II Jornadas de Actualización en el tratamento de la Diabetes Mellitus -HUCA
Oviedo 1 de Marzo 2017

Innovaciones Tecnológicas para mejorar el control de la Diabetes Nuevos Horizontes

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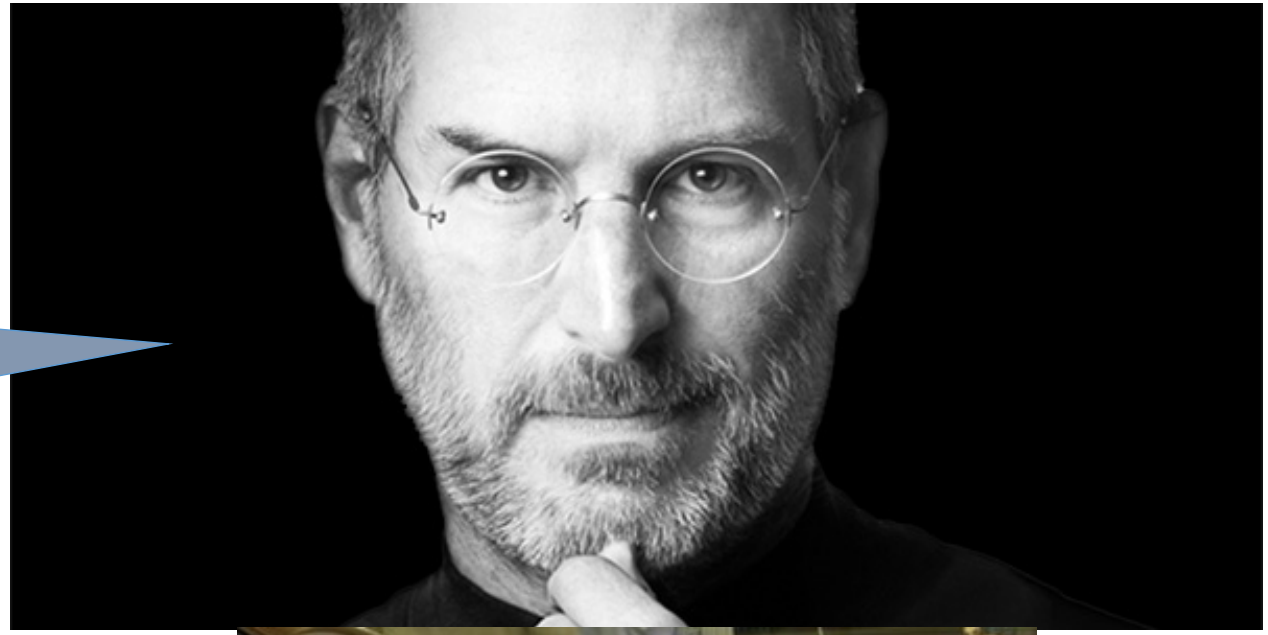
Disclaimer

- Has served as principle investigator or served as clinical advisor for the following:
    - Abbott Diabetes Care
    - Dexcom
    - C8 Medisense
    - Lilly
    - Sanofi-Aventis
    - NovoNordisk

Nadie puede predecir el futuro ,salvo algo quizás, algunas “mentes brillantes”

“I think the biggest innovation of the 21th century will be at the intersection of biology and technology”
Steve Jobs
1955-2011



OBJETIVOS

- Necesidad de la tecnologia para alcanzar los objetivos de control de la Diabetes

- Importancia de los avances tecnológicos en la Diabetes

- Mirada al futuro de los sistemas de administración de insulina y de la medición de la glucosa

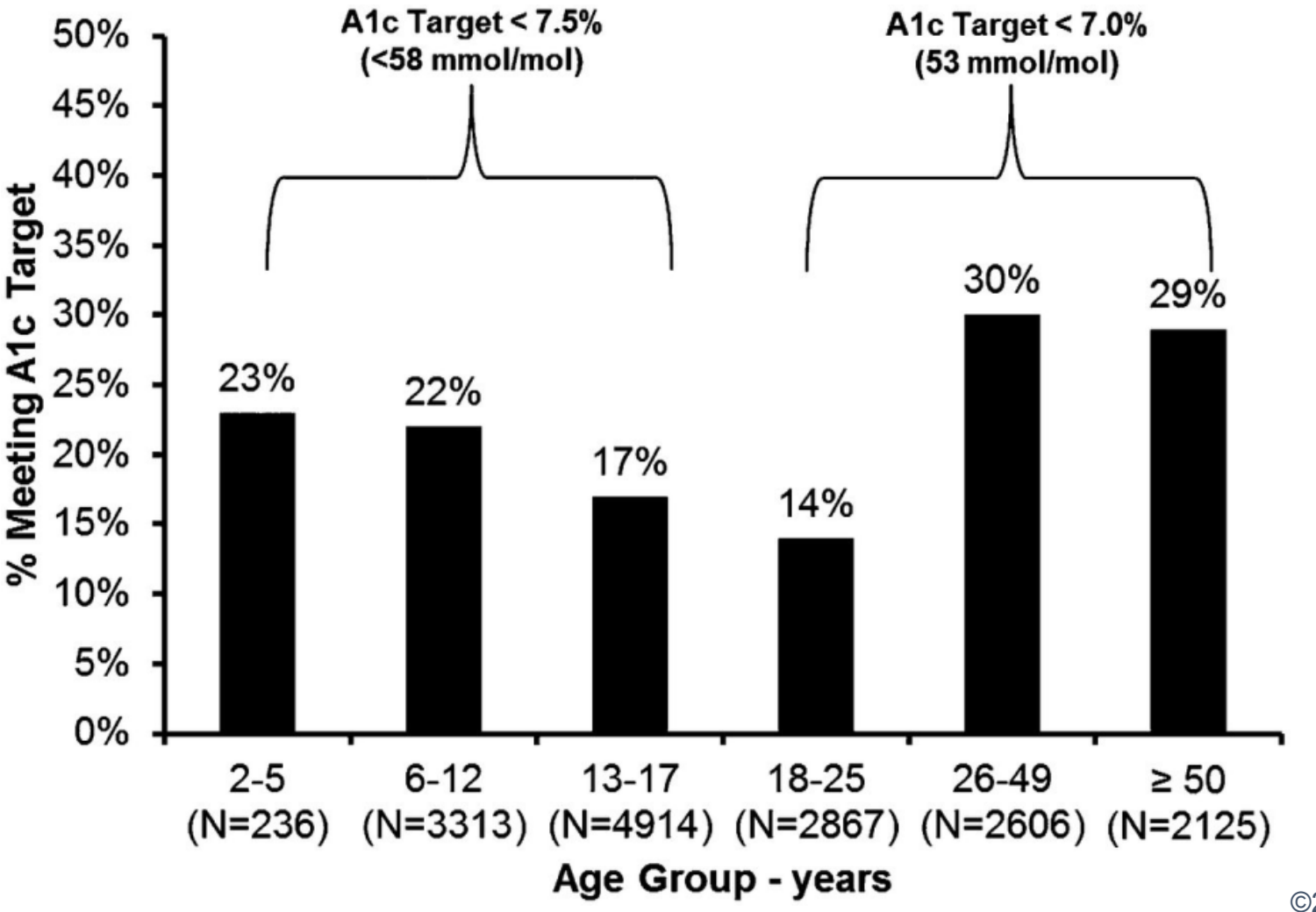
T1D Exchange

- T1D Exchange registry was founded in 2010

- Health data from 28,000+ patients revealing trends, insights and discoveries about type 1
- 75 clinics across the country with an group of clinicians caring for more than 100,000 people with type 1 and performing real-world research

t1dexchange.org

Percent of patients achieving A1c targets by age-group



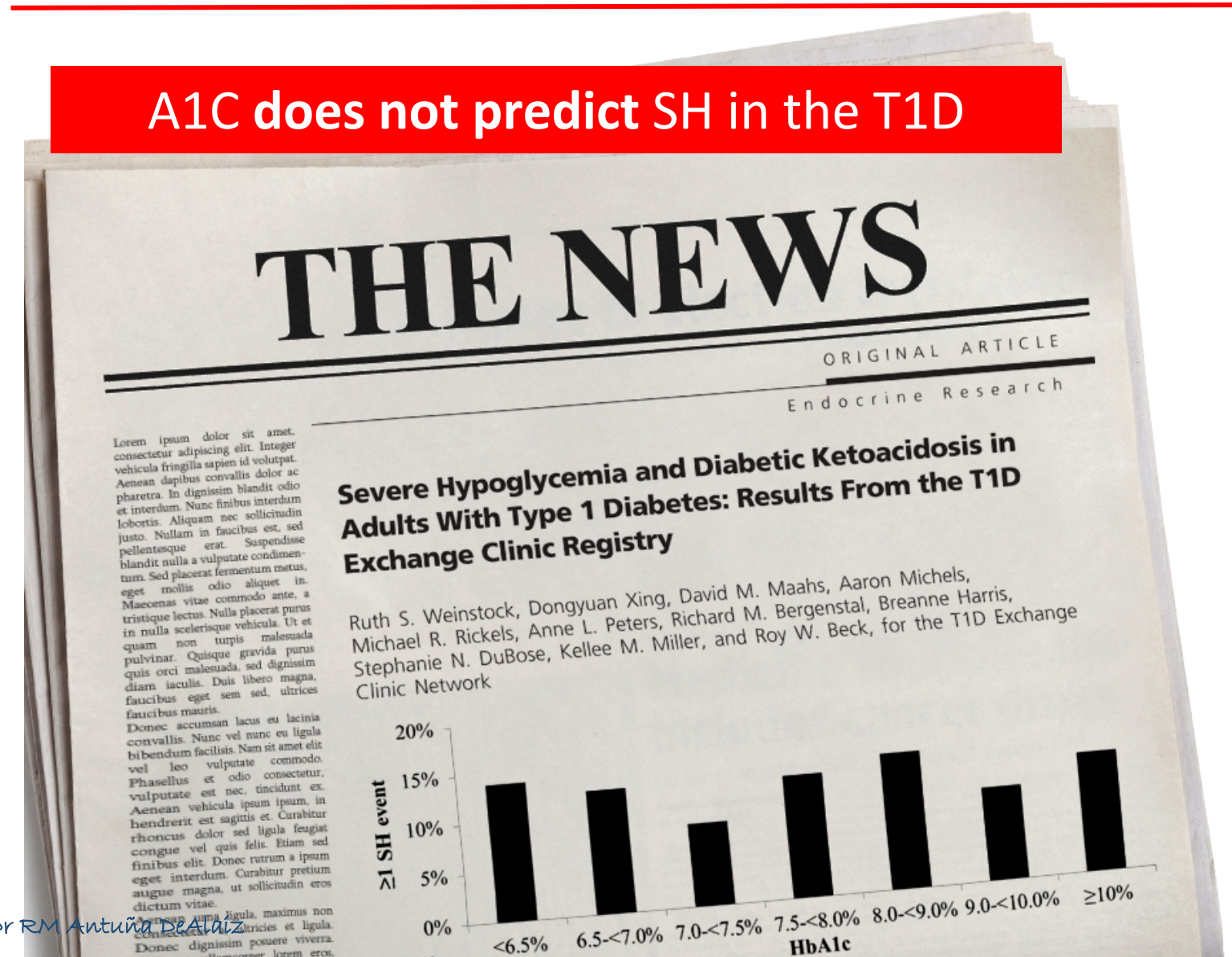
Clinical impact of hypoglycemia

- La hipoglucemia es la complicación más frecuente
- Constituye la mayor barrera para lograr los objetivos de control
- Afecta de una manera muy importante a la calidad de vida
- Las hipoglucemias de repetición ,llevan a hipoglucemias asintomáticas y estos tienen un alto riesgo de hipoglucemias graves
- Pueden tener consecuencias muy graves o incluso irreversibles.
- Tienen un coste social muy elevado

A1C IS NOT AN INDICATOR OF

Severe Hypoglycemia (SH) risks

A1C does not predict SH in the T1D



THE NEWS

ORIGINAL ARTICLE

Endocrine Research

Severe Hypoglycemia and Diabetic Ketoacidosis in Adults With Type 1 Diabetes: Results From the T1D Exchange Clinic Registry

Ruth S. Weinstock, Dongyuan Xing, David M. Maahs, Aaron Michels, Michael R. Rickels, Anne L. Peters, Richard M. Bergenstal, Breanne Harris, Stephanie N. DuBose, Kellee M. Miller, and Roy W. Beck, for the T1D Exchange Clinic Network

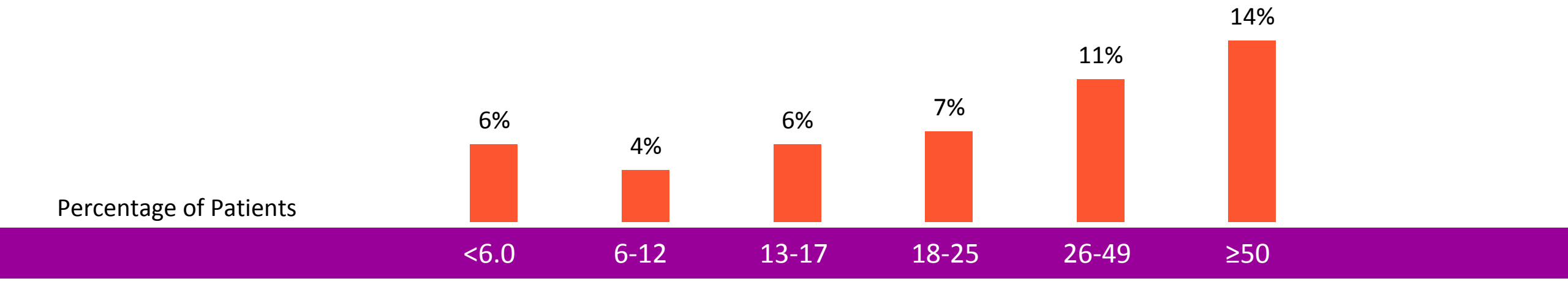
"…the **high rates of SH in poorly controlled patients** demonstrate that **elevated A1c levels**, per se, **do not protect against SH.**" in the T1D Exchange

Weinstock et al, J Clin Endocrinol Metab 98: 3411–3419, 2013

12-MONTH FREQUENCY OF SEVERE HYPOGLYCEMIA*

(SH) According to Age

Risk of severe hypoglycemia in the elderly 1.5 to 3 fold higher



Presentation at the Advanced Technologies and Treatments for Diabetes meeting in Barcelona, Spain, February 2012 by .Dr I.B.Hirsch from the TD1 Exchange Study Group

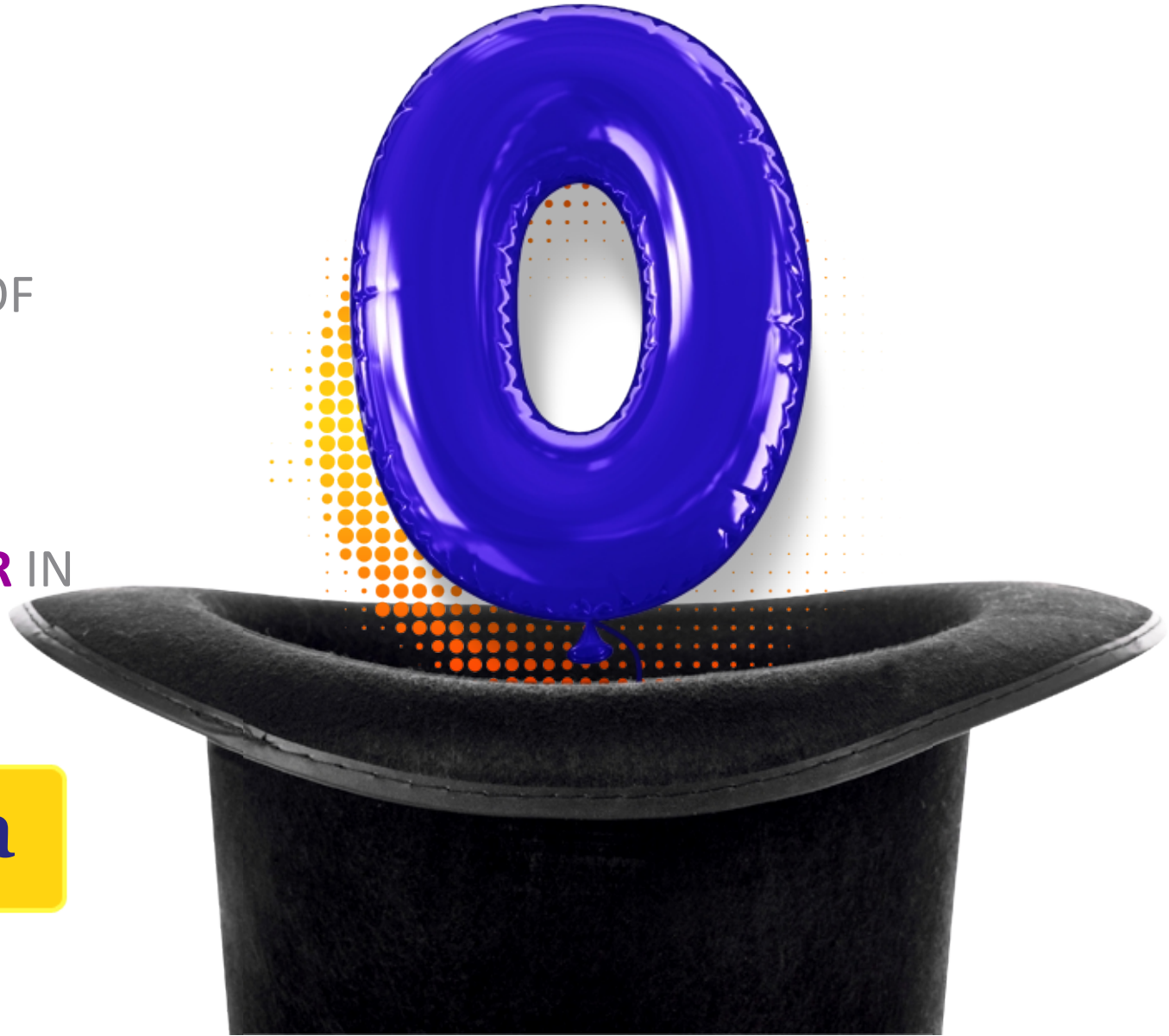
A1C

A **MAGIC NUMBER** WITH A LOT OF LIMITATIONS AND TELL US

NOTHING

ABOUT **THE MOST LIMITING FACTOR** IN THE GLYCEMIC MANAGEMENT:

the hypoglycemia



Dr RM Antuña DeAlaíz

Moving beyond A1C

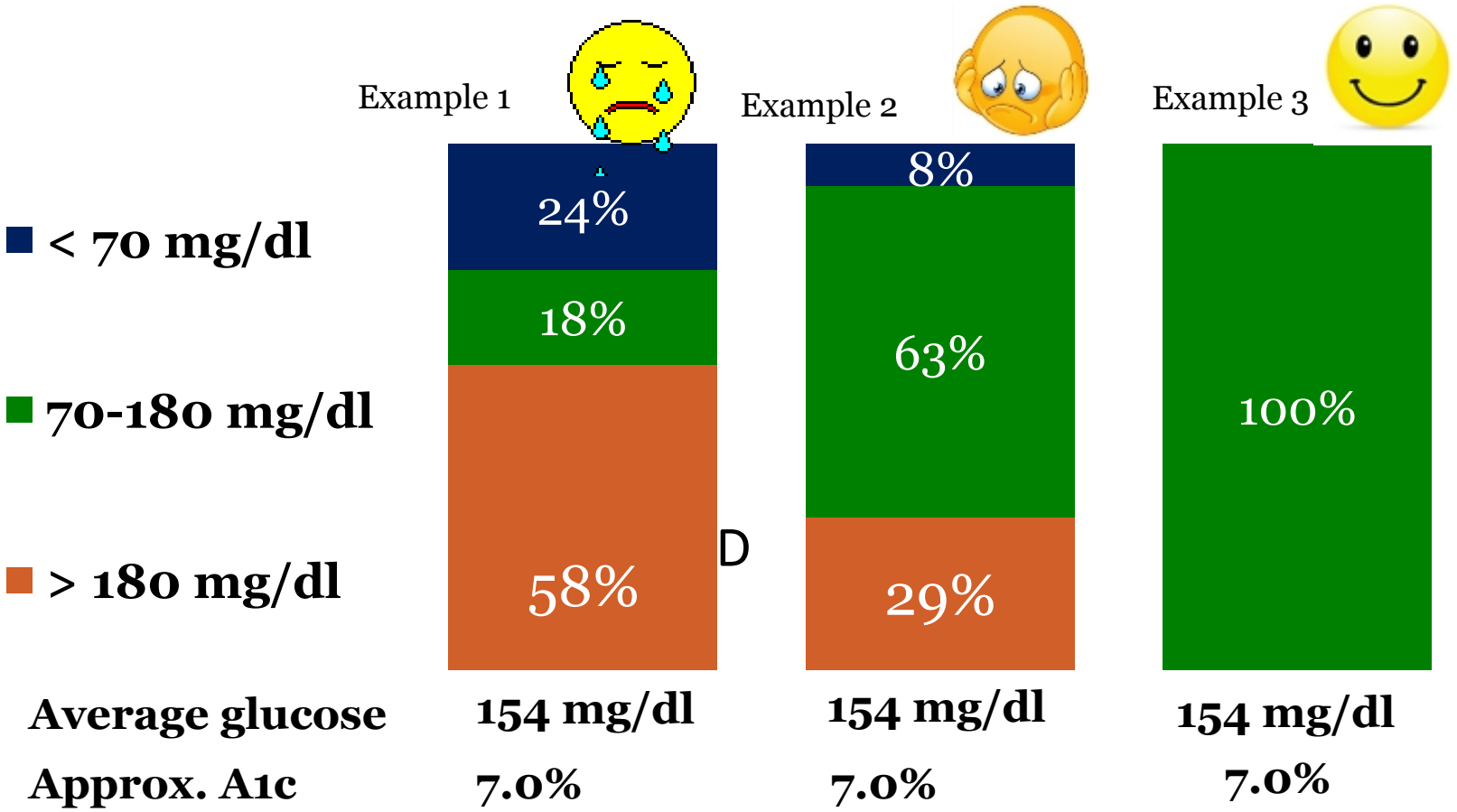
- **Overall control**
  - Optimize A1c
  - Minimize hypoglycemia
  - Minimize glucose variability
  - Increase time-in-range
  - Increase QoL

HbA_{1c} = 6.8 %

HbA_{1c} =6. 8%

Source Hirsch I B et al JAMA 2010:303:2291-2292

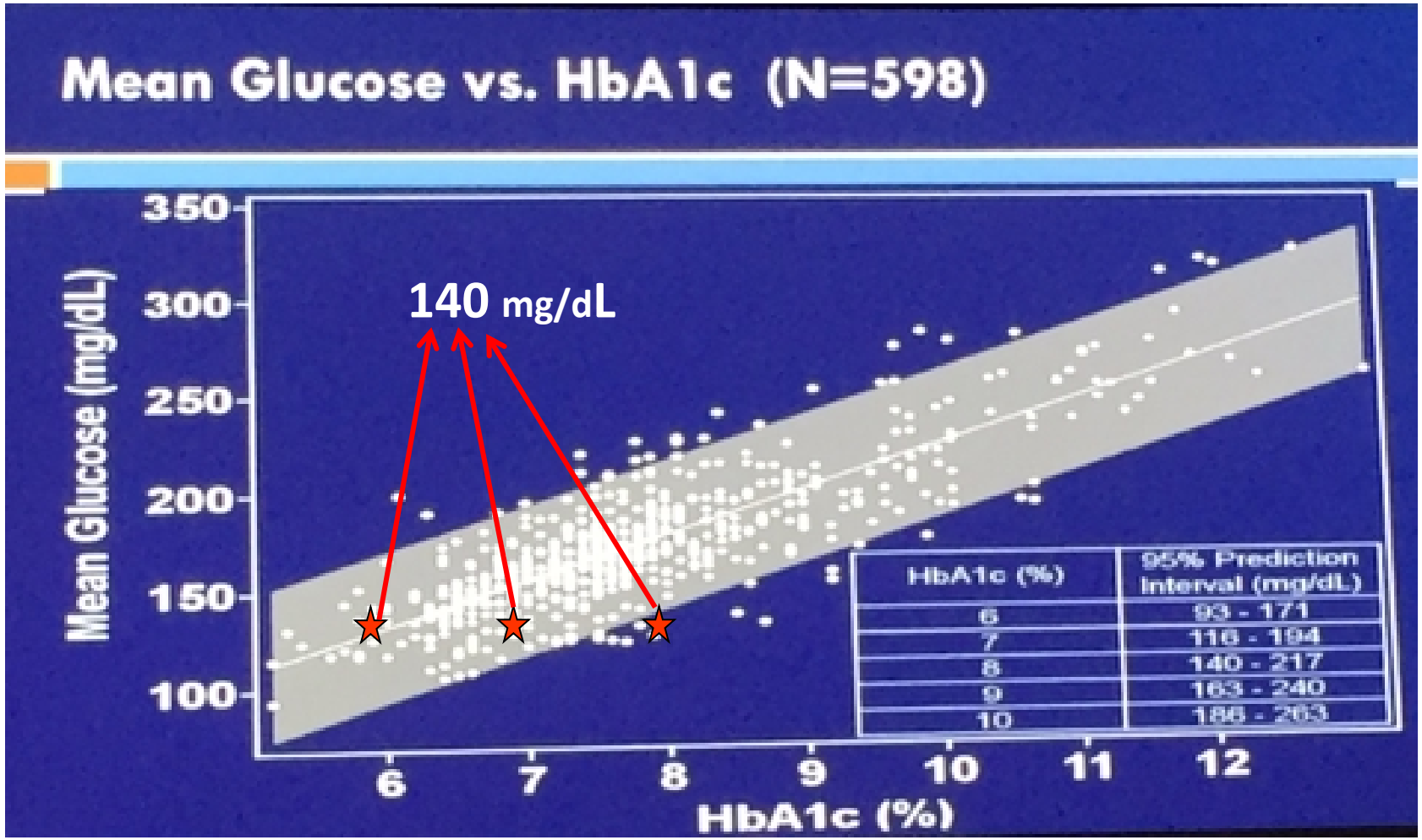
The many faces of a 7% A1c
One metric cannot tell the full story



Time in range, and thus 'Quality of A1c*, can be dramatically different!

Source: Dr. David Nathan et al., *Diabetes Care* 2008

Mean Glucose vs A1c in the T1D exchange Study (N=598)
A1c sometimes can be “tricky”



A1C is an average, more weighted over the past 30 days, with large CIs

One can’t compare the A1C levels between 2 people!

umpublished data

What Alters A1c

Hematologic conditions
- Anemia
- Accelerated erythrocyte turnover
- Thalassemia
- Sickle cell disease
- Reticulocytosis
- Hemolysis

Physiologic States
- Values Different Ethnicities

Drugs/Medications
- Alcohol
- Opioids
- Vitamin C
- Vitamin E
- Aspirin
- Erythropoetin
- Dapsone
- Ribavirin

In a typical diabetes practice, 14-25% of A1C measurements are misleading

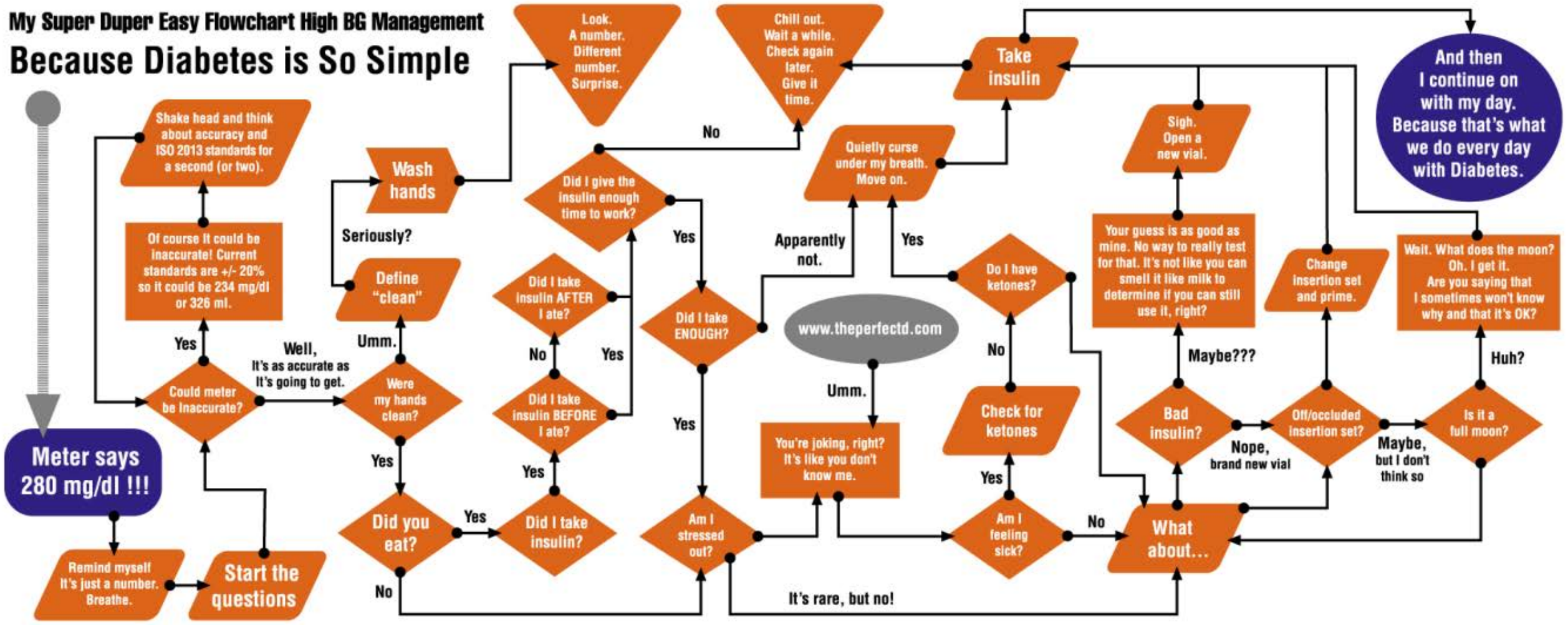
Disease States
- HIV infection
- Uremia
- Hyperbilirubinemia
- Dyslipidemia
- Cirrhosis
- Hypothyroidism*

Medical Therapies
- transfusion
- dialysis

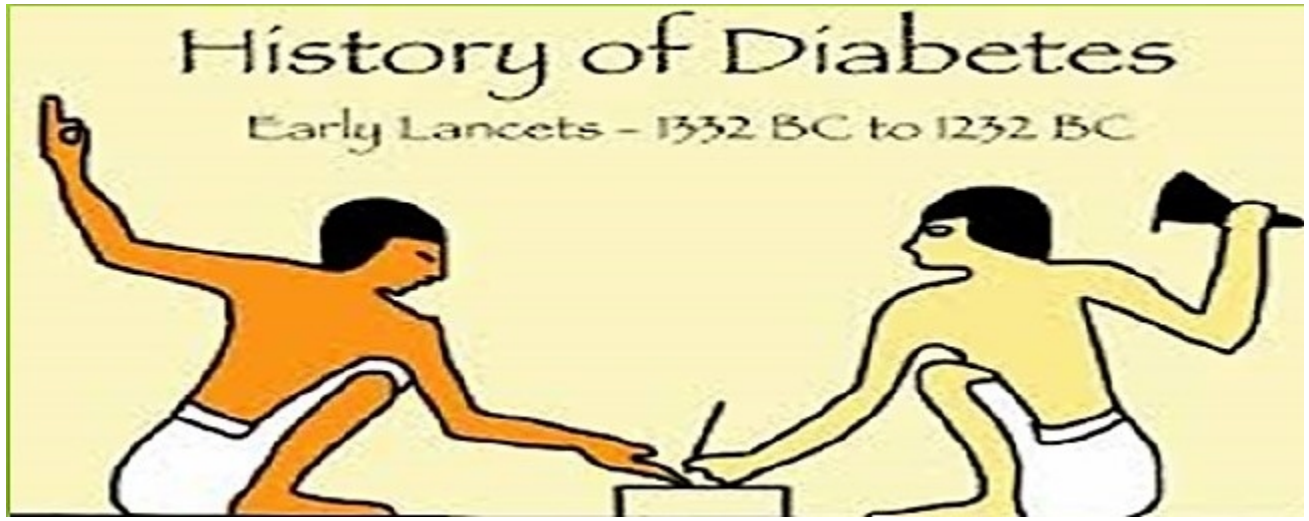
- Glycation rate
- Protein turnover
- Race and ethnicity*
- Laboratory assay
- Glycemic Variability
- Smoking
- Mechanical heart valves?
- Exogenous testosterone?

by courtesy of Dr Irl B. Hirsch

Diabetes Care
Easy Flowchart

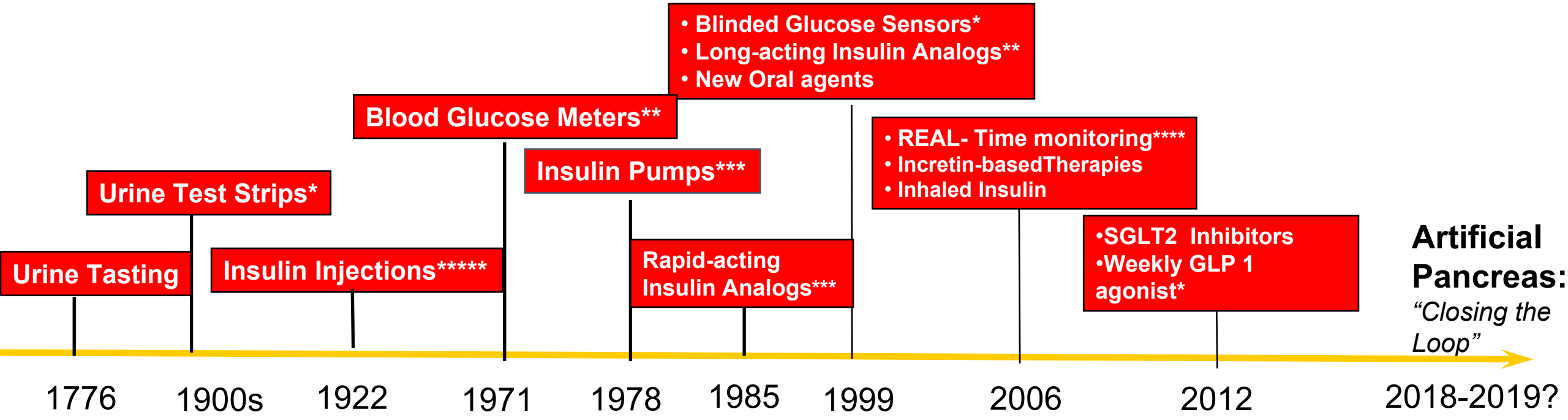


Historia de la diabetes



Veremos como la innovacíon tecnológica va mejorando la **calidad de vida** a nuestros pacientes

Evolution of Diabetes Technology Innovations and Treatments: Timeline

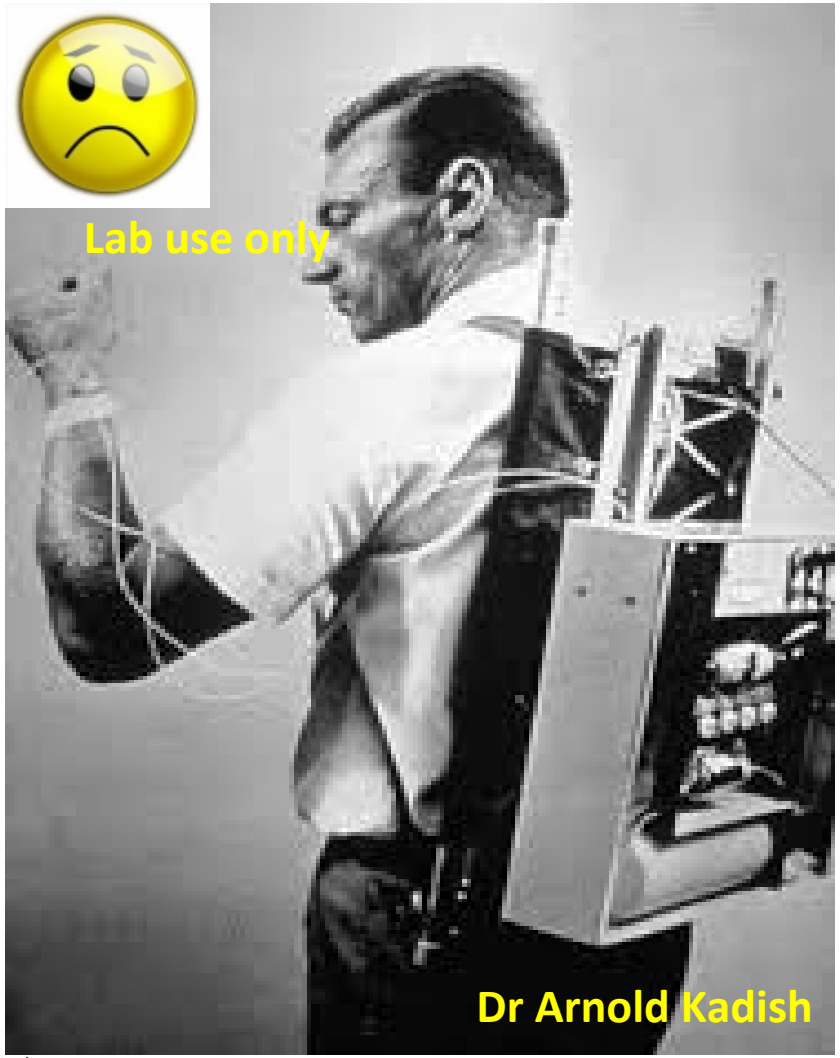


Progresos en los métodos de poner insulina

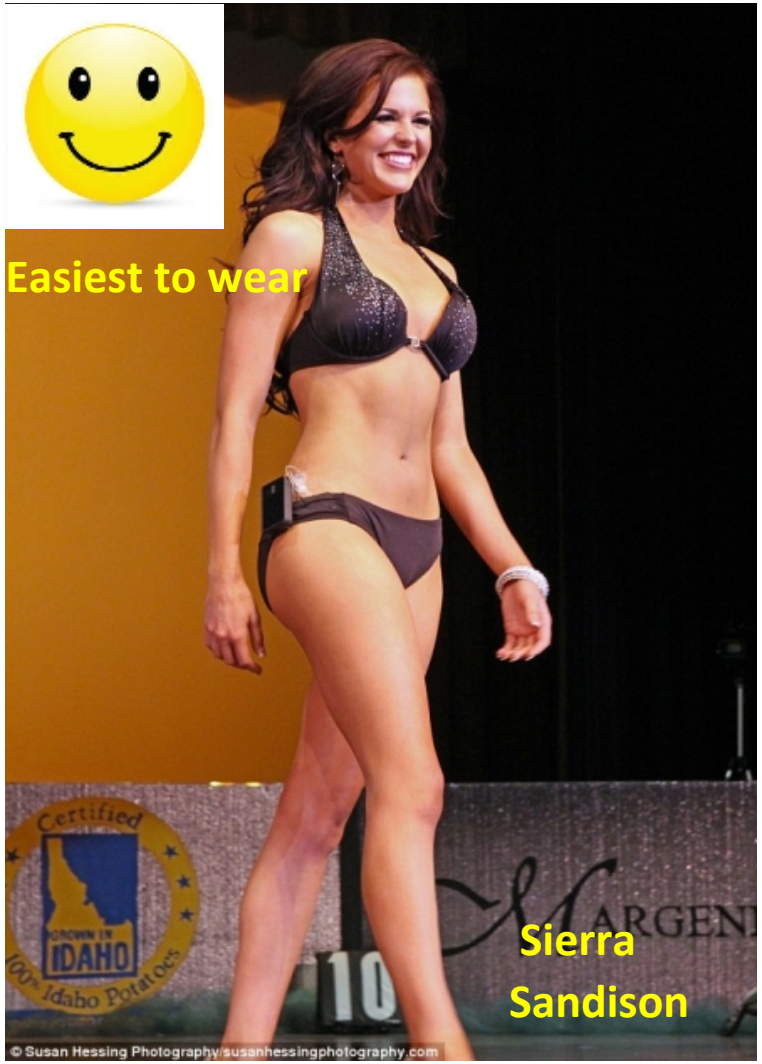
Coming soon during 2017 **Esysta BT** – **eco insulin pen** allows direct transfer of insulin data automatically **keep a diary**

Insulin Pump History

1963 First "wearable" insulin Pump



2014 T-Slim First insulin Pump with a touchscreen interface



SMBG history

1971 Dextrostix Ames

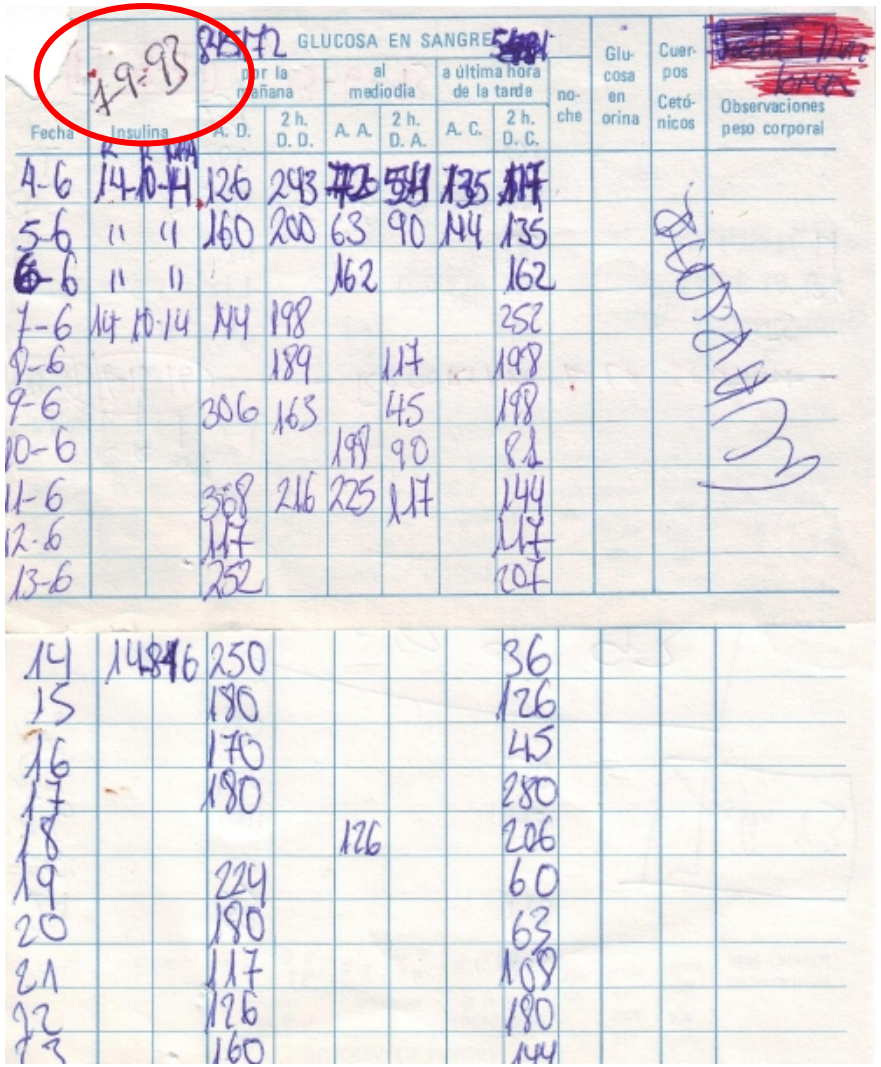
1985 Glucometer M Glucofacts

2012 First Bolus calculator with phone connectivy

Supercopa de Europa de la UEFA

MANY PATIENT AND PROVIDERS KEEP USING

the old Patient Log Book



Old Technology designed in the last century, **belongs to the last century**

Los sistemas de autocontrol de ANTES son muy útiles ,pero los de ahora suman SEGURIDAD

CGM History

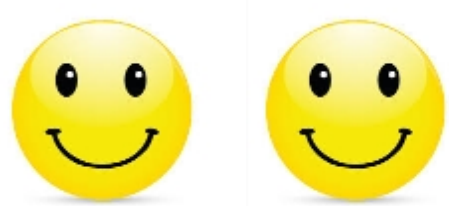
1999 First "wearable" CGM system

Clinicall use and retrospective

2006 First real-time CGM for patient´s use

Real-time and convenient for patient´s

2016 First real-time CGM approved for insulin adjustment doses



The needs are similar for MDI or Pump users

Many have elevated HbA1c or problematic hypoglycemia. All patients on intensive insulin therapy make management decisions, multiple times each day. They all

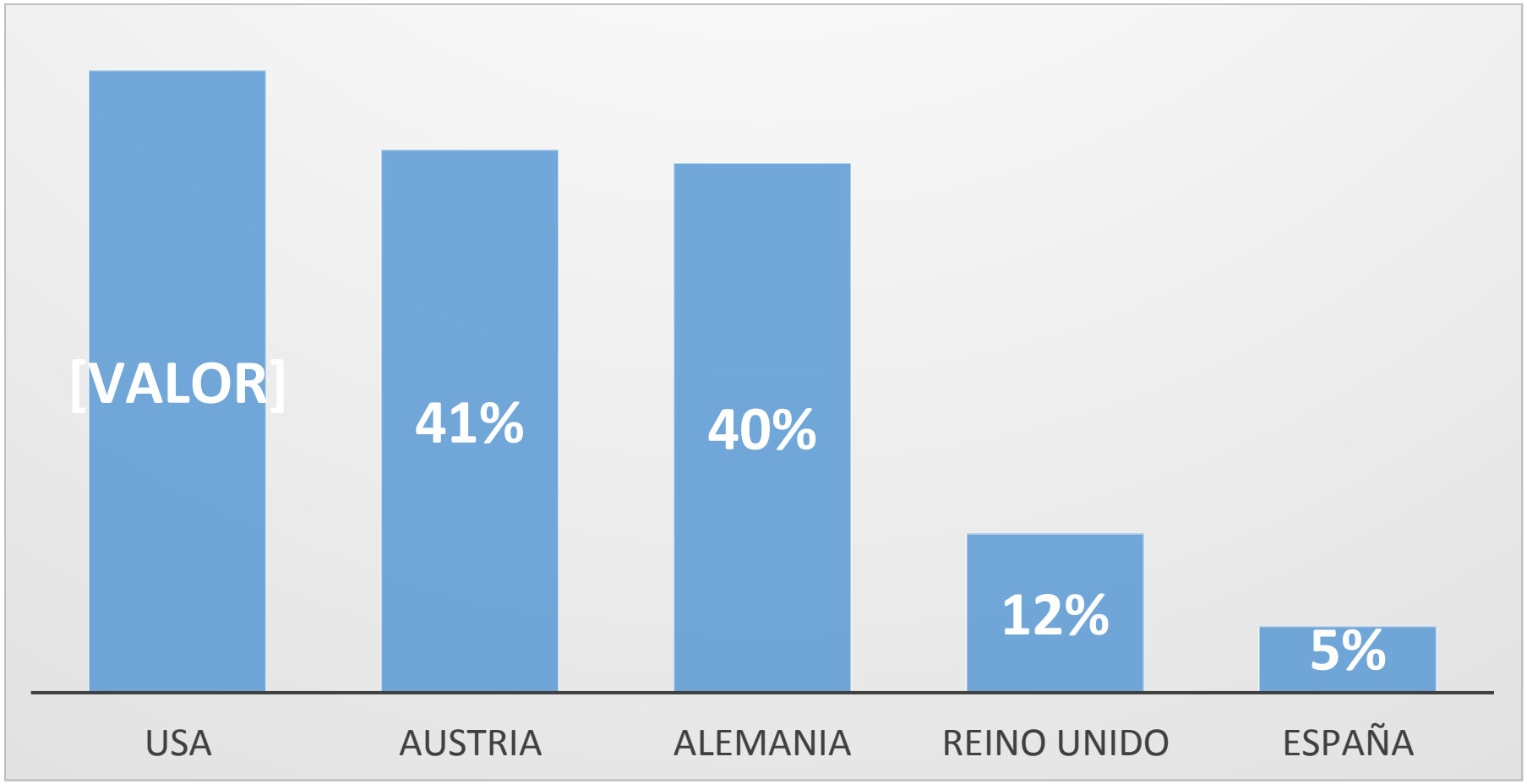
Cada dia tiene que tomar entre 50 y 100 decisiones relacionadas con la diabetes

Eat

Work

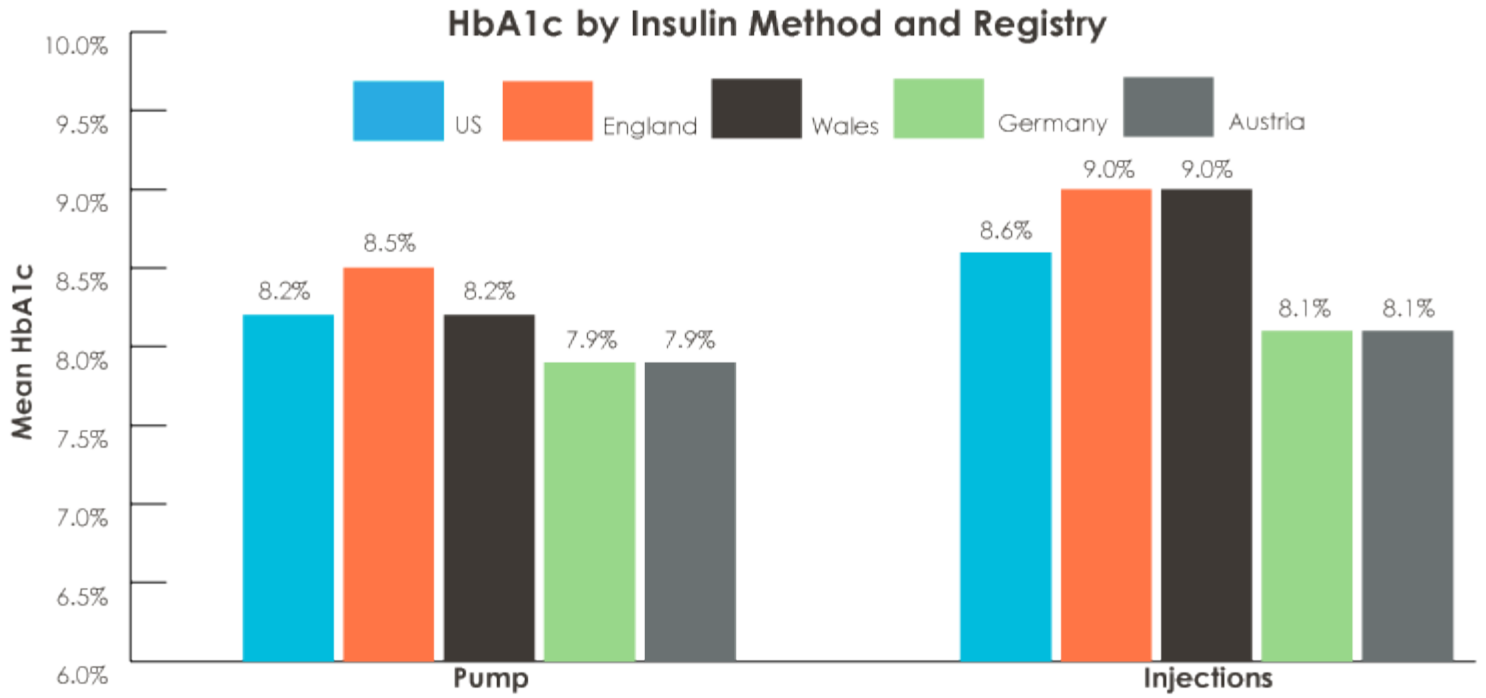
Sleep

Overall Pump use in several countries (2015)



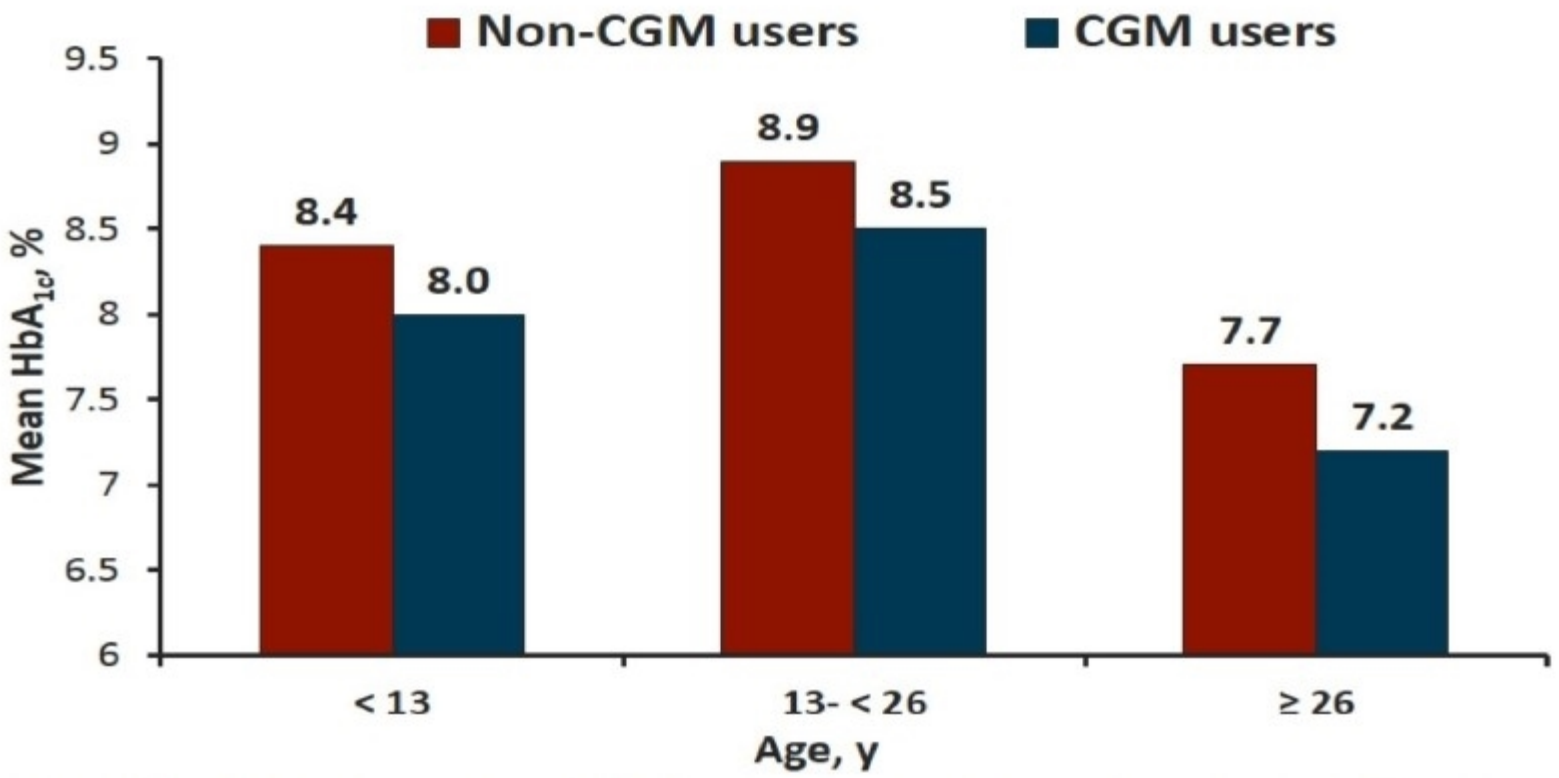
Kellee M. Miller et al. Dia Care 2015;38:971-978

Mean A1c by country and insulin delivery method



US T1D Exchange, UK National diabetes Audit ,Austria&Germany DPV Inititative 2015

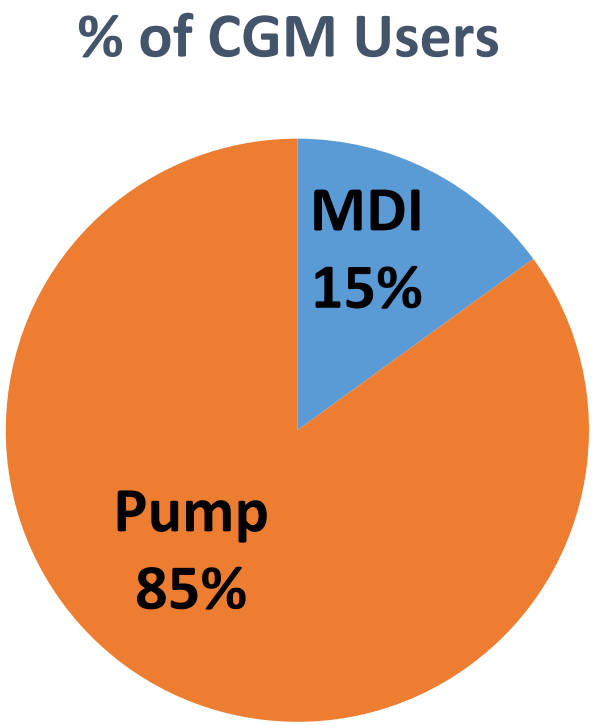
Mean A1c by CGM in T1D Exchange



Miller KM, et al. *T1D Exchange Annual Meeting The Patient-Centric Approach to Diabetes: Change Starts Here*. April 30-May 1, 2015. Boston, Massachusetts.

Use of CGM by Insulin Delivery Method 2016 Data

Today most CGM users are on pumps



Foster N, et al. *Diabetes Care*. 2016;39(6):e81-e82.

Could real-time CGM also be succesful in patients with MDI

JDRF CGM study(2008)

-CGM can improve glycemic control in adults with t1 diabetes

-Not designed to differentiate between SAP and MDI+CGM

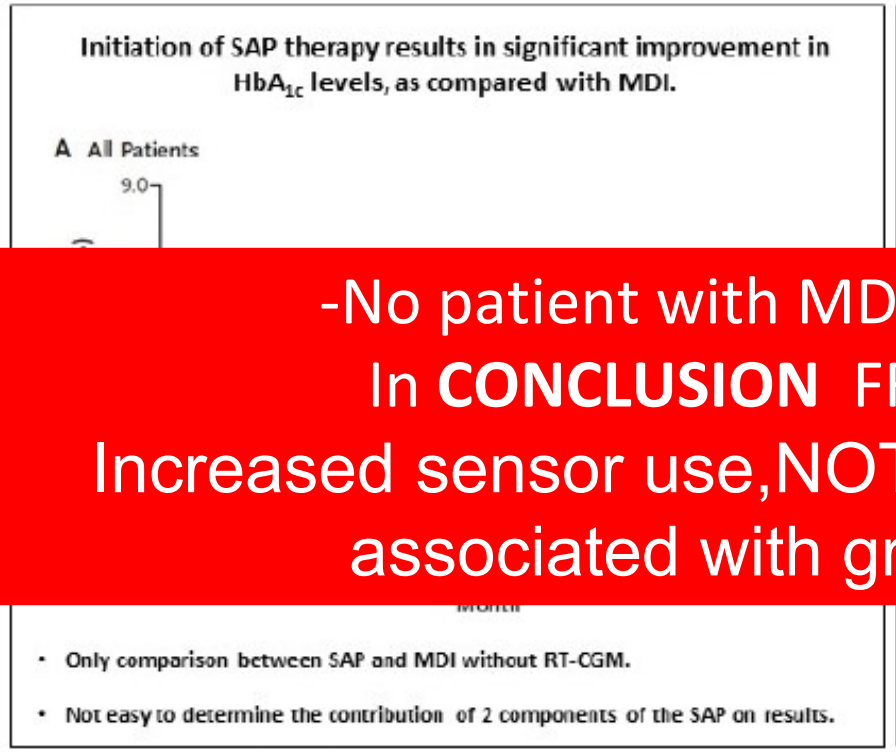
Similar decline in HbA_{1c} at 26 weeks ≥25 Years

	CGM	Control
Insulin Modality Pump	N=43	N=39
Baseline Glycated Hemoglobin (%) *mean ± SD*	7.5 ± 0.4	7.7 ± 0.5
Change from baseline (%) *mean ± SD*	−0.50 ± 0.51	+0.02 ± 0.47
Insulin Modality Multiple Daily Injections	N=9	N=7
Baseline Glycated Hemoglobin (%) *mean ± SD*	7.9 ± 0.6	7.3 ± 0.4
Change from baseline (%) *mean ± SD*	−0.54 ± 0.85	+0.04 ± 0.34

NEJM 2008:359:1464-1476

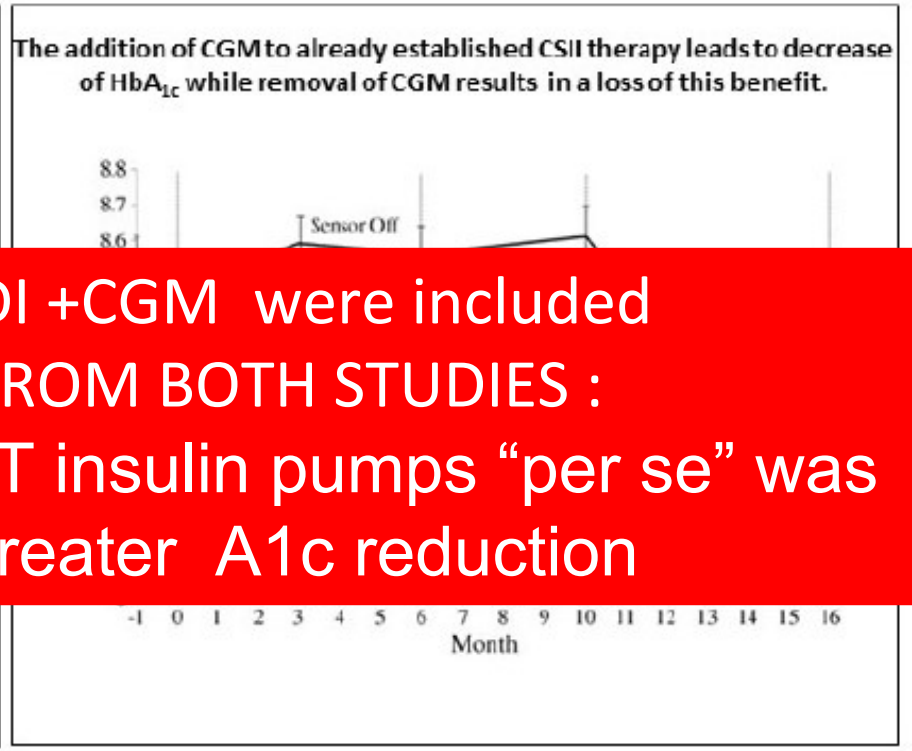
Arguments for real-time CGM in patients with insulin pumps

STAR 3 Study



1 year randomized crossover trial in 30 Canada and US of children and adults(n=420) with A1C 7.4-9.5%

The SWITCH Study



Randomized crossover trial in Seven EU sites of children & adults (n=153) on CSII with A1C 7.5–9.5%.

-No patient with MDI +CGM were included

In **CONCLUSION** FROM BOTH STUDIES :

Increased sensor use,NOT insulin pumps “per se” was associated with greater A1c reduction

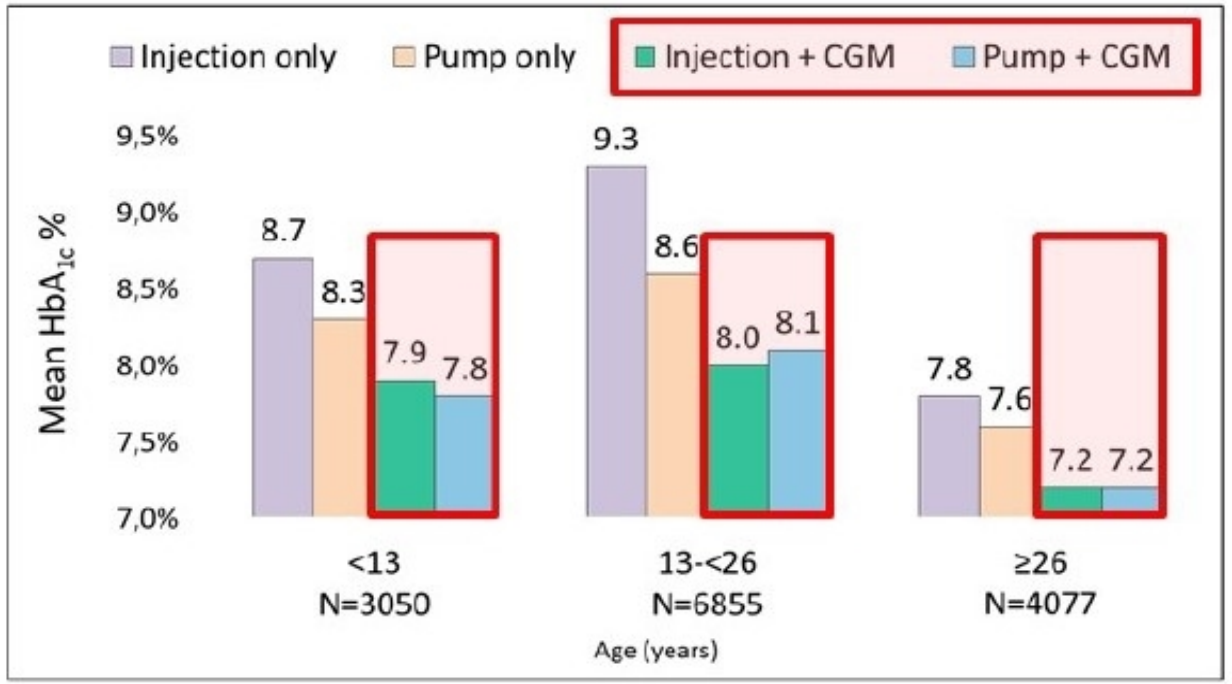
Bergesntal et al START study NEJM 2010//Battelino et al SWITCH study Diabetologia 2012

Lower A1c in CGM users
Regardless of insulin delivery method

T1D Exchange clinic registry 2015

- 15,147 patients with T1D
- 63% of patients are on insulin pumps (~9000 pts)
- 12% of patients are on CGM irrespective of insulin delivery method (~1800 pts)

HbA_{1c} in CGM Users is Lower Regardless of Insulin Delivery Method



T1D Exchange. 2015

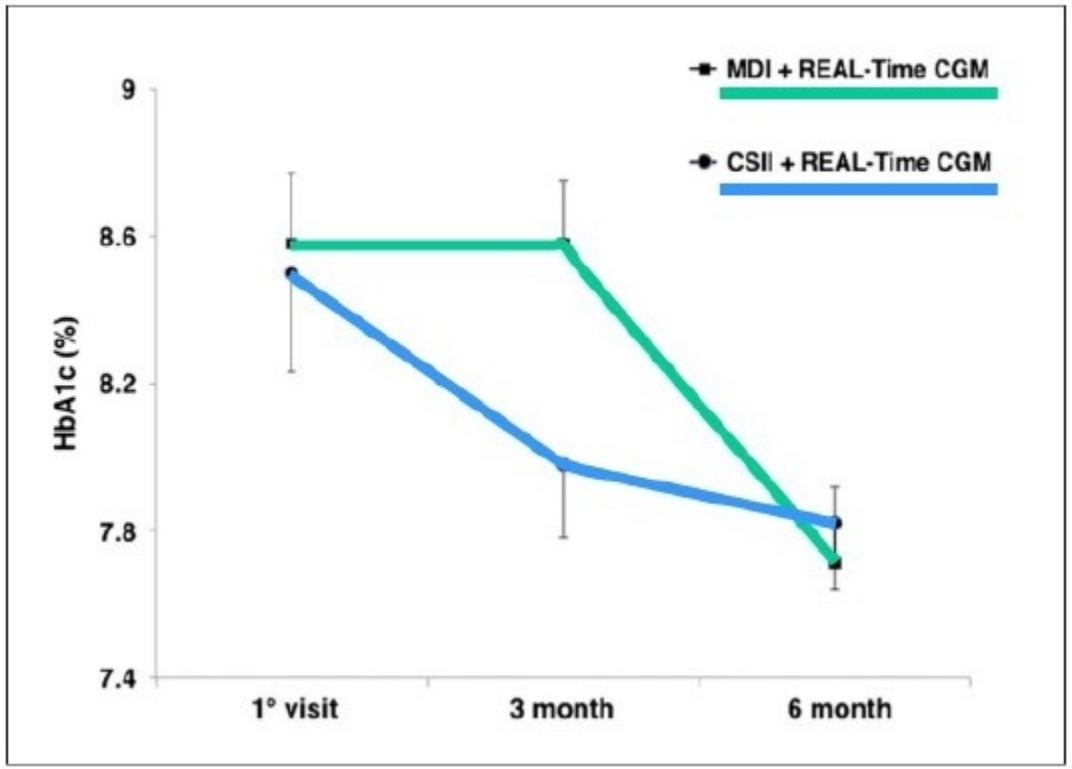
Data from the T1DExchange 2015

Could real-time CGM also be succesfull in patients with MDI?

Tumminia el. al. (2015)

- 20 T1D patients
- HbA_{1c} > 8% (>64 mmol/mol)
- 14 (8 on MDI and 6 on CSII) wore CGM for > 40% of the time.
- **Both groups with CGM improved glycemic control.**
- **MDI + CGM group even had the greatest improvement in A1c and hypoglycemia.**

Both groups using CGM > 40% of the time had improved HbA_{1c}



Tuminia et al .Diabetes/metab Research&Metabolism 2015;31:61-

Could real-time CGM also be succesfull in patients with MDI?
Comisair Study

52 patients followed for 1 year (3 groups):

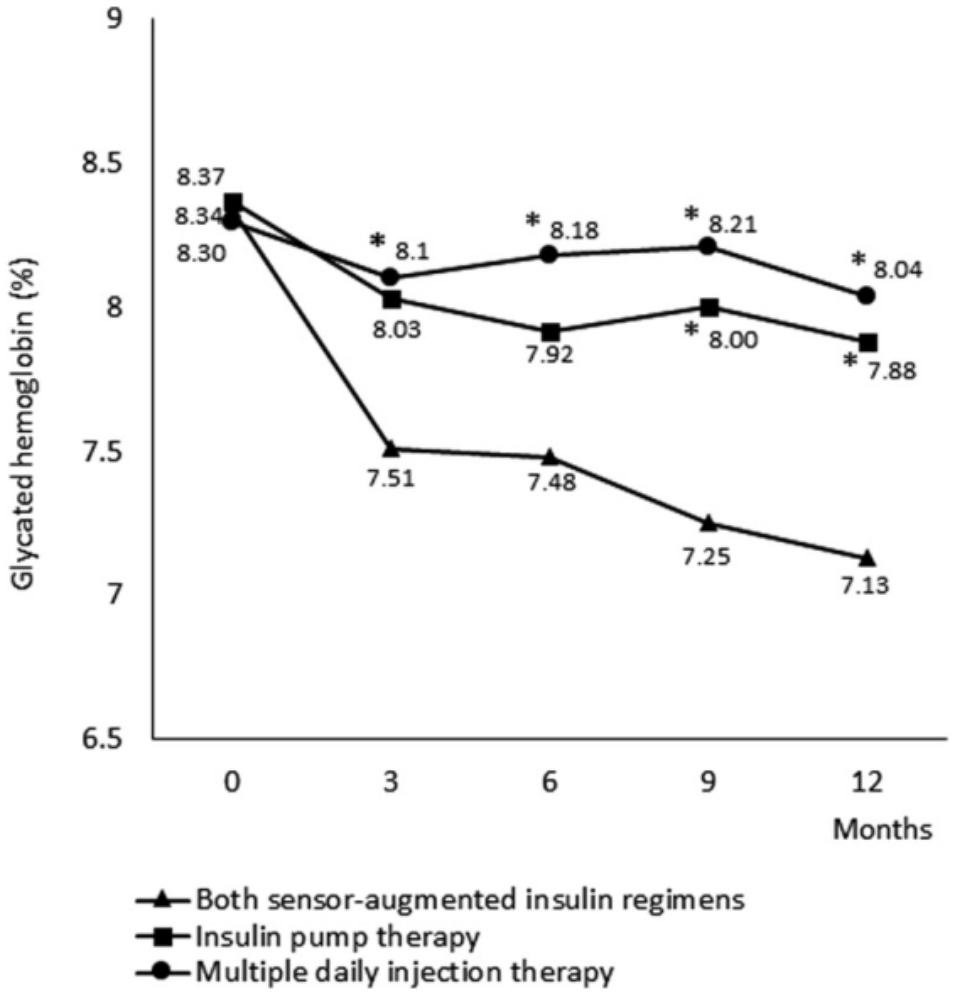
- 17 patients: RT-CGM added to MDI or pump
- 18 patients on pump alone (no CGM)
- 17 patients control group of MDI + SMBG

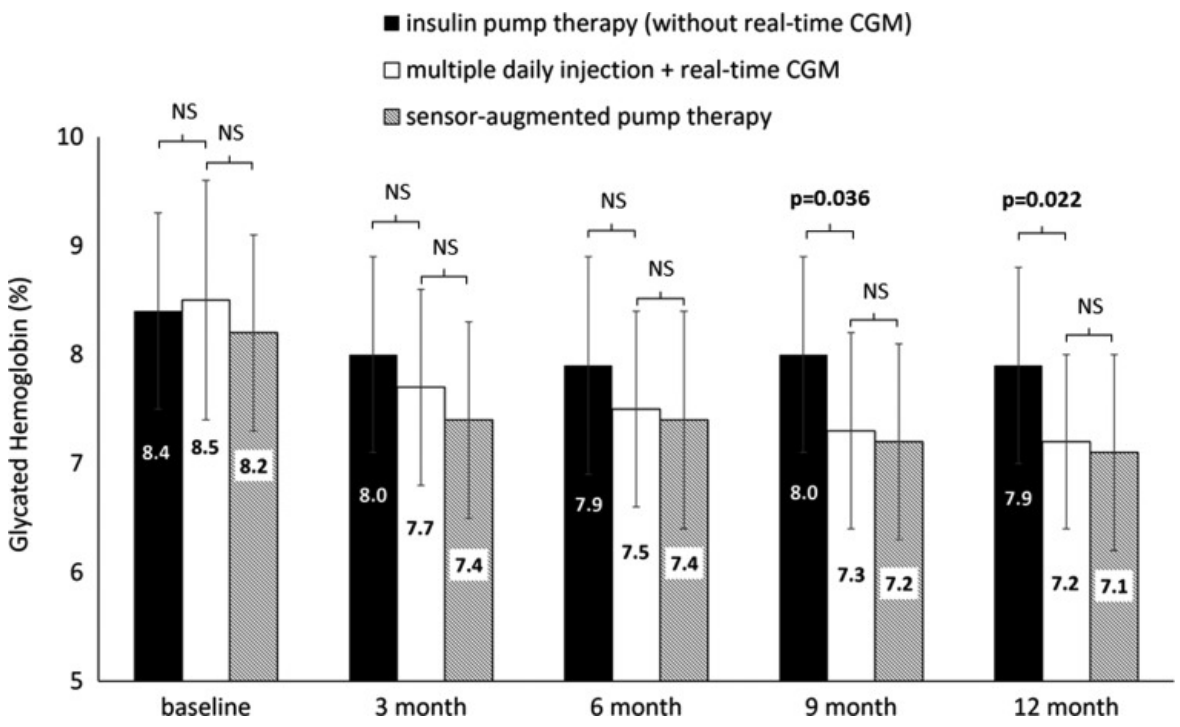
Endpoints:

- *A1c*
- *Glucose variability*
- Incidence of hypoglycemia

Soupal et al DT&T 201618:532-538

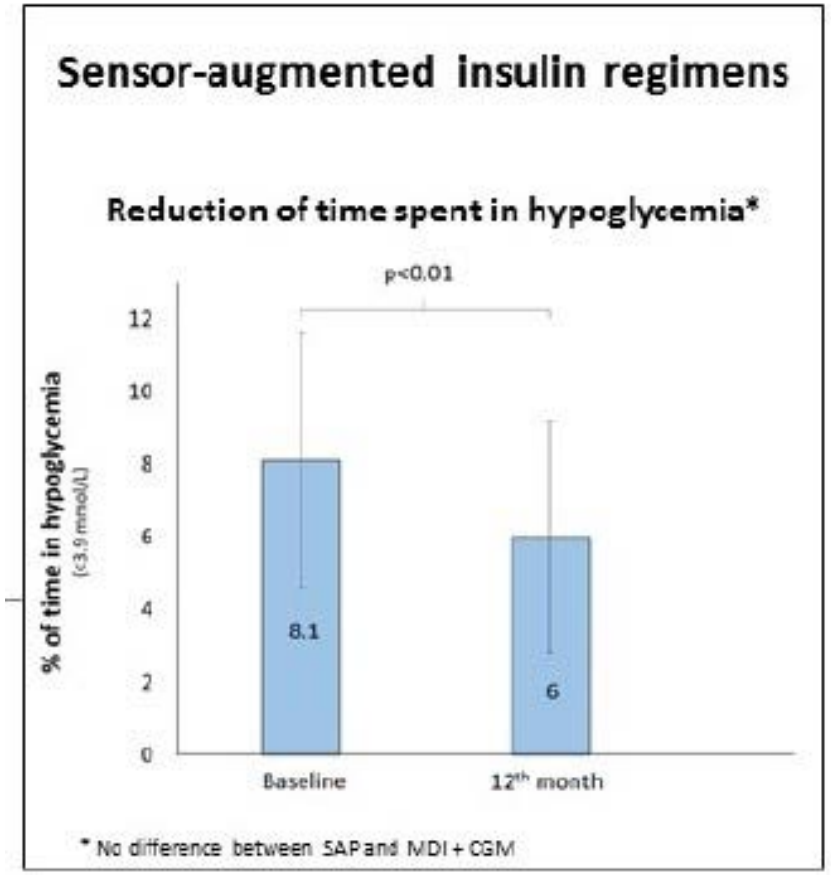
Could real-time CGM also be succesfull in patients with MDI?
Comisair Study

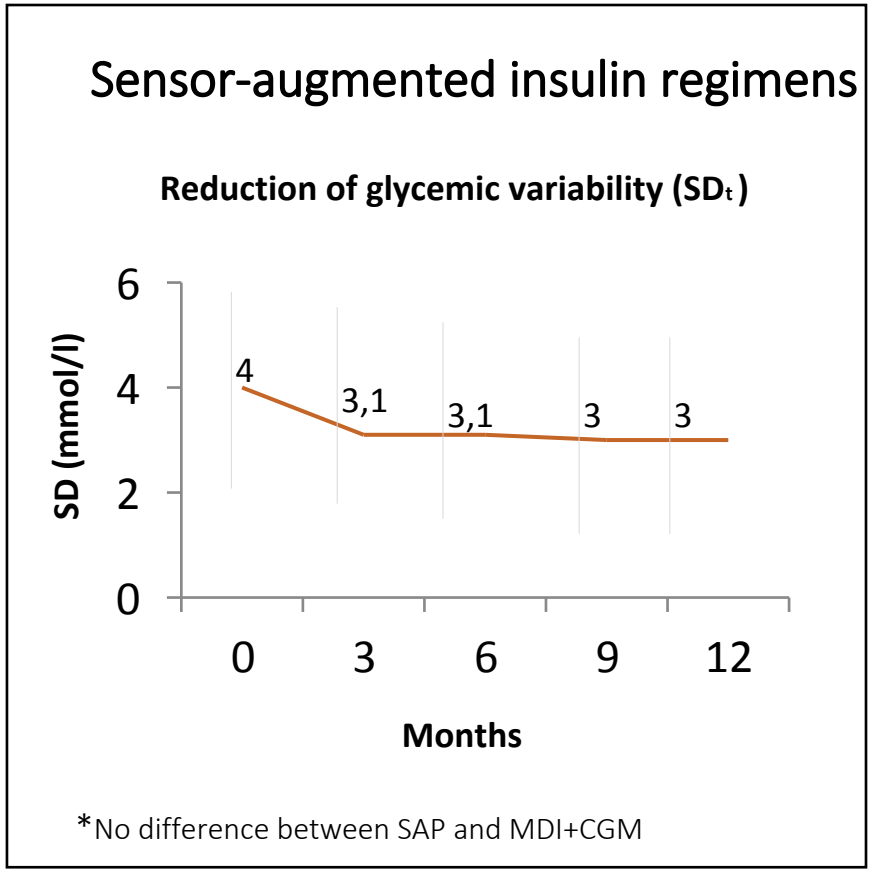




Soupal et al DT&T 201618:532-538

Hypoglycemia and glucose variability
Comisair study





Soupal et al DT&T 201618:532-538

Conclusion
Comisair Study

The usage of CGM resulted in a significant A1c reduction in patients with CSII as well as in patients on MDI

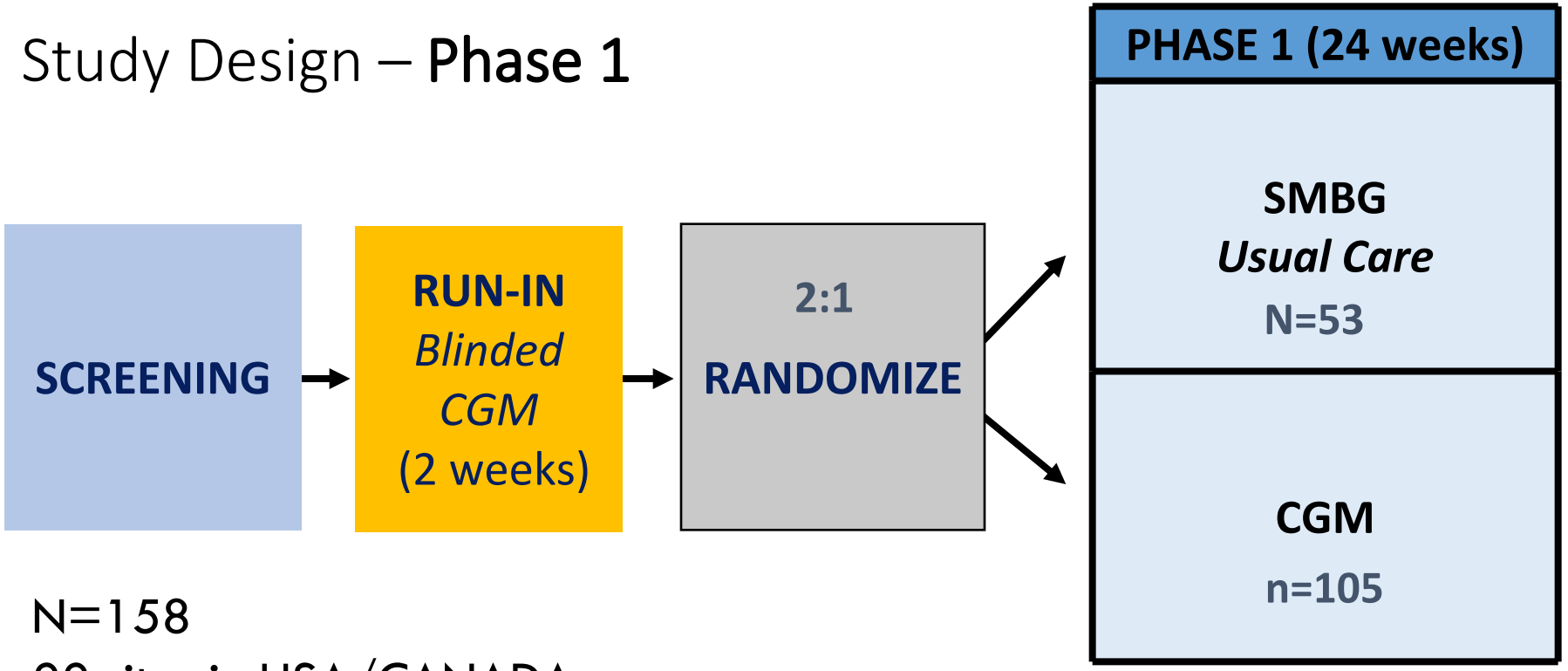
The improvement was greater than the improvement with insulin pumps alone

The combination of CGM +MDI can be a suitable alternative to the SAP

Soupal et al DT&T 201618:532-538

The value of CGM in Patients with type 1 Diabetes using MDI
DIaMond Study

Study Design – **Phase 1**



N=158
22 sites in USA/CANADA
ITT design
Primary endpoint: between groups HbA1c difference vs baseline at wk 24

JAMA published ONLINE January 24, 2017

Secondary endpoints
DIaMonD Study

Overall control

% of patients with

HbA1c <7%, HbA1c <7.5%

Decrease in HbA1c of ≥1%

% of time in range (70-180 mg/dL)

Glucose variability

Hypoglycemia

Number of severe hypoglycemia events

% of time <70 mg/dL, <60 mg/dL, and <50 mg/dL

Hyperglycemia

% of time >180 mg/dL, >250 mg/dL, and >300 mg/dL

JAMA published ONLINE January 2017

Key inclusión criteria
DIaMonD Study

Age ≥25 years

Using MDI

HbA1c of 7.5%-10%, measured by central lab (Northwest Lipids)

Stable control of diabetes

Stable diabetes medication regimen

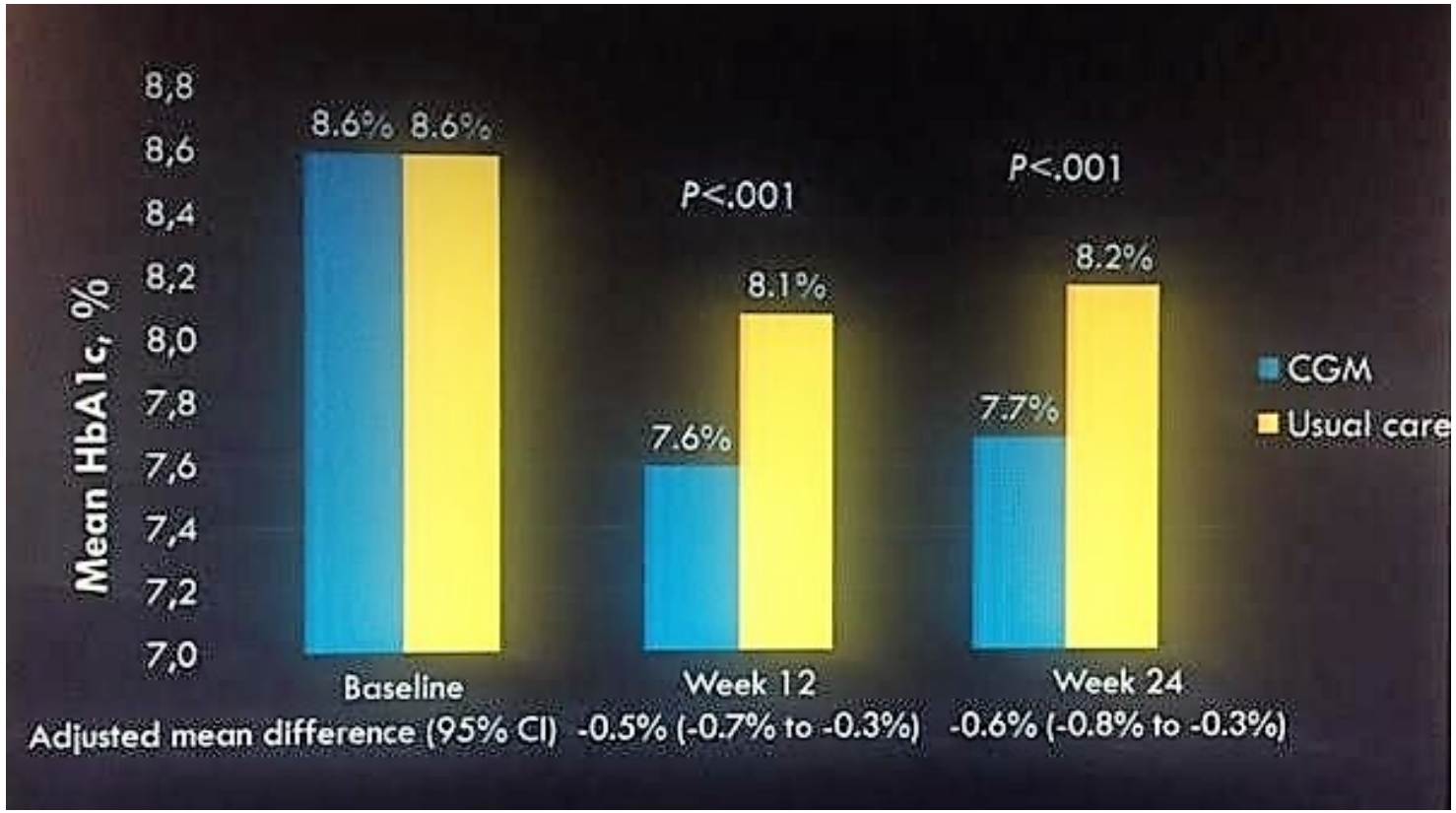
Stable weight

Currently performing SMBG an average of ≥3 times/day

JAMA published ONLINE January 2017

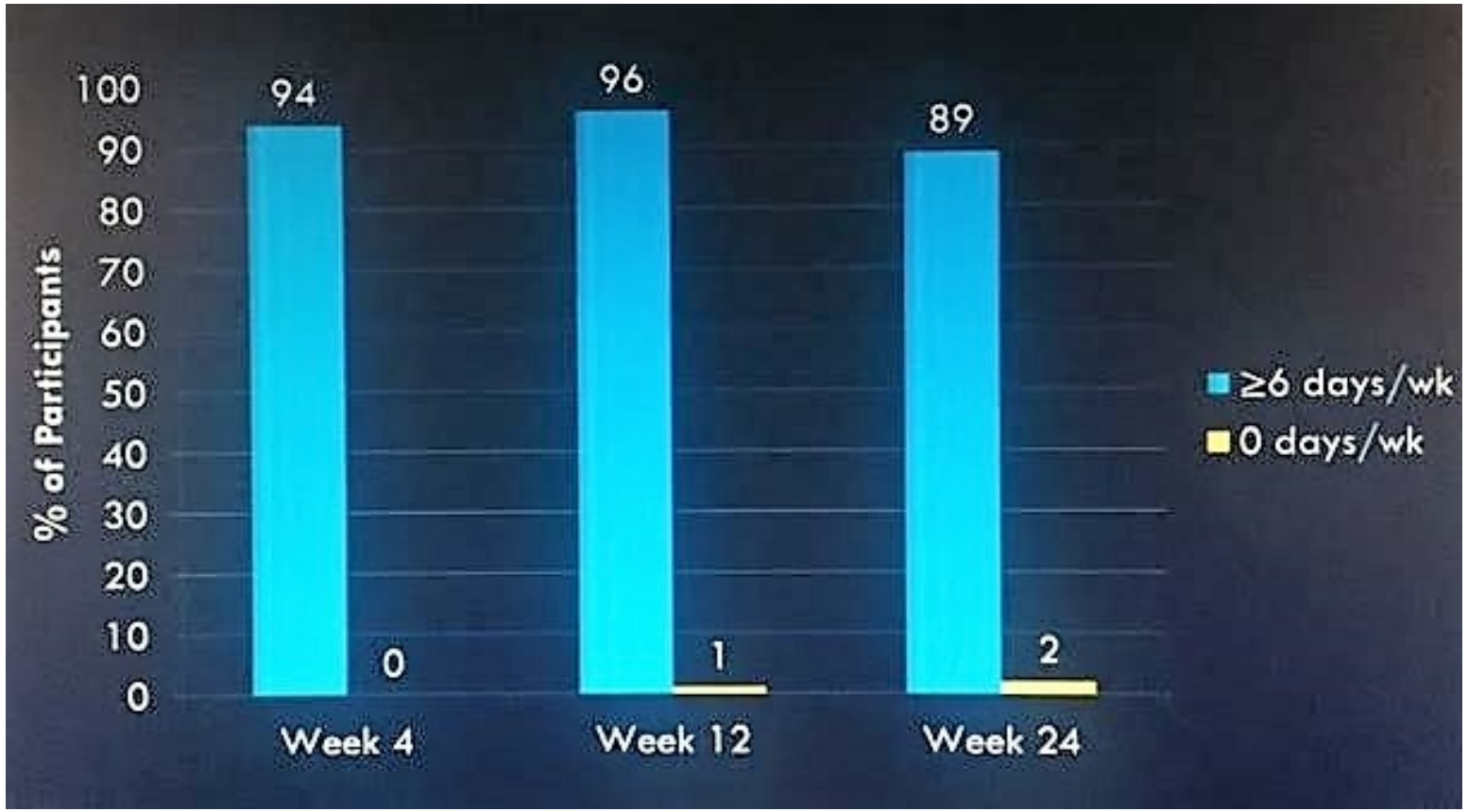
A1c Treatment Group Differences

DIaMonD Study



JAMA published ONLINE January 2017

CGM use ≥6 days/week
DIaMonD Study



JAMA published ONLINE January,24 2017

Results
DIaMonD Study

	CGM	Fingersticks
A1c Reduction	0.9% improvement	0.4% improvement
Time spent < 70 mg/dl	30% improvement (-23 minutes per day)	17% improvement (-15 minutes per day)
Time spent < 50 mg/dl	50% improvement (-11 minutes per day)	21% improvement (-6 minutes per day)
Time spent >180 mg/dl	12% improvement (-83 minutes per day)	1% worse (+9 minutes per day)
Time in range (70-180 mg/dl)	11% improvement (+72 minutes per day)	2% worse (-15 minutes per day)
Glycemic variability	4% reduction	No change

*Hypoglycemia defined as glucose levels <70 mg/dL

JAMA published ONLINE January,24 2017

Conclusion
DIaMonD Study

Significant A1c reduction In patients on MDI compared to control

Increase time-in-range

Reduction in time in “mild and dangerous hypoglycemia

Reduction in glycemic variabiliry

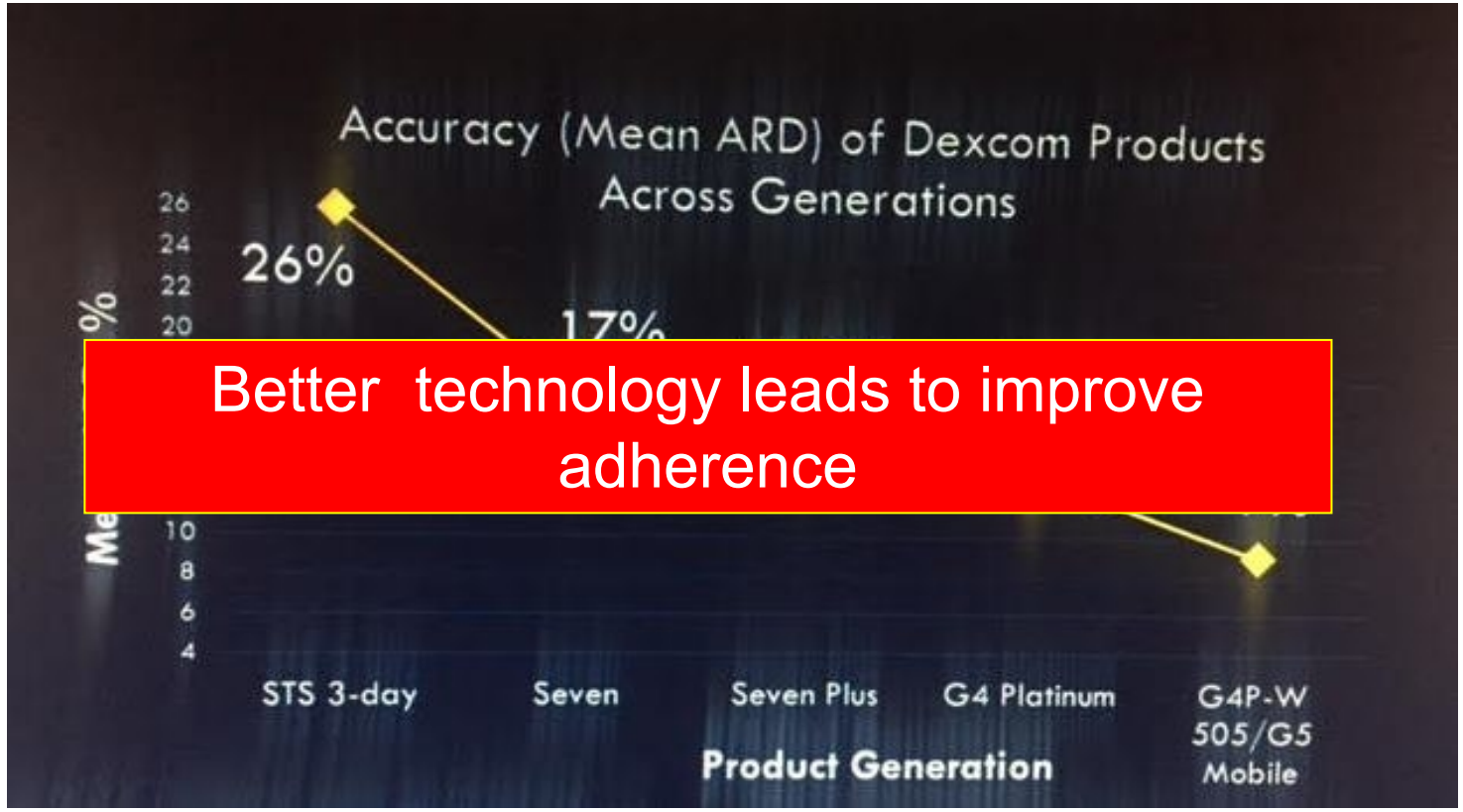
JAMA published ONLINE January,24 2017

Phase 2
DIaMonD Study

- 75 patients from the CGM cohort of Ph. 1 were randomized into pump vs multiple daily injection (MDI) groups and followed for an additional 24 weeks**. Data showed the addition of pumps did not have a statistically significant improvement in A1c** – in fact A1c for the pump+CGM group increased 0.3% vs a 0.1% increase in the CGM+MDI group. Time in range was improved in the pump group.
-

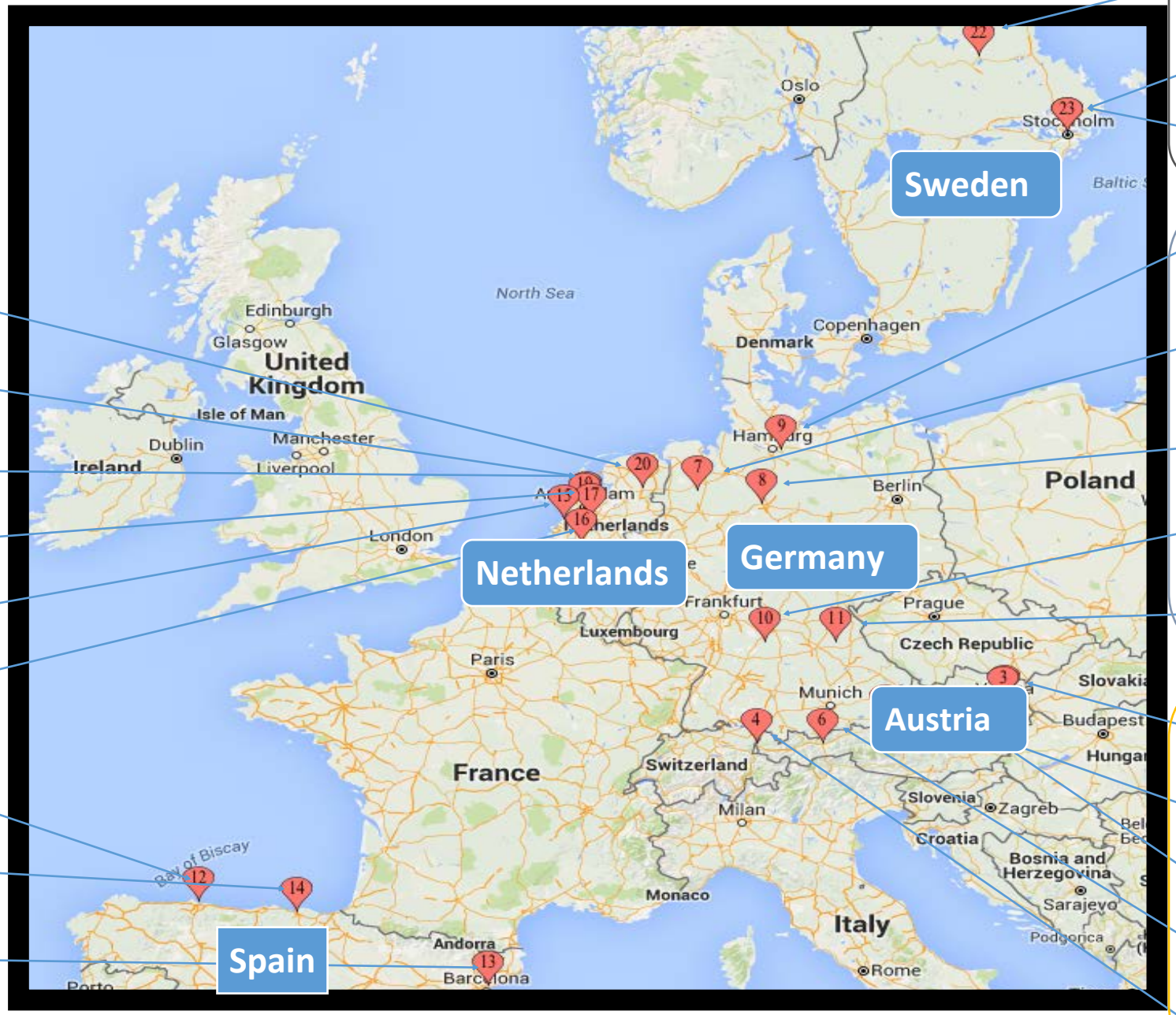
Preliminary data presented at the ATTD meeting in Paris February 2017 by Andrew Ahman

Will the Enhanced Performance of Current CGM Systems Improve Adherence and Outcomes?



Bailey TS, et al. *J Diabetes Sci Technol.* 2015;9:209-214.

Impact Study
Sites 23 in 5 EU countries



- 20. Bethesda Diabetes Research Center, Hoogeveen
- 19. Vanderbilt University Medical Center, Amsterdam
- 18. Onze Lieve Vrouwe Gasthuis, Amsterdam
- 17. St. Antonius, Utrecht
- 15. Medisch Centrum Haaglanden, Den Haag
- 16. Amphia Ziekenhuis, Breda

- 12. Clinica Diabetologica, Gijon
- 14. Hospital Unversitario Cruces, Cruces-Barakaldo
- 13. Hospital Universari Germans Trias i Pujol , Badalona

- 22. Falu Lasarett , Falun
- 23. Karolinska Universitetssjukhuset Huddinge, Stockholm
- 21. Karolinska Universitetssjukhuset Solna, Stockholm

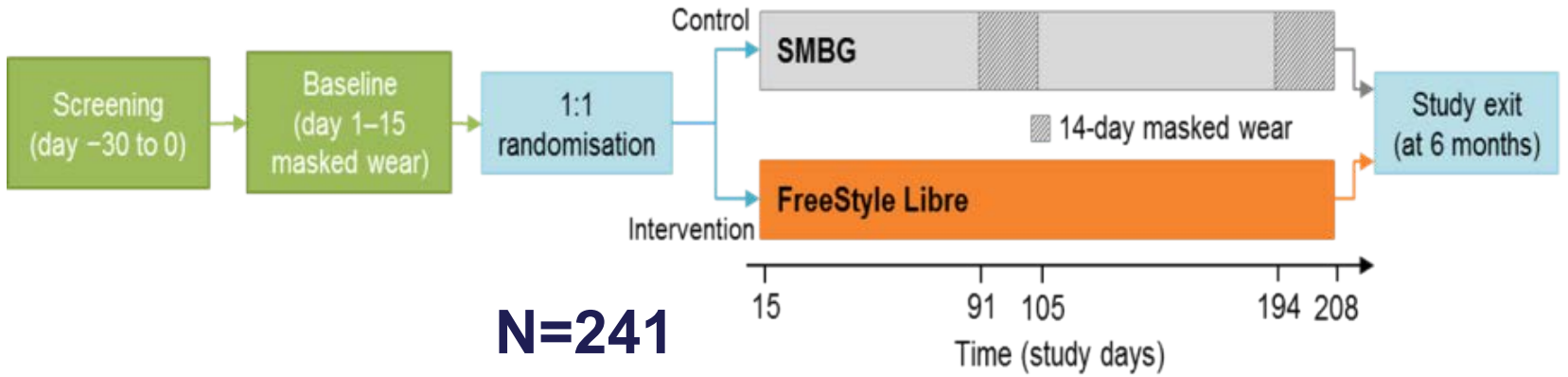
- 9. Zentrum für Diabetologie Hamburg-Bergedorf, Hamburg
- 7. Christliches Krankenhaus Quakenbrück gemeinnützige GmbH, Quakenbrück
- 8. Diabetes- Zentrum Hannover--Nord, Hannover
- 10. Diabetes Zentrum Mergentheim, Bad Mergentheim
- 11. Versdias GmbH, Sulzbach-Rosenberg

- 3. Wilhelminenspital Medizin, Wien
- 1. Diakonissen-Krankenhaus Salzburg
- 2. Medizinische Universität Graz
- 6. Universitätsklinik für Innere Medizin I, Innsbruck
- 4. VIVIT--Institut am Akad. Lehrkrankenhaus Feldkirch

IMPACT STUDY A 6 Month Randomised Controlled Trial

- To evaluate the effectiveness of the FreeStyle Libre system in reducing hypoglycemia compared to SMBG

Study Design



N=241

Primary Study End Point

- Difference in time <3.9 mmol/L (70 mg/dL) from control

Key Secondary End Points

- Number of hypoglycemic events
- Time in hyperglycaemia (>13.3 mmol/L [240 mg/dL])
- Time in Range (3.9-10.0 mmol/L [70-180 mg/dL])
- Patient Reported Outcome measures
- HbA1c
- Glucose Variability
- Number of scans/fingerstick tests per day

Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R
Lancet. 2016 Nov 5;388(10057):2254-2263

Major inclusion and exclusión criteria Impact Study

Inclusion:

- Age ≥ 18 years
- Current insulin regimen ≥ 3 months
- SMBG ≥ 3 times/day
- HbA1c
  - ≤ 58 mmol/mol
  - ≤ 7.5 %

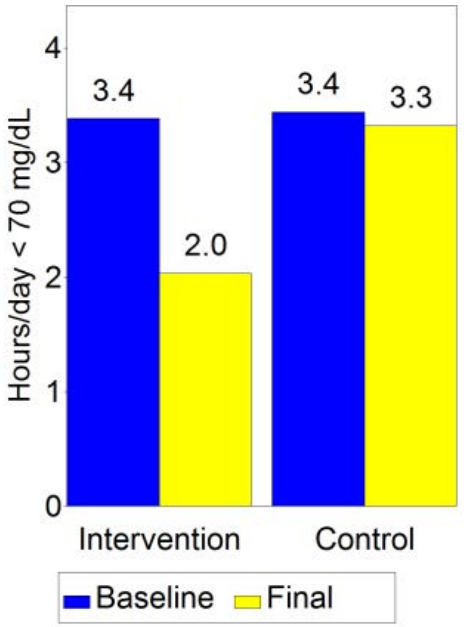
Exclusion:

- Hypoglycemia unawareness
- DKA or MI within preceding 6 months
- Allergy to medical-grade adhesives
- On CGM or Sensor-Augmented Pump Therapy
- Pregnancy

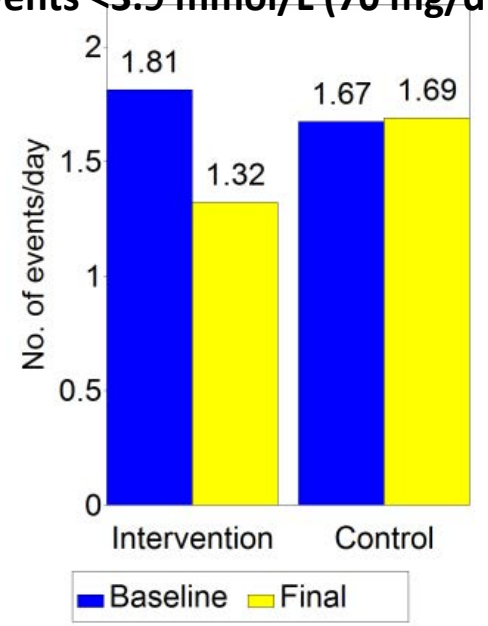
Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R
Lancet. 2016 Nov 5;388(10057):2254-2263

Primary End Point and Hypoglycemia Events Impact Study

Time (hrs/day) <3.9 mmol/L (70 mg/dL)



Events <3.9 mmol/L (70 mg/dL)



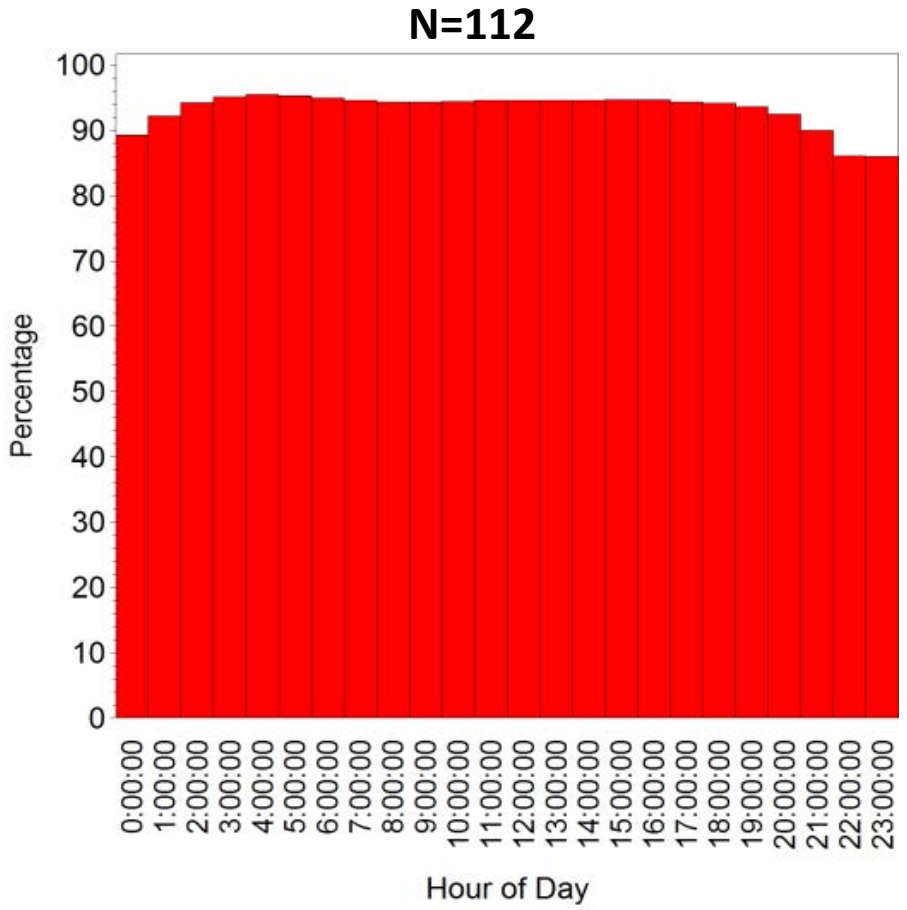
	Difference (vs control) in Change from baseline – Adjusted Mean	Standard Error	p value	Reduction vs. control
Time <3.9 mmol/L (70 mg/dL)	-1.24	±0.24	<0.0001	38%
Events <3.9 mmol/L (70 mg/dL)	-0.45	±0.09	<0.0001	26%

Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser RLancet. 2016 Nov 5;388(10057):2254-2263

CGM use ≥6 days/week Impact Study

Definition: Proportion of available data collected assuming device was worn continuously for 6 months:

- Mean ± SD = 92.8% ± 7.3%
- Median = 95.2%
- 6.5 days per week



Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Lancet. 2016 Nov 5;388(10057):2254-2263

Hypoglycemia and A1c Impact Study

Time in hypoglycemia (<3.9 mmol/L, 70 mg/dL) was significantly reduced (p<0.0001)

by 1.24 ± 0.24 hrs/day

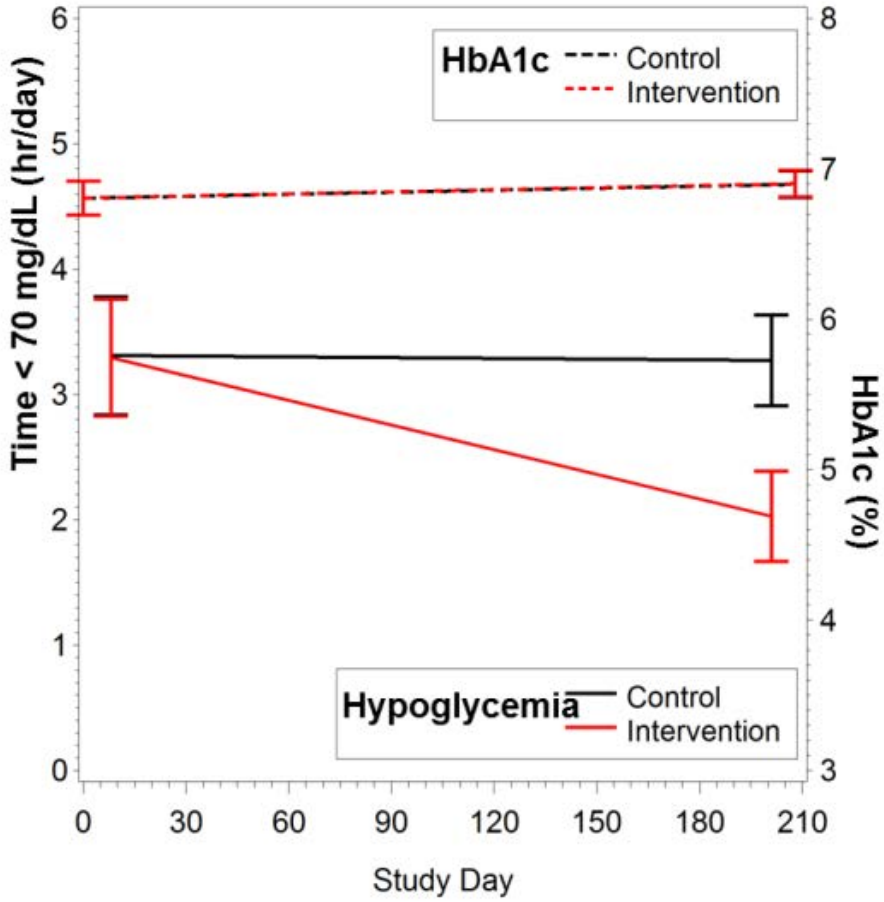
(adjusted mean ± standard error)

38% reduction compared to control

There was no significant change in HbA1c (%) between intervention and control

I: 6.79 + 0.52 → 6.94 + 0.65

C: 6.78 + 0.64 → 6.95 + 0.56



Mean values, error bars are 95% confidence intervals

Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R Lancet. 2016 Nov 5;388(10057):2254-2263

Impact Summary

- -Gran aumento de la frecuencia de la medición de glucosa
- -Reducción importante de las hipoglucemias tanto en tiempo con en numero y además igualmente por el dia que por la noche
- -Reducción del tiempo en hiperglucemia
- - Aumento del tiempo en objetivo
- -Reducción de la variabilidad glucémica
- - NO subidas de las glucemias medias del sensor ni de la A1c
- -Mejoria en la calidad de vida

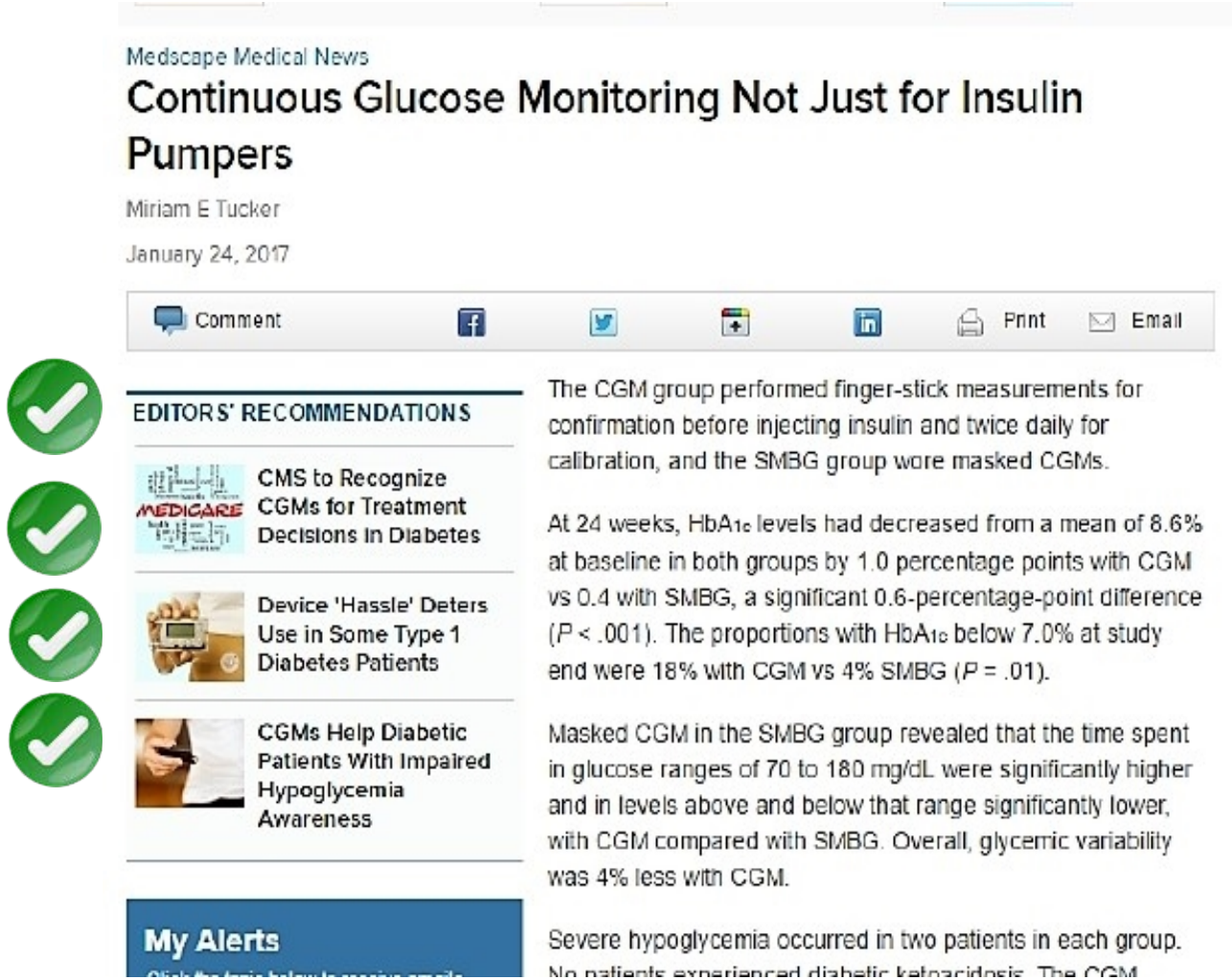
Conclusion
IMPACT Study

En pacientes adultos con T1D y **buen control de glucemia** el uso del sistema FSL puede sustituir al sistema convencional de autocontrol sanguineo,consiguiendo una mayor reducción del tiempo y numero de hipoglucemias,sin aumento de la A1c y con mejora de la calidad de vida

Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R
Lancet. 2016 Nov 5;388(10057):2254-2263

Evidencias de que la MCG es la primera opción para aquellos pacientes T1D que no logran el control

JDRF
Tuminia
Comisair Study
DIaMonD Study



Medscape Medical News

Continuous Glucose Monitoring Not Just for Insulin Pumpers

Miriam E Tucker

January 24, 2017

Comment Print Email

EDITORS' RECOMMENDATIONS

CMS to Recognize CGMs for Treatment Decisions in Diabetes

Device 'Hassle' Deters Use in Some Type 1 Diabetes Patients

CGMs Help Diabetic Patients With Impaired Hypoglycemia Awareness

My Alerts

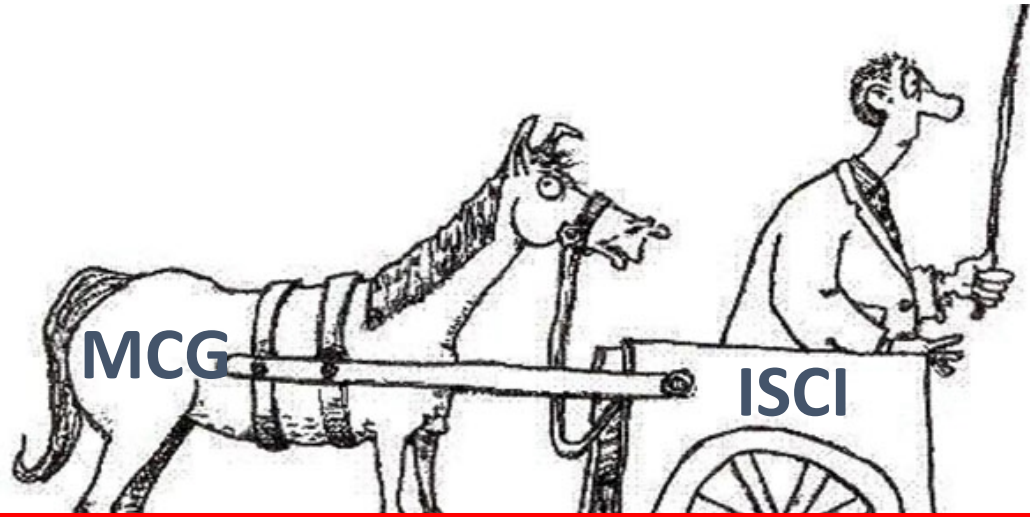
The CGM group performed finger-stick measurements for confirmation before injecting insulin and twice daily for calibration, and the SMBG group wore masked CGMs.

At 24 weeks, HbA_{1c} levels had decreased from a mean of 8.6% at baseline in both groups by 1.0 percentage points with CGM vs 0.4 with SMBG, a significant 0.6-percentage-point difference ($P < .001$). The proportions with HbA_{1c} below 7.0% at study end were 18% with CGM vs 4% SMBG ($P = .01$).

Masked CGM in the SMBG group revealed that the time spent in glucose ranges of 70 to 180 mg/dL were significantly higher and in levels above and below that range significantly lower, with CGM compared with SMBG. Overall, glycemic variability was 4% less with CGM.

Severe hypoglycemia occurred in two patients in each group.

¿Poner la bomba de insulina antes que la MCG en 2017 ?



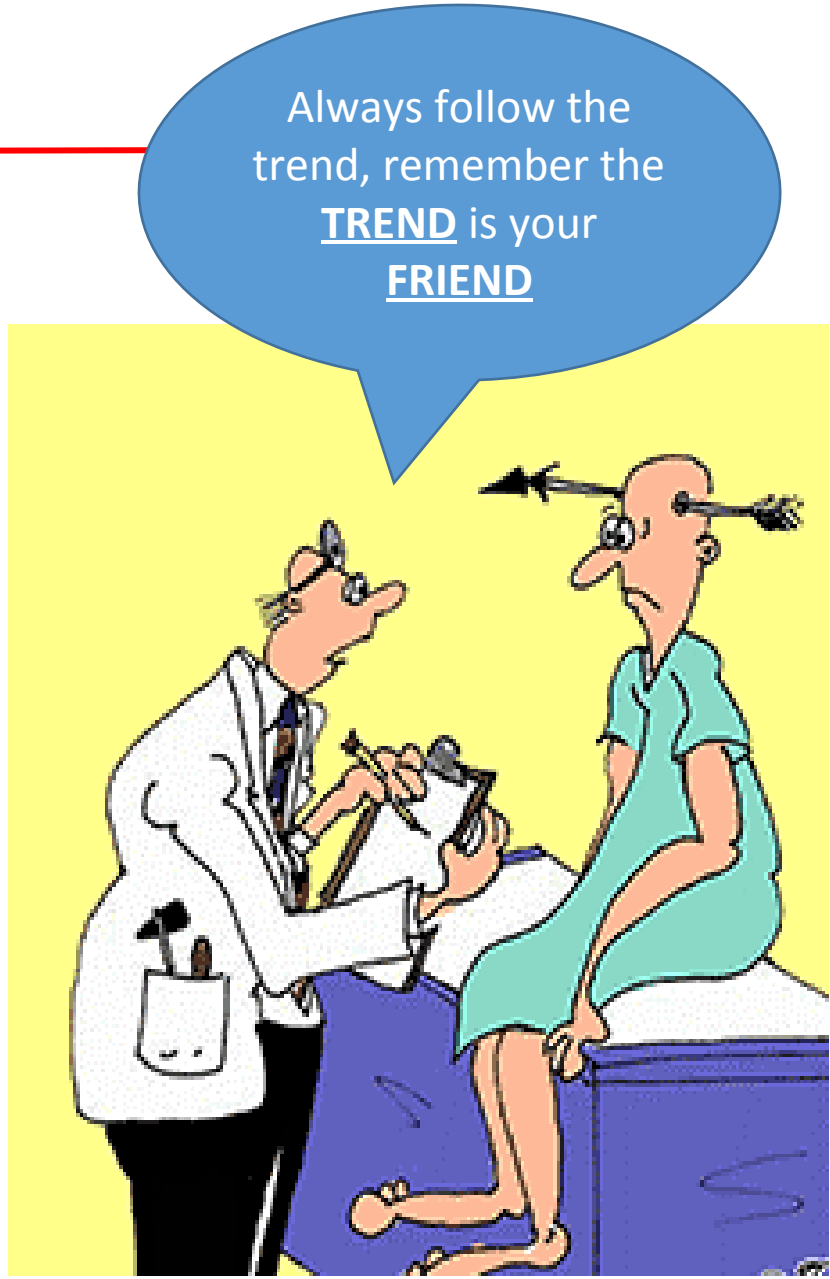
2016 AACE/ACE Position Statement, recomendaba con un **“alto nivel de evidencia” la MCG para todos los pacientes con diabetes tipo 1 mientras que** las ventajas de **las bombas de insulina sobre las multidosis de insulina ,obtuvieron un “bajo nivel de evidencia” científica**

CGM Take Home Message

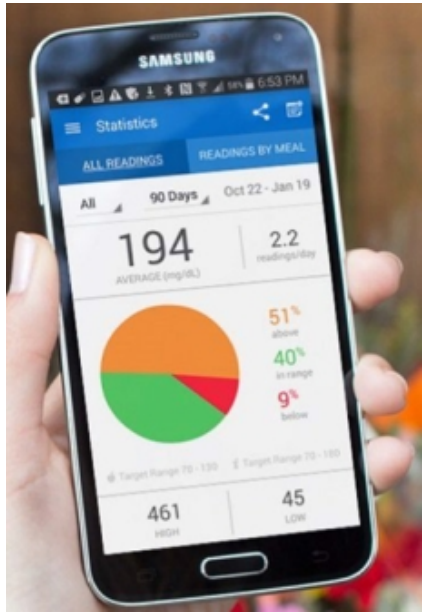
1 Decreases in A1c and hypoglycemia are primarely due to CGM

2 Everyday insulin decisions are made based on glucose data

3 Good glucose data,including speed and direction of glucose change,should come BEFORE insulin delivery decisions



Mientras se logra la universalización de la la MCG Aprovechemos la tecnología que YA tenemos



Sin Coste añadido.
Ya para todos.

SMARTMETER: Glucómetros inalámbricos,

en Diabetes, mejor conectados

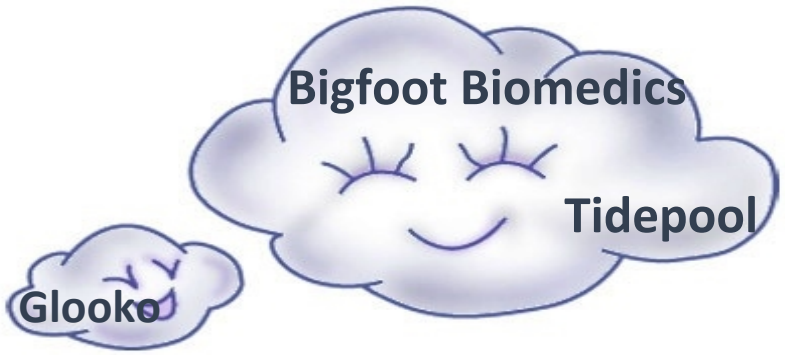
Glucose Monitoring, Looking Forward in this *"awesome"* new CGM Era

Improvements in progress:

- Glucose data-sharing via the Internet- just began
- Use of additional displays (different alarms, and pre-alarms)
- Improved usability ,more user friendly devices like **skin patch that detects low blood sugar and automatically delivers glucagon or l**ong term fully Implanted glucose sensor with a very long duration or low cost wifi CGM systems like Band-Aid CGM

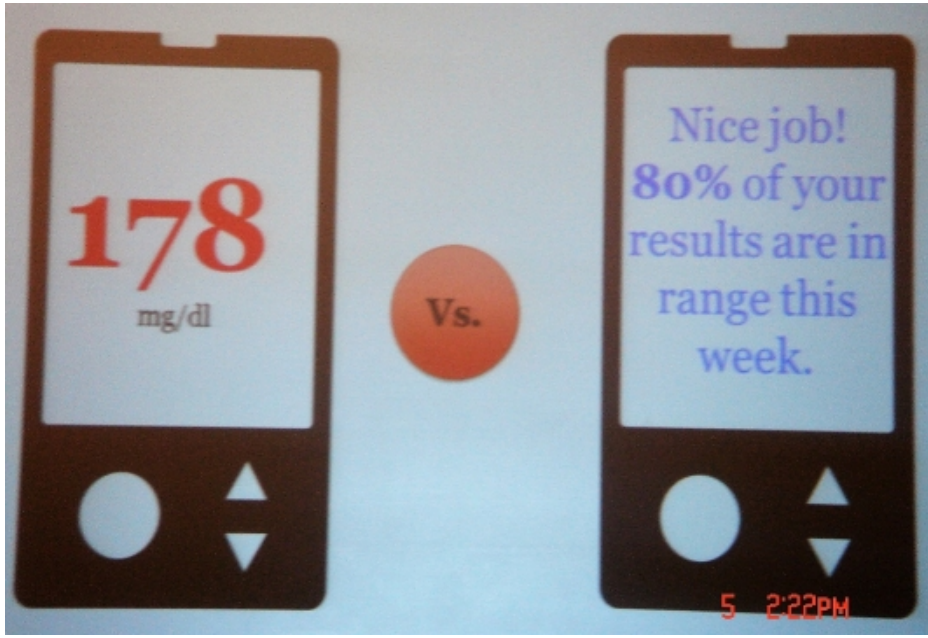
Parnership and collaborations to transform “Diabetes Digital Health” in progress

IBM-Watson Health-Medtronic-Novonordisk
Watson Health-Glooko-Novonordisk
Verily-Qualcom-Dexcom-Sanofi

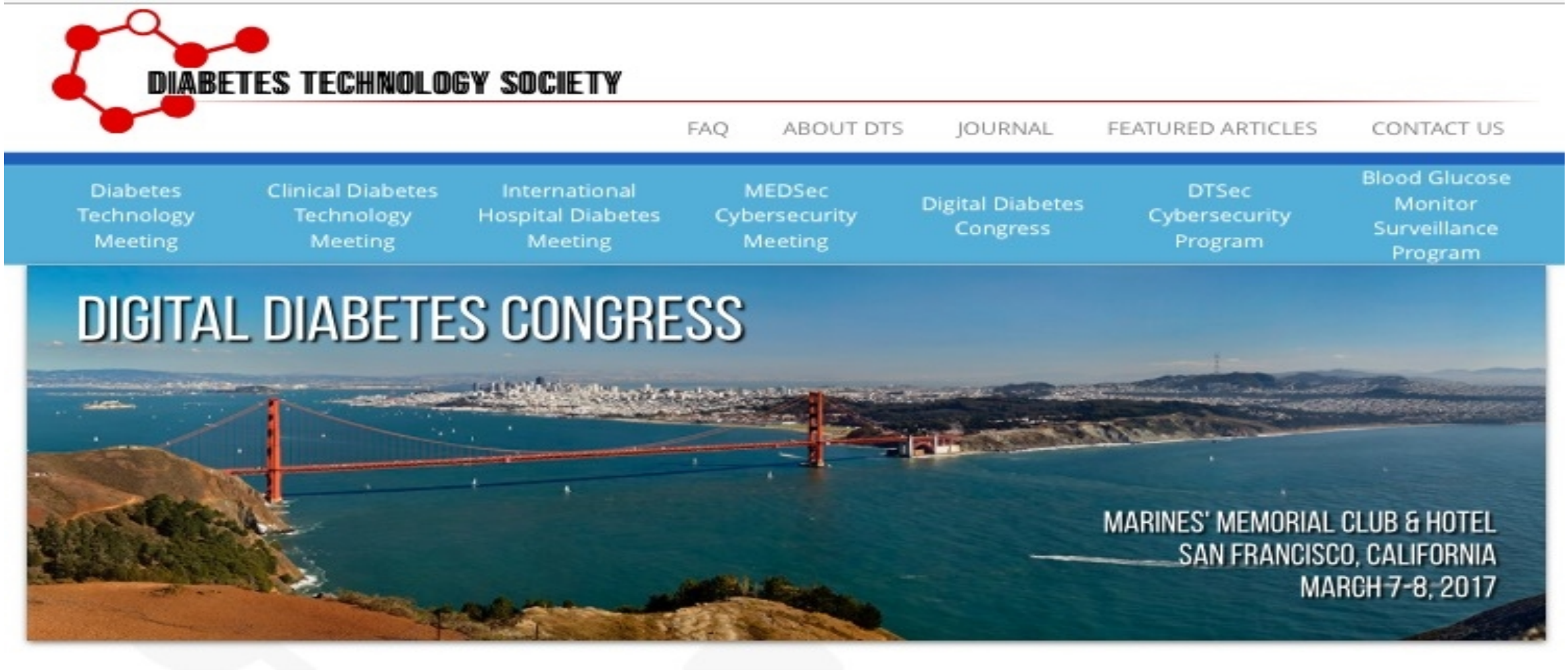


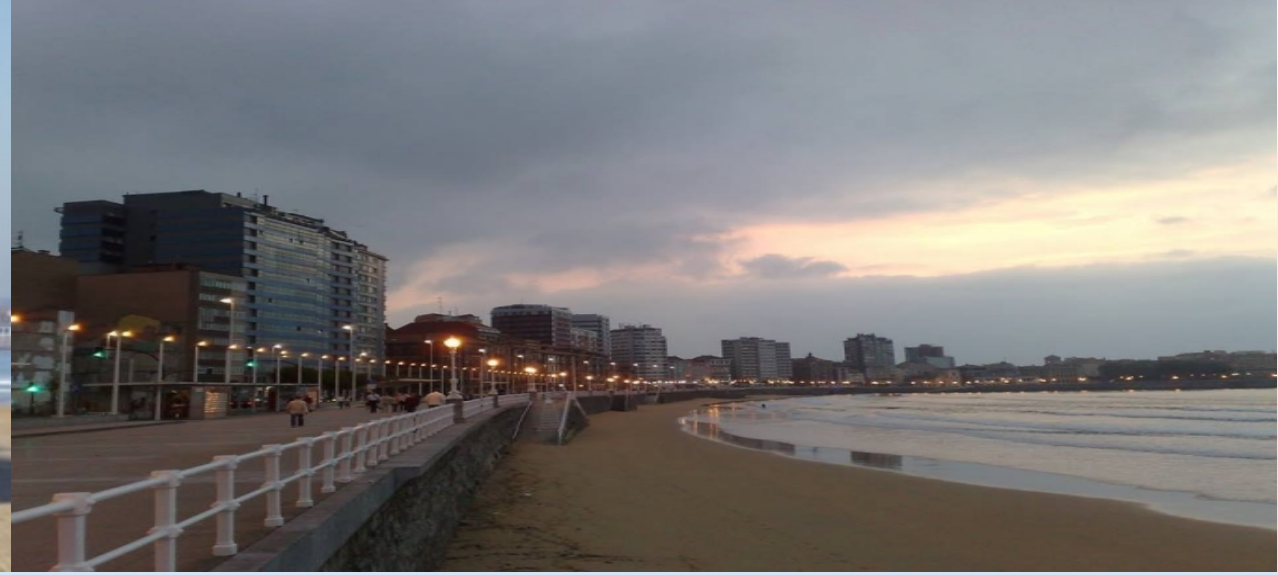
Standardized integration and connectivity using multiple data inputs CGMs, bluetooh insulin pens,pumps will allow **“a CGM smartloop automated “insulin delivery service” with, the use of Artificial Inteligence**
will make able receving not only insulin adjustment recommendations but **also empowering messages** to make it **FUN and ADDICTIVE**

All the new CGM developments and new studies may broaden the appeal and applicability of CGM in T1D an T2D but cost will be always a challenge



Digital -connected-health has arrived and will change all the landscape of way diabetes will be managed





· Gracias por su atención

ramiro.antuna@clinidiabet.com