Control of Glycemic Variability for Reducing Hypoglycemia

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SAMSUNG MEDICAL CENTER

Conflict of interest disclosure

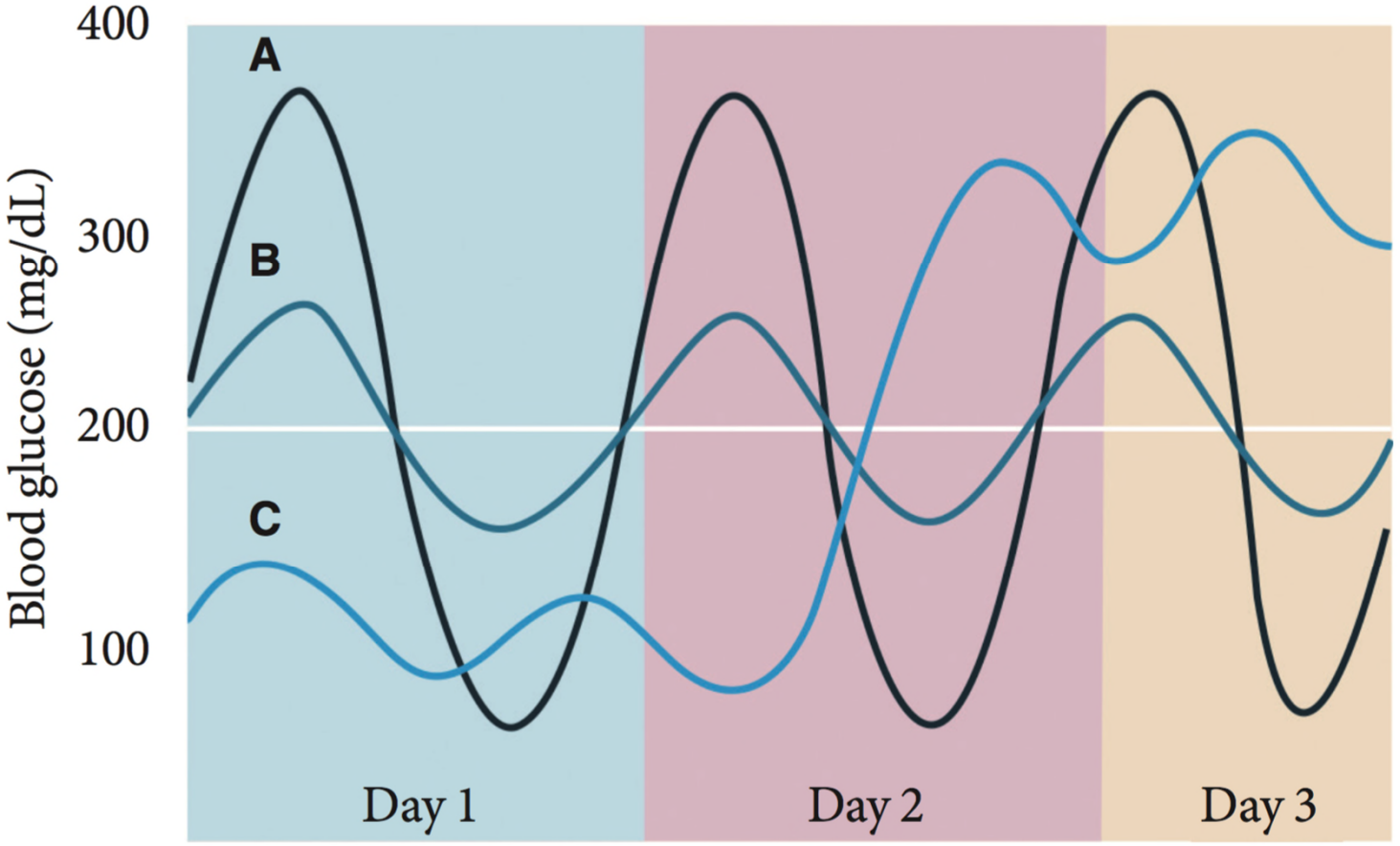
None

Committee of Scientific Affairs

Contents

- What is glycemic variability
- Glycemic variability increases hypoglycemic risk
- Decreased β-cell function increases glycemic variability
- Evidence for use of professional CGM & real-time CGM (FGM) in T2D
- Evidence for use of real-time CGM, SAP-LGS, Hybrid CL in T1D

What is glycemic variability ?



Indices of GV

- GV
  - Mean amplitude of glucose excursion (MAGE)
  - Continuous overall net glycemic action (CONGA)
  - Mean of daily differences (MODD)
  - **Standard deviation (SD)**
  - **% Coefficient of variation (Relative GV)**
- Quality of glycemic control and GV
  - J index, Low blood glucose index (LBGI)/High blood glucose index (HBGI)
  - Average daily risk range (ADRR)
  - Index of glycemic control (IGC)
  - The glycemic risk assessment diabetes education (GRADE)

Absolute GVs, but not relative GV (CV), are associated with mean glucose

	Regression coefficient (β), 95% CI	r^2	P
SD	0.231, 0.181–0.281	0.331	< 0.001
MODD	0.239, 0.184–0.294	0.303	< 0.001
MAGE	0.381, 0.255–0.507	0.172	< 0.001
CV (SD/mean)	–0.013, –0.043–0.018	0.004	0.411

Values were generated by a linear regression analysis in which mean glucose was the independent variable and each glycaemic variability index was the dependent variable.
CV, coefficient of variation; MAGE, mean amplitude of glycaemic excursion; MODD, mean of daily differences.

Jin SM et al. DRCP 2015

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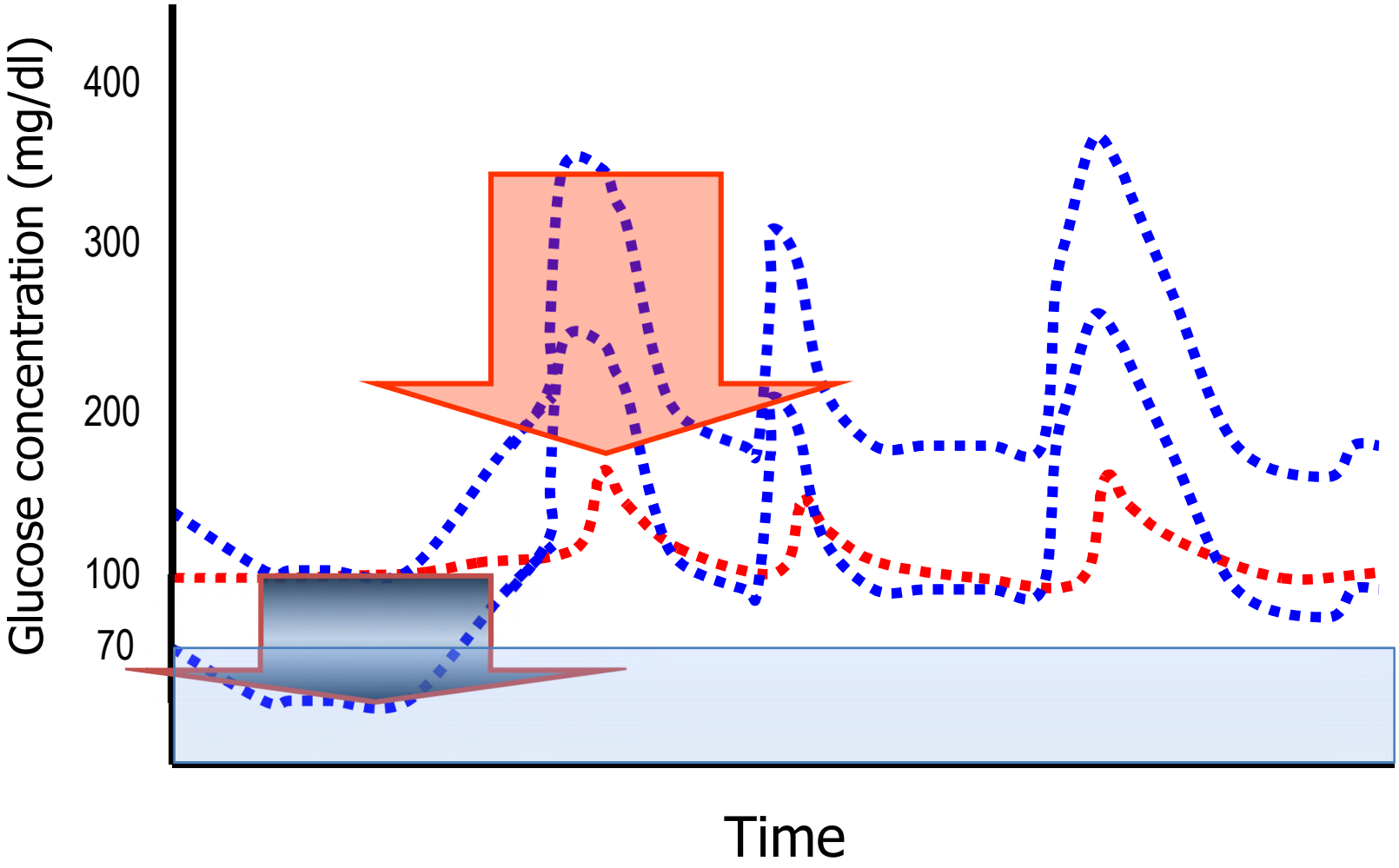
Glycemic variability & hypoglycemia

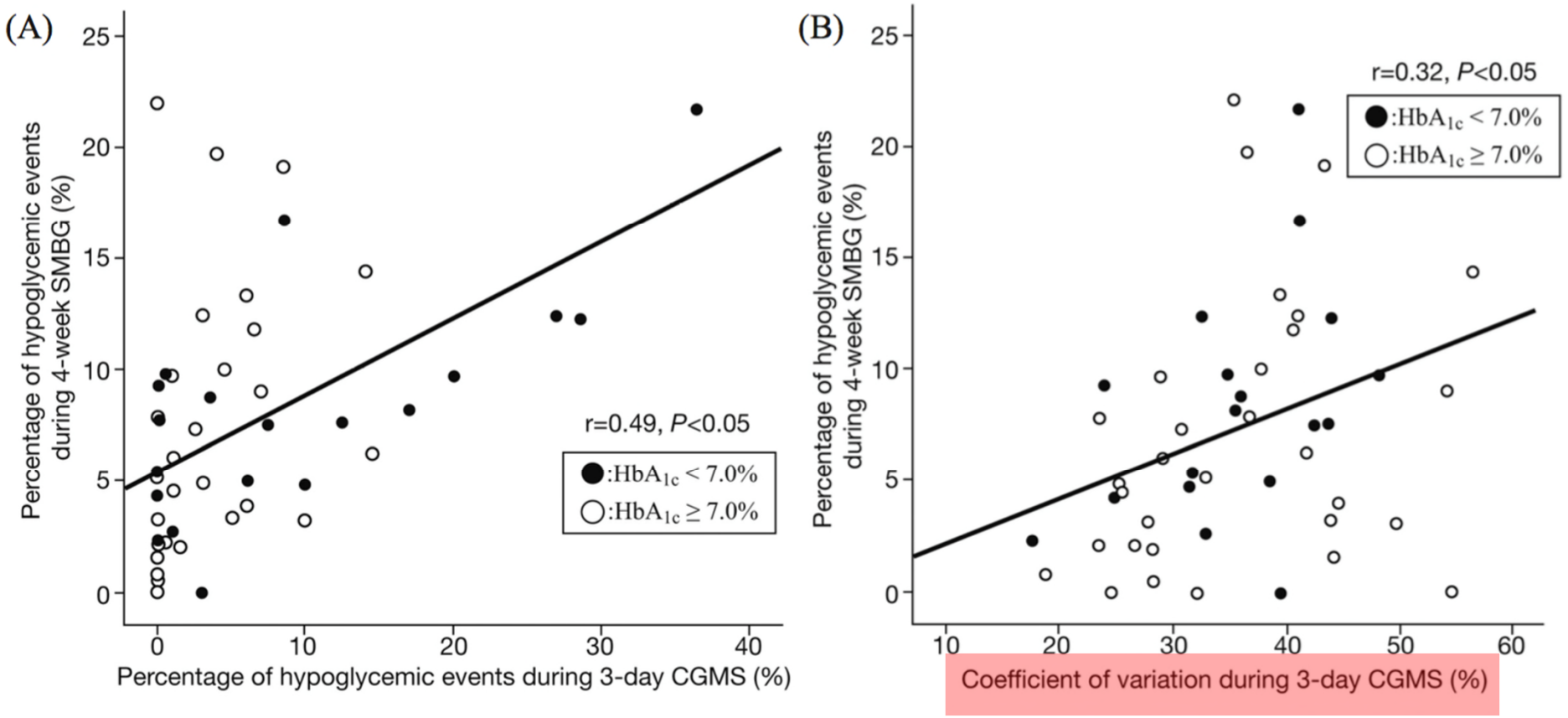
Lowering glucose vs. Reducing GV



Three-day continuous glucose monitoring for rapid assessment of hypoglycemic events and glycemic variability in type 1 diabetic patients

Soo Kyoung Kim, Sunghwan Suh, Mi Yeon Kim, Hye Soo Chung, Kyu Yeon Hur, Sun Wook Kim, Jae Hoon Chung, Myung-Shik Lee, Yong-Ki Min, Kwang-Won Kim and Jae Hyeon Kim

Kim SK et al. Endocrine J 2011



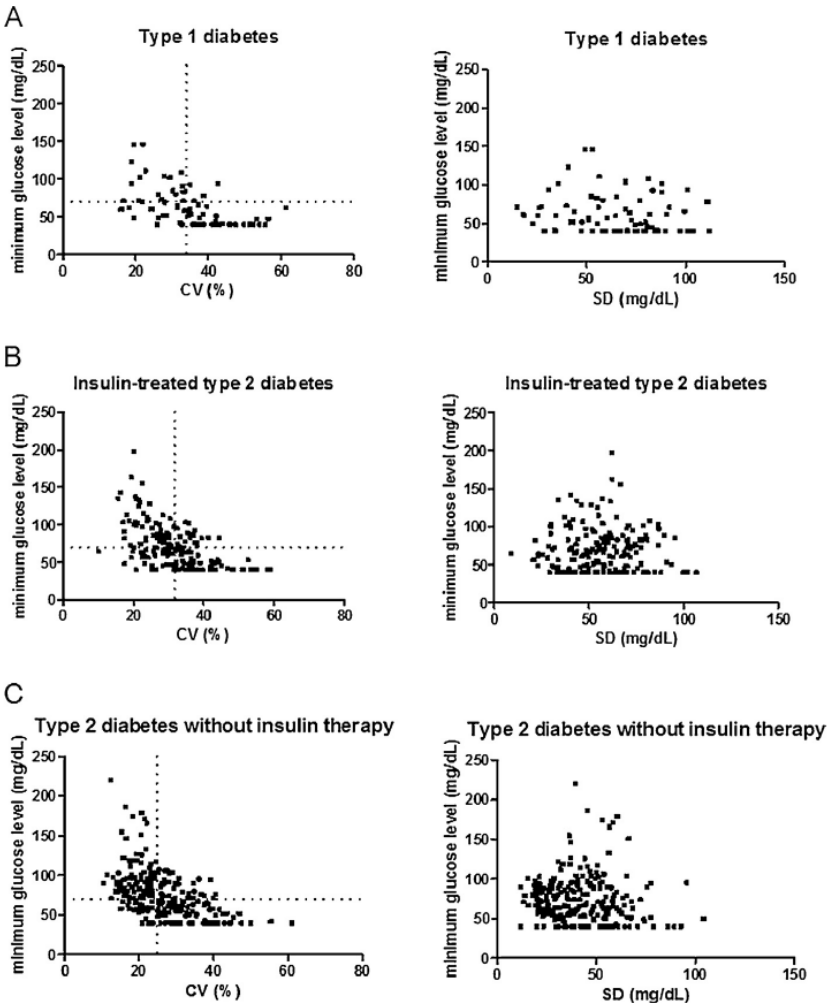
Clinical factors associated with absolute and relative measures of glycemic variability determined by continuous glucose monitoring: An analysis of 480 subjects

Sang-Man Jin [1], *Tae-Hun Kim* [1], *Ji Cheol Bae, Kyu Yeon Hur, Myung-Shik Lee, Moon-Kyu Lee, Jae Hyeon Kim* [*]

Jin SM et al. DRCP 2014

Absolute GV : Standard Deviation (SD)
Relative GV: Coefficient of Variation (CV) = SD/mean

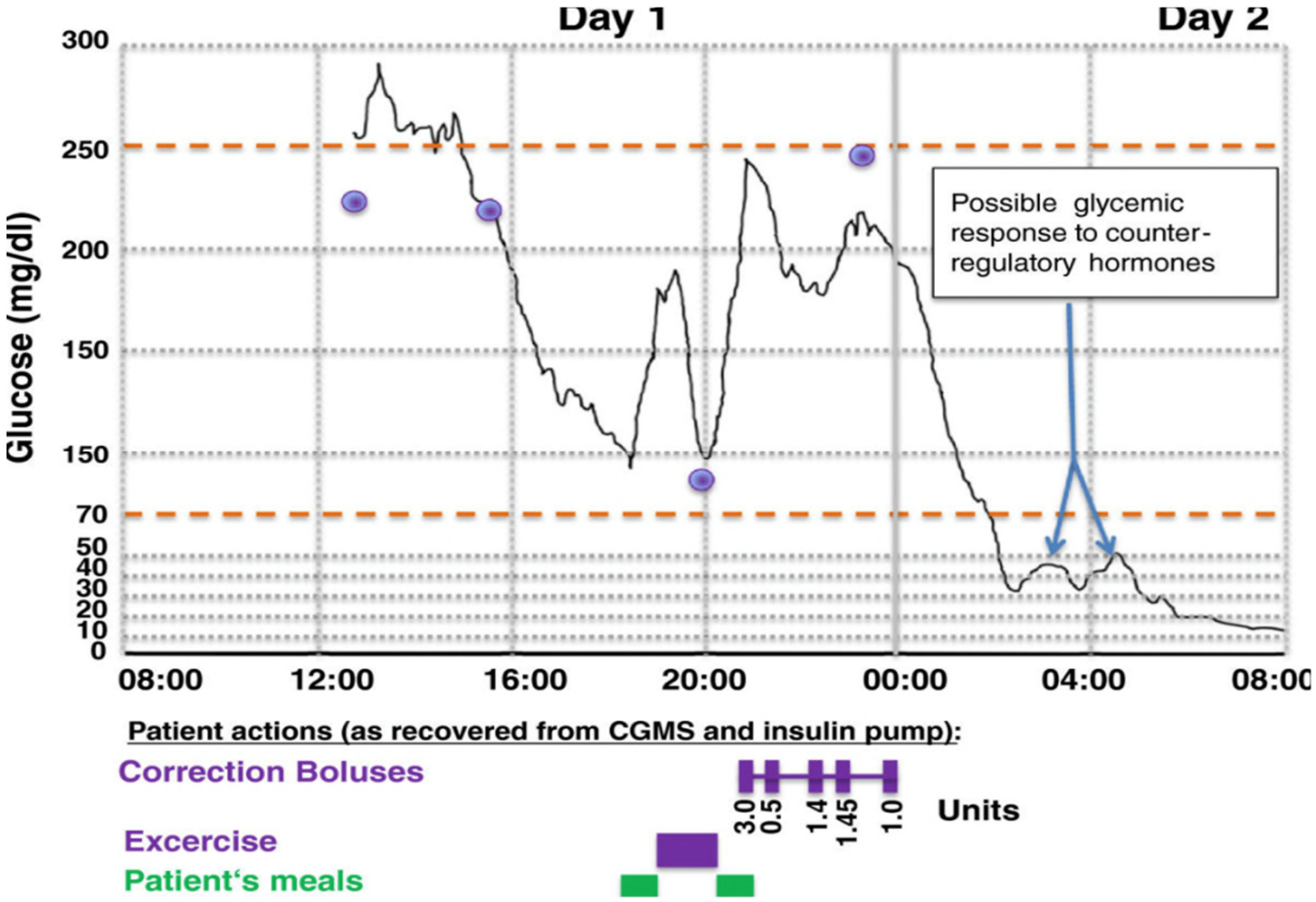
Regardless of the type of diabetes and insulin therapy, higher CV, but not SD, was significantly associated with hypoglycemia



CONFIRMATION OF HYPOGLYCEMIA IN THE "DEAD-IN-BED" SYNDROME, AS CAPTURED BY A RETROSPECTIVE CONTINUOUS GLUCOSE MONITORING SYSTEM

Robert J. Tanenberg, MD, FACP[1]; Christopher A. Newton, MD[2]; Almond J. Drake III, MD, FACE[1]

Endocr Pract. 2010;16:244-248



Australian mother who lost daughter from dead in bed syndrome launches CGM initiative

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Decreased insulin secretion and lower level insulin resistance are associated with glycemic variability

	Type 1 diabetes (n = 81)		Insulin-treated type 2 diabetes (n = 168)		Type 2 diabetes without insulin therapy (n = 231)	
	SD	log (CV)	SD	log (CV)	SD	log (CV)
Age (years)					0.289*	
BMI (kg/m^2)		−0.031**			0.837*	
DM duration (years)		0.017**		0.007**		
HbA1c (%)			3.400***		2.720**	
C-peptide (ng/mL)	−14.224**		−3.961**	−0.092***		
HDL (mg/dL)		0.007**			0.298**	0.004*
LDL (mg/dL)						−0.002**
Triglyceride (mg/dL)					0.029*	
Use of pre-mixed insulin (vs. MDI/CSII)	6.797*	0.182*				
Use of sulfonylurea					8.906***	0.204***

Values represent unstandardized regression coefficient (β) estimated by stepwise multiple regression analysis. Categorical variables were treated as dummy variables. Logarithmic transformation was performed for CV before each analysis to secure the normality of the residuals. HbA1c, hemoglobin A_{1C}; SD, standard deviation; CV, coefficient of variance; BMI, body-mass index; DM, diabetes mellitus; HDL, high density lipoprotein–cholesterol; LDL, low density lipoprotein–cholesterol; MDI, multiple daily injection; CSII, continuous subcutaneous insulin infusion.

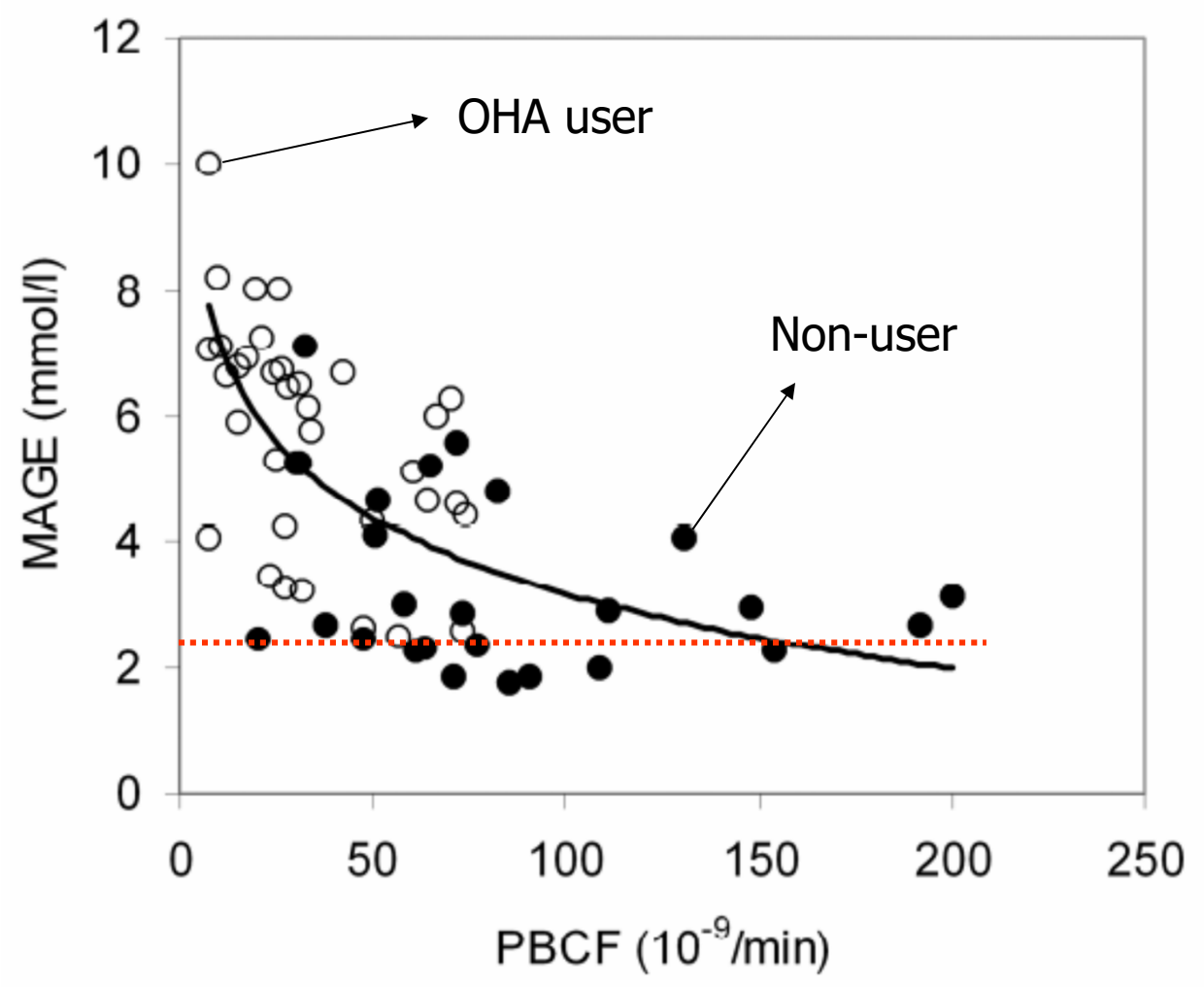
Jin SM et al. DRCP 2014

Glycemic Variability Strongly Correlates with Postprandial ß-cell Dysfunction in a Segment of Type 2 Diabetic Patients Using Oral Hypoglycemic Agents

	SU, MTF, SU+MTF OHA users	Non-users	*P* value
N	34	25	
Sex (M/F)	15/19	16/9	0.13
Age (years)	65.0 (57.0 – 71.0) 8.5	64.0 (62.0 – 69.0)	0.65
Diabetes duration (years)	8.5 (3.0– 11.0)	2.0 (1.0 – 6.0)	0.003
HbA1c (%)	6.8 ± 1.2	6.1 ± 0.6	0.013
Fasting C-peptide (nmol/l)	0.92 (0.70 – 1.26)	0.91 (0.71 – 1.25)	0.90
Glycemic variability			
MAGE (mmol/l)	5.7 ± 1.8	3.6 ± 1.9	<0.001
MMT-derived parameters			
Fasting glucose (nmol/l)	8.1 (7.4 – 11.5)	7.0 (6.0 – 7.8)	<0.001
Incremental glucose peak (mmol/l)	4.2 (3.3 – 4.8)	2.4 (1.6 – 3.2)	<0.001
$IAUC_{Glucose}$ (mmol • l^{-1} • 150 min^{-1})	254.5 (187.0 – 305.0)	117.5 (54.5 – 156.5)	<0.001
Fasting plasma insulin (nmol/l)	0.11 (0.07 – 0.14)	0.10 (0.09 – 0.13)	0.77
Incremental insulin peak (mmol/l)	0.55 (0.27 – 0.81)	0.67 (0.45 – 0.80)	0.62
$IAUC_{Insulin}$ (mmol • l^{-1} • 150 min^{-1})	38.0 (25.0 – 42.9)	43.8 (21.5 – 44.9)	0.06
Fasting ß-cell function (10^{-9}/min)	7.1 (4.9 – 8.8)	9.0 (8.1 – 11.1)	0.005
Postprandial (10^{-9}/min)	27.4 (15.7 – 46.3)	71.4 (50.4 – 108.8)	<0.001
Insulin sensitivity			
HOMA-S (%)	44.6 ± 17.1	53.0 ± 13.1	0.045

Kohnert KD et al. Diabetes Care 2009

Glycemic Variability Strongly Correlates with Postprandial ß-cell Dysfunction in a Segment of Type 2 Diabetic Patients Using Oral Hypoglycemic Agents



Kohnert KD et al. Diabetes Care 2009

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Hypoglycemia in Type 2 Diabetes - More Common Than You Think: A Continuous Glucose Monitoring Study

Journal of Diabetes Science and Technology
2015, Vol. 9(5) 999–1005

DOI: 10.1177/1932296815581052
dst.sagepub.com
SAGE

Richa Redhu Gehlaut, MD[1], Godwin Y. Dogbey, PhD[2], Frank L. Schwartz, MD, FACE[3], Cynthia R. Marling, PhD[4], and Jay H. Shubrook, DO, FACOFP, FAAFP, BC-ADM[5]

108 patients with T2DM wore a continuous glucose monitoring system (CGMS) for 5 days

50% had at least 1 **hypoglycemic episode** (mean 1.74 episodes/patient/ 5 days of CGMS).

75% of those patients experienced at least 1 **asymptomatic hypoglycemic** episode.

Hypoglycemia was more frequent in individuals on insulin (alone or in combination) ($P = .02$) and those on oral hypoglycemic agents ($P < .001$) compared to noninsulin secretagogues.

CGMS analysis resulted in **treatment modifications in 64% of the patients**.

Effectiveness of 3-Day Continuous Glucose Monitoring for Improving Glucose Control in Type 2 Diabetic Patients in Clinical Practice

DMJ 2014

Soo Kyoung Kim[1,*], Hye Jeong Kim[2,*], Taehun Kim[2], Kyu Yeon Hur[2], Sun Wook Kim[2], Moon-Kyu Lee[2], Yong-Ki Min[2], Kwang-Won Kim[2], Jae Hoon Chung[2], Jae Hyeon Kim[2]

Insulin user

Variable	CGMS group (n=20)	Control group (n=78)	P value
Change in insulin regimens	7 (35.0)	8 (10.3)	0.036
Adding or change in OHAs	5 (25.0)	4 (5.1)	0.012
No change in regimen	8 (40.0)	66 (84.6)	0.001

Values are presented as number (%).
CGMS, continuous glucose monitoring system; OHA, oral hypoglycemic agent.

Non-insulin user

Variable	CGMS group (n=45)	Control group (n=223)	P value
Add insulin therapy	1 (2.2)	1 (0.5)	0.324
Adding or change in OHAs	35 (77.8)	85 (38.1)	0.001
No change	9 (20.0)	137 (61.4)	0.001

Values are presented as number (%).
CGMS, continuous glucose monitoring system; OHA, oral hypoglycemic agent.

72h CGM in 65 patients with T2D

37% experienced the hypoglycemia events during 3day-CGMS (33% in OHA, 45% in insulin user)

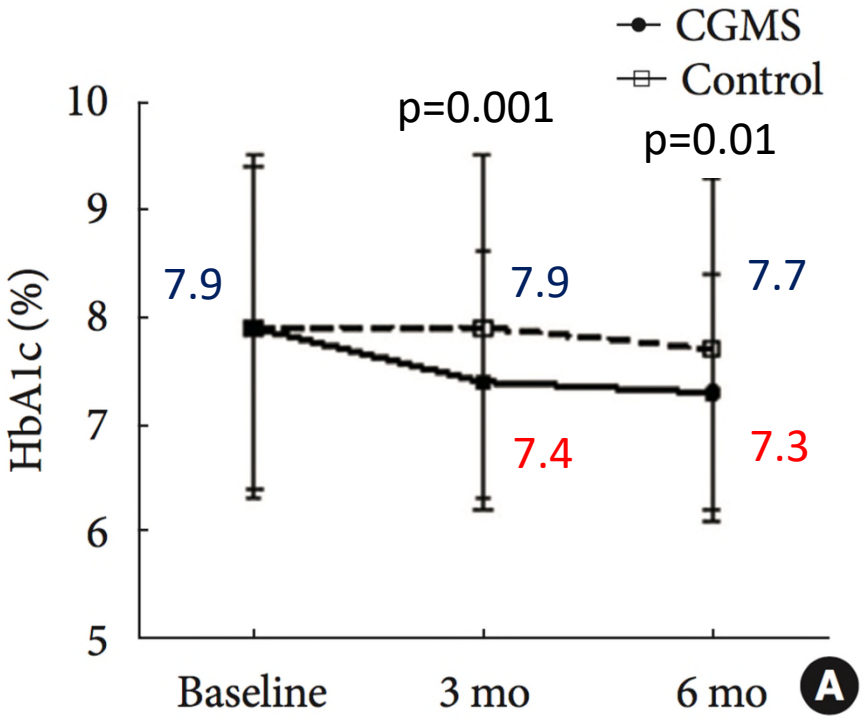
60% of insulin user changed treatment regimens

80% of non-insulin user changed treatment regimens

Effectiveness of 3-Day Continuous Glucose Monitoring for Improving Glucose Control in Type 2 Diabetic Patients in Clinical Practice

Soo Kyoung Kim[1,*], Hye Jeong Kim[2,*], Taehun Kim[2], Kyu Yeon Hur[2], Sun Wook Kim[2], Moon-Kyu Lee[2], Yong-Ki Min[2], Kwang-Won Kim[2], Jae Hoon Chung[2], Jae Hyeon Kim[2]

Characteristic	Propensity score matched sample		
	CGMS group (n=65)	Control group (n=301)	P value
Age, yr	59.0±10.0	59.1±11.0	0.945
Body mass index, kg/m^2	25.9±3.3	25.7±3.3	0.925
Sex female	18 (27.7)	89 (29.6)	1.000
Duration of diabetes, yr	11.9±6.9	11.4±7.3	0.628
HbA1c, %	7.9±1.5	7.9±1.6	0.939
Treatment			
OHAs	45 (69.2)	223 (74.1)	0.442
SU	29 (64.4)	141 (63.2)	1.000
Metformin	37 (82.2)	170 (76.2)	0.441
TZD	13 (28.9)	29 (13.0)	0.012
Glinide	0	9 (4.0)	0.364
AGI	8 (17.8)	62 (27.8)	0.195
DPP4 inhibitor	7 (15.6)	4 (1.8)	<0.001
Basal insulin+OHAs	11 (16.9)	41 (13.6)	0.556
Insulin twice a day	8 (12.3)	36 (12.0)	1.000
Multiple daily injection	1 (1.5)	1 (0.3)	0.324



DMJ 2014

Improving HbA1c in T2DM using retrospective CGM

Author	Date	Population	Design	# Subjects	Results and Caveats
Mohan	2016	Adult/T2	Prospective non-randomized	149	HbA1C decrease 0.6% in 3 months; therapy changes made in 84.2% of subjects; Subjects with therapy changes had a mean change in HbA1C of −0.7% compared with subjects who did not have therapy changes (−0.43%). May be selection bias.
Young	2015	Adult/T2	RCT	35	Decrease 0.61% HbA1C from baseline to study completion (3 months):
Kim	2014	Adult/T2	Retrospective review with propensity matching 1:5	65	HbA1C decrease 0.5% in the 45 patients on oral agents at 3 months. There may have been selection bias.
Blackberry	2014	Adult/T2	RCT	92	HbA1C decreased 2.7% with CGM vs. 2.4% with SMBG. Glulisine was initiated in 26/48 in the CGM group vs. 7/44 in the SMBG group; $p < 0.001$. There were two interventions: GP's and CGM
Leinung	2014	Adult/T2	Retrospective chart review	37	HbA1C decreased by 0.5% overall with those in the mainly hyperglycemic group (N = 19) decreasing from 9.8% to 9.0%, $p = <0.03$; in the mainly hypoglycemic group from 9.0% to 8.5% (N-4), $p = <0.02$. May be selection bias.
Pepper	2012	Adult/T1 and T2 on insulin	Retrospective chart review	102	No change in HbA1C (7.7% vs. 7.8%). May be selection bias. No description of therapy changes and no analysis of hypoglycemia.
Cosson	2009	Adult/T2 on insulin only	RCT vs. BG meters	25	HbA1C −0.63% at 3 months. Used micro-dialysis device for 48 h. 41% (20/48) of the randomized patients failed to complete the study. Details of the treatment changes were not provided.
Allen	2008	Adult/T2	RCT	52	Decrease in HbA1C of 1.2% with while control group decreased 0.3%; $p < 0.05$.
Murphy	2008	Adult Pregnant T2 on insulin	RCT	25	A1C and macrosomia were reduced with retrospective CGM done every 4–6 weeks.

Open access Protocol

BMJ Open

GP-OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in general practice

Aim of study: To examine **intermittent r-CGM** use (up to 14 days every three months) in **T2D in general practice (GP)**

Methods and analysis: General Practice Optimising Structured MOnitoring To achieve Improved Clinical Outcomes is a two-arm RCT asking '**does intermittent r-CGM in adults with T2D in primary care improve HbA1c?**'

Primary outcome Absolute difference in mean HbA1c at 12months follow-up between intervention and control arms.

Secondary outcomes: (a) r-CGM percent time in target (4–10mmol/L) range, at baseline and 12 months;

Flash glucose monitoring (FGM): no need of calibration with fingerstick glucose, but still provides trend arrows

FreeStyle Libre (Abbott)

FreeStyle Libre Pro: retrospective

FreeStyle Libre: real-time

"Why prick when you can scan?"

Differences between real-time CGM and FGM

	Real-time CGM	FGM
Provider (procurement option)	Several	One
Calibration	Daily	Factory calibrated by the manufacturer
Lancing required	Yes[a]	No[b]
Sensor insertion under the skin required	Yes	Yes
Form required for cost absorption	Yes	Basically not currently covered by the National Association of Statutory Health Insurance Funds
Statements on this topic on the Internet	Yes	Many
Glucose measurement in ISF, not in blood	Yes	Yes
Maximum duration of sensor use	7 days	14 days
Test result displayed on an external device	Yes (also insulin pump)	Yes
Permanent connection to an external device	Yes	No
(Hypo) alarms	Yes	No
Current value displayed	Yes	Yes
Trend arrow displayed	Yes	Yes
Adjustment of the insulin dose based on test results	Not to date	Yes (limited)
BG replacement claim	No	Yes (with exceptions in special situations)
Connection to pump	Yes (most systems)	No
Usability with artificial pancreas	Yes	No (at this current technological state)
User	Type 1	Type 1 and type 2
Number of users	Rather few	Many ("mass-produced product")

Dexcom G5

Heinemann et al., JDST 2015

Reduced glycemic variability and hypoglycemia by FGM in insulin-treated type 2 diabetes without BGM

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 Diab Ther 2017

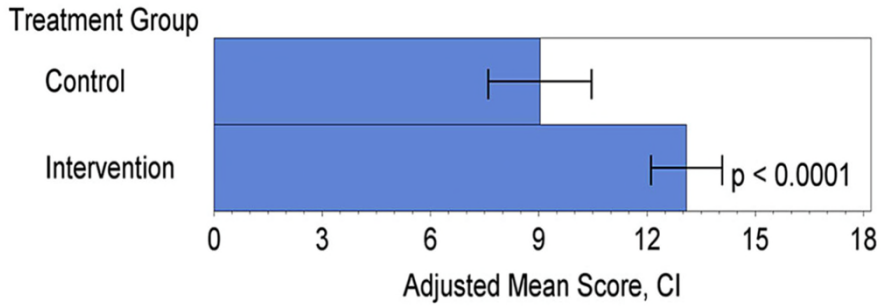
Open label RCT, 26 European Diabetes Center
Aged ≥ 18 years with **T2D treated with insulin** for at least 6months and on their current regimen **(MDI or CSII therapy) for 3 months** or more, an HbA1c level (7.5–12.0%), SMBG testing (≥10/week)
Following 2 weeks of blinded sensor wear, (intervention/control) randomization (149:75) (FGM/SMBG)
6m follow-up, 2weeks FGM vs. blinded FGM & SMBG

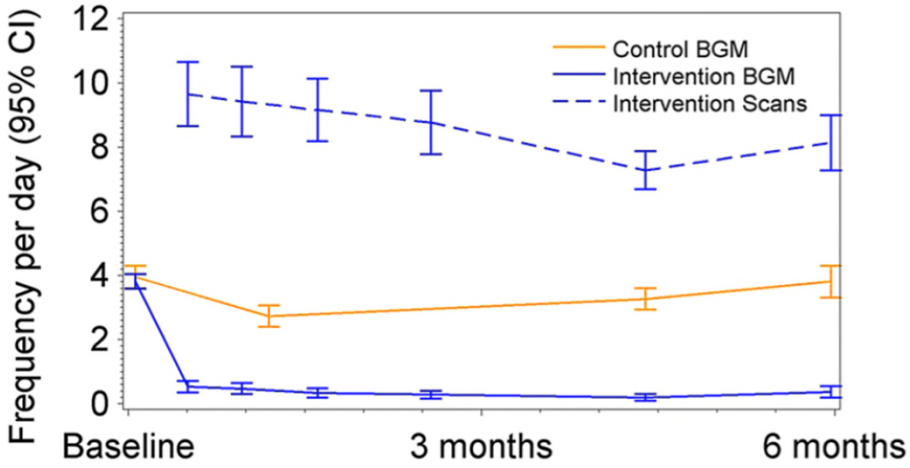
FGM reduced GV, time spent and events of hypoglycemia without increase in HbA1c in T2DM with MDI or pump

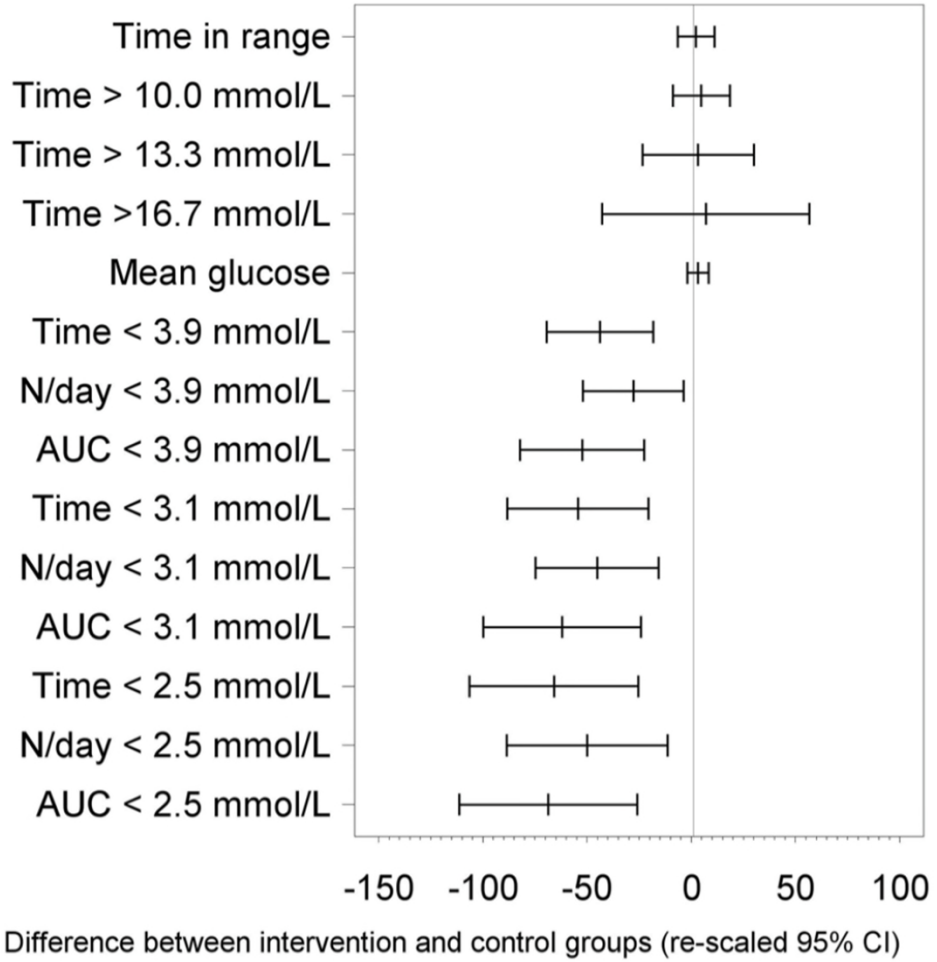
Glycemic measure	Baseline mean (SD)		Study end mean (SD)		Difference in adjusted means in intervention vs control (SE)	Difference in intervention vs control (%)	*p* value
	Intervention (*n* = 149)	Control (*n* = 75)	Intervention (*n* = 149)	Control (*n* = 75)			
HbA1c (mmol/mol)	71.0 (11.1)	72.1 (10.7)	68.0 (9.0)	67.7 (12.4)	0.3 (1.25)	N/A	0.8259
HbA1c (%)	8.65 (1.01)	8.75 (0.98)	8.37 (0.83)	8.34 (1.14)	0.03 (0.114)	N/A	0.8222
Time with glucose 3.9–10.0 mmol/L (70–180 mg/dL) (h)	13.9 (4.5)	13.5 (5.2)	13.6 (4.6)	13.2 (4.9)	0.2 (0.58)	1.1	0.7925
Glucose <3.9 mmol/L (70 mg/dL) within 24 h							
Events	0.64 (0.63)	0.63 (0.66)	0.38 (0.45)	0.53 (0.59)	−0.16 (0.065)	−27.7	0.0164
Time (h)	1.30 (1.78)	1.08 (1.58)	0.59 (0.82)	0.99 (1.29)	−0.47 (0.134)	−43.1	0.0006
AUC (h × mg/dL)	20.15 (35.21)	14.05 (26.35)	7.23 (12.35)	13.59 (22.31)	−7.80 (2.20)	−51.1	0.0005
Glucose <3.9 mmol/L (70 mg/dL) at night (23.00–06.00) within 7 h							
Events	0.25 (0.28)	0.27 (0.32)	0.14 (0.20)	0.27 (0.33)	−0.12 (0.03)	−44.9	0.0003
Time (h)	0.55 (0.84)	0.49 (0.71)	0.23 (0.43)	0.51 (0.72)	−0.29 (0.08)	−54.3	0.0001
Glucose <3.1 mmol/L (55 mg/dL) within 24 h							
Events	0.34 (0.50)	0.27 (0.44)	0.14 (0.24)	0.24 (0.36)	−0.12 (0.037)	−44.3	0.0017
Time (h)	0.59 (1.13)	0.38 (0.83)	0.19 (0.37)	0.37 (0.69)	−0.22 (0.068)	−53.1	0.0014
AUC (h × mg/dL)	6.02 (13.23)	3.40 (9.16)	1.64 (3.85)	3.66 (7.97)	−2.51 (0.76)	−60.3	0.0012
Glucose <3.1 mmol/L (55 mg/dL) at night (23.00–06.00) within 7 h							
Events	0.15 (0.23)	0.13 (0.20)	0.06 (0.13)	0.13 (0.21)	−0.07 (0.02)	−53.0	0.0012
Time (h)	0.27 (0.58)	0.18 (0.35)	0.09 (0.22)	0.19 (0.40)	−0.12 (0.04)	−58.1	0.0032
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

FGM increase patient satisfaction in T2DM with MDI or insulin pump

Total treatment satisfaction score







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Reduced hypoglycemia by FGM in type 1 diabetes without impaired awareness of hypoglycemia

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

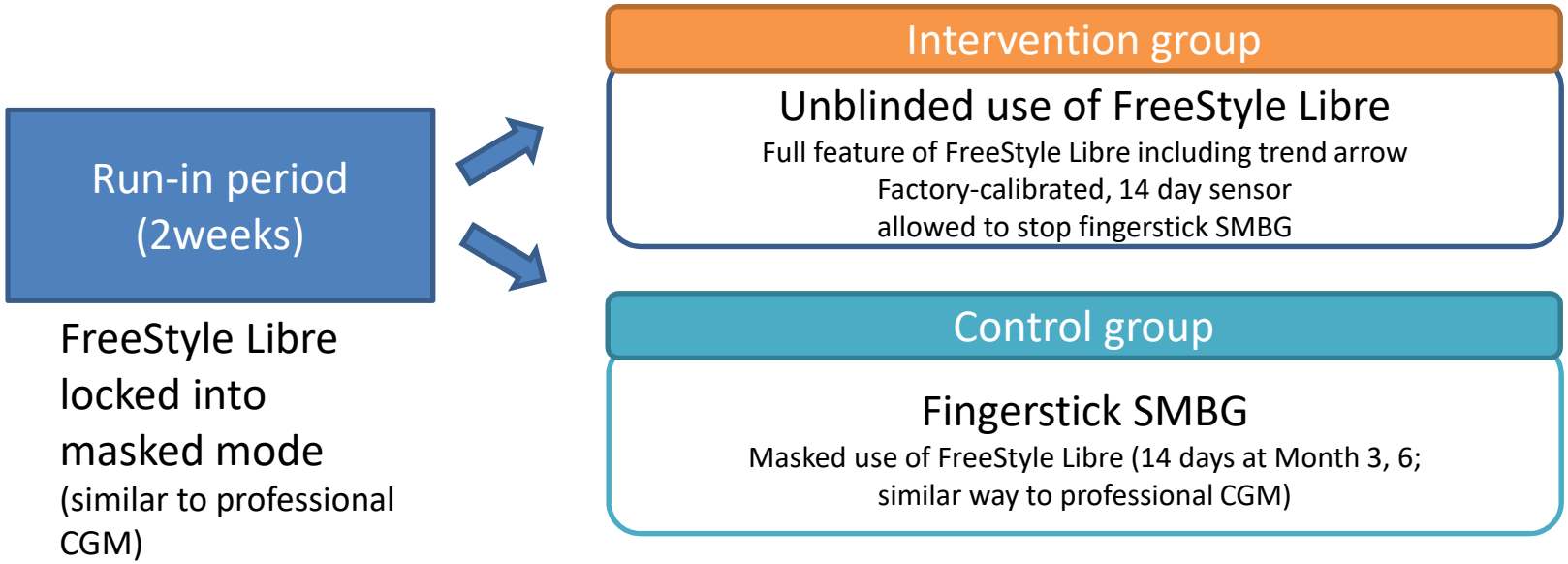
THE LANCET

- RCT at 23 European diabetes centers (n = 328)
- Inclusion criteria: Adults with **well-controlled T1D (HbA1c <7.5%),** regular SMBG (≥3 times a day) for 2 months, **insulin pump user**
- Exclusion criteria: hypoglycemic unawareness, recent DKA, recent use of CGM or sensor-augmented pump

Bolinder J et al., Lancet 2016

FGM in type 1 diabetes without impaired awareness of hypoglycemia: intervention in the RCT

- Intervention (6 months)



- Primary outcome: **change in time spent in hypoglycemia** (<70mg/dL) for the 14 days preceding the end of the 6 month study period

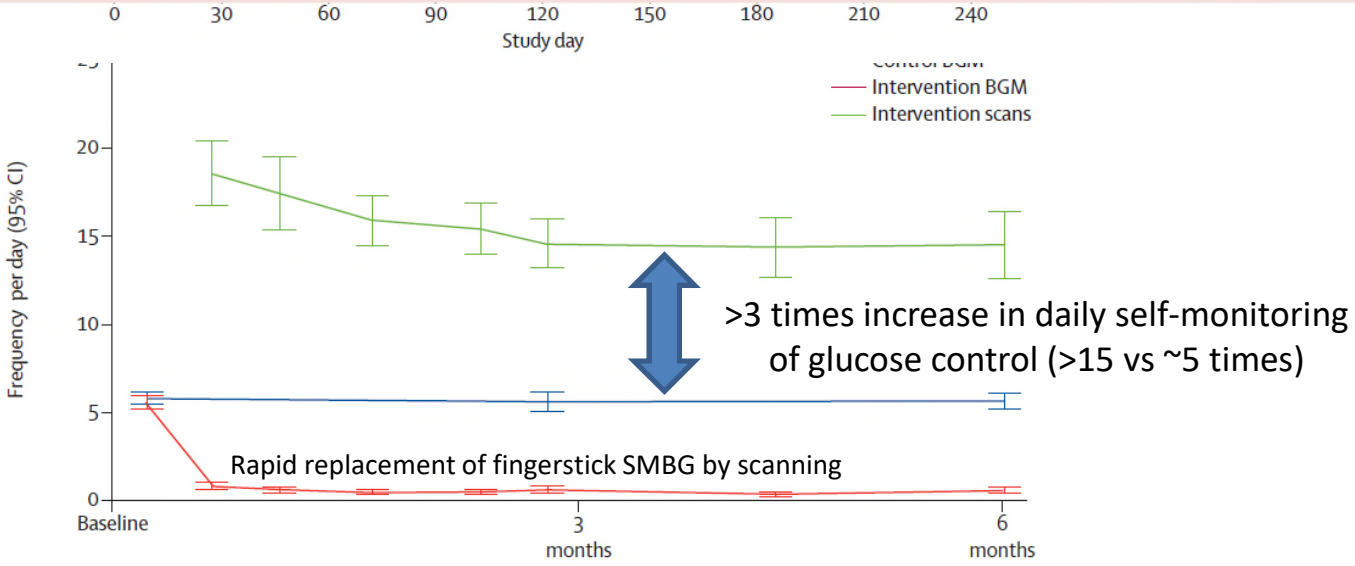
Bolinder J et al., Lancet *2016*

FGM reduced time spent and events of hypoglycemia and GV without increase in HbA1c

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

Highest scanning frequency in the evening

Significant reduction in both event number of and time spent in **nocturnal hypoglycemia**



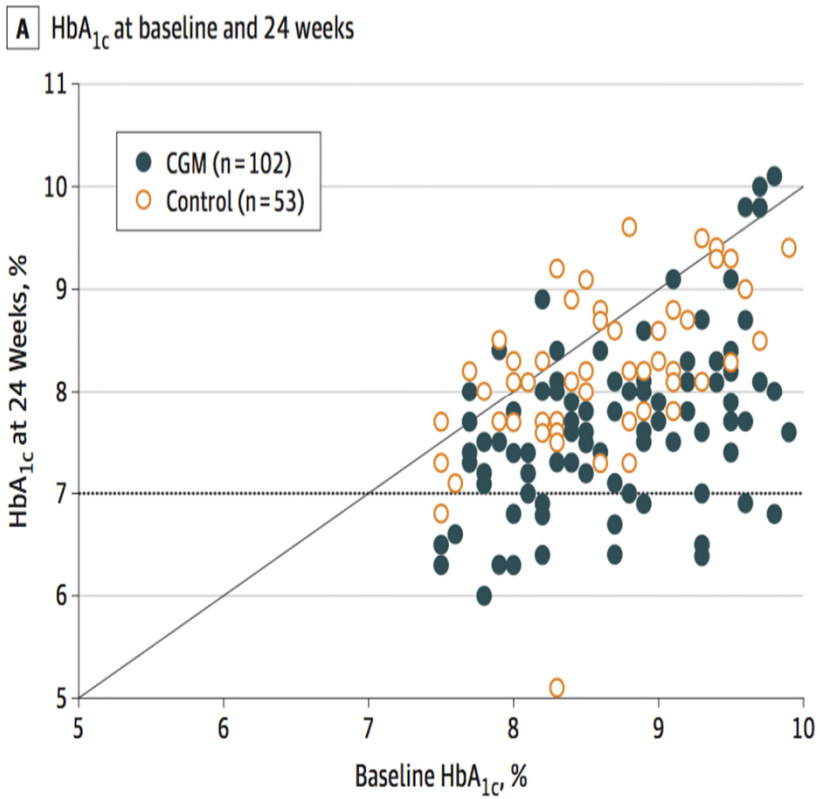
Bolinder J et al., Lancet *2016*

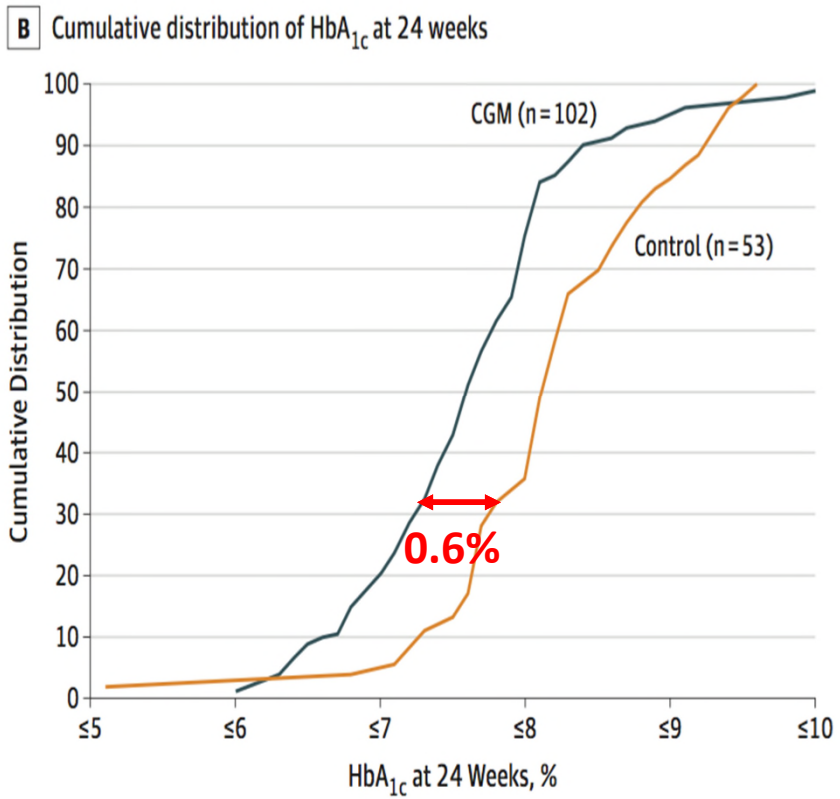
JAMA | Original Investigation

Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections

The DIAMOND Randomized Clinical Trial

Poorly controlled (A1C > 7.5%) T1D with insulin pen





Beck RW et al. JAMA 2017

JAMA | Original Investigation

Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections

The DIAMOND Randomized Clinical Trial

Beck RW et al. JAMA 2017

Poorly controlled (A1C > 7.5%) T1D with insulin pen

	Baseline		12 and 24 Weeks Pooled[a]			
	CGM Group (n = 105)	Control Group (n = 53)	CGM Group (n = 103)	Control Group (n = 53)	Mean Adjusted Difference (99% CI)[b]	*P* Value[b]
Hours of data, mean (SD)	322 (50)	325 (51)	301 (41)	301 (54)		
Prespecified secondary outcomes						
Glucose variability: coefficient of variation, mean (SD), %	42 (7)	42 (7)	38 (6)	42 (7)	−4 (−6 to −2)	<.001
Minutes per day in range 70-180 mg/dL, mean (SD)	660 (179)	650 (170)	736 (206)	650 (194)	77 (6 to 147)	.005
Hypoglycemia, median (IQR)						
Minutes per day <70 mg/dL	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL	13 (5 to 29)	18 (4 to 39)	6 (2 to 12)	20 (4 to 42)		.001
Hyperglycemia, median (IQR)						
Minutes per day >180 mg/dL	687 (554 to 810)	725 (537 to 798)	638 (503 to 807)	740 (625 to 854)		.03
Minutes per day >250 mg/dL	301 (190 to 401)	269 (184 to 383)	223 (128 to 351)	347 (241 to 429)		<.001
Minutes per day >300 mg/dL	129 (66 to 201)	109 (71 to 204)	78 (36 to 142)	167 (89 to 226)		<.001
Prespecified exploratory outcome						
Mean glucose, mean (SD), mg/dL	187 (27)	186 (30)	180 (27)	189 (25)	−9 (−19 to 0)	.01
Post hoc outcomes, median (IQR)[c]						
Area above curve 70 mg/dL	0.5 (0.3 to 1.1)	0.7 (0.2 to 1.4)	0.3 (0.2 to 0.5)	0.7 (0.2 to 1.3)		<.001
Area under curve 180 mg/dL	34 (25 to 46)	33 (26 to 45)	27 (17 to 40)	40 (31 to 51)		<.001

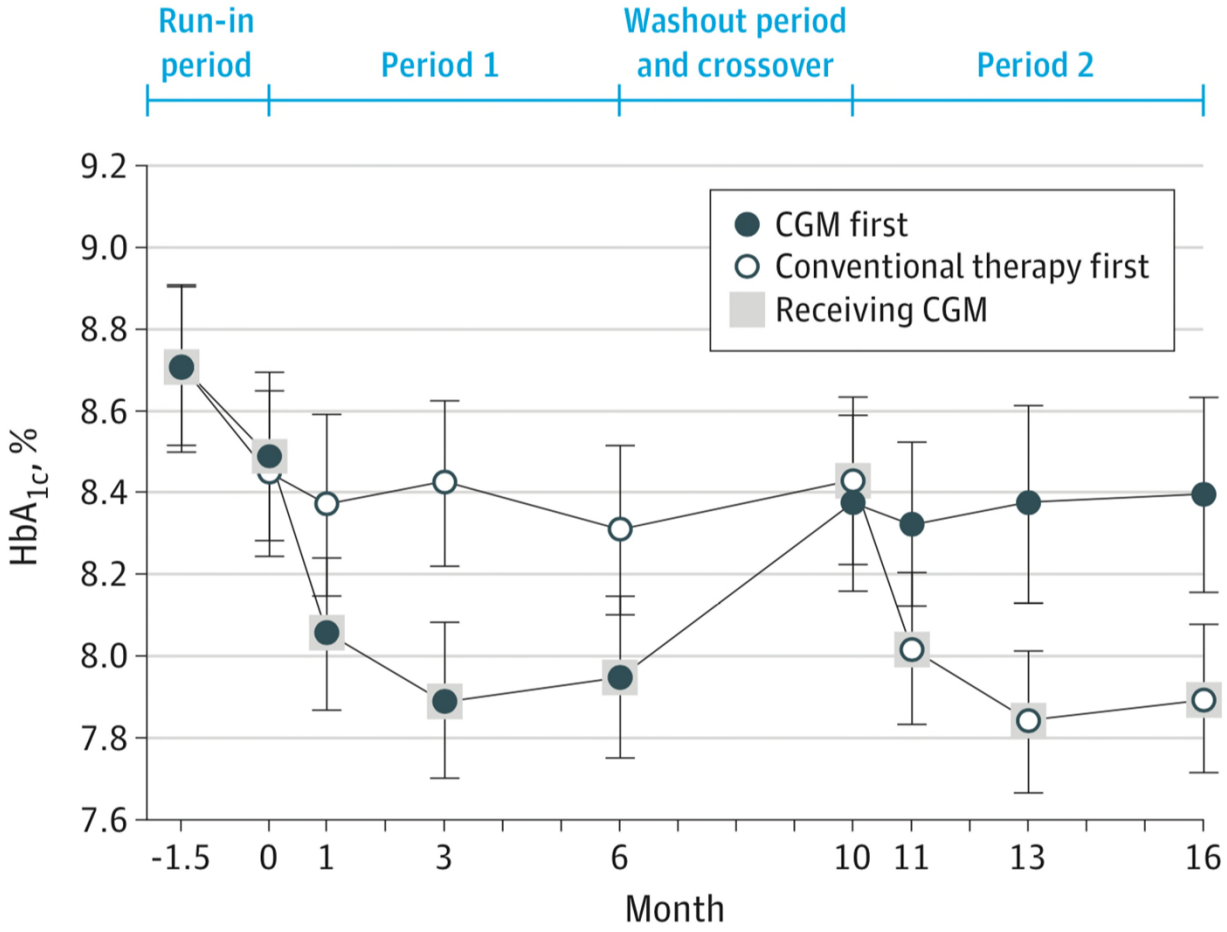
JAMA | Original Investigation

Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections

The GOLD Randomized Clinical Trial

JAMA 2017

Sweden, Poorly controlled T1D with insulin pen (A1C >7.5%)



0.43%

JAMA | Original Investigation

Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections

The GOLD Randomized Clinical Trial

JAMA 2017

Sweden, Poorly controlled T1D with insulin pen (A1C >7.5%)

	CGM (Dexcom G4)	*Conventional therapy*	*Least square mean (95% CI)[a] for difference CGM-conventional treatment*	P
SD of glucose levels (mg/dL) (measured by CGM during 2 weeks)				
Daytime 06:00–23:59	69.31 (67.09–71.53) $n=123$	77.49 (75.14–79.84) $n=125$	−8.42 (−10.69 to −6.15)	<0.001
Nighttime 00:00–05:59	64.33 (61.52–67.13) $n=123$	71.32 (68.20–74.43) $n=125$	−7.16 (−10.59 to −3.74)	<0.001
Daytime 06:00–21:59	68.86 (66.63–71.10) $n=123$	76.71 (74.28–79.14) $n=125$	−8.07 (−10.50 to −5.63)	<0.001
Nighttime 22:00–05:59	66.17 (63.51–68.83) $n=123$	74.33 (71.50–77.17) $n=125$	−8.37 (−11.40 to −5.34)	<0.001
CV of glucose levels (mg/dL) (measured by CGM during 2 weeks)				
Daytime 06:00–23:59	0.37 (0.36–0.38) $n=123$	0.41 (0.39–0.42) $n=125$	−0.04 (−0.05 to −0.03)	<0.001
Nighttime 00:00–05:59	0.35 (0.33–0.36) $n=123$	0.38 (0.36–0.40) $n=125$	−0.03 (−0.05 to −0.02)	<0.001
Daytime 06:00–21:59	0.37 (0.36–0.38) $n=123$	0.41 (0.40–0.42) $n=125$	−0.04 (−0.05 to −0.03)	<0.001
Nighttime 22:00–05:59	0.35 (0.34–0.36) $n=123$	0.38 (0.37–0.40) $n=125$	−0.04 (−0.05 to −0.02)	<0.001

JAMA | Original Investigation

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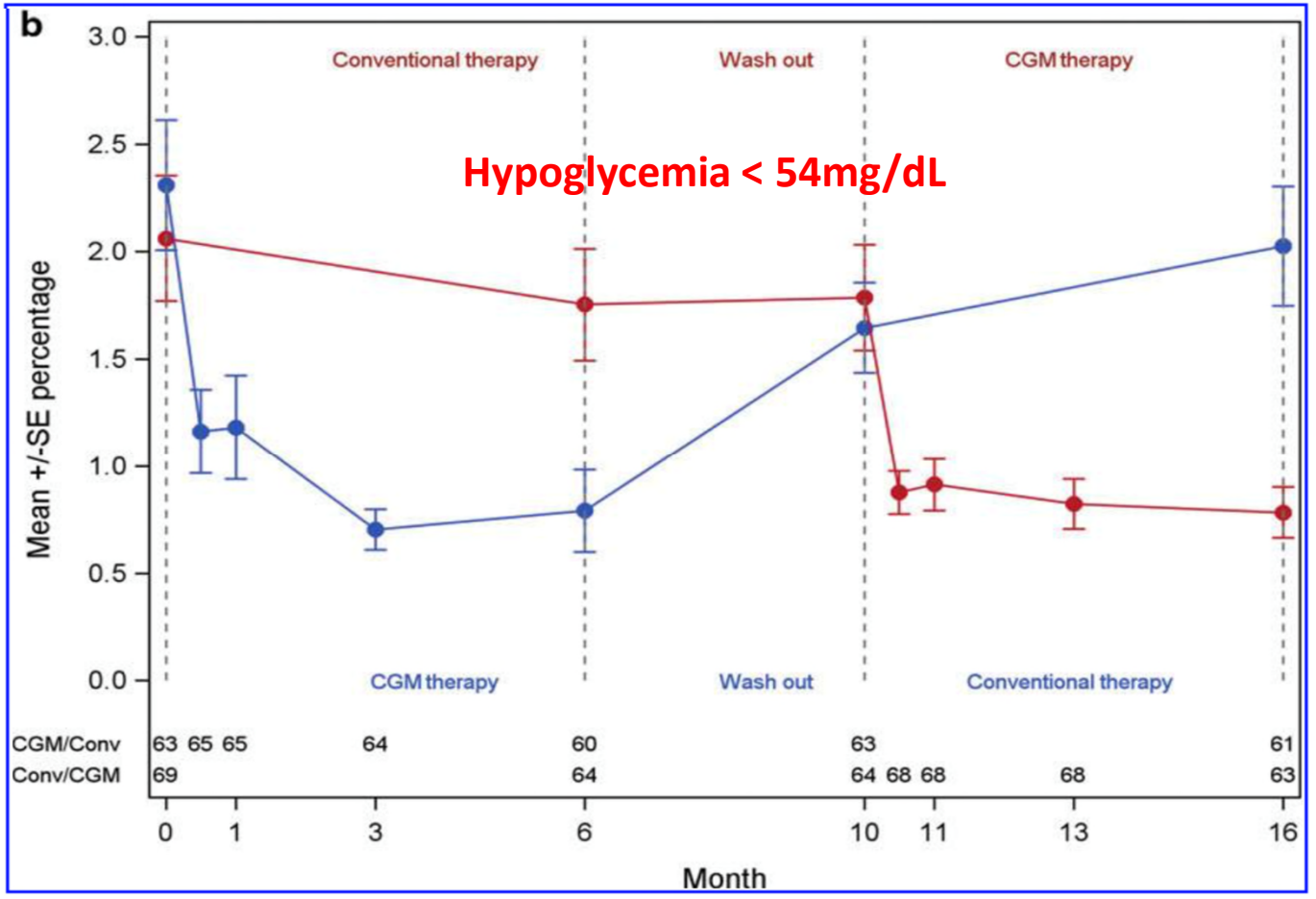
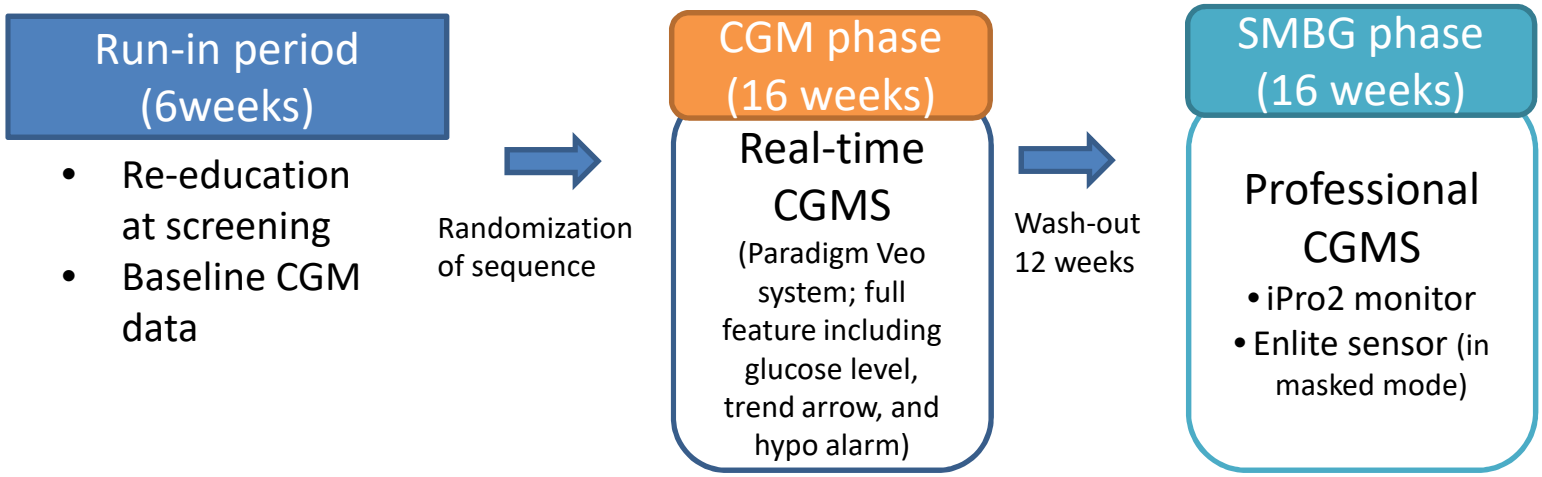


Real-time CGM in type 1 diabetes with impaired awareness of hypoglycemia: IN CONTROL study (CSII & MDI)

- Randomized, open-label, crossover trial at two centers
- Eligibility criteria
  - **Type 1 diabetes with impaired awareness of hypoglycemia (Gold score ≥4)**,
  - **Either CSII or MDI,** ≥3 SMBG/day
- Primary outcome: mean difference in % time spent in normoglycemia (72-180mg/dL) over the total intervention periods
- Intervention (either sequence of CGM-SMBG phases or SMBG-CGM phase)



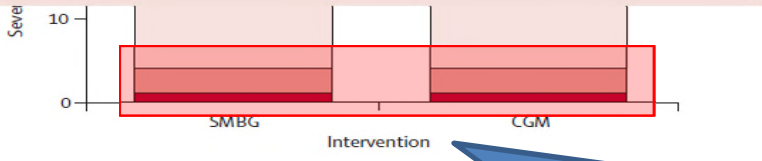
Beers CA et al., Lancet Diabetes Endocrinol. *2016*

IN CONTROL study: RT-CGM increased time spent in normoglycemia, reduced hypoglycemia and GV by RT-CGM

Reduction in CGM-measured

	CGM phase	SMBG phase	Mean difference (95% CI)	p value
Mean glucose concentration (mmol/L)	8·3 (8·0–8·6)	8·7 (8·4–9·0)	−0·4 (−0·6 to −0·2)	0·001
Within-day SD of glucose concentration (mmol/L)	2·8 (2·7–2·9)	3·3 (3·1–3·4)	−0·5 (−0·6 to −0·4)	<0·0001
Coefficient of variation of glucose concentration				
Overall	39·5 (38·2–40·8)	46·3 (44·9–47·6)	−6·7 (−8·0 to −5·5)	<0·0001
Within day	33·5 (32·4–34·6)	38·0 (36·9–39·1)	−4·5 (−5·5 to −3·6)	<0·0001
Between days	18·4 (17·5–19·4)	23·1 (22·2–24·1)	−4·7 (−5·9 to −3·5)	<0·0001
MAG (mmol/L per h)	1·7 (1·7–1·8)	1·8 (1·7–1·9)	−0·1 (−0·1 to −0·0)	0·049
MODD (mmol/L)	3·3 (3·1–3·5)	4·2 (4·0–4·4)	−0·9 (−1·1 to 0·7)	<0·0001
$CONGA_1$ (mmol/L)	1·7 (1·6–1·8)	1·8 (1·7–1·9)	−0·1 (−0·2 to −0·0)	0·002

Data are mean (95% CI). CGM=continuous glucose monitoring. SMBG=self-monitoring of blood glucose. AUC=area under the curve. MAG=mean absolute glucose change. MODD=mean of daily difference. $CONGA_1$=continuous overall net glycaemic action at 1 h intervals.

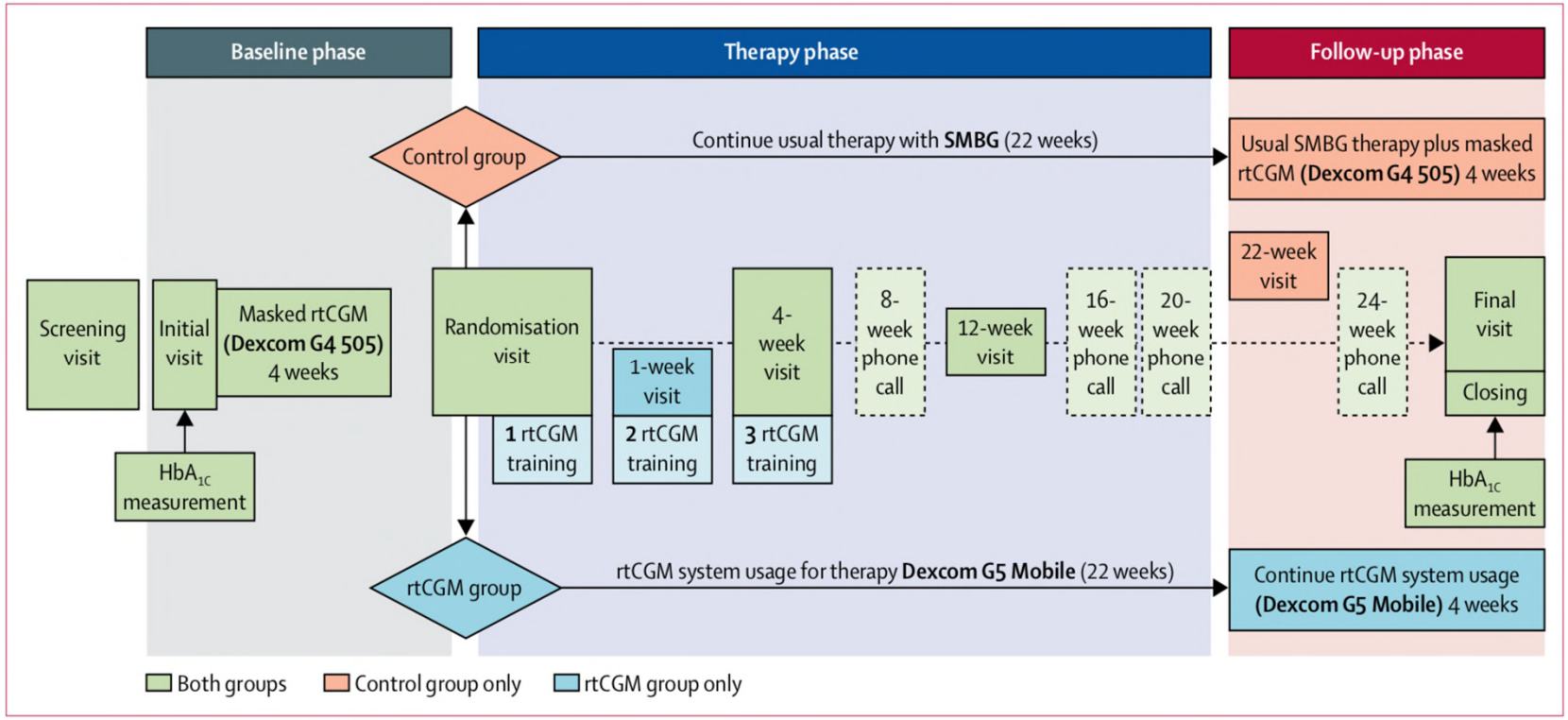


Reduction in severe hypoglycemia

Beers CA et al., Lancet Diabetes Endocrinol. *2016*

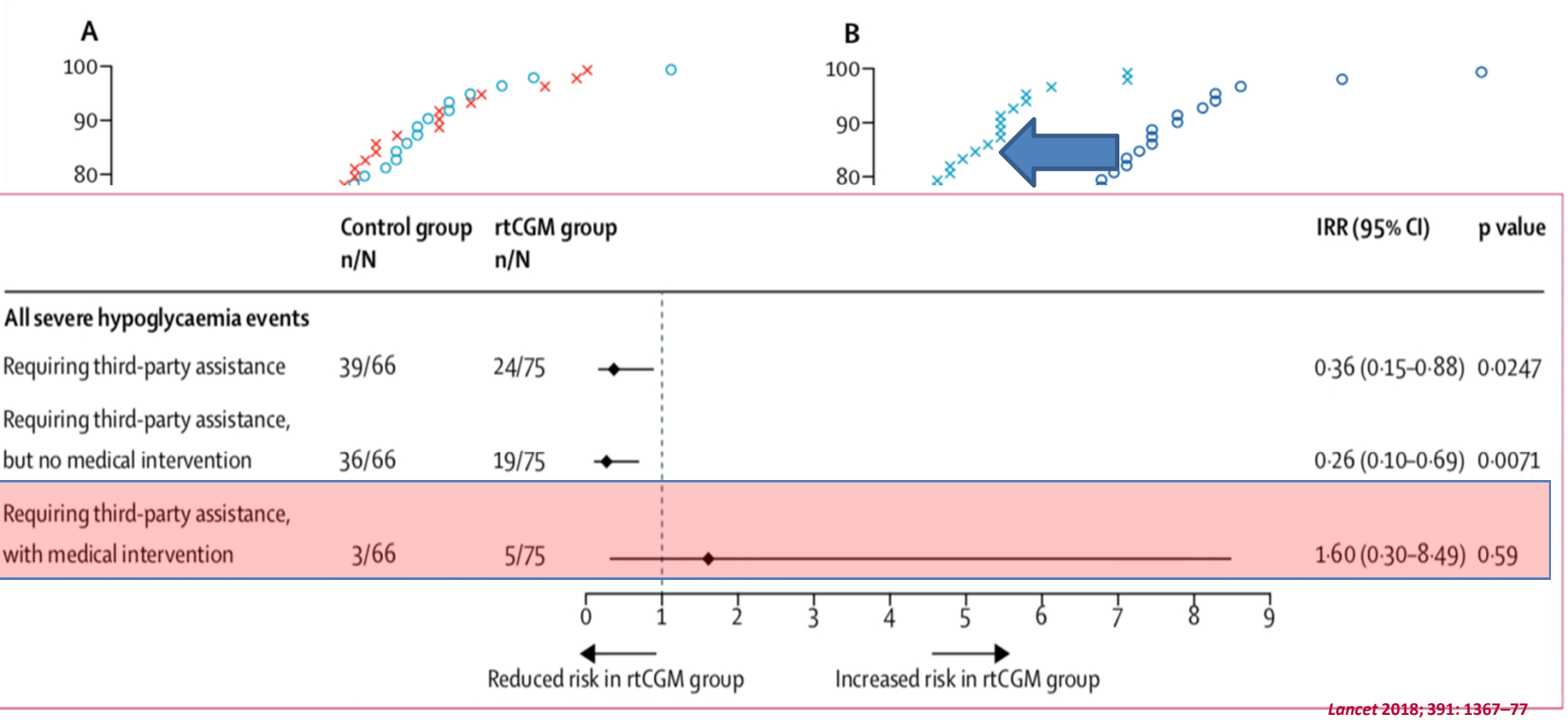
Real-time CGM in type 1 diabetes with impaired awareness of hypoglycemia : HypoDE study (Insulin pen user)

a multicenter, open-label, parallel, RCT with a 6-month study (n=150)
Inclusion criteria: T1DM with problematic hypoglycemia or impaired unawareness
MDI user, A1C <= 9.0%
3 rtCGM training sessions



Lancet 2018; 391: 1367–77

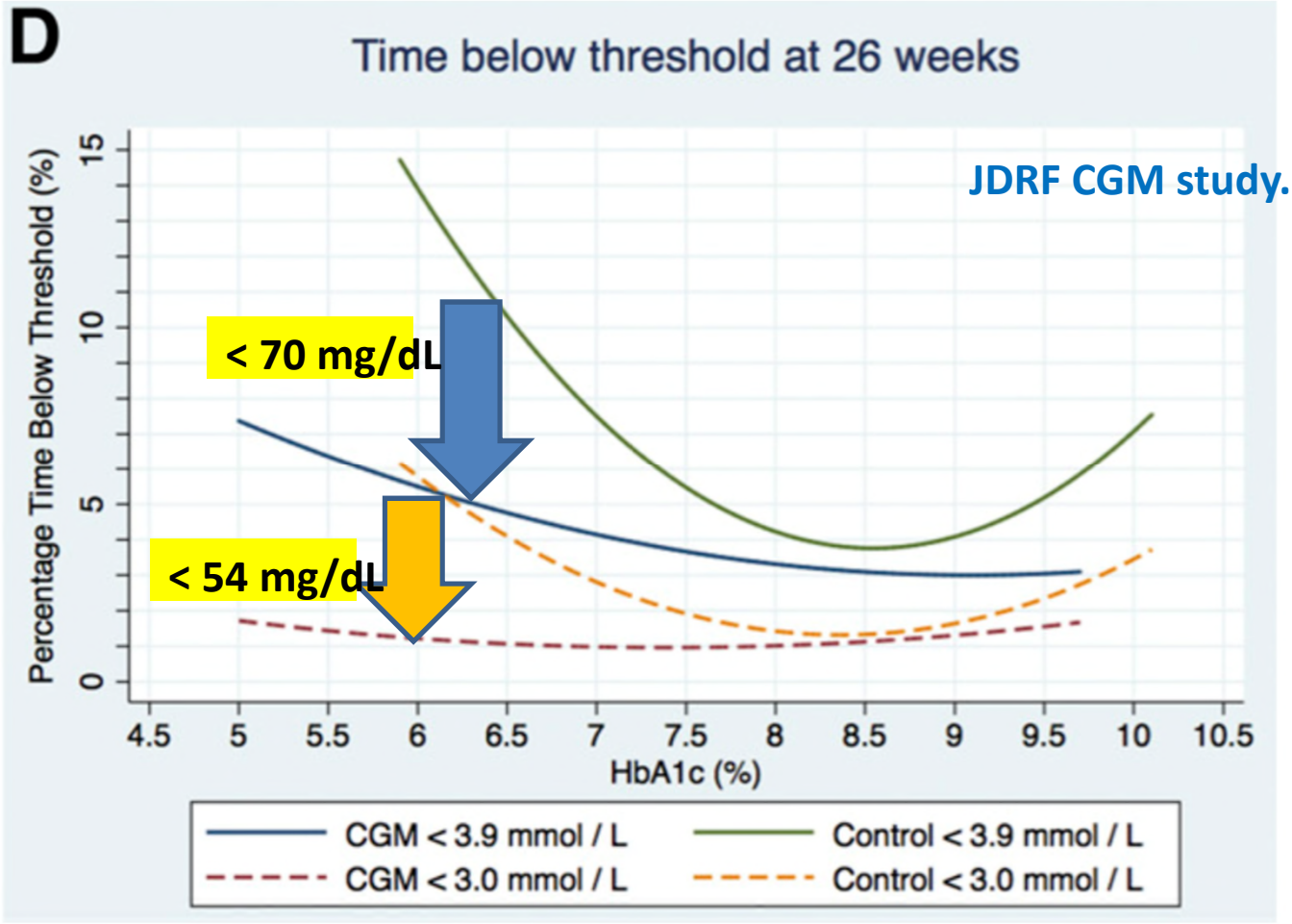
Real-time CGM in type 1 diabetes with impaired awareness of hypoglycemia (insulin pen user): HypoDE study -> Level 2 hypoglycemia (<54 mg/dL)



Lancet 2018; 391: 1367–77

Revisiting the Relationships Between Measures of Glycemic Control and Hypoglycemia in Continuous Glucose Monitoring Data Sets

Diabetes Care 2018;41:326–332 | https://doi.org/10.2337/dc17-1597



JDRF CGM study. NEJM 2008

Real-time CGM as a standard therapy

International Consensus on Use of Continuous Glucose Monitoring

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

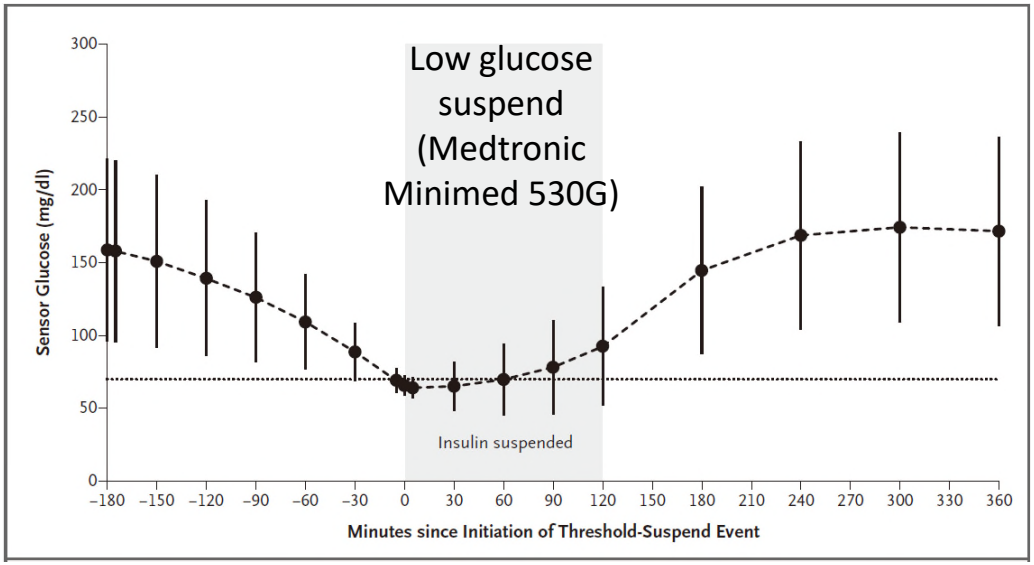
CGM should be considered in conjunction with A1C for glycemic status assessment and therapy adjustment in **1) all patients with T1D** & **2) patients with T2D treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia**

CGM data should be used to assess hypoglycemia and glucose variability.

Sensor-augmented insulin pump (SAP) with predictive low glucose suspension (LGS)

Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group*



N ENGL J MED 369;3 NEJM.ORG JULY 18, 2013

- Minimed 530G suspends insulin delivery once hypoglycemia is reached.

FDA Approves Medtronic's MiniMed 630G System, Ships in September

8/30/16 - NEW NOW NEXT

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1 TYPE

By Brian Levine and Adam Brown

Adds waterproof, color screen, and remote meter bolus. Will it speed FDA review of the 670G hybrid closed loop?

Earlier this month, Medtronic unexpectedly announced FDA approval of the MiniMed 630G. This

- Minimed 630G suspends insulin delivery if hypoglycemia is predicted to occur within 30 minutes.
- FDA approval; Aug 10, 2016 (also licensed in Korea, **Minimed 640G**)

FDA approval of the first hybrid closed-loop (2016) (Hybrid CL)

Medtronic

FDA APPROVES MINIMED 670G SYSTEM – WORLD'S FIRST HYBRID CLOSED LOOP SYSTEM

Posted by **Hooman Hakami** On September 28, 2016 In **Meaningful Innovation**

I have wonderful news to share with you today. I am extremely proud to announce that the FDA has just approved our groundbreaking MiniMed 670G system – *the first hybrid closed loop system in the world!*

- "Hybrid CL"
  - **Closed-loop basal insulin control** plus bolus calculator
  - Requires input of carbohydrate estimates by patient
  - Requires periodical calibration of sensor by fingerstick SMBG
- New Enlite 3 sensor
  - Much better than the current Medtronic Enlite sensor (MARD **10.3%**; Abbott FreeStyle Libre ~11%, Dexcom G5 ~9%)
- The insulin pump has built-in control algorithm.
  - Not requiring smartphone

Medtronic Minimed 670G: clinical outcomes

(non-randomized study for safety evaluation)

RESEARCH LETTER

Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes

- Patients: Type 1 Diabetes >2 years, insulin pump >6 months, A1C<10%
- Study purpose: to evaluate safety
- Run-in period without automated features for 2 weeks, then 3 months study period (initial 6 day; data collection for the algorithm)
- Results (run-in vs study period)
  - A 0.5% reduction in A1C (7.4% → 6.9%)
  - A 44% reduction in time spent with hypoglycemia (<70 mg/dl)
  - An 11% decline in time spent over 180 mg/dl and an 8% improvement in time-in-range (71-180 mg/dl)

	No. of Events	
Adverse Event	Run-in Period[b]	Study Period[b]
Total	8	20
Skin irritation	3	1
Hyperglycemia	0	6
Rash	0	1
Severe hyperglycemia[c]		
Due to infusion set	5	6
Due to software or hardware issues	0	5
Due to sensor issues	0	1

few serious or device-related adverse events

JAMA Published online September 15, 2016

BMJ Open Effect of 6 months of hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol

Age 25-70

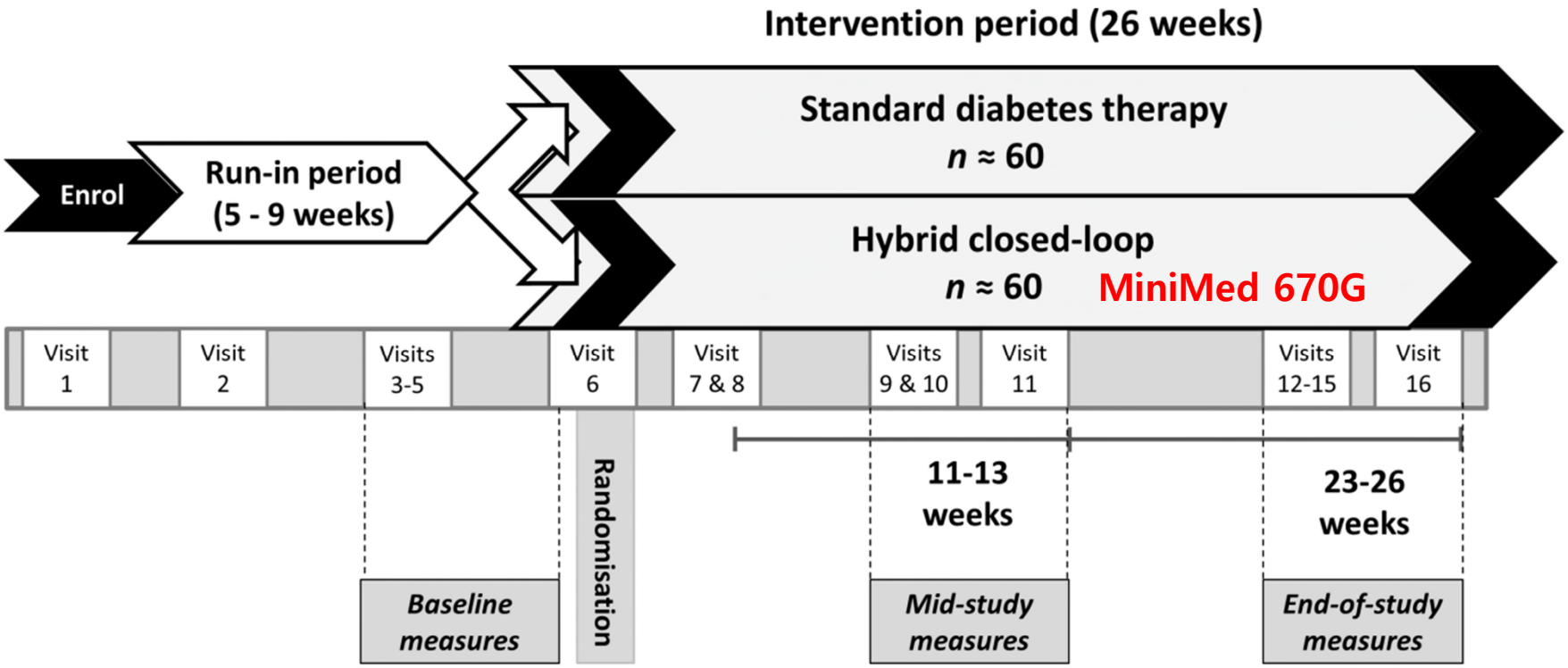
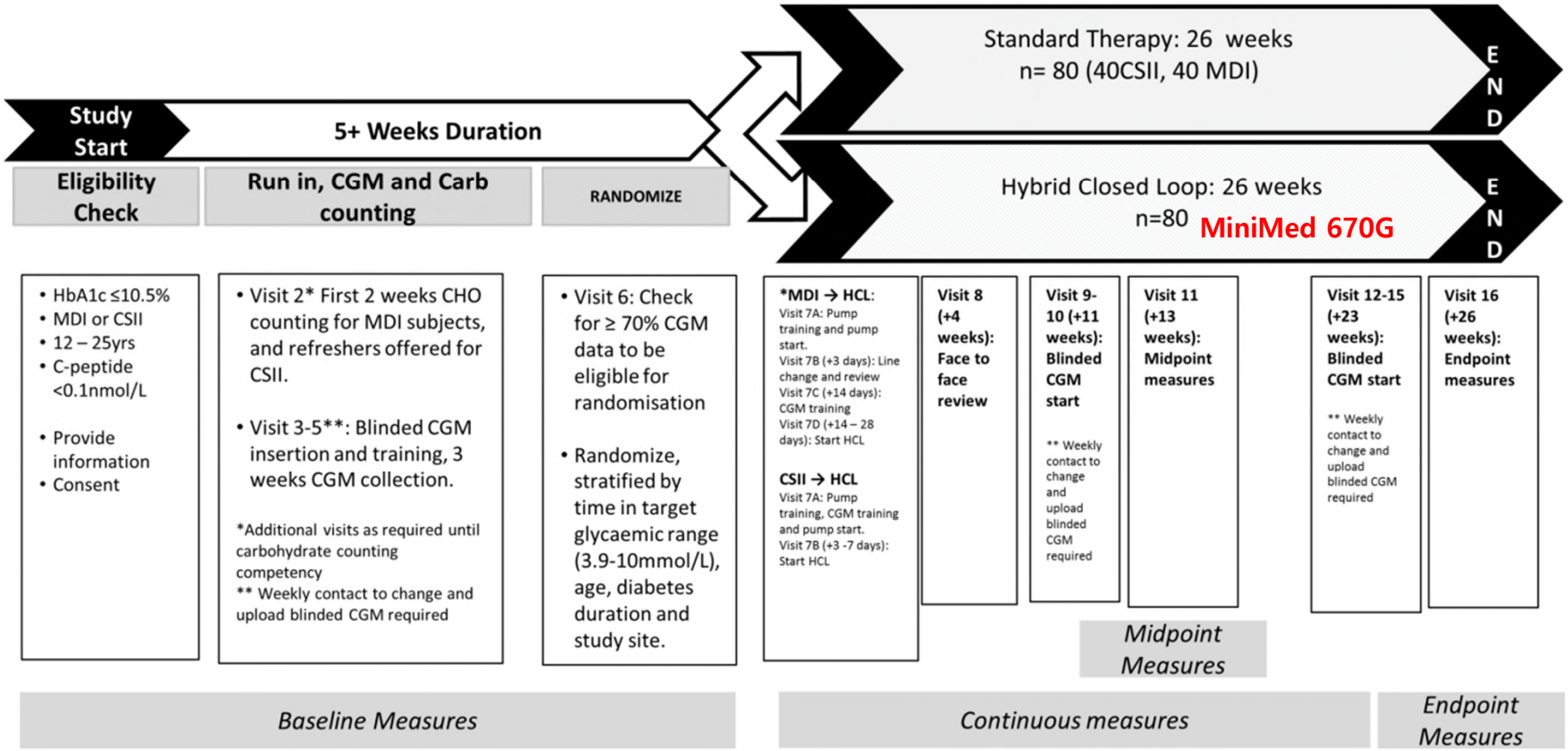


Figure 1 Study protocol overview.

BMJ Open Effect of 6 months hybrid closed-loop insulin delivery in young people with type 1 diabetes: a randomised controlled trial protocol

Age 12-24

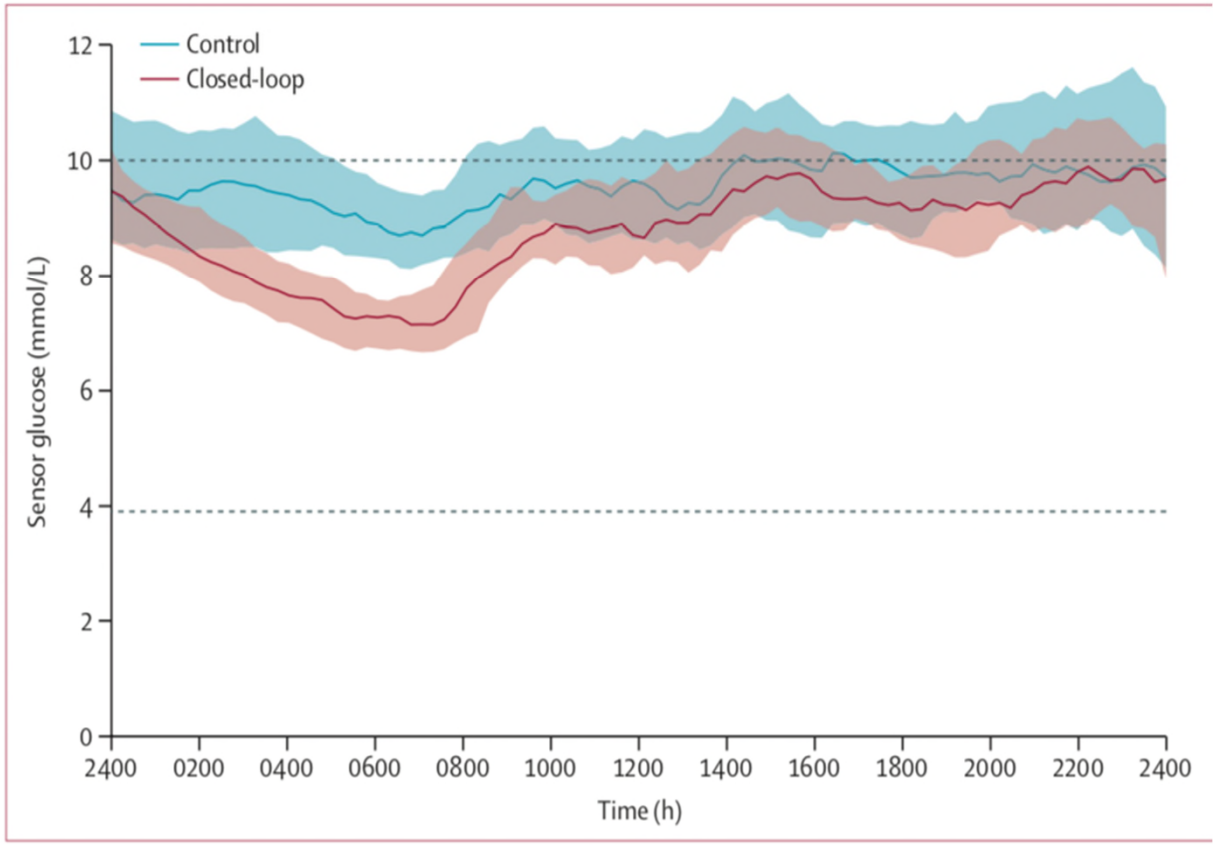


Hybrid CL-LGS vs. SAP

Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial

*Martin Tauschmann, Hood Thabit, Lia Bally, Janet M Allen, Sara Hartnell, Malgorzata E Wilinska, Yue Ruan, Judy Sibayan, Craig Kollman, Peiyao Cheng, Roy W Beck, Carlo L Acerini, Mark L Evans, David B Dunger, Daniela Elleri, Fiona Campbell, Richard M Bergenstal, Amy Criego, Viral N Shah, Lalantha Leelarathna, Roman Hovorka, on behalf of the APCam11 Consortium**

Lancet 2018



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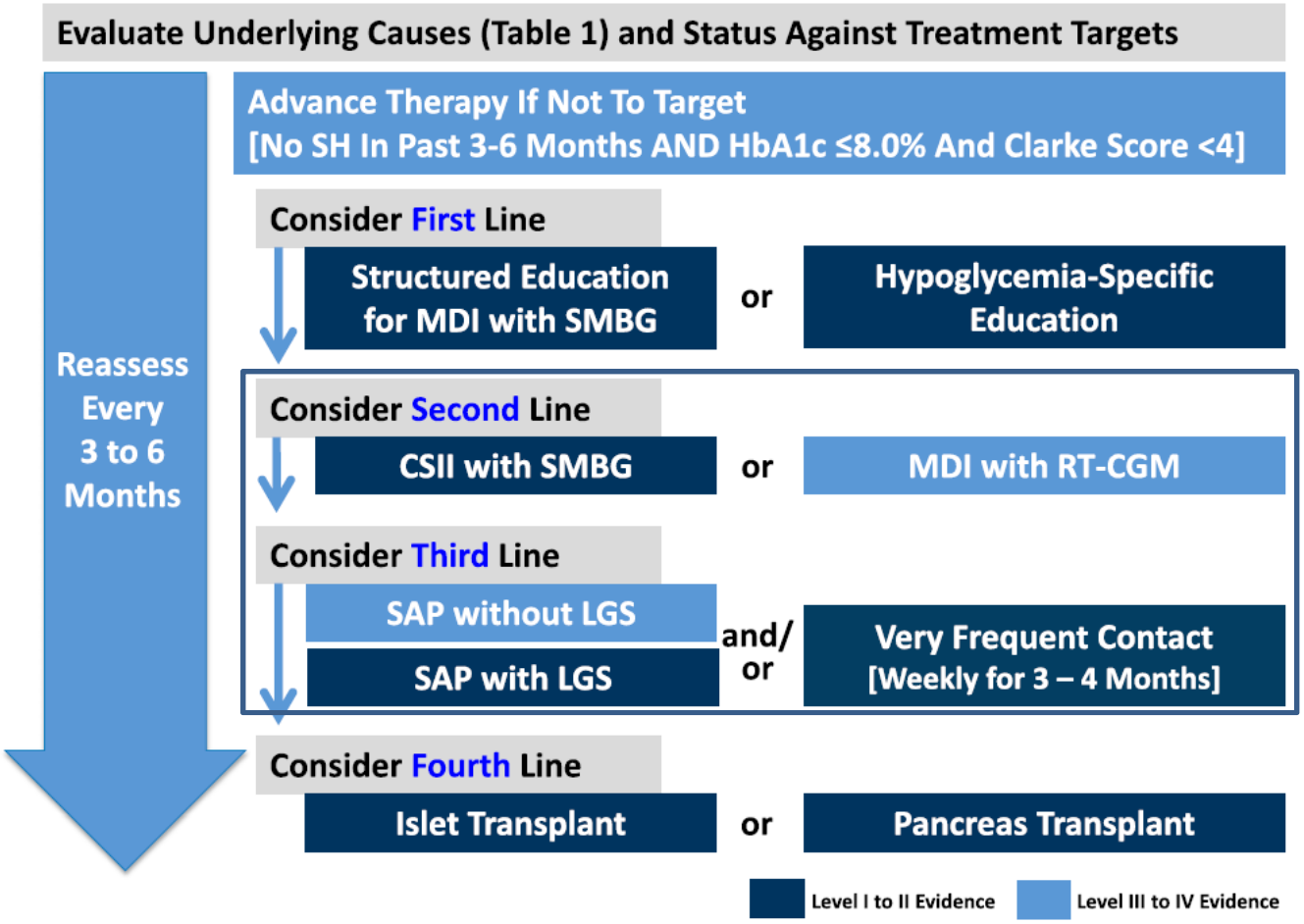
Lancet 2018

	Baseline		12 weeks		Difference (95% CI)*	p value*
	Closed-loop (n=46)	Control (n=40)	Closed-loop (n=46)	Control (n=40)		
Percentage of time with sensor glucose concentration in range						
3·9 to 10·0 mmol/L†	52% (10)	52% (9)	65% (8)	54% (9)	10·8 (8·2 to 13·5)	<0·0001
Less than 3·9 mmol/L **<70 mg/dL**	3·5% (2·0 to 5·4)	3·3% (1·2 to 5·5)	2·6% (1·9 to 3·6)	3·9% (1·7 to 5·3)	−0·83 (−1·40 to −0·16)‡	0·0130
Less than 3·5 mmol/L	1·8% (0·8 to 3·2)	1·9% (0·6 to 3·3)	1·4% (0·9 to 1·9)	2·0% (0·9 to 3·0)	−0·33 (−0·81 to 0·04)‡	0·08
Less than 2·8 mmol/L	0·4% (0·1 to 1·0)	0·5% (0·1 to 1·0)	0·3% (0·2 to 0·6)	0·5% (0·2 to 0·9)	−0·09 (−0·24 to 0·01)‡	0·11
More than 10·0 mmol/L **>180 mg/dL**	44% (11)	44% (11)	32% (8)	42% (10)	−10·3 (−13·2 to −7·5)	<0·0001
More than 16·7 mmol/L	5·5% (3·3 to 8·3)	4·9% (2·7 to 7·3)	3·5% (1·9 to 4·6)	4·4% (2·9 to 6·5)	−1·42 (−2·20 to −0·69)‡	<0·0001
Glycated haemoglobin						
Percentage	8·0% (0·6)	7·8% (0·6)	7·4% (0·6)	7·7% (0·5)	−0·36% (−0·53 to −0·19)	<0·0001
mmol/mol of non-glycated haemoglobin	63 (7)	62 (6)	57 (7)	60 (6)	−4·0 (−5·8 to −2·2)	<0·0001
SD of sensor glucose, mmol/L	3·9 (0·5)	3·8 (0·5)	3·5 (0·5)	3·8 (0·5)	−0·35 (−0·48 to −0·22)	<0·0001
Coefficient of variation of sensor glucose	40% (5)	39% (5)	40% (4)	40% (4)	−0·4% (−1·4 to 0·7)	0·50

Proposed treatment algorithm for patients with T1D with problematic hypoglycemia (ADA)

Current **best medical care** of **problematic hypoglycemia** = **SAP (with low glucose suspend feature)**

Hybrid CL-LGS



American Diabetes Association clinical recommendation; Diabetes Care 2015

Summaries

- **Absolute GV indices (SD, MAGE & MODD)** are correlated with **mean glucose** but **relative GV (CV)** is not
- **Relative GV (CV)** is associated with **hypoglycemic risk**
- **Decreased β-cell function** increases **GV**
- **Professional CGM** can be effective to reduce A1C in **T2D** and **FGM** reduce GV and hypoglycemia in **insulin-treated T2D patients**
- **FGM, real-time CGM, SAP-LGS and Hybrid-CL** are effective to reduce GV, A1C and hypoglycemia in **patients with T1D**
- **Stepwise approach** is needed for **T1D patients with problematic hypoglycemia**