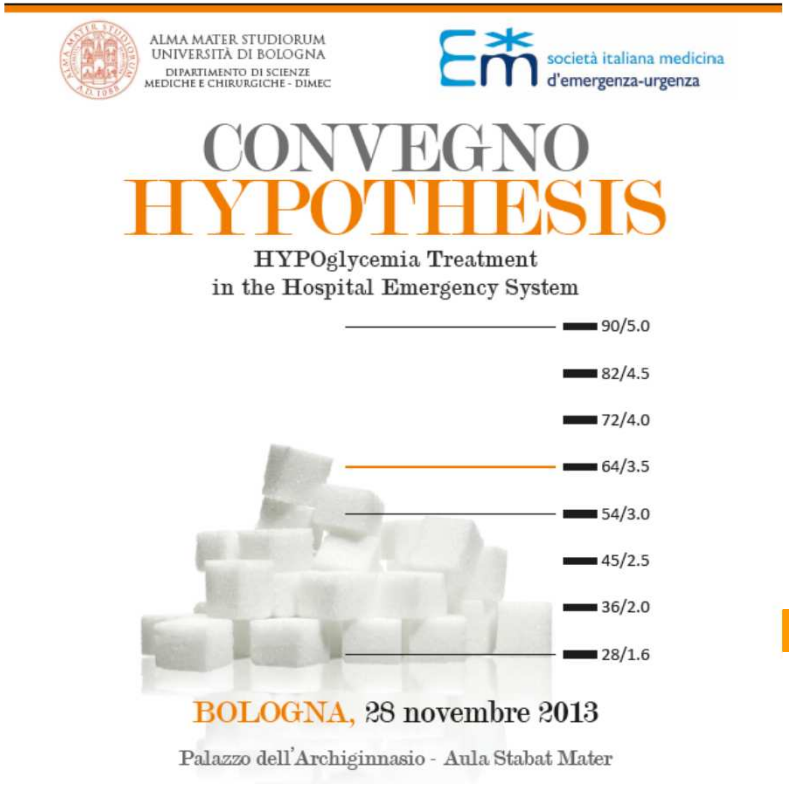


Paolo Di Bartolo
U.O di Diabetologia
Dip. Malattie Digestive & Metaboliche
AULS Prov. di Ravenna

Ipoglicemie e Monitoraggio Glicemico

Management of Hypoglycaemia

….if hypoglycemia is a problem, **the principles of intensive glycaemic therapy should be considered and applied**.

Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline.
J Clin Endocrinol Metab, March 2009, 94(3):709–728

Frequent SMBG and… in some instances CGM

Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline.
J Clin Endocrinol Metab, March 2009, 94(3):709–728

We have to ask our patients to intesify SMBG, but….

SMBG Frequency

Totals: 631 pts

P. Di Bartolo et al. Is there an Agreement Between Physicians and Patients with Type 1 Diabetes on Objectives of Insulin Therapy? **An AMD Survey in Type 1 Diabetes.** (Unpublished Data)

Unpublished Data

Real Time Continuous Glucose Monitoring Systems (rtCGM)

Navigator Abbot

Guardian Medtronic

DexCom G4

Why Do We Monitor the Glucose Level in the Interstitial Fluids?

Under physiological conditions there is a free and rapid exchange of glucose molecules between blood plasma and interstitial fluid and, for this reason, changes in blood glucose and interstitial glucose are strongly correlated…. Nevertheless, changes of glucose levels in interstitial fluid do not occur at the same time …; they occur with a delay.

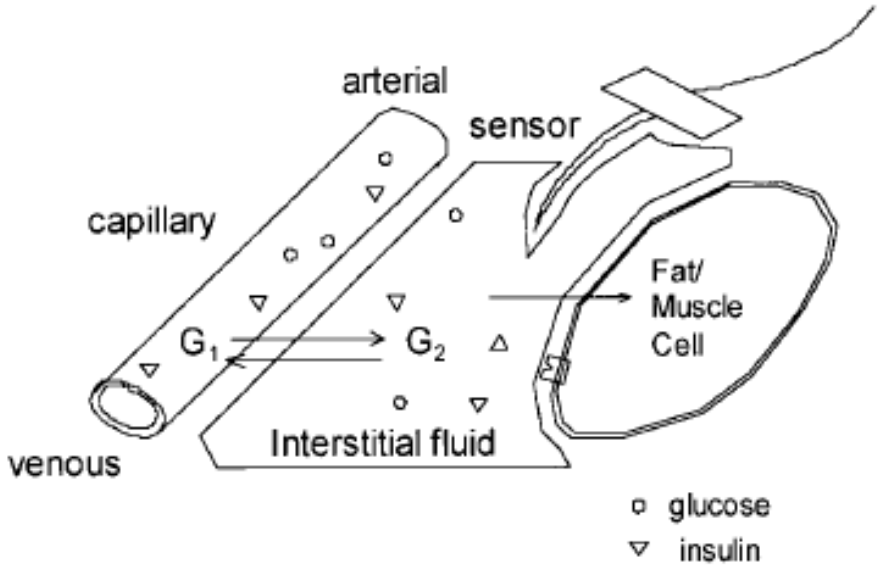


Figure 1. Glucose electrode inserted in subcutaneous tissue. Glucose diffuses from the intravasal compartment (G_1) into the interstitial compartment (G_2) and is then taken up by cells if insulin is present (modified after [11])

Sensors for glucose monitoring: technical and clinical aspects.
T. Koschinsky. L. Heinemann. Diabetes Metab Res Rev 2001; 17: 113–123.

Continuous Glucose Monitoring in Interstitial Subcutaneous Adipose Tissue and Skeletal Muscle Reflects Excursions in Cerebral Cortex

Jannik Kruse Nielsen, Christian Born Djurhuus, Claus Højbjerg Gravholt, Andreas Christiansen Carus, Jacob Granild-Jensen, Hans Ørskov, and Jens Sandahl Christiansen

DIABETES, VOL. 54, JUNE 2005

We show time-wise similar changes, thus making subcutaneous adipose tissue a sensible tissue to monitor glucose changes in patients with diabetes. Although this study was performed in pigs under experimental conditions, we have no reason to doubt that similar results would have been found in humans….

Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Glycemic Outcomes at 26 Weeks, According to Age.*

Mean mg/dl/min — baseline/26 wk¶	0.73/0.68	0.72/0.74	0.07	0.85/0.84	0.86/0.87	0.48	0.84/0.82	0.83/0.83	0.66

The use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age

The Effect of Continuous Glucose Monitoring in Well-Controlled Type 1 Diabetes

Diabetes Care 32:1378–1383, 2009

JUVENILE DIABETES RESEARCH FOUNDATION
CONTINUOUS GLUCOSE MONITORING
STUDY GROUP*

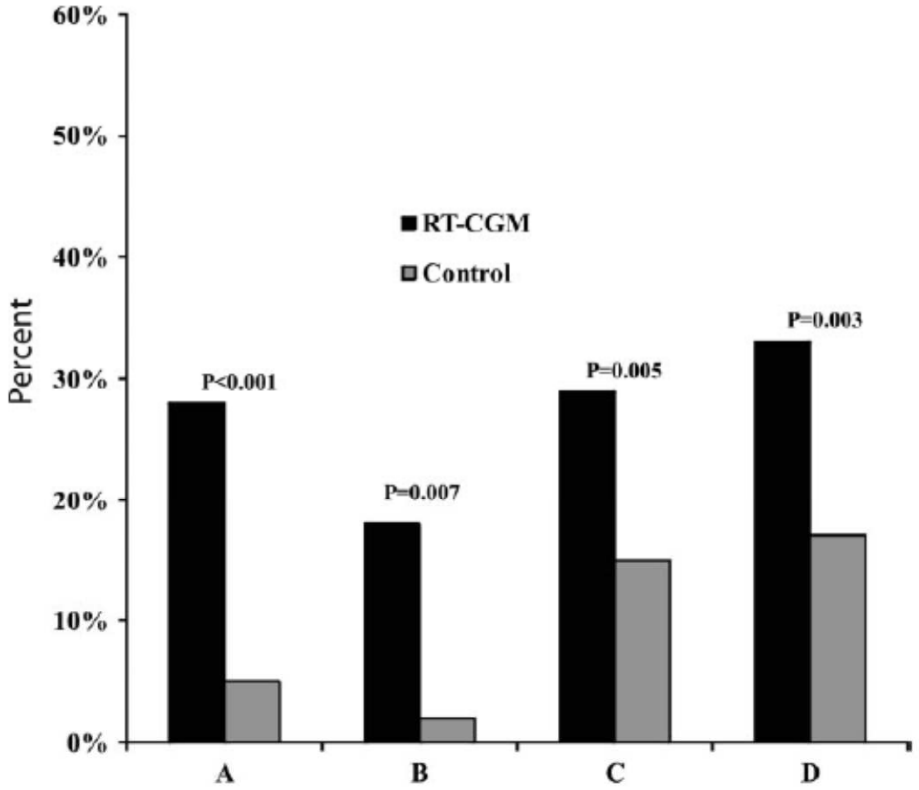
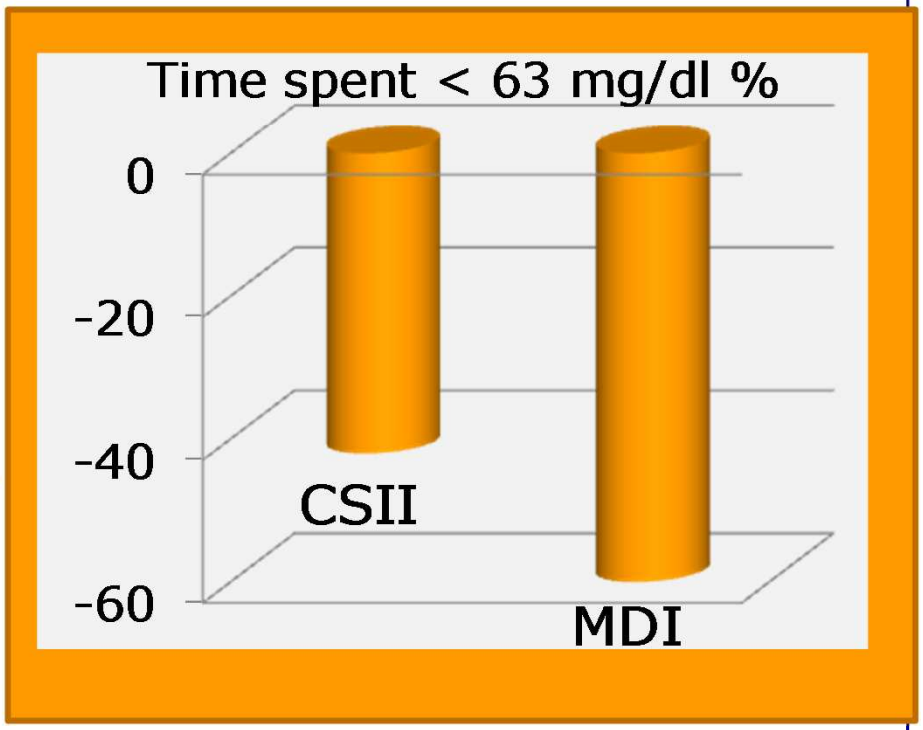


Figure 1—*Combined A1C and hypoglycemia outcomes. Four outcomes are shown: A, combined outcome of A1C improved by ≥0.3% from baseline to 26 weeks and no severe hypoglycemic events; B, combined outcome of A1C improved by ≥0.3% from baseline to 26 weeks and CGM-measured hypoglycemia (≤70 mg/dl) not increased from baseline to 26 weeks by ≥43 min/day (3% of the day); C, combined outcome of A1C not worse by ≥0.3% and CGM-measured hypoglycemia (≤70 mg/dl) decreased from baseline to 26 weeks by ≥43 min/day (3% of the day); D, combined outcome of either B or C.*

129 pts
Aged 8-69 years
HbA1c < 7 %
26 wks RCT

Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes

TADEJ BATTELINO, MD, PHD[1]
MOSHE PHILLIP, MD[2]
NATASA BRATINA, MD, PHD[1]
REVITAL NIMRI, MD[2]
PER OSKARSSON, MD, PHD[3]
JAN BOLINDER, MD, PHD[3]



Diabetes Care April 2011 34:795

RCT, multicenter study,.
-120 children and adults on intensive therapy for type 1 diabetes and HbA1c < 7.5%
-Randomly assigned to:

Control group performing conventional SMBG (5.3 $\pm$ 2.2/day) and wearing a masked CGM every 2nd week for five days

Active Group with real-time continuous glucose monitoring.

The primary outcome was the time spent in hypoglycemia (interstitial glucose concentration < 63 mg/dL) over a period of 26 weeks.

CGM Vs Fingerpricks

References	Primary Outcome	Active Group CGM	Control Group SMBG	Who Won?
D. Deis et al. Diabetes Care 2006	HbA1c	4.6 ± 1.4	5.0 ± 1.5 5.1 ± 1.8	CGM
JDRF, NEJM 2009	HbA1c	Adults: 6.5 ± 2.3 Adol: 5.6 ± 2.1 Ped: 6.7 ± 2.1	6.6 ± 2.2 6.1 ± 2.6 7.1 ± 2.5	CGM
Batalino T et al. Diabetes Care 2011	Time Spent in Hypo	5.1 ± 2.5	5.3 ± 2.2	CGM
Garg S et al. Diabetes Care 2006	Time Spent in Hypo	6+2	6+2	CGM

Sensor Augmented Pumps (SAPs)

Animas Vibe

Medtronic Veo

Accucheck Combo + Dexcom G4

Sensor Augmented Pump (SAP) STAR 3 (NEJM 2010: 363: 311-320)

Before randomization, all patients received training in intensive diabetes management, including carbohydrate counting and the administration of correction doses of insulin

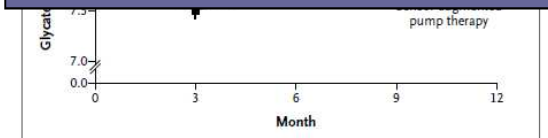


Figure 1. Glycated Hemoglobin Levels at 3, 6, 9, and 12 Months in All Patients and in Subgroups According to Age.
Values are means ±SE. Asterisks denote P<0.001 for all comparisons between pump therapy and injection therapy at each time point.

All patients used diabetes-management software (CareLink). Between visits, communication with clinicians was initiated at the discretion of the patient.

Hypoglycaemia: From DCCT to Star3 …….Something Happened

	Star 3		DCCT
All Patients	SAR	MDI	Intesive Arm
SH rate 100 persons/year	- 80 %!!!		62
HbA1c at the end of the Study	7.5 % (p< 0.001	8.1 %	% 4
Children			
SH rate 100 Children/year	8.9 P = NS	5.0	85.7
HbA1c at the end of the Study	7.9 % (p< 0.001)	8.5 %	8.1 %

Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data

John C Pickup *professor of diabetes and metabolism*[1], Suzanne C Freeman *medical statistics student*[2 3], Alex J Sutton *professor of medical statistics*[2]

Conclusions Continuous glucose monitoring was associated with a significant reduction in HbA_{1c} percentage, which was greatest in those with the highest HbA_{1c} at baseline and who most frequently used the sensors. Exposure to hypoglycaemia was also reduced during continuous glucose monitoring. The most cost effective or appropriate use of continuous glucose monitoring is likely to be when targeted at people with type 1 diabetes who have continued poor control during intensified insulin therapy and who frequently use continuous glucose monitoring.

BMJ

BMJ 2011;343:d3805 doi: 10.1136/bmj.d3805

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

336-347.

Figur

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72

68

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Table 2. Summary of the Subgroup Analyses in the Between-Group Change From Baseline HbA_{1c} Among Patients With T1DM Comparing rt-CGM with SMBG

Analysis	Studies Included (Participants Included), *n (n)*	Mean Difference in HbA_{1c} (95% CI), %	I^2, %
All studies*	8 (1066)†	−0.26 (−0.33 to −0.19)	66.6
Adults ≥18 y‡	3 (312)§	−0.38 (−0.53 to −0.23)	77.3
Children <18 y‖	5 (434)¶	−0.13 (−0.27 to 0.01)	46.0
Adherence >60%	7 (705)**	−0.36 (−0.44 to −0.27)	40.8

Ann Intern Med. 2012;157(5):336-347. doi:10.7326/0003-4819-157-5-201209040-00508

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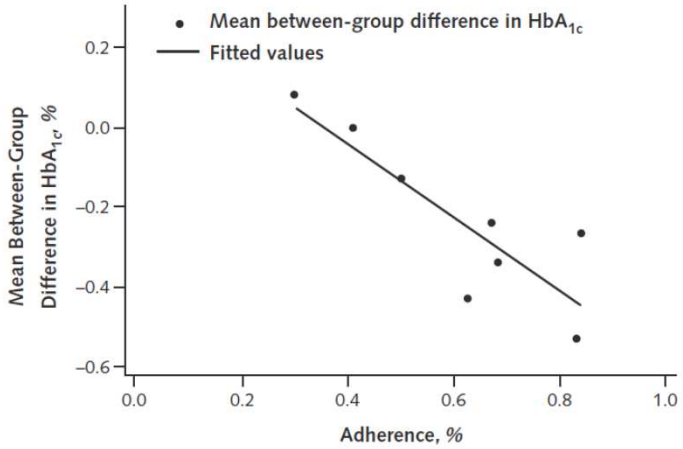
Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Comparative Effectiveness and Safety of Methods of Insulin Delivery and Glucose Monitoring for Diabetes Mellitus: A Systematic Review and Meta-analysis

Ann Intern Med. 2012;157(5):336-347. doi:10.7326/0003-4819-157-5-201209040-00508

Appendix Figure 2. Adherence with sensor use and mean between-group difference between rt-CGM and SMBG in HbA_{1c} changed from baseline.



HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitoring; SMBG = self-monitoring of blood glucose.

Figure Legend:

Adherence with sensor use and mean between-group difference between rt-CGM and SMBG in HbA_{1c} changed from baseline.
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Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data

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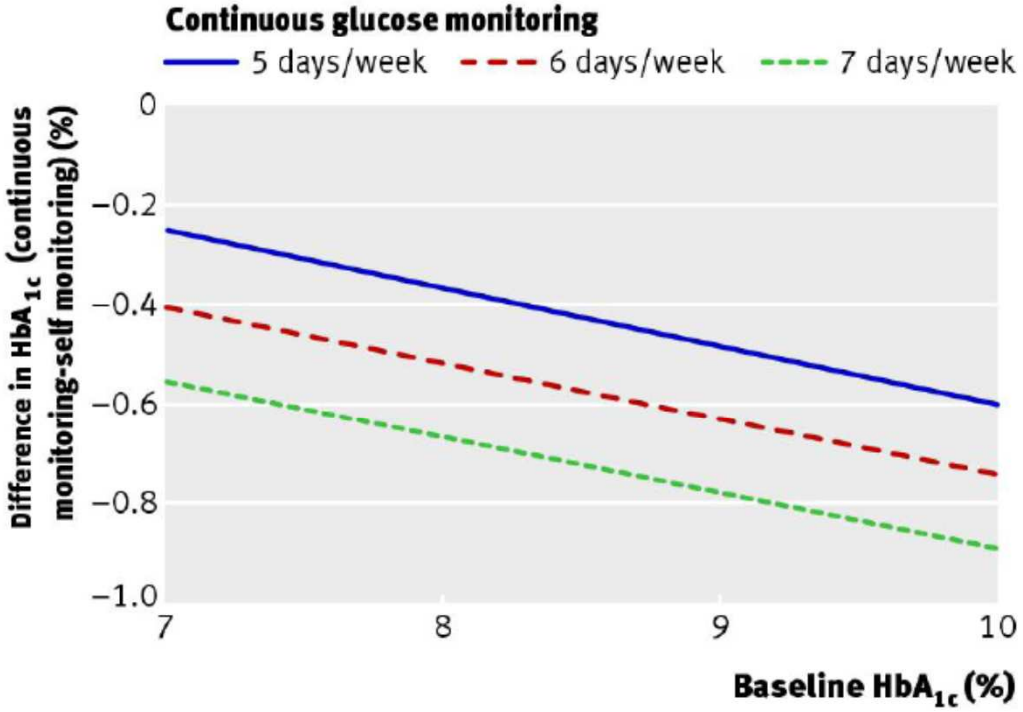

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	rt-CGM vs. SMBG		SAP vs. MDI	
	Adults and Children With T1DM		Adults and Children With T1DM	
	Findings	Strength of Evidence	Findings	Strength of Evidence
HbA_{1c}	Favors rt-CGM	High	Favors pump	Moderate
Hyperglycemia	Favors rt-CGM	Moderate	Favors pump	Moderate
Severe hypoglycemia	No difference	Low§	No difference	Moderate

Indications for rt-CGM in Adults with T1DM

Consensus of experts from SFD, EVADIAC and SFE

- A type 1 adult diabetic who—notwithstanding intensive treatment and management involving multiple injections or a pump, appropriate therapeutic education and SMBG several times a day, presents:
  - An HbA1c over the target (**Grade A**)
  - And/or undetected or frequent mild hypoglycaemias, particularly nocturnal ones. (**Grade B**.)
  - And/or frequent severe hypoglycaemias. (**Professional agreement**)
- In the course of pregnancy or preparation for pregnancy, recommended HbA1c targets unattained or attained at the cost of mild frequent hypoglycaemias. (**Professional agreement**)

Diabetes Metab. 2012 Jul;38 Suppl 4:S67-83

Indications for rt-CGM in Children and Adolescent with T1DM

Consensus of experts from SFD, EVADIAC and SFE

The effectiveness of CGM is significantly correlated
to the length of time sensors are used.
Efforts to increase sensor use
are important, particularly in the paediatric population.
A CGM trial period of generally less than one month
should be proposed to candidates.
Evaluation at 1 month almost always makes
it possible to tell if a patient has been adhering to sensor use,
accepts the constraints imposed by the
method and sees its advantages

Diabetes Metab. 2012 Jul;38 Suppl 4:S67-83

Hypoglycaemia has three adverse effects

- Hypoglycaemic episodes in themselves
- Fear of recurrence
- Long-term complications, which result from **allowing poor control in order to avoid hypoglycaemia**.

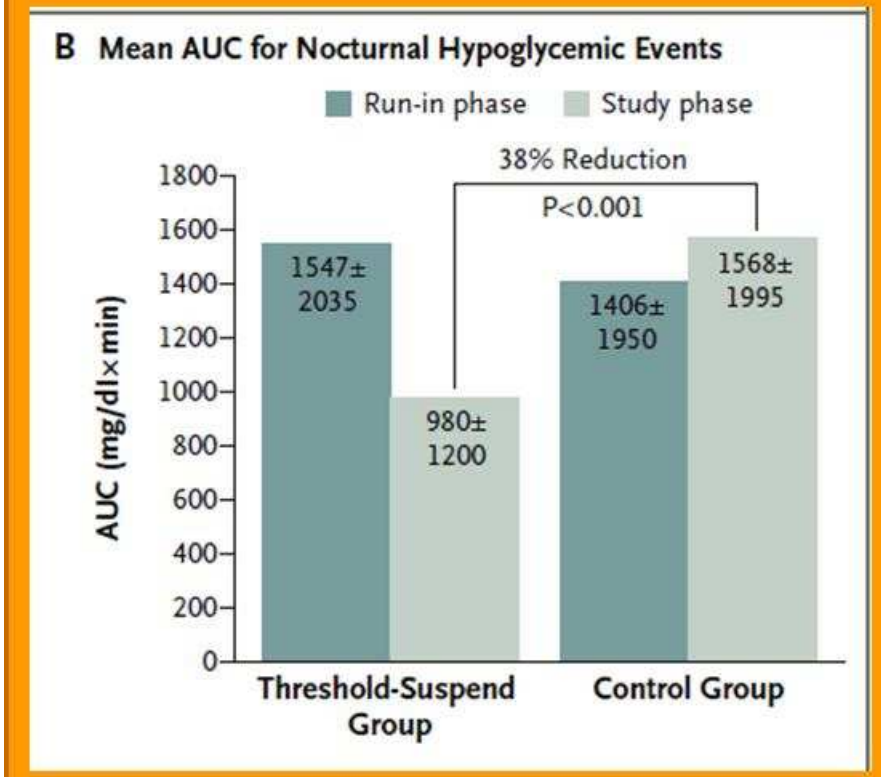
Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation
Health Technology Assessment 2010; Vol. 14: No. 11

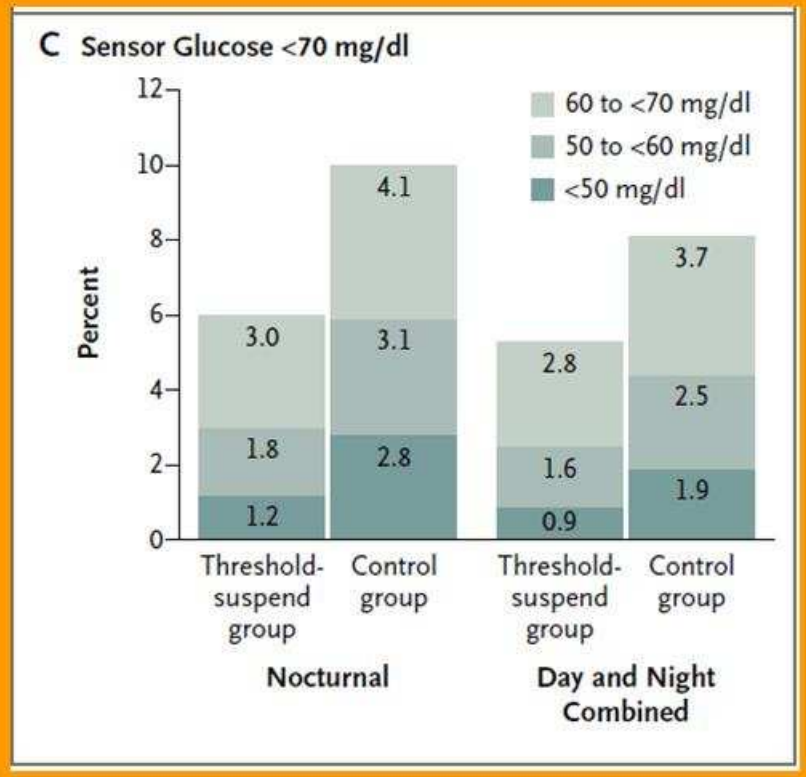
We have to remember that:

- Some Hypo is Inevitable, Even in Very Well Managed Patients
  - **But…. it should not be more than 2 or 3 mild, symptomatic episodes a week!!!**

- Many patients, also with impaired awareness of hypoglycaemia, could have high HbA1c as their blood glucose values swing between over-correction of hyperglycaemia to overcorrection of the resultant hypoglycaemia

Pratik Choudhary et al. Hypoglycemia: Current management and controversies. Postgrad Med J 2011; 87: 2298-306


B Mean AUC for Nocturnal Hypoglycemic Events
Run-in phase
Study phase
38% Reduction
P<0.001
AUC (mg/dl×min)
1800
1600
1400
1200
1000
800
600
400
200
0
1547±
2035
980±
1200
1406±
1950
1568±
1995
Threshold-Suspend Group
Control Group


C Sensor Glucose <70 mg/dl
60 to <70 mg/dl
50 to <60 mg/dl
<50 mg/dl
Percent
12
10
8
6
4
2
0
3.0
1.8
1.2
4.1
3.1
2.8
2.8
1.6
0.9
3.7
2.5
1.9
Threshold-suspend group
Control group
Threshold-suspend group
Control group
Nocturnal
Day and Night Combined

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Insulin Pump Therapy With Automated Insulin Suspension
Toward Freedom From Nocturnal Hypoglycemia

Pratik Choudhary, MBBS, MRCP, MD

- About 30% of patients with type 1diabetes have impaired awareness of hypoglycemia, which increases with increasing duration of diabetes.
- These patients are at a 3- to 6-fold greater risk of severe hypoglycemia.
- Although structured education courses, such as Dose Adjustment for Normal Eating (DAFNE), has been demonstrated to restore awareness in up to half of those who enter the program with impaired hypoglycemic awareness, in clinical practice this level of awareness is difficult to achieve and even more difficult to sustain.

Original Investigation

Effect of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension vs Standard Insulin Pump T A

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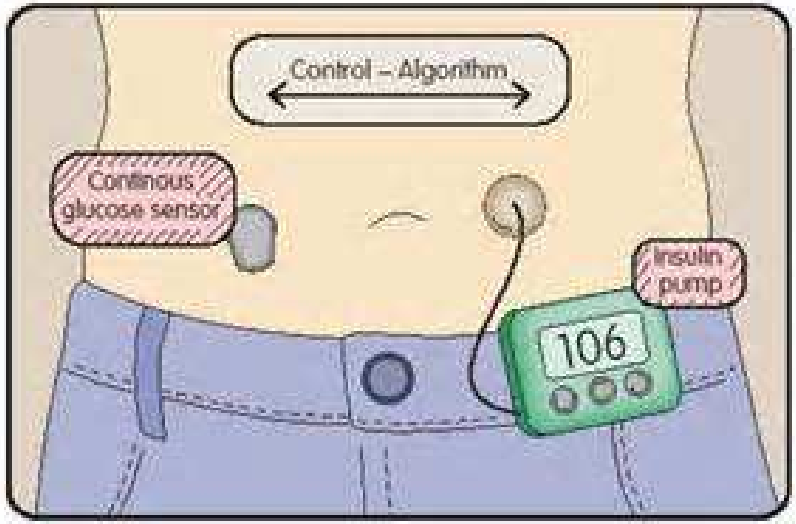
Conclusion

Sensor-augmented pump therapy with automated insulin suspension reduced the combined rate of severe and moderate hypoglycemia in patients with type 1 diabetes.

18



JDRF Juvenile Diabetes Research Foundation International

dedicated to finding a cure

First Generation | Second Generation | Third Generation

1	2	3	4	5	6
Very Low Glucose Insulin Off Pump Pump shuts off when user not responding to low-glucose alarm	**Hypoglycemia Minimizer** Predictive hypoglycemia causes alarms followed by reduction or cessation of insulin delivery below low threshold	**Hypoglycemia/ Hyperglycemia Minimizer** Same as Product #2 but added feature allowing insulin dosing above high threshold (e.g., 200mg/dl)	**Automated Basal/Hybrid Closed Loop** Closed loop at all times with meal-time manual assist bolusing	**Fully Automated Insulin Closed Loop** Manual meal-time bolus eliminated	**Fully Automated Multi-Hormone Closed Loop**

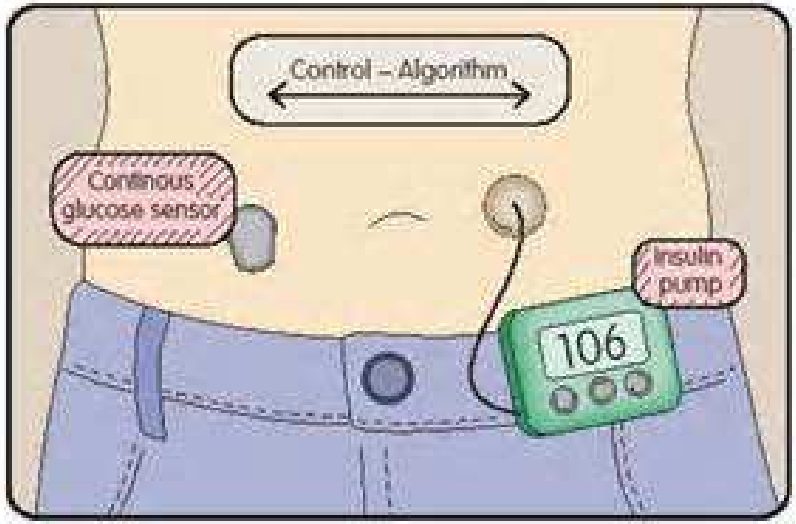
Cite this as: *BMJ* 2011;342:d1855

Conclusion These two small crossover trials suggest that closed loop delivery of insulin may improve overnight control of glucose levels and reduce the risk of nocturnal hypoglycaemia in adults with type 1 diabetes.

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions
Patients at a diabetes camp who were treated with an artificial-pancreas system had less nocturnal hypoglycemia and tighter glucose control than when they were treated with a sensor-augmented insulin pump

patient-oriented clinical outcomes.



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J Clin Endocrinol Metab, March 2009, 94(3):709–728

Conclusion

- Self Managent
  - Definition of new glycemic/A1c targets
  - Treatment Adjustment
  - MNT
    - Hypoglycemia correction
    - Hypoglycemia Prevention
- Therapy
  - Best Option

    SAP (LGS)

    CSII

    MDI (Glargine/detemir + Rapid Acting Insulin Analogues)
- Glucose Monitoring
  - Frequent SMBG
  - rtCGM