NAPOLI, 17-20 maggio 2017

XXI CONGRESSO NAZIONALE AMD

“Il monitoraggio flash del glucosio: dall’evidence based medicine alla pratica clinica”

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Disclosure Statement

- Stefano Genovese has participated in clinical research, scientific advisory boards, served as a consultant or received honoraria for:
  - Abbott Diabetes Care
  - AstraZeneca
  - Boehringer Ingelheim
  - Bristol-Myers Squibb
  - Bruno Farmaceutici
  - Eli Lilly
  - Janssen
  - Lifescan
  - Menarini
  - Merck Sharp & Dohme
  - Novartis
  - Novo Nordisk
  - Sanofi
  - Takeda

Obiettivi glicemici: target per bambini, adolescenti e adulti con T1DM

Table 11.1—Plasma blood glucose and A1C goals for type 1 diabetes across all pediatric age-groups

Plasma blood glucose goal range			
Before meals	Bedtime/overnight	A1C	Rationale
90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<7.5%	A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia

Key concepts in setting glycemic goals:

- Goals should be *individualized*, and lower goals may be reasonable based on benefit-risk assessment.
- Blood glucose goals should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to help assess glycemia in those on basal–bolus regimens.

Table 5.2—Summary of glycemic recommendations for nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Standard ADA, Diabetes Care 2016

Tabella 9. Obiettivi glicemici in diabetici adulti tipo 1 e 2

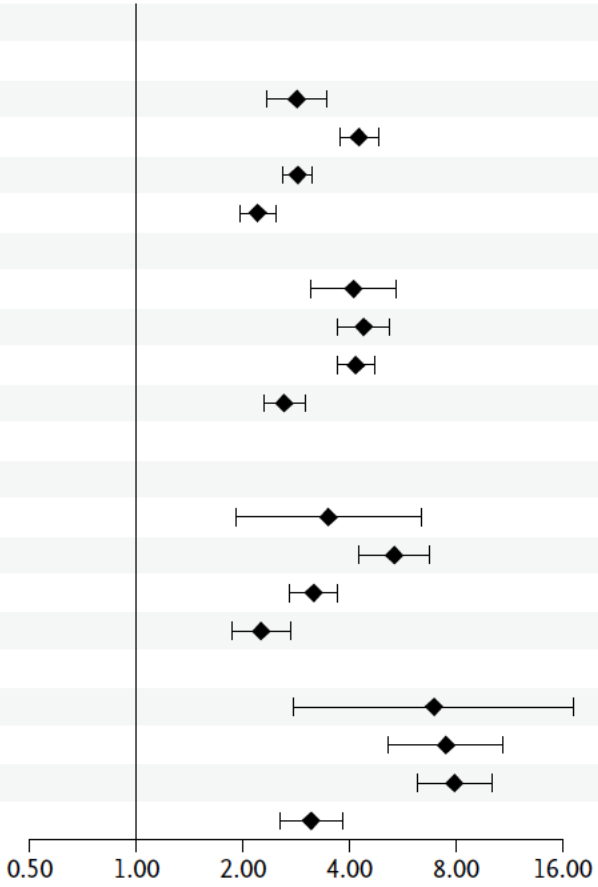
HbA_{1c} <53 mmol/mol (<7,0%)* (≤48 mmol/mol [≤6,5%] in singoli pazienti)
Glicemia a digiuno e preprandiale 70-130 mg/dl
Glicemia postprandiale§ <160 mg/dl

* Facendo riferimento ai valori di 20-42 mmol/mol (4,0-6,0%) della popolazione non diabetica, con il metodo utilizzato dal DCCT.

§ La misurazione della glicemia postprandiale deve essere effettuata tra 1 e 2 ore dopo l'inizio del pasto (IDF 2011).

Hazard Ratios for Death from Any Cause and for Death from Cardiovascular Causes According to Age and Sex

Subgroup	Type 1 Diabetes	Reference	Hazard Ratio (95% CI)	P Value
	no. of events (%)			
Death from any cause				
Male				
18–34 yr	160 (1.6)	283 (0.6)	2.84 (2.34–3.45)	<0.001
35–49 yr	428 (8.9)	524 (2.2)	4.26 (3.75–4.84)	<0.001
50–64 yr	631 (21.6)	1217 (8.4)	2.86 (2.60–3.15)	<0.001
≥65 yr	367 (50.3)	1046 (29.2)	2.20 (1.96–2.48)	<0.001
Female				
18–34 yr	90 (1.1)	110 (0.3)	4.11 (3.11–5.43)	<0.001
35–49 yr	239 (6.2)	280 (1.4)	4.39 (3.70–5.22)	<0.001
50–64 yr	482 (19.6)	638 (5.2)	4.17 (3.70–4.69)	<0.001
≥65 yr	304 (43.4)	737 (21.3)	2.62 (2.29–3.00)	<0.001
Death from cardiovascular causes				
Male				
18–34 yr	18 (0.2)	26 (0.1)	3.49 (1.91–6.36)	<0.001
35–49 yr	144 (3.0)	140 (0.6)	5.36 (4.25–6.77)	<0.001
50–64 yr	238 (8.2)	414 (2.9)	3.17 (2.70–3.72)	<0.001
≥65 yr	149 (20.4)	416 (11.6)	2.25 (1.87–2.72)	<0.001
Female				
18–34 yr	11 (0.1)	8 (0.0)	6.94 (2.79–17.25)	<0.001
35–49 yr	67 (1.7)	46 (0.2)	7.50 (5.16–10.92)	<0.001
50–64 yr	161 (6.5)	112 (0.9)	7.92 (6.22–10.08)	<0.001
≥65 yr	139 (19.8)	282 (8.1)	3.12 (2.55–3.83)	<0.001

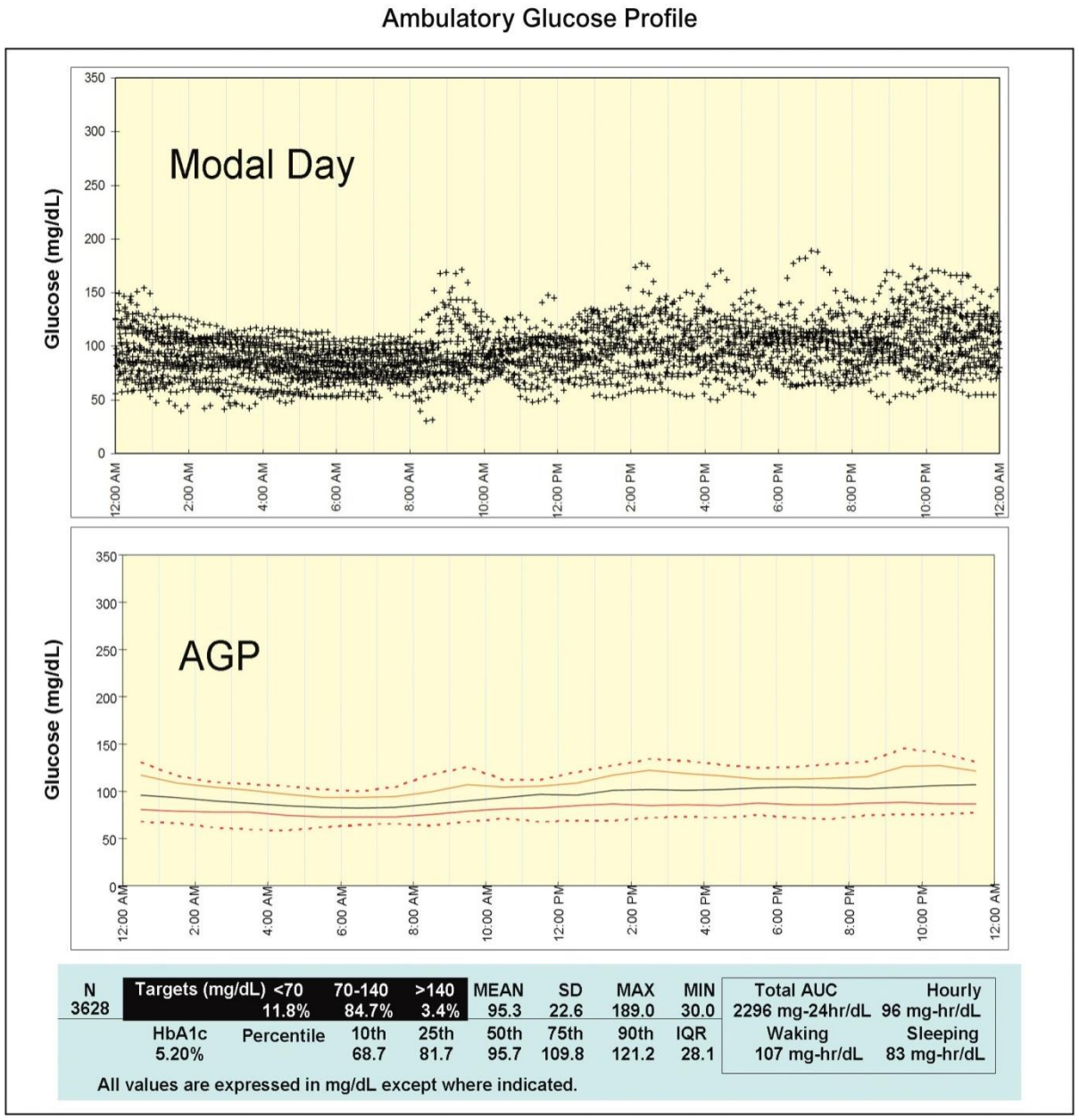


Marcus Lind et al. N Engl J Med 2014;371:1972-82.

Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

Marcus Lind et al. N Engl J Med 2014;371:1972-82.



The modal day and the AGP depict 3,628 continuous glucose readings measured for 30 days. The modal day shows each data point graphed without regard to date. The AGP replaces the individual data points with five smoothed frequency curves, which represent the underlying glycemic pattern. (accounting for outlier values). The statistical summary (shown separately, but contained in the AGP report) is customizable.

Center solid line is the median, next two outer solid lines (25th and 75th percentiles) represent the IQR, the dotted lines depict the 10th and 90th percentiles

Mazze RS et al. Diabetes Technol Ther. 2008 Jun;10(3):149-59

The barrier of hypoglycemia


PERSPECTIVES IN DIABETES

The Barrier of Hypoglycemia in Diabetes

Philip E. Cryer

Diabetes, 2008

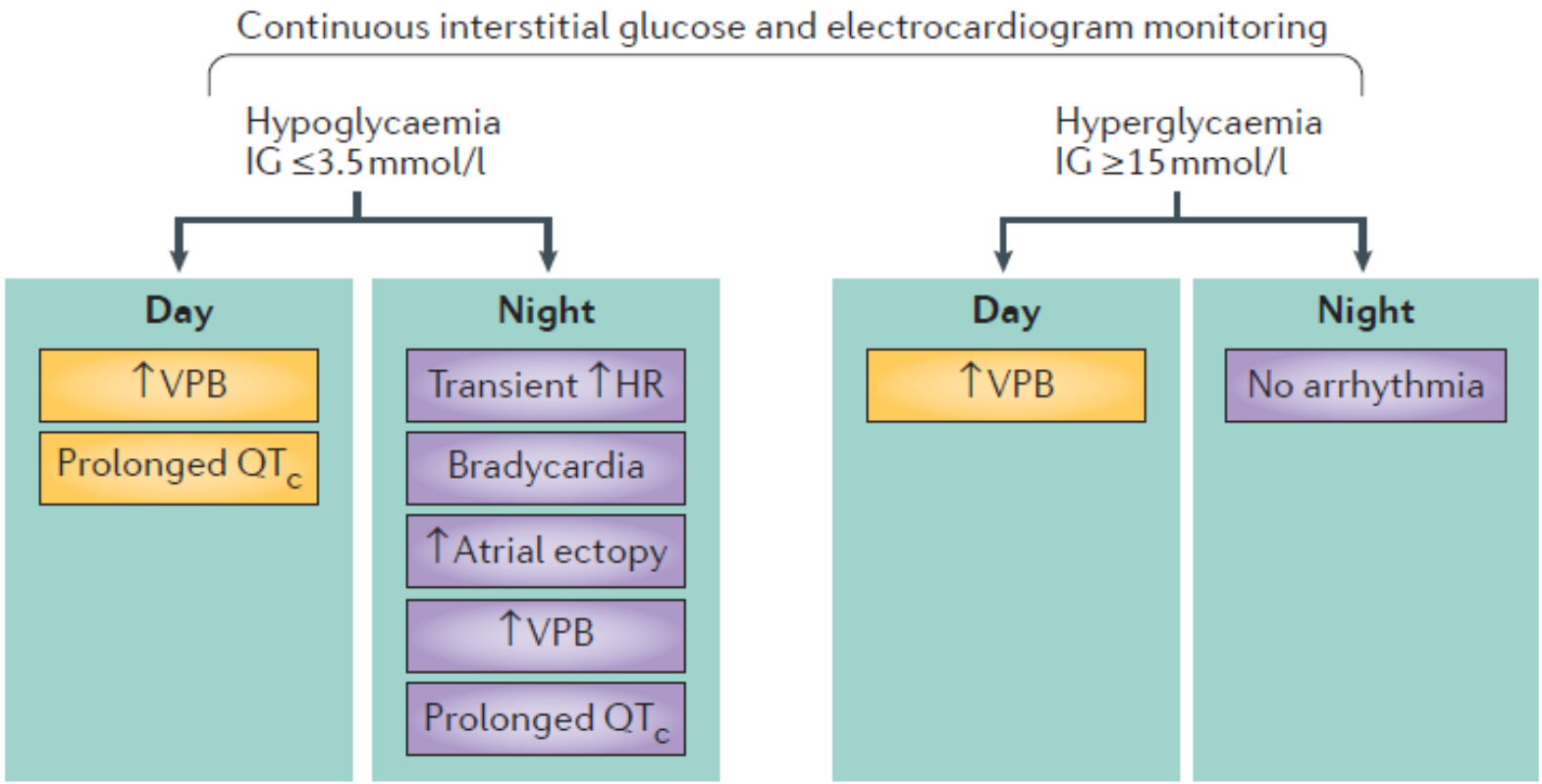
Glycemic control, a worthwhile goal for people with diabetes, is **limited by the barrier** of iatrogenic hypoglycemia. Iatrogenic hypoglycemia:

1) causes recurrent morbidity in most people with type 1 diabetes and many with advanced type 2 diabetes and is sometimes fatal
2) compromises physiological and behavioral defenses against subsequent falling plasma glucose concentrations and thus causes a vicious cycle of recurrent hypoglycemia
3) precludes maintenance of euglycemia over a lifetime of diabetes and therefore full realization of the vascular benefits of glycemic control

Implications of Hypoglycaemia

- Hypoglycaemia associated autonomic failure
- Hypoglycaemia unawareness
- Cardiovascular risk
- Poor quality of life

Differential effects of daytime vs night hypoglycaemia on cardiovascular risk

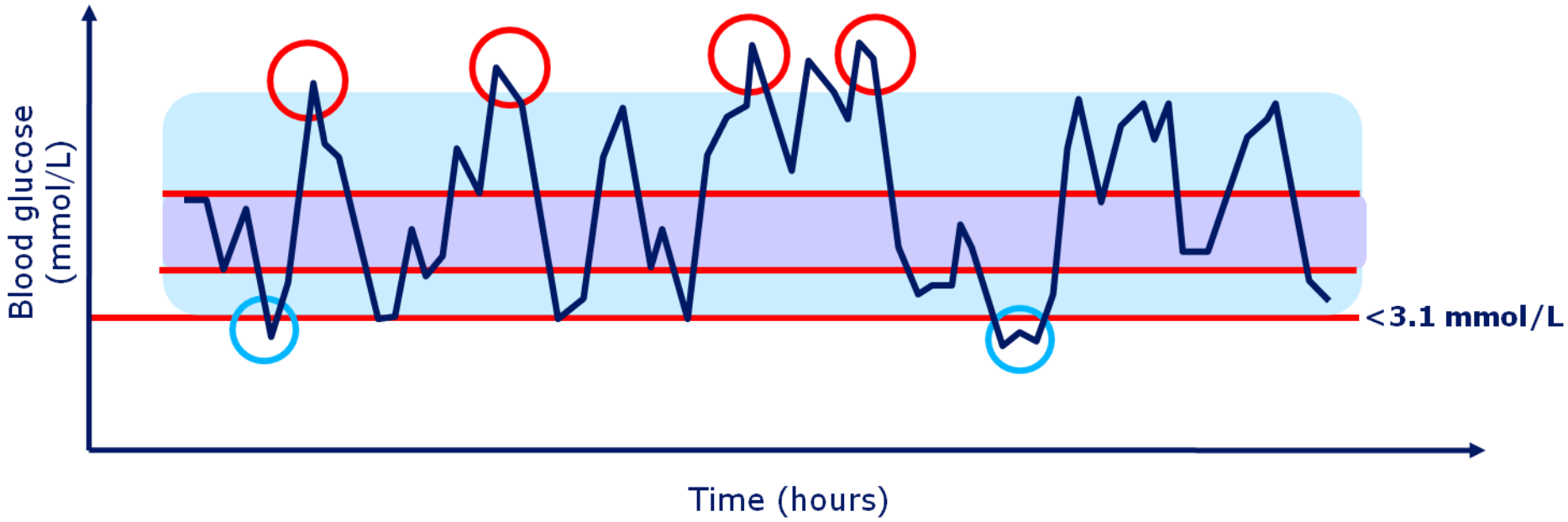


HR, heart rate; IG, interstitial glucose; QTc, cardiac repolarization interval; VPB, ventricular premature beats.

Umpierrez G et al, Nat Rev Endocrinol, 2016

Defining glucose variability

- Hypoglycaemic events
- Postprandial glucose excursions
- Minor fluctuations in blood glucose levels



Hyperglycemia following recovery from hypoglycemia worsens endothelial damage and thrombosis activation in type 1 diabetes and in healthy controls

- Hypoglycemia affected ($p < 0.01$ *vs* baseline):
  - Von Willebrand factor (vWF)
  - prothrombin fragment 1 fl 2 (F1 fl 2)
  - thrombine-antithrombin III-complexes (TAT)
  - P-selectin
  - plasminogen activator inhibitor-1 (PAI-1)
  - nitrotyrosine
  - 8-iso-prostaglandin F2a (8-iso-PGF2a)
- Recovery with normoglycemia improved all parameters ($p <0.01$ *vs* hypoglycemia)
- Recovery with hyperglycemia after hypoglycemia worsened all parameters ($p <0.01$ *vs* normoglycemia)
- This effect persisted even after additional 6 hours of normoglycemia and was partially counterbalanced when vitamin C was infused ($p <0.01$ vs hyperglycemia alone)

- **Hyperglycemia following hypoglycemia may activate thrombosis through the oxidative stress production**

Ceriello A et al Nutr Metab Cardiovasc Dis. 2014 Feb;24(2):116-23

Beyond Haemoglobin A1c—Need for Additional Markers of Risk for Diabetic Microvascular Complications

"Glucometrics" - the complete descriptive analysis of all aspects of glycemia - are rapidly evolving, along with software programs that can download and analyze these data

for assessing variability with continuous glucose monitoring and home blood glucose monitoring

Hirsch IB, Brownlee M. *JAMA. 2010;303(22):2291-2292*

Common measures of glucose variability

- Consecutive fasting blood glucose (FBG) values
  - SD or CV of FBG values
- Self-monitoring blood glucose (SMBG) profiles
  - SD or CV of blood glucose values
  - Average daily risk range
    - Computed average daily blood glucose range over 30 days
- Continuous glucose monitoring system (CGMS)
  - Mean blood glucose levels
  - SD of blood glucose levels
  - Mean amplitude of glucose excursions (MAGEs)
    - Measured as the mean of the differences between consecutive peaks and dips provided that the differences are greater than 1 SD of the mean glucose value
  - AGP (Ambulatory Glucose Profile) – interquartile ranges

SD, standard deviation; CV, coefficient of variation

Il sensore FreeStyle Libre

- Di piccole dimensioni (35 mm x 5 mm)
  - Discreto/comodo da indossare sotto i vestiti
- Disegnato per rimanere applicato sul corpo fino a 14 giorni
  - Richiede l'applicazione ogni 2 settimane
- Non richiede calibrazione con puntura del dito
  - Elimina il dolore delle punture al dito richieste per la calibrazione
- Resistente all'acqua
  - Può essere indossato durante il bagno, la doccia, il nuoto e l'attività fisica
- Applicabile dal paziente
  - Applicatore facile da usare per applicare il sensore
- Acquisisce automaticamente le letture giorno e notte
  - Con un semplice scan, è possibile vedere le variazioni del glucosio, inclusi gli abbassamenti notturni

Il sensore FreeStyle Libre

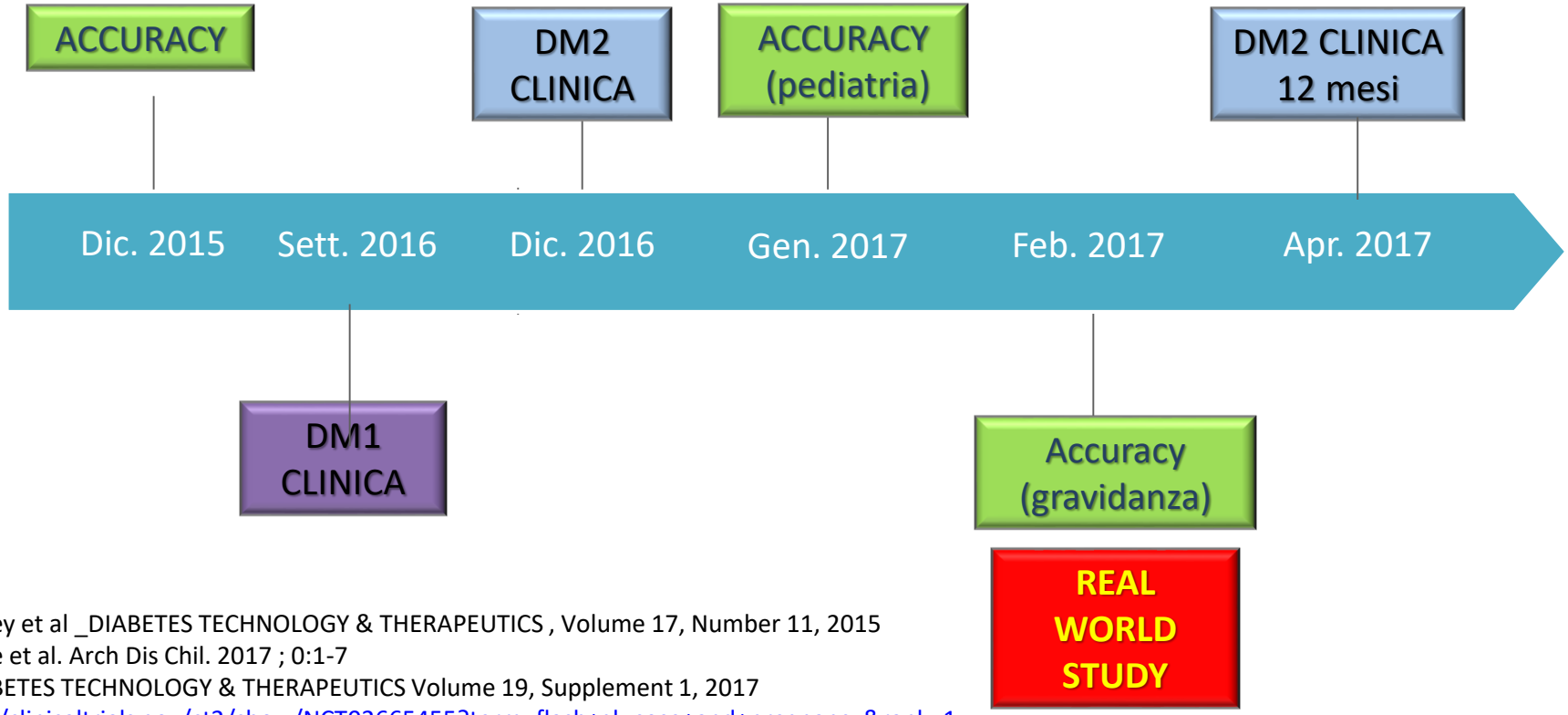
Touchscreen

Porta USB
Per caricare il lettore e collegarlo al Mac o PC

Porta della striscia
Per inserire una striscia nel misuratore incorporato della glicemia e chetonemia

Pulsante inizio (home)
Accende e spegne il lettore, consente di tornare alla schermata Inizio

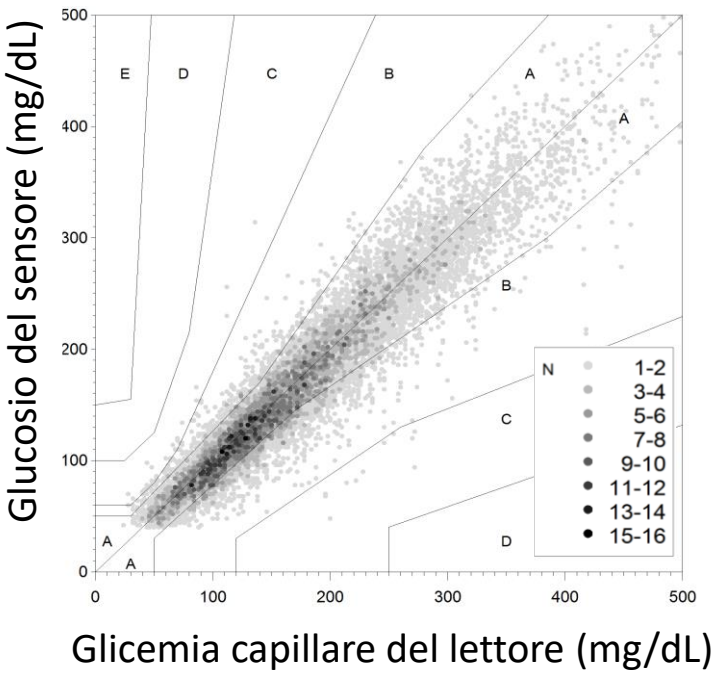
Monitoraggio Flash della Glicemia: evidenze dalla letteratura



1. Bailey et al _DIABETES TECHNOLOGY & THERAPEUTICS , Volume 17, Number 11, 2015
2. Edge et al. Arch Dis Chil. 2017 ; 0:1-7
3. DIABETES TECHNOLOGY & THERAPEUTICS Volume 19, Supplement 1, 2017
https://clinicaltrials.gov/ct2/show/NCT02665455?term=flash+glucose+and+pregnancy&rank=1
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/s13300-016-0223-6
6. Haak et al Diabetologia (2016) 59 (Suppl 1):S1–S581
7. https://clinicaltrials.gov/ct2/show/NCT02821117?term=Selfy+and+flash&rank=1
8. DIABETES TECHNOLOGY & THERAPEUTICS Volume 19, Supplement 1, 2017
Diabetes Ther. 2017 Apr;11(1)

Accuratezza

Consensus Error Grid



- L' 86.7% dei risultati del sensore nella Zona A clinicamente accurata.
- Il 99.7% dei risultati del sensore erano nelle Zone A & B clinicamente accettabili

Risultati per zona Error Grid						
	A	B	C	D	E	Totale
%	86.7	13.0	0.3	0	0	100
N	11439	1718	38	0	0	13195

Bailey et al _DIABETES TECHNOLOGY & THERAPEUTICS , Volume 17, Number 11, 2015

Accuratezza *vs* YSI

Sottoinsieme di dati, quando disponibili entrambi i metodi di riferimento venoso YSI e BG.

Livello di Glucosio mg/dL (mmol/L)	FreeStyle Libre vs. glicemia capillare (BG)			FreeStyle Libre vs. Venoso YSI		
	MAD mg/dL (mmol/L)	MARD %	N	MAD mg/dL (mmol/L)	MARD %	N
≤ 50 (2.8)	26.0 (1.4)	-	2	15.5 (0.9)	-	2
51 – 80 (2.8 – 4.4)	8.5 (0.5)	-	46	9.5 (0.5)	-	53
81 – 120 (4.5 – 6.7)	-	13.3	247	-	14.0	256
121 – 200 (6.7 – 11.1)	-	12.0	652	-	11.8	643
201 – 300 (11.2 – 16.7)	-	11.1	261	-	9.7	255
301 – 400 (16.7 – 22.2)	-	11.8	28	-	8.4	29
> 400 (22.2)	-	34.1	2	-	-	0
Tutti	-	12.2	1238	-	11.8	1238

Bailey et al _DIABETES TECHNOLOGY & THERAPEUTICS , Volume 17, Number 11, 2015

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.

Published Online
September 12, 2016
http://dx.doi.org/10.1016/S0140-6736(16)31535-5

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

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Caratteristiche dei pazienti arruolati

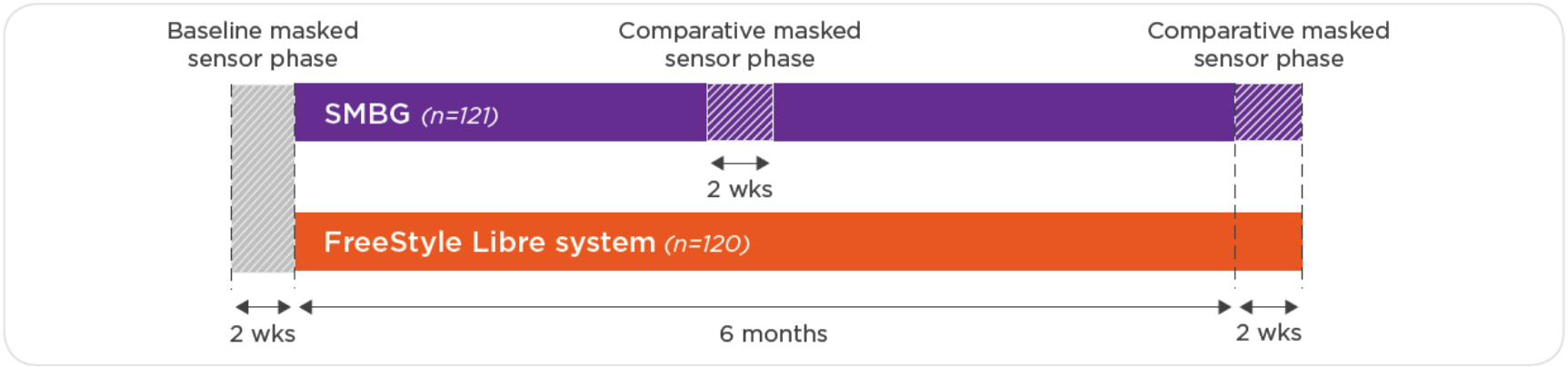
	Intervention (n=119)	Control (n=120)
Men	77 (65%)*	59 (49%)*
Women	42 (35%)	61 (51%)
Race		
White	119 (100%)	119 (99%)
Black	0	1 (1%)
Age (years)	42 (33–51)	45 (33–57)
BMI (kg/m^2)	25·2 (3·6)	24·8 (3·5)
Duration of diabetes (years)	20 (13–27)	20 (12–32)
Screening HbA_{1c} (%; mmol/mol)	6·7 (0·5); 50·1 (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

IMPACT – Disegno dello Studio

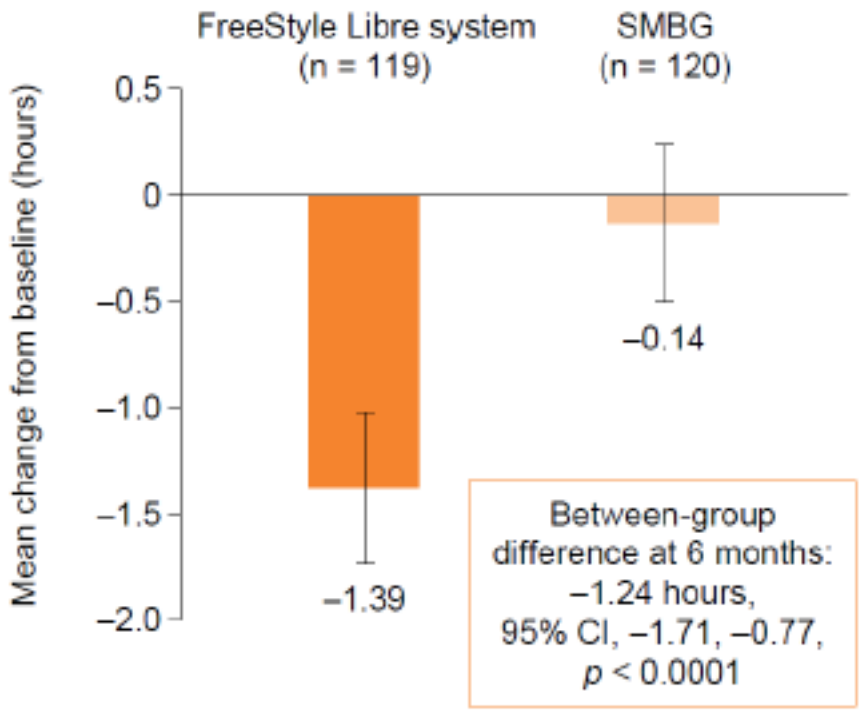
IMPACT è stato uno studio **controllato randomizzato** condotto in **23 centri europei** (6 nei Paesi Bassi, 3 in Spagna, 6 in Austria, 3 in Svezia e 5 in Germania)



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

Risultati - Endpoint primario

Tempo trascorso in ipoglicemia (<70mg/dL) nelle 24 ore



Riduzione media del tempo in ipoglicemia del 38% (74 minuti)

	Basale (±SD)	6 mesi (±SD)	Differenza (vs SMBG) dal basale(±SE)	p value
	FSL/SMBG	FSL/SMBG		
Ore per giorno	3.38/3.44 (±2.31/2.62)	2.03/3.27 (±1.93/2.58)	-1.24 (±0.24)	<0.0001

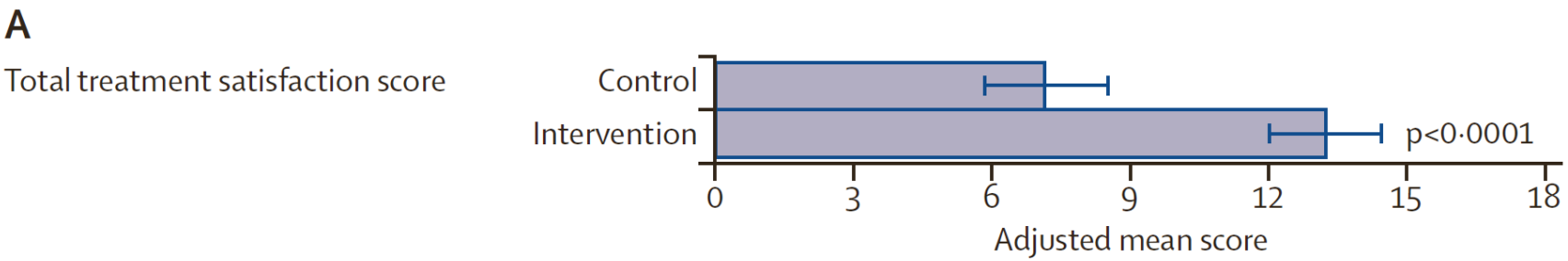
Bolinder et al. Lancet. 2016 -6736(16)31535-5

Risultati - Endpoints secondari

	Baseline		Study end		Difference in adjusted means in intervention vs control	Difference in intervention vs control (%)	p value
	Intervention (n=119)	Control (n=119)	Intervention (n=119)	Control (n=119)			
HbA1c							
HbA_{1c} (mmol/mol)	50·7 (5·7)	50·6 (7·0)	52·4 (7·2)	52·4 (7·2)	0·0 (0·65)	NA	0·9543
HbA_{1c} (%)	6·79 (0·52)	6·78 (0·64)	6·94 (0·65)	6·95 (0·66)	0·00 (0·059)	NA	0·9556
Tempo trascorso in ipoglicemia (<70 mg/dL) di notte							
Glucose <3·9 mmol/L (70 mg/dL) at night (2300–0600 h) within 7 h							
Events	0·47 (0·32)	0·46 (0·29)	0·27 (0·23)	0·40 (0·29)	−0·14 (0·029)	−33·2%	<0·0001
Time in h	1·32 (1·07)	1·48 (1·29)	0·68 (0·97)	1·23 (1·10)	−0·47 (0·118)	−39·8%	<0·0001
Time in range (70-180 mg/dL)							
Time with glucose 3·9–10·0 mmol/L (70–180 mg/dL) in h	15·0 (2·5)	14·8 (2·8)	15·8 (2·9)	14·6 (2·9)	1·0 (0·30)	NA	0·0006

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

Altri endpoints secondari: Diabetes Treatment Satisfaction (DTSQ)



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

IMPACT: Conclusioni

- In soggetti con DM1 in buon controllo metabolico il monitoraggio FGM è associato a:
  - Riduzione del tempo trascorso in ipoglicemia
  - Alcun peggioramento dei valori di HbA1c
  - Ottima accettabilità da parte dei pazienti
  - Assenza di significativi effetti collaterali

- Poichè la ipoglicemia è un delle principali barriere al controllo glicemico ottimale, **l'uso dell' FGM offre grandi potenzialità come alternativa più efficace all'SBGM convenzionale**

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

Received: November 9, 2016

ABSTRACT

Introduction: Glycemic control in participants with insulin-treated diabetes remains challenging. We assessed safety and efficacy of new flash glucose-sensing technology to replace self-monitoring of blood glucose (SMBG).

Methods: This open-label randomized controlled study (ClinicalTrials.gov, NCT02082184) enrolled adults with type 2 diabetes on intensive insulin therapy from 26 European diabetes centers. Following 2 weeks of blinded sensor wear, 2:1 (intervention/control) randomization (centrally, using biased-coin minimization dependant on study center and insulin administration) was to control (SMBG) or intervention (glucose-sensing technology). Participants and investigators were not masked to group allocation. Primary outcome was difference in HbA1c at 6 months in the full analysis set. Prespecified secondary outcomes

Conclusion: Flash glucose-sensing technology use in type 2 diabetes with intensive insulin therapy results in no difference in HbA1c change and reduced hypoglycemia, thus offering a safe, effective replacement for SMBG.

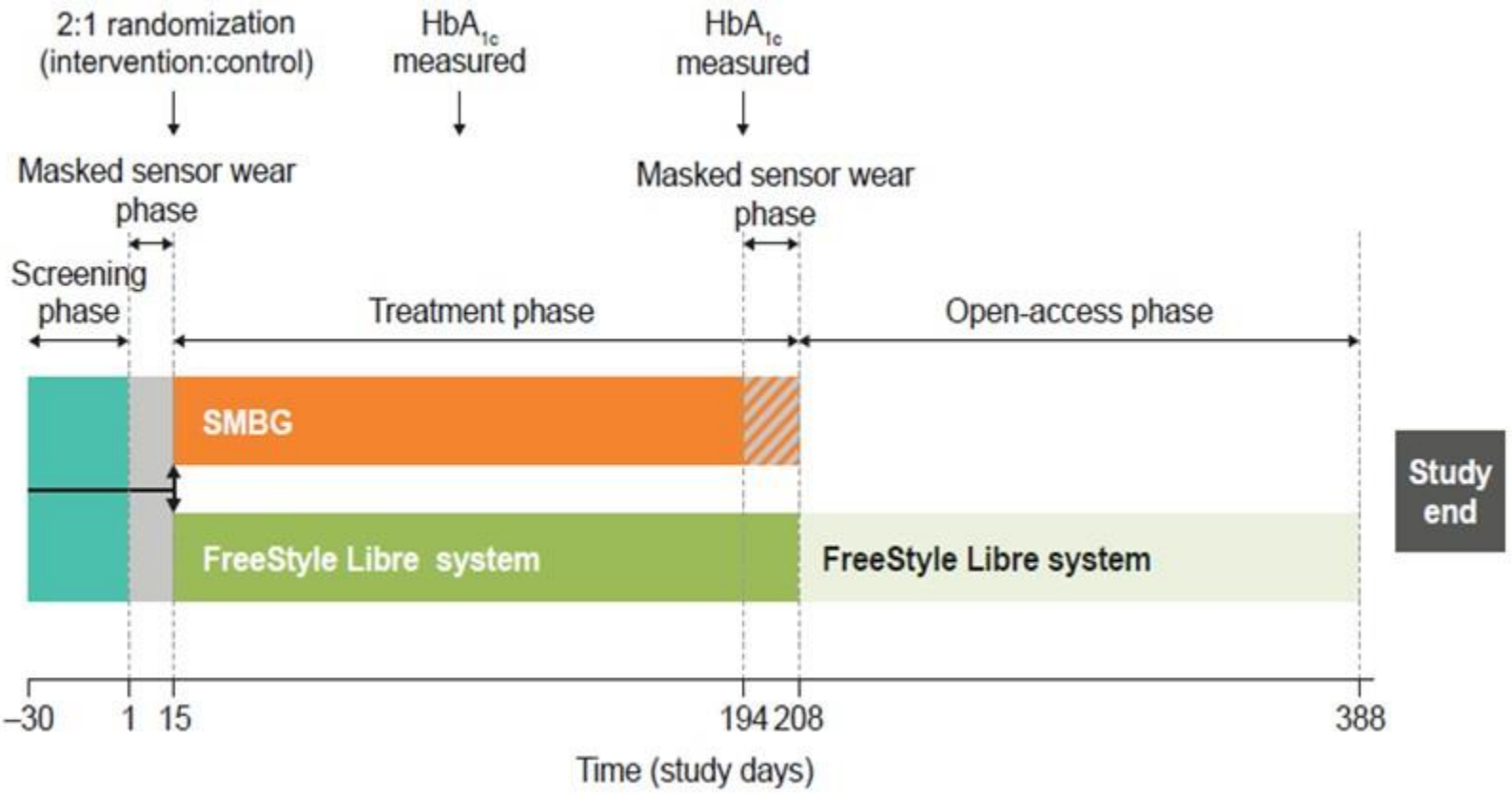
Trial registration: ClinicalTrials.gov identifier: NCT02082184.

Enhanced content To view enhanced content for this article go to http://www.medengine.com/Redeem/8A47F0602144B45F.

Electronic supplementary material The online version of this article (doi:10.1007/s13300-016-0223-6) contains supplementary material, which is available to authorized users.

REPLACE - Scopo e disegno dello studio

REPLACE è stato uno studio **controllato randomizzato** condotto in **26 centri europei** (8 in Francia, 10 in Germania ed 8 in UK)
Lo scopo dello studio REPLACE è stato quello di valutare il ruolo di FGMrispetto al controllo glicemico tradizionale in soggetti con diabete tipo 2 in trattamento insulinico intensivo o con microinfusore (CSII)



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REPLACE - Endpoints

- Primario
  - Differenza di HbA1c tra gruppo controllo e gruppo di intervento a 6 mesi
- Secondari
  - Analisi dei sottogruppi per età
  - Numero e durata episodi di ipoglicemia
  - Tempo in range
  - Numero e durata episodi di iperglicemia
  - Indici di variabilità glicemica
  - Numero di misurazioni di glicemia capillare e di scan
  - Cambiamento della dose totale di insulina, BMI e peso
  - Questionari per utilizzatori ed operatori sanitari
  - Sicurezza

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Caratteristiche dei pazienti arruolati

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/m^2)	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 pen device	140 (94%)	71 (95%)
CSII	8 (5%)	4 (5%)
Insulin syringe	1 (1%)	0 (0%)
Previous CGM use	11 (7%)	4 (5%)

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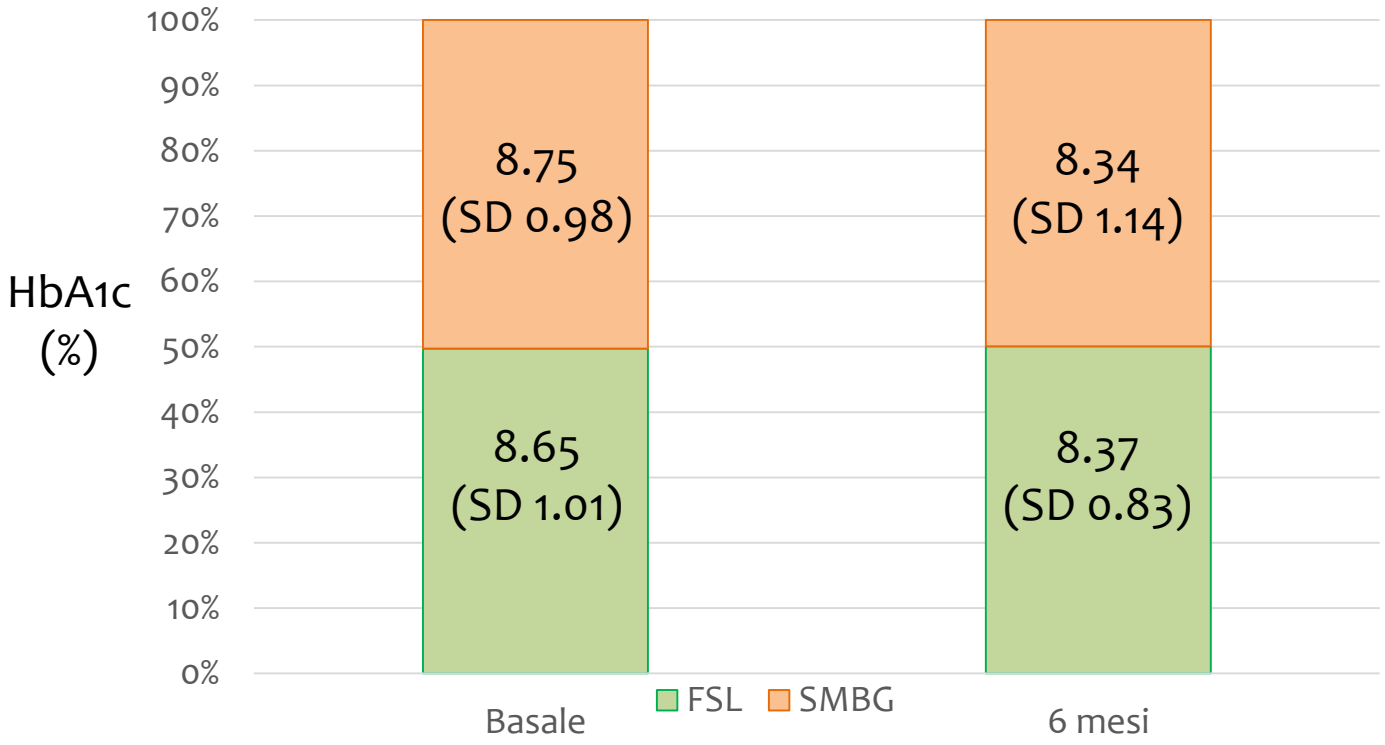
Enpoint primario: Variazione media HbA1c

Glycemic measure	Baseline mean (SD)		Study end mean (SD)		Difference in adjusted means in intervention vs control (SE)	Difference in intervention vs control (%)	*p* value
	Intervention (*n* = 149)	Control (*n* = 75)	Intervention (*n* = 149)	Control (*n* = 75)			
HbA1c (mmol/mol)	71.0 (11.1)	72.1 (10.7)	68.0 (9.0)	67.7 (12.4)	0.3 (1.25)	N/A	0.8259
HbA1c (%)	8.65 (1.01)	8.75 (0.98)	8.37 (0.83)	8.34 (1.14)	0.03 (0.114)	N/A	0.8222



p=0.822, ns

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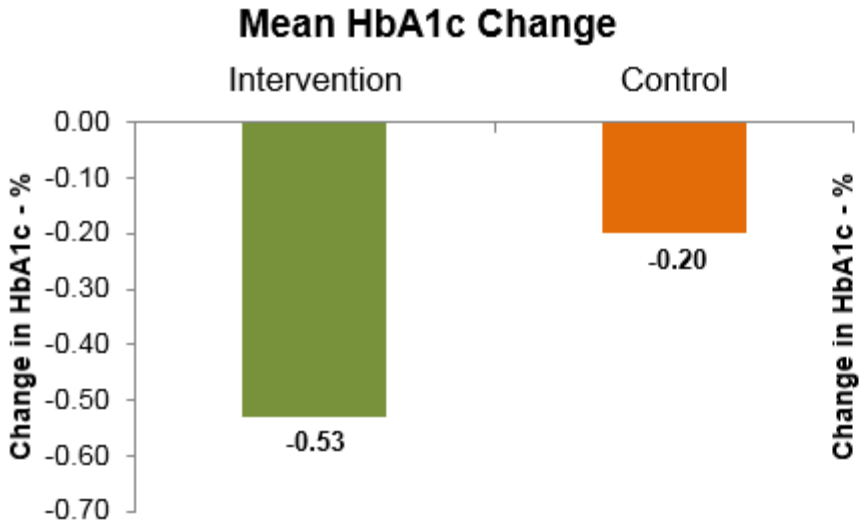
Endpoint secondario: Variazione media di HbA1c nei pazienti <65 e ≥ 65 anni

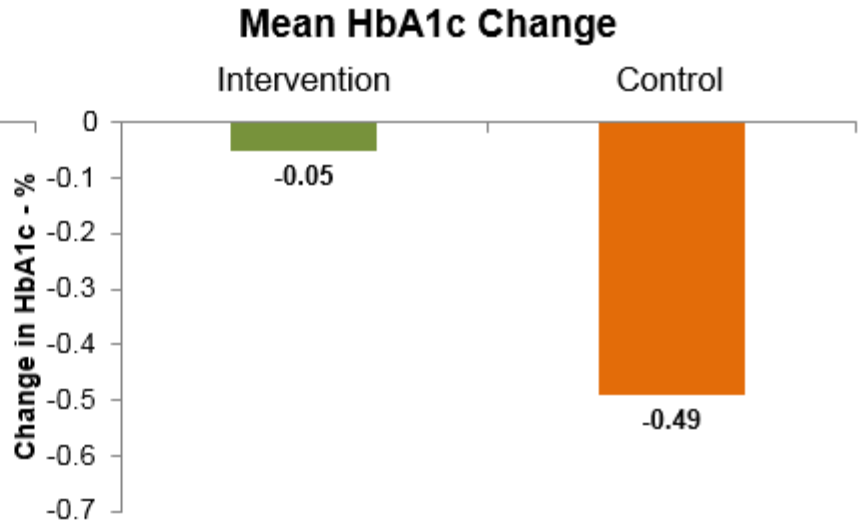
HbA_{1c} (%)	FreeStyle Libre (n = 95)	SMBG (n = 47)	Difference
Mean (± SD) HbA_{1c} at baseline	8.81 (± 1.06)	8.93 (± 1.08)	
Mean (± SD) HbA_{1c} at 6 months[a]	8.38 (± 0.88)	8.60 (± 1.24)	
HbA_{1c} change from baseline			
Mean (± SD)	−0.43 (± 1.07)	−0.33 (± 0.93)	
Adjusted mean (± SE)	−0.53 (± 0.088)	−0.20 (± 0.120)	−0.33 (± 0.149)
95% CI for adjusted mean	−0.70, -0.35	−0.44, 0.04	−0.62, −0.03
p value, FreeStyle Libre vs SMBG			0.0301

HbA_{1c} (%)	FreeStyle Libre (n = 54)	SMBG (n = 28)	Difference
Mean (± SD) HbA_{1c} at baseline	8.36 (± 0.86)	8.44 (± 0.71)	
Mean (± SD) HbA_{1c} at 6 months[a]	8.36 (± 0.73)	7.90 (± 0.79)	
HbA_{1c} change from baseline			
Mean (± SD)	0.00 (± 0.85)	−0.54 (± 1.09)	
Adjusted mean (± SE)	−0.05 (± 0.100)	−0.49 (± 0.133)	0.44 (± 0.161)
95% CI for adjusted mean	−0.25, 0.14	−0.76, -0.23	0.12, 0.76
p value, FreeStyle Libre vs SMBG			0.0081

< 65 years



≥ 65 years



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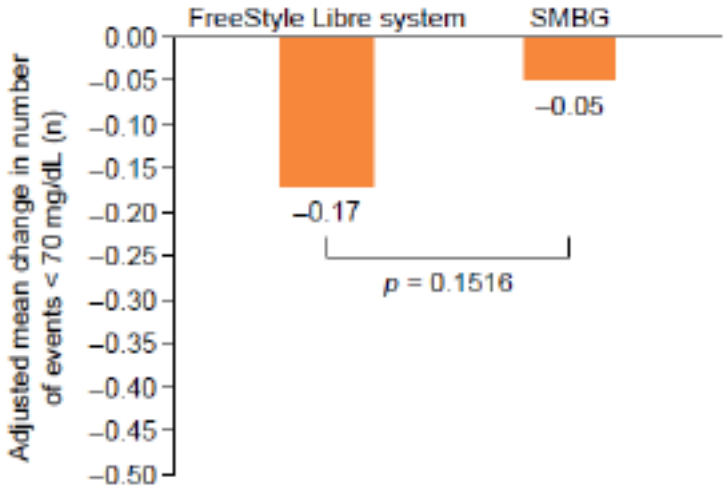
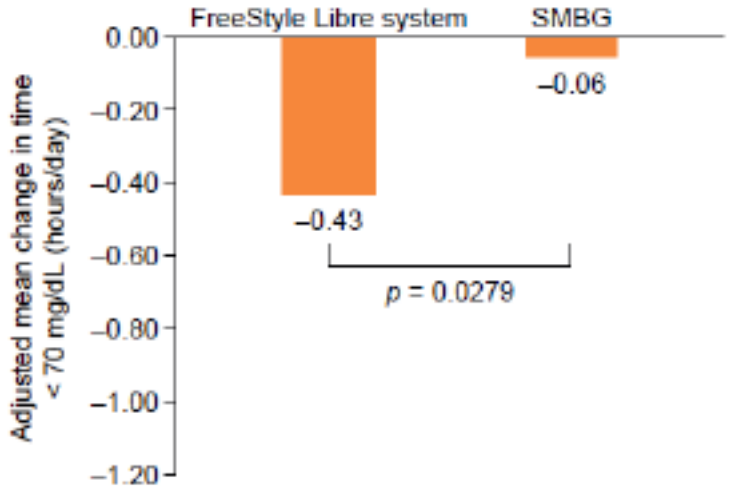
Enpoint secondario: tempo in ipoglicemia e numero di eventi ipoglicemici (glicemia <70 mg/dl) nei pz <65 anni

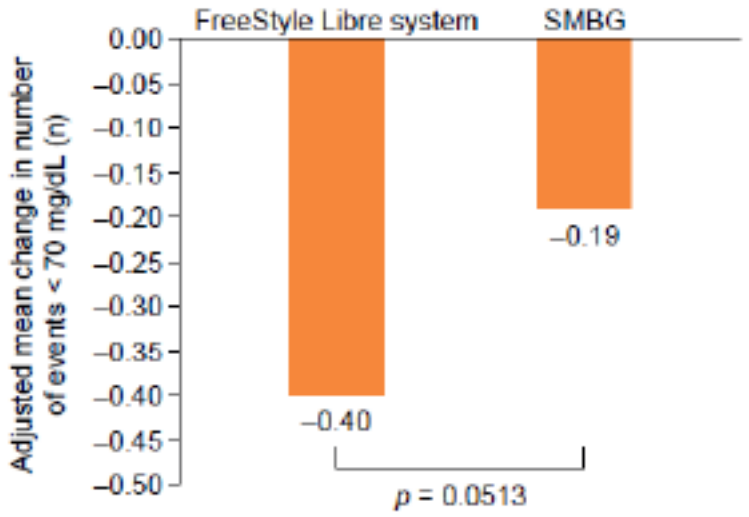


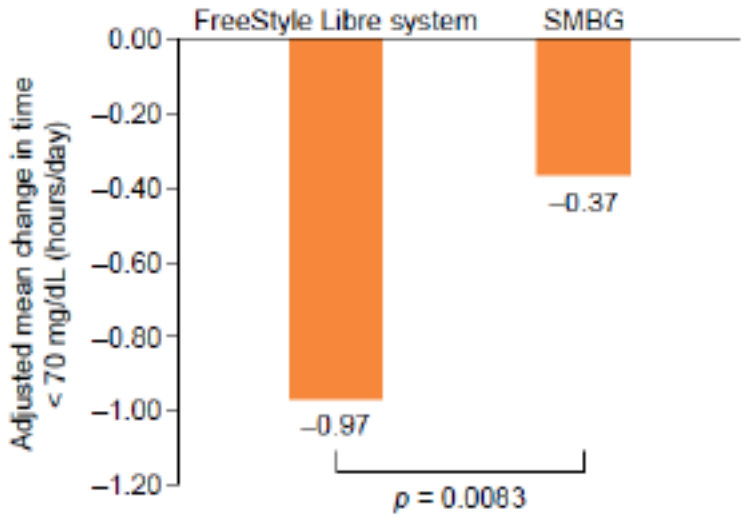


FreeStyle Libre: n = 149 SMBG: n = 75		Baseline phase, mean (± SD)		Final phase, mean (± SD)		Change from baseline, adjusted mean (± SE)[a]			Adjusted difference vs SMBG, %	*p* value vs SMBG
Glucose level	**Measure**	**FreeStyle Libre**	**SMBG**	**FreeStyle Libre**	**SMBG**	**FreeStyle Libre**	**SMBG**	**Difference**		
Participants aged < 65 years										
< 70 mg/dL (3.9 mmol/L)	No. of episodes[b]	0.58 (± 0.59)	0.55 (± 0.59)	0.39 (± 0.50)	0.50 (± 0.50)	−0.17 (± 0.052)	−0.05 (± 0.073)	−0.12 (± 0.083)	−22.1	0.1516
	Time[c]	1.17 (± 1.60)	0.98 (± 1.41)	0.64 (± 0.95)	0.96 (± 1.08)	−0.43 (± 0.105)	−0.06 (± 0.147)	−0.37 (± 0.168)	−35.4	0.0279
	AUC[d]	17.88 (± 29.57)	12.34 (± 19.94)	8.27 (± 14.65)	12.80 (± 17.13)	−7.27 (± 1.65)	−1.51 (± 2.31)	−5.76 (± 2.64)	−39.6	0.0305

Haak et al. Diabetes Ther. 2017, 1:55-73

Enpoint secondario: tempo in ipoglicemia e numero di eventi ipoglicemici (glicemia <70 mg/dl) nei pz ≥65 anni





FreeStyle Libre: n = 149 SMBG: n = 75		Baseline phase, mean (± SD)		Final phase, mean (± SD)		Change from baseline, adjusted mean (± SE)[a]			Adjusted difference vs SMBG, %	*p* value vs SMBG
Glucose level	Measure	FreeStyle Libre	SMBG	FreeStyle Libre	SMBG	FreeStyle Libre	SMBG	Difference		
Participants aged ≥ 65 years										
< 70 mg/dL (3.9 mmol/L)	No. of episodes[b]	0.76 (± 0.68)	0.75 (± 0.76)	0.35 (± 0.35)	0.56 (± 0.71)	−0.40 (± 0.069)	−0.19 (± 0.091)	−0.21 (± 0.106)	−36.7	0.0513
	Time[c]	1.53 (± 2.06)	1.26 (± 1.83)	0.49 (± 0.52)	1.03 (± 1.61)	−0.97 (± 0.144)	−0.37 (± 0.189)	−0.60 (± 0.220)	−55.9	0.0083
	AUC[d]	24.14 (± 43.43)	16.92 (± 34.81)	5.40 (± 6.29)	14.91 (± 29.36)	−17.22 (± 2.51)	−6.36 (± 3.30)	−10.86 (± 3.85)	−70.9	0.0061

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Endpoint secondario: tempo in iperglicemia e variabilità glicemica

Glycemic measure	Baseline mean (SD)		Study end mean (SD)		Difference in adjusted means in intervention vs control (SE)	Difference in intervention vs control (%)	*p* value
	Intervention (*n* = 149)	Control (*n* = 75)	Intervention (*n* = 149)	Control (*n* = 75)			
Time with glucose >10.0 mmol/L (180 mg/dL) (h)	8.8 (5.0)	9.4 (5.8)	9.8 (4.8)	9.8 (5.4)	0.3 (0.63)	3.5	0.5970
Time with glucose >13.3 mmol/L (240 mg/dL) (h)	3.1 (3.3)	3.9 (4.5)	3.5 (3.7)	3.9 (4.2)	0.1 (0.46)	2.1	0.8729
Glucose variability							
BGRI	9.5 (5.1)	10.4 (6.7)	9.9 (5.6)	10.5 (6.1)	0.0 (0.70)	N/A	0.9431
CV glucose (%)	34.1 (7.2)	33.1 (6.7)	31.4 (6.2)	33.0 (8.0)	−2.26 (0.71)	N/A	0.0017
LBGI	1.1 (1.3)	1.0 (1.2)	0.6 (0.7)	0.9 (1.0)	−0.3 (0.11)	N/A	0.0029
MAGE (mg/dL; average)	128 (29)	131 (33)	125 (29)	131 (33)	−4 (3.3)	N/A	0.1909
Mean glucose (mg/dL)	165 (34)	171 (43)	174 (33)	174 (38)	3 (4.3)	N/A	0.4236
Standard deviation of glucose (mg/dL)	56 (14)	56 (15)	54 (13)	56 (15)	−1.67 (1.45)	N/A	0.2538
CONGA 2 h (mg/dL)	49 (11)	50 (14)	47 (12)	51 (11)	−3 (1.3)	N/A	0.0385
CONGA 4 h (mg/dL)	61 (16)	61 (19)	57 (18)	64 (17)	−5 (2.2)	N/A	0.0133
CONGA 6 h (mg/dL)	63 (21)	62 (22)	58 (23)	65 (23)	−8 (3.0)	N/A	0.0046

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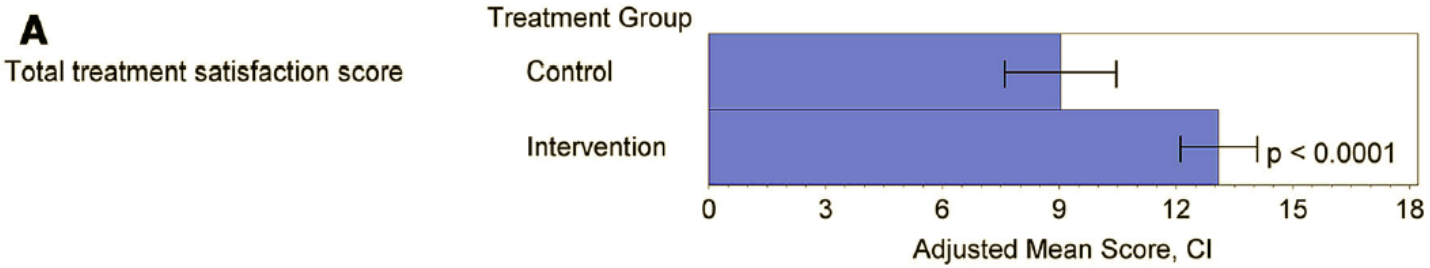
Risultati altri endpoints secondari: Diabetes Treatment Satisfaction (DTSQ)



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Studio REPLACE: Conclusioni

- In pazienti con DM2 in trattamento insulinico:
  - L'utilizzo del sensore vs il monitoraggio standard del glucosio si traduce in una simile riduzione dell'HbA1c
  - Quando si confronta il sensore con il monitoraggio classico del glucosio non è stata riscontrata alcuna problematica di sicurezza e l'utilizzo di questa tecnologia si è associato ad una marcata:
    - **riduzione di tutti gli indici di ipoglicemia**
    - **riduzione della variabilità glicemica**
    - **miglioramento della qualità di vita e degli indici del trattamento**
  - Nel complesso i risultati dimostrano che la tecnologia flash del glucosio è sicura ed efficace quando utilizzata al posto dell'automonitoraggio quotidiano per la gestione della glicemia in soggetti affetti da diabete tipo 2 ed in trattamento insulinico intensivo

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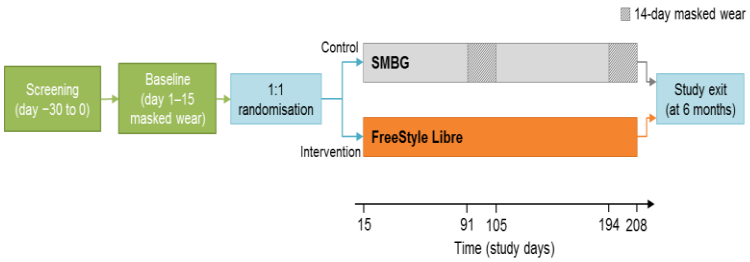
Studio IMPACT[4]
DM1 e HbA1c ≤ 7.5%



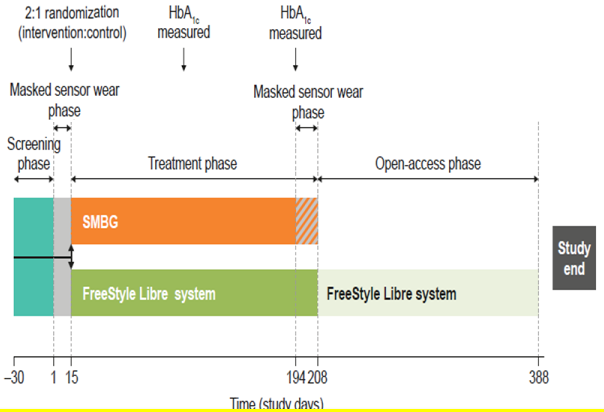
Riduzione del 38% del **tempo** in ipoglicemia < 70 mg/dL

Riduzione significativa di tutti gli altri indicatori clinici di ipoglicemia

Riduzione significativa time in range e cariabilità glicemica

I pazienti diabetici T1 che utilizzano **Freestyle Libre** si testano in media **14,5 volte al giorno** ricorrendo al sistema tradizionale in media **0,5 volte al giorno**.

Studio REPLACE[5]
DM2 e 7.5 ≤HbA1c ≥12%



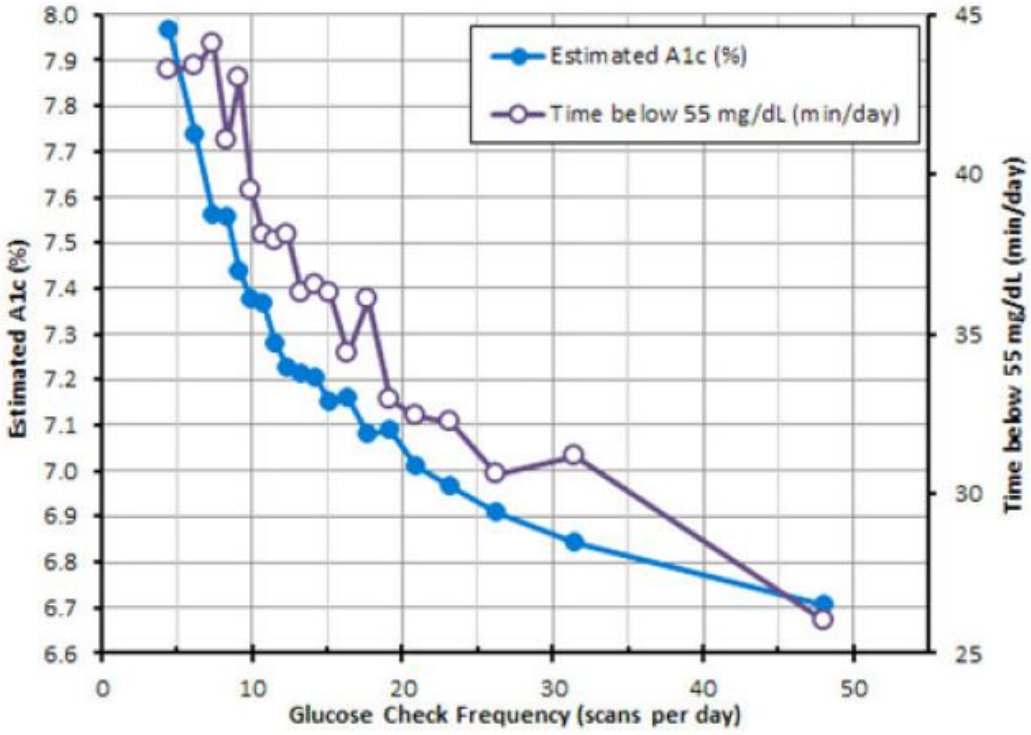
Nessun aumento dell'HbA1c e nell'analisi di un sottogruppo prespecificato composto da soggetti con meno di 65 anni hanno ottenuto una **riduzione statisticamente significativa dell'HbA1c** (-0,33%) vs SMBG

Riduzione significativa di tutti gli altri indicatori clinici di ipoglicemia

I pazienti diabetici T2 che utilizzano **Freestyle Libre** si testano in media **8,3 volte al giorno** ricorrendo al sistema tradizionale in media **0,3 volte al giorno**.

Real World Evidence

- ✓ Utilizzo real world di 50.831 readers e **279.446 sensori** (86.4 milioni di ore di monitoraggio attraverso 63.8 milioni di scansioni)
- ✓ Media di **16.3** scans al giorno(mediana 14, range interquartile 10-20)
- ✓ Nell'utilizzo nella vita reale la frequenza elevata degli scans si è dimostarto essere associata ad un miglioramento delle misure del glucosio incluse una **riduzione** del glucosio medio e tempo in iper ed ipoglicemia cosi come un **aumento** del time in range



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REPLACE 12 mesi follow up

- I 139 pazienti che hanno completato la fase di 6 mesi di intervento hanno poi continuato la fase di open-access fino a 12 mesi
- A 12 mesi è stato osservato che:
  - tempo in ipoglicemia (3.9 mmol/L (70 mg/dL) ridotto del 50%; p = 0.0002
  - Tempo in ipoglicemia notturna (3.9 mmol/L (70 mg/dL) ridotto del 52%; p = 0.0002
  - numero medio di test capillari ridotto da 3.9 al giorno a 0.2 al giorno con una frequenza media di scan di 7.1
  - nessun evento avverso serio dovuto al device

L'utilizzo per 12 mesi della tecnologia flash per la gestione dei pazienti affetti da diabete tipo 2 in trattamento insulinico intensivo si associa ad una **sostanziale riduzione dell'ipoglicemia** e ad una sicura ed **efficace sostituzione dell'automonitoraggio tradizionale**

Haak et al. Diabetes Ther. 2017 April 2017. DOI 10.1007/s13300-017-0255-6

DIABETES RESEARCH AND CLINICAL PRACTICE 118 (2016) 168–171

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

The evolving frontier of diabetes therapy: The renaissance of glycemology

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[c] *Diabetes Research Institute, San Raffaele Hospital and San Raffaele Vita-Salute University, Milan, Italy*

A modern, updated approach to glycemic control in people with diabetes, in fact, must focus not only on reaching and maintaining optimal HbA1c levels as soon as possible, but to obtain this result by reducing postprandial hyperglycemia and glycemic variability, while avoiding hypoglycemia.

Universo digitale FreeStyle Libre

Healthcare Provider

A FREE **secure, cloud-based** diabetes management system offering a **convenient, clear** and **easy** way to view patients' glucose data[1]

Patient

A FREE[2] app designed to work with the FreeStyle Libre sensor, which can replace the FreeStyle Libre reader.[3] One quick scan **discretely checks** glucose data and **stores securely** in the LibreView cloud

LibreView

LibreLink

LibreLinkUp

Family, Friends and Caregivers

A FREE[2] app designed to work with LibreLink providing family, friends and caregivers the option to **remotely monitor** glucose readings

Other Apps

Seamless integration with:

diasend.com

mySugr

Flash Glucose Monitoring in Italia

- Emilia Romagna[7,13]
- Lazio[8]
- Basilicata[9]
- Toscana[10]
- Umbria[11]
- Piemonte[12]
- Friuli Venezia Giulia[14]
- Campania[15]
- P.A. Trento
- Veneto

7: Circolare Sanità n. 13 del 9/10/2015
8: Determinazione n. G08900 del 3/08/2016
9: Deliberazione di Giunta Regionale 29.04.2016, n. 452
10: DGR n.829 del 30/08/2016
11: Deliberazione della Giunta Regionale N. 1411 seduta del 05/12/2016
12: Linee di indirizzo regionali per un uso appropriato dei dispositivi per l'autocontrollo e l'autogestione nel Diabete Mellito.Protocollo n. 592/A1404A. Classificazione 14.110.40 Regione Piemonte Direzione Sanità.
13: Circolare Sanità n. 12 del 15/09/2016 con oggetto: Indicazioni per l'utilizzo del dispositivo medico Flash Glucose Monitoring per il monitoraggio della glicemia in un sottogruppo della popolazione pediatrica (4-11 anni) con Diabete Mellito Tipo 1. Regione Emilia Romagna