II SESSIONE • Dibattito sulle nuove metriche

Moderatori: Cristina Romano, Emanuela Zarra

11:30 Quali evidenze per TITR e GRI?
Matteo Conti, Sergio Di Molfetta

Quali evidenze per il GRI?

Sergio Di Molfetta, MD, PhD

Unità Operativa Complessa di Endocrinologia
Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari
Direttore Prof. Francesco Giorgino

AZIENDA OSPEDALIERA POLICLINICO BARI

Il Dr Sergio Di Molfetta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Ascensia Diabetes Care
- Menarini Diagnostics
- Roche Diabetes Care Italy
- SANOFI

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...)

Standardized CGM Metrics for Clinical Care

1. Number of days CGM worn (recommend 14 days) (42,43)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days) (41,42)	
3. Mean glucose	
4. Glucose management indicator (GMI) (75)	
5. Glycemic variability (%CV) target ≤36% (90)*	
6. Time above range (TAR): % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2
Use of Ambulatory Glucose Profile (AGP) for CGM report	

CGM, continuous glucose monitoring; CV, coefficient of variation

Battelino T et al. Diabetes Care. 2019 Aug;42(8):1593-1603

Estimate of A1C for a Given TIR Level Based on T1D and T2D Studies

Beck et al. (26) (n = 545 participants with type 1 diabetes)			Vigersky and McMahon (27) (n = 1,137 participants with type 1 or type 2 diabetes)	
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)	95% CI for predicted A1C values, %	TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)
20%	9.4 (79)	(8.0, 10.7)	20%	10.6 (92)
30%	8.9 (74)	(7.6, 10.2)	30%	9.8 (84)
40%	8.4 (68)	(7.1, 9.7)	40%	9.0 (75)
50%	7.9 (63)	(6.6, 9.2)	50%	8.3 (67)
60%	7.4 (57)	(6.1, 8.8)	60%	7.5 (59)
70%	7.0 (53)	(5.6, 8.3)	70%	6.7 (50)
80%	6.5 (48)	(5.2, 7.8)	80%	5.9 (42)
90%	6.0 (42)	(4.7, 7.3)	90%	5.1 (32)
Every 10% increase in TIR = ~0.5% (5.5 mmol/mol) A1C reduction			Every 10% increase in TIR = ~0.8% (8.7 mmol/mol) A1C reduction	

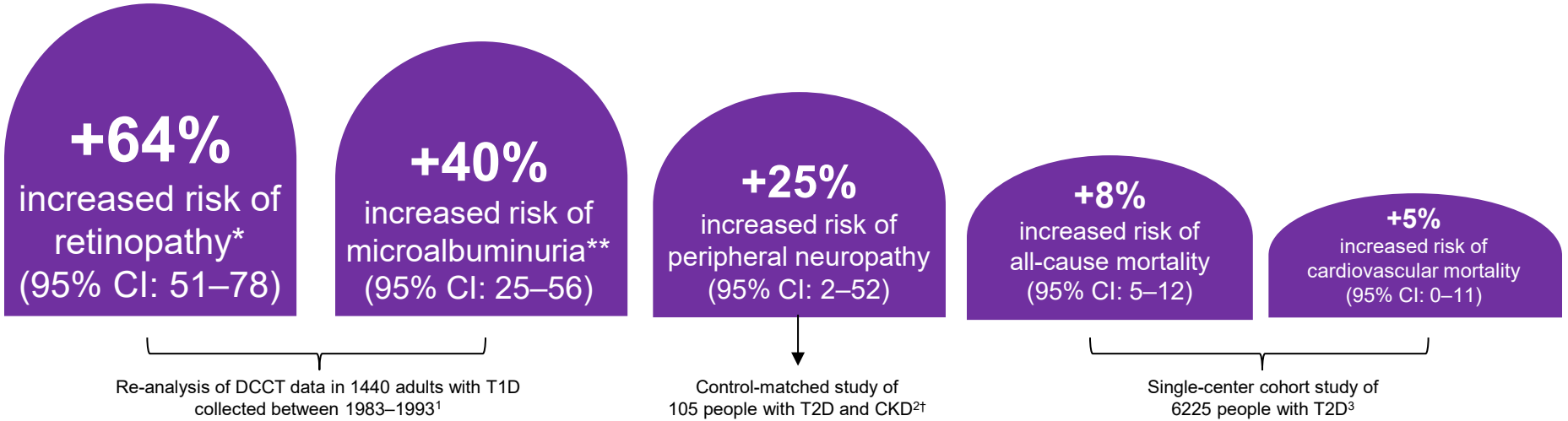
The difference between findings from the two studies likely stems from differences in number of studies analyzed and subjects included (RCTs with subjects with type 1 diabetes vs. RCTs with subjects with type 1 or type 2 diabetes with CGM and SMBG).

A1c, glycated hemoglobin; CGM, continuous glucose monitoring; CI, confidence interval; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time in range

Battelino T et al. Diabetes Care. 2019 Aug;42(8):1593-1603

Time in Range as Predictor of Long-Term Complications of Diabetes

Each 10% drop in TIR is associated with increased frequency of:



*For assessment of retinopathy, DCCT definitions of primary prevention were used: no retinopathy at baseline (n=726) and retinopathy at baseline (n=714). **For assessment of microalbuminuria, 1283 participants with an AER <30 mg/24 h were included in the analysis. †Out of 105 participants, 81 were participations with moderate-to-severe CKD (eGFR <60 ml/min/1.73m^2) and 23 were matched control participants with eGFR ≥ 60 ml/min/1.73m^2. ‡HR: 0.54 (CI: 0.40–0.73), for time to first severe hypoglycemia when TIR is >70% (vs TIR ≤50%); HR: 0.60 (CI: 0.43–0.85), for time to first microvascular complication when TIR is >70% (vs TIR ≤50%); HR: 0.69 (CI: 0.52–0.91), for time to first MACE when TIR is >70% (vs TIR ≤50%).

CI, confidence interval; CKD, chronic kidney disease; DCCT, Diabetes Control and Complications Trial; MACE, major adverse cardiac events.

1. Beck RW, et al. Diabetes Care 2019;42:400–5; 2. Mayeda L, et al. BMJ Open Diab Res Care 2020;8:e000991; 3. Lu J, et al. Diabetes Care 2021;44:549–55; 4. Bergenstal R, et al. Presented at ADA 2020 (21-LB).

Correlation between TIR and Time in Hypo- or Hyperglycemic Range

	%TIR	*%Hyperglycemia*
%Hyperglycemia		
T1D—two data sets	−0.97	
T1D data set 1	−0.98	
T1D data set 2	−0.95	
T2D	−0.98	
Mean,T1D, T2D	−0.98	
T1D, T2D	−0.90	
%Hypoglycemia		
T1D—two data sets	0.09	−0.33
T1D data set 1	0.21	−0.40
T1D data set 2	−0.09	−0.23
T2D	0.21	−0.40
Mean, T1D, T2D	0.12	−0.37
T1D, T2D	−0.10	−0.31

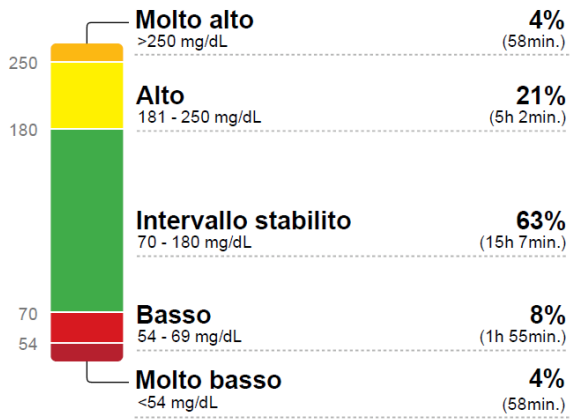
From above downward each cell shows the correlations between two metrics, based on (1) T1D two data sets[47]; (2) T1D data set 1[47]; (3) T1D data set 2[47]; (4) T2D[48]; (5) Mean for T1D and T2D rows 1 and 4[47,48]; (6) T1D, T2D from Refs.[44–46]; (7) T1D from Ref.[49]

T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time in range

Rodbard D. Diabetes Technol Ther. 2018 May;20(5):325-334

The Many Faces of a Same TIR Level

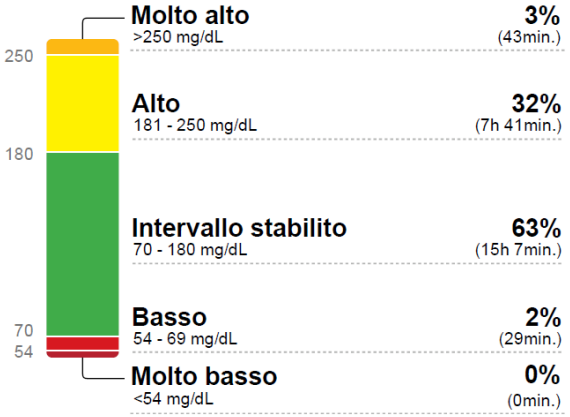
56 yrs



GMI 6.6%

CV 54.1%

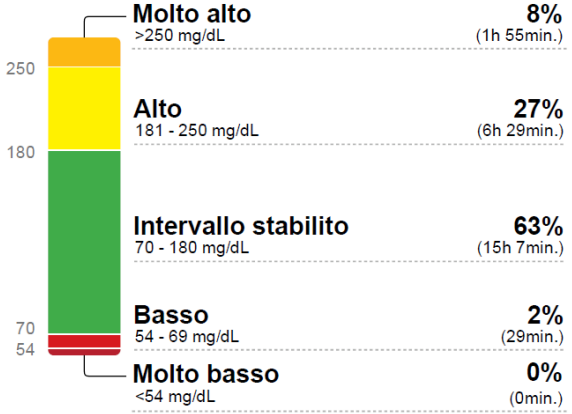
51 yrs



GMI 7.2%

CV 30.4%

33 yrs

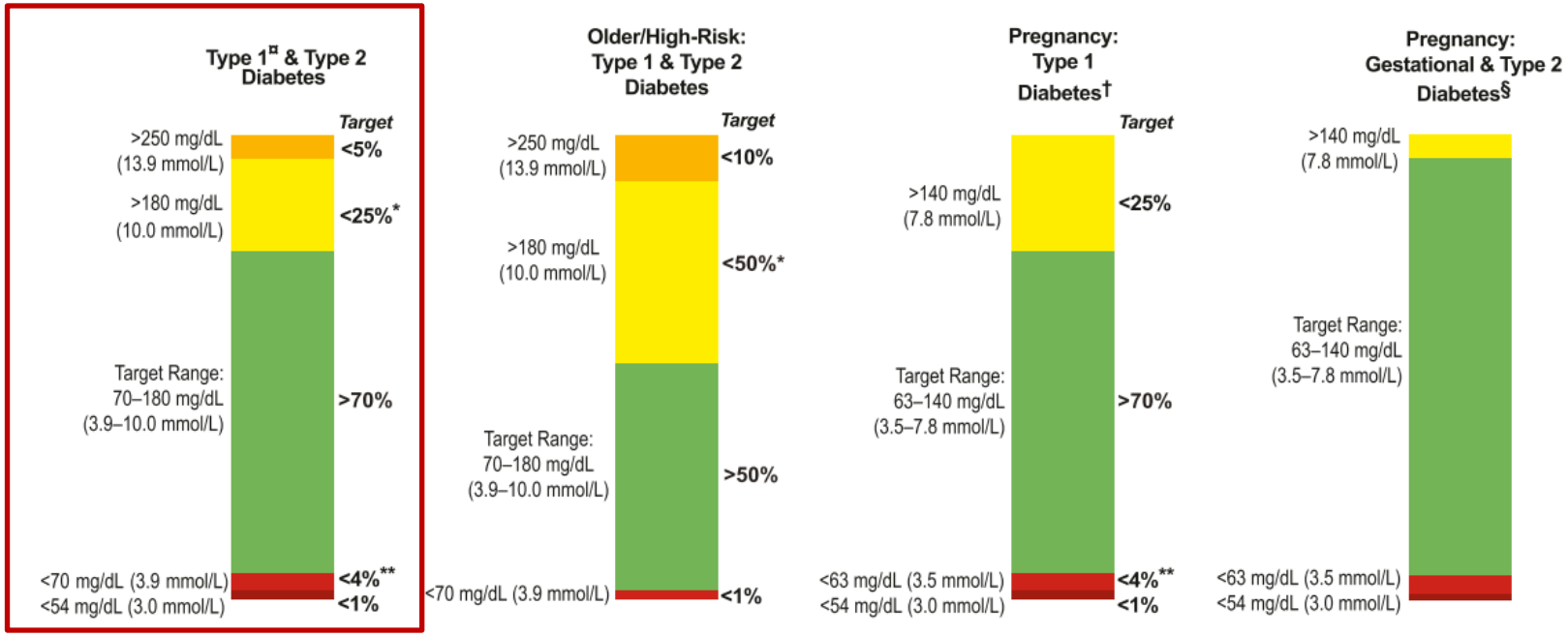


GMI 7.3%

CV 34.6%

CV, coefficient of variation; GMI, glucose management indicator; TIR, time in range

CGM-Based Targets for Different Populations with Diabetes



¤ 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).

A1c, glycated hemoglobin; CGM, continuous glucose monitoring

Battelino T et al. Diabetes Care. 2019 Aug;42(8):1593-1603

Assessment of Glycemic Status - Standards of Care in Diabetes

Recommendations

6.1 Assess glycemic status by A1C **A** and/or continuous glucose monitoring (CGM) metrics such as time in range, time above range, and time below range. **B** Fructosamine or CGM can be used for glycemic monitoring when an alternative to A1C is required. **B**

6.2 Assess glycemic status at least two times a year, and more frequently (e.g., every 3 months) for individuals not meeting glycemic goals or with recent treatment changes, frequent or severe hypoglycemia or hyperglycemia, or changes in health status, or during periods of rapid growth and development in youth. **E**

A1c, glycated hemoglobin; CGM, continuous glucose monitoring

Diabetes Care. 2025 Jan 1;48(Supplement_1):S128-S145

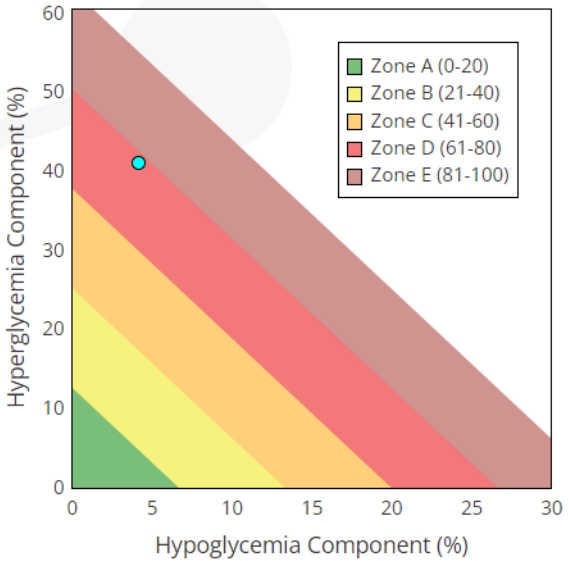
Glycemia Risk Index

To calculate the Glycemia Risk Index for CGMs, please enter into the boxes below the percent of time spent in the VLow, Low, VHigh, and High ranges.

% VLow (<54 mg/dL; <3.0 mmol/L)	1
% Low (54–<70 mg/dL; 3.0–< 3.9 mmol/L)	4
% VHigh (>250 mg/dL; > 13.9 mmol/L)	27
% High (>180–250 mg/dL; >10.0–13.9 mmol/L)	28
Hypoglycemia Component = VLow + (0.8 × Low)	4.2
Hyperglycemia Component = VHigh + (0.5 × High)	41
GRI = (3.0 × HypoComponent) + (1.6 × HyperComponent)	78

Equivalently,

GRI = (3.0 × VLow) + (2.4 × Low) + (1.6 × VHigh) + (0.8 × High)



CGM, continuous glucose monitoring; GRI, glycemia risk index

Correlation between GRI and Classic Glycometric Parameters in T1D

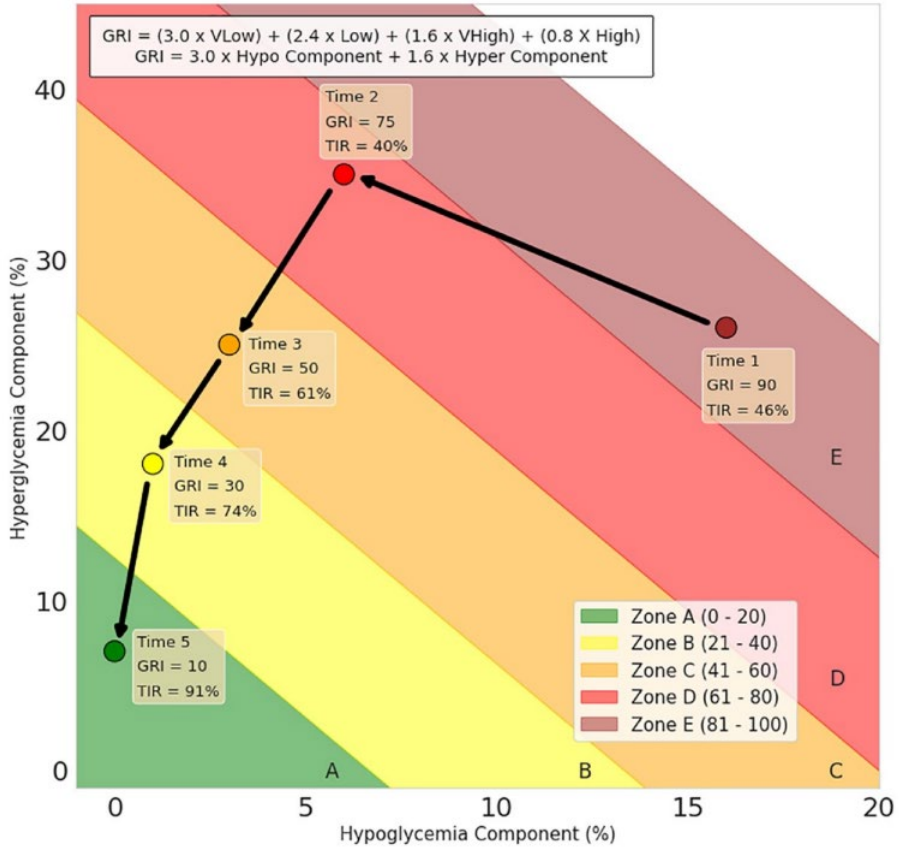
Cross-Sectional Study, n = 202, Age 28.6 ± 15.7 yrs, HbA1c 7.3 ± 1.1%

Parámetros		GRI	CHypo	CHyper	HbA1c	Mean glucose	SD	GMI	TBR < 54	TBR 54–70	TIR 70–180	TAR 180–250	TAR > 250	CV
GRI	*R*	1 -	0.398	0.801	0.617	0.677	0.778	0.650	0.481	0.217	−0.917	0.460	0.801	0.605
	p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	<0.001	<0.001

Chypo, component of hypoglycemia; Chyper, component of hyperglycemia; CV, coefficient of variation; GMI, glucose management indicator; GRI, glycemia risk index; HbA1c, glycosylated hemoglobin A1c; NS, not significant; p, p-value; R, Pearson's correlation coefficient; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range

Pérez-López P et al. Endocrine. 2023 Dec;82(3):560-568

Case Example – Sequential Changes in GRI and TIR over Time

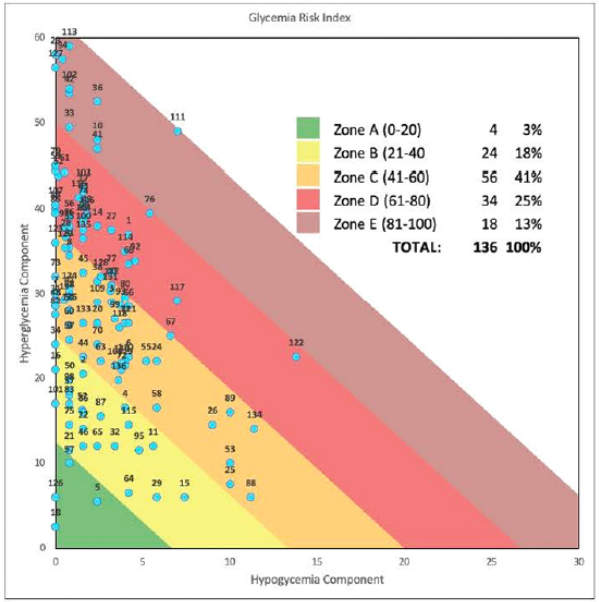


GRI, glycemia risk index; TIR, time in range

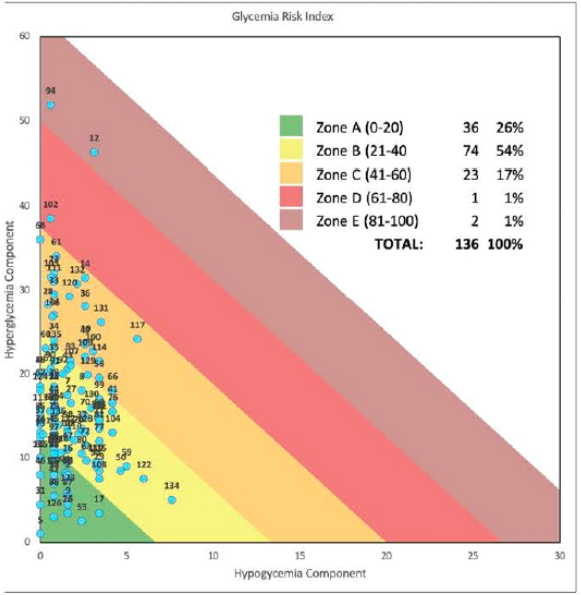
Klonoff DC et al. J Diabetes Sci Technol. 2023 Sep;17(5):1226-1242

GRI before and 6 Months after Initiation of a Hybrid Closed Loop System

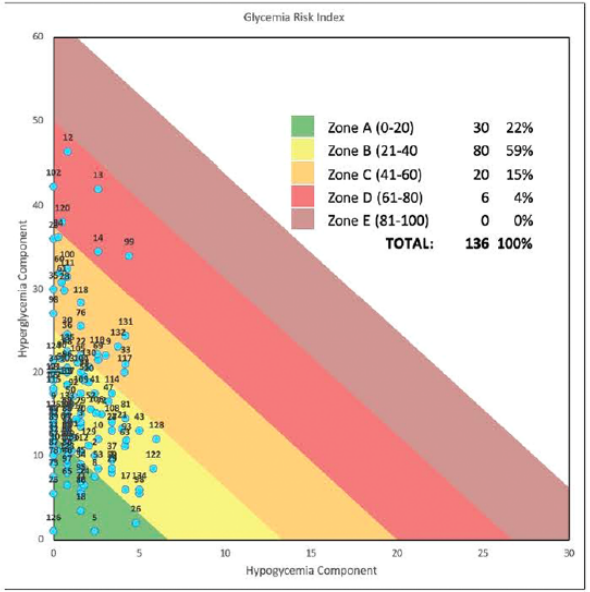
Retrospective Study, n = 136, Age 42.5 ± 14.3 yrs, Diabetes Duration 23.1 ± 12.1 yrs



GRI à M0



GRI à M3



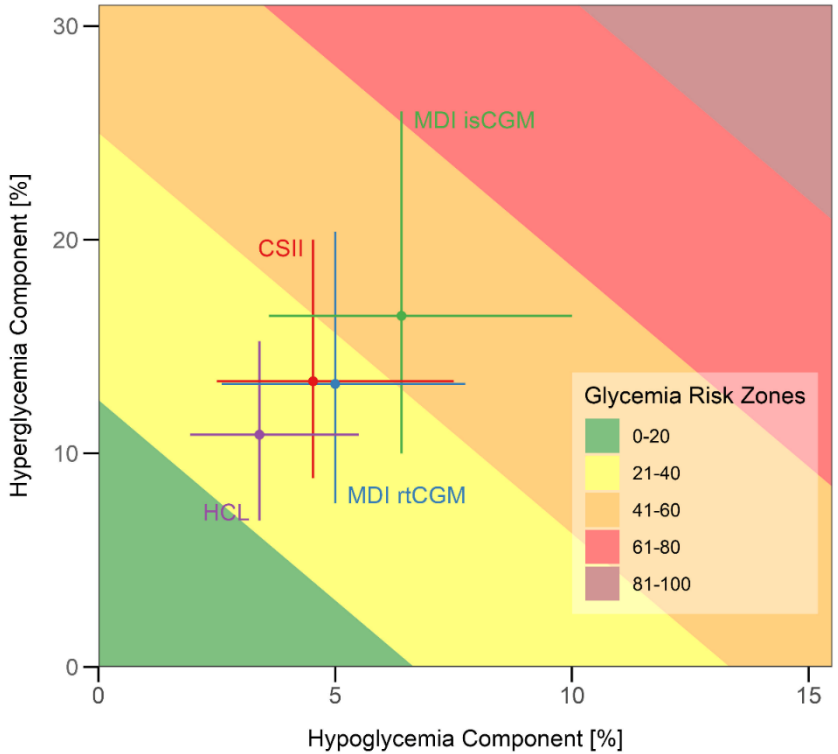
GRI à M6

Fig. 1. GRI (= Glucose Risk Index) grids for the whole population (n=136) before hybrid closed loop initiation (M0), at 3 months (M3) and at 6 months (M6). Each grid is displayed with the number and the proportion of patients in the 5 GRI zones (A to E). Each patient is represented by a blue circle with an identification number (from 1 to 136).

Picard S et al. Diabetes Metab. 2025 Mar;51(2):101617

Glycemia Risk Index by Treatment Modalities in T1D

Czech Pediatric Diabetes Registry, n = 3,251, Age 13.4 ± 3.8 yrs, Diabetes Duration 6.1 ± 3.6 yrs



CSII, continuous subcutaneous insulin infusion; GRI, glycemia risk index; HCL, hybrid closed loop; isCGM, intermittently-scanned continuous glucose monitoring; MDI, multiple daily injections; rtCGM, real-time continuous glucose monitoring; T1D, type 1 diabetes

Sumnik Z et al. Horm Res Paediatr. 2024;97(1):70-79

Associations between GRI and Albuminuria in Type 1 Diabetes

Cross-Sectional Study, n = 330, Age 45.1 ± 15.7 yrs, HbA1c 7.3 ± 1.0%

	OR (95% CI)	*P*
Per one-zone increase in GRI		
Unadjusted	1.51 (1.16-1.96)	.002
Adjusted (Model 1)	1.54 (1.17-2.02)	.002
Adjusted (Model 2)	1.75 (1.26-2.45)	.001
Adjusted (Model 3)	1.70 (1.19-2.41)	.003
Adjusted (Model 4)	1.63 (1.01-2.62)	.044
Adjusted (Model 5)	1.45 (1.003-2.11)	.048
Adjusted (Model 6)	1.37 (0.91-2.05)	.129
Per one-quintile increase in the hyperglycemia component		
Unadjusted	1.59 (1.27-1.98)	<.001
Adjusted (Model 1)	1.57 (1.25-1.97)	<.001
Adjusted (Model 2)	1.73 (1.31-2.28)	<.001
Adjusted (Model 3)	1.76 (1.31-2.37)	<.001
Adjusted (Model 4)	2.15 (1.34-3.46)	.002
Adjusted (Model 5)	1.51 (1.10-2.06)	.010
Adjusted (Model 6)	1.44 (1.05-1.98)	.024
Per one-quintile increase in the hypoglycemia component		
Unadjusted	0.81 (0.66-0.995)	.044
Adjusted (Model 1)	0.87 (0.70-1.08)	.202
Adjusted (Model 2)	0.85 (0.66-1.09)	.200
Adjusted (Model 3)	0.85 (0.65-1.10)	.206
Adjusted (Model 4)	0.87 (0.67-1.11)	.267
Adjusted (Model 5)	0.87 (0.67-1.13)	.291
Adjusted (Model 6)	0.91 (0.70-1.18)	.454

ORs for the presence of albuminuria were estimated by logistic regression analyses.
Model 1: adjusted for age and sex.
Model 2: Model 1 + duration of diabetes, hypertension, eGFR, and use of RAS inhibitors.
Model 3: Model 2 + body mass index.
Model 4: Model 2 + achievement of TIR target (>70% or ≤70%).
Model 5: Model 2 + achievement of HbA1c target (<7% or ≥7%).
Model 6: Model 2 + HbA1c.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; GRI, glycemia risk index; OR, odds ratio; RAS, renin-angiotensin system; TIR, time in range (70-180 mg/dL).

Kim JY et al. J Diabetes Sci Technol. 2025 Jan 8:19322968241310850

Association between GRI and DPN in Type 2 Diabetes

Cross-Sectional Study, n = 862, Age 52.95 ± 12.02 yrs, HbA1c 8.4 ±1.9%, Insulin 17.2%

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
GRI quartiles								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	1.293 (0.883, 1.891)	0.186	1.271 (0.858, 1.884)	0.232	1.258 (0.841, 1.880)	0.264	1.194 (0.796, 1.792)	0.391
Q3	1.353 (0.925, 1.981)	0.119	1.242 (0.838, 1.842)	0.281	1.170 (0.775, 1.765)	0.454	1.070 (0.703, 1.629)	0.752
Q4	2.066 (1.406, 3.036)	<0.001	1.867 (1.253, 2.781)	0.002	1.754 (1.159, 2.654)	0.008	1.631 (1.071, 2.484)	0.023
P for trend	<0.001		0.004		0.016		0.043	

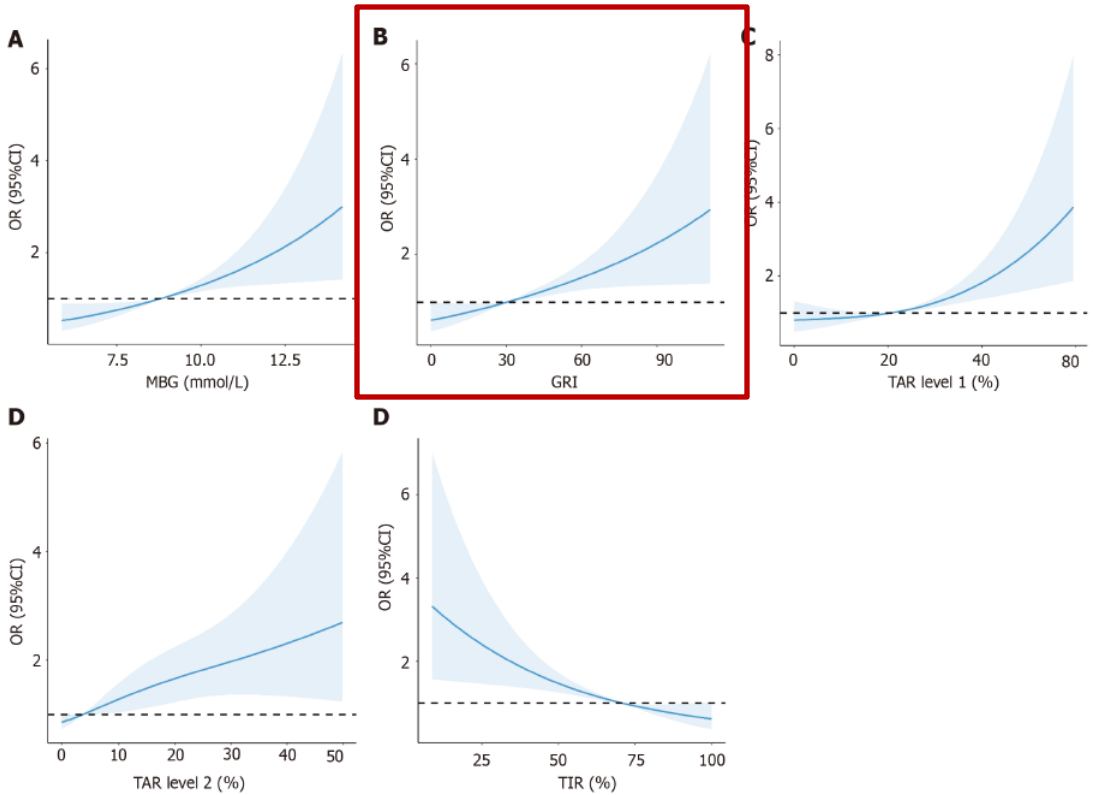
Notes: Multivariable logistic regression was used to assess the association between the GRI quartiles (Q1: GRI≤8.28, Q2: 8.28<GRI≤16.79, Q3: 16.79<GRI≤33.76 and Q4: GRI>33.76) and DPN. Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, BMI, diabetes duration, blood pressure, creatinine, urinary albumin-to-creatinine ratio, and lipid profile; Model 4: Model 3 + glycated hemoglobin. *P* <0.05 was considered statistically significant.

DPN, diabetic peripheral neuropathy ; CI, confidence interval; GRI, glycemia risk index; OR, odds ratio; Q, quartile

Tang Y et al. Diabetes Metab Syndr Obes. 2024 Nov 6;17:4191-4198

Association between GRI and Diabetic Foot in Type 2 Diabetes

Cross-Sectional Study, n = 591, Age 61.7 ± 12.7 yrs, HbA1c 9.1 ± 2.4%, Insulin 51.9%



GRI, glycemia risk index; MBG, mean blood glucose; TAR, time above range; TIR, time in range

Geng XQ et al. World J Diabetes. 2025 Mar 15;16(3):99277

Association between GRI and Arterial Stiffness in Type 2 Diabetes

Cross-Sectional Study, n = 342, Age 70.3 ± 6.8 yrs, Oral 85.7%, GLP1-RA 5.3%, Insulin 19.3%

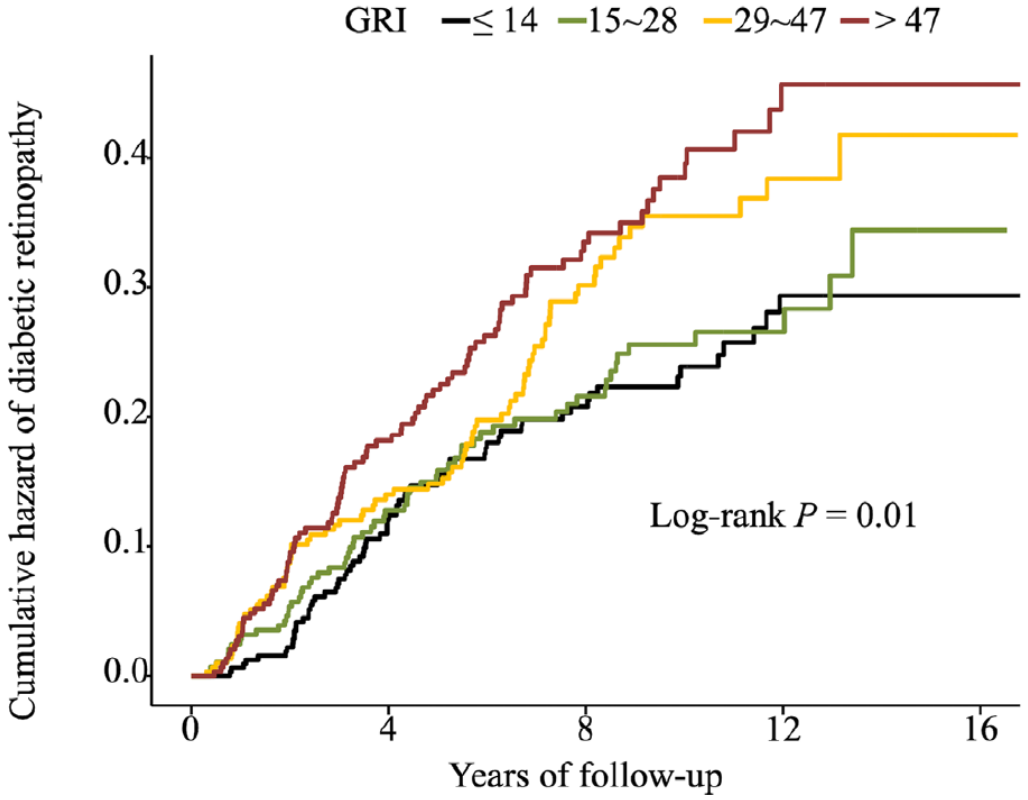
	baPWV, m/s					
	Unadjusted		Model 1		Model 2	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
GRI	0.02 (0.001, 0.03)	0.047	0.02 (0.001, 0.03)	0.038	0.02 (0.001, 0.03)	0.033
Q1	0.00 (Ref.)		0.00 (Ref.)		0.00 (Ref.)	
Q2	0.64 (−0.47, 1.73)	0.252	0.60 (−0.45, 1.64)	0.261	0.50 (−0.51, 1.51)	0.332
Q3	0.68 (−0.41, 1.78)	0.217	0.83 (−0.22, 1.88)	0.120	0.62 (−0.41, 1.64)	0.236
Q4	1.32 (0.22, 2.41)	0.019	1.38 (0.33, 2.43)	0.010	1.34 (0.28, 2.40)	0.013
P for trend	0.024		0.010		0.016	
Hypoglycemia component	−0.004 (−0.10, 0.09)	0.937	0.01 (−0.09, 0.10)	0.915	0.02 (−0.07, 0.11)	0.698
Q1	0.00 (Ref.)		0.00 (Ref.)		0.00 (Ref.)	
Q2	−0.12 (−1.23, 1.00)	0.839	−0.11 (−1.18, 0.95)	0.836	0.07 (−0.96, 1.10)	0.893
Q3	−0.54 (−1.63, 0.54)	0.326	−0.35 (−1.39, 0.69)	0.507	−0.30 (−1.30, 0.71)	0.561
Q4	0.06 (−1.05, 1.16)	0.920	0.28 (−1.03, 1.08)	0.959	0.10 (−0.95, 1.14)	0.858
P for trend	0.874		0.919		0.940	
Hyperglycemia component	0.02 (−0.001, 0.04)	0.063	0.02 (−0.002, 0.04)	0.071	0.02 (−0.002, 0.04)	0.080
Q1	0.00 (Ref.)		0.00 (Ref.)		0.00 (Ref.)	
Q2	0.14 (−0.93, 1.21)	0.800	0.26 (−0.76, 1.28)	0.614	0.34 (−6.57, 1.33)	0.507
Q3	1.19 (0.10, 2.28)	0.032	1.34 (0.30, 2.39)	0.012	1.11 (0.08, 2.15)	0.036
Q4	1.02 (−0.07, 2.12)	0.067	1.13 (0.09, 2.18)	0.033	1.13 (0.09, 2.18)	0.034
P for trend	0.019		0.008		0.013	

Data are expressed as regression coefficients (95% CI). Model 1 was adjusted for sex and age. Model 2 was further adjusted for body mass index, duration of diabetes, current smoking status, systolic blood pressure, triglycerides, HDL cholesterol and LDL cholesterol. baPWV, brachial-ankle pulse wave velocity; GRI, glycemia risk index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Cai L et al. J Diabetes Investig. 2024 May;15(5):614-622

Association between GRI and Incident DR in Type 2 Diabetes

Dynamic Cohort Study, n = 1,204, Age 58 yrs (52, 65), HbA1c 8.2% (7.1, 9.8), w/o DR, Insulin 57%



DR, diabetic retinopathy; GRI, glycemia risk index

Wang Y et al. Diabetes Obes Metab. 2023 Sep;25(9):2457-2463

STRENGHTS	LIMITATIONS

The content on the slide reflects the speaker's personal opinion.
CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; GRI, glycemia risk index; RCT, randomized controlled trial


Grazie