

Implementing an Early T1D Clinic for Patients with Stage 1 and Stage 2 Type 1 Diabetes

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Background



- Teplizumab-mzwv was approved for **delaying onset of stage 3 type 1 diabetes** in November 2022
- We designed an early T1D clinic to identify individuals eligible for treatment per stage 2 ADA criteria
- We provided guidance around treatment options



Methods

- In December 2023, we opened a weekly clinic staffed with a nurse, physician and psychologist
- Potential candidates were identified by
 - **General population screening study**
 - **High risk screening study**
 - **Community referral**



Methods cont'd

- Individuals with islet autoimmunity and concern for dysglycemia complete metabolic staging, which includes:
 - **Fasting glucose level**
 - **HbA1C**
 - **2-hour OGTT**
 - **10-day CGM wear**
- Patients are offered a health and behavior assessment



Methods cont'd

- Metabolic staging results are obtained during clinic and treatment options are discussed
- If a patient desires Teplizumab-mzww therapy, we prescribe and initiate a PA



Results

- Using ADA T1D staging criteria, **17/22(77%)** patients are **stage 2**, **4/22 (18%)** are **stage 1**, and **one** patient was diagnosed as **stage 3**.
- Of those with stage 2, we have **successfully infused 6 patients**.
- Patients with Stage 1 T1D are not currently eligible for teplizumab therapy, but they may be eligible for other trials.



Results cont'd

- One patient initially classified as stage 2 progressed to symptomatic T1D before treatment.
- **Eleven stage 2 patients have been authorized** for teplizumab-mzwv treatment and **five are under review** for treatment by their insurance carriers.

Results cont'd

	HbA1c(%)	Fasting Glucose (mg/dl)	OGTT 120 Glucose (mg/dl)	CGM time >140 mg/dl (%)
1	5.2	90	64	8%
2	6	76	196	63%
3	6.1	93	184	16%
4	5.4	74	154	5%
5	5	60	122	9%
6	5.6	89	98	6%
7	5.2	83	85	12%
8	5.4	97	157	5%
9	6.3	145	234	46%
10	5.7	88	136	7%
11	5.8	97	107	16%
12	5.7	90	231	18%
13	6	145	268	44%
14	5.9	110	292	28%
15	5.4	92	142	15%
16	5.7	87	216	36%
17	5.7	77	130	28%
18	6.1	149	328	33%
19	5.4	102	181	6%
20	6.4	125	245	24%
21	5.1	77	143	TBD
22	6.3	112	167	28%

Stage of T1D by Monitoring Tool Used in Early T1D Clinic

	Stage 1	Stage 2	Stage 3
HbA1c	9	13	0
Fasting Blood Glucose	15	4	3
2-Hour OGTT Glucose	7	8	7

Individuals in Stage 1 (n=4), CGM time \geq 140 mg/dl (7.8 mmol/L) 6 to 12%
 Stage 2 (n=17), CGM time \geq 140 mg/dl (7.8 mmol/L) 5 to 63%
 Stage 3 (n=1), CGM time \geq 140 mg/dl (7.8 mmol/L) 46%

Next Steps

- For those that received treatment
 - Follow-up visits at 1 month post and then 6 mos with intermittent CGM wear every 3 months
- For stage 1 patients that did **not** qualify
 - Follow-up every 6 months (annually in adults)

Conclusions

- Individuals attending Early T1D clinic tolerated complete metabolic staging per ADA guidelines.
- We **successfully treated 6 eligible patients** as of September 2023.



DiabetesWisePro



THE LEONA M. AND HARRY B.
HELMSLEY
CHARITABLE TRUST



Our Journey

4 Deployed **DiabetesWise**, site for people with diabetes.

Developed **DiabetesWise Pro**, site for HCPs



1 Identified the problem – no free, unbiased, unbranded resource to compare and contrast diabetes devices



2 Explored options, talked to people with diabetes, HCPs, designers. Decided on a digital + online resource - **DiabetesWise**



5

Developed Prescription Tool that includes up-to-date payer/insurance data from claims, how to access devices, and essential forms.



Created algorithm to personalize recommendations.

3

Created content:
Device Features
Wisdom
Comparison Tool
Share with HCP

OVERVIEW

DiabetesWise for people
with diabetes

Launched June 2019

Features

- Check Up
- Sensors
- Device Finder
- Wisdom
- Resources

5 questions about...

- Current Devices
- Distress
- Priorities
- Concerns

DiabetesWise

The screenshot shows the DiabetesWise.org website in a browser. The browser's address bar displays "diabeteswise.org". The website's navigation menu includes "Check Up", "Sensors", "Device Finder", "Wisdom", and "Resources". The main content area features the heading "Helping You Find The Right Diabetes Devices For Your Life." Below this, there are two sections: "CHECKUP" and "WISDOM". The "CHECKUP" section asks "DO YOUR DEVICES STILL WORK FOR YOUR LIFE?" and includes a "Check Up" button. The "WISDOM" section states "CHOOSING YOUR DEVICES IS AN INCREDIBLY PERSONAL DECISION." and encourages users to hear from others. Illustrations of various diabetes devices, including a glucometer, insulin pen, pump, sensor, and insulin vial, are shown on the right side of the "CHECKUP" section.

DiabetesWise.org

Check Up Sensors Device Finder Wisdom Resources

Helping You Find The Right Diabetes Devices For Your Life.

CHECKUP

DO YOUR DEVICES STILL WORK FOR YOUR LIFE?

Take a quick quiz to see what might be your next diabetes care upgrade.

Check Up

WISDOM

CHOOSING YOUR DEVICES IS AN INCREDIBLY PERSONAL DECISION.

Hear what people with similar experiences are saying.

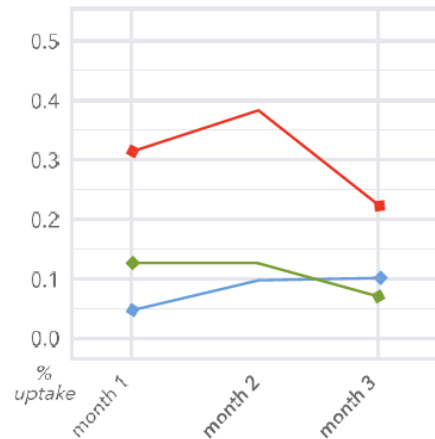
RESULTS

Clinical Research Study on [DiabetesWise](#)

Complete data on 458 people
with insulin-requiring diabetes.

- 75% on injections
- 2% on CGM
- 59% care outside specialty clinic
- 41% income below 50k
- good geographic representation

DiabetesWise



- ◆ Initiating a conversation with provider
- ◆ Getting a prescription for a device
- ◆ Starting a device

Most likely to engage with platform:

- People with fewer diabetes resources
- People receiving diabetes care through primary care
- People using meter & injections


Received: 17 January 2023 | Revised: 12 April 2023 | Accepted: 19 April 2023

DOI: 10.1111/1753-0407.13401

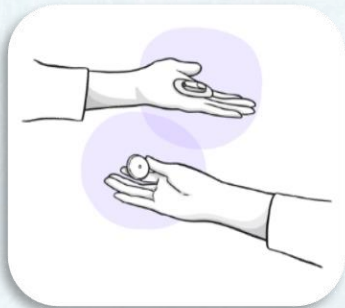
ORIGINAL ARTICLE

Journal of Diabetes  WILEY

DiabetesWise: An innovative approach to promoting diabetes device awareness

Jessie J. Wong¹  | Ananta Addala¹ | Sarah J. Hanes¹ | Sara Krugman² | Diana Naranjo¹ | Sierra Nelmes¹ | Kyle Jacques Rose³ | Molly L. Tanenbaum^{4,5} | Korey K. Hood^{1,2}

VALUE PROPOSITIONS



- **HCPs who take care of people with diabetes** use **DiabetesWisePro** to improve matching to devices.
- **HCPs access the prescription tool** in **DiabetesWisePro** for more efficient prescription of diabetes devices.
- **HCPs access insurance data** in **DiabetesWisePro** to determine insurance coverage information based on published policy data

diabeteswise.org

pro.diabeteswise.org

kkhood@stanford.edu

FEATURE

S

1. Browse Devices
2. Browse Wisdom
3. Compare Devices
4. Choose the right fit
5. Prescribe

Are you a person with Diabetes? [Visit DiabetesWise.org](https://www.diabeteswise.org)

DiabetesWisePro

Devices Prescriptions Resources About Us

Device Library **ALL DEVICES** 20 options **GLUCOSE MONITORING** 7 options **INSULIN DELIVERY** 9 options **AUTOMATED SYSTEMS (AID)** 4 options [Compare 2 Devices](#)




Selection Options

Device Details

- Overview**
basics about each diabetes device or system
- Affordability and Access
- Data Monitoring Options
- Data View Options
- Duration and Storage
- Vision / Auditory / Dexterity

Patient Considerations

Glucose Monitoring Devices

	Dexcom Dexcom G6	Small sensor can be worn in multiple areas.	See Details >	Add to Compare +
	Abbott Freestyle Libre 2	All-in-one glucose sensor/transmitter with low and high blood glucose alarms can be worn on the upper arm.	See Details >	Add to Compare +
	Abbott Freestyle Libre 2	Smallest, thinnest, all-in-one glucose sensor/transmitter with low and high blood glucose alarms can be worn on the upper arm.	See Details >	Add to Compare +

DiabetesWisePro

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Chelsea

"I DIDN'T DECIDE TO GET A PUMP UNTIL MY DOCTOR SAID TO ME, "YOU ARE GIVING YOURSELF THE BEST CARE POSSIBLE WHILE ON INJECTIONS. IF YOU WANT YOUR NUMBERS TO GET BETTER, THE TYPE OF TECHNOLOGY YOU'RE USING HAS TO CHANGE."

"I have yet to find an individual who could not benefit from at least one of the potential diabetes related technology devices out there."

Dr. Sumera Ahmed
MD, BC-ADM

Fact:

Devices are tested in a process called Human Factors testing that the FDA requires to be usable by the majority of people, safely. Using technology may take a bit to learn, but once you do, almost anyone can use them.

FEATURE

S

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- 3. Compare Devices**
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Dexcom G7
▼

Freestyle Libre 3
▼



Components

*Available in early 2023 Sensor



Sensor uses a thin, flexible filament inserted just under the skin to measure glucose levels every minute. Push-button applicator allows sensor to be placed on the body in one step.



Sensor

Sensor uses a thin, flexible filament inserted just under the skin to measure glucose levels every minute. Push-button applicator allows sensor to be placed on the body in one step.

Patient Considerations

Active Lifestyle

Waterproof when submerged in 2.4 meters of water and must be within 20 (unobstructed) feet of the receiver or mobile device.

Water-resistant for up to 3 feet deep for 30 minutes and light on the body, does not get in the way of activity.

Avoiding Highs and Lows

Custom alerts can be set for highs, lows, and rapidly rising or falling glucose levels. Trend arrows show the direction glucose is heading, with the rate of change.

Optional glucose alerts for low and high glucose levels. Trend arrows show the direction glucose is heading, with the rate of change.

Comfort

Low profile and low maintenance sensor application.

Lowest profile sensor and smallest adhesive (about the size of two stacked U.S. pennies).

FEATURE

S

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5. Prescribe

DiabetesWisePro

[← Back to Device Library](#)



Dexcom G6

This sensor lasts for 10 days and only needs finger sticks as a backup. Dexcom G6 has 3 parts - sensor, transmitter, and receiver. Data can be viewed on a compatible mobile device or a separate receiver. Optional low and high blood sugar notifications are available for this system.

*FDA approved for insertion on the abdomen (indicated for patients age 2 years and older) or the upper buttocks (ages 2-17 years).

- Compatible with Tandem t:slim X2, Control IQ, Omnipod 5, Loop
- Supports English (United States)



What is Needed to Start

Sensor

Sensor uses a thin, flexible filament inserted just under the skin to measure glucose levels every minute. Push-button applicator allows sensor to be placed on the body in one step.



Transmitter

Sends readings from sensor to device, clips into sensor. Can be used for 90 days.



Receiver

Receives data automatically from the transmitter. Can be substituted by compatible smartphone and smartwatch. Available for both iOS and Android devices.



PRESCRIPTION TOOL

1. Browse Devices
2. Browse Wisdom
3. Compare Devices
4. Choose the right fit
5. **Prescribe**

- **Choose an insurance**
- Gather details
- Send prescription

Input: Select the device type, state, plan type, and payer information

Select a Device

Dexcom G6

Select a State

California

Insurance Plan

Medicaid

Medicare

Private Insurance

Insurance Provider

Anthem

Anthem in California has Dexcom G6 on their formulary and is distributed by IngenioRx. All policies require prior authorization.

Output: Summary of coverage will appear based on data from






PRESCRIPTION TOOL

DiabetesWisePro

Fill out forms and send them to the vendor.

Devices often come in parts or Components, each needing it's own prescription. The following is a list of components and prescription information and forms. It is best to submit paperwork all together and have a dedicated staff member follow up.

Component	Quantity	NDC Code (Pharmacy)	HCPCS Code (DME)	Refills
 Sensor	3 per box	08627-0053-03	K0553	Every 30 days
 Transmitter	1	08627-0016-01	K0553	Every 3 months
 Receiver	1	08627-0091-11	K0554	Once a year (optional)

Forms & Documents

Certificate of Medical Necessity



DEXCOM
DETAILED WRITTEN ORDER

MEMBER INFORMATION (required) PROVIDER INFORMATION (required)

MEMBER NAME: _____ PROVIDER NAME: _____
 MEMBER ID #: _____ SPECIALTY: _____
 DATE OF BIRTH: _____ OFFICE PHONE: _____
 STREET ADDRESS: _____ OFFICE FAX: _____
 CITY: _____ STATE: _____ ZIP: _____ OFFICE STREET ADDRESS: _____
 PHONE: _____ CITY: _____ STATE: _____ ZIP: _____

DEVICE INFORMATION (required) DEVICE TO BE USED

DEVICE NAME: _____
 DEVICE TYPE: _____
 Continuous Glucose Monitor (CGM)
 Insulin Delivery
 Automated Insulin Delivery (AID)

[View Sample](#)

Prior Authorization Form



PRESCRIPTION PRIOR AUTHORIZATION REQUEST FORM

MEMBER INFORMATION (required) PROVIDER INFORMATION (required)

MEMBER NAME: _____ PROVIDER NAME: _____
 MEMBER ID #: _____ SPECIALTY: _____
 DATE OF BIRTH: _____ OFFICE PHONE: _____
 STREET ADDRESS: _____ OFFICE FAX: _____
 CITY: _____ STATE: _____ ZIP: _____ OFFICE STREET ADDRESS: _____
 PHONE: _____ CITY: _____ STATE: _____ ZIP: _____

DEVICE INFORMATION (required) DEVICE TO BE USED

DEVICE NAME: _____
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 Continuous Glucose Monitor (CGM)
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 Automated Insulin Delivery (AID)

[View Sample](#)

1. Browse Devices
2. Browse Wisdom
3. Compare Devices
4. Choose the right fit
5. Prescribe
 - Choose an insurance
 - **Gather details**
 - Send prescription

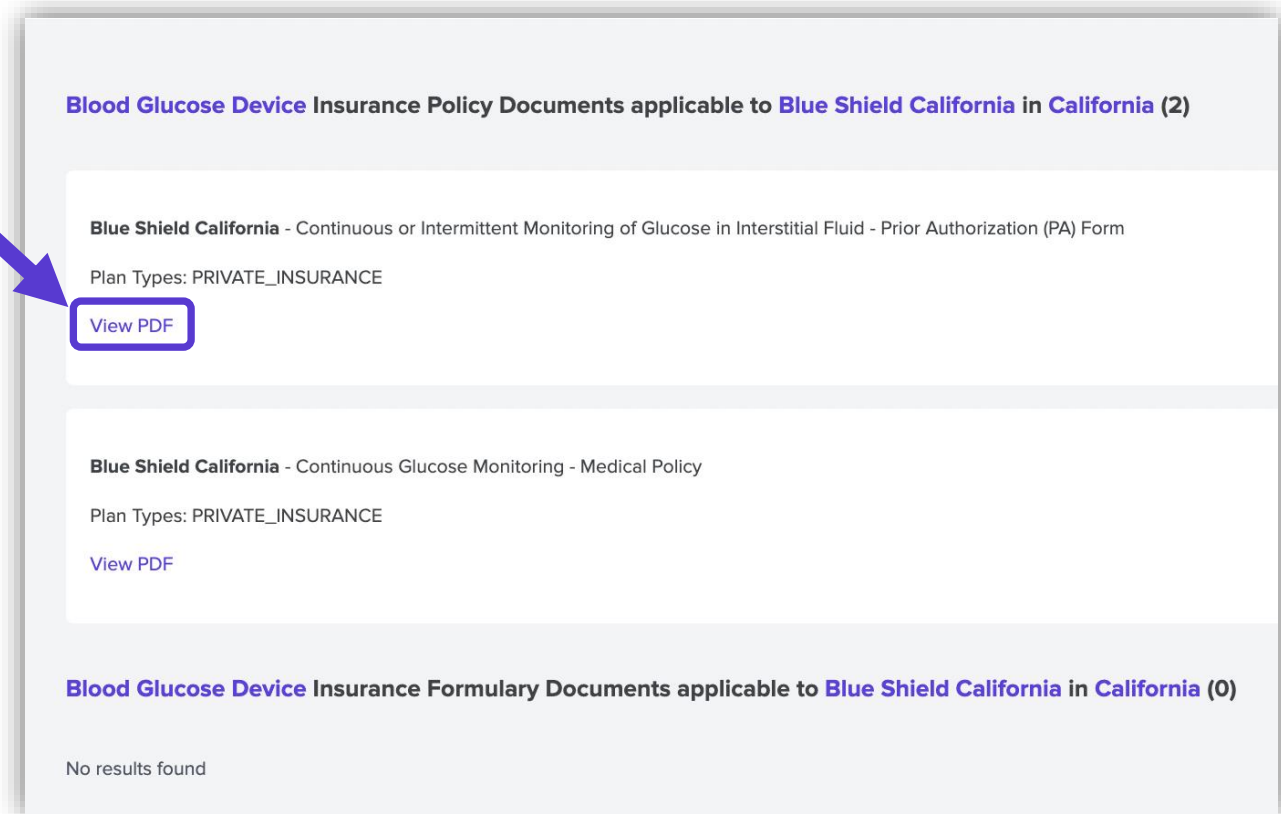
PRESCRIPTION TOOL

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5. **Prescribe**

- Choose an insurance
- Gather details
- **Send prescription**

* If more information is needed before prescribing, direct links to policy documents will also be provided in the prescription tool output

DiabetesWisePro



Blood Glucose Device Insurance Policy Documents applicable to Blue Shield California in California (2)

Blue Shield California - Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid - Prior Authorization (PA) Form
Plan Types: PRIVATE_INSURANCE
[View PDF](#)

Blue Shield California - Continuous Glucose Monitoring - Medical Policy
Plan Types: PRIVATE_INSURANCE
[View PDF](#)

Blood Glucose Device Insurance Formulary Documents applicable to Blue Shield California in California (0)

No results found

SUMMARY

- DiabetesWisePro was built to inform and improve the **prescription process** for diabetes devices
- **Features** include device library, comparison tools, and prescription support
- Supported by Helmsley so we can be **free, unbranded** and untethered to device manufacturers
- Our only bias is that we need to get more people on devices by increasing **access and awareness**



diabeteswise.org

pro.diabeteswise.org

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Insulins and Rescue Medications

New Therapies and Devices for Early Career Practitioners

Grenye O'Malley

Assistant Professor

Division of Endocrinology, Diabetes and Bone Diseases

Icahn School of Medicine at Mount Sinai

New York, NY, USA



Icahn
School of
Medicine at
**Mount
Sinai**

Presenter Disclosure

Grenye O'Malley

Research Support: Dexcom, Abbott, Tandem Diabetes, Insulet

Overview

1. Know your insulins
2. Know your devices
3. Know your rescue medications
4. Know your team

Know your insulins

- ▶ Explosion of generic pens
 - Make sure you are on the same page
 - Streamline communication with pharmacies
 - Cost caps
 - Streamline your prescribing
(and your January)



Know your insulins

- ▶ Explosion of generic pens
 - Make sure you are on the same page
 - Streamline communication with pharmacies
 - Cost caps
 - Streamline your prescribing
(and your January)
- ▶ Think outside the pen
 - Connected pens
 - Inhaled insulin
 - Insulin patches
- ▶ Put pharma to work



Know your devices

Tandem



Medtronic



Omnipod 5



ilet



Know your devices

Tandem



112.5-160mg/dL
Sleep:112.5-120mg/dL

Medtronic



670/770G:120mg/dL
780G: 100-120mg/dL

Omnipod 5







110-150mg/dL

ilet







Usual:120mg/dL
Lower:110mg/dL
Higher:130mg/dL





Know your devices

Tandem	Medtronic	Omnipod 5	ilet
 <p>112.5-160mg/dL Sleep:112.5-120mg/dL</p>	 <p>670/770G:120mg/dL 780G: 100-120mg/dL</p>	 <p>110-150mg/dL</p>	 <p>Usual:120mg/dL Lower:110mg/dL Higher:130mg/dL</p>
<p>Basal rates Carb ratios Sensitivity factors</p>	<p>Carb ratios Active insulin time</p>	<p>Carb ratios Correction factors Active insulin time</p>	<p>Usual, Lower, Higher Sleep</p>





Know your devices

Tandem	Medtronic	Omnipod 5	ilet
 <p>112.5-160mg/dL Sleep:112.5-120mg/dL</p>	 <p>670/770G:120mg/dL 780G: 100-120mg/dL</p>	 <p>110-150mg/dL</p>	 <p>Usual:120mg/dL Lower:110mg/dL Higher:130mg/dL</p>
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<p>Carb counting and timing</p>	<p>Carb counting and timing</p>	<p>Carb counting and timing</p>	<p>Smaller, usual, larger Carb timing/consistency</p>





Know your devices

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<p>Exercise mode</p>	<p>Hypo protect</p>	<p>Activity Mode</p>	





Know your devices

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<p>Phone boluses</p>	<p>Phone boluses coming</p>	<p>Phone boluses rolling out</p>	

Know your devices

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<p>Exercise mode</p>	<p>Hypo protect</p>	<p>Activity Mode</p>	
<p>Phone boluses</p>	<p>Phone boluses coming</p>	<p>Phone boluses rolling out</p>	
	<p>Calibrations 3-4x/day</p>		

Know your devices

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<p>Phone boluses</p>	<p>Phone boluses coming</p>	<p>Phone boluses rolling out</p>	
	<p>Calibrations 3-4x/day</p>		
	<p>Back up changes for manual</p>	<p>Back up changes for manual</p>	<p>Average dosing available to guide backup pen use</p>

Know your devices

- ▶ Check on who you are prescribing to
 - QI and Equity opportunities
- ▶ Streamline how to offer technology
- ▶ Manage your team
 - Options
 - Trainings
 - Infusion sets



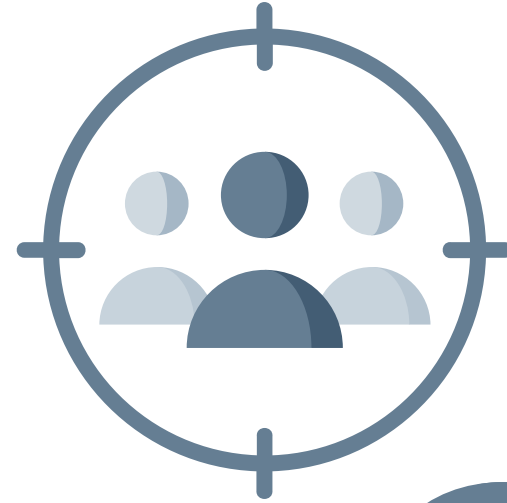
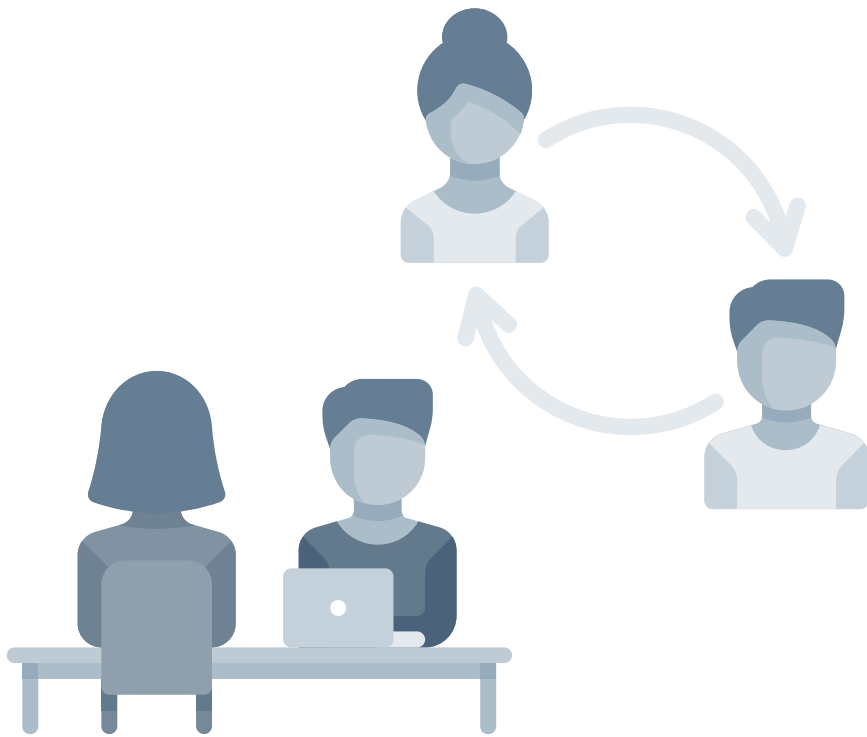
Know your rescue medications

- ▶ Vial and syringe
- ▶ Auto-injectors
- ▶ Nasal powder

- ▶ One and two packs
- ▶ Make sure patients have them BEFORE they need them
- ▶ Tailor training



Know your team





HASSENFELD
**CHILDREN'S
HOSPITAL**
AT NYU LANGONE

Adjunctive Treatments in T1D

Emily Breidbart, MD

Assistant Professor of Pediatric Endocrinology

NYU School of Medicine

NYU Pediatric Diabetes Center

11/14/2023

Goals of Adjunctive Treatments

- Control metabolic state of people with T1D without increasing weight gain
 - Excessive weight gain from intensive insulin can offset benefit of strict glucose targets and increase cardiovascular events
- Analysis of T1DX and Prospective Diabetes Follow-up (DPV) registries revealed that 5.4% of T1DM population in US use non-insulin antihyperglycemic agents in addition to insulin

Lyons SK, Hermann JM, Miller KM, et al. Use of adjuvant pharmacotherapy in type 1 diabetes: international comparison of 49,996 individuals in the prospective diabetes follow-up and t1d exchange registries. *Diabetes Care*. 2017;40(10):e139-e140.

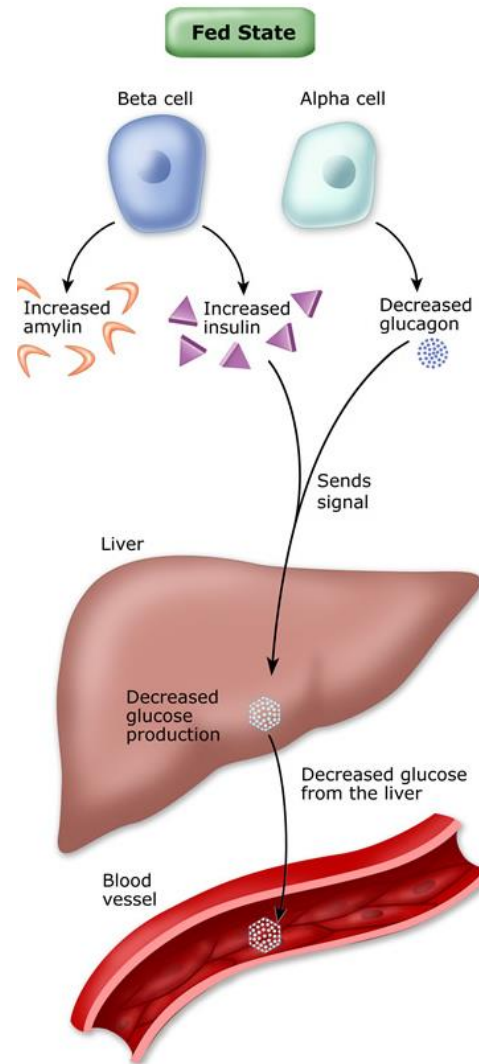


Adjunctive Therapies

- Amylin
- Metformin
- SGLT-2s
- GLP-1s

Amylin (Pramlintide)

The Effect of Amylin



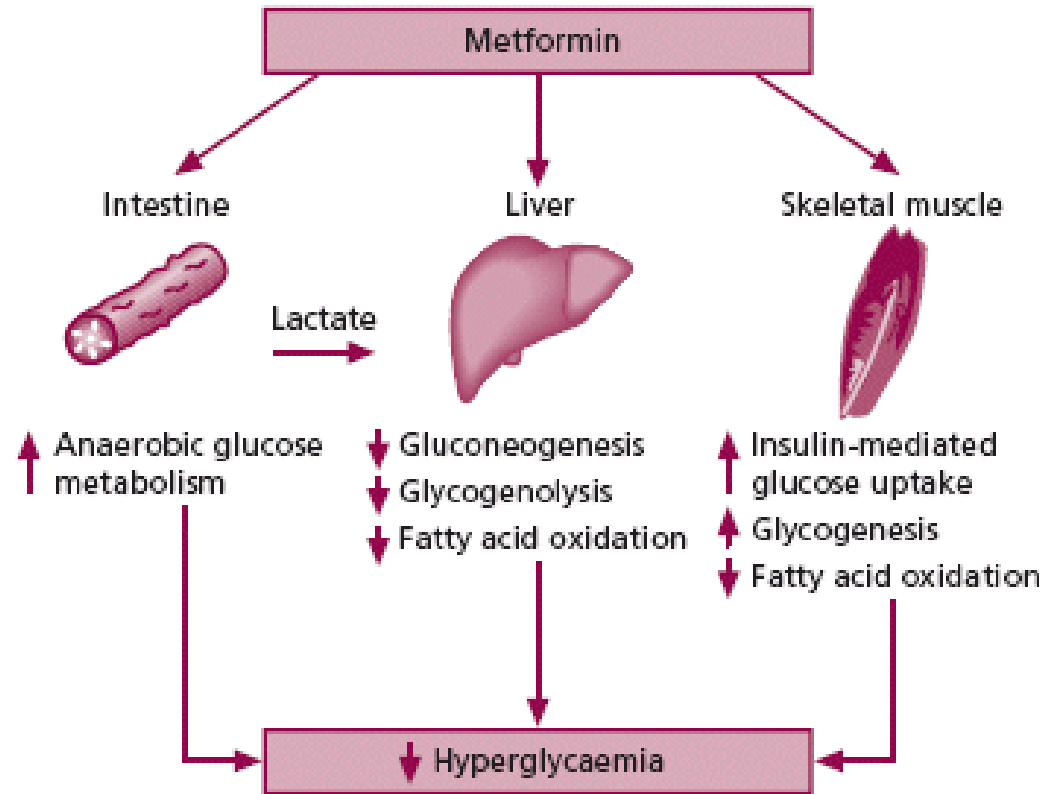
Amylin

- Pramlinitide is the only adjunctive therapy that HAS been FDA approved for use in T1D (2005)
- Lower A1C ~ 0.5%
- 1kg weight loss
- Reduction in total daily insulin by 6-12%
- Postprandial hypoglycemia
- Despite approval in 2005, few patients on it because requires 3-4 additional sq injections daily
- \$\$\$\$

Adjunctive Therapies

- Amylin
- Metformin
- SGLT-2s
- GLP-1s

Metformin



Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherbourne Gibbs, Birmingham UK, 2004

Metformin

- Licensed for T1D only in France, but used off-label frequently
- **2015 T1Dx Trial**- adolescents had modest reductions in insulin requirement and weight, transient A1C change not sustained beyond 3 months
- Significant GI side effects → Metformin not supported
- **REMOVAL trial** (multi-site, placebo controlled, adults, powered for CV outcome)- no difference in carotid intima media thickness, 1.2 kg weight loss, small reduction in LDL, and 2 unit per day insulin reduction, only 0.13% A1C lowering.
- **Clamp study**- 3 mos of metformin significantly improved whole-body and related peripheral insulin sensitivity in overweight/obese youth with type 1 diabetes

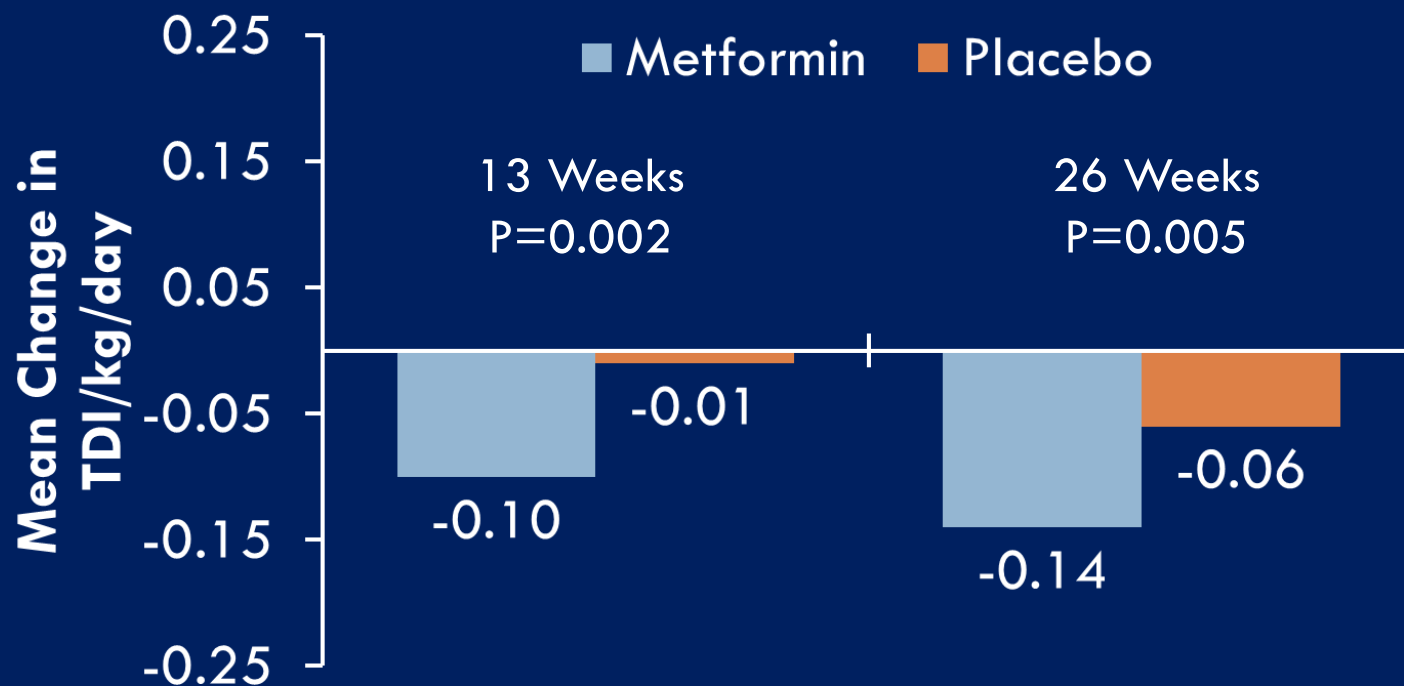
Libman IM, Miller KM, DiMeglio LA, et al. Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial. *JAMA*. 2015;314(21):2241-2250.

Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (Removal): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(8):597-609.

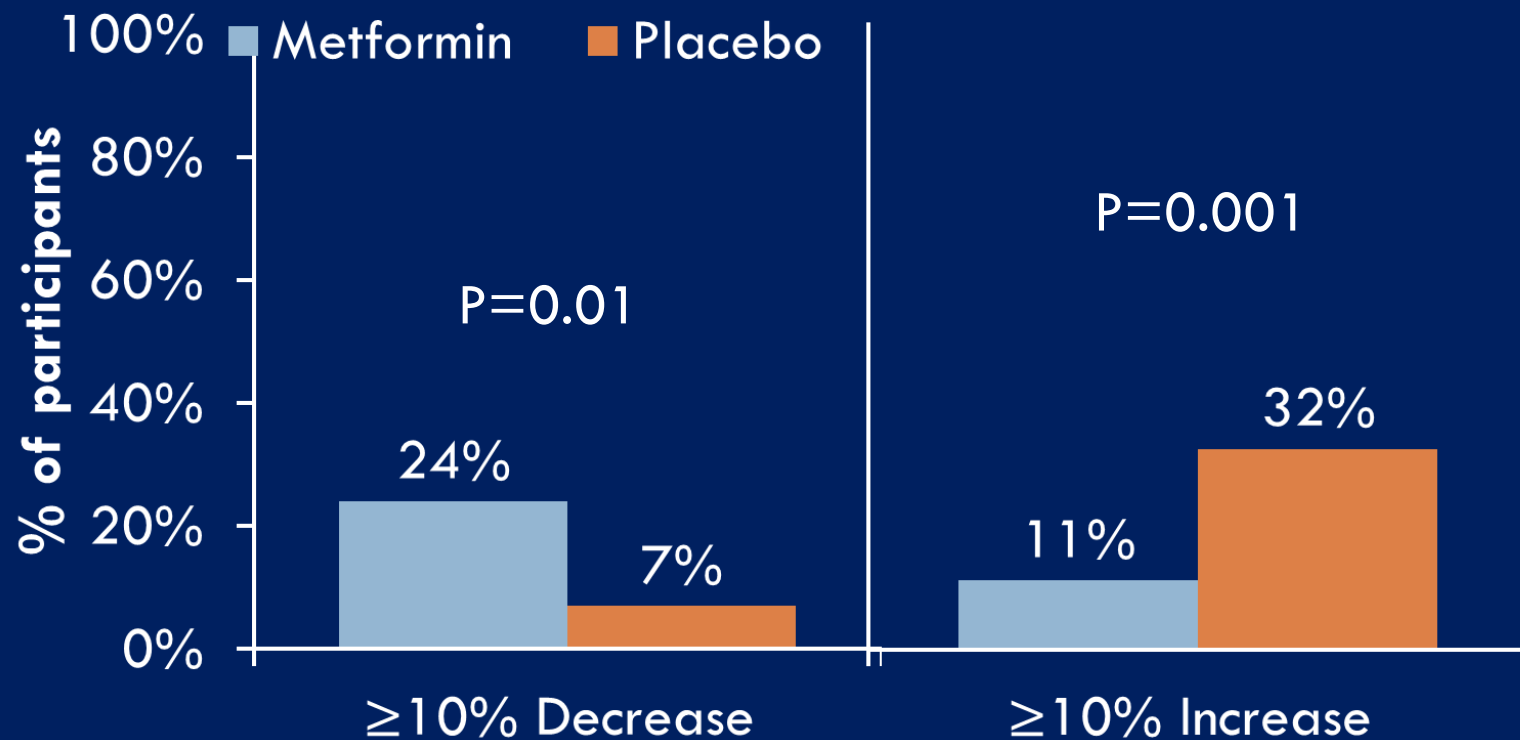
Cree-Green M, Bergman BC, Cengiz E, et al. Metformin improves peripheral insulin sensitivity in youth with type 1 diabetes. *J Clin Endocrinol Metab*. 2019;104(8):3265-3278.



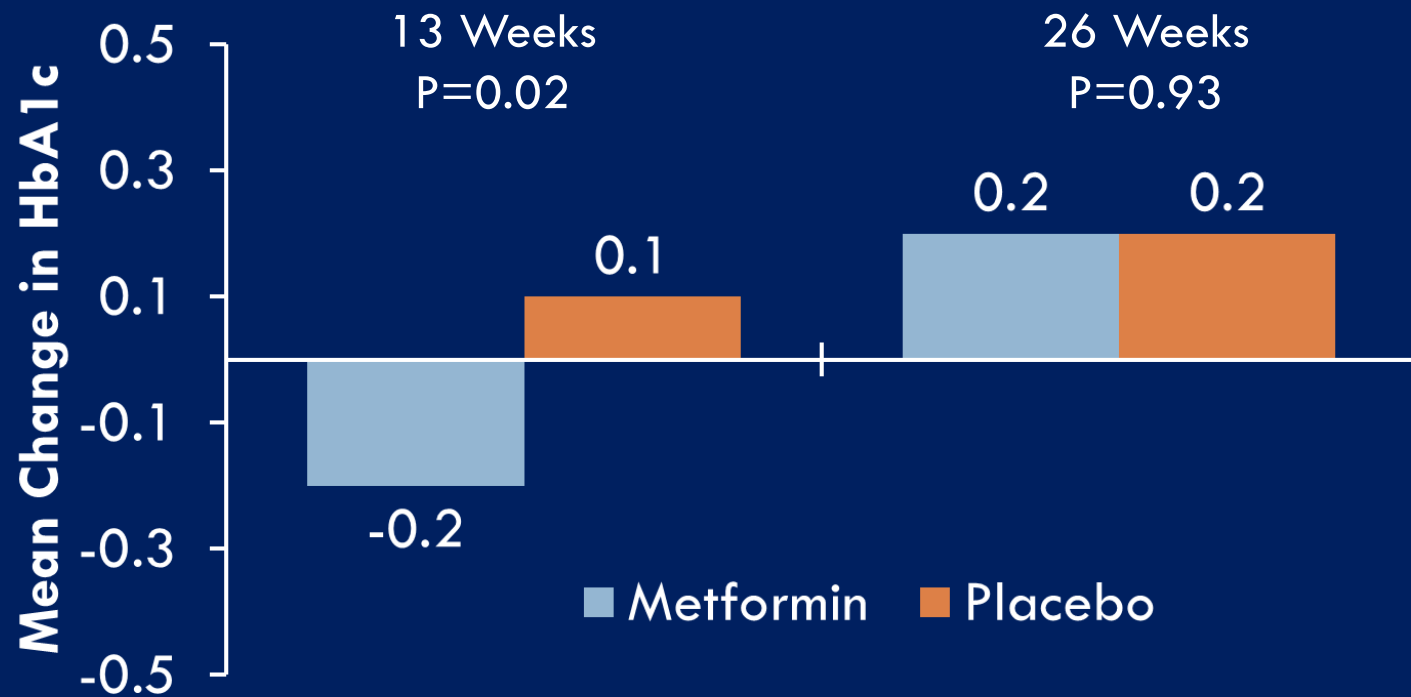
Change from Baseline in Total Daily Insulin (units/Kg/day)



Change in BMI Z Score - Baseline to 26 wk



Change from Baseline in HbA1c

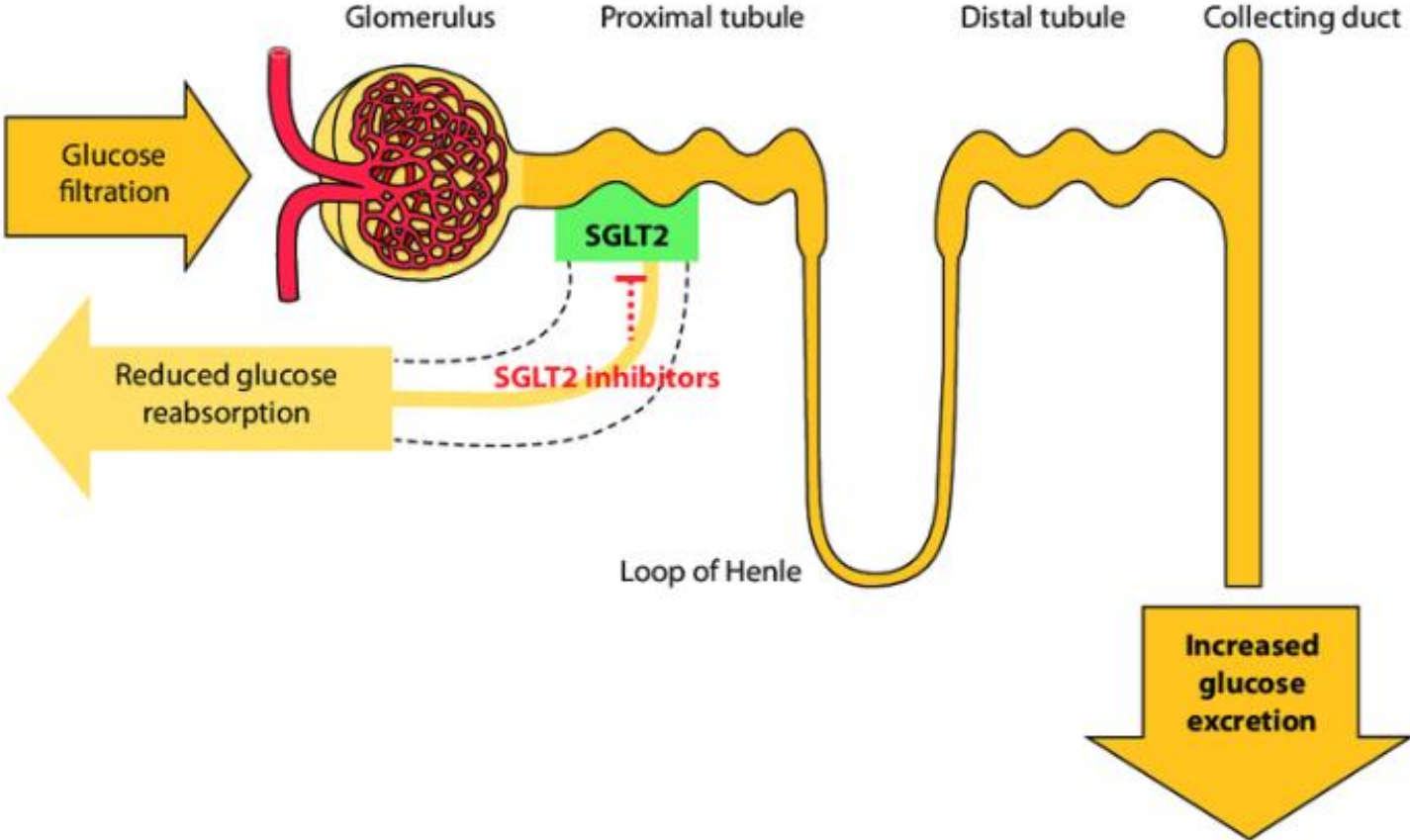


Adjunctive Therapies

- Amylin
- Metformin
- SLGT-2s
- GLP-1s

SGLT2 Inhibitors

(dapagliflozin, empagliflozin, canagliflozin, ertugliflozin)



SGLT2 inhibitors

- Ipragliflozin and Dapagliflozin are licensed in Japan
- In Europe Dapagliflozin approved in overweight people with T1DM with suboptimal glycemia in 2019
- **Withdrawn** in UK and Europe in 2021 by AstraZeneca (cited not due to safety)

SGLT2 inhibitors

- Eight double masked clinical trials in T1D
- **DEPICT trials**- reductions in A1C of up to 0.36% with weight loss of up to 2.9 kg
- **EASE programme** – reduction of A1C of up to 0.54% with modest-high doses, weight loss up to 3.4 kg, reduction of total daily insulin dose to 6.4-13.1%
- **Tandem1 and Tandem2**- significant increase in TIR, up to 12.7% change in higher doses
- A1C lowering was greatest at 24-26 weeks, waning by about 0.1-0.15% at 52 weeks; most weight loss has also occurred at this point
 - Mediated by compensatory increase in food intake?

Mathieu C, Dandona P, Gillard P, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (The depict-2 study): 24-week results from a randomized controlled trial. *Diabetes Care*. 2018;41(9):1938-1946.

Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the ease trials. *Diabetes Care*. 2018;41(12):2560-2569.

Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the north american intandem1 study. *Diabetes Care*. 2018;41(9):1970-1980.

Danne T, Cariou B, Banks P, et al. Hba1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the european intandem2 study. *Diabetes Care*. 2018;41(9):1981-1990.



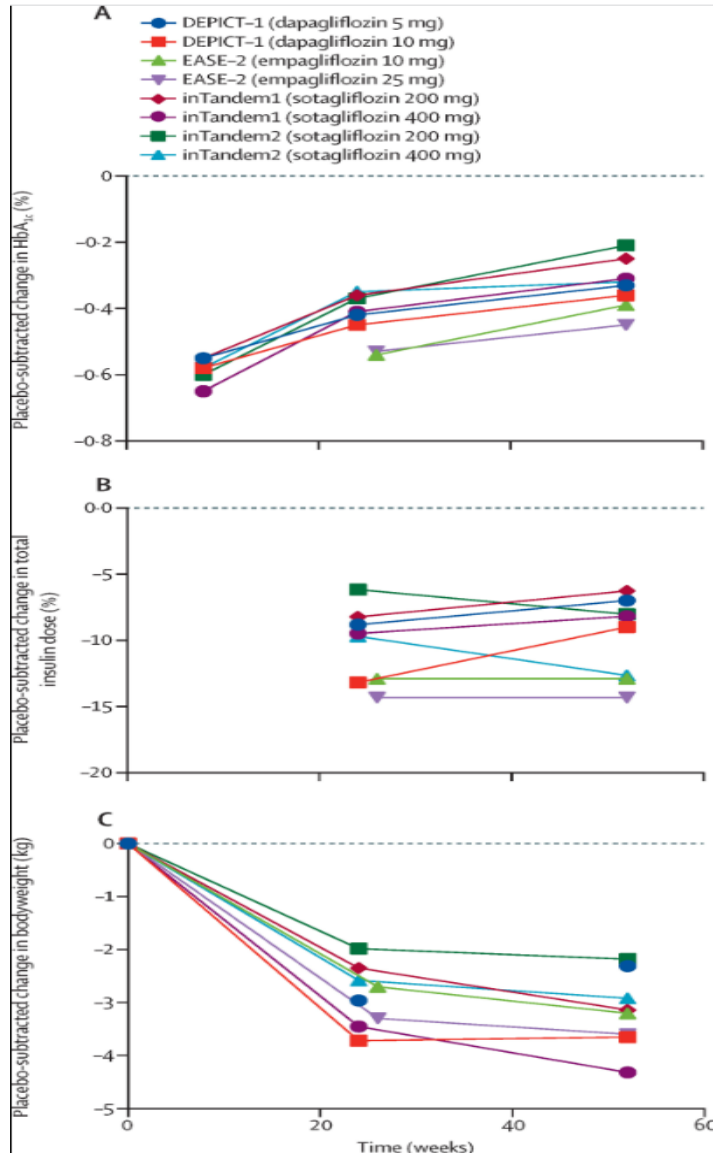


Figure 2. Progression of HbA_{1c} (A), insulin dose (B), and bodyweight (C) over time in four clinical trials of SGLT2 inhibitors in patients with type 1 diabetes with 52 weeks of follow-up. (DEPICT-1 [dapagliflozin], inTandem1 [sotagliflozin], inTandem2 [sotagliflozin], and EASE-2 [empagliflozin]). The graphs depict point estimates of placebo-subtracted changes in (A) HbA, (B) insulin dose, and (C) bodyweight.

Taylor SI, Blau JE, Rother KI, Beitelshes AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol.* 2019;7(12):949-958.

	Severe hypoglycaemia	Adjudicated ketoacidosis	Urinary tract infections	Genital mycotic infections (male/female participants)*
18-week phase 2 canagliflozin trial¹²				
Canagliflozin 100 mg	2.6% (3/117)	4.3% (5/117)	4.3% (5/117)	0%/4.2%
Canagliflozin 300 mg	6.8% (8/117)	6.0% (7/117)	5.1% (6/117)	0%/21.2%
Placebo	1.7% (2/117)	0% (0/117)	1.7% (2/117)	0%/5.6%
DEPICT-1 trial^{13,14}				
Dapagliflozin 5 mg	10.5% (29/277)	4.0% (11/277)	11.6% (32/277)	7.6%/21.5%
Dapagliflozin 10 mg	8.4% (25/296)	3.4% (10/296)	5.4% (16/296)	8.6%/18.8%
Placebo	11.5% (30/260)	1.9% (5/260)	8.1% (21/260)	0%/6.3%
DEPICT-2 trial¹⁵				
Dapagliflozin 5 mg	1.8% (5/271)	2.6% (7/271)	6.6% (18/271)	2.5%/15.7%
Dapagliflozin 10 mg	0% (0/270)	2.2% (6/270)	3.7% (10/270)	1.7%/12.8%
Placebo	0.4% (1/272)	0% (0/272)	4.4% (12/272)	0%/3.3%
EASE-2/3 trials (pooled)¹⁶				
Empagliflozin 10 mg	4.1% (20/491)	4.3% (21/491)	9.6% (46/491)	12.8% (62/491)
Empagliflozin 25 mg	2.7% (13/489)	3.3% (16/489)	8.4% (41/489)	14.3% (70/489)
Placebo	3.1% (15/484)	1.2% (6/484)	8.5% (41/484)	4.3% (21/484)
EASE-3 trial¹⁶				
Empagliflozin 2.5 mg	1.2% (3/241)	0.8% (2/241)	5.4% (13/241)	5.4% (13/241)
Placebo	2.5% (6/241)	1.2% (3/241)	4.6% (11/241)	2.5% (6/241)
inTandem1 trial¹⁷				
Sotagliflozin 200 mg	6.5% (17/263)	3.4% (9/263)	9.9% (26/263)	9.1% (24/263)
Sotagliflozin 400 mg	6.5% (17/262)	4.2% (11/262)	4.2% (11/262)	13.0% (34/262)
Placebo	9.7% (26/268)	0.4% (1/268)	7.1% (19/268)	3.4% (9/268)
inTandem2 trial¹⁸				
Sotagliflozin 200 mg	5.0% (13/261)	2.3% (6/261)	4.2% (11/261)	9.2% (24/261)
Sotagliflozin 400 mg	2.3% (6/263)	3.4% (9/263)	6.8% (18/263)	11.0% (29/263)
Placebo	5.0% (13/258)	0% (0/258)	5.0% (13/258)	2.3% (6/258)
inTandem3 trial¹⁸				
Sotagliflozin 400 mg	3.0% (21/699)	3.0% (21/699)	3.6% (25/699)	6.4% (45/699)
Placebo	2.4% (17/703)	0.6% (4/703)	3.8% (27/703)	2.1% (15/703)
<p>Data are % (n/N). The definitions of ketoacidosis varied among the eight clinical trials. In the canagliflozin trial,¹² diabetic ketoacidosis events were reported as serious adverse events, defined as diabetic ketoacidosis requiring hospital admission. In the other seven trials, committees were established to adjudicate serious adverse ketoacidosis events.¹³⁻¹⁸ In the dapagliflozin trials, "definite" diabetic ketoacidosis events were reported, based on three criteria: venous pH less than 7.3; serum bicarbonate less than 18 mmol/L; and one or more of hyperventilation, dehydration, or depressed consciousness or confusion. In the sotagliflozin trials,¹⁶⁻¹⁸ adjudicated diabetic ketoacidosis was diagnosed on the basis of evidence of anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause for anion-gap acidosis. However, the adjudication committee was empowered to make a final decision to diagnose metabolic acidosis (including diabetic ketoacidosis) on the basis of their best clinical judgment. In the empagliflozin trials, "certain" diabetic ketoacidosis events were reported, based primarily on whether pH was less than 7.3. If pH data were unavailable, then the diagnosis could be based on serum bicarbonate less than 18 mmol/L. If neither were available, then the diagnosis could be based on neurologic status. Notwithstanding any of these criteria, the final case assessment was at the discretion of members of the adjudication committee. Single or multiple episodes consisting of β-hydroxybutyrate concentrations higher than 1.5 and less than 3.8 mmol/L were classified as ketosis (rather than ketoacidosis) and did not undergo adjudication if typical ketoacidosis symptoms, hospital admission, or serious adverse event reporting were absent. Such episodes might have been associated with pH less than 7.3 and would have been adjudicated as ketoacidosis in trials with dapagliflozin or sotagliflozin. The unweighted means of the risk of adjudicated ketoacidosis were 0.59% (SE 0.27%) for placebo; 3.48% (0.36%) for the lower dose of study drug; and 3.64% (0.45%) for the higher dose of study drug. SGLT2=sodium-glucose co-transporter-2. *Data for genital mycotic infections by sex were only available for the canagliflozin and dapagliflozin trials; for the empagliflozin and sotagliflozin trials, combined totals are shown.</p>				
Table: Summary of selected safety outcomes in eight clinical trials of SGLT2 inhibitors as adjunctive therapy in combination with insulin in patients with type 1 diabetes				

Taylor SI, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol.* 2019;7(12):949-958.

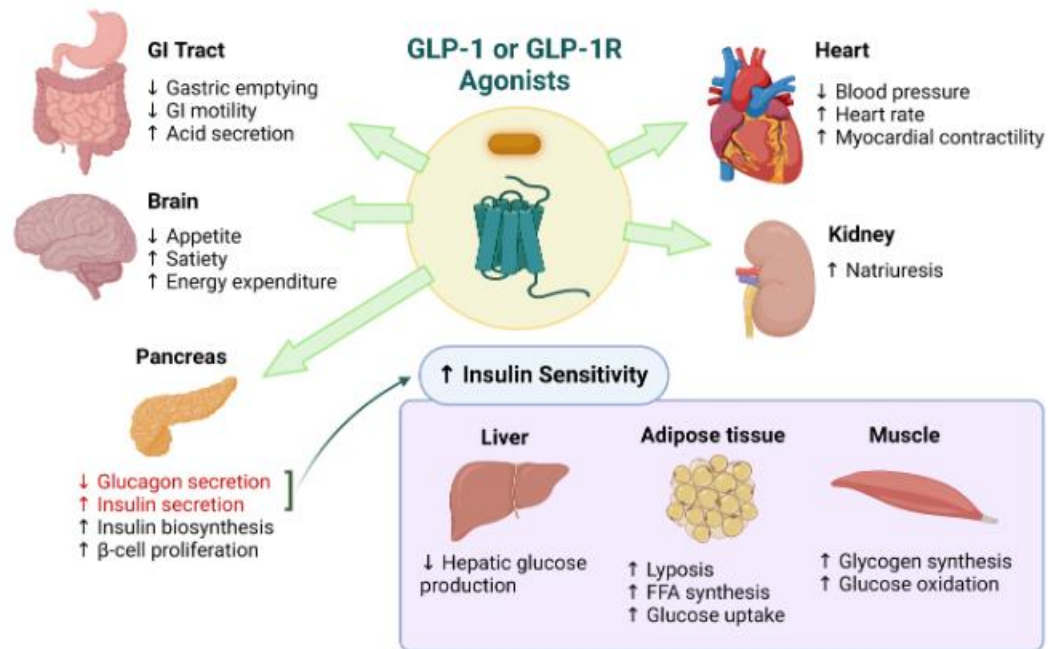
SGLT2 inhibitors

- Euglycemic DKA- absolute insulin deficiency, glucose can be normal given loss through urine → delay in detection
 - Proportion of pts with DKA was 3.5% in lower-dose SGLT2 groups and 3.6% in higher-dose groups, compared with 0.6% in placebo
- Significant rates of ketosis and DKA have prevented widespread uptake **DEPICT trials** showed 4- to 5-fold increases in genital infections and 2- to 3-fold increase in DKA
- Models predict additional case of ketoacidosis for every 26 patient-years of adjunctive therapy (16 deaths per year for every 100,000 patient treated)
- Future research: what is optimal method and frequency of ketone measurement to catch ketosis?
- What are CV and renal outcomes?

Adjunctive Therapies

- Amylin
- Metformin
- SLGT-2s
- GLP-1s

GLP-1s



GLP-1s

- Meta-analyses have shown reduced prandial and basal insulin
- ADJUNCT trials and pooled analysis showed that GLP-1s reduced body weight in patients with T1D:
 - Liraglutide reduced body weight by 4.0 kg
 - Exenatide reduced body weight by 8.3 kg
- A1C reduction modest, with Liraglutide 1.8mg having largest change of -0.28%
 - C-peptide positive pts have highest A1C decline
- Limited data for long-acting agents
- Mohandas et al. first study to look at this, in 2023
 - increased time in range by a mean difference of 12 points
 - decreased 14-day mean BG by 19 mg/dl
 - decreased 14-day BG standard deviation by 8.5 mg/dl
 - decreased incidence of DKA hospitalization
 - decrease in weight by 3.2 kg

Albèr A, Brønden A, Knop FK. Short-acting glucagon-like peptide-1 receptor agonists as add-on to insulin therapy in type 1 diabetes: A review. *Diabetes Obes Metab.* 2017;19(7):915-925.

Park J, Ntelis S, Yunasan E, et al. Glucagon-like peptide 1 analogues as adjunctive therapy for patients with type 1 diabetes: an updated systematic review and meta-analysis. *J Clin Endocrinol Metab.* Published online August 10, 2023:dgad471.

Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the adjunct one treat-to-target randomized trial. *Diabetes Care.* 2016;39(10):1702-1710.

Ahrén B, Hirsch IB, Pieber TR, et al. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the adjunct two randomized trial. *Diabetes Care.* 2016;39(10):1693-1701.

Mohandas D, Calma J, Gao C, Basina M. Evaluating the efficacy and safety of long-acting GLP-1 receptor agonists in T1DM patients *Endocrines* 4(1) 2023



GLP-1s

- Hypoglycemia increased, but odds of severe or symptomatic hypoglycemia were not significantly elevated
- Higher rates of ketosis
 - Likely due to GI side effects of drug such as vomiting and/or withdrawal/decrease of insulin
 - Decreased oral intake may also contribute to ketosis events
 - Compared to SGLT2s, considerably lower risk
- Current trials starting to address macro/microvascular outcomes

Albèr A, Brønden A, Knop FK. Short-acting glucagon-like peptide-1 receptor agonists as add-on to insulin therapy in type 1 diabetes: A review. *Diabetes Obes Metab.* 2017;19(7):915-925.

In Summary

Adjunctive Therapies

- Amylin
 - Despite FDA approval 18 years ago, poor uptake
- Metformin
 - Safe and most commonly used, but mixed data
- SGLT-2s
 - Meet many criteria for an ideal adjunct therapy, but significant concerns of ketoacidosis
- GLP-1s
 - Some early convincing evidence, more studies needed