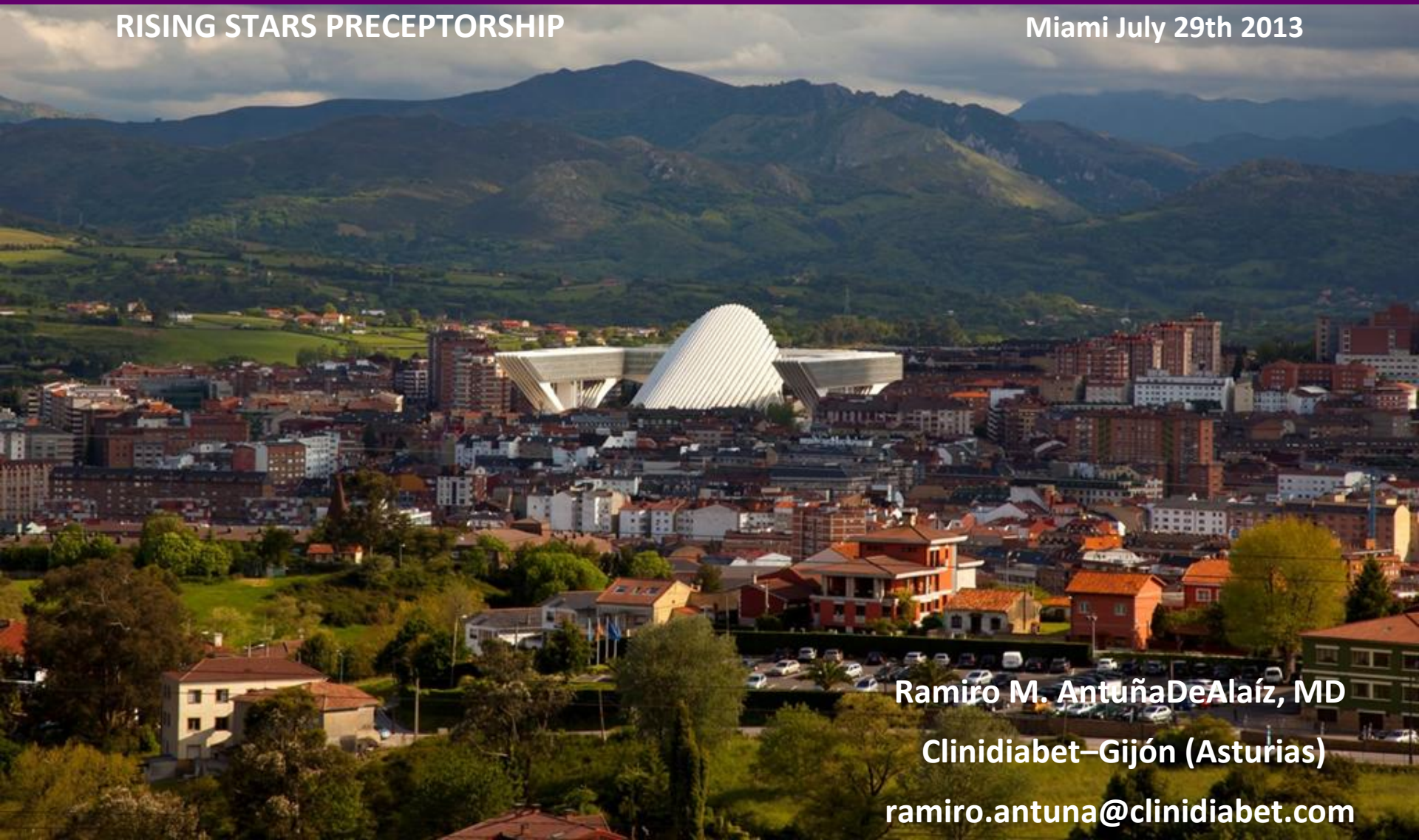


Practical Aspects of CGM

What we have learned and where are we heading?

RISING STARS PRECEPTORSHIP


Miami July 29th 2013



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Disclosures

Consultant: Abbot , Dexcom, C8 Medisense

Research support : Lilly, Sanofi-Aventis, NovoNordisk

Presentation Overview

1.- Some key Basic Concepts of CGM

- Components of a CGM system
- Commercially available CGM systems
- Issues with the interstitial lag time
- Issues with calibration

2.- Benefits and Pitfalls of CGM

3.- Indications of CGM. Patient selection criteria

- Lessons learned from clinical trials
- Lessons learned from the “real world” observation

4.- Practical Tips for a successful CGM experience.

5.- Conclusions, a look into the future and Patients testimonies

Diabetes Monitoring History



Before 1978



1978-2006



2006.....

Now we are at the beginning of the 3rd era in
Diabetes Management





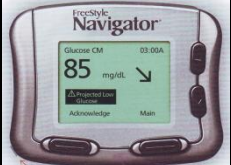
Never before in the history of Diabetes was there an option
available to tighten control of glucose levels without increasing the
risk of hypoglycemia

Components of a CGM System

- The sensor connected to a transmitter via a percutaneous electrical contact held in place by an adhering support on the surface of the skin
- The transmitter reads the electrical current from the sensor, generated by the oxidation of glucose in the interstitial fluid, and sends a radio frequency signal to a hand held receiver
- The receiver displays the glucose results and has alarms, displays glucose trends and store ,meal ,insulin and exercise details that can be analyzed when downloaded to a computer

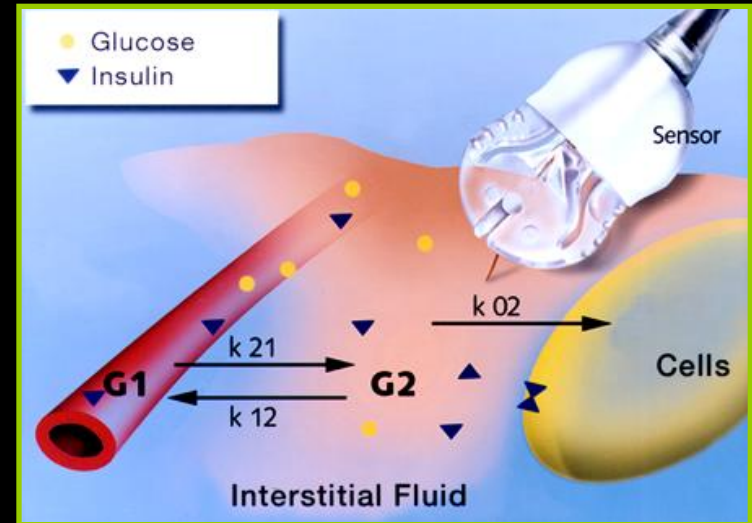


CGM devices that are available and approved by the US Food and Drug Administration

Application	Name	Purpose	Features	Image
Diagnostic use (professional)	DexCom G4 Platinum	Professional/ diagnostic	G4 device that can be "blinded"	
	Medtronic iPro 2	Professional/ diagnostic	Small recording Device with minimal patient interaction	
Patient use (personal/real time)	DexCom G4 Platinum	Patient use	Dexcom G4 receiver and transmitter	
	Medtronic Paradigm/	Patient use	Continuous glucose monitoring can be combined with pump or used alone	
	Abbott Navigator II	Patient use	Integrated with self monitoring of blood glucose	

Physiology of Interstitial Fluid Glucose

- **Approx 45% of human skin is IF**
- **IF :SQ tissue <dermis**
- **Capillary glucose-IF glucose by simple diffusion**
- **IF values dependent on:**
- **Amount of glucose diffused from the capillaries**
- **Rate of glucose uptake by the cells**



Average lag time between BG and IF in steady state is not clear :3-13 min (range 0-45 min)

Physiological Factors that Affect Interstitial Fluid Glucose

- Tissue perfusion
- Glucose supply from the blood vessel
- Capillary permeability
- Metabolic rate of adjacent cells
- Size of the adipocytes
- Other factors that influence cellular glucose uptake (e.g insulin)
 - Local temperature, Oxygen tension in the interstitial space, other potential as yet unidentified factors

¹ Cengiz & Tamborlane W.V .Diabetes Technology&Therapeutics 2009

³ Menseh, Wisinslewski, Neil, Burnett Diabetes Technology&Therapeutic in press

Issues with the lag time

It happens because interstitial glucose lag behind blood glucose levels by 3 to 13 min (average lag time 5.2 min)

Total Time Lag = Biological Time Lag + Instrument Time Lag

- Occurs with all the subcutaneous sensors ^{1,2,,3}
- Delay alarms for hypoglycemia
- May not show recovery from hypoglycemia (on sensor)
- May affect calibration of sensor depending on each system^{4,5} (in some systems should no be done when glucose values are changing rapidly)

⁴Baquette BW. Jnl Dia Sci Tech 2011. 4(2): 404-418. ⁵Satish et al; Diabetes Research and Clinical Practice 2010: 87, 348-353- ⁶Mazze et al; Diabetes Technology & Therapeutics 2009: 11, 11-18 - ⁷Weinstein et al. Diabetes Care 2007; ⁸ Kamath A, et al., Diabetes Technol Ther, 2009 Nov;11(11):689-95.

Importance of calibrations

- Quality is more important than quantity
(Follow manufacturer's recommendations)



- Calibrations teaches the sensor the correlation between current volume and sensor glucose reading
 - Use the sensor “trend” data and the 1h-3h-6h graph to ensure a good moment for calibration
 - Calibrate routinely without waiting to be required by the device. Check timing to avoid to calibrate in the “middle of the night”

Interfering Substances

SMBG

- Acetaminophen
- Ascorbic Acid
- Uric acid
- Salicylic acid

CGM

- Acetaminophen
- Ascorbic acid
- Uric acid
- Isoniazid
- Glutathion

- All of these substances nonspecifically oxidize H_2O_2 and therefore interfere both, the glucose oxidase-based BG test strips and glucose sensor electrodes

CGM vs conventional SMBG

- Conventional BG monitoring is like a few snapshots; CGM is like a video so it provides continuous information about how blood glucose changes over time

And it can help to :

- Guide adjustments in insulin, eating or exercise promoting behaviour changes
- Reduce blood glucose variability
- Decrease the risk of low blood glucose
- Increase the amount of time in the target blood glucose range

- NOTE: Changes in insulin administration should not be done on sensor glucose alone-always double-check with SMBG

CGM Provides a lot of Information

105120

Glycemic values with CGM
288 a day x365

1460

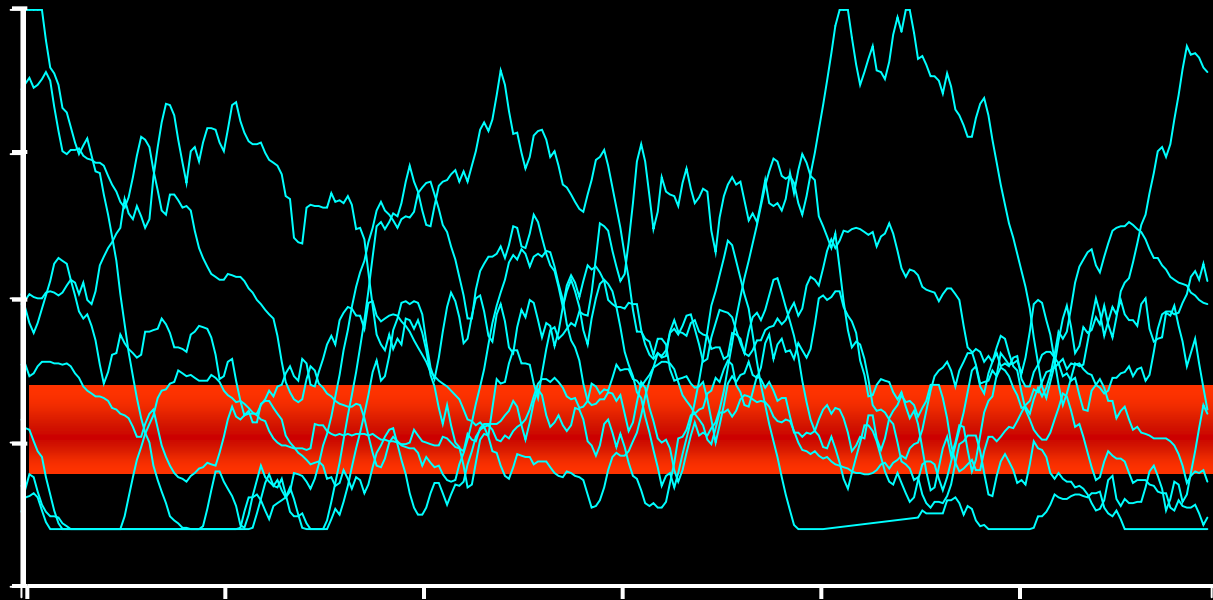
Glycemic values with 4 BG
4 a day x365

Main advantage of CGM

Knowing the direction and the speed that the glucose is changing is the TRUE advantage of CGM, so it doesn't matter if they are not yet as accurate as blood glucose meters specially in the hypoglycemic range.

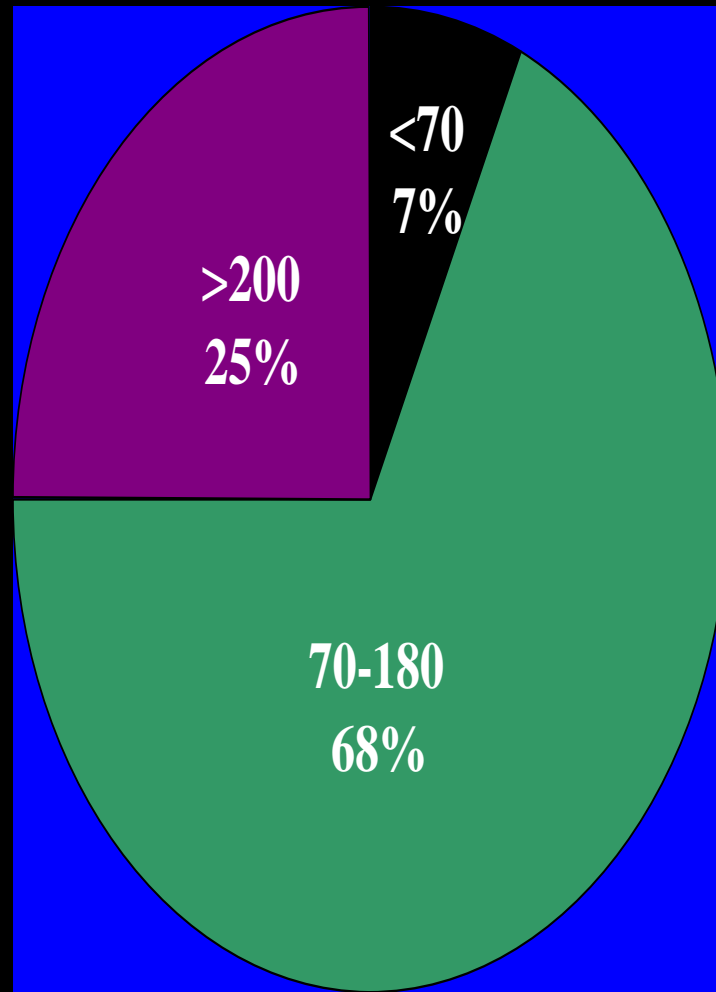


24 hour Glycemic Fluctuations in a Type 1 diabetes patient with a A1C value of 6.7 %



No one disagrees that the MORE the variability the GREATER the risk of hypoglycemia

Real glycemic distribution in a patient with a A1c value of 6.8 %



A statistics joke: a statistician put his head in an oven and his feet in a refrigerator

- Temperature measurements from head to toe
 - Foot=32 °F (0 °C)
 - Ankle=55 °F (12.8 °C)
 - Knee, waist, chest, shoulders=98.6 °F (37 °C)
 - Chin=150 °F (65.5 °C)
 - Forehead=200 °F (93.3 °C)

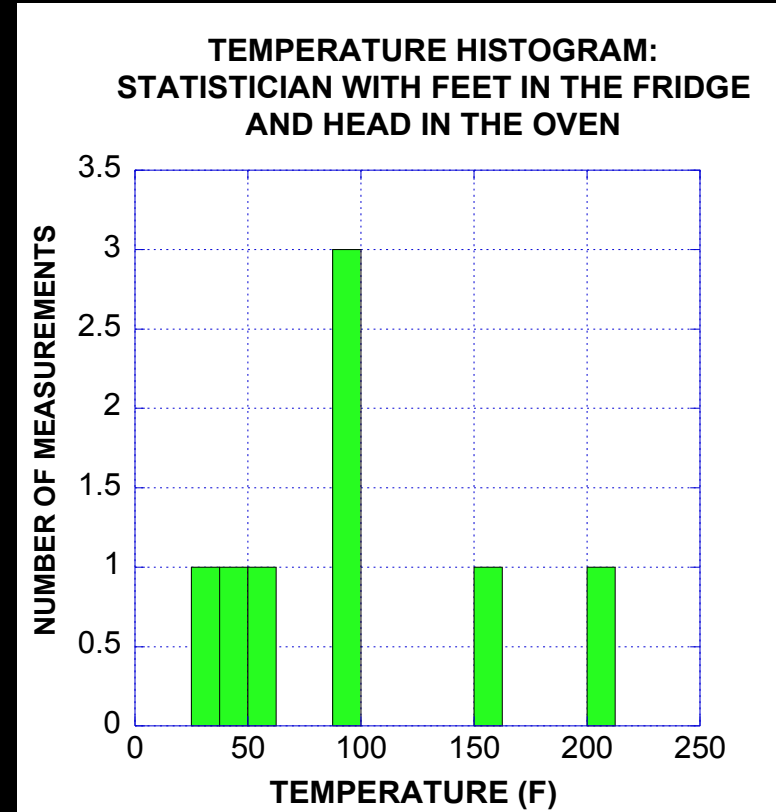


When he was asked how he felt, he said "On average, pretty good"

Thomas A Peiser with permission

A statistic joke...*

- A statistician with head in the oven and feet in the refrigerator (continued)
- Min= 32 °F (0 °C)
- Max=200 °F (93.3 °C)
- Mean=97.5 °F (36.4 °C)
- Median=98.6 °F (37 °C)

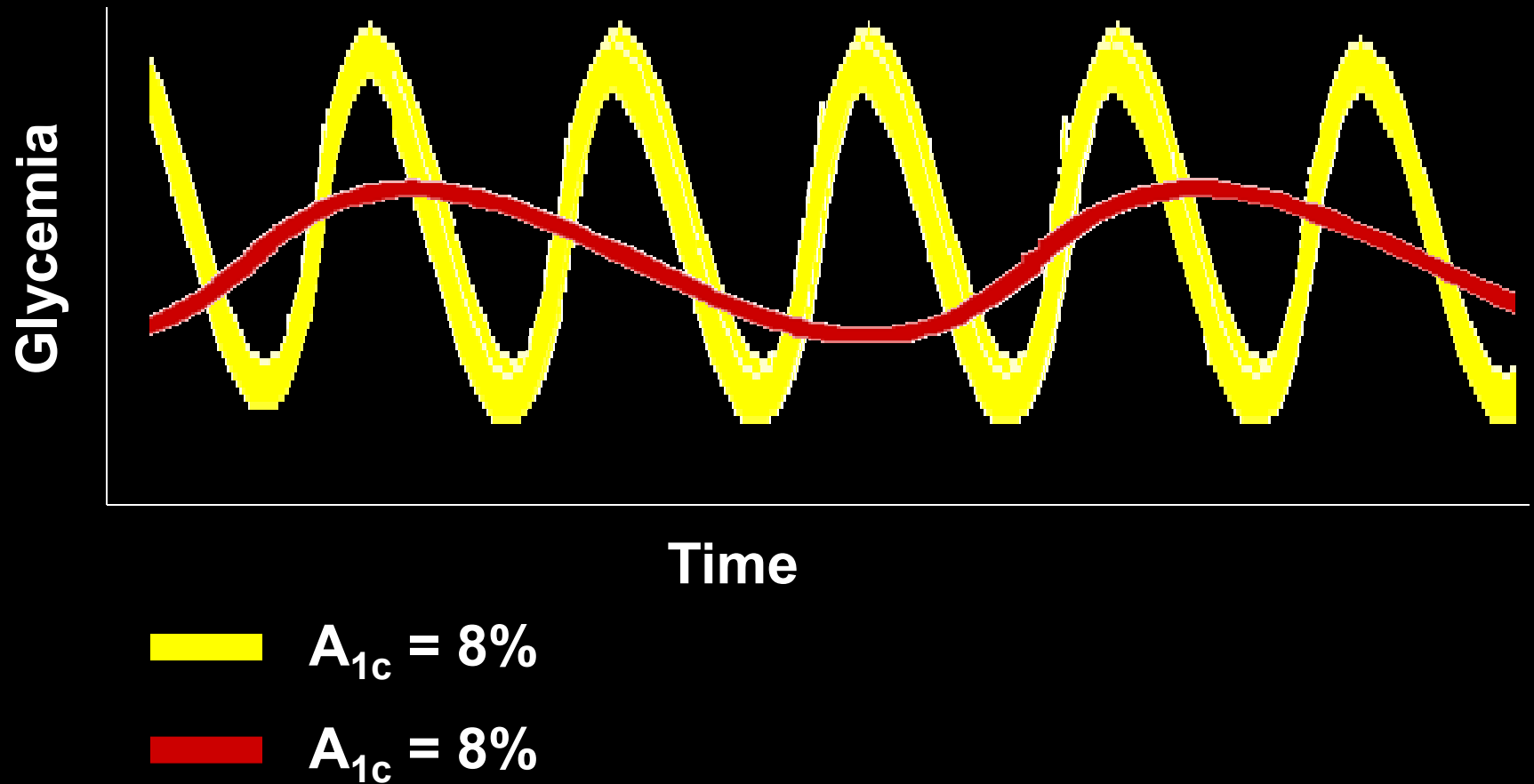


Conclusion: a single number does not always describe a data set well and we are putting too much emphasis into a A1c number

Glucose Variability May Exacerbate Complications Pathways

- Monnier et al.⁽²⁰⁰⁶⁾:
 - Type 2 Patients – Mean Age 63.6
 - Mean A1c – 9.6%
 - Acute Glucose Swings Activate Oxidative Stress Pathways
- Intensive management may reduce risk of developing complications by both reducing A1c and by reducing variability ^(Brownlee and Hirsch, 2006)
- *We don't have yet a long-term trial showing that by improving glycemic variability can improve the outcome*

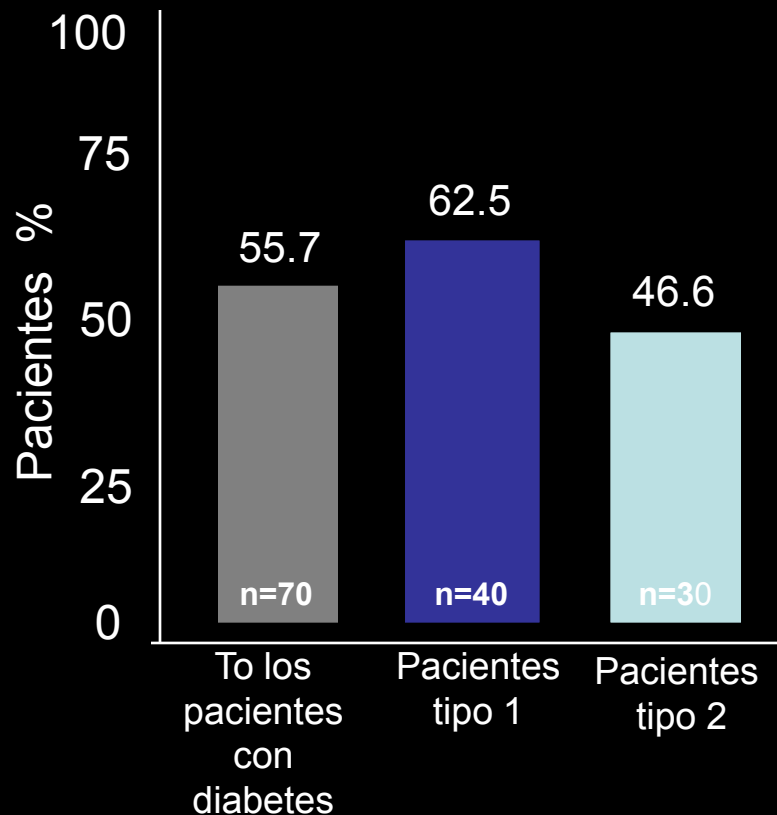
ALL the A1c numbers are NOT created equal



Reflections

Normalization of A1C can not be considered the equivalent of normoglycemia in view of our ability to measure other markers, elevated post-challenge glucose, the availability of continuous glucose monitoring and increased CVD in the normal range of A1c so we have to measure also the **QUALITY** of the A1c

Frecuencia de las Hipoglucemias Asintomáticas



Porcentaje de pacientes con ≥ 1 episodios de hipoglucemia no detectada.

- En un grupo de pacientes con diabetes más del 50% tuvieron hipoglucemia asintomática (no reconocida) identificada por MCG¹
- Otros investigadores también han encontrado resultados similares^{2,3}

¹⁴ Chico A, et al. *Diabetes Care* 2003;26(4):1153-1157.

¹⁵ Weber KK, et al. *Exp Clin Endocrinol Diabetes* 2007;115(8):491-494.

¹⁶ Zick R, et al. *Diab Technol Ther* 2007;9(6):483-492.

Severe Hypoglycemia

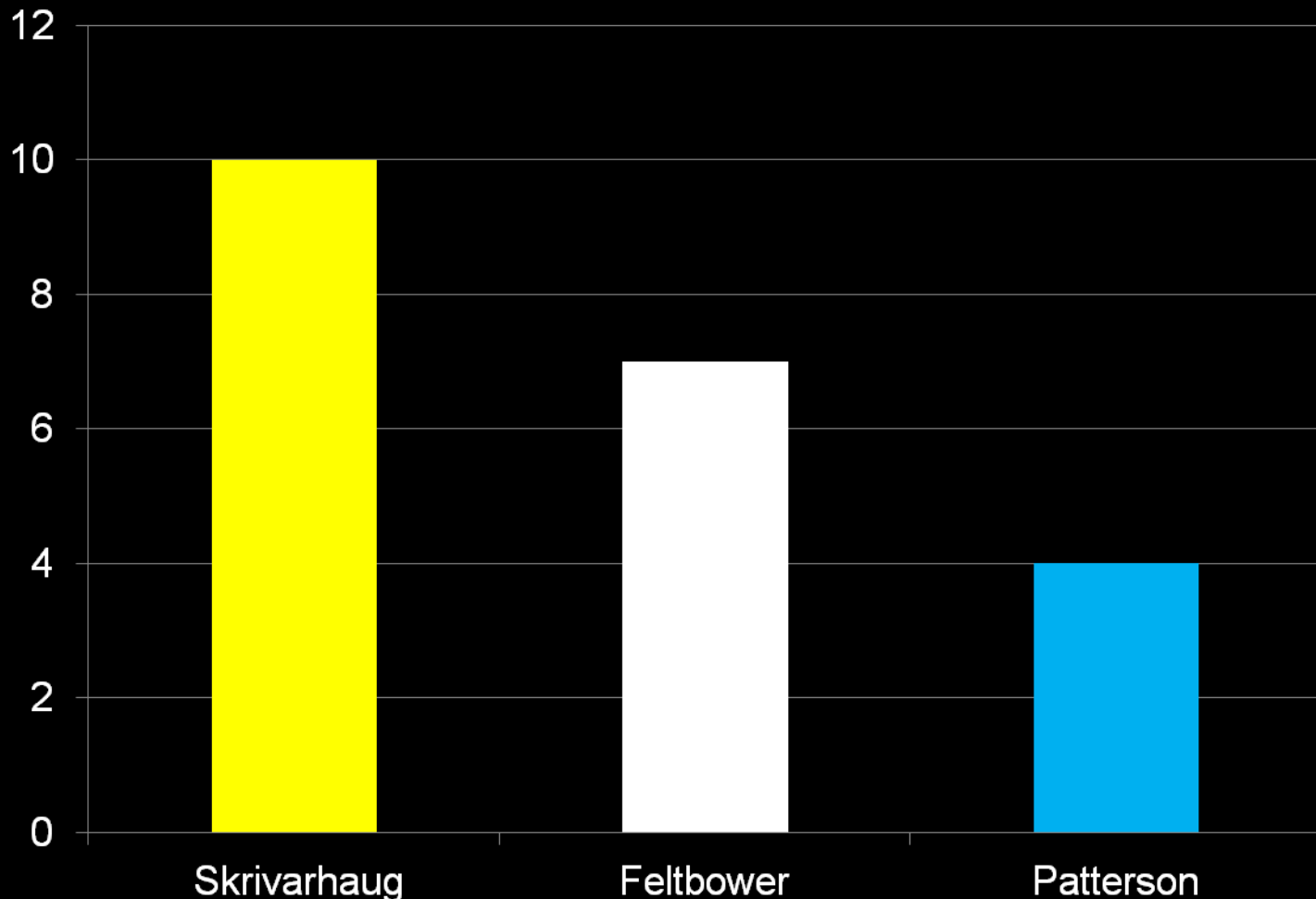
- Dead in bed Syndrome.
Is the most frequent mortality cause in type 1 diabetes patients < 40 years old
- 30% of type 1 patient has an impairment in contrarregulation
- Increase between 2-6 fold the risk of severe hypoglycemia

Detection of Hypoglycemia in children younger than 7 yr

- A recent Swedish study (2013) used blinded Medtronic CGMS Gold in children ≤ 7 y/o children with a mean A1c $\geq 7.5\%$
- There was a very low detection rate, 32% of all the hypoglycemic events despite a high frequency of BG testing (10 test per day)
- At night 98% of all the hypoglycemic events were asymptomatic
- They recommend the use of CGM specially to this group of patients

Hypoglycemia As The Cause of Death in Pediatric and Young Adult Type 1 Diabetes

This is a very SERIOUS PROBLEM



¹⁹Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. *Diabetologia*. 2006;49:298-305; ²⁰Feltbower RG, Bodansky HJ, Patterson CC, et al. *Diabetes Care*. 2008;31:922-926; ²¹Patterson CC, Dahlquist G, Harjutsalo V, et al. *Diabetologia*. 2007;50:2439-2442.

Acceptance of CGM technology can lead to ongoing use and reduced fear of hypoglycemia

- A recent Italian study (2012) used a Dexcom SevenPlus and Animas pump combination in children ≤ 7 y/o
- There was a 0.9% reduction in A1c in children with baseline A1c $\geq 7.5\%$ (average use 5.8 days/week)
- The Dexcom SevenPlus and Animas combination was *“accepted and appreciated by both the children and the parents with a great overall satisfaction”*
- The greatest perceived benefits of the Dexcom SevenPlus CGM
 - Reduced fear of hypoglycemia
 - Usefulness of alarms

Can Real-Time CGM Prevent Hypoglycemia ?

Hypoglycemia remains far too common while using a sensor :

- In patients with well-controlled diabetes **hypoglycemia (<70mg/dl was present ~1 hour a day**^{1,2}
- Nocturnal hypoglycemia **ocurred in >50% of patients with well-controlled diabetes**³

²³ JDRF Study Group. Diabetes Care 2009;32:1378-1383. ²⁴ Battelino T, Phillip M. et al Diabetes Care 2011;34:795-800

²⁵ Raju B, Arbelaez AM, Cryer PE. J.Clin.Endocrinol.Metab.2006;91:2087-2092

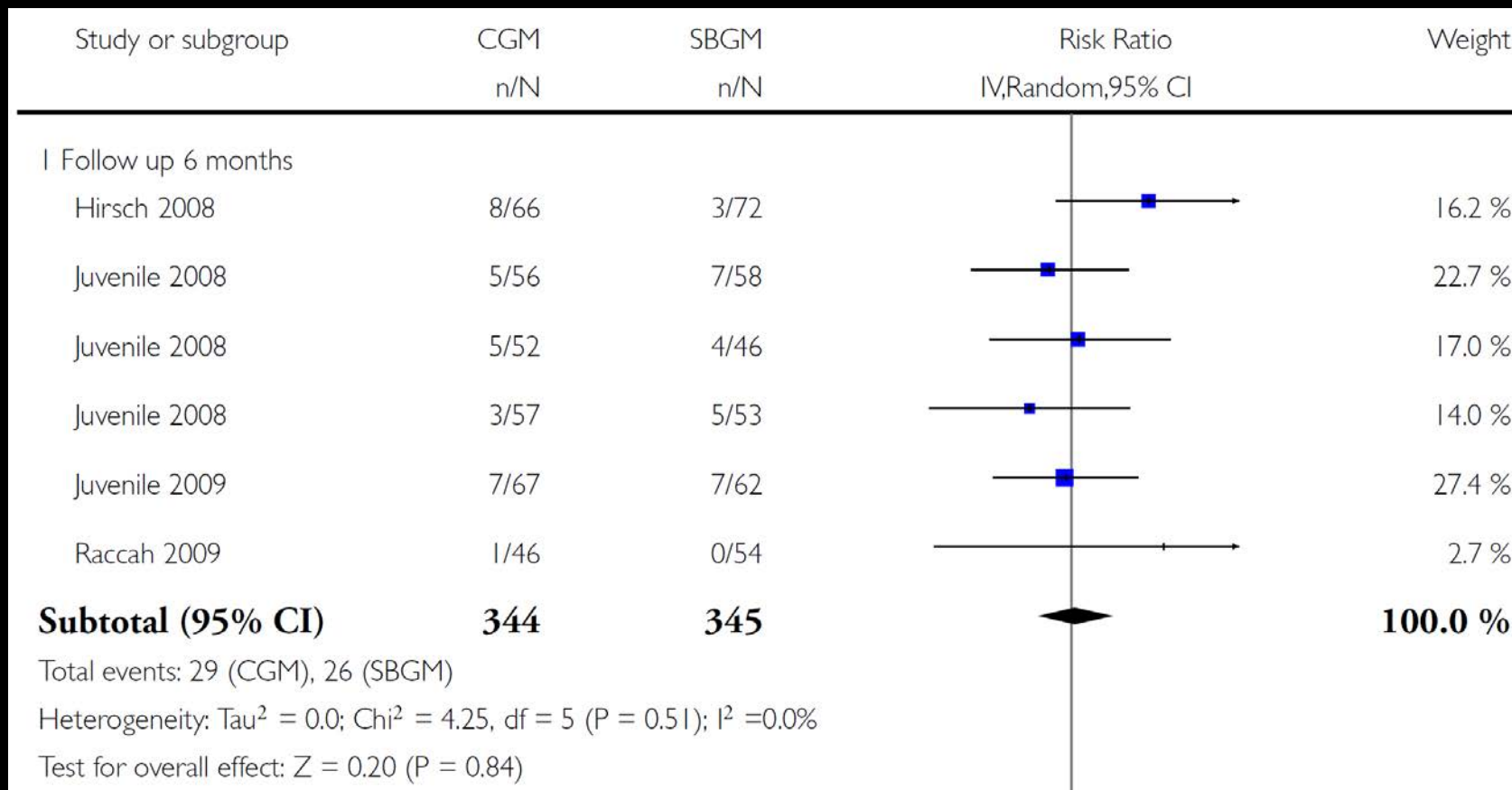
Can Real-Time CGM Prevent Severe Hypo ?

THE SHORT ANSWER IS

**NO
YET COMPLETELY**

Cochrane Meta-analysis

Real-Time CGM, Severe Hypo



Mean Absolute Difference and MARD Between Measurements with the Different BG Meters and the YSI 2300

Blood glucose meter	Mean bias		MARD			Subjects (n)	Measurements (n)
	mg/dL	%	%	95% CI	SD (%)		
FreeStyle Lite	0.8	1.0	4.9	4.1 to 5.7	7.5	240	480
FreeStyle							
Freedom Lite	0.3	1.0	5.5	4.8 to 6.3	8.5	244	488
Accu-Chek Aviva	7.2	5.3	6.8	6.1 to 7.6	7.5	252	504
Contour	−1.2	−0.2	9.0	8.3 to 9.8	12.0	255	510
OneTouch UltraEasy	6.3	4.6	9.7	8.9 to 10.4	12.1	246	492

Minimizing Hypoglycemia July 2013

- Better and NEWER insulin analogues ^{1,2}

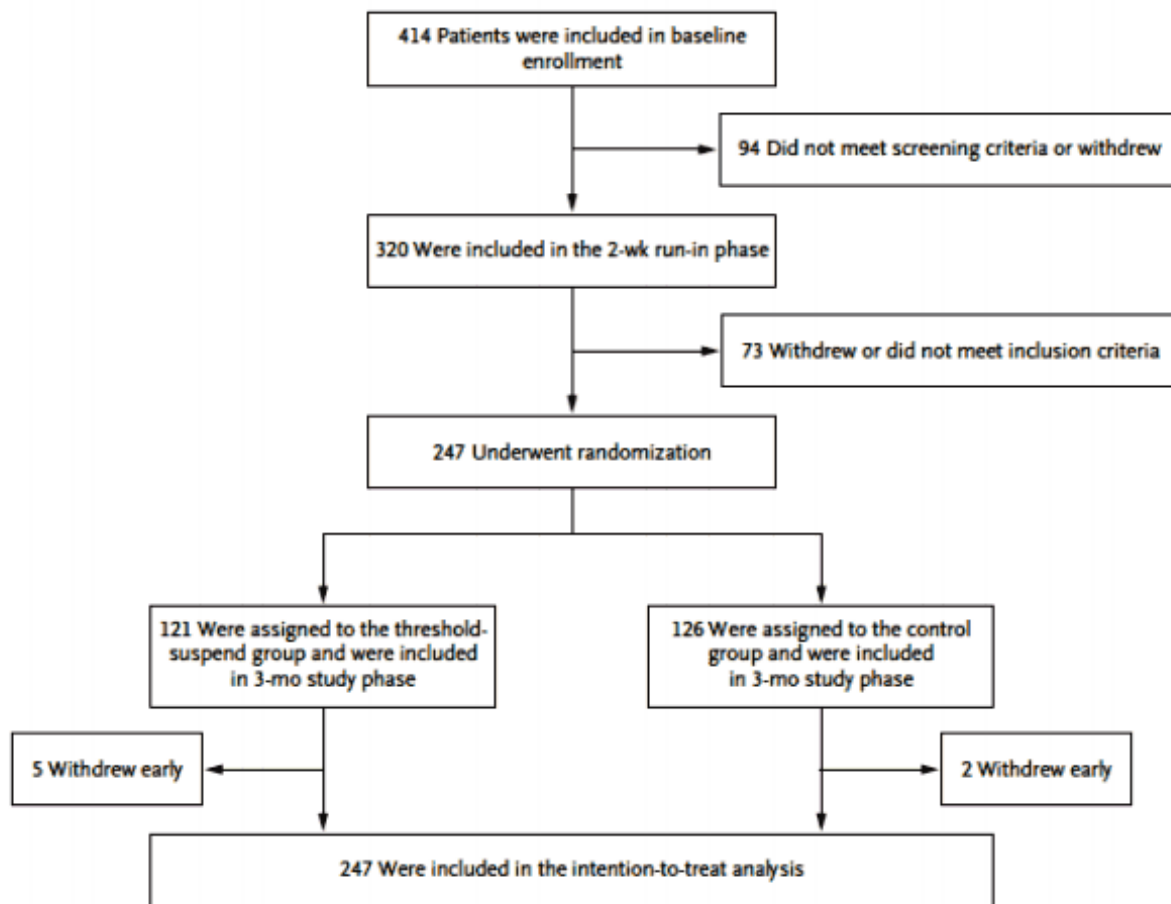
- More conservative glucose targets and strict avoidance of hypoglycemia ³

- **CGM**

- Low glucose suspend integrations between pump and sensors
LGS ^{5,6,7}

²⁶ Degludec DRF Study Group. Diabetes Care 2009;32:1378-13833. ²⁷ Rodbard H. Abstract #279. AACE Annual Scientific and Clinical Congress; 2013; Phoenix. ²⁸ Raju B, Arbelaez AM, Cryer PE. J. Clin. Endocrinol. Metab. 2006;91:2087-2092. ²⁹ Battelino T, Phillip M, et al. Diabetes Care 2011;34:795-800. ³⁰ Aspire In Home Study Group. June 22, 2013 DOI: 10.1056/NEJMoa1303576. Trang Ly, Nicholas JA. Diabetes Care. 2013 July; 35(7): 1462–1465.

Enrollment, Randomization and inclusion in the Study Phase



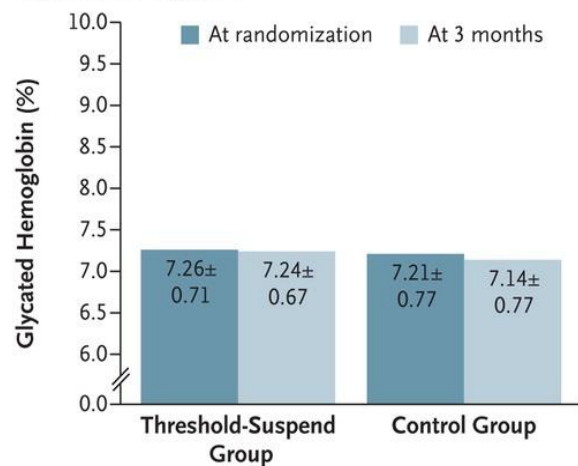
Reduction in hypoglycemia in the threshold Suspend Group

Automatic insulin delivery appears to be an important strategy to reduce the amount of time, the duration and the severity of the hypoglycemic events

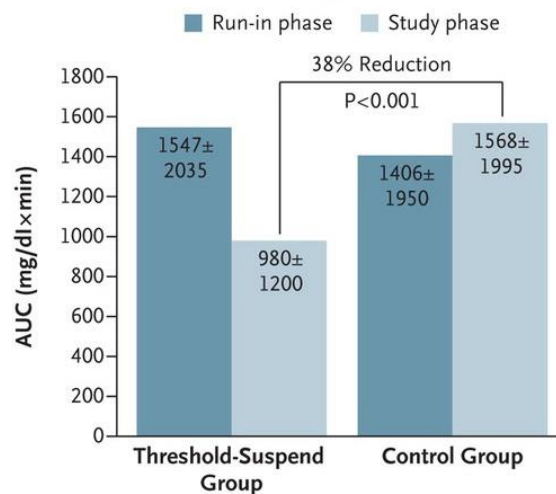
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Value
Age (yr)	13.8±1.8
Weight (kg)	56.0±13
Height (cm)	162.9±11.5
Body-mass index†	
Value	20.8±2.9
SD score	0.4±0.8
Glycated hemoglobin	
Measured as a percentage	8.0±0.7
Measured in mmol/mol‡	63.6±7.6
Diabetes duration (yr)	7.0±3.5
Pump-therapy duration (yr)	4.8±2.8
Daily insulin dose	
Total units	46.4±17.7
Units/kg	0.8±0.3

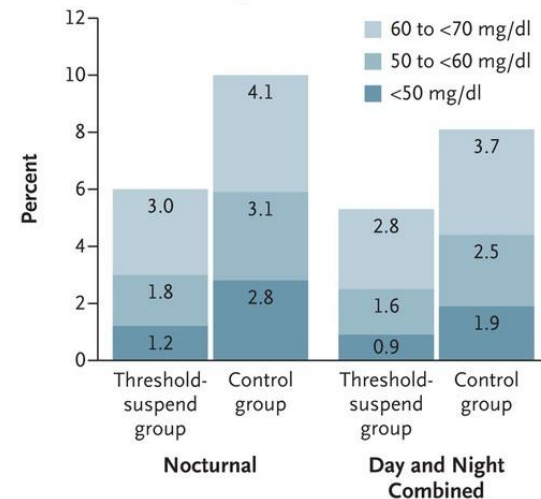
A Glycated Hemoglobin



B Mean AUC for Nocturnal Hypoglycemic Events



C Sensor Glucose <70 mg/dl

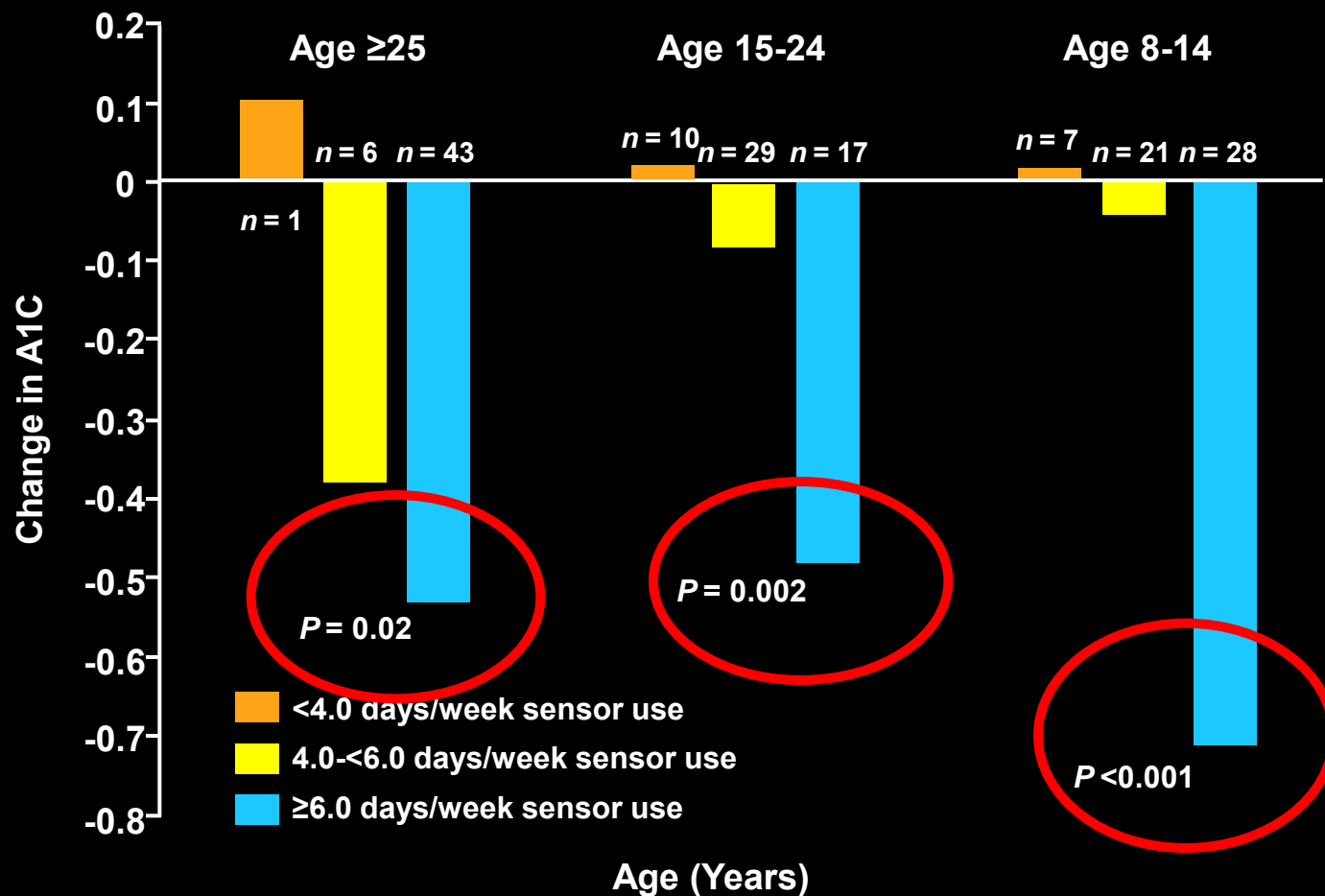


First time found that near daily use of CGM is associated with significant decrease in A1c

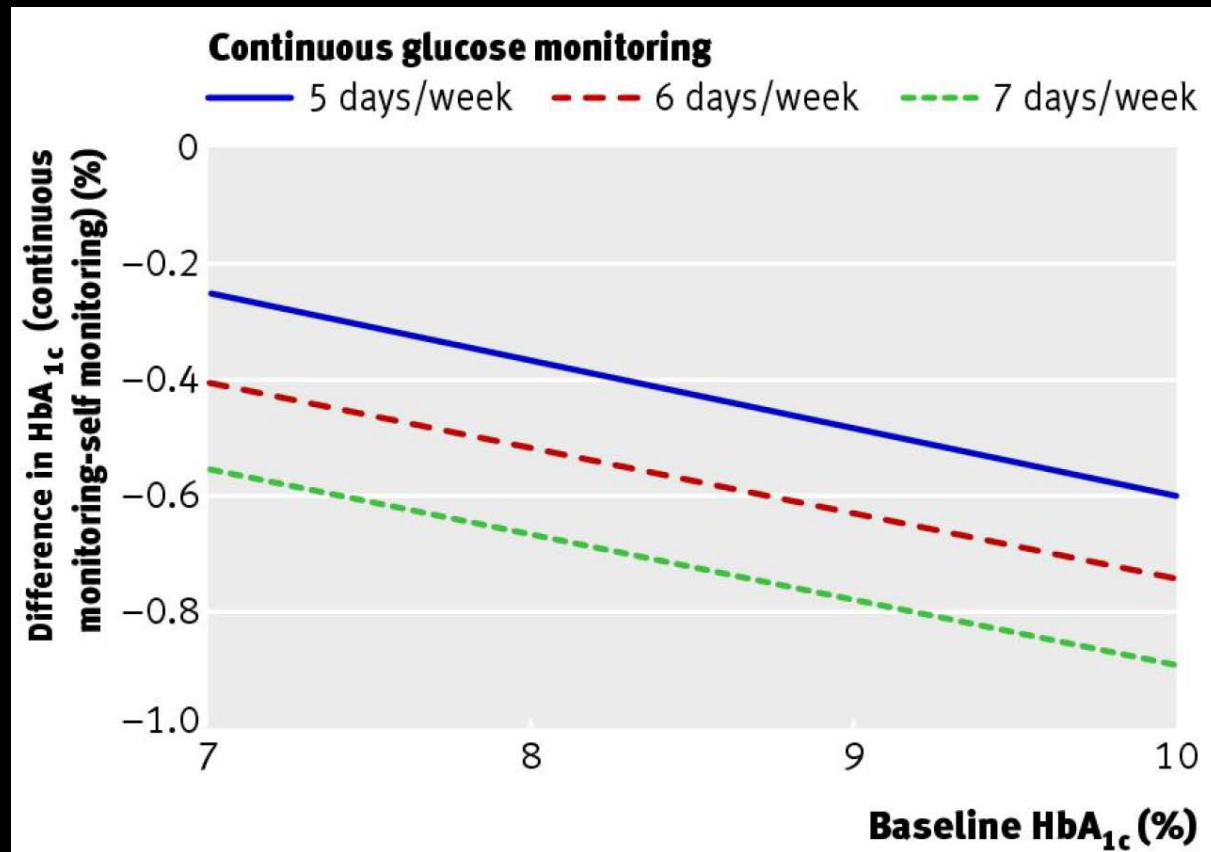
JDRF CGM STUDY GROUP the Landmark CGM Study

- The use of continuous monitoring averaged 6 days per week for:
 - 83% of patients 25 years of age or older
 - 30% for those from 15-24
 - 50% for those 8 to 12 years of age
- Baseline to 26 weeks: mean difference of -0.53% (CI -0.71 to -0.35; $p < .001$) in patients 25 years and older
- A1c benefits are linked to more frequent use of the CGM
- Hypoglycemia DID NOT increase, even in the adult group with lower A1c

Sustained users vs. not (≥ 6 days/week)

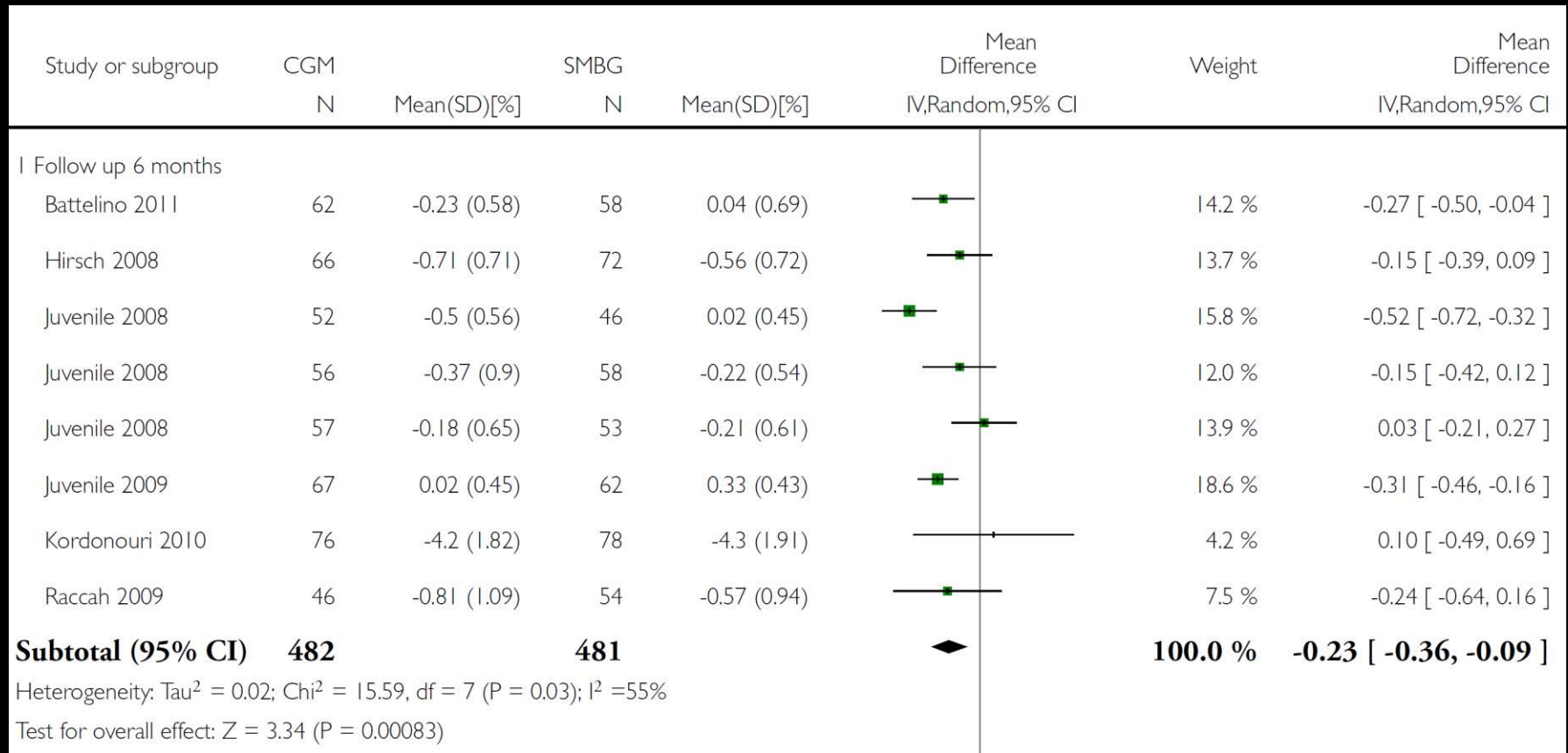


Individual data Meta-analysis



Cochrane Meta-analysis A1c

Real-Time CGM > 24w



CGM Continued to Show Clinical Benefit One Year After Initiation

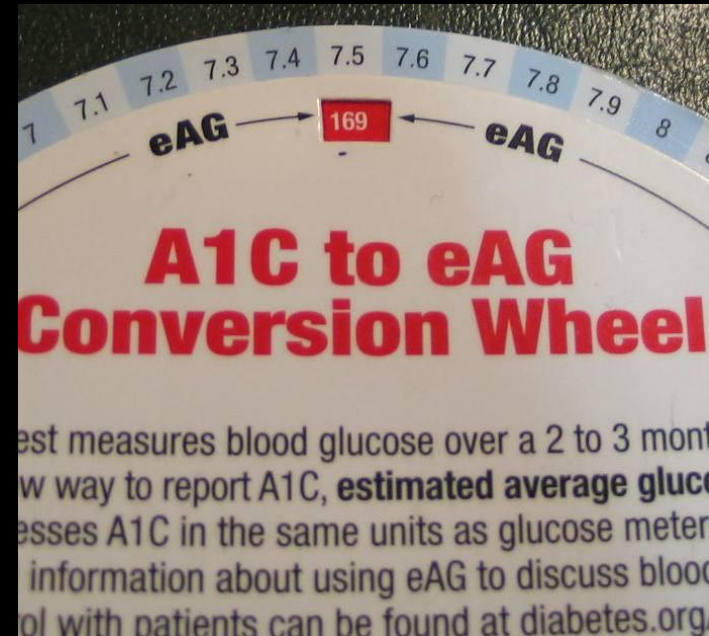
Sub-analysis of the JDRF CGM study of the > 25 year old participants at 12 months of use.

- CGM use continued to be > 6 days/week.(median 6.8 days/week)
- Regardless of A1c level, CGM continued to benefit subjects by either maintaining reduction in A1c or maintaining target A1c without increasing hypoglycemia
 - Rate of severe hypoglycemia was reduced even more at 12 months
- Glycemic variability reduced significantly from baseline
- Significant increases in time spent at target range.
(71-180 mg/dL)

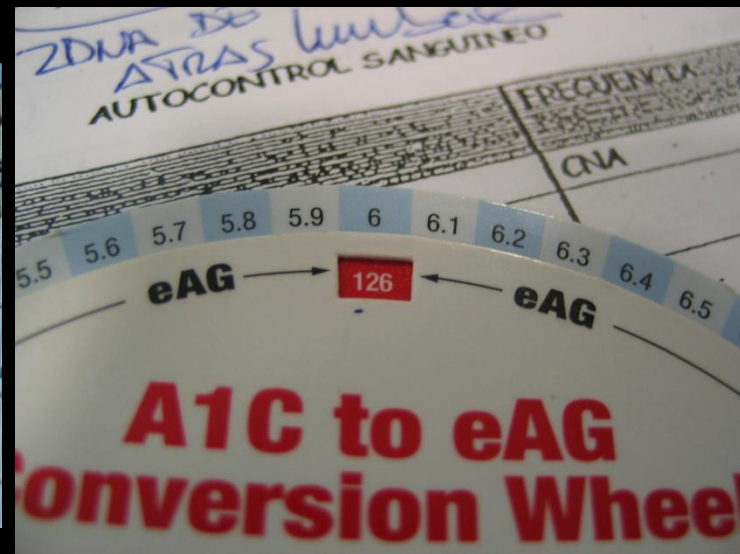
My own informal Survey

When patient use it continuously you can almost predict in most of the patients the lab A1c value when downloading the data

Stat	Totals
# Readings	15303
Average	169,4
Minimum	20



Stat	Totals	128
# Readings	3426	158
Average	128,2	156
Minimum	39	54
Quartile 25	88	118



Why to use a CGM system?

Lessons learned from both "real world" observation and clinical trials

- Prevention of low blood glucose levels
- Prevention of hyperglycemia
- To have better outcomes in diabetes pregnancies
- As behavior modification tool and helps you to measure your improvement daily
- To "live better" and to feel "in charge" of your own body
- To help live better to your family and significant ones
- To prevent or diminish diabetes complications ???

Indications for a CGM system (1)

Lessons learned from both "real world" observation and clinical trials

- Poor glycemic control (A1c) and or high glucose variability
- Severe hypoglycemic episodes, unawareness of hypoglycemia or when hypoglycemia is a barrier to achieve optimal glycemic control
- Pre-pregnancy planning and Pregnancy
- Improvement of quality of life
- Intensive diabetes treatment in type 1 patients living alone

Indications for a CGM system (2)

Lessons learned from both "real world" observation and clinical trials

- Initiation of CSII therapy
- Patients with severe gastroparesia
- Surveillance of critically ill patients (with or without diabetes)
- Negative C-peptide type 2 patient
- As Educational as and Empowering tool for improving A1c for both type 1 and type 2 patients¹

Reimbursement indications for CGM in children in Europe as July 2013

- Sweden: IF SMBG > 10/day
- Holland: IF DIAGNOSIS OF TYPE 1 DIABETES
- Slovenia: IF DIAGNOSIS OF TYPE 1 DIABETES AND AGE < 7 YEARS
- Estonia: for children 0-4 years 48 sensors/year; for children 5-18 YEARS 12 sensors/year if type 1 Diabetes with poor metabolic control (HbA1c > 10%)
- Slovakia: FOR CHILDREN < 15 YEARS OF AGE, IF TYPE 1 DIABETES TREATED WITH PUMP AND IF SEVERE HYPOS
- In Italy depending on the region. In the Lazio region the reimbursement is recognized in case of insulin therapy with pump (16 sensor/year)
- Spain and the majority of EU countries *is Just a Dream*

Changes in ADA Clinical Practice Guideliness

2008

CGM is a potential
supplemental tool
In lowering A1C
Explicitly limits CGM
recommendations
to type 1 diabetes patients

2013

CGM can be a useful tool in
lowering A1c in adults ≥ 25 yrs
of age
CGM is beneficial for those with
hypo unawareness and/or
frequent hypoglycemic events

Some younger patients may
also benefit
from CGM use

CGM use in the “real world” Challenges”

- In all the RCTs the greater the use the greater the benefit

THE “REAL WORLD” Shows us :

- Most patients use the CGM intermittently for different causes :
 - Cost
 - Pain at insertion
 - Adhesive or allergic problems
 - Alarm fatigue syndrome
 - Family distress
 - Unrealistic Expectations
 - Need of a “diabetes vacation”

Other CGM Findings

- Subjects with low A1c values may actually go up slightly due to having less frequent episodes of hypoglycemia
- The CGM system is highly valuable to patients willing to use the technology but not to others
- As a rule those who don't do the "basics" are not good candidates for CGM
- We need tools to help the patient keep using the CGM system on daily bases and how identify the best candidates.

Classes for Prospective candidates for CGM

A monthly class about CGM covering the following topics :

- What is a GCM system and how it works
- Types of CGM system commercially available
- Advantages and disadvantages of the current CGM
- When possible we invite a CGM patient to give testimonials
- Finally to those interested we offer the opportunity to wear the device during a week as “trial wear”, before they purchase it
- On request we offer this educational opportunity through the internet with video conferencing for those patients not able to come to our clinic

Education is needed for a successful Outcome



cartoon by Dan Belkin with permission

How to Prevent the “Alarm fatigue syndrome?”

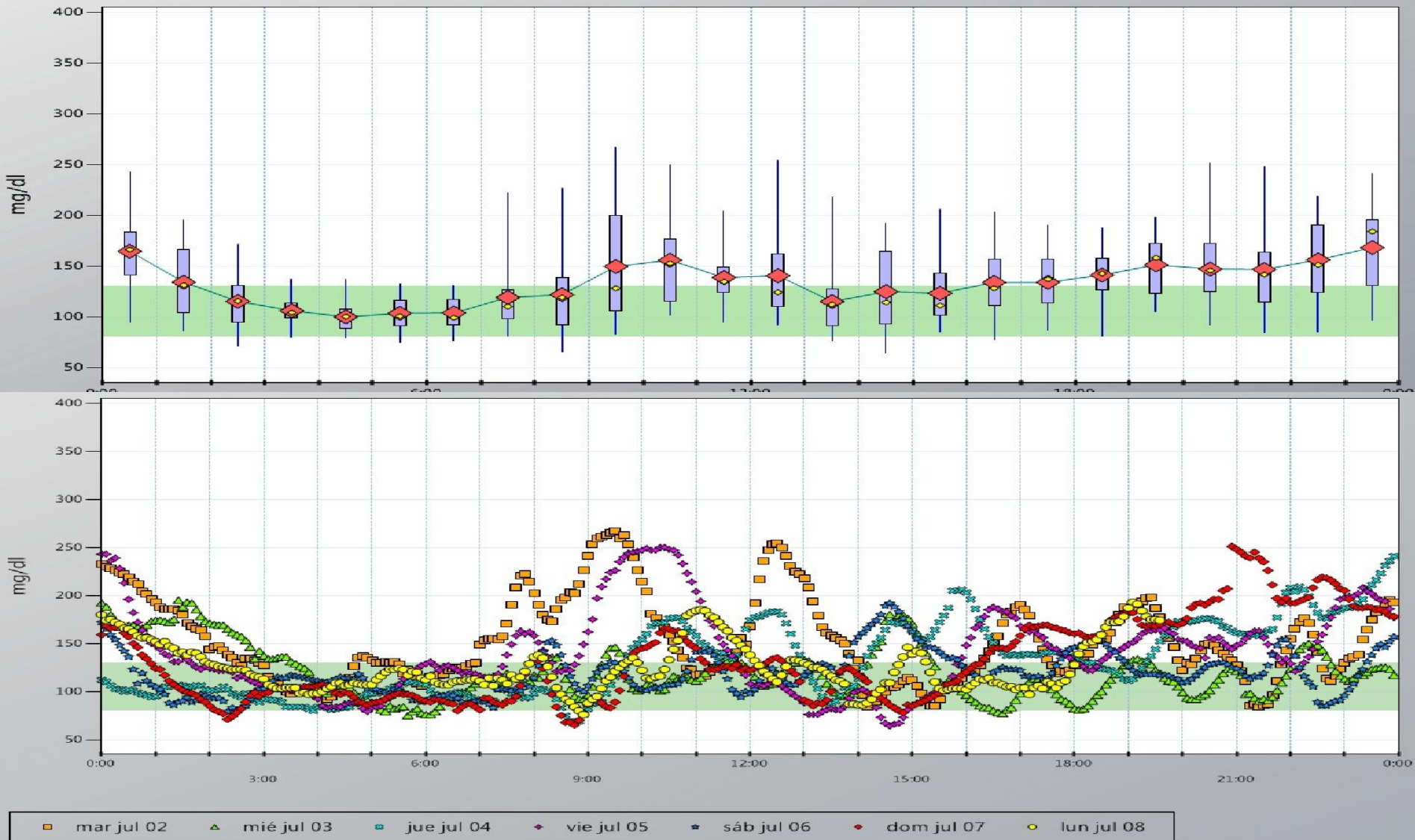
- Setting REALISTICS alarm thresholds specially at the beginning of CGM
- Turning off ALL the alarms ,except the low glucose alarms during special times as sleep,school,church etc
- Starting with trend alarms ONLY after a few months of use when you are handling correctly the low and high alarms

Usefulness of Retrospective Data Analysis

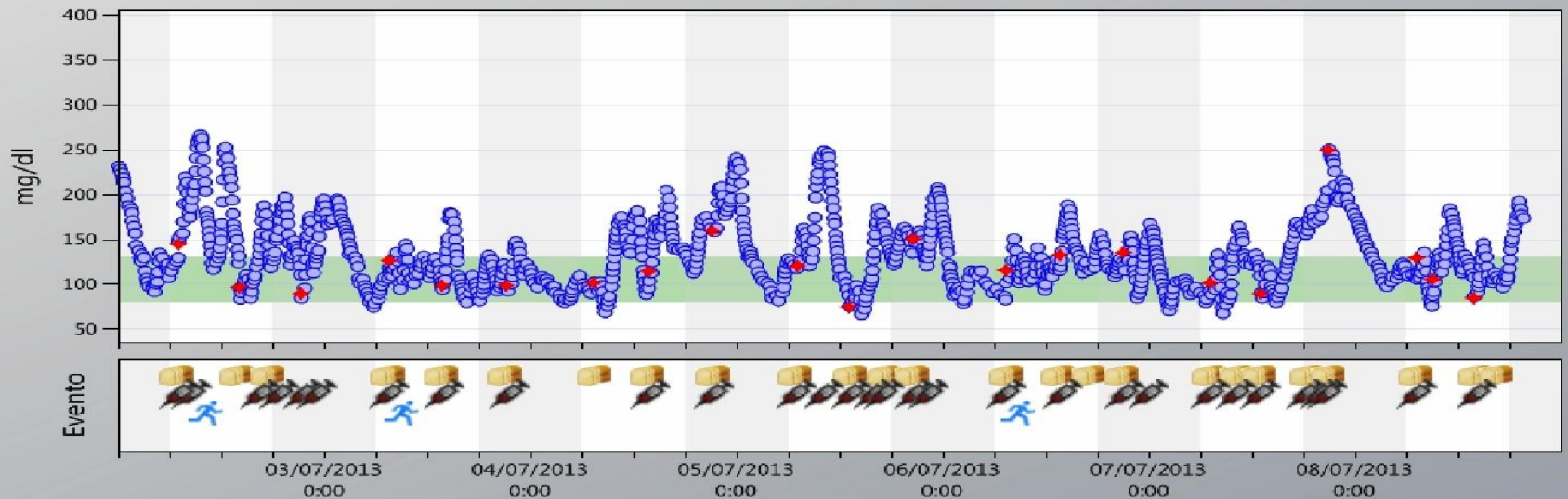
- Fine Tuning for the insulin regime. Don't fix too much at once
- Review the effects of different food choices
- To check the effects of your activity level
- To understand other behaviors and how they impact blood glucose levels
- Short-term trends for bolus corrections (1h-3h screen)
- Long-term trends for basal insulin adjustments (12h-24h screen)

Downloading CGM data

Trend graphs



Downloading CGM data

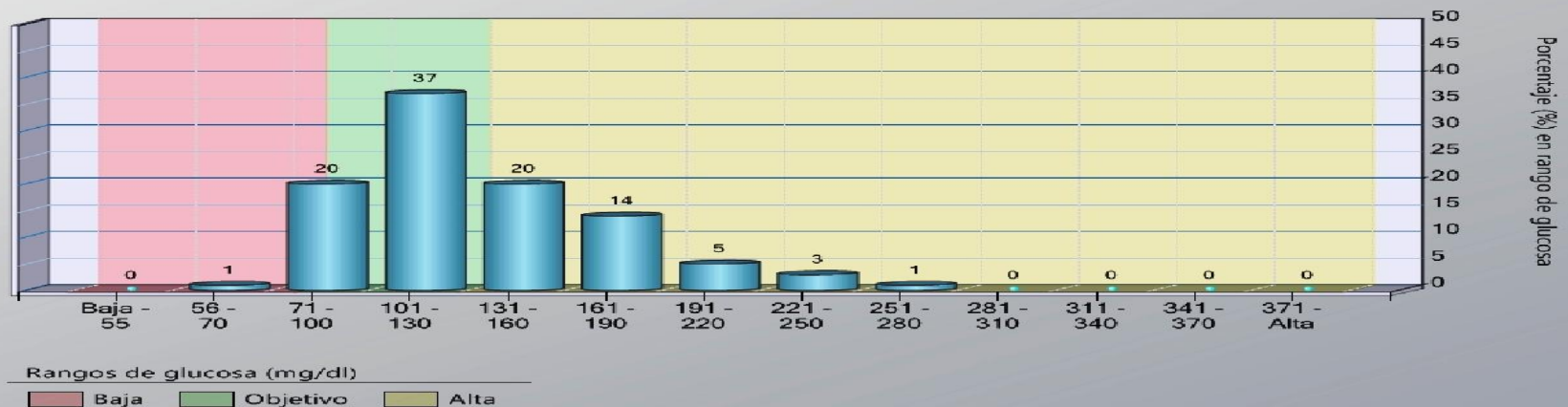


○ Sensor
★ Medidor
🍴 Carbohidratos
💉 Insulina
🏃 Ejercicio
❤ Salud



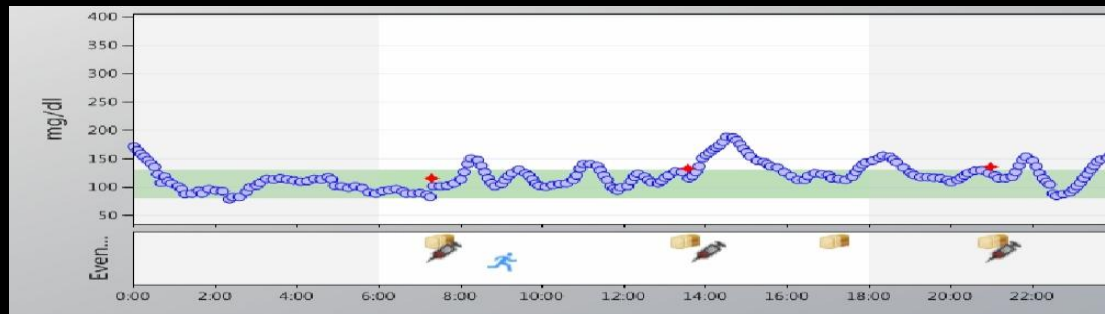
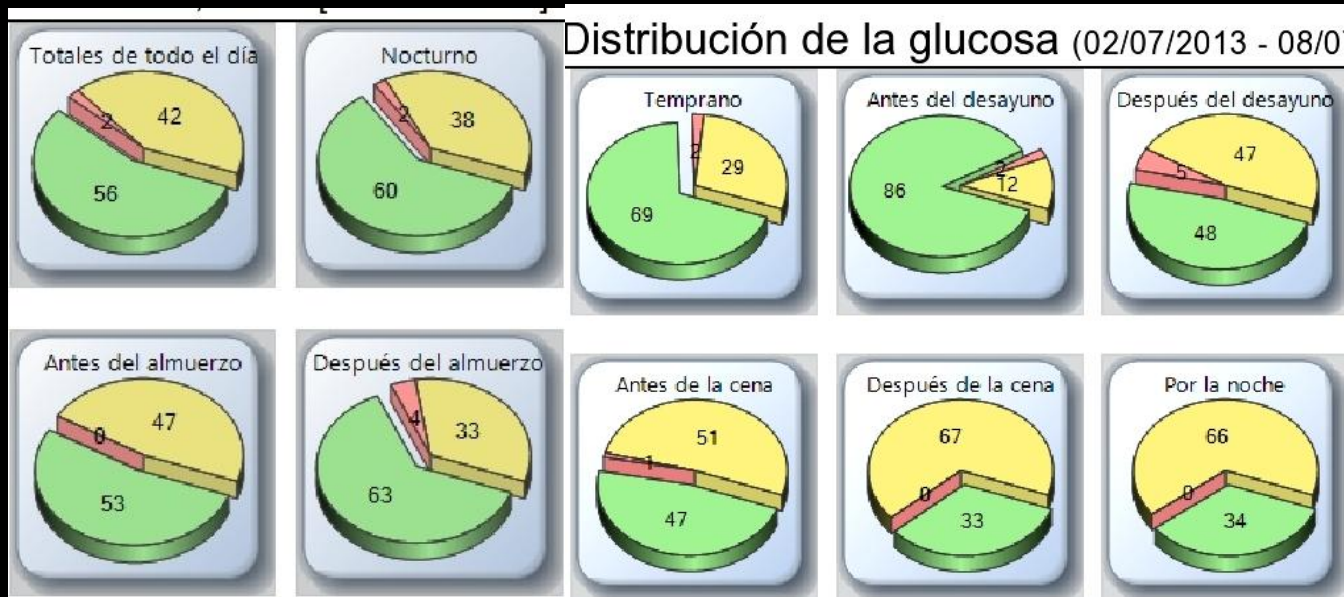
Rango	% de lecturas	N.º de lecturas	Media	Mediana	DS
Objetivo (80 - 130)	56	1093	107	107	14
Baja (Baja - 79)	2	39	74	76	5
Alta (131 - Alta)	42	831	169	163	30

Distribución de la glucosa - Lecturas 1963 Totales de todo el día



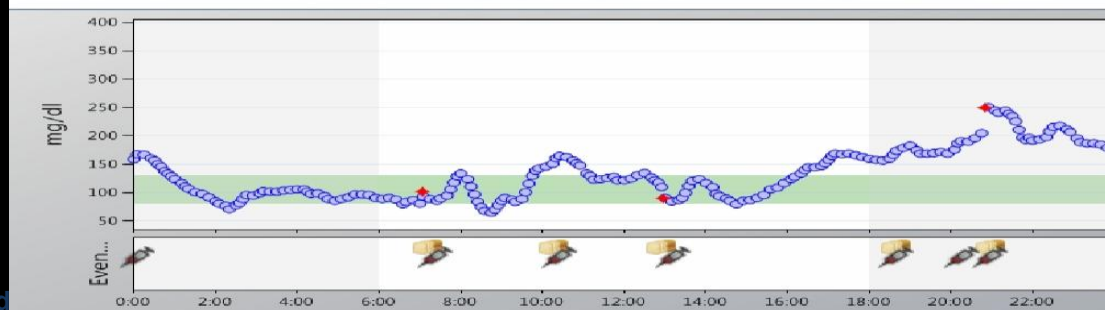
Downloading CGM data

Pie charts



sábado, 06 de julio de 2013

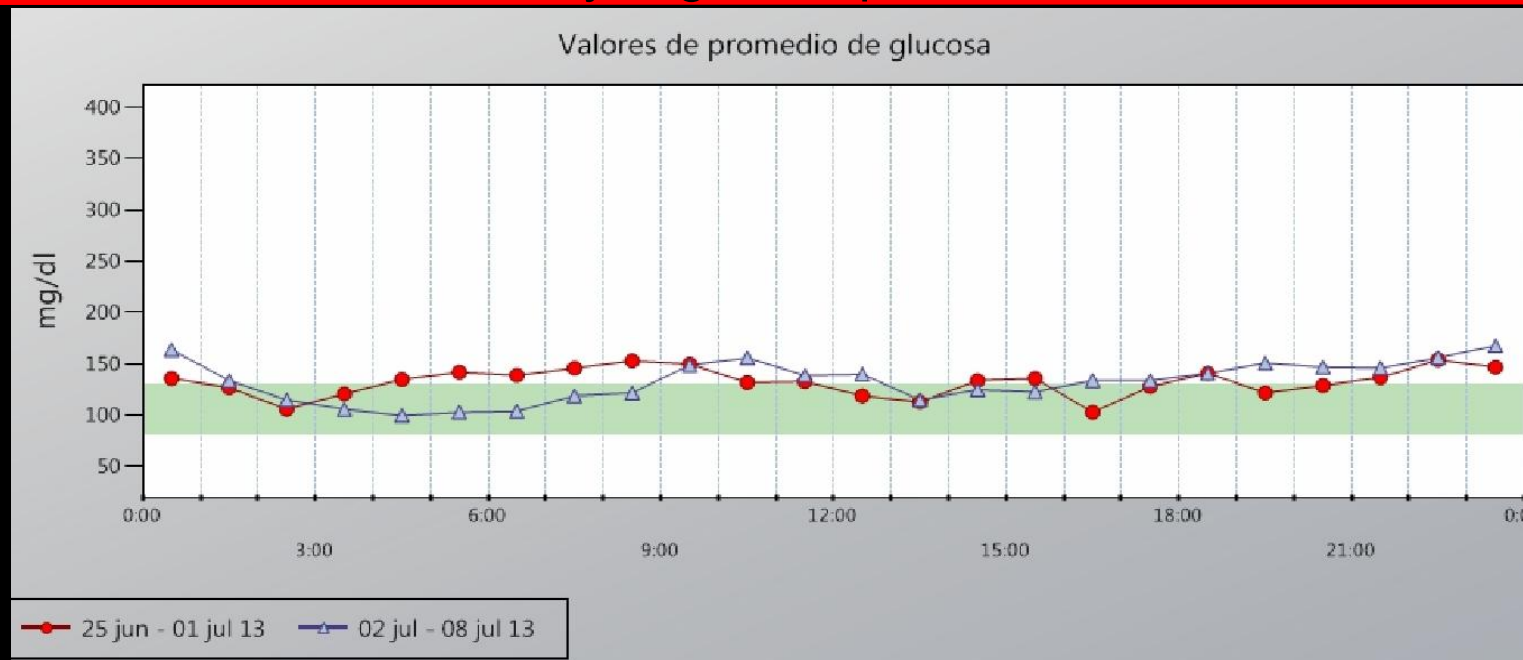
- 7:31 Carbohidratos 80 gramos
- 7:39 Insulina 0,75 unidades
- 9:05 Ejercicio Moderado (120 minutos)
- 13:32 Carbohidratos 80 gramos
- 14:08 Insulina 0,5 unidades
- 17:11 Carbohidratos 20 gramos
- 21:04 Carbohidratos 100 gramos
- 21:21 Insulina 0,75 unidades



domingo, 07 de julio de 2013

- 0:07 Insulina 0,25 unidades
- 7:14 Carbohidratos 80 gramos
- 7:26 Insulina 0,5 unidades
- 10:20 Carbohidratos 20 gramos
- 10:27 Insulina 0,2 unidades
- 12:58 Carbohidratos 100 gramos
- 13:15 Insulina 0,5 unidades
- 18:42 Insulina 0,25 unidades
- 18:43 Carbohidratos 20 gramos
- 20:18 Insulina 0,25 unidades
- 21:00 Carbohidratos 100 gramos
- 21:01 Insulina 1 unidades

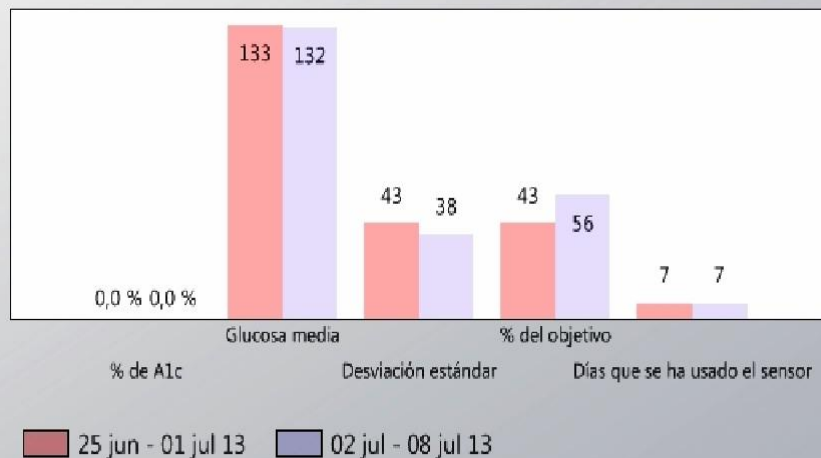
Downloading CGM data



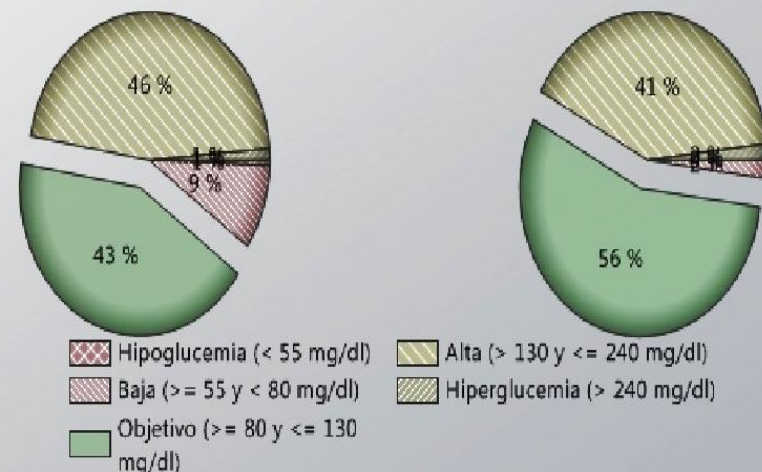
66771]

Informe MySuccess™

Medidas de éxitos clave



25 jun - 01 jul 13 Rangos de glucosa 02 jul - 08 jul 13



How to review Retrospective data from the CGM

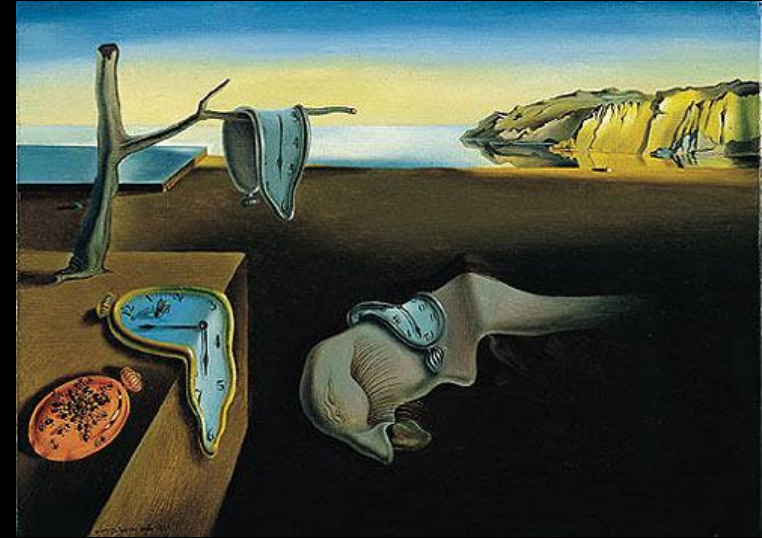
- Don't get overwhelmed
- Review download report with the patient shoulder to shoulder
- Start with multiple day sensor overlay and review "target" box setting

Review the following :

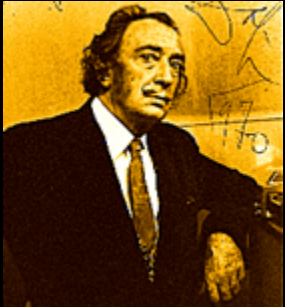
- Hypoglycemia –presence of recurrent a /o nocturnal
- Overnight glucose control
- Postprandial control
- Pre prandial control

Review Pie Charts

- Review for percentage of BG in/out of target
- Breakdown by times of day a/o meals



Have no fear of perfection; you'll never reach it"



Salvador Dali (1909-1989)

CONCLUSIONS (1)

- 1 Thanks to the evolution of CGM technologies the stage is set for a revolutionary shift in diabetes care
- 2 Sensors in the hypoglycemic range are not as accurate as BG meters but this limitation is compensated by the additional glucose dynamics information
- 3 Education about the technology helps the motivation and the behavior changes that are extremely important
- 4 Patients need guidance on how to derive benefit from all the additional information without being overwhelmed by the amount of data
- 5 Some patients can reduce A1c and hypoglycemic episodes with the help of this technology both CSII and MDI patients get similar benefits

CONCLUSIONS (2)

- 6 CGM adoption in diabetes care will depend on the development of “CGM units” for training and follow-up care
- 7 Like most diabetes tech devices ,success is difficult to show in traditional RCTs because so many factors are involved. they are very much needed to clarify if CGM can :
 - Reduce the long-term complication of DM**
 - Reduce diabetes healthcare cost**
- 8 CGM landed in the “diabetes field” to stay

CGM sensors will be able to “talk” with different insulin pumps

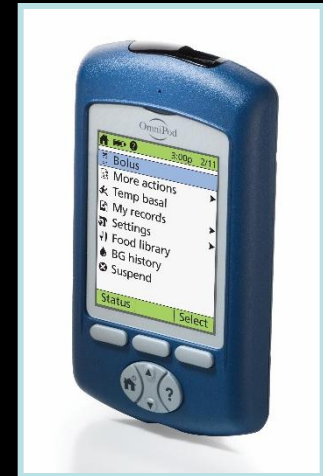
Marked as approved!

28



et CGM*-enabled
mas Vibe.
formance that's
ply advanced.

ulin pump that's fully integrated with
nd Dexcom G4* Sensing technology
lved CE mark approval.



My view of the Future (1)

CGM systems will improve in accuracy, reproducibility, and better predictability of hypos and software will be developed with better indices to measure glucose variability.

CGM studies will be required for all the companies developing new drugs for diabetes control

Within 5 to 10 years with proper **Reimbursement** it will become the standard of diabetes care for almost all type 1 patients

My view of the Future (2)

A secure network will allow patients to make realtime adjustment sharing information with their HCP, it is sure that CGM would flourish in a patient-driven system , spite the challenging economic environment

Development of a real close-loop system that may incorporate delivery of counterregulatory hormones will prevent or minimize hypoglycemia and will **Make Easier to Live with diabetes** until we find a cure

Some patient testimonies

Guillermo & Mila 's testimonies (long-term CGM patients)

• It is really amazing, I am wearing my CGM device for almost 5 years and I am continuously learning new things about my diabetes because everyday is a different story

Guillermo (Oviedo)

39 yo with type 1 diabetes for 20 years

His comments during a routine follow-up visit, May 9,2011

• Now I can see what is coming, it is the first time in my 31 years with diabetes that I can relax, now I am “in charge” of my diabetes instead of the other way around

Milagros (Madrid)

45 yo with type 1 diabetes for 31 years

Received by email March 4,2011

*My gratitude,
admiration and
special thanks
GO to*

All my patients

*who cope bravely with
diabetes, in their own
unique ways. They
constantly amaze me
and teach me every
single day.*



*thank you
for your attention*



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