INSELSPITAL
Universitätsklinik
für Diabetologie, Endokrinologie,
Ernährungsmedizin und Metabolismus

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Insights from the ADA 2022:
Therapeutics / New Technologies

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Type 1 Diabetes

Current landscape of Automated Insulin Delivery Systems (AID)

Medtronic 670G & 780G
US&EU
Age ≥7yrs

Tandem Control IQ
US&EU
Age ≥6yrs

CamAPS FX
EU & Australia
Age ≥1yr, pregnancy, ultrarapid insulin

Diabeloop Roche
4 EU countries (not UK), ≥18yrs

Omnipod Horizon
FDA approved, undergoing CE-marking, ≥6yrs

Tidepool Loop
Submitted to FDA

Inreda
CE-marked
Not commercial

Beta Bionics iLet
Insulin-only, submitted to FDA (≥6yrs)

Keeping track of the systems - not an easy task…

- Differences in terms of
  - Control algorithm
  - Target options
  - Auto correction
  - Compatible devices (pump, sensor)
  - Data management system
  - Safety parameters
  - Approved indications for use
  - Modifiable settings
  - Algorithm learning

Increasing the aggressiveness

Example 1: MiniMed 780G

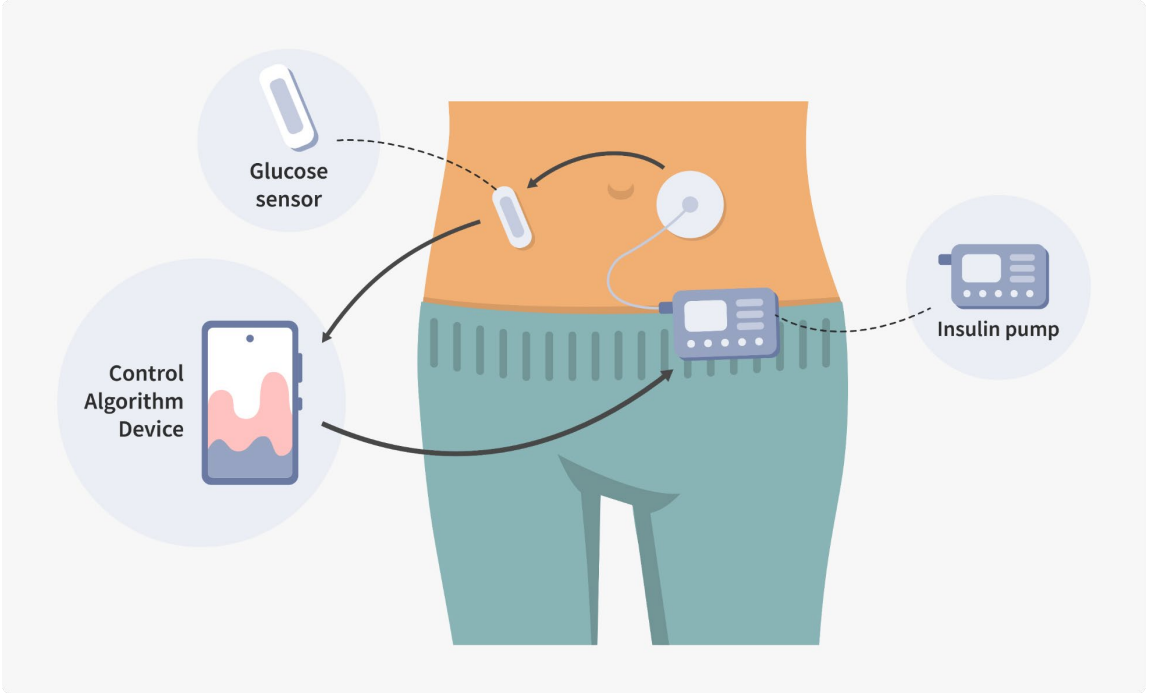
Active insulin duration
Target value (5.6, 6.1, 6.7mM)

Example 2: Control-IQ

Correction factor
Basal rate settings
Overnight target for daytime

AID system workshop in Bern, March 2023

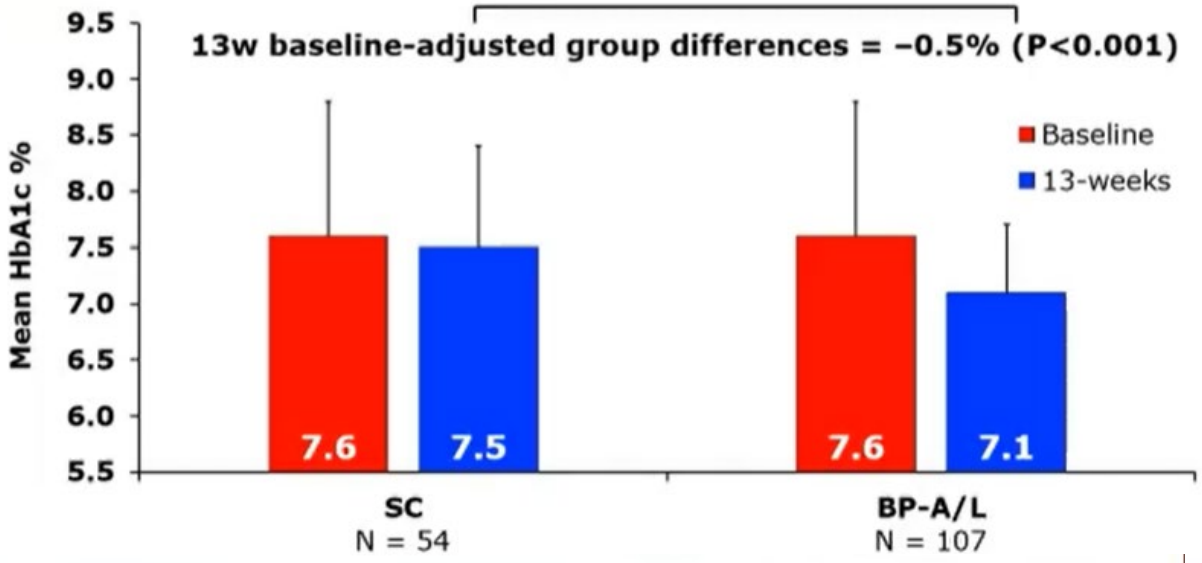
- Insights into control algorithms
- Differences between systems
- When and how to tune systems
- HCL and hypoglycemia correction
- HCL and challenging meals
- HCL and exercise
- HCL and pregnancy
- HCL and adjuvant treatments
- CL in Type 2 Diabetes



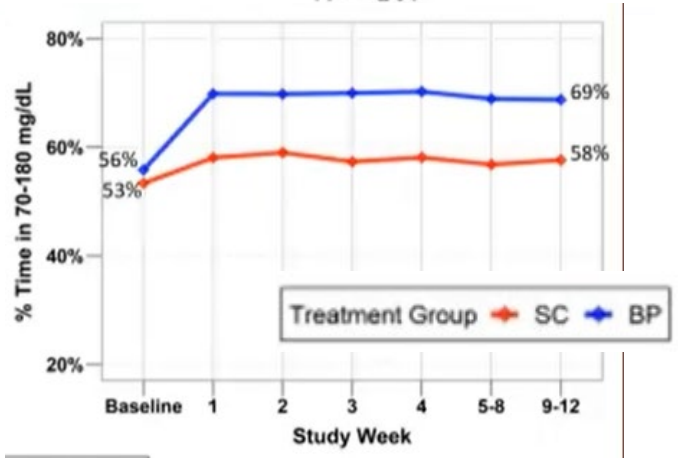
Beta Bionics iLet – The Insulin-Only Bionic Pancreas Pivotal Trial

Methods

- *n*=275 adults, *n*=165 children with T1D, broad inclusion criteria
- Randomised to either BP vs. any insulin delivery method (in adults additional arms with BP+rapid-acting vs. BP +ultra-rapid acting)
- 13 weeks
- Primary endpoint: HbA_{1c} after 13 weeks



Compared to standard-of-care, the bionic pancreas reduced HbA_{1c} by 0.5% overall and in sub-groups without increasing hypoglycemia.



ADA 82th Scientific Sessions 2022

Efficacy of hybrid closed-loop insulin delivery

Glycemic outcomes

↑ TIR ≈ 9-16 % (> 2 h/day)
TBR =/↓

Benefit more pronounced during night

↓ HbA_{1c} 0.3 – 0.5 %

Greatest in those with higher baseline HbA1c

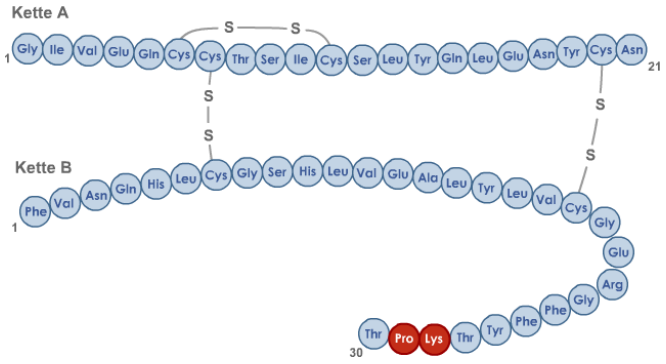
Quality of life (PROs)

↓ diabetes burden
↑ freedom
↑ sleep quality
↓ fear of hypoglycaemia

Utility (time in auto mode)

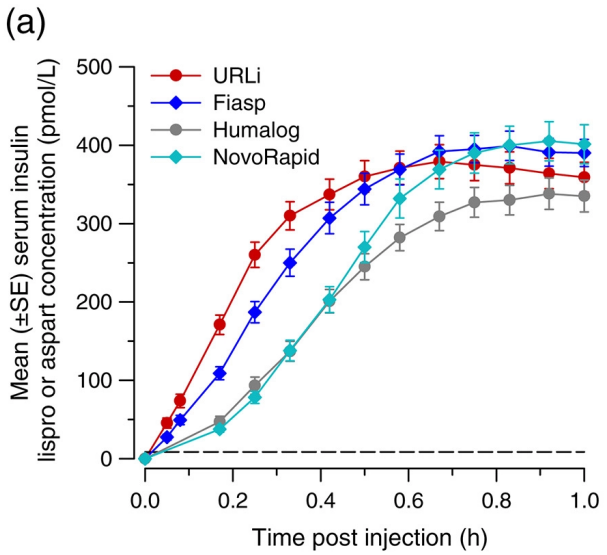
Medtronic 670G: 81%
Tandem Control-IQ: 94%
(real-life data)

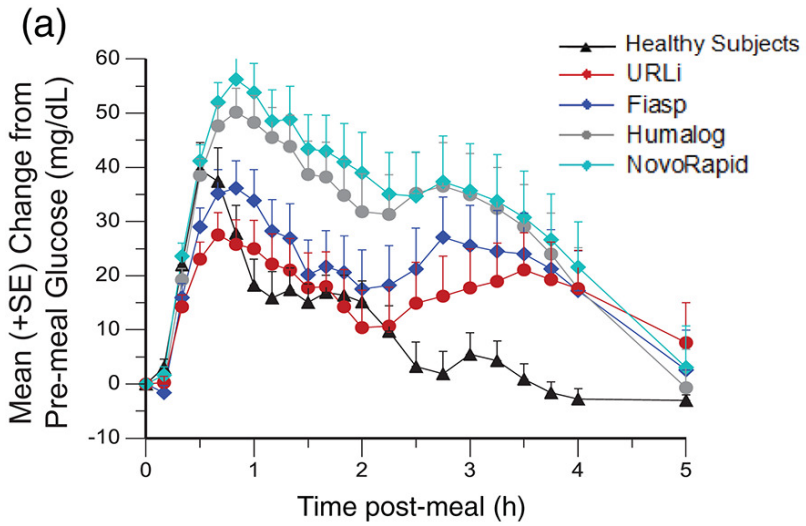
Faster insulin – Ultrarapid insulin lispro (Lyumjev®)



+ treprostonil → ↑ vasodilation
+ citrate → ↑vascular permability

→ ↑ **absorption**[1,2]





1. Pratt et al, ADA Abstract (2017)
2. Michael et al., ADA Abstract (2017)
3. Heise et al., DOM (2020)

Add-on SGLT-2-inhibitor in type 1 diabetes – benefit vs. risk

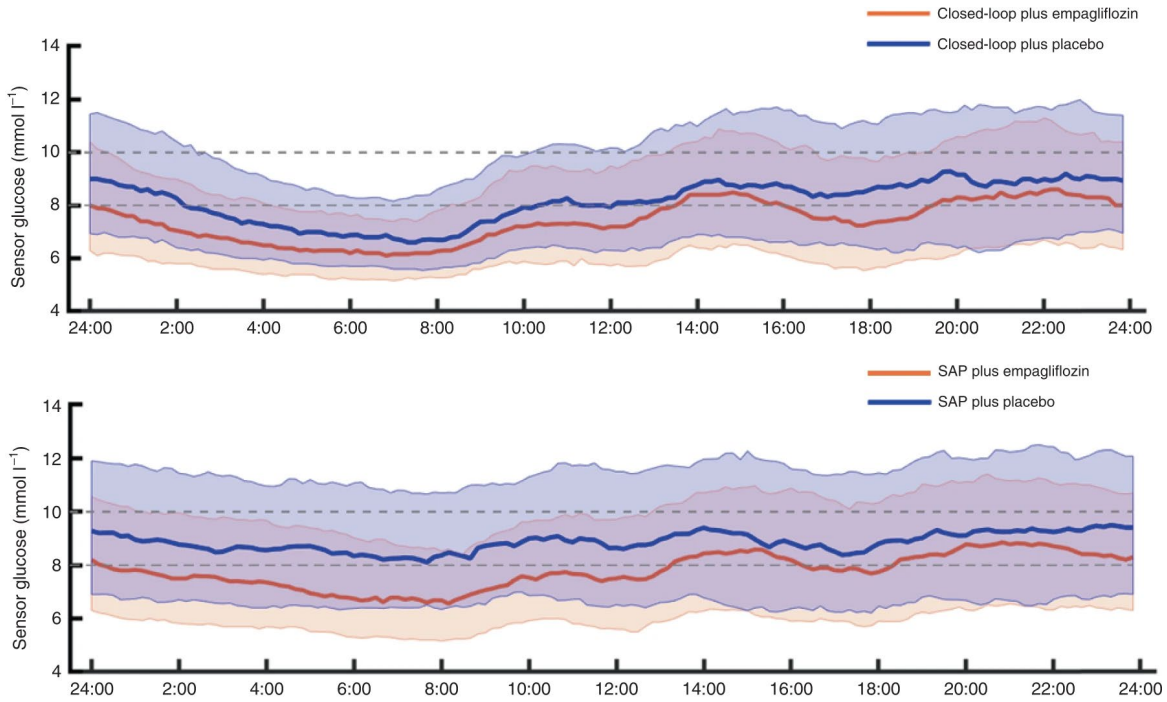
AID + empagliflozin (vs. placebo)

Benefits

- 25 mg/d[1]: ↑TIR +7.2% with HCL, +11.4% with SAP
- 5 mg/d[2]: ↑TIR +9.9% with HCL, +16.5% with PGLS

Risks

- 25 mg/d[1]
  - no DKA
  - ketosis: 5 in HCL+empa, 1 in all other arms
- 5 mg/d[2]
  - 1 with DKA in the HCL+empagliflozin arm
  - ketosis: 13 in HCL+empa vs. 3 in HCL+placebo; 7 in PGLS+empa vs. 2 in PGLS+placebo



Empagliflozin (5 and 25 mg/d) added to AID improves glycemic control but increases ketosis compared to placebo.

→ **Low-dose empagliflozin (2.5 mg/d)?**

1. Haidar et al., nature medicine (2022)
2. Garcia-Tirado et al., DTT (2022)

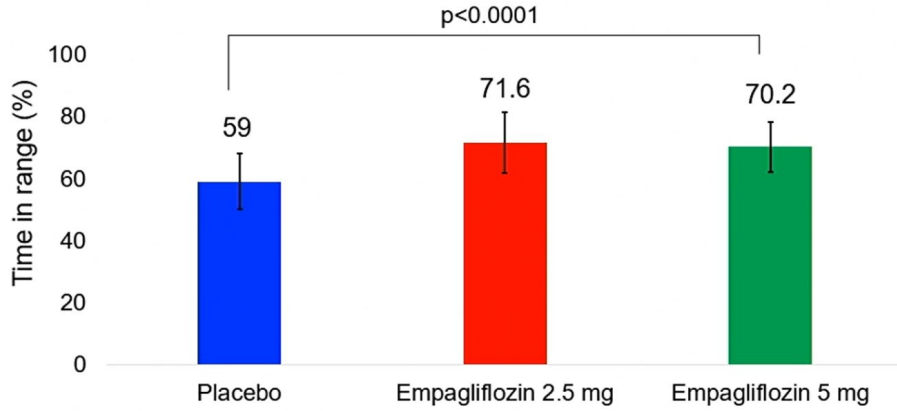
Add-on SGLT-2-inhibitor in type 1 diabetes – benefit vs. risk

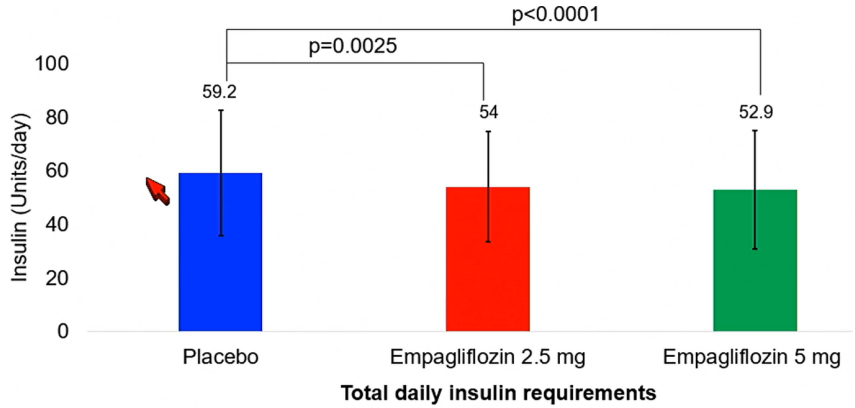
Methods

- HCL system + randomised to empagliflozin 2.5 mg/d vs. 5 mg/d vs. placebo, cross-over
- *n*=24, adults, T1D with HbA1c 7.5–10.5%
- Daily morning ketone levels

Outcome	Placebo	Empagliflozin 2.5 mg	Empagliflozin 5 mg	Empagliflozin 2.5 mg vs Placebo; P-value	Empagliflozin 5 mg vs Placebo; P-value
Morning ketone level (mmol/L), mean ± SD	0.15 ± 0.23	0.15 ± 0.10	0.17 ± 0.10	0.28	0.25

Outcome	Placebo	Empagliflozin 2.5 mg	Empagliflozin 5 mg
Number of days with ketone levels ≥ 1.5 mmol/L	1	2	1





Low dose empagliflozin increased glycemic control in a moderately controlled population with T1D on HCL therapy and did not affect morning ketone levels.

1. Pasqua et al, ADA Abstract (2022)

Sensing beyond glucose? - continuous ketone monitoring (CKM)

Possible clinical implications[1]

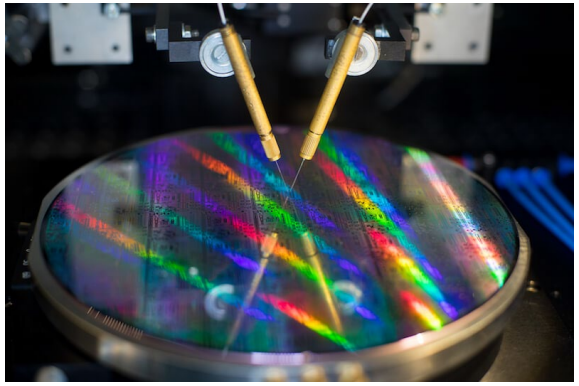
- Less cumbersome
- Early detection and prevention of DKA
- Integration in AIDs
- Enable SGLT2-i add-on therapy in T1D

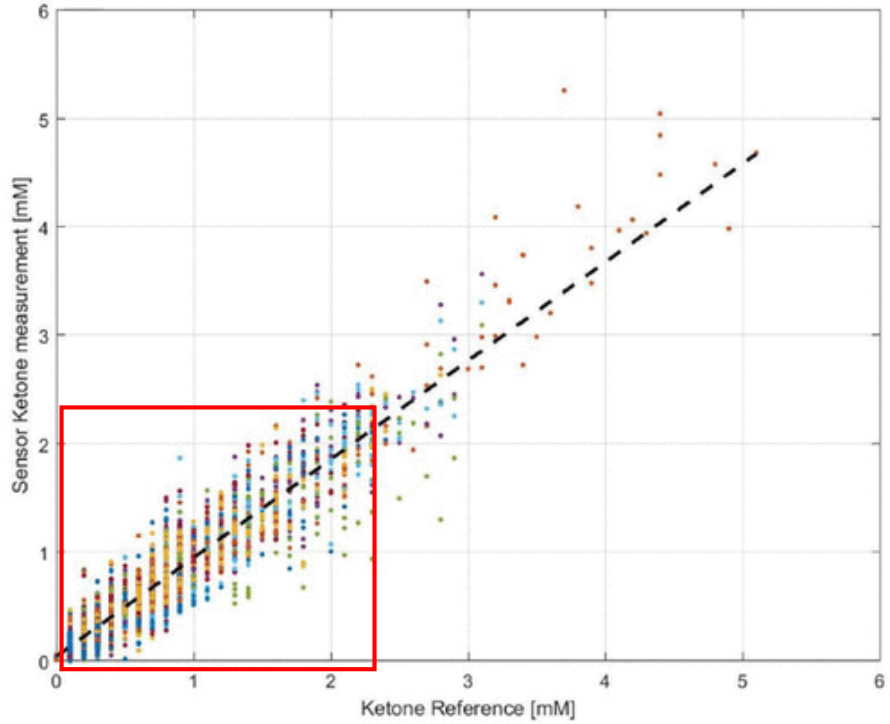
Feasibility study[2]

- CKM sensor with wired enzyme technology
- in-vitro characterisation and in-vivo performance in *n*=12 healthy individuals on low-carb diet

Lingo

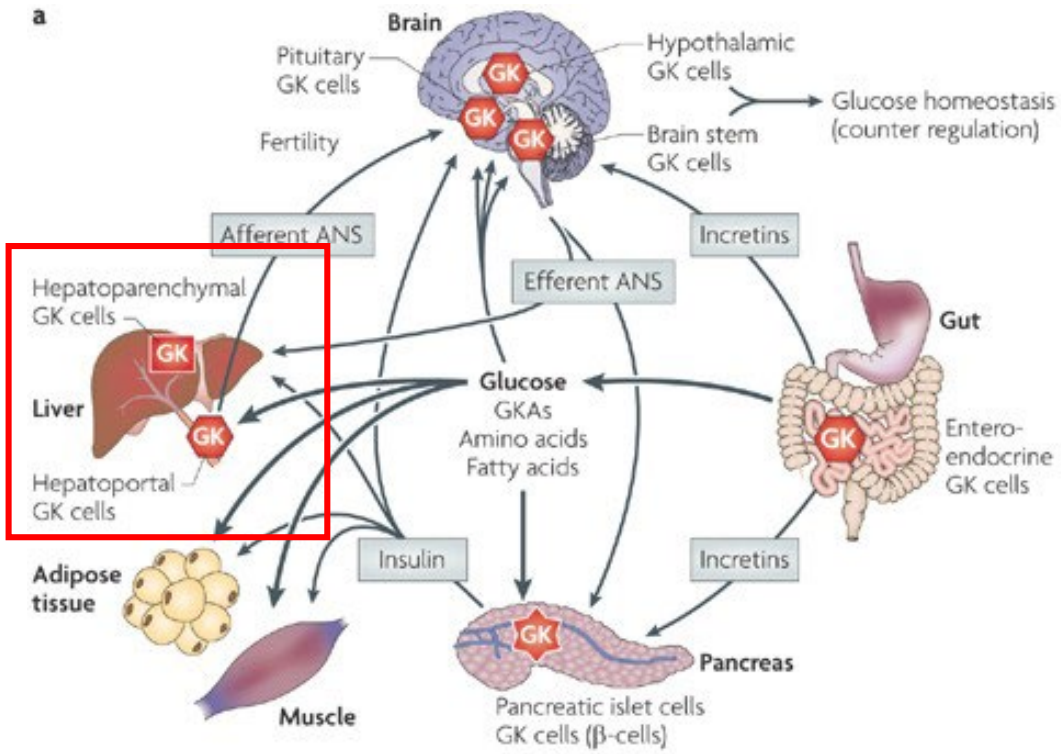
Indigo → spectrometric





1. Nguyen et al., Journal of Diabetes Science and Technology (2021)
2. Alva et al, Journal of Diabetes Science and Technology (2021)
3. Abbott's Biowearable: One Sensor for Glucose, Ketones | Newsroom (2022)

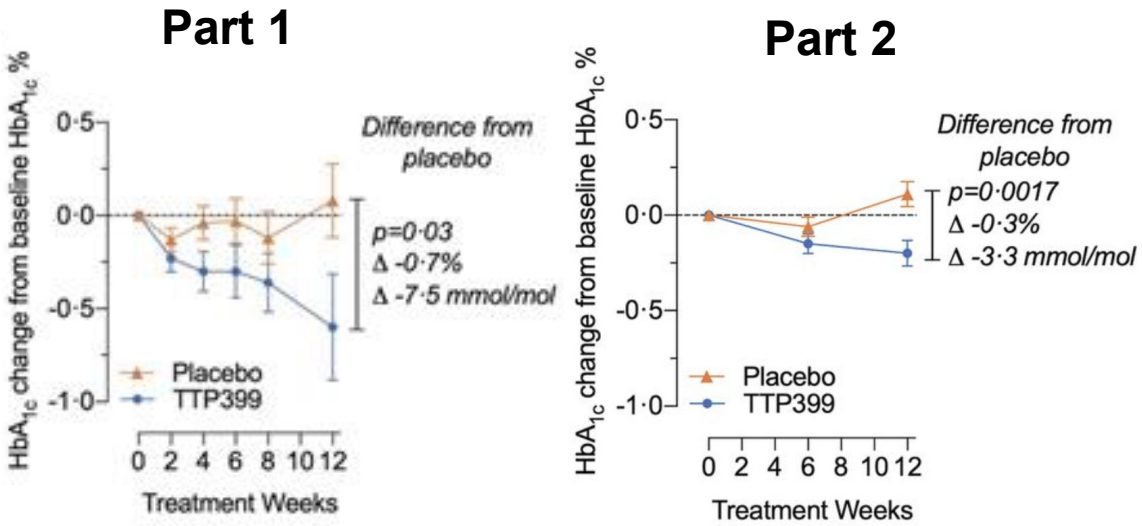
Other targets? Hepatoselective glucokinase activator TTP399



1

Methods[2]

- Two parts:
  - Part 1: *n*=20 with T1D + CSII
  - Part 2: *n*=85 with T1D + CSII or MDI
- 800 mg TTP399 vs. placebo, 12 weeks



1. Matschinsky, nature reviews drug discovery (2009)
2. Klein et al., Diabetes Care (2021)

Type 2 Diabetes

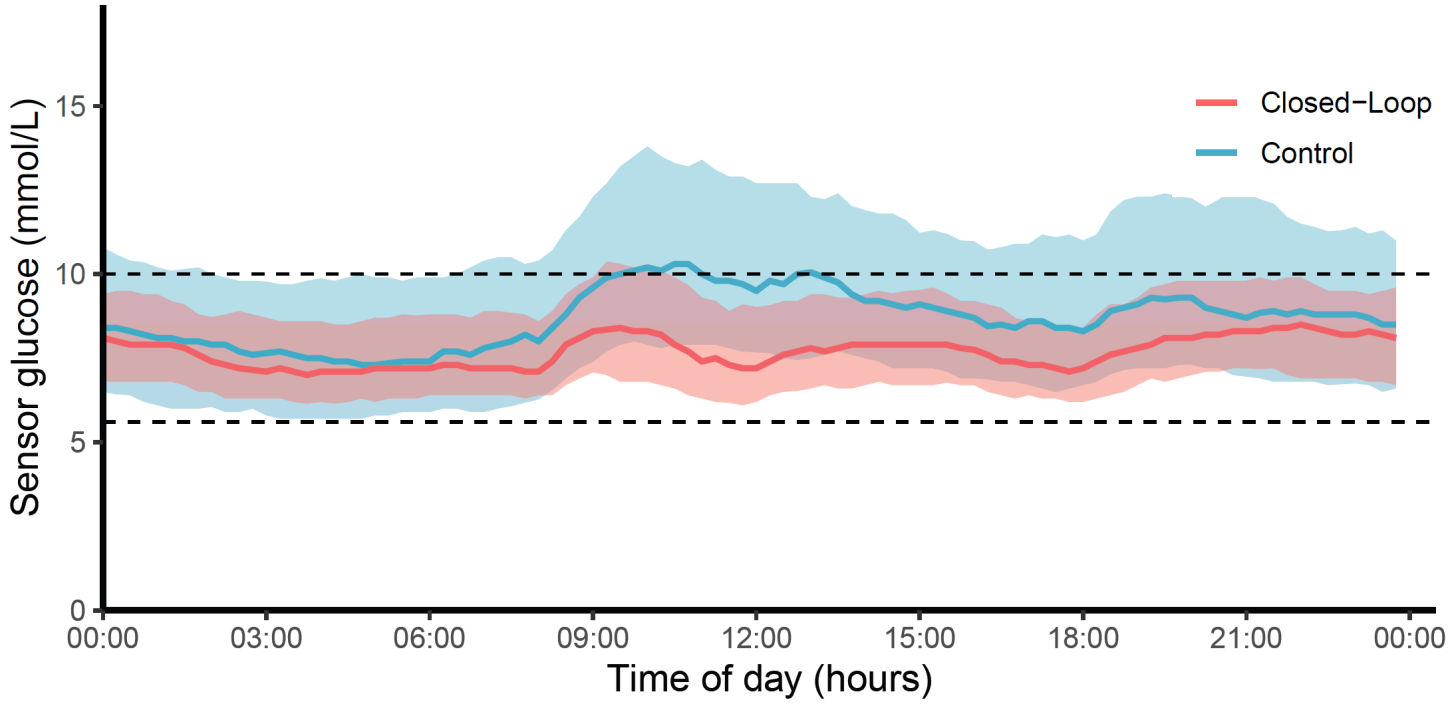
Perioperative fully closed-loop in hospitalised patients with non-type 1 diabetes

Methods

- Randomized, single-center, open-label, parallel
- Adults with diabetes (other than type 1), *n*=23 closed-loop vs. *n*=22 control
- Mixed elective surgery (abdominal, thoracic, vascular, orthopaedic, neuro)
- Hospital admission to discharge

% TIR (5.6-10.0mM) closed loop = 76.7 ± 10.1 %
%TIR control = 54.7 ± 20.8 %

p<0.001



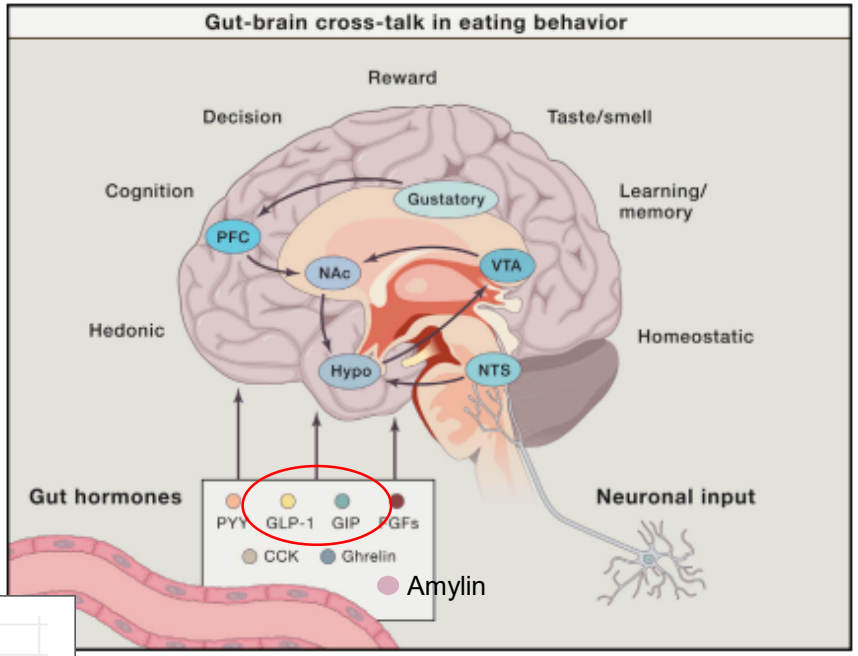
Significantly improved glucose control (TIR↑22%, >5h/day) without increasing the risk of hypoglycemia.

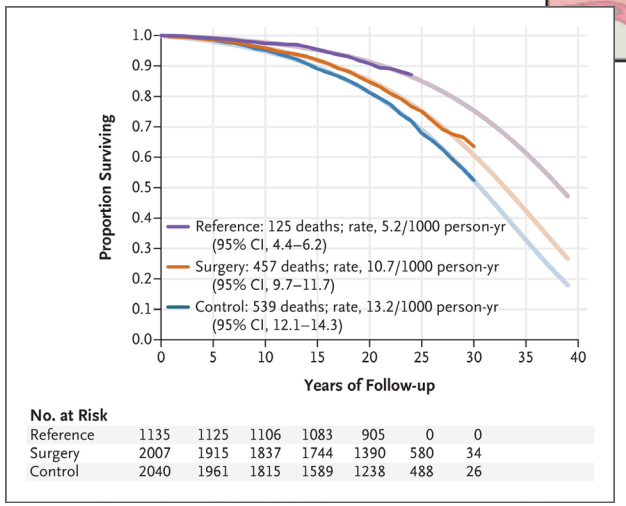
Outpatient setting?

Herzig et al., Diabetes Care (2022)

Weight loss ≥10-15% as a central therapeutic goal

- 90% of people with type 2 diabetes are overweight or obese
- DIRECT study[1]: formula diet, ↓calory intake (825-853 kcal/d), *n*=306 with T2D → **weight loss ≥15%** in people with early type 2 diabetes (<6yrs) achieves **diabetes remission** in 86%
- **Benefits beyond glucose control[2]:** bariatric surgery → reduced cardiovascular (30%) and cancer-related mortality (23%) compared to standard obesity care





1. Lean et al., Lancet (2018)
2. Carlsson et al., NEJM (2020)
3. Clemmenson et al, Cell (2017)

SURMOUNT-1 trial – Tirzepatide in obesity

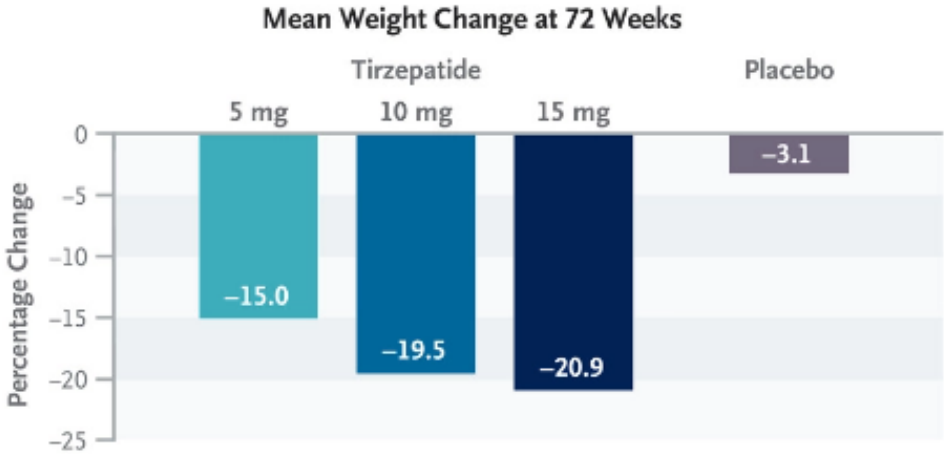
The NEW ENGLAND JOURNAL of MEDICINE

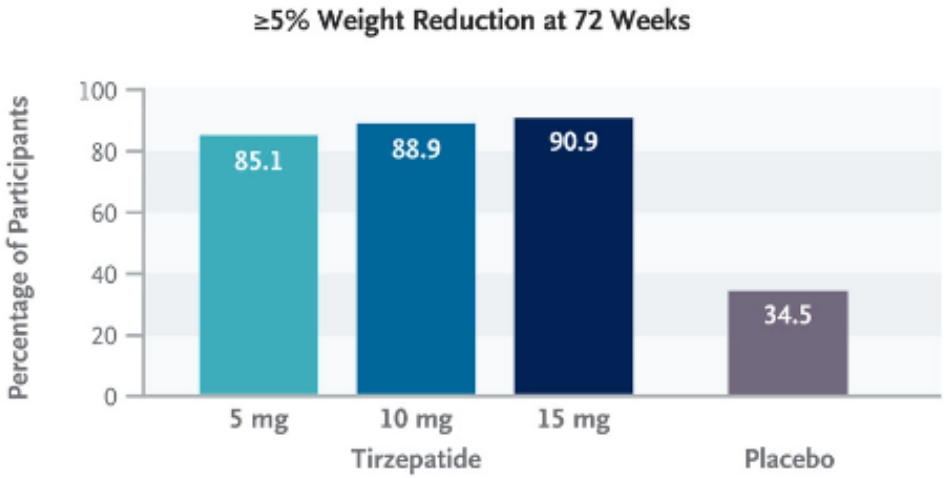
ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

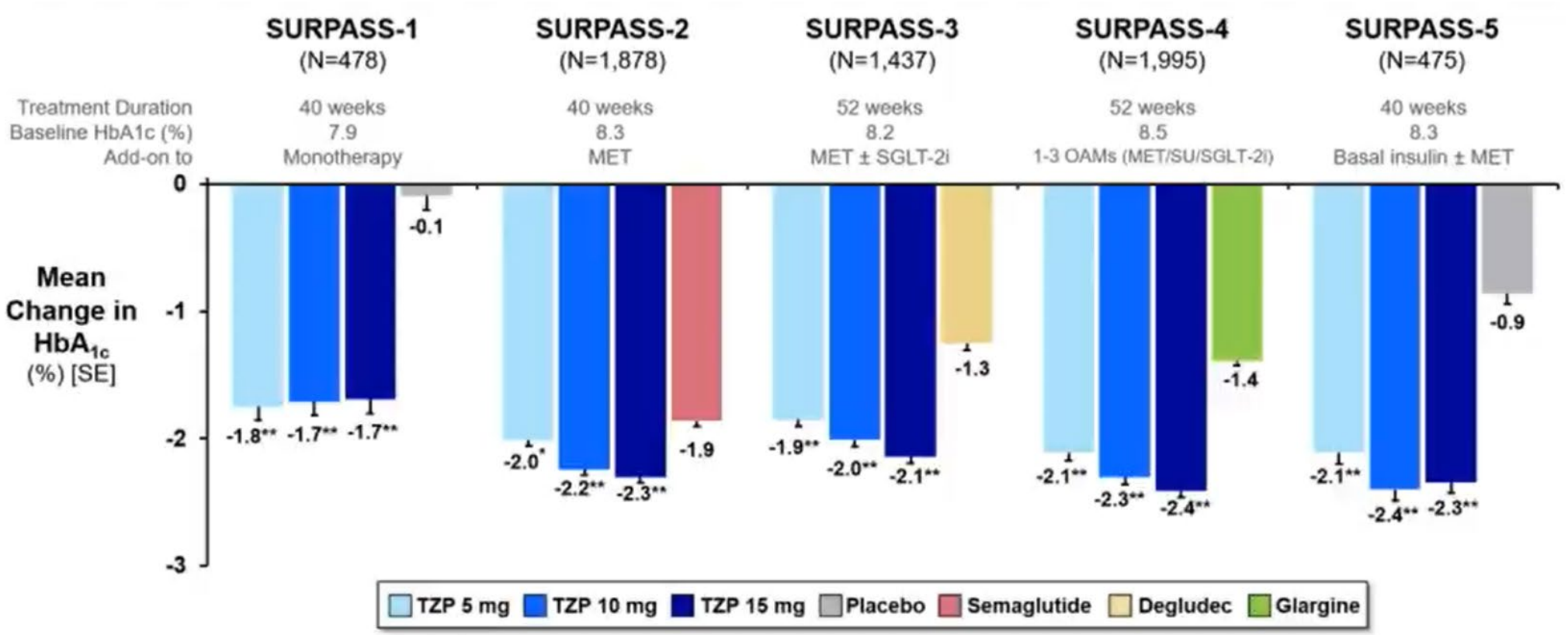
All 3 doses of once-weekly tirzepatide led to clinically meaningful weight reduction in obese adults without diabetes.





Jastreboff et al., NEJM (2022)

SURPASS-trials – Tirzepatide in type 2 diabetes



Once-weekly tirzepatide led to significant reduction of HbA1c compared to placebo or active comparator in adults with type 2 diabetes.

1. Rosenstock et al., Lancet (2021)
2. Frias et al. NEJM (2021)
3. Ludvik et al., Lancet (2021)
4. Del Prato et al., Lancet (2021)
5. Dahl et al., JAMA (2022)

Smart Pens

«Smart»?

- Digital dose capture
- Real-time connectivity (app, glucose sensor)
- Integration with personalised dosing decision support

Legacy → Tracking → Smart

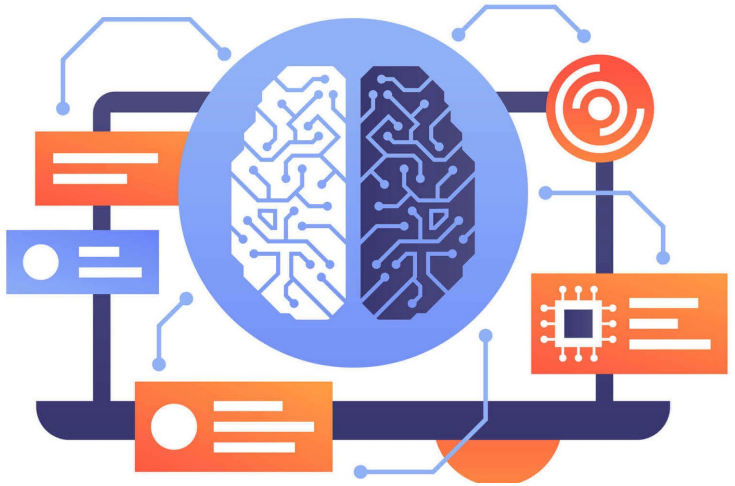
NovoPen 6/Echo

CE-mark 2019

Medtronic InPen

FDA 2017
CE-mark 05/2021

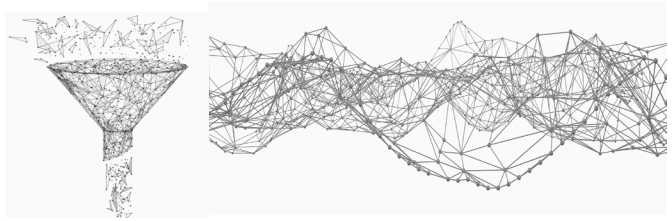
Next step: Advanced decision support



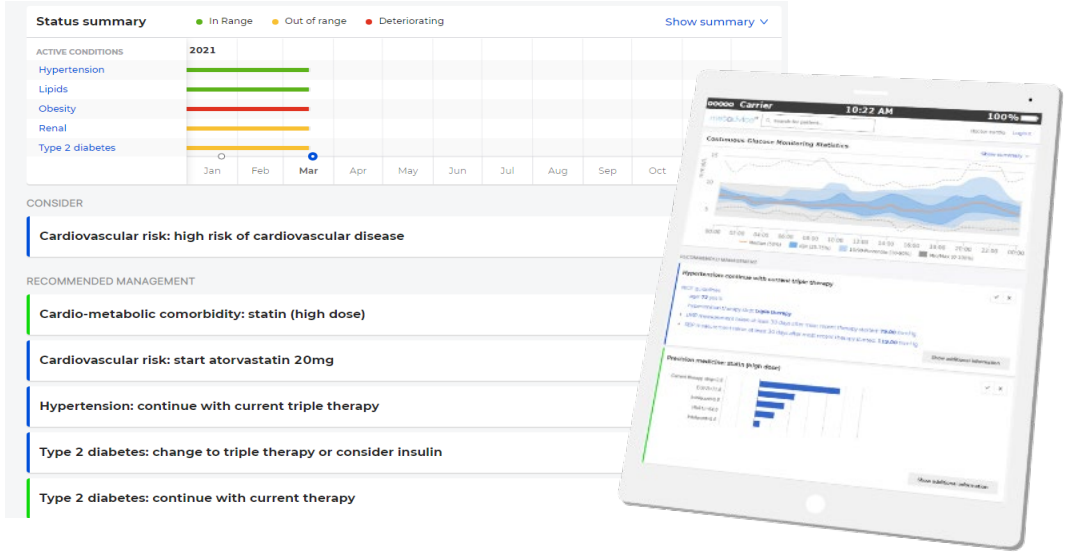
Kompala et al., Journal of Diabetes Science and Technology (2022)

Use of artificial intelligence (+ clinical knowledge from diabetes experts)

Clinical AI Companion for Diabetes Optimisation using Digital Data from Continuous Glucose Monitoring

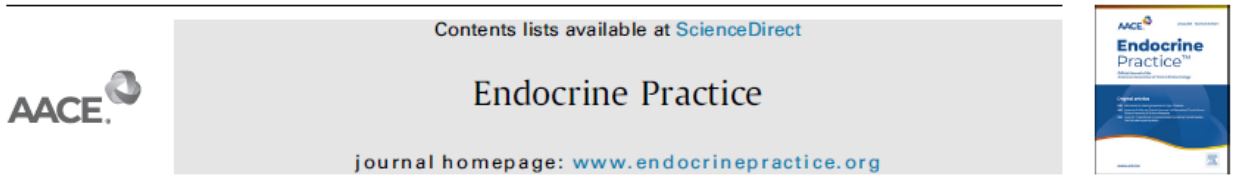


Artificial intelligence via neuronal network core



Insulin dose optimization using an automated artificial intelligence-based decision support system in youths with type 1 diabetes

Revital Nimri[1], Tadej Battelino[2], Lori M. Laffel[3], Robert H. Slover[4], Desmond Schatz[5], Stuart A. Weinzimer[6], Klemen Dovc[2], Thomas Danne[7], Moshe Phillip[1,8] and NextDREAM Consortium*



Review Article

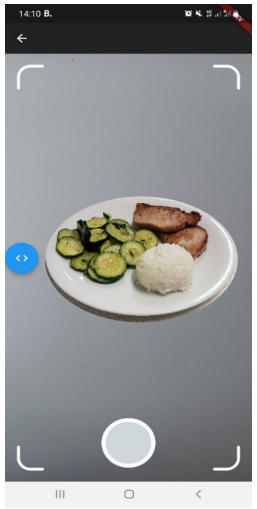
New Digital Health Technologies for Insulin Initiation and Optimization for People With Type 2 Diabetes

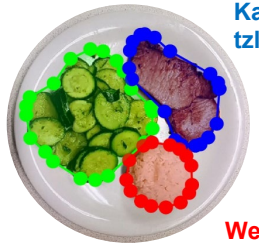
David Kerr, MBChB, DM [1,*], Steven Edelman, MD [2], Giacomo Vespasiani, MD [3], Kamlesh Khunti, MD, PhD [4]

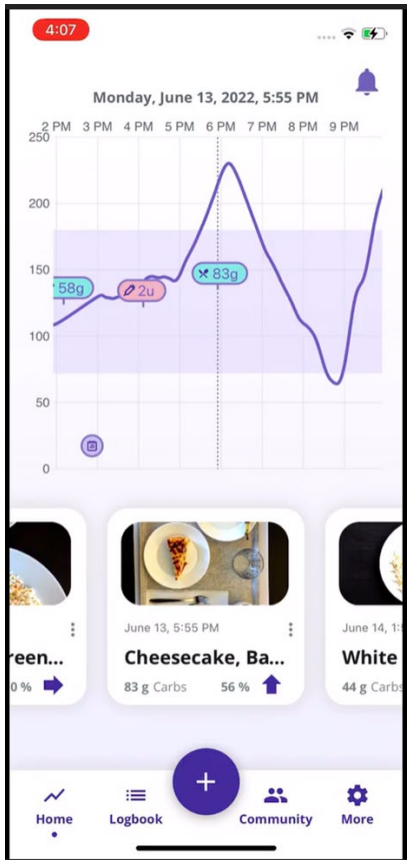
[1] Sansum Diabetes Research Institute, Santa Barbara, California

Nimri et al., nature medicine (2020)
Nimri et al., ADA Abstract (2022)
Kerr et al., Endocrine Practice (2022)

Do not forget nutrition as a treatment modality…







Rein *et al. BMC Medicine* (2022) 20:56
https://doi.org/10.1186/s12916-022-02254-y

Effects of personalized diets by prediction of glycemic responses on glycemic control and metabolic health in newly diagnosed T2DM: a randomized dietary intervention pilot trial

Michal Rein[1,2,3†], Orly Ben-Yacov[1,2†], Anastasia Godneva[1,2†], Smadar Shilo[1,2,4], Niv Zmora[5,6,7], Dmitry Kolobkov[1,2], Noa Cohen-Dolev[1,2], Bat-Chen Wolf[1,2], Noa Kosower[1,2], Maya Lotan-Pompan[1,2], Adina Weinberger[1,2], Zamir Halpern[6,7], Shira Zelber-Sagi[3], Eran Elinav[5*] and Eran Segal[1,2*]

Benefits beyond glucose control

THE LANCET

Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial

Javier Delgado-Lista, Juan F Alcala-Diaz*, Jose D Torres-Peña, Gracia M Quintana-Navarro, Francisco Fuentes, Antonio Garcia-Rios, Ana M Ortiz-Morales, Ana I Gonzalez-Requero, Ana I Perez-Caballero, Elena M Yubero-Serrano, Oriol A Rangel-Zuñiga, Antonio Camargo, Fernando Rodriguez-Cantalejo, Fernando Lopez-Segura, Lina Badimon, Jose M Ordovas, Francisco Perez-Jimenez, Pablo Perez-Martinez†, Jose Lopez-Miranda†, for the CORDIOPREV Investigators‡*

The NEW ENGLAND JOURNAL of MEDICINE

April 8, 2021
N Engl J Med 2021; 384:1312-1322

ORIGINAL ARTICLE

Glycemic Index, Glycemic Load, and Cardiovascular Disease and Mortality

David J.A. Jenkins, M.D., Ph.D., Mahshid Dehghan, Ph.D., Andrew Mente, Ph.D., Shrikant I. Bangdiwala, Ph.D., Sumathy Rangarajan, M.Sc., Kristie Srichaikul, M.D., Viswanathan Mohan, D.Sc., Alvaro Avezum, M.D., Rafael Díaz, M.D., Annika Rosengren, M.D., Fernando Lanas, M.D., Patricio Lopez-Jaramillo, M.D., et al., for the PURE Study Investigators*

Key requirements to reach a «connected diabetes ecosystem»

- Data accessibility/interoperability
- Regulatory clearance (AI-driven decision support systems)
- Direct integration into EHR
- Reimbursement of CGM other ehealth application (regardless of treatment modality) and remote care models
- Privacy and safety of patients

End goal: Virtual Diabetes Clinic

Phillip et al., DTT (2021)

Summary New Technologies and Therapeutics

Type 1 Diabetes

Automated Insulin Delivery (AID) Systems

Ultrarapid Insulin lispro

Potential add-on Therapeutics

- Low-dose SGLT-2i
- Hepatoselective glucokinase activators

Type 2 Diabetes

Tirzepatide (dual GLP-1/GIP Agonist

Smart Pens (also for Type 1)

Fully Closed-Loop Insulin Delivery in the inpatient and perioperative Setting

AI based Decision Support
Personalized/Precision Nutrition
Virtual Diabetes Clinic

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Thank you for your attention.