Verso un sistema integrato

Davide Brancato
UOC Medicina Interna
CRR Diabetologia e Impianto Microinfusori
Direttore: Vincenzo Provenzano
Ospedale Civico di Partinico (PA)

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti **indiretti** di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario: Novo Nordisk, IBSA.

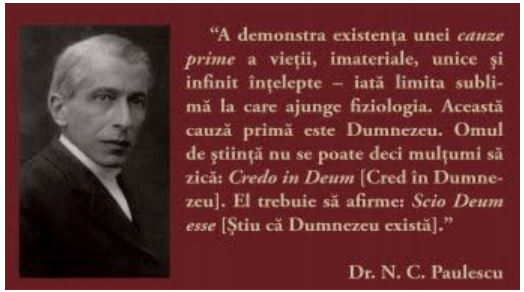
Agenda

- Sistema integrato: i fondamentali
- Dalla SAP al pancreas artificiale: quale evidenza scientifica ?
- Sistema integrato nella pratica clinica: quale, quando, come

La terapia del diabete mellito

Roma, 8-11 novembre 2018

ITALIAN CHAPTER

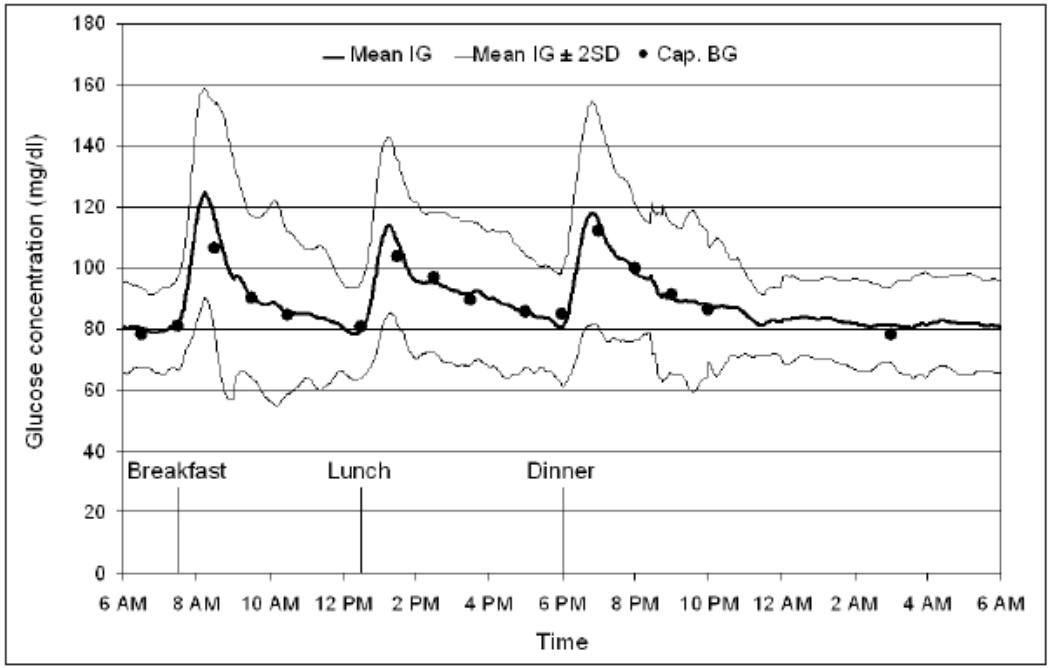


"…in using insulin it would of course be ideal if it could be supplied so as to imitate the natural process…"

J.J.R. Macleod and W.R. Campbell, 1925

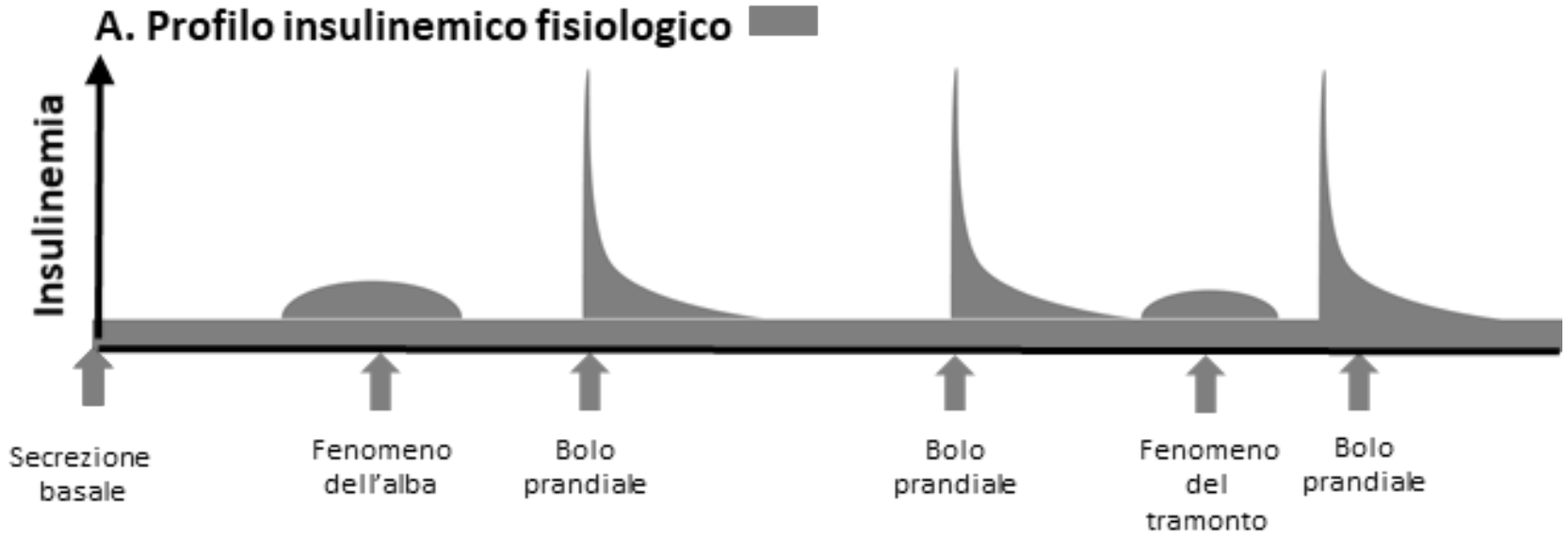
La terapia del diabete mellito dovrebbe mirare ad ottenere un profilo glicemico fisiologico…

Glycemic profiles of normal subjects



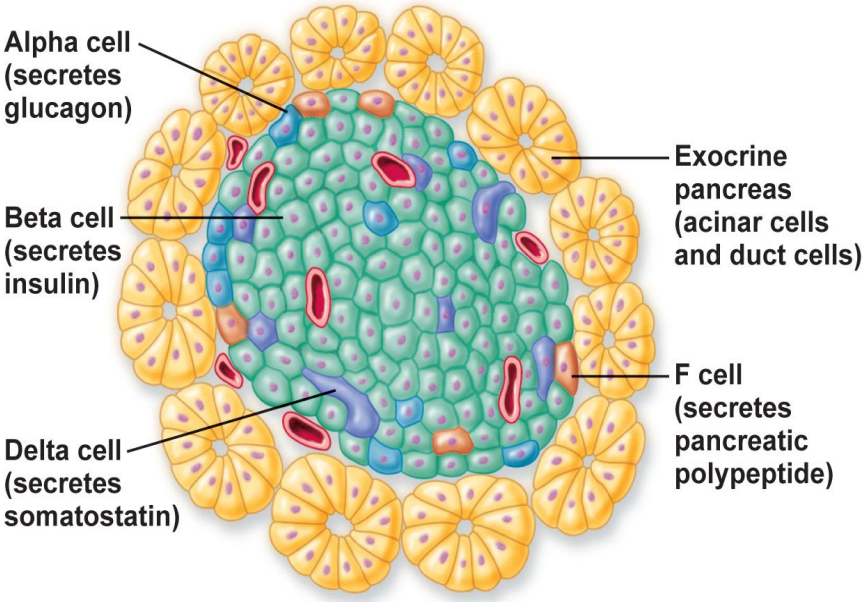
Freckmann G et al. J Diabetes Sci Technol 2007;1(5):695-703

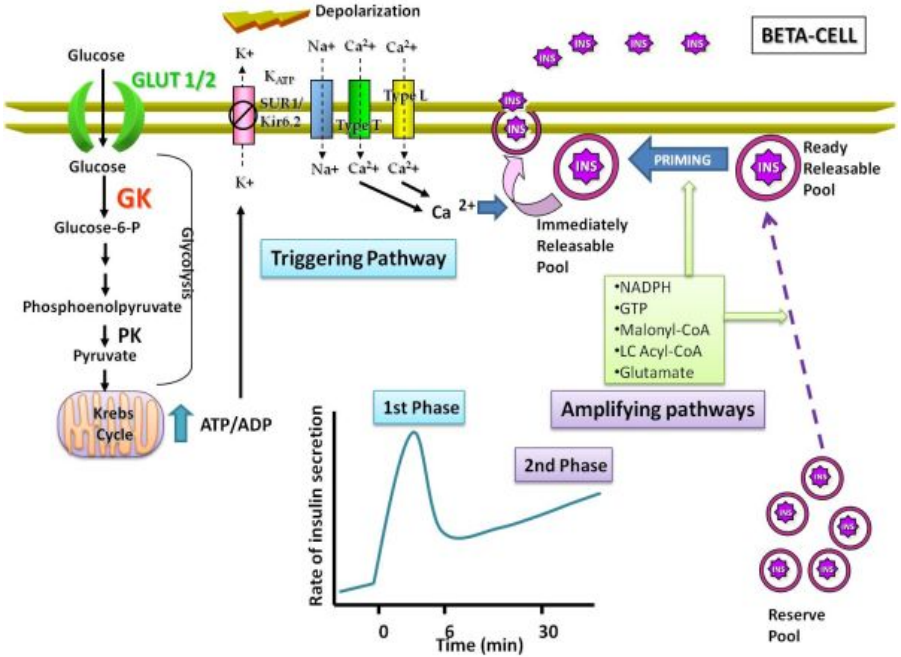
…attraverso un profilo insulinemico il più possibile fisiologico…



Brancato D, Provenzano V, ITJM 2018

...mimando il funzionamento del pancreas endocrino





Modello di funzionamento del pancreas endocrino e tecnologie sviluppate per imitarlo

Componenti funzionali del pancreas endocrino		Tecnologie sviluppate per imitare il pancreas endocrino	Componenti funzionali del pancreas artificiale
Sistema afferente	Glucosio circolante Altri nutrienti circolanti Incretine S. Nervoso Vegetativo	Gusto dell'urina Glicosuria Automonitoraggio glicemico **Sensore glicemico**	**Sensore glicemico**
Meccanismo integrante	Biochimica delle α e β cellule	Intelligenza umana **Microprocessore** **Algoritmi** Rete neurale	**Algoritmo di controllo**
Sistema effettore	Insulina Glucagone Altri ormoni	Siringhe, Penne, **Microinfusori**, Inalatori, Sistemi di Rilascio Orale, Infusione Intraperitoneale Insuline Animali, Umane ed Analoghi, Glucagone, Altri Ormoni	**Microinfusore mono o multi-ormonale**

Brancato D, Provenzano V, ITJM 2018

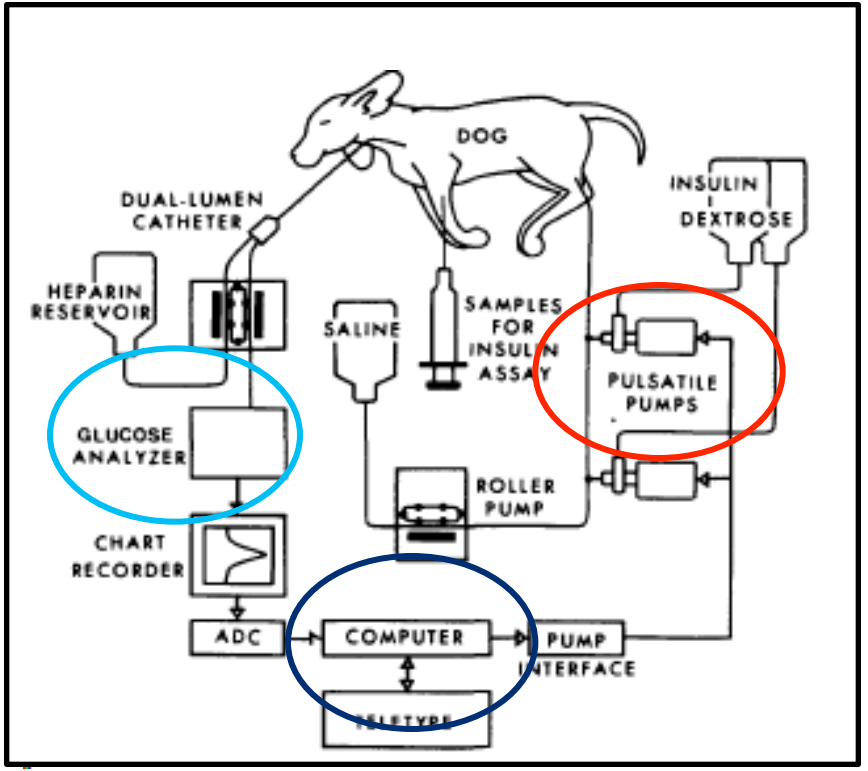
Il pancreas artificiale

An Artificial Endocrine Pancreas

A. M. Albisser, M.A.Sc., Ph.D., B. S. Leibel, M.Sc., M.D., T. G. Ewart, M.A.Sc., Z. Davidovac, M.D., C. K. Botz, M.A.Sc., and W. Zingg, M.Sc., M.D.,
Toronto, Ontario, Canada

DIABETES, VOL. 23, NO. 5 MAY, 1974

«... The normal pancreas secretes insulin as it is required within the normal range of blood sugars in order to prevent any changes beyond the physiological limits. A **computerized control system** has been devised which **closely simulates this particular endocrine function of the pancreas…**»

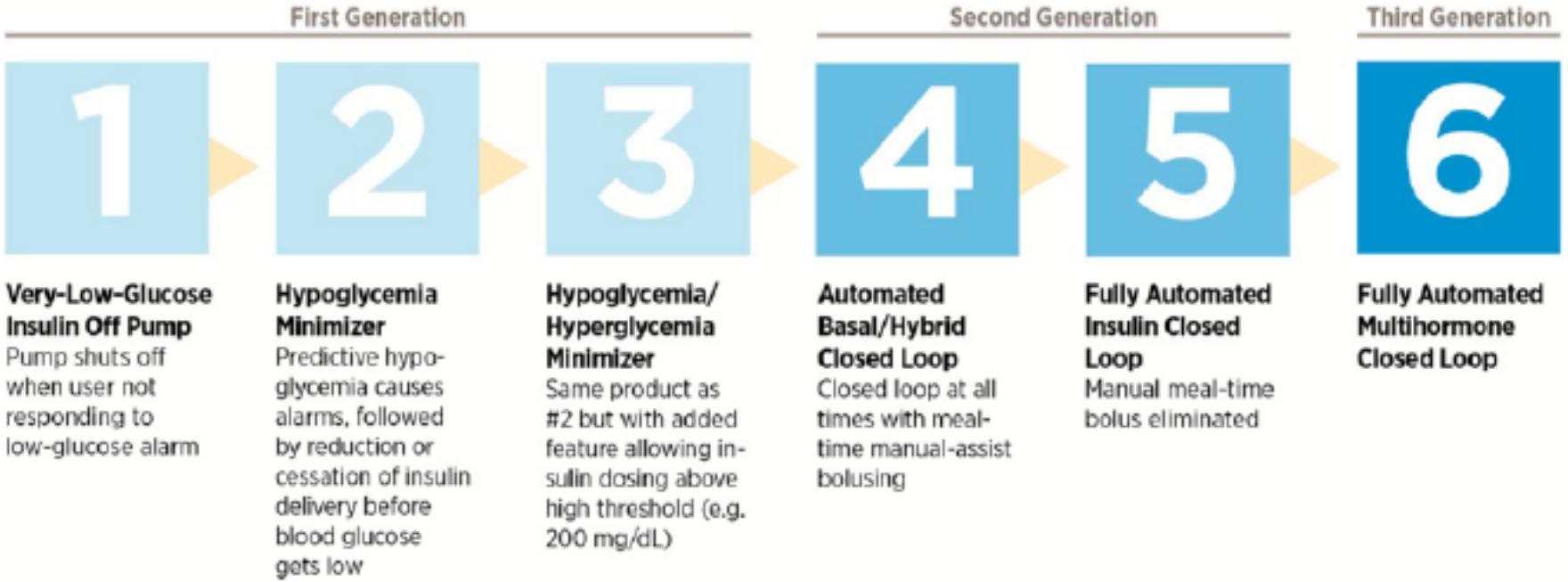


Sistema integrato: i fondamentali. Terminologia

Sigla		Caratteristica
SAP	Sensor Augmented Pump	Dati del sensore sul display della pompa
LGS	Low Glucose Suspend	Sospende automaticamente l'infusione insulinica quando i dati del sensore indicano glicemia < di una soglia
PLGS	Predictive Low Glucose Suspend	Sospende automaticamente l'infusione insulinica quando i dati del sensore prevedono glicemia < di una soglia
HHM	Hypoglycemia/Hyperglycemia Minimizer	Sospende automaticamente l'infusione insulinica quando i dati del sensore prevedono glicemia > di una soglia
HCL	Hybrid Closed Loop	Regola automaticamente l'infusione di insulina basale in funzione dei dati del sensore, ma necessita di intervento umano per i boli prandiali
CL	Closed Loop - Artificial Pancreas	Regola automaticamente l'infusione di insulina in funzione dei dati del sensore, senza alcun intervento umano

Mod. da Cohen O., et al. DTT 2016; 19: 379-380

Sistema integrato: i fondamentali. Step evolutivi



JDRF. Available at: http://jdrf.org/research/treat/artificial-pancreas-project/.

Sistema integrato: i fondamentali. Approcci ormonali

- **“Automated insulin-alone delivery” (AID)**, mono-ormonale

- **“Multi-hormone” (MH)**, multi-ormonale (eroga insulina + glucagone), mimando la fisiologia e la complementarietà di tali ormoni

Trevitt S, et al. J Diabetes Sci Technol. 2016; 10: 714-23.

Sistema integrato: i fondamentali. Algoritmi di controllo

- **“Model predictive control” (MPC)**: predicono la glicemia in uno specifico tempo del futuro prossimo (con possibilità di apprendimento ed adattamento all’impiego routinario del pz. e del clinico);
- **“Proportional integral derivative” (PID)**: rispondono alle misurazioni glicemiche ed alle relative variazioni;
- **“Fuzzy logic” (FL)**: calcolano le dosi insuliniche da infondere, imitando ciò che avrebbe fatto un clinico esperto basandosi sulle misurazioni ottenute dal CGM;
- **“Bio-inspired”**: basati su modelli matematici che mimano come le beta-cellule secernono l’insulina in funzione delle variazioni glicemiche.

Trevitt S, et al. J Diabetes Sci Technol. 2016; 10: 714-23.

Sistema integrato: i fondamentali.
Strategie per il raggiungimento dell'euglicemia

- **"Treat to range" (TTR)**: mirata a raggiungere e mantenere la glicemia entro un range personalizzato

- **"Treat to target" (TTT)**: mirata a mantenere la glicemia più vicino possibile ad un determinato valore

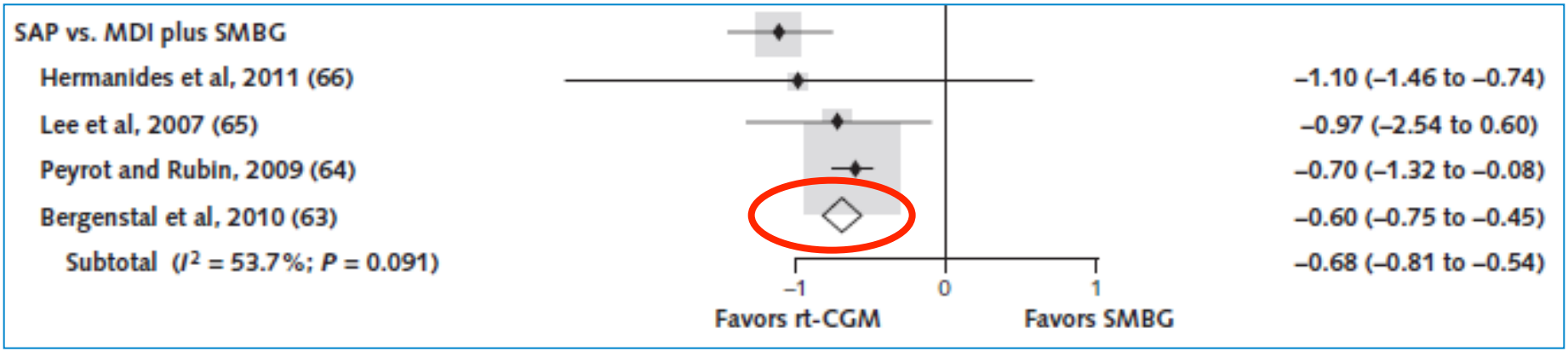
Trevitt S, et al. J Diabetes Sci Technol. 2016; 10: 714-23.

Agenda

- Sistema integrato: i fondamentali
- Dalla SAP al pancreas artificiale: quale evidenza scientifica ?
- Sistema integrato nella pratica clinica: quale, quando, come

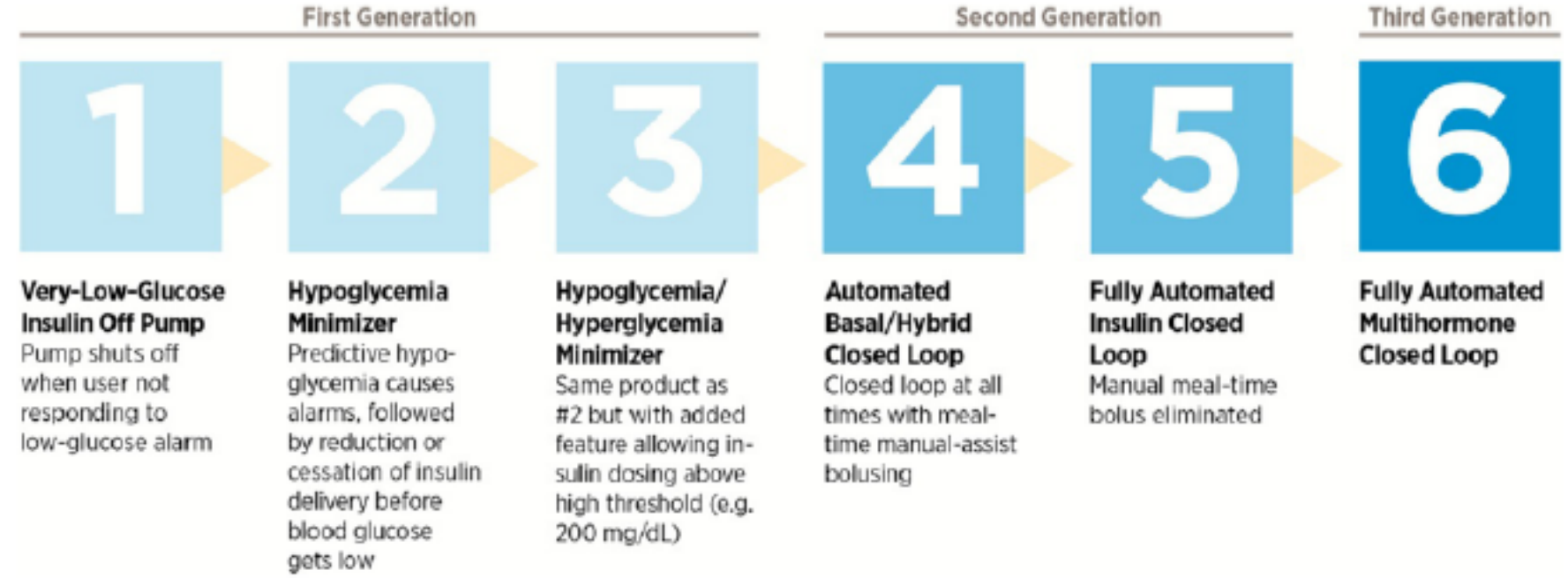
Sensor Augmented Pump (SAP)
Evidenza scientifica

La terapia con Sensor Augmented Pump nel DMT1 **riduce significativamente l'HBA1c** rispetto alla terapia multi-iniettiva (senza aumentare il rischio di ipoglicemie)



Yeh HC et al., Ann Intern Med. 2012;157:336-347

Step evolutivi



JDRF. Available at: http://jdrf.org/research/treat/artificial-pancreas-project/.

Step 1. Low Glucose Suspend (LGS)

Step	1
Name	LGS
Synonyms	Threshold suspend (TS)
Description	Insulin shuts off upon crossing preset threshold such as 70 mg/dL and resumes after 2 h
2015 status	Commercialized globally
Example of supporting data	Reduction in hypoglycemia, reduction in severe hypoglycemia, maintenance of A1C (29,43)

Kowalski A. Diabetes Care 2015;38:1036–1043

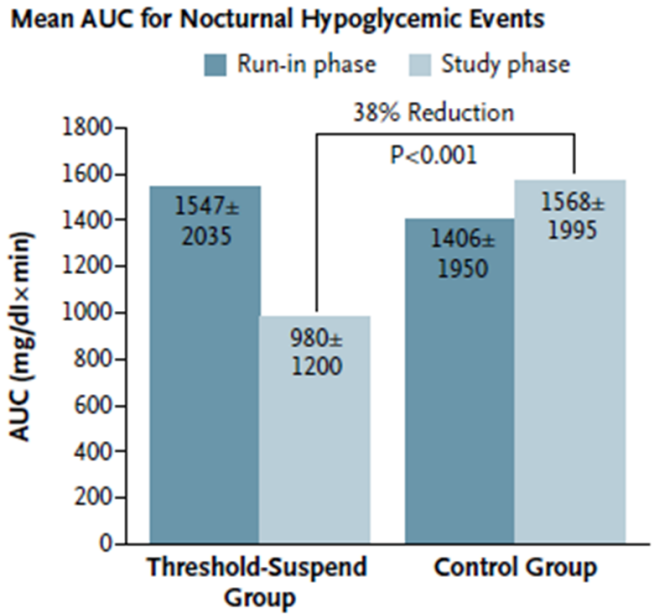
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*

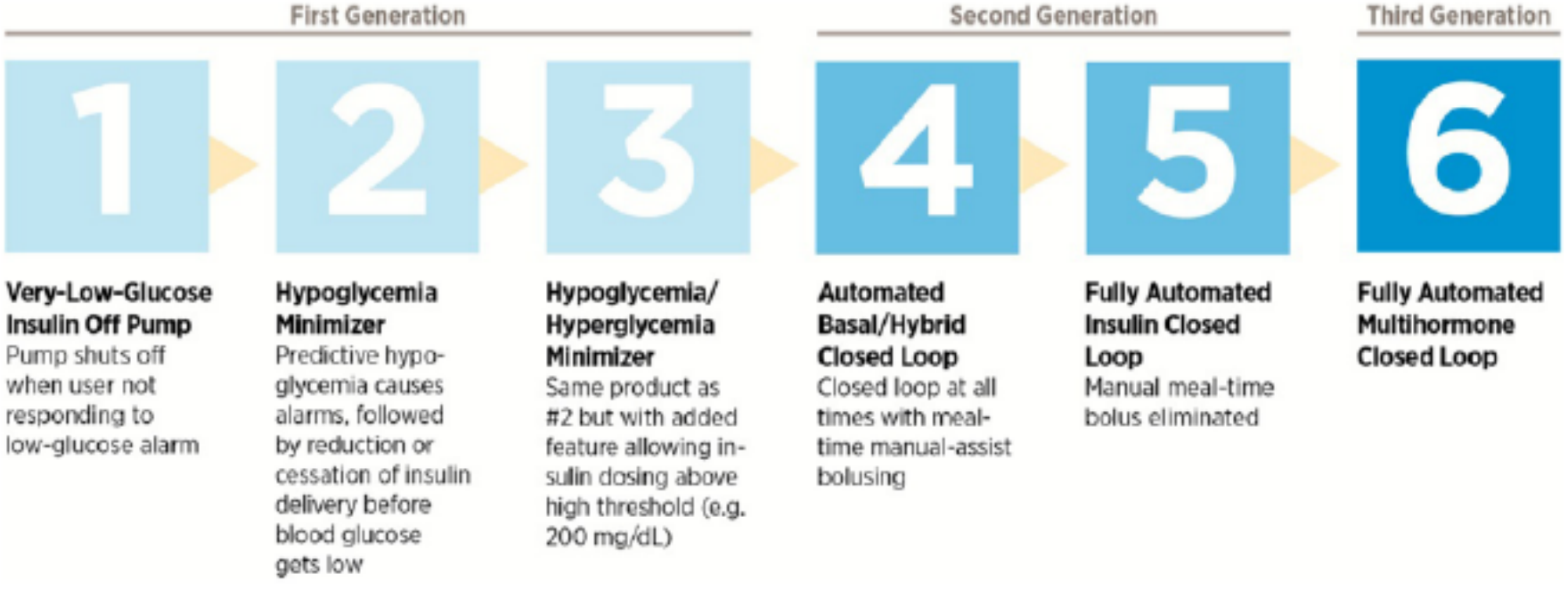
N ENGL J MED 369;3 NEJM.ORG JULY 18, 2013

RCT, T1D, 121 pt. con LGS vs 126 pt. con SAP

The mean AUC for nocturnal hypoglycemic events was 37.5% lower in the LGS group (P<0.001)



Step evolutivi



JDRF. Available at: http://jdrf.org/research/treat/artificial-pancreas-project/.

Step 2. Predictive Low Glucose Suspend (PLGS)

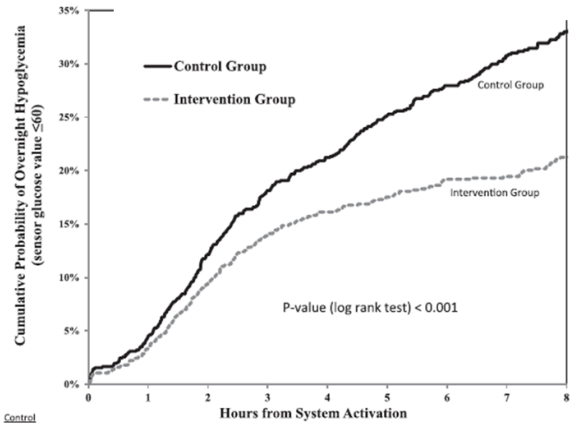
Step	2
Name	Predictive LGS (PLGS)
Synonyms	Predictive low-glucose management system (PLGM)
Description	Insulin shuts off or is attenuated upon prediction of impending hypoglycemia and resumes delivery when hypoglycemia risk is gone
2015 status	Regulatory approval outside U.S., commercial availability in Australia
Example of supporting data	Reduction in severe and moderate hypoglycemia (20,44)

Kowalski A. Diabetes Care 2015;38:1036–1043

A Randomized Trial of a Home System to Reduce Nocturnal Hypoglycemia in Type 1 Diabetes

Diabetes Care 2014;37:1885–1891 | DOI: 10.2337/dc13-2159

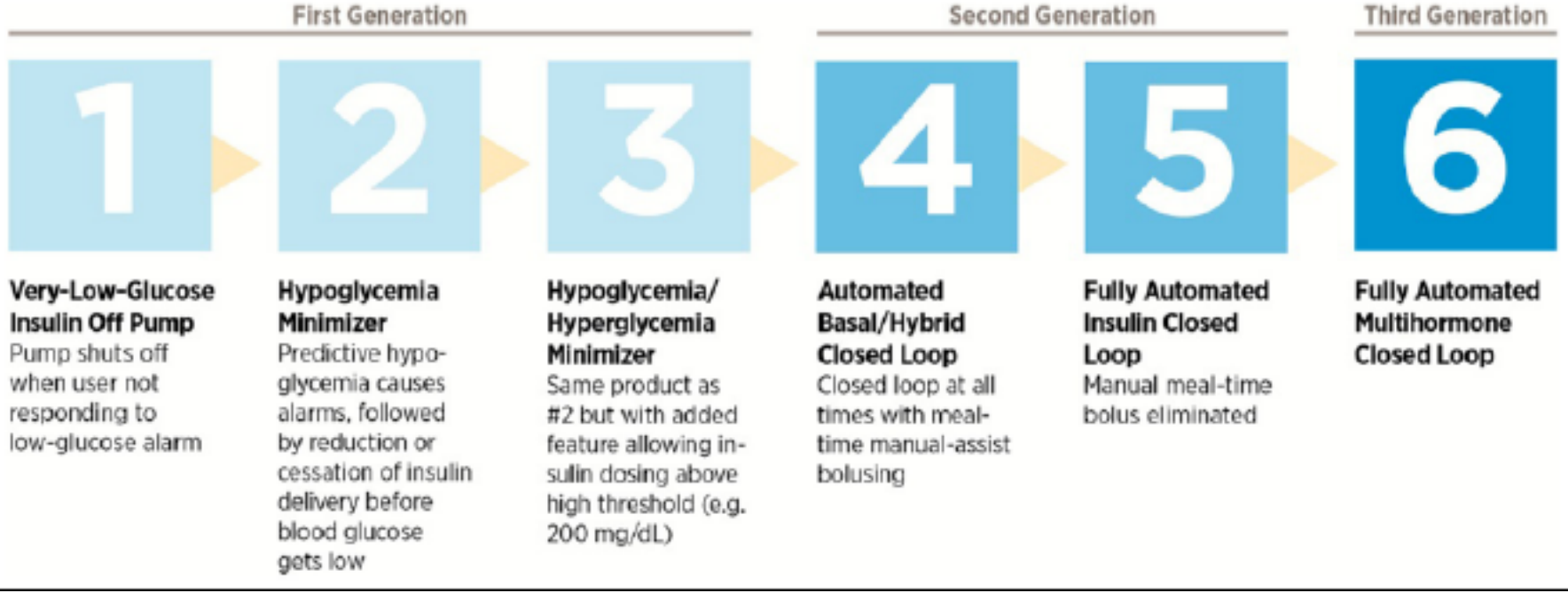
*David M. Maahs,[1] Peter Calhoun,[2] Bruce A. Buckingham,[3] H. Peter Chase,[1] Irene Hramiak,[4] John Lum,[2] Fraser Cameron,[5] B. Wayne Bequette,[5] Tandy Aye,[3] Terri Paul,[4] Robert Slover,[1] R. Paul Wadwa,[1] Darrell M. Wilson,[3] Craig Kollman,[2] and Roy W. Beck,[2] for the In Home Closed Loop Study Group**



45 pt. aged 15-45 years with T1D in which each night was assigned randomly to either having PLGS or SAP.

Overnight hypoglycemia with at least one CGM value ≤60 mg/dL occurred on 21% PLGS nights versus 33% SAP nights (P < 0.001).

Step evolutivi



JDRF. Available at: http://jdrf.org/research/treat/artificial-pancreas-project/.

Step 3. Hypoglycemia/Hyperglycemia Minimizer (HHM)

Step	3
Name	Hypoglycemia hyperglycemic minimizer (HHM)
Synonyms	Treat-to-range system (TTR)
Description	Same as step 2 but with automatic insulin dosing to reduce hyperglycemia exposure. Does not target euglycemia, rather the minimization of time spent above a certain threshold, i.e., 180 mg/dL
2015 status	In commercial development
Example of supporting data	Reduction in time spent hyperglycemic and hypoglycemic and increased time in target range in outpatient settings (45)

Kowalski A. Diabetes Care 2015;38:1036–1043

Closed-Loop Control Performance of the Hypoglycemia-Hyperglycemia Minimizer (HHM) System in a Feasibility Study

Journal of Diabetes Science and Technology
2014, Vol. 8(1) 35–42

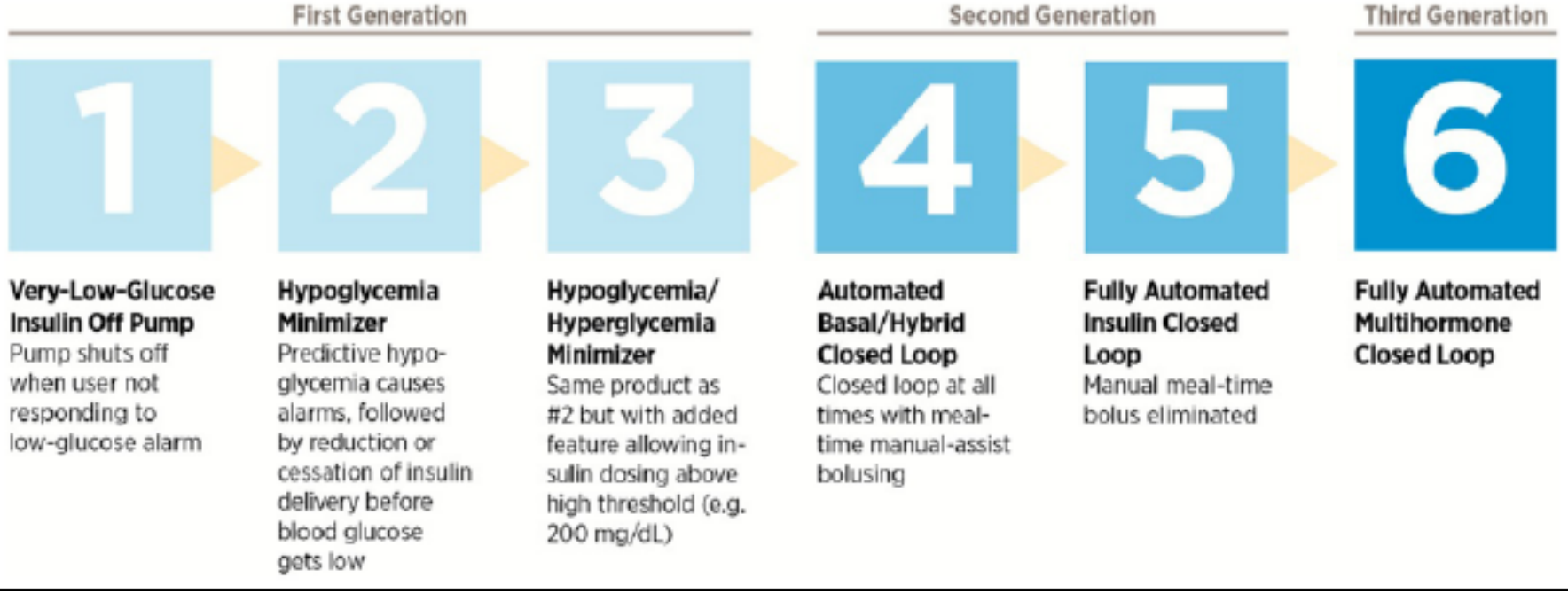
DOI: 10.1177/1932296813511730
dst.sagepub.com
SAGE

Daniel A. Finan, PhD[1], Thomas W. McCann Jr, MBA[1], Linda Mackowiak, MS[1], Eyal Dassau, PhD[2,3], Stephen D. Patek, PhD[4], Boris P. Kovatchev, PhD[4], Francis J. Doyle III, PhD[2,3], Howard Zisser, MD[2,3], Henry Anhalt, DO[1], and Ramakrishna Venugopalan, PhD[1]

nonrandomized, uncontrolled, 13 adults with T1D, using HHM for 20 h the predictive HHM System:

- **decreased insulin infusion rates** below preset basal rates in advance of below-zone excursions (CGM < 90 mg/dl), delivering 80.4% less insulin than basal during those excursions
- **increased insulin infusion rates** above preset basal rates during above-zone excursions (CGM > 140 mg/dl), delivering 39.9% more insulin than basal during those excursions.

Step evolutivi



JDRF. Available at: http://jdrf.org/research/treat/artificial-pancreas-project/.

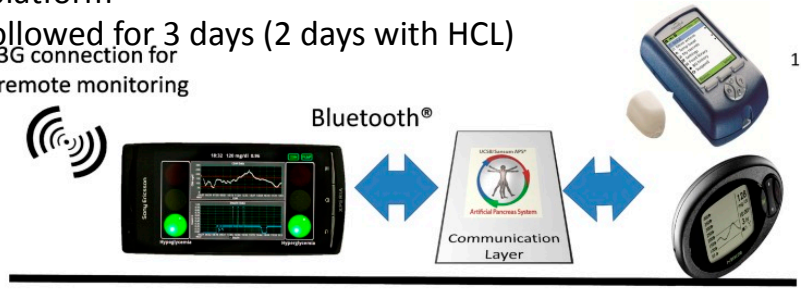
Step 4. Hybrid Closed Loop (HCL)

Step	4
Name	Hybrid closed loop (HCL)
Synonyms	Treat-to-target system (TTT)
Description	Algorithm aims for euglycemic target, not range, but relies on mealtime insulin bolus
2015 status	In commercial development
Example of supportin data	Reduction in time spent hyperglycemic and hypoglycemic and increased time in target range in outpatient settings (24,46)

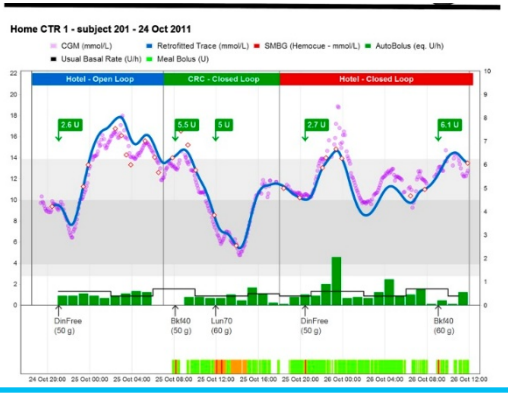
Kowalski A. Diabetes Care 2015;38:1036–1043

Observational study, first **outpatient** trial of a wearable AP based on a smartphone computational platform

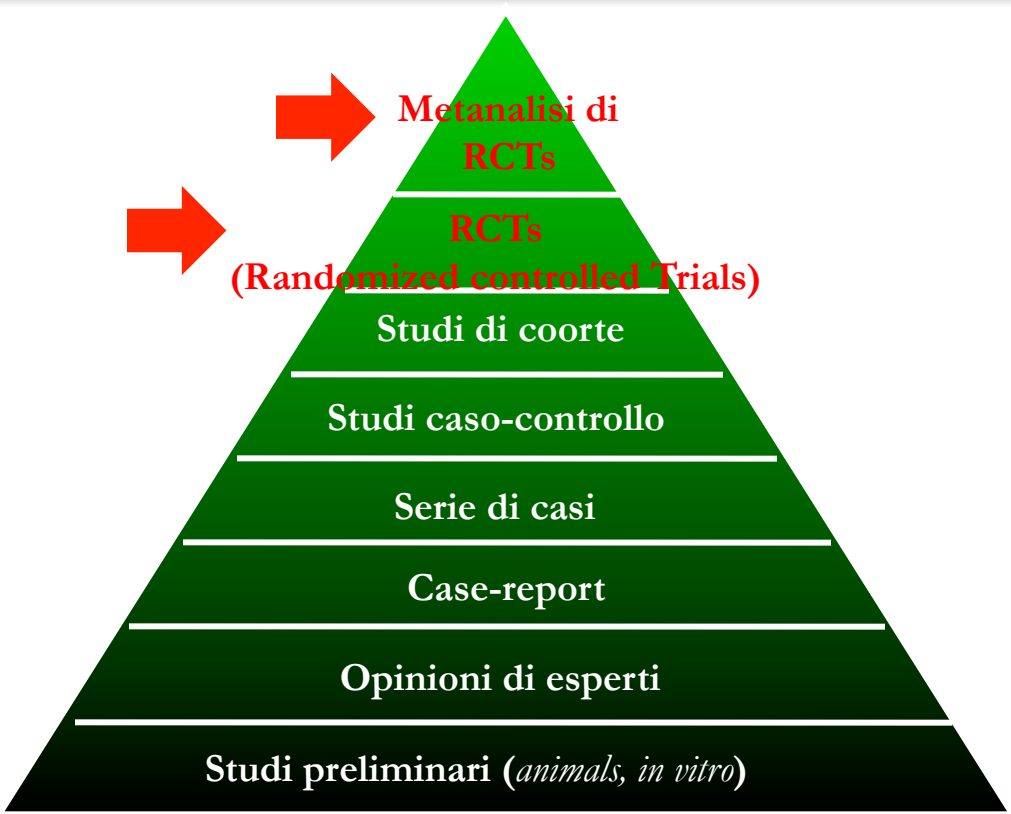
2 pt with T1D, followed for 3 days (2 days with HCL)



HCL avoided hypoglycemia (< 3.9 mmol/L)
and major hyperglycemia (> 15 mmol/L)
in both cases.



Quale evidenza: metanalisi di RCT e RCT

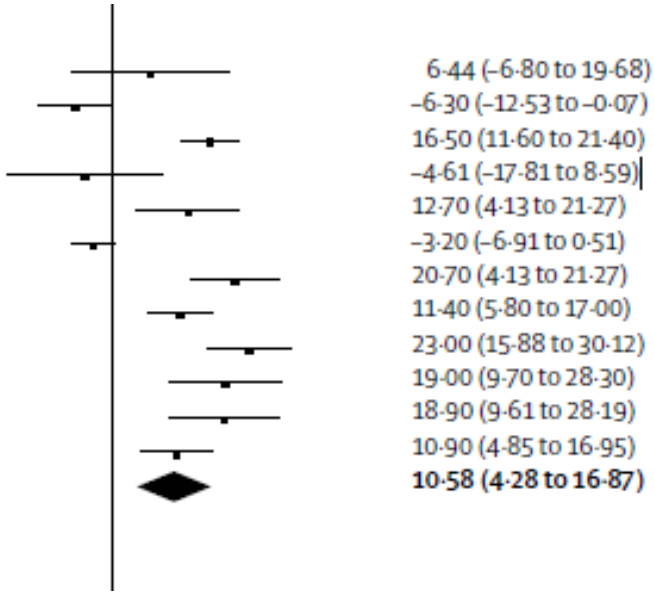


Step 4. Hybrid Closed Loop (HCL)

Metanalisi di 24 RCT, 585 partecipanti, SAP vs HCL, end point primario: **Time into target**

24 h						
De Bock et al (2015)‡[32]	67·41 (9·8)	8	60·97 (16·4)	8	3·0%	6·44 (–6·80 to 19·68)
Del Favero et al (2016)‡[33]	56·8 (13·5)	30	63·1 (11)	30	4·4%	–6·30 (–12·53 to –0·07)
El-Khatib et al (2017)†[34]	78·4 (6)	39	61·9 (14·4)	39	4·7%	16·50 (11·60 to 21·40)
Kovatchev et al (2014)‡[24]	66·13 (18·58)	18	70·74 (21·7)	18	3·0%	–4·61 (–17·81 to 8·59)
Leelarathna et al (2014)‡[37]	74·5 (13·19)	17	61·8 (12·3)	17	4·0%	12·70 (4·13 to 21·27)
Ly et al (2015)‡[39]	69·9 (3·3)	10	73·1 (5)	10	4·9%	–3·20 (–6·91 to 0·51)
Russell et al (2014 [adult])†[23]	79·5 (8·3)	20	58·8 (14·6)	20	4·2%	20·70 (4·13 to 21·27)
Russell et al (2014 [paediatric])†[23]	75·9 (7·9)	32	64·5 (14·1)	32	4·6%	11·40 (5·80 to 17·00)
Russell et al (2016)†[44]	80·6 (7·4)	19	57·6 (14)	19	4·3%	23·00 (15·88 to 30·12)
Tauschmann et al (2016 [p 1168])‡[46]	72 (13·33)	12	53 (9·63)	12	3·8%	19·00 (9·70 to 28·30)
Tauschmann et al (2016 [p 2019])‡[45]	66·6 (7·9)	12	47·7 (14·4)	12	3·8%	18·90 (9·61 to 28·19)
Thabit et al (2015 [adult])‡[27]	67·7 (10·6)	33	56·8 (14·2)	33	4·5%	10·90 (4·85 to 16·95)
Subtotal (95% CI)		**250**		**250**	**49·1%**	**10·58 (4·28 to 16·87)**

Heterogeneity: τ^2=106·65; χ^2=112·69, df=11 (p<0·0001); I^2=90%
Test for overall effect: Z=3·29 (p=0·0010)



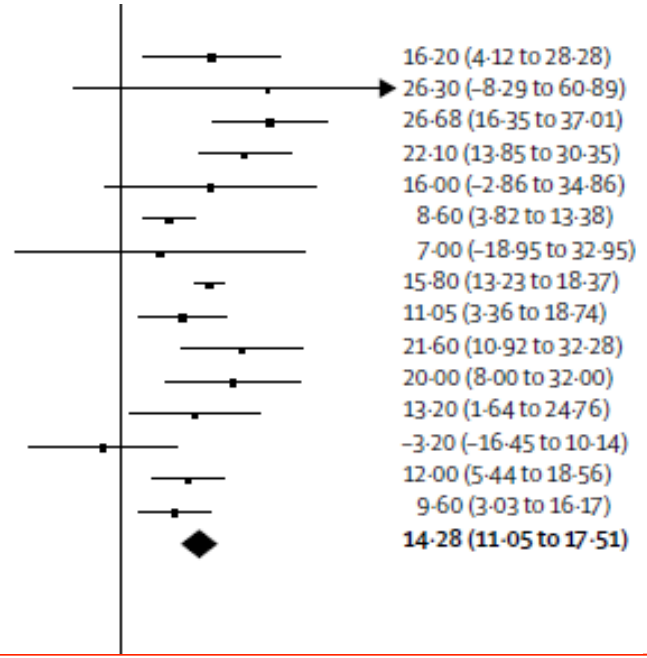
Con l'HCL aumenta significativamente il Time into Target (p < 0.0001) durante le 24 h,
indipendentemente da età, algoritmo di controllo, monitoraggio remoto, mono- multiormonalità

Step 4. Hybrid Closed Loop (HCL)

Metanalisi di 24 RCT, 585 partecipanti, SAP vs HCL, end point primario: **Time into target**

Overnight						
Blauw et al (2016)†[30]	84·7 (4·15)	10	68·5 (19·04)	10	3·2%	16·20 (4·12 to 28·28)
Brown et al (2015)‡[31]	85·4 (21)	19	59·1 (51·7)	19	0·9%	26·30 (–8·29 to 60·89)
Haidar et al (2015)§[28]	80·682 (12·86)	33	54 (27·41)	33	3·6%	26·68 (16·35 to 37·01)
Haidar et al (2016)§[29]	92·1 (14·4)	28	70 (17)	28	4·0%	22·10 (13·85 to 30·35)
Hovorka et al (2014)‡[35]	85 (19·3)	16	69 (33·3)	16	2·1%	16·00 (–2·86 to 34·86)
Kropff et al (2015)‡[36]	66·7 (10·1)	32	58·1 (9·4)	32	4·7%	8·60 (3·82 to 13·38)
Ly et al (2014)‡[38]	62 (42·96)	20	55 (40·74)	20	1·4%	7·00 (–18·95 to 32·95)
Ly et al (2016)‡[40]	66·4 (4·2)	21	50·6 (4·3)	21	5·0%	15·80 (13·23 to 18·37)
Nimri et al (2014)‡[41]	47·41 (15·36)	19	36·36 (7·51)	19	4·1%	11·05 (3·36 to 18·74)
Nimri et al (2014)‡[42]	87 (14)	15	65·4 (15·78)	15	3·5%	21·60 (10·92 to 32·28)
Phillip et al (2013)‡[43]	55 (36·11)	54	35 (26·85)	54	3·2%	20·00 (8·00 to 32·00)
Sharifi et al (2016 [adult])‡[26]	57·7 (18·6)	16	44·5 (14·5)	16	3·3%	13·20 (1·64 to 24·76)
Sharifi et al (2016 [paediatric])‡[26]	61·7 (17·6)	12	64·9 (15·7)	12	3·0%	–3·20 (–16·45 to 10·14)
Thabit et al (2014)‡[47]	73·2 (9)	24	61·2 (13·7)	24	4·4%	12·00 (5·44 to 18·56)
Thabit et al (2015 [paediatric])‡[27]	61·2 (11·9)	25	51·6 (11·8)	25	4·4%	9·60 (3·03 to 16·17)
Subtotal (95% CI)		**335**		**335**	**50·9%**	**14·28 (11·05 to 17·51)**

Heterogeneity: τ^2=16·28; χ^2=29·04, df=14 (p=0·01); I^2=52%
Test for overall effect: Z=8·67 (p<0·0001)



Con l'HCL aumenta significativamente il Time into Target (p < 0.0001) durante la notte,
indipendentemente da età, algoritmo di controllo, monitoraggio remoto, mono- multiormonalità

Step 4. Hybrid Closed Loop (HCL)

Metanalisi di 24 RCT, 585 partecipanti, SAP vs HCL, end point primario: **Time into target**

Con l'HCL si riduce significativamente ($p < 0.003$) il tempo in ipoglicemia, indipendentemente da:

- Età
- Periodo del giorno (overnight o 24 h)
- Algoritmo di controllo
- Mono- o multiormonalità

Step 4. Hybrid Closed Loop (HCL)

DIABETIC Medicine

DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

Invited Review

Psychosocial impacts of hybrid closed-loop systems in the management of diabetes: a review

Diabetes Technology & Therapeutics, VOL. 20, NO. 10 |

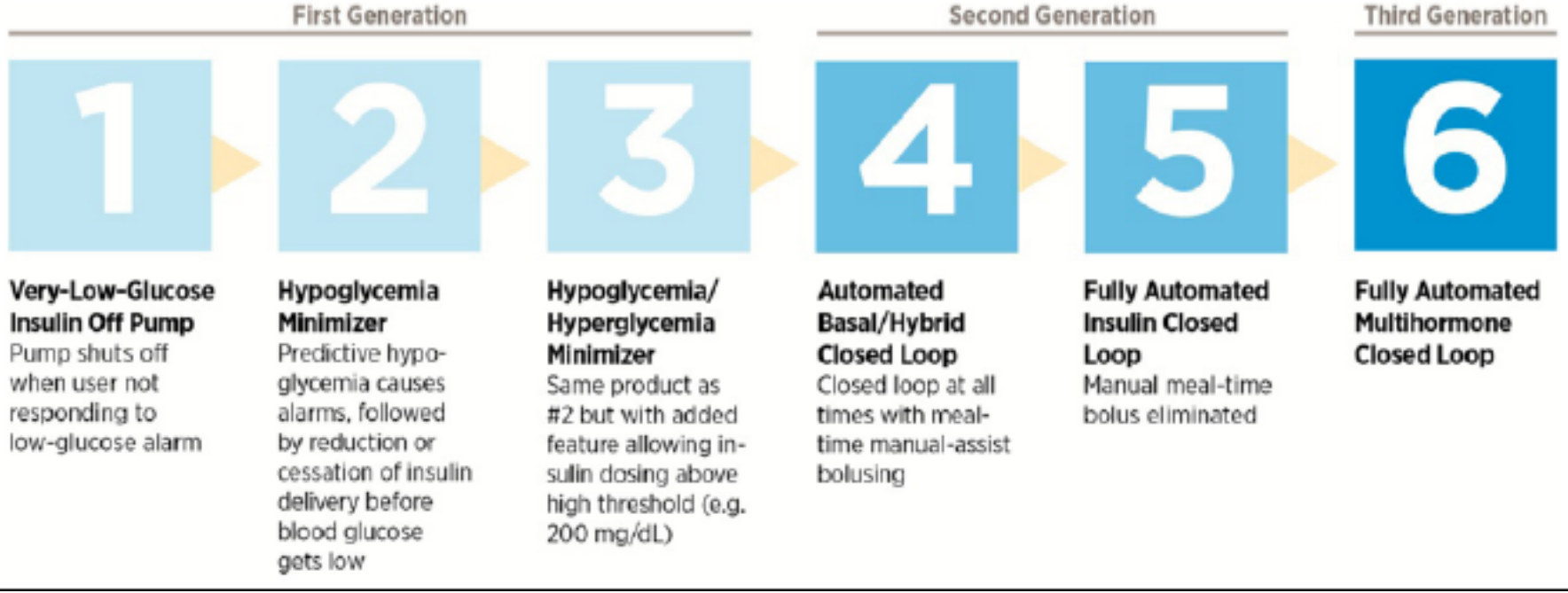
normal

Psychosocial and Human Factors During a Trial of a Hybrid Closed Loop System for Type 1 Diabetes Management

Rebecca N. Adams, Molly L. Tanenbaum, Sarah J. Hanes, Jodie M. Ambrosino, Trang T. Ly, David M. Maahs, Diana Naranjo, Natalie Walders-Abramson, Stuart A. Weinzimer, Bruce A. Buckingham, and Korey K. Hood

Published Online: 26 Sep 2018 | https://doi.org/10.1089/dia.2018.0174

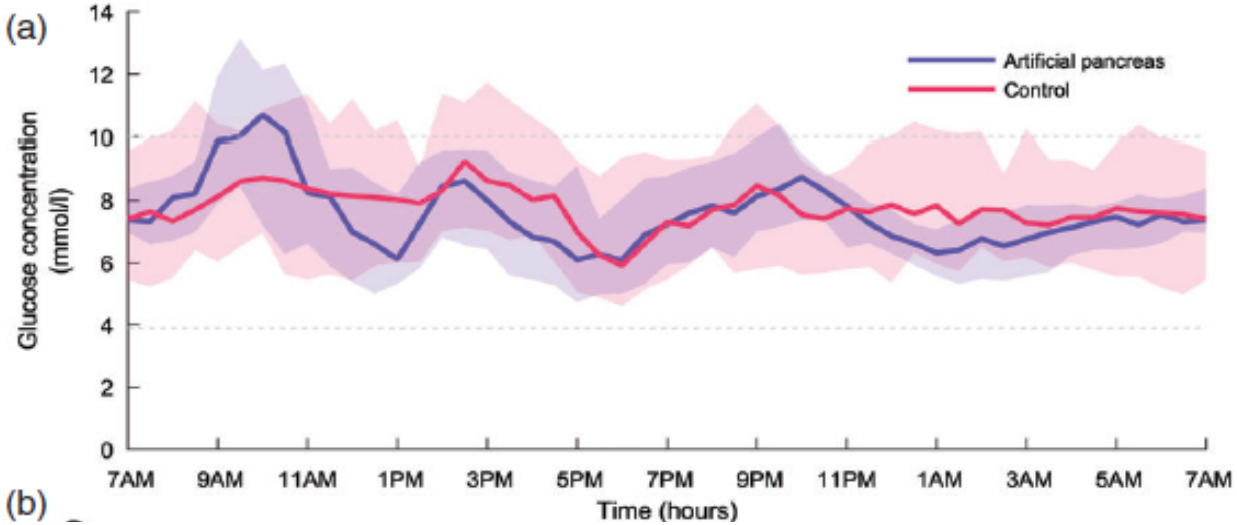
Step evolutivi



JDRF. Available at: http://jdrf.org/research/treat/artificial-pancreas-project/.

Step 5 e 6. Multihormone Closed Loop (CL)

RCT, 10 adults (**day and night**) with T1D, each 1 day at clinical research center + 3 days at home, CL vs CSII



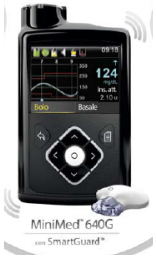
The time spent in euglycaemia (3.9–10 mmol/l) was longer during use of the artificial pancreas than CSII (p=0.007). Time in hypoglycaemia was not different (p=0.139).

Blauw H., et al. Diabetes, Obesity and Metabolism 18: 671–677, 2016.

Agenda

- Sistema integrato: i fondamentali
- Dalla SAP al pancreas artificiale: quale evidenza scientifica ?
- Sistema integrato nella pratica clinica: quale, quando, come

PLGS: MiniMed 640G



Studio osservazionale retrospettivo, MiniMed 640G system users (n = 4818), MiniMed 530G system users (n = 39,219), and MiniMed Paradigm Veo system users (n = 43,193)

TABLE 2. DURATION OF NIGHTTIME HYPOGLYCEMIA

	MiniMed Paradigm Veo		*MiniMed 530G*		*MiniMed 640G*	
Setting	*Suspend on low OFF*	*Suspend on low ON*	*Suspend on low OFF*	*Suspend on low ON*	*Suspend before low OFF*	*Suspend before low ON*
Hypoglycemia, hours/night, Mean ± SD	0.4 ± 0.8	0.2 ± 0.5	0.4 ± 1.0	0.2 ± 0.4	0.4 ± 1.0	0.1 ± 0.3
	$P < 0.001$		$P < 0.001$		$P < 0.001$	
Users, *N*	24,715	30,785	13,166	34,402	1230	4480

Night time = 8:00 PM–8:00 AM. Hypoglycemia was defined as ≤70 mg/dL (3.9 mmol/L).

Days in which the 'PLGS feature was enabled had lower percentages of hypoglycemia readings (< 70 mg/dL) or hyperglycemia (>240 mg/dL) than days when it was not enabled (P < 0.001 for each).

Users who switched from the MiniMed Paradigm Veo system to the MiniMed 640G system had fewer excursions below 70 mg/dL (P < 0.001) and over 240 mg/dL (P < 0.001).

Roma, 8-11 novembre 2018

PLGS: Tandem Diabetes Care t:slim X2 pump + Basal-IQ + Dexcom G5

ITALIAN CHAPTER

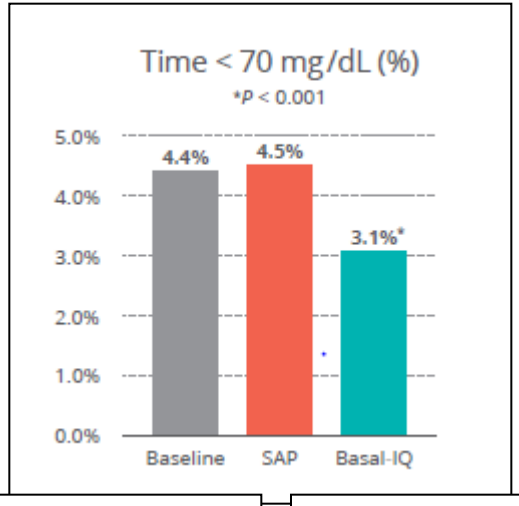
Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial

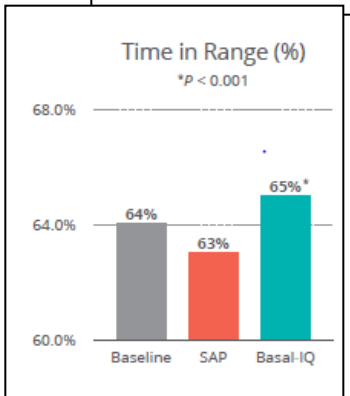
Gregory P. Forlenza[1], Zoey Li[2], Bruce A. Buckingham[3], Jordan E. Pinsker[4], Eda Cengiz[5], R. Paul Wadwa[1], Laya Ekhlaspour[3], Mei Mei Church[4], Stuart A. Weinzimer[5], Emily Jost[1], Tatiana Marcal[3], Camille Andre[4], Lori Carria[5], Vance Swanson[6], John W. Lum[2]⇑, Craig Kollman[2], William Woodall[2] **and** Roy W. Beck[2]

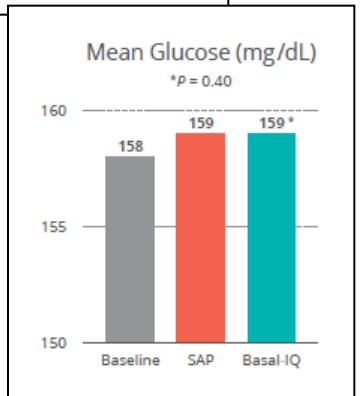
+ Author Affiliations

Corresponding author: John W. Lum, jl_manuscripts@jaeb.org.

Diabetes Care 2018 Oct; 41(10): 2155-2161.
https://doi.org/10.2337/dc18-0771







The Tandem Diabetes Care Basal-IQ PLGS system **significantly reduced hypoglycemia without rebound hyperglycemia**

HCL: MiniMed 670G

RESEARCH LETTER

Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes

Not randomized study, 124 adolescents and adults, A1c < 10%, before with insulin pump, after with HCL

Table 1. Device-Related Adverse Events Among Patients Using Hybrid Closed-Loop Insulin Systems[a]

Adverse Event	No. of Events	
	Run-in Period[b]	Study Period[b]
Total	8	20
Skin irritation	3	1
Hyperglycemia	0	6
Rash	0	1
Severe hyperglycemia[c]		
Due to infusion set	5	6
Due to software or hardware issues	0	5
Due to sensor issues	0	1

Over 12 389 patient-days,
no episodes of severe hypoglycemia or ketoacidosis were observed.

Bergenstal RM,et al. JAMA 2016;316:1407–1408.

HCL: MiniMed 670G

News From the Food and Drug Administration

November 15, 2016

"Artificial Pancreas" Is Approved

Rebecca Voelker, MSJ

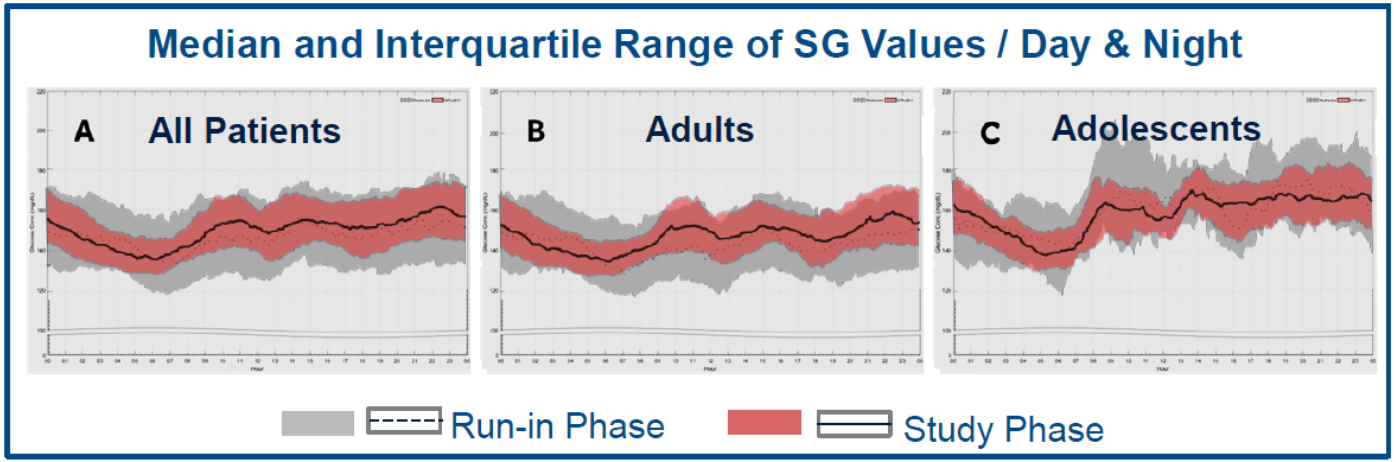
JAMA. 2016;316(19):1957. doi:10.1001/jama.2016.16344

A new device that automatically monitors blood glucose levels and adjusts insulin levels has received FDA approval. The device, manufactured by Dublin-based Medtronic PLC, is the first such system to gain the agency's blessing.

The new MiniMed 670G hybrid closed-loop system is intended for people aged 14 years or older who have type 1 diabetes. Because it operates with a smart algorithm that learns an individual's insulin needs and delivers appropriate basal doses 24 hours a day, little user input is required. Patients who use the system will only have to enter their mealtime carbohydrates, accept bolus correction recommendations, and periodically calibrate the sensor.

HCL: MiniMed 670G

Pivotal trial, 94 **adults** and 30 **adolescents** (**day and night**) with T1D, for **3 months** without HCL and, thereafter, with HCL



Hybrid closed loop resulted in:

- Increased time in range
- Reduced time spent low and high
- Reduced variability

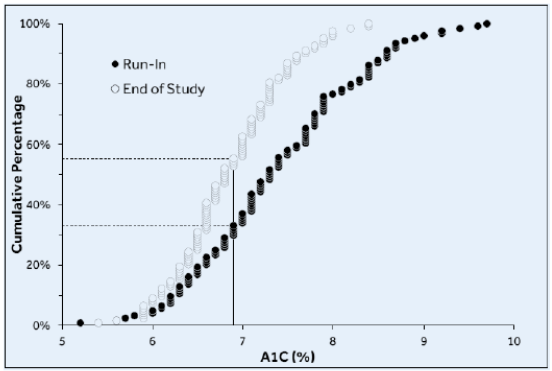
Garg SK, et al. Diabetes Technol Ther. 2017 Mar;19(3):155-163

HCL: MiniMed 670G

Pivotal trial, 94 **adults** and 30 **adolescents** (**day and night**) with T1D, for **3 months** without HCL and, thereafter, with HCL

Pivotal Trial A1C Results

- A1C baseline run-in = 7.4±0.9%
- A1C at study end = 6.9±0.6%
- A1C change = -0.5% (*p*<0.001)



A1C range	Run-in: *n* (%)	Study end: *n* (%)	Mean Δ A1C
< 7.0%	41 (33.1%)	68 (55.3%)	-0.1%
7.0 to 7.5%	31 (25.0%)	39 (31.7%)	-0.3%
> 7.5%	52 (41.9%)	16 (13.0%)	-1.0%

Garg SK, et al. Diabetes Technol Ther. 2017 Mar;19(3):155-163

HCL: MiniMed 670G

BMJ Open

Effect of 6 months of hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol

Sybil A McAuley,[1,2] Martin I de Bock,[3,4,5] Vijaya Sundararajan,[1] Melissa H Lee,[1,2] Barbora Paldus,[1] Geoff R Ambler,[6] Leon A Bach,[7,8] Morton G Burt,[9,10] Fergus J Cameron,[11,12,13] Philip M Clarke,[14] Neale D Cohen,[15] Peter G Colman,[16] Elizabeth A Davis,[3,4,5] Jan M Fairchild,[17] Christel Hendrieckx,[18,19] D Jane Holmes-Walker,[20,21] Jodie C Horsburgh,[2] Alicia J Jenkins,[1,2,22] Joey Kaye,[23] Anthony C Keech,[22] Bruce R King,[24] Kavita Kumareswaran,[7,15] Richard J MacIsaac,[1,2] Roland W McCallum,[25] Jennifer A Nicholas,[3,4] Catriona Sims,[1] Jane Speight,[18,19] Stephen N Stranks,[9,10] Steven Trawley,[19,26] Glenn M Ward,[2,27] Sara Vogrin,[1] Timothy W Jones,[3,4] David N O'Neal[1,2]

McAuley SA, *et al. BMJ Open* 2018;**8**:e020274. doi:10.1136/bmjopen-2017-020274

HCL: MiniMed 670G

Diabetes Technology & Therapeutics, VOL. 20, NO. 10 |

normal

Retrospective Analysis of 3-Month Real-World Glucose Data After the MiniMed 670G System Commercial Launch

Michael P. Stone, , Pratik Agrawal, , Xiaoxiao Chen, , Margaret Liu, , John Shin, , Toni L. Cordero , and Francine R. Kaufman

Published Online: 26 Sep 2018 | https://doi.org/10.1089/dia.2018.0202

HCL: mylife OmniPod® IPX8

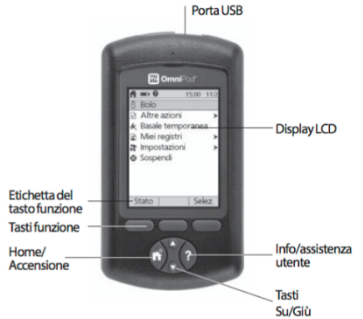
DIABETES TECHNOLOGY & THERAPEUTICS
Volume 20, Number 4, 2018
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2017.0346

DTT

ORIGINAL ARTICLE

Safety and Feasibility of the OmniPod Hybrid Closed-Loop System in Adult, Adolescent, and Pediatric Patients with Type 1 Diabetes Using a Personalized Model Predictive Control Algorithm

Bruce A. Buckingham, MD,[1] Gregory P. Forlenza, MD,[2] Jordan E. Pinsker, MD,[3] Mark P. Christiansen, MD,[4] R. Paul Wadwa, MD,[2] Jennifer Schneider, MD,[5] Thomas A. Peyser, PhD,[5] Eyal Dassau, PhD,[6] Joon Bok Lee, PhD,[7] Jason O'Connor, BS,[7] Jennifer E. Layne, PhD,[7] and Trang T. Ly, MBBS, FRACP, PhD[7]



HCL: Do-It-Yourself (DIY) & OpenAPS

OPENAPS.ORG

#WeAreNotWaiting to reduce the burden of Type 1 diabetes

OpenAPS Is Designed For Safety

OpenAPS means basic overnight closed loop APS technology is more widely available to anyone with compatible medical devices who is willing to build their own system.

How Do I Get Started?

The documentation and reference design implementation code is available on Github. Take a look below for FAQs, reference design, and links to open source repository and documentation.

Does It Really Work For Everyone?

OpenAPS follows the same basic diabetes math that a person would do to calculate a needed adjustment to their BG – but it is automated and precise.

https://openaps.org/

HCL: Do-It-Yourself (DIY) & OpenAPS

Letter to the Editor

Real-World Use of Open Source Artificial Pancreas Systems

Journal of Diabetes Science and Technology
2016, Vol. 10(6) 1411

DOI: 10.1177/1932296816665635
dst.sagepub.com
SAGE

Dana Lewis[1], Scott Leibrand[1], and the #OpenAPS Community

While using OpenAPS, self-reported median **HbA1c dropped from 7.1% to 6.2%,** and median percent **time in range (80-180 mg/dL) increased from 58% to 81%.** All but one respondent reported some improvement in sleep quality.

HCL: Do-It-Yourself (DIY) & OpenAPS

Closing the Loop with OpenAPS in People with Type 1 Diabetes—Experience from Italy

VINCENZO PROVENZANO, EDOARDO GUASTAMACCHIA, DAVIDE BRANCATO, GERARDO CAPPIELLO, ANTONIO MAIOLI, RAFFAELE MANCINI, GIUSEPPE CRISPINO, ARIELLA DE MONTE, SALVATORE TURCO, GIANCARLO TONOLO, *Partinico, Italy, Bari, Italy, Acerenza, Italy, Potenza, Italy, Catanzaro, Italy, Vibo Valentia, Italy, Trieste, Italy, Marano di Napoli, Italy, Olbia, Italy*

Diabetes 2018, 67(S1): 993P

… Closing the loop with OpenAPS in people with T1D is **effective in decreasing A1c and TIHypo, and in increasing TIR,** without any serious adverse event... in people who showed a good baseline metabolic control (A1c of 7.21%). However, given the spontaneous use of OpenAPS by patients, we have to be very careful to record any adverse event.

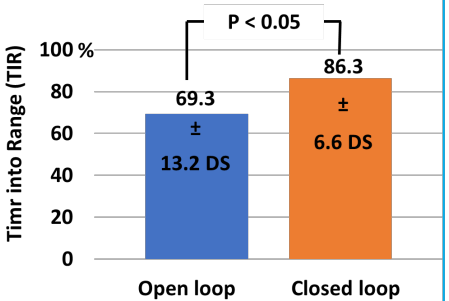


Fig. 3. TIR before and after closing the loop

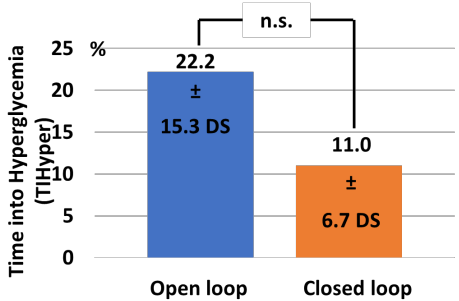


Fig. 4. TIHyper before and after closing the loop

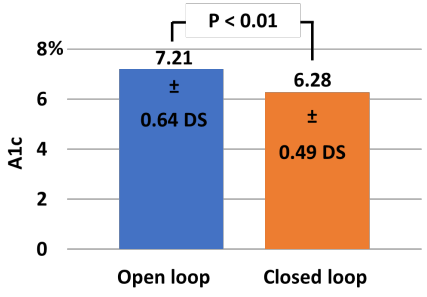


Fig. 1. A1c before and after closing the loop

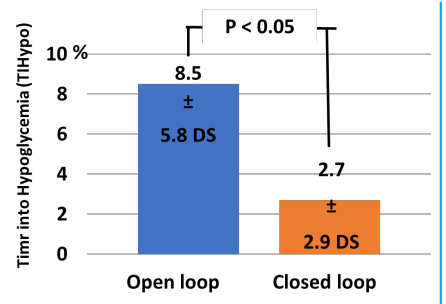


Fig. 2. TIHypo before and after closing the loop

HCL: Do-It-Yourself (DIY) & OpenAPS

Hacking diabetes: DIY artificial pancreas systems

Ethical issues arise when patients create their own systems. Conor Farrington reports.

Since these systems are not sold as medical devices, they are not subject to regulation by the FDA, UK Medicines and Healthcare products Regulatory Agency, or other similar bodies → ethical questions

Farrington C. www.thelancet.com/diabetes-endocrinology Vol 5 May 2017

Take home messages

- I sistemi integrati possono essere classificati in relazione a: livello di automazione, tipologia dell'algoritmo di controllo, strategia di raggiungimento dell'euglicemia, approccio ormonale
- Un sistema completamente automatizzato non è ancora disponibile
- L'evidenza scientifica indica che, tanto più automatizzato è un sistema, migliore è l'outcome in termini di Time into Range, Time into Hypoglycemia
- Un HCl «alternativo» è quello offerto da OpenAPS, sviluppato spontaneamente da pazienti e caregivers

Efficacia dei sistemi di integrazione: in sintesi

Sigla	Sistema	Efficacia
SAP	Sensor Augmented Pump	Vs MDI: **riduzione dell'HbA1c** [-0.68 % (-0.81, -0.54); p = 0.091], ma senza effetto sulle ipoglicemie severe
LGS	Low Glucose Suspend	Vs SAP: **riduzione degli eventi ipoglicemici** (del 37.5%) **e del tempo in ipoglicemia notturna e diurna** (di circa 1/3) senza significative variazioni dell'HbA1C né degli eventi avversi
PLGS	Predictive Low Glucose Suspend	Vs SAP: **riduzione delle notti** in cui si è verificata almeno un'ipoglicemia (di circa 1/3) **e del tempo in ipoglicemia** (7 vs 23%)
HCL	Hybrid Control Loop	Vs altri sistemi: **riduzione dell'HbA1c** (- 0.5 e 0.6%), **del tempo in ipoglicemia, del tempo in iperglicemia**; **incremento del time into range del 10%**

Sistemi di integrazione disponibili: in sintesi

- L'uso delle **funzioni avanzate** è determinante nella riduzione dell'A1C in soggetti in terapia con microinfusore

- In atto, in Italia sono commercializzati due sistemi integrati:
  - l'**Animas Vibe**, che è un sistema SAP, e che è più efficace della MDI nel ridurre l'A1C
  - il **Medtronic 640G**, che è un sistema PLGS, e che è più efficace della SAP nel ridurre le ipoglicemie

- Negli USA è autorizzato per uso clinico il **Medtronic 670G**, che è un sistema HCL

- Un HCl «alternativo» è quello offerto da **OpenAPS**, sviluppato spontaneamente da pazienti e caregivers

- Un pancreas artificiale completamente automatizzato non è ancora disponibile