Diabetes Technology

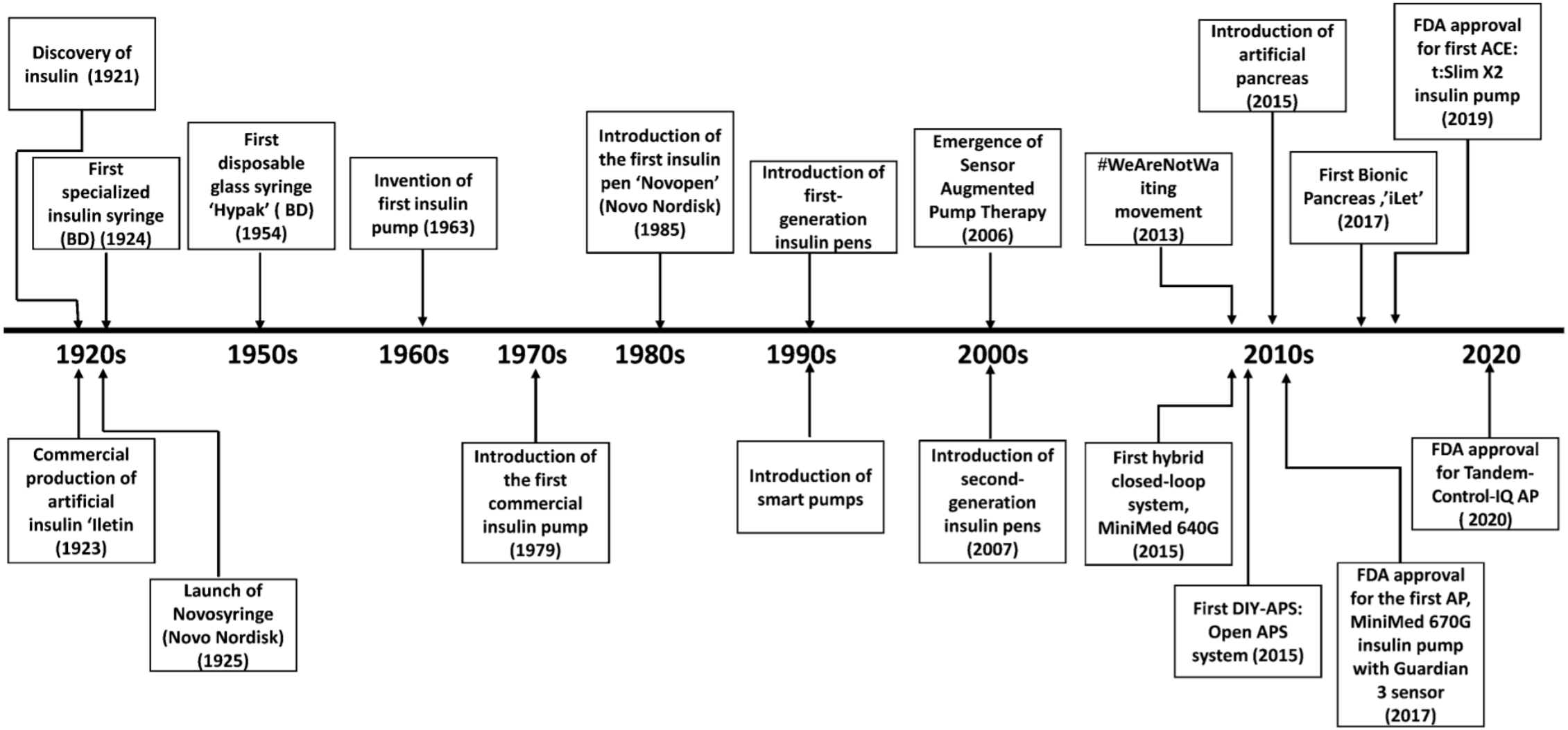
Objectives

To review emerging diabetes technology, including:

- Continuous Glucose Monitoring (CGM)**
- Basics of Insulin Pumps
- Insulin Pump and CGM Integration
- Artificial Pancreas/Hybrid Closed Loop Technology

** For in-depth details on CGM, see the slide library titled “Continuous Glucose Monitoring (CGM) in the Diabetes Resource Center

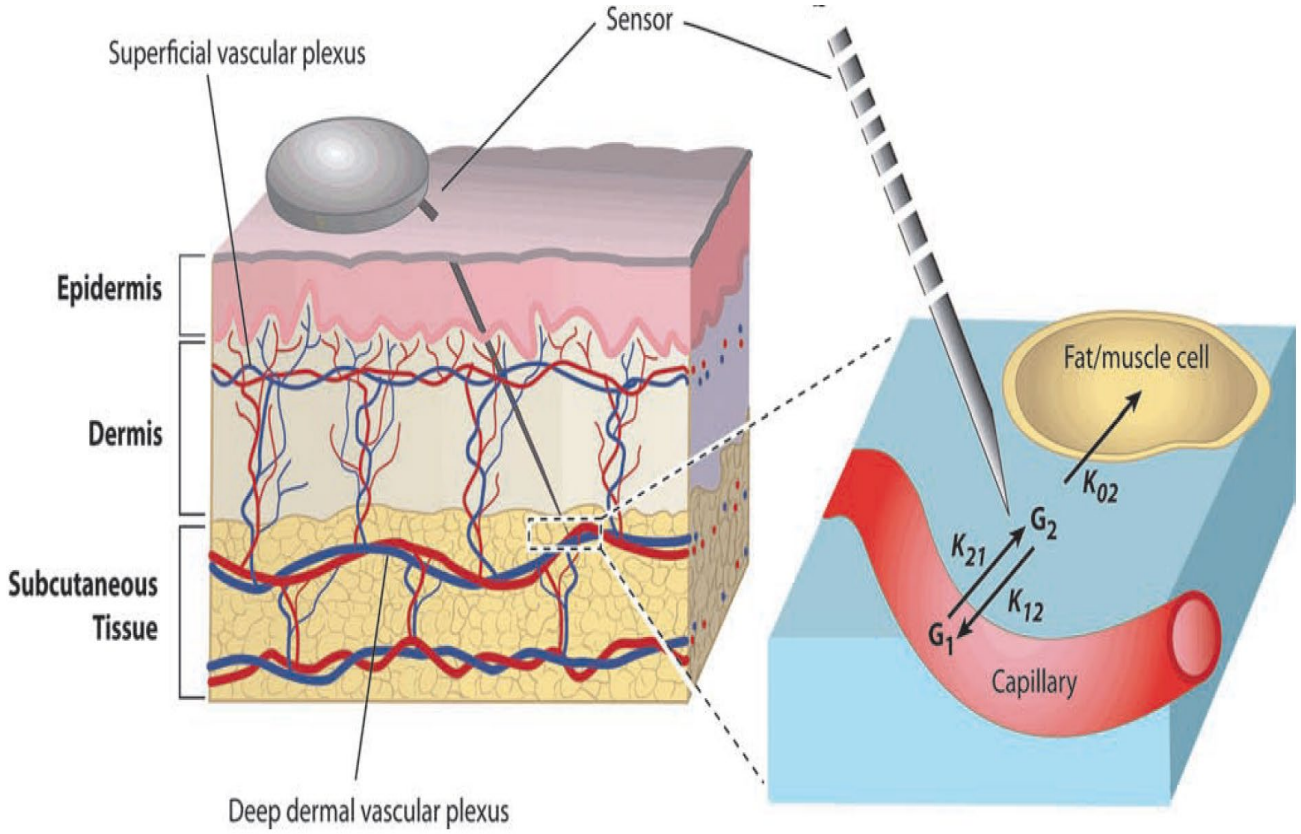
Diabetes Technology Timeline



Kesavadev et al. Diabetes Ther. 2020 Jun;11(6):1251-1269. doi: 10.1007/s13300-020-00831-z.

Continuous Glucose Monitoring (CGM)

Monitoring Glycemic Control: Continuous Glucose Monitoring (CGM)



- With CGM, a small sensor is placed under the skin, to measure the interstitial glucose levels in intervals of 5 to 15 minutes[1]
- CGM provides a more comprehensive assessment of glycemic control
- CGM can inform patients of impending glucose excursions using glucose trend arrows and influence treatment decisions[2]
- CGM devices continue to become easier to use, more accurate, and more accessible to patients[2]

Figure: Cengiz and Tamborlane. Diabetes Technol Ther. 2009. Jun;11 (Suppl 1)

1. Bergenstal et al. *Diabetes Care*. 2018 Nov;41(11):2275-2280.
2. Ajjan et al. *Adv Ther*. 2019 Mar;36(3):579-596.

Indications for CGM Therapy

International Consensus:[1]
- All patients with T1D
- T2D treated with intensive insulin therapy, not meeting glycemic goals
- Those with problematic hypoglycemia

AACE:[3]
- T1D with hypoglycemia/unawareness or not meeting glycemic goals
- T2D on intensive insulin therapy, high risk for hypoglycemia, or unappreciated hyperglycemia

American Diabetes Association:[2]
- T1D not meeting glycemic goals (consider in T2D)
- Hypoglycemia/unawareness
- Sensor-augmented pump therapy
- Consider in pregnancy

1. Danne et al. *Diabetes Care* 2017; 40:1631-1640.
2. ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S71-S80.
3. Handelsman et al. *Endocr Pract*. 2015 Apr;21 Suppl 1:1-87.

Current Commercially-Available CGM systems

Abbott

No user calibration required

Medtronic

Dexcom®

CONTINUOUS GLUCOSE MONITORING

eversense®

Continuous Glucose Monitoring System

Only implantable CGM

No user calibration required

Continuous Glucose Monitoring

- 3 types of CGM systems:
  - Real-time CGM
    - Provides continuous data on sensor glucose values, trends and alarms to the CGM receiver or smartphone
  - Intermittent scanned CGM
    - Glucose data and trend information are available after scanning the CGM sensor with the receiver or smartphone
    - Newer versions have real-time optional alarms
  - Professional CGM
    - A blinded CGM sensor is placed on the patient and worn for two weeks to obtain data on glucose values and trends
    - No real-time glucose data or alarms, only retrospective review of sensor glucose data

Key features of current personal CGM devices

	rt-CGM						is-CGM
CGM Category	Dexcom G6[13]	Dexcom G5[12]	Dexcom G4 Platinum[16]	Medtronic Guardian 3[10,11]	Medtronic Enlite 2[17]	Senseonic Eversense[18]	Abbott Freestyle Flash Libre[19,20]
Population Age (y)	≥2	≥2	≥2	≥7	≥16	≥18	United States: ≥18 Non–United States: ≥4
Pregnancy Approval	No	No	No	No	No	No	United States: no Non–United States: yes
Warm-up time (h)	2	2	2	2	2	24	10 d: 12 14-d: 1
Sensor wear (d)	10	7	7	7	6	United States: 90 Non–United States: 180	10–14
Calibrations	None	2/d	2/d	2–4/d	2/d	2/d	None
Nonadjunctive Use	Yes	Yes	No	No	No	Yes	Yes
Audible Alarms/Alerts	Yes Hypoglycemia predictive alerts	Yes	Yes	Yes Predictive alerts	Yes Predictive alerts	Yes Predictive alerts (vibrates)	No
Trend Arrows	Yes	Yes	Yes	Yes	Yes	Yes	Yes

1. Kravarusic J, Aleppo G. *Endocrinol Metab Clin North Am.* 2020 Mar;49(1):37-55.

Key features of current personal CGM devices

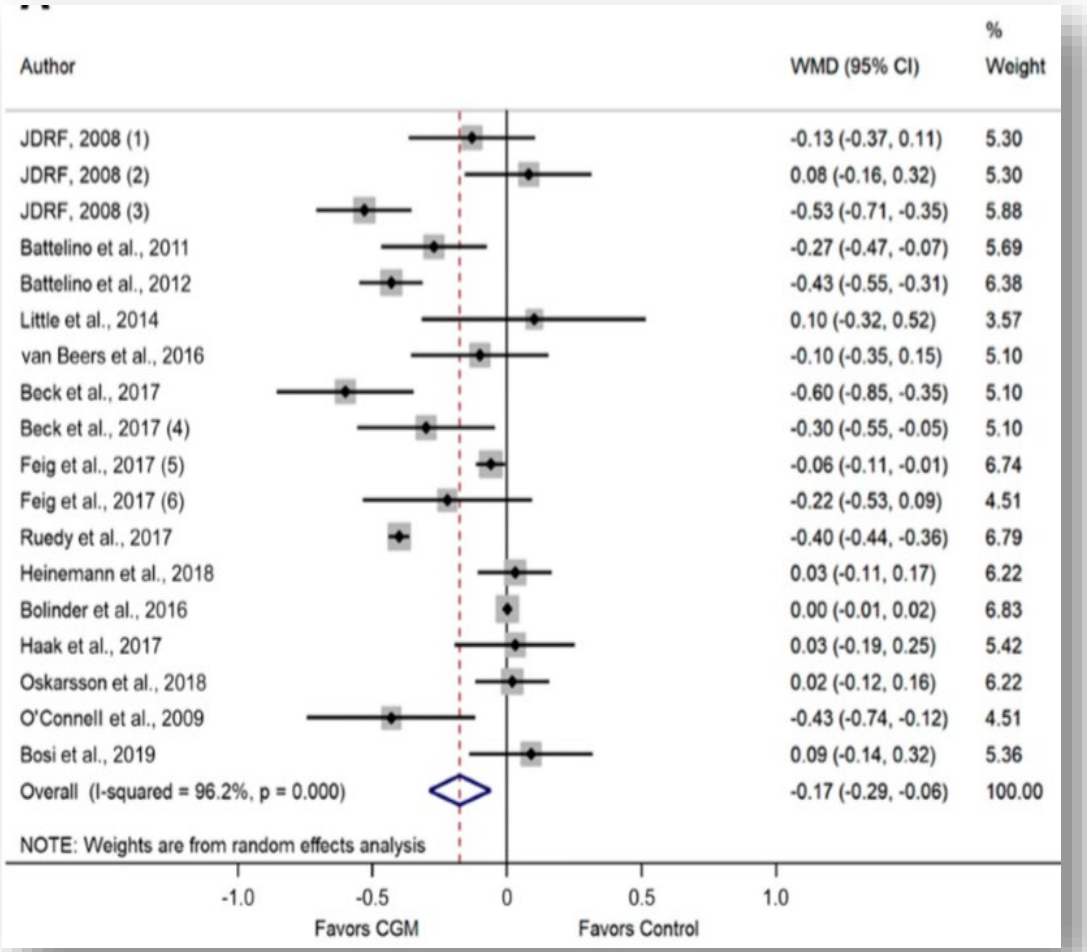
	Personal						
	rt-CGM						is-CGM
CGM Category	Dexcom G6[13]	Dexcom G5[12]	Dexcom G4 Platinum[16]	Medtronic Guardian 3[10,11]	Medtronic Enlite 2[17]	Senseonic Eversense[18]	Abbott Freestyle Flash Libre[19,20]
Share features	Yes	Yes	Yes	Guardian Connect Mobile only (Apple)	No	Yes	14-d system only (LibreLink)
Pump integration	Tandem t:slim X2 with Basal IQ	Tandem t:slim X2	Animas Vibe Tandem t:slim G4	Medtronic 670G	Medtronic Revel, 530G, 630G	None	None
Software Compatibility	Dexcom CLARITY Glooko Tidepool	Dexcom CLARITY Glooko Tidepool	Dexcom Studio Glooko Tidepool	Medtronic CareLink Tidepool	Medtronic CareLink	Glooko	LibreView Tidepool (reader only)
Acetaminophen Interference	No	Yes	Yes	Yes	Yes	No	No
MARD (%)	9	9	9	Abdominal 10.6[a]-9.6[b] Arm 9.1[a]-8.7[b]	13.6	8.8	10 d: 9.7 14 d: 9.4
Radiograph/MRI Compatible	No	No	No	No	No	Yes	No

is-CGM = intermittent scanned CGM
NA = not available
rt-CGM = real time CGM

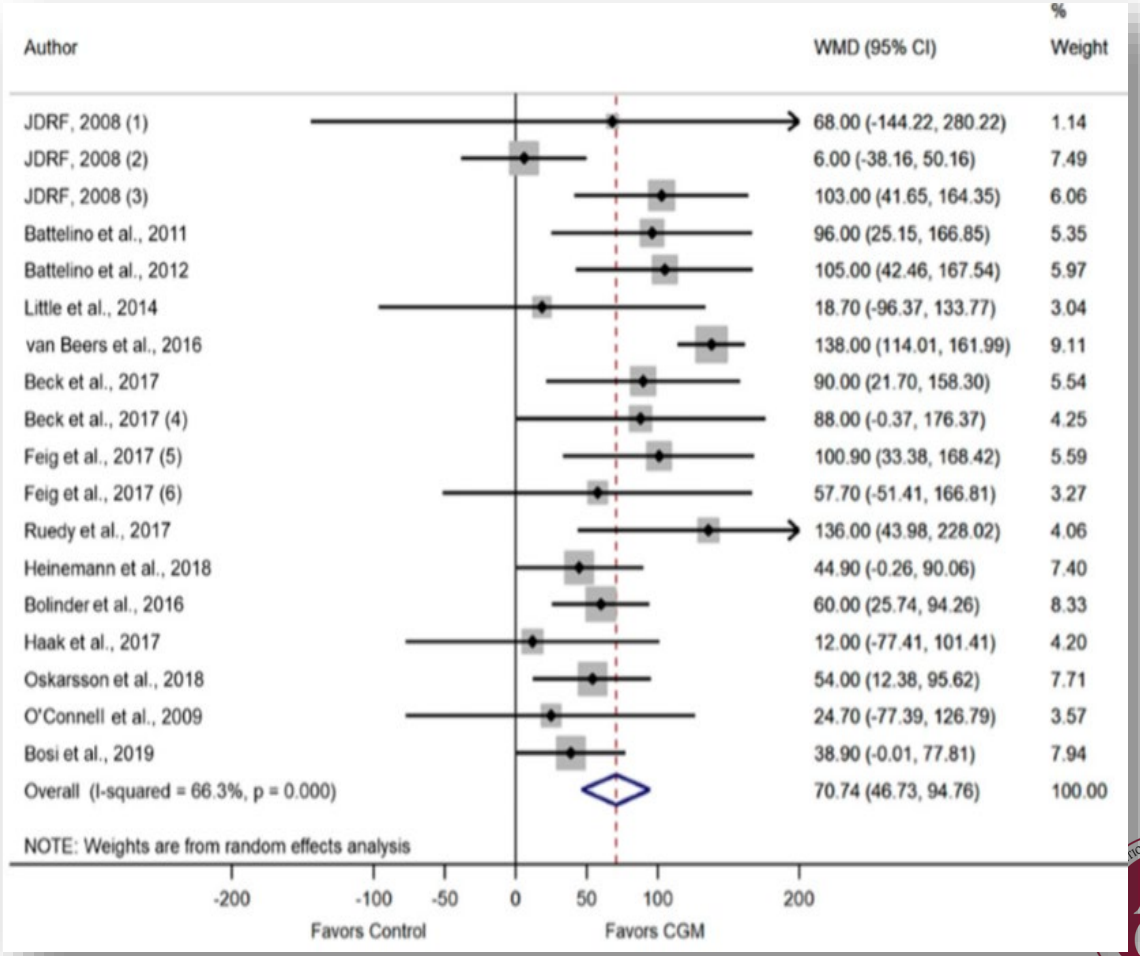
1. Kravarusic J, Aleppo G. *Endocrinol Metab Clin North Am.* 2020 Mar;49(1):37-55.

Meta-analysis of CGM trials in T1D and T2D

Change in Hemoglobin A1C

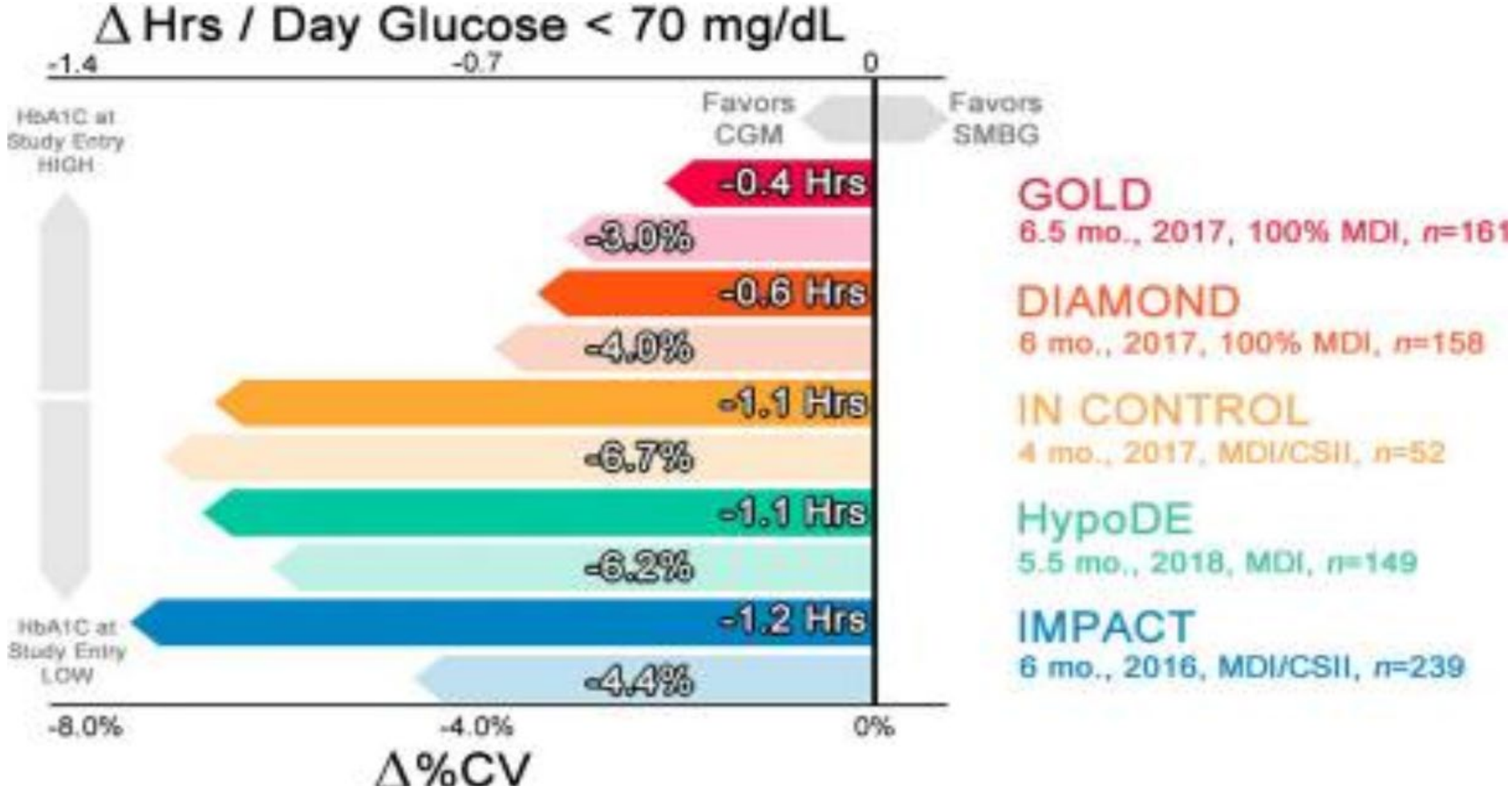


Time in Target Glucose Range



Maiorino et al. *Diabetes Care*. 2020;43:1146–1156.

Magnitude of reduction in time in hypoglycemia and CV according to baseline A1c with CGM



Martin et al. Curr Diab Rep. 2019; 19(8): 50.
Published online 2019 Jun 27. doi: 10.1007/s11892-019-1177-7

Basics of Insulin Pump Therapy

What is Insulin Pump Therapy?

- Also called Continuous Subcutaneous Insulin Infusion (CSII)
- Allows for continuous administration of rapid-acting insulin analogs (i.e. aspart or lispro insulin) via a small subcutaneous plastic catheter that is changed every 2-3 days
- Insulin administration is based on insulin pump settings (basal rates, bolus dosing, corrective dosing) determined by the provider

Who is a candidate for insulin pump therapy?

Insulin Pump Guidelines: AACE

Type 1 Diabetes

- Not meeting glycemic control goals on MDI
- Especially those with:
  - High glycemic variability
  - Frequent severe hypoglycemia and/or unawareness
  - Significant “dawn phenomenon”
  - Extreme insulin sensitivity
- Consider for flexibility and QoL
- Special populations
  - Preconception, pregnancy
  - Children, adolescents
  - Competitive athletes

Type 2 Diabetes

- Select patients on insulin with any/all of the below:
  - C-peptide positive, but with suboptimal control on MDI
    - Note: CMS only covers insulin pump therapy for those who are c-peptide deficient
  - Substantial “dawn phenomenon”
  - Erratic lifestyle
  - Severe insulin resistance (candidate for U500 insulin by CSII)
  - Selected patients with other types of DM (e.g. post-pancreatectomy)

Grunberger G., et al. AACE/ACE 2018 Position Statement on Integration of Insulin Pumps and CGM in Patients with DM. Endocrin Pract. March 2018, Vol 24, No.3 pp 302-308

Insulin Pump Guidelines: Endocrine Society

Type 1 Diabetes

- With HbA1c above goal on MDI
- With continued hypoglycemia and glycemic variability, even if HbA1c is at goal
- Requiring lifestyle flexibility or improvement in QoL

Type 2 Diabetes

- With poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications

"as long as the patient and caregivers are willing and able to use the device"

Peters et al. J Clin Endocrinol Metab
.2016 Nov;101(11):3922-3937. doi: 10.1210/jc.2016-2534. Epub 2016 Sep 2.

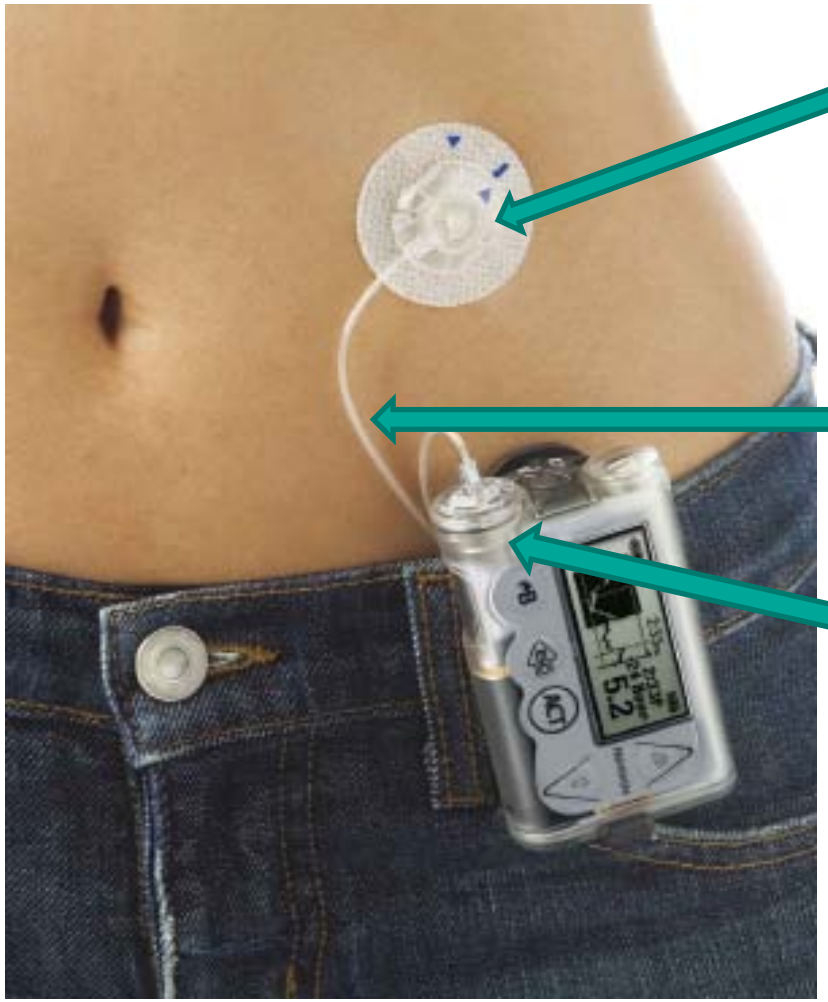
Insulin Pump Guidelines: Other Considerations

Characteristics suggesting patient may not be a good candidate for insulin pump therapy:

- Unable/unwilling to perform MDI, recommended glucose testing or carbohydrate counting
- Lack of motivation to achieve tighter glucose control, history of non-adherence
- Concerns about pump therapy interfering with lifestyle
- History of serious psychological or psychiatric condition
- Unable to recognize the limitations of insulin pump therapy
  - Unrealistic expectations (e.g. the insulin pump will eliminate patient responsibility for diabetes management)

Peters AL et al. J Clin Endocrinol Metab. 2016 Nov;101(11)
Grunberger G, et al. Endocrine Practice: May 2014, Vol. 20, No. 5, pp. 463-489.

Anatomy of the Insulin Pump



Infusion site/cannula:

- Small flexible plastic cannula inserted into SC tissue by a small retractable needle

Tubing::component of each insulin pump (except Omnipod)

- Connects insulin reservoir to infusion site

Reservoir::insulin storage

- Between 200-300 units

Current Commercially-Available Insulin Pumps

Medtronic

t:slim X2™
Insulin Pump

omnipod
DASH

Insulin Pump Settings

- **Basal Rate**
  - Continuous infusion of rapid-acting insulin to provide basal/long-acting coverage
  - Entered as units of insulin/hour and can be programmed to have different rates for different times of day
  - Temporary increases or decreases in basal rates can also be programmed
- **Insulin-to-Carb Ratio**
  - Used to calculate insulin bolus dose to cover carbohydrate/meal intake
- **Sensitivity Factor**
  - Used to calculate corrective insulin dosing for hyperglycemia
- **Target Glucose**
  - Entered as a single target glucose value or target glucose range (i.e. 90-150 mg/dL)
    - Corrects hyperglycemia using sensitivity factor at upper limit
    - Subtracts insulin from bolus dose if pre-meal blood sugar is under lower limit
- **Active Insulin Time**
  - Estimated duration of insulin action (usually 3-4 hours)

Advantages of Insulin Pump Therapy

- Ability to more closely approximate physiologic insulin secretion
- Ability to administer very small doses of insulin accurately
- Flexibility in insulin dosing to accommodate lifestyle needs (i.e. reduced basal rates for physical activity)
- Improved quality of life for many patients
- Improvement in glycemic control[1]
- Reduction in rates of severe hypoglycemia and DKA[2]

[1] and [2] – see references at end of slide deck.

Possible Disadvantages of Insulin Pump Therapy

- High cost, need for insurance coverage
- Labor-intensive
  - Site changes every 2-3 days
  - Close monitoring for any device/site malfunction
  - Maintaining adequate supplies
  - May not improve quality of life for some patients
- Appearance/Device wear
- Adhesive allergy

Integrating CGM and Insulin Pump Technology

- Insulin pump therapy can help improve glycemic control and reduce hypoglycemia, but it requires close monitoring and attention from the patient

- The use of insulin pump and CGM technology together has progressed towards automated insulin delivery, where infusion of insulin is automated and driven by CGM glucose values

Integrating CGM and Insulin Pump Technology

- **Sensor-augmented pump (SAP) therapy**
  - Use of insulin pump and CGM, but without cross-talk between them
- **Threshold or low glucose suspend**
  - Suspends insulin infusion at a predetermined glucose value
- **Predictive low glucose suspend (PLGS)**
  - Suspends insulin infusion prior to reaching threshold low glucose value
- **Automated insulin delivery (AID) or Hybrid Closed-Loop (HCL)**
  - Algorithm-based modulation of insulin infusion according to CGM glucose values and trends, including PLGS functions.

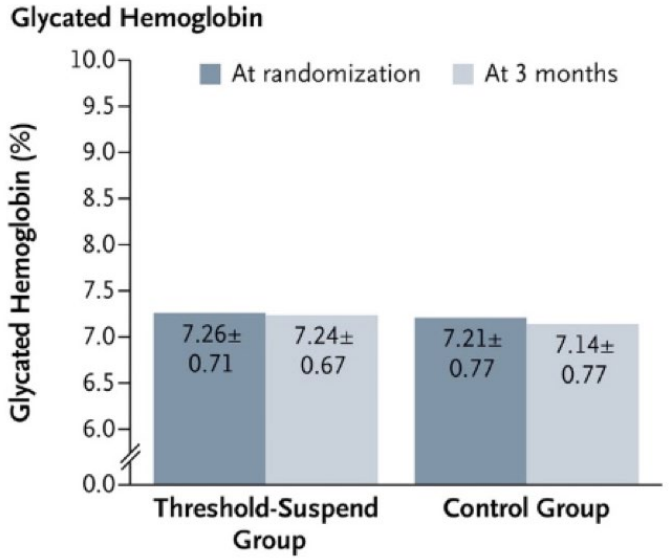
Integrating CGM and Insulin Pump Technology

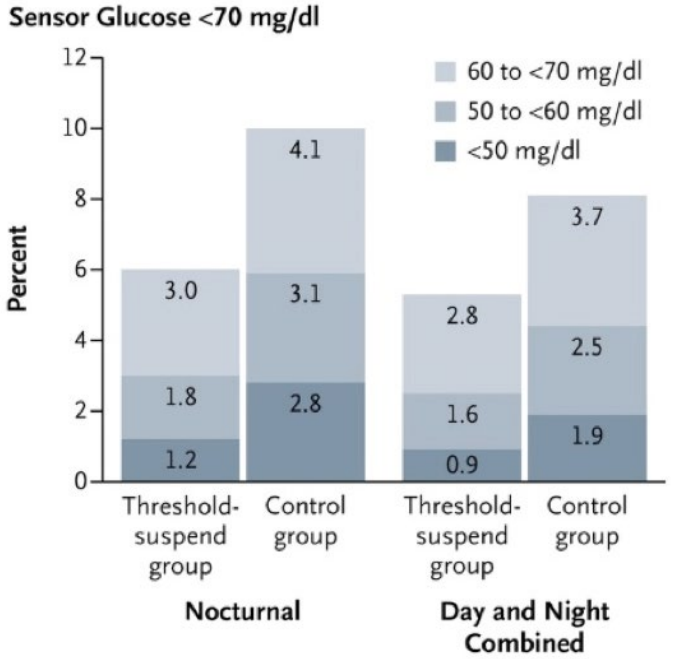
	Threshold suspend	Predictive-low glucose suspend	Automated Insulin Delivery
Medtronic			
530G (SmartGuard)	X		
630G (SmartGuard)	X		
670G (SmartGuard)		X	X
Tandem			
t:slim X2 (Basal IQ)		X	
t:slim X2 (Control IQ)		X	X
Insulet			
Omnipod5/Horizon*		X	X

*In phase 3 trial

Threshold Suspend

- **Multicenter RCT comparing SAP with or without TS therapy**
- T1D, age 16-70 years, A1C 5.8%-10%, used SAP for >6 months
- **Primary outcomes**:
  - Primary safety endpoint was change in A1C
  - Primary efficacy end point: AUC for nocturnal hypoglycemic events
  - Secondary end points: % sensor glucose values <70 mg/dL
- **Results**: Use of TS resulted in a significant decrease in nocturnal and overall hypoglycemia with no significant rise in A1C



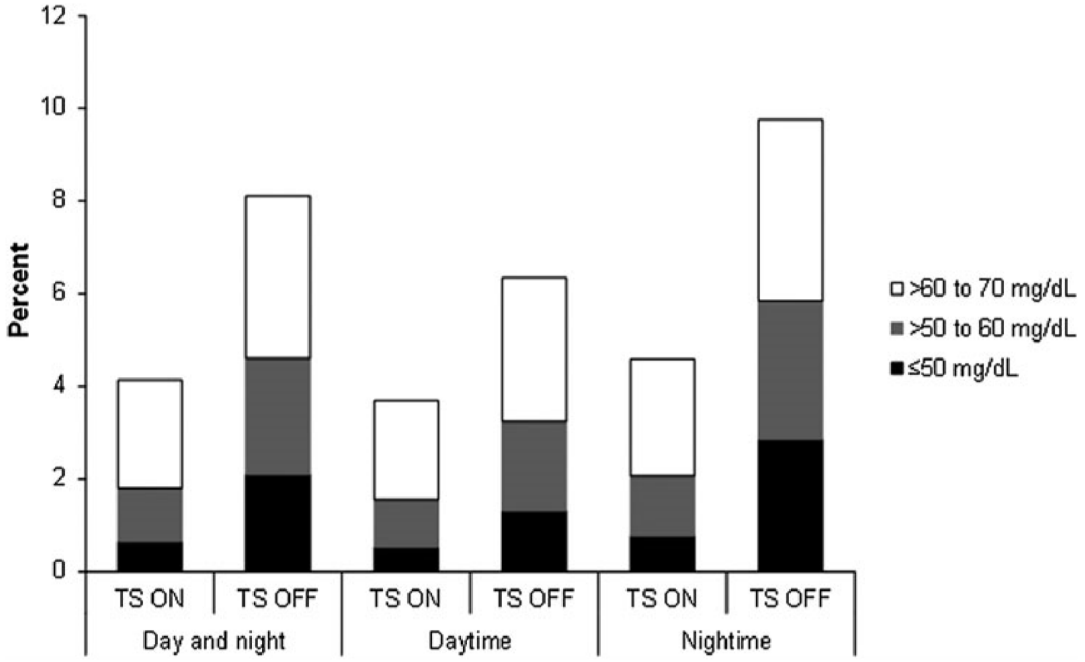


Bergenstal RM et al. *N Engl J Med.* 2013 Jul 18;369(3)

A1C, hemoglobin A1C; AUC, area under the curve; RCT, randomized controlled trial; SAP, sensor-augmented pump; T1D, type 1 diabetes; TS, threshold suspend.

Threshold Suspend in the Real World

- **Retrospective analysis of data from patients using MiniMed 530G to assess effectiveness of TS feature in a real-world setting**
- Data from 20,973 patients analyzed for TS featured enabled (TS ON) vs not enabled (TS OFF) and daytime vs nighttime collection and %SG values indicating hypoglycemia and hyperglycemia were calculated
- **Primary outcomes**: Hypoglycemia and hyperglycemia events as indicated by SG values during TS ON and TS OFF days
- **Results**: TS use reduced hypoglycemia when used consistently



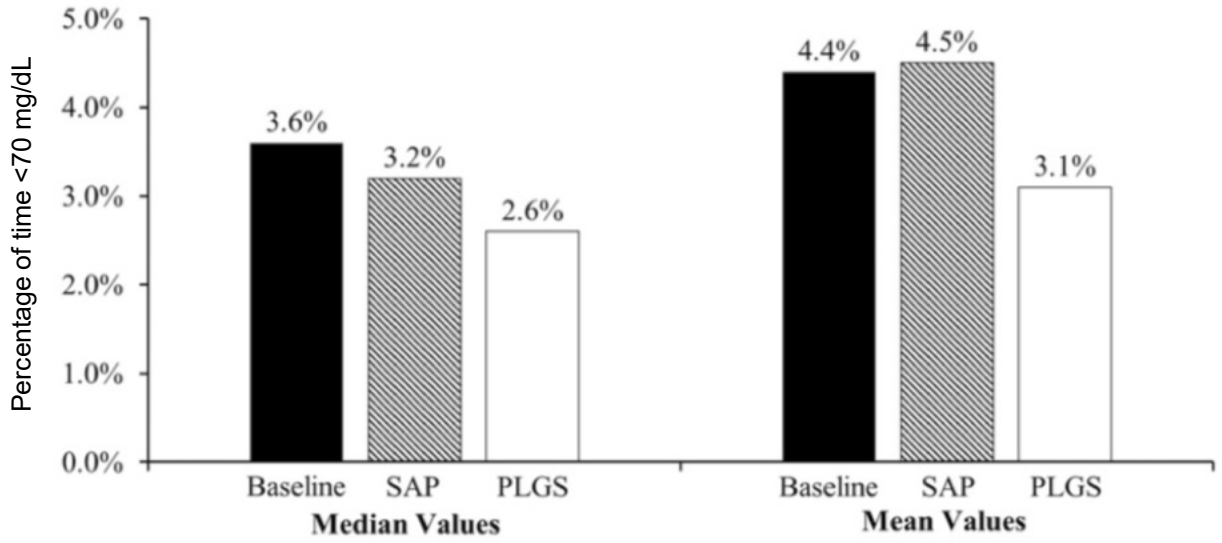
SG distributions in the hypoglycemic range for TS ON vs TS OFF days

Agrawal P et al. *Diabetes Technol Ther*. 2015 May;17(5)

SG, sensor glucose TS, threshold suspend.

PROLOG Trial: Tandem t:slim with PLGS

- **Multicenter, crossover RCT comparing SAP with and without PLGS system**
- Enrollment criteria: age ≥6 years, T1D with insulin use ≥1 year, no medical contraindications to participation
- **Primary outcome**: % time SG<70 mg/dL in each 3-week period (SAP vs PLGS)
  - Secondary outcomes: % glucose <60 mg/dL, <50 mg/dL, AOC (70 mg/dL), low blood glucose index, and frequency of CGM hypoglycemic events
- **Results**: PLGS significantly reduced time with SG <70 mg/dL (overall 31% reduction) without increasing % time in hyperglycemia.

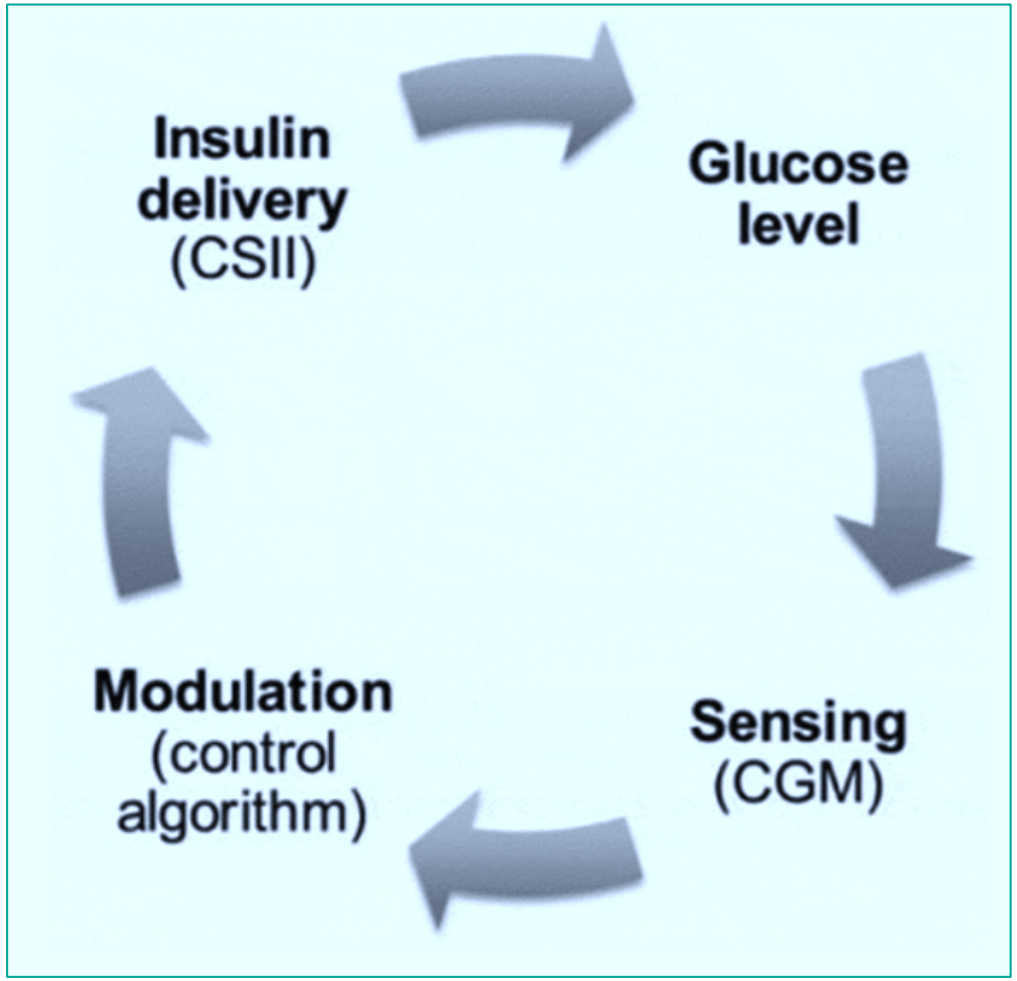


Percentage of time <70 mg/dL at baseline and during SAP and PLGS arms. Baseline values are from patient characteristics at enrollment. The SAP and PLGS values are from the 102 participants who completed the postrandomization phase of the study.

AOC, area over the curve; CGM, continuous glucose monitoring; PLGS, predictive low-glucose suspend; PROLOG, PLGS for Reduction Of LOw Glucose; RCT, randomized controlled trial; T1D, type 1 diabetes; SAP, sensor-augmented pump; SG, sensor glucose.

Forlenza et al. *Diabetes Care* 2018 Oct; 41(10): 2155-2161

Automated Insulin Delivery/Hybrid Closed-Loop (HCL) Technology



Majeed W, Thabit H. Closed-loop insulin delivery: current status of diabetes technologies and future prospects. Expert Review of Medical Devices. 2018;15(8):579-590.

Hybrid Closed-Loop System: Medtronic 670G

- Approved US FDA September 2017 for patients with T1D ≥14 years old, then expanded to ages 7-13 years in June 2018[1]
- Auto mode
  - Preset glucose target 120 mg/dL
  - Temp target of 150 mg/dL up to 12 hours
  - Adjustment of basal rate every 5 minutes
  - Requires announcement of meals/carbohydrates for bolus calculation
- Predictive low-glucose suspend
  - Stops insulin infusion up to 30 minutes before reaching your preset low limit
- Manual mode
  - Standard insulin pump settings

[1]Knebel et al. Clin Diabetes. 2019 Jan;37(1):94-95.

Medtronic 670G: Safety and Efficacy

- **Single-arm, multicenter trial to evaluate safety and effectiveness of in-home HCL systems**
- Patients enrolled were adolescents and adults with T1D with insulin pump therapy >6 months with or without CGM
- **Primary outcome**: A1C, improvement in time in target range, hypoglycemia
- **Results**: A1C, 7.7% (*P*<0.001) in adolescents and 7.3% (*P*<0.001) in adults; time in target range, 60.4 (*P*<0.001) in adolescents and 68.8 to 73.8 (*P*<0.001) in adults

CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	*Adolescents (N = 30)*	*Adults (N = 94)*
Female, *N* (%)	16 (53.3)	53 (56.4)
Male, *N* (%)	14 (46.7)	41 (43.6)
Age, mean ± SD, years	16.5 ± 2.29	44.6 ± 12.79
Weight, mean ± SD, kg	67.4 ± 12.98	79.9 ± 18.20
BMI, mean ± SD, kg/m^2	23.7 ± 3.80	27.1 ± 5.42
Duration of diabetes, mean ± SD, years	7.7 ± 4.15	26.4 ± 12.43
TDD, mean ± SD, U/kg/day	0.8 ± 0.24	0.6 ± 0.20
HbA1C, mean ± SD, % (IQR)	7.7 ± 0.84 (7.1–8.4)	7.3 ± 0.91 (6.7–7.8)

A1C, hemoglobin A1C; BMI, body mass index; CGM, continuous glucose monitoring; hb, hemoglobin; HCL, hybrid closed-loop; IQR, interquartile range; SD, standard deviation; T1D, type 1 diabetes; TDD, total daily dose.

Garg SK et al. *Pubmed*. 2017 Mar; 28134564

Medtronic 670G: Glucose Profiles in Adolescents and Adults

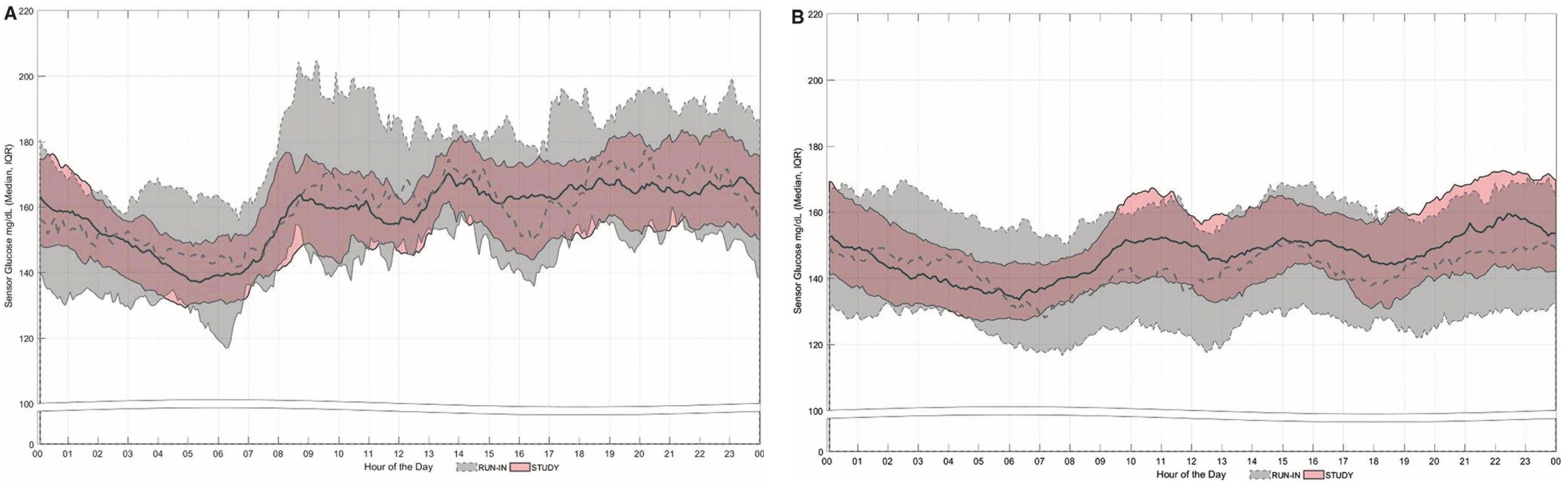


FIG. Sensor glucose profiles during the run-in and study phase. Median and interquartile range of sensor glucose values throughout the day and night, beginning at midnight (00, on x-axis), in (A) adolescents and (B) adults. The gray band and dotted line represent data from the run-in phase; the pink band and solid line represent data from the study phase.

Garg SK et al. *Pubmed.* 2017 Mar;28134564

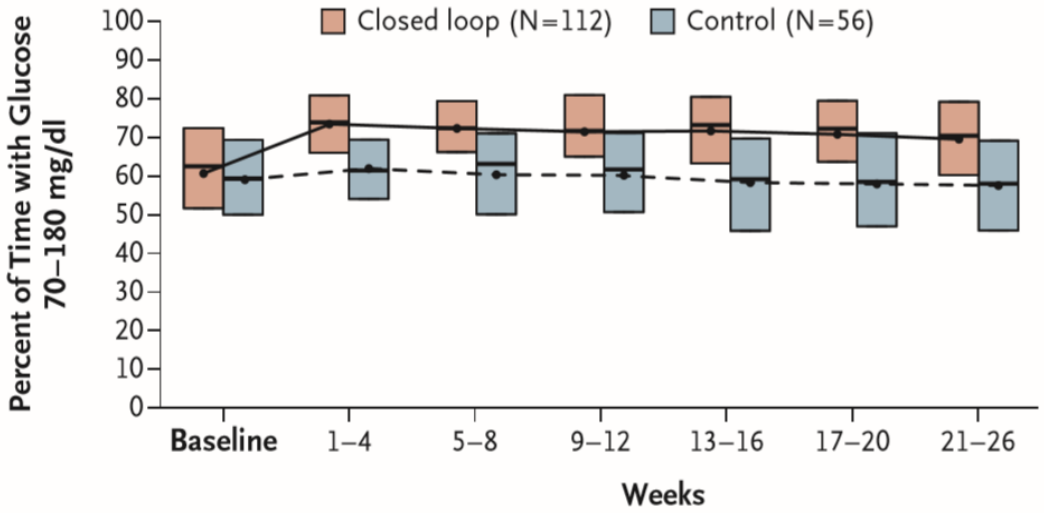
Hybrid Closed -Loop System: Tandem t:slim X2 with Control-IQ

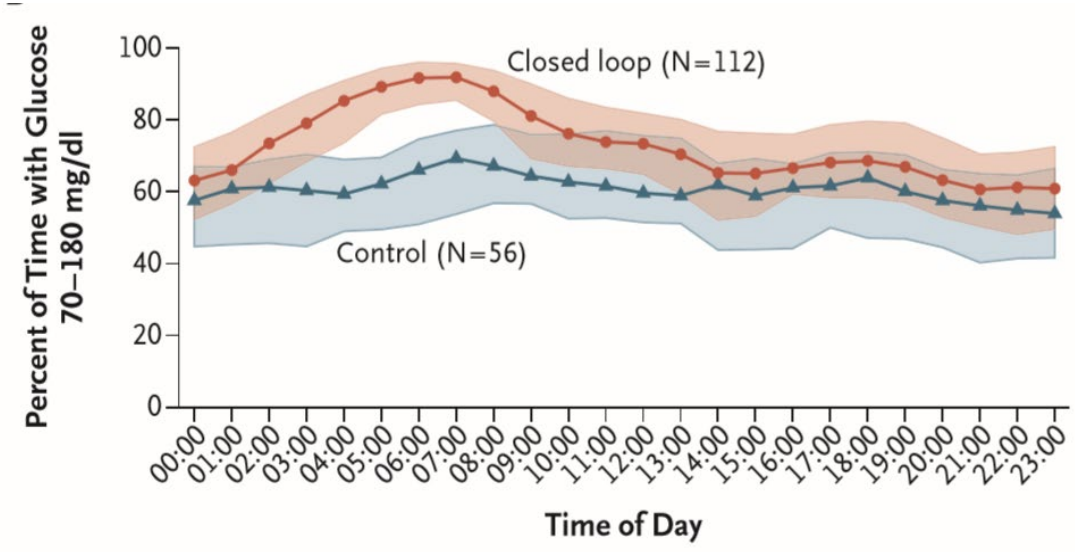
	Delivers	Delivers an automatic correction bolus if sensor glucose is predicted to be above 180 mg/dL
180		
	Increases	Increases basal insulin delivery if sensor glucose is predicted to be above 160 mg/dL
160		
	Maintains	Maintains active Personal Profile settings
112.5		
	Decreases	Decreases basal insulin delivery if sensor glucose is predicted to be below 112.5 mg/dL
70 mg/dL		
	Stops	Stops basal insulin delivery if sensor glucose is predicted to be below 70 mg/dL

https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq.
Accessed on September 11, 2020.

Tandem HCL algorithm

- **Multicenter RCT comparing SAP to closed-loop therapy with Control-IQ algorithm**
- 168 patients with T1D > 1 year on insulin therapy, age 14-71 years, A1C 5.4%-10.6%
- **Primary outcomes**: Percentage of time in target glucose range (70-180 mg/dL)
- **Results**: Use of the Control-IQ closed-loop algorithm resulted in a greater percentage of time spent in target glucose range compared to SAP (71±12% vs. 59±14%, P<0.001).



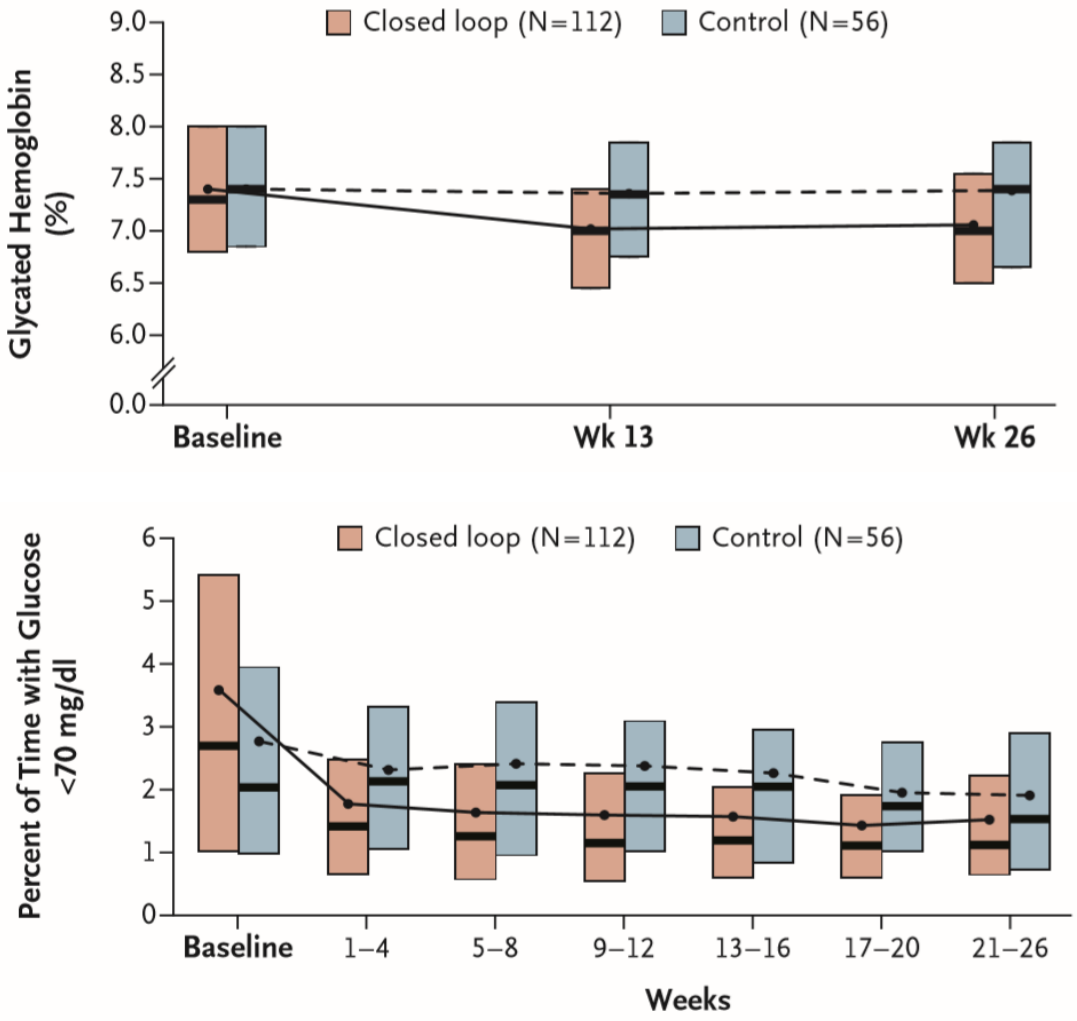


HCL, hybrid closed-loop; MDI, multiple daily injections; A1C, hemoglobin A1C; AUC, area under the curve; RCT, randomized controlled trial; SAP, sensor-augmented pump; T1D, type 1 diabetes;

Brown SA et al. *N Engl J Med.* 2019 Oct 31;381(18)

Tandem Control-IQ HCL algorithm

- **Secondary Outcomes:**
  - Prespecified secondary outcomes included change in A1c and time with glucose <70 mg/dL, with results favoring the closed-loop group as below
  - The mean change in A1c was −0.33 percentage points (95% CI, −0.53 to −0.13; P = 0.001)
  - The mean difference in the percentage of time glucose level was less <70 mg/dL was −0.88 percentage points (95% CI, −1.19 to −0.57; P<0.001)



Brown SA et al. *N Engl J Med.* 2019 Oct 31;381(18)

HCL Systems in Development: Omnipod5/Horizon

GLYCEMIC OUTCOMES OVER THE 36-H HYBRID CLOSED-LOOP PHASE

Parameter	*Adults*[a] *(n = 24)*	*Adults (n = 10)*	*Adolescents (n = 12)*	*Pediatrics (n = 12)*
Mean sensor glucose, mg/dL	161.5 (20.1)	155.0 (14.8)	153.4 (21.6)	156.9 (20.4)
Standard deviation, mg/dL	54.0	46.2	48.6	53.3
Coefficient of variation, %	33.4	29.8	31.8	34.0
Percentage time in glucose range				
<54 mg/dL	0.1 (0.3)	0.1 (0.3)	0.2 (0.3)	0.2 (0.7)
<60 mg/dL	0.2 (0.6)	0.2 (0.6)	0.7 (0.9)	0.6 (1.2)
<70 mg/dL	0.7 (1.7)	0.7 (1.2)	2.0 (2.4)	2.0 (2.6)
70 to 140 mg/dL	41.5 (18.1)	41.9 (16.3)	40.2 (15.5)	39.4 (16.1)
70 to 180 mg/dL	69.5 (14.4)	73.0 (15.0)	72.6 (15.5)	70.1 (12.3)
>180 mg/dL	29.7 (14.4)	26.3 (14.4)	25.4 (16.1)	27.9 (13.2)
≥250 mg/dL	8.0 (7.5)	3.6 (3.7)	4.9 (6.3)	6.7 (5.6)
≥300 mg/dL	2.0 (2.9)	0.5 (1.1)	0.1 (0.5)	1.0 (2.2)

- **Single-arm, multicenter observational trial evaluating safety and feasibility of OmniPod MPC algorithm in pediatric, adolescent, and adult patients with T1D**
- Population: 6-65 years, T1D ≥1 year, A1C 6%-10% in past 6 months, insulin pump use ≥6 months, and total daily insulin dose >0.4U/ kg
- **Primary outcomes:** % time sensor glucose was <70 mg/dL and % time in ≥ 250 mg/dL during HCL phase
  - Secondary endpoints: Sensor mean glucose, % time ≤50, ≤60, 70-140, 70-180, ≥180, ≥300 mg/dL, SD, CV of CGM values
- Omnipod MPC algorithm was safe during day and night for all three populations; longer term studies will assess safety and performance under independent living situations in all ages

Buckingham et al. *Diabetes Technol Ther*. 2018. 20(4). Republished by Pubmed 29431513

Do-It-Yourself Hybrid Closed-Loop Systems

- Medtronic 670G is the only first generation artificial pancreas system available
  - Several other systems are under evaluation in clinical trials[1]
- Frustration with the slow pace of such trials has led to ”looping” with DIY HCL systems, thus creating momentum for patient-led healthcare innovation[1]
- An online community of “loopers” exists for support and can be found via the hashtag #WeAreNotWaiting[1]
- DIY systems are not FDA approved, and in May 2019 the FDA issued its first-ever warning statement about their use[2]
  - This warning was based on a non-fatal accidental insulin overdose in a patient with T1D who used a DIY system
  - A joint statement from 3 online DIY system developers highlighted the fact that the warning was based on outcomes from a single patient who was outside of the US, and that the patient has since recovered

1. Marshall et al. *Diabetes Ther.* 2019 Aug 22. [Epub ahead of print]
2. Caffrey. https://www.ajmc.com/newsroom/fda-issues-warning-on-do-it-yourself-artificial-pancreas. 2019.

Do-It-Yourself Hybrid Closed-Loop Systems

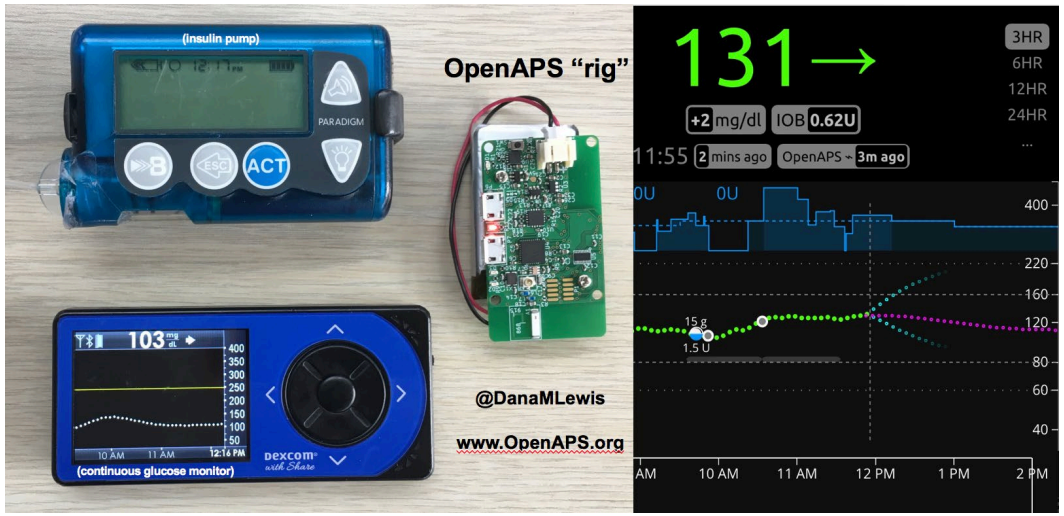
- DIY systems are comprised of a compatible insulin pump, a CGM sensor and a third-party device, a microcomputer or a smartphone, that contains a system-specific algorithm[1]
- The third-party device enables communication between the algorithm, insulin pump and the CGM sensor[1]
- DIY systems are also referred to as “open-source,” as the algorithm and user instructions can be obtained without cost via the Internet[1]
- Three main DIY systems are currently available[1]:
  - OpenAPS
  - AndroidAPS
  - Loop
- A 2019 international survey of 209 caregivers of children and adolescents, representing the largest study of DIY APS users, reported improved glycemic control in all groups[2]

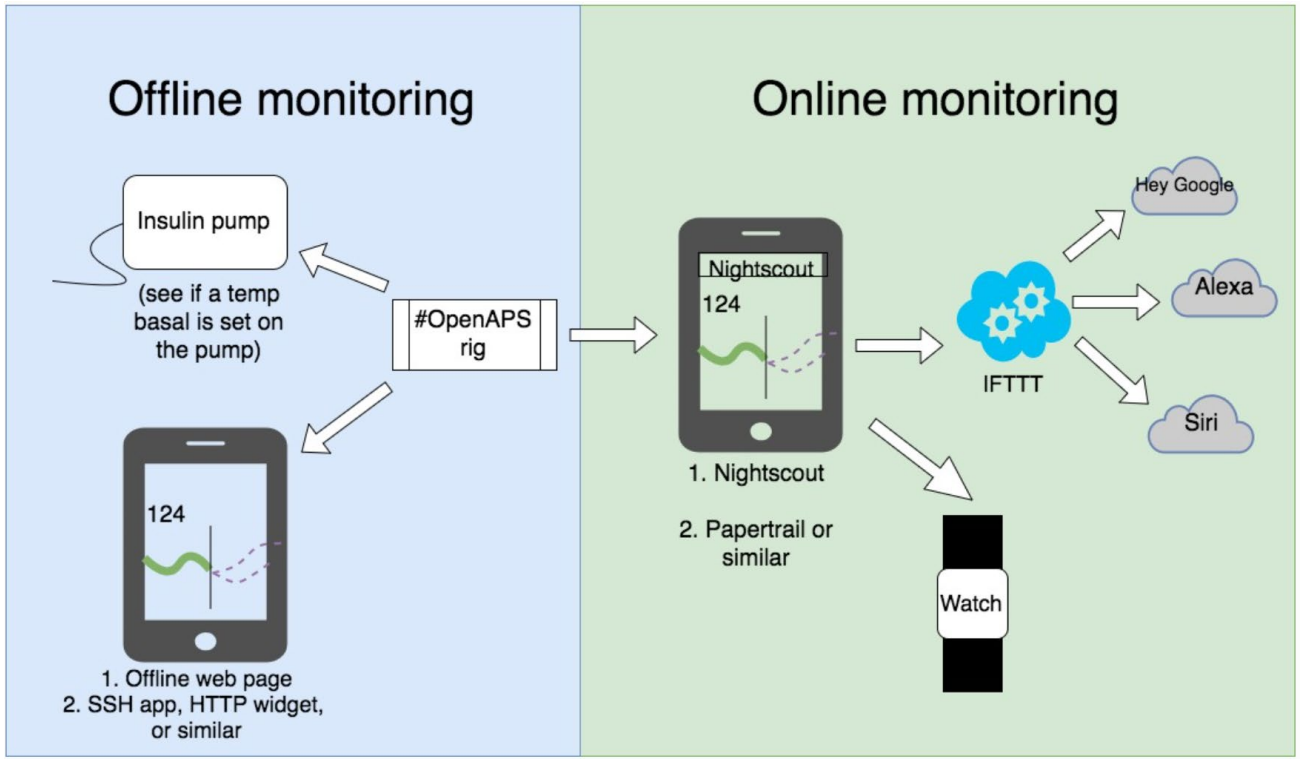
1. Melmer et al. *Diabetes Obes Metab*. 2019 Oct;21(10):2333-2337.
2. Braune et al. *JMIR Mhealth Uhealth.* 2019 Jul 30;7(7):e14087. 2019.

APS, artificial pancreas system;

Do-It-Yourself Hybrid Closed-Loop Systems

- Available DIY HCL Systems:
  - Open APS
  - Android APS
  - Loop



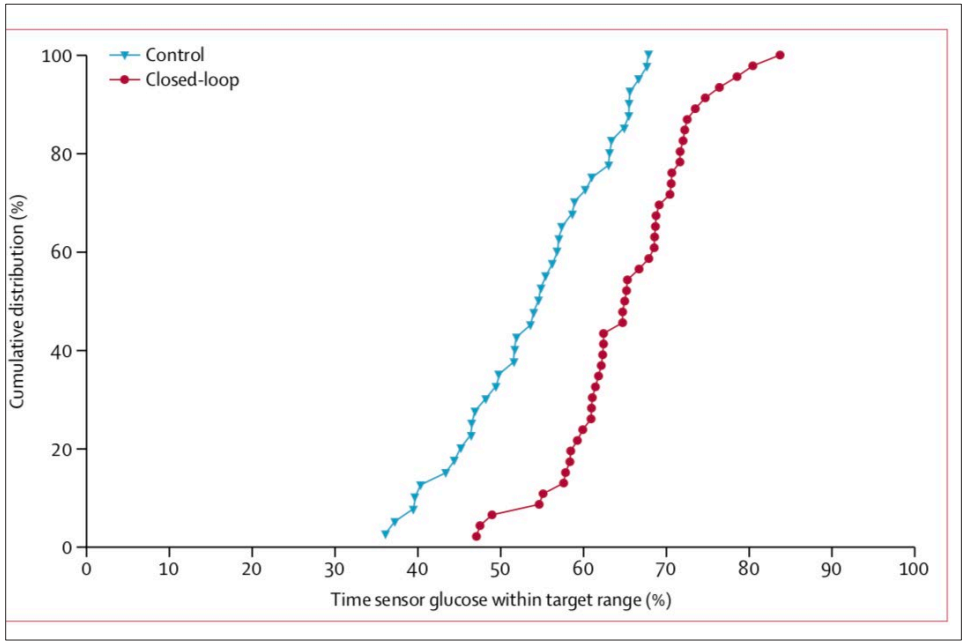


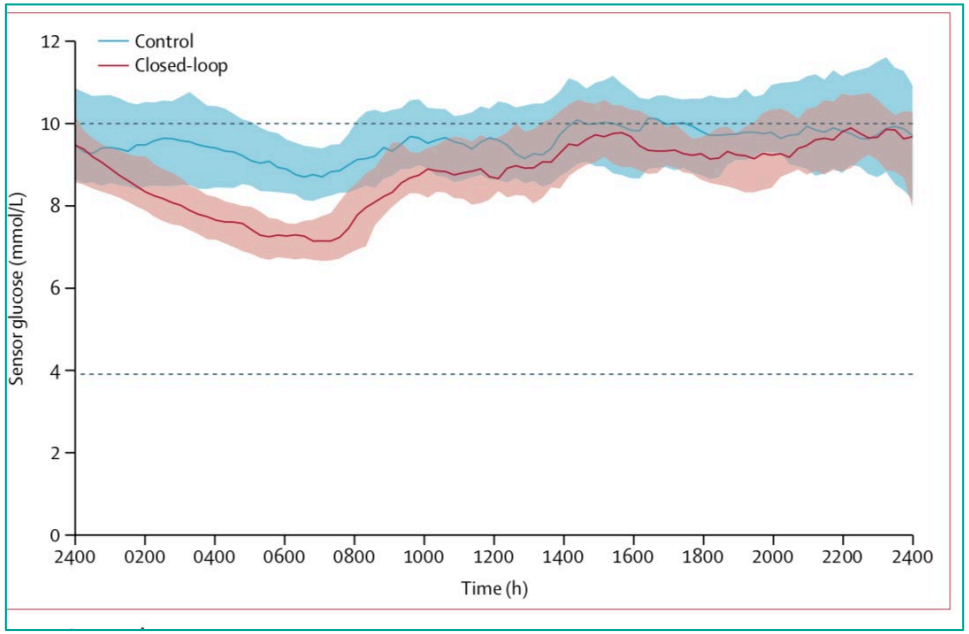
APS, artificial pancreas system; DIY, do-it-yourself; HCL, hybrid closed loop.

https://openaps.readthedocs.io/en/latest/docs/While%20You%20Wait%20For%20Gear/monitoring-OpenAPS.html
Accessed on September 11, 2020.

HCL Therapy in Sub-Optimally Controlled T1D

- **Open-label RCT to evaluate efficacy of HCL in improving glucose control and reducing hypoglycemia**
- **Patient enrollment criteria:** T1D, age ≥6 years, on insulin pump therapy, and A1C 7.5%-10%
- **Primary outcome**: Time in target glucose range (70-180 mg/dL) at 12 weeks
  - Secondary endpoints: A1C, SD and CV of glucose, % time in hypo- and hyperglycemia, AUC <3.5mmol/L, insulin requirements, bodyweight, and PedsQL score
- **Results**: TIR was significantly higher in the HCL group vs control group (65% [SD 8%] vs 54% [9%]; *P*<0.0001); A1C in HCL group was reduced from 8.3% (0.6%) to 7.4% (0.6%) after 12-weeks





Tauschmann et al. *Lancet*. 2018 Oct;392.

HCL Therapy in Sub-optimally Controlled T1D

	Baseline		12 weeks		Difference (95% CI)*	p value
	Closed-loop (n=46)	Control (n=40)	Closed-loop (n=46)	Control (n=40)		
Day (0800 h to 2359 h)						
Percentage of time with sensor glucose level in range						
3·9–10·0 mmol/L	52% (10)	51% (9)	59% (9)	53% (9)	5·9 (3·1 to 8·7)	<0·0001
Less than 3·5 mmol/L	1·6% (0·9 to 2·7)	1·9% (0·8 to 3·3)	1·6% (0·9 to 2·1)	2·2% (0·9 to 2·8)	NA†	NA†
Glucose, mmol/L	10·0 (1·2)	9·9 (1·1)	9·3 (0·8)	9·8 (1·0)	−0·51 (−0·77 to −0·24)	0·0003
SD of sensor glucose, mmol/L	4·0 (0·6)	3·9 (0·5)	3·7 (0·5)	3·9 (0·5)	−0·26 (−0·40 to −0·12)	0·0003
Night (2400 h to 0759 h)						
Percentage of time with sensor glucose level in range						
3·9–10·0 mmol/L	54% (13)	53% (14)	77% (8)	56% (13)	21·5 (17·9 to 25·0)	<0·0001
Less than 3·5 mmol/L	1·8% (0·6 to 4·1)	1·8% (0·5 to 3·9)	1·0% (0·7 to 1·8)	2·2% (0·7 to 3·3)	NA†	NA†
Glucose, mmol/L	9·5 (1·4)	9·6 (1·5)	8·0 (0·7)	9·4 (1·2)	−1·46 (−1·76 to −1·16)	<0·0001
SD of sensor glucose, mmol/L	3·6 (0·5)	3·5 (0·5)	2·9 (0·5)	3·6 (0·5)	−0·67 (−0·84 to −0·49)	<0·0001

Data are mean (SD) or median (IQR). *Difference is closed-loop minus control. †p value not computed as 24-h result was not significantly different; thus, separate day and night comparisons were not done.

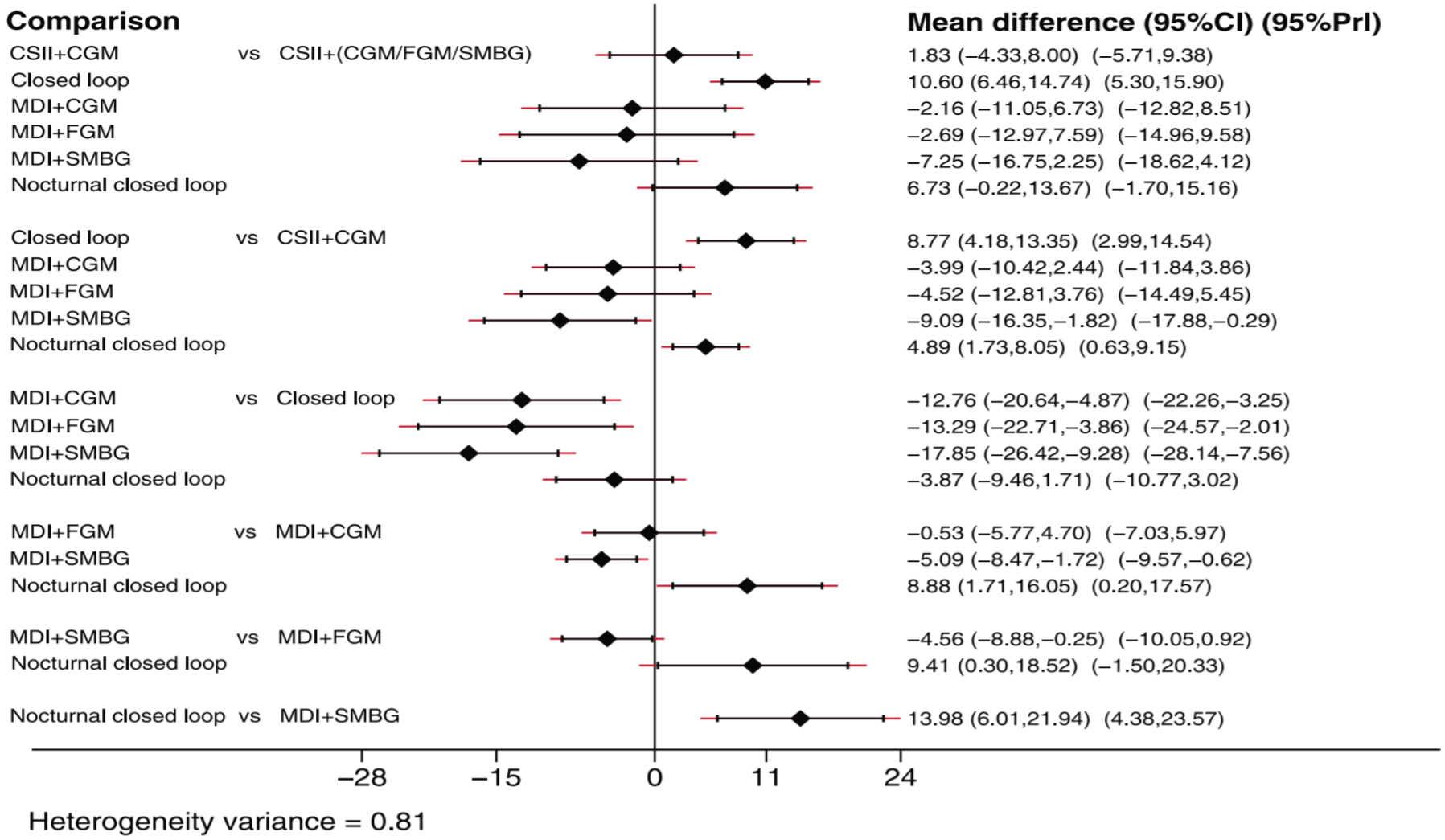
***Table 3*: Day-and-night glucose control during closed-loop and control periods**

Advantages of closed loop therapy were more pronounced during the night

CI, confidence interval; IQR, interquartile range; NA, not applicable; SD, standard deviation; T1D, type 1 diabetes.

Tauschmann et al. *Lancet*. 2018 Oct;392.

More time in range with HCL compared to other technologies



Diabetes Care 2020;43:1967–1975 | https://doi.org/10.2337/dc19-1785

Specific Metrics to Consider in Hybrid Closed-Loop Therapy

- Duration of report: 14-day windows are standard
- % sensor usage
- % time in range, 70-180 mg/dL (goal ≥70%)
- % <70 mg/dL (goal ≤4%)
- % <54 mg/dL (goal ≤1%)
- Assess mean glucose (mg/dL)
- Assess glucose variability with CV (goal <36%)
- Assess time in HCL (goal >80%)

- Reasons listed for HCL exits
- Average basal delivery in HCL vs preset basal rates (units)
- Frequency and patterns of basal suspensions
- Frequency of correction boluses
- Use of setpoint changes for activity or sleep
  - Medtronic 670G: Temp target of 150 mg/dL
  - Tandem X2 with Control:IQ: Exercise or Sleep mode with modified target range

Ekhlaspour et al. *Journal Diab Sci Tech*. 2019. 13(4) 645-663.

CV, coefficient of variation; HCL, hybrid closed loop.

Summary

- Advances in CGM technology and closed loop systems coupled with open source algorithms have transformed diabetes management
- New metrics for assessing glycemic control are emerging to accommodate advances in technology and will help guide glycemic control targets
- DIY hybrid closed loop systems have enabled a more patient-driven approach to disease management, but are not FDA approved
- While insurance coverage for diabetes technology is expanding, the high cost of this technology may still not be feasible for many patients

CGM, continuous glucose monitoring; DIY, do-it-yourself; FDA, Food and Drug Administration.

Contributors

- AACE would like to thank the following clinicians for their contributions.

  - Dr. Georgia Davis, MD
  - Dr. Francisco Pasquel, MD, MPH
  - Dr. Archana Sadhu, MD, FACE

References [1]

- Eitler, K. et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia 51, 941–951 (2008). PubMed Article CAS Google Scholar
- Fatourechi, M. M. et al. Clinical review: hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J. Clin. Endocrinol. Metab. 94, 729–740 (2009). PubMed Article CAS Google Scholar
- Monami, M., Lamanna, C., Marchionni, N. & Mannucci, E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetol. 47 (Suppl. 1), 77–81 (2010).

References [2]

- Beato-Víbora, P. et al. Sustained benefit of continuous subcutaneous insulin infusion on glycaemic control and hypoglycaemia in adults with Type 1 diabetes. Diabet. Med. 32, 1453–1459 (2015).Return to ref 20 in article. PubMed Article CAS Google Scholar
- Joubert, M. et al. Cross-sectional survey and retrospective analysis of a large cohort of adults with type 1 diabetes with long-term continuous subcutaneous insulin infusion treatment. J. Diabetes Sci. Technol. 8, 1005–1010 (2014). PubMed PubMed Central Article CAS Google Scholar
- Orr, C. J., Hopman, W., Yen, J. L. & Houlden, R. L. Long-term efficacy of insulin pump therapy on glycemic control in adults with type 1 diabetes mellitus. Diabetes Technol. Ther. 17, 49–54 (2015). PubMed Article CAS Google Scholar
- Johnson, S. R., Cooper, M. N., Jones, T. W. & Davis, E. A. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia 56, 2392–2400 (2013). PubMed Article CAS Google Scholar
- Steineck, I. et al. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. BMJ 350, h3234 (2015). PubMed Central Article Google Scholar
- Pickup, J. C. & Sutton, A. J. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet. Med. 25, 765–774 (2008).

Common Acronyms (Diabetes)

Acronym	Meaning	Acronym	Meaning
A1C	HEMOGLOBIN A1C	CGM	Continuous Glucose Monitoring
AGP	Ambulatory glucose profile	CV	COEFFICIENT OF VARIATION
AUC	Area under curve (in reference to a graphic)	DIY	Do-it-yourself
Avg	Average	eA1C	Estimated hemoglobin A1C
BMI	Body Mass Index	FDA	Food and Drug Administration (United States)

Common Acronyms (Diabetes)

Acronym	Meaning	Acronym	Meaning
GMI	Glucose management indicator	OAD	Oral antidiabetic drugs
HCL	Hybrid Closed-loop	PLGS	Predictive low-glucose suspend
Hb	Hemoglobin	Rt	Real time
I	Integrated	SD	Standard deviation
IQR	Interquartile range	T1D	Type 1 Diabetes
MAGE	Mean amplitude of glucose excursions	T2D	Type 2 Diabetes
MODD	Mean of daily differences	TDD	Total daily dose