interactive EXCHANGE

THE KIDNEYS IN TYPE 2 DIABETES

DISTURBED GLUCOSE HOMEOSTASIS TO MECHANISM-BASED THERAPY

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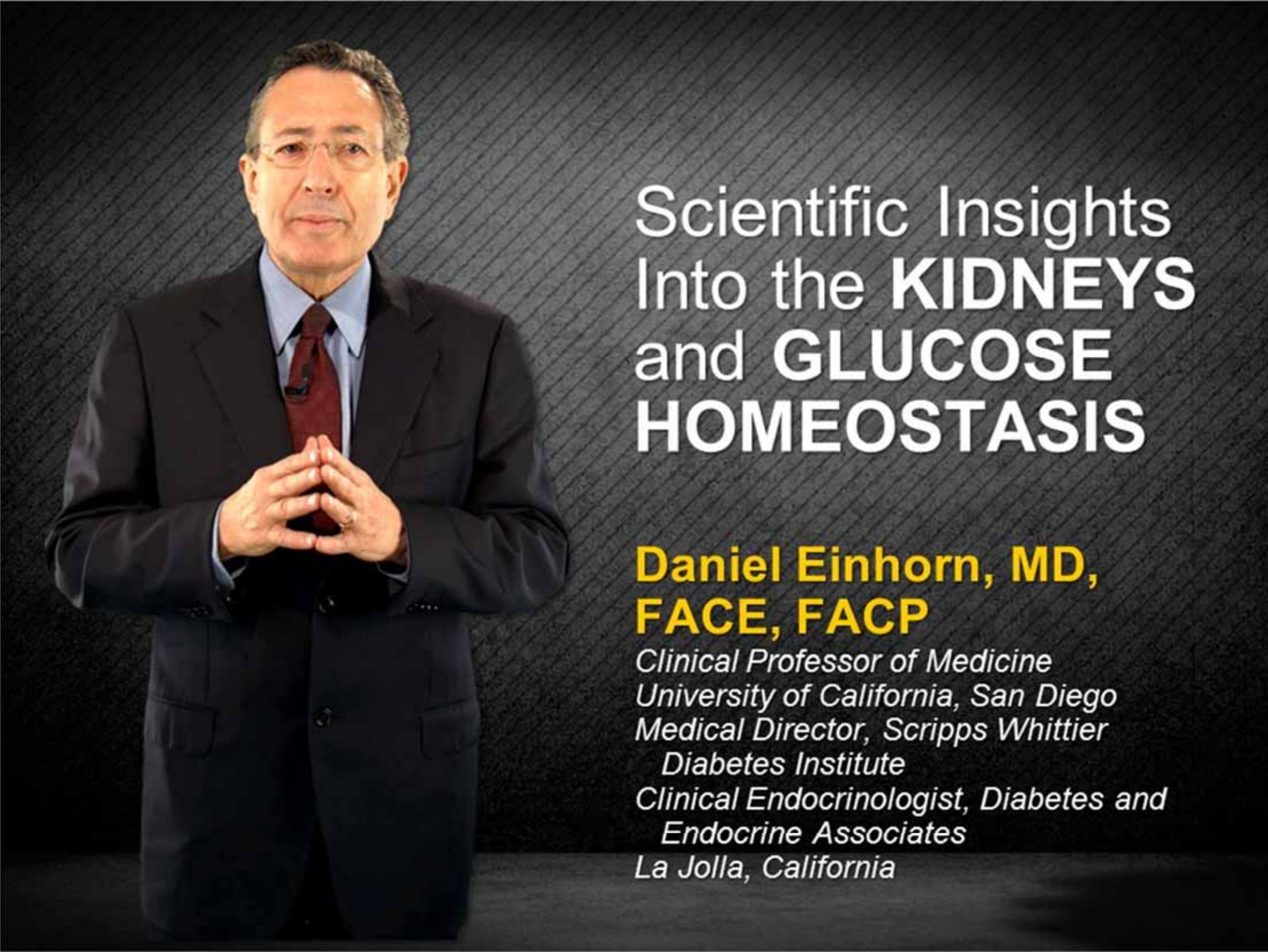
Educational Objectives

- Discuss the role of the kidney in glucose homeostasis
- Individualize treatment goals for patients with T2DM that reflect the degree of hyperglycemia, comorbid conditions, disease duration, and responses to therapy
- Educate patients with T2DM about lifestyle modifications, benefits and risks of antihyperglycemic therapy, and the importance of treatment adherence
- Evaluate the mechanisms of action and clinical profiles of SGLT-2 inhibitors for the treatment of T2DM
- Develop patient-centered therapeutic regimens for T2DM to maximize efficacy and minimize hypoglycemia, weight gain, and other potential treatment-related risks

SGLT-2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.


Scientific Insights
Into the KIDNEYS
and GLUCOSE
HOMEOSTASIS
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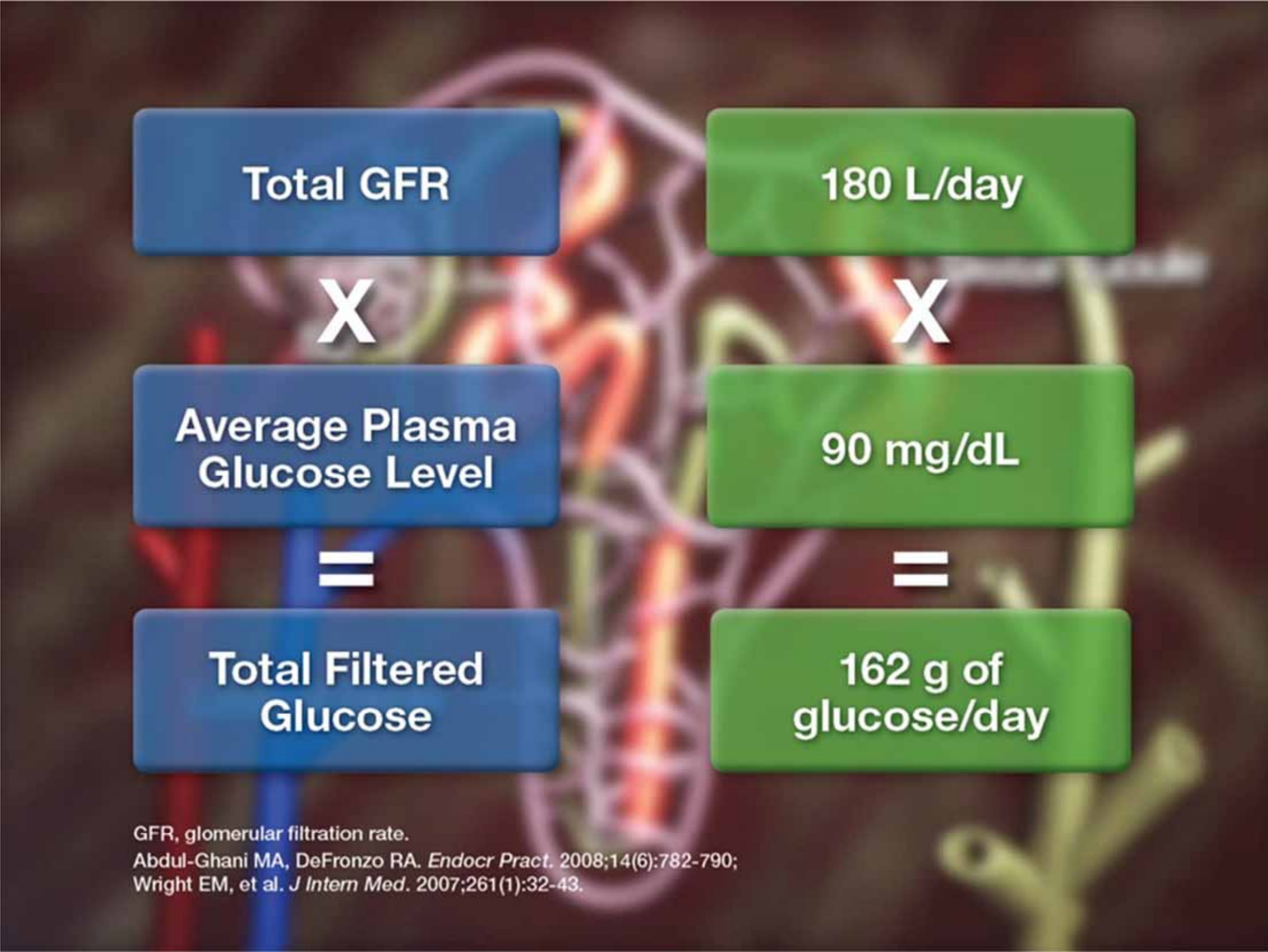
GLUCOSE RELEASE INTO THE CIRCULATION

Sources in the Postabsorptive State

Source and Mechanism	Rate of Release, μmol/kg/min	Relative Contribution to Overall Release Rate, %[a]
Hepatic Contribution	7.5-8.0	75-80
• Glycogenolysis	4.5-5.0	45-50
• Gluconeogenesis	2.5-3.0	25-30
Renal Contribution	2.0-2.5	20-25
• Glycogenolysis	0	0
• Gluconeogenesis	2.0-2.5	20-25

[a]After an overnight fast, glucose is released into the circulation at a rate of approximately 10 μmol/kg/min.

Gerich JE. *Diabetes Obes Metab*. 2000;2(6):345-350; Gerich JE. *Diabet Med*. 2010;27(2):136-142; Landau BR, et al. *J Clin Invest*. 1996;98(2):378-385; Stumvoll M, et al. *Diabetologia*. 1997;40(7):749-757.

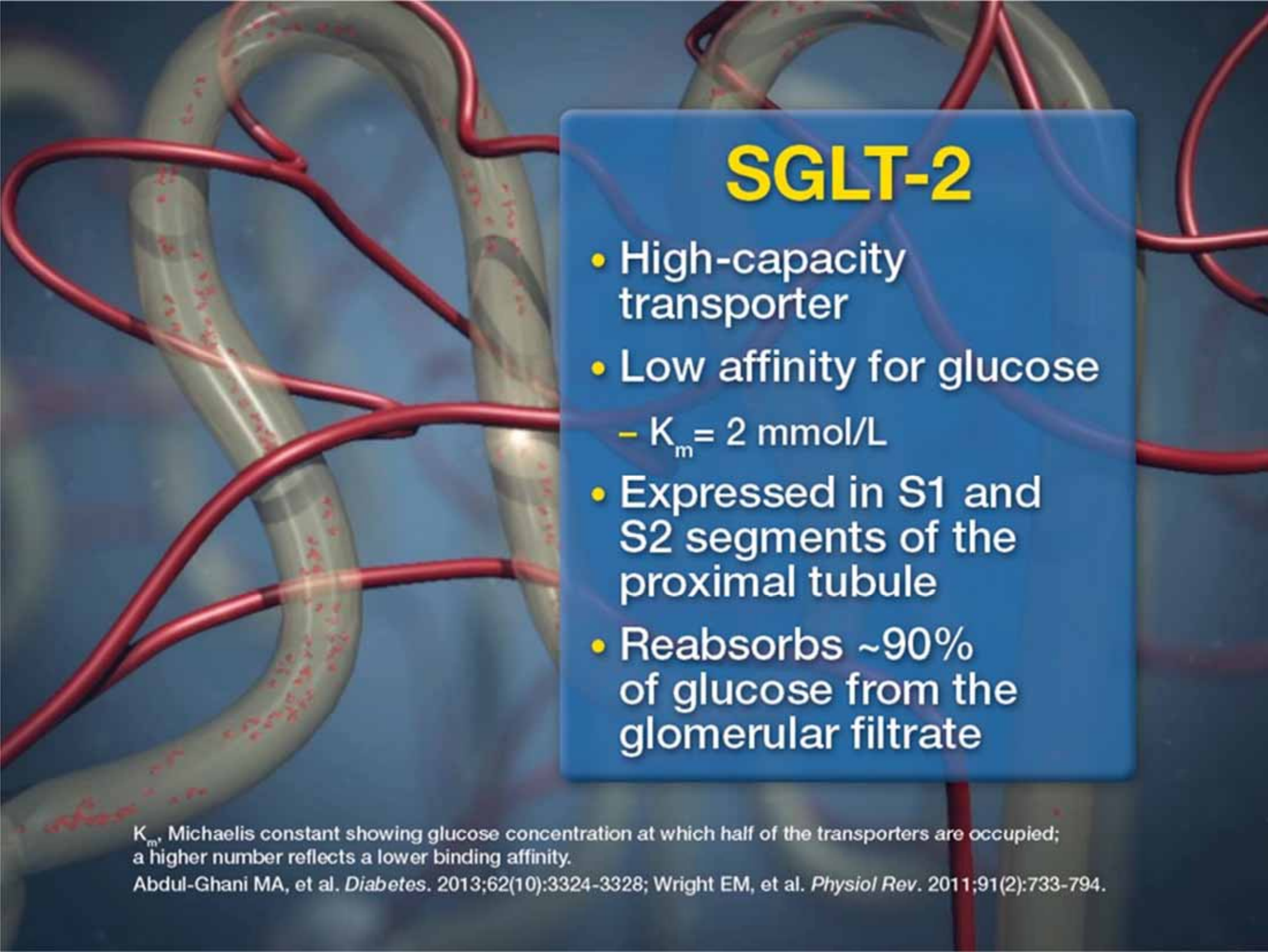


GFR, glomerular filtration rate.

Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14(6):782-790;
Wright EM, et al. *J Intern Med*. 2007;261(1):32-43.

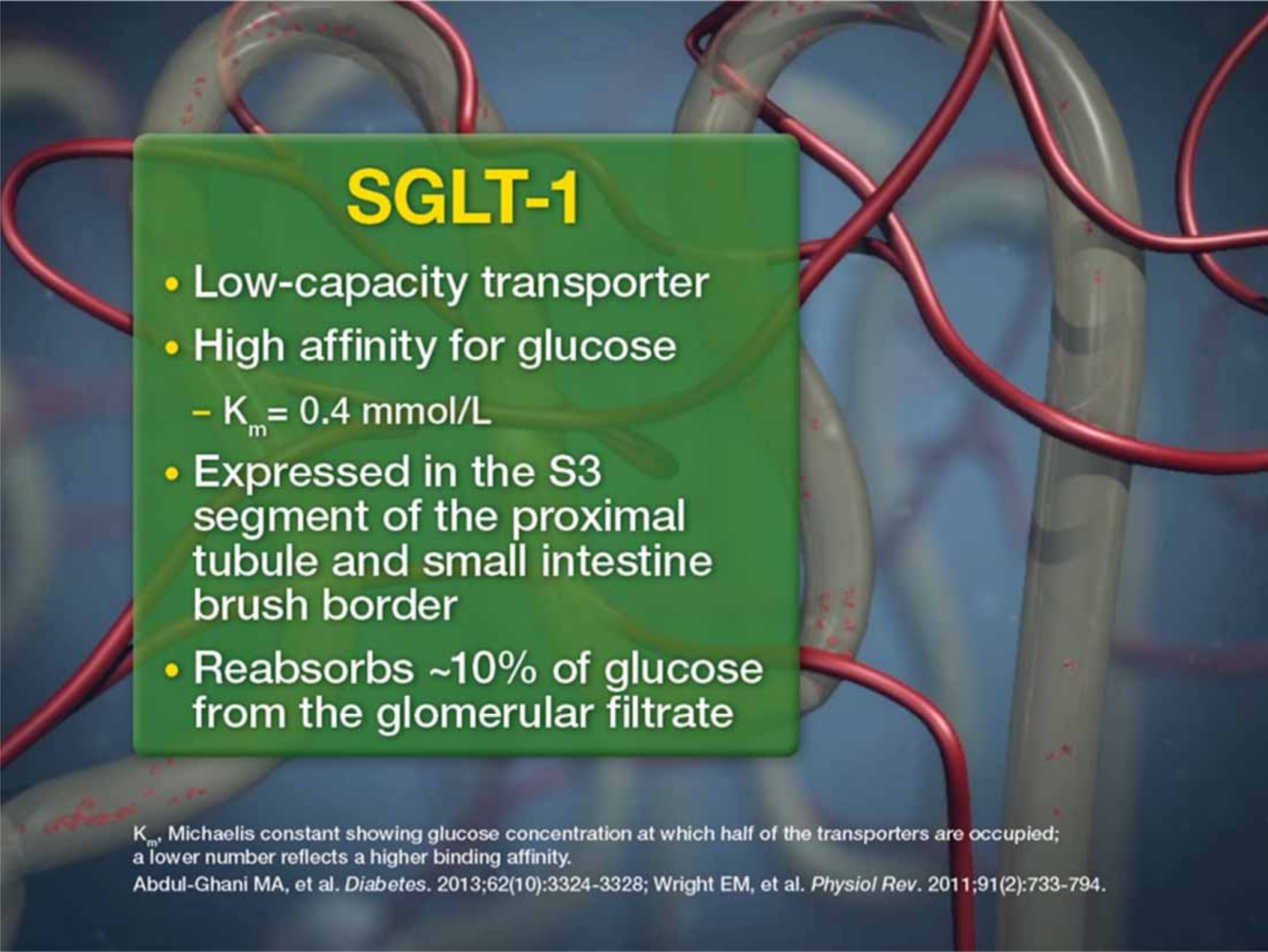
Sodium-**GL**ucose
co**T**ransporters (SGLTs)

reabsorb glucose from the glomerular filtrate into the epithelial cells lining the proximal tubule



K_m, Michaelis constant showing glucose concentration at which half of the transporters are occupied; a higher number reflects a lower binding affinity.

Abdul-Ghani MA, et al. *Diabetes*. 2013;62(10):3324-3328; Wright EM, et al. *Physiol Rev*. 2011;91(2):733-794.



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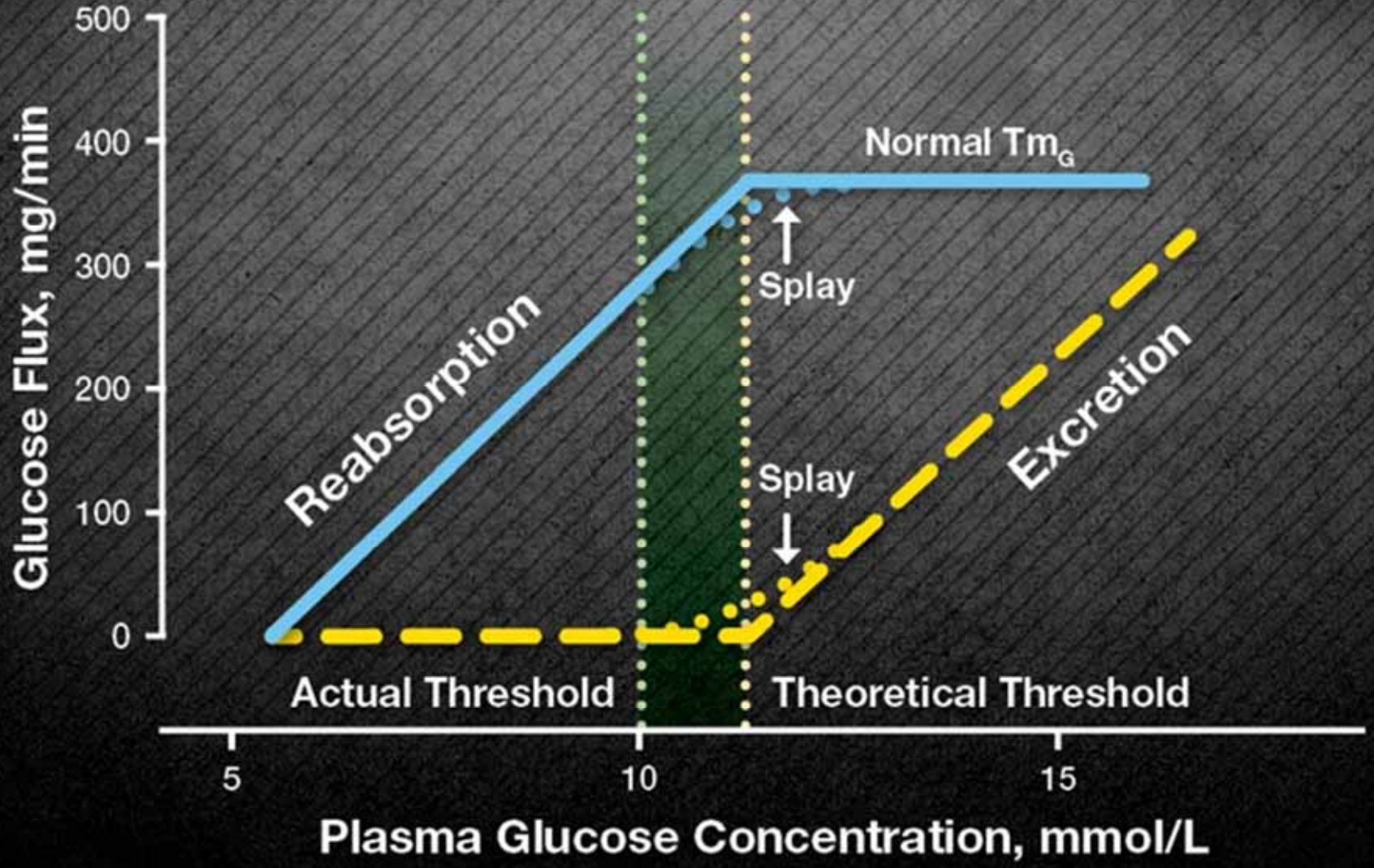
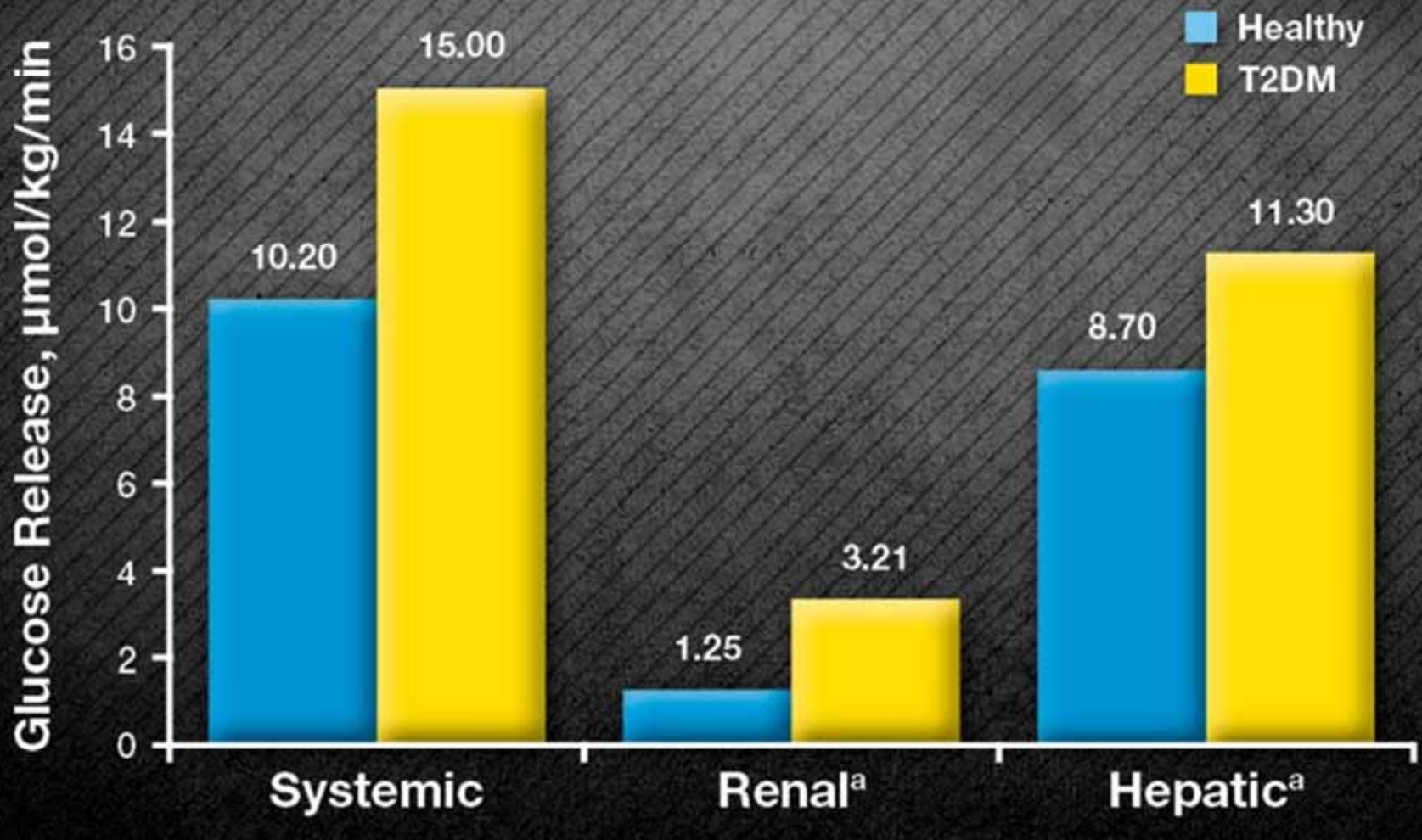
RENAL REABSORPTION AND EXCRETION OF GLUCOSE



Tm_G, glucose transport maximum.

Bays H. *Diabetes Ther*. 2013;4(2):195-220; DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14(1):5-14.

RENAL GLUCONEOGENESIS IN T2DM

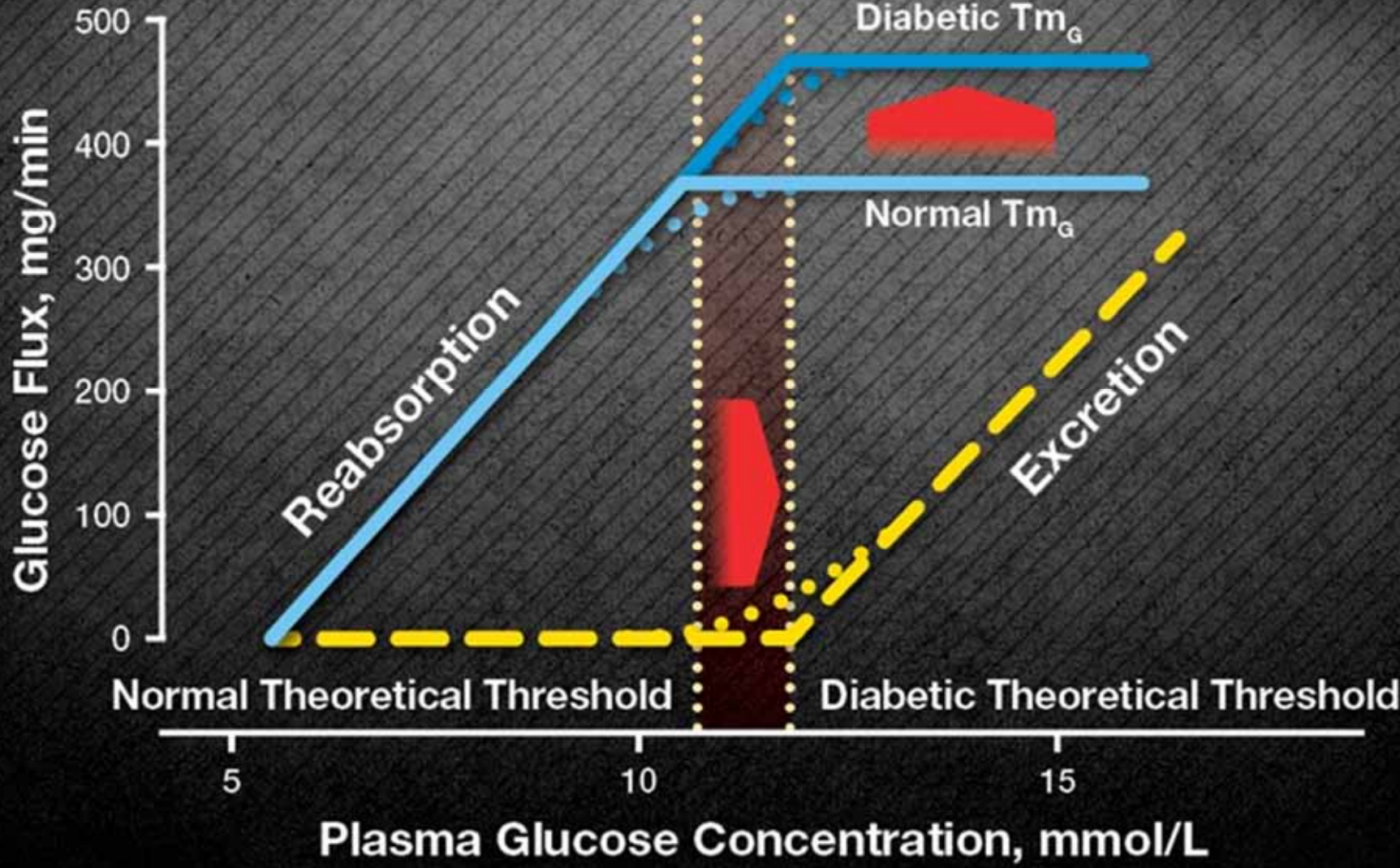


[a]All renal glucose release is a result of gluconeogenesis, whereas hepatic glucose release reflects both gluconeogenesis and glycogenolysis.

N=10 healthy volunteers and 10 patients with T2DM.

Meyer C, et al. *J Clin Invest*. 1998;102(3):619-624.

RENAL REABSORPTION AND EXCRETION OF GLUCOSE IN T2DM



Bays H. *Diabetes Ther*. 2013;4(2):195-220; DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14(1):5-14.

Scientific Insights Into the Kidneys and Glucose Homeostasis

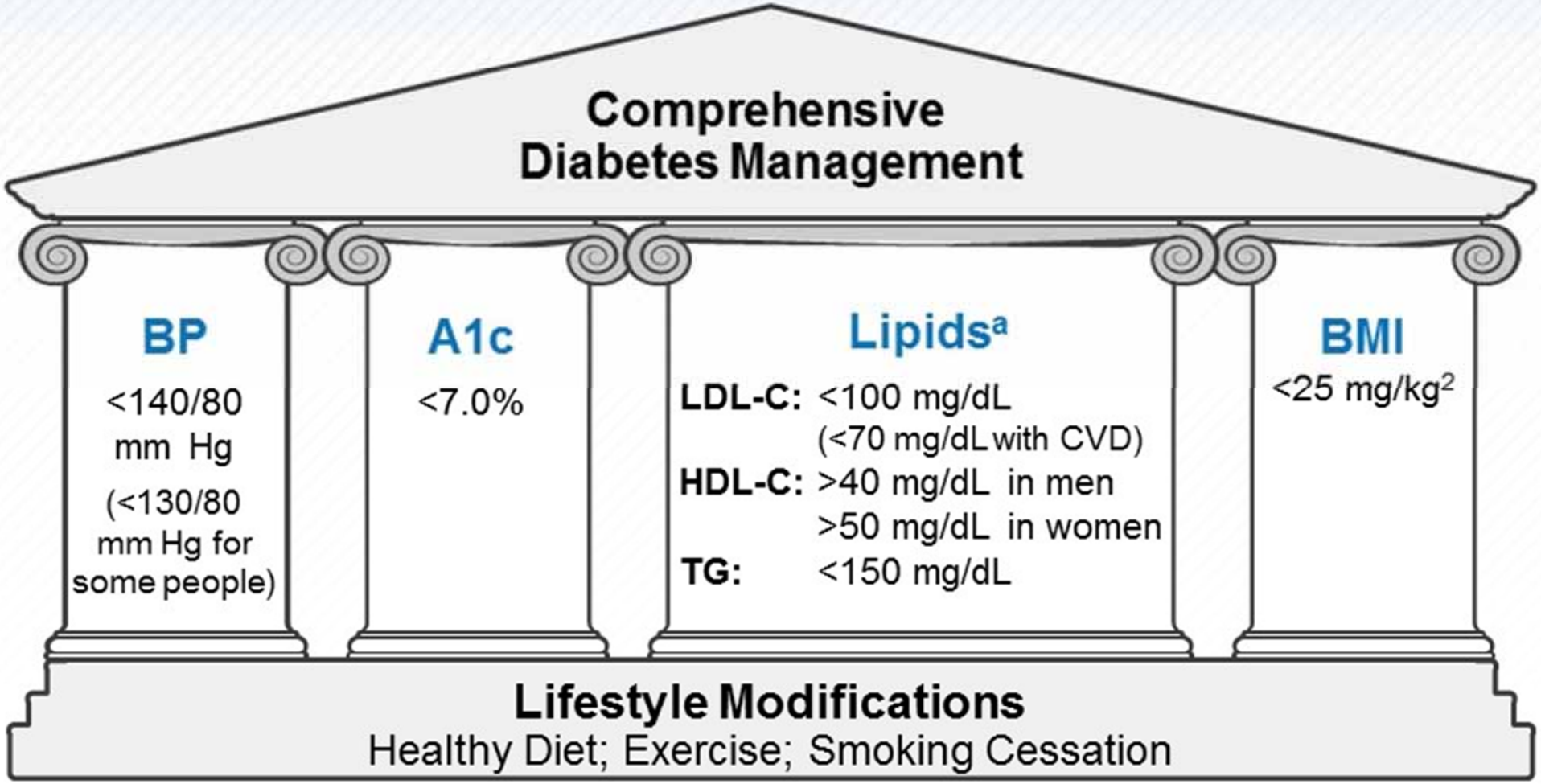
Key Points

- 3 major renal processes involved in glucose homeostasis[1]
  - Gluconeogenesis, glomerular filtration of glucose from the bloodstream, and glucose reabsorption from the glomerular filtrate
- SGLT-2 actively reabsorbs ~90% of glucose filtered into the renal tubule[2]
  - Specifically expressed in the kidney's proximal tubule
  - Glucose passed back into circulation via facilitated glucose transporters
  - Glucose levels exceeding the maximal reabsorptive capacity of the proximal tubule result in glucosuria
- T2DM linked to increases in renal gluconeogenesis, SGLT-2 expression, and SGLT-2 activity[2]
  - Increased maximal reabsorptive capacity for glucose
  - Maintenance of a renal threshold for blood glucose above the level at which glucosuria normally occurs in those without diabetes

1. Gerich JE. *Diabet Med.* 2010;27(2):136-142; 2. Wright EM, *J Intern Med.* 2007;261(1):32-43.

Reducing T2DM Complications

Multidimensional Treatment Goals



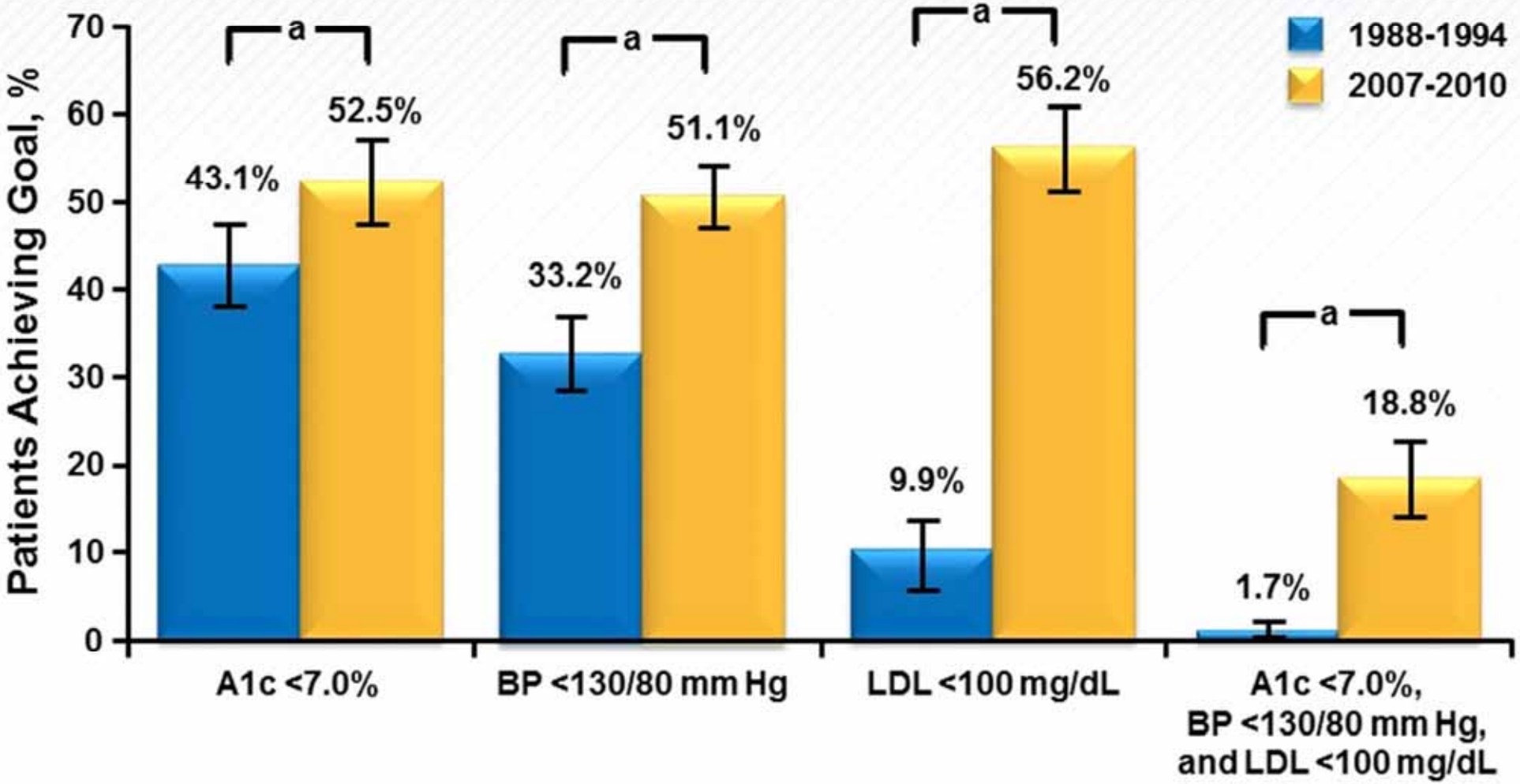
[a]2013 ACC/AHA guidelines on treatment of blood cholesterol: Based on 10-year ASCVD risk, use high-intensity (lower LDL-C by ≥50%) or moderate-intensity (lower LDL-C by 30% to <50%) statin therapy for patients aged 40-75 years with T2DM and initial LDL-C ≥70 mg/dL.

A1c, glycated hemoglobin; ASCVD, atherosclerotic CVD; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, low-density lipoprotein cholesterol; LDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

ADA. *Diabetes Care*. 2014;37(suppl 1):S14-S80; Stone NJ, et al *Circulation*. 2013 Nov 12. [Epub ahead of print].

Achieving Treatment Goals

Room for Improvement in T2DM



[a]*P*<0.01.

N=1497 (1998-1994) and 1447 (2007-2010) adults aged ≥20 years with a self-reported diagnosis of diabetes.

Retrospective analysis of data obtained from the National Health and Nutrition Examination Surveys.

Stark Casagrande S, et al. *Diabetes Care*. 2013;36(8):2271-2279.

CASE 1: Tony
Background

- 59-year-old Caucasian man
  - Accountant at large firm
  - Married with 1 son at college
- Dietary habits
  - Primarily cereal, pasta, and red meat
  - Few fruits or vegetables
  - Drinks 1-3 alcoholic drinks (beer or whiskey) daily
- Smokes 1-2 packs of cigarettes weekly
- Family history
  - Father treated for T2DM and died of MI at 55 years of age
- Medical history
  - Diagnosis of dyslipidemia 8 years ago
    - Atorvastatin 40 mg daily
  - Diagnosis of T2DM 5 months ago
    - A1c at diagnosis, 8.7%
    - Target A1c, <7.0%
    - Initiated on metformin 500 mg twice daily
    - Counseled on the importance of smoking cessation
    - Referred to certified diabetes educator for skills-based diabetes education

ADA. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

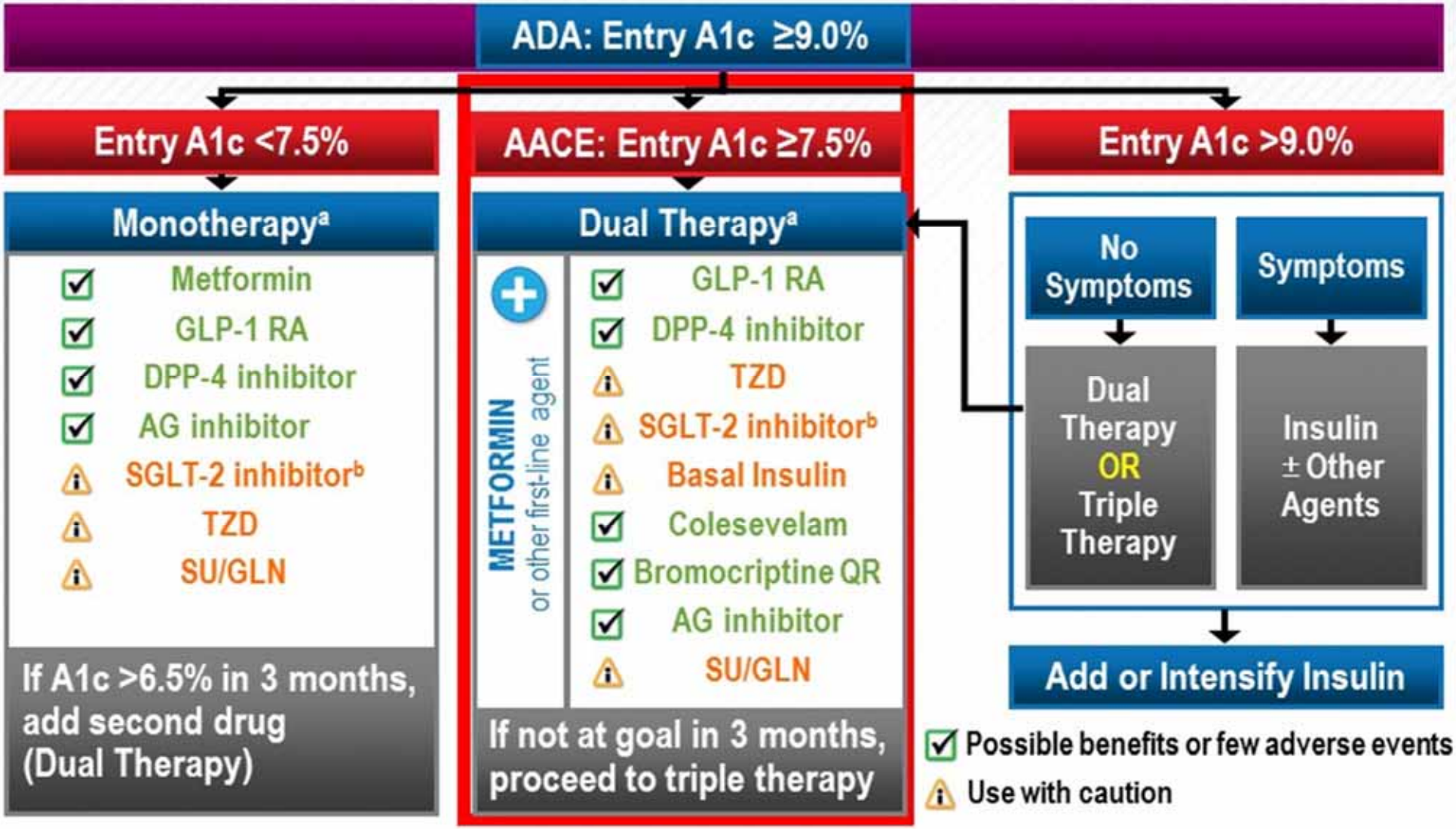
Tony
Current Workup

- BMI, 31.0 kg/m^2 (obese)
  - Waist circumference, 100 cm
- BP, 129/75 mm Hg
- T2DM
  - Metformin has been titrated to 1000 mg twice daily
  - A1c, 8.0%
    - Initial A1c, 8.7%
    - Target A1c, <7.0%
  - FPG, 175 mg/dL
- Lipids
  - TC, 165 mg/dL
  - TG, 150 mg/dL
  - LDL-C, 95 mg/dL
  - HDL-C, 40 mg/dL
  - ApoB, 82 mg/dL
- eGFR, 84 mL/min/1.73 m^2
- Sensory and eye exams unremarkable

Should Tony have been initially treated with a combination of antidiabetic agents?

ApoB, apolipoprotein B; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TC, total cholesterol.

AACE/ACE Algorithm for Glycemic Control



[a]Order of medications listed are a suggested hierarchy of usage; [b]Based on phase 3 clinical trials.
AG, α-glucosidase; GLN, glinide; GLP-1 RA, GLP, receptor agonist; QR, quick release; SU, sulfonylurea; TZD, thiazolidinedione.
Garber AJ, et al. *Endocr Pract.* 2013;19:536-557.

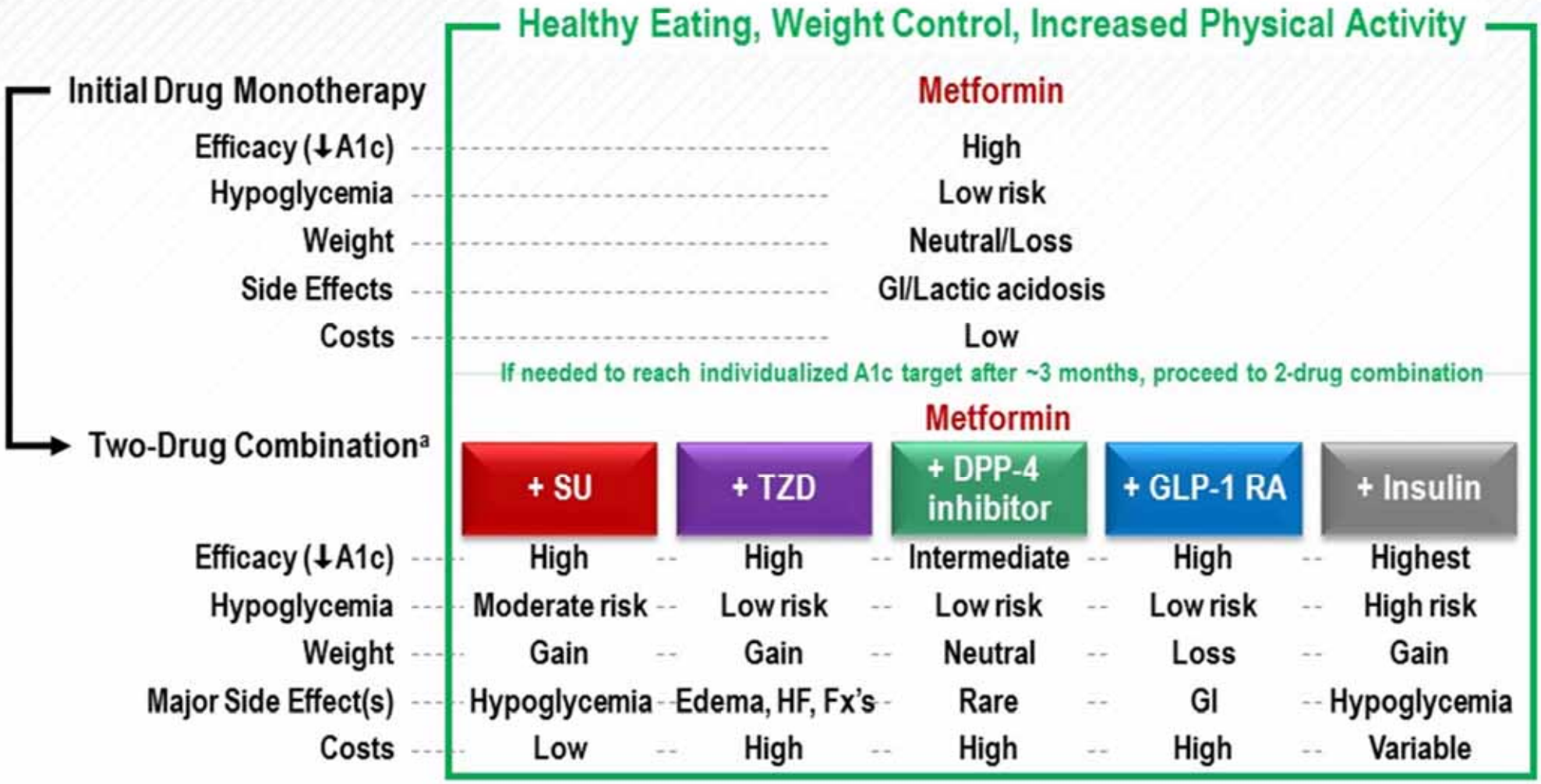
Tony
Overview

- 59-year-old Caucasian man
- BMI, 31.0 kg/m^2 (obese)
  - Waist circumference, 100 cm
- BP, 129/75 mm Hg
- Smoker with poor diet
- T2DM diagnosis 5 months ago
  - A1c, 8.0%
    - Target A1c, <7.0%
  - FPG, 175 mg/dL
  - Metformin 1000 mg twice daily
  - Referred to a certified diabetes educator
- Medical history
  - Statin-treated dyslipidemia
    - TC, 165 mg/dL
    - TG, 150 mg/dL
    - LDL-C, 95 mg/dL
    - HDL-C, 40 mg/dL
    - ApoB, 82 mg/dL
- Family history
  - Father treated for T2DM and died of MI at 55 years of age
- Renal function, sensory exam, eye exam, and all other tests are normal

In addition to encouraging a better diet, smoking cessation, and adherence to other lifestyle recommendations, which add-on therapy would you chose to help Tony achieve his A1c target?

ADA/EASD Recommendations

Managing Hyperglycemia in T2DM

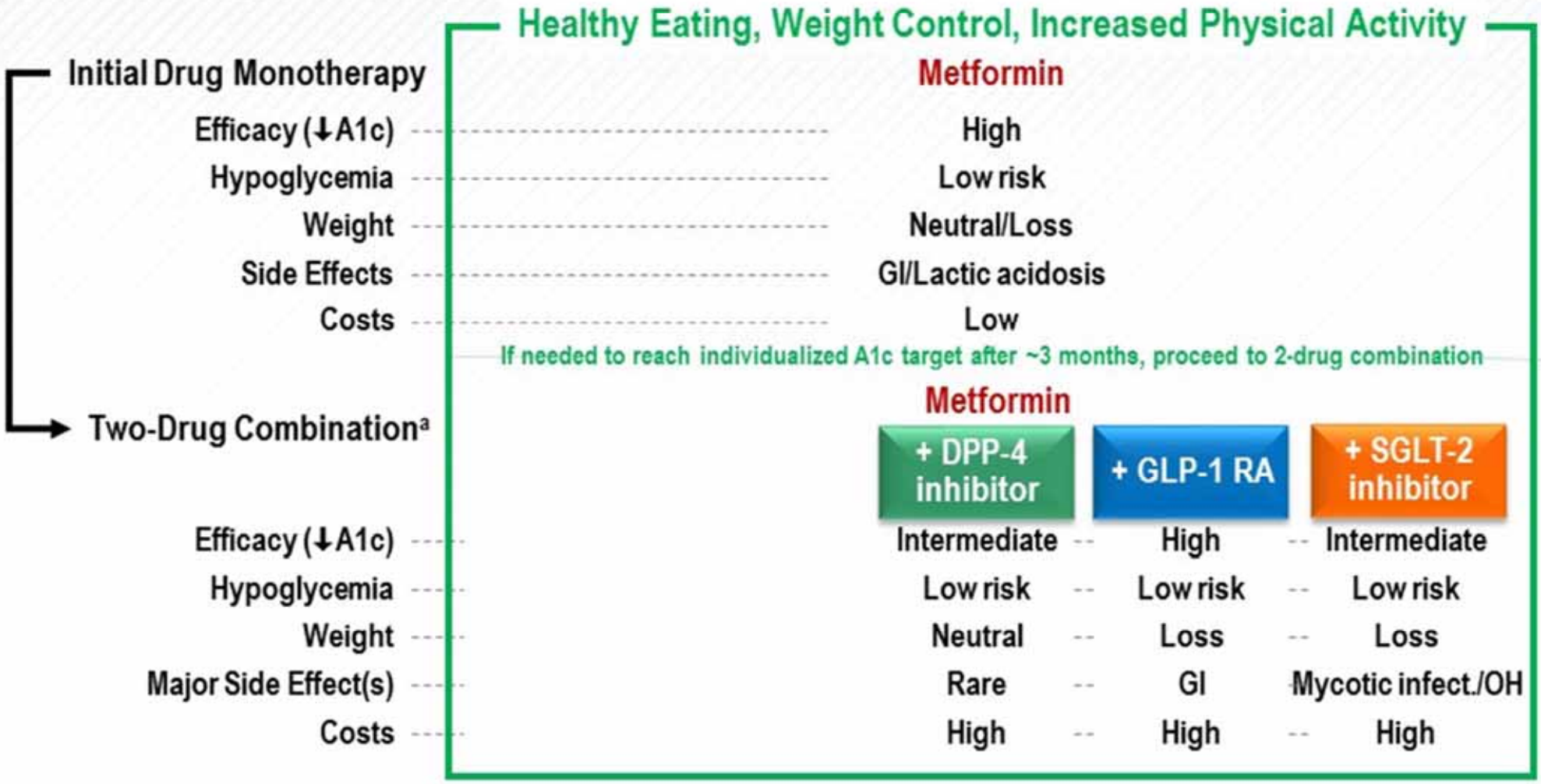


[a]Consider beginning at this stage in patients with very high A1c (eg, ≥9%).

EASD, European Association for the Study of Diabetes; Fx's, bone fractures; GI, gastrointestinal; HF, heart failure.

Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379.

Treatments With Low Risks for Hypoglycemia and Weight Gain



[a]Consider beginning at this stage in patients with very high A1c (eg, ≥9%).

OH, orthostatic hypotension.

Adapted from Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379; Riser Taylor S, Harris KB. *Pharmacotherapy*. 2013;33(9):984-999.

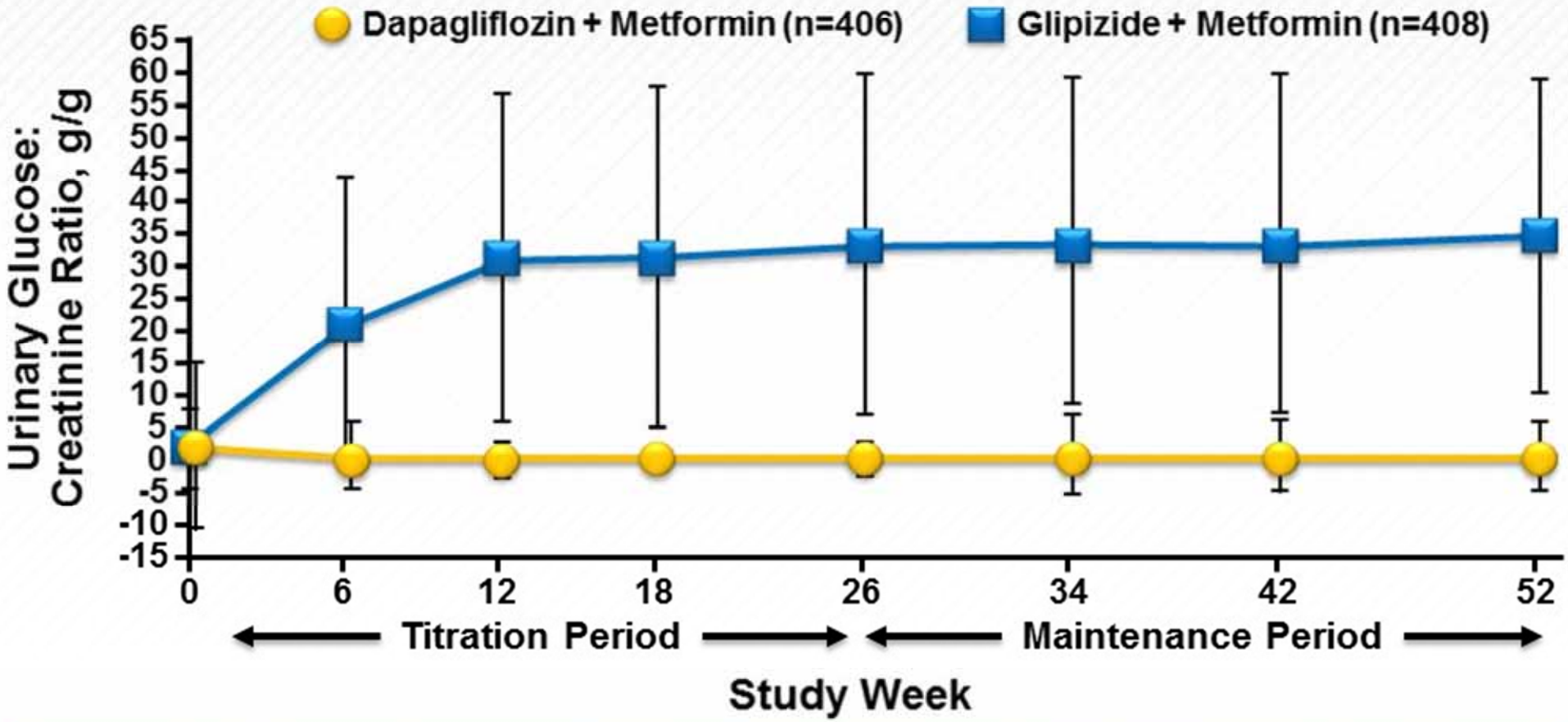
Inhibition of SGLTs
Inducing Glucosuria

- Urine normally contains 0.03-0.3 g of glucose/day[1]
- Clues from congenital conditions[1-3]
  - Familial renal glucosuria: *SGLT2* gene mutations
    - Excretion of 1-170 g of glucose/day
    - No consistent physical or clinical manifestations
  - Glucose-galactose malabsorption: *SGLT1* gene mutations
    - Severe gastrointestinal symptoms, diarrhea, and potentially fatal dehydration
    - Treated with a glucose-free, galactose-free diet

1. Calado J, et al. *Nephrol Dial Transplant*. 2008;23(12):3874-3879; 2. Santer R, et al. *J Am Soc Nephrol*. 2003;14(11):2873-2882;
3. Wright EM, et al. *J Intern Med*. 2007;261(1):32-43.

SGLT-2 Inhibitor and Urinary Glucose

Consistently Elevated Excretion



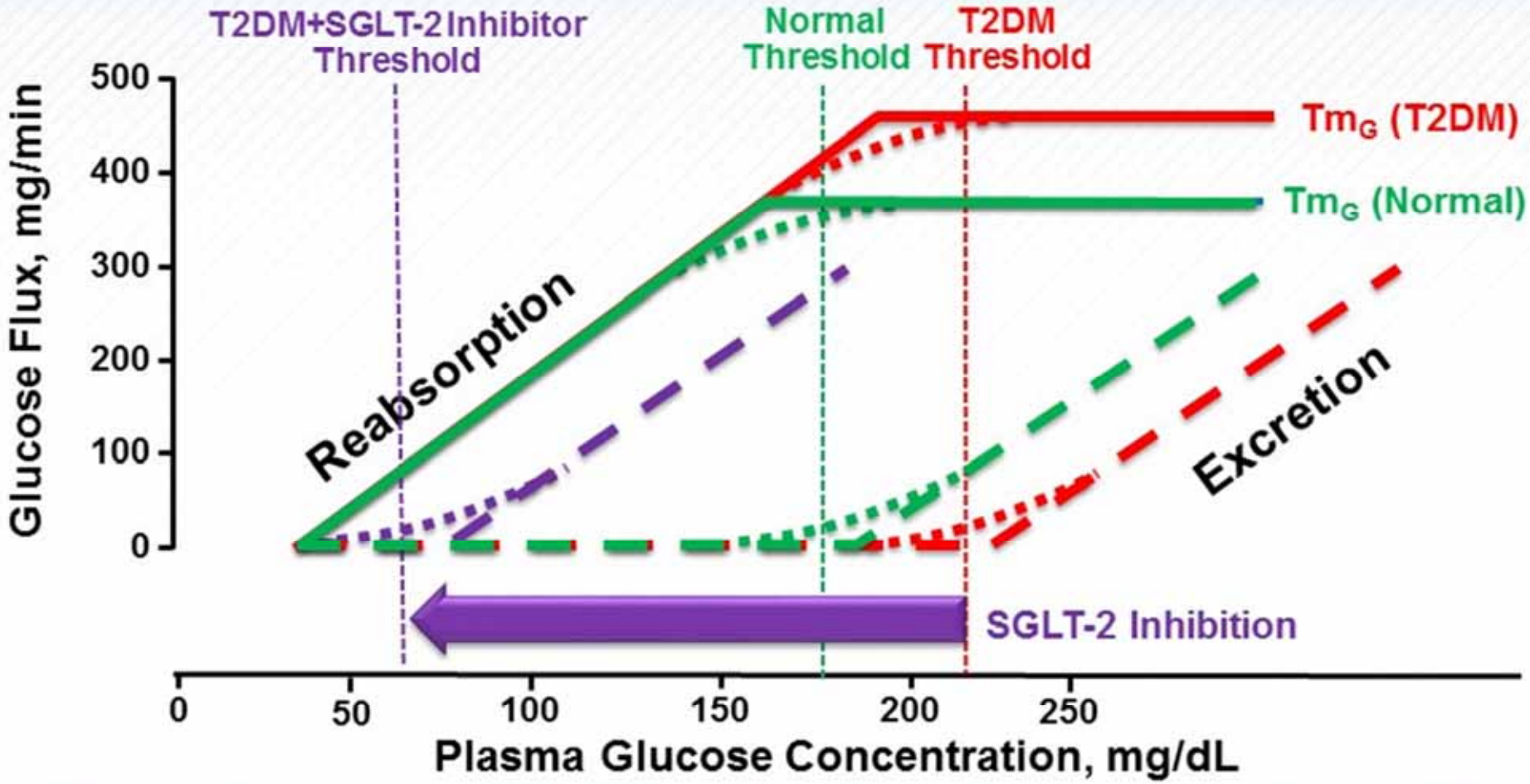
Urinary excretion of glucose, ~50-85 g/day

Data are means ± standard deviations obtained from morning spot urine checks in a fasting state.

N=814 patients with T2DM treated with metformin and randomized to add-on dapagliflozin or glipizide.

DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14(1):5-14; Nauck MA, et al. *Diabetes Care*. 2011;34(9):2015-2022.

SGLT-2 Inhibitors and Glucose Reabsorption in T2DM



SGLT-2 inhibitors inhibit 30%-50% of glucose reabsorption

Tm_G, glucose transport maximum.

Abdul-Ghani MA, DeFronzo RA; *Endocr Pract.* 2008;14(6):782-790; Bays H. *Diabetes Ther.* 2013;4:195-220; Nair S, Wilding JP. *J Clin Endocrinol Metab.* 2010;95(1):34-42.

FDA-Approved SGLT-2 Inhibitors

	Indication	Contraindications	Dosing
Canagliflozin[1]	Adjunct to diet and exercise to improve glycemic control in adults with T2DM	• Canagliflozin hypersensitivity • Severe renal impairment, ESRD, or dialysis	• 100 mg once daily, taken before the first meal of the day • Titrate to 300 mg, if eGFR ≥60 mL/min/1.73 m^2 and additional glycemic control is needed • Not recommended if eGFR <45 mL/min/1.73 m^2
Dapagliflozin[2]	Adjunct to diet and exercise to improve glycemic control in adults with T2DM	• Dapagliflozin hypersensitivity • Severe renal impairment, ESRD, or dialysis	• 5 mg once daily, taken in the morning, with or without food • Titrated to 10 mg, if additional glycemic control is needed • Not recommended if eGFR <60 mL/min/1.73 m^2

ESRD, end-stage renal disease; FDA, US Food and Drug Administration.

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf).

Canagliflozin and Glucose Control

Mean Changes From Baseline

Therapy[a]	Duration (weeks)	N	ΔA1c, % 100 mg	ΔA1c, % 300 mg	ΔFPG, mmol/L 100 mg	ΔFPG, mmol/L 300 mg
Monotherapy[1,a]	26	584	-0.77 (0.14)	-1.03 (0.14)	-1.50 (0.50)	-1.90 (0.50)
Added to MET[2,b]	12	451	-0.76 (-0.22)	-0.92 (-0.22)	-1.40 (0.20)	-1.40 (0.20)
Added to SU+MET[3,a,c]	52	469	-0.85 (-0.13)	-1.06 (-0.13)	-1.00 (0.20)	-1.70 (0.20)
Added to PIO ± MET[4,a,c]	52	342	-0.89 (-0.26)	-1.03 (-0.26)	-1.50 (0.10)	-1.80 (0.10)
Added to Insulin[5,a,d,e]	18	278	-0.76 (0.10)	-0.79 (0.10)	-1.04 (0.33)	-1.37 (0.33)

Data are mean changes from baseline and placebo values are shown in parentheses.

All changes are significant compared with placebo ($P<0.001$), except for insulin study in which statistical analysis was not performed.

[a]Data from phase 3 study; [b]Data from phase 2 study; [c]Values at week 26; [d]Statistical analysis not performed

[e]With or without other antidiabetic agents.

MET, metformin; PIO, pioglitazone.

1. Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15(4):372-378; 2. Rosenstock J, et al. *Diabetes Care*. 2012;35(6):1232-1238;
3. Wilding JP, et al. *Int J Clin Pract*. 2013;67(12):1267-1282; 4. Forst T, et al. *Diabetes Obes Metab*. 2014;16(5):467-477;
5. Dumas R, et al. *Can J Diabetes*. 2013;37(suppl 4):S28.

Canagliflozin and Body Weight

Mean Changes From Baseline

Therapy	Duration (weeks)	N	Δ Body Weight, kg 100 mg	Δ Body Weight, kg 300 mg
Monotherapy[1,a]	26	584	-2.50 (-0.50)	-3.40 (-0.50)
Added to MET[2,b]	12	451	-2.26 (-0.80)	-2.90 (-0.80)
Added to SU+MET[3,a,c]	52	469	-1.90 (-0.80)	-2.50 (-0.80)
Added to PIO ± MET[4,a,c]	52	342	-2.60 (-0.20)	-3.70 (-0.20)
Added to Insulin[5,a,d,e]	18	278	-1.78 (0.00)	-2.68 (0.00)

Data are mean changes from baseline and placebo values are shown in parentheses.

All changes are significant compared with placebo ($P<0.001$), except for insulin study in which statistical analysis was not performed.

[a]Data from phase 3 study; [b]Data from phase 2 study; [c]Values at week 26; [d]Statistical analysis not performed; [e]With or without other antidiabetic agents.

1. Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15(4):372-378; 2. Rosenstock J, et al. *Diabetes Care*. 2012;35(6):1232-1238; 3. Wilding JP, et al. *Int J Clin Pract*. 2013;67(12):1267-1282; 4. Forst T, et al. *Diabetes Obes Metab*. 2014;16(5):467-477; 5. Dumas R, et al. *Can J Diabetes*. 2013;37(suppl 4):S28.

Dapagliflozin and Glucose Control

Mean Changes From Baseline

Therapy	Duration (weeks)	N	Δ A1c, % 5 mg	Δ A1c, % 10 mg	Δ FPG, mmol/L 5 mg	Δ FPG, mmol/L 10 mg
Monotherapy[1]	24	485	-0.77 (-0.23)	-0.89 (-0.23)	-1.34 (-0.23)	-1.60 (-0.23)
Added to MET[2]	24	546	-0.70 (-0.30)	-0.84 (-0.30)	-1.19 (-0.33)	-1.30 (-0.33)
Added to SU+MET[3]	24	597	-0.63 (-0.13)	-0.82 (-0.13)	-1.18 (-0.11)	-1.58 (-0.11)
Added to PIO±MET[4,b]	48	420	-0.82[a] (-0.42)	-0.97 (-0.42)	-1.38 (-0.31)	-1.64 (-0.31)
Added to Insulin[5,b,c]	48	808	-0.89 (-0.39)	-0.96 (-0.39)	-1.12	-1.10

Data are mean changes from baseline and placebo values are shown in parentheses.

All changes are significant compared with placebo ($P<0.001$ or $P<0.0001$).

[a]Values at week 24; [b]With or without up to 2 oral antidiabetic agents.

1. Ferrannini E, et al. *Diabetes Care.* 2010;33(10):2217-2224; 2. Bailey CJ, et al. *Lancet.* 2010;375(9733):2223-2233;
3. Strojek K, et al. *Diabetes Obes Metab.* 2011;13(10):928-938; 4. Rosenstock J, et al. *Diabetes Care.* 2012;35(7):1473-1478;
5. Wilding JP, et al. *Ann Intern Med.* 2012;156(6):405-415.

Dapagliflozin and Body Weight
Mean Changes From Baseline

Therapy	Duration (weeks)	N	Δ Body Weight, kg 5 mg	Δ Body Weight, kg 10 mg
Monotherapy[1]	24	485	-2.80 (-2.20)	-3.20 (-2.20)
Added to MET[2,a]	24	546	-3.00 (-0.90)	-2.90 (-0.90)
Added to SU+MET[3,b]	24	597	-1.56 (-0.72)	-2.26 (-0.72)
Added to PIO±MET[4,a,d]	48	420	0.09 (1.64)	-0.14 (1.64)
Added to Insulin[5,c-e]	48	808	-1.00 (0.43)	-1.61 (0.43)

Data are mean changes from baseline and placebo values are shown in parentheses.

[a]*P*<0.0001 compared with placebo for both doses; [b]*P*<0.0001 (10 mg) and *P*<0.01 (10 mg) compared with placebo; [c]*P*<0.001 compared with placebo for both doses; [d]Values at week 24; [e]With or without up to 2 oral antidiabetic agents.

1. Ferrannini E, et al. *Diabetes Care.* 2010;33(10):2217-2224; 2. Bailey CJ, et al. *Lancet.* 2010;375(9733):2223-2233; 3. Strojek K, et al. *Diabetes Obes Metab.* 2011;13(10):928-938; 4. Rosenstock J, et al. *Diabetes Care.* 2012;35(7):1473-1478; 5. Wilding JP, et al. *Ann Intern Med.* 2012;156(6):405-415.

SGLT-2 Inhibitor Active Comparator Trials

Mean A1c Changes From Baseline

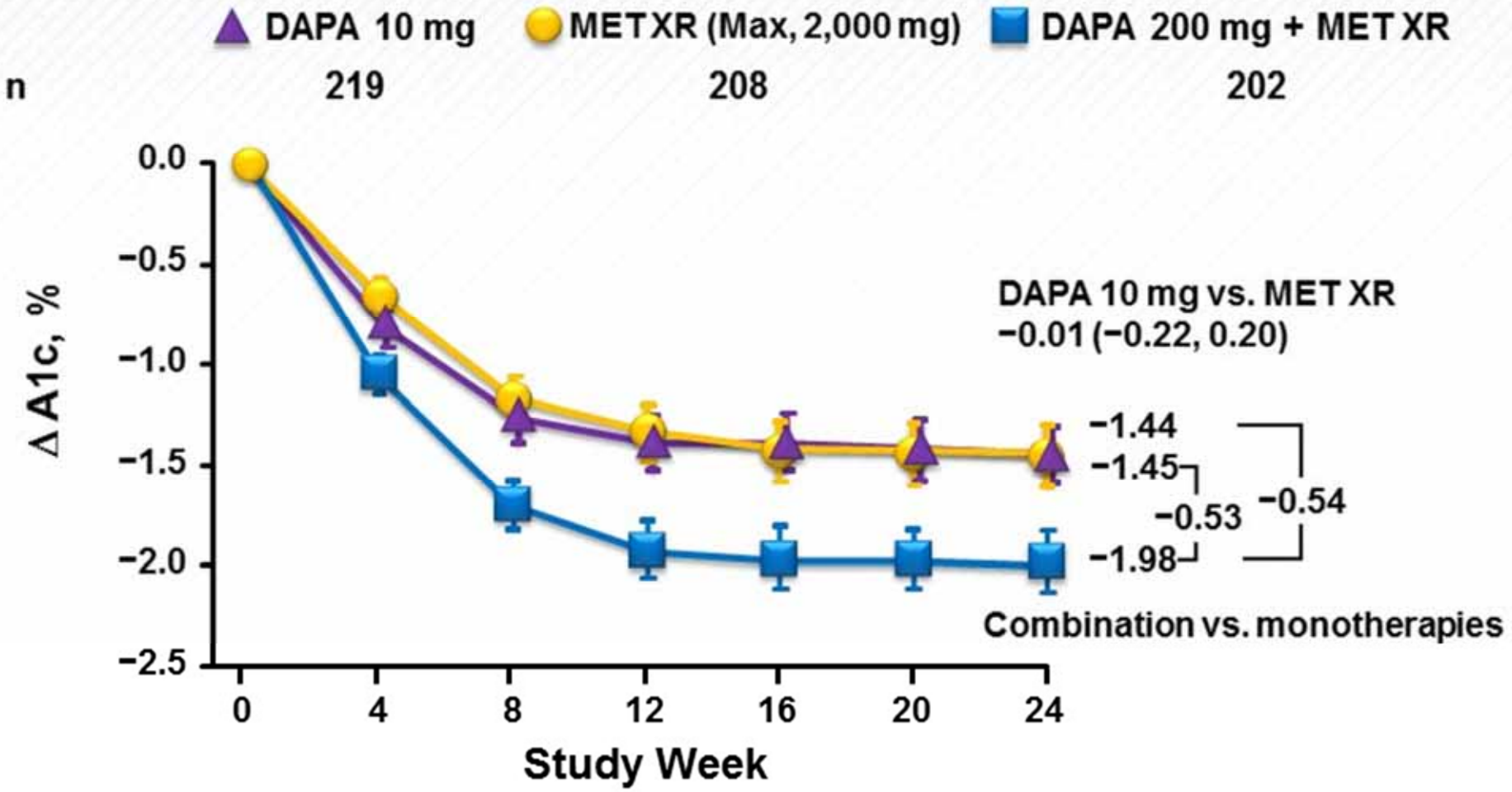
Therapies [Background]	Wks	N	SGLT-2 Dose 1 ΔA1c, %	SGLT-2 Dose 2 ΔA1c, %	COMP ΔA1c, %	SGLT-2 Dose 1 vs COMP (95% CI)	SGLT-2 Dose 2 vs COMP (95% CI)
DAPA 5 mg vs METXR[1,a]	24	598	-1.19	N/A	-1.35	0.16[b]	N/A
DAPA 10 mg vs METXR[1,a]	24	638	-1.45	N/A	-1.44	-0.01[c] (-0.2, 0.2)	N/A
DAPA 10 mg vs GLIP [MET][2]	52	801	-0.52	N/A	-0.52	0.00[c] (-0.11, 0.11)	N/A
CANA 100 mg or 300 mg vs SITA [MET][3]	52	1284	-0.73	-0.88	-0.73	0.00[c] (-0.12, 0.12)	-0.15[c,d] (-0.27,-0.03)
CANA 300 mg vs SITA 100 mg [MET+SU][4]	52	755	-1.03	N/A	-0.66	-0.37[c,d] (-0.50, -0.25)	N/A
CANA 100 mg or 300 mg vs GLIM[e] [MET][5]	52	1450	-0.82	-0.93	-0.81	-0.01[c] (-0.11, 0.09)	-0.12[c,d] (-0.22, -0.02)

[a]Metformin XR titrated up to maximum of 2000 mg daily; [b]Noninferiority not tested by study design; [c]SGLT-2 noninferior vs COMP based on CI upper limit and prespecified noninferiority margin; [d]SGLT-2 statistically superior vs COMP; [e]GLIM titrated to 6 mg or 8 mg.
CANA, canagliflozin; COMP, comparator; DAPA, dapagliflozin; GLIP, glipizide; GLIM, glimepiride; N/A, not applicable; SITA, sitagliptin.

1. Henry RR, et al. *Int J Clin Pract.* 2012;66(5):446-456; 2. Nauck MA, et al. *Diabetes Care.* 2011;34(9):2015-2022;
3. Lavalle-González FJ, et al. *Diabetologia.* 2013;56(12):2582-2589; 4. Schernthaner G, et al. *Diabetes Care.* 2013;36(9):2508-2515;
5. Cefalu WT, et al. *Lancet.* 2013;382(9896):941-950.

Dapagliflozin vs Metformin XR vs Combination Therapy

A1c at Week 24



P<0.0001 vs monotherapy with either agent.

Henry RR et al. *Int J Clin Pract*. 2012;66(5):446-560.

SGLT-2 Inhibitor Active Comparator Trials

Mean Body Weight Changes From Baseline

Therapies [Background]	Wks	N	SGLT-2 Dose 1 ΔWeight	SGLT-2 Dose 2 ΔWeight	COMP ΔWeight	SGLT-2 Dose 1 vs COMP (95% CI)	SGLT-2 Dose 2 vs COMP (95% CI)
DAPA 5 mg vs METXR[1,c]	24	598	-2.61 kg	N/A	-1.29 kg	-1.32 kg[d]	N/A
DAPA 10 mg vs METXR[1,c]	24	638	-2.73 kg	N/A	-1.36 kg	-1.37 kg[a] (-2.03, -0.71)	N/A
DAPA 10 mg vs GLIP [MET][2]	52	801	-3.22 kg	N/A	1.44 kg	-4.65 kg[a] (-5.14, -4.17)	N/A
CANA 100 mg or 300 mg vs SITA [MET][3]	52	1284	-1.3%	-3.8%	-4.2%	-2.4%[b] (-3.0, -1.8)	-2.9%[b] (-3.4, -2.3)
CANA 300 mg vs SITA 100 mg [MET+SU][4]	52	755	-2.5%	N/A	0.3%	-2.8%[b] (-3.3, -2.2)	N/A
CANA 100 mg or 300 mg vs GLIM[e] [MET][5]	52	1450	-4.2%	-4.7%	1.0%	-5.2%[b] (-5.7, -4.7)	-5.7%[b] (-6.2, -5.1)

[a]*P*<0.0001 for SGLT-2 vs COMP; [b]*P*<0.001 for SGLT-2 vs COMP; [c]Metformin XR titrated up to maximum of 2000 mg daily; [d]Statistical analysis not tested by study design; [e]GLIM titrated to 6 mg or 8 mg.

1. Henry RR, et al. *Int J Clin Pract.* 2012;66(5):446-456; 2. Nauck MA, et al. *Diabetes Care.* 2011;34(9):2015-2022; 3. Lavalle-González FJ, et al. *Diabetologia.* 2013;56(12):2582-2589; 4. Schernthaner G, et al. *Diabetes Care.* 2013;36(9):2508-2515; 5. Cefalu WT, et al. *Lancet.* 2013;382(9896):941-950.

Select SGLT Inhibitors in Development

Compound	Clinical Status	SGLT-2 Selectivity (IC_{50} [nM])[a]
Empagliflozin	• Phase III/Filed • Approval delayed in US over manufacturing concerns • Approved in Europe	2677
Ipragliflozin	• Not currently under development in US • Approved in Japan	254
Tofogliflozin	• Phase III	2912
Luseogliflozin	• Approved in Japan	1765
Ertugliflozin	• Phase III	2235
LX4211[b]	• Phase IIb	0.05

[a]SGLT-2 selectivity calculated using IC_{50} SGLT-1/IC_{50} SGLT-2; [b]Dual SGLT-1/SGLT-2 inhibitor.
IC_{50}, half maximum inhibitory concentration.
Malla P, et al. *Med Res Rev.* 2014 Mar 14. [Epub ahead of print]; Tahrani AA, et al. *Lancet Diabetes Endocrinol.* 2013;1(2):140-151.

Empagliflozin and Glucose Control

Mean Changes From Baseline

Therapy	Duration (weeks)	N	ΔA1c, % 10 mg	ΔA1c, % 25 mg	ΔFPG, mmol/L 10 mg	ΔFPG, mmol/L 25 mg
Monotherapy[1,a]	24	899	-0.66 (0.08)	-0.78 (0.08)	-1.08 (0.65)	-1.36 (0.65)
Added to MET[2,a,]	24	637	-0.70 (-0.13)	-0.77 (-0.13)	-1.11 (0.35)	-1.24 (0.35)
Added to SU+MET[3,a]	24	666	-0.82 (-0.17)	-0.77 (-0.17)	-1.29 (0.31)	-1.29 (0.31)
Added to PIO ± MET[4,a]	24	498	-0.59 (-0.11)	-0.72 (-0.11)	-0.94 (0.36)	-1.22 (0.36)
Added to Insulin[5,b]	78	494	-0.48 (-0.02)	-0.64 (-0.02)	-0.56 (0.17)	-0.83 (0.17)

Data are mean changes from baseline and placebo values are shown in parentheses.

All changes are significant compared with placebo ($P<0.001$).

[a]Data from phase 3 study; [b]Data from phase 2b study.

1. Roden, M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208-219; 2. Häring HU, et al. *Diabetes Care*. 2014 Apr 10 [Epub ahead of print]; 3. Häring HU, et al. *Diabetes Care*. 2013;36(11):3396-3404; 4. Kovacs CS, et al. *Diabetes Obes Metab*. 2013 Aug 1 [Epub ahead of print]; 5. Rosenstock J, et al. *Can J Diabetes*. 2013;37(suppl 4):S32.

Empagliflozin and Body Weight
Mean Changes From Baseline

Therapy	Duration (weeks)	N	Δ Body Weight, kg 10 mg	Δ Body Weight, kg 25 mg
Monotherapy[1,a]	24	899	-2.26 (-0.33)	-2.48 (-0.33)
Added to MET[2,a]	24	637	-2.08 (-0.45)	-2.46 (-0.45)
Added to SU+MET[3,a]	24	666	-2.16 (-0.39)	-2.39 (-0.39)
Added to PIO ± MET[4,a]	24	498	-1.62 (0.34)	-1.47 (0.34)
Added to Insulin[5,b]	78	494	-2.2 (0.70)	-2.0 (0.70)

Data are mean changes from baseline and placebo values are shown in parentheses.

All changes are significant compared with placebo ($P<0.001$).

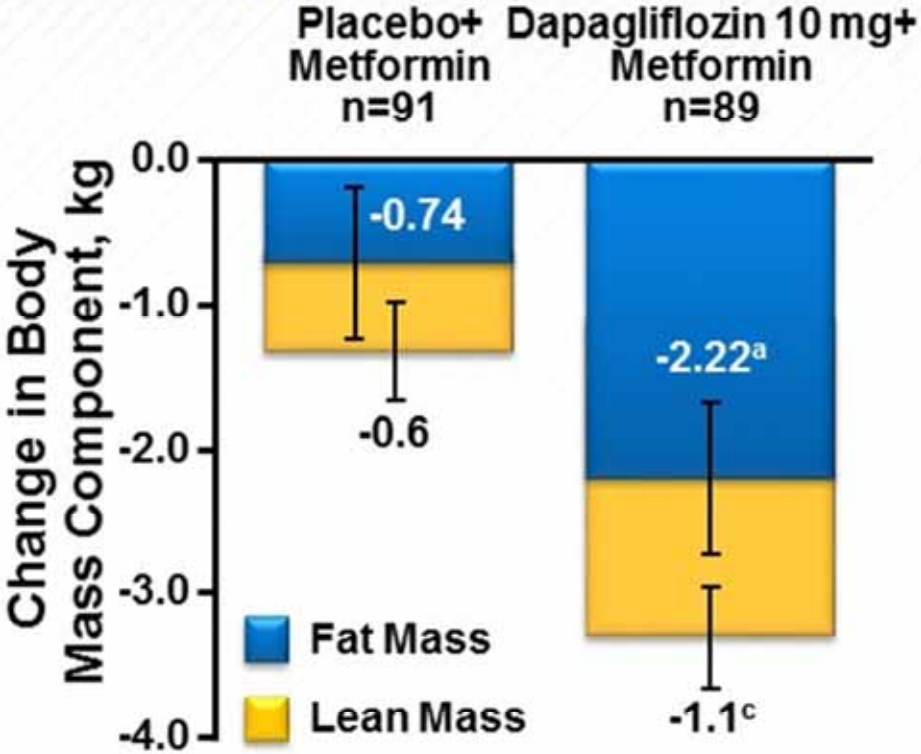
[a]Data from phase 3 study; [b]Data from phase 2b study.

1. Roden, M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208-219; 2. Häring HU, et al. *Diabetes Care*. 2014 Apr 10 [Epub ahead of print]; 3. Häring HU, et al. *Diabetes Care*. 2013;36(11):3396-3404; 4. Kovacs CS, et al. *Diabetes Obes Metab*. 2013 Aug 1 [Epub ahead of print]; 5. Rosenstock J, et al. *Can J Diabetes*. 2013;37(suppl 4):S32.

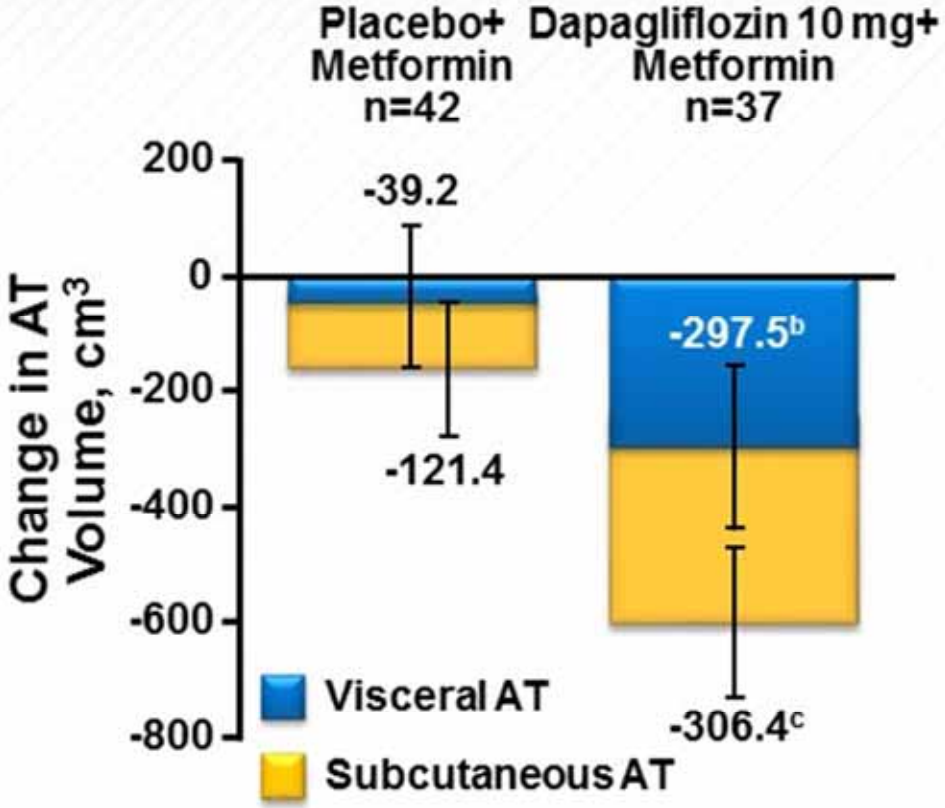
Dapagliflozin and Weight Loss

Fat Mass, Lean Mass, and Adipose Tissue Distribution

Body Mass Components[d]



Visceral Fat Volume[e]



[a]*P*=0.0001; [b]*P*<0.01; [c]*P*<0.05;

[d]Changes measured using dual-energy x-ray absorptiometry; [e]Changes measured in a patient subset using MRI.

Data are adjusted mean change from baseline and 95% CI.

AT, adipose tissue; MRI, magnetic resonance imaging.

N=182 patients with T2DM had placebo or dapagliflozin 10 mg daily added to open-label metformin for 24 weeks.

Bolinder J, et al. *J Clin Endocrinol Metab*. 2012;97(3):1020-1031.

SGLT-2 Inhibitors
Safety: Adverse Reactions

- Generally well-tolerated with good safety profile[1,2]
  - No gastrointestinal effects
  - Modest increase in urine volume

Most Common Adverse Reactions, % of Patients[a]

Adverse Reaction[3,4]	PBO for CANA	CANA 100 mg	CANA 300 mg	PBO for DAPA	DAPA 5 mg	DAPA 10 mg
Female genital mycotic infections	3.2	10.4	11.4	1.5	8.4	6.9
UTIs	4.0	5.9	4.3	3.7	5.7	4.3
Increased urination	0.8	5.3	4.6	1.7	2.9	3.8
Male genital mycotic infections	0.6	4.2	3.7	0.3	2.8	2.7

[a]Adverse reactions occurring in ≥2% of patients compared with placebo for ≥1 of 4 drug doses in 4 pooled 26-week studies for canagliflozin or 12 pooled 12- to 24-week studies for dapagliflozin.
UTI, urinary tract infection.

1. Abdul-Ghani MA, Defronzo RA. *J Intern Med*. 2014 Apr 1; 2. List JF, et al. *Diabetes Care*. 2009;32(4):650-657;
3. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf);
4. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf).

SGLT-2 Inhibitors

Safety: Renal Impairment

Warning	Canagliflozin[1]	Dapagliflozin[2]
Renal impairment	• Associated with a dose-dependent increase in serum creatinine and decrease in eGFR • Values returned toward baseline by study end	• Associated with increased serum creatinine and decreased eGFR • With normal or mildly baseline impaired renal function, values returned to baseline by week 24
Recommendation	• Evaluate renal function before initiating treatment and during therapy • Do not exceed 100 mg/day in patients with eGFR between 45 and <60 mL/min/1.73 m^2 – More frequent monitoring if eGFR <60 mL/min/1.73 m^2 • Do not use if eGFR is <45 mL/min/1.73 m^2	• Evaluate renal function before initiating treatment and during therapy • Do not use if eGFR is <60 mL/min/1.73 m^2

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf).

SGLT-2 Inhibitors
Safety: Hypotension

Warning	Canagliflozin[1]	Dapagliflozin[2]
Hypotension	• Canagliflozin causes intravascular volume depletion • Can cause symptomatic hypotension • Particularly vulnerable populations – eGFR <60 mL/min/1.73 m^2 – Elderly patients – Patients with low systolic BP – Patients on loop diuretics or medications that interfere with RAAS	• Dapagliflozin causes intravascular volume depletion • Can lead to symptomatic hypotension • Particularly vulnerable populations – eGFR <60 mL/min/1.73 m^2 – Elderly patients – Patients on loop diuretics
Recommendations	• Before initiating treatment, assess volume status • Correct hypovolemia in the elderly, in patients with renal impairment or low systolic BP, and in patients on diuretics, ACEi, or ARB • Monitor signs and symptoms during therapy	• Before initiating treatment, assess volume status • Correct hypovolemia in the elderly, in patients with renal impairment or low systolic BP, and in patients on diuretics • Monitor signs and symptoms during therapy

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; RAAS, renin-angiotensin-aldosterone system.

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf).

SGLT-2 Inhibitors
Safety: Additional Considerations

- Mean plasma lipid changes from baseline in clinical trials[1,2]
  - Canagliflozin 300 mg: 8.0% increase in LDL-C relative to placebo
  - Dapagliflozin 10 mg: 3.9% increase in LDL-C relative to placebo
  - Monitor LDL-C and treat per standard of care
- Canagliflozin and hyperkalemia[1]
  - Transient increases in serum potassium observed early after initiation in patients with moderate renal impairment
  - Monitor potassium levels in patients with impaired renal function or predisposition to hyperkalemia
- Dapagliflozin and bladder cancer in clinical trials[2]
  - Imbalance of bladder cancers with dapagliflozin (0.17%, n=6045) vs placebo/comparator (0.03%, n=3156)
  - SGLT-2 inhibitors not linked to neoplasia in preclinical studies[3]
  - Do not use in patients with active bladder cancer and use caution in patients with history of bladder cancer

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf);
3. Reilly TP, et al. *Diabetes Ther*. 2014 Jan 29. [Epub ahead of print].

CASE 1: Tony
Concluding Comments

- Multiple metabolic goals should be targeted in each patient
  - A1c
  - Blood pressure
  - BMI
  - Lipids
- SGLT-2 inhibitors increase urinary excretion of glucose
  - Counteract T2DM-induced elevation of the maximum reabsorptive capacity for glucose in the kidney's proximal tubule
  - Effects are associated with decreased hyperglycemia, removal of calories from the body, and reductions in body weight
- Patient selection requires consideration of renal function and risks related to hypotension
- Primary adverse events include genital infections, urinary tract infections, and effects associated with hypotension

Case 2: Sidney
Background

- 70-year-old African American woman
  - Retired teacher
- Lives alone, across town from her son and his family
  - Husband died of pancreatic cancer of 5 years ago
- Family history
  - Mother died of Alzheimer's disease at 74
  - Father died at 64 after multiple “heart attacks”
  - Son admitted to hospital 6 months ago for episode of unstable angina
- Medical history
  - T2DM diagnosis 13 years ago
    - Metformin 750 mg twice daily
    - Insulin glargine 30 units at bedtime
  - Hypertension diagnosis 5 years ago
    - Lisinopril 40 mg daily
    - Atenolol 50 mg daily

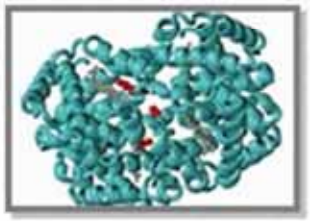
Sidney
Routine Check-up

- Sidney's son brings her in for a check-up
  - Last visit 8 months ago
  - Missed last 2 appointments
    - No longer drives and her son has been busy with his own health issues
- Follows a DASH diet
- Walks with neighborhood friends 2-3 times/week
- Reports that once or twice each month she wakes with a headache and damp sheets from sweating
- BMI, 27.5 kg/m^2
  - Gained 10 lbs
  - Previous value, 25.8 kg/m^2
- BP, 142/88 mm Hg
- A1c, 7.9%
  - Previous value, 7.4%
  - Target, 7.0%
    - Never reached A1c goal despite titration of her insulin
- FPG, 135 mg/dL
- PPG, 220 mg/dL
- Sensory exam normal
- eGFR, 66 mL/min/1.73 m^2
- Lipids are in normal ranges

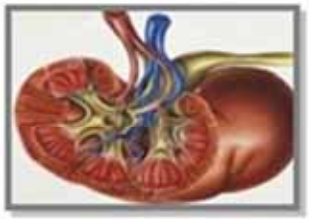
DASH, Dietary Approaches to Stop Hypertension; PPG, postprandial glucose.

Sidney

Setting Glycemic Targets



Age, 70 years 13-Year History of T2DM	A1c, 7.9% Current Target, 7.0%	History of Missing A1c Target	Recent Episodes of Nocturnal Hypoglycemia



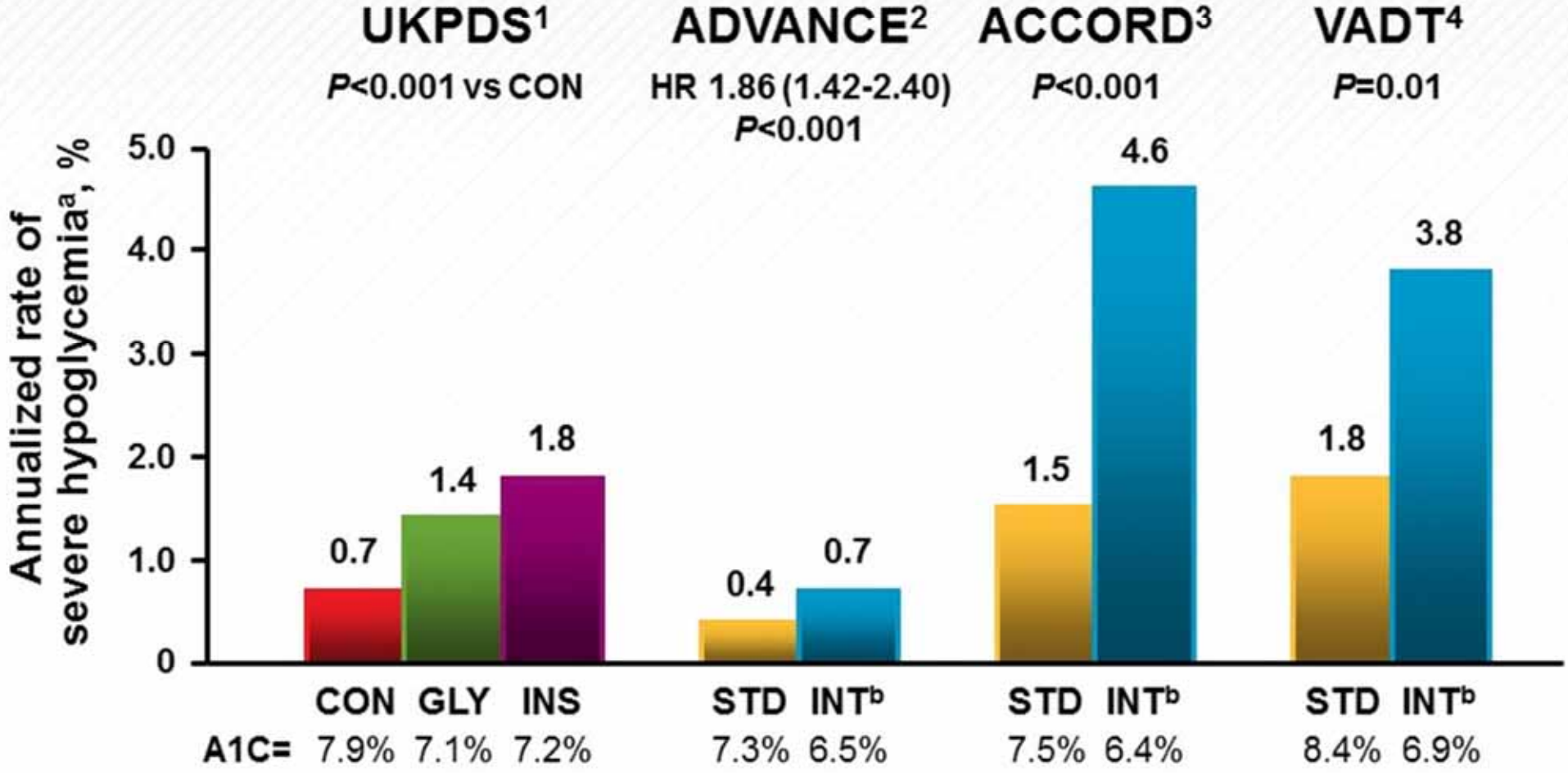
BMI, 27.5 kg/m^2	Hypertension	Normal Renal Function	Lives Alone

Would you adjust Sidney's A1c target?

Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379.

Rates of Severe Hypoglycemia

Intensive vs Standard Therapy

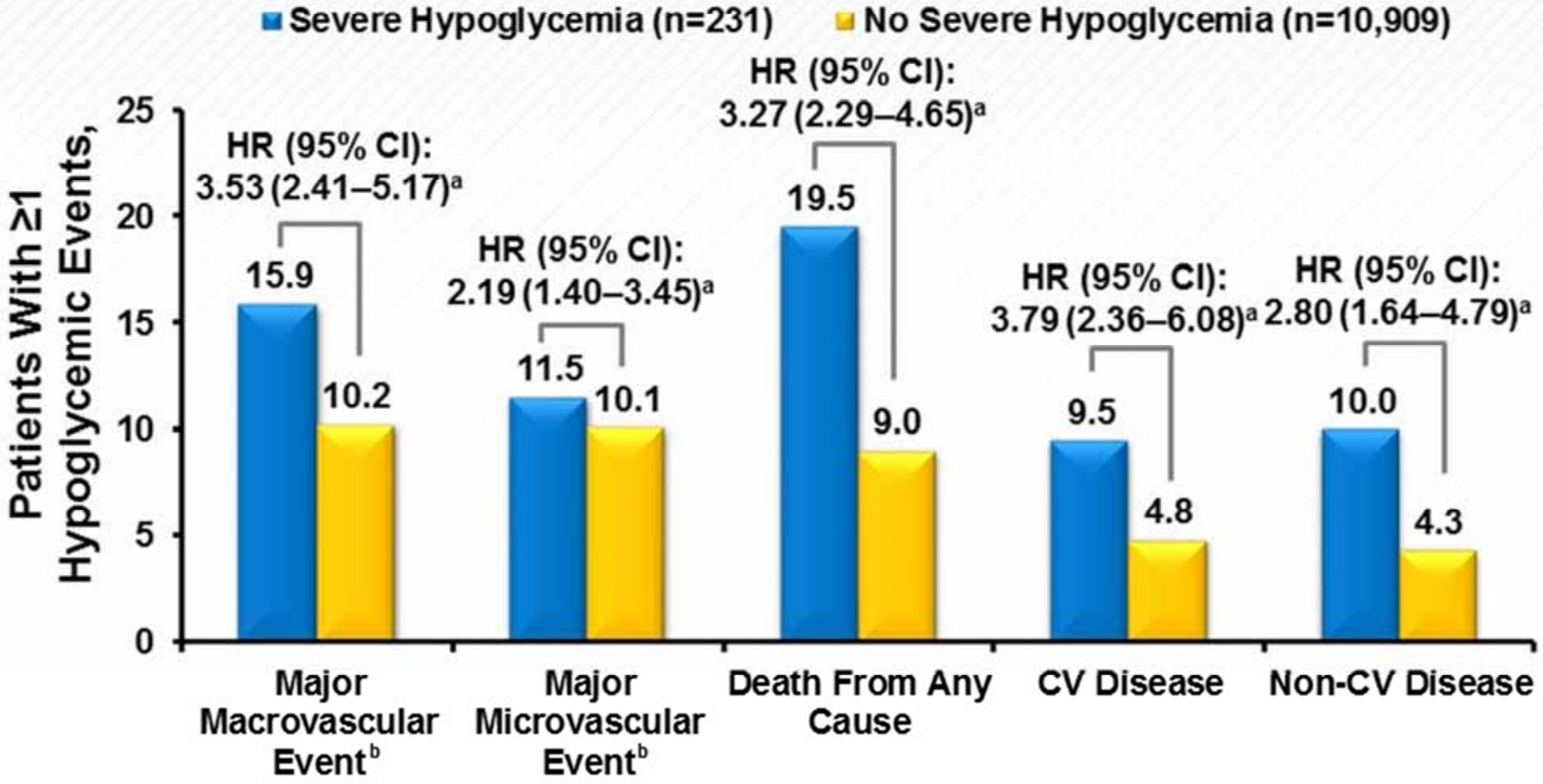


[a]Hypoglycemia requiring any assistance; [b]Intensive glycemic control was defined differently in these trials.
CON, conventional therapy; GLY, glibenclamide; HR, hazard ratio; INS, insulin; INT, intensive therapy; STD, standard therapy.

1. UKPDS Group. *Lancet*. 1998;352(1931):837-853; 2. Patel A, et al; [ADVANCE]. *N Engl J Med*. 2008;358(24):2560-2572;
3. Gerstein HC, et al; [ACCORD]. *N Engl J Med*. 2008;358(24):2545-2559; 4. Duckworth W, et al. *N Engl J Med*. 2009;360(2):129-139.

ADVANCE

Severe Hypoglycemia vs Adverse End Points

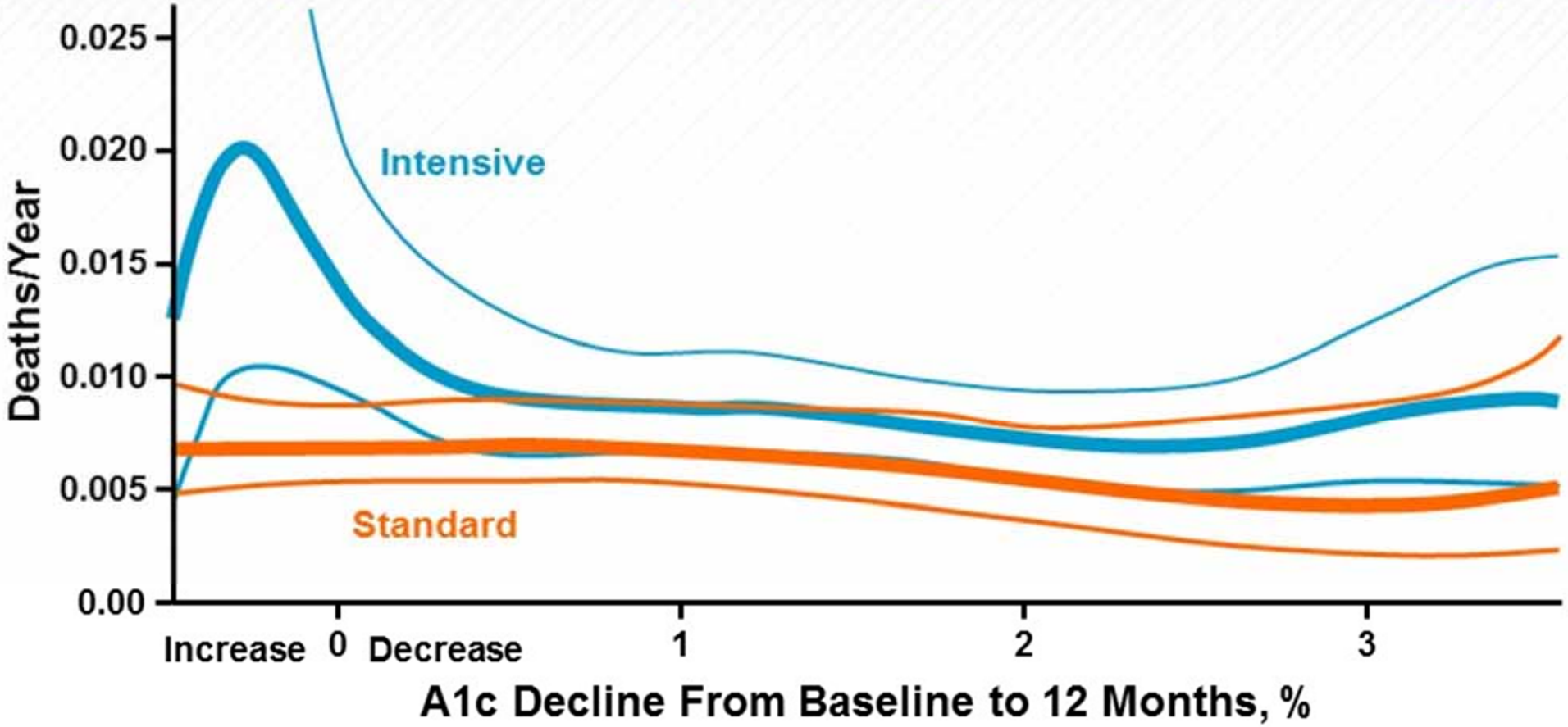


[a]Adjusted for multiple baseline covariates; [b]Primary end points.
Major macrovascular event=CV death, nonfatal myocardial infarction, or nonfatal stroke.
Major microvascular event=new or worsening nephropathy or retinopathy.
Zoungas S, et al. *N Engl J Med*. 2010;363(15):1410-1418.

ACCORD

Mortality vs 1-Year ΔA1c

Adjusted Mortality Rates by Treatment Strategy



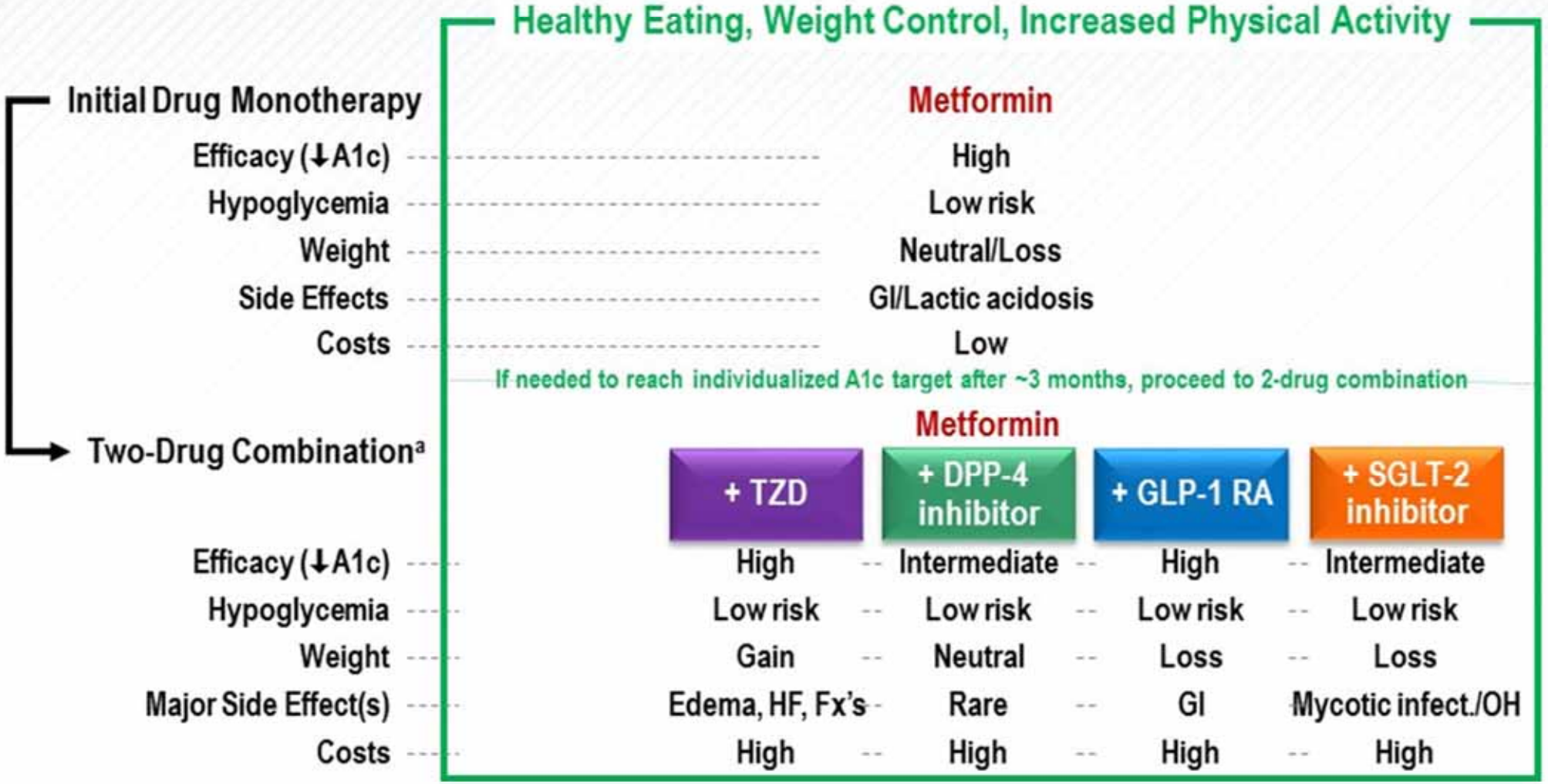
Thin lines represent 95% CIs.
N=10,251 patients with T2DM (mean age, 62 years; median T2DM duration, 10 years; median A1c, 8.1%) randomly assigned to treatment strategies targeting A1c <6.0% (intensive) or 7.0-7.9% (standard).
Riddle MC, et al. *Diabetes Care*. 2010;33(5):983-990.

Sidney
Treatment Tailoring

- Adherent to diet and exercise regimen
- Potential episodes of nocturnal hypoglycemia
- BMI, 27.5 kg/m^2
- BP, 142/88 mm Hg
  - Lisinopril 40 mg daily
  - Atenolol 50 mg daily
- A1c, 7.9%
- FPG, 135 mg/dL
- PPG, 220 mg/dL
- eGFR, 66 mL/min/1.73 m^2
- Lipid values are within normal ranges

Given Sidney's reports of hypoglycemia and significant postprandial hyperglycemia, how would you adjust her therapy?

Treatments With Low Risk of Hypoglycemia



[a]Consider beginning at this stage in patients with very high A1c (eg, ≥9%).

Adapted from Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379; Riser Taylor S, Harris KB. *Pharmacotherapy*. 2013;33(9):984-999.

Canagliflozin and Hypoglycemia

Summary of Clinical Studies[a]

Therapy	Duration (weeks)	N	Hypoglycemia, % Placebo	Hypoglycemia, % 100 mg	Hypoglycemia, % 300 mg
Monotherapy	26	584	2.6	3.6	3.0
Added to MET	26	918	1.6	4.3	4.6
Added to SU	18	215	5.8	4.1	12.5
Added to SU+MET	26	469	15.4	27.4	30.1
Added to PIO+MET	24	342	2.6	2.7	5.3
Added to Insulin[b]	24	1718	36.8	49.3	48.6

Among these studies, 12 severe hypoglycemic events were observed with CANA 100 mg and 17 severe events were observed with CANA 300 mg (placebo arms, severe 15 events)[c]

[a]Hypoglycemia data reflect patients experiencing hypoglycemia episode based on either biochemically documented episode or severe event; [b]With or without other oral antidiabetic agents; [c]Major episodes defined as those where the patient required third-party assistance, lost consciousness, or experienced a seizure regardless of whether biochemical documentation was obtained.
See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf).

Dapagliflozin and Hypoglycemia

Summary of Clinical Studies[a]

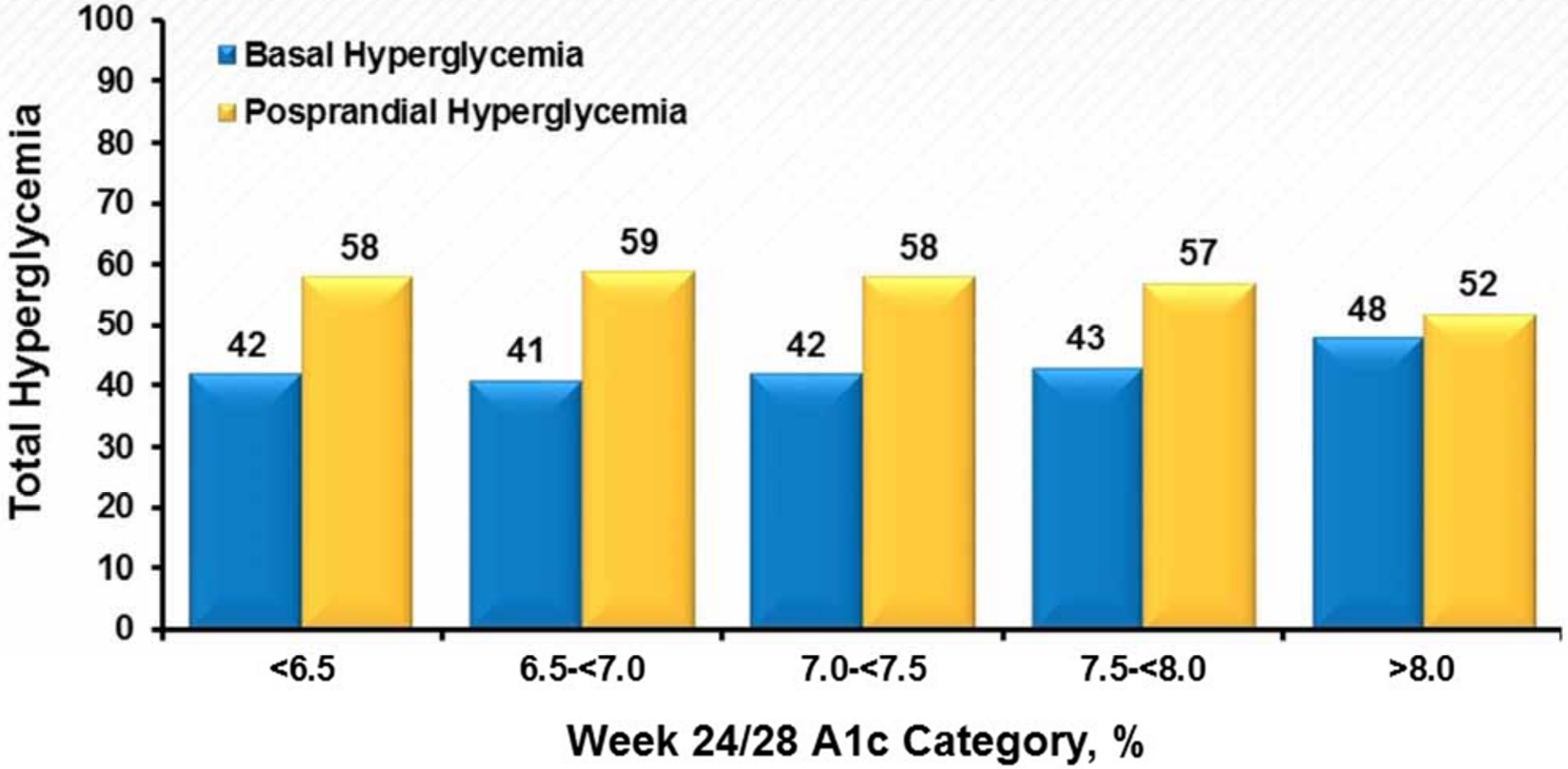
Therapy	Duration (weeks)	N	Hypoglycemia, % Placebo	Hypoglycemia, % 5 mg	Hypoglycemia, % 10 mg
Monotherapy	24	209	0	0	0
Added to MET	24	409	0	1.5	0.7
Added to SU	24	442	2.1	5.5	1.7
Added to PIO	24	420	0	2.1	6.0
Added to DPP-4 Inhibitor±MET	24	451	1.3	N/A	2.2
Added to Insulin[b]	24	605	34.5	43.9	40.8

Among these studies, 1 severe hypoglycemic event was observed with DAPA 5 mg and 2 severe events were observed with DAPA 5 mg (placebo arms, severe 1 event)[c]

[a]Hypoglycemia data reflect patients experiencing major or minor episode; [b]With or without other oral antidiabetic agents; [c]Severe episodes defined as symptomatic episodes requiring external (third-party assistance) due to severe impairment in consciousness or behavior, with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.
See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf).

Postprandial Hyperglycemia and Overall A1c

Pooled Analysis From 6 Clinical Trials[1]

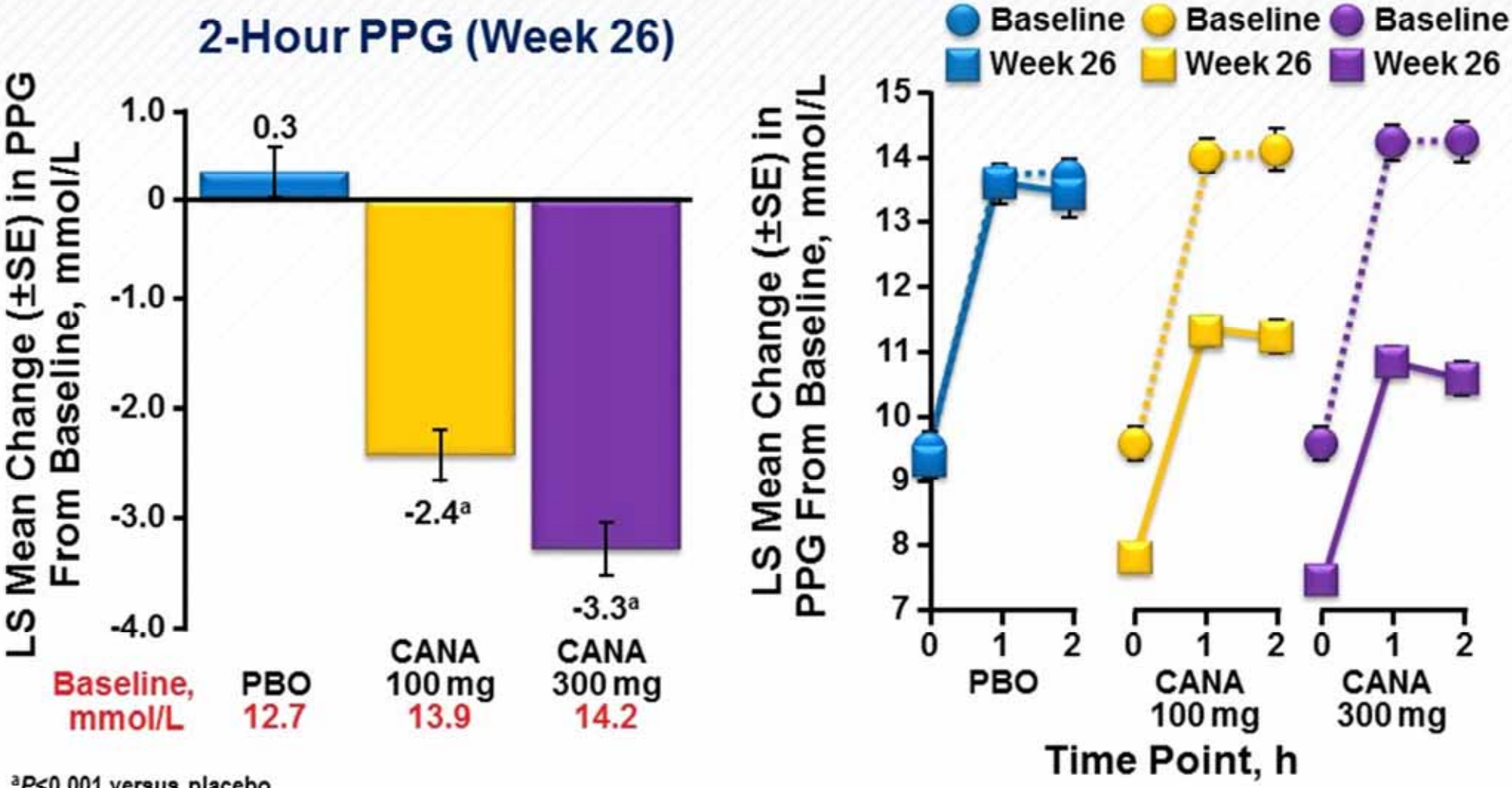


N=1699 patients with T2DM who were on oral therapy and underwent treatment intensification with insulin (premixed, basal, lispro, or human insulin) for 24 or 28 weeks.

1. Riddle M, et al. *Diabetes Care.* 2011;34(12):2508-2514; 2. Monnier L, et al. *Diabetes Care.* 2003;26(3):881-885.

Canagliflozin and PPG Levels

Phase 3 Study



[a]*P*<0.001 versus placebo.

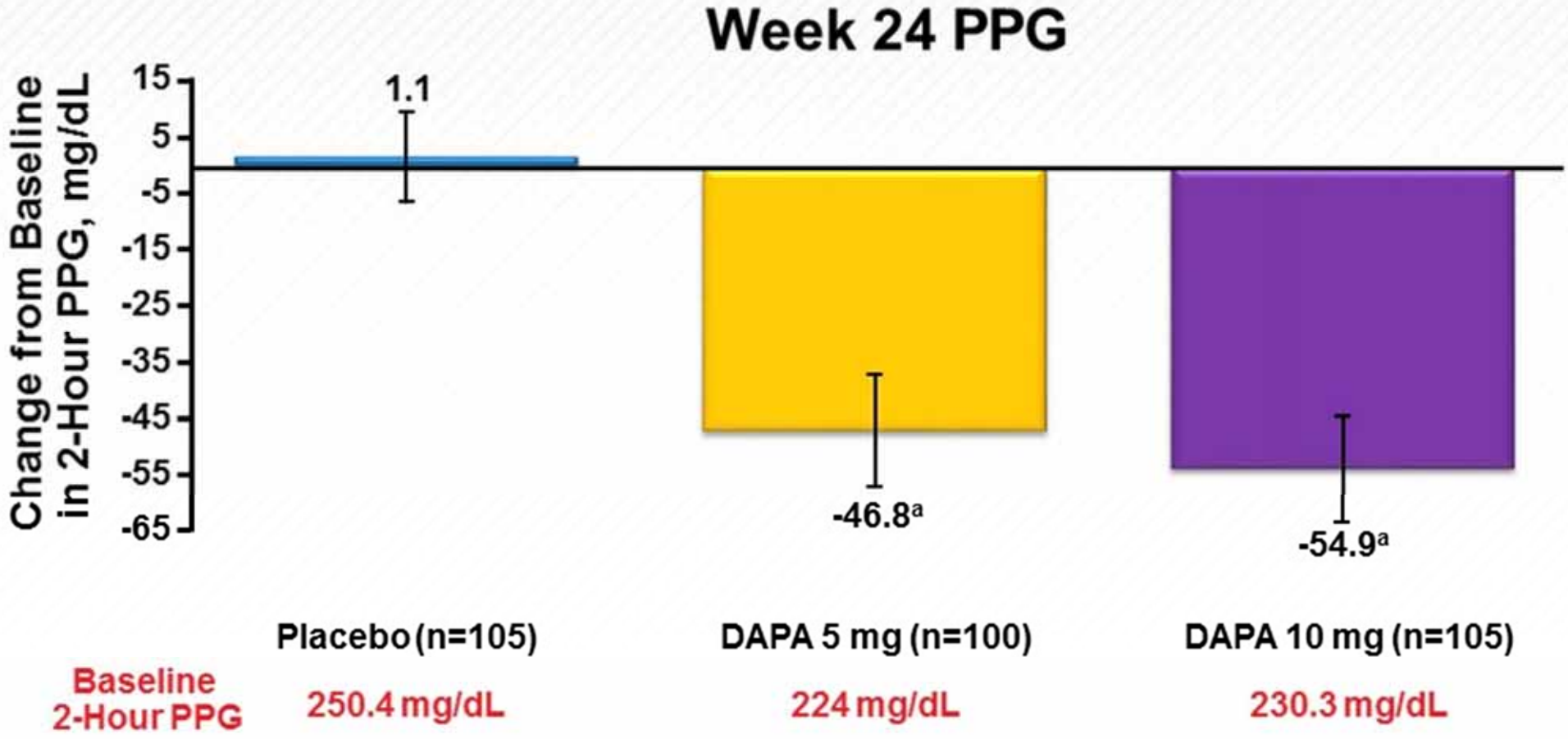
N=584 drug-naïve individuals with T2DM treated with canagliflozin as monotherapy.

LS, least squares; PBO, placebo; SE, standard error.

Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15(4):372-378.

Dapagliflozin and PPG

Phase 3 Study



[a]*P*<0.0001 compared with placebo.

N=310 antidiabetic drug-naive patients with T2DM (A1c, ≥7.5% and ≤10.5%) inadequately controlled with diet and exercise.

Data from 2-hour PPG measurement after liquid meal challenge at week 24.

Ji L, et al. *Clin Ther*. 2014;36(1):84-100.

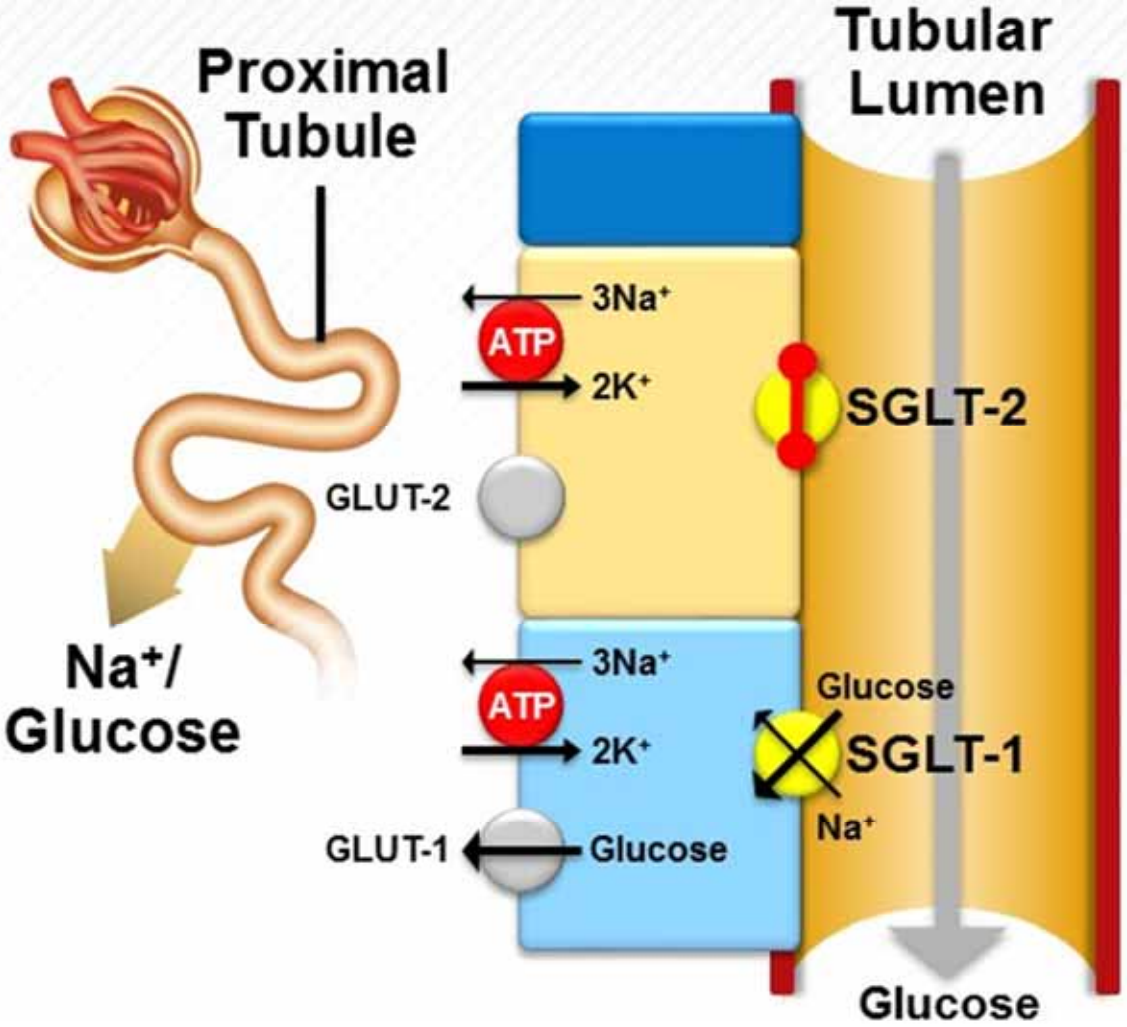
Sidney
Treatment Tailoring

- Adherent to diet and exercise regimen
- Potential episodes of nocturnal hypoglycemia
  - Advised to eat a snack before bedtime
- BMI, 27.4 kg/m^2
- BP, 142/88 mm Hg
  - Lisinopril 40 mg daily
  - Atenolol 50 mg daily
- A1c, 7.9%
- FPG, 135 mg/dL
- PPG, 220 mg/dL
- eGFR, 76 mL/min/1.73 m^2
- Lipid values are within normal ranges

What are some other considerations when selecting a therapy or therapies for Sidney?

SGLT-2 Inhibition

Insulin-Independent Reversal of Glucotoxicity



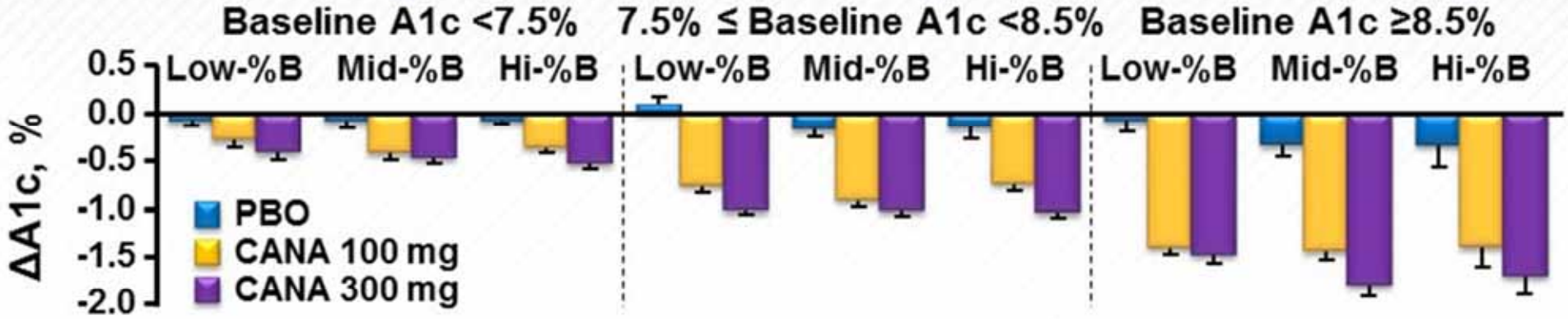
- ↑ Insulin sensitivity in muscle[1,2]
- ↑ Insulin sensitivity in liver[2]
- ↓ Gluconeogenesis[2,3]
- ↑ Improved β-cell function[4,5]

1. DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14(1):5-14; 2. Merovci A, et al. *J Clin Invest*. 2014;124(2):509-514;
3. Marsenic, O. *Am J Kidney Dis*. 2009;53(5):875-883; 4. Ferrannini E, et al. *J Clin Invest*. 2014;124(2):499-508;
5. Polidori D, et al. *Diabetologia*. 2014;57(5):891-901.

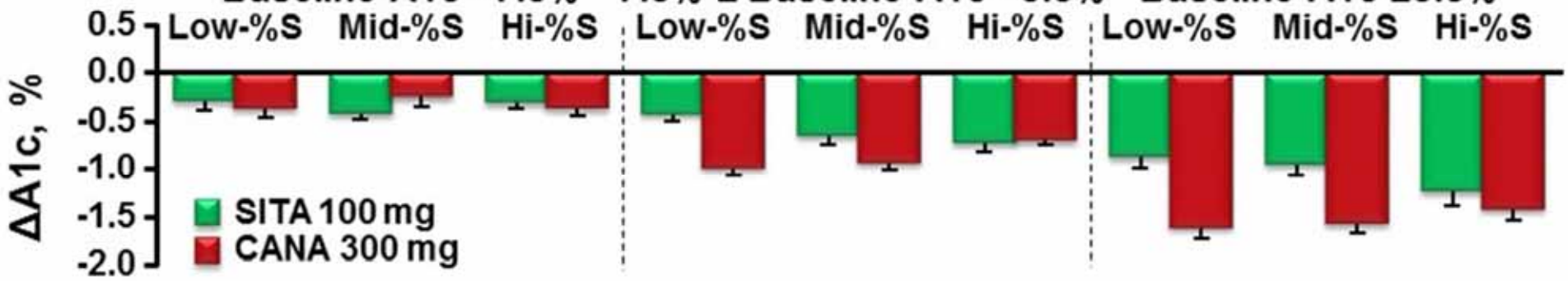
Canagliflozin Efficacy and β-Cell Function

Analysis of Placebo- and Active-Controlled Studies

Efficacy vs Baseline HOMA2-%B (PBO-Controlled Studies[a])



Efficacy vs Baseline HOMA2-%S (Active-Controlled Studies[b])

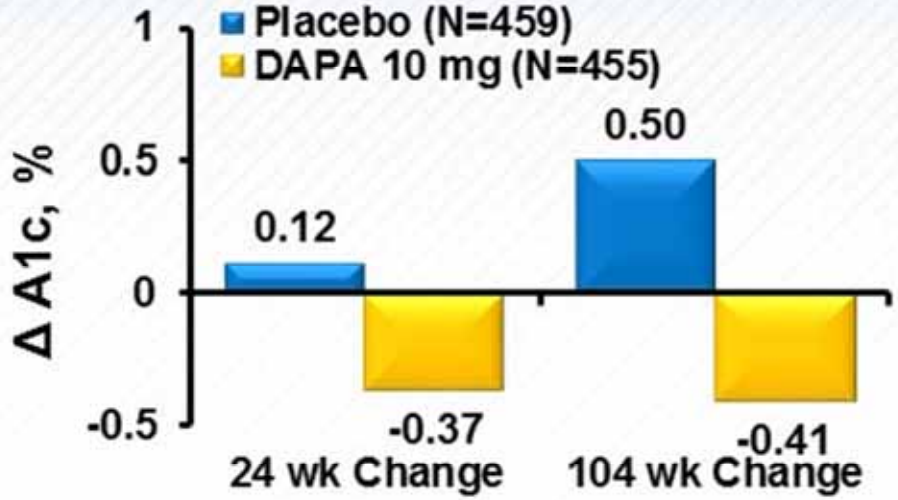


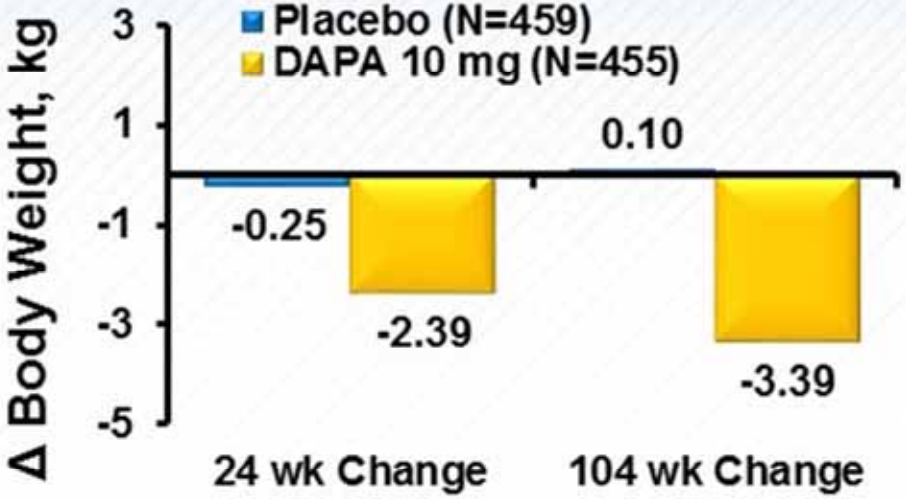
[a]26-week placebo-controlled studies of canagliflozin (N=2613); HOMA2-%B used as a measure of β-cell function;
[b]52-week active-controlled studies comparing canagliflozin and sitagliptin (N=1488); HOMA2-%S used as a measure of insulin sensitivity.
HOMA, homeostatic model assessment.

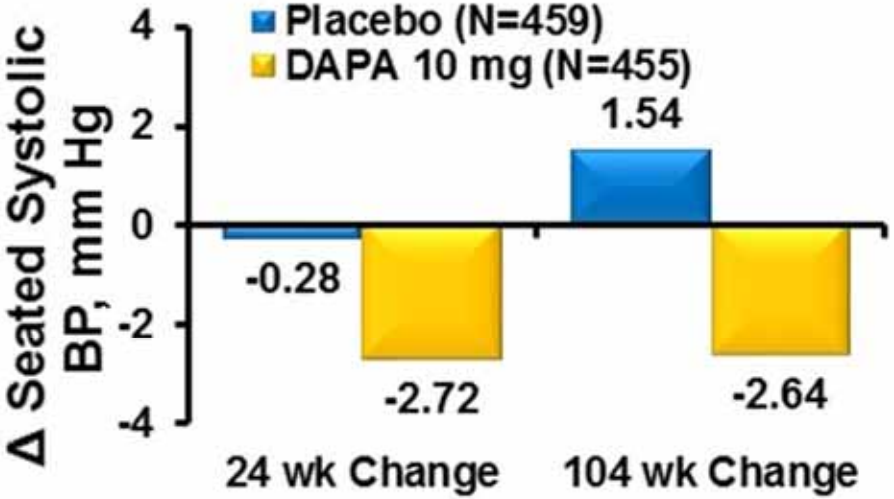
Matthews D, et al. Glycemic efficacy of canagliflozin (CANA) is largely independent of baseline beta-cell function or insulin sensitivity. Poster presented at American Diabetes Association 74th Scientific Sessions; June 13-17, 2014; San Francisco, CA. Abstract 1096-P.

Dapagliflozin in Patients With Hypertension and Pre-existing CVD

104-Week Study







- Mean patient age, 63 years
  - 42% were ≥65 years old
- Baseline values
  - A1c, 8.1%
  - Body weight, 93.1 kg
  - BP, 133/77 mm Hg
- 52% used insulin ± oral antidiabetics
- No unexpected safety findings

All 104-week changes significant vs placebo based on 95% CIs.

N=914 inadequately controlled T2DM, pre-existing CVD, and hypertension randomized to DAPA 10 mg or placebo plus usual care.

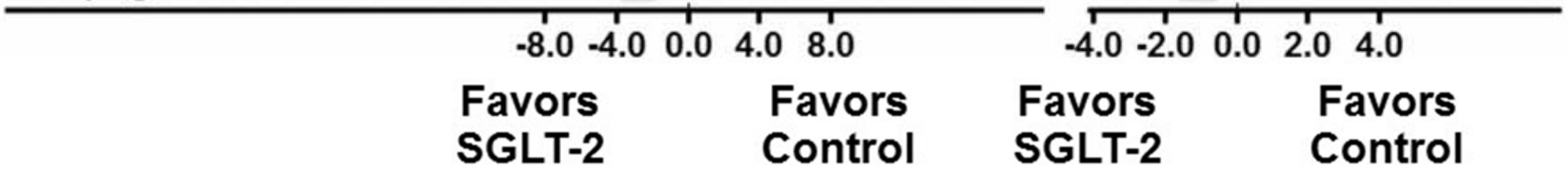
Cefalu WT, et al. Long-term efficacy and safety of dapagliflozin in patients with type 2 diabetes, cardiovascular disease, and hypertension. Poster presented at American Diabetes Association. 74th Scientific Sessions; June 13-17, 2014; San Francisco, CA. Abstract 1099-P.

SGLT-2 Inhibitors

Effects on Blood Pressure

Meta-analysis of 27 Randomized Controlled Trials

Comparison	N	Systolic BP	95% CI	Diastolic BP	95% CI
All Drugs	12960		-3.96		-1.59
Placebo-Controlled	7875		-3.82		-1.45
Active-Controlled	5085		-4.17		-1.87
Canagliflozin[a]	5607		-4.38		-2.02
Dapagliflozin[b]	5280		-3.78		-1.41
Empagliflozin[c]	1359		-3.02		-1.01



[a]Only FDA-approved doses for canagliflozin included in analysis (100 or 300 mg/day);
[b]Daily doses ranged from 1 mg to 10 mg/; [c]Daily doses ranged from 1 mg to 50 mg;
[d]Daily doses ranged from 12.5 mg to 300 mg/day.

Baker WL, et al. *J Am Soc Hypertens*. 2014 Jan 26. [Epub ahead of print].

SGLT-2 Inhibitors
Cardiovascular Risk

- No increases in cardiovascular risk in clinical trials
- Large clinical trials are ongoing

Trial	Agent	Patients (N)	Max Duration (years)	Patient-Years	Estimated Completion Date
CANVAS (NCT01032629)	Canagliflozin	4330	7	38970	2017
DECLARE-TIMI58 (NCT01730534)	Dapagliflozin	22200	6	133200	2019
NCT01131676	Empagliflozin	7000	5	35000	2015

National Institutes of Health. http://www.clinicaltrials.gov. Accessed June 2, 2014.

Canagliflozin and High-Dose Insulin

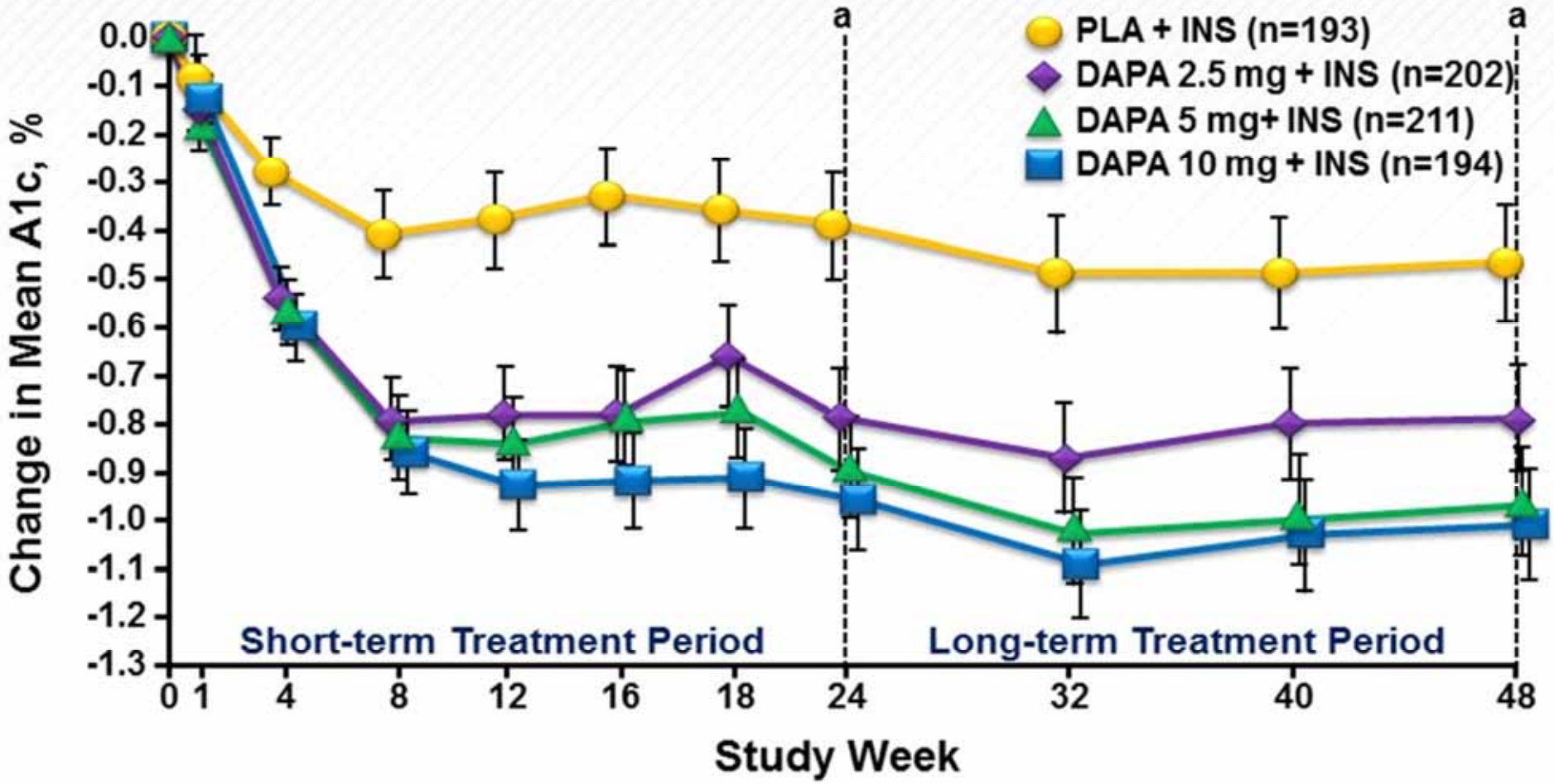
18-Week CANVAS Substudy

Efficacy Parameter	Placebo (n=88)	Canagliflozin 100 mg (n=86)	Canagliflozin 300 mg (n=104)
A1c baseline, %	8.3±0.8	8.4 ± 0.9	8.2 ± 0.8
Δ A1c,% [95% CI]	–	-0.86 [-1.07 to -0.65]	-0.89 [-1.09 to -0.69]
FPG baseline, mg/dL	158.0 ± 51.6	158.4 ± 39.9	153.3 ± 40.4
Δ FPG, mg/dL [95% CI]	–	-24.7 [-37.4 to -11.9]	-30.8 [-43.0 to -18.6]
Weight baseline, kg	102.3 ± 22.9	97.5 ± 23.7	99.2 ± 20.2
Δ Weight, % [95% CI]	–	-1.8 [-2.7 to -0.9]	-2.7 [-3.6 to -1.8]

Data were obtained from a modified intent-to-treat population with the LOCF from the basal insulin subset.
Data in the 3 Δ rows are LS mean values for changes vs placebo.
N=278 patients T2DM on stable, nontitrated, nonprandial basal insulin at ≥30 units per day ± other antihyperglycemic agents.
CANVAS, canagliflozin cardiovascular assessment study; LOCF, last observation carried forward.
Rosenstock J, et al. Effects of canagliflozin added on to basal insulin ± other antihyperglycemic agents in type 2 diabetes. Poster presented at the 73rd Scientific Sessions of the ADA. June 21-25, 2013; Chicago, IL; Poster 1084-P.

Dapagliflozin and High-Dose Insulin

Long-term Efficacy



[a]*P*<0.001 vs placebo for all doses at analysis points (weeks 24 and 48).

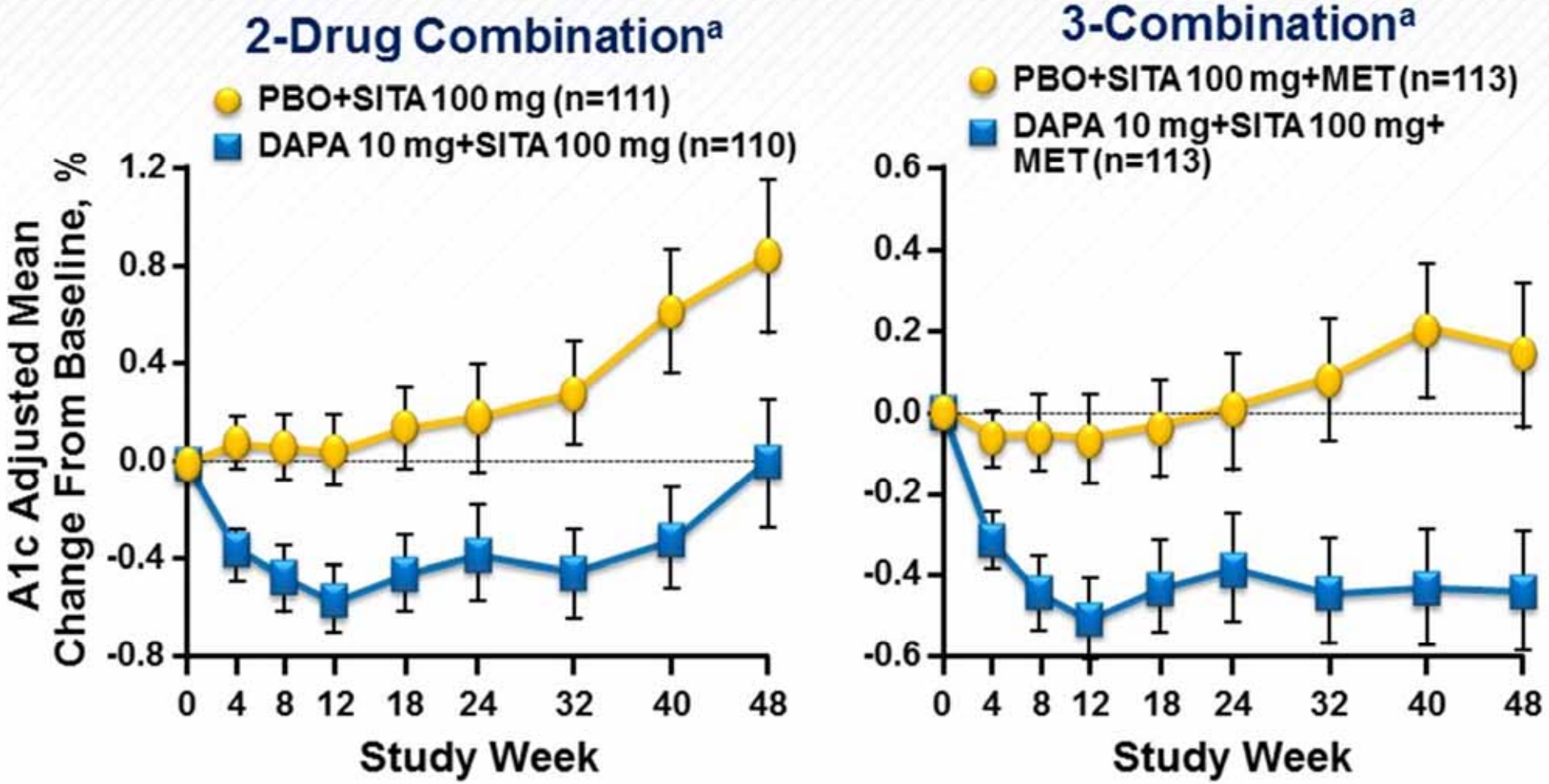
Error bars show 95% CI.

N=808 patients with T2DM receiving ≥30 U of insulin daily, with or without ≤2 oral antidiabetic drugs.

Wilding JP, et al. *Ann Intern Med*. 2012;156(6):405-415.

Dapagliflozin Add-on to Sitagliptin

Phase 3 Study



N=432 patients with T2DM (A1c between ≥7.0% and ≤10.0%) randomized to dapagliflozin 10 mg or placebo in addition to sitagliptin (100 mg/day) ± metformin (≥1500 mg/day).

Jabbour SA, et al. *Diabetes Care*. 2014;37(3):740-750.

Select Combination Agents With SGLT-2 Inhibitors Under Development

Fixed Dose Combinations	Clinical Status
Dapagliflozin+Metformin[1]	Filed in US; Approved in the EU
Canagliflozin+Metformin[2]	Filed in US; Approved in the EU
Empagliflozin+Metformin[3]	Phase III
Dapagliflozin+Saxagliptin[4]	Phase III
Empagliflozin+Linagliptin[3]	Phase III
Ertugliflozin+Sitagliptin[5]	Phase III

1. Press Release. http://www.astrazeneca.com/Media/Press-releases/Article/20142101--xigduo-dapagliflozin-and-metformin-hydrochloride;
2. Press Release. http://www.investor.jnj.com/releasedetail.cfm?ReleaseID=842748;
3. Pipeline Report. http://www.boehringer-ingelheim.com/research_development/drug_discovery/pipeline.html;
4. Dapagliflozin and Saxgliptin. NCT01606007. www.clinicaltrials.gov; 5. Press Release. http://press.pfizer.com/press-release/merck-co-inc-and-pfizer-enter-worldwide-collaboration-agreement-develop-and-commercial.
All sources accessed June 6, 2014.

Dapagliflozin/Saxagliptin Combination

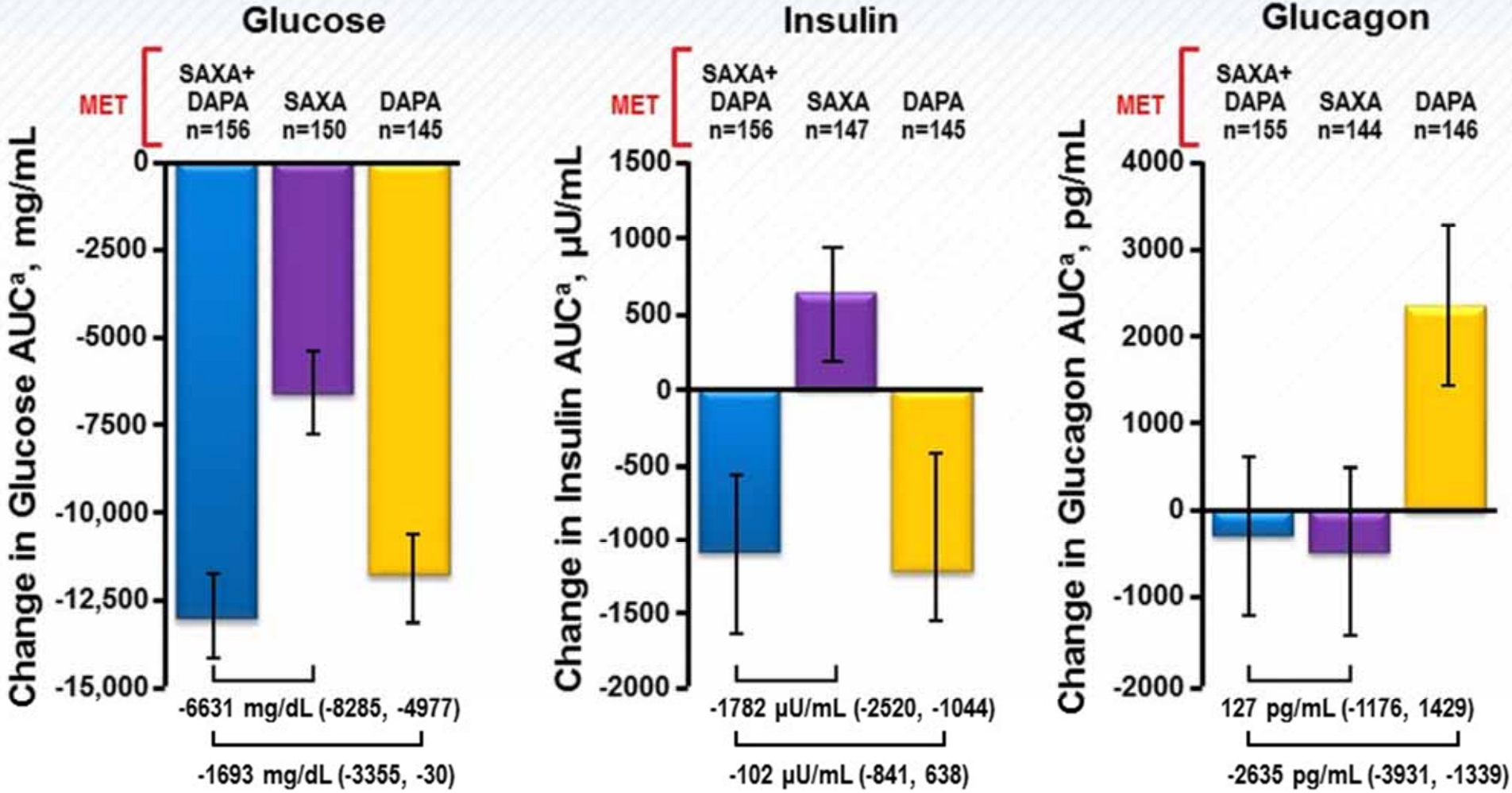
24-Week Phase 3 Study

Parameters	DAPA/SAXA 10/5 mg	SAXA 5 mg and PBO	DAPA 10 mg and PBO
ΔA1c, %	-1.47	-0.88	-1.20
Difference vs DAPA/SAX, % [95% CI]	N/A	-0.59 [-0.81, -0.37][a]	-0.27 [-0.48, -0.05][b]
Patients achieving A1c <7%, %	41	18	22
Difference vs DAPA/SAX[c], % [95% CI]		23 [14.7, 31.5]	19 [10.1, 28.1]
Δ Body Weight, kg[c]	-2.1	0.0	-2.4
Hypoglycemia, %[d]	1.1	0.6	1.1

[a]*P*<0.0001; [b]*P*<0.0166; [c]Not tested for significance; [d]Data reflects minor episodes; no major episodes of hypoglycemia.
N=534 patients with T2DM (A1c, ≥8.0% and ≤12.0%) treated with metformin XR ≥1500 mg daily.
Rosenstock J, et al. Dual add-on therapy in poorly controlled type 2 diabetes on metformin: randomized, double-blind trial of saxagliptin+dapagliflozin vs. saxagliptin and dapagliflozin alone. Poster presented at American Diabetes Association 74th Scientific Sessions; June 13-17, 2014; San Francisco, CA. Abstract 127-LB.

Dapagliflozin/Saxagliptin Combination

Mean Change in $AUC_{0\text{-}180min}$ During an MTT



[a]Data are adjusted mean changes from baseline.

N=534 patients with T2DM (A1c, ≥8.0% and ≤12.0%) on stable metformin XR ≥1500 mg daily.

Rosenstock J, et al. Dual add-on therapy in poorly controlled type 2 diabetes on metformin: randomized, double-blind trial of saxagliptin+dapagliflozin vs. saxagliptin and dapagliflozin alone. Poster presented at American Diabetes Association 74th Scientific Sessions; June 13-17, 2014; San Francisco, CA. Abstract 127-LB.

Empagliflozin/Linagliptin Combination

Phase 3 Study in Drug-Naïve Patients

	EMPA 25 mg/ LINA 5 mg (n=134)	EMPA 10 mg/ LINA 5 mg (n=135)	LINA 5 mg (n=133)
A1c, %			
Change from baseline, week 24	-1.08	-1.24	-0.67
Difference vs LINA 5 mg	-0.41 (-0.61, -0.22)[a]	-0.57 (-0.76, -0.37)[a]	-
FPG, mg/dL			
Change from baseline, week 24	-29.6	-28.2	-5.9
Difference vs LINA 5 mg	-23.6 (-31.1, -16.2)[a]	-22.3 (-29.7, -14.9)[a]	-
Body weight (kg)			
Change from baseline, week 24	-2.0	-2.7	-0.8
Difference vs LINA 5 mg	-1.2 (-2.2, -0.2)[b]	-2.0 (-3.0, -1.0)[a]	-

[a]*P*<0.001; [b]*P*<0.05.

N=674 drug-naive individuals with T2DM (week 24 data analyzed before completion of 52-week study).

Lewin A, et al. Fixed dose combinations of empagliflozin/linagliptin for 24 weeks in drug-naïve patients with type 2 diabetes (T2DM). Poster presented at American Diabetes Association. 74th Scientific Session; 2014 June 13-17th; San Francisco, CA.

Sidney
Concluding Comments

- Target A1c levels should reflect risks of hypoglycemia, disease duration, and responses to therapy over time
  - Avoiding hypoglycemia is particularly important in patients with long-standing disease or those who have not responded to intensification of therapy
- SGLT-2 inhibitors have additional potential benefits in addition to reduction in FPG and weight loss
  - Improved PPG
  - Reduced blood pressure
  - Relatively low rates of hypoglycemia
    - Care is required with concomitant SU or insulin therapy