

CONVEGNO SID AMD UMBRIA

Nel Cuore del Diabete: cardio-diabetologia, approccio integrato, multidisciplinarietà, nuove tecnologie, engagement del paziente/operatore

Perugia, 28 OTTOBRE 2017

UNO SGUARDO AL FUTURO

Basta la tecnologia a prevenire l'ipoglicemia?

Carmine G. Fanelli

MISEM

Azienda Ospedaliera Universitaria di Perugia

Santa Maria della Misericordia

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974 ANNO DI FONDAZIONE

SID fondata nel 1964 Società Italiana di Diabetologia

Il sottoscritto dichiara di aver ricevuto, negli ultimi due anni, finanziamenti o compensi dalle seguenti aziende:

Sanofi
Menarini

Hypoglycemia in Diabetes: the Size of the Problem

….The average patient with T1DM suffers two episodes of moderate hypoglycemia/week, thousands of such episodes over a lifetime of diabetes and one episode of temporarily disabling hypoglycemia, often with seizure or coma, per year.

Impaired awareness of hypoglycemia increases the risk of severe hypoglycemia sixfolds and affects 30 % of adults with type 1 diabetes.

An estimated 2-4% of people with T1DM die from hypoglycemia.

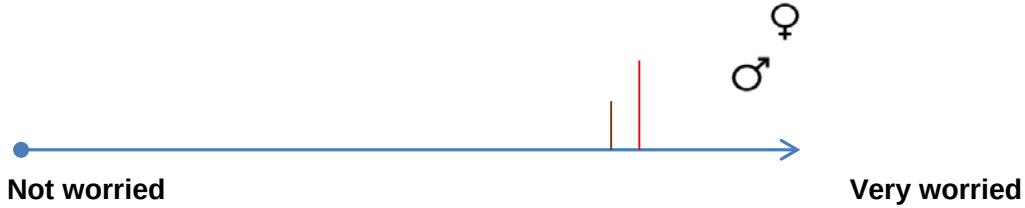
Cryer PE. Endocrnol Metab Clin North Am. 2010, 39:641-654

The fear of hypoglycaemia in 411 persons with type 1 DM

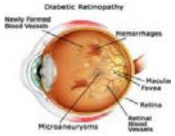
Mild Hypoglycemia

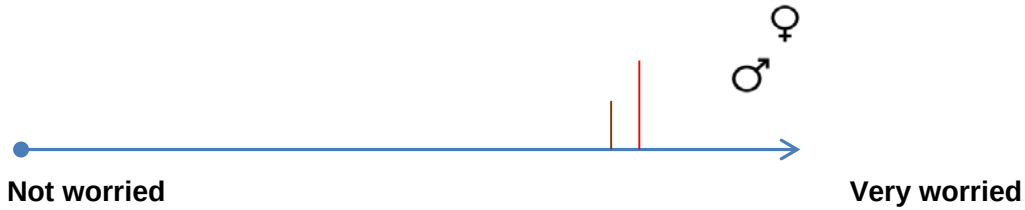


Severe Hypoglycemia



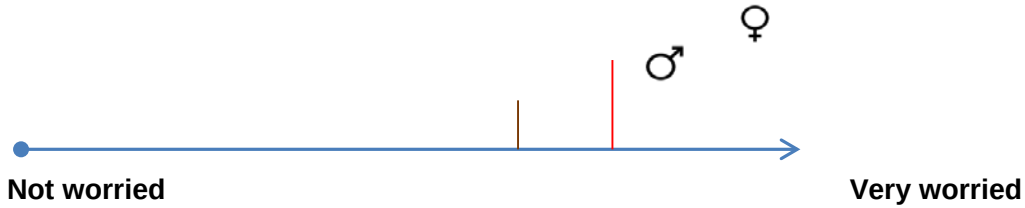
Blindness





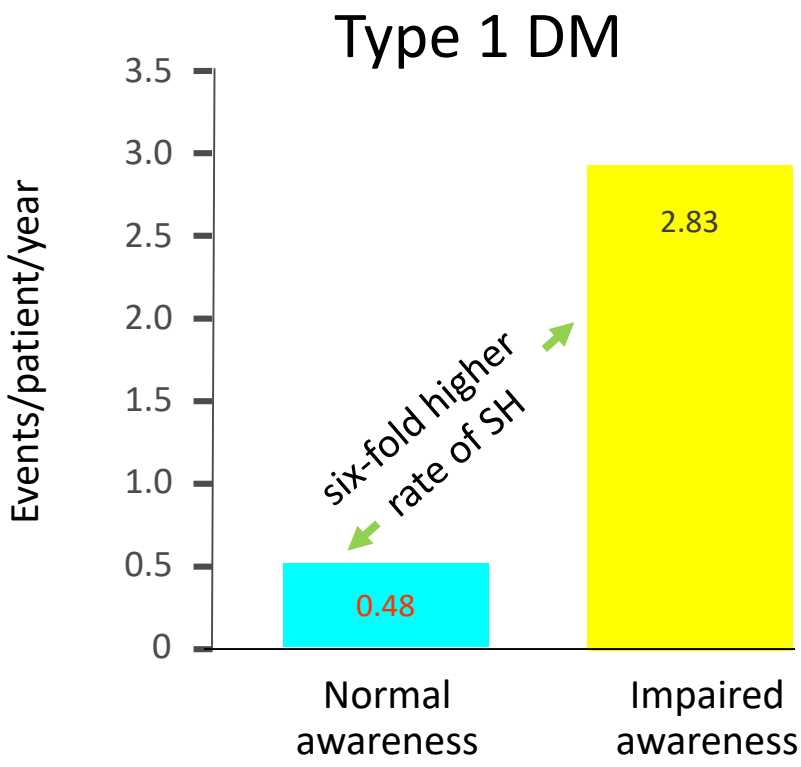
Kidney Complications



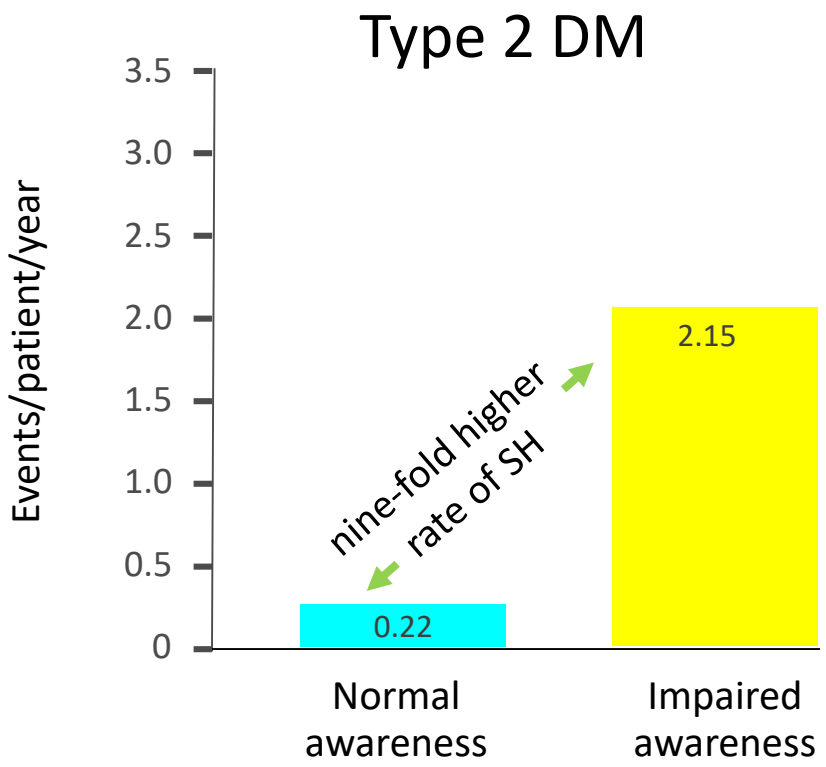


Pramming S. et al. Diabetic Medicine, 1991;8:217-2

Loss of Awareness Increases the Risk of Severe Hypoglycemia (SH)



Gold A.E. et al.
Diabetes Care 17:697-703, 1994

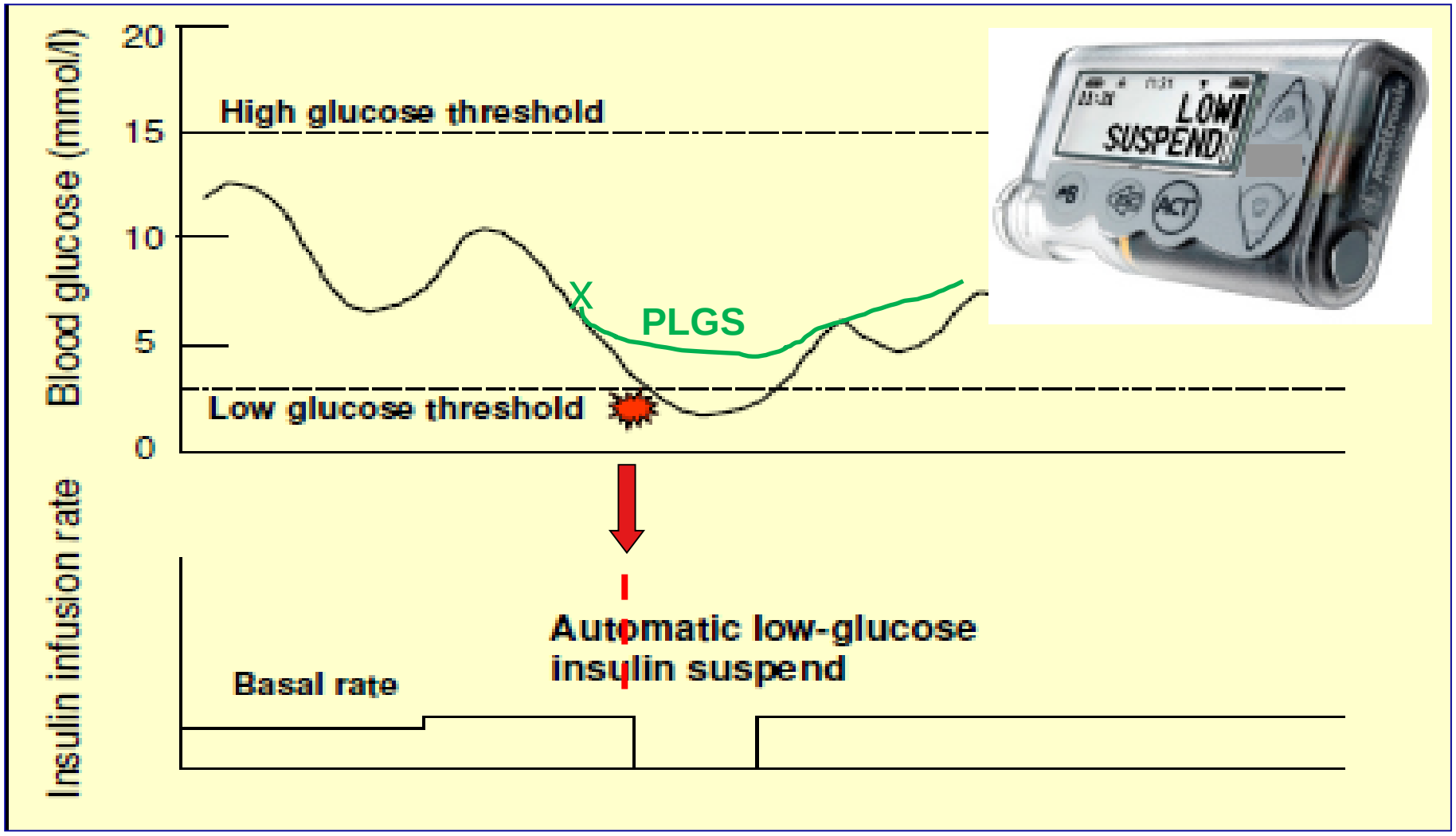


Henderson J.N. et al.
Diabetic Med 20:10161021,2003

Tecnologia e diabete

- Analoghi dell'insulina
- La terapia con microinfusore (CSII)
- Misurazione della glicemia - monitoraggio in continuo del glucosio (continuous glucose monitoring, CGM); Flash glucose monitoring
- Integrazione tra un sistema di infusione di insulina e un sensore (sensor-augmented therapy, SAP)
- Funzione "low glucose suspend" (LGS)
- "predictive low glucose suspend" (PLGS)

SAP and hypoglycemia: the "Low Glucose Suspend" Feature

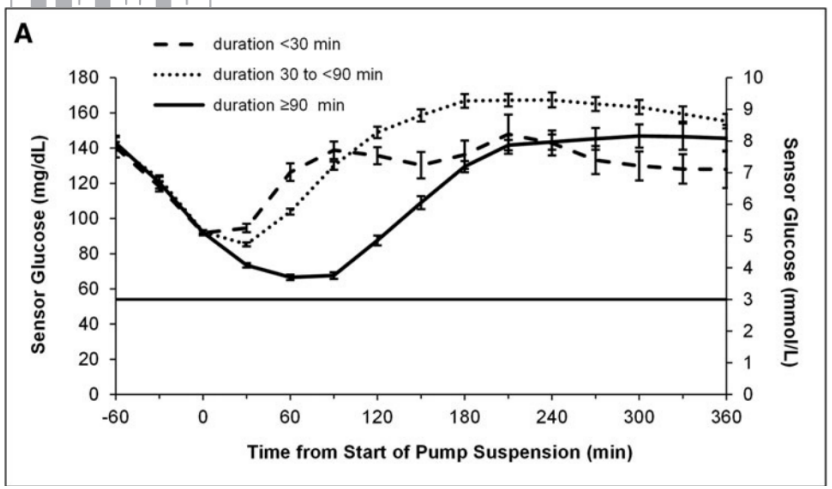


DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 5, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2015.0324

ORIGINAL ARTICLE

Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management

Pratik Choudhary, MD,[1] Birthe S. Olsen, MD,[2] Ignacio Conget, MD,[3] John B. Welsh, MD, PhD,[4] Linda Vorrink, MSc,[5] and John J. Shin, PhD[4]



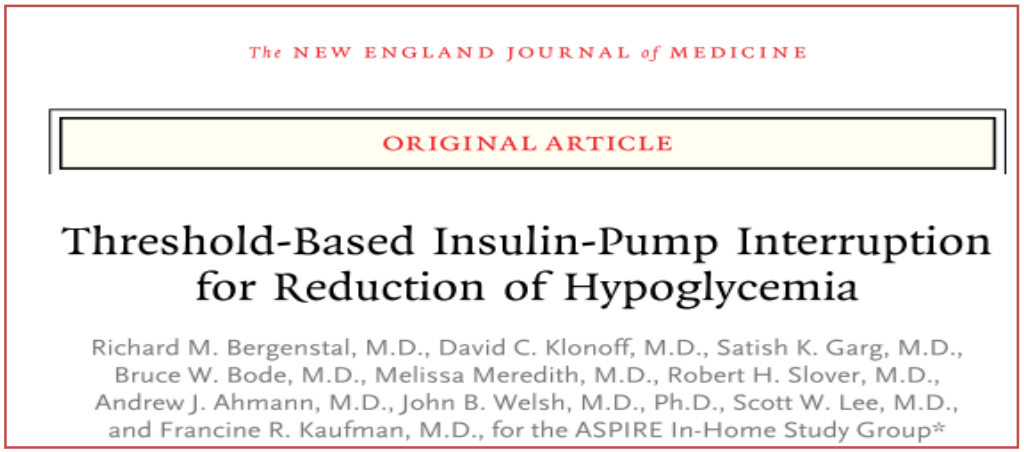
Background: The MiniMed 640G sensor-augmented insulin pump system (Medtronic, Inc., Northridge, CA) can automatically suspend insulin delivery in advance of predicted hypoglycemia and restart it upon recovery. The aims of this analysis were to determine the rate at which predicted hypoglycemia was avoided with this strategy, as well as to assess user acceptance of the system and its insulin management features.

Subjects and Methods: Forty subjects with type 1 diabetes used the system for 4 weeks. We retrospectively evaluated performance of the system, using downloaded pump and sensor data, and evaluated user acceptance via questionnaires.

Results: There were 2,322 suspend before low events (2.1 per subject-day). The mean (– SD) duration of pump suspension events was 56.4 – 9.6 min, and the mean subsequent sensor glucose (SG) nadir was 71.8 – 5.2 mg/dL. SG values following 1,930 (83.1%) of the predictive suspensions did not reach the preset low limit. Nadir SG values of £50 and £60 mg/dL were seen in 207 (8.9%) and 356 (15.3%) of the predictive suspensions, respectively. Blood glucose (BG) and SG values before and during the study were comparable ($P > 0.05$). The mean absolute relative difference between paired SG and BG values was 10.9 – 13.8%. Subjects felt confident using the system, agreed that it helped protect them from hypoglycemia, and wished to continue using it.

Conclusions: Automatic insulin pump suspension as implemented in the MiniMed 640G system can help patients avoid hypoglycemia, without significantly increasing hyperglycemia.

Insulin-Pump Interruption for Hypoglycemia: the ASPIRE in-Home Study



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

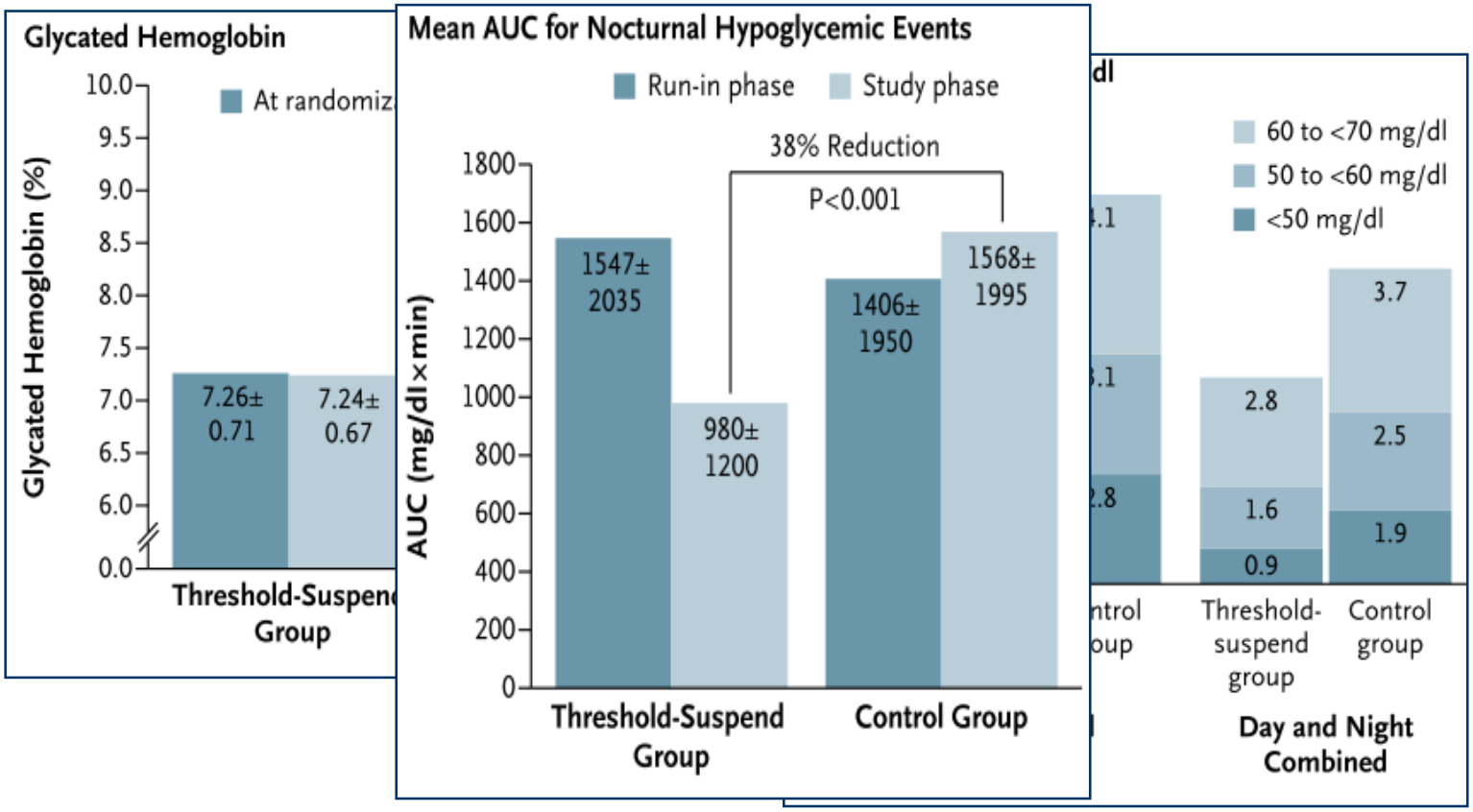
Multicenter, randomized parallel trial (ASPIRE in-home)

•247 patients with T1DM and documented nocturnal hypoglycemia

•Treatment: - 121 SAP with LGS
- 126 standard SAP for three months

•Primary outcome: - AUC for nocturnal hypoglycemic events

Insulin-Pump Interruption for Hypoglycemia



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



Research

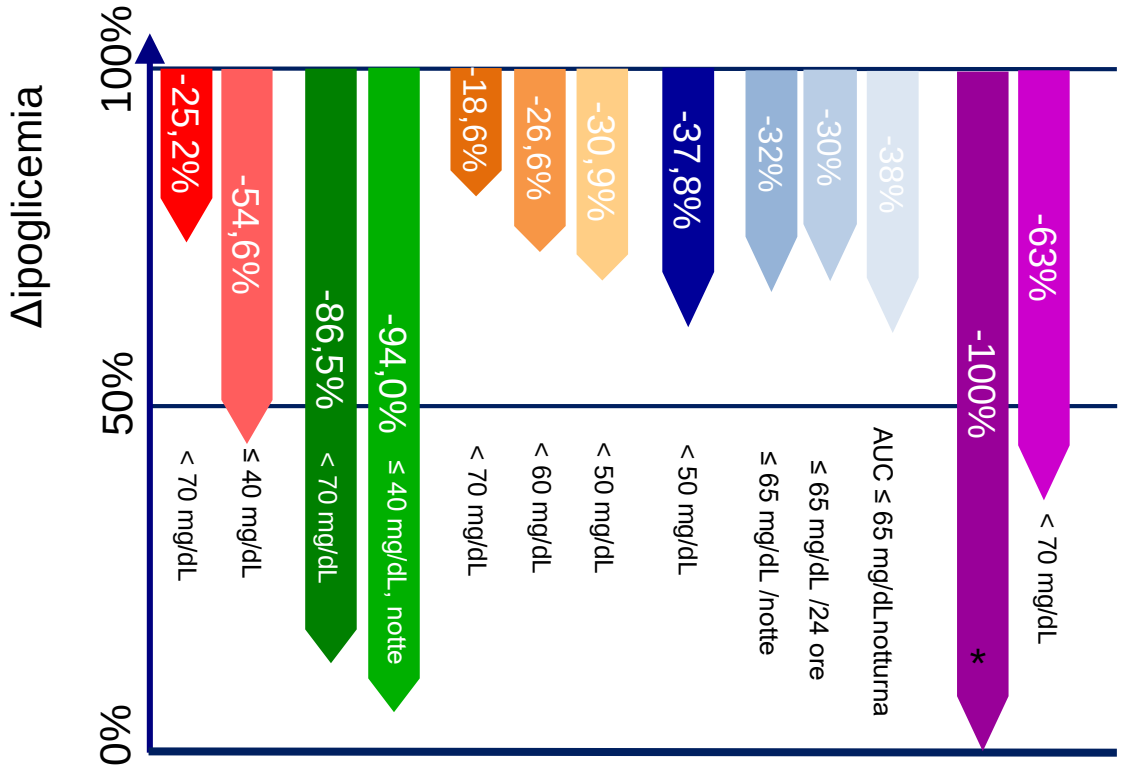
Original Investigation

Effect of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension vs Standard Insulin Pump Therapy on Hypoglycemia in Patients With Type 1 Diabetes

A Randomized Clinical Trial

	Insulin Pump (n = 49)	Sensor-Augmented Pump With Low-Glucose Suspension (n = 46)
Severe hypoglycemia[a]		
Baseline		
Rate per 100 patient-months (95% CI)	2.1 (0.8 to 4.6)	1.8 (0.6 to 4.3)
No. of events (total No. of patients)	6 (49)	5 (46)
End point		
6-Month rate per 100 patient-months (95% CI)	2.2 (0.5 to 6.5)	0 (0 to 2.4)
No. of events (total No. of patients)	6 (45)	0 (41)
Incidence rate difference from baseline to end point (95% CI)		1.5 (0.3 to 2.7)
P value		.02

Hypoglycemia: SaP + LGS



* Ipoglicemia severa (perdita di conoscenza o intervento 3° persona)

Danne

6 settimane SaP+LGS vs. 2 sett. SaP senza LGS, n=21 (bambini)

Soglia per LGS : 70 mg/dL

Miglioramento HbA1c 7,7 → 7,5%

Choudhary

4 settimane SaP+LGS vs 2 sett. SaP senza LGS, n=31

Soglia per LGS : 40-50 mg/dL

Agrawal

Anallisi dati CareLink ; Ø 7 mesi, n=935

Sottogruppo con valori con/senza LGS: n= 278

Soglia per LGS: 50-60 mg/dL

ASPIRE in clinica (Garg)

RCT (studio cross-over) con esercizio, n=50

Soglia per LGS : 70 mg/dL

ASPIRE a casa (Bergenstal)

RCT , 3 mesi, n=247, patzienti con alta frequenza di ipoglicemia notturna

Soglia per LGS : 70 mg/dL

Australiano SaP-LGS (Ly)

RCT , 6 mesi, n=95, pazienti con ipoglicemia asintomatica

Soglia per LGS: 70 mg/dL

A Cost-Effectiveness Analysis of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension versus Standard Pump Therapy for Hypoglycemic Unaware Patients with Type 1 Diabetes



VALUE IN HEALTH 17 (2014) 561–569

Trang T. Ly, MBBS, DCH, FRACP[1,2,3], Alan J.M. Brnabic, MA Statistics[4], Andrew Eggleston, BPharm, MMedSc (clin epi)[5], Athena Kolivos, BPharm, MCom, MA, MPH[5], Margaret E. McBride, PhD[5], Rudolf Schrover, MSc[6], Timothy W. Jones, MBBS, FRACP, MD[1,2,3,]*

OBJECTIVE:
To assess the cost-effectiveness of sensor-augmented insulin pump therapy with "Low Glucose Suspend" (LGS) functionality versus standard pump therapy with self-monitoring of blood glucose in patients with type 1 diabetes who have impaired awareness of hypoglycemia.
METHODS:
A clinical trial-based economic evaluation was performed in which the net costs and effectiveness of the two treatment modalities were calculated and expressed as an incremental cost-effectiveness ratio (ICER). The clinical outcome of interest for the evaluation was the rate of severe hypoglycemia in each arm of the LGS study. Quality-of-life utility scores were calculated using the three-level EuroQol five-dimensional questionnaire. Resource use costs were estimated using public sources.
RESULTS:
After 6 months, the use of sensor-augmented insulin pump therapy with LGS significantly reduced the incidence of severe hypoglycemia compared with standard pump therapy (incident rate difference 1.85 [0.17-3.53]; P = 0.037). Based on a primary randomized study, the ICER per severe hypoglycemic event avoided was $18,257 for all patients and $14,944 for those aged 12 years and older. Including all major medical resource costs (e.g., hospital admissions), the ICERs were $17,602 and $14,289, respectively. Over the 6-month period, the cost per quality-adjusted life-year gained was $40,803 for patients aged 12 years and older.
CONCLUSIONS:
Based on the Australian experience evaluating new interventions across a broad range of therapeutic areas, sensor-augmented insulin pump therapy with LGS may be considered a cost-effective alternative to standard pump therapy with self-monitoring of blood glucose in hypoglycemia unaware patients with type 1 diabetes.

Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

NICE National Institute for Health and Care Excellence

Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system)

NICE guidance

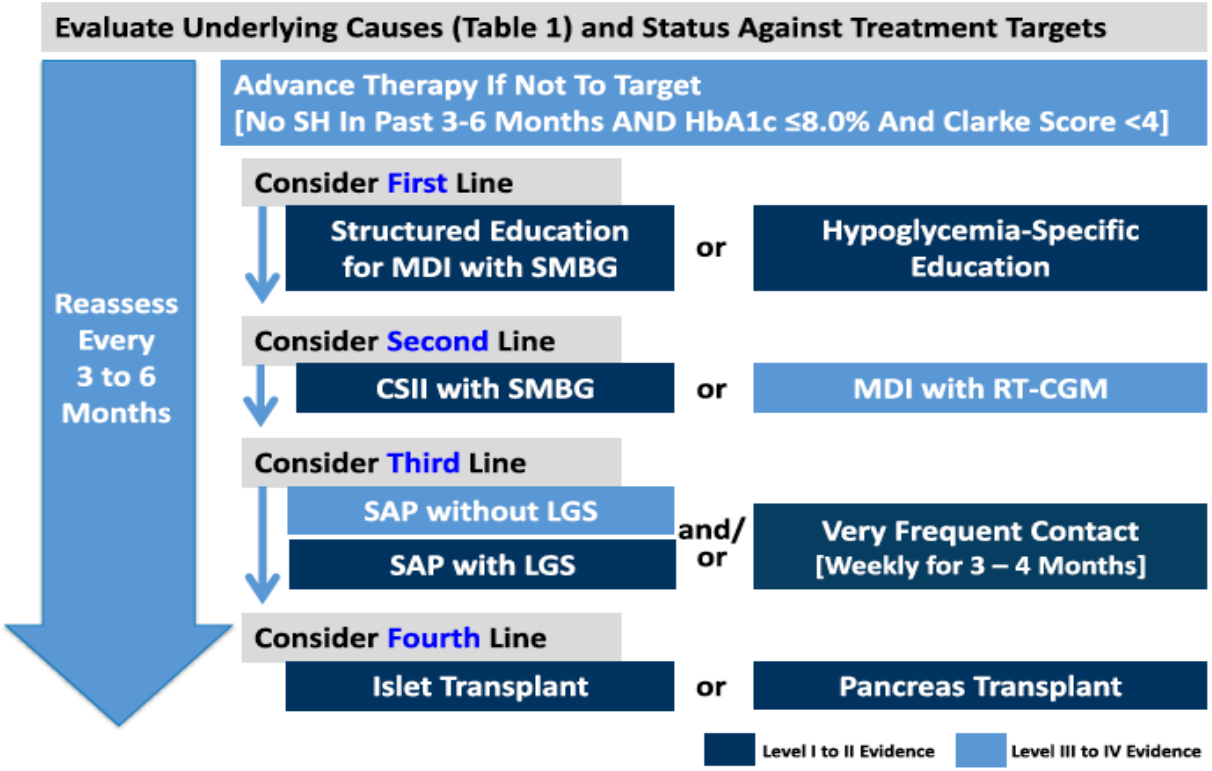
Published: 12 February 2016
nice.org.uk/guidance/dg21

Al momento non esistono linee-guida internazionali che identifichino la popolazione da trattare con SAP piuttosto che con CSII tradizionale. L'unica indicazione deriva da una recente valutazione del NICE, pubblicata nel febbraio 2016, che ha analizzato le evidenze relative esclusivamente ai sistemi MiniMed Paradigm Veo e Vibe con sensore G4 Platinum e che suggerisce l'uso del sistema Paradigm VEO nei pazienti tipo 1 con ipoglicemia invalidante nonostante la terapia con CSII. Le indicazioni del NICE sottolineano come l'impiego del sistema SAP richieda la capacità del paziente a comprendere e usare il sistema, la disponibilità all'uso continuativo del sensore (almeno il 70% del tempo) e l'adesione a un programma strutturato di educazione terapeutica.

Evidence-Informed Clinical Practice Recommendations for Treatment of Type 1 Diabetes Complicated by Problematic Hypoglycemia

Pratik Choudhary,[1] Michael R. Rickels,[2] Peter A. Senior,[3] Marie-Christine Vantyghem,[4] Paola Maffi,[5] Thomas W. Kay,[6] Bart Keymeulen,[7] Nobuya Inagaki,[8] Frantisek Saudek,[9] Roger Lehmann,[10] and Bernhard J. Hering[11]

Diabetes Care 2015;38:1016–1029 | DOI: 10.2337/dc15-0090



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 Weitgasser

Summary

Background Tight control of blood glucose in type 1 diabetes delays onset of macrovascular and microvascular diabetic complications; however, glucose levels need to be closely monitored to prevent hypoglycaemia. We aimed to assess whether a factory-calibrated, sensor-based, flash glucose-monitoring system compared with self-monitored glucose testing reduced exposure to hypoglycaemia in patients with type 1 diabetes.

Method In this multicentre, prospective, non-masked, randomised controlled trial, we enrolled adult patients with well controlled type 1 diabetes (HbA_{1c} ≤58 mmol/mol [7·5%]) from 23 European diabetes centres. After 2 weeks of all participants wearing the blinded sensor, those with readings for at least 50% of the period were randomly assigned (1:1) to flash sensor-based glucose monitoring (intervention group) or to self-monitoring of blood glucose with capillary strips (control group). Randomisation was done centrally using the biased-coin minimisation method dependent on study centre and type of insulin administration. Participants, investigators, and study staff were not masked to group allocation. The primary outcome was change in time in hypoglycaemia (<3·9 mmol/L [70 mg/dL]) between baseline and 6 months in the full analysis set (all participants randomised; excluding those who had a positive pregnancy test during the study). This trial was registered with ClinicalTrials.gov, number NCT02232698.

Findings Between Sept 4, 2014, and Feb 12, 2015, we enrolled 328 participants. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycaemia changed from 3·38 h/day at baseline to 2·03 h/day at 6 months (baseline adjusted mean change −1·39) in the intervention group, and from 3·44 h/day to 3·27 h/day in the control group (−0·14); with the between-group difference of −1·24 (SE 0·239; p<0·0001), equating to a 38% reduction in time in hypoglycaemia in the intervention group. No device-related hypoglycaemia or safety issues were reported. 13 adverse events were reported by ten participants related to the sensor—four of allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate). There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device.

Interpretation Novel flash glucose testing reduced the time adults with well controlled type 1 diabetes spent in hypoglycaemia. Future studies are needed to assess the effectiveness of this technology in patients with less well controlled diabetes and in younger age groups.

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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(16)31582-3

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4. Bolinder et al. Lancet. 2016 Sep 9. pii: S0140-6736(16)31535-5. doi: 10.1016/S0140-6736(16)31535-5
5. Haak et al. Diabetes Ther. 2016 Dec 20. doi: 10.1007/s13300-016-

Caratteristiche dei pazienti arruolati

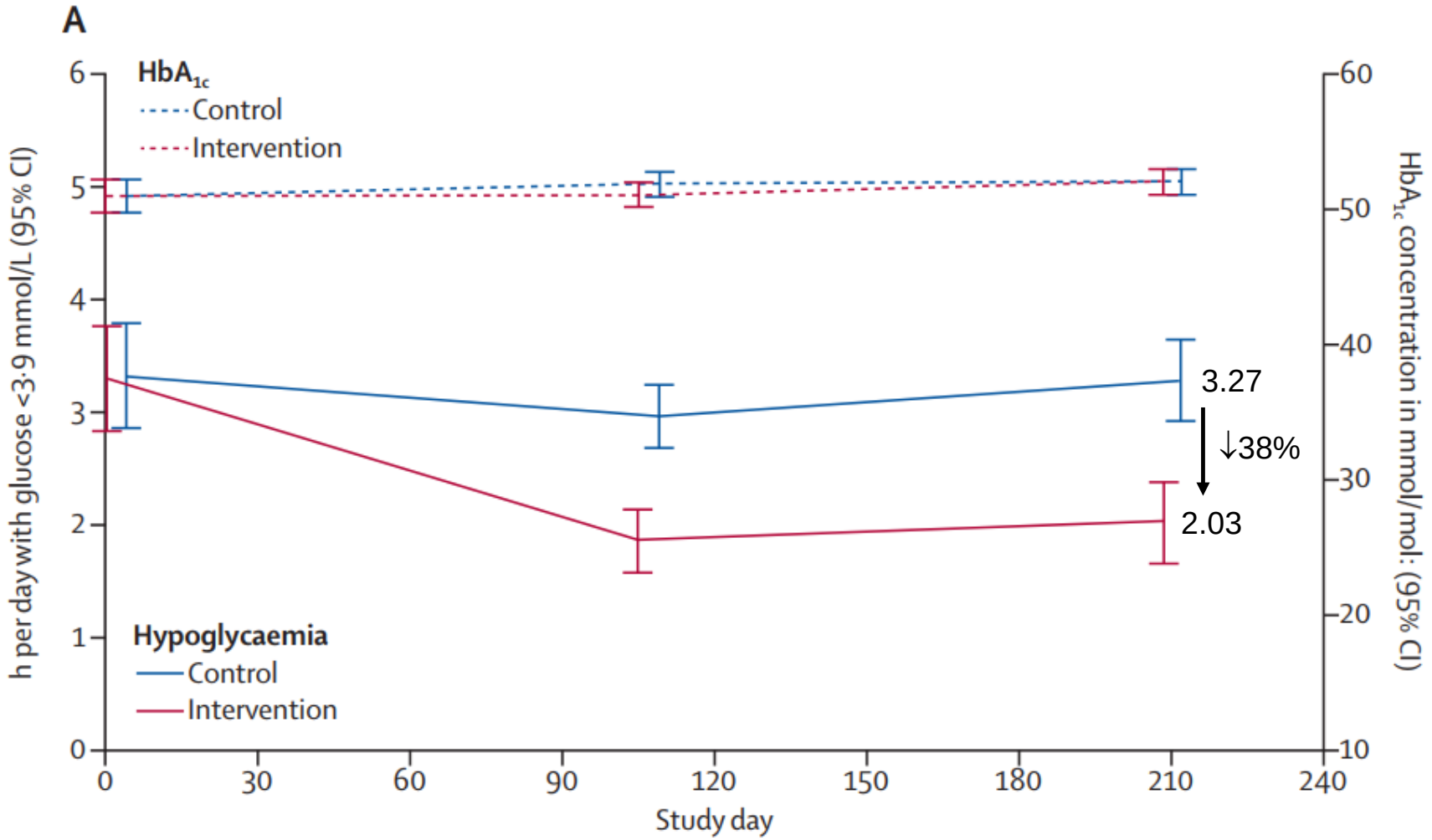
	Intervention (n=119)	Control (n=120)
Men	77 (65%)*	59 (49%)*
Women	42 (35%)	61 (51%)
Race		
White	119 (100%)	119 (99%)
Black	0	1 (1%)
Age (years)	42 (33–51)	45 (33–57)
BMI (kg/m²)	25·2 (3·6)	24·8 (3·5)
Duration of diabetes (years)	20 (13–27)	20 (12–32)
Screening HbA_{1c} (%; mmol/mol)	6·7 (0·5); 50·1 (5·7)	6·7(0·6); 50·2 (6·5)
Self-reported blood glucose frequency per day	5·4 (2·0)	5·6 (2·3)
Insulin administration method		
Multiple daily injections	81 (68%)	80 (67%)
Continuous subcutaneous insulin infusion	38 (32%)	40 (33%)
Insulin, total daily dose		
Basal (units)	25·7 (13·9)	20·9 (10·0)
Bolus (units)	24·2 (13·5)	22·2 (13·4)
Continuous subcutaneous insulin infusion (units)	41·4 (17·1)	35·9 (15·6)

Data are n (%), median (IQR), or mean (SD). *p=0·0153.

Bolinder et al. Lancet. 2016 -6736(16)31535-5

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

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Diabetes Ther
DOI 10.1007/s13300-016-0223-6

ORIGINAL RESEARCH

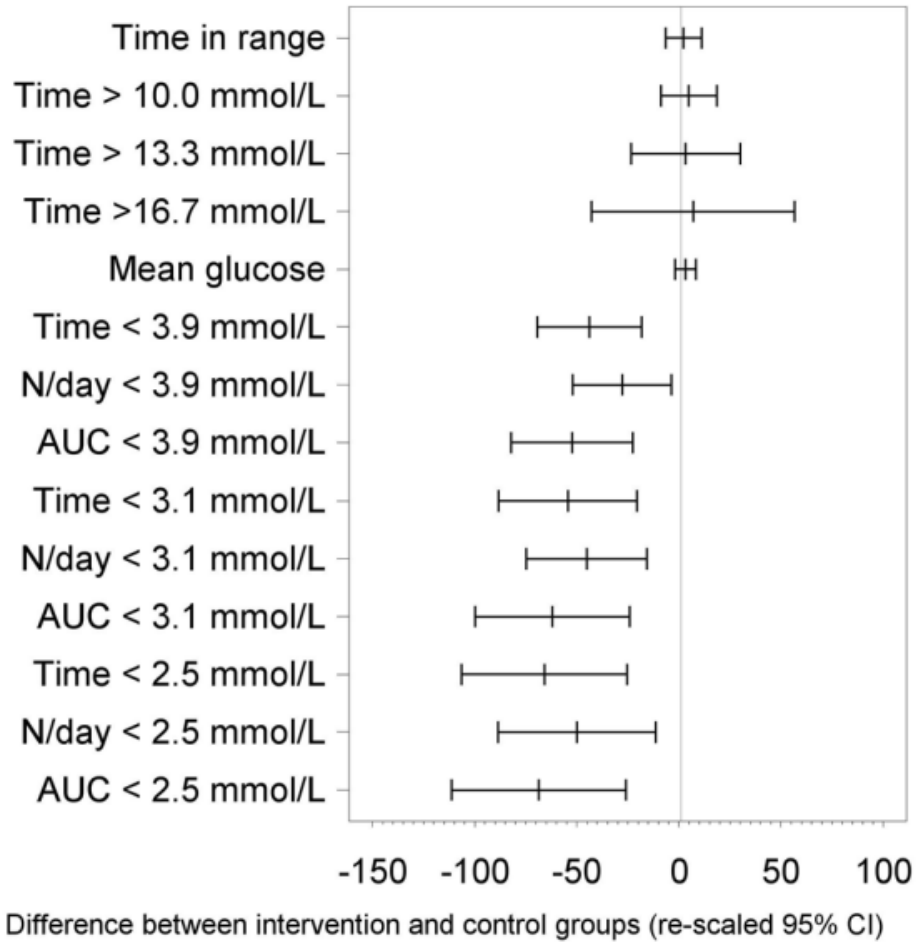
Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial

Thomas Haak · Hélène Hanaire · Ramzi Ajjan · Norbert Hermanns · Jean-Pierre Riveline · Gerry Rayman

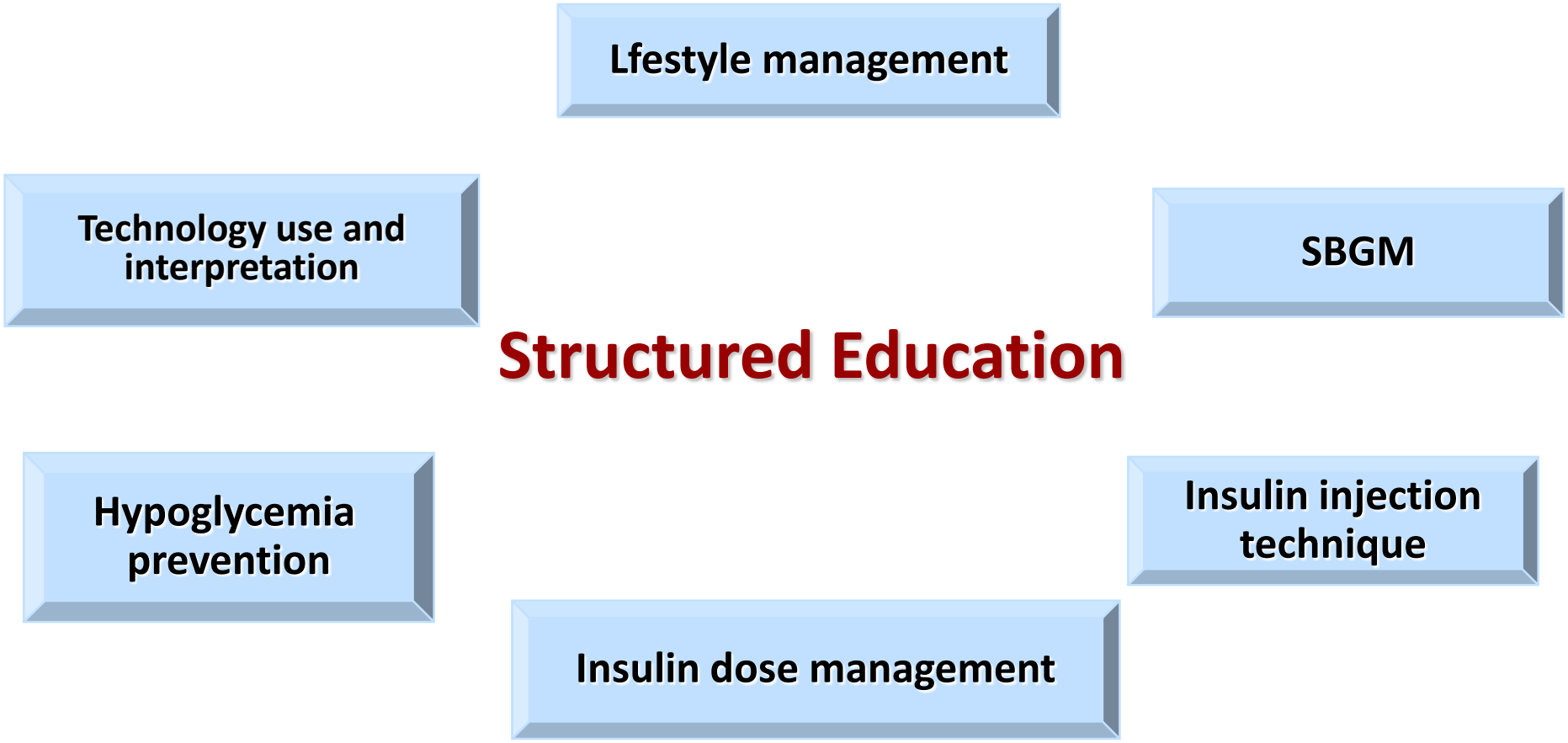
Table 1 Baseline characteristics

	Intervention ($N = 149$)	Control ($N = 75$)
Age (years)	59.0 ± 9.9 (33, 81)	59.5 ± 11.0 (22, 80)
Weight (kg)	98 ± 21 (51, 170)	99 ± 19 (61, 161)
BMI (kg/m²)	33.1 ± 6.2 (18.8, 54.1)	33.3 ± 5.5 (23.7, 52.4)
Duration of diabetes (years)	17 ± 8 (2, 43)	18 ± 8 (4, 37)
Duration of insulin use (years)	9 ± 6 (0, 40)	10 ± 7 (1, 35)
Screening HbA1c (mmol/mol)	72.0 ± 10.6 (59, 103)	73.5 ± 11.3 (59, 104)
(%)	8.74 ± 0.97 (7.5, 11.6)	8.88 ± 1.04 (7.5, 11.7)
Self-reported blood glucose frequency per day	3.6 ± 1.28 (1, 10)	3.9 ± 1.33 (2, 10)
Insulin, total daily dose		
Basal (units)	40.4 ± 22.6 ($n = 138$)	42.3 ± 25.1 ($n = 70$)
Bolus (units)	50.5 ± 32.5 ($n = 141$)	54.8 ± 32.7 ($n = 70$)
CSII (units)	76.9 ± 49.8 ($n = 8$)	82.6 ± 37.0 ($n = 3$)
Gender, male	94 (63%)	56 (75%)
White	141 (95%)	70 (93%)
Black	2 (1%)	1 (1%)
Asian/Pacific Islander	3 (2%)	2 (3%)
Other	3 (2%)	2 (3%)
Insulin pen device	140 (94%)	71 (95%)
CSII	8 (5%)	4 (5%)
Insulin syringe	1 (1%)	0 (0%)
Previous CGM use	11 (7%)	4 (5%)
Employed	62 (42%)	34 (45%)
Not employed/retired/other	83 (56%)	40 (53%)
Insulin management training		
<1 year ago	44 (30%)	28 (37%)
>1 year ago	100 (67%)	42 (56%)
Carbohydrate counting training		
<1 year ago	44 (30%)	27 (36%)
>1 year ago	53 (36%)	25 (33%)
Bolus dose titration based on meal content	96 (64%)	47 (63%)
Bolus dose titration based on current glucose level	116 (78%)	60 (80%)
Bolus dose titration using sliding scale	57 (38%)	32 (43%)

Data are presented as mean ± SD (min, max) or n (%)



Basta la tecnologia a prevenire l'ipoglicemia?



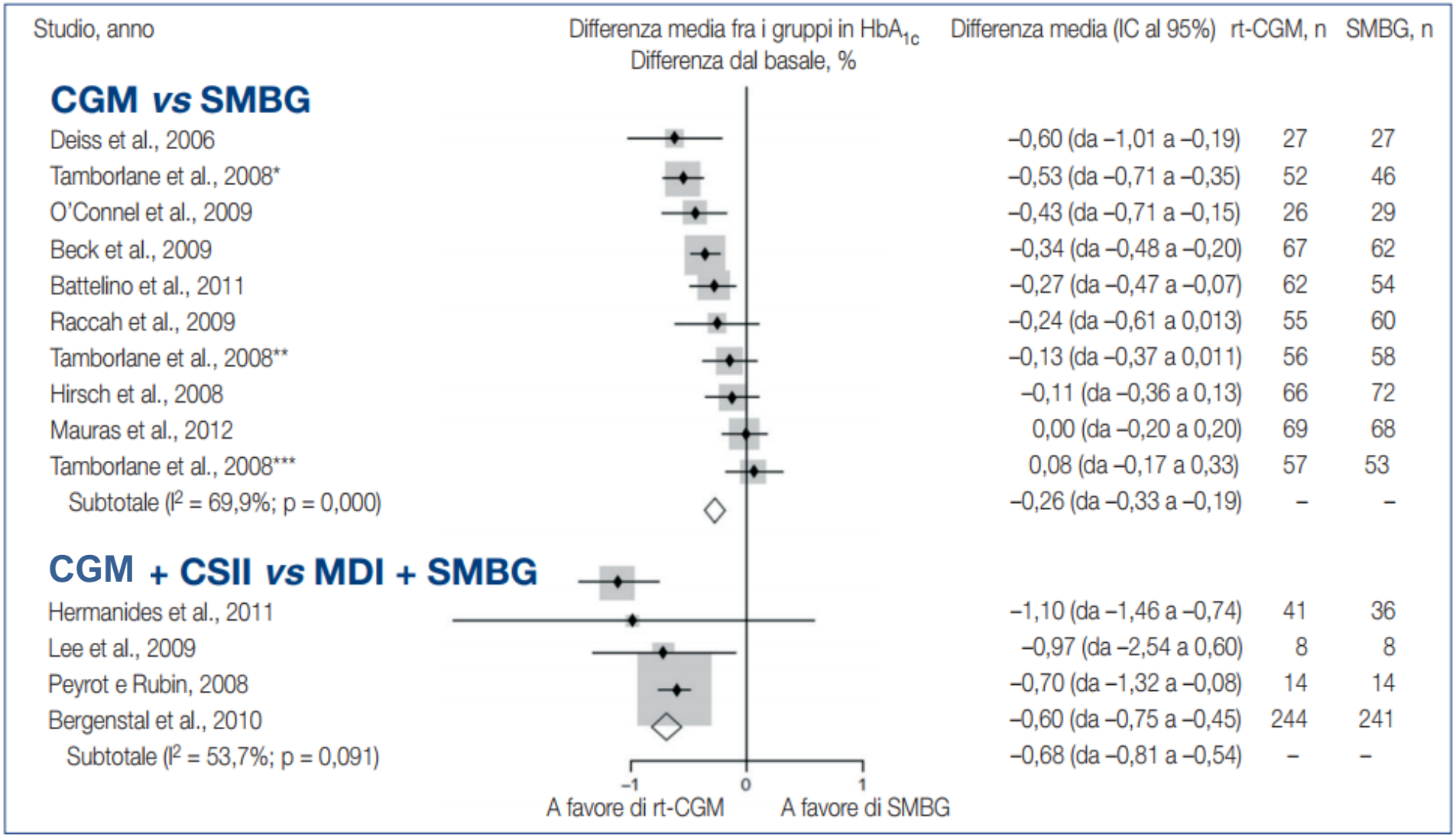
EDUCAZIONE

Precipitating factors for severe hypoglycemia in people with diabetes	Mechanism
Excessive insulin or insulin secretagogue dose	**⇑ glucose utilization** **⇓ glucose production**
Reduced carbohydrate intake	**⇑ insulin sensitivity**
Exercise	**⇑ glucose utilization** **⇑ insulin sensitivity (after exercise)**
Alcohol ingestion	**⇓ glucose production** **⇓ counterregulation**
Night ***Weight reduction*** ***Improved glycemic control*** ***Drugs that increase insulin sensitivity***	**⇑ insulin sensitivity** **⇑ insulin sensitivity** **⇑ insulin sensitivity**
Injection depth (intramuscular) ***Site*** ***Temperature*** ***Lipohypertrophy***	**⇑ glucose utilization** **⇓ glucose production** **⇑ insulin sensitivity** **⇑ insulin sensitivity** **⇑ variability of insulin absorption**
Renal failure	**⇓ insulin clearance** **⇓ glucose production**

EDUCAZIONE

Essential factors necessary to prevent hypoglycemia in diabetes
Consider the risk of hypoglycemia, including at night, for each individual patient then use the safest treatment and glycemic targets (individualize the goals)
Maintain frequent contacts between the diabetes team and patient
Practice frequent blood glucose monitoring
Measure blood glucose at night (especially in patients with hypoglycemia unawareness)
Prevent hypoglycemia (treat glucose values <70mg/dl; 3.9 mmol/l)
When present, reverse hypoglycemia unawareness
If necessary, use technological support to detect and correct hypoglycemia.
Provide structured education about prevention and treatment of hypoglycemia

Grazie per l’attenzione



Confronto fra studi che hanno comparato il monitoraggio in continuo della glicemia (CGM) e monitoraggio capillare (SMBG) e fra sistemi combinati (CGM + CSII) e terapia iniettiva con monitoraggio capillare (MDI + SMBG) (*Yeh HC. et al. Ann Intern Med 2012;157:336-47*)

*Pazienti di età 15-24 anni. **Pazienti di età 8-14 anni. ***Pazienti di età > 25 anni.