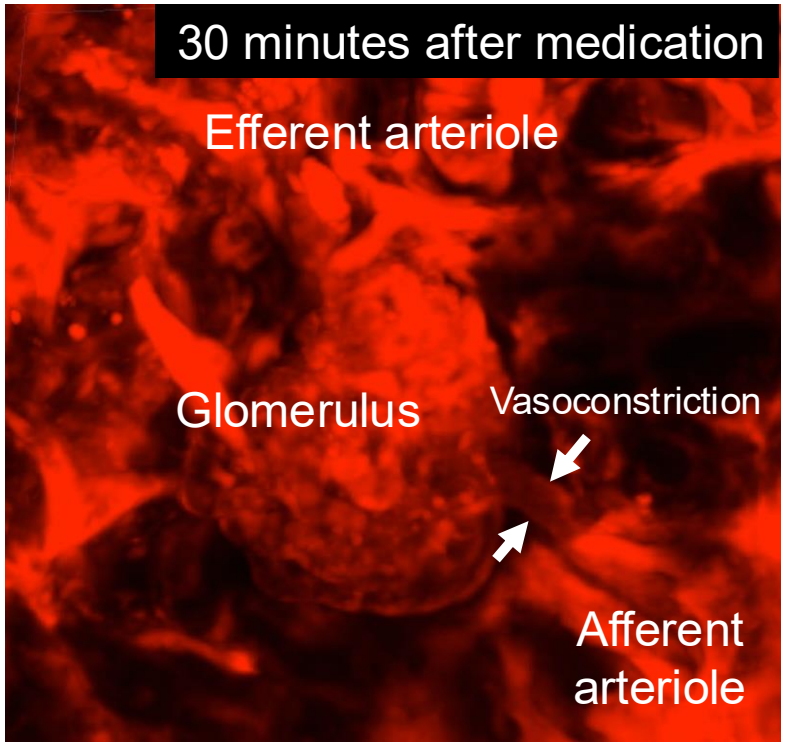


SGLT2i: renal tubular effects



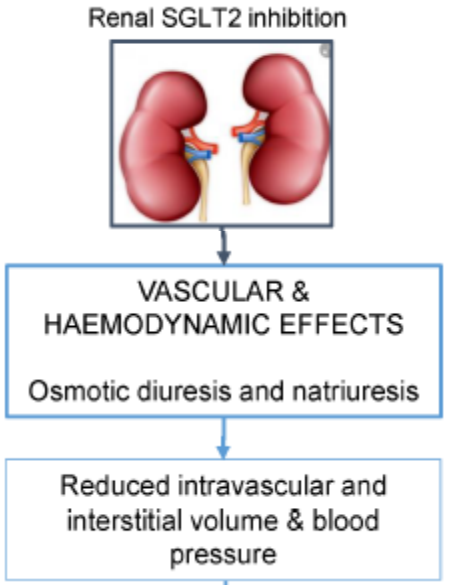
In vivo imaging showed that SGLT2i (empagliflozin) increased afferent arteriole tone in diabetic mice

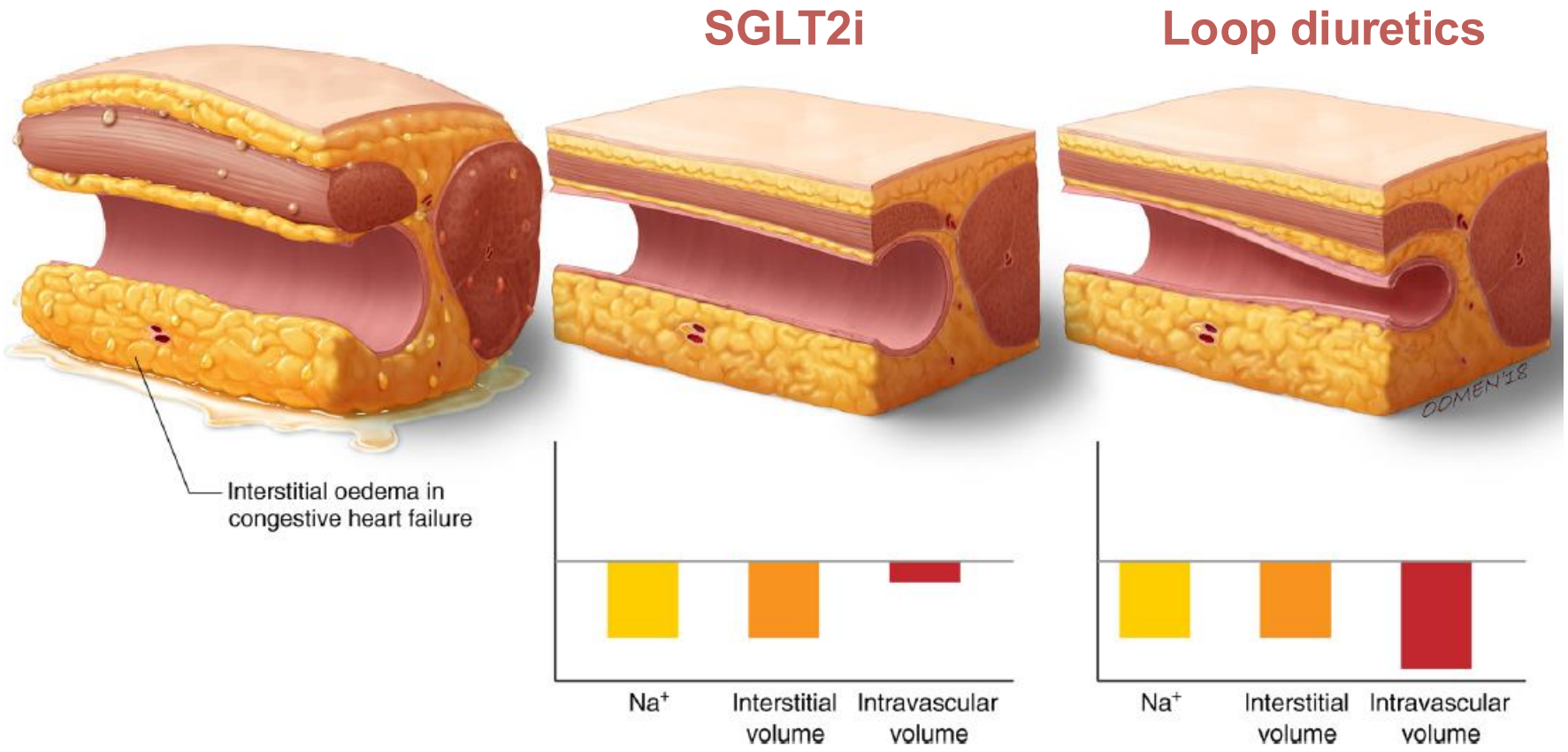




Kidokoro et al., *Circulation*, 2019

SGLT2i: vascular & haemodynamic effects

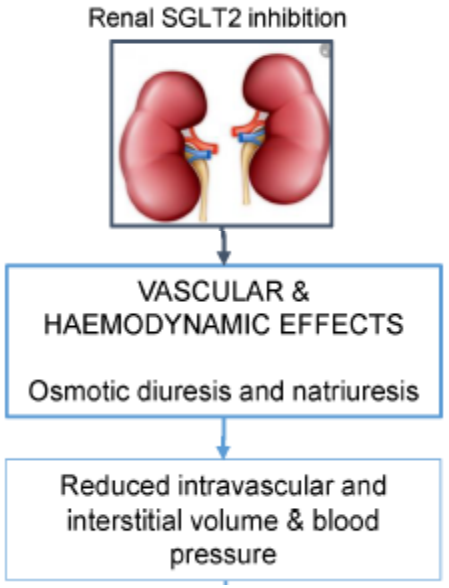


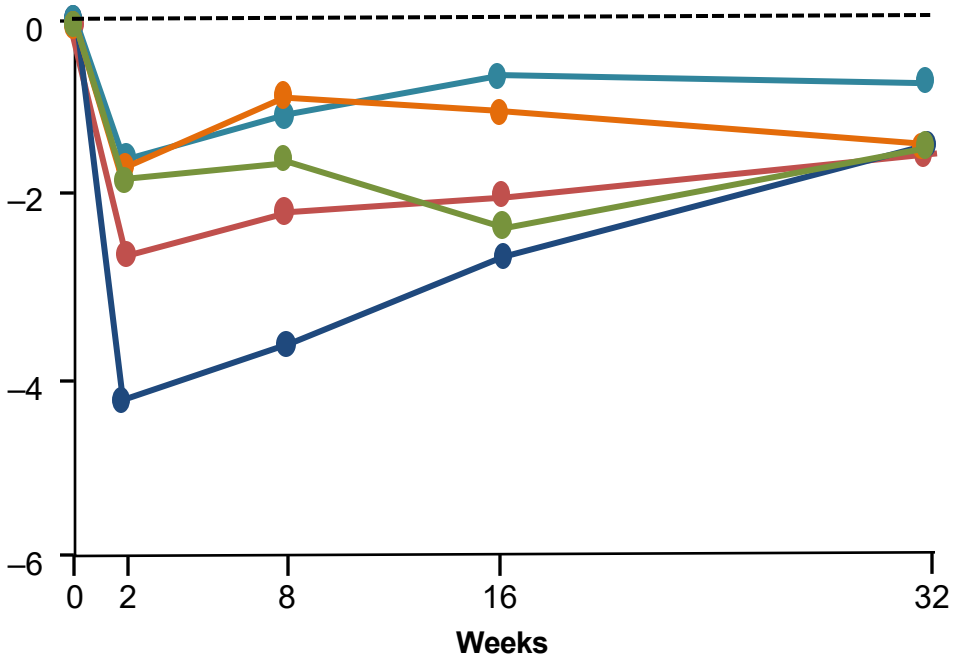


Verma & McMurray et al., *Diabetologia*, 2018

SGLT2i: vascular & haemodynamic effects

DAPA-HF





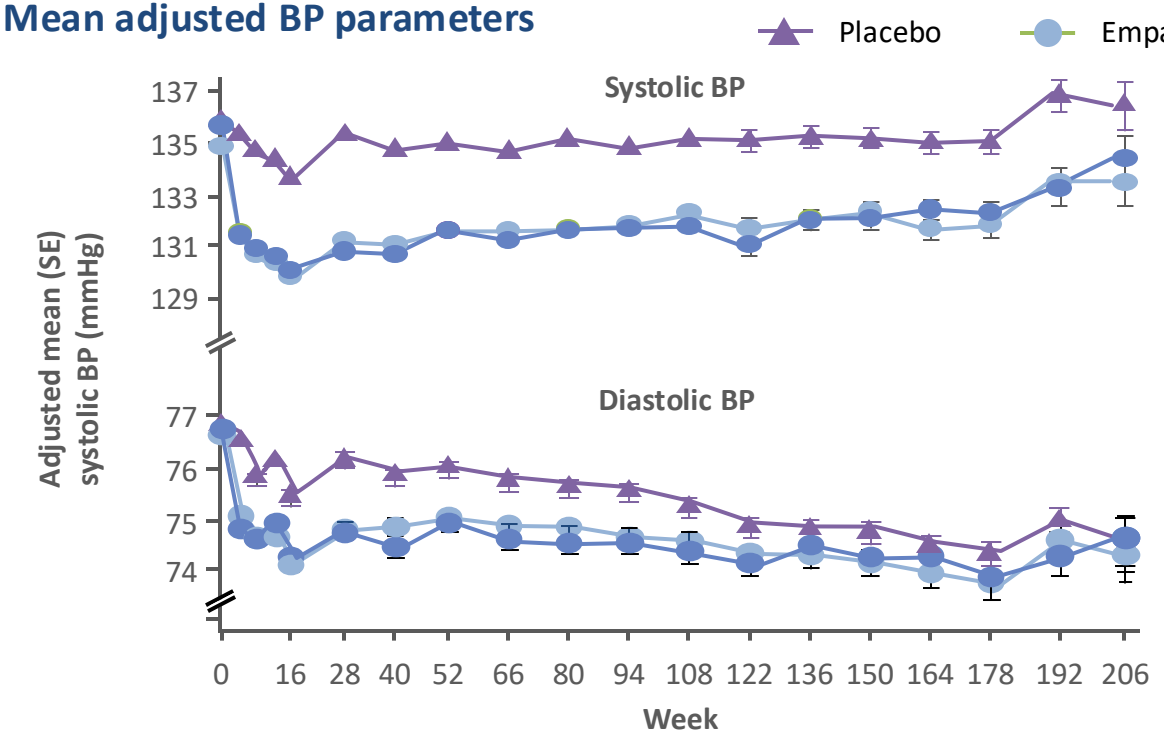
Placebo-Corrected Change in SBP (mm Hg)[a] From Baseline to 4 Months (95% CI)[1,2]

Overall	T2D[b]	No T2D
–1.84 (–2.67 to –1.00)	–1.6 (–2.8 to –0.4)	–1.8 (–2.8 to –0.8)
	Interaction p-value[c] = 0.43	

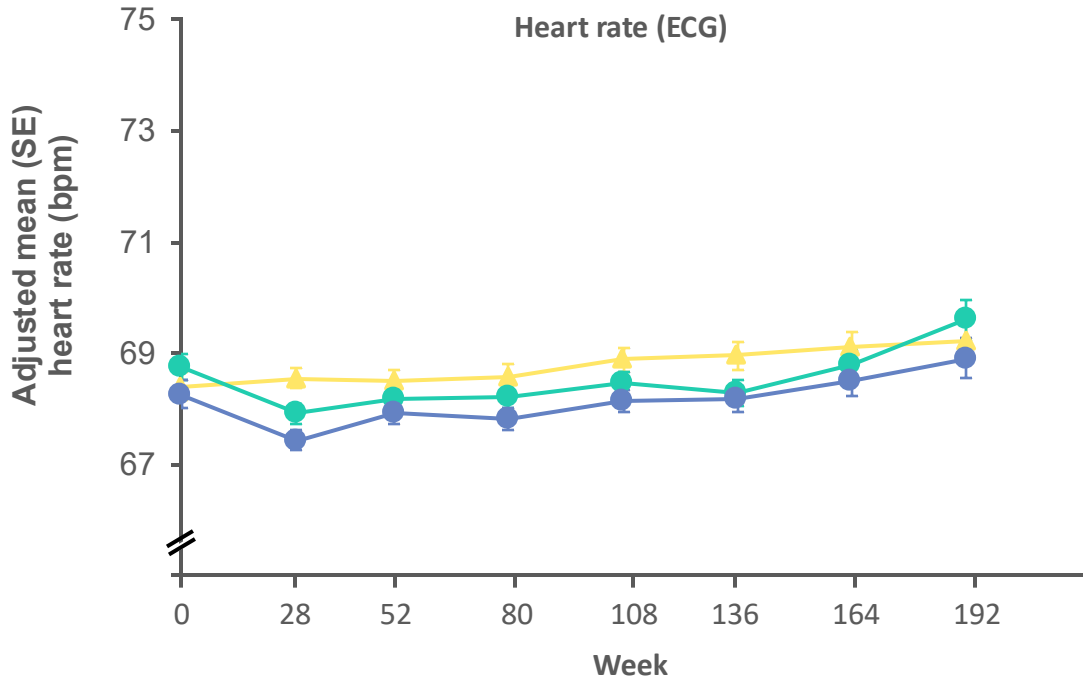
SGLT2i: vascular & haemodynamic effects

In EMPA-REG OUTCOME Empagliflozin was associated with small reductions in blood pressure and no increases in heart rate

Mean adjusted BP parameters



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216



Placebo	2174	2127	2032	1928	1796	1300	1002	552
Empagliflozin 10 mg	2205	2137	2064	2006	1877	1366	1045	597
Empagliflozin 25 mg	2192	2127	2066	2006	1907	1383	1086	633

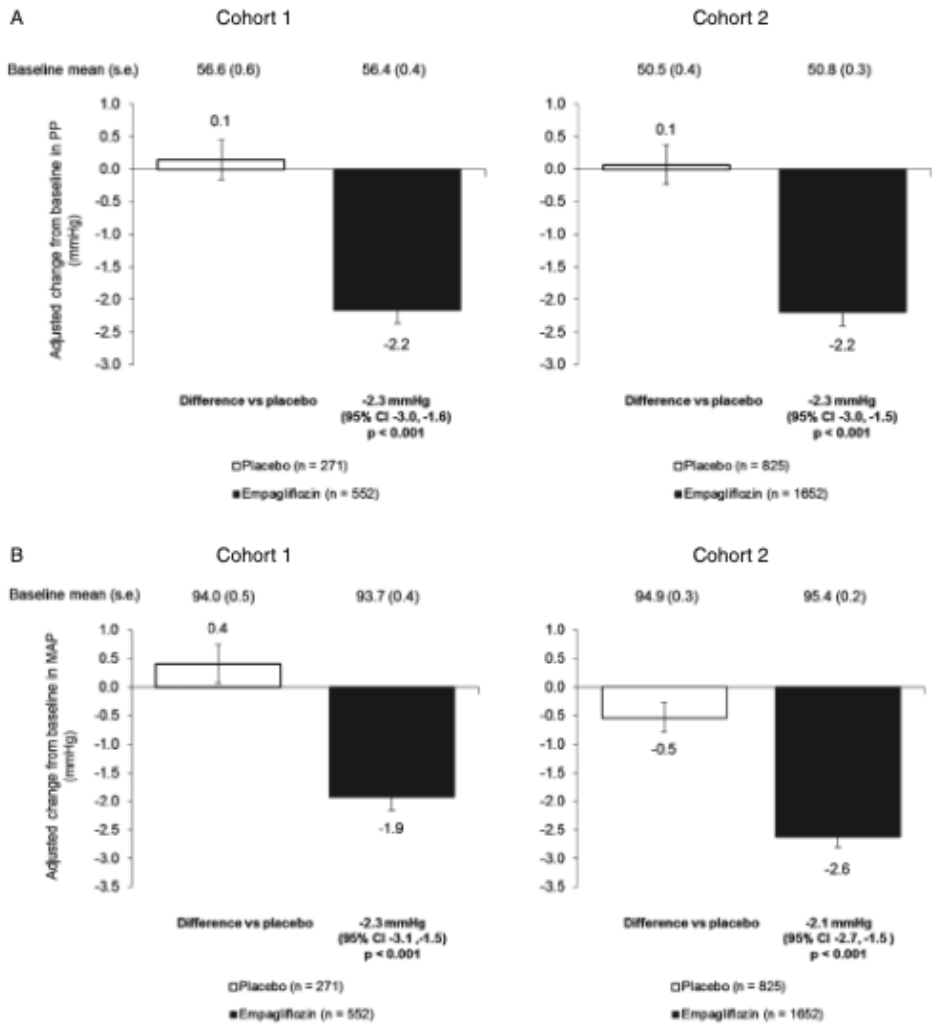
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intention to treat). X-axes: time points with reasonable amount of data available for prescheduled measurements. ECG, electrocardiogram

Zinman B et al. N Engl J Med 2015;373:2117

Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes

SPB

MAP



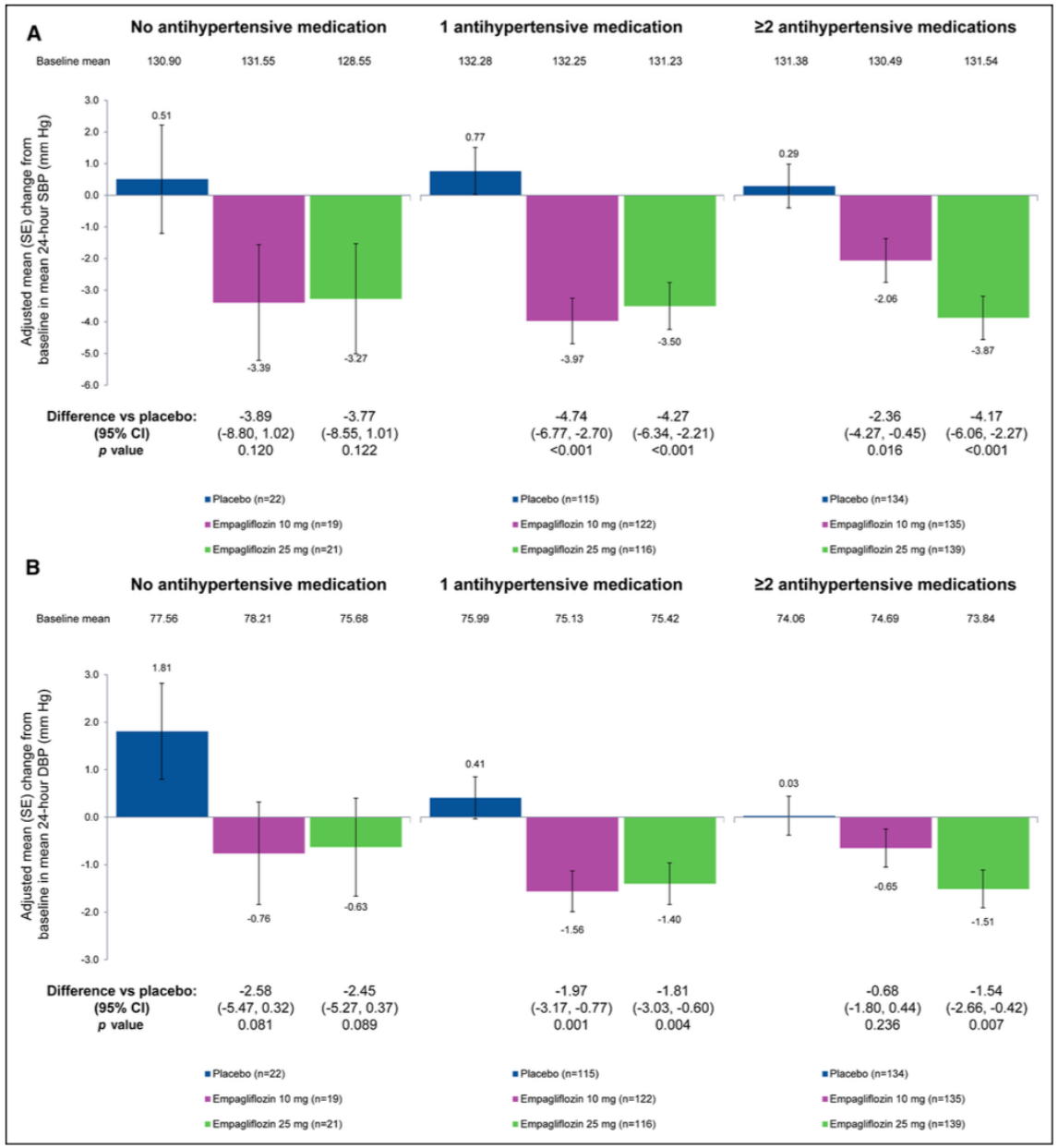
Cohort 1: EMPA-REG BP™ trial

Cohort 2: pivotal trials of empagliflozin required for regulatory submissions: EMPA-REG MONO™, EMPA-REG MET™, EMPA-REG METSU™ and EMPA-REG PIO™

Diabetes, Obesity and Metabolism 17: 1180–1193, 2015.

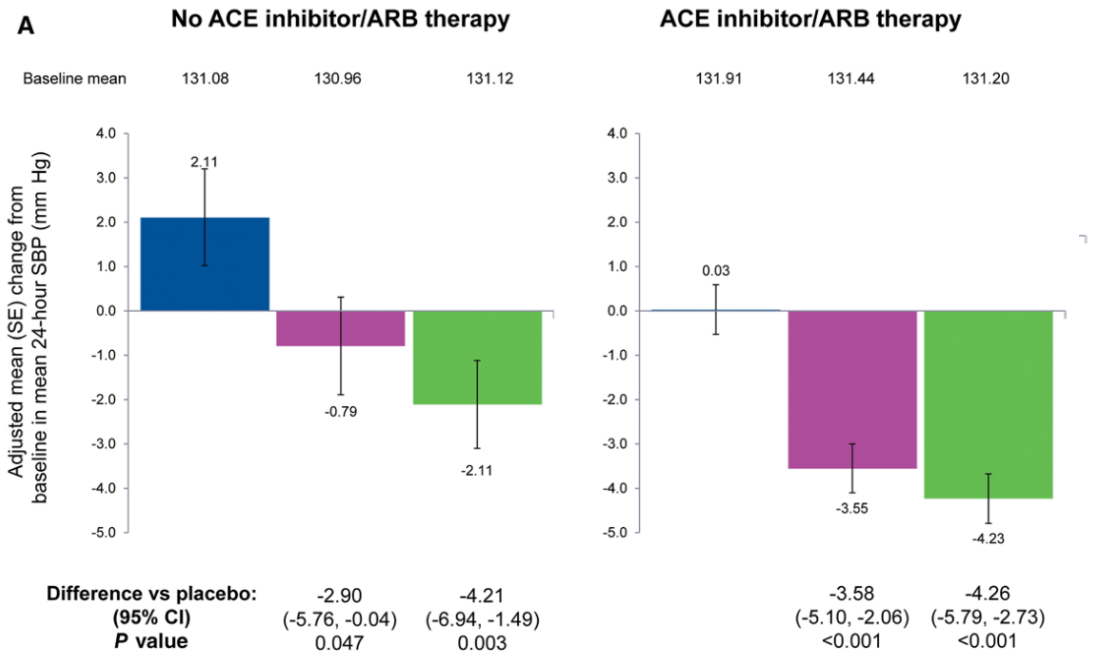
SPB

DPB



Impact of Empagliflozin on Blood Pressure in Patients With Type 2 Diabetes Mellitus and Hypertension by Background Antihypertensive Medication

Giuseppe Mancia, Christopher P. Cannon, Ilkka Tikkanen, Cordula Zeller, Ludwin Ley, Hans J. Woerle, Uli C. Broedl, Odd Erik Johansen



Hypertension. 2016;68:1355-1364. DOI: 10.1161/HYPERTENSIONAHA.116.07703.

ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–98
https://doi.org/10.1093/eurheartj/ehad192
ESC GUIDELINES

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

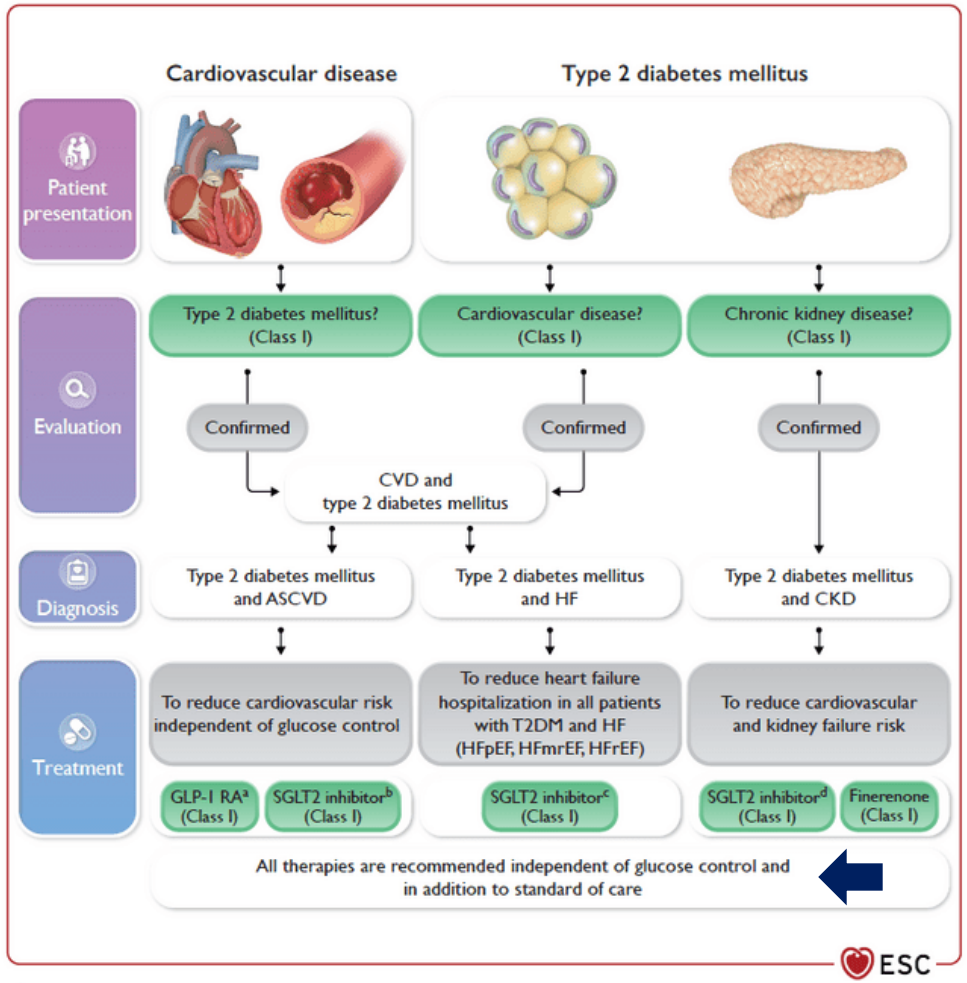


Figure 1 Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; s.c. subcutaneous; SGLT2, sodium–glucose co-transporter-2; T2DM, type 2 diabetes mellitus. [a]GLP-1 RAs with proven cardiovascular benefit: lirglutide, semaglutide s.c., dulaglutide, efpeglenatide. [b]SGLT2 inhibitors with proven cardiovascular benefit: empagliflozin, canagliflozin, dapagliflozin, sotagliflozin. [c]Empagliflozin, dapagliflozin, sotagliflozin in HFrEF; empagliflozin, dapagliflozin in HFpEF and HFmrEF. [d]Canagliflozin, empagliflozin, dapagliflozin.

ESC European Society of Cardiology
European Heart Journal (2024) 00, 1–123
https://doi.org/10.1093/eurheartj/ehae177
ESC GUIDELINES

2024 ESC Guidelines for the management of chronic coronary syndromes

Recommendation Table 19 — Recommendations for sodium–glucose cotransporter 2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with chronic coronary syndrome (see also Evidence Table 19)

Recommendations	Class[a]	Level[b]
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit[c] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[86,688,695,697,700]	I	A
GLP-1 receptor agonists with proven CV benefit[d] are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.[710,711]	I	A

[a]Class of recommendation.
[b]Level of evidence.
[c]Canaglifozin, dapagliflozin, empagliflozin, sotagliflozin (listed in alphabetical order).
[d]Dulaglutide, efpeglenatide, liraglutide, semaglutide (listed in alphabetical order).

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3912–4018
https://doi.org/10.1093/eurheartj/ehae178
ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Recommendations	Class[a]	Level[b]
In patients with diabetic or non-diabetic moderate-to-severe CKD and confirmed BP ≥130/80 mmHg, lifestyle optimization and BP-lowering medication are recommended to reduce CVD risk, provided such treatment is well tolerated.[275,766]	I	A
In adults with moderate-to-severe CKD who are receiving BP-lowering drugs and who have eGFR >30 mL/min/1.73 m^2, it is recommended to target systolic BP to 120–129 mmHg, if tolerated. Individualized BP targets are recommended for those with lower eGFR or renal transplantation.[274,779]	I	A
In hypertensive patients with CKD and eGFR >20 mL/min/1.73 m^2, SGLT2 inhibitors are recommended to improve outcomes in the context of their modest BP-lowering properties.[776,777]	I	A
ACE inhibitors or ARBs are more effective at reducing albuminuria than other BP-lowering agents and should be considered as part of the treatment strategy for patients with hypertension and microalbuminuria or proteinuria.[780–782]	IIa	B

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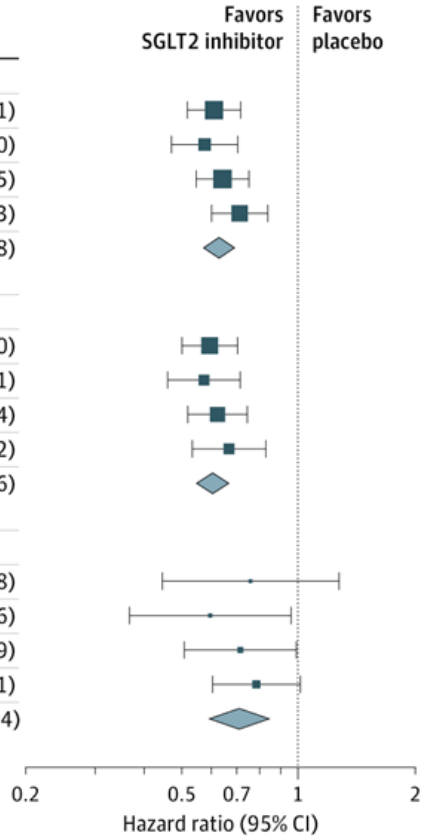
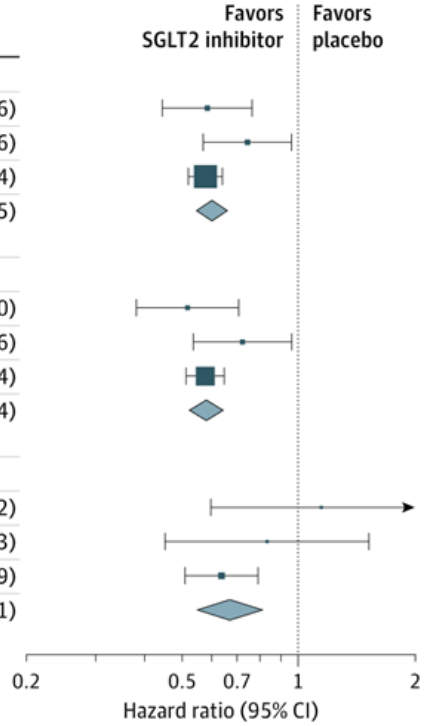
SGLT2 Inhibitors and Kidney Outcomes by Glomerular Filtration Rate and Albuminuria: A Meta-Analysis

Baseline estimated GFR, mL/min/1.73 m^2	No. of participants/total No. (%) SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)
All participants			
≥60	271/23 164 (1.2)	369/19 951 (1.8)	0.61 (0.52-0.71)
45 to <60	164/6255 (2.6)	273/5902 (4.6)	0.57 (0.47-0.70)
30 to <45	274/5561 (4.9)	389/5323 (7.3)	0.64 (0.54-0.75)
<30	241/1928 (12.5)	333/1966 (16.9)	0.71 (0.60-0.83)
Overall	950/36 911 (2.6)	1364/33 146 (4.1)	0.62 (0.57-0.68)
Trend by baseline estimated GFR: *P* = .16			
Participants with diabetes			
≥60	246/19 861 (1.2)	335/16 665 (2.0)	0.59 (0.50-0.70)
45 to <60	137/4355 (3.1)	226/4004 (5.6)	0.57 (0.46-0.71)
30 to <45	213/3586 (5.9)	306/3368 (9.1)	0.62 (0.52-0.74)
<30	139/1122 (12.4)	199/1105 (18.0)	0.66 (0.53-0.82)
Overall	735/28 940 (2.5)	1066/25 165 (4.2)	0.60 (0.55-0.66)
Trend by baseline estimated GFR: *P* = .39			
Participants without diabetes			
≥60	25/3303 (0.8)	34/3286 (1.0)	0.75 (0.45-1.28)
45 to <60	27/1900 (1.4)	47/1898 (2.5)	0.59 (0.37-0.96)
30 to <45	61/1975 (3.1)	83/1955 (4.2)	0.71 (0.51-0.99)
<30	102/788 (12.9)	134/837 (16.0)	0.78 (0.60-1.01)
Overall	215/7971 (2.7)	298/7981 (3.7)	0. 70 (0.59-0.84)
Trend by baseline estimated GFR: *P* = .57			



GFR

Baseline UACR, mg/g	No. of participants/total No. (%) SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)
All participants			
<30	94/15 973 (0.6)	125/13 595 (0.9)	0.58 (0.44-0.76)
30 to 300	109/7583 (1.4)	128/6519 (2.0)	0.74 (0.57-0.96)
>300	637/7575 (8.4)	999/7275 (13.7)	0.57 (0.52-0.64)
Overall	843/31 407 (2.7)	1252/27 644 (4.5)	0.60 (0.55-0.65)
Trend by baseline UACR: *P* = .49			
Participants with diabetes			
<30	73/13 984 (0.5)	108/11 645 (0.9)	0.52 (0.38-0.70)
30 to 300	89/6365 (1.4)	103/5309 (1.9)	0.72 (0.53-0.96)
>300	503/5849 (8.6)	786/5497 (14.3)	0.57 (0.51-0.64)
Overall	668/26 464 (2.5)	997/22 696 (4.4)	0.58 (0.52-0.64)
Trend by baseline UACR: *P* = .96			
Participants without diabetes			
<30	21/1988 (1.1)	17/1950 (0.9)	1.15 (0.59-2.22)
30 to 300	20/1218 (1.6)	25/1210 (2.1)	0.83 (0.45-1.53)
>300	134/1726 (7.8)	213/1778 (12.0)	0.63 (0.51-0.79)
Overall	175/4943 (3.5)	255/4948 (5.2)	0.66 (0.55-0.81)
Trend by baseline UACR: *P* = .07			



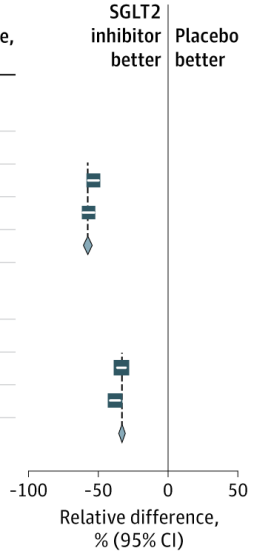
ALBUMINURIA

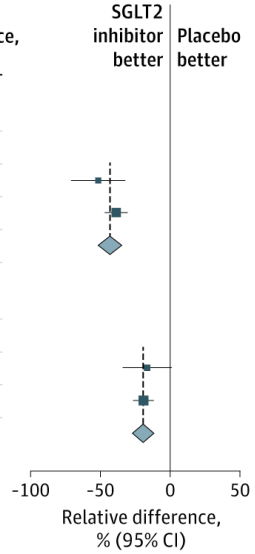
JAMA
Published Online: November 7, 2025
doi: **SGLT2 Inhibitors and Kidney Outcomes by Glomerular Filtration Rate and Albuminuria**A Meta-Analysis

Effects of Sodium Glucose Cotransporter 2 Inhibitors by Diabetes Status and Level of Albuminuria: A Meta-Analysis

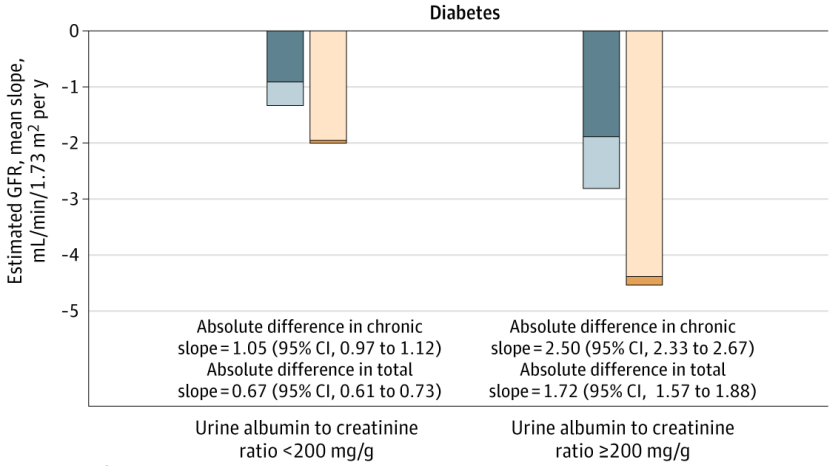
A Relative effects

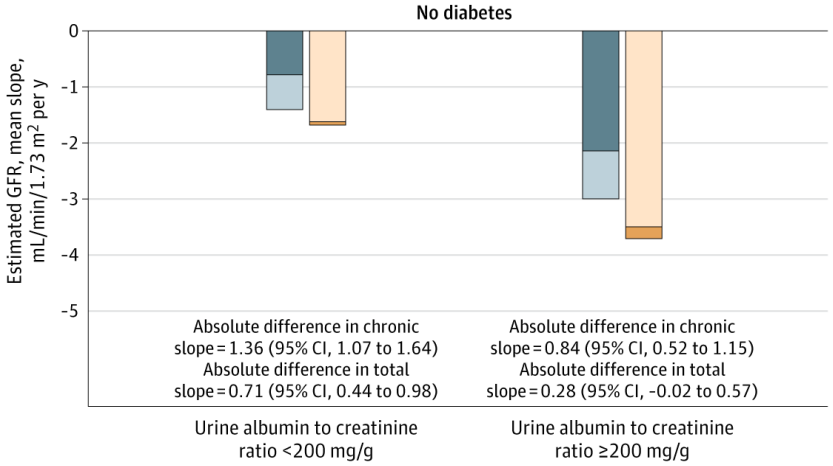
	Diabetes: Estimated GFR, mean (SE) slope, mL/min/1.73 m² per y				No diabetes: Estimated GFR, mean (SE) slope, mL/min/1.73 m² per y			
	SGLT2 inhibitor	Placebo	Relative difference, % (95% CI)	*P* for heterogeneity by albuminuria status[a]	SGLT2 inhibitor	Placebo	Relative difference, % (95% CI)	*P* for heterogeneity by albuminuria status[a]
Chronic slope[b] *P* = .002 for heterogeneity by diabetes status								
Urine albumin to creatinine ratio, mg/g								
<200	-0.91 (0.03)	-1.95 (0.03)	-54 (-57 to -50)		-0.78 (0.11)	-1.62 (0.11)	-52 (-71 to -32)	
≥200	-1.89 (0.06)	-4.39 (0.06)	-57 (-61 to -53)	.21	-2.14 (0.10)	-3.50 (0.10)	-39 (-47 to -31)	.23
Overall	-1.00 (0.03)	-2.36 (0.03)	-58 (-61 to -54)		-1.50 (0.08)	-2.64 (0.08)	-43 (-52 to -35)	
Total slope[c] *P* = .001 for heterogeneity by diabetes status								
Urine albumin to creatinine ratio, mg/g								
<200	-1.33 (0.02)	-2.00 (0.02)	-33 (-36 to -30)		-1.40 (0.11)	-1.68 (0.11)	-17 (-34 to 1)	
≥200	-2.81 (0.05)	-4.54 (0.06)	-38 (-41 to -35)	.05	-3.00 (0.10)	-3.71 (0.10)	-19 (-27 to -12)	.78
Overall	-1.59 (0.02)	-2.37 (0.02)	-33 (-35 to -31)		-2.23 (0.08)	-2.76 (0.08)	-19 (-27 to -12)	





B Absolute effects





JAMA
Published Online: November 7, 2025
doi: 10.1001/jama.2025.20835

Estimated GFR slope

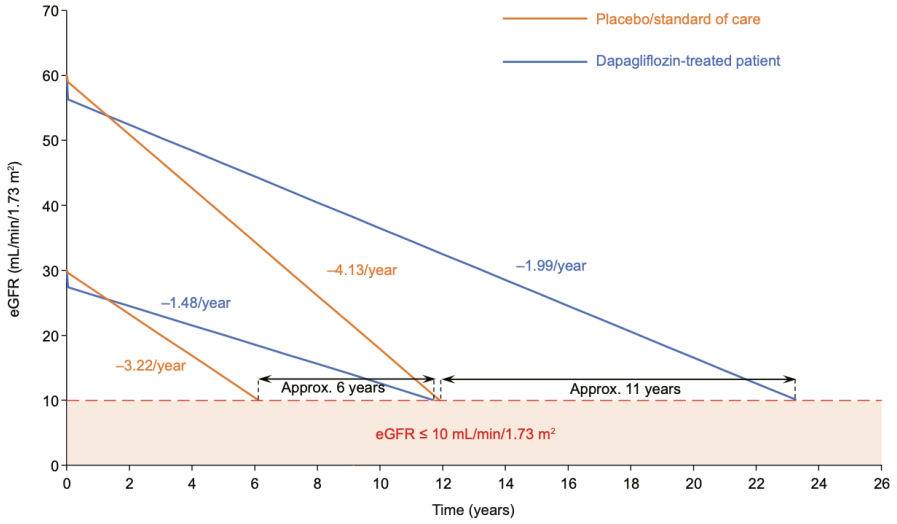


Figure 2. Extrapolation of data from the placebo-controlled DAPA-CKD clinical trial suggests that initiation of SGLT2 inhibitors at a higher eGFR could delay kidney failure by a longer time than initiation at a lower eGFR.[51] Initial eGFR decline over the first 2 weeks was estimated using eGFR slope data from the acute phase of the DAPA-CKD trial. Projections are based on the eGFR from week 2 to end of treatment (DAPA-CKD chronic phase) and assume linear progression of eGFR decline. Example patient with initial eGFR of 60 mL/min/1.73 m² used eGFR slope data from the DAPA-CKD trial subgroup with eGFR ≥ 45 mL/min/1.73 m²; eGFR at the start of the chronic phase: dapagliflozin 10 mg, 56.3 mL/min/1.73 m²; placebo, 59.0 mL/min/1.73 m². Example patient with initial eGFR of 30 mL/min/1.73 m² used eGFR slope data from the DAPA-CKD trial subgroup with eGFR < 45 mL/min/1.73 m²; eGFR at the start of the chronic phase: dapagliflozin 10 mg, 27.4 mL/min/1.73 m²; placebo, 29.6 mL/min/1.73 m². Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose co-transporter-2.

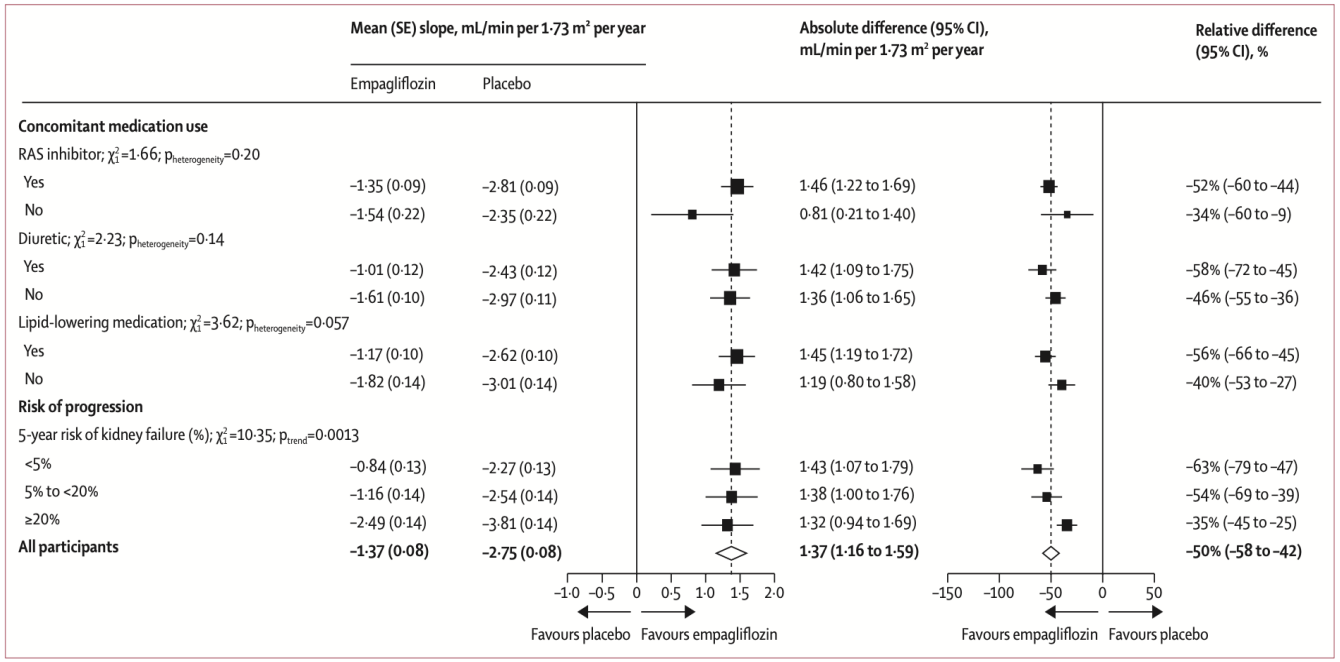


Figure 3: **Effect of allocation to empagliflozin on chronic slopes, by other subgroups**
eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio.

-50% risk of progression of kidney failure

Kidney Med. 6(8):100851. Published online June 8, 2024.

doi: 10.1016/j.xkme.2024.100851

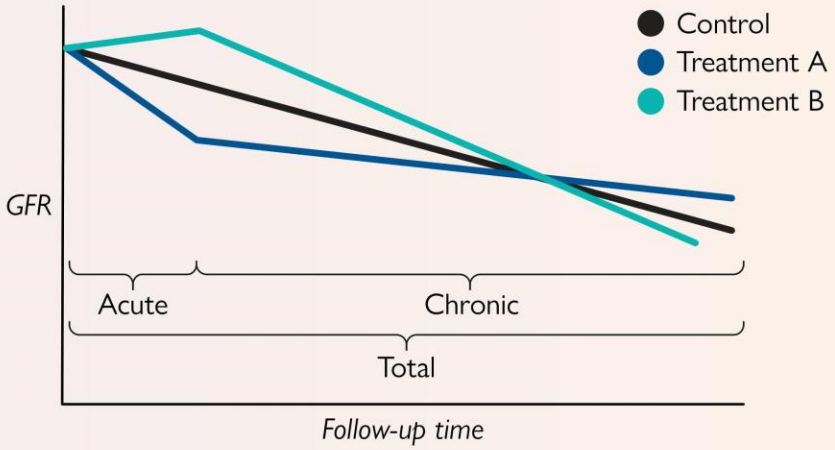
Lancet Diabetes Endocrinol
2024; 12: 39–50

Decline in GFR as an endpoint in heart failure clinical trials

Cardiovascular-kidney-metabolic syndrome

- CKD and heart failure often coexist in the same individual, with growing evidence for common therapeutic approaches for both diseases
- The ability to evaluate the efficacy of treatments for heart failure and CKD progression within the same trial would provide significant benefits to patients, clinicians, and regulatory agencies
- Endpoints based on slowing GFR decline have advanced the design of trials for CKD progression. Applying similar endpoints in heart failure trials could yield comparable progress

Factors to consider while selecting the optimal endpoint of GFR decline



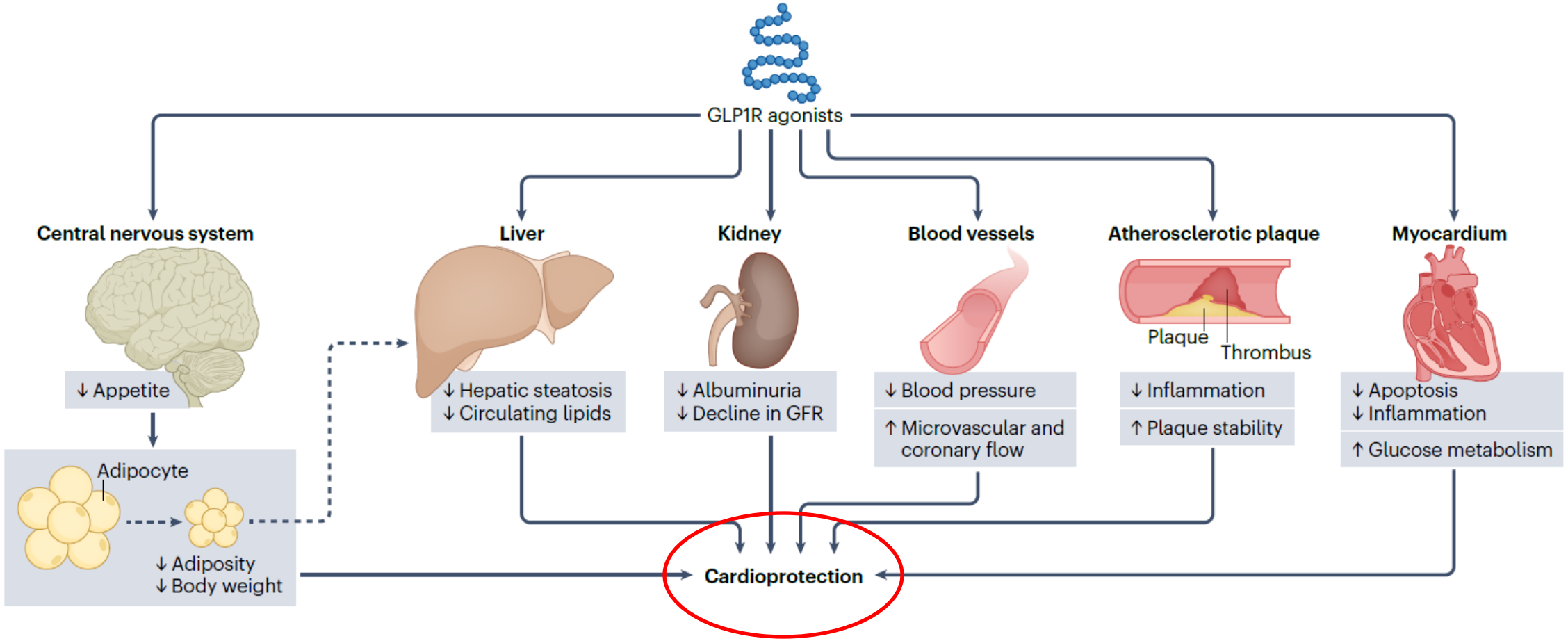
- Acute effects on GFR
- Rate of competing events
- Severity of CKD
- Changes in body composition
- Heterogeneity of the heart failure population

Chronic kidney disease and cardiovascular disease are tightly interconnected, with common mechanisms that underlie the development and progression of both diseases, recently articulated into the framework of the cardiovascular-kidney-metabolic syndrome.

CKD, chronic kidney disease; **GFR**, glomerular filtration rate

Inker LA, *et al. European Heart Journal.*

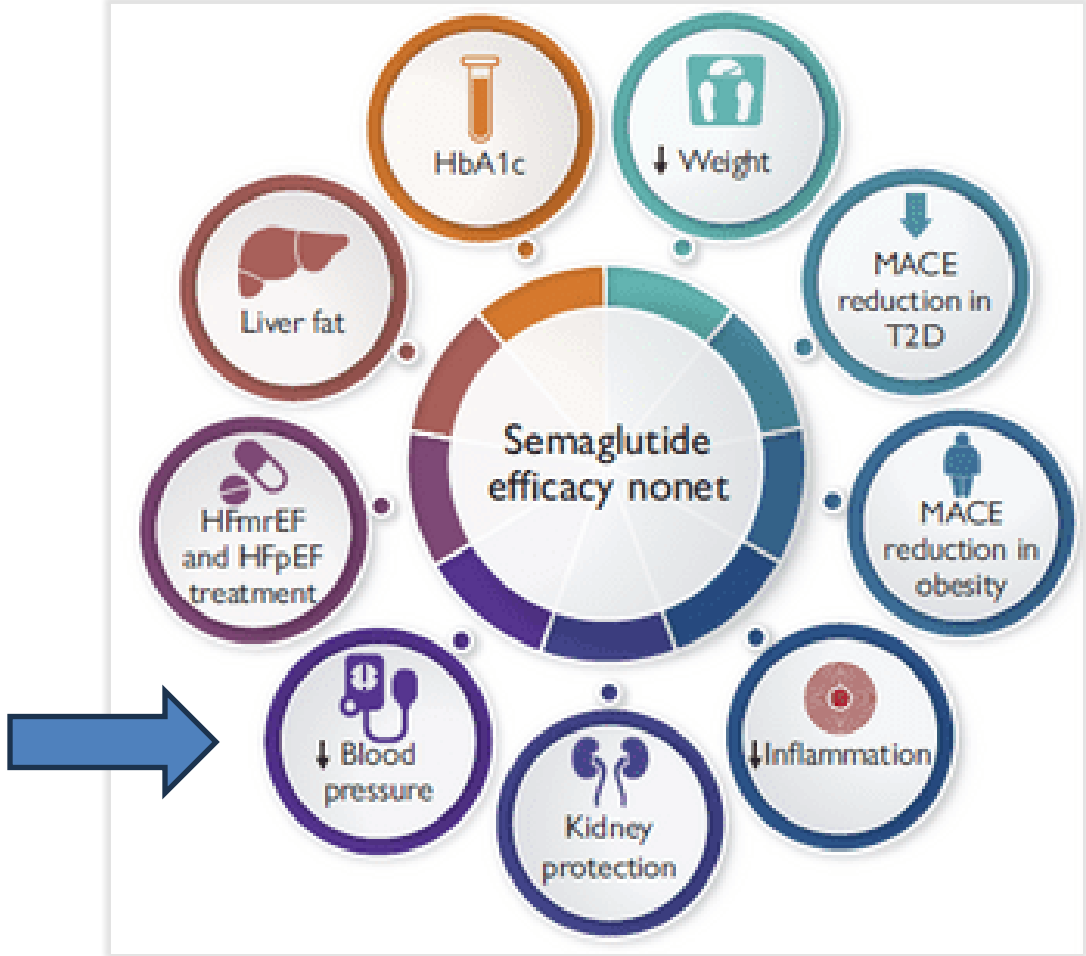
Una azione su più target con un fine comune: protezione cardiovascolare



John R. Ussher 1,2 & Daniel J. Drucker. Nature reviews cardiology 2023. https://doi.org/10.1038/s41569-023-00849-3

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehae744
EDITORIAL
Diabetes and metabolic disorders

Pump, pipes, filter, sugar, weight, and more: the pluripotent prowess of semaglutide



GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1C, glycated haemoglobin; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.

Semaglutide shows cardio-reno-metabolic benefits[1-4]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

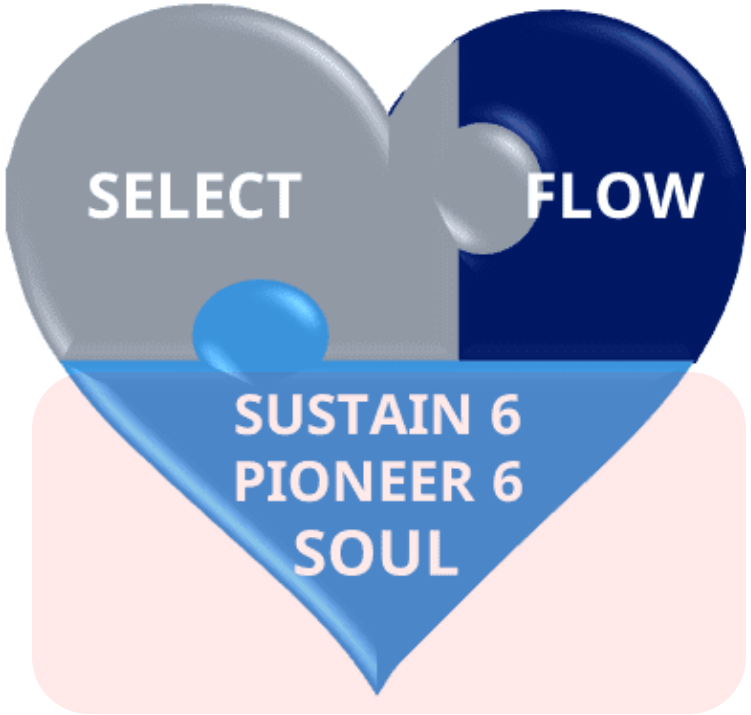
A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., 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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Mansoor Husain, M.D., Andreas L. Birkenfeld, M.D., Morten Donsmark, Ph.D., Kathleen Dungan, M.D., M.P.H., Freddy G. Eliaschewitz, M.D., Denise R. Franco, M.D., Ole K. Jeppesen, M.Sc., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Ofri Mosenzon, M.D., Sue D. Pedersen, M.D., Cees J. Tack, M.D., Mette Thomsen, M.D., D.M.Sc., Tina Vilsbøll, M.D., D.M.Sc., Mark L. Warren, M.D., and Stephen C. Bain, M.D., for the PIONEER 6 Investigators*

PIONEER 6[1], SUSTAIN 6[2], SOUL[5], SELECT[3] & FLOW[4]

1. Husain M et al. N Engl J Med 2019;381:841–51; 2. Marso SP et al. N Engl J Med 2016;375:1834–44; 2. 3. Lincoff AM, et al. N Engl J Med. 2023 Dec 14;389(24):2221-2232. 4. Perkovic V, et al. N Engl J Med. 2024;391(2):109-121. 5. Clinicaltrials.gov: NCT03914326

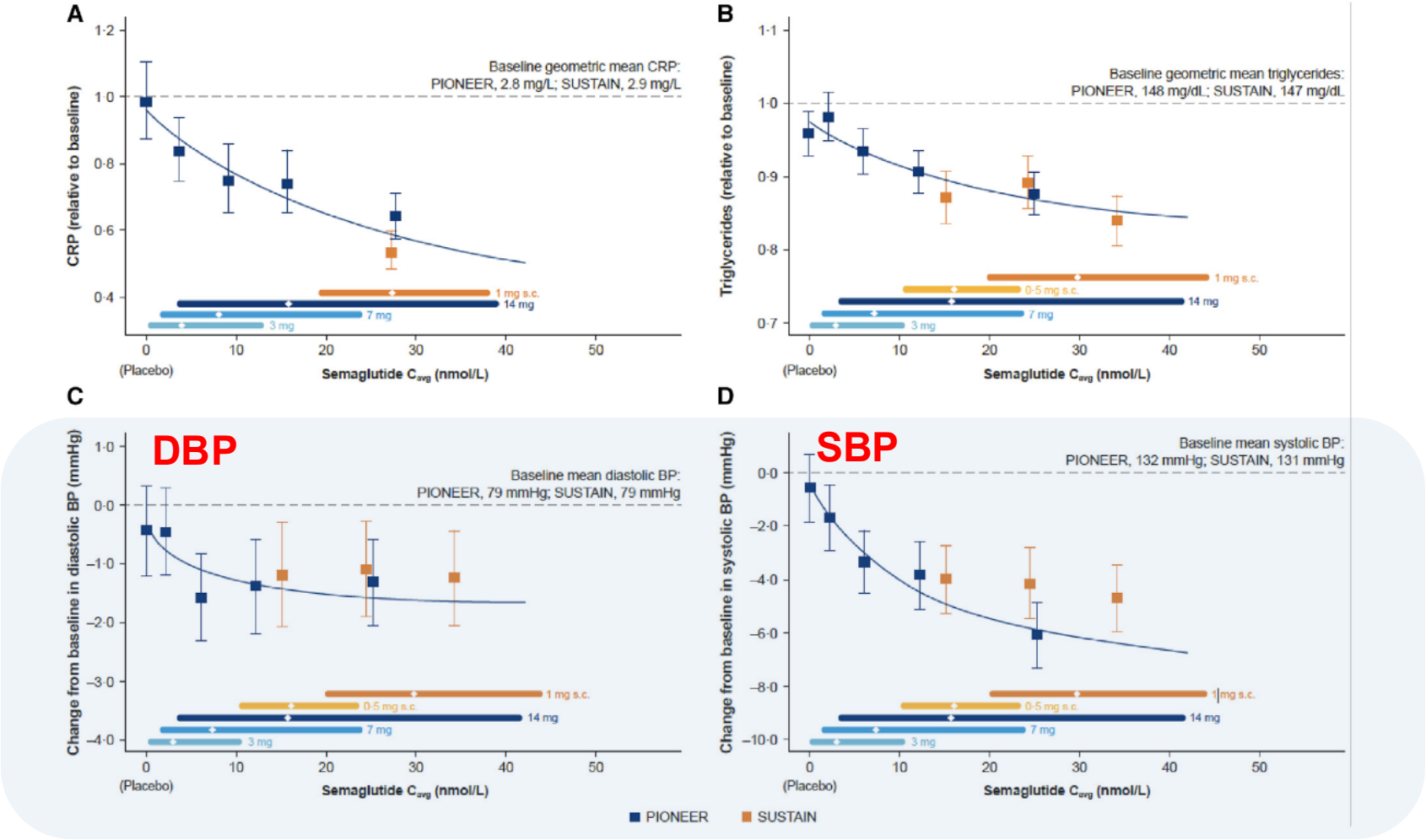


Figure 5. Change in CRP, triglycerides, and blood pressure reflect semaglutide exposure in the PIONEER and SUSTAIN trials

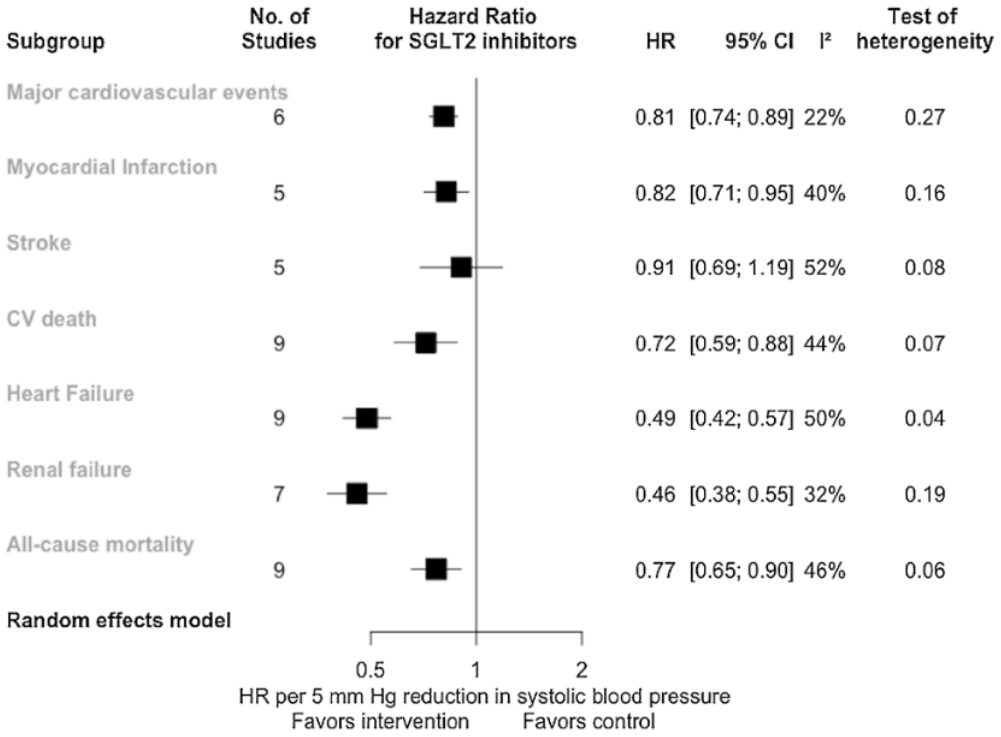
Data are means and 95% CIs. Exposure is presented as quantiles of C_{avg} for semaglutide and 1 quantile for placebo (at C_{avg} of 0 nmol/L). The fitted solid line represents model-derived relations not adjusted for covariate factors, based on the PIONEER program. Triglycerides and systolic and diastolic BP: data from PIONEER 1, 2, 3, 5, 8, and 9 at week 26 and SUSTAIN 1, 2, and 3 and SUSTAIN Japan OAD at week 30. CRP: PIONEER 1, 2, and 5 data at week 26 and SUSTAIN 3 data at week 56. BP, blood pressure; CRP, C-reactive protein.

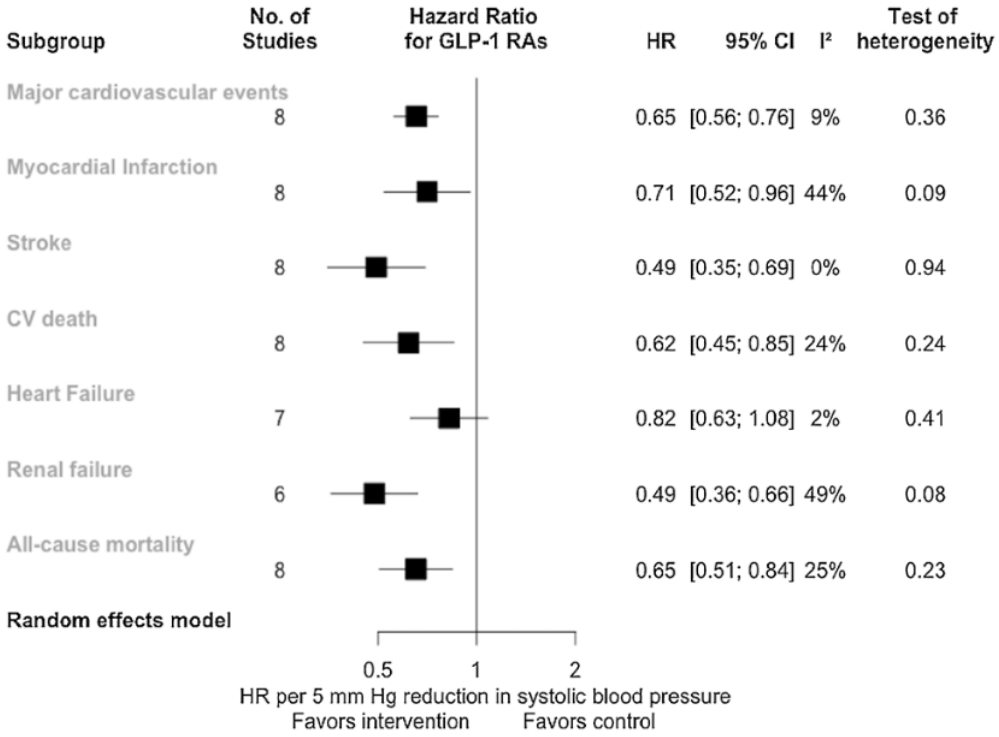
Cell Reports Medicine 2, 100387, September 21, 2021

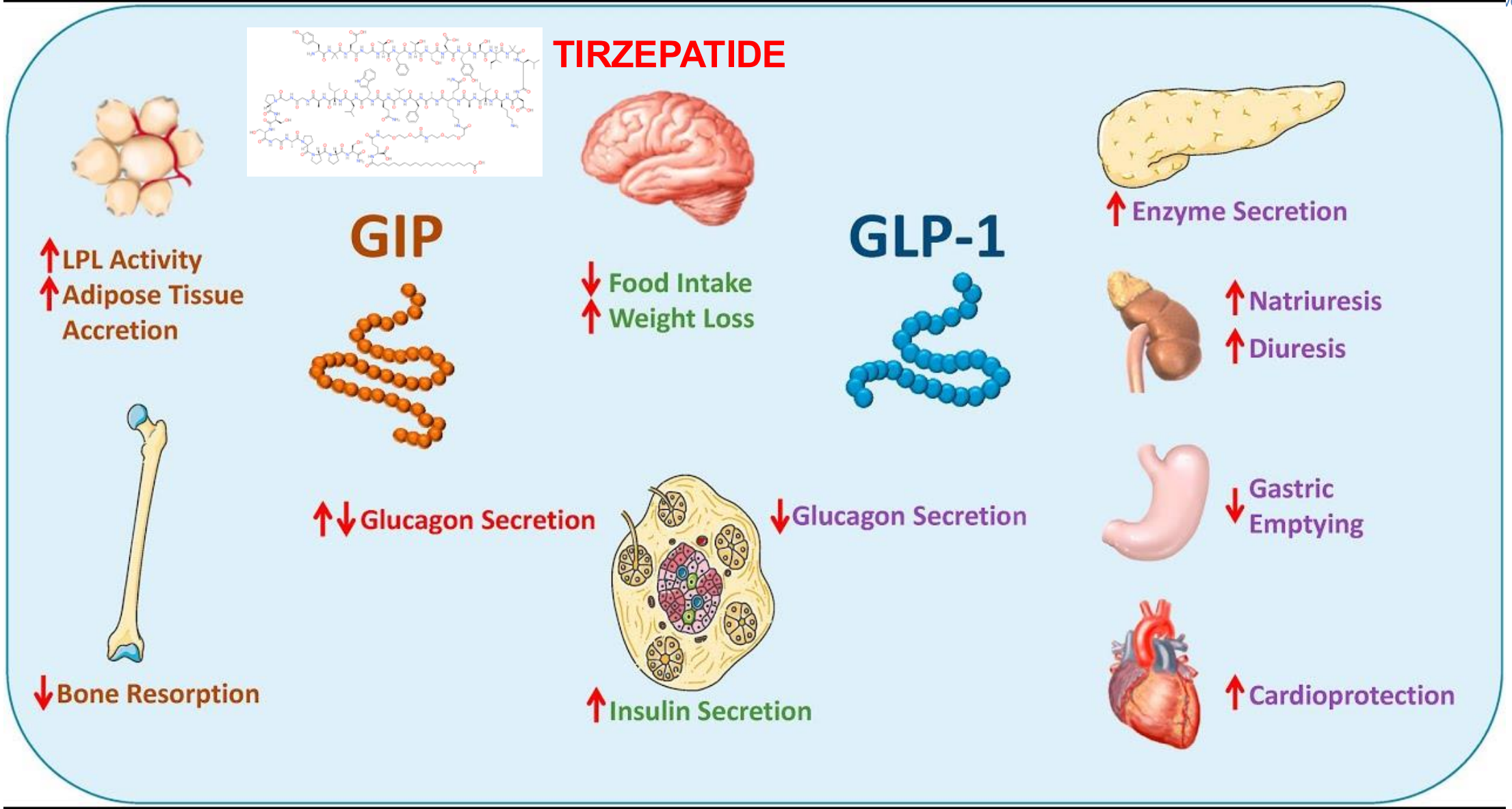
Association between BP-lowering and all-cause mortality

Each 5-mmHg reduction in systolic BP significantly reduced **the risk of all-cause mortality by 23%** (HR 0.77; 95% CI 0.65–0.90) in patients treated with SGLT2 inhibitors (left panel). The corresponding absolute relative risk (ARR), in events per 1000 patient-years of follow-up, was **3.69** (95% CI 0.67–6.71).

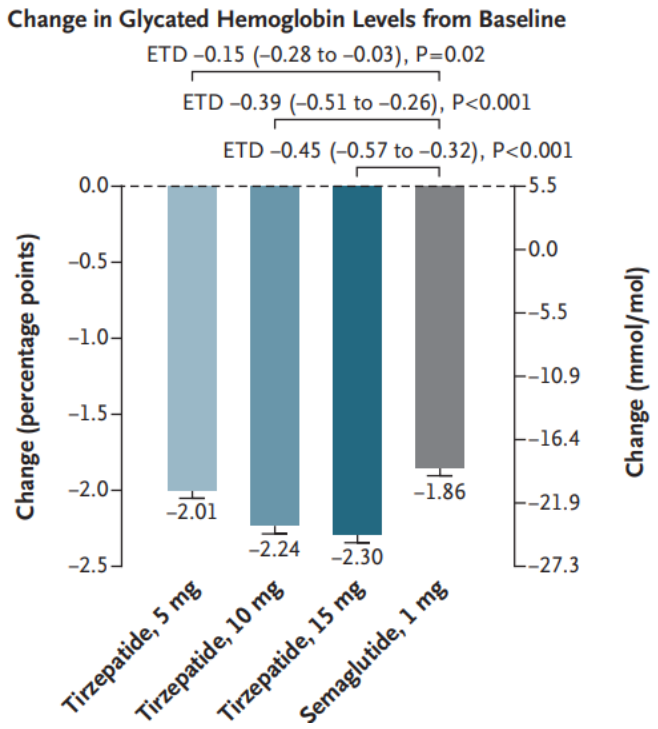
In those treated with GLP-1 RAs, **the risk of all-cause mortality was reduced by 35%** (0.65 (0.51–0.84; right panel), and the corresponding ARR was **4.42** (2.51–6.32) events per 1000 patient-years of follow-up

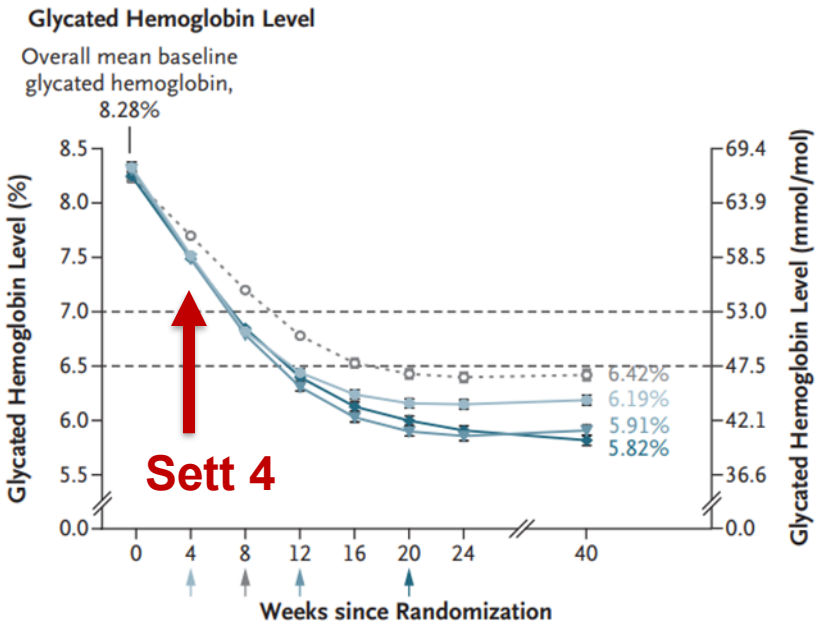


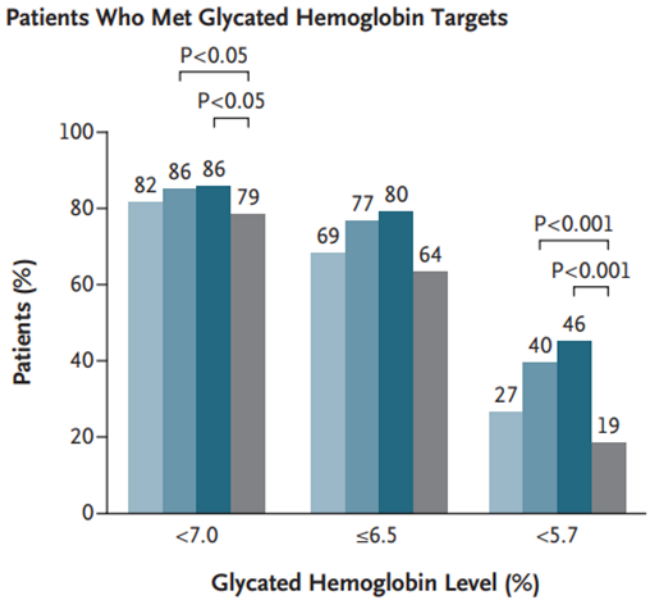



TIRZEPATIDE
GIP
GLP-1
↑LPL Activity
↑Adipose Tissue Accretion
↓Bone Resorption
↓Food Intake
↑Weight Loss
↑↓Glucagon Secretion
↑Insulin Secretion
↓Glucagon Secretion
↑Enzyme Secretion
↑Natriuresis
↑Diuresis
↓Gastric Emptying
↑Cardioprotection

SURPASS 2: efficacia significativamente superiore sulla riduzione della glicata vs semaglutide 1 mg con maggiore velocità di risposta

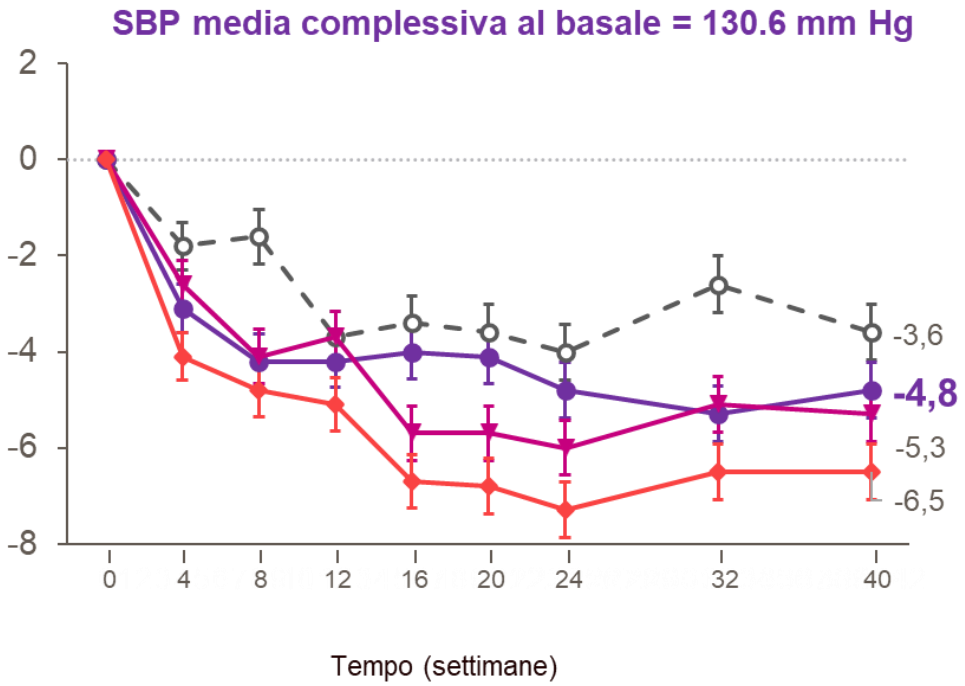


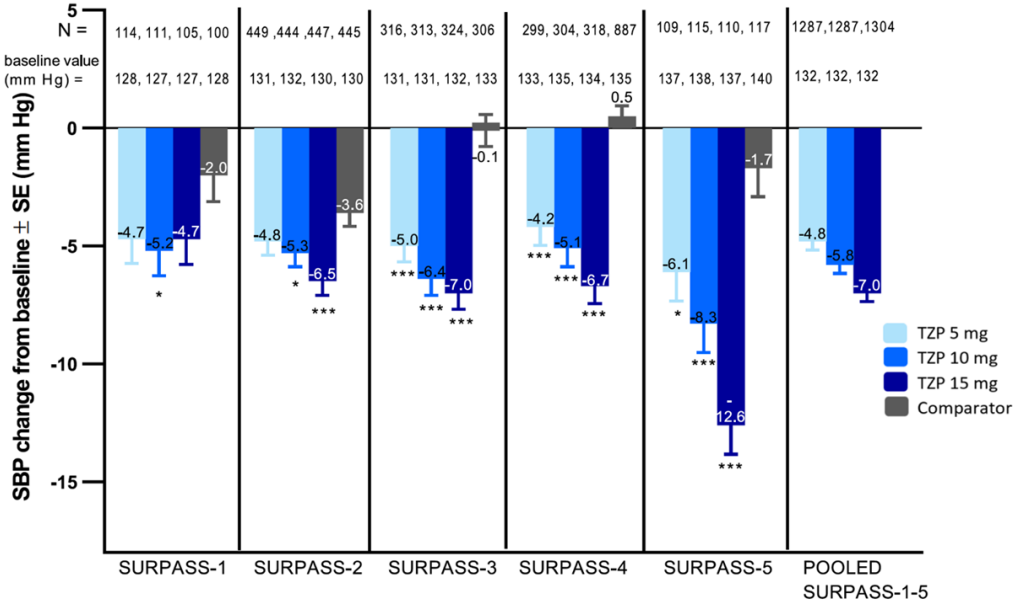




Frias JP, et al. N Engl J Med. 2021

Controllo efficace dei fattori di rischio CV modificabili: pressione arteriosa sistolica





Rosenstock J, Lancet. 2021 Jul 10;398(10295):143-155. Frías JP,. N Engl J Med. 2021 Aug 5;385(6):503-515. Ludvik B, Lancet. 2021 Aug 14;398(10300):583-598.Del Prato S, Lancet. 2021 Nov 13;398(10313):1811-1824.Dahl D, JAMA. 2022 Feb 8;327(6):534-545.Rosenstock J,. JAMA. 2023 Nov 7;330(17):1631-1640.

Frias JP, et al. N Engl J Med. 2021

HFpEF + Obesity

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for Heart Failure in Patients with Obesity

A PLAIN LANGUAGE SUMMARY

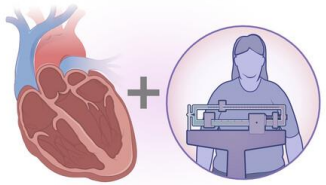
Based on the NEJM publication: Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity by M. Packer et al. (published November 16, 2024)

In this trial, researchers examined cardiovascular outcomes of treatment with tirzepatide in patients with heart failure with preserved ejection fraction and obesity.

Most patients with **heart failure and a preserved ejection fraction** also have obesity, and visceral adiposity contributes to the evolution and progression of heart failure.

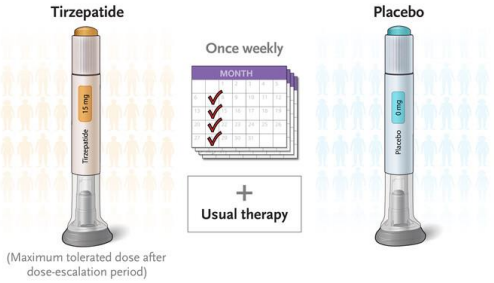
WHY WAS THE TRIAL DONE?

Tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, causes considerable weight loss, but data on its effects on cardiovascular outcomes are lacking.



HOW WAS THE TRIAL CONDUCTED?

Adults with chronic heart failure, an ejection fraction of at least 50%, and a body-mass index (BMI) of at least 30 were assigned to receive subcutaneous tirzepatide (up to 15 mg per week) or placebo, in addition to usual therapy. The two primary end points were a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event resulting in hospitalization, intravenous therapy in an urgent care setting, or intensification of oral diuretic therapy, and the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; range, 0 to 100, with higher scores indicating better quality of life) at 52 weeks.



PATIENTS

WHO

- 731 adults
- Age: at least 40 years (mean, 65 years)
- Women: 54%; Men: 46%

CLINICAL STATUS

- Chronic heart failure (NYHA class II to IV)
- Left ventricular ejection fraction: at least 50%
- BMI: at least 30
- 6-minute walk distance: 100 to 425 m
- KCCQ-CSS: 80 or lower
- One of the following: an elevated NT-proBNP level, left atrial enlargement, or elevated filling pressures
- Heart-failure decompensation within 12 months before baseline or an eGFR of less than 70 ml per minute per 1.73 m² at baseline

TRIAL DESIGN

- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 129 CENTERS IN 9 COUNTRIES

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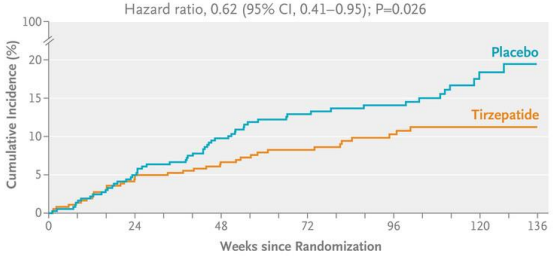
RESULTS

During a median follow-up of 2 years, death from cardiovascular causes or a worsening heart-failure event occurred significantly less often in the tirzepatide group than in the placebo group. At 52 weeks, improvement in the KCCQ-CSS was significantly greater in the tirzepatide group.

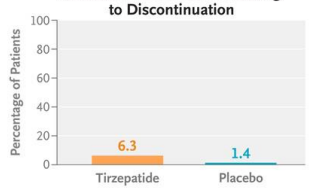
Death from Cardiovascular Causes or a Worsening Heart-Failure Event

Hazard ratio, 0.62 (95% CI, 0.41–0.95); P=0.026



Nonfatal adverse events leading to discontinuation of the regimen — mainly gastrointestinal events — were more common in the tirzepatide group.

Nonfatal Adverse Events Leading to Discontinuation



BODY-MASS INDEX

The risk of heart failure (especially in patients with preserved ejection fraction) increases as BMI increases. The mean BMI of patients in this trial was 38.3 at baseline.

LIMITATIONS AND REMAINING QUESTIONS

- This study included only patients with a BMI of 30 or greater; however, many patients with heart failure with preserved ejection fraction have a BMI of less than 30 but an abnormal waist-to-height ratio, which is a more reliable indicator of excess visceral adiposity. More study is needed in these patients.

CONCLUSIONS

Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04847557

Trial funding: Eli Lilly

Full citation: Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med 2025;392:427-37. DOI: 10.1056/NEJMoa2410027.

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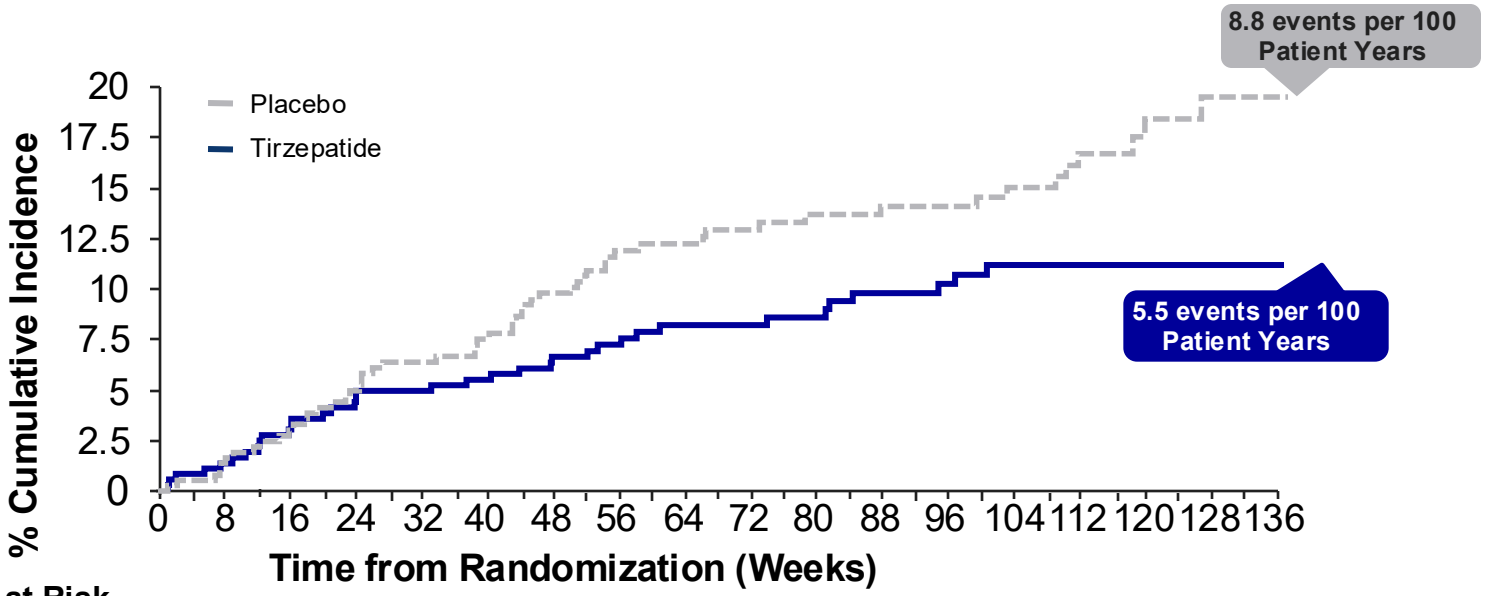
SUMMIT: Tirzepatide migliora gli outcome di scompenso in pazienti HFpEF



Participants at Risk																		
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

HR 0.62
(95% CI 0.41-0.95)
P=0.026

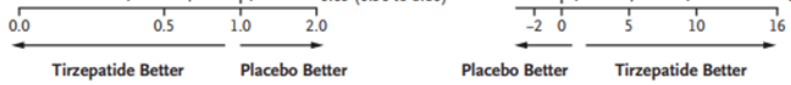
RRR 38%

- [a]Worsening HF event was defined as heart failure symptoms requiring hospitalization, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.

Packer M et al . NEJM Nov 2024

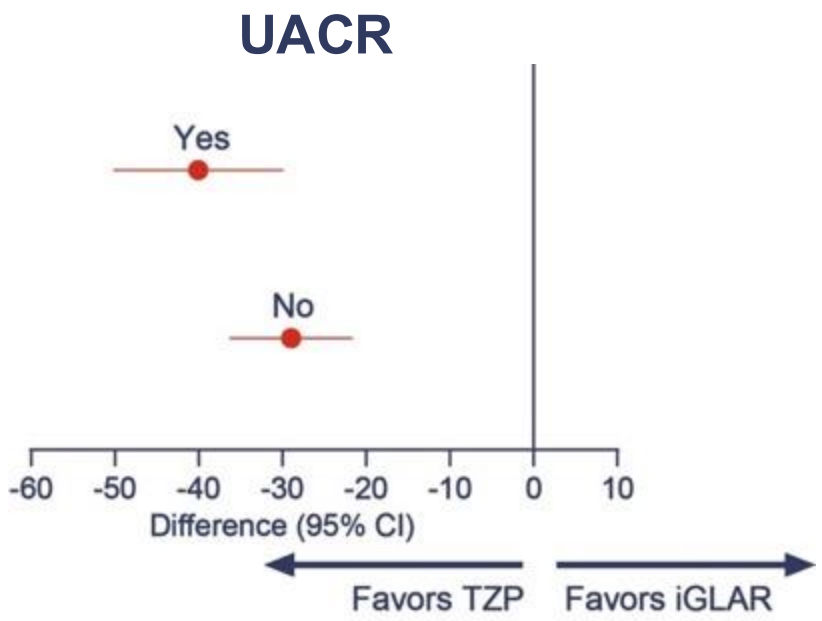
SUMMIT: Tirzepatide migliora gli outcome di scompenso in pazienti HFpEF con e senza T2DM

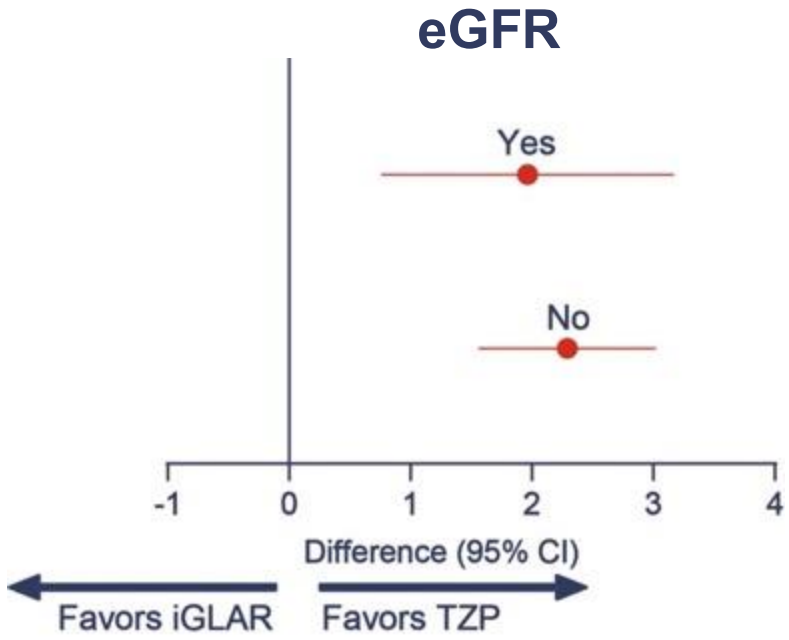
Subgroup	Tirzepatide (no. of patients with event/ no. of patients at risk)	Placebo (no. of patients with event/ no. of patients at risk)	Hazard Ratio for Death from Cardiovascular Causes or a Worsening Heart-Failure Event (95% CI)	KCCQ-CSS Treatment Difference (95% CI)
Age				
<65 yr	13/158	17/166	0.79 (0.38 to 1.64)	6.41 (1.29 to 11.53)
≥65 yr	23/206	39/201	0.53 (0.32 to 0.89)	7.86 (3.45 to 12.25)
Sex				
Female	20/200	29/193	0.66 (0.38 to 1.18)	8.11 (3.50 to 12.72)
Male	16/164	27/174	0.61 (0.33 to 1.13)	5.50 (0.87 to 10.12)
Body-mass index				
<35	12/147	23/148	0.47 (0.23 to 0.95)	4.56 (−0.52 to 9.65)
≥35	24/217	33/219	0.72 (0.43 to 1.23)	8.30 (3.99 to 12.62)
History of type 2 diabetes				
Yes	16/174	28/178	0.58 (0.31 to 1.07)	6.23 (1.77 to 10.70)
No	20/190	28/189	0.66 (0.37 to 1.18)	7.47 (2.67 to 12.26)
HFpEF-ABA score				
<0.8	8/133	12/140	0.68 (0.28 to 1.67)	3.60 (−1.66 to 8.87)
≥0.8	28/231	44/227	0.60 (0.38 to 0.97)	8.91 (4.69 to 13.12)
Recent heart-failure decompensation				
Yes	19/171	24/172	0.75 (0.41 to 1.38)	7.22 (2.33 to 12.11)
No	17/193	32/195	0.52 (0.29 to 0.95)	6.49 (2.03 to 10.95)
Ejection fraction				
<60%	18/141	28/144	0.60 (0.33 to 1.09)	5.30 (−0.12 to 10.73)
≥60%	18/223	28/223	0.60 (0.33 to 1.09)	8.08 (3.97 to 12.19)
NT-proBNP				
<200 pg/ml	11/186	24/197	0.44 (0.22 to 0.90)	6.56 (2.13 to 11.00)
≥200 pg/ml	25/178	32/170	0.77 (0.45 to 1.29)	7.38 (2.37 to 12.40)
KCCQ-CSS				
<Median	20/173	39/192	0.52 (0.30 to 0.90)	9.07 (3.71 to 14.43)
≥Median	16/191	17/174	0.79 (0.40 to 1.56)	4.43 (0.05 to 8.81)
Estimated GFR				
Systolic blood pressure				
<130 mm Hg	18/185	36/189	0.47 (0.27 to 0.83)	7.27 (2.44 to 12.10)
≥130 mm Hg	18/179	20/178	0.90 (0.48 to 1.70)	6.21 (1.64 to 10.77)
Yes	16/131	24/125	0.58 (0.31 to 1.09)	10.10 (4.56 to 15.65)
No	20/233	32/242	0.63 (0.36 to 1.10)	5.22 (1.09 to 9.34)



48% have T2DM at baseline

Tirzepatide riduce l'albuminuria e stabilizza l'eGFR in pazienti con T2DM *indipendentemente dall'uso di SGLT2i*





SGLT2-i use at baseline	N	UACR change (95%CI)	
		TZP	iGLAR
Yes	498	-7.9 (-19.7, 5.7)	55.2 (34.5, 79.0)
No	1488	-10.4 (-19.6, -0.0)	26.6 (13.5, 41.2)

SGLT2-i use at baseline	No. of patients	eGFR slope (mL/min/1.73m²/year)	
		TZP	iGLAR
Yes	498	-1.2 (0.4)	-3.2 (0.4)
No	1488	-1.5 (0.3)	-3.8 (0.3)

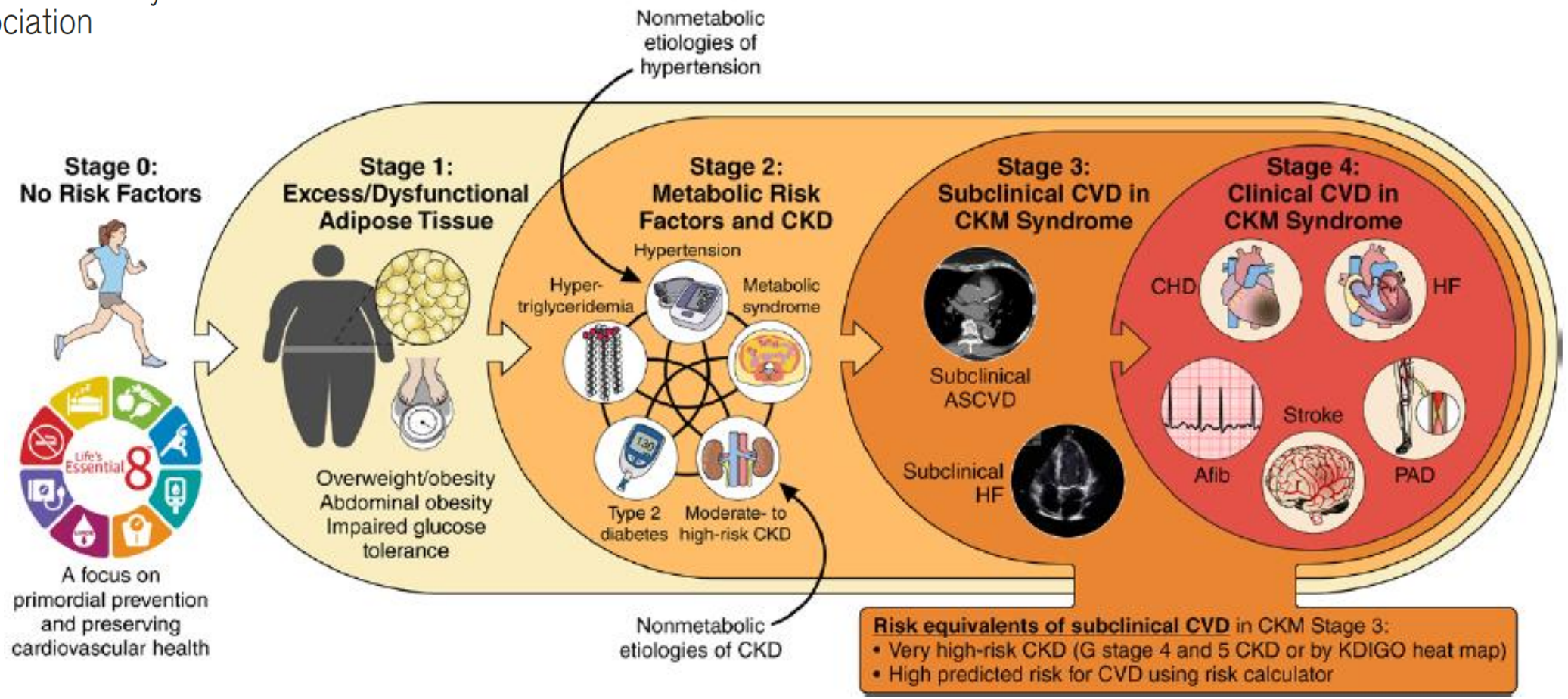
Mean percent changes in log-transformed UACR and changes in eGFR from baseline to end of treatment. Slope data are mean decline (SE) per year and differences between TZP and iGLAR are with 95% CI. CI=confidence interval; eGFR=estimated glomerular filtration rate; iGLAR=insulin glargine; N=number of participants in specified population; TZP=Tirzepatide; SE=standard error; SGLT-2i=sodium-glucose co-transporter 2 inhibitor; UACR=urine albumin-creatinine ratio.

Lancet Diabet Endocrinol 2022;10:774-785

Cardiovascular-Kidney-Metabolic Syndrome

AHA PRESIDENTIAL ADVISORY

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association



Ndumele et al., *Circulation*, 2023

GRAZIE!!!