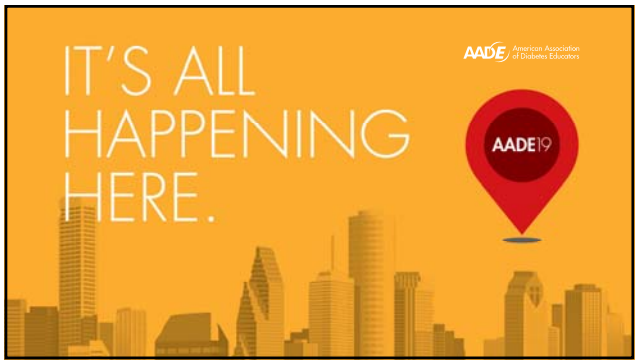

1

Off the Beaten Path: Non-Insulin Medications to Manage Type 1 Diabetes

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2

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3

Learning Objectives

- Explain the rationale for non-insulin therapies in the management of type 1 diabetes.
- Describe the clinical evidence of non-insulin agents in the management of type 1 diabetes.
- Outline treatment plans for metformin, GLP-1 agonists, and SGLT-2 inhibitors in type 1 diabetes.

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Disclosure to Participants

- Notice of Requirements For Successful Completion
  - Please refer to learning goals and objectives
  - Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours
- Conflict of Interest (COI) and Financial Relationship Disclosures:
  - Presenter: Jennifer N. Clemens, PharmD, FCCP, BCPS, CDE, BCACP – No COI/Financial Relationship to disclose
  - Presenter: Diana Isaacs, PharmD, BCPS, BC-ADM, CDE – Advisory Board-Sanofi
- Non-Endorsement of Products:
  - Accredited status does not imply endorsement by AADE, ANCC, ACPE or CDR of any commercial products displayed in conjunction with this educational activity
- Off-Label Use:
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Epidemiology

Patients with type 1 diabetes (T1DM) often have difficulty achieving hemoglobin A1C (HbA1C) goals due to hypoglycemia risk.

Overweight and obesity is an increasing problem in T1DM, with an estimated prevalence of 50%.

Patients with T1DM are 8x more likely to develop cardiovascular (CV) disease than the general population.

Pieber et al. Diabetes Obes Metab 2015;17(10):928–35.

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6

Importance of Glycemic Control

Diabetes Control and Complications Trial

Retinopathy ↓ 76%

Nephropathy ↓ 50%

Neuropathy ↓ 60%

[Average weight gain = 4.75 kg]

The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977–86.
Purnell et al. Circulation 2013;127:180–7.

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7

T1DM and Weight Trends

Pittsburgh Epidemiology of Diabetes Complications Study

Baseline:	18 years later:
28.6% overweight	47% overweight
3.4% obese	23.8% obese

Conway et al. Diabet Med 2010;27(4):398–404.

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8

Other Considerations

Weight Gain

- CV disease (CVD)
- Heart failure
- Death from CVD
- Death

Edqvist et al. Diabetes Care 2019 May 2. pii: dc181446. doi: 10.2337/dc18-1446.

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Limitations with Basal-Bolus Insulin

- Hypoglycemia
- Weight gain
- Adherence with regimen
- Untreated glucagon dysfunction
- Stress/Mental burden

Priya et al. Diabetes Ther 2018;9(1):349–61.

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10

Priorities for Patients with T1DM

1. Simplified, predictable management
2. HbA1C within target
3. Time within range
4. Lower mental burden

"The majority (93%) of patients had a preference for the adjunct therapy (either dose [sotagliflozin 200 or 400 mg]) over placebo."

Pettus et al. Diabetes Technol Ther 2019 May 16. doi: 10.1089/dia.2019.0027. [Epub ahead of print]

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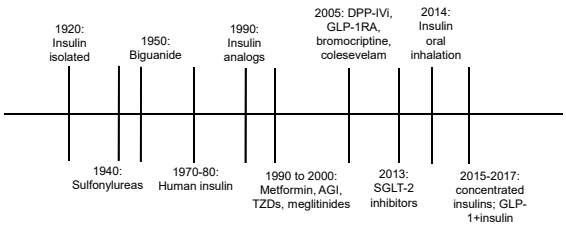
TIMELINE OF APPROVALS: DIABETES MELLITUS



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Pathophysiology	Defects	Medications
Gluconeogenesis		Metformin (primary action) TZD (secondary action)
Beta-cells: ↓ insulin secretion Alpha-cells: ↑ glucagon	 β cells α cells	Beta-cells: Sulfonylureas, glinides, DPP-IV inhibitors, GLP-1 agonists Alpha-cells: DPP-IV inhibitors, GLP-1 agonists, amylin derivative
Insulin resistance		TZD (primary action) Metformin (secondary action)
Insulin resistance ↑ free fatty acids - triglycerides		TZD (primary action) Metformin (secondary action)

Images available in public domain through Google.

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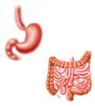
Pathophysiology	Defects	Medications
↑ carbohydrate intake		Alpha-glucosidase inhibitor
↓ incretin effect		GLP-1 agonists
Insulin resistance - ↓ satiety		GLP-1 agonists, amylin derivative
↑ glucose reabsorption		SGLT-2 inhibitors

Images available in public domain through Google.

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Metformin

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Metformin

Activation of AMP-activated protein kinase	Reduces hepatic gluconeogenesis
	Decreases intestinal glucose absorption
	Promotes glucose uptake in periphery

Priya et al. Diabetes Ther 2018;9(1):349–61.

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Benefits of Metformin

- HbA1C reduction
- Microvascular benefit
- Macrovascular benefit
- Mortality
- Low risk of hypoglycemia
- Weight loss
- Generic / low cost

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Metformin in Adults with T1DM

Type of Study	Inclusion Criteria	Baseline Characteristics	Mean Reduction in HbA1C (%)	Mean Reduction in Insulin Doses (units)	Mean Reduction in Weight (kg)
Meta-analysis	Randomized trials, at least 1 week in length with metformin vs placebo	10 to 92 patients (per trial) with metformin 1000 to 2550 mg per day over 7 days to 12 months	0.6 to 0.9	5.7 to 10	1.7 to 6

Vella et al. Diabetologia 2010;53(5):809–20.

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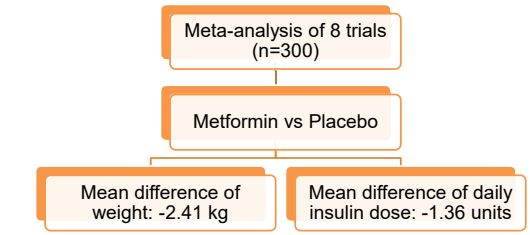
Metformin in Adults with T1DM



Liu et al. Diabetes Technol Ther 2015;17(2):142–8.

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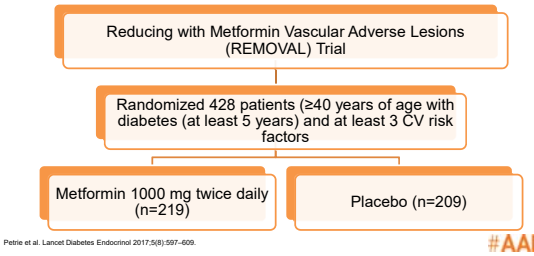
Metformin in Adults with T1DM



Petrie et al. Lancet Diabetes Endocrinol 2017;5(8):597–609.

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Metformin in Adults with T1DM

- REMOVAL Study (cont)
  - ↓ HbA1C by 0.13%
    - P-value = 0.0060
  - ↓ insulin dose by 0.023 units per kg
    - P-value = 0.5450
  - ↑ gastrointestinal adverse events
    - 27% vs 12% with placebo; P-value = 0.0002
  - ↑ vitamin B12 deficiency
    - 12% vs 5% with placebo; P-value = 0.0094

Petrie et al. Lancet Diabetes Endocrinol 2017;5(8):597–609.

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21

Gastrointestinal Side Effects

Start with low doses and titrate slowly (i.e., weekly) to maximum effective dose of 2000 mg per day.

Take with food, preferably after meals.

Effects will lessen over several weeks. If not, change from immediate to extended release formulation.

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Lactic Acidosis

Use caution or temporarily discontinue in situations that could lead to increased metformin concentrations.

Be aware and monitor for tissue hypoperfusion (↑ lactic acid production) or impaired hepatic function (↓ lactic acid removal).

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Renal Impairment

eGFR (mL/min per 1.73 m^2)	Recommendations
≥ 60	No adjustment with metformin. Monitor renal function every year.
< 60 and ≥ 45	Prescribe metformin with caution. Monitor renal function every 3 to 6 months.
< 45 and ≥ 30	Reduce metformin by 50% or half-maximal dose. Monitor renal function every 3 months.
< 30	Discontinue metformin.

Lipska et al. Diabetes Care 2011;34(6):1431–7.

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24

Meet Mark

- … who is a 35 yo male with T1DM (for 20 years).
  - Currently, he is injecting Lantus 50 units at bedtime and Novolog 15 units with meals.
  - He also has gastroparesis.
  - HbA1c = 8.1% (no change in 6 months despite lifestyle modifications).

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What Else Would You Most Like to Know about Mark?

A. Vitamin B12 level?
B. Renal function?
C. Weight?
D. Cardiovascular risk factors?

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Is Mark a Candidate for metformin?

A. Yes
B. No

Why or why not?

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If starting metformin, what would be the best recommendation for the insulin regimen?

A. Continue basal and bolus.
B. Decrease by 10% basal and bolus.
C. Decrease by 10% bolus only.
D. Increase by 10% bolus only.

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Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA)

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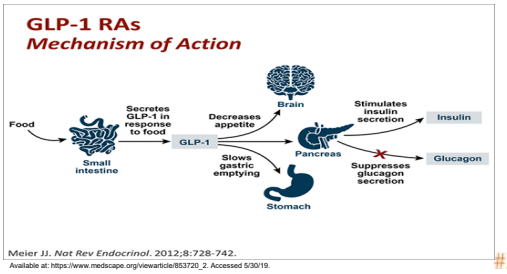
The Mechanism of GLP-1 RA



Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.
Available at: https://www.medscape.org/viewarticle/853720_2. Accessed 5/30/19.

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30

Benefits of GLP-1 RA

- HbA1C reduction
- Macrovascular benefits
- Renal outcomes
- Weight loss
- Low risk of hypoglycemia (monotherapy)

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Review of GLP-1 RA

	Short-acting	Long-acting
Administration	Subcutaneous	Subcutaneous
Frequency	Twice-daily or once-daily (lixisenatide)	Once-daily (liraglutide) or once-weekly
Effect on HbA1c	Moderate	High
Effect on FBG	Moderate	High
Effect on PPBG	High	Moderate
Adverse Effects	Nausea, vomiting, weight loss	Nausea, vomiting, weight loss, injection site nodules

Short-acting: exenatide immediate-release, lixisenatide
Long-acting: exenatide extended-release, liraglutide, dulaglutide, semaglutide

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GLP-1 RA in T1DM

Study Year	Study Duration (weeks)	Number of Patients	Duration of T1DM (years)
2011[1]	4	39	3.7 to 23.1
2015[2]	12	40	18.3 to 19.5
2016[3]	12	72	20 to 30
2016[4]	24	100	20 to 25
2016[5]	52	1398	20.9 to 21.6
2016[6]	26	835	20.7 to 21.4

1-Kielgast et al. Diabetes Care 2011;34(7):1463–8. 2-Frandsen et al. Diabetes Care 2015;38(12):2250–7.
3-Kuhadiya et al. Diabetes Care 2016;39(6):1027–35. 4-Dejgaard et al. Lancet Diabetes Endocrinol 2016;4(3):221–32.
5-Mathieu et al. Diabetes Care 2016;39(10):1702–10. 6-Ahren et al. Diabetes Care 2016;39(10):1693–701.

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GLP-1 RA in T1DM

Study Year	Most Effective Treatment Arm	Reduction in HbA1C (%)	Change in insulin dose	Reduction in body weight (kg)
2011[1]	C-peptide negative with liraglutide 1.2 mg SC QD	0.47	↓ 0.13 units per kg	2.3
2015[2]	Liraglutide 1.2 mg SC QD	0.6	NR	3.1
2016[3]	Liraglutide 1.2 mg SC QD	0.78	↓ 12.1 units	5
2016[4]	Liraglutide 1.8 mg SC QD	0.5	↑ 4.1 units	5.9
2016[5]	Liraglutide 1.8 mg SC QD	0.54	↓ 5%	4
2016[6]	Liraglutide 1.8 SC QD	0.35	NR	5.1

NR = not reported

1-Kielgast et al. Diabetes Care 2011;34(7):1463–8. 2-Frandsen et al. Diabetes Care 2015;38(12):2250–7.
3-Khadilya et al. Diabetes Care 2016;39(6):1027–35. 4-Dejgaard et al. Lancet Diabetes Endocrinol 2016;4(3):221–32.
5-Mathieu et al. Diabetes Care 2016;39(10):1702–10. 6-Ahren et al. Diabetes Care 2016;39(10):1693–701.

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Gastrointestinal Side Effects

- Counsel on the frequency, depending on the products.
- Encourage smaller portions.
- Inform about tolerance after 2 to 6 weeks, depending on product.
- Do not use with history of pancreatitis or severe gastrointestinal disease.

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Other Safety Concerns

- Symptomatic Hypoglycemia

Trial	Treatment Arm	Relative Risk (RR)
ADJUNCT ONE	Liraglutide 1.2 mg SC QD	1.31
ADJUNCT ONE	Liraglutide 1.8 mg SC QD	1.27
ADJUNCT TWO	Liraglutide 1.2 mg SC QD	1.31

Mathieu et al. Diabetes Care 2016;39(10):1702–10.
Ahren et al. Diabetes Care 2016;39(10):1693–701.

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Other Safety Concerns

- Hyperglycemia with Ketosis
  - ADJUNCT Trials
    - Liraglutide 1.8 mg SC QD: RR 2.22 to 3.96
      - Lower risk among C-peptide positive patients
  - ADJUNCT ONE
    - Risk factors and C-peptide status
  - ADJUNCT TWO
    - Initial two months and insulin dose titrations

Mathieu et al. Diabetes Care 2016;39(10):1702–10.
Ahren et al. Diabetes Care 2016;39(10):1693–701.

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Meet Vince

- … who is 28 yo male (BMI=33kg/m^2).
  - Medical history includes: T1DM x 11 years, celiac disease, Hashimoto's thyroiditis
  - He currently uses Tandem Basal IQ with CGM.
  - Weight has steadily increased since high school.
  - HbA1C = 7.2% (improved from 8% with insulin pump, but recently gained 10-lbs) and TG = 250 mg/dL.

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What Else Would You Most Like to Know about Vince?

A. Insulin antibodies?
B. C-peptide level?
C. Frequency of missed insulin doses?
D. Frequency of alcohol intake?

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Is Vince a Candidate for a GLP-1 RA?

A. Yes
B. No

Why or why not?

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If starting liraglutide, what would be the best recommendation for the insulin regimen?

A. Decrease by 20% basal and bolus.
B. Decrease by 20% bolus only.
C. Decrease by 10% basal and bolus.
D. Decrease by 10% bolus only.

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Sodium Glucose Cotransporter Inhibitors (SGLT Inhibitors)

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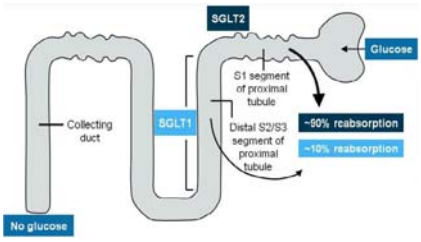
SGLT and the Kidney



Available at: http://www.diabetesincontrol.com/sglt2-inhibitors-a-new-class-of-diabetes-medications/. Accessed 5/30/19.

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SGLT-2 Inhibitors: Comparison

Drug	Dosing	Renal Threshold for Initiation	Outcomes	CV Indication
Canagliflozin (Invokana)	100-300 mg QAM eGFR 45-59: max 100 mg daily	eGFR >45mL/min	CANVAS, CREDENCE	Reduce risk of heart attack, stroke or CV death in T2DM
Dapagliflozin (Farxiga)	5-10 mg QAM	eGFR >45mL/min	DECLARE-TIMI 58, Dapa-CKD, Dapa-HF	No
Empagliflozin (Jardiance)	10-25 mg QAM	eGFR >45mL/min	EMPA-REG OUTCOME, EMPERPR-Preserved, EMPEROR-Reduced	Reduce risk of CV death in T2DM
Ertugliflozin (Steglatro)	5-15 mg QAM	eGFR >60mL/min	VERTIS CV	No

Clinical Resource, Diabetes Medications and Cardiovascular Impact. Pharmacist's Letter/Prescriber's Letter. January 2019

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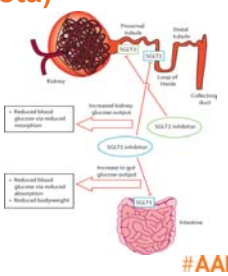
Sotagliflozin (Zynquista)

- Dual SGLT1/SGLT2 inhibitor:
  - SGLT1: small intestine
  - SGLT2: nephron (proximal convoluted tubules)
- Hypothesis:
  - SGLT2 inhibition leads to SGLT1 upregulation
  - Decrease postprandial glucose
  - Suppress glucagon



Sima et al. Diabet Med 2018;35(8):1037-48.
Frandsen et al. Lancet Diabetes Endocrinol 2016;4(9):766–80.

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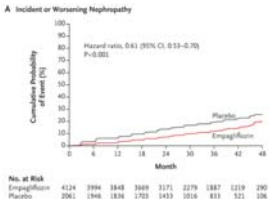
Renal Benefits

- Patients with T1DM are more likely to develop end stage renal disease (ESRD) – approximately 30%.
- EMPA-REG OUTCOME trial
  - Slower progression of kidney disease
  - Lower rates of doubling of serum creatinine level and initiation of renal-replacement therapy



Krolewski et al. Diabetes Care 2015; 38(6):954–62.
Wanner et al. N Engl J Med. 2016;375:323–34.

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Renal Benefits: The Credence Trial

Double-blind randomized controlled trial to evaluate a primary outcome: composite ESRD (dialysis, transplant, eGFR<15), doubling serum creatinine or death from renal/CV causes

4401 patients T2DM, median follow-up: 2.62 years, stopped early

RRR 34% (HR=0.66, P<0.001)

Perkovic et al. N Engl J Med 2019 Apr 14 doi: 10.1056/NEJMoa1811744. [Epub ahead of print].

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Benefits of SGLT-2 Inhibitors

HbA1C reduction	Weight loss	Cardiovascular benefits
Renal outcomes	Reduction in insulin doses	Blood pressure reduction

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Side Effects of SGLT-2 Inhibitors

- Genitourinary infections
- Urinary tract infections
- Increased urination
- Hypotension
- Hyperkalemia
- Amputation
- Decreased bone mineral density
- Bladder cancer
- Diabetic ketoacidosis (DKA)

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Sotagliflozin Clinical Trials

Trial	N	Population	Treatment	Outcomes
inTandem 1	793	T1DM Average age: 46 yrs Race: 91% white Average A1C: 8.2% Average BMI: 29 kg/m^2 Insulin pump: 60%	Randomized, double-blind, placebo-controlled Follow-up: 52 weeks	**HbA1c change** from baseline of 7.57% vs. placebo (Primary) Sotagliflozin 200 mg: -0.36%, Sotagliflozin 400 mg: -0.41%, P<0.001 for comparisons **DKA** Sotagliflozin 200 mg: 3.4%, Sotagliflozin 400 mg: 4.2%, Placebo: 0.4% **Severe hypoglycemia** Sotagliflozin 200 mg: 6.5%, Sotagliflozin 400 mg: 6.5%, Placebo: 9.7%
inTandem 2	782	T1DM Average age: 41 yrs Race: 96% white Average A1C: 8.2% Average BMI: 29.66 kg/m^2 Insulin pump: 25%	Randomized, double-blind, placebo-controlled Follow-up: 52 weeks	**HbA1c change** from baseline of 7.8% vs placebo (Primary) Sotagliflozin 200 mg: -0.37%, Sotagliflozin 400 mg: -0.35%, P<0.001 for comparisons **DKA** Sotagliflozin 200 mg: 2.3%, Sotagliflozin 400 mg: 3.4%, Placebo: 0% **Severe hypoglycemia** Sotagliflozin 200 mg: 5.0%, Sotagliflozin 400 mg: 2.3%, Placebo: 5.0%
inTandem 3	1402	T1DM Average age: 43 yrs Average A1C: 8.2% Average BMI: 28 kg/m^2 Insulin pump: 40%	Randomized, double-blind, placebo-controlled Follow-up: 24 weeks	Patients achieving **HbA1c lower than 7.0% without DKA** (Primary) Sotagliflozin: 200 of 699 patients (28.6%), Placebo: 107 of 703 (15.2%), P<0.001 **Adverse effects** Genital mycotic infections more common in sotagliflozin group Severe hypoglycemia occurred in 3% of the sotagliflozin group and 2.4% in placebo group **DKA** 3.0% sotagliflozin vs 0.6% placebo

Buse et al. Diabetes Care 2018;41(9):1970–80.
Danne et al. Diabetes Care 2018;41(9):1981–90.
Garg et al. N Engl J Med 2017;377:2337–48.

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Dapagliflozin Clinical Trials

Trial	N	Population	Treatment	Outcomes
DEPICT 1	833	T1DM Average age: 42 yrs Race: 96% white Average A1C: 8.53% Average BMI: 28 kg/m^2 Insulin pump: 37% DM Duration: 20 yrs	Randomized, double-blind, placebo-controlled Follow-up: 24 weeks	Primary: **Change in A1C** vs. placebo Dapagliflozin 5 mg: −0.42% [95% CI −0.56 to −0.28; p<0.0001] Dapagliflozin 10 mg: −0.45% [−0.58 to −0.31; p<0.0001] Time in range increased 43.2% vs placebo **DKA** Dapagliflozin 5 mg: 1%, Dapagliflozin 10 mg: 2%, Placebo: 1% Other adverse effects: Similar rates of hypoglycemia More UTIs with dapagliflozin 5 mg (7%), dapagliflozin 10 mg (4%) vs placebo (5%)
DEPICT 2	1465	T1DM Average Age: 43 yrs Race: 80% white Average A1C: 8.2% Average BMI: 27 kg/m^2 Insulin pump: 34% DM Duration: 19 yrs	Randomized, double-blind, placebo-controlled Follow-up: 24 weeks	Primary: **Change in A1C** vs. placebo Dapagliflozin 5 mg: -0.37% vs placebo **Total insulin dose**: -10.78%, body weight: -3.21%. Dapagliflozin 10 mg: -0.42% vs placebo Total insulin dose: -11.08%, body weight: - 3.21% (P<0.001 for all comparisons above) **DKA**: Dapagliflozin 10 mg: 13 events, Dapagliflozin 5 mg: 5 events, none with placebo Hypoglycemia similar between groups

Dandona et al. Lancet Diabetes Endocrinol 2017;8587(17):1–13.
Mathieu et al. Diabetes Care 2018;41(9):1938–46.

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Empagliflozin Clinical Trials

Trial	N	Population	Treatment	Outcomes
EASE 1	75	T1DM Average age: 40 yrs Race: 96% white Average A1C: 8.53% Average BMI: 28 kg/m² Insulin pump: 37% DM Duration: 20 yrs	Randomized, double-blind, placebo-controlled Follow-up: 4 weeks	Primary: **Change in A1C** vs. placebo Mean body weight was reduced by empagliflozin vs placebo (1.5-1.9kg, p<0.001) and A1C was reduced (0.35-0.49%, p<0.05). **No cases of DKA**
EASE 2	730	T1DM Average age: 42 yrs Race: 80% white Average A1C: 8.1% Average BMI: 27 kg/m² Insulin pump: 34% DM Duration: 20 yrs	Randomized, double-blind, placebo-controlled Follow-up: 26-52 weeks	Primary: **Change in A1C** vs. placebo A1C was reduced with all study doses compared to placebo -0.28%, -0.54%, and -0.53%, respectively (p<0.0001 for all). **Weight reduction** 5 mg: 1.8kg, 10 mg: 3kg, 25 mg: 3.4kg respectively after 26 weeks (p<0.001 for all). CGM demonstrated a 2.9 hour/day increased in time in range with empagliflozin 10 mg and 3.1 hours/day with empagliflozin 25 mg (p<0.0001 for both doses). **DKA** occurred more in the 10 mg (4.3%) and 25 mg group (3.3%), compared to the 2.5 mg group (1.2%) and placebo (0.8%)
EASE 3	977		Randomized, double-blind, placebo-controlled Follow-up: 26 weeks	

Rosenstock et al. Diabetes Care 2018;41(12):2560–69.
Pieber et al. Diabetes Obes Metab. 2015;17(10):928–35.
Ease 2 and Ease 3 Published concurrently in 1 manuscript

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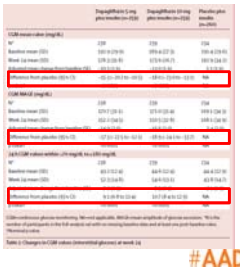
CGM Changes

EASE 2/3

DEPICT-2



Rosenstock et al. Diabetes Care 2018;41(12):2560–69.
Mathieu et al. Diabetes Care 2018;41(9):1938–46.

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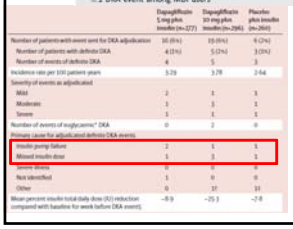
The Link to DKA

InTandem-1

Positively adjudicated adverse events	Placebo (n = 268)	Sotagliflozin 200 mg (n = 263)	Sotagliflozin 400 mg (n = 262)
≥1 severe hypoglycemia event†	26 (9.7)	17 (6.5)	17 (6.5)
≥1 severe nocturnal hypoglycemia event†**	10 (3.7)	10 (3.8)	2 (0.8)
≥1 DKA event	1 (0.4)	9 (3.4)	11 (4.2)
≥1 DKA event among CSII users	1/160 (0.6)	8/156 (5.1)	7/157 (4.5)
≥1 DKA event among MDI users	0/108	1/107 (0.9)	4/105 (3.8)

DEPICT-1



Dandona et al. Lancet Diabetes Endocrinol 2017;8587(17):1–13.
Buse et al. Diabetes Care 2018;41(9):1970–80.

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SGLT Clinical Trials in T1DM Summary

Trial	Drug	HbA1c improvement	Hypoglycemia	DKA	Insulin dose	Weight	BP
EASE-1	Empagliflozin	Yes	→	→	↓	↓	↓
EASE-2/EASE-3	Empagliflozin	Yes	→	↑	↓	↓	↓
DEPICT-1	Dapagliflozin	Yes	→	→	↓	↓	-
DEPICT-2	Dapagliflozin	Yes	→	↑	↓	↓	-
inTandem1	Sotagliflozin	Yes	↓	↑	↓	↓	↓
inTandem2	Sotagliflozin	Yes	→	↑	↓	↓	↓
inTandem3	Sotagliflozin	Yes	→	↑	↓	↓	↓
Henry et al.	Canagliflozin	Yes	→	↑	↓	↓	-

Buse et al. Diabetes Care 2018;41(9):1970–80. Danne et al. Diabetes Care 2018;41(9):1981–90. Garg et al. N Engl J Med 2017;377:2337–48. Dandona et al. Lancet Diabetes Endocrinol 2017;858(17):1–13. Mathieu et al. Diabetes Care 2018;41(9):1938–46. Rosenstock et al. Diabetes Care 2018;41(12):2560–69. Pieber et al. Diabetes Obes Metab. 2015;17(10):928–35. Henry RR et al. Diabetes Care. 2015 Dec;38(12):2258-65.

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FDA Submissions

- Dapagliflozin submitted to EU and FDA
  - EMA recommended approval for T1DM who meet certain criteria
    - BMI >27kg/m^2 not at glycemic targets despite high insulin doses
  - Insulin doses need to be continuously optimized by a diabetes specialist
  - Waiting on decision from FDA
- Sotagliflozin submitted to EU and FDA
  - FDA advisory committee voted 8-8 if benefits outweigh risks
  - FDA rejected
  - EU approved with same criteria as dapagliflozin
- Ipragliflozin approved for T1DM in Japan

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Why DKA?

- Several mechanisms
  - Reduction of total daily insulin dose may cause failure to suppress lipolysis and ketogenesis
  - Association with increase in glucagon
  - Reduction in renal clearance of ketone bodies

Danne et al. Diabetes Care 2019;42(6):1147–54.

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Risk of DKA

High	• Reduced basal by more than 10-20%; insulin pump or infusion site failure; reduced or consistent carbohydrate intake; excessive alcohol, illicit drugs, dehydration, acute illness, vomiting
Moderate	• Vigorous or prolonged exercise; reduced prandial insulin by more than 10-20%; travel with disruption in usual schedule or insulin regimen; insulin pump use
Low	• BMI <25kg/m^2; inconsistent calorie intake; moderate alcohol use; female

Danne et al. Diabetes Care 2019;42(6):1147–54.

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Insulin Dose Adjustments

HbA1C <7.5%

- 10-20% insulin reduction

SGLT-2 inhibitors

- More basal or equal basal/bolus reductions

HbA1C ≥7.5%

- Only slight or no insulin reduction

SGLT-1/2 inhibitors

- More bolus reductions, less impact on basal

Start with lowest dose possible: even consider ½ tablets

Danne et al. Diabetes Care 2019;42(6):1147–54.

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Monitoring

- Blood ketones: beta-hydroxybutyrate
  - Urinary ketones are second best (cheaper) but only measures acetoacetate.
- Frequency: individualize
- DKA symptoms
  - Malaise, fatigue, nausea, vomiting, changes in diet/activity, insulin, infection, dehydration, surgery, injury, pump occlusion, stress

Danne T et al. Diabetes Care 2019 Feb; dc182316.

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Holding Therapy

- Nausea, vomiting, abdominal discomfort
- Hospitalization
- Acutely ill
- Not eating normally
- Prior to medical procedure (3 days)

Danne et al. Diabetes Care 2019;42(6):1147–54.

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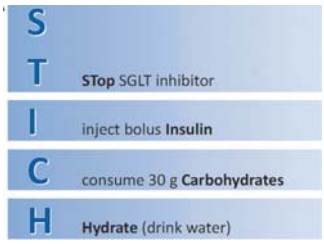
If Ketones are Present…



Garg et al. Diabetes Technol Ther 2018;20(9):571–5.
Danne et al. Diabetes Care 2019;42(6):1147–54.

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Meet Anna

- … who is 42 yo female.
  - Medical history: T1DM x 25 years; retinopathy; mild peripheral neuropathy
  - She is injecting insulin degludec 34 units Sc QD, insulin aspart 1 units/10 grams of carb, 1:25 sensitivity for BG>120.
  - Other information include BMI = 29kg/m^2 and HbA1C = 8.2%.

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What Else Would You Like to Know?

A. Alcohol use?
B. Frequency of DKA (i.e., last episode)?
C. Meal schedule; calorie intake; carbs/day?
D. Missed insulin doses?
E. Knowledge of/access to ketone testing?
F. Level of engagement?

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Is Anna a Candidate for a SGLT Inhibitor?

A. No, because she's not on an insulin pump.
B. No, because she has already development diabetes complications.
C. Yes, because she's over 40 years of age.
D. Yes, because she has no major risk factors for DKA.

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If starting a SGLT-2 inhibitor, what would be the best recommendation for the insulin regimen?

A. Decrease by 20%
   - Insulin degludec 27 units daily
   - Insulin aspart: 1 unit for 12 grams of carbs, sensitivity: 30
B. Decrease by 10%
   - Insulin degludec 31 units daily
   - Insulin aspart: 1 unit for 11 grams of carbs, sensitivity: 28
C. Decrease by 10% basal only
   - Insulin degludec 31 units daily
   - Insulin aspart: 1 unit for 10 grams of carbs, sensitivity: 25
D. Decrease by 5%
   - Insulin degludec: 32 units daily
   - Insulin aspart: 1 unit for 10.5 grams of carbs, sensitivity: 26

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CONCLUSION / UNANSWERED QUESTIONS

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QUESTIONS

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