Treatment of Type 2 Diabetes: Getting To Goal and Reducing Cardiovascular Risk

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Disclosures

- No active disclosures

Learning objectives

- Explain the magnitude and briefly review the pathophysiology of type 2 diabetes mellitus (T2DM)
- Examine studies correlating glucose control with the risk for complications
- Identify medications used to treat T2DM and explain their impact on cardiorenal risk
- Describe the guidelines for pharmacologic management of people with T2DM

Diabetes around the world in 2021

537 million

Approximately **537 million adults** (20-79 years) are living with diabetes.

643 million by 2030

The total number of people living with diabetes is projected to rise to **643 million by 2030** and **783 million by 2045**.

3 in 4

3 in 4 adults with diabetes **live in low- and middle-income countries**

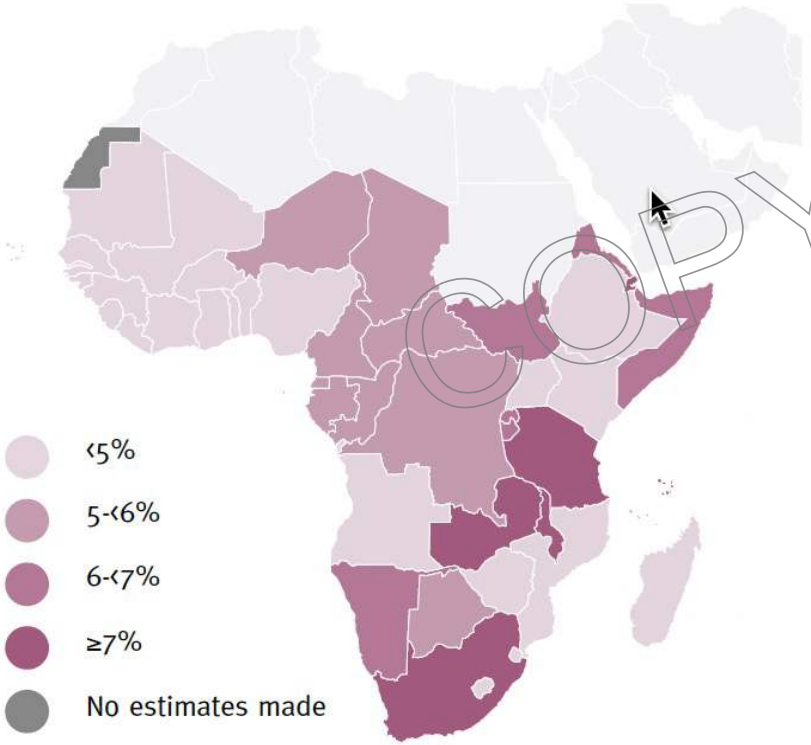
643m

adults predicted to have diabetes by 2030

240m

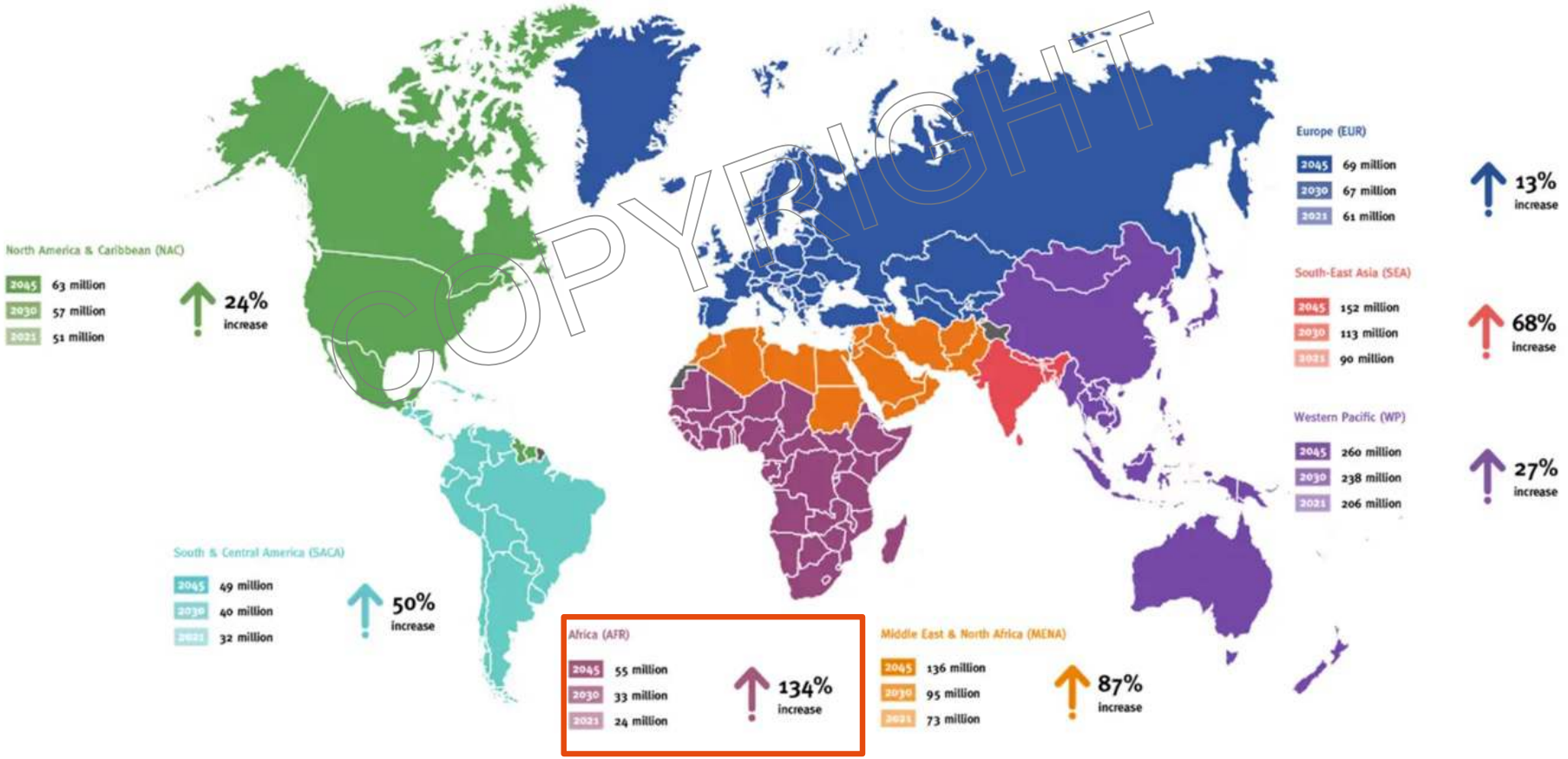
People living with undiagnosed diabetes

Diabetes in Africa



Top 5 countries for age-adjusted prevalence of people with diabetes (20–79 years)	2011	2021
United Republic of Tanzania	2.8%	12.3%
Zambia	4.8%	11.9%
Comoros	8.6%	11.7%
South Africa	7.1%	10.8%
Seychelles	12.4%	8.5%

Projected increase in prevalence of diabetes

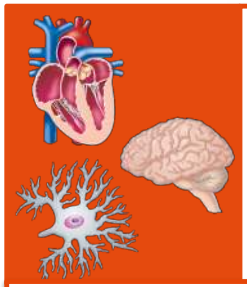


www.idf.org

Diabetes in Africa: Highlights

- Total number – 24 million
- Percent undiagnosed – 54 (highest in the world)
- Projected increase – 134% (highest in the world)
- Expected number of adults with diabetes in 2045
  - 55 million
- Africa has 2nd lowest diabetes-related expenditure
  - USD 13 billion (1% of global expenditure)

Elevated glucose levels are associated with increased CV risk in people with diabetes



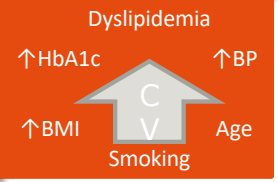
- Macrovascular complications of diabetes (defined as metabolic injury to large vessels) affect:
  - Heart (coronary artery disease)
  - Brain (cerebrovascular disease)
  - Extremities (peripheral vascular disease)

- CV risk, which is increased 2-fold in people with T2DM,[1] rises with escalating HbA1c levels[2-4]

>75%
due to CV

- Over three-quarters of all hospitalizations for diabetes complications are due to macrovascular disease[5]

- CV mortality is increased in people with diabetes and rises further with additional CV risk factors[6]



1. Green JB. Postgrad Med 2014;126:190–204; 2. Iribarren C et al. Circulation 2001;103:2668–2673;
3. Khaw KT et al. Ann Intern Med 2004;141:413–420; 4. Stratton IM et al. BMJ 2000;321:405–412;
5. Basa AL & Garber AJ. Ochsner J 2001;3:132–137; 6. Stamler J et al. Diabetes Care 1993;16:434–444.

Key trials have shown that good glycemic control reduces macrovascular complications

DCCT/ EDIC

- Good glycemic control reduces CV risk in people with T1DM
  - Significantly ↓ non-fatal MI, stroke or death from CVD[1]
  - Significantly ↓ CV events[1]

UKPDS

- Good glycemic control reduces CV risk in people with T2DM
  - Significantly ↓ MI (after 24 years follow-up)[2]

ADVANCE ACCORD VADT

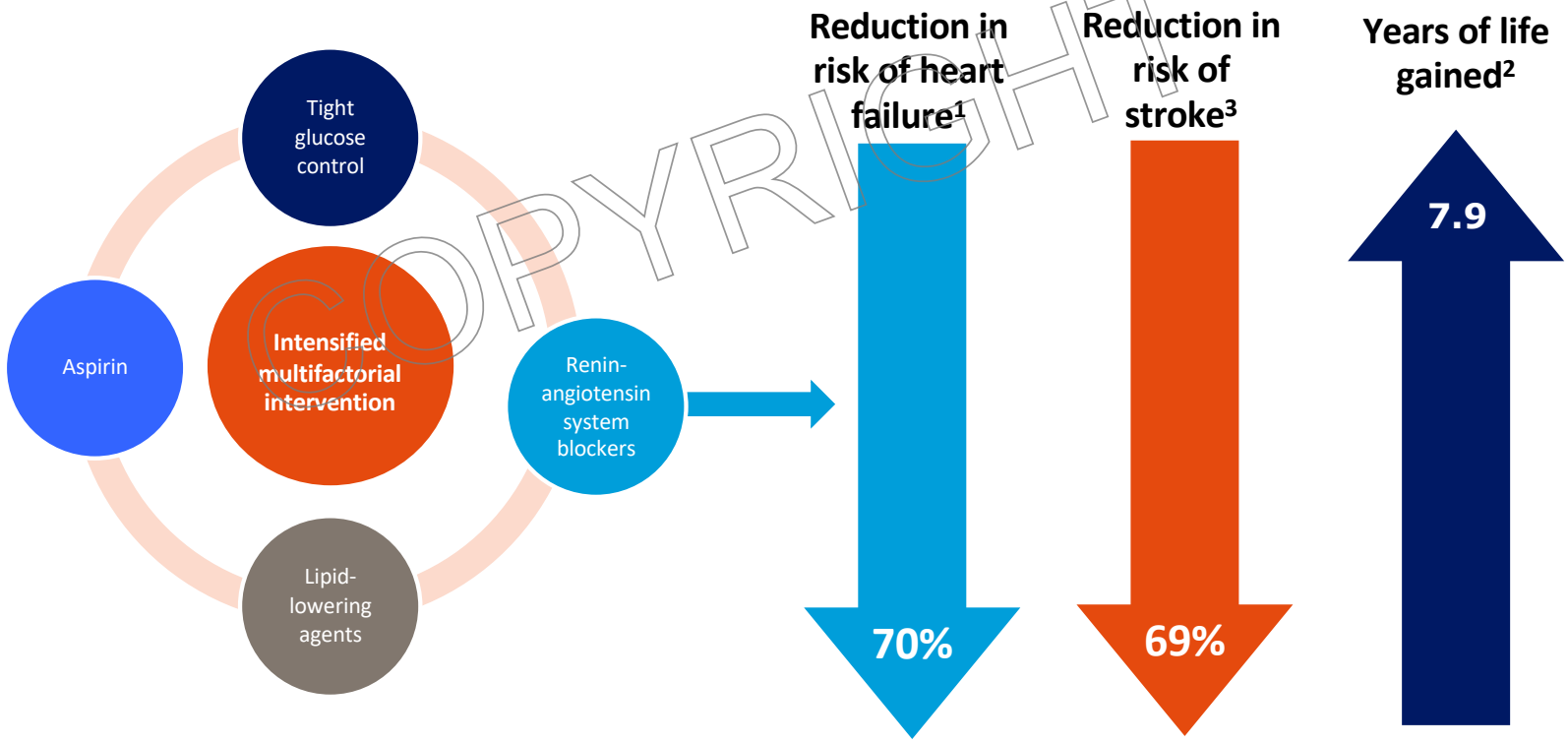
- However, the more advanced the disease and the longer the duration of diabetes, the more difficult it becomes to reduce CV events and mortality[3-7]

Steno-2

- Multifactorial treatment is key to reducing the risk of CVD
- Diabetes management should include management of lipids and blood pressure plus aspirin use in addition to glucose control, leading to ↓ CV events and mortality[8]

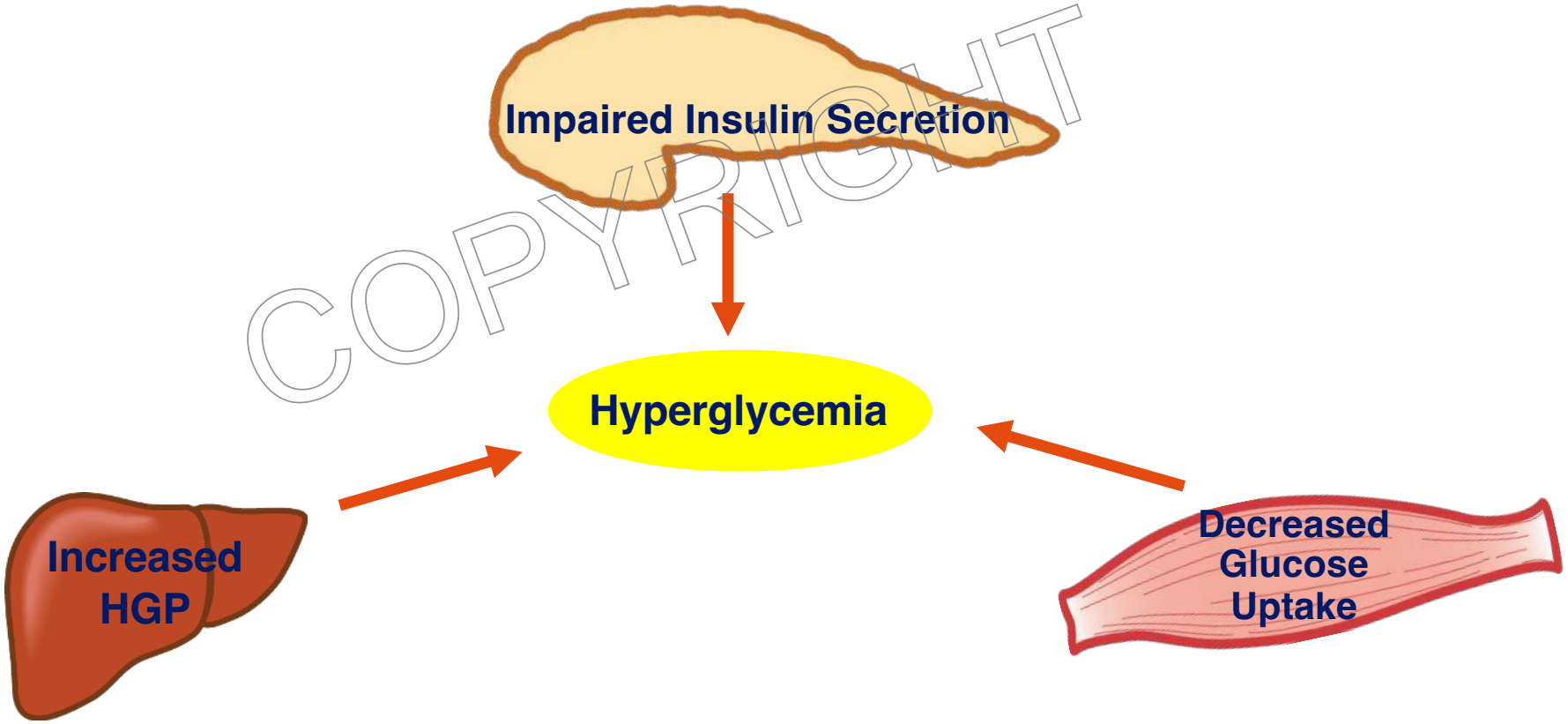
1. DCCT/EDIC. N Engl J Med 2005;353:2643–2653; 2. Holman RR et al. New Engl J Med 2008;359:1577–1589; 3. Gerstein HC et al. N Engl J Med 2008; 358:2545–2559; 4. Patel A et al. N Engl J Med 2008;358:2560–2572; 5. Zoungas S et al. N Engl J Med 2014; 371:1392–1406; 6. Duckworth W et al. N Engl J Med 2009;360:129–139; 7. Hayward RA et al. N Engl J Med 2015;372:2197–2206; 8. Gaede P et al. N Engl J Med 2008;358:580–591.

Intensive multifactorial intervention continues to have long-term benefits: 21-year Steno-2 data



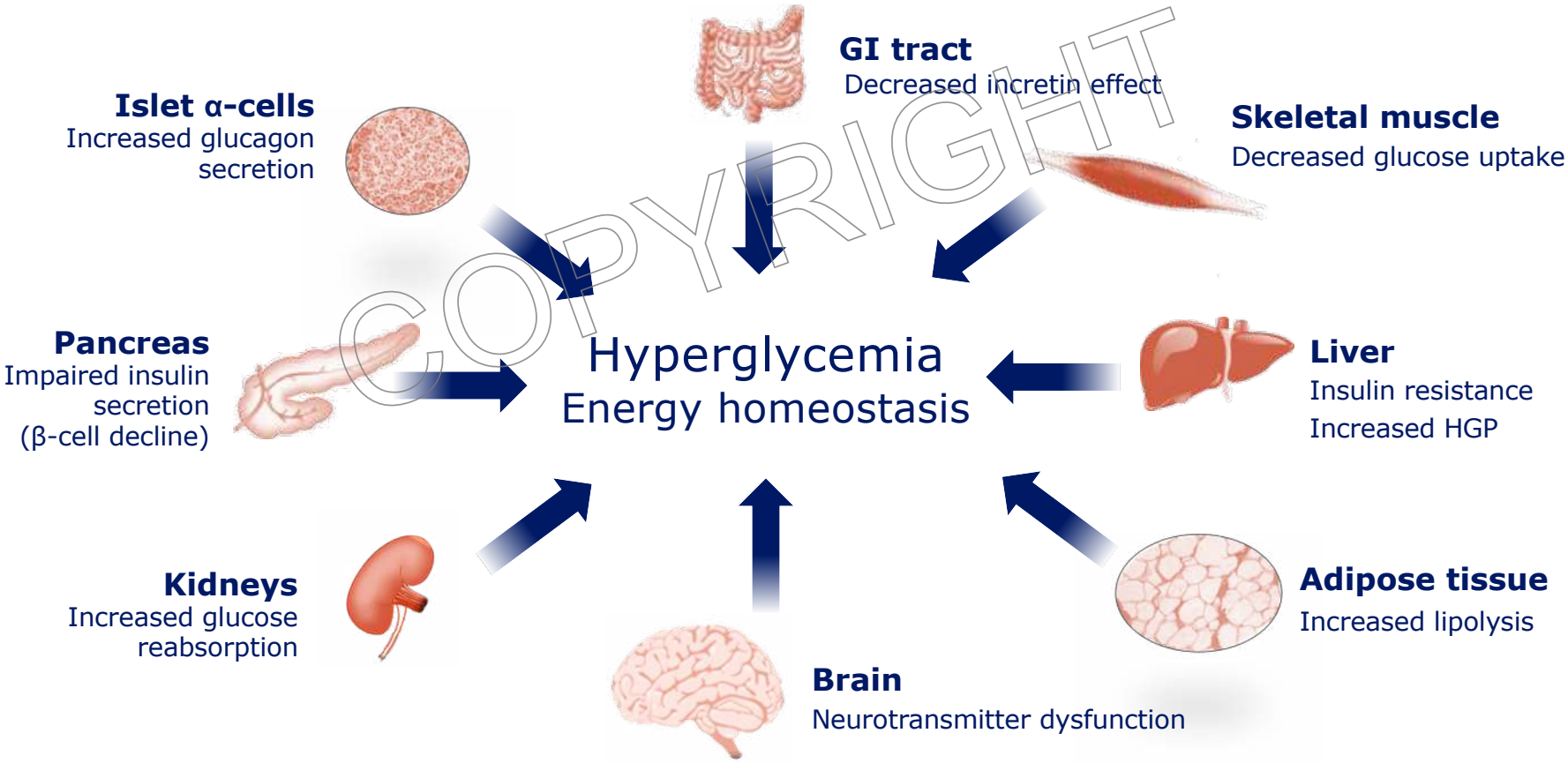
1. Oellgaard J et al. Diabetologia 2018;6:1724–1733;
2. Gaede P et al. Diabetologia 2016;59:2298–2307;
3. Gaede P et al. Diabetologia 2019;62:1575–1580.

Pathogenesis of type 2 diabetes: from the triumvirate



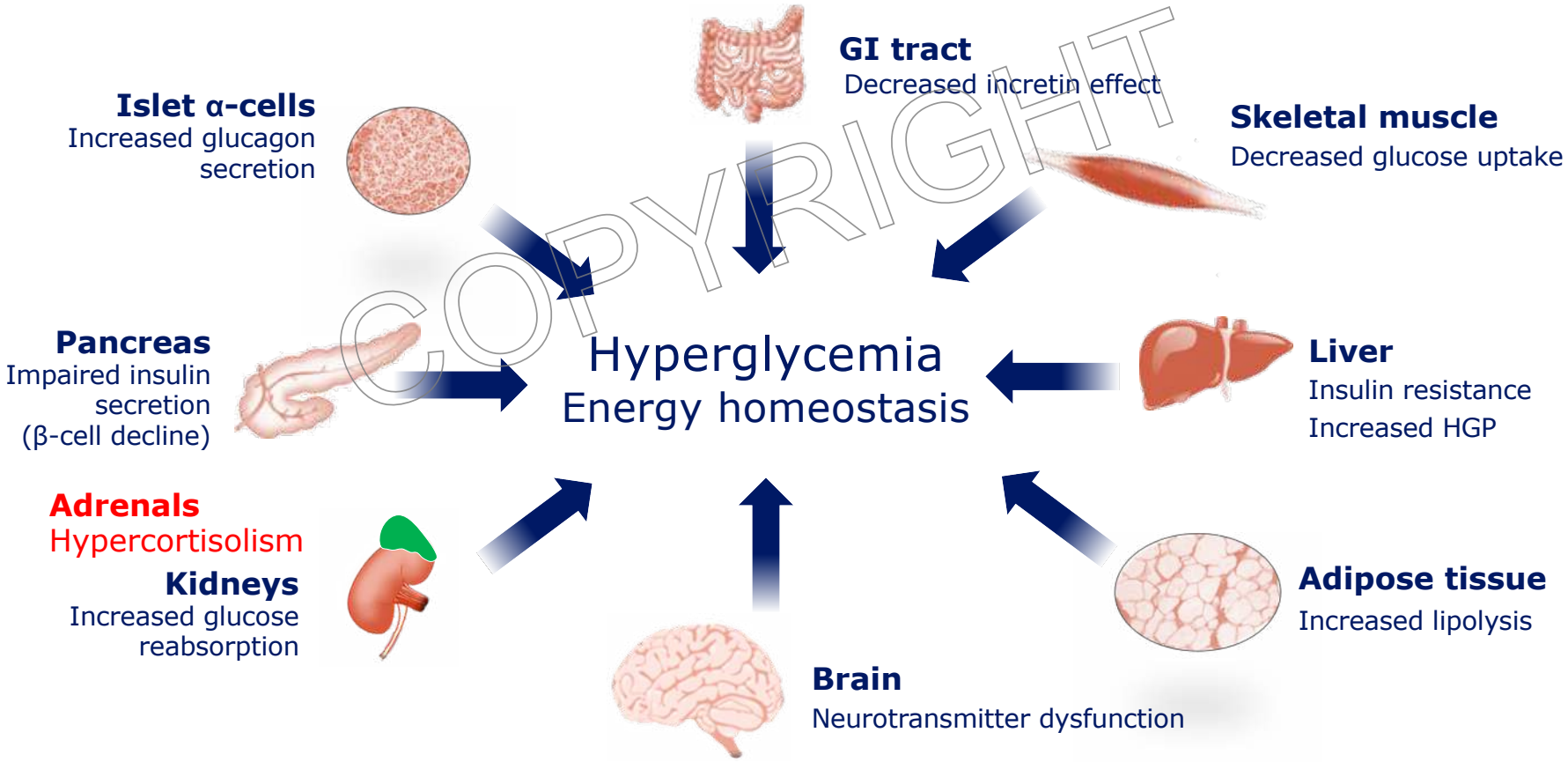
DeFronzo RA, Diabetes 37:667-687, 1988

Pathogenesis of T2DM: To The Ominous Octet



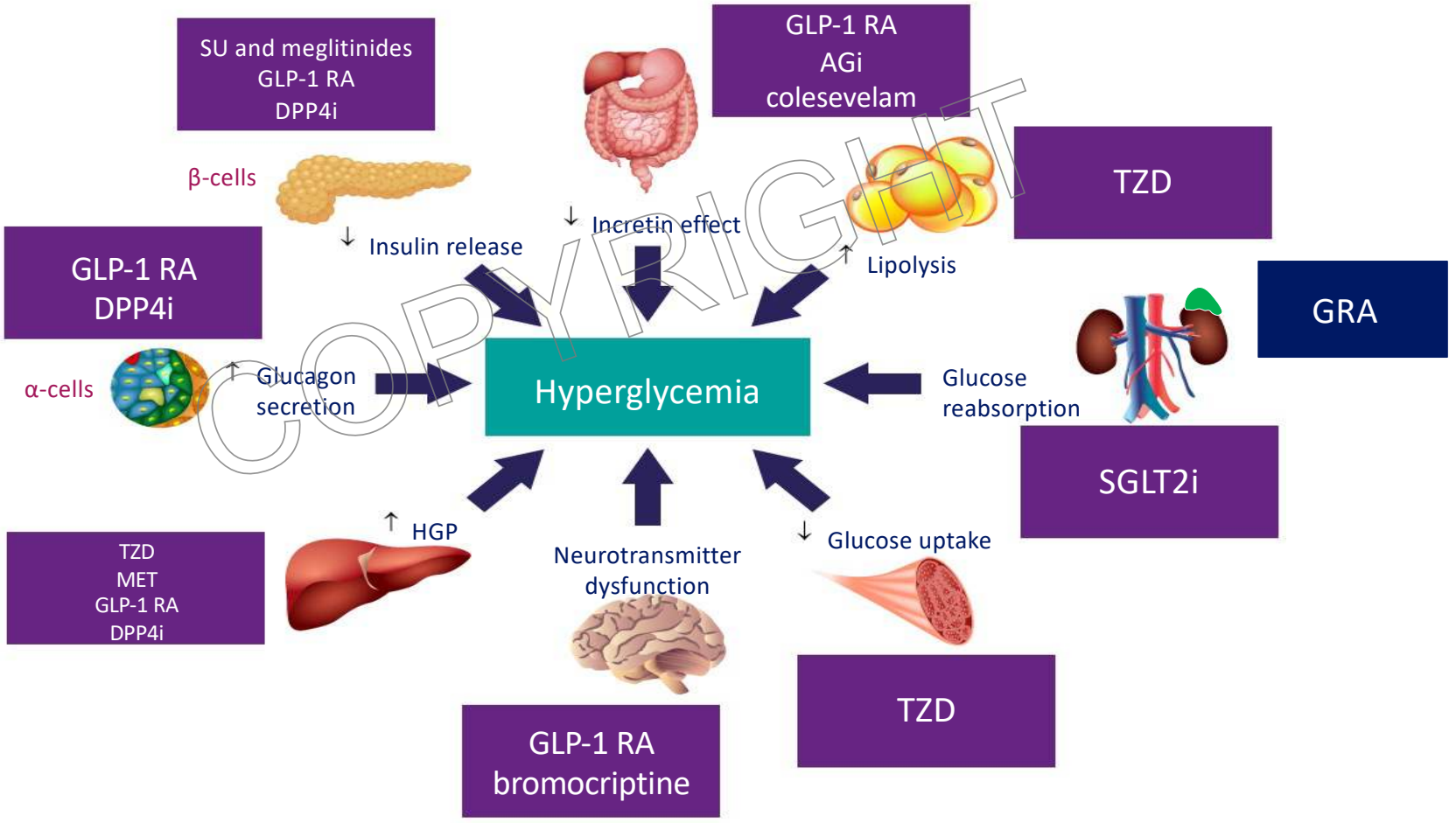
GI, gastrointestinal; HGP, hepatic glucose production; SU, sulphonylurea; T2D, type 2 diabetes
DeFronzo RA. *Diabetes* 2009;58:773–795

Pathogenesis of T2DM: To The Noxious Nine



GI, gastrointestinal; HGP, hepatic glucose production; SU, sulphonylurea; T2D, type 2 diabetes
DeFronzo RA. *Diabetes* 2009;58:773–795

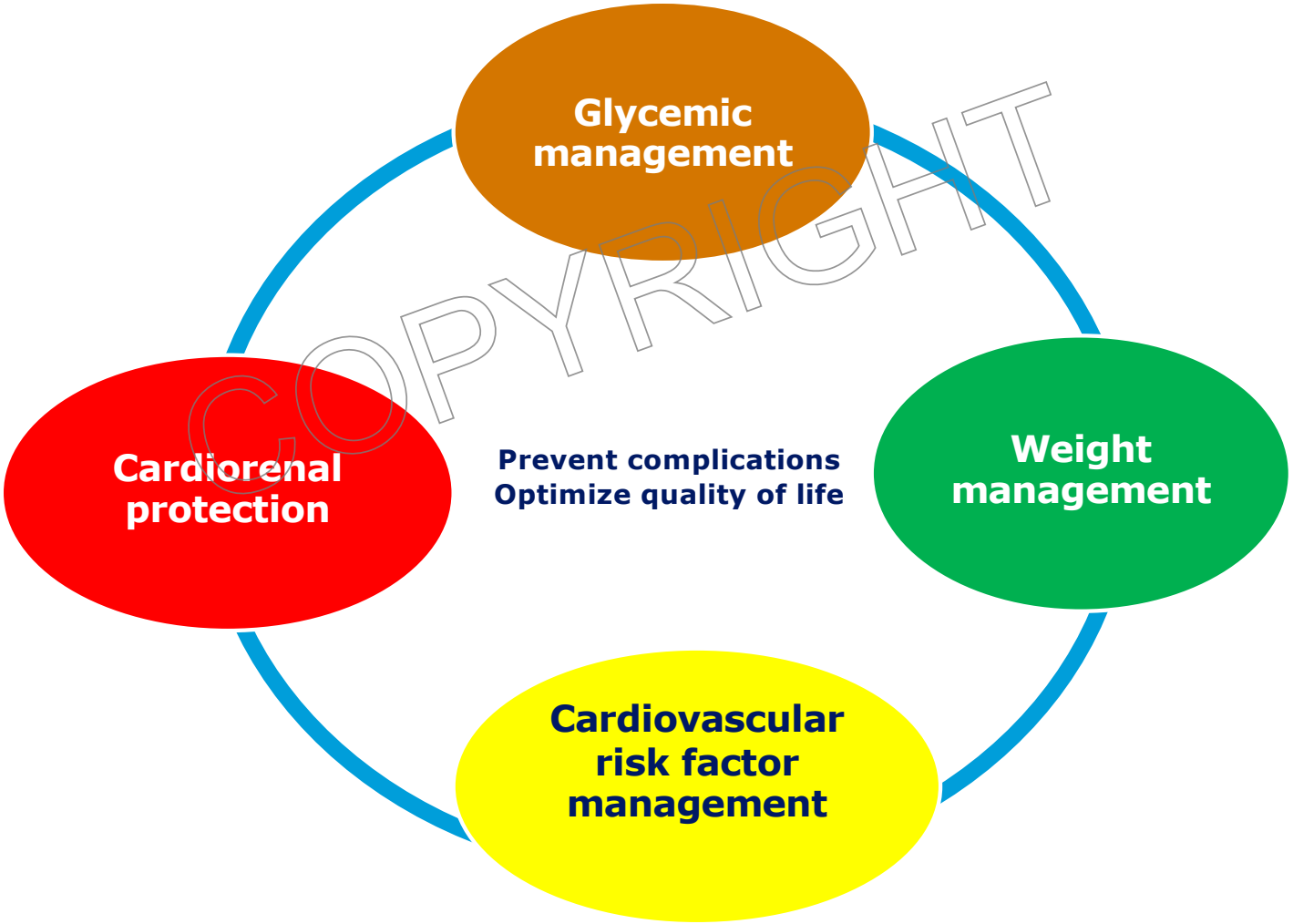
Sites of action of non-insulin therapeutic agents



AGi, α-glucosidase
GLP-1Ra, GLP-1 receptor agonists; HGP, hepatic glucose production;
SU, sulphonylureas; TZDs, thiazolidinediones;
GRA, glucocorticoid receptor antagonist

Ferrannini E, DeFronzo RA. Eur Heart J 2015;36:2288–2296.

Pharmacologic management of T2DM: a 4-pronged approach



Meet Mr L

- 63-year-old part-time teacher
- Diagnosed with Type 2 diabetes (T2DM) 6 years ago
- Comorbidities – hypertension, hyperlipidemia, coronary artery disease
- Has normal systolic and diastolic cardiac function
- BMI: 29.4 kg/m^2
- HbA1c: 6.7%
- eGFR: 68 $mL/min/1.73m^2$
- Normal LFTs
- Normal urine microalbumin

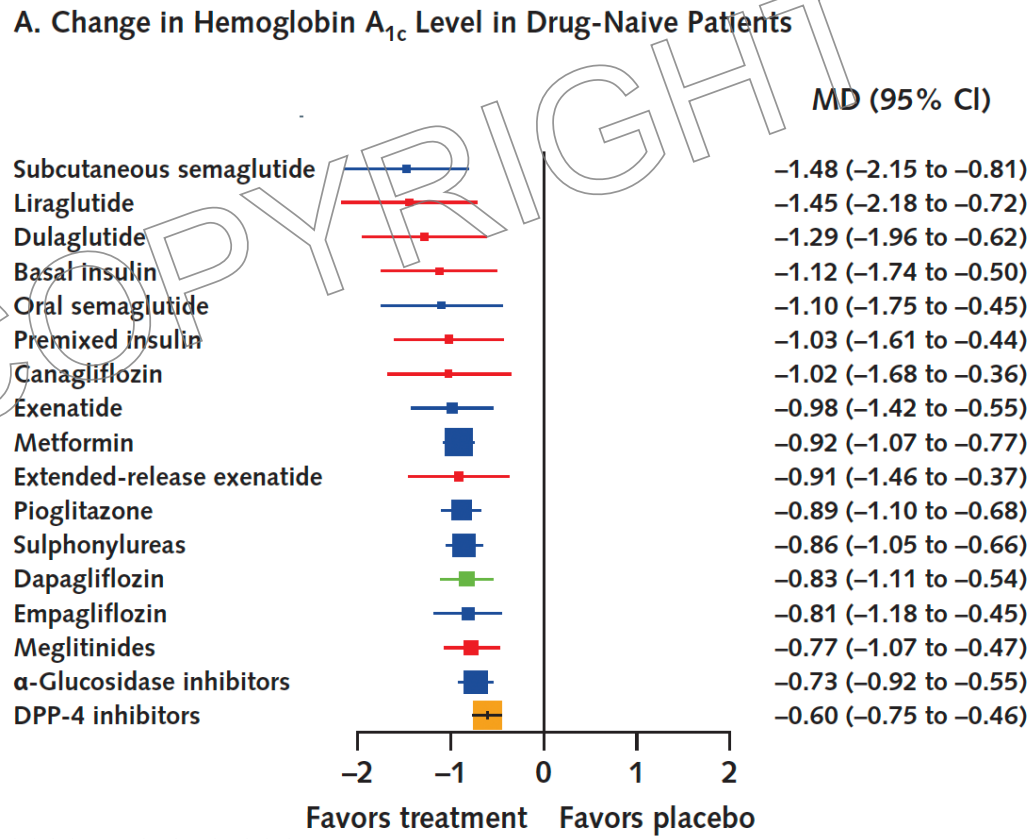
Current medication

Metformin: 2000 mg/day
Glipizide: 10 mg/day
Atorvastatin: 10 mg/day
Lisinopril : 40 mg/day
HCTZ: 12.5 mg/day
Aspirin: 81 mg/day

What would you do next?

a. Continue current treatment – he is at goal A1c
b. Add a SGLT-2i – sodium-glucose cotransporter 2 inhibitor
c. Add a GLP-1 RA – glucagon-like peptide 1 receptor agonist
d. Add GLP-1 RA and stop the sulfonylurea (SU)
e. Add SGLT-2i and stop the SU

Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis



Tsapas et al. Ann Intern Med. 2020;173:278-286

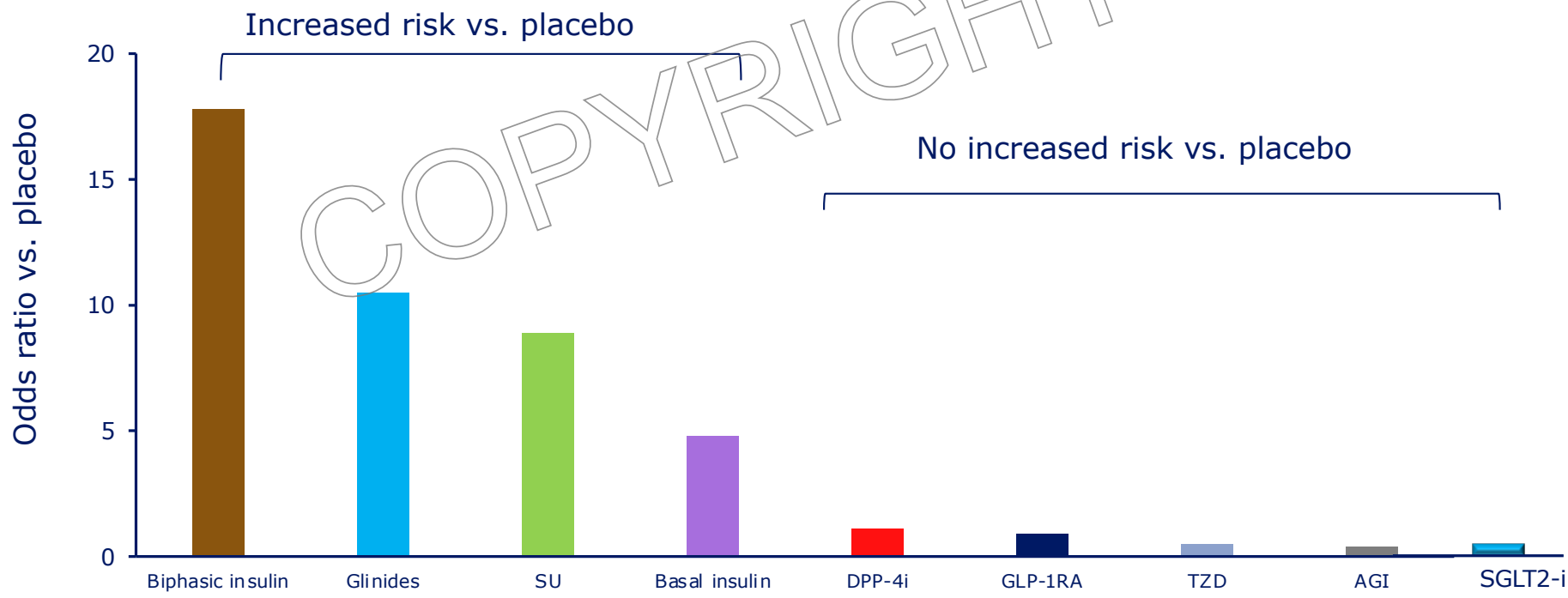
General Treatment Considerations: Glycemic Targets

- Individualization is key!
  - Tighter targets (≤6.5%) - younger, healthier, long life expectancy
  - Looser targets (7.0 - 8.0% +) - older, comorbidities (e.g. coronary heart disease, multiple microvascular complications), hypoglycemia prone, shorter life expectancy etc
- **Aim for best possible control that can be achieved safely**

What do we mean by ”safely”?

- Use medications that:
  - Reduce risk of hypoglycemia
  - Reduce weight gain/promote weight loss
  - Reduce cardiovascular risk

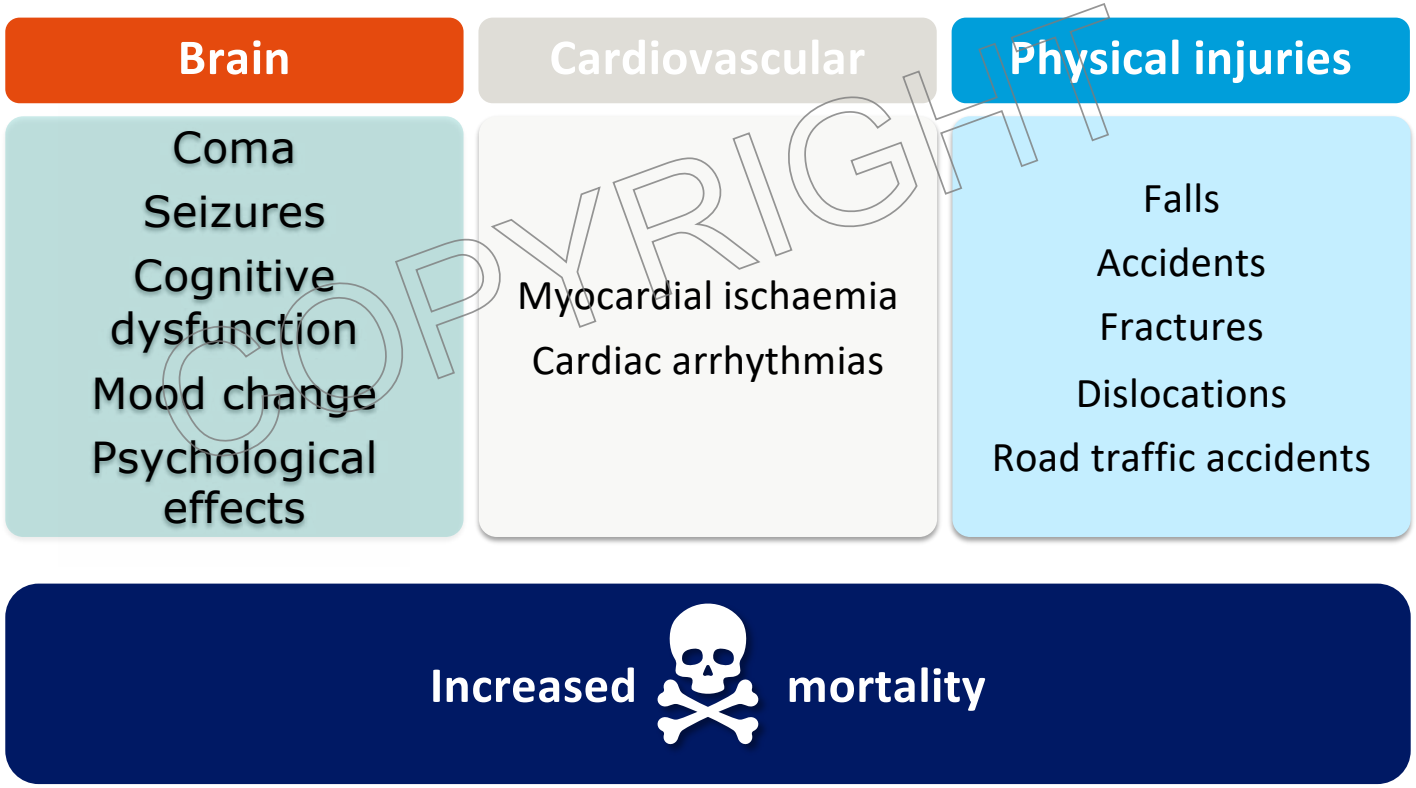
Hypoglycemic risk with antihyperglycemic agents added to metformin



AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione

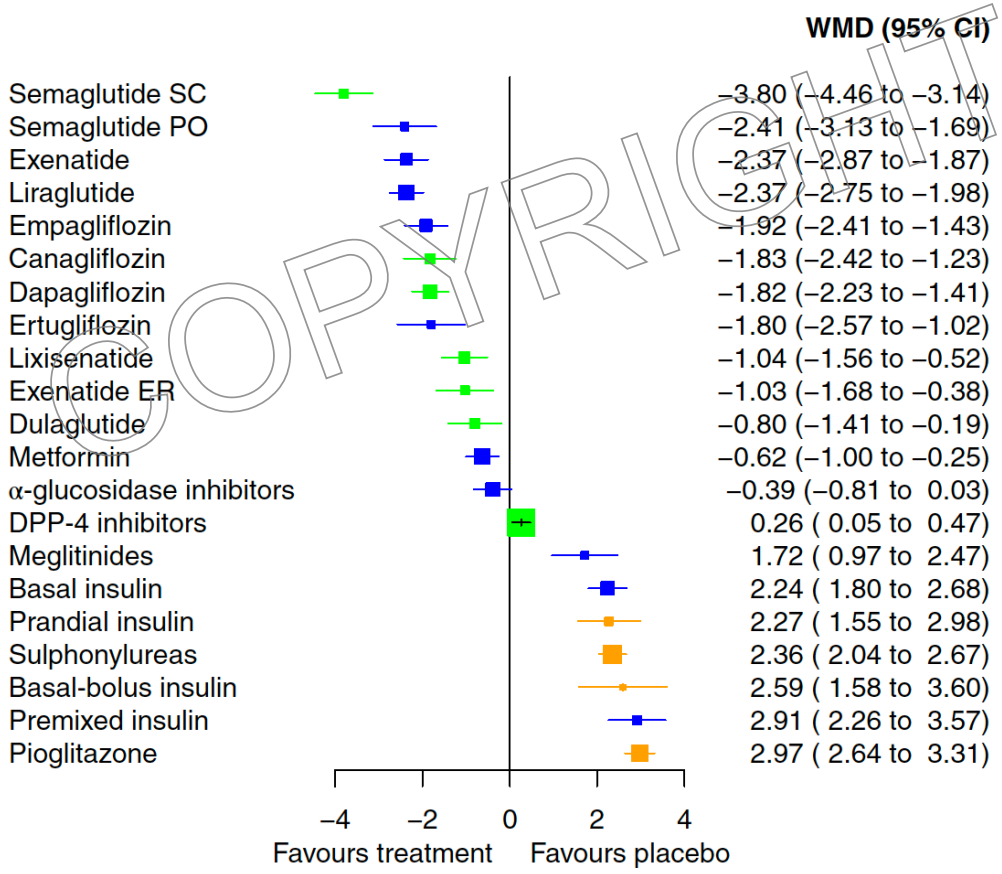
Liu *et al*. *Diabetes Obes Metab* 2012;14:810–20; Liu *et al. J Diabetes Complications* 2015;29:1295–303

Acute consequences of hypoglycemia



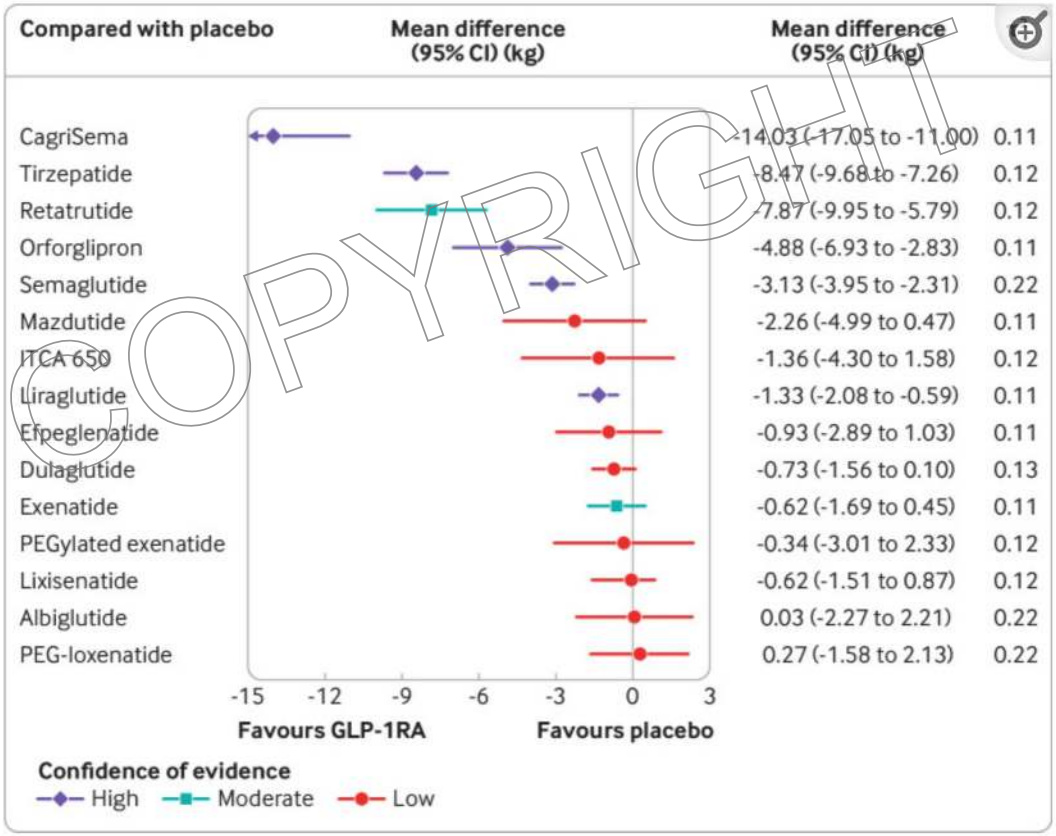
Seaquist ER et al. Diabetes Care 2012;35:409–414.

Comparative efficacy of glucose-lowering medications on body weight in T2DM



Tsapas et al. Diabetes Obes Metab. 2021;23:2116–2124

Comparative effectiveness of GLP-1 RA: weight loss



Yao, H et al. BMJ 2024 Jan 29:384:e076410. doi: 10.1136/bmj-2023-076410

Summary of 'older' non-insulin medications used in type 2 diabetes

	Metformin	Thiazolidinediones	Sulphonylureas	Alpha glucosidase inhibitors
Glucose-lowering efficacy	High	High	High	Moderate
Hypoglycemia	No	No	Yes	No
Weight	Neutral mainly, occasionally some loss	Gain	Gain	Neutral
CV effects	Neutral	Neutral	Neutral	Neutral
Possible side effects	Diarrhea, flatulence B12 deficiency (rare)	Fluid retention, bone fractures, exacerbate CHF	Very well tolerated	Diarrhea, flatulence

“Newer” glucose lowering medications and cardiovascular outcomes trials (CVOT) in diabetes

Major adverse cardiovascular events (MACE)

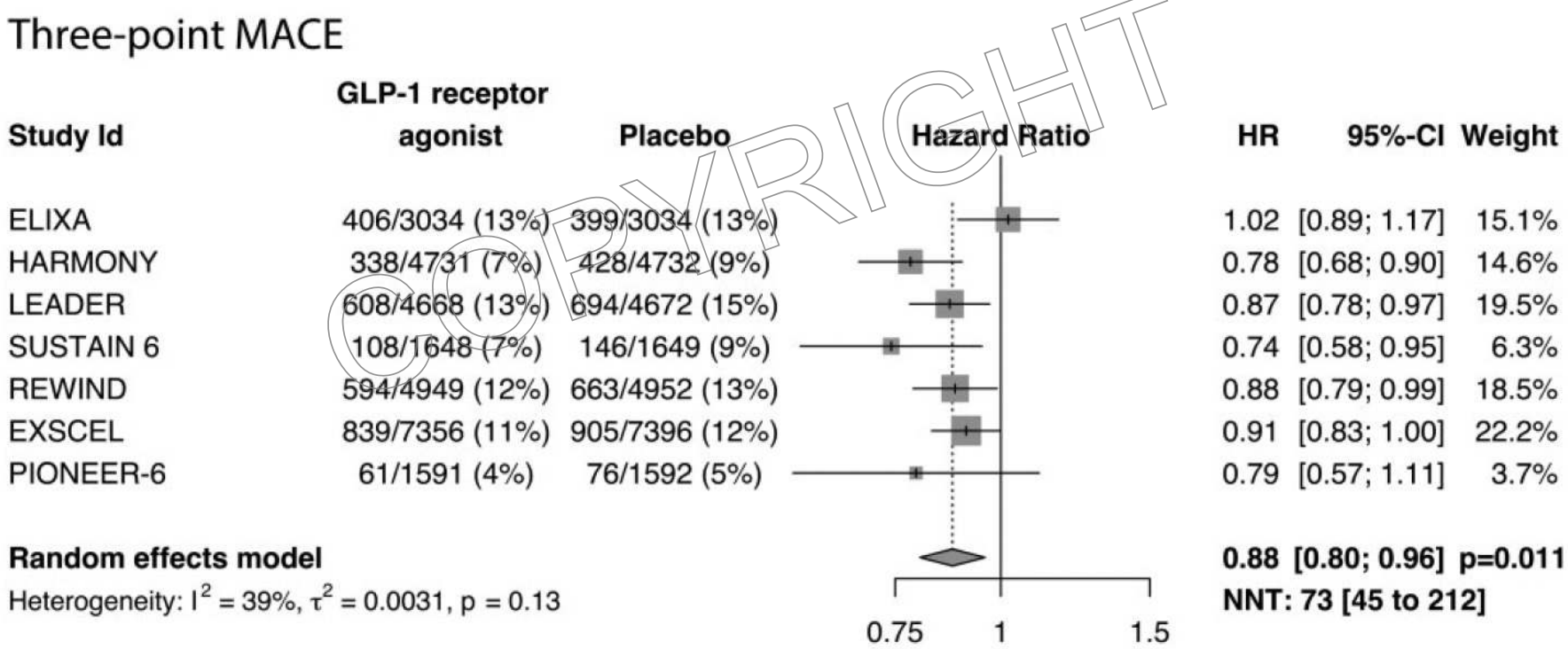
- Myocardial infarction
- Stroke
- Cardiovascular death

CVOT in diabetes: DPP-4 inhibitors, GLP-1 RA and SGLT-2 inhibitors

DPP-4 Inhibitors[1–4] SAVOR-TIMI, EXAMINE, TECOS, CARMELINA	• Neutral MACE
GLP-1 RA[5–10] EXSCEL, LEADER, SUSTAIN-6, REWIND, PIONEER-6, Harmony Outcomes, SOUL	• Long-acting GLP-1 RA and oral GLP-1 RA significantly reduced MACE – primary and secondary prevention • Renoprotective effects
SGLT-2 inhibitors[11–14] EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI, EMPEROR-Reduced	• Reduced MACE (secondary prevention only) • Reduced hospitalisation for HF • Renoprotective effects

1. Scirica BM et al. N Engl J Med 2013;369:1317–1326; 2. Zannad F et al. Lancet 2015;385:2067–2076; 3. Green JB et al. N Engl J Med 2015;373:232–242; 4. Rosenstock J et al. JAMA 2019;321:69-79. 5. Holman RR, et al. N Engl J Med 2017;377:1228–39; 6. Marso SP et al. N Engl J Med 2016;375:311–322; 7. Marso SP et al. N Engl J Med 2016;375:1834–1844; 8. Gerstein HC et al. Lancet. 2019 pii: S0140-6736(19)31149–3. 9. Husain M et al. N Engl J Med 2019;381:841–851 10. Hernandez et al. Lancet. 2018;392:1519–1529; 11. Zinman B et al. N Engl J Med 2015;373:2117–2128; 12. Neal B et al. N Engl J Med 2017;377:644-657; 13. Wiviott SD et al. N Engl J Med. 2019;380:347–357; 14. Packer M ,et al. N Engl J Med 2020;383:1413–1424. McGuire DK et al. N Engl J Med. DOI: 10.1056/NEJMoa2501006

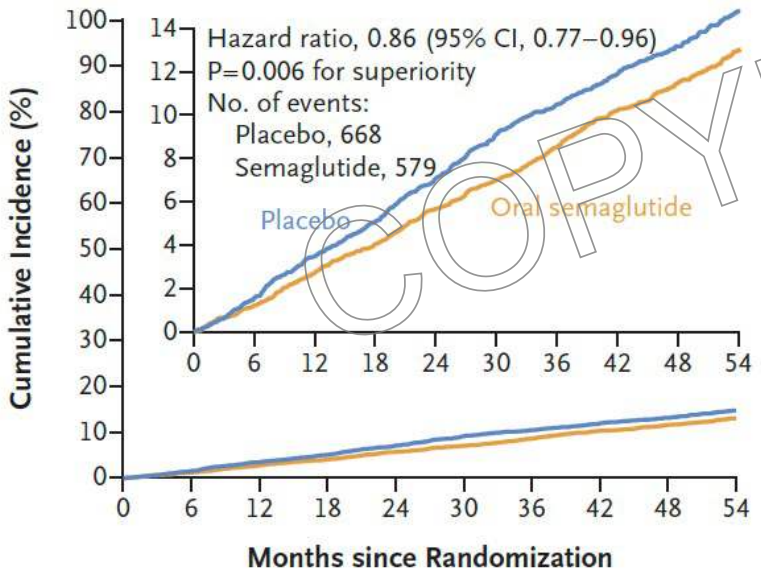
Long acting GLP-1 RA reduce MACE in T2DM



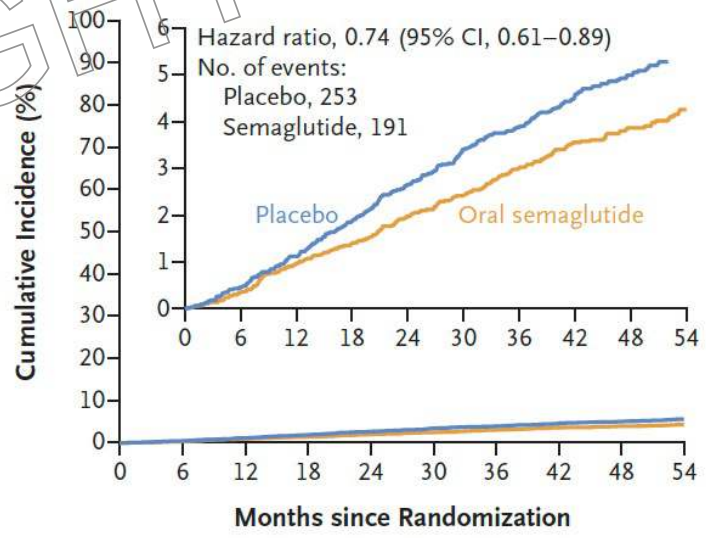
Marsico F et al. European Heart Journal (2020) 41, 3346–3358

Oral semaglutide significantly reduces MACE

MACE



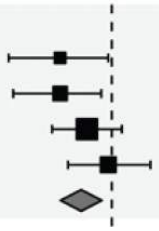
Nonfatal MI



McGuire DK et al. N Engl J Med. 2025; *DOI: 10.1056/NEJMoa2501006*

Some SGLT2i reduce MACE in T2DM

	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	Hazard Ratio (95% CI)
	no. / total no. (%)		*no. per 1000 patient years*		
Diabetes at high risk for ASCVD trials					
EMPA-REG OUTCOME	490/4687 (10.5)	282/2333 (12.1)	37.4	43.9	0.86 (0.74-0.99)
CANVAS Program	585/5795 (10.1)	426/4347 (9.8)	26.9	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582 (8.8)	803/8578 (9.4)	22.6	24.2	0.93 (0.84-1.03)
VERTIS-CV	735/5499 (13.4)	368/2747 (13.4)	40.0	40.3	0.99 (0.88-1.12)
Group estimate (FE; p-heterogeneity=0.32)					0.91 (0.86-0.97)



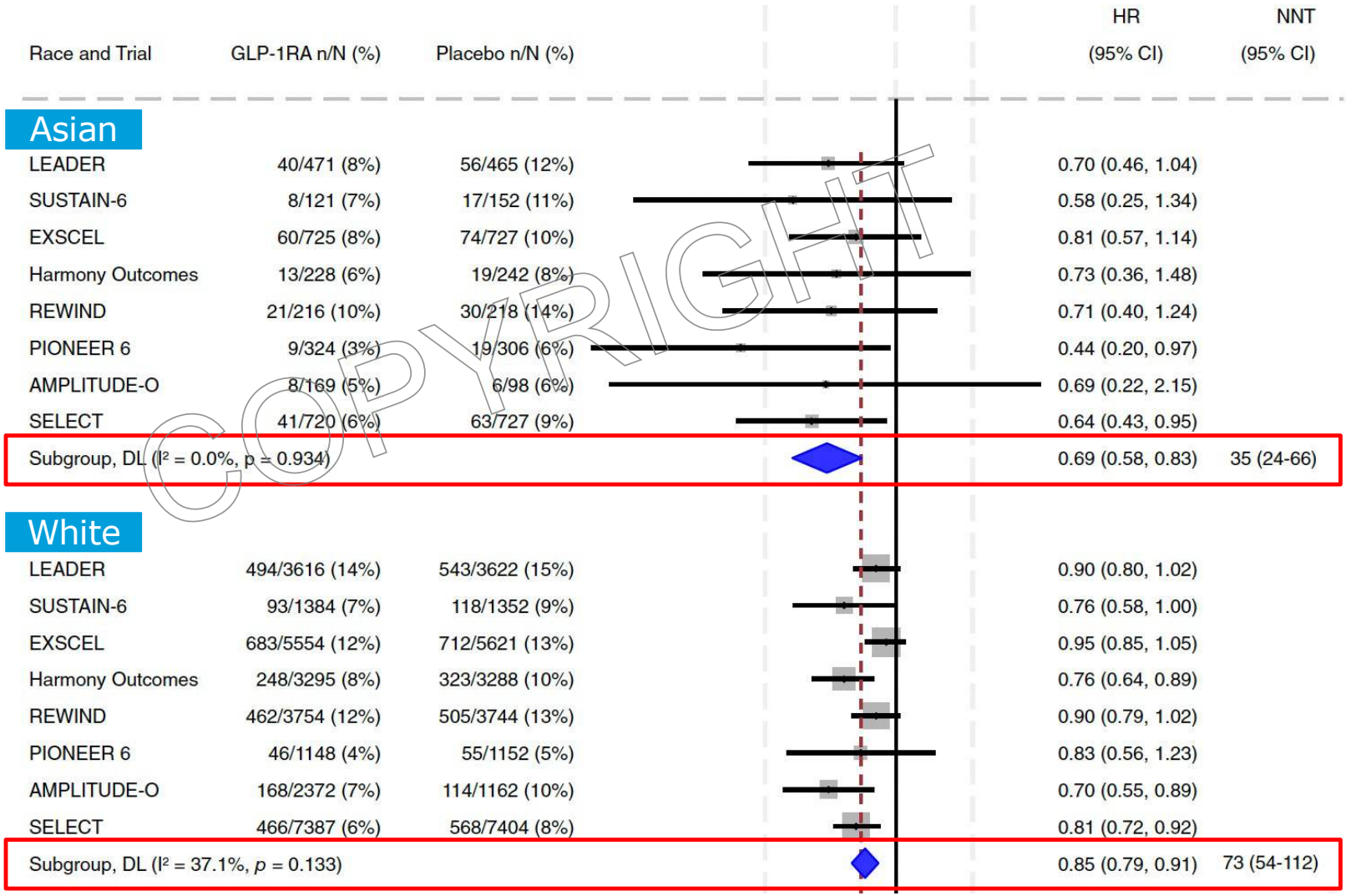
Patel, S et al. Circulation. 2024;149:1789–1801

Do all racial/ethnic groups derive the same CV benefit from these newer medications?

Comparative Efficacy of Glucagon-Like Peptide 1 Receptor Agonists for Cardiovascular Outcomes in Asian Versus White Populations: Systematic Review and Meta-analysis of Randomized Trials of Populations With or Without Type 2 Diabetes and/or Overweight or Obesity

Matthew M.Y. Lee, Nazim Ghouri, Anoop Misra, Yu Mi Kang, Martin K. Rutter, Hertzel C. Gerstein, Darren K. McGuire, and Naveed Sattar

Diabetes Care 2025;48(3):489–493 | https://doi.org/10.2337/dc24-1533


Race and Trial
GLP-1RA n/N (%)
Placebo n/N (%)
HR (95% CI)
NNT (95% CI)
Asian
LEADER 40/471 (8%) 56/465 (12%) 0.70 (0.46, 1.04)
SUSTAIN-6 8/121 (7%) 17/152 (11%) 0.58 (0.25, 1.34)
EXSCEL 60/725 (8%) 74/727 (10%) 0.81 (0.57, 1.14)
Harmony Outcomes 13/228 (6%) 19/242 (8%) 0.73 (0.36, 1.48)
REWIND 21/216 (10%) 30/218 (14%) 0.71 (0.40, 1.24)
PIONEER 6 9/324 (3%) 19/306 (6%) 0.44 (0.20, 0.97)
AMPLITUDE-O 8/169 (5%) 6/98 (6%) 0.69 (0.22, 2.15)
SELECT 41/720 (6%) 63/727 (9%) 0.64 (0.43, 0.95)
Subgroup, DL (I² = 0.0%, p = 0.934) 0.69 (0.58, 0.83) 35 (24-66)
White
LEADER 494/3616 (14%) 543/3622 (15%) 0.90 (0.80, 1.02)
SUSTAIN-6 93/1384 (7%) 118/1352 (9%) 0.76 (0.58, 1.00)
EXSCEL 683/5554 (12%) 712/5621 (13%) 0.95 (0.85, 1.05)
Harmony Outcomes 248/3295 (8%) 323/3288 (10%) 0.76 (0.64, 0.89)
REWIND 462/3754 (12%) 505/3744 (13%) 0.90 (0.79, 1.02)
PIONEER 6 46/1148 (4%) 55/1152 (5%) 0.83 (0.56, 1.23)
AMPLITUDE-O 168/2372 (7%) 114/1162 (10%) 0.70 (0.55, 0.89)
SELECT 466/7387 (6%) 568/7404 (8%) 0.81 (0.72, 0.92)
Subgroup, DL (I² = 37.1%, p = 0.133) 0.85 (0.79, 0.91) 73 (54-112)

Research

The Royal Society of Medicine

Journal of the Royal Society of Medicine; 2024, Vol. 117(8) 267–283
DOI: 10.1177/01410768231198442

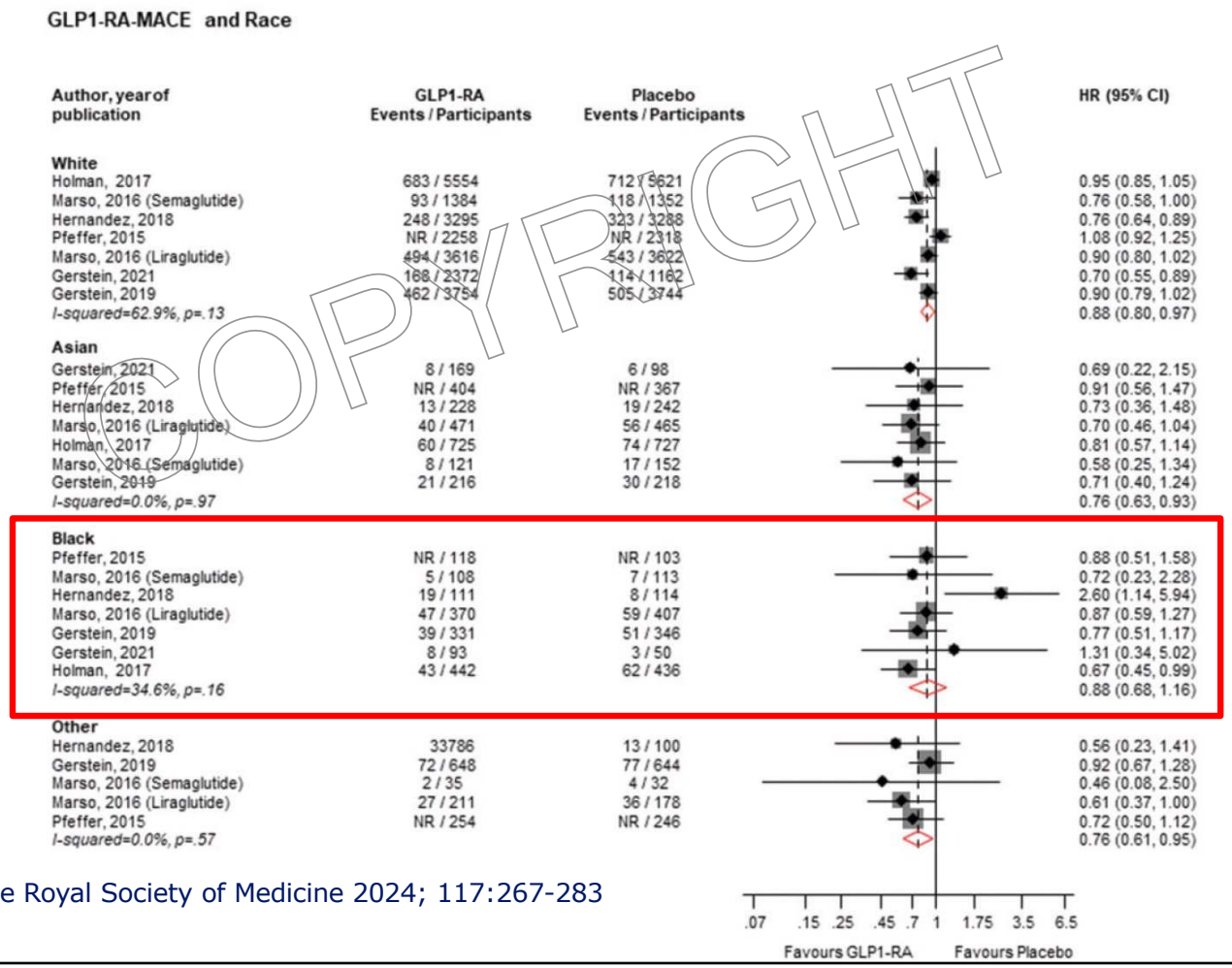
Racial, ethnic and regional differences in the effect of sodium–glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists on cardiovascular and renal outcomes: a systematic review and meta-analysis of cardiovascular outcome trials

Setor K Kunutsor, Kamlesh Khunti and Samuel Seidu

Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester LE5 4WP, UK

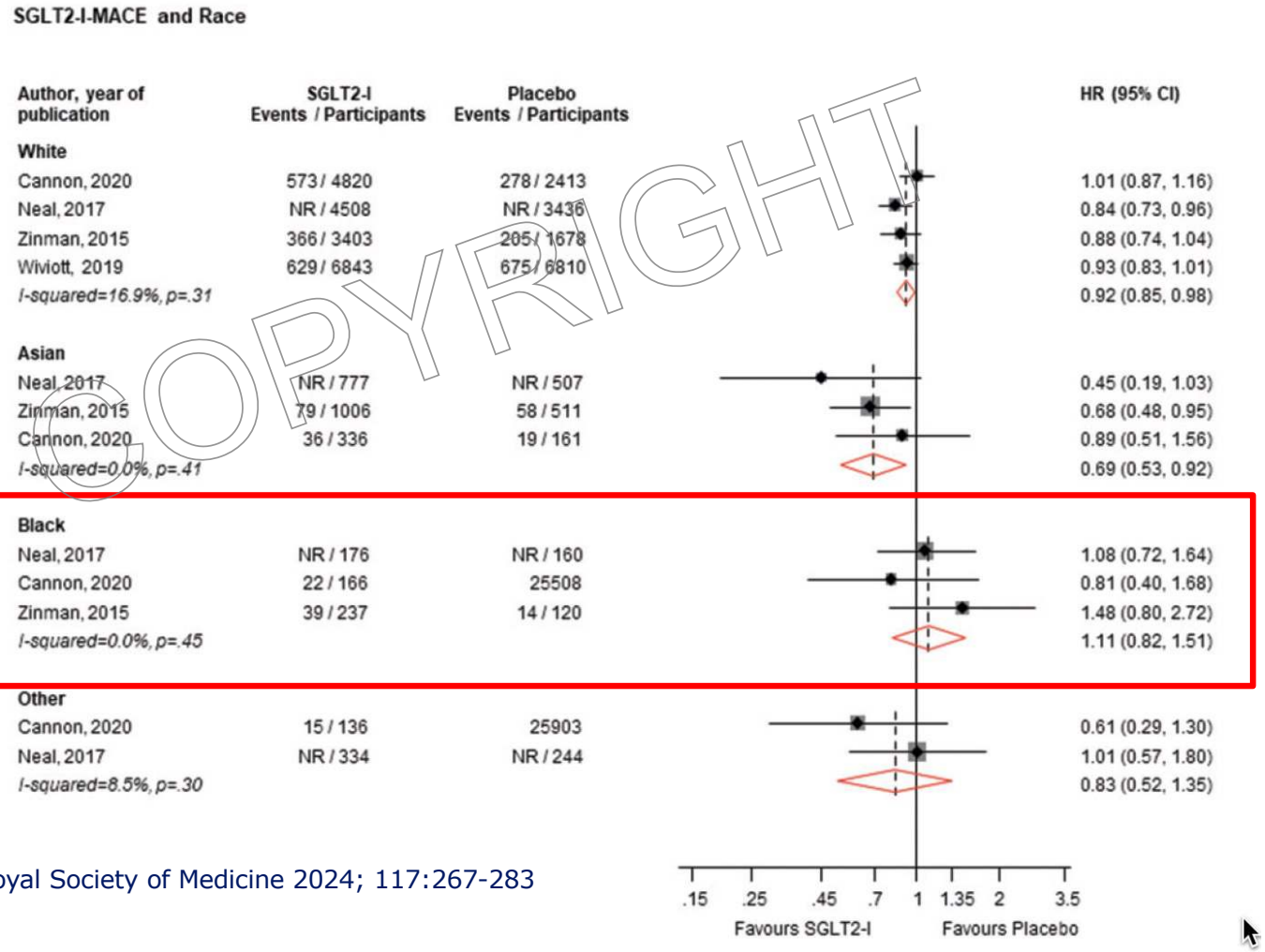
Corresponding author: Samuel Seidu. Email: sis11@le.ac.uk

GLP-1 RA MACE and race



Kunutsor,SK et al. J of the Royal Society of Medicine 2024; 117:267-283

SGLT2i MACE and race



Kunutsor,SK et al. J of the Royal Society of Medicine 2024; 117:267-283

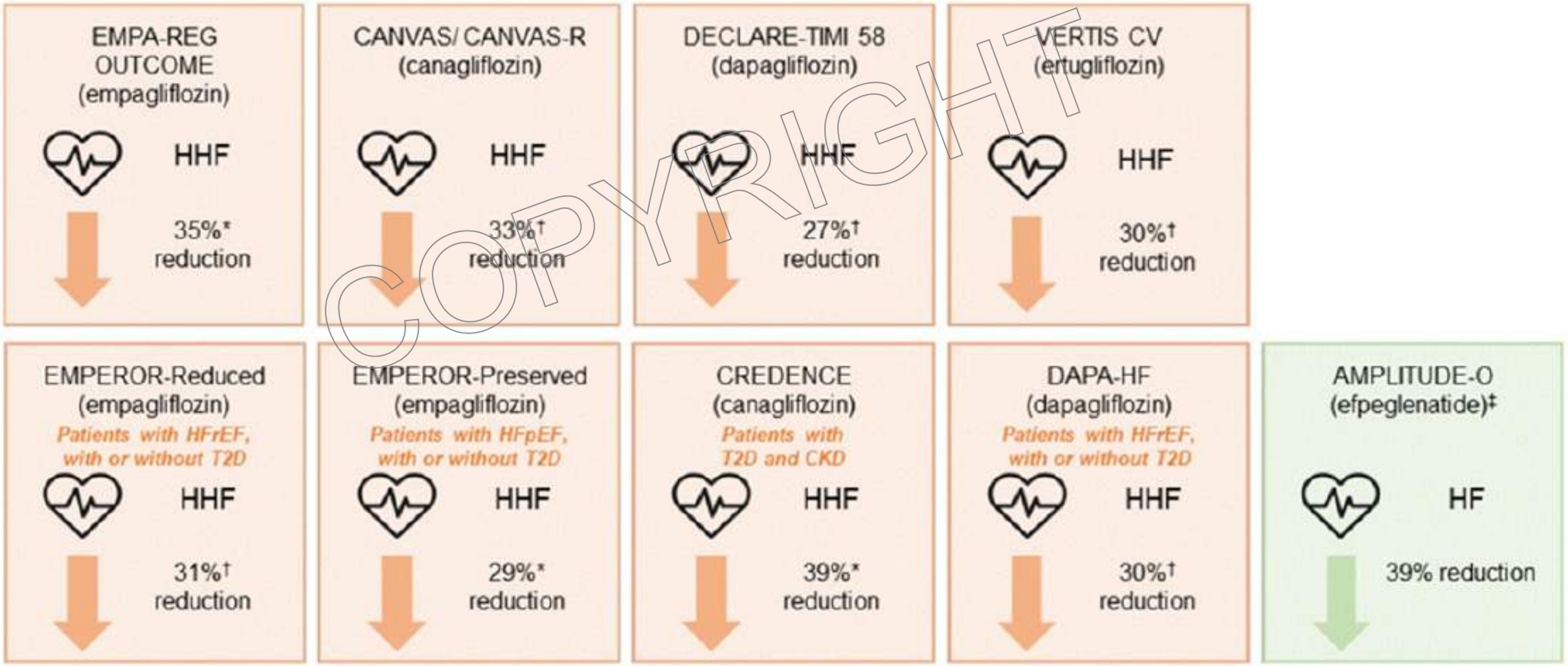
"No significant beneficial effects were observed in Black populations for both interventions and for all the evaluated outcomes, except for HF hospitalizations in relation to SGLT2-Is."

What is the possible explanation for this?

1. More severe cardiorenal disease
2. CVD risk factors less adequately treated
3. Black populations underrepresented in trials
4. Differences in PK and PD characteristics in this population group

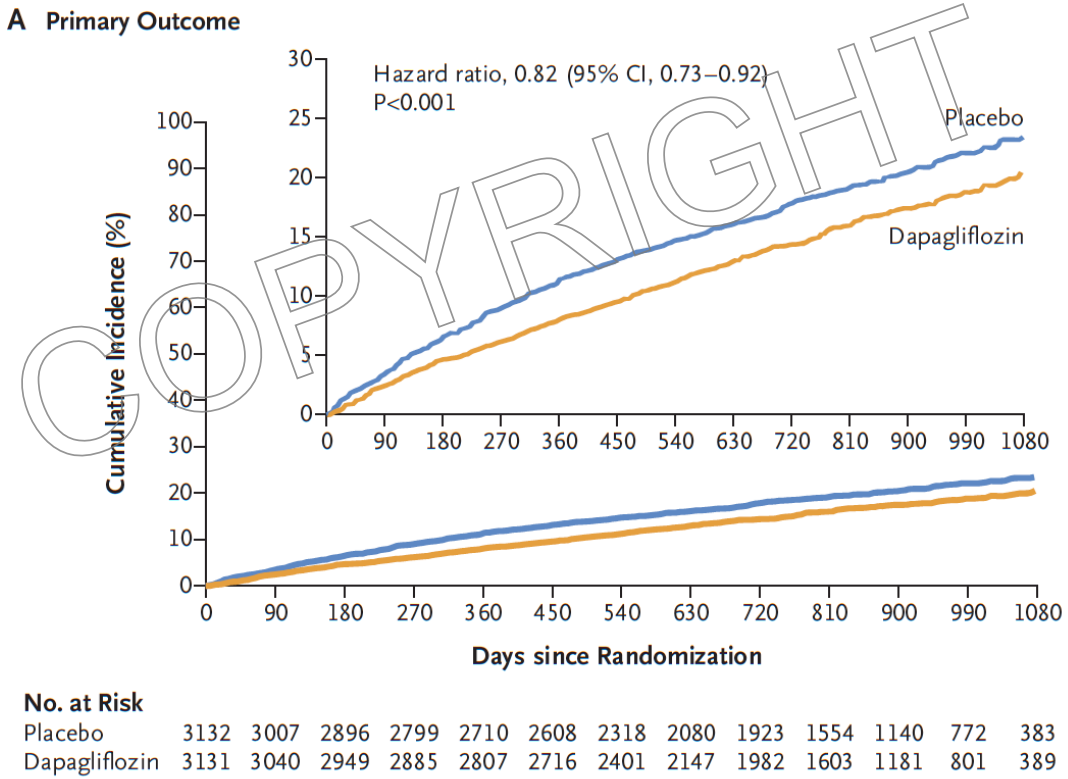
Kunutsor,SK et al. J of the Royal Society of Medicine 2024; 117:267-283

Summary - SGLT2 inhibitors and heart failure



Davies, M et al. Cardiovascular Diabetology (2022) 21:144
https://doi.org/10.1186/s12933-022-01575-9

Dapagliflozin reduces hospitalization for heart failure, worsening of heart failure and death from CV disease by 18% in people with HF and preserved or slightly reduced EF



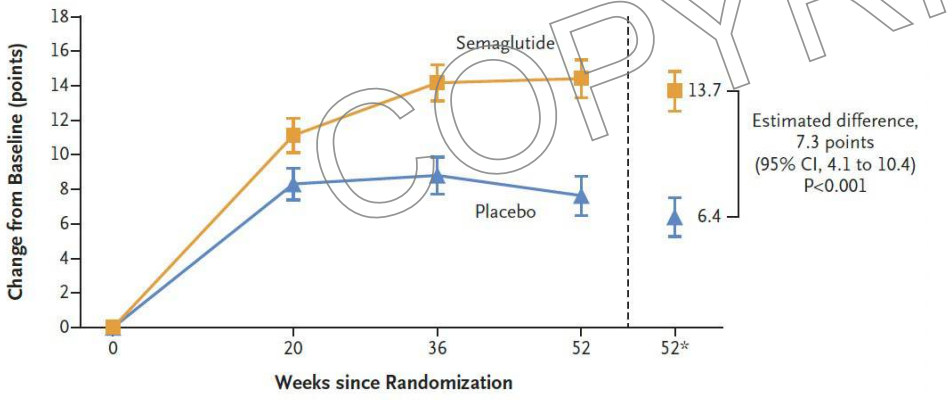
With or without type 2 diabetes

Solomon S et al. New Engl J Med 2022; DOI: 10.1056/NEJMoa2206286

Semaglutide in people with T2DM and HFpEF

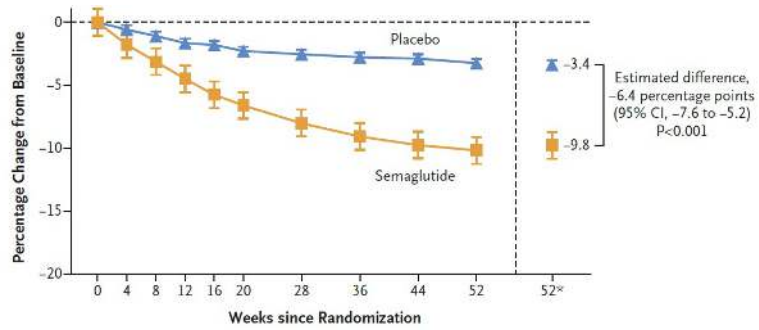
Improved heart failure related symptoms and reduction in body weight

Change in KCCQ-CSS



No. of Participants					
Semaglutide	310	289	274	281	310
Placebo	306	284	270	272	306

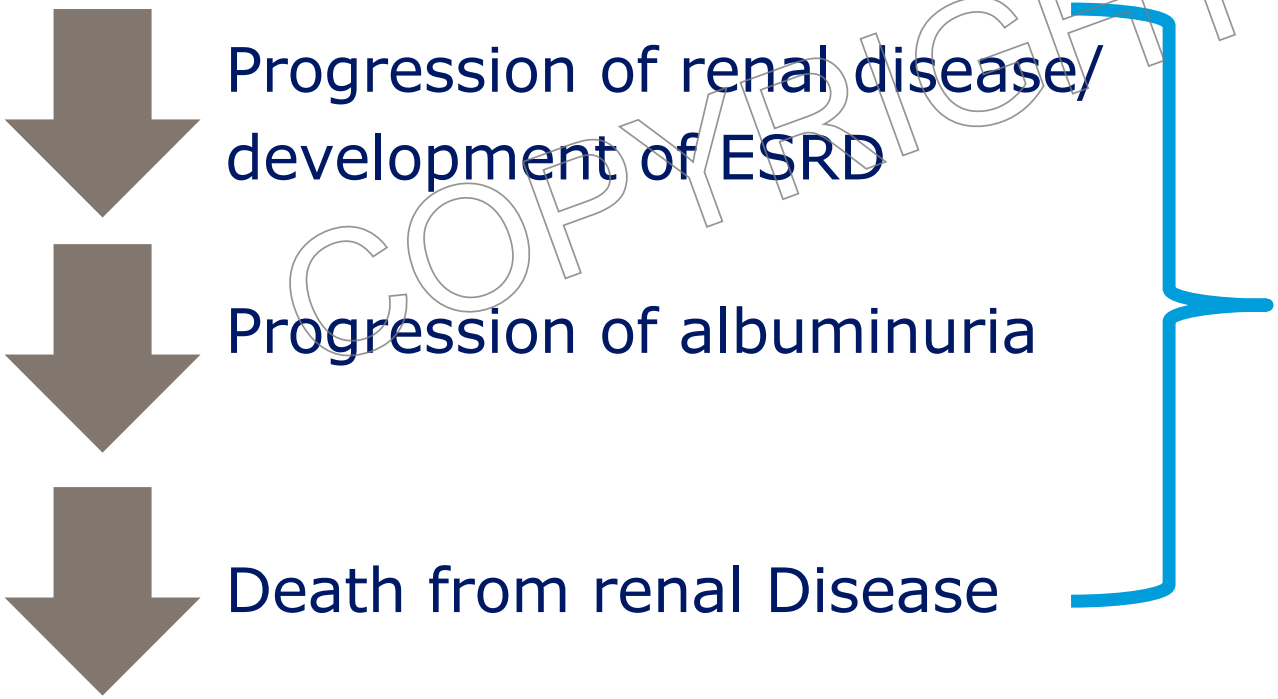
Change in Body Weight



No. of Participants											
Semaglutide	310	307	297	299	290	292	283	286	282	286	310
Placebo	306	300	298	287	292	289	282	278	273	278	306

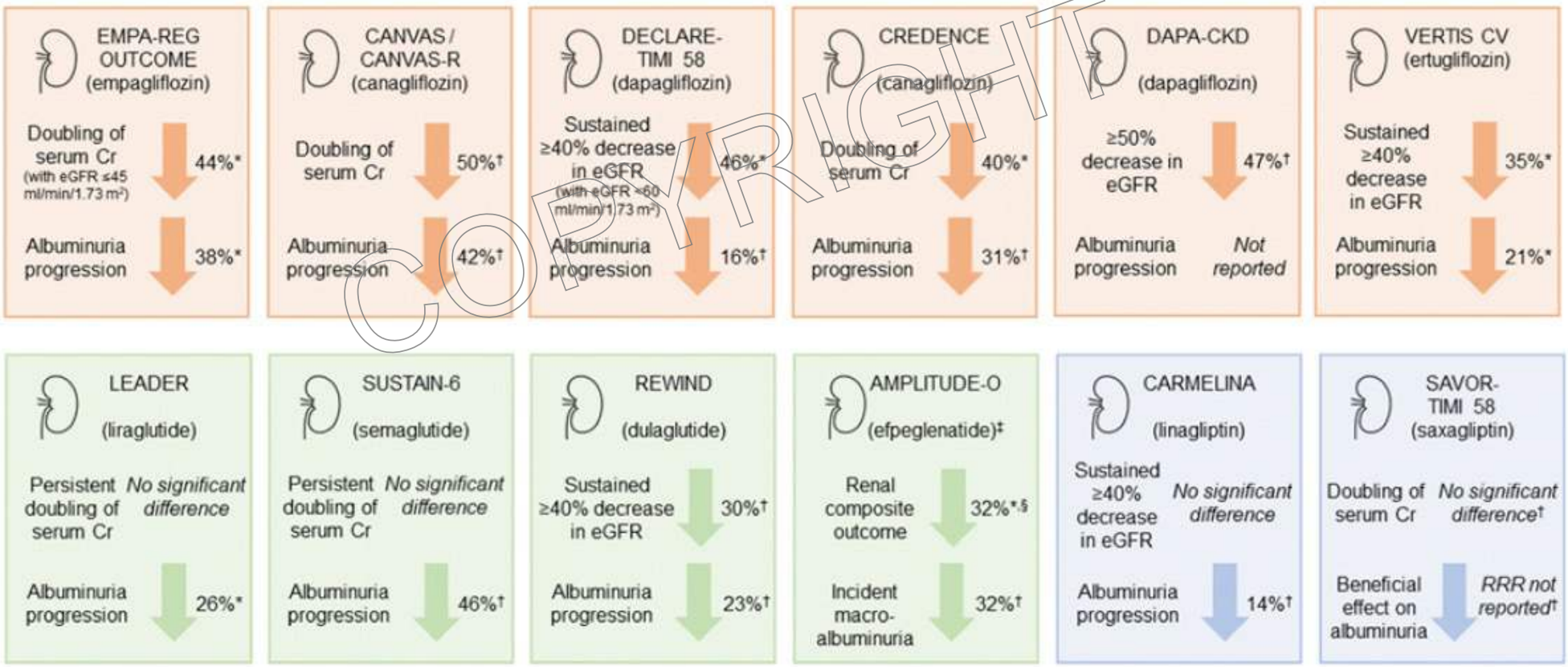
Kosiborod. NEJM. 2024;390:1394.

SGLT2 inhibitors Also Confer Renal Benefits



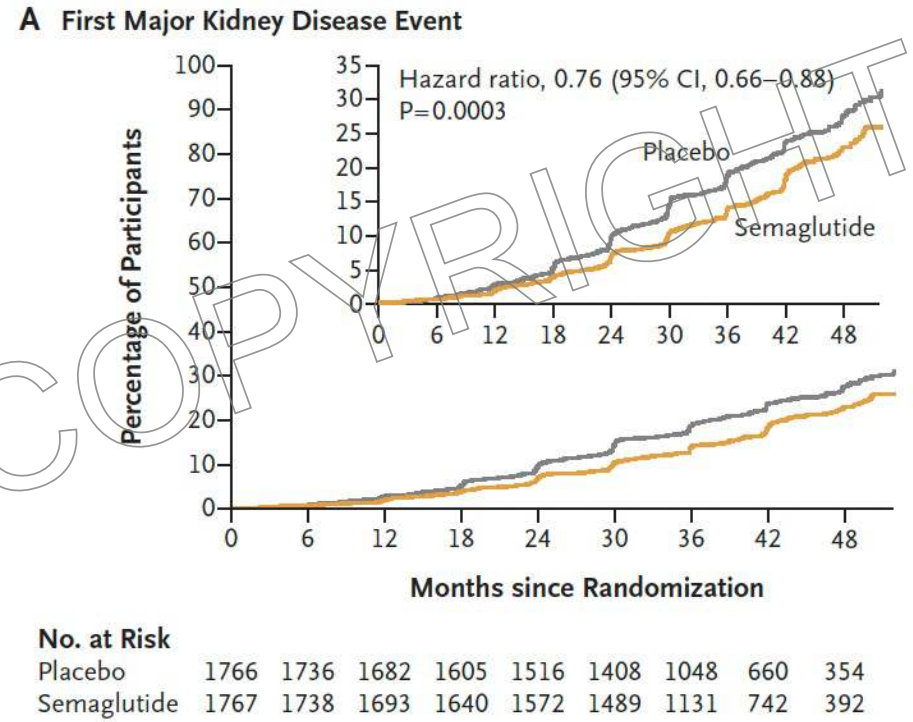
- *Specific FDA indication to *treat diabetic kidney disease (DKD)* in adults with T2DM and DKD
- Empagliflozin being reviewed for this

Summary - newer glucose lowering drugs and renal outcomes



Davies, M et al. Cardiovascular Diabetology (2022) 21:144
https://doi.org/10.1186/s12933-022-01575-9

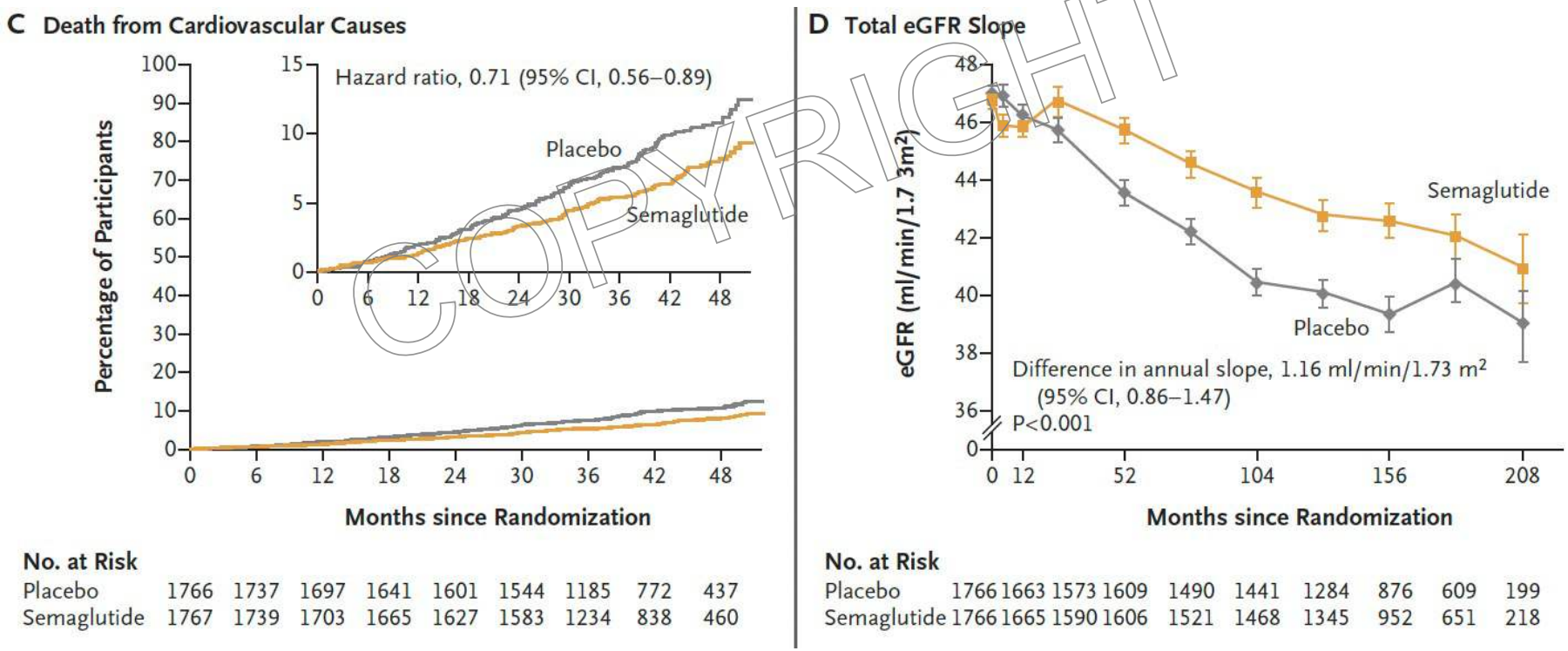
Semaglutide in T2DM has renoprotective effects



24% reduction in development of end stage renal disease, > 50% reduction in eGFR death from renal or cardiovascular causes

Perkovic, V et al. DOI: 10.1056/NEJMoa2403347 Published online May 24, 2024

Cardiorenal protective effects of semaglutide in T2 DM



Perkovic, V et al. DOI: 10.1056/NEJMoa2403347 Published online May 24, 2024

Summary of 'newer' glucose-lowering agents used in T2DM

	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT-2 inhibitors
Glucose-lowering efficacy	Intermediate	High	Intermediate
Hypoglycemia	No	No	No
Weight	Neutral	Loss	Loss
CV effects	Neutral	Benefit: Liraglutide, Semaglutide sc Dulaglutide	Benefit: Empagliflozin, Canagliflozin
CHF	Saxagliptin potential risk	Benefit: Semaglutide Tirzepatide	Benefit: Empagliflozin, Canagliflozin Dapagliflozin, Ertugliflozin
Renal effects	Neutral	Benefit: Semaglutide	Benefit: Canagliflozin, Empagliflozin Dapagliflozin, Ertugliflozin
Adverse events	Joint pain, potential acute pancreatitis	GI effects, potential acute pancreatitis	Genitourinary infections, volume depletion, hypotension

GI, gastrointestinal

American Diabetes Association. Diabetes Care 2021;44(Suppl 1):S111–S124.

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American Diabetes Association. Diabetes Care 2021;44(Suppl 1):S111–S124.

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonism

Central Nervous System
↑ satiety
↓ food intake
↑ nausea
↓ body weight

Pancreas
↑ insulin
↓ glucagon

Stomach
↓ gastric emptying

Systemic
↓ hyperglycemia

Liver
↑ insulin sensitivity
↓ hepatic glucose production
↓ ectopic lipid accumulation

Glucagon-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonism

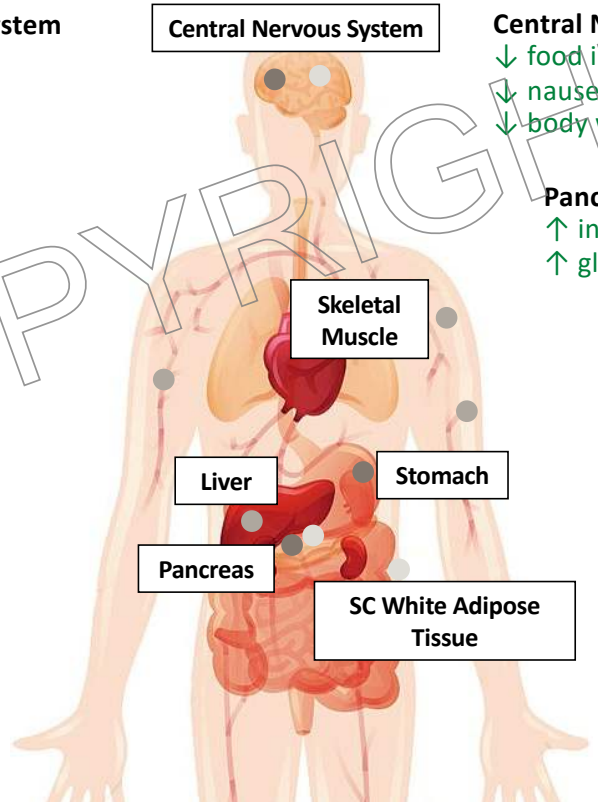
Central Nervous System
↓ food intake
↓ nausea
↓ body weight

Pancreas
↑ insulin
↑ glucagon

SC White Adipose Tissue
↑ insulin sensitivity
↑ lipid buffering capacity
↑ blood flow
↑ storage capacity
↓ proinflammatory immune cell infiltration

Systemic
↓ hyperglycemia
↓ dietary triglyceride

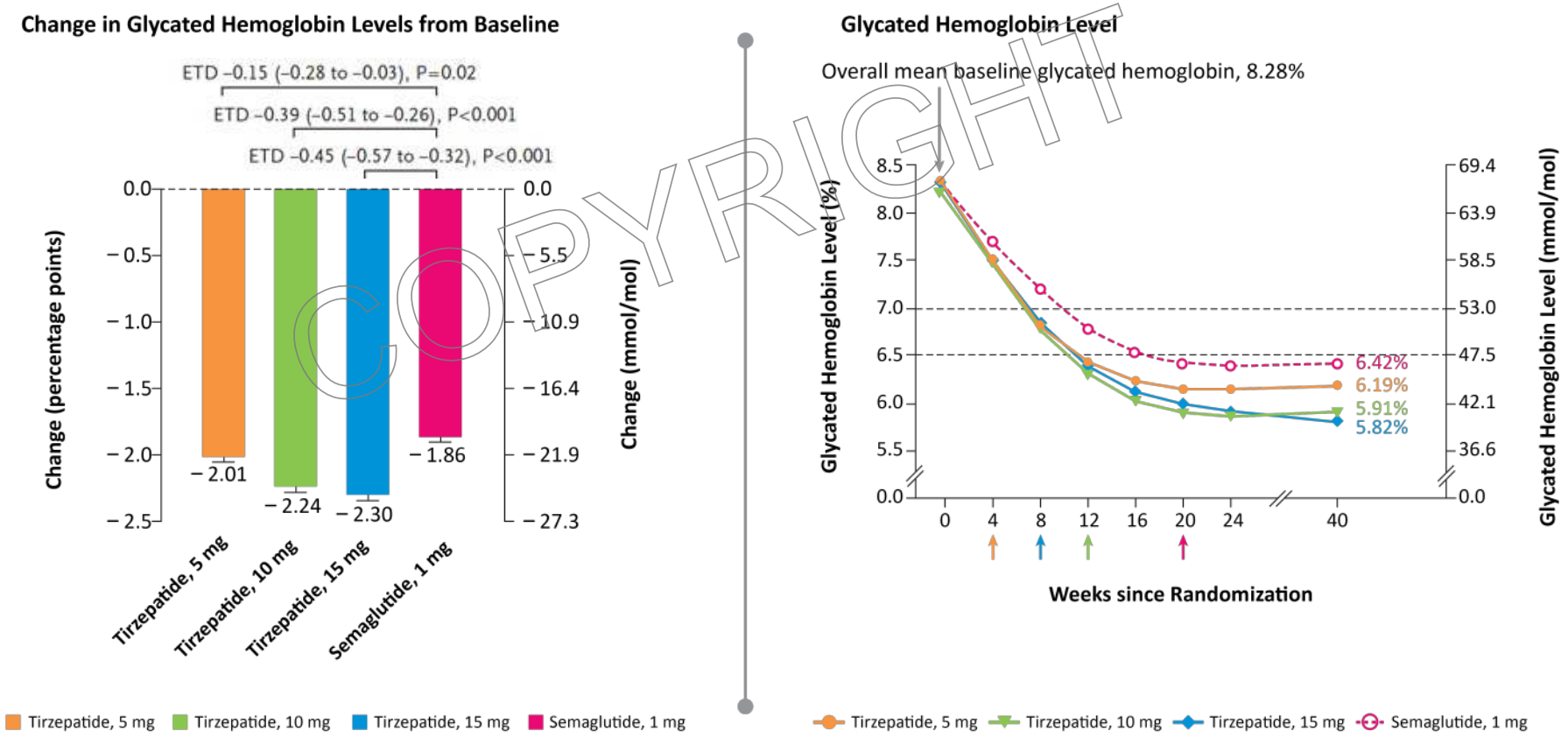
Skeletal Muscle
↑ insulin sensitivity
↑ metabolic flexibility
↓ ectopic lipid accumulation



- Glucose-dependent insulinotropic polypeptide receptor agonism
- Glucagon-like peptide-1 receptor agonism
- Indirect action

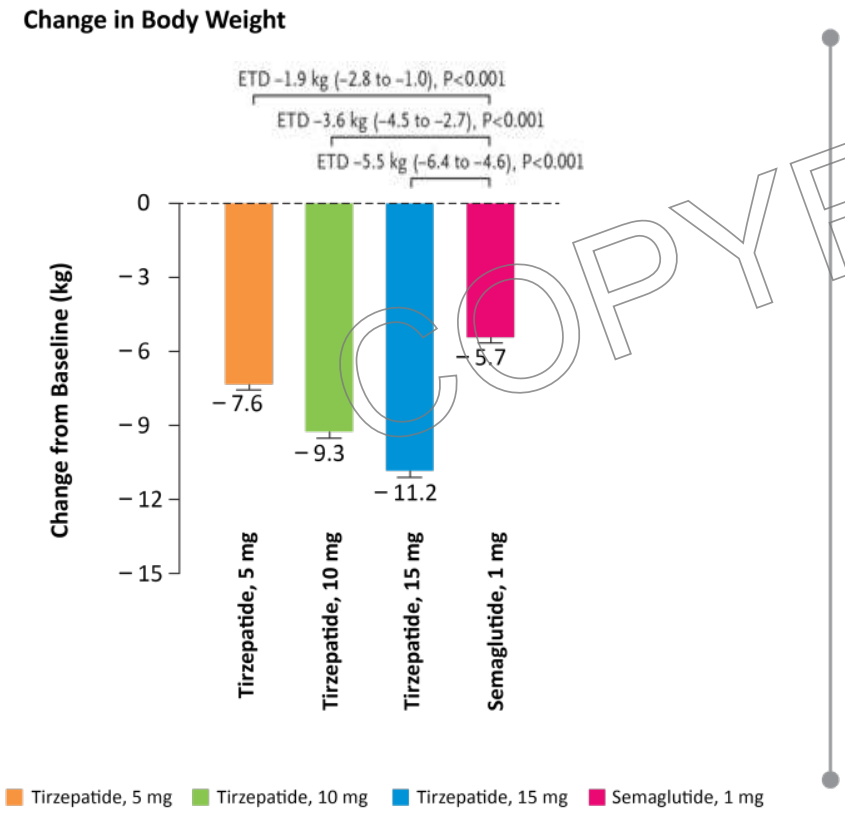
Samms. Trends Endocrinol Metab. 2020;31:410.

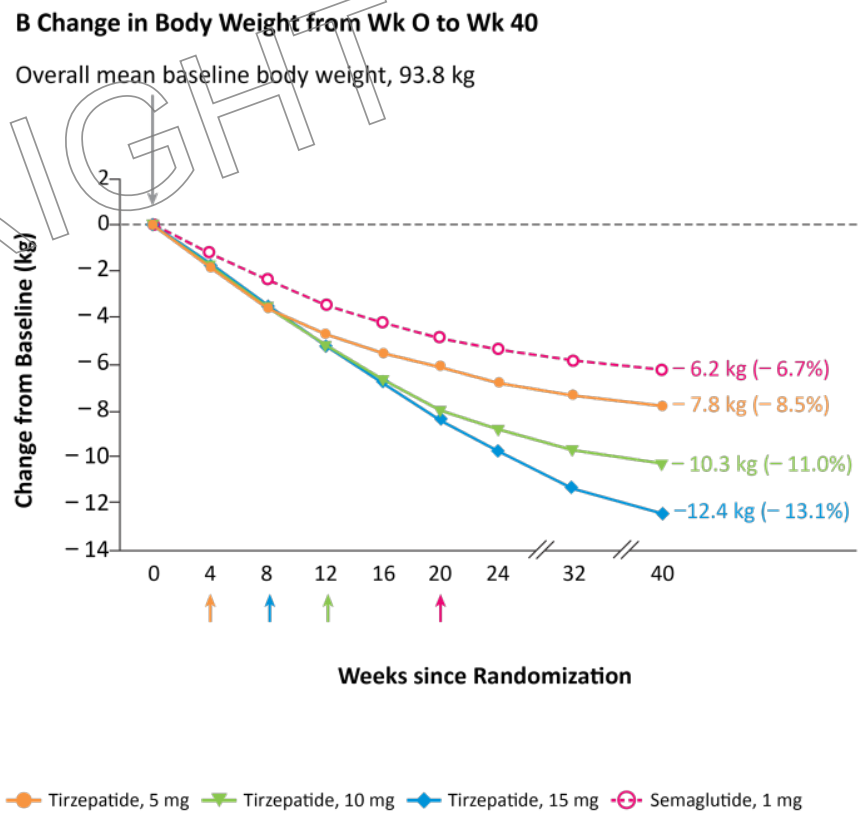
Tirzepatide vs Semaglutide in T2DM – Change in HbA1c



Adapted from Frias J et al. N Engl J Med 2021;385:503-15.

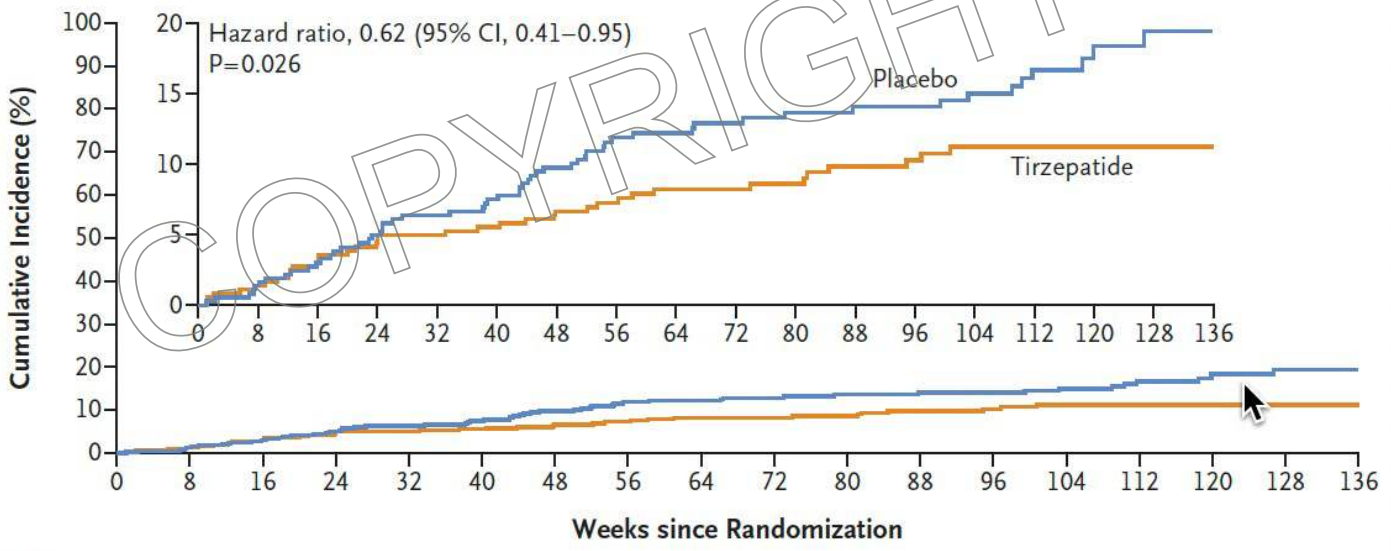
Tirzepatide vs Semaglutide in T2DM – Change in Weight





Adapted from Frias J et al. N Engl J Med 2021;385:503-15.

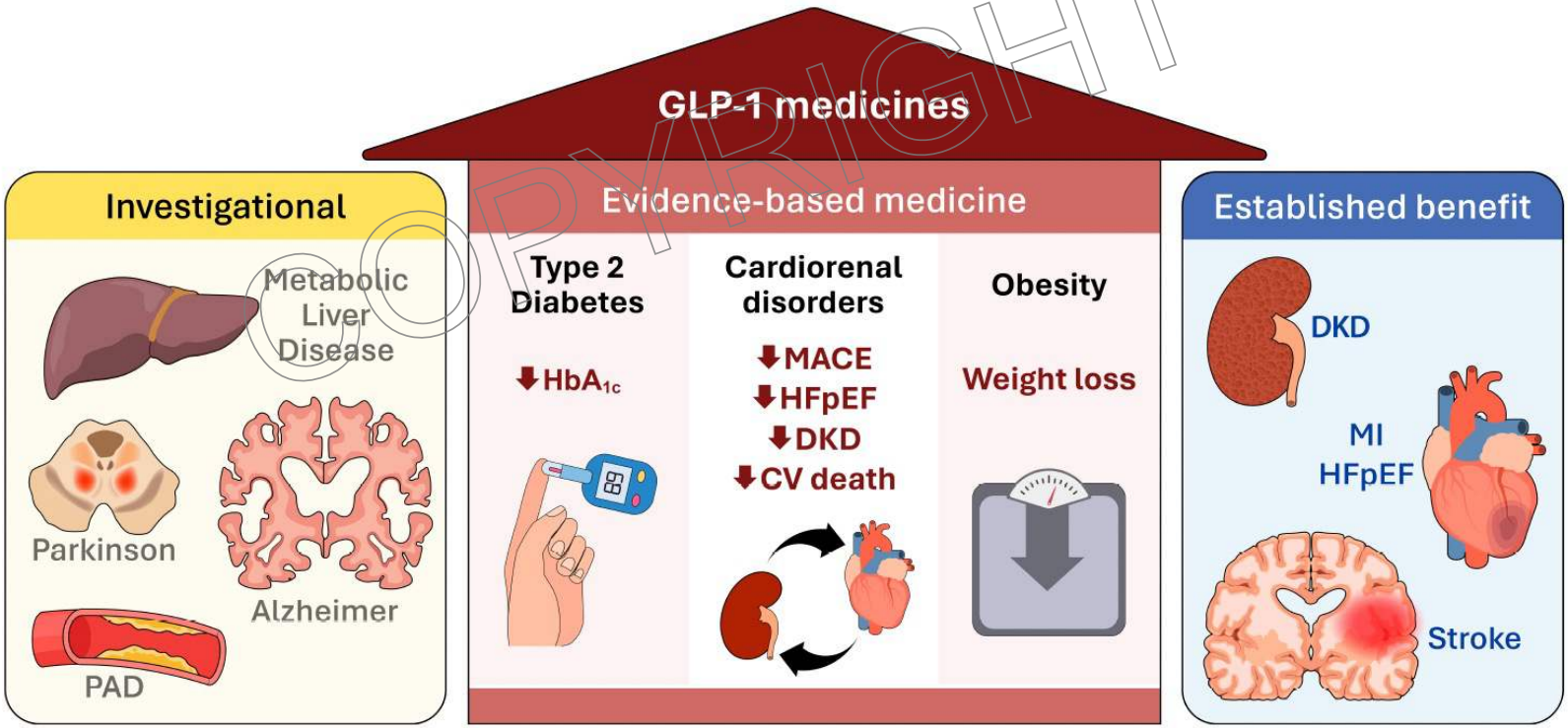
Tirzepatide lowers risk of cardiovascular death and worsening of heart failure by 38% in people with obesity with or without T2DM



No. 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

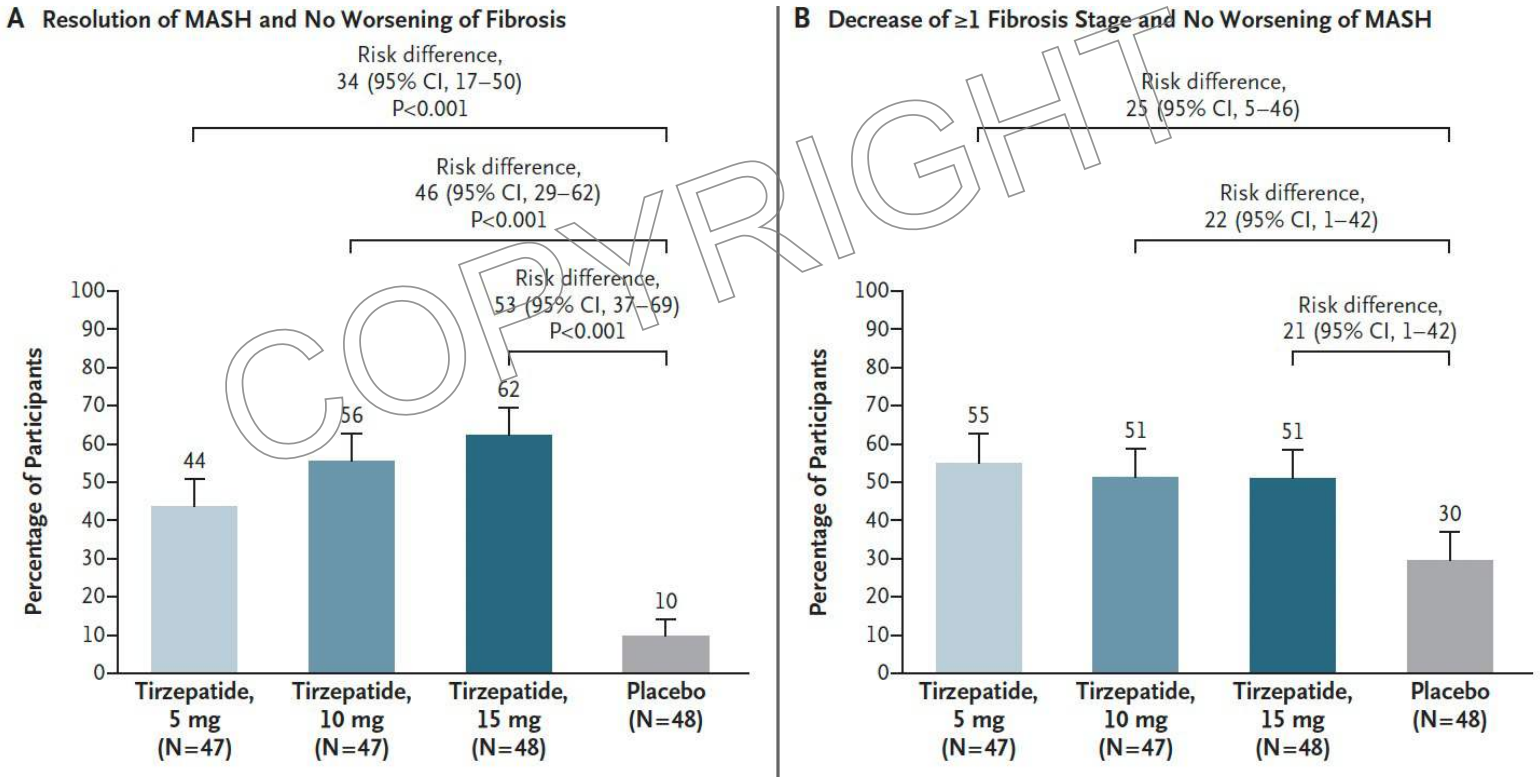
Packer, M et al. New Engl J Med. 2024. DOI: 10.1056/NEJMoa2410027

Established and emerging benefits of GLP 1 RA



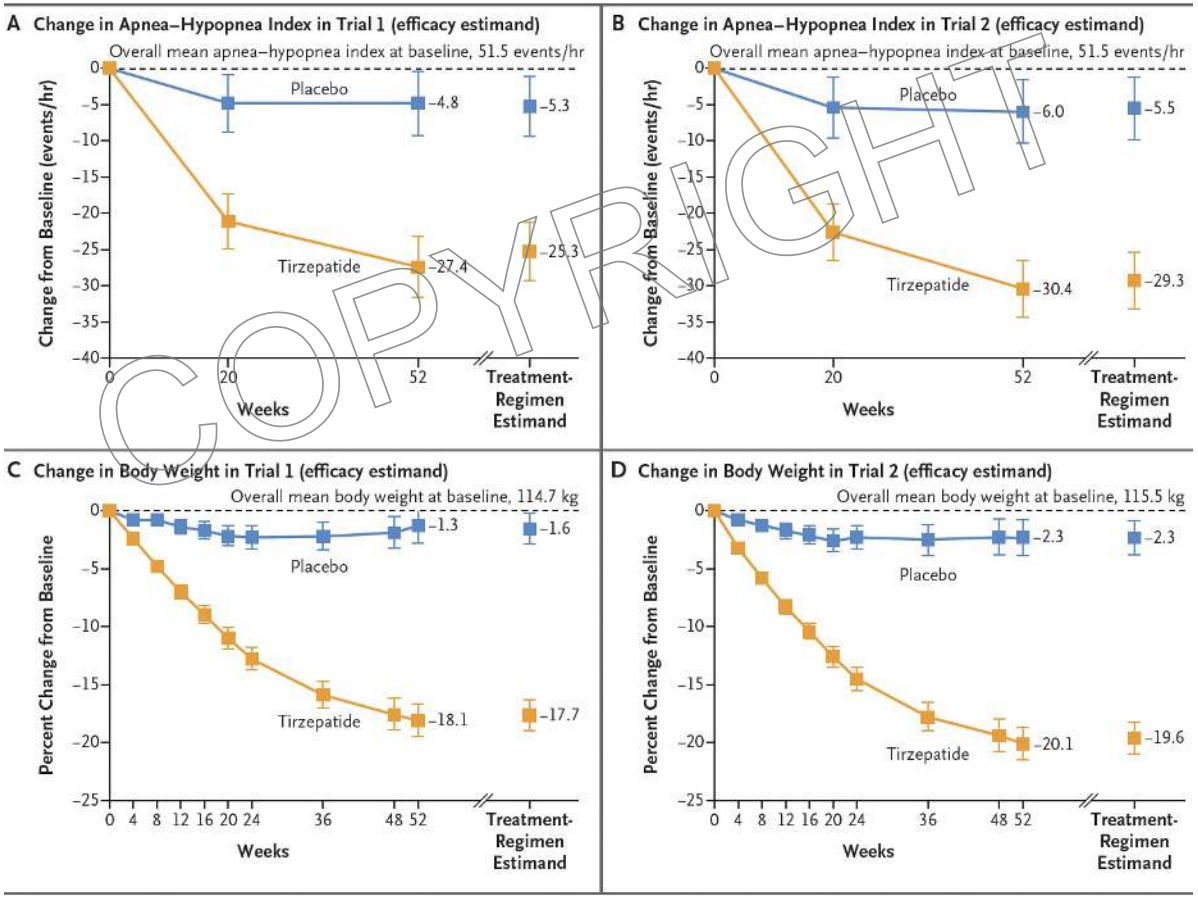
Drucker DJ, Diabetes Care 2024;47(00):1–16

Tirzepatide improves MASH



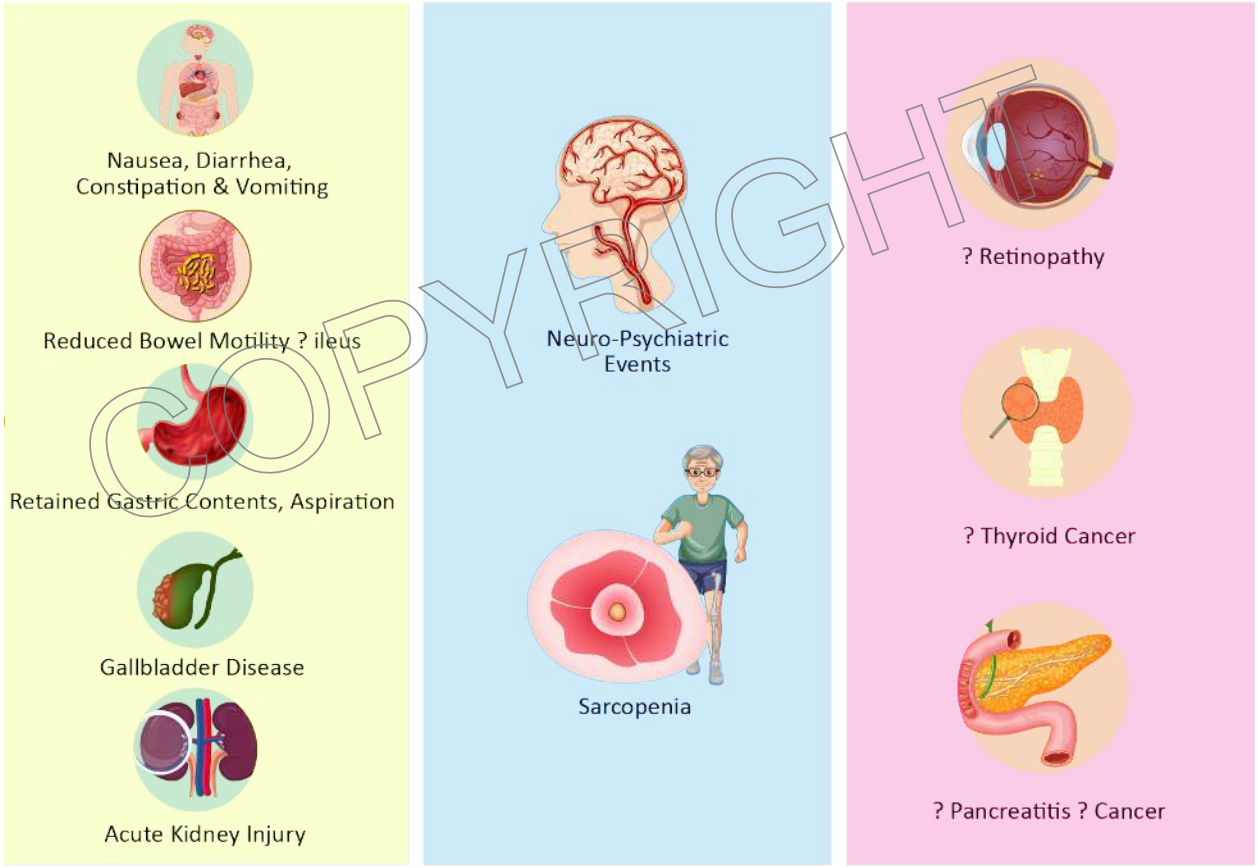
Loomba, R et al. NEJM 2024; DOI:10.1056/NEJMoa2401943

Tirzepatide improves sleep apnea



Malhotra, A et al. NEJM 2024; DOI: 10.1056/NEJMoa2404881

Adverse Events Associated with GLP 1 RA



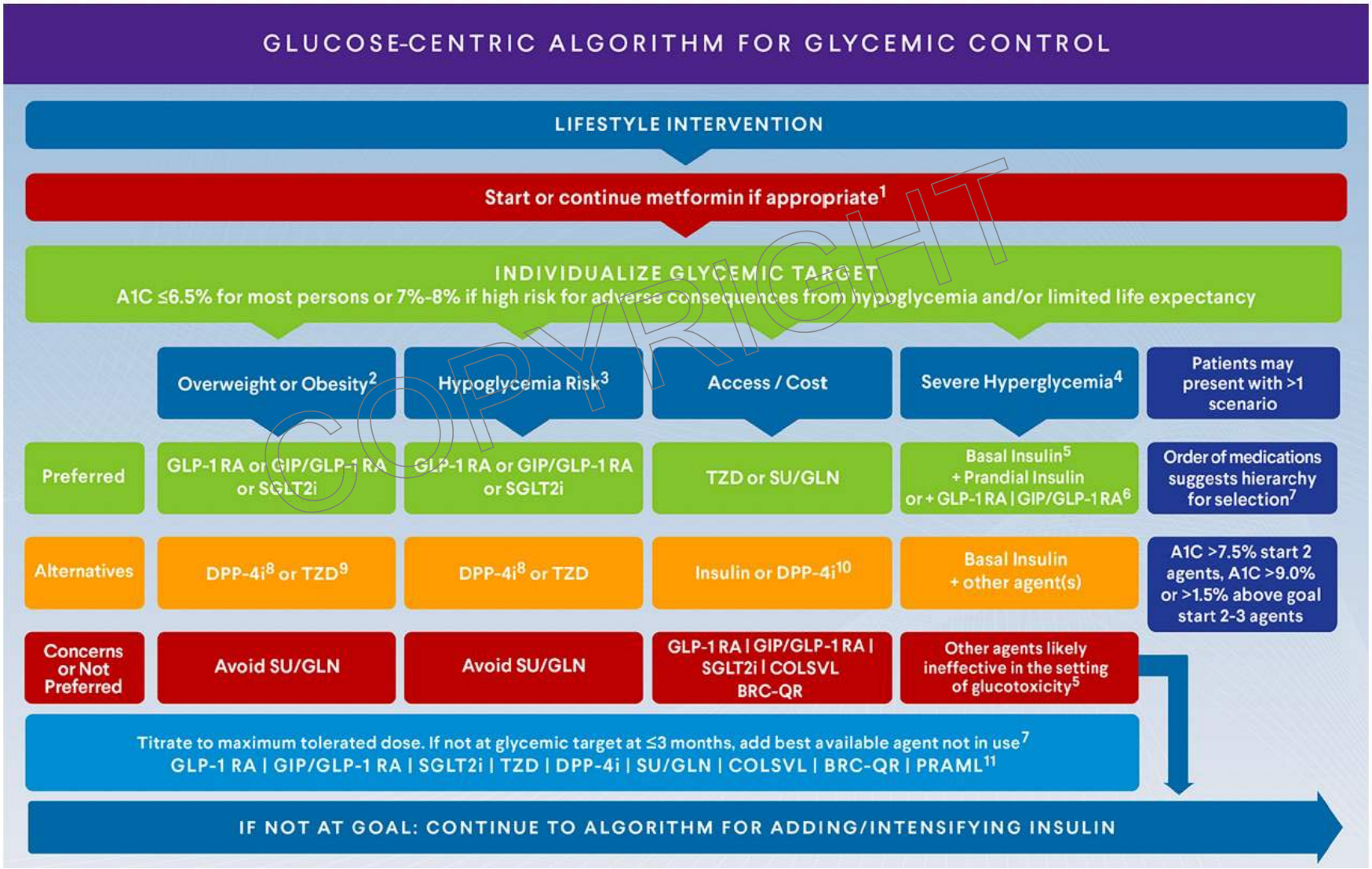
Adapted from Drucker DJ, Diabetes Care 2024;47(00):1–16

Back to our patient: what would you do next?

- 63 year old male
- Type 2 diabetes, ASCVD, hypertension, hyperlipidemia
- Normal cardiac function
- A1c 6.7%
- Taking metformin and glipizide for glucose control

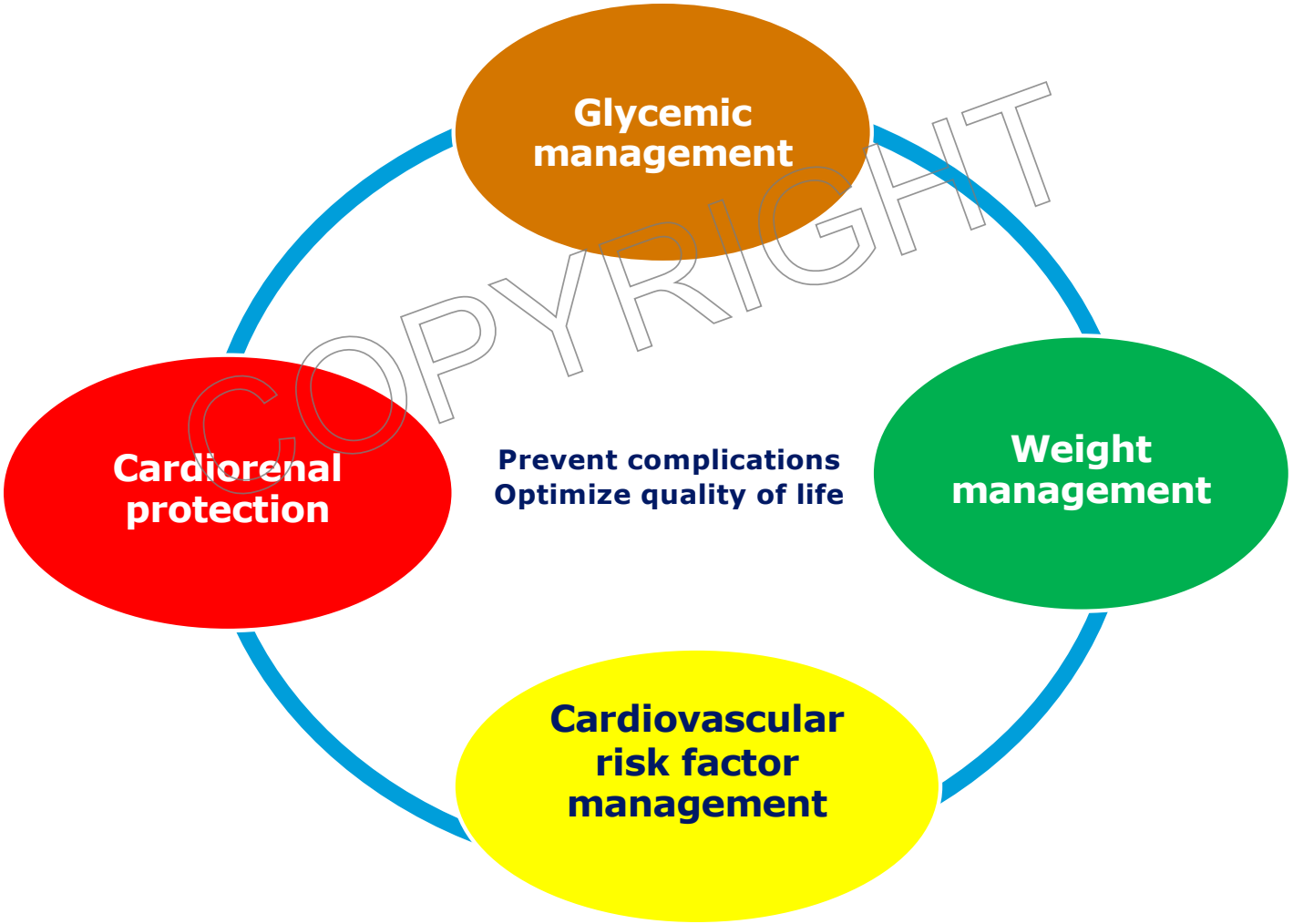
a. Continue current treatment – he is a goal A1c
b. Add a SGLT-2i
c. Add a GLP-1 RA
d. Add GLP-1 RA and stop the SU
e. Add SGLT-2i and stop the SU

What do the guidelines tell us?



Samson SL et al. Endocrine Practice 29 (2023) 305 - 340

4-pronged approach to diabetes care



2025 ADA Standards of Care: Pharmacologic Approaches to Glycemic Treatment

Goal: Achievement and maintenance of weight and glycemic goals

Glycemic management: choose approaches that provide the efficacy to achieve goals

Metformin or other agent (including COMBINATION therapy) that provides adequate EFFICACY to achieve and maintain glycemic goals

Prioritize avoidance of hypoglycemia a priority in high-risk individuals

Efficacy for glucose lowering

Very high:
- Dulaglutide (high dose), semaglutide, tirzepatide
- Insulin
- Combination oral, combination injectable (GLP-1 RA/insulin)

High: GLP-1 RA (not listed above), pioglitazone, metformin, SGLT2i, SU, TZD

Intermediate: DPP-4i

Achievement and maintenance of weight management goals

Set individualized weight management goals

- Lifestyle: medical nutrition therapy/eating patterns/exercise
- Intensive evidence-based structured weight management
- Consider medication for weight loss
- Consider metabolic surgery

Efficacy for weight loss

Very high: Semaglutide, tirzepatide

High: Dulaglutide, liraglutide

Intermediate: GLP-1 RA (not listed above), SGLT2i

Neutral: DPP-4i, metformin

Diabetes Care 2025;48(Suppl. 1):S181 – S 206

ADA/EASD Recommendations for Weight Reduction Among Patients with T2D

Weight loss of 5-15% should be a primary target in management for many people living with T2DM

Weight loss may exert benefits that extend beyond glycemic management to improve risk factors for cardiometabolic disease and QOL

Greater weight reduction results in better outcomes

5-10% loss leads to metabolic improvement

≥10-15% loss of body weight can have a disease-modifying effect, leading to diabetes remission

Diabetes Care 2024;47(Suppl. 1):S145-S157

2025 ADA Standards of Care: Pharmacologic Approaches to Glycemic Treatment

Goal: Cardiorenal risk reduction in high-risk patients with T2DM (plus comprehensive CV risk management)

ASCVD or indicators of high risk

GLP-1 RA with proven CVD benefit

Either or

SGLT2i with proven CVD benefit

If A1c is above goal

- For patients on GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- Pioglitazone

Heart failure (HFrEF or HFpEF)

SGLT2i with proven HF benefit in this population

CKD (on max tolerated ACEi or ARB)

SGLT2i with primary evidence of reducing CKD progression.
SGLT2i can be started in people with eGFR ≥20 mL/min/1.73m^2
Continue until initiation of dialysis or transplantation
Glucose lowering efficacy is reduced with eGFR < 45 mL/min/1.73m^2

OR

GLP-1 RA with proven CVD benefit

If A1c is above goal, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities and/or glycemic lowering is needed

HFrEF: HF with reduced ejection fraction; HFpEF: HF with preserved injection fraction; eGFR: estimated glomerular filtration rate

Diabetes Care 2025;48(Suppl. 1):S181 – S 206

2025 ADA Standards of Care: Pharmacologic Approaches to Glycemic Treatment

If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities and/or glycemic lowering is needed

+Mitigating risk of MASLD or MASH

Agents with potential benefit in MASLD or MASH

GLP-1 RA or dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA and pioglitazone

Use insulin in the setting of decompensated cirrhosis

Diabetes Care 2025;48(Suppl. 1):S181 – S 206

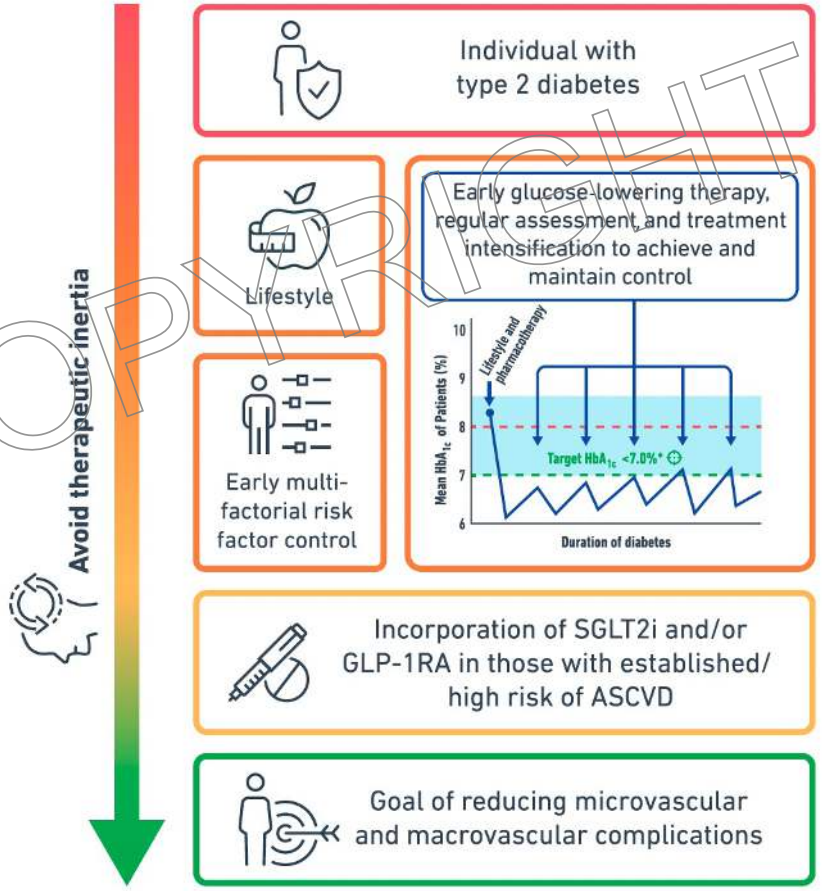
ASCVD and indicators of high risk

- ASCVD
  - Established cardiovascular disease (MI, stroke, any revascularization procedure)
  - TIA
  - Unstable angina
  - Amputations
  - Symptomatic or asymptomatic coronary artery disease
- Indicators of high risk
  - Age ≥ 55 years with 2 or more of the following:
    - Obesity
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria

ASCVD = atherosclerotic cardiovascular disease

Diabetes Care 2024;47(Suppl. 1):S158–S178

A practical approach to managing type 2 diabetes



Khunti et al. Diabetes Care 2022; 45:766–768

Key points

Type 2 diabetes results from an interplay of many pathophysiological abnormalities

"Noxious Nine"

Therapeutic goals must be individualised based on the characteristics of the patient

"One size does not fit all"

We can optimise care using therapies that are safer and associated with less risk of hypoglycemia, weight loss, and reduced cardiovascular risk

Key points

Medication choice is based on the presence or absence of ASCVD, CHF or CKD, risk of hypoglycemia, need for weight loss, and cost

There are many "newer" effective combination treatments including that can be utilized in people not at goal on metformin

Combining basal insulin with a GLP-1 RA is as effective at lowering A1c as basal insulin plus prandial insulin – with less hypoglycemia and weight gain