From HbA1c to GMI – Novel Aspects of Diabetes Management

02 – HbA1c and GMI – Complementary indicators

Disclosures: Richard M. Bergenstal, MD

- **I have no personal financial disclosures**
- My employer, the non-profit HealthPartners Institute, contracts for my services, and I receive no personal income from the following activities:

  I have participated in clinical research, been a member of a scientific advisory board, and served as a consultant for:

  - Abbott Diabetes Care, Ascensia, CeQur, Dexcom, Eli Lilly, Hygieia, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Onduo, Roche, Sanofi and United Healthcare
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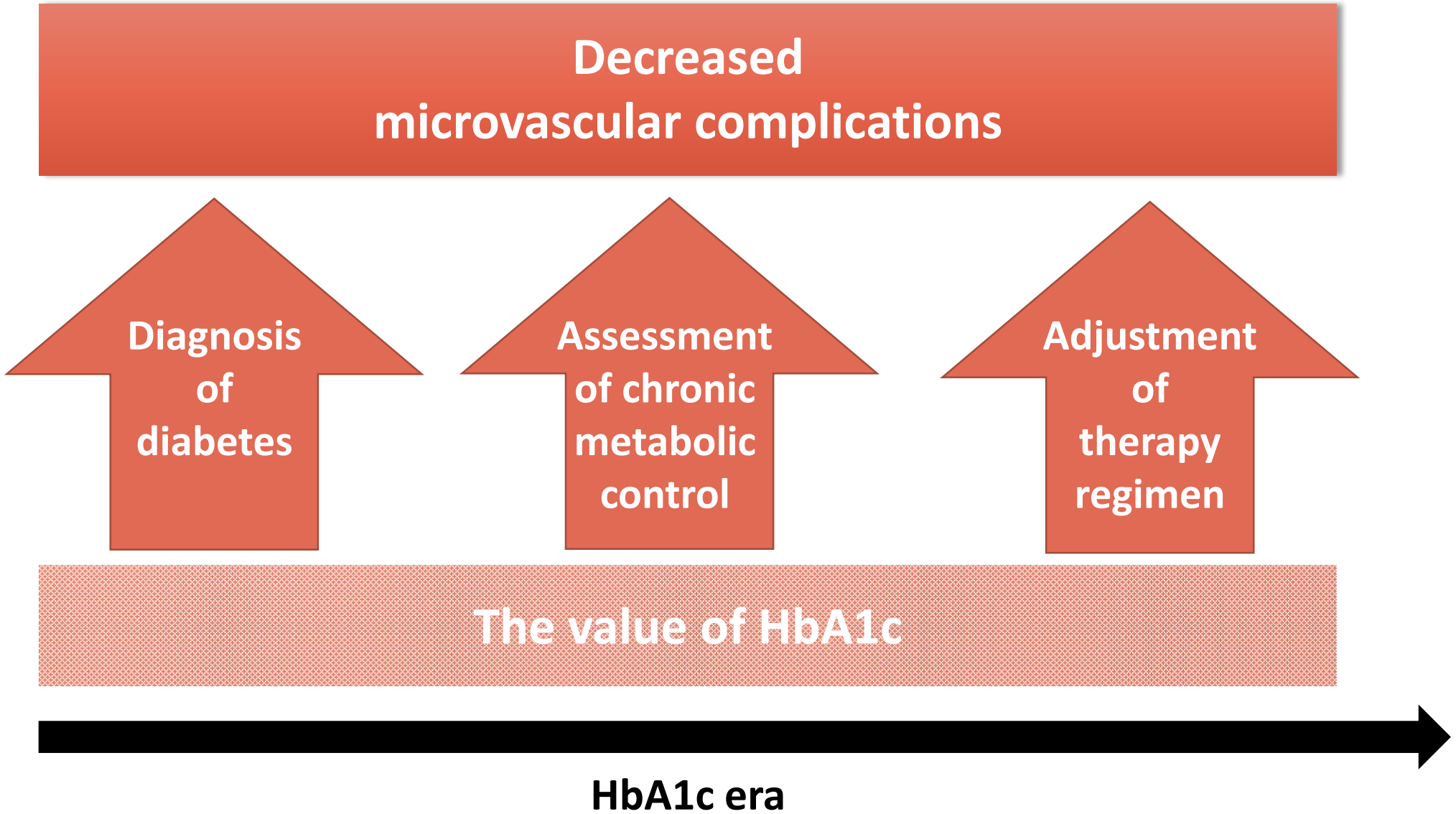
Index

CGM, continuous glucose measurement; GMI, glucose management indicator; HbA1c, glycated hemoglobin A1c

Clinical significance of HbA1c in diabetes management



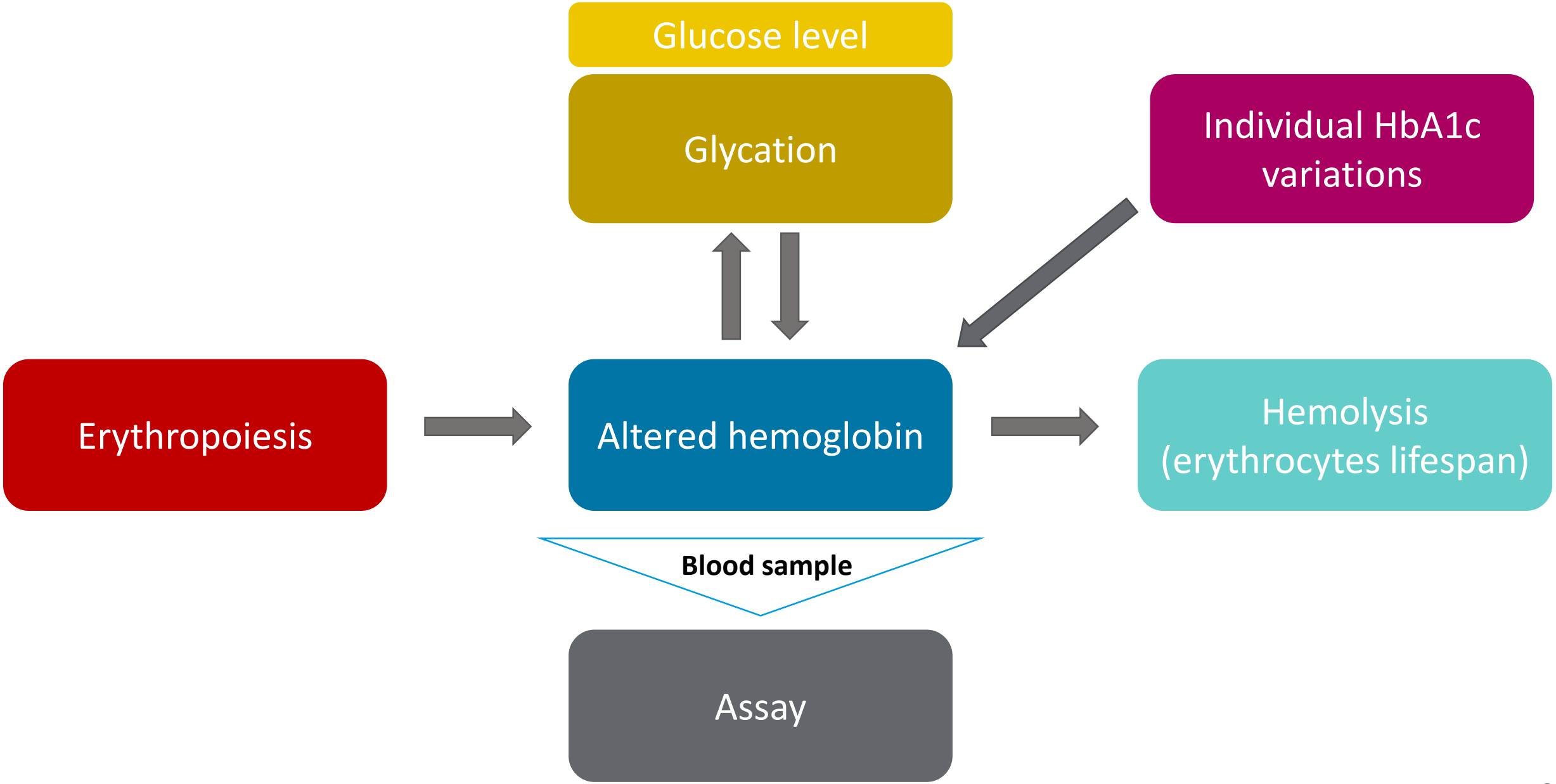
HbA1c in diabetes – Missing information using the gold standard

Because of its **biochemical properties**, some relevant aspects of the glycemic status can not be assessed using HbA1c.

- **Delay of 3 months** to obtain data on the glycemic status (mean glucose level of the past 3 months)
- **No short-term information** on the glucose level
- No information regarding **hypo- and hyperglycemic events** (frequency and duration)
- No information on **glycemic variability**
- HbA1c is subject to **individual differences** because of a variety of factors (e.g., genetic and physiological factors, medication)
- Limited correlation between HbA1c and mean glucose
- **Various factors affect the informative value of HbA1c**

Ajjan R.A., Diabetes Technol Ther. 2017;19(S2):S27-S36; American Diabetes Association. Diabetes Care. 2020;43(S1):S66-S76

Individual factors influencing the HbA1c



Gallagher E.J. et al., J Diabetes. 2009;1(1):9-17

Factors influencing the HbA1c – Specific examples

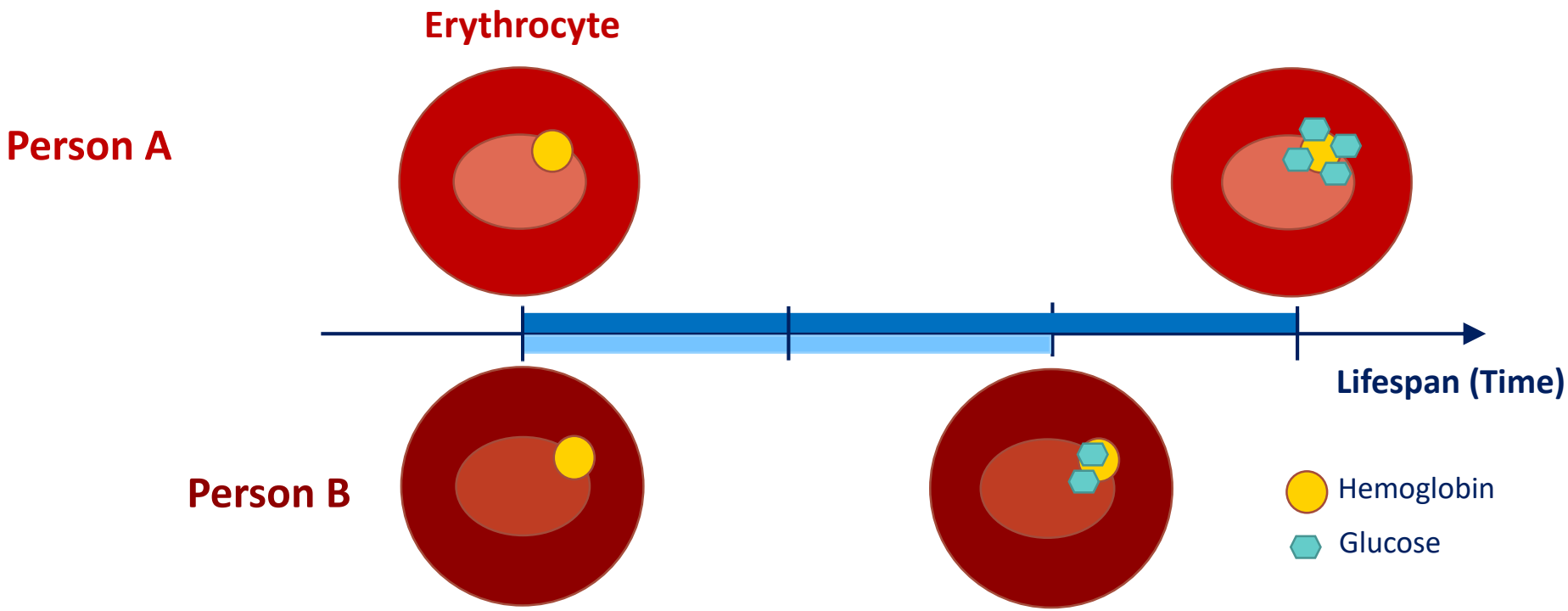
	Erythropoiesis	Hemolysis (erythrocytes lifespan)	Altered hemoglobin
Falsely low HbA1c ⇩	**Increased erythropoiesis** • Iron supplementation • Hemorrhage • Administration of erythropoietin • Pregnancy • High altitude	**Decreased erythrocytes lifespan** • Splenomegaly • Chronic liver / kidney disease • Hemolytic anemia • Hemoglobinopathies (HbS, HbC, HbD) • Antiretrovirals • Further undetermined causes	• Fetal hemoglobin • Hemoglobinopathies • Methemoglobin
Falsely high HbA1c ⇧	**Decreased erythropoiesis** • Iron deficiency • Different anemia (iron deficiency, infections, tumor)	**Increased erythrocytes lifespan** • Splenectomy • Different anemia (iron deficiency, infections, tumor) • Hemoglobinopathies (HbH, HbF (Thalassemia))	• Fetal hemoglobin • Hemoglobinopathies

	Glycation	Assay-related artefacts	Individual HbA1c variations
Falsely low HbA1c ⇩	• Ingestion of aspirin, vitamin C, vitamin E • Certain hemoglobinopathies • Increased erythrocyte pH		• Genetic and epigenetic determinants • Diet-related • Reduced glycation rate
Falsely high HbA1c ⇧	• Alcoholism • Chronic renal failure • Decreased erythrocyte pH	• Aspirin-induced acetylated hemoglobin • Alcoholism (acetaldehyde) • Cigarette-associated carboxyhemoglobin • Carbamylhemoglobin (renal disease) • Hemoglobinopathies (HbS, HbC, HbD)	• Genetic and epigenetic determinants • Age • Hypertriglyceridemia • Organ transplantation • Increased glycation rate

Gallagher E.J. et al., J Diabetes. 2009;1(1):9-17; Consultant: Volume 53 - Issue 10 - October 2013, https://www.consultant360.com/articles/when-a1c-unreliable;
Praxisempfehlungen der Deutschen Diabetes Gesellschaft, Diabetologie und Stoffwechsel. 2020;15(S1):S1-S272; Timper K. et al., Schweiz Med Forum. 2012;12(23):466–469; Campbell L. et al., J Clin Pathol. 2019;72:12-19

Factors influencing the HbA1c glycation

Erythrocytes lifespan (glucose exposition time)



» The **erythrocytes lifespan** is **inter-individually different** and is influenced by different factors.

» Longer erythrocytes lifespan→ longer exposition time to glucose level → higher HbA1c glycation level

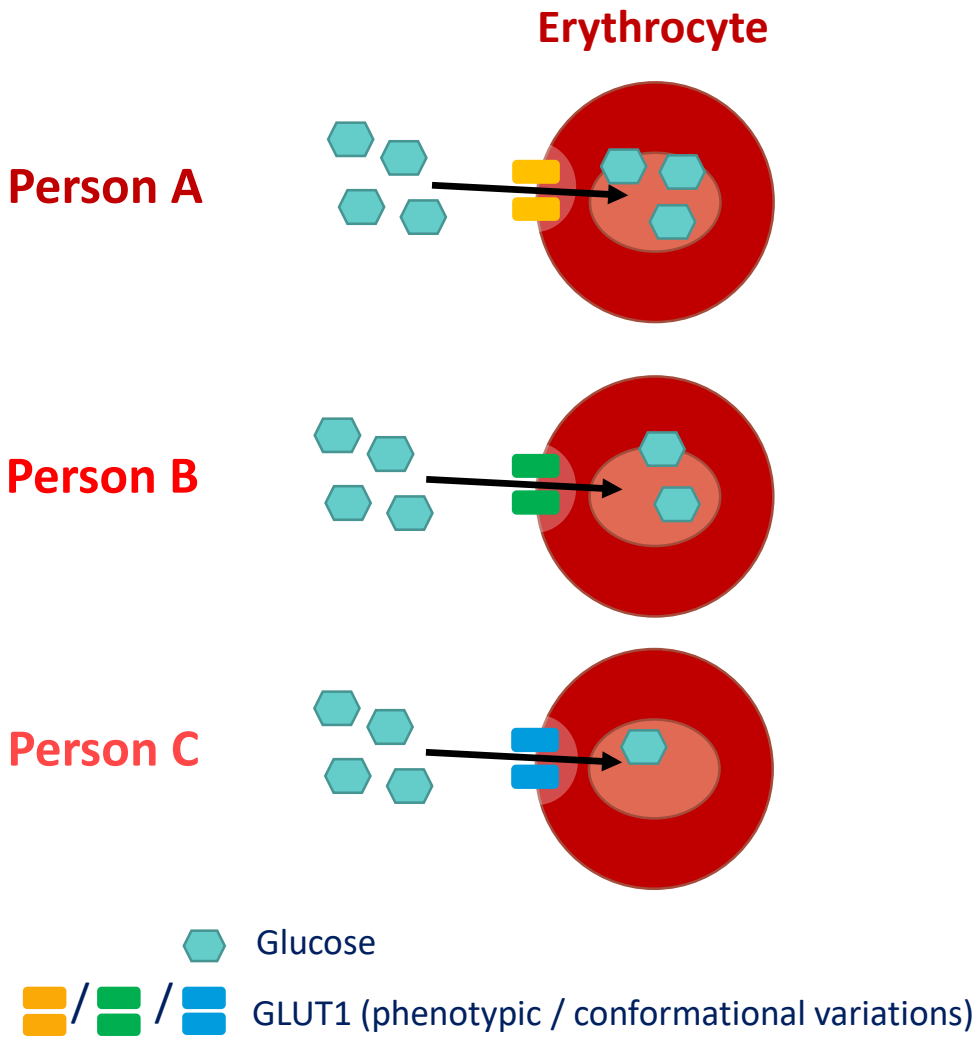
» Shorter erythrocytes lifespan → shorter exposition time to glucose level → lower HbA1c glycation level

Factors influencing the HbA1c glycation rate

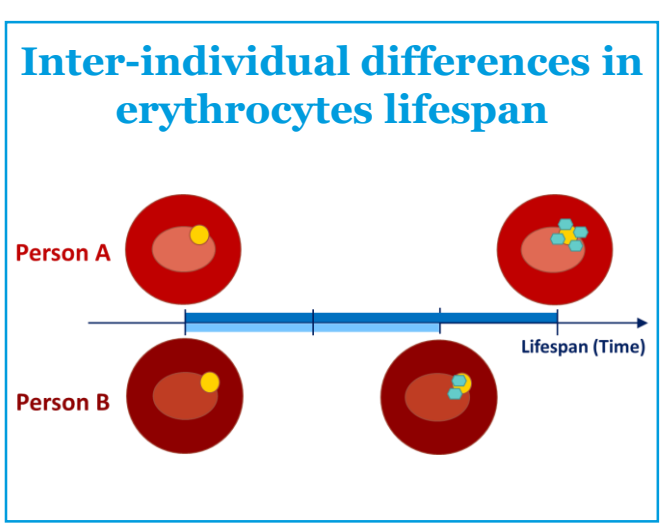
Glucose transport rate

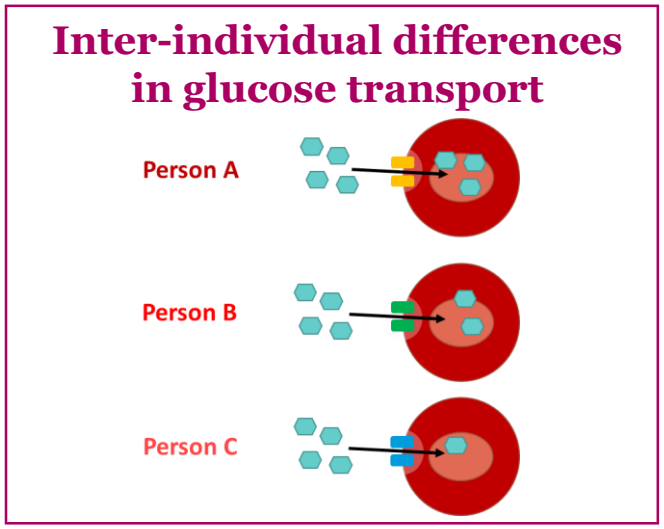
» Given the same blood glucose level, the level of glucose transported into the erythrocytes may vary between different individuals.

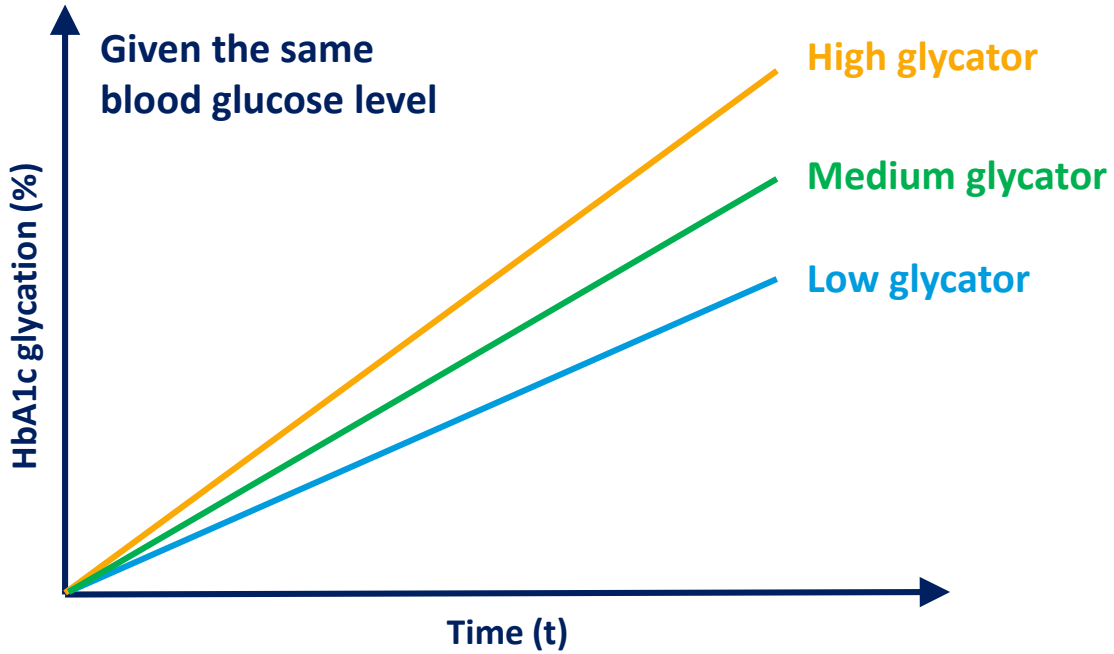
» These differences may be caused by **inter-individual phenotypic / conformational variations** in the **glucose transporter 1 (GLUT1)**.



Factors influencing the HbA1c – Differences in glycation rate





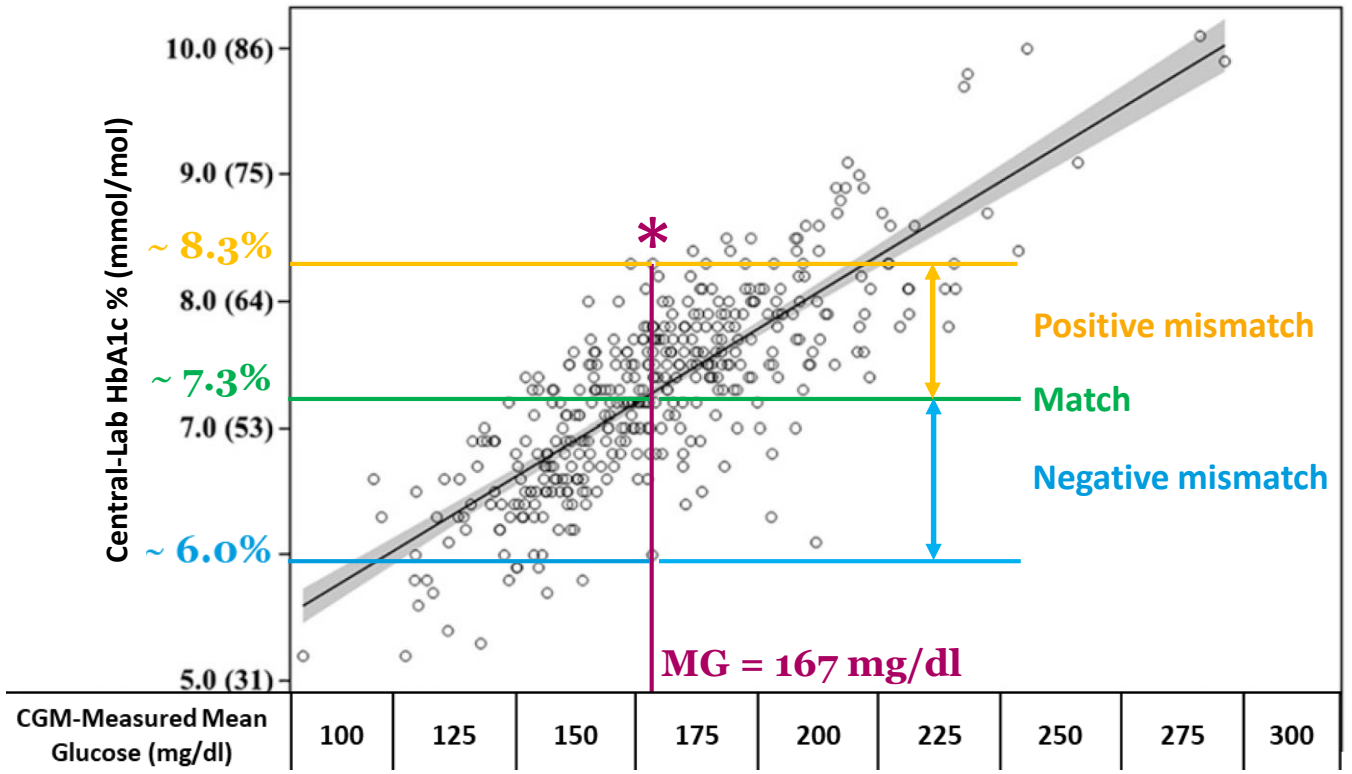


» Erythrocytes lifespan and glucose transport are factors affecting considerably **the cumulative HbA1c glycation over time** → Persons have different **HbA1c glycation trajectories and** can be categorized as **high, medium,** and **low glycators**.

Factors influencing the HbA1c – Differences in glycation rate

» Two persons with the same measured mean blood glucose of **~ 167 mg/dl** can have different laboratory-measured HbA1c varying from **6.0%** to **8.3% (∗).** This means that:

» For the same extracellular measured blood glucose, there can be differences in the intracellular measured glycated HbA1c.

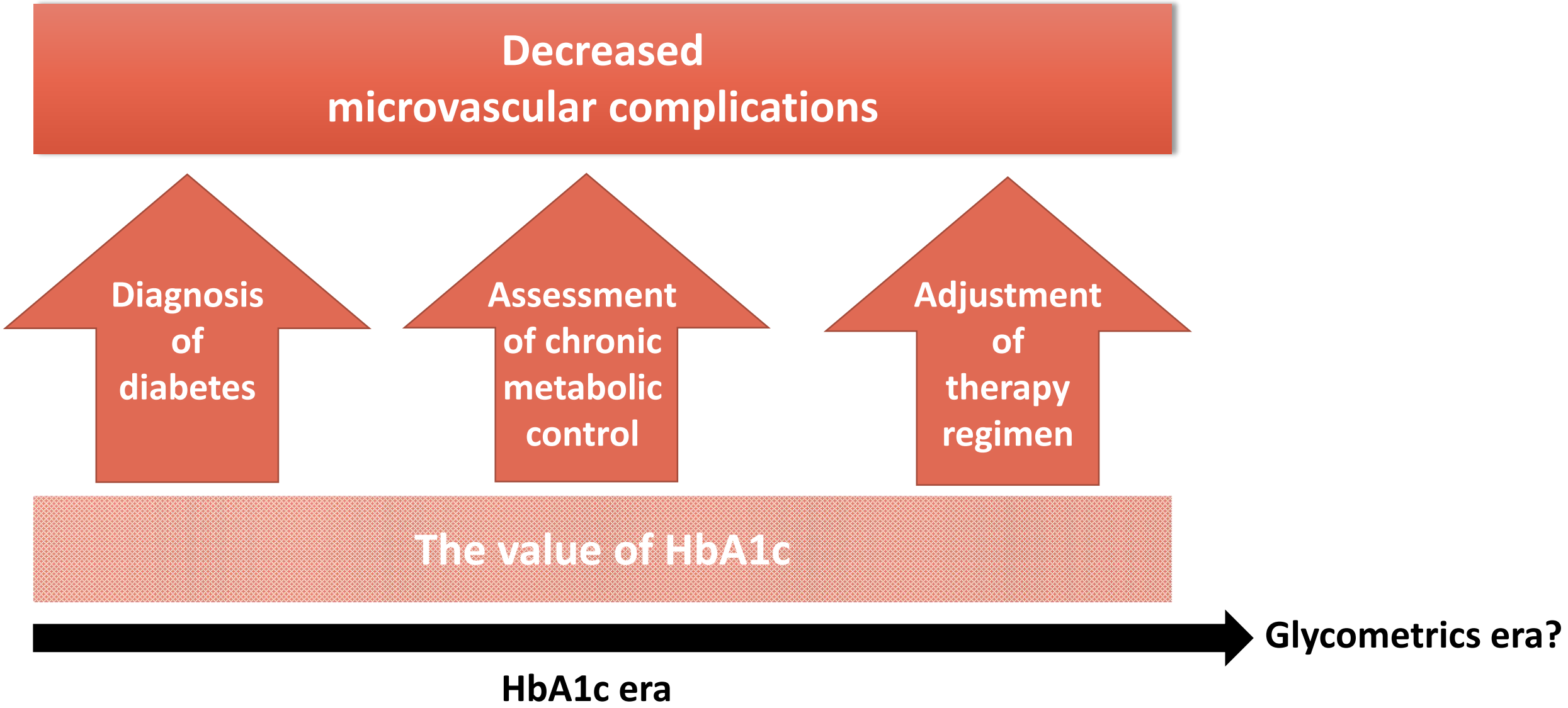


(91 days of CGM data, median amount of CGM data: 66 days)

Various factors affect the informative value of HbA1c → Use of CGM to minimize the information gap

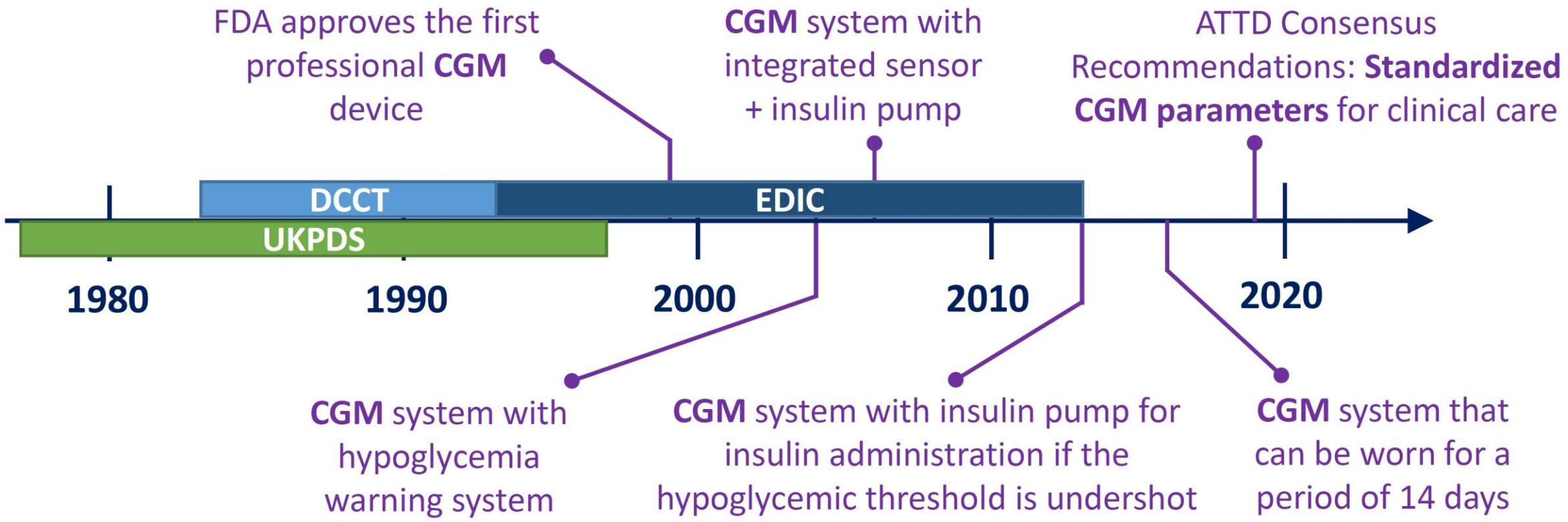
Beck R.W. et al., Diabetes Care. 2017;40:994-999

Clinical significance of HbA1c in diabetes management



Continuous Glucose Monitoring
Basis for new indispensable glucose metrics

Continuous Glucose Monitoring (CGM*) – A revolution in home glucose monitoring



*CGM systems mentioned in the figure comprises FGM, isCGM and rtCGM systems

Hirsch I.B. et al., American Diabetes Association. 2018 Aug; doi: 10.2337/db20181; Battelino T. et al., Diabetes Care. 2019;42(8):1593-1603; Danne T. et al., Diabetes Care. 2017;40:1631-1640

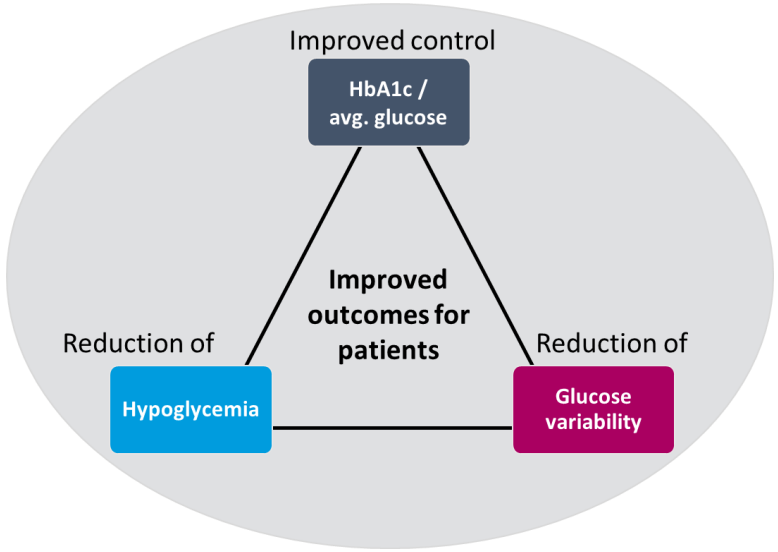
10 core CGM metrics (International Consensus 2019)

Standardized CGM metrics for clinical care: 2019
1. Number of days CGM worn (recommend 14 days)
2. Percentage of time CGM is active (recommend 70% of data from 14 days)
3. Mean glucose
4. Glucose management indicator (GMI)
5. Glycemic variability (%CV) target ≤ 36%
6. Time above range (TAR): % of readings and time >250 mg/dl (>13.9 mmol/l)
7. Time above range (TAR): % of readings and time 181-250 mg/dl (10.1-13.9 mmol/l)
8. Time in range (TIR): % of readings and time 70-180 mg/dl (3.9-10.0 mmol/l)
9. Time below range (TBR): % of readings and time 54-69 mg/dl (3.0-3.8 mmol/l)
10. Time below range (TBR): % of readings and time <54 mg/dl (<3.0 mmol/l)

The new standardized CGM metrics allow the assessment of **glycemic variability** and **glycemic excursions**.

CV, coefficient of variation; Battelino T. et al., Diabetes Care. 2019;42(8):1593-1603; Danne T. et al., Diabetes Care. 2017;40:1631-1640

New standardized CGM metrics – Assessment of glycemic excursions and glycemic variability

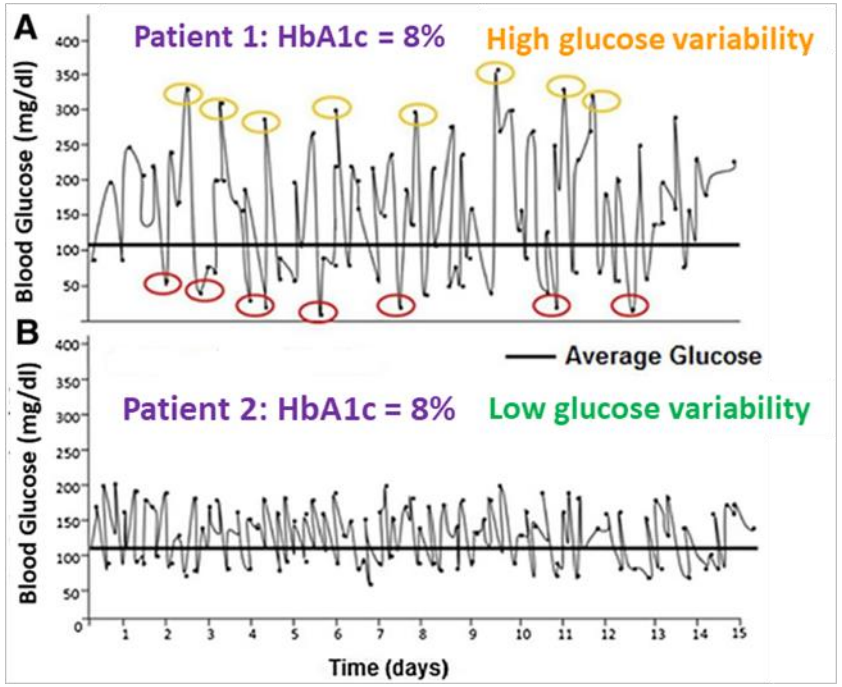


HbA1c

- Biochemical nature of HbA1c & different factors impacting it → necessary and timely to complement HbA1c with further glucose metrics to assess **hypoglycemia** and **glucose variability**
- Hypoglycemia and glucose variability: Major role in the development of short- and long-term comorbidities → **relevant complementary information**

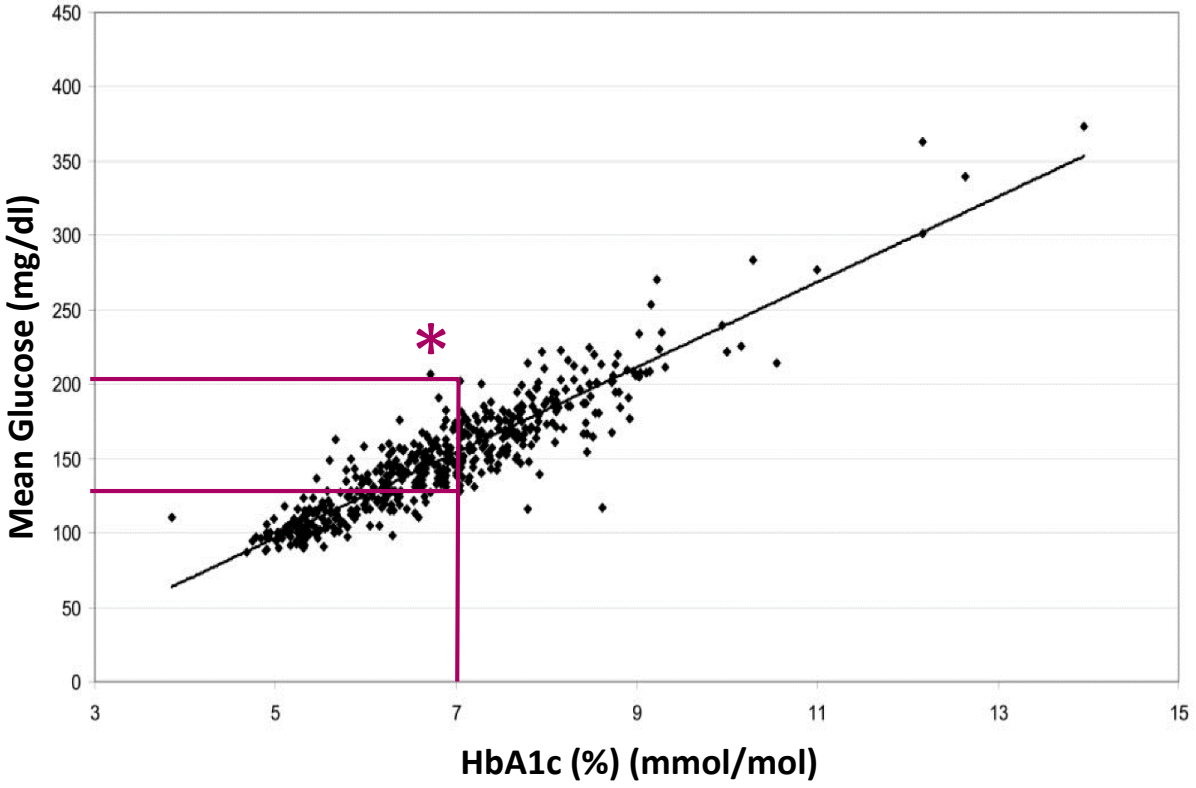
CGM metrics

- Standardized CGM metrics: Effective assessment of **hypo- and hyperglycemic excursions** and **glucose variability**
  - Use of CGM metrics to complement HbA1c



Battelino T. et al., Diabetes Care. 2019;42(8):1593-1603; Rayman G., British Journal of Diabetes. 2016;16:3-6; Monnier L. & Colette C., Current Diabetes Reports. 2008;8:368-374; Chehregosha H. et al., Diabetes Ther. 2019;10:853-863

Standardized CGM metrics
Mean glucose to assess glycemic control



» For a laboratory-measured **HbA1c of 7%**, the estimated mean glucose varies from **~ 130 mg/dl** to **~ 200 mg/dl (*).**

- A wide range of mean glucose values is associated with a given laboratory-measured HbA1c.

» The adequate measurement of mean glucose using CGM (recommended **70% of data from 14 days**) allows the calculation of a **medium-term indicator** as an estimation of HbA1c.

» Since this indicator is based only on CGM-measured mean glucose, it is not prone to other factors, such as those influencing HbA1c →

- **A complementary parameter to HbA1c**

Nathan D.M. et al., Diabetes Care. 2008;31:1473-1478; Danne T. et al., Diabetes Care. 2017;40:1631-1640; Battelino T. et al., Diabetes Care. 2019;42(8):1593-1603

From HbA1c to GMI – An overview
estimated A1c (eA1C)

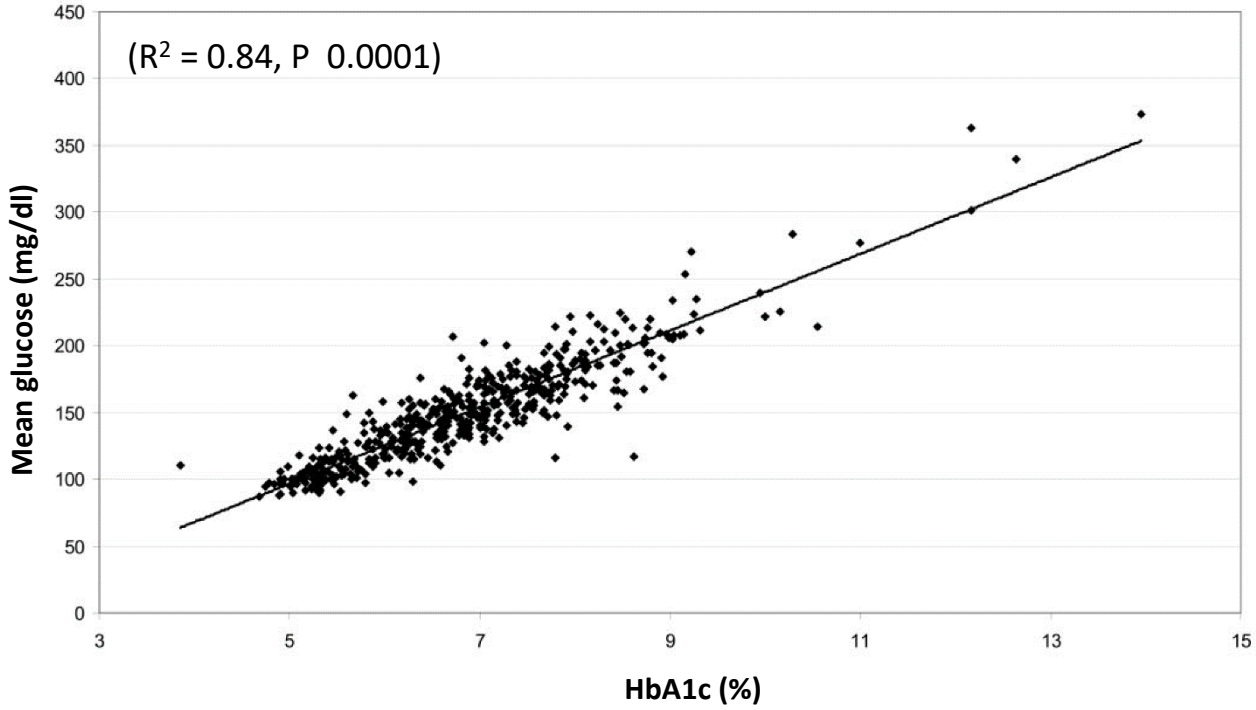
A1c-Derived mean Glucose (ADAG) study, 2006-2007

» **Aim:**

- Defining the mathematical relationship between HbA1c and mean glucose (MG) levels
- Determining whether HbA1c could be expressed and reported as MG in the same units as used in self-monitoring

» Patients: T1DM (n = 268), T2DM (n = 159) and non-diabetic (n = 80)

» Median of 13 days of CGM measurements plus 39 days of fingerstick blood glucose measurements (7-point daily profiles)



Estimated mean glucose (eMG)	Conversion of the equation	Estimated HbA1c
$eMG_{mg/dl} = 28.7 \times A1C - 46.7$	⇒	$eA1c\ (\%) = (MG_{mg/dl} + 46.7) / 28.7$
$eMG_{mmol/l} = 1.59 \times A1C - 2.59$		$eA1c_{mmol/mol} = (MG_{mmol/l} + 2.59) / 1.59$

Nathan D.M. et al., Diabetes Care. 2008;31:1473-1478

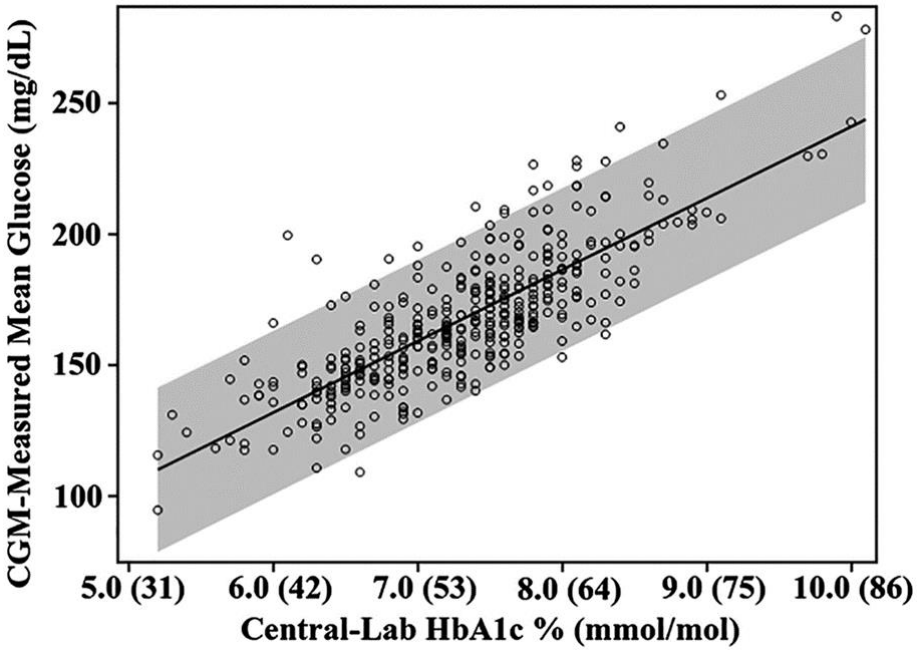
From HbA1c to GMI – An overview

Precursor formula for the Glucose Management Indicator (GMI)

Further study conducted by Beck et al., 2017

» **Aim 1:** Estimating mean glucose concentration for a given HbA1c using CGM procedure (91 days of CGM data, median amount of CGM data: 66 days)

» 387 participants (T1DM and T2DM) in three randomized trials



	Estimated mean glucose concentration (mg/dl) for a given HbA1c, 95% CI	
HbA1c, % (mmol/mol)	Current study (*N* = 387)	ADAG study (*N* = 507)
6 (42)	101–163	100–152
7 (53)	128–190	123–185
8 (64)	155–218	147–217
9 (75)	182–249	170–249
10 (86)	209–273	193–282

Modified after Beck R.W. et al., 2017

» In comparison with the ADAG study: Comparable results for the estimated mean glucose concentration for a given HbA1c.

Beck R.W. et al., Diabetes Care. 2017;40:994-999

From HbA1c to GMI – An overview

Precursor formula for the Glucose Management Indicator (GMI)

	Estimated mean glucose concentration (mg/dl) for a given HbA1c, 95% CI
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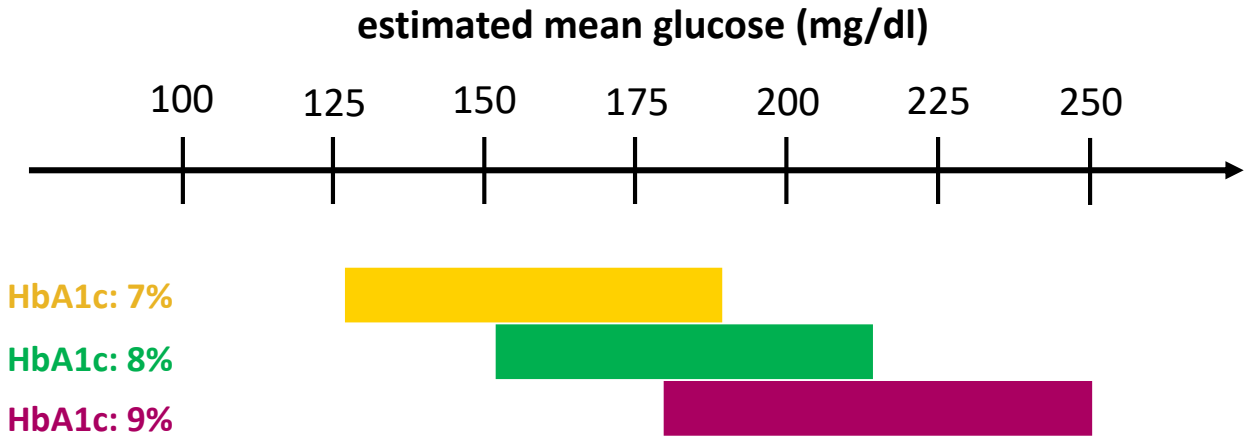
Modified after Beck R.W. et al., 2017



» An **HbA1c of 8.0%** could be associated with good, fair, or poor glycemic control as judged by potential mean glucose levels of **128 to 249 mg/dl**.

» HbA1c may not be accurate enough to estimate the individual's glycemic control because of the wide range of mean glucose that can be associated with a given HbA1c.

Beck R.W. et al., Diabetes Care. 2017;40:994-999

From HbA1c to GMI – An overview

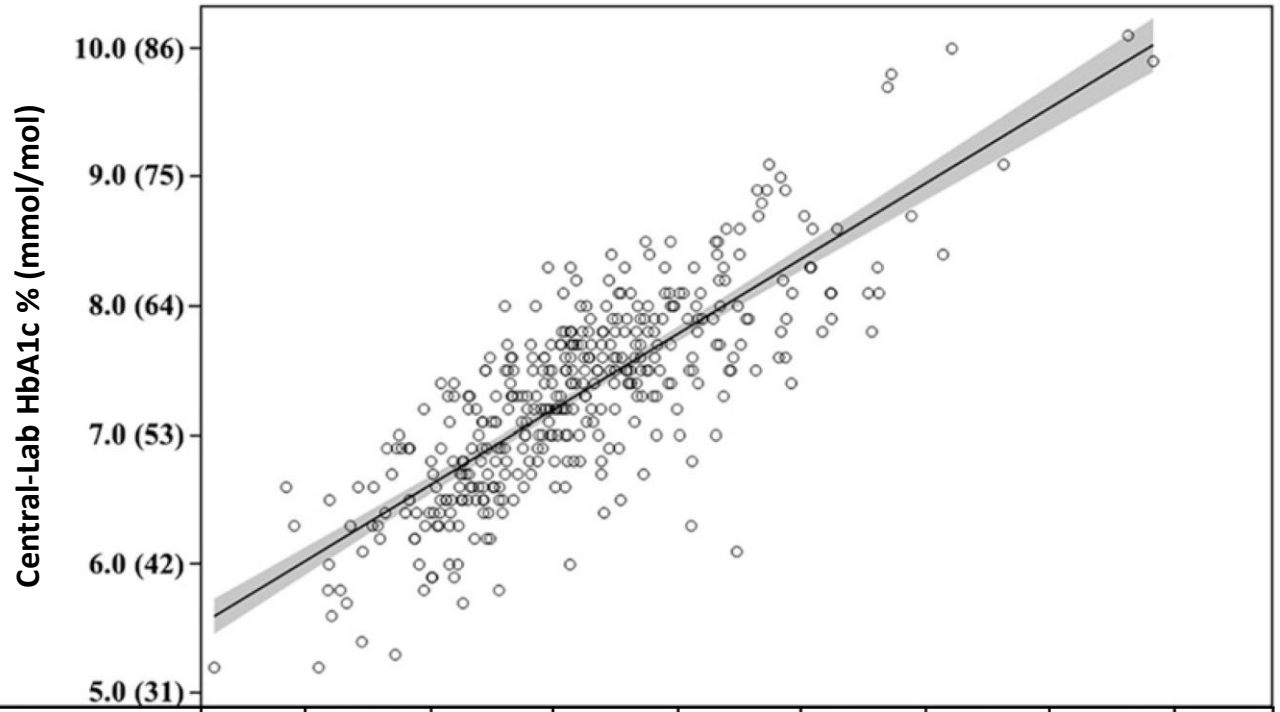
Precursor formula for the Glucose Management Indicator (GMI)

» **Aim 2:** Calculating an estimated HbA1c (eA1c) for a given mean glucose concentration (CGM-measured) and comparing the calculated eA1c with the laboratory-measured HbA1c

- Inform how well HbA1c measurement estimates the mean glucose concentration for a patient
- Comparing the estimated HbA1c with the laboratory-measured HbA1c

Equation to estimate HbA1c for a given mean glucose concentration

$$eA1c\ (\%) = 3.38 + 0.02345 \times AG_{mg/dl}$$



CGM-Measured Mean Glucose (mg/dl)	100	125	150	175	200	225	250	275	300
eA1C % (mmol/mol)	5.7 (39)	6.3 (46)	6.9 (52)	7.5 (58)	8.1 (65)	8.7 (71)	9.2 (78)	9.8 (84)	10.4 (90)

Beck R.W. et al., Diabetes Care. 2017

» Formula is derived from the regression line computed from a plot of mean glucose points (mg/dl) on the x-axis and laboratory-measured HbA1c values on the y-axis.

Beck R.W. et al., Diabetes Care. 2017;40:994-999

Equation of the Glucose Management Indicator (GMI)

Equation to estimate HbA1c for a given mean glucose concentration (Beck et al., 2017)

$$eA1c\ (\%) = 3.38 + 0.02345 \times MG_{mg/dl}$$

Equation derived from the HypoDE study (Heinemann et al., 2018)

$$eA1c\ (\%) = 3.15 + 0.02505 \times MG_{mg/dl}$$

GMI equation for a given mean glucose concentration (Bergenstal et al., 2018)

$$GMI\ (\%) = 3.31 + 0.02392 \times MG_{mg/dl}$$

$$GMI_{mmol/mol} = 12.71 + 4.70587 \times MG_{mmol/l}$$

The new calculated parameter, **GMI**, using the new generated equation offers a mathematically **better approximation of HbA1c** than **eA1c**.

GMI calculated for various CGM-derived mean glucose concentrations

CGM-derived mean glucose (mg/dl)	GMI (%)
100	5.7
125	6.3
150	6.9
175	7.5
200	8.1
225	8.7
250	9.3
275	9.9
300	10.5
350	11.7
CGM-measured mean glucose (mmol/l)	**GMI (mmol/mol)**
5	36.2
6	40.9
7	45.7
8	50.4
9	55.1
10	59.8
12	69.2
14	78.6
16	88.0
18	97.4

Modified after Bergenstal R.M. et al., 2018

Bergenstal R.M. et al., Diabetes Care. 2018;41:2275-2280; Beck R.W. et al., Diabetes Care. 2017;40:994-999; Heinemann L. et al., Lancet. 2018;391:1367-1377

Why renaming eA1c into GMI was a necessary step?

- "Estimated A1C" (eA1C) is based on CGM- (partly SMBG-) measured mean glucose → approximation of laboratory-measured HbA1c
- However, eA1c can be lower or higher than the actual HbA1c → clinicians and patients were confused because of this discordance
- A new calculated parameter offers a mathematically better approximation of HbA1c
- Interdisciplinary panel: Addressing the question of choosing an unambiguous name for the new parameter succeeding eA1C
- Avoiding terms such as "estimated", "A1c", and "Index" → misleading association with HbA1c and other indicators
- Designations containing terms such as "control" can be perceived as negative or judgmental. On the other hand, "management" is perceived as more positive and empowering →

Agreement on the term **Glucose Management Indicator (GMI)**

Nathan D.M. et al., Diabetes Care. 2008;31:1473-1478; Bergenstal R.M. et al., Diabetes Care. 2018;41:2275-2280

Standardization of the CGM metrics (International Consensus Reports 2017 and 2019)

Standardized CGM metrics 2017 (international consensus on CGM metrics)	Standardized CGM metrics for clinical care 2019
1. Number of days CGM worn	1. Number of days CGM worn (recommend 14 days)
2. Percentage of time CGM is active	2. Percentage of time CGM is active (recommend 70% of data from 14 days)
3. Mean glucose	3. Mean glucose
4. Estimated A1C (eA1C)	4. Glucose management indicator (GMI)
5. Glycemic variability (%CV or SD)	5. Glycemic variability (%CV) target ≤ 36%
6. Time >250 mg/dl (>13.9 mmol/l)	6. Time above range (TAR): % of readings and time >250 mg/dl (>13.9 mmol/l)
7. Time >180 mg/dl (>10.0 mmol/l)	7. Time above range (TAR): % of readings and time 181-250 mg/dl (10.1-13.9 mmol/l)
8. Time 70–180 mg/dl (3.9–10.0 mmol/l)	8. Time in range (TIR): % of readings and time 70-180 mg/dl (3.9-10.0 mmol/l)
9. Time <70 mg/dl (<3.9 mmol/l)	9. Time below range (TBR): % of readings and time 54-69 mg/dl (3.0-3.8 mmol/l)
10. Time <54 mg/dl (<3.0 mmol/l)	10. Time below range (TBR): % of readings and time <54 mg/dl (<3.0 mmol/l)
11. LBGI and HBGI (risk indices)	
12. Episodes (hypoglycemia and hyperglycemia) 15 min	
13. Area under the curve	
14. Time blocks (24-h, day, night)	

Battelino T. et al., Diabetes Care. 2019;42(8)1593-1603; Danne T. et al., Diabetes Care. 2017;40:1631-1640

HbA1c and GMI – Comparison of different aspects

	HbA1c	GMI
Definition	Main fraction of glycated hemoglobin A (HbA), composed of covalently bound glucose at the amino-end of Hb β-chain	A calculated value based on mean glucose measured using CGM for at least 14 days approximating so the expected laboratory-measured HbA1c level
Measurement method	Laboratory-measured value from blood sample using standardized measurement methods	Formula-calculated value based on measured mean glucose ideally derived from at least 14 days of CGM data
What is measured?	How much glucose has attached to the hemoglobin in the red blood cells over the life of each red blood cell **(≈ 120 days)**	Mean glucose concentration (CGM measurement of glucose in interstitial fluid (under the skin) every 1-5 min) from **≥ 14 days** of CGM data
Effect of acute events (e.g., hypoglycemia, diabetic ketoacidosis, medication) on HbA1c and GMI	Acute events such as hypo- and hyperglycemic episodes influence the HbA1c value. However, they can not be individually detected by HbA1c, since it reflects glucose levels primarily over the last 2-3 months	Acute events such as hypo- and hyperglycemic episodes influence the CGM-calculated GMI. However, these events can be detected and analyzed using further CGM metrics (TIR, TBR, TAR and %CV)

GMI and **CGM** give a detailed description of the patient's glucose status for a shorter and more specific period.

CV, coefficient of variation; https://www.jaeb.org/gmi/; [1]Wilson D.M. et al., Diabetes Care. 2011;34:540-544; Bergenstal R.M. et al., Diabetes Care. 2018;41:2275-2280

GMI and HbA1c – Absolute value of difference

- 19% of the time GMI and laboratory-measured HbA1c have an identical value.
- 51% of the time they differ by 0.3% (HbA1c points) or more and 28% of the time they differ by 0.5% (HbA1c points) or more.
- Since the value of difference is absolute, the difference between GMI and laboratory-measured HbA1c can be either positive or negative.
- Because of the discrepancies between GMI and laboratory-measured HbA1c, it is crucial to understand why they differ. This can be used to **refine and personalize each individual's glucose management plan**.

Difference between GMI (calculated from CGM-derived mean glucose) and laboratory-measured HbA1c (*N* = 528)

Absolute value of difference between GMI and laboratory HbA1c (%)	Percentage of values (%)	95% CI (%)
0 to <0.1	19	16–22
≥0.1	81	78–84
≥0.2	67	63–71
≥0.3	51	47–55
≥0.4	39	34–43
≥0.5	28	24–32
≥0.6	19	15–22
≥0.7	12	9–15
≥0.8	8	5–10
≥0.9	4	3–6
≥1.0	3	2–4

Modified after Bergenstal R.M. et al., 2018

Scenarios for different GMI and laboratory-measured HbA1c values

Higher GMI than HbA1c	Lower GMI than HbA1c

- **Factors influencing HbA1c (erythropoiesis, hemolysis, assay, glycation trajectories, other factors)**
- **Non-representative time sample for the CGM-based GMI calculation (e.g., unusual hypo-/ hyperglycemic events at analyzed time sample)**

- **During short periods of hyperglycemia**
  - » Illness
  - » Steroid administration
  - » Diabetic ketoacidosis

- **Increased likelihood for discrepancy with increasing age and in women[1]**
- **During short periods of much lower-than-usual glucose reading**
  - » Starting a new carbohydrate-reduced diet
  - » An intensive exercise regimen
  - » During the first weeks after starting a new effective glucose-lowering medication

Bergenstal R.M. et al., Diabetes Care. 2018;41:2275-2280; Gallagher E.J. et al., J Diabetes. 2009; 53(10), Consultant: Volume 53 - Issue 10 - October 2013, https://www.consultant360.com/articles/when-a1c-unreliable; Timper K. et al., Schweiz Med Forum. 2012;12(23):466-469
[1] estimated A1c: Stimson R.H. et al., J Diabetes Sci Technol. 2020. doi: 10.1177/1932296820967335

GMI and HbA1c: A more consistent and complete glycemic picture