

Diabetes Mellitus 2021 Treatment Update

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The background is a dark teal color. It features several light teal circles of various sizes. A vertical red bar is located in the top right corner. A horizontal line with a red-to-yellow gradient runs across the top of the slide, positioned above the main text.

I have no conflict of interest or financial interest to disclose.

DECEMBER 8, 2003

TIME

**JACK
ACTS
HIS
AGE!**

Hillary Carroll, 11,
has "adult-onset"
diabetes

DIABETES ARE YOU AT RISK?

- WHO'S GETTING IT
- WHY IT'S STRIKING SO MANY
- WHAT YOU CAN DO TO FIGHT IT

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A SNAPSHOT

DIABETES IN THE UNITED STATES

DIABETES

**34.2
MILLION**

34.2 million people have diabetes



PREDIABETES

**88
MILLION**



88 million adults — more than 1 in 3 — have prediabetes

MORE THAN

8 IN 10

adults don't know they have prediabetes



If you have prediabetes, losing weight by:



EATING HEALTHY

&



BEING MORE ACTIVE

can cut your risk of getting type 2 diabetes in **HALF**



COST



**\$327
BILLION**

Total medical costs and lost work and wages for people with diagnosed diabetes

Risk of early death for adults with diabetes is

**60%
HIGHER**

than for adults without diabetes



People who have diabetes are at higher risk of serious health complications:



BLINDNESS



KIDNEY FAILURE



HEART DISEASE



STROKE



LOSS OF TOES, FEET, OR LEGS

COMMON TYPES OF DIABETES

TYPE 1

BODY DOESN'T MAKE ENOUGH INSULIN

- Can develop at any age
- No known way to prevent it

In adults, type 1 diabetes accounts for approximately

5-10%

of all diagnosed cases of diabetes



Just over 18,000 youth diagnosed each year in 2014 and 2015

TYPE 2

BODY CAN'T USE INSULIN PROPERLY

- Can develop at any age
- Most cases can be prevented

In adults, type 2 diabetes accounts for approximately

90-95%

of all diagnosed cases of diabetes



Nearly 6,000 youth diagnosed each year in 2014 and 2015

RISK FACTORS FOR TYPE 2 DIABETES:

1.5 MILLION

People 18 years or older diagnosed with diabetes in 2018



BEING OVERWEIGHT



HAVING A FAMILY HISTORY



BEING PHYSICALLY INACTIVE



BEING 45 OR OLDER

WHAT CAN YOU DO?

You can **prevent** or **delay** type 2 diabetes



LOSE WEIGHT IF NEEDED



EAT HEALTHY



BE MORE ACTIVE

LEARN MORE AT www.cdc.gov/diabetes/prevention OR SPEAK TO YOUR DOCTOR

You can **manage** diabetes



WORK WITH A HEALTH PROFESSIONAL



EAT HEALTHY



STAY ACTIVE

LEARN MORE AT www.cdc.gov/diabetes/managing OR SPEAK TO YOUR DOCTOR

REFERENCES

Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2020.

American Diabetes Association. Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019 Jan 1; 42 (Supplement 1).

American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018; 41(5):917-928.

CDC's Division of Diabetes Translation works toward a world free of the devastation of diabetes



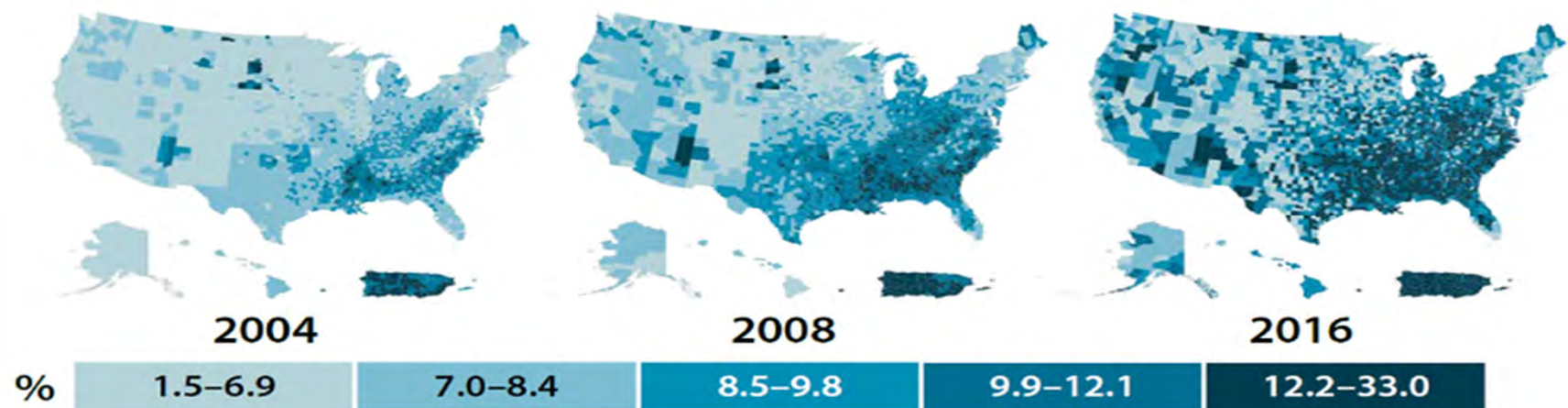
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

FS311643B

County-level Prevalence Among Adults

- ▶ Among US adults aged 20 years or older, age-adjusted, county-level data indicated:
 - ▶ In 2016, estimates of diagnosed diabetes prevalence varied across US counties, ranging from 1.5% to 33.0%
 - ▶ Median county-level prevalence of diagnosed diabetes increased from 7.8% in 2004 to 13.1% in 2016

Figure 3. Age-adjusted, county-level prevalence of diagnosed diabetes among adults aged 20 years or older, United States, 2004, 2008, and 2016



Note: Data were unavailable for some US territories.

Data sources: US Diabetes Surveillance System; Behavioral Risk Factor Surveillance System.

Clinical Impact of Diabetes

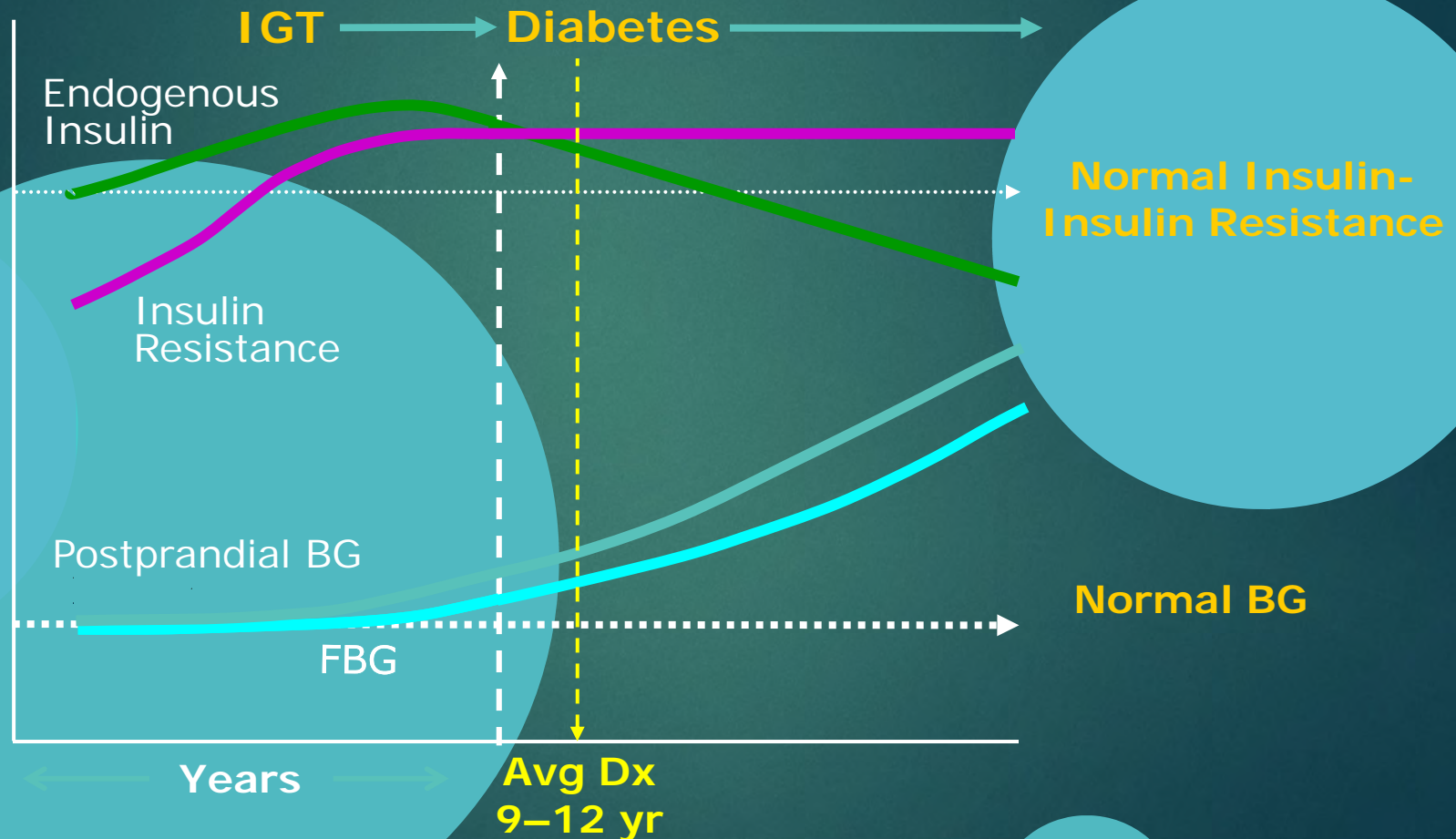
- Major cause of premature death and disability in the US
- Leading cause of new cases of blindness in working-aged adults
- 50% of nontraumatic lower extremity amputations
- 35% of new cases of end-stage renal disease
- 2 to 4-fold increase in cardiovascular risk

In a Single Year in the United States...

- ▶ 82,000 amputations are performed because of diabetes
- ▶ 12,000-24,000 people lose their eyesight from diabetes
- ▶ 41,000 people begin treatment for end-stage kidney disease
- ▶ 213,000 people die from diabetes and its complications

Progressive Nature of Type 2 Diabetes

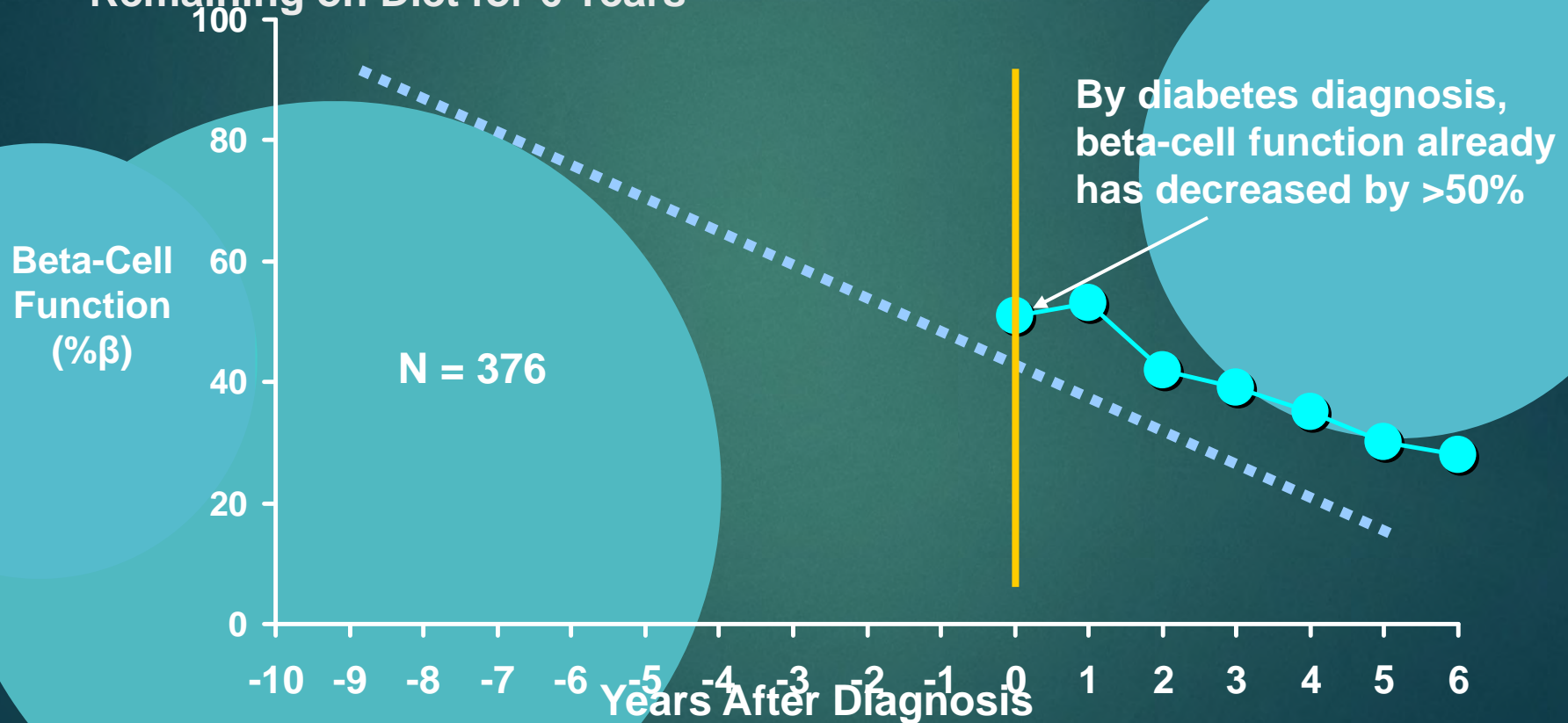
Insulin Deficiency Due to β -Cell Failure



Bergenstal RM et al. In: DeGroot LJ et al, eds. *Endocrinology*. 4th ed. Philadelphia: WB Saunders; 2001:821. Originally in *Type 2 Diabetes BASICS* (Minneapolis, International Diabetes Center, 2000). Adapted with permission from International Diabetes Center

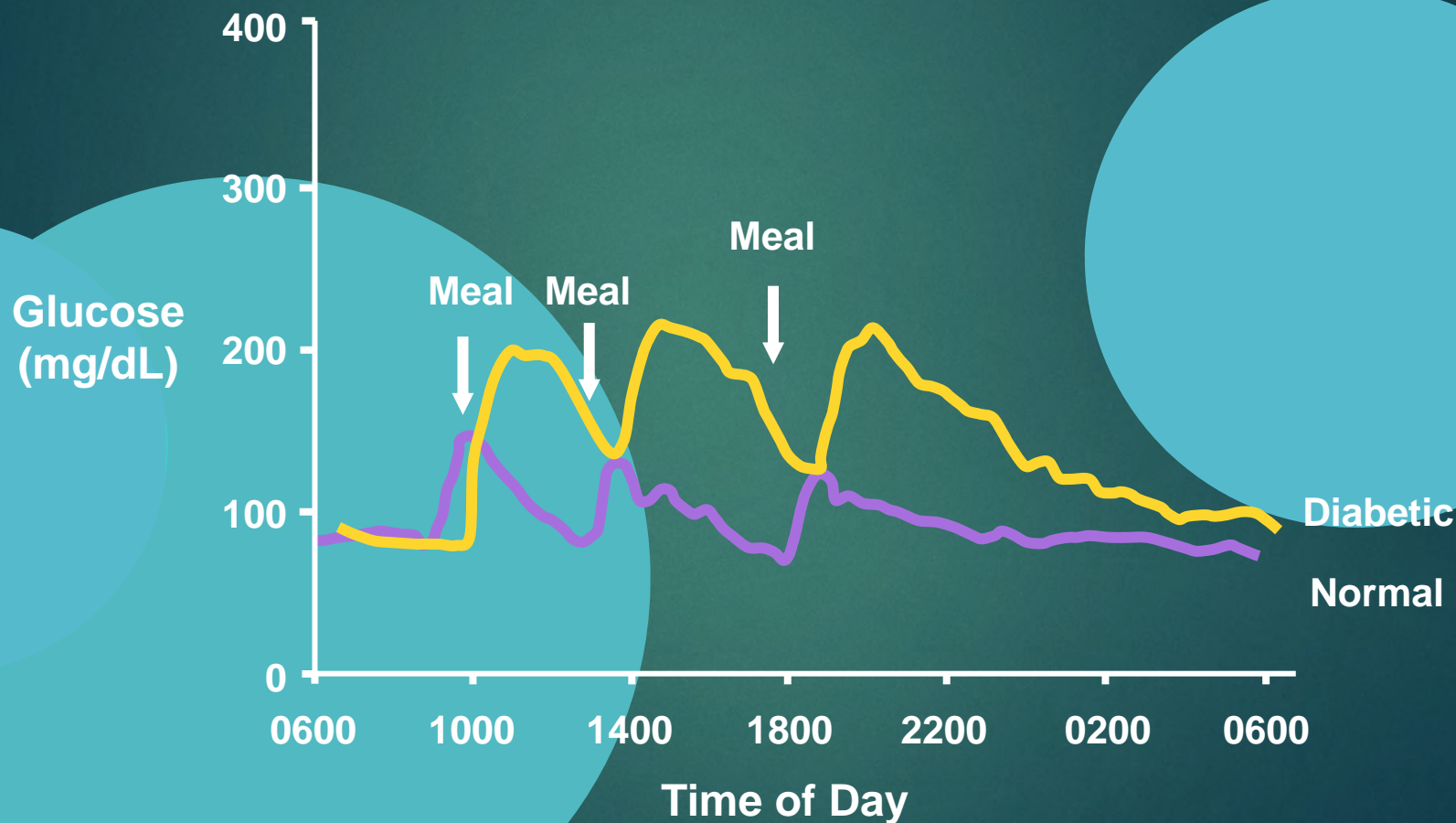
By the Time of Diagnosis, Beta-Cell Decline Exceeds 50%

UKPDS: Beta-Cell Function for Patients with Type 2 Diabetes
Remaining on Diet for 6 Years



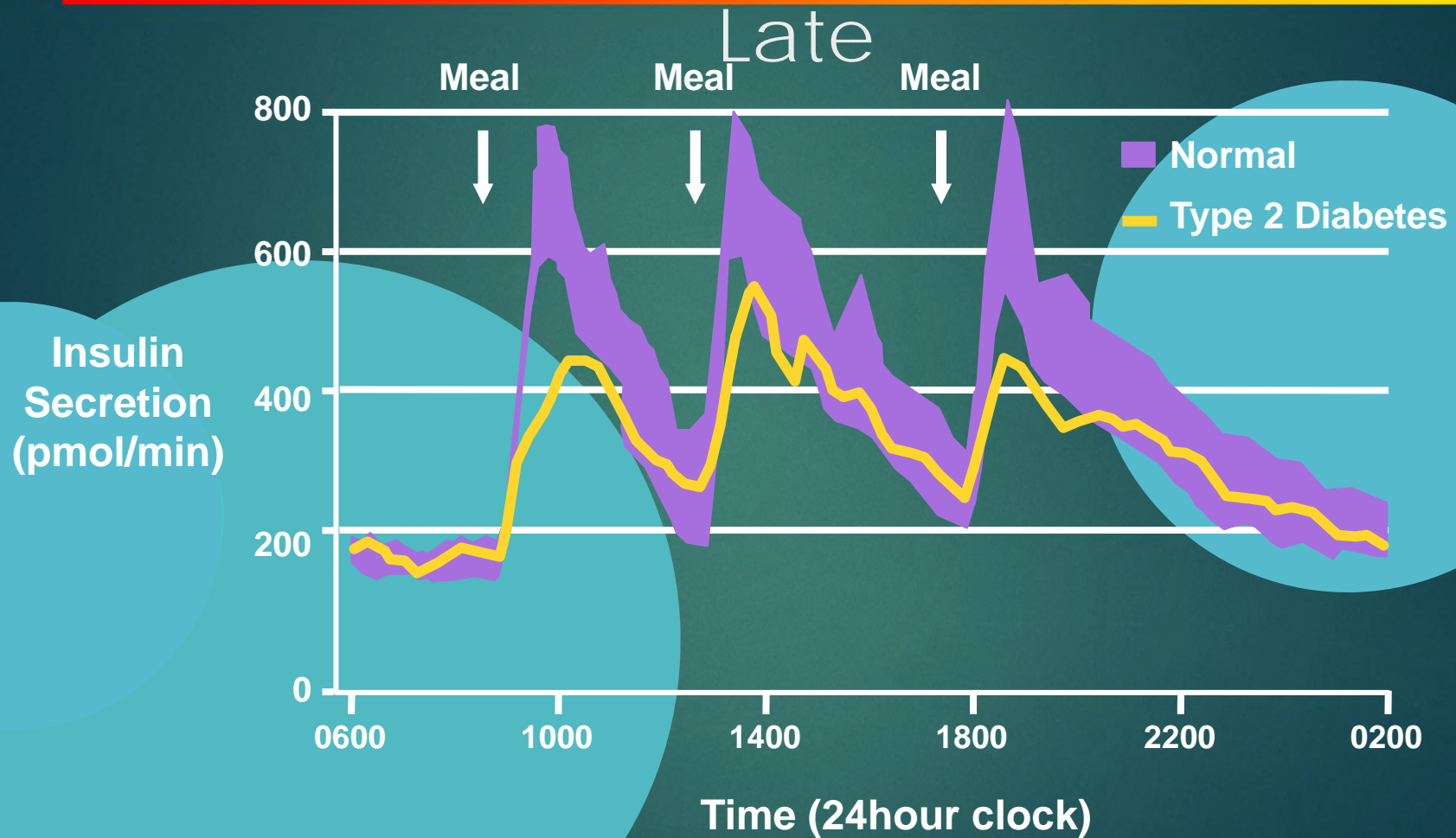
Adapted from UKPDS Group. *Diabetes*. 1995;44:1249.

Glucose Excursions in Type 2 Diabetes: PPG Elevations Even When FBG Is Normalized



Polonsky KS et al. *N Engl J Med.* 1988;318(19):1231–1239.

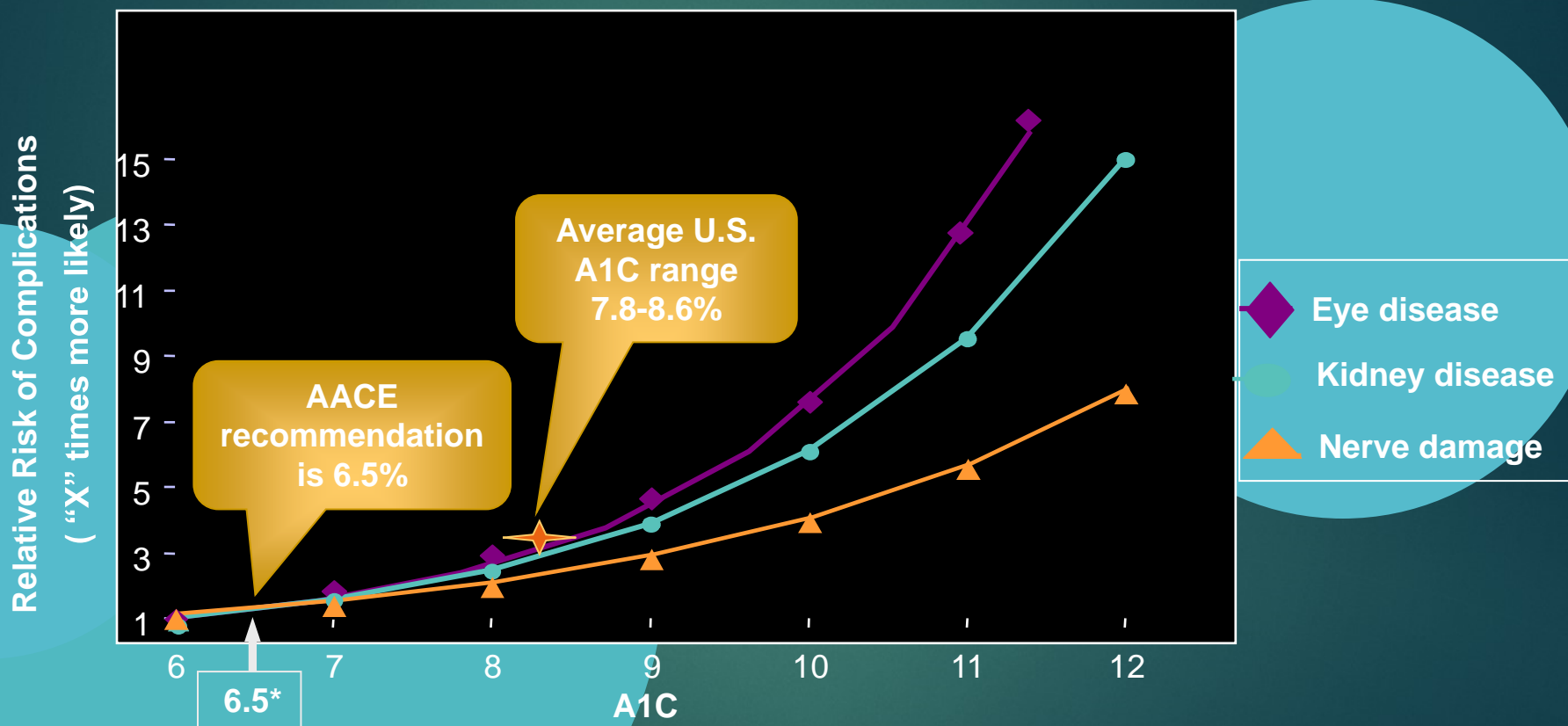
Insulin Secretion in Type 2 Diabetes Is Delayed and Blunted: Too Little, Too Late



Polonsky KS et al. *N Engl J Med.* 1996;334(12):777-783.

DCCT Results

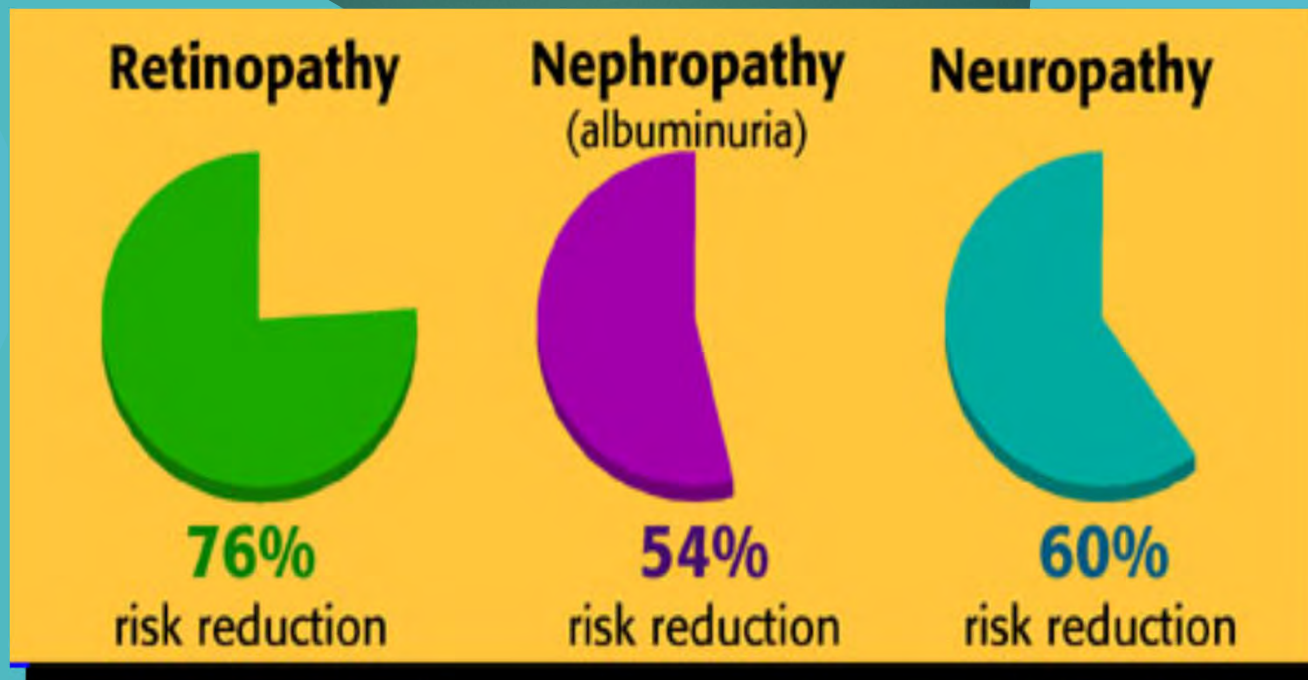
A1C and Relative Risk of Diabetic Complications



Skyler, J: Chronic Complications of Diabetes Endo Met Clin Am, vol 25, 2, p.243- 254, June 1996 Adapted from DCCT Research Group: *N England Journal of Medicine*. 1993;329:977-986. *Endocrine Practice 2002, 8 (supp 1), pg. 7. AACE recommends less than or equal to 6.5 HbA1c. Minshall M, Roze S, Palmer A, et al. Treating diabetes to accepted standards of care: a 10-year projection of the estimated economic and health impact in patients with type 1 and type 2 diabetes in the US. *Clin Ther*. 2005;27:940-950.

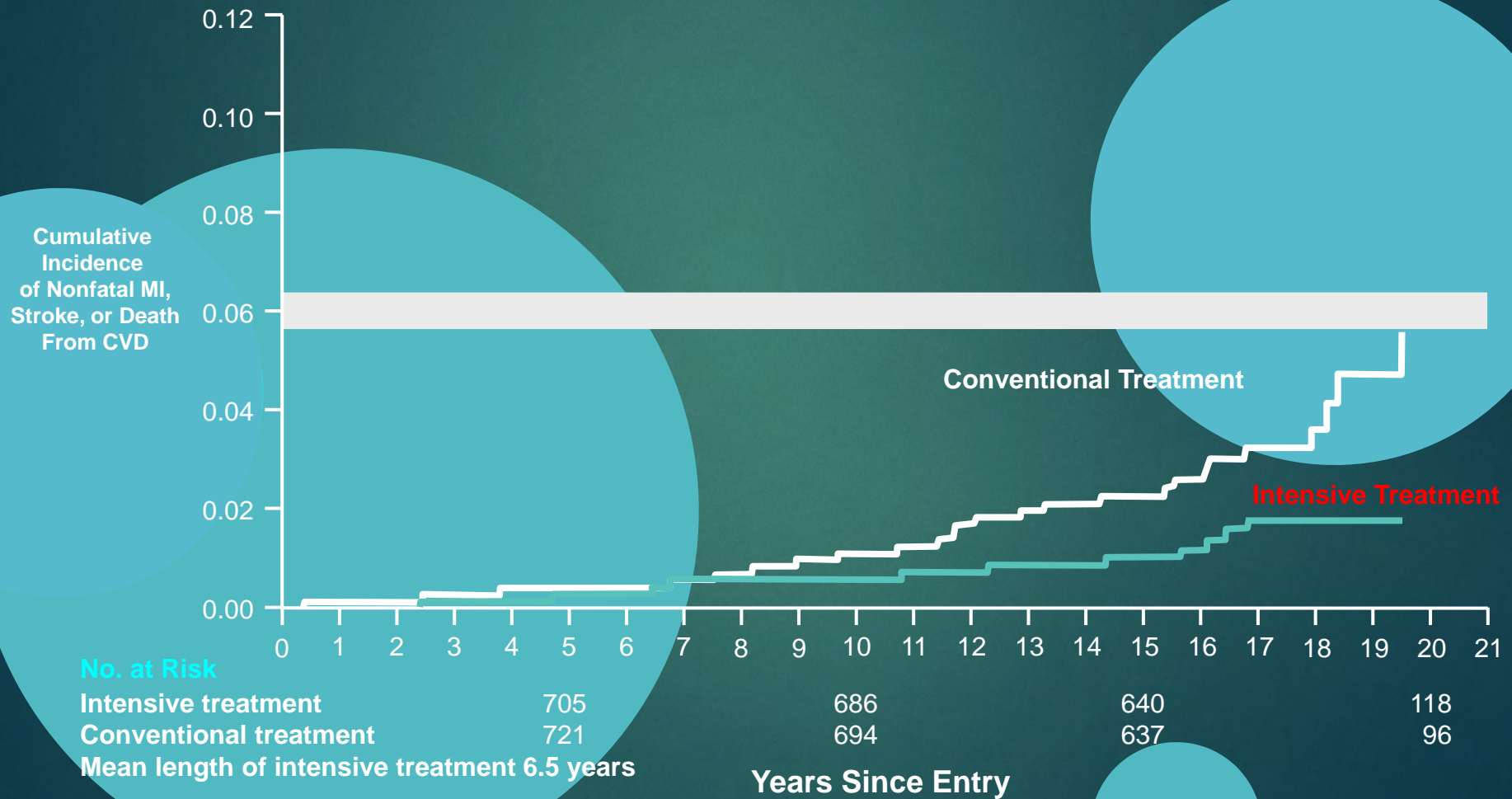
Diabetes Control and Complications Trial (DCCT)

- ▶ Tight control ($\text{HbA}_{1c} \leq 7.2\%$) significantly reduces the risk of diabetes complications in type 1 diabetes



Risk of First Occurrence of Nonfatal MI, Stroke, or Death From CVD Reduced by 57% Over the Long Term With Intensive Treatment

DCCT/EDIC: Mean 17 Years of Follow-Up



DCCT/EDIC. *N Engl J Med.* 2005;353:2643-2653.

EDIC – Type 1 Diabetes and CV Events

Conclusions

- ▶ First long-term study to show that early intensive control of A1C can reduce CV events relative to conventional control
 - 42% risk reduction in all CV events
 - 57% risk reduction in nonfatal MI, stroke and CV death
- ▶ These risk reductions are greater than those seen in hypertension or lipid treatment studies to date
- ▶ The beneficial CV results were mediated by reductions in A1C
Controlled A1C accounted for 97% of CV event reduction

The Need for Tight Glycemic Control

According to the United Kingdom Prospective Diabetes Study (UKPDS) 35, Every 1% Decrease in A1C Resulted in:

21%

Decrease
in risk of any
diabetes-related
end point
($P < .0001$)

14%

Decrease
in risk of MI
($P < .0001$)

12%

Decrease
in risk of
stroke
($P = .04$)

37%

Decrease
in risk of
microvascular
complications
($P < .0001$)

Progression of Diabetic Retinopathy

- Diabetic retinopathy is frequently present at diagnosis of Type 2 diabetes¹
- Once present, diabetic retinopathy tends to progress, resulting in²:
 - Microaneurysms
 - Retinal hemorrhages
 - Severe retinal hemorrhages
- Diabetic retinopathy may lead to diabetic macular edema
- Glycemic, blood pressure, and lipid control are necessary
- Diabetic retinopathy may require laser treatment and/or treatment with photocoagulation
- Costs of diabetic retinopathy are extremely high, accounting for \$500 million per year in the US³

¹UKPDS Group. *Lancet*. 1998;352:837-853.

²Stratton IM, et al. *Diabetologia*. 2001;44:156-163.

³Porta M, Bandello F. *Diabetologia*. 2002;45:1617-1634.

Diabetic Peripheral Neuropathy

- Most prevalent of the distal polyneuropathies
- Affects up to 50% of patients with diabetes
- Symptoms present in up to 20% of these patients
- Can significantly decrease quality of life in up to 10%

Impact of Diabetic Peripheral Neuropathy



Early tissue damage



Clawing toes, callus,
superficial ulceration



Plantar ulcer, callus



Calluses scraped away
revealing ulcers

Screening and Diagnosis for Diabetic Peripheral Neuropathy



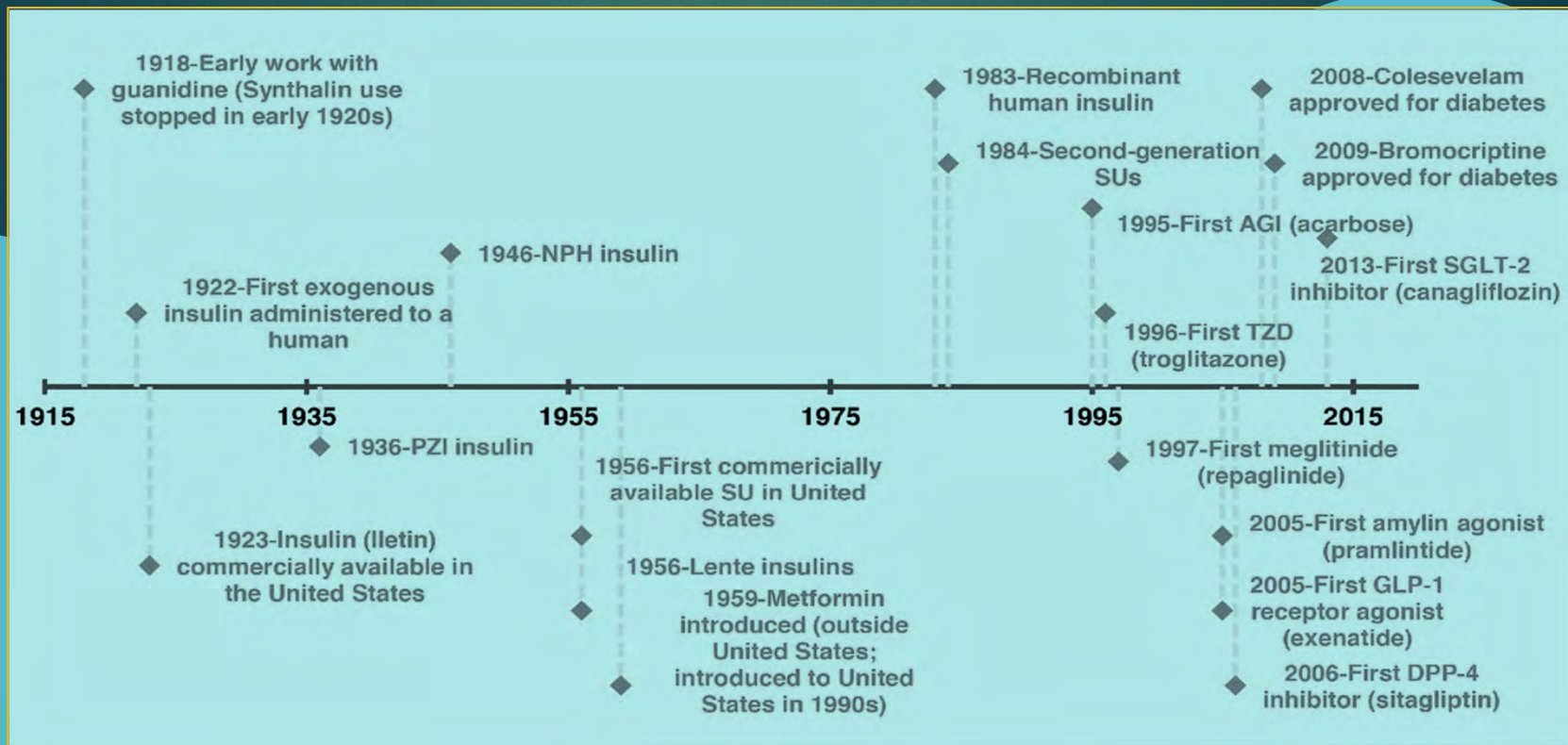
Tuning Fork



**Monofilament
screening test**

- **History/physical exam**
 - Eliminate causes other than DPN
- **Neurological exam**
 - Vibration detection threshold (VDT)
 - Tuning fork
 - Proprioception
 - Position sensitivity by flexion/extension of great and small toe
 - Deep tendon reflexes
 - Reflex hammer
 - Pressure sensation
 - Monofilament
 - Pain sensation
 - Pin prick
 - Light touch sensation
 - Cotton-wool swab
- **Diagnosis**
 - Can be supported by:
 - Electrophysiology
 - Quantitative sensory testing

History of Diabetes Medications



White JR Jr. *Diabetes Spectr.* 2014;27:82-86.

Case Study

- Derek is a 56-year-old man with a history of T2DM, HTN, and hyperlipidemia for 10 years
- Recent positive stress test
- Meds:
 - HCTZ 25 mg daily
 - Lisinopril 5 mg daily
 - Atorvastatin 20 mg daily
 - Glyburide 5 mg daily
 - Sitagliptin 100 mg daily
 - Metformin 500 mg twice daily

Case Study *(continued)*

- ▶ Family history
 - Father had T2DM; died from MI at age 60
- ▶ Physical examination
 - BMI 33 kg/m²
 - BP 145/92 mmHg
 - Pulse, 92 bpm; + S4 gallop
 - Lungs clear
 - No edema
- ▶ Laboratory evaluation
 - FPG: 145 mg/dL
 - HbA1c: 8.0%,
 - LDL: 106 mg/dL
 - TG:198 mg/dL
 - Creatinine: 1.3 mg/dL

Case Study Question

What do you do next to optimize this patient's regimen and reduce his risks?

- ▶ Increase metformin
- ▶ Increase glyburide
- ▶ Add basal insulin
- ▶ Stop glyburide and start basal insulin
- Add pioglitazone
- Add a GLP 1 RA
- Stop sitagliptin and add a GLP 1 RA
- Other

Insulin secretion

- ↑ Sulfonyureas
- ↑ Meglitinides
- ↑ Incretins

Glucagon secretion

- ↓ Incretins
- ↓ Amylin

GI

- Incretins
- α glucosidase inhibitors
- Amylin
- Bile acid sequestrant



Appetite control

- Incretins
- Amylin

Hyperglycemia

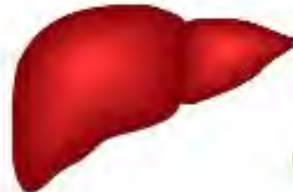


Glucose reabsorption

- ↓ SGLT2 inhibitors

Hepatic glucose output

- ↓ Metformin
- ↓ Thiazolidinediones

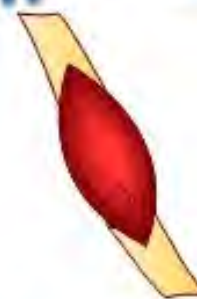


Lipotoxicity

- Thiazolidinediones
- Salicylates

Glucose uptake and utilization

- ↑ Thiazolidinediones
- ↑ Metformin



Pharmacologic Therapy

Insulin Sensitizers:

▶ Biguanides

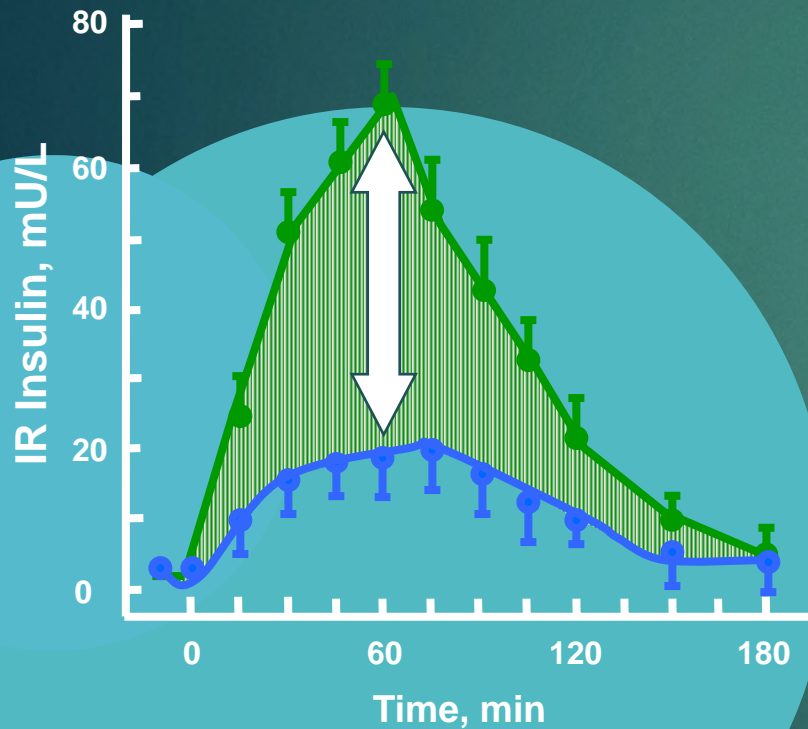
- ▶ Decrease hepatic glucose production
- ▶ Decrease intestinal glucose absorption
- ▶ Increase peripheral glucose uptake and utilization

▶ Metformin

- ▶ Primary cellular target for metformin is believed to be complex I of mitochondrial oxidative phosphorylation
- ▶ Metformin inhibits mitochondrial complex I and increases the AMP/ATP ratio, which leads to the activation of the energy-sensing kinase AMPK (adenosine monophosphate-activated protein kinase)

The Incretin Effect Is Diminished in Subjects With Type 2 Diabetes

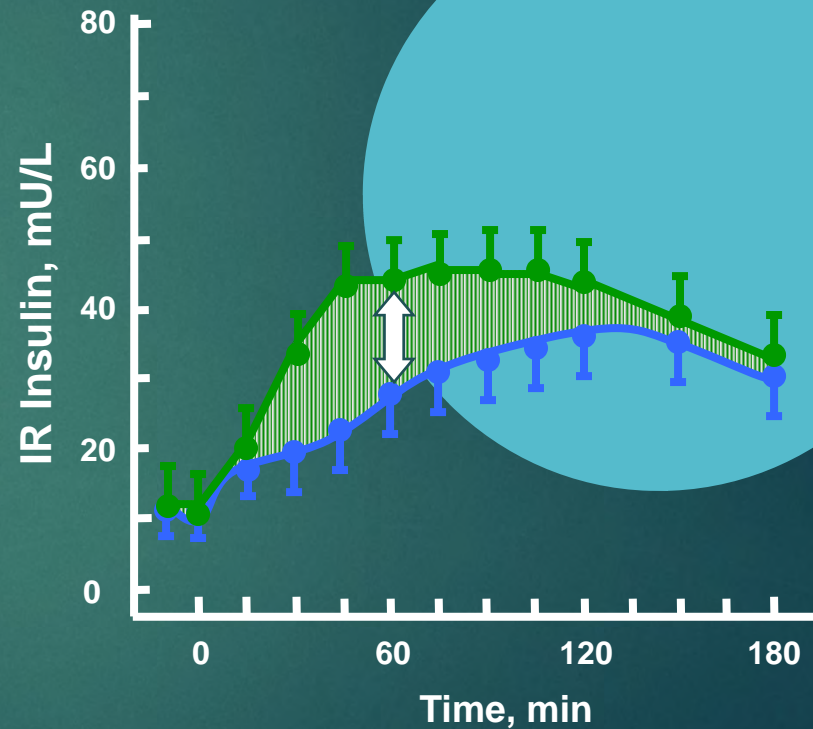
**Control Subjects
(n=8)
Normal Incretin Effect**



●—● Oral glucose load

●—● Intravenous (IV) glucose infusion

**Subjects With Type 2 Diabetes
(n=14)
Diminished Incretin Effect**

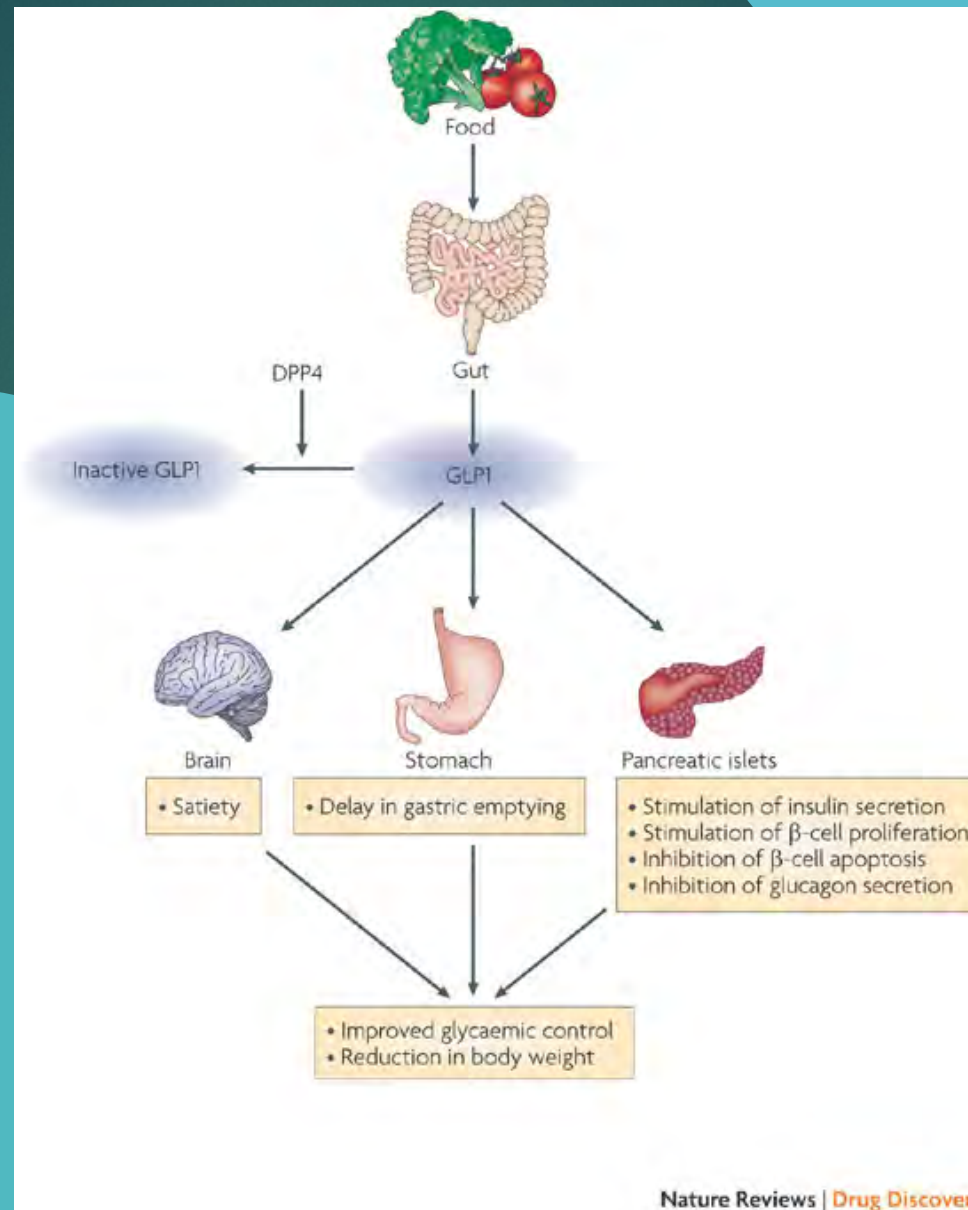


Pharmacologic Therapy

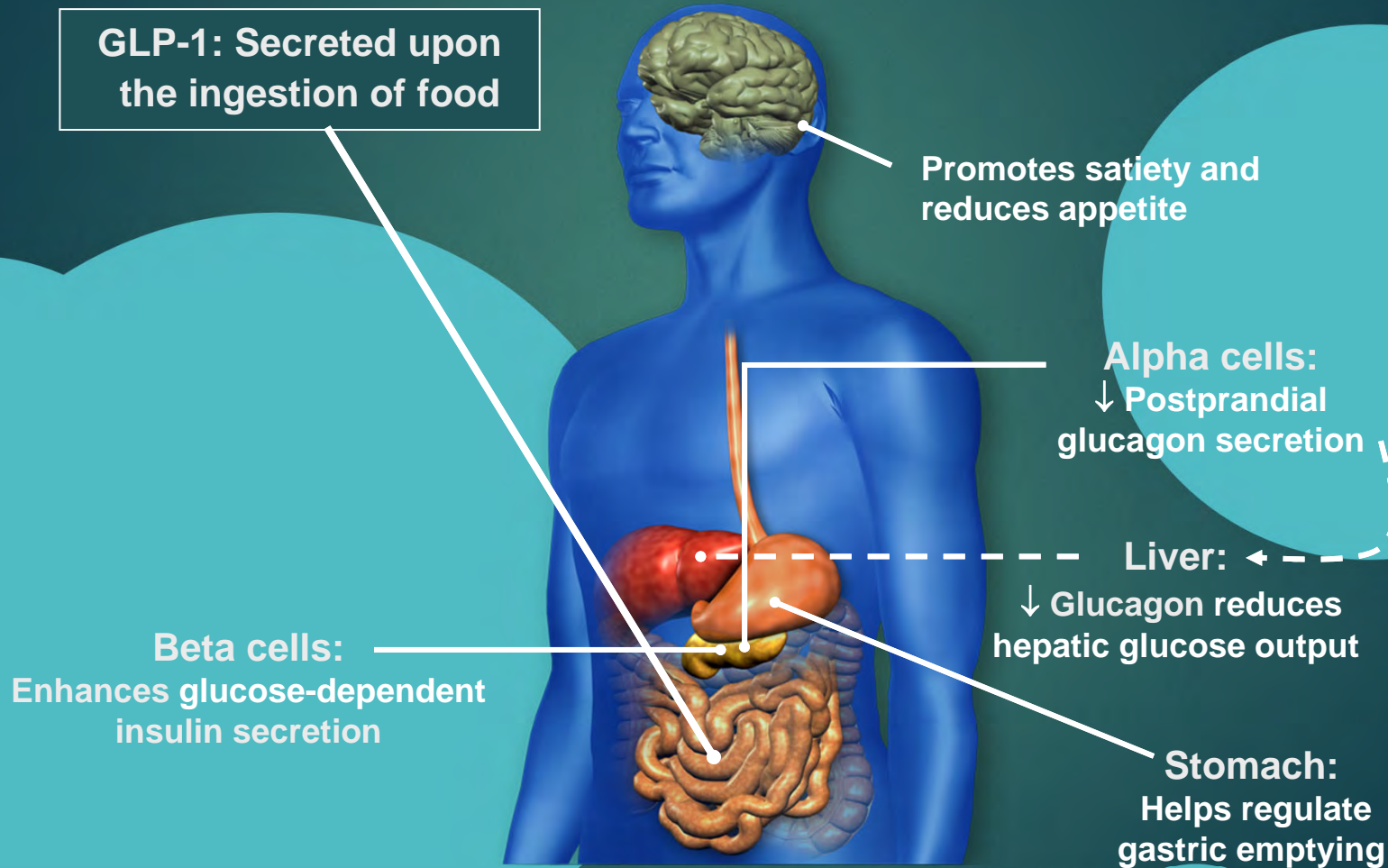
Incretins:

- Group of gastrointestinal hormones that stimulate a decrease in blood glucose levels. They include glucagon-like peptide-1 (GLP-1); glucose-dependent insulinotropic peptide (GIP; previously known as gastric inhibitory peptide); and, pituitary adenylate cyclase-activating polypeptide (PACAP)
 - Stimulate insulin release from β cells in a glucose dependent manner
 - Decrease GI motility, thus delaying gastric emptying and leading to earlier satiety
 - GLP-1 agonists
 - **Exenatide (immediate release and extended release)**
 - **Liraglutide**
 - **Albiglutide**
 - **Dulaglutide**
 - **Semaglutide**
 - DPP-4 Inhibitors
 - Increase endogenous GLP-1 levels
 - **Sitagliptin**
 - **Saxagliptin**
 - **Linagliptin**
 - **Alogliptin**

Modulation of Insulin and Glucagon Levels: The Enteroinsular Axis



GLP-1 Modulates Numerous Functions in Humans



Data from Flint A, et al. *J Clin Invest.* 1998;101:515-520; Data from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422
Data from Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553; Data from Drucker DJ. *Diabetes.* 1998;47:159-169

GLP-1 and GIP Are Incretin Hormones

GLP-1

- Is released from L cells in ileum and colon^{1,2}
- Stimulates insulin response from beta cells in a glucose-dependent manner¹
- Inhibits gastric emptying^{1,2}
- Reduces food intake and body weight²
- Inhibits glucagon secretion from alpha cells in a glucose-dependent manner¹

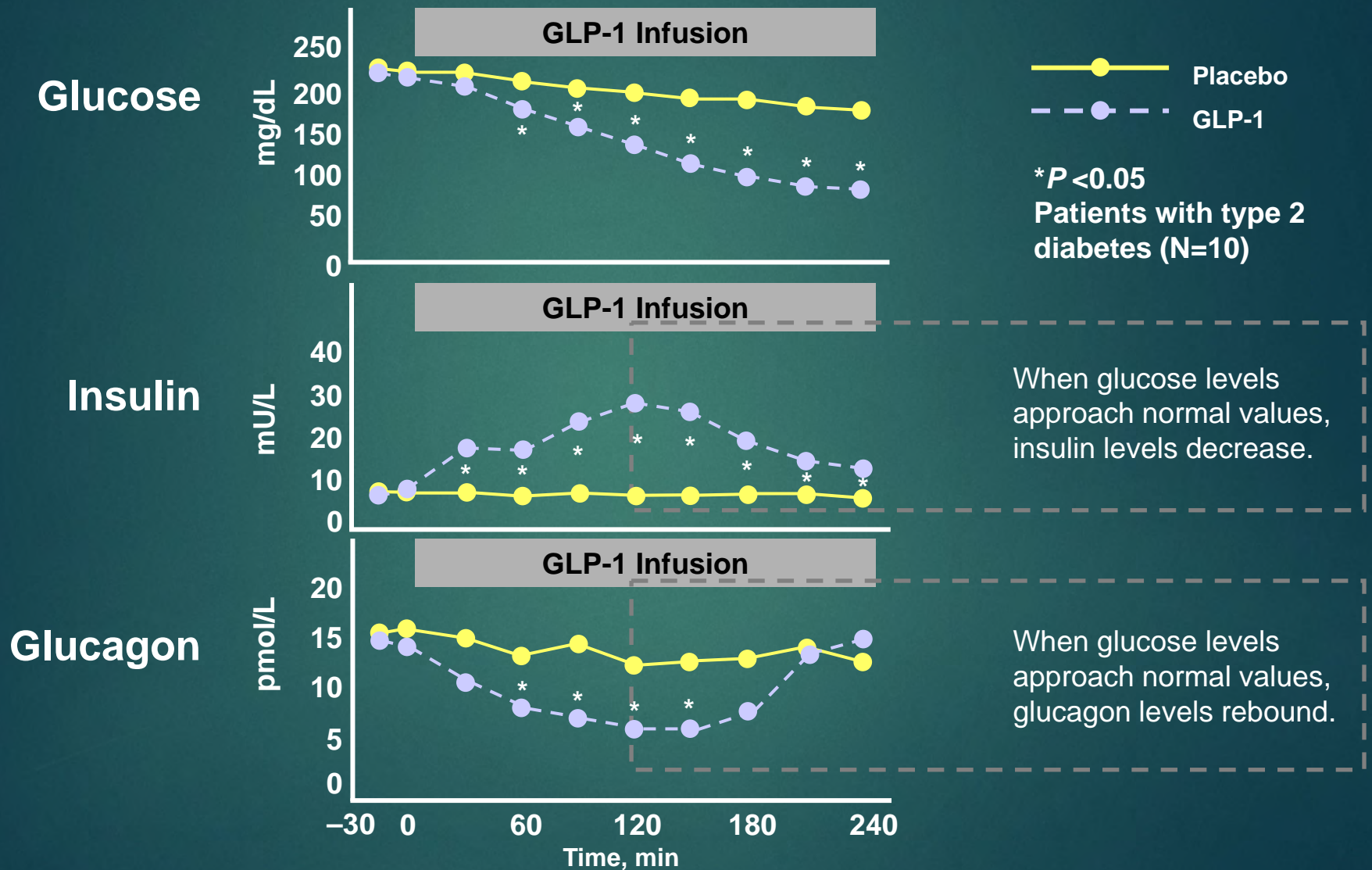
GIP

- Is released from K cells in duodenum^{1,2}
- Stimulates insulin response from beta cells in a glucose-dependent manner¹
- Has minimal effects on gastric emptying²
- Has no significant effects on satiety or body weight²
- Does not appear to inhibit glucagon secretion from alpha cells^{1,2}

1. Meier JJ et al. *Best Pract Res Clin Endocrinol Metab.* 2004;18:587–606.

2. Drucker DJ. *Diabetes Care.* 2003;26:2929–2940.

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

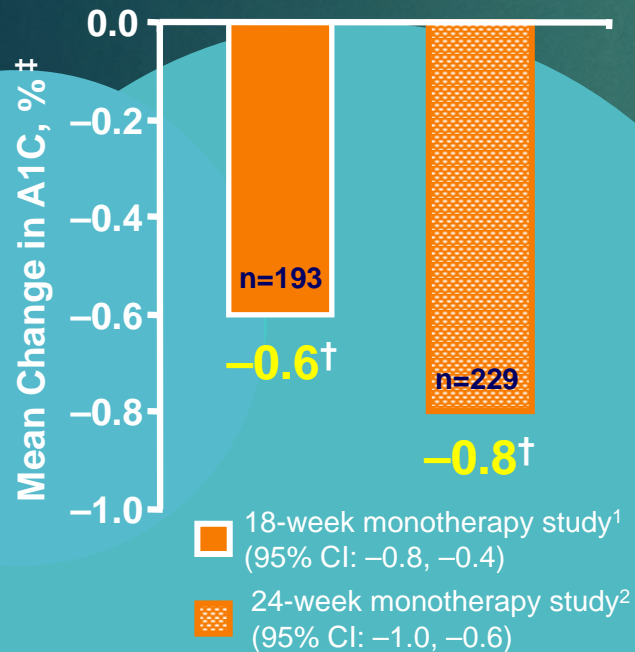


JANUVIA™ (sitagliptin): Significant A1C Reductions as Monotherapy

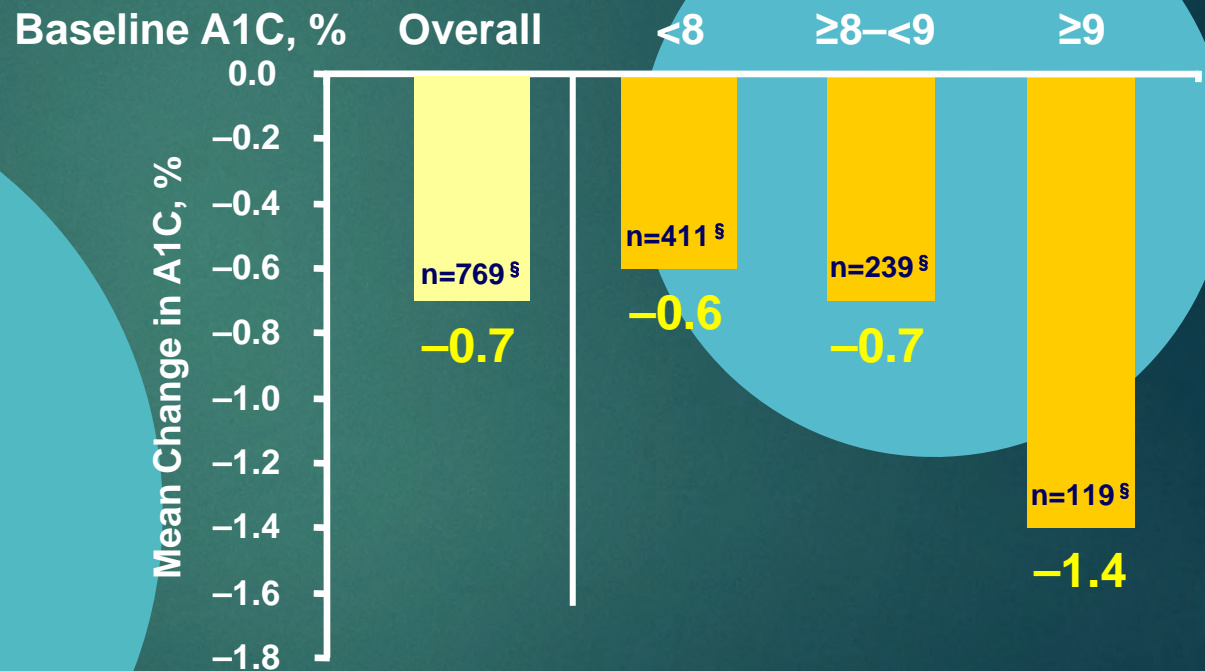
Placebo-adjusted results

A1C

Mean Baseline: 8.0%
P<0.001*



Inclusion Criteria: 7%–10%
Prespecified Pooled Analysis at 18 Weeks^{||}



CI=confidence interval. *Compared with placebo. [†]Least-squares means adjusted for prior antihyperglycemic therapy status and baseline value. [‡]Difference from placebo. [§]Combined number of patients on JANUVIA or placebo. ^{||}P<0.001 overall and for treatment-by-subgroup interactions.

1. Raz I et al. *Diabetologia*. 2006;49:2564–2571.

2. Aschner P et al. *Diabetes Care*. 2006;29:2632–2637.

Pharmacologic Therapy

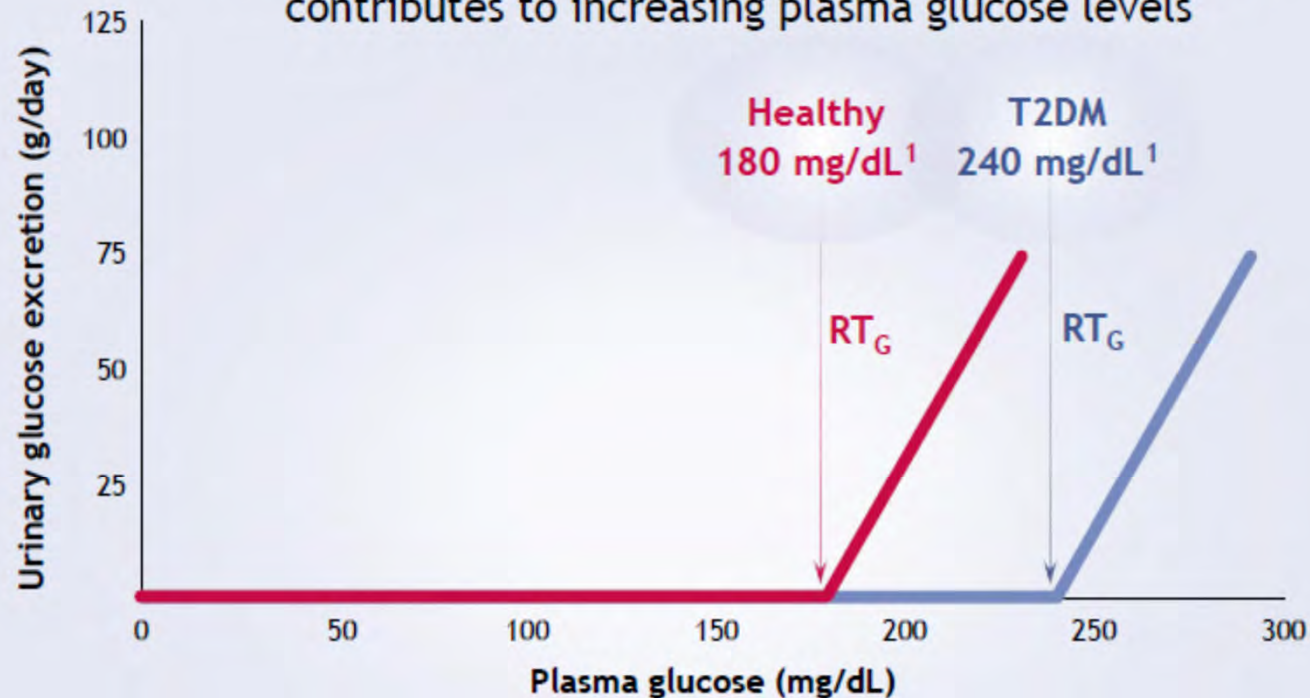
Inhibitors of Renal Glucose Reabsorption:

- ▶ Sodium-Glucose Transporter (SGLT) 2 SGLT2 is a high-capacity, low-affinity glucose transporter (GLUT) located in the early convoluted segment (S1) of the proximal tubule. The SGLT2 transporter mediates 90% of renal glucose reabsorption
- ▶ **SGLT2 inhibitors**
 - Canagliflozin
 - Dapagliflozin
 - Empagliflozin
 - Ertugliflozin

Renal Glucose Reabsorption

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

Renal glucose reabsorption is increased in T2DM, which contributes to increasing plasma glucose levels

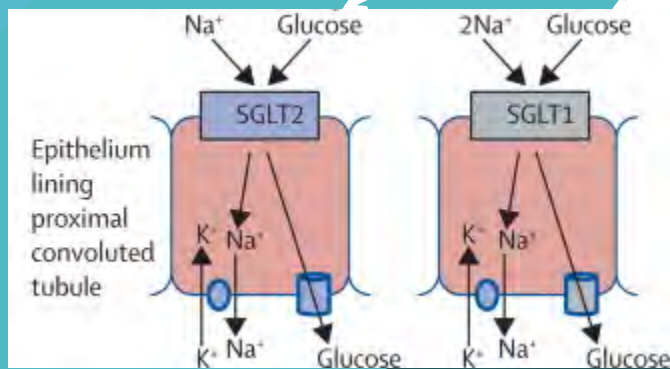
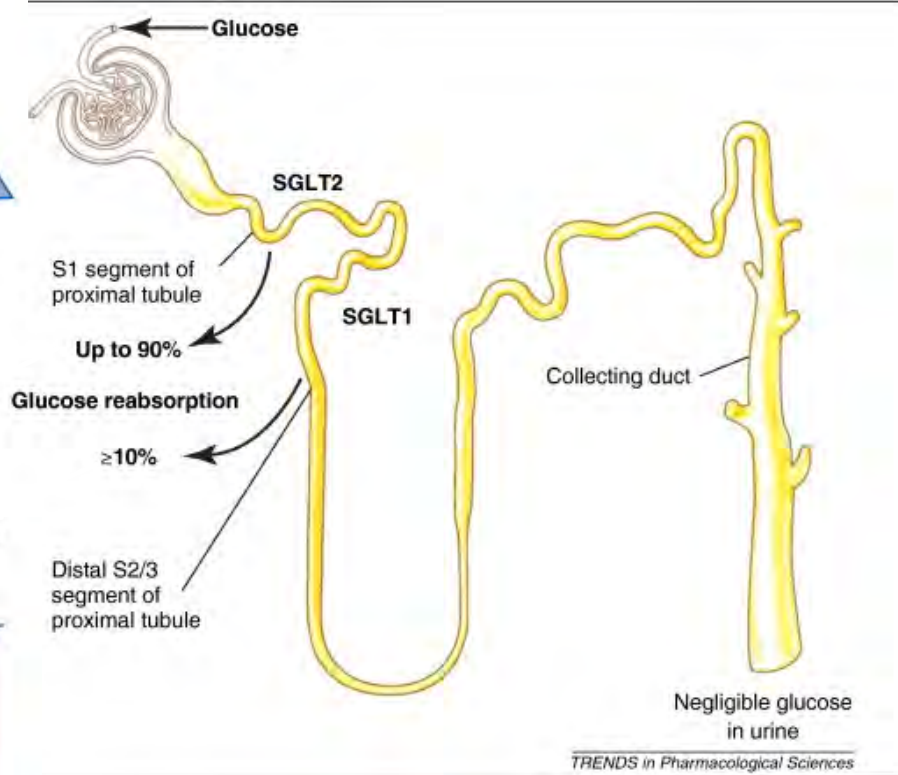
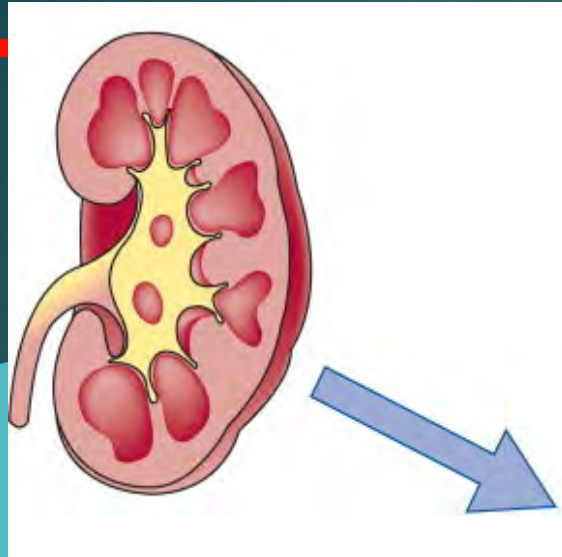


Adapted with permission from Abdul-Ghani, DeFronzo RA.

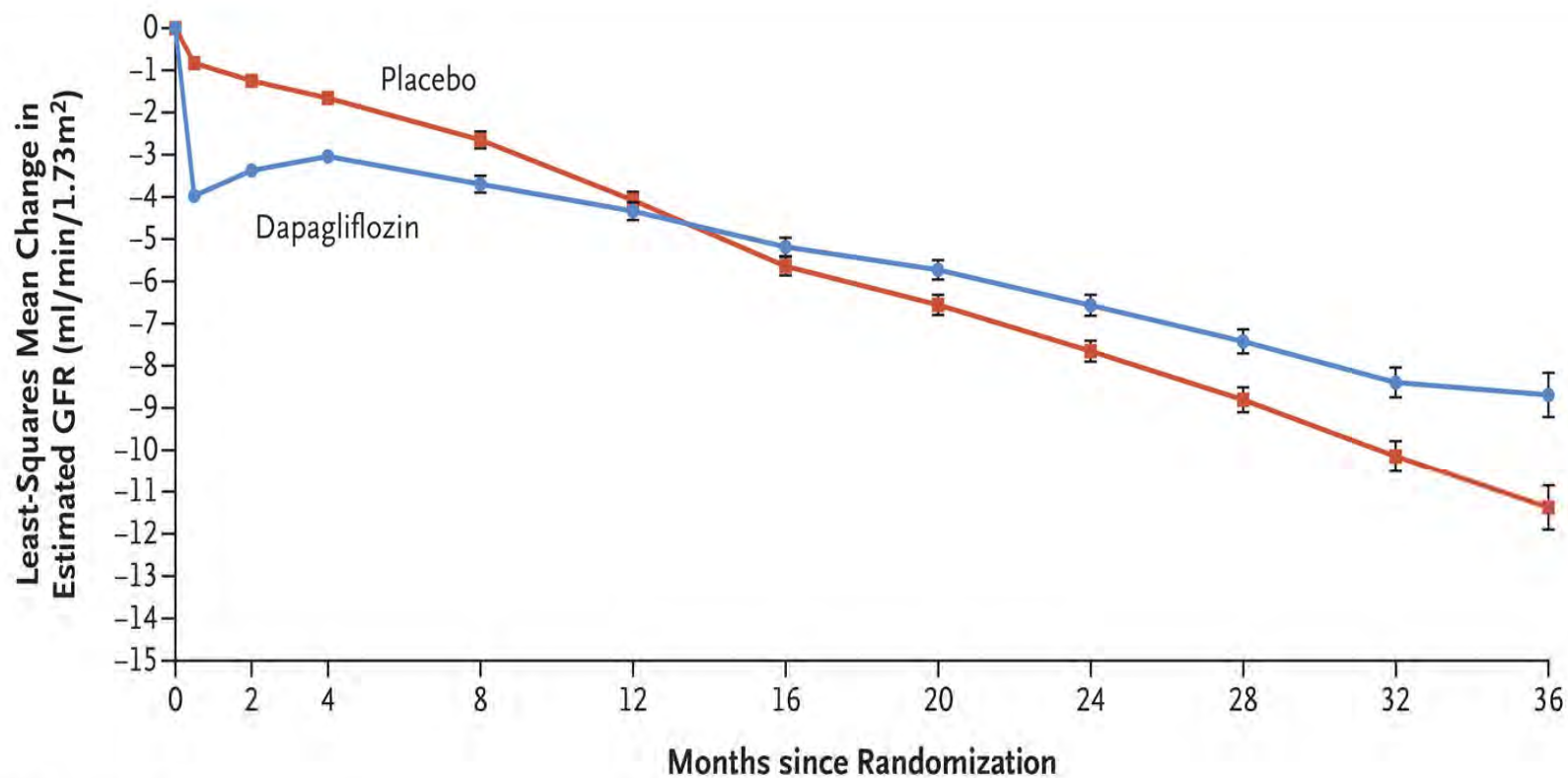
T2DM = type 2 diabetes mellitus.

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.

Renal Glucose Reabsorption



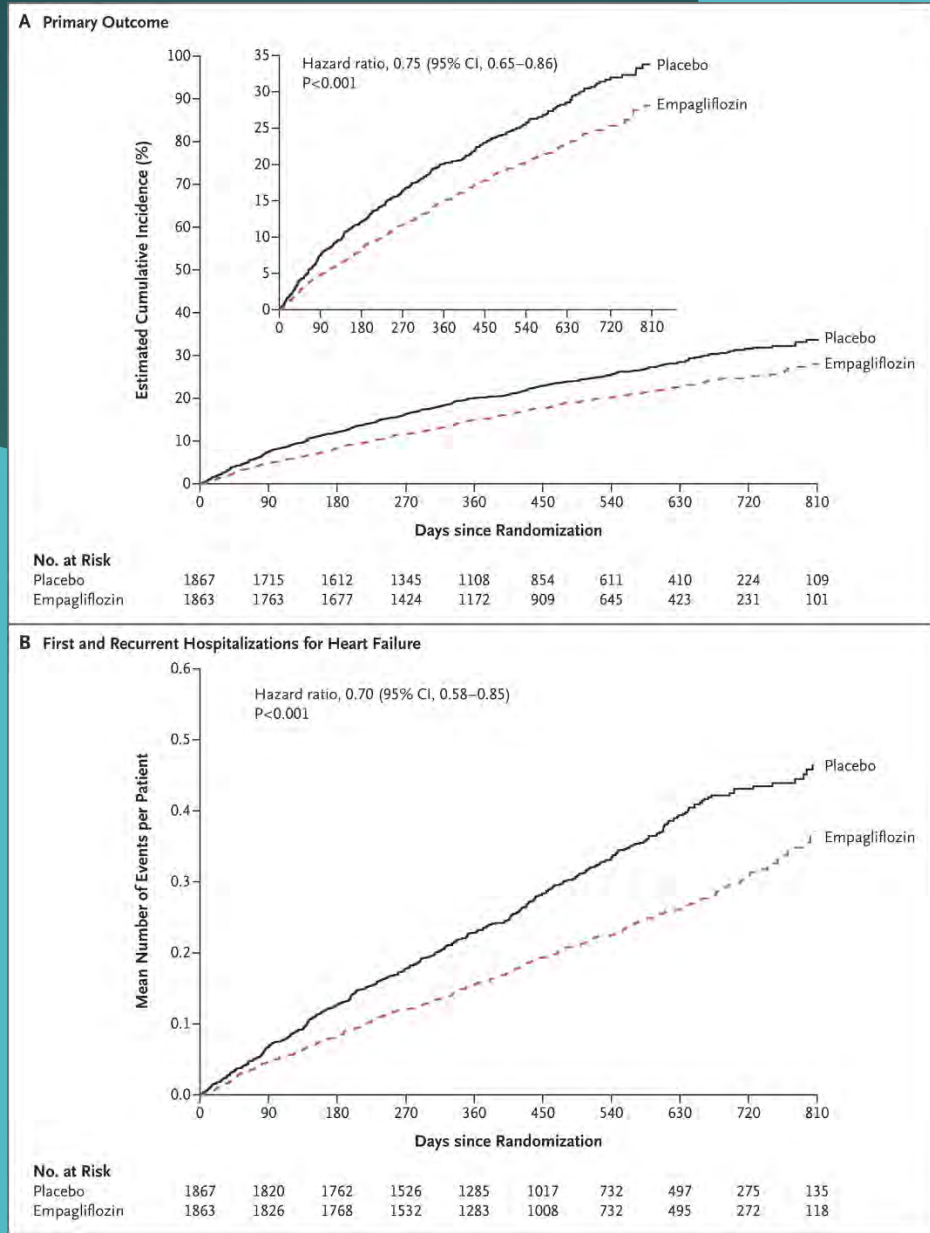
Change from Baseline in Estimated GFR



No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

Primary Outcome and Total Hospitalizations for Heart Failure



What is Glucagon-like Peptide-1 (GLP-1)?

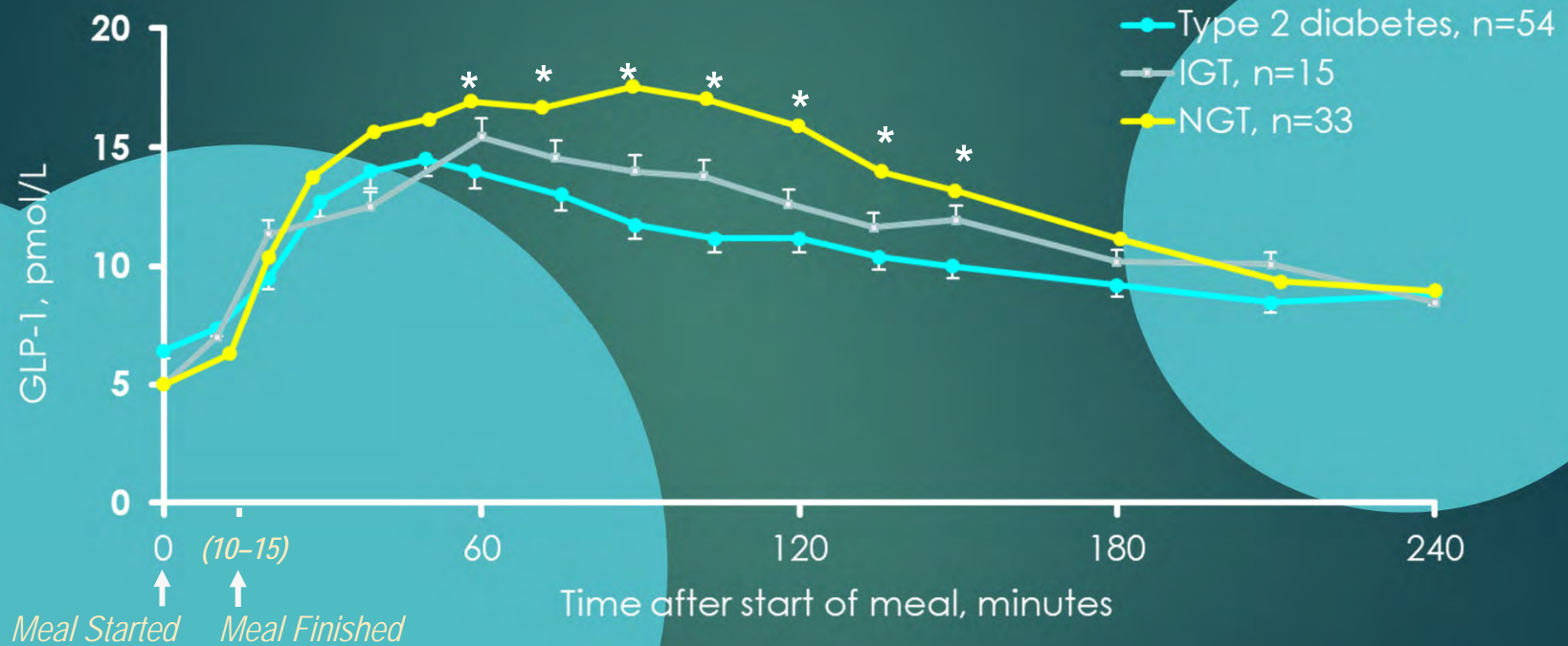
- ▶ Incretin hormone released from L cells in ileum and colon^{1,2}
- ▶ In the pancreas
 - Stimulates insulin response from beta cells in a glucose-dependent manner¹
 - Inhibits glucagon secretion from alpha cells in a glucose-dependent manner¹
 - Increases glucose sensitivity in glucose resistant beta cells³
 - Stimulates beta cell proliferation and neogenesis³
 - Inhibits beta cell apoptosis³
- ▶ Inhibits gastric emptying^{1,2}
- ▶ Reduces food intake and body weight²
- ▶ Inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4)³

1. Meier JJ et al. *Best Pract Res Clin Endocrinol Metab.* 2004;18:587-606.

2. Drucker DJ. *Diabetes Care.* 2003;26:2929-2940.

3. Campbell JE, Drucker DJ. *Cell Metabolism.* 2013;17:819-837.

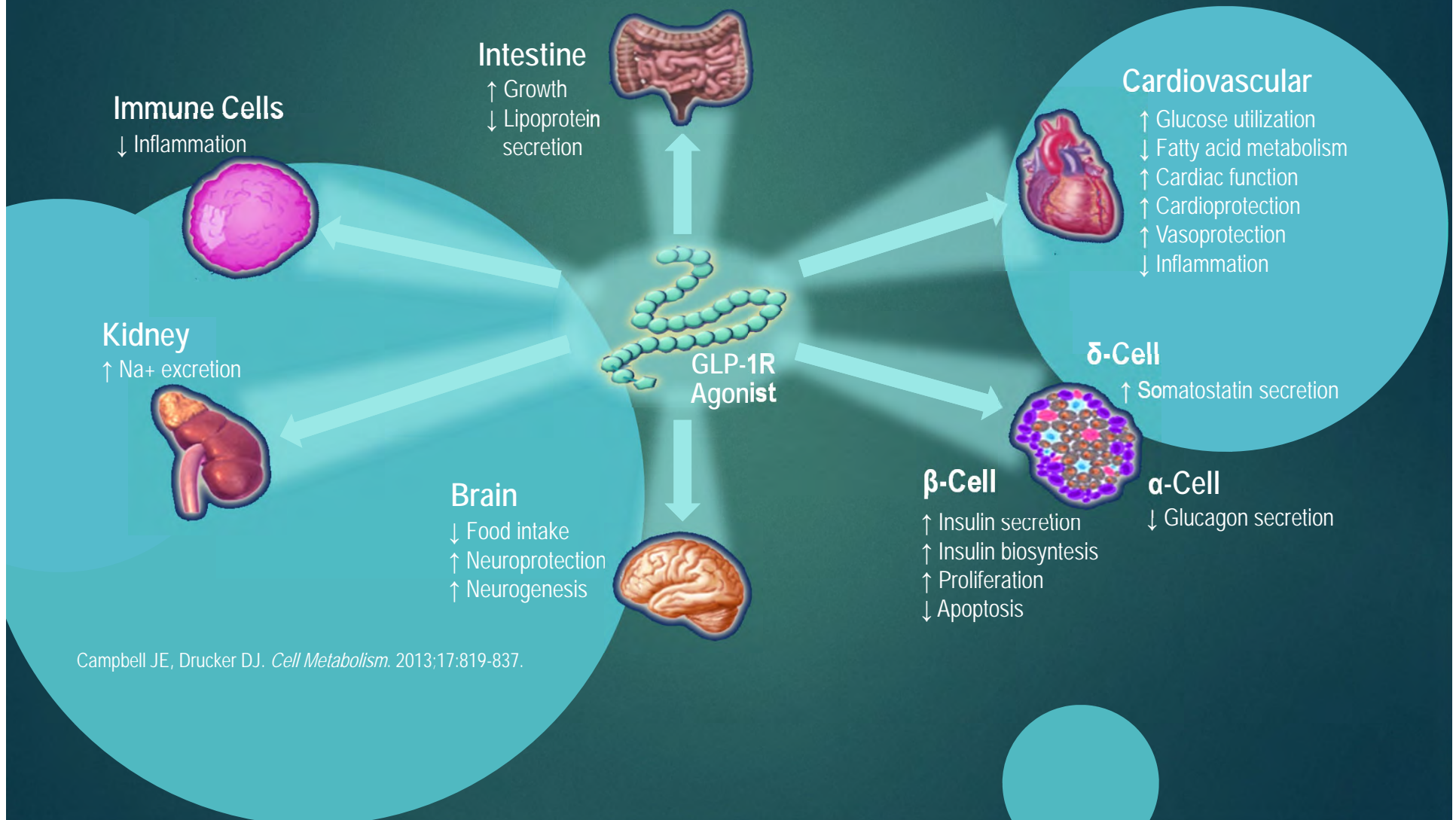
T2DM: Decreased Postprandial GLP-1 Levels



* $P < 0.05$, T2DM vs NGT

Toft-Nielsen MB et al. *J Clin Endocrinol Metab.* 2001;86:3717-3723.2001;86:3717-3723

Direct Pharmacological Actions of GLP-1 RAs



GLP-1 RAs Currently FDA-approved

Drug	Dosing Frequency	Route of administration	Year Approved
Exenatide	Twice daily	Subcutaneous injection	2005
Exenatide ER	Weekly	Subcutaneous injection	2012
Liraglutide	Daily	Subcutaneous injection	2010
Dulaglutide	Weekly	Subcutaneous injection	2014
Lixisenatide	Daily	Subcutaneous injection	2016
Semaglutide	Weekly	Subcutaneous injection	2017
Semaglutide	Daily	Oral	2019

Class Effects of GLP-1 RAs

- Lowers A1c by approximately 1%
- Very low rates of hypoglycemia when used without other hypoglycemic agents
- Weight loss:
 - -1.5-2.5 kg vs placebo
 - -4.8 kg vs insulin

Aroda VR. *Diabetes Obes Metab.* 2018;20(Suppl1):22-33.

Hinnen D. *Diabetes Spectr.* 2017;20:202-210.

GLP-1 RAs as a Class

Side Effects/Precautions

- ▶ GI side effects: nausea, vomiting, diarrhea
- ▶ Slows gastric emptying; do not use in gastroparesis
- ▶ Some HA
- ▶ Pancreatitis
 - ▶ Acute pancreatitis; causality not demonstrated
 - ▶ Pancreatic cancer; causality not established
- Pancreatitis (*continued*)
 - Not studied in patients with a history of pancreatitis
 - Stop if pancreatitis develops
- Renal
 - Cases of ARF with exenatide, use caution if GFR <50 mL/min/1.73m², do not use with GFR <30 mL/min/1.73m²
 - Too little data to assure safety and efficacy with other GLP-1 RAs for GFR 15-29 mL/min/1.73m²

GLP-1 RAs as a Class

Side Effects/Precautions

▶ Thyroid

- Liraglutide and dulaglutide associated with benign and malignant c-cell tumors in rats
- In humans, calcitonin levels not increased
- Not recommended in patients with a personal or family hx of MTC or MEN 2A or 2B

▶ Immunology

- Antibodies may develop, usually wanes with time, will not affect glycemic control

Aroda VR. *Diabetes Obes Metab.* 2018;20(Suppl1):22-33.

Hinnen D. *Diabetes Spectr.* 2017;20:202-210.

Table 3. Clinical Trials Showing Cardiovascular Benefit of Glucose-Lowering Agents in Patients with Type 2 Diabetes.*

Class and Drug with CVD Benefit in Specific Study Populations	Clinical Trial	Primary and Secondary Outcomes with Significant Risk Reductions	
		Major Adverse Cardiovascular Events†	Hospitalization for Heart Failure
Established CVD			
GLP-1 receptor agonists			
Liraglutide	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) ²⁷	Primary outcome‡	
Semaglutide§	Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) ²⁸	Primary outcome‡	
Dulaglutide	Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) ²⁹	Primary outcome‡	
SGLT2 inhibitors			
Empagliflozin	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) ¹⁰	Primary outcome‡	Secondary outcome
Canagliflozin	Canagliflozin Cardiovascular Assessment Study (CANVAS) ³¹	Primary outcome‡	Secondary outcome
Dapagliflozin	Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) ³²		Primary outcome‡¶
Ertugliflozin	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) ³³		Secondary outcome
Multiple CVD risk factors			
GLP-1 receptor agonist, dulaglutide	Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) ²⁹	Primary outcome‡	
SGLT2 inhibitor, dapagliflozin	Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) ³²		Primary outcome‡¶
Heart failure with reduced ejection fraction			
SGLT2 inhibitors			
Dapagliflozin	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) ^{14‡}		Primary outcome‡¶
Empagliflozin	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) ³⁵		Primary outcome¶
Albuminuric chronic kidney disease**			
SGLT2 inhibitors			
Canagliflozin	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRENCE) ¹⁶	Secondary outcome	Secondary outcome‡
Dapagliflozin	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) ³⁷	Secondary outcome	Secondary outcome

* Some agents are beneficial in reducing the risk of worsening nephropathy as a secondary outcome, but only cardiovascular benefits are shown. GLP1 denotes glucagon-like peptide-1 and SGLT2 sodium-glucose transporter type 2.

† Major adverse cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular disease (CVD).

‡ These agents have a label indication from the Food and Drug Administration indicating a reduction in this cardiovascular outcome in the specific population of patients listed with type 2 diabetes.

§ Only the injectable version of semaglutide has demonstrated CVD benefit.

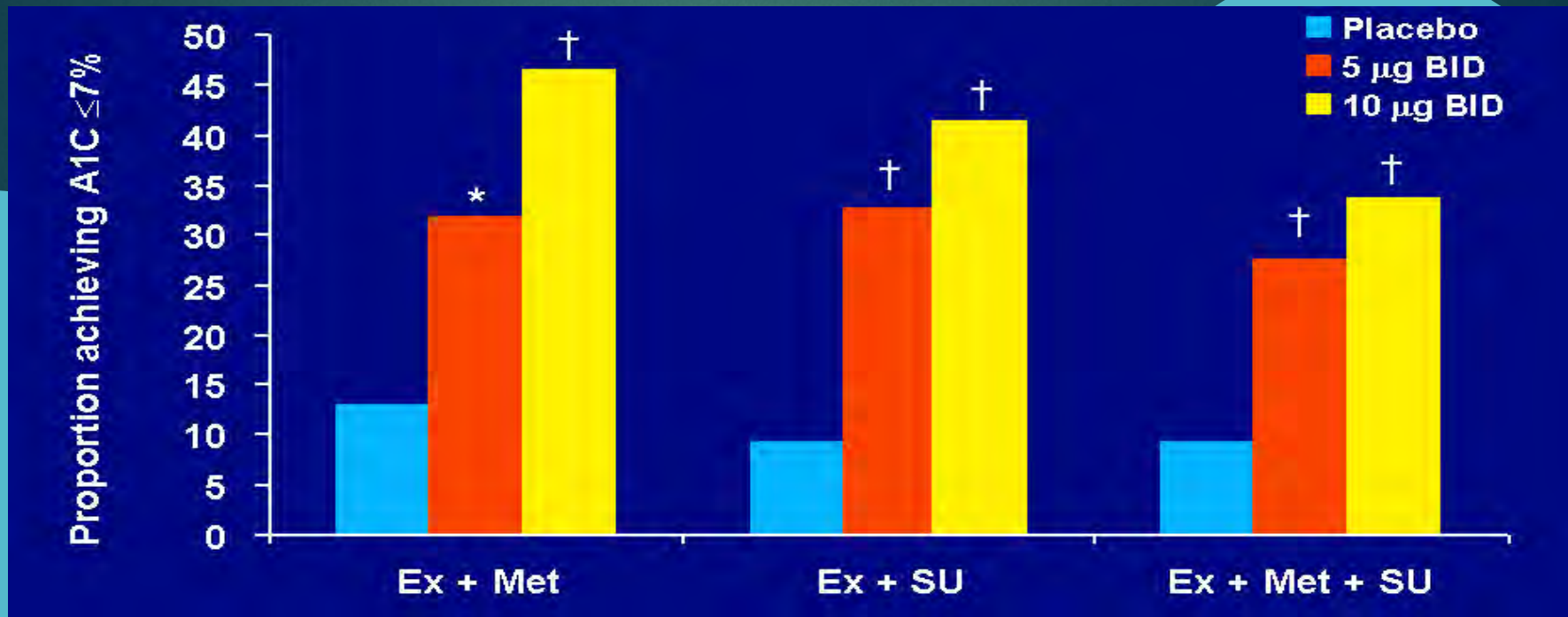
¶ The primary outcome included hospitalization for heart failure and cardiovascular death (and, in DAPA-HF, an urgent visit for heart failure).

| Ongoing placebo-controlled trials are investigating the use of dapagliflozin (ClinicalTrials.gov number, NCT03619213) and empagliflozin (ClinicalTrials.gov number, NCT03057951) in the treatment of heart failure with preserved ejection fraction.

** Ongoing placebo-controlled trials are investigating the use of empagliflozin (ClinicalTrials.gov number, NCT03594110) and semaglutide, (ClinicalTrials.gov number, NCT03819153) in patients with chronic kidney disease.

Exenatide

AMIGO Trials Show Efficacy in Managing Hyperglycemia

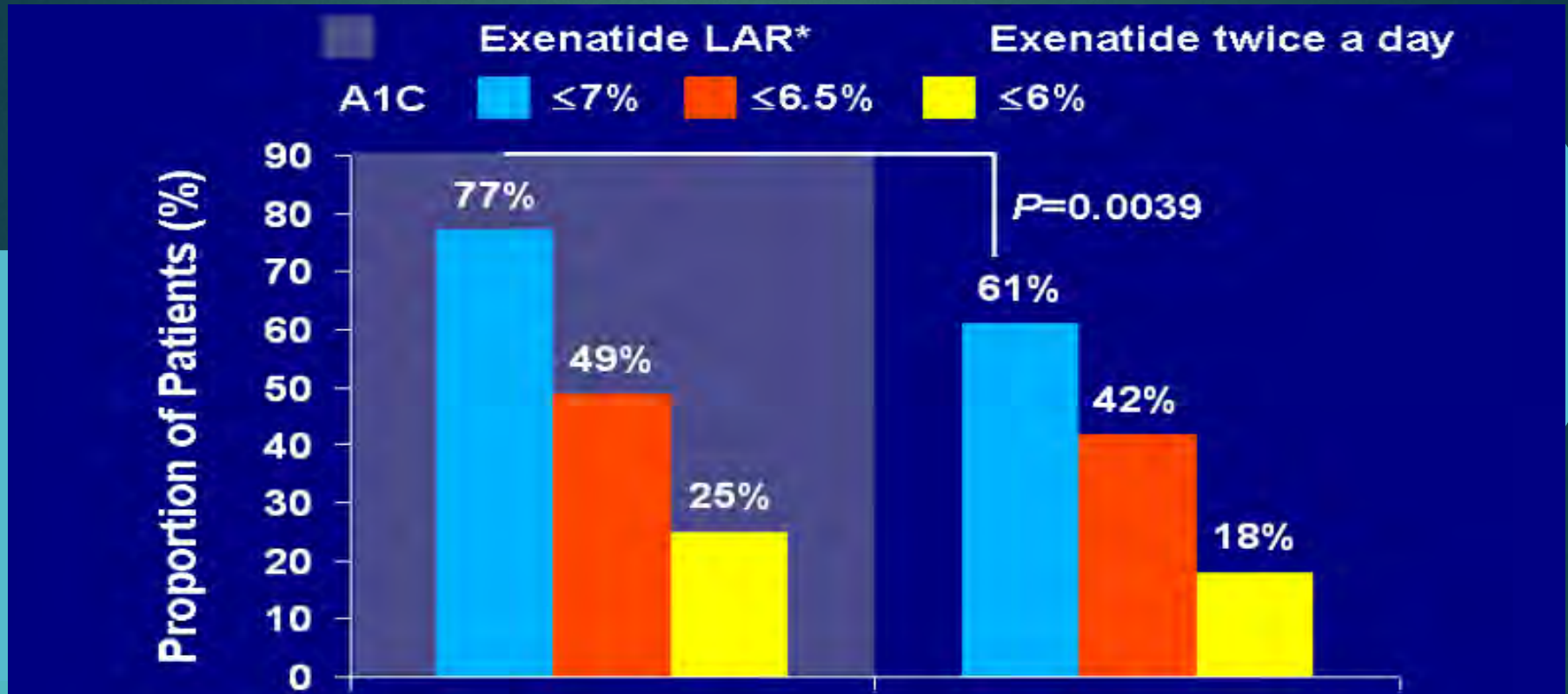


Ex=exenatide; Met=metformin; SU=sulfonylurea. * $P < 0.001$ vs placebo; † $P < 0.0001$ vs placebo.

Buse JB et al. *Diabetes Care*. 2004;27:2628-2635. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. Kendall DM et al. *Diabetes Care*. 2005;28:1083-1091.

DURATION-1

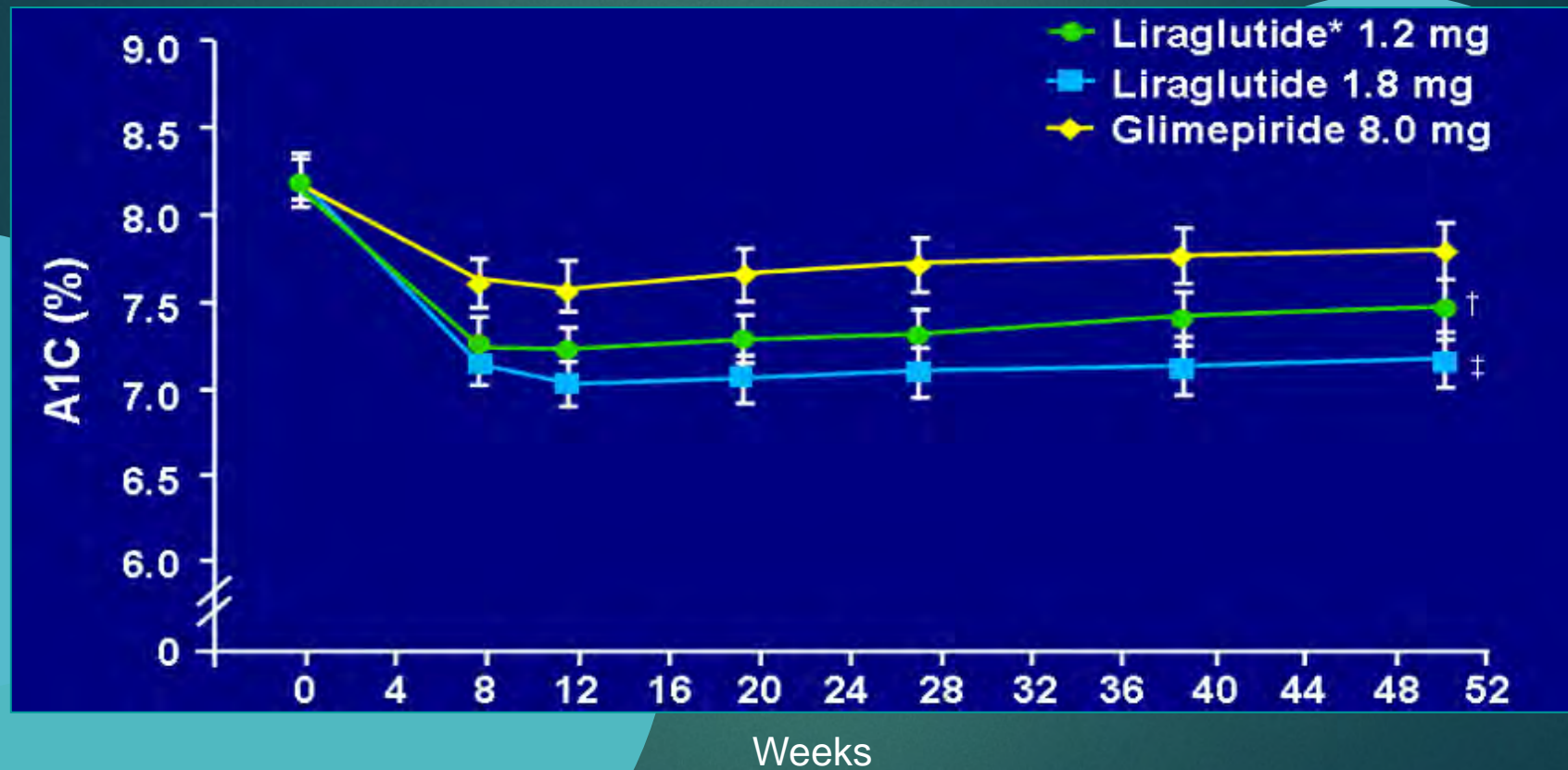
Exenatide Once Weekly vs Exenatide Twice-Daily



*Long-acting release

Drucker DJ et al. *Lancet*. 2008;372:1240-1250.

LEAD-3: Liraglutide Lowers A1c



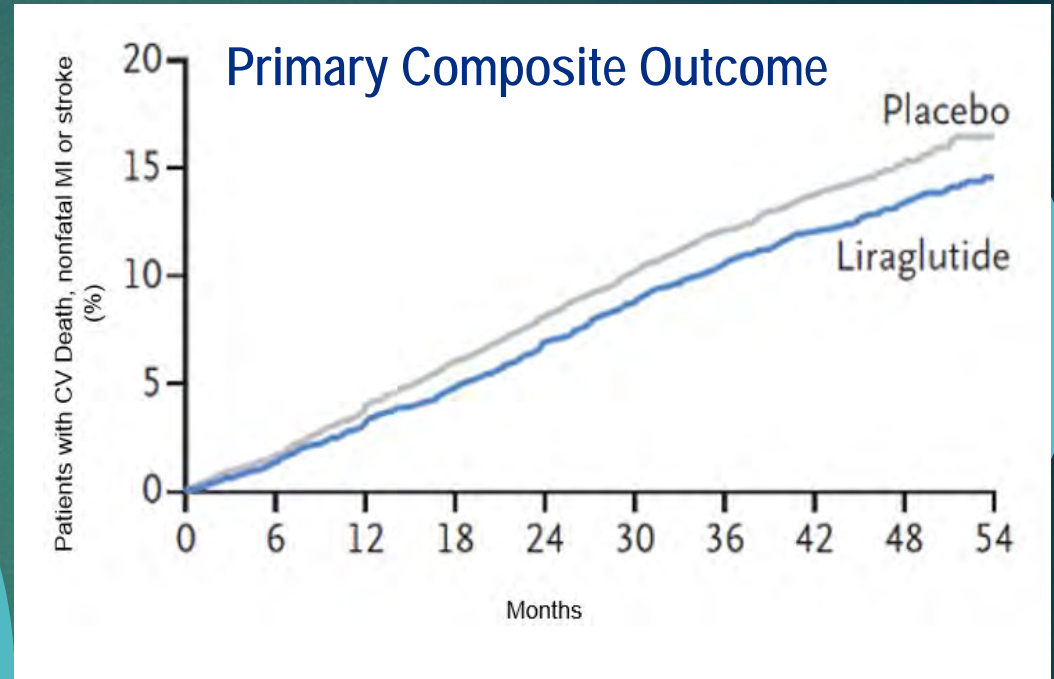
[†] $P = 0.0014$ vs glimepiride; [‡] $P = 0.0001$ vs glimepiride.

Garber A et al. *Lancet*. 2009;373:473-481.

LEADER

Fewer Cardiovascular Events with Liraglutide

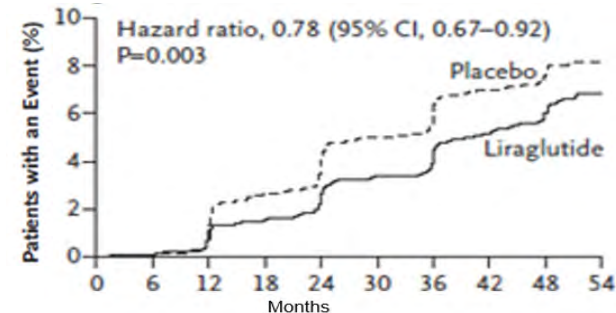
- ▶ Primary composite outcome
 - ▶ CV death or first occurrence of nonfatal MI or stroke
- ▶ Primary outcome
 - 13.0% liraglutide group
 - 14.9% placebo group
- Hazard ratio 0.87 (95% CI, 0.78 – 0.97)
- $P < 0.001$ for non-inferiority
- $P = 0.01$ for superiority



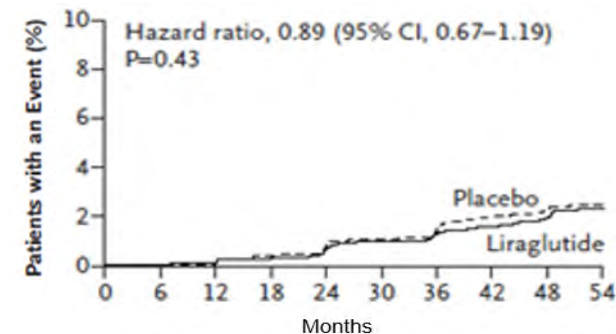
LEADER: Liraglutide and Renal Outcomes

- Liraglutide led to lower rates of development and progression of diabetic renal disease
- Result primarily driven by decrease in new onset macroalbuminuria
- Pre-specified secondary renal outcomes: new onset persistent macroalbuminuria; persistent serum creatinine doubling; ESRD; death due to renal causes

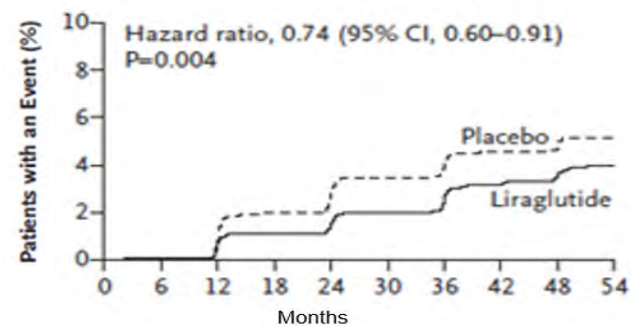
Composite Renal Outcome



Persistent Doubling of Serum Creatinine Level



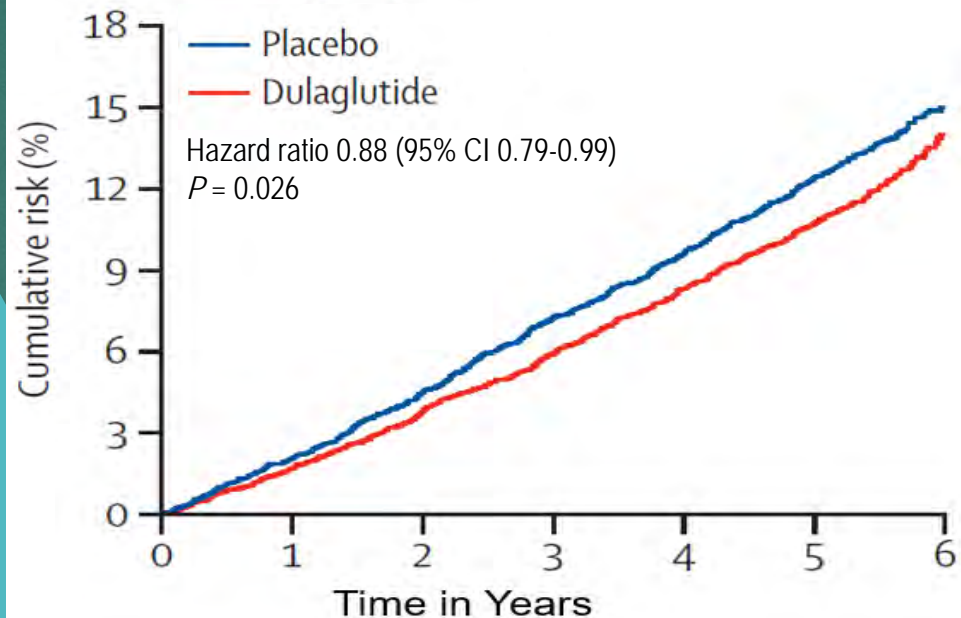
New Onset of Persistent Macroalbuminuria



REWIND: Dulaglutide and CV Outcomes

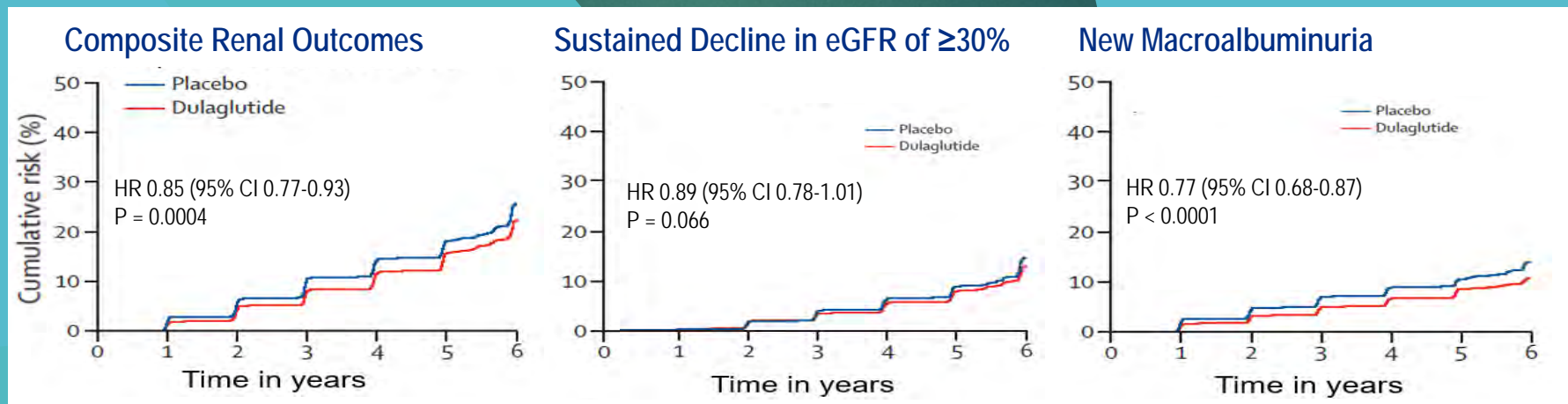
- ▶ Patients with previous CV event or CV risk factors
- ▶ Primary outcome: first occurrence CV death, non-fatal MI, non-fatal stroke

Cumulative Risk of Composite Cardiovascular Outcomes



REWIND: Dulaglutide and Renal Outcomes

- ▶ Composite renal outcomes were the first occurrence of new macroalbuminuria (UACR >33.9 mg/mmol), a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy
- ▶ Renal outcomes developed in 17.1% randomized to dulaglutide and 19.6% randomized to placebo

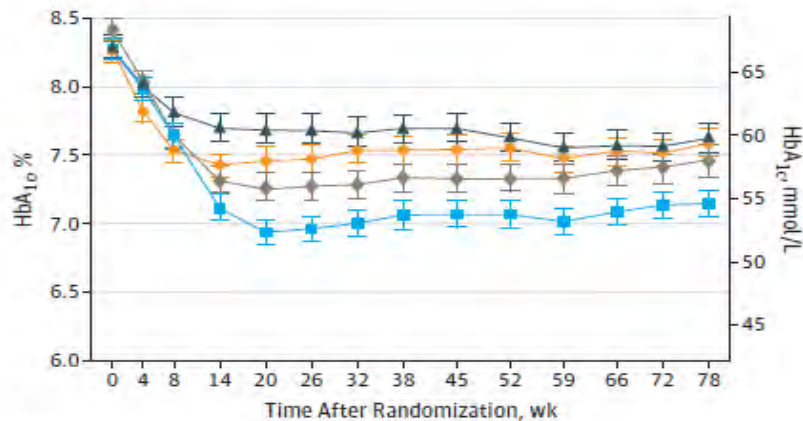


Semaglutide

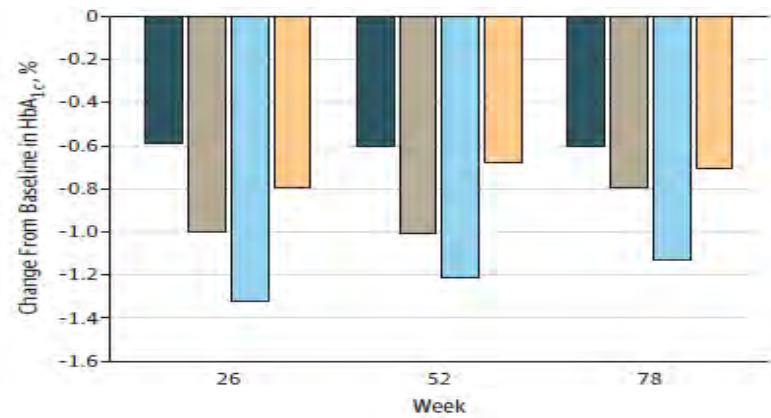
- Start 0.25 mg for 4 weeks
- Increase to 0.5 mg for 4 weeks
- Can increase to 1 mg weekly if needed

PIONEER-3: Phase IIIa Trial of Oral Semaglutide

Observed Absolute A1c



Estimated Change from Baseline in A1c

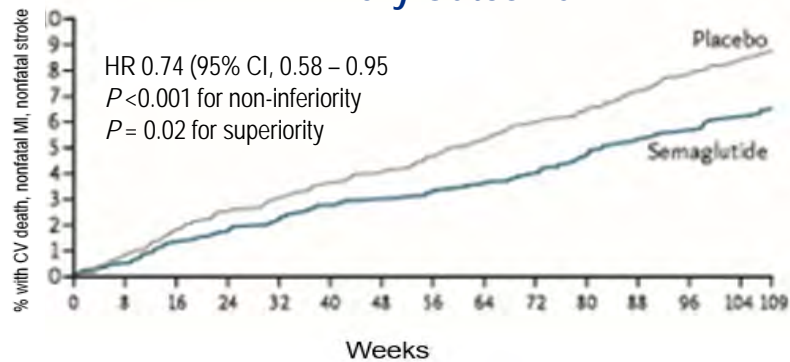


▲ Oral semaglutide, 3 mg/d ◆ Oral semaglutide, 7 mg/d ■ Oral semaglutide, 14 mg/d ● Sitagliptin, 100 mg/d

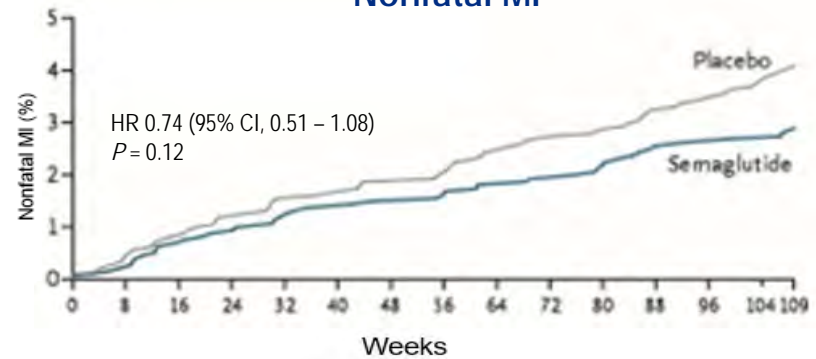
Oral semaglutide 7 mg and 14 mg significantly reduced both **A1c** and **body weight** compared to sitagliptin 100 mg ($P < 0.001$ for both).

SUSTAIN 6: Semaglutide and CV Outcomes

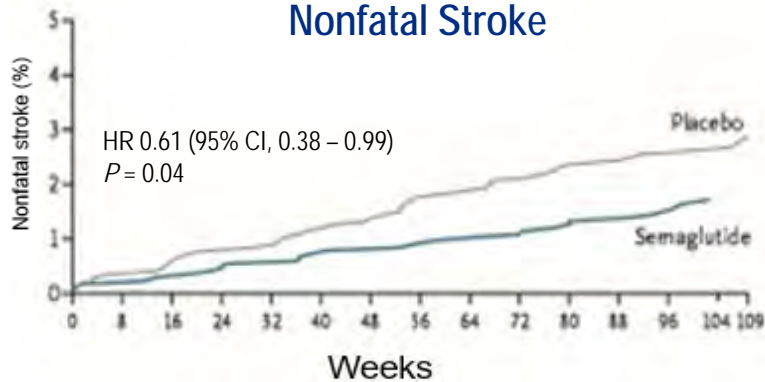
Primary Outcome



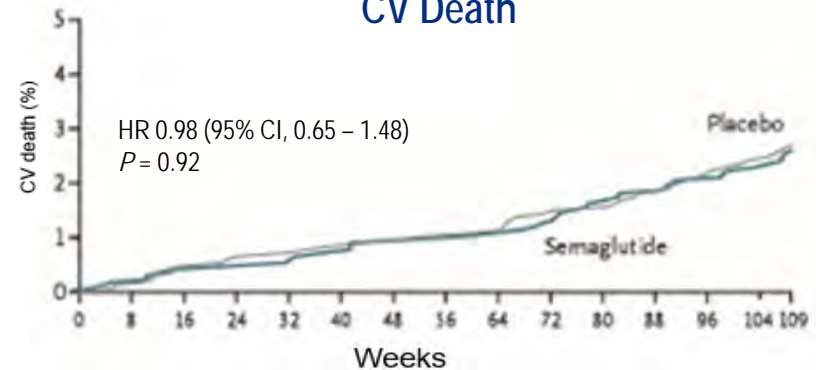
Nonfatal MI



Nonfatal Stroke

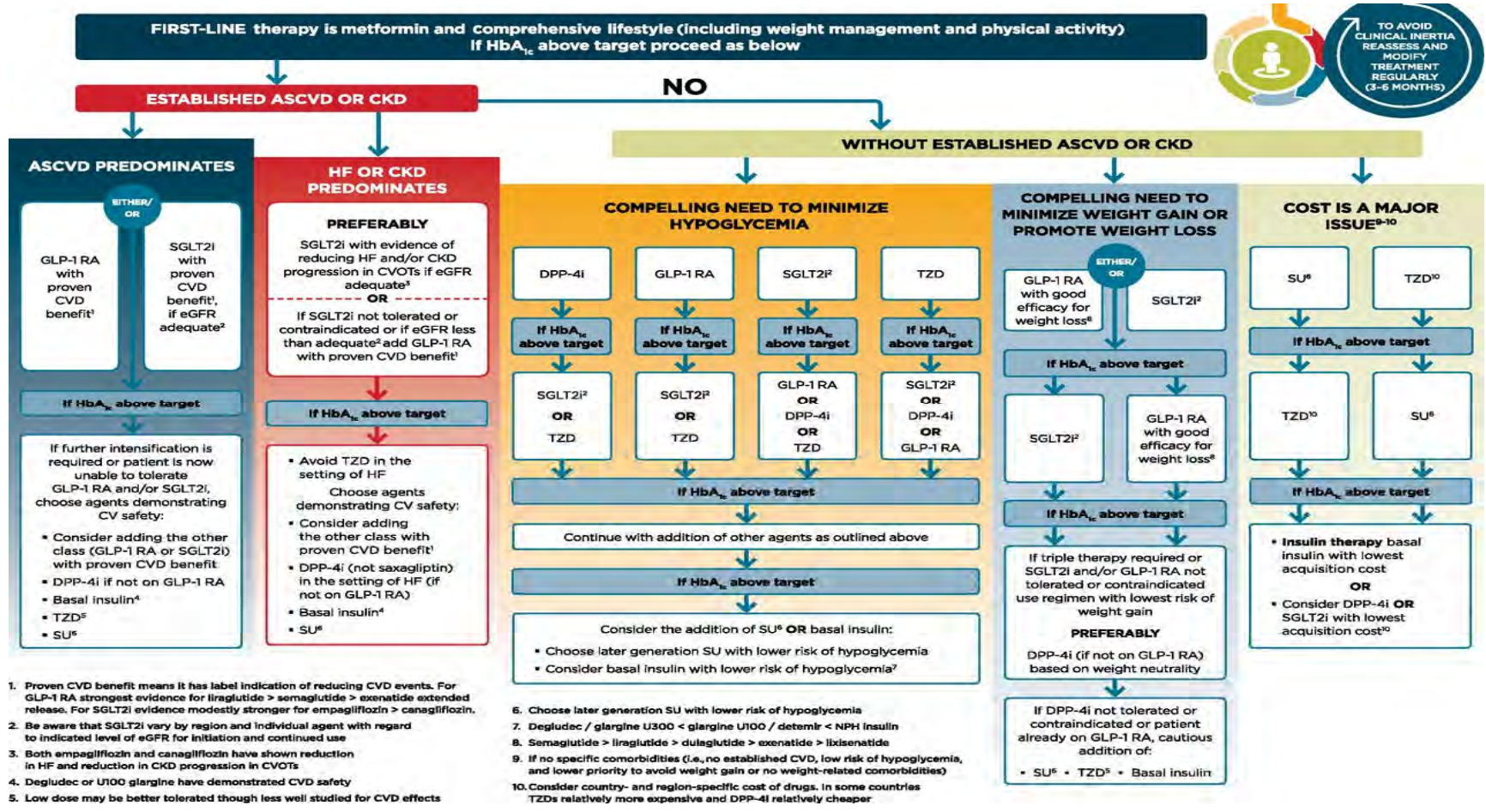


CV Death



ADA 2019 Standards of Care

Many Agents, Each Its Own Place in the Algorithm



- Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
- Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVDs
- Degludec or U100 glargine have demonstrated CVD safety
- Low dose may be better tolerated though less well studied for CVD effects

- Choose later generation SU with lower risk of hypoglycemia
- Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- 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)
- Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Consider Properties Beyond Ability to Lower Blood Glucose Levels and A1c

▶ Hypoglycemia

- ▶ Frequent, particularly with insulin and sulfonylureas
- ▶ If severe, one of the strongest predictors of macrovascular events, adverse clinical outcomes, and mortality in T2DM
- ▶ Agents that cause hypoglycemia – SUs, glinides, and insulin

➤ Hypoglycemia (*continued*)

- To reduce or eliminate risk, SGLT-2 inhibitors and GLP-1 RAs are good options for T2DM patients with cardiovascular disease (CVD)
- Weight effects
- CV effects
 - ASCVD
 - CHF
- Renal effects

Why Considering Anti-hyperglycemic Medication Effect on CVD is Important

- ▶ CVD occurs 14.6 years earlier, with greater severity, and with more diffuse distribution than in those without DM
- ▶ Approximately two-thirds of deaths in T2DM are attributable to CVD:
 - ▶ ~40% are from ischemic heart disease
 - ▶ ~15% other forms of heart disease, principally congestive heart failure
 - ▶ ~10% from stroke
- ▶ CVD death rates lower now for T2DM but still higher than non-diabetes population

ASCVD remains principal cause of death and disability among patients with T2DM

Return to Case Study

- Derek is a 56-year-old man with a history of T2DM, HTN, and hyperlipidemia for 10 years
- Recent positive stress test
- Meds:
 - HCTZ 25 mg daily
 - Lisinopril 5 mg daily
 - Atorvastatin 20 mg daily
 - Glyburide 5 mg daily
 - Sitagliptin 100 mg daily
 - Metformin 500 mg twice daily

Case Study *(continued)*

▶ Family history

- ▶ Father had T2DM; died from MI at age 60

▶ Physical examination

- ▶ BMI 33 kg/m²
- ▶ BP 145/92 mm Hg
- ▶ Pulse, 92 bpm; + S4 gallop
- ▶ Lungs clear
- ▶ No edema

• Laboratory evaluation

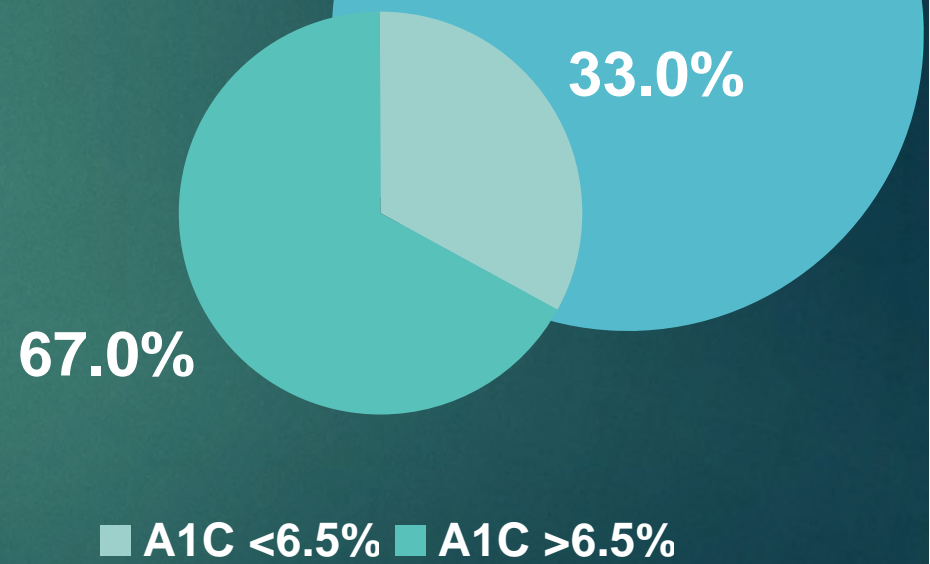
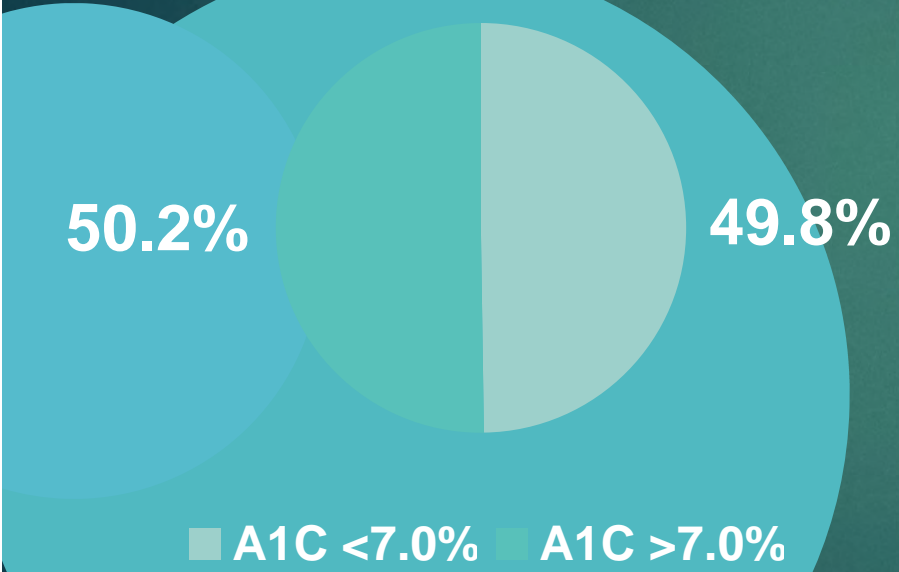
- FPG: 145 mg/dL
- HbA1c: 8.0%
- LDL: 106 mg/dL
- TG: 198 mg/dL
- Creatinine: 1.3 mg/dL

Starting a GLP-1 RA is a very good choice for this patient

The Majority of US Patients Are Failing to Achieve A1C Goals

▶ 50.2% fail to meet American Diabetes Association's goal of <7.0%¹

▶ 67.0% fail to meet American Association of Clinical Endocrinologists' goal of <6.5%²



1. Resnick HE et al. *Diabetes Care*. 2006;29:531–537.
2. American Association of Clinical Endocrinologists. *State of Diabetes in America*. Available at: <http://www.aace.com/public/awareness/stateofdiabetes/DiabetesAmericaReport.pdf>. Accessed December 20, 2006.

Challenges in Achieving Glycemic Goals in Diabetes

- ▶ Less aggressive treat-to-target approach by some clinicians¹
- ▶ Suboptimal use of available therapies¹
- ▶ Inability of any single agent's MOA to address all core defects of type 2 diabetes²
- ▶ Potential for increased side effects with use of multiple agents³
- ▶ Suboptimal adherence to lifestyle measures¹
- ▶ Underuse of medications as a result of
 - Cost⁴
 - Complexity of therapy⁵

1. Blonde L. *Clin Cornerstone*. 2005;7(suppl 3):S6–S17.

2. Van Gaal LF et al. *Diabetologia*. 2003;46(suppl 1):M44–M50.

3. McDonald HP et al. *JAMA*. 2002;288:2868–2879.

4. Piette JD et al. *Diabetes Care*. 2004;27:384–391.

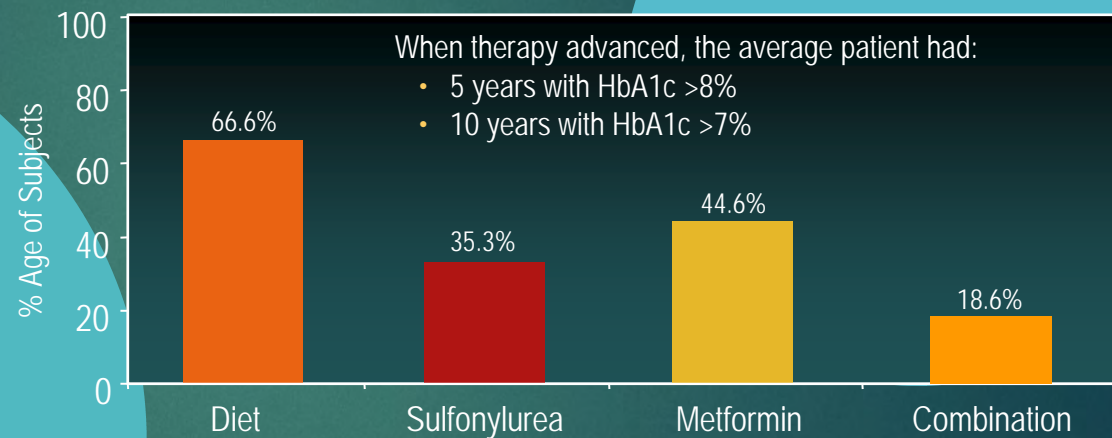
5. Donnan PT et al. *Diabet Med*. 2002;19:279–284.

Clinical Inertia

Failure to Advance Therapy When Required

Practitioners recognize
poor control . . . *AND*
agree medication should
be intensified . . . *YET*
TAKE NO ACTION

Percentage of Patients Advancing When HbA1c >8%



Delays in Providing Adequate Treatment Can Be Associated with Significant CV Morbidity

- ▶ One-year delay in intensifying therapy (goal A1c <7.0%) is associated with significantly increased:
 - ▶ MI by 67%
 - ▶ Stroke by 51%
 - ▶ HF by 64%
 - ▶ Composite CVE by 62%

Reasons for Clinical Inertia

▶ Provider

- ▶ Time constraints
- ▶ Lack of knowledge
- ▶ Potential risks of hypoglycemia
- ▶ Variations in guideline recommendations

• Patient

- Non-adherence
- Concerns about hypoglycemia and weight gain

• Healthcare System

- Cost of newer medications

Decisions Need to Be Shared

- ▶ Goal of shared decision-making (SDM): Ensure that treatment decisions align with each patient's preferences
 - ▶ Often includes patient education and decision-support tools
 - ▶ Becomes a partnership between clinician and patient
- Potential benefits of SDM in T2D
 - Patients have vested interest in their care
 - Increased patient knowledge
 - Less anxiety over the process of care
 - Improved health outcomes
 - Reductions in inappropriate costs



Lee EO et al. *N Engl J Med*. 2013;368:6-8.

VA. *Shared Decision Making with the Patient with Diabetes*. 2012.

www.healthquality.va.gov/guidelines/CD/diabetes/cpgSDMDMPOCKETFinalPRESS022513.pdf

Study Overview

- Intensive glucose lowering targeting glycated hemoglobin levels of less than 6.0% was unexpectedly associated with an increase in overall mortality in high-risk patients with type 2 diabetes in the ACCORD trial
- The findings identify a previously unrecognized risk of intensive glucose lowering in such patients



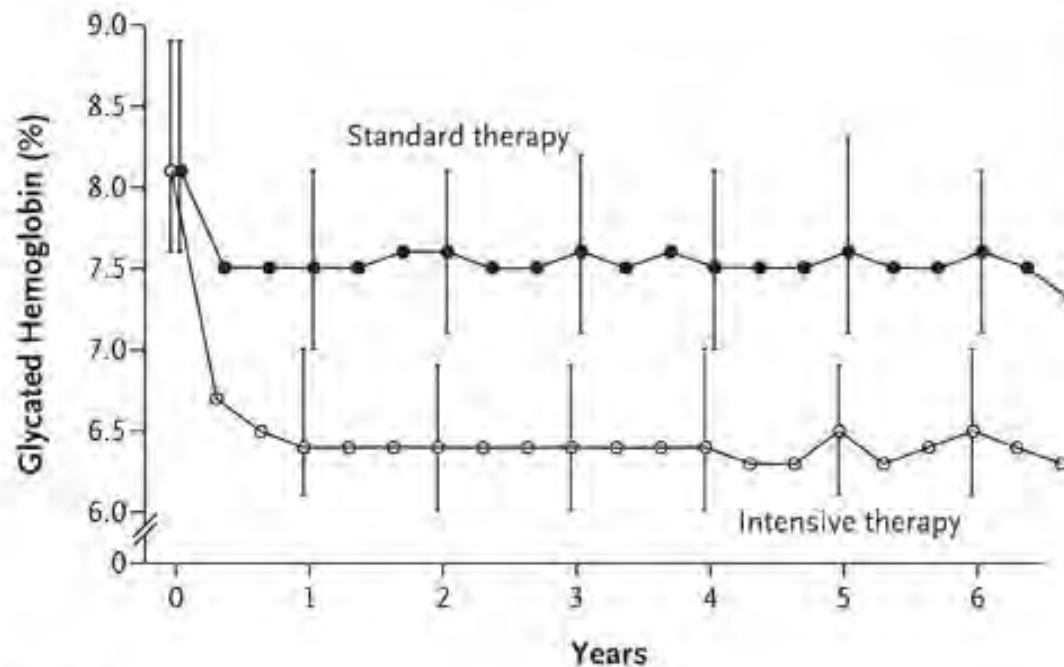
Characteristics of the Patients at Baseline

Table 1. Characteristics of the Patients at Baseline.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)
Age (yr)	62.2±6.8	62.2±6.8
Female sex (%)	38.7	38.4
Median duration of diabetes (yr)	10	10
Previous cardiovascular event (%)	35.6	34.8
Previous congestive heart failure (%)	4.9	4.8
Race or ethnic group (%) [†]		
White	64.4	64.5
Black	19.7	18.9
Hispanic	7.0	7.4
Education (%)		
Less than high school	15.7	14.0
High-school graduate	26.1	26.7
Some college	32.7	32.9
College degree or higher	25.5	26.4
Cigarette-smoking status (%)		
Current	14.3	13.7
Former	44.4	44.0
Never	41.3	42.3
Weight (kg)	93.5±18.7	93.6±18.7
Body-mass index	32.2±5.5	32.2±5.5
Waist circumference (cm)	106.8±14.3	106.8±13.8
Blood pressure (mm Hg)		
Systolic	136.2±17.0	136.5±17.2
Diastolic	74.8±10.6	75.0±10.7
Medications (%)		
Insulin	34.1	35.7
Metformin	59.7	60.0
Any sulfonylurea	30.8	49.4
Any thiazolidinedione	19.5	19.2
Any antihypertensive agent	84.9	86.0
Angiotensin-converting-enzyme inhibitor	53.0	53.0
Aspirin	34.8	54.1
Beta-blocker	28.7	29.9
Any thiazide diuretic	26.5	26.4
Statin	61.7	62.4
Glycated hemoglobin (%)		
Mean	8.3±1.1	8.3±1.1
Median	8.1	8.1
Fasting serum glucose (mg/dl)	174.9±56.0	175.7±56.5
Cholesterol (mg/dl)		
Total	183.3±42.1	183.3±41.6
Low-density lipoprotein	104.9±34.0	104.9±33.8
High-density lipoprotein		
Women	47.2±13.0	46.9±12.2
Men	38.4±9.5	38.8±9.8
Median triglyceride (mg/dl)	156	154
Potassium (mg/dl)	4.5±0.4	4.5±0.7
Serum creatinine (mg/dl)	0.9±0.2	0.9±0.2

* Plus-minus values are means ±SD. There were no significant differences between the two study groups at baseline. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
[†] Race was self-reported, and patients could check multiple categories.

Median Glycated Hemoglobin Levels at Each Study Visit



No. at Risk

Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Primary and Secondary Outcomes

Table 4. Primary and Secondary Outcomes.*

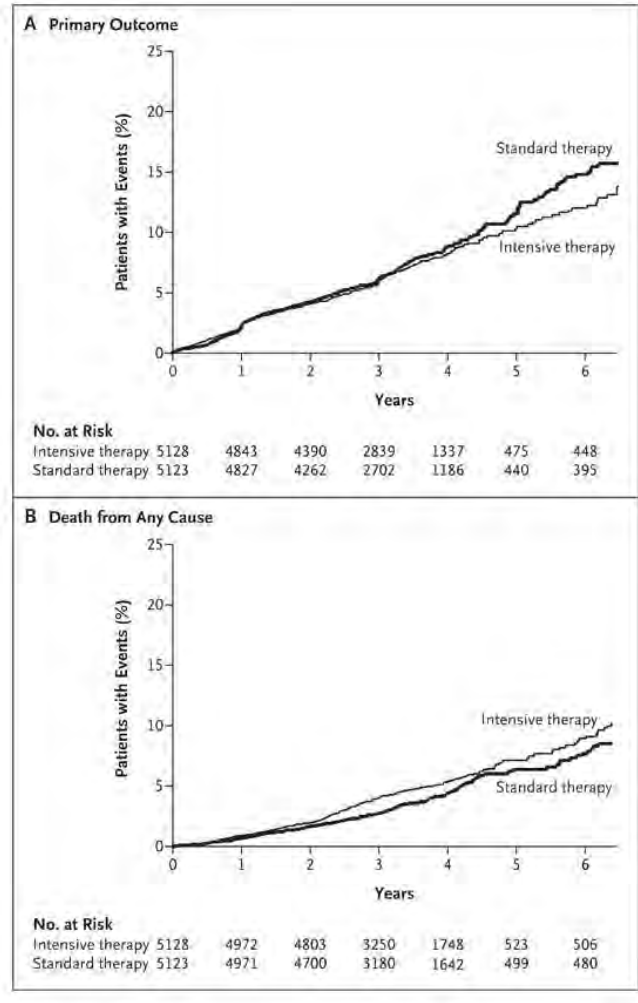
Outcome	Intensive Therapy (N=5128)		Standard Therapy (N=5123)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per yr	no. of patients (%)	% per yr		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease‡	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			

* The primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Data within categories are not mutually exclusive, and patients who were classified as having more than one possible cause of death are listed in the relevant categories. Hazard ratios are for the intensive-therapy group as compared with the standard-therapy group.

† This condition was a component of the outcome of fatal cardiovascular disease.

‡ Additional details are provided in the Supplementary Appendix.

Kaplan-Meier Curves for the Primary Outcome and Death from Any Cause



The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-2559



The NEW ENGLAND
JOURNAL of MEDICINE

Conclusion

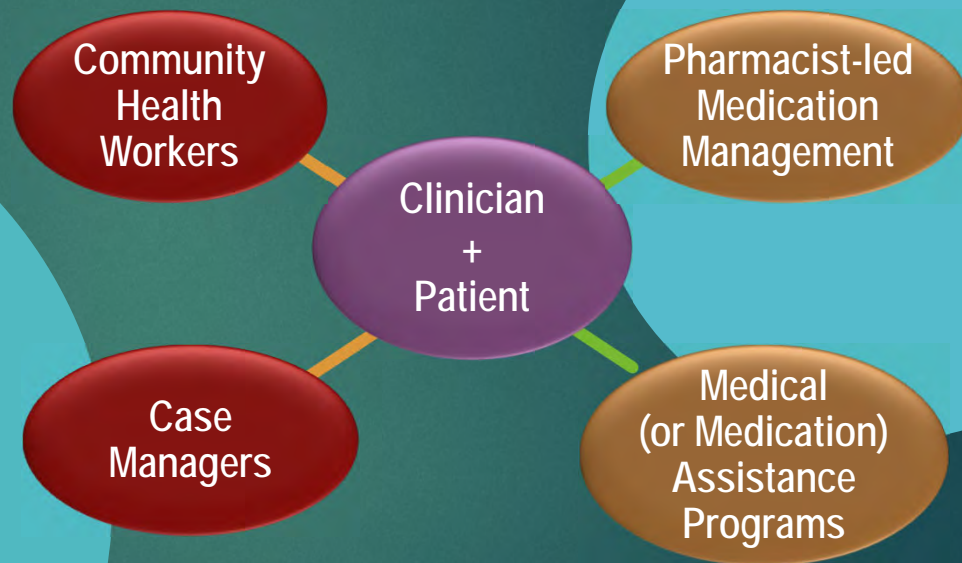
- As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events
- These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes



Beyond the Doctor: Create a Team Approach

Enhancing Patient Engagement in Diabetes Care

- Help overcome social, cultural, linguistic barriers
- Act as powerful change agents



Adapted from Baig AA et al. *Med Care Res Rev.* 2010;67(5 Suppl):163S-197S.

Recent & New Developments in Diabetes Mellitus

- ▶ Sotaglifloxin (Dual SGLT1/SGLT2 inhibitor)
- ▶ SOLOIST trial reduced the risk for CV death, hospitalizations for heart failure & urgent HF visits by 33%
- ▶ SCORED showed the risk for CV death, hospitalization for heart failure and urgent heart failure visits by 26% in patients with diabetes and CKD
- ▶ Walmart private ReliOn brand launching analog insulin retailing up to 75% off cash price
- ▶ Tirzepatide dual incretin agonists that showed marked improvements in glycemic response and significant reductions in body weight with hypoglycemia