Pharmacology Update for Advanced Practice Nurses

SNAP 2014

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Approaches to Preventing Diabetes

- Making Lifestyle Changes
  - Walking 5 days a week for 30 minutes. Lowering intake of calories and fat.
- Taking Medications as Prescribed
  - Metformin® (glucophage)

Diabetes Prevention Program

- Participants were overweight and had higher than normal levels of blood glucose many had family history of type 2 diabetes.

- Tested 3 approaches to preventing diabetes
  - Making lifestyle change
  - Taking the diabetes medication Metformin®
  - Receiving Education about diabetes

Diabetes Prevention Program

According to the study:

Lifestyle change group showed the best outcomes

People in this group:

Reduced their risk of developing diabetes by 34%

Even more effective in those age 60 and older: the risk was reduced by 49%

ALSO- had fewer heart disease risk factors, lower blood pressure, and triglyceride levels.

Diabetes Prevention Program

According to the study:

those whom started taking medication

Metformin®

reduced their risk of developing diabetes by 18%

Which of these apply to your patients

- ❑ 45 years +
- ❑ Overweight
- ❑ Have a parent or sibling with diabetes
- ❑ Family background in African American, Alaska Native, American Indian, Asian American, Hispanic/Latino, or Pacific Islander American.
- ❑ Had gestational diabetes
- ❑ High Blood Pressure
- ❑ Gave birth to a baby weighing more than 9 pounds
- ❑ Increased cholesterol
- ❑ HDLs below 35
- ❑ Triglycerides greater than 250
- ❑ Polycystic Ovary Syndrome
- ❑ Acanthosis nigricans

Do you think Sleep matters?

Yes!

Studies show that untreated sleep, including sleep apnea, can increase a persons risk for diabetes.

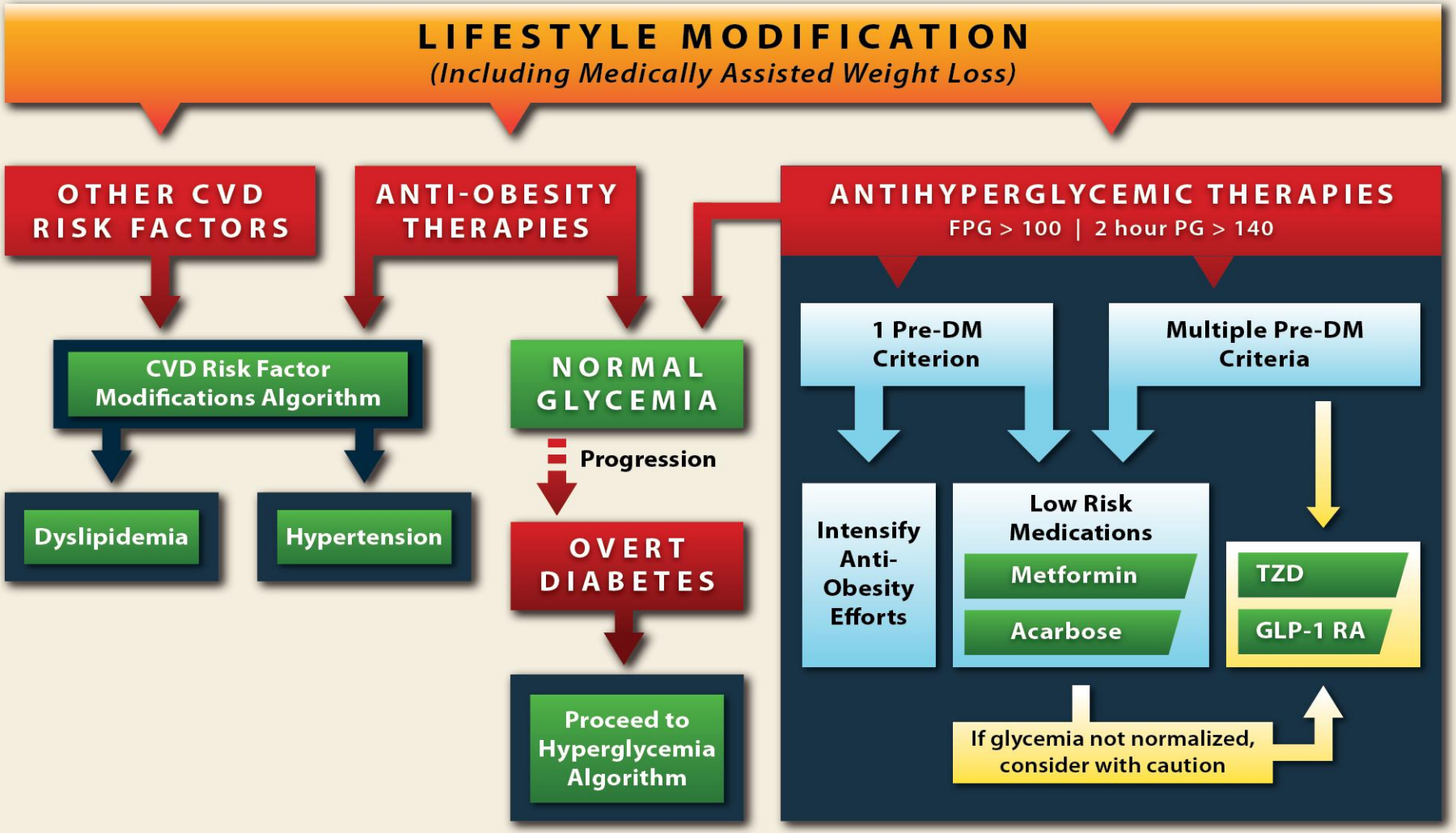
More information about sleep problems is available at www.hhlbi.nih.gov/health/public/sleep

How can your patients reduce their risk?

- Increase physical activity
- Reducing fat and calorie intake
- Losing weight
- Taking medications as prescribed
- Keeping blood pressure within normal limits
- Lowering cholesterol levels

Prediabetes Algorithm

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2005)



Reprinted with permission from American Association of Clinical Endocrinologists. Garber AJ, Abrahamson, MJ, Barzilay JI, et al. AACE Comprehensive Diabetes Management Algorithm. Endocr Pract. 2013;19:327-336."

Prediabetes

- Failing pancreatic compensation to an underlying state of insulin resistance
- Criteria for diagnosing: impaired glucose tolerance, impaired fasting glucose or metabolic syndrome
- 5 fold increase in future T2DM risk

Prediabetes Management

- Primary goal of prediabetes management is weight loss
  - Lifestyle modification
  - Pharmacological assistance
  - Bariatric surgery
- Antihyperglycemic Medications
  - Metformin and Acarbose
    - Reduce future diabetes incidence by 25-30%
  - Thiazolididinediones
    - have been shown to prevent 60-75% of future diabetes
    - Associated with increase risk of bone fractures and fluid retention and may worsen underlying heart failure

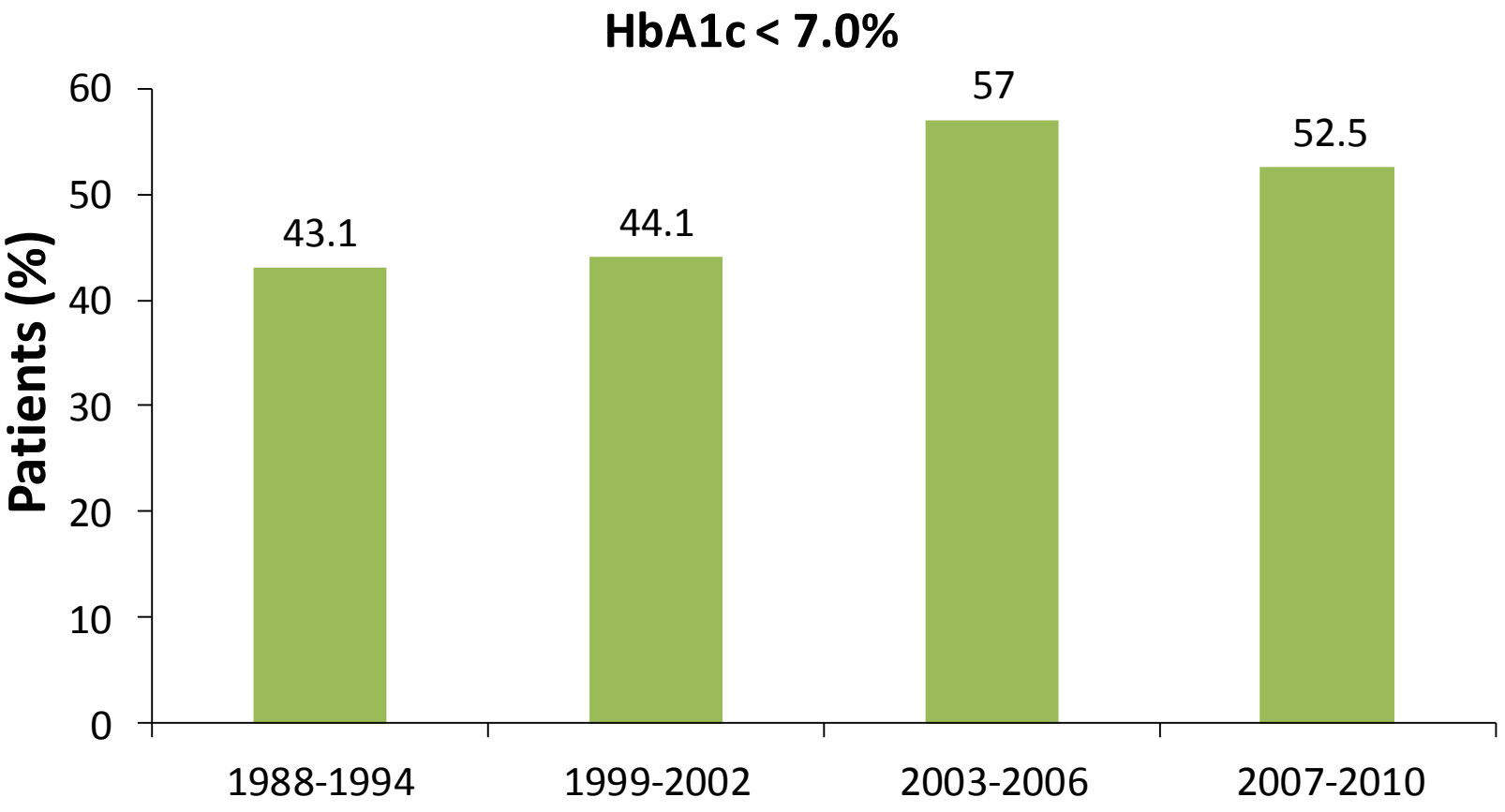
Glycemic Control Recommendations for T2DM: AACE 2013 and ADA 2013

Target Treatment Goals	AACE 2013[1]	ADA 2013[2]
HbA1c	≤6.5%	<7.0%
Fasting glucose	FPG: <110 mg/dL	Preprandial capillary plasma glucose: <70-130 mg/dL
Postprandial glucose	2-hour postprandial glucose: <140 mg/dL	Peak postprandial capillary plasma glucose: <180 mg/dL

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; FPG, fasting plasma glucose.

1. Mechanick JI, et al. *Endocr Pract.* 2013;19(2):337-372.
2. American Diabetes Association. *Diabetes Care*. 2013;36(suppl 1):S11-S66.

Diabetes Control in the United States



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

Key Sites of Action of Oral Medications for Type 2

- Pancreas – Insulin Secretion
  - Sulfonylureas, Meglitinides, Incretins
- Liver – Glucose Production
  - Biguanides, Thiazolidinediones, Incretins
- Peripheral Glucose Uptake
  - Thiazolidinediones, Biguanides
- Intestine – Glucose Absorption
  - Alpha-glucosidase-inhibitor, Incretins
- Kidney – Block renal glucose reabsorption
  - SGLT-2 Inhibitor

SULFONYLUREAS

Generic Names and (Brand Names)

DIABETA®, MICRONASE®, GLYNASE® (Glyburide)

GLUCOTROL®, GLUCOTROL XL® (Glipizide)

AMARYL® (Glimepiride)

Increases insulin production by the pancreas.

A1C reduction of .4 to 1.2 %

These drugs are generally taken one to two times a day, before meals. Need to have meals & take meds at the same time every day.

Side Effects: Can cause low blood sugar (hypoglycemia), weight gain, and skin rashes. Some sulfonylureas can interact with alcohol to cause vomiting, flushing, or sickness.

MEGLITINIDES

Generic Name and (Brand Names)

PRANDIN® (Repaglinide)

STARLIX® (Nateglinide)

Increases insulin production by the pancreas.

A1C reduction of .4 to 1.2 %

Take at start of each and every meal.

Side Effects: Can cause low blood sugar (hypoglycemia), stomach upset and weight gain.

BIGUANIDES

GLUCOPHAGE®, GLUCOPHAGE XR®, GLUMETZA®, FORTAMET®, RIOMET® (Metformin)

Activation of intracellular adenosine monophosphate-kinase, which reduces hepatic glucose output and secondarily may improve beta cell function and insulin resistance.

- Lowers A1C by 1-1.5% at maximum or near maximum dose.
- Usual dose: 1500-2000 mg/day
- Side effects: diarrhea, nausea & vomiting, gas, abdominal bloating, metallic taste, weight loss. Take with meals to reduce side effects.

BIGUANIDES

- Hypoglycemia is uncommon to rare
- Risk of lactic acidosis therefore contraindicated in patients with impaired renal function
  - Creatine > 1.5 mg/dL males and 1.4 mg/dL females or
  - eGFR < 60
  - this limitation has been challenged, however, and lower doses have been proposed for patients with moderate renal insufficiency.
- Avoid excessive alcohol intake
- Lowers Vitamin B12 levels
- May decrease triglyceride levels and total LDL

THIAZOLIDINEDIONES

AVANDIA® (Rosiglitazone)
ACTOS® (Pioglitazone)

Decreases insulin resistance at the muscle and liver.

Lowers A1C by .7-1.2% .

Typically takes 4-6 weeks to see an effect on blood sugar.

THIAZOLIDINEDIONES

- Side Effects:
  - Weight gain and fluid retention which may contribute to chronic edema and heart failure, and adverse metabolic effects on bone causing an increased risk of fractures.
  - Liver damage
    - Check liver function prior to treatment Then, every two months for the first year and periodically thereafter.
  - May cause women who are not ovulating and have not gone thru menopause to begin ovulating, enabling them to conceive. Oral contraceptives may be less effective when taking these meds.
  - Avandia®: Carries a potential increased risk of heart attack

ALPHA-GLUCOSIDASE INHIBITORS

Generic Name and (Brand Names)

PRECOSE® (Acarbose) and GLYSET ® (Miglitol)

Lowers postprandial glucose by inhibiting the gut enzyme that break down complex carbohydrates, thus delaying polysaccharide absorption.

A1C lowering effect 0.4 to 0.7%.

Take with the 1st BITE of each a meal

- Hypoglycemia treatment: with glucose (dextrose) tablets, milk, apple or orange juice. DO NOT use table sugar or soda they are less effective.
- Side effects: gas, abdominal pain, diarrhea. Start low and increase slowly to minimize side effects.

DPP-4 Inhibitor

NESINA®(Aloglipin)

TRADJENTA® (Linagliptin)

ONGLYZA®(Saxaglipitin)

JANUVIA® (Sitagliptin)

Inhibits the enzyme that breaks down the incretin hormones. Increases insulin production after a meal and decreases the liver's production of glucose.

A1C lowering effect 0.5 to 0.9%.

Concerns regarding increased risk of pancreatitis and pancreatic cancer remain unresolved.

Excreted by kidneys except Linagliptin. Dose restrictions may be advisable for some patients.

Side effects: include upper respiratory tract infection, stuffy or runny nose and sore throat, and headache.

Dopamine-2 Agonist

CYCLOSET® (Bromocriptine)

Blocks the release of the hormone prolactin from the pituitary gland.

A1C lowering effect about .5%

Blood sugar lowering mechanism of action unknown.

Should be taken within 2 hours of wakening

Side effects: may cause N/V, dizziness upon standing, headache & worsening of liver problems.

Bile Acid Sequestrants

WELCHOL® (Colesevelam)

Lowers glucose modestly through an unknown mechanism.

A1C lowering effect .4% to .6%

Side effects include GI upset, abdominal pain, weakness, & muscle pain.

Needs to be taken at least 4 hours before glyburide, birth control pills, synthroid, dilantin, or vitamins.

INCRETIN MIMETIC

- Byetta® (Exenatide)
  Bydureon® (Exenatide extended release)
  Victoza ® (Liraglutide)

- Stimulate insulin secretion from the beta-cells of pancreas and reduce glucagon secretion from the alpha cells and slow gastric emptying.
- A1C lowering effect .8 to 2%, weight loss 1-4kg

INCRETIN MIMETIC

Bydureon® and Victoza® carry a black box warning.

Thyroid C-cell Tumor Risk in rats

Instruction for Use

Victoza®: Inject anytime of day.

Byetta®: Inject within 60 min before breakfast & dinner

Bydureon®: It is taken once a week, any time of the day & on the same day each week. May be taken with or without food. If you want to change your dosing day, your new dosing day must be at least 3 days apart from your original dosing day.

Inject in thigh, abdomen, or upper arm

Amylin Analogue

Symlin® (Pramlintide)

Uses

- Mimics the effects of a naturally occurring substance in the body called **Amylin** **which is** secreted along with insulin in response to food intake.
- As an add on therapy for patients receiving insulin who are not adequately controlled
- Helps improve post meal glucose levels.
- Slows gastric emptying and controls appetite.
- Decrease the livers production of glucose.

Symlin® (Pramlintide)

Do not mix with Insulin

Separate site of injection from insulin

Inject in the stomach or thigh area…do not use arms

If vial becomes cloudy… discard

May affect absorption of many medications that are taken by mouth

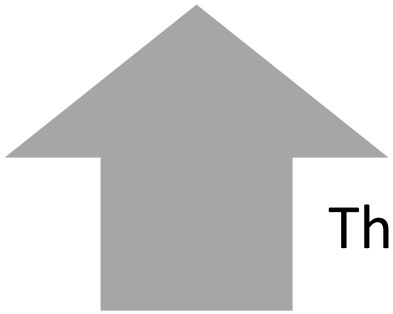
Take other meds 1 hour before or

2 hours after symlin injection.

Role of the Kidney in T2DM

A Look at the Kidney in Patients With T2DM

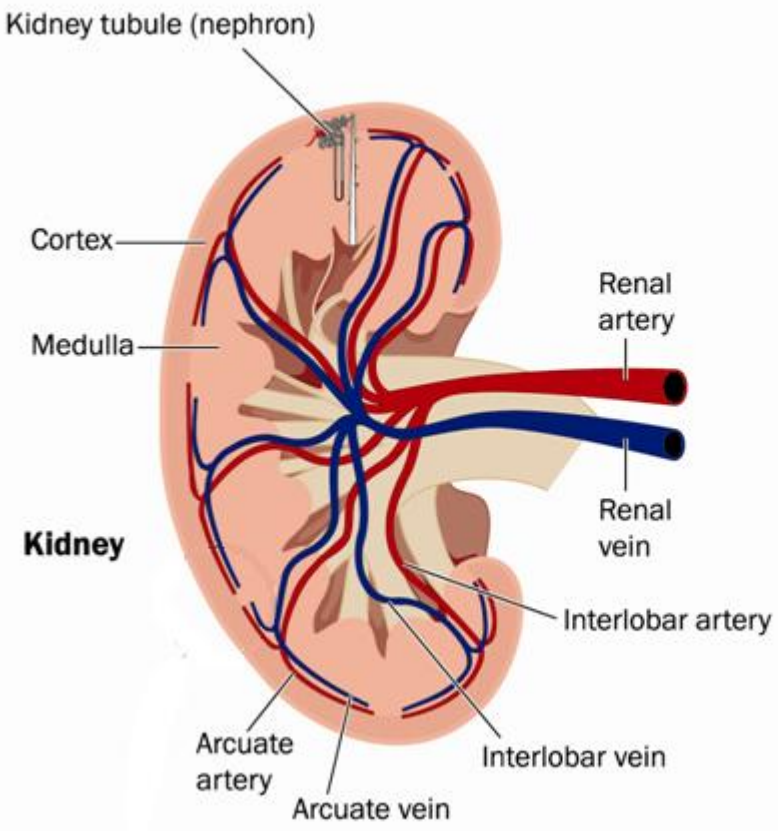
- Patients with T2DM have altered mechanisms of handling glucose, including increased renal:
  - Gluconeogenesis
  - Glucose uptake
  - Glucose reabsorption



Thus, contributing to further hyperglycemia

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

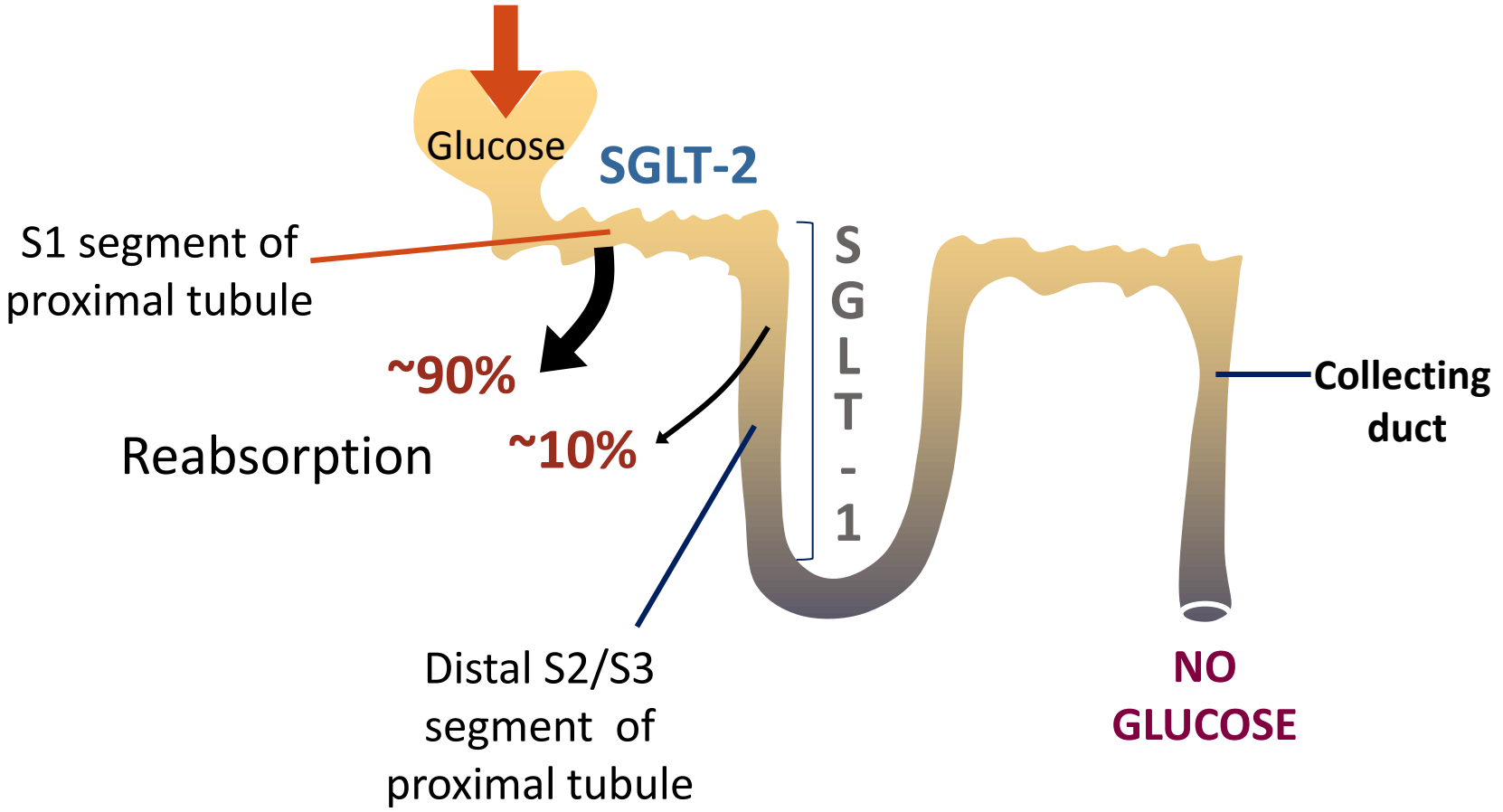
Kidney and Glucose Homeostasis



- Site of glucose filtration
- Filters 180 g/d; almost all is reabsorbed
- Reabsorbed by the SGLT-1 and SGLT-2 co-transporters in the proximal tubules
- Amount excreted in the urine is <0.5 g/d

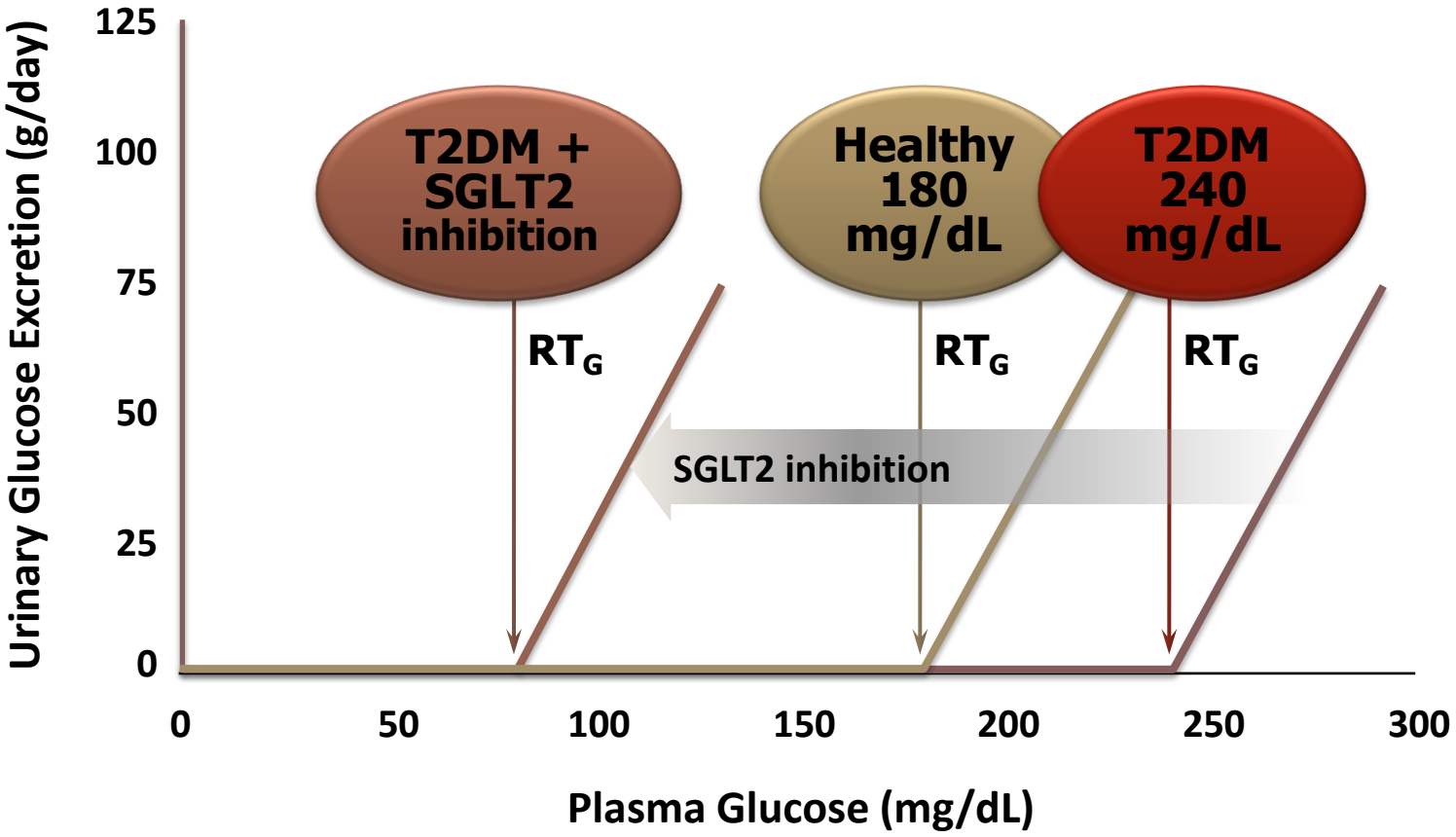
Gerich JE, et al. *Diabetes Care*. 2001;24(2):382-391.
Image: Blamb/Shutterstock.com.

Renal Glucose Reabsorption



Chao EC, Henry RR. *Nat Rev Drug Discov*. 2010;9(7):551-559.

SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion (RT_G)



T2DM=Type 2 Diabetes Mellitus
Adapted with permission from Abdul-Ghani MA, DeFronzo RA.

Abdul-Ghani MA, DeFronzo RA. *Endocr Pract.* 2008; Nair S, Wilding JP. *J Clin Endocrinol Metab.* 2010.

SGLT-2 Inhibitors

- Canagliflozin
- Dapagliflozin
- Empagliflozin (BI 10773) *
- Ipragliflozin (ASP1941) *

*These agents have not been approved by the FDA, but they are in Phase 3 clinical trials.

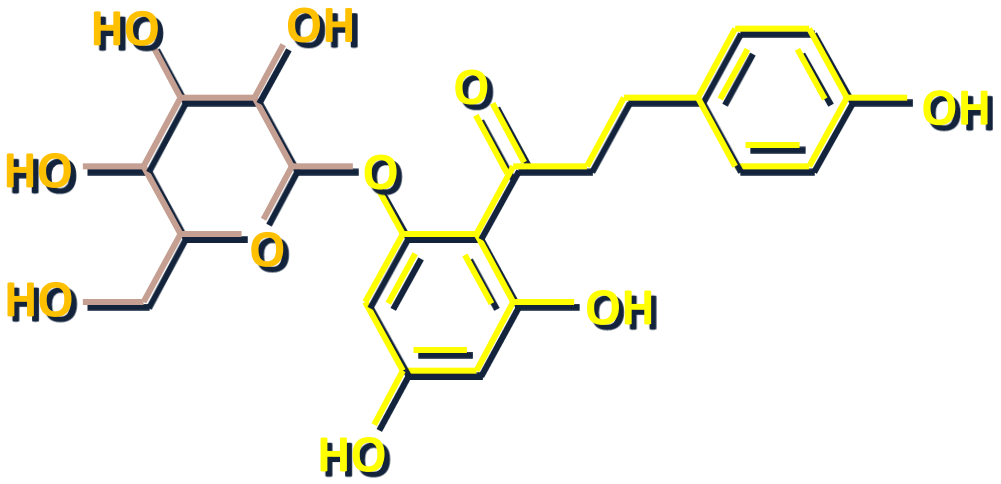
SGLT2 Inhibitors

- DAPAGLIFOZIN® (Farxiga)
- CANAGLIFLOZIN® (Invokana)

Glucose in the bloodstream passes through the kidneys that filter wastes from the blood and form urine. They send urine to the bladder, where it can either be excreted or reabsorbed. Sodium-glucose transporter 2 (SGLT2) works in the kidney to reabsorb glucose. **SGLT2 Inhibitors** block this action, causing excess glucose to be eliminated in the urine.

Side effects can include urinary tract and yeast infections.

Phlorizin: The 'Prototype' SGLT Inhibitor

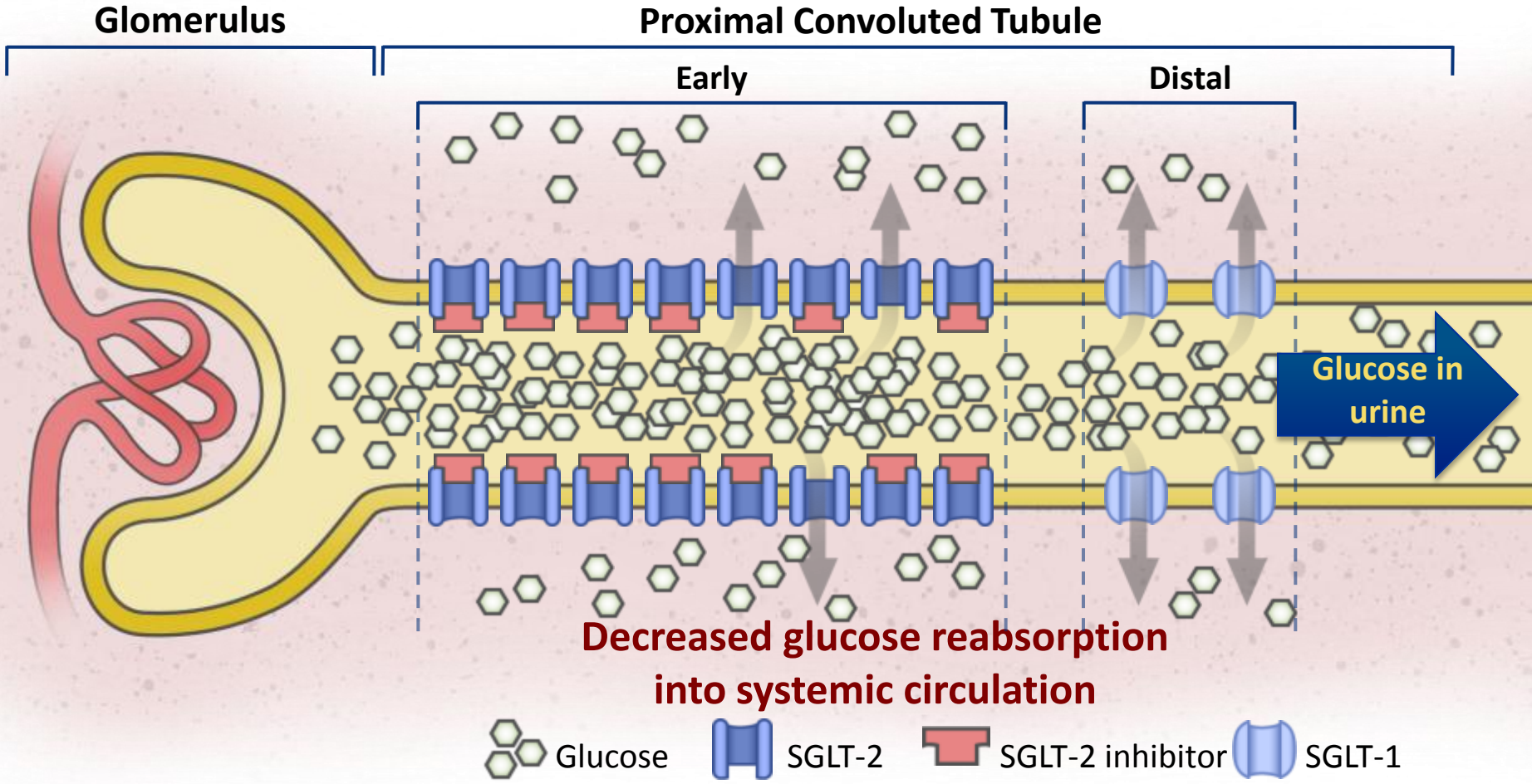


- First described in the mid-19th century
- Isolated from the root bark of the apple tree
- Utilized in the exploration of SGLT function
- Nonselective inhibitor of SGLT1 and SGLT2

Ehrenkranz JR. *Diabetes Metab Res Rev*. 2005.

Mechanism of Action

- Increase the removal of glucose via SGLT-2 inhibitors



Rothenberg PL, et al. Poster presented at: 46th Annual Meeting of the European Association for the Study of Diabetes; September 20-24, 2010; Stockholm, Sweden. Abstract 876.

Monotherapy Trials

	Canagliflozin 100 mg[1] (n = 75)	Canagliflozin 300 mg[1] (n = 75)	Dapagliflozin 10 mg[2] (n = 70)
Duration (wk)	12	12	24
Total patients in trial	383	383	485
Age (y)	57.7±10.5	57.1±10.1	50.6±9.97
BMI (kg/m^2)	25.61±4.64	25.89±3.68	33.6±5.4
Initial HbA1c (%)	8.05±0.86	8.17±0.81	8.01±0.96
Placebo-corrected change in HbA1c (%)	–0.91 *P*<0.01[a]	–0.99 *P*<0.01[a]	–0.66 *P*<0.0001[a]
Placebo-corrected change in weight (kg)	–1.73 *P*<0.01[a]	–2.41 *P*<0.01[a]	–1.0 (NS)

[a]*P* value versus placebo.

1. Inagaki N, et al. *Diabetes Obes Metab.* doi:10.1111/dom.12149.
2. Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-2224.

Monotherapy Trials (cont)

	Canagliflozin 100 mg[1] (n = 75)	Canagliflozin 300 mg[1] (n = 75)	Dapagliflozin 10 mg[2] (n = 70)
Baseline SBP	Data not available	Data not available	Data not available
Δ SBP (mm Hg)	–7.1±1.2 *P*<0.01[a]	–8.7±1.2 *P*<0.01[a]	–3.6±1.9
Baseline DBP	Data not available	Data not available	Data not available
Δ DBP (mm Hg)	–3.9±0.9 *P*<0.05[a]	–4.2±0.8 *P*<0.01[a]	–2.0±1.1
Genital infections [N (%)]	1 (1.4) [Pbo: 0]	1 (1.4) [Pbo:0]	9 (12.9) [Pbo: 1 (1.3)]
UTI [N (%)]	0 [Pbo: 0]	0 [Pbo: 0]	4 (5.7) [Pbo: 3 (4)]
Hypoglycemia [N (%)]	1 (1.4) [Pbo: 0]	1 (1.3) [Pbo: 0]	2 (2.9) [Pbo: 2 (2.7)]

SBP, systolic blood pressure; **Δ,** change; DBP, diastolic blood pressure; UTI, urinary tract infection.
[a]*P* value versus placebo.

1. Inagaki N, et al. *Diabetes Obes Metab.* doi:10.1111/dom.12149.
2. Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-2224.

Monotherapy Data

	Empagliflozin 25 mg[1] (n = 82)	Ipragliflozin 50 mg[2] (n = 67)
Duration (wk)	12	12
Total patients in trial	408	363
Age (y)	57	52.6±10.7
BMI (kg/m^2)	28.3	32.2±5.9
Initial HbA1c (%)	7.8±0.8	8.05±0.81
Placebo-corrected change in HbA1c (%)	–0.67 *P*<0.0001[a]	–0.65 *P*<0.001[a]
Placebo-corrected change in weight (kg)	–2.03 *P*<0.0001[a]	–0.66

[a]*P* value versus placebo.

1. Ferrannini E, et al. *Diabetes Obes Metab*. 2013;15(8):721-728.
2. Fonseca VA, et al. *J Diabetes Complications*. 2013;27(3):268-273.

Monotherapy Data (cont)

	Empagliflozin 25 mg[1] (n = 82)	Ipragliflozin 50 mg[2] (n = 67)
Baseline SBP (mm Hg)	129.3	Data not available
Δ SBP (mm Hg)	–0.69 to –3.55	–2.6
Baseline DBP (mm Hg)	79.8	Data not available
Δ DBP (mm Hg)	–0.69 to –3.55	+1.2
Genital infections [N (%)]	2 (2.4) [Pbo: 0]	8 (11.9) [Pbo: 1 (1.4)]
UTI [N (%)]	1 (1.2) [Pbo: 1]	9 (13.4) [Pbo: 6 (8.7)]
Hypoglycemia [N (%)]	0	1 (1.5) [Pbo: 0]

1. Ferrannini E, et al. *Diabetes Obes Metab*. 2013;15(8):721-728.
2. Fonseca VA, et al. *J Diabetes Complications*. 2013;27(3):268-273.

Addition to Metformin

	Canagliflozin[1] 300 mg vs Pbo/SITA (n = 64)	Dapagliflozin[2] 10 mg vs Pbo (n = 135)	Empagliflozin[3] 10 mg vs Pbo/SITA + MET (n = 70)
Duration (wk)	12	24	12
Total patients studied	451	546	495
Age (y)	52.3±7.1	53	59±9.0
BMI (kg/m^2)	31.6±4.9	31.4	31.4±4.0
Initial HbA1c	7.69±1.02	7.9	7.9±0.7
Placebo-corrected change in HbA1c (%)	–0.70[a] *P*≤0.001[b]	–0.51 *P*<0.0001[b]	–0.71 *P*≤0.0001[b]
Placebo-corrected change in weight (kg)	–2.3 *P*≤0.001[b]	–2.24 *P*≤0.0001[b]	–1.6 *P*≤0.001[b]

SITA, sitagliptin; MET, metformin.
[a]Sitagliptin 100 mg: –0.52%; [b]*P* value versus placebo.

1. Rosenstock J, et al. *Diabetes Care*. 2012;35(6):1232-1238.
2. Bailey CJ, et al. *Lancet*. 2010;375(9733):2223-2233.
3. Rosenstock J, et al. *Diabetes Obes Metab*. doi:10.1111/dom.12185.

Addition to Metformin (cont)

	Canagliflozin[1] 300 mg vs Pbo/SITA	Dapagliflozin[2] 10 mg vs Pbo	Empagliflozin[3] 10 mg vs Pbo/SITA+MET
Baseline SBP (mm Hg)	126±12	126±16	132.4
Δ SBP (mm Hg)	–4.9±1.5	–0.3	–4.39±13.09 [Pbo: –2.23±14.84]
Baseline DBP (mm Hg)	79±8	79±10	79.1
Δ DBP (mm Hg)	–2.1±1.1	–1.2	–1.70±7.50 [Pbo: –1.01±8.27]
Genital infections [N (%)]	2(3) [Pbo: 1(2); SITA 1(2)]	17 (12.6) [Pbo: 7 (5.1)]	7 (9.9) [Pbo: 0; SITA: 2(2.8)]
UTI [N (%)]	2 (3) [Pbo: 4 (6); SITA: 1(2)]	18 (13.3) [Pbo: 11 (8)]	3 (4.2) [Pbo: 2(2.8); SITA: 3(4.2)]
Hypoglycemia [N (%)]	0 [Pbo: 1(2); SITA: 3(5)]	7 (5.2) [Pbo: 8 (5.8)]	3 (4.2) [Pbo: 0; SITA: 2(2.8)]

1. Rosenstock J, et al. *Diabetes Care*. 2012;35(6):1232-1238.
2. Bailey CJ, et al. *Lancet*. 2010;375(9733):2223-2233.
3. Rosenstock J, et al. *Diabetes Obes Metab*. doi:10.1111/dom.12185.

Canagliflozin Compared to Sitagliptin in Patients not Controlled on Metformin + SU

	Sitagliptin 100 mg (N = 378)	Canagliflozin 300 mg (N = 377)
Duration (wk)	52	52
Total patients in trial	755	755
Age (y)	56.7±9.3	56.6±9.6
BMI (kg/m^2)	31.7±6.9	31.5±6.9
Initial HbA1c (%)	8.1±0.9	8.1±0.9
Change from baseline in HbA1c (%)	–0.66	–1.03 *P*<0.05[a]
Change from baseline in weight (kg)	0.1 kg	–2.3 *P*<0.001

[a]*P* value versus sitagliptin.

Schernthaner G, et al. *Diabetes Care*. 2013;36(9):2508-2515.

Canagliflozin Compared to Sitagliptin in Patients not Controlled on Metformin + SU (cont)

	Sitagliptin 100 mg (N = 378)	Canagliflozin 300 mg (N = 377)
Baseline SBP (mm Hg)	130.1±14.0	131.2±13.2
Δ SBP (mm Hg)	0.9±0.7	–5.1±0.7 *P*<0.00[a]
Baseline DBP (mm Hg)	78.6±8.9	79.2±7.8
Δ DBP (mm Hg)	–0.3±0.4	–3.0±0.4
Genital infections [N (%)]		
Male	1 (0.5)	19 (9.2)
Female	7 (4.3)	26 (15.3)
UTI [N (%)]	21 (5.6)	15 (4.0)

[a]*P* value versus sitagliptin.

Schernthaner G, et al. *Diabetes Care*. 2013;36(9):2508-2515.

Dapagliflozin Added to Stable Insulin Dose (± OAs)

	Canagliflozin[1] 300 mg vs Pbo (n = 587)	Dapagliflozin[2] 10 mg vs Pbo (n = 194)
Duration (wk)	18	48
Total patients in trial	1594	808
Age (y)	63.4±7.6	59.3
BMI (kg/m^2)	33.8±6.0	33.4
Insulin (U/d)	82±52	78
Initial HbA1c (%)	>7	8.57
Placebo-corrected change in HbA1c (%)	–0.73 *P*<0.001	–0.54 *P*<0.001
Placebo-corrected change in weight (kg)	–2.3 *P*<0.001	–2.43 *P*<0.001

OAs, oral agents.

1. Matthews DR, et al. Paper presented at: 48th Annual Meeting of the European Association for the Study of Diabetes; October 1-5, 2012; Berlin, Germany. Abstract 764.
2. Wilding JP, et al. *Ann Intern Med*. 2012;156(6):405-415.

Dapagliflozin Added to Stable Insulin Dose (± OAs)

	Canagliflozin[1] 300 mg vs Pbo (n = 587)	Dapagliflozin[2] 10 mg vs Pbo (n = 194)
Baseline SBP (mm Hg)	132.8 [Pbo: 138.2]	140.6 [Pbo: 136]
Δ SBP (mm Hg)	–6.9[a] [Pbo: –2.5]	–4.09[a] [Pbo: –1.49]
Baseline DBP (mm Hg)	76.4 [Pbo: 76.9]	79.9 [Pbo: 80.0]
Δ DBP (mm Hg)	–3.0[a] [Pbo: –1.2]	–2.85[a] [Pbo: –1.31]
Genital infections [N (%)]	52(9) [Pbo: 6 (1)]	21 (10.7) [Pbo: 5 (2.5)]
UTI [N (%)]	20 (3.4) [Pbo: 12(2.1)]	14 (7.1) [Pbo: 8 (4.1)]
Hypoglycemia [N (%)]	285 (48.6%) [Pbo: 207 (36.8%)]	105 (53.6%) [Pbo: 102 (51.8%)]

[a]Adjusted mean change from baseline.

1. Matthews DR, et al. Paper presented at: 48th Annual Meeting of the European Association for the Study of Diabetes; October 1-5, 2012; Berlin, Germany. Abstract 764.
2. Wilding JP, et al. *Ann Intern Med*. 2012;156(6):405-415.

General Observations Across Clinical Trials

- No significant changes in plasma electrolytes
- Slight increase in Hct and decreases in serum uric acid
- Improvement in triglycerides and HDL cholesterol
- Slight increase in LDL cholesterol—seen with canagliflozin (5%-6% increase from baseline)
- Consistent decreases in SBP, DBP, and weight
- Consistent increase in “genital infections”
- Inconsistent increase in lower urinary tract infections

Risk of Cancer With SGLT-2 Inhibitors?

- The FDA Advisory Committee Meeting recommended that more data were needed for dapagliflozin; no signal with canagliflozin, ipragliflozin, or empagliflozin
- Clinical trial data:
  - Bladder cancer:
    - 9 bladder cancers in dapagliflozin group (N = 5478)
    - 1 bladder cancer in control group (N = 3156)
  - Breast cancer:
    - 9 breast cancers in dapagliflozin group
    - 1 breast cancer in control group

Irony I. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM264312.pdf. Accessed September 19, 2013.

Use in Patients With Renal or Hepatic Impairment

Renal impairment

- Canagliflozin recommendations[1]:
  - Patients tolerating the starting dose of 100 mg/d who have an eGFR of ≥60 mL/min/1.73 m^2 and require additional glycemic control, the dose may be increased to 300 mg/d
  - Canagliflozin is limited to 100 mg/d in patients with moderate renal impairment with an eGFR of 45-60 mL/min/1.73 m^2
  - Canagliflozin should not be initiated in patients with an eGFR of <45 mL/min/1.73 m^2
- Dapagliflozin recommendations[2]:
  - Dapagliflozin not recommended for use in patients with moderate to severe renal impairment (patients with CrCl <60 mL/min or eGFR <60 ml/min/1.73 m^2)

Hepatic impairment

- Well tolerated by patients with mild, moderate, or severe hepatic impairment

eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance.

1. Invokana [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013.
2. Forxiga [package insert]. Middlesex, UK: Bristol-Myers Squibb/AstraZeneca EEIG; 2012.

SGLT-2 Inhibitors

- Despite the many different classes of antihyperglycemic agents, there are unmet needs in the treatment of T2DM patients that might be addressed by some newer medications
- SGLT-2 inhibitors act by a novel mechanism and may be useful in patients who have not achieved goal HbA1c levels
- Recent research reports that SGLT-2 inhibitors lower HbA1c levels and also have the benefit of weight reduction in patients with T2DM
- SGLT-2 inhibitors have been generally well tolerated, with most AEs being mild to moderate

Current Recommendations

The ADA/EASD treatment algorithm

Healthy eating, weight control, increased physical activity

Initial Drug Monotherapy	Metformin
Efficacy (HbA1c)	High
Hypoglycemia	Low risk
Weight	Neutral/loss
Major Side Effect(s)	GI/lactic acidosis
Costs	Low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination.
(Order not meant to denote any specific preference.)

Stepwise *individualized patient therapy:* weighing benefits and risks

2-Drug Combinations	Metformin +				
	SU	TZD	DPP-4 Inhibitor	GLP-1 Receptor Agonist	Insulin (usually basal)
Efficacy (HbA1c)	High	High	Intermediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major Side Effect(s)	Hypoglycemia	Edema, HF, fx	Rare	GI	Hypoglycemia
Costs	Low	High	High	High	Variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination.
(Order not meant to denote any specific preference.)

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

SGLT-2 Inhibitors: Where Do These Agents Fit in?

	Oral Agents				Injectables	
	Metformin +					
	SU	TZD	DPP-4 Inhibitor	SGLT-2 Inhibitors	GLP-1 Receptor Agonist	Insulin (usually basal)
Efficacy (HbA1c)	High	High	Intermediate	High	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Loss	Gain
Major Side Effect(s)	Hypoglycemia	Edema, HF, Fx's	Rare	GU	GI	Hypoglycemia
Costs	Low	High	High	High	High	Variable

HF, heart failure; Fx's, bone fractures; GU, genitourinary.

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

AACE COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013

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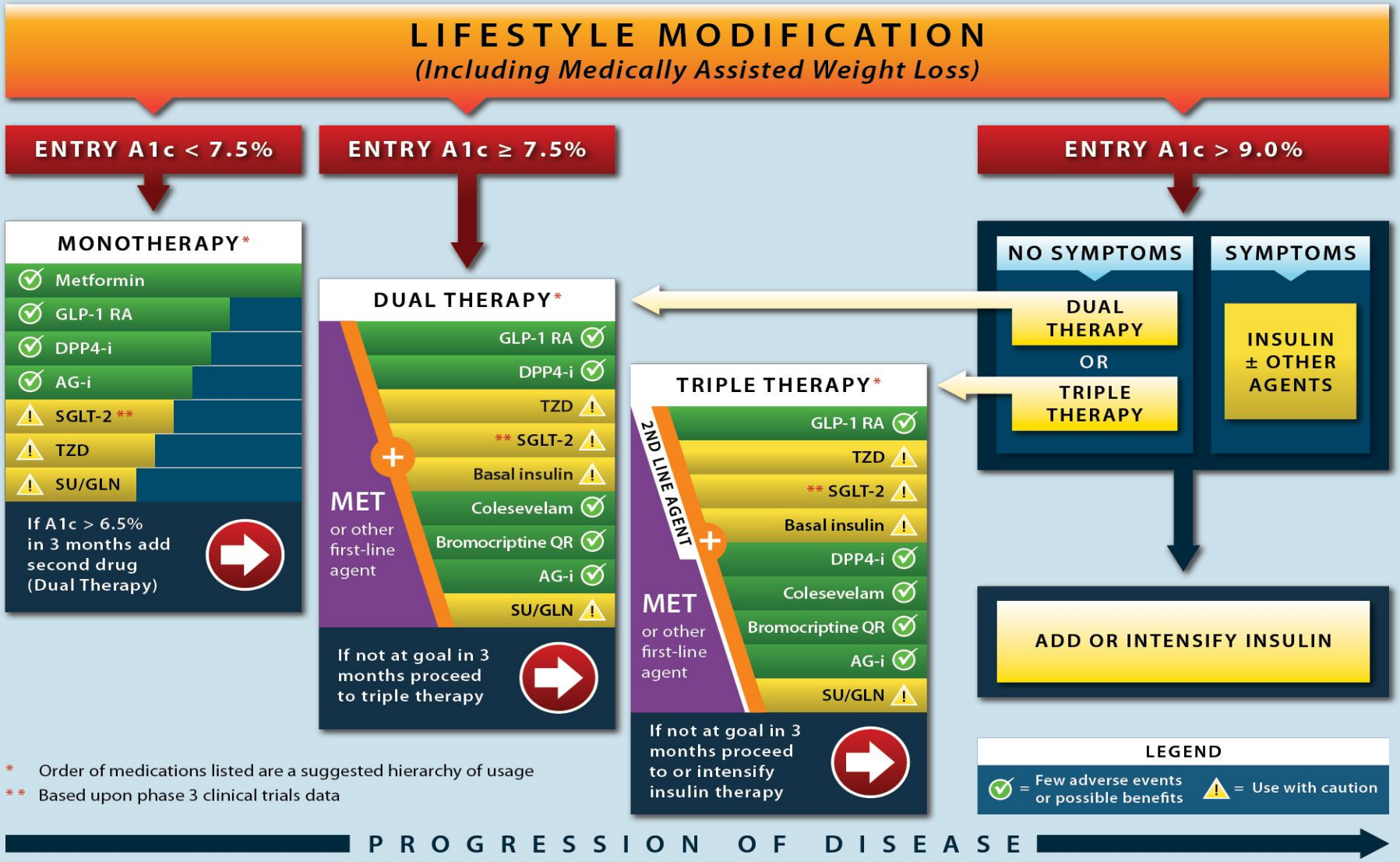
Glycemic Control Algorithm



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Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

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

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Algorithm for Adding/Intensifying Insulin

START BASAL (long-acting insulin)

A1c < 8% → **TDD 0.1–0.2 U/kg**

A1c > 8% → **TDD 0.2–0.3 U/kg**

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 4 U
  - **FBG** 140–180 mg/dL: add 2 U
  - **FBG** 110–139 mg/dL: add 1 U
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

**** Glycemic Goal:**

- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the absence of hypoglycemia.
- A1c and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

Glycemic Control Not at Goal**

INTENSIFY (prandial control)

Add GLP-1 RA or DPP4-i

Add Prandial Insulin

TDD: 0.3-0.5 U/kg
50% Basal Analog
50% Prandial Analog
Less desirable: NPH and regular insulin or premixed insulin

Insulin titration every 2–3 days to reach glycemic goal:

- Increase basal TDD as follows:
  - Fixed regimen: Increase TDD by 2 U
  - Adjustable regimen:
    - FBG > 180 mg/dL: add 4 U
    - FBG 140–180 mg/dL: add 2 U
    - FBG 100–139 mg/dL: add 1 U
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
- If between meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

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Insulin Pump Therapy

Automated Bolus Calculators

Accu-Chek Aviva Expert

- All the factors to help calculate your bolus insulin in seconds
- 3 simple steps to optimal diabetes control
- Track results and patterns with full color graphs in the palm of your hand.
- Available soon in USA

Continuous Glucose Monitoring

VGO – Disposable Insulin Delivery