Tecnologia per tutti: i piu recenti progressi e le prospettive

Giuseppe Lepore
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ASST Papa Giovanni XXIII Bergamo

Il Dr. Giuseppe Lepore dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- Astrazeneca
- MSD
- Novo Nordisk
- Sanofi

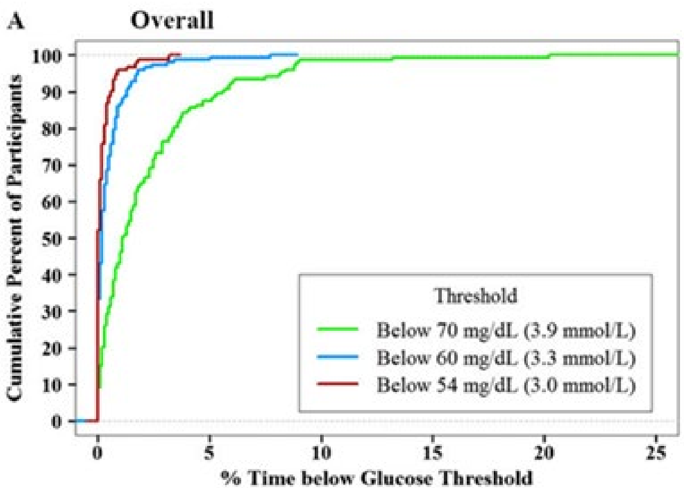
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

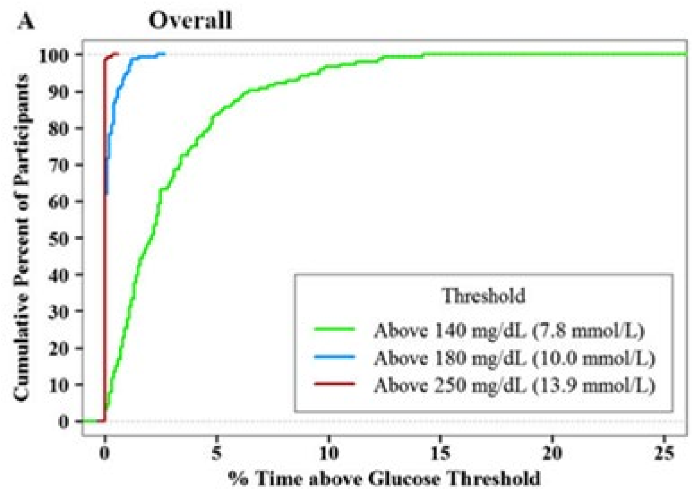
Continuous Glucose Monitoring Profiles in Healthy Nondiabetic Participants: A Multicenter Prospective Study

Summary of Glucose Metrics Over a 24-h Period (n = 153)

Overall glucose distribution and variability	
Mean, mg/dL (mean ± SD)	99 ± 7
SD, mg/dL (mean ± SD)	17 ± 3
CV, % (mean ± SD)	17 ± 3
Percentage of glucose sensor values, median (IQR)	
>180 mg/dL	0.0 (0.0–0.2)
>160 mg/dL	0.3 (0.1–0.9)
>140 mg/dL	2.1 (0.9–3.9)
70–140 mg/dL	96 (93–98)
70–120 mg/dL	89 (82–92)
<70 mg/dL	1.1 (0.3–2.9)
<60 mg/dL	0.2 (0.0–0.6)
<54 mg/dL	0.0 (0.0–0.2)

70—140 mg/dL 96%





Shah VN et al., J Clin Endocrinol Metab, 2019, 104:4356–4364

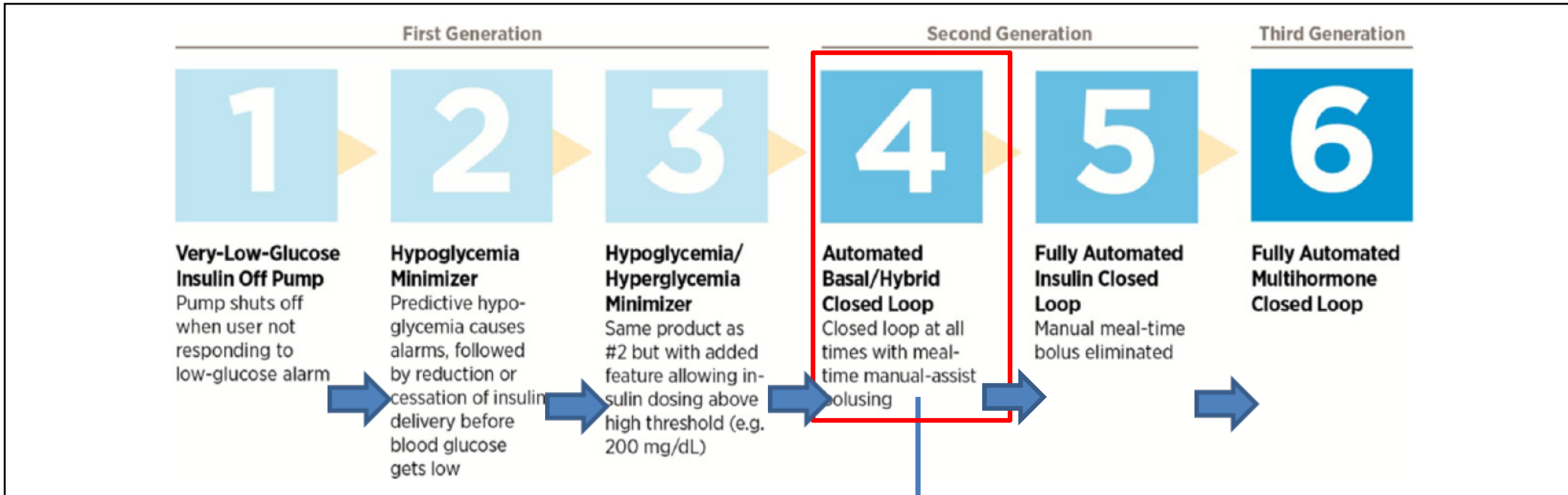
Continuous glucose monitoring and metrics for clinical trials: an international consensus statement

Time in tight range (TITR)

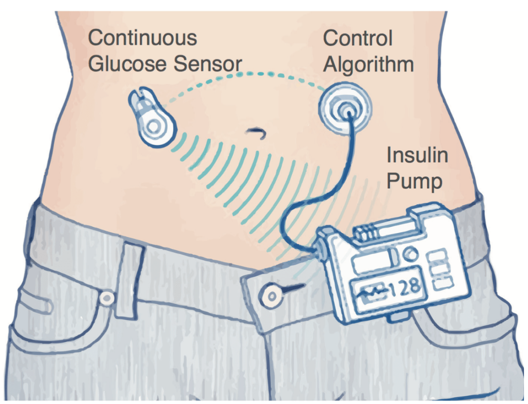
	Measure	Aim
Time in tight range	A secondary measure of time in range, measures the percentage of time spent in target glucose range 70–140 mg/dL (3.9–7.8 mmol/L)	Suggested time in tight range aim is >70% of each day

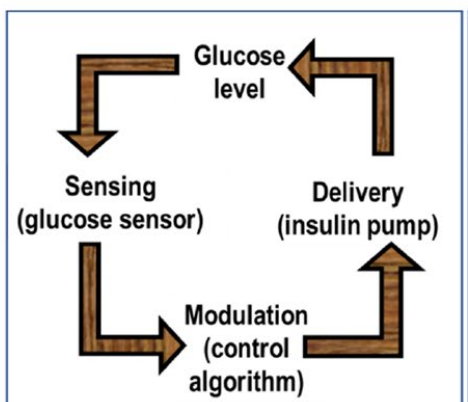
Battelino T et al., Lancet Diabetes Endocrinol. 2023 Jan;11(1):42-57

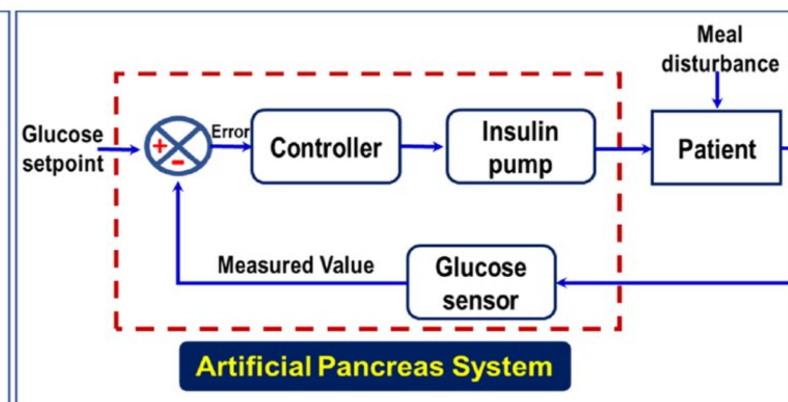
Automated insulin delivery



AHCL System



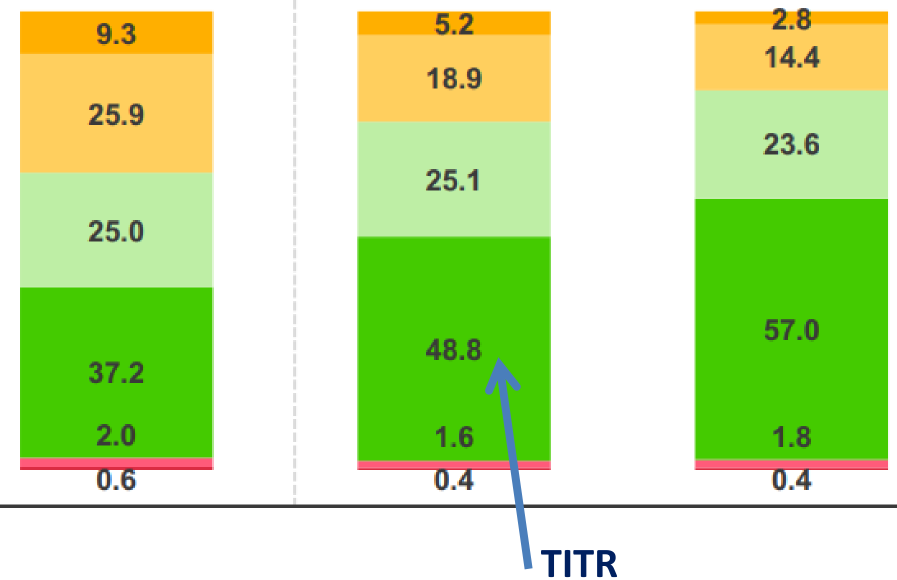


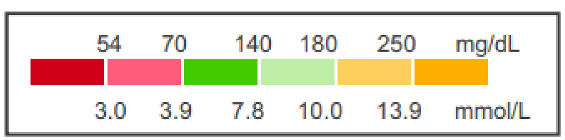


Time in Tight Glucose Range in Type 1 Diabetes: Predictive Factors and Achievable Targets in Real-World Users of the M.....780G System

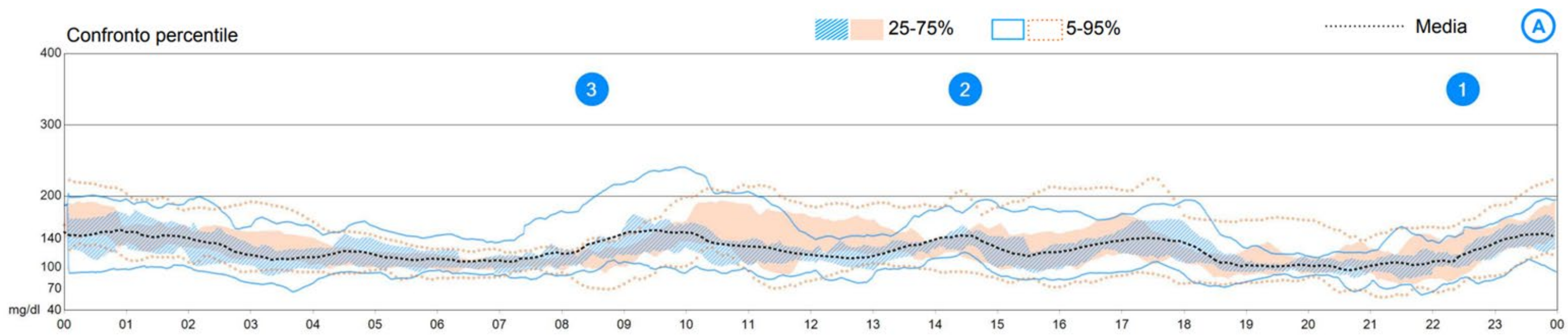
	>15 years		
	Baseline	Post-AHCL	
		Overall	Optimal Settings
Users, n	9,699	9,699	510
Time in AHCL, %		90.0 ± 16.0	93.5 ± 11.8
Mean SG, mg/dL	164.2 ± 24.0	150.0 ± 16.5	139.2 ± 11.8
Standard Deviation of SG, mg/dL	55.7 ± 11.5	50.1 ± 9.8	45.2 ± 8.5
Mean GMI, %	7.2 ± 0.6	6.9 ± 0.4	6.6 ± 0.3
Time in tight range (70-140 mg/dL), %	37.2 ± 13.6	48.8 ± 10.9	57.0 ± 9.1
Time in range (70-180 mg/dL), %	62.3 ± 14.7	73.9 ± 10.2	80.6 ± 7.5

Time in ranges, %

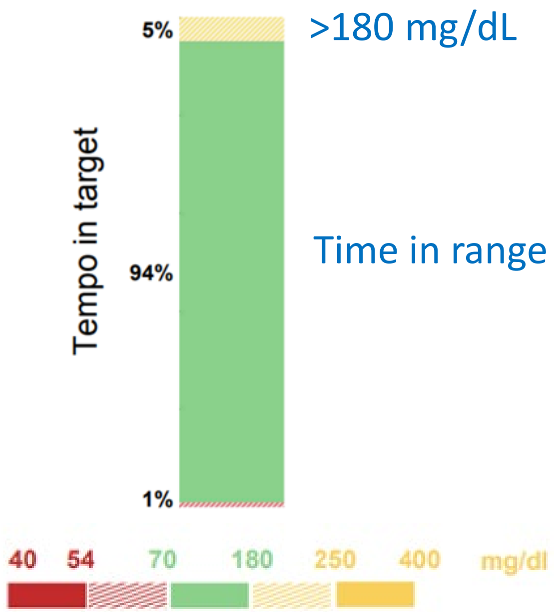


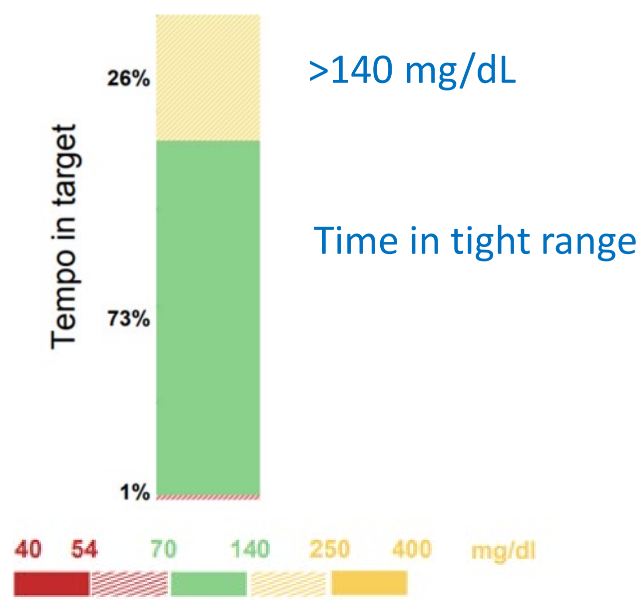


Castaneda J et al., Diabetes Care 2024; 47:790-797



Media glucosio sensore ± DS	125 ± 33 mg/dl
GMI***	6,3%





Automated Insulin Delivery: Benefits, Challenges, and Recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association

J.L. Sherr, L. Heinemann, A. Fleming, R.M. Bergenstal, D. Bruttomesso, H. Hanaire, R.W. Holl, J.R. Petrie, A.L. Peters, M. Evans

Table 2—Limitations of AID systems

Physiological

1. Time lag in sensor glucose values as measured in ISF vs. blood
2. Delayed absorption of insulin from subcutaneous depot; pharmacodynamic effects of applied insulin are different from physiological secreted insulin

Technological

1. Suboptimal analytical accuracy of CGM systems in low glucose range
2. Compression of tissue around sensor insertion site leads to falsely detected hypoglycemia
3. Missing sensor glucose data (e.g., due to transmission failures) and sensor warm-up time
4. Glucose sensor overreading and inadvertent overdelivery of insulin
5. Infusion set failures or pod failure
6. Outright pump failure due to software or hardware issues
7. Issues with data uploading, regular exchange of batteries, loss of communication between components of the AID system/cloud network
8. Server interruptions leading to inability to remotely track data
9. Cybersecurity/data protection/data privacy
10. Need for regular update of software/operating systems/apps
11. Impact of work or environmental conditions has to be considered (i.e., exposure to high or low temperatures, magnetic fields, or water)

Behavioral

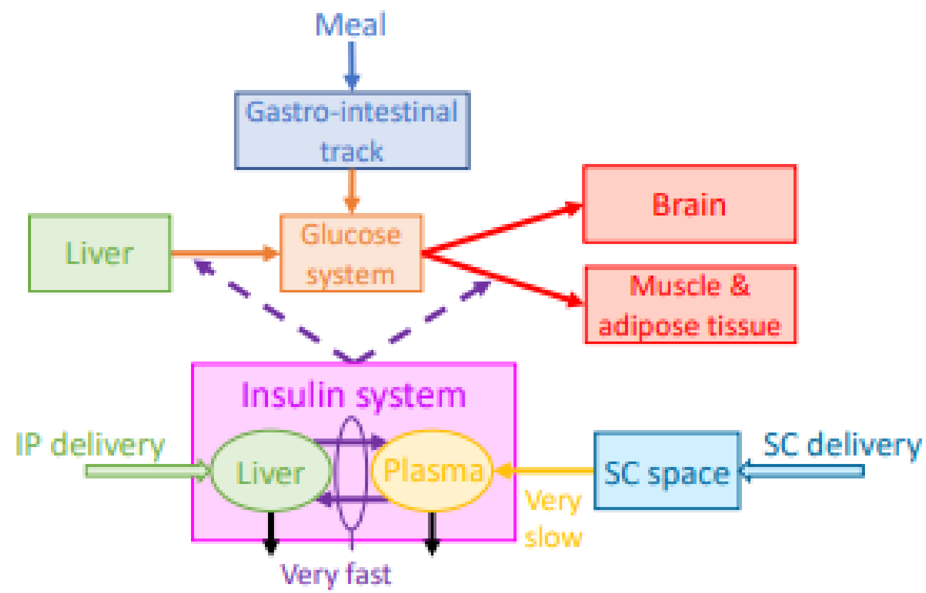
1. Patient needs to bolus prandial insulin
2. Requirement of correction boluses
3. Problem-solving for hyperglycemia (i.e., detect failed infusion sets, broken system components)
4. Avoidance of hyperglycemia overcorrections and avoiding adding fake carbs, etc.
5. Overtreatment of hypoglycemia
6. Limitations and challenges of exercise
7. Need for backup supplies

Diabetes Care. 2022 Oct 6:dci220018. doi: 10.2337/dci22-0018

Somministrazione intraperitoneale

Vantaggi

- Azione insulinica rapida e riproducibile
- Fisiologico gradiente insulinico vena porta – circolo sistemico
- Ridotta insulinizzazione periferica
- Utilizzo di di algoritmo PID (non necessario algoritmo predittivo)
- Fully closed-loop: non necessario l'annuncio dei pasti



Toffanin C., Lalo M., Cobelli, C.
IEEE Trans. Med. Robot. Bionics 2021, 3, 306–314

Automated Insulin Delivery: Benefits, Challenges, and Recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association

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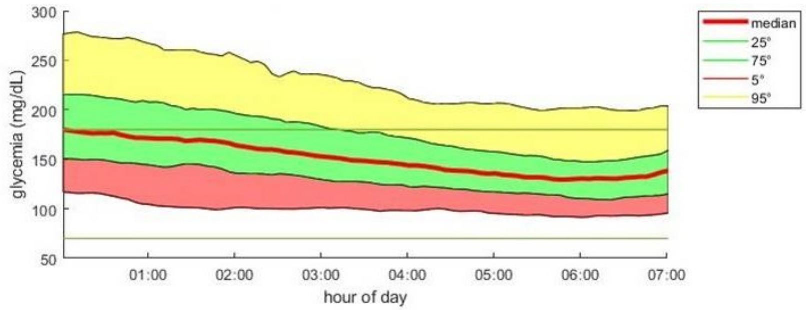
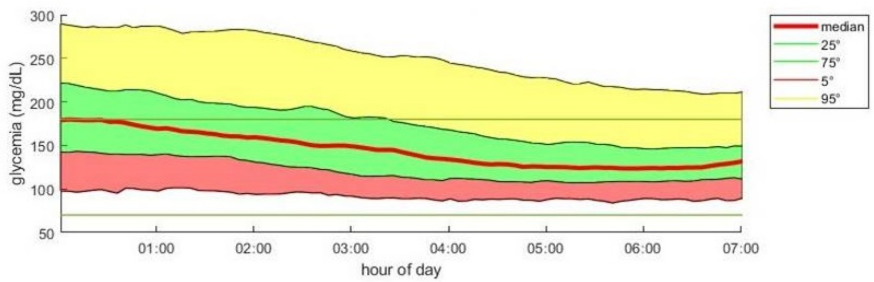
Diabetes Care. 2022 Oct 6:dci220018. doi: 10.2337/dci22-0018

Comparison of the night-time effectiveness in achieving glycemic targets in adults with type 1 diabetes of three advanced hybryd closed-loop systems

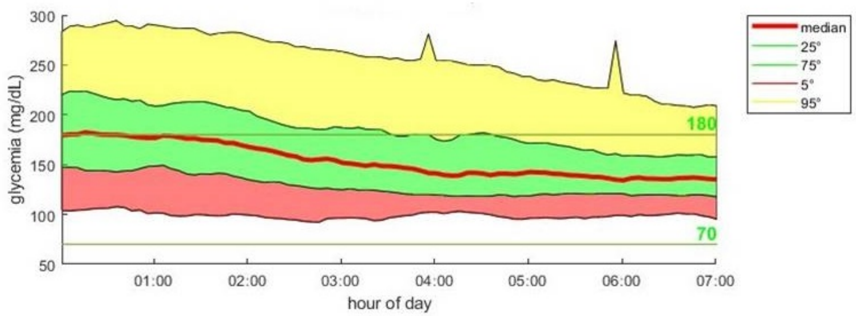
Nicolò Diego Borella[1] · Antonio Ferramosca[2] · Giona Castagna[1] · Silvia Ippolito[1] · Sara Ceresoli[2] · Antonio Taverna[1]
Beatrice Sonzogni[2] · Roberto Trevisan[1,3] · Giuseppe Lepore[1]



M….780G n=22



C…… IQ n=18



D….L… n=15

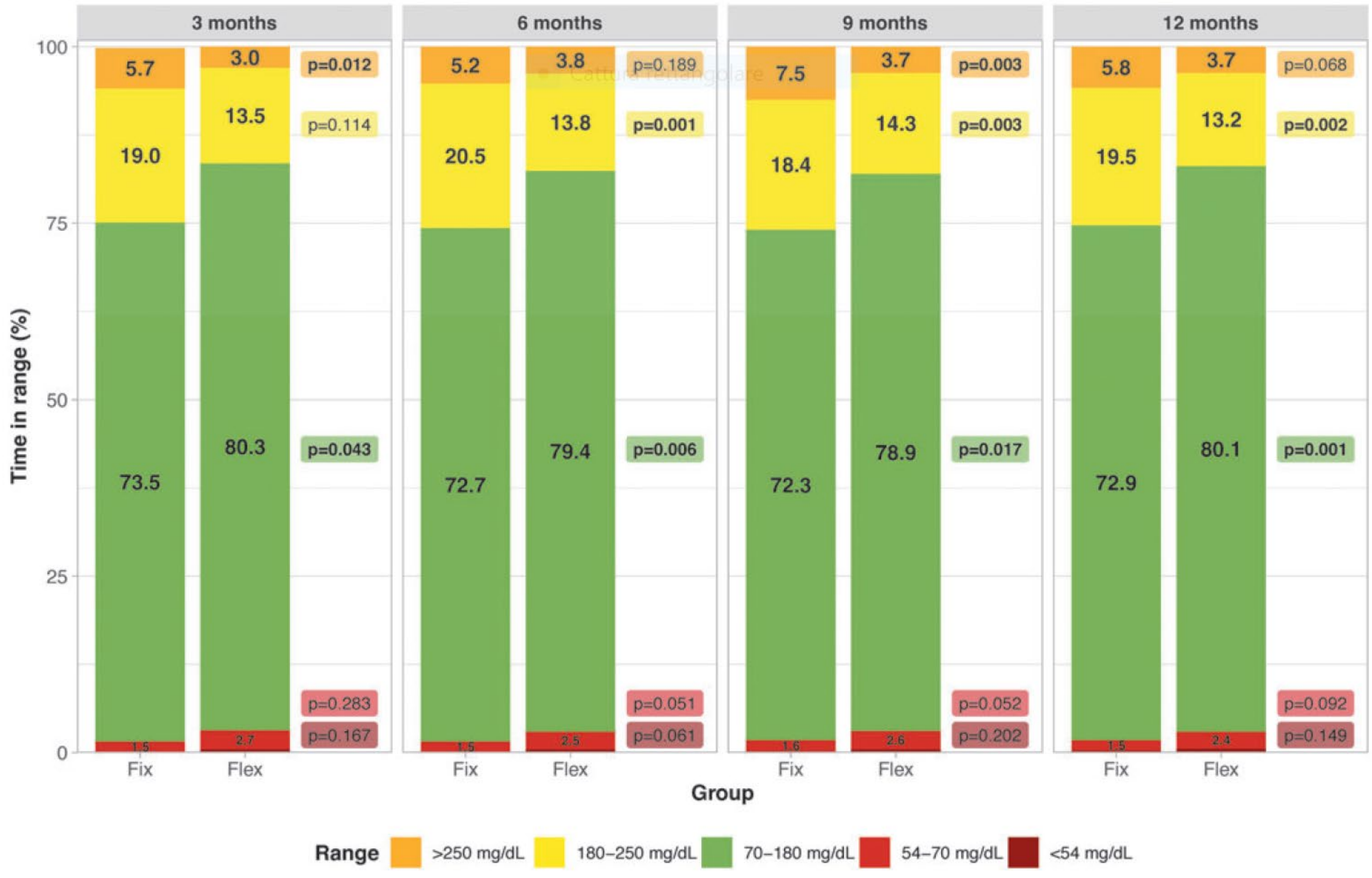
Acta Diabetologica, 2024, https://doi.org/10.1007/s00592-024-02397-9

Sistemi AHCL: boli prandiali

	M…780G	C… IQ	D…op	C.. APS	I… et O…od
Bolo standard	Bolo immediato	Bolo immediato	Bolo immediato Bolo bifasico	Bolo immediato	Bolo immediato
	Conteggio CHO	Conteggio CHO	Conteggio CHO o quantità CHO preimpostata (piccola, media, grande)	Conteggio CHO o quantità CHO preimpostata (piccola, media, grande, molto grande)	Conteggio CHO
Pasto a lenta digestione		Bolo esteso	Bolo pasto ricco di grassi	Bolo pasto a lenta digestione	
Bolo manuale	No	Sì		Sì	

Twelve-Month Follow-up from a Randomized Controlled Trial of Simplified Meal Announcement Versus PreciseCarbohydrate Counting in Adolescents with Type 1 Diabetes Using the M……™ 780G Advanced Hybrid Closed-Loop System

Flex meal management: preciso conteggio CHO
Fix meal management: annuncio pasti semplificato con tre quantitativi CHO prefissati



Petrovsky G et al., Diabetes Technol Ther. 2024 Mar;26(S3):76-83. doi: 10.1089/dia.2023.0429

Carbohydrate Tolerance Threshold for Unannounced Snacks in Children and Adolescents With Type 1 Diabetes Using an Advanced Hybrid Closed-Loop System

Snack non annunciato

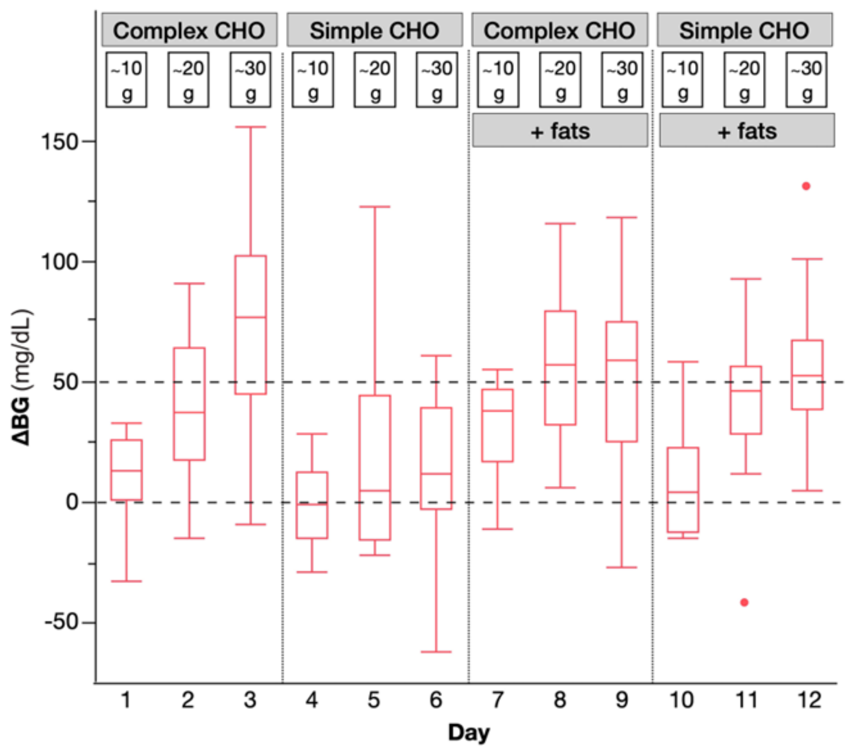


Figure 1—Box plot with differences between blood glucose (BG) before and 2 h after unannounced snacks (ΔBG = 2-h postmeal BG − premeal BG).

Tornese G et al., Diabetes Care 2022: 45: 1486-1488

Fast-Acting Insulin Aspart Versus Insulin Aspart Using a Second-Generation Hybrid Closed-Loop System in Adults With Type 1 Diabetes: A Randomized, Open-Label, Crossover Trial

due periodi di sei settimane

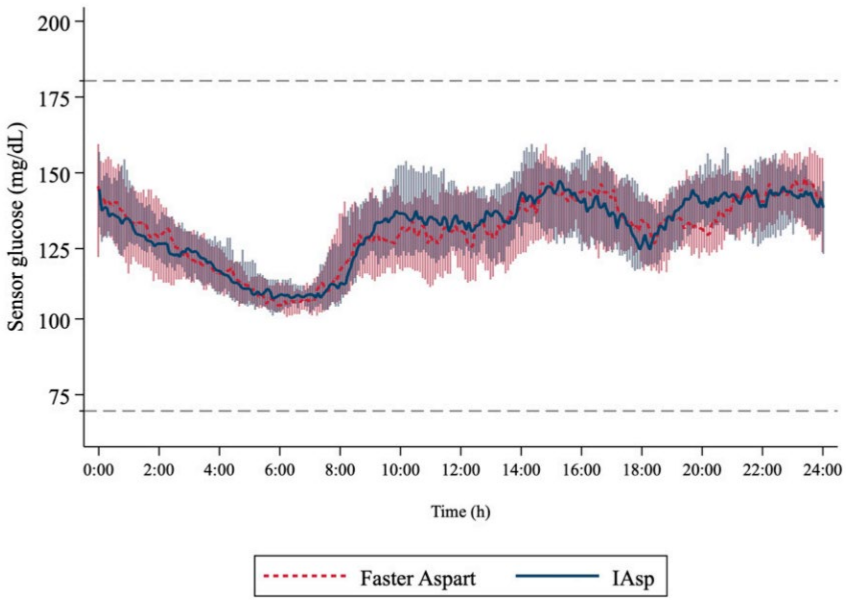


Figure 1—24-h SG levels during CL for the study duration. Faster aspart (red) and IAsp (blue) data lines represent median values, and shaded regions represent IQRs. Dashed gray lines denote glucose target range (70–180 mg/dL).

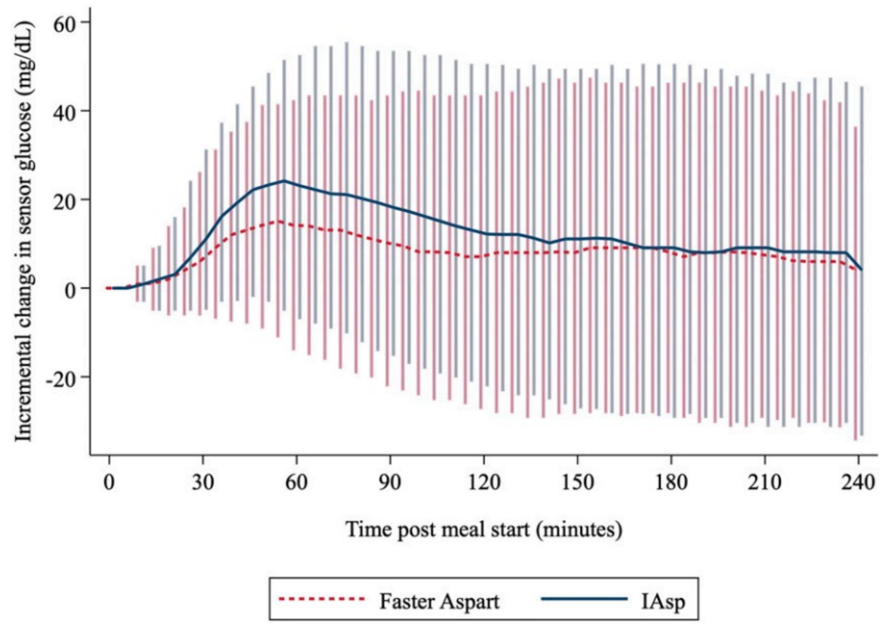


Figure 2—Incremental change in SG from baseline for combined (all meals) 4-h postprandial period. Faster aspart (red) and IAsp (blue) lines represent median values, and vertical bars represent IQRs.

Lee MH et al., Diabetes Care 2021;44:2371–2378 | https://doi.org/10.2337/dc21-0814

Faster Compared With Standard Insulin Aspart During Day-and-Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial

due periodi di 27 ore
pasti standard non annunciati
esercizio moderato-vigoroso nel pomeriggio

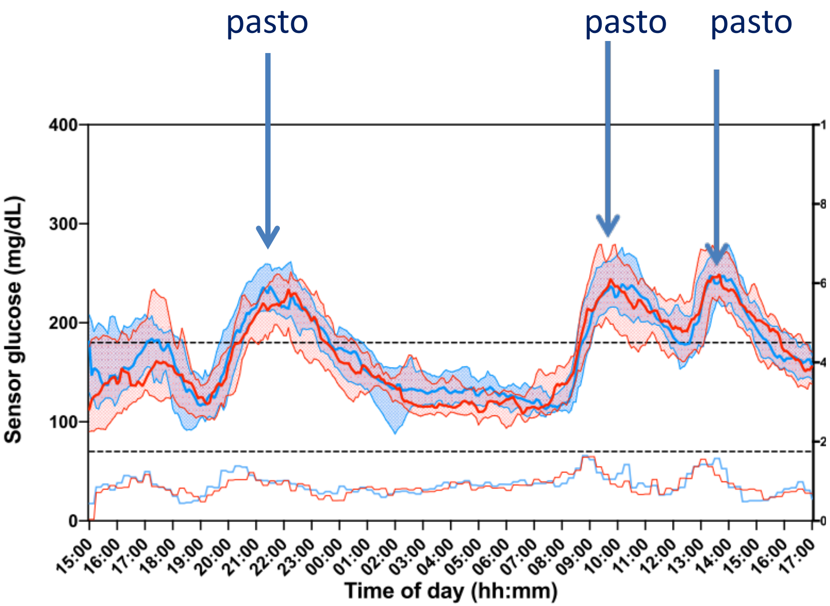
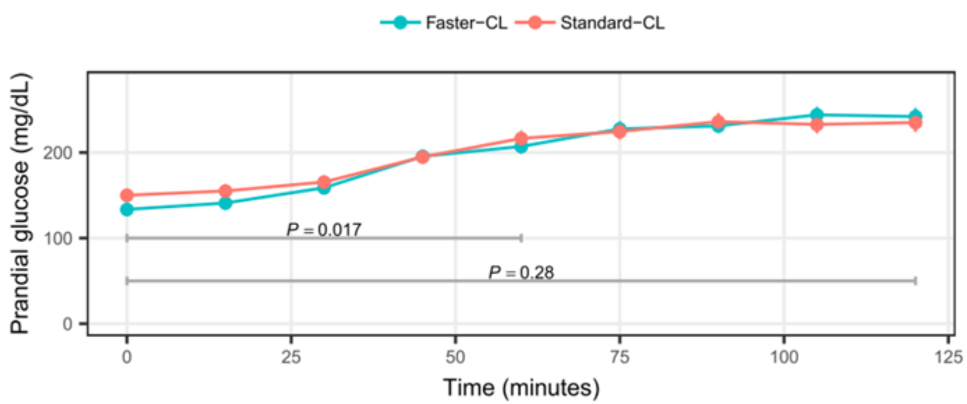


Figure 1—Sensor glucose and insulin delivery. Shown are the median (IQR) sensor glucose levels during the day-and-night Faster-CL (blue) and Standard-CL (red). Dashed horizontal lines indicate the target glucose range between 70 and 180 mg/dL.

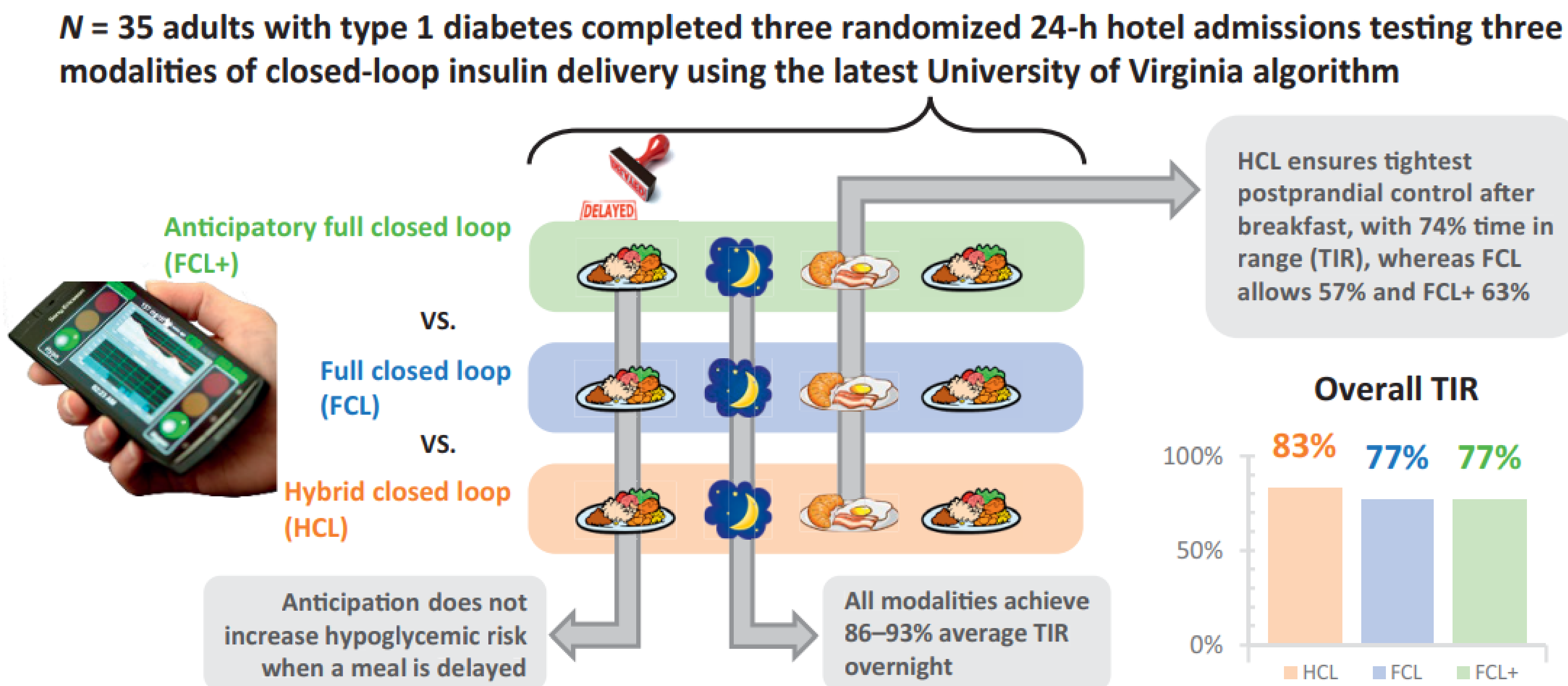
Postprandial glucose levels



Faster Aspart: TIR 53.8%, overnight TIR 83.9%
Aspart: TIR 58.6%, overnight TIR: 88%

Dovc K et al., Diabetes Care 2020: 43: 29-36

Assessment of Meal Anticipation for Improving Fully Automated Insulin Delivery in Adults WithType 1 Diabetes



Garcia-Tirado G et al., Diabetes Care 2023;46:1652–1658

Study protocol for a randomised open label clinical trial examining the safety and efficacy of the Android Artificial Pancreas System (AAPS) with advanced bolus-free features in adults with type 1 diabetes: the 'CLOSE IT' (Closed Loop Open SourcE In Type 1 diabetes) trial.

Confronto fra un sistema AID utilizzato in modalità full closed-loop vs

lo stesso sistema AID utilizzato in modalità HCL (durata 12 settimane)

Estensione dello studio: FCL with faster aspart vs aspart (4 settimane)

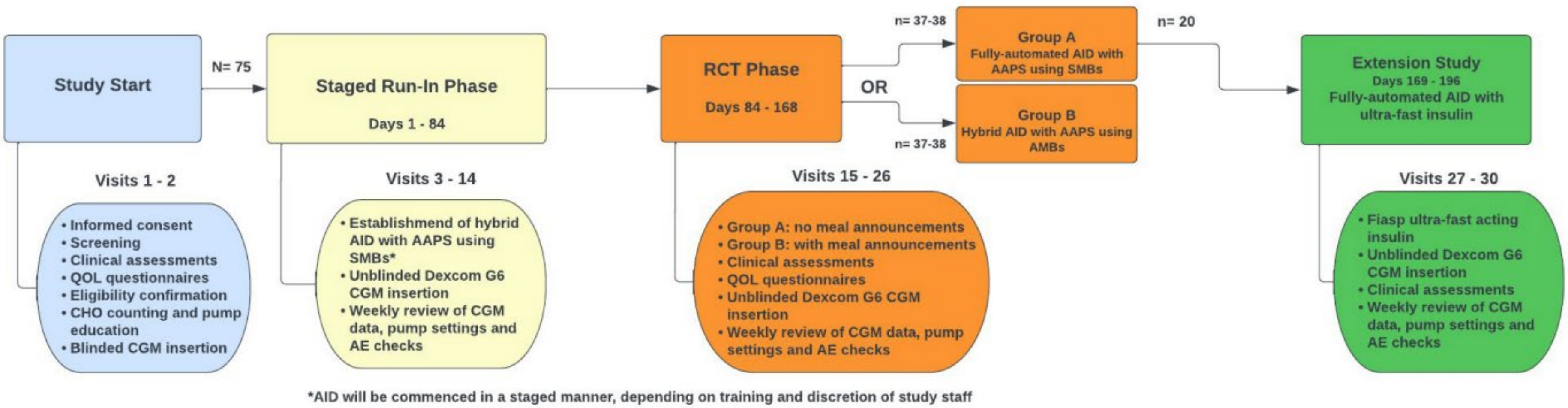
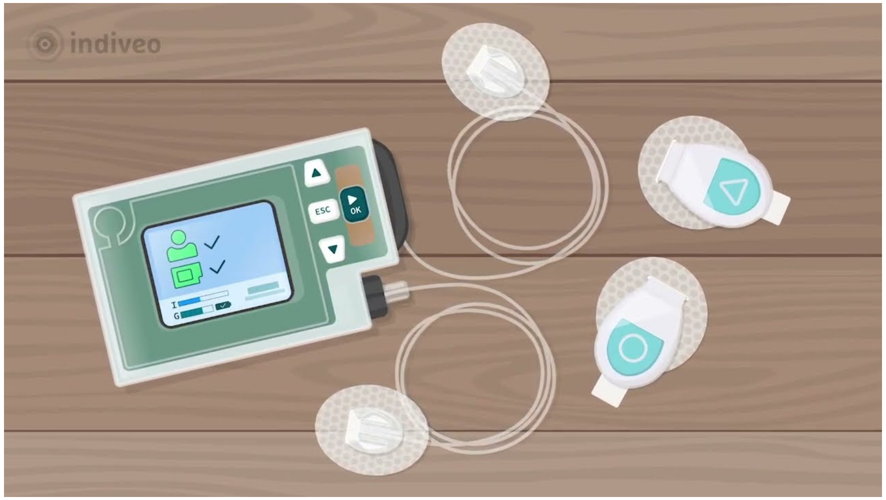


Figure 1 Study flow diagram. AAPS, Android Artificial Pancreas System; AE, adverse event; AID, automated insulin delivery; CGM, continuous glucose monitoring; QOL, quality of life; RCT, randomised controlled trial; SMB, super micro boluses.

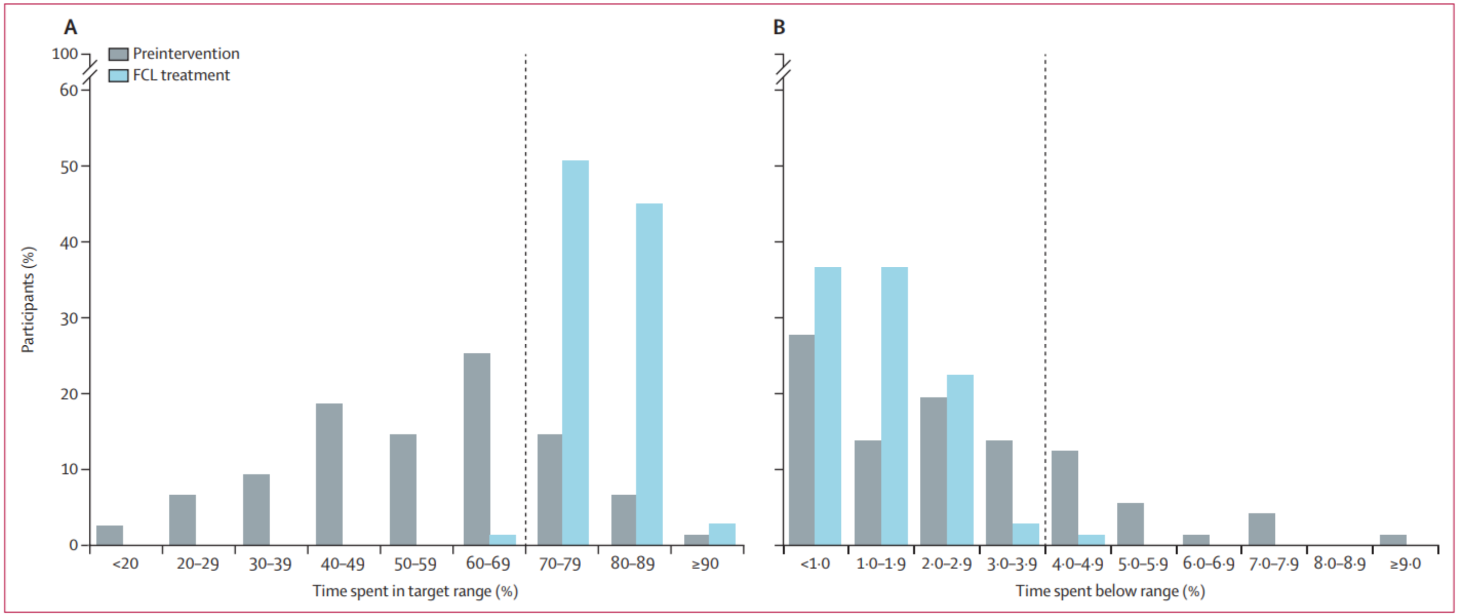
Wilkinson T et al., BMJ Open2024;14:e078171. doi:10.1136/bmjopen-2023-078171

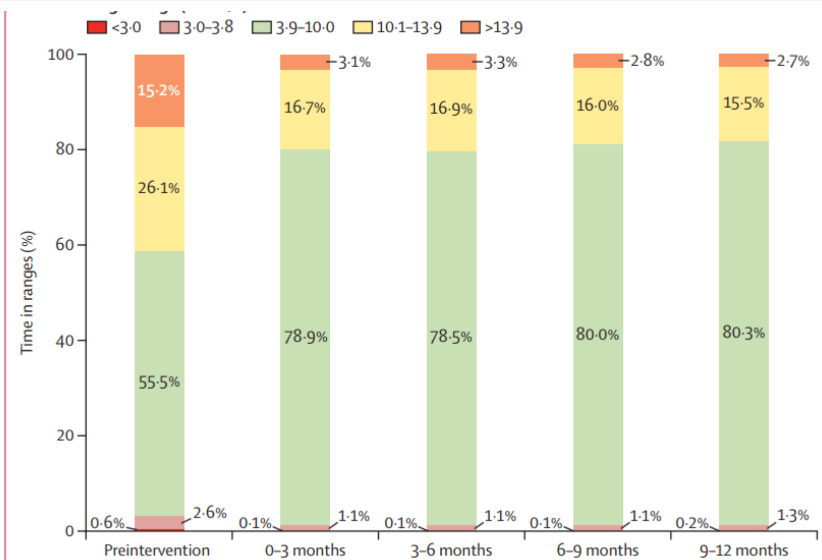
Bihormonal fully closed-loop system for the treatment of type 1 diabetes: a real-world multicentre, prospective, single-arm trial in the Netherlands



Van Bon AC et al., Lancet Digit Health 2024 Apr;6(4):e272-e280

Bihormonal fully closed-loop system for the treatment of type 1 diabetes: a real-world multicentre, prospective, single-arm trial in the Netherlands

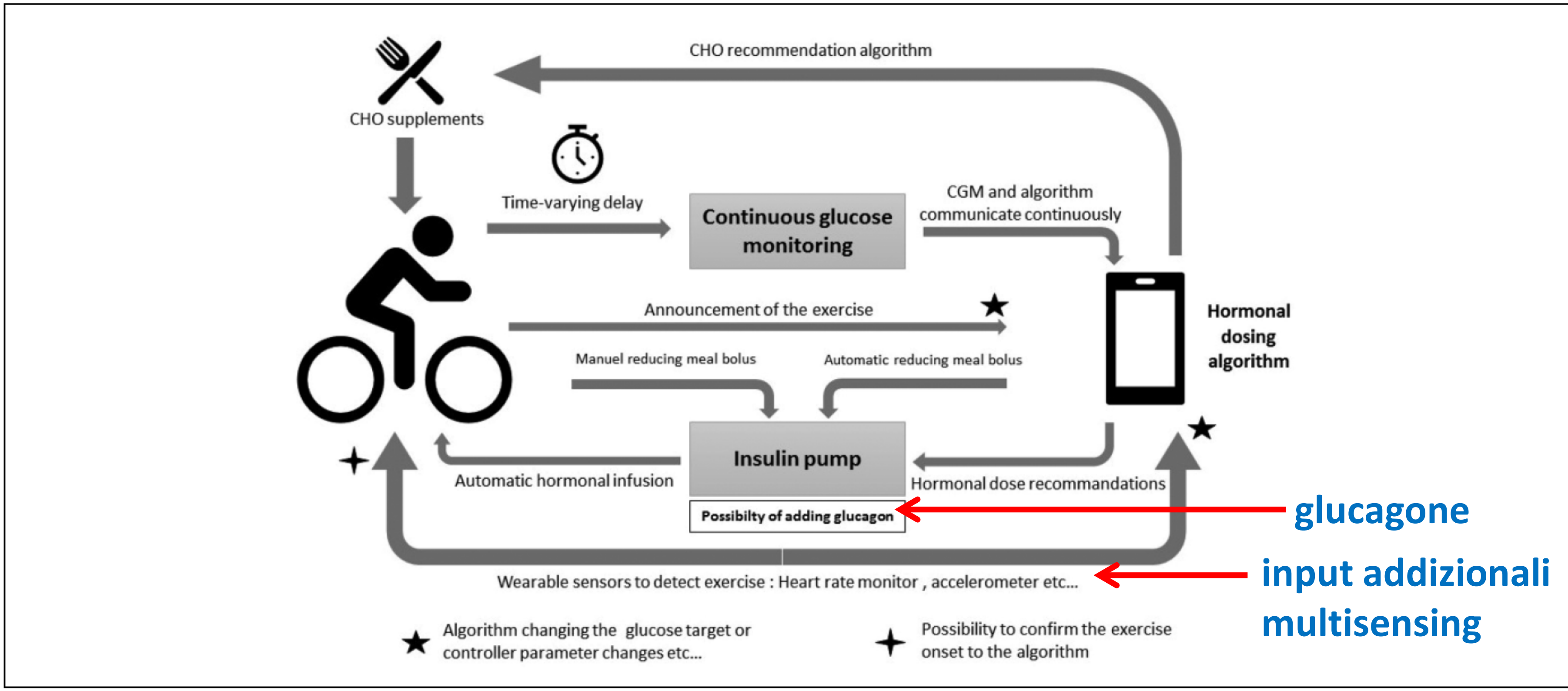




Van Bon AC et al., Lancet Digit Health 2024 Apr;6(4):e272-e280

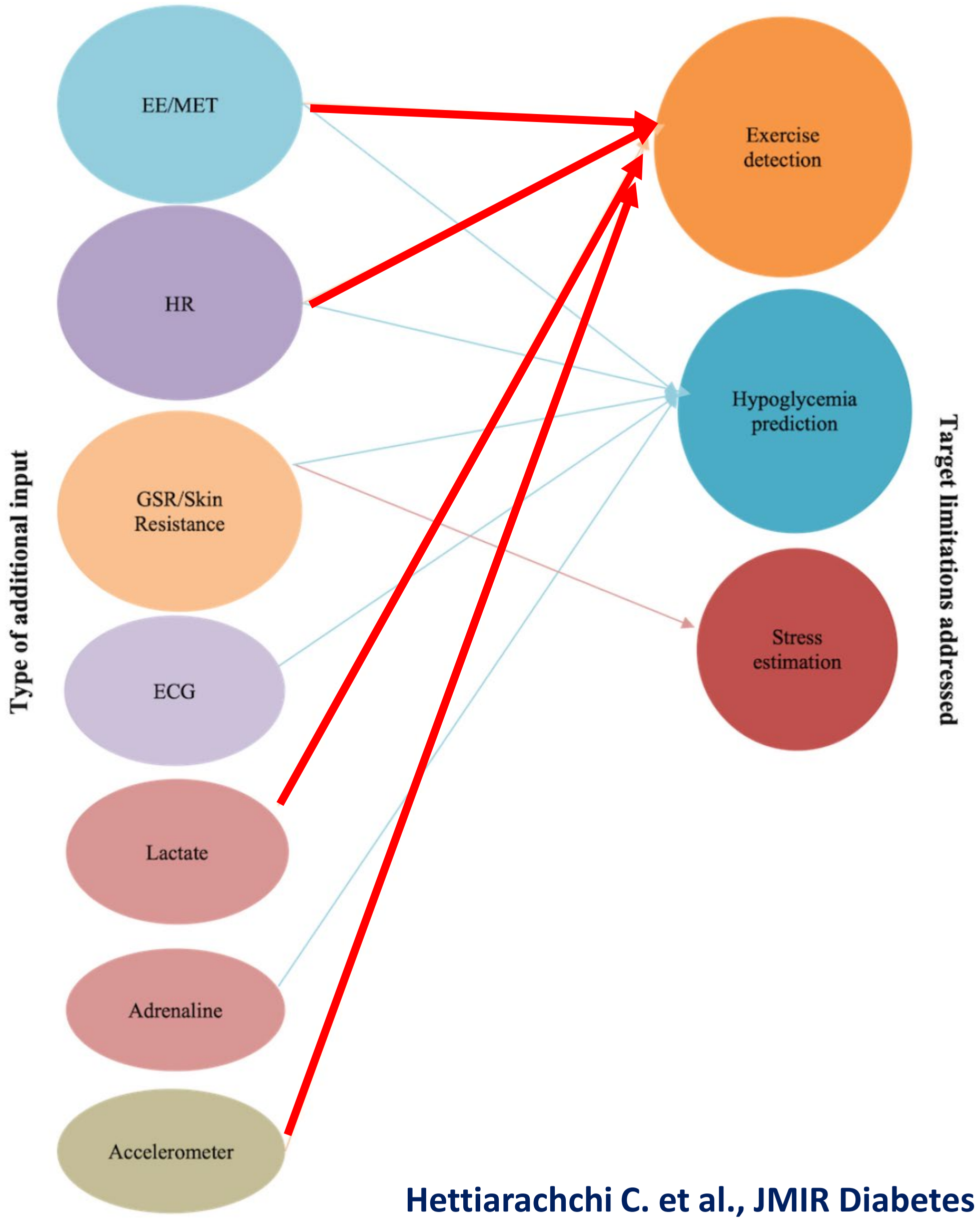
Sistemi AHCL: attività fisica

	M...780G	C... IQ	D...op	C.. APS	I... et O...od
Target glicemico attivita' fisica	150 mg/dL	140 – 160 mg/dL	Incremento target glicemico e soglie ipo- e iperglicemia (+70mg/dL)	Incremento target glicemico (+45 mg/dL)	150 mg/dL
Terminologia target attivita' fisica	Target temporaneo	Attività esercizio (possono essere creati fino a 6 profili personalizzati)	Attività fisica	Ease-off	Activity Feature
Informazioni addizionali	Durata programmabile; si disattiva al termine del periodo previsto	Avvio/termine manuali	Riduce aggressività sistema per 10 ore. Suggerisce assunzione CHO di emergenza.	Riduce aggressività sistema del 50%	Durata programmabile; si disattiva al termine del periodo previsto
	Boli automatici disabilitati.	Corregge iperglicemie in modo standard. Annulla attivita' sonno.	Programmare ora di inizio, durata, intensità (bassa, moderata, intensa)		Boli abilitati



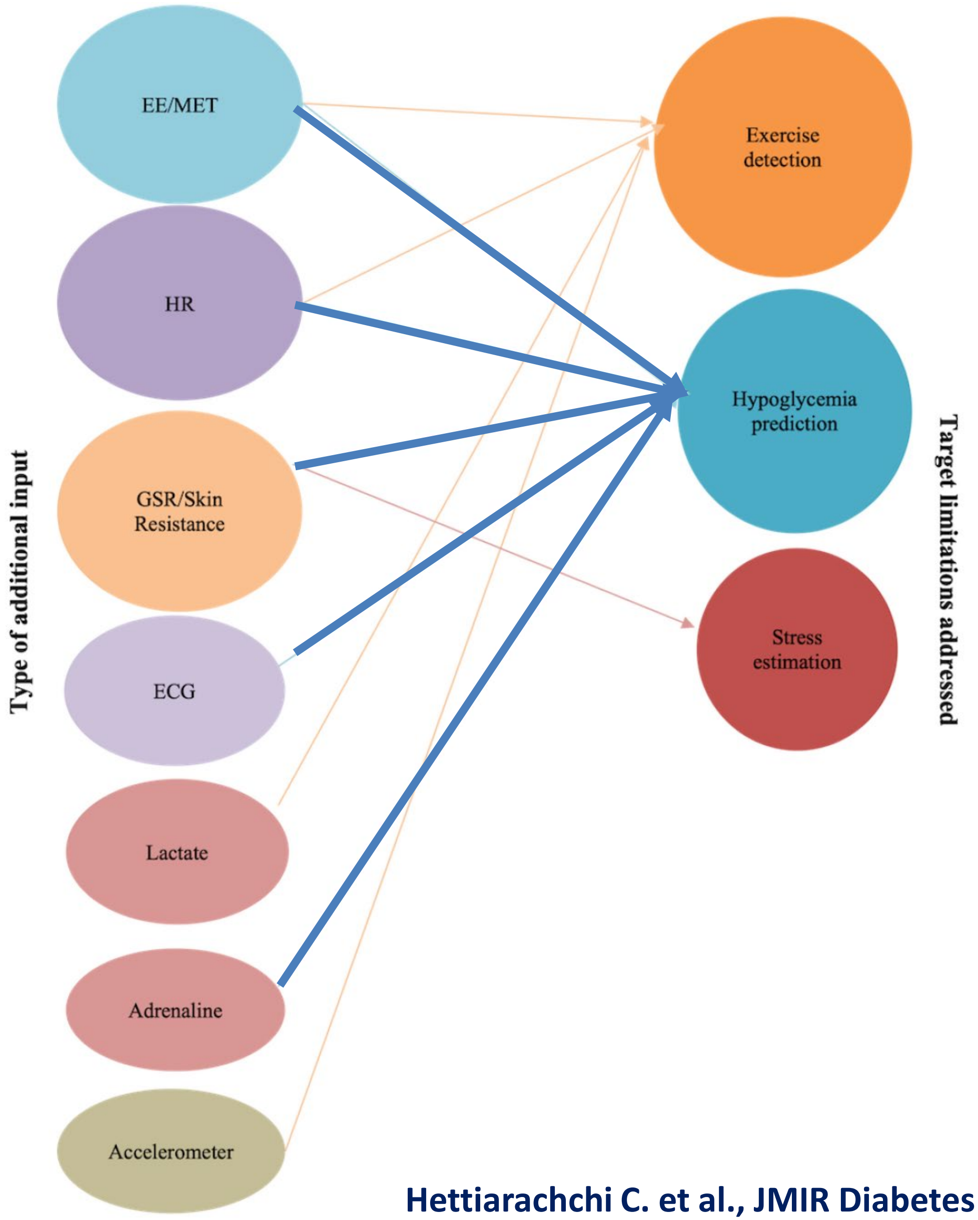
J Diabetes Sci Technol. 2019 Nov;13(6):1077-1090.

Multi-input APS



Hettiarachchi C. et al., JMIR Diabetes 2022 | vol. 7 | e28861

Multi-input APS



Hettiarachchi C. et al., JMIR Diabetes 2022 | vol. 7 | e28861

Integrating metabolic expenditure information from wearable fitness sensors into an AI-augmented automated insulin delivery system: a randomised clinical trial

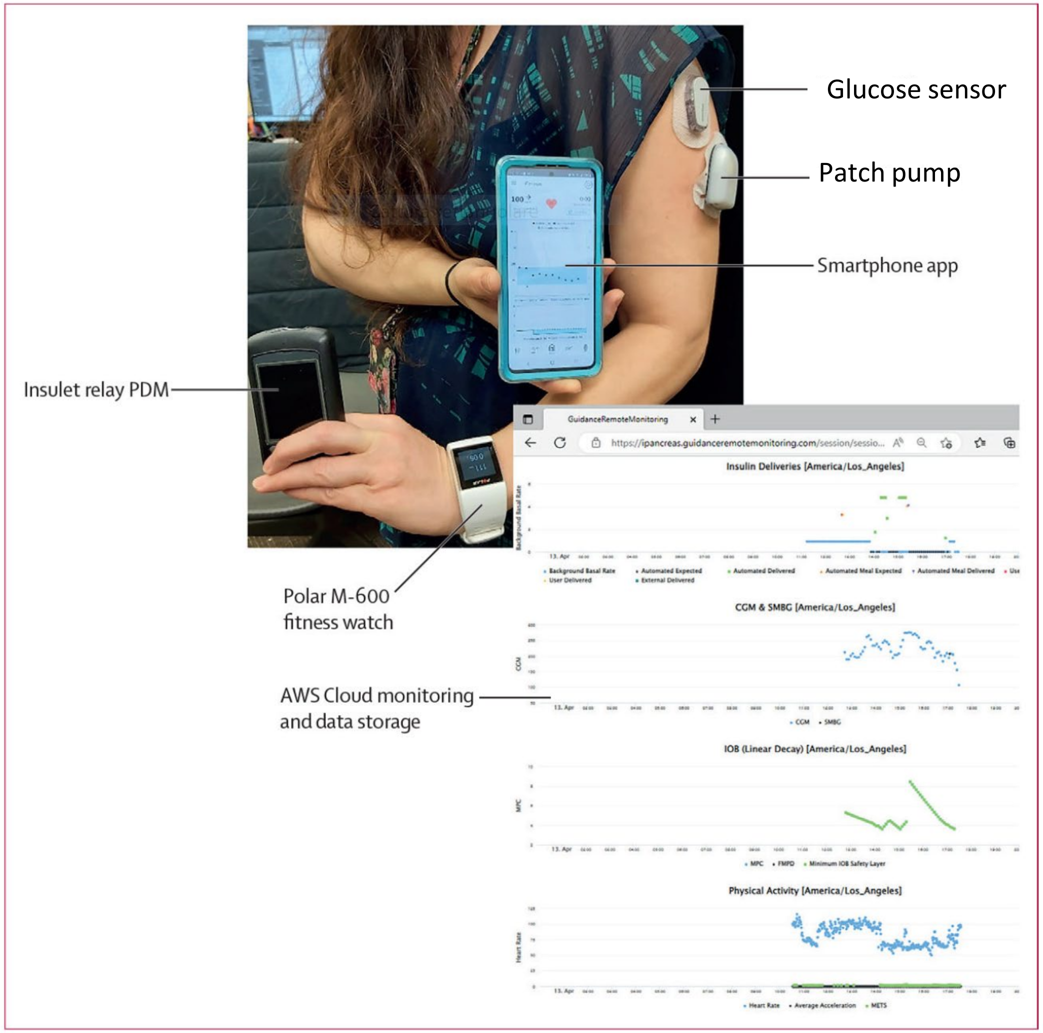
- Studio crossover, randomizzato, non in cieco su 27 adulti con DMT1
- Durata: 2 periodi di 76 ore utilizzando :

- un AID con **algoritmo proporzionale derivativo adattivo (exAPD)** che rileva l'esercizio calcolando i MET. Se MET >4 chiede conferma all'utente dell’attività fisica e, se confermata, sospende l‘infusione di insulina durante l'esercizio

- un AID che, tramite un **algoritmo predittivo di controllo (ex MPC)** consapevole dell’attività fisica, automatizza gli aggiustamenti dell'insulina utilizzando dati di fitness in tempo reale (frequenza cardiaca ed accelerometro).

Jacobs PJ et al., ancet Digit Health. 2023 September ; 5(9): e607–e617.

Integrating metabolic expenditure information from wearable fitness sensors into an AI-augmented automated insulin delivery system: a randomised clinical trial



Jacobs PG et al., Lancet Digit Health. 2023 September ; 5(9): e607–e617.

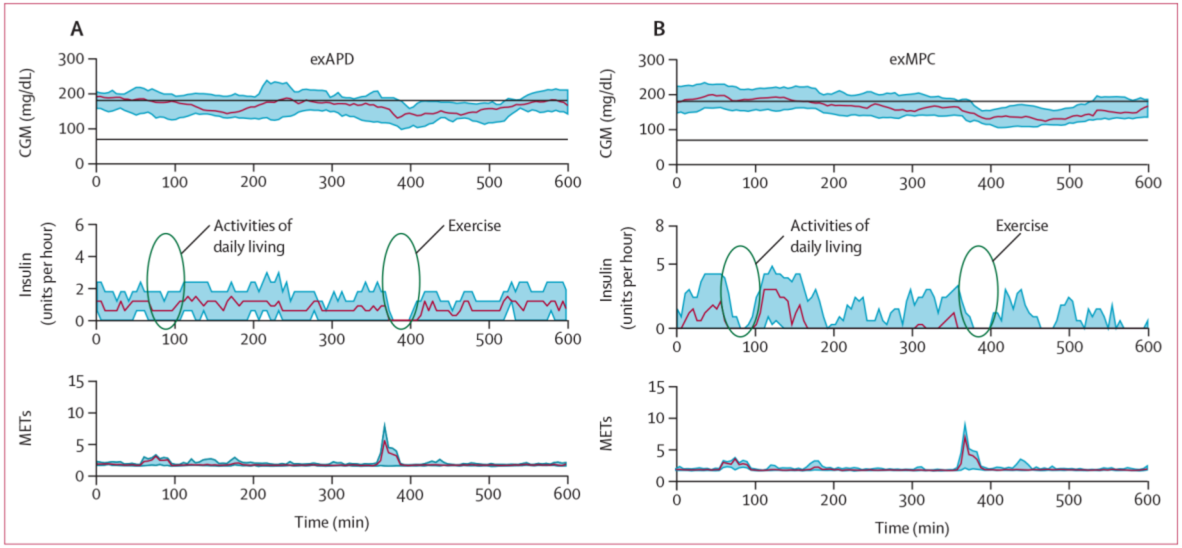


Figure 3: CGM data, insulin, and METs during the primary in-clinic session (0700–1900 h)

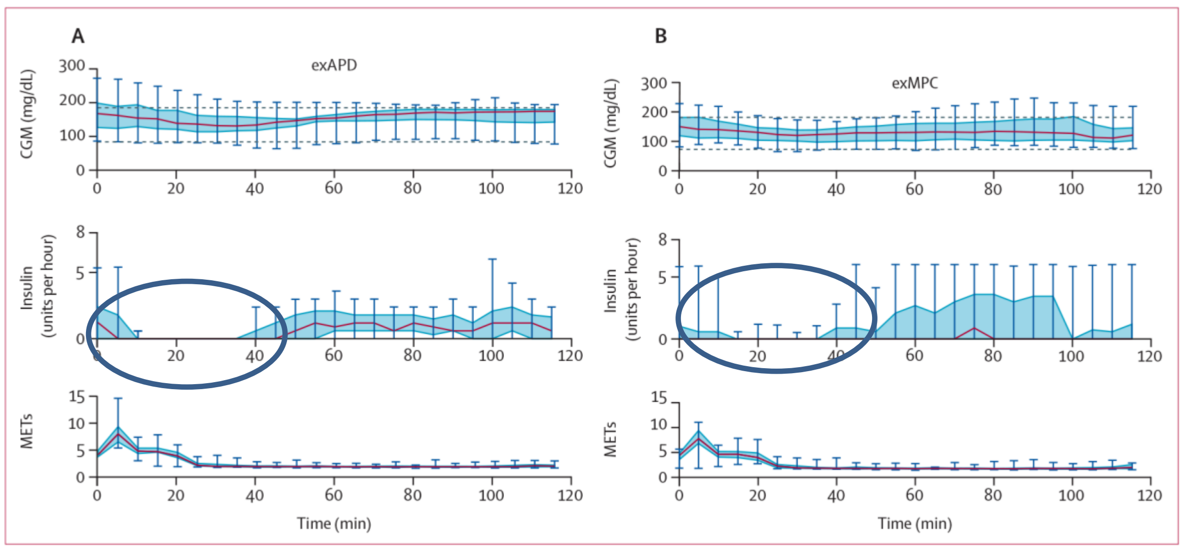


Figure 4: CGM data, insulin, and METs during the 2 h after the start of the primary in-clinic session structured exercise

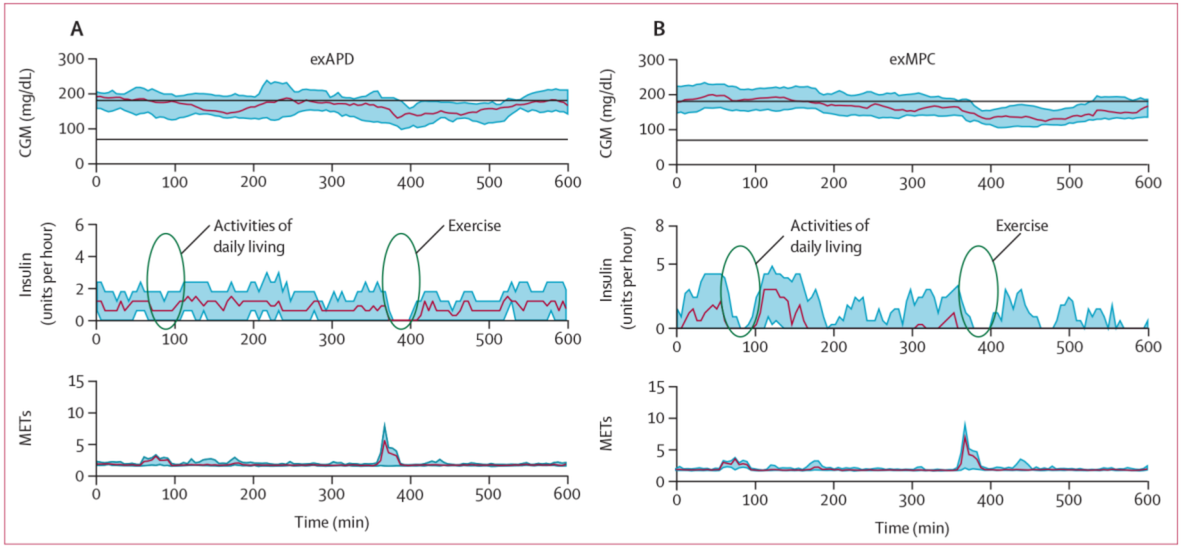


Figure 3: CGM data, insulin, and METs during the primary in-clinic session (0700–1900 h)

Table 2:

Outcome metrics comparing the exAPD algorithm versus the exMPC algorithm during the primary in-clinic session

	exAPD	exMPC	Difference	p value (exAPD *vs* exMPC)	p value (sequence)	p value (period)
% time below range (<3·9 mmol/L)*	2·5 (7·0)	1·3 (2·9)	−1·2 (7·3)	0·46	0·50	0·22
% time in range (3·9–10·0 mmol/L)	59·4 (23·1)	63·2 (23·9)	3·8 (29·8)	0·49	0·41	0·047
% high glucose (>10 mmol/L)	38·1 (21·4)	35·5 (24·4)	−2·6 (28·4)	0·63	0·34	0·012
% very low glucose (<3·0 mmol/L)	0·27 (0·87)	0	··	··	··	··
% very high glucose (>13·9 mmol/L)	8·0 (15·8)	7·5 (11·4)	−0·5 (16·0)	0·87	0·65	0·24
Mean glucose (mmol/L)	9·4 (1·6)	9·2 (1·6)	−0·2 (1·8)	0·63	0·59	0·15
Rescue carbohydrate (count)†	1·09 (2·16)	0·58 (0·93)	−0·51 (2·36)	0·33	0·31	0·33
Insulin (units)‡	21·2 (8·0)	21·4 (10·0)	0·3 (4·7)	0·94	0·60	0·60

Current Status and Emerging Options for Automated Insulin Delivery Systems

- **Continuous ketone monitoring**:
  - absolute insulin deficiency and DKA
  - fat burning in those attempting to lose weight.
- **Lactate sensing**:
  - prolonged activity/exercise
  - early indicator for severe illness.
- **Cortisol, epinephrine/norepinephrine, glucagon, and growth hormone concentrations**:
  - correlated with the current degree of insulin resistance
  - increase or decrease the aggressiveness of an AID controller to match current conditions.
- **Alcohol sensing**:
  - useful to predict changes in hepatic gluconeogenesis correlated basal rates
  - early alerts for impaired selfawareness.

Forlenza GP and Lal RA., Diabetes Technol Ther. 2022 May;24(5):362-371.

Continuous Ketone Monitoring

- I sistemi CKM misurano il beta-idrossibutirrato a livello dei fluidi interstiziali con metodica elettrochimica simile a quella dei sensori per il glucosio
- L'integrazione del CKM all'algoritmo di un sistema AID permetterebbe di identificare condizioni di imminente chetoacidosi quali:

- interruzione dell'infusione insulinica
- malattie intercorrenti

Huang J et al., J Diabetes Sci Technol. 2024, 18: 714-726

Continuous Ketone Monitoring

Ketone monitoring system

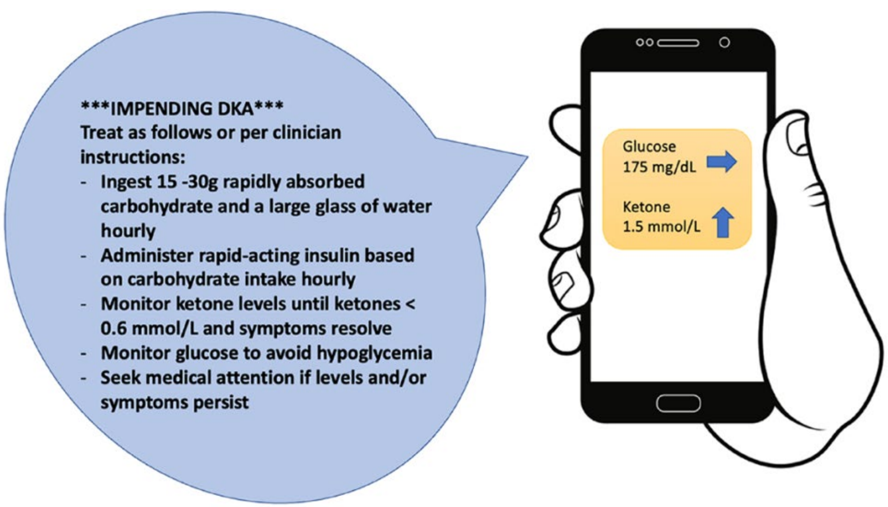
Glucose-ketone dual monitoring system

The Clinical Case for the Integration of a Ketone Sensor as Part of a Closed Loop Insulin Pump System

Esercizio fisico ad alta intensità (caratterizzato da glicemia bassa ma concomitante chetosi dovuta ad attivazione degli ormoni controregolatori).

Un sistema AID attuale sospenderebbe l'infusione insulinica, con peggioramento della chetosi.

Un algoritmo integrato con CKM suggerirebbe di assumere CHO senza interrompere l'infusione insulinica



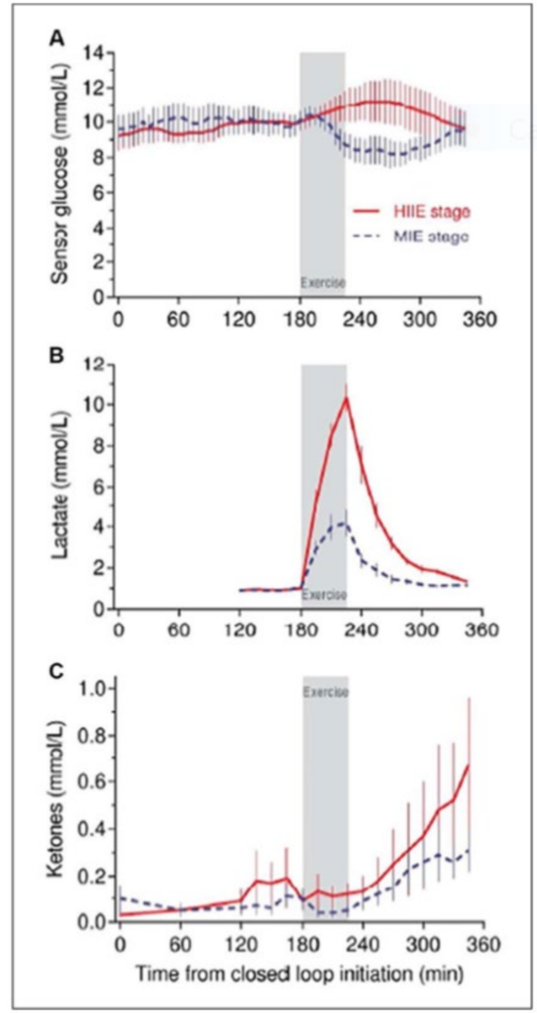
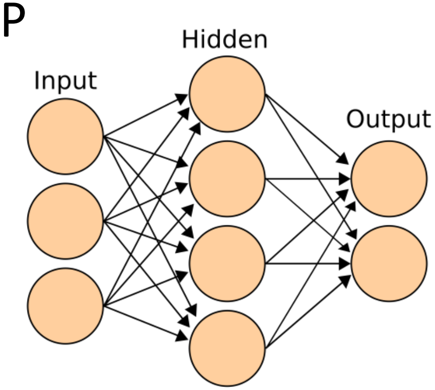


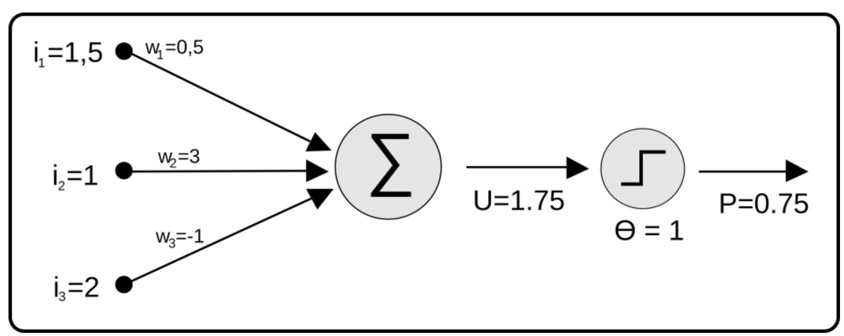
Figure 1. Biochemical profiles during CL with high-intensity exercise (HIIE) and moderate-intensity exercise (MIE) in participants with type 1 diabetes.[9]

Lee MH et al., J Diabetes Sci Technol. 2019 Sep;13(5):967-973

Neural-Net Artificial Pancreas: A Randomized Crossover Trial of a First-in-Class Automated Insulin Delivery Algorithm

- Codifica di un algoritmo AID in una rete neurale artificiale (Neural-Net Artificial Pancreas – NAP)
- 17 adulti con DMT1 che utilizzavano un sistema AID hanno eseguito due sessioni di 20 ore in hotel utilizzando il sistema NAP e l'algoritmo originale AID
- Risultati: NAP: TIR 86%, TBR 2%   AID originale: TIR 87%, TBR 1,8%
- La domanda computazionale (la quantità di potenza di calcolo, tempo e risorse necessarie per risolvere un problema) è risultata 6 volte inferiore con NAP





Kovatchev B et al., Diabetes Technol Ther. 2024 Jun;26(6):375-382

Take home messages

- I sistemi AHCL hanno dei limiti dovuti principalmente alla via di somministrazione sottocutanea dell’insulina e alla necessita’ di interventi manuali per i boli prandiali e per l’attività fisica
- I prototipi di sistemi fully closed-loop sono in grado di ridurre il peso della gestione del diabete, ma non hanno ancora dimostrato di poter conseguire le metriche glicemiche raccomandate
- Ulteriori progressi a breve termine potranno derivare da:

- sistemi fully closed-loop biormonali
- dall’aggiunta di input addizionali, che permetteranno all’algoritmo di controllo di identificare situazioni come l’attività fisica, l’ipoglicemia, la chetoacidosi
- dall’AI

- I sistemi di infusione automatica da soli non garantiscono il successo della terapia: rimane tuttora fondamentale il ruolo della persona (utilizzatore, team di cura).


Grazie per l'attenzione!