Advances in T2D Treatment: Elevating Management in the Primary Care Setting with New Therapeutic Options

A New Therapeutic Option in Primary Care

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Disclosures

Robert Gorman, MD, FAAFP reports no financial relationships; **Serge Jabbour, MD, FACP, FACE** has received consulting fees from Eli Lilly & Co, Janssen Pharmaceuticals, and AstraZeneca; **Louis Kuritzky, MD**, has received consulting fees from Eli Lilly & Co, Janssen Pharmaceuticals, Novo Nordisk, Sanofi-Aventis, Pfizer, Inc., Boehringer Ingelheim, and AstraZeneca; **Marc Sandberg, MD, FACP, CDE** has received consulting fees from Janssen Pharmaceuticals, and has served on the speakers' bureau for Eli Lilly & Co, AstraZeneca, Novo Nordisk, Boehringer Ingelheim, and Valeritas

Theresa Barrett, PhD, Jack Douglass, Charles Goldthwaite, PhD (Planners) and Everett Schlam, MD (reviewer) report no financial relationships

Conflicts have been resolved according to NJAFP policy

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Speaker Disclosure

Dolores Gomez, MD, has indicated that she has nothing to disclose relevant to this activity.

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Learning Objectives

- Explain the role of the kidney in glucose homeostasis.
- Discuss the impact of diabetes on the population and the importance of glycemic control
- Describe the rationale, mechanisms, and clinical consequences of SGLT2 inhibition
- Discuss how to integrate SGLT2 Inhibitors into the management of diabetes
- Create individualized treatment plans for patients with type 2 diabetes, using the most appropriate pharmacotherapy available

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Housekeeping

- Complete the pre-test questions now.
- There is a space to record your answers for the case study
- Complete the post-test at the end of the session
- Complete the evaluation form and claim your credit
- Return the form to a staff member or at the registration desk

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The Impact of Type 2 Diabetes

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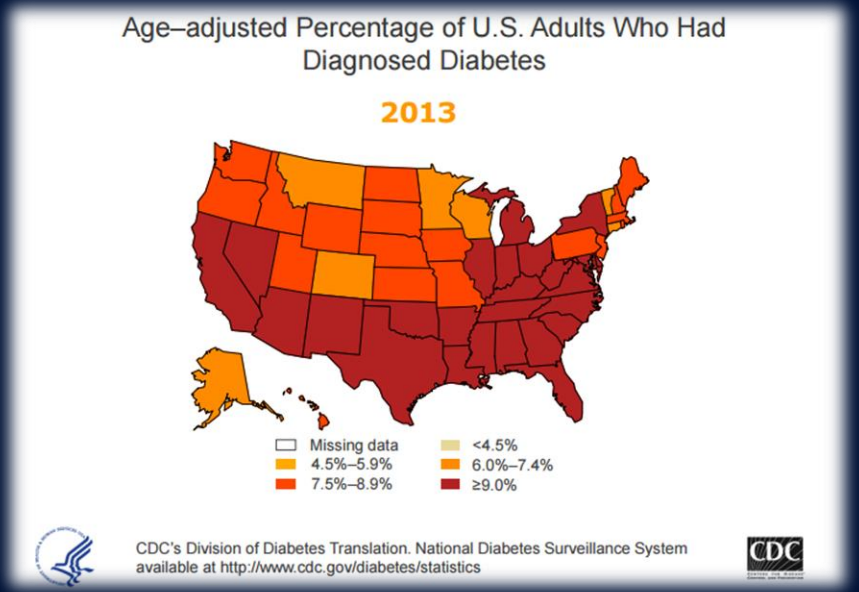
The Diabetes Epidemic

- ~29 million individuals in the US have diabetes (8.1 million are undiagnosed).[1]
- 7th leading cause of death in the US[1]



- In 2012, diabetes cost ~$245 billion in the US (> $1,000 per American).[2,3]
- An estimated 242,000 new cases per year in the US in next 20 years.[4]

Sources: [1]CDC. National diabetes statistics report, 2014; [2]American Diabetes Association. *Diabetes Care* 2013;36:1033-46; [3]Dall TM, et al. *Diabetes Care* 2014;37:3172-79; [4]Guariguata L, et al. *Diabetes Res Clin Pract* 2014;103:137-49.

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Hallmarks of Type 2 Diabetes

- Insulin resistance in the muscles, liver, and adipose tissue
- Progressive decline in pancreatic β-cell function
- Uncontrolled hyperglycemia

Type 2 diabetes accounts for 90-95% of diabetes cases.

Source: ADA. *Diabetes Care.* 2015;8(Suppl 1):S8-S16.

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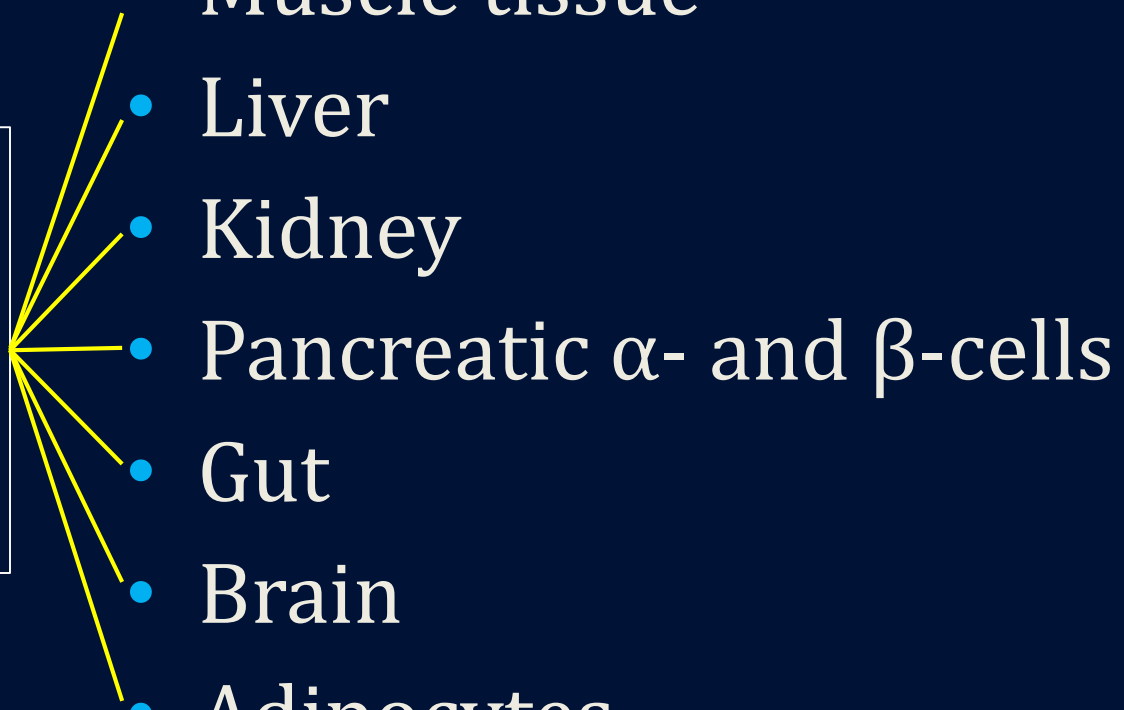
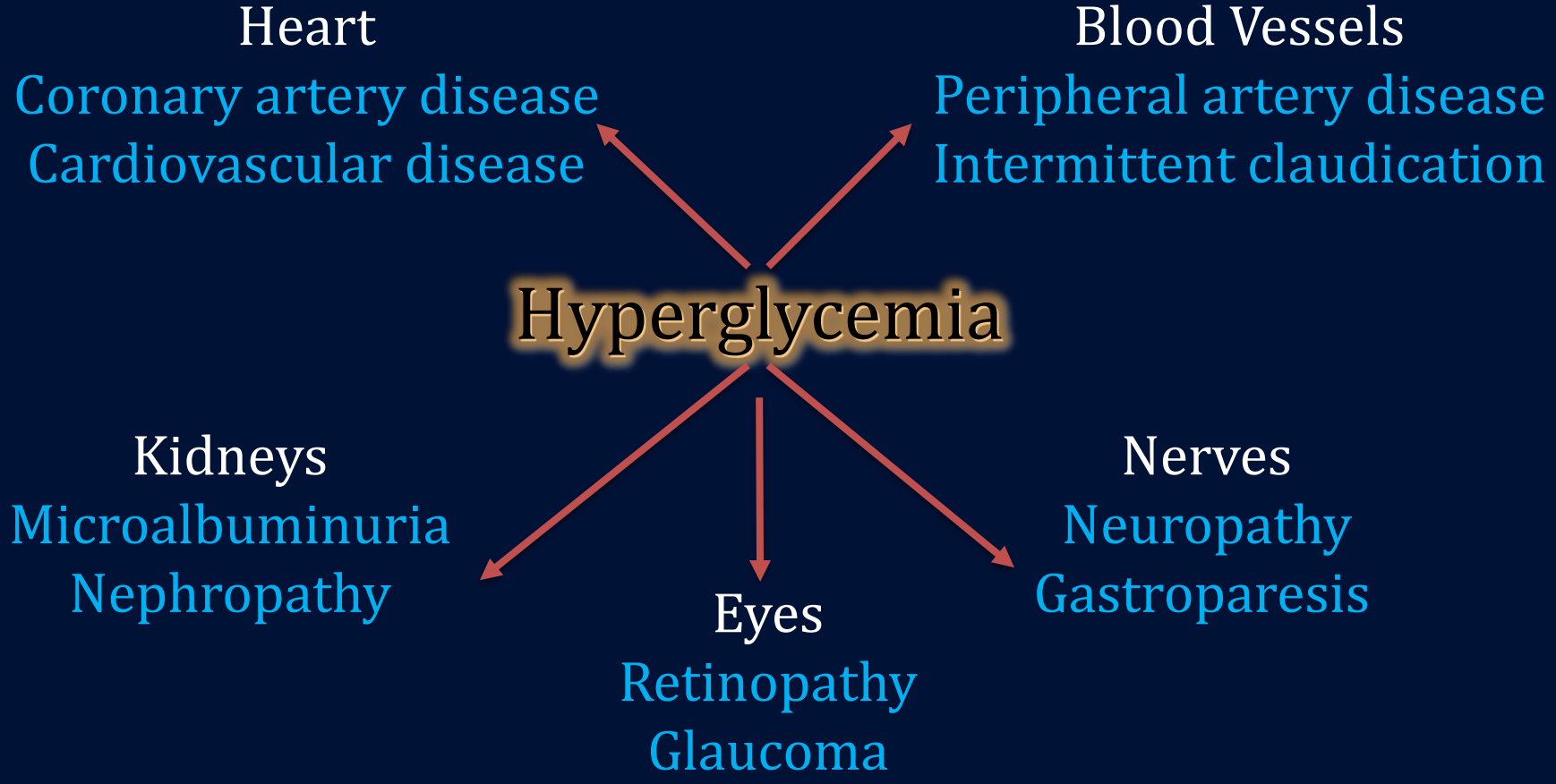
Type 2 Diabetes Impacts Multiple Organs

The "Ominous Octet" of Glucose Intolerance



Source: DeFronzo RA. *Diabetes* 2009;58:773-795.

Complications of Type 2 Diabetes



Source: ADA. *Diabetes Care.* 2010;33(Suppl 1):S11-S61.

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Establishing Glycemic Control is Essential to Manage Disease

- Microvascular and macrovascular benefits are associated with glycemic control.[1-8]
- Target glucose levels should be individualized.
- Hypoglycemia should be avoided.

Sources: [1]UKPDS Group. *Lancet* 1998;352:837-53; [2]UKPDS Group. *Lancet* 1998;352:854-65; [3]Stratton IM, et al. *BMJ* 2000;321:405-12; [4]Diabetes Control and Complications Research Group. *N Engl J Med* 1993;329:977-86; [5]DCCT/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 2000;342:381-89; [6]Gaede P, et al. *N Engl J Med* 2003;348:383-93; [7]Lawson ML, et.al. *Diabetes Care* 1999;22 (suppl 2):B35-B39; [8]Nathan DM, et al. *N Engl J Med* 2005;353:2643-53.

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American Diabetes Association Glycemic Recommendations

A_{1c}	< 7.0%
Preprandial plasma glucose	80-130 mg/dL
Peak postprandial plasma glucose	< 180 mg/dL

Individualize based on age/life expectancy, duration of diabetes, comorbidities, known CVD or advanced microvascular complications, hypoglycemia unawareness, and patient preferences. More or less stringent goals may be appropriate for some patients.

Source: American Diabetes Association. *Diabetes Care* 2015;38(Suppl 1):S33-S40.

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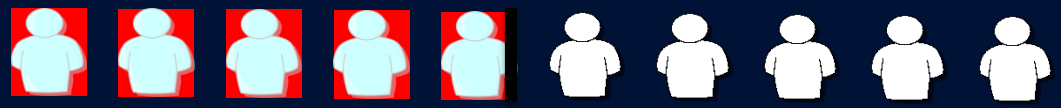
Reaching Glycemic Targets: Are We There Yet?



In 2010, 47% of American adults with diabetes had not achieved the ADA's management goal of A_{1c} < 7.0%.*

*Data from the National Health and Nutrition Examination Surveys (NHANES); 1988-2010.

Source: Stark Casagrande S, et.al. *Diabetes Care* 2013;36:2271-79.

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Managing Diabetes

- Lifestyle interventions (diet, activity) for overweight/ obese individuals geared toward an initial loss of 5-10% of baseline body weight
- Cardiovascular risk management (e.g., hypertension, dyslipidemia, microalbuminuria)
- Normalizing blood glucose level
- Patient preferences and individualized goals

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The Kidney's Role in Glucose Homeostasis

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Glucose Regulation

Kidney

- Generates glucose through gluconeogenesis pathway
- Reabsorbs glucose through the proximal renal tubules

Liver

- Generates glucose through gluconeogenesis pathway
- Produces glucose by glycogenolysis

Sources: Jabbour SA. *Postgrad Med* 2014;126:111-17; Gerich JE. *Diabet Med* 2010;27:136-42; Meyer C, et.al. *Am J Physiol Endocrinol Metab* 2002;282:E419-E27.

Glucose Reabsorption in the Kidney

- Blood glucose freely filtered by glomerulus
- Nearly all of the ~180 g of glucose filtered daily in glomeruli of healthy adult is reabsorbed, mostly in proximal renal tubules[1]
- < 1% excreted in urine[2]
- Glucose transport from tubule to tubular epithelial cells accomplished by sodium-glucose cotransporters (SGLTs)

Sources: [1]Neumiller JJ, et.al. *Drugs* 2010;70:377-85; [2]Bakris GL, et.al. *Kidney Int* 2009;75:1272-77.

The SGLT Family

- Membrane proteins that transport glucose, amino acids, vitamins, ions, and osmolytes across the brush-border membrane of proximal renal tubules.
- The specific SGLTs involved with glucose transport (but not the transport of amino acids, etc) are SGLT2 in the proximal segment of the renal proximal tubule and SGLT1 in the distal segment of the renal proximal tubule.

Source: Neumiller JJ, et.al. *Drugs* 2010;70:377-85.

SGLT1 and SGLT2

SGLT1

- "Low-capacity, high-affinity receptor"
- Reabsorbs essentially all of the glomerular filtrate glucose not reabsorbed by SGLT2

SGLT2

- "High-capacity, low-affinity receptor"
- Responsible for ~90% of renal glucose reabsorption

Source: Jabbour SA. *Postgrad Med* 2014;126:111-17.

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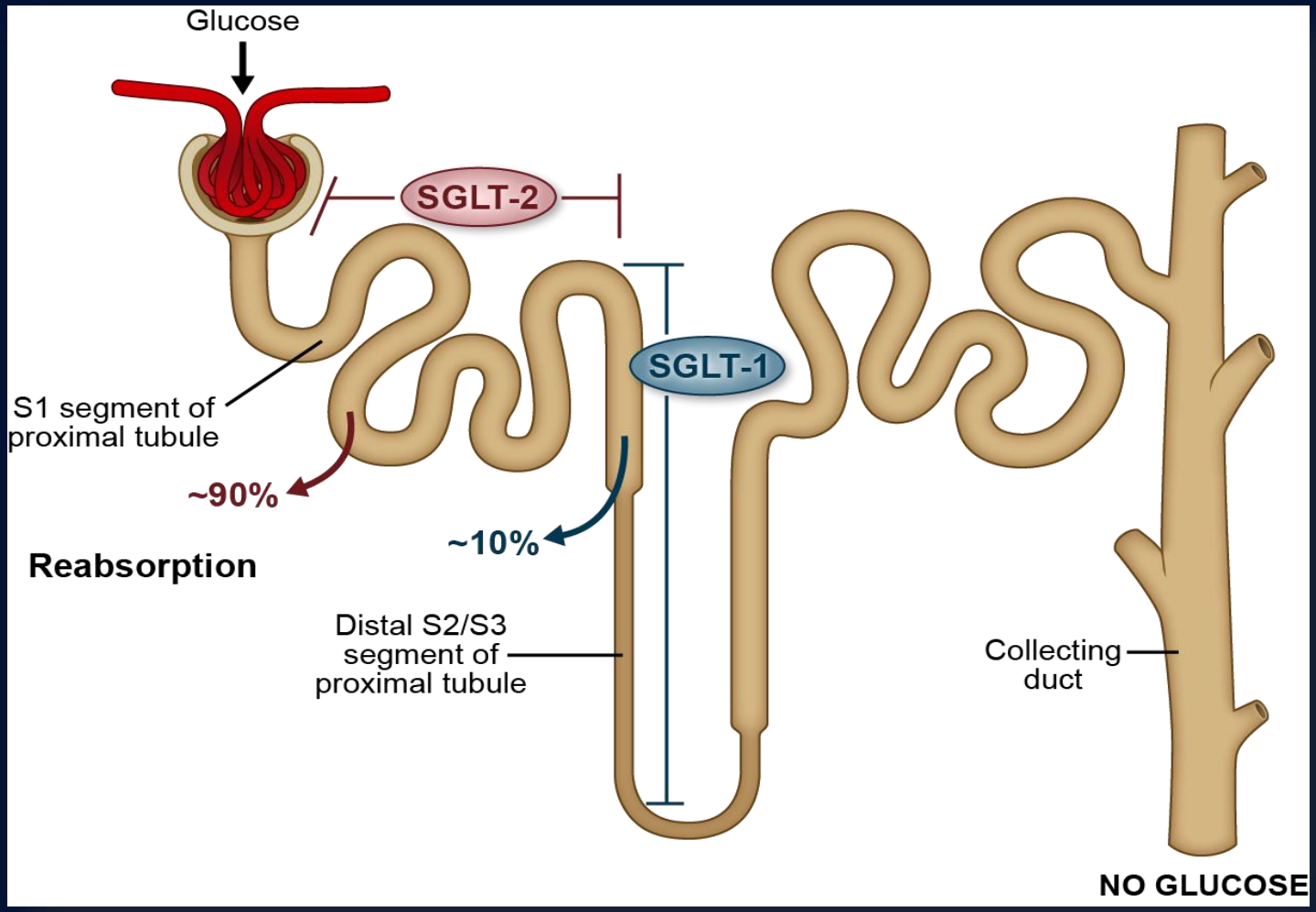
Renal Glucose Reabsorption



Source: Reprinted with permission from Jabbour, MedScape Test-n-Teach Review, *SGLT2 Inhibitors in Type 2 Diabetes* (2014).

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Type 2 Diabetes Alters Glucose Homeostasis

- Increased renal gluconeogenesis following glucose induction[1]
- Excessive renal glucose release after meal[1]
- Increased use of glucose by kidneys during fasting and postprandially[1]
- Increased SGLT2 expression in proximal tubule cells[2]

Sources: [1]Meyer C, et.al. *Am J Physiol Endocrinol Metab* 2004;287:E1049-E56; [2]Jabbour SA. *Postgrad Med* 2014;126:111-17.

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Type 2 Diabetes and Glycosuria

- In healthy individuals, the SGLT-based glucose transport system saturates at plasma glucose (PG) concentrations > 180 mg/dL, causing excess glucose to spill into urine.
- Type 2 diabetes increases renal capacity to absorb glucose; glycosuria occurs at PG > 220 mg/dL.

Source: Peene B, Benhalima K. *Ther Adv Endocrinol Metab* 2014;5:124-36.

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SGLT2 Inhibition: A New Treatment Paradigm

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How SGLT2 Inhibitors Work

- Inhibit reabsorption of 30-50% of glucose filtered daily by the glomeruli[1]
- Lower threshold at which glucose begins to be excreted in urine (typically to ~70 mg/dL)[2]

SGLT2 inhibitors can promote the urinary excretion of 50-90 grams of glucose daily.

Sources: [1]DeFronzo RA, et al. *Diabetes Care* 2013;36:3169-76; [2]Liu JJ, et.al. *Diabetes* 2012;61:2199-204.

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A New Treatment Paradigm

- Elevated glycosuria traditionally viewed as cause for concern
- SGLT2 inhibitors can concomitantly lower A_{1c} and elevate glycosuria

To use SGLT2 inhibitors effectively, clinicians must consider the kidney a potential treatment target (rather than a site of organ damage) in type 2 diabetes.

Source: Bays H. *Curr Med Res Opin* 2009;25:671-81.

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Clinical Implications of Promoting Glycosuria

- Persons with familial renal glucosuria (FRG) have non-functional SGLT2 receptors (and thus chronic glycosuria without diabetes)
- FRG not associated with any impact on CVD, mortality, or diabetic complications[1,2]
- FRG-related chronic glycosuria (10-120g/day) mostly asymptomatic[2-4]

Long-term observation of normoglycemic persons with FRG suggests that chronic glycosuria does not in itself cause negative clinical sequelae.[3]

Sources: [1]Kim Y, Babu A. *Diabetes Metab Syndr Obes* 2012;5:313-27; [2]Santer R, Calado J. *Clin Am J Soc Nephrol* 2010;5:133-41; [3]Chao EC, Henry RR. *Nat Rev Drug Discov* 2010;9:551-59; [4]Marsenic O. *Am J Kidney Dis* 2009;53:875-83.

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FDA-Approved SGLT2 Inhibitors

- Canagliflozin*
- Dapagliflozin*
- Empagliflozin

*Also available as FDA-approved fixed-dose tablets with metformin hydrochloride.

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SGLT2 Inhibitors: Indications

- Indicated as adjuncts to diet and exercise to improve glycemic control in adults who have type 2 diabetes (but not for treatment of type 1 diabetes or for diabetic ketoacidosis)

- Contraindicated w/severe renal impairment, end-stage renal disease, dialysis, or hypersensitivity to given agent
- FDA Pregnancy Category C

Sources: Package inserts for canagliflozin, dapagliflozin, and empagliflozin.

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SGLT2 Inhibitors: Safety Warning

- On May 15, 2015, the US FDA issued a safety warning stating that SGLT2 inhibitors may lead to ketoacidosis.
- No changes to the prescribing information were made with this announcement.
- FDA recommends that clinicians evaluate patients for acidosis and discontinue SGLT2 inhibitors if confirmed.

Source: US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. May 15, 2015.

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SGLT2 Inhibitors: Side Effects

- Genital mycotic infections*
- Urinary tract infections*
- Increased urination

*More commonly affect women, but are generally mild-to-moderate and usually respond to standard treatment.

Source: Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74.

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SGLT2 Inhibitors: Antihyperglycemic Efficacy

- Clinically significantly reduce fasting plasma glucose, postprandial plasma glucose, and A_{1c}[1-4]
- Effective as monotherapy or in combination with other oral antihyperglycemics or insulin[5]
- Reduce A_{1c} by -0.66% [95% CI, -0.73% to -0.58%] compared to placebo (45 studies; n=11,232)[5]

Note: Data from single-agent studies only; SGLT2 agents have not been compared in head-to-head trials.

Sources: [1]Bakris GL, et.al. *Kidney Int* 2009;75:1272-77; [2]Bołdys A, Okopień B. *Pharmacol Rep* 2009;61:778-84; [3]Brooks AM. *Ann Pharmacother* 2009;43:1286-93; [4]Polidori D, et al. *Diabetes Care* 2013;36:2154-61; [5]Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74.

SGLT2 Inhibitors: Hypoglycemia Risk

- Insulin-independent mechanism of action
- Low intrinsic capacity to promote hypoglycemia
- Hypoglycemic risk with SGLT2 inhibitors slightly higher than placebo (odds ratio: 1.28) but comparable to that observed with other antihyperglycemics (odds ratio; 1.01) (45 studies; n=11,232)

Note: Absolute risk reflects combination of agents used.

Source: Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74.

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SGLT2 Inhibitors: Pleiotropic Effects

- Significant and potentially long-term weight loss (mean reduction of 1.80 kg [95%CI, -3.50 to 0.11 kg]) (45 trials; n=11,232)[1,2]
- Mild osmotic diuresis[3]
- Significant reduction in systolic BP (weighted mean difference, -4.0 mm Hg; 95% CI, -4.4 to -3.5 mm Hg) and diastolic BP (weighted mean difference, -1.6 mm Hg; [95% CI, -1.9 to -1.3 mm Hg]) (27 trials; n=12,960)[4]

Sources: [1]Peene B, Benhalima K. *Ther Adv Endocrinol Metab* 2014;5:124-36; [2]Vasilakou D, et al. *Ann Intern Med* 2013;159:262-74; [3]Bailey CJ. *Trends Pharmacol Sci* 2011;32:63-71; [4]Baker WL, et al. *J Am Soc Hypertens* 2014;8:262-75.

Integrating SGLT2 Inhibitors into Type 2 Diabetes Management

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Commonly-Used Oral Antihyperglycemic Agents

- Sulfonylureas (SUs)
- Biguanides (metformin)
- Thiazolidinediones (TZDs)
- SGLT2 inhibitors
- Dipeptidyl peptidase-4 (DPP-4) inhibitors

Properties of Oral Antihyperglycemic Agents

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylureas	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
TZDs	• PPAR-γ activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low
SGLT2 inhibitors	• **Inhibits SGLT2 in proximal nephron** • **Increases glucosuria**	• **↓ Weight** • **No hypoglycemia** • **↓ BP** • **Effective at all stages**	• **GU infections** • **Polyuria** • **Volume depletion** • **↑ LDL-C**	**High**

Source: Adapted from slide deck that accompanies Inzucchi SE, et.al. *Diabetes Care* 2015;38:140-49. Available at: http://care.diabetesjournals.org/content/38/1/140/suppl/DC2.

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Integrating SGLT2 Inhibitors into Treatment

- AACE includes SGLT2 inhibitors as monotherapy for patients with $A_{1c} < 7.5\%$ or in combination regimens for patients with $A_{1c} \geq 7.5\%$.[1]
- ADA/European Association for the Study of Diabetes (EASD) recommends SGLT2 inhibitors in combination with metformin (dual therapy) or metformin + SU, TZD, DPP-4 inhibitor, or insulin (triple therapy).[2]

Sources: [1]Garber AJ, et al. *Endocr Pract* 2013;19:327-36; [2]Inzucchi SE, et al. *Diabetes Care* 2015;38:140-49.

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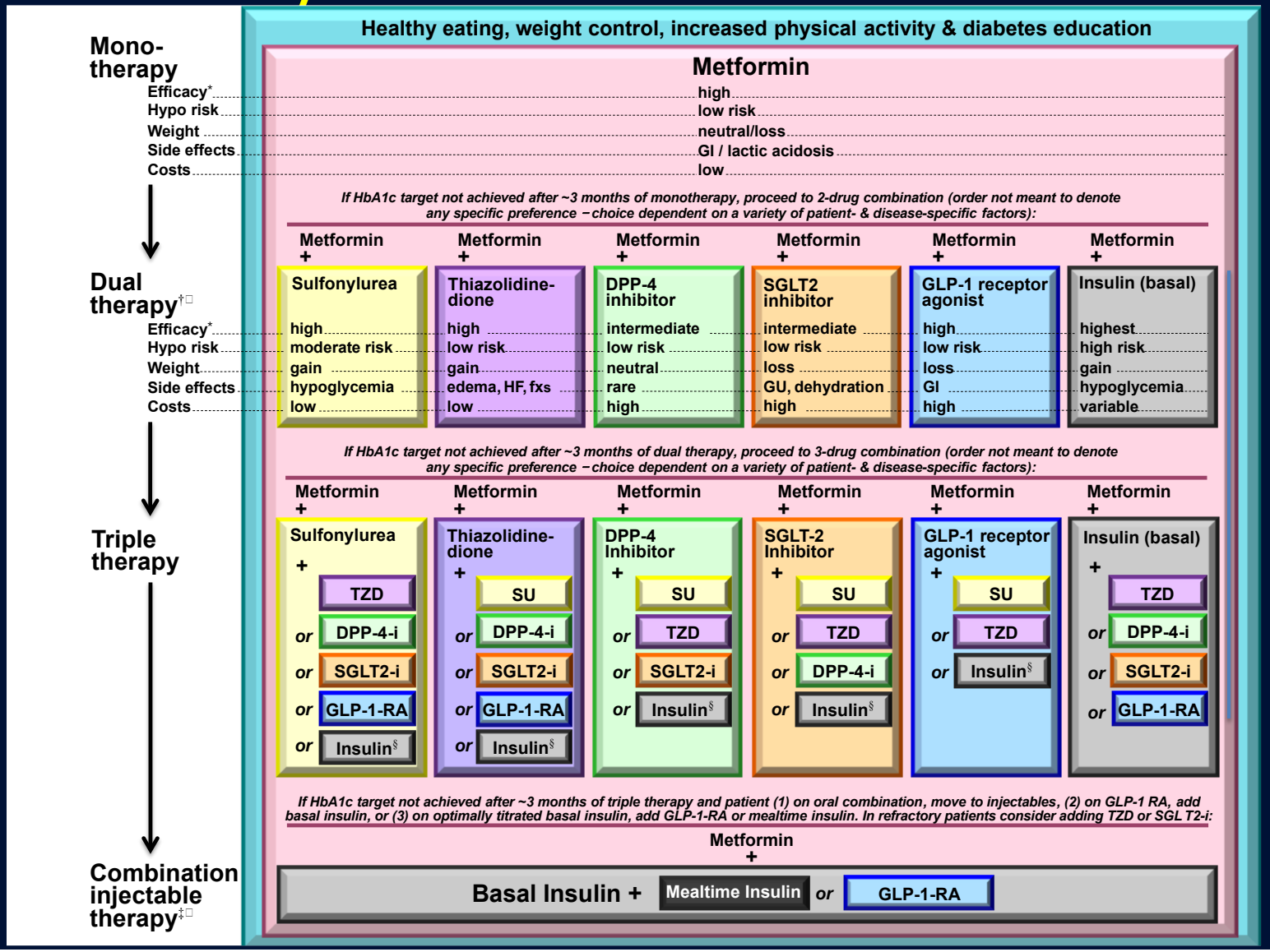
ADA/EASD Recommendations



Source: Slide deck that accompanies Inzucchi SE, et.al. *Diabetes Care* 2015;38:140-49. Available at: http://care.diabetesjournals.org/content/38/1/140/suppl/DC2.

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Shared Decision-Making in Diabetes Management

- Personalized management plan
- Self-management education
- Adherence to treatment
- Appropriate follow-up and monitoring

The ADA/EASD recommendations support a shared decision-making approach that applies to primary care practices.

Source: Inzucchi SE, et al. *Diabetes Care* 2015;38:140-49.

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Management Requires Active Patient Participation

- Maintain daily diet/exercise diary
- Identify/avoid high-risk situations
- Reward success
- Set realistic goals

- Establish a self-management plan based on what the patient feels that he/she can achieve confidently

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Online Resources

Organization	URL
American Diabetes Association	www.diabetes.org
American Academy of Family Physicians	www.aafp.org
American Association of Diabetes Educators	www.diabeteseducator.org
American Association of Clinical Endocrinologists	www.aace.com

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Case Study

Jade

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Case Study: Jade

- 58-year-old African-American with diabetes (BMI = 31 kg/m^2)
- Takes metformin, a statin, an ACE inhibitor, and daily low-dose aspirin
- Wishes to lose weight
- Walks 30 min/day and monitors diet, but gains approximately 3 pounds/year
- Received diabetes education at diagnosis (2 years ago)

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Case Study: Jade

Jade's laboratory workup values include:

- A_{1c}: 8.0%
- Blood pressure: 142/90 mm Hg
- eGFR: 85 mL/min/1.73 m^2
- No signs of volume depletion

Case Study: Jade

1. According to ADA guidelines, which of the following is a reasonable A_{1c} goal for Jade?

a) 5.8%
b) 6.0%
c) 6.5%
d) 7.0%
e) 8.0%

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Case Study: Jade

2. According to the ADA, which classes of agents could be added to metformin to help control Jade's hyperglycemia?

a) DPP-4 inhibitor
b) Sulfonylurea
c) Thiazolidinedione
d) Insulin
e) SGLT2 inhibitor
f) GLP-1 receptor agonist
g) All of the above

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Case Study: Jade

Jade expresses concerns about initiating insulin at this point, given that she is trying to lose weight and that she views insulin therapy as a last-line effort that indicates that she is succumbing to her disease.

Case Study: Jade

3. While you agree that insulin is not strictly necessary at this point in her management, you should use this opportunity to:

a) Tell Jade that she will never need insulin if she meets her A_{1c} goal with oral medications
b) Tell her that she will likely eventually require insulin as part of disease management; it can be considered an option at any point going forward
c) State that insulin is a highly effective treatment; its use will enable her to control her diabetes
d) Agree with her that insulin should be postponed as long as possible, given the emotional toll associated with its use
e) a) and d) only
f) b) and c) only

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Case Study: Jade

4. Jade has expressed a desire to lose weight. Based on this criterion, would an SGLT2 inhibitor be appropriate?

a) Yes; SGLT2 inhibitors are associated with weight loss
b) No; SLGT2 inhibitors have been associated with weight gain
c) Possibly, although the relationship between SGLT2 inhibitors and weight has not been explored in many clinical trials

Case Study: Jade

5. Jade prefers to use an oral agent at this point, so you recommend adding SGLT2 to her regimen of metformin. What SGLT2-specific potential side effects or issues should you discuss with Jade before initiating treatment?

a) Kidney stones
b) Diarrhea
c) Mycotic or urinary tract infection
d) Vomiting
e) Increased urination
f) a), c), and e)
g) c) and e)

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Case Study: Jade

6. Based on the mechanism of action of SGLT2 inhibitors, would you expect Jade to experience significant hypoglycemia with the new regimen?

a) Yes. Because SGLT2 inhibitors promote urinary excretion of glucose, they are associated with increased risk of hypoglycemia, especially in combination with other antihyperglycemic agents.

b) No. The insulin-independent mechanism of action of SGLT2 inhibitors suggests that the agents have a low intrinsic capacity to promote hypoglycemia.

Case Study: Jade

7. Jade calls the office two weeks after initiating SGLT2 treatment, complaining of vaginal itching and discharge. What should you recommend?

a) Discontinue SGLT2 immediately
b) Continue SGLT2 treatment, treat the infection topically for a week with an over-the-counter medication, and follow-up
c) Recommend that she come to the office immediately for glucose monitoring

Case Study: Jade

Going forward, you should consider the following with Jade:

- Arrange for her to receive counseling from a Certified Diabetes Educator and dietitian
- Schedule a follow-up visit in three months
- Advise her that increased urinary volume is to be expected and that she stay hydrated.

Conclusions

- Type 2 diabetes is a progressive disorder that affects numerous organs and tissues.
- Achieving glycemic control is essential to manage diabetes and its complications.
- Management may require multiple antihyperglycemic agents with complementary mechanisms of action.
- SGLT2 inhibitors are a new class of oral agents that reduce renal glucose reabsorption independently of insulin.
- SGLT2 inhibitors do not promote hypoglycemia and are associated with weight loss and reduction in blood pressure.

Questions

To learn more about SGLT2 Inhibitors and earn additional CME credit visit

http://www.njafp.org/learning-groups

Scroll down to *Type 2 Diabetes Management: A New Therapeutic Option in Primary Care, SGLT2 Inhibition* *and click on the link*

Don't forgot to complete your evaluation and claim credit. Return the completed form to a staff member.

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