

Update on Type 2 Diabetes: Nutrition and Pharmacology

*St. Vincent's Health System
October 29, 2020*

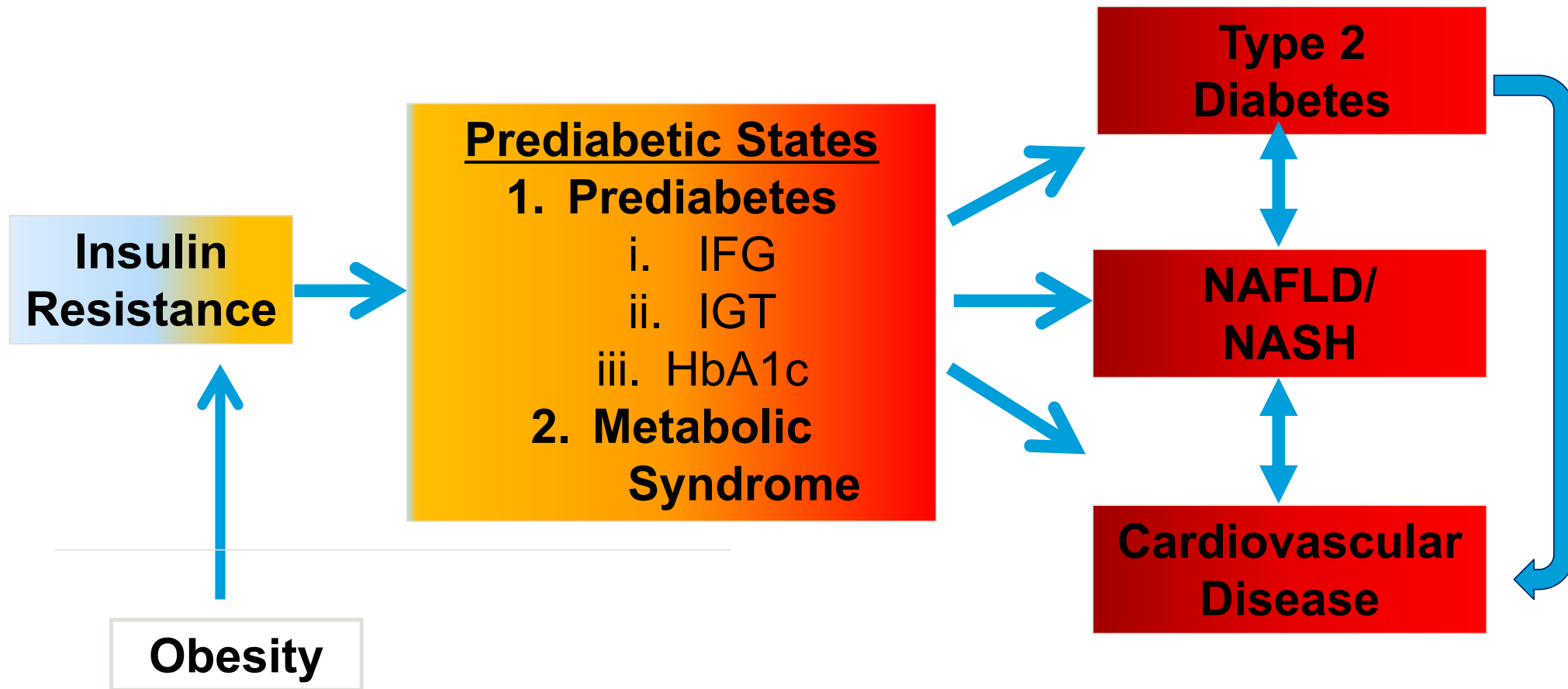
W. Timothy Garvey, MD

Butterworth Professor, Department of Nutrition Sciences
University of Alabama at Birmingham
Director, UAB Diabetes Research Center

Outline

1. Natural history of T2DM and treatment implications
2. Guiding principles of diabetes pharmacotherapy
3. Current diabetes medications and guidelines, with emphasis on GLP-1 agonists and SGLT2 inhibitors
4. Weight loss therapy for treatment and prevention
5. What lies ahead for the future?

The Spectrum of Cardiometabolic Disease

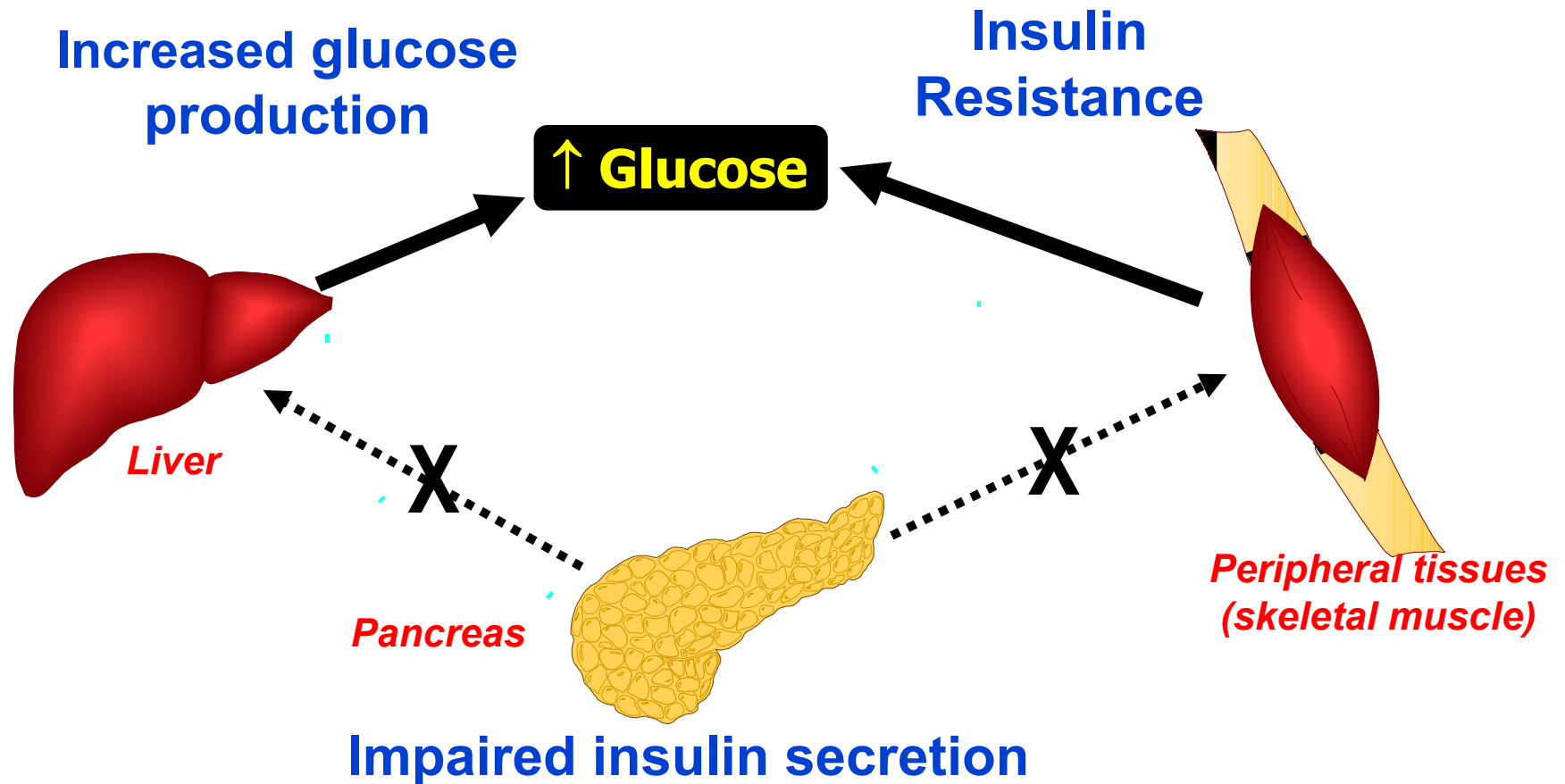


Three Points Based on Natural History of Cardiometabolic Disease

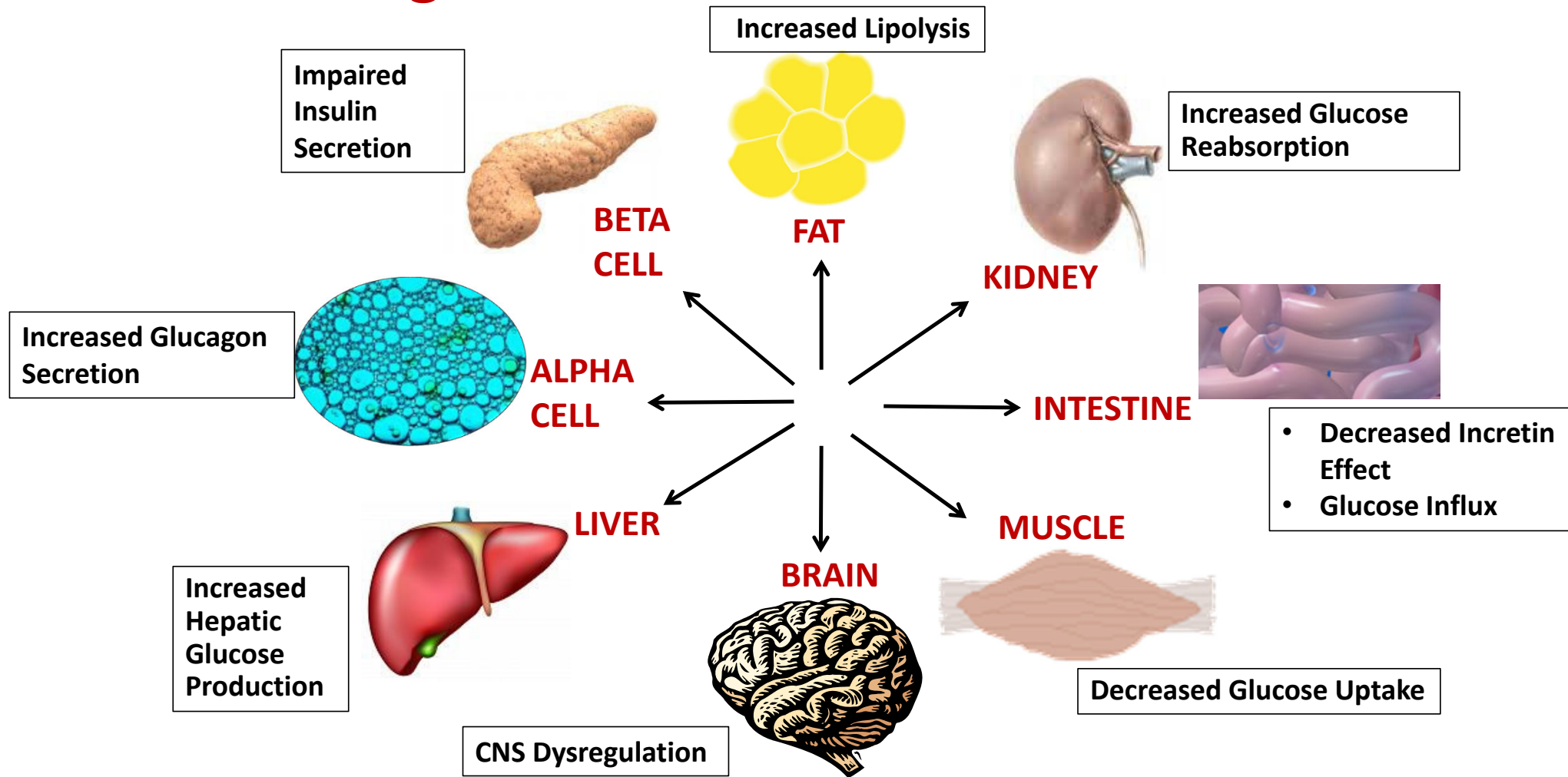
1. This is a chronic disease with T2DM as an end stage manifestation. Need to prevent disease progression in those patients with clinical signs of insulin resistance.
2. The care of patients with T2DM must be comprehensive and address CVD, myocardial dysfunction & CHF, NASH, CKD, as well as diabetes
3. In patients with overweight or obesity, weight loss therapy is a powerful approach for preventing disease progression and for treatment of T2DM

Causes of Hyperglycemia in Type 2 Diabetes

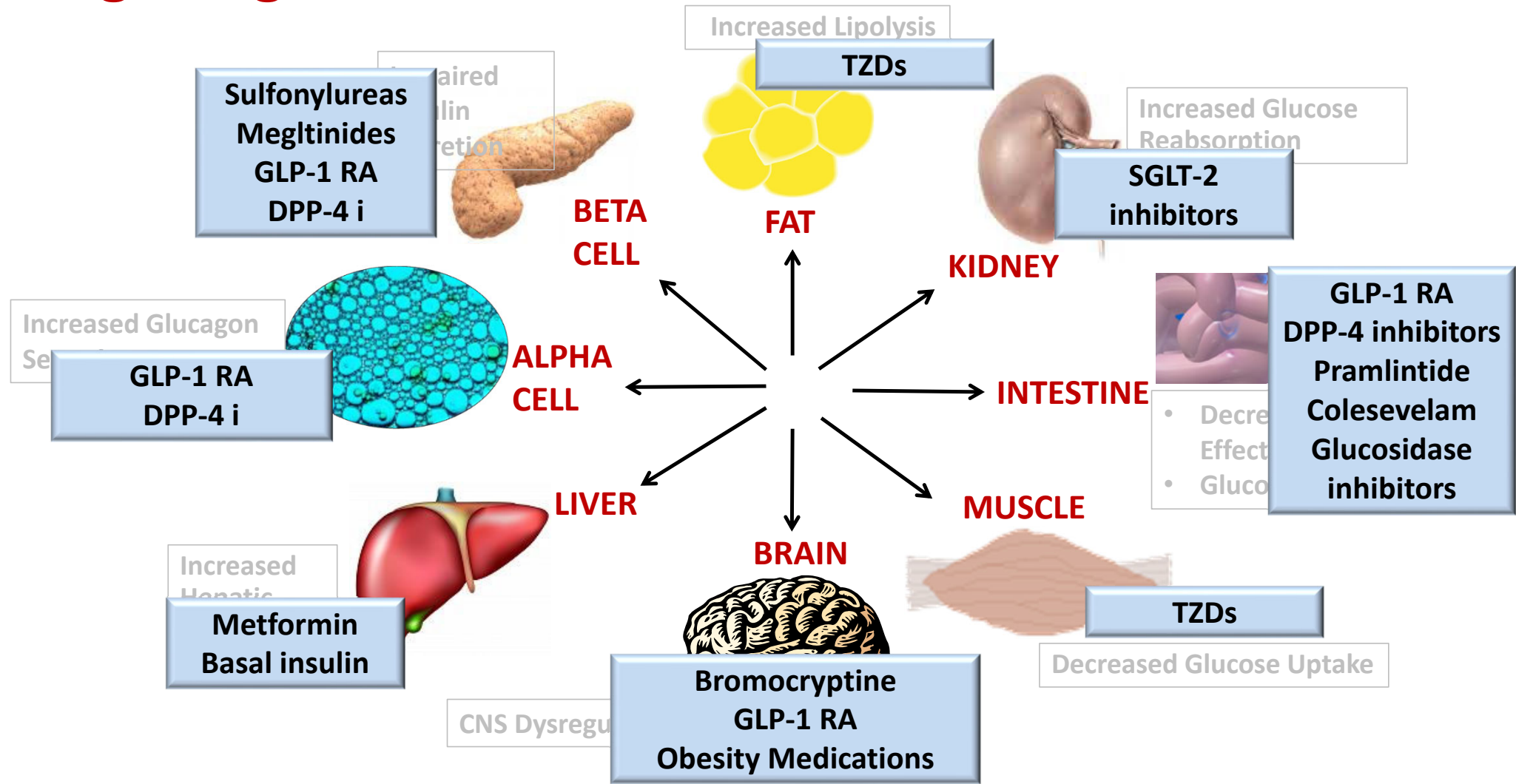
“the classic view”



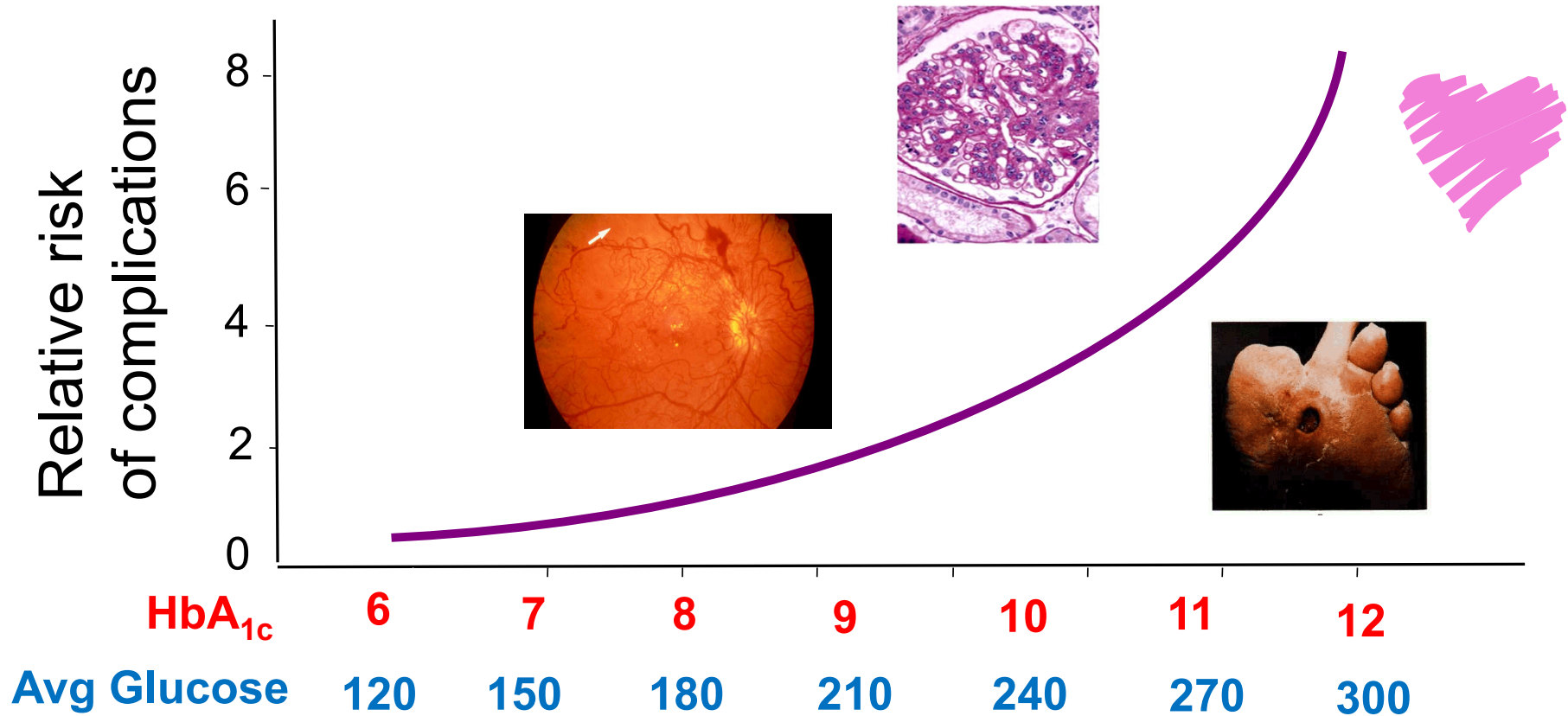
Defects Causing T2DM



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 Diabetes¹

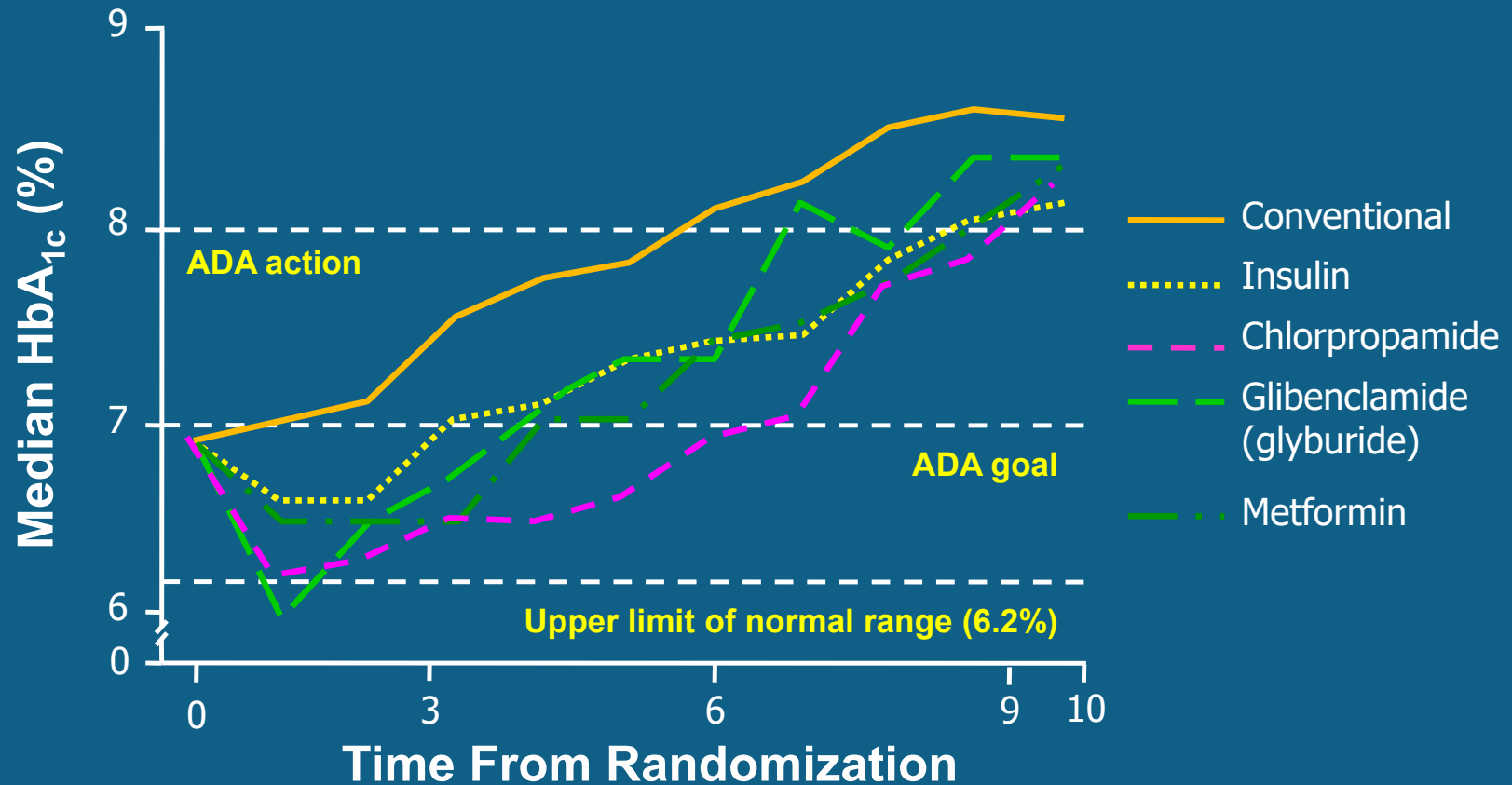
Measurement		Normal	ADA Goal	AACE Goal
Plasma glucose				
Preprandial	mmol/L	<5.6	4.4-7.2	<6.1
	mg/dl	<100	80-130	<110
Postprandial	mmol/L	<7.8	< 10.0*	<7.8
	mg/dl	<140	<180*	<140
HbA _{1c} (%)		<6	<7	<6.5

Principle 1

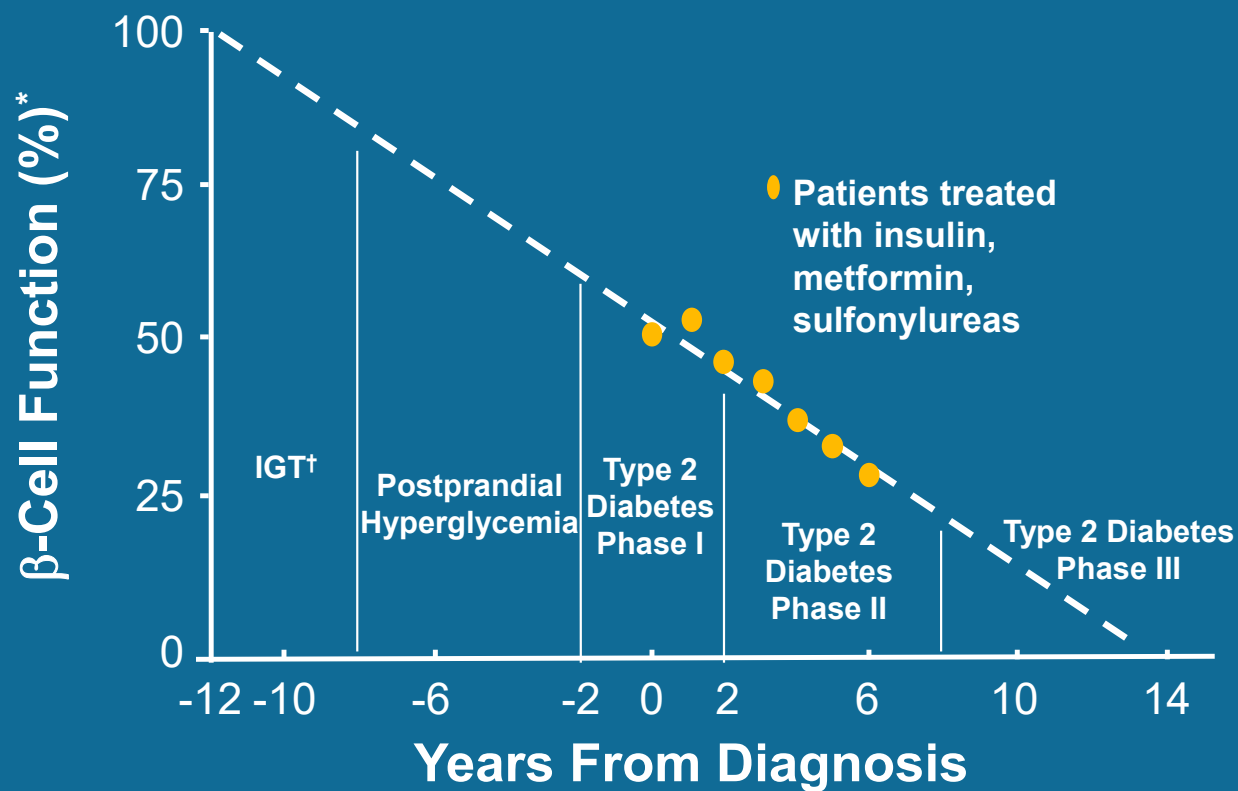
- Diabetes is a progressive disease
- Need medications with long-term efficacy

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

United Kingdom Prospective Diabetes Study (UKPDS)



UKPDS: β -Cell Loss Over Time

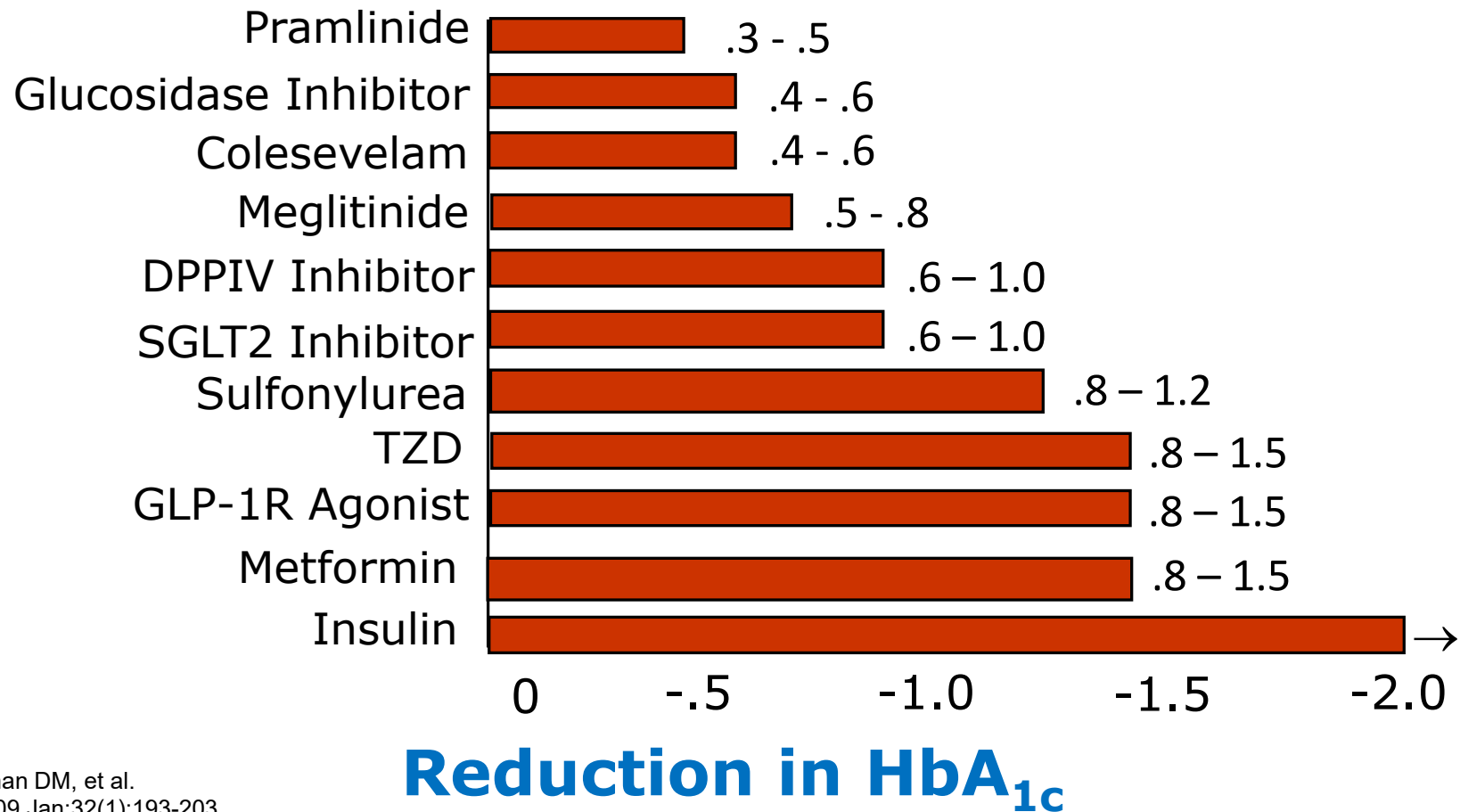


*Dashed line shows extrapolation forward and backward from years 0 to 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS.

[†]IGT=impaired glucose testing

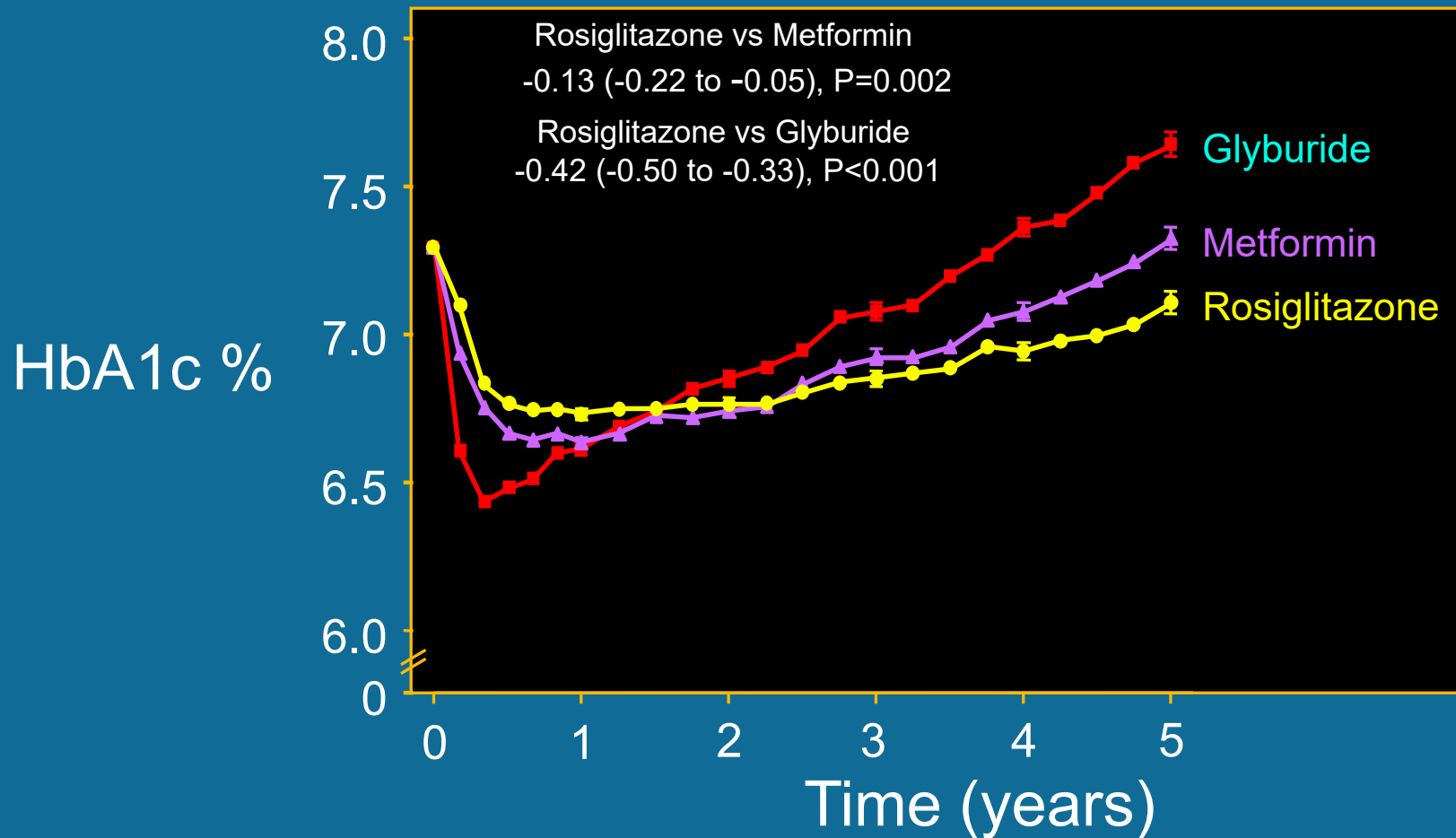
Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

Relative Efficacy for Lowering HbA_{1c} (when used as monotherapy)

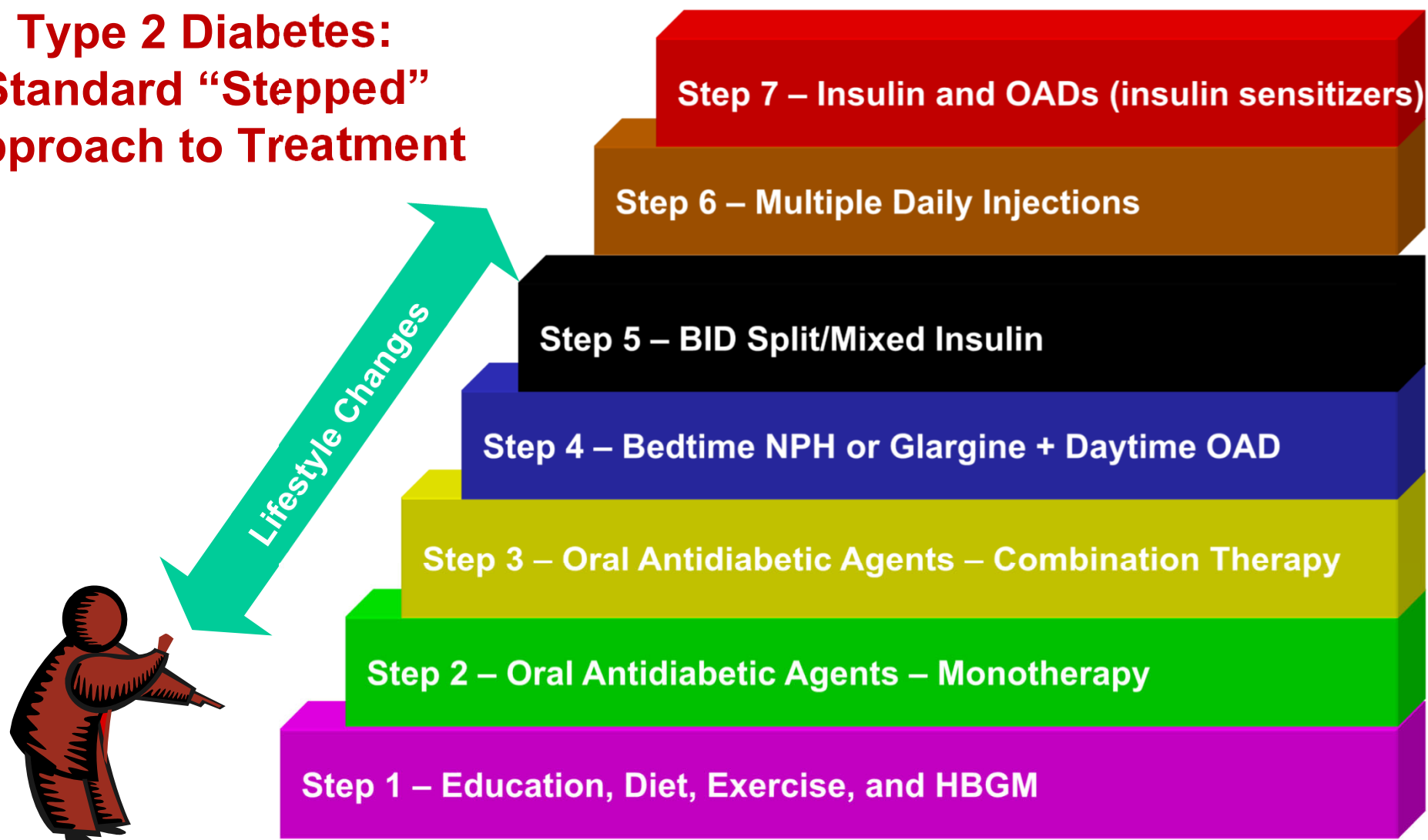


Adapted from Nathan DM, et al.
Diabetes Care. 2009 Jan;32(1):193-203.

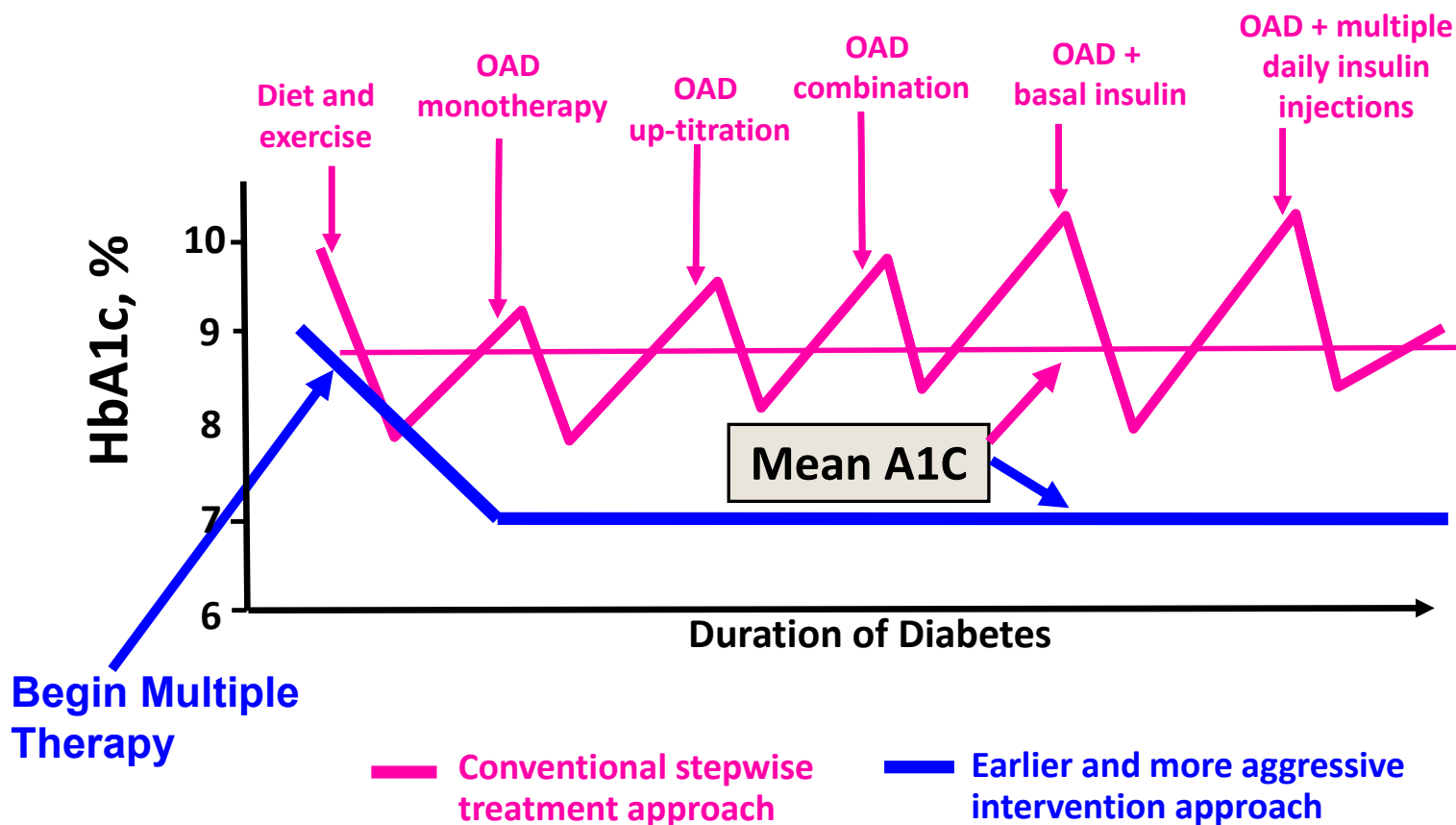
ADOPT: HbA1c Over Time



Type 2 Diabetes: Standard “Stepped” Approach to Treatment



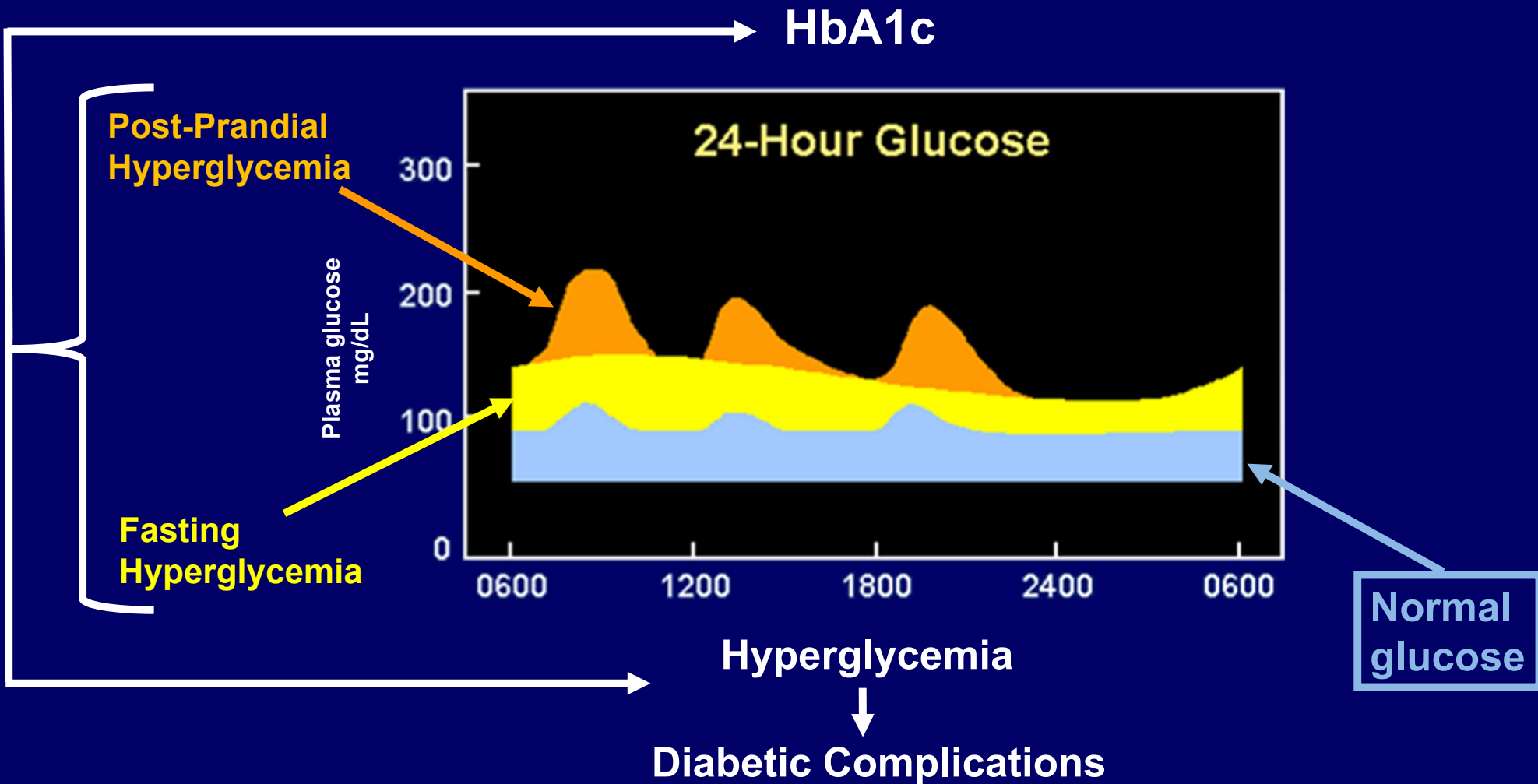
Earlier and More Aggressive Intervention May Reduce Lifetime HbA1c



Principle 2

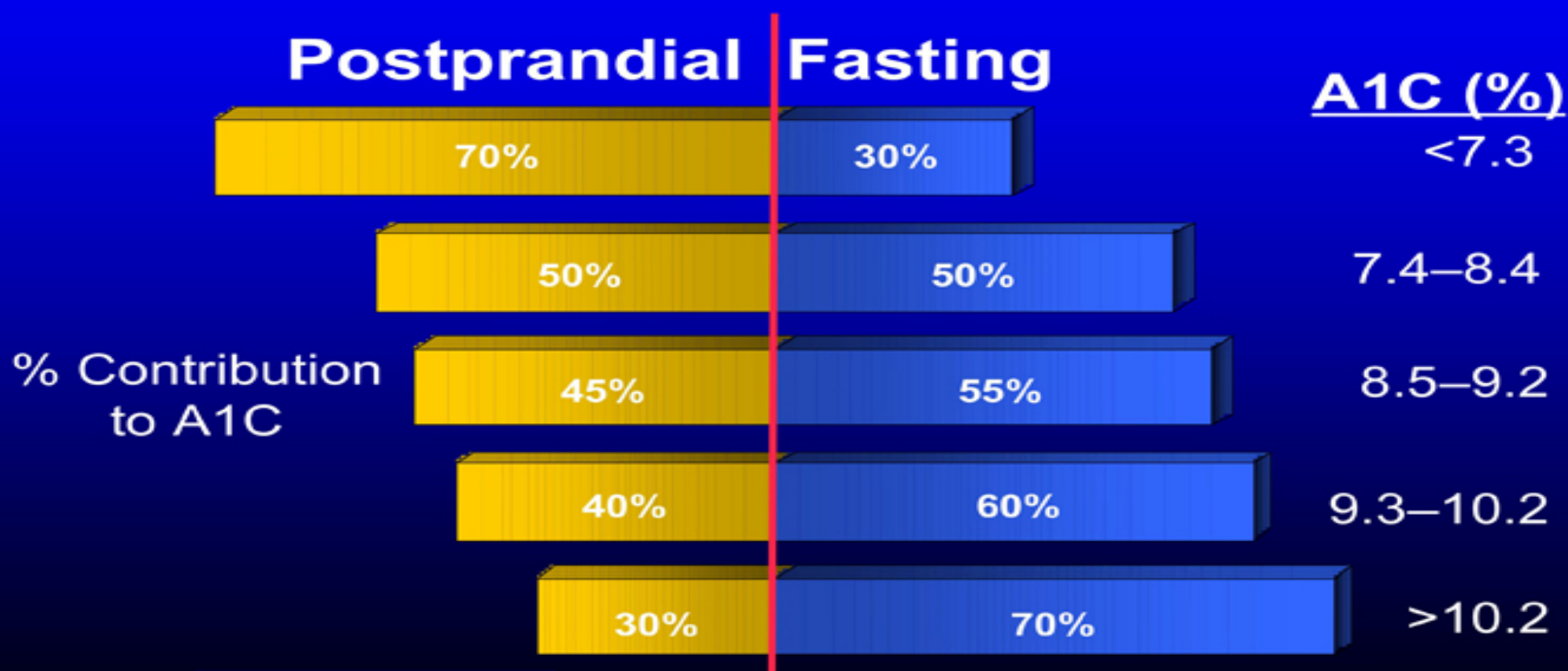
- To reach HbA1c target, there is a need to control both basal and post-prandial glucose
- In combination therapy, use medications with different mechanisms of action

Both FPG and PPG Contribute to Elevated A1C Levels



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

Principle 3

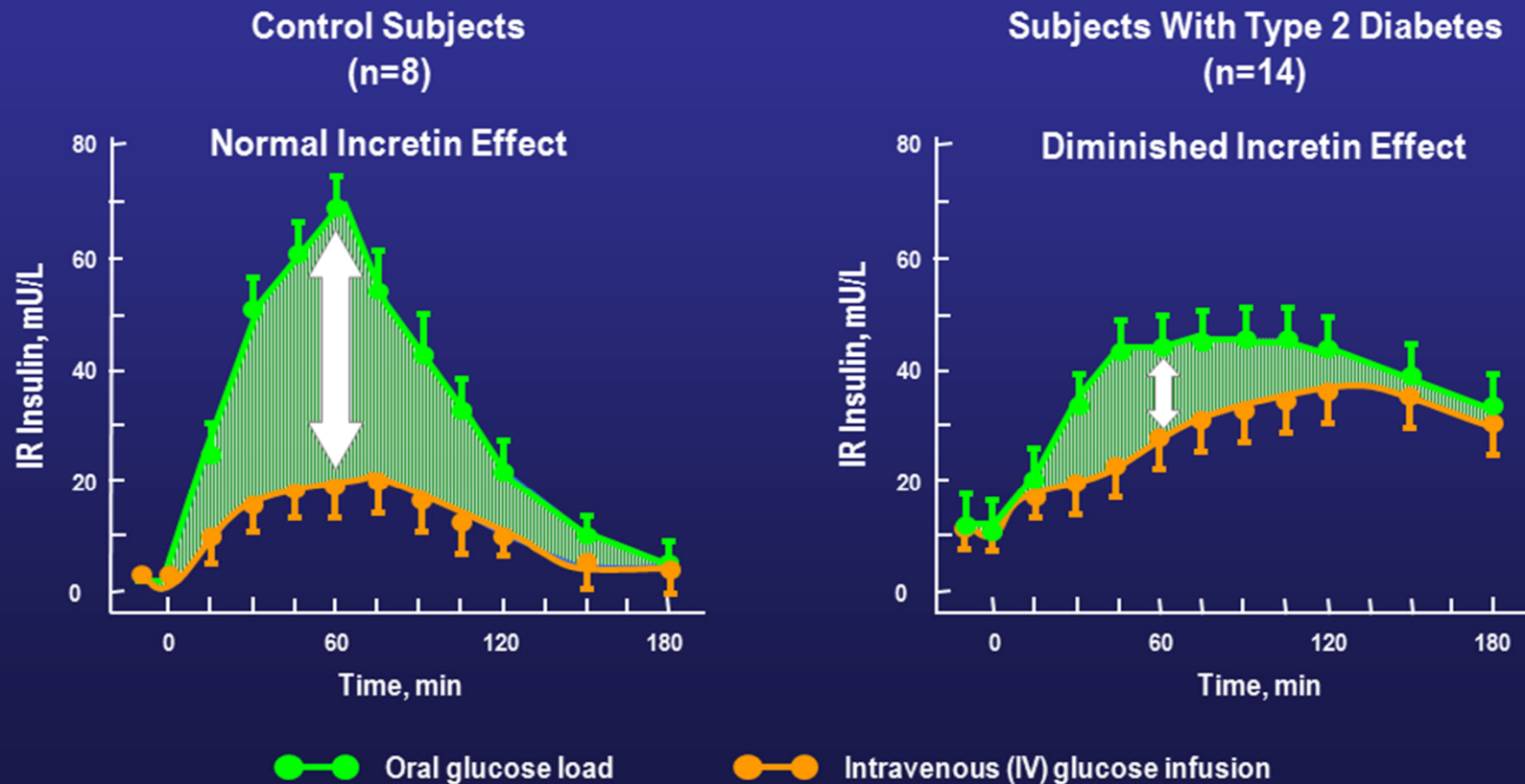
- Avoid hypoglycemia
- Avoid weight gain

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

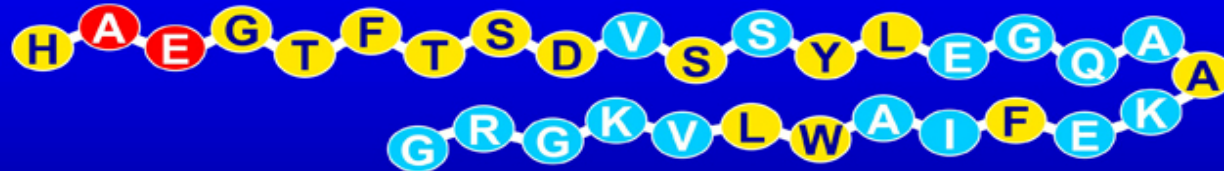
The Incretin Effect Is Diminished in Subjects With Type 2 Diabetes¹



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.

GLP-1: Glucagon-Like Peptide 1



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

GIP: Gastric Inhibitory Polypeptide

Glucose-Dependent Insulinotropic Polypeptide



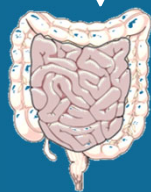
Secreted by K cells in the duodenum; no effects on GI motility; food intake, or glucagon secretion

Role of Incretins in Glucose Homeostasis

Ingestion of food



Release of Incretins



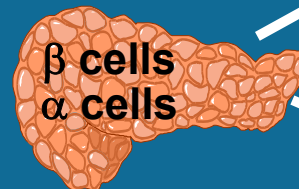
Active
GLP-1 & GIP

DPP-IV
enzyme

Inactive
GLP-1

Inactive
GIP

**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

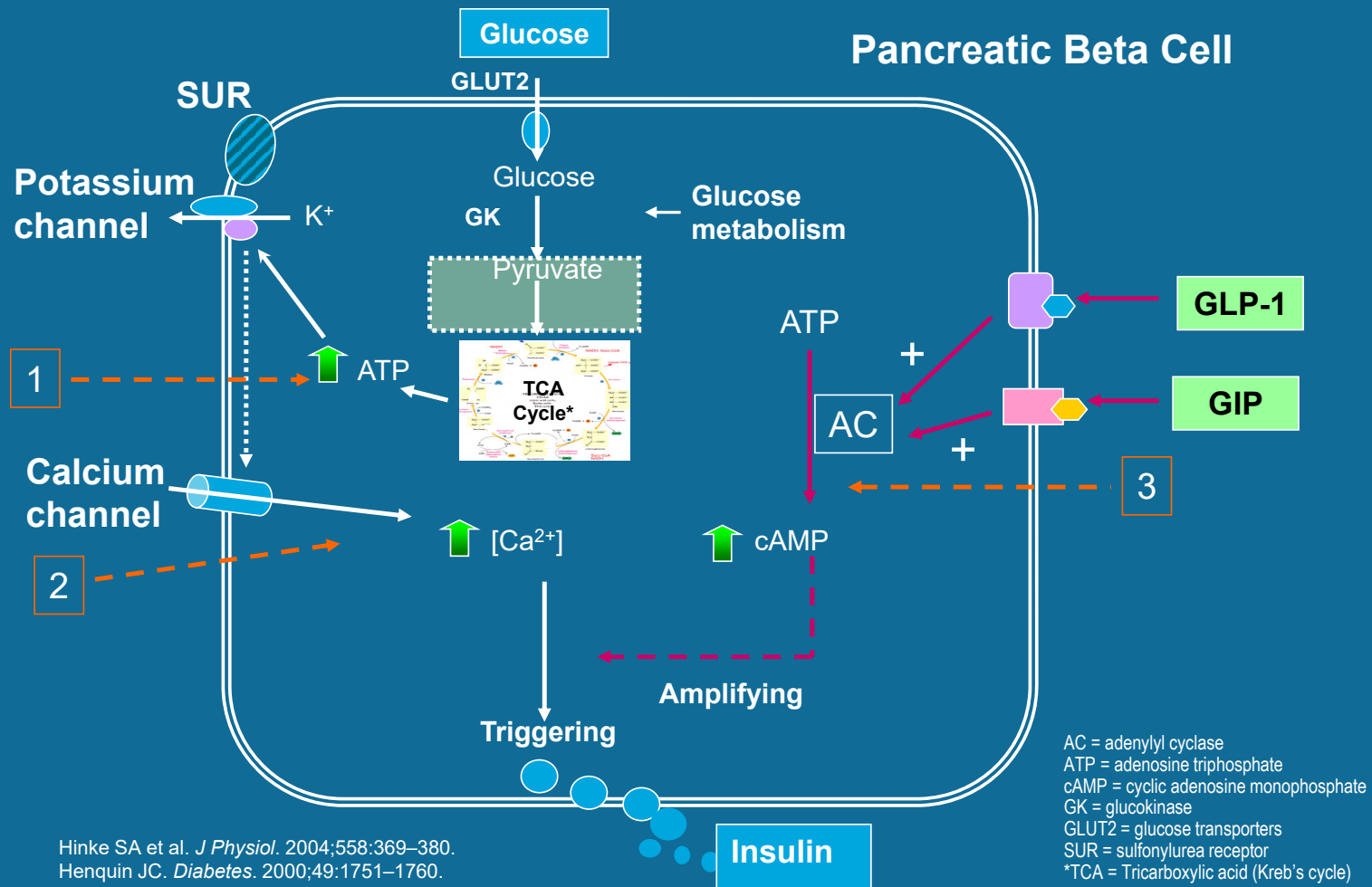
↓ Blood
glucose

DPP-IV= dipeptidyl-peptidase IV

1. Kieffer TJ, Habener JF. *Endocr Rev.* 1999;20:876–913.
3. Drucker DJ. *Diabetes Care.* 2003;26:2929–2940.

2. Ahren B. *Curr Diab Rep.* 2003;2:365–372.
4. Holst JJ. *Diabetes Metab Res Rev.* 2002;18:430–441.

Glucose-Stimulated Secretion of Insulin



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

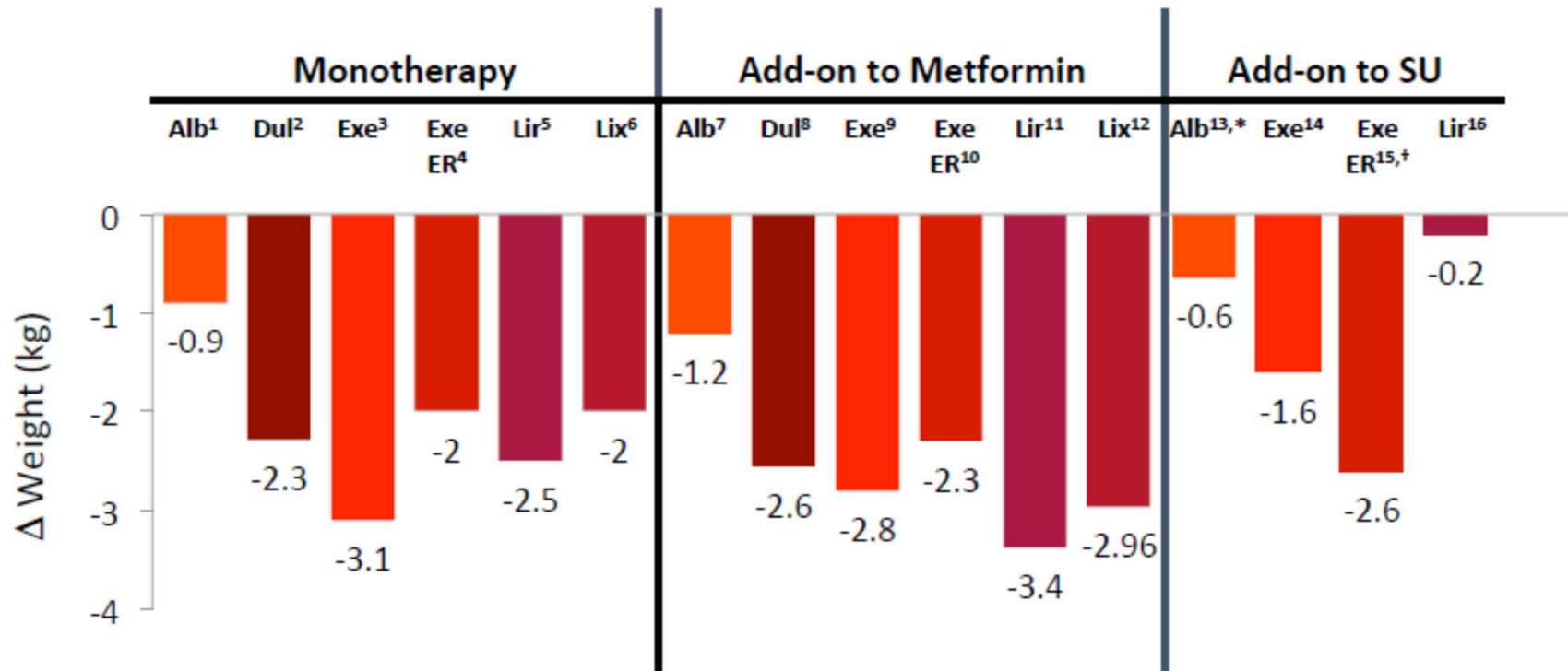
Strategies for Enhancing GLP-1 Action

- GLP-1 receptor agonists
 - Activators of the GLP-1 receptor
 - Structurally modified to confer resistance to degradation by dipeptidyl peptidase-4 (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

Effects of GLP-1 Agonists on Weight in T2DM

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

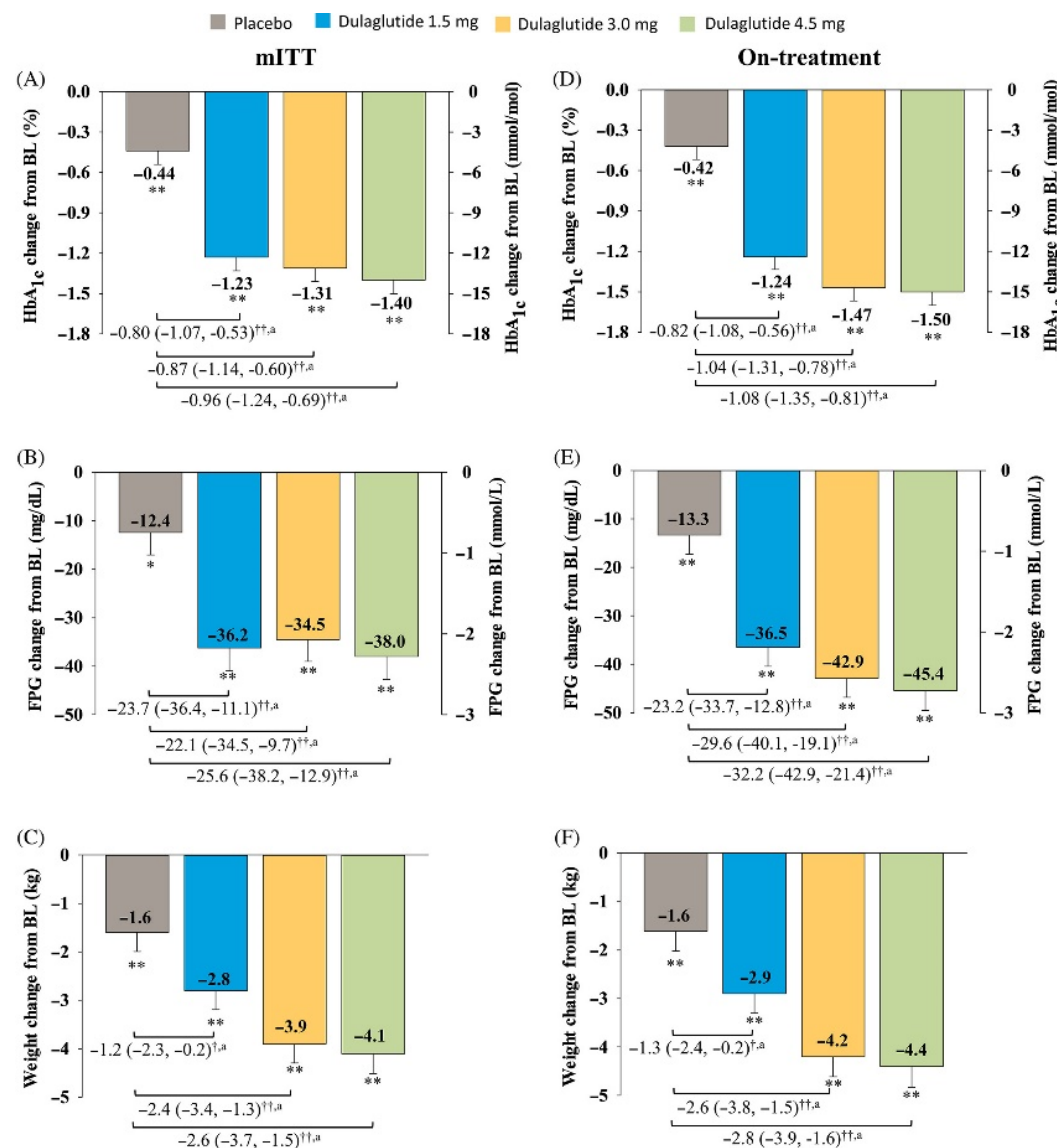


1. Tanzeum (albiglutide) injection prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2014.
2. Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176.
3. Moretto TJ, et al. *Clin Ther*. 2008;30:1448-1460.
4. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258.
5. Garber A, et 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.

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

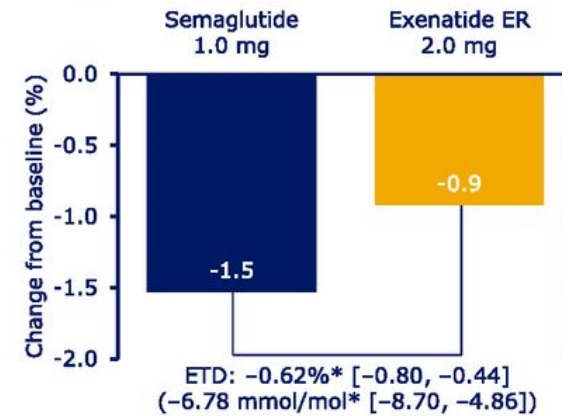
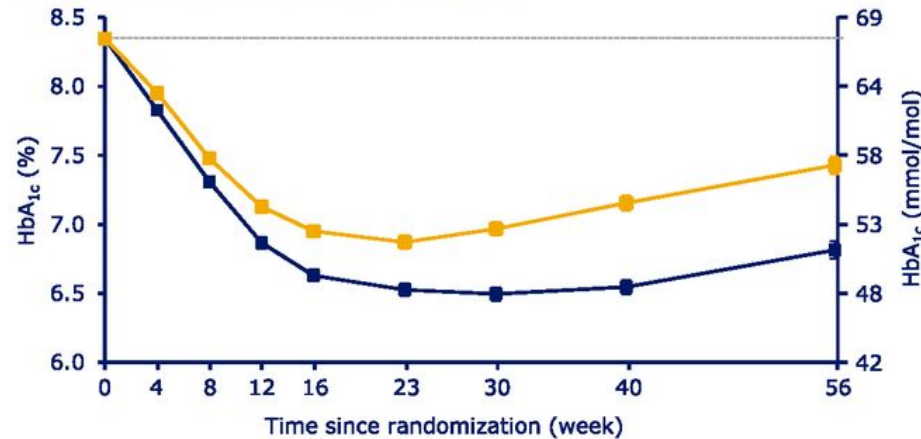
Frias JP et al. Diabetes, Obesity and Metabolism. 2020; 21(9):2048-2057



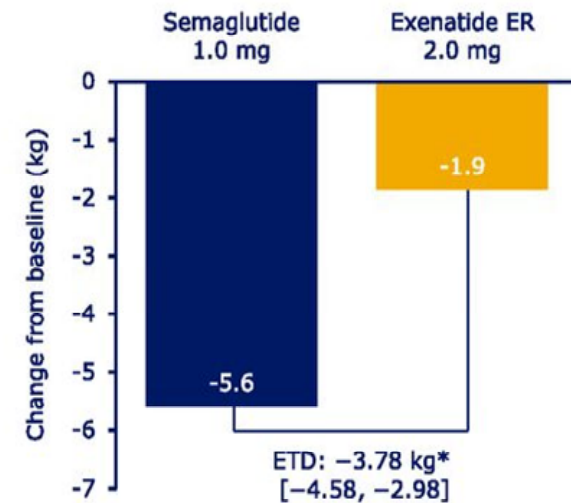
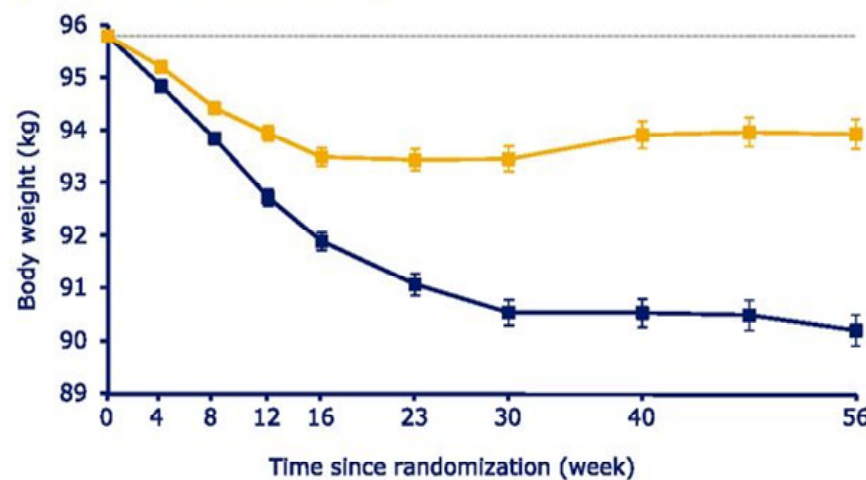
Semaglutide VS Exenatide

Effects on HbA1c and Weight

Overall mean at baseline: 8.3% (67 mmol/mol)

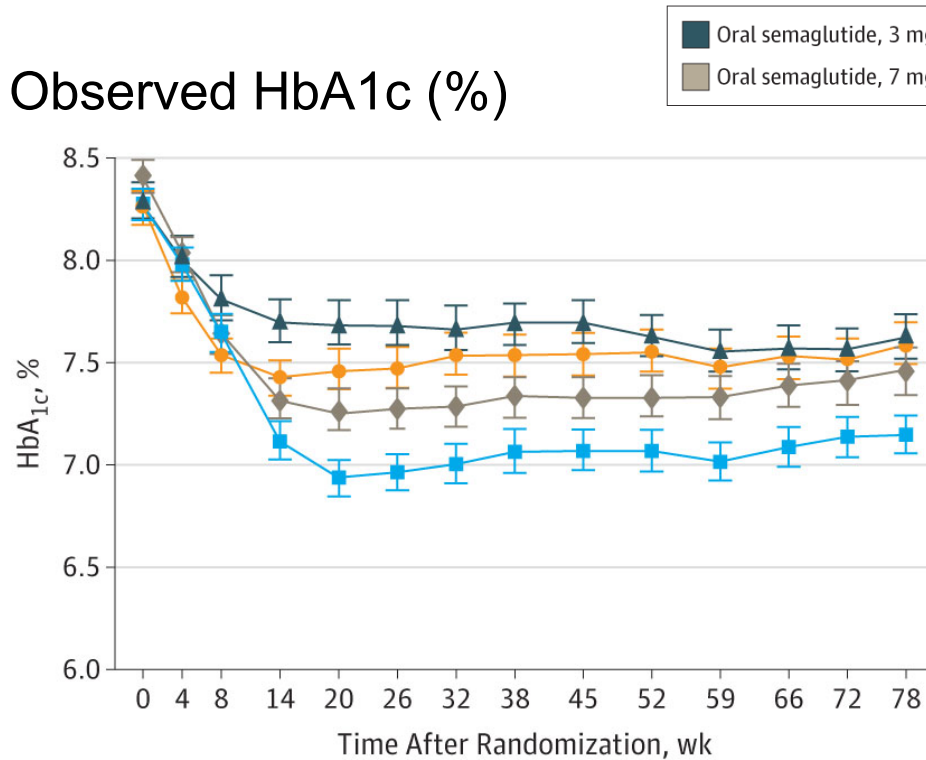


Overall mean at baseline: 95.8 kg

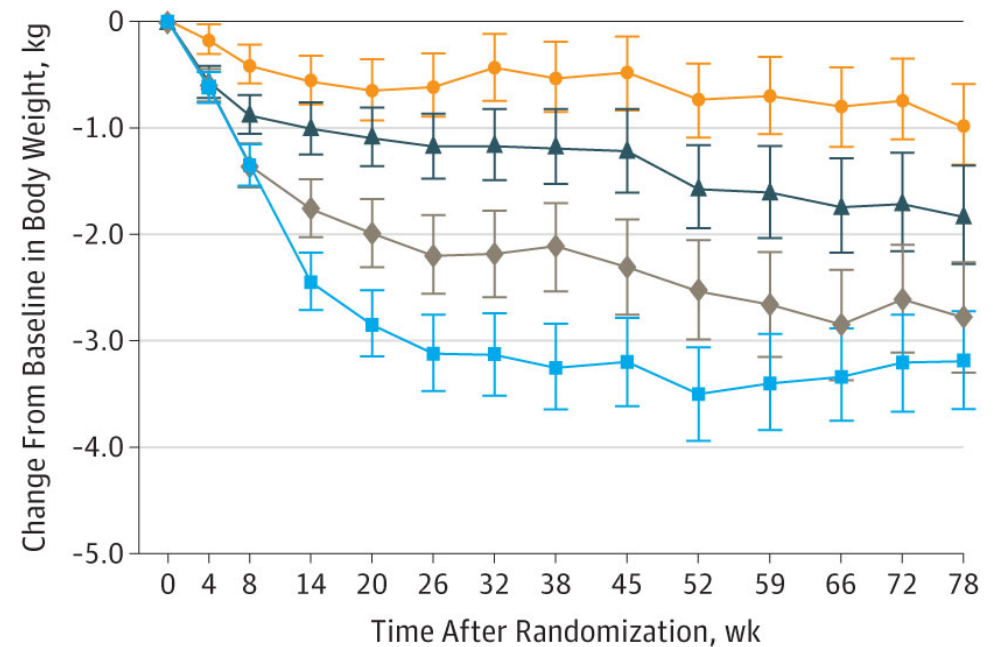


Oral Semaglutide Decreases both HbA1c and Body Weight in T2DM

Observed HbA1c (%)



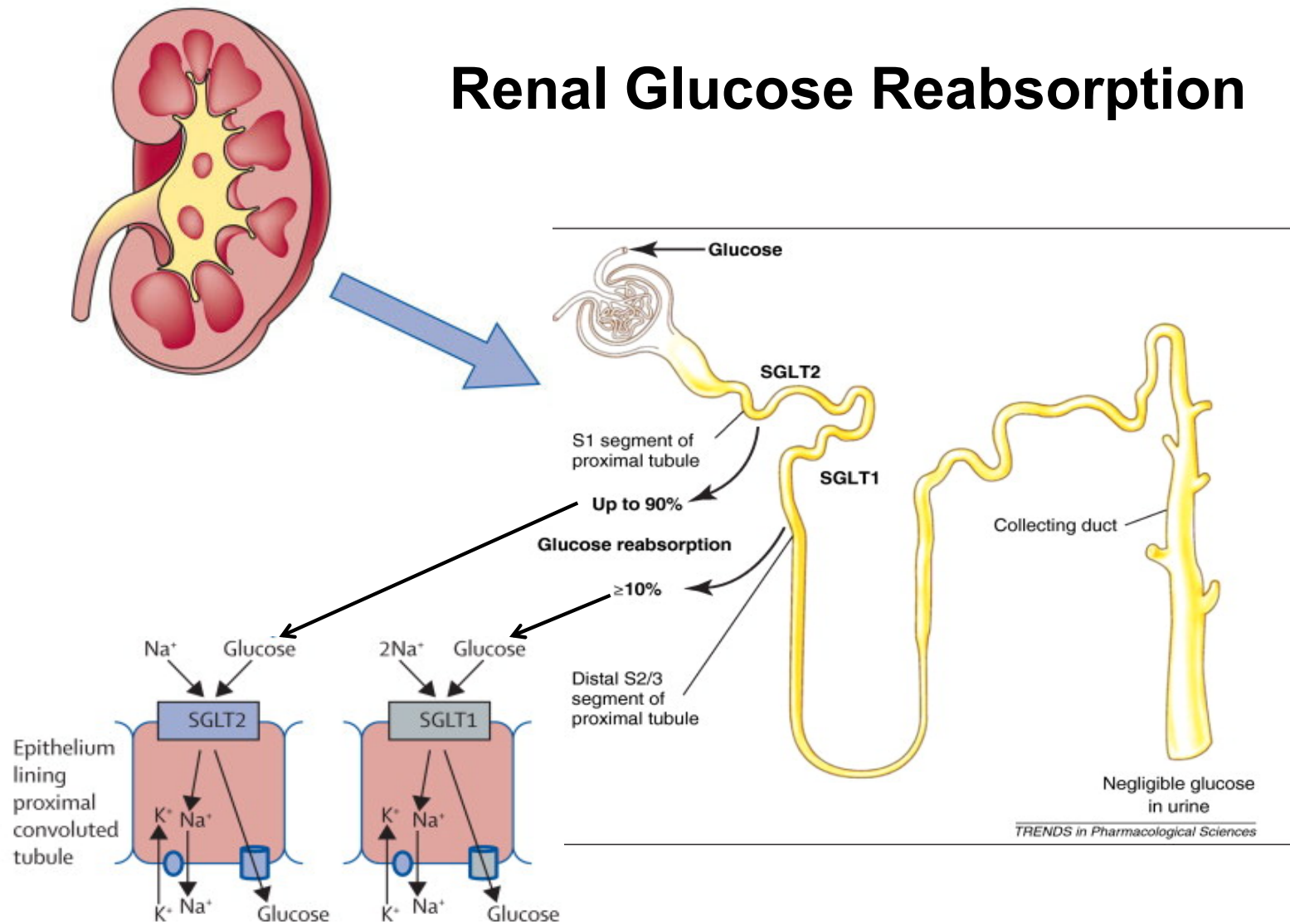
Change in Weight (kg)



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.

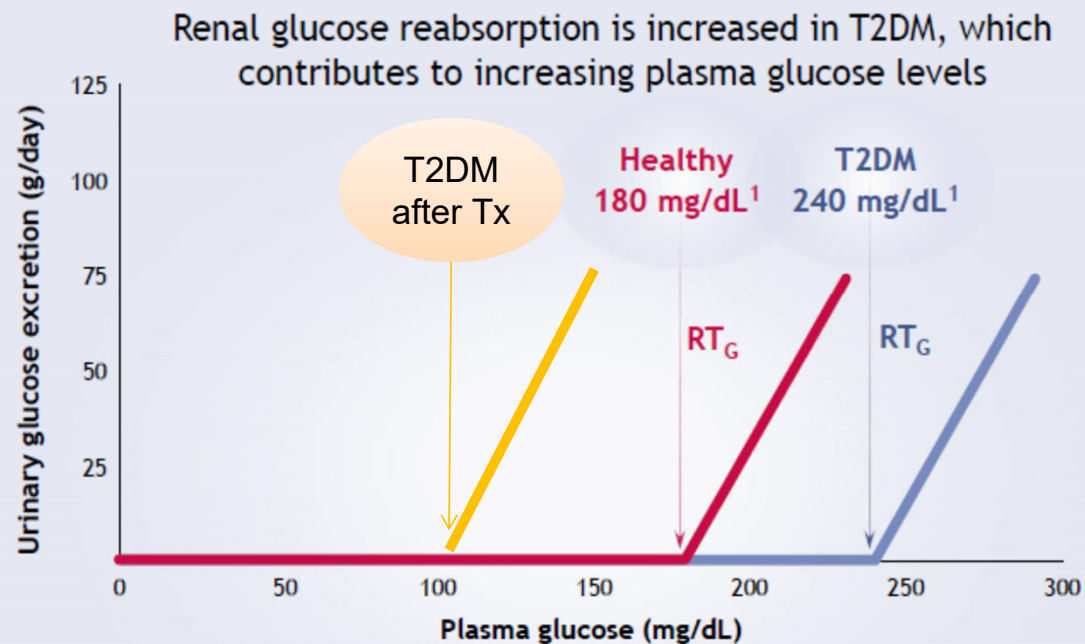
SGLT2 Inhibitors

Renal Glucose Reabsorption



Renal Glucose Reabsorption

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

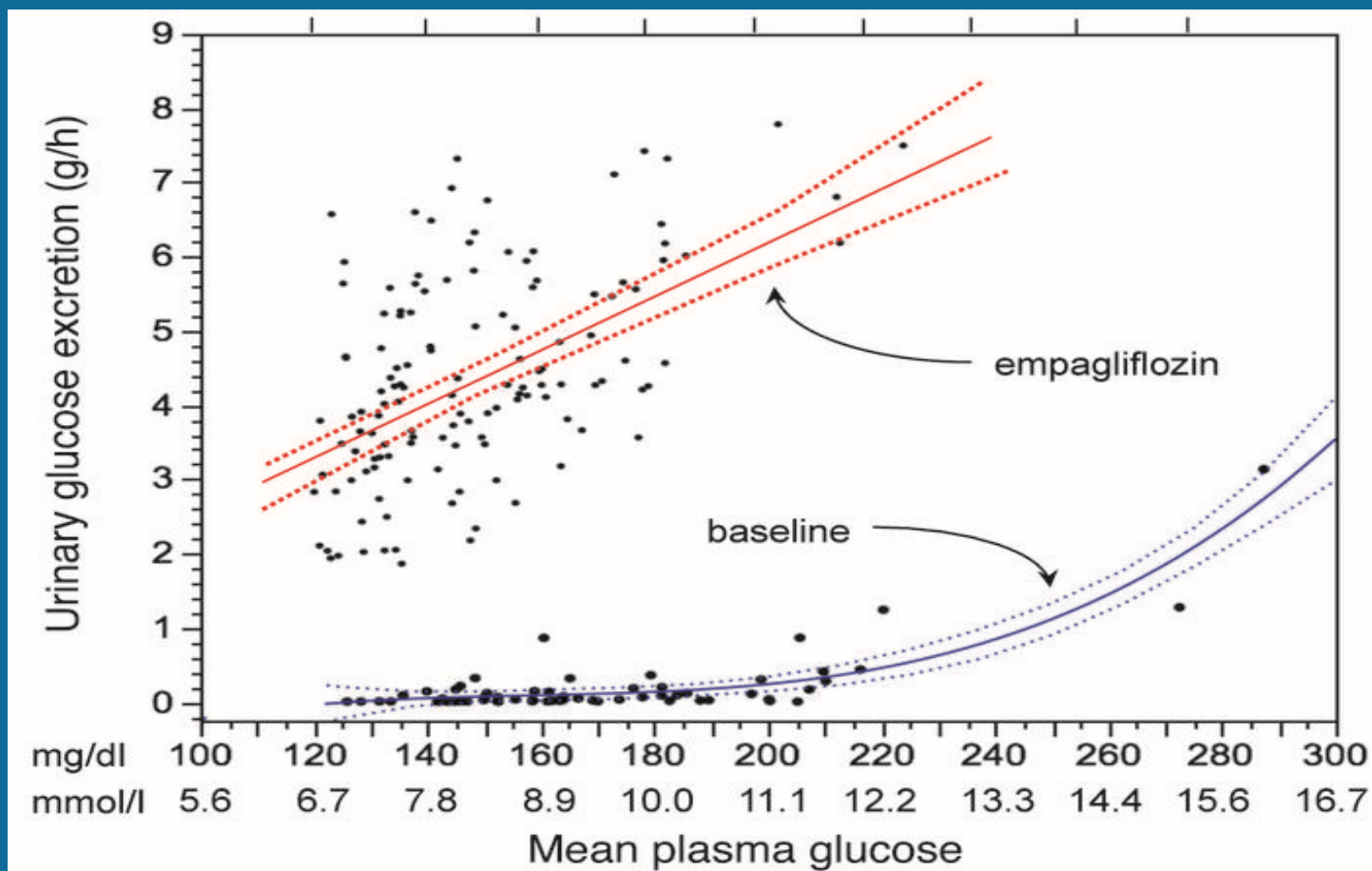


Adapted with permission from Abdul-Ghani, DeFronzo RA.

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

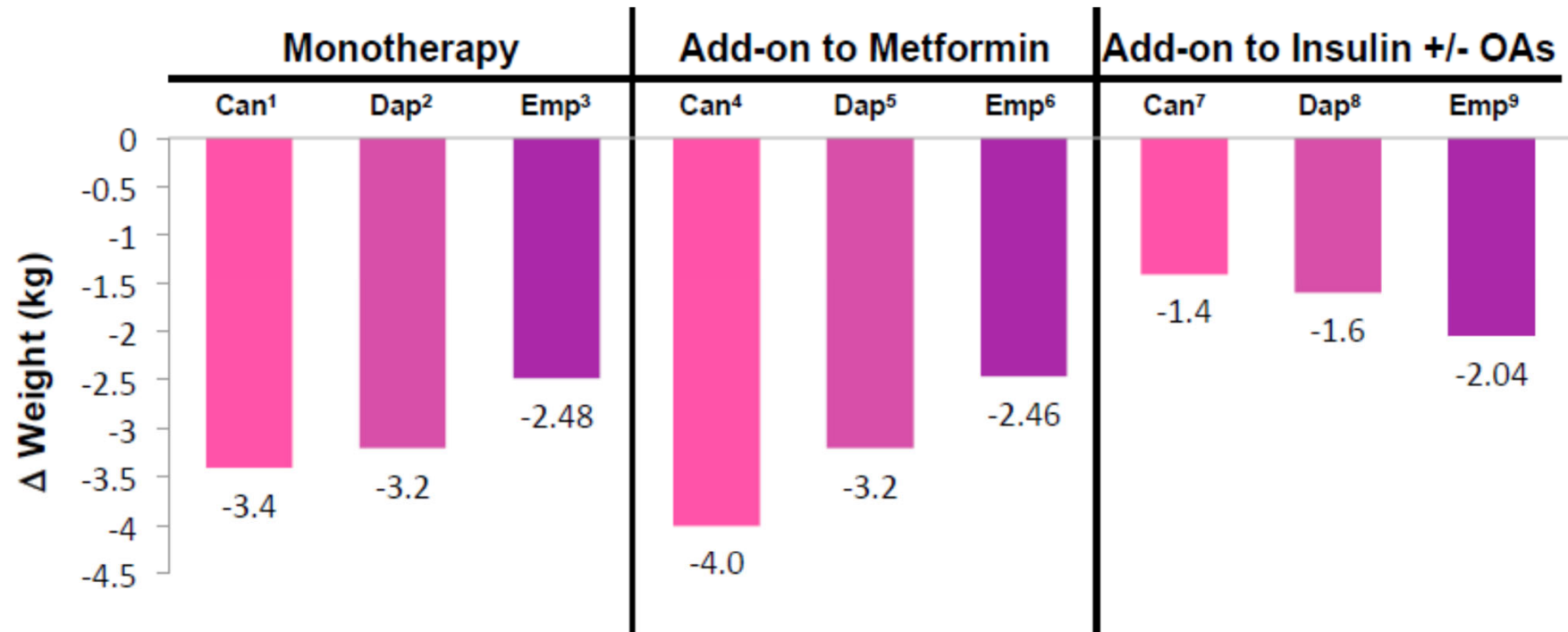
SGLT2 Inhibitors

- Induce glycosuria by decreasing renal T_m 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
Ertagliflozin	5, 15 mg/day	SGLT2

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.

Principle 4

Select diabetes medications based on the risk or presence of

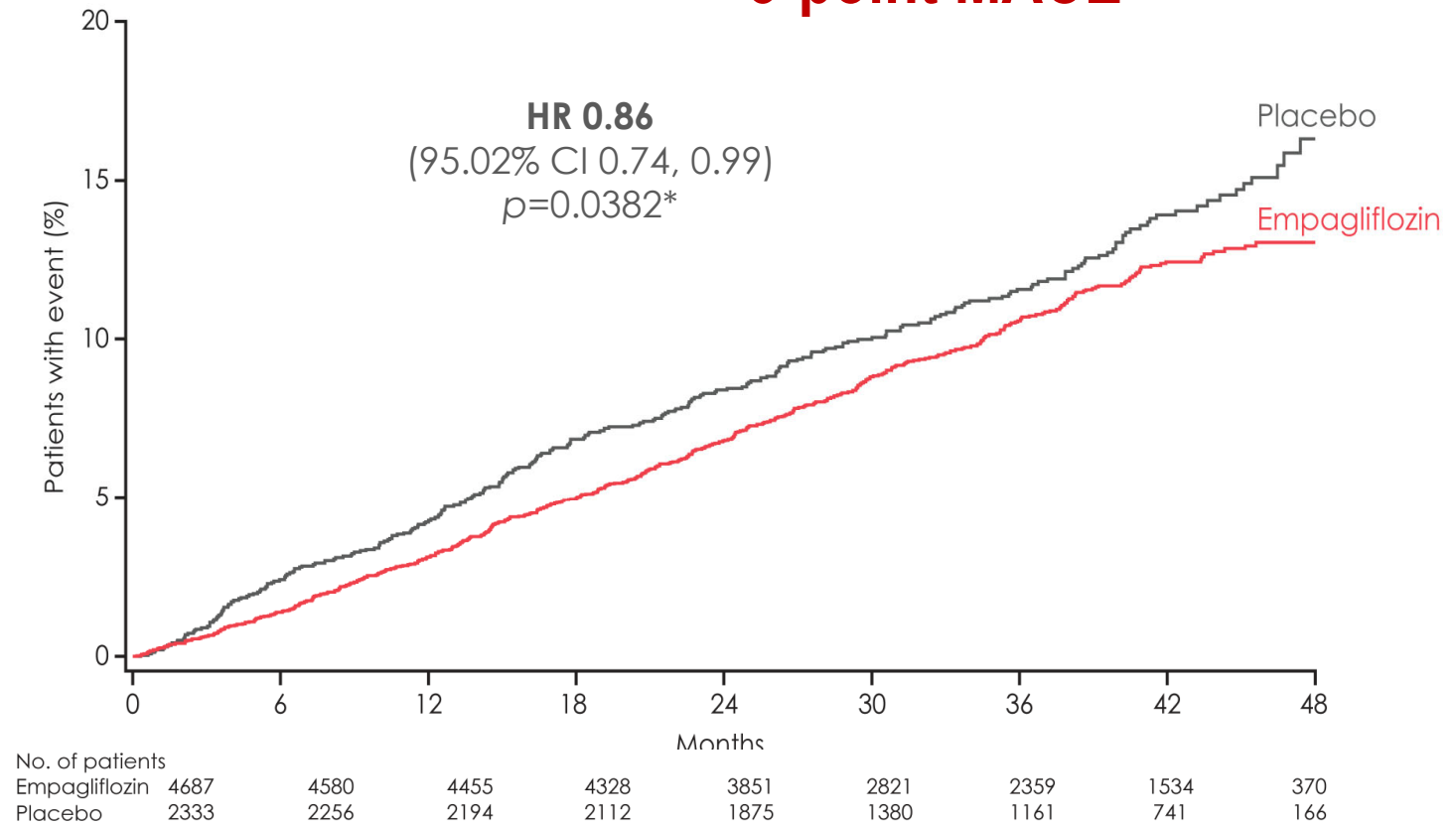
- CVD
- Stroke
- CHF
- Renal Decline

Empagliflozin

Primary outcome: 3-point MACE

P D F H

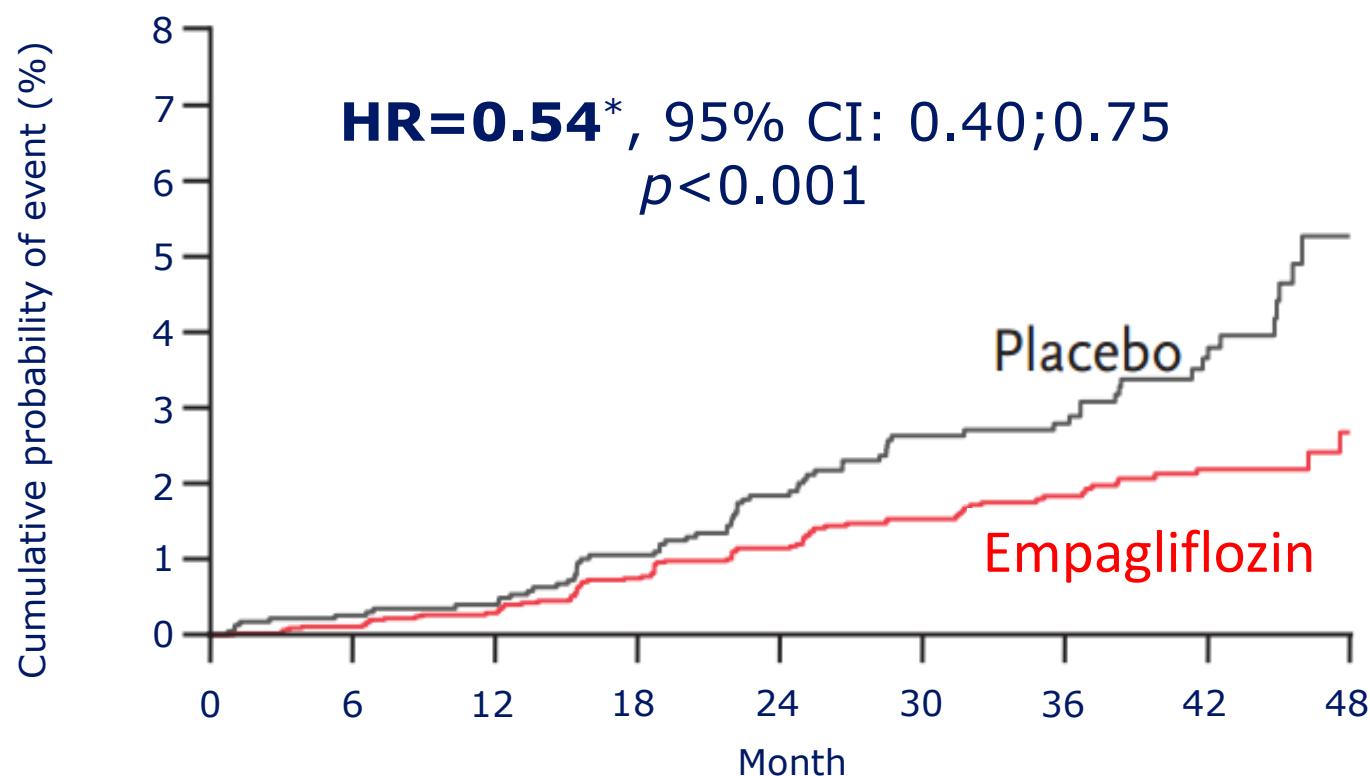
- FY#ghdwk
- Qrq0bwkde# P L
- Qrq0bwkde#
vurnh



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

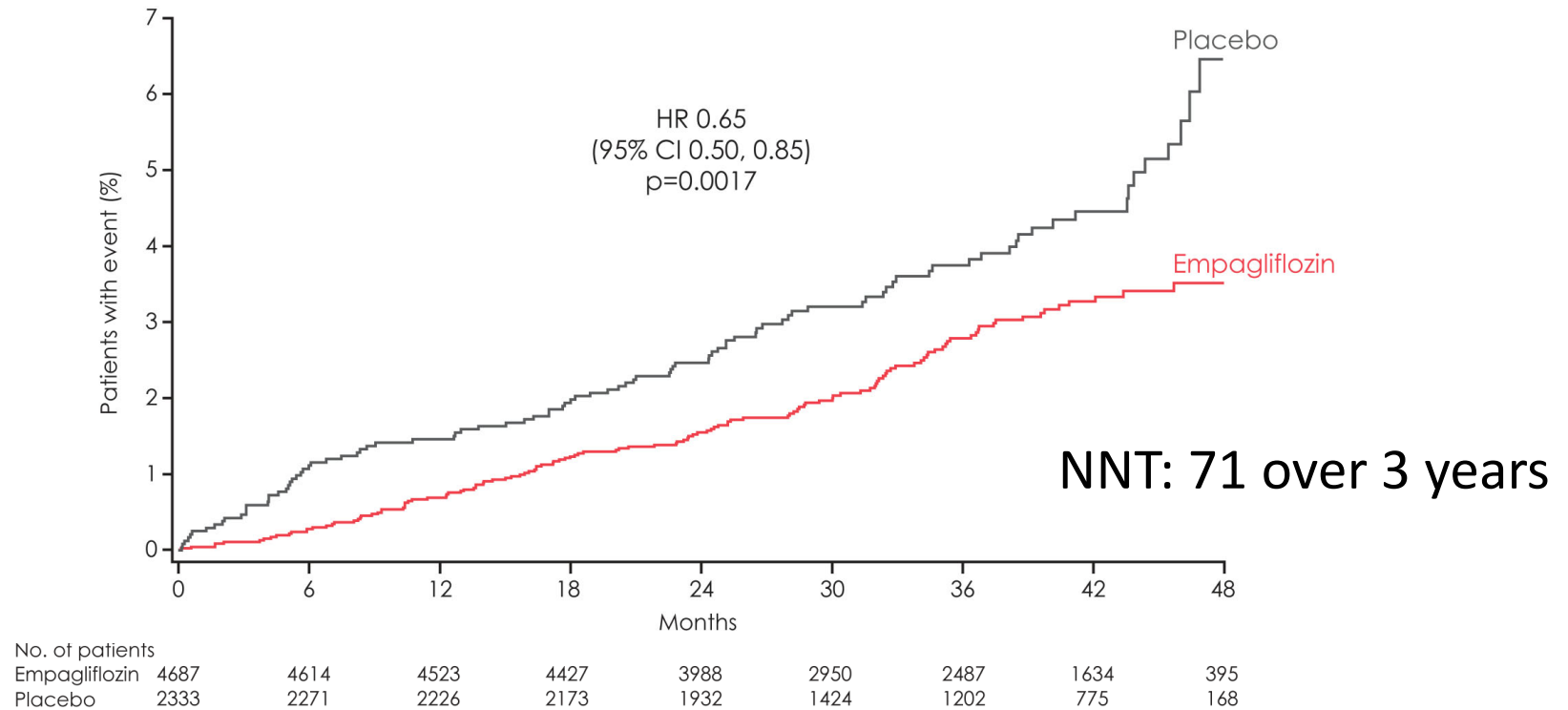


*CI, confidence interval; HR, hazard ratio

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

EMPA-REG - Empagliflozin

Hospitalization for heart failure, secondary outcome



Cumulative incidence function. HR, hazard ratio

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

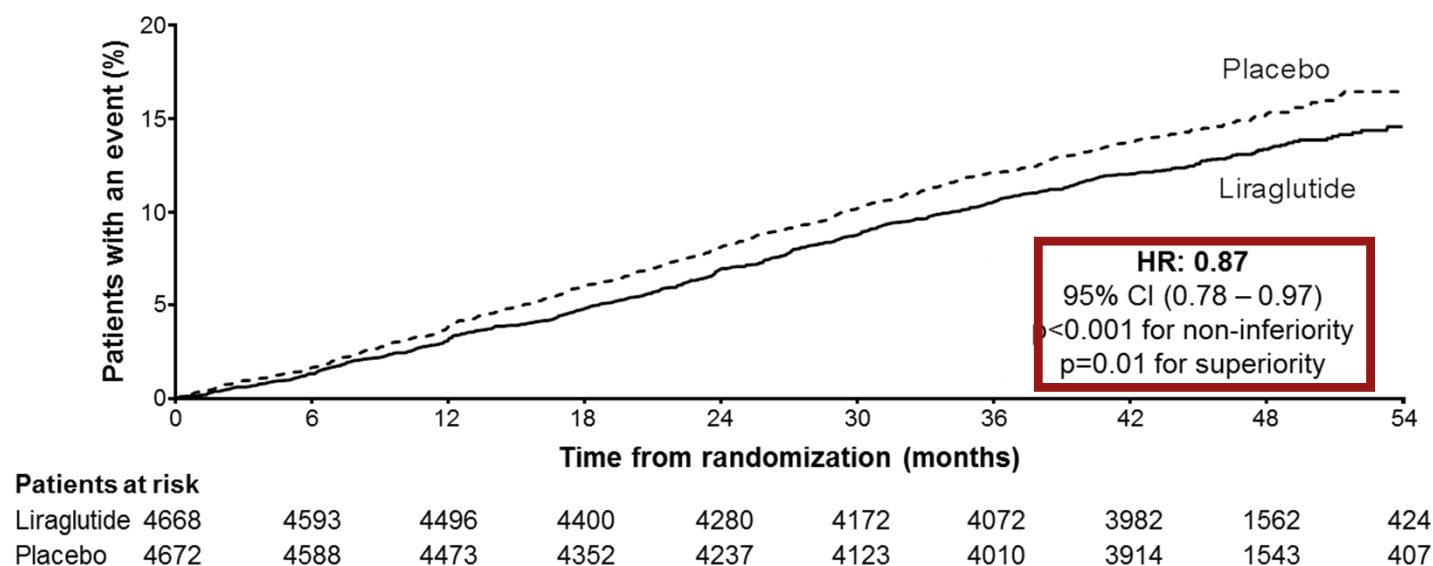
All studies show superiority for dual outcome CV death or hospital for CHF)

Mechanick JJ, 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

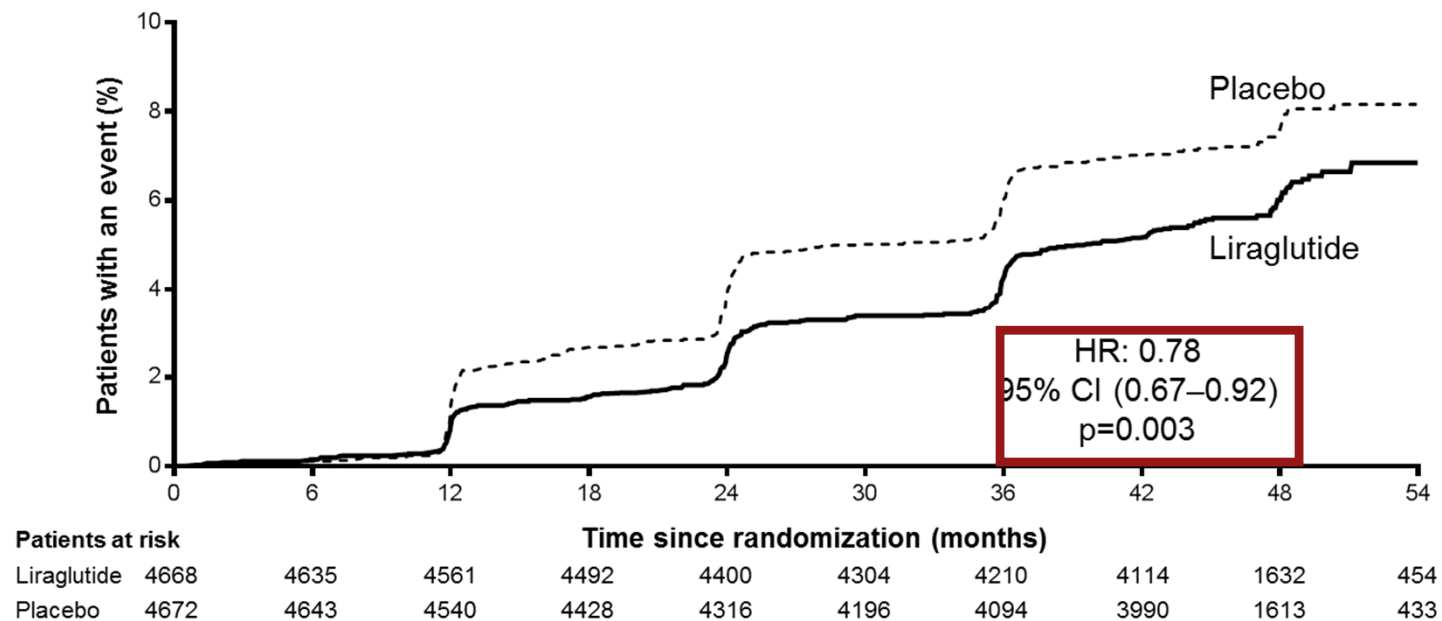


The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox 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

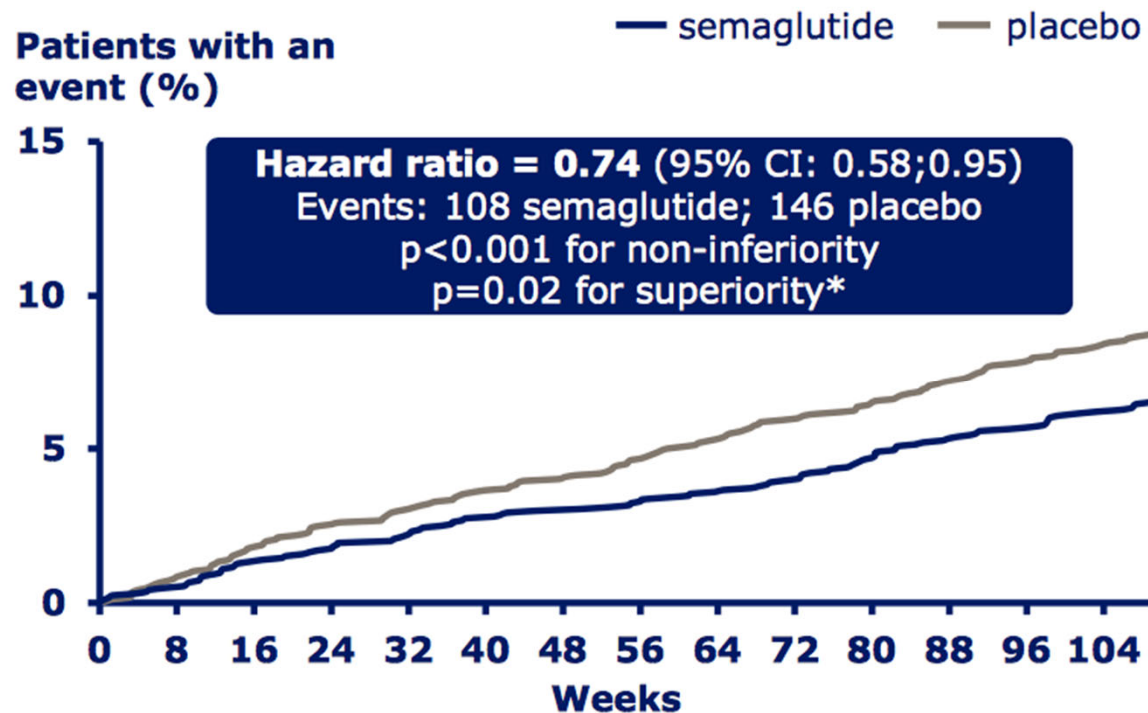


The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence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

Semaglutide demonstrated 26% reduction in composite CV outcome compared with placebo



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

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE
TYPE 2 DIABETES
MANAGEMENT ALGORITHM

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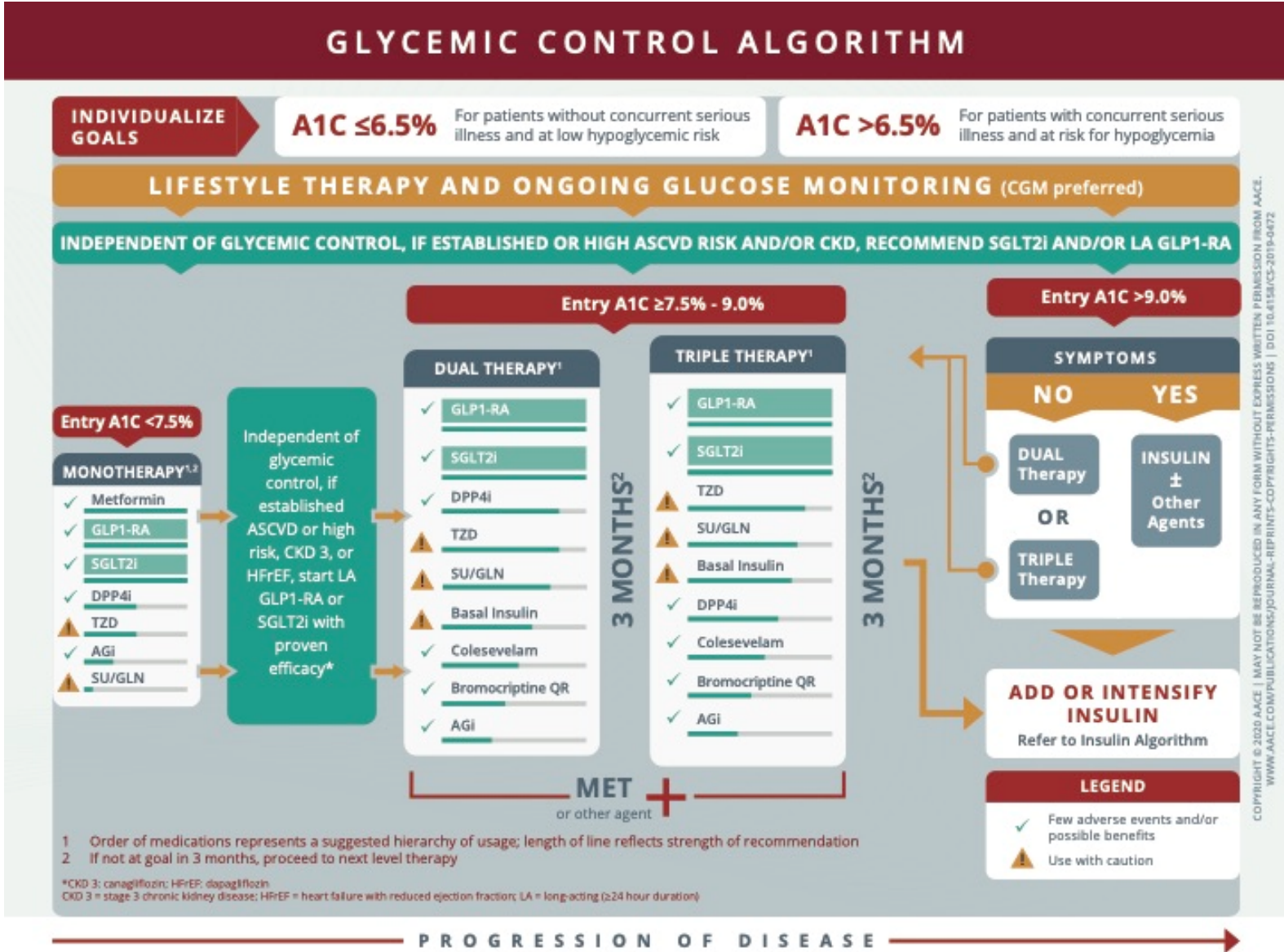
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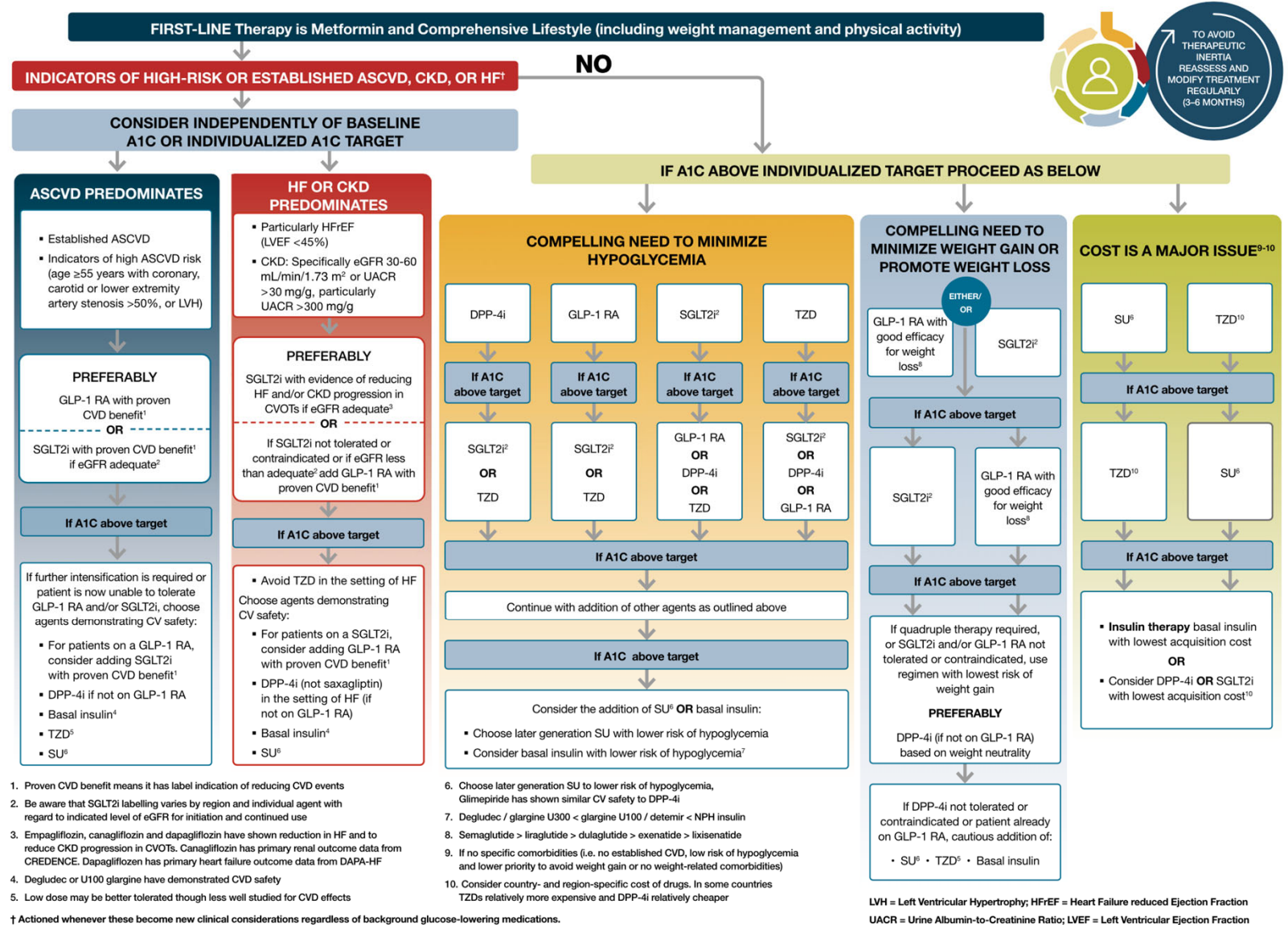


AACE
Diabetes
Algorithm
2020
Garber A et
al. Endocr
Pract 2020;
26(1):107-139



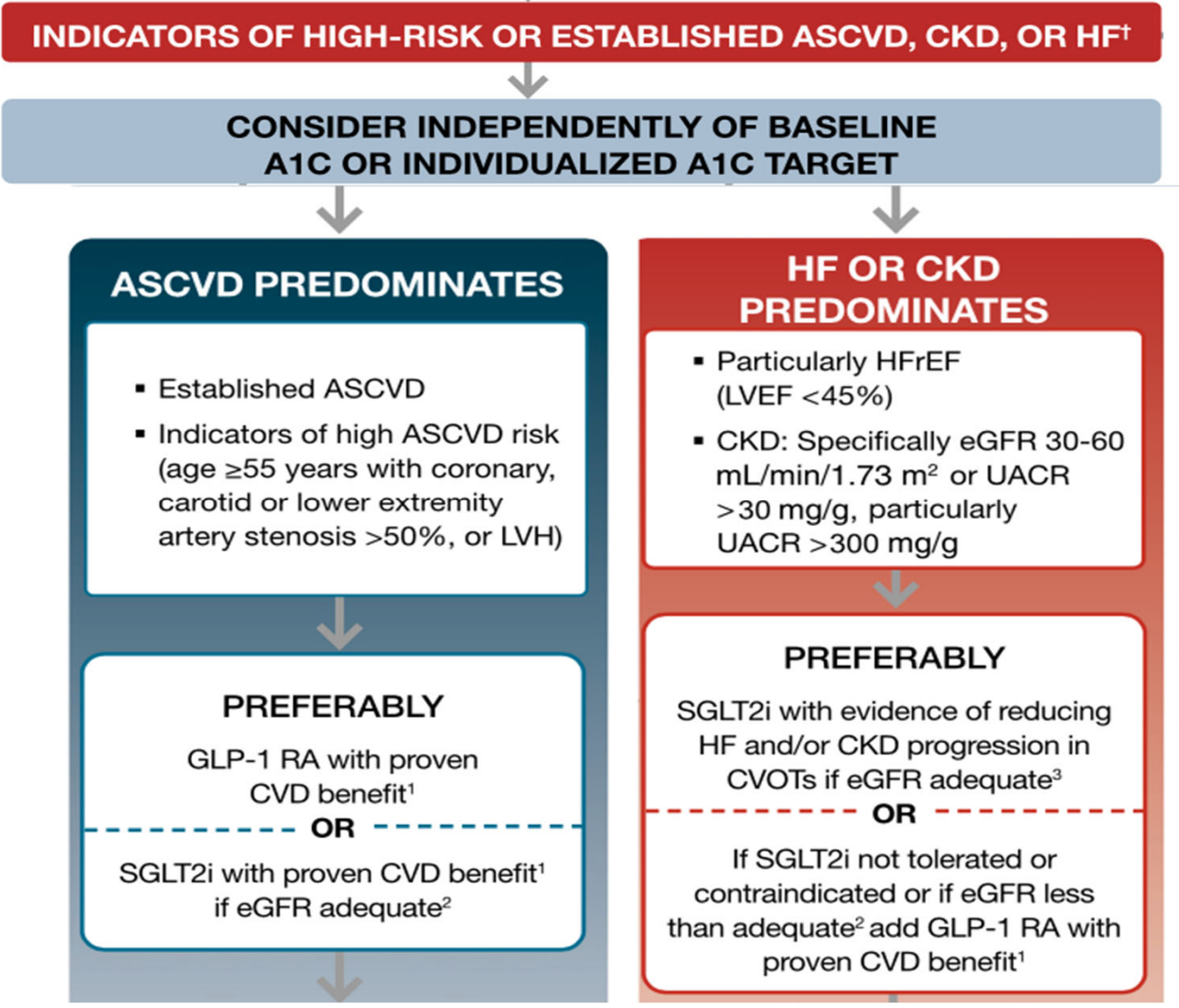
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ADA/EASD T2DM Algorithm



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

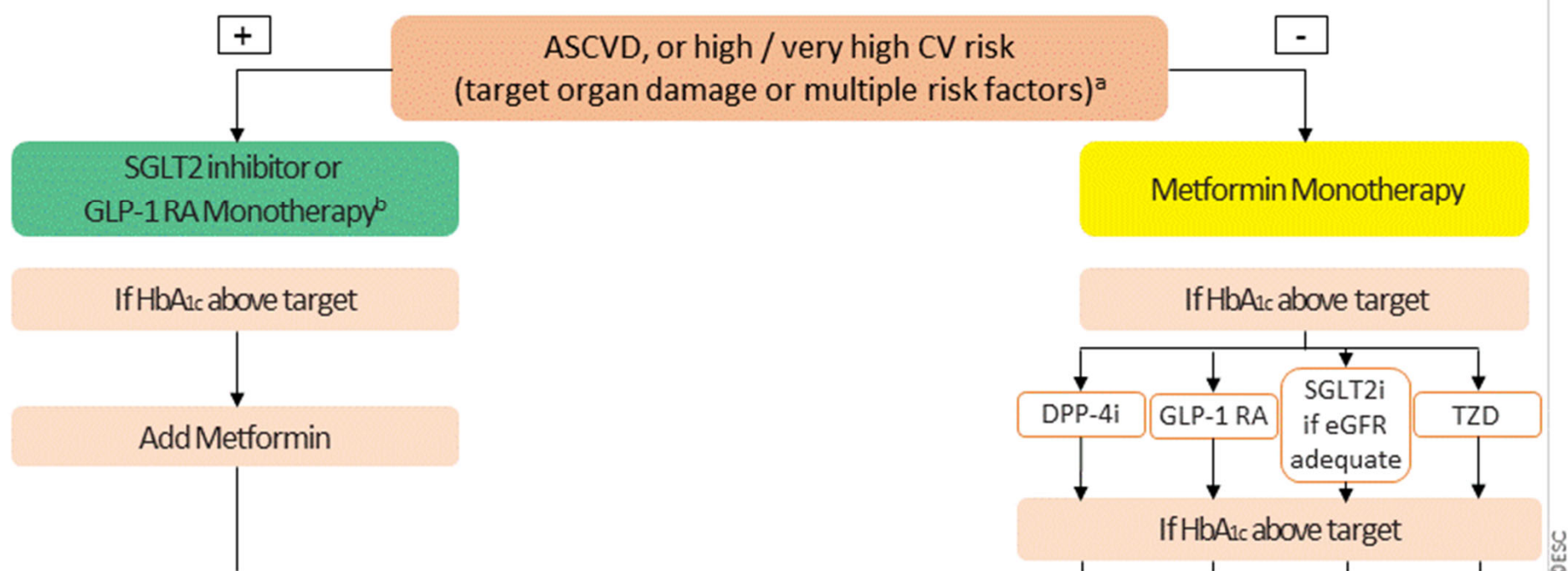
ADA/EASD T2DM Algorithm



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)

a) Type 2 DM - Drug naïve patients



What if there was a treatment for T2D that:

1 Reduce

medications

2

3

4

5

6

7

8

9

10

This is the therapeutic
profile of weight loss in T2D

a

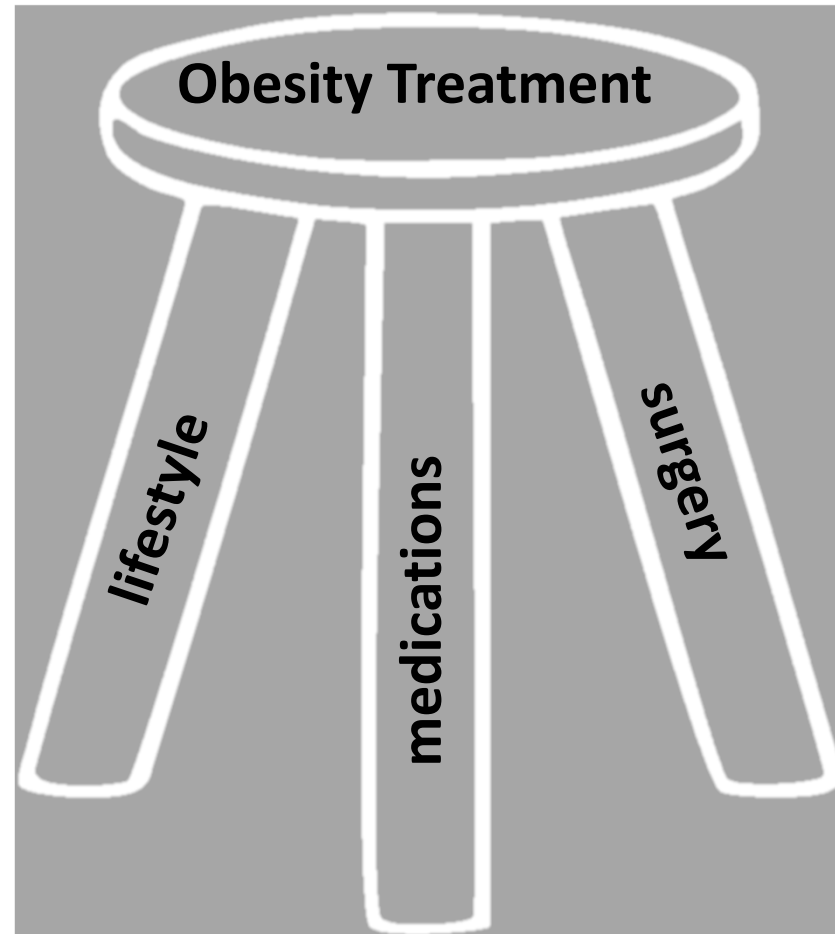
can produce diabetes remission

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;

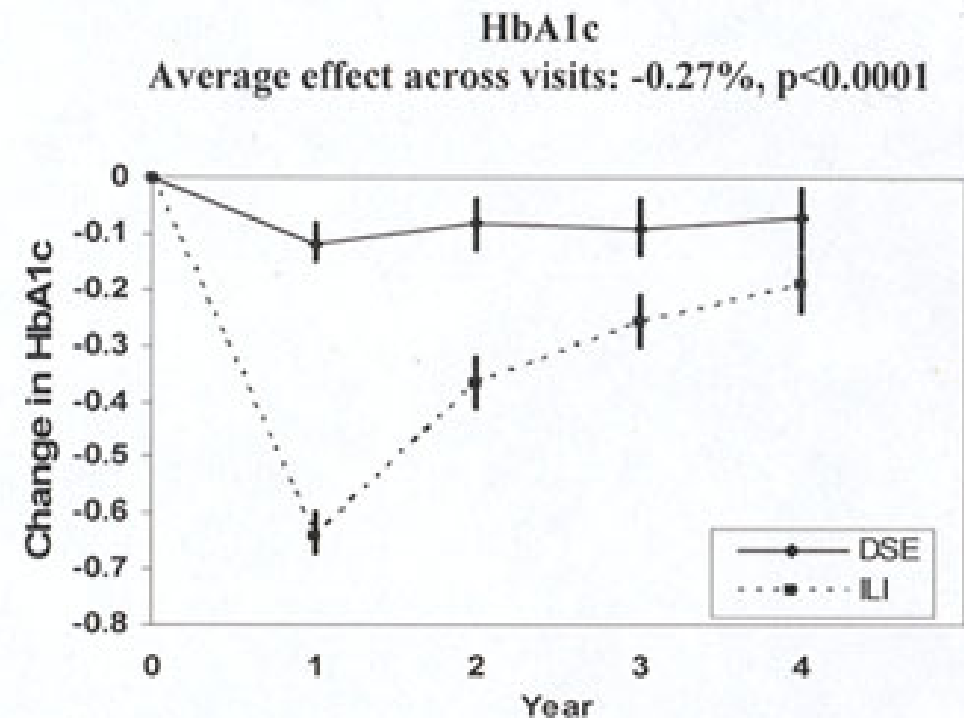
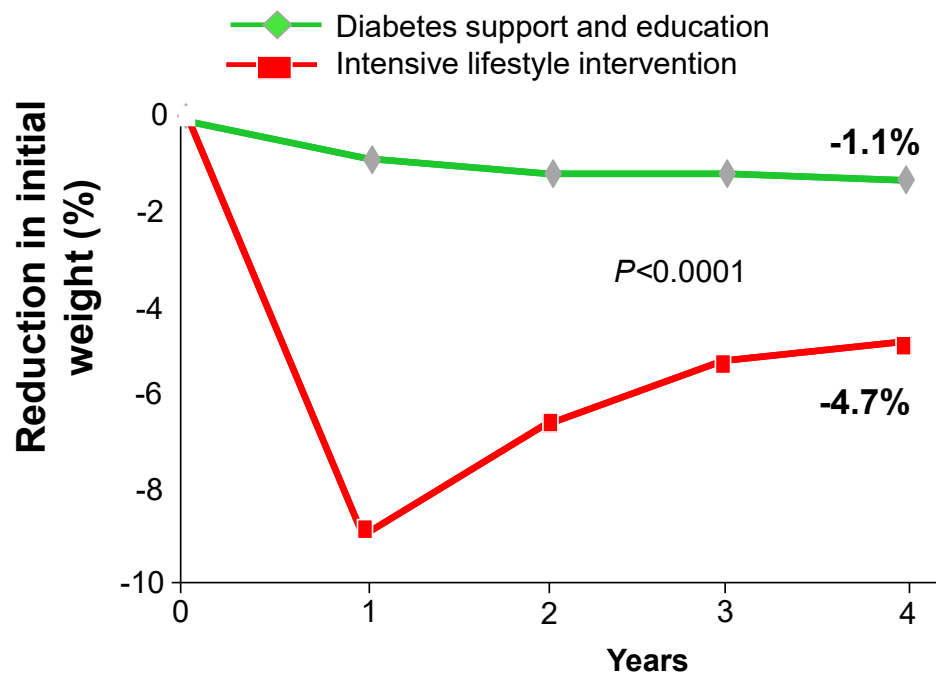
3. Lean M et al. *Lancet* 2018;391:541–51; 4. Davies MJ et al. *JAMA* 2015;314:687–99

Treatment Modalities for ABCD Patients



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

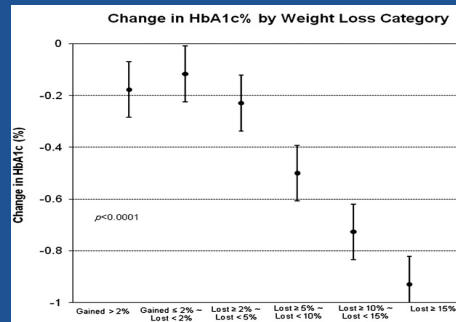
Look AHEAD Trial (N=5145)



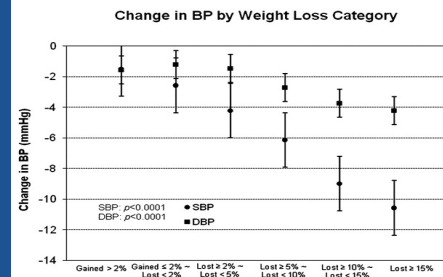
The Look AHEAD Research Group. Long Term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes: Four Year Results of the Look AHEAD Trial. [Arch Intern Med. 2010 Sep 27; 170\(17\): 1566–1575.](https://doi.org/10.1001/archinternmed.2010.1566)

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

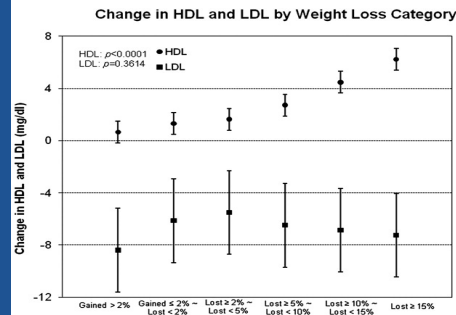
HbA1c
($\Delta\%$)



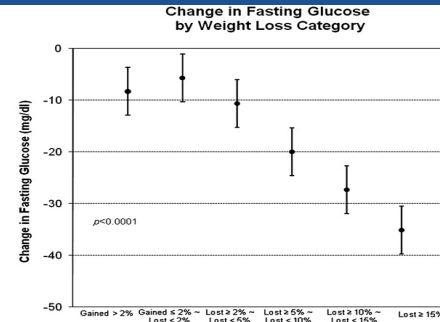
DBP and SBP
(Δ mmHg)



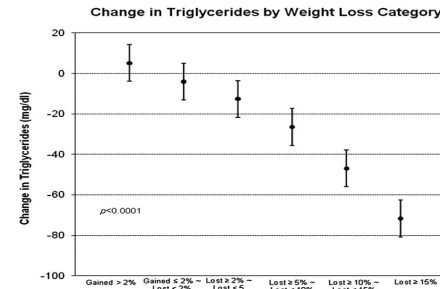
HDL and LDL
(Δ mg/dl)



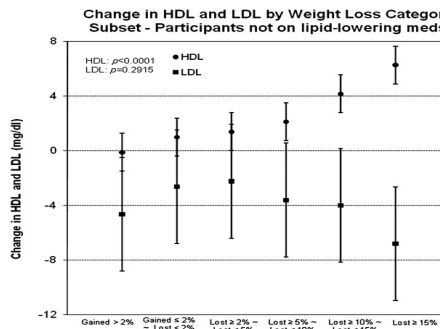
Fasting
Glucose
(Δ mg/dl)



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%

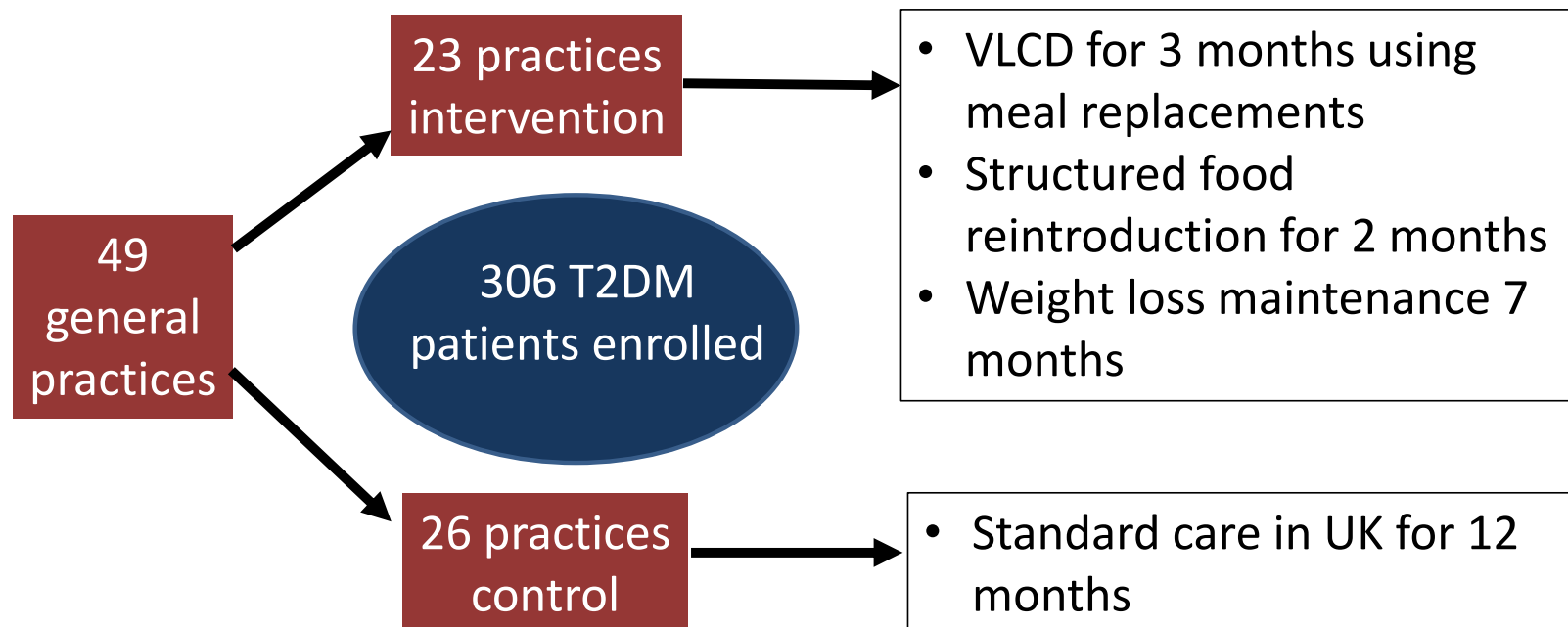
->15%

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Lean ME et al. Lancet 391(10120):541-551, 2018

THE LANCET

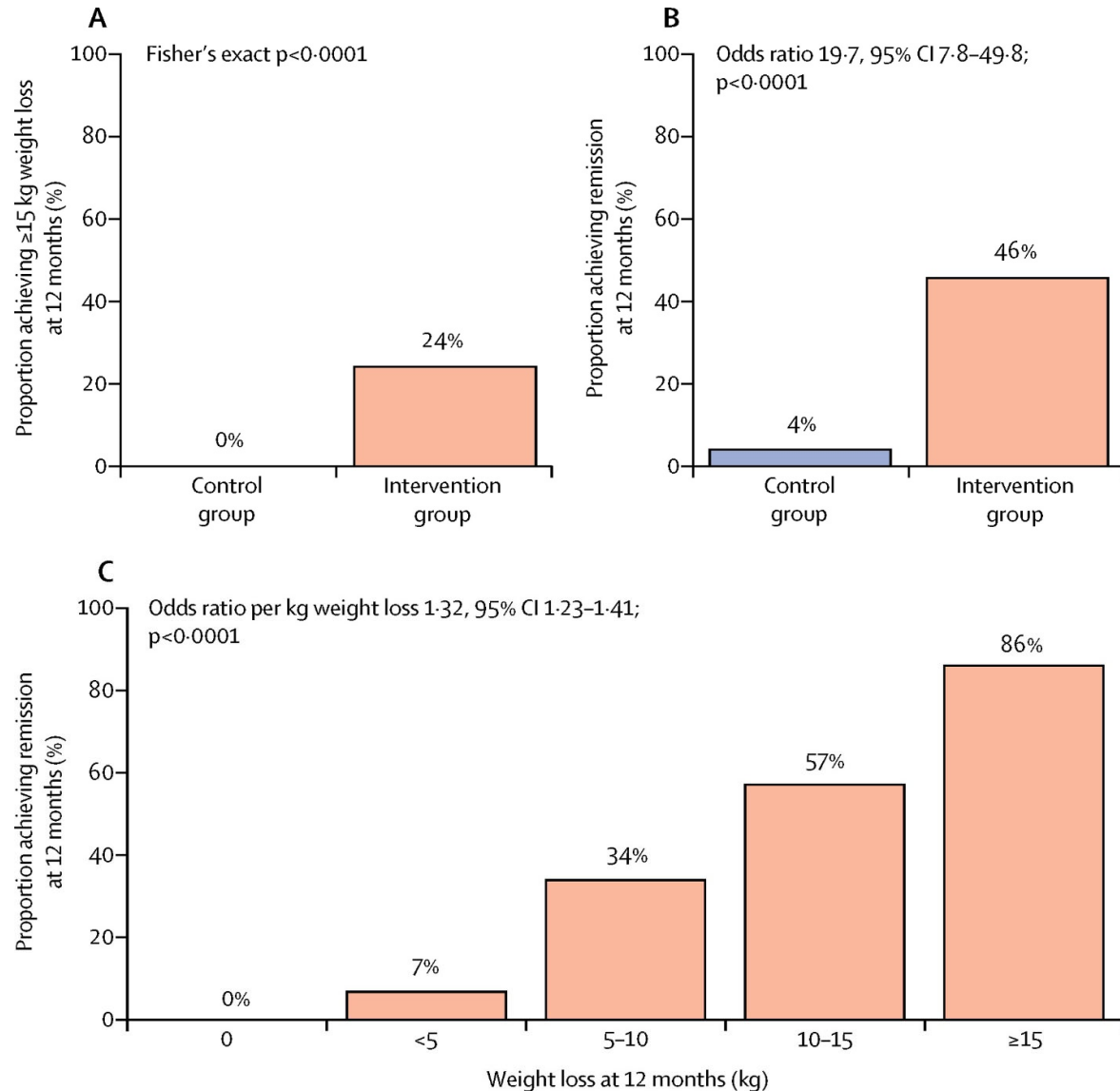
"About half of the medical students in the USA and European Union are women, but leadership in medicine globally does not reflect this gender balance."



DIRECT Study:

Weight loss and diabetes remission in primary care practices

Lean ME et al. Lancet
391(10120):541-551, 2018

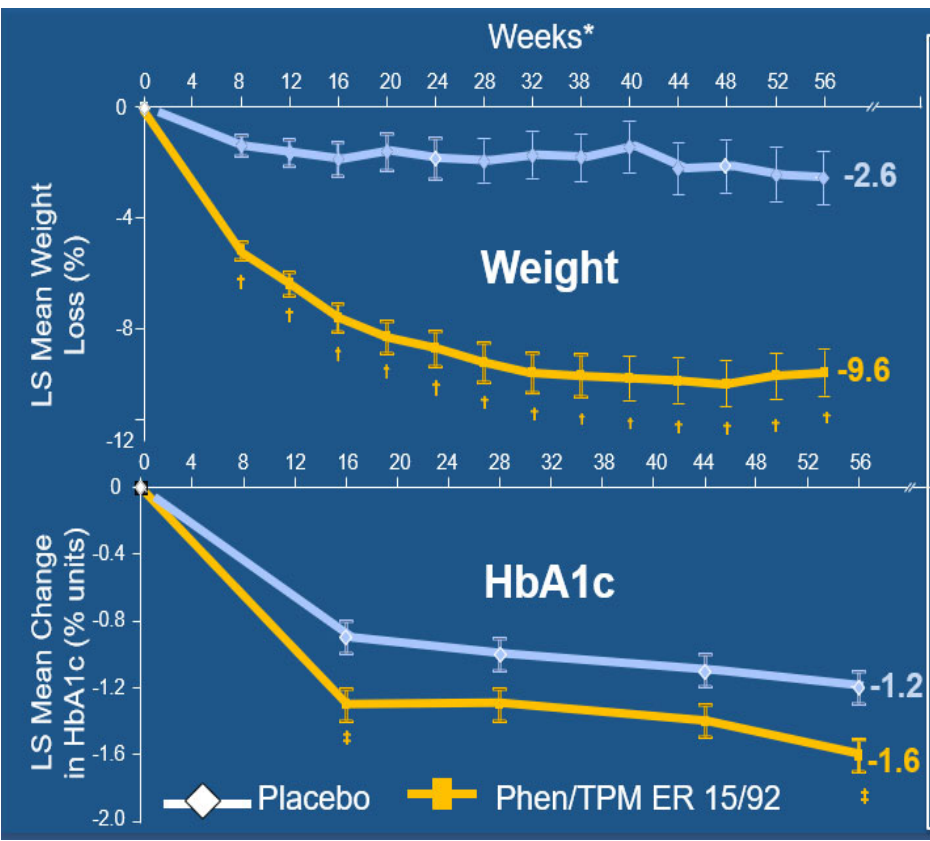


Obesity Pharmacotherapy

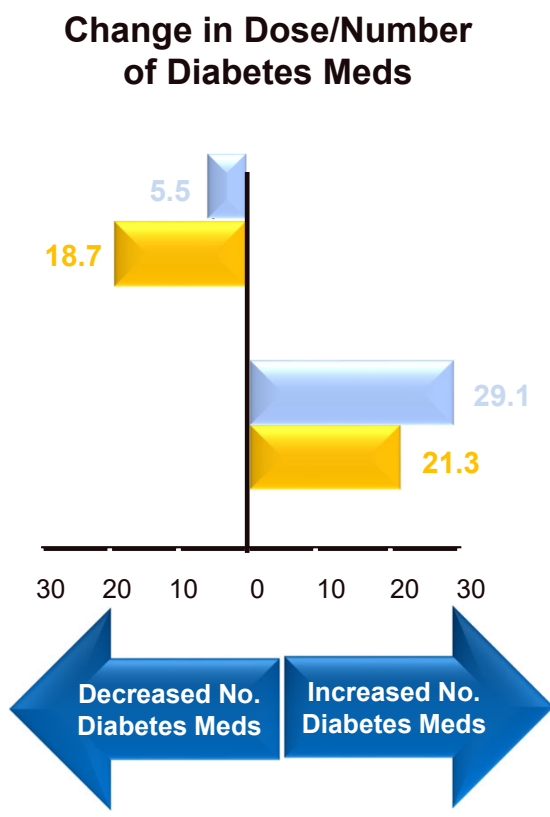
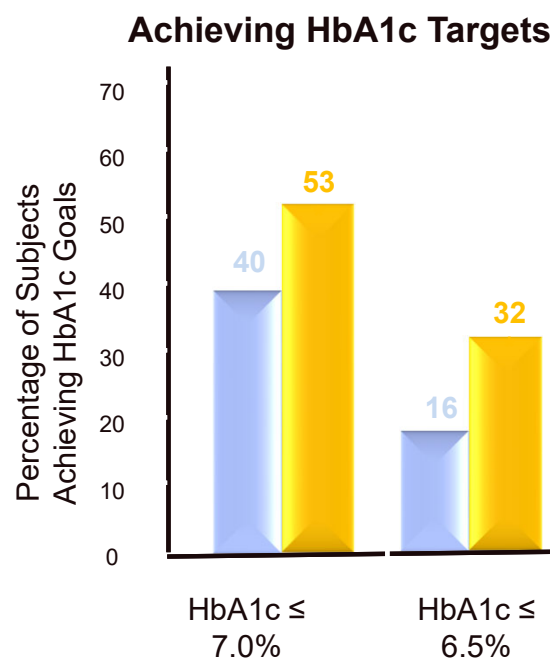
Agents	Action	Approval
<i>Previously available</i>		
Phentermine	• Sympathomimetic	• 1959
Orlistat	• GI lipase inhibitor	• 1997
<i>Recently Approved</i>		
Phentermine/ Topiramate ER	• Sympathomimetic/Anticonvulsant (GABA receptor modulation?)	• Approved, Summer 2012
Lorcaserin	• 5-HT_{2C} serotonin receptor agonist	• 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

Treatment of Obesity with Phentermine/Topiramate ER in T2DM

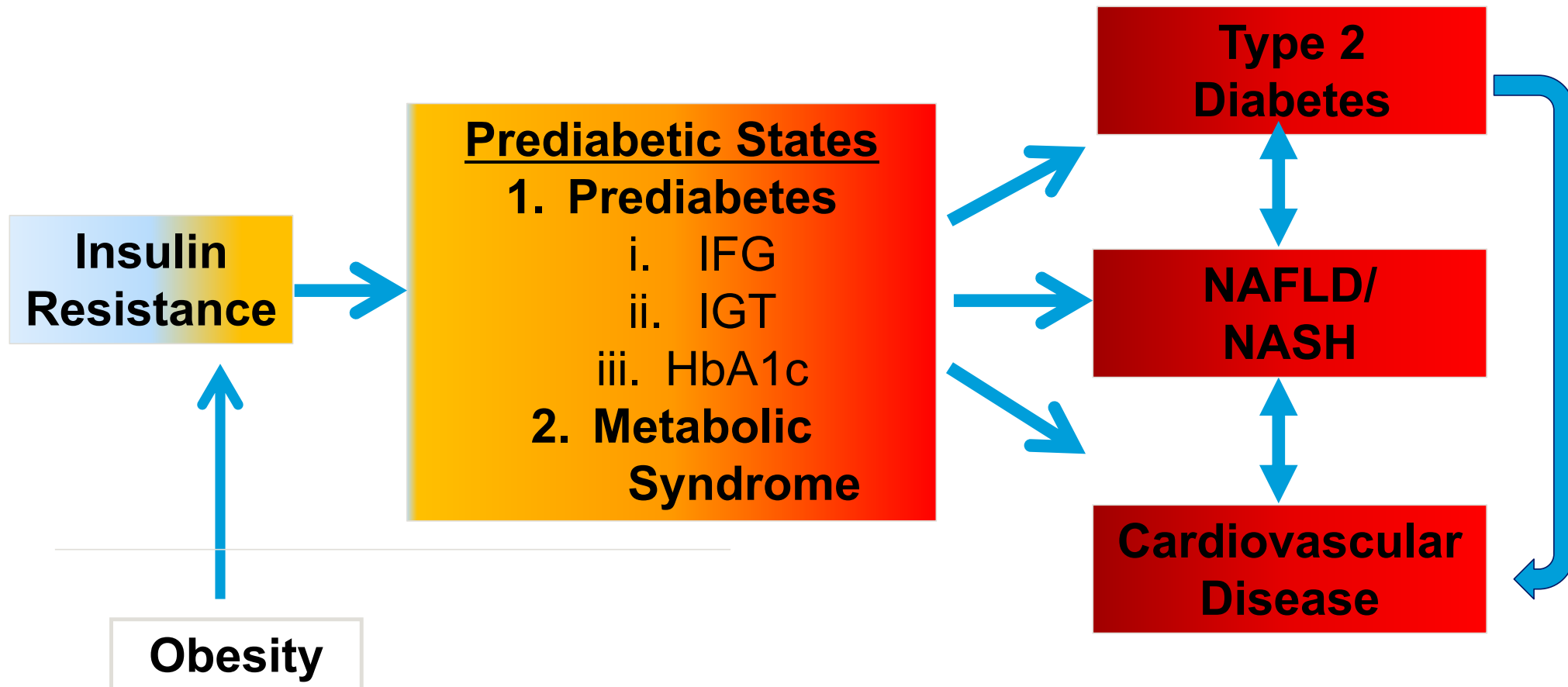
Garvey WT, et al. Diabetes Care 2014; 37(12):3309-3316



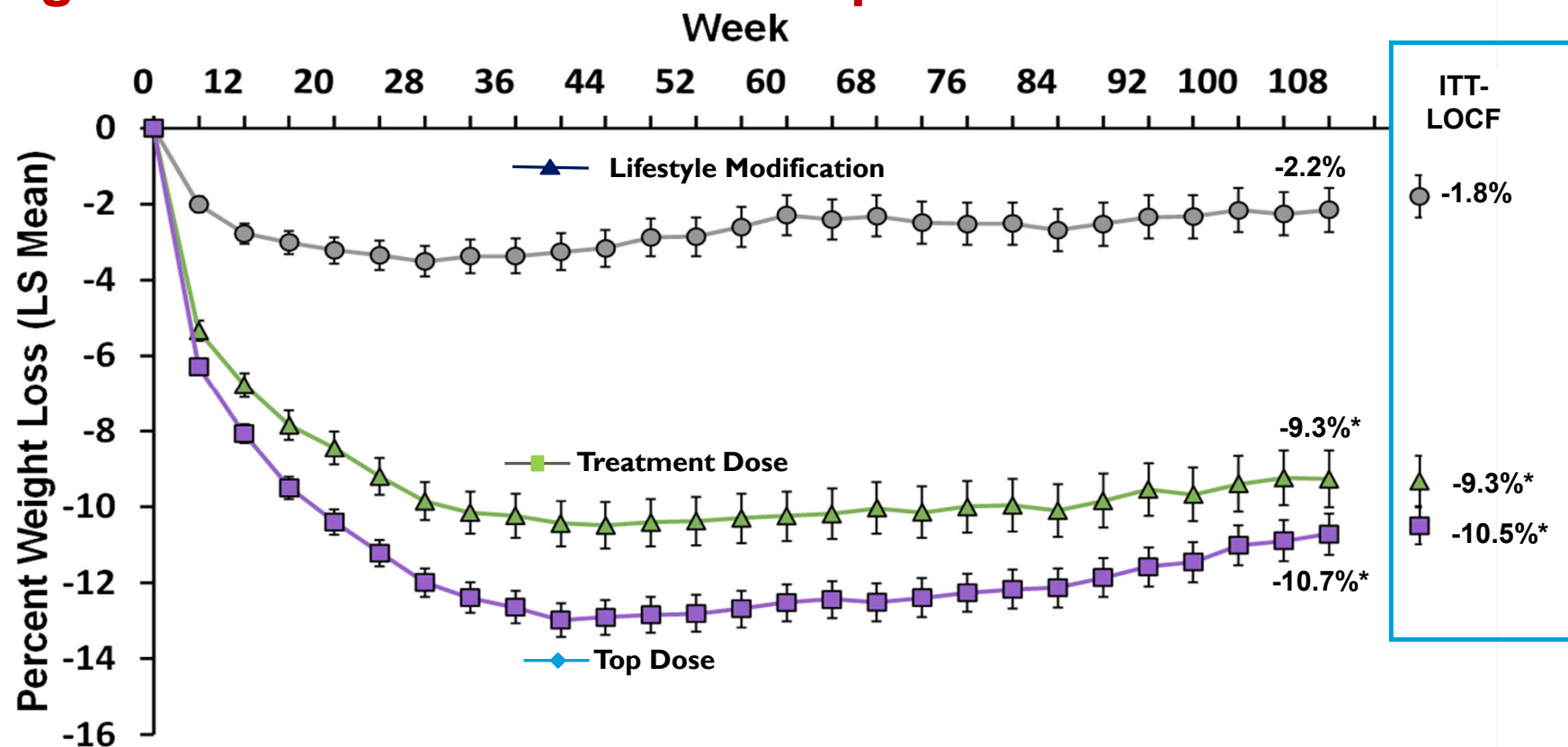
Placebo (n=55)
PHEN/TPM ER 15/92 (n=75)



The Spectrum of Cardiometabolic Disease



Phentermine/Topiramate ER and the SEQUEL STUDY: Weight Loss Over 2 Years in Completers

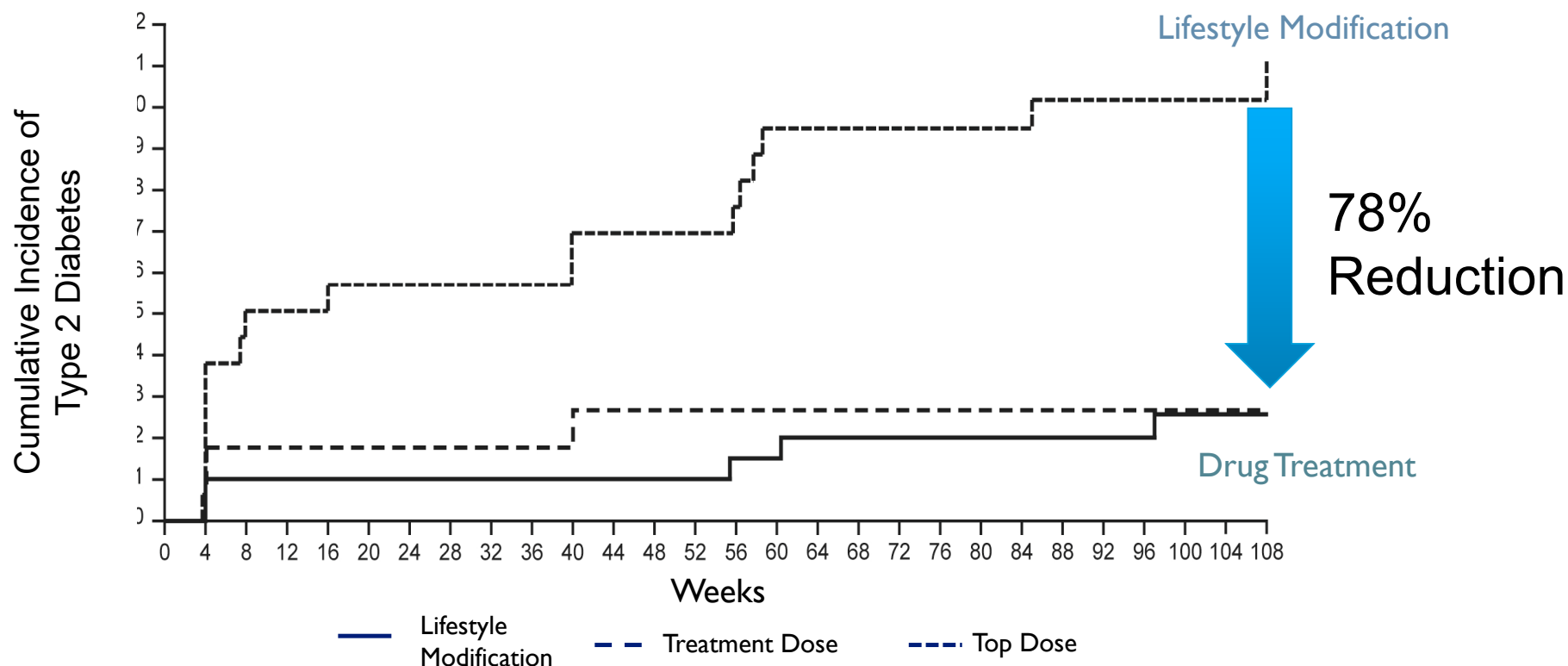


* $P < 0.0001$ vs placebo

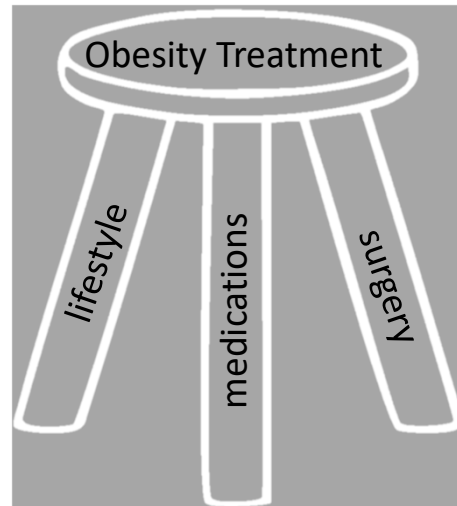
Garvey WT, et al. *Am J Clin Nutr.* 2012;95(2):297-308 2012

Prevention of Type 2 Diabetes in Patients with Prediabetes or Metabolic Syndrome at Baseline

Phentermine/Topiramate and the 2-Year SEQUEL STUDY



Evolution of Diabetes Therapy



**If you want to help patients with T2DM and
overweight/obesity -
Get Serious about Weight Loss Therapy**

THANK YOU