SICOM & AOCO 2024
SOMS International Conference on Obesity & Metabolism
in conjunction with Asia-Oceania Conference on Obesity
Hosted by SOMS Society for Korean Obesity and Metabolism Studies
Co-Hosted by aoaso Asia Oceania Association for the Study of Obesity
Empowering Health, Inspiring Change: Practical Solutions for Obesity
Date October 24 (Thu)~26 (Sat), 2024
Venue aT Center, Seoul, Republic of Korea (3F Segyero Room & 4F Changjo Room)

Protecting Kidney in Patients with Obesity and Diabetes: Focusing on SGLT2 Inhibitor and GLP-1 Receptor Agonist

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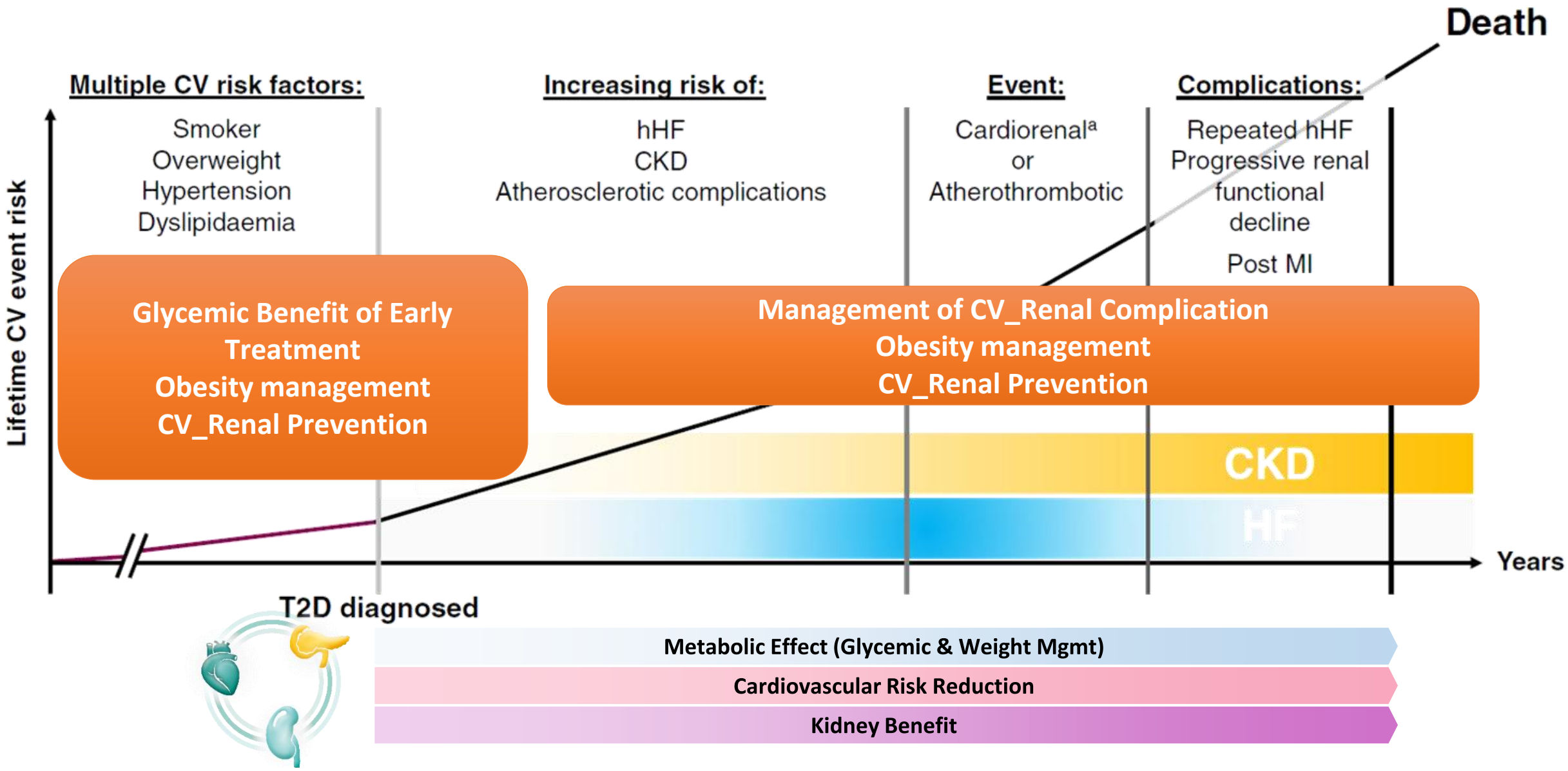
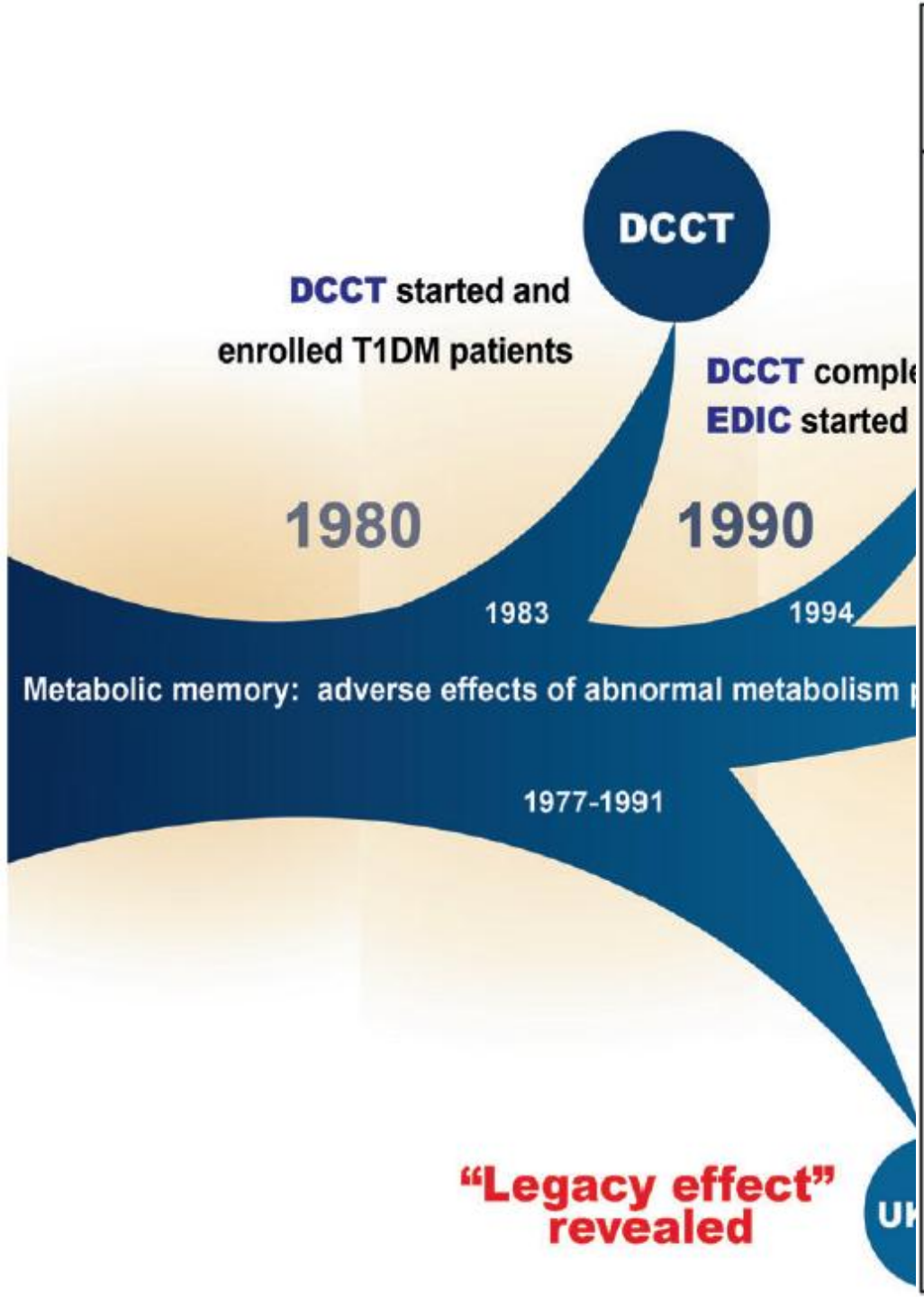
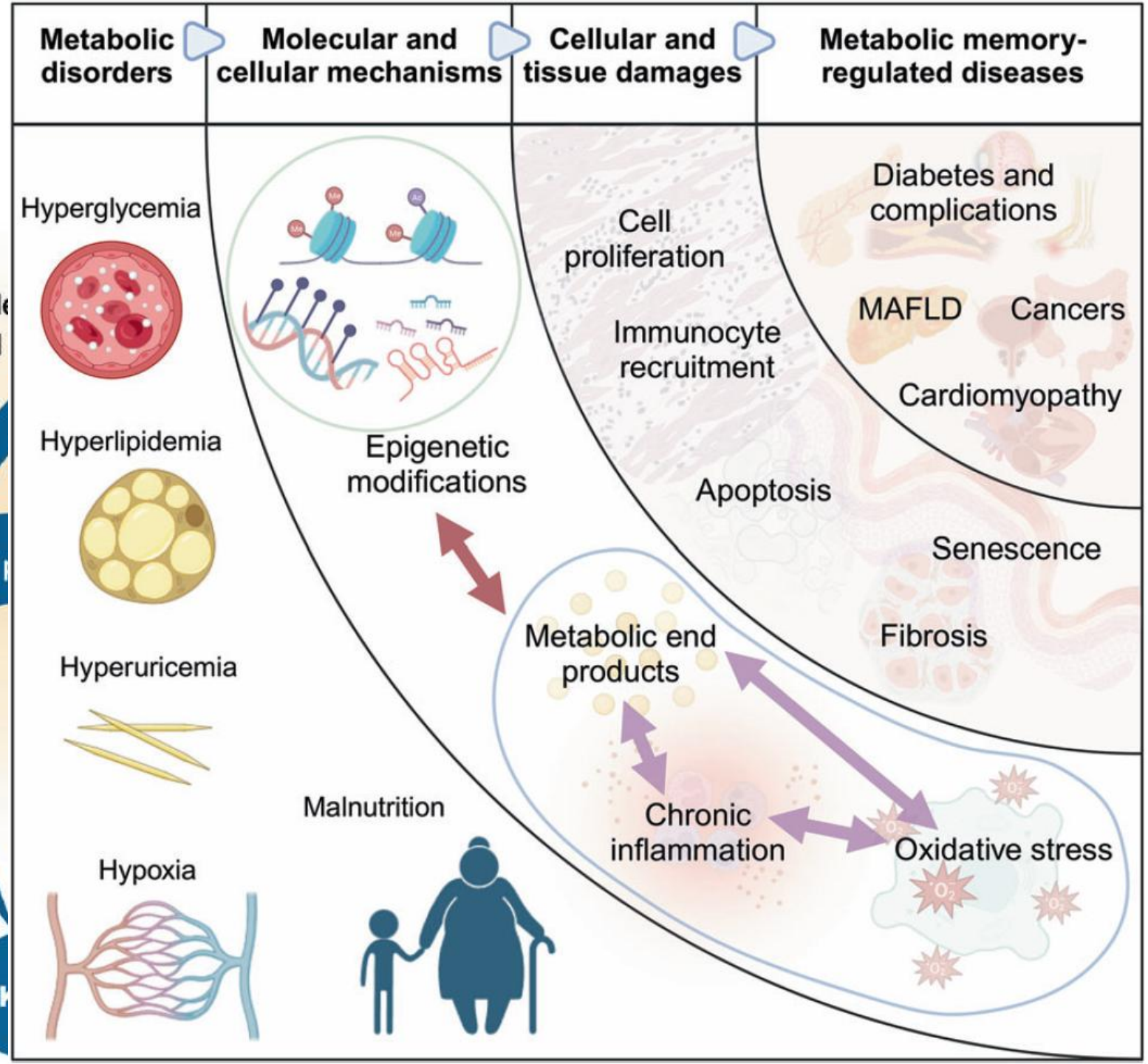
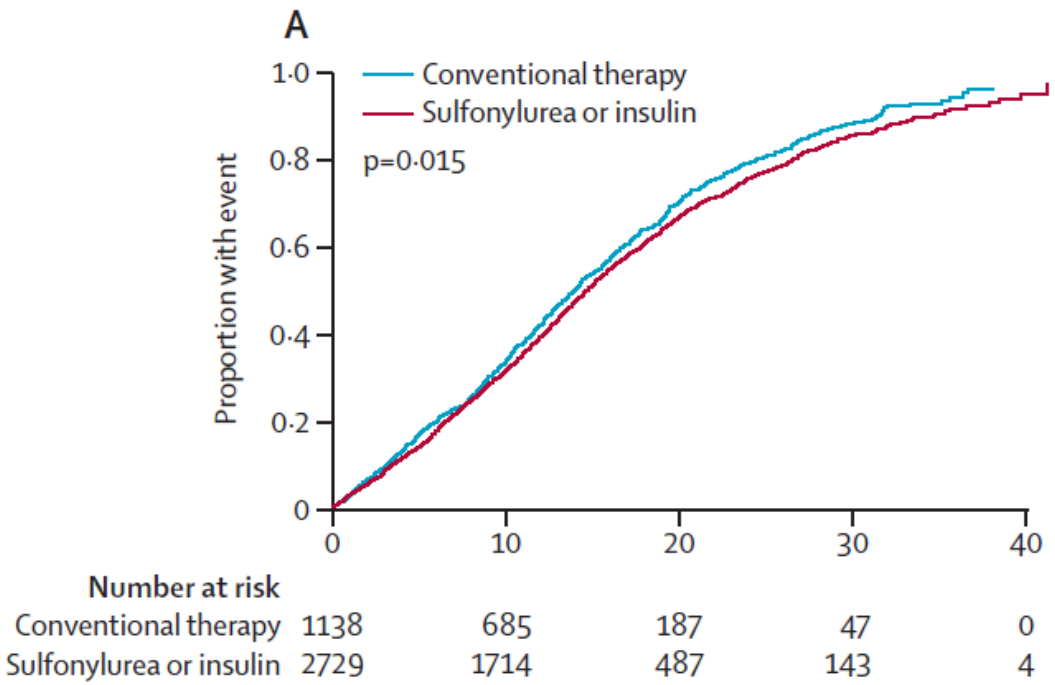
Division of Endocrinology, Daejeon Eulji Medical Center, Eulji University, Republic of Korea

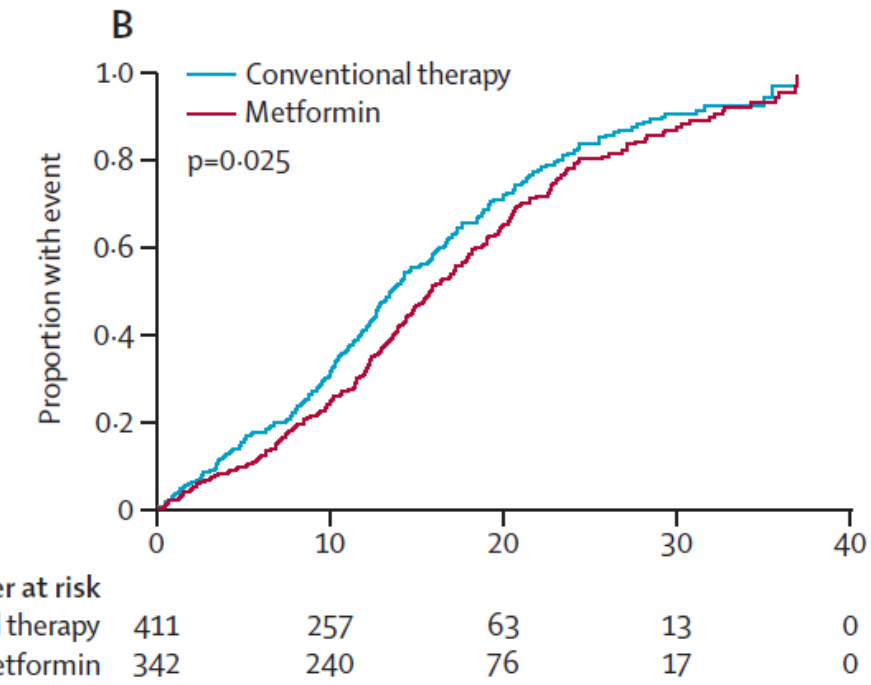
Be proactive for your T2D patient! Cardio-renal-metabolic disease continuum and comprehensive treatment should aim early to target multiple risk factors with SGLT2i



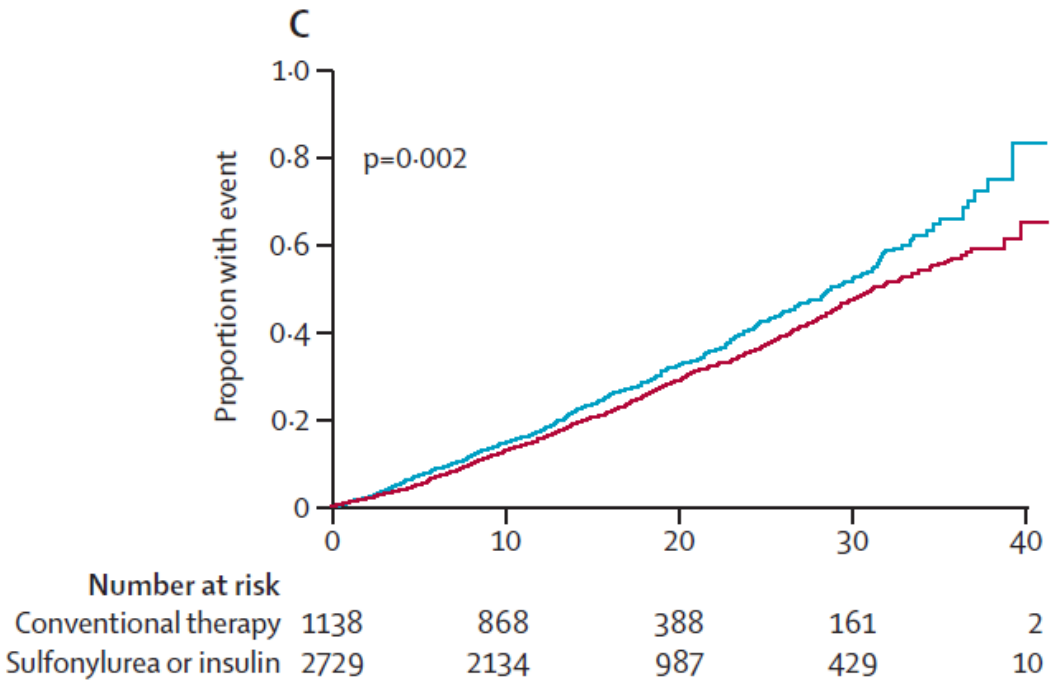

DCCT
DCCT started and
enrolled T1DM patients
DCCT comple
EDIC started
1980
1990
1983
1994
Metabolic memory: adverse effects of abnormal metabolism
1977-1991
"Legacy effect"
revealed

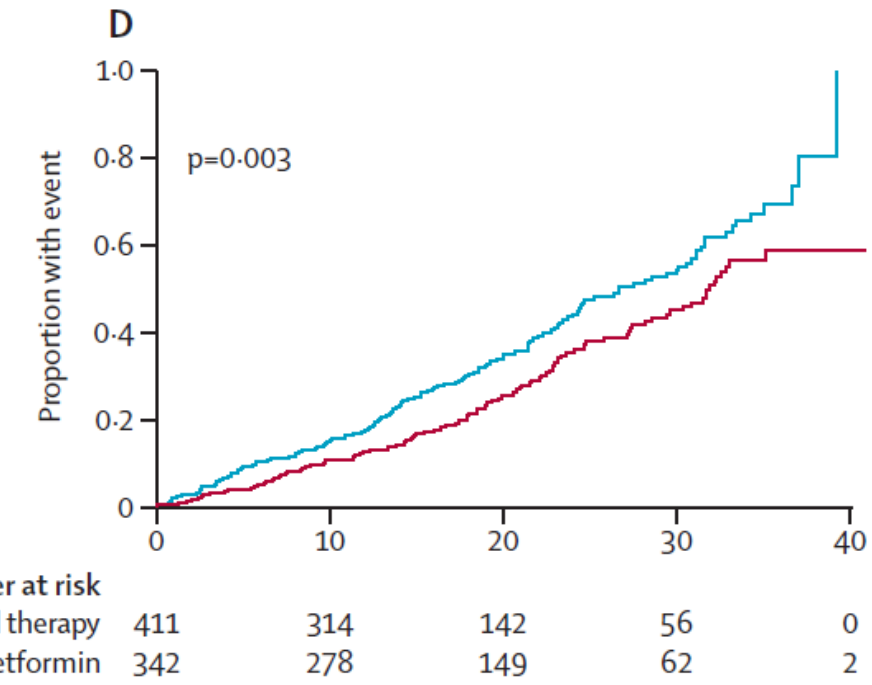

Metabolic disorders
Molecular and cellular mechanisms
Cellular and tissue damages
Metabolic memory-regulated diseases
Hyperglycemia
Hyperlipidemia
Hyperuricemia
Hypoxia
Malnutrition
Epigenetic modifications
Cell proliferation
Immunocyte recruitment
Apoptosis
Metabolic end products
Chronic inflammation
Oxidative stress
Diabetes and complications
MAFLD
Cancers
Cardiomyopathy
Senescence
Fibrosis



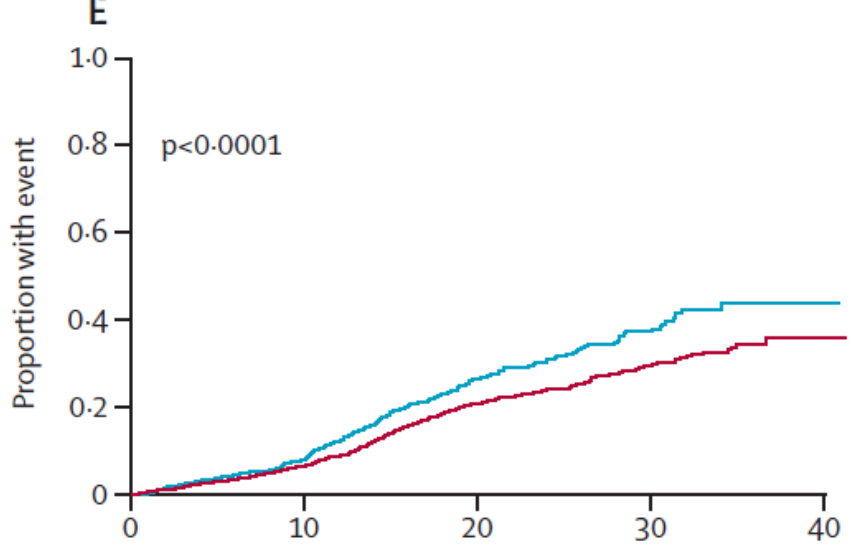


any diabetes-related endpoint

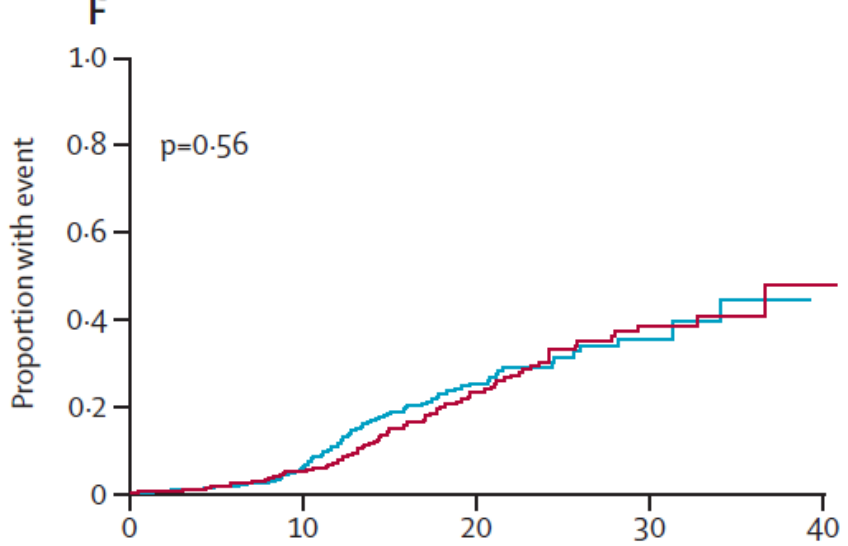




myocardial infarction

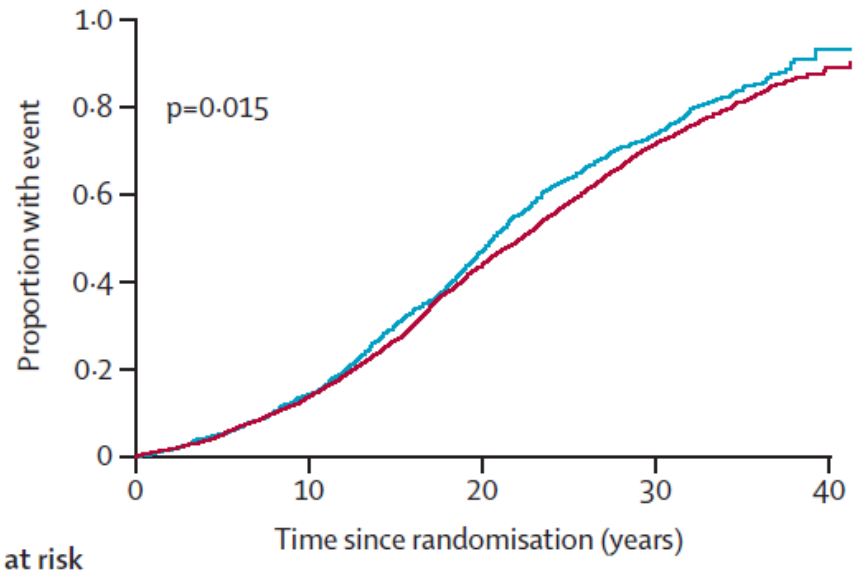


Number at risk					
Conventional therapy	1138	864	334	119	1
Sulfonylurea or insulin	2729	2130	879	349	9

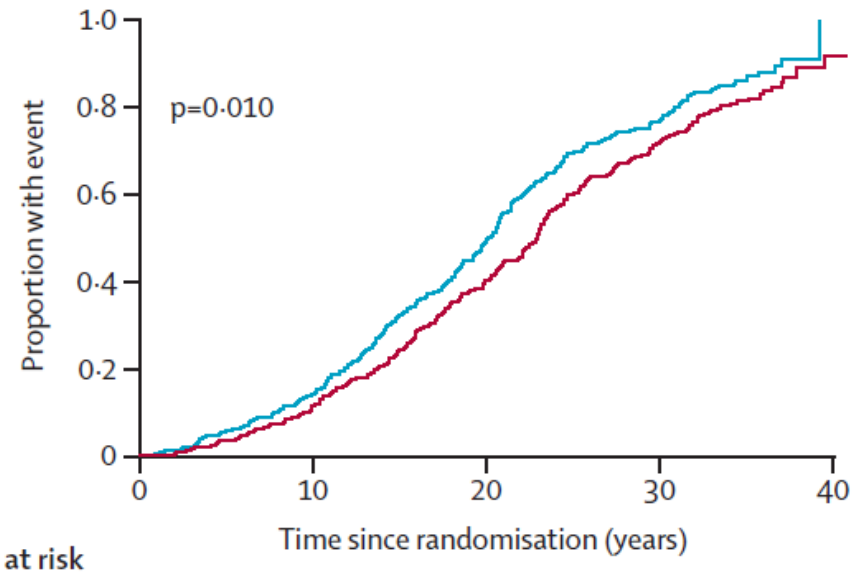


Number at risk					
Conventional therapy	411	324	115	40	0
Metformin	342	282	126	43	2

microvascular disease

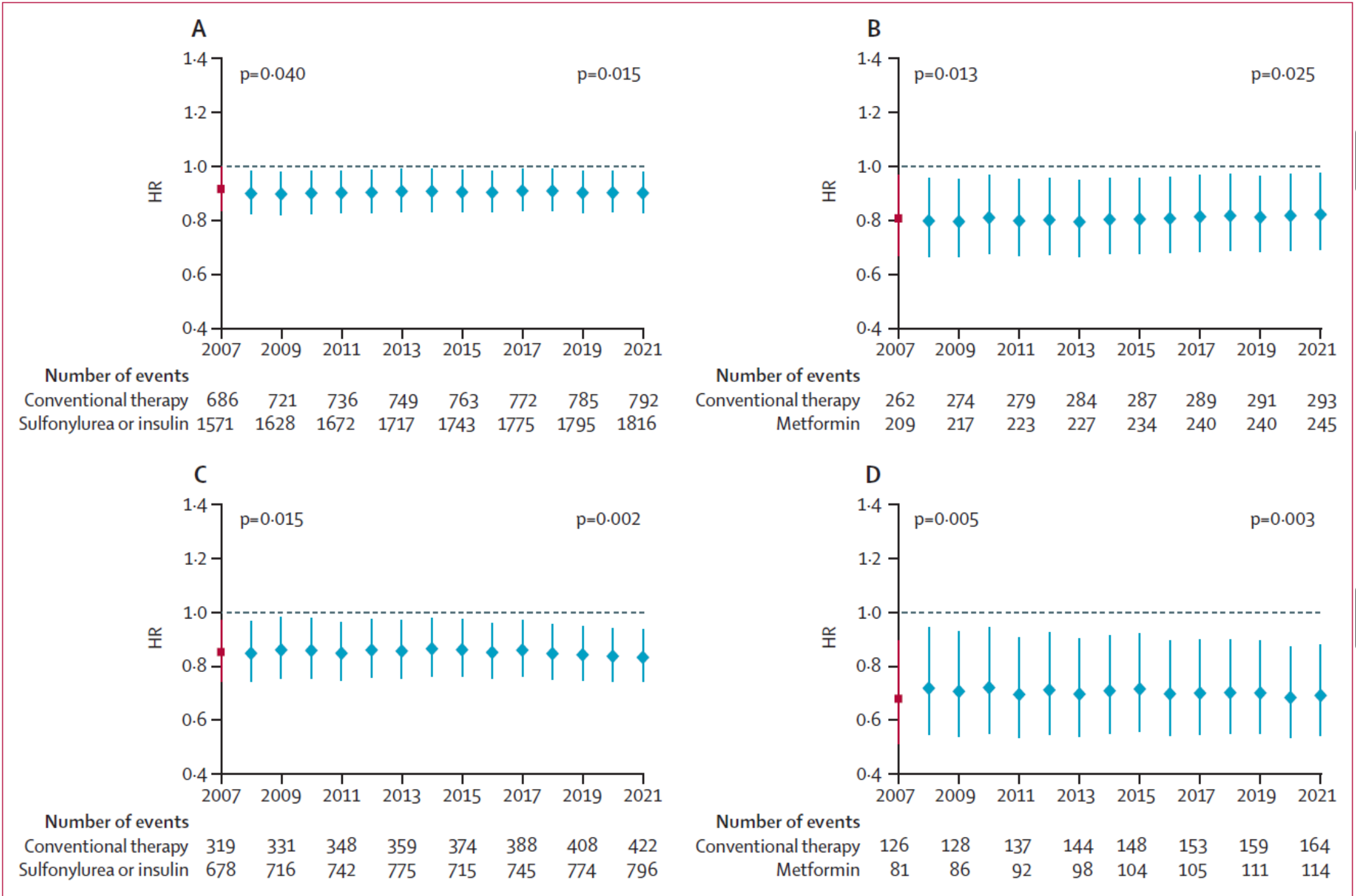


Number at risk					
Conventional therapy	1138	939	442	206	2
Sulfonylurea or insulin	2729	2276	1112	529	14



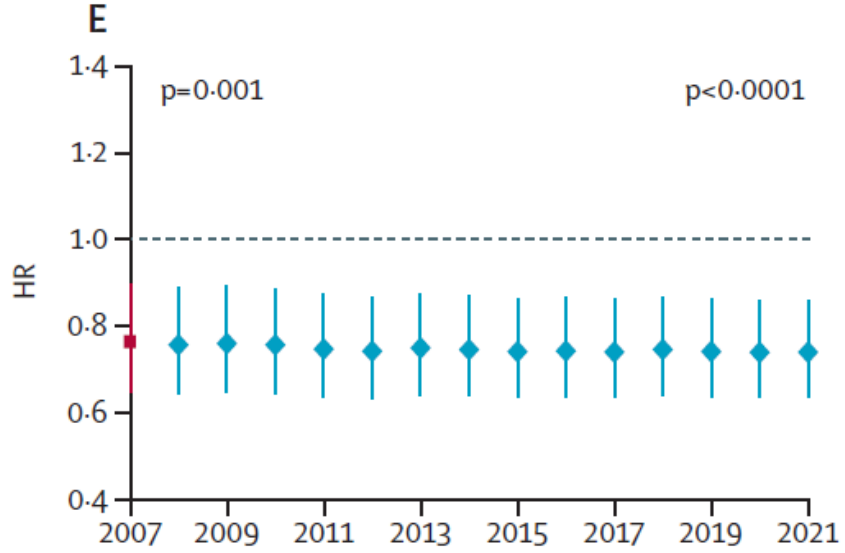
Number at risk					
Conventional therapy	411	345	158	71	0
Metformin	342	296	162	75	3

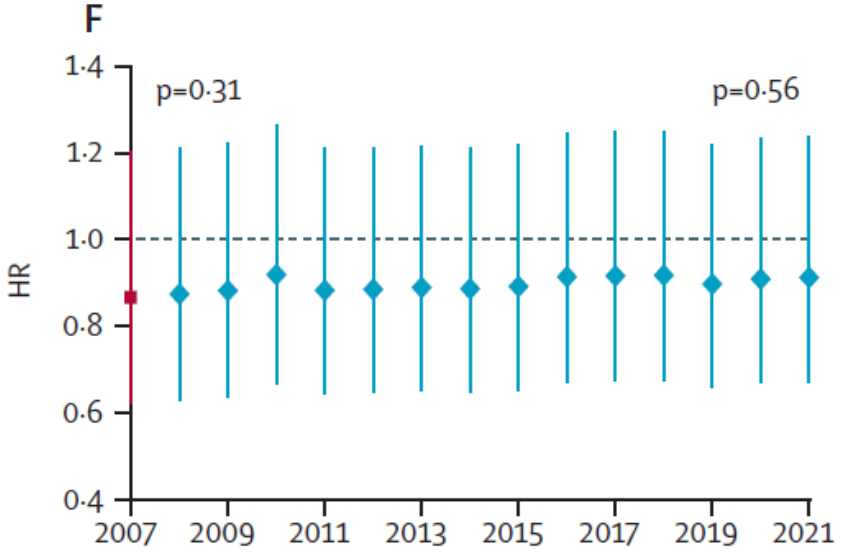
who died from any cause



any diabetes-related endpoint

myocardial infarction

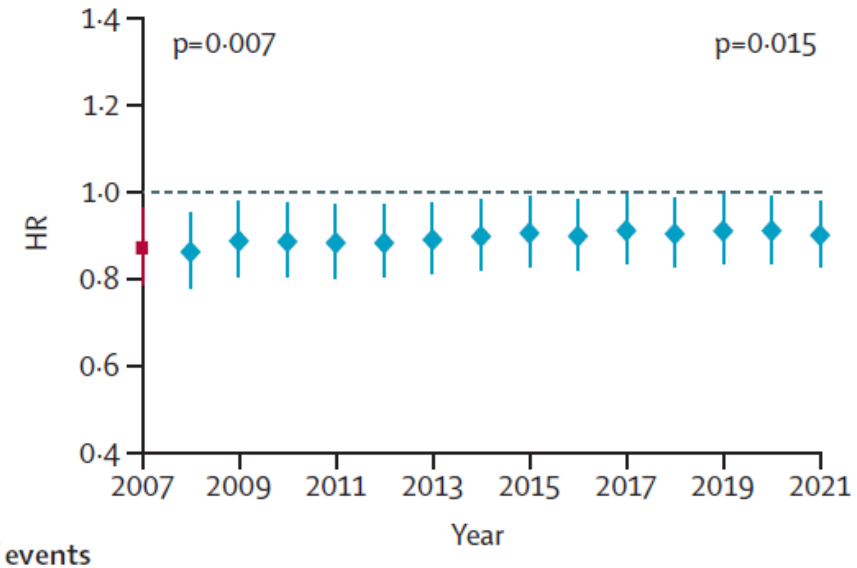


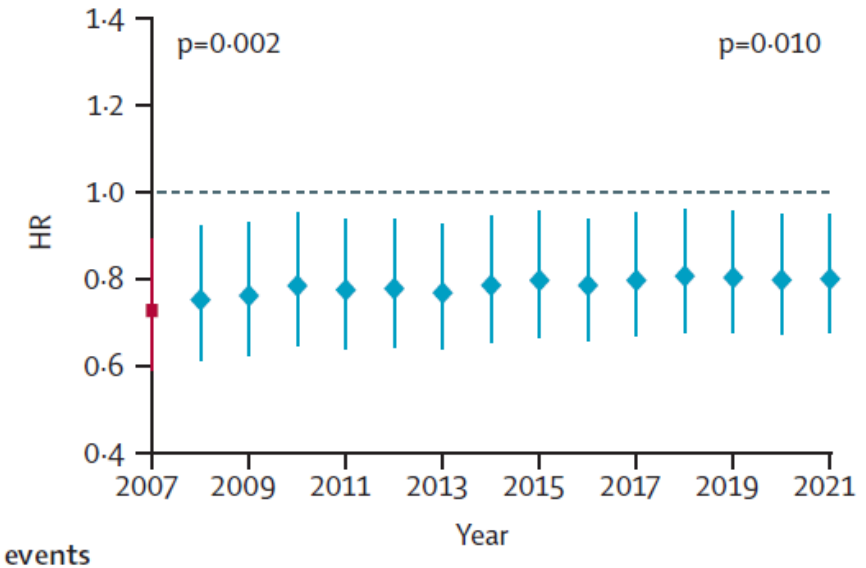


Number of events								
Conventional therapy	222	229	236	242	249	254	259	261
Sulfonylurea or insulin	429	441	447	463	472	482	494	497

Number of events								
Conventional therapy	78	79	74	75	76	76	78	78
Metformin	66	68	73	74	75	77	78	79

microvascular disease





Number of events								
Conventional therapy	537	570	616	648	679	710	740	770
Sulfonylurea or insulin	1163	1270	1372	1458	1561	1642	1714	1778

Number of events								
Conventional therapy	217	229	246	260	270	280	290	301
Metformin	152	169	186	196	212	221	233	243

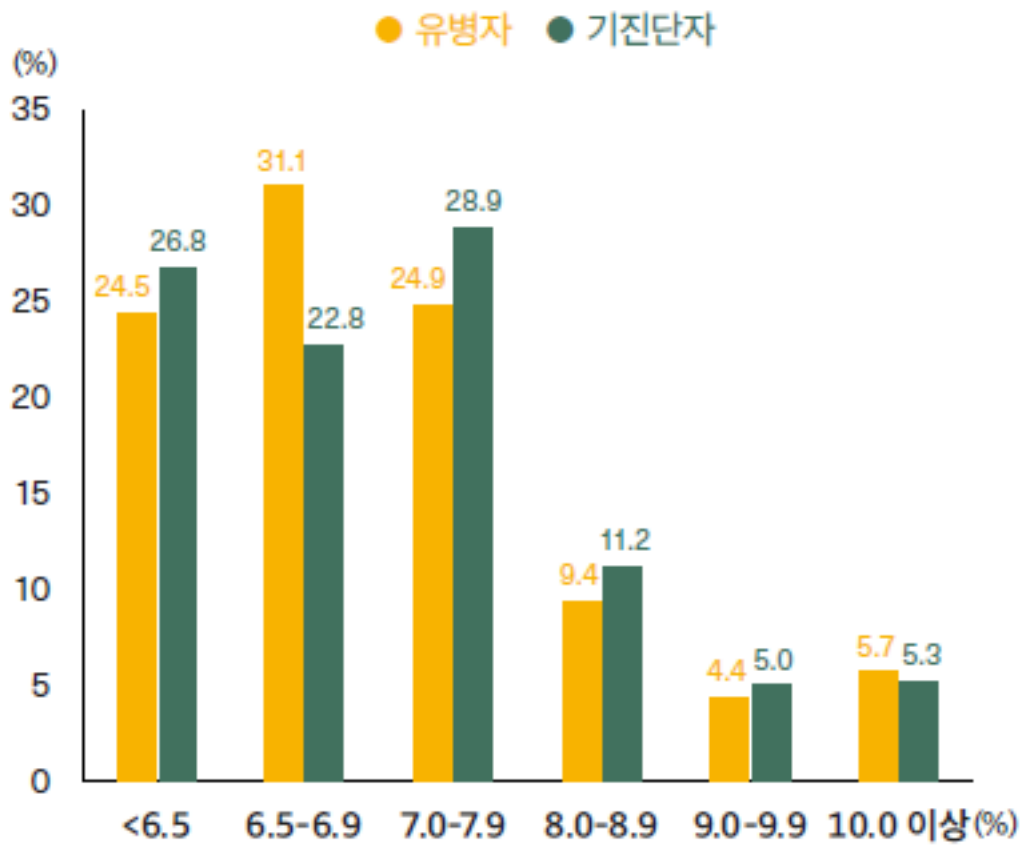
who died from any cause

혈당 조절 상태

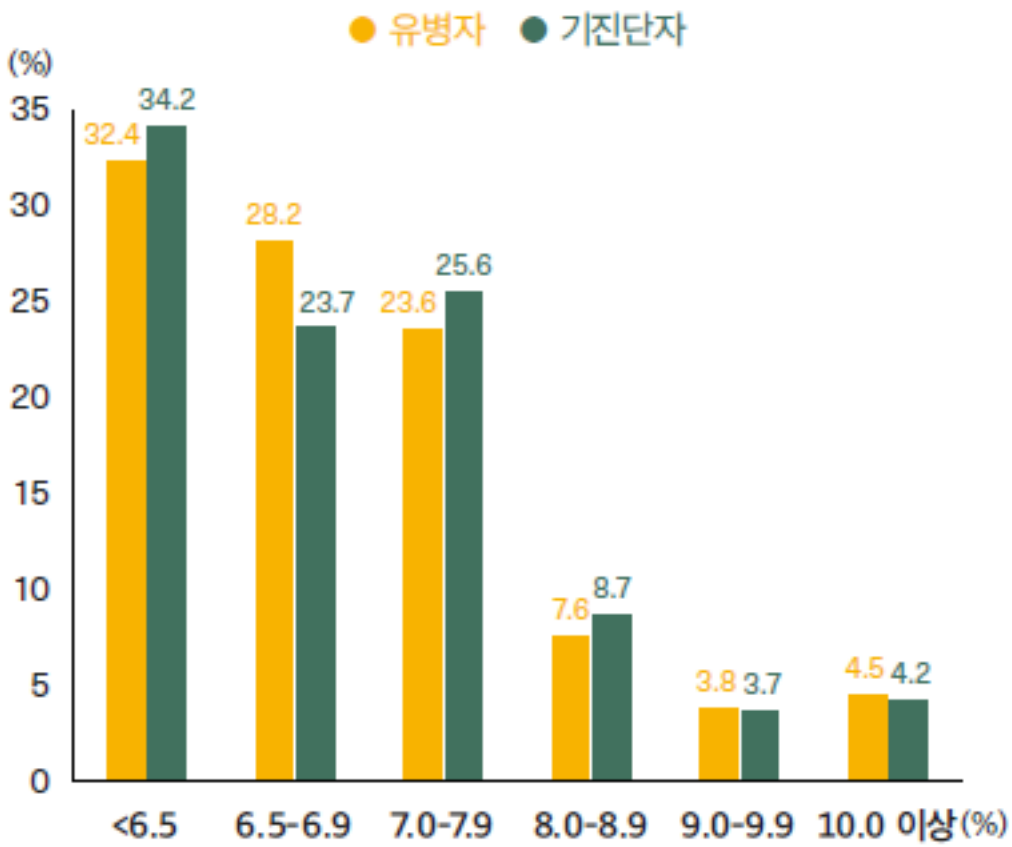
당뇨병 유병자 중 당화혈색소가 6.5% 미만인 경우는 3명 중 1명 (32.4%) 밖에 되지 않았고,
당화혈색소가 7.0% 미만으로 조절되는 경우는 60.6%임.
당화혈색소가 8.0% 이상으로 적극적인 치료가 필요한 경우는 16%임.
2019-2020년 보다 2021-2022년 통합자료에서 기진단자의 혈당조절 상태가 매우 좋아짐.

<6.5%, 기진단자
34.2%

2019-2020년 통합

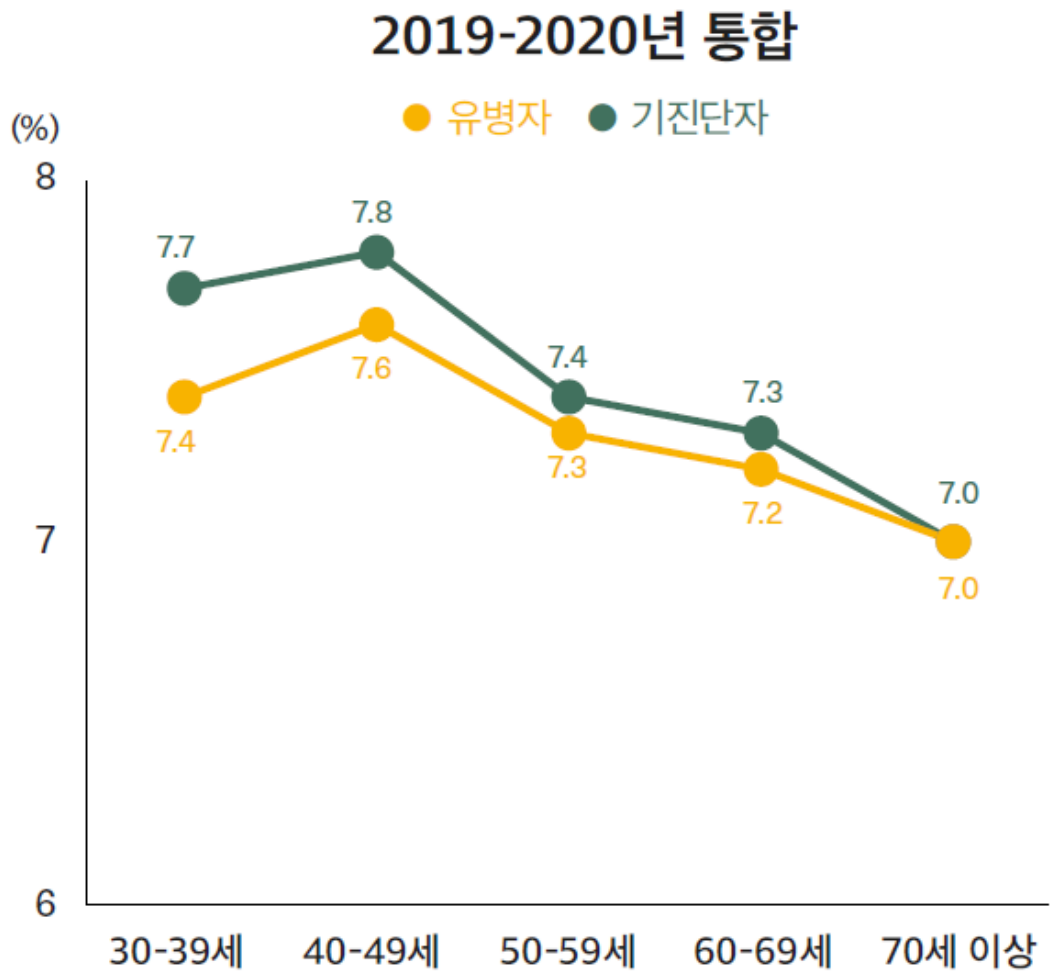


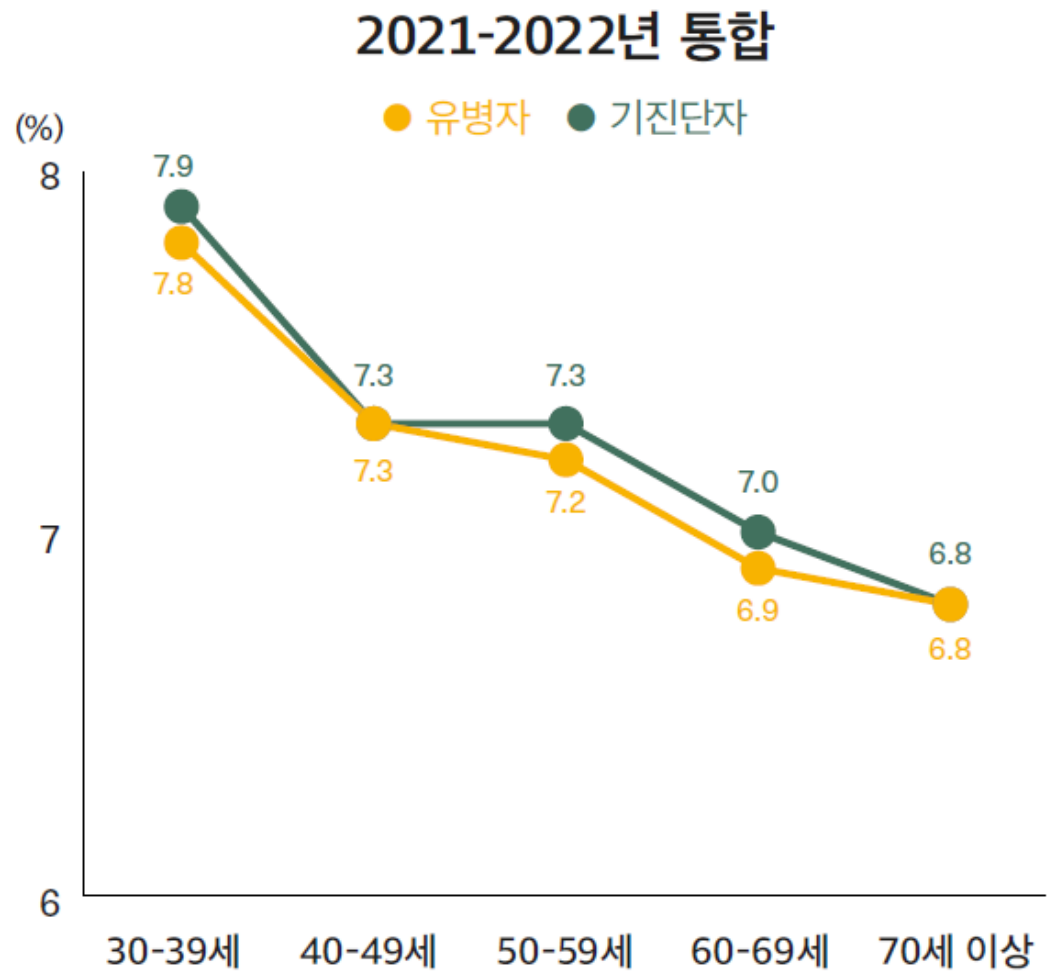
2021-2022년 통합



연령대별 평균 당화혈색소

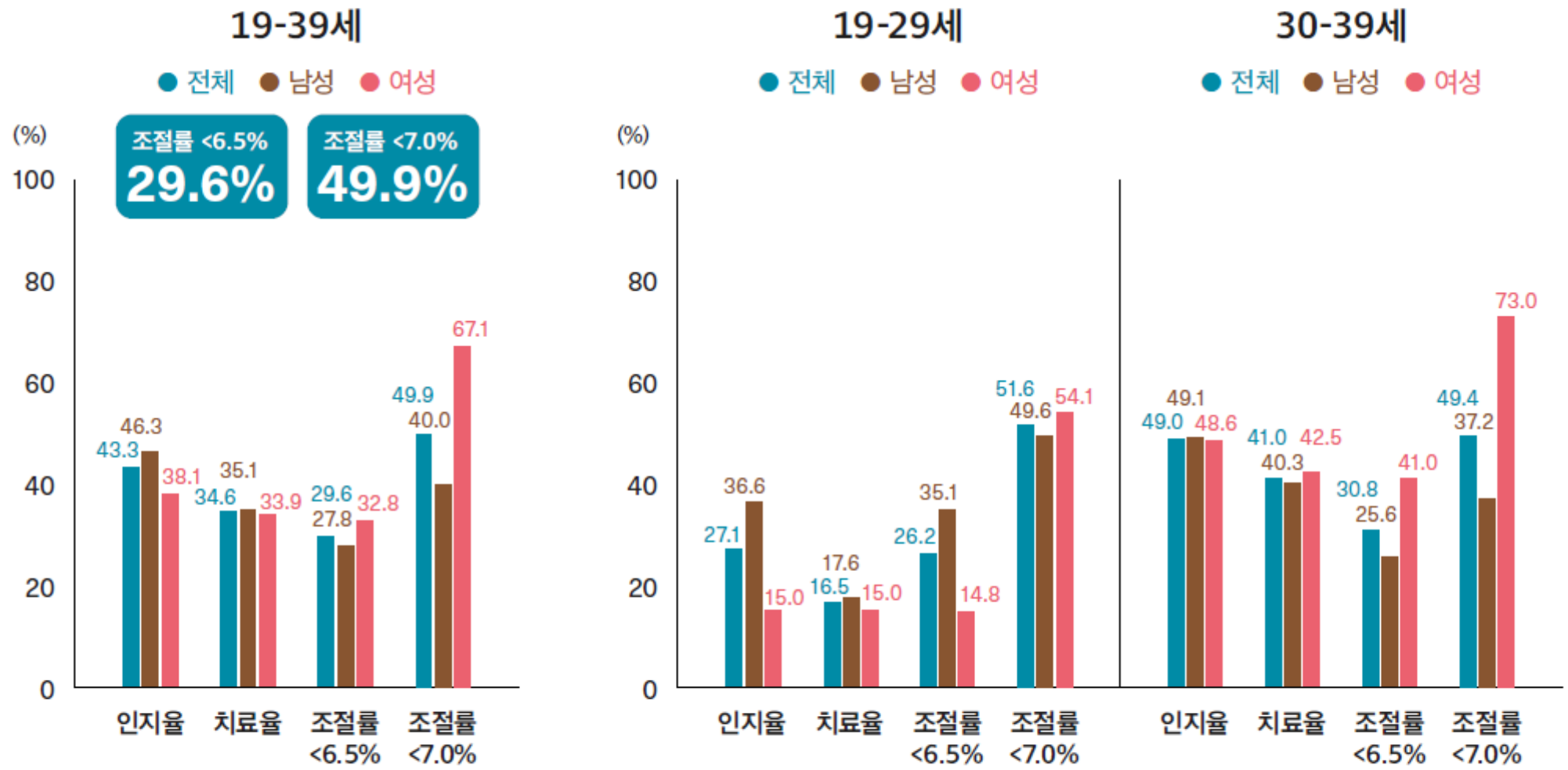
연령대별 평균 당화혈색소는 30-40대에서 다른 연령대에 비해 더 높음.
40대 이후 평균 당화혈색소가 2021-2022년도 향상되었으나 30대에서는 이전에 비해 더 높은 수치를 보임.





청년 당뇨병 관리 수준 (2019-2022년 통합)

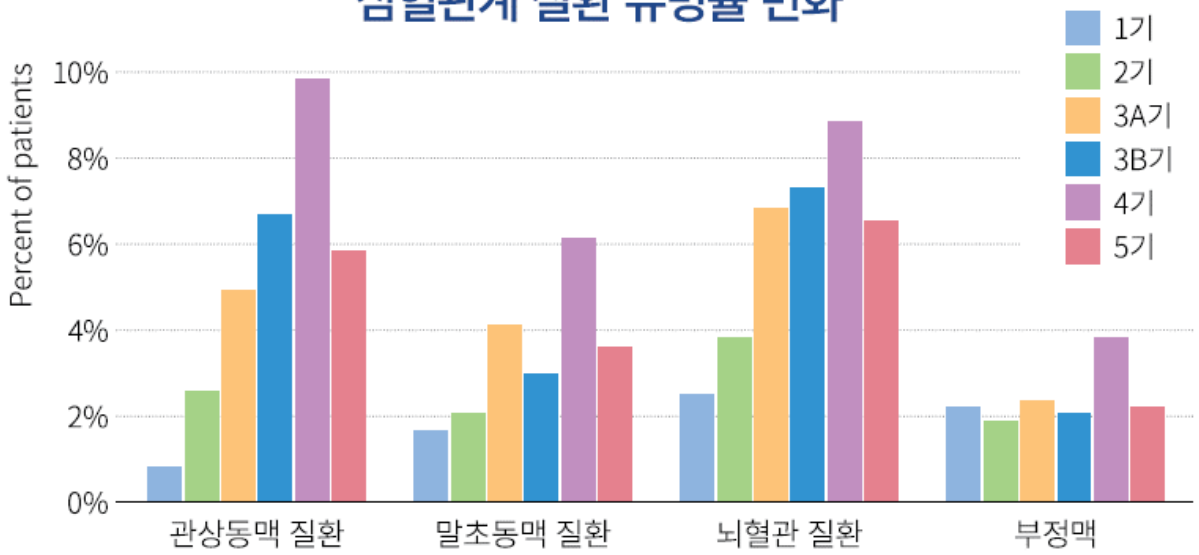
청년당뇨병환자의 43%만이 당뇨병을 진단받았고, 35% 정도만 당뇨병약제로 치료 중임.
당화혈색소 6.5% 기준으로 10명 중 3명만이 혈당조절 목표에 도달함.
청년층 중에서도 20대에서 인지율과 치료율이 매우 낮고, 특히 조절률에서는 남녀간 심한 차이를 보임.



당뇨병 유병자: 공복혈당이 126 mg/dL 이상이거나 의사로부터 당뇨병을 진단받았거나 당뇨병약제로 치료 중이거나 당화혈색소가 6.5% 이상인 경우
당뇨병 인지율: 당뇨병 유병자 (당화혈색소 기준) 중 의사로부터 당뇨병 진단을 받은 분율 / 당뇨병 치료율: 당뇨병 유병자 (당화혈색소 기준) 중 현재 당뇨병약제로 치료 중인 분율
당뇨병 조절률: 당뇨병 유병자 (당화혈색소 기준) 중 당화혈색소가 6.5% 미만인 분율, 당화혈색소가 7.0% 미만인 분율

숫자로 보는
우리나라 만성콩팥병 환자의 심혈관계 질환

만성콩팥병 진행에 따른 심혈관계 질환 유병률 변화



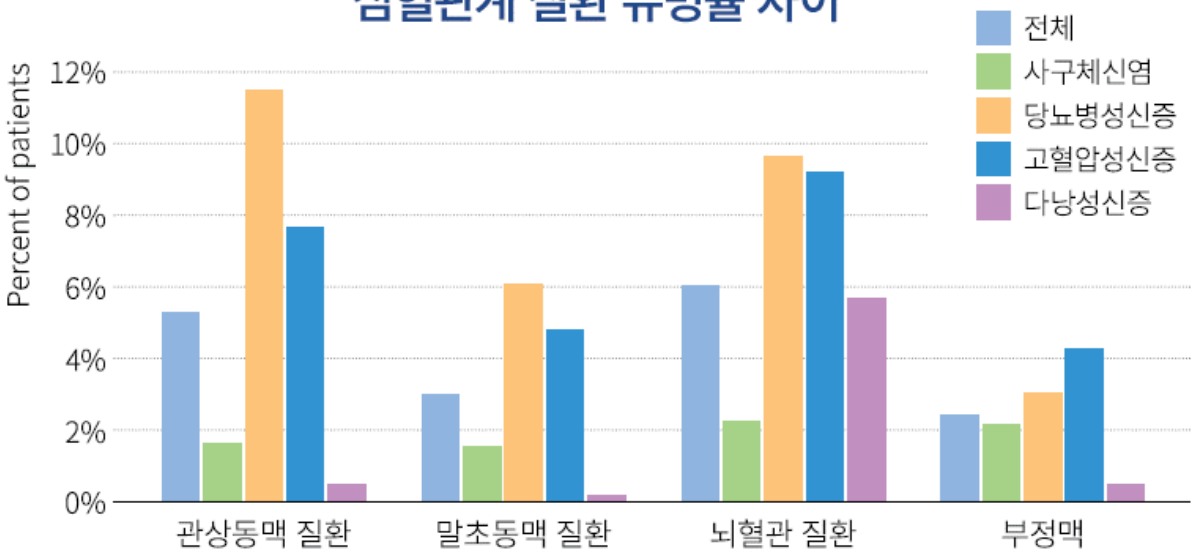
관상동맥 질환

1기 0.8% → 4기 9.8%

뇌혈관 질환

1기 3.8% → 4기 8.8%

만성콩팥병 원인 질환에 따른 심혈관계 질환 유병률 차이



관상동맥 질환

당뇨병성신증 11.6%

다낭성신증 0.5%

뇌혈관 질환

당뇨병성신증 9.8%

사구체신염 2.3%

CKD Screening and Diagnosis

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

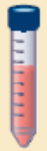
T2D Yearly starting at diagnosis

Both the ADA and KDIGO recommend annual screening of patients with diabetes for CKD

How to screen?

Spot urine ACR

and



eGFR

What to do with a positive result?

Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

Persistence for at least 3 months is therefore required for diagnosis

9. Pharmacologic Approaches to Glycemic Treatment- T2D

NEW **9.19** 심부전 (*p*EF/*r*EF)에는 SGLT2i을 권고 **A**

- 혈당 조절과 심부전 입원 예방

NEW **9.20** CKD*: SGLT2i 반드시 사용 **A**

- CKD 진행 최소화
- CV event/ 심부전 입원 감소

**(eGFR 20 – 60 and/or albuminuria)*

NEW **9.21** T2D+CKD (eGFR<30) 에서 GLP-1 RA는 혈당조절 목적으로 선호됨 **B**

- 저혈당 위험 감소/ CV event 감소

ADA 2024 : 11. Chronic Kidney Disease and Risk Management

- **임신하지 않은 당뇨병 및 고혈압 환자의 약제 선택**

2023

ACEi or ARB 권고

→

2024

ACEi or ARB 권고

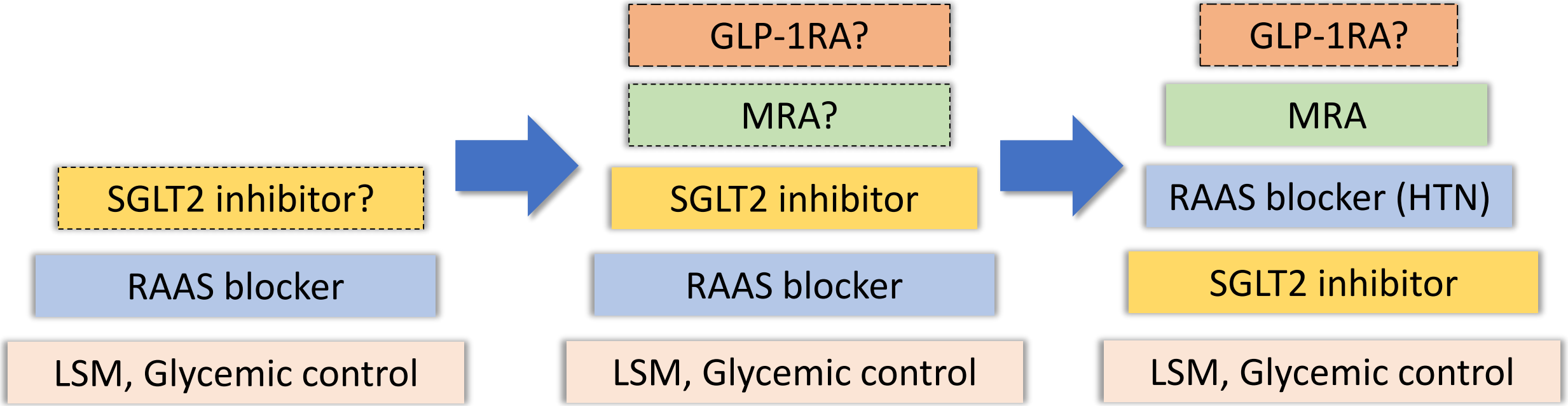
- ACR 30-299 **B**
- ACR ≥300 and/or eGFR <60 mL/min/1.73 m^2 **A** (strongly recommended)

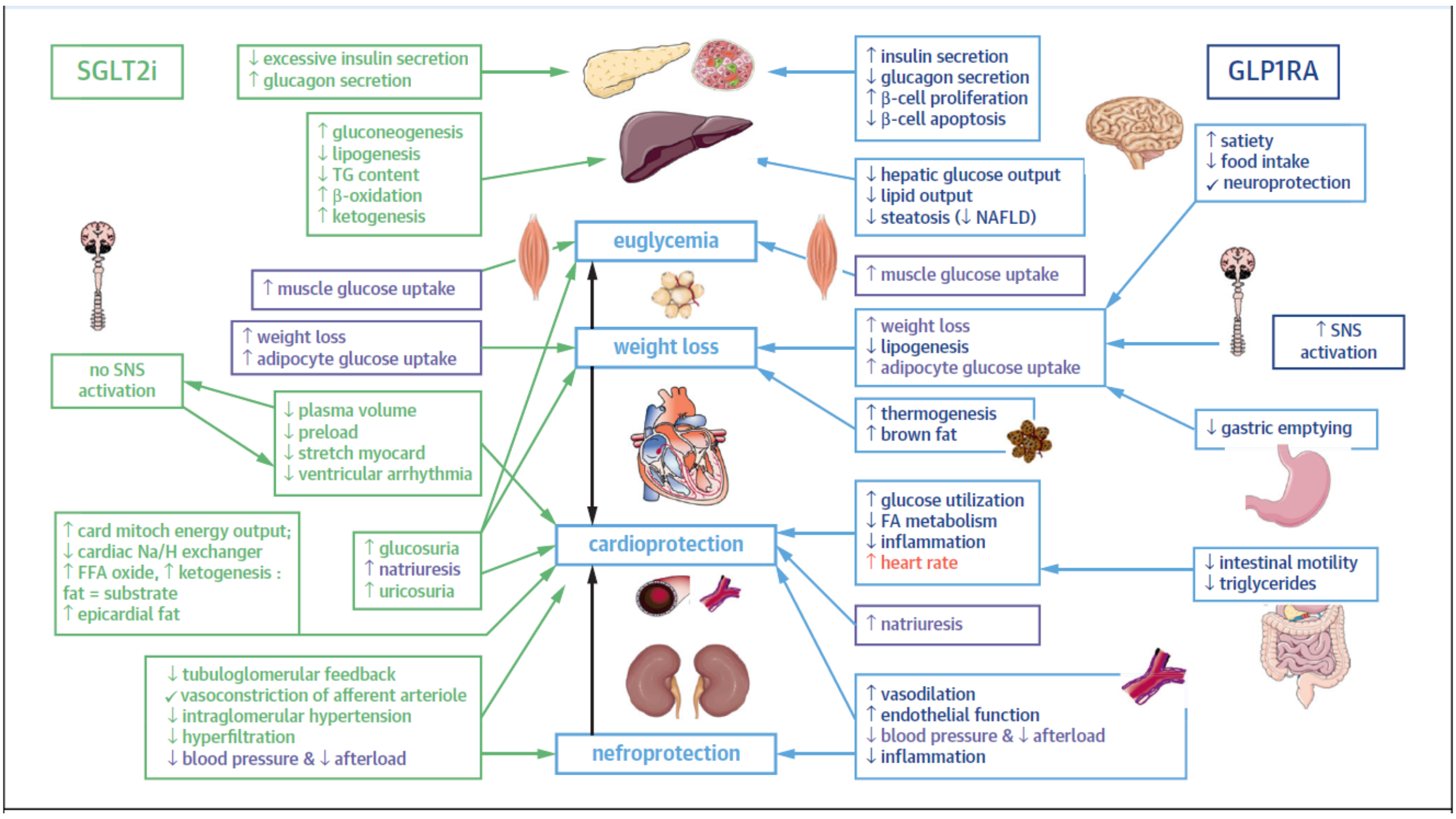
NEW (CKD 진행 및 CV events 감소 목적)

11.7 단백질 섭취

- 투석 전 G3 이상 CKD: 0.8 g/Kg BW 목표 **A**
- 투석 시 1.0–1.2 g/kg/day 섭취를 고려 (should be considered) **B** NEW
  (since protein energy wasting is a major problem in dialysis)

Current DKD management




SGLT2i
↓ excessive insulin secretion
↑ glucagon secretion
↑ gluconeogenesis
↓ lipogenesis
↓ TG content
↑ β-oxidation
↑ ketogenesis
↑ muscle glucose uptake
↑ weight loss
↑ adipocyte glucose uptake
no SNS activation
↓ plasma volume
↓ preload
↓ stretch myocard
↓ ventricular arrhythmia
↑ card mitoch energy output;
↓ cardiac Na/H exchanger
↑ FFA oxide, ↑ ketogenesis :
fat = substrate
↑ epicardial fat
↑ glucosuria
↑ natriuresis
↑ uricosuria
↓ tubuloglomerular feedback
✓ vasoconstriction of afferent arteriole
↓ intraglomerular hypertension
↓ hyperfiltration
↓ blood pressure & ↓ afterload
euglycemia
weight loss
cardioprotection
nefroprotection
↑ insulin secretion
↓ glucagon secretion
↑ β-cell proliferation
↓ β-cell apoptosis
↓ hepatic glucose output
↓ lipid output
↓ steatosis (↓ NAFLD)
↑ muscle glucose uptake
↑ weight loss
↓ lipogenesis
↑ adipocyte glucose uptake
↑ thermogenesis
↑ brown fat
↑ glucose utilization
↓ FA metabolism
↓ inflammation
↑ heart rate
↑ natriuresis
↑ vasodilation
↑ endothelial function
↓ blood pressure & ↓ afterload
↓ inflammation
GLP1RA
↑ satiety
↓ food intake
✓ neuroprotection
↑ SNS activation
↓ gastric emptying
↓ intestinal motility
↓ triglycerides

Nephrol Dial Transplant, 2024, 0, 1–10
https://doi.org/10.1093/ndt/gfae032
Advance access publication date: 6 February 2024

How do SGLT2 inhibitors protect the kidney? A mediation analysis of the EMPA-REG OUTCOME trial

Christoph Wanner [1], Masaomi Nangaku[2], Bettina J. Kraus[3,4,5], Bernard Zinman[6], Michaela Mattheus[7], Stefan Hantel[8], Martin Schumacher[9], Kristin Ohneberg[9], Claudia Schmoor[10] and Silvio E. Inzucchi[11]

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[4]Department of Internal Medicine I, University Hospital Würzburg, Würzburg, Germany
[5]Comprehensive Heart Failure Centre, University of Würzburg, Würzburg, Germany
[6]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada
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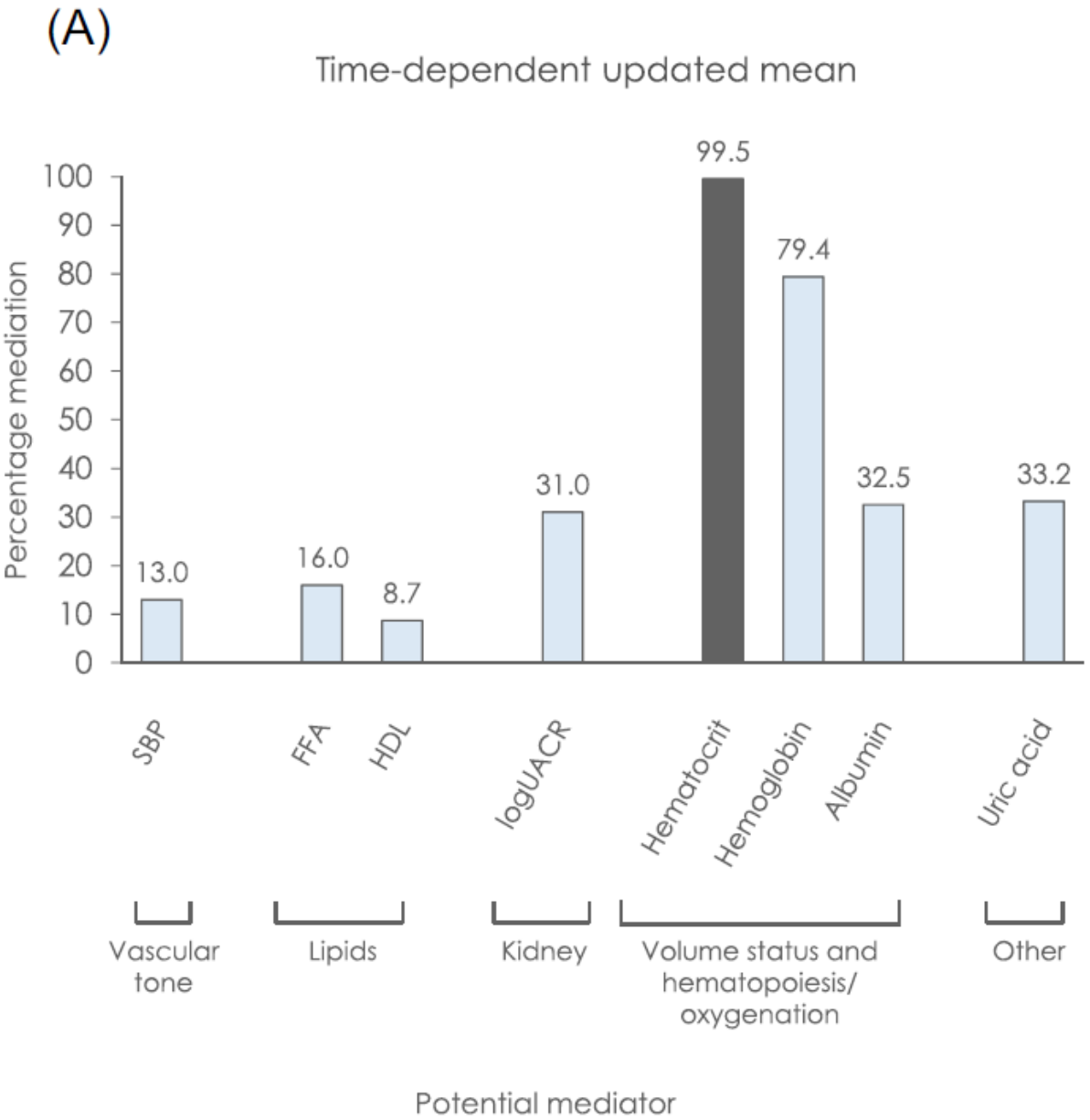
[8]Biostatistics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[9]Institute for Medical Biometry and Statistics and Clinical Trials Unit, Faculty of Medicine, and Medical Center, University of Freiburg, Freiburg, Germany
[10]Clinical Trials Unit, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany
[11]Section of Endocrinology, Yale University School of Medicine, New Haven, CT, USA
Correspondence to: Christoph Wanner; E-mail: wanner_c@ukw.de

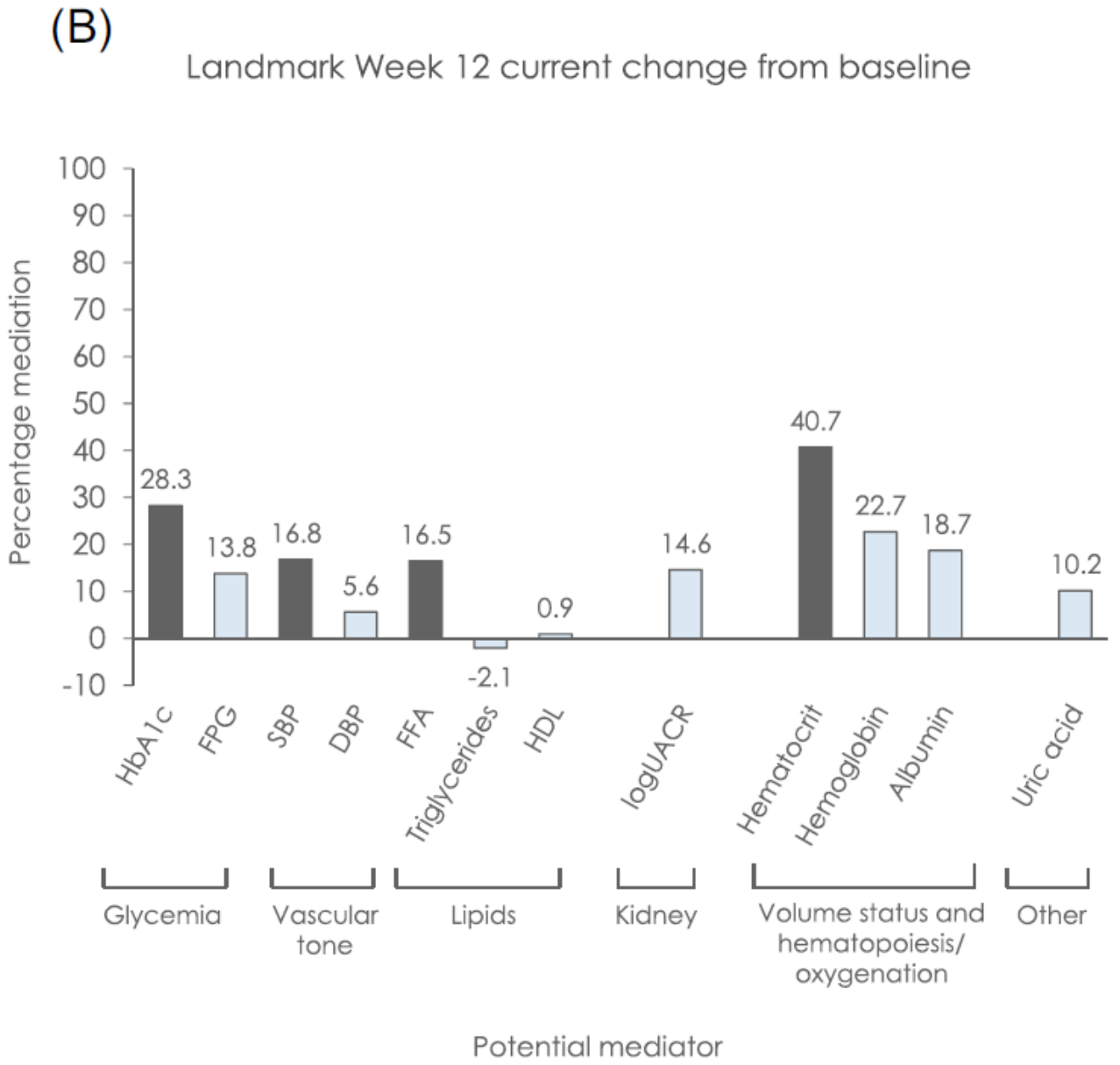
Potential mechanisms underlying the kidney benefits of SGLT2 inhibitors

- Activation of tubuloglomerular feedback (leading to reduction of intraglomerular pressure and glomerular hyperfiltration)
- Reduced proximal tubule metabolic stress and hypoxia
- Reduced mitochondrial damage
- Reduced hyperglycemia-induced inflammation
- Reduced oxidative phosphorylation and less production of reactive oxygen species and angiotensinogen
- Improved oxygenation/reduction in plasma volume

Nephrol Dial Transplant , 2024, 0 , 1–10

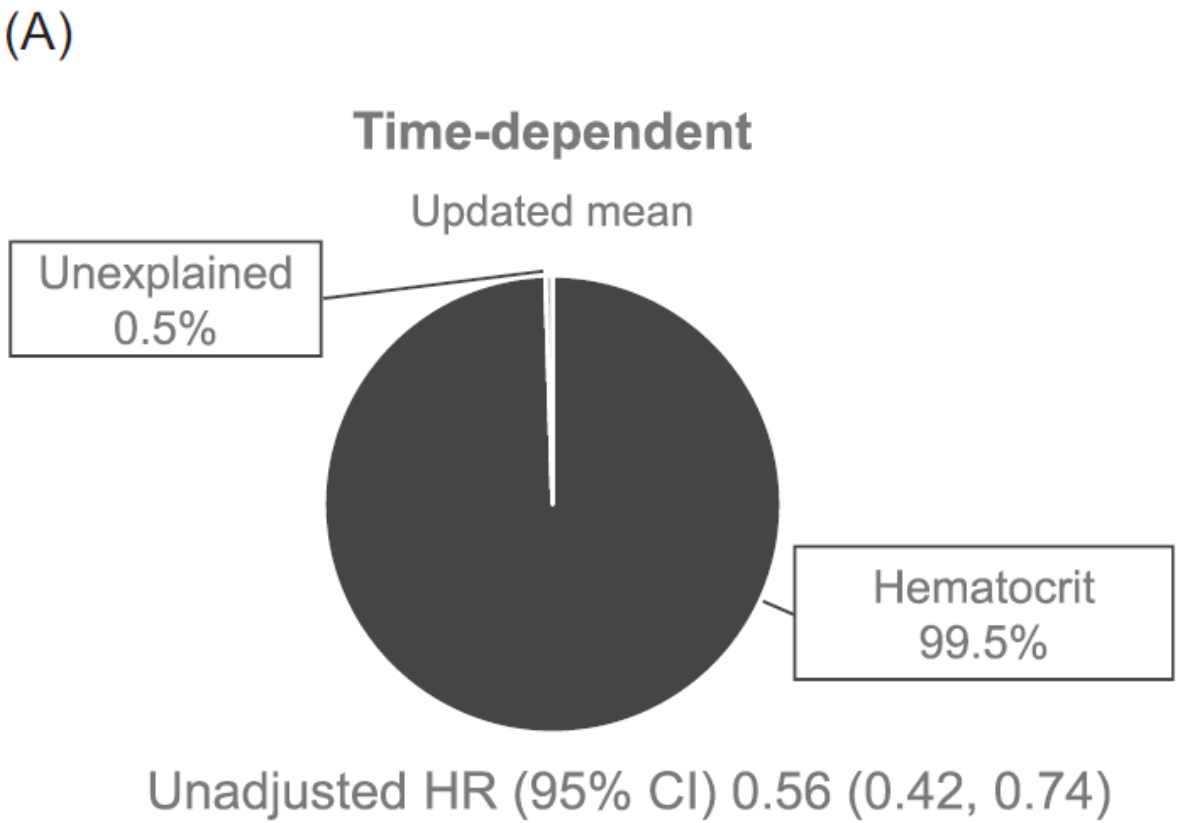
The empagliflozin treatment effect on the composite kidney outcome

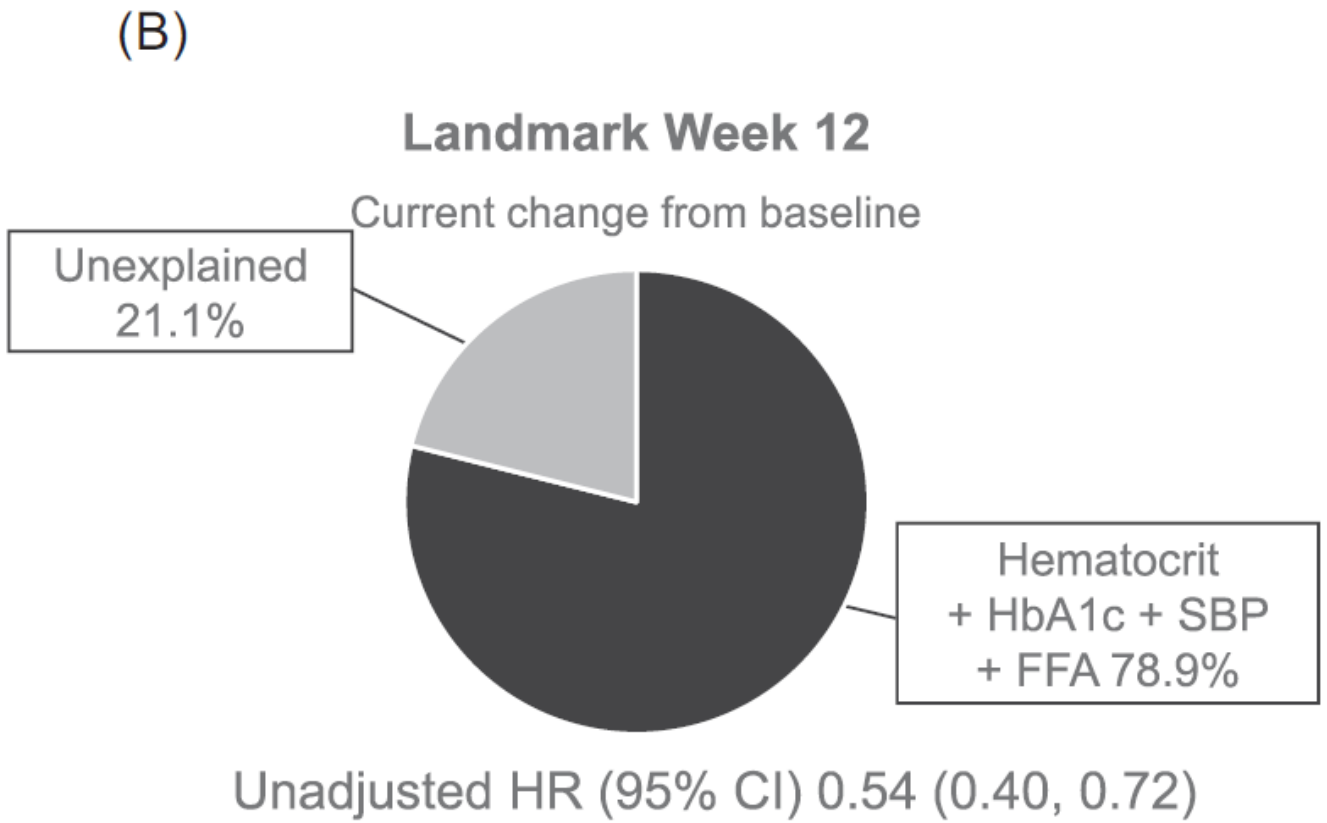




Nephrol Dial Transplant , 2024, 0 , 1–10

Percentage mediation of the empagliflozin treatment effect on the composite kidney outcome





Nephrol Dial Transplant , 2024, 0 , 1–10

NGSP	5.4				
IFCC	36				
eAG	108				
Creatinine	0.73		-	mg/dL	
estimated GFR	84.05		-	-	
Microalbumin(u)/Creatin			-	-	~
Microalbumin(Random Urir	5.9		-	mg/dL	~
Creatinine(Urine)	194.04		-	mg/dL	~
Microalbumin(u)/Creatin	30.41		-	㎍/mg	~ <30
Glucose(Urine)	9		-	mg/dL	~
Lipid battery_Em			-	-	
T-Cholesterol	242		▲	mg/dL	1 ~ 240
HDL-Cholesterol	73		-	mg/dL	28 ~ 84
Triglyceride	82		-	mg/dL	1 ~ 250
LDL-Cholesterol	161		▲	mg/dL	0 ~ 129
CBC_Em			-		
WBC	6.79		-	x10³ /㎕	3.8 ~ 10.5
RBC	4.20		-	백만/㎕	3.5 ~ 5.5
HGB	12.3		-	g/dL	12.0 ~ 16.0
HCT	37.3		-	%	35.0 ~ 47.0
MCV	88.9		-	fl	80.0 ~ 100.0
MCH	29.3		-	pg	26.0 ~ 35.0
MCHC	32.9		-	g/dL	31.0 ~ 37.0
RDW	12.7		-	%	11.0 ~ 16.0
PDW	39.0		-	%	25.0 ~ 65.0
PLT	311		-	x10³ /㎕	130.0 ~ 450.0
Neutrophil	42.3	#2.88	-	%	37 ~ 75
Lymphocyte	49.2	#3.34	-	%	12 ~ 50

51/F
158cm, 64kg
25.63 kg/m²

ACR: 42.58%

Jardiance 25mg Qd

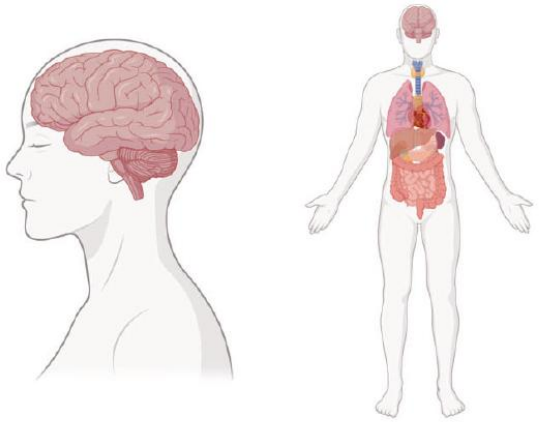
Hct: 7.5%

NGSP	5.5				
IFCC	37				
eAG	111				
Creatinine	0.66		-	mg/dL	
estimated GFR	94.42		-	-	
Microalbumin(u)/Creatin			-	-	~
Microalbumin(Random Urir	2.0		-	mg/dL	~
Creatinine(Urine)	114.57		-	mg/dL	~
Microalbumin(u)/Creatin	17.46		-	㎍/mg	~ <30
Glucose(Urine)	3658		-	mg/dL	~
Lipid battery_Em			-	-	
T-Cholesterol	144		-	mg/dL	1 ~ 240
HDL-Cholesterol	63		-	mg/dL	28 ~ 84
Triglyceride	65		-	mg/dL	1 ~ 250
LDL-Cholesterol	61		-	mg/dL	0 ~ 129
CBC_Em			-		
WBC	6.23		-	x10³ /㎕	3.8 ~ 10.5
RBC	4.56		-	백만/㎕	3.5 ~ 5.5
HGB	13.2		-	g/dL	12.0 ~ 16.0
HCT	40.1		-	%	35.0 ~ 47.0
MCV	87.8		-	fl	80.0 ~ 100.0
MCH	28.9		-	pg	26.0 ~ 35.0
MCHC	32.9		-	g/dL	31.0 ~ 37.0
RDW	13.0		-	%	11.0 ~ 16.0
PDW	40.2		-	%	25.0 ~ 65.0
PLT	303		-	x10³ /㎕	130.0 ~ 450.0
Neutrophil	47.0	#2.93	-	%	37 ~ 75
Lymphocyte	43.5	#2.71	-	%	12 ~ 50

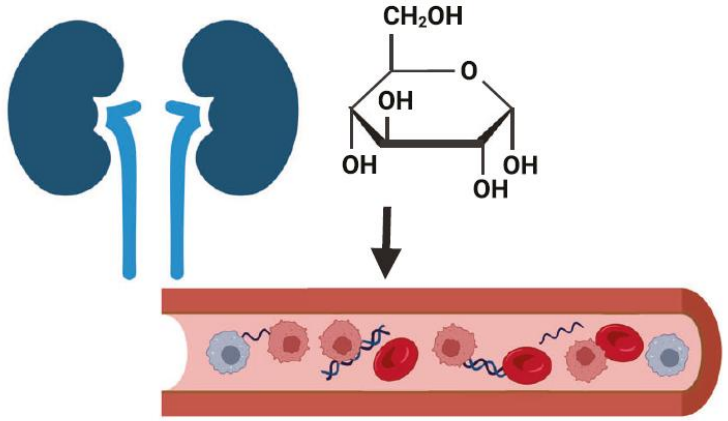
51/F
158cm, 63.2kg
25.34 kg/m²

The relationship between SGLT2 and systemic blood pressure regulation

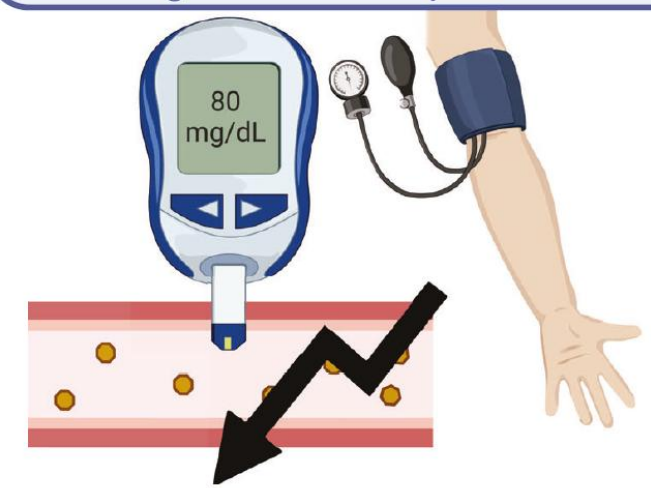
1 SGLT2 is found in various parts of the body and brain.



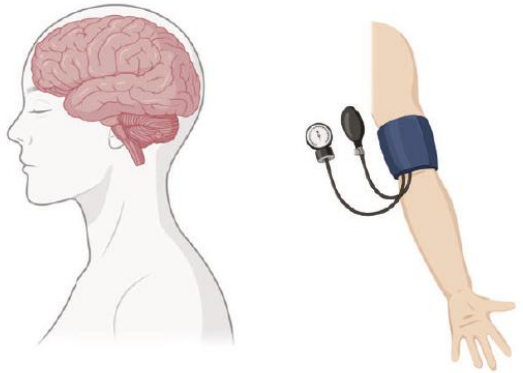
2 SGLT2 in the kidney reabsorbs glucose into the bloodstream.



3 SGLT2 inhibitors decrease blood sugar and blood pressure.

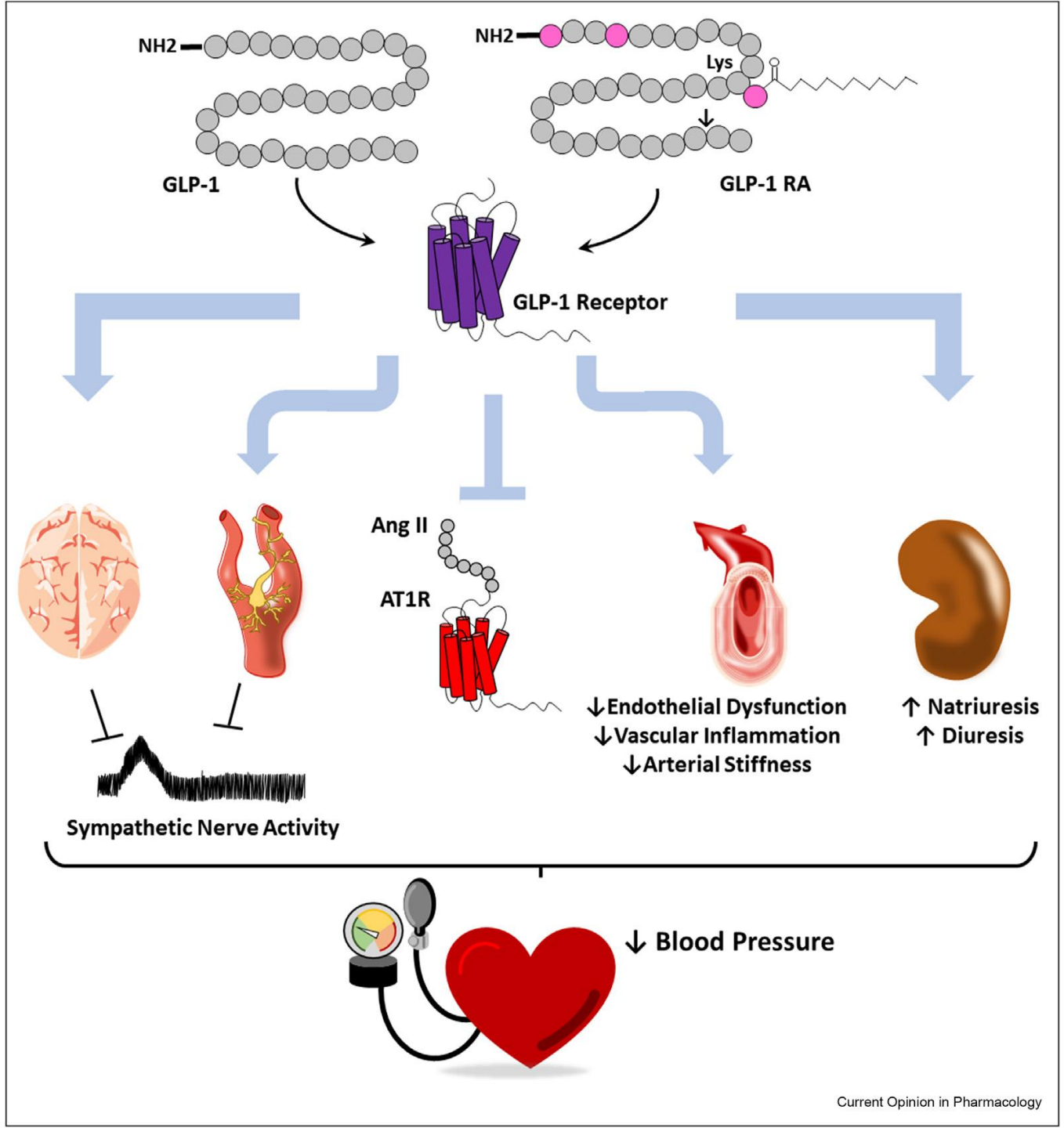


4 The role of SGLT2 in the brain may also influence blood pressure.



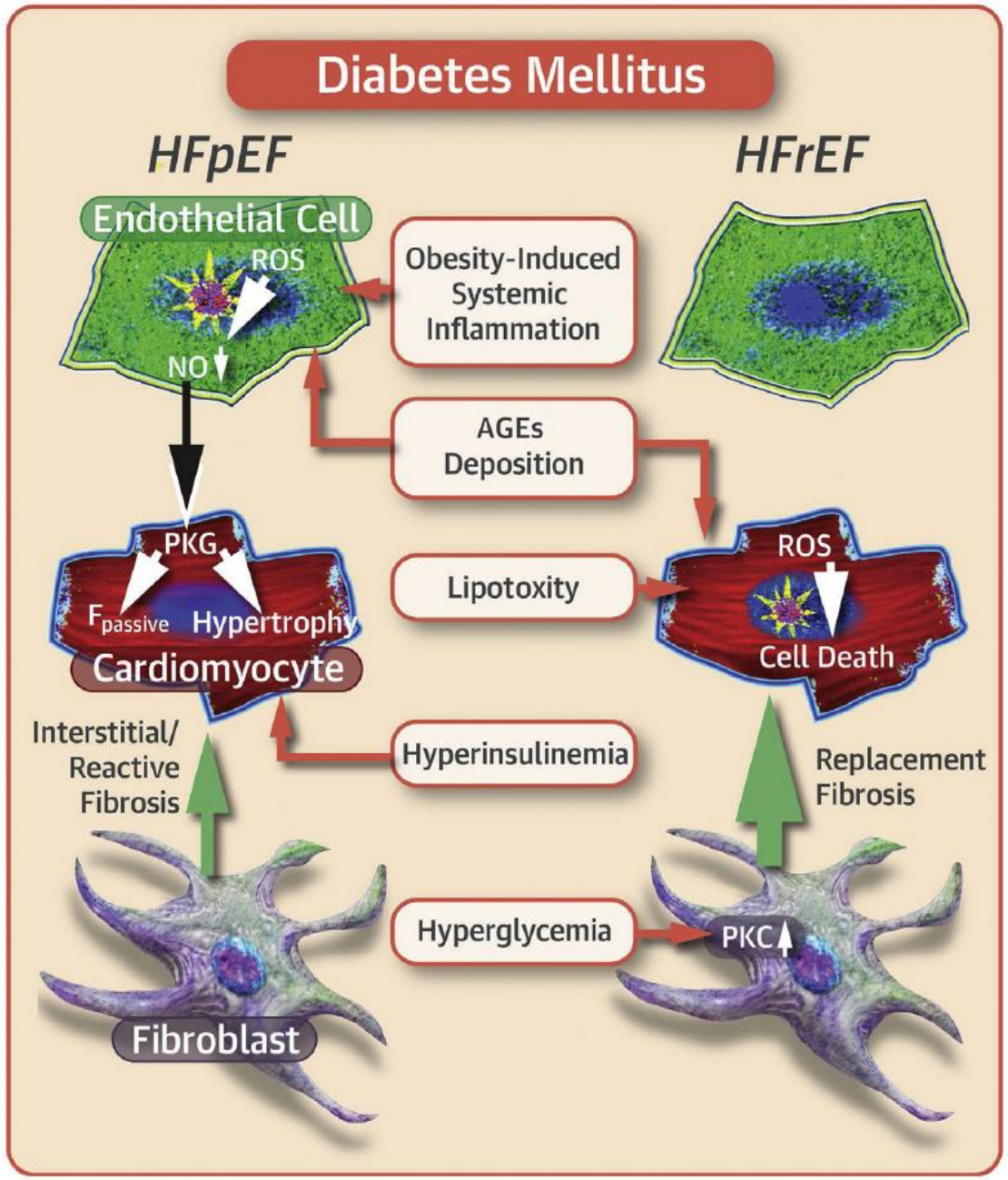
Hypertension Research (2024) 47:2094–2103

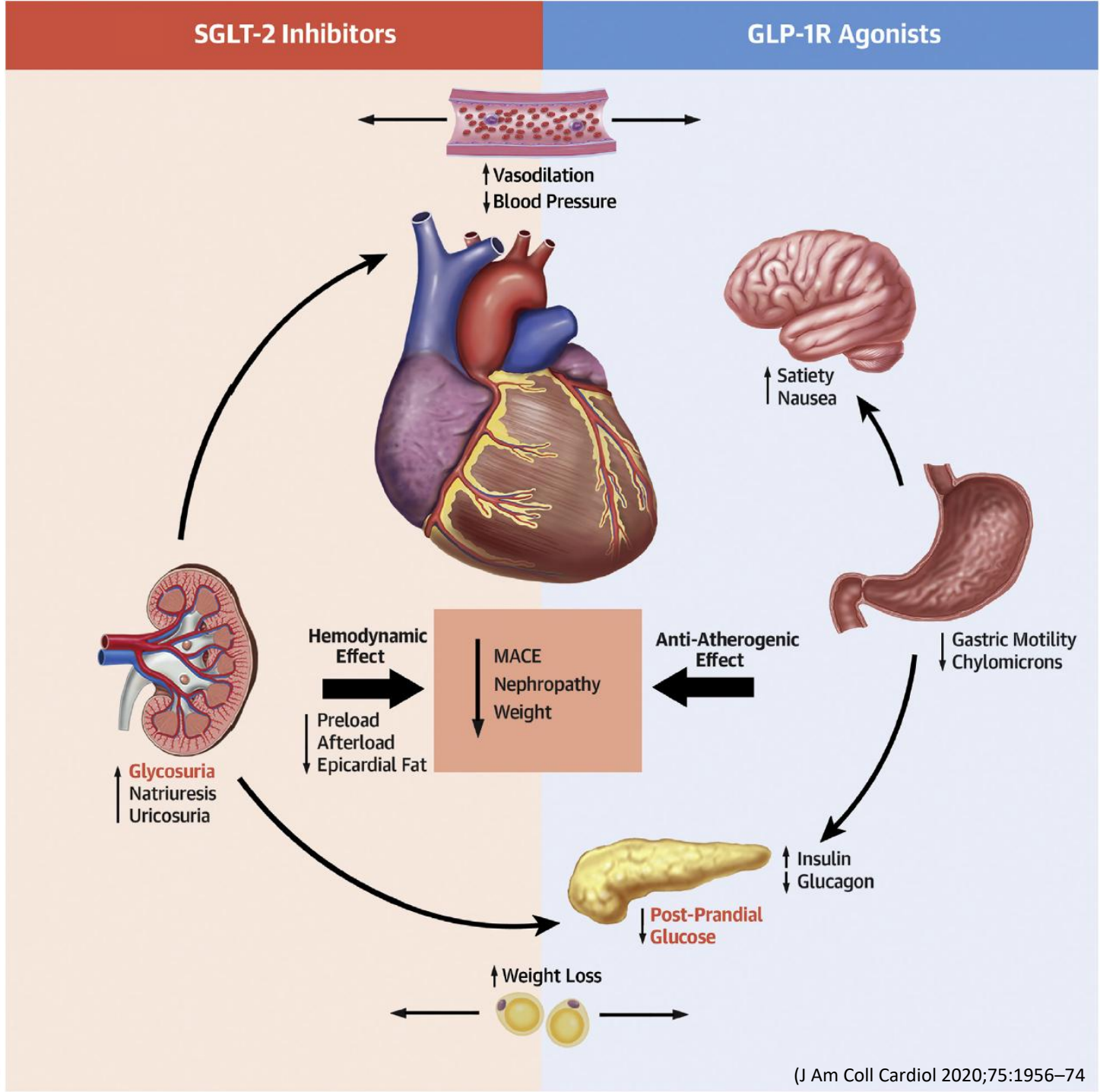
Mechanisms underlying the blood pressure lowering effects of GLP-1RAs



Current Opinion in Pharmacology 2023, 69:102355

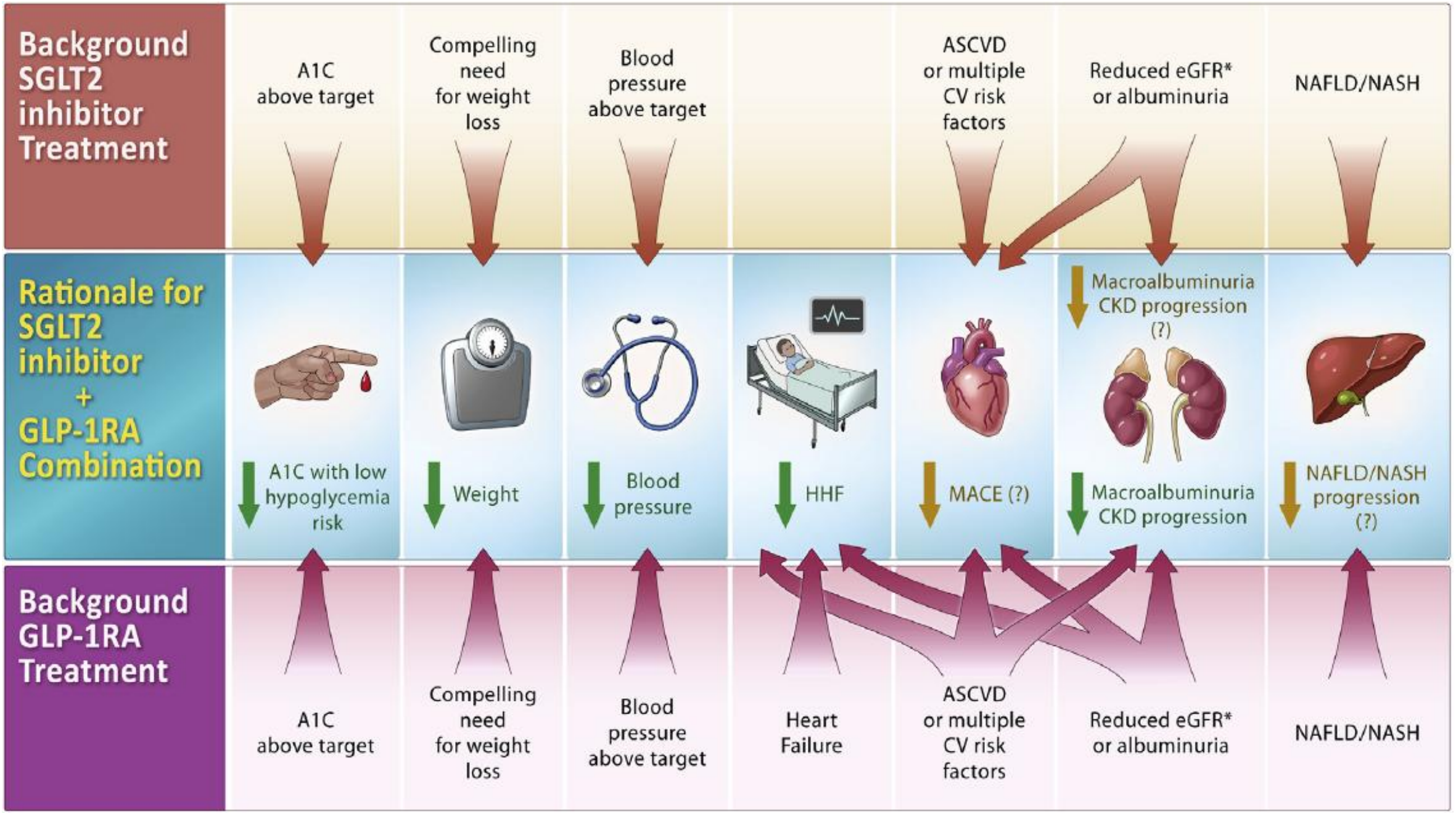
Diabetes & IHD





(J Am Coll Cardiol 2020;75:1956–74

Rationale for combining a GLP-1RA with a SGLT2 inhibitor



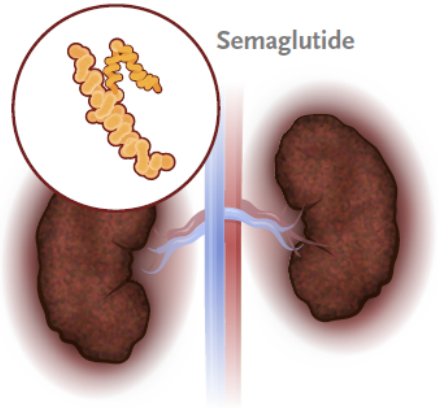
Effect of GLP-1 RAs and SGLT2 inhibitors on metabolic/cardiovascular/renal parameters.

	GLP-1 RAs	SGLT2i	GLP-1 RA/SGLT2i
MACE	↓↓	↓↓	↓↓↓
Atherogenesis	↓	–	↓
Hemodynamic benefit	↑	↑↑	↑↑
Glycemic control (A1c)	↓↓	↓↓	↓↓↓
Insulin sensitivity	↑	↑	↑↑
Beta cell function	↑↑↑	↑↑	↑↑↑↑
Blood pressure	↓	↓	↓↓
Lipid profile	↑	–	↑
Body weight	↓↓	↓	↓↓↓
Visceral fat	↓	↓	↓↓
NAFLD/NASH	↓	–	↓
Inflammation	↓	–	↓
Endothelial function	↑	–	↑
Natriuretic	↑	↑↑	↓↑
Diabetic nephropathy	↓	↓↓	↓↓
Diabetic retinopathy	↑?	–	↑?

Diabetes Obes Metab. 2017 October ; 19(10): 1353–1362. doi:10.1111/dom.12982.

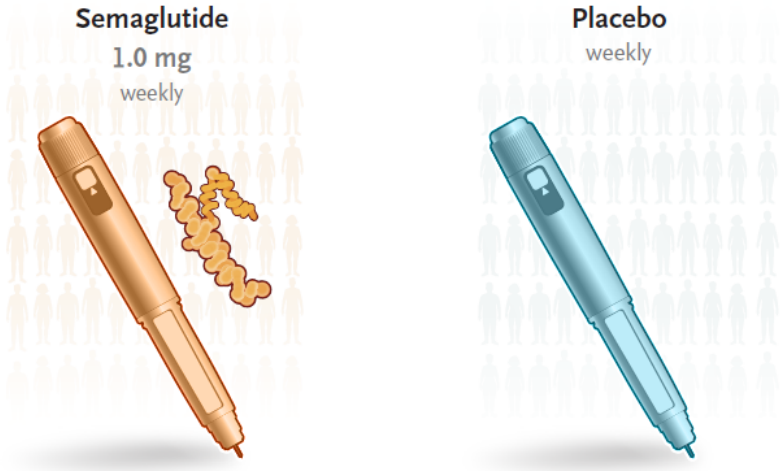
WHY WAS THE TRIAL DONE?

Semaglutide has been shown to improve glycemic control, lead to weight loss, and reduce cardiovascular events in patients with type 2 diabetes. Its effect on kidney outcomes in patients who also have chronic kidney disease is incompletely understood.



HOW WAS THE TRIAL CONDUCTED?

3533 participants with type 2 diabetes and chronic kidney disease were randomly assigned to receive weekly subcutaneous semaglutide (1.0 mg) or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (initiation of dialysis, kidney transplantation, or an estimated glomerular filtration rate [eGFR] of <15 ml per minute per 1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes.



PARTICIPANTS

WHO	3533 adults
	Mean age, 67 years
	Men: 70%; Women: 30%
CLINICAL STATUS	High-risk chronic kidney disease
	Type 2 diabetes

TRIAL DESIGN

- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 387 SITES IN 28 COUNTRIES

LAND
DICINE

VOL. 391 NO. 2

ic Kidney Disease Diabetes

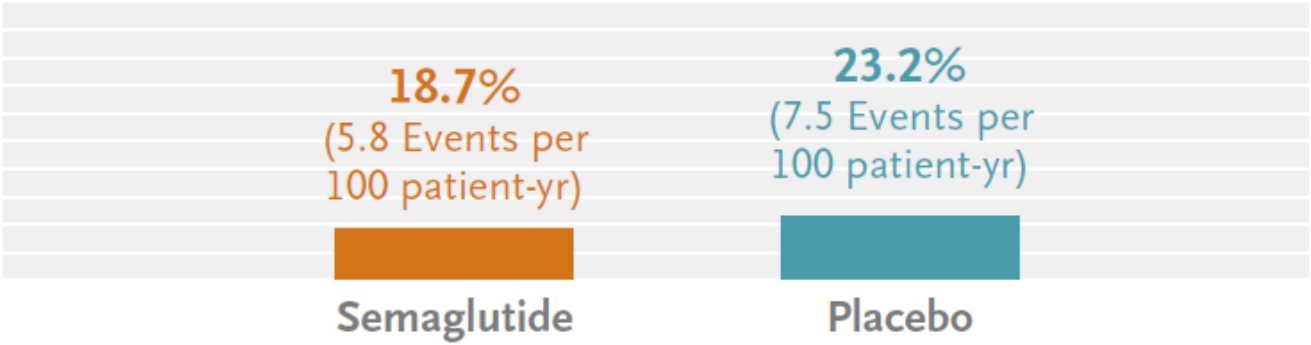
, Peter Rossing, M.D., D.M.Sc.,
kris, M.D., Florian M.M. Baeres, M.D.,
anna Leonora Lausvig, M.Sc., and
ees and Investigators*

T2DM with CKD
eGFR 50~75 ml/min/1.73 m^2
and a urinary ACR 300~5000
or
eGFR 25~50 ml/min/1.73 m^2
and a urinary ACR 100~5000

N Engl J Med 2024;391:109-21.

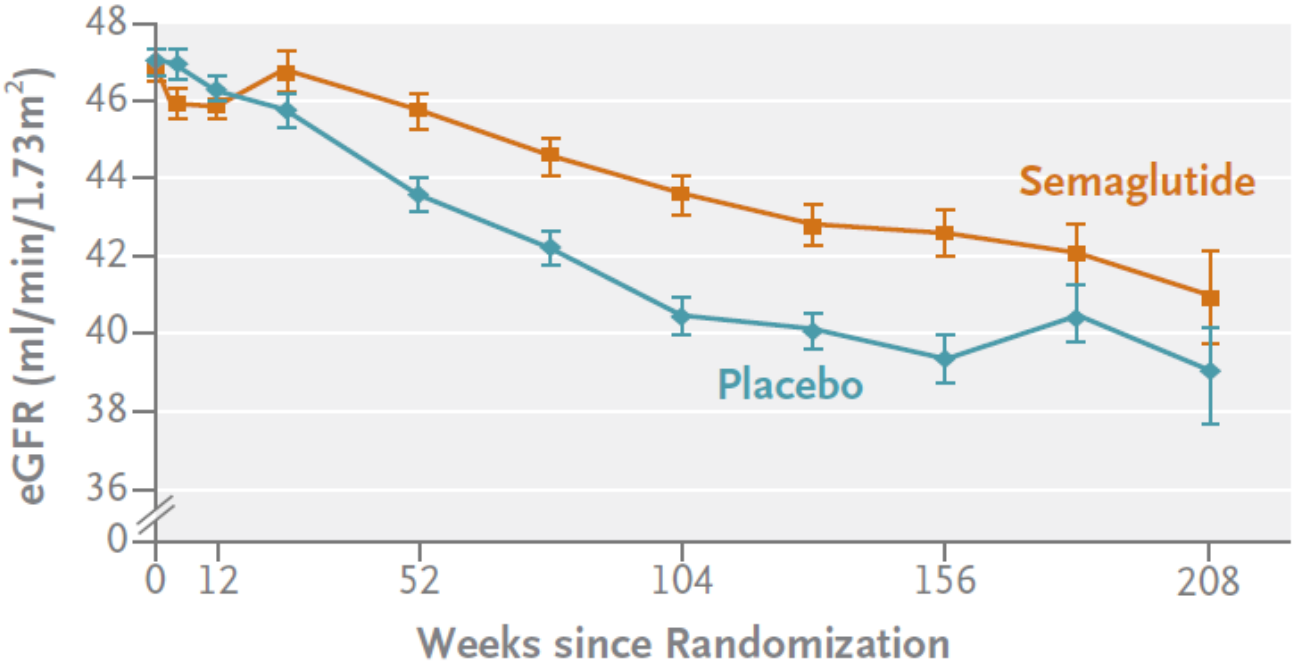
Major Kidney Disease Events

Hazard ratio, 0.76 (95% CI, 0.66–0.88); P=0.0003



Decline in Kidney Function

Difference in mean annual decline, 1.16 ml/min/1.73 m²
95% CI, 0.86–1.47; P<0.001



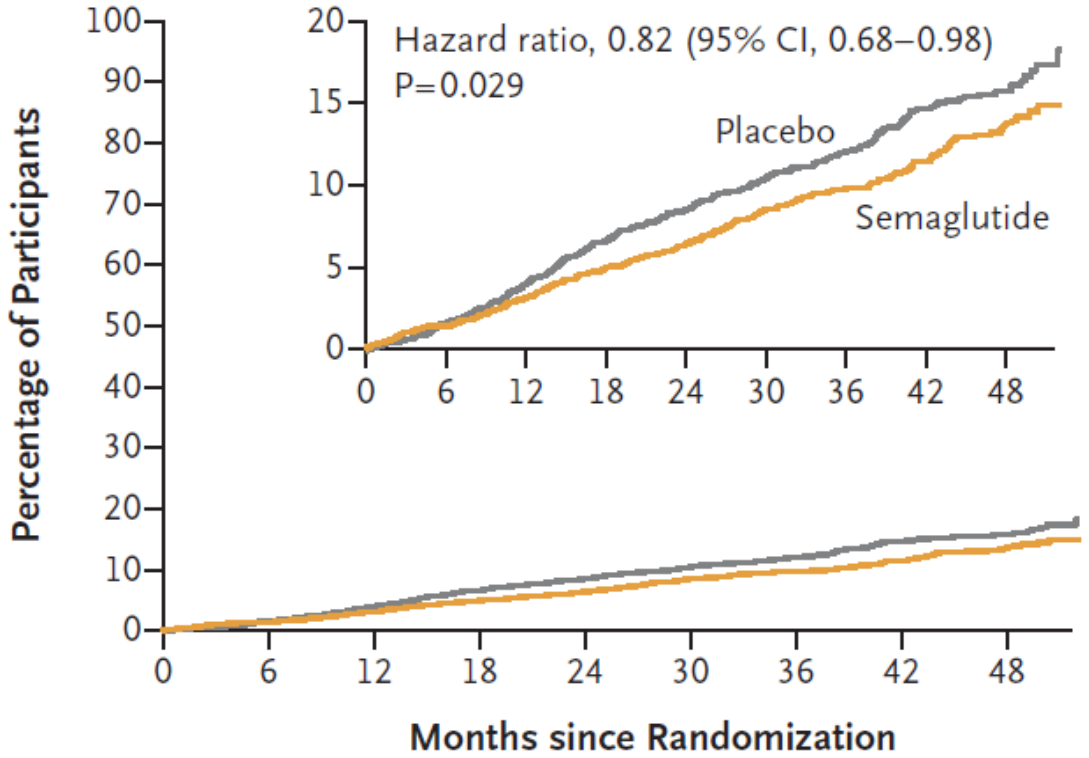
CONCLUSIONS

In adults with type 2 diabetes and chronic kidney disease, semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes.

N Engl J Med 2024;391:109-21.

Mean change in body weight from baseline to week 104 — kg	−5.55	−1.45	—	−4.10 (−4.56 to −3.65)	—
Mean change in glycated hemoglobin level from baseline to week 104 — percentage points	−0.87	−0.06	—	−0.81 (−0.90 to −0.72)	—
Mean change in systolic blood pressure from baseline to week 104 — mm Hg	−3.79	−1.55	—	−2.23 (−3.33 to −1.13)	—
Mean change in diastolic blood pressure from baseline to week 104 — mm Hg	−0.23	−1.01	—	0.78 (0.16 to 1.41)	—

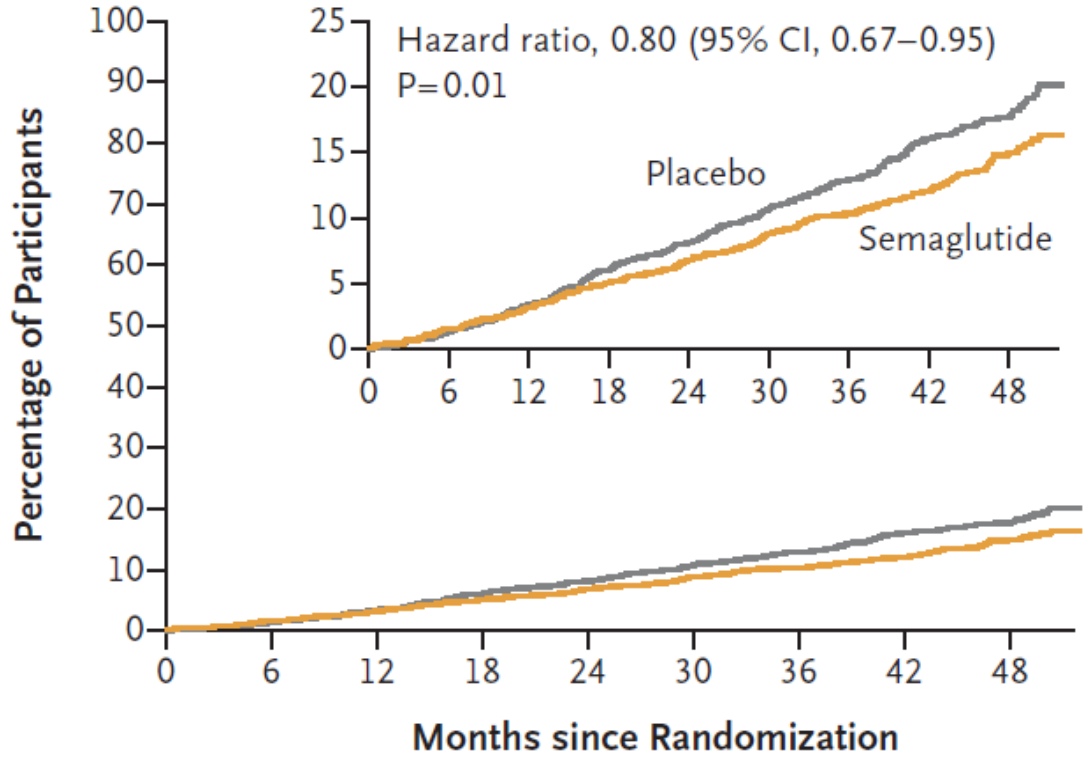
E **First Major Cardiovascular Event**



No. at Risk

Placebo	1766	1721	1663	1583	1535	1478	1133	731	418
Semaglutide	1767	1725	1672	1622	1575	1515	1176	793	430

F **Death from Any Cause**



No. at Risk

Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

nature medicine

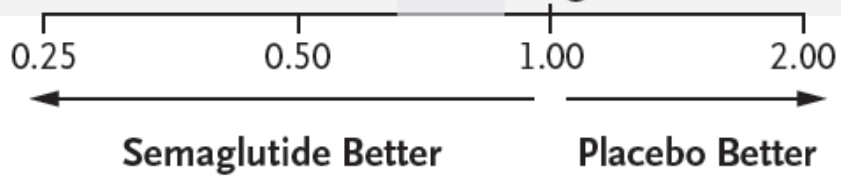
Article

https://doi.org/10.1038/s41591-024-03133-0

Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial

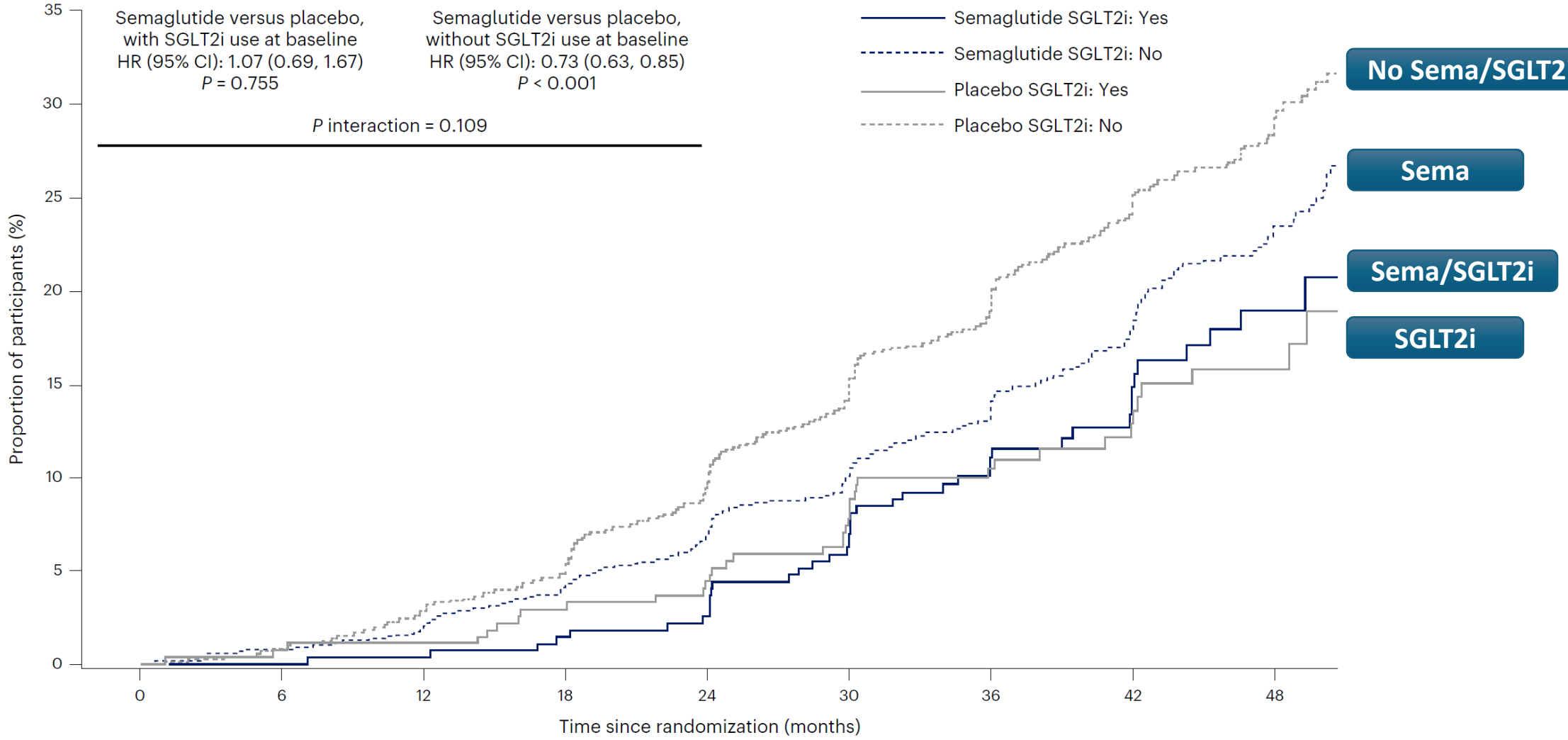
Nature Medicine | Volume 30 | October 2024 | 2849–2856

Medication use — no. (%)				
SGLT2 inhibitor			277 (15.7)	273 (15.5)	550 (15.6)
ACE inhibitor			625 (35.4)	615 (34.8)	1240 (35.1)
ARB			1066 (60.3)	1061 (60.1)	2127 (60.2)
SGLT2 inhibitor use					
No	290/1490	372/1493			0.73 (0.63–0.85)
Yes	41/277	38/273			1.07 (0.69–1.67)



Outcomes for semaglutide 1.0 mg versus placebo in subgroups with/without SGLT2i use at baseline for the primary five-component outcome

a



No Sema/SGLT2i

Sema

Sema/SGLT2i

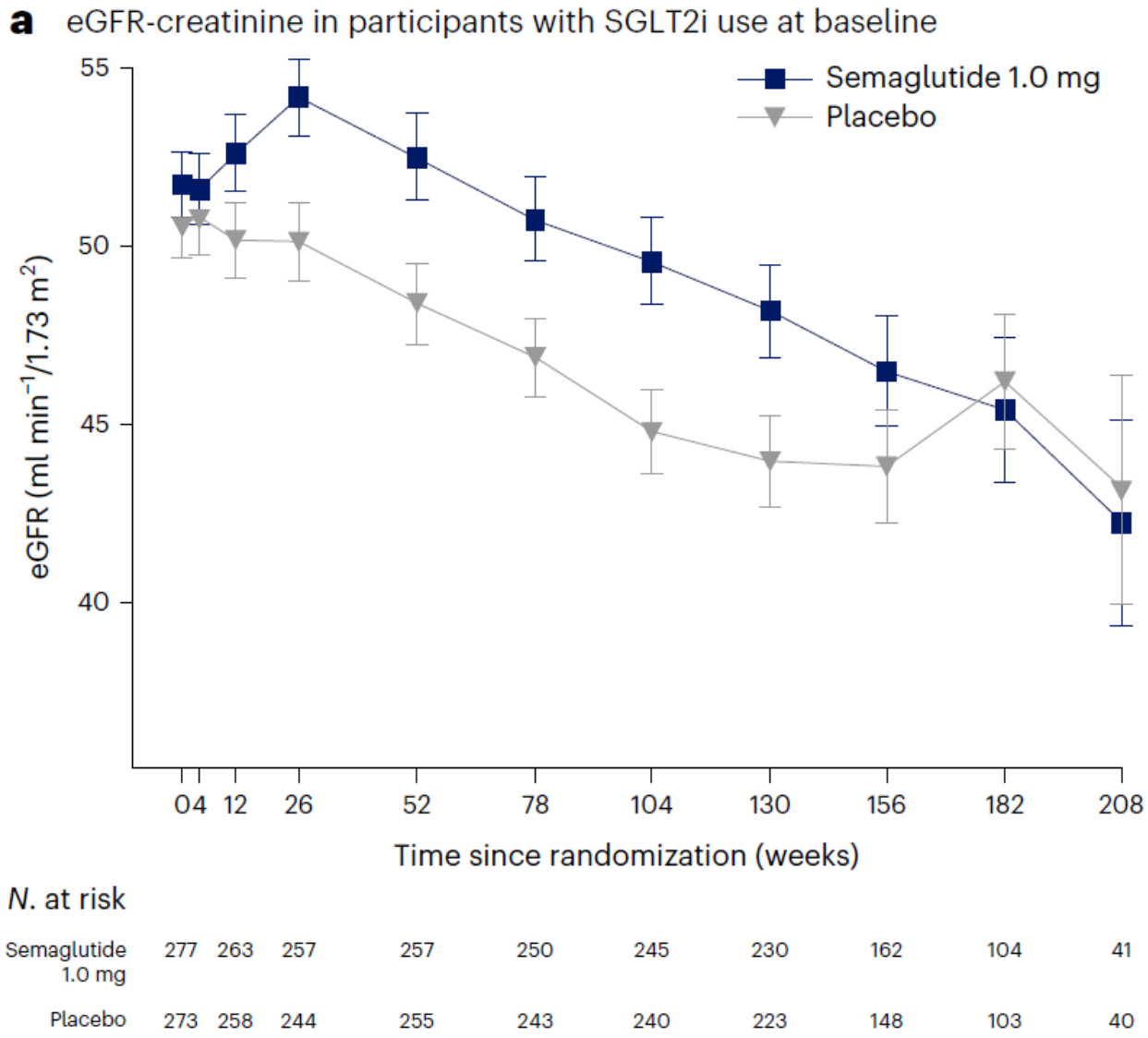
SGLT2i

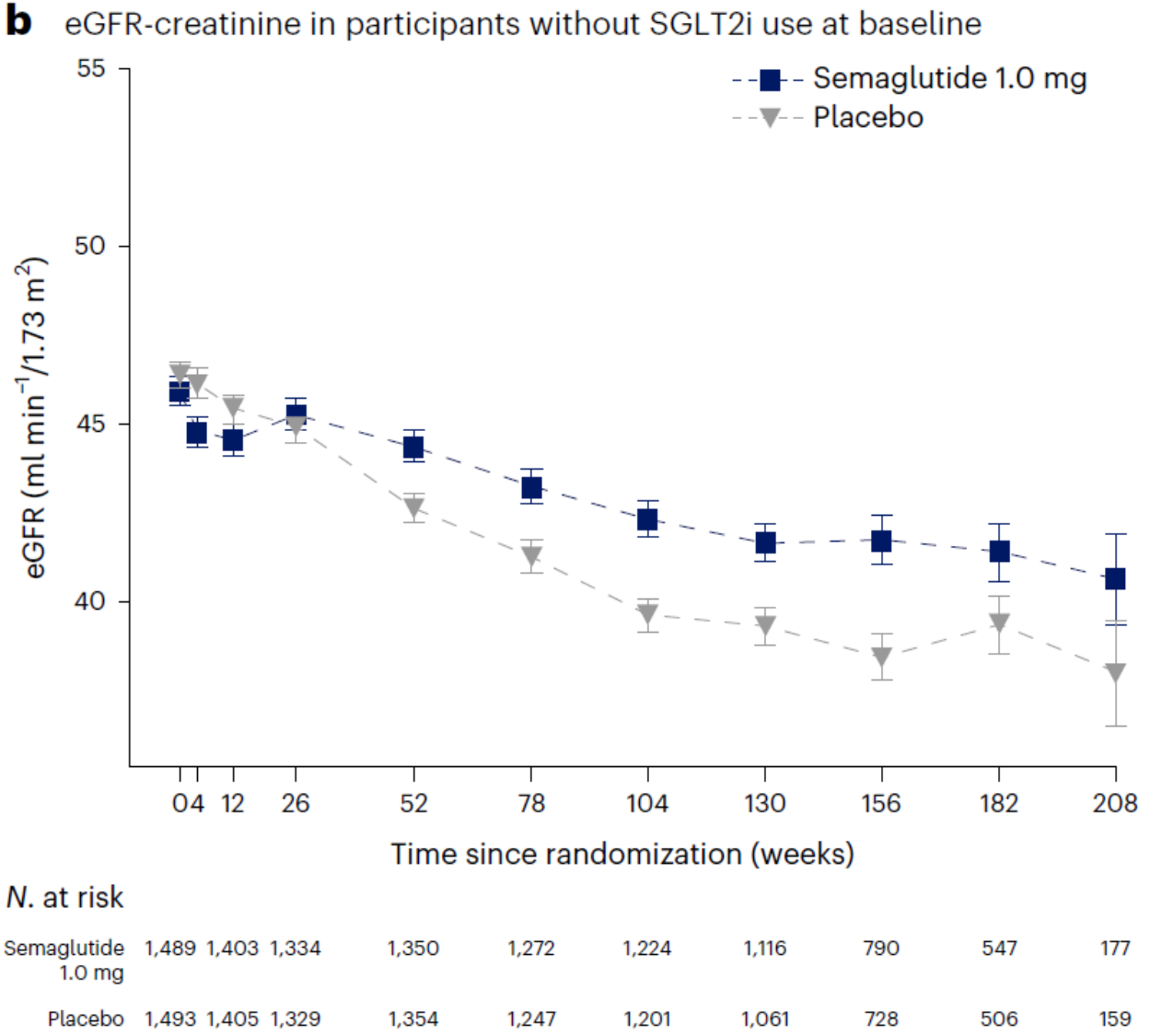
N. at risk

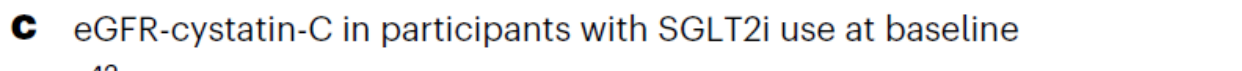
Semaglutide SGLT2i: Yes	277	273	269	263	255	240	172	112	60
Semaglutide SGLT2i: No	1,490	1,465	1,424	1,377	1,317	1,249	959	630	332
Placebo SGLT2i: Yes	273	268	266	255	251	236	177	116	69
Placebo SGLT2i: No	1,493	1,468	1,416	1,350	1,265	1,172	871	544	285

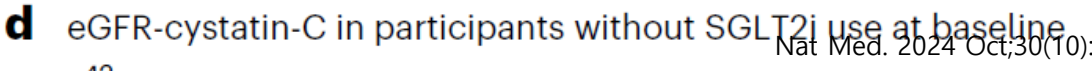
Nat Med. 2024 Oct;30(10):2849-2856.

eGFR over time with/without SGLT2i use at baseline, based on serum creatinine and tatin C



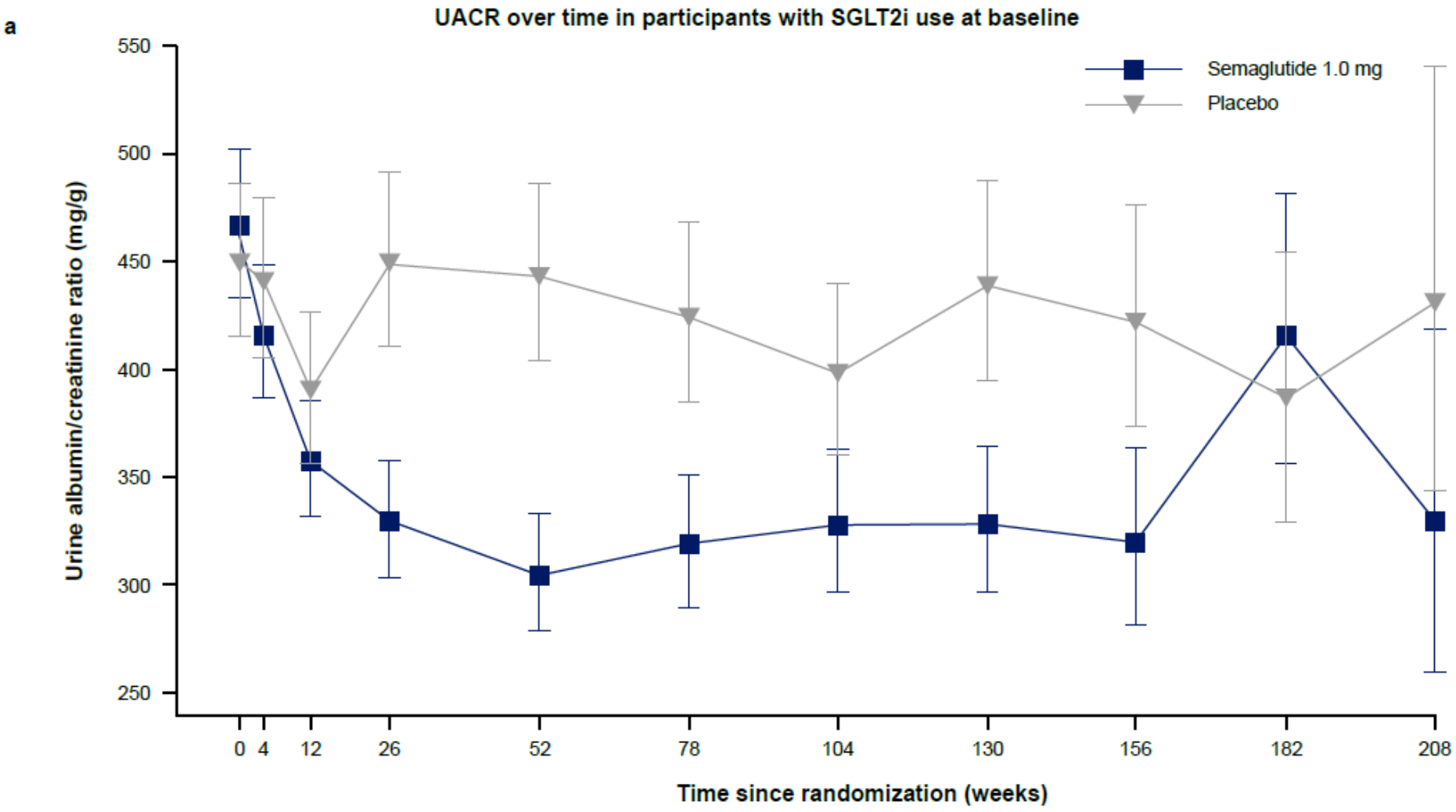






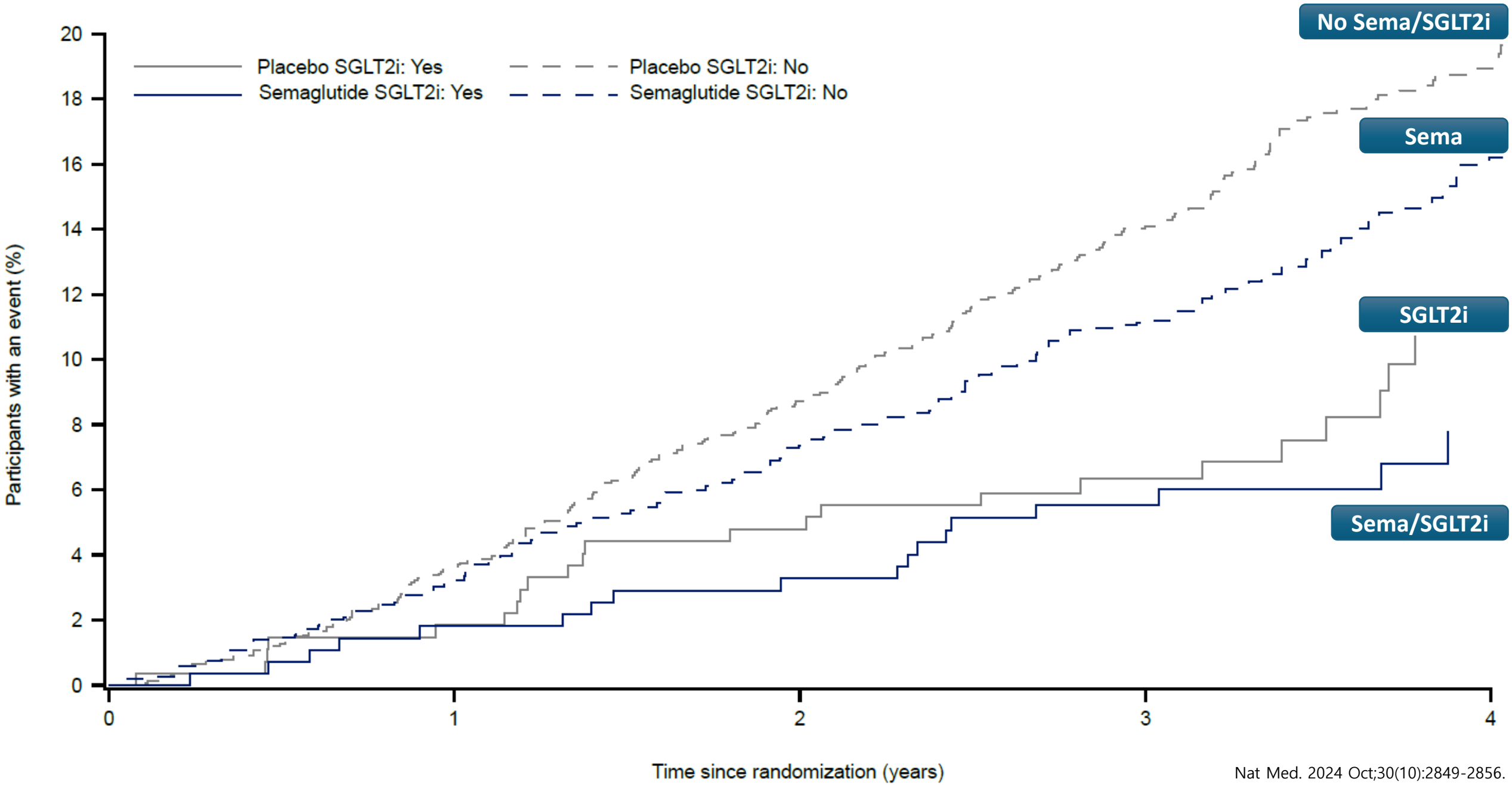
Nat Med. 2024 Oct;30(10):2849-2856.

Semaglutide lowered UACR at week 104; 24% with SGLT2i and 34% without SGLT2i use



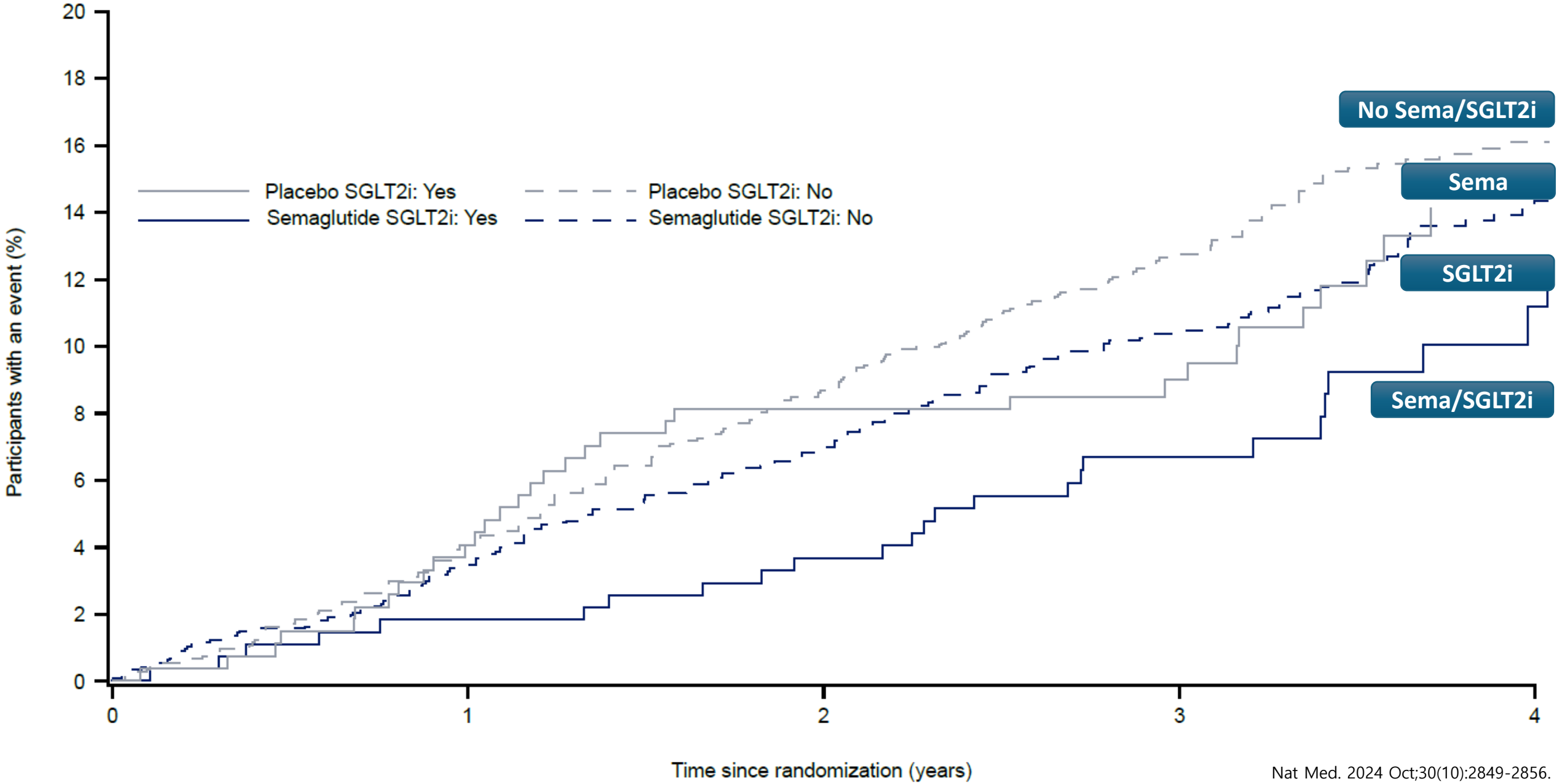
Nat Med. 2024 Oct;30(10):2849-2856.

Time to all-cause death with semaglutide or placebo according to baseline use of SGLT2i



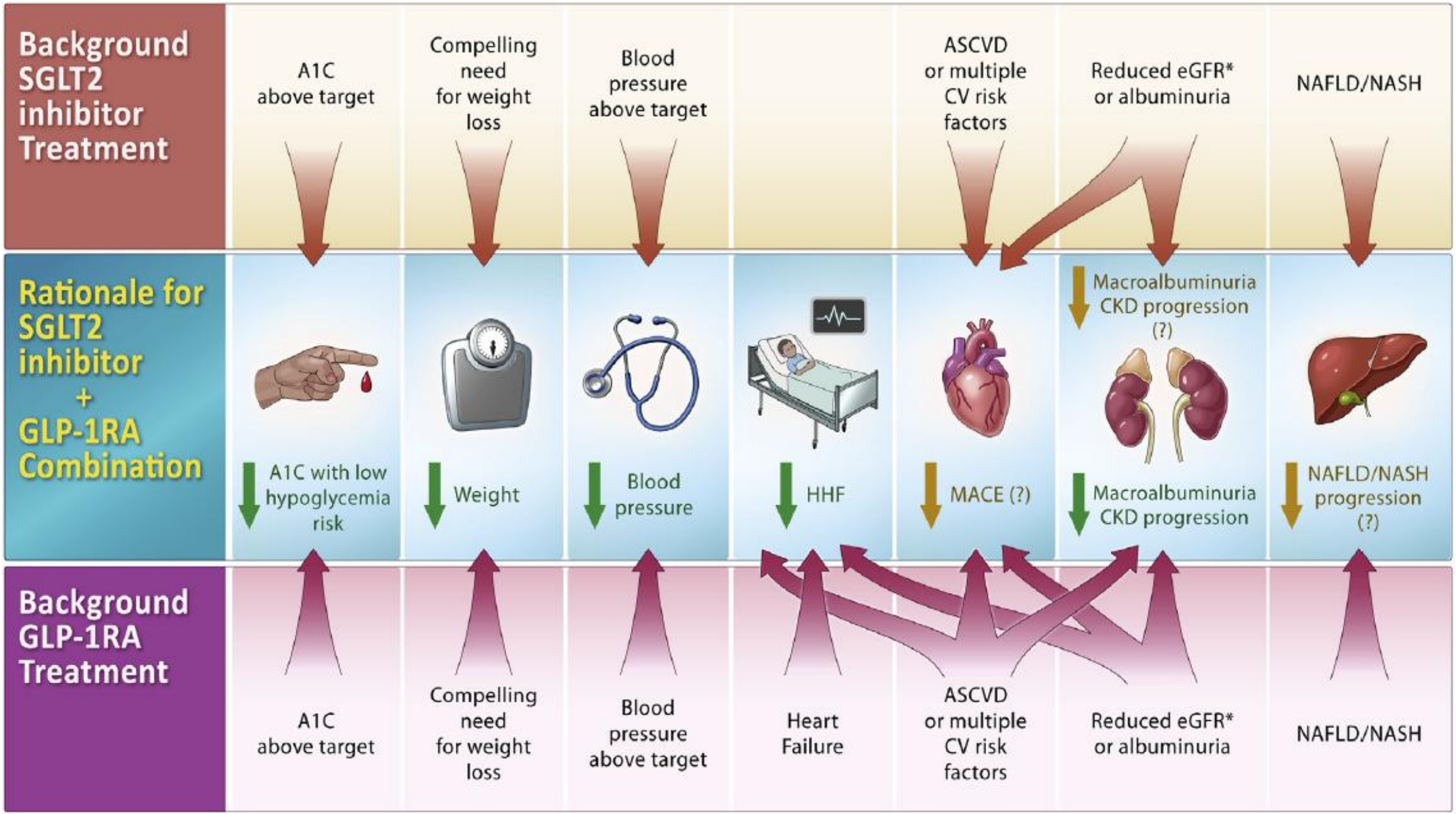
Nat Med. 2024 Oct;30(10):2849-2856.

Time to first MACE with semaglutide or placebo according to baseline use of SGLT2i.



Nat Med. 2024 Oct;30(10):2849-2856.

Summary: Combination of a GLP-1RA with a SGLT2 inhibitor



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Empowering Health, Inspiring Change: Practical Solutions for Obesity

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Thank you for your attention !!