Emanuele Bosi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Abbott
- Roche
- Takeda
- Novartis
- Astra Zeneca
- Medtronic
- Sanofi
- MSD
- Lifescan

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

24° Congresso Interassociativo AMD-SID Lombardia 2018
Coccaglio (BS), Hotel Touring, 27 Ottobre 2018

Al di là dell'emoglobina glicata: l'interpretazione dei dati

Emanuele Bosi

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Ospedale San Raffaele, Università Vita Salute San Raffaele, Milano

OSPEDALE SAN RAFFAELE

DIABETES RESEARCH INSTITUTE

UNIVERSITÀ VITA-SALUTE SAN RAFFAELE
UniSR
QUID EST HOMO?

Hyperglycemia and diabetes

Hyperglycemia is:

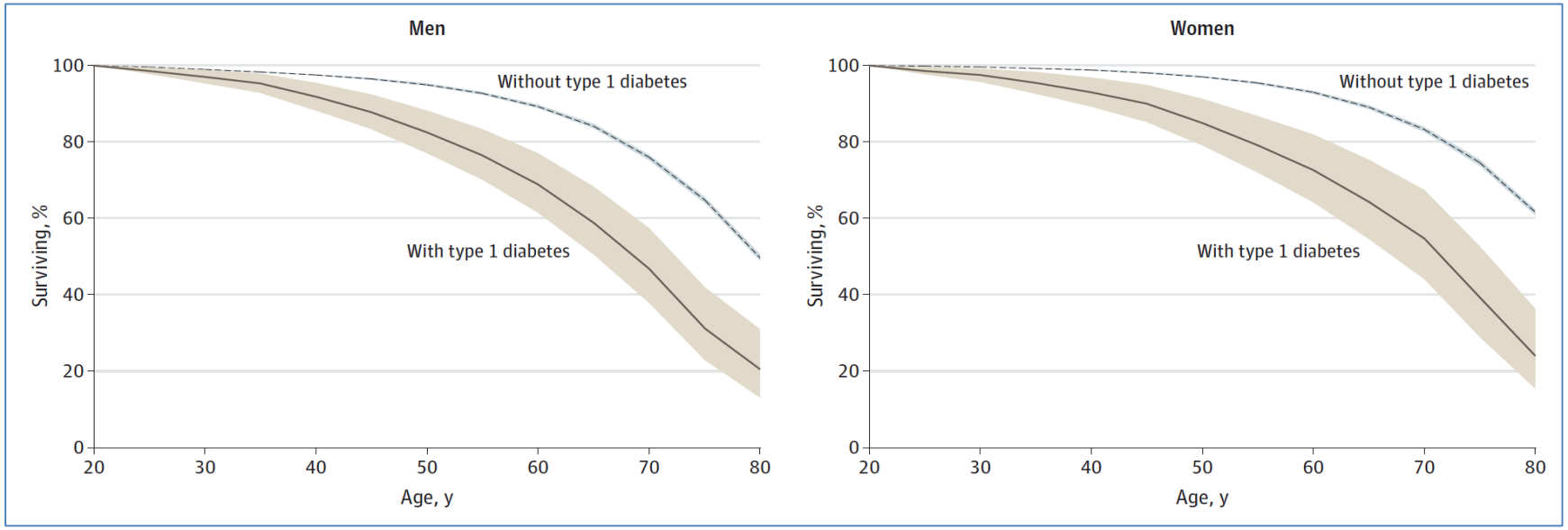
- the hallmark of all forms of diabetes, including the most common type 1 (T1D) and type 2 (T2D);
- the pathogenetic determinant of diabetes-specific microvascular disease retinopathy, nephropathy and neuropathy;
- a major risk factor for cardiovascular diseases (CVD), including myocardial infarction, stroke and limb ischemia, associated with diabetes

Glucose control and diabetes complications

- Landmark intervention trials, such as the DCCT/EDIC in T1D and the UKPDS in T2D have demonstrated that intensive therapy, aiming at correcting, or at least mitigating hyperglycaemia (as measured by HbA1c), is effective in preventing or delaying microvascular complications;
- The effect of glucose control on reducing CVD risk is less obvious and requires a longer time to become assessable .

However,
we still have a problem

Percentage Surviving by Age Among Those With Type 1 Diabetes Compared With the General Population Without Type 1 Diabetes



Estimated life expectancy for patients with type 1 diabetes in Scotland based on data from 2008 through 2010 indicated a loss of subsequent life expectancy at age 20 years of approximately 11 years for men and 13 years for women compared with the general population without type 1 diabetes.

Livingstone SJ et al. JAMA. 2015;313:37-44

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

Marcus Lind, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D., Soffia Gudbjörnsdottir, M.D., Ph.D., Aldina Pivodic, M.Sc., Hans Wedel, Ph.D., Sofia Dahlqvist, Mark Clements, M.D., Ph.D., and Annika Rosengren, M.D., Ph.D.

CONCLUSIONS

In our registry-based observational study, patients with type 1 diabetes and HbA1c ≤6.9% had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls.

N Engl J Med 2014;371:1972-82.

Adjusted Hazard Ratios for Death in Patients with Type 1 Diabetes versus Controls, According to HbA1c

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)

N Engl J Med 2014;371:1972-82.

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N Engl J Med 2014; 371:1972-1982.

INTERPRETATION

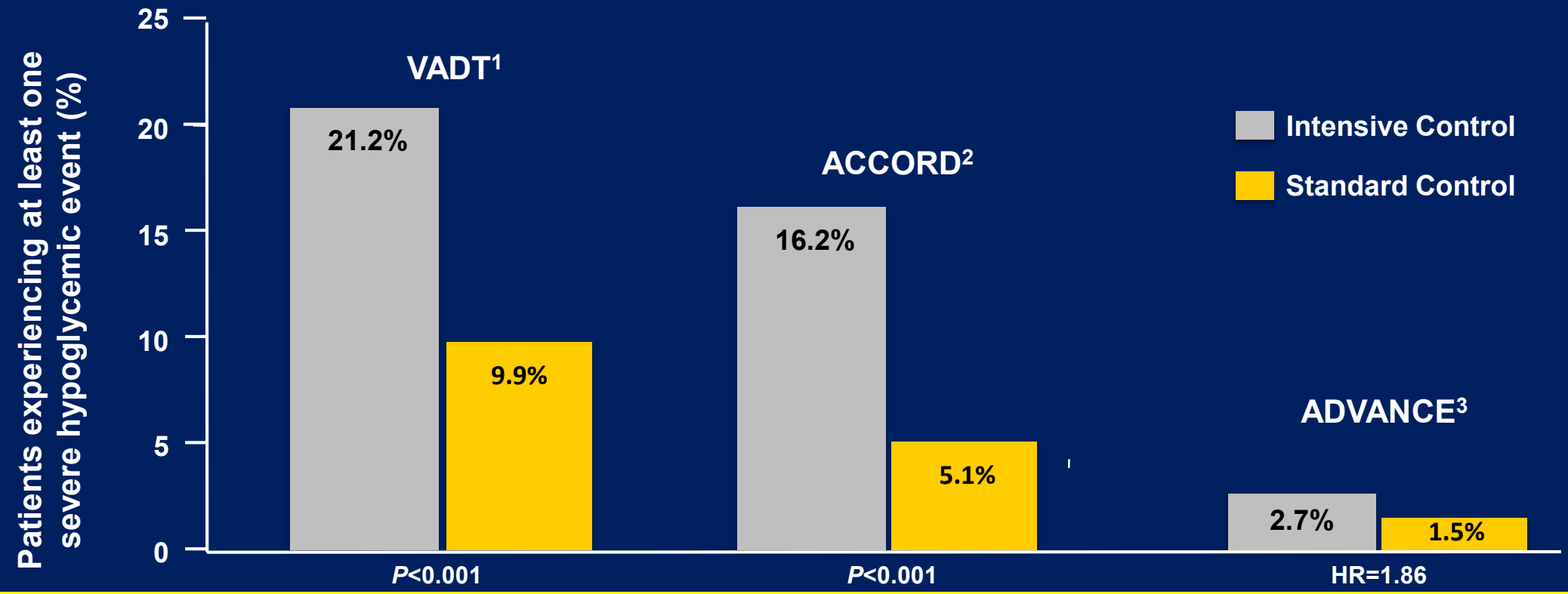
Since type 1 diabetes is a model of pure hyperglycaemic disease, with no or marginal contribution by obesity, hypertension and dyslipidemia typical of type 2, the increased risks of death in patients who have good glycemic control seems, at a first glance, unexplained.

Dissecting HbA1c in patients with diabetes

The different kinds and facets of hyper/dysglycaemia:

- average glucose (HbA1c):
  - fasting glucose;
  - post prandial glucose;
- hyperglycemic peaks;
- hypoglycemia
- glucose variability.

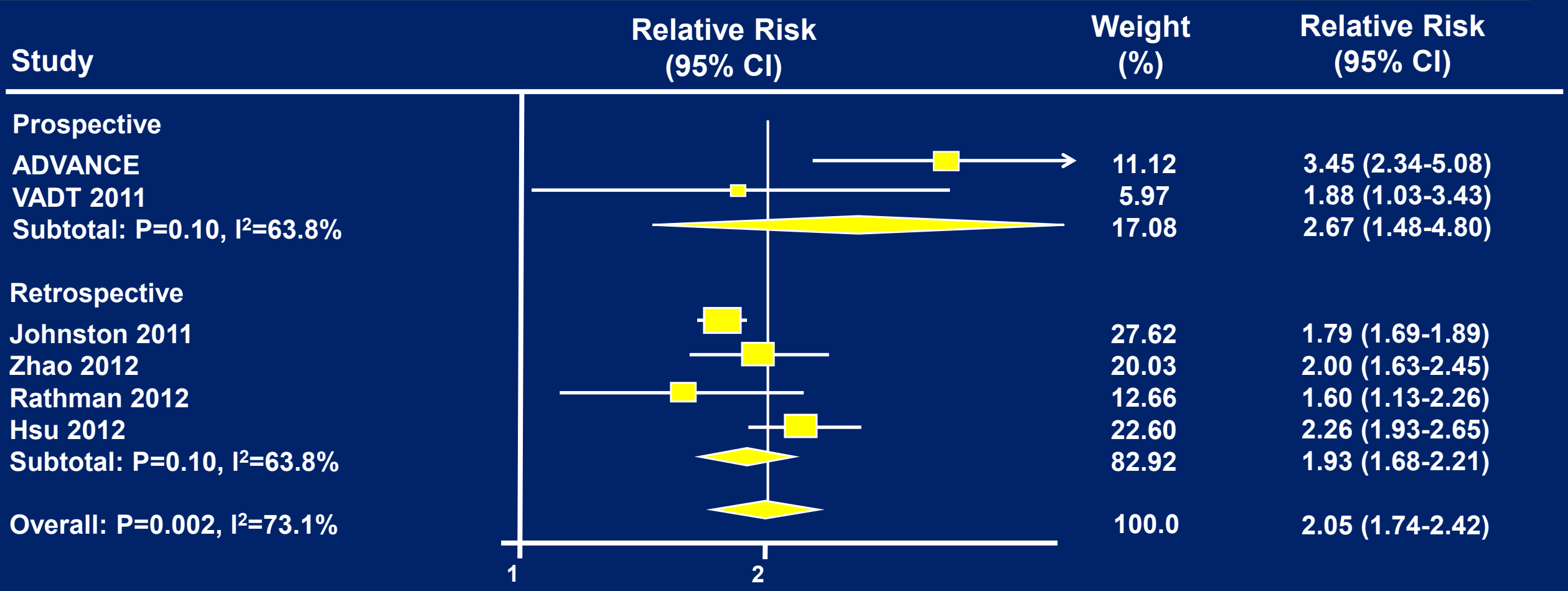
Severe hypoglycaemic events in ACCORD, ADVANCE and VADT



In all three trials an episode of severe hypoglycemia was associated with an increased risk of subsequent mortality

1. *VADT Investigators. N Engl J Med. 2009;360:129-139.* ***2.*** *Bonds DE, et al, BMJ. 2010;340:b4909.* ***3***. *ADVANCE Study Group. N Engl J Med. 2008;358(24):2560-2572.*

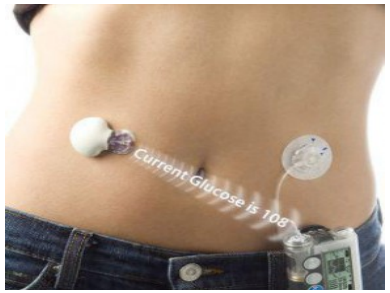
Meta-analysis of studies on severe hypoglycemia and CVD

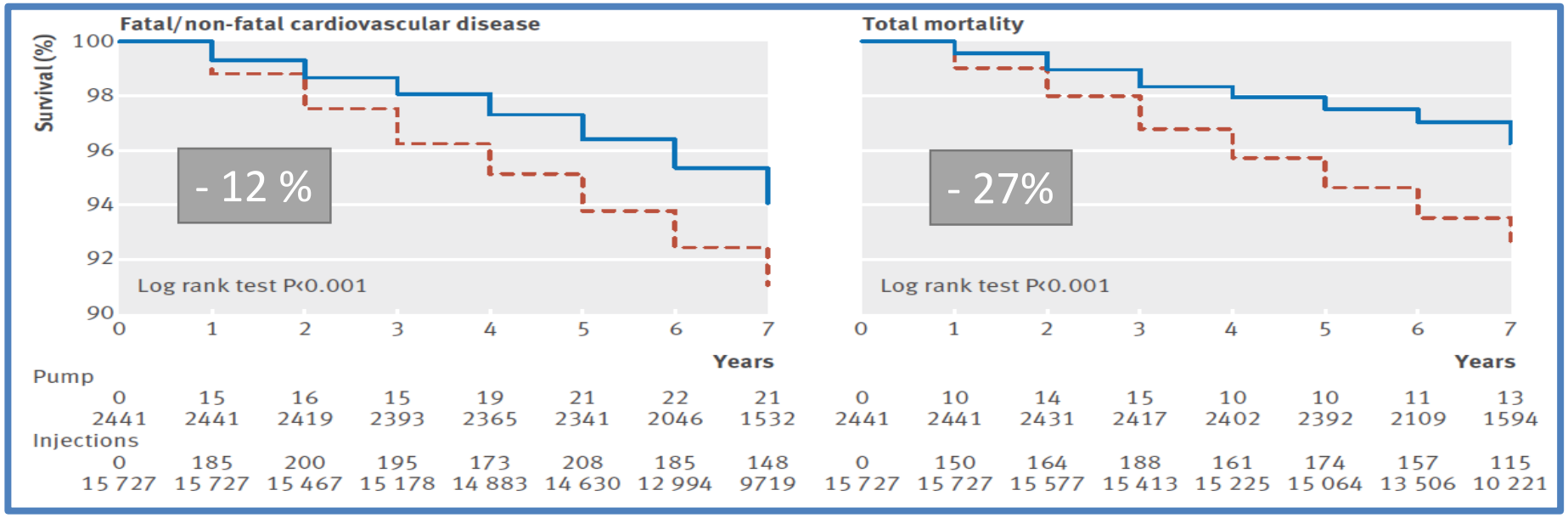


Severe hypoglycemia is associated with a higher risk of CVD (~2 fold)

Goto A et al. BMJ. 347:f4533, 2013.

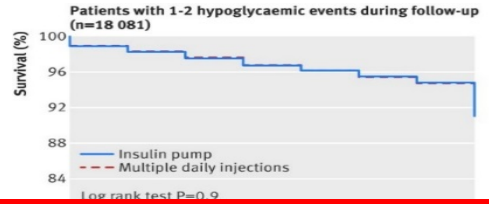
Insulin pump therapy, multiple daily injections, and cardiovascular mortality in type 1 diabetes: The Swedish National Diabetes Register





Steineck I et al., BMJ 2015;350:h3234

Insulin pump therapy, multiple daily injections, and cardiovascular mortality in type 1 diabetes: The Swedish National Diabetes Register



Reduced number of severe hypoglycaemic episodes in pump

Message: reducing hypoglycemia, in addition to overall good glucose control (i.e. HbA1c), improves survival in type 1 diabetes

Steineck I et al., BMJ 2015;350:h3234

Hypoglycemia in type 1 diabetes

Hypoglycemia is the most serious and threatening complication of insulin therapy.

In type 1 diabetes:

- acute hypoglycemia can lead to loss of consciousness, seizures and even death[1];
- recurrent hypoglycemia is responsible for hypoglycemia unawareness and associated autonomic failure[1];
- on the long term, hypoglycemia is a risk factor for cardiovascular diseases[2], the major determinant of reduced life expectancy of people with type 1 diabetes[3];
- on the long term, hypoglycemia may affect cognitive functions and brain structure[4];
- hypoglycemia and fear of hypoglycemia have a significant impact on quality of life, mood and activities of daily living[5].

[1]Seaquist ER et al. Diabetes Care. 2013;36:1384-95

[2]Lung TW et al. Diabetes Care 2014;37:2974-81

[3]Lind M et al. N Engl J Med 2014;371:1972-82

[4]Bednarik P et al. Front Neurosci. 2017 Sep 25;11:529

[5]Davis RE e al. Curr Med Res Opin. 2005;21:1477-83.

Relevance of glucose control for CVD in diabetes

Evidence:

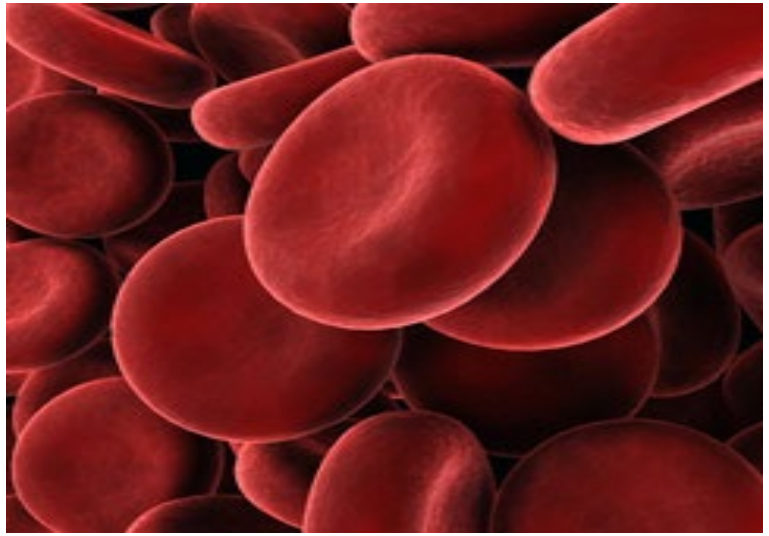
- Both in type 1 and type 2 diabetes, hypoglycaemia may counterbalance the potential benefit of intensive glucose control;

Actions:

1) therapeutic approaches with lower risk of hypoglycaemia: new insulin analogues and pumps in type 1; new drugs (DPP-4i, SGLT-2i, GLP-1) in type 2;

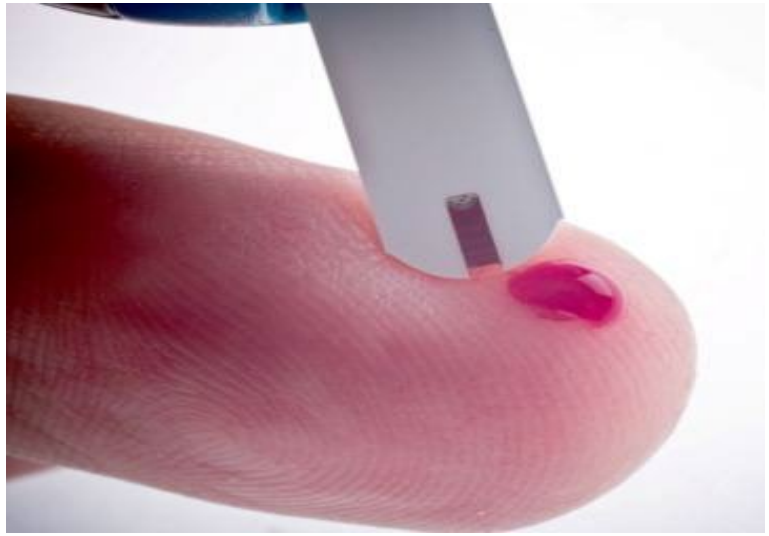
2) Improvement of glucose monitoring in patients with diabetes.

How can we monitor glucose in patients with diabetes?



HbA1c

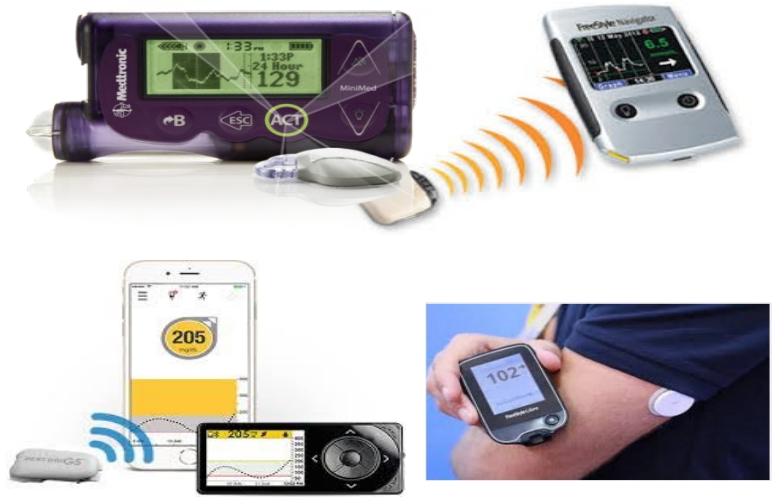
Global glycaemic control



SMBG

Unstructured (random)
Structured

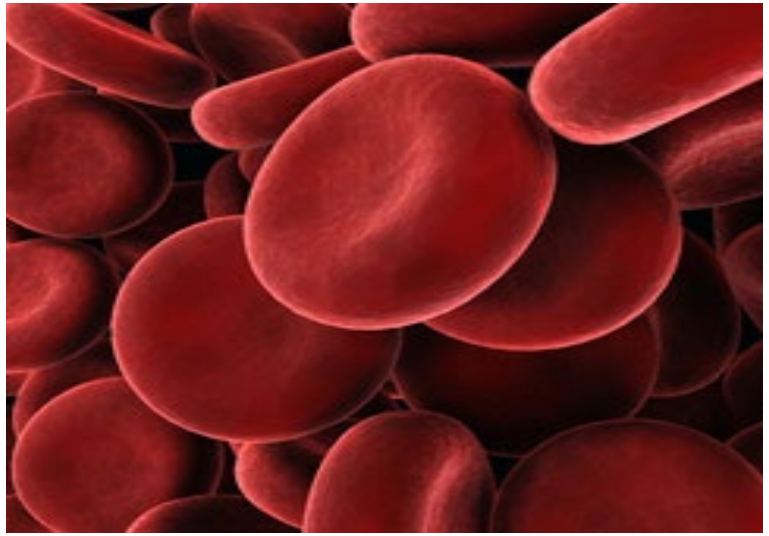
Daily self management



CGM & FGM

Daily self management

How can we monitor glucose in patients with diabetes?



HbA1c

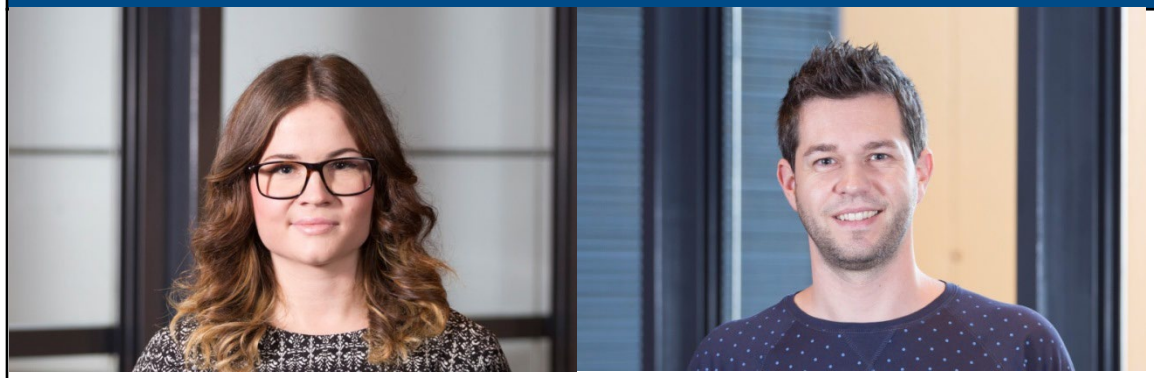
Global glycaemic control

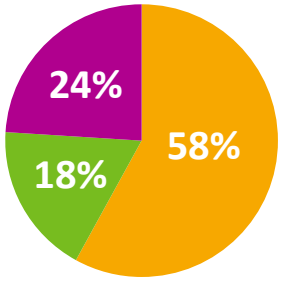
HbA1c: adequacies and inadequacies

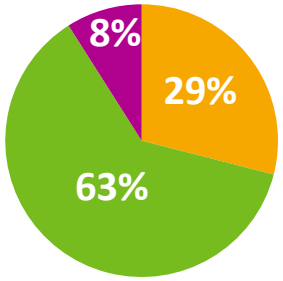
- integrated measure of mean blood glucose over the previous 2-3 months;
- the most important marker of glucose control, commonly used to judge and correct diabetes treatment;
- established relationship with average glucose, with some caveats;
- predictor of long term microvascular and macrovascular complications;
- as sole marker of glucose control, insufficient for long term prognosis.

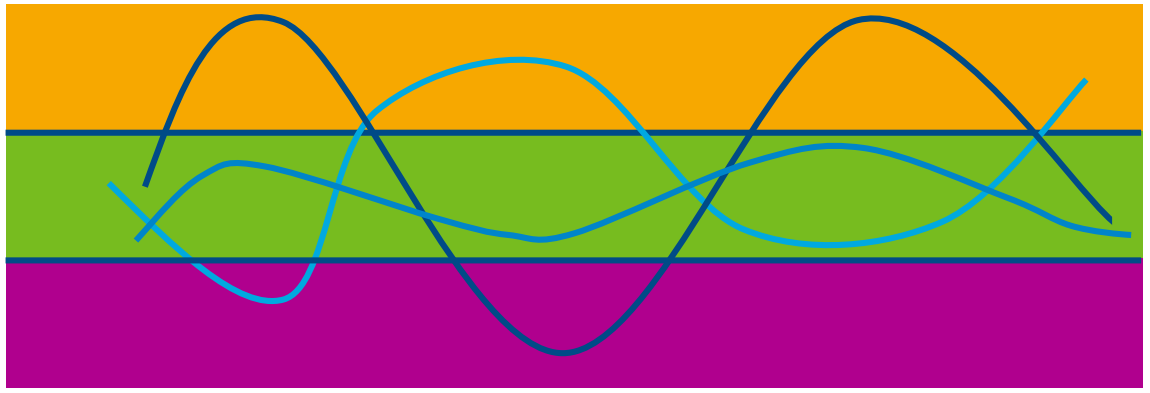
THE MANY FACES OF HBA1C

The many faces of a HbA1c of 7%









>180 mg/dL (10 mmol/L)

70 - 180 mg/dL (3.9 - 10 mmol/L)

<70 mg/dL (3.8 mmol/L)

The limitation of HbA1c is now part of the Standards of Care 2018 of the ADA

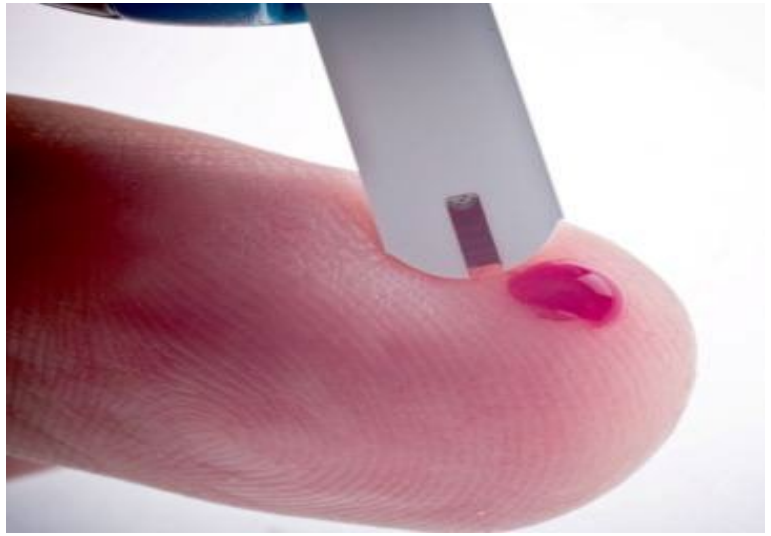
6. Glycemic Targets: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

Diabetes Care 2018;41(Suppl. 1):S55–S64 | https://doi.org/10.2337/dc18-S006

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially patients with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from A1C and SMBG or CGM.

How can we monitor glucose in patients with diabetes?



SMBG

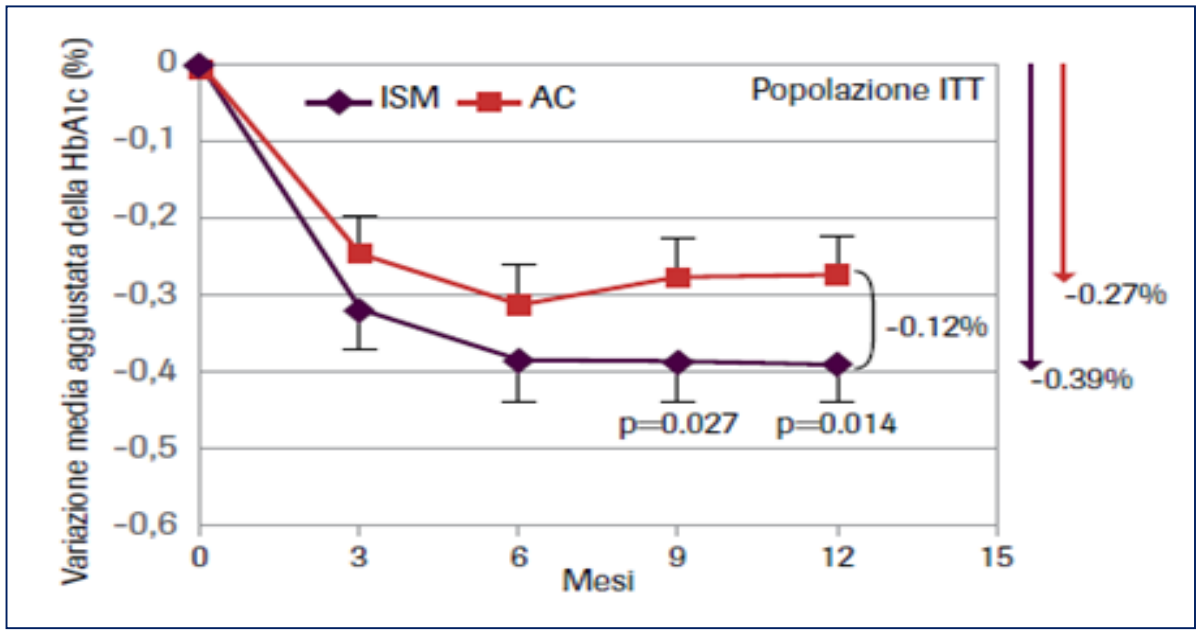
Unstructured (random)
Structured

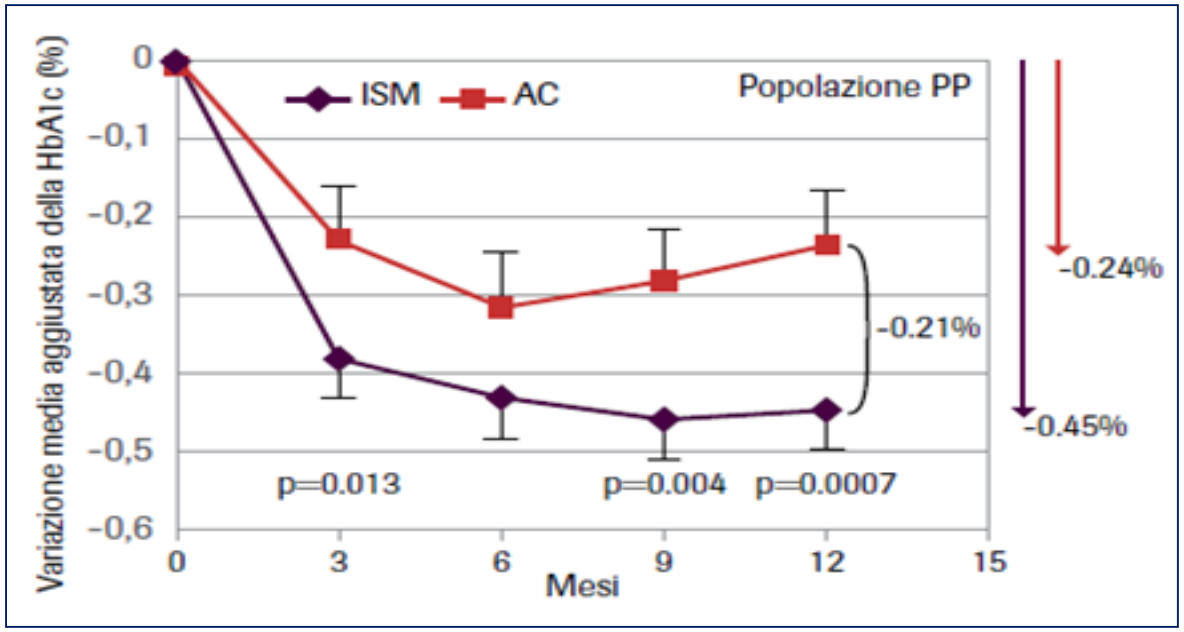
Daily self management

SMBG: adequacies and inadequacies

- integral component of diabetes care, provides information on fasting and post-prandial glucose, symptomatic and asymptomatic hypoglycemia and glucose excursions related to medications and lifestyle change;
- need for structured approaches, in timing and frequency, of glucose reports and analysis, incorporating educational and therapeutic components;
- remains a point measurement, needs puncturing fingers several times a day, can be painful, difficult to perform for some people, potentially associated with risk of infection and blood dissemination.

Structured vs unstructured SMBG in T2D not treated with insulin: change in HbA1c





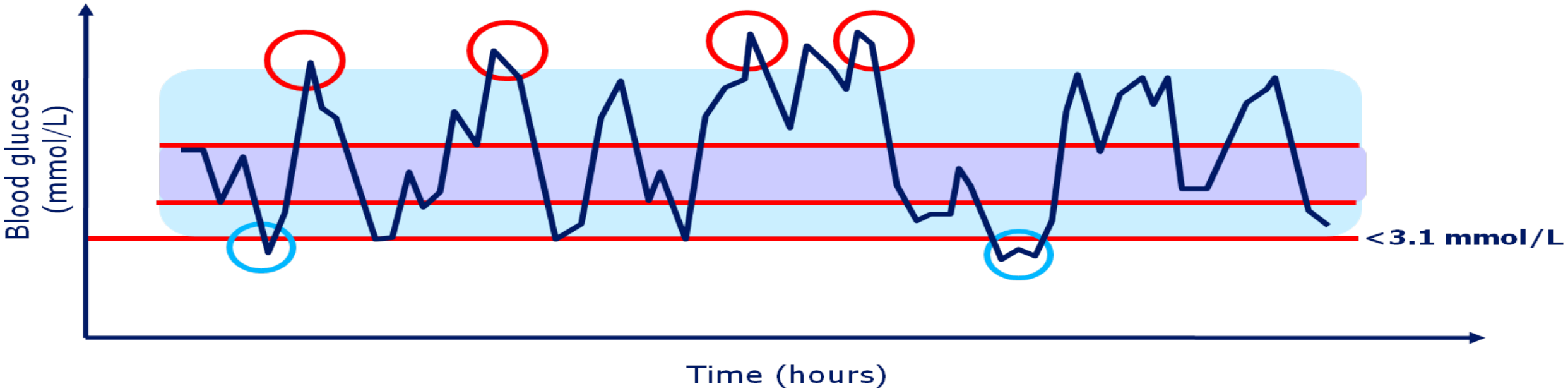
Data are Least Square Means ± Standard Error

Adjusted for baseline HbA1c, center and diabetes treatment at baseline

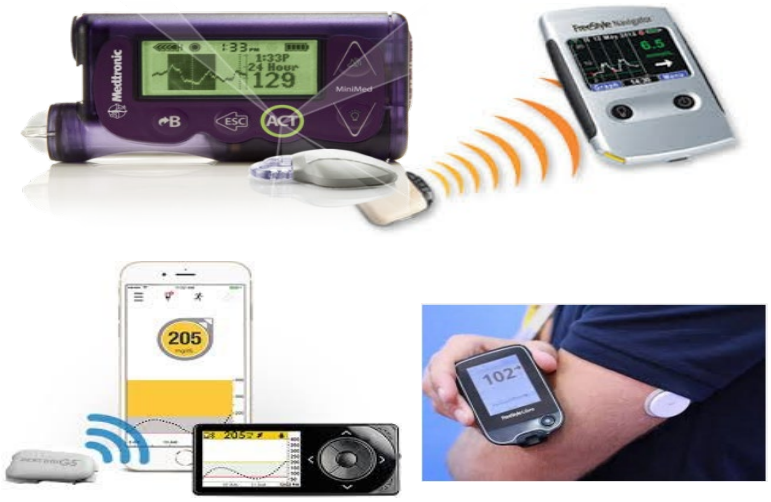
Bosi E et al. Diabetes Care 2013;36:2887-94

Introducing glucose variability and the way to detect it: SMBG and CGM

- Hypoglycaemic events
- Postprandial glucose excursions and hyperglycemic peaks
- Minor fluctuations in blood glucose levels



How can we monitor glucose in patients with diabetes?



CGM & FGM

Daily self management

CGM & FGM: adequacies and inadequacies

- Wearable and Real Time Continuous Glucose Monitoring (CGM) represent the most advanced systems of glucose measurement;
- The ability of detecting hyperglycemic peaks, hypoglycemic events and glucose fluctuations is enormously improved by the use of CGM;
- The efficacy in improving the overall glucose control has been demonstrated, although many more studies are needed to fully elucidate the potential of these systems on patient outcomes and quality of life;
- The cost-effectiveness and psychological impact are also to be evaluated.

FGM in prospective RCTs:
The IMPACT and REPLACE Studies

Type 1 Patients: IMPACT


THE LANCET

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

Lancet. 2016 Nov 5;388(10057):2254-2263

Type 2 Patients: REPLACE


Diabetes Therapy

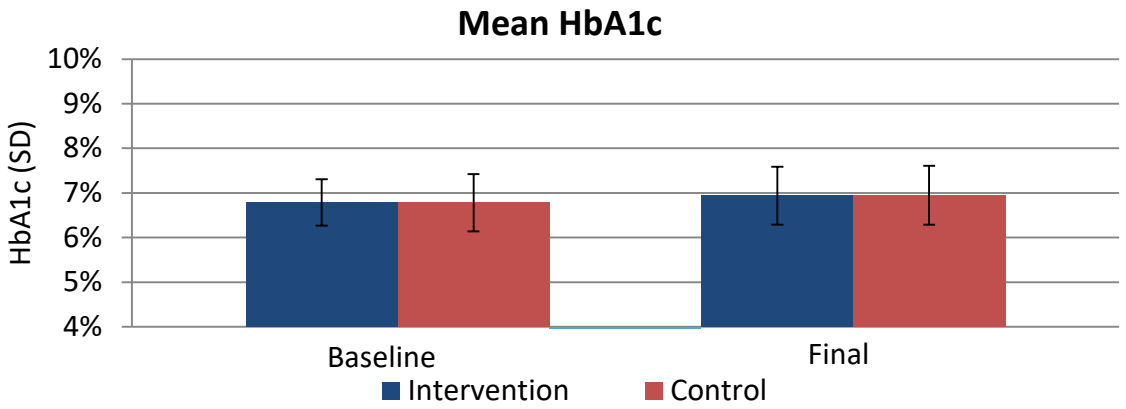
Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial

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

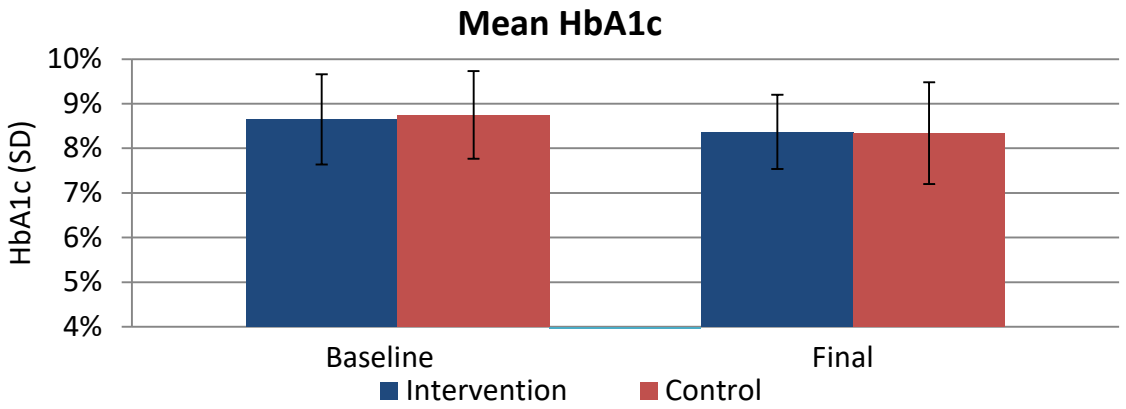
Diabetes Ther. 2017 Feb;8(1):55-73

FGM in prospective RCTs:
The IMPACT and REPLACE Studies
Results: HbA1c

IMPACT



REPLACE



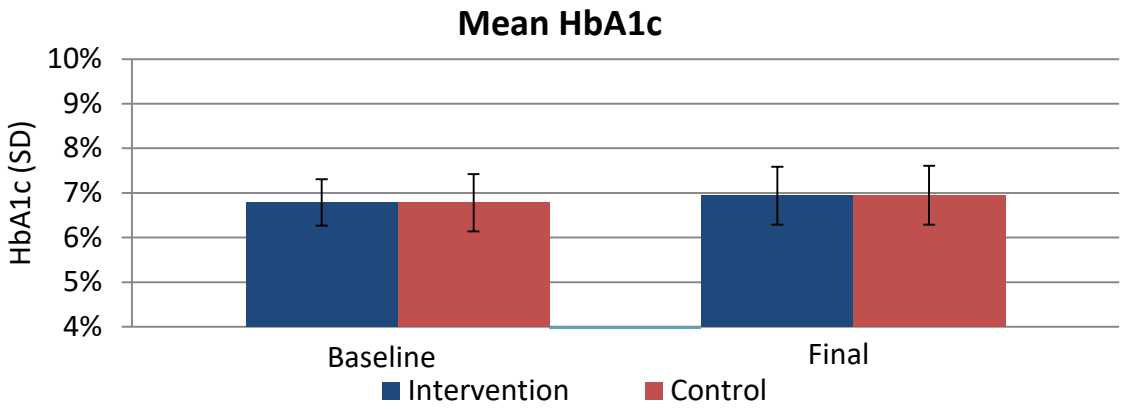
There was no significant change in HbA1c in FGM users versus SMBG

Bolinder J et al. Lancet. 2016 Nov 5;388(10057):2254-2263

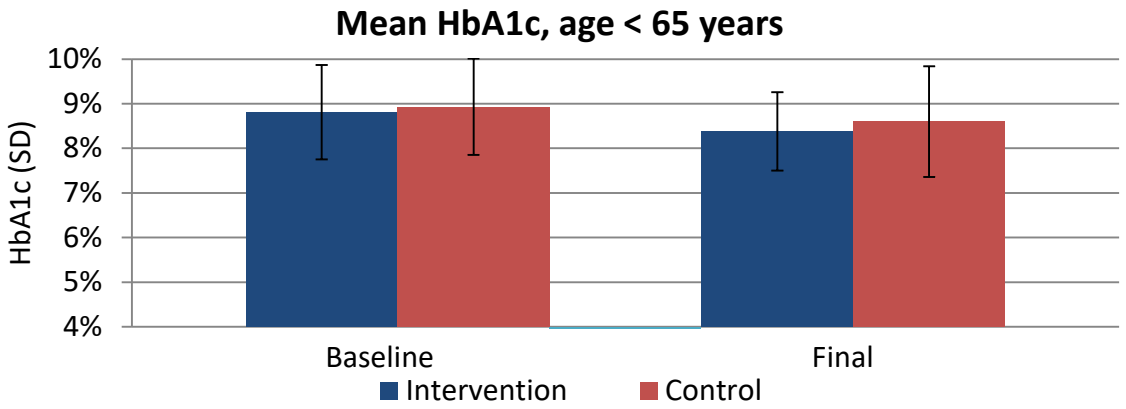
Haak T et al. Diabetes Ther. 2017 Feb;8(1):55-73

FGM in prospective RCTs:
The IMPACT and REPLACE Studies
Results: HbA1c

IMPACT



REPLACE



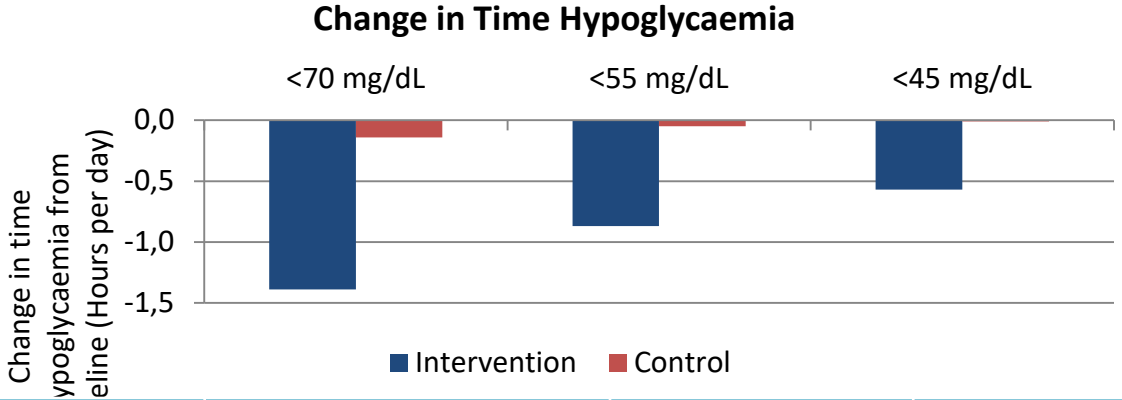
For REPLACE, <65 years old subgroup, there was a significant decrease in HbA1c in FGM users versus conventional SMBG.
Mean change: -0.33%, p = 0.03

Bolinder J et al. Lancet. 2016 Nov 5;388(10057):2254-2263

Haak T et al. Diabetes Ther. 2017 Feb;8(1):55-73

FGM in prospective RCTs: The IMPACT and REPLACE Studies Results: Time In Hypoglycaemia

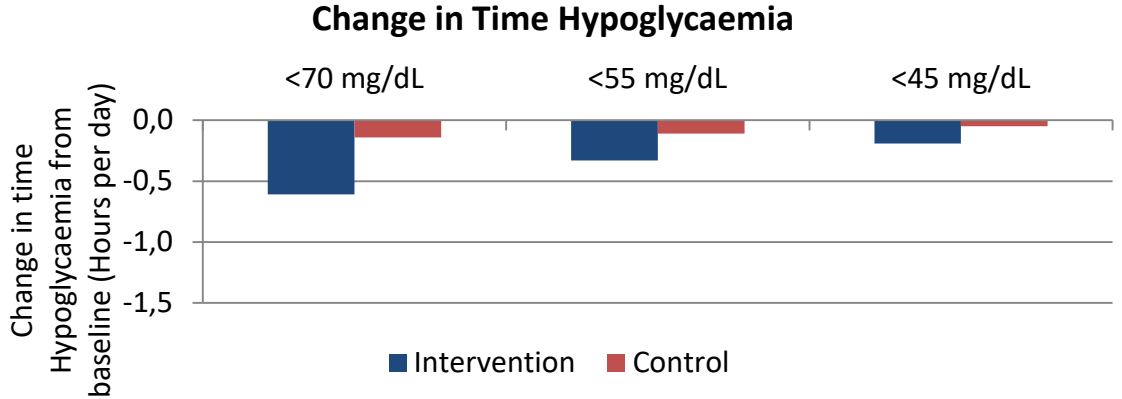
IMPACT



Glucose Level	Difference (vs control) in change from baseline	Significance (vs control)	Reduction vs control
<70 mg/dL	-1.24	P<0.0001	38%
<55 mg/dL	-0.82	P<0.0001	50%
<45 mg/dL	-0.55	P<0.0001	60%

Bolinder J et al. Lancet. 2016 Nov 5;388(10057):2254-2263

REPLACE



Glucose Level	Difference (vs control) in change from baseline	Significance (vs control)	Reduction vs control
<70 mg/dL	-0.47	P<0.001	43%
<55 mg/dL	-0.22	P=0.0014	53%
<45 mg/dL	-0.14	P=0.0013	64%

Haak T et al. Diabetes Ther. 2017 Feb;8(1):55-73

IMPACT Study in T1D: Glucose variability

	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)			
Glucose variability							
BGRI	8·2 (2·3)	8·3 (2·7)	7·3 (2·4)	8·4 (2·6)	−0·9 (0·26)	..	0·0004
CV glucose (%)	43·0 (7·0)	42·5 (6·6)	37·6 (5·7)	41·8 (6·8)	−4·4 (0·62)	..	<0·0001
LBGI	2·7 (1·5)	2·7 (1·7)	1·8 (1·4)	2·6 (1·7)	−0·8 (0·16)	..	<0·0001
MAGE (mg/dL; average)	142 (29)	144 (31)	132 (27)	141 (31)	−8 (3·0)	..	0·0055
Mean glucose (mg/dL)	141 (19)	142 (23)	146 (20)	143 (23)	3 (2·3)	..	0·1479
Standard deviation of glucose (mg/dL)	60·6 (12·6)	60·1 (12·9)	55·0 (10·9)	59·7 (13·8)	−5·0 (1·16)	..	<0·0001
CONGA							
2 h (mg/dL)	56 (13)	56 (14)	49 (12)	58 (13)	−9 (1·3)	..	<0·0001
6 h (mg/dL)	71 (25)	69 (26)	61 (25)	72 (28)	−12 (3·4)	..	0·0004

Bolinder J et al. Lancet. 2016 Nov 5;388(10057):2254-2263

REPLACE Study in T2D: Glucose variability

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 ($n = 75$)			
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

AUC area under curve, *BGRI* blood glucose risk index, *CV* coefficient of variation, *LBGI* low blood glucose index, *MAGE* mean amplitude of glycemic excursions, *CONGA* continuous overall net glycemic action × hours

Haak T et al. Diabetes Ther. 2017 Feb;8(1):55-73

The 2017 December issue of Diabetes Care……

"Periodically, a new idea, method, or tool leads to a turning point in the management of diabetes. We believe such a moment is now upon us, brought by development of reliable devices for continuous glucose monitoring (CGM)."

Diabetes Care Volume 40, December 2017

Maturation of CGM and Glycemic Measurements Beyond HbA_{1c}— A Turning Point in Research and Clinical Decisions

Matthew C. Riddle,[1] Hertzel C. Gerstein,[2] and William T. Cefalu[3]

Diabetes Care 2017;40:1611–1613 | https://doi.org/10.2337/dci17-0049

International Consensus on CGM

Diabetes Care Volume 40, December 2017

International Consensus on Use of Continuous Glucose Monitoring

Diabetes Care 2017;40:1631–1640 | https://doi.org/10.2337/dc17-1600

Thomas Danne,[1] Revital Nimri,[2] Tadej Battelino,[3] Richard M. Bergenstal,[4] Kelly L. Close,[5] J. Hans DeVries,[6] Satish Garg,[7] Lutz Heinemann,[8] Irl Hirsch,[9] Stephanie A. Amiel,[10] Roy Beck,[11] Emanuele Bosi,[12] Bruce Buckingham,[13] Claudio Cobelli,[14] Eyal Dassau,[15] Francis J. Doyle III,[15] Simon Heller,[16] Roman Hovorka,[17] Weiping Jia,[18]

The purpose was to provide guidance in utilizing, interpreting and reporting CGM data in clinical care and research

International Consensus on CGM: 7 main topics

1. Limitations of HbA1c
2. Use of glucose monitoring methodologies (SMBG and CGM) to guide management and assess outcomes in different patient populations
3. Minimal requirements for CGM performance
4. Definition and assessment of hypoglycemia in clinical studies
5. Assessment of glycemic variability (GV)
6. “Time in range”
7. Visualization, analysis and documentation of key CGM metrics

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Definition and assessment of hypoglycemia in clinical studies

The following classifications of hypoglycemia should be used in categorizing levels of hypoglycemia:

- **Level 1:** A hypoglycemia alert glucose value of <70-54 mg/dL (<3.9-3.0 mmol/L) with or without symptoms. This should be considered an alert
- **Level 2:** A glucose level of <54 mg/dL (<3.0 mmol/L) with our without symptoms. This should be considered clinically significant hypoglycemia requiring immediate attention.
- **Level 3:** Severe hypoglycemia. This denotes cognitive impairment requiring external assistance for recovery, but is not defined by a specific glucose value.

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Assessment of glycemic variability (GV)

- Numerous studies have focused on glycemic variability (GV) as an independent risk factor for diabetes complications, particularly CVD and on the effects of GV on cognitive function and quality of life;
- GV is a reflection of a dynamic process, and its understanding and measuring are less apparent that that of HbA1c;
- Standard deviation (SD), coefficient of variation (CV) and mean amplitude of glucose excursions (MAGE) are widely used to quantify GV;

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Time in Ranges

- Time in range (TIR) generally refers to the time spent in an inidividual's target glucose range (usually 70-180 mg/dL, but occasionally, as in pregnancy, 70-140 mg/dL).
- TIR measurements add valuable information to assess the level of current glycemic control in addition to what is known from the HbA1c.

Visualization, analysis and documentation of key CGM metrics

Standardizing glucose reporting and analysis is vital to optimizing clinical decision making in diabetes.

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Recommendations

14 key metrics should be utilized to assess glycemic control and document:

1. Mean glucose.
2. Percentage/time in Level 2 hypoglycemic range (<54 mg/dL [3.0 mmol/L]). Urgency for action: *Clinically significant / Very low / Immediate action required.*
3. Percentage/time in Level 1 hypoglycemic range (<70-54 mg/dL [<3.9-3.0 mmol/L]). Urgency for action: *Alert / Low / Monitor.*
4. Percentage/time in target range: 70-180 mg/dL / 3.9-10.0 mmol/L (default); 70-140 mg/dL / 3.9-7.8 mmol/L (secondary); Individual targets closer to the physiological range can be defined, depending on age, comorbidities and/or patient adherence.
5. Percentage/time in Level 1 hyperglycemic range (<180 mg/dL [10.0 mmol/L]). Urgency for action: *Alert / High / Monitor.*
6. Percentage/time in Level 2 hyperglycemic range (<250 mg/dL [13.9 mmol/L]). Urgency for action: *Clinically significant / Very elevated / Immediate action.*
7. Glycemic variability, reported as CV.
8. Estimated HbA1c (eA1c).
9. Data for glucose metrics (1-7) reported in 3 time blocks (sleep, wake, 24 hours).
10. Data sufficiency - minimum 2 weeks of data.
11. Data sufficiency - 70-80% of possible CGM readings over 2-week period.
12. Episodes of hypoglycemia.
13. Area under the curve (AUC) (recommended for research purposes).
14. Risk of hypoglycemia and hyperglycemia (LBGI and HBGI recommended).

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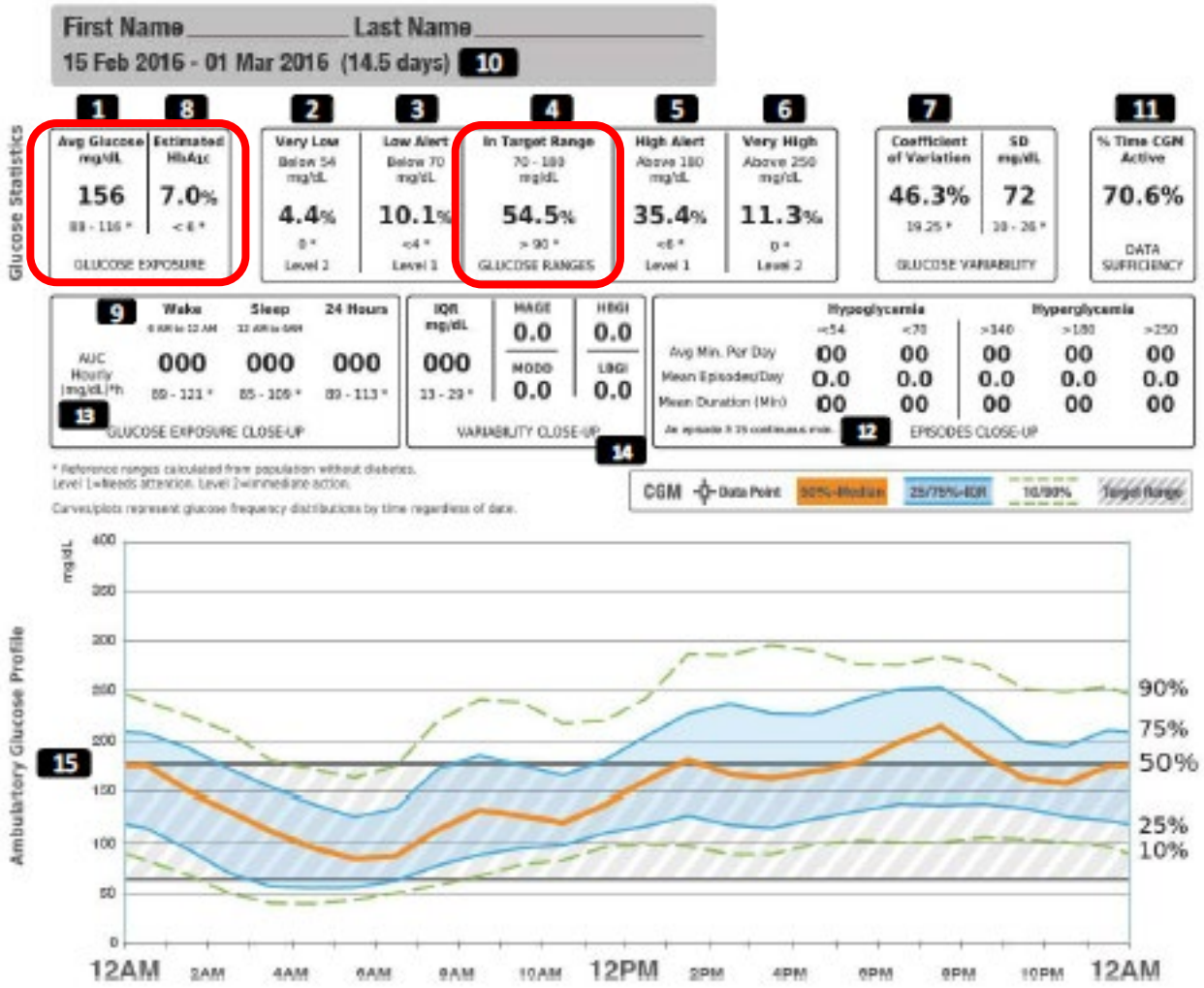

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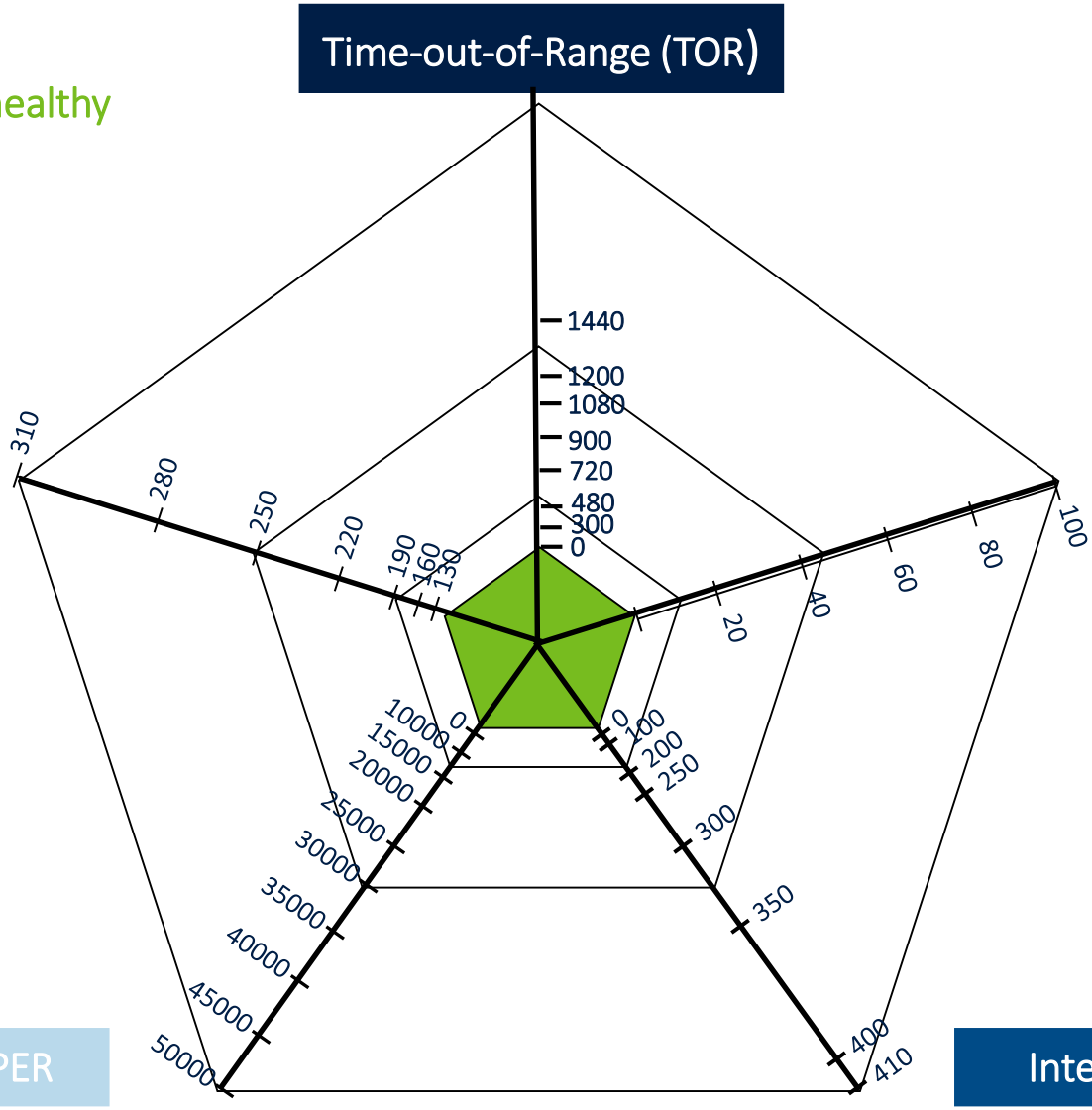
COMPREHENSIVE GLUCOSE PENTAGON MODEL[1]

- Green area: standard area for healthy subjects



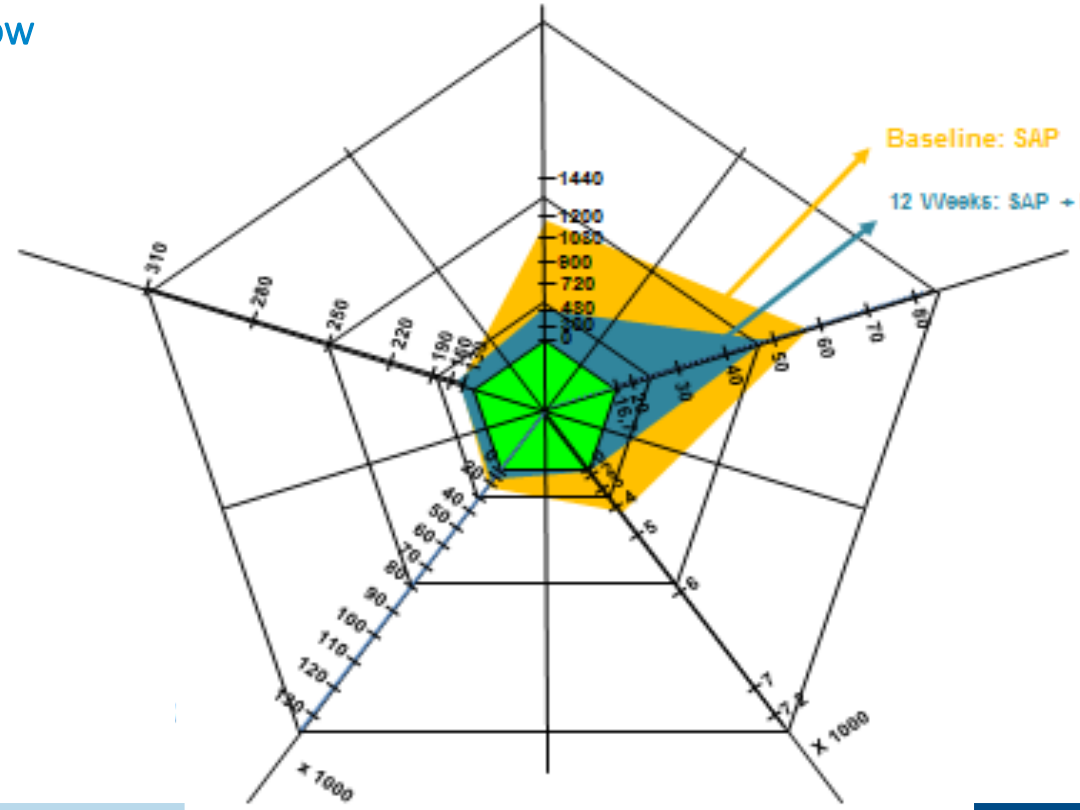
1. Vigersky R.A. et al. J Diabetes Sci Technol. 2018;12(1):114-123.

COMPARISON OF NEW VS. TRADITIONAL METRICS OF HYPOGLYCAEMIA
RESULTS OF THE ASPIRE IN-HOME TRIAL[1,2]

- Green area: standard area for healthy subjects
- **Baseline: SAP (No automation)**
- 12 weeks: SAP + Suspend on low

Time-out-of-Range (TOR)

Mean glucose (mg/dL)



$CV_{Glucose}$ (mg/dL)

Intensity HYPER (mg/dL x min^2)

Intensity HYPO (mg/dL x min^2)

1.Bergenstal R.M., et al. N Engl J Med. 2013;369:224-32.
2. Vigersky R.A. et al. J Diabetes Sci Technol. 2018;12(1):114-123.

International Consensus on Use of Continuous Glucose Monitoring

Conclusions

1. CGM is a robust research tool, and continuous glucose data should be recognized as a valuable and meaningful endpoint to be used in clinical trials of new drugs and devices for diabetes treatment.
2. The identification of hypoglycemia is as important as the measurement of time in range in clinical trials.
3. Quantifying the duration and magnitude of hyperglycemic excursions provides another means of assessing glucose control.
4. In clinical practice, the advanced metrics of assessing continuous glucose data are appropriate as outcome parameters that complement HbA1c for a wide range of patients with diabetes and should be considered for use to help them to improve glycemic control, provided appropriate educational and technical support is available.

Danne T et al. Diabetes Care 2017; 40:1631-1640

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Grazie

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