Type 2 Diabetes:

Established Principles and Evolving Pharmacotherapy

St. Vincent's Health System
August 30, 2022

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DISCLOSURES

- Volunteer consultant on advisory boards for Jazz Pharmaceuticals, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Pfizer without any financial compensation

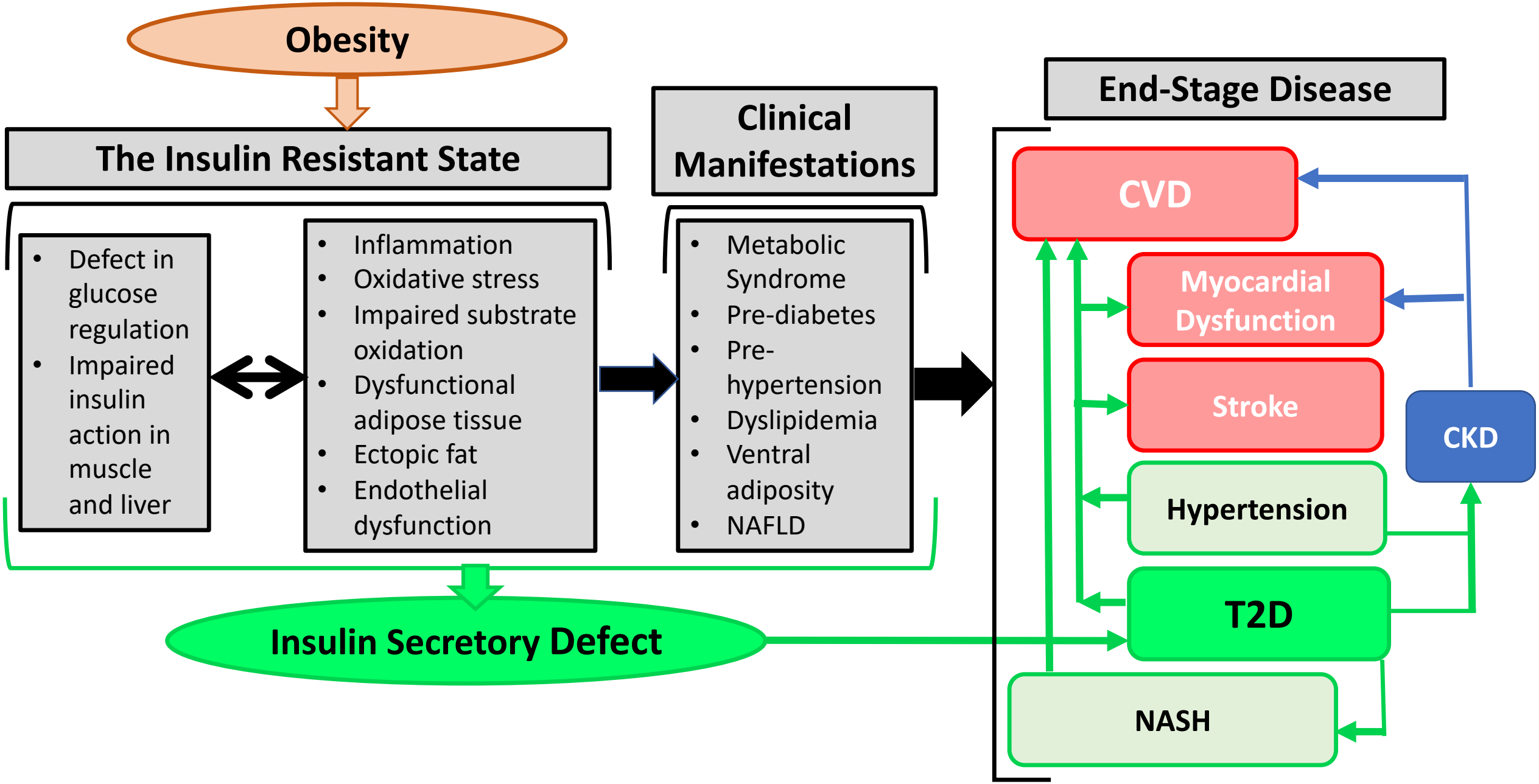
- Consultant on advisory boards for Fractyl Health, Alnylam Pharmaceuticals, Novo Nordisk, and Boehringer-Ingelheim where financial compensation was accepted.

- Site principal investigator for multi-centered clinical trials sponsored by the university and funded by Eli Lilly, Novo Nordisk, Epitomee, and Pfizer.

Outline

1. Natural history of cardiometabolic disease and treatment implications for T2D
2. Guiding principles of diabetes pharmacotherapy
3. Diabetes medications and guidelines, the evolution of pharmacotherapy, with emphasis on GLP-1 agonists and SGLT2 inhibitors
4. Weight loss therapy for treatment and prevention of T2D, the beginning of a transformation in care.

The Spectrum of Cardiometabolic Disease

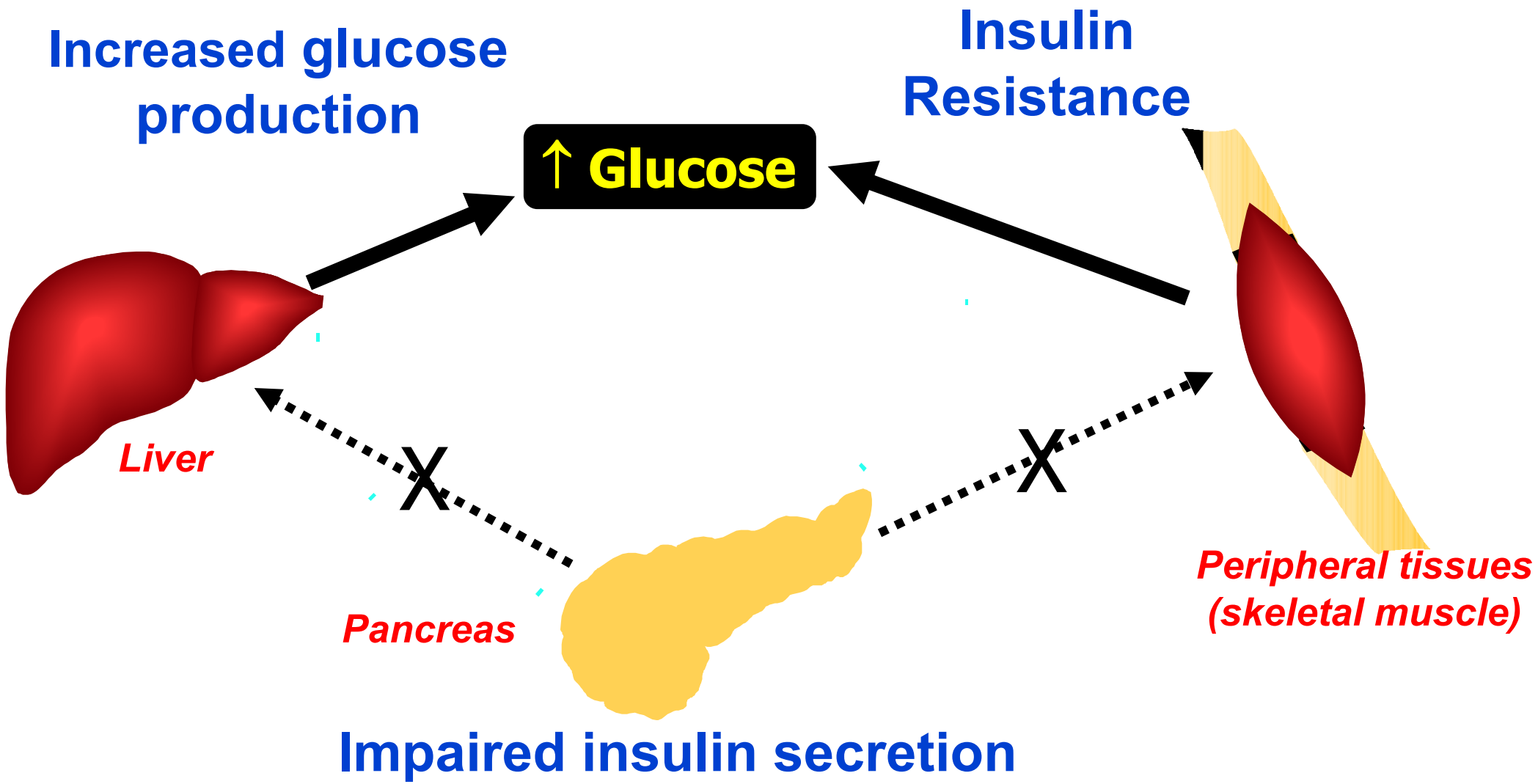


Three Points Based on Natural History of Cardiometabolic Disease

1. T2D is an end stage manifestation of cardiometabolic disease. Need to prevent disease progression in those patients with clinical signs of insulin resistance.
2. In patients with overweight of obesity, weight loss therapy is a powerful approach for preventing and treating T2D
3. The care of patients with T2D must be comprehensive and address CVD, myocardial dysfunction & CHF, NASH, CKD, as well as diabetes

Causes of Hyperglycemia in Type 2 Diabetes

"the classic view"



Defects Causing T2DM

Increased Lipolysis

Impaired Insulin Secretion

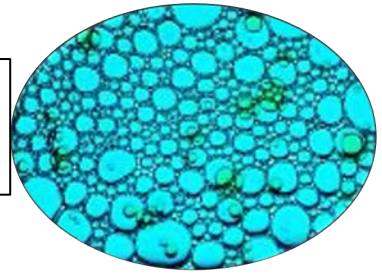
BETA CELL

FAT

KIDNEY

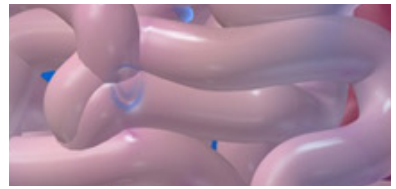
Increased Glucose Reabsorption

Increased Glucagon Secretion



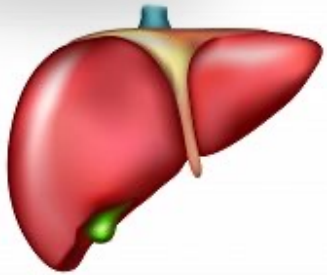
ALPHA CELL

INTESTINE



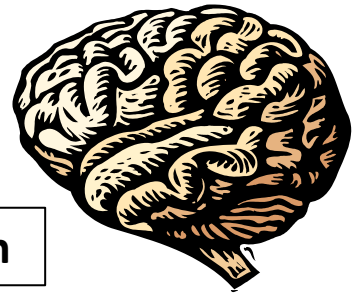
- Decreased Incretin Effect
- Glucose Influx

LIVER



Increased Hepatic Glucose Production

BRAIN

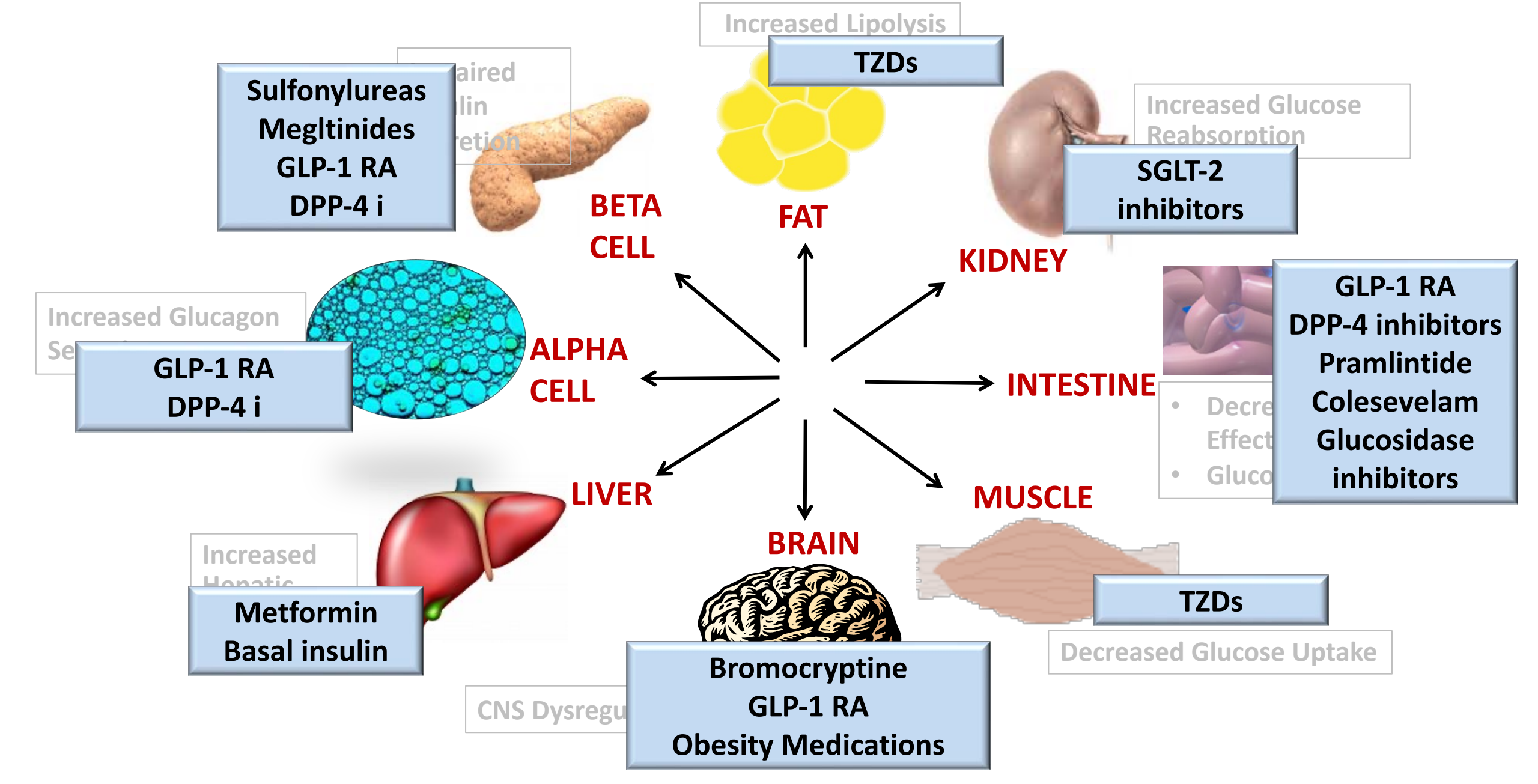


CNS Dysregulation

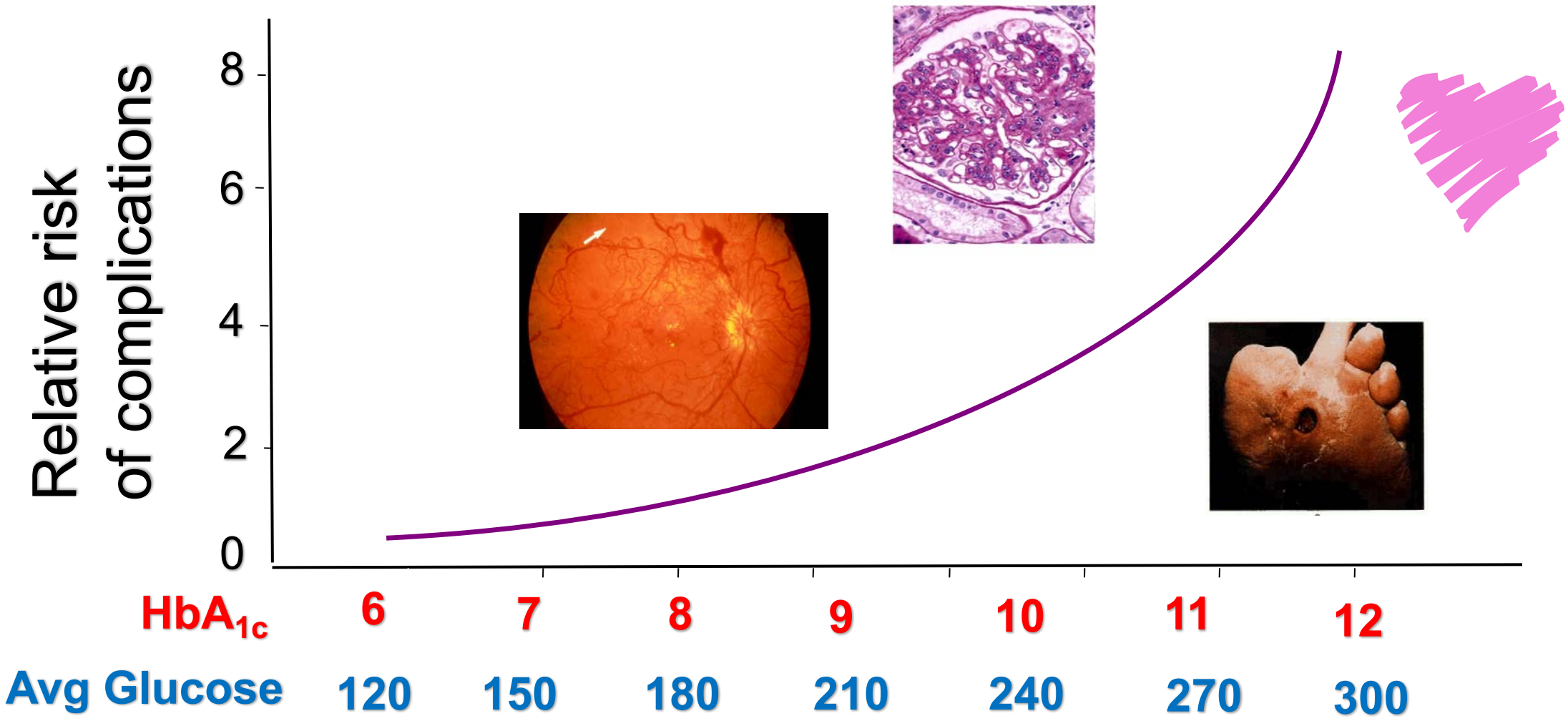
MUSCLE

Decreased Glucose Uptake

Drugs Target Defects



Complications Risk in Diabetes



Adapted from: Skyler JS. *Endocrinol Metab Clin North Am*. 1996;25(2):243-254.
DCCT Study Group. *N Engl J Med* . 1993;329:977-986; UKPDS 35; Stratton IM. *BMJ.* 2000;321:405-412.

Glycemic Control Targets in Diabetes[1]

Measurement		Normal	ADA Goal	AACE Goal
Plasma glucose				
Preprandial	**mmol/L**	**<5.6**	**4.4-7.2**	**<6.1**
	mg/dl	**<100**	**80-130**	**<110**
Postprandial	**mmol/L**	**<7.8**	**< 10.0***	**<7.8**
	mg/dl	**<140**	**<180***	**<140**
HbA_{1c} (%)		**<6**	**<7**	**<6.5**

American Diabetes Association - *Diabetes Care* 2020;43(Suppl 1):S66-S76
AACE Endocrine Practice 2020;26(1):107-139

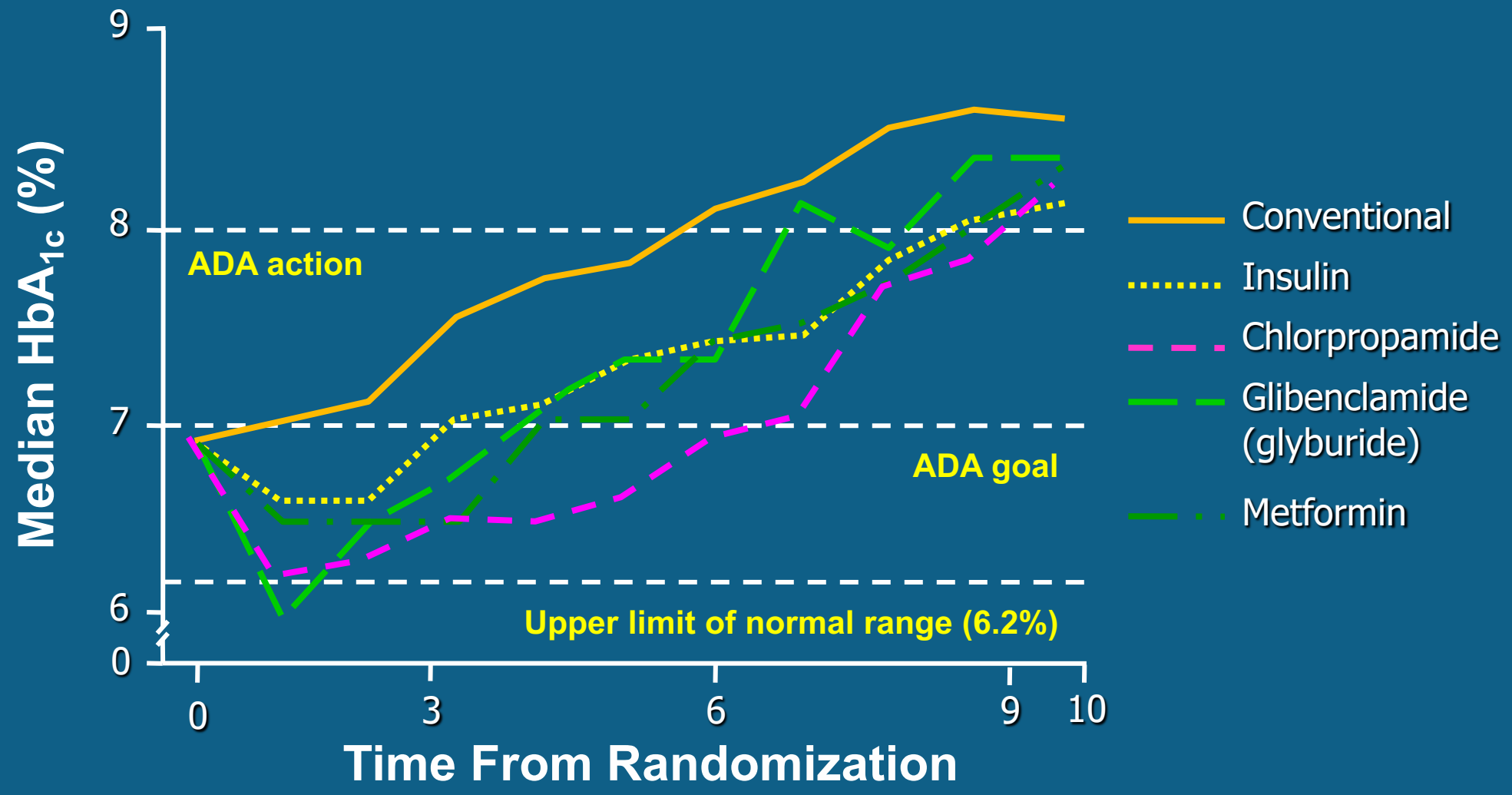
[1] Goals should be individualized * Peak postpandial

Principle 1

- Diabetes is a progressive disease
- Need medications with long-term efficacy

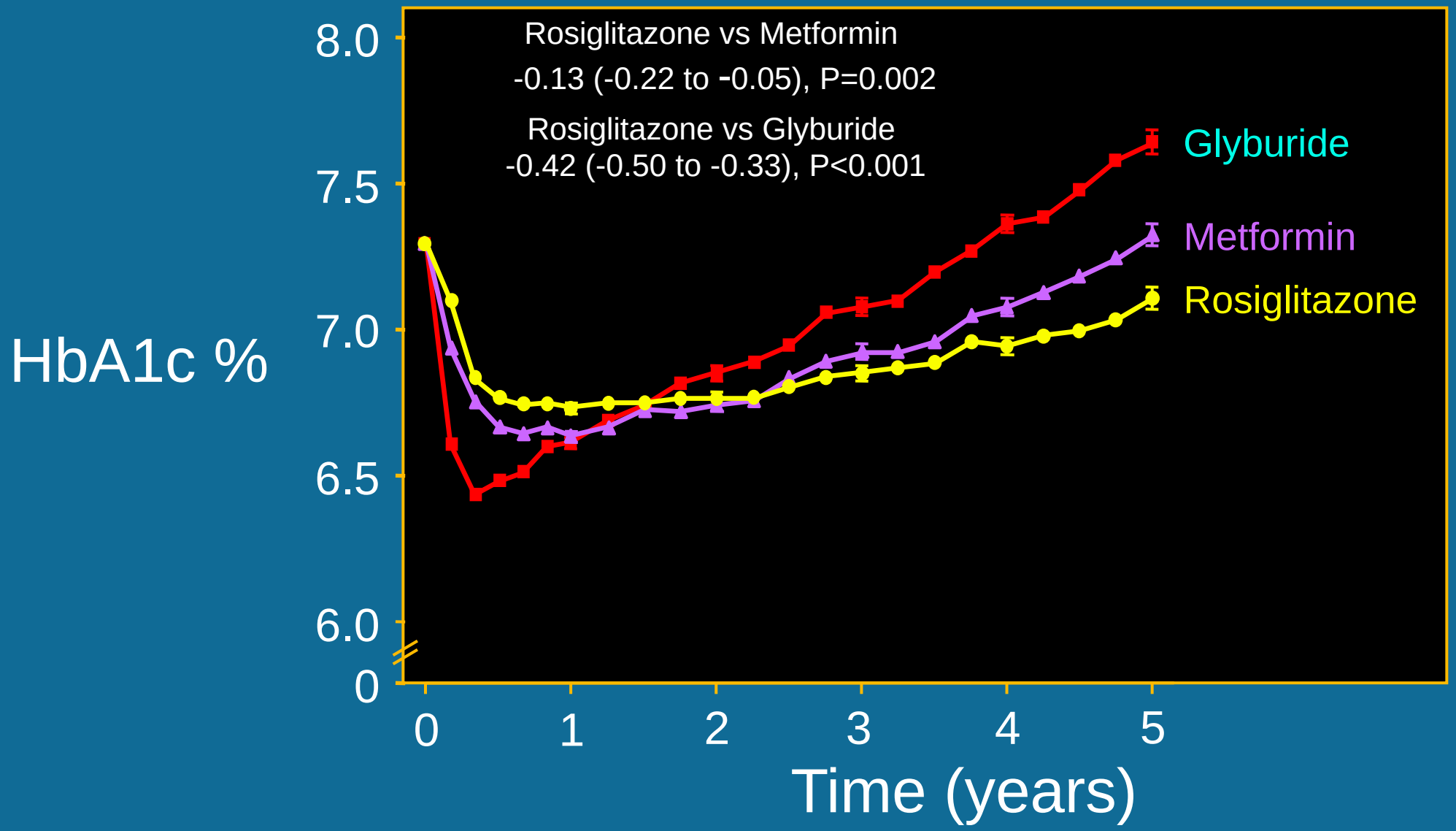
Intensive Treatments and Increase in HbA_{1c} Over Time

United Kingdom Prospective Diabetes Study (UKPDS)



UK Prospective Diabetes Study (UKPDS 34) Group. *Lancet*. 1998;352:854-65.

ADOPT: HbA1c Over Time

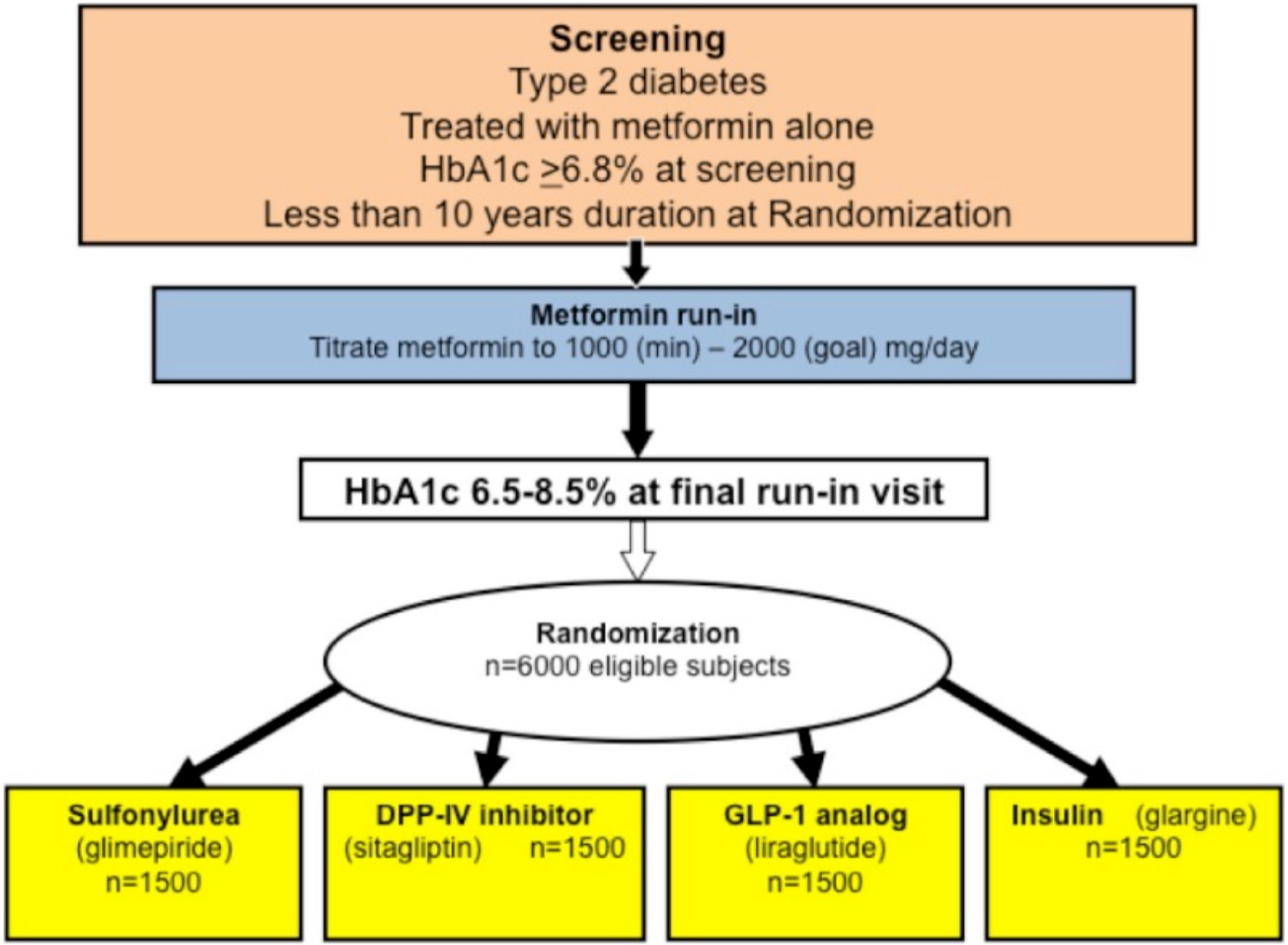


Kahn SE et al: N Engl J Med 355:2427-2443; 2006

GRADE

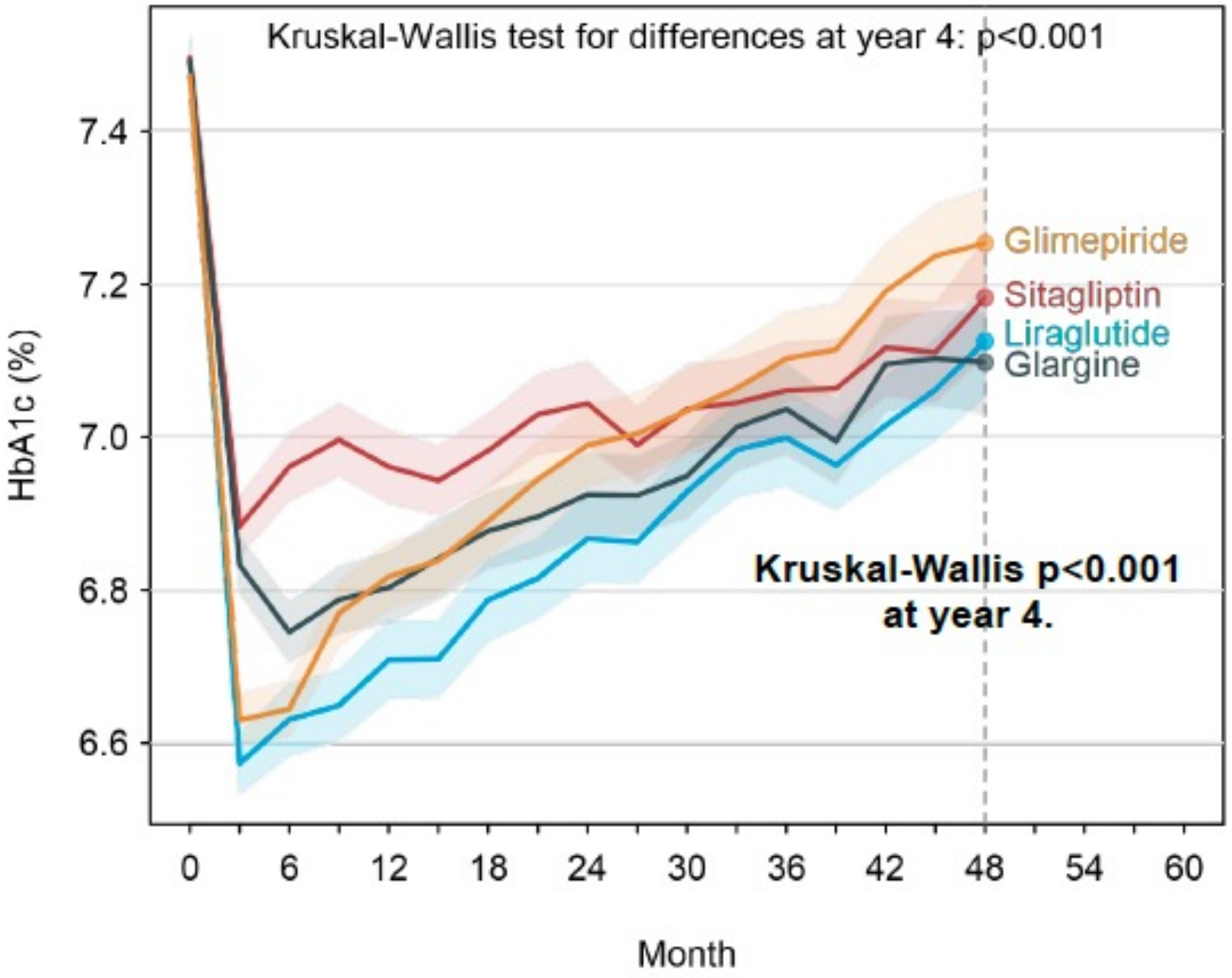
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Wexler DJ et al. Baseline Characteristics of Randomized Participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2019;42(11):2098-2107



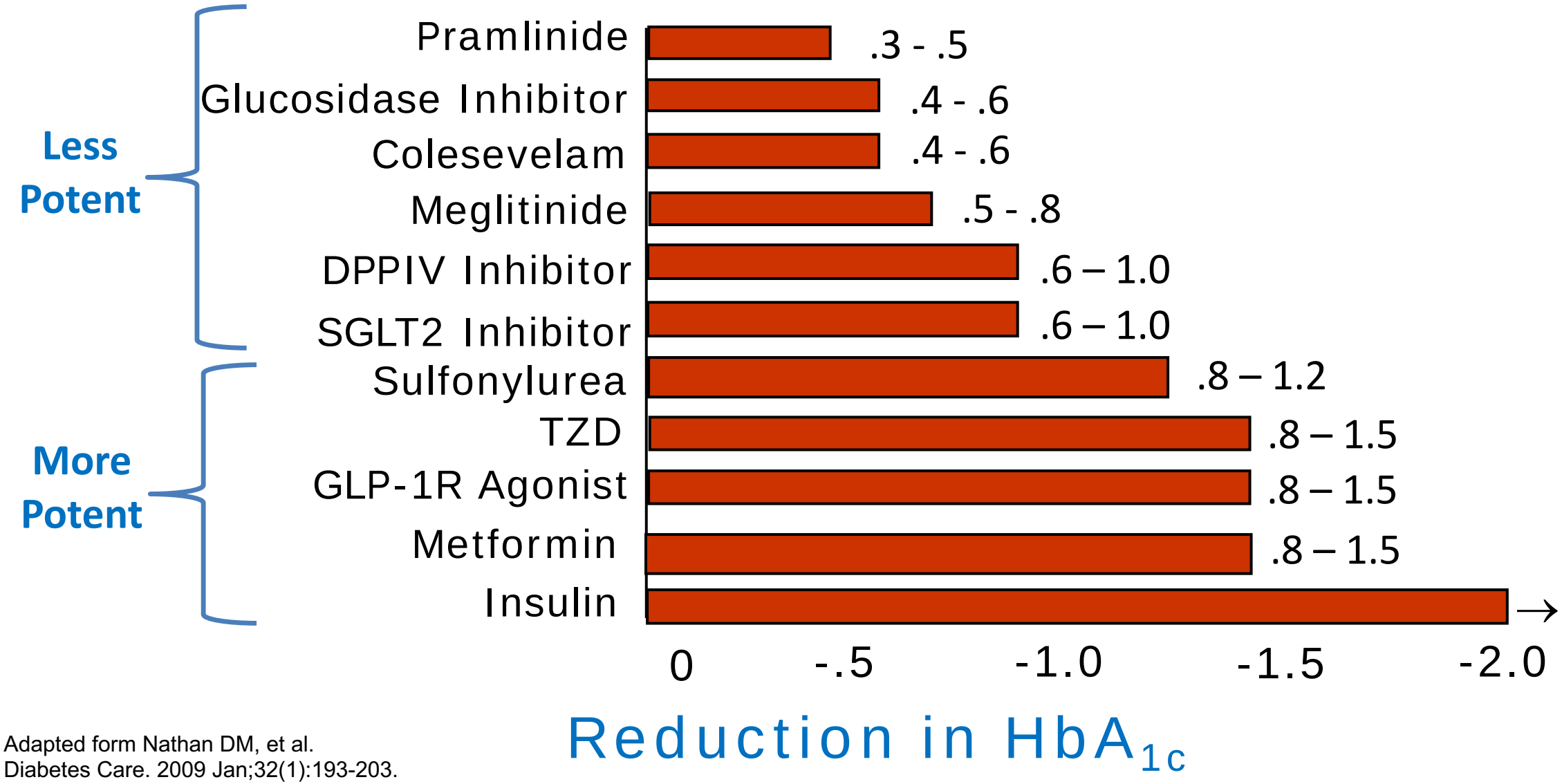
GRADE Study: Rise in HbA1c over time:

patients on metformin and randomized to addition of metformin, sitagliptin, liraglutide, or glargine



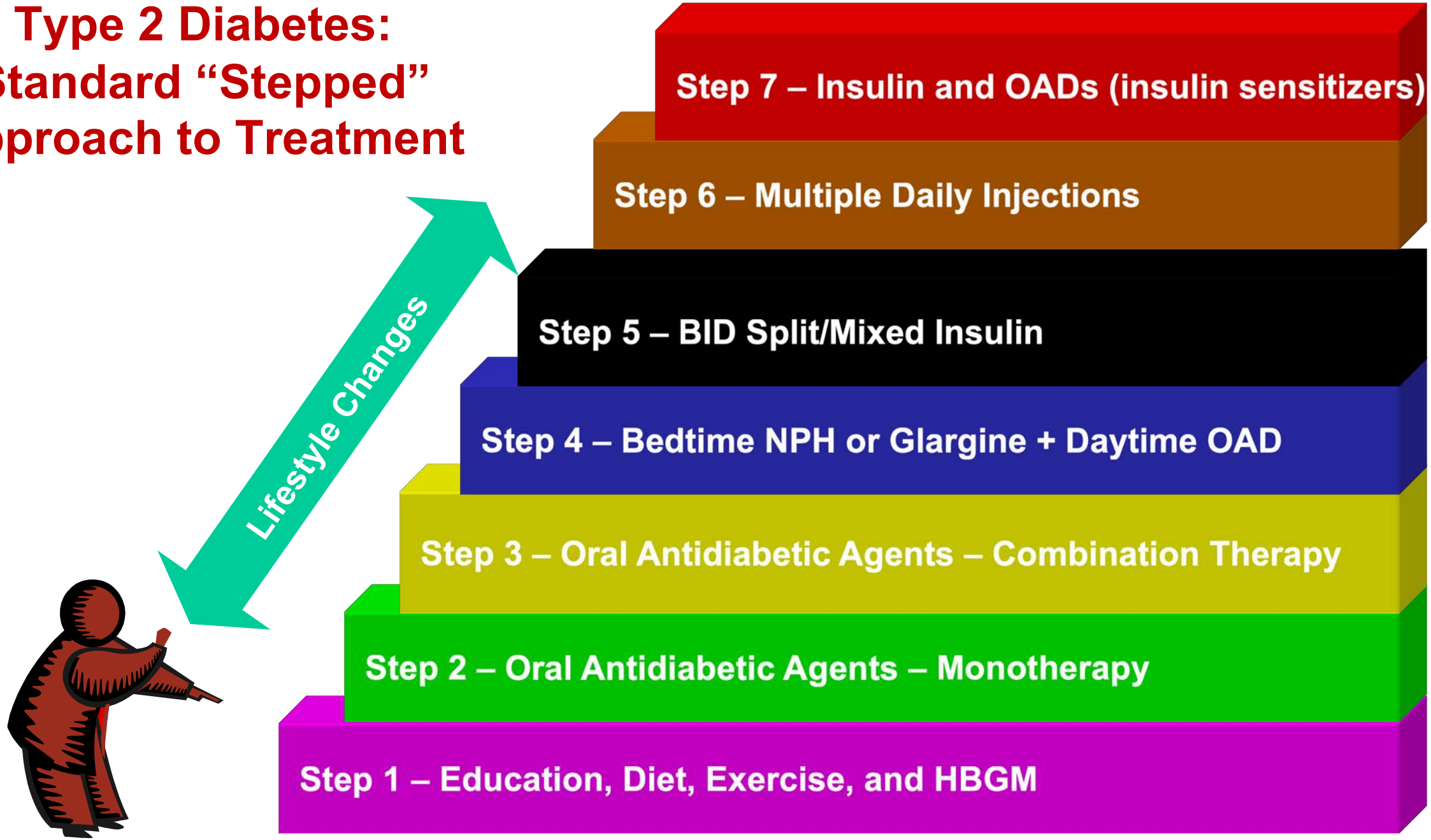
Relative Efficacy for Lowering HbA_{1c}

(when used as monotherapy)

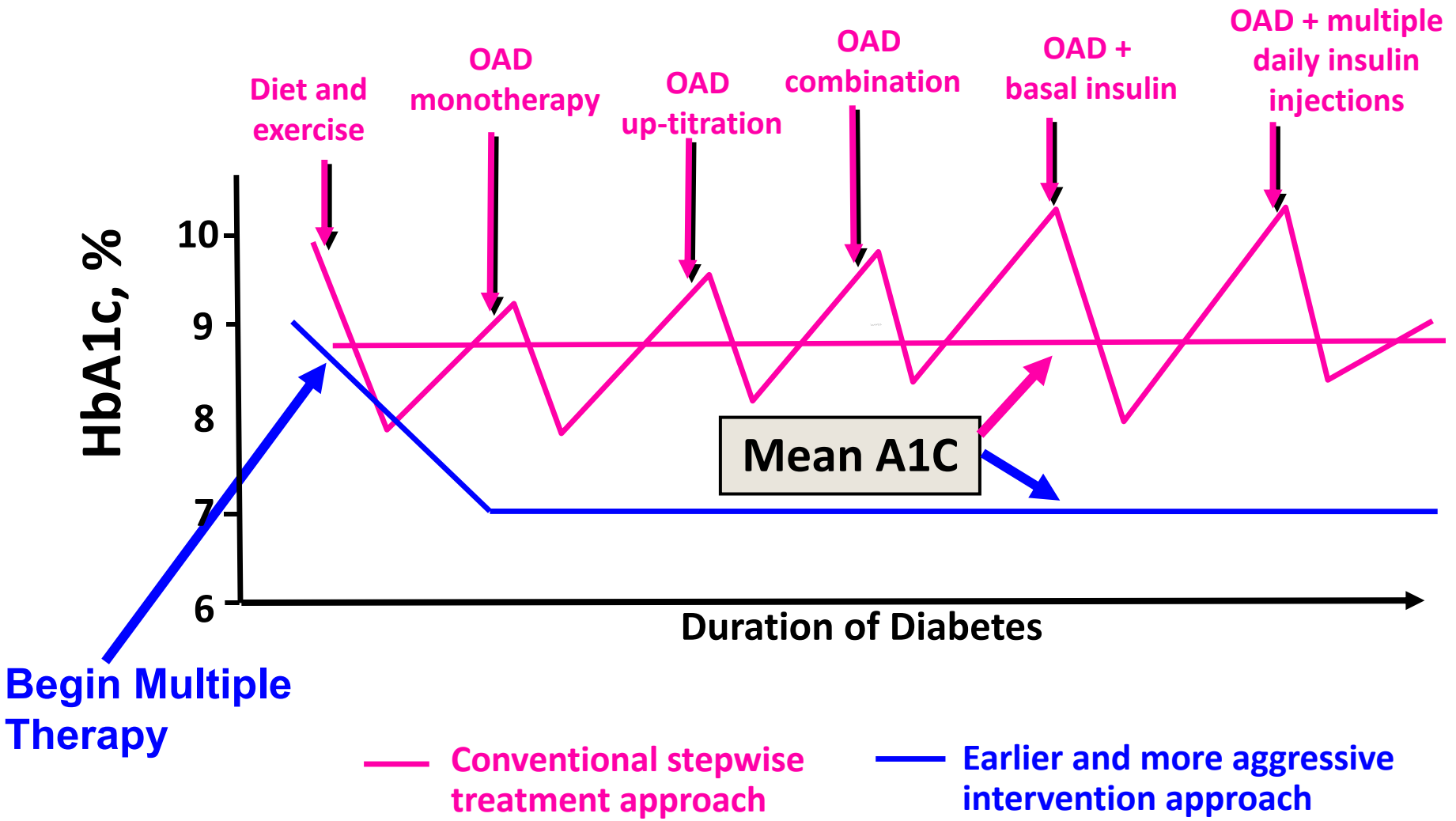


Adapted form Nathan DM, et al.
Diabetes Care. 2009 Jan;32(1):193-203.

Type 2 Diabetes: Standard "Stepped" Approach to Treatment



Earlier and More Aggressive Intervention May Reduce Lifetime HbA1c



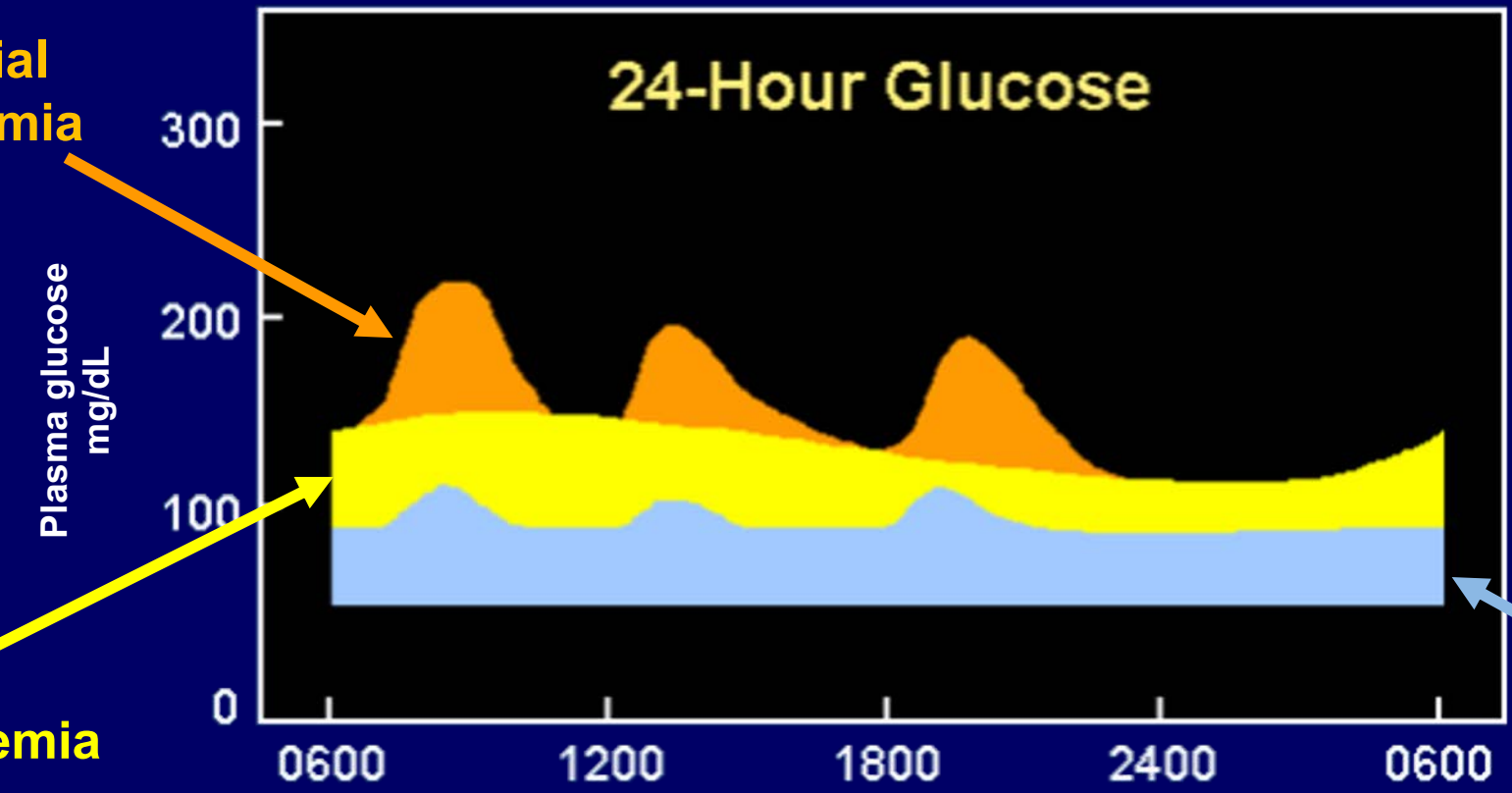
Principle 2

- To reach HbA1c target, there is a need to control both basal and post-prandial glucose
- In combination therapy, use medications with different mechanisms of action

Both FPG and PPG Contribute to Elevated A1C Levels

HbA1c

Post-Prandial Hyperglycemia



Fasting Hyperglycemia

Normal glucose

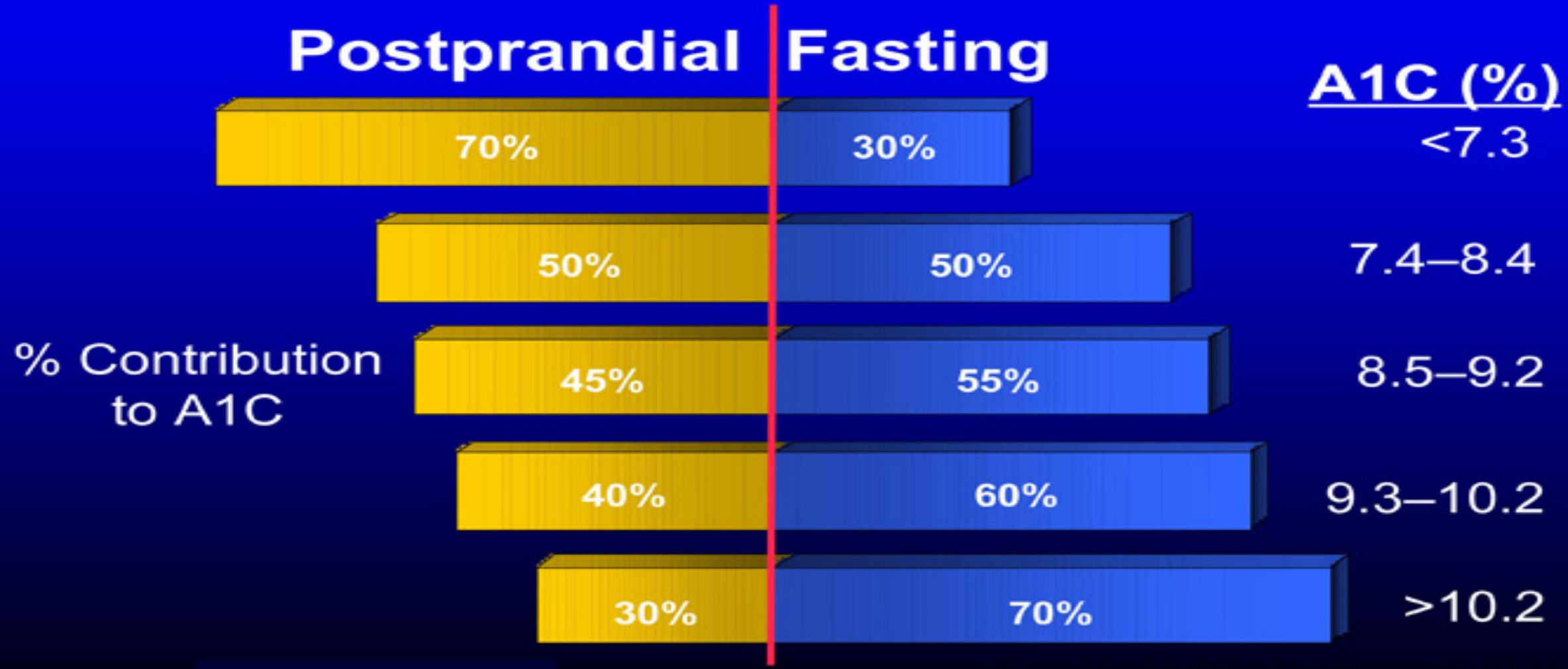
Hyperglycemia

↓

Diabetic Complications

FPG and PPG: Contribution to A1C

As Patients Approach A1C Goal, the Need to Manage PPG Increases



Monnier. *Diabetes Care*. 2003;26:881.

Rational Combination Therapy

Approved Drugs for Type 2 Diabetes (US)

Mostly Target Fasting Hyperglycemia	Mostly Target Post-Prandial Hyperglycemia
Insulin (long-acting)	Insulin (rapid-acting)
Sulfonylureas	Pramlintide
Metformin	Glucosidase Inhibitors
Thiazolidinediones	Meglitinides
Bromocryptine	DDPIV Inhibitors
GLP-1 Agonists/Analogs	GLP-1 Agonists/Analogs
SGLT2 Inhibitors	SGLT2 Inhibitors

Principle 3

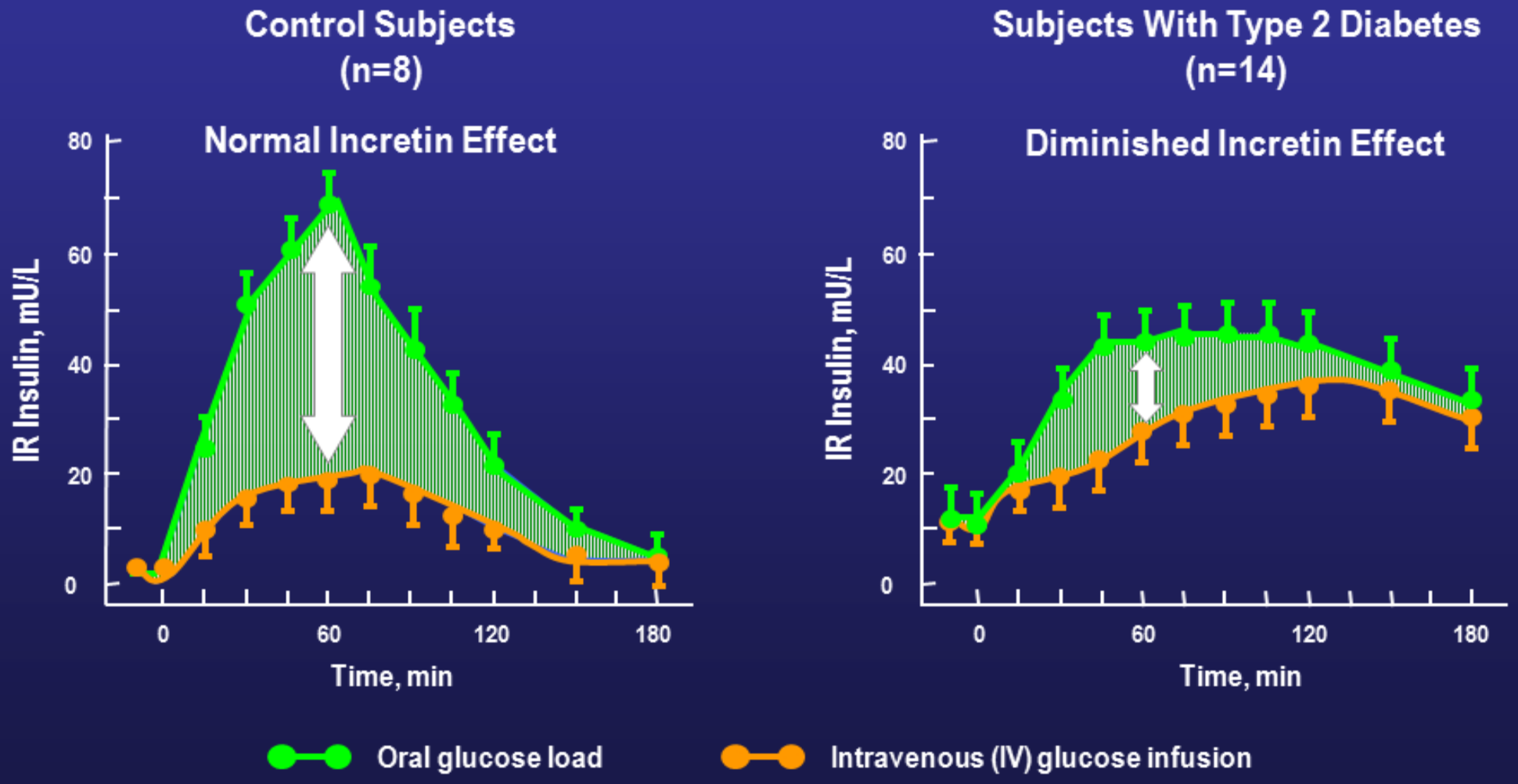
- Avoid hypoglycemia
- Avoid weight gain

Differential Effects of T2DM Treatments

Treatment	Effect on Weight	Risk of Hypoglycemia
Lifestyle Therapy	↓↓	→
Lifestyle + Weight Loss Medication	↓↓↓	→
Insulin	↑↑	↑↑↑
Sulfonylureas	↑↑	↑↑↑
Thiazolidinediones	↑↑	→
Glinides	↑	↑
DPPIV Inhibitors	→	→
Colesevelam	→	→
Bromocriptine	→	→
α-glucosidase Inhibitor	→	→
Metformin	↓	→
GLP-1 Agonists	↓↓	→
SGLT2 Inhibitors	↓↓	↑→

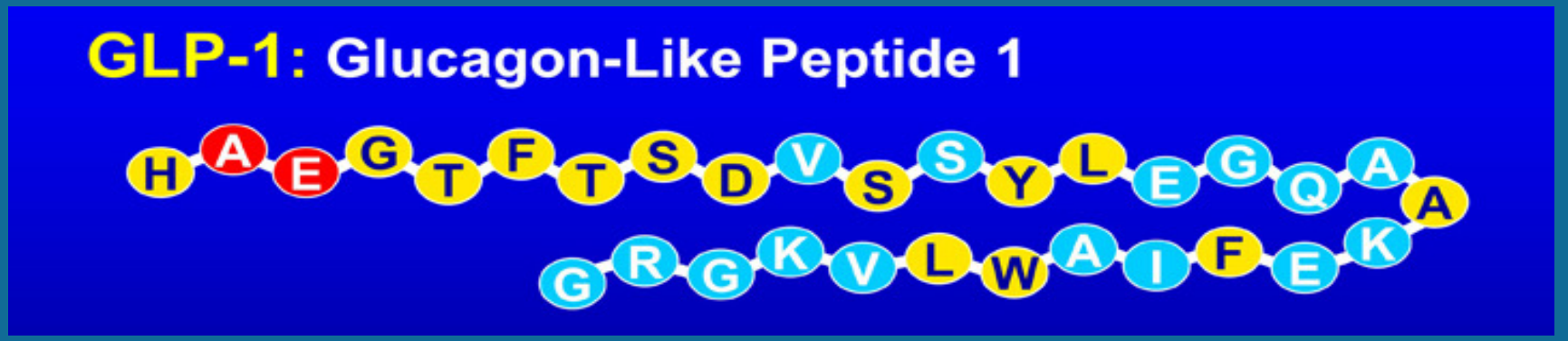
GLP-1 Receptor Agonists

The Incretin Effect Is Diminished in Subjects With Type 2 Diabetes[1]

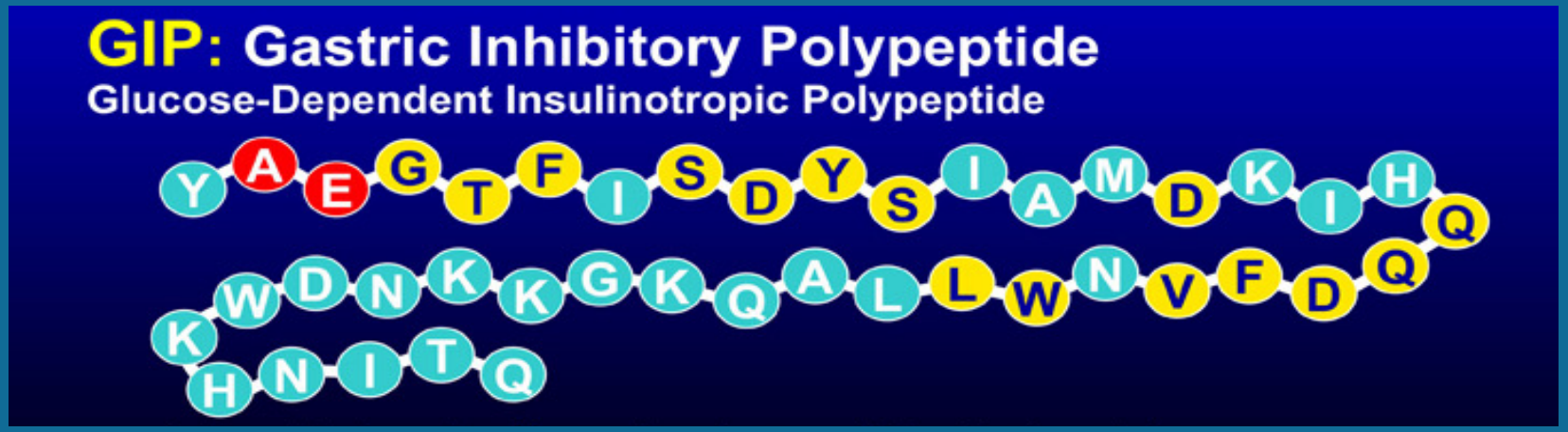


IR=immunoreactive.

1. Reproduced with permission of Springer, from Nauck M et al. *Diabetologia* 1986;29:46–52. Permission conveyed through Copyright Clearance Center, Inc.



Secreted by L cells in the ileum and colon; inhibits gastric emptying and GI motility; inhibits food intake; inhibits glucagon secretion

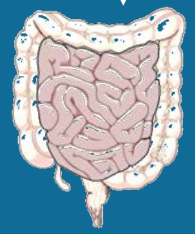


Secreted by K cells in the duodenum; no effects on GI motility; food intake, or glucagon secretion

Role of Incretins in Glucose Homeostasis

Ingestion of food

Release of Incretins



Active GLP-1 & GIP

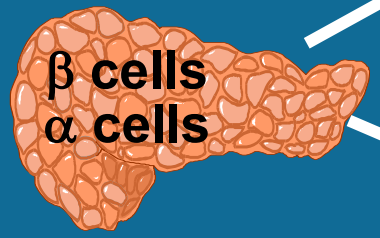
DPP-IV enzyme

Inactive GLP-1

Inactive GIP

DPP-IV= dipeptidyl-peptidase IV

Glucose-dependent
↑ Insulin from β cells (GLP-1 and GIP)



Glucose dependent
↓ Glucagon from α Cells (GLP-1)

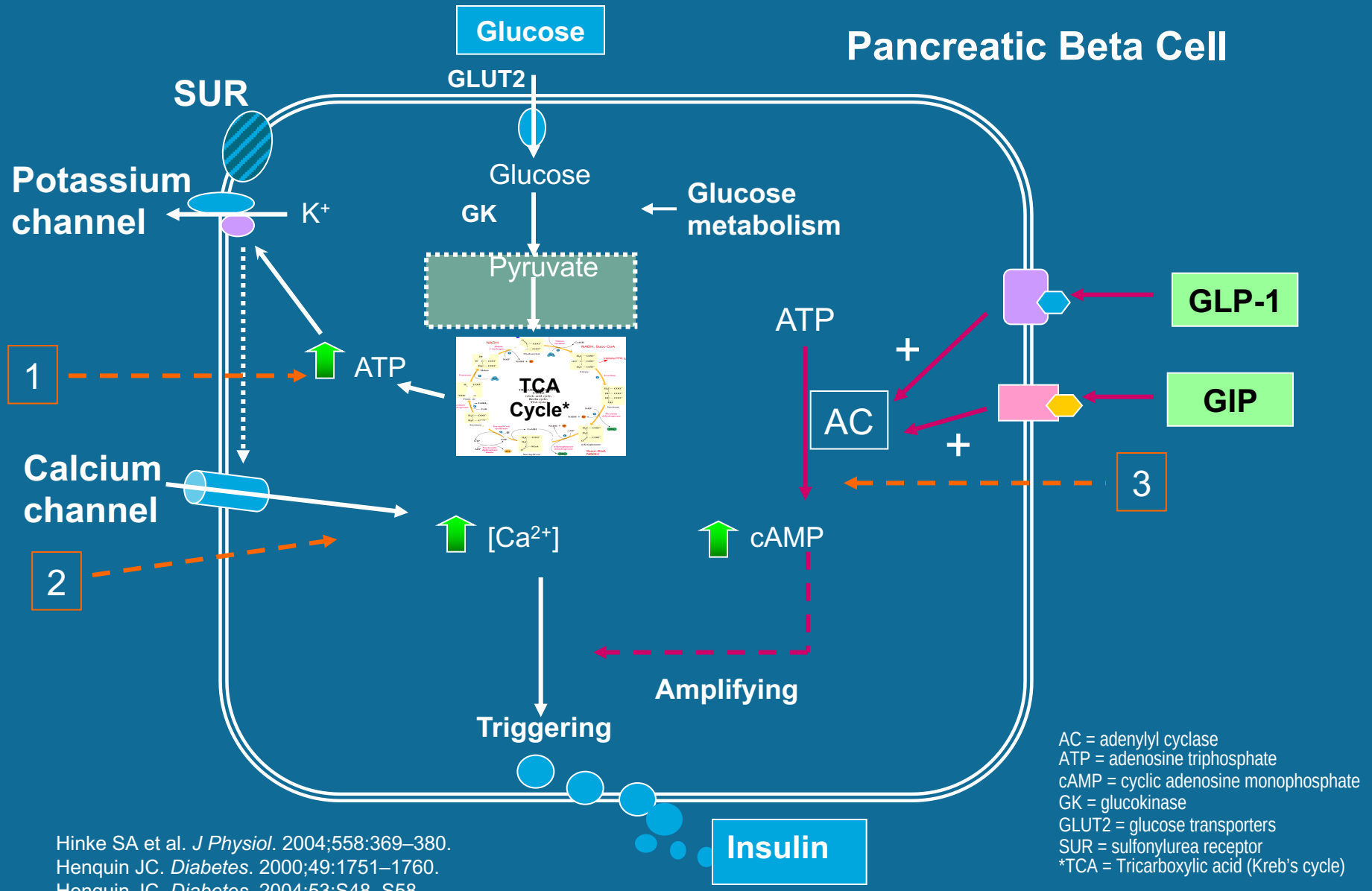
↑ Glucose uptake by muscles

↓ Glucose production by liver

↓ Blood glucose

1. Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876–913.
2. Ahrén B. *Curr Diab Rep*. 2003;2:365–372.
3. Drucker DJ. *Diabetes Care*. 2003;26:2929–2940.
4. Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.

Glucose-Stimulated Secretion of Insulin



Hinke SA et al. *J Physiol*. 2004;558:369–380.
Henquin JC. *Diabetes*. 2000;49:1751–1760.
Henquin JC. *Diabetes*. 2004;53:S48–S58.

AC = adenylyl cyclase
ATP = adenosine triphosphate
cAMP = cyclic adenosine monophosphate
GK = glucokinase
GLUT2 = glucose transporters
SUR = sulfonylurea receptor
*TCA = Tricarboxylic acid (Kreb's cycle)

Strategies for Enhancing GLP-1 Action

- Dipeptidyl peptidase-4 (DPP-IV) inhibitors
  - Extend half-life of endogenous GLP-1 by inhibiting the actions of DPP-IV

Name	Administration Frequency	Degradation
Sitagliptin	Q day	renal
Vildagliptin	Q/day or 2x/day	renal
Saxagliptin	Q day	renal
Linagliptin	Q day	feces
Alogliptin	Q day	renal

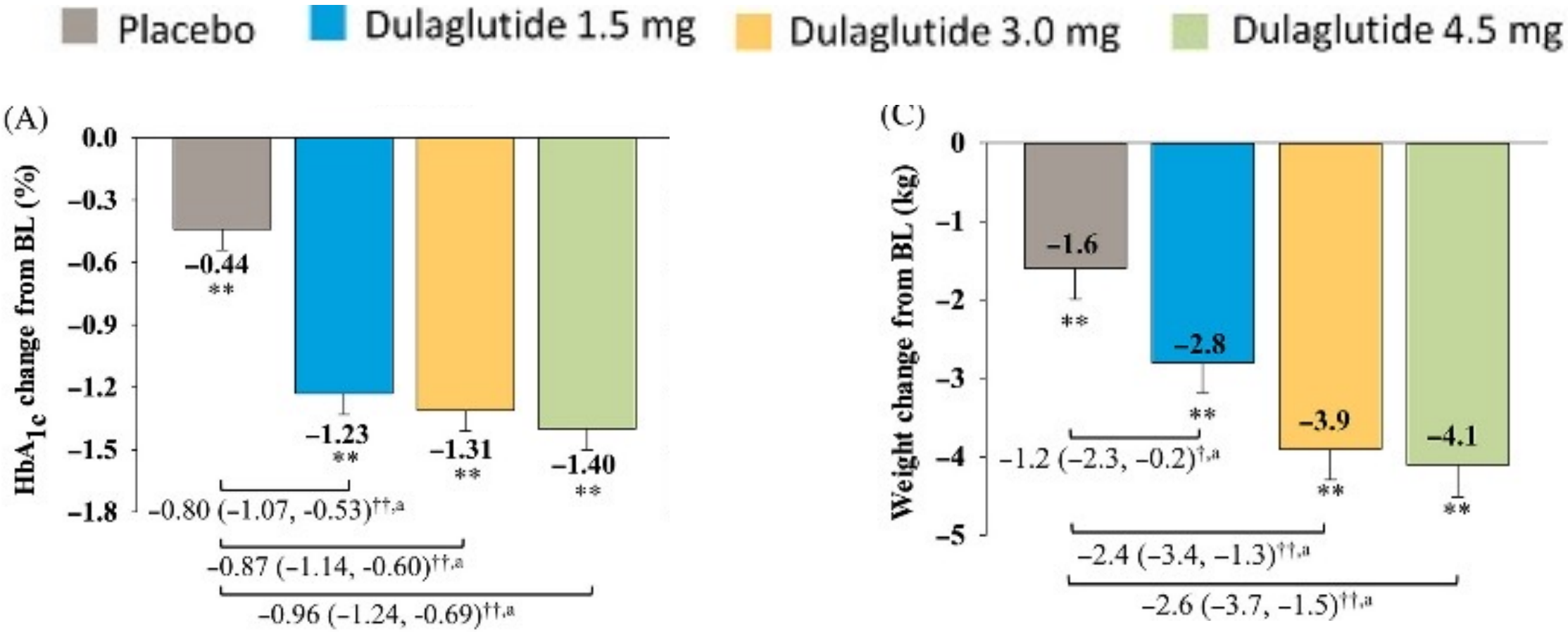
Strategies for Enhancing GLP-1 Action

- GLP-1 receptor agonists
  - Activators of the GLP-1 receptor
  - Structurally modified to confer resistance to degradation by DPPIV)

Name	Structural modification	Administration Frequency
Exenatide	exendin-4; homolog from Gila Monster	2x/day
Liraglutide	acylation allows binding to albumin	Q day
Lixisenatide	first 39 AA of exendin-4, des-38-pro and lysine tail	Q day
Exenatide LA	biodegradable microsphere suspension	Q week
Albiglutide	GLP-1 dimer fused to albumin	Q week
Dulaglutide	fusion with human Fc fragment of Ig G4	Q week
Semaglutide	Acylation for albumin bind and AA change	Q week

High Dose Dulaglutide

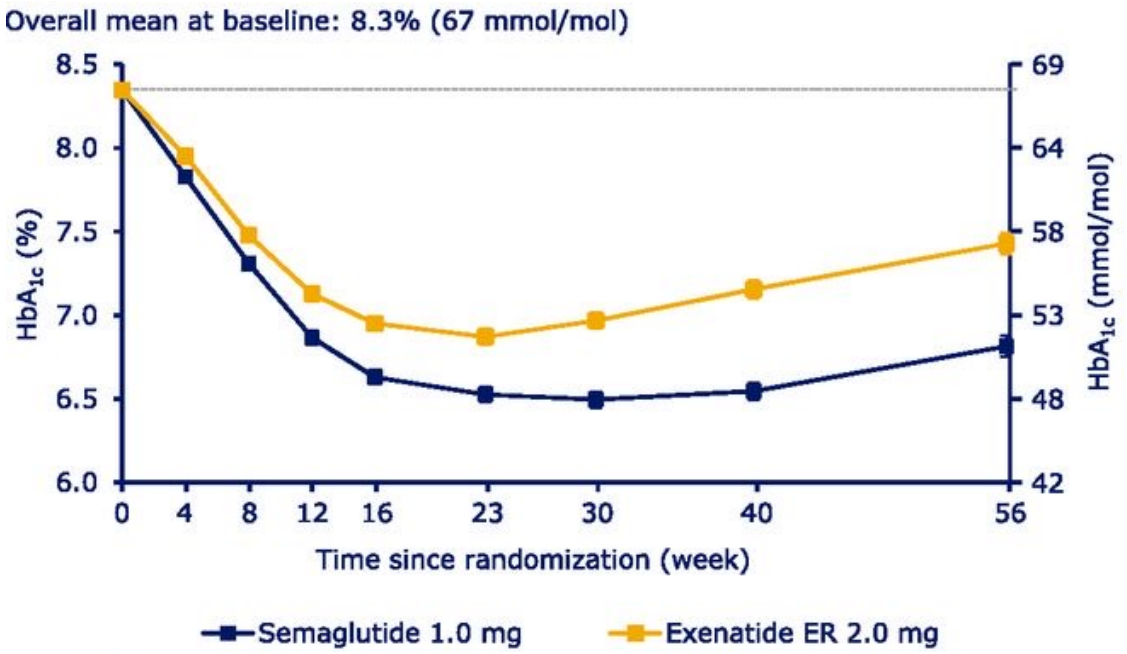
Efficacy and safety of an expanded dulaglutide dose range: A phase 2, placebo-controlled trial in patients with type 2 diabetes using metformin

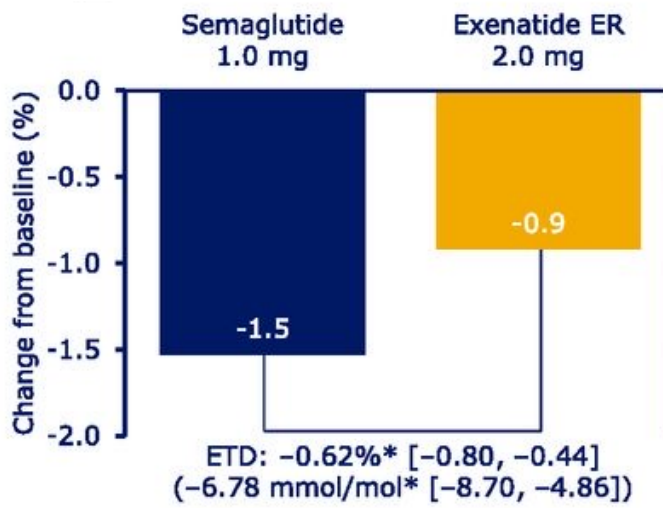


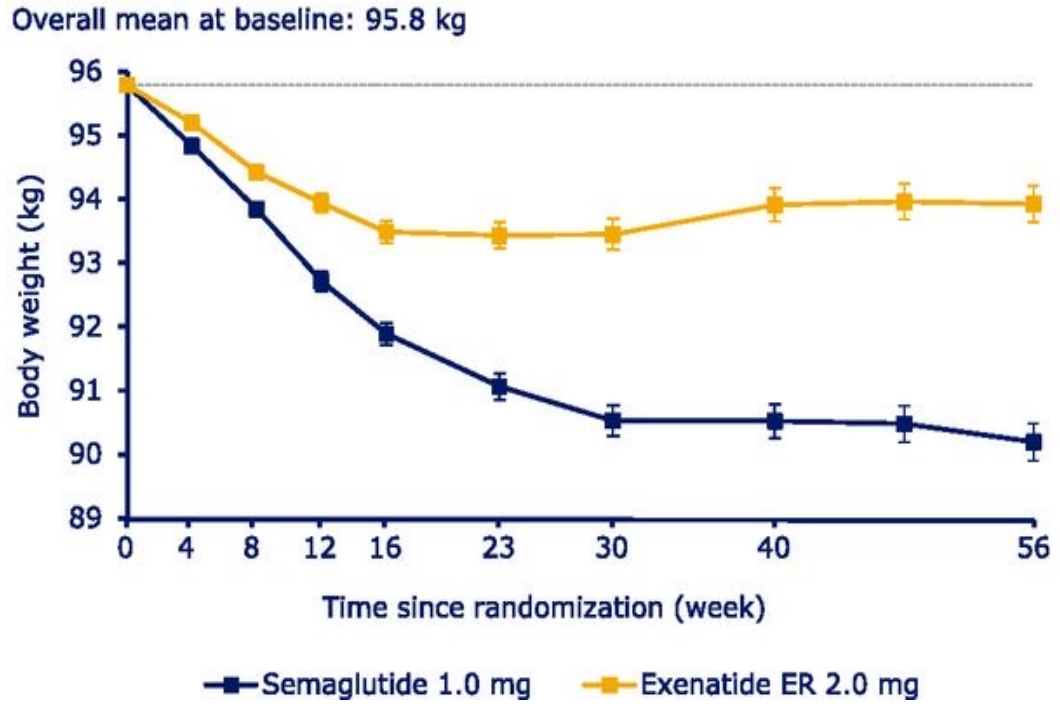
Frias JP et al. Diabetes, Obesity and Metabolism. 2020; 21(9):2048-2057

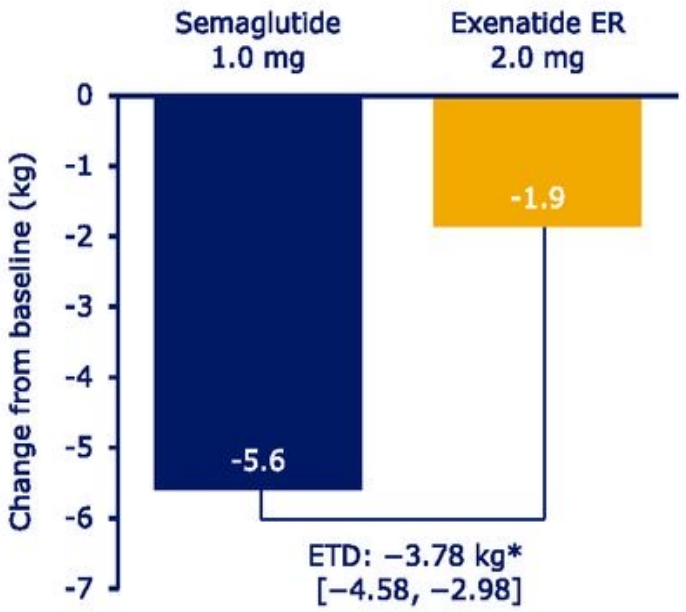
Semaglutide VS Exenatide

Effects on HbA1c and Weight





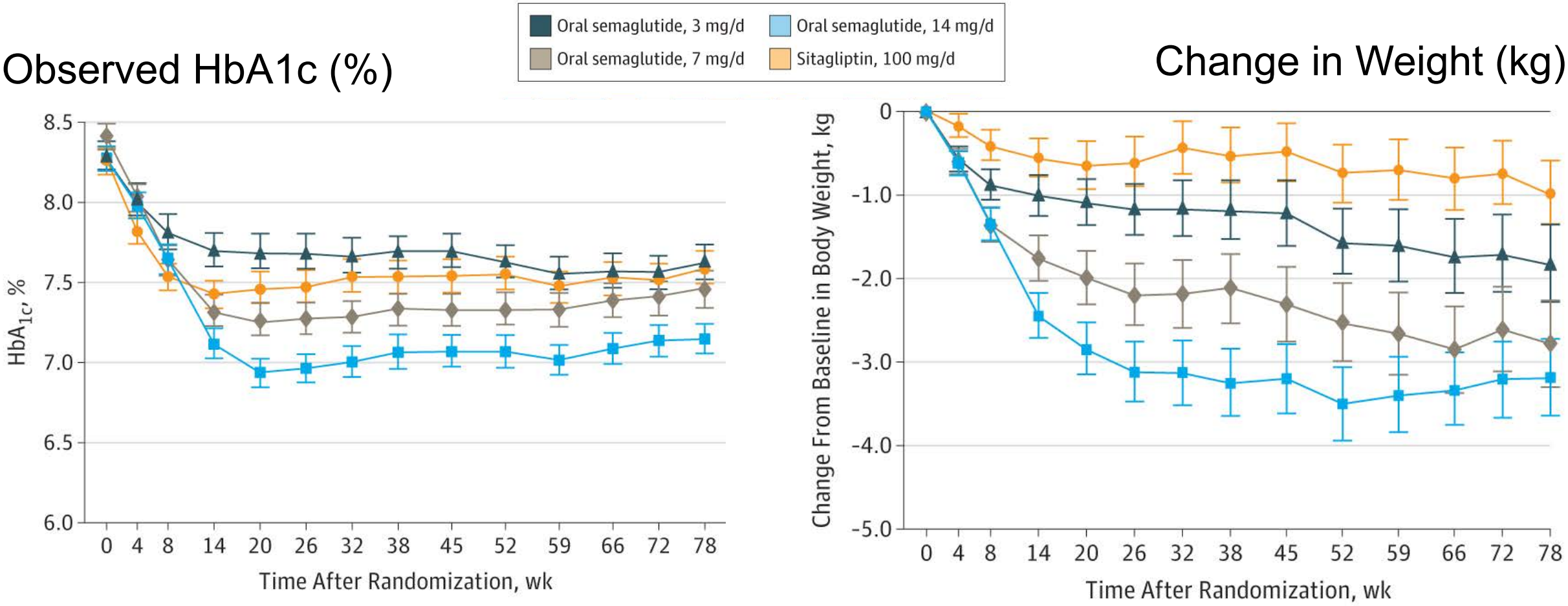




Ahmann AJ et al. Diabetes Care. 2018; 41(2):248-266

Oral Semaglutide Decreases both HbA1c and Body Weight in T2DM

Observed HbA1c (%)

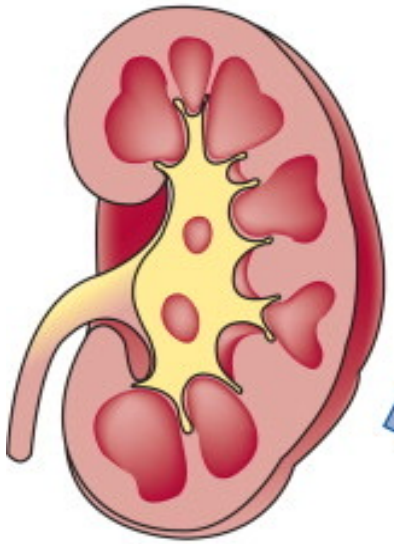


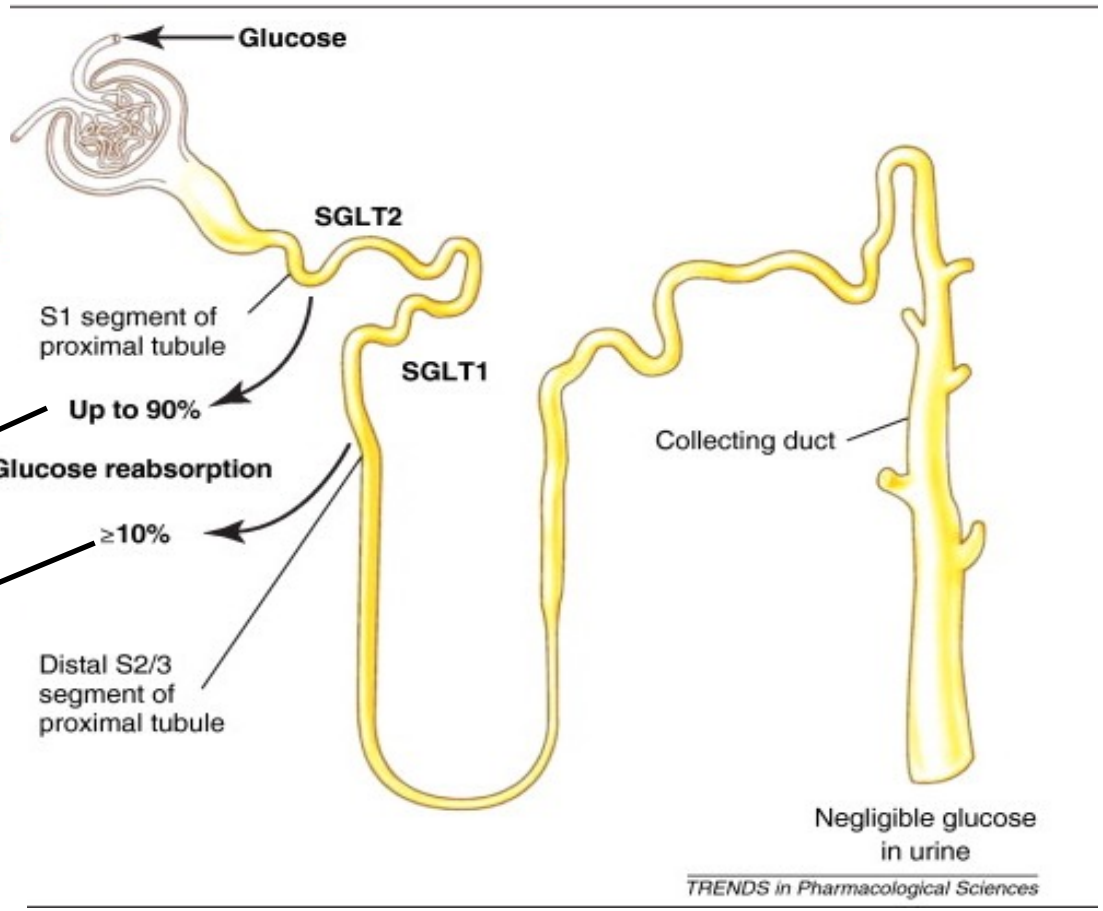
Change in Weight (kg)

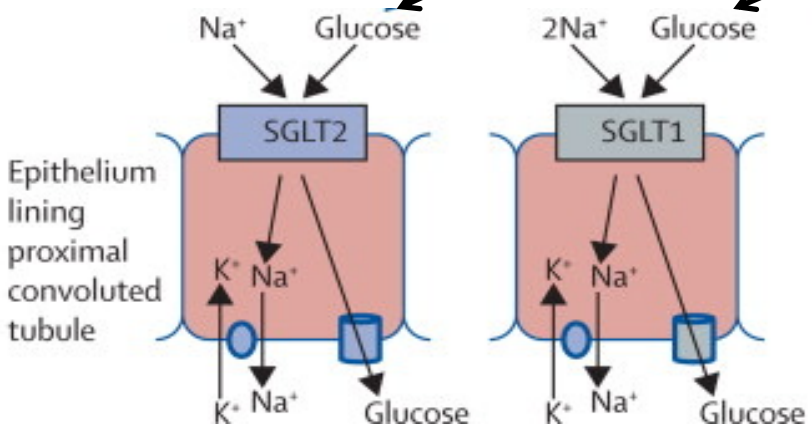
Rosenstock J et al. Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466-1480.

SGLT2 Inhibitors

Renal Glucose Reabsorption

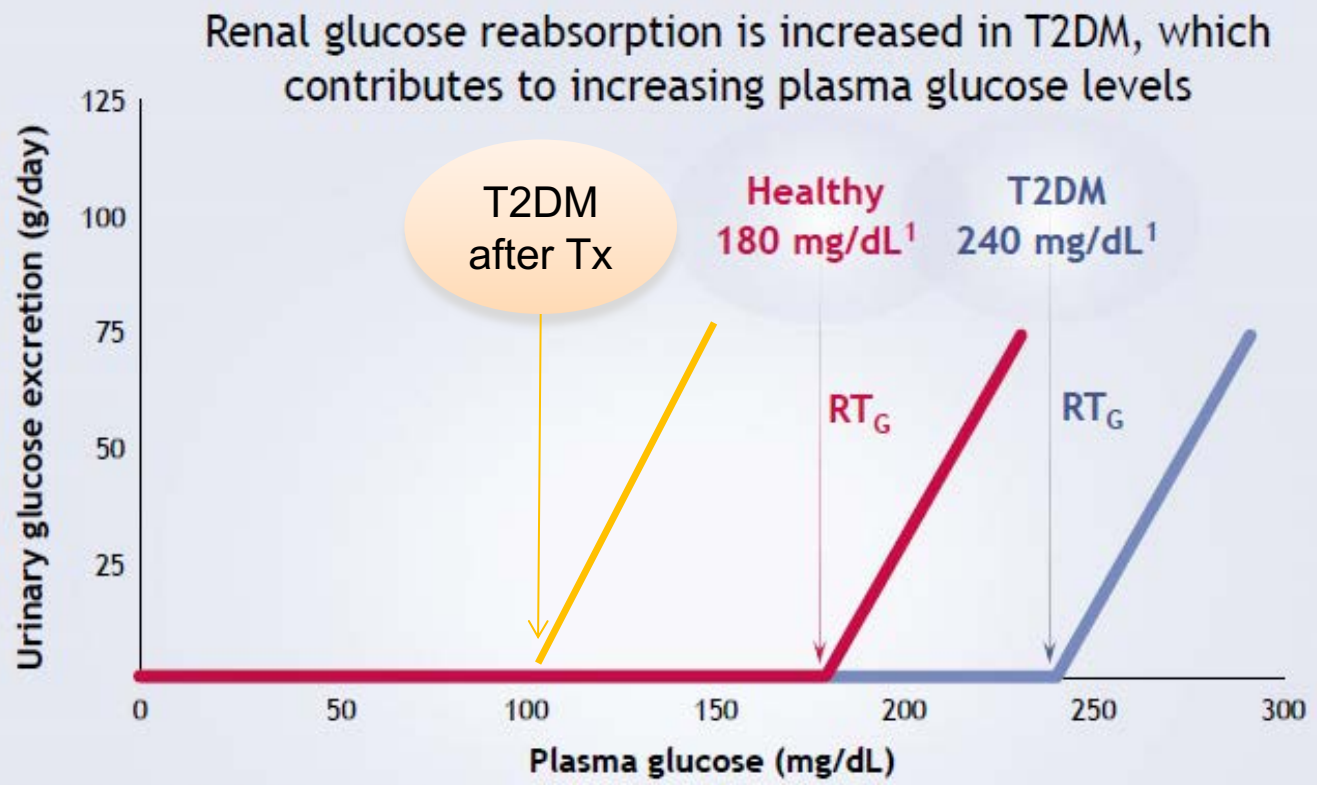






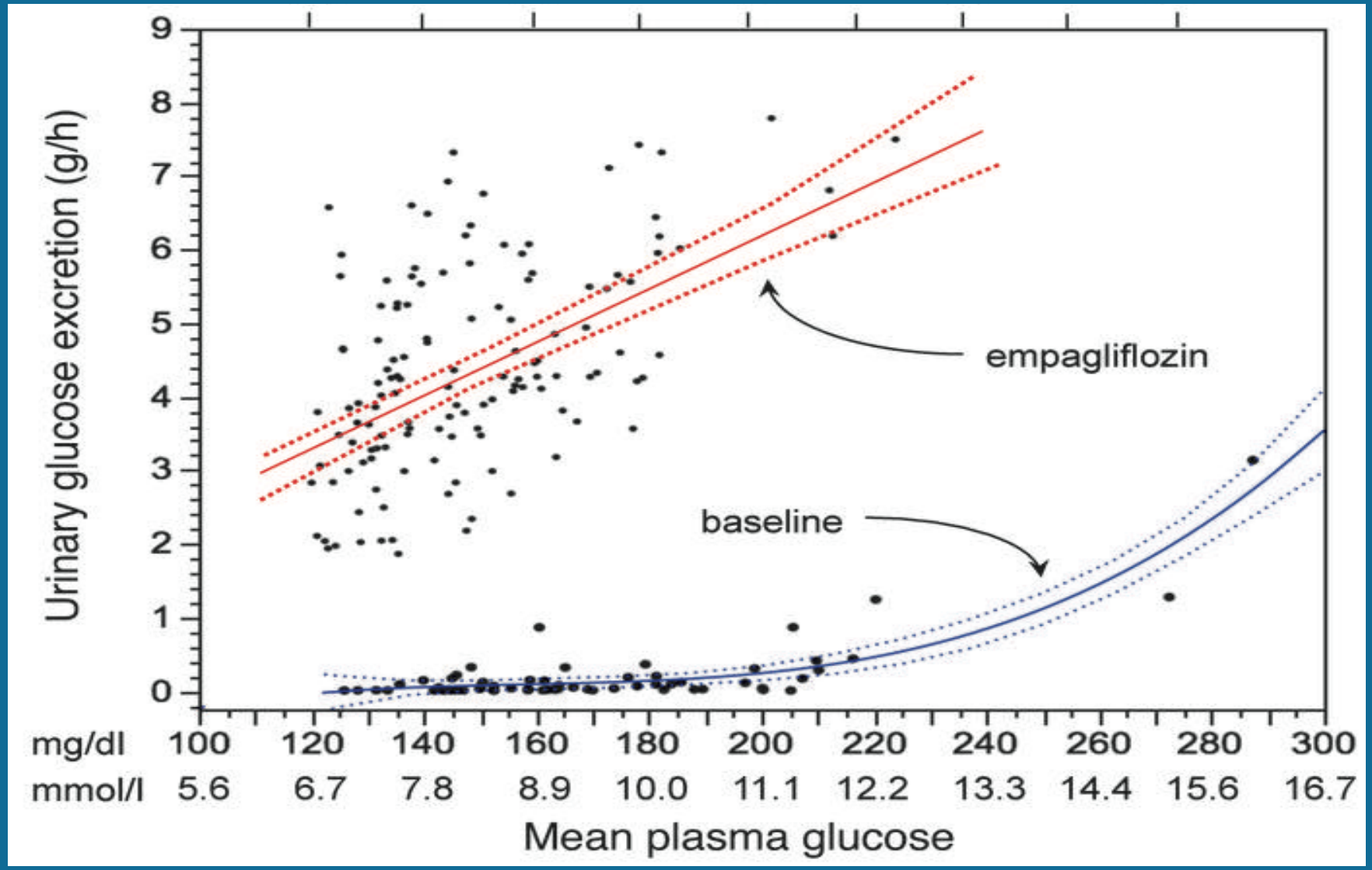
Renal Glucose Reabsorption

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



Adapted with permission from Abdul-Ghani, DeFronzo RA.
T2DM = type 2 diabetes mellitus.
1. Farber SJ et al. *J Clin Invest*. 1951;30(2):125-129. 2. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 3. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790.

Effects of SGLT2 Inhibitors on GLUCOSE EXCRETION RATES



J Clin Invest. 2014; 124(2):499–508

SGLT2 Inhibitors

- Induce glycosuria by decreasing renal Tm for glucose
- Lowers blood glucose through insulin-independent mechanism
- Lowers blood pressure and body weight, but increases LDL-c
- Watch for genital infections and dehydration, and DKA
- Avoid if eGFR < 30-60 ml/min

Name	Dose	Specificity
Canagliflozin	100, 300 mg/day	SGLT2 and low SGLT1
Dapagliflozin	5, 10 mg/day	SGLT2
Empagliflozin	10, 25 mg/day	SGLT2
Ertagluflozin	5, 15 mg/day	SGLT2

Principle 4

Evolving Pharmacotherapy:

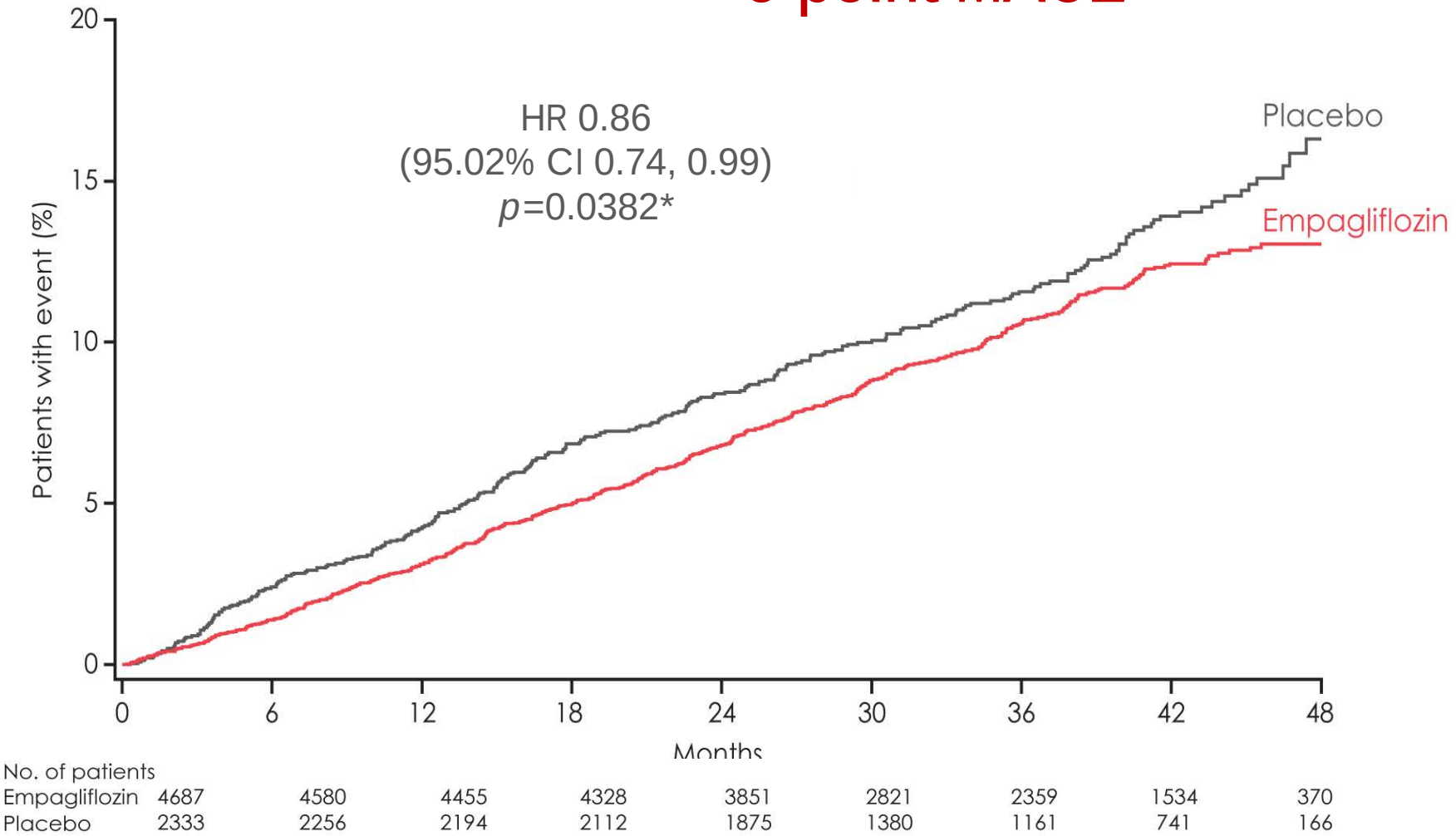
select diabetes medications based on the risk or presence of

- CVD
- Stroke
- CHF
- Renal Decline

Empagliflozin

Primary outcome: 3-point MACE

MACE
- CV death
- Non-lethal MI
- Non-lethal stroke

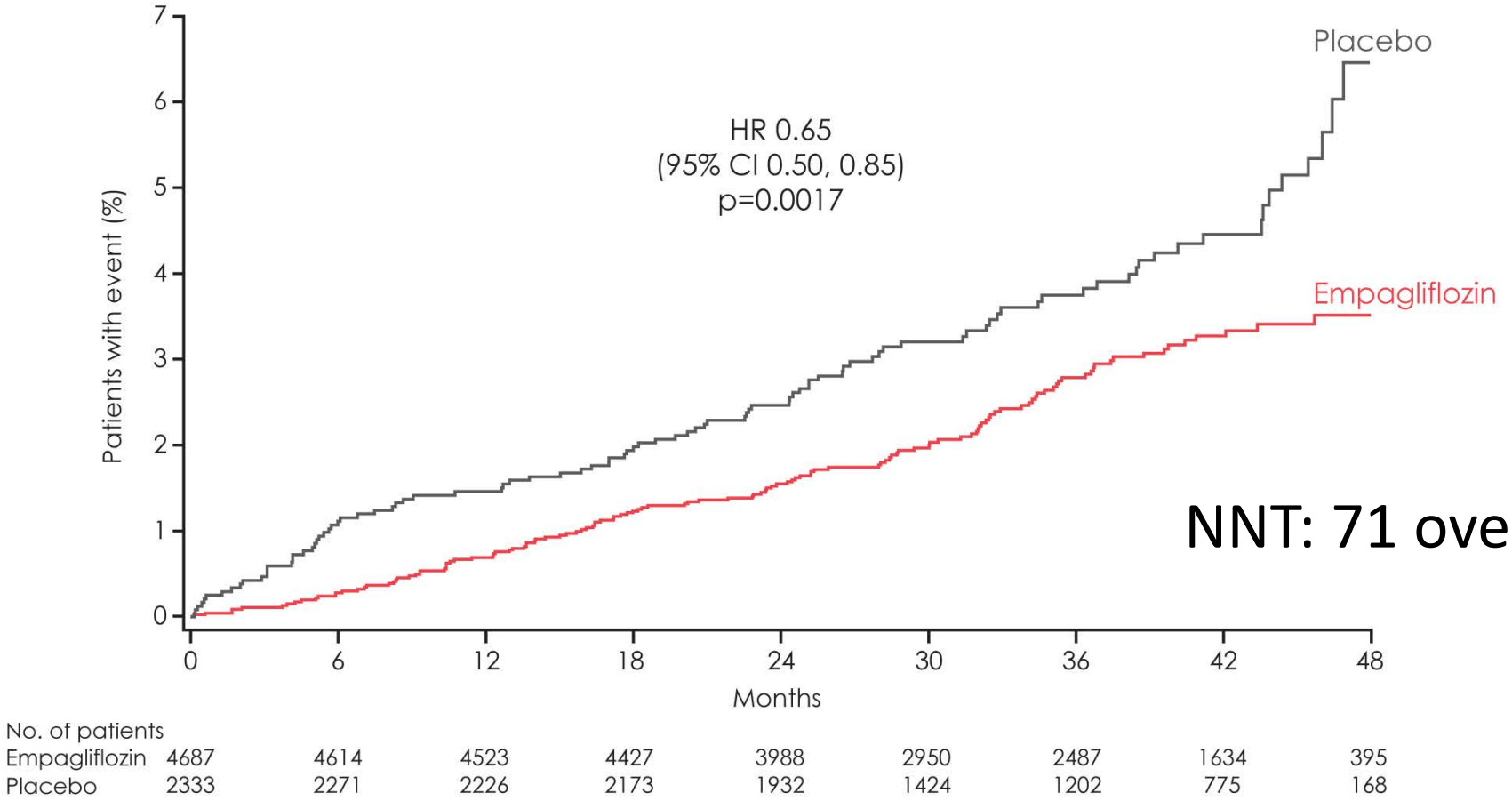


Zinman *et al. N Engl J Med* 2015;373:2117–28

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG - Empagliflozin

Hospitalization for heart failure, secondary outcome



NNT: 71 over 3 years

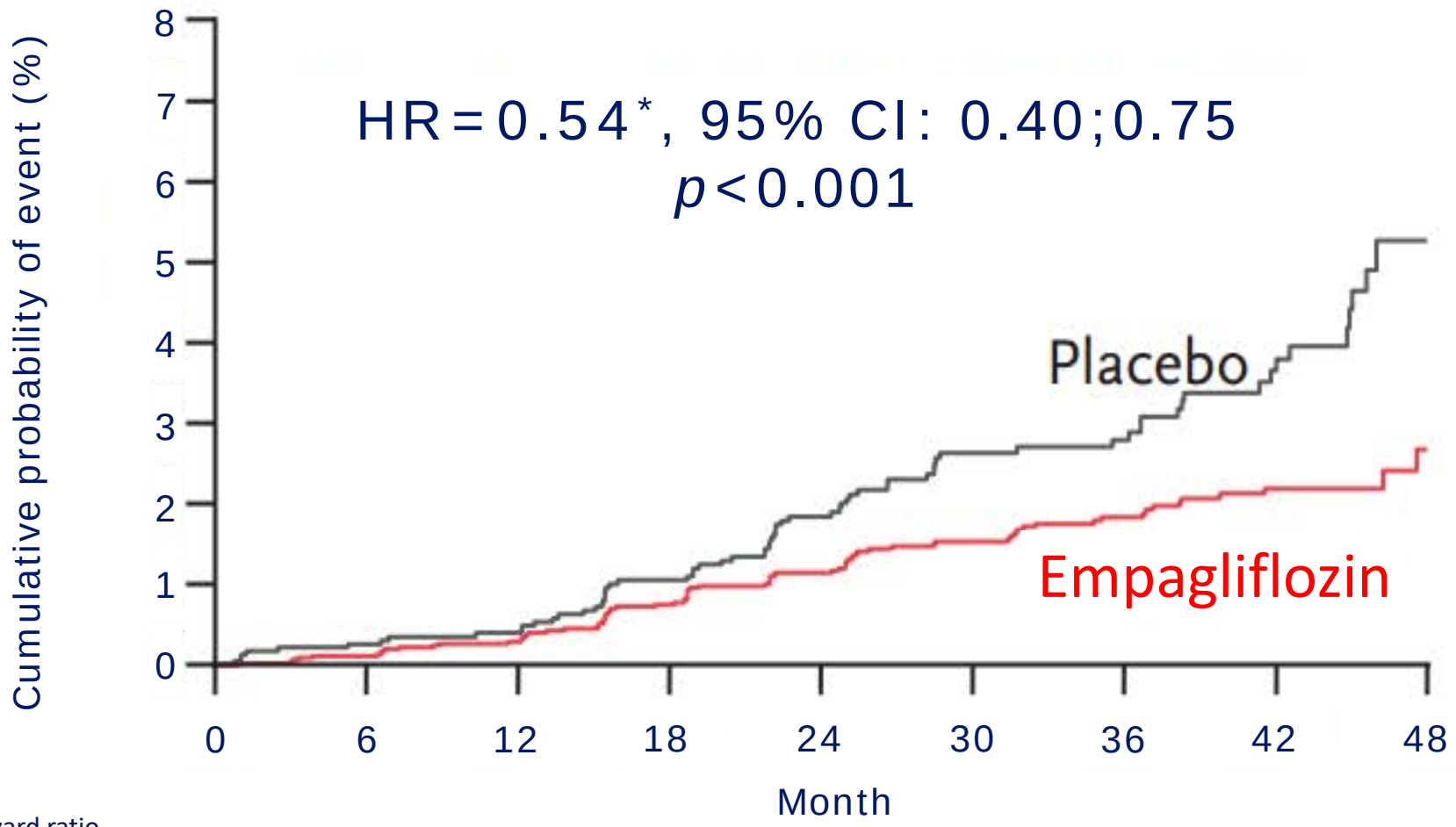
Cumulative incidence function. HR, hazard ratio

Zinman *et al. N Engl J Med* 2015;373:2117–28

EMPA-REG - Empagliflozin

Time to first renal event (secondary outcome)

Doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease



*CI, confidence interval; HR, hazard ratio

Wanner *et al. N Engl J Med* 2016;375:323-34

SGLT2 inhibitors: CVOTs

DRUG	TRIAL	MACE	CV Death	Non-fatal MI	Non-fatal Stroke	% with CVD	Hospital for CHF	Renal Outcome
Empagliflozin	EMPA-REG	**0.86 (.74-.99)**	✓	-	-	99	**0.65 (.55-.79)**	**0.61 (.53-.70)**
Canagliflozin	CANVAS	**0.86 (.67-.91**	-	-	-	66	**0.78 (.67-.91**	**0.60 (.47-.77)**
Canagliflozin	CREDENCE	**0.80 (.67-.95**	✓			50	**0.69 (.57-.83)**	**0.70 (.59-.83)**
Dapagliflozin	DECLARE-TIMI 58	NI	-	-	-	41	**0.83 * (.73-.95)**	**0.53 (.43-.66)**
Empagliflozin	EMPEROR-Reduced		NI				**0.69 * (.59-.81)**	**0.50 (.32-.77)**
Ertugliflozin	VERTIS	NI	-	-	-		**0.70 (.54-.90**	NI

* = with and without diabetes

NI - = non-inferior

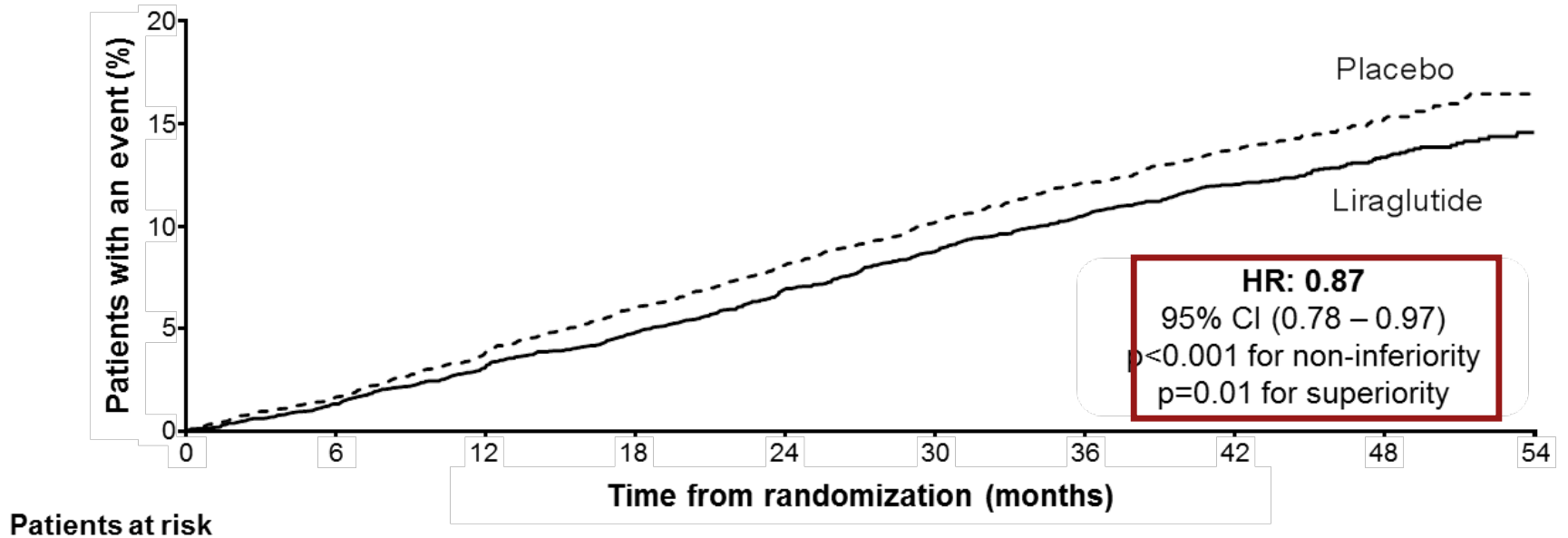
All studies show superiority for dual outcome CV death or hospital for CHF)

Mechanick JI, Farkouh ME, Newman JD, Garvey WT. Cardiometabolic-Based Chronic Disease, Addressing Knowledge and Clinical Practice Gaps: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(5):539-555

LEADER Trial: Liraglutide in patients with T2DM

MACE Outcome:

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

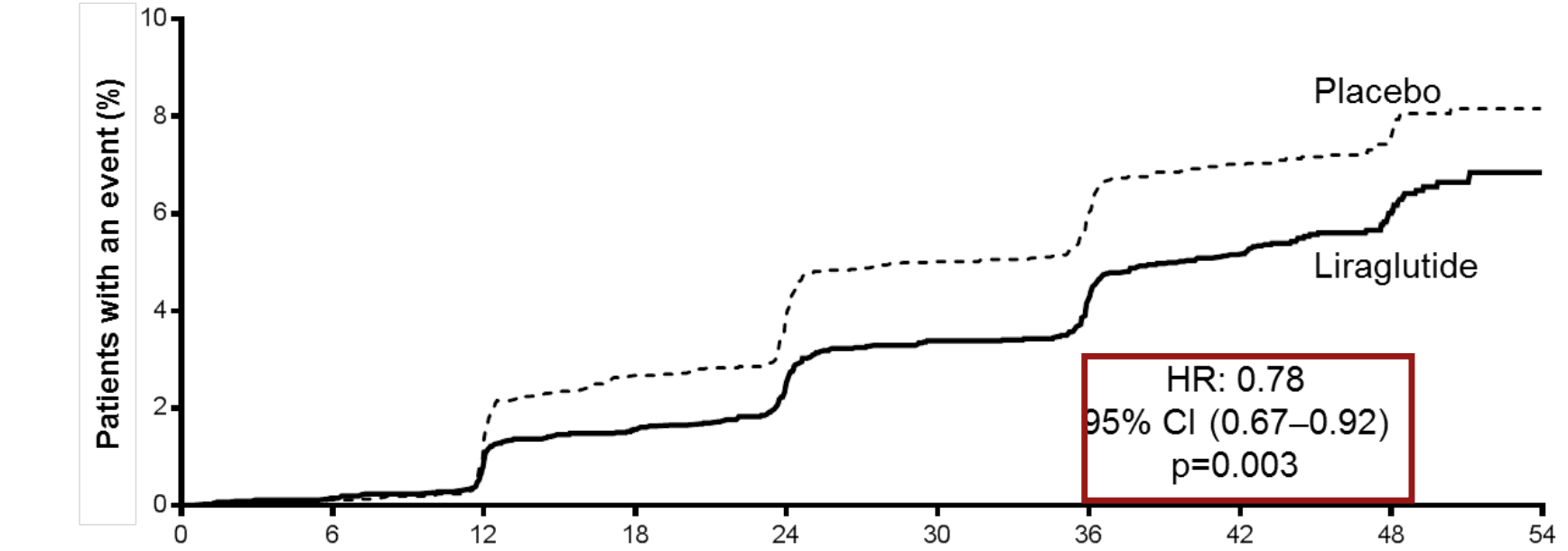
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER Trial: Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

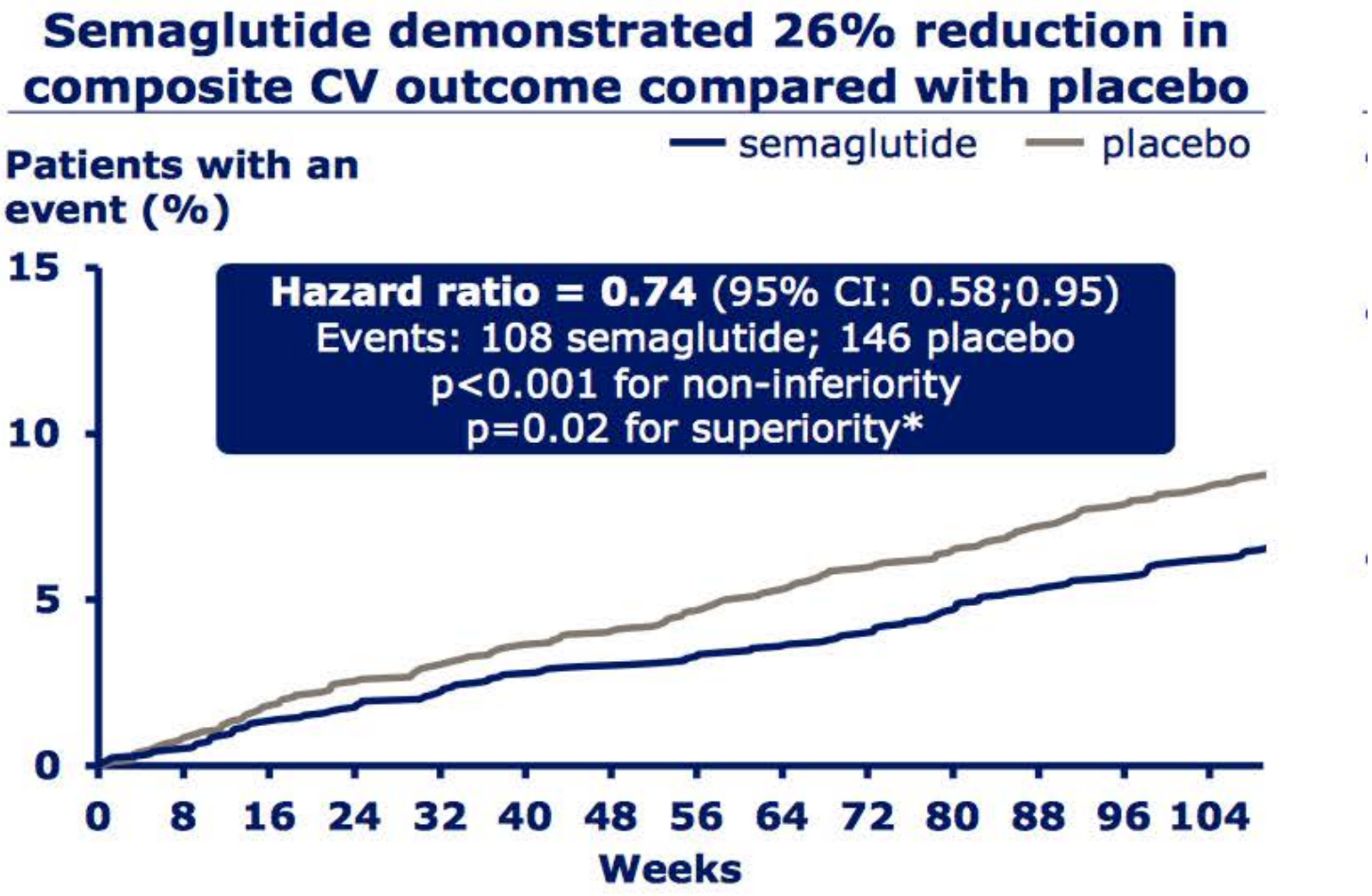


Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

SUSTAIN 6 Trial: Semaglutide in Patients with T2DM



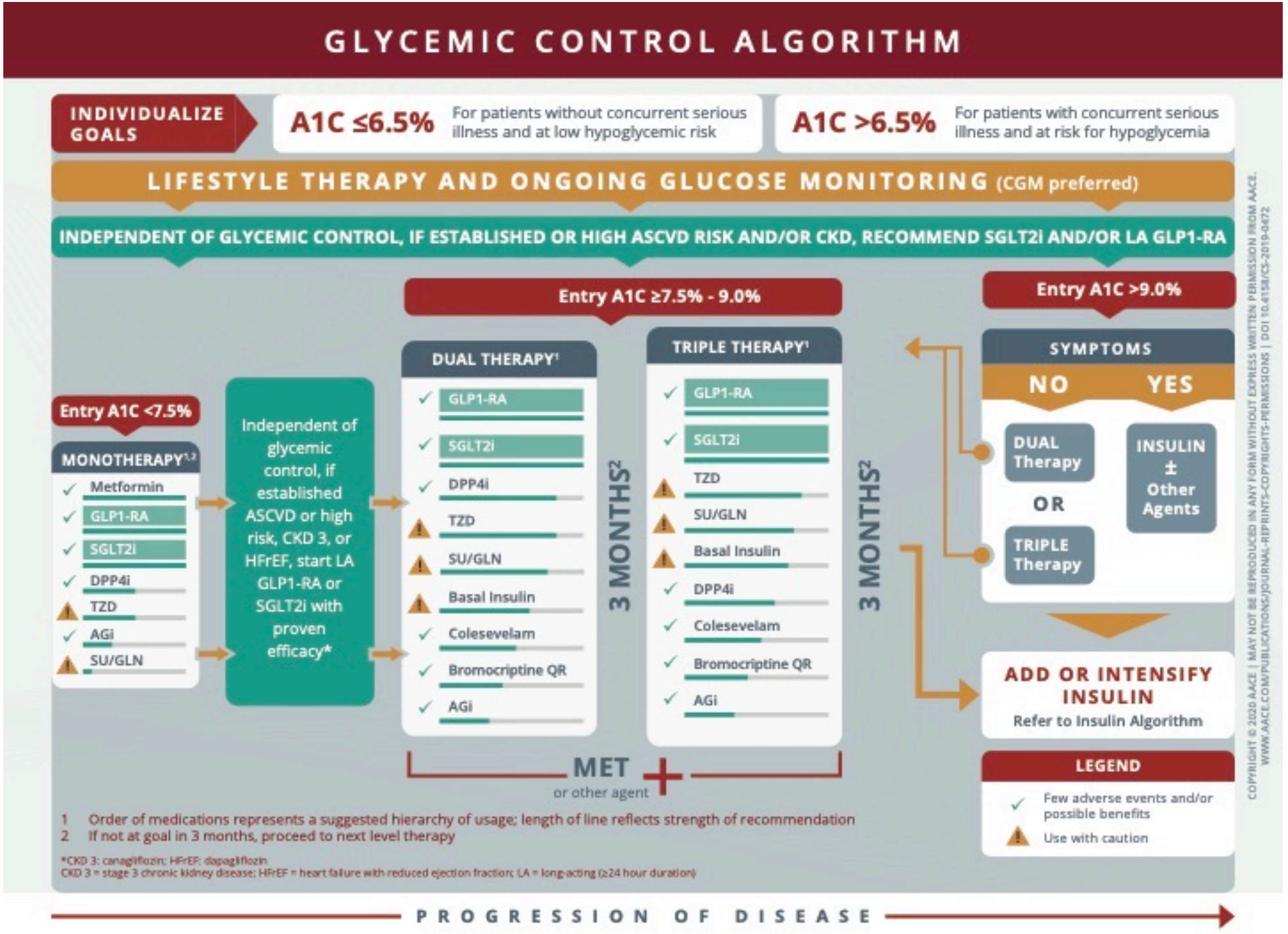
Note: p-value is two-sided, pooled data reported for both semaglutide and placebo
MACE: Major adverse cardiovascular event; 3-point MACE comprises cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; CI: Confidence interval
* No adjustment for multiple tests
Source: Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. 2016

GLP-1 Receptor Agonists: CVOTs

DRUG	TRIAL	MACE	CV Death	Non-fatal MI	Non-fatal Stroke	% with CVD	Hospital for CHF	Renal Outcome
Lixisenatide	ELIXA	NI	-	-	-	100	NI	NS
Liraglutide	LEADER	**0.87 (.78-.97)**	✓	-	-	81	NI	**0.78 (.67-.92)**
Semaglutide	SUSTAIN-6	**0.74 (.58-.95)**	-	-	✓	83	NI	**0.64 (.46-.88)**
Exenatide	EXCEL	NI	-	-	-	73	NI	**0.85 (.73-.98)**
Albiglutide	HARMONY	**0.78 (.68-.90)**	-	✓	-	100	NI	
Dulaglutide	REWIND	**0.88 (.79-.99)**	-	-	✓	32	NI	**0.85 (.77-.93)**
Semaglutide (oral)	PIONEER 6	NI	-	-	-	85	NI	

NI – non-inferior

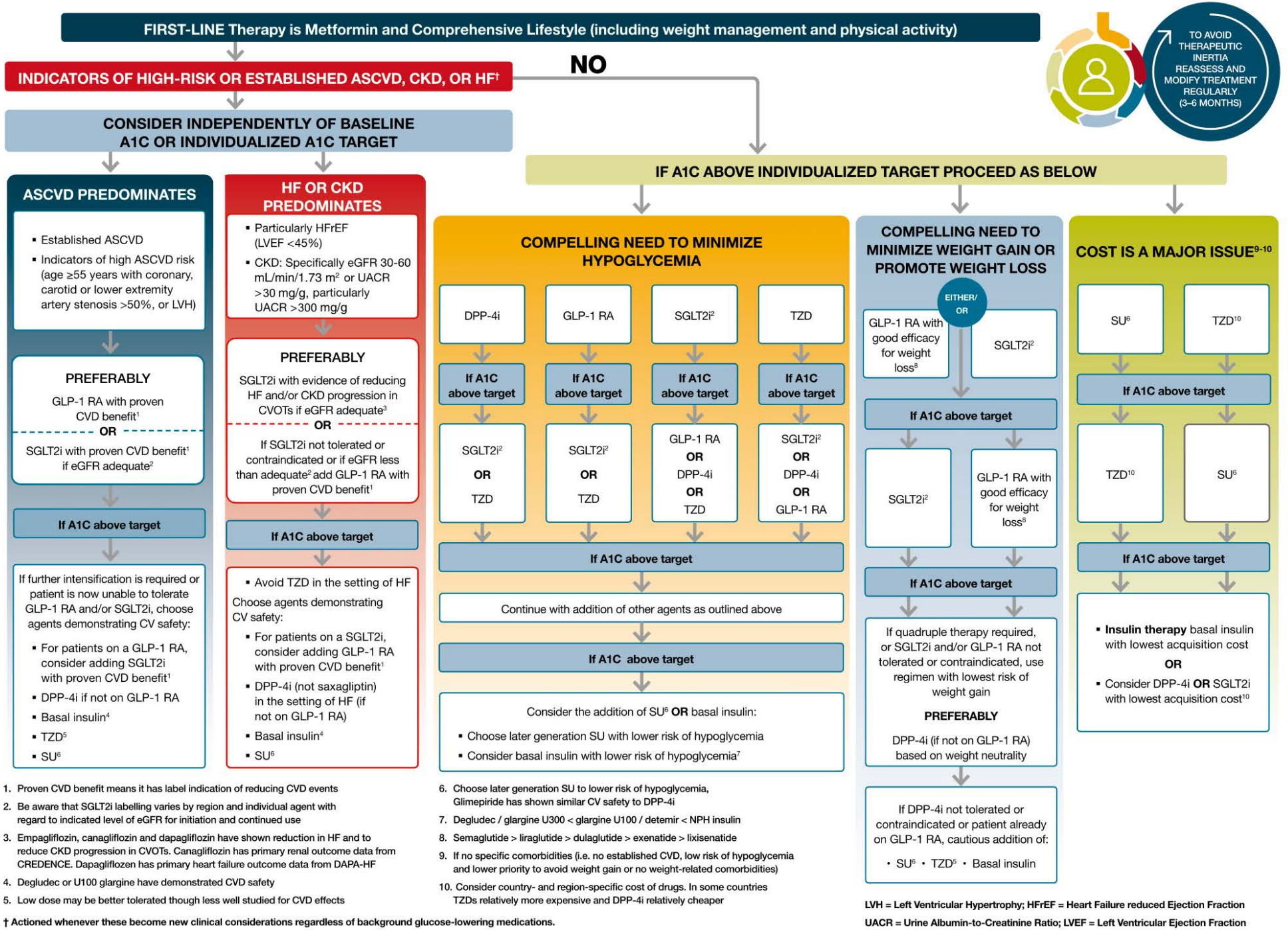
Mechanick JI, Farkouh ME, Newman JD, Garvey WT. Cardiometabolic-Based Chronic Disease, Addressing Knowledge and Clinical Practice Gaps: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(5):539-555



AACE Diabetes Algorithm 2020

Garber A et al. Endocr Pract 2020; 26(1):107-139

ADA/EASD T2DM Algorithm



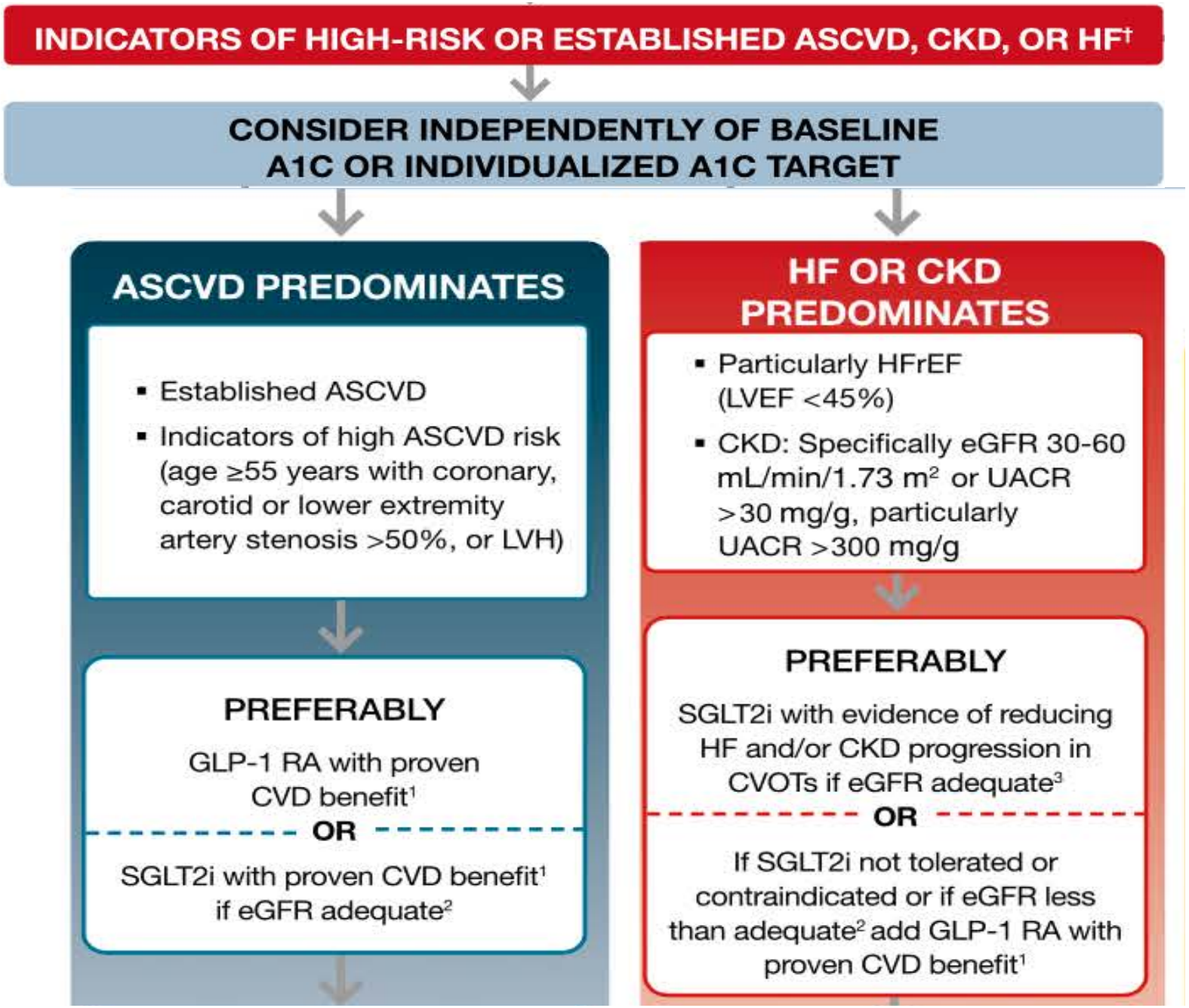
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

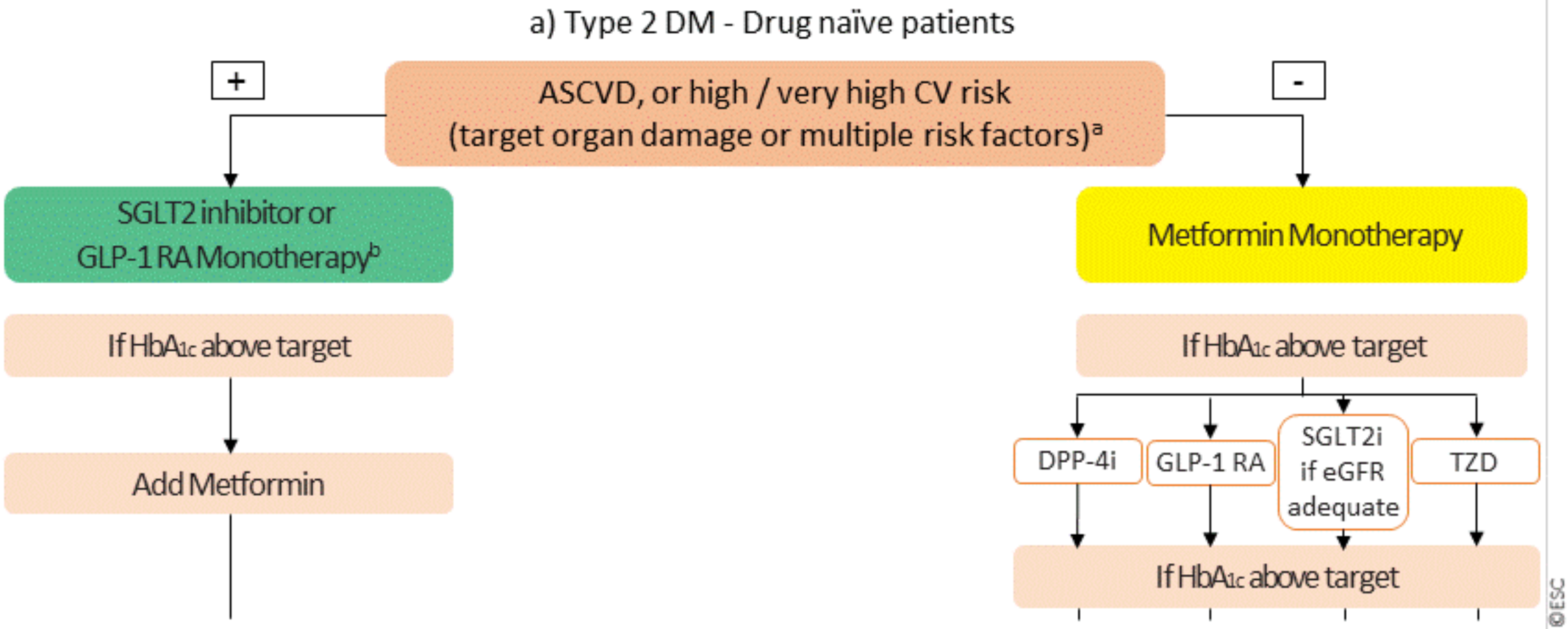
American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes- 2020. Diabetes Care 2020;43(Suppl. 1):S98–S110

ADA/EASD T2DM Algorithm



American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes- 2020. Diabetes Care 2020;43(Suppl. 1):S98–S110

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - drug naïve (1)



ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Table of Contents

ASCVD Risk Factor Modifications Algorithm

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:**	Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

DOI 10.4158/CS-2017-0153

Principle 5

Weight loss as a primary therapeutic modality for treating both Diabetes and Obesity: a transformation in care enabled by new tools

What if there was a treatment for T2D that:

1 Reduc…edications

2

3

4

5

6 …a

7

8

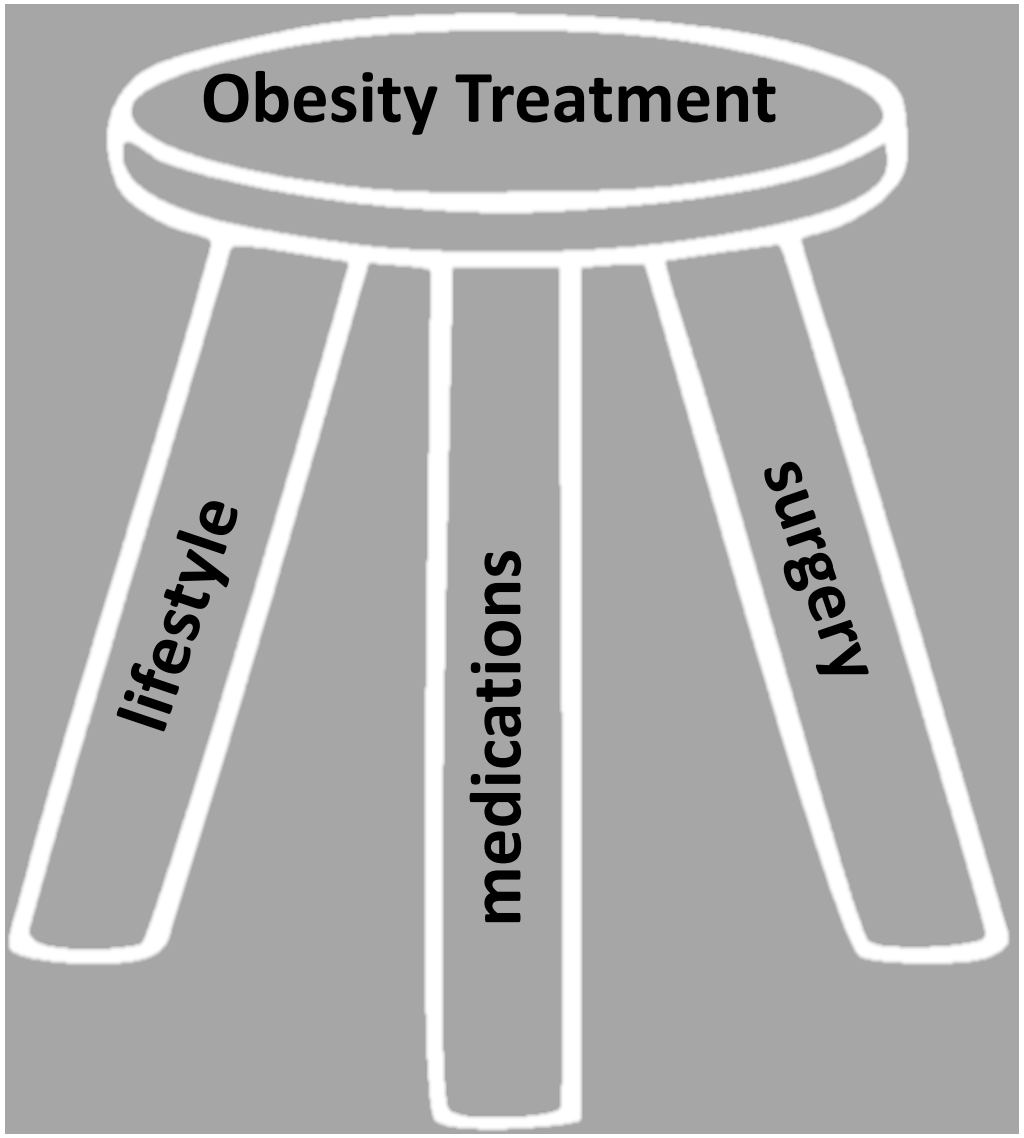
9

10 …can produce diabetes remission

This is the therapeutic profile of weight loss in T2D

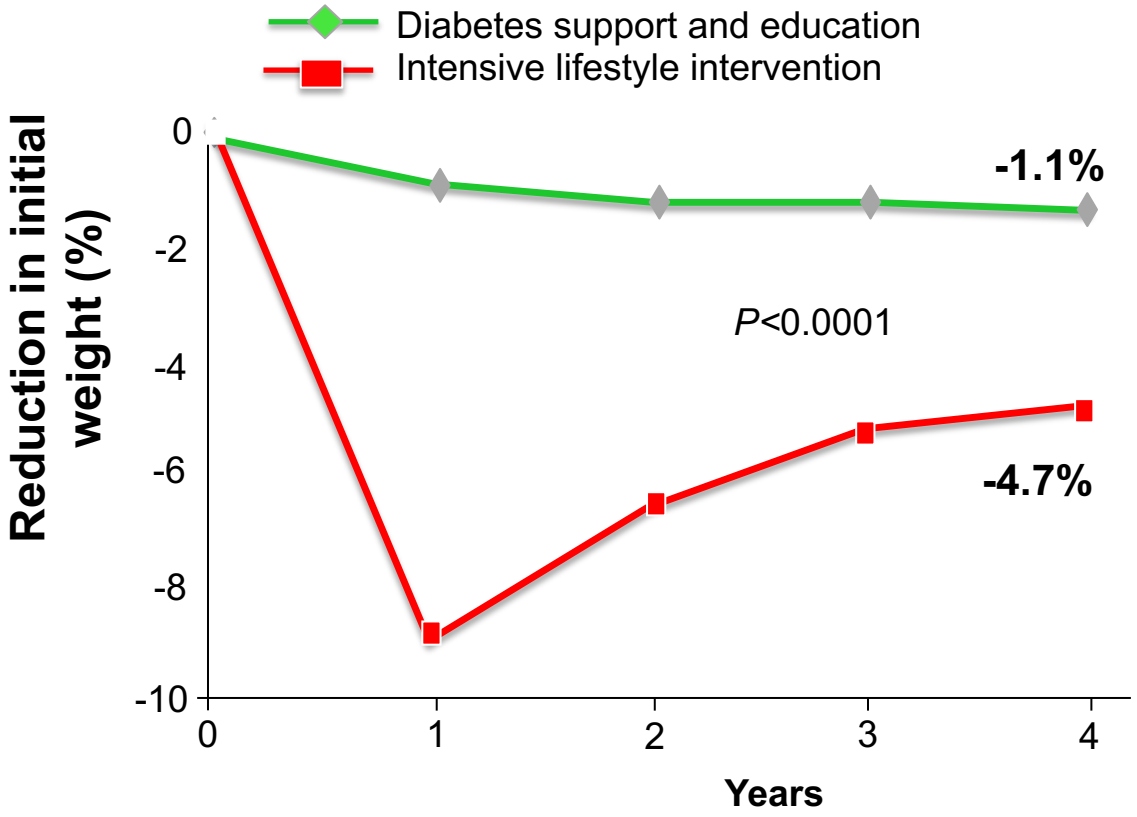
Look AHEAD study references. Phase 3 trials for weight loss meds
1. Look Ahead Research Group. *Diabetes Care* 2007;30:1374–83; 2. Look Ahead Research Group. *N Engl J Med* 2013;369:145–54;
3. Lean M et al. *Lancet* 2018;391:541–51; 4. Davies MJ *et al. JAMA* 2015;314:687–99

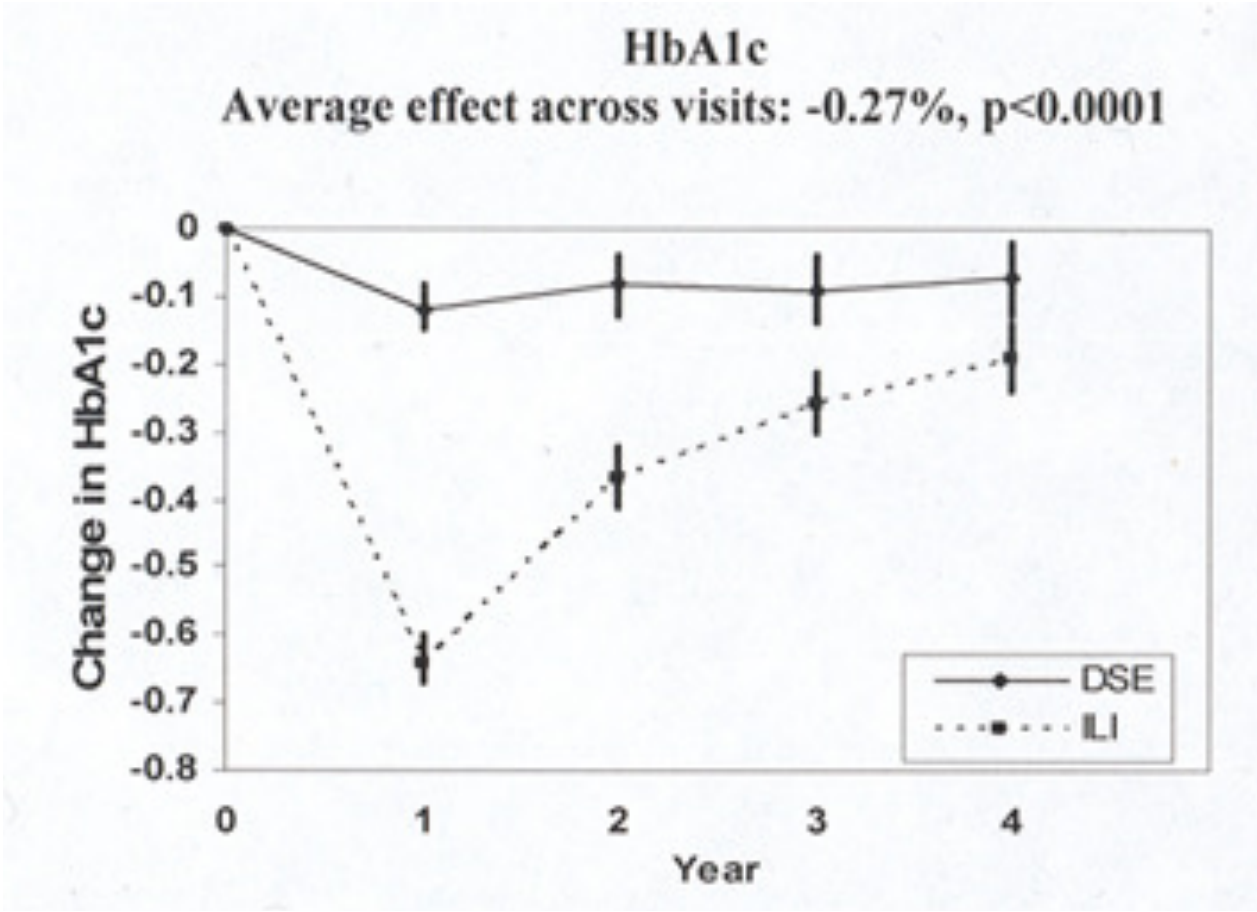
Treatment Modalities for ABCD Patients



Intensive Intervention in T2DM: Weight Regain over 4 Years in Look AHEAD

Look AHEAD Trial (N=5145)





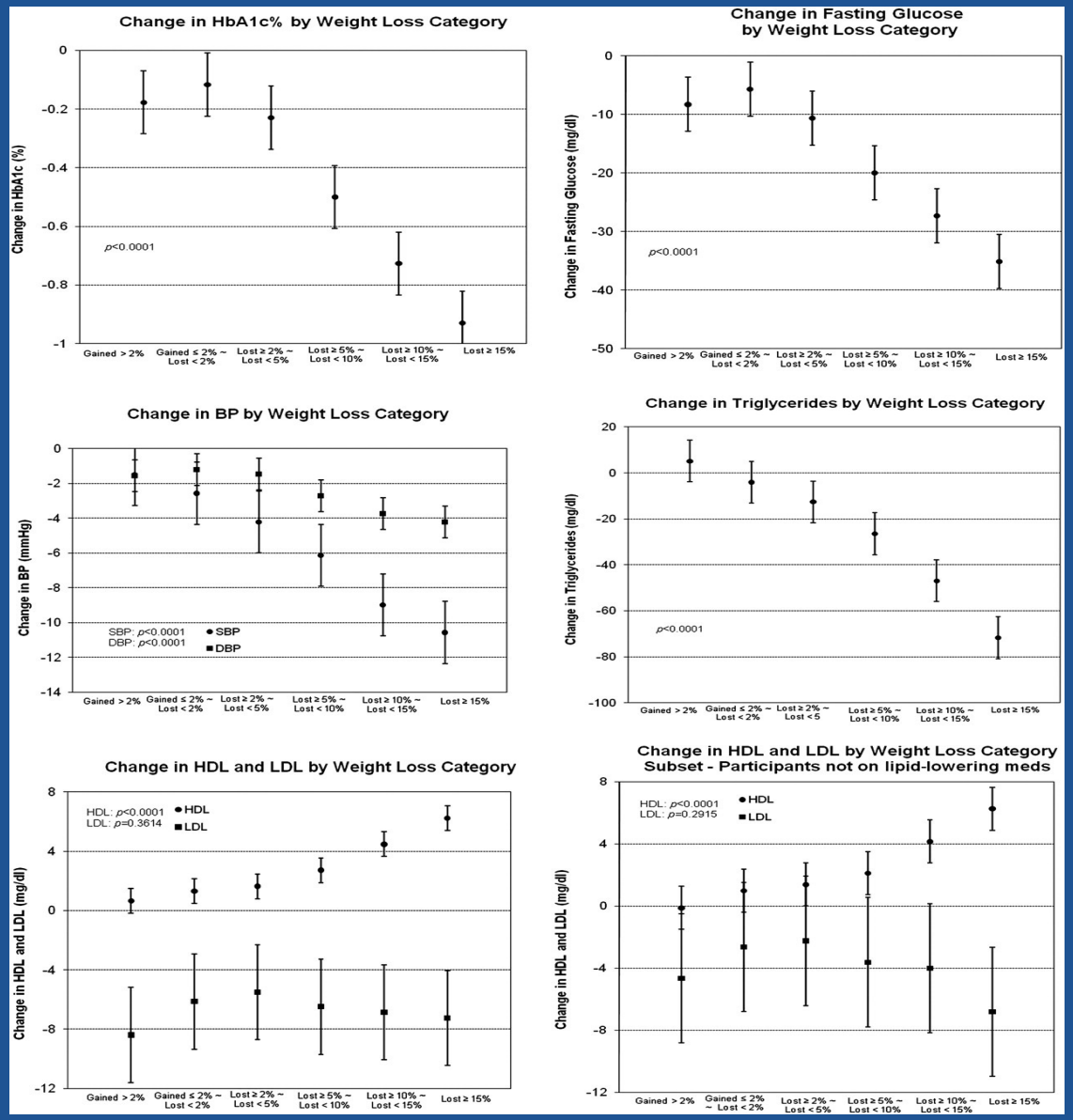
The Look AHEAD Research Group. Long Term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes: Four Year Results of the Look AHEAD Trial. Arch Intern Med. 2010 Sep 27; 170(17): 1566–1575.

Change in risk factors by weight loss categories for the Look AHEAD cohort.

HbA1c (Δ%)

DBP and SBP (Δ mmHg)

HDL and LDL (Δ mg/dl)



Fasting Glucose (Δ mg/dl)

Triglycerides (Δ mg/dl)

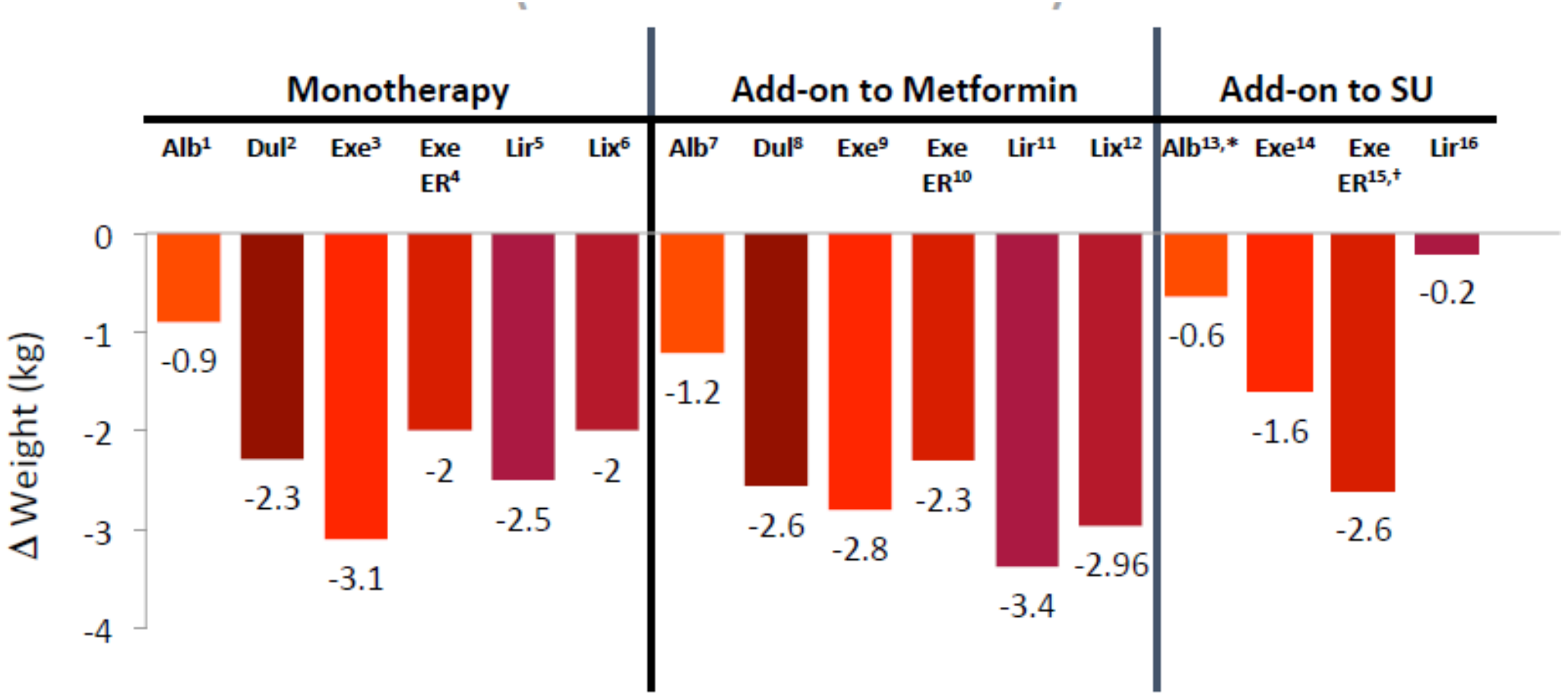
HDL and LDL no lipid meds (Δ mg/dl)

Weight Loss Categories
+>2%
+2% to -2%
-2% to -5%
-5% to -10%
-10% to -15%
->15%

Wing R R et al. Diabetes Care 2011;34:1481-1486

Effects of GLP-1 Agonists on Weight in T2DM

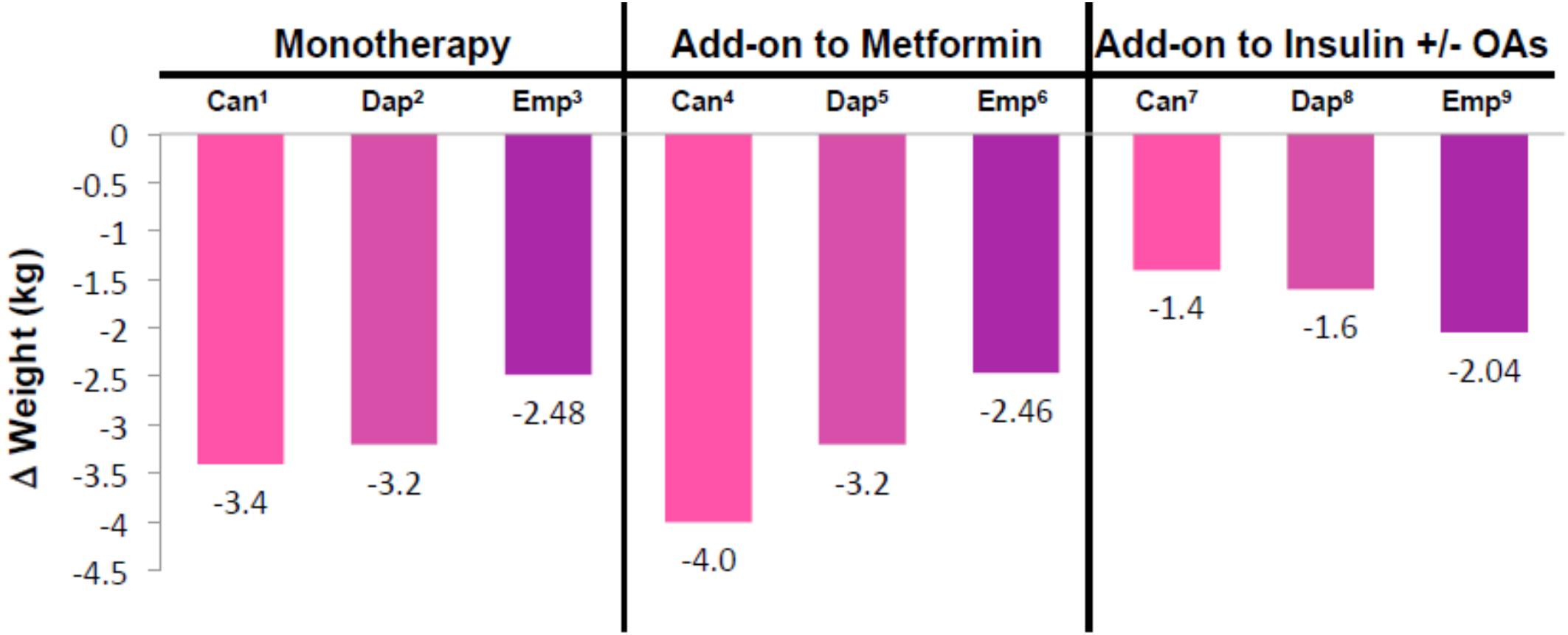
Absolute change from baseline; No head-to-head comparisons



1. Tanzeum (albiglutide) injection prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2014.
2. Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176. 3. Moretto TJ, et al. *Clin Ther*. 2008;30:1448-1460. 4. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258. 5. Garber A, et al. *Lancet*. 2009;373:473-481. 6. Fonseca VA, et al. *Diabetes Care*. 2012;35:1225-1231. 7. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 8. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 9. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 10. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 11. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 12. Rosenstock J, et al. *Diabetes Care*. 2013;36:2945-2951. 13. Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2014;2:289-297. 14. Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635. 15. Diamant M, et al. *Lancet*. 2010;375:2234-2243. 16. Marre M, et al. *Diabet Med*. 2009;26:268-278.

Effects of SGLT2 Inhibitors on Body Weight in T2DM

Absolute change from baseline in kg; No head-to-head comparisons



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 Loss Required to Ameliorate ABCD/Obesity Complications

COMPLICATION	% Weight Loss	Notes	References
Diabetes Prevention	7% to 10%	Maximum benefit 10%	DPP (Knowler et al, Lancet 2009) SEQUEL (Garvey et al, Diab Care 2013)
Hypertension	5% to >15%	BP still decreasing >15% in T2D	Look AHEAD (Wing et al, Diab Care 2011)
Dyslipidemia	5% to >15%	TG still decreasing at >15% in T2D	Look AHEAD (Wing et al, Diab Care 2011)
HbA1c	5% to >15%	HbA1c still decreasing at >15% in T2D	Look AHEAD (Wing et al, Diab Care 2011)
CVD and Mortality	>10-15%	Based on bariatric surgery literature and sub-analysis of Look AHEAD trial	Adams et al, NEJM 2007; Arterburn et al, JAMA 2015; Benotti et al, JAHA 2017; Kwok et al, Internat J Cardiol 2014; Look AHEAD, Lancet Diabet Endocrinol 2016
NAFLD	>10%	Improves steatosis, inflammation, fibrosis	Assy et al, Gut 2007; Pomrat et al, Hepatol 2010; Liu et al, Obes Surg 2007; Barker et al, Am J Gartroenterol 2006
Sleep Apnea (AHI)	≥10%	Little or no benefit at ≤ 5%	Sleep AHEAD (Foster et al, Arch Int Med 2009); Winslow et al, Sleep 2012
Osteoarthritis	5-10%	Improves symptoms and joint stress mechanics	Christensen et al, Ann Rheum Dis 2007; Felson et al, Ann Int Med 1992; Aaboe et al, Osteoarthritis Cartilage 2011

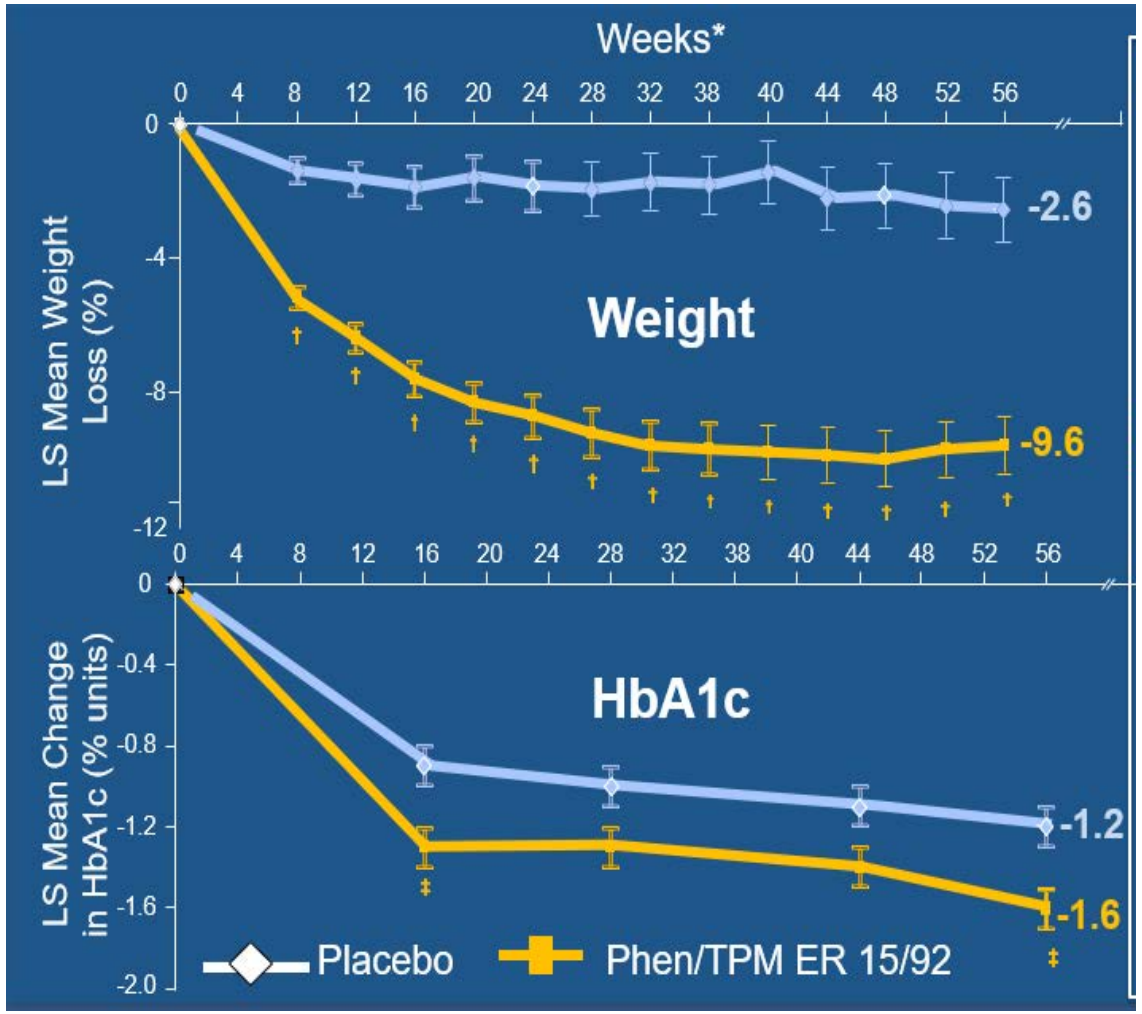
DPP=Diabetes Prevention Program; NAFLD= non-alcoholic fatty liver disease; AHI=apnea hypopnea index; BP=blood pressure; TG=triglycerides

Obesity Pharmacotherapy

Agents	Action	Approval
Previously available		
Phentermine	• Sympathomimetic	• 1959
Orlistat	• GI lipase inhibitor	• 1997
Recently Approved		
Phentermine/ Topiramate ER	• Sympathomimetic/Anticonvulsant (GABA receptor modulation?)	• Approved, Summer 2012
Naltrexone ER/ Bupropion ER	• Dopamine/noradrenaline reuptake inhibitor/Opioid receptor antagonist	• Approved, September 2014
Liraglutide 3 mg	• GLP-1 receptor agonist	• Approved, December 2014
Semaglutide 2.4 mg/week	• GLP-1 receptor agonist	• Approved, June, 2021
Tirzepatide 15 mg/week	• GLP-1 / GIP receptor dual agonist	• Approved, May, 2022 for T2D

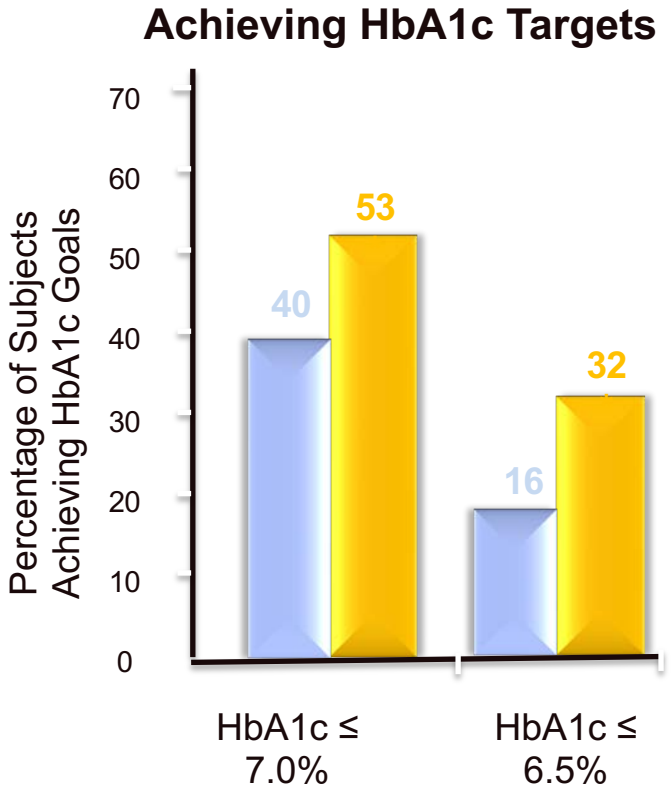
Treatment of Obesity with Phentermine/Topiramate ER in T2DM

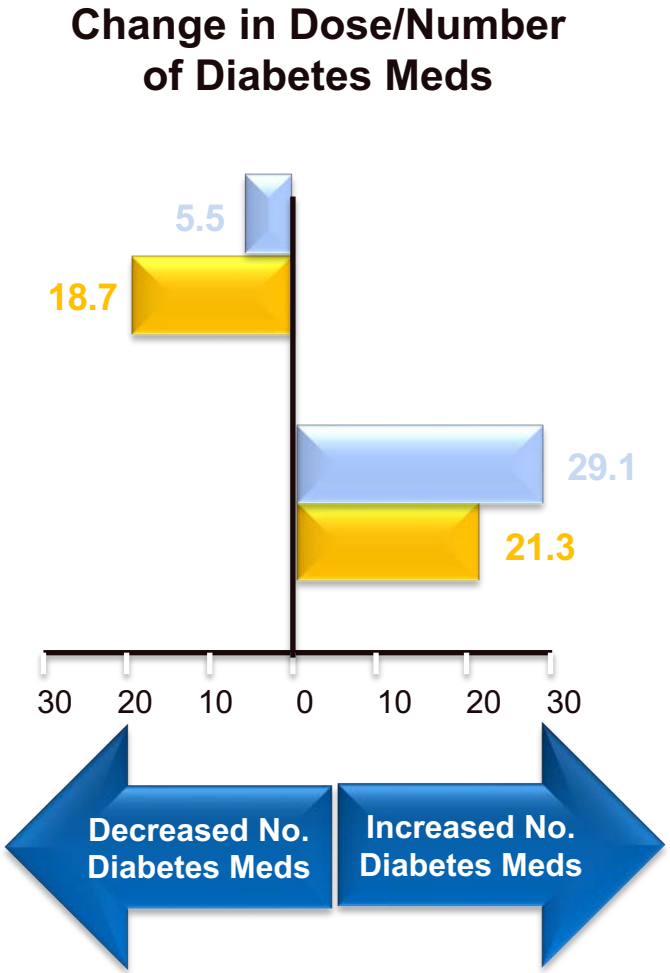
Garvey WT, et al. Diabetes Care 2014; 37(12):3309-3316



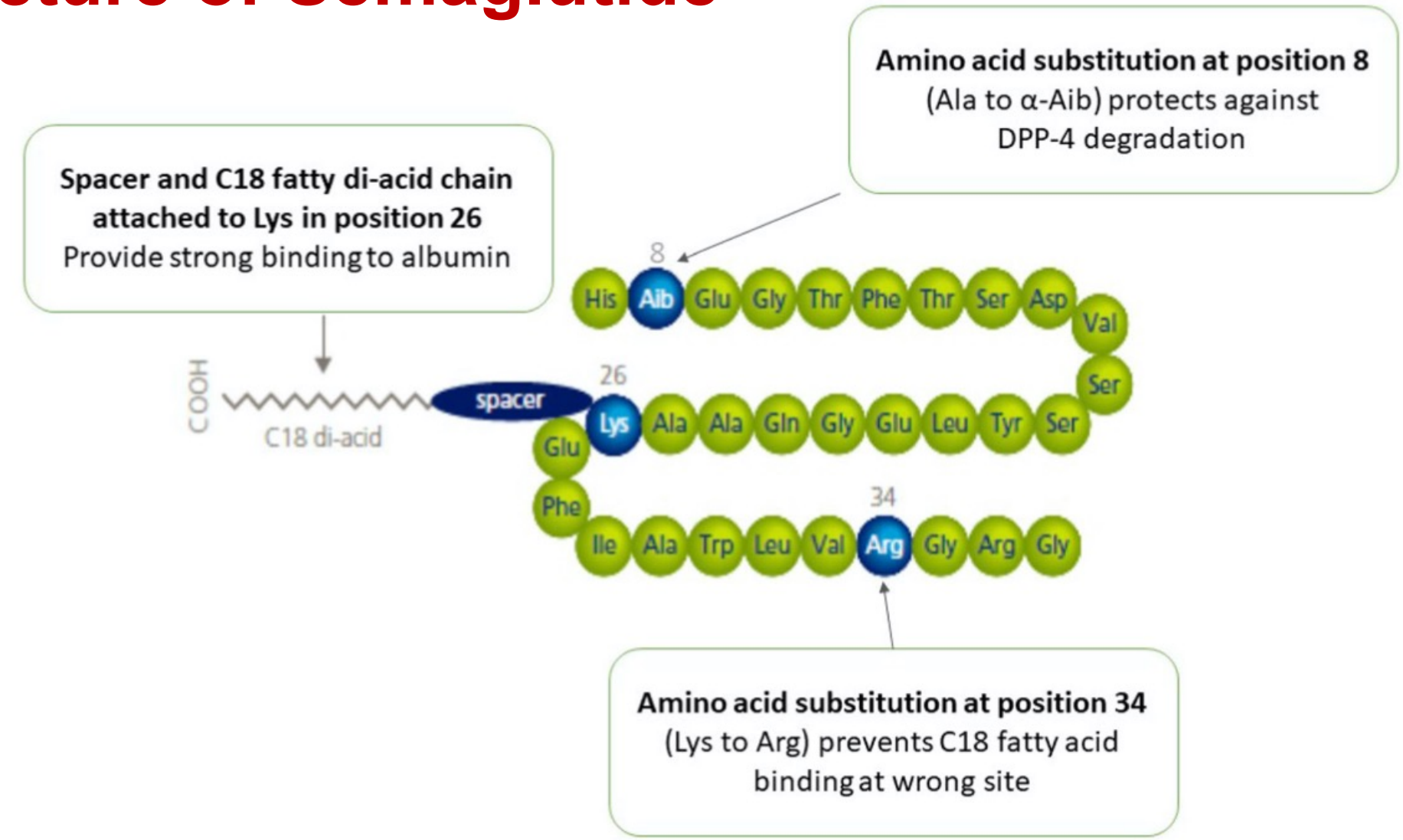
Placebo (n=55)

PHEN/TPM ER 15/92 (n=75)





Structure of Semaglutide



Kalra S, Sahay R. A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Ther. July 28, 2020. https://doi.org/10.1007/s13300-020-00894-y

Completed trials in the phase 3 STEP program

STEP 1	STEP 2	STEP 3	STEP 4
Weight management	**Weight management in T2D**	**Weight management with IBT**	**Sustained weight management**
Overweight or obesity without T2D	Overweight or obesity with T2D	Overweight or obesity without T2D	Overweight or obesity without T2D
68-week trial plus ongoing extension	68-week trial	68-week trial	68-week trial
Semaglutide 2.4 mg vs placebo	Semaglutide 2.4 mg vs placebo and vs semaglutide 1.0 mg	Semaglutide 2.4 mg vs placebo, both with IBT (diet*, increased physical activity, and counseling sessions)	20-week semaglutide run-in for all, then continued semaglutide 2.4 mg vs switch to placebo

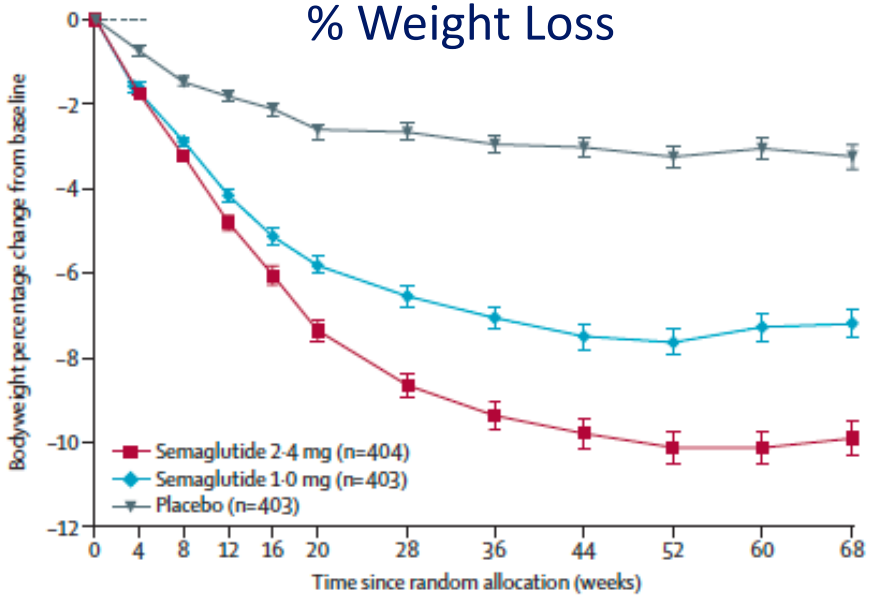
In STEP 1, 3, and 4, participants were required to have a baseline BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity (not T2D), or a baseline BMI ≥30 kg/m^2. In STEP 2, participants were required to have a baseline BMI ≥27 kg/m^2 and T2D. All treatment was given subcutaneously once weekly as adjunct to lifestyle intervention.
*A low-calorie, meal-replacement diet for the first 8 weeks, followed by a reduced calorie diet for the rest of the trial.
BMI, body mass index; IBT, intensive behavioral therapy; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes.

NEJM, 2021; 384(11):989
Lancet, 2021; 397(10278):971-984
JAMA, 2021; 325(14):1403-1413
JAMA, 2021; 32(14)1414-1425

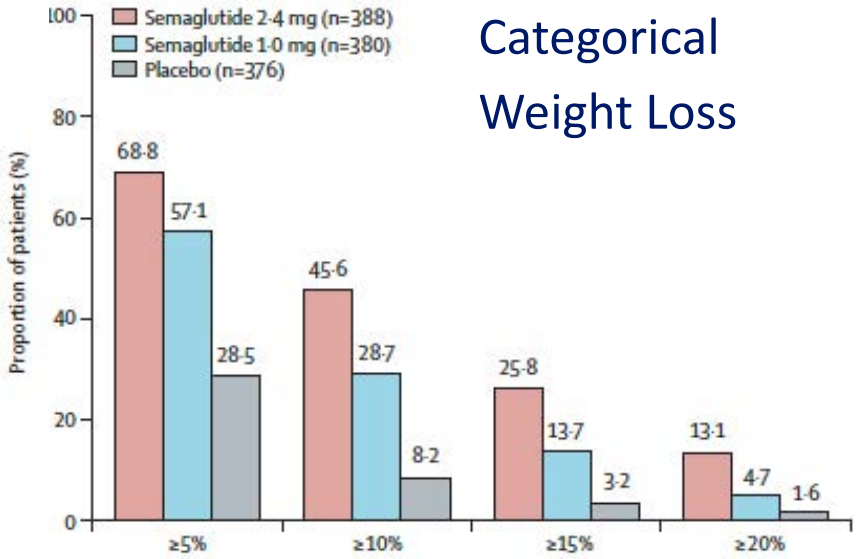
STEP 2 Trial: Once Weekly Semaglutide Reduces Weight and HbA1c in T2D

Semaglutide 2·4 mg (n=388)
Semaglutide 1·0 mg (n=380)
Placebo (n=376)

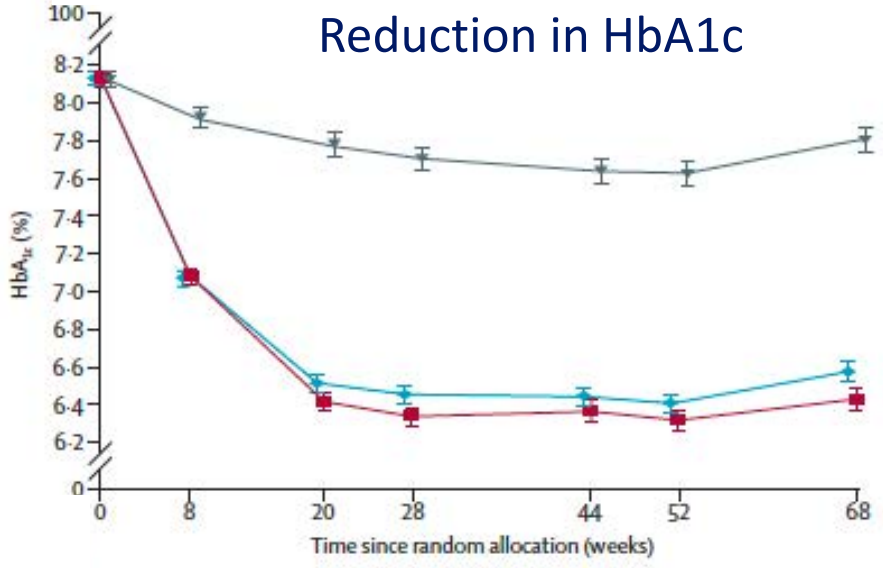
% Weight Loss



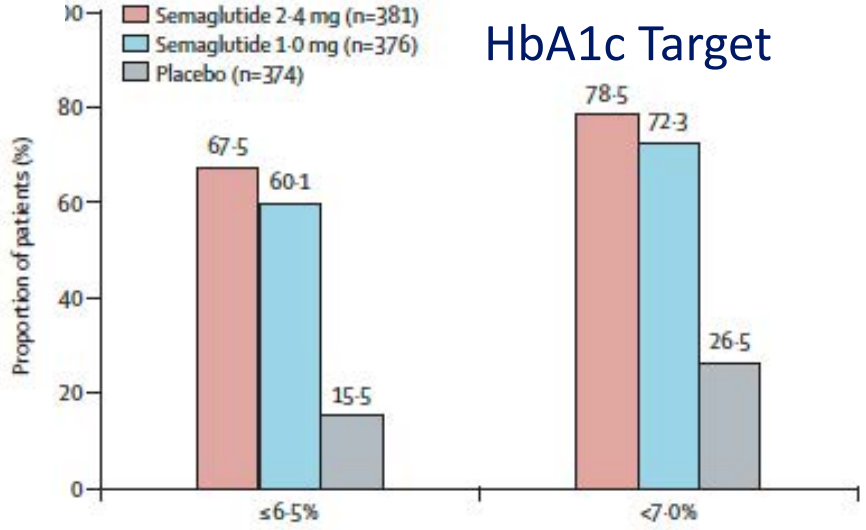
Categorical Weight Loss



Reduction in HbA1c



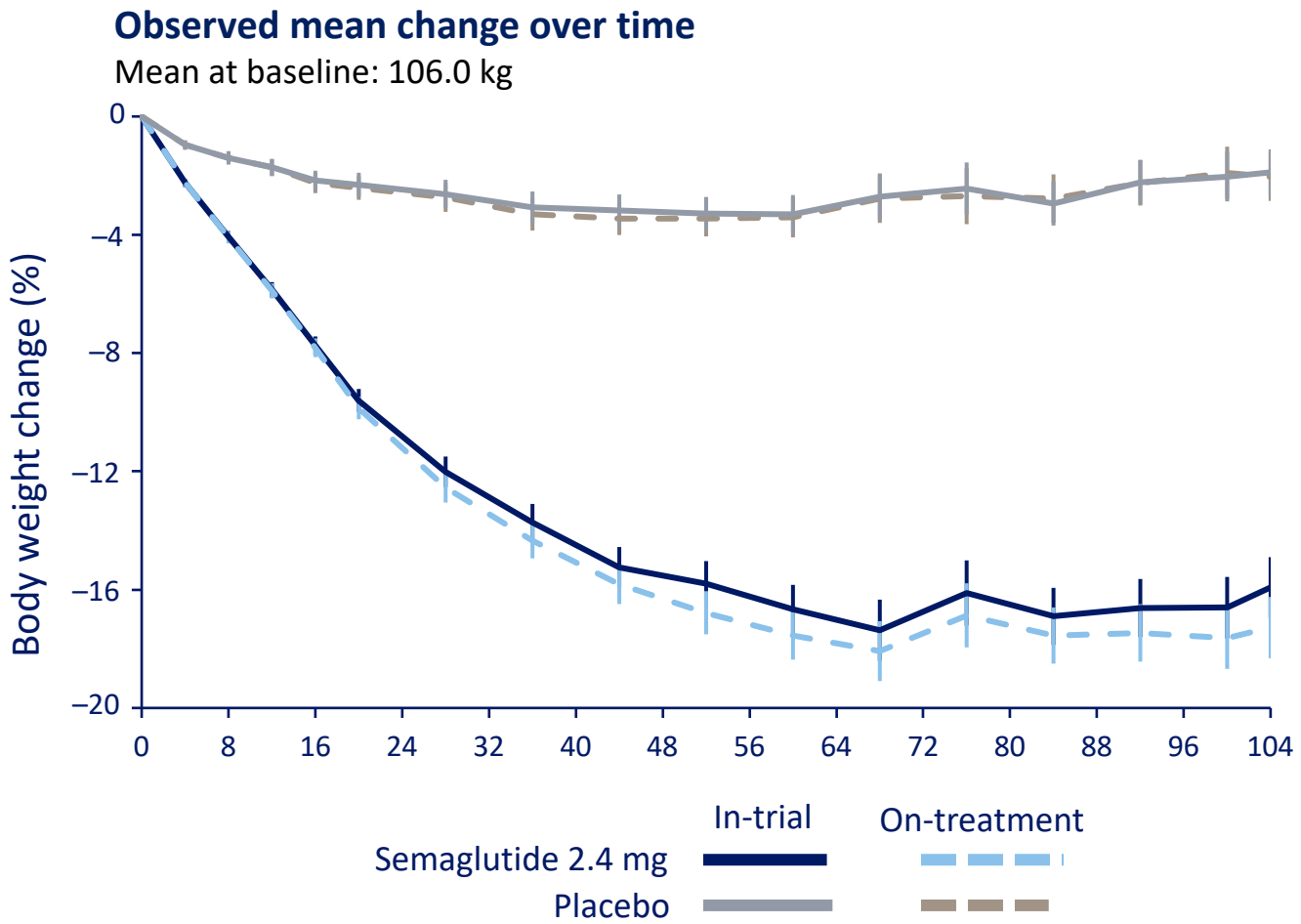
% Reaching HbA1c Target

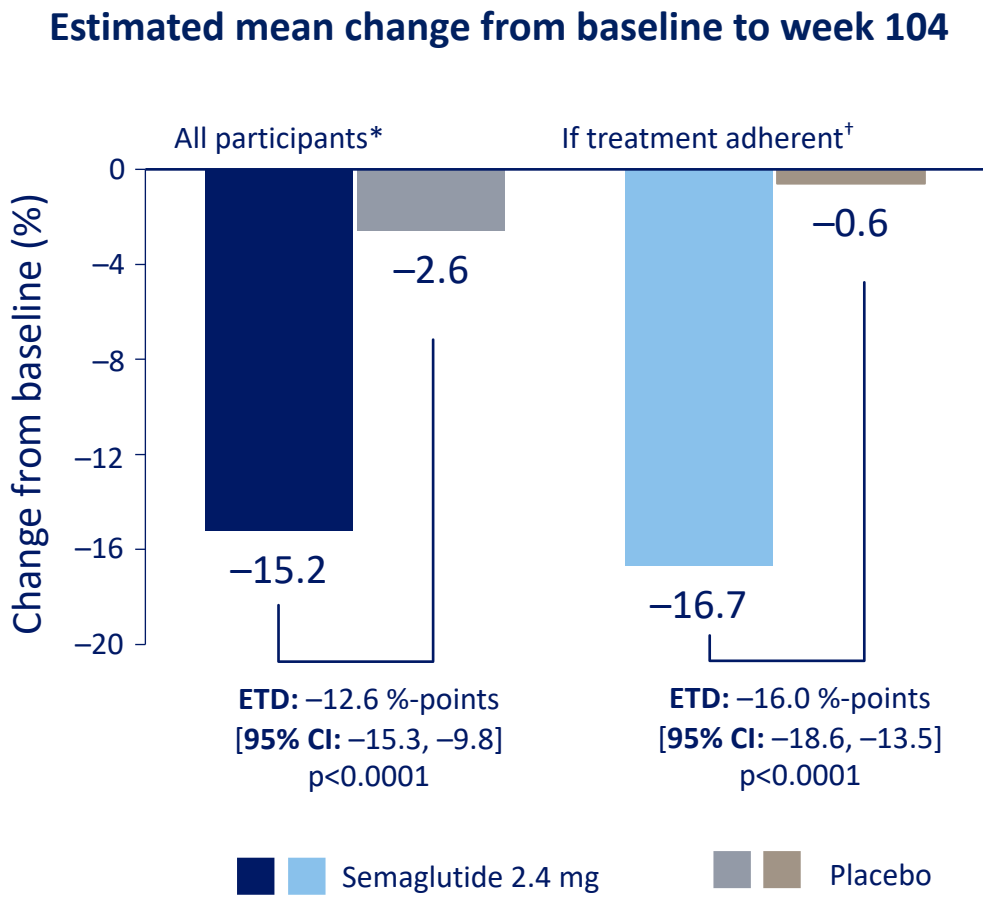


Davies M et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity and Type 2 Diabetes. Lancet 397:971, 2021

Two Year Efficacy of Semaglutide 2.4 mg in the STEP 5 Trial:

Change in body weight over 2 years (%)



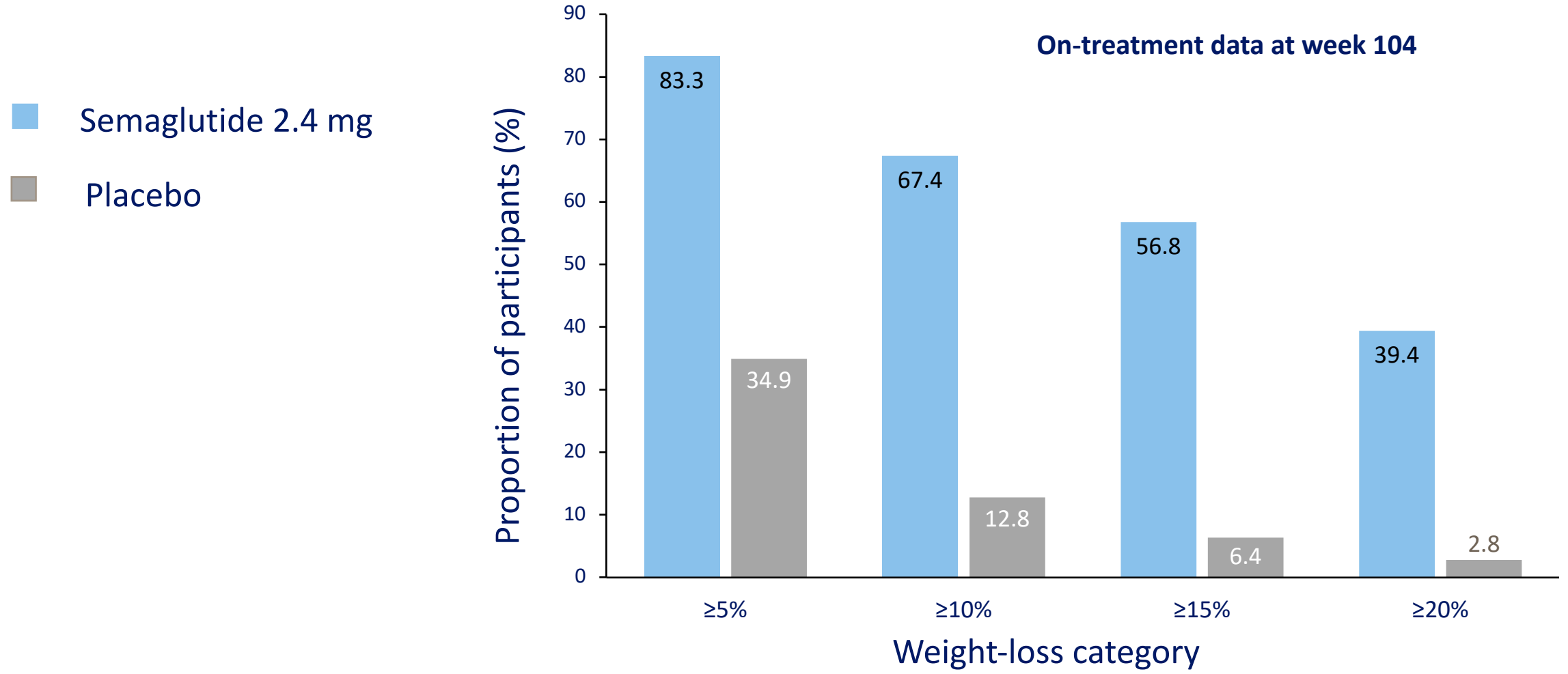


**Treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention); †Trial product estimand (assesses treatment effect if trial product was taken as intended). CI, confidence interval; ETD, estimated treatment difference.*

Garvey WT, et al. Two-year effect of semaglutide 2.4 mg vs placebo in adults with overweight or obesity (STEP 5). 39th Annual Meeting (virtual) of ObesityWeek 2021, November 1-5, 2021.

Two Year Efficacy of Semaglutide 2.4 mg in the STEP 5 Trial:

Categorical Weight Loss (%)



Garvey WT, et al. Two-year effect of semaglutide 2.4 mg vs placebo in adults with overweight or obesity (STEP 5). 39th Annual Meeting (virtual) of ObesityWeek 2021, November 1-5, 2021.

Rationale for Unimolecular Multi Hormonal Agonists in Obesity

Glucagon-Like Peptide-1 (GLP-1)

1. Produces weight loss via CNS effects to suppress appetite
2. Augments insulin secretory responses for glycemic control

Glucagon

1. Counterintuitive since raises glucose, increases HGO, and is elevated in T2DM
2. Thermogenic and lipolytic

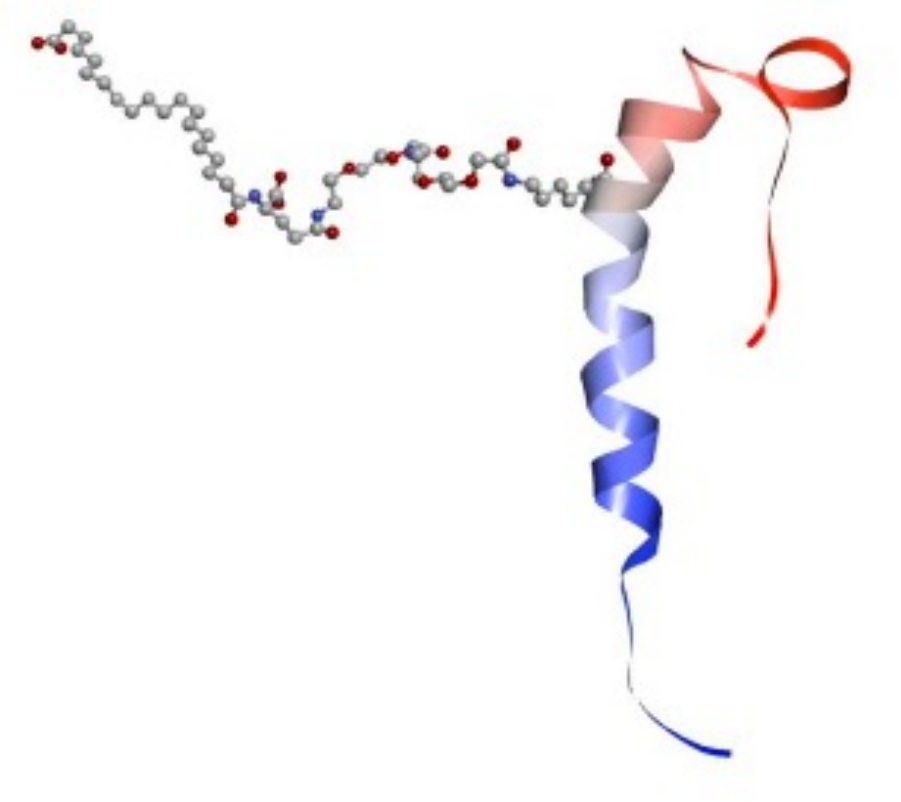
Gastric Inhibitory Peptide (GIP)

1. GIP agonism and antagonism both justified in literature.
2. Can amplify effects of GLP-1, and is insulinotropic
3. GIPR KO in rodents and blocking Ab in primates are protective against obesity

Garvey W.T, et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

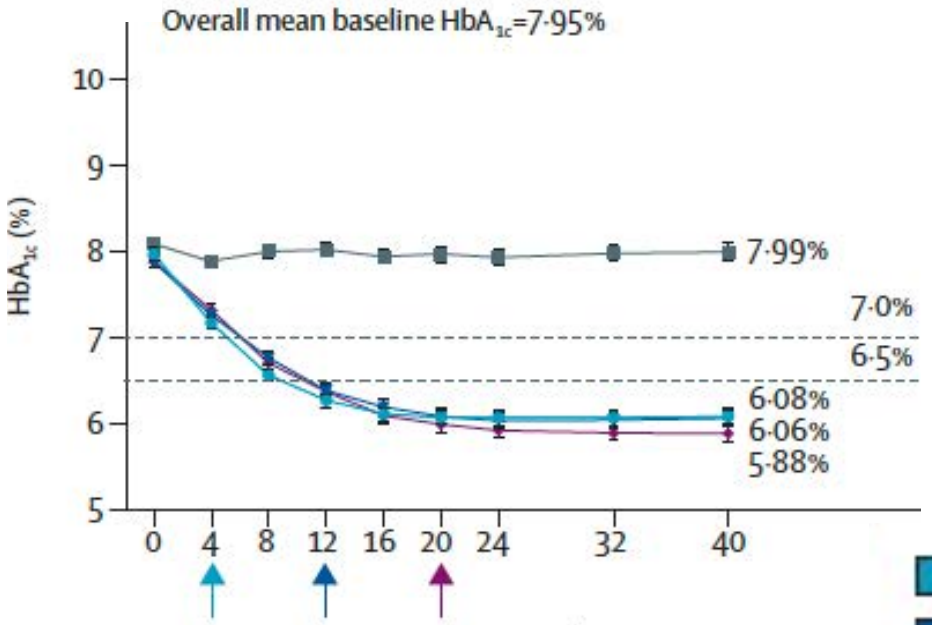
Tirzepatide: A New Medication Approved for T2D and in Development for Obesity

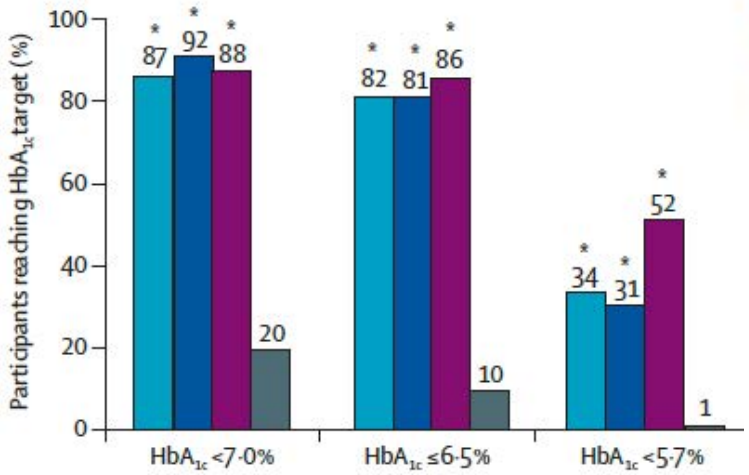
- 39 AA peptide engineered to bind to both GLP-1 and GIP receptors
- Includes a C20 fatty acid moiety that allows binding to albumin
- Mean half life of 5 days allows weekly subcutaneous dosing
- Plasma levels not affected by hepatic or renal impairment
- Increases insulin secretion and insulin sensitivity and produces weight loss



Tirzepatide (GLP-1/GIP Agonist) in Patients with T2D and Obesity: Surpass 1

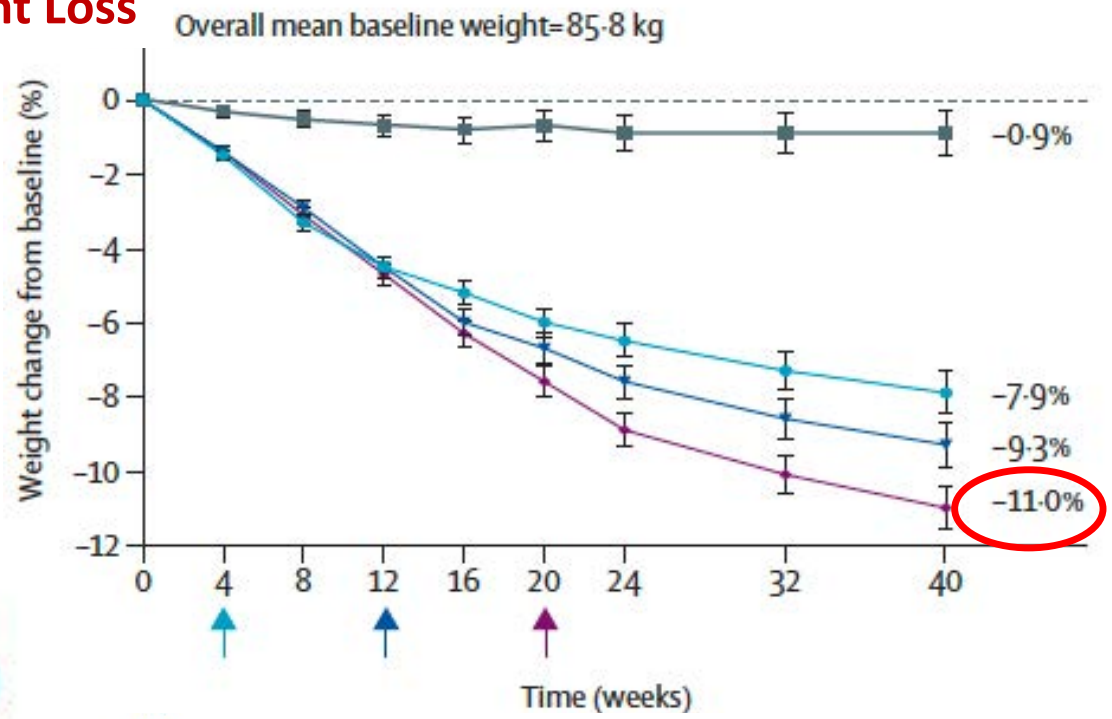
HbA1c

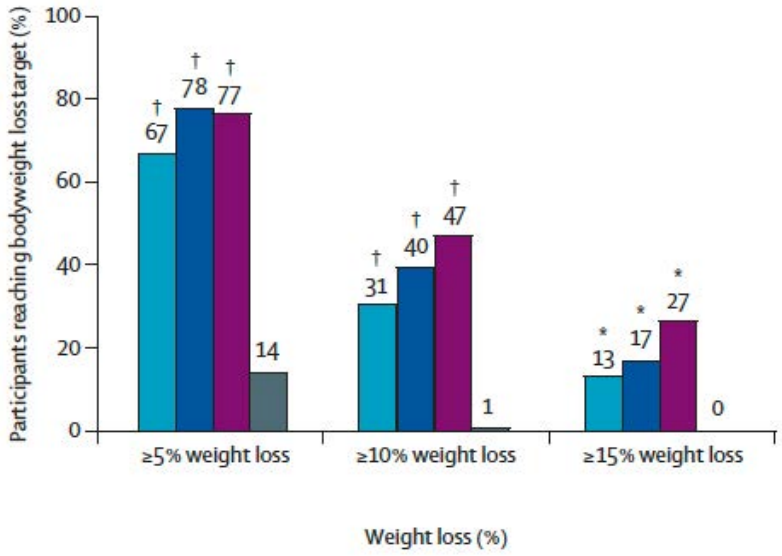




Tirzepatide 5mg
Tirzepatide 10mg
Tirzepatide 15mg
Placebo

% Weight Loss

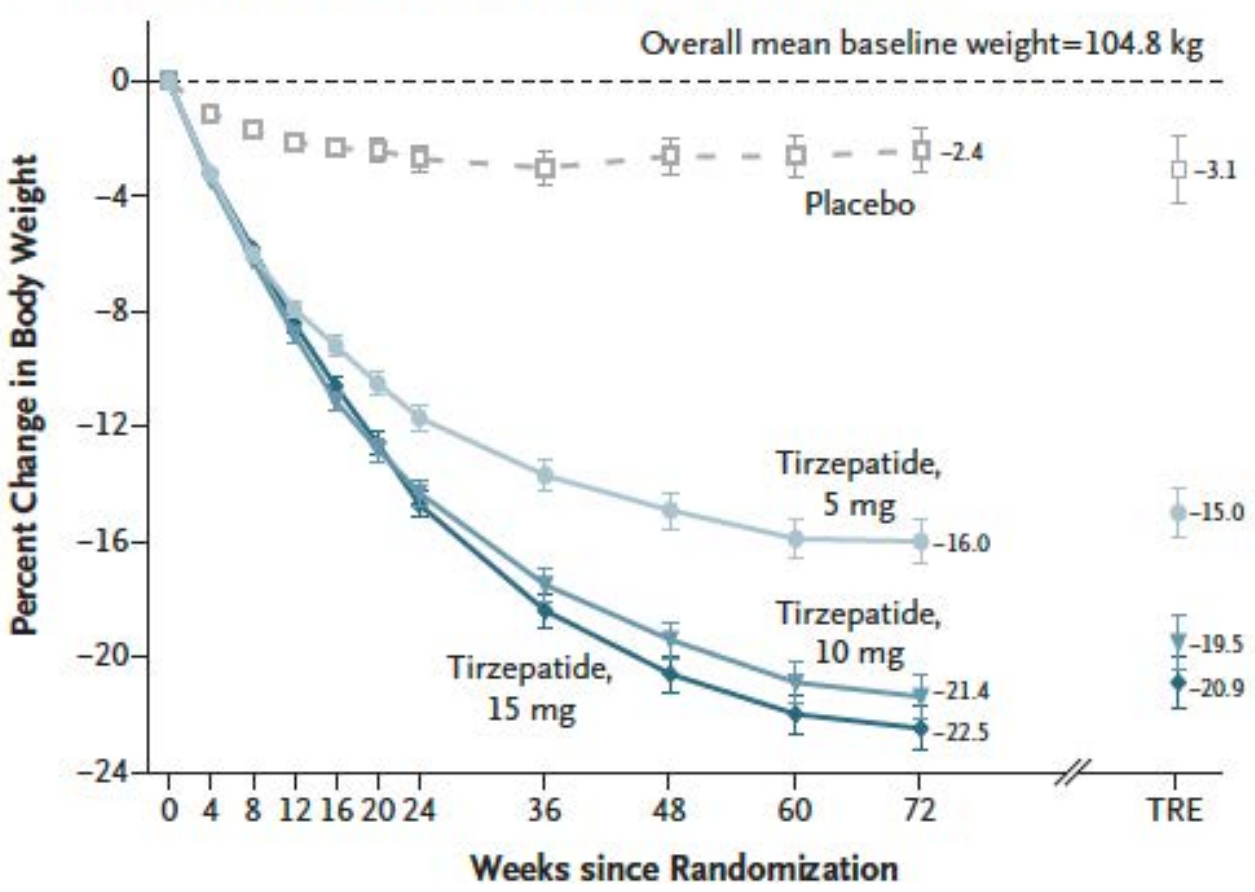




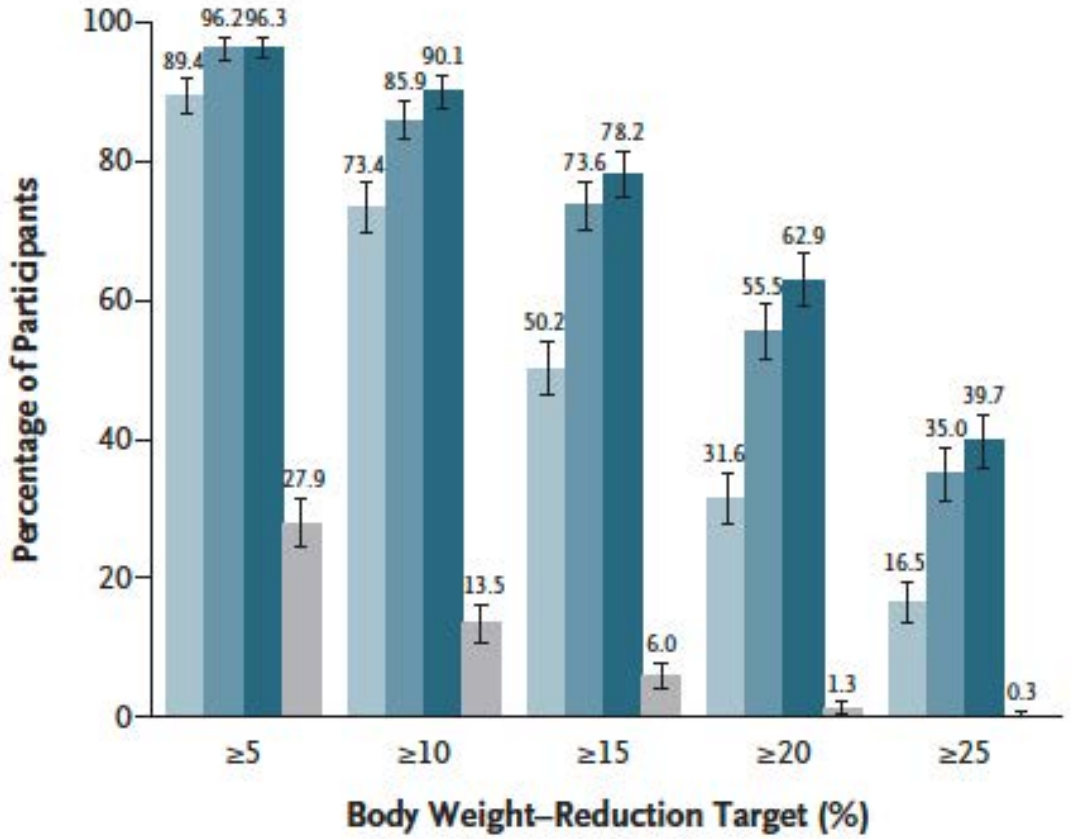
Rosenstock J, et al. Lancet. 2021 Jul 10;398(10295):143-155.

Tirzepatide (GLP-1/GIP Agonist) in Patients with Obesity: Surmount 1

% Change in Body Weight by Week (efficacy estimand)



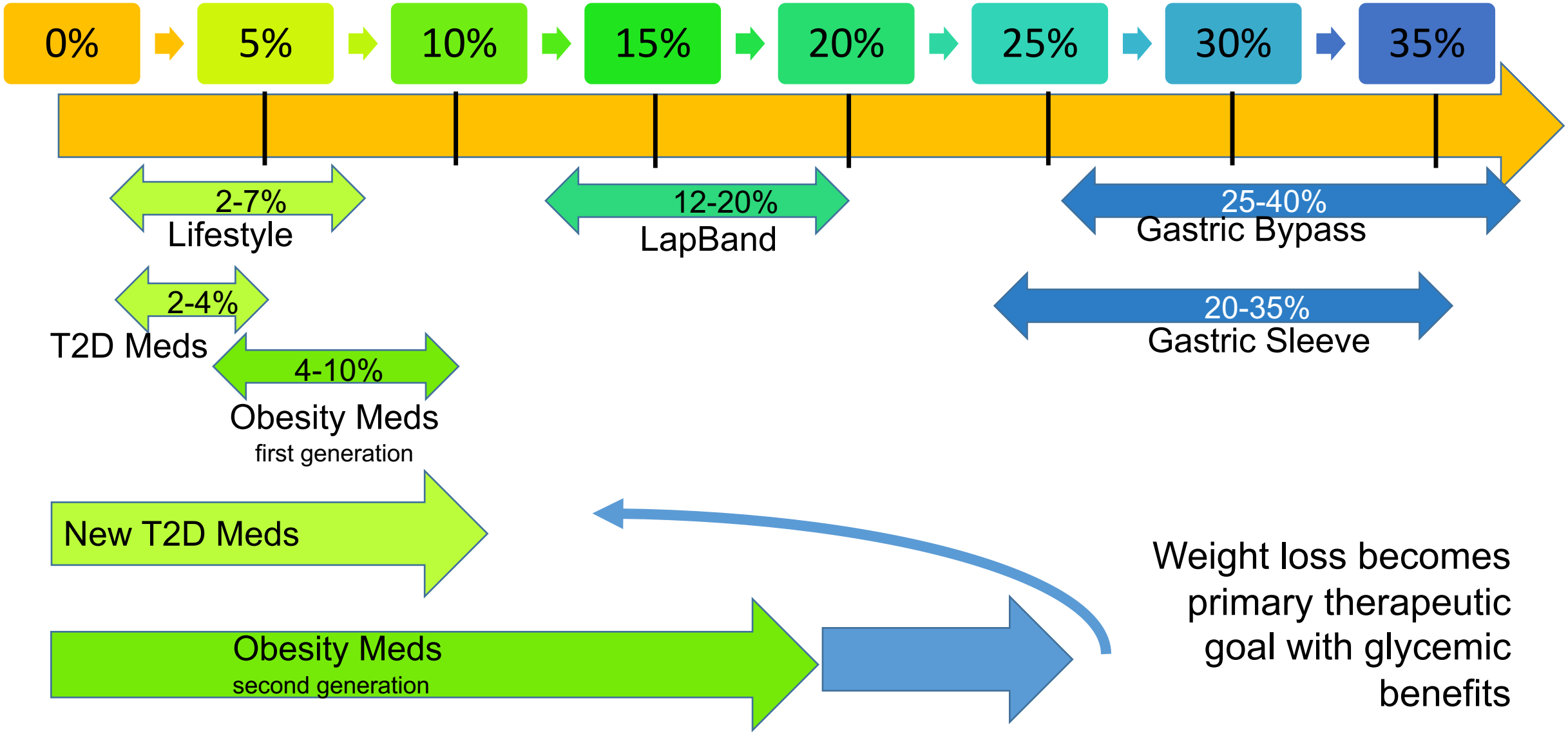
Categorical Weight Loss: % Meeting Weight Reduction Targets (efficacy estimand)



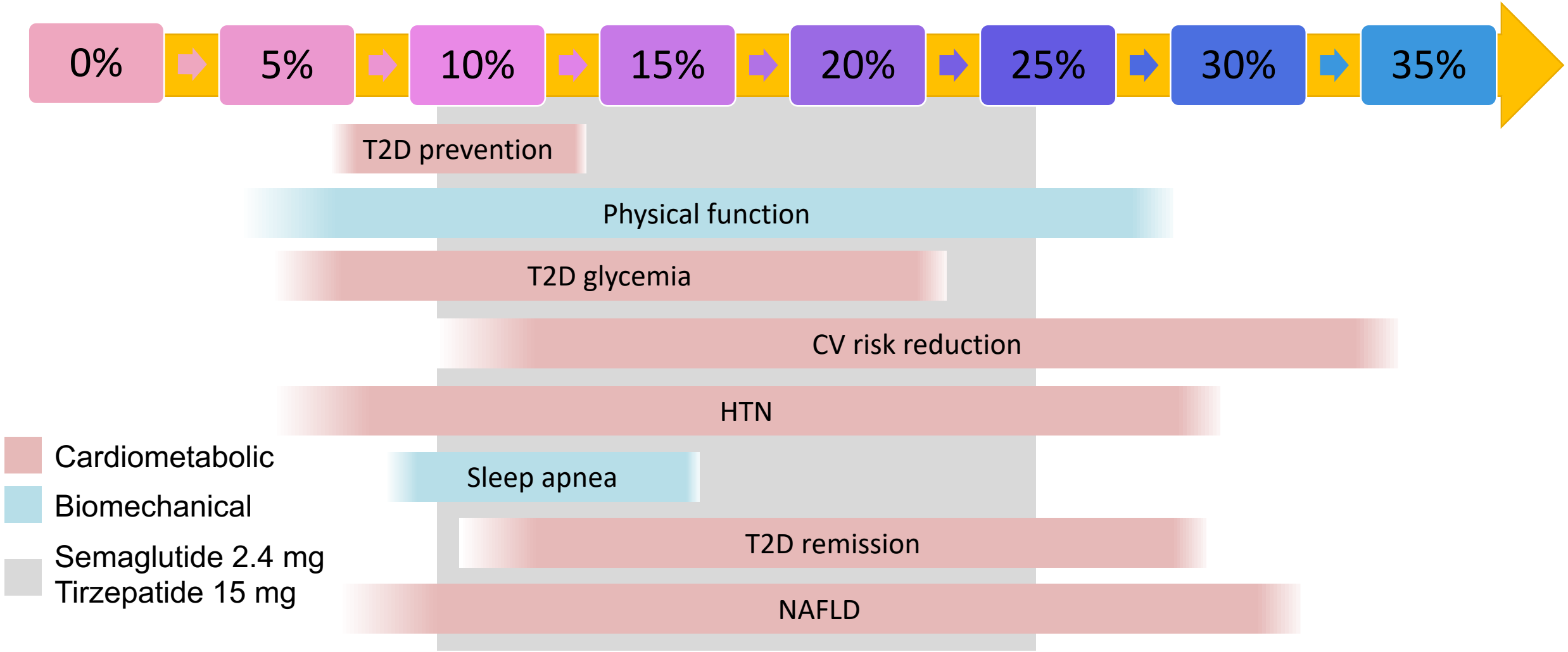
Tirzepatide, 5 mg Tirzepatide, 10 mg Tirzepatide, 15 mg Placebo

Jastreboff AM et al. N Engl J Med. 2022 Jun 4. doi: 10.1056/NEJMoa2206038. Epub ahead of print

Weight Loss Therapies: Range of Efficacy

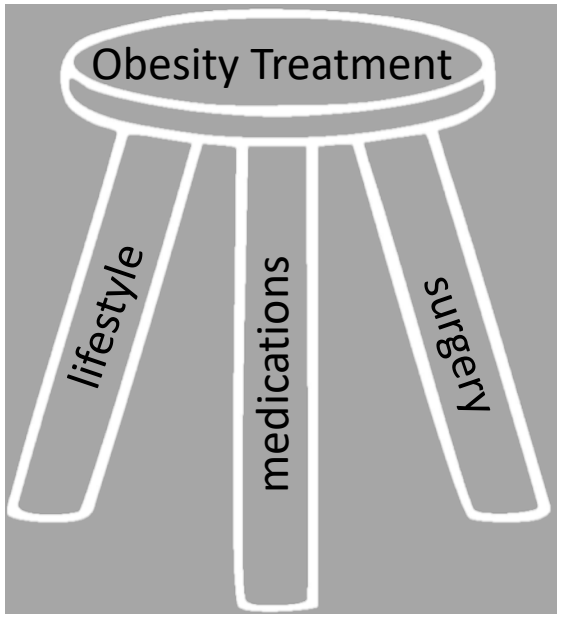


New medications: treating ABCD/Obesity to target



Garvey WT. New Horizons: A New Paradigm for Treating to Target with Second Generation Obesity Medications. JCEM. 2022 Mar 24;107(4):e1339-e1347

Evolution of Diabetes Therapy



If you want to help patients with T2DM and overweight/obesity -

Get Serious about Weight Loss Therapy

THANK YOU