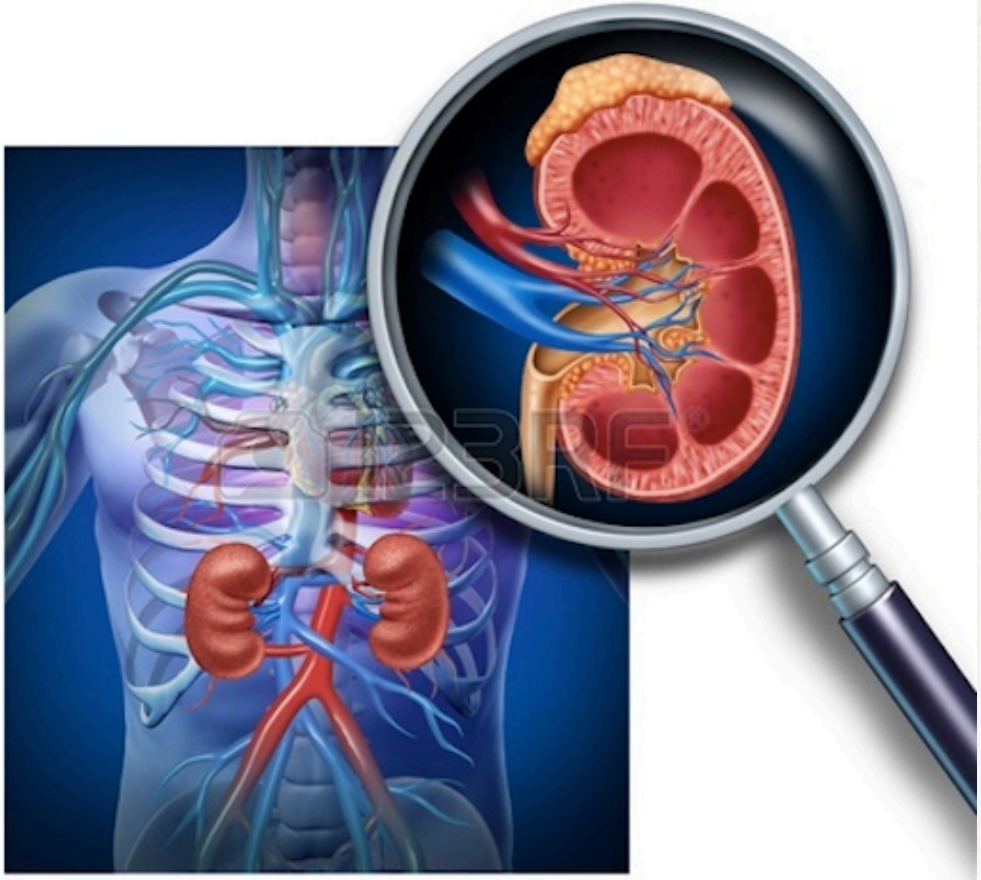
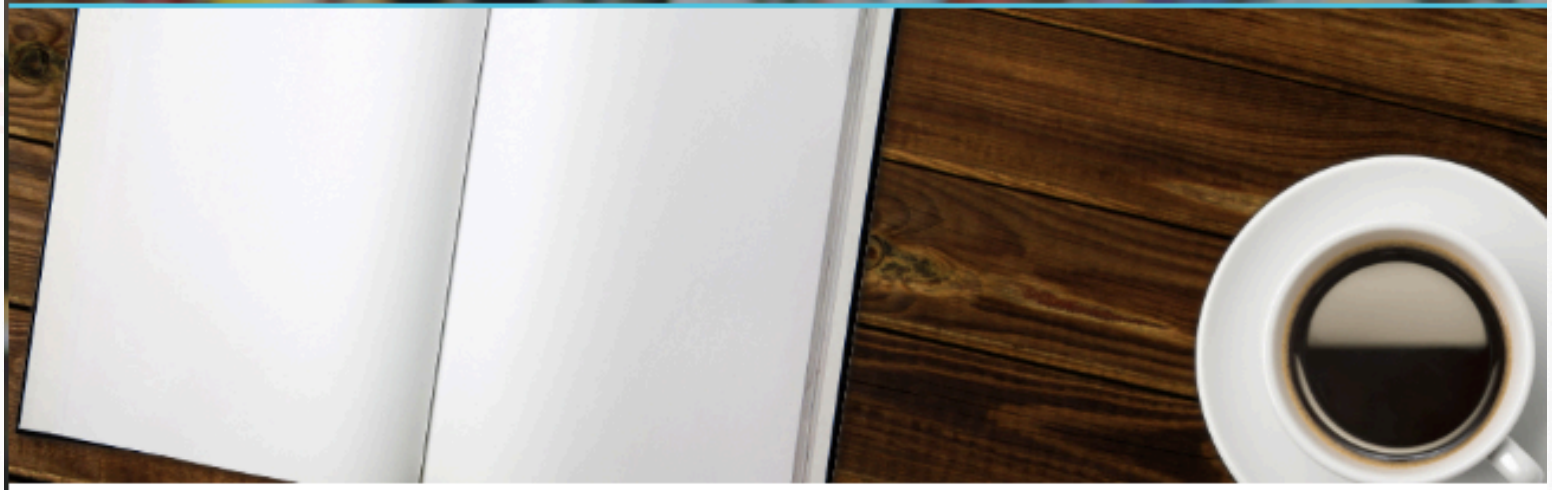
The Role of the Kidneys in Type 2 Diabetes: Focus on SGLT2 Inhibitors



A Sudbury Journal Club Presentation

Speakers:
Kaitlin Bynkoski
&
Ken Burns$_{CDE}$

Sudbury Journal Club



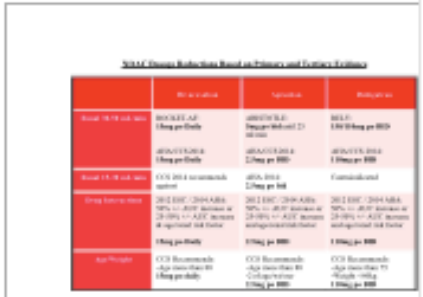
September 29th, 2014: Not Another AFib Talk

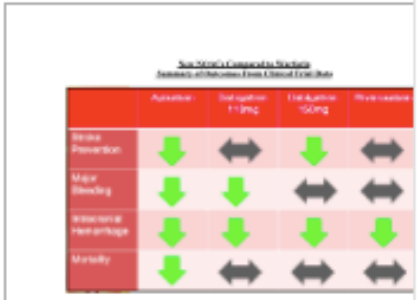
Presentation Slides:

Not Another Afib Talk Presentation
Download File

Not Another Afib Talk Podcast:

00:00 00:00





DISCLOSURE OF COMMERCIAL SUPPORT

- **This program has received financial support from Janssen Inc.**
- **This program has received in-kind support from Janssen Inc. in the form of logistical support for the meeting.**

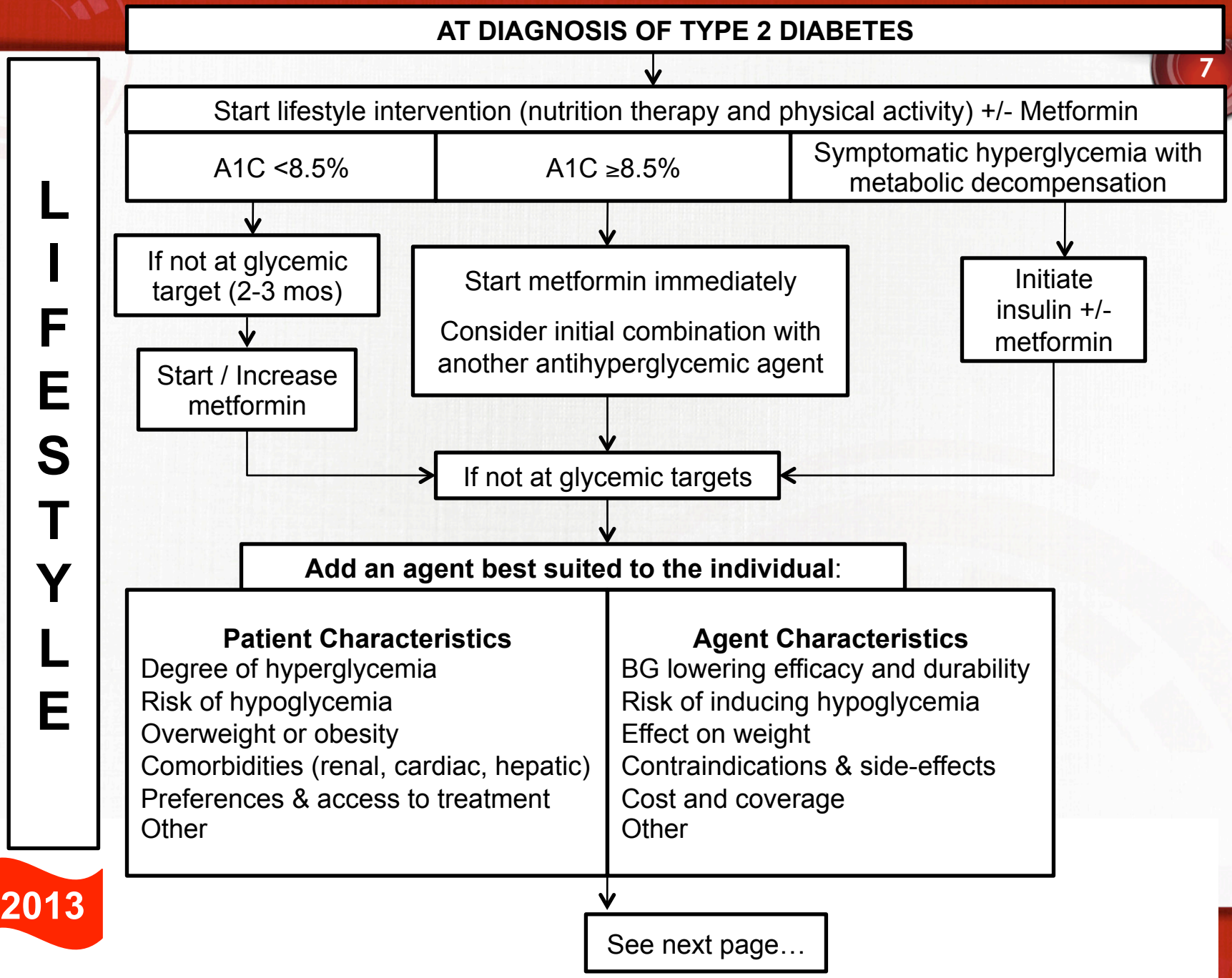
LEARNING OBJECTIVES

- Describe the mechanism for the reabsorption of glucose in the kidneys;
- Describe the SGLT2 inhibitors (sodium/glucose *cotransporter 2*), their mode of action and pharmacodynamic effects;
- Discuss the potential role of SGLT2 inhibitors in the treatment of type 2 diabetes;

PRESENTATION OUTLINE

- Overview of Treatment Guidelines and Options for T2DM
- Role of Kidneys in Glucose Regulation
- Mechanism of Action of SGLT2 Inhibitors
- Efficacy and Safety Data for SGLT2 Inhibitors
  - A1C, Weight, Hypoglycemia, Blood Pressure, Other Side Effects
- Renal Considerations
- CV Risks
- Metabolism and Drug Interactions
- Practical Tips and Considerations in Using SGLT2 Inhibitors

QUICK REVIEW


AT DIAGNOSIS OF TYPE 2 DIABETES
LIFESTYLE
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin
A1C <8.5%
A1C ≥8.5%
Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)
Start / Increase metformin
Start metformin immediately
Consider initial combination with another antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic targets
Add an agent best suited to the individual:
Patient Characteristics
Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Comorbidities (renal, cardiac, hepatic)
Preferences & access to treatment
Other
Agent Characteristics
BG lowering efficacy and durability
Risk of inducing hypoglycemia
Effect on weight
Contraindications & side-effects
Cost and coverage
Other
See next page…

2013

From prior page…

LIFESTYLE

Add an agent best suited to the individual (agents listed in alphabetical order):

Class	Relative A1C lowering	Hypo-glycemia	Weight	Other therapeutic considerations	Cost
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓	Improved postprandial control, GI side effects	$$
Incretin agents:					
DPP-4 Inhibitors	↓↓	Rare	neutral to ↓		$$$
GLP-1 receptor agonists	↓↓ to ↓↓↓	Rare	↓↓	GI side effects	$$$$
Insulin	↓↓↓	Yes	↑↑	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue:					
Meglitinide	↓↓	Yes	↑	Less hypoglycemia in context of missed meals but usually requires TID to QID dosing	$$
Sulfonylurea	↓↓	Yes	↑	Gliclazide and glimepiride associated with less hypoglycemia than glyburide	$
TZD	↓↓	Rare	↑↑	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓	GI side effects	$$$

If not at glycemic target

- Add another agent from a different class
- Add/Intensify insulin regimen

Make timely adjustments to attain target A1C within 3-6 months

2013

LIFESTYLE

AT DIAGNOSIS OF TYPE 2 DIABETES

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

A1C < 8.5%	A1C ≥ 8.5%	Symptomatic hyperglycemia with metabolic decompensation

If not at glycemic target (2-3 mos)

Start / Increase metformin

Start metformin immediately

Consider initial combination with another antihyperglycemic agent

Initiate insulin +/- metformin

If not at glycemic targets

Add an agent best suited to the individual:

Patient Characteristics	**Agent Characteristics**
Degree of hyperglycemia	BG lowering efficacy and durability
Risk of hypoglycemia	Risk of inducing hypoglycemia
Overweight or obesity	Effect on weight
Comorbidities (renal, cardiac, hepatic)	Contraindications & side-effects
Preferences & access to treatment	Cost and coverage
Other	Other

See next page…

ANTI-HYPERGLYCEMIC DIABETES AGENTS: Outcomes Comparison Summary Table

Glucose Lowering Agents

J Bareham BSP, L Regier BSP BA, L Lu BSP © www.RxFiles.ca

Oct 2014

Drug Class	Sulfonylureas		TZDs			Meglitinides	Incretin Related Agents					Insulin in T2DM		SGLT2 inh USA
Generic ⇨ BRAND	Metformin (MF) GLUCOPHAGE, GLYCON	Gliclazide DIAMICRON [Glipizide GLUCOTROL USA SPREAD-DIMCAD]	Glyburide DIABETA	Pioglitazone ACTOS	Rosiglitazone AVANDIA	Acarbose GLUCOBAY	Repaglinide GLUCONORM / Nateglinide STARLIX	Linagliptin TRAJENTA	Sitagliptin JANUVIA	Saxagliptin ONGLYZA	Liraglutide VICTOZA	Exenatide BYETTA	Range of Intensity: Less (NPH at HS + metformin)	Range of Intensity: More (Multiple daily doses)	Dapagliflozin FARXIGA/FORXIGA / Canagliflozin INVOKANA
								PO	PO	PO	SC	SC			
Major trials to support findings/ Outcomes*	UKPDS-33,34,80 (ADOPT; some use in ADVANCE)	ADVANCE	UKPDS-33,80 (ADOPT)	ProACTIVE Ferwana M. Meta-analysis 2013.	Meta-analysis. RECORD Interim, ADOPT, DREAM.	(Prevention trial: Stop-NIDDM)	–	SAVOR-TIMI 53: Saxagliptin vs placebo for CV outcomes, 2013. (At 2yrs, n= >16,000: no benefit, some harms [↑HF admit otherwise CV neutral]) See RxFiles Trial Summary online at www.RxFiles.ca: EXAMINE: Alogliptin vs placebo for CV outcomes, 2013; (At median of 1.5yrs: neutral CV outcomes; no benefit, minimal harm)					UKPDS-33,80; ADVANCE, ACCORD, VADT. (T1DM: DCCT/EDIC) (Also Boussageon et al. Meta-analysis. BMJ 2011;343:d4169)		CV outcome safety trials in progress: (CANVAS; DECLARE-TIMI 58)
↓ Risk of Death / Major CV	✓✓✓ In Obese UKPDS-34 ↓ Mortality NNT=14/10yr	✓ [Glipizide ↑risk vs MF, NNT=10/5yr] SPREAD-DIMCAD	✓	✓	X??	✓✓	?	?	?	? ↔ 2yr SAVOR-TIMI 53	?	? ↑HR	✓✓?	✓✓? XX?	? (X: transient ↑ CV/stroke in 1st mo with Cana-)
Effect on A1C**	✓✓✓	✓✓✓	✓✓✓	✓✓	✓✓	✓	✓✓ / ✓	✓	✓	✓	✓✓	✓	✓✓	✓✓✓	✓✓
Weight (wt loss vs neutral vs wt gain)	✓✓✓	✓	✓	XX	XX	✓✓✓	✓	✓	✓✓?	✓	✓✓	✓✓	✓	XX	✓✓✓
↓ Risk of Hypoglycemia	✓✓✓	X ? If less risk with MR formulation	X X Severe occurs at 1.4%/yr	✓✓✓	✓✓✓	✓✓✓	✓ / ✓✓✓	✓✓?	✓✓?	✓✓?	✓✓?	✓✓?	✓	XX Rate of 1.8%/yr	✓✓ Risk only when given with sulfonylurea or insulin
↓ Risk of HF / Edema	✓✓ (1st line in stable HF)	✓✓	✓✓	XX	XX	✓✓	✓✓	?	X ↑admissions (observational)	X ↑admissions SAVOR-TIMI 53	?	?	✓	✓	?
								Emerging questions/concerns about ? ↑HF risk							
Effect on LDL	✓✓✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓✓	✓✓	✓	✓	X ↑LDL: Cana > Dapa
Effect on GI tolerability	X Start low & titrate	✓✓	✓✓ Rate of 1.8%/yr	✓✓	✓✓	XX	✓✓	✓✓	✓✓	✓✓	✓ Nausea, vomiting, diarrhea	✓ Nausea, vomiting, diarrhea	✓✓✓	✓✓✓	✓ Nausea/ diarrhea with dapagliflozin
Cost	✓✓✓	✓✓	✓✓✓	X	XX	✓	✓	X	X	X	XX	XX	✓	XX	XX
Other	May have to hold or ↓ dose in acute illness/HF/ renal dysfx. 1st line for obese T2DM.	ADVANCE: used in combination with metformin.	Caution:↓ renal function (& older adults).	X ↑risk of fractures & macular edema. Rosi: Restricted access- in CDN (EDS) (↑CV risk concerns/controversy) Pio: Risk of bladder cancer (NNH ~ 21,000/4yrs)		✓✓ PPG, Possible benefit of laxative effect in some? TID dosing	✓✓ PPG, flexibility with meals TID dosing	✓ PPG X new agents – data on safety & hard outcomes is still limited. Possible ↑ risk of infection e.g. URTI. Risk of pancreatitis. Linagliptin: Dose adjustment for renal function not required.			✓ PPG X new agents – data on safety & hard outcomes is still limited. Injection site irritation, Risk of pancreatitis, Possible risk of thyroid cancer with liraglutide.		✓ Fear/ perception of insulin injections	✓✓PPG Fear/ perception of insulin injections	X: New agents Outcome data limited/concerns. ↑glucose in urine &↑risk of UTI/yeast infections. ↓ intravascular volume;↓BP. ?Bladder/prostate/ breast cancer. Caution:↓ renal fx.
Overall	✓✓✓	✓✓	✓✓	✓?	X?	✓	✓	?	?	?		?	✓ / ✓✓	✓✓ / X	X?

*Drugs that lower blood glucose come with various levels of evidence regarding their balance of benefits & harms. This chart relies on current evidence, especially that from randomized controlled trials that have evaluated patient oriented outcomes. Direct comparisons between agents have not been done so one is left to evaluate each drug for its relative advantages & disadvantages.

**A1C will vary depending on dose, combinations & initial A1C.

Individualize approach to balance potential benefits & harms. Over aggressive pursuit of targets can ↑ mortality ACCORD

Dapagliflozin: FDA Jan/14 . FDA Aug'14: Empagliflozin. Canagliflozin: avail : USA & CDN.

See also RxFiles Diabetes Landmark Trials Summary at: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

An Advantage ✓✓✓	✓✓	Neutral ✓	X	A Disadvantage XX

Antihyperglycemic Medications

Alpha-glucosidase Inhibitors

Delay the absorption of glucose from starch and sucrose

Biguanides

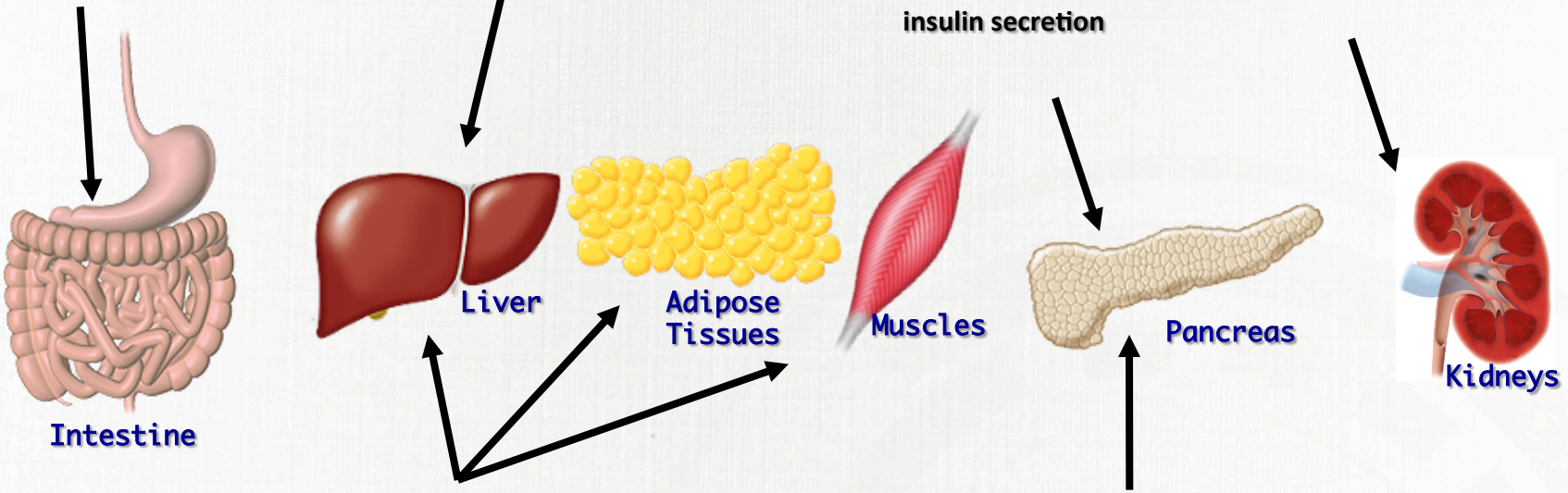
Reduce hepatic gluconeogenesis

Insulin Secretagogues

Sulfonylureas and meglitinides stimulate insulin secretion

SGLT2 Inhibitors

Reduce the reabsorption of glucose by the kidneys : glucosuria



Thiazolidinediones

Improve insulin resistance

DPP-4 Inhibitors and GLP-1 Agonists

Increase insulin secretion, inhibit glucagon secretion

Krentz AJ, Bailey CJ. Drugs 2005; 65:385-411.

Antihyperglycemic Medications

Added Therapy	Change in A_{1C} (%)	Change in Weight (kg)	Hypoglycemia Odds Ratio vs placebo
Sulfonylureas	-0.82	2.17	8.86
Meglitinides	-0.71	1.40	10.51
Thiazolidinediones	-0.82	2.46	0.45
Alpha-glucosidase Inhibitors	-0.66	-1.01	0.40
DPP-4 Inhibitors	-0.69	0.23	1.13
GLP-1 Receptor Agonists	-1.02	-1.66	0.92
Basal Insulin	-0.88	1.38	4.77

Meta-analysis (add-on to metformin)

Liu, Sung-Chen *et al. Diab Obes & Metab* 14:810-820, 2012.

THE ROLE OF KIDNEYS IN GLUCOSE REGULATION

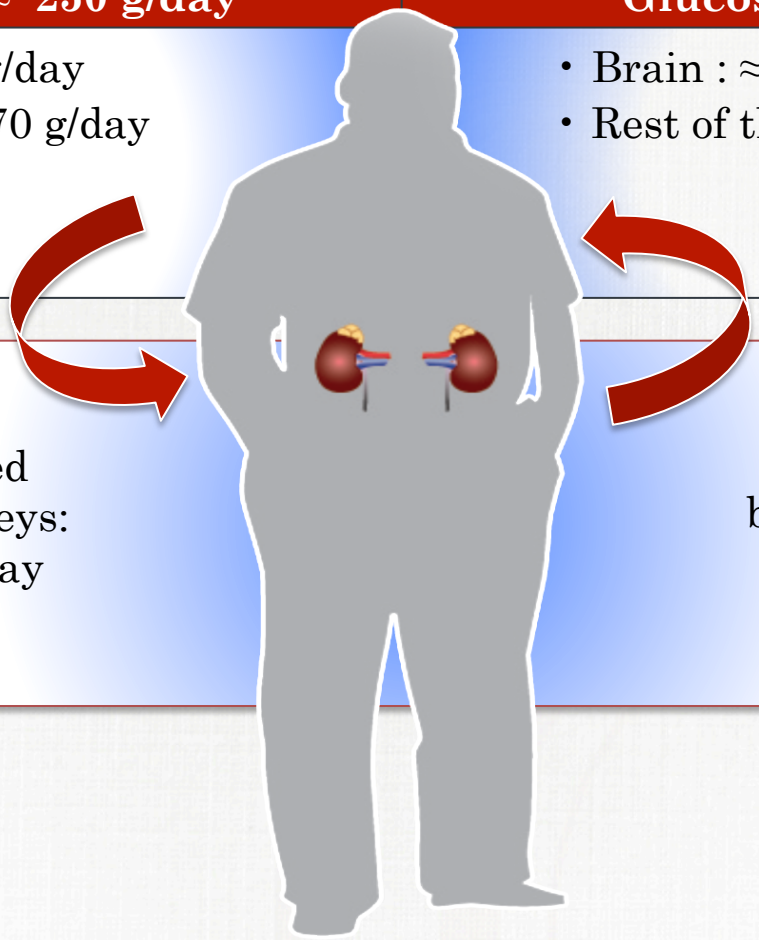
Glucose Homeostasis in the Body

Glucose input: ≈ 250 g/day

- Dietary intake: ≈ 180 g/day
- Glucose production: ≈ 70 g/day
  - Gluconeogenesis
  - Glycogenolysis

Glucose uptake : ≈ 250 g/day

- Brain : ≈ 125 g/day
- Rest of the body : ≈ 125 g/day



Glucose reabsorbed by the kidneys: ≈ 180 g/day

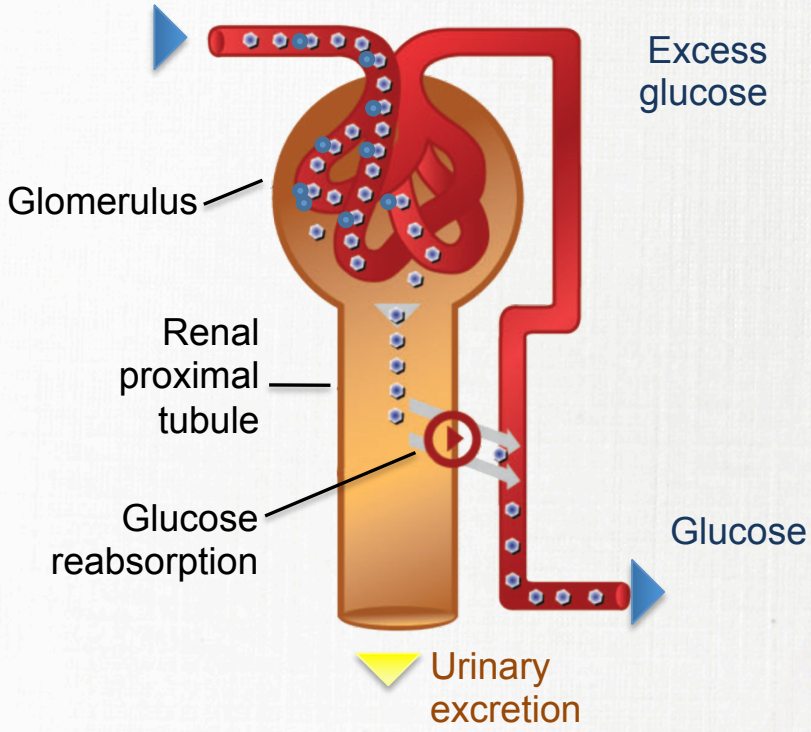
Glucose filtered by the kidneys: ≈ 180 g/day

Wright EM et al. J Intern Med. 2007;261:32-43; 2. MarsenicO. Am J Kidney Dis. 2009;53:875-83

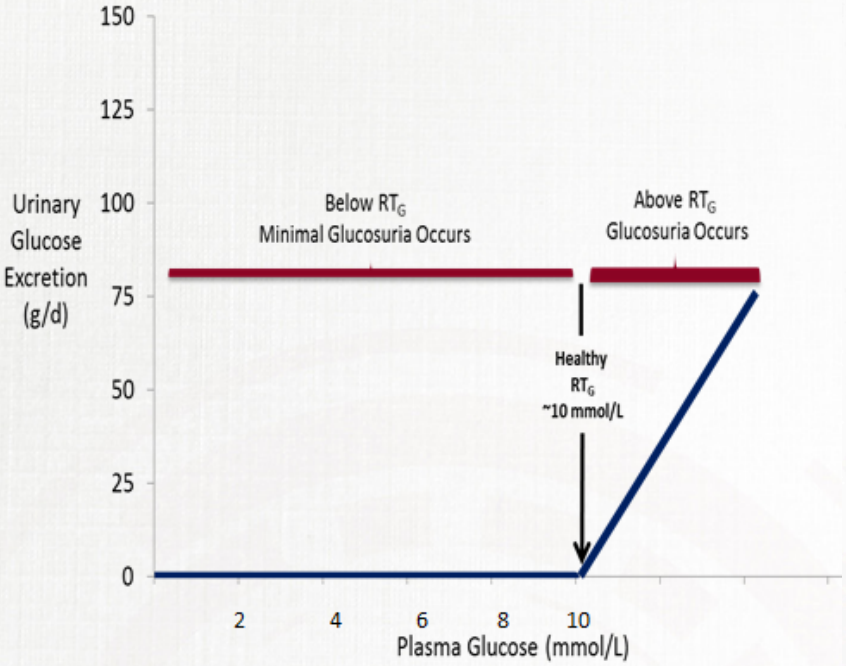
Net : approximately 0 g/day

RENAL GLUCOSE HANDLING IN THE NON-DIABETIC

Healthy patient (normal kidney function & glucose tolerance)

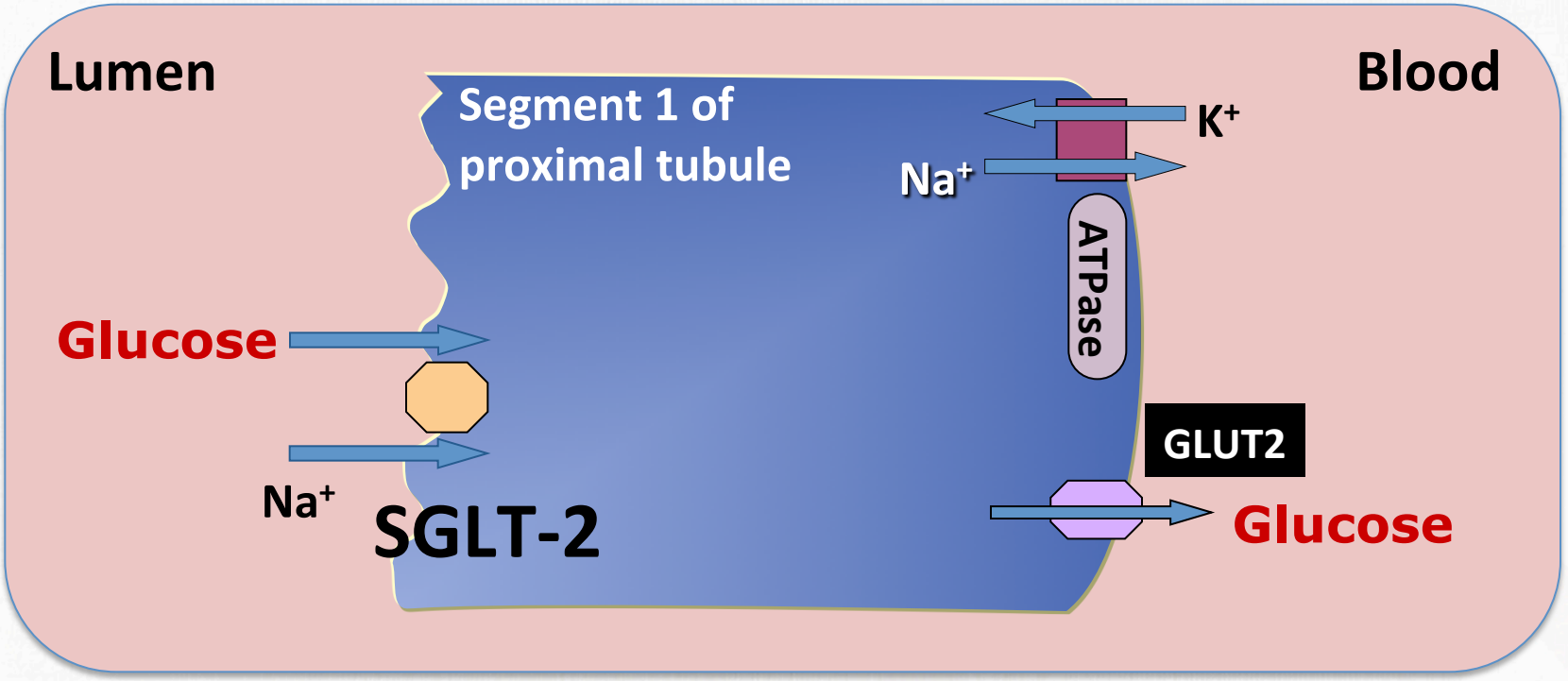


RT_G in Healthy Subjects



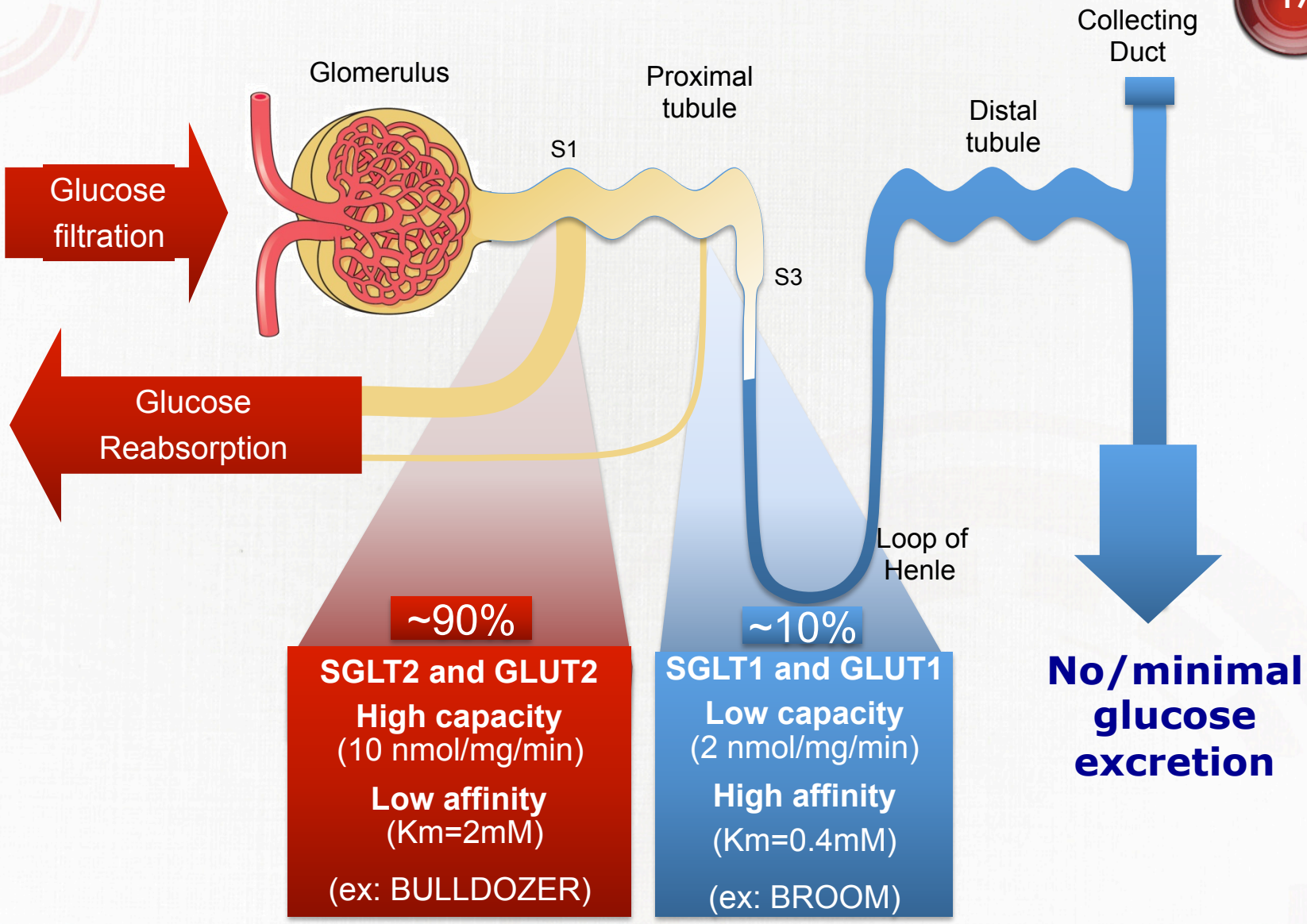
Adapted from:
1. Chao EC & Henry RR. Nature Reviews Drug Discovery 2010;9:551-559.
2. DeFronzo RA, et al. Diab Obes Metab 2012;14:5-14.
3. Washburn WN. J Med Chem 2009;52:1785-1794.
4. Guyton AC, Hall JE. Textbook of Medical Physiology. 11th ed. Philadelphia, PA: Elsevier Saunders; 2006.

SGLT2 TRANSPORTERS



1. Chao EC et Henry RR. Nature Reviews Drug Discovery 2010;9:551-9.

MECHANISM OF ACTION OF SGLT2 INHIBITORS



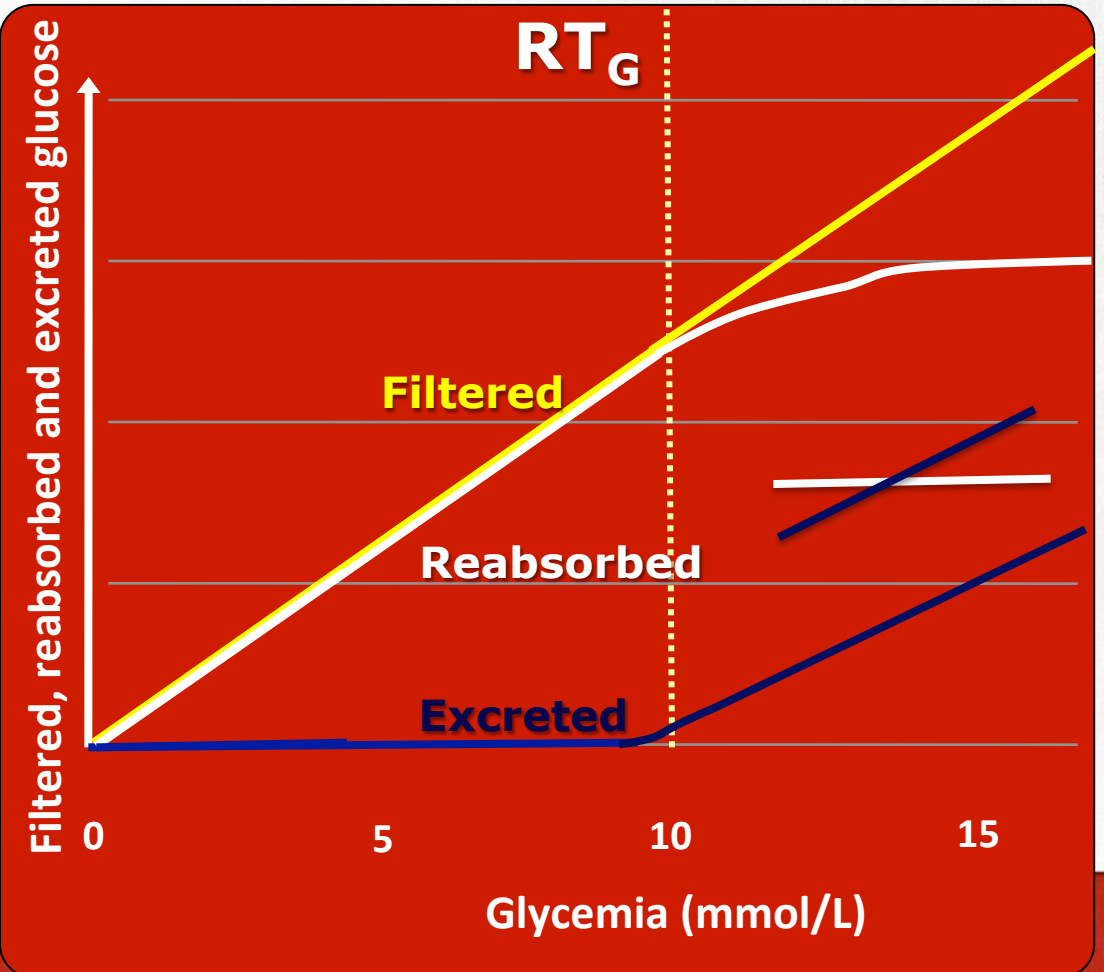
SGLT=Sodium/GLucose co-Transporter; GLUT=GLUcose Transporter.

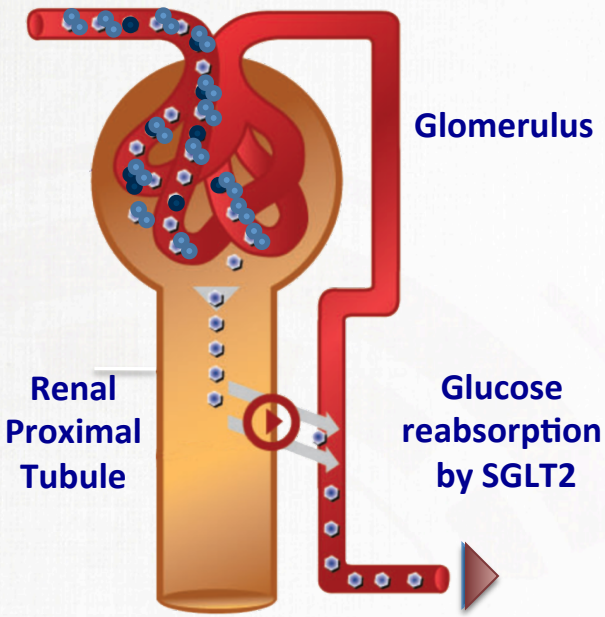
Abdul-Ghani MA, DeFronzo, RA. Endocr Pract. 2008;14(6):782-790. Bays H. Curr Med Res Opin. 2009;25(3):671-681.

Mechanism of Action: Induces Glucosuria

Beyond a given glycemia, called the renal threshold for glucose (RT$_G$), the amount of glucose filtered by the glomerulus increases with glycemia. Glucose is entirely reabsorbed from the proximal tubule by SGLT2 transporters. No glucosuria at normal or mildly elevated blood glucose levels.

SGLT2 inhibition reduces the glucose reabsorption capacity of the renal tubule, leading to a decrease in the RT$_G$ and the appearance of glucosuria at normal fasting glycemia.

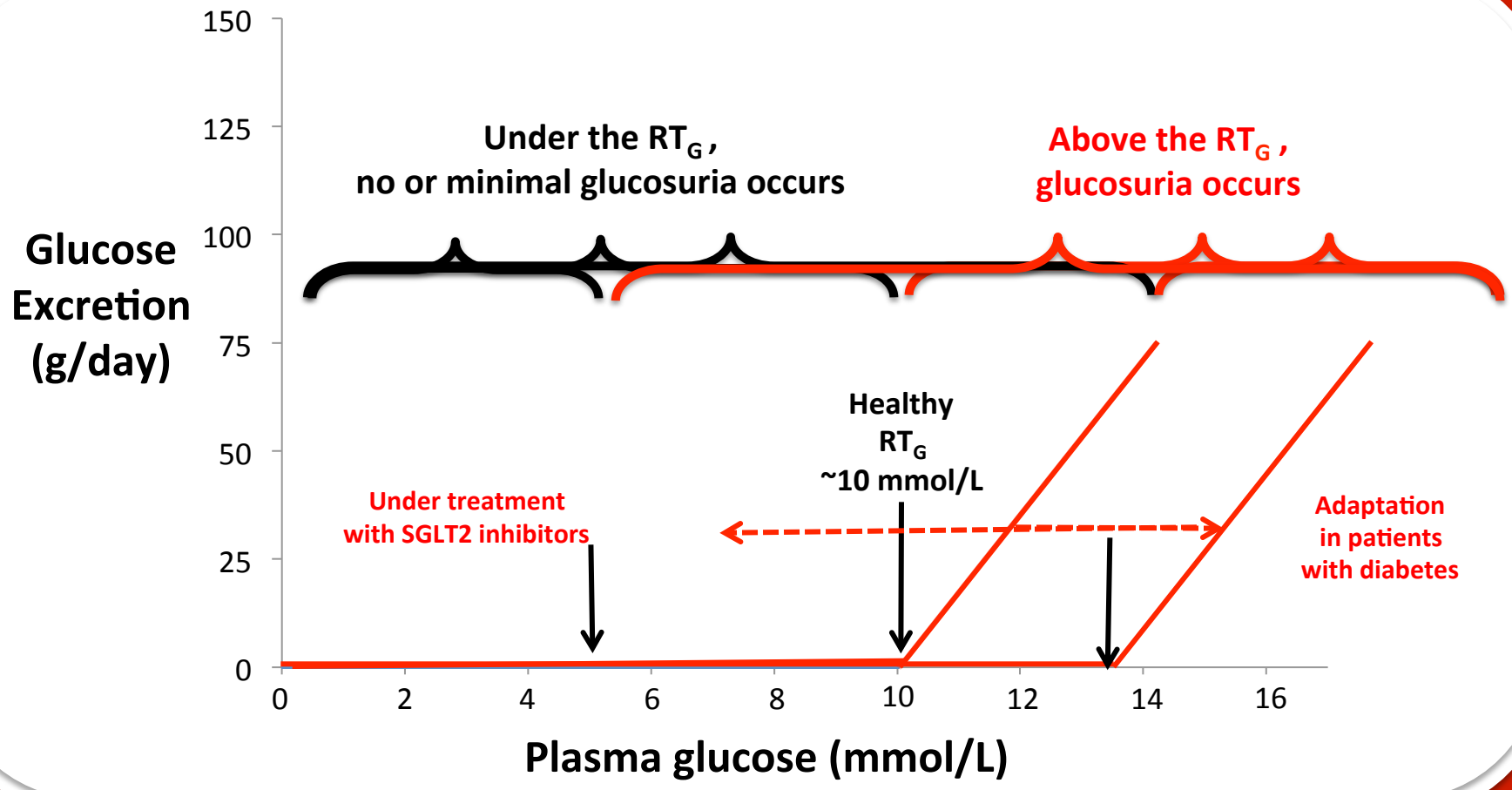




No glucosuria

1. Chao EC et Henry RR. *Nature Reviews Drug Discovery* 2010;9:551-559.
2. DeFronzo RA, *et al. Diab Obes Metab* 2012;14:5-14.
3. Washburn WN. *J Med Chem* 2009;52:1785-1794.

Effects of SGLT2 Inhibitors on RT_G



Nair S & Wilding J. J Clin Endocrinol Metab. 2010;95:34-42.
Polidori D, et al. American Diabetes Association Meeting, June 25-29, 2010, Orlando, Florida; Abstract 2186-PO

EFFICACY & SAFETY DATA FOR SGLT2 INHIBITORS

SGLT2 INHIBITORS

Agent	Manufacturer	Status
Canagliflozin	**Janssen Inc.**	**Approved in Canada, the United States, Australia, Europe and Mexico**
Dapagliflozin	**AstraZeneca**	**Approved in Europe Australia and United States**
Empagliflozin	**Boehringer Ingelheim/Eli Lilly**	**Approved in Europe**
Ertugliflozin	Merck/Pfizer	
Ipragliflozin	Astellas/Kotobuki	**Approved in Japan**
Luseogliflozin	Taisho	
Tofogliflozin	Chugai/ Roche	

INHIBITING SGLT2 IN DIABETES: IMPACT

A_1C

- RT_G moves closer to that of patients without diabetes and glycosuria occurs until plasma glucose falls below RT_G. Blood sugar and A_1C fall. Little or no hypoglycemia.

Wt

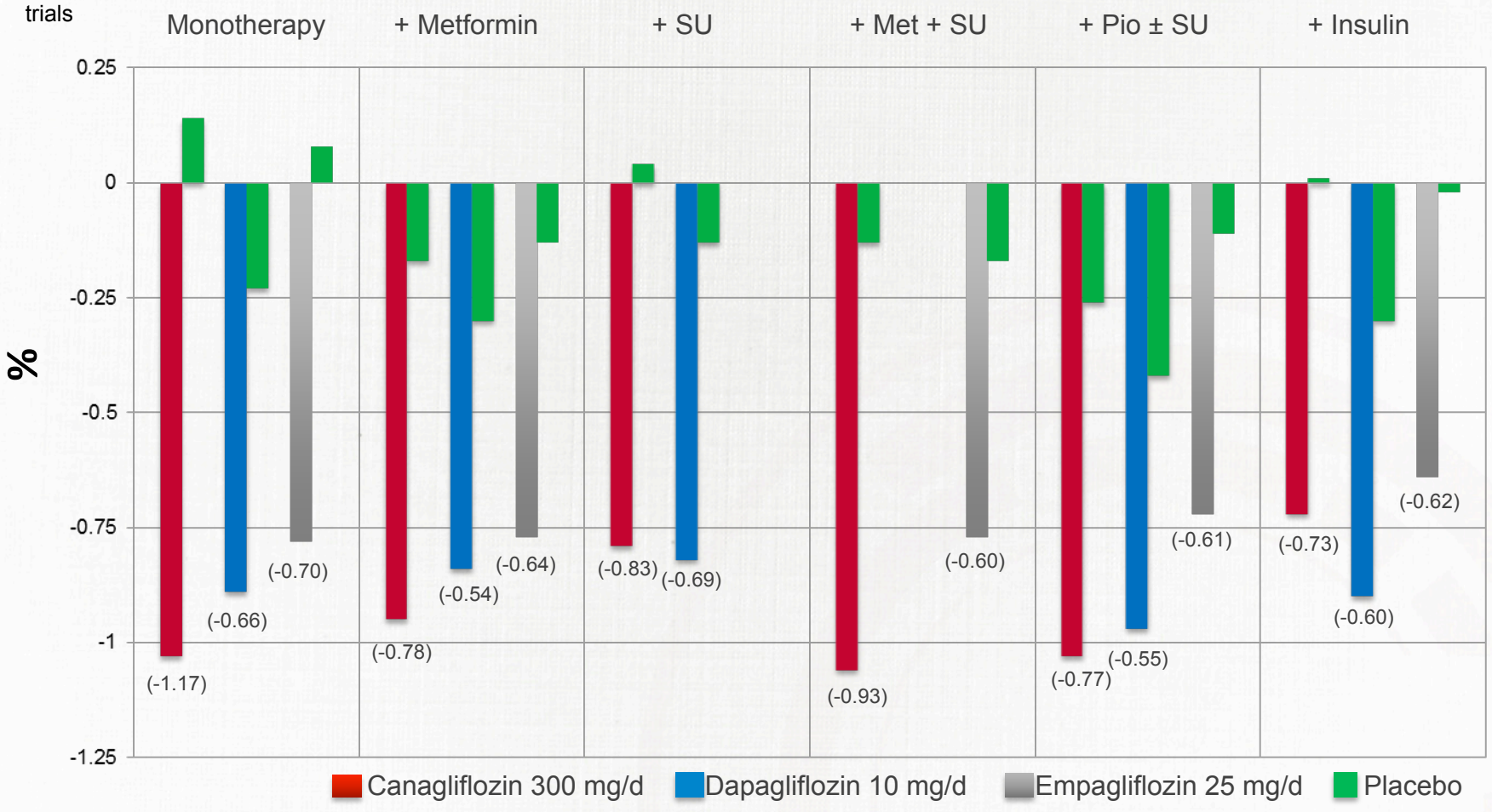
- Net loss of glucose amounts to 80-100g/day (300-400cal/day). There is the potential for 3-4 kg of durable weight loss.

BP

- Increased sodium excretion due to blockade of SGLT2 will lead to a diuretic effect and lower BP, approximately 5mm/Hg in systolic BP (similar to thiazide diuretics).

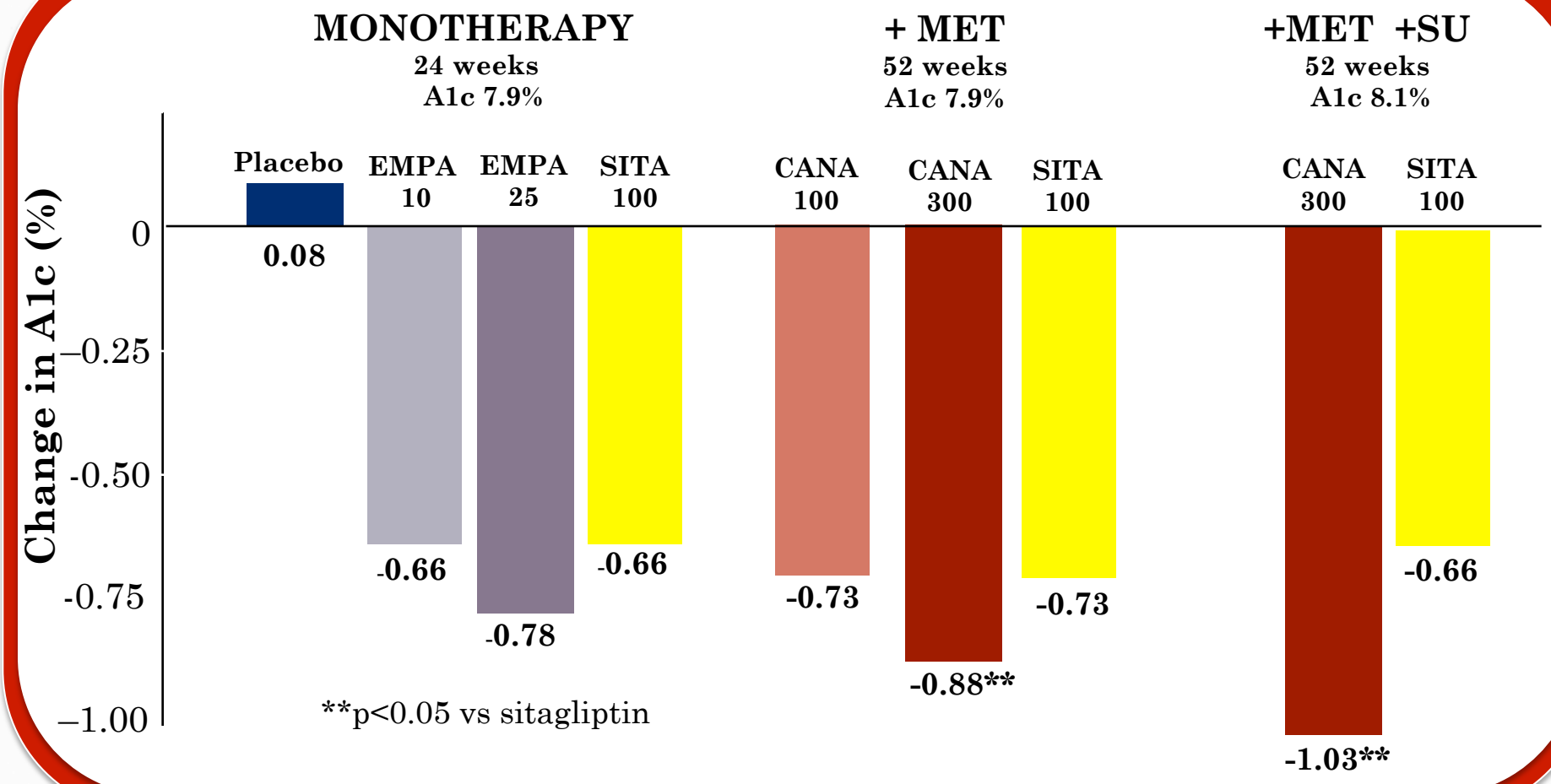
EFFECTS OF SGLT2 INHIBITORS ON A1C LEVELS AT 24 WEEKS (52 WEEKS FOR EMPA-CORE)

*These are not head to head trials



1. CANA: Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013
2. DAPA: Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm
3. EMPA: ADA Annual Meeting 2013: Roden M et al 1085-P; Haring H et al: 1092-P; Kovacs C et al: 1120-P and Rosenstock J et al 1102P.

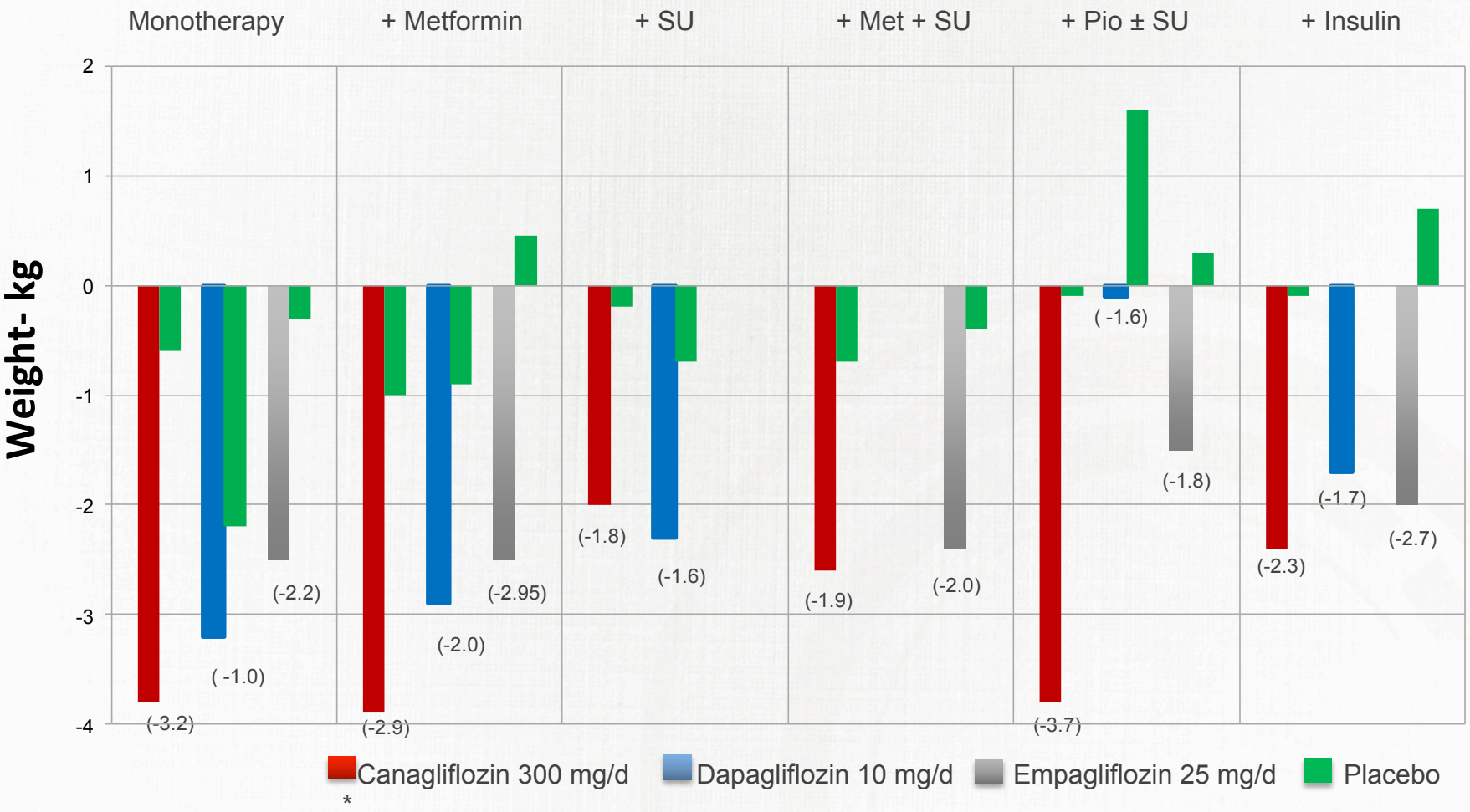
A_1C: SGLT2 Inhibitors vs DPP-4 Inhibitors



Roden M *et al.* ADA Annual Meeting, 2013; 1085-P. Lavalle Gonzalez FJ *et al.* ADA Annual Meeting, 2013; 238-OR.
Schernthaner G *et al. Diabetes Care* 2013.

EFFECTS OF SGLT2 INHIBITORS ON BODY WEIGHT

*These are not head to head trials



1. CANA: Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013
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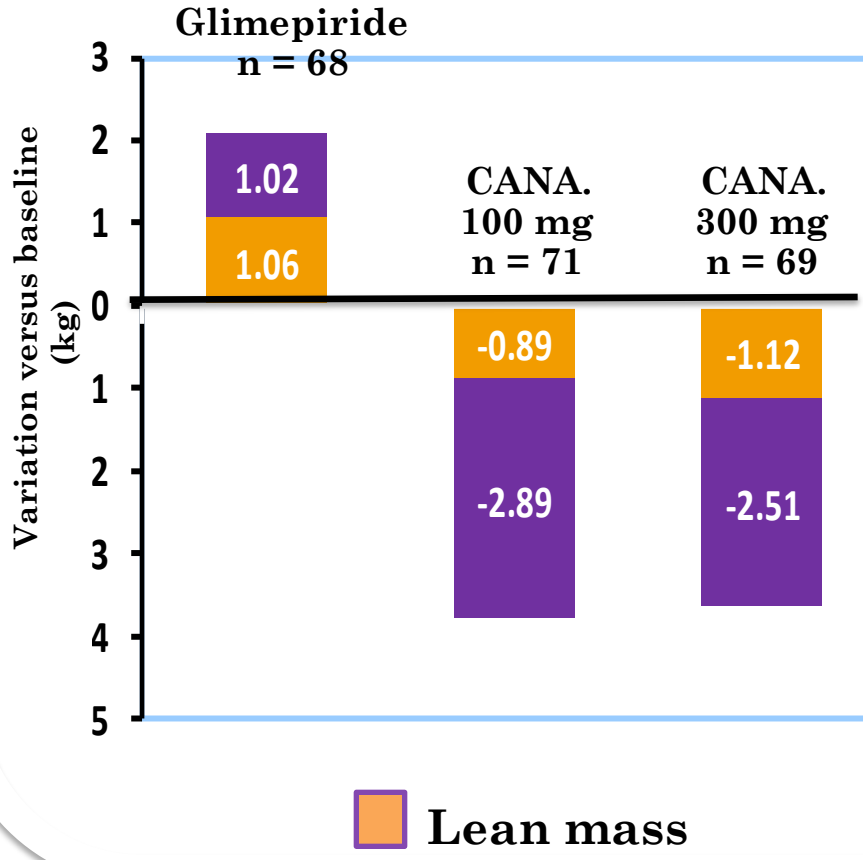
Body Composition Studies with SGLT2 Inhibitor Treatment

(DEXA measurements)

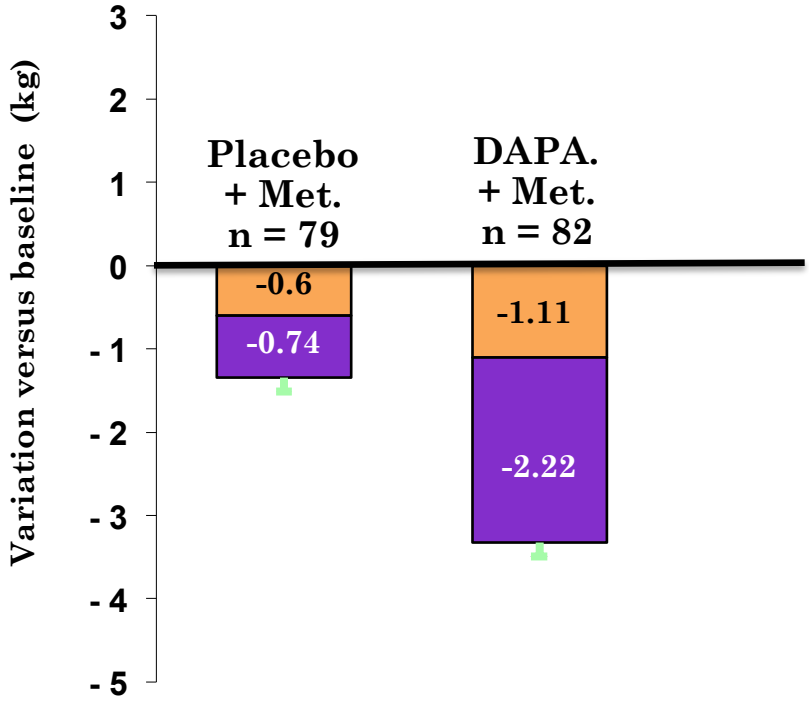
Canagliflozin

Variation at week 52



Dapagliflozin

Variation at week 24



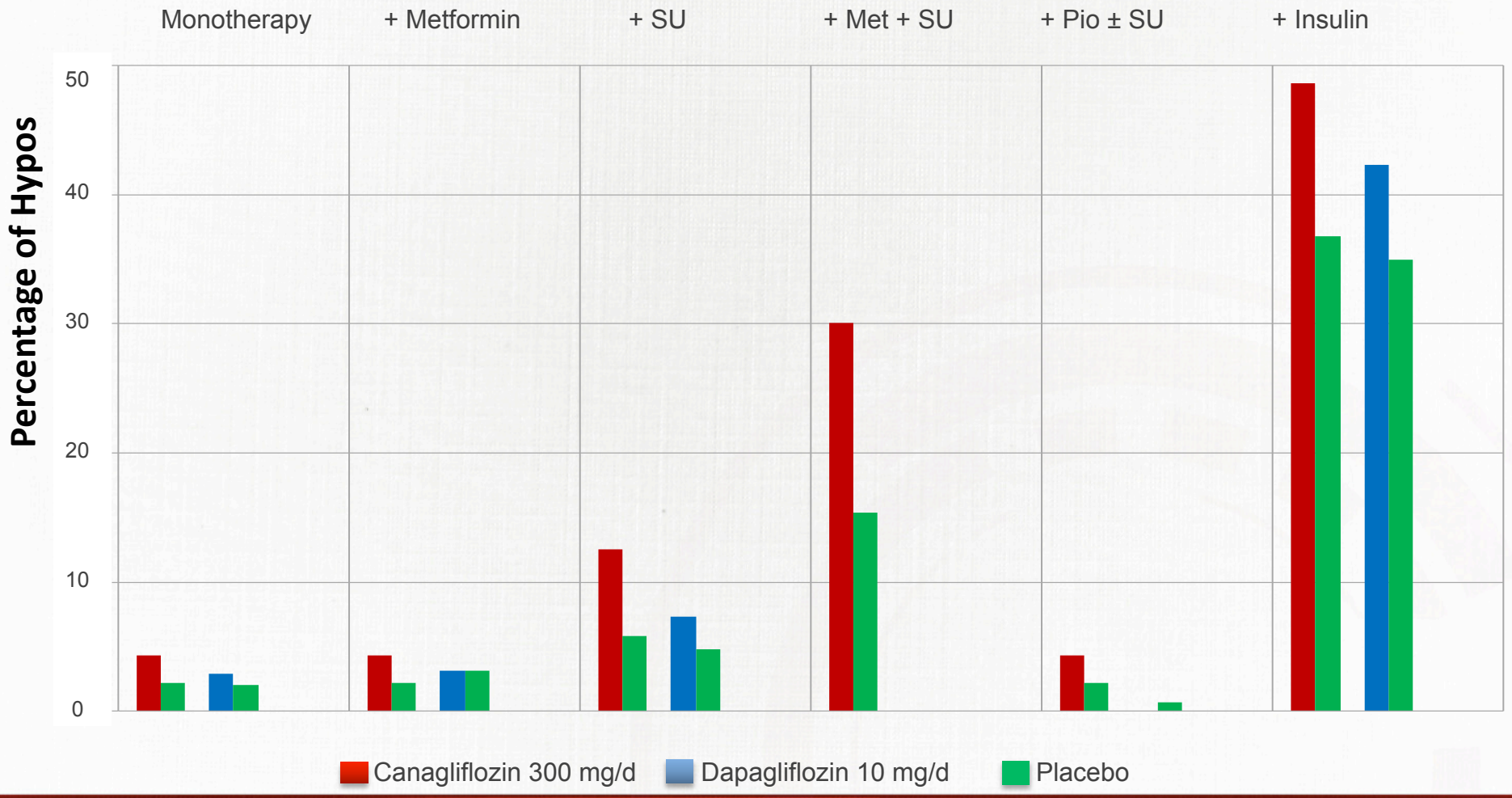
Lean mass

Fat mass

Toubro S *et al*.EASD Annual Meeting, 2012. Abstract 762.
Bolinder J *et al. J Clin Endocrinol Metab*. 97; 2012.

EFFECTS OF SGLT2 INHIBITORS ON HYPOGLYCEMIA

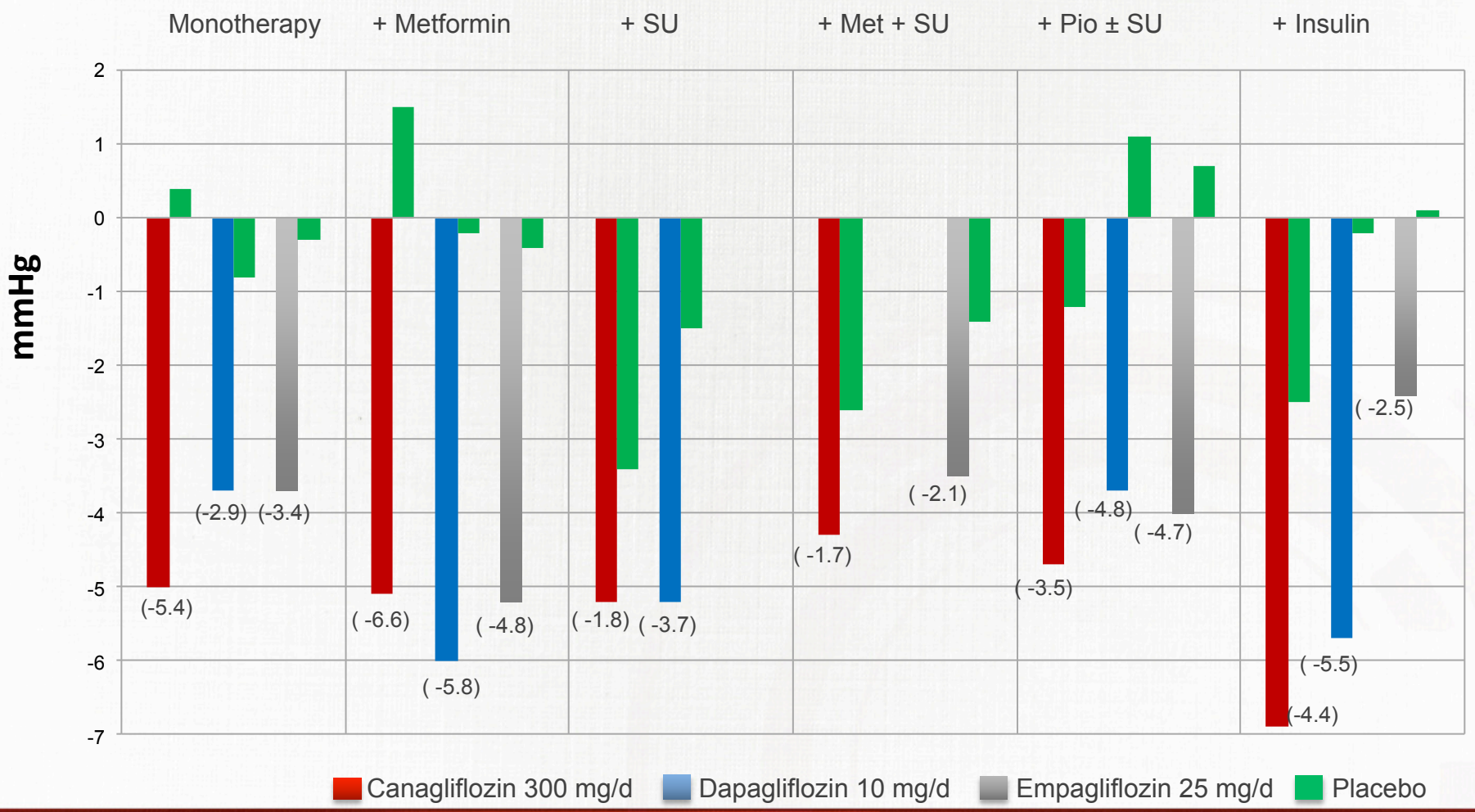
*These are not head to head trials



1. CANA: Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013
2. DAPA: Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

EFFECTS OF SGLT2 INHIBITORS ON BLOOD PRESSURE

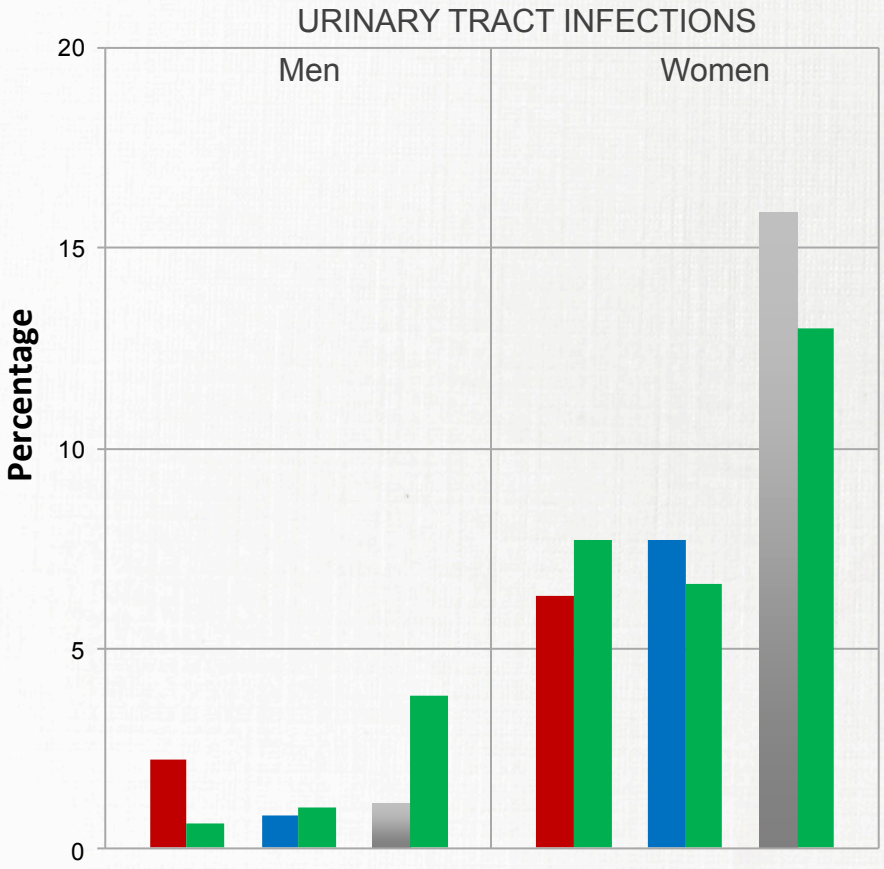
*These are not head to head trials

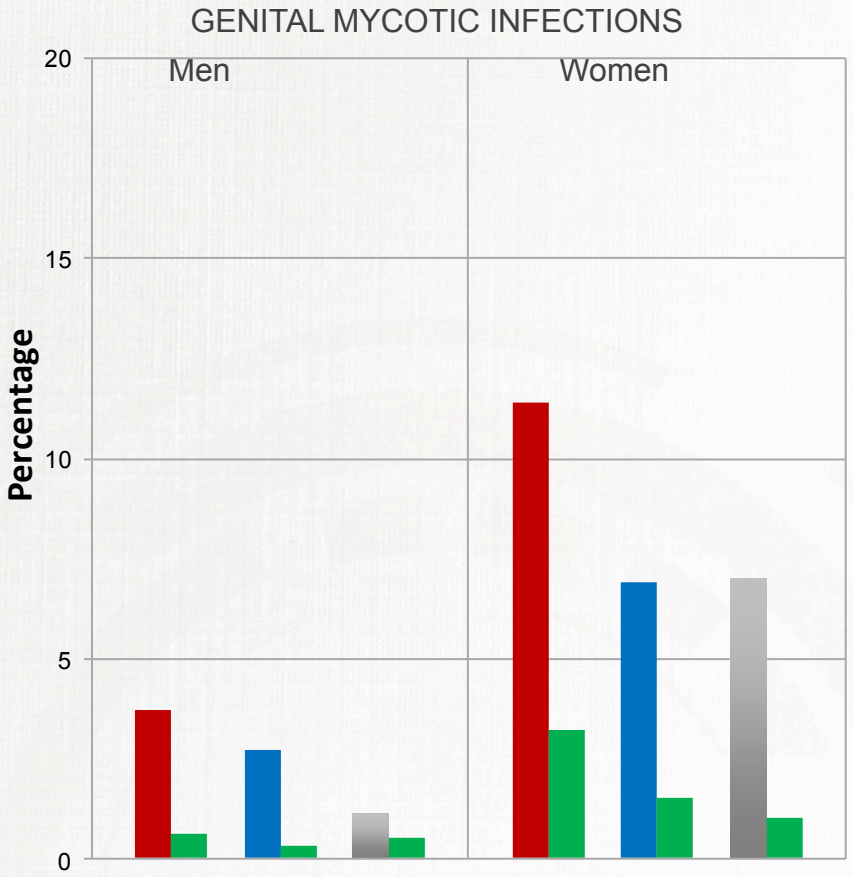


1. CANA: Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013
2. DAPA: Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm
3. EMPA: ADA Annual Meeting 2013: Roden M et al 1085-P; Haring H et al: 1092-P; Kovacs C et al: 1120-P and Rosenstock J et al 1102P.

INCREASE IN GENITAL MYCOTIC INFECTIONS; UTI?
EFFECTS OF SGLT2 INHIBITORS ON INFECTIONS

*These are not head to head trials





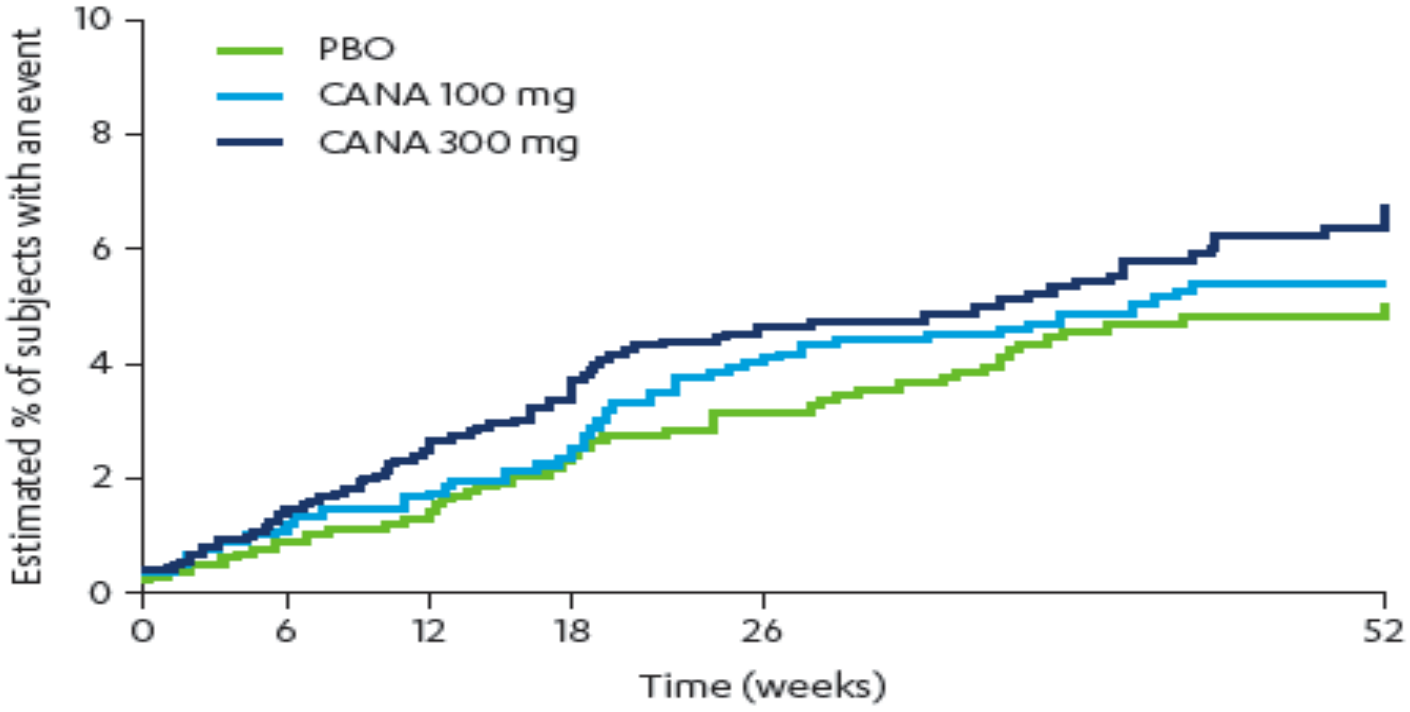
Canagliflozin 300 mg/d | Dapagliflozin 10 mg/d | Empagliflozin 25 mg/d | Placebo

1. CANA: Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013
2. DAPA: Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm
3. EMPA: ADA Annual Meeting 2013: Roden M et al 1085-P; Haring H et al: 1092-P; Kovacs C et al: 1120-P and Rosenstock J et al 1102P.

URINARY TRACT INFECTION WITH CANA

Time to First UTI AE

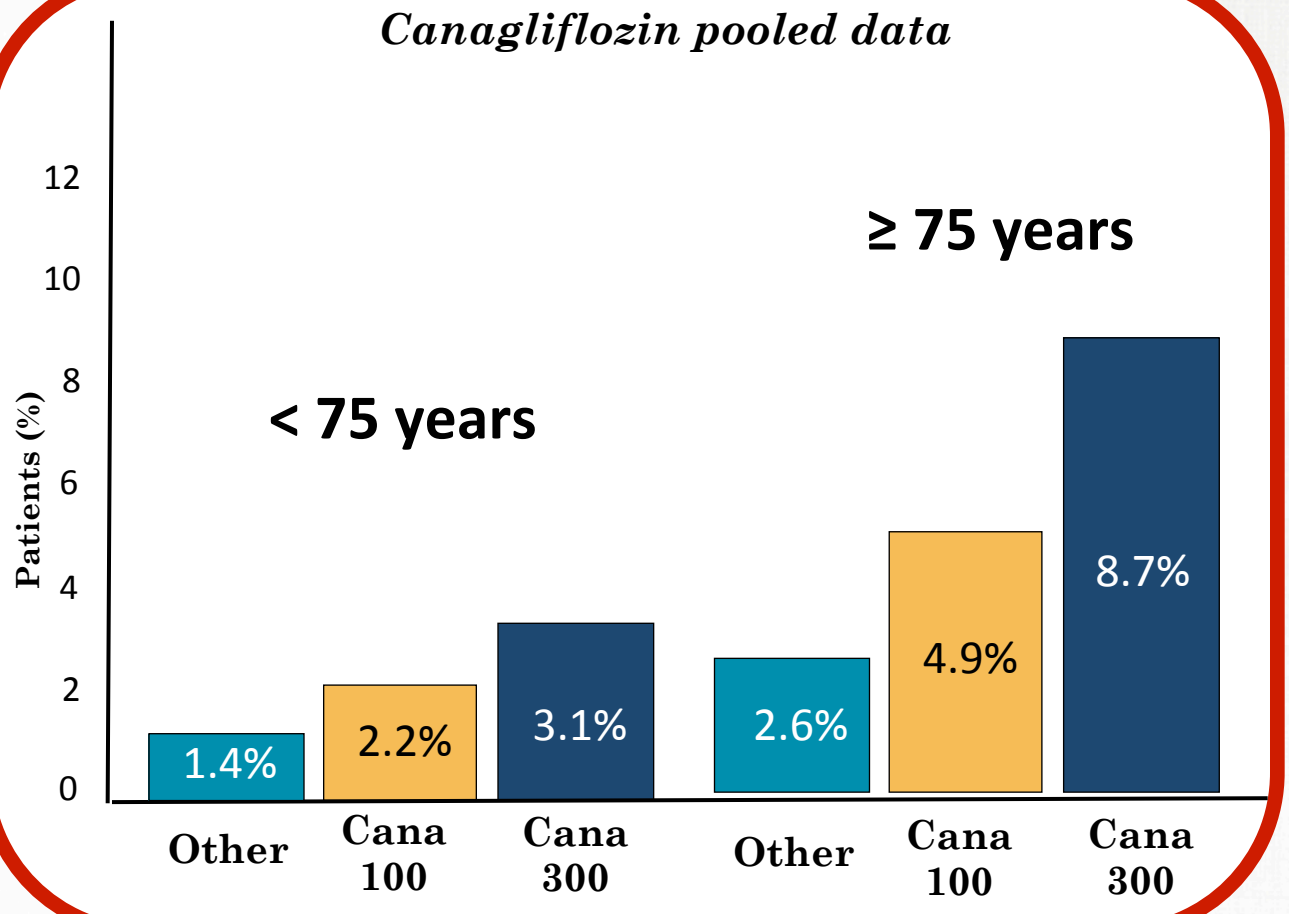
Figure 1. Kaplan-Meier plot of time to the first UTI AE (Population 3).



PBO	1,441	1,422	1,361	1,303	1,259	453
CANA 100 mg	1,445	1,424	1,381	1,348	1,298	480
CANA 300 mg	1,441	1,410	1,337	1,299	1,247	457

):

Side Effects of SGLT2 Inhibitors
Volume Depletion
in relation to circulating volume

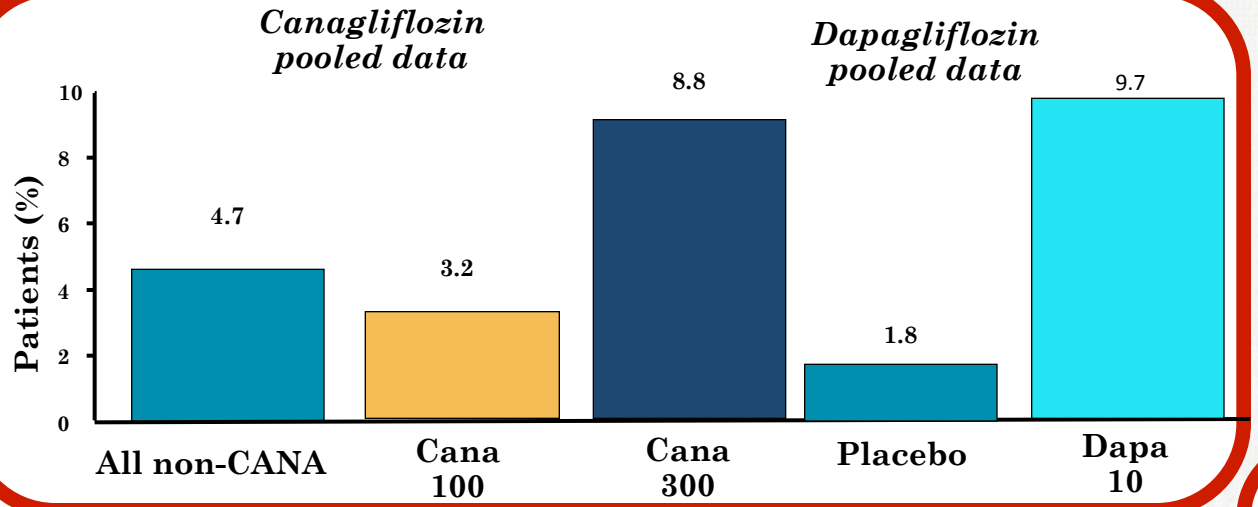


- Events of interest:
  - Hypotension
  - Postural Hypotension
  - Dehydration
  - Syncope
  - Reduced urinary output

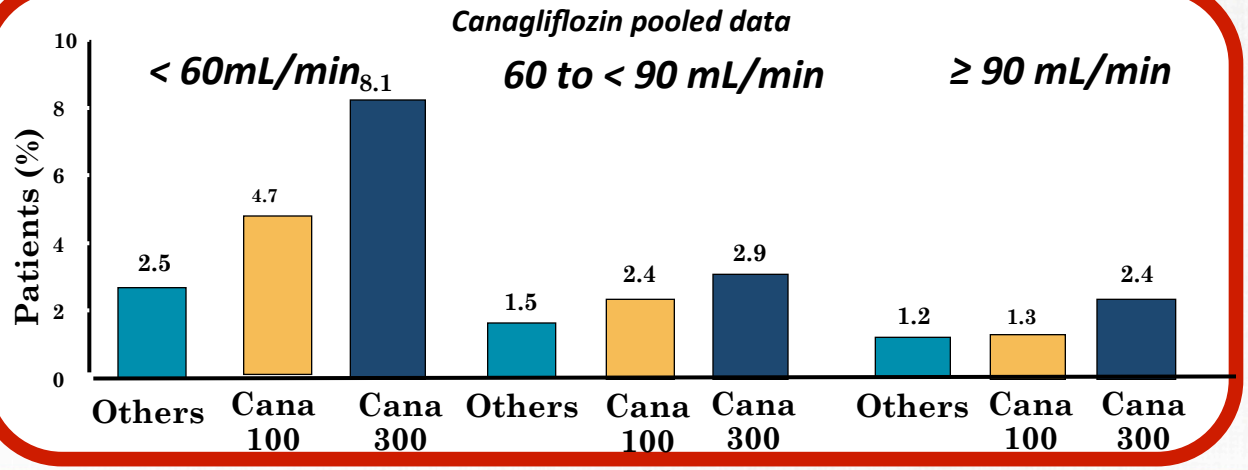
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

RISK FACTORS FOR VOLUME DEPLETION SYMPTOMS

Patients on loop diuretics



Patients with low baseline eGFR



Population at risk > 75 yo

- Events of interest:
  - Hypotension
  - Postural hypotension
  - Dehydration
  - Syncope
  - Decreased urinary output

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs /EndocrinologicandMetabolicDrugs AdvisoryCommittee/UCM336236.pdf. Consulted January 23, 2013. FDA Advisory Committee, July 19 2011 : http://www.fda.gov.

RENAL SAFETY

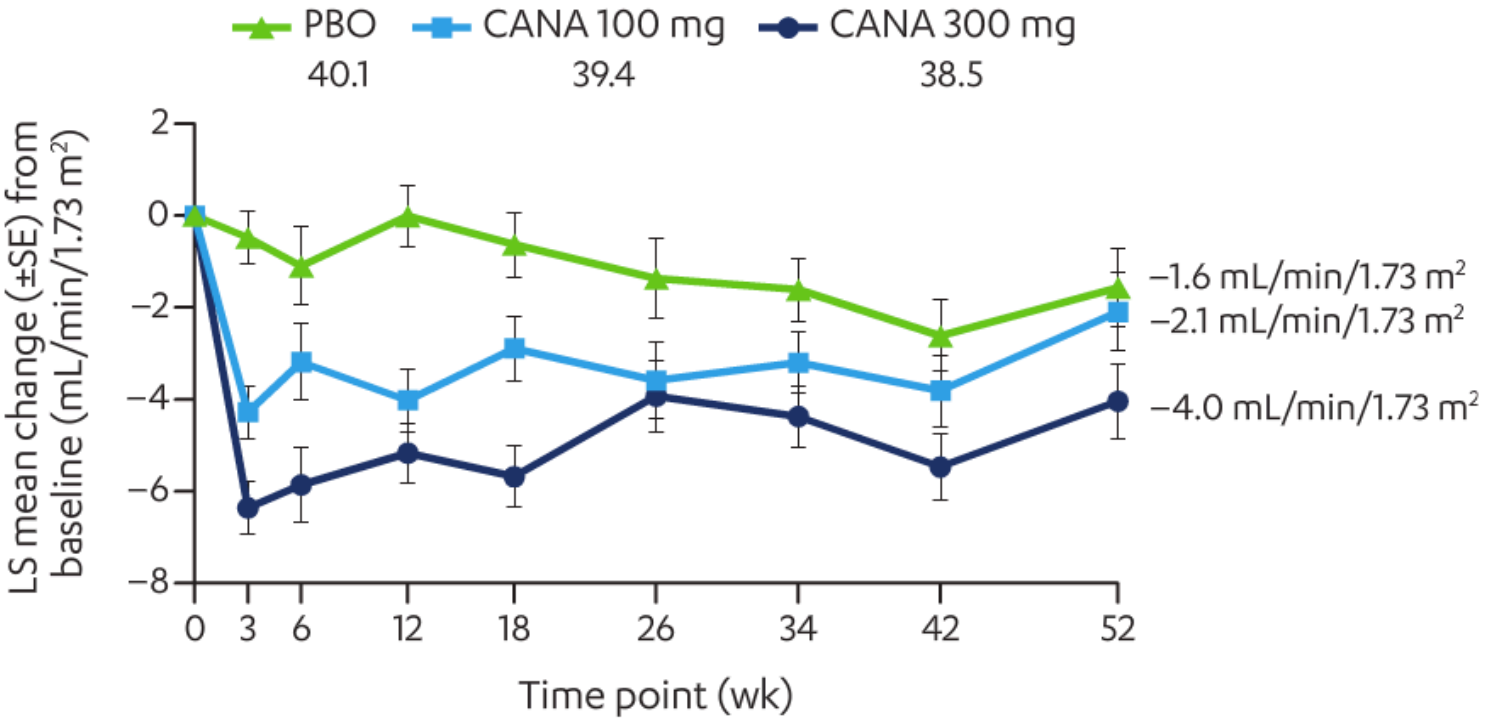
DIABETIC NEPHROPATHY: BASIC PRINCIPLES

- Elevated plasma glucose (not tubular glucose) leads to increased glomerular mesangial matrix production and glomerular injury

- Increased tubular glucose resulting in glycosuria likely has no significant effect on the glomerulus or the microvascular system
  - Patients with renal glycosuria do not develop diabetic nephropathy

EFFECTS of SGLT2 Inhibitors on eGFR in presence of moderate renal failure

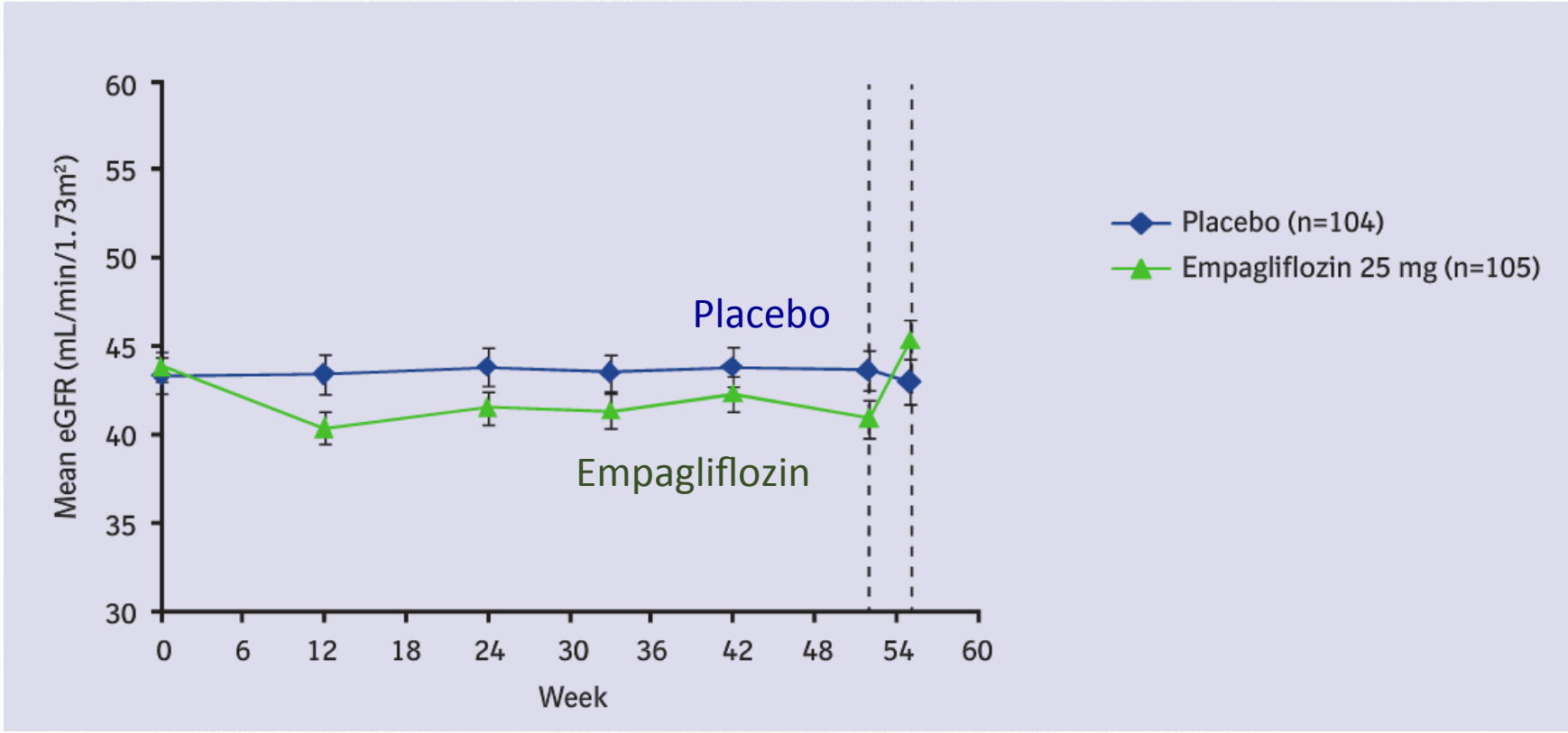
The eGFR decreases slightly, then increases slowly towards baseline in presence of moderate renal failure



Yale JF et al. ADA Annual Meeting 2013. Abstract 1075-P.

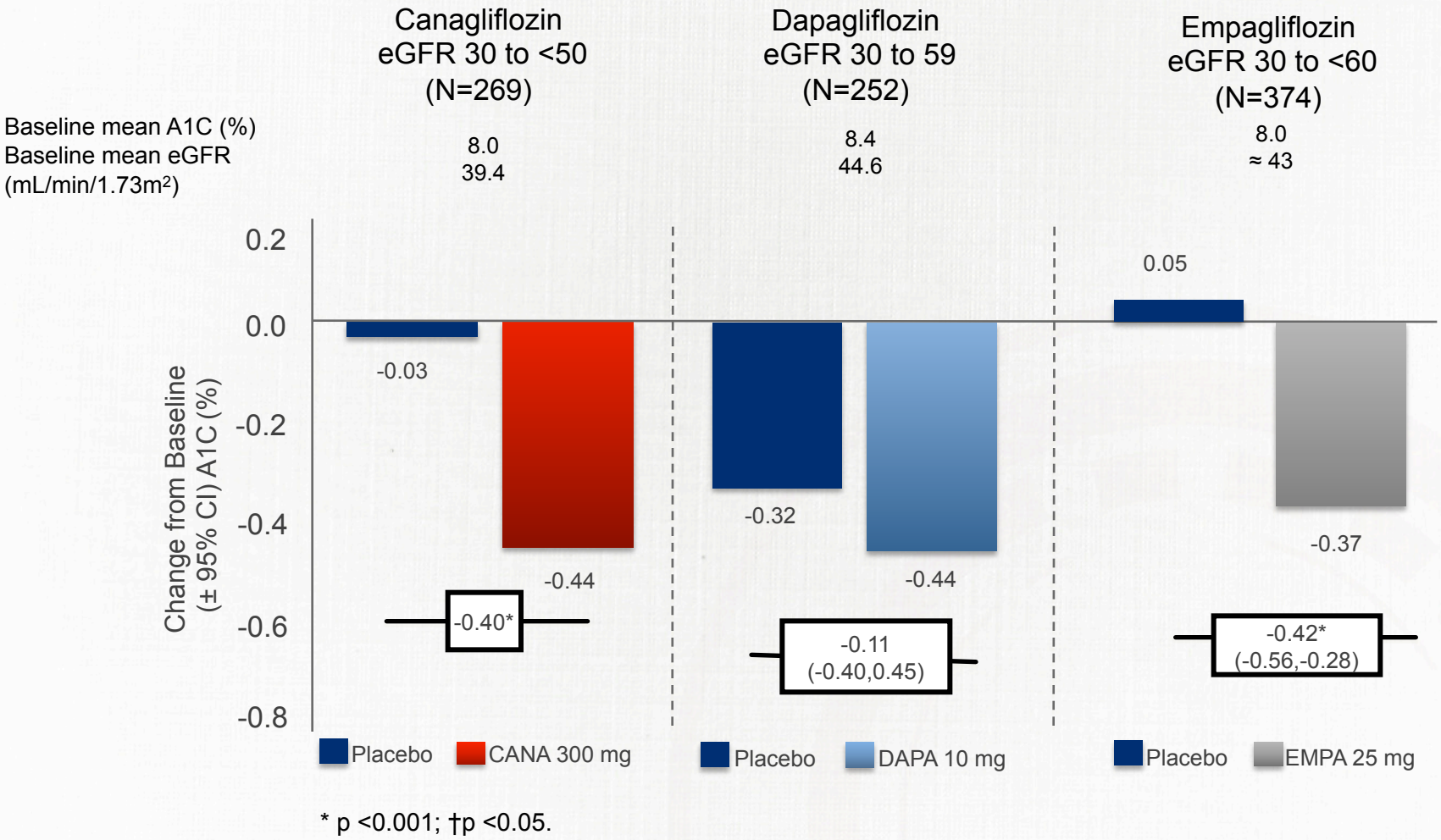
EFFECTS of SGLT2 Inhibitors on eGFR in presence of moderate renal failure

The eGFR decreases slightly, then increases slowly towards baseline In presence of moderate renal failure



EFFECTS of SGLT2 INHIBITORS on A1c LEVELS in CKD

In moderate renal failure, the A1C reduction is halved



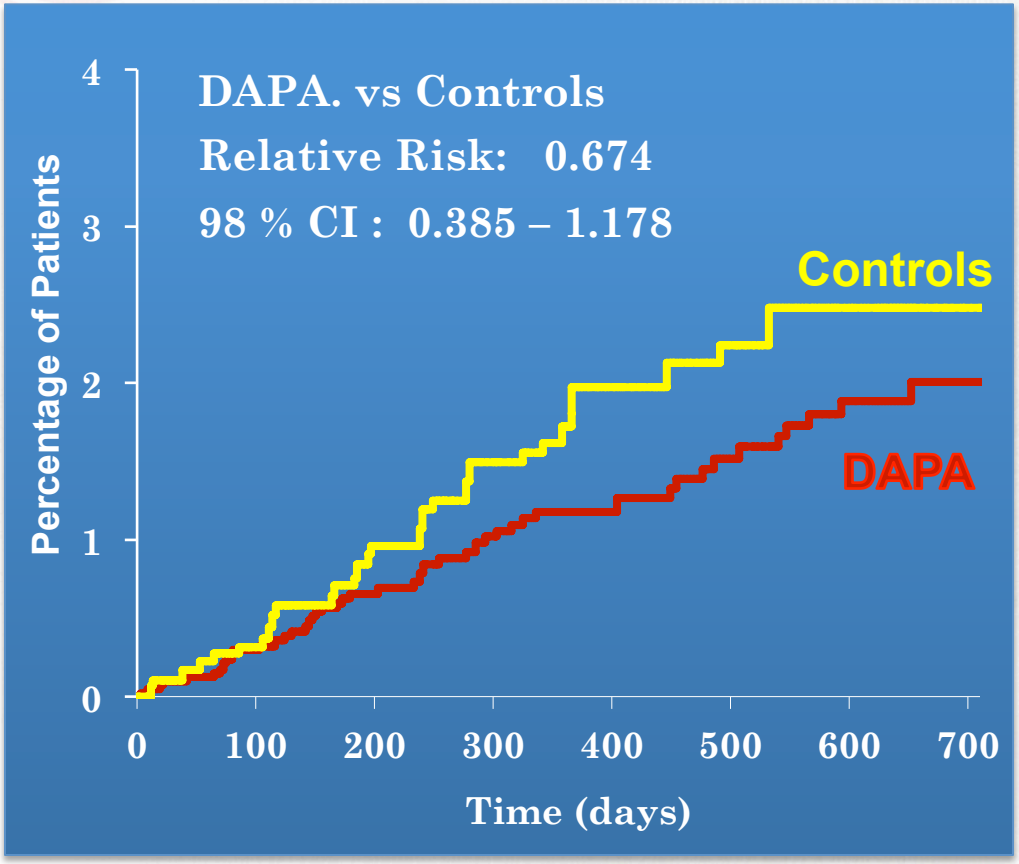
* p <0.001; †p <0.05.

Yale JF et al. Diabetes Obesity & Metabolism 2013;15:463-473. Kohan D et al. J Am Soc Nephrol 2011;22:232A:TH-PO524.
Barnett A et al. ADA Annual Meeting 2013. Abstract 1104-P.

CV RISK

Dapagliflozin: Cardiovascular Risk

Phase 2/3 Studies



Number of patients								
DAPA.	4 097	3 826	2 767	2 350	1 532	1 368	1 062	585
Controls	1 850	1 696	1 197	1 004	622	538	415	233

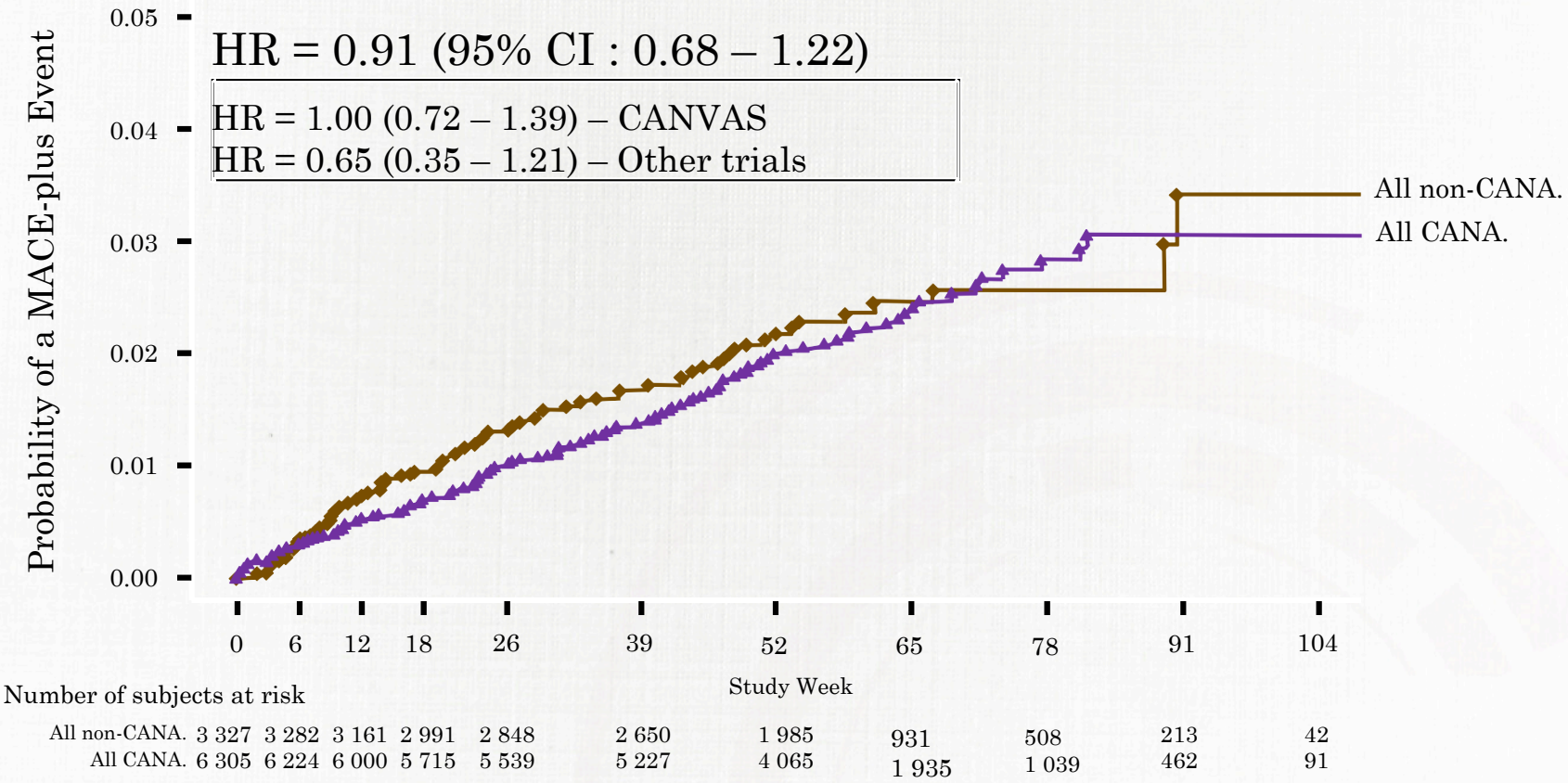
	DAPA		Controls	
	Number of first events	Event Rate	Number of first events	Event Rate
Patients with an event	48	1.13 %	30	1.66 %
CV Deaths	8	0.19 %	4	0.22 %
MI	18	0.42 %	18	1.00 %
CVA	11	0.26 %	5	0.28 %
Unstable angina	11	0.26 %	3	0.17 %

Langkilde A *el al*. American Heart Association Meeting, 2011; abstract 8947.

CANAGLIFLOZIN : MACE-PLUS

All phase 2/3 studies, including CANVAS

Kaplan-Meyer estimate



***Note** : Includes all studies with data base lock prior to January 31, 2012; mTTT analysis set; events within 30 days of last dose*

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Consulted January 23, 2013.

SGLT-2 Inhibitors: Ongoing CV Trials

	Treatment	n	Population	Endpoints	Results
CANVAS	Canagliflozin vs Placebo	4 363	CVD or high risk for CVD	CV death, non-fatal MI or non-fatal CVA	June 2018
C-SCADE 8	Empagliflozin vs Placebo	7 000	CVD	CV death, non-fatal MI or non-fatal CVA	March 2018
DECLARE	Dapagliflozin vs Placebo	17 150	CVD or high risk for CVD	CV death, non-fatal MI or non-fatal CVA	April 2019

Clinicaltrials.gov.

SGLT2 METABOLISM

Canagliflozin (Invokana®)
UGT1A9
UGT2B4

Dapagliflozin (Farxiga®)
UGT1A9 - major substrate
OAT3 – substrate
P-glycoprotein- weak substrate
Cytochrome P450 metabolism - undefined, minor pathway

Empagliflozin (Jardiance®)
UGT2B7, UGT1A3, UGT1A8, and UGT1A9 - substrate
OAT3 – substrate
OATP1B1 and OATP1B3- substrate
P-glycoprotein- substrate
BCRP - substrate

DRUG INTERACTIONS

	VIA	Canagliflozin	Dapagliflozin	Empagliflozin
Diuretics (loop, aldosterone antagonists)	↑urine volume and frequency of voids ↓volume depletion			
Rifampin	UGT		No Effect	No Effect
Phenytoin/CBZ	UGT		No Effect	No Effect
Ritonavir/ Efavirenz	UGT		No Effect	No Effect
Barbituates	UGT		No Effect	No Effect
Digoxin	Weak PGP inhibitor		No Effect	No Effect
Drugs that raise potassium (ie. ACE/ARB)	Hyperkalemia			
St Johns Wort	Weak CYP3A4 inhibitor		No Effect	No Effect

GUIDELINE STATEMENT ON SGLT2

- The American Association of Clinical Endocrinologists' (AACE) Comprehensive Diabetes Management Algorithm 2013 Consensus Statement lists SGLT2 inhibitors as a monotherapy option for T2DM patients with A1C <7.5%, or as a dual- or triple-therapy option for patients with baseline A1C ≥7.5% or patients who did not reach their A1C goal after 3 months of noninsulin monotherapy.

- The consensus statement cites the ability of SGLT2 inhibitors to provide glucose lowering without weight gain or risk of hypoglycemia as justification for their recommendation.

- In patients where weight loss is a therapeutic goal, the AACE recommends using an SGLT2 inhibitor or a GLP-1 receptor agonist along with metformin and intensive lifestyle management in preference over other therapies that promote weight gain.

- The most recent guidelines published by the American Diabetes Association do not address the use of SGLT2 inhibitors in the treatment of T2DM.

PRACTICAL TIPS AND CONSIDERATIONS IN STARTING SGLT2 INHIBITORS

INITIATING THERAPY

Drug	Dosage Form	Typical Dosage Range	Maximum Dose	Food
Canagliflozin (Invokana®)	**Tablet** 100mg 300mg	**Starting** 100mg once daily **Maintenance** 100 - 300mg once daily	300mg/day	Take before first meal of the day
Dapagliflozin (Farxiga®)	**Tablet** 5mg 10mg	**Starting** 5mg once daily **Maintenance** 5 - 10mg once daily	10mg/day	Take in morning with or without food
Empagliflozin (Jardiance®)	**Tablet** 10mg 25mg	**Starting** 10mg once daily **Maintenance** 10 - 25mg once daily	25mg/day	Take in morning with or without food

MONITORING PARAMETERS

Parameter	Interval	Comments
A1C	q3 months	
FG and PPG	SMBG, q3 months	
Renal Function -EGF and ACR	Prior, 1 month, q3months	More frequent monitoring in patients with eGFR <60ml/min
Electrolytes -Potassium	Prior, 1 month, q3-6months	Check more often with certain medications/ medical conditions
Weight	1 month	Peak wt loss at 6 months
Blood Pressure	1 month	Peak BP loss at 6 months
Cholesterol	3 months then q year	LDL, TG, HDL
Dehydration Status	1 month	BUN, electrolytes, SCr
Genital Mycotic Infections	Check at refills and new antibiotic Rxs	Most common in first 4 months

CONSIDERATIONS

Benefit	Risk Considerations
Reduced A1C >0.8%	Increased Yeast and UTI Infections
Effects both FBG and PPG	Reduced Intravascular Volume (in susceptible patients)
Low Risk Hypoglycemia	Increased LDL-Cholesterol
Reduced Triglycerides	Not indicated with eGFR < 45 ml/min
Reduced Blood Pressure	Long term clinical efficacy and safety is unknown
Reduced Weight	
Oral medication, Once Daily	
Can be combined with any drug therapy in T2DM and used at any stage of T2DM	

SUMMARY:

- SGLT2 inhibitors induce glucosuria, resulting in a loss of glucose in the urine.
- A1c is reduced by 0.5 to 1.2 %
- Body weight is reduced by 1.0 to 3.7 kg
- SGLT2 inhibitors rarely induce hypoglycemia, except when added to insulin or insulin secretagogues.
- Blood pressure is reduced by 1.7 to 6.6 mm Hg
- The following side effects can be observed: genital mycotic infections and side effects related to volume depletion.

CASE DISCUSSIONS WITH KEN BURNS

CASE #1

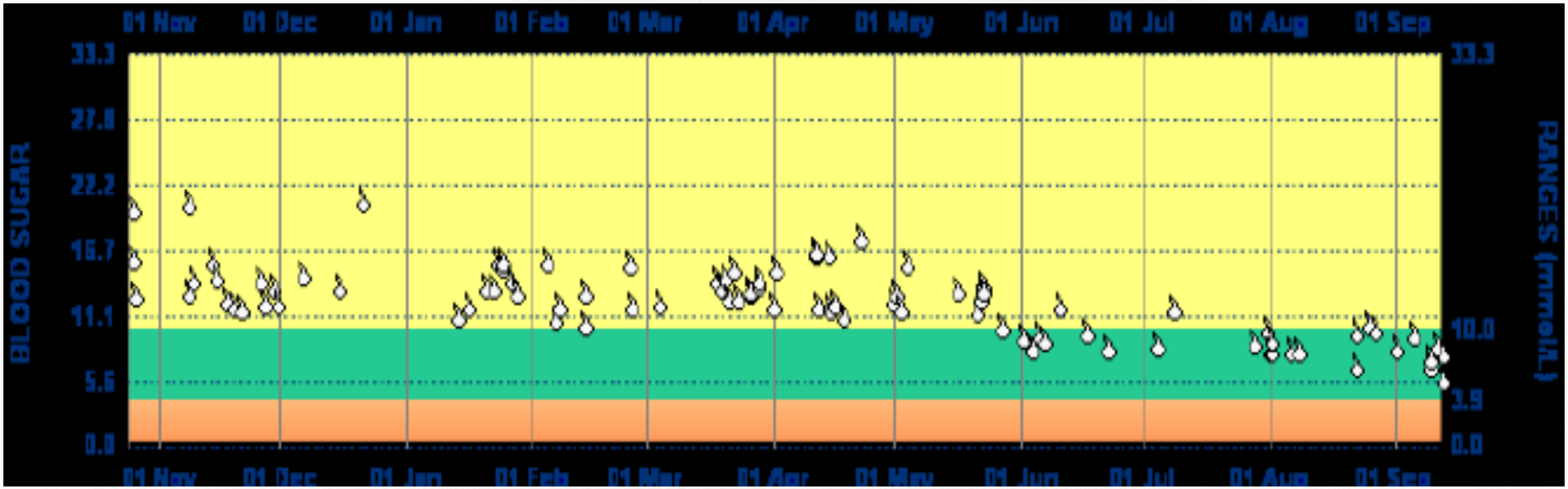
Patient R:

- Female, 56
- Type 2 diabetes
- Overweight
- Sedentary through winter

CASE #1

Blood sugar	Metformin	500mg at lunch and at supper
Blood sugar	Onglyza	5mg in the morning
Blood pressure	Norvasc	10mg at night
Blood pressure	Diovan	80mg in the morning
Cholesterol	Crestor	10mg in the morning
Breathing	Flovent	250mcg inhaler 2 puffs twice daily
Breathing	Bricanyl turbuhaler	Use as directed
Supplement	Vitamin D	1000 units daily
Supplement	Omega 3	Fish oil 1000mg EPA/DHA twice daily
Thyroid	levothyroxine	0.1mg daily

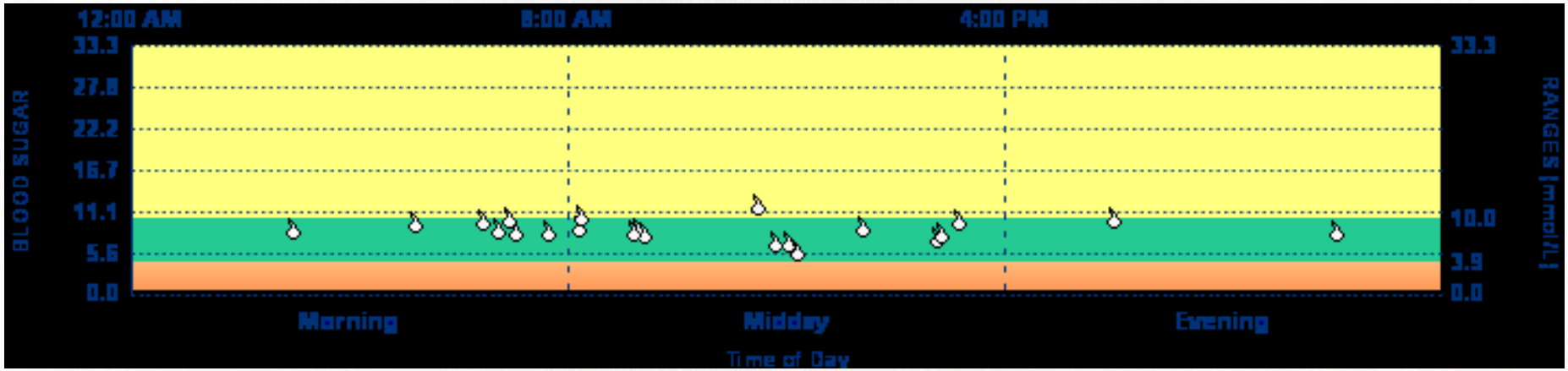
CASE #1


01 Nov
01 Dec
01 Jan
01 Feb
01 Mar
01 Apr
01 May
01 Jun
01 Jul
01 Aug
01 Sep
33.3
27.8
22.2
16.7
11.1
5.6
0.0
BLOOD SUGAR
RANGES (mmol/L)
10.0
3.9

Options?

- Increase metformin
- Secretagogue
- Incretin
  - GLP-1
- TZD
- Acarbose
- Xenical
- Insulin
- SGLT2
- Dietary changes and physical activity

CASE #1


12:00 AM
8:00 AM
4:00 PM
33.3
27.8
22.2
16.7
11.1
5.6
0.0
BLOOD SUGAR
33.3
10.0
3.9
0.0
RANGES [mmol/L]
Morning
Midday
Evening
Time of Day

CASE #1

Issues and concerns:

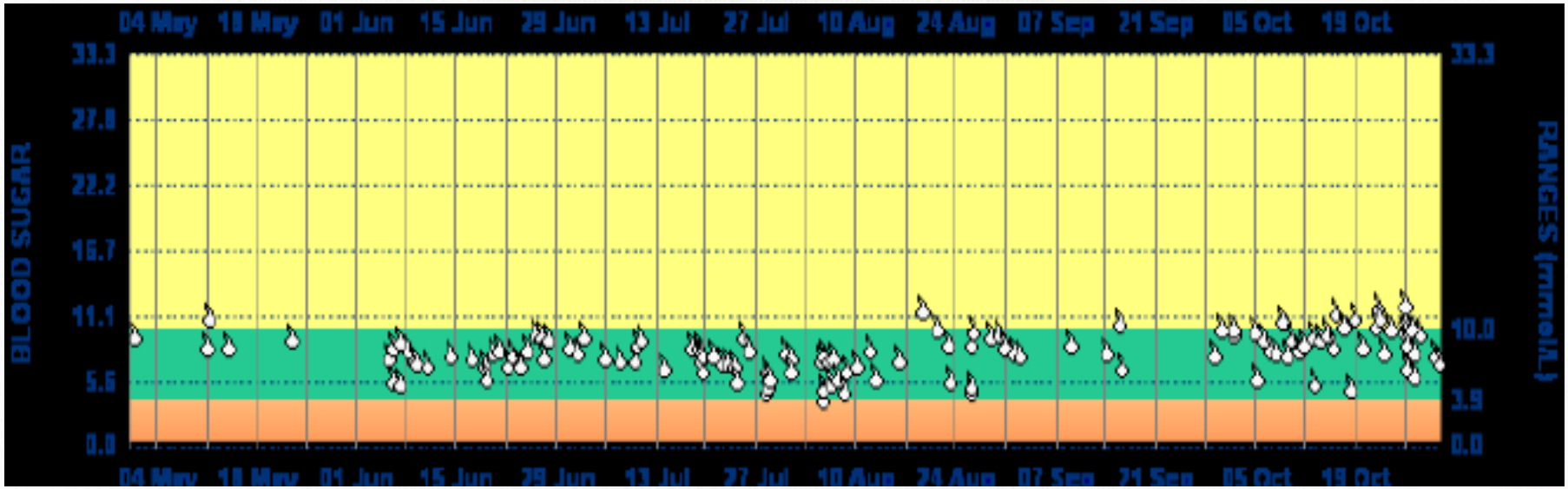
- Does not want insulin
  - Hectic work/life schedule
  - Meals erratic
- Boss makes her eat at her desk if she has time
- Lives with daughter and food choices are her daughters
- Metformin causes GI side effects over 1000mg per day
- Not a fan of weight gain

CASE #2

Patient P:

- Female, 48 years old
- Type 2 diabetes
- Obese
- Chronic pain, fibromyalgia, osteopenia

Blood sugar	Metformin	1000mg twice daily
Blood sugar	Gliclazide	30mg MR daily
Blood pressure	Telmisartan	40mg daily
Water pill	Amiloride and hydrochlorothiazide	5mg/50mg daily
Cholesterol	Rosuvastatin	20mg daily
Stomach	Rabeprazole	20mg daily
Pain	Naproxen	500mg daily
Iron	Ferrous fumarate	300mg twice daily
Supplement	Vitamin C	1000mg
Supplement	Coenzyme Q-10	1 or 2 daily
Supplement	Cranberry	Once daily
Supplement	Calcium/magnesium	1-2 daily (Jamieson brand)
Supplement	Vitamin D	1000 units daily
Supplement	Omega 3	Wild fish oil blend
Supplement	Quercetin	
Asthma	Advair	250mcg inhaler 2 puffs twice daily
Nose	Omnaris	Used when has a cold
Supplement	Centrum select	Adult 50plus once daily
Supplement	Vitalux	For eye health
Supplement	Glucosamine/chondroitin/MSM	3 daily
Supplement	Melatonin	5mg before bed
Supplement	Digestive enzymes	Webber
Supplement	Chromium	500mcg once daily
	Zeal	Nutrient supplement

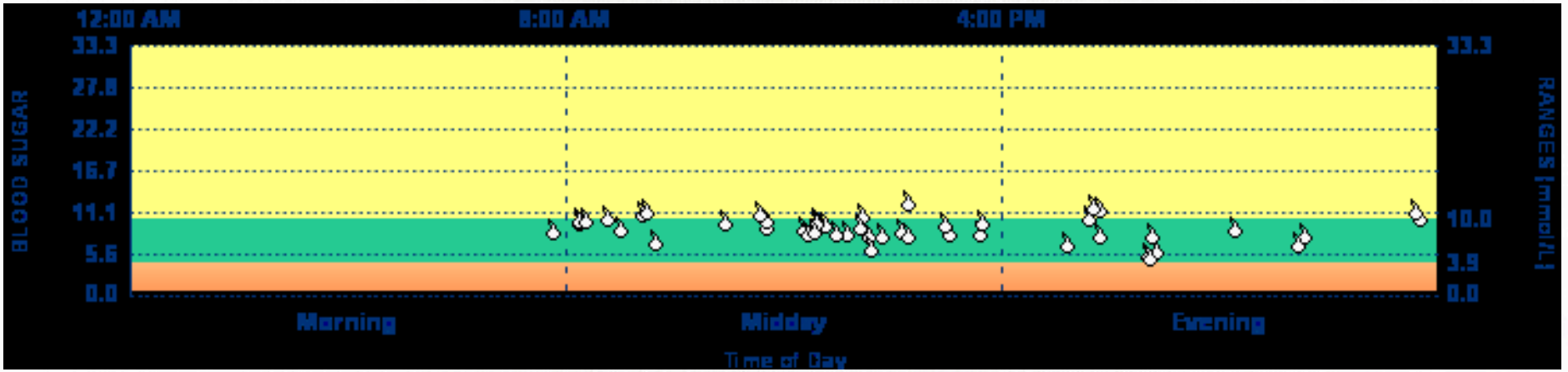

04 May
18 May
01 Jun
15 Jun
29 Jun
13 Jul
27 Jul
10 Aug
24 Aug
07 Sep
21 Sep
05 Oct
19 Oct
BLOOD SUGAR
33.3
27.8
22.2
16.7
11.1
5.6
0.0
RANGES (mmol/L)
33.3
10.0
3.9
0.0

CASE #2

Options?

- Increase Gliclazide
- Incretin
  - DPP4
  - GLP-1
- TZD
- Acarbose
- Xenical
- Insulin
- SGLT2
- Dietary changes and physical activity

CASE #2


12:00 AM
8:00 AM
4:00 PM
33.3
27.8
22.2
16.7
11.1
5.6
0.0
BLOOD SUGAR
33.3
10.0
3.9
0.0
RANGES [mmol/L]
Morning
Midday
Evening
Time of Day

CASE #2

Issues and concerns:

- Weight gain
- Levels improved, but then got worse again
- I don’t want insulin
  - I don’t like needles
  - I don’t want to gain wait
- I thought sugar was bad for my kidney
- Then can I eat whatever I want?

What do we want to do?

CASE #2

Patients therapeutic problem(s). ***P was initiated on gliclazide earlier this year. Glycemic control improved for 2 to 3 months, and then worsened again to previous levels. P states she has not changed her diet or activity levels, and denies any increased levels of stress or fatigue or illness that may contribute to poor control. This suggests the possibility that progressive pancreatic beta cell failure that was unable to increase insulin production with sulfonylurea therapy for more than 3 months. It also suggests a different target for glycemic therapy.***

R = Recommendations

Solution focused recommendation(s); **Invokana is a reasonable choice, starting at 100mg daily and increasing to300mg daily as needed and tolerated. Optimum effects will be at 300mg daily**

Rationale: ***Invokana works on renal excretion of glucose and is independent of insulin action. This effect is not subject to declining beta cell function. The 300mg dose is appropriate as a target dose as this patients eGFR was over 120 in June, 2014, and there are no significant interactions with current therapy. The risks of mycotic infections has been discussed.***

BONUS CASE

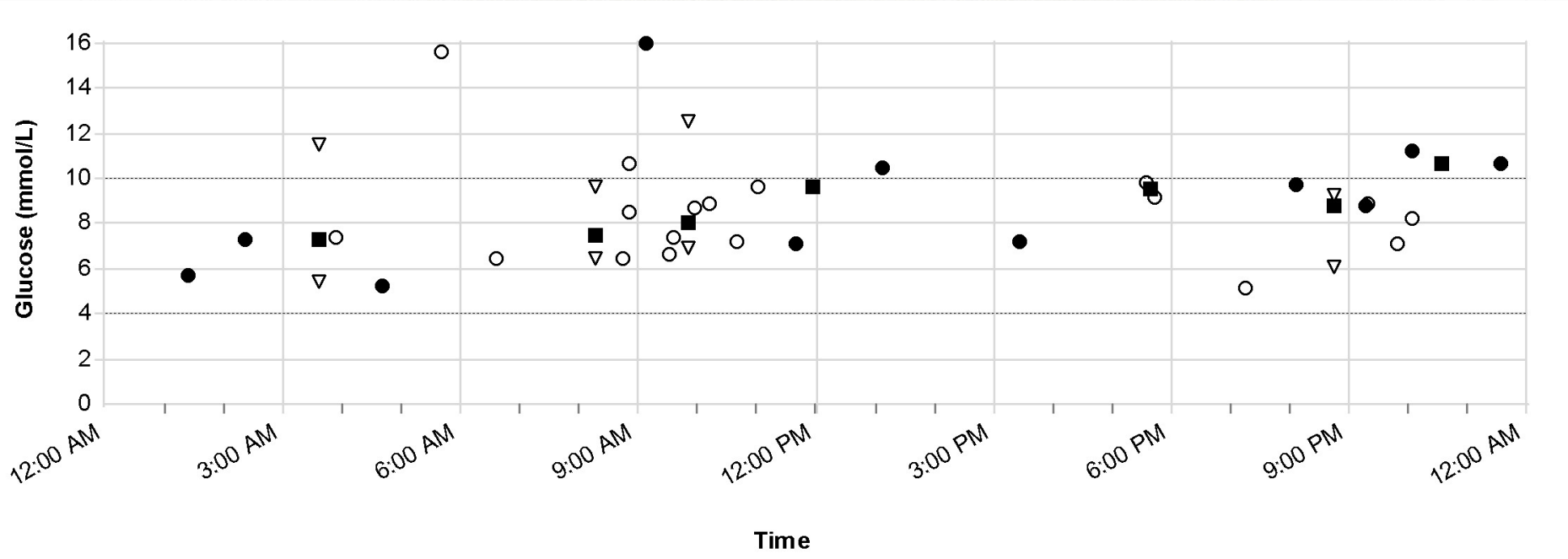
Patient D:

- Male, 64
- Type 2 diabetes
- Overweight
- Chronic pain

BONUS CASE

Blood sugar	Janumet	50mg/850mg twice daily
Blood sugar	Gliclazide	30mg MR once daily
Blood pressure	Avapro	150mg daily
Blood pressure	Metoprolol	75mg twice daily
Cholesterol	Niacin	500mg three times daily
Cholesterol	Ezetrol	10mg daily
Cholesterol	Atorvastatin	80mg daily
Antiplatelet	Clopidogrel	75mg daily
Stomach	Rabeprazole	20mg daily
Nose	Avamys	Use one spray in each nostril at bedtime
Mood	Cipralex	10mg daily
Gout	Allopurinol	300mg daily
Gout	Colchicine	0.6mg twice daily
Gout	Indomethacin	25mg when needed for gout
Pain	Tramadol and acetaminophen	37.5/325mg every 4 hours when needed
Sleep	Zopiclone	7.5mg at bedtime
Prophylaxis	Amoxicillin	2g 1 hour before appointment
Pain	Tylenol #3	When required

BONUS CASE


Glucose (mmol/L)
16
14
12
10
8
6
4
2
0
12:00 AM
3:00 AM
6:00 AM
9:00 AM
12:00 PM
3:00 PM
6:00 PM
9:00 PM
12:00 AM
Time

BONUS CASE

Options?

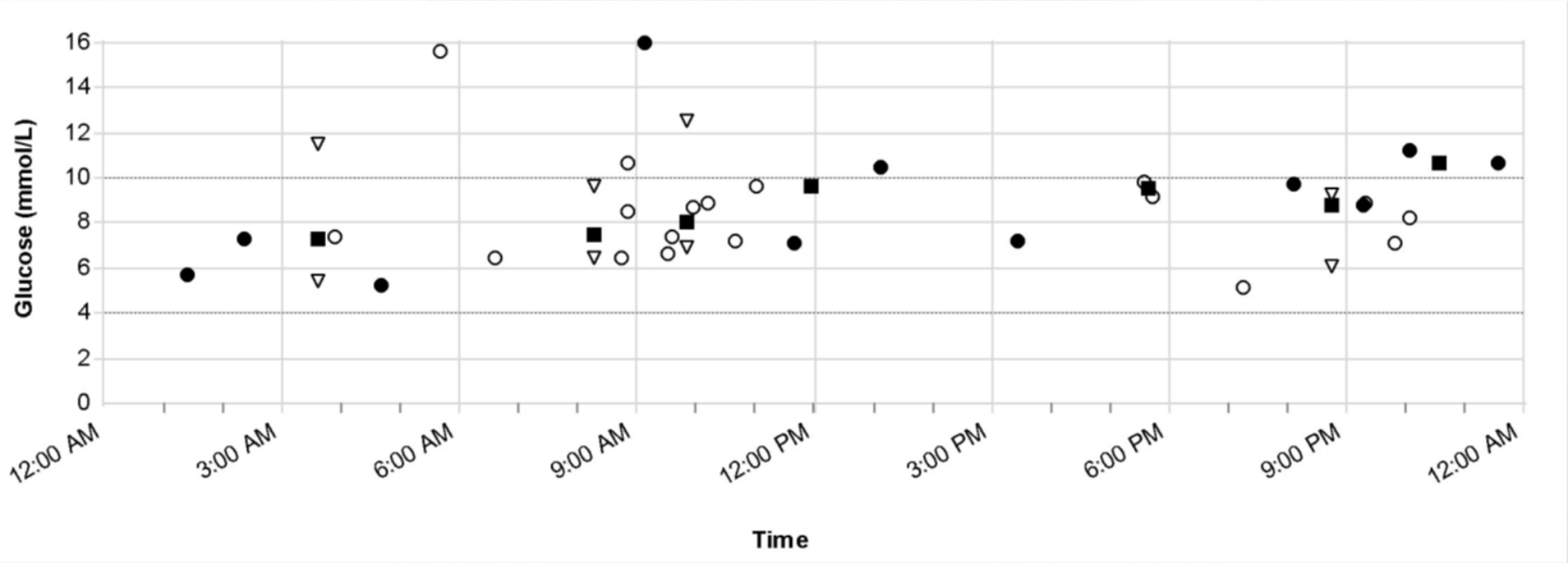
- Increase gliclazide
- Incretin
  - GLP-1
- Increase metformin
- TZD
- Acarbose
- Xenical
- Insulin
- SGLT2
- Dietary changes and physical activity

BONUS CASE

Issues and concerns:

-
  - Just starting to take diabetes seriously
  - Didn’t know much about diabetes before
  - Willing to make changes
  - What is next after diet and exercise are changed?

BONUS CASE


Glucose (mmol/L)
16
14
12
10
8
6
4
2
0
12:00 AM
3:00 AM
6:00 AM
9:00 AM
12:00 PM
3:00 PM
6:00 PM
9:00 PM
12:00 AM
Time

Thank You