The Emerging Role of SGLT Inhibitors in Individualized Treatment of T2DM

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Learning Objectives

- Define individual T2DM and cardiovascular disease targets
- Establish patient targets for the "ABCs": **A**$_{1C}$, **B**lood pressure, and **C**holesterol
- Explain the rationale for targeting renal glucose transport, and interpret related clinical data and the potential role of SGLT2 inhibition in personalized T2DM therapies
- Distinguish the potential differences among new SGLT2 inhibitors and discuss the clinical implications of these differences on appropriate patient selection

Glucose Homeostasis

Euglycemia

Hypoglycemia

- Cognitive impairment
- Seizure
- Coma
- Brain death
- Arrhythmia
- Heart attack
- Palpitations

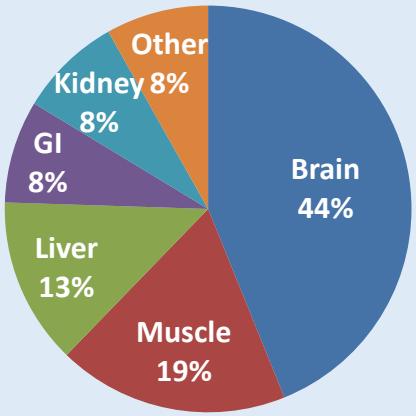
Hyperglycemia

- CV disease
- Retinopathy
- Neuropathy
- Nephropathy
- Glucotoxicity

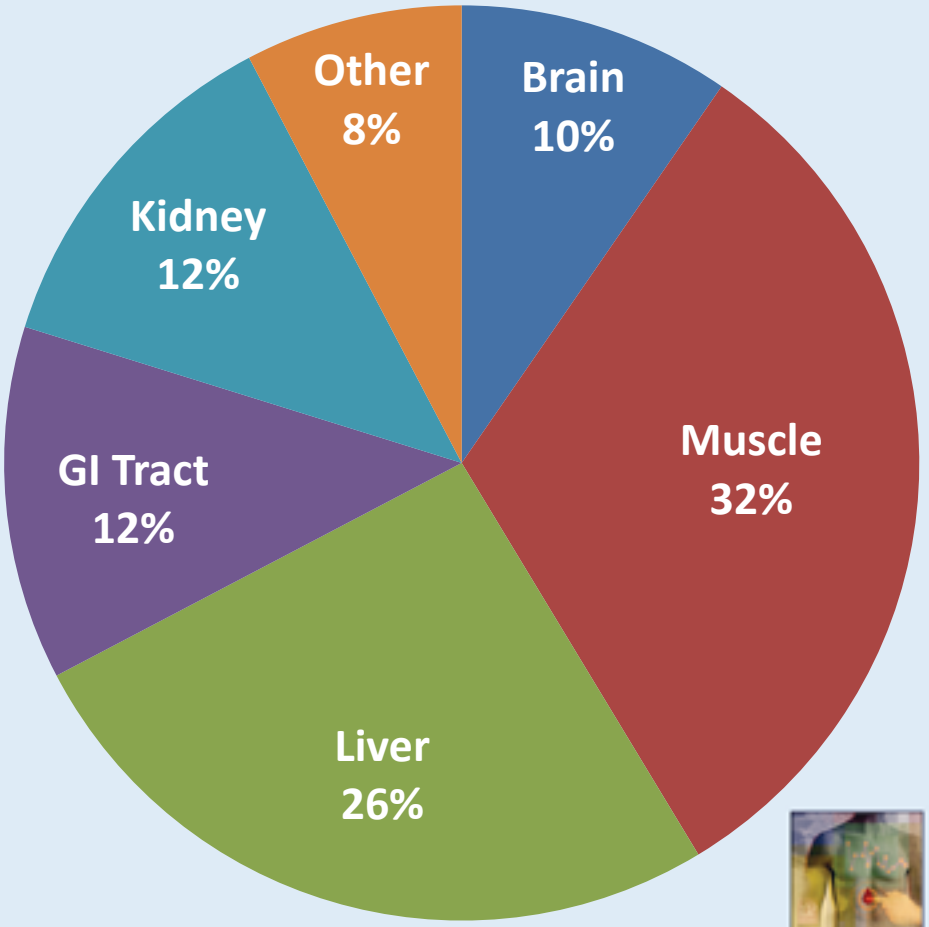
Adapted from CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes.* 2008;32(suppl 1):S1-S201.

Contribution of Tissues to Glucose Uptake

Postabsorptive State
2 mg/Kg/min
(mainly insulin independent)



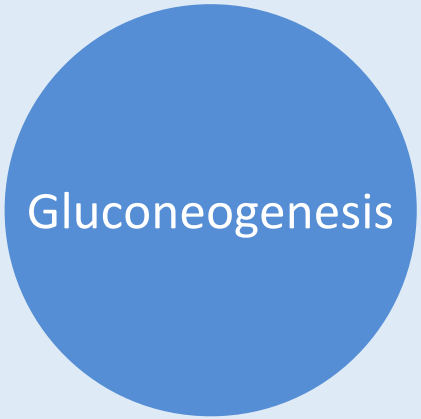
Postprandial State
10 mg/Kg/min
(mainly insulin stimulated)



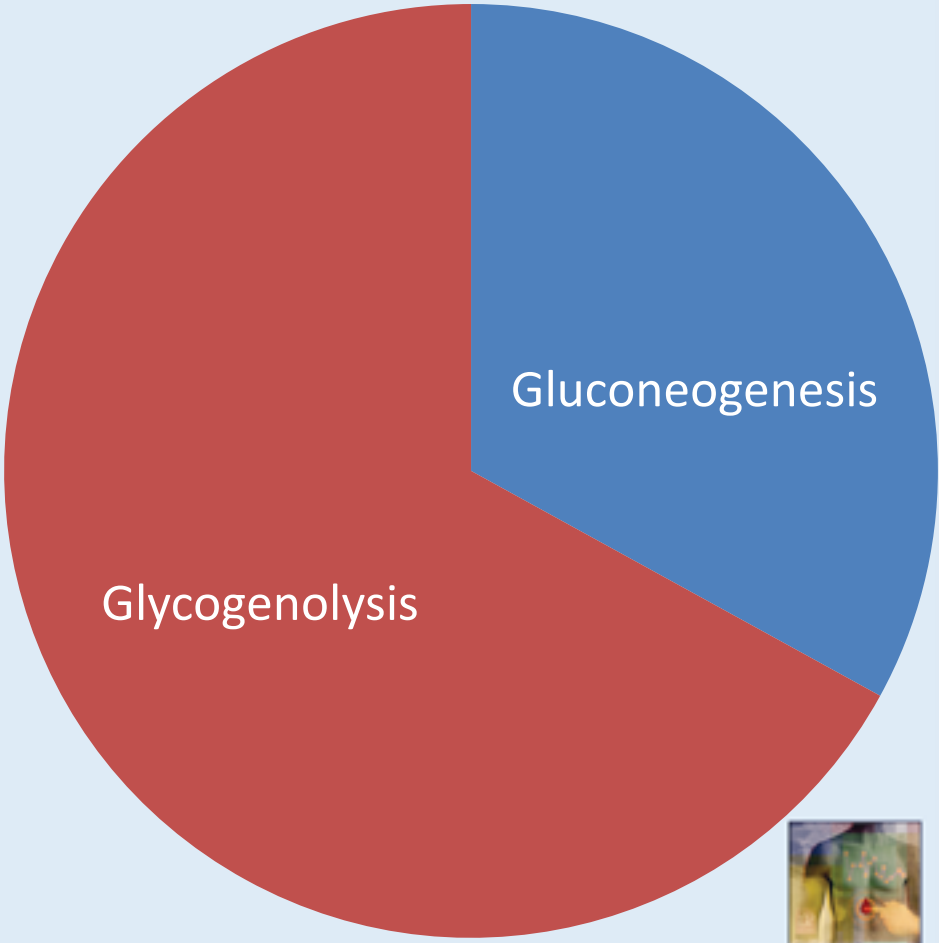
Gerich JE. *Diabet Med*. 2010;27(2):136-142.

Contribution of Tissues to Fasting Plasma Glucose

Kidney
20%

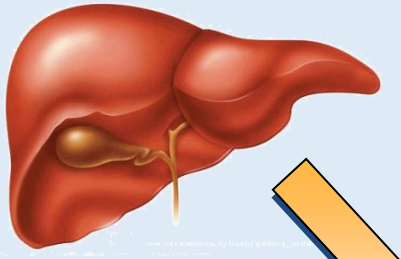


Liver
80%

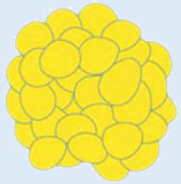


Gerich JE. *Diabet Med*. 2010;27(2):136-142.

Multiple Therapies for Type 2 Diabetes



Metformin
Insulin

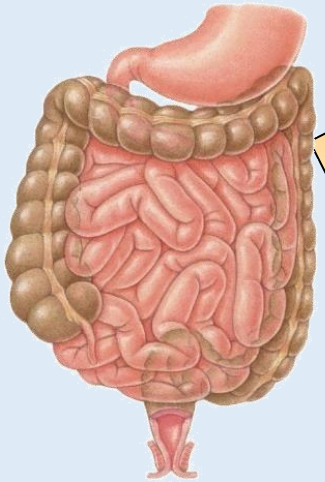


Thiazolidinediones
Insulin

α-glucosidase
inhibitors

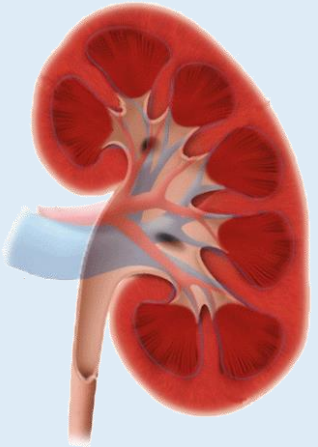
Reduce
Hyperglycemia

SGLT2 Inhibitors
Insulin



GLP-1 analogues
DPP-4 inhibitors

Sulfonylureas
Glitinides



GLP = glucagon-like peptide;
DPP = didpeptidyl peptidase

Diabetes Drugs Impact Multiple Endpoints

Drug	BW	Hyper-tension	Dys-lipidemia	Hypoglycemia Risk
α-glucosidase inhibitors	Neutral	Improved	Neutral/ Improved	Low
DPP-4 inhibitors	Loss/Neutral	Neutral	Improved	Low
GLP-1 agonists	Loss	Improved	Improved	Low
Insulin	Gain	Neutral*	Improved	High
Meglitinides	Gain	Neutral	Neutral	Moderate
Metformin	Loss/Neutral	Neutral	Improved	Low
SGLT2 inhibitors	Loss	Improved	?	Low
Sulfonylureas	Gain	Neutral	Variable	Moderate
TZD	Gain	Improved	Improved	Low

*Hyperinsulinemia is associated with hypertension

Basile JN. *J Diabetes Complications*. 2013;27(3):280-286.

Learning Objectives

- **Define individual T2DM and cardiovascular disease goals**
- Formulate a patient management strategy that targets the "ABCs": A_{1C}, Blood pressure, and Cholesterol
- Explain the rationale for targeting renal glucose transport, and interpret related clinical data and the potential role of SGLT2 inhibition in individualized T2DM therapies
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Treatment Goals: ABCs of Diabetes

- **HbA_{1c}**
  - < 7 % for many people
  - Preprandial capillary plasma glucose 70–130 mg/dl
  - Peak postprandial (1-2 hours) capillary plasma glucose < 180 mg/dl
- **Blood pressure (mmHg)**
  - Systolic < 140 for most people
  - Diastolic < 80 (< 90 per Joint National Committee-8 2014 guideline)

Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379.
http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=114. Accessed Nov 2013.
James PA, et al. *JAMA*. 2013 Dec 18. [Epub ahead of print]. http://jama.jamanetwork.com. Accessed Dec 2013.
American Diabetes Association. *Diabetes Care.* 2014; 37:S14-S80.

Treatment Goals: ABCs of Diabetes (cont.)

- **Cholesterol – Lipid Profile (mg/dl)**
  - LDL Cholesterol < 100
    - LDL < 70 with overt CVD
  - HDL Cholesterol Men > 40, Women > 50
  - Triglycerides < 150

Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379.
http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=114. Accessed Nov 2013.
James PA, et al. *JAMA*. 2013 Dec 18. [Epub ahead of print]. http://jama.jamanetwork.com. Accessed Dec 2013.
American Diabetes Association. *Diabetes Care.* 2014; 37:S14-S80.

Impact of ABC Control

Overview

- **Glucose Control**
  - Benefits both type 1 or type 2 diabetes
  - Every point drop in HbA_{1C} reduces risk of complications
    - Microvascular 40% lower
    - Macrovascular 16% lower
- **Blood Pressure Control**
  - Reduces the risk of CV disease by 33 to 50%
  - Reduces the risk of microvascular complications by about 33%
  - A 10 mmHg reduction in systolic BP reduces the risk for any complication related to diabetes by 12 percent
  - Systolic BP goal < 140 mmHg based on expert opinion

NIDDK National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics, 2011. http://diabetes.niddk.nih.gov/dm/pubs/statistics/#pdc. Accessed Nov 2013.

Impact of ABC Control

Overview (cont.)

- **Control of Blood Lipids**
  - Improved control of LDL can reduce CV complications by 20 to 50%

NIDDK National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics, 2011. http://diabetes.niddk.nih.gov/dm/pubs/statistics/#pdc. Accessed Nov 2013.

BP Intervention Trials in T2DM

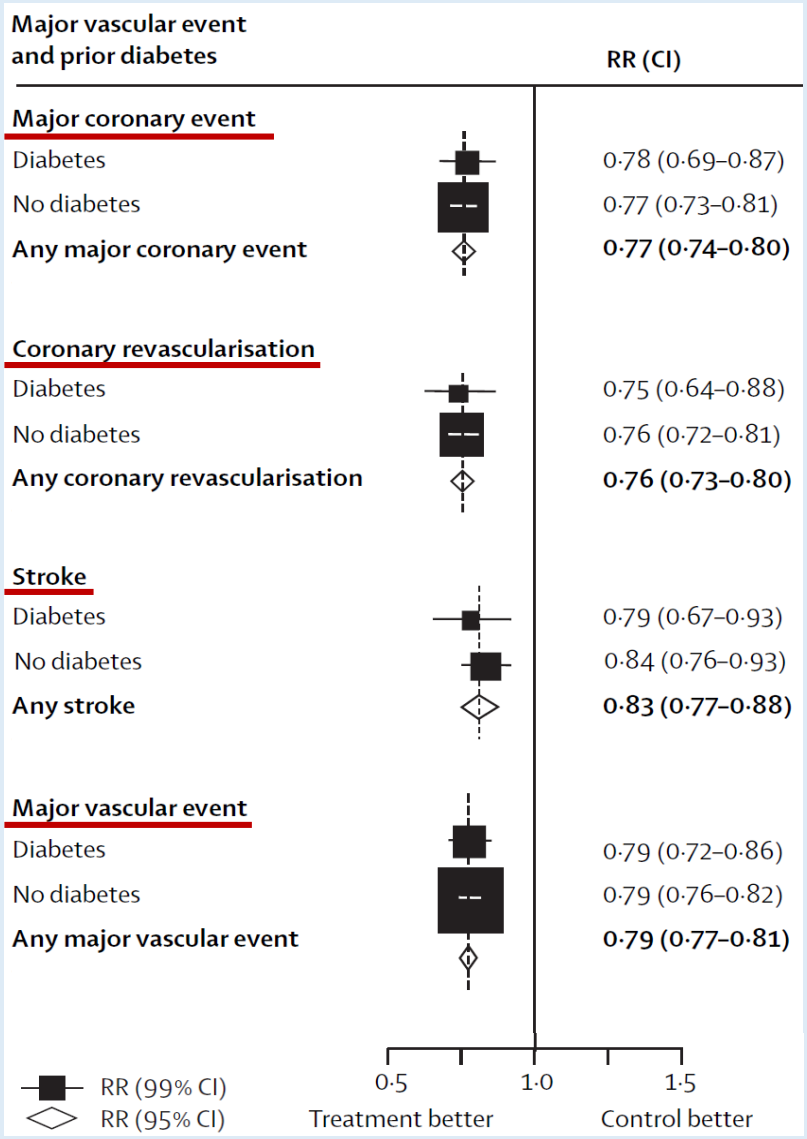
UKPDS

- Tight SBP (target < 150 mmHg) vs standard (< 180)
- Adults with new diagnosis of T2DM (mean age 46 at 10 y follow-up)
- No reductions in
  - Stroke
  - MI
  - All-cause mortality
- Reduced peripheral vascular disease during trial
- Improvements not sustained after relaxation of BP control

Holman RR, et al. *N Engl J Med.* 2008;359:1565-1576.

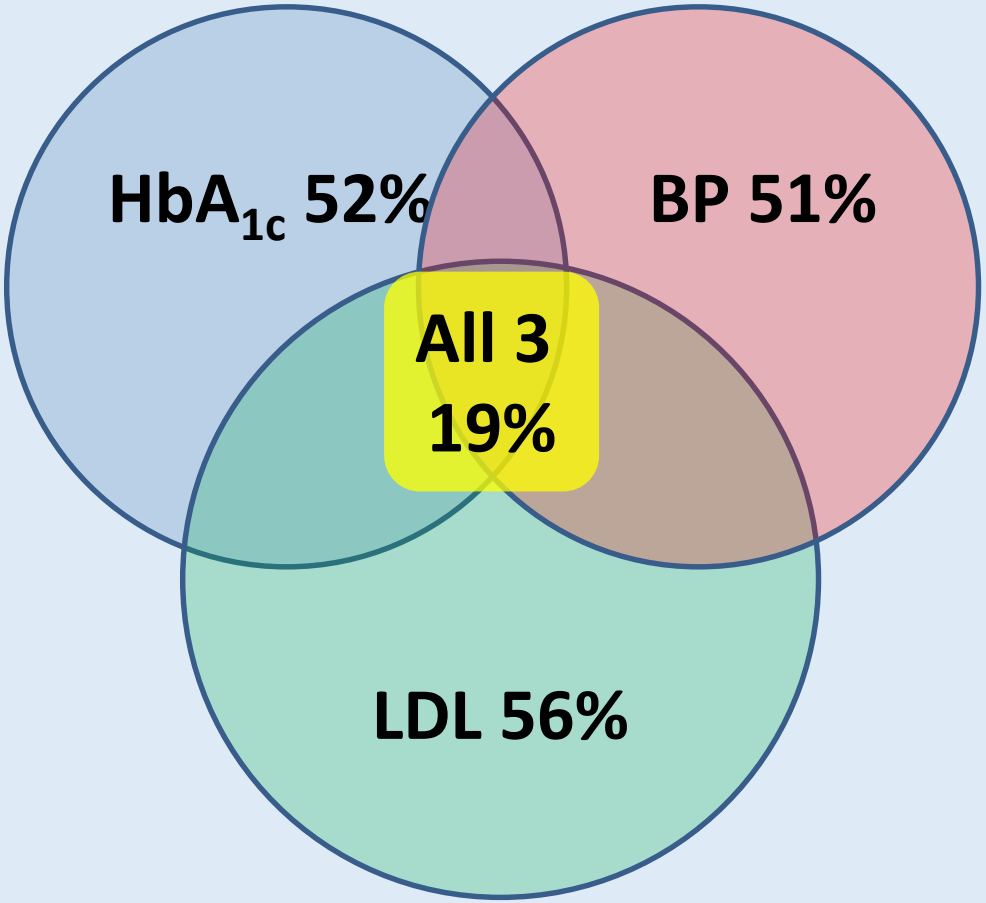
Impact of LDL Control

- Meta-analysis of statin trials
  - 14 randomized trials
  - 17,220 patients with T2DM
  - 71,370 patients without diabetes
- All-cause mortality reduced with statin treatment (per mmol/L)
  - Diabetes: 9% ($P = 0.02$)
  - No diabetes: 13% ($P < 0.0001$)



Kearney PM, et al. *Lancet.* 2008;371(9607):117-125.

Diabetes Patients at Goal



Stark Casagrande S, et al. *Diabetes Care*. 2013;36(8):2271-2279.
Ali MK, et al. *N Engl J Med*. 2013;368(17):1613-1624.

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- **Formulate a patient management strategy that targets the "ABCs": A_{1C}, Blood pressure, and Cholesterol**
- Explain the rationale for targeting renal glucose transport, and interpret related clinical data and the potential role of SGLT2 inhibition in individualized T2DM therapies
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Considerations for Patient Management

- Where is the patient now?
- What are the goals for this patient?
- What are the specific approaches to A, B, and C?
- Monitoring and office visit frequency

Considerations for Patient Management (cont.)

- How is this patient special?
  - Multiple medications/interactions
  - Efficacy of current medications
  - Side effects experienced
  - Adherence
    - Willingness to take medications
    - Cognitive state
    - Support
    - Cost
    - Pill burden/needle aversion
    - Side effect tolerance

Diabetes Management Schedule

	Each Visit	Quarterly	Annually
Weight and BP	X		
Foot exam	X		
Smoking cessation and alcohol use	X		
Review medications	X		
Self management: glucose monitoring, diet, physical activity	X		
Assess for depression/mood disorder	x		
HbA_{1c}		X	
Lipids, serum creatinine, urine albumin/creatinine ratio			X
Eye, foot, dental exams			X
Influenza vaccination			X

http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=114. Accessed Dec 2013.

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Role of the Kidney in Glucose Metabolism

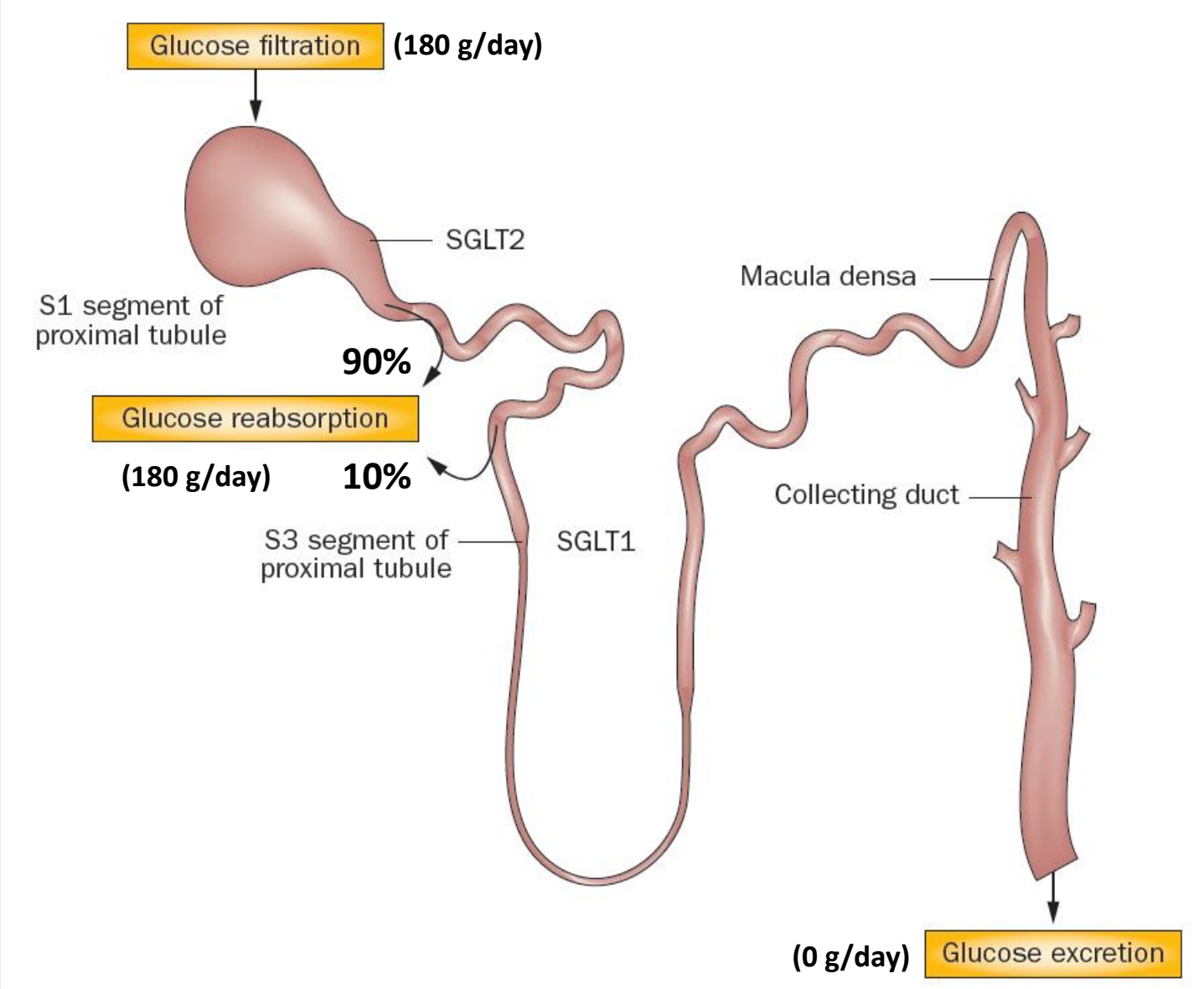
Production

Utilization

Reabsorption

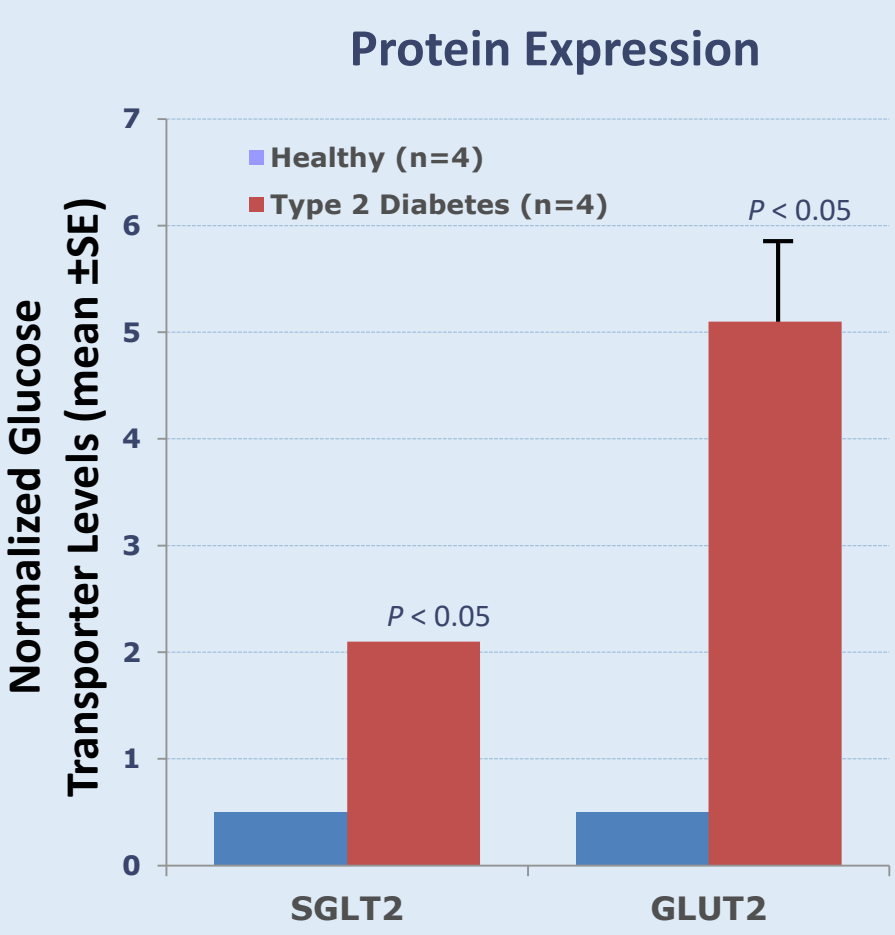
Wright EM, et al. *J Intern Med*. 2007;261(1):32-43.

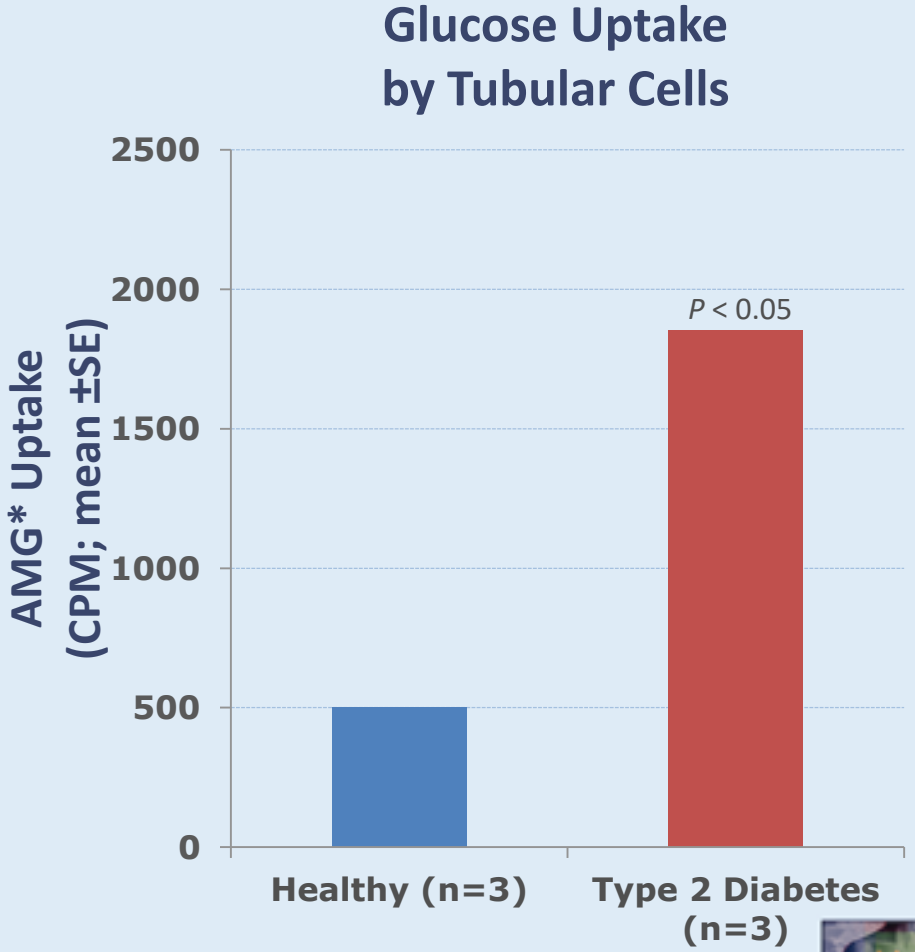
Glucose: From Blood to Urine



Ferrannini E, Solini A. *Nat Rev Endocrinol*. 2012;8:495-502.

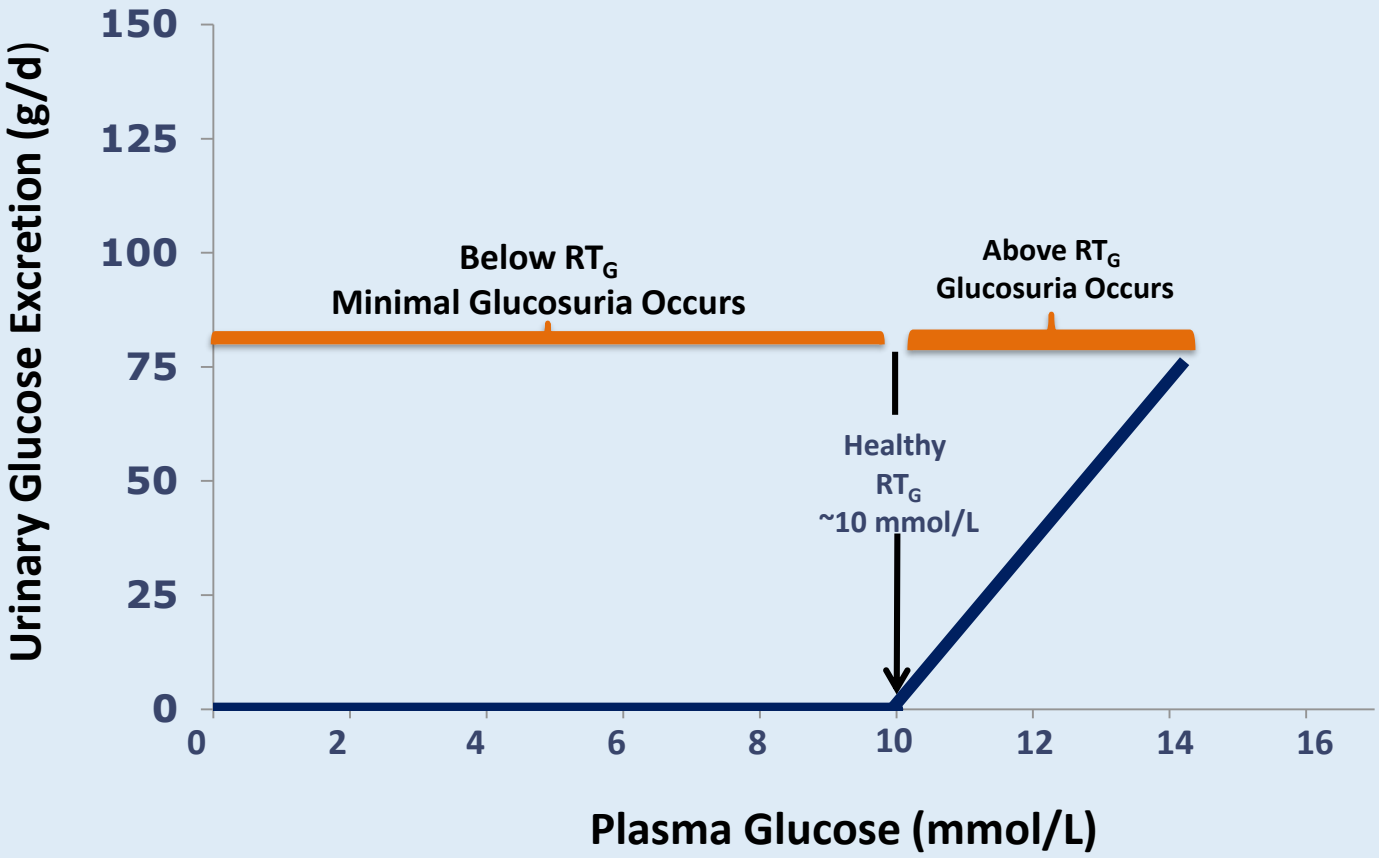
Upregulation of SGLT2 Transporter and Enhanced Cellular Glucose Uptake in Type 2 Diabetes





Rahmoune H, et al. *Diabetes.* 2005;54(12):3427-3434.

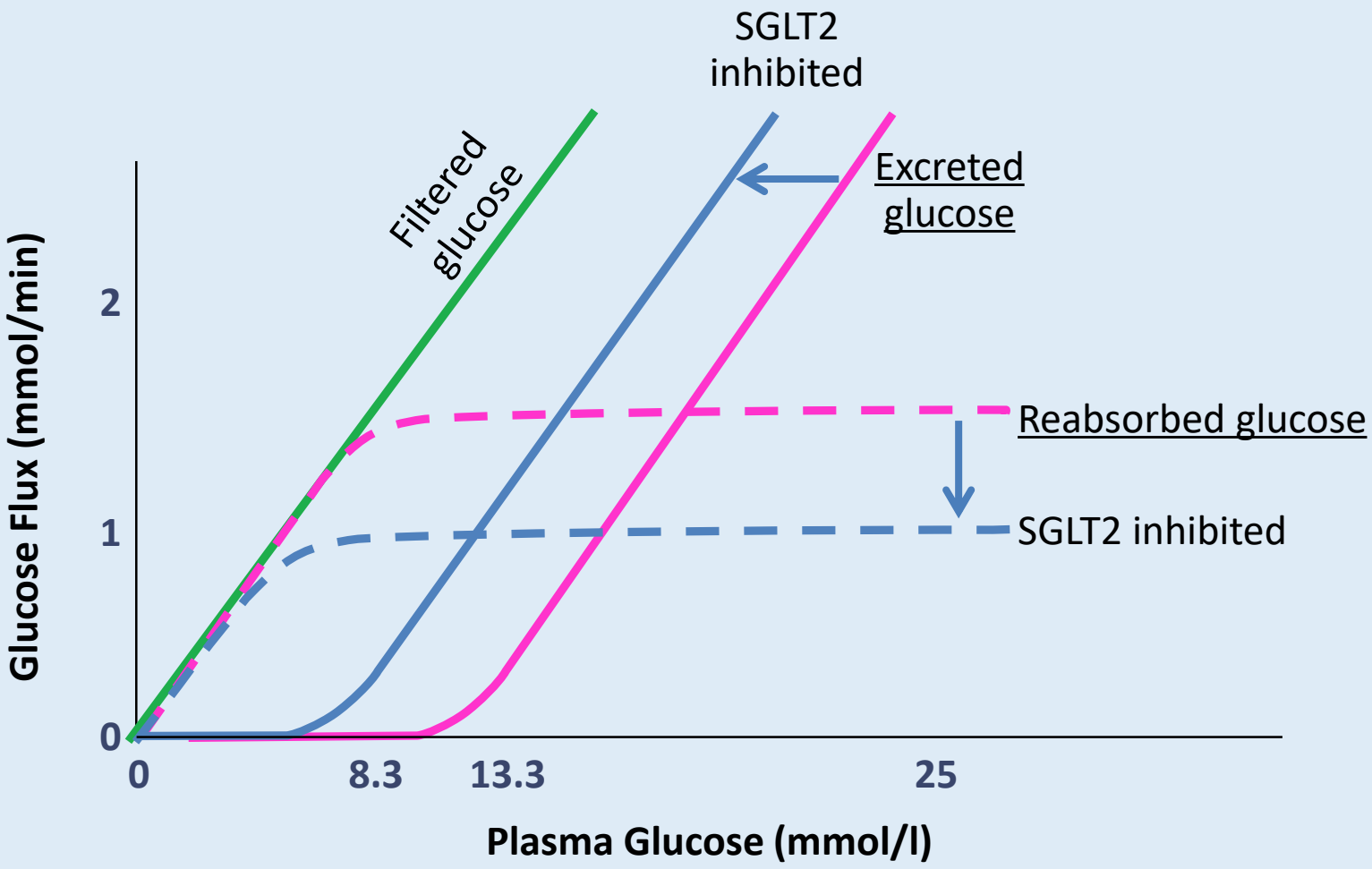
The Renal Glucose Threshold (RT_G) Concept in Healthy Subjects



Adapted from:

1. Guyton AC, Hall JE. *Textbook of Medical Physiology*. 11th ed. Philadelphia, PA: Elsevier Saunders; 2006.
2. DeFronzo RA, et al. *Diab Obes Metab.* 2012;14:5-14.

Renal Glucose Re-Absorption

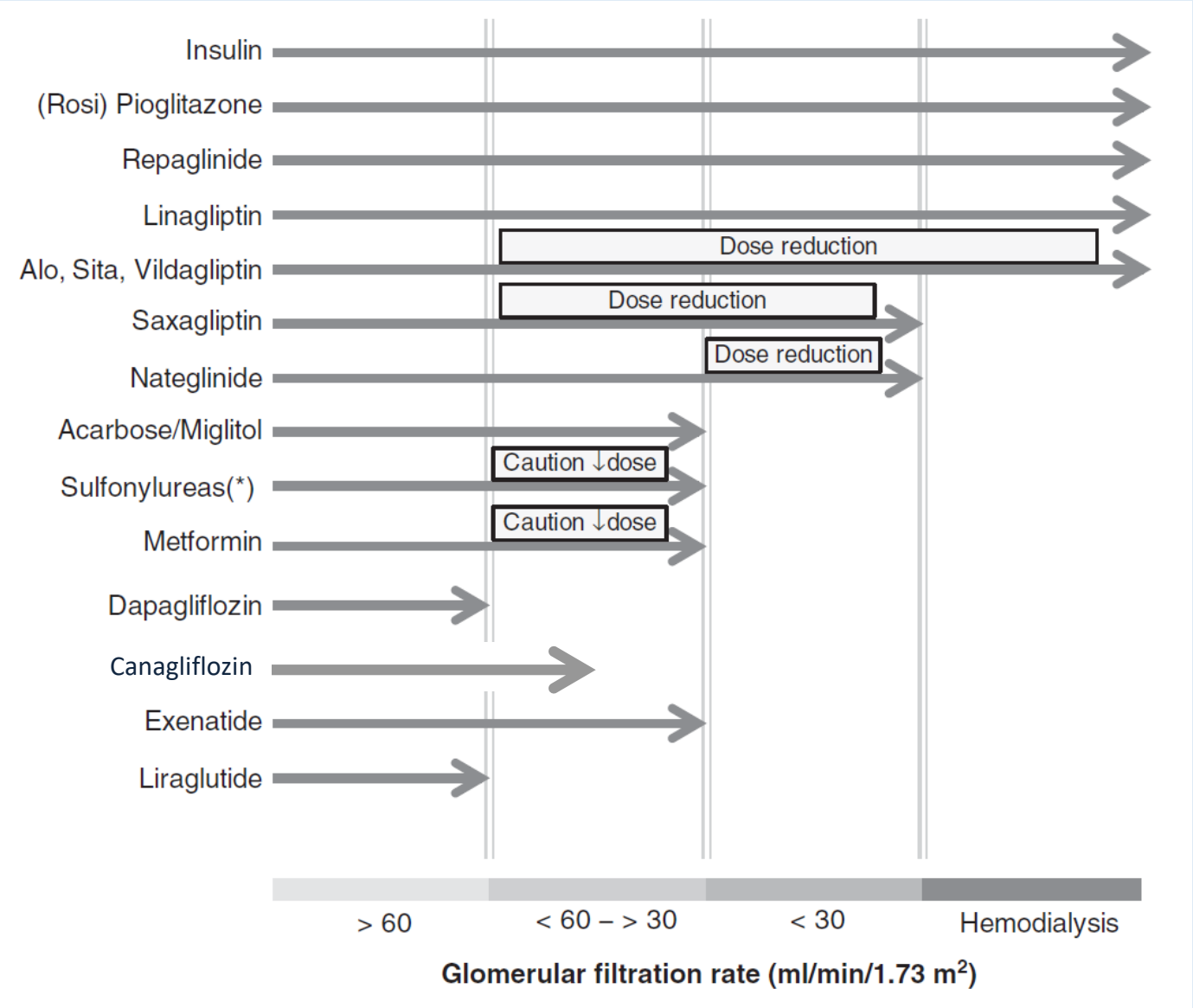


Nair S, Wilding JPH. *J Clin Endocrinol Metab*. 2010;95(1):34-42.

Renal Reuptake Summary

- In type 2 diabetes, enhanced renal glucose reabsorption contributes to hyperglycemia
- The glucose transporter SGLT2 is responsible for 90% of this glucose reabsorption
- Inhibition of SGLT2 will
  - Decrease glucose reabsorption
  - Increase urinary glucose excretion
- Predict weight loss and reduction in blood pressure

Renal Impairment Restricts Diabetes Options



Adapted from Scheen AJ. *Expert Opin Drug Metab Toxicol*. 2013;9(5):529-550.

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Weighing SGLT2 Inhibition

Potential Benefits

- HbA_{1c} lowering
- Mechanism complementary to other therapies
- Improved beta cell function
- Weight loss
- Reduced blood pressure
- Renal protection?

Potential Risks

- Vaginitis, balanitis
- Hypovolemia symptoms
- Increased LDL
- Polyuria
- Hyperkalemia

Regulatory Status of SGLT2 Inhibitors

- **Canagliflozin:** Approved in United States 2013
  Approved in Europe 2013
- **Dapagliflozin:** Approved in United States 2014
  Approved in Europe 2012
- **Empagliflozin:** Application submitted to EMA and FDA 2013
  Approval likely in 2014

Taylor SR, et al. *Pharmacotherapy.* 2013;33(9):984-999.

SGLT2 Inhibitors Reduce HbA_{1c}

Monotherapy

		Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	-1.14% vs placebo	8.0%
• Dapagliflozin[2] – 24 weeks, 10 mg	-0.66% vs placebo	7.82%
• Empagliflozin[3] – 90 weeks open label, 25 mg	-0.47% vs baseline	7.99%
• Ipragliflozin[4] – 12 weeks, 300 mg	-0.81% vs placebo	7.90%

1. Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15:372-382.
2. FDA Background Document Dapagliflozin. www.fda.gov. Accessed Jan 2014.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.
4. Fonseca VA, et al. *J Diabetes Complications.* 2013;27(3):268-273.

SGLT2 Inhibitors Reduce HbA_{1c}

Added to Metformin

		Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	-0.77% vs placebo	8.0%
• Dapagliflozin[2] – 52 weeks, up to 10 mg	-0.52% vs baseline	7.69%
• Empagliflozin[3] – 90 weeks open label, 25 mg	-0.63% vs baseline	7.89%
• Ipragliflozin[4] – 12 weeks, 300 mg	-0.48 % vs placebo	7.87%

1. Lavalle-González FJ, et al. *Diabetologia*. 2013;56(12):2582-2592.
2. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.
4. Wilding JP, et al. *Diabetes Obes Metab*. 2013;15(5):403-409.

SGLT2 Inhibitors Reduce Body Weight

Monotherapy

		Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	-2.9 kg vs placebo	86.9 kg
• Dapagliflozin[2] – 24 weeks, 10 mg	-0.97 kg vs placebo	94.1 kg
• Empagliflozin[3] – 90 weeks open label, 25 mg	-2.61 kg vs baseline	83.5 kg
• Ipragliflozin[4] – 12 weeks, 300 mg	-1.67 kg vs placebo	86.7 kg

1. Stenlöf K, et al. Diabetes Obes Metab. 2013;15:372-382.
2. Forxiga Summary of Product Characteristics. http://www.ema.europa.eu. Accessed Jan 2014.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.
4. Fonseca VA, et al. *J Diabetes Complications.* 2013;27(3):268-273.

SGLT2 Inhibitors Reduce Body Weight

Added to Metformin

		Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	-2.9 kg vs placebo	85.4 kg
• Dapagliflozin[2] – 24 weeks, 10 mg	-2.08 kg vs placebo	88.4 kg
• Empagliflozin[3] – 90 weeks open label, 25 mg	-4.03 kg vs baseline	89.7 kg
• Ipragliflozin[4] – 12 weeks, 300 mg	-1.73 kg vs placebo	89.3 kg

1. Lavalle-González FJ, et al. *Diabetologia*. 2013;56(12):2582-2592.
2. Bolinder J, et al. *J Clin Endocrinol Metab*. 2012;97(3):1020-1031.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.
4. Wilding JP, et al. *Diabetes Obes Metab*. 2013;15(5):403-409.

SGLT2 Inhibitors Reduce SBP

Monotherapy

	All in mmHg:	Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	-5.4 vs placebo	128.5
• Dapagliflozin[2] – 12 weeks, 10 mg	-8.3 vs placebo	141
• Empagliflozin[3] – 90 weeks open label, 25 mg	-1.7 vs baseline	131.9
• Ipragliflozin[4] – 12 weeks, 300 mg	-2.6 vs baseline	Not Available (NA)

1. Stenlöf K, et al. Diabetes Obes Metab. 2013;15:372-382.
2. Lambers Heerspink HJ, et al. *Diabetes Obes Metab*. 2013;15(9):853-862.
3. Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.
4. Fonseca VA, et al. *J Diabetes Complications.* 2013;27(3):268-273.

SGLT2 Inhibitors Reduce SBP

Added to Metformin

	All in mmHg:	Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	-6.6 vs placebo	128.7
• Dapagliflozin[2] – 24 weeks, 10 mg	-2.8 vs placebo	135.9
• Empagliflozin[3] – 12 weeks, 25 mg	-6.3 vs placebo	135.3
• Ipragliflozin[4] – 12 weeks, 300 mg	-4.3 vs placebo	NA

1. Lavalle-González FJ, et al. *Diabetologia*. 2013;56(12):2582-2592.
2. Bolinder J, et al. *J Clin Endocrinol Metab*. 2012;97(3):1020-1031.
3. Rosenstock J, et al. *Diabetes Obes Metab*. 2013;15(12):1154-1160.
4. Wilding JP, et al. *Diabetes Obes Metab*. 2013;15(5):403-409.

SGLT2 Inhibitors Increase LDL

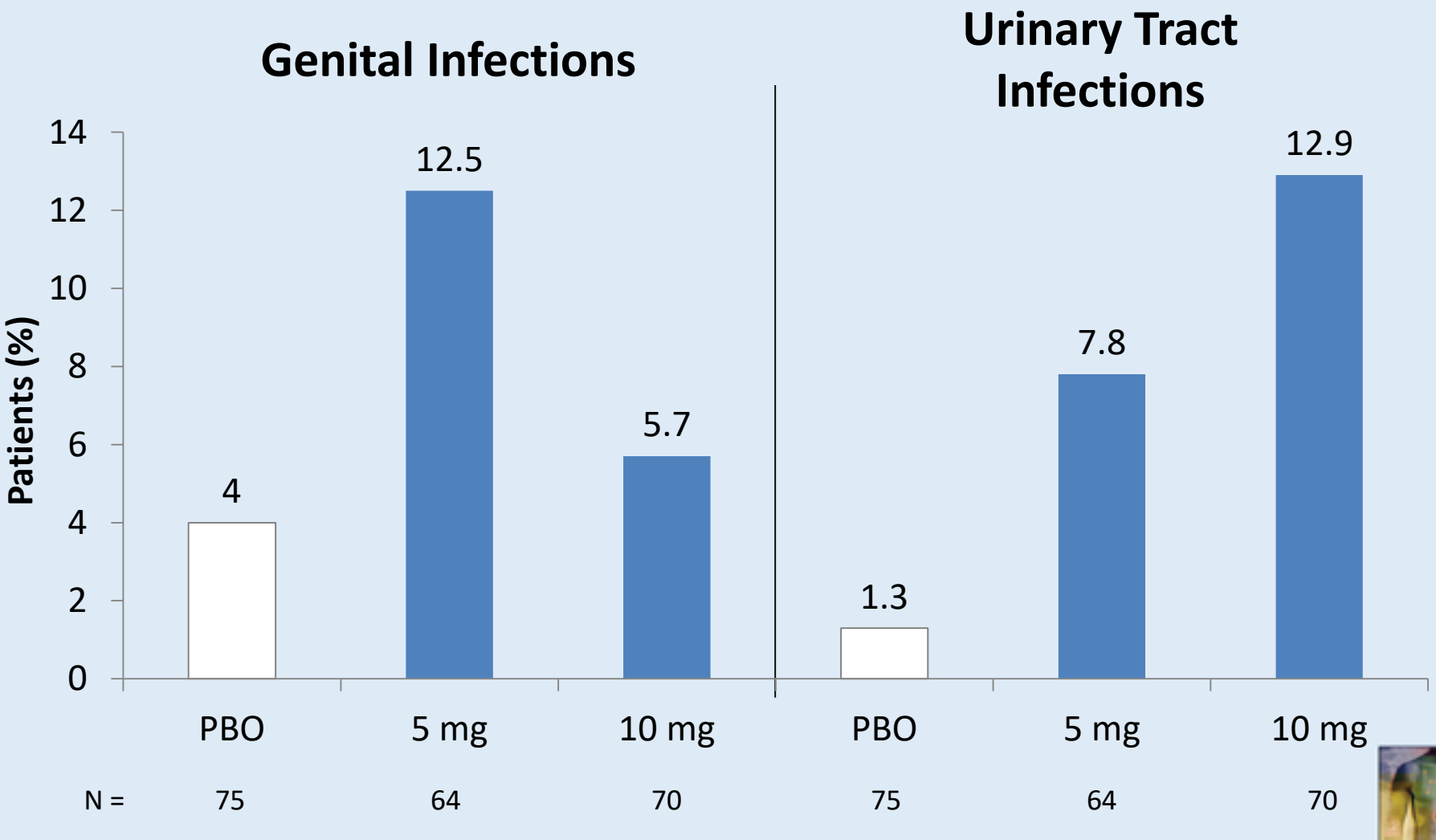
Monotherapy

	All in mg/dL:	Treatment Group Baseline
• Canagliflozin[1] – 26 weeks, 300 mg	↑ +8.2 vs placebo	112
• Dapagliflozin[2] – 24 weeks, 10 mg	↑ +3.7 vs placebo	NA
• Empagliflozin[3] – 12 weeks, 25 mg	↑ +2.7 vs placebo	66

1. Canagliflozin Prescribing Information. http://www.accessdata.fda.gov.
2. FDA Background Document Dapagliflozin. www.fda.gov. Accessed Jan 2014.
3. Rosenstock J, et al. *Diabetes Obes Metab*. 2013;15(12):1154-1160.

Dapagliflozin: Infections

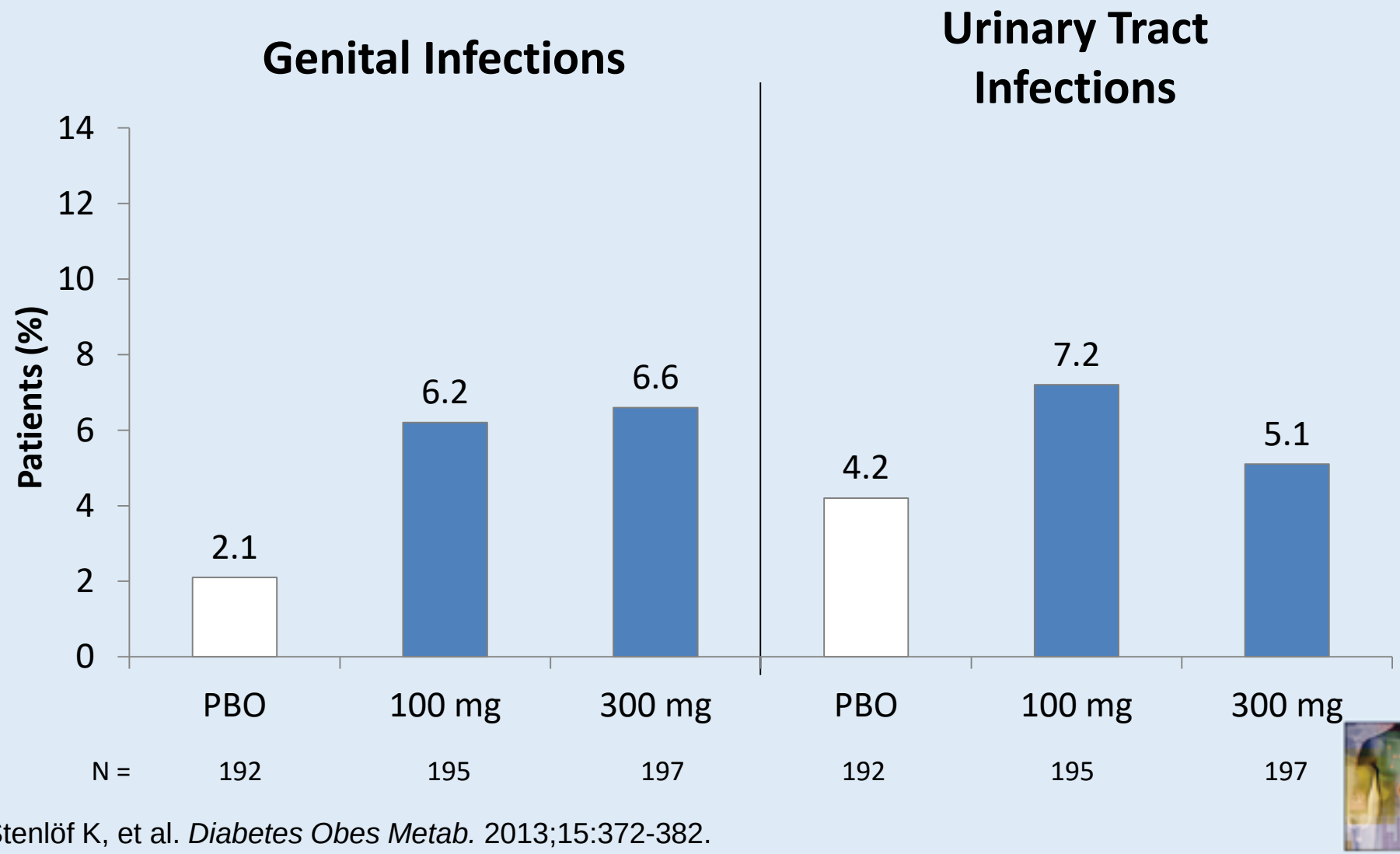
Monotherapy, 24 weeks



Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-2224.

Canagliflozin: Infections

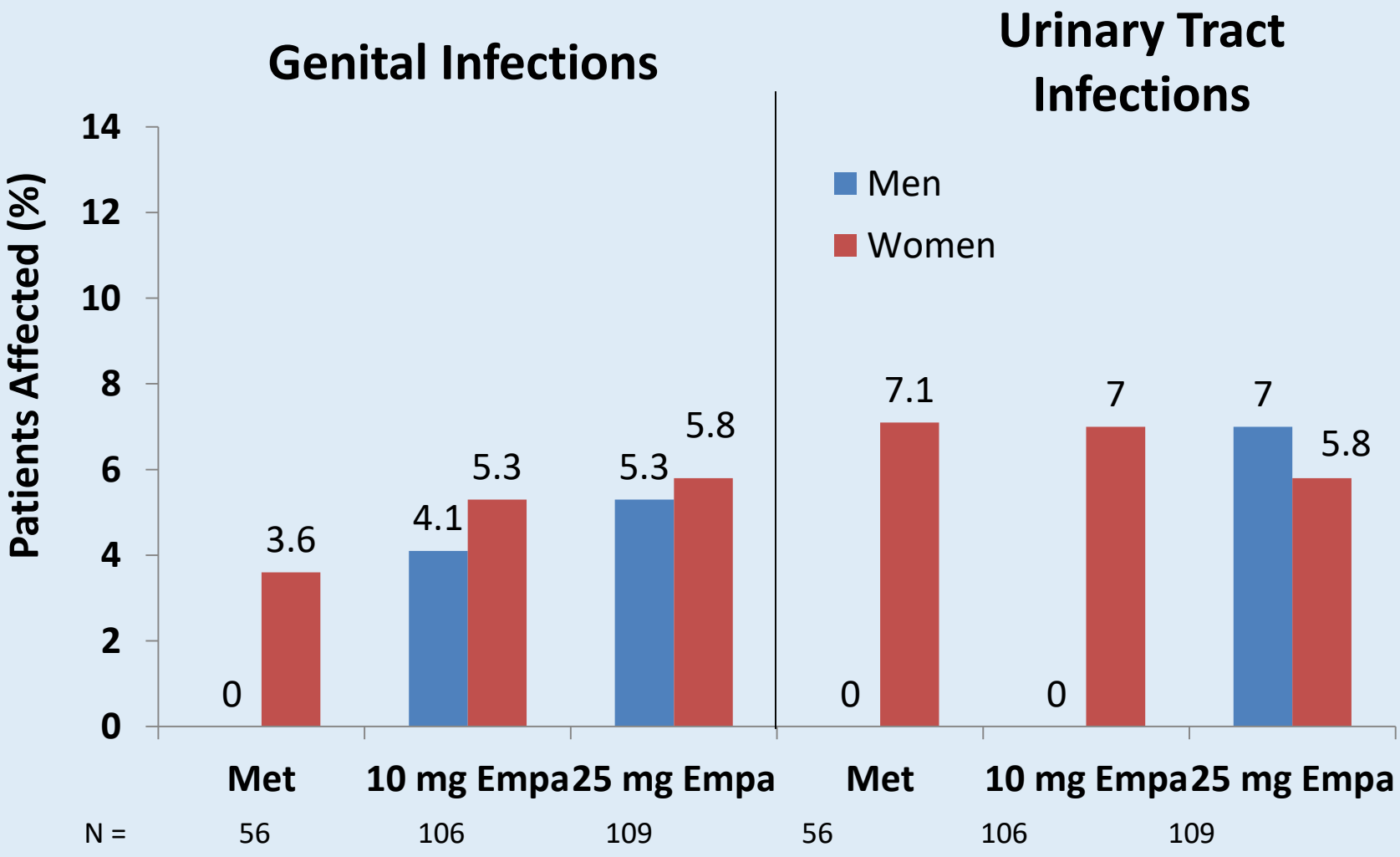
Monotherapy, 26 weeks



Stenlöf K, et al. *Diabetes Obes Metab.* 2013;15:372-382.

Empagliflozin: Infections

78 Week Open Label Extension Study



Ferrannini E, et al. *Diabetes Care*. 2013;36(12):4015-4021.

SGLT2 Inhibitors: Adverse Events

- Increased genital mycotic infection
  - 2% to 8% excess over placebo
- Bacterial urinary tract infections
  - 1% to 12% excess over placebo
  - No observed episodes of pyelonephritis or urosepsis
- Infections were manageable and rarely led to discontinuation of treatment
  - Managed with standard antimycotic creams and hygienic measures

Ferrannini E, et al. *Diabetes Obes Metab*. 2013;15(8):721-728.
Fonseca V, et al. *J Diabetes Complications*. 2013;27:268-273.
Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022.
Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15:372-382.
Wilding JPH, et al. *Diabetes Obes Metab*. 2013;15:403-409.

SGLT2 Inhibition as a Treatment for Diabetes

- Efficacy
  - Reduction in HbA_{1C} of 0.5% to 1.0%
  - Weight reduction of ~3 kg
  - Reduction in systolic BP of 3 to 5 mmHg
  - Effective as monotherapy and in combination
- Safety
  - Little or no risk of hypoglycemia
  - Increased risk of mycotic genital infections
  - Uncommon hyperkalemia in select populations
    - Elderly
    - ACE inhibitors
    - ARB
    - Diuretic
- Side Effects
  - Polyuria
  - Transient mild hypotension

Clinical Outcome: MACE

CV Death, MI, Stroke

- Canagliflozin[1] HR = 0.91
- Dapagliflozin[2] HR = 0.77

1. Canagliflozin FDA Advisory Committee Meeting. January 10, 2013.
2. FDA Background Document Dapagliflozin. www.fda.gov. Accessed Jan 2014.

Summary

- Glucose, lipid, and blood pressure control are all important in managing patients with diabetes
  - Less than 20% of patients are at goal for all 3
- Glucose reuptake in the kidney is a new mechanism for managing hyperglycemia
- Drugs that inhibit SGLT2 have positive effects on

  A: HbA_{1c}

  B: blood pressure

  And body weight!
- Lipid effects vary with inhibitor, class effect not clear
- SGLT2 inhibitors may impact CV events
- Major adverse effect is increased genital infection