Disrupt T2D with Next Generation Incretin Therapy

Speaker
洪逸芷 醫師
中國醫藥大學附設醫院 新陳代謝科

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Disclosure

I hereby disclose that my relationship with Eli Lilly and Company includes: Speaker

Outline

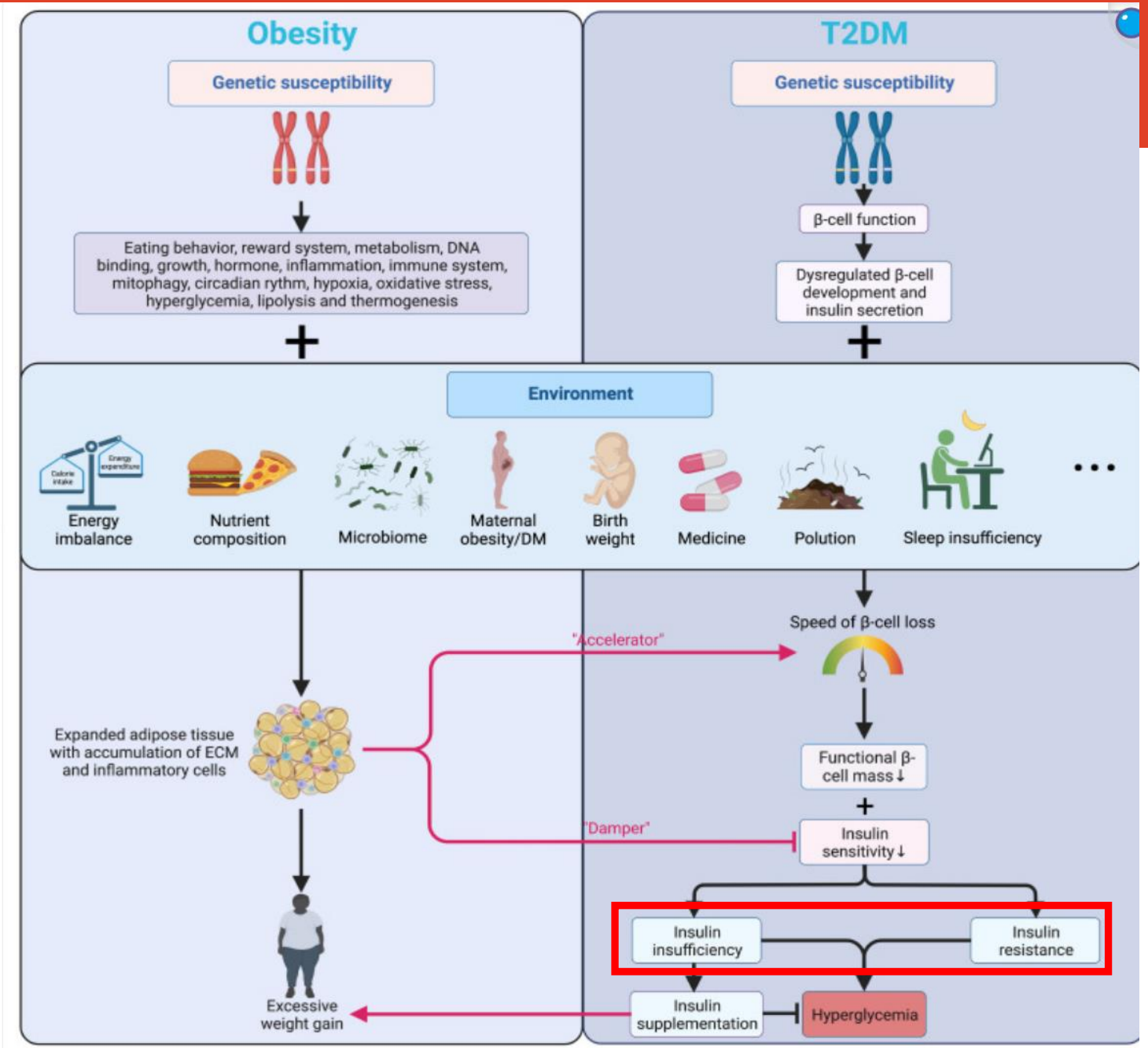
- Obesity and T2DM
- Beta-cell Function Restore in Patients with T2DM
- Insulin Resistance and Possible Therapeutic Strategies
- The Next Generation Incretin Therapy

T2D=type 2 diabetes mellitus.

Outline

- **Obesity and T2DM**
- **Beta-cell Function Restore in Patients with T2DM**
- **Insulin Resistance and Possible Therapeutic Strategies**
- **The Next Generation Incretin Therapy**

T2D=type 2 diabetes mellitus.

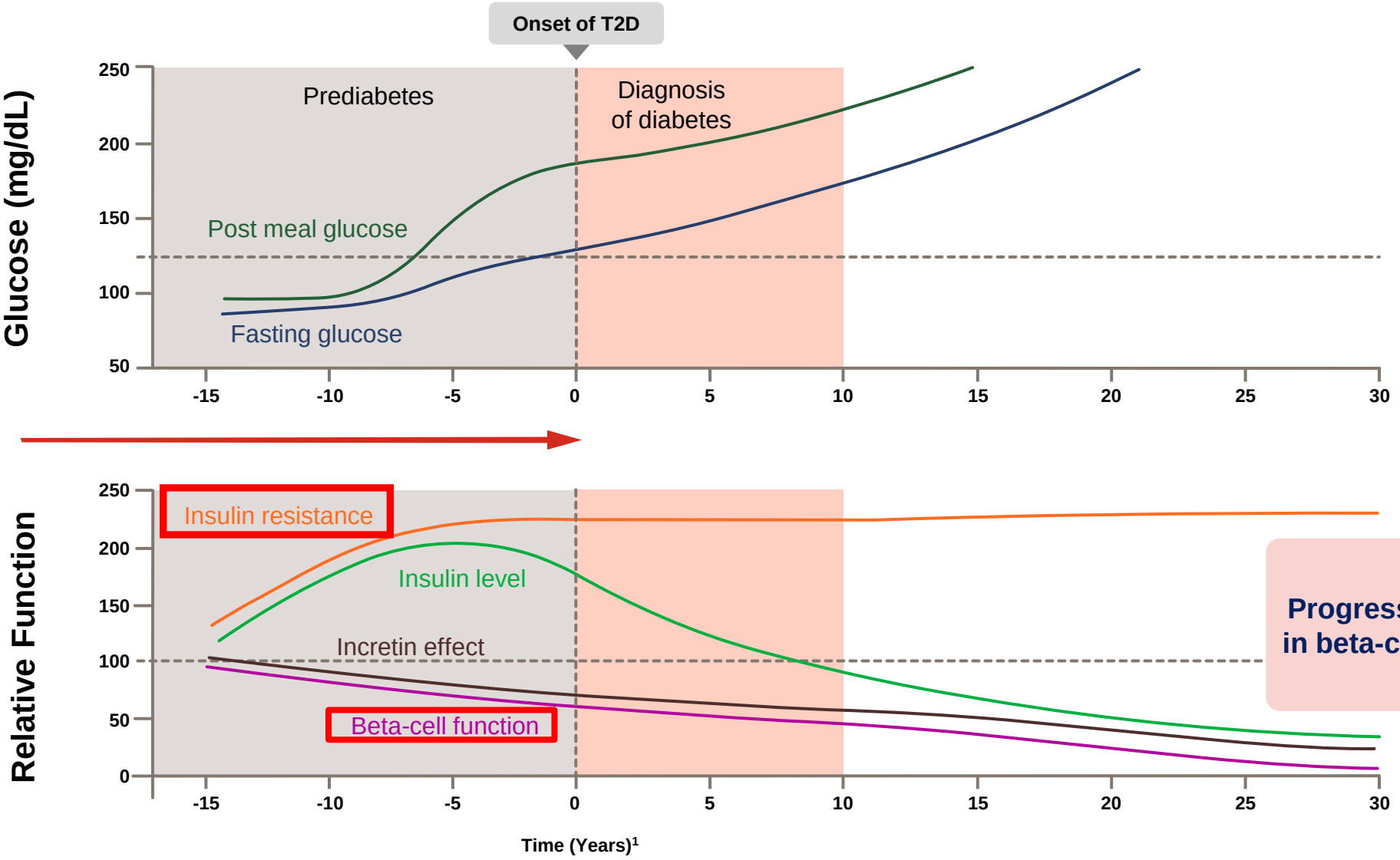


Front Endocrinol (Lausanne). 2023 Apr 21;14:1161521

Progressive Process of T2D

At least 50% reduction

in beta-cell function at the time of T2D diagnosis[2]



Progressive decline in beta-cell function[2]

1.Wysham C, Shubrook J. Beta-cell failure in type 2 diabetes: Mechanisms, markers, and clinical implications. Postgrad Med. 2020;132(8):676-686. 2. DeWitt DE, Hirsh IB. Outpatient insulin therapy in type 1 and type 2 diabetes. JAMA. 2003;289(17):2254-2264

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WILEY

RESEARCH LETTER

Beta-cell function in treatment-naïve patients with type 2 diabetes mellitus: Analyses of baseline data from 15 clinical trials

Diabetes Obes Metab.2023;25:1403–1407

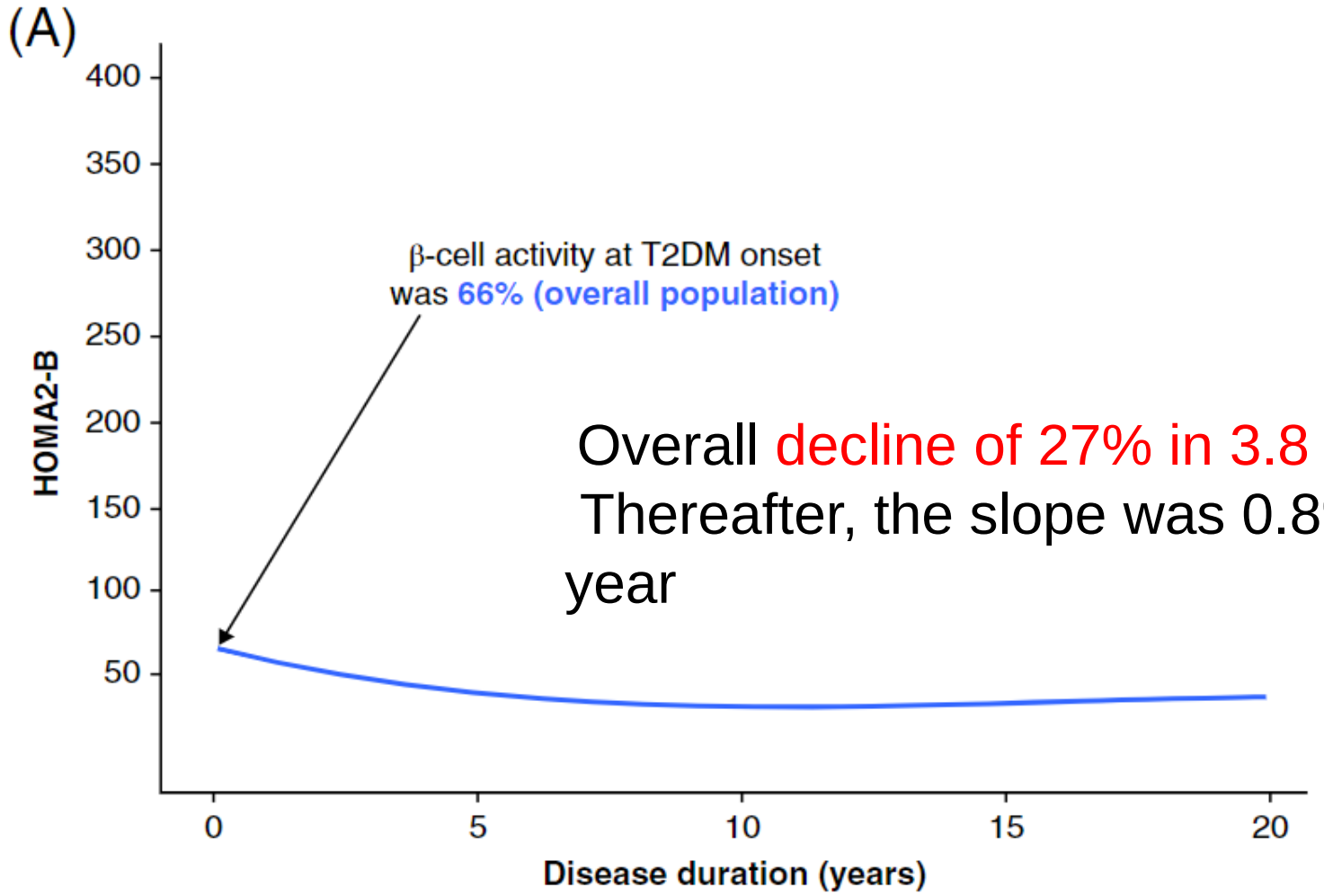
Baseline characteristics and demographics

TABLE 1 Baseline characteristics and demographics

Characteristics	IGT, n = 909	Treatment-naïve, n = 6706
Age, years	63.2 ± 8.3	54.7 ± 10.7
T2DM duration, years	Unknown	1.7 ± 2.3
Body mass index, kg/m^2	31.1 ± 5.7	30.4 ± 5.5
Women, %	52.7%	45.5%
HbA1c, mmol/mol (%)	41.0 ± 0.5 (5.9 ± 0.5)	62.8 ± 1.3 (7.9 ± 1.3)
HOMA2-B	95.0 ± 42.1	55.4 ± 43.3
HOMA2-S	72.9 ± 48.5	77.5 ± 73.3
Insulinogenic index	92.6 ± 166.8 (n = 839)	54.1 ± 106.6 (n = 1242)
Disposition index	1.2 ± 1.5 (n = 839)	0.9 ± 1.7 (n = 1241)
Fasting glucose, mmol/L	6.1 ± 0.5	9.3 ± 2.8
Fasting insulin, pmol/L	97.2 ± 66.1	102.3 ± 85.3

Diabetes Obes Metab.2023;25:1403–1407

β-cell function (HOMA-B) in treatment-naïve patients with type 2 diabetes mellitus

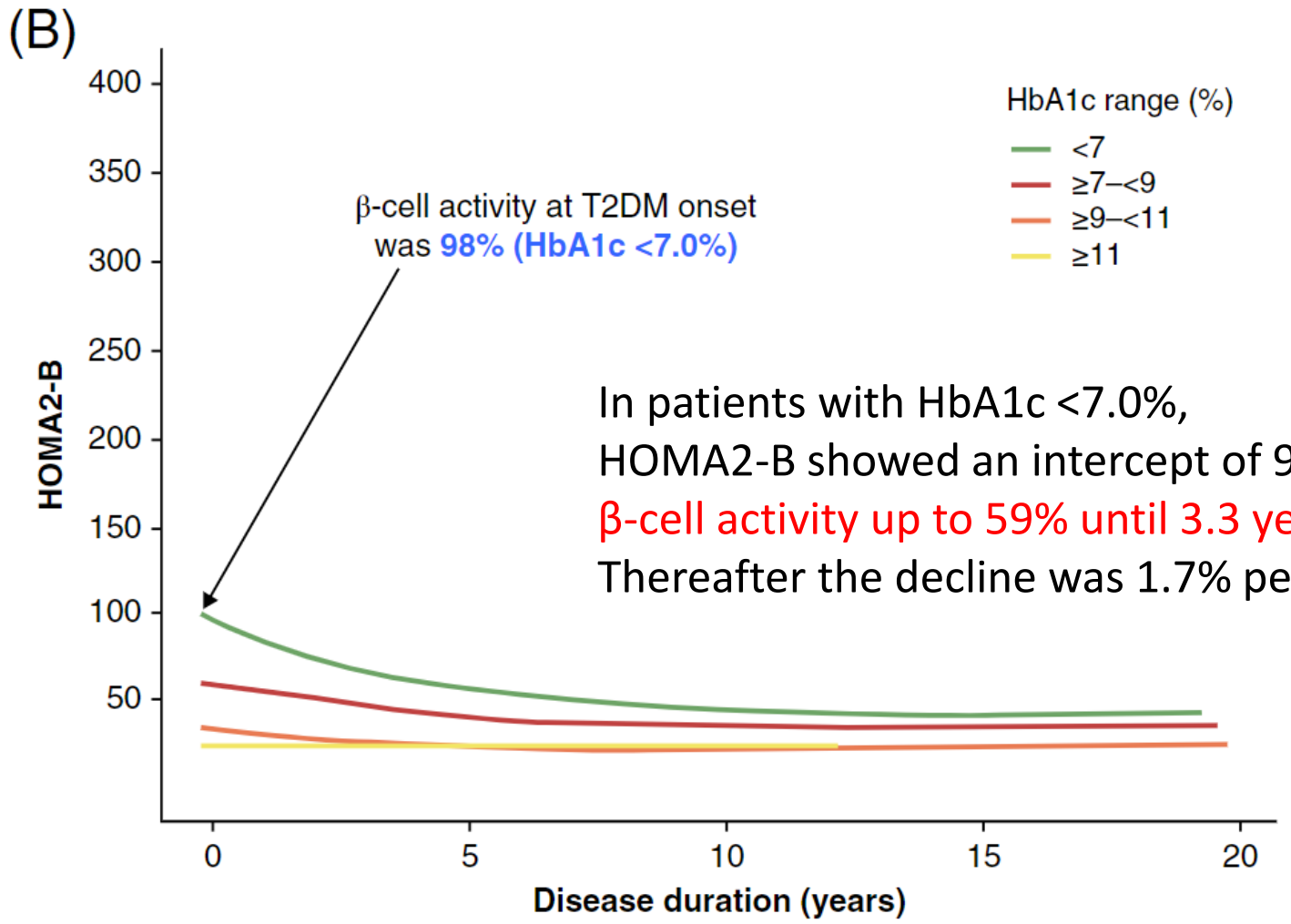


Overall decline of 27% in 3.8 years

Thereafter, the slope was 0.8% per year

Diabetes Obes Metab.2023;25:1403–1407

β-cell function (HOMA-B) in treatment-naïve patients with type 2 diabetes mellitus

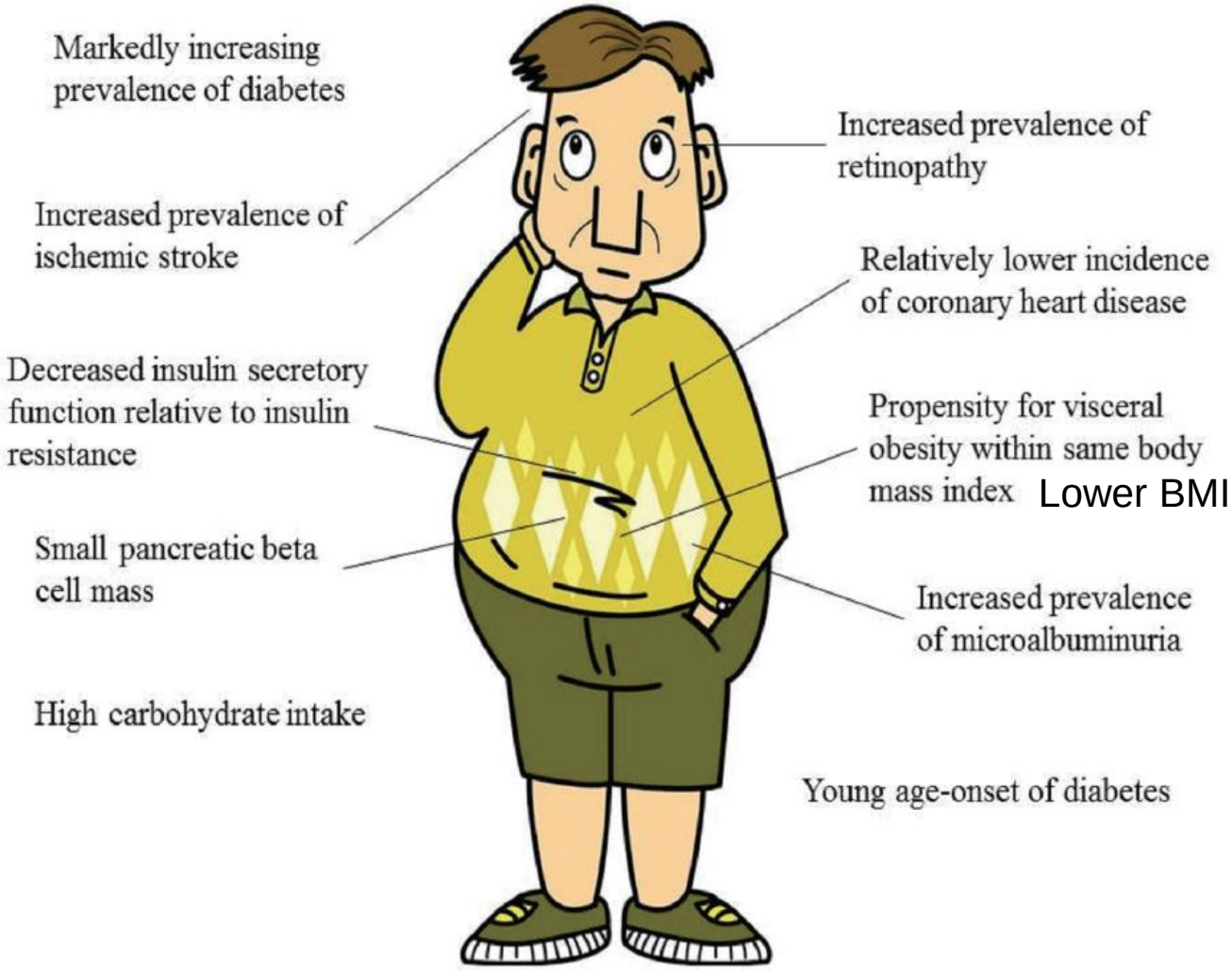


In patients with HbA1c <7.0%,
HOMA2-B showed an intercept of 98% and sustained β-cell activity up to 59% until 3.3 years
Thereafter the decline was 1.7% per year

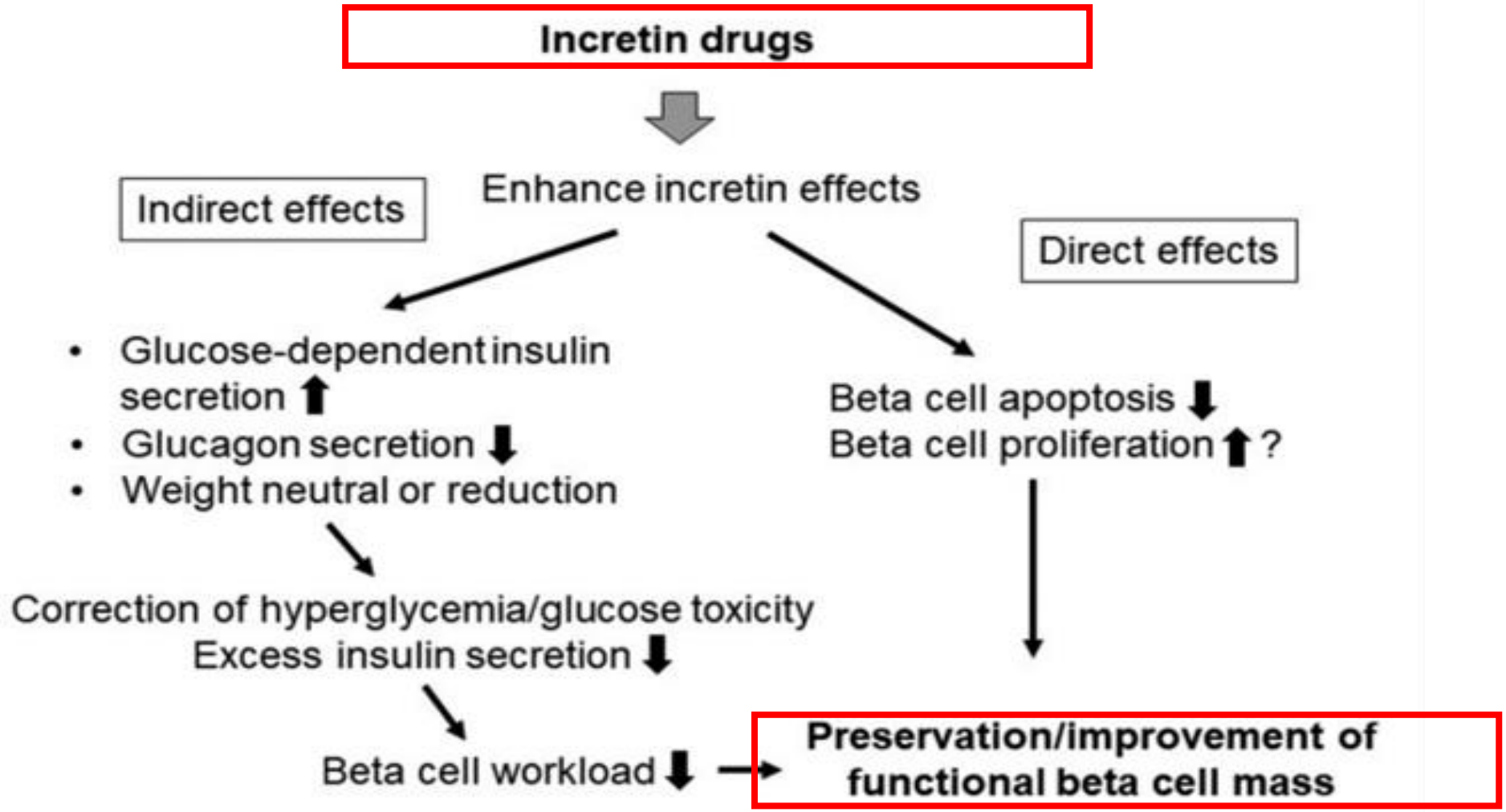
Diabetes Obes Metab.2023;25:1403–1407

Young-onset diabetes (YOD) is a unique feature in Asians

- Asians are known for dysfunctional pancreatic insulin secretory function
- Asians could benefit from treatment that preserve pancreatic islet functioning



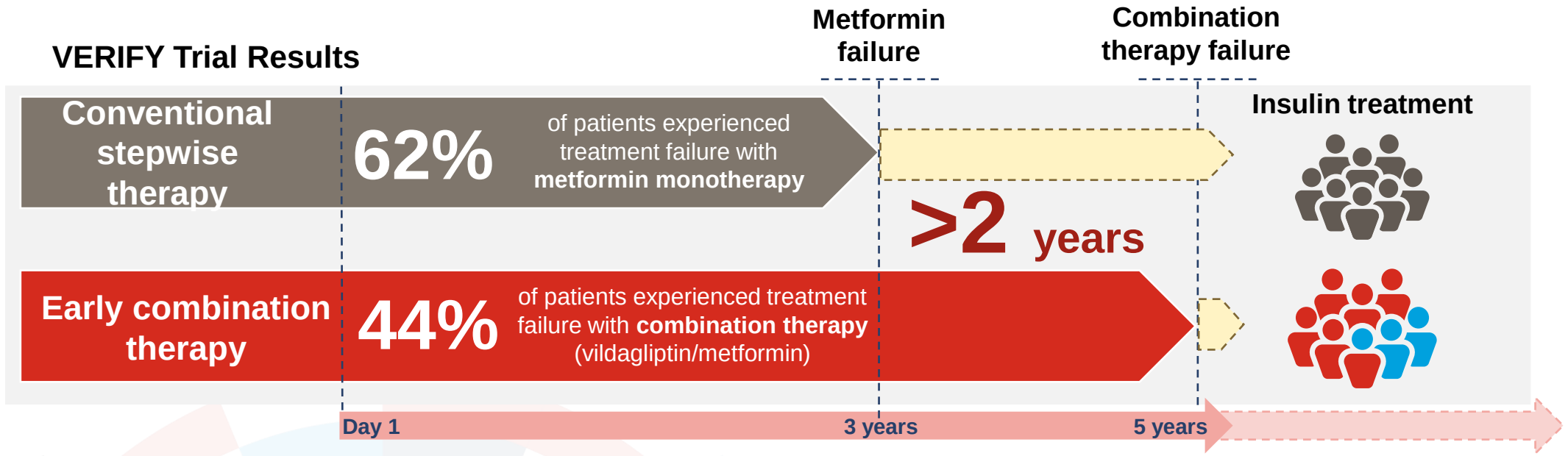
Endocrinol Metab (Seoul). 2015 Sep; 30(3): 263–269.



EXPERT OPINION ON PHARMACOTHERAPY 2020, VOL. 21, NO. 13, 1565–1577

VERIFY Study

Early Combination Treatment Targeting Multiple Mechanisms Reduces Time to Initial and Secondary Treatment Failures[1]



49%

Relative risk reduction from time-to-initial treatment failure with vildagliptin/metformin combination vs. metformin alone

26%

Relative risk reduction in time to secondary treatment failure with initial combination therapy vs. sequential addition of treatment

VERIFY was a 5-year, randomized, 1:1, double-blind, parallel-group study (n≈2000) designed to compare early initiation of a vildagliptin-metformin combination with standard-of-care initiation of metformin monotherapy, followed by the stepwise addition of vildagliptin when glycemia deteriorated. Participants with further deterioration were treated with insulin. Treatment failure was defined as a loss of glycemic control (2 consecutive values of HbA1c ≥7%).[1,2]

VERIFY=Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes.

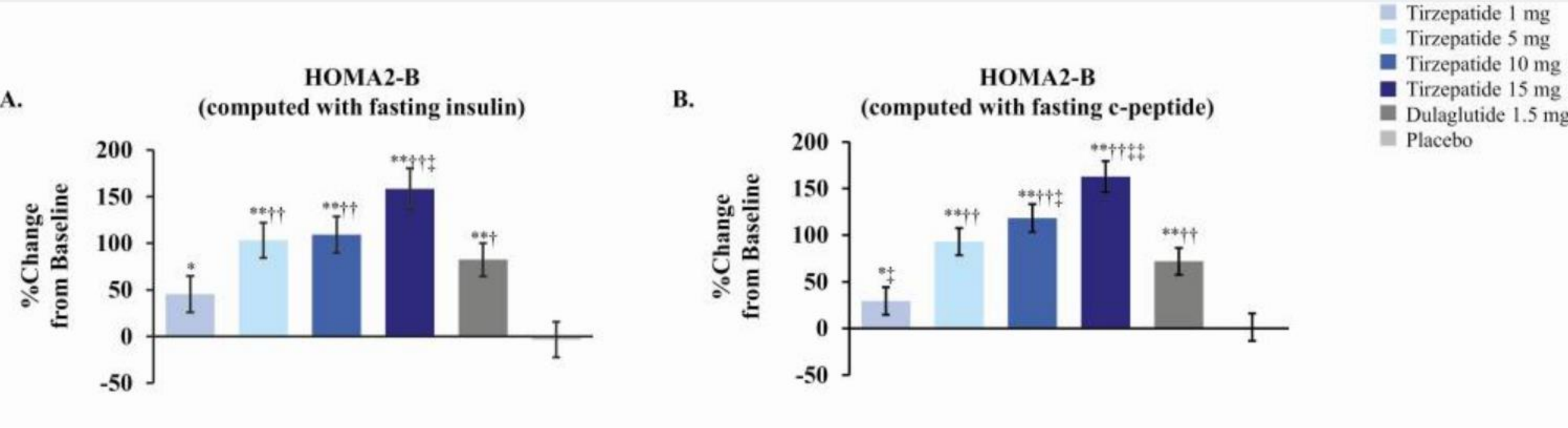
1. Matthews D, et al. *Diabetes Ther.* 2020;11(11):2465-2476. 2. Del Prato S, et al. *Diabet Med.* 2014;31(10):1178-1184.

Different glucose-lowering agents impacts to beta cell function[1,2]

	Glucose (HbA1c) lowering efficacy	Risk of hypoglycemia	Effect On weight	Beta cell protective Effect	Restore islet function
Metformin	Moderate to Strong	Low	Neutral to Loss	Yes	-
DPP4i	Moderate	Low	Neutral	Yes	↑
GLP-1 RA	Strong	Low	**Loss**	Yes	↑
SGLT2i	Moderate	Low	Loss	Yes	-
α-glucosidase inhibitor	Modest	Low	Neutral	Yes	-
TZD	Moderate	Low	Gain	Yes	-
SU	Strong	High	Gain	**No**	↓
Glinide	Modest to Moderate	Low to Moderate	Neutral	**No**	↓
insulin	Very Strong	High	Gain	Yes	-

1.Yoshifumi Saisho. EXPERT OPINION ON PHARMACOTHERAPY.2020
An emerging new concept for the management of type 2 diabetes with a paradigm shift from the glucose-centric to beta cell-centric concept of diabetes - an Asian perspective
2.Del Prato S, Camisasca R, Wilson C, et al. Diabetes Obesity Metab. 2014;16(12):1239–1246.
Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study.

Tirzepatide Improves Beta-cell Function in Type 2 Diabetes



J Clin Endocrinol Metab. 2020 Nov 24;106(2):388–396

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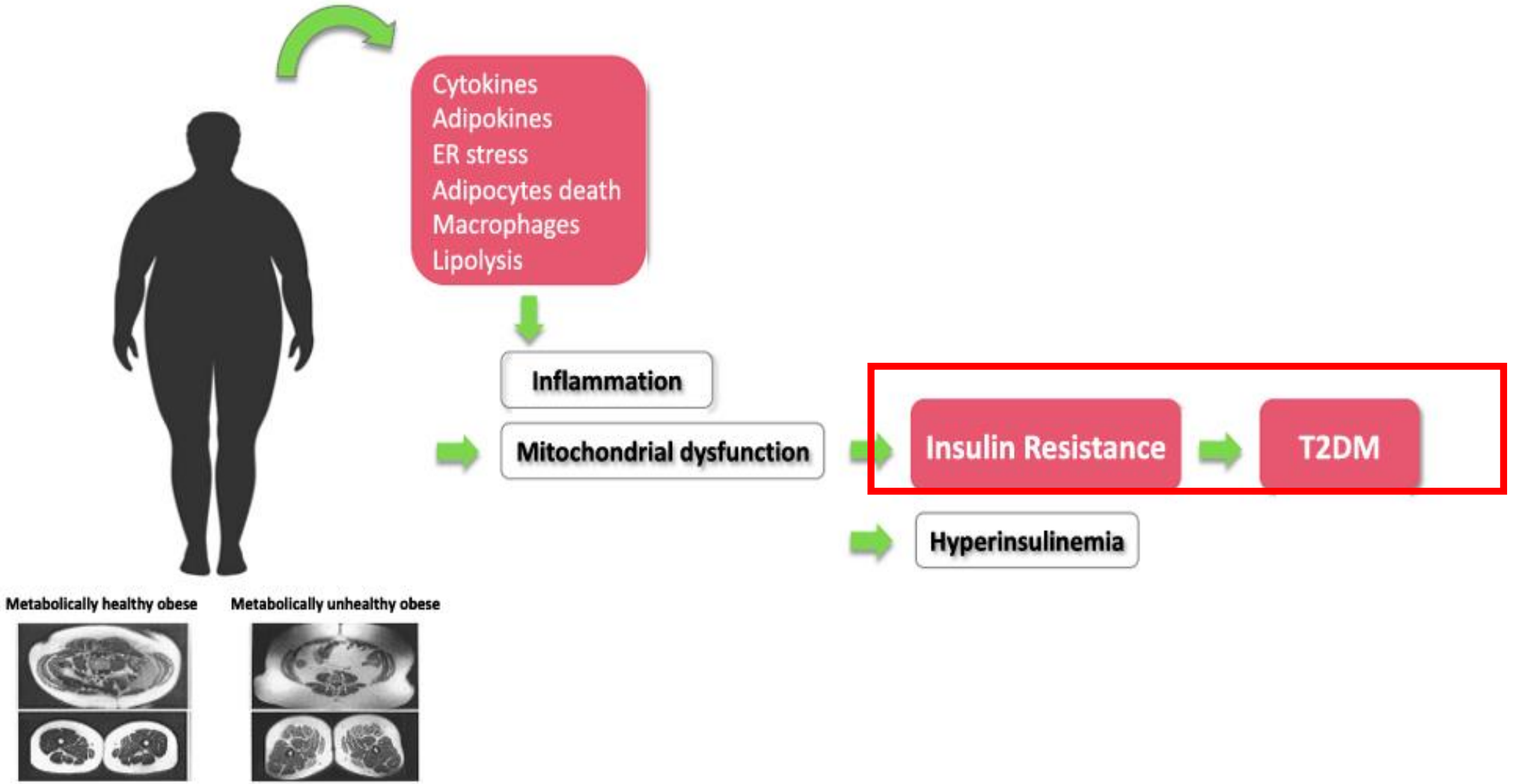
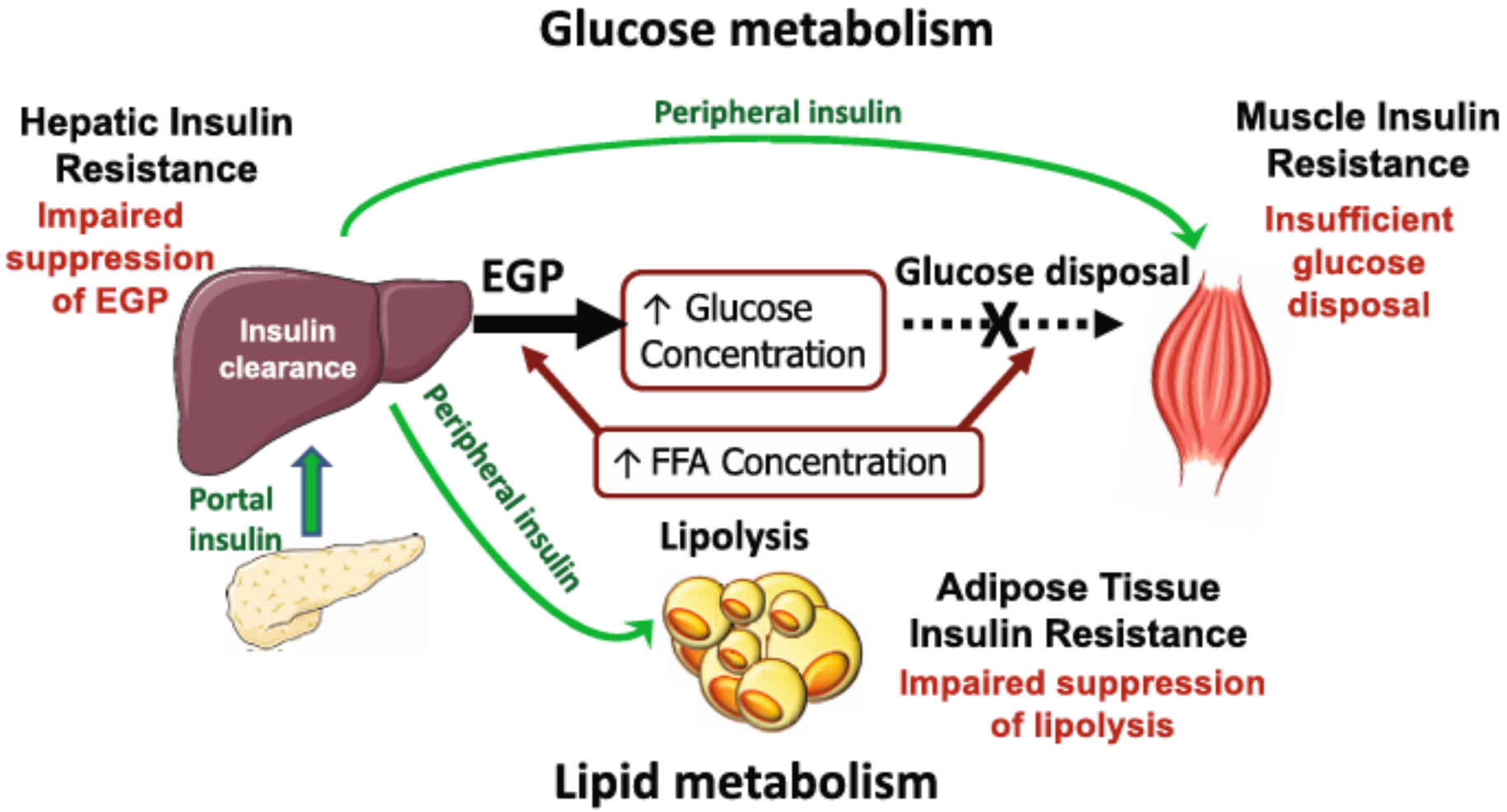
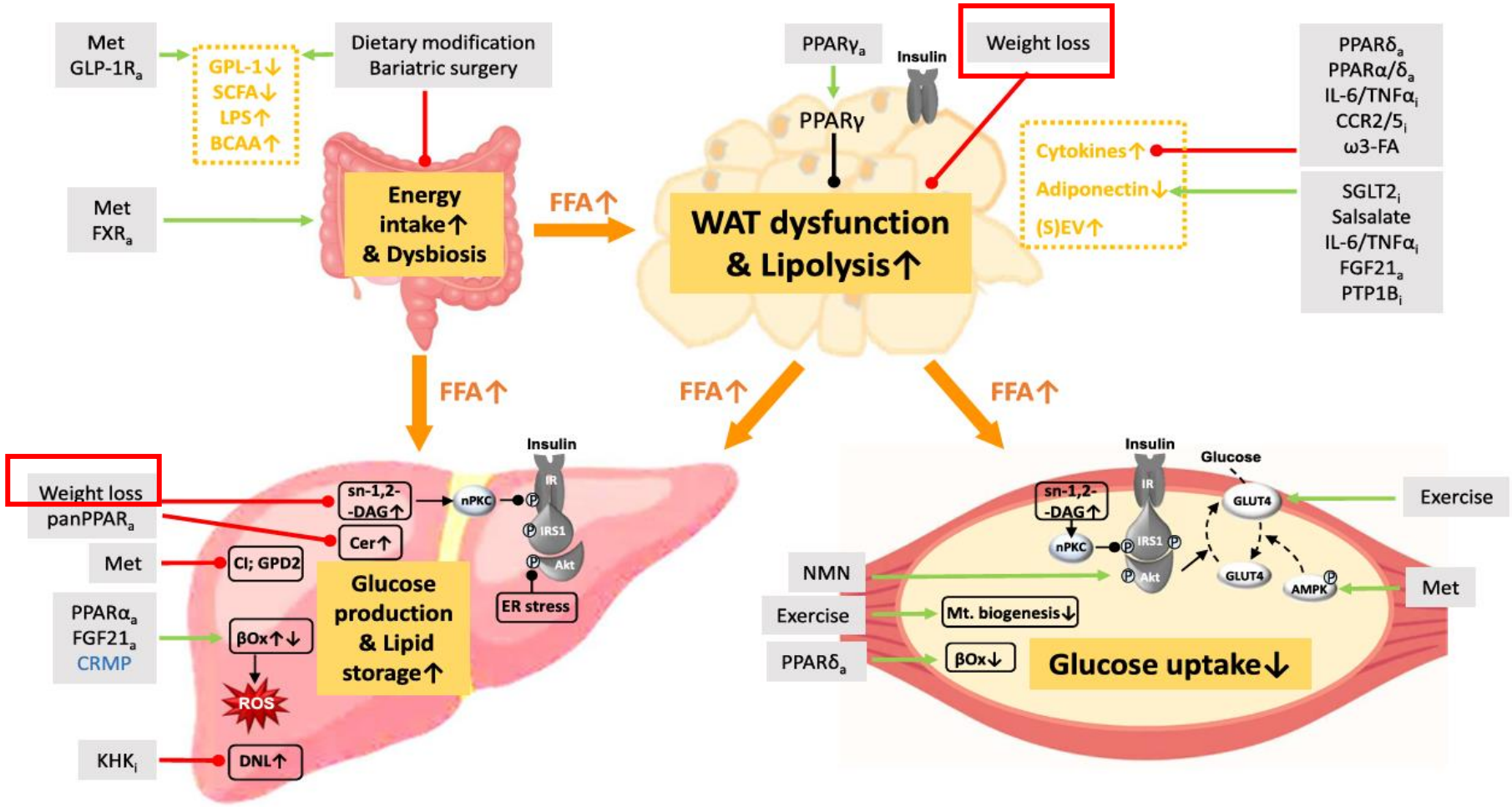


Diabetes Research and Clinical Practice 202 (2023) 110773

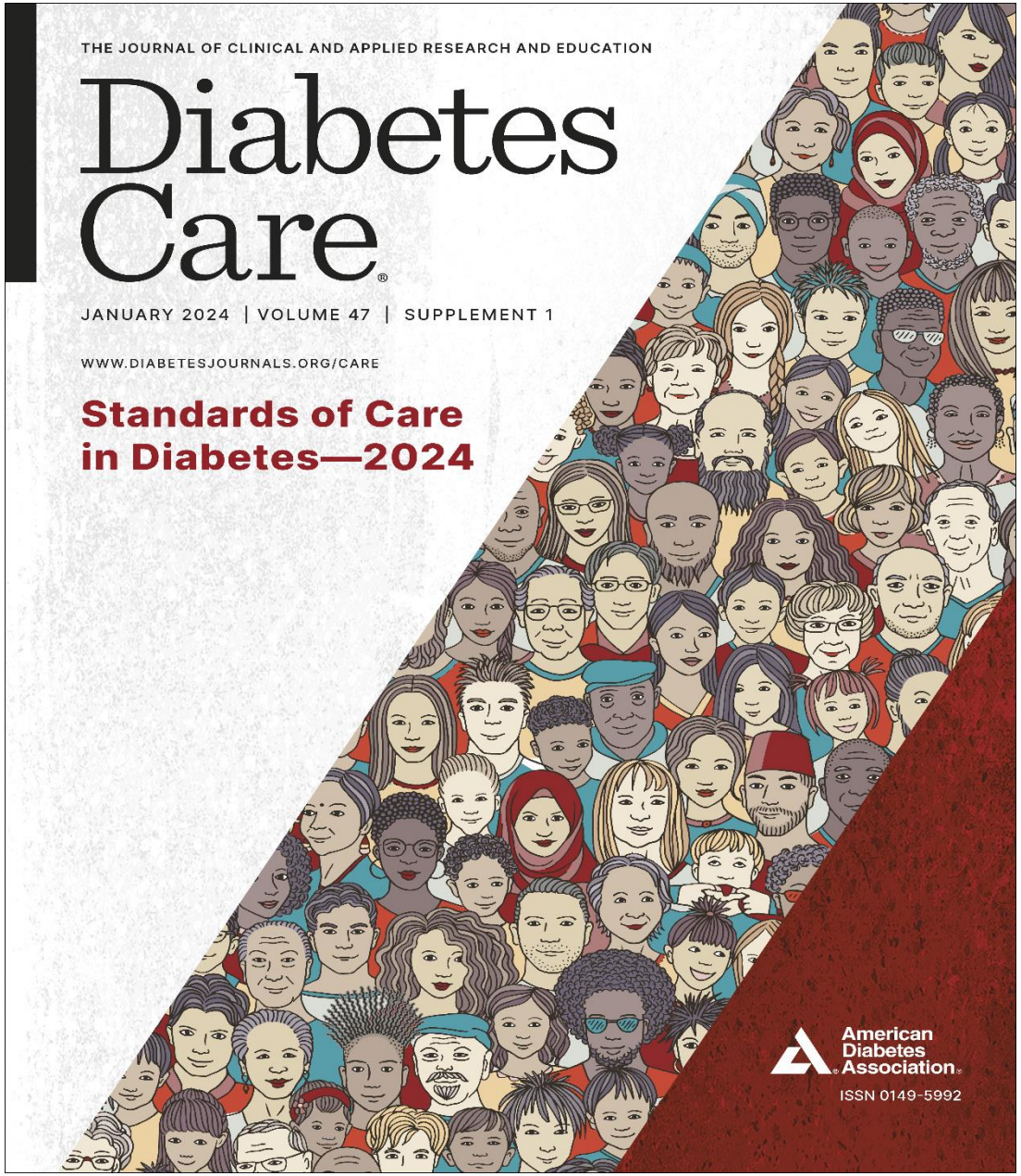


Obesity(SilverSpring).2022;30:1549–1563

Insulin resistance and possible therapeutic strategies

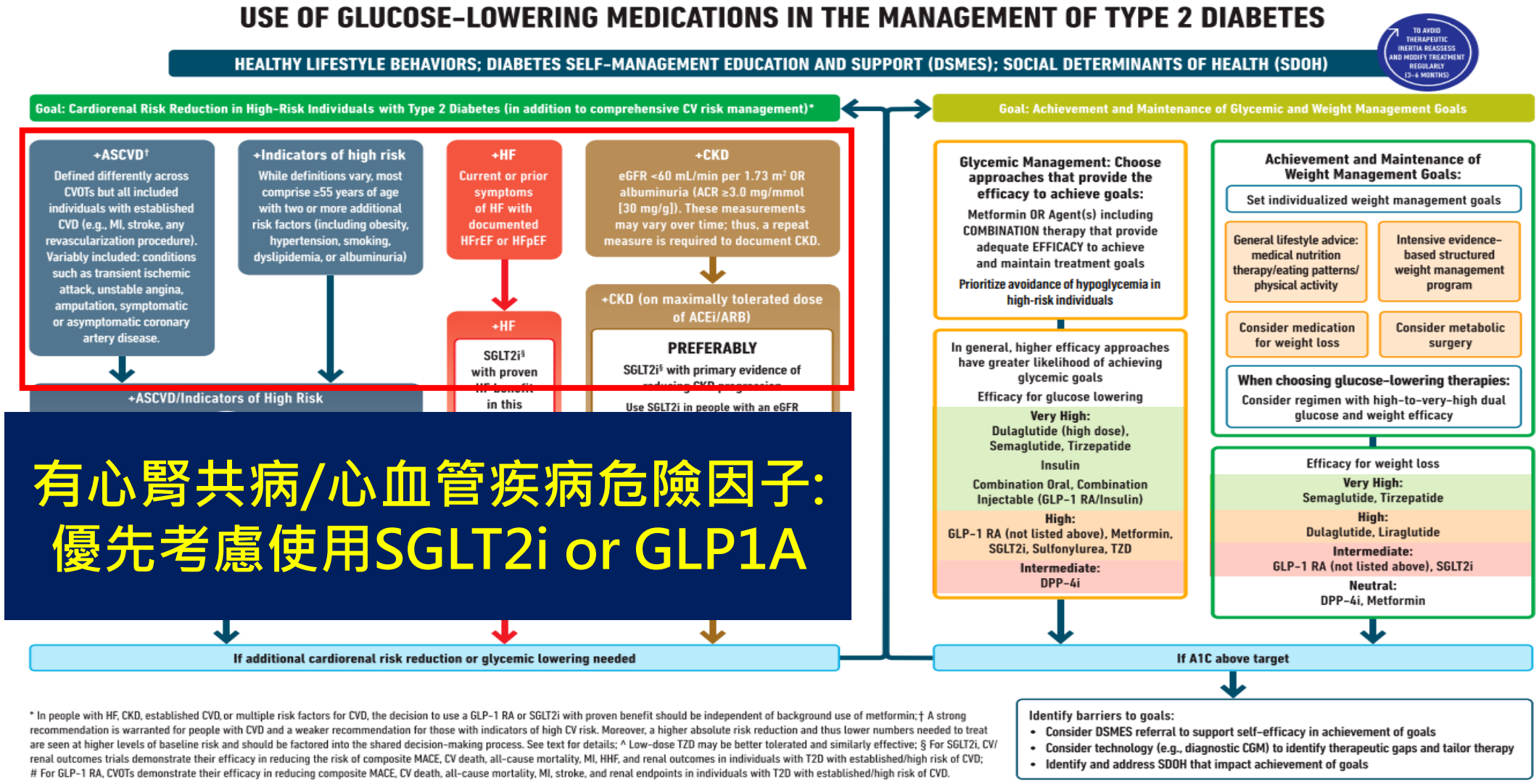


Metabolism Clinical and Experimental 125 (2021) 154892



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

2024 ADA Standard Care of Diabetes



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

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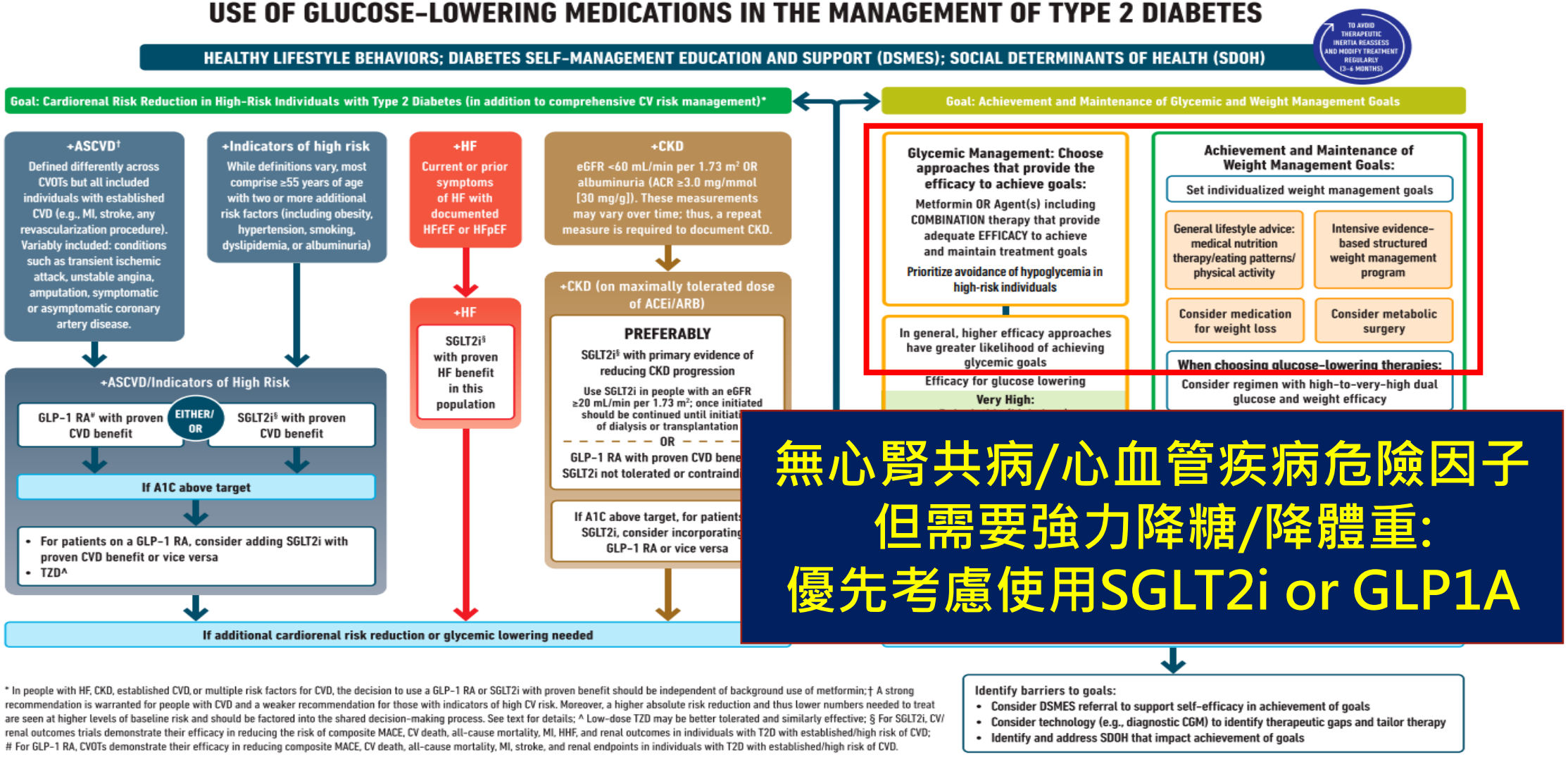
2024 ADA Standard Care of Diabetes



無心腎共病/心血管疾病危險因子
但需要強力降糖/降體重:
優先考慮使用SGLT2i or GLP1A

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

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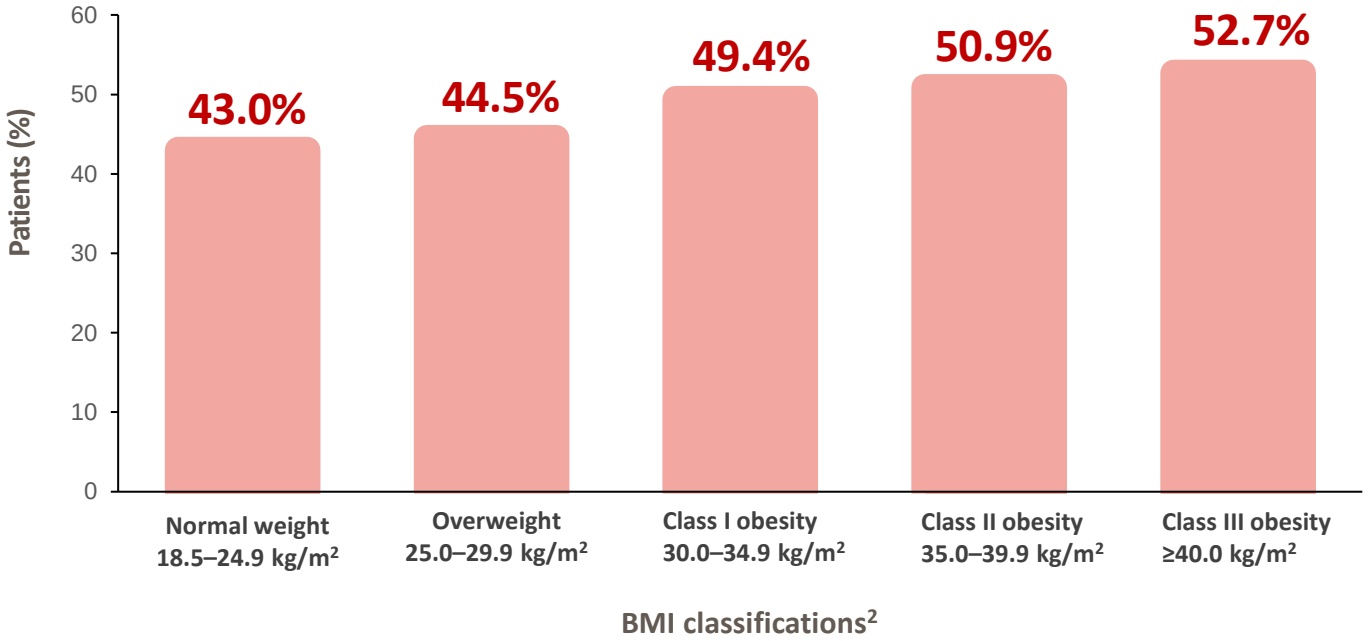
Higher BMI Is Associated With a Higher Proportion of Patients With Uncontrolled HbA1c[1]

Proportion of patients with T2D and HbA1c ≥7% across BMI categories (2019)[1]

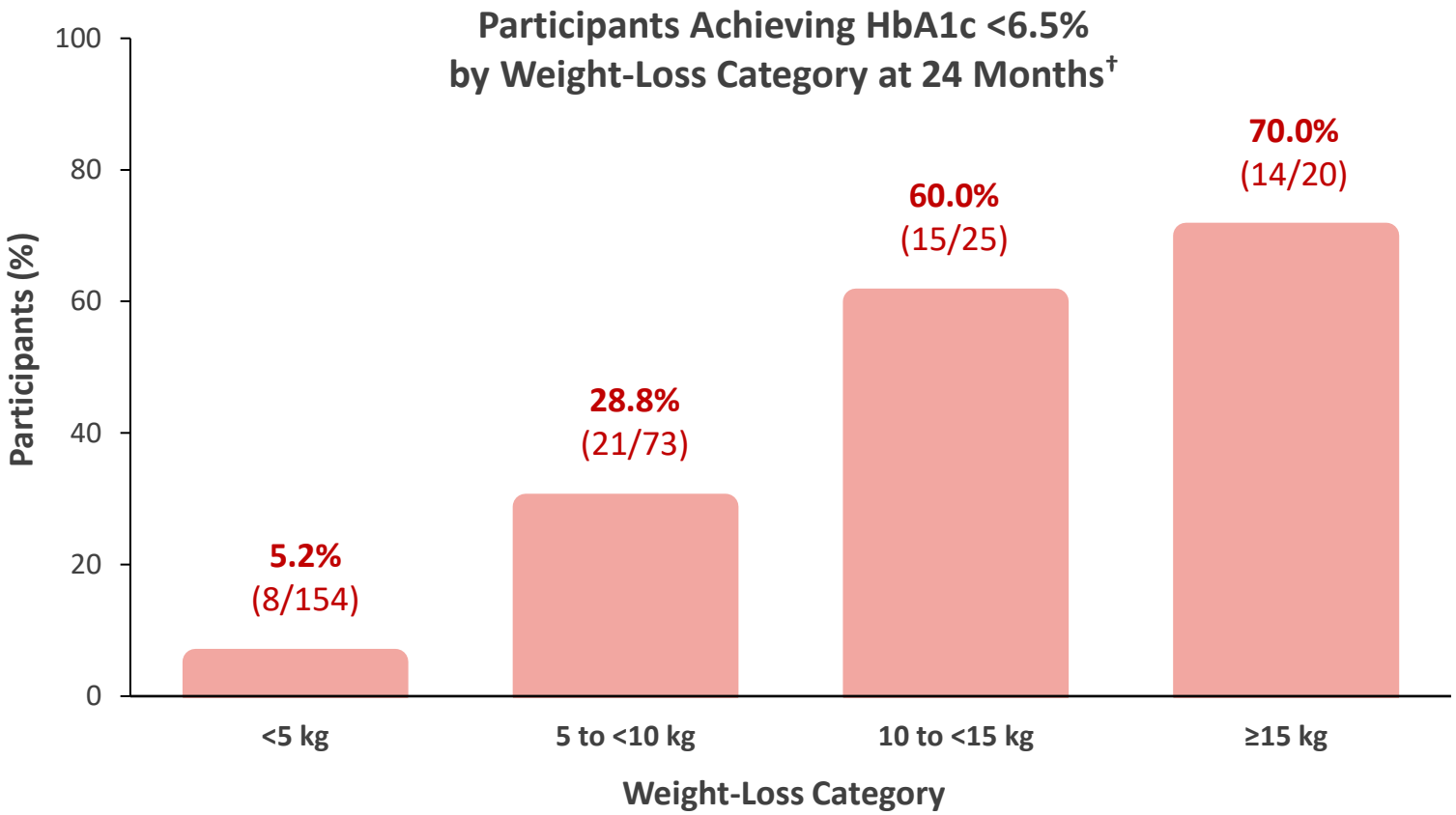


- Increased BMI is associated with worse glycaemic control (HbA1c ≥7%), with each higher class of BMI having increased proportions of uncontrolled HbA1c.[1]
- Both **BMI** and **waist circumference** (a correlate or indirect measure of excess abdominal fat) are strongly associated with **insulin resistance,** a core pathophysiological defect in T2D.[3,4]

BMI=body mass index; HbA1c=glycated hemoglobin; T2D=type 2 diabetes mellitus.

[1]Boye KS, et al. Diabetes Ther. 2021;12(7): 2077–2087. [2]Centers for Disease Control and Prevention. https://www.cdc.gov/obesity/adult/defining.html. Accessed 27 February 2023. [3]Cheng YH, et al. Medicine (Baltimore). 2017;96(39): e8126. [4]Racette SB, et al. Diabetes Care. 2006;29(3): 673–678.

Early Weight Reduction Is Associated With Improvement in HbA1c



Odds ratio (per kilogram of weight loss): 1.25 (95% CI, 1.16-1.35; *P*<0.0001)

*DiRECT was a cluster-randomized clinical trial to assess the effect of weight loss on T2D remission. For this post hoc analysis, eligible participants had T2D, were between 20 -65 years of age, and had a BMI of 27-45 kg/m^2. Intervention participants stopped all oral antidiabetes and antihypertensive drugs at baseline and received a 24-month weight-management program, while control participants remained on diabetes management per current best practices. Participants were not recruited if they had lost >5 kg in the last 6 months or had serious health problems.

†Participants from the weight-management intervention and standard of care control group were pooled for this analysis by weight-loss category.

CI=confidence interval; DiRECT=Diabetes Research on Patient Stratification.

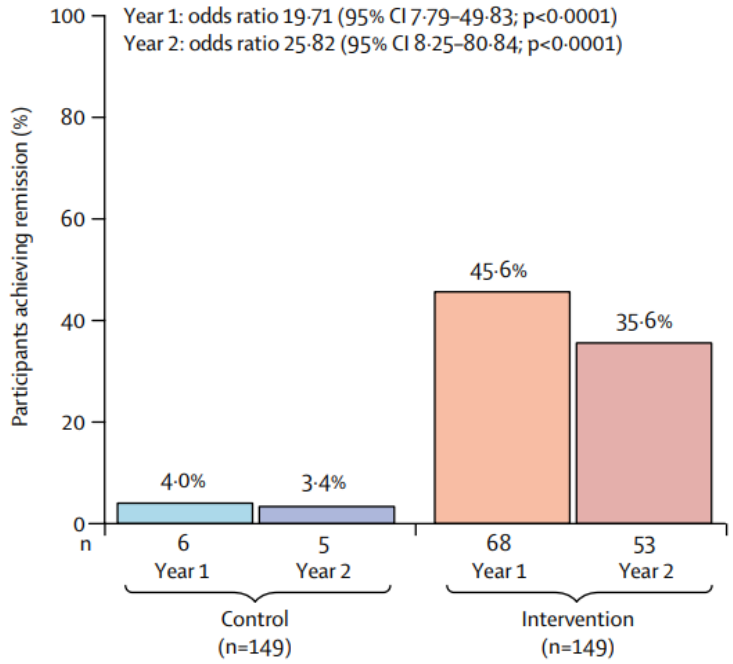
1. Lean MEJ, et al. *Lancet Diabetes Endocrinol*. 2019;7(5):344-355.

Weight loss intervention in an early T2D stage is associate with A1C reduction even T2D remission

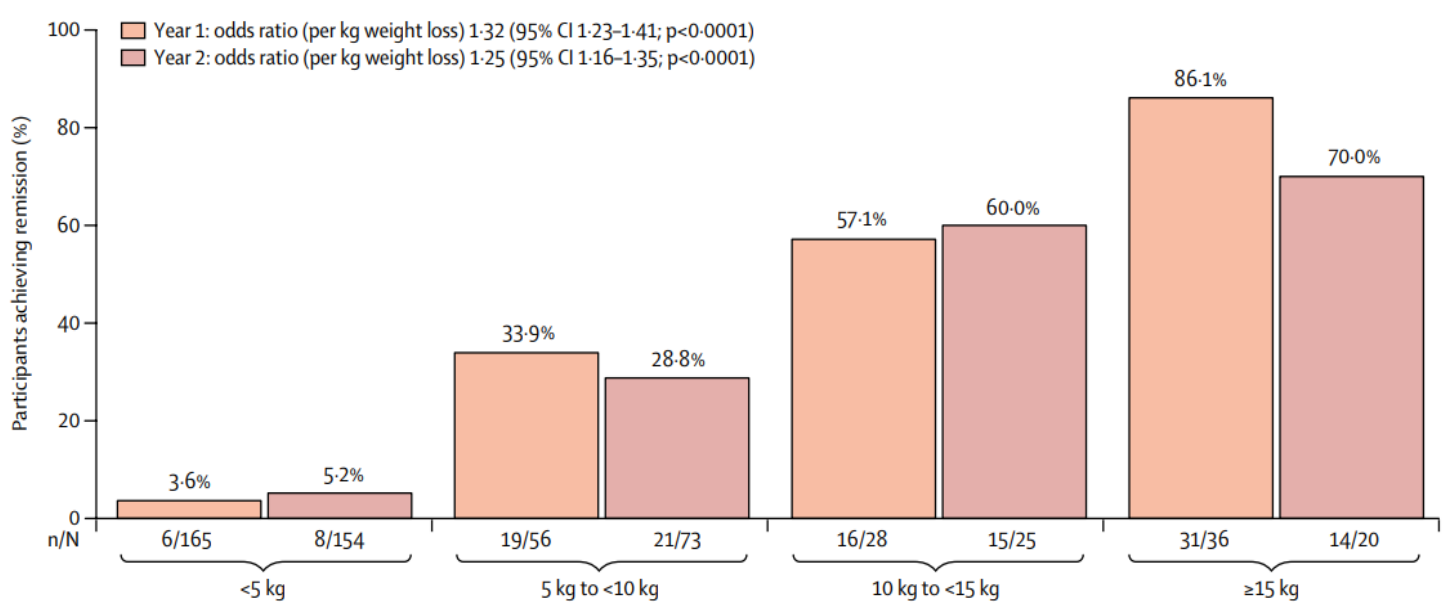
The DiRECT trial assessed remission of type 2 diabetes during a primary care-led weight-management program.

The **DiRECT trial** enrolled patients who had T2D for <6 years; results showed that weight loss was associated with HbA1c <6.5% without the use of antihyperglycemic medications.

Remission of T2D by randomized group



Remission of T2D in relation to weight loss



- The intervention consisted of withdrawal of antidiabetes and antihypertensive drugs, total diet replacement, stepped food reintroduction, and structured support for weight-loss maintenance.
- The control participants continued with best-practice routine care with no change to dietary, medication, or exercise advice.
- Definition of remission: A1C < 6.5% and off antidiabetes drugs since baseline.

Lancet Diabetes Endocrinol. 2019;7(5): 344–355.

A Focus on Weight-Loss Goals Is Part of Holistic T2D Management

Weight loss of ***3-7%*** of baseline weight **improves glycemia** and other intermediate cardiovascular risk factors[a]

Sustained loss of ***>10%*** of body weight usually confers greater benefits, including disease-modifying effects and **possible remission of T2D**[a]

[a]Remission of diabetes is defined as normal blood glucose levels for ≥3 months in the absence of pharmacological therapy.[1]
ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes; T2D=Type 2 Diabetes.
Diabetes Care 2024;47(Suppl. 1):S145–S157

ADA-EASD Consensus Report

Highlights of Guideline-based Recommendations for Weight Management in T2D[1,2*]

Exercise

As little as 30 minutes a week of moderate-intensity physical activity improves metabolic profiles

- Break up prolonged sitting every 30 minutes with short bouts of physical activity
- Aim to increase average steps per day by 500

Nutrition

Accommodate individual preferences while aiming for a net energy deficit that can be maintained[1,2,†]

- Consider low-calorie diets, including nutrient-dense foods such as whole grains, vegetables, fruits, legumes, low-fat dairy, lean meats, nuts, and seeds

Sleep

Sleep disorders are common in people with T2D and are associated with an increased risk of obesity and impairments in glucose metabolism

- Aim for consistent, uninterrupted sleep
- "Catch-up" weekend sleep alone is not enough to reverse the impact of insufficient sleep

Medication

Medications for T2D that support weight management are effective adjuncts to healthy behaviors

- Newer therapies for T2D have demonstrated very high efficacy for weight management in people with T2D and excess weight

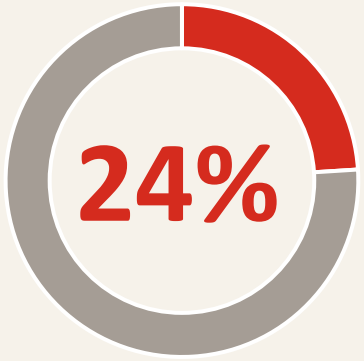
*Discussion of metabolic surgery deferred as it does not apply to patient case. †According to the ADA, weight loss can be attained with lifestyle programs that achieve a 500-750 kcal/day energy deficit or provide ~1200-1500 kcal/day for women and 1500-1800 kcal/day for men, adjusted for the individual's baseline body weight.[2]

1. Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.
2. American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S33-S43.

DiRECT Clinical Trial:

Achieving and Maintaining Weight Loss Associated With Lifestyle Interventions Alone Can Be Challenging[1,2]

Despite a high level of support for lifestyle changes and additional support of **relapse management** during the maintenance phase[1]:



of participants in the intervention group achieved **15 kg of weight loss** at 12 months

12 Months

of participants in the intervention group were able to maintain the weight loss for 2 years[1]

24 Months

In a post hoc analysis, only **24% of participants** were able to achieve **≥10 kg of weight loss** at 2 years[1]

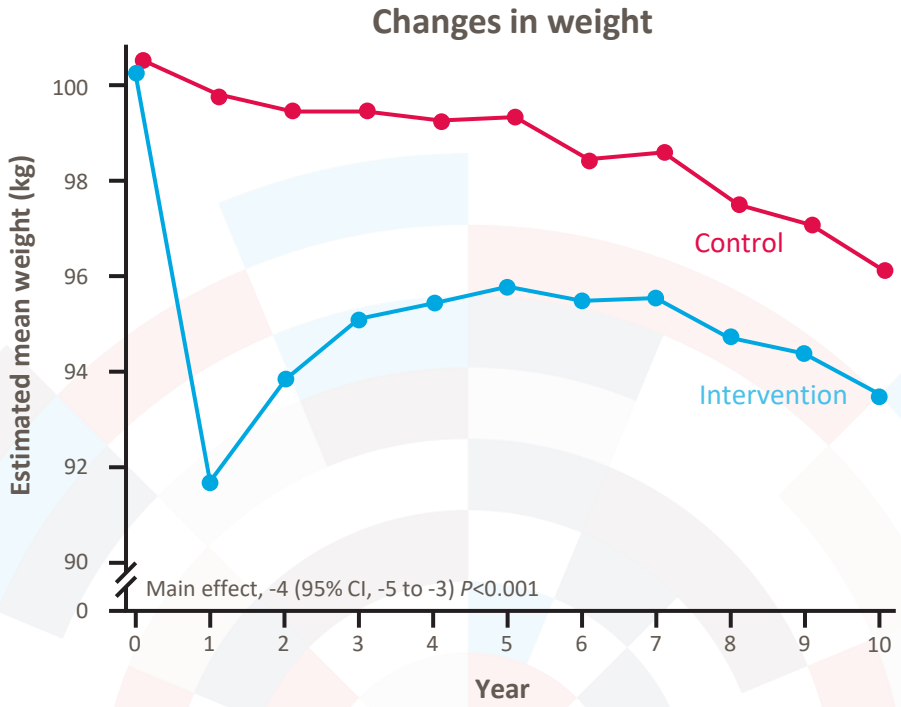
1. Lean MEJ, et al. *Lancet Diabetes Endocrinol*. 2019;7(5):344-355.
2. Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

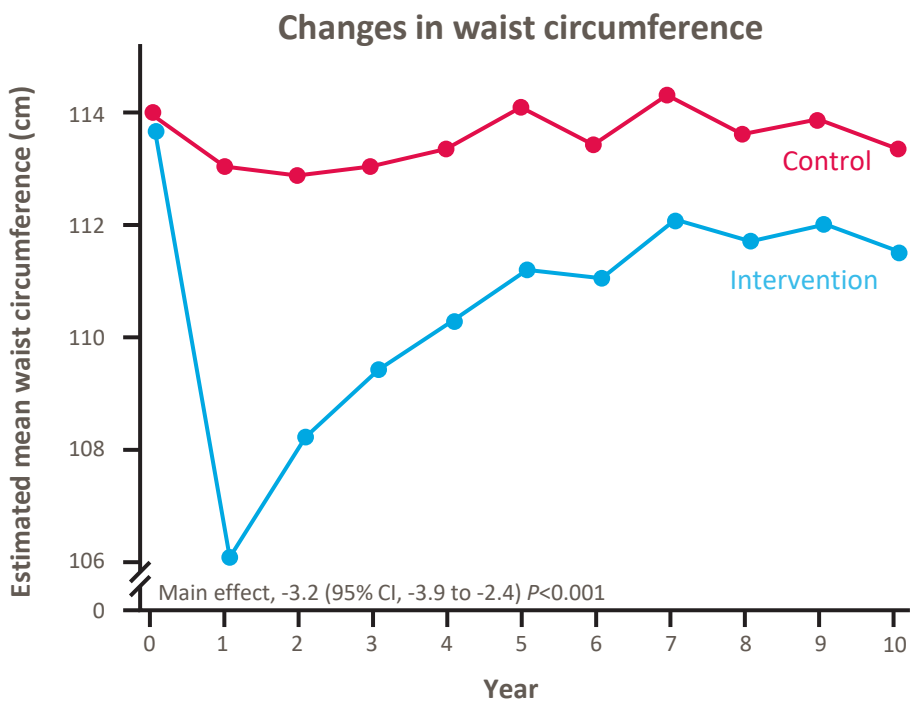
Look AHEAD:

Maintaining Initial Weight Loss is Possible but Challenging for Patients with T2D

Patients who received **intensive lifestyle intervention,** including ongoing monthly support:

- achieved the highest amount of reduction in body weight and waist circumference at 1 year
- regained a portion of initially lost weight and waist circumference over the course of the study (10 years).





Look AHEAD was a multicenter, randomized, controlled trial of lifestyle intervention in 5145 overweight or obese individuals with T2D aged 45–67 years old.
CI=confidence interval; T2D=type 2 diabetes mellitus.
Look AHEAD Research Group. N Engl J Med. 2013;369(2): 145—154.

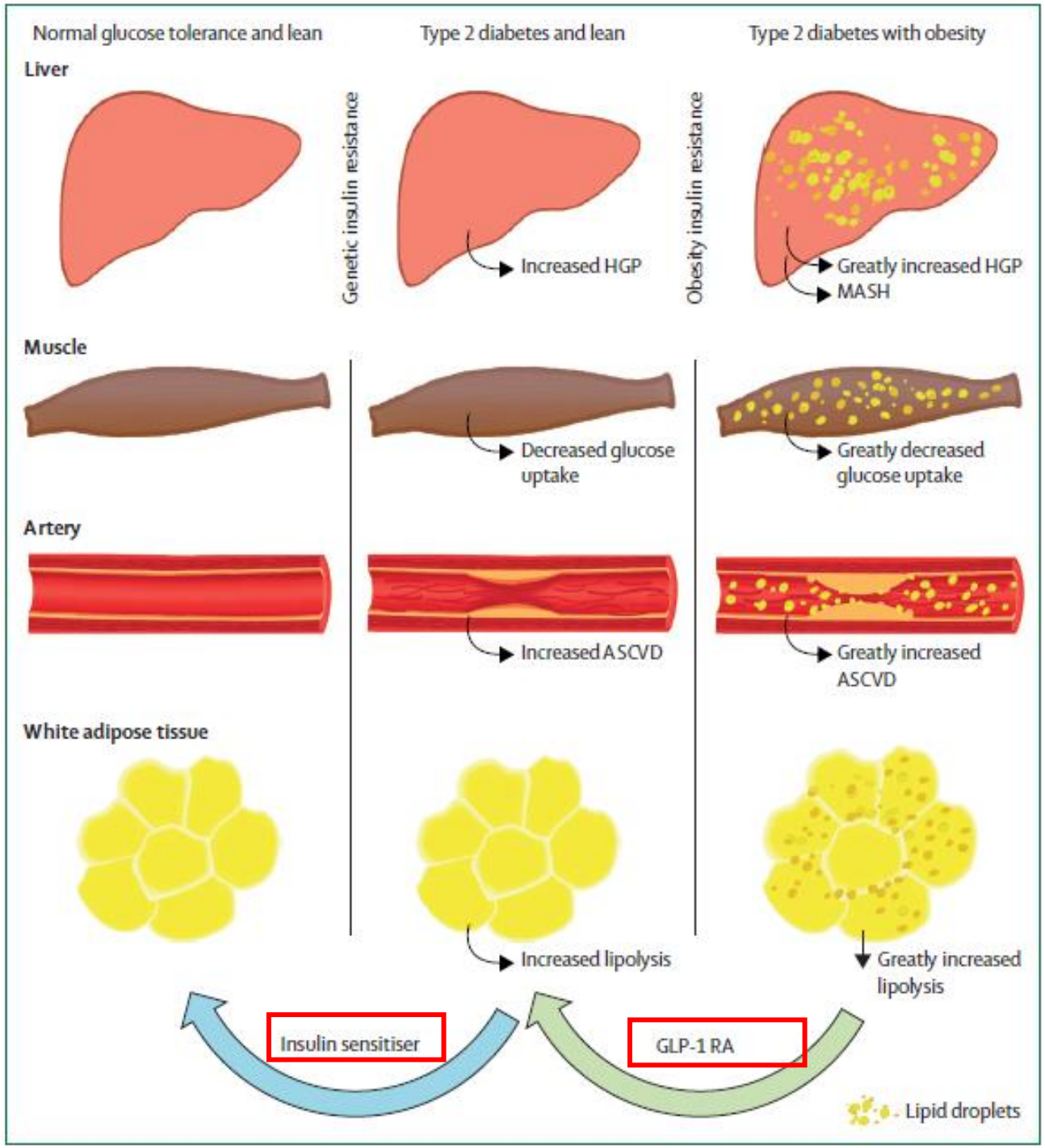
Insulin-stimulated glucose disposal in people before and 1 year after Roux-en-Y gastric bypass

	Obese BMI, normal glucose tolerance		Obese BMI, type 2 diabetes		Lean BMI, normal glucose tolerance
	Before	After	Before	After	
Insulin-stimulated glucose disposal (μmol/min per kg/FFM)	26·2 (±13·5)	38·5* (±13·1)	15·7 (±22·4)	42·2* (±8·2)	64·0 (±17·1)

Values are mean (±SEM). Data from Camastra et al.[11] FFM=fat-free mass. *p=0·002 after versus before Roux-en-Y gastric bypass.

Lancet Diabetes Endocrinol 2024; 12: 674–80

Diabetologia 2011; 54: 2093–102



Lancet Diabetes Endocrinol 2024; 12: 674–80

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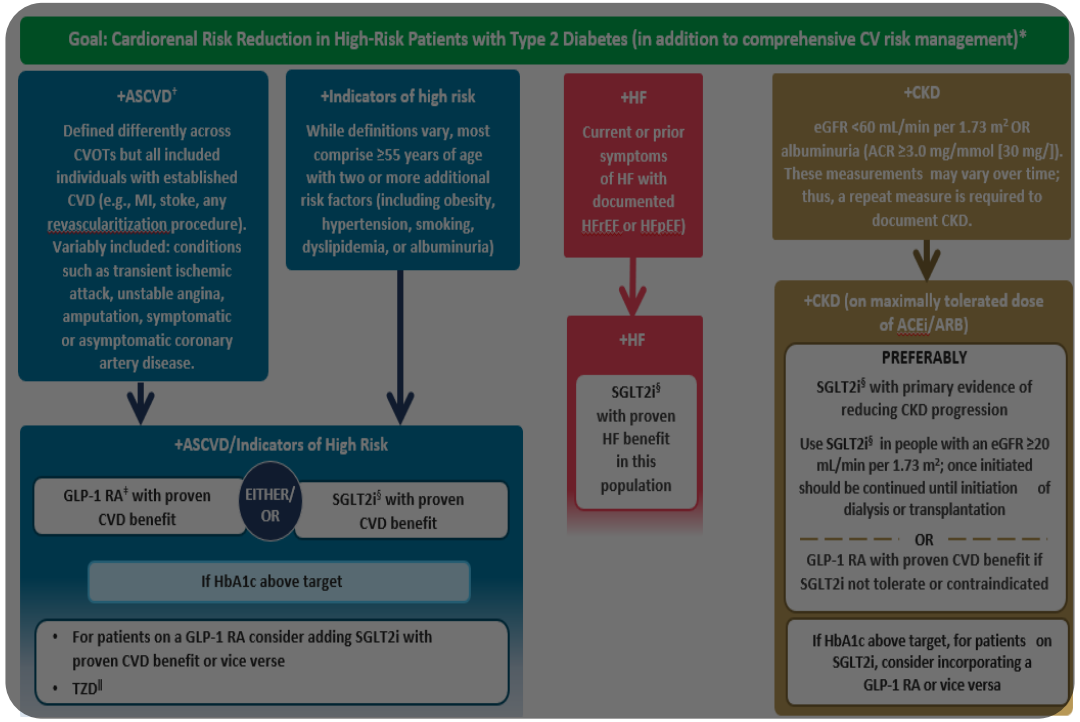
2024 ADA Standards of Care Pharmacologic Recommendation



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

Consider avoidance of hypoglycemia a priority 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

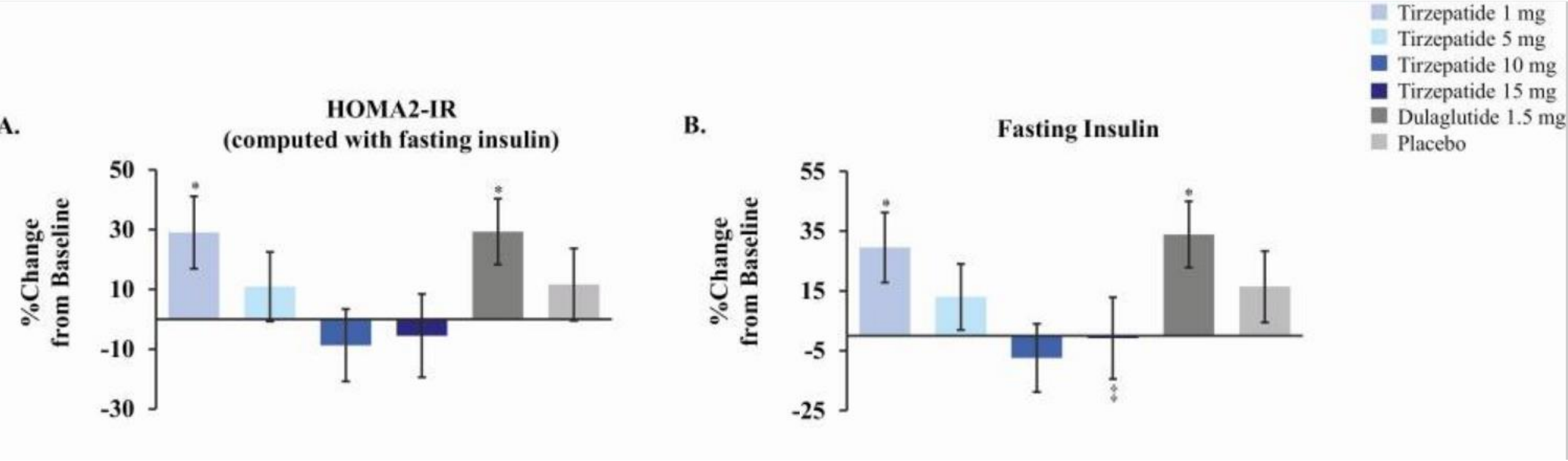
High:
Dulaglutide, liraglutide

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

Neutral:
DPP-4i, metformin

*In people with HF, CVD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT1i 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. ‡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. §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. ‖Low-dose TZD may be better tolerated and similarly effective. ACEi=angiotensin-converting enzyme inhibitor; ACR=albumin-to-creatinine ratio; ARB=angiotensin receptor blockers; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; eGFR=estimated glomerular filtration rate; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; hHF=hospitalization for heart failure; MACE=major adverse cardiovascular events; MI=myocardial infarction; SGLT2i=sodium-glucose cotransporter 2 inhibitor. 1. Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786.

Tirzepatide Improves Insulin Sensitivity in Type 2 Diabetes



J Clin Endocrinol Metab. 2020 Nov 24;106(2):388–396

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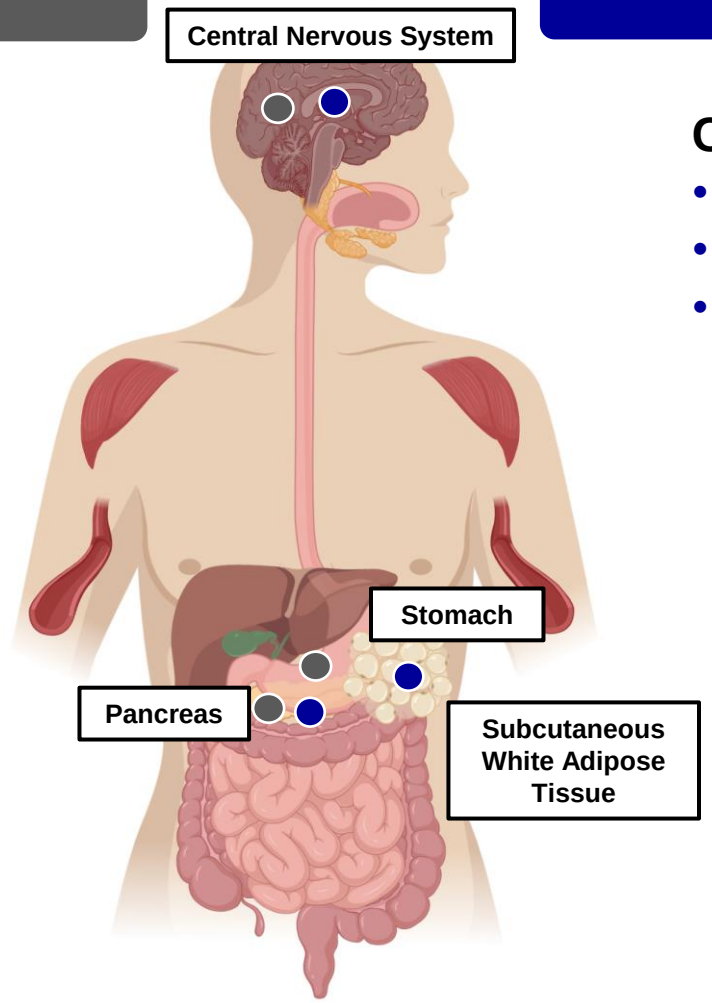
Proposed Actions of GIP Receptor Agonist and GLP-1 Receptor Agonist in Humans

GLP-1 Receptor Agonism

Central Nervous System
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying



- GLP-1 Receptor Agonism
- GIP Receptor Agonism

GIP Receptor Agonism

Central Nervous System
- ↓ Food intake
- ↓ Nausea
- ↓ Body weight

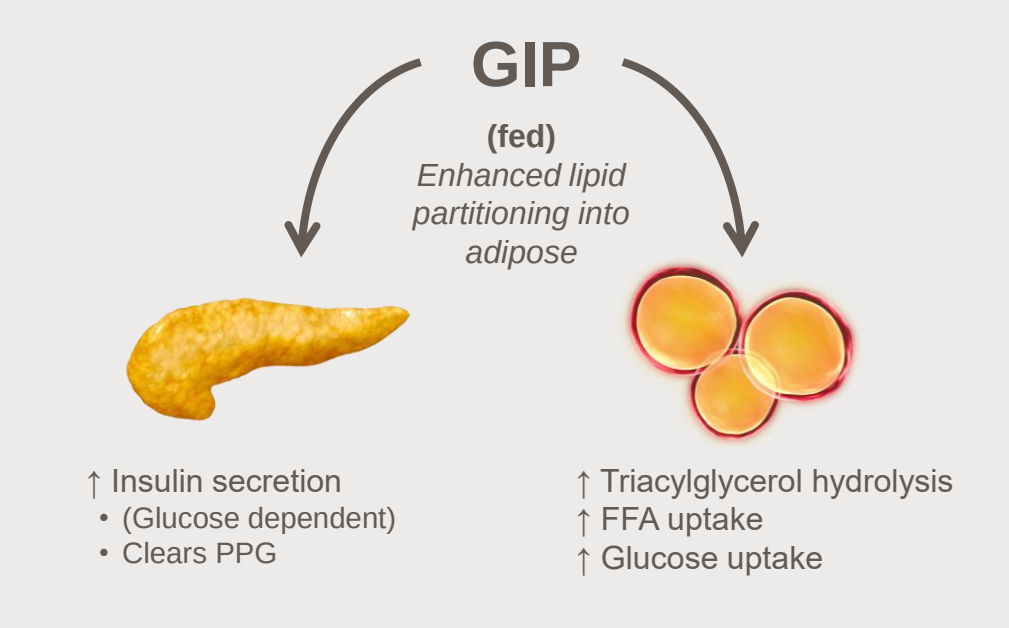
Pancreas
- ↑ Insulin
- ↑ Glucagon

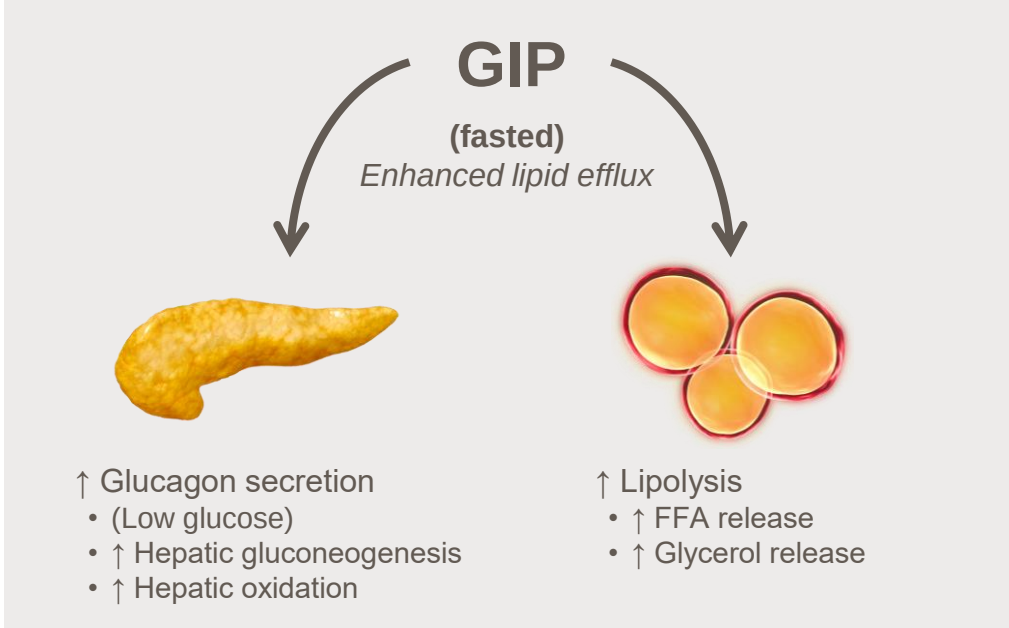
Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity

Disclaimer: Actions of GIP mentioned above are proposed and based on clinical and preclinical studies, and not all have been confirmed in humans.
Data presented in this figure come from human and animal studies.
GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.
Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421.

GIP Receptor Agonism for Regulation of Lipid Metabolism in Adipocyte[1-6]

Proposed Fed/Fasted Model of GIPR Agonism to Enhance Nutrient Partitioning





GIP regulation of plasma lipid and glucose under postprandial/hyperglycemic conditions

Native GIP infusions demonstrate **enhanced triglyceride clearance**.

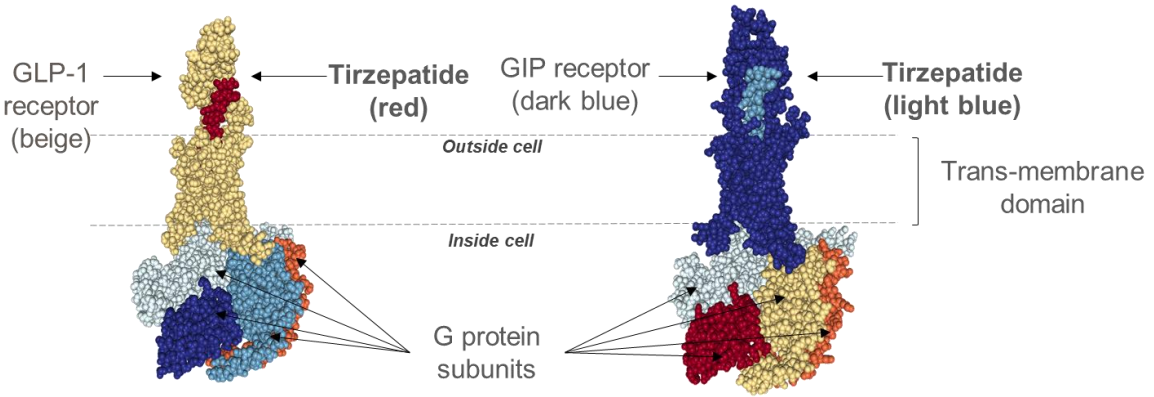
GIP regulation of plasma lipid and glucose under postabsorptive/fasted/hypoglycemic conditions

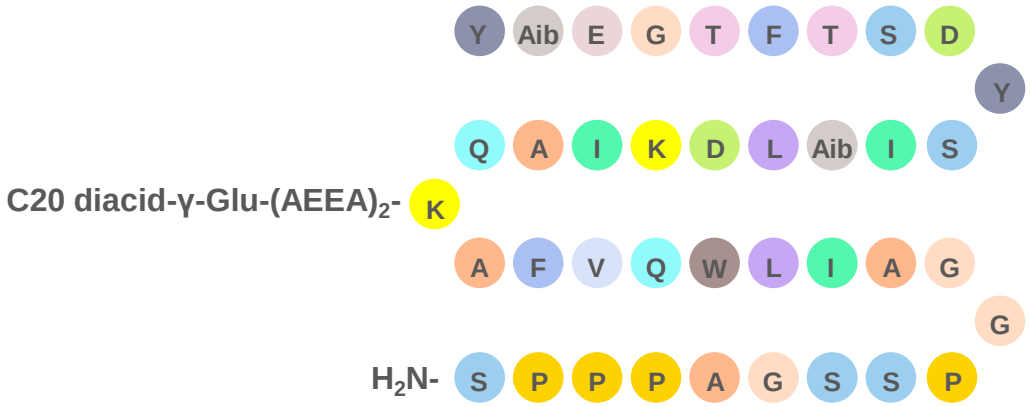
Native GIP infusions demonstrate elevated FFA and glycerol in hypoglycemic clamp recovery (insulin off), suggesting the potential to regulate **lipolysis**.

1. Asmar M, et al. *Diabetes*. 2017;66(9):2363-2371. 2. Asmar M, et al. *Am J Physiol Endocrinol Metab.* 2010;298(3):E614-621. 3. Data on File. Eli Lilly and Company. 2021. 4. Data on File. Eli Lilly and Company. 2021. 5. Kim SJ, et al. *J Biol Chem*. 2007;282(12):8557-8567. 6. Regmi, Ajit et al. *Cell Metab.* 2024 Jul 2;36(7):1534-1549.e7.

Tirzepatide: A Once-Weekly GIP/GLP-1 Receptor Agonist

- Tirzepatide is a long-acting GIP receptor and GLP-1 receptor agonist[1]
- It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life[1]
- Mean half-life of approximately 5 days (116.7 h), enabling once-weekly dosing[1]
- Its plasma concentrations in patients with renal and hepatic impairment do not differ from those in healthy people[2]

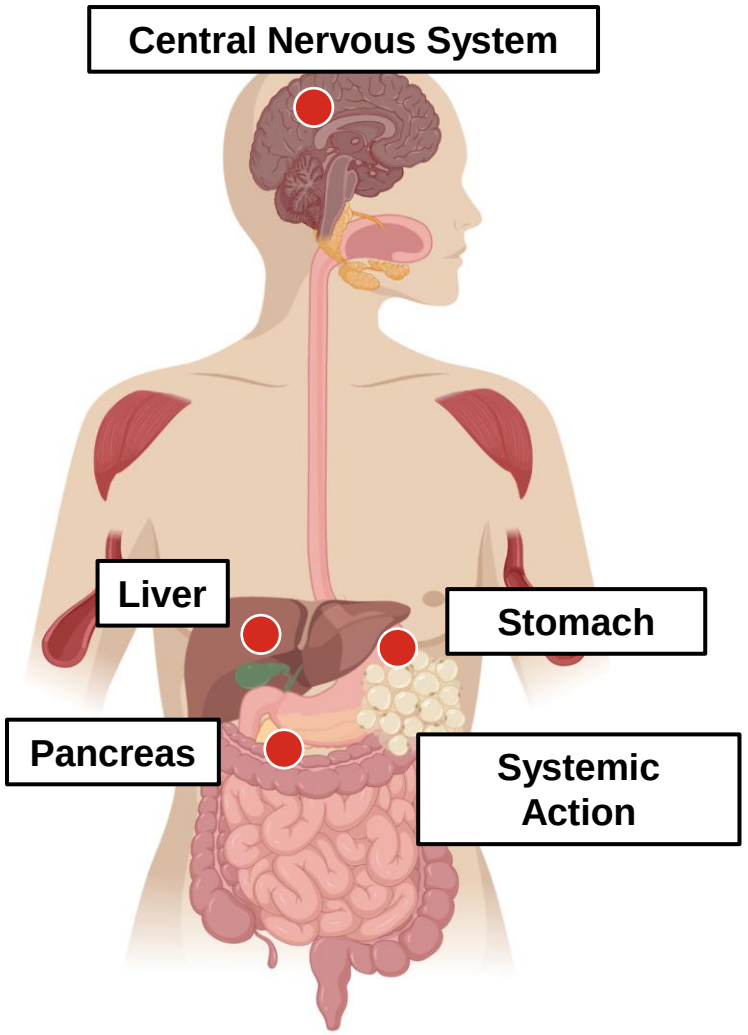




GIP=Glucose-Dependent Insulinotropic Polypeptide; GIPR=Glucose-Dependent Insulinotropic Polypeptide Receptor; GLP-1R=Glucagon-Like Peptide-1 Receptor.

1. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2. Urva S, et al. *Diabetes*. 2020;69(1):Abstract 971-P.

Mechanism of Action of Tirzepatide[1-3]



Central Nervous System
- ↓ Appetite[1]
- ↓ Food intake[1]

Liver
- ↓ Liver fat content[3]

Pancreas
- Improves β-cell glucose sensitivity[2]
- ↑ Insulin secretion[2]
- ↓ Glucagon secretion[2]

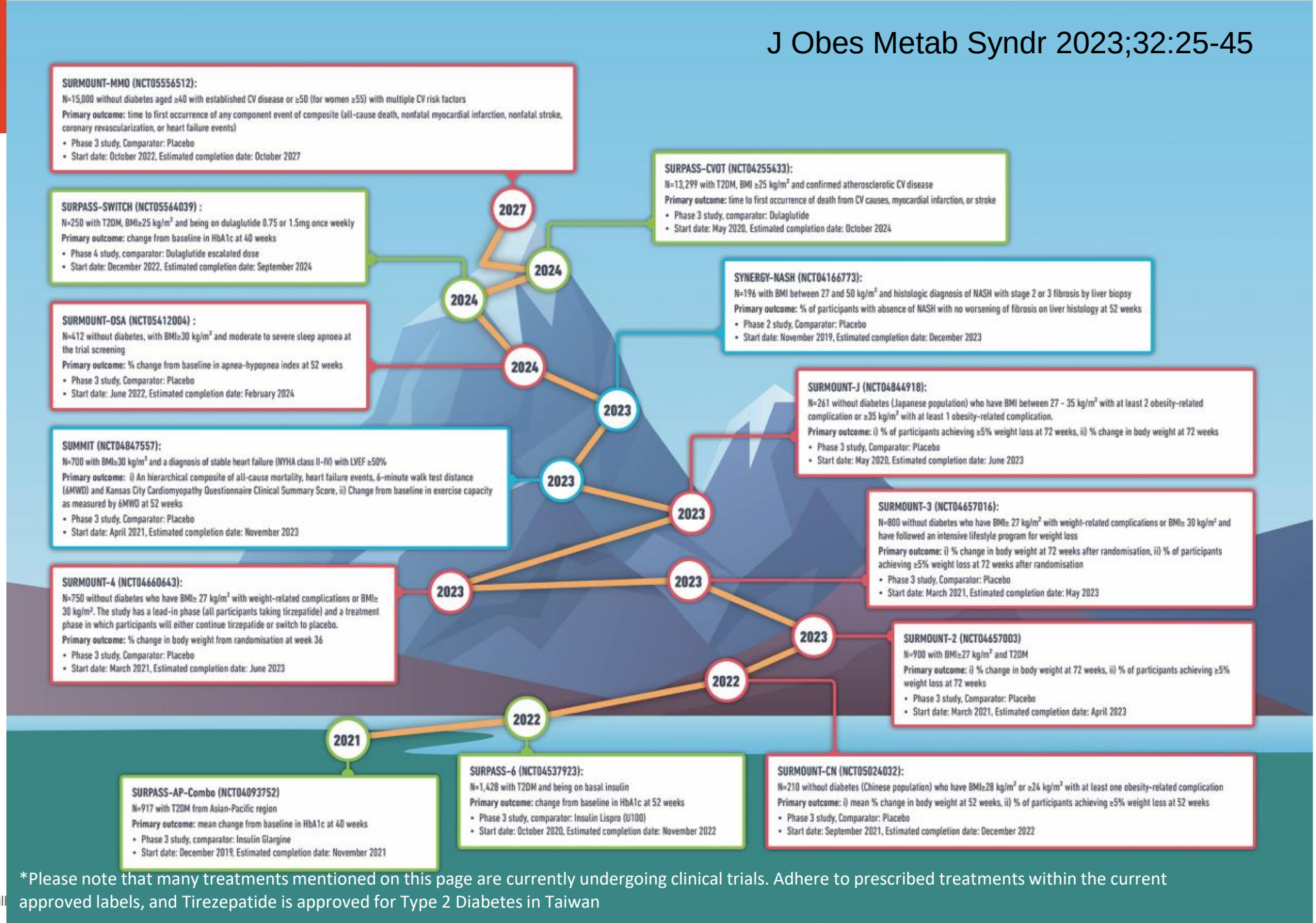
Stomach
- ↓ Gastric Emptying[4]

Systemic Action
- ↑ Insulin Sensitivity[2]

SC = subcutaneous.

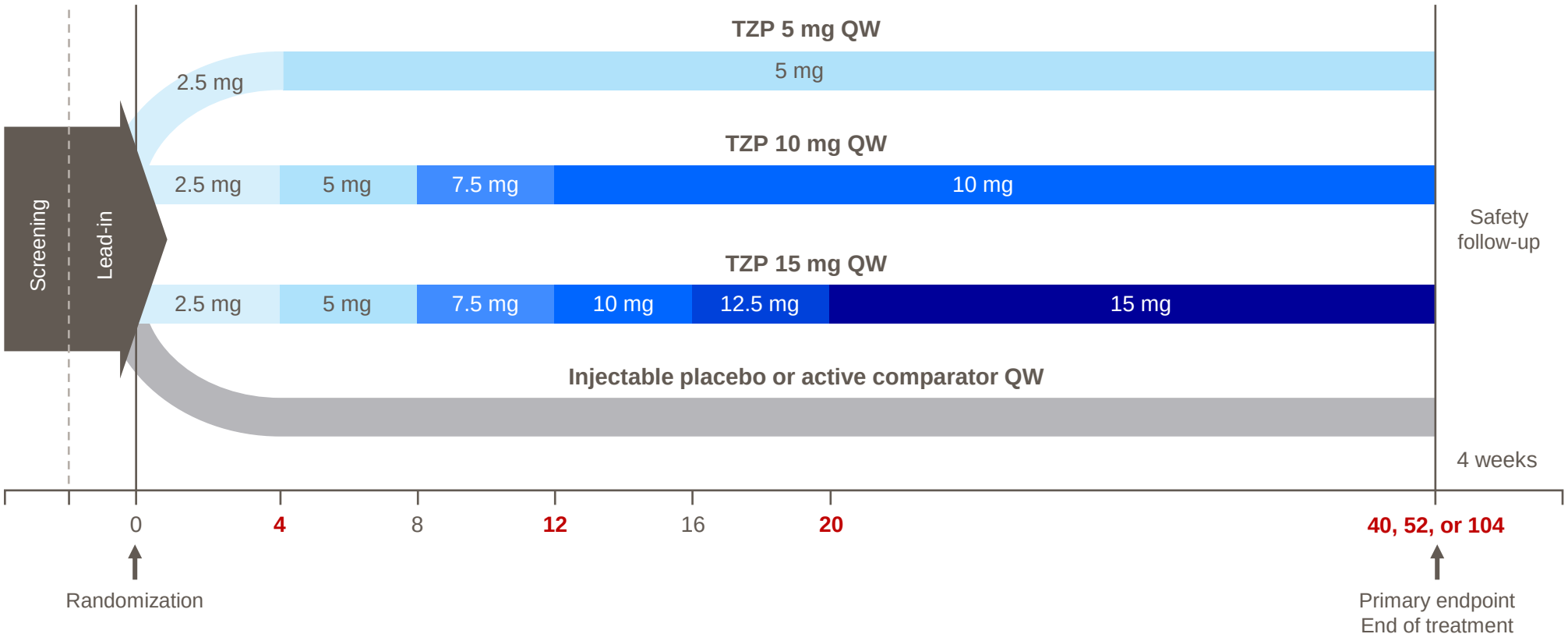
1. Heise T, et al. Oral presentation at: *ADA* 2022. Abstract 338-OR. 2. Heise T, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):418-429. 3. Gastaldelli A, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406. 4. Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421.

J Obes Metab Syndr 2023;32:25-45



*Please note that many treatments mentioned on this page are currently undergoing clinical trials. Adhere to prescribed treatments within the current approved labels, and Tirezepatide is approved for Type 2 Diabetes in Taiwan

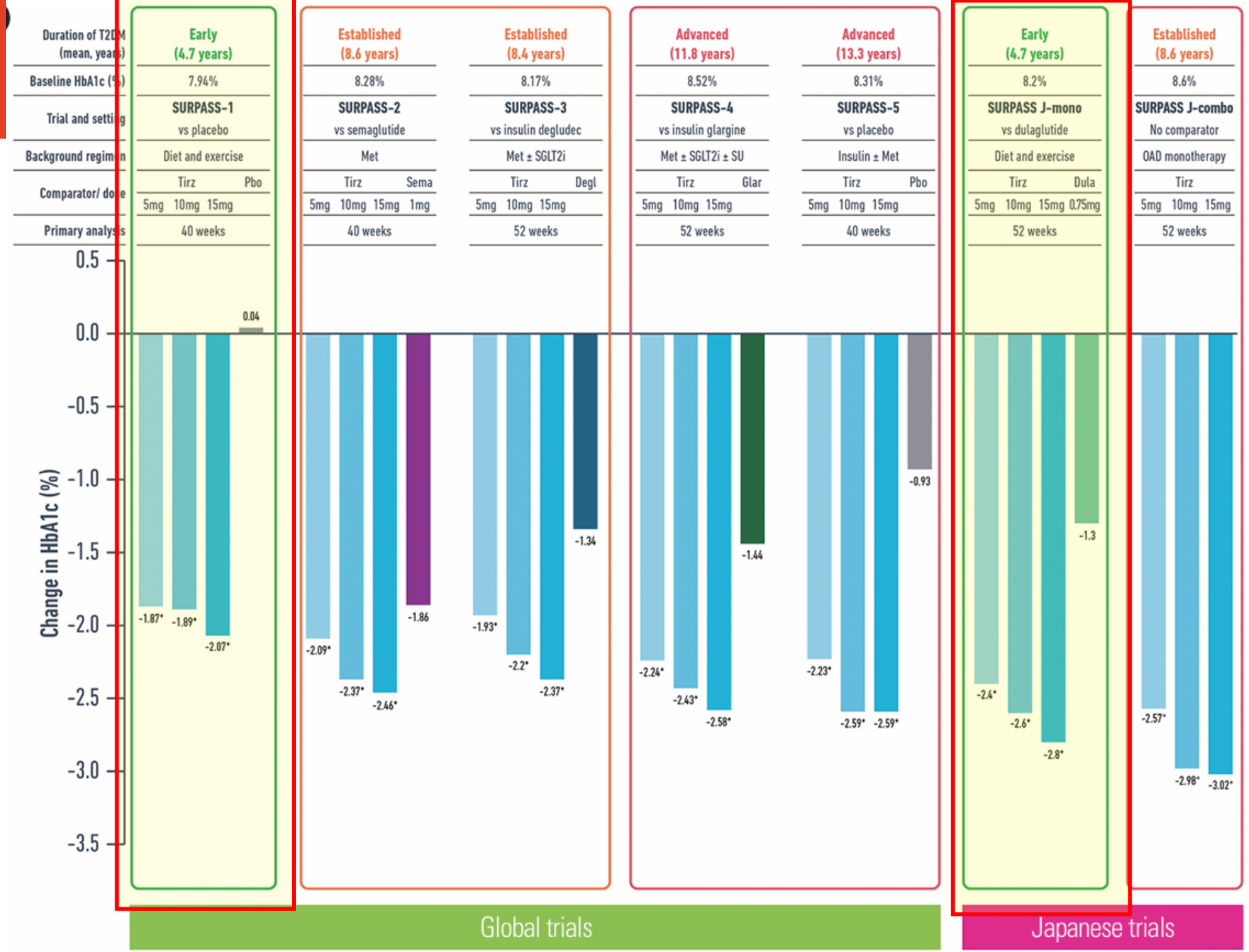
SURPASS General Study Design[1-6]



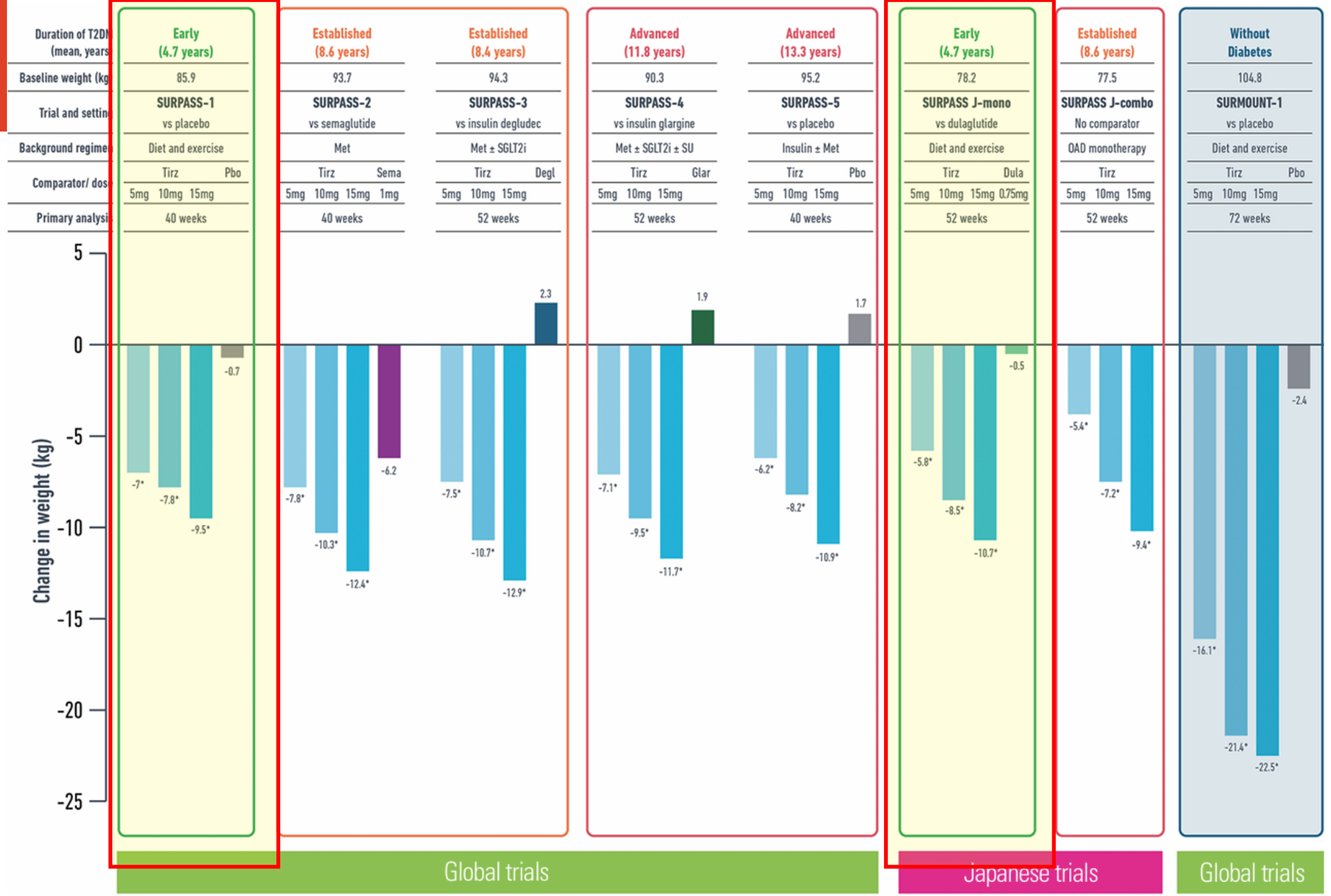
Primary Objective: Superiority and/or noninferiority of TZP 5 mg and/or 10 mg and/or 15 mg vs. placebo or active comparator in mean change in HbA1c from baseline at 40 or 52 weeks.

HbA1c = glycated hemoglobin; QW = once weekly; TZP = tirzepatide.

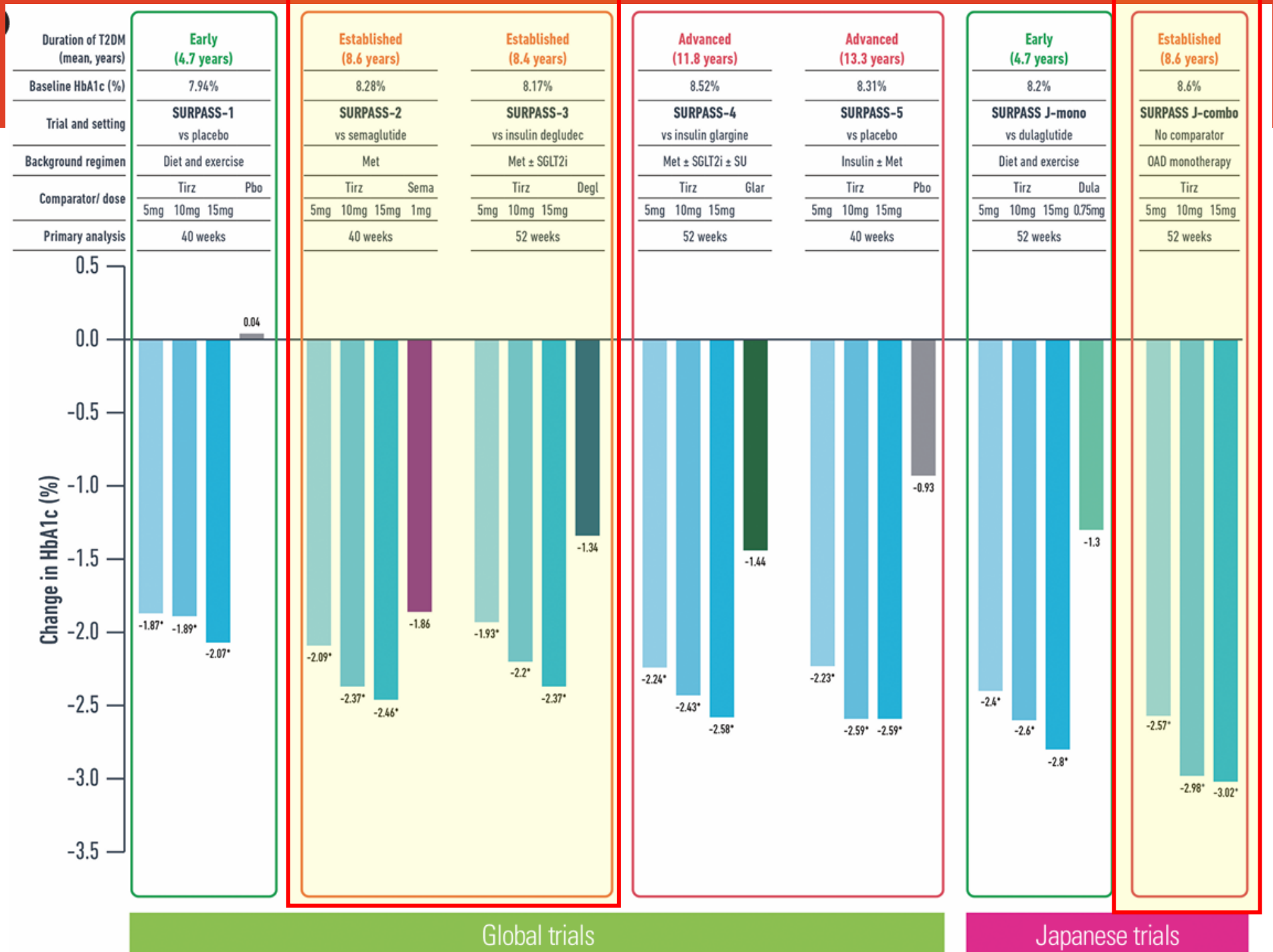
1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. Rosenstock J, et al. Poster presented at: ADA 2023. Poster 750-P.



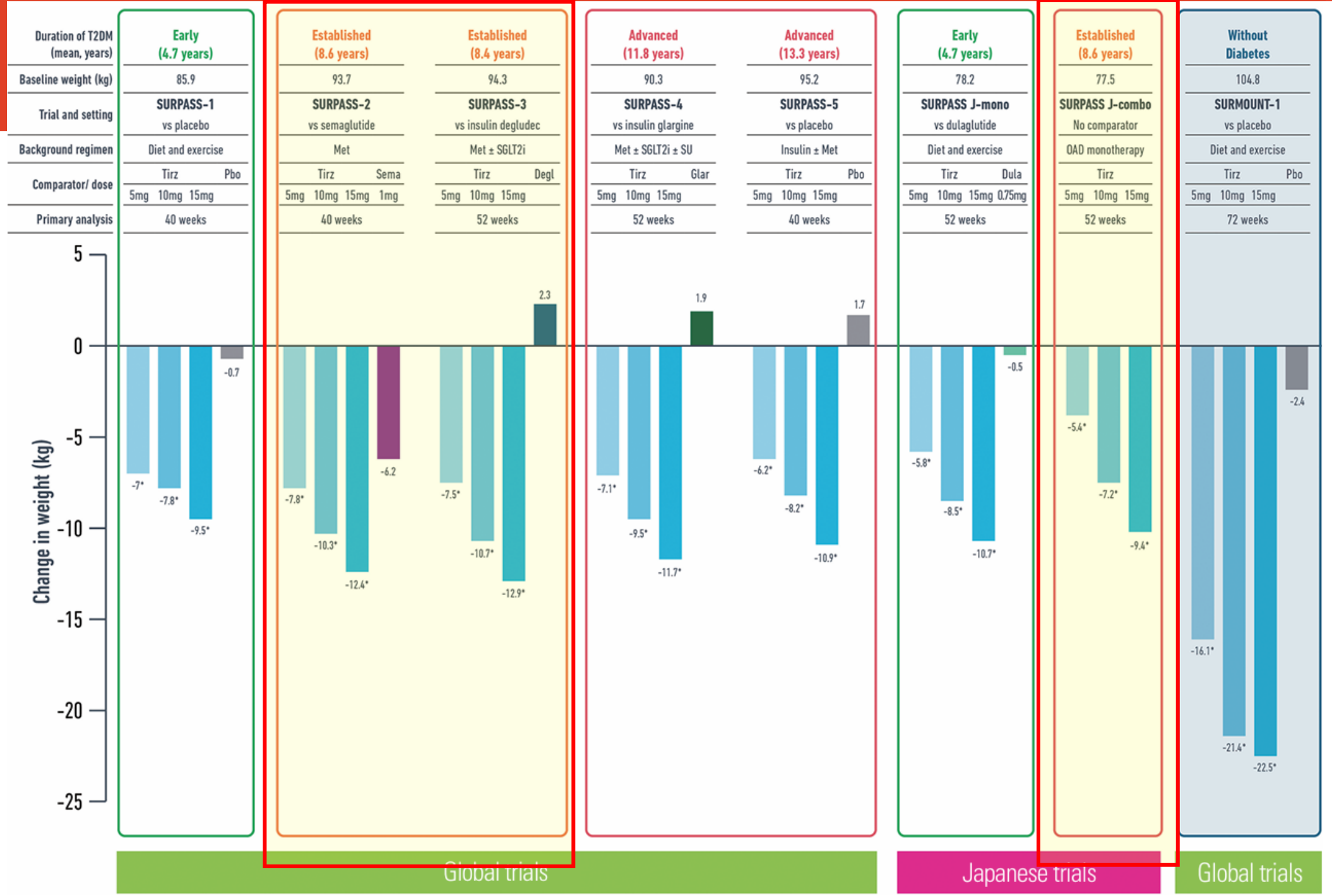
J Obes Metab Syndr 2023;32:25-45



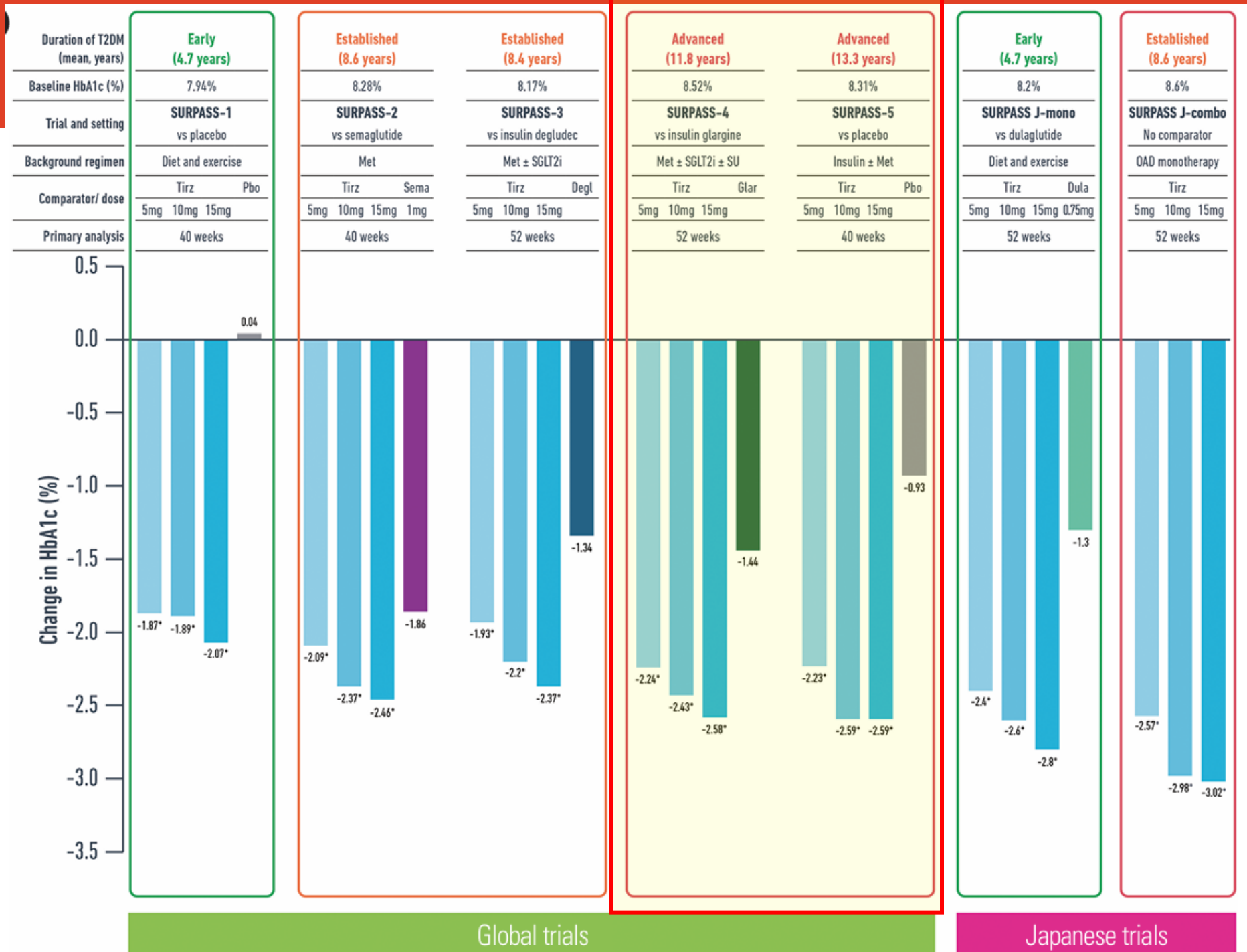
J Obes Metab Syndr 2023;32:25-45



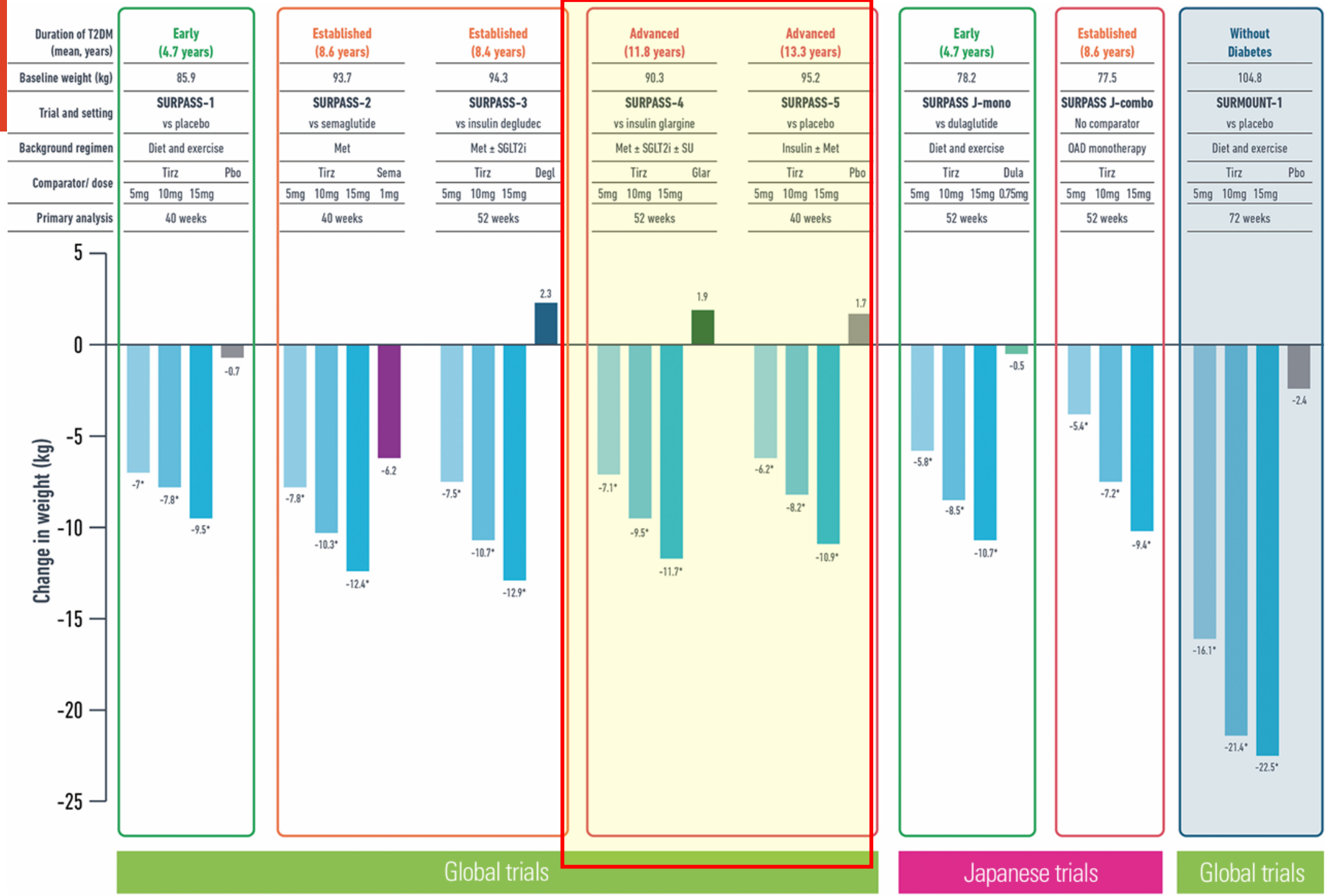
J Obes Metab Syndr 2023;32:25-45



J Obes Metab Syndr 2023;32:25-45



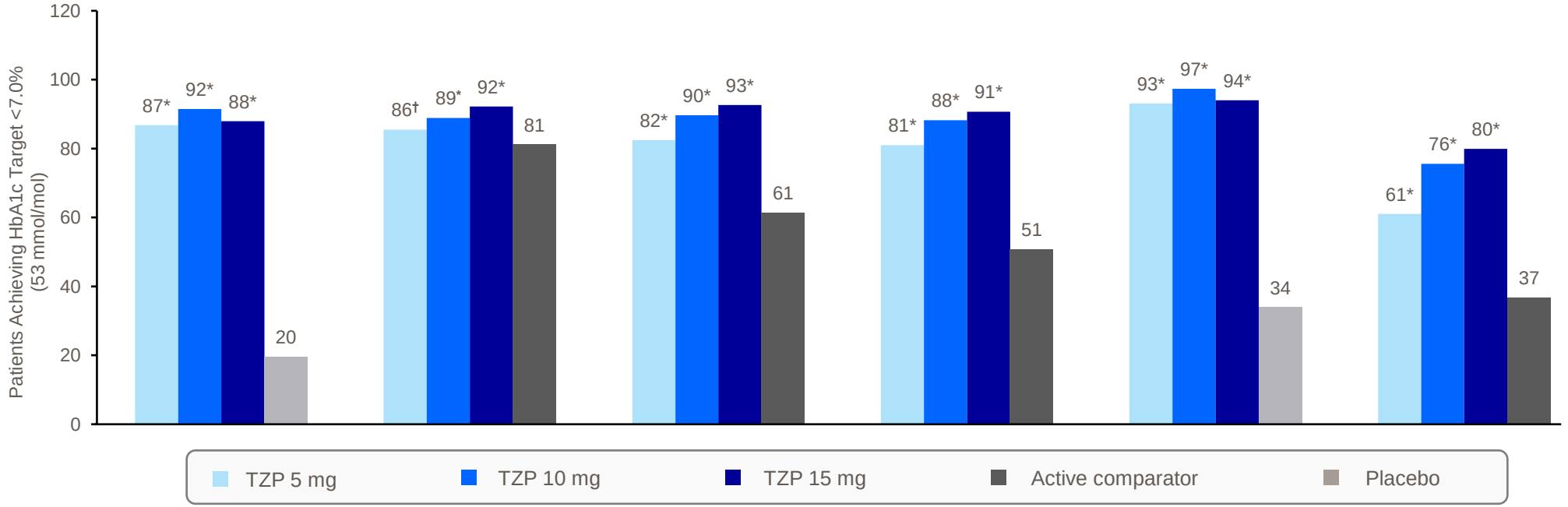
J Obes Metab Syndr 2023;32:25-45



J Obes Metab Syndr 2023;32:25-45

Proportion of Patients Achieving HbA1c <7.0%

Efficacy Estimand



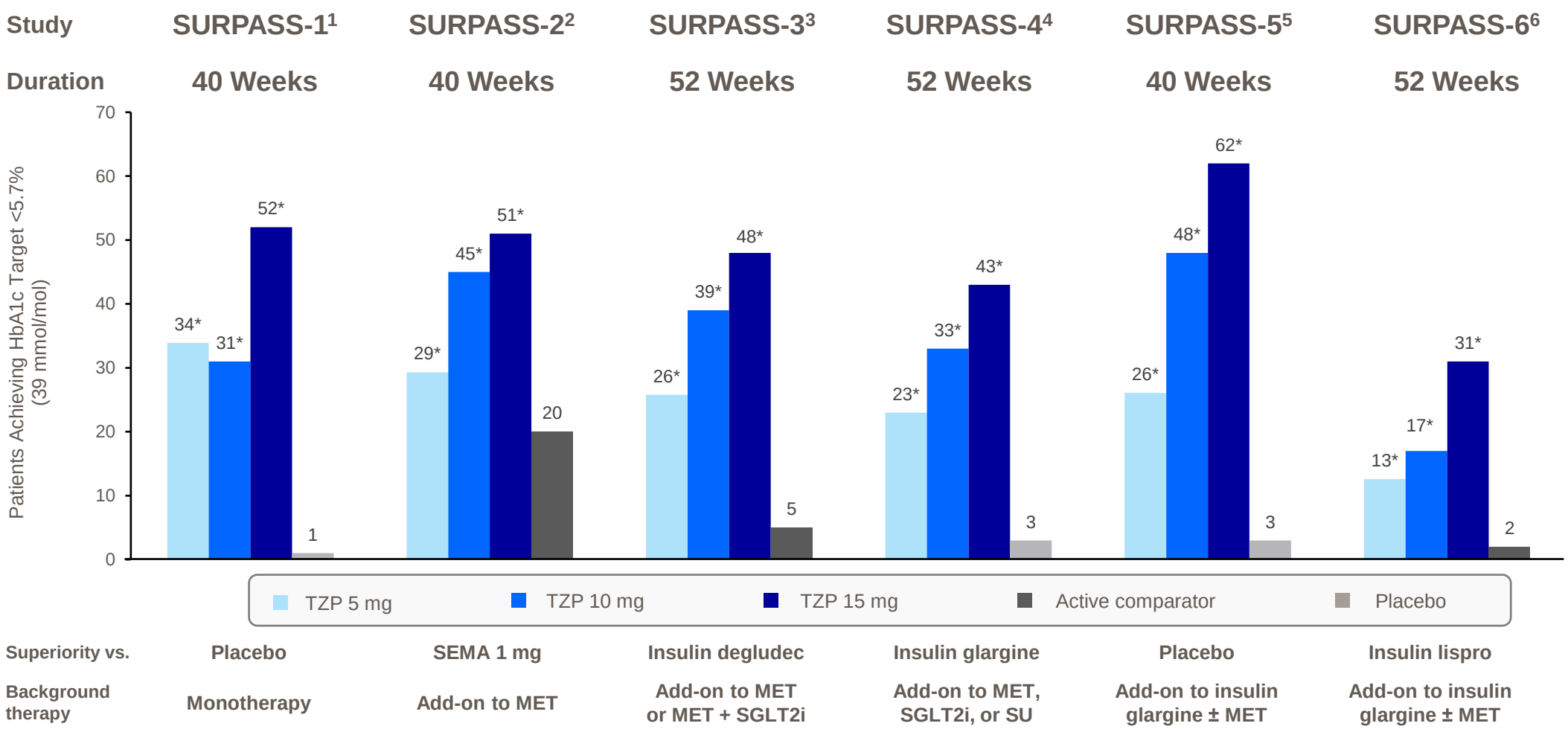
Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]	SURPASS-6[6]
Duration	40 Weeks	40 Weeks	52 Weeks	52 Weeks	40 Weeks	52 Weeks
Superiority vs.	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Insulin lispro
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET	Add-on to insulin glargine ± MET

*p<0.001, †p<0.05 vs. placebo or active comparator.
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
DPP4i= Dipeptidyl Peptidase-4 Inhibitor; HbA1c = glycated hemoglobin; MET = metformin; mITT = modified intent-to-treat; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. Rosenstock J, et al. Poster from: *ADA 2023*. Poster 750-P.

Proportion of Patients Achieving HbA1c <5.7%

Efficacy Estimand



*p<0.001 vs. placebo or active comparator.
Data are estimated mean; mITT population (efficacy analysis set). Logistic regression.
HbA1c = glycated hemoglobin; MET = metformin; mITT = modified intent-to-treat; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulphonylurea; TZP = tirzepatide.

1. Rosenstock J, et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B, et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S, et al. *Lancet*. 2021;398(10313):1811-1824. 5. Dahl D, et al. *JAMA*. 2022;327(6):534-545. 6. Rosenstock J, et al. Poster presented at: *ADA 2023*. Poster 750-P.

Overview of Adverse Events

SURPASS-2_v.s. semaglutide 1 mg

Parameters	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Participants with ≥1 TEAE	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)	1246 (66.3)
Participants with ≥1 SAEs	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)	98 (5.2)
Deaths[a]	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)	13 (0.7)
AEs leading to discontinuation of tirzepatide or semaglutide	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)	127 (6.8)
AEs occurring in ≥5% of patients in any treatment group					
Nausea	82 (17.4)	90 (19.2)	104 (22.1)	84 (17.9)	360 (19.2)
Diarrhoea	62 (13.2)	77 (16.4)	65 (13.8)	54 (11.5)	258 (13.7)
Vomiting	27 (5.7)	40 (8.5)	46 (9.8)	39 (8.3)	152 (8.1)
Dyspepsia	34 (7.2)	29 (6.2)	43 (9.1)	31 (6.6)	137 (7.3)
Decreased appetite	35 (7.4)	34 (7.2)	42 (8.9)	25 (5.3)	136 (7.2)
Constipation	32 (6.8)	21 (4.5)	21 (4.5)	27 (5.8)	101 (5.4)
Abdominal pain	14 (3.0)	21 (4.5)	24 (5.1)	24 (5.1)	83 (4.4)
All gastrointestinal AEs	188 (40.0)	216 (46.1)	211 (44.9)	193 (41.2)	808 (43.0)

[a]Deaths are also included as SAEs and discontinuations due to AE.

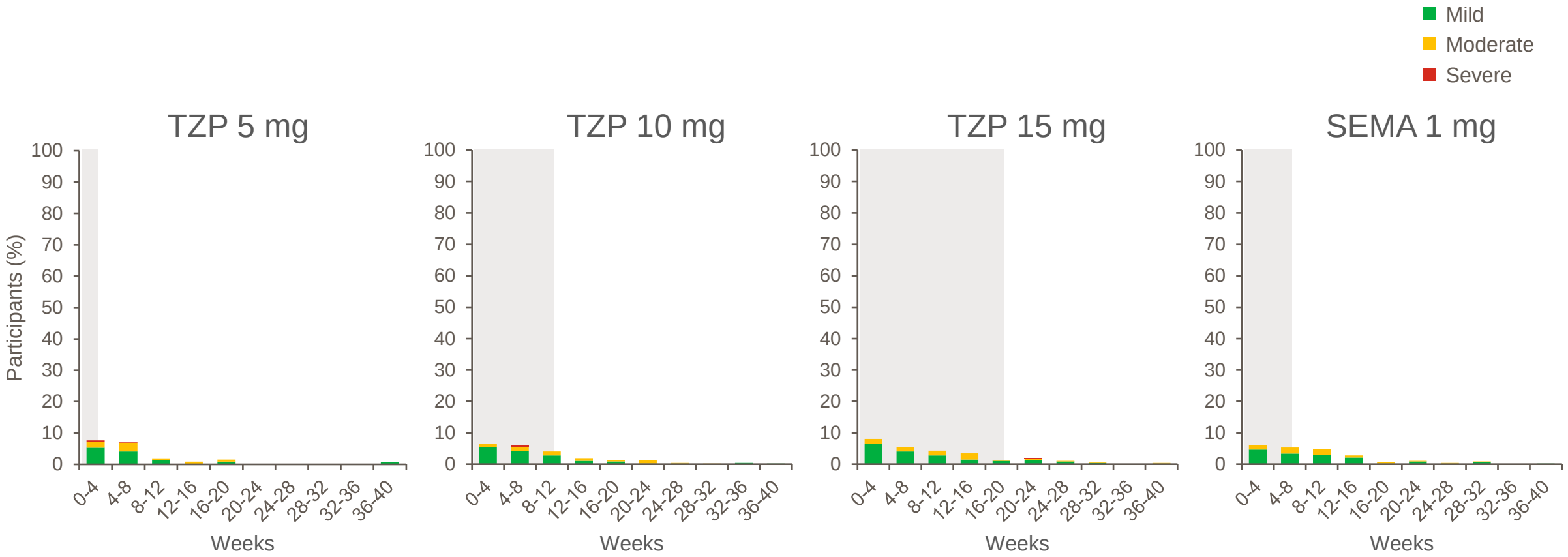
Note: Data are n (%); mITT population (safety analysis set). Patients may be counted in more than 1 category.

AE=Adverse Event; SAEs=Serious Adverse Events; TEAE=Treatment-Emergent Adverse Event.

Frias JP, et al. *N Engl J Med*. 2021;385(6):503-515.

Incidence of Nausea Over Time Through 40 Weeks

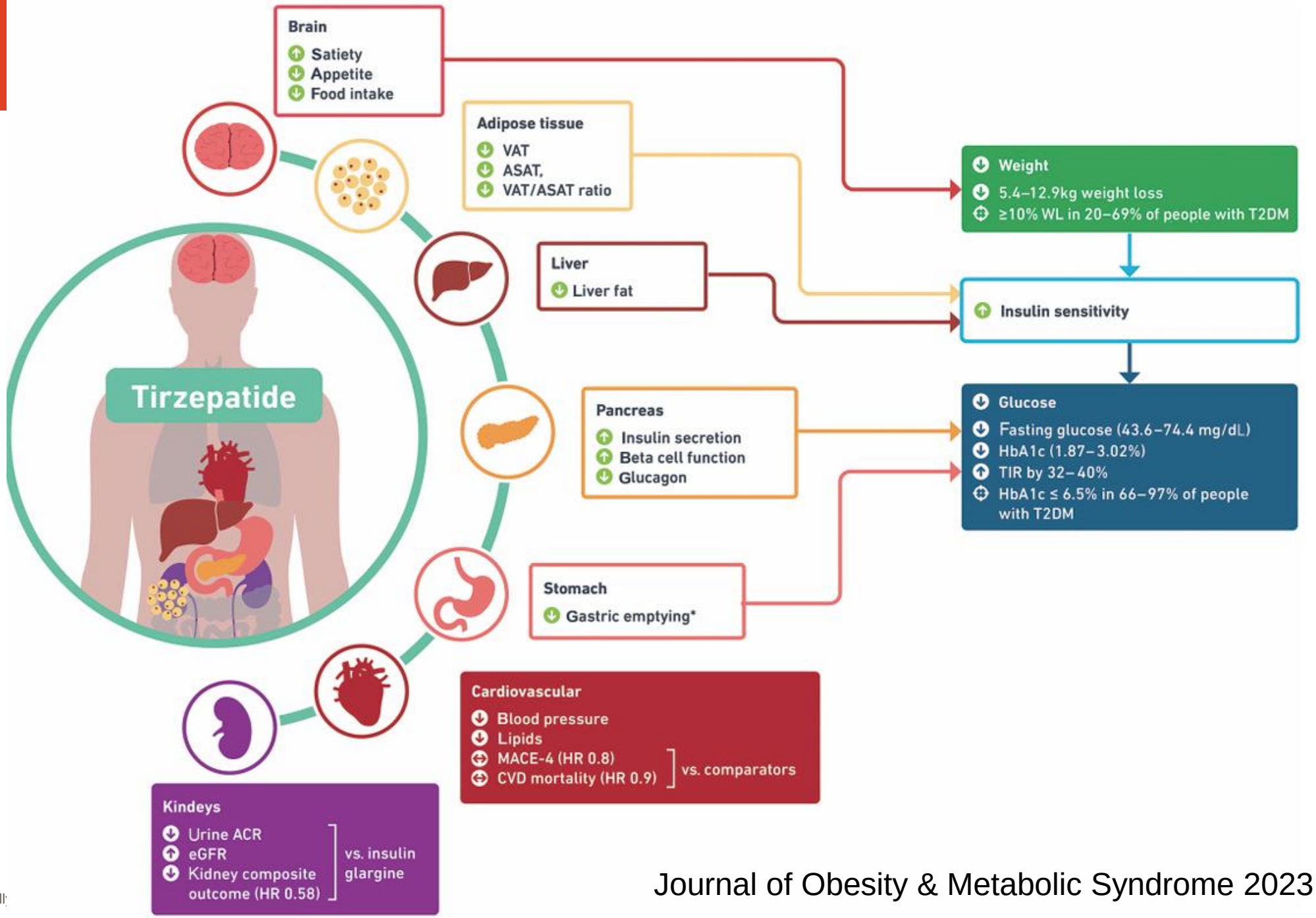
SURPASS-2_v.s. semaglutide 1 mg



Most cases of nausea were mild to moderate, transient, and occurred during the dose-escalation period in all groups

Data are percentage of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments. Incidence refers to the proportion of participants who have a new event during a time interval. mITT = modified intent to treat; SEMA = semaglutide; TZP = tirzepatide.

Frias JP, et al. *N Eng J Med*. 2021;385(6):503-515.



Journal of Obesity & Metabolic Syndrome 2023;32:25-45

Summary

- **Tirzepatide is a single molecular GIP/GLP-1 receptor agonist that targets both GLP-1 and GIP receptors**
- **Tirzepatide could improve beta-cell and whole-body insulin sensitivity, and also decrease liver fat content**
- **In the SURPASS clinical trial program, treatment with tirzepatide 5, 10, and 15 mg in people with T2D:**
  - A robust and clinically relevant lowering of HbA1c and weight greater than placebo, semaglutide 1 mg, and basal insulin
- **The most common AEs with tirzepatide treatment were gastrointestinal in nature, mostly mild or moderate in severity and occurred early (during dose-escalation)**

簡易仿單

猛健樂® 筆
MOUNJARO® KwikPen (tirzepatide)

適應症:
作為飲食及運動療法之外的輔助治療，用於改善第二型糖尿病成人病人之血糖控制。
說明: MOUNJARO 可做為單一療法或與其他糖尿病治療藥物合併使用。

用法用量:

- MOUNJARO 建議起始劑量為一週一次 2.5 mg 皮下注射。劑量 2.5 mg 是治療起始劑量，不適用於血糖控制。4 週後，將劑量增加至每週一次 5 mg 皮下注射。若需更佳的血糖控制，可在使用當前劑量至少 4 週後，應以 2.5 mg 為單位逐次增加劑量。MOUNJARO 的最大劑量為每週一次 15 mg 皮下注射。
- MOUNJARO 每週給藥一次，可在一天當中的任何時間，不須考慮進食與否。以皮下注射方式在腹部、大腿或上臂注射 MOUNJARO。

禁忌:
MOUNJARO 禁用於患有下列疾病的病人：

- 個人或是家族有甲狀腺髓質癌 (MTC) 病史的病人或第二型多發性內分泌腫瘤綜合症 (MEN 2) 的病人。
- 已知對 tirzepatide 或 MOUNJARO 的任何賦形劑嚴重過敏反應。

警語及注意事項:
應注意甲狀腺髓質癌、胰臟炎、併用促胰島素分泌劑或胰島素而發生的低血糖、過敏反應、急性腎損傷、嚴重胃腸疾病、有糖尿病視網膜病變史的病人之糖尿病視網膜病變併發症、急性膽囊疾病的風險。絕不要在病人間共用MOUNJARO KwikPen。

不良反應:
發生率 ≥ 5% 的不良反應包括噁心、腹瀉、食慾不振、嘔吐、便祕、消化不良和腹痛。

詳細資料、不良反應、警語與注意事項等請參照猛健樂®筆藥品說明書。

猛健樂®筆	2.5 mg/0.6 mL	衛部藥輸字第 028800 號
猛健樂®筆	5 mg/0.6 mL	衛部藥輸字第 028801 號
猛健樂®筆	7.5 mg/0.6 mL	衛部藥輸字第 028802 號
猛健樂®筆	10 mg/0.6 mL	衛部藥輸字第 028803 號
猛健樂®筆	12.5 mg/0.6 mL	衛部藥輸字第 028804 號
猛健樂®筆	15 mg/0.6 mL	衛部藥輸字第 028805 號

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Thank you