Metrics Beyond HemoglobinA1c

Diabetes Management Anno 2022

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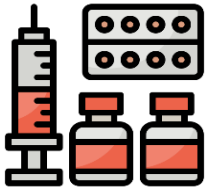
Data in diabetes care and research

Decisions are driven by numbers



Gain **insight** into behaviour of patients

Drive clinical **research**

icons taken from Flaticon

Type 1 diabetes data

image taken from AIMultiple

Type 1 diabetes data

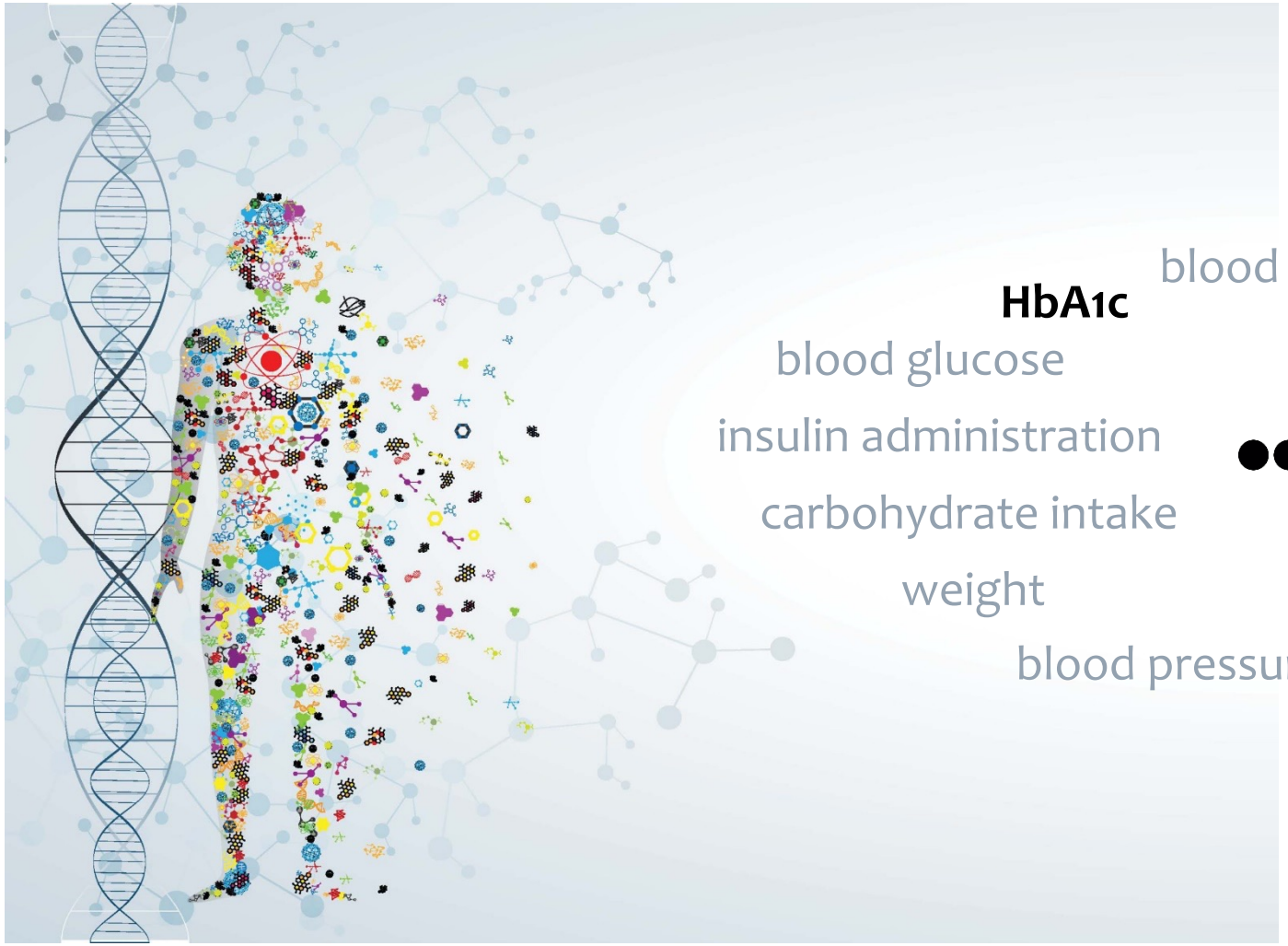
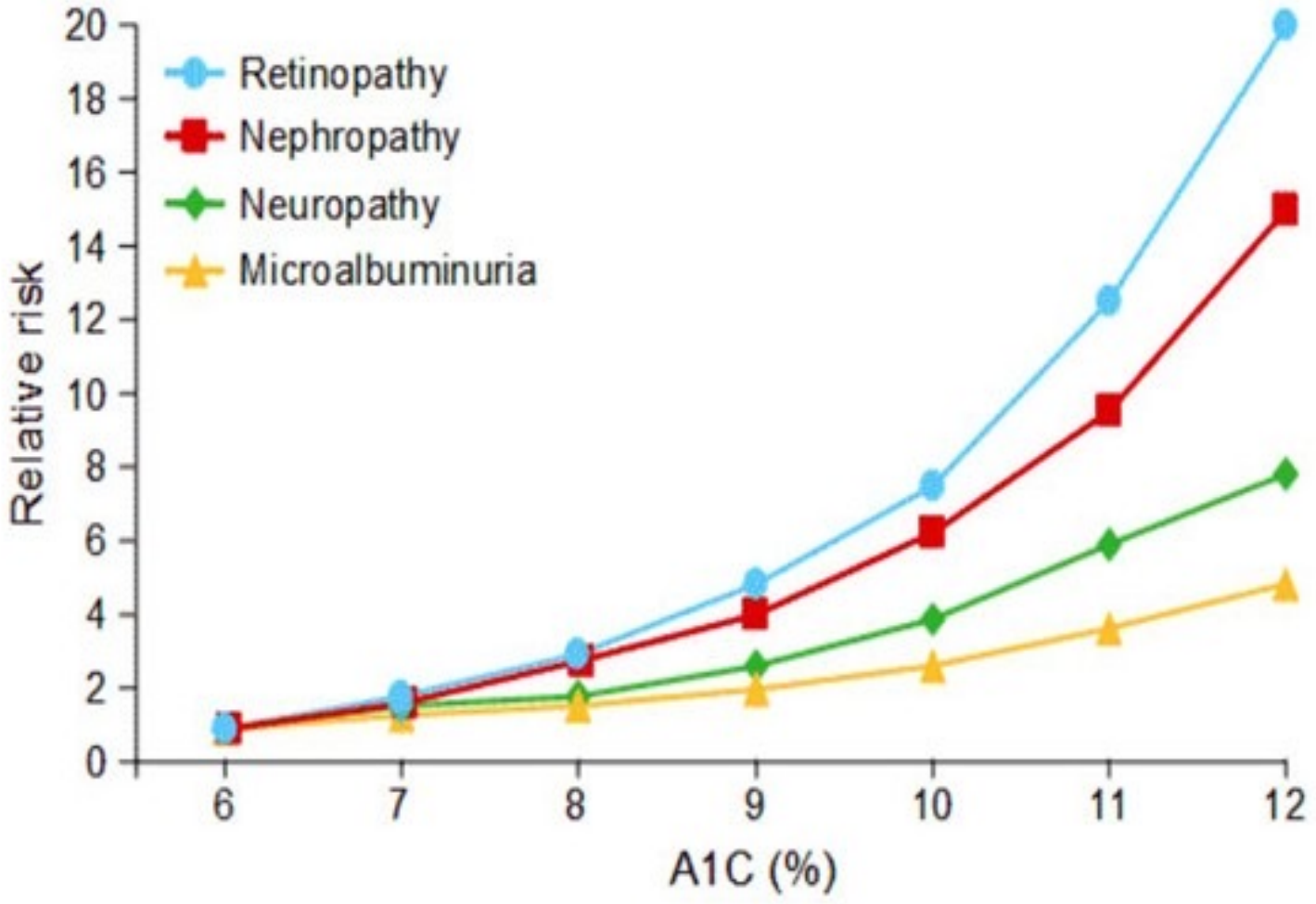


image taken from AIMultiple

Strenght of HbA1c



High within person reliability

Assay standardization widely available

DCCT/EDIC Research Group. Arch Intern Med. 2009;169(14):1307-1316.
Skyler JS. J. Endocrinol Metab Clin North Am. 1996;25(2):243-254.

Limitations of HbA1c in personalized diabetes management

HbA1c is an unreliable measure in

hemoglobinopathies

anemia

iron deficiency

pregnancy

different races

Beck RW *et al*. Diabetes Care, 2017.

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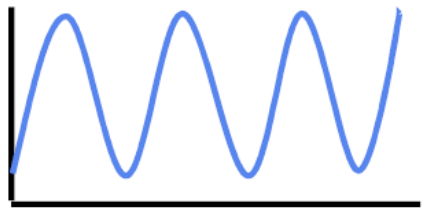
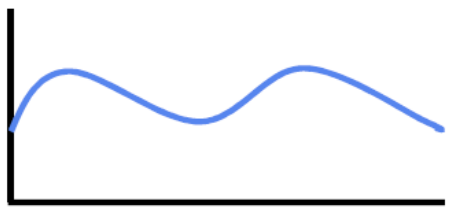
HbA1c = 7%

high glycemic variability



low glycemic variability



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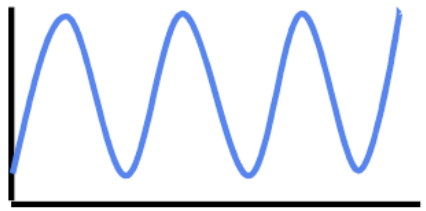

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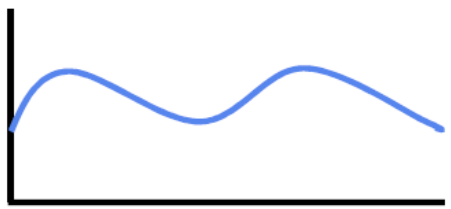
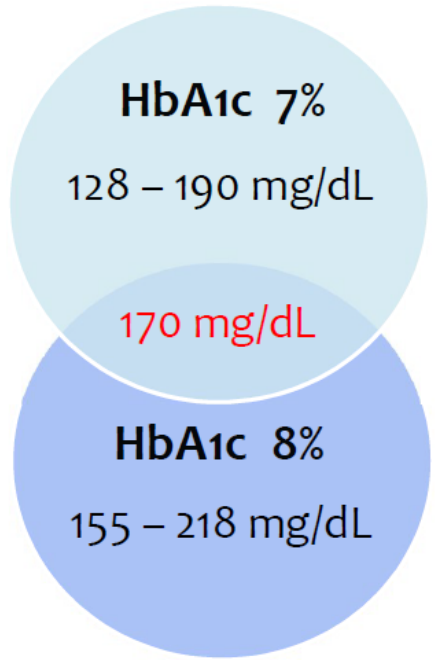


Mean glucose versus HbA1c



Beck RW *et al*. Diabetes Care, 2017.

Limitations of HbA1c in personalized diabetes management

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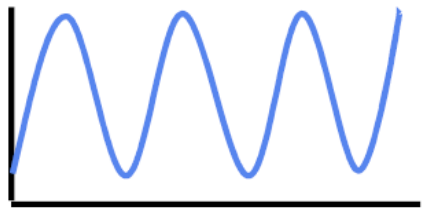

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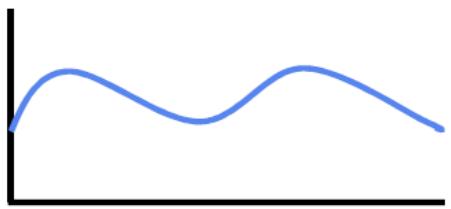
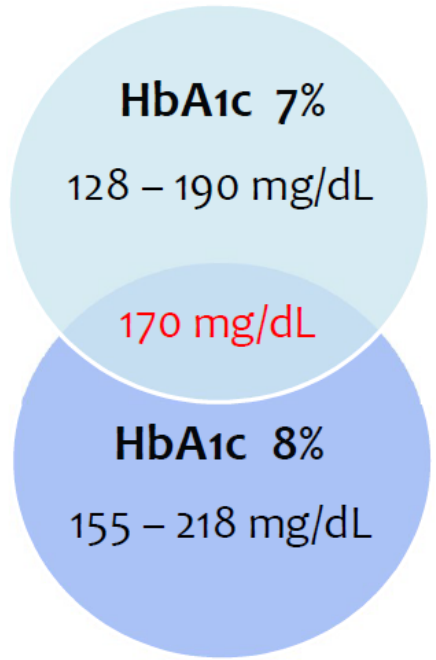


Mean glucose versus HbA1c



need to look beyond HbA1c

Beck RW *et al*. Diabetes Care, 2017.

Type 1 diabetes data

blood lipids
HbA1c
heart rate
blood glucose
activity data
insulin administration
●●●
eye fundus
carbohydrate intake
kidney function
weight
blood pressure
QOL

image taken from AIMultiple

Not so long ago …

… people with type 1 diabetes did not have many glucose data to make on-the-go therapy decisions

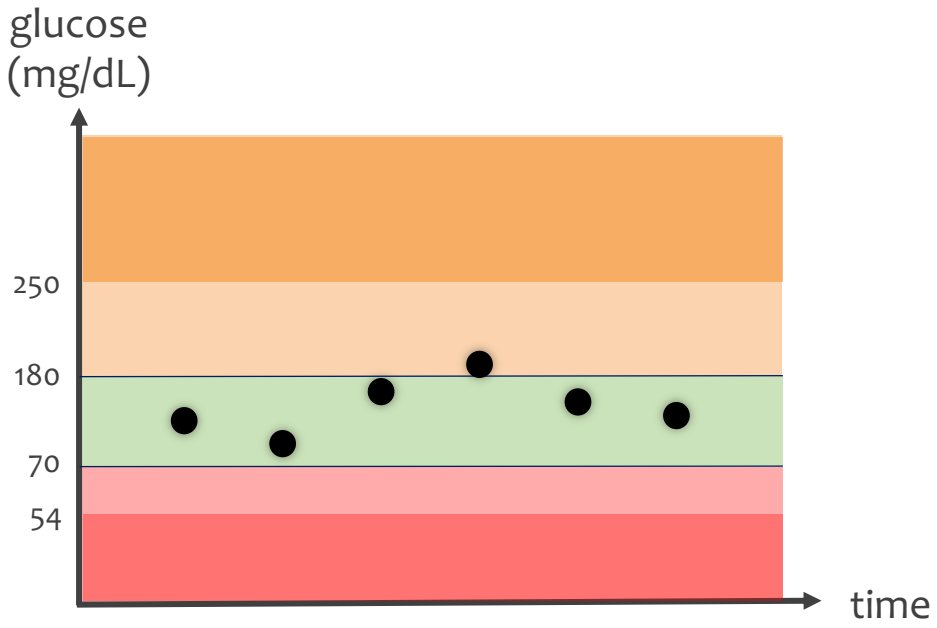
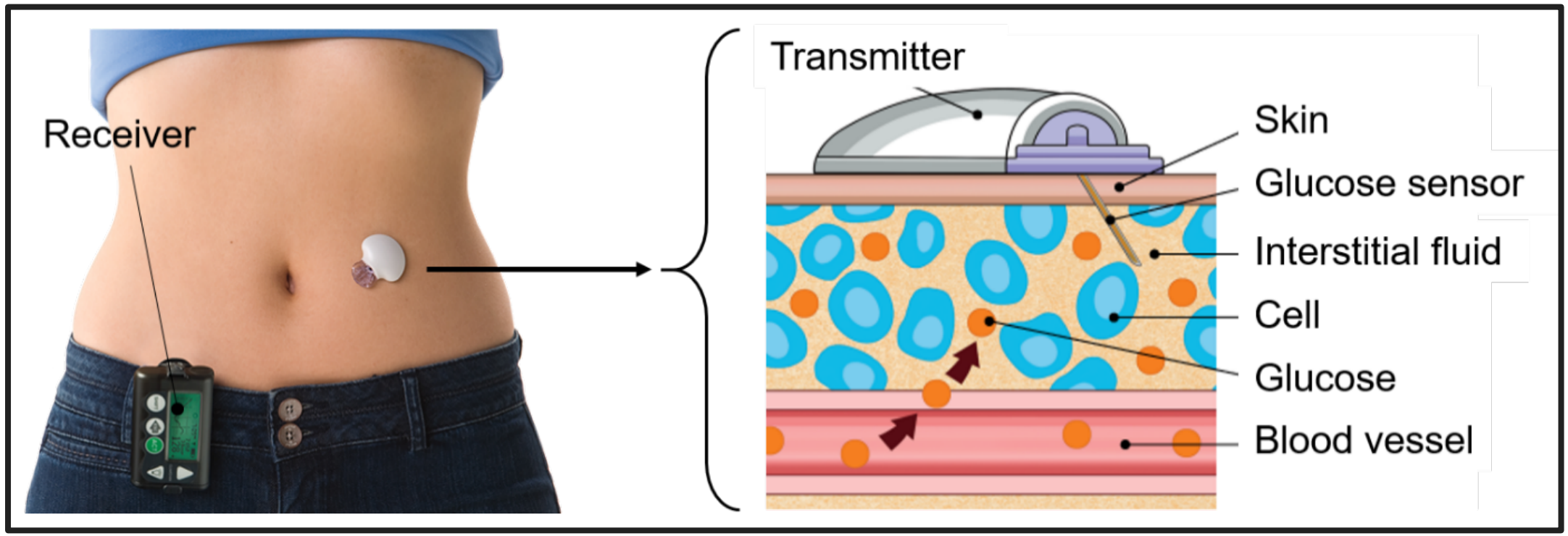


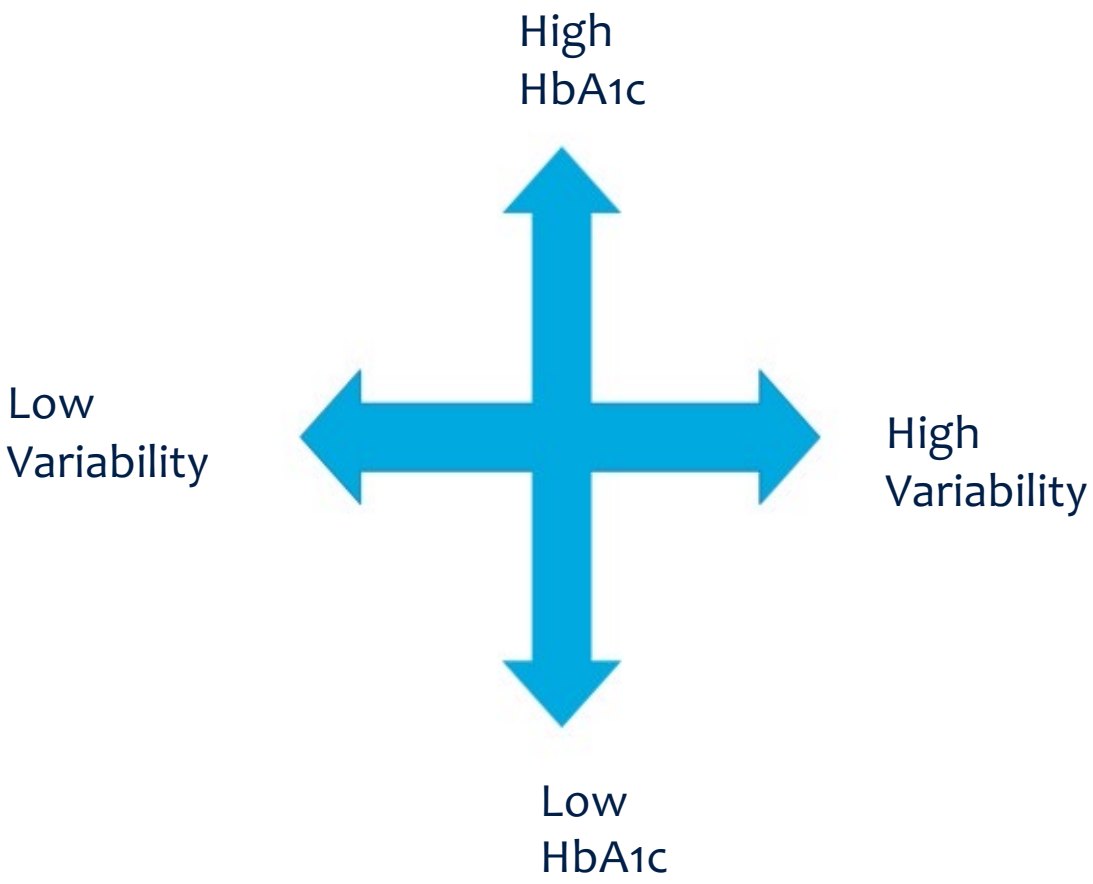
image on the right taken from Adobe Stock

What is continuous glucose monitoring?



CGM data revolutionized the way people with T1D deal with their diabetes

New Metrics in Diabetes Management

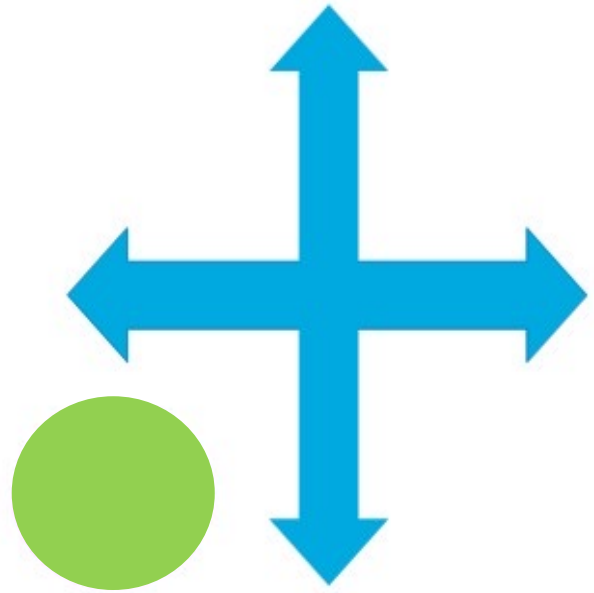


New Metrics in Diabetes Management

TIME IN RANGE

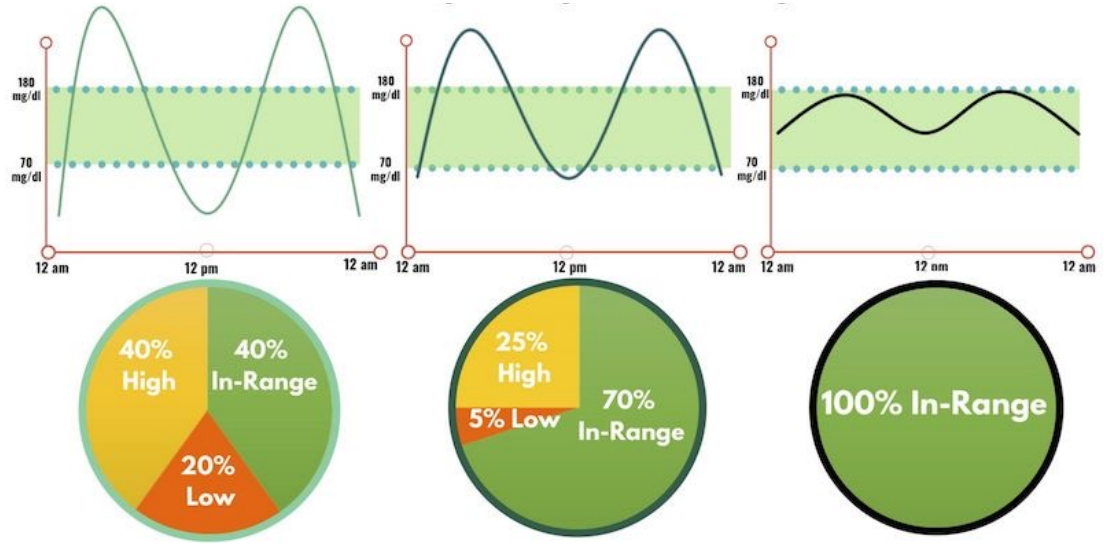
High
HbA1c

Low
Variability



High
Variability

Low
HbA1c

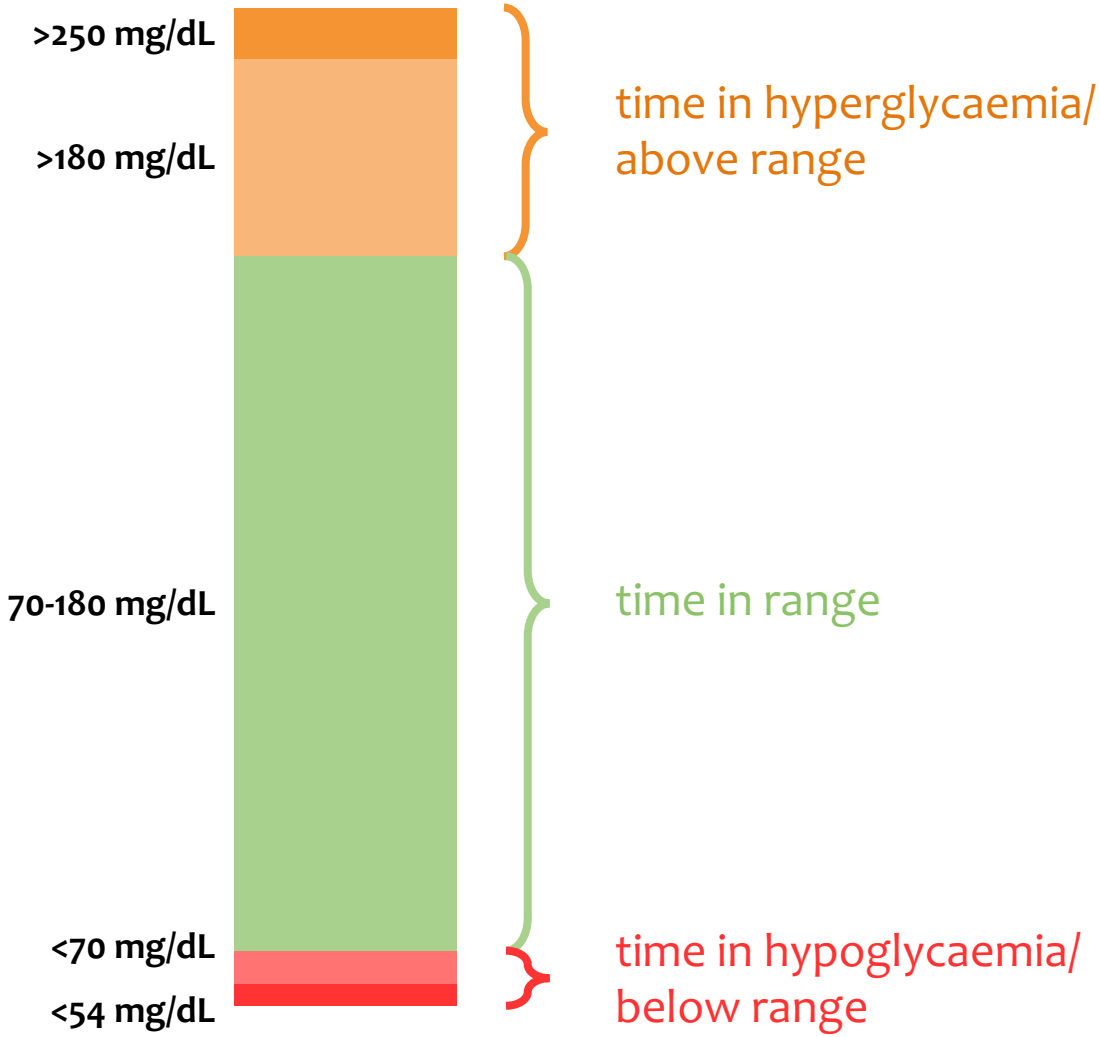


High
Time in Range

Combination mean + variability

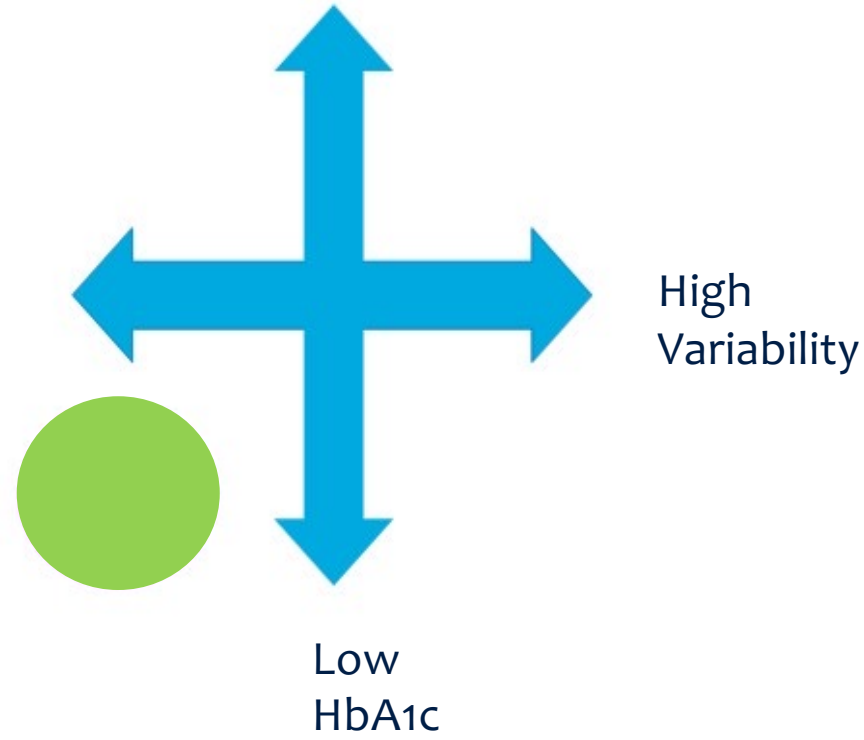
New Metrics in Diabetes Management

TIME IN RANGE



New Metrics in Diabetes Management

TIME IN RANGE



High
Time in Range

Combination
mean +
variability

Impact for patients

Easier to understand

Higher TIR = Often Lower HYPO + HYPER
(not always; include Time in Hypo)

"Take the ball early"

New Metrics in Diabetes Management

TIR in Relation to HbA1c

Time in Range

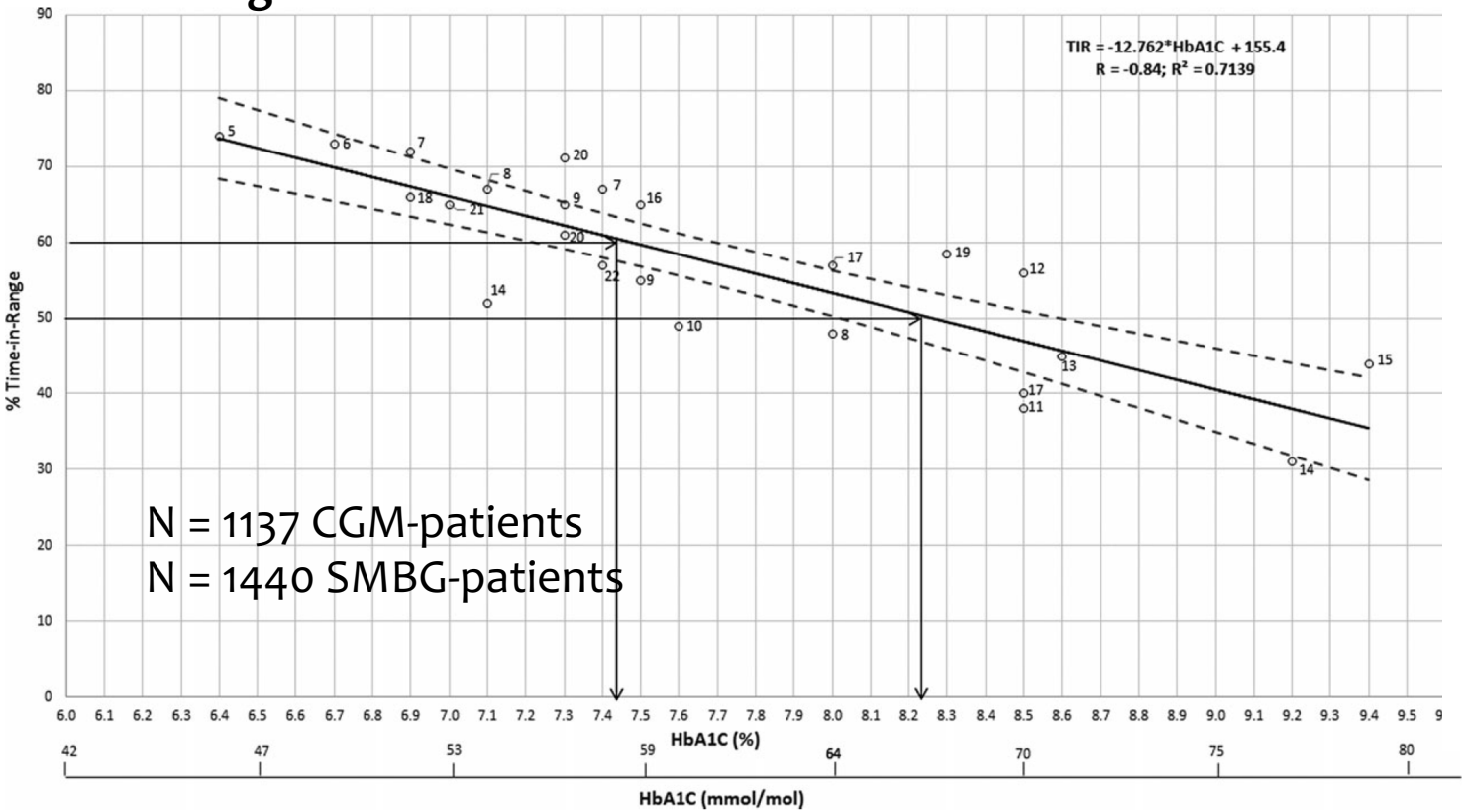


TABLE 2. HEMOGLOBIN A1C IN % AND MMOL/MOL AT EACH DECILE OF TIME-IN-RANGE PER EQUATION IN THE FIGURE

Time-in-range	*HbA1C (%)*	*HbA1C (mmol/mol)*
0%	12.1	109
10%	11.4	101
20%	10.6	92
30%	9.8	84
40%	9.0	75
50%	8.3	67
60%	7.5	59
70%	6.7	50
80%	5.9	42
90%	5.1	32
100%	4.3	23

Vigersky and McMahon (Medtronic Employees), DTT, 2019, vol 21, nr 1

New Metrics in Diabetes Management

TIR in Relation to HbA1c

A. Estimation of A1C for a given TIR Level of CGM metric

	Baseline (N = 455)			Month 6 (N = 545)		
	Estimate	95% CI for the predicted value[b]	95% CI for the mean[b]	Estimate	95% CI for the predicted value[b]	95% CI for the mean[b]
	Estimated A1C (%)					
TIR[70-180]						
20%	9.4	(8.0, 10.7)	(9.2, 9.5)	8.8	(7.9, 9.8)	(8.7, 9.0)
30%	8.9	(7.6, 10.2)	(8.7, 9.0)	8.4	(7.5, 9.4)	(8.3, 8.5)
40%	8.4	(7.1, 9.7)	(8.3, 8.5)	8.0	(7.1, 9.0)	(8.0, 8.1)
50%	7.9	(6.6, 9.2)	(7.9, 8.0)	7.6	(6.7, 8.6)	(7.6, 7.7)
60%	7.4	(6.1, 8.8)	(7.4, 7.5)	7.2	(6.3, 8.2)	(7.2, 7.3)
70%	7.0	(5.6, 8.3)	(6.9, 7.0)	6.8	(5.8, 7.8)	(6.8, 6.9)
80%	6.5	(5.2, 7.8)	(6.4, 6.6)	6.4	(5.4, 7.4)	(6.3, 6.5)
90%	6.0	(4.7, 7.3)	(5.9, 6.2)	6.0	(5.0, 7.0)	(5.9, 6.1)

Beck et al, JDST, 1-13, 2019

Increasing Importance of New CGM-based Metrics

International Consensus on Use of Continuous Glucose Monitoring

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

in clinical practice, CGM metrics are appropriate as outcome parameters that complement HbA_{1c}

Danne T, *et al*. Diabetes Care, 2017.

Increasing Importance of New CGM-based Metrics

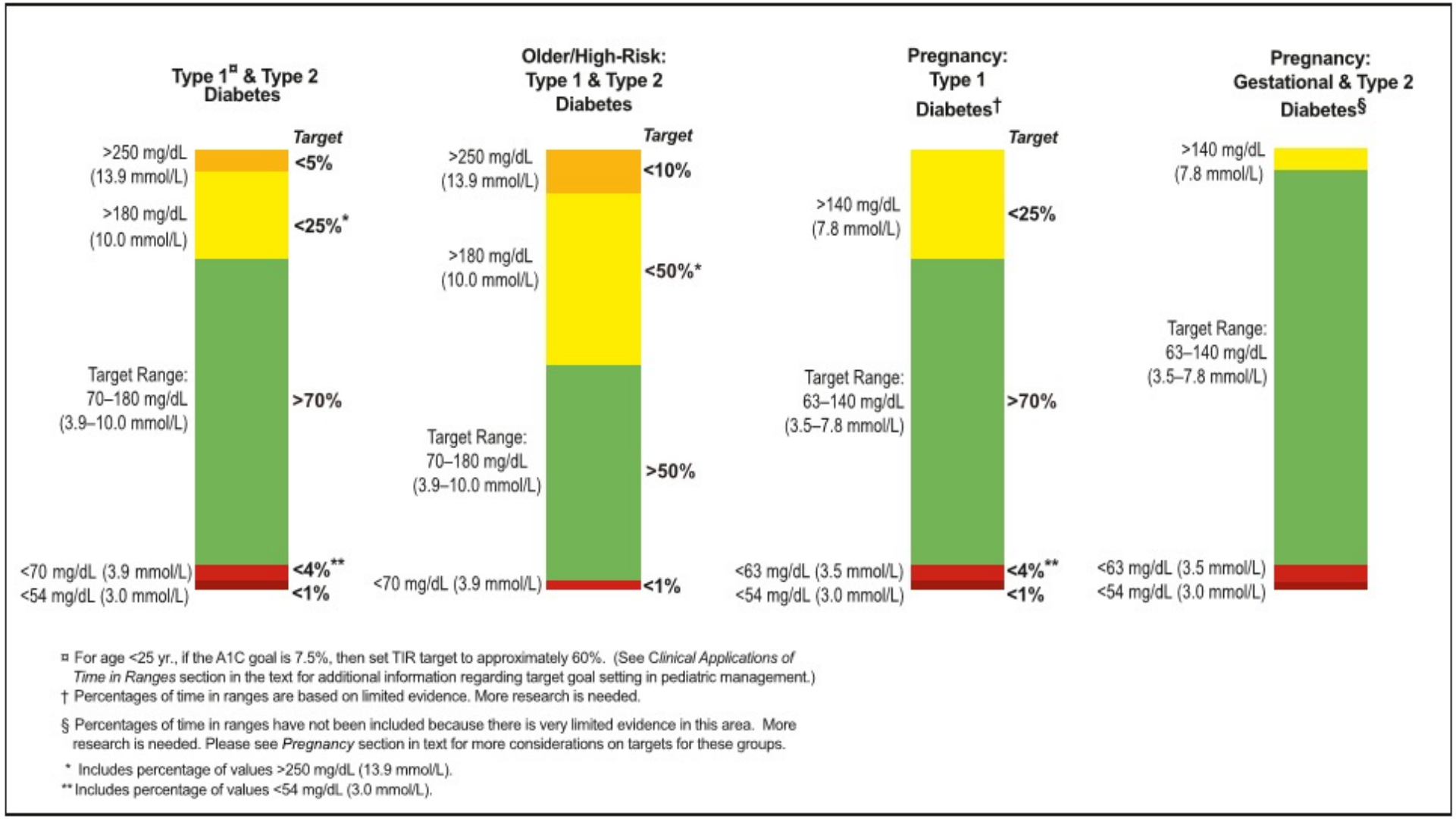
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

➡ CGM is recommended to provide more complete information during drug tests

EMA Guideline CPMP/EWP/1080/00 Rev. 2, 29 January 2018

time in ranges: consensus targets



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

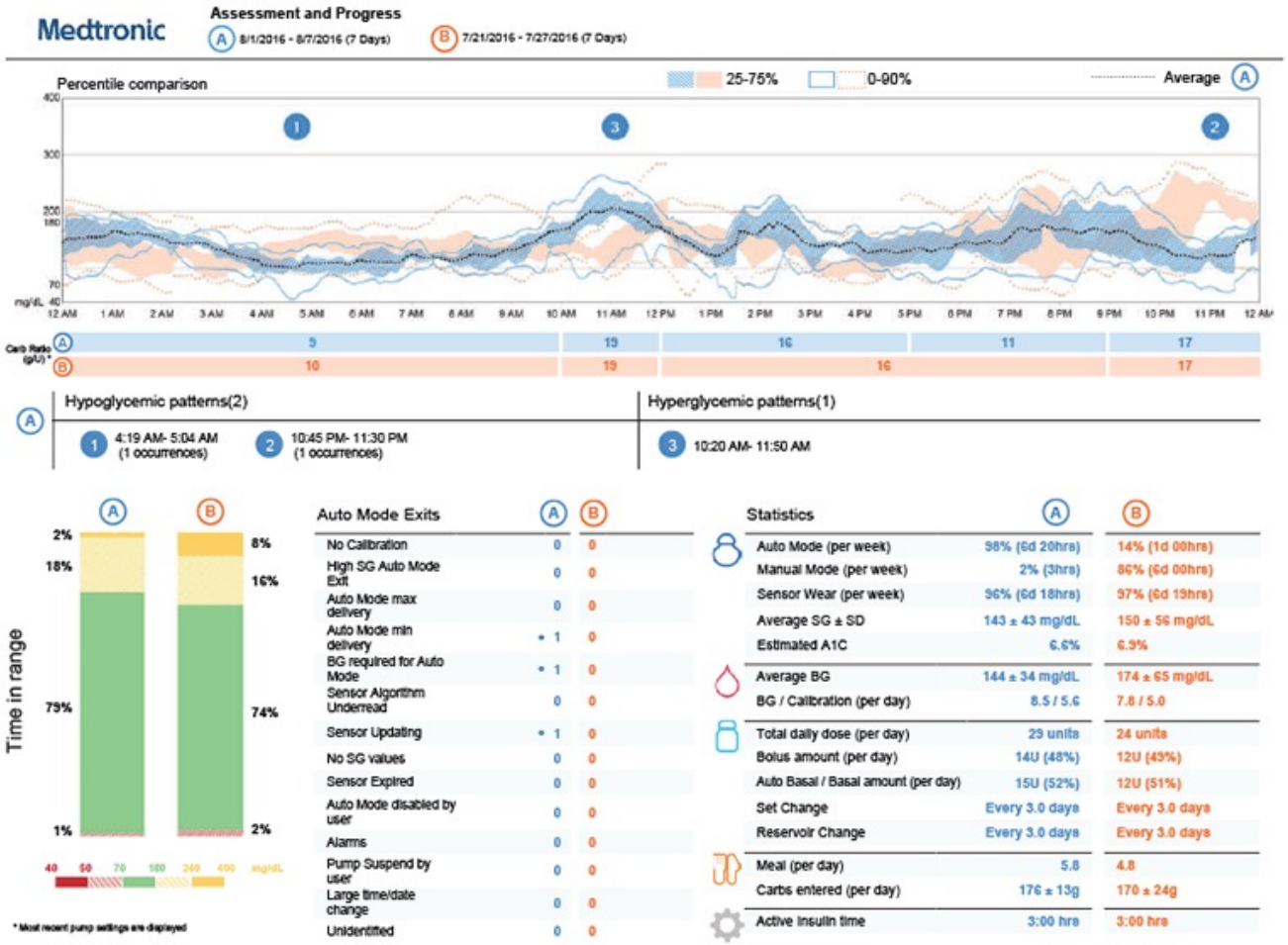
Beck RW *et al.* Diabetes Care, 2019.

New outcome measures – time in ranges

CGM metrics	Target level
Number of days CGM worn	>14 days
Percentage of time CGM is active	>70%
Mean glucose	
GMI, %*	
Glycemic variability, %CV	≤36%
TIR: % time 70-180 mg/dL	>70%
Time in hyperglycemia	
% time >250 mg/dL	<5%
TAR: % time >180mg/dL	<25%
Time in hypoglycemia	
% time <54 mg/dL	<1%
TBR: % time <70 mg/dL	<4%
Use of Ambulatory Glucose Profile for CGM report	

*GMI = 3.31 + 0.02392 x [mean glucose in mg/dL]. CGM, continuous glucose monitoring; GMI, glucose management indicator; CV, coefficient of variation; TIR, time in range; TAR, time above range; TBR, time below range. Adapted from (115).

New outcome measures – time in ranges



Case 1

GLUCOSESTATISTIEKEN EN -DOELEN

29 oktober 2020 - 25 november 2020 — **28 Dagen**

% tijd sensor is actief — **100%**

Bereiken en doelen voor: Type 1 of Type 2 diabetes

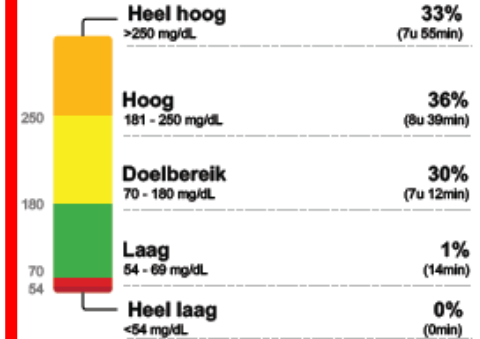
Glucosebereiken	Doelen % waarden (uur/dag)
Doelbereik 70-180 mg/dL	Hoger dan 70% (16u 48min)
Onder 70 mg/dL	Lager dan 4% (58min)
Onder 54 mg/dL	Lager dan 1% (14min)
Boven 180 mg/dL	Lager dan 25% (6u)
Boven 250 mg/dL	Lager dan 5% (1u 12min)

Elke verhoging van 5% in tijd binnen (70-180 mg/dL) bereik is klinisch gunstig.

Gemiddelde glucose	**218** mg/dL
Glucosebeheer indicator (GMI)	**8,5% of 70 mmol/mol**
Glucosevariatie	**32,4%**

Gedefinieerd als percentage variatiecoëfficiënt (%CV); bereik ≤36%

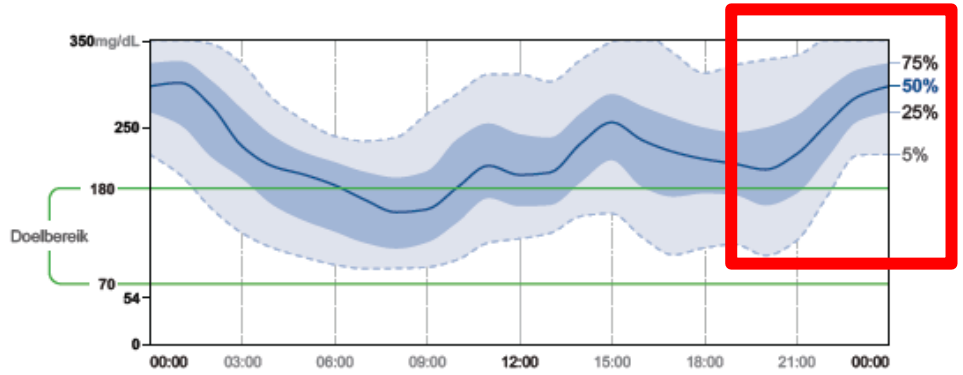
TIJD IN BEREIKEN



Heel hoog	>250 mg/dL	33% (7u 55min)
Hoog	181 - 250 mg/dL	36% (8u 39min)
Doelbereik	70 - 180 mg/dL	30% (7u 12min)
Laag	54 - 69 mg/dL	1% (14min)
Heel laag	<54 mg/dL	0% (0min)

AMBULATOIR GLUCOSEPROFIEL (AGP)

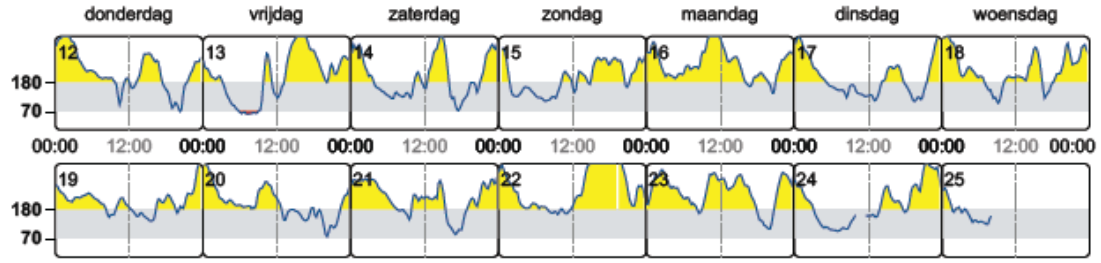
AGP is een overzicht van glucosewaarden van de rapportageperiode, met mediaan (50%) en andere percentielen die worden getoond alsof ze voorkomen op één enkele dag.



DAGELIJKSE GLUCOSEPROFIELEN

De meest recente 14 dagen. Zie het wekelijks samenvattingsrapport voor meerdere dagen.

Elk dagelijks profiel geeft een periode weer van middernacht tot middernacht waarbij de datum in de linkerbovenhoek wordt weergegeven.

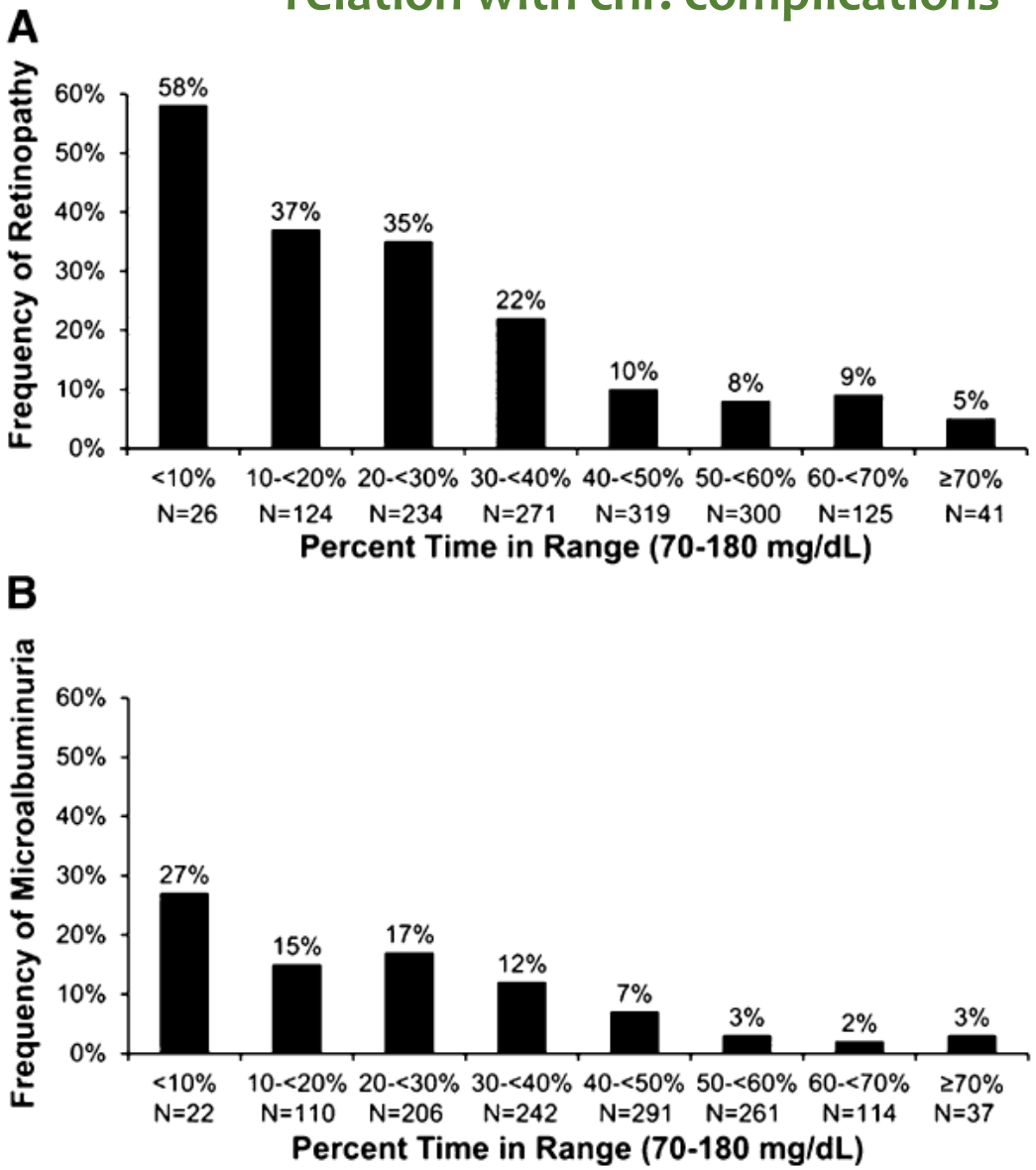


Hypo-fear:

- **Late evening snack,**
- **Too little insulin**

Validation of Time in Range as Outcome Parameter

relation with chr. complications



Beck et al, Diabetes Care, 2019 Mar;42(3):400-405.

Validation of Time in Range as Outcome Parameter

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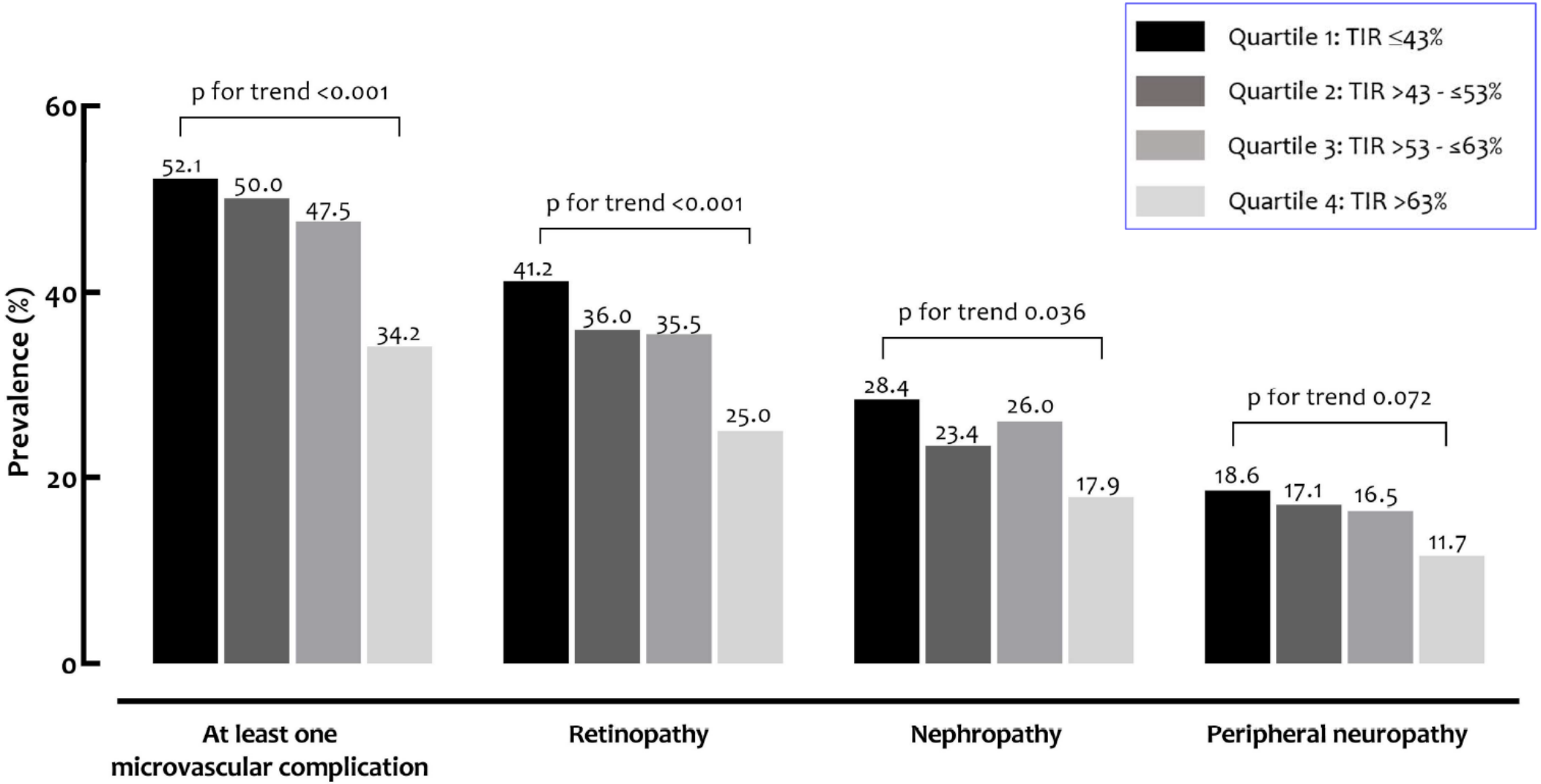

Jolien De Meulemeester et al, OP ATTD 2022

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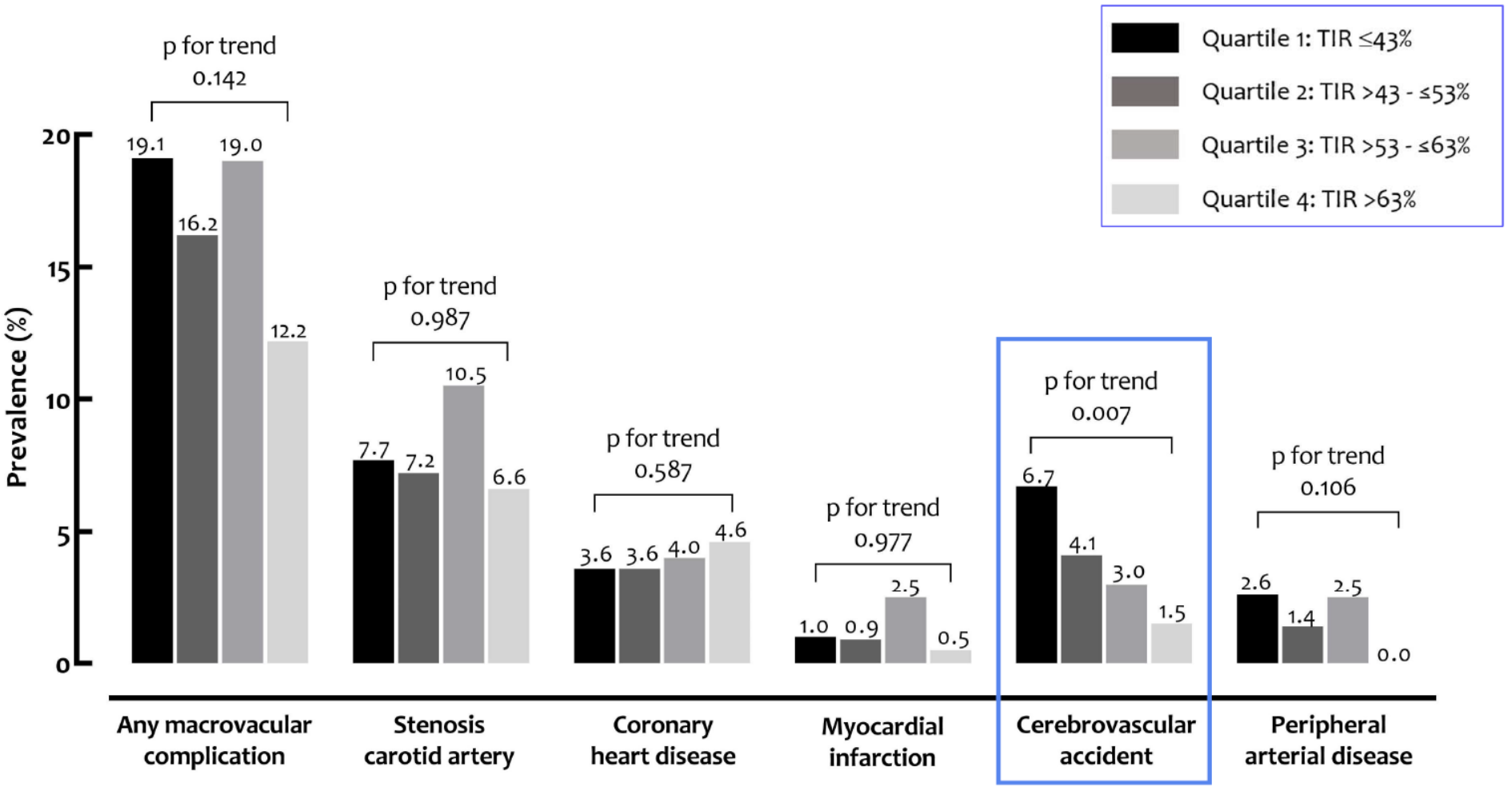
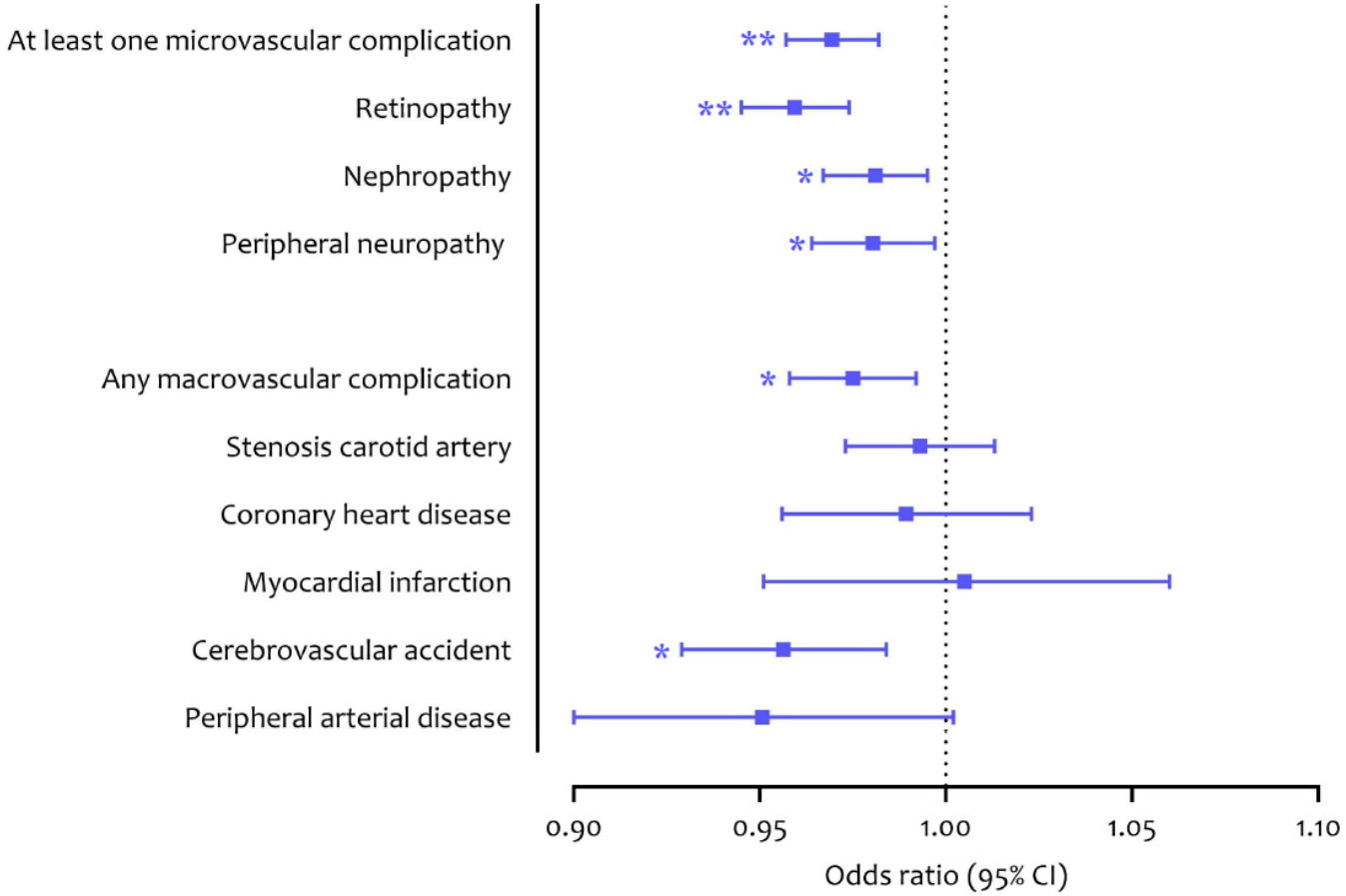


Jolien De Meulemeester et al, OP ATTD 2022

Validation of Time in Range as Outcome Parameter

relation with chr. complications

model 1



*p<0.05, **p<0.001.

After correction for sex, age, diabetes duration, BMI, blood pressure, lipid profile, smoking, using lipid lowering and antihypertensive agents.

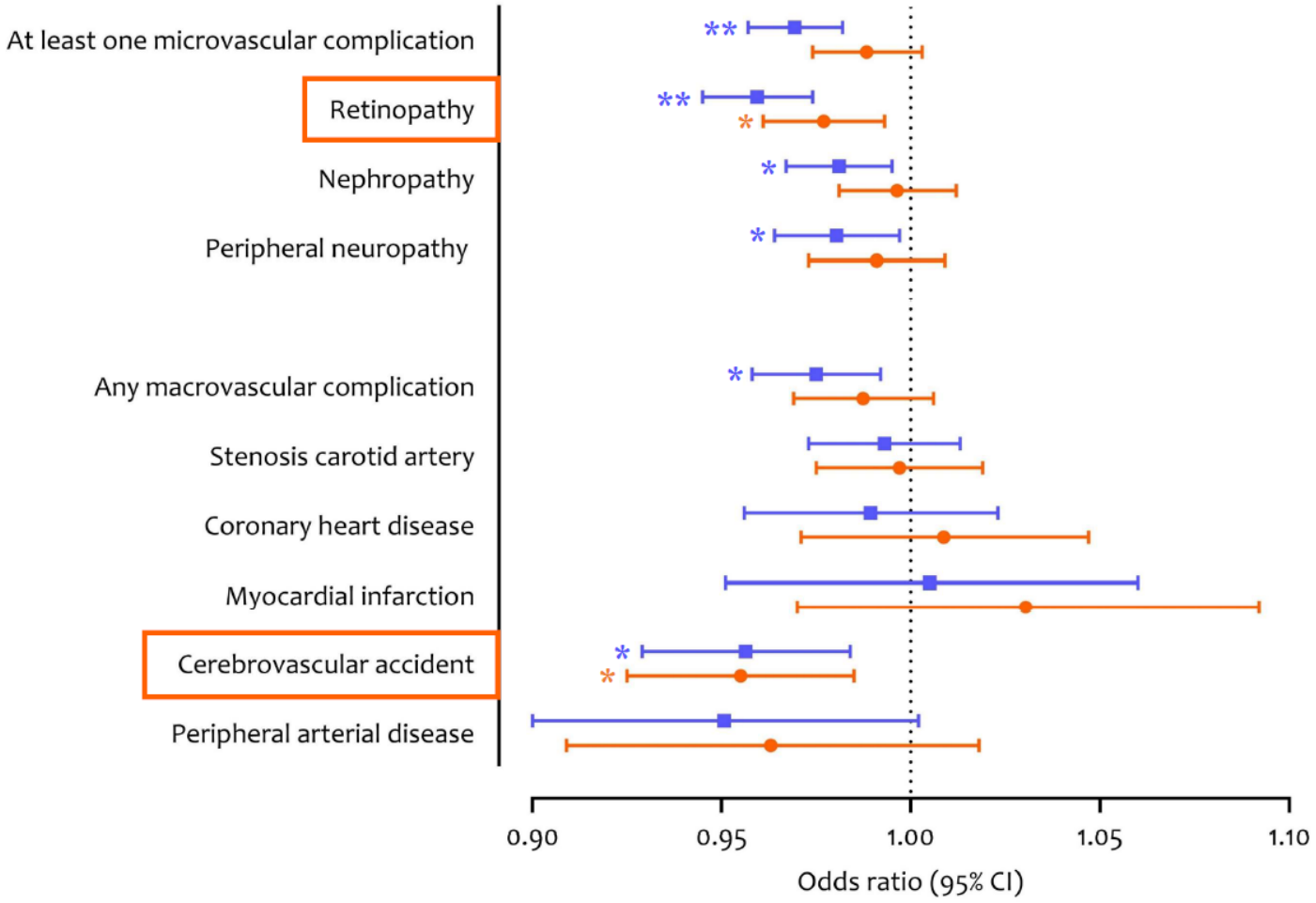
Jolien De Meulemeester et al, OP ATTD 2022

Validation of Time in Range as Outcome Parameter

relation with chr. complications

model 1

model 2



*p<0.05, **p<0.001.

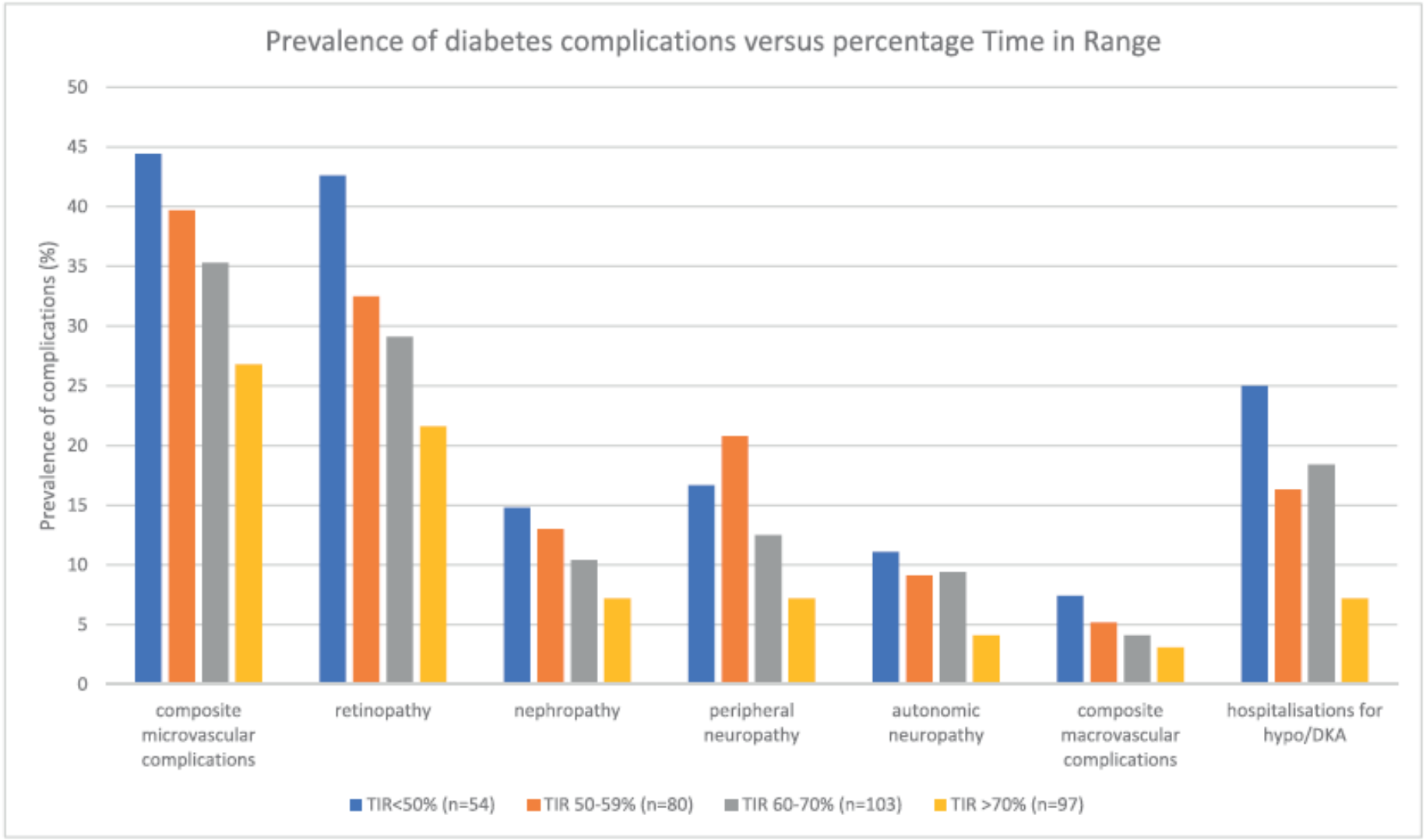
After correction for sex, age, diabetes duration, BMI, blood pressure, lipid profile, smoking, using lipid lowering and antihypertensive agents.

After correction for the above + HbA1c.

Jolien De Meulemeester et al, OP ATTD 2022

Validation of Time in Range as Outcome Parameter

relation with chr. complications



El Malahi et al *The Journal of Clinical Endocrinology & Metabolism*, 2022, Vol. 107, No. 2, e570–e581

TIR as Outcome in Randomised controlled trials

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

Randomised controlled trial – ALERTT1

who

6 multidisciplinary diabetes centres

254 adults with type 1 diabetes with isCGM

isCGM vs rtCGM

what

glycaemic control

quality of life

acute diabetes complications

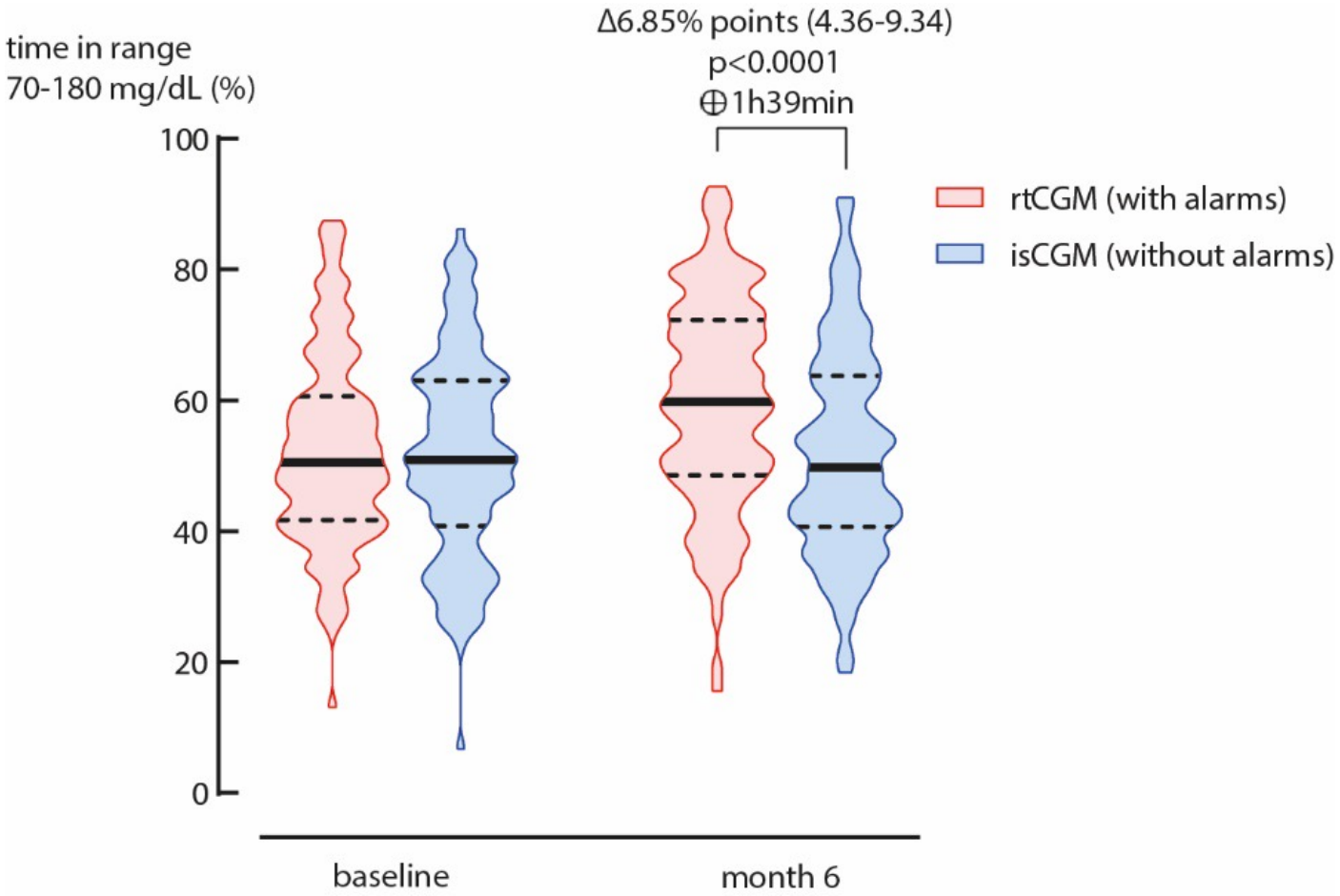
when

Jan 2019 – Sep 2022

6 months RCT

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

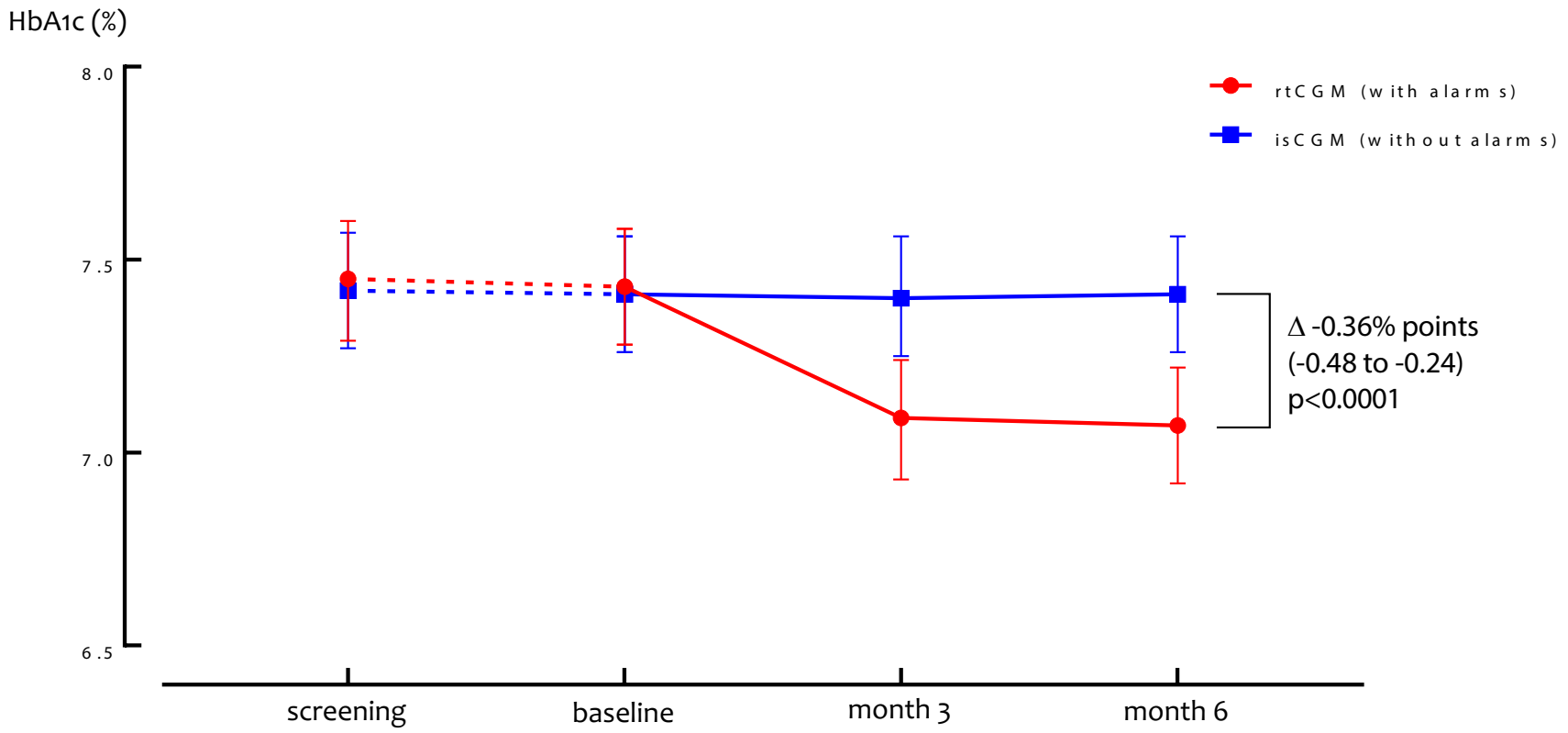
ALERTT1 – difference in time in range



Violin plots show distribution per group. Mean group difference (95% CI).

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

ALERTT1 – difference in HbA1c



Data represent least-squares mean with 95% CI. Mean group difference (95% CI).

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/ml in type 1 diabetes: The head-to-head randomized controlled InRange trial

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Email: tadej.battelino@mf.uni-lj.si

Funding information
Sanofi

Abstract

Aim: To use continuous glucose monitoring (CGM)-based time-in-range (TIR) as a primary efficacy endpoint to compare the second-generation basal insulin (BI) analogues insulin glargine 300 U/ml (Gla-300) and insulin degludec 100 U/ml (IDeg-100) in adults with type 1 diabetes (T1D).

Materials and Methods: InRange was a 12-week, multicentre, randomized, active-controlled, parallel-group, open-label study comparing glucose TIR and variability between Gla-300 and IDeg-100 using blinded 20-day CGM profiles. The inclusion criteria consisted of adults with T1D treated with multiple daily injections, using BI once daily and rapid-acting insulin analogues for at least 1 year, with an HbA1c of 7% or higher and of 10% or less at screening.

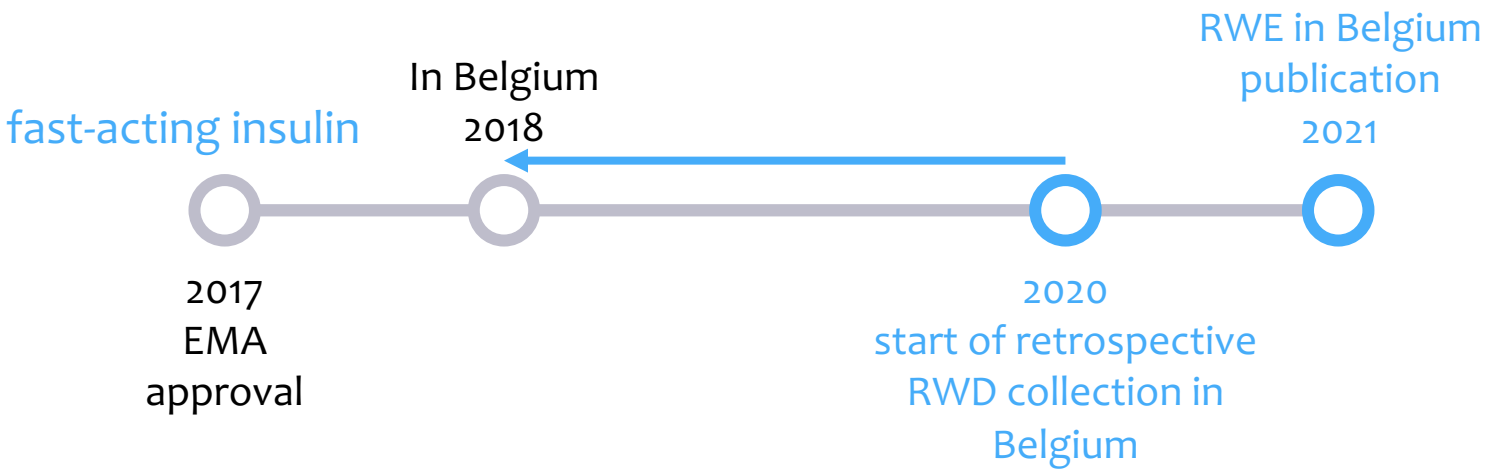
Results: Overall, 343 participants were randomized: 172 received Gla-300 and 171 IDeg-100. Non-inferiority (10% relative margin) of Gla-300 versus IDeg-100 was shown for the primary endpoint (percentage TIR ≥ 70 to ≤ 180 mg/dl): least squares (LS) mean (95% confidence interval) 52.74% (51.06%, 54.42%) for Gla-300 and 55.09% (53.34%, 56.84%) for IDeg-100; LS mean difference (non-inferiority): 3.16% (0.88%, 5.44%) (non-inferiority $P = .0067$). Non-inferiority was shown on glucose total coefficient of variation (main secondary endpoint): LS mean 39.91% (39.20%, 40.61%) and 41.22% (40.49%, 41.95%), respectively; LS mean difference (non-inferiority) −5.44% (−6.50%, −4.38%) (non-inferiority $P < .0001$). Superiority of Gla-300 over IDeg-100 was not shown on TIR. Occurrences of self-measured and CGM-derived hypoglycaemia were comparable between treatment groups. Safety profiles were consistent with known profiles, with no unexpected findings.

Conclusions: Using clinically relevant CGM metrics, InRange shows that Gla-300 is non-inferior to IDeg-100 in people with T1D, with comparable hypoglycaemia and safety profiles.

Retrospective RWE studies new insulins

RWE = real-world evidence

Retrospective RWE studies new insulins



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ORIGINAL ARTICLE

WILEY

Glucose control using fast-acting insulin aspart in a real-world setting: A 1-year, two-centre study in people with type 1 diabetes using continuous glucose monitoring

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EMA = European Medicines Agency; RWD = real-world data; RWE = real-world evidence

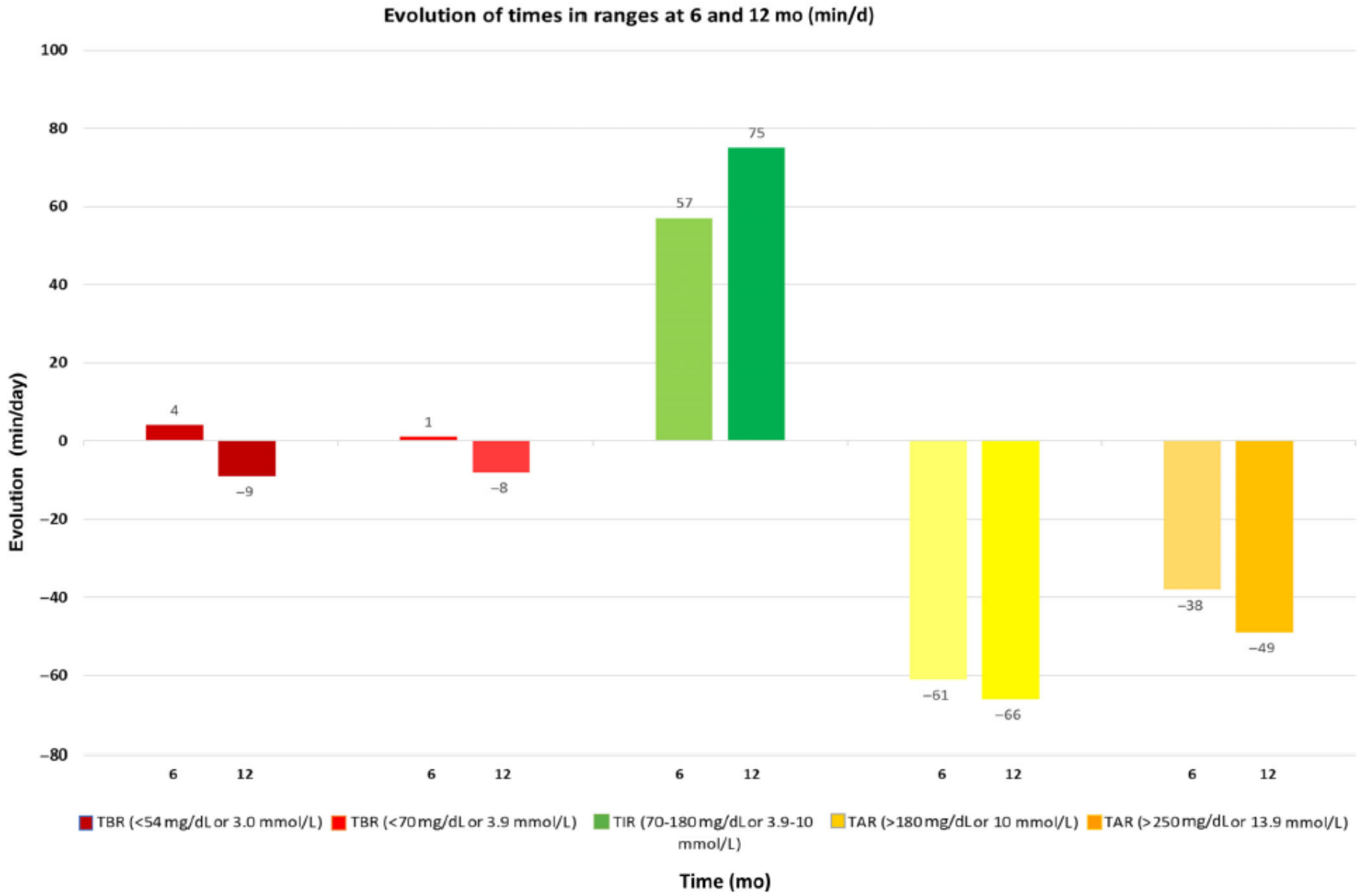
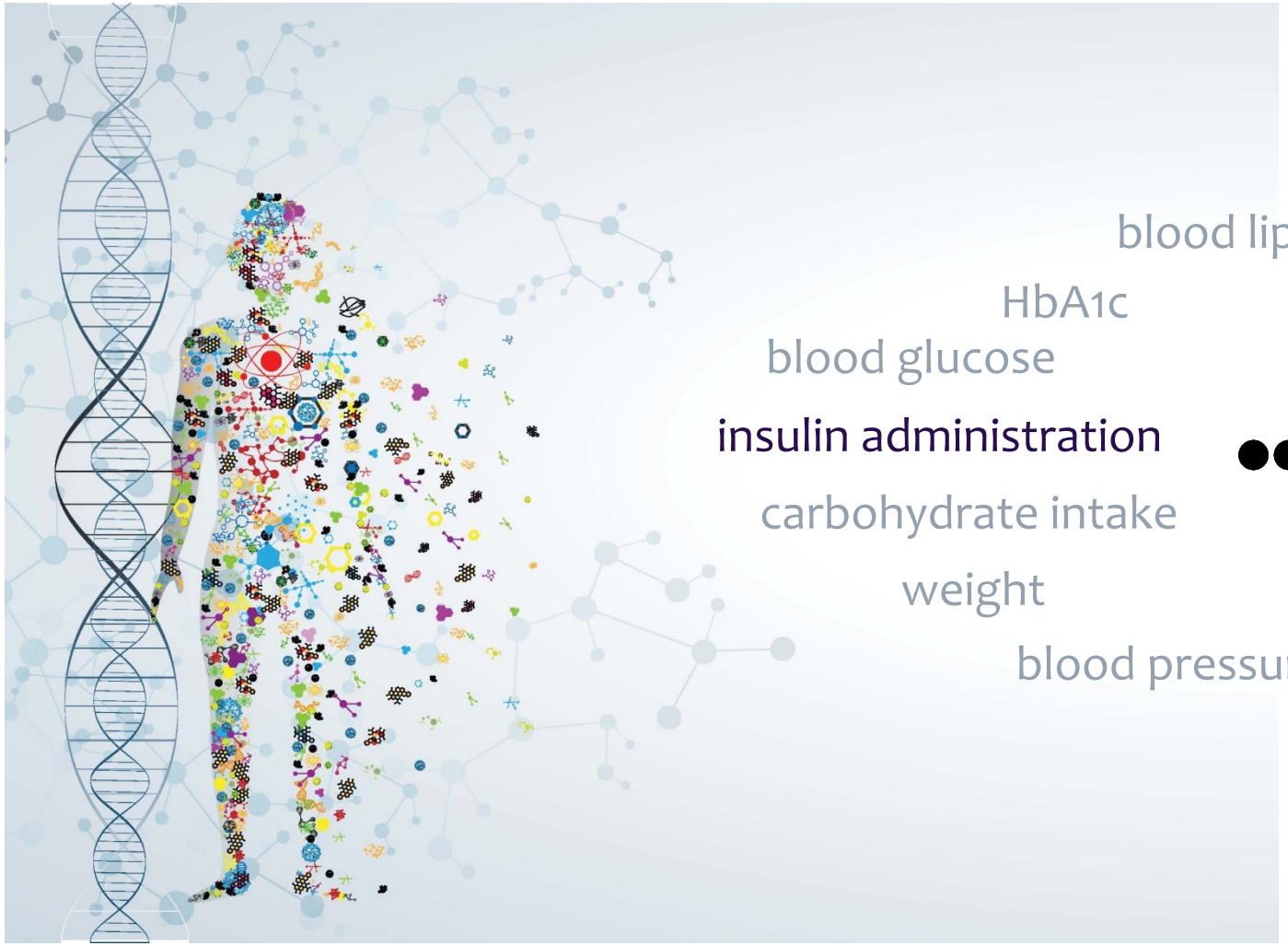


FIGURE 2 Evolution of glucometrics at 6 and 12 months in the total study population in change in min/d

Type 1 diabetes data



blood lipids

HbA1c

heart rate

blood glucose

insulin administration

activity data

carbohydrate intake

eye fundus

weight

kidney function

blood pressure

QOL

image taken from AIMultiple

Smart pens


Calculate Dose
40 u
Active Insulin
118 mg/dL
Current Glucose
Today
Rapid-acting
4 u
Glucose
118
Carbs
20 g
Rapid-acting
5.5 u
Glucose
125
HOME
LOGBOOK
REPORTS
SETTINGS

Type 1 diabetes data

blood lipids

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QOL

image taken from AIMultiple


photo by Ian Stauffer on Unsplash

Patient-reported outcomes

important in person-centred care

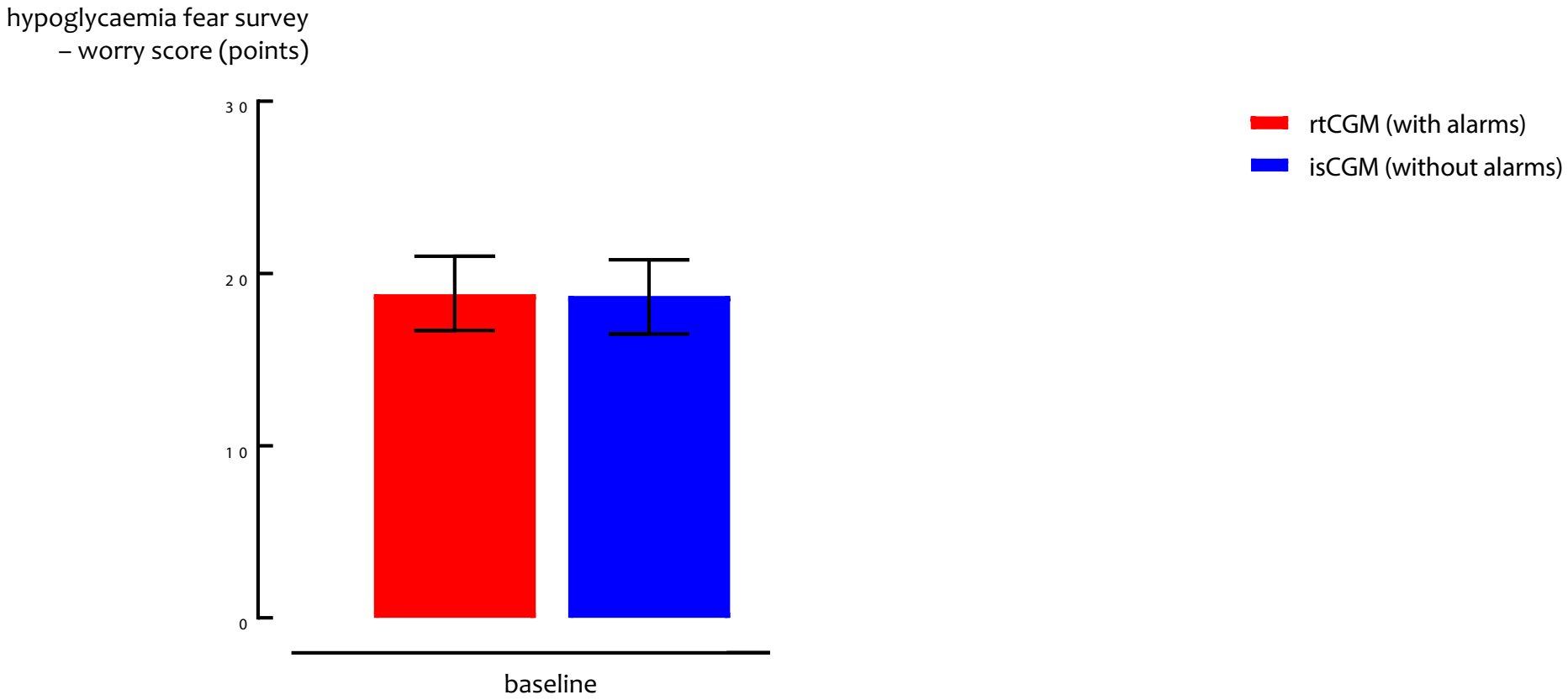
information that comes directly from the person

captured by e.g. questionnaires or diaries

generate a lot of data

www.fda.gov/media/109626/download

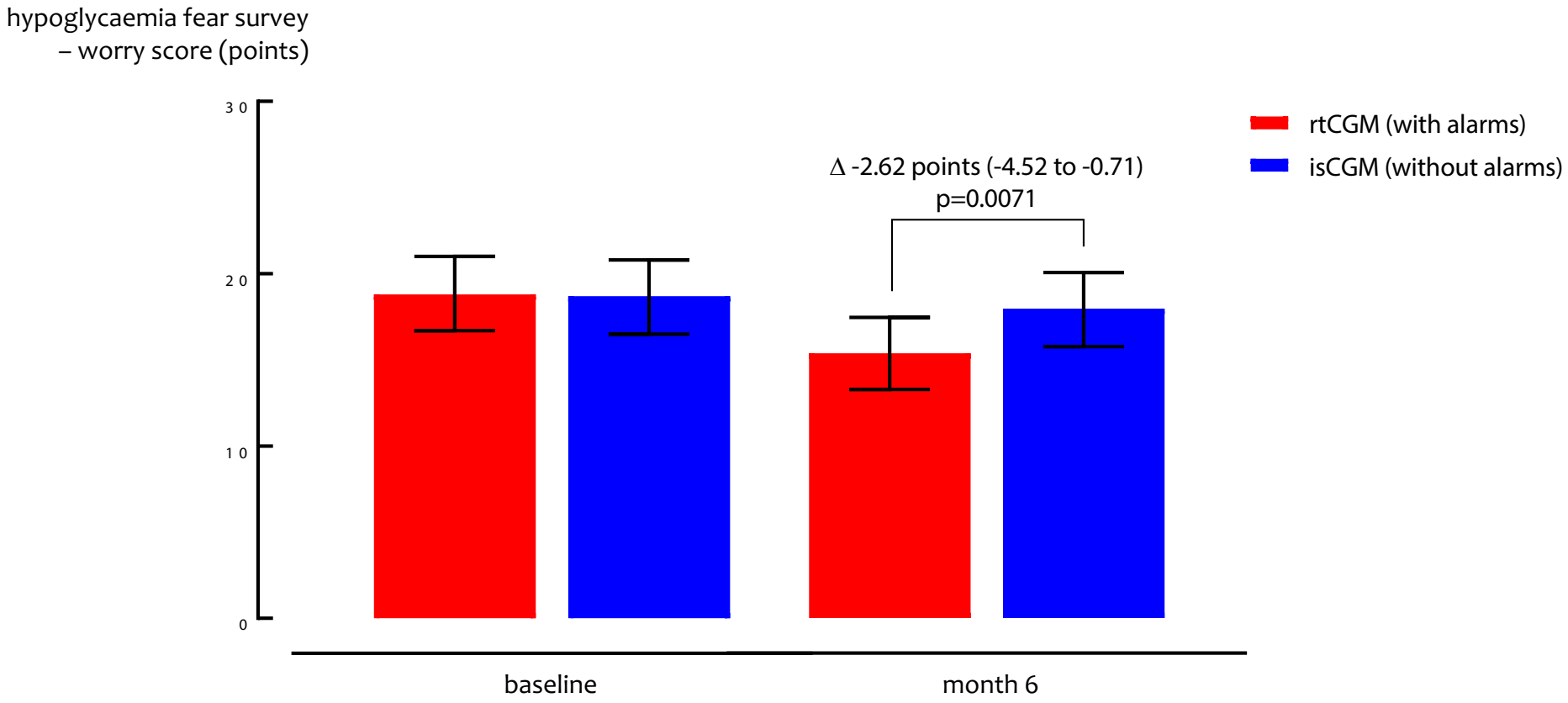
ALERTT1 – difference in quality of life



Data represent least-squares mean with 95% CI. HFS-worry score ranges 0–72.

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

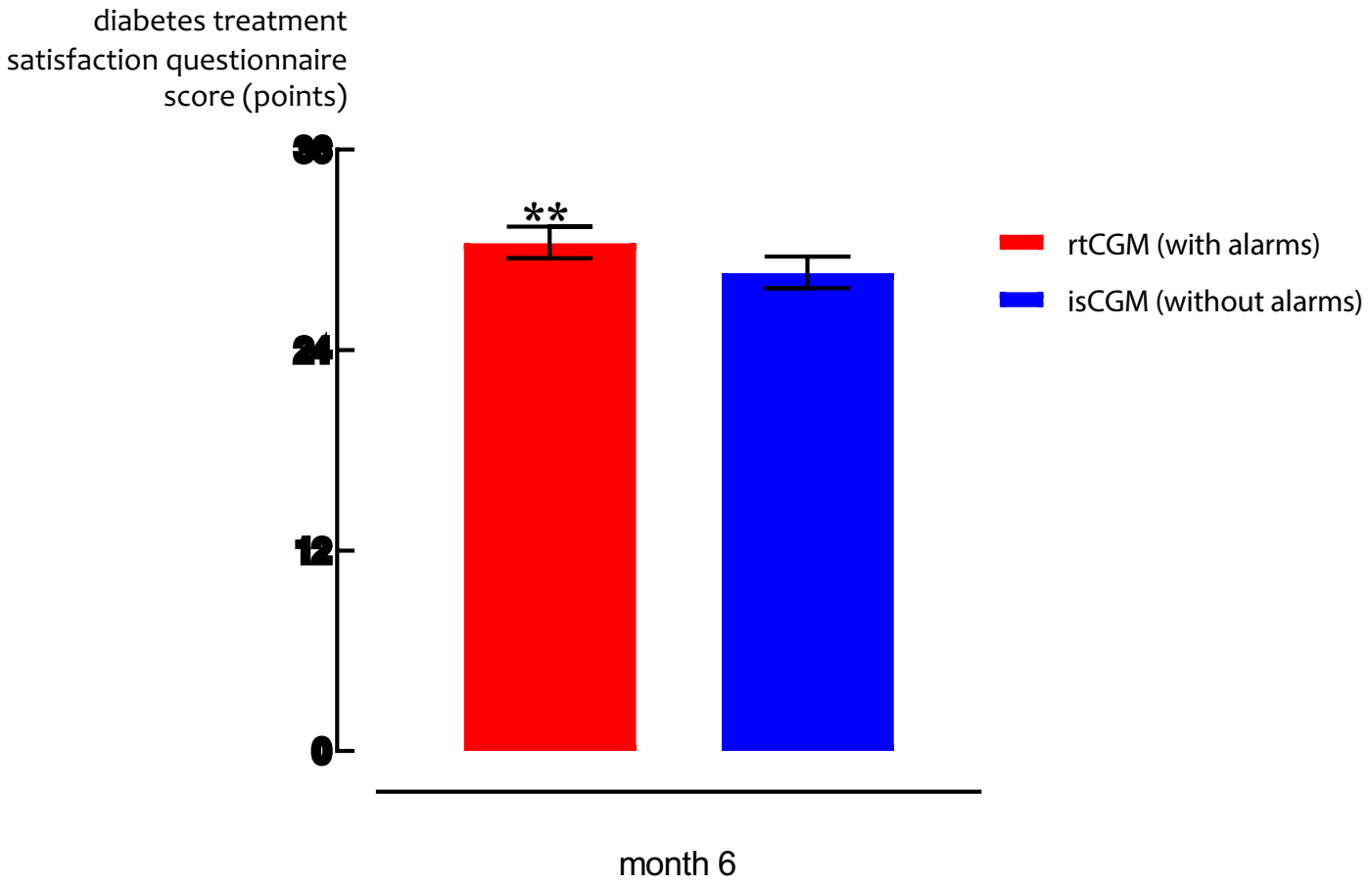
ALERTT1 – difference in quality of life



Data represent least-squares mean with 95% CI. Mean group difference (95% CI). HFS-worry score ranges 0–72.

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

ALERTT1 – difference in quality of life



Data represent least-squares mean with 95% CI. DTSQ score ranges 0–36.

Visser MM *et al*. Lancet 2021. doi: 10.1016/S0140-6736(21)00789-3

Type 2 diabetes data?

blood lipids

HbA1c

heart rate

blood glucose

insulin administration

activity data

carbohydrate intake

eye fundus

weight

kidney function

blood pressure

QOL

image taken from AIMultiple

Conclusion

TIR is a valuable outcome parameter, both in clinical care and diabetes research

TIR targets are increasingly used by patients to evaluate glycemic control

Relation between TIR and complications is becoming clear, but the exact nature of the relationship (dependent/independent of HbA1c) is still unclear

Conclusion

Data determine how we evaluate, treat and follow our patients

People with diabetes are intensively using data to balance their glucose control during daily life

Clinical research is now unthinkable without the use of data

Other data such as patient reported outcome measure are becoming part of integrated care and research

Data from smart pens will expand the use of insulin data to people on MDI

Digitalisation of diabetes data has changed the diabetes world forever…
and will continue to do so in the upcoming years