



**7° CONGRESSO CONGIUNTO
SID - AMD SICILIA 2022
FOCUS SUL DIABETE IN SICILIA:
INNOVAZIONE, APPROPRIATEZZA E CONDIVISIONE**

HOTEL VILLA DIODORO - TAORMINA
VIA BAGNOLI CROCI, 75

11 - 12 NOVEMBRE 2022



Terapia insulinica: quali novità ?

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UNIVERSITÀ
DEGLI STUDI
DI PALERMO

promise

Dipartimento di Promozione della Salute, Materno-Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"

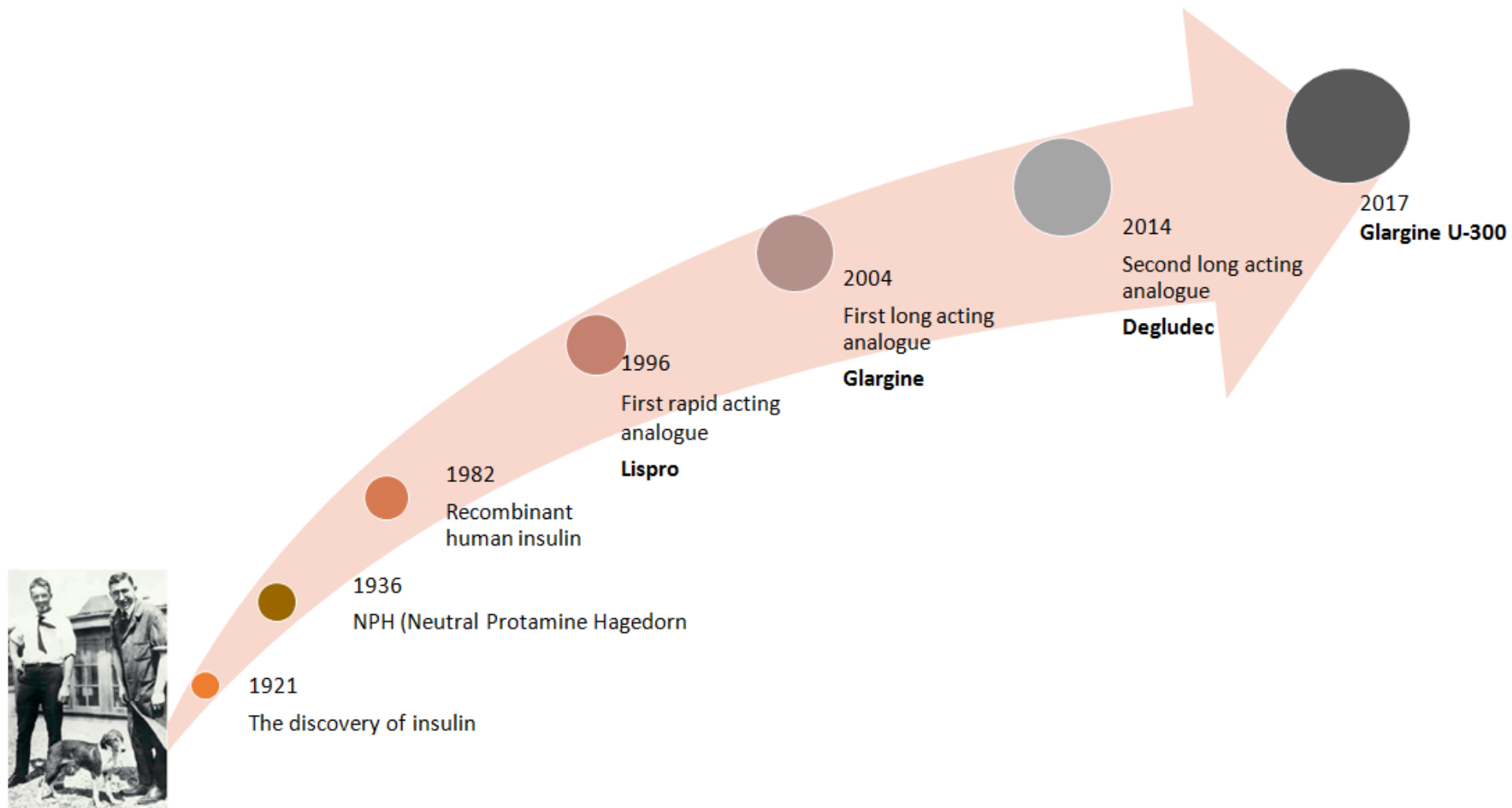


Carla Giordano dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

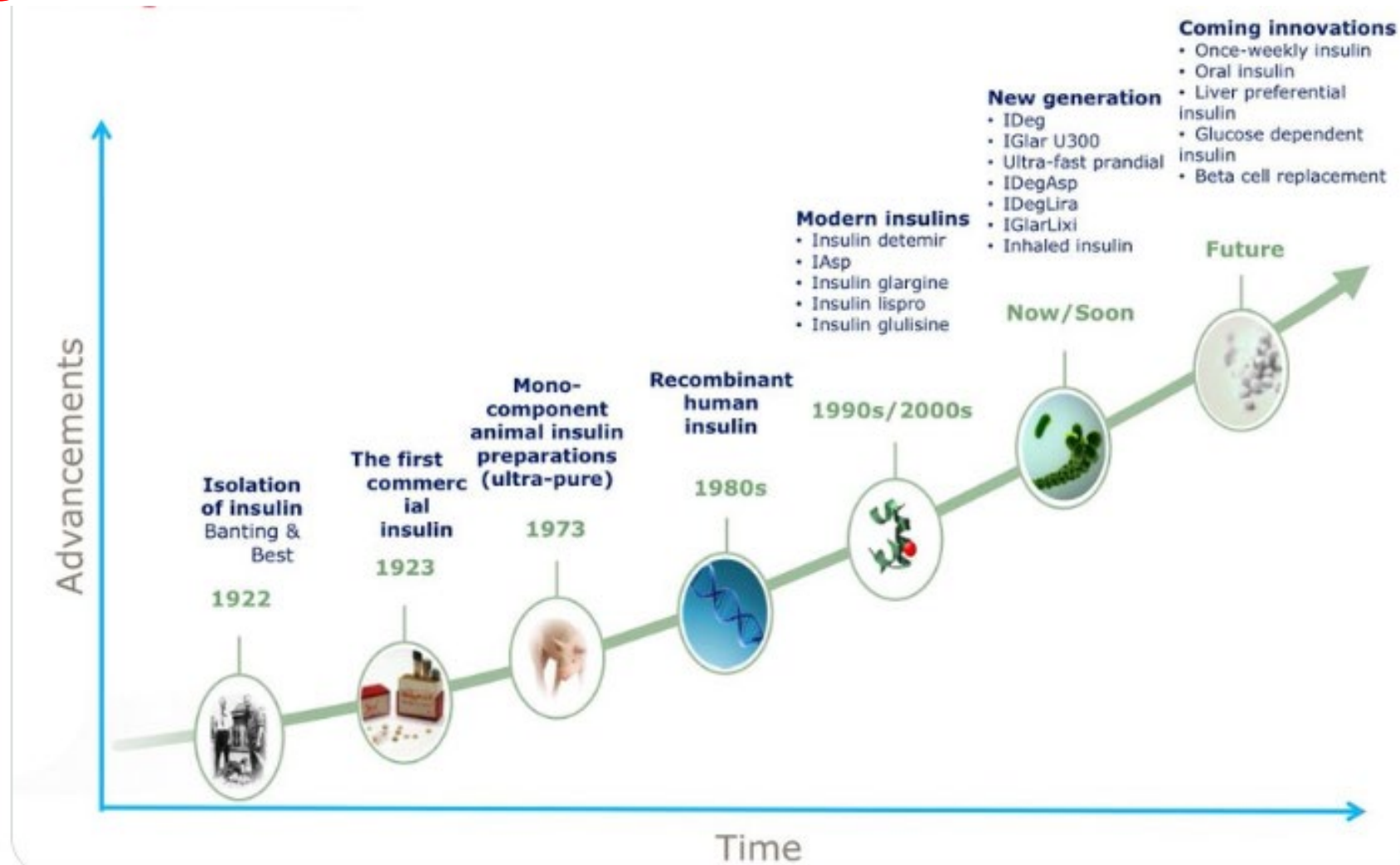
- Eli Lilly, Novo Nordisk, Astra Zeneca, Sanofi
- IBSA, Savio Pharma
- Menarini, Becton Dickinson
- Recordati, Eisai, Ipsen

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.).

Timeline dell'insulina



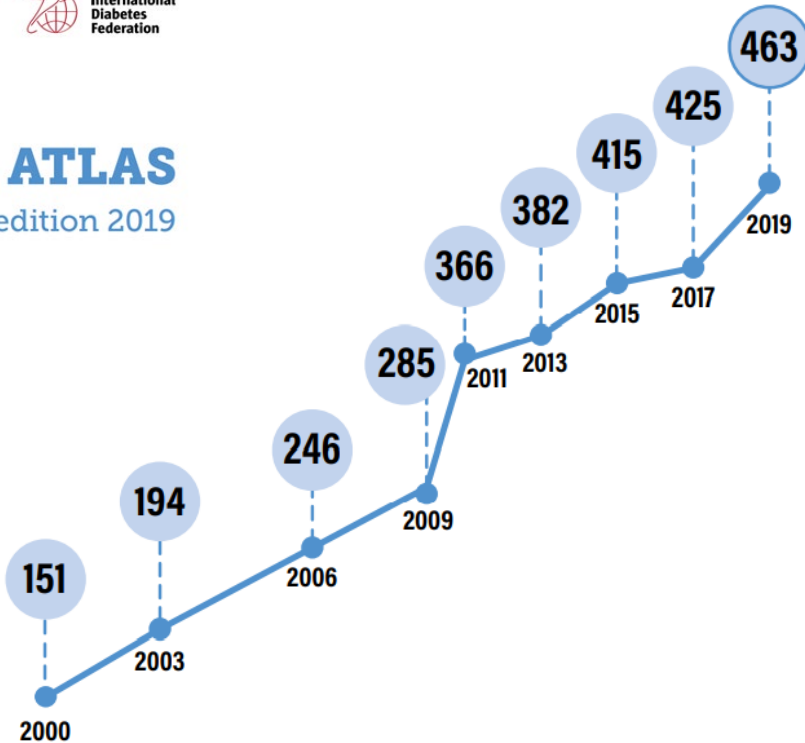
La lunga storia dell'insulina



Estimates and projections of the global prevalence of diabetes in the 20–79 year age group (millions)

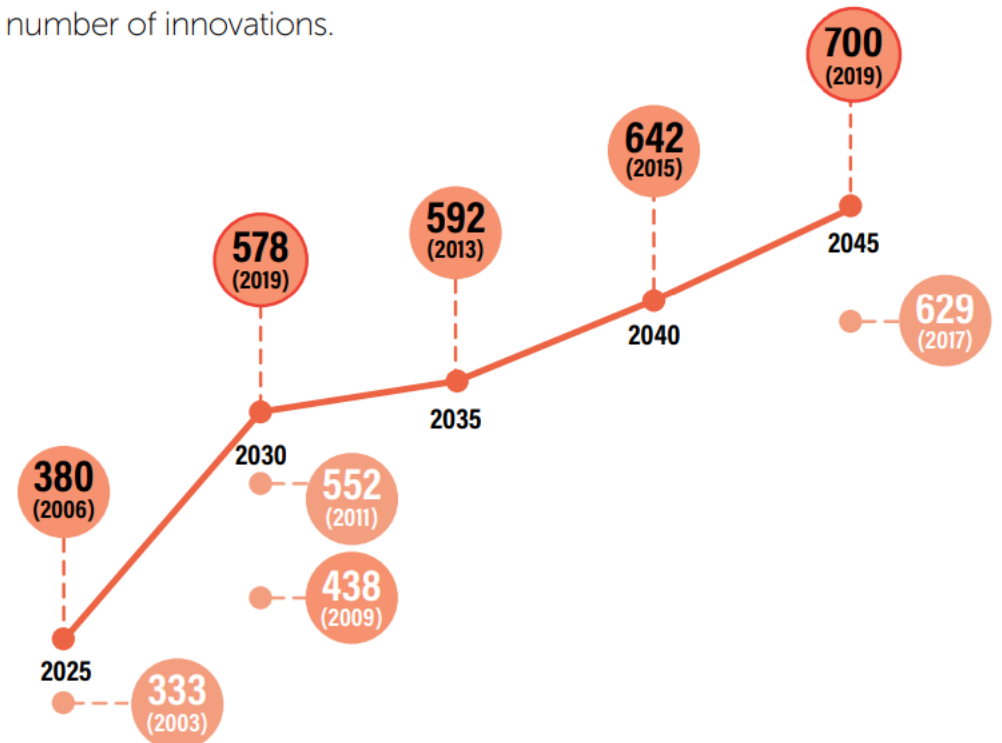


IDF DIABETES ATLAS
Ninth edition 2019



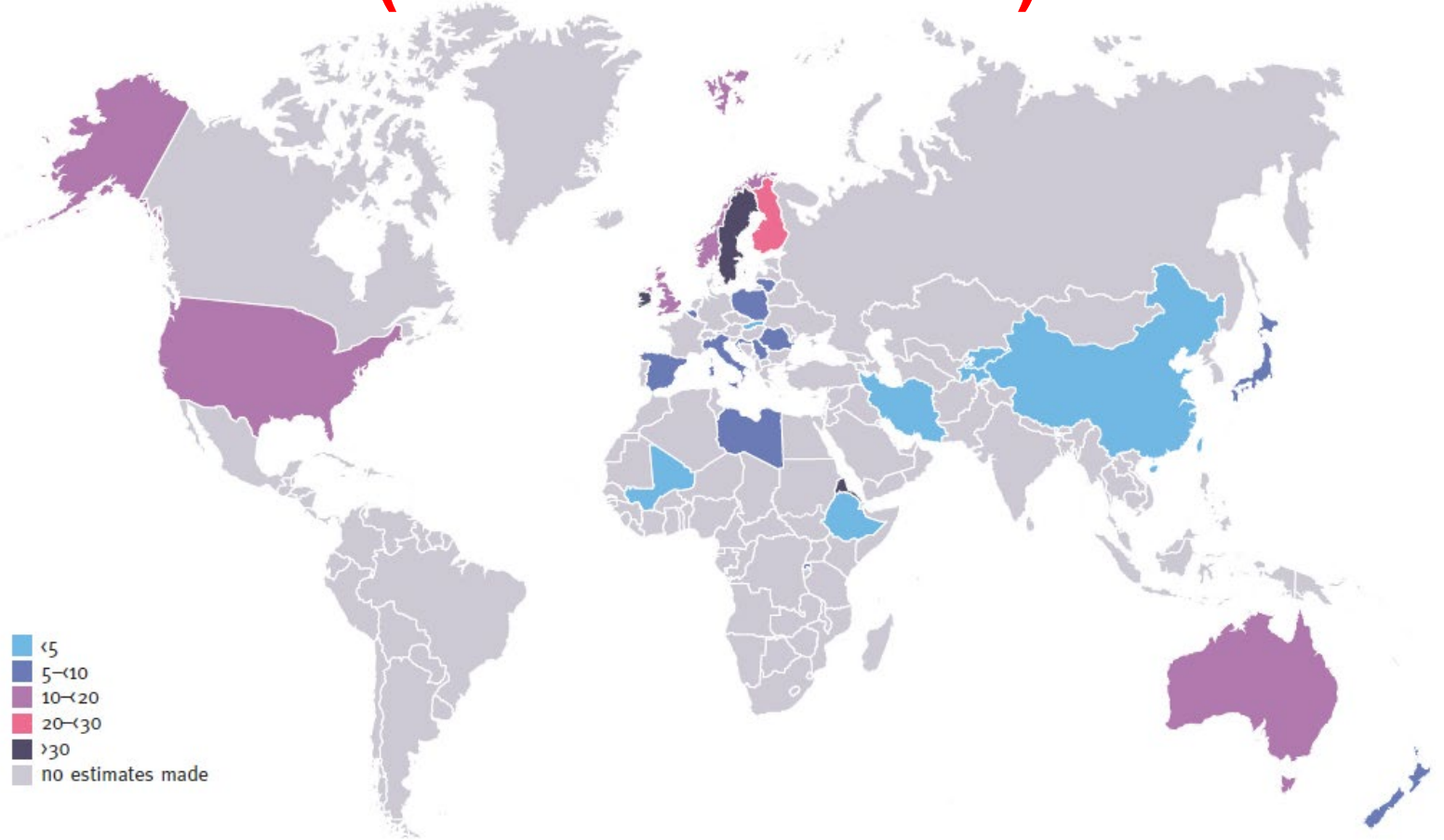
—●— Estimates
—●— Projections (year made)

methods used, and also incorporates a number of innovations.



Incidenza dell'esordio di diabete tipo 1 negli adulti (20-40 anni di età)

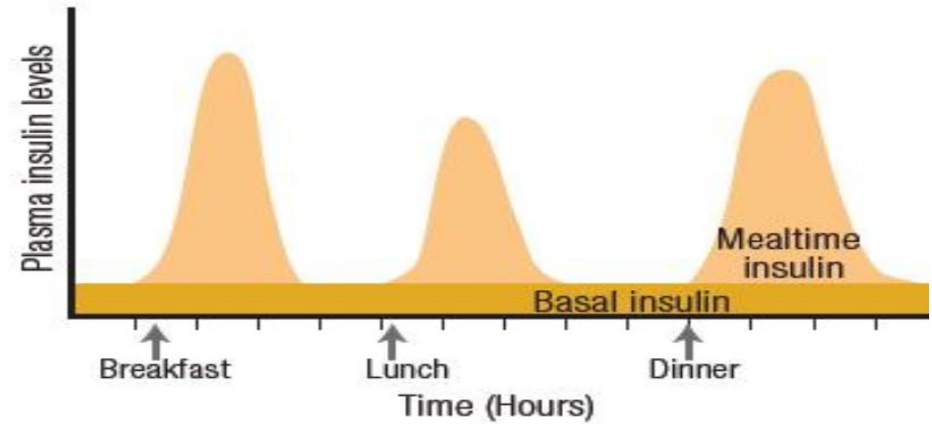
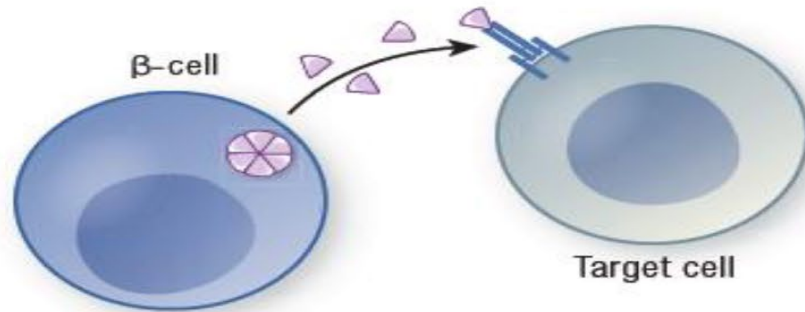
L'incidenza in età adulta rispecchia quella in età infantile nella regione in indagine



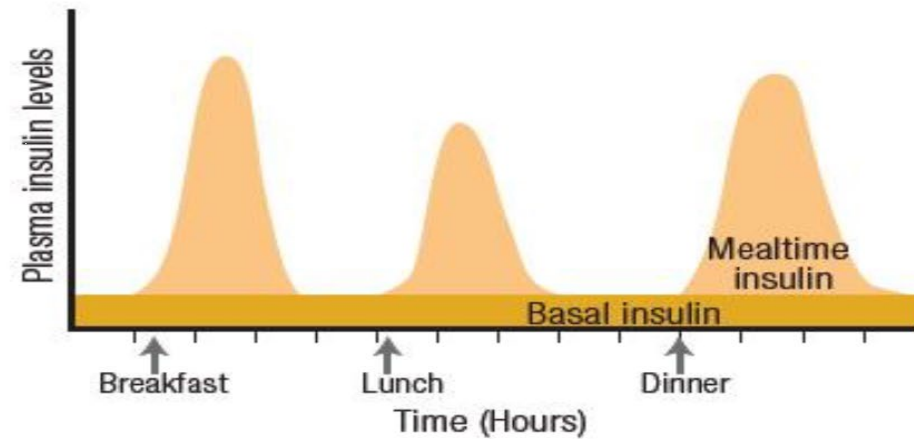
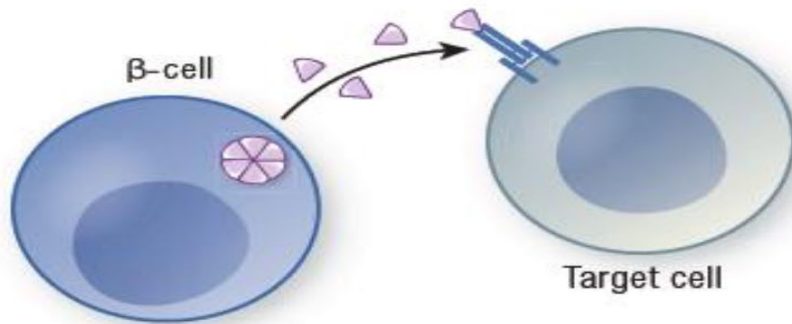
Incidenza annua del diabete di tipo 1 (per 100000 per anno) tra gli adulti di 20-40 anni per paese (stimato da studi del periodo 1973-2020)

UNMEETS OF INSULIN THERAPY

Endogenous insulin



Endogenous insulin



Terapia insulinica

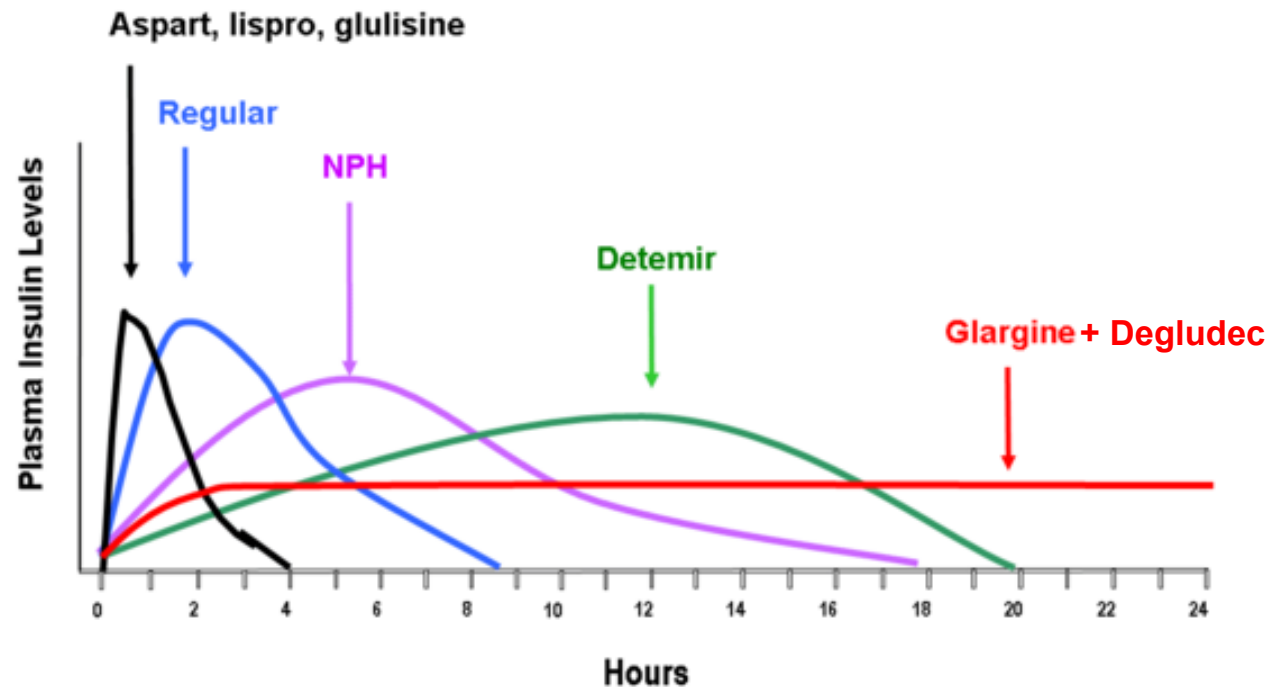
Quali insuline ho a disposizione?

➤ **BASALE**

- Insulina NPH
- Detemir
- Glargine U100 e U300
- Degludec

➤ **RAPIDA**

- Umana regolare
- Aspart
- Lispro
- Glulisina



ADA-EASD Consensus for T1 management

Diabetes Care

1



The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

<https://doi.org/10.2337/dci21-0043>

Richard I.G. Holt,^{1,2} J. Hans DeVries,^{3,4}
Amy Hess-Fischl,⁵ Irl B. Hirsch,⁶
M. Sue Kirkman,⁷ Tomasz Klupa,⁸
Barbara Ludwig,⁹ Kirsten Nørgaard,^{10,11}
Jeremy Pettus,¹² Eric Renard,^{13,14}
Jay S. Skyler,¹⁵ Frank J. Snoek,¹⁶
Ruth S. Weinstock,¹⁷ and Anne L. Peters¹⁸

lin needs may be obtained if they are administered twice daily. Trials have demonstrated that the latest basal analogs may cause less hypoglycemia than first-generation basal analogs and NPH insulin, while rapid-acting analogs achieve better mealtime coverage and less post-meal hypoglycemia than short-acting (regular) human insulin (87,88). Insulin analogs are, therefore, considered the insulins of choice.

Ultra-rapid analogs have a slightly ear-

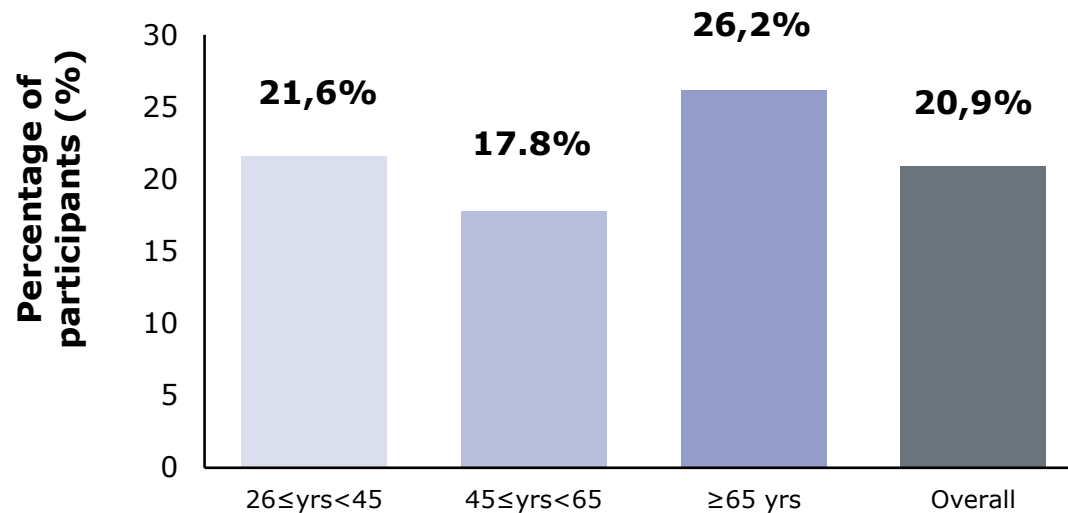
Ultra-rapid analogs have a slightly earlier time of onset and peak action than rapid-acting analogs. These insulins reduce postprandial hyperglycemia but have otherwise not been shown to reduce HbA_{1c} or hypoglycemia to a greater extent than rapid-acting analogs (3). Currently, recombinant human insulin or analogs of human insulin account for the vast majority of insulin used worldwide.

HbA_{1c}, TIR, and TBR are improved further when physiological MDI or pump regimens are augmented with CGM usage (89), with the greatest benefits seen with algorithm-driven automated basal (and in some systems correction) insulin delivery, which is commonly called hybrid closed-loop therapy (90, 91).

Il controllo glicemico rimane sub-ottimale per molte persone con il diabete di tipo 1 (DT1)

SAGE (T1D)

Individualized HbA1c target achievement by age group*



Studio SAGE :

Studio multicentrico, in più nazioni, osservazionale non interventistico, cross-sectional. Ha coinvolto 3903 partecipanti con lo scopo di valutare il raggiungimento del target glicemico in adulti con diabete tipo 1. End point primario era la percentuale di persone con DT1 con HbA1c <7%.



Un controllo glicemico inadeguato può portare a complicanze micro- e macro- vascolari e può portare al peggioramento di PROs (patient related outcomes) come astenia e ansia.

Renard E, et al. Diabetes Metab Res Rev 2021;37:e3430;

Stratton I, et al. Brit Med J 2000;321:405–12;

Hasan R, et al. J Vasc Surg 2016;63:S22–8;

De Wit M, et al. Presented at EASD 2021;Abstract 522.

Mancato raggiungimento dei target e ipoglicemia

38%* delle persone con diabete riferisce ≥ 1 ipoglicemia severa per anno
2.42** eventi per persona per anno¹

Le persone con ipoglicemie frequenti sono a maggior rischio di:



Ospedalizzazione ²



Accessi al pronto soccorso³



Morbilità ⁴ o morte^{5,6}

Il rischio ipoglicemico può portare a paura dell'ipoglicemia con conseguenti implicazioni sociali, ad es. :



Alterazione delle attività quotidiane (guidare)⁷



Sintomi depressive e ansia⁷



Alterazione delle relazioni interpersonali⁸

• *95% CI: 35.7–40.4; **95% CI: 2.36–2.49. CI, confidence interval.

• 1. Ratzki-Leewing A, et al. Oral presentation at IDF 2021; 2. Dalal M, et al. Adv Ther 2017;34:2083–92; 3. Leiter L, et al. Can J Diabetes 2005;29:186–92; 4. Frier BM. Nat Rev Endocrinol 2014;10:711–22.; 5. Bonds D, et al. Brit Med J 2010;340:b4909; 6. Cryer P. Diabetes Care. 2012;35:1814–6; 7. Barendse S, et al. Diabet Med 2012;29:293–302; 8. Ratzki-Leewing A, et al. Diabetes Ther 2019;10:2305–11.

Linea Guida della Associazione dei Medici Diabetologi (AMD), della Società Italiana di Diabetologia (SID) e della Società Italiana di Endocrinologia e Diabetologia Pediatrica (SIEDP)

La terapia del diabete mellito di tipo 1
12 marzo 2022



1

In soggetti con diabete mellito di tipo 1 si suggerisce di utilizzare schemi insulinici basal-bolus rispetto a schemi con insuline pre-miscelate.

2

In soggetti con diabete mellito di tipo 1 che utilizzano schemi insulinici basal-bolus si raccomanda di utilizzare come insulina basale un analogo lento dell'insulina rispetto a insulina umana NPH.

3

In soggetti con diabete mellito di tipo 1 in terapia insulinica intensiva si raccomanda di usare come insulina prandiale un analogo rapido dell'insulina.

4

In soggetti con diabete mellito di tipo 1 scompensato si raccomanda di offrire al paziente l'opzione di una terapia insulinica mediante microinfusore di insulina rispetto alla terapia insulinica multiniettiva per i vantaggi sui livelli di emoglobina glicata, le ipoglicemie severe, la qualità di vita e la soddisfazione per il trattamento.

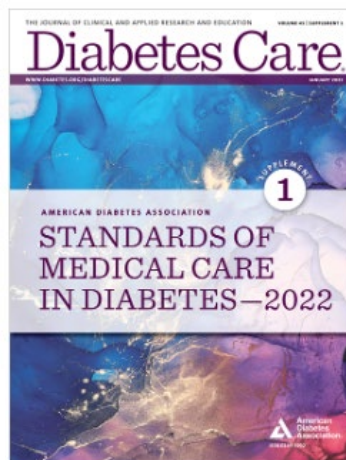
5

In soggetti con diabete mellito di tipo 1 non scompensato si suggerisce di offrire al paziente l'opzione di una terapia insulinica mediante microinfusore di insulina rispetto alla terapia insulinica multiniettiva per i vantaggi su variabilità glicemica, qualità di vita e soddisfazione per il trattamento.

6

In soggetti con diabete mellito di tipo 1 scompensato nonostante l'utilizzo di microinfusore e sensore si raccomanda l'utilizzo di sistemi costituiti da microinfusore e sensore con automatismo rispetto all'uso di sistemi senza automatismo.

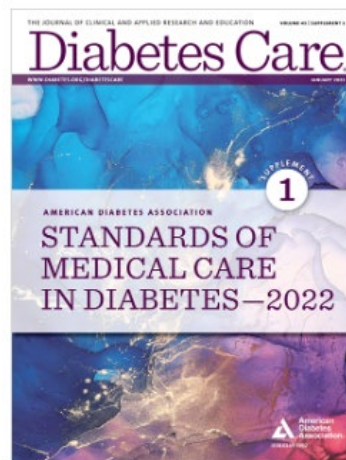
Standards of medical care in diabetes- 2022



Recommendations

- 9.1** Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**
- 9.2** Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**
- 9.3** Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. **B**

Standards of medical care in diabetes- 2022



Representative relative attributes of insulin delivery approaches in people with type 1 diabetes¹

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++

Less-preferred, alternative injected insulin regimens

MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	+++++
Insulin pump with threshold/predictive low-glucose suspend	++++	++++	++++
Insulin pump therapy without automation	+++	+++	++++

Figure 9.1—Choices of insulin regimens in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. ¹The number of plus signs (+) is an estimate of relative association of the regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Reprinted from Holt et al. (5).

Currently explored technologic approaches to increase half-life of basal insulin

Insulin icodec

Once-weekly basal insulin icodec, a novel long-acting insulin analog

Glucose-lowering effect in patients with type 2 diabetes

Qdct bdc dnyxl `stb cdf q`c`snm

Qdct bdc hmr t kmqpbdsnql dch sdc bld`q`nbd

Time-action profile ($t_{1/2}$ = approx. 8 days) supports once-weekly dosing in humans

Currently in Phase 3 Trials

Basal Insulin Fc

Novel single-chain variant of insulin fused to human IgG Fc domain

Homo-dimer

Reduced insulin receptor potency with full agonism

Time-action profile ($t_{1/2}$ = approx. 17 days) supports once-weekly dosing in humans³

Currently in Phase 2 Trials

- 1. Moyers J et al. Preclinical Characterization of Once Weekly Basal Insulin Fc (BIF) Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A442, <https://doi.org/10.1210/jendso/bvab048.903>; 2. Heise T et al. Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus, Journal of the Endocrine Society, Volume 5, Issue Supplement_1, April-May 2021, Page A329, <https://doi.org/10.1210/jendso/bvab048.672>.

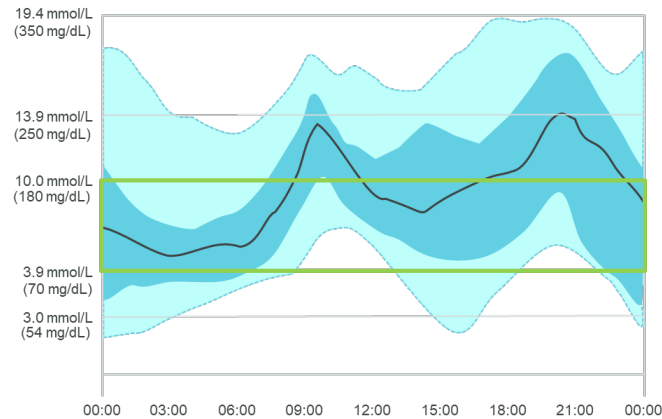
Blood glucose data may come to you in various formats

Blood glucose data may not be available



		BLOOD GLUCOSE TEST RESULTS mmol/L								COMMENTS
DATE		Breakfast		Lunch		Dinner		Bed Time	Over-Night	Dietary, Ketones, Activities, Stress etc.
		Before	After	Before	After	Before	After			
Sunday	Time									
	BG Insulin	8.8	5.72	6.22	7.40	11.04	9.00	10.93		Waffle
Monday	Time									
	BG Insulin	10.71	9.77			9.04				juicy dress mashed burger afternoon snack
Tuesday	Time									
	BG Insulin	13.1		3.27	16.6	17.99	7.94			frick today mashed veg 8.10.15.8.21
Wednesday	Time									
	BG Insulin	6.99	6.16		11.54					juicy only pizza/salad
Thursday	Time									
	BG Insulin	5.77			12.99			6.55		
Friday	Time									
	BG Insulin	6.72	10.10		11.43	16.04	22.37	25.63		spaghetti, lamb bruschetta
Saturday	Time									
	BG Insulin	14.26			7.99			12.65		

Written logbook^a



AGP report

	06:00	08:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	00:00
Mon	3.4	10.6		8.7	5.8		9.4	15.3	12.2	
Tue		8.4		7.8			9.6		8.8	
Wed	6.7			8.3	2.5		13.1	13.8	14.5	
Thu	13.4	14.4		9.2			10.1			
Fri	4.5			6.4			11.3		6.7	
Sat	2.9	9.2		11.9	14.6			11.6	15.8	12.8

- Very high
- High
- Target range
- Low
- Very low

Digital logbook

Data for a hypothetical patient.

^aWritten logbooks can be problematic for patients and their HCPs as they contain large volumes of complex information, errors and information gaps, and patients can forget to bring their logbook to visits.¹

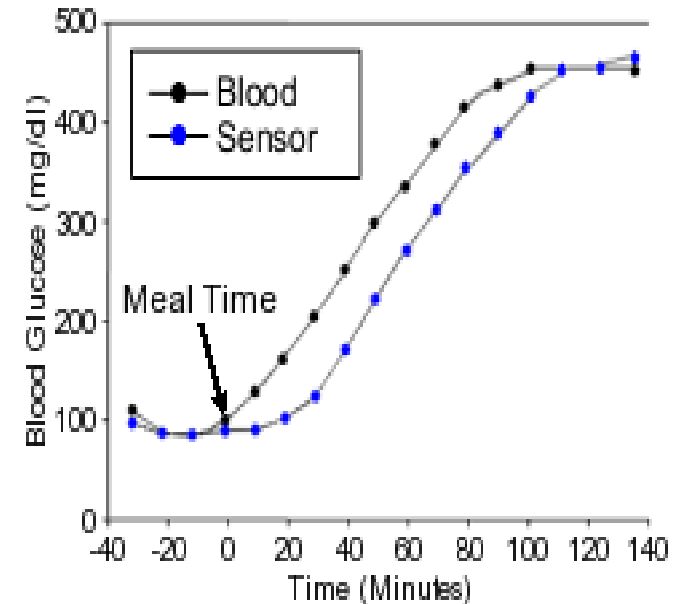
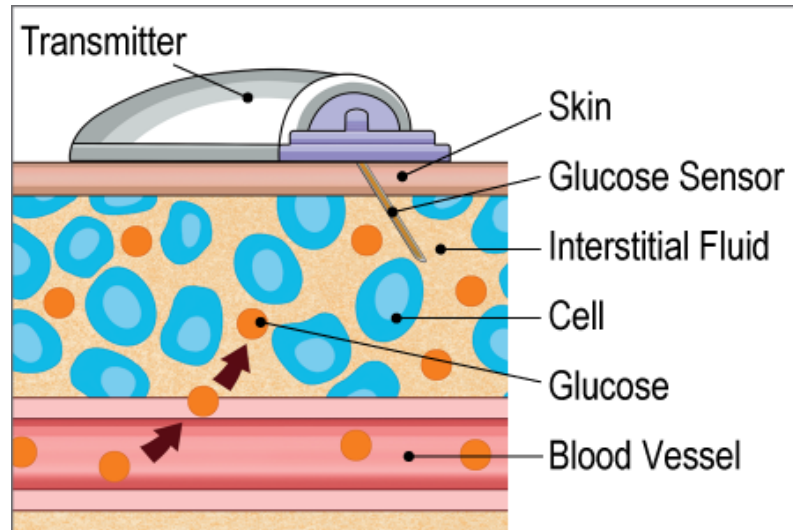
^bIncludes percentage of values >13.9 mmol/L (>250 mg/dL). ^cIncludes percentage of values <3.0 mmol/L (<54 mg/dL).

AGP, ambulatory glucose profile; BG, blood glucose; HCPs, healthcare professionals; TIRs, time in ranges.

¹Hinnen DA, et al. Journal of Diabetes Science and Technology. 2015;9(2): 293–301; ²Battelino T, et al. Diabetes Care. 2019;42(8): 1593–1603.

Monitoraggio glicemico in continuo

- È un sistema che misura il glucosio interstiziale permettendo così di avere un elevato numero di misurazioni glicemiche al giorno e di esaminare il trend dell'andamento della glicemia.
- Il sensore rileva la glicemia, il trasmettitore trasmette i dati al lettore in continuo.
- L'analisi retrospettiva dei profili permette di calcolare il tempo speso in ipo- e iper-glicemia.
- Il glucosio diffonde dal sangue capillare nei fluidi interstiziali, ciò provoca un fisiologico ritardo della variazione dei livelli di glucosio nei fluidi interstiziali. Ne deriva un ritardo nella lettura dei valori glicemici. → buona norma è verificare sempre il capillare.
- Sono dotati di allarmi per le ipo- e le iper-glicemie.



DOCUMENTO DEL GRUPPO DI STUDIO INTERSOCIETARIO AMD - SID - SIEDP

“TECNOLOGIA E DIABETE”



Utilizzo del **CGM** nei pazienti adulti con DMT1:

- il CGM riduce l'HbA1c quando applicato in modalità continuativa in pazienti in terapia insulinica intensiva
- le valutazioni metanalitiche suggeriscono che rispetto al SMBG, il CGM riduce la HbA1c dello 0,3% circa e del tempo speso in iperglicemia, specie in pazienti adeguatamente selezionati e motivati all'utilizzo del CGM per la maggior parte del tempo
- Il CGM in diversi studi ha contribuito a ridurre le ipoglicemie e le iperglicemie facilitando il loro precoce riconoscimento e l'intervento correttivo/preventivo

DOCUMENTO DEL GRUPPO
DI STUDIO INTERSOCIETARIO
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“TECNOLOGIA E DIABETE”

Impiego di rtCGM in Pazienti con Diabete Tipo 1 Adulti (dispositivi ad ago sottocutaneo e dispositivi impiantabili sottocute)

- Per ipoglicemia severa o inavvertita o problematica per la vita del paziente.

[N.B.: per ipoglicemia problematica si intende: »2 episodi di ipoglicemia severa negli ultimi 12 mesi o 1 episodio di ipoglicemia severa negli ultimi 12 mesi associato a ipoglicemia inavvertita o a estrema labilità glicemica o a paura delle ipoglicemie ricorrenti tale da impattare negativamente sulla gestione della vita quotidiana (cfr. Choudhary P 2015)]

Cfr. Bode 2009; Battelino 2011; Battelino 2012; New JP 2015; van Beers CA 2016; Heinemann L 2018

- Per emoglobina glicata persistentemente superiore al target desiderabile per il paziente, nonostante terapia insulinica intensiva e ottimizzata.

Cfr. Deiss D 2006; Tamborlane WV 2008; O'Connell MA 2009; Rivelino 2012; Battelino 2012; Beck 2009a; Beck 2009b; Pickup 2011; Yeh 2012

- In donne con diabete tipo 1 in gravidanza, per migliorare il compenso metabolico e gli outcome neonatali **(solo dispositivi ad ago sottocutaneo)**.

Cfr. Murphy HR 2008; Secher AL 2013; Yu F 2014; Feig DS 2017

- Può essere utile in pazienti con condizioni lavorative o stili di vita in cui un controllo molto frequente è consigliabile ma non praticabile (ad es., minatori, subacquei, lavoratori dell'edilizia, ecc.).

Il rtCGM non dovrebbe essere impiegato se si verificano le seguenti condizioni:

- Mancanza di motivazione e di compliance alla terapia e all'utilizzo adeguato del sensore
- Paura/mancanza fiducia sistemi tecnologici
- Patologie psichiatriche gravi, non compensate, in atto
- Inabilità/incapacità ad usare lo strumento.

DOCUMENTO DEL GRUPPO DI STUDIO INTERSOCIETARIO AMD - SID - SIEDP “TECNOLOGIA E DIABETE”



CARATTERISTICHE DEL PAZIENTE IDEALE

Il paziente da avviare a RT-CGM continuativo deve essere già in terapia intensiva MDI ottimizzata e già educato alla corretta gestione della terapia insulinica. Le caratteristiche del paziente associate a migliori outcome sono:

- disponibilità all'impiego continuativo (eventuale mese di prova)
- disponibilità a effettuare SMBG come suggerito
- capacità di gestire correttamente lo strumento e di interpretare i dati derivanti dal monitoraggio e utilizzarli per opportune decisioni
- buona compliance alla terapia e al programma di follow-up (visite periodiche)
- aspettative realistiche.

Cfr. AACE-ACE 2016; Endocrine Society 2016; Standard Italiani per la cura del Diabete

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DOCUMENTO DEL GRUPPO DI STUDIO INTERSOCIETARIO AMD - SID - SIEDP “TECNOLOGIA E DIABETE”



FGM

Impiego di FGM in pazienti adulti tipo 1 e tipo 2 in terapia insulinica intensiva (MDI o CSII), in buon controllo metabolico, con l'obiettivo di ridurre le ipoglicemie.

Cfr. Bolinder 2016; Haak 2017a; Haak 2017b; Reddy 2018; Oskarsson 2018

L'uso di FGM può essere utile in pazienti adulti tipo 1 e tipo 2 in terapia insulinica intensiva (MDI o CSII) per migliorare il controllo metabolico e la qualità della vita.

Cfr. Bolinder 2016; Ish-Shalom M 2016; Dover AR 2017; McKnight JA 2017; Dunn 2018

L'uso di FGM può essere utile in pazienti pediatrici in terapia insulinica intensiva (MDI o CSII) per migliorare il controllo metabolico e la qualità della vita

Cfr. Edge 2017

Ulteriori condizioni in cui FGM può essere considerato, soprattutto se ostative alla implementazione della terapia:

>10 SMBG/giorno

Agofobia.

Il FGM non dovrebbe essere impiegato se si verificano le seguenti condizioni:

- Situazioni cliniche caratterizzate da ipoglicemia non awertita
- Mancanza di motivazione e di compliance alla terapia e all'utilizzo adeguato del sensore
- Paura/mancanza di fiducia nei sistemi tecnologici
- Patologie psichiatriche gravi, non compensate, in atto
- Inabilità/incapacità ad usare lo strumento

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“TECNOLOGIA E DIABETE”

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Current Management of Glycemia in Children with Type 1 Diabetes Mellitus

Mark A. Sperling, M.D., and Lori M. Laffel, M.D., M.P.H.

N ENGL J MED 386;12 NEJM.ORG MARCH 24, 2022

KEY CLINICAL POINTS

CURRENT MANAGEMENT OF GLYCEMIA IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

- Type 1 diabetes mellitus is one of the most common chronic diseases of childhood, with incidence increasing worldwide.
- Control of glucose levels to near normal reduces the risk of long-term microvascular and macrovascular complications.
- Newer biochemically modified insulins have durations of action ranging from very long (24 hours of basal insulin level) to ultrarapid (for glycemic control at meal or snack times).
- Technologies that have improved management of type 1 diabetes mellitus in children include continuous glucose monitors that replace painful fingerstick glucose checks, smart insulin pen injectors that receive data from continuous glucose monitors and assist with insulin dose calculations, and improved formulations of glucagon for autoinjection or nasal administration.
- Newer hybrid closed-loop systems combine an insulin pump, a continuous glucose monitoring device, and control algorithms that automate insulin delivery to maintain glucose levels within predetermined ranges and avoid hypoglycemia or hyperglycemia.
- High costs of newer insulins and diabetes technologies reduce their universal accessibility, resulting in disparities that warrant remedy.



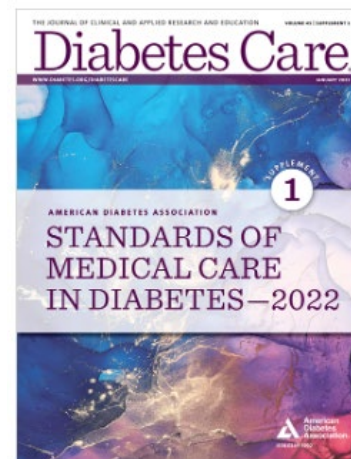
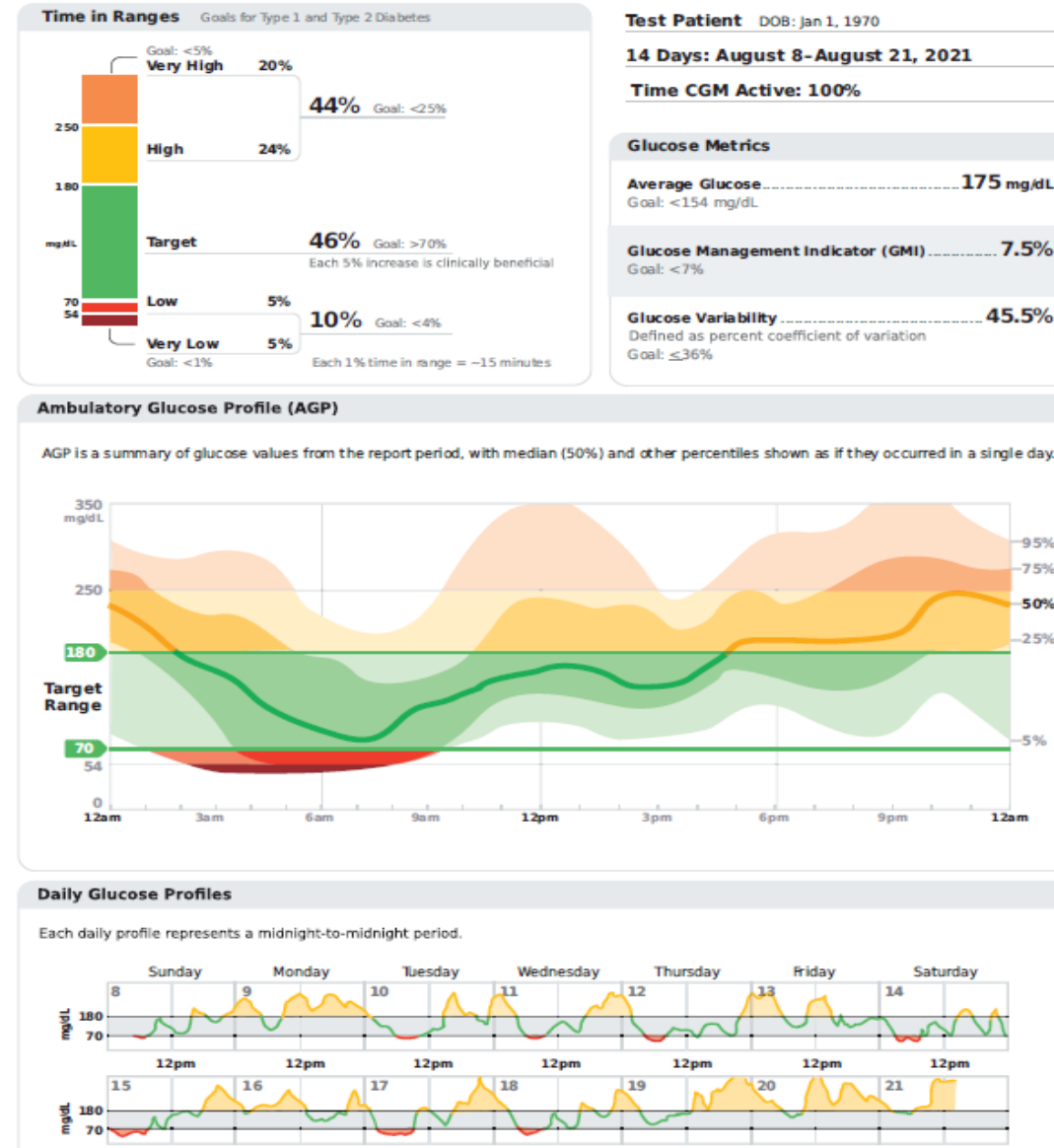
Report AGP

Glucose Assessment by Continuous Glucose Monitoring

Recommendations

- 6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**
- 6.4 Time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control. Additionally, time below target and time above target are useful parameters for the evaluation of the treatment regimen (Table 6.2). **C**

AGP Report: Continuous Glucose Monitoring



Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections

The DIAMOND Randomized Clinical Trial

Roy W. Beck, MD, PhD; Tonya Riddlesworth, PhD; Katrina Ruedy, MSPH; Andrew Ahmann, MD; Richard Bergenstal, MD; Stacie Haller, RD, LD, CDE; Craig Kollman, PhD; Davida Kruger, MSN, APN-BC; Janet B. McGill, MD; William Polonsky, PhD; Elena Toschi, MD; Howard Wolpert, MD; David Price, MD; for the DIAMOND Study Group

Table 3. Continuous Glucose Monitoring Metrics

	Baseline		12 and 24 Weeks Pooled ^a		Mean Adjusted Difference (99% CI) ^b	P Value ^b
	CGM Group (n = 105)	Control Group (n = 53)	CGM Group (n = 103)	Control Group (n = 53)		
Hours of data, mean (SD)	322 (50)	325 (51)	301 (41)	301 (54)		
Prespecified secondary outcomes						
Glucose variability: coefficient of variation, mean (SD), %	42 (7)	42 (7)	38 (6)	42 (7)	−4 (−6 to −2)	<.001
Minutes per day in range 70–180 mg/dL, mean (SD)	660 (179)	650 (170)	736 (206)	650 (194)	77 (6 to 147)	.005
Hypoglycemia, median (IQR)						
Minutes per day <70 mg/dL	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL	13 (5 to 29)	18 (4 to 39)	6 (2 to 12)	20 (4 to 42)		.001
Hyperglycemia, median (IQR)						
Minutes per day >180 mg/dL	687 (554 to 810)	725 (537 to 798)	638 (503 to 807)	740 (625 to 854)		.03
Minutes per day >250 mg/dL	301 (190 to 401)	269 (184 to 383)	223 (128 to 351)	347 (241 to 429)		<.001
Minutes per day >300 mg/dL	129 (66 to 201)	109 (71 to 204)	78 (36 to 142)	167 (89 to 226)		<.001
Prespecified exploratory outcome						
Mean glucose, mean (SD), mg/dL	187 (27)	186 (30)	180 (27)	189 (25)	−9 (−19 to 0)	.01
Post hoc outcomes, median (IQR) ^c						
Area above curve 70 mg/dL	0.5 (0.3 to 1.1)	0.7 (0.2 to 1.4)	0.3 (0.2 to 0.5)	0.7 (0.2 to 1.3)		<.001
Area under curve 180 mg/dL	34 (25 to 46)	33 (26 to 45)	27 (17 to 40)	40 (31 to 51)		<.001

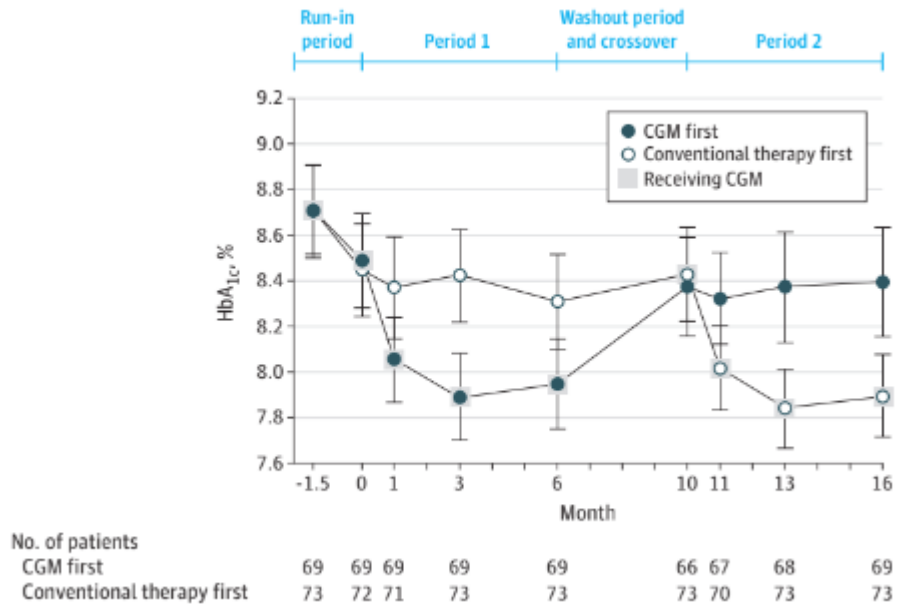
Key Points

- Question** For adults with type 1 diabetes who are using multiple daily insulin injections, does continuous glucose monitoring improve hemoglobin A_{1c} (HbA_{1c}) levels compared with self-monitored blood glucose management?
- Findings** In a randomized clinical trial of 158 adults with type 1 diabetes, there was a significantly greater decrease in HbA_{1c} level during 24 weeks with continuous glucose monitoring vs usual care (−1.0% vs −0.4%).
- Meaning** Continuous glucose monitoring resulted in better glycemic control compared with usual care, but further research is needed to assess clinical outcomes, as well as effectiveness, in a typical clinical population.

Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections

The GOLD Randomized Clinical Trial

Marcus Lind, MD, PhD; William Polonsky, PhD; Irl B. Hirsch, MD; Tim Heise, MD; Jan Bolinder, MD, PhD; Sofia Dahlqvist; Erik Schwarz, MD, PhD; Arndís Finna Ólafsdóttir, RN; Anders Frid, MD, PhD; Hans Wedel, PhD; Elsa Ahlén, MD; Thomas Nyström, MD, PhD; Jarl Hellman, MD



IMPORTANCE The majority of individuals with type 1 diabetes do not meet recommended glycemic targets.

OBJECTIVE To evaluate the effects of continuous glucose monitoring in adults with type 1 diabetes treated with multiple daily insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Open-label crossover randomized clinical trial conducted in 15 diabetes outpatient clinics in Sweden between February 24, 2014, and June 1, 2016 that included 161 individuals with type 1 diabetes and hemoglobin A_{1c} (HbA_{1c}) of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections.

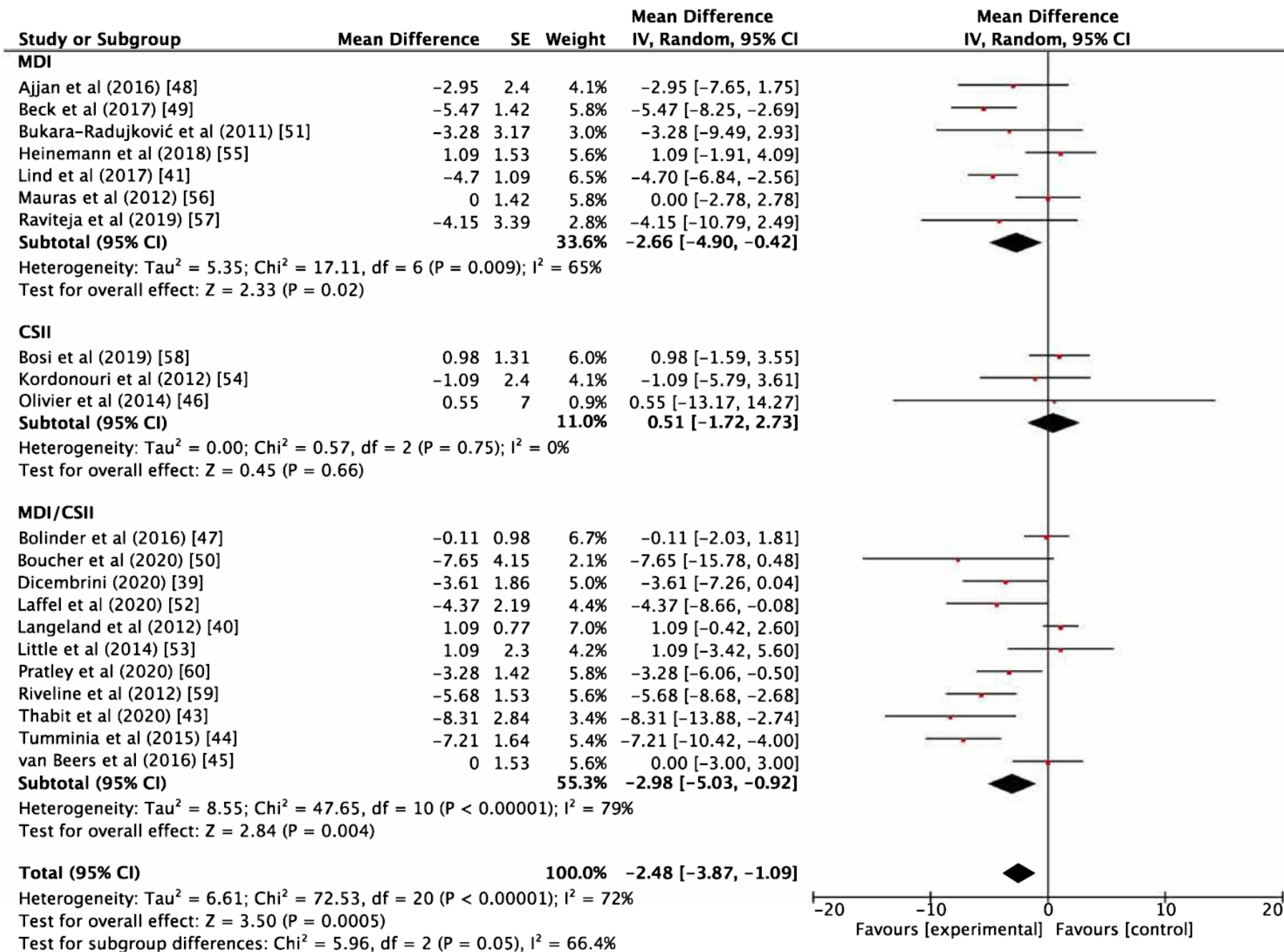
INTERVENTIONS Participants were randomized to receive treatment using a continuous glucose monitoring system or conventional treatment for 26 weeks, separated by a washout period of 17 weeks.

MAIN OUTCOMES AND MEASURES Difference in HbA_{1c} between weeks 26 and 69 for the 2 treatments. Adverse events including severe hypoglycemia were also studied.

RESULTS Among 161 randomized participants, mean age was 43.7 years, 45.3% were women, and mean HbA_{1c} was 8.6% (70 mmol/mol). A total of 142 participants had follow-up data in both treatment periods. Mean HbA_{1c} was 7.92% (63 mmol/mol) during continuous glucose monitoring use and 8.35% (68 mmol/mol) during conventional treatment (mean difference, -0.43% [95% CI, -0.57% to -0.29%] or -4.7 [-6.3 to -3.1 mmol/mol]; *P* < .001). Of 19 secondary end points comprising psychosocial and various glycemic measures, 6 met the hierarchical testing criteria of statistical significance, favoring continuous glucose monitoring compared with conventional treatment. Five patients in the conventional treatment group and 1 patient in the continuous glucose monitoring group had severe hypoglycemia. During washout when patients used conventional therapy, 7 patients had severe hypoglycemia.

CONCLUSIONS AND RELEVANCE Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of continuous glucose monitoring compared with conventional treatment for 26 weeks resulted in lower HbA_{1c}. Further research is needed to assess clinical outcomes and longer-term adverse effects.

Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis



Frecce di tendenza

Recommendations for Using Real-Time Continuous Glucose Monitoring (rtCGM) Data for Insulin Adjustments in Type 1 Diabetes

Jeremy Pettus, MD¹ and Steven V. Edelman, MD¹

Adjusted Glucose Value for Dosing	
 Glucose is <u>not</u> increasing/decreasing >1 mg/dl (0.06 mmol/l) per min	No Adjustment. Dose for current glucose value.
 Glucose increasing 1-2 mg/dl (0.06-0.11 mmol/l) per minute	Adjust UP -- current value <u>plus</u> 50 mg/dl <i>Actual Range: 30-60 mg/dl</i>
 Glucose increasing 2-3 mg/dl (0.11-0.17 mmol/l) per minute	Adjust UP -- current value <u>plus</u> 75 mg/dl <i>Actual Range: 60-90 mg/dl</i>
 Glucose increasing >3 mg/dl (0.17 mmol/l) per minute	Adjust UP -- current value <u>plus</u> 100 mg/dl <i>Actual Range: 90-150 mg/dl</i>
 Glucose decreasing 1-2 mg/dl (0.06-0.11 mmol/l) per minute	Adjust DOWN -- current value <u>minus</u> 50 mg/dl <i>Actual Range: 30-60 mg/dl</i>
 Glucose decreasing 2-3 mg/dl (0.11-0.17 mmol/l) per minute	Adjust DOWN -- current value <u>minus</u> 75 mg/dl <i>Actual Range: 60-90 mg/dl</i>
 Glucose decreasing >3 mg/dl (0.17 mmol/l) per minute	Adjust DOWN -- current value <u>minus</u> 100 mg/dl <i>Actual Range: 90-150 mg/dl</i>

The most conservative response to down arrows is to delay insulin administration until the trend arrow turns horizontal.

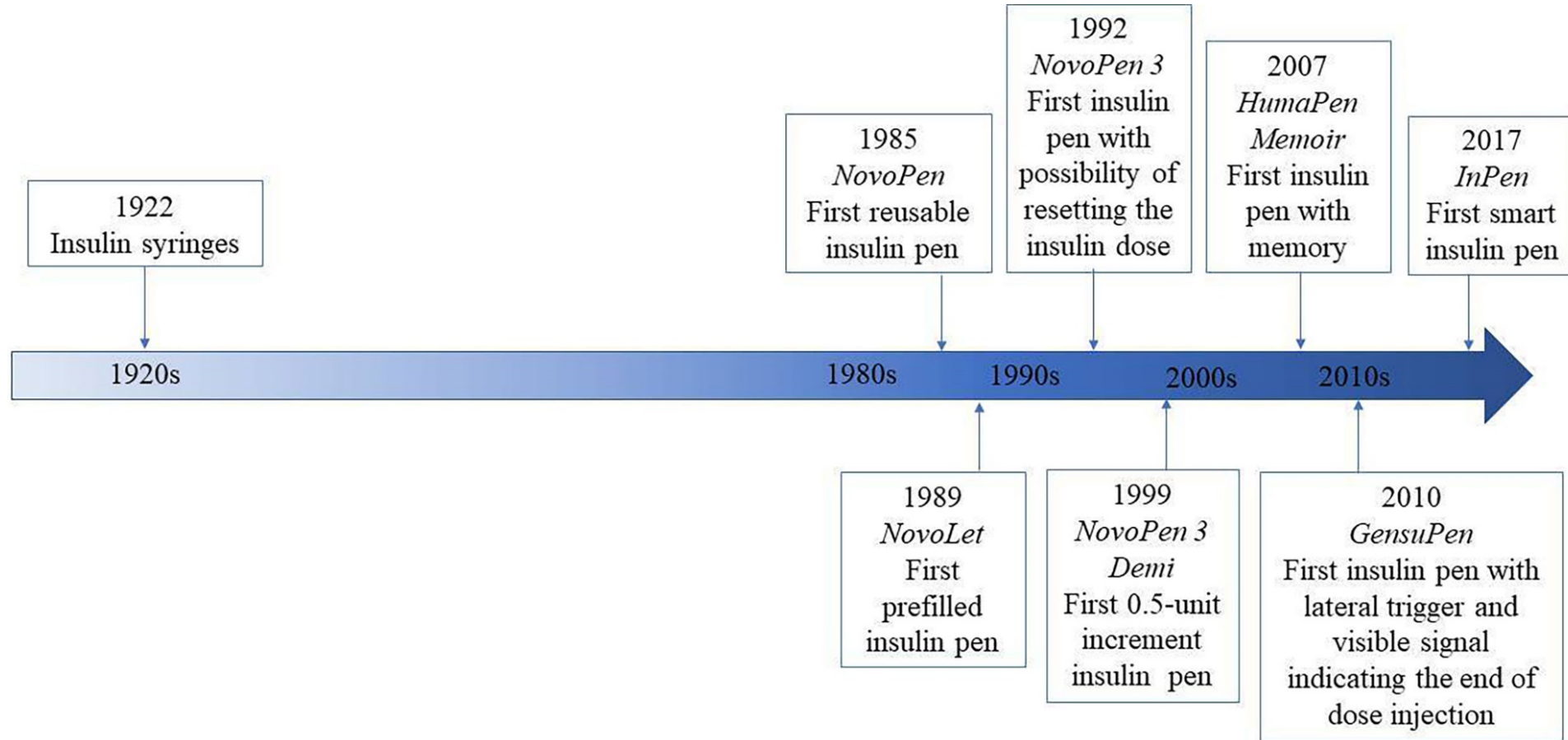
MICROINFUSORI

- CSII: continuous Subcutaneous Insulin Infusion, microinsufore insulinico
- CSII + CGM (continuum glucose monitoring) sistema non integrato
- SAP: sensor augmented insulin pump, microinfusore integrato con sensore per il monitoraggio glicemico in tempo reale (RT-CGM) assemblati in un unico sistema, detto integrato
 - con funzione LGS: low glucose suspend: microinfusore con sensore integrato in grado di sospendere infusione di insulina basale per 2 ore in caso di ipoglicemia
 - con funzione PLGS: pre low glucose suspend: sospensione predittiva

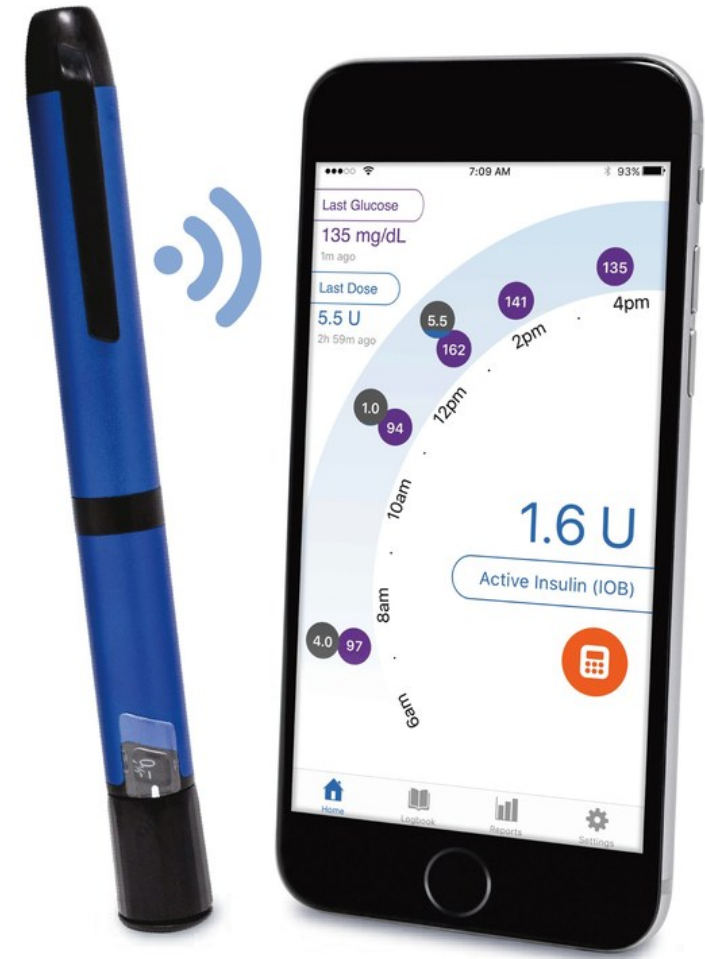
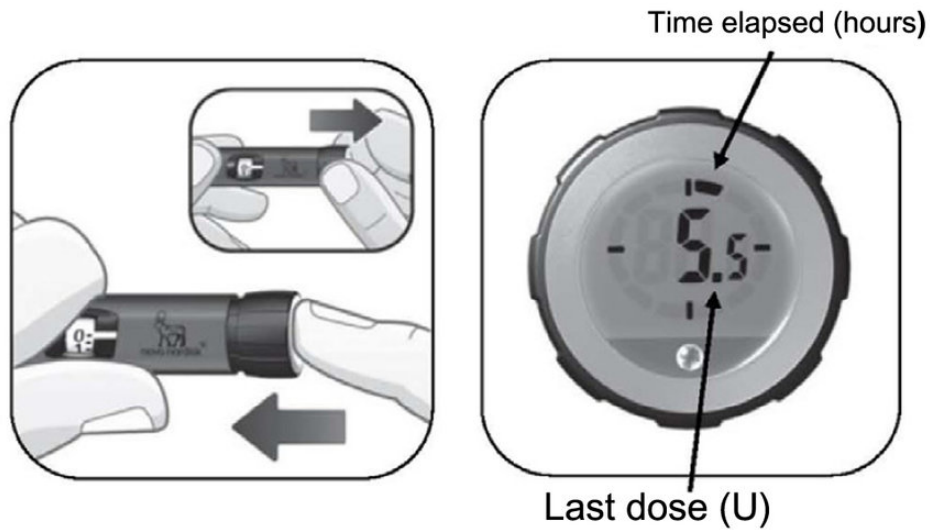


...E il futuro?

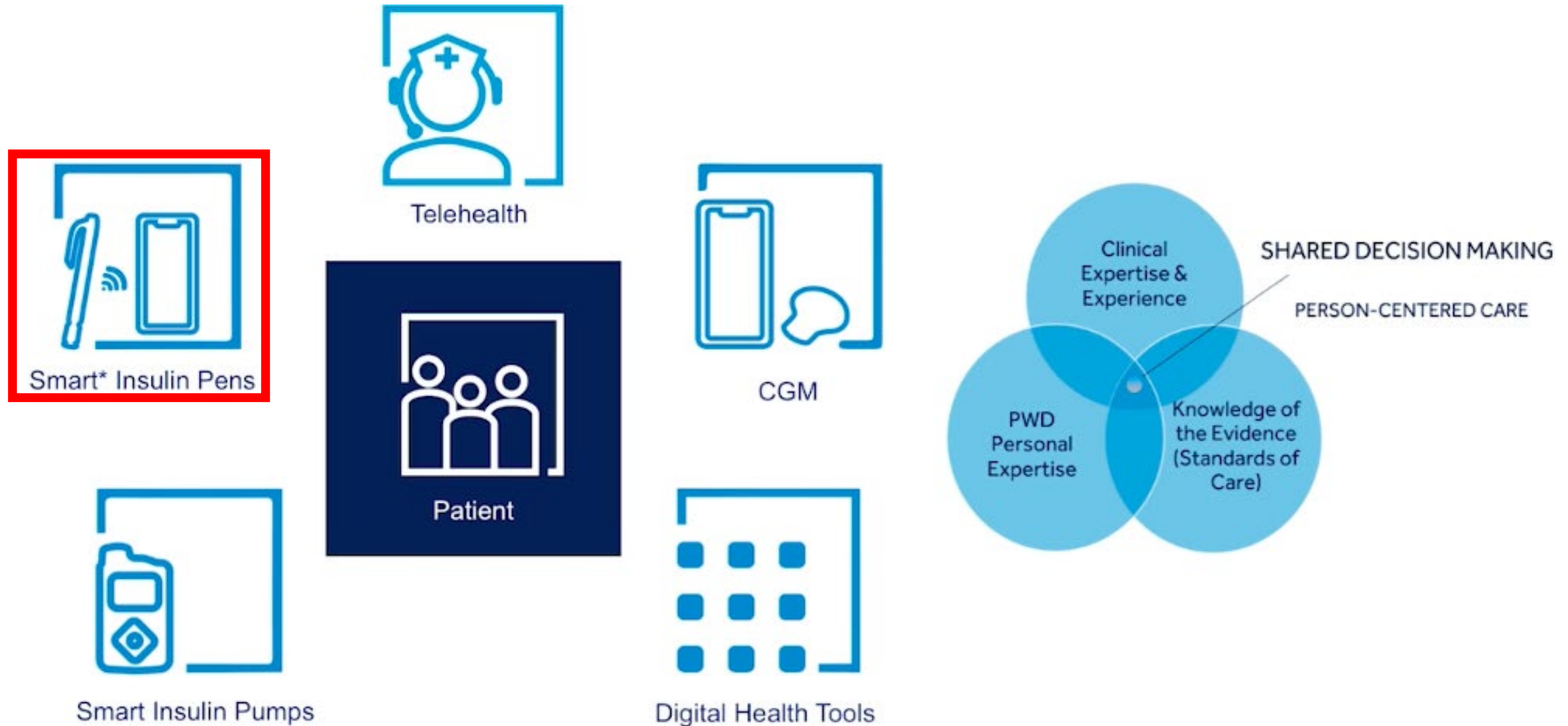
Penne intelligenti



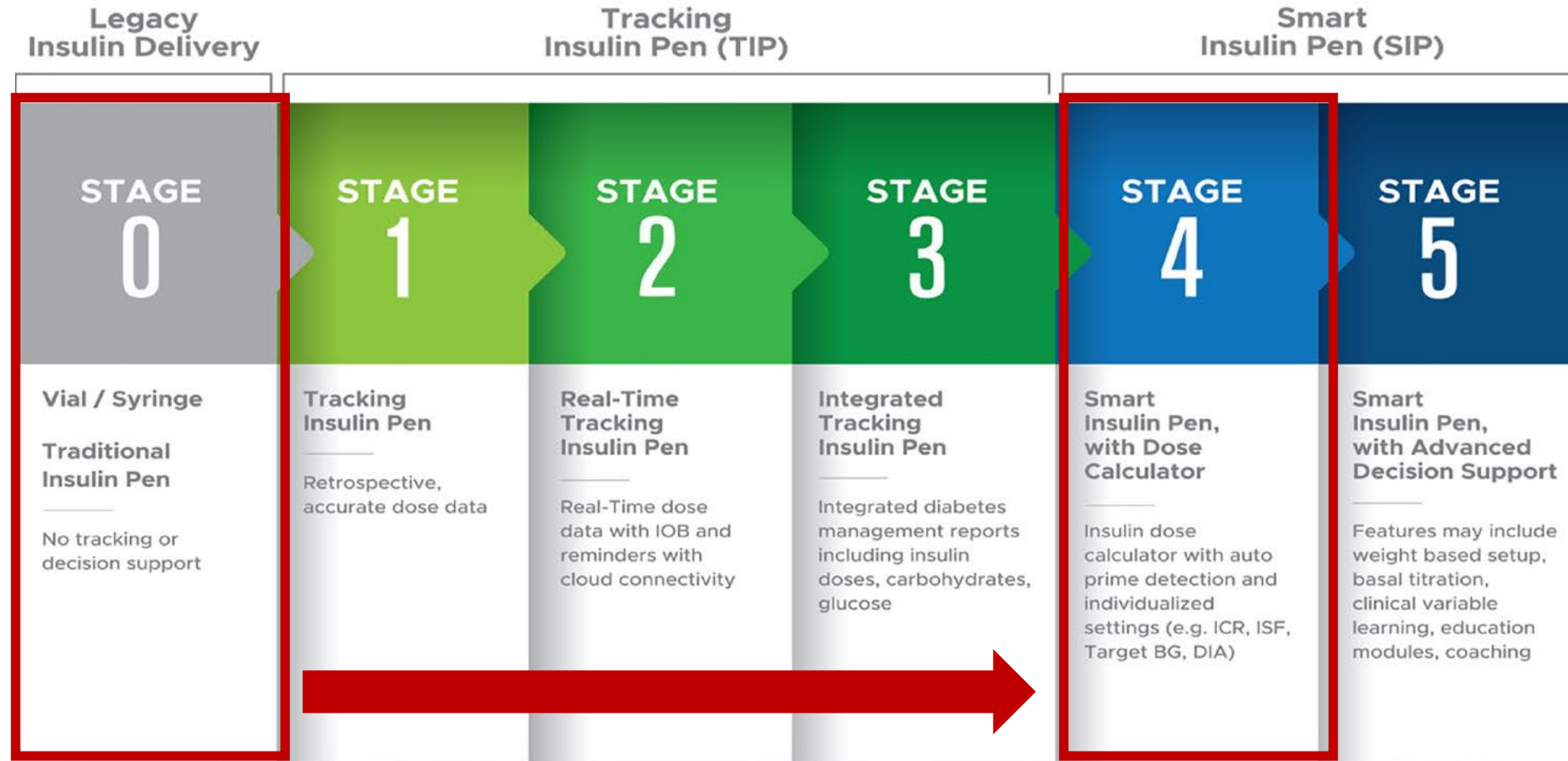
Penne intelligenti



Can Smart insulin pens help in a more technological world?

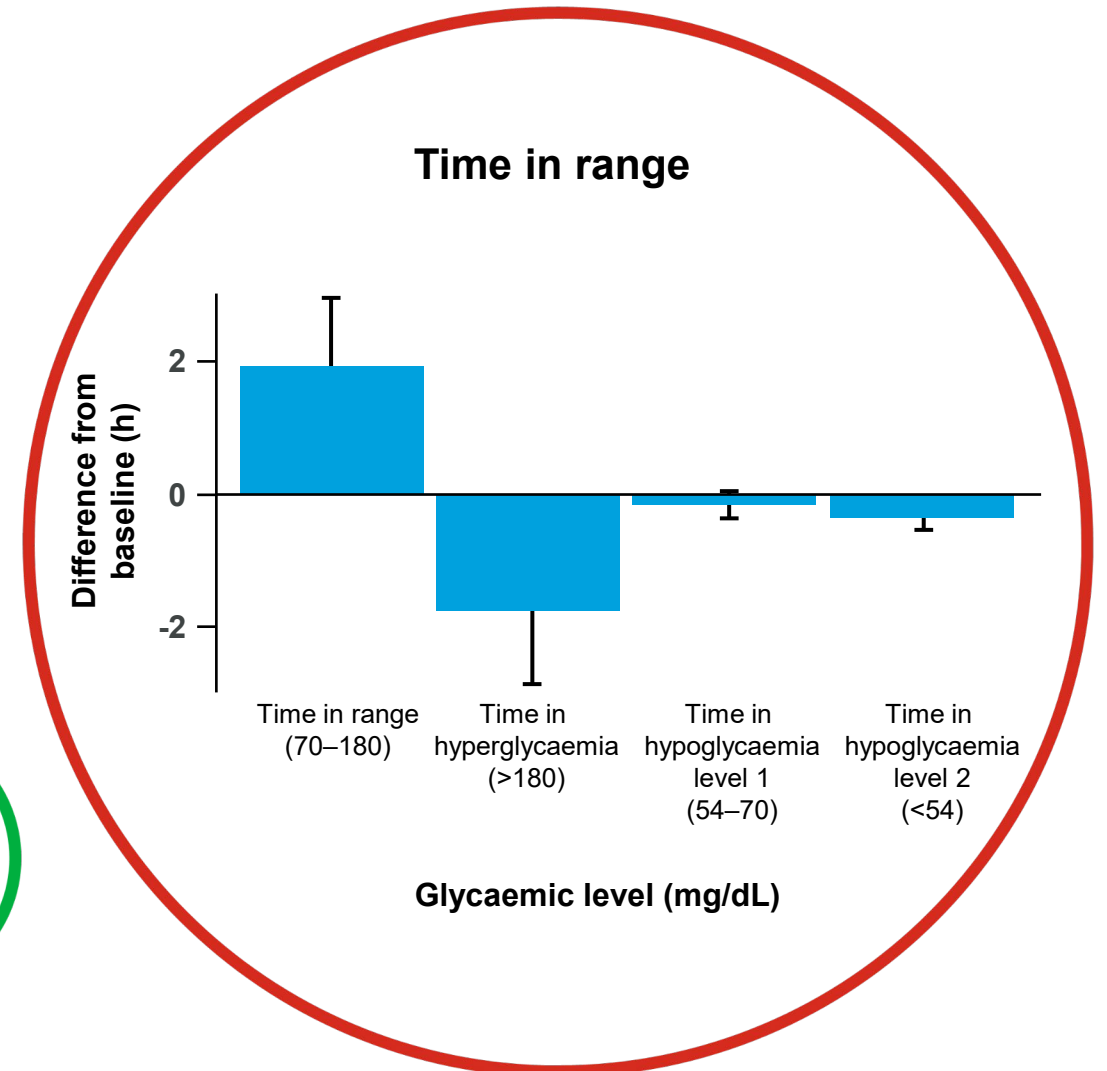


Insulin Pen roadmap

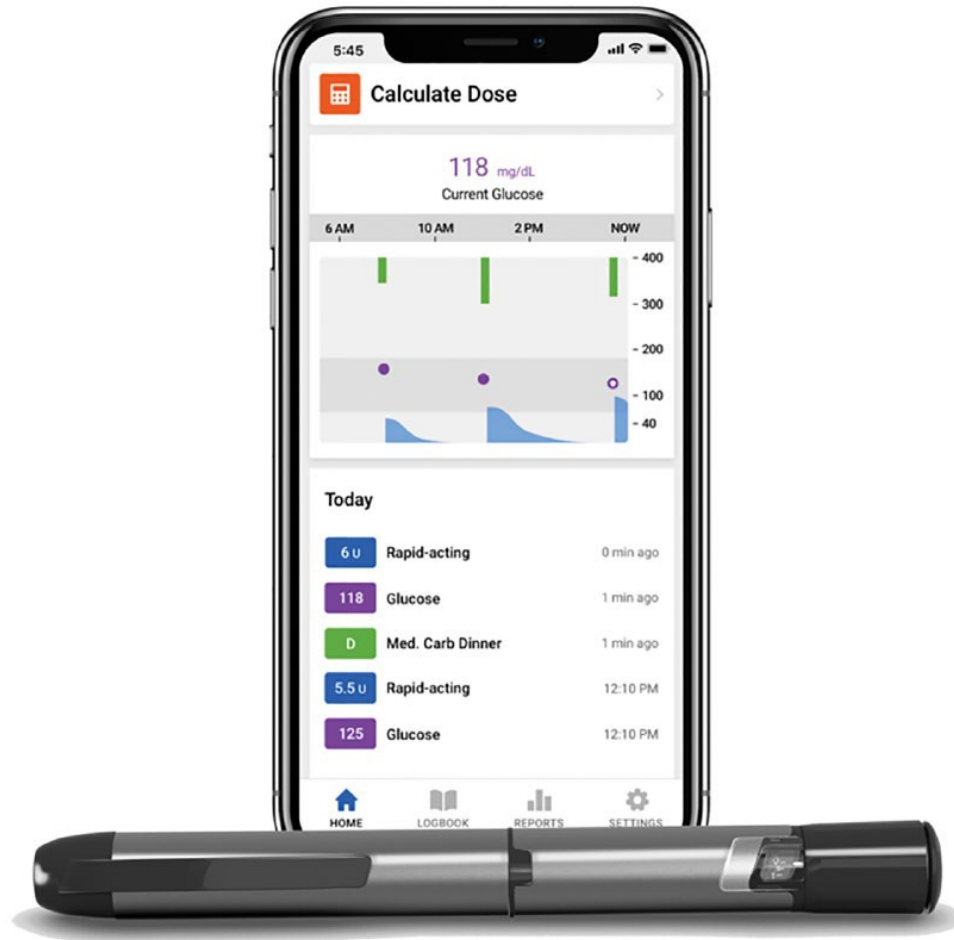


- Smart pens can support good injection behaviour, with fewer missed and more well-dosed mealtime injections and greater time in glycaemic range. This could lead to better glycaemic control
- Time spent in normal glycaemic range increased significantly from 9.2 to 11.1 hours/day ($P<0.001$)
- Reductions in hyperglycaemia and level 2 hypoglycaemia were also observed

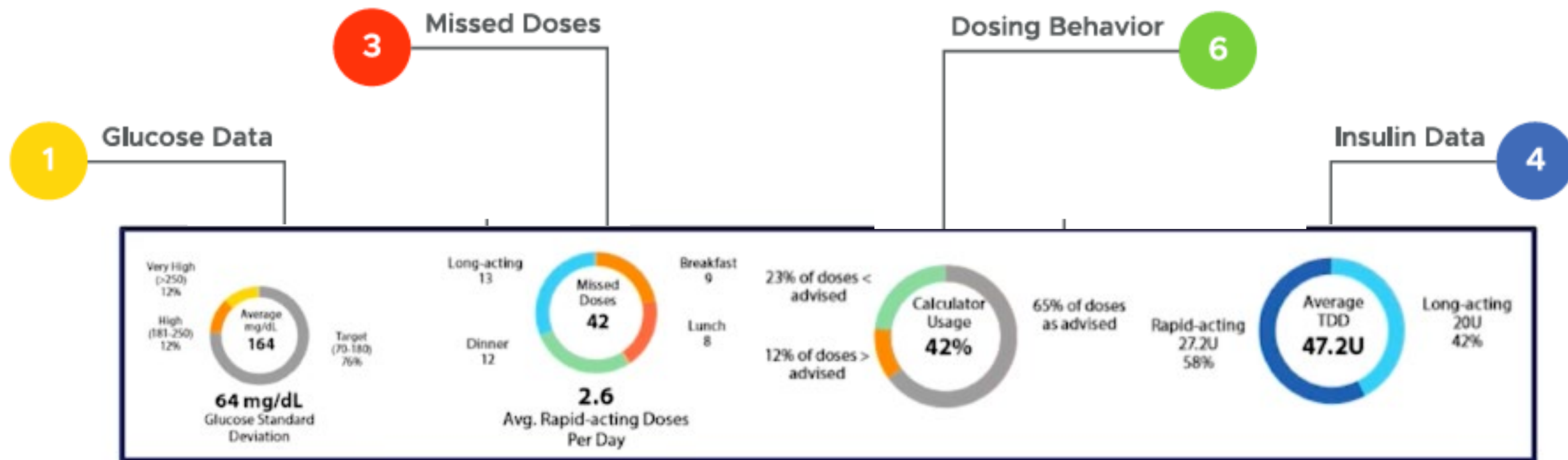
Smart pen users with T1D saw a **43% decrease** ($P=0.002$) in the average daily number of missed mealtime doses



Rechargeable Smart Insulin Pen



Rechargeable Smart Insulin Pen data report



Pre-filled Pen Smart System

“SMART PEN”



(basal insulin)



(mealtime insulin)



(fast-acting mealtime insulin)

The “**SMART PEN**” is a modified version of existing prefilled disposable insulin pen designed to work with the Smart Button.

“Smart Button”



- Device that can be attached to the Smart Pen dose knob
- Aids the compatible mobile application in the automated logging of insulin dose information

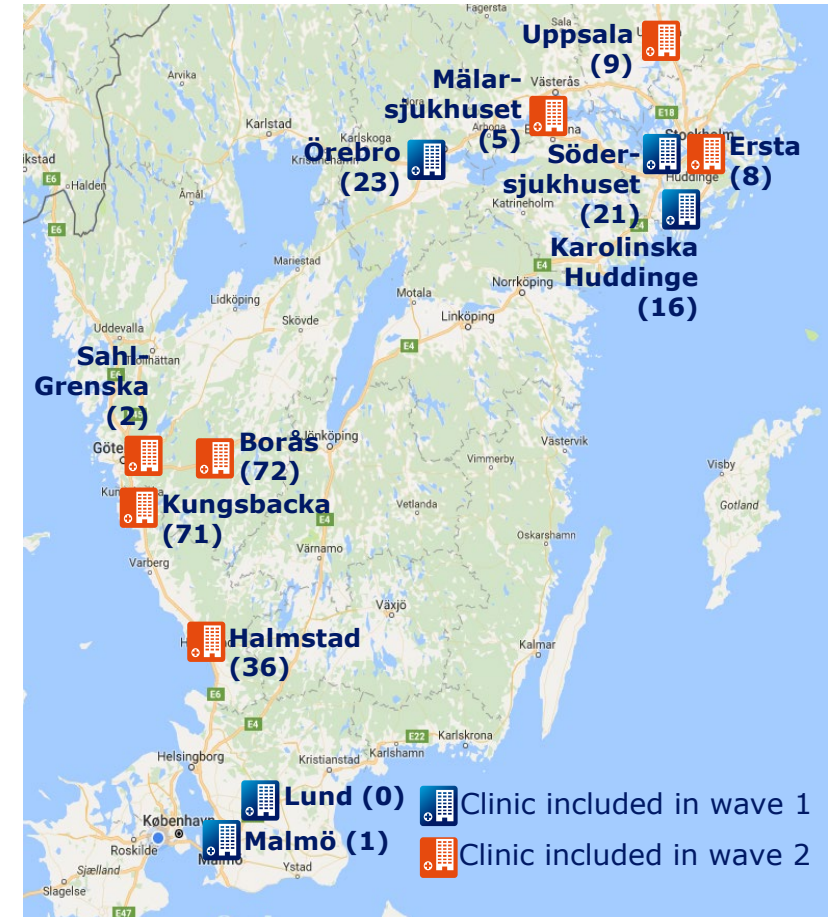
Compatible Apps and Software



A Clinical Proof of Concept study with **SMART PEN** in 12 T1 diabetes centres in Sweden: a non-interventional study

SMART PEN data downloaded at clinic
(no app available at this early stage)

- ➔ Number of units injected
- ➔ Date and time of dosing



**Pens downloaded in collection period
(Total: 270*)**

Questo prodotto ha ottenuto la certificazione CE ma non è disponibile sul mercato.

Increased Time in Range and Fewer Missed Bolus Injections After Introduction of a Smart Connected Insulin Pen. Adolfsson P, Hartvig NV, Kaas A, Møller JB, Hellman J. Diabetes Technol Ther. 2020 Oct;22(10):709-718. doi: 10.1089/dia.2019.0411. Epub 2020 Mar 11.

Adolfsson P. et. al. ADA 2019; Improved Insulin Adherence after Introduction of a Smart Connected Insulin Pen. 126-LB

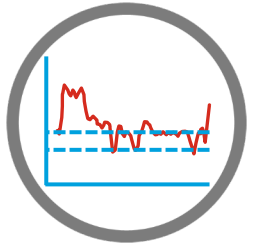
Key take-aways



Time and effort required to track insulin doses can be challenging¹



Smart pens can lead to improved adherence and time in range⁵



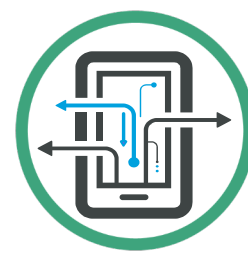
Missing insulin doses can reduce time in range and can increase time above range²



Electronic logbooks may help HCPs and patients optimise their time⁶



Complexity of diabetes treatment³ can cause emotional distress and reduce medication adherence⁴



Digital solutions help to address challenges in diabetes management⁷

HCP, healthcare provider.

¹Peyrot M, et al. Diabetic Medicine. 2012;29(5): 682–689; ²Edwards S, et al. Poster presented at: International Conference on ATTD; 19–22 February 2020; ³American Diabetes Association. Diabetes Care. 2019;42 Suppl 1: S1–S193; ⁴Polonsky WH, et al. Patient Preference and Adherence. 2016;10: 1299–1307; ⁵Adolfsson P, et al. Diabetes Technology & Therapeutics. 2020;22(10): 709–718; ⁶Hinnen DA, et al. Journal of Diabetes Science and Technology. 2015;9(2): 293–301; ⁷Warshaw H, et al. The Diabetes EDUCATOR. 2020;46(S4): 3S–20S.

Presente e futuro

Pancreas artificiale



Microinfusore di insulina in continuo senza catetere



Il presente



**International
Diabetes
Federation**



Grazie per la Vs Attenzione



**Carla
Giordano**

Conclusioni

- 1. Il diabete** è tra le patologie croniche a più alta incidenza e prevalenza con una **elevata mortalità per complicanze cardiovascolari e renali.**
- 2. I farmaci innovativi e i nuovi dispositivi**, come device, sensori e microinfusori **migliorano l'aderenza** alle cure, la qualità di vita dei pazienti e **migliorano gli outcome clinici**, riducendo in maniera significativa il rischio di ipoglicemie
- 3. L'applicazione appropriata delle Linee Guida**, potrebbe generare una riduzione delle spese legate ai ricoveri, spese diagnostiche et al, **riducendo il rischio di mortalità per eventi cardiovascolari, scompenso cardiaco, progressione della nefropatia**
- 4. L'innovazione tecnologica e farmacologica**, pur generando un lieve aumento dei costi per i farmaci nel breve termine (7-8% dell'intera spesa sostenuta per i pz diabetici), **riduce in maniera significativa i costi globali nel medio/lungo termine**, con un impatto positivo sulla vita delle persone affette da Diabete e delle loro famiglie.

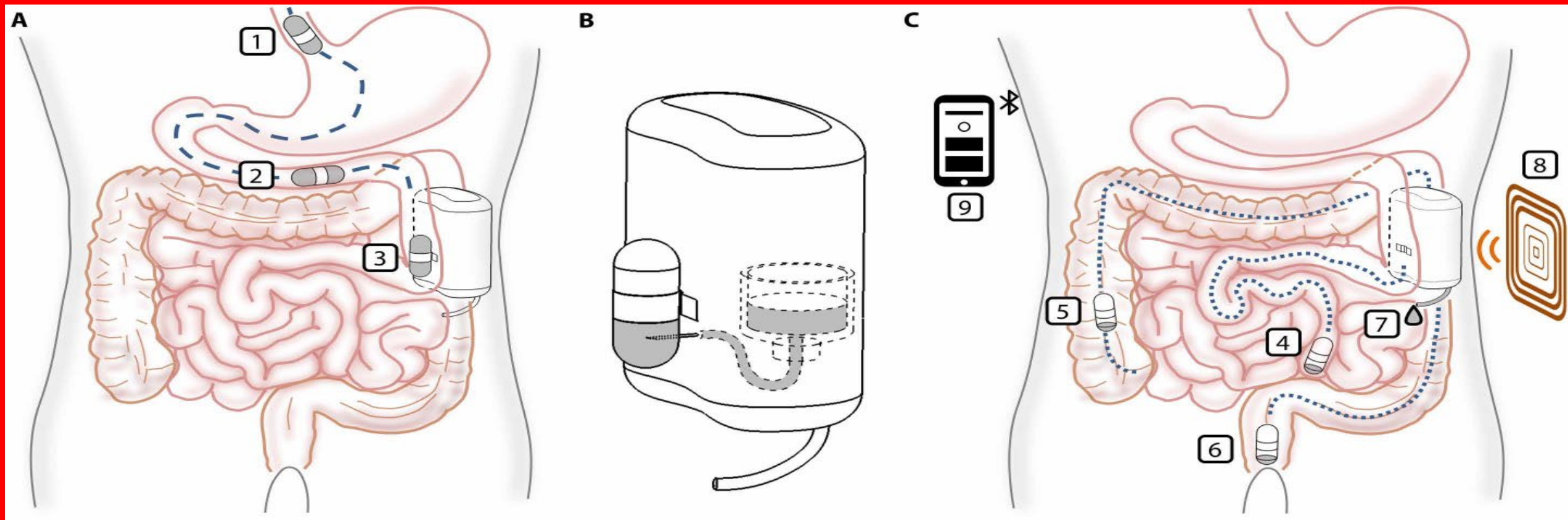
MEDICAL ROBOTS

A fully implantable device for intraperitoneal drug delivery refilled by ingestible capsules

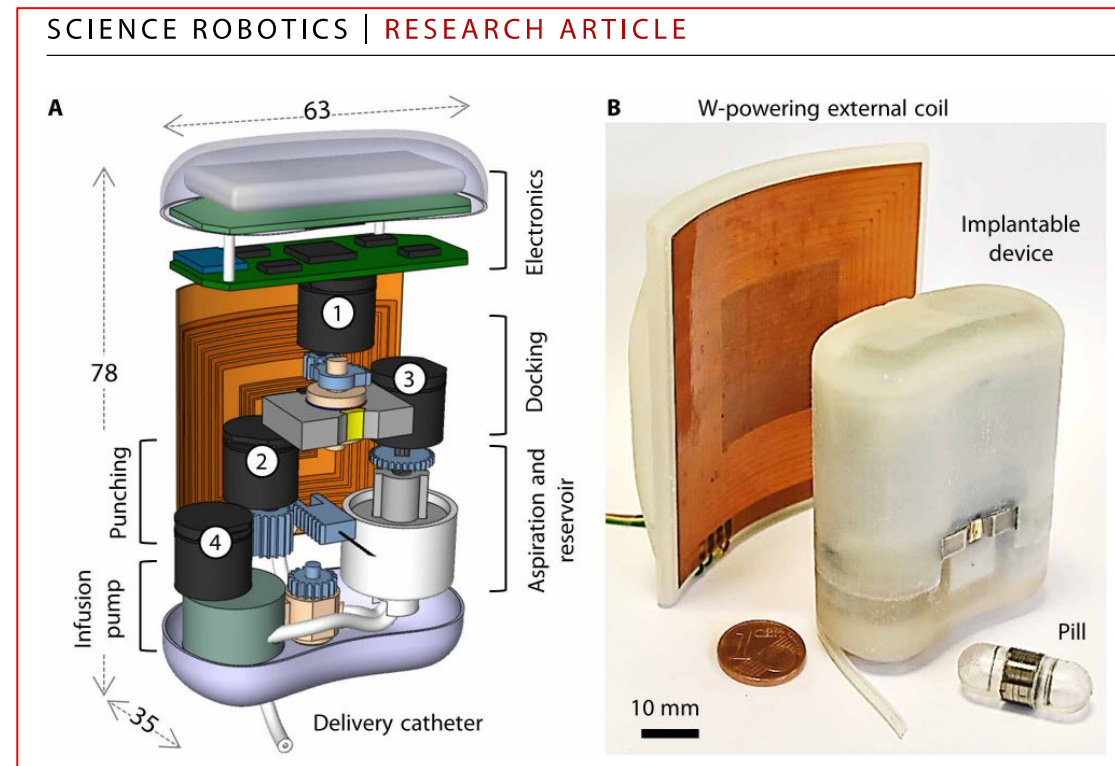
Veronica Iacovacci^{1,2,3†}, Izadyar Tamadon^{1,2†}, Emanuele Federico Kauffmann⁴, Stefano Pane^{1,2}, Virginia Simoni^{1,2}, Leonardo Marziale^{1,2}, Michele Aragona⁵, Luigi Cobuccio⁶, Massimo Chiarugi⁶, Paolo Dario^{1,2,7,8,9}, Stefano Del Prato⁵, Leonardo Ricotti^{1,2}, Fabio Vistoli⁴, Arianna Menciasci^{1,2*}

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to original U.S.
Government Works

Iacovacci *et al.*, *Sci. Robot.* 6, eabh3328 (2021) 18 August 2021



PILLSID system schematic depiction and prototype



PILLSID IN VIVO TESTING

SCIENCE ROBOTICS | RESEARCH ARTICLE

