Diabetes & The Heart

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30 th Annual Convention & Reunion

UERMMMC MAAAI

Renaissance Hotel

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Objectives

1. To update the physicians with regards to the different FDA approved medications for diabetes management

2. Review the different therapeutic options of achieving lower HBA1c with lesser risk of hypoglycemia

3. To review the different clinical trials with improved cardiovascular outcome

Questions

1. Consider Metformin therapy for delay or prevention of diabetes mellitus type 2 in patients with the following:

   prediabetes

   BMI > 35 kg/m2, age < 60 years old and women with

   prior history of gestational diabetes (True or False)

2. The ACCORD Trial showed decrease mortality in the Intensive Group (True or False)

3. GLP 1 (Glucagon Like Peptide 1) enhances glucose stimulated insulin release (True or False)

4. SGLT1 is the key renal transporter for glucose reabsorption

   (True or False)

5. EMPA-REG Outcome: Empaglifozin reduces cardiovascular events and

   mortality in high risk type 2 diabetes (True or False)

6. The LEADER Clinical Trial shows significant lower rates of all cause

   death and CV death with liraglutide

KEY FACTS

- Nearly 26 million children and adults in the United States have diabetes
- 79 million Americans have prediabetes
- 1.9 million Americans are diagnosed with diabetes every year
- Nearly 10 % of the entire U.S. population has diabetes, including over 25 % of seniors
- As many as 1 in 3 American adults will have diabetes in 2050 if present trends continue
- The economic cost of diagnosed diabetes in the U.S. is $245 billion per year

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

OR

A random plasma glucose ≥200 mg/dL (11.1 mmol/L)

American Diabetes Association.

ADA. 2. Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S9; Table 2.1

Categories of Increased Risk for Diabetes (Prediabetes)*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose in the 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

ADA. 2. Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S10; Table 2.3

Cardiovascular Disease

- CVD is the major cause of morbidity, mortality for those with diabetes
  - Largest contributor to direct/indirect costs
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for CVD
- Diabetes itself confers independent risk
- Benefits observed when individual cardiovascular risk factors are controlled to prevent/slow CVD in people with diabetes

ADA. 8. Cardiovascular Disease and Risk Management. Diabetes Care 2015;38(suppl 1):S49

Criteria for Testing for Diabetes in Asymptomatic Adult Individuals (1)

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2* or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing >9 lb or were diagnosed with GDM
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Women with polycystic ovarian syndrome (PCOS)
- A1C ≥5.7%, IGT, or IFG on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of CVD

ADA. 2. Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S10; Table 2.2

Recommendations: Prevention/Delay of Type 2 Diabetes

- Consider metformin for prevention of type 2 diabetes if IGT **A**, IFG **E**, or A1C 5.7–6.4% **E**
  - Especially for those with BMI >35 kg/m^2, age <60 years, and women with prior GDM **A**
- In those with prediabetes, monitor for development of diabetes annually **E**
- Screen for and treat modifiable risk factors for CVD **B**
- DSME/DSMS programs are approparite venues for people with prediabetes to develop and maintain behaviors that can prevent or delay the onset of diabetes **C**

ADA. 5. Prevention/Delay of Type 2 Diabetes. Diabetes Care 2015;38(suppl 1):S31

Recommendations: Physical Activity

- Children with diabetes/prediabetes: engage in at least 60 min/day physical activity **B**
- Adults with diabetes: at least 150 min/wk of moderate -intensity aerobic activity (50–70% of maximum heart rate),over at least 3 days/wk with no more than 2 consecutive days without exercise **A**
- Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce sedentary time, particularly by breaking up extended amoungs of time (>90 min) spent sitting **B**
- If not contraindicated, adults with type 2 diabetes should perform resistance training at least twice weekly **A**

ADA. 4. Foundations of Care. Diabetes Care 2015;38(suppl 1):S24

Glycemic Recommendations for Nonpregnant Adults with Diabetes (1)

A1C	<7.0%*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

*Goals should be individualized.
†Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

American Diabetes Association.

ADA. 6. Glycemic Targets. Diabetes Care 2015;38(suppl 1):S37; Table 6.2

Glycemic Recommendations for Nonpregnant Adults with Diabetes (2)

- Goals should be individualized based on
  - Duration of diabetes
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemia unawareness
  - Individual patient considerations

ADA. 6. Glycemic Targets. Diabetes Care 2015;38(suppl 1):S37; Table 6.2

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1C ≤ 6.5%

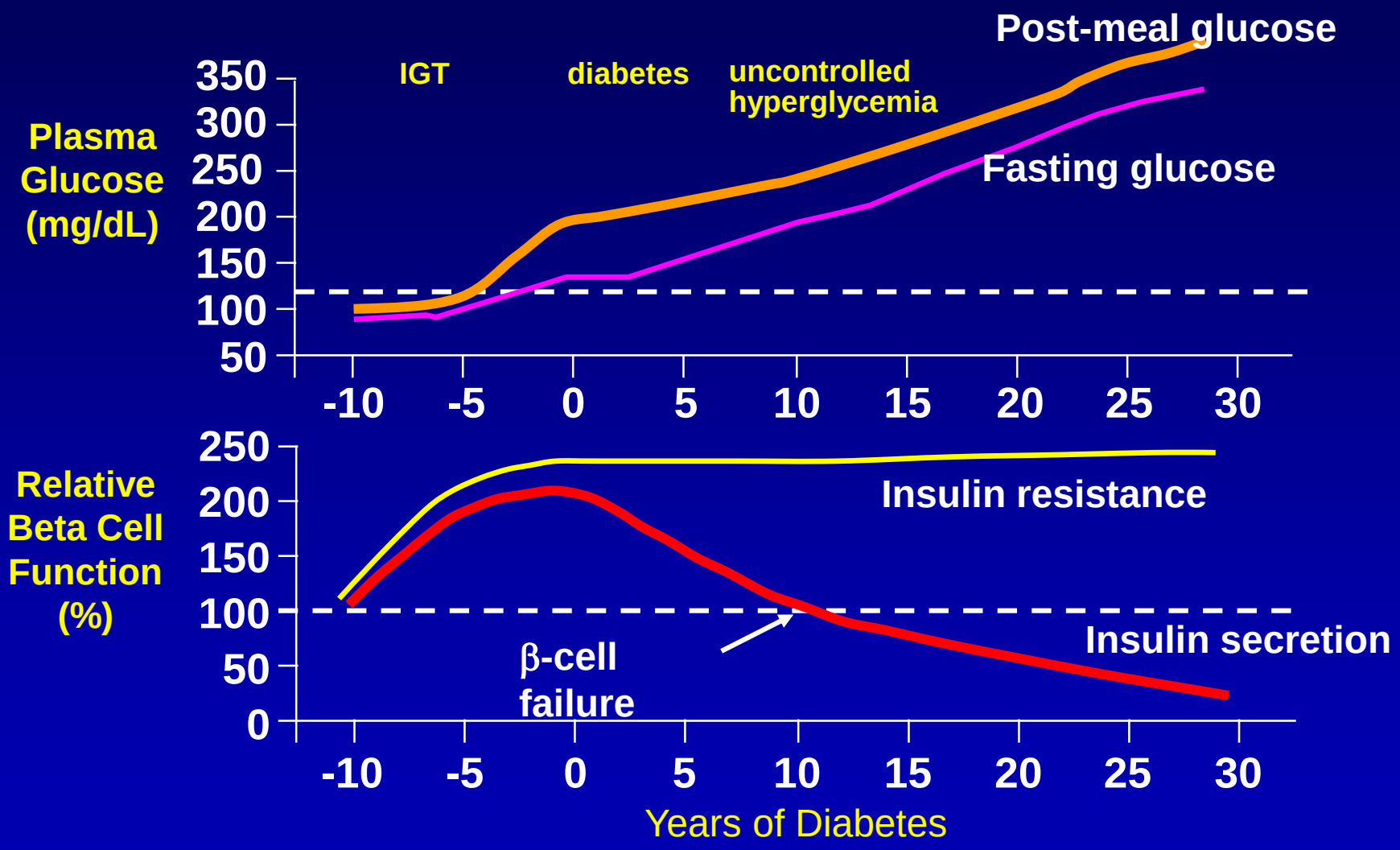
For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%

For patients with concurrent serious illness and at risk for hypoglycemia

TYPE 2 DIABETES . . . A PROGRESSIVE DISEASE

Natural History of Type 2 Diabetes



Adapted from: International Diabetes Center (Minneapolis, Minnesota).

Glycemic control and microvascular complications in T2DM

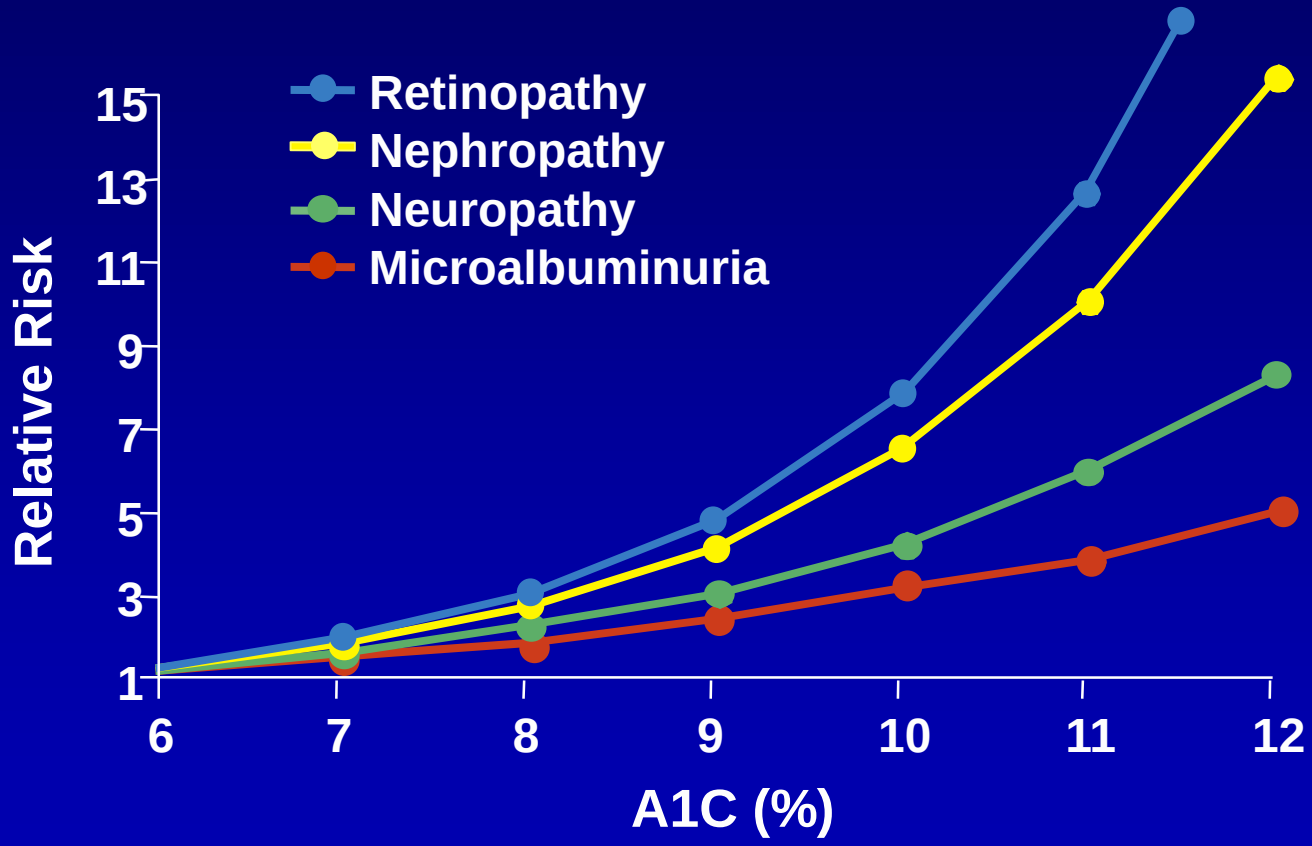
	n	HbA_{1C} (%)		Follow-up (years)	Beneficial effects on		
		Con	Int		Retinopathy	Nephropathy	Neuropathy
Kumamoto[1]	110	9.4	7.1	6.0	Yes	Yes	Yes
UKPDS[2]	**3,867**	**7.9**	**7.0**	**10.0**	**Yes**	**Yes**	**Yes**
Steno-2[3]	130	9.1	7.8	7.8	Yes	Yes	Yes*

Con=conventional therapy; Int=intensive therapy

*Autonomic neuropathy

1. Ohkubo Y, et al. Diabetes Res Clin Pract 1995;28:103–17.
2. UKPDS Group. Lancet 1998;352:837–53.
3. Gaede P, et al. N Engl J Med 2003;348:383–93.

Relationship of A1C to Risk of Microvascular Complications



Adapted with permission from Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243

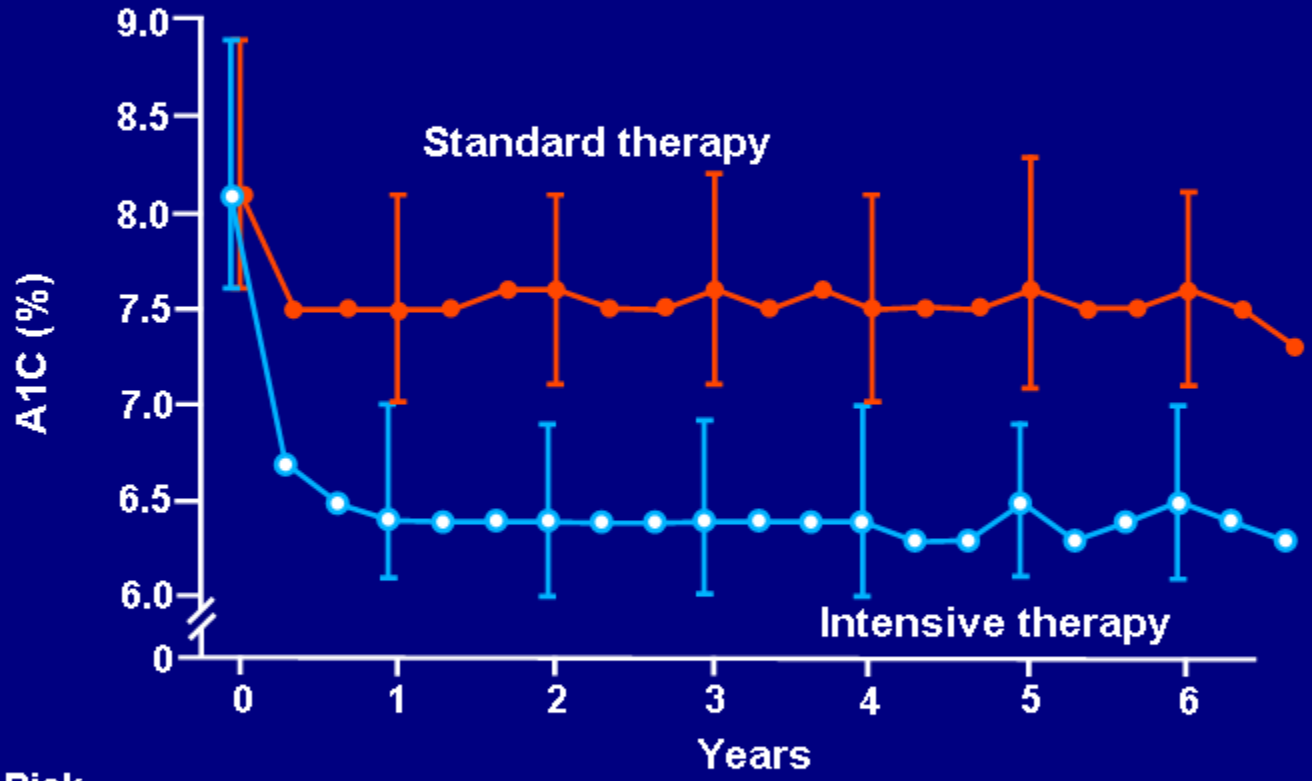
ACCORD: Study Design

- N=10,251 patients with type 2 diabetes (mean baseline A1c 8.1%)
- Randomized to:
  - Intensive therapy (target A1c <6.0%) *or*
  - Standard therapy (target A1c 7.0%–7.9%)
- Primary outcome (composite): nonfatal MI, nonfatal stroke, or CVD death
- Glucose-lowering trial of ACCORD stopped early (after ~3½ year follow-up; ~17 months early) due to increased total mortality in the intensive-treatment arm

A1c=glycated hemoglobin; CVD=cardiovascular disease; MI=myocardial infarction
ACCORD=Action to Control Cardiovascular Risk in Diabetes

The ACCORD Study Group. *N Engl J Med*. 2008;358(24):2545-2559.

ACCORD Trial: Intensive Blood Glucose Control in Patients With Type 2 Diabetes



No. at Risk							
Standard	5,109	4,774	4,588	3,186	1,744	455	436
Intensive	5,119	4,768	4,585	3,165	1,706	476	471

The ACCORD Study Group. *N Engl J Med*. 2008;358(24):2545-2559.

ACCORD: A1c Levels, Hypoglycemia, and Weight Gain

	Intensive therapy (n=5,128)	Standard therapy (n=5,123)	*P*
On-Rx A1c (median)[a]	6.4% (IQR 6.1–7.0)	7.5% (IQR 7.0–8.1)	*P*<0.05
Hypoglycemia requiring medical assistance	538 (10.5%)	179 (3.5%)	*P*<0.001
Weight gain >10 kg from baseline (no/total no/%)	1399/5036 (27.8%)	713/5042 (14.1%)	*P*<0.001

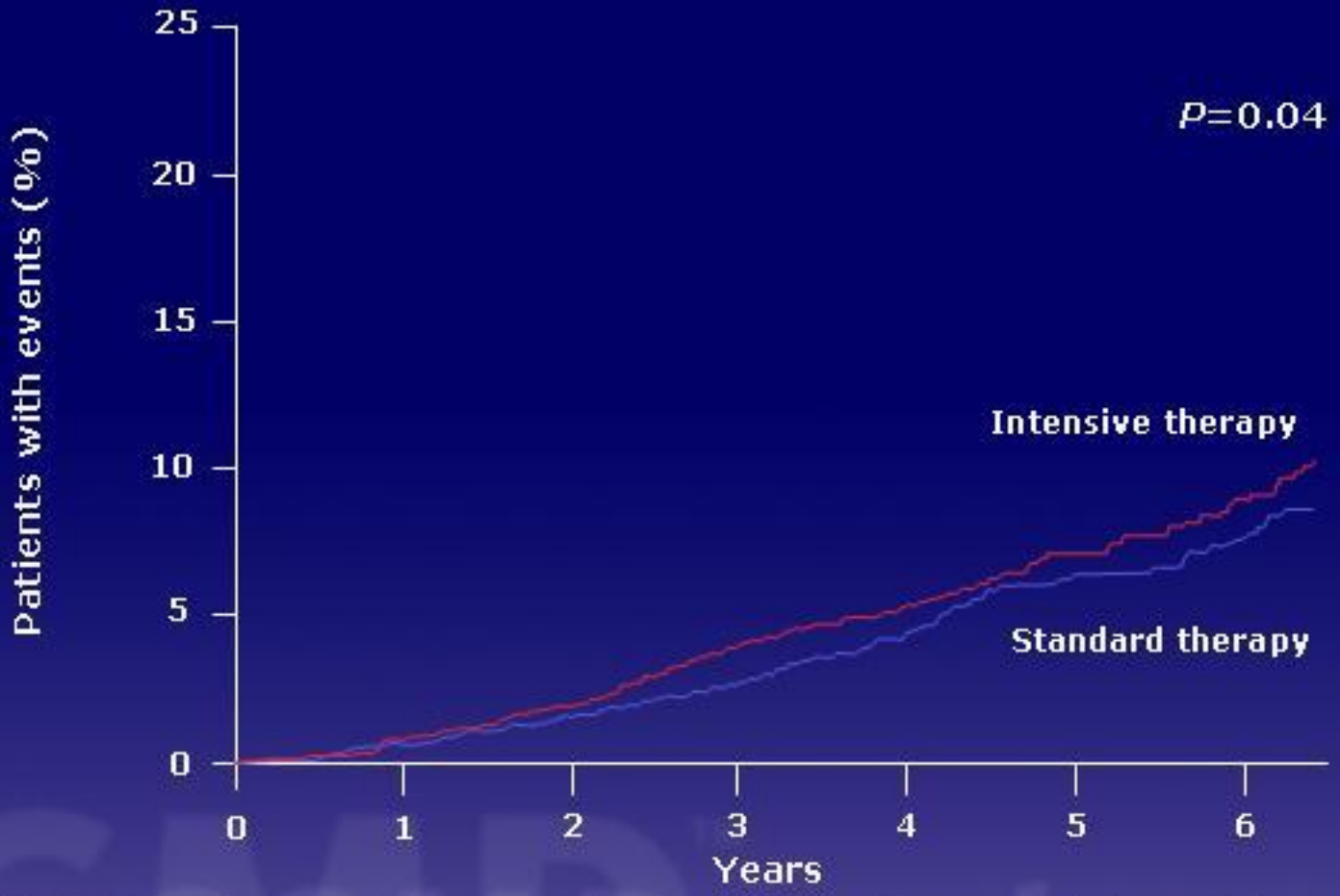
[a]Median baseline A1c: 8.1%; target A1c: <6.0% with intensive therapy; 7.0%–7.9% with standard therapy

IQR=interquartile range

ACCORD=Action to Control Cardiovascular Risk in Diabetes

Reprinted from ACCORD Study Group. *N Engl J Med*. 2008;358(24):2545-2559.

ACCORD: Death from Any Cause



Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

ACCORD=Action to Control Cardiovascular Risk in Diabetes

Reprinted from ACCORD Study Group. *N Engl J Med*. 2008;358(24):2545-2559.

ACCORD: Results

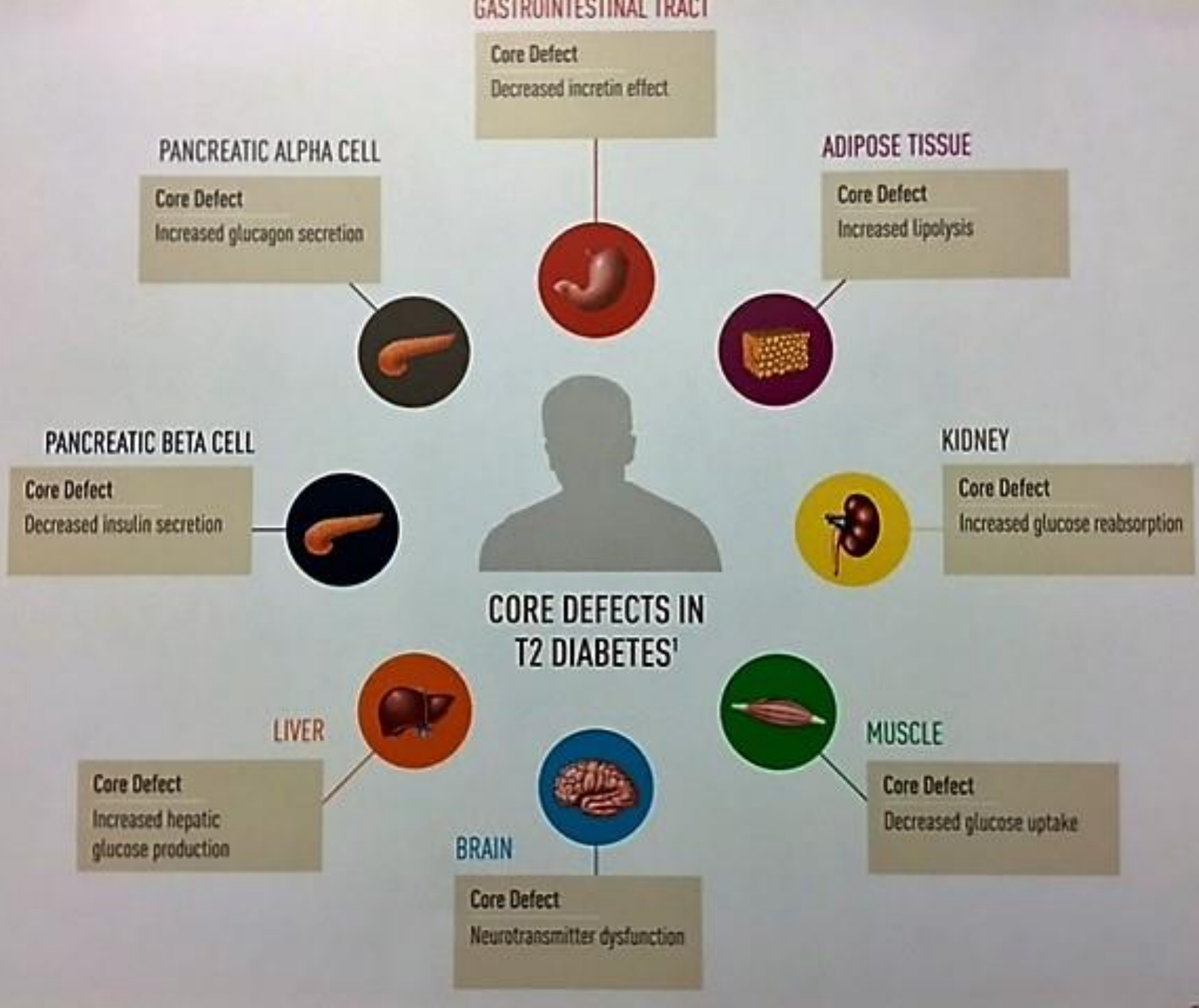
	Intensive therapy (n=5,128)	Standard therapy (n=5,123)	HR	*P*
Primary outcome	352 (6.9%)	371 (7.2%)	0.90	*P*=0.16
Death from any cause	257 (5.0%)	203 (4.0%)	1.22	*P*=0.04

Intensive therapy caused:

- *NS trend to decreased primary endpoint, BUT*
- ***Increased*** *total mortality*

CV=cardiovascular; HR=hazard ratio; NS=not significant
ACCORD=Action to Control Cardiovascular Risk in Diabetes

The ACCORD Study Group. *N Engl J Med*. 2008;358(24):2545-2559.


GASTROINTESTINAL TRACT
Core Defect
Decreased incretin effect
PANCREATIC ALPHA CELL
Core Defect
Increased glucagon secretion
ADIPOSE TISSUE
Core Defect
Increased lipolysis
PANCREATIC BETA CELL
Core Defect
Decreased insulin secretion
KIDNEY
Core Defect
Increased glucose reabsorption
CORE DEFECTS IN T2 DIABETES[1]
LIVER
Core Defect
Increased hepatic glucose production
MUSCLE
Core Defect
Decreased glucose uptake
BRAIN
Core Defect
Neurotransmitter dysfunction

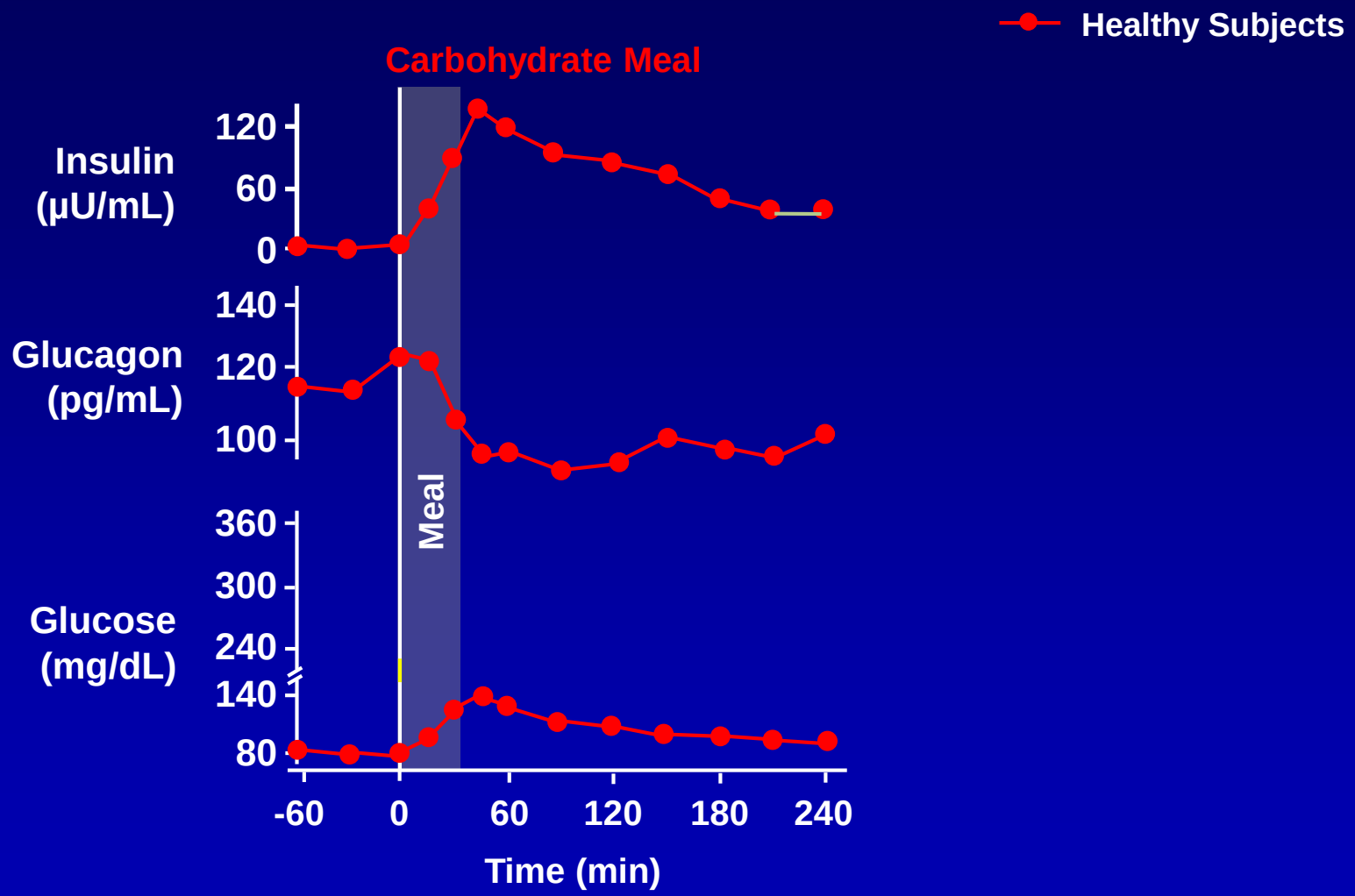
PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated CKD Stage 3B,4,5	Exenatide Not Indicated CrCl < 30	Not Effective with eGFR < 45 / Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Possible Benefit	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CARDIAC ASCVD	Benefit					Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

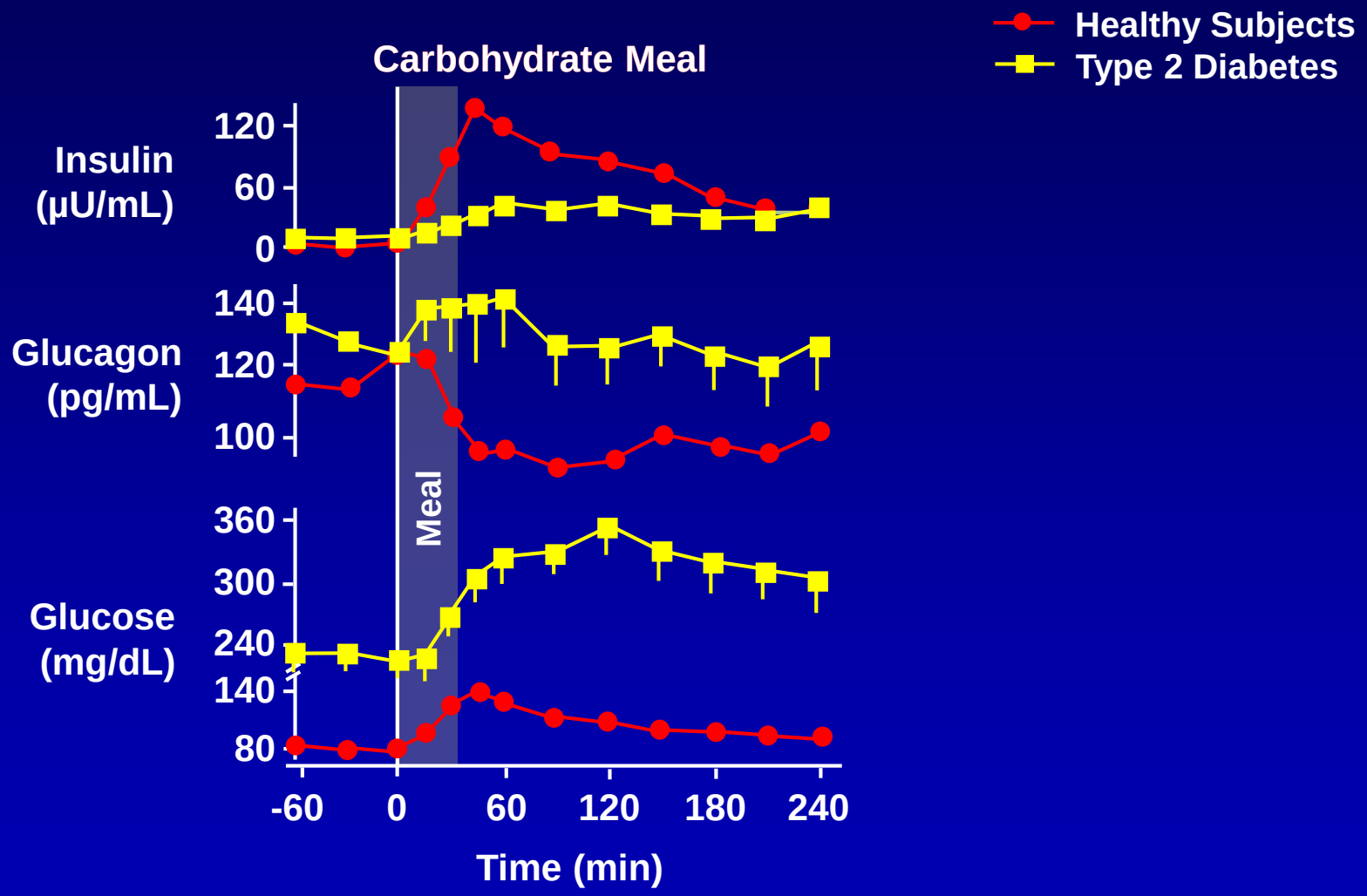
The INCRETIN HORMONE

β-Cell Workload and Response Are Balanced in Healthy Subjects



n = 14; Mean ± SE
Data from Müller WA, et al. *N Engl J Med.* 1970;283:109-115.

β-Cell Workload Outpaces Response in Type 2 Diabetes



N = 26; Mean ± SE
Data from Müller WA, et al. *N Engl J Med.* 1970;283:109-115.

Glucagon-Like Peptide-1 (GLP-1) Is an Important Incretin Hormone

- **Incretins**
  - Gut hormones that enhance insulin secretion in response to food
  - Glucose-dependent insulin secretion
- **GLP-1**
  - **Secreted from L cells of the intestines**
  - **Most well-characterized incretin**
  - **Diminished in type 2 diabetes**
- Glucagon
  - Secreted from pancreatic alpha cells
  - Counterregulatory hormone to insulin
  - Elevated in type 2 diabetes

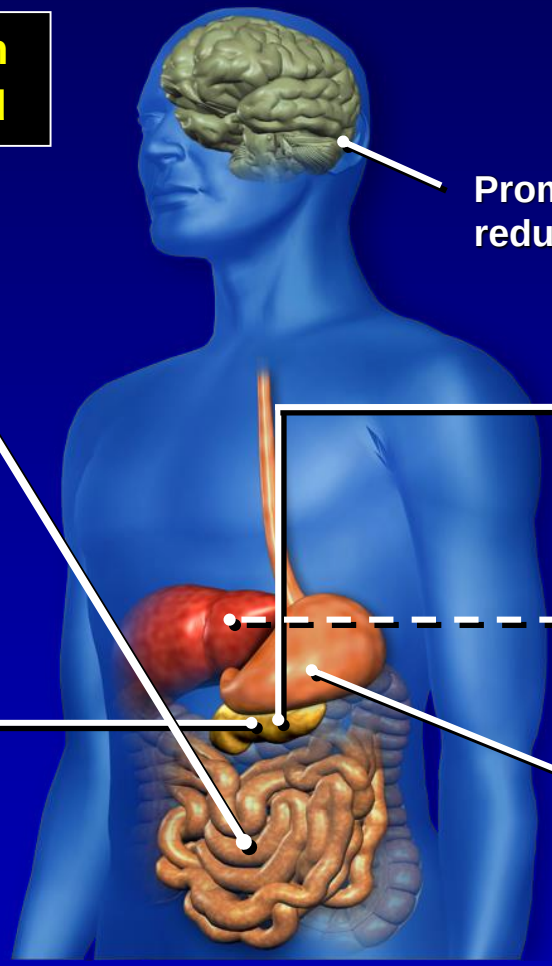
Adapted from Aronoff SL, et al. *Diabetes Spectrum*. 2004;17:183-190.

Glucagon-Like Peptide-1

- Secreted from intestinal L-cells with meal ingestion
- In humans and animals
  - enhances glucose-stimulated insulin release
  - decreases glucagon release
  - slows gastric emptying
  - reduces food intake
- In animals and in vitro
  - increases insulin gene transcription
  - increases β-cell mass and β-cell differentiation

Drucker DJ. *Curr Pharm Des*. 2001;7:1399-1412.
Drucker DJ. *Mol Endocrinol*. 2003;17:161-171.

GLP-1 Modulates Numerous Functions in Humans



GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

α cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

β cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

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.

Leveraging the Therapeutic Potential of GLP-1

- **GLP-1**
  - Short half-life (<2 minutes)
    - Rapidly degraded by **dipeptidyl peptidase-IV (DPP-IV)**
  - DPP-IV inhibition -Could extend endogenous GLP-1 half-life
  - Sitagliptin (Januvia) – 25 mg, 50 mg, 100 mg

    Saxagliptin (Onglyza) – 2.5 mg, 5 mg

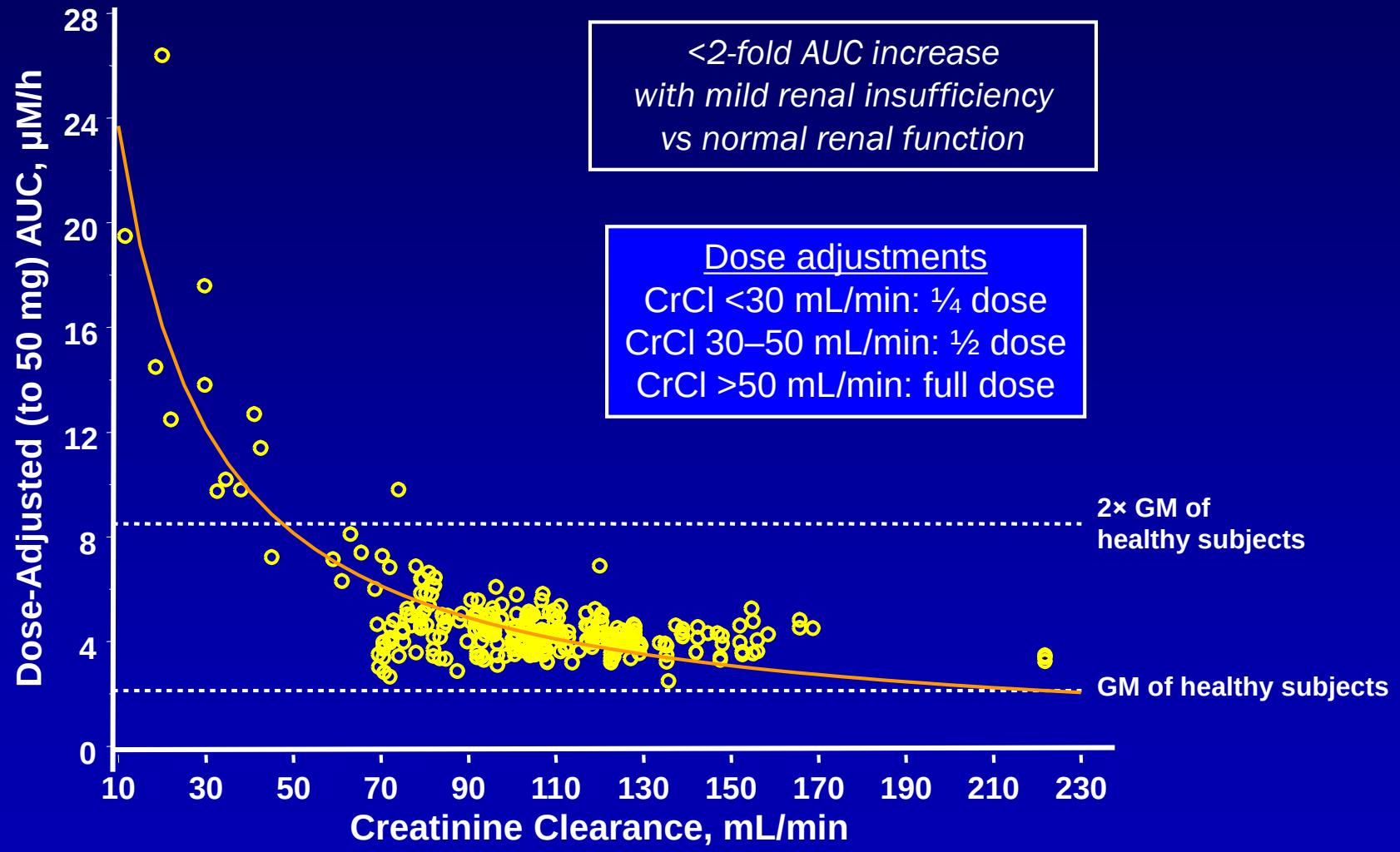
    Linagliptin (Tradjenta)

    Alogliptin (Nesina)

    Vildaglipitin
- **Incretin mimetics** - GLP-1 AGONIST
  - Resistant to DPP-IV
    - **GLP-1 analogs**
    - **Exenatide (Byetta), BYDUREON**
    - **Liraglutide (Victoza)**
    - **ALBIGLUTIDE (TANZEUM)**

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

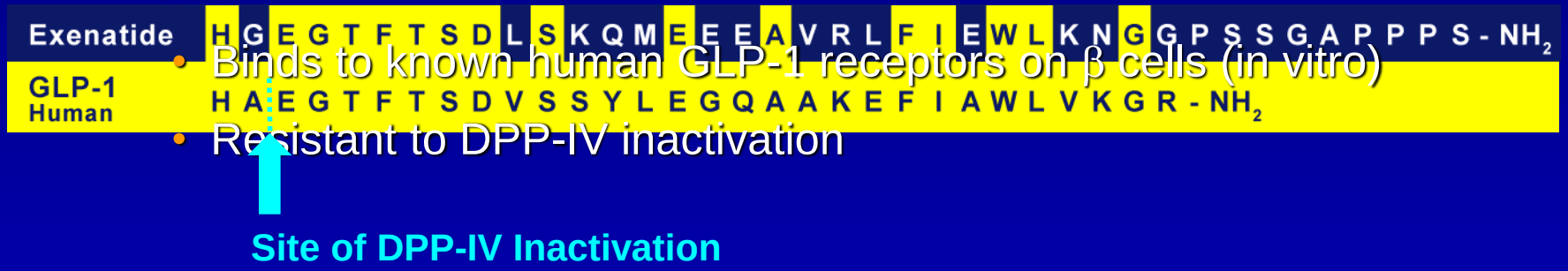
Sitagliptin Dosage Needs to Be Adjusted in Patients With Renal Insufficiency



AUC=area under the curve; CrCl=creatinine clearance; GM=geometric mean.
Data available on request from Merck & Co., Inc. Please specify 20950986(1)-JAN.

The Beginning

- Exenatide
  - Synthetic version of salivary protein found in the Gila monster
  - More than 50% amino acid sequence identity with human GLP-1



- Binds to known human GLP-1 receptors on β cells (in vitro)
- Resistant to DPP-IV inactivation

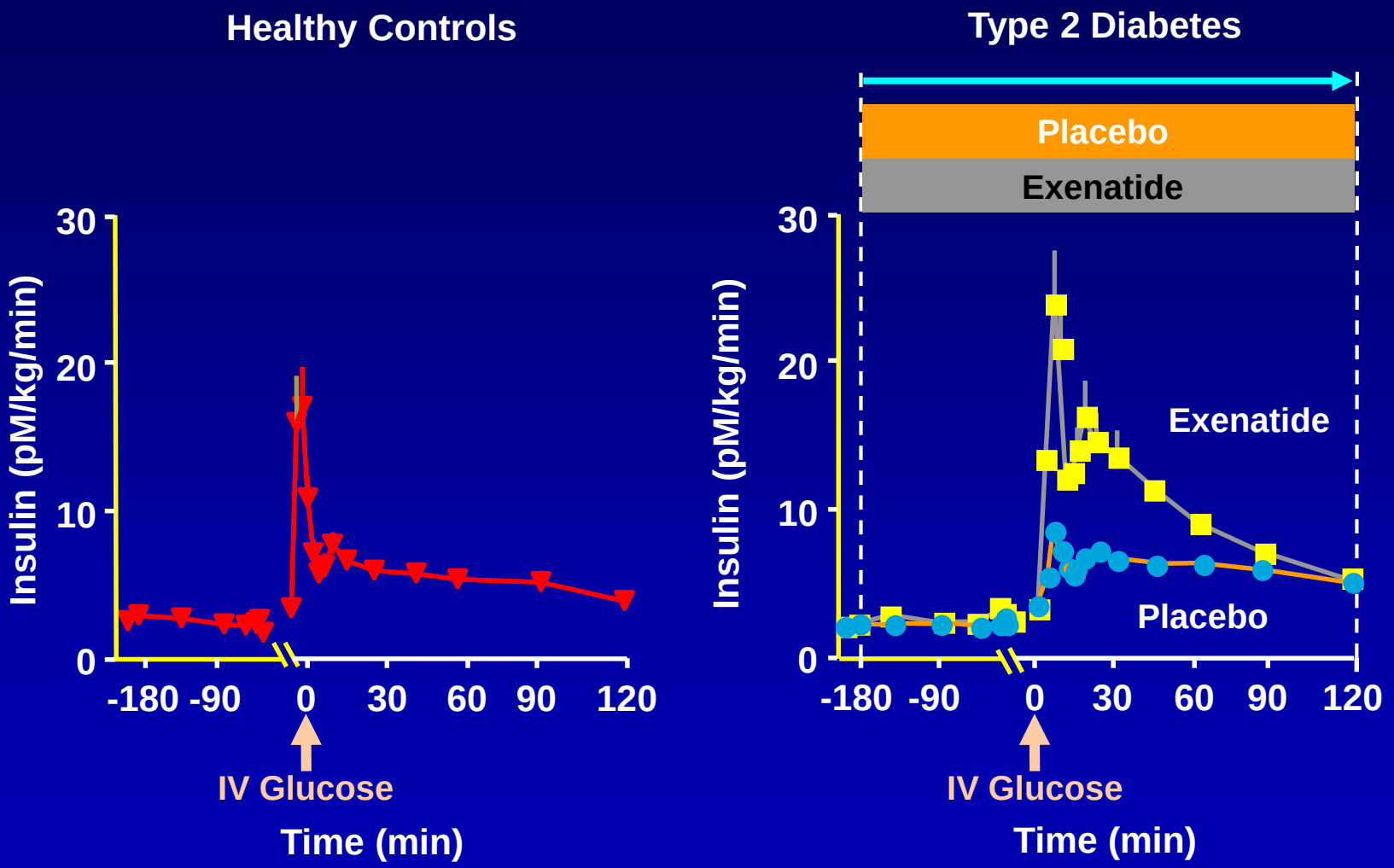
- Following injection, exenatide is measurable in plasma for up to 10 hours

Adapted from Nielsen LL, et al. *Regul Pept*. 2004;117:77-88.
Adapted from Kolterman OG, et al. *Am J Health-Syst Pharm*. 2005;62:173-181.

Exenatide Mimics Many Properties of GLP-1

	GLP-1	Exenatide
↑ Glucose-dependent insulin secretion	✓	✓
↓ Glucagon secretion	✓	✓
↓ Hepatic glucose output		
Regulates gastric emptying	✓	✓
↓ Rate of nutrient absorption		
↓ Food intake	✓	✓
↓ Plasma glucose acutely to near-normal levels	✓	✓
Resistant to DPP-IV degradation		✓
Duration in plasma following a subcutaneous (SC) injection	Short	Long

Exenatide Restored First-Phase Insulin Response



Evaluable; N = 25; Mean ± SE
Data from Fehse F, et al. *Diabetologia*. 2004;47(suppl 1):A279.

Other Adverse Events
Large Phase 3 Clinical Studies – Combined

Results of 30-Week Exenatide Studies

	Placebo (N = 483)	Exenatide BID 5 µg and 10 µg (N = 963)
Nausea	18%	44%
Vomiting	4%	13%
Diarrhea	6%	13%
Feeling Jittery	4%	9%
Dizziness	6%	9%
Headache	6%	9%
Dyspepsia	3%	6%

ITT; Overall incidence ≥5% and incidence of exenatide > placebo
Exenatide Prescribing Information, 2006

GLP-1 Receptor Agonists

FDA-Approved Agents

- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
- Exenatide (Byetta)
- Exenatide ER (Bydureon)
- Liraglutide (Victoza)
- Lixisenatide (Adlyxin)

Key Features

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

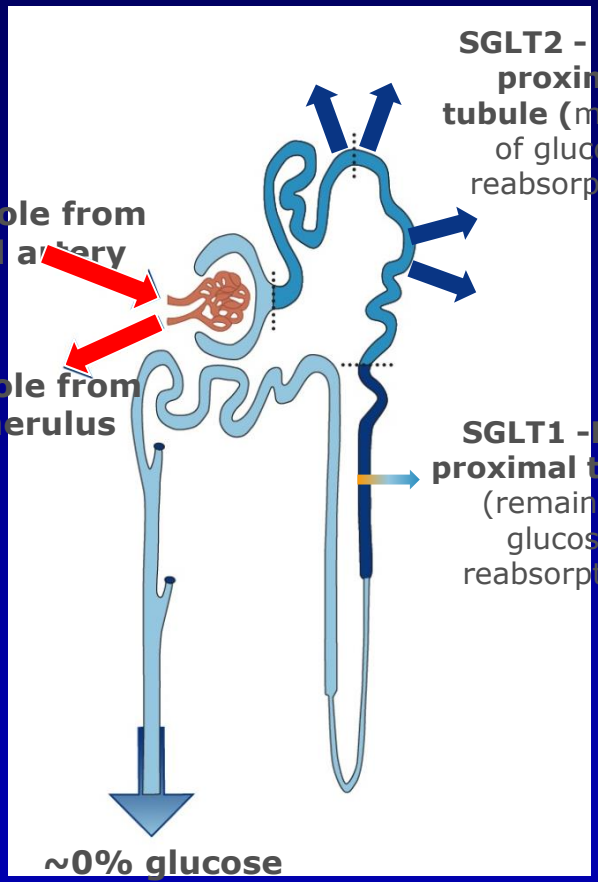
ER, extended release; GLP-1, glucagon-like peptide 1.

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.

Selective SGLT2 Inhibition Therapeutic Target for T2DM

- SGLT2 is the key renal transporter for glucose reabsorption
- Mutations in SGLT2 cause renal glucosuria

	SGLT1	SGLT2
Site	Small intestine (most), kidney, heart	Kidney
Renal Location	Late proximal tubule	Early proximal tubule
Affinity	High	Low
Capacity for glucose transport	Low	High
% of renal glucose reabsorption	~10%	~90%



T2DM : type 2 diabetes mellitus; SGLT: sodium glucose co-transporter

Chao & Henry. *Nature Rev Drug Discovery* 2010;9:551-559.

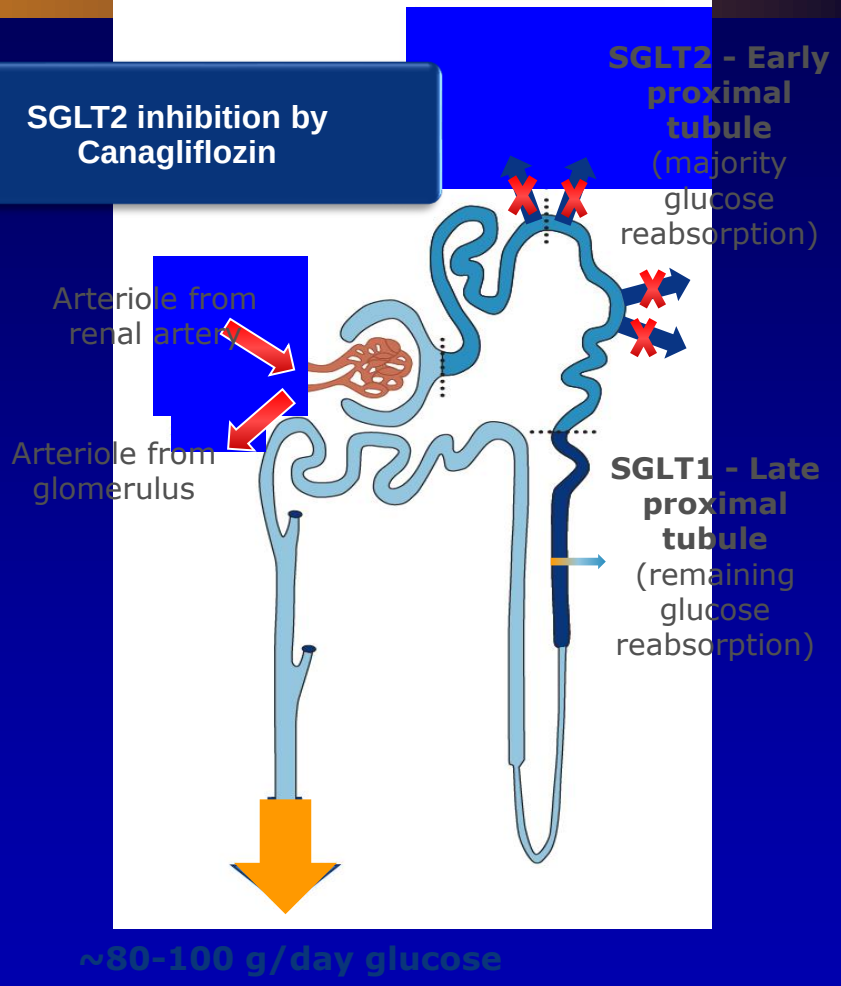
INVOKANA – Mechanism of Action

CANA blocks SGLT2 leading to renal glucosuria

Increases urinary glucose excretion: ~80-100 g/day in patients with T2DM[1-3]

Selectivity[4]:

SGLT2 IC_{50} = 4.4 nmol/L
SGLT1 IC_{50} = 684 nmol/L



T2DM: type 2 diabetes mellitus; CANA – canagliflozin; SGLT: sodium glucose co-transporter

1. Sha et al. Poster presented at ADA 70th Scientific Sessions; Orlando, FL; June 25-29, 2010. Abstract #0568-P. 2. Devineni et al. *Diabetes Obes Metab* 2012;14:539-45. 3. Data on file. Janssen Pharmaceuticals, Inc. 4. Liang et al. *PLoS ONE* 2012;7:e30555.

SGLT2 INHIBITORS

CANAGLIFOZIN (INVOKANA)
- 100 MG, 300 MG

DAPAGLIFOZIN (FARXIGA)
- 5 MG, 10 MG

EMPAGLIFOZIN (JARDIANCE)
- 10 MG , 25 MG

Dose Adjustments: Renal Impairment and Concomitant Use of UGT Enzyme Inducers

Renal Function	Dosage Adjustment
Mild impairment	No adjustment in patients with eGFR ≥60 mL/min/1.73 m^2
Moderate impairment	Dose is limited to 100 mg once daily in patients who have an eGFR of 45 to <60 mL/min/1.73 m^2. Do not initiate INVOKANA or discontinue INVOKANA if eGFR is persistently <45 mL/min/1.73 m^2
Severe impairment	Contraindicated in patients with eGFR <30 mL/min/1.73 m^2, ESRD, or patients on dialysis

Concomitant Use of UGT Inducers*	Dosage Adjustment
Patients with eGFR ≥60 mL/min/1.73 m^2 and who require additional glycemic control	Consider increasing the dosage to 300 mg once daily in patients currently tolerating INVOKANA 100 mg once daily
Patients with eGFR of 45 to <60 mL/min/1.73 m^2	Consider another antihyperglycemic agent

*Examples of UGT inducers include rifampin, phenytoin, phenobarbital, and ritonavir.

eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; UGT=UDP-glucuronosyltransferase.

INVOKANA™ (canagliflozin) [package insert]. Janssen Pharmaceuticals, Inc; Titusville, NJ.

Volume Depletion-related AEs (DS3)

	Non-CANA N=3262 n (%)	CANA 100 mg N=3092 n (%)	CANA 300 mg N=3085 n (%)
Any adverse events (AEs)	78 (2.4)	99 (3.2)	141 (4.6)
Serious AEs	11 (0.3)	12 (0.4)	8 (0.3)
Specific AE Terms			
Blood pressure decreased	1 (<0.1)	2 (0.1)	2 (0.1)
Dehydration	**13 (0.4)**	**6 (0.2)**	**13 (0.4)**
Dizziness postural	**24 (0.7)**	**26 (0.8)**	**33 (1.1)**
Hypotension	**20 (0.6)**	**47 (1.5)**	**60 (1.9)**
Hypovolemia	1 (<0.1)	0	0
Hypovolemic shock	0	0	1 (<0.1)
Orthostatic hypotension	**6 (0.2)**	**8 (0.3)**	**27 (0.9)**
Orthostatic intolerance	1 (<0.1)	1 (<0.1)	1 (<0.1)
Presyncope	9 (0.3)	4 (0.1)	3 (0.1)
Syncope	**13 (0.4)**	**12 (0.4)**	**20 (0.6)**
Urine output decreased	1 (<0.1)	0	0

CANA: canagliflozin

Data on file. Janssen Pharmaceuticals, Inc.

Summary of Specific Adverse Events (DS1)

	Placebo N=646 n (%)	CANA 100 mg N=833 n (%)	CANA 300 mg N=834 n (%)
Female genital mycotic infection*	10 (3.2)	44 (10.4)	49 (11.4)
Vulvovaginal pruritus	0 (0)	7 (1.6)	13 (3.0)
Urinary tract infection†	26 (4.0)	49 (5.9)	36 (4.3)
Increased urination‡	5 (0.8)	44 (5.3)	38 (4.6)
Male genital mycotic infection§	2 (0.6)	17 (4.2)	15 (3.7)
Constipation	6 (0.9)	15 (1.8)	19 (2.3)
Nausea	9 (1.5)	18 (2.2)	18 (2.3)
Thirst¶	1 (0.2)	23 (2.8)	19 (2.3)

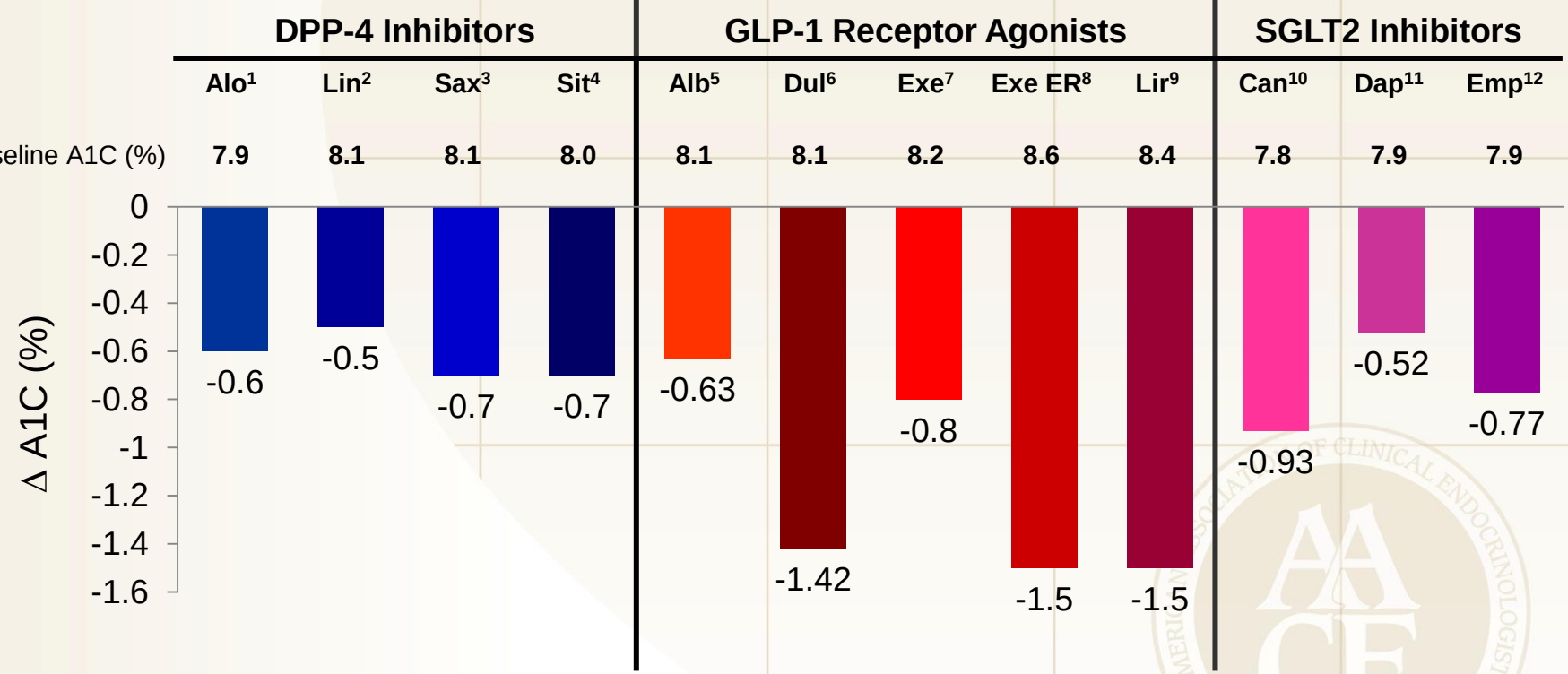
* Female genital mycotic infections include: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.
† Urinary tract infections include: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.
‡ Increased Urination includes: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.
§ Male genital mycotic infections include: Balanitis, Balanoposthitis, Balanitis candida, and Genital infection fungal.
¶ Thirst includes: Thirst, Dry mouth, and Polydipsia.

- Female genital mycotic infection: 20/93 (22%) had >1 event on CANA vs 1/10 (10%) on placebo
- Male genital mycotic infection: 7/32 (21.9%) had >1 event on CANA vs none on placebo
- Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop an infection

INVOKANA™ (canagliflozin) [package insert]. Janssen Pharmaceuticals, Inc; Titusville, NJ. Data on file. Janssen Pharmaceuticals, Inc.

Glucose Reduction

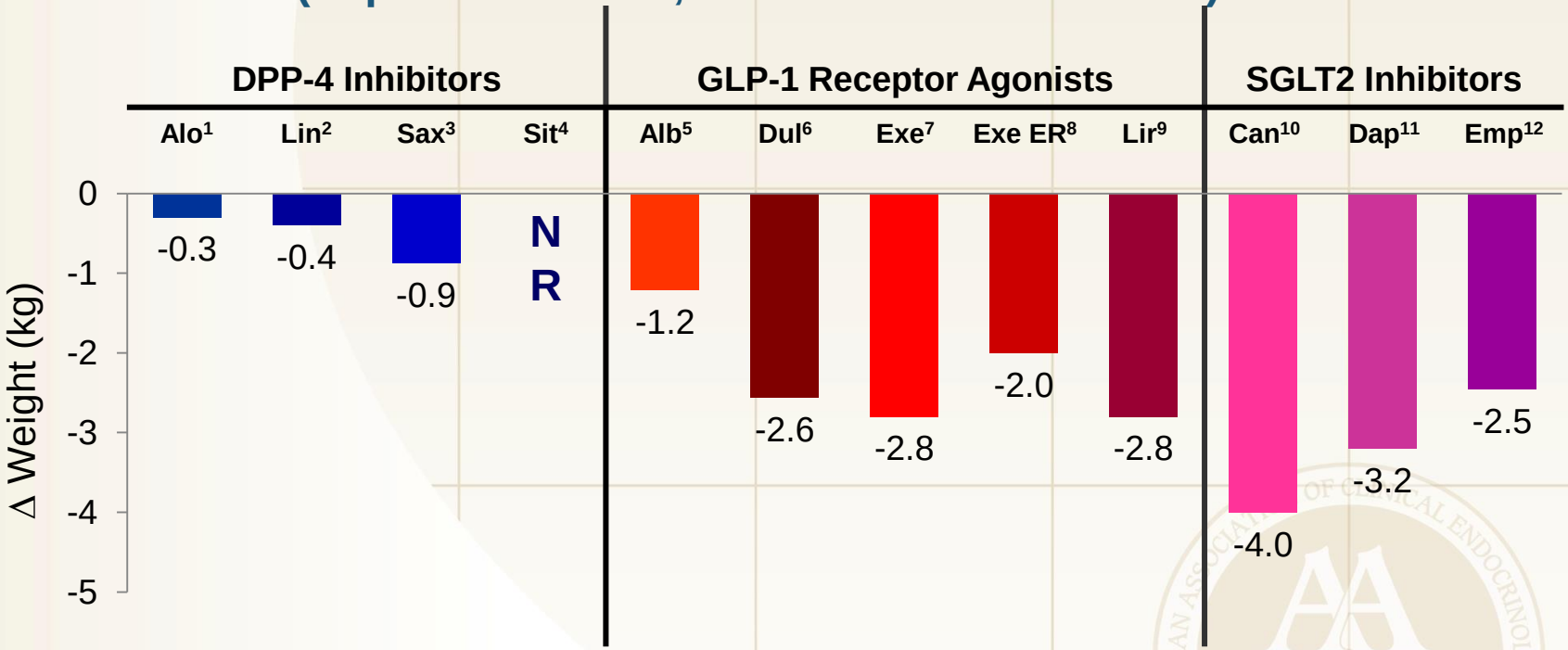
DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin (Absolute Changes from Baseline; Not Head-to-Head Trials)



1. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 2. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 4. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 5. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 6. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 7. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 8. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 9. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 10. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 11. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 12. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659.

Weight Reduction

DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin (Separate Studies; Not Head-to-Head Trials)



NR, not reported.

1. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 2. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 4. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 5. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 6. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 7. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 8. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 9. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 10. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 11. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 12. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659.

Effects of Antihyperglycemic Therapies on Blood Pressure

Meta-analyses

Class	Δ Systolic BP, mmHg (95% CI)	Δ Diastolic BP, mmHg (95% CI)
Newer therapies		
GLP-1 receptor agonists[1]	**-3.57** (-5.49 to -1.66)	**-1.38** (-2.02 to -0.73)
DPP-4 inhibitors[2]	-0.1 (-1.2 to 0.8)	—
SGLT2 inhibitors[3]	**-3.77** (-4.65 to -2.90)	**-1.75** (-2.27 to -1.23)
Older therapies		
Metformin[4]	-1.09 (-3.01 to 0.82)	-0.97 (-2.15 to 0.21)
TZDs[5]	-4.70 (-6.13 to -3.27)	-3.79 (-5.82 to -1.77)

1. Vilsbøll T, et al. *BMJ*. 2012 Jan 10;344:d7771. doi: 10.1136/bmj.d7771.
2. Monami M, et al. *Diabetes Obes Metab*. 2013;15:112-120.
3. Vasilakou D, et al. *Ann Intern Med*. 2013;159:262-274.
4. Wulffelé M, et al. *J Intern Med*. 2004;256:1-14.
5. Qayyum R, Adomaityte J. *J Clin Hypertens (Greenwich)*. 2006;8:19-28.

Clinical Outcomes with Antihyperglycemic Agents

EMPA-REG OUTCOME

(EMPAGLIFLOZIN CARDIOVASCULAR OUTCOME EVENT TRIAL IN TYPE 2 DIABETES MELLITUS PATIENTS)

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME

Study Design

- **N=7020 patients with T2D and CVD**
- **Randomization**
  - **Empagliflozin: n=4687**
  - **Placebo: n=2333**
- **Noninferiority study: prespecified HR margin = 1.3 for primary endpoint**
  - **Primary endpoint: composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke**
  - **Secondary endpoint: composite of CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina**

Key Results

- Median follow-up: 3.1 years
- Week 206 A1C, difference from placebo
  - Empagliflozin 10 mg: -0.24% (95% CI, -0.40% to -0.08%)
  - Empagliflozin 25 mg: -0.36% (95% CI, -0.51% to -0.20%)
- CV outcomes (pooled analysis)
  - Primary: HR 0.86 (95% CI 0.74 to 0.99); *P*=0.04 for superiority
  - Secondary HR: 0.89 (95% CI 0.78 to 1.01); *P*<0.001 for noninferiority and *P*=0.08 for superiority
- **Significantly lower rates of all-cause death, CV death, and HF hospitalization with empagliflozin**
- Increased rates of genital infections in empagliflozin-treated patients

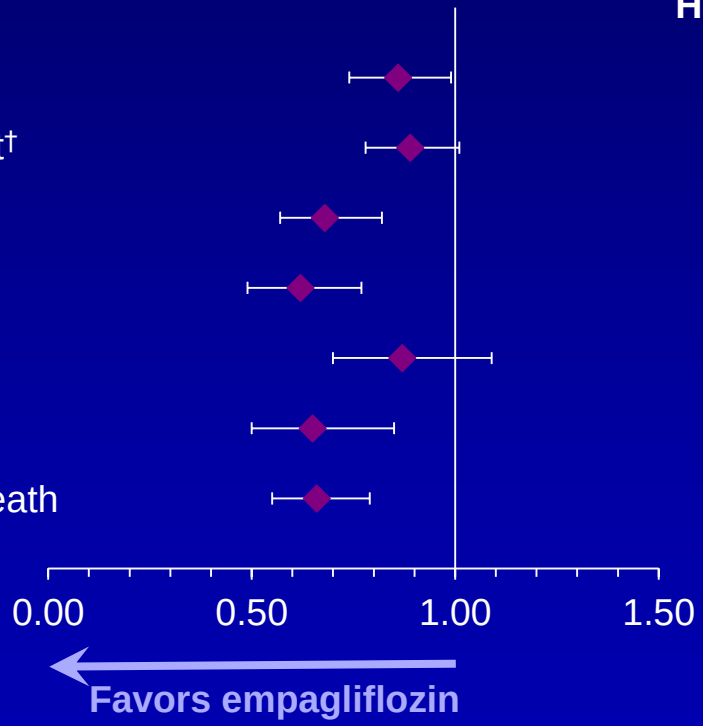
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001



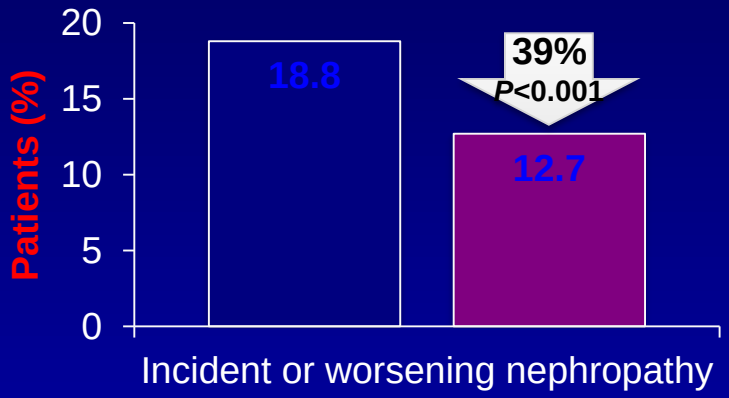
*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

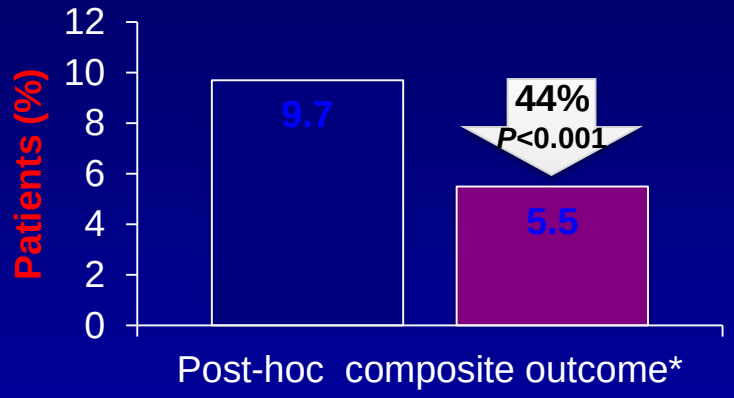
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

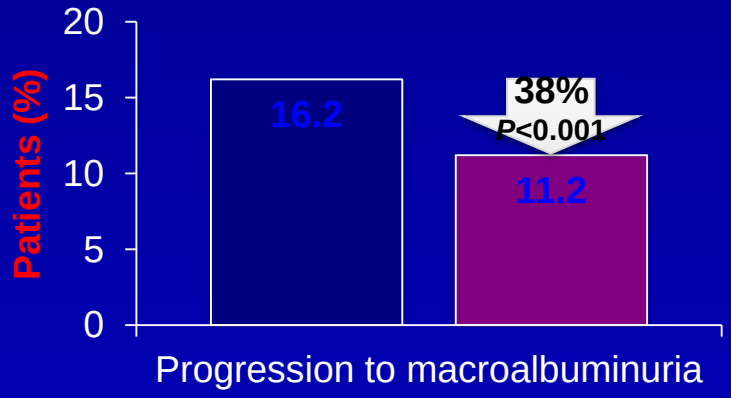
Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Renal Outcomes with Empagliflozin Over 3.2 Years

EMPA-REG RENAL (N=7020)







Arrows = relative risk reduction.

*Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.

CI, confidence interval; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Wanner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

Clinical Outcomes with Antihyperglycemic Agents

LEADER

(LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS)

Clinical Outcomes with Liraglutide

LEADER

Study Design

- N=9340 patients with T2D and high CV risk
- Randomization
  - Liraglutide: n=4672
  - Placebo: n=4668
- Noninferiority study: prespecified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

Key Results

- Median follow-up: 3.5 years
- Difference from placebo at 36 months
  - A1C: −0.40% (95% CI, −0.45% to −0.34%)
  - Weight: −2.3 kg (95% CI, −2.0 to −2.5 kg)
  - SBP: −1.2 mm Hg (95% CI, −0.5 to −1.9 mm Hg)
- CV outcomes
  - Primary: HR 0.87 (95% CI 0.78 to 0.97); *P*=0.01 for superiority
  - Secondary HR: 0.88 (95% CI 0.81 to 0.96); *P*=0.005 for superiority
- ***Significantly lower rates of all-cause death and CV death with liraglutide***
- Increased rates of gastrointestinal events in liraglutide-treated patients
- Lower numerical incidence of pancreatitis in liraglutide group (not statistically significant)

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med*. 2016 Jun 13. [Epub ahead of print]

Questions

1. Consider Metformin therapy for delay or prevention of diabetes mellitus type 2 in patients with the following:

   prediabetes

   BMI > 35 kg/m2, age < 60 years old and women with

   prior history of gestational diabetes (True or False)

2. The ACCORD Trial showed decrease mortality in the Intensive Group (True or False)

3. GLP 1 (Glucagon Like Peptide 1) enhances glucose stimulated insulin release (True or False)

4. SGLT1 is the key renal transporter for glucose reabsorption

   (True or False)

5. EMPA-REG Outcome: Empaglifozin reduces cardiovascular events and

   mortality in high risk type 2 diabetes (True or False)

6. The LEADER Clinical Trial shows significant lower rates of all cause

   death and CV death with liraglutide

- FROM THE

UERMMMC MICHIGAN CHAPTER

THANK YOU

GOD BLESS


EXIT