Glycaemic Variability – Assessment with CGM / AGP

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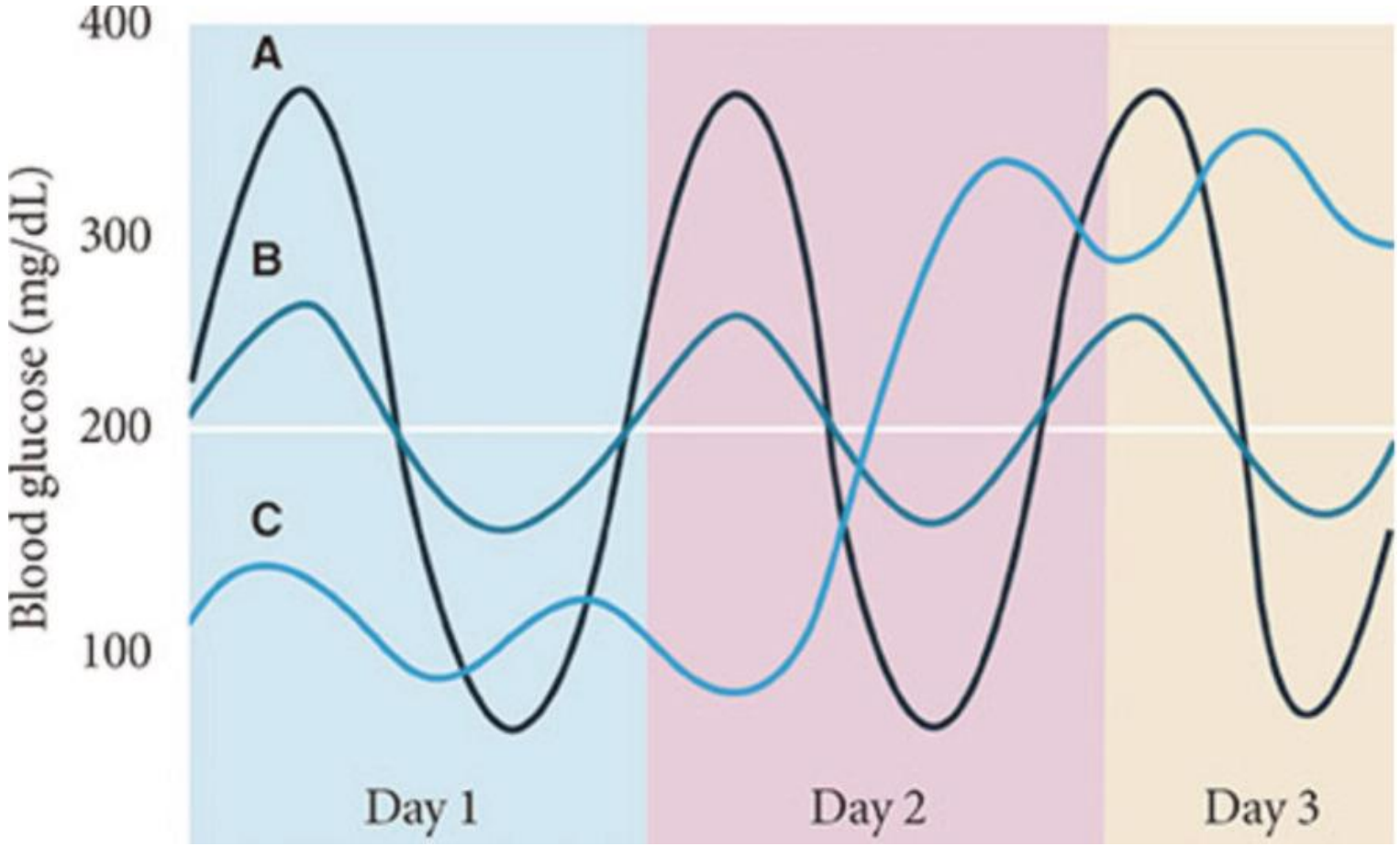
Disclosures

- Dr Cranston has received research grants, speaker fees or consultation advisory fees from the following:
  - Eli Lilly, Boehringer-Ingelheim, NovoNordisk, Sanofi, Janssen, MSD, AstraZeneca, BMS, Roche Diagnostics, Johnson & Johnson, Animas, Abbott Diabetes Care, Takeda

- Dr Cranston is a share-holding director of the following Diabetes-related companies
  - Southern Diabetes Medical Services LLP
  - The AGP Clinical Academy Ltd

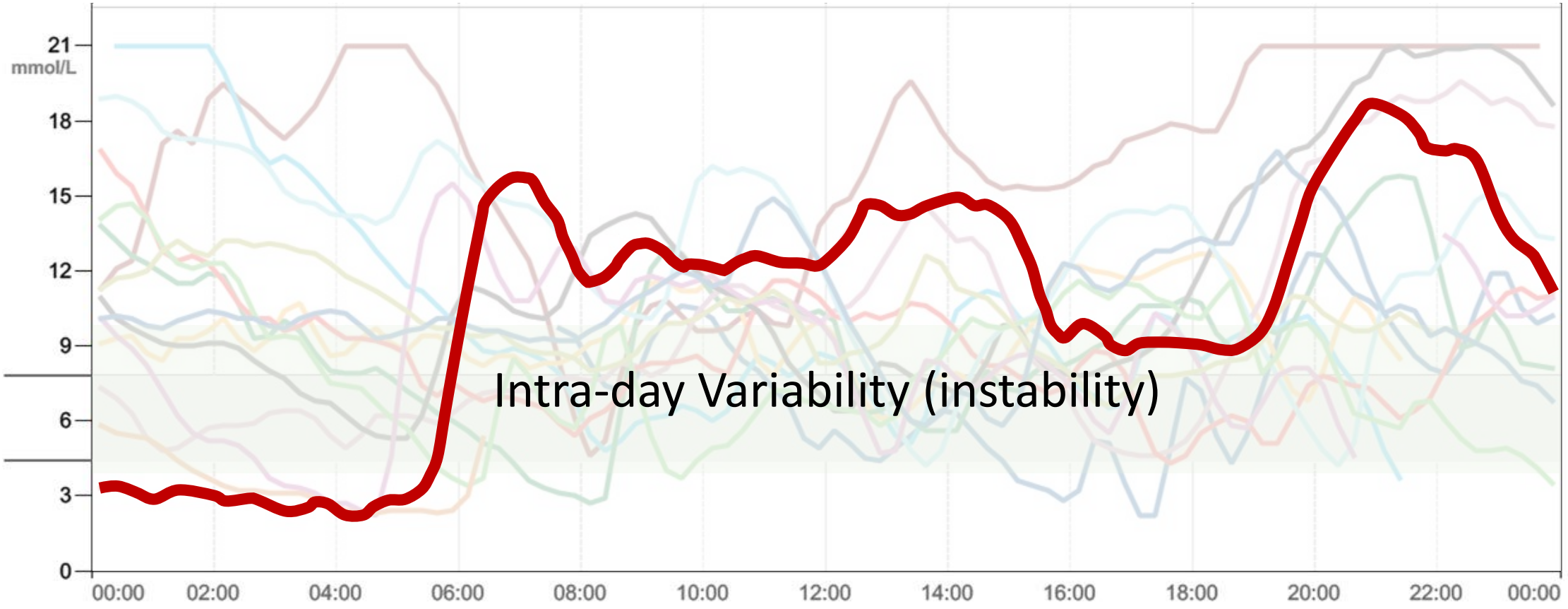
Defining Glycaemic Variability

“deviation from steady state”



Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J 2015;39:273-82.http://dx.doi.org/10.4093/dmj.2015.39.4.273

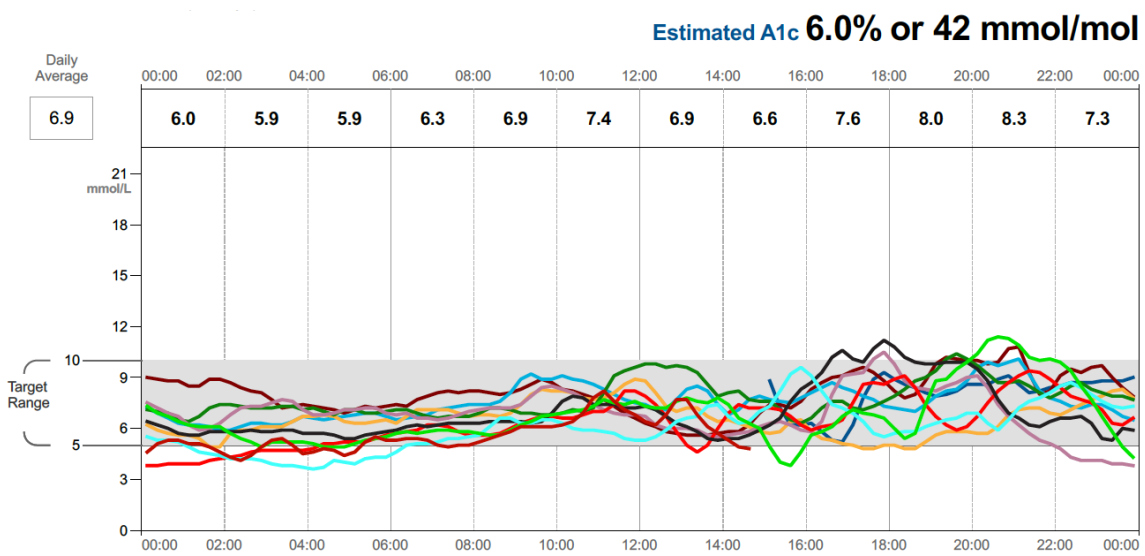
CGM and Inter-day Variability

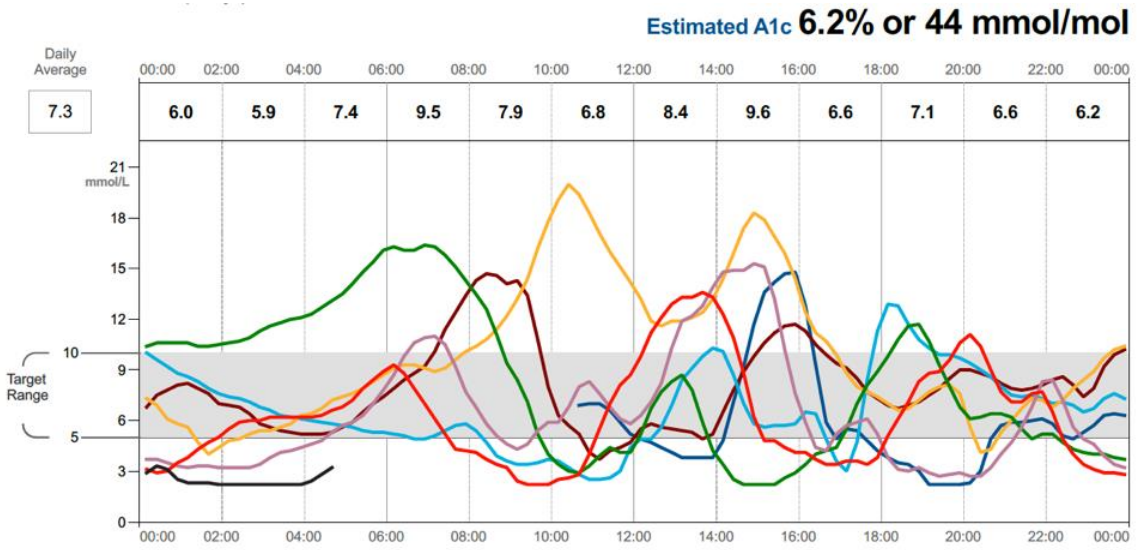


Relationship between A1c and GV

‘To achieve a near target HbA1c there cannot be excessive GV’

FALSE!

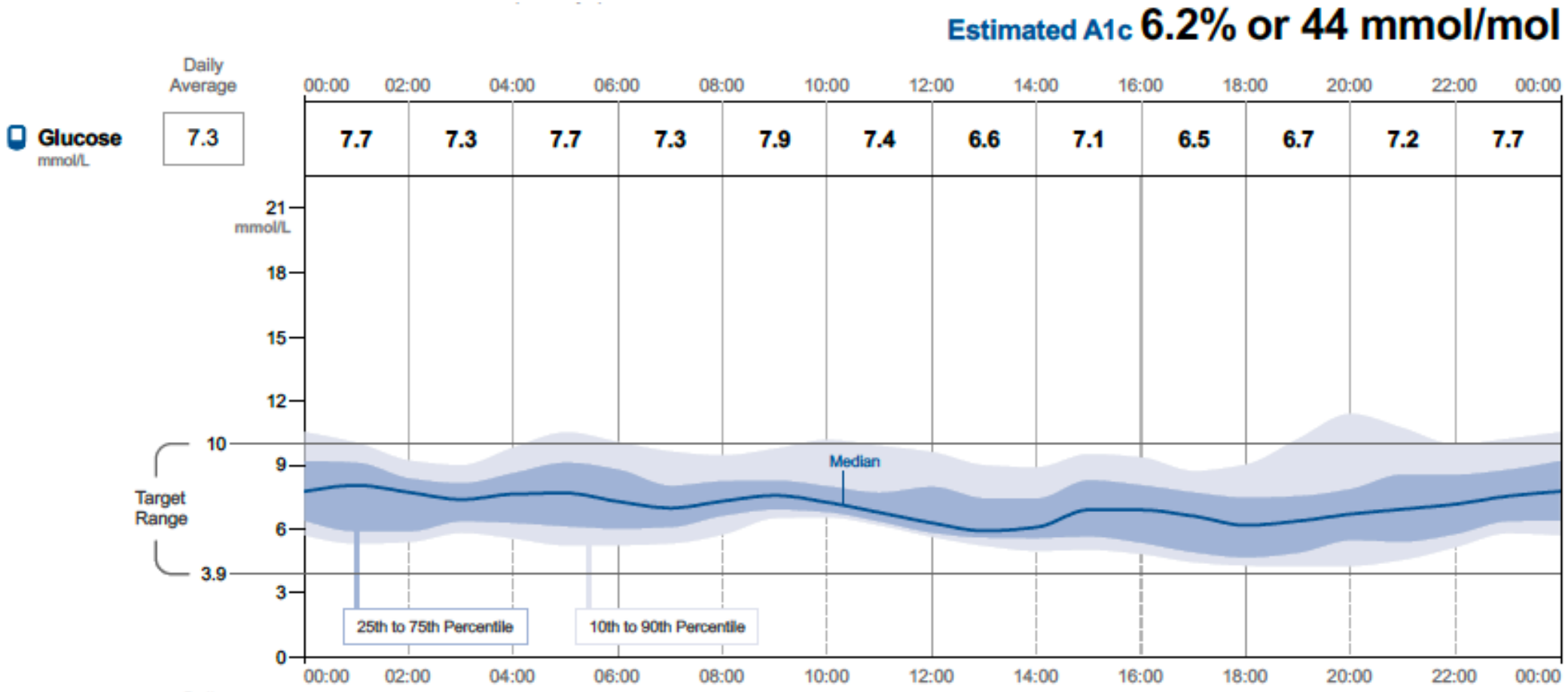




Assessment of GV

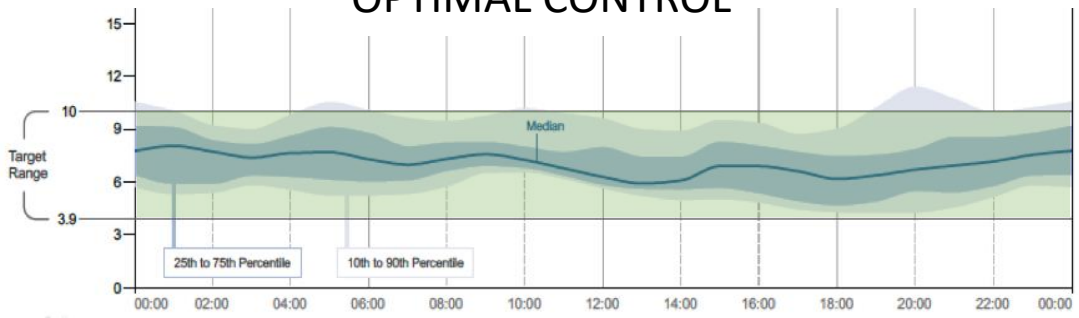
- HbA1c is not useful
- SMBG *can* be useful but requires careful utilisation
  - Surrogates such as fasting variability have been used to describe increased CV and other outcome risks in a number of different populations
- The “Gold Standard” for assessment of GV is Continuous Glucose Monitoring
  - The only way to visualise inter-day variability constructively is the AGP
  - AGP metrics such as IQR / IDR are useful non-parametric measures of GV
  - Many numeric formulae exist but no single metric can describe the clinical features of GV which require intervention

AGP Representing ‘Good Diabetes Control’

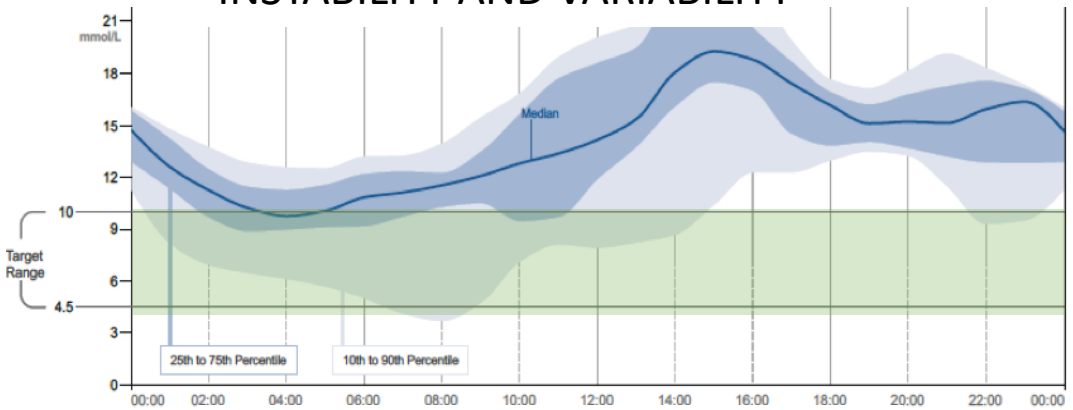


AGP and Variability

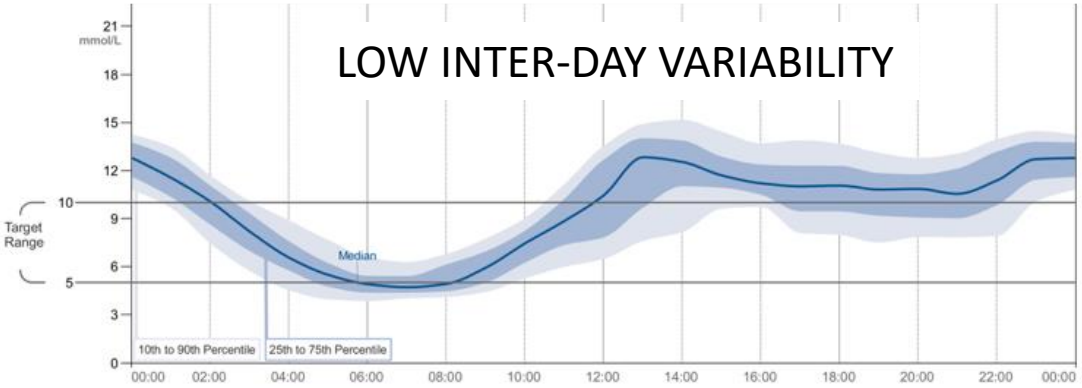
OPTIMAL CONTROL



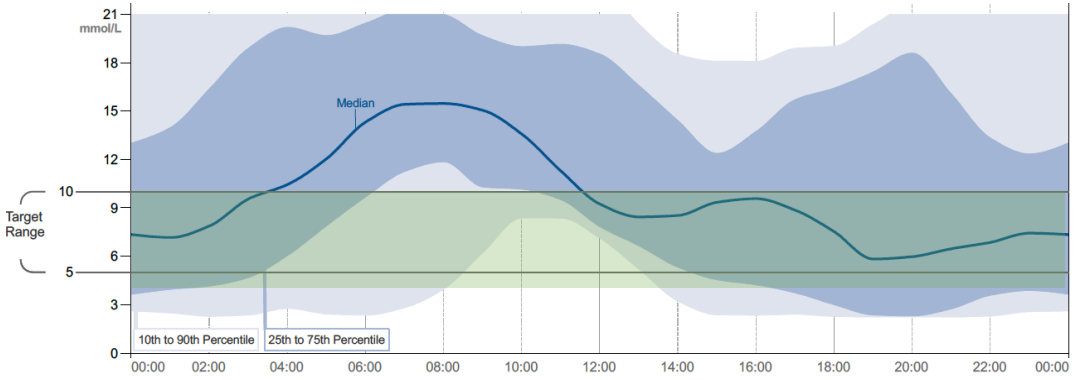
INSTABILITY AND VARIABILITY



LOW INTER-DAY VARIABILITY



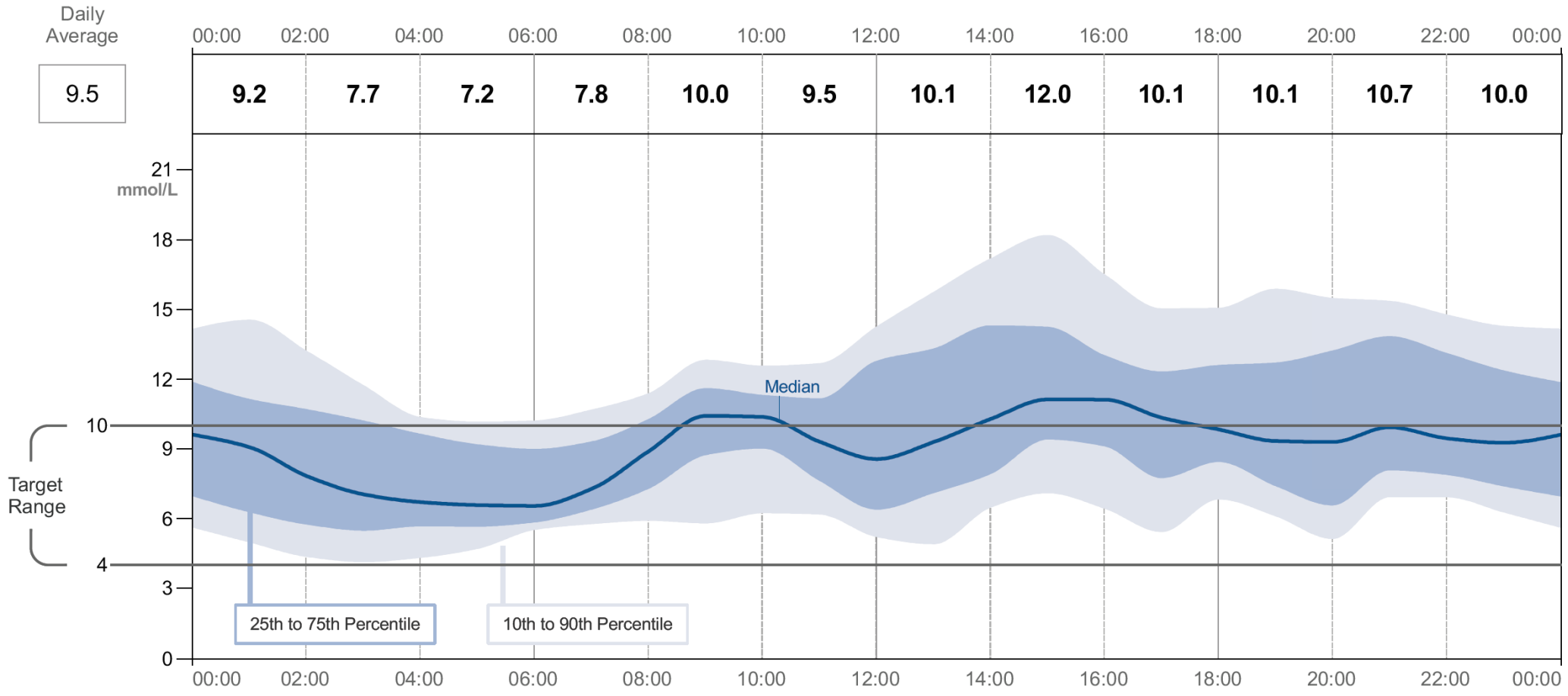
EXTREME INTER-DAY VARIABILITY



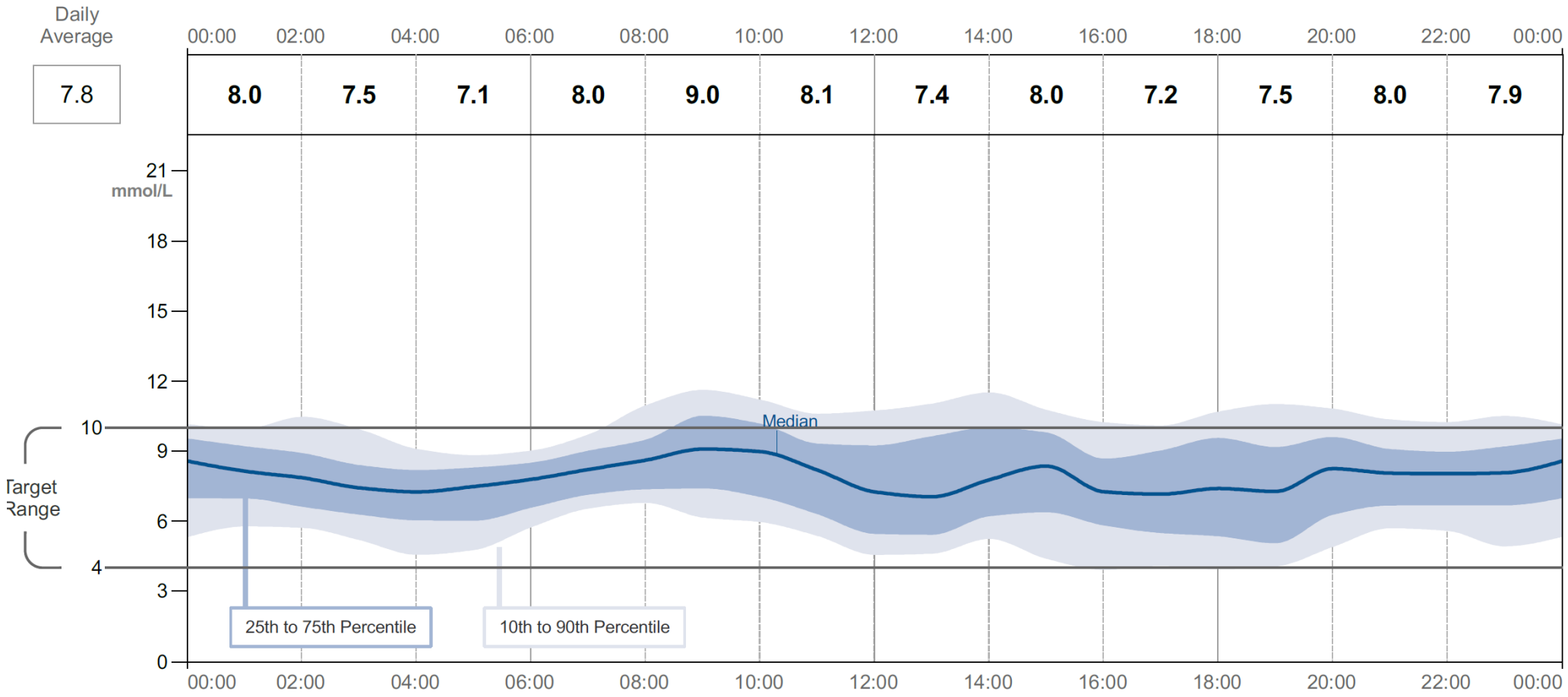
Andrew

- 44 yr old man Senior Police Officer
- Type 1 diabetes since aged 11 / BMI 27
- Retinopathy / hypertension
- A1c generally in 7.5 – 8.5% range (most recently 8.3%)
- No significant hypoglycaemia history
- Treatment with basal / bolus MDI (Lantus / Humalog DAFNE alumnus)
- 28units Lantus / 1:10 iCHO and 1:3 ISF (TDD 50-55units)

1st 2 weeks sensor wear

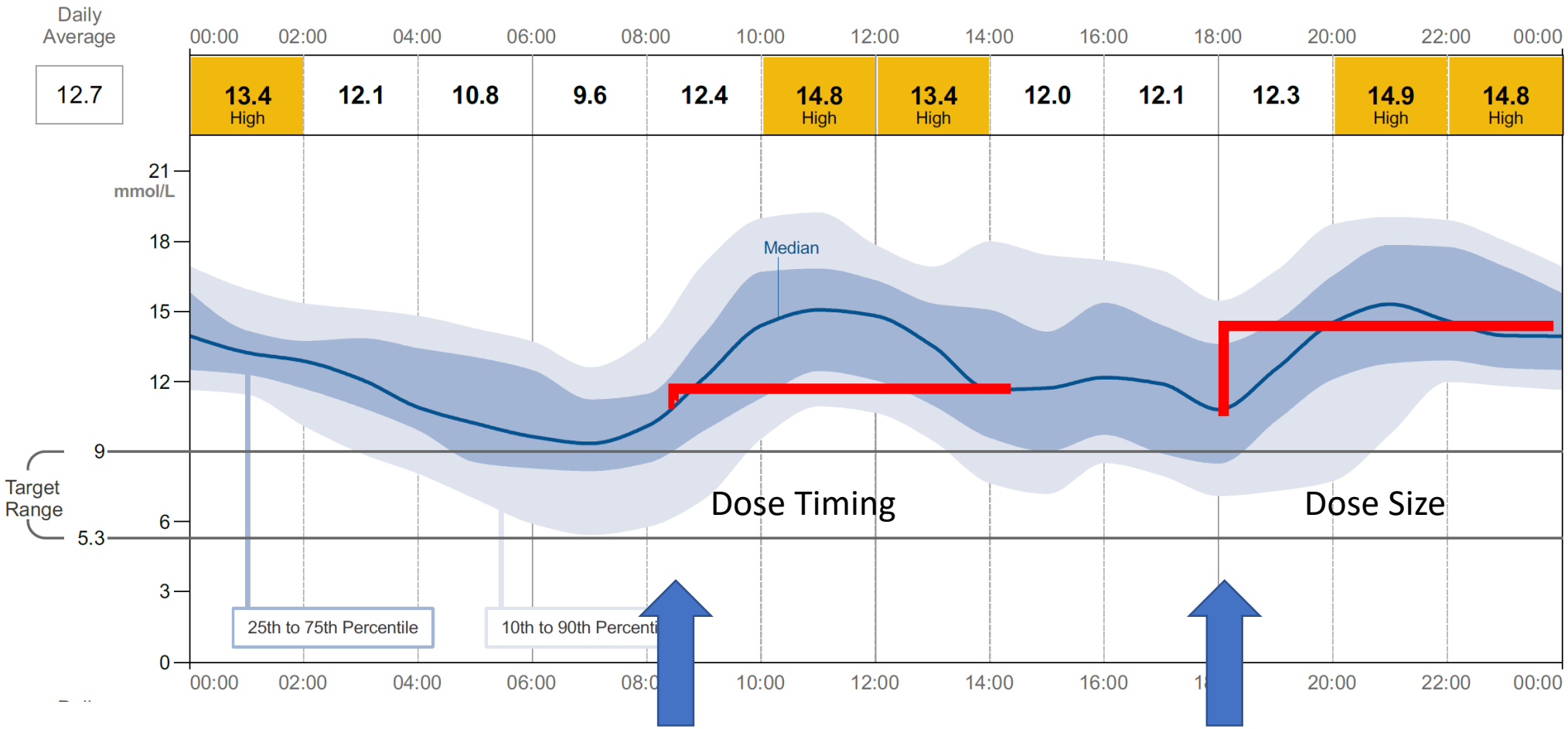


1 month after intervention

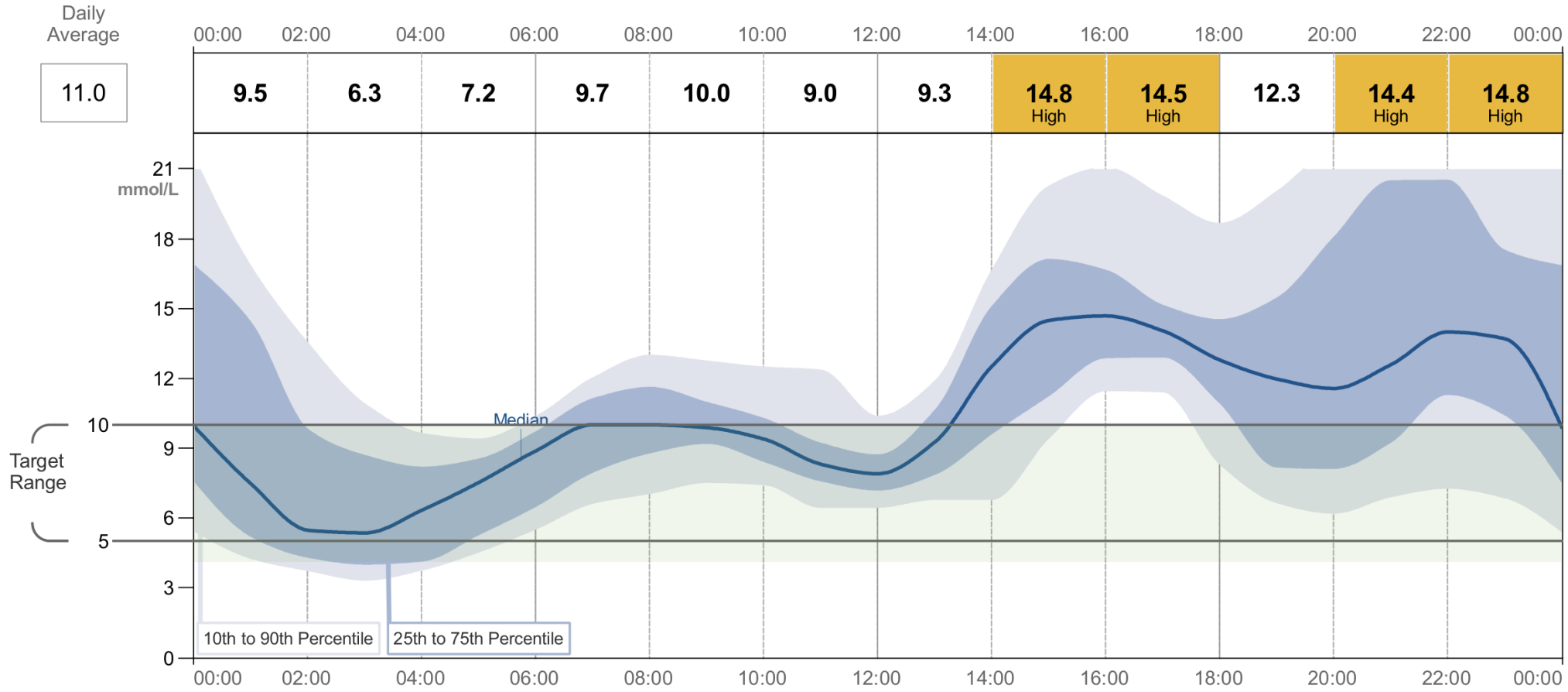


Anna

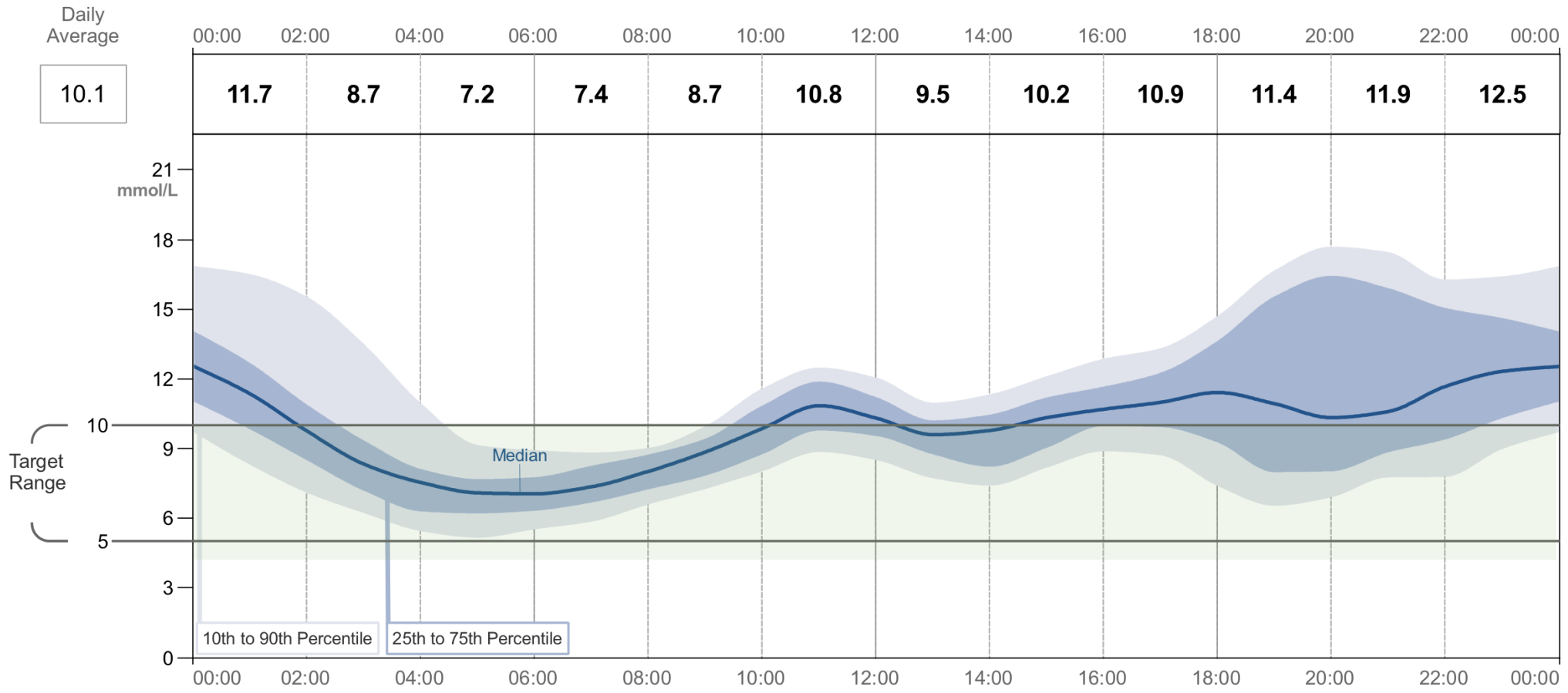
- 38yrs Estate Agent; T1DM since aged 21
- Struggles with weight and fibromyalgia
- Eats 2 meals per day (B’fast and Evening)
- Basal / Bolus insulin regimen (Lantus / Novorapid)
- Last HbA1c 9.2% - concerned with hyperglycaemia around meals
- Tried “low carb” – no real difference but had occasional hypo


Daily Average
12.7
00:00
02:00
04:00
06:00
08:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
00:00
13.4 High
12.1
10.8
9.6
12.4
14.8 High
13.4 High
12.0
12.1
12.3
14.9 High
14.8 High
21
mmol/L
18
15
12
9
6
5.3
3
0
Target Range
Median
Dose Timing
Dose Size
25th to 75th Percentile
10th to 90th Percenti

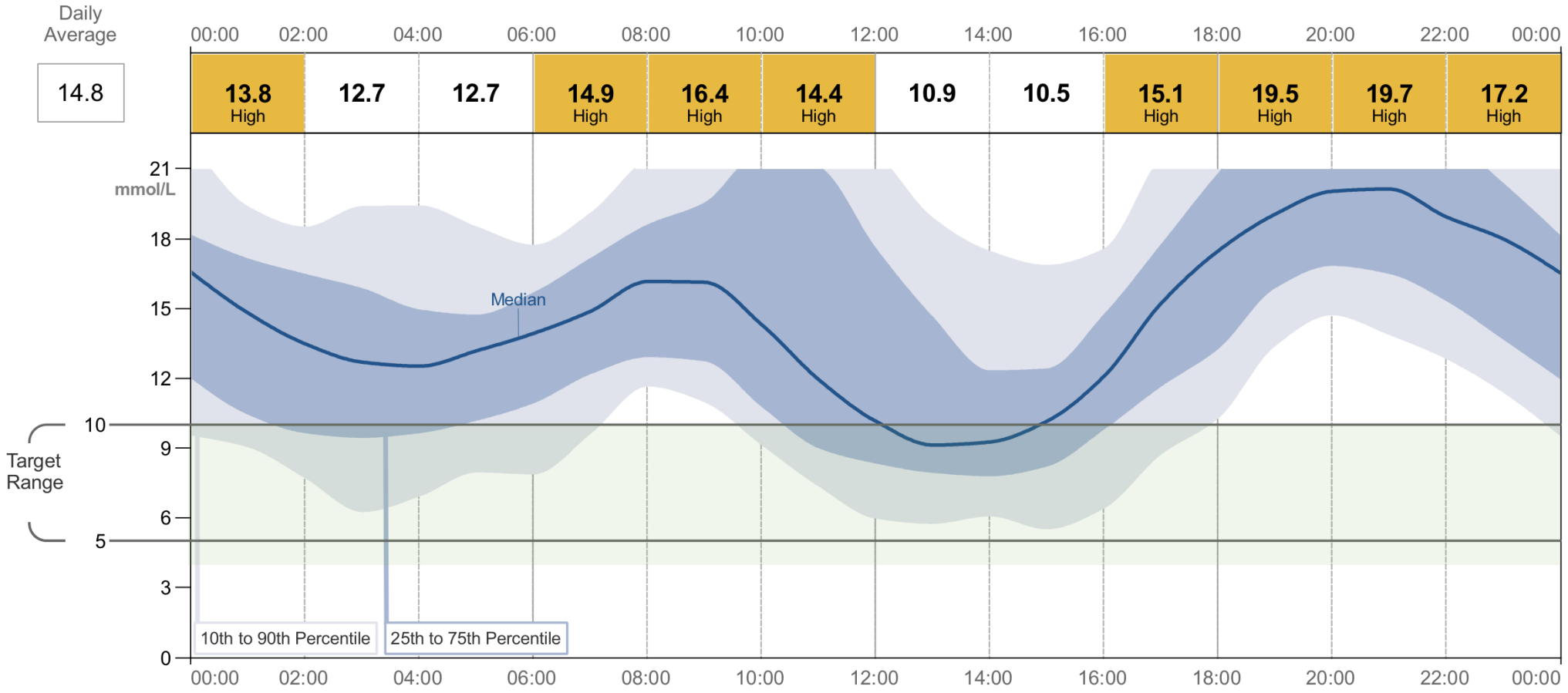
Mr J is a businessman, he is on a basal bolus regimen with am Tresiba and Novorapid, he experienced a recent hypo after work & has been shaken by it



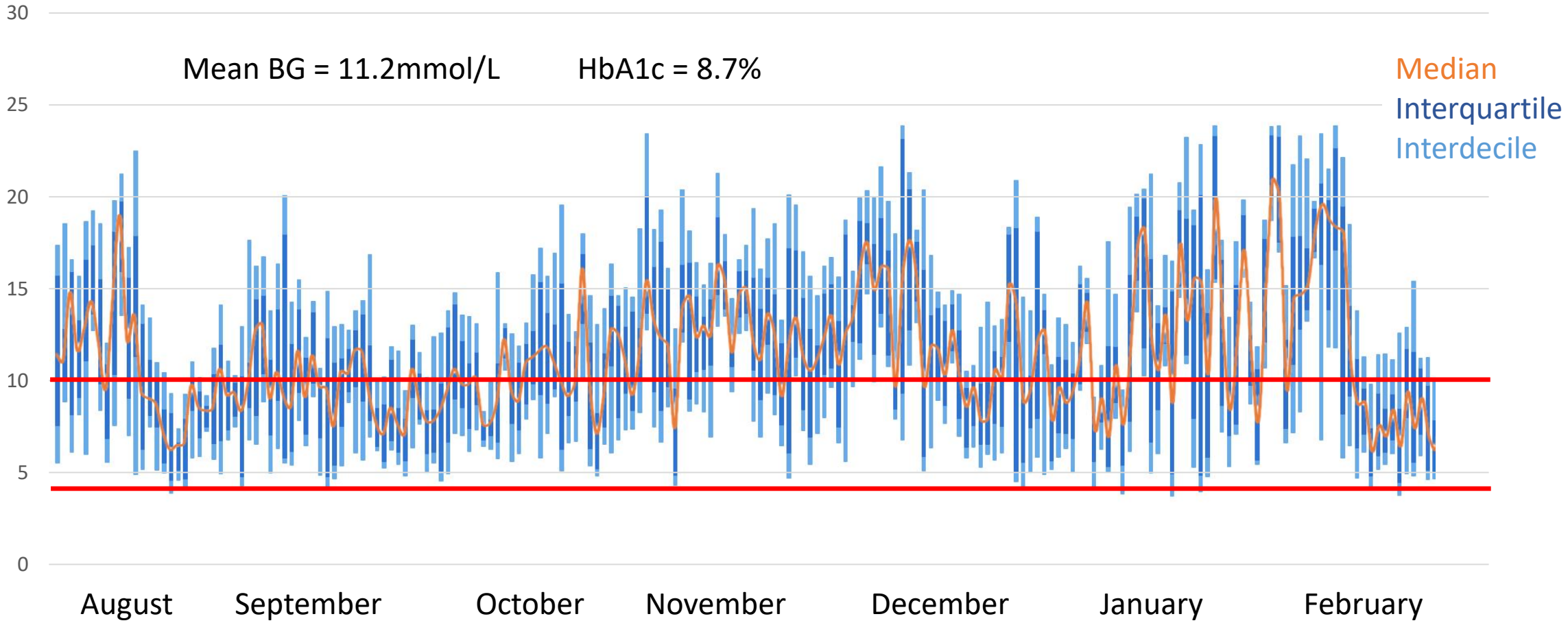
Miss R eats at 8am, 1pm and 6pm
she uses twice daily Levemir and Humalog at meals



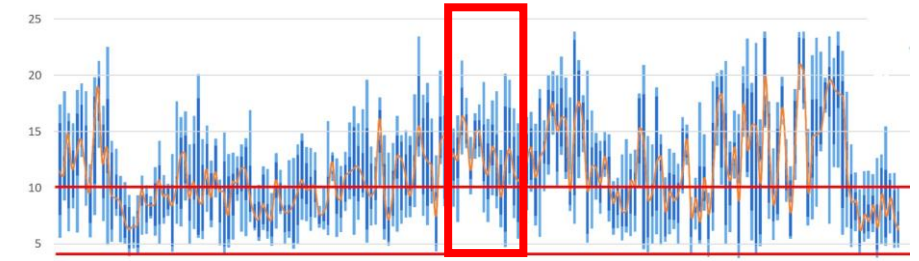
Mr A tells you he uses basal bolus insulin and tests 3x daily before meals, this is his first AGP trace, collected using a professional (blinded) sensor and he's shocked by it…

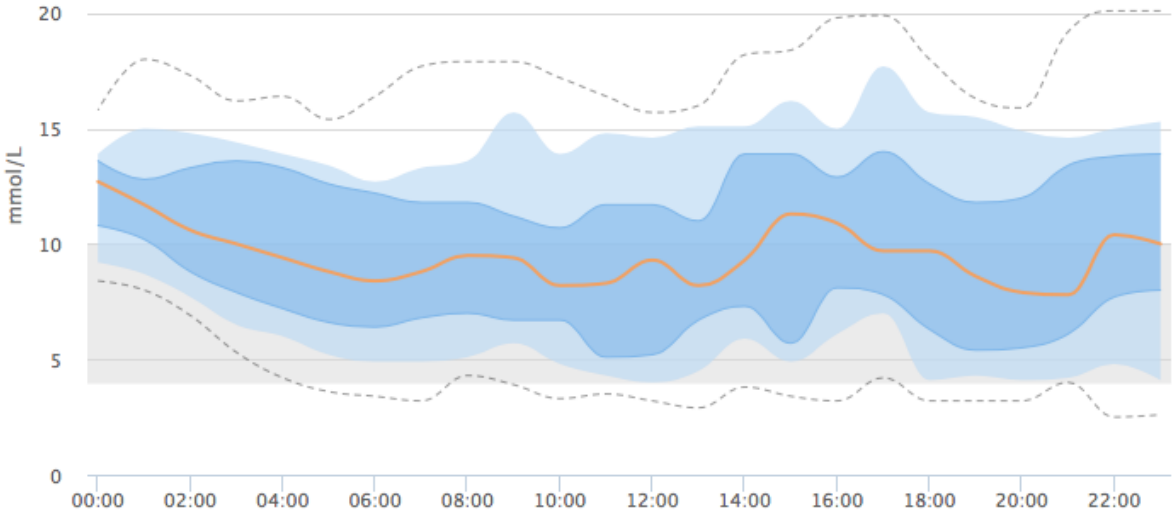


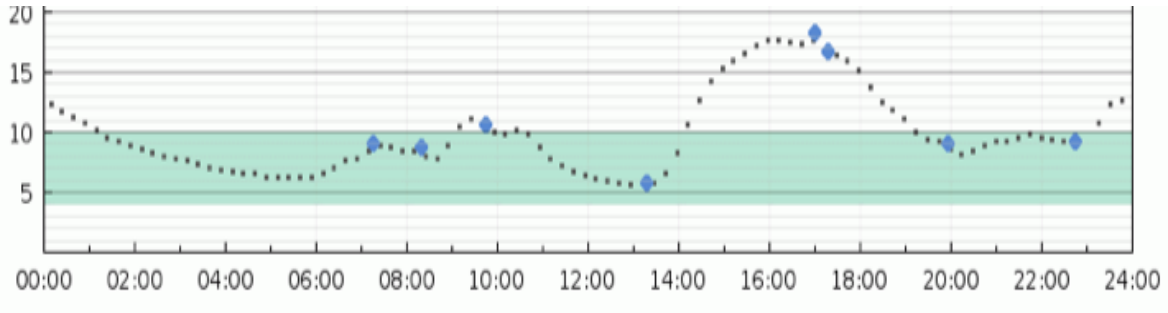
glucose variability is variable over time!



what made the difference?







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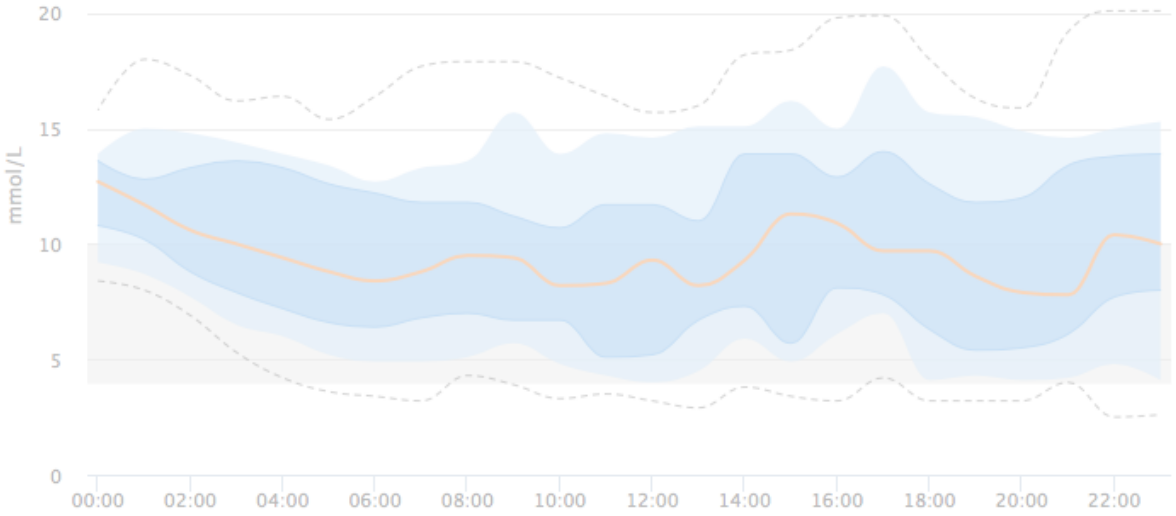
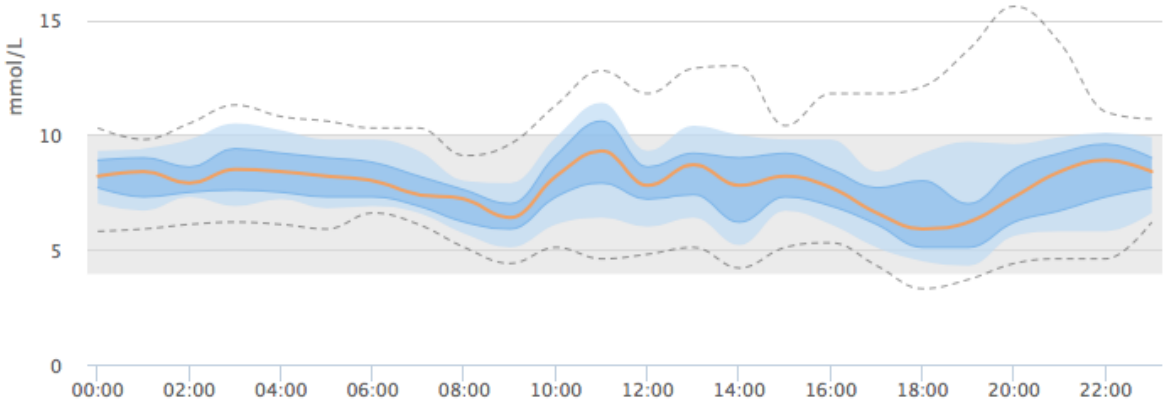
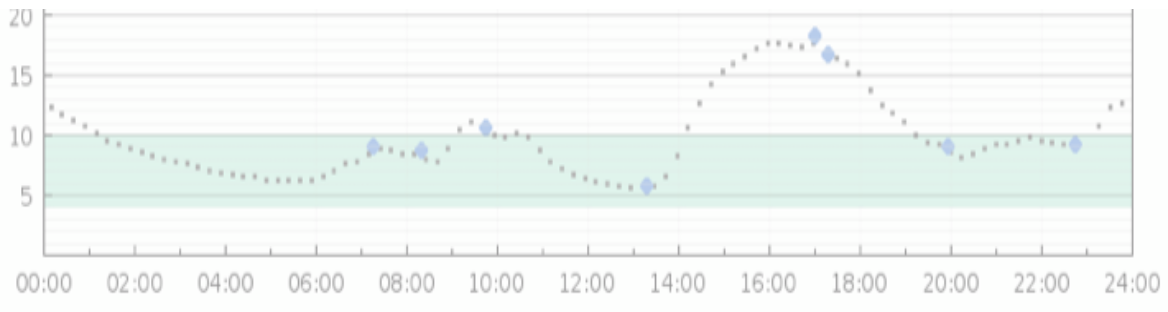
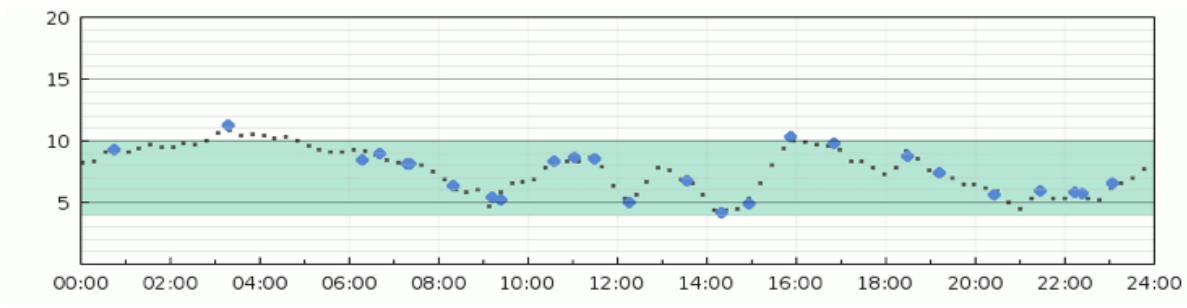








A clinical approach to minimising GV

- Do not assume a single cause
- Distinguish Variability from instability (but recognise co-existence!)
- Target the time of day with the greatest variability first
- Target a single change and review (KaiZen)

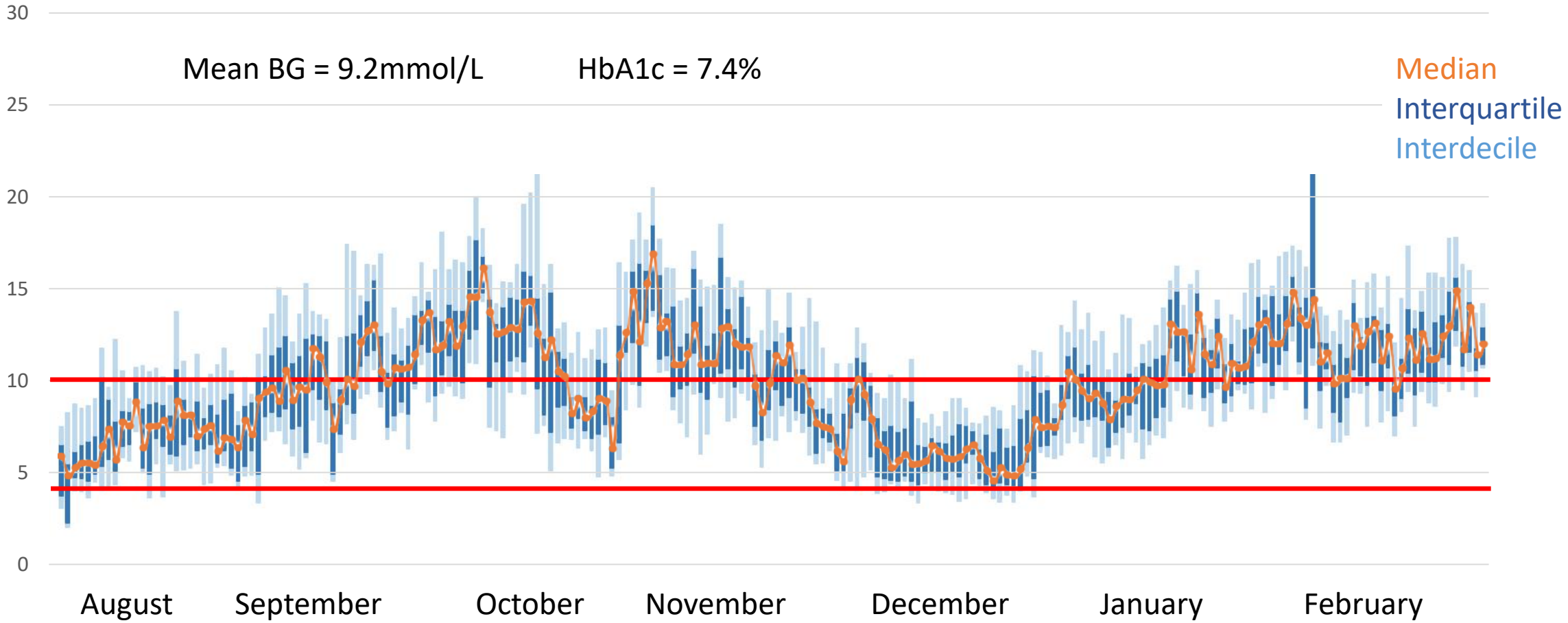
- Combined use of history taking and AGP analysis can highlight the most likely causes (using individual day profiles to confirm theories)
- Variability is most commonly addressed by behavioural rather than therapy changes, so explanation and agreement on strategy is key!

Summary

- Glycaemic Variability represents a key cause of detrimental outcomes in diabetes care (both physical and emotional)
- It can be readily assessed through use of CGM
- CGM data should be clinically interpreted using the AGP

- Using AGP and working towards an increased “time in range” approach rather than an exposure-driven approach results in reduced GV
- Reduced GV improves both QOL and reduces adverse outcomes

glucose variability over time (CGM)



GV Indices

Table 6.1 Summary of main glycemic parameters in CGM [2]

Parameters	Name	Calculation method	Features/clinical significance
Glycemic level	MBG	Mean of daily continuous 24-h blood glucose	Reflects the overall blood glucose level
	Pre-meal 1-h MBG	MBG within 1–60 min before three meals	Reflects the characteristics of preprandial or postprandial blood glucose, that is, the impact of food intake on blood glucose
	Post-meal 3-h MBG	MBG within 1–180 min after three meals	
	PT	Frequency and total time of blood glucose values above, below, and within the target range (presented by pie chart and statistics)	Emphasizes on reflecting the characteristics of blood glucose changes, which is simple and easy to understand, suitable for diabetes education
	AUC	Area between the target blood glucose curve and CGM measurement curve	A comprehensive statistical method for analyzing the time and extent of blood glucose changes
Glycemic variability	SDBG	Standard deviation of blood glucose measurements during CGM	Reflects overall deviation from the mean, without discriminating major and small fluctuations
	LAGE	Difference between maximum and minimum blood glucose concentrations within a day	Reflects the range of glucose fluctuations
	MAGE	Mean of amplitude of glucose excursions (more than one SDBG) based on the direction of the first qualifying AGE	Truly reflects the degree of glycemic excursions rather than discrete features by removal of small amplitudes that do not exceed a certain threshold
	MODD	Mean of the absolute difference between paired blood glucose values in two consecutive 24-h periods	Assesses the degree of inter-day glucose fluctuations and reflects the repeatability of daily blood glucose

Notes: *MBG* mean blood glucose, *PT* percentage of time, *AUC* area under the curve, *SDBG* standard deviation of blood glucose, *LAGE* largest amplitude of glycemic excursion, *MAGE* mean amplitude of glycemic excursion, *MODD* mean of daily differences

Table 6.2 Summary of glycemic variability measures in CGM

Parameter	Definition	Formula	Variables
SDBG	Standard deviation of blood glucose	$\sqrt{\frac{\sum\left(G-\bar{G}\right)^2}{N-1}}$	G = glucose measured N = number of observations
CV	Coefficient of variation	$\frac{\text{SDBG}}{\bar{G}}$	$\bar{G}$ = mean of glucose measured
LAGE	Difference between maximum and minimum blood glucose concentration within a day	$G_{\max} - G_{\min}$	$G_{\max}$ = maximum glucose measured $G_{\min}$ = minimum glucose measured
MAGE	Valid glycemic excursion is defined as more than 1 SDBG during 24-h CGM. Amplitude of glycemic excursion is calculated based on the direction of first valid excursion. MAGE is the average value of all AGEs	$\text{MAGE} = \sum\frac{\lambda}{x} \quad \text{if } \lambda > v$	λ = blood glucose changes from peak to nadir x = number of observations v = 1 SD of mean glucose for a 24-h period