Ask the Experts: Practice Pearls for SGLT2 Inhibitors

Presented as a Live Webinar

Thursday, March 12, 2015
12:00 p.m. – 1:00 p.m. ET

www.ashpadvantage.com/go/sglt2/experts

Planned by ASHP Advantage and supported by an educational grant from AstraZeneca.

Ask the Experts: Practice Pearls for SGLT2 Inhibitors

Activity Overview

This activity will focus on current issues related to the use of SGLT2 inhibitors in patients with diabetes. The faculty will address these issues and provide practice pearls for pharmacists.

The content for this activity is based on questions raised by participants in a recent educational symposium on this topic. Time for questions and answers from the webinar audience will be provided at the end of the presentation.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Apply ADA clinical practice recommendations to the use of SGLT2 inhibitors.
- Discuss the use of SGLT2 inhibitors with insulin.
- Compare SGLT2 inhibitors to GLP-1 agonists with regards to potential benefits beyond blood glucose lowering.
- Recommend appropriate dosing of SGLT2 inhibitors based on renal function.
- Discuss the role of SGLT2 inhibitors in the hospital setting.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-15-419-L01-P for the live activity and ACPE activity #0204-0000-15-419-H01-P for the on-demand activity).

Participants will process CPE credit online at http://elearning.ashp.org/my-activities, with the option of printing a CE certificate. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of a live activity or completion of a home study activity.

Webinar Information

Visit www.ashpadvantage.com/go/sglt2/experts experts to find

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Activity Faculty

Susan Cornell, **Pharm.D., CDE, FAPhA, FAADE,** ***Activity Chair***
Assistant Director of Experiential Education
Associate Professor
Department of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, is Assistant Director of Experiential Education and Associate Professor, Department of Pharmacy Practice at Midwestern University Chicago College of Pharmacy in Downers Grove, Illinois. Dr. Cornell is also a certified diabetes educator and clinical pharmacy consultant, specializing in community and ambulatory care practice.

Dr. Cornell has over 24 years of practice in community pharmacy where she has practiced as a clinical pharmacist, diabetes educator, and preceptor, as well as the inaugural coordinator of the American Diabetes Association (ADA)-recognized Dominick's Pharmacy Diabetes Self-Management Education program. Dr. Cornell's current clinical practice is with the Access Community Health Network, where she trains, educates, and supervises students from the colleges of medicine, pharmacy, and health sciences as they provide diabetes education classes for patients in underserved community clinics.

Dr. Cornell received her Bachelor of Science degree in pharmacy from the University of Illinois, College of Pharmacy in 1986 and her Doctor of Pharmacy degree from Midwestern University in 2002.

Dr. Cornell recently completed her term as President of the Illinois Pharmacists Association in October 2011. She has received numerous awards and recognitions, including the 2010 Teacher of the Year Award, the 2010 American Association of Colleges of Pharmacy Student Engaged Community Service Award, and the 2005 Midwestern University Golden Apple Teaching Award. In 2008, she received fellow recognition from the American Association of Diabetes Educators (AADE) and the American Pharmacists Association. She is an active member of the ADA, as well as the AADE, where she served on the board of directors from 2004 to 2007.

Dr. Cornell has served as an invited speaker nationally and internationally on diabetes and its related conditions and is recognized as a key opinion leader in the field of diabetes education. She has contributed to many peer-reviewed print and online publications in this field.

Ask the Experts: Practice Pearls for SGLT2 Inhibitors

Curtis L. Triplitt, Pharm.D., CDE
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Curtis L. Triplitt, Pharm.D., CDE, is Associate Professor and Certified Diabetes Educator at the University of Texas Health Science Center at San Antonio (UTHSCSA) where he oversees many diabetes research projects. In addition, he clinically manages people with diabetes with an endocrinologist at the Texas Diabetes Institute.

Dr. Triplitt earned his Bachelor of Science degree in pharmacy from the University of Iowa and his Doctor of Pharmacy degree from the University of Texas at Austin and the Health Science Center at San Antonio. He completed a primary-care residency accredited by the American Society of Health-System Pharmacists at the William S. Middleton Veteran Administration's Hospital in Madison, Wisconsin.

Dr. Triplitt is well respected as a clinician, researcher, and author. He is an investigator in several ongoing research studies related to diabetes, and he has published several book chapters on diabetes, as well as articles in peer-reviewed journals, including *Diabetes Care, Diabetes Spectrum, Expert Review of Endocrinology & Metabolism, Pharmacotherapy,* and *Drugs*. Dr. Triplitt is currently Secretary of the Texas Diabetes Council (TDC), which is legislatively mandated to develop and implement a state plan for diabetes treatment, education, and training. The TDC's mission is also to develop standards of care for the prevention, identification, and treatment of patients with diabetes mellitus in Texas.

Disclosure Statement

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- Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, declares she has served on the advanced practitioner advisory board for AstraZeneca and Sanofi.
- Curtis Triplitt, Pharm.D., CDE, declares he has served on the speakers bureau for AstraZeneca, Boehringer Ingelheim, and Janssen Pharmaceuticals, Inc.
- All other faculty and planners report no financial relationships relevant to this activity.

Additional Educational Opportunities and Resources

- On-demand activity "Novel Treatments for the Management of Type 2 Diabetes: Focus on SGLT2 Inhibitors" (1.5 hour CPE)
- Engaging the Experts podcasts featuring interviews with faculty (March 2015)
- e-Newsletters with new and emerging information (coming soon)

www.ashpadvantage.com/go/sglt2

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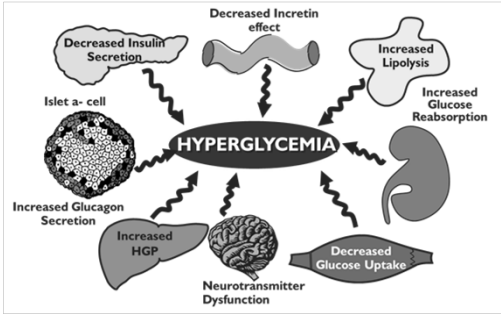
The Ominous Octet



HGP=hepatic glucose production

Pharmacotherapy Options

Insulin

Bolus insulin
- Insulin lispro
- Insulin aspart
- Insulin glulisine
- Regular human insulin

Basal insulin
- Insulin NPH
- Insulin detemir
- Insulin glargine
- Insulin degludec*

- **Oral Medications**
  - α-glucosidase inhibitors (AGI)
  - Biguanides
  - Bile acid sequestrants (BAS)
  - Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
  - Dopamine agonists
  - Glitinides
  - Sulfonylureas (SU)
  - Sodium glucose cotransporter-2 inhibitors (SGLT2i)
  - Thiazolidinediones (TZDs or glitazones)
- **Non-insulin injectable agents**
  - Glucagon-like peptide-1 (GLP-1) agonists
  - Amylinomimetic

*not FDA approved at this time

SGLT2/1 Inhibitors

- The kidney plays a major role in glucose homeostasis through gluconeogenesis and glomerular filtration, and reabsorption of glucose in the proximal convoluted tubules
- Therefore, a new approach for therapeutic target was to inhibit SGLT, which is a large group of sodium substrate cotransporters
- SGLT2 is responsible for the majority of renal glucose reabsorption in the early proximal tubule of the kidney
- SGLT1 is responsible for approximately 10% of glucose reabsorption in the late proximal tubule of the kidney, as it is primarily responsible for glucose absorption in the GI tract

Neumiller JJ et al. *Drugs*. 2010; 70:377-85.
Idris I et al. *Diabetes Obes Metab*. 2009; 11:79-88.

Sodium Glucose Cotransporter-2 (SGLT2) Inhibitors

Name	Approval Status or Phase
Canagliflozin	Approved March 29, 2013
Dapagliflozin	Approved January 28, 2014
Empagliflozin	Approved August 1, 2014
Ipragliflozin	Phase III (approved in Japan)
Tofogliflozin	Phase III
Ertugliflozin	Phase III
Remogliflozin	Phase II
LX4211*	Phase IIb

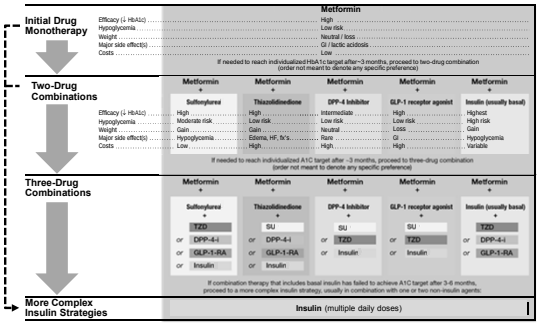
*LX4211 is a dual sodium-dependent glucose cotransporter-1 (SGLT1) and SGLT2 inhibitor.

For More Background

- *Novel Treatments for the Management of Type 2 Diabetes: Focus on SGLT2 Inhibitors*
  - On-demand activity capturing the symposium at the Midyear Clinical Meeting
- www.ashpadvantage.com/sglt2

Do we always start with metformin?

2012 Management of T2DM Approach

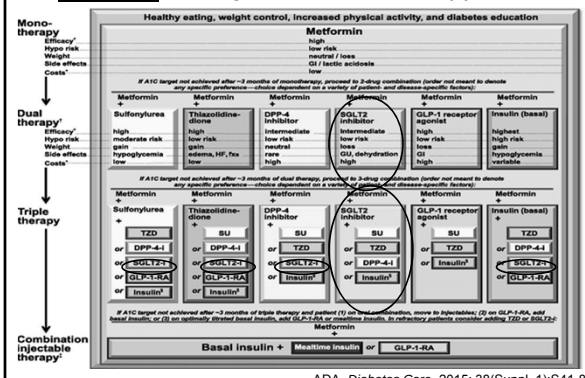


T2DM=Type 2 Diabetes Mellitus

Inzucchi SE et al. *Diabetes Care.* 2012; 35:1364-79.

See enlargement p. 14

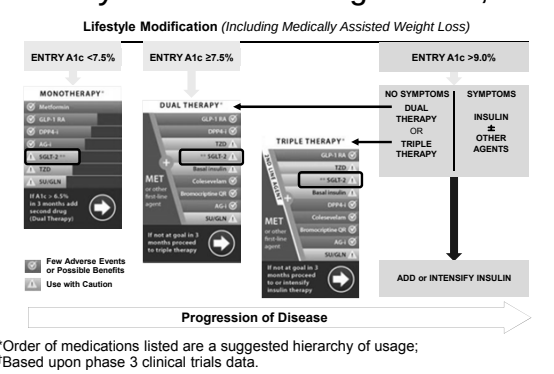
2015 Management of T2DM Approach



ADA. *Diabetes Care*. 2015; 38(Suppl. 1):S41-8.
Inzucchi SE et al. *Diabetes Care*. 2015; 38:140-9. Used with permission.

See enlargement p. 14

Glycemic Control Algorithm*,†



*Order of medications listed are a suggested hierarchy of usage;
†Based upon phase 3 clinical trials data.

Garber AJ et al. *Endocr Pract*. 2013; 19:327-36. Used with permission.

See enlargement p. 15

Case #1: HM

- HM is a 53 year-old Asian-American female with newly diagnosed T2DM. She has a history of IBS and GI flatulence.
- Occupation: School bus driver
- Labs:

BMI = 24 kg/m^2 SCr = 0.9 mg/dL
A1c = 7.5% BP = 142/84 mmHg
FPG = 140 mg/dL
PPG = 220 mg/dL

IBS=irritable bowel syndrome, GI=gastrointestinal, BMI=body mass index, A1c=hemoglobin A1c, FPG=fasting plasma glucose, PPG=postprandial glucose, SCr=serum creatinine, BP=blood pressure

What pharmacotherapy would you recommend?

a. DPP-4 inhibitor
b. GLP-1 agonist
c. Metformin
d. SGLT2 inhibitor
e. No pharmacotherapy at this time – start with diet/exercise only

Case Considerations

- HM is newly diagnosed
  - Aggressive therapy and tight BG control may be warranted, since she is early in the disease progression
  - A1c goal would be acceptable near 6.5%
  - A1c needs ~0.5 to 1.0% lowering
    - Need to target postprandial, as well as fasting blood glucose
      - A1c of 7.5% is ~ 35% fasting and 65% postprandial
    - Adverse effects must be considered
      - Weight loss is needed, but not excessive
      - Risk of hypoglycemia must be minimized
      - GI side effects should be considered

Possible Pharmacotherapy for HM

	A1c Lowering Potential & BG target	Weight Effect	Hypo-glycemia	β-Cell Protection	Other Considerations
Diet/exercise only	PPG & FPG	Loss/ neutral	Low risk	Possible	Is most effective in the first few years after diagnosis
Metformin	1.5% FPG	Loss	Low risk	Possible	GI side effects
GLP-1 agonist	0.8-1.9% Short – PPG Long – FPG & PPG	Loss	Low risk	Possible	GI adverse effects (nausea), cost, injectable
DPP-4 inhibitor	0.5-0.7% PPG	Neutral	Low risk	Possible	Minimal adverse effects, cost
SGLT2 inhibitor	0.6-1.0% FPG	Loss	Low risk	Possible	UTI and urogenital infections, fluid volume depletion/disruption

UTI=urinary tract infection

See enlargement p. 15

How effective are SGLT2 inhibitors when added to insulin?

SGLT2i: In Combination with Insulin

EMPAgliflozin or placebo

Added to multiple daily injections in obese T2DM
52 week data
HbA1c: 8.3% BMI: 34.8 Insulin dose average: 92 units/day
Insulin was titrated to maximize effect, but stayed stable (+/-10%) from week 40-52

	Placebo	EMPA 10mg	EMPA 25mg	Significance
A1c (Δ) from baseline	-0.81%	-1.18%	-1.27%	P<0.001 vs. placebo
A1c (%)	7.5	7.2	7.1	
Weight (Δ kg)	0.44	-1.95	-2.04	P<0.001 vs. placebo
Insulin/day (Δ units)	10.2	1.3	-1.1	NR
SBP (mmHg)	-2.9	-3.4	-3.8	NS
DBP(mmHg)	-0.5	-1.2	-2.5	NS

SBP=systolic blood pressure, DBP=diastolic blood pressure, EMPA=empagliflozin, NR=not recorded, NS=not significant.

Rosenstock et al. *Diabetes Care.* 2014; 37:1815-23.

See enlargement p. 16

SGLT2i: In Combination with Insulin

DAPAgliflozin or placebo daily

Added to multiple daily injections in obese T2DM
104 week data
HbA1c: 8.5% BMI: 33 kg/m^2 Insulin dose average: ~78 units/day

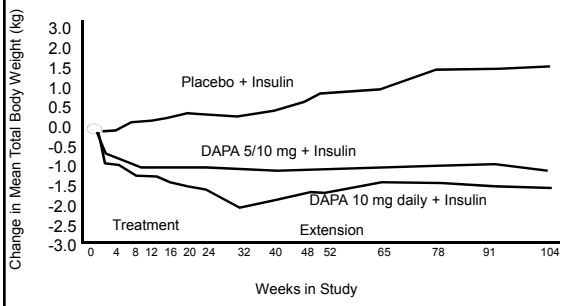
	Placebo	DAPA 5mg	DAPA 10mg
A1c (Δ) from baseline	-0.43	-0.82%	-0.78%
Weight (Δ kg)	1.83	-1.82	-2.43
Insulin/day (Δ units)	18.3	1.6	-0.8
SBP (mmHg)	-0.5	-2.6	-7.5
DBP(mmHg)	-1.3	-2.9	-4.0

DAPA= Dapagliflozin

Wilding JP et al. *Diabetes Obes Metab.* 2014; 16:124-36.

See enlargement p. 16

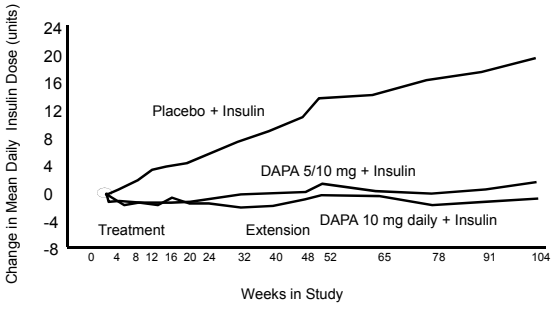
SGLT2 inhibitors Limit Weight Gain with Insulin Therapy



Wilding JP et al. *Diabetes Obes Metab.* 2014; 16:124-36.

See enlargement p. 17

SGLT2 inhibitors Limit Insulin Dose Increase



Wilding JP et al. *Diabetes Obes Metab.* 2014; 16:124-36.

See enlargement p. 17

Case #2: BA

- BA is 67 year-old male and has had T2DM for 15 years.
- He takes metformin and sitagliptin at maximal doses, insulin glargine 80 units at bedtime, enalapril 20 mg twice a day, and atorvastatin 40 mg daily
- Labs:

BMI = 32 kg/m^2 BP = 138/78 mmHg
A1c = 8.2% MDRD eGFR = 60's
FPG = 169 mg/dL
SCr = 1.1 mg/dL

MDRD eGFR = estimated glomerular filtration (eGFR) rate using the Modification of Diet in Renal Disease (MDRD) study equation

The clinician decides to add an SGLT2 inhibitor. For BA, are there sound reasons to start a particular SGLT2 inhibitor?

a. Yes, we should add canagliflozin
b. Yes, we should add dapagliflozin
c. Yes, we should add empagliflozin
d. No, any of the three would be appropriate

SGLT2 Inhibitors in Type 1 Diabetes (T1D)

Do you think an SGLT2 inhibitor would be useful in patients with T1D?

a. Yes
b. No
c. Unsure

Metabolic Syndrome in T1D

- Common for patients with T1D to develop metabolic syndrome due to:
  - weight issues
  - insulin therapy
    - higher insulin doses
  - more hypoglycemic events
- Therefore, it is becoming more common for people with T1D to be prescribed drugs commonly used to treat T2D
  - in addition to their insulin regimen

Non-Insulin Therapies Used in T1D

- Pramlintide – approved
- Metformin – used off-label
- GLP-1 agonist – used off-label
- DPP-4 inhibitor – used off-label
- SGLT2 inhibitor – used off-label

SGLT2 Inhibitors in T1D

- Several studies are in progress with SGLT2 inhibitor use in adults with T1D
- Early reports suggest SGLT2 inhibitor use in T1D:
  - well-tolerated
  - improved A1c
  - reduced rates of hypoglycemia
  - substantial reduction in insulin requirements
  - weight loss

Perkins BA et al. *Diabetes Care*. 2014; 37:1480-3.
Henry RR et al. *Diabetes Care*. 2014. Sep 30. [Epub ahead of print]

SGLT2 Inhibitors in T1D

- Further long term trials are needed to determine:
- Potential cardiovascular benefits through:
  - decreases in triglycerides
  - reduction in systolic blood pressure

Perkins BA et al. *Diabetes Care*. 2014; 37:1480-3.
Henry RR et al. *Diabetes Care*. 2014. Sep 30. [Epub ahead of print]

How does the weight loss associated with an SGLT2 inhibitor compare to GLP-1 agonist weight loss?

There are no head-to-head trials looking at this question

SGLT2i Weight Effects - Meta Analysis

	Mean difference	Upper 95% CI	Lower 95% CI
Absolute change (kg)			
SGLT2i vs. PLB	-1.74	-2.03	-1.45
SGLT2i vs. active agent	-1.11	-1.46	-0.76
% change from baseline			
SGLT2i vs. PLB	-2.37	-2.73	-2.02
SGLT2i vs. active agent	-2.14	-3.02	-1.25

PLB = placebo

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

See enlargement p. 18

GLP-1 agonist Weight Loss - Meta Analysis

Study #	Mean change (kg)	
	GLP-1 group	Control group
1	-2.3	-0.5
2	-1.6	-0.6
3	-1.6	-0.9
4	-3.4	-1.0
5	-3.1	-1.4
6	-2.8	-1.5
7	-2.5	1.0
8	-2.6	1.4
9	-2.8	1.5
10	-1.8	-0.4
…		
21	-2.5	2.9

Average weight loss over all studies vs. control group

-2.9 kg
(-3.6 to -2.2)

Vilsbøll T et al. *BMJ*. 2012; 344:d7771.

Mechanistic Differences in Weight Loss

- SGLT2 inhibitors
  - Mechanism: glucose loss in urine
  - 1 gram glucose = 4 kcal
  - Loss of potentially 200-300 kcal/day
  - Maximum weight loss at approximately 6 months
  - Weight loss is, in general, maintained
- GLP-1 agonists
  - Mechanism: central satiety, other mechanisms?
  - Direct stimulation of several areas of brain
  - Maximum weight loss at approximately 6 months
  - Weight loss is, in general, maintained

How does renal insufficiency affect the safety and efficacy of SGLT2 inhibitors?

SGLT2 inhibitors - Renal Insufficiency

52 week study

Canagliflozin 100 mg, 300 mg, or placebo daily

Systolic BP	**Placebo**	**Cana 100 mg**	**Cana 300 mg**
Mean baseline, mmHg	~132	~136	~137
Difference vs. PBO (95% CI)		–5.5 (–9.3, –1.7)	–6.7 (–10.5, –2.9)
Diastolic BP			
Mean baseline, mmHg	~74 mmHg for all groups		
Difference vs. PBO (95% CI)		–0.7 (–3.1, 1.8)	–1.0 (–3.5, 1.5)
eGFR (mL/min/1.73m²)			
Mean ± SD baseline	40.1 ± 6.8	39.7 ± 6.9	38.5 ± 6.9
Difference vs. PBO (95% CI)		-1.4 (-7.4, 4.5)	-6.6 (-12.3, -0.9)

BP=blood pressure, Cana=canagliflozin, PBO=placebo, eGFR=estimated glomerular filtration rate (MDRD formula), SD=standard deviation

Yale JF et al. *Diabetes Obes Metab*. 2014; 16:1016-27.

See enlargement p. 18

Efficacy and Safety of Canagliflozin in Subjects with T2DM and Chronic Kidney Disease (CKD)

Glycemic Control (HbA1c %)	**Placebo**	**Cana 100 mg**	**Cana 300 mg**
Mean ± SD baseline	8.0 ± 0.9	7.9 ± 0.9	8.0 ± 0.8
Difference vs. PBO (95% CI)		-0.27 (–0.532, 0.001)	–0.41 (–0.676, –0.142)
Fasting Plasma Glucose			
Mean ± SD baseline, mmol/L	8.9 ± 2.4	9.4 ± 2.6	8.8 ± 3.2
Difference vs. PBO (95% CI)		–0.7 (–1.5, 0.2)	–0.8 (–1.7, 0.1)
Weight (kg)			
Mean ± SD baseline	92.8 ± 17.4	90.5 ± 18.4	90.2 ± 18.1
Difference vs. PBO (95% CI)		-1.3 (-2.3, -0.3)	-0.8 (-1.8, 0.2)

Yale JF et al. *Diabetes Obes Metab*. 2014; 16:1016-27.

See enlargement p. 19

SGLT2 Inhibitors: Renal Dosing

Agent	Dosing in CKD stages 3, 4 and 5 (non-dialysis)
Canagliflozin	• **eGFR 45-59 ml/min/1.73m²** Do not exceed 100 mg/day PO • **eGFR < 45 ml/min/1.73m²** Do not initiate and discontinue in patients currently receiving drug
Dapagliflozin	• **eGFR <60 mL/min/1.73 m²** Do not initiate and/or discontinue
Empagliflozin	• **eGFR < 45 ml/min/1.73m²** Do not initiate and discontinue in patients currently receiving drug. No limit on dosing

- Glycemic efficacy becomes less pronounced with decreasing eGFR
- If the kidney doesn't filter as much glucose, the SGLT2 inhibitor can't prevent reabsorption

Invokana (canagliflozin) prescribing information. 2014 May.
Farxiga (dapagliflozin) prescribing information. 2014 Aug.
Jardiance (empagliflozin) prescribing information. 2014 Aug.

Can SGLT2 inhibitors be used inpatient?

Insulin-Only Use for Hyperglycemia in the Inpatient Hospital Setting

- Supported by:
  - American Diabetes Association
  - American Association of Clinical Endocrinologists
  - The Endocrine Society

ADA. *Diabetes Care*. 2014; 37(Suppl. 1):S14-80.
Moghissi ES et al. *Diabetes Care*. 2009; 32:1119-31.
Umpierrez GE et al. *J Clin Endocrinol Metab*. 2012; 97:16-38.

Insulin-Only in the Inpatient Hospital Setting

- Recommend against the use of non-insulin therapies in the hospital setting due to:
  - No data on the safety and efficacy in this acute care environment
  - Drug contraindications with tests/procedures
  - Meal time irregularities
  - Not working fast enough to handle the rapid changes in blood glucose levels in stressed hospitalized patients

ADA. *Diabetes Care*. 2014; 37(Suppl. 1):S14-80.

Drug	Considerations
Metformin	Test/procedures where contrast dye is indicated will need to be delayed for 48 hours due to metformin's contraindication.
Secretagogues (sulfonylureas and glinides)	Require patients to eat at scheduled times to reduce hypoglycemic risk. e.g., If SU is administered in the morning and the patient misses lunch, there is a significant risk for hypoglycemia. Also, evening doses of SU may result in nocturnal hypoglycemic events.
Thiazolidinedione (TZDs or glitazones)	Require 4-8 weeks to take effect, have an increased risk of edema and are contraindicated in patients with congestive heart failure (CHF).
Glucagon like peptide-1 (GLP-1) agonists	Affect GI motility which can result in nausea and vomiting. Also, short-acting GLP-1 agonists must be dosed around meals.
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Can have adverse effects that impact the immune system.
Sodium glucose cotransporter-2 (SGLT2) inhibitors	Can have decreases in estimated glomerular filtration rate and renal adverse reactions (genital-urinary infections).

See enlargement p. 19

Summary

- Diabetes care and guidelines are constantly evolving.
  - Pharmacists must stay current with the trends
  - Newer therapies may have more benefits with less adverse effects
- Many T1D patients have metabolic syndrome
  - Meds commonly used in type 2 are being used (successfully) in T1D

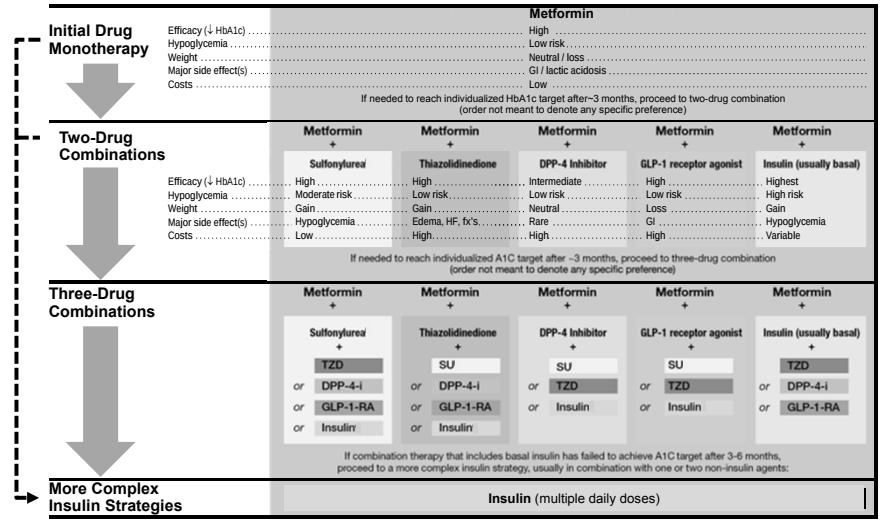
Summary

- All SGLT2 inhibitors may be used with insulin
  - Modest A1c reduction, but limit weight and increases in insulin dose
- Weight loss is due to glucosuria and averages 1-3 kg

Summary

- Renal insufficiency and SGLT2 inhibitors
  - Glucose control - less efficacious
  - Weight loss - still seen
  - BP reduction - still seen
  - Renal injury - rare
  - Renal protection - unproven
- Despite pharmacotherapy advances, insulin remains the preferred drug of choice in the inpatient setting.

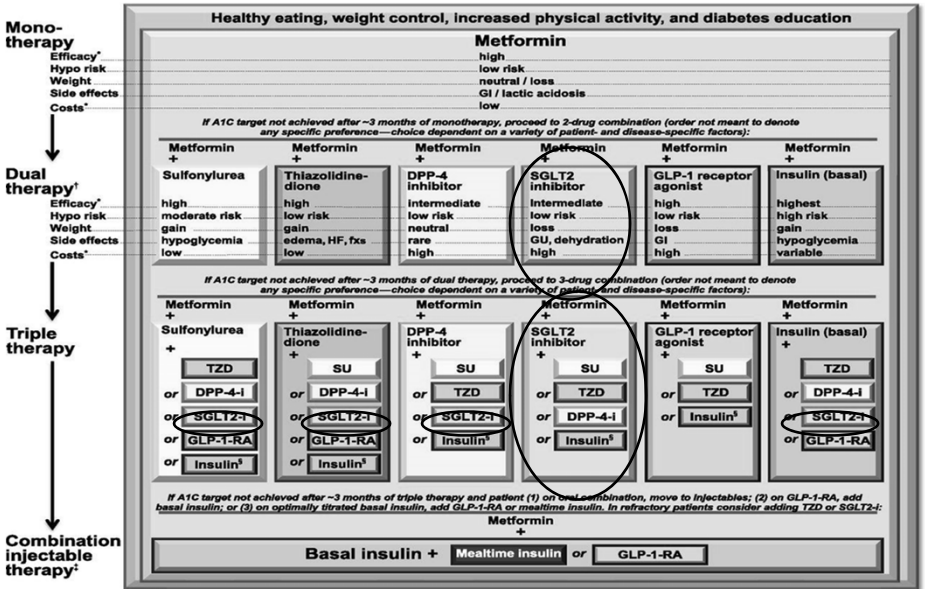
2012 Management of T2DM Approach



T2DM=Type 2 Diabetes Mellitus

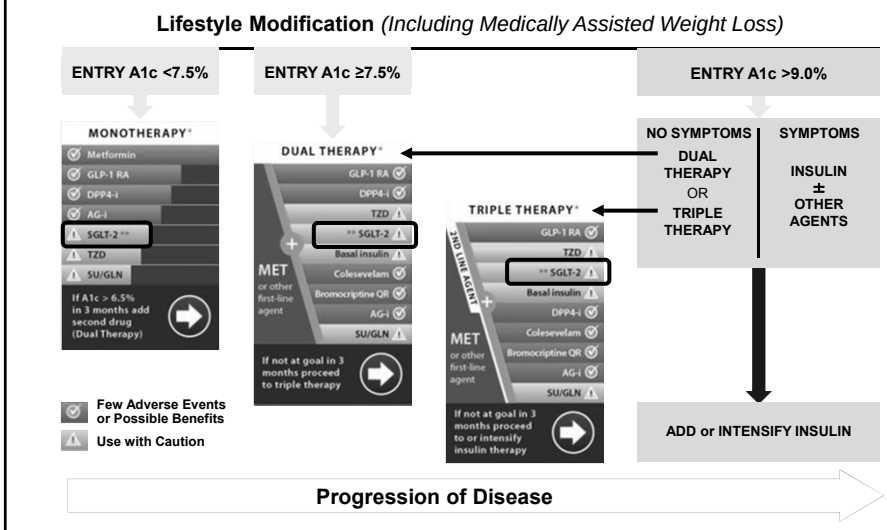
Inzucchi SE et al. *Diabetes Care.* 2012; 35:1364-79.

2015 Management of T2DM Approach



ADA. *Diabetes Care*. 2015; 38(Suppl. 1):S41-8.
Inzucchi SE et al. *Diabetes Care*. 2015; 38:140-9. Used with permission.

Glycemic Control Algorithm*,†



*Order of medications listed are a suggested hierarchy of usage;
†Based upon phase 3 clinical trials data.

Garber AJ et al. *Endocr Pract*. 2013; 19:327-36. Used with permission.

Possible Pharmacotherapy for HM

	A1c Lowering Potential & BG target	Weight Effect	Hypo-glycemia	β-Cell Protection	Other Considerations
Diet/exercise only	PPG & FPG	Loss/ neutral	Low risk	Possible	Is most effective in the first few years after diagnosis
Metformin	1.5% FPG	Loss	Low risk	Possible	GI side effects
GLP-1 agonist	0.8-1.9% Short – PPG Long – FPG & PPG	Loss	Low risk	Possible	GI adverse effects (nausea), cost, injectable
DPP-4 inhibitor	0.5-0.7% PPG	Neutral	Low risk	Possible	Minimal adverse effects, cost
SGLT2 inhibitor	0.6-1.0% FPG	Loss	Low risk	Possible	UTI and urogenital infections, fluid volume depletion/disruption

UTI=urinary tract infection

SGLT2i: In Combination with Insulin

EMPAgliflozin or placebo

Added to multiple daily injections in obese T2DM
52 week data
HbA1c: 8.3% BMI: 34.8 Insulin dose average: 92 units/day
Insulin was titrated to maximize effect, but stayed stable (+/-10%) from week 40-52

	Placebo	EMPA 10mg	EMPA 25mg	Significance
A1c (Δ) from baseline	-0.81%	-1.18%	-1.27%	P<0.001 vs. placebo
A1c (%)	7.5	7.2	7.1	
Weight (Δ kg)	0.44	-1.95	-2.04	P<0.001 vs. placebo
Insulin/day (Δ units)	10.2	1.3	-1.1	NR
SBP (mmHg)	-2.9	-3.4	-3.8	NS
DBP(mmHg)	-0.5	-1.2	-2.5	NS

SBP=systolic blood pressure, DBP=diastolic blood pressure, EMPA=empagliflozin, NR=not recorded, NS=not significant.

Rosenstock et al. *Diabetes Care.* 2014; 37:1815-23.

SGLT2i: In Combination with Insulin

DAPAgliflozin or placebo daily

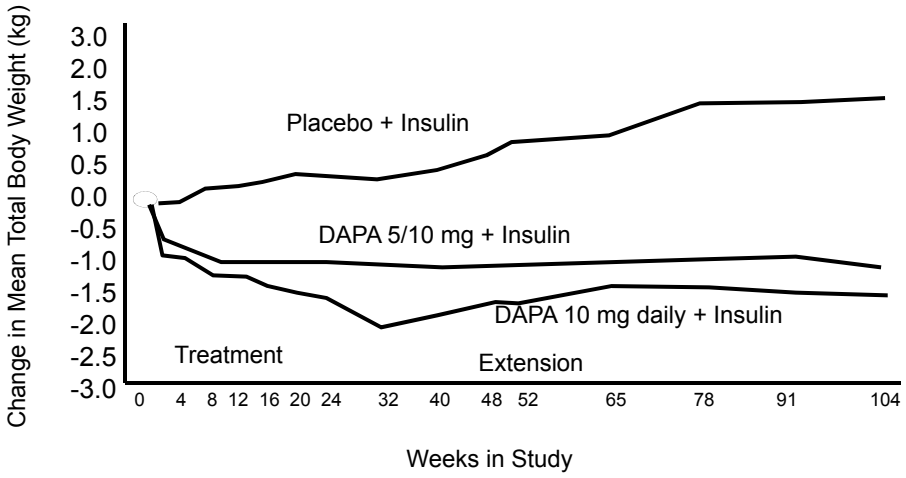
Added to multiple daily injections in obese T2DM
104 week data
HbA1c: 8.5% BMI: 33 kg/m^2 Insulin dose average: ~78 units/day

	Placebo	DAPA 5mg	DAPA 10mg
A1c (Δ) from baseline	-0.43	-0.82%	-0.78%
Weight (Δ kg)	1.83	-1.82	-2.43
Insulin/day (Δ units)	18.3	1.6	-0.8
SBP (mmHg)	-0.5	-2.6	-7.5
DBP(mmHg)	-1.3	-2.9	-4.0

DAPA= Dapagliflozin

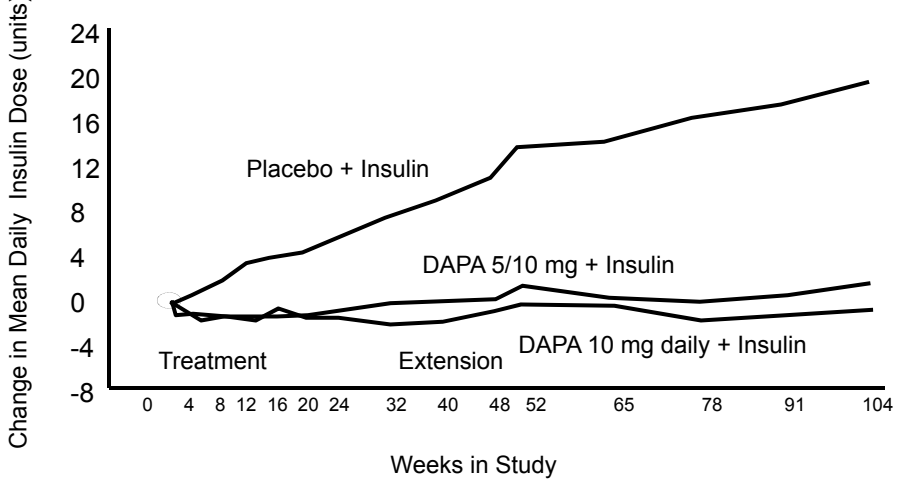
Wilding JP et al. *Diabetes Obes Metab.* 2014; 16:124-36.

SGLT2 inhibitors Limit Weight Gain with Insulin Therapy



Wilding JP et al. *Diabetes Obes Metab.* 2014; 16:124-36.

SGLT2 inhibitors Limit Insulin Dose Increase



Wilding JP et al. *Diabetes Obes Metab.* 2014; 16:124-36.

SGLT2i Weight Effects - Meta Analysis

	Mean difference	Upper 95% CI	Lower 95% CI
Absolute change (kg)			
SGLT2i vs. PLB	-1.74	-2.03	-1.45
SGLT2i vs. active agent	-1.11	-1.46	-0.76
% change from baseline			
SGLT2i vs. PLB	-2.37	-2.73	-2.02
SGLT2i vs. active agent	-2.14	-3.02	-1.25

PLB = placebo

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

SGLT2 inhibitors - Renal Insufficiency

52 week study

Canagliflozin 100 mg, 300 mg, or placebo daily

Systolic BP	**Placebo**	**Cana 100 mg**	**Cana 300 mg**
Mean baseline, mmHg	~132	~136	~137
Difference vs. PBO (95% CI)		–5.5 (–9.3, –1.7)	–6.7 (–10.5, –2.9)
Diastolic BP			
Mean baseline, mmHg	~74 mmHg for all groups		
Difference vs. PBO (95% CI)		–0.7 (–3.1, 1.8)	–1.0 (–3.5, 1.5)
eGFR (mL/min/1.73m^2)			
Mean ± SD baseline	40.1 ± 6.8	39.7 ± 6.9	38.5 ± 6.9
Difference vs. PBO (95% CI)		-1.4 (-7.4, 4.5)	-6.6 (-12.3, -0.9)

BP=blood pressure, Cana=canagliflozin, PBO=placebo, eGFR=estimated glomerular filtration rate (MDRD formula), SD=standard deviation

Yale JF et al. *Diabetes Obes Metab*. 2014; 16:1016-27.

Efficacy and Safety of Canagliflozin in Subjects with T2DM and Chronic Kidney Disease (CKD)

Glycemic Control (HbA1c %)	Placebo	Cana 100 mg	Cana 300 mg
Mean ± SD baseline	8.0 ± 0.9	7.9 ± 0.9	8.0 ± 0.8
Difference vs. PBO (95% CI)		-0.27 (–0.532, 0.001)	–0.41 (–0.676, –0.142)
Fasting Plasma Glucose			
Mean ± SD baseline, mmol/L	8.9 ± 2.4	9.4 ± 2.6	8.8 ± 3.2
Difference vs. PBO (95% CI)		–0.7 (–1.5, 0.2)	–0.8 (–1.7, 0.1)
Weight (kg)			
Mean ± SD baseline	92.8 ± 17.4	90.5 ± 18.4	90.2 ± 18.1
Difference vs. PBO (95% CI)		-1.3 (-2.3, -0.3)	-0.8 (-1.8, 0.2)

Yale JF et al. *Diabetes Obes Metab*. 2014; 16:1016-27.

Drug	Considerations
Metformin	Test/procedures where contrast dye is indicated will need to be delayed for 48 hours due to metformin's contraindication.
Secretagogues (sulfonylureas and glinides)	Require patients to eat at scheduled times to reduce hypoglycemic risk. e.g., If SU is administered in the morning and the patient misses lunch, there is a significant risk for hypoglycemia. Also, evening doses of SU may result in nocturnal hypoglycemic events.
Thiazolidinedione (TZDs or glitazones)	Require 4-8 weeks to take effect, have an increased risk of edema and are contraindicated in patients with congestive heart failure (CHF).
Glucagon like peptide-1 (GLP-1) agonists	Affect GI motility which can result in nausea and vomiting. Also, short-acting GLP-1 agonists must be dosed around meals.
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Can have adverse effects that impact the immune system.
Sodium glucose cotransporter-2 (SGLT2) inhibitors	Can have decreases in estimated glomerular filtration rate and renal adverse reactions (genital-urinary infections).

Self-assessment Questions

1. According to the 2015 American Association of Clinical Endocrinologists management of T2DM approach, which of the following is NOT listed as a use with caution, monotherapy option?

    a. GLP-1 agonists.
    b. SGLT2 inhibitors.
    c. Sulfonylureas.
    d. Thiazolidinediones.

2. Choose the correct statement in regards to weight loss between the addition of GLP-1 agonists and the addition of SGLT2 inhibitors

    a. SGLT2 inhibitors have shown superior weight loss.
    b. There is insufficient head-to-head evidence to compare.
    c. GLP-1 agonists have shown superior weight loss.
    d. There is near equal weight loss with both medication classes.

3. Considerations against the use of SGLT2 inhibitors in the inpatient setting are

    a. Patients can have decreases in estimated glomerular filtration rate and genital-urinary infections with SGLT2 inhibitors.
    b. SGLT2 inhibitors require 4-8 weeks to take effect, have an increased risk of edema, and are contraindicated in patients with CHF.
    c. SGLT2 inhibitor use requires patients to eat at scheduled times to reduce hypoglycemic risk.
    d. Test/procedures where contrast dye is indicated will need to be delayed for 48 hours due to contraindications with SGLT2 inhibitors.

Answers

1. a
2. b
3. a