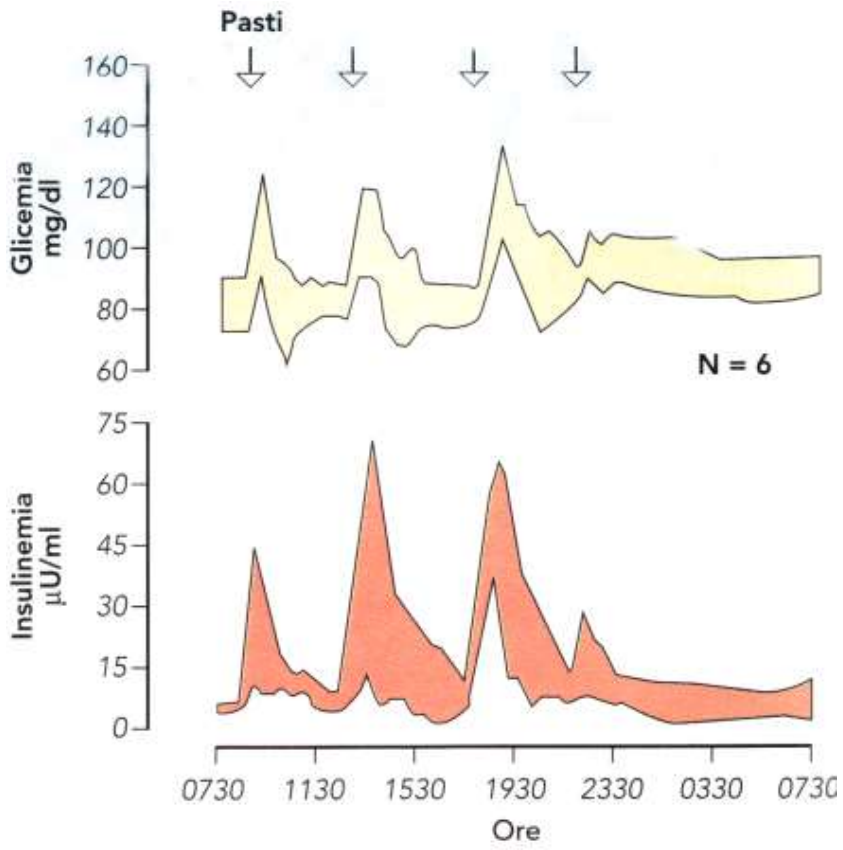
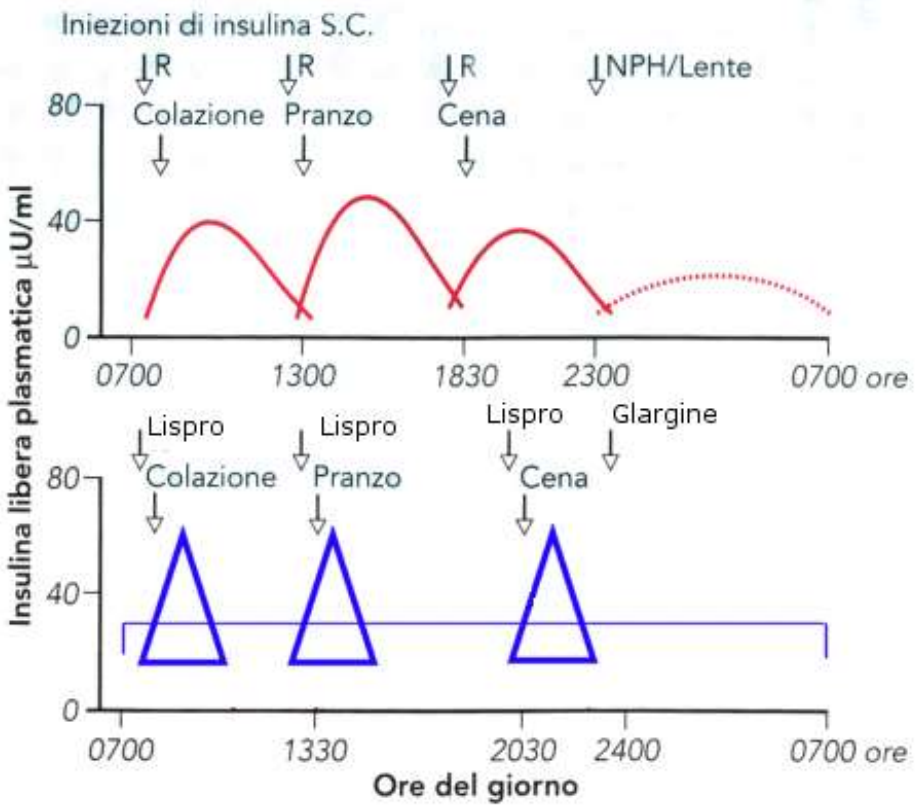
COME LA TECNOLOGIA PUÒ AIUTARE AD OTTIMIZZARE IL CONTROLLO GLICEMICO NEL DIABETE INSULINO-DIPENDENTE: MICROINFUSORI, SENSORI

Federico Bertuzzi

S.S.D. DIABETOLOGIA
A.O. "Ospedale Niguarda Ca'Granda" – Milano

Ottimizzazione compenso glicemico in presenza di un deficit di insulina: una sfida spesso difficile

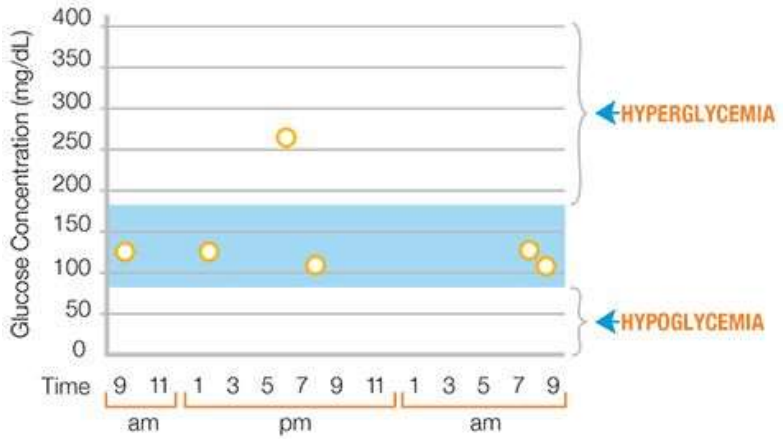


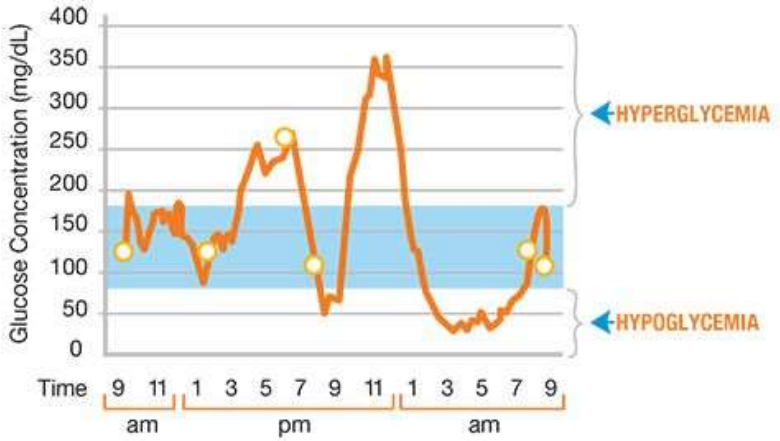


OBIETTIVO EUGLICEMIA

CONTROLLO GLICEMICO ⟷ **TERAPIA INSULINICA**

Monitoraggio glicemico





I Sistemi di Monitoraggio 24H su 24H rivelano delle informazioni che i sistemi di monitoraggio SMBG potrebbero non rivelare.

Bode BW, Schwartz S, Stubbs HA, Block JE. Glycemic characteristic in continuously monitored patients with type 1 and type 2 diabetes. *Diabetes Care*. 2005 October;28(10):2361-6

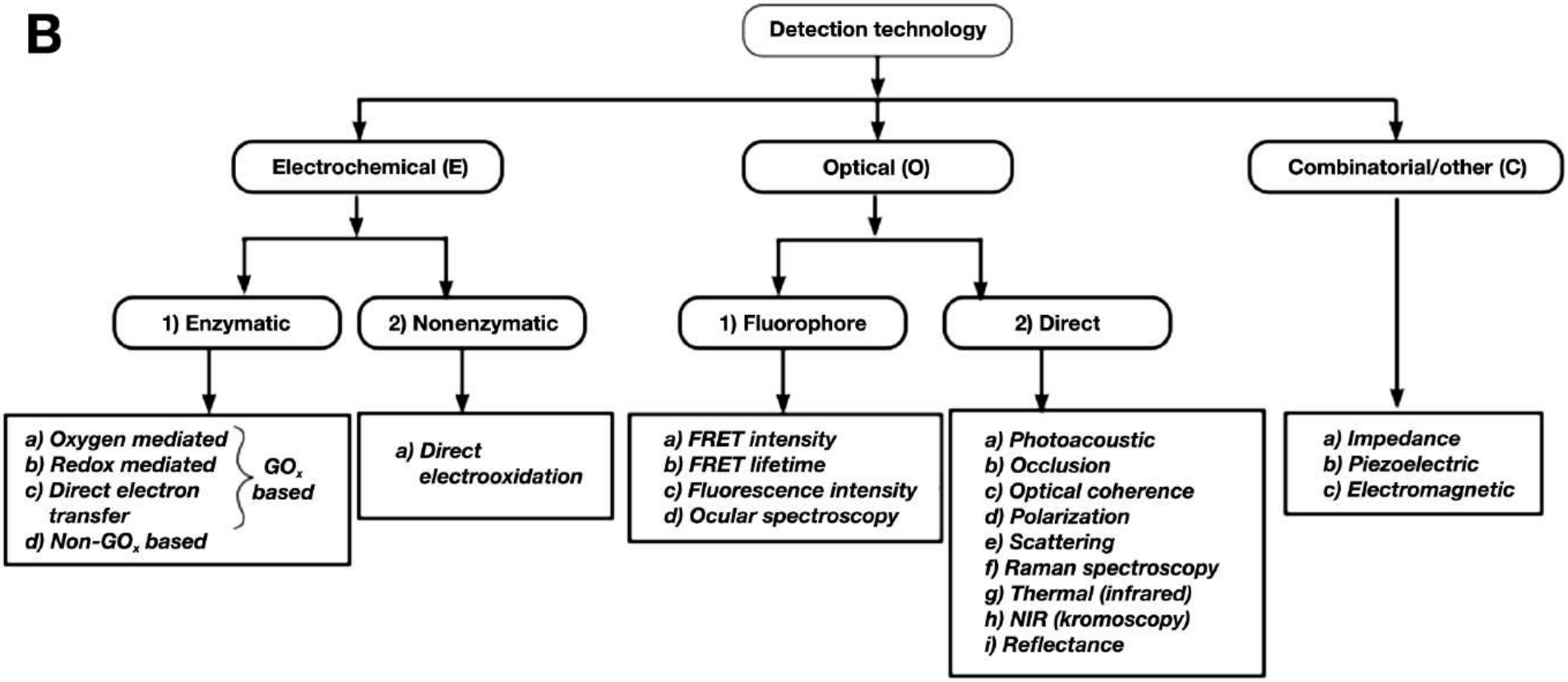
Journal of Diabetes Science and Technology
Volume 4, Issue 6, November 2010

ORIGINAL ARTICLES

Technologies for Continuous Glucose Monitoring: Current Problems and Future Promises

Santhisagar Vaddiraju, Ph.D.,[1,2] Diane J. Burgess, Ph.D.,[3] Ioannis Tomazos, Ph.D., M.B.A.,[2] Faquir C. Jain, Ph.D.,[4] and Fotios Papadimitrakopoulos, Ph.D.[1,5]

B



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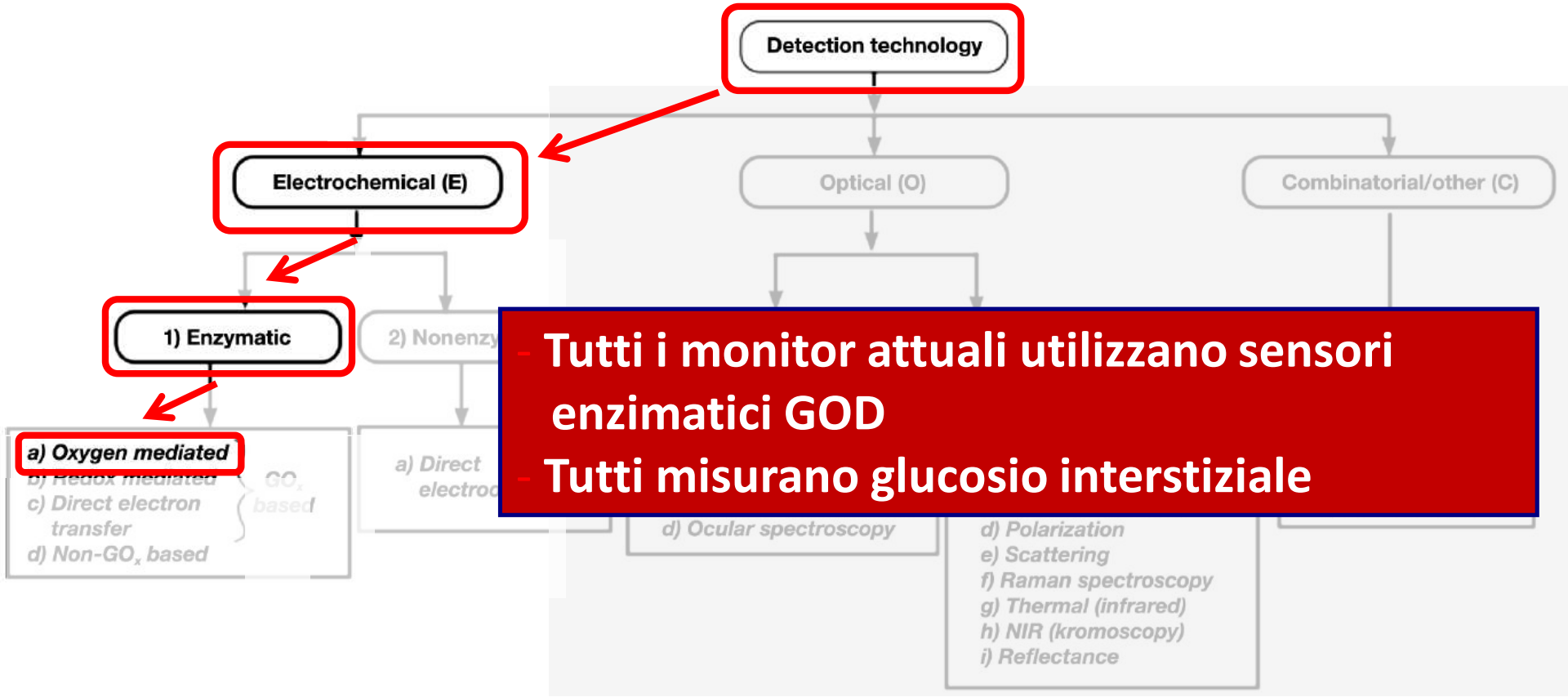


- Tutti i monitor attuali utilizzano sensori enzimatici GOD
- Tutti misurano glucosio interstiziale

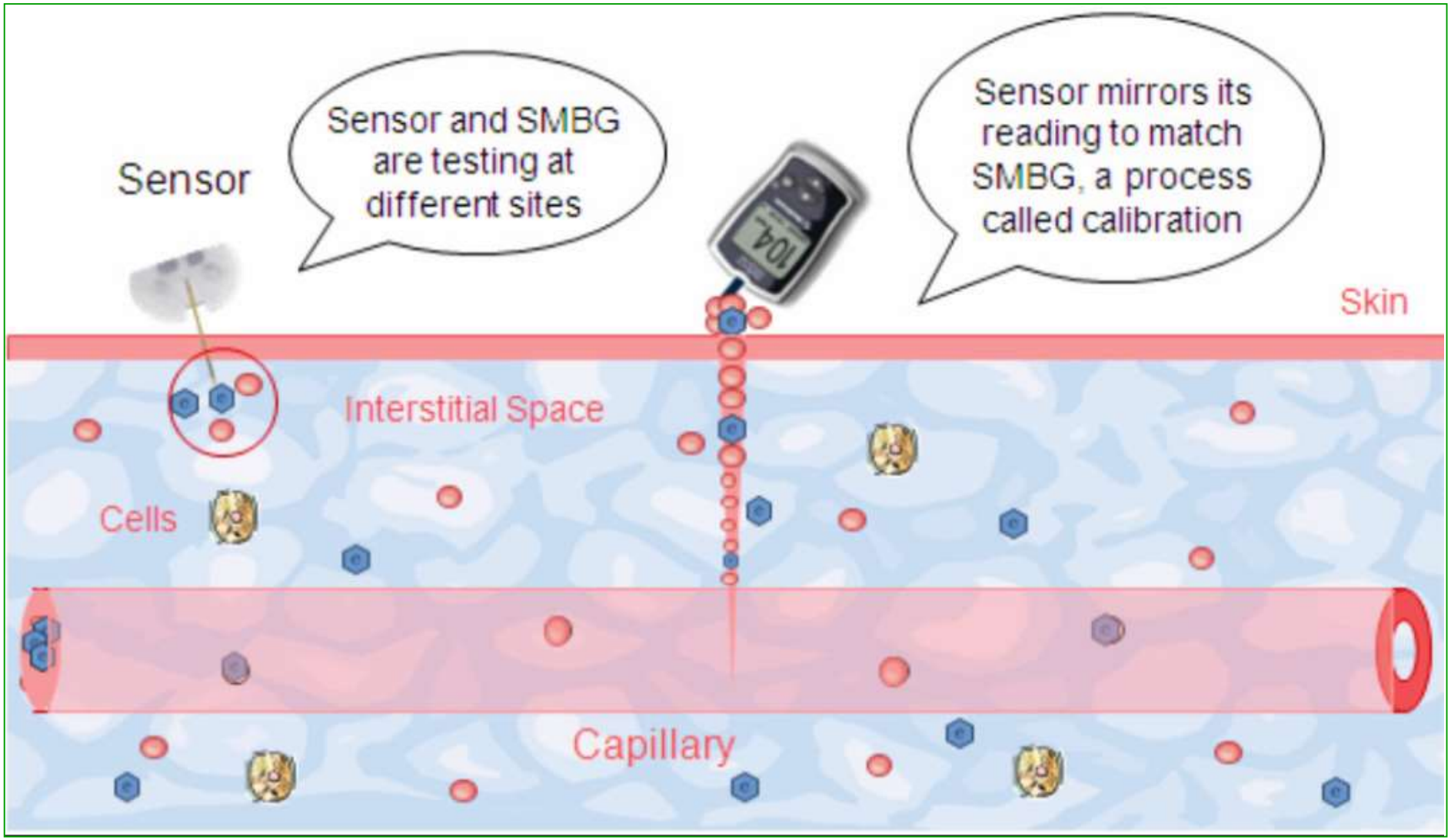
Journal of Diabetes Science and Technology
Volume 4, Issue 2, March 2010
© Diabetes Technology Society

CLINICAL APPLICATIONS

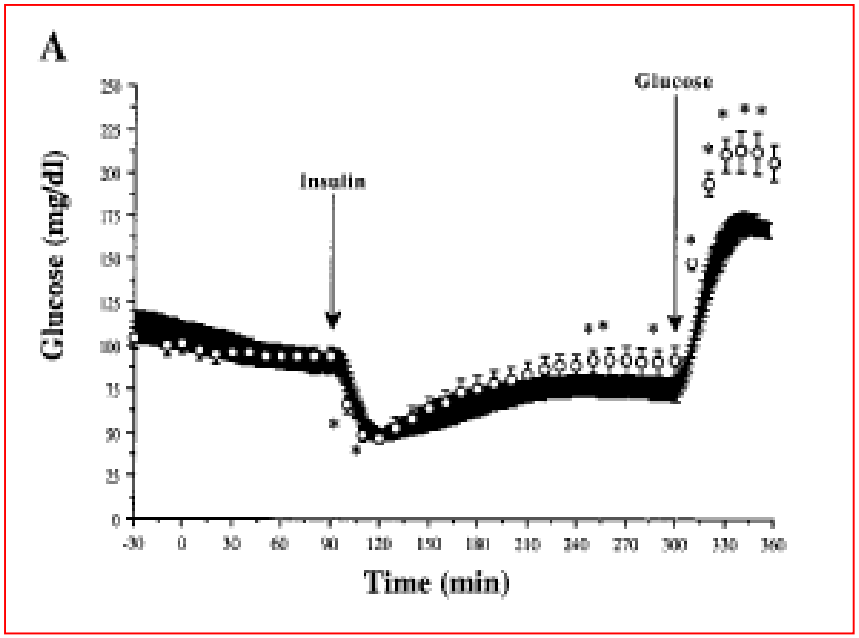
Professional Continuous Glucose Monitoring in Clinical Practice 2010

Thomas C. Blevins, M.D., FACE

INTERSTIZIO/SANGUE



“the relationship between glycemia and the interstitial glucose concentration is not simple”

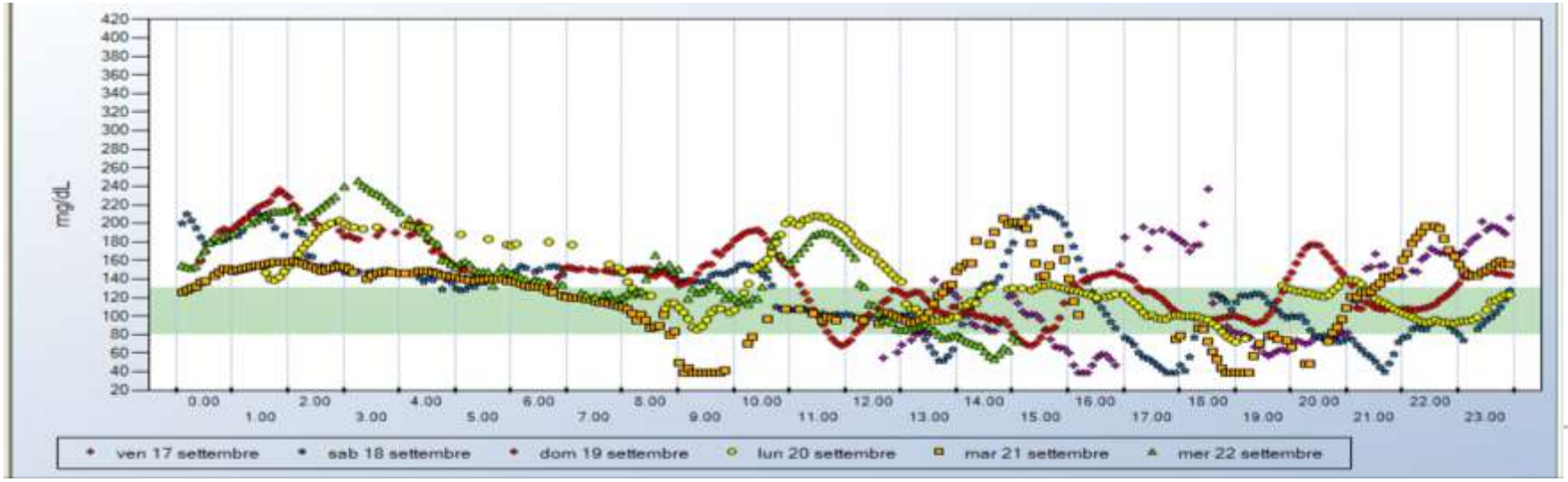


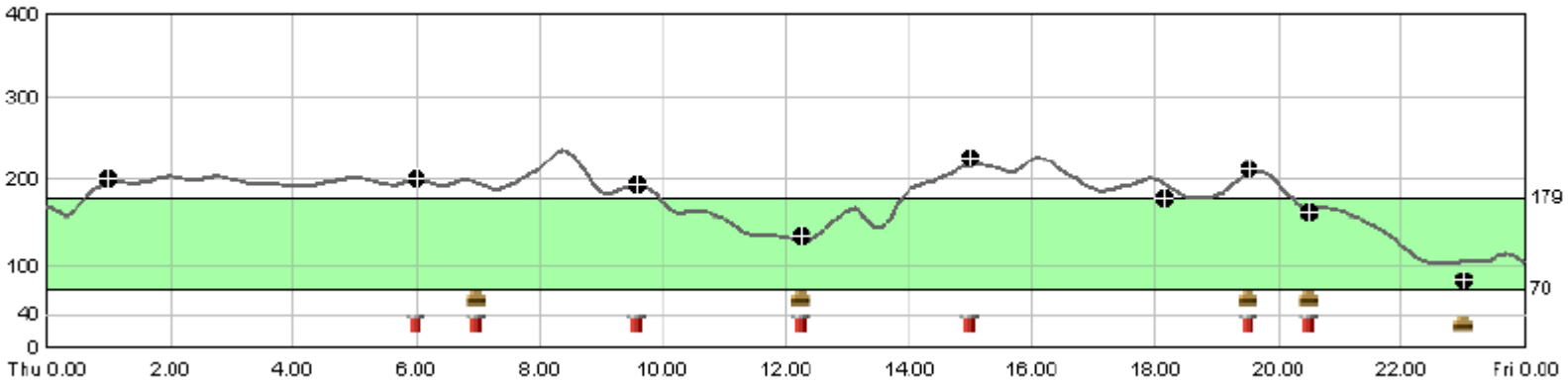
- **in condizioni di stabilità GIF e glicemia plasmatica sono equivalenti**
- **modificazioni rapide,in discesa e in salita,delle concentrazioni di glucosio sono ritardate a livello interstiziale (lag-time)**

B.Aussedat – Am J Physiol Endocrinol Metab, 2000

MONITOR RETROSPETTIVI

SENSOR DAILY DETAILS





MONITOR “REAL TIME”

ORIGINAL ARTICLE

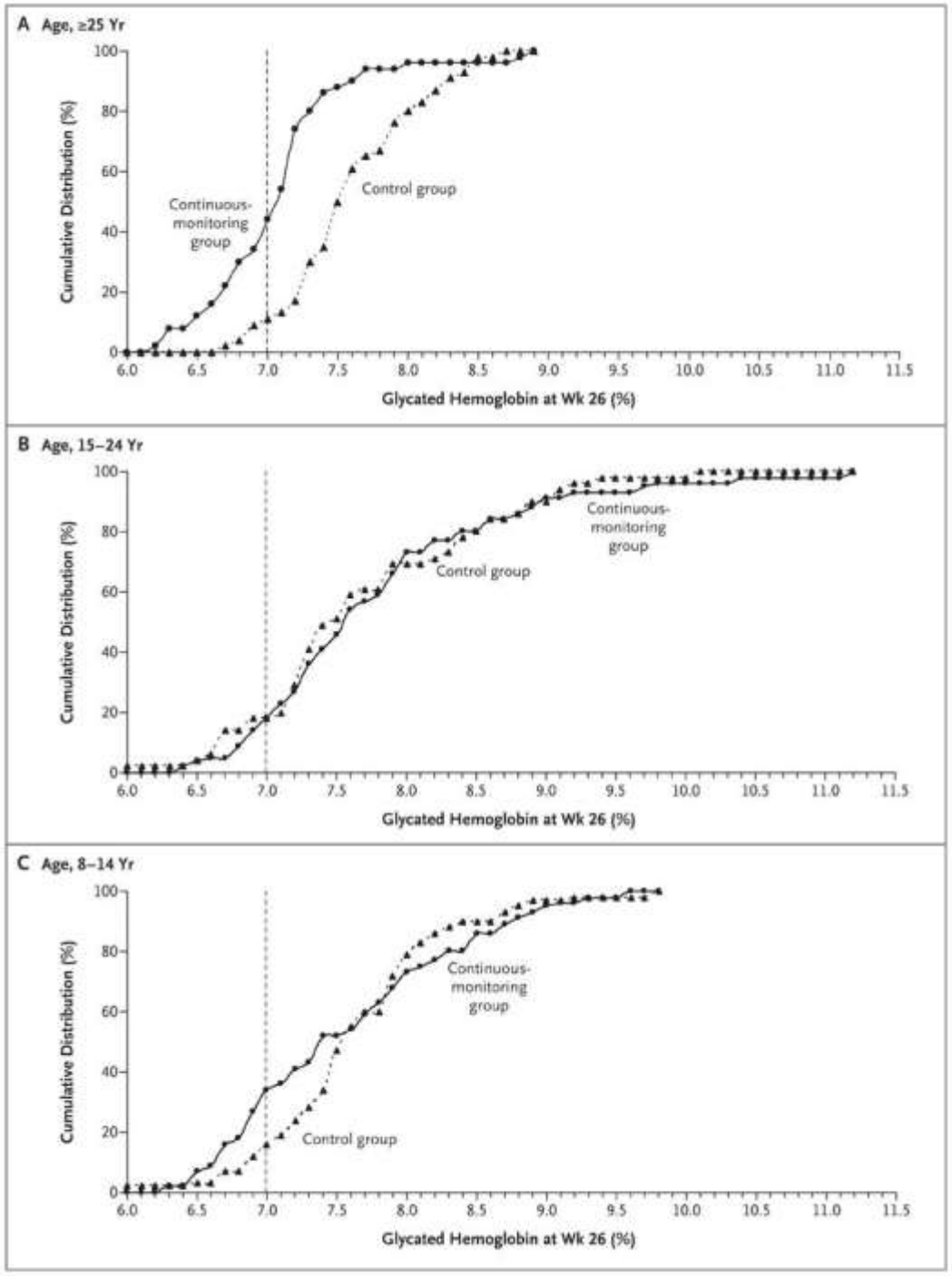
Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group*

N Engl J Med
Volume 359(14):1464-1476
October 2, 2008

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Distribution of Glycated Hemoglobin Levels, According to Age



The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. N Engl J Med 2008;359:1464-1476

The NEW ENGLAND JOURNAL of MEDICINE

Continuous glucose monitoring systems for type I diabetes mellitus (Review)

Langendam MW, Luijf YM, Hooft L, DeVries JH, Mudde AH, Scholten RJPM

The search identified 1366 references

THE COCHRANE COLLABORATION®

Twenty-two RCTs meeting the inclusion criteria of this review were identified

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 1

http://www.thecochranelibrary.com

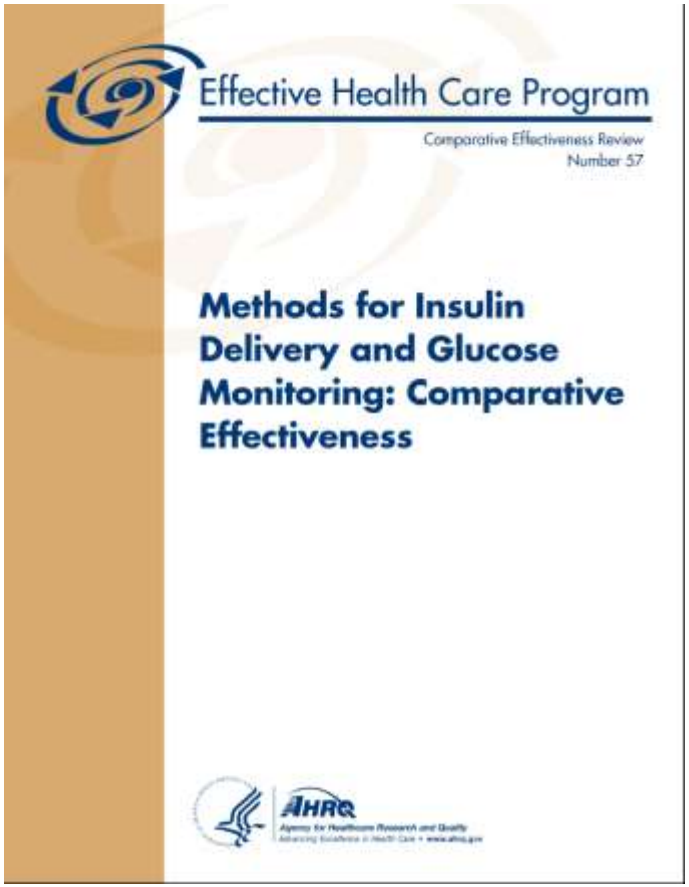
2012,157:336-347

REVIEW | Annals of Internal Medicine

Comparative Effectiveness and Safety of Methods of Insulin Delivery and Glucose Monitoring for Diabetes Mellitus

A Systematic Review and Meta-analysis

Hsin-Chieh Yeh, PhD; Todd T. Brown, MD, PhD; Nisa Maruthur, MD, MHS; Padmini Ranasinghe, MD, MPH; Zackary Berger, MD, PhD; Yong D. Suh, MBA, MSc; Lisa M. Wilson, ScM; Elisabeth B. Haberl, BA; Jessica Brick, MD; Eric B. Bass, MD, MPH; and Sherita Hill Golden, MD, MHS



2012,157:336-347

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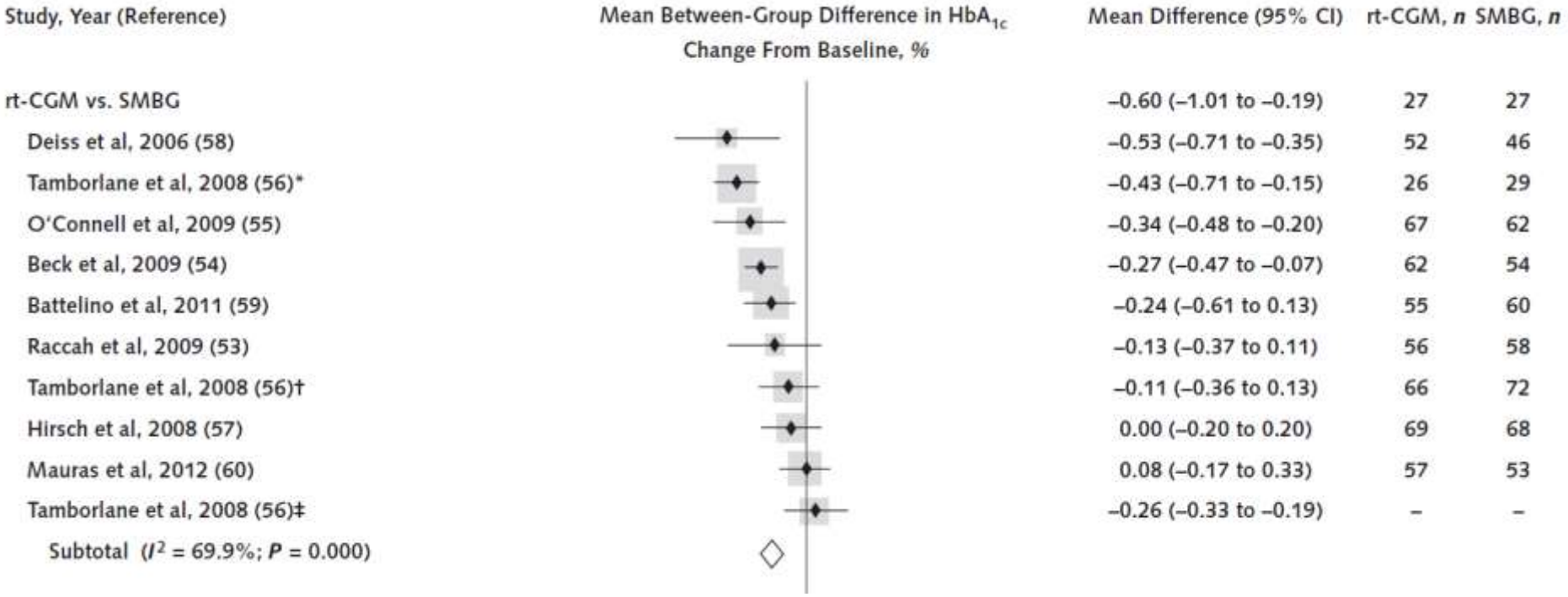
RT CGM vs SMBG: HbA1c



2012,157:336-347

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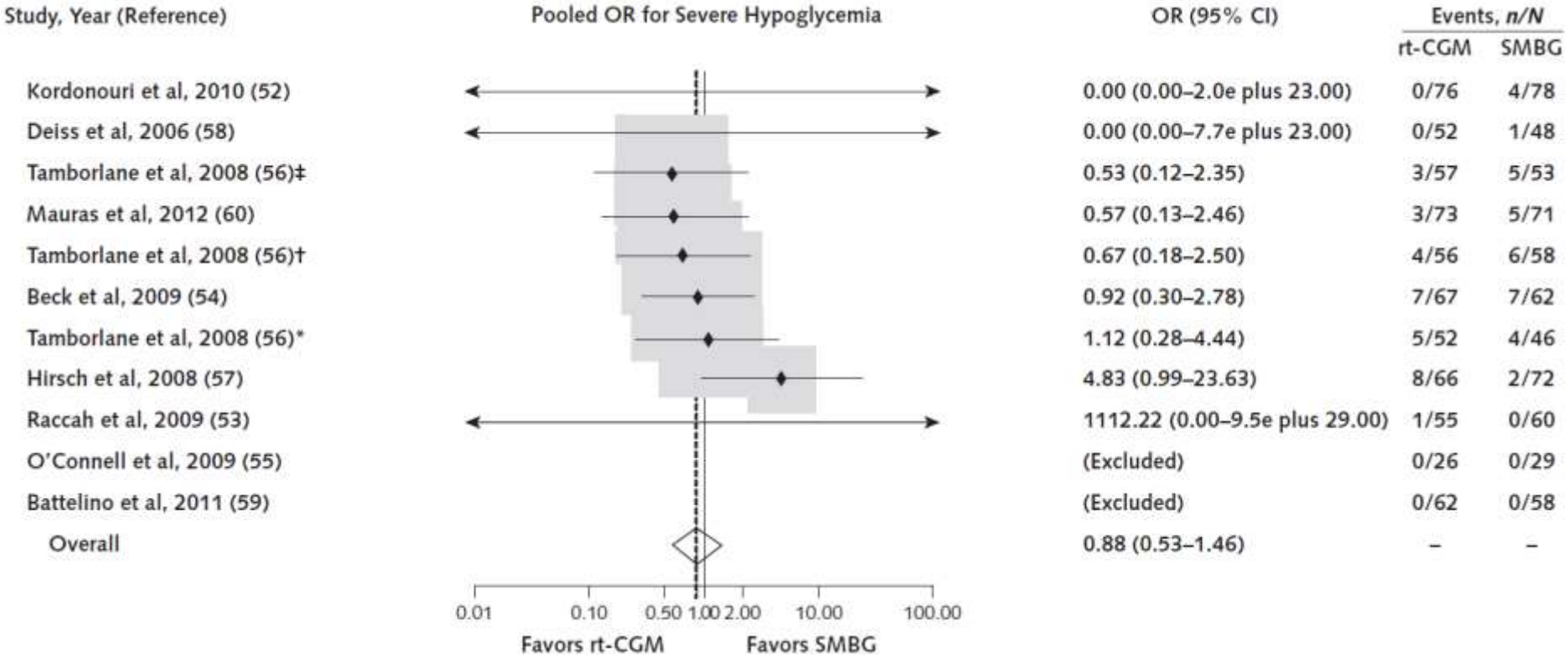
RT CGM vs SMBG: ipoglicemia



Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial

Jan Bolinder, Ramiro Antuna, Petronella Geelhoed-Duijvestijn, Jens Kröger, Raimund Weitg

www.thelancet.com Vol 388 November 5, 2016

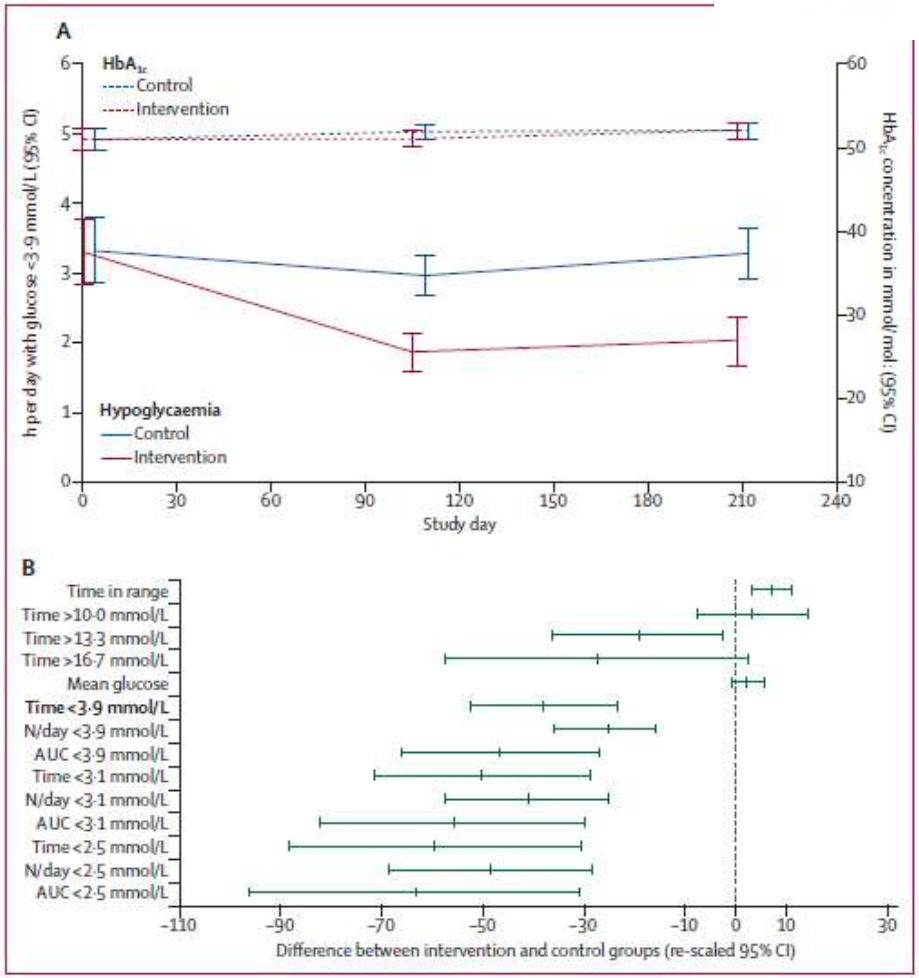


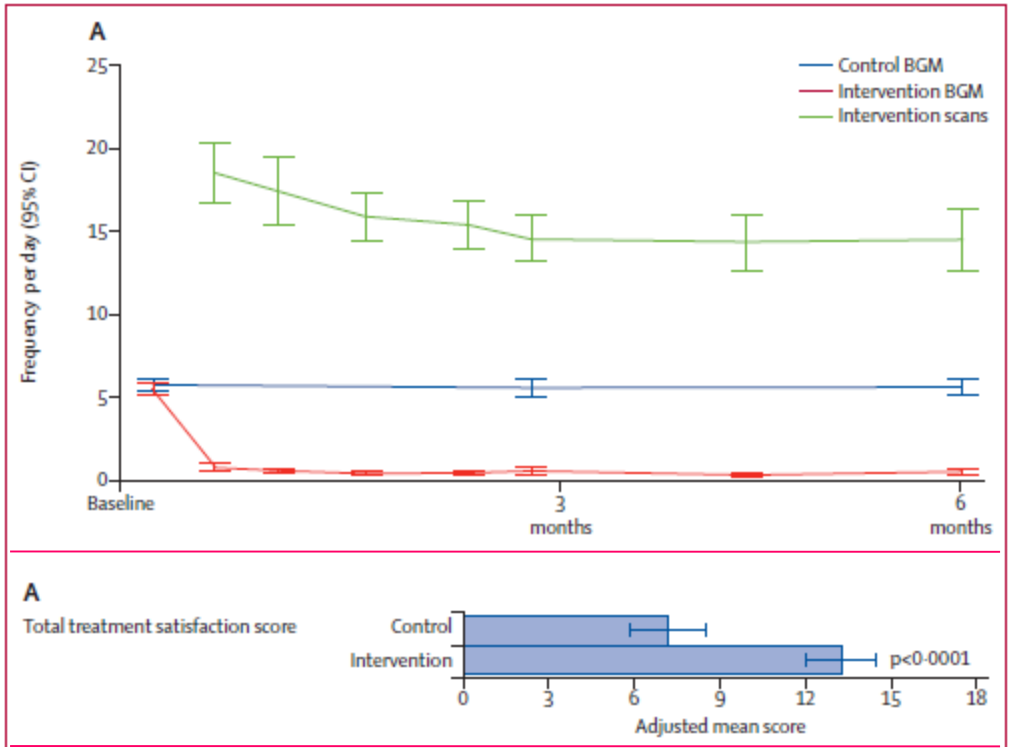
Figure 2: **Difference in groups for changes in time with hypoglycaemia and HbA_{1c} (A) and with glucose higher or lower than glycaemic thresholds (B)**

In A, control and intervention study day offset for clarity. In B, re-scaled confidence intervals are confidence intervals for the difference in the intervention group from the control group at 6 months expressed as a percentage of the control group adjusted mean.

Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial

Jan Bolinder, Ramiro Antuna, Petronella Geelhoed-Duijvestijn, Jens Kröger, Raimund W

www.thelancet.com Vol 388 November 5, 2016



Standard italiani per la cura del diabete mellito 2014

Il monitoraggio glicemico continuo (CGM) in associazione alla terapia insulinica intensiva, in pazienti con diabete tipo 1 selezionati e di età superiore ai 25 è uno strumento utile per ridurre l'HbA_{1c}.
(Livello della prova I, Forza della raccomandazione A)

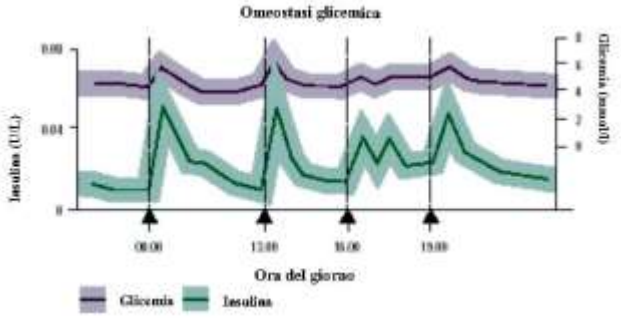
Il CGM può essere di utilità nel ridurre l'HbA_{1c} in diabetici tipo 1 in altre classi di età, in particolare nei bambini e comunque nei soggetti che dimostrano una buona aderenza all'utilizzo continuativo dello strumento.
(Livello della prova II, Forza della raccomandazione C)

Il CGM può contribuire a ridurre le ipoglicemie e può essere utile nel trattamento di soggetti proni all'ipoglicemica o con sindrome da ipoglicemia inavvertita.
(Livello della prova VI, Forza della raccomandazione E)

OBIETTIVO EUGLICEMIA

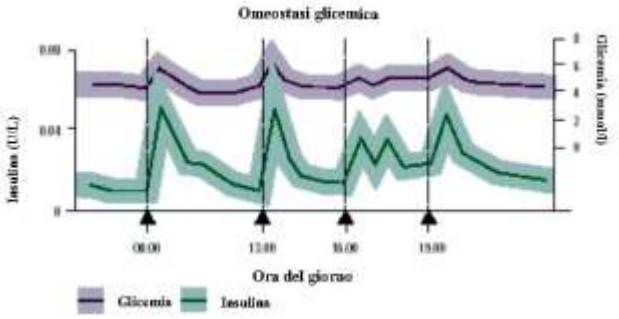
CONTROLLO GLICEMICO ⟷ **TERAPIA INSULINICA**

I microinfusori



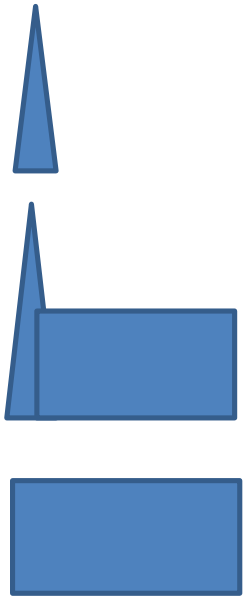
Caratteristiche microinfusori: componente basale

- Modalità di insulinizzazione fisiologica
- Possibilità di gestire fabbisogni insulinici molto ridotti
- Flessibilità:
  - Possibilità di variazioni temporanee
  - Disponibilità di schemi alternativi per situazioni ricorrenti



CARATTERISTICHE CSII componente bolus

- **Semplicità di erogazione in ogni situazione**
- **Facilità nella somministrazione di boli aggiuntivi**
- **Disponibilità di tipologie diverse di boli**



Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type I diabetes mellitus (Review)

Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J

The Cochrane Library 2010, Issue 1

CSII versus multiple insulin injections for type 1 diabetes mellitus

THE COCHRANE COLLABORATION®

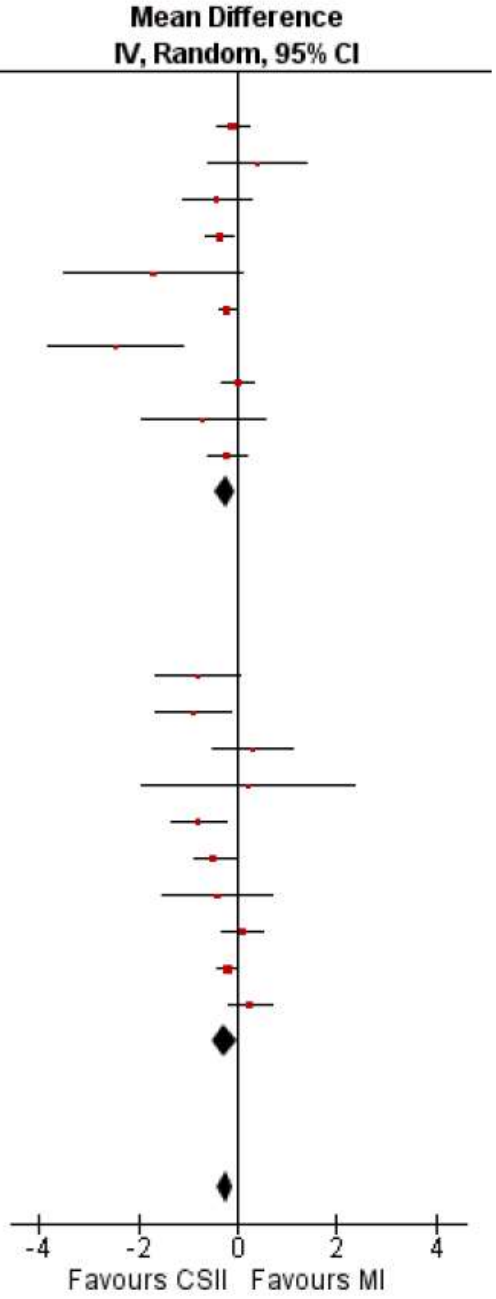
Main results

- **Twenty three studies randomised 976 participants with type 1 diabetes to either intervention.**
- **Statistically significant difference in HbA1c favouring CSII (weighted mean difference -0.3%).**
- **No obvious differences between the interventions for non-severe hypoglycaemia, but severe hypoglycaemia appeared to be reduced in those using CSII.**
- **Quality of life measures suggest that CSII is preferred over MI.**
- **No significant difference was found for weight.**

THE COCHRANE COLLABORATION®

HbA1c

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Cross-over trials				
Bruttomesso 2008	-0.1	0.168367	8.3%	-0.10 [-0.43, 0.23]
Chiasson 1984 and 1985	0.4	0.5	2.0%	0.40 [-0.58, 1.38]
Cohen 2003	-0.42	0.35	3.6%	-0.42 [-1.11, 0.27]
Hanaire-Broutin 2000	-0.35	0.14	9.4%	-0.35 [-0.62, -0.08]
Home 1982	-1.7	0.918367	0.7%	-1.70 [-3.50, 0.10]
Hoogma 2005	-0.22	0.08	11.9%	-0.22 [-0.38, -0.06]
Nathan 1982	-2.48	0.704082	1.1%	-2.48 [-3.86, -1.10]
Saurbrey 1988	0	0.16	8.6%	0.00 [-0.31, 0.31]
Schmitz 1989	-0.7	0.632653	1.3%	-0.70 [-1.94, 0.54]
Weintrob 2004	-0.2	0.2	7.1%	-0.20 [-0.59, 0.19]
Subtotal (95% CI)			**54.2%**	**-0.25 [-0.45, -0.05]**
Heterogeneity: Tau² = 0.04; Chi² = 18.61, df = 9 (P = 0.03); I² = 52%				
Test for overall effect: Z = 2.43 (P = 0.02)				
1.1.2 Parallel trials				
DeVries 2002	-0.8	0.433673	2.6%	-0.80 [-1.65, 0.05]
Doyle 2004	-0.9	0.397959	3.0%	-0.90 [-1.68, -0.12]
Lepore 2003	0.3	0.423469	2.7%	0.30 [-0.53, 1.13]
Meschi 1982	0.2	1.091837	0.5%	0.20 [-1.94, 2.34]
Nosadini 1988	-0.8	0.280612	4.9%	-0.80 [-1.35, -0.25]
Nuboer 2008	-0.48	0.214286	6.7%	-0.48 [-0.90, -0.06]
Oslo Study 1985 to 1992	-0.4	0.566327	1.6%	-0.40 [-1.51, 0.71]
Pozzilli 2003	0.1	0.209184	6.8%	0.10 [-0.31, 0.51]
Skogsberg 2008	-0.2	0.112245	10.6%	-0.20 [-0.42, 0.02]
Tsui 2001	0.25	0.221939	6.4%	0.25 [-0.18, 0.68]
Subtotal (95% CI)			**45.8%**	**-0.26 [-0.52, -0.00]**
Heterogeneity: Tau² = 0.08; Chi² = 19.06, df = 9 (P = 0.02); I² = 53%				
Test for overall effect: Z = 1.99 (P = 0.05)				
Total (95% CI)			**100.0%**	**-0.25 [-0.40, -0.10]**
Heterogeneity: Tau² = 0.04; Chi² = 37.68, df = 19 (P = 0.007); I² = 50%				
Test for overall effect: Z = 3.25 (P = 0.001)				



Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

Isabelle Steineck,[1] Jan Cederholm,[2] Björn Eliasson,[3] Araz Rawshani,[4] Katarina Eeg-Olofsson,[3] Ann-Marie Svensson,[4] Björn Zethelius,[5,6] Tarik Avdic,[4] Mona Landin-Olsson,[7] Johan Jendle,[8] Soffia Gudbjörnsdóttir[3,4] the Swedish National Diabetes Register

the bmj | *BMJ* 2015;350:h3234 | doi: 10.1136/bmj.h3234

WHAT THIS STUDY ADDS

Treatment of type 1 diabetes with an insulin pump is associated with significantly lower adjusted hazard ratios for fatal coronary heart disease, fatal cardiovascular disease, and all cause mortality, as well as non-significant reduction in hazard ratios for non-fatal or fatal cardiovascular disease

Patient education and frequency of blood glucose monitoring might have influenced the observed association

POMPE INTELLIGENTI ("SMART PUMPS")

- **Supporto decisionale** (previa programmazione)
  - Obiettivi glicemici nelle differenti fasi giornaliere
  - FS personale nelle diverse fasi giornaliere
  - I/CHO personale nelle differenti fasi giornaliere.
  - Suggerimento bolo in base a:
    - glicemia riscontrata all'autocontrollo
    - quantitativo di CHO introdotti con il pasto
    - attività insulinica residua

INTEGRATED SYSTEMS (SAP)

POTENTIAL ADVANTAGES

- Possible more aggressive therapeutical approach
- Pursuit of more physiological glucose targets
- Greater psychological confidence

SOSPENSIONE PER GLICEMIA BASSA

Obiettivo della funzione Sospensione Glicemia Bassa è di ridurre la severità delle ipoglicemia, non di prevenirle

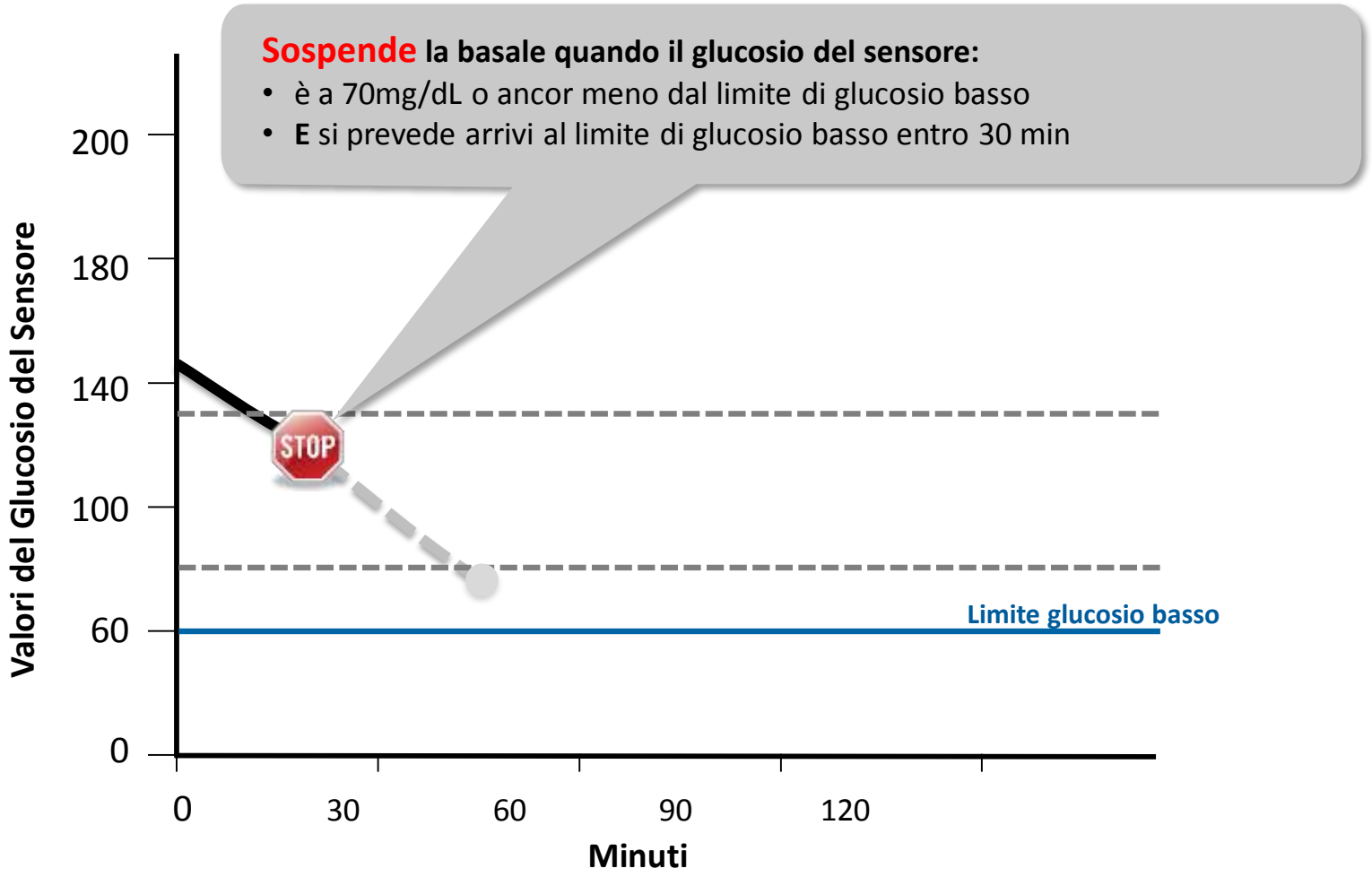
SAP: INTERAZIONE SENSORE-INFUSORE

- **Trasmissione dei dati del sensore all'infusore, e visualizzazione sul display**

- **Sospensione per glicemia bassa («Threshold Suspend Feature»)**

- **Sospensione preventiva per glicemia in discesa («Predictive Low Glucose Management» System)**

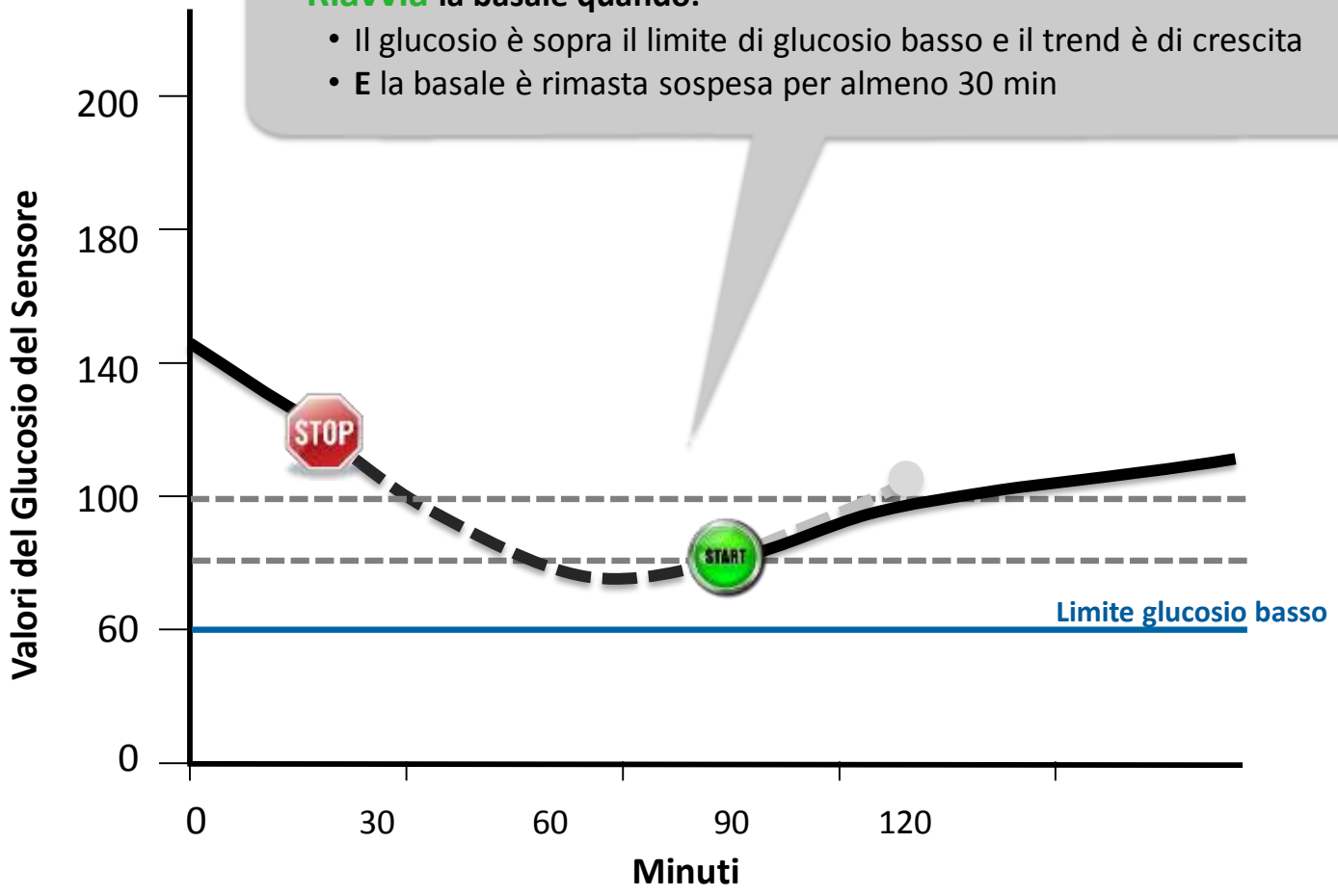
PREDICTIVE LOW GLUCOSE MANAGEMENT
SOSPENSIONE PREVENTIVA INFUSIONE



PREDICTIVE LOW GLUCOSE MANAGEMENT
RIAVVIO AUTOMATICO BASALE

Riavvia la basale quando:

- Il glucosio è sopra il limite di glucosio basso e il trend è di crescita
- **E** la basale è rimasta sospesa per almeno 30 min



Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

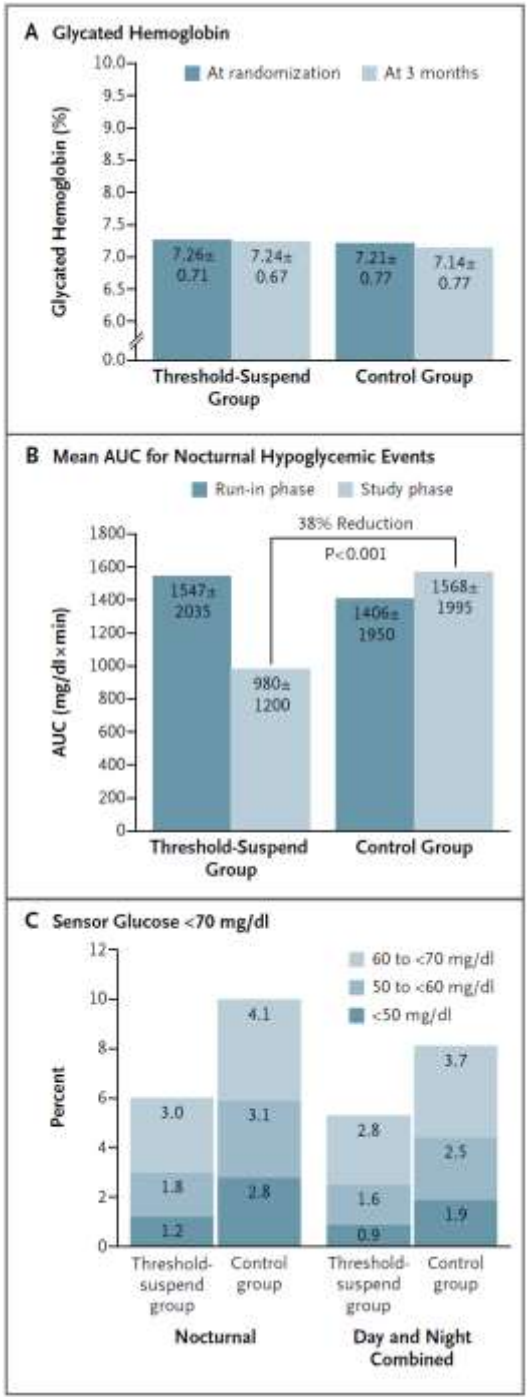
Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahrmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*

N Engl J Med 2013;369:224-32.

change in HbA1c negligible in both groups

mean AUC for nocturnal hypo-glycemic events: 37.5% less than that of the control group (P<0.001)

% sensor glucose values < 70 lower in the threshold-suspend than in the control group, whether during night (6.0% vs. 10.0%) or during day and night combined (5.3% vs. 8.1%).



Standard italiani per la cura del diabete mellito 2014

In soggetti selezionati che, malgrado un regime basal-bolus ottimale, presentino scarso controllo glicemico e/o ipoglicemie ricorrenti, può essere considerata l'indicazione all'uso del microinfusore da parte di un team esperto nel suo utilizzo.
(Livello della prova III, Forza della raccomandazione B)

Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial

Yves Reznik, Ohad Cohen, Ronnie Aronson, Ignacio Conget, Sarah Runzis, Javier Castaneda, Scott W Lee, for the OpT2mise Study Group

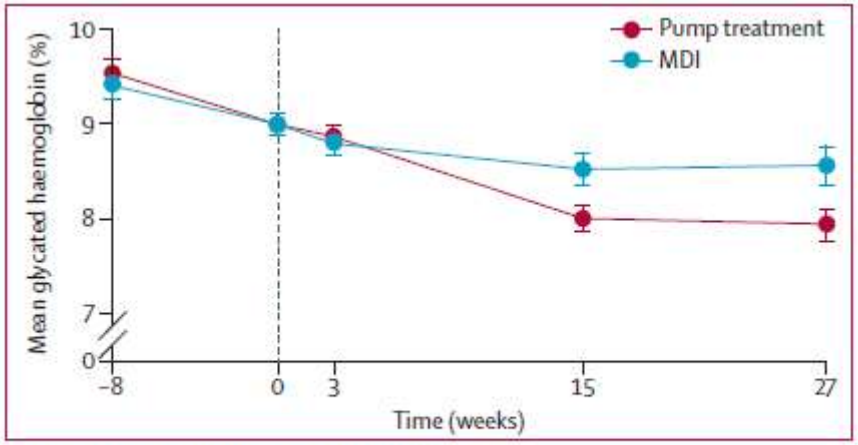


Figure 2: **Changes in glycated haemoglobin**
Error bars are 95% CIs. MDI=multiple daily injection.

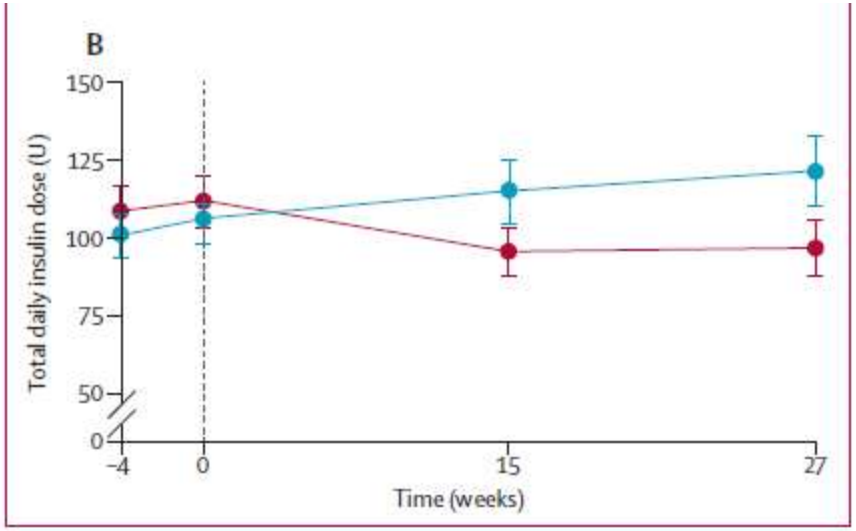


Figure 3: **Cumulative distribution of glycated haemoglobin at 6 months (A) and total daily insulin dose (B)**
Error bars are 95% CIs. MDI=multiple daily injection.

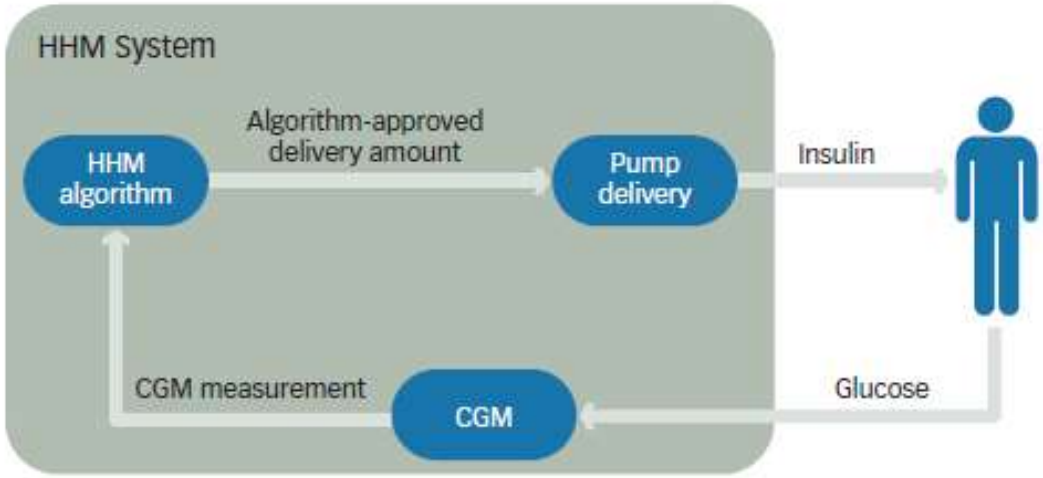
The Hypoglycaemia-Hyperglycaemia Minimizer System in the Management of Type 1 Diabetes

Brian L Levy, Thomas W McCann, Jr and Daniel A Finan

Animas Corporation, Wayne, USA

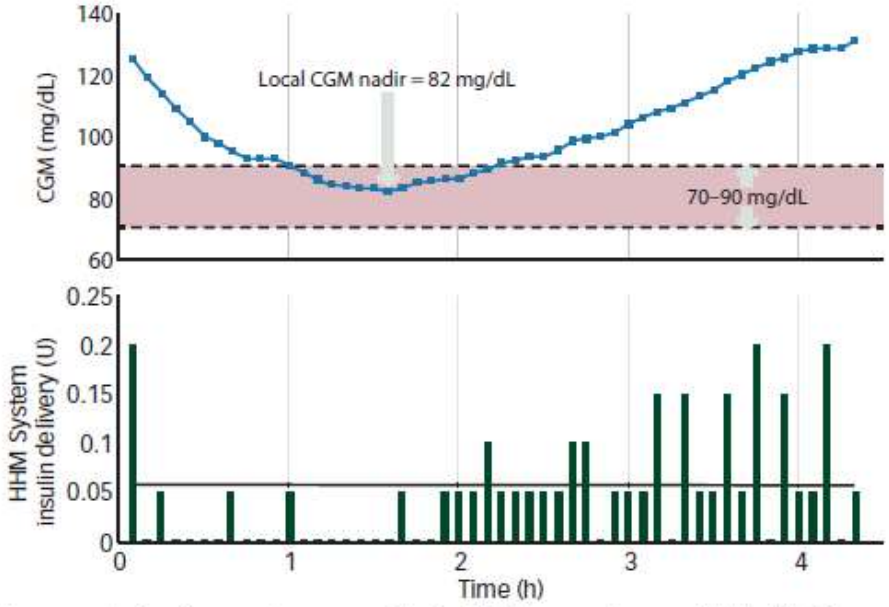
Received: 16 December 2015 **Accepted**: 25 January 2016 **Citation**: *European Endocrinology*, 2016;12(1):18–23
Correspondence: Daniel A Finan, Animas Corporation, 965 Chesterbrook Blvd, Wayne, PA 19087, US E: DFinan@its.jnj.com

Figure 1: Schematic Diagram Showing the Mechanism of Action of the Hypoglycaemia-Hyperglycaemia Minimizer System



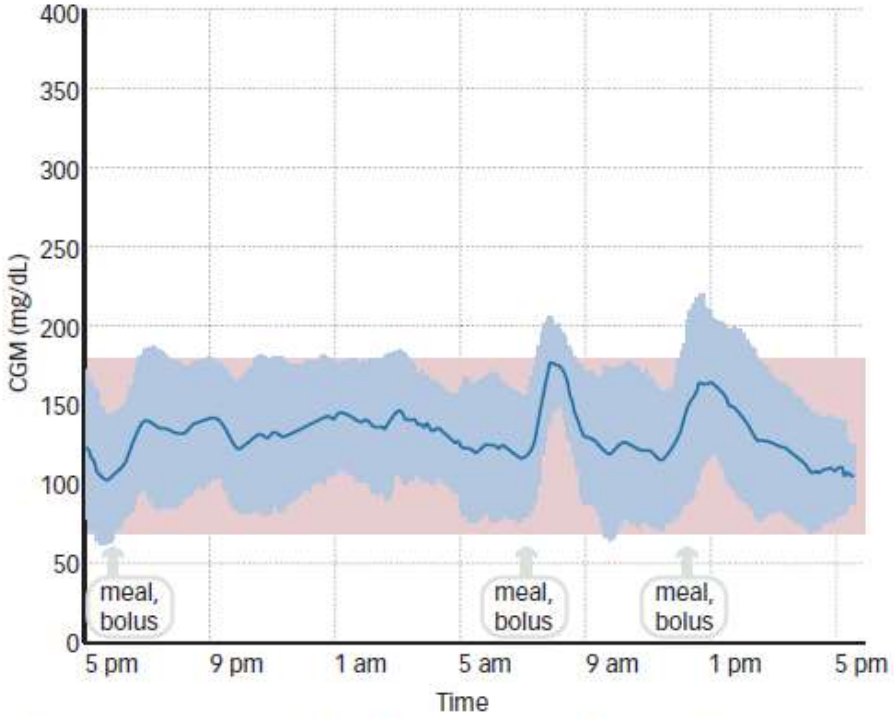
CGM = Continuous glucose monitoring; HHM = Hypoglycaemia-Hyperglycaemia Minimizer.

Figure 3: Example of a Potential Prevention of a Hypoglycaemic Excursion by the Hypoglycaemia-Hyperglycaemia Minimizer System



Upper graph: Continuous glucose monitoring (CGM) curve shown with the 70–90 mg/dL range. Lower graph: Hypoglycaemia-Hyperglycaemia Minimizer (HHM) System's insulin delivery (bars) shown relative to the current basal rate (black line). This participant's CGM was trending downward when the HHM System effectively suspended insulin delivery. Subsequently, the CGM reached a nadir of 82 mg/dL and began to rise. Source: Finan et al., 2013.[55]

Figure 4: Mean Glucose Levels of Patients using the Hypoglycaemia-Hyperglycaemia Minimizer System for 24 Hours



Mean Glucose Levels, ± 1 Standard Deviation (SD), of Patients using the Hypoglycaemia-Hyperglycaemia Minimizer System for 24 Hours CGM = Continuous glucose monitoring. Adapted from Finan et al., 2014.[54]

Feasibility of Outpatient Fully Integrated Closed-Loop Control

First studies of wearable artificial pancreas

Boris P. Kovatchev, PhD[1]
Eric Renard, MD, PhD[2]
Claudio Cobelli, PhD[3]
Howard C. Zisser, MD[4]
Patrick Keith-Hynes, PhD[1]
Stacey M. Anderson, MD[1]
Sue A. Brown, MD[1]
Daniel R. Chernavvsky, MD[1]
Marc D. Breton, PhD[1]
Anne Farret, MD, PhD[2]
Marie-Josée Pelletier, MD[2]
Jérôme Place, MSc[2]
Daniela Bruttomesso, MD, PhD[3]
Simone Del Favero, PhD[3]
Roberto Visentin, MSc[3]
Alessio Filippi, MD[3]
Rachele Scotton, MD[3]
Angelo Avogaro, MD, PhD[3]
Francis J. Doyle III, PhD[5]

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