DIABETES AND CARDIOVASCULAR DISEASE

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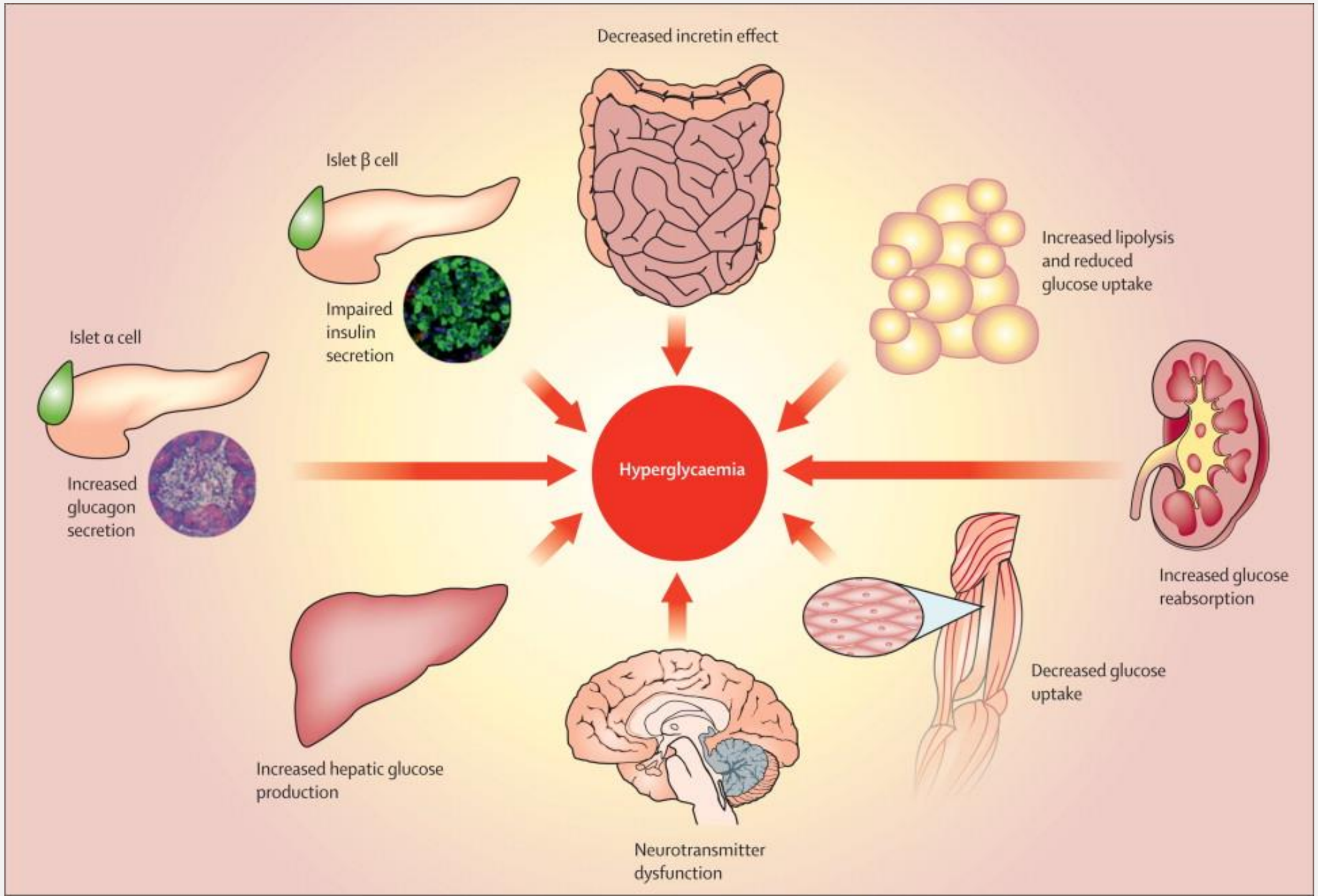
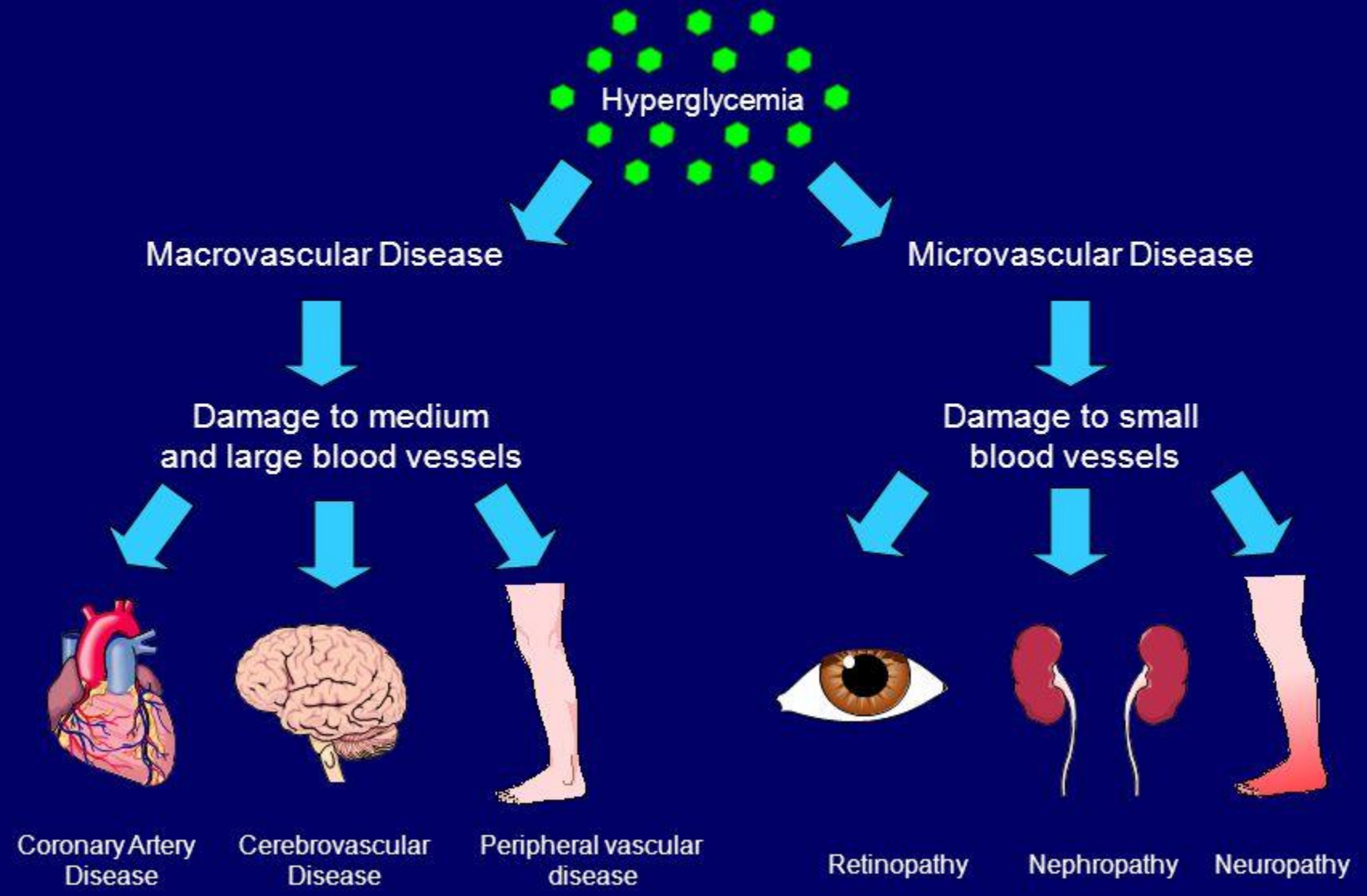
- Disclosures: None

OBJECTIVES

- Overview of Type II Diabetes Pathophysiology
- Focus on GLP-1 agonists and SGLT2 Inhibitors
  - Mechanism of Action
  - Benefits
  - Side Effects
  - Cardiovascular Effects
  - Major Findings / FDA labeling
- General Approach to Management of Type 2 Diabetes


Decreased incretin effect
Islet β cell
Impaired insulin secretion
Islet α cell
Increased glucagon secretion
Increased lipolysis and reduced glucose uptake
Hyperglycaemia
Increased glucose reabsorption
Decreased glucose uptake
Increased hepatic glucose production
Neurotransmitter dysfunction

Long-term Complications of Type 2 Diabetes



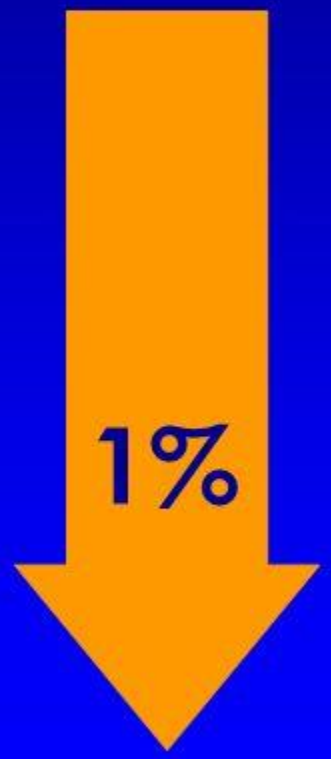
HYPERGLYCEMIA AND MICROVASCULAR COMPLICATIONS

- Kummamoto Study and UK Prospective Diabetes Study (UKPDS)
  - Examined the effects of "intensive insulin therapy" (Kummamoto) and "intensive blood glucose control" with metformin, sulfolyurea, or insulin (UKPDS)
  - Mean A1c lowering
    - 9.4 → 7.1% (Kummamoto)
    - 7.9 → 7.0% (UKPDS)
    - Lower rates of complications in intervention arms
- 10 year follow up (UKPDS): continued reductions microvascular risk and risk of MI and death from any cause

Rationale for near-normoglycemia Lessons from UKPDS: Better control means fewer complications

EVERY 1% reduction in HBA_{1C}

REDUCED RISK*



Deaths from diabetes	-21%
Heartattacks	-14%
Microvascular complications	-37%
Peripheral vascular disorders	-43%

UKPDS 35. BMJ 2000; 321: 405-12

Main Findings from the ACCORD and ADVANCE Studies

ACCORD

10,251 participants
Mean age: 62 years
Median duration of diabetes mellitus: 10 years
Mean A1C at entry: 8.3%
Known heart disease or at least 2 risk factors

Standard	Intensive
A1C 7.0%–7.9%	A1C <6.0%

CONCLUSION: Intensive glucose-lowering did not significantly reduce CVD events (primary outcome) may cause harm in high-risk patients with type 2 diabetes (increased mortaltiy).

ADVANCE

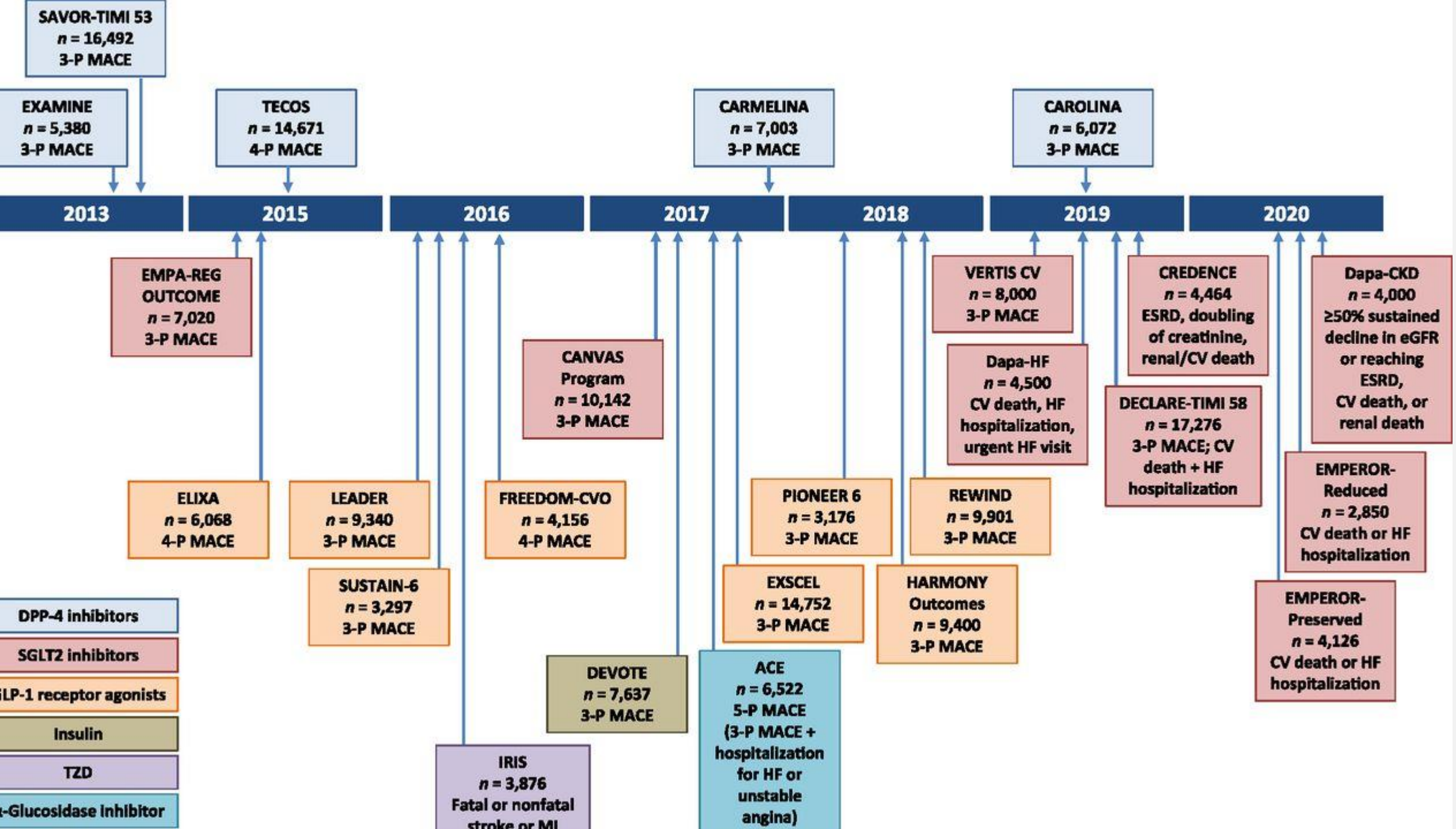
11,140 participants
Mean age: 66 years
Mean duration of diabetes mellitus: 8 years
Mean A1C at entry: 7.48%
History of major CV event or at least 1 risk factor

Standard	Intensive
A1C usual care	A1C ≤6.5%

CONCLUSION: Intensive glucose-lowering did not significantly reduce CVD events (primary outcome) reduces renal complications in high-risk patients by 21% (95% CI, 7–34%) and did not increase mortality

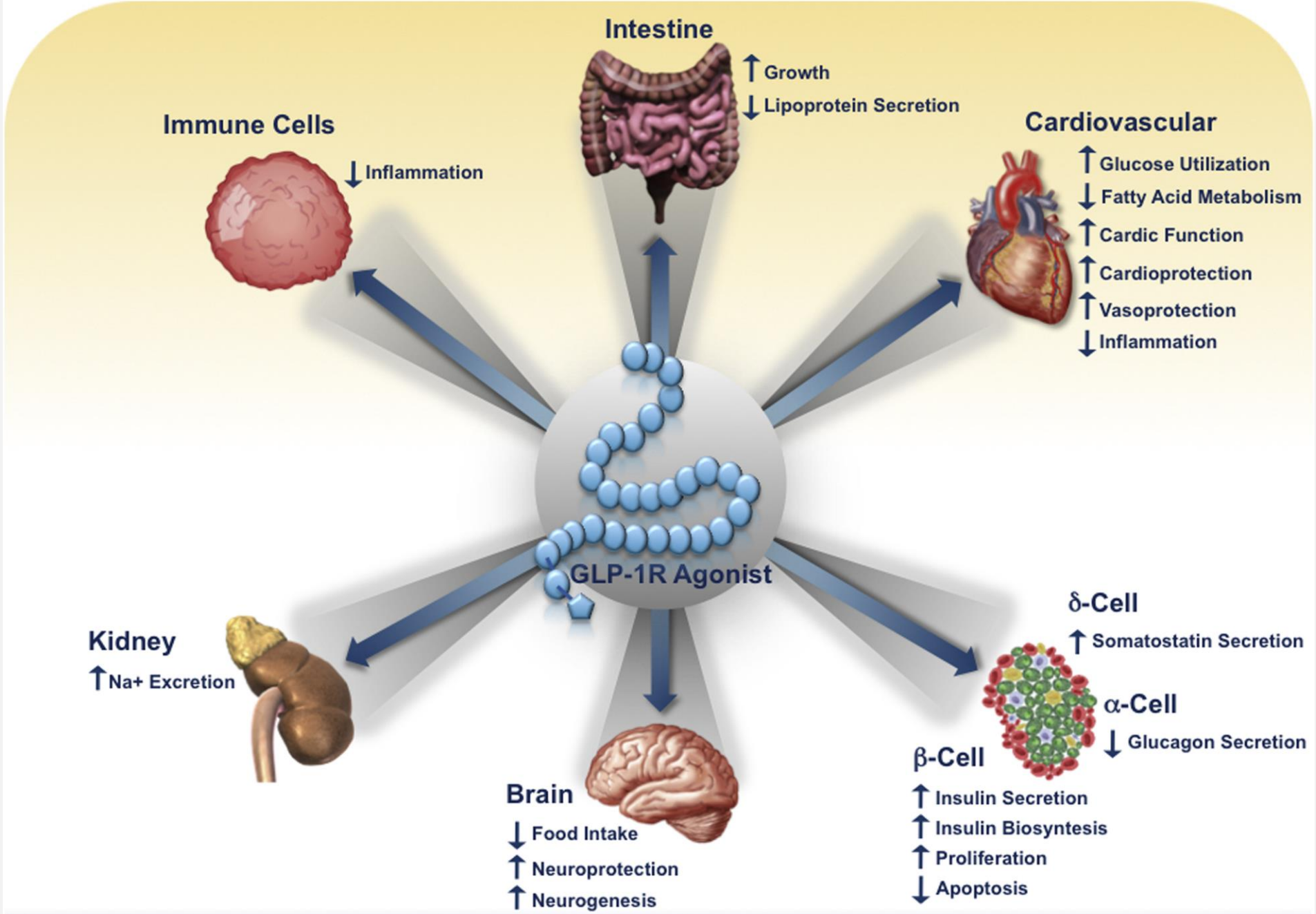
ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559 |
ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.

Slide Source:
Lipids Online Slide Library
www.lipidsonline.org


SAVOR-TIMI 53
n = 16,492
3-P MACE
EXAMINE
n = 5,380
3-P MACE
TECOS
n = 14,671
4-P MACE
CARMELINA
n = 7,003
3-P MACE
CAROLINA
n = 6,072
3-P MACE
2013
2015
2016
2017
2018
2019
2020
EMPA-REG OUTCOME
n = 7,020
3-P MACE
CANVAS Program
n = 10,142
3-P MACE
VERTIS CV
n = 8,000
3-P MACE
Dapa-HF
n = 4,500
CV death, HF hospitalization, urgent HF visit
CREDENCE
n = 4,464
ESRD, doubling of creatinine, renal/CV death
DECLARE-TIMI 58
n = 17,276
3-P MACE; CV death + HF hospitalization
Dapa-CKD
n = 4,000
≥50% sustained decline in eGFR or reaching ESRD, CV death, or renal death
ELIXA
n = 6,068
4-P MACE
LEADER
n = 9,340
3-P MACE
SUSTAIN-6
n = 3,297
3-P MACE
FREEDOM-CVO
n = 4,156
4-P MACE
PIONEER 6
n = 3,176
3-P MACE
REWIND
n = 9,901
3-P MACE
EXSCEL
n = 14,752
3-P MACE
HARMONY Outcomes
n = 9,400
3-P MACE
EMPEROR-Reduced
n = 2,850
CV death or HF hospitalization
EMPEROR-Preserved
n = 4,126
CV death or HF hospitalization
DEVOTE
n = 7,637
3-P MACE
ACE
n = 6,522
5-P MACE
(3-P MACE + hospitalization for HF or unstable angina)
IRIS
n = 3,876
Fatal or nonfatal stroke or MI
DPP-4 inhibitors
SGLT2 inhibitors
LP-1 receptor agonists
Insulin
TZD
-Glucosidase inhibitor

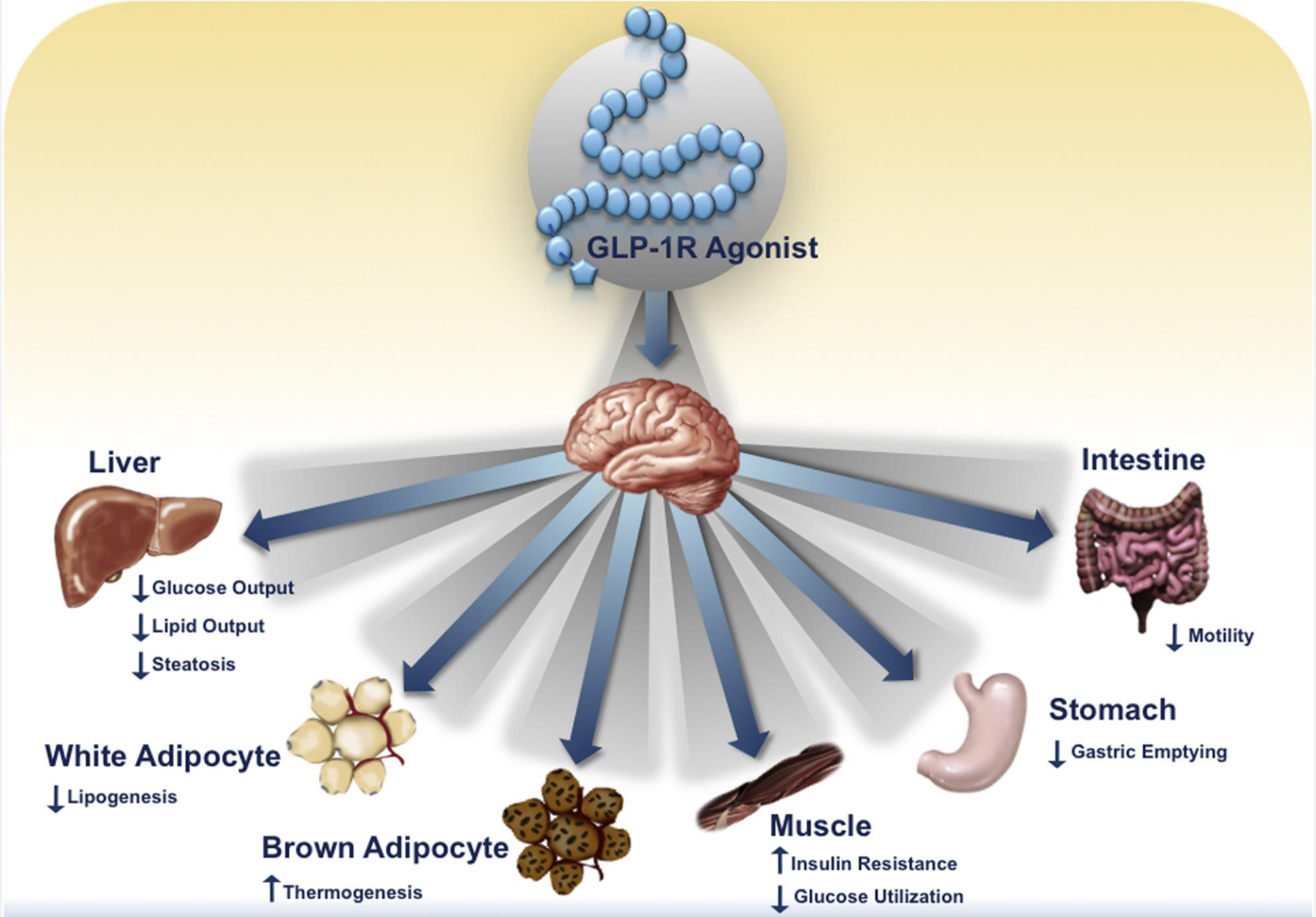
TYPE 2 DM MEDICATIONS: CARDIOVASCULAR BENEFITS

- SGLT2 inhibitors
- Glucagon-Like Peptide-1 (GLP-1) agonists

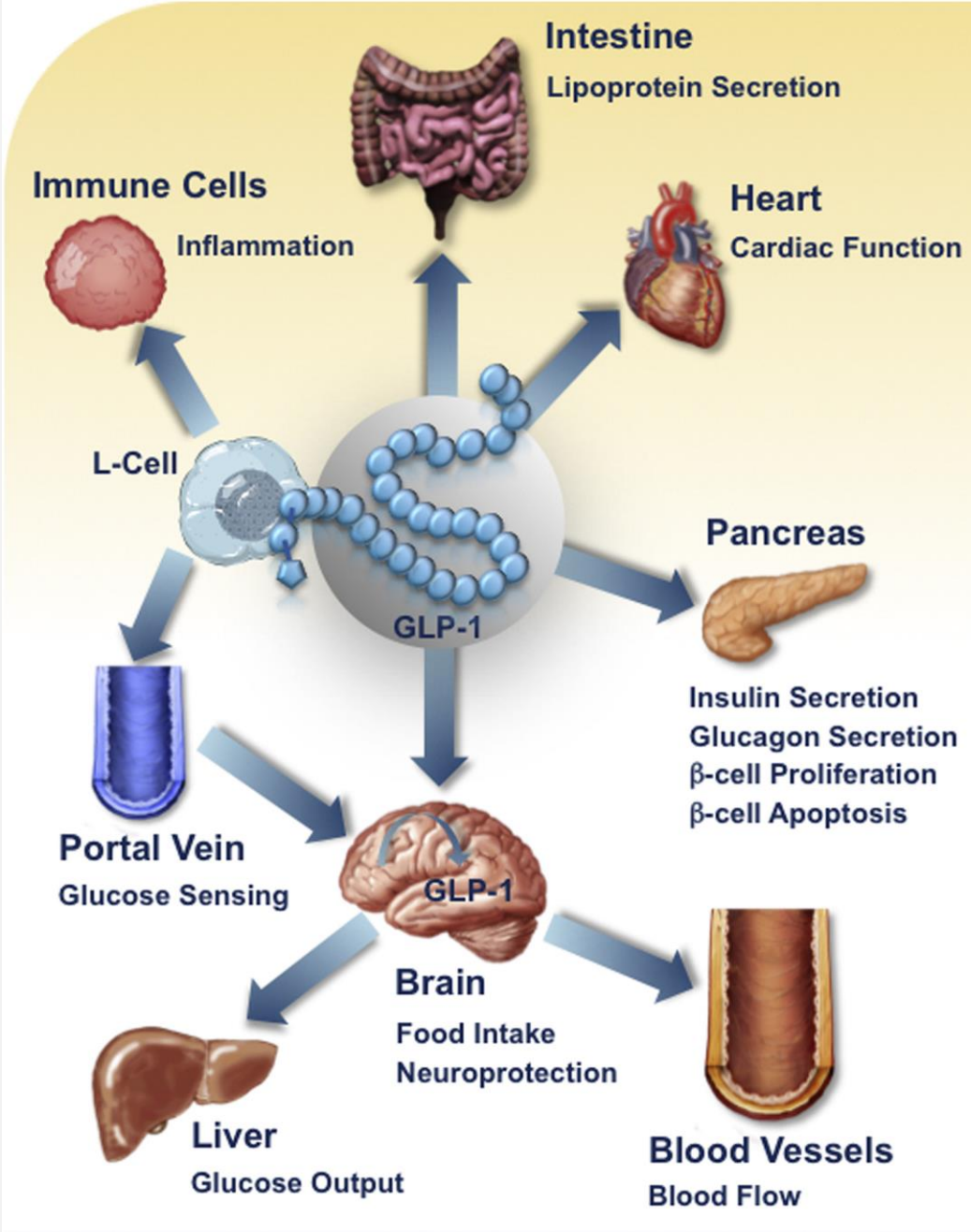


Direct Pharmacological Actions of GLP-1R Agonists

Jonathan E. Campbell, Daniel J. Drucker,
Pharmacology, Physiology, and Mechanisms of Incretin Hormone Action,
Cell Metabolism,
Volume 17, Issue 6,
2013,
Pages 819-837,

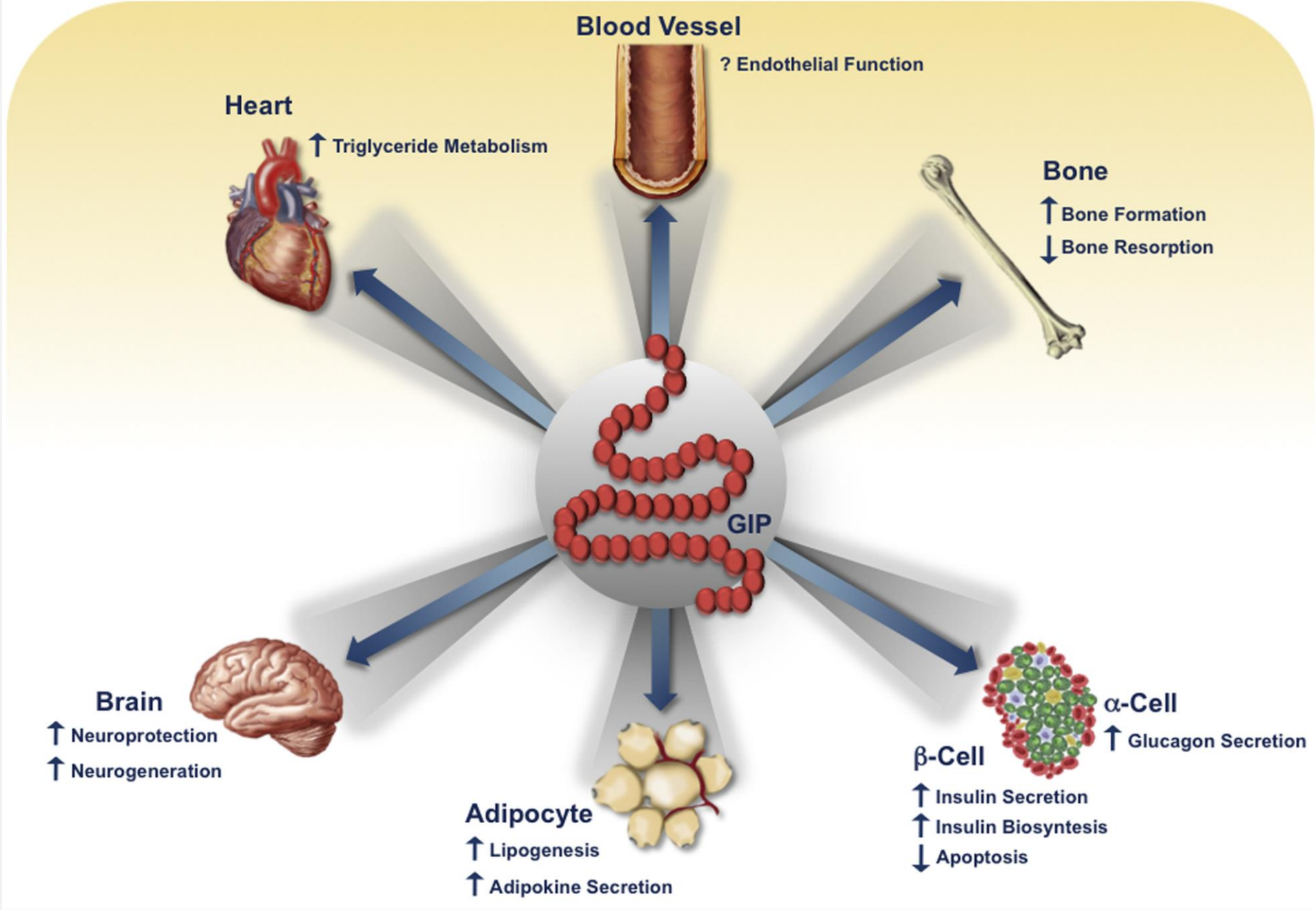


Indirect Pharmacological Effects of GLP-1R Agonists



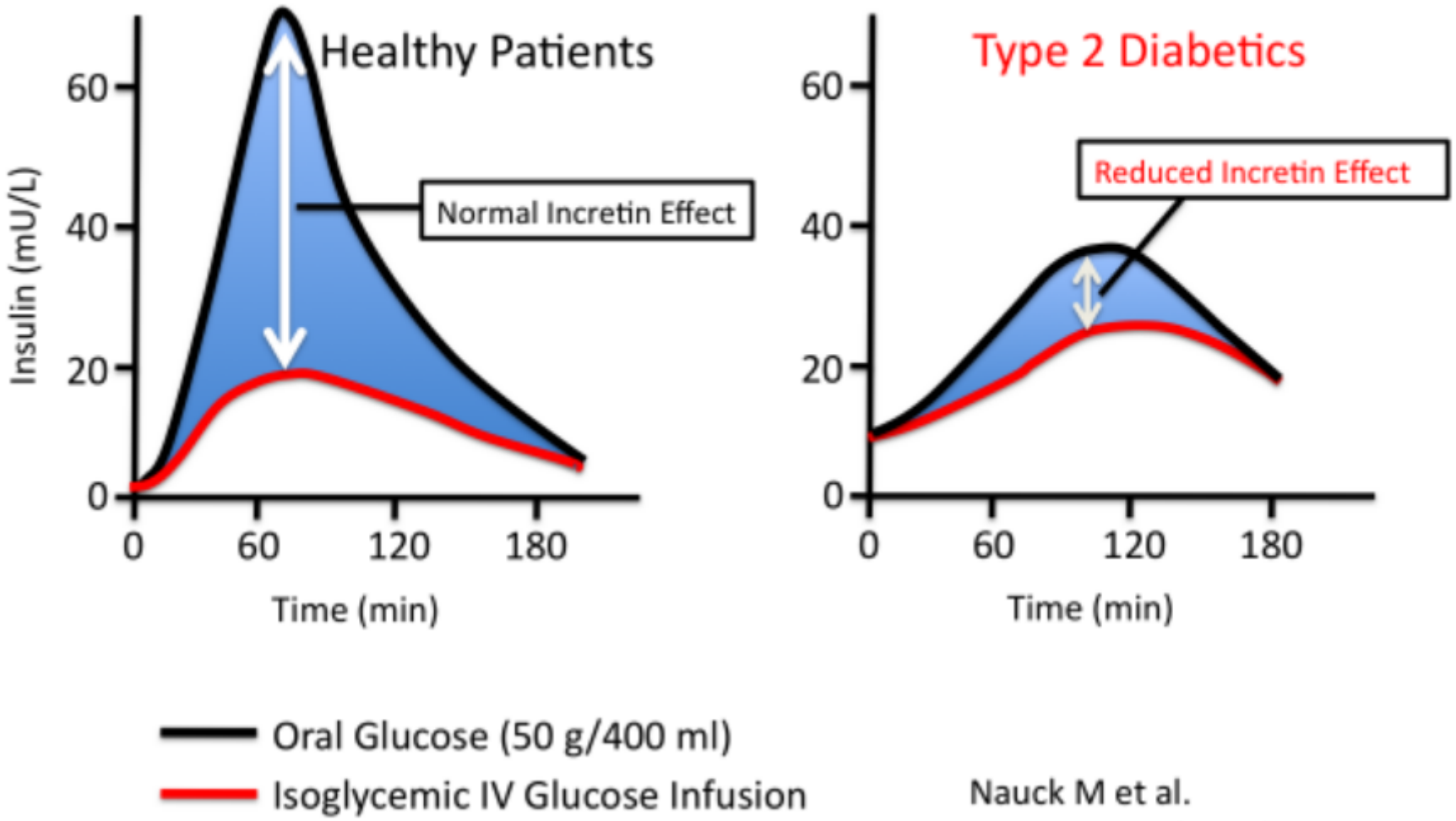
Physiological Actions of GLP-1

Physiology	Impairment of GLP-1 action
Fasting Glucose	Increased
Glucose-Dependent Insulin Secretion	Decreased
Glucagon Secretion	Increased
β-cell Signal Transduction	Abnormal
β-cell Apoptosis	Increased
β-cell Proliferation	Decreased
Islet Size	Decreased
Food Intake	Increased
Energy Expenditure	Increased
Locomotion	Increased
Body Weight	Increased
Portal Glucose Sensing	Decreased
Postprandial Lipid Metabolism	Decreased
CNS Control of Blood Flow	Decreased
Cardiovascular Function	Decreased
CNS Stress Response	Increased
Susceptibility to Neural Injury	Increased
Immune System	Decreased
Gastric Emptying	Normal
Susceptibility to Pancreatitis	Normal



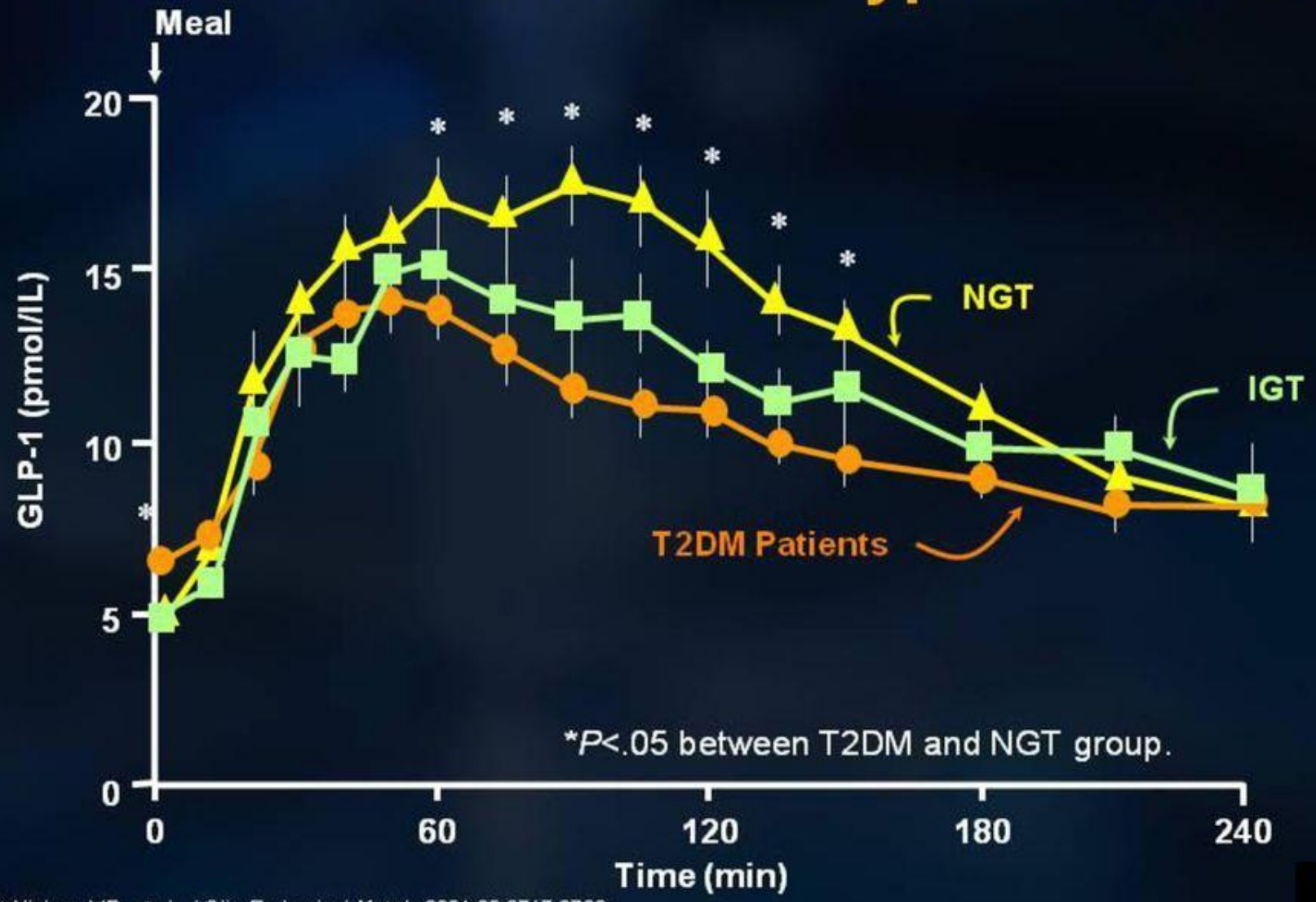
Physiological Actions of GIP

Diabetes & The "Incretin Effect"



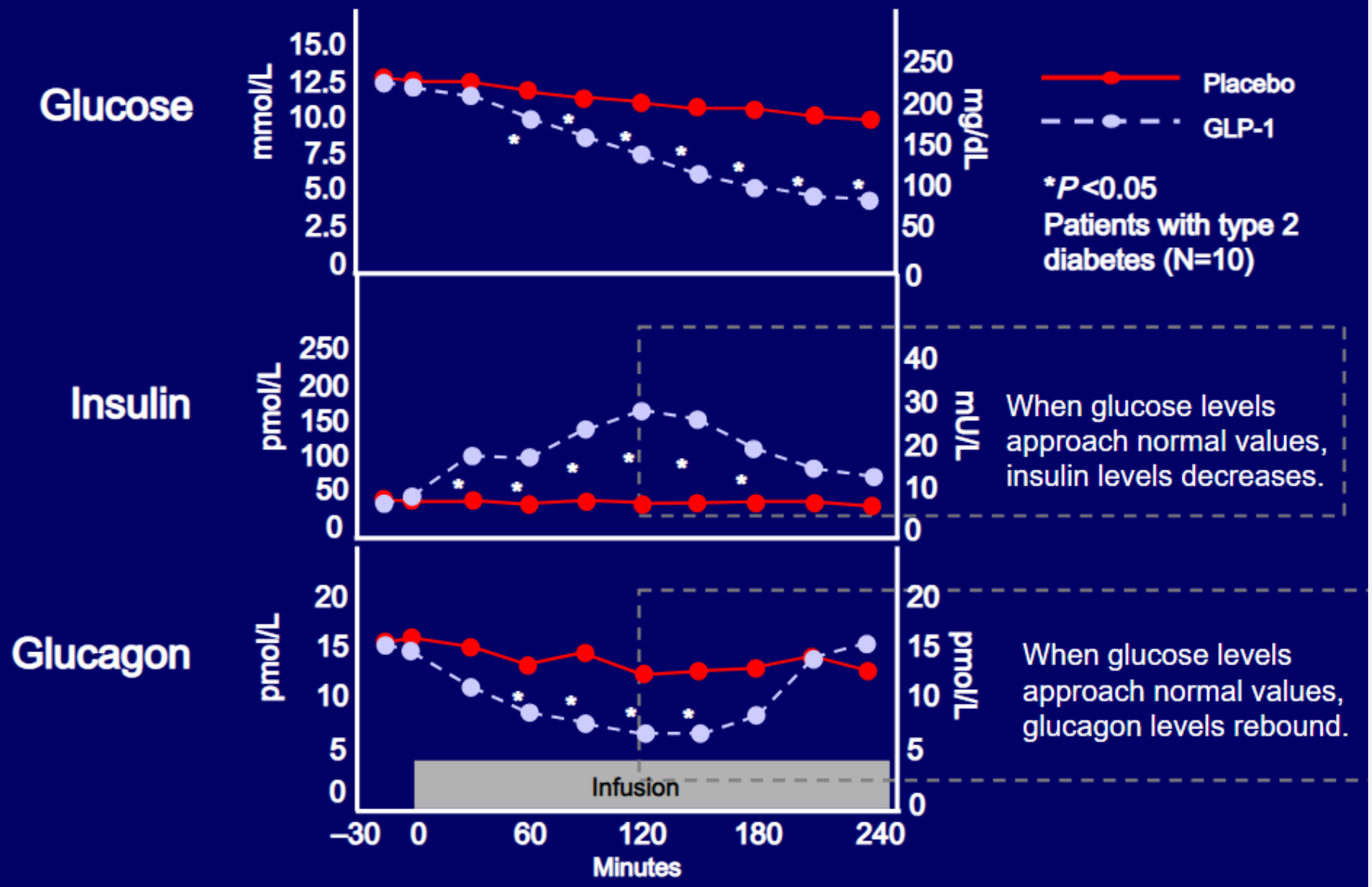
Nauck M et al.
Diabetologia (1986) 29:46-52

Postprandial GLP-1 Levels Are Decreased in Patients With IGT and Type 2 Diabetes



Toft-Nielsen MB, et al. *J Clin Endocrinol Metab.* 2001;86:3717-3723.

Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon Levels in Patients With Type 2 Diabetes



Adapted with permission from Nauck MA et al. *Diabetologia*. 1993;36:741–744. Copyright © 1993 Springer-Verlag.

GLP-1 RECEPTOR AGONISTS

FDA-APPROVED AGENTS

- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
- Exenatide (Byetta)
- Exenatide ER (Bydureon)
- Liraglutide (Victoza)
- Semaglutide (Ozempic)

KEY FEATURES

- Injectable administration
- Mimic action of native GLP-1
- Increase glucose-dependent insulin secretion
- Suppress glucagon production
- Slow gastric emptying
- Suppress Appetite

CARDIOVASCULAR DISEASE & GLP-1 AGONISTS

LEADER TRIAL

- "Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results"
- Cardiovascular (CV) outcomes trial in patients with type 2 diabetes at high CV risk
- Compared liraglutide (n = 4668) with placebo (n = 4672)
- Primary composite endpoint of 3-point major adverse CV events: CV death, non-fatal MI, or stroke
- Conclusion: liraglutide is superior to placebo in improving glycemic control and reducing CV events and mortality in patients with DM2 and high CV risk, including among patients with CKD.

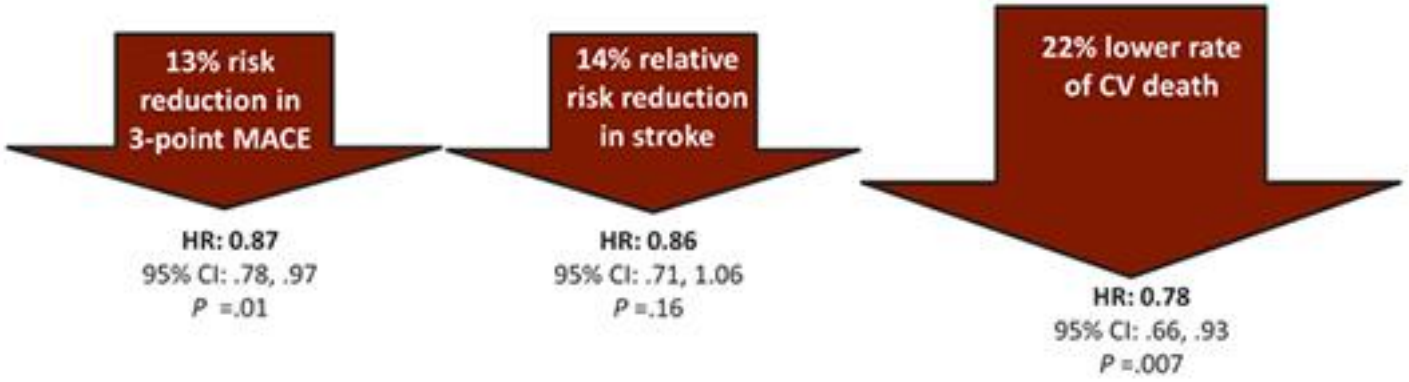
REWIND TRIAL (DULAGLUTIDE)

- Dulaglutide was ***superior*** to placebo in improving glycemic control and reducing CV events in patients with T2DM and high CV risk.
- Significant reduction in nonfatal strokes
- Renal effects:
  - Moderate effect on the composite renal outcome
  - Reduced **new** microalbuminuria

LEADER
Liraglutide CVOT

Liraglutide vs placebo

- Duration: 3.8 years
- Study population: 9340 adults with T2D and high CV risk
- Reduction in the risk of heart attack, stroke, and cardiovascular death



Marso SP, et al. *N Engl J Med*. 2016. [Epub ahead of print]

SUSTAIN-6 TRIAL

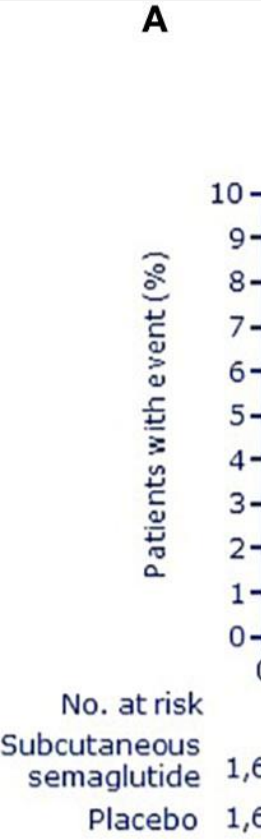
- "Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes“
- Objective: Determine whether semaglutide was non-inferior to placebo in terms of CV events among people with T2DM + high risk for CVD
- Randomized 3297 patients: semaglutide (weekly, 0.5 mg or 1.0 mg) vs placebo
- Composite primary outcome (CV mortality, nonfatal MI, or stroke)
  - 6.6% (semaglutide group)
  - 8.9% (placebo group)
- **Semaglutide found to be *superior* to placebo for this composite CVD outcome**
- Adverse effects:
  - More frequent GI events
  - Higher incidence of retinopathy vs placebo

Table 2: Outcomes of the LEADER and SUSTAIN 6 trials

Outcomes	LEADER Hazard ratio (95 % CI) p-value	LEADER % risk reduction (stat significant/ non-significant)	SUSTAIN 6 Hazard ratio (95% CI) p-value	SUSTAIN 6 Reduction (stat significant/non-significant)
Primary composite MACE	0.87 (0.78–0.97) 0.01	13% reduction (significant)	0.74 (0.58–0.95) 0.02	26% reduction (significant)
CV death	0.78 (0.66–0.93) 0.007	22% reduction (significant)	0.98 (0.65–1.48) 0.92	2% reduction (non-significant)
Non-fatal MI	0.88 (0.75–1.03) 0.046	12% reduction (non-significant)	0.74 (0.51–1.08) p=0.12	26% reduction (non-significant)
Non-fatal stroke	0.89 (0.72–1.11) 0.16	11% reduction (non-significant)	0.61 (0.38–0.99) p=0.04	39% reduction (significant)
Death from any cause	0.85 (95% CI, 0.74–0.97) p=0.02	15% reduction (significant)	1.05 (0.74–1.50) 0.79	5% increase (non-significant)
Hospitalization for heart failure	0.87 (0.73–1.05) 0.14	13% reduction (non-significant)	1.11 (0.77–1.61) 0.57	11% increase (non-significant)
Microvascular endpoints				
New or worsening Nephropathy	0.78 (0.67–0.92) 0.003	22% reduction (significant)	0.64 (0.46–0.88) 0.005	36% reduction (significant)
Retinopathy	1.15 (0.87–1.52) 0.33	15% non-significant increase	1.76 (1.11–2.78) 0.02	76% increase

CI = confidence interval; CV = cardiovascular; MACE = major adverse cadiac event; MI = myocardial infarction

PIONEER-6
(ORAL SEMAGLUTIDE)

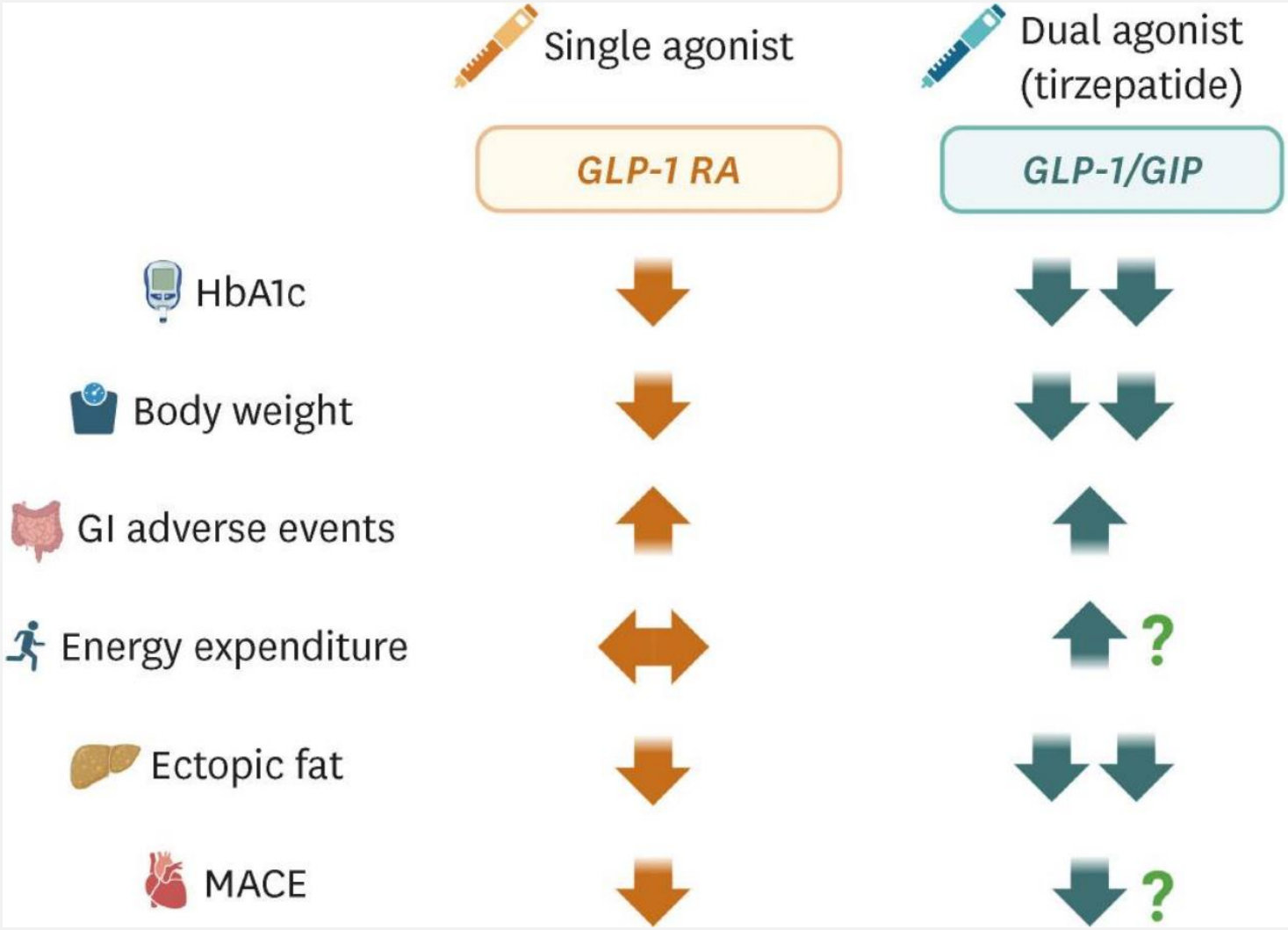


Results showed <u>noninferiority</u> but not superiority of oral semaglutide vs placeo in cardiovascular risk

ACC Expert Consensus Recommendations on Considerations for Drug Initiation and Monitoring in Patients Starting a GLP-1 RA with CV Benefit[12]

- If HbA_{1c} is well-controlled at baseline or known history of frequent hypoglycemic events, wean or stop sulfonylurea and consider reducing total daily insulin dose by ~20% when starting therapy.
- Instruct patients to more closely monitor glucose at home for the first 4 weeks of therapy. Consider discontinuing any sulfonylurea or glinide. For patients taking insulin, consider modestly reducing total daily insulin dose (by up to 20%).
- Discontinue DPP-4 inhibitor before starting.
- To mitigate nausea, recommend small portion sizes for meals, start at the lowest dose, and up-titrate as tolerated toward the goal doses used in CV outcome trials.
- Advise patients to undergo appropriate, guideline-recommended eye examinations before starting therapy if not done within the last 12 months.
- Discuss potential risk of diabetic retinopathy complications (for dulaglutide or injectable semaglutide).
- Avoid in patients with diabetic gastroparesis or active gallbladder disease.

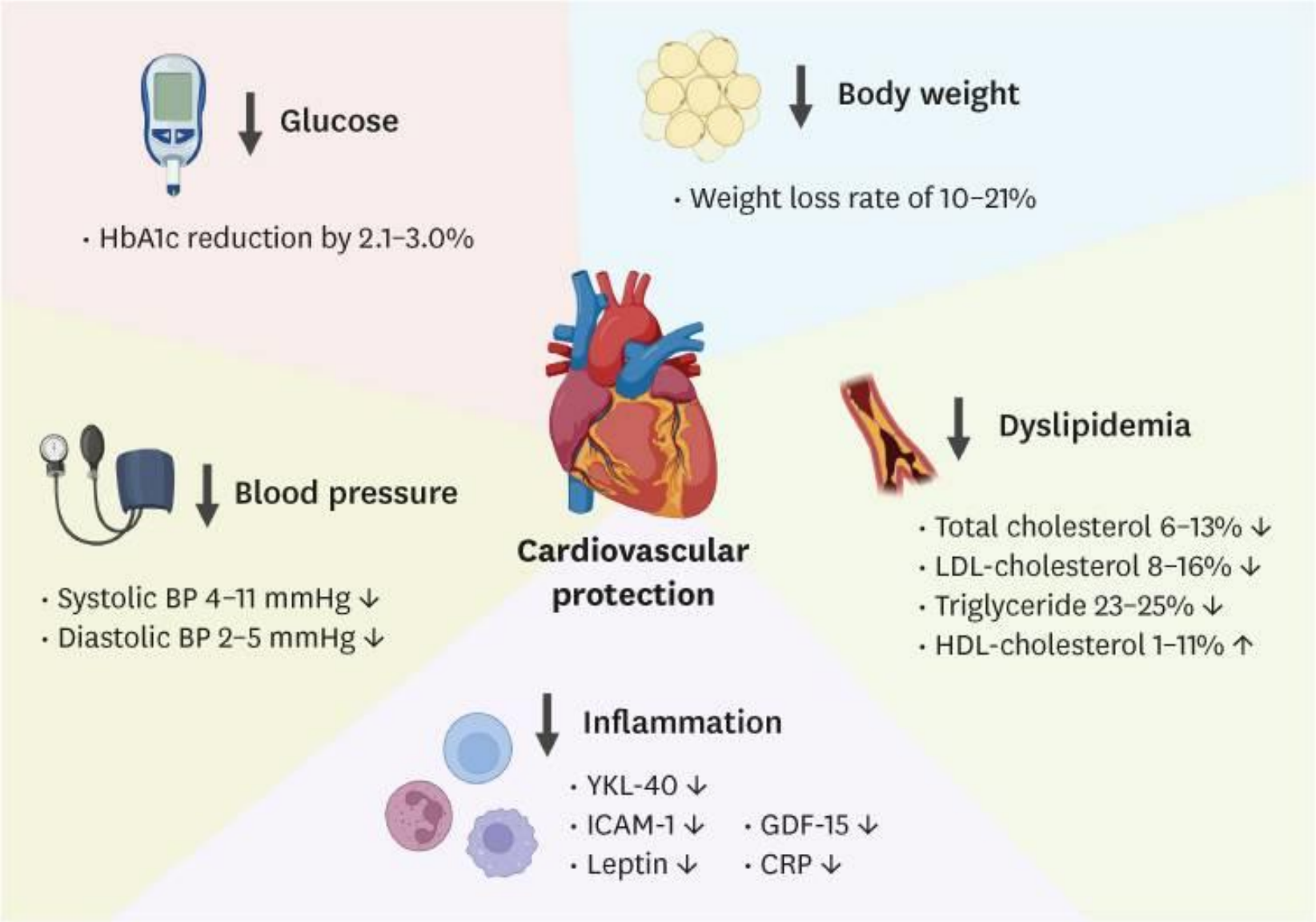
TIRZEPATIDE: GLP-1/GIP DUAL AGONIST



Comparison between GLP-1 RA and the GLP-1/GIP dual agonist (tirzepatide)

The main results of tirzepatide in phase 3 clinical trials

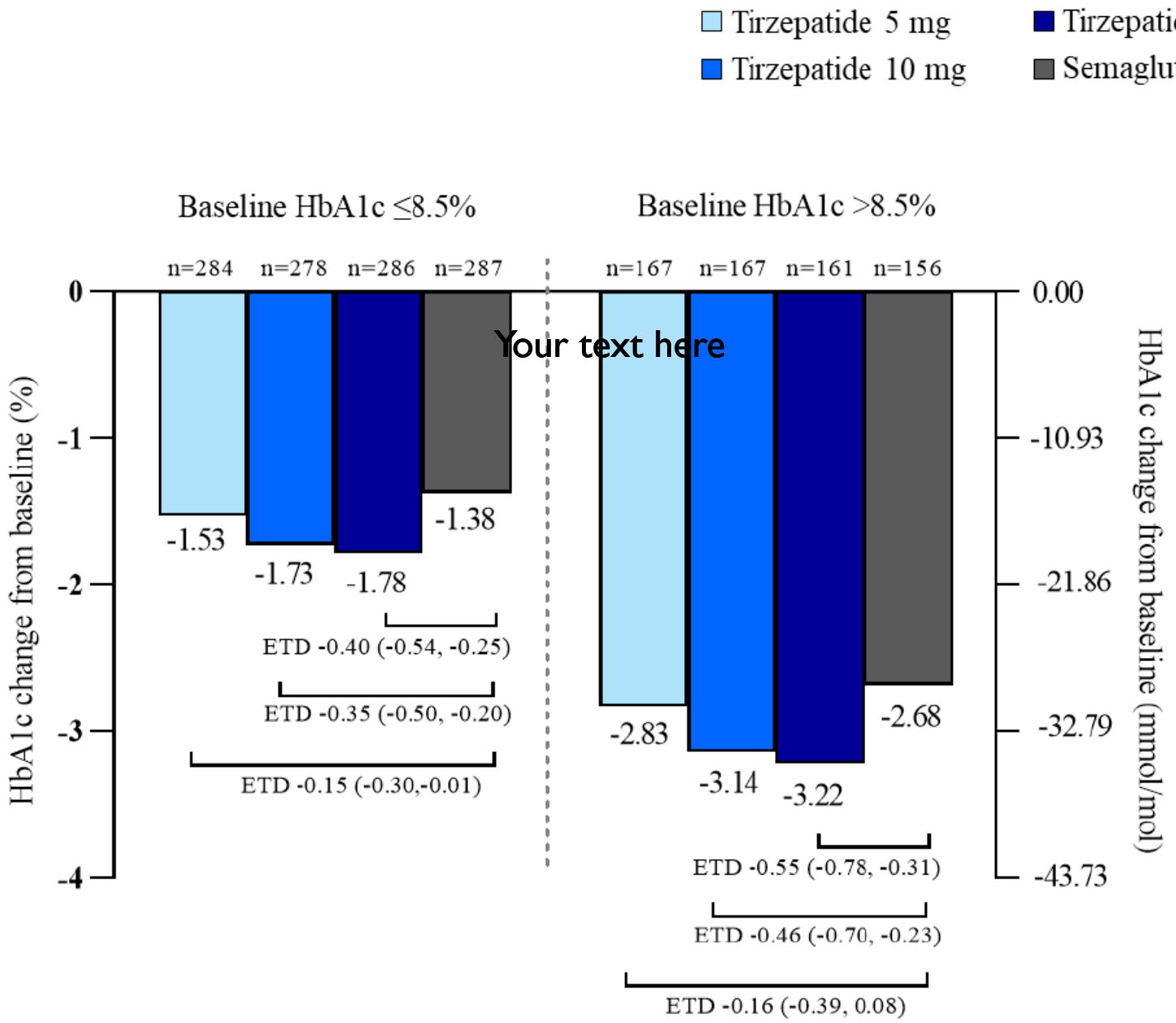
Study name	Enrolled patients	Study arms	Duration (wk)	ΔHbA1c (%)	ΔBW (kg)	ΔSBP (mmHg)	ΔDBP (mmHg)	ΔLDL-C (%)	ΔTG (%)	ΔHDL-C (%)
SURPASS 1[2]	T2DM	Placebo	40	0.04	−0.7	−2.0	−1.4	−1.6	4.7	−3.8
		Tirzepatide (5, 10, 15 mg)		−1.87, −1.89, −2.07	−7.0, −7.8, −9.5	−4.7, −4.7, −5.2	−2.-, −3.1, −3.4	−6.7, −7.6, −12.4	−18.5, −18.2, −21.0	4.8, 3.2, 7.5
SURPASS 2[3]	T2DM	Semaglutide 1 mg	40	−1.86	−5.7	−3.6	−1.0	−6.4	−11.5	4.4
		Tirzepatide (5, 10, 15 mg)		−2.01, −2.24, −2.30	−7.6, −9.3, −11.2	−4.8, −5.3, −6.5	−1.9, −2.5, −2.9	−7.7, −5.6, −5.2	−19.0, −24.1, −24.8	6.8, 7.9, 7.1
SURPASS 3[4]	T2DM	Insulin Degludec	52	−1.34	2.3	0.5	0.4	−2.71	−12.2	1.03
		Tirzepatide (5, 10, 15 mg)		−1.93, −2.20, −2.37	−7.5, −10.7, −12.9	−4.9, −6.6, −5.5	−2.0, −2.5, −1.9	−6.01, −5.70, −6.55	−15.4, −26.7, −25.2	5.49, 10.22, 10.20
SURPASS 4[5]	T2DM	Insulin Glargine	52	−1.44	1.9	1.3	0.7	1.4	−6.4	2.9
		Tirzepatide (5, 10, 15 mg)		−2.24, −2.43, −2.58	−7.1, −9.5, −11.7	−2.8, −3.7, −4.8	−1.0, −0.8, −1.0	−6.8, −8.3, −7.9	−16.3, −20.1, −22.5	6.7, 9.7, 10.8
SURPASS 5[6]	T2DM*	Placebo	40	−0.86	1.6	−1.7	−2.1	2.8	−6.8	1.7
		Tirzepatide (5, 10, 15 mg)		−2.11, −2.40, −2.34	−5.4, −7.5, −8.8	−6.1, −8.3, −12.6	−2.0, −3.3, −4.5	−8.9, −12.8, −15.5	−15.2, −19.3, −24.9	2.1, 1.8, 0.9
SURPASS J-Mono[27]	T2DM	Dulaglutide 0.75 mg	52	−1.3	−0.5	−1.4	0.1	−4.8	−8.2	0
		Tirzepatide (5, 10, 15 mg)		−2.4, −2.6, −2.8	−5.8, −8.5, −10.7	−6.5, −8.8, −11.0	−3.2, −4.0, −5.6	−12.0, −12.8, −19.3	−27.1, −32.8, −37.7	3.8, 5.4, 5.9



Potential mechanisms by which tirzepatide imparts cardiovascular benefits

SURPASS-2 Trial:
Tirzepatide
vs
Semaglutide

Figure S8. Change from Baseline in HbA1c at 40 Weeks by Baseline HbA1c (HbA1c ≤8.5% and >8.5%)



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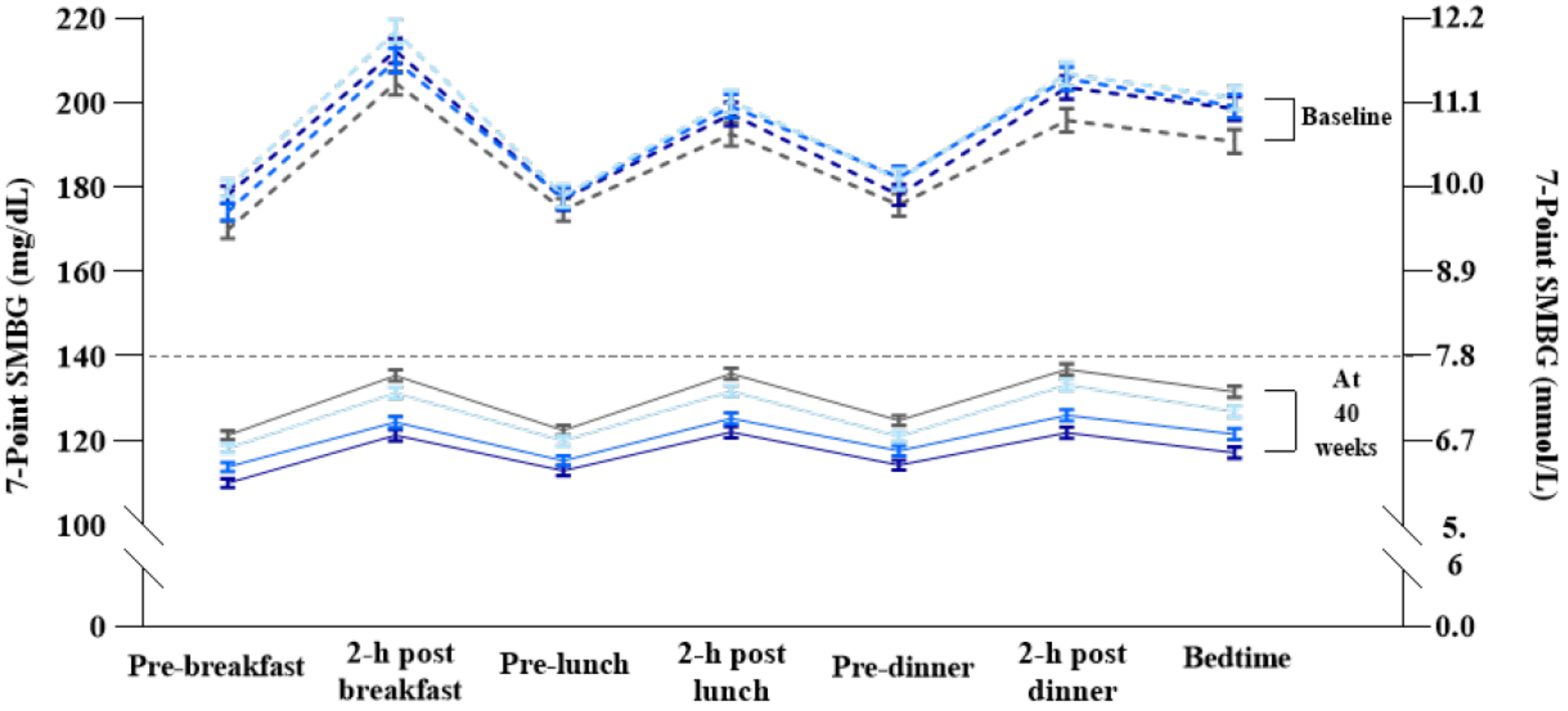
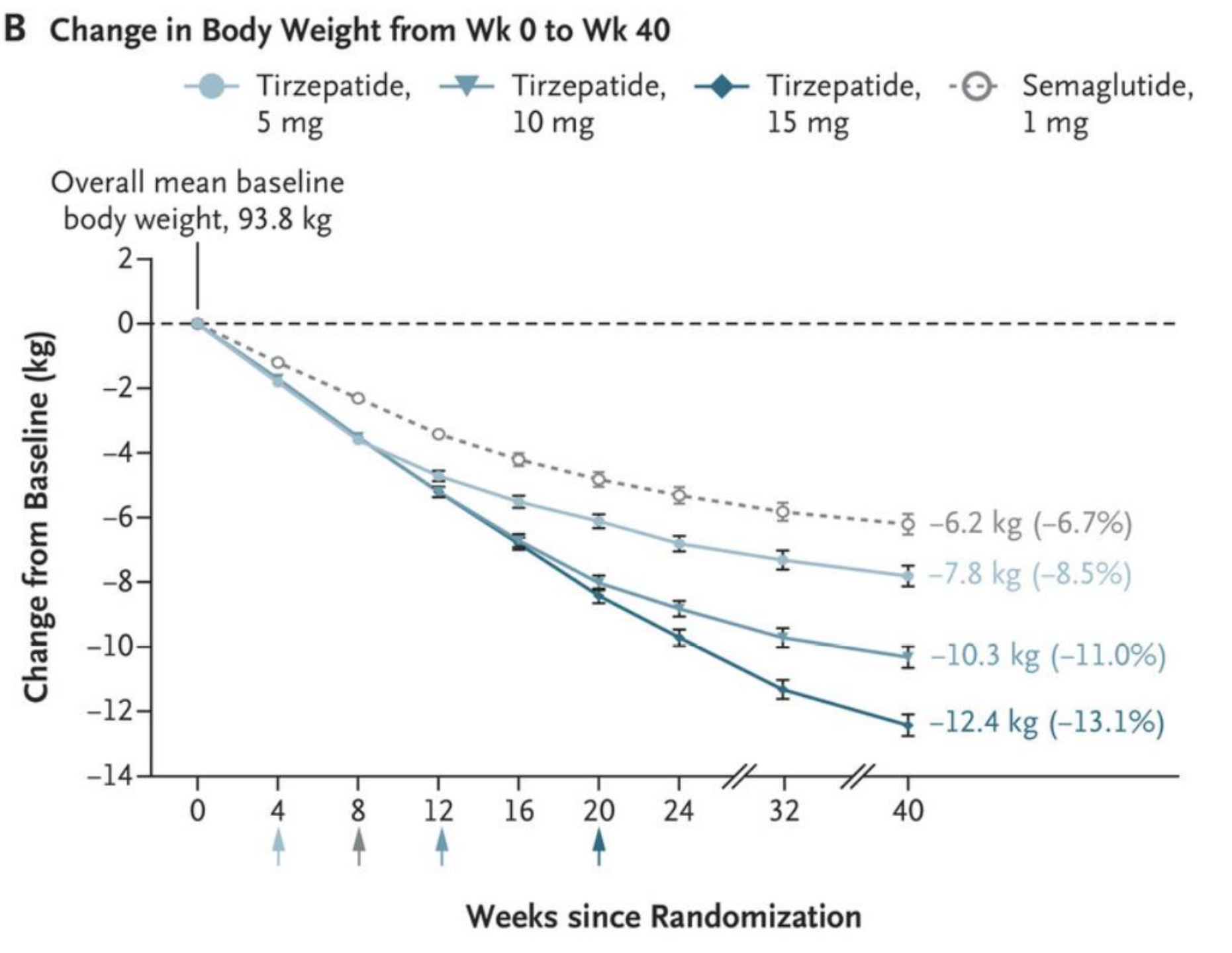
7-point SMBG Profiles at Baseline and 40 Weeks




B Change in Body Weight from Wk 0 to Wk 40
Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
Semaglutide, 1 mg
Overall mean baseline body weight, 93.8 kg
Change from Baseline (kg)
2
0
−2
−4
−6
−8
−10
−12
−14
−6.2 kg (−6.7%)
−7.8 kg (−8.5%)
−10.3 kg (−11.0%)
−12.4 kg (−13.1%)
0
4
8
12
16
20
24
32
40
Weeks since Randomization

CV FINDINGS: SURPASS-4 TRIAL (TIRZEPATIDE VS GLARGINE)

- 1995 Participants randomly assigned and received either SQ injection of weekly tirzepatide (5 mg, 10 mg, or 15 mg) vs glargine
  - Titrated to FBG<100 mg/dL
- Primary Endpoint: non-inferiority of tirzepatide vs glargine in a1c reduction
- Treatment duration: 52 weeks to 104 weeks or until study completion for MACE (major adverse CV events)
- MACE-4 events (CV death, MI, stroke, unstable angina hospitalizations) not increased on tirzepatide compared with glargine
- Reduction in a1c: tirzepatide > glargine
- Hypoglycemia: tirzepatide < glargine
- GI effects (N/V, diarrhea, decreased appetite): tirzepatide > glargine
- SURPASS-CVOT: Ongoing cardiovascular outcome trial of tirzepatide
  - "A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes"

CARDIOVASCULAR DISEASE AND SGLT2 INHIBITORS

SGLT2 INHIBITORS

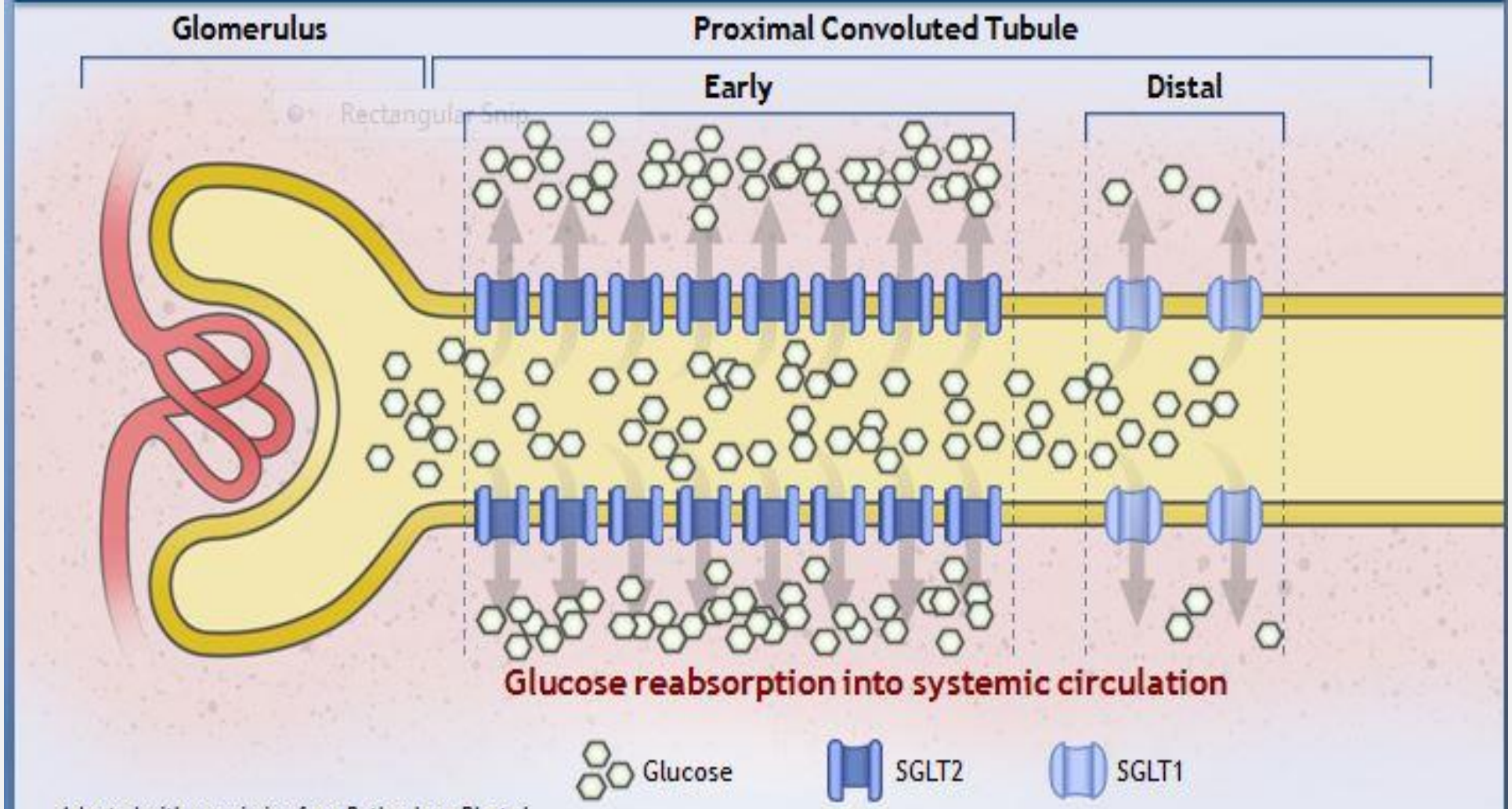
FDA APPROVED AGENTS

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin (Dec. 2017)

KEY FEATURES

- Oral administration
- Inhibit reabsorption of glucose into the bloodstream from the kidney
- Improve glycemic control
- Weight loss
- Blood pressure reduction

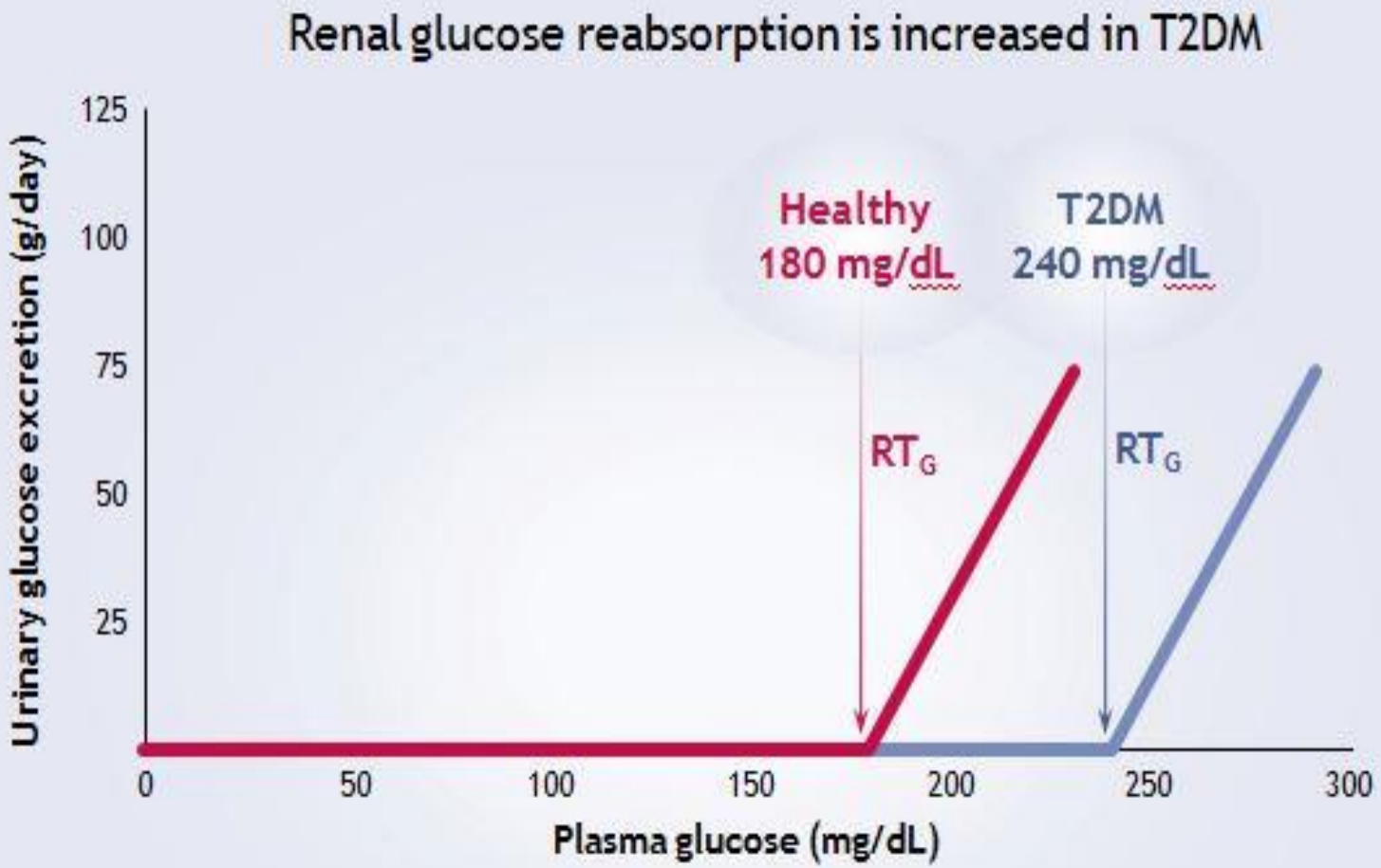
Normal Kidney: Glucose Reabsorption
(Plasma Glucose ≤180 mg/dL)



Adapted with permission from Rothenberg PL et al.
SGLT = sodium-glucose co-transporter.

1. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 2. You G et al. *J Biol Chem.* 1995;270(49):29365-29371. 3. Rothenberg PL et al. Poster presented at: 46th European Association for the Study of Diabetes Annual Meeting; September 20-24, 2010; Stockholm, Sweden.

Renal Threshold for Glucose Excretion (RT_G) Is Increased in T2DM



Adapted with permission from Abdul-Ghani, DeFronzo RA.
T2DM = type 2 diabetes mellitus.

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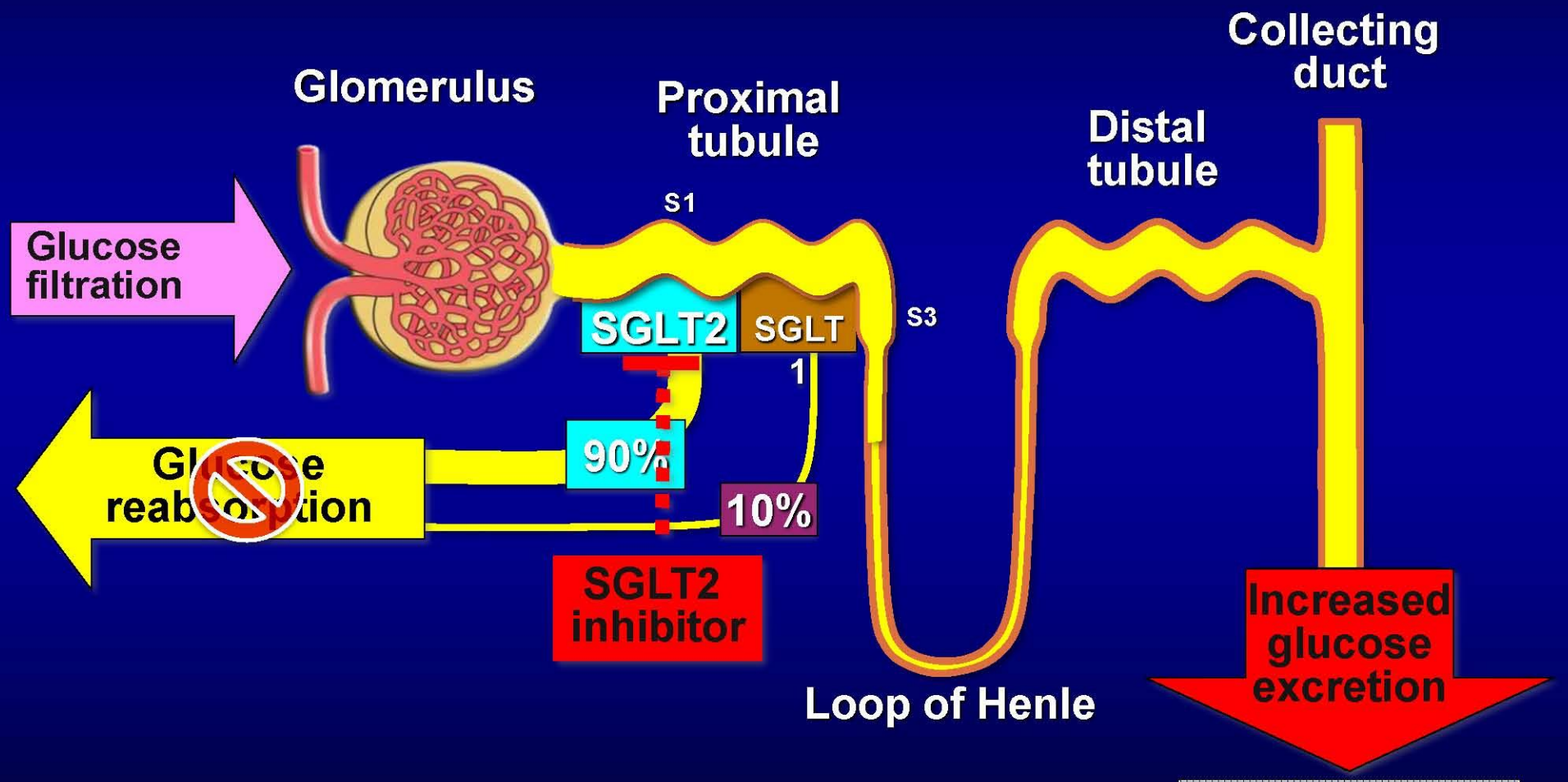
SGLT2 Inhibition Reduces Renal Glucose Reabsorption



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Lee YJ et al. Kidney Int Suppl. 2007;106:S27-S35;
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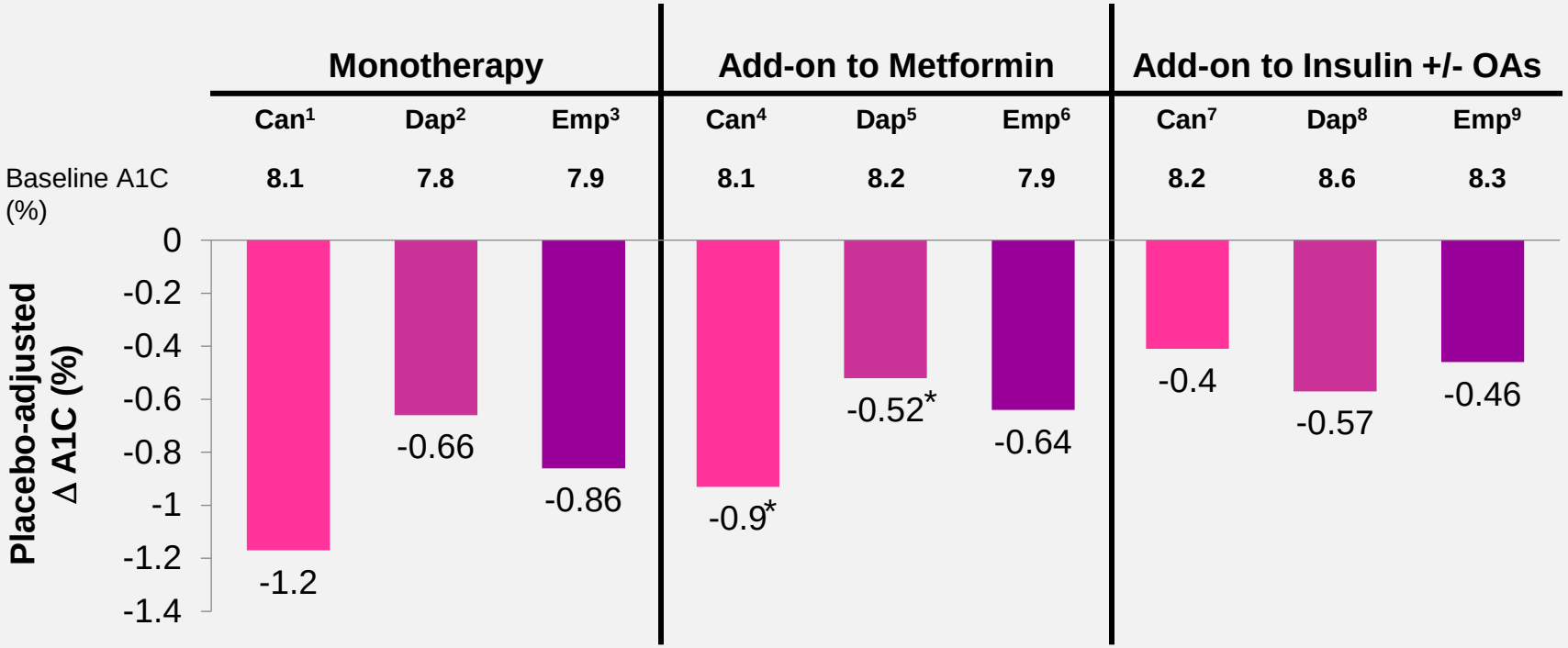
GLUCOSE CONTROL WITH SGLT2 INHIBITORS

Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)

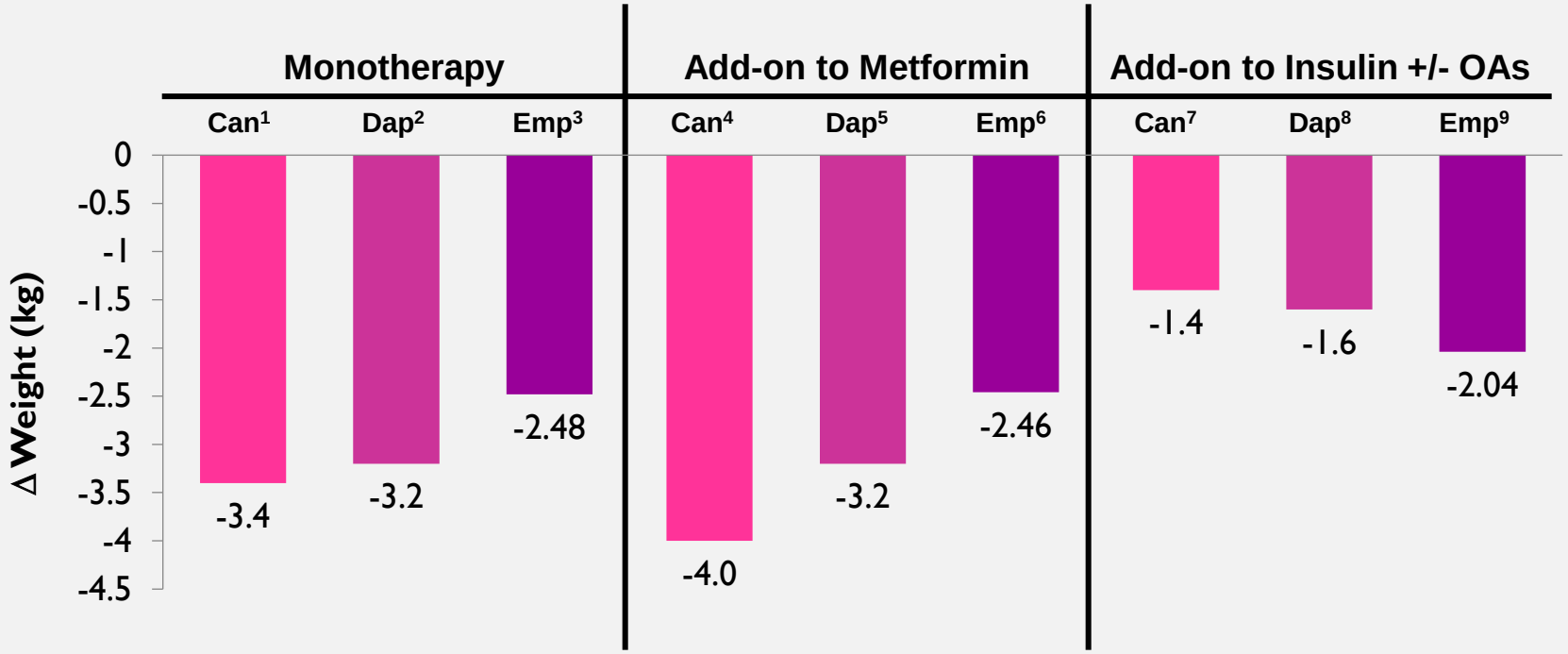


*Absolute change from baseline (active-controlled trial).

1. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382. 2. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224. 3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219. 4. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659. 7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473. 8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415. 9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.

WEIGHT CHANGE WITH SGLT2 INHIBITORS

Absolute Change from Baseline (Not Head-to-Head Trials)



1. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382. 2. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224. 3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219. 4. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659. 7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473. 8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415. 9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.

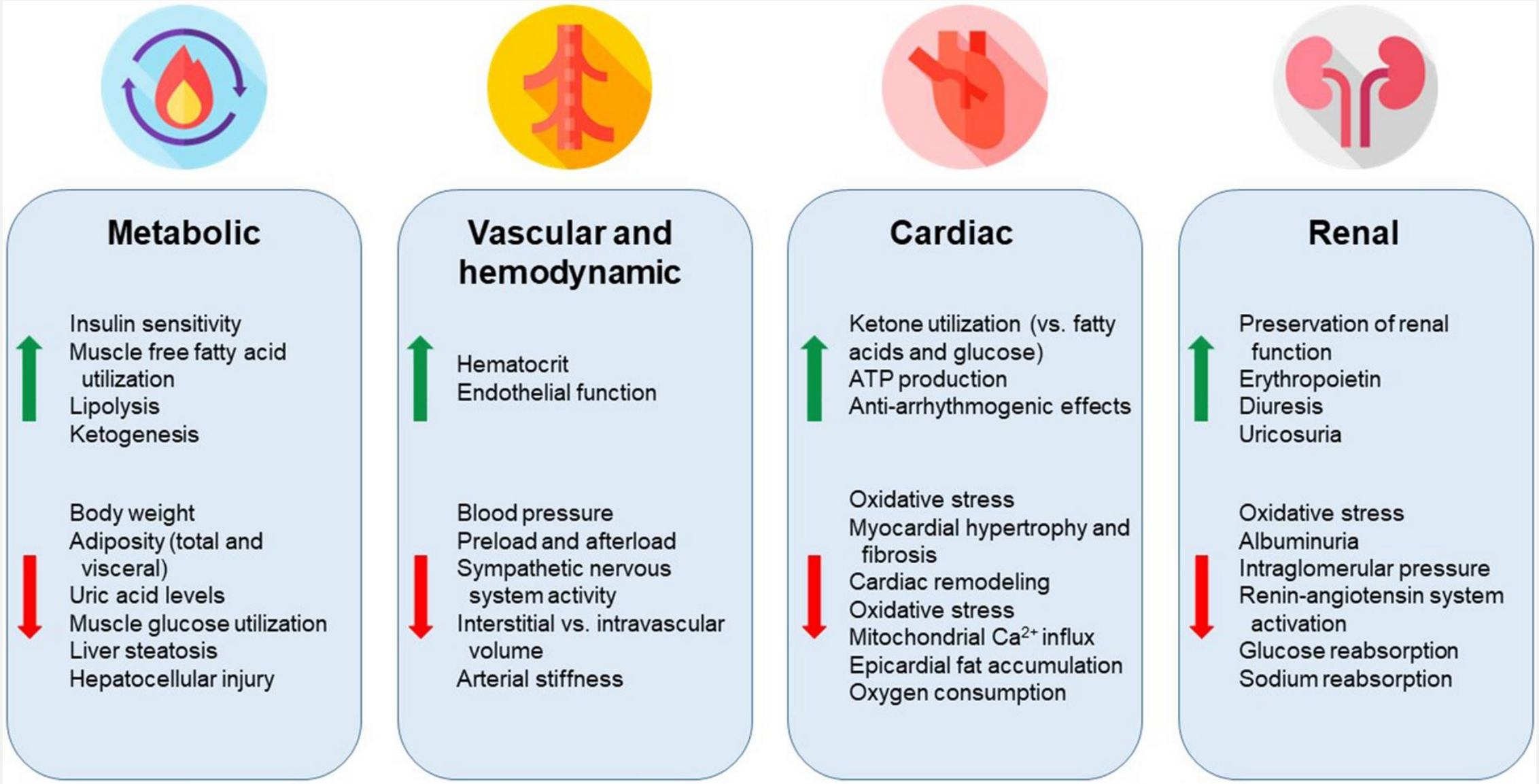
	EMPA-REG OUTCOME (2015)[10]	CANVAS (2017) [7]	DECLARE-TIMI 58 (2019) [19]	VERTIS CV (2020) [11]
Treatment	Empagliflozin Placebo	Canagliflozin Placebo	Dapagliflozin Placebo	Ertugliflozin Placebo
Patient population	Patients (N=7020); T2D and established CVD	Patients (N=10142); T2D and established CVD or ≥2 CVD risk factors	Patients (N=17160); T2D and established CVD or ≥1 CVD risk factors	Patients (N=8246); T2D and established CVD
Established CVD (%)	>99%	65.6%	41%	100%
T2D (%)	100%	100%	100%	100%
Primary outcome	MACE	MACE	MACE CVD death or HHF	MACE
Risk of MACE HR (95% CI); *P* value	0.86 (0.74–0.99); *P* = 0.04	0.86 (0.75–0.97); *P* = 0.02	0.93 (0.84–1.03); *P* = 0.17	0.97 (0.85–1.11); *P* < 0.001 for noninferiority
HHF HR (95% CI); *P* value	–35% 0.65 (0.50–0.85); *P* = 0.002	–33% 0.67 (0.52–0.87); NR	–27% 0.73 (0.61–0.88); NR	–30% 0.70 (0.54–0.90); NR
HHF or CV death HR (95% CI); *P* value	–34% 0.66 (0.55–0.79); *P* < 0.001	–22% 0.78 (0.67–0.91); NR	–17% 0.83 (0.73–0.95); *P* = 0.005	–12% 0.88 (0.75–1.03); *P* = 0.11

	DAPA-HF (2019) [12]	EMPEROR-Reduced (2020) [13]	SOLOIST-WHF (2021) [22]	EMPEROR-Preserved (2021) [30]
Treatment	Dapagliflozin Placebo	Empagliflozin Placebo	Sotagliflozin Placebo	Empagliflozin Placebo
Patient population	Patients (N=4744) with NYHA class II-IV HFrEF	Patients (N=3730) with NYHA class II-IV HFrEF	Patients (N=1222) with HFrEF or HFpEF	Patients (N=5988) with NYHA class II-IV HFpEF
Duration of followup	18.2 months	16 months	9.2 months SOTA; 8.9 months PBO	26.2 months
Ischemic HF (%)	56%	52%	NR	35.4
T2D (%)	42%	50%	100%	49.1
Primary outcome	Worsening HF† or CV death	HHF or CV death	CV death, HHF, and urgent visits for HF	HHF or CV death
Results	**Risk reduction**	**Risk reduction**	**Risk reduction**	**Risk reduction**
Worsening HF‡ or CV death HR (95% CI; *P* value)	–26%* 0.74 (0.65–0.85); *P* < 0.001; NNT = 21	NR	NR	NR
HHF§ HR (95% CI); *P* value	–30%† 0.70 (0.59–0.83) NR	–31%† 0.69 (0.59–0.81); NR	–36%† 0.64 (0.49–0.83); *P* < 0.001	–29%† 0.71 (0.60–0.83); NR
HHF or CV death HR (95% CI); *P* value	–25%† 0.75 (0.65–0.85); *P* < 0.001)	–25%* 0.75 (0.65–0.86); *P* < 0.001); NNT = 19	NR	–21%* 0.79 (0.69–0.90); *P* < 0.001
CV death HR (95% CI); *P* value	–18%† 0.82 (0.69– 0.98); NR	–8%† 0.92 (0.75–1.12); NR	–16%† 0.84 (0.58–1.22); NR	–9%† 0.91 (0.76–1.09) NR
Worsening HF‡ HR (95% CI); *P* value	–30%† 0.70 (0.59–0.83); NR	NR	NR	NR
CV death, HHF, and urgent visits for HF HR (95% CI); *P* value	NR	NR	–33%† 0.67 (0.52–0.85; *P* < 0.001	NR

SGLT2-I'S AND HEART FAILURE

- DAPA-HF study
  - Dapagliflozin became the first SGLT2I approved for treatment to reduce the risk of CV death and HHF in adults with HFrEF
- EMPEROR-Reduced study
  - Empagliflozin received FDA approval for use to reduce the risk of CV death and HHF in adult patients with HFrEF
- EMPEROR-Preserved study
  - Empagliflozin approved for the treatment of HF***p***EF

Possible mechanisms underlying the cardioprotective effects of SGLT2is on HF



SGLT2-I ADVERSE EFFECTS

- Genital Mycotic Infections
  - Yeast infections in women
  - Balanitis in men (more frequent if uncircumsized)
- UTI's
- Fournier's Gangrene (necrotizing fasciitis of perineum)
- Hypotension
  - Intravascular volume contraction
  - Susceptible Patients: +CKD, low SBP, elderly, on diuretics
- Hypoglycemia (when added to insulin or sulfonylurea)
- (Euglycemic) DKA

Euglycemic DKA

Assessment and Precipitating Factors

Assess for DKA when symptoms are present, even if glucose <250 mg/dL

- Nausea/vomiting
- Abdominal pain
- Generalized malaise
- Shortness of breath

Consider factors that predispose to DKA before and during treatment with an SGLT2 inhibitor

- Reduced caloric intake
- Pancreatic insulin deficiency
- Alcohol abuse
- Insulin dose reduction

SGLT2 inhibitors are currently not approved for the treatment of type 1 diabetes.

Rosenstock J, et al. *Diabetes Care*. 2015;38:1638-1642; Erondu N, et al. *Diabetes Care*. 2015;38:1680-1686; Peters AL, et al. *Diabetes Care*. 2015;38:1687-1693.

DRUG-SPECIFIC ADVERSE EFFECTS

- Canagliflozin
  - Lower Limb Amputations (in patients with T2DM + CVD)
  - Consider the following before initation
    - Neuropathy
    - PVD
    - Prior history of foot infections, ulcers, or amputations

American Diabetes Association

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

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

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

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), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate: DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

- General lifestyle advice: medical nutrition therapy/eating patterns/physical activity
- Intensive evidence-based structured weight management program
- Consider medication for weight loss
- Consider metabolic surgery

When choosing glucose-lowering therapies: Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High: Semaglutide, Tirzepatide

High: Dulaglutide, Liraglutide

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

Neutral: DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

Diabetes Care. 2023;47(Supplement_1):S158-S178. doi:10.2337/dc24-S009

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

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Diabetes Care. 2023;47(Supplement_1):S111-S125. doi:10.2337/dc24-S006

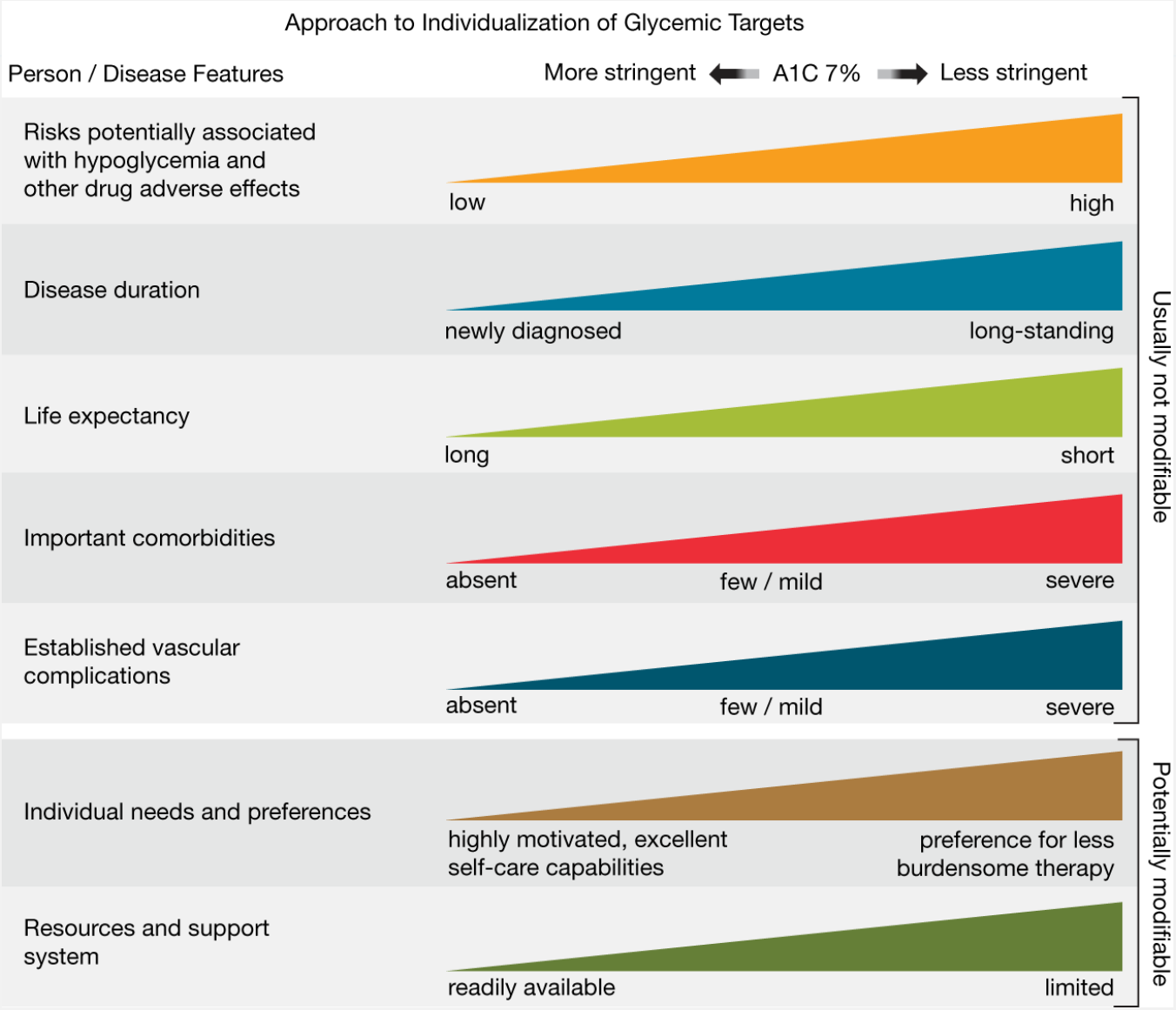

Figure Legend:

Person and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (36).

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THANK YOU