Applying technologies to type 1 diabetes management

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Declaration of interests

I have received research support from Dexcom and Roche Diabetes and have participated in advisory groups for Dexcom, Medtronic and Roche Diabetes. I have received fees for speaking from Dexcom and Roche Diabetes.

Technology

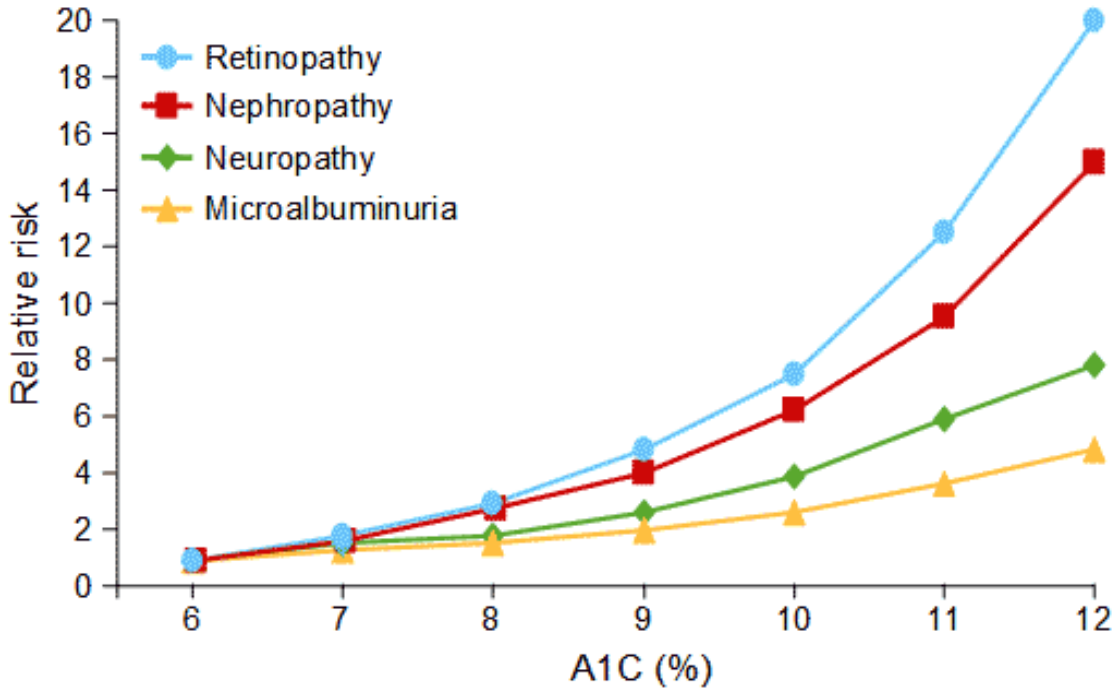
Research: Health Economics

Setting research priorities for Type 1 diabetes

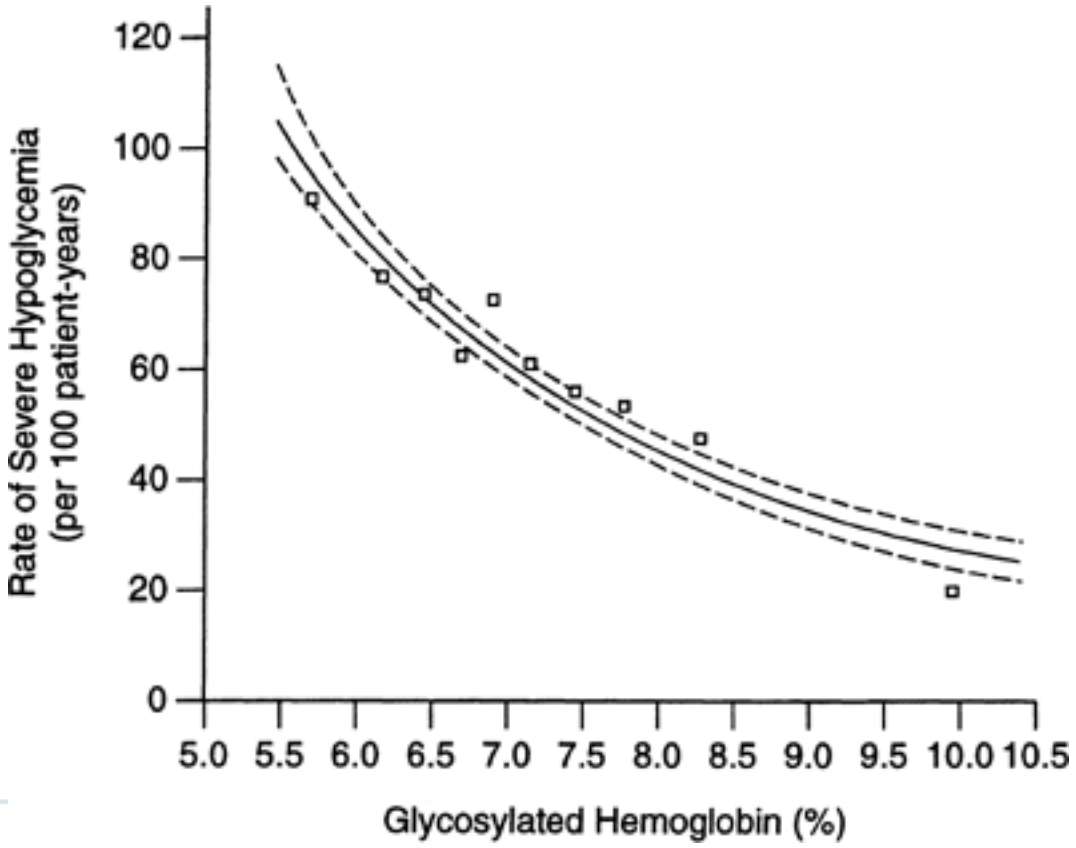
R. Gadsby[1], R. Snow[2], A. C. Daly[3], S. Crowe[4], K. Matyka[5], B. Hall[1] and J. Petrie[6]

1. Is it possible to constantly and accurately monitor blood sugar levels, in people with Type 1 diabetes, with a discrete device (non-invasive or invasive)?
2. Is insulin pump therapy effective (immediate vs. deferred pump, and comparing outcomes with multiple injections)?
3. Is an artificial pancreas for Type 1 diabetes (closed loop system) effective?
4. What are the characteristics of the best Type 1 diabetes patient education programmes (from diagnosis to long-term care) and do they improve outcomes?
5. What are the cognitive and psychological effects of living with Type 1 diabetes?
6. How can awareness of and prevention of hypoglycaemia in Type 1 diabetes be improved?
7. How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with Type 1 diabetes?
8. Does treatment of people with Type 1 diabetes by specialists (e.g. doctors, nurses, dieticians, podiatrists, ophthalmologists and psychologists) trained in person-centred skills provide better blood glucose control, patient satisfaction and self-confidence in the management of Type 1 diabetes, compared with treatment by non-specialists with standard skills?
9. What makes self management successful for some people with Type 1 diabetes, and not others?
10. Which insulins are safest and have the fewest long-term adverse effects?

Background

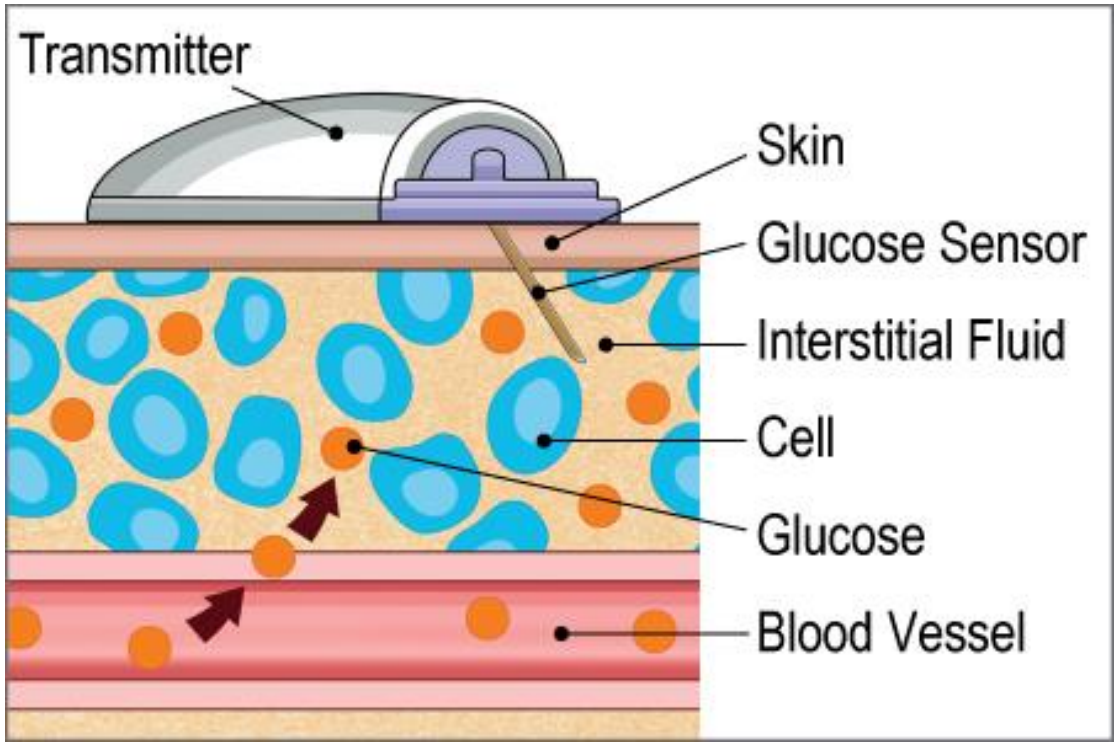


DCCT. New England Journal Medicine 1993

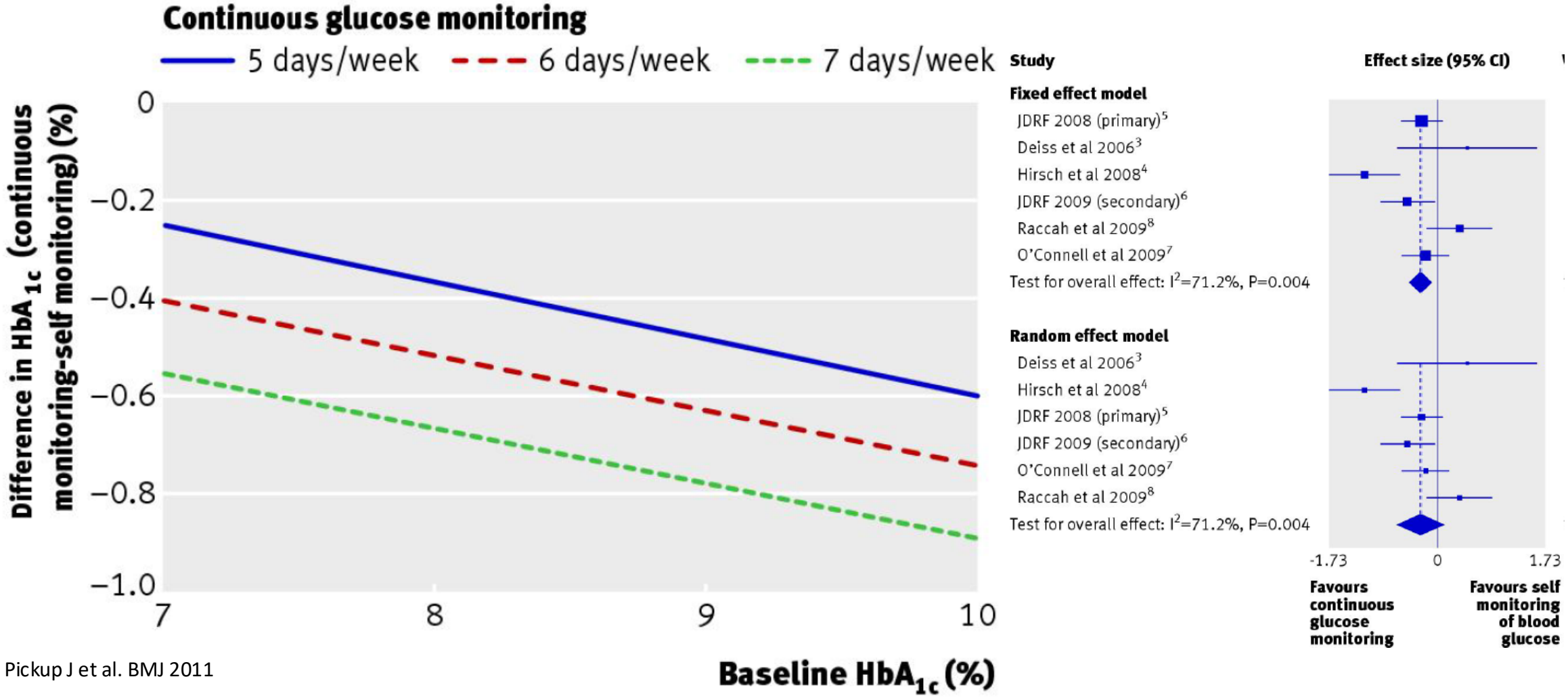


Hypoglycemia in the DCCT. Diabetes Care 1997

Continuous Glucose Monitoring



Continuous Glucose Monitoring



Pickup J et al. BMJ 2011

GOLD Study

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

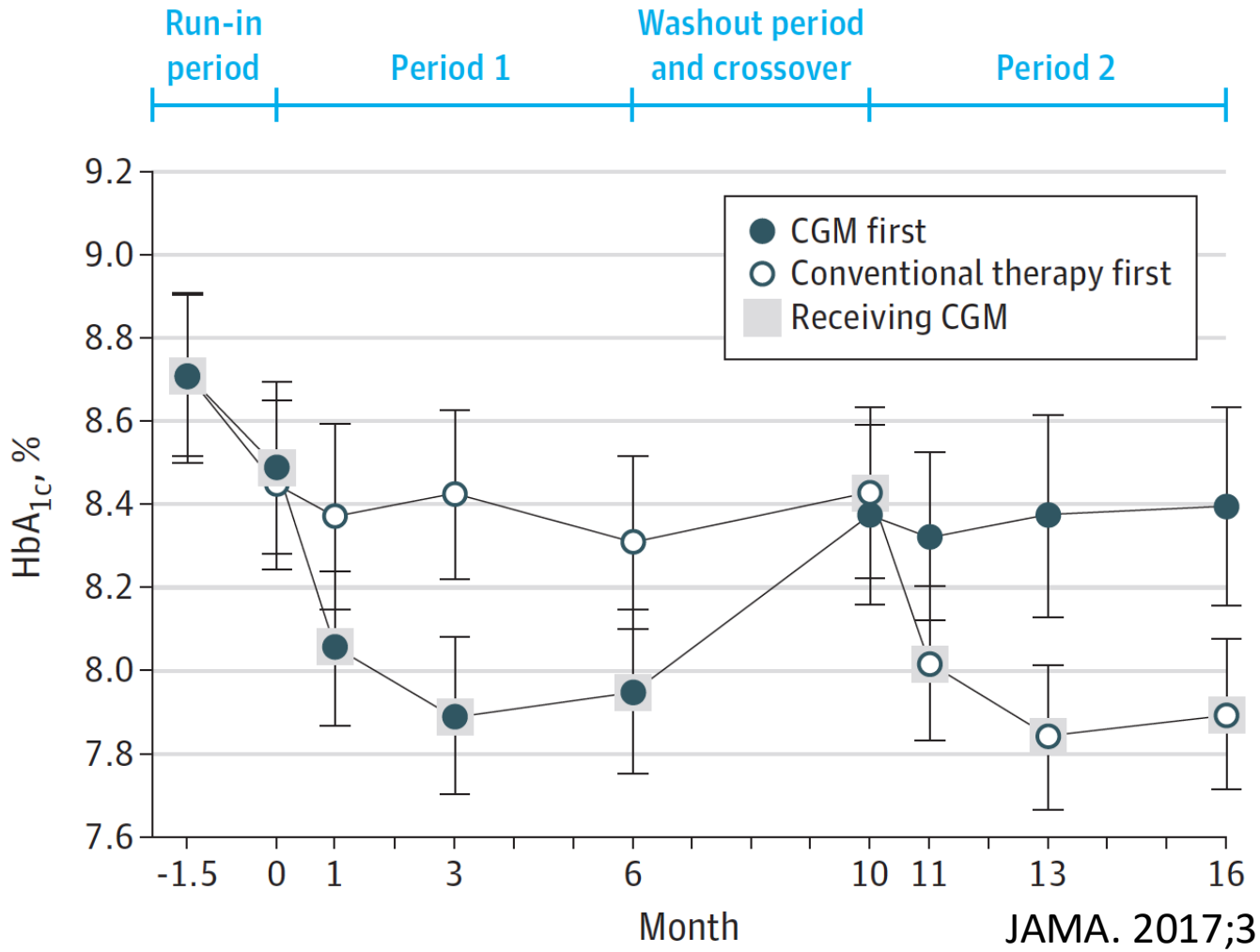
Marcus Lind, MD, PhD; William Polonsky, PhD; Irl B. Hirsch, MD; Tim Heise, MD; Jan Bolinder, MD, PhD; Sofia Dahlqvist; Erik Schwarz, MD, PhD; Arndís Finna Ólafsdóttir, RN; Anders Frid, MD, PhD; Hans Wedel, PhD; Elsa Ahlén, MD; Thomas Nyström, MD, PhD; Jarl Hellman, MD

Continuous Glucose Monitoring

Variable	CGM First (n = 69)	Conventional Therapy First (n = 73)
Demographic and Clinical Data		
Age at inclusion visit, mean (SD), y	46.7 (13.0)	42.6 (12.2)
Sex, No. (%)		
Men	37 (53.6)	43 (58.9)
Women	32 (46.4)	30 (41.1)
Race, No. (%)		
Black	0	1 (1.4)
White (including Middle East and North Africa)	69 (100.0)	72 (98.6)
Hispanic ethnicity	0	0
Weight at randomization visit, mean (SD), kg	81.3 (14.7)	83.0 (17.1)
Body mass index at randomization visit, mean (SD)	27.0 (4.1)	27.2 (4.8)
HbA_{1c} (NGSP) at inclusion visit, mean (SD), %	8.71 (0.8)	8.70 (0.9)
HbA_{1c} (NGSP) at randomization visit, mean (SD), %	8.49 (0.9)	8.45 (0.9)
Time from diabetes onset to inclusion visit, mean (SD), y	23.4 (11.9)	21.0 (11.7)
Smoking at inclusion visit, No. (%)		
Current	7 (10.1)	10 (13.7)
Previous	17 (24.6)	15 (20.5)
Never	45 (65.2)	48 (65.8)
Treatment Use at Randomization Visit		
Base insulin type, No. (%)		
Insulatard (NPH insulin)	2 (2.9)	1 (1.4)
Glargine	55 (79.7)	57 (78.1)
Detemir	8 (11.6)	12 (16.4)
Degludec	4 (5.8)	3 (4.1)
Meal insulin type, No. (%)		
Lispro	28 (40.6)	25 (34.2)
Aspart	35 (50.7)	45 (61.6)
Glulisine	4 (5.8)	3 (4.1)
Insulin regular human	2 (2.9)	0 (0.0)
Total daily meal insulin dose, mean (SD), U	26.8 (14.1)	28.2 (12.7)
Total daily base insulin dose, mean (SD), U	29.6 (11.9)	30.9 (15.5)
Total daily insulin dose, U		
Mean (SD)	56.4 (21.6)	59.1 (24.7)
No. of insulin injections, mean (SD), per d	4.90 (1.06)	4.75 (0.86)
Median (range)	5.00 (1.00-7.00)	5.00 (2.00-8.00)
No. of insulin injections (categories), No. (%), per d		
<3	2 (2.9)	1 (1.4)
≥3	67 (97.1)	72 (98.6)
Metformin used, No. (%)	2 (2.9)	0
Other glucose-lowering medication, No. (%)	0	0

JAMA. 2017;317(4):379-387. doi:10.1001/jama.2016.19976

Continuous Glucose Monitoring



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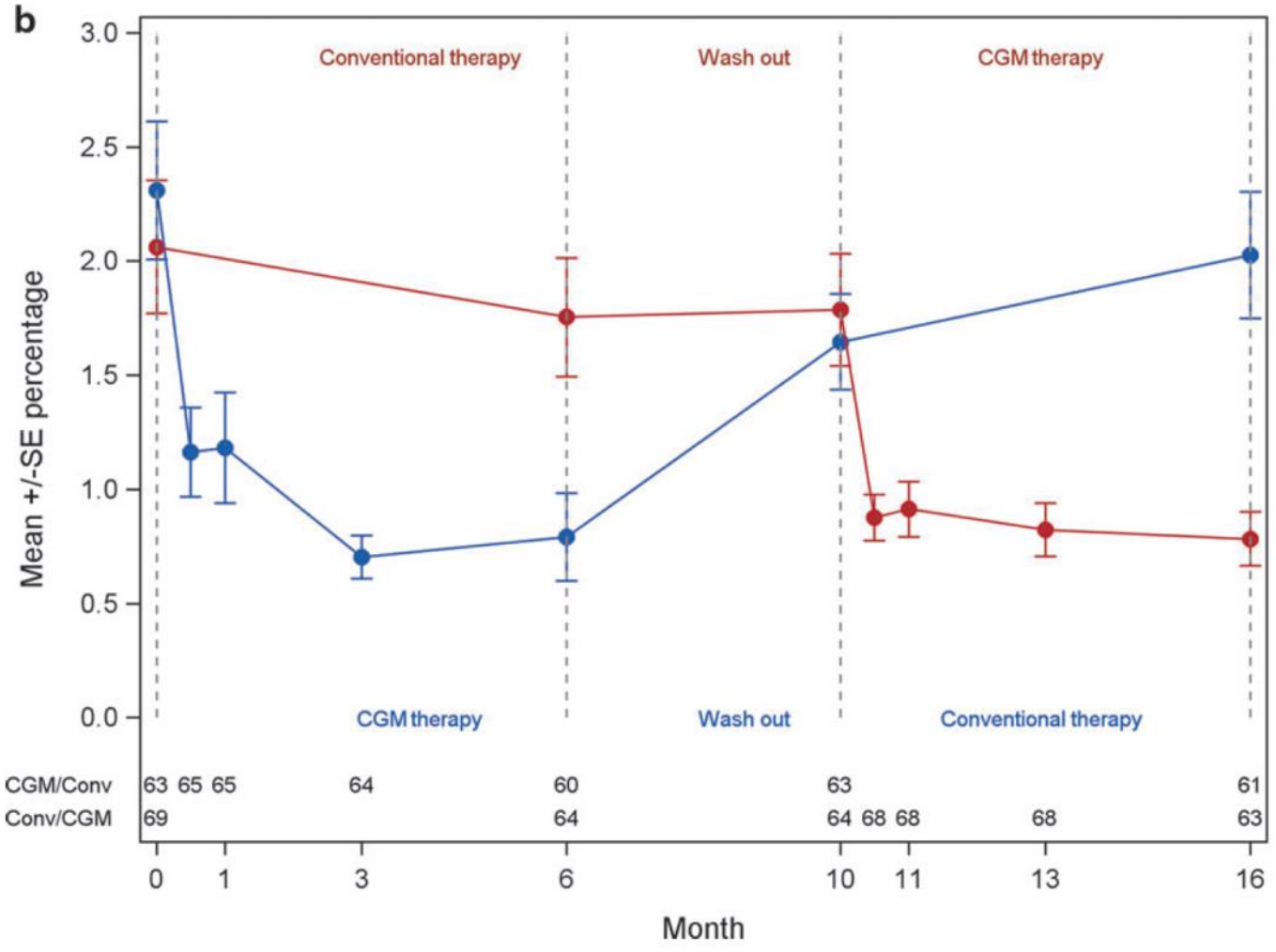
Continuous Glucose Monitoring



- Compared with SMBG, CGM improved:
  - Time <3.9, <3.0mmol/L
  - Number episodes <3.9, <3.0mmol/L
  - SD
  - CV
  - MAGE
  - Daytime, night-time and overall

DOI: 10.1089/dia.2017.0363

DIAMOND Study

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

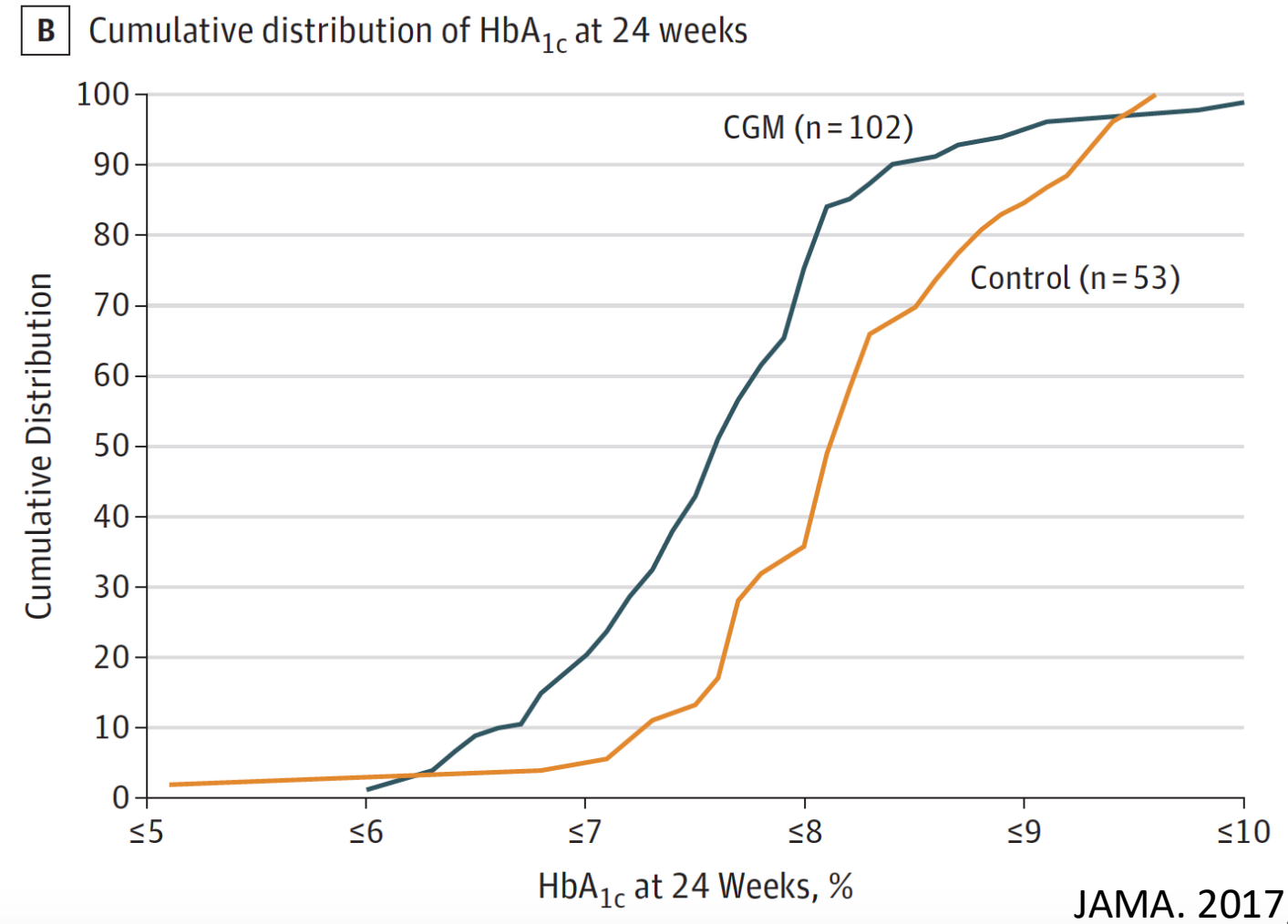
Roy W. Beck, MD, PhD; Tonya Riddlesworth, PhD; Katrina Ruedy, MSPH; Andrew Ahmann, MD; Richard Bergenstal, MD; Stacie Haller, RD, LD, CDE; Craig Kollman, PhD; Davida Kruger, MSN, APN-BC; Janet B. McGill, MD; William Polonsky, PhD; Elena Toschi, MD; Howard Wolpert, MD; David Price, MD; for the DIAMOND Study Group

Continuous Glucose Monitoring

	Group, No. (%)	
	CGM (n = 105)	Control (n = 53)
Age, y		
25-<45	53 (50)	16 (30)
45-<60	32 (30)	23 (43)
≥60	20 (19)	14 (26)
Mean (SD) [range]	46 (14) [26-72]	51 (11) [26-73]
Diabetes duration, median (IQR), y	19 (9-29)	19 (11-35)
Female sex	47 (45)	23 (43)
Highest education[a]		
<Bachelor's degree	47 (47)	22 (43)
Bachelor's degree	43 (43)	19 (37)
Graduate degree	10 (10)	10 (20)
BMI, mean (SD)	28 (6)	27 (5)
Weight, mean (SD), kg	84 (20)	81 (18)
HbA_{1c}, %		
7.5-<8.5	47 (45)	24 (45)
8.5-≤9.9	58 (55)	29 (55)
Mean (SD) [range]	8.6 (0.7) [7.5-9.9]	8.6 (0.6) [7.5-9.9]
Self-reported No. of self-monitoring blood glucose tests per day, mean (SD)	3.9 (1.3)	4.1 (1.6)

JAMA. 2017;317(4):371-378. doi:10.1001/jama.2016.19975

Continuous Glucose Monitoring



JAMA. 2017;317(4):371-378. doi:10.1001/jama.2016.19975

Continuous Glucose Monitoring

	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 /3.9mmol/L	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL /3.3mmol/L	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL /2.8mmol/L	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. 2017;317(4):371-378. doi:10.1001/jama.2016.19975

HypoDE Study

Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial

Lutz Heinemann, Guido Freckmann, Dominic Ehrmann, Gabriele Faber-Heinemann, Stefania Guerra, Delia Waldenmaier, Norbert Hermanns

Summary

Background The effectiveness of real-time continuous glucose monitoring (rtCGM) in avoidance of hypoglycaemia among high-risk individuals with type 1 diabetes treated with multiple daily insulin injections (MDI) is unknown. We aimed to ascertain whether the incidence and severity of hypoglycaemia can be reduced through use of rtCGM in these individuals.

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S0140-6736(18)30297-6

Continuous Glucose Monitoring

	Control group (n=74)*	rtCGM group (n=75)*
Demographic and medical characteristics		
Age, years	47·3 (11·7)	45·8 (12·0)
Women	25 (34%)	35 (47%)
Men	49 (66%)	40 (53%)
Body-mass index, kg/m²	26·0 (4·6)	26·1 (6·7)
Diabetes duration, years	21·6 (13·9)	20·9 (14·0)
HbA_{1c}, %†	7·3% (1·0)	7·6% (1·0)
HbA_{1c}, mmol/mol†	56·7 (10·6)	59·3 (10·9)
Treatment characteristics		
Treated with analogue basal insulin	73 (99%)	71 (95%)
Treated with one basal insulin injection per day	47 (64%)	39 (52%)
Daily dose of basal insulin, IU	20·1 (10·8)	23·9 (16·2)
Treated with analogue bolus insulin‡	66 (89%)	67 (91%)
Daily dose of bolus insulin, IU§	24·3 (12·2)	26·8 (29·5)
Problematic hypoglycaemia		
Any severe hypoglycaemia in the past 12 months	45 (61%)	47 (63%)
Hypoglycaemia unawareness (hypoglycaemia unawareness score ≥4)	68 (92%)	71 (95%)
Hypoglycaemia unawareness score	4·7 (1·3)	5·0 (1·1)

http://dx.doi.org/10.1016/S0140-6736(18)30297-6

Continuous Glucose Monitoring

	Baseline phase		Follow-up phase		Adjusted between-group differences (95% CI)	p value*
	Control group (n=66)	rtCGM group (n=75)	Control group (n=66)	rtCGM group (n=75)		
Mean duration of rtCGM wear during baseline and follow-up phases, days	26·4 (1·7)	27·0 (1·5)	27·0 (1·8)	27·7 (1·5)	0·02 (–0·49 to 0·54)	0·9233
Primary outcome, low glucose events ≤3·0 mmol/L						
Mean number of hypoglycaemic events per 28 days	14·4 (12·4)	10·8 (10·0)	13·7 (11·6)	3·5 (4·7)	0·28 (0·20 to 0·39)†	<0·0001‡
Secondary outcomes, rtCGM characteristics						
Mean number of nocturnal hypoglycaemic events per 28 days	2·4 (2·6)	2·3 (2·4)	2·7 (2·8)	1·0 (1·0)	0·35 (0·22 to 0·56)†	<0·0001‡
Mean rtCGM glucose, mmol/L	8·7 (1·5)	9·0 (1·6)	8·9 (1·5)	9·5 (1·6)	0·28 (–0·05 to 0·62)	0·0982
Median percentage of rtCGM values ≤3·9 mmol/L	6·9% (3·6 to 12·3)	5·0% (2·7 to 9·0)	6·4% (3·7 to 12·0)	1·6% (0·9 to 3·7)	..	<0·0001
Median percentage of rtCGM values ≤3·0 mmol/L	2·7% (1·0 to 5·7)	1·7% (0·7 to 3·8)	2·5% (1·0 to 6·1)	0·3% (0·1 to 0·9)	..	<0·0001
Mean percentage of rtCGM values >3·9 mmol/L and ≤10·0 mmol/L	59·1% (13·3)	57·8% (15·4)	56·5% (12·2)	58·5% (17·7)	3·1 (0·0 to 6·2)	0·0535
Mean percentage of rtCGM values >10·0 mmol/L	32·8% (15·5)	35·4% (17·5)	35·3% (15·2)	38·8% (18·7)	1·3 (–2·3 to 4·9)	0·4681
Median duration of rtCGM ≤3·9 mmol/L per day, min	99·5 (52·3 to 178·1)	70·9 (38·8 to 130·2)	92·2 (51·8 to 172·6)	23·9 (12·9 to 54·5)	..	<0·0001
Median duration of rtCGM ≤3·0 mmol/L per day, min	36·3 (13·1 to 79·7)	24·1 (8·9 to 51·0)	32·9 (13·1 to 83·9)	3·8 (1·1 to 11·9)	..	<0·0001
Mean duration of rtCGM values >3·9 mmol/L and ≤10·0 mmol/L per day, min	851·0 (191·7)	831·9 (221·5)	814·2 (176·0)	842·9 (225·2)	44·9 (–0·3 to 90·0)	0·0513
Mean duration of rtCGM values >10·0 mmol/L per day, min	471·7 (223·1)	509·8 (252·2)	509·1 (219·1)	558·6 (268·4)	–18·7 (–70·3 to 32·9)	0·4744
Mean rtCGM variability, coefficient of variation	40·5% (7·0)	39·3% (7·6)	41·1% (6·9)	34·1% (5·6)	6·2 (5·0 to 7·5)	<0·0001
Median low blood glucose index (rtCGM-LBGI)	1·60 (0·88 to 2·92)	1·26 (0·70 to 2·15)	1·53 (0·84 to 2·97)	0·52 (0·25 to 0·98)	..	<0·0001

- In a high risk population, compared with SMBG, CGM significantly improved
  - Low glucose events <3.0mmol/L
  - Nocturnal hypoglycaemia
  - %time <3.9mmol/L
  - %time <3.0mmol/L
  - Duration <3.9mmol/L
  - Duration <3.0mmol/L
  - Glucose CV
  - LBGI

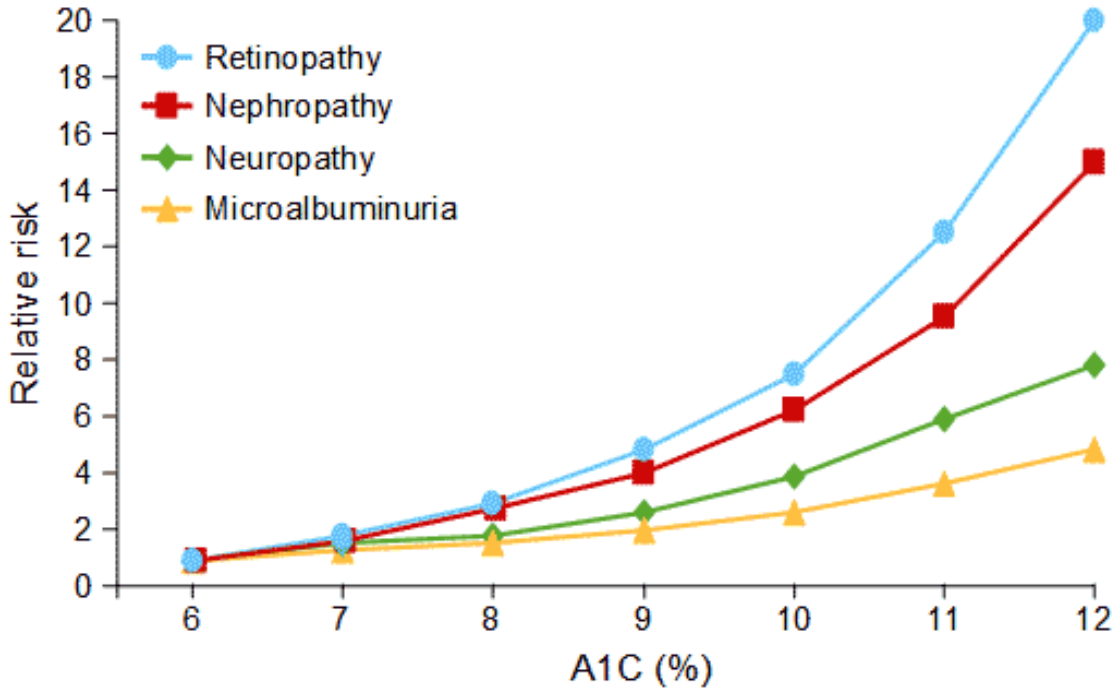
CONCEPTT

- Number needed to treat (NNT) with CGM
  - 6 pregnant women NNT to prevent one NICU admission
  - 6 pregnant women NNT to prevent one large for gestational age
  - 8 pregnant women NNT to prevent one case of neonatal hypoglycemia

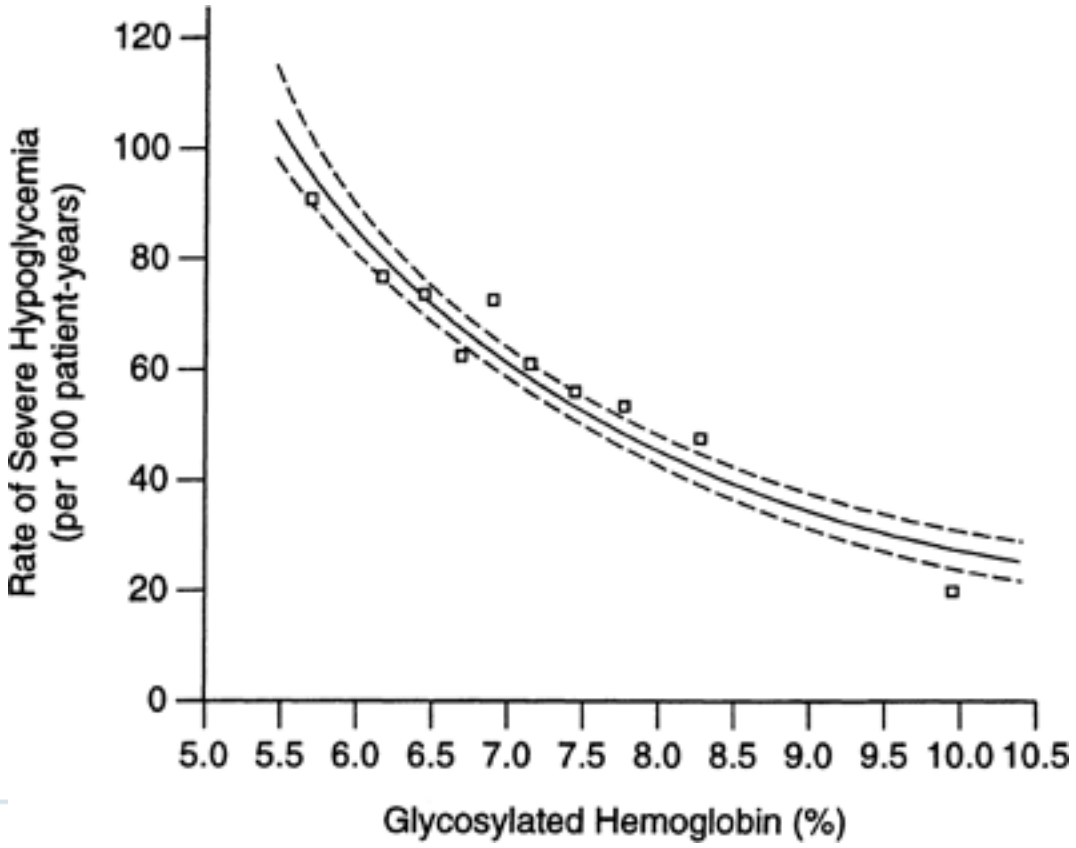
- From 2020 all pregnant women with type 1 diabetes will be offered CGM

Feig et al. Lancet 2017. http://dx.doi.org/10.1016/S0140-6736(17)32400-5

DCCT



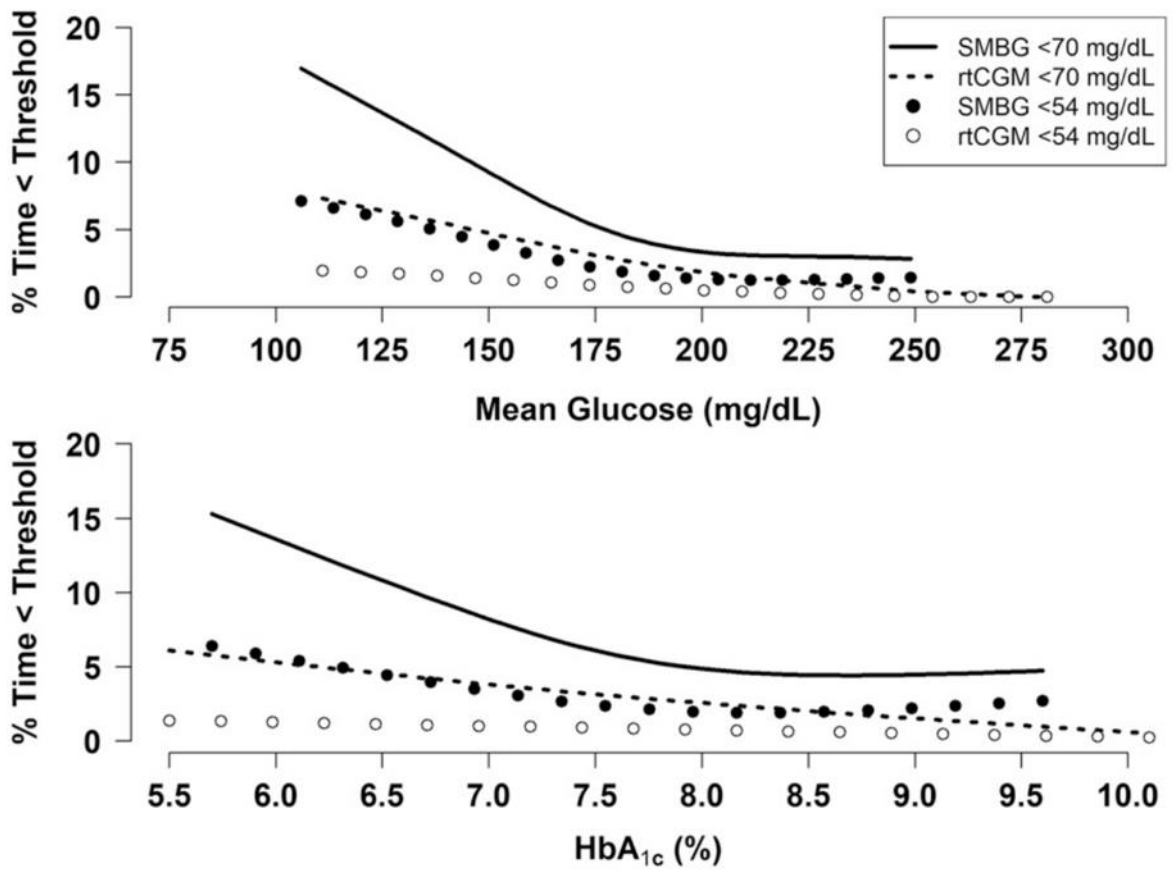
DCCT. New England Journal Medicine 1993



Hypoglycemia in the DCCT. Diabetes Care 1997

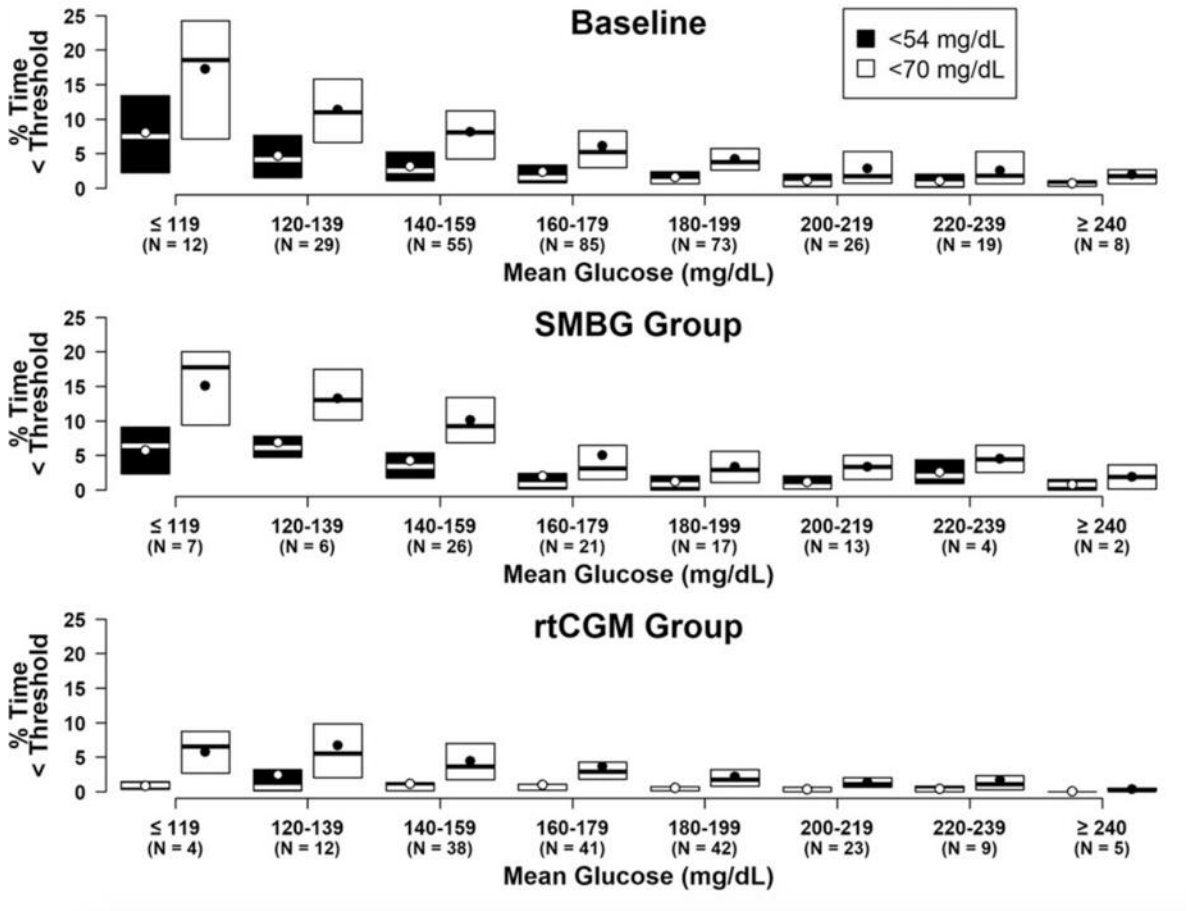
Changing the relationship between HbA1c and hypoglycaemia

- Combined HypoDE and DIAMOND studies
- Older adults
- All MDI
- Above target
- Impaired awareness of hypoglycaemia/ SH



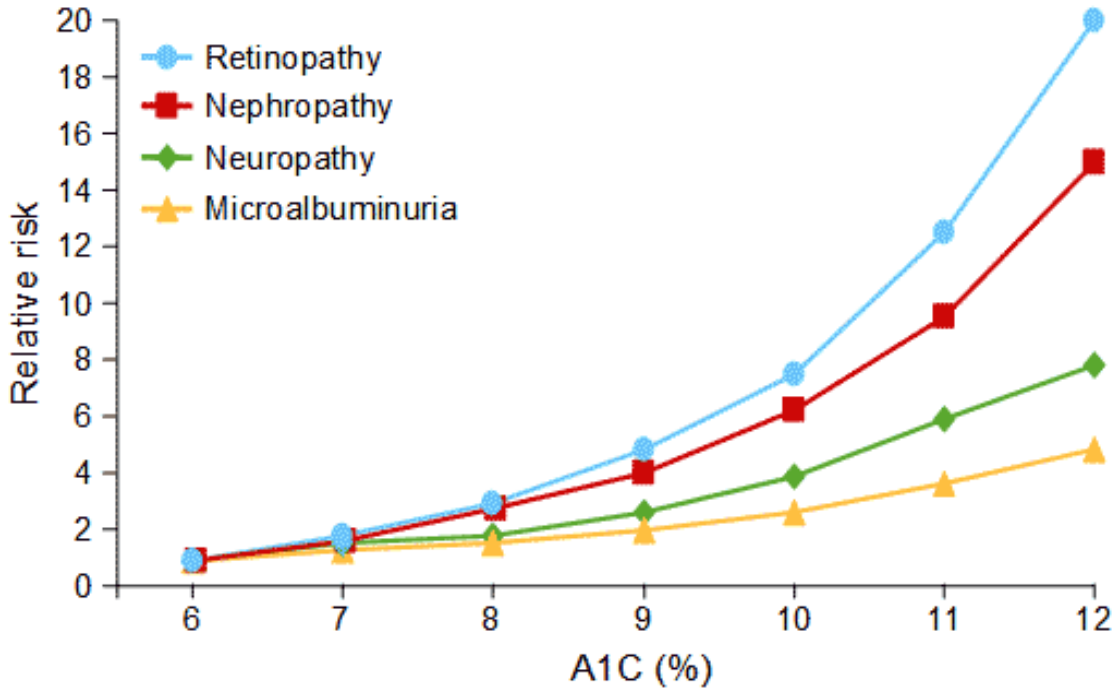
Oliver et al. https://doi.org/10.2337/dc19-0977

Changing the relationship between HbA1c and hypoglycaemia



Oliver et al. https://doi.org/10.2337/dc19-0977

DCCT



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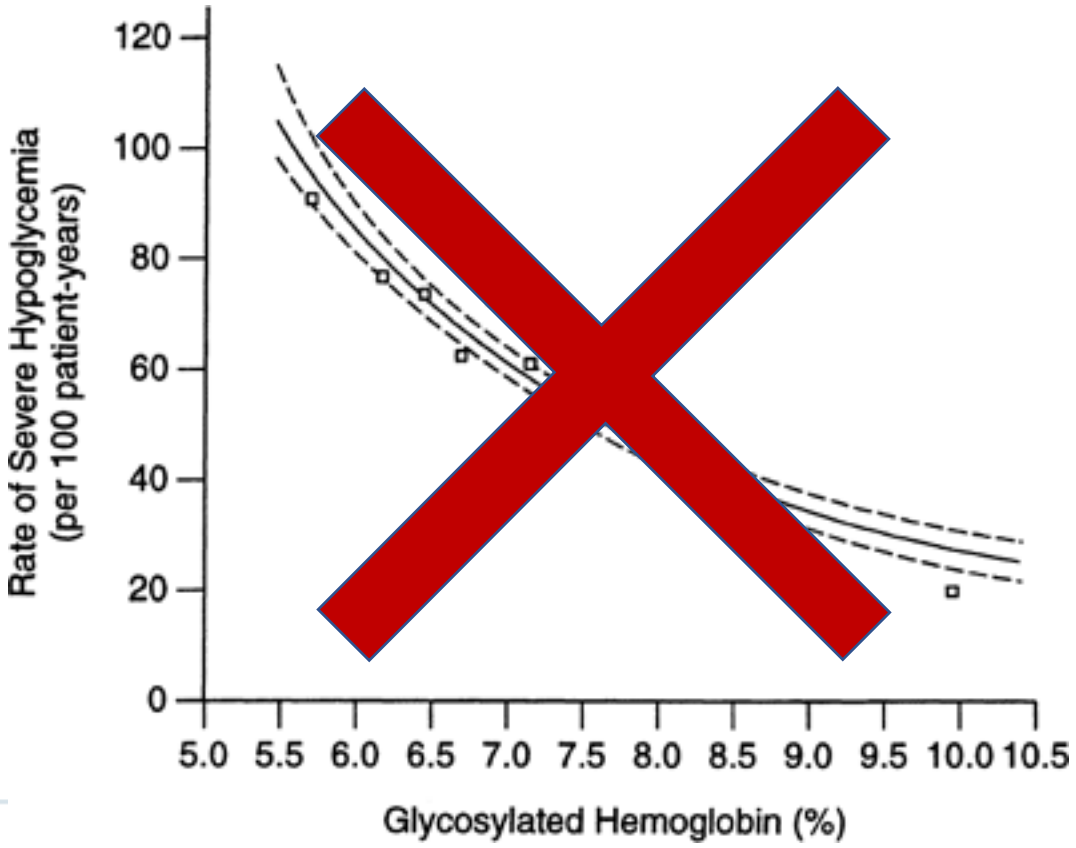


Hypoglycemia in the DCCT. Diabetes Care 1997

Continuous Glucose Monitoring

- Mean HbA1c reduction of > 0.4%
- Reduction in exposure to hypoglycaemia
- Reduced severe hypoglycaemia in people at highest risk
- Permits any level of HbA1c without changing hypo risk
- Effectiveness independent of insulin modality
- (Improves maternofetal outcomes in T1DM pregnancy – CONCEPTT)
- (Sustained for 3 years – COMISAIR)
- (Reduced hospital admissions – Belgium real world data)
- (Reduced work absenteeism - Belgium real world data)

Flash Glucose Monitoring

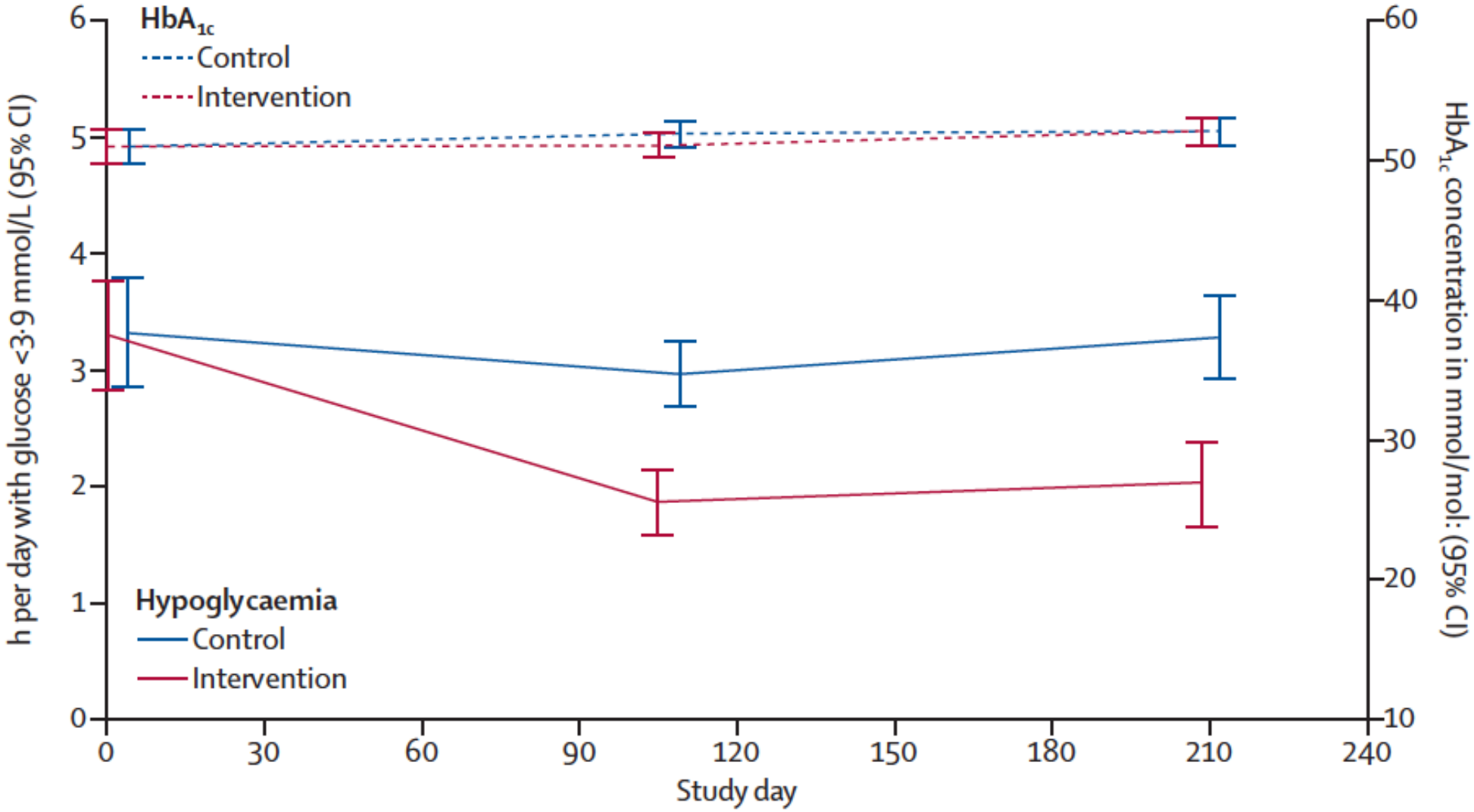
❌ No alerts or alarms

- Continuous glucose recorder (‘Flash glucose monitoring’)
- Glucose value
- Trend arrow
- 8 hours retrospective continuous data
- 14 days wear
- No ability to calibrate

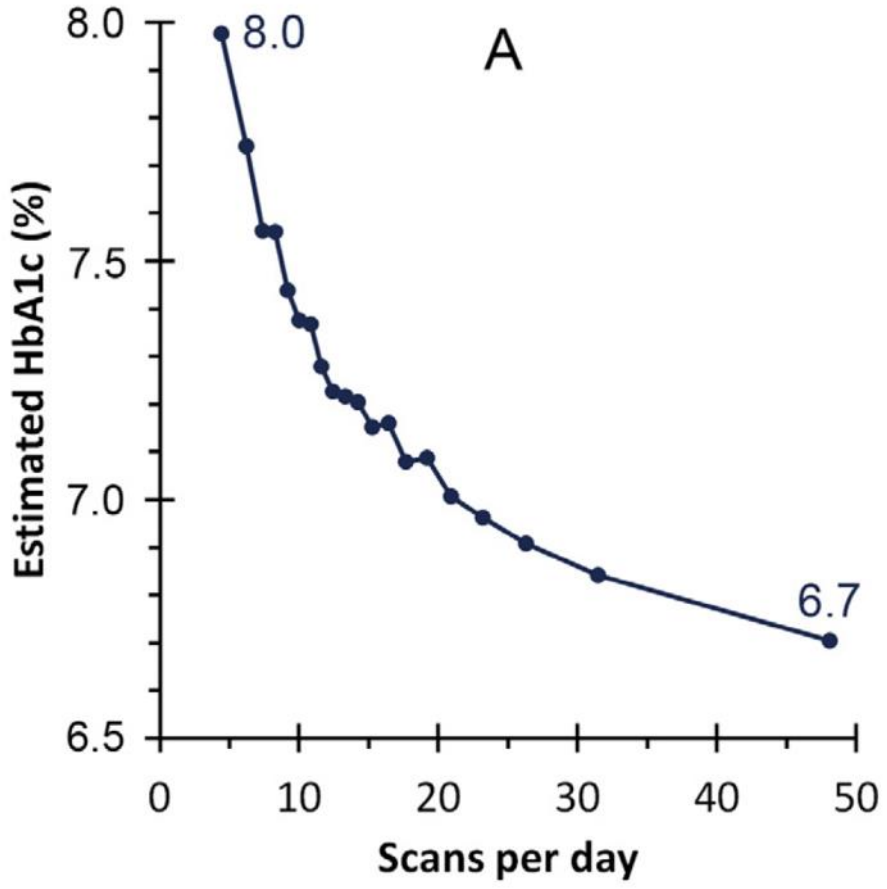
IMPACT study

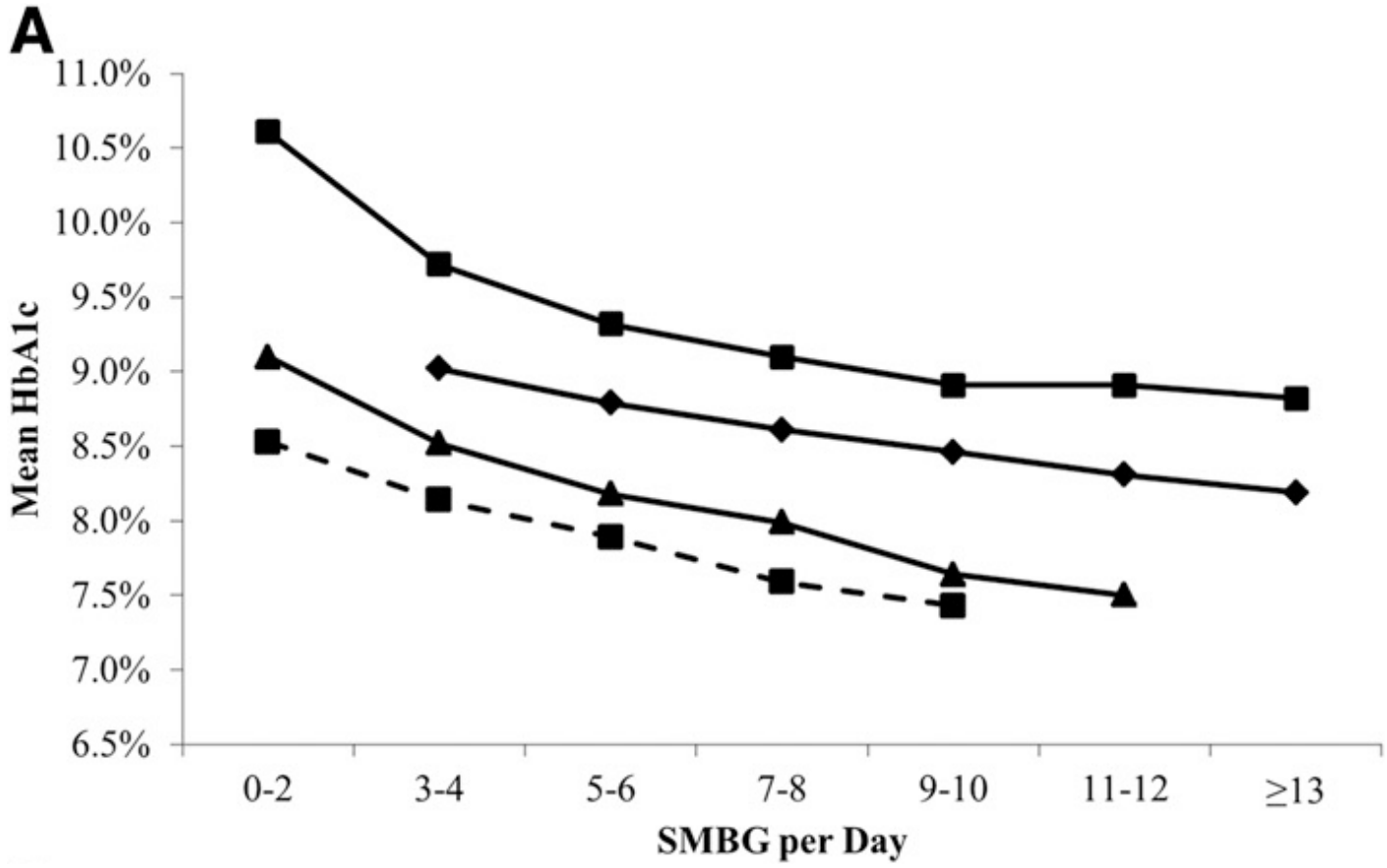
	Intervention (n=119)	Control (n=120)
Men	77 (65%)*	59 (49%)*
Women	42 (35%)	61 (51%)
Race		
White	119 (100%)	119 (99%)
Black	0	1 (1%)
Age (years)	42 (33–51)	45 (33–57)
BMI (kg/m^2)	25·2 (3·6)	24·8 (3·5)
Duration of diabetes (years)	20 (13–27)	20 (12–32)
Screening HbA_{1c} (%; mmol/mol)	6·7 (0·5); 50·1 (5·7)	6·7(0·6); 50·2 (6·5)
Self-reported blood glucose frequency per day	5·4 (2·0)	5·6 (2·3)
Insulin administration method		
Multiple daily injections	81 (68%)	80 (67%)
Continuous subcutaneous insulin infusion	38 (32%)	40 (33%)
Insulin, total daily dose		
Basal (units)	25·7 (13·9)	20·9 (10·0)
Bolus (units)	24·2 (13·5)	22·2 (13·4)
Continuous subcutaneous insulin infusion (units)	41·4 (17·1)	35·9 (15·6)

IMPACT study



Real world data

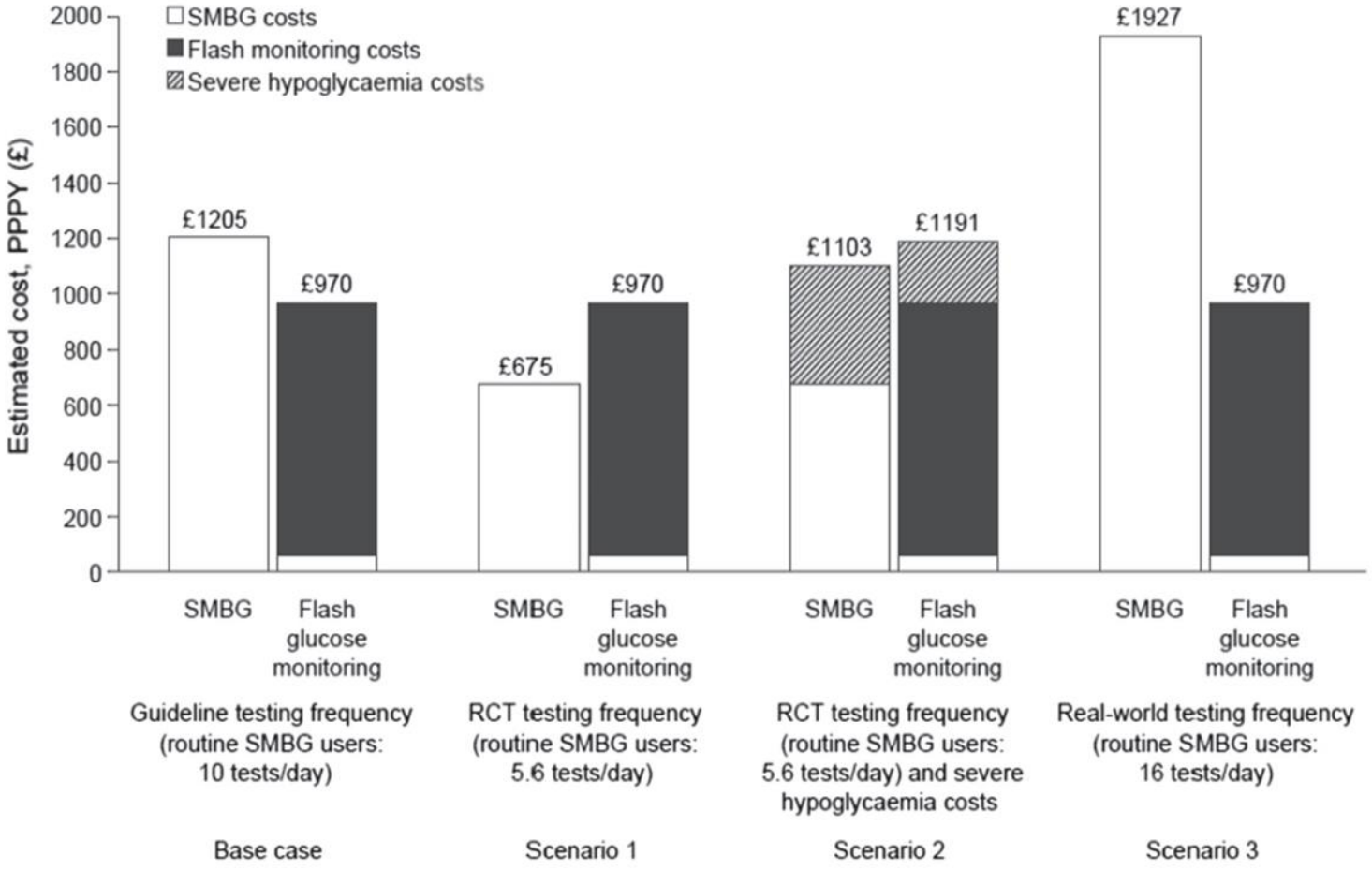




Dunn et al. Diabetes Res Clin Pract. doi.org/10.1016/j.diabres.2017.12.015

Miller at al. Diabetes Care 2013 Jul; 36(7): 2009-2014

Flash cost effectiveness



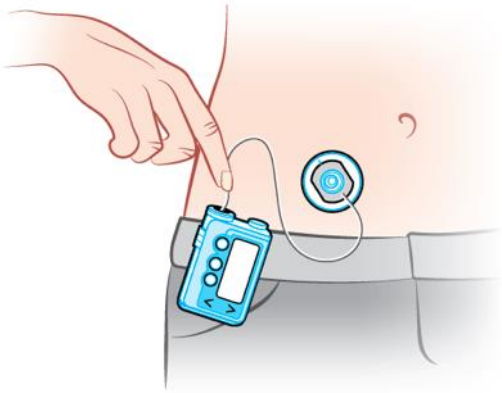
Hellmund R et al. https://doi.org/10.1016/j.diabres.2018.01.028

Flash glucose monitoring

- Reduction in time spent below 3.9mM in well-controlled group
- No HbA1c reductions in RCTs (type 1 or type 2 diabetes)
- Real world data may show small HbA1c benefit
- Possible increase in treatment satisfaction
- Budget impact neutral for very small group of people

Insulin Pumps

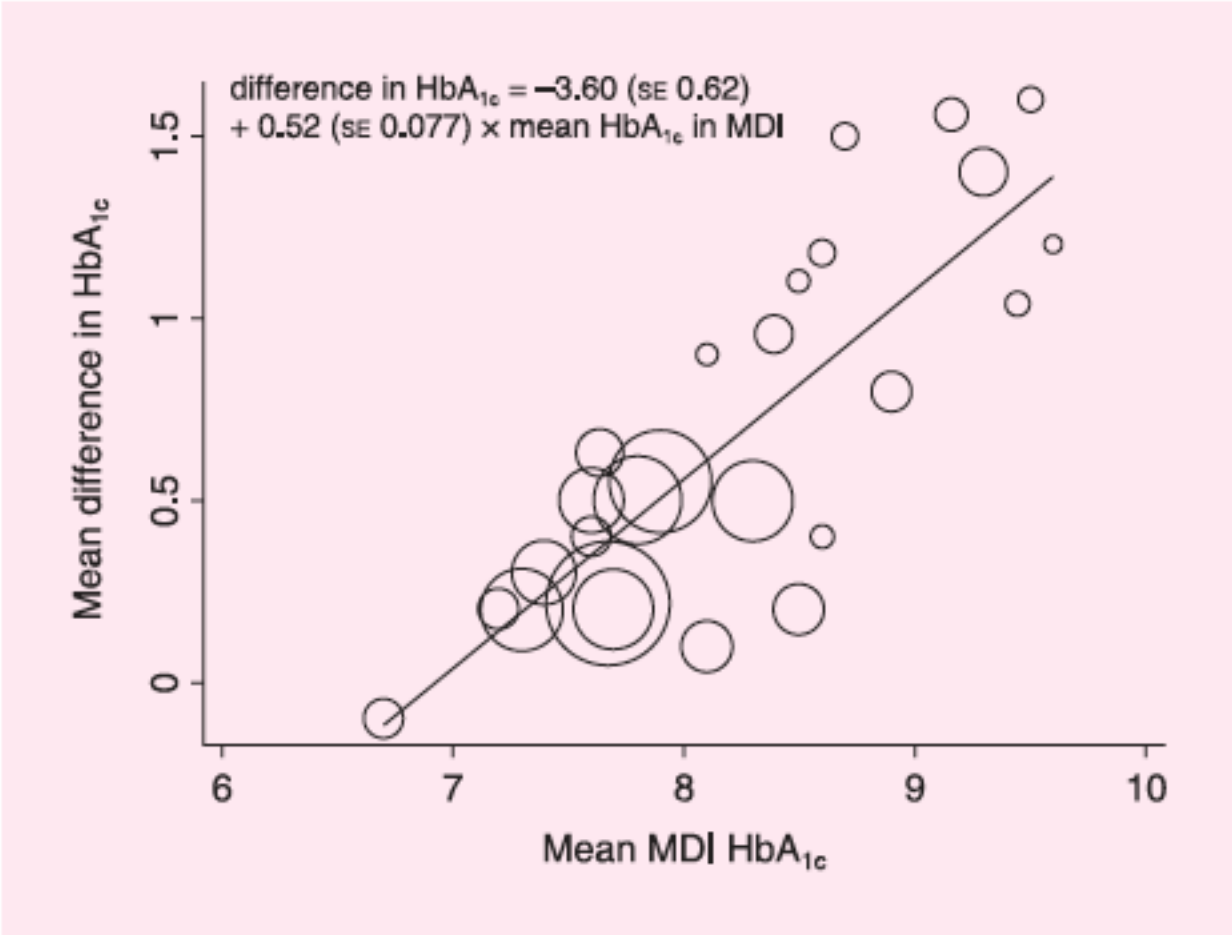
Patch or tubeless



Infusion set

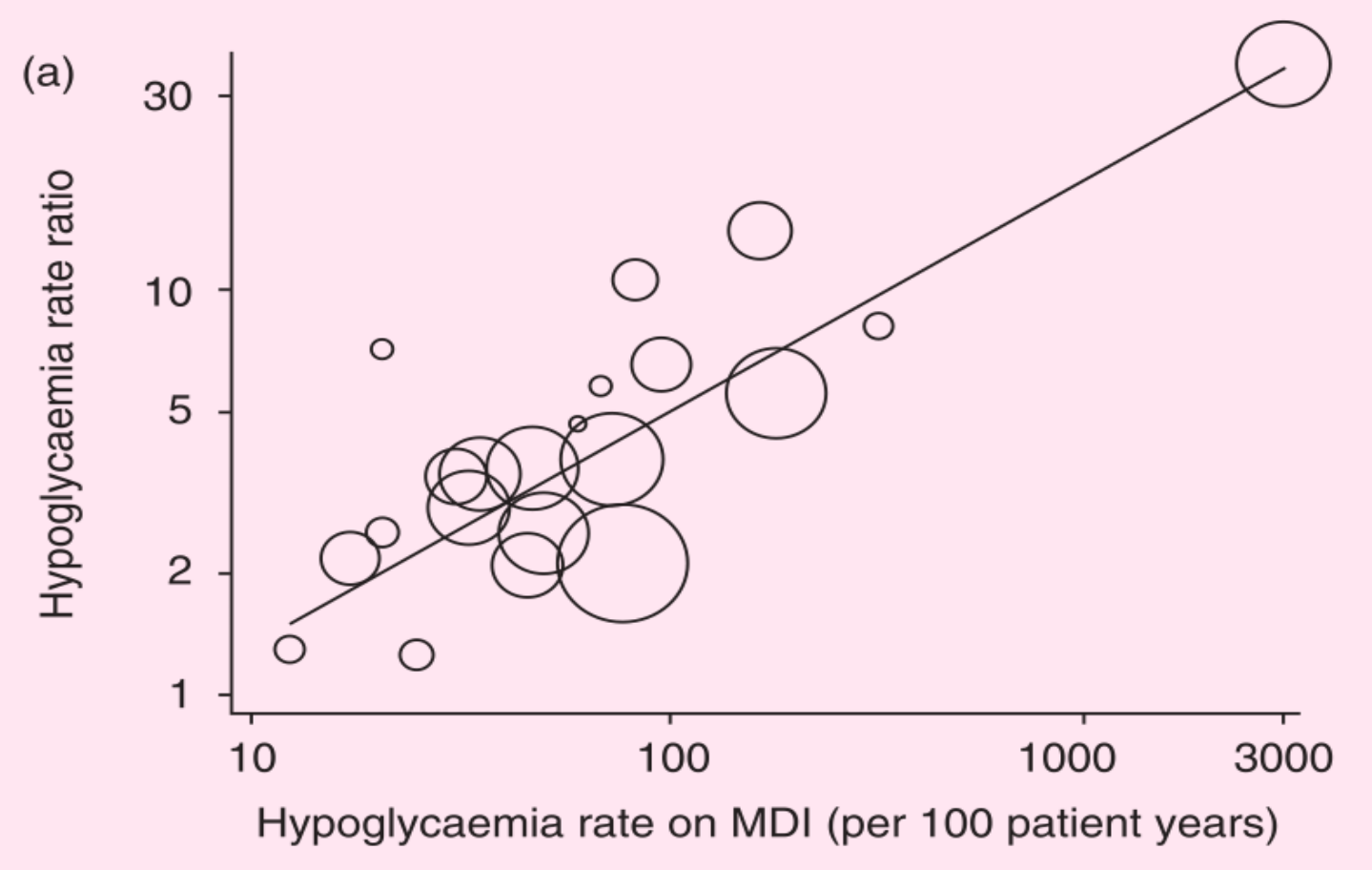
- Short acting insulin only
- Continuous infusion of small amounts
- Personalised daily insulin pattern
- Temporary rates for illness, exercise, stress, alcohol
- Injections shapes with food can be changed

HbA1c



Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Pickup JC, Sutton AJ. Diabetic Medicine 2008;25:765-774

Hypoglycaemia

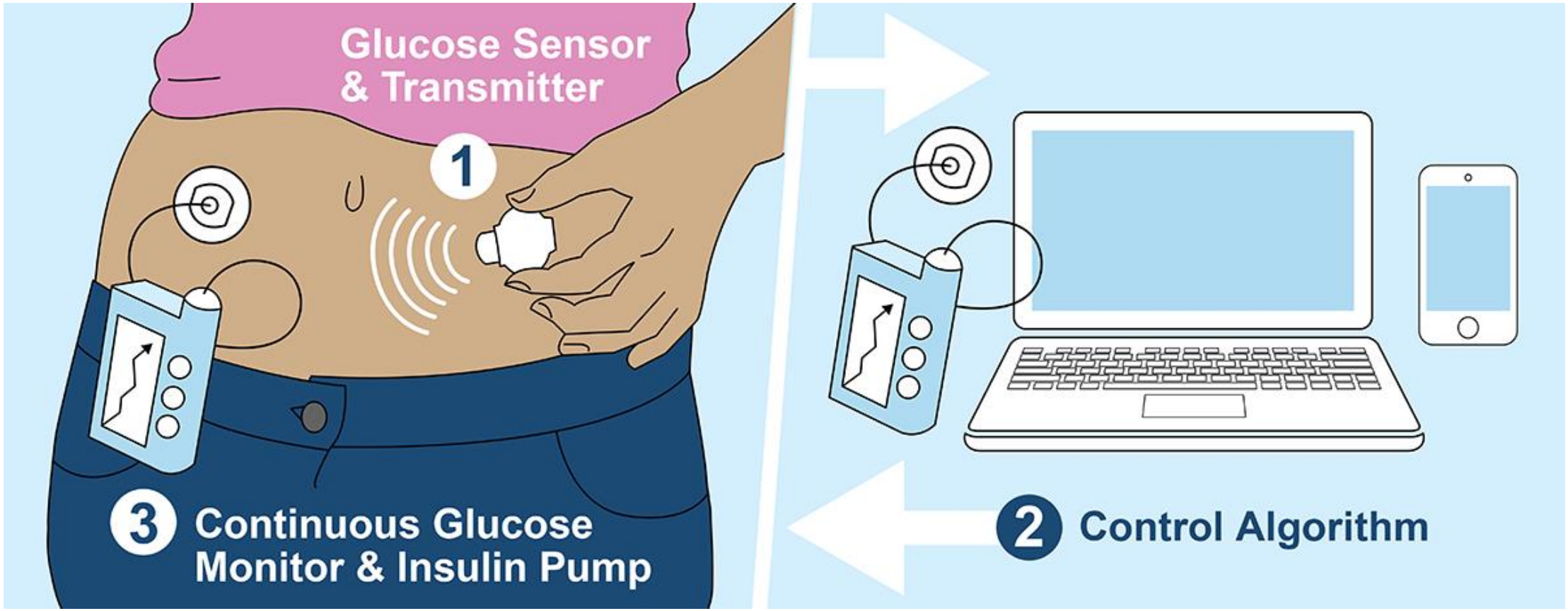


Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Pickup JC, Sutton AJ. Diabetic Medicine 2008;25:765-774

Insulin Pumps

- Mean HbA1c reduction of > 0.4%
- Reduction in exposure to hypoglycaemia
- Reduced severe hypoglycaemia in people at highest risk
- Reduce 24 hour insulin requirements
- Weight neutral
- Cost effective for hypoglycaemia reduction and HbA1c lowering (NICE TA151 2008)

Hybrid Closed Loop



Hybrid Closed Loop

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

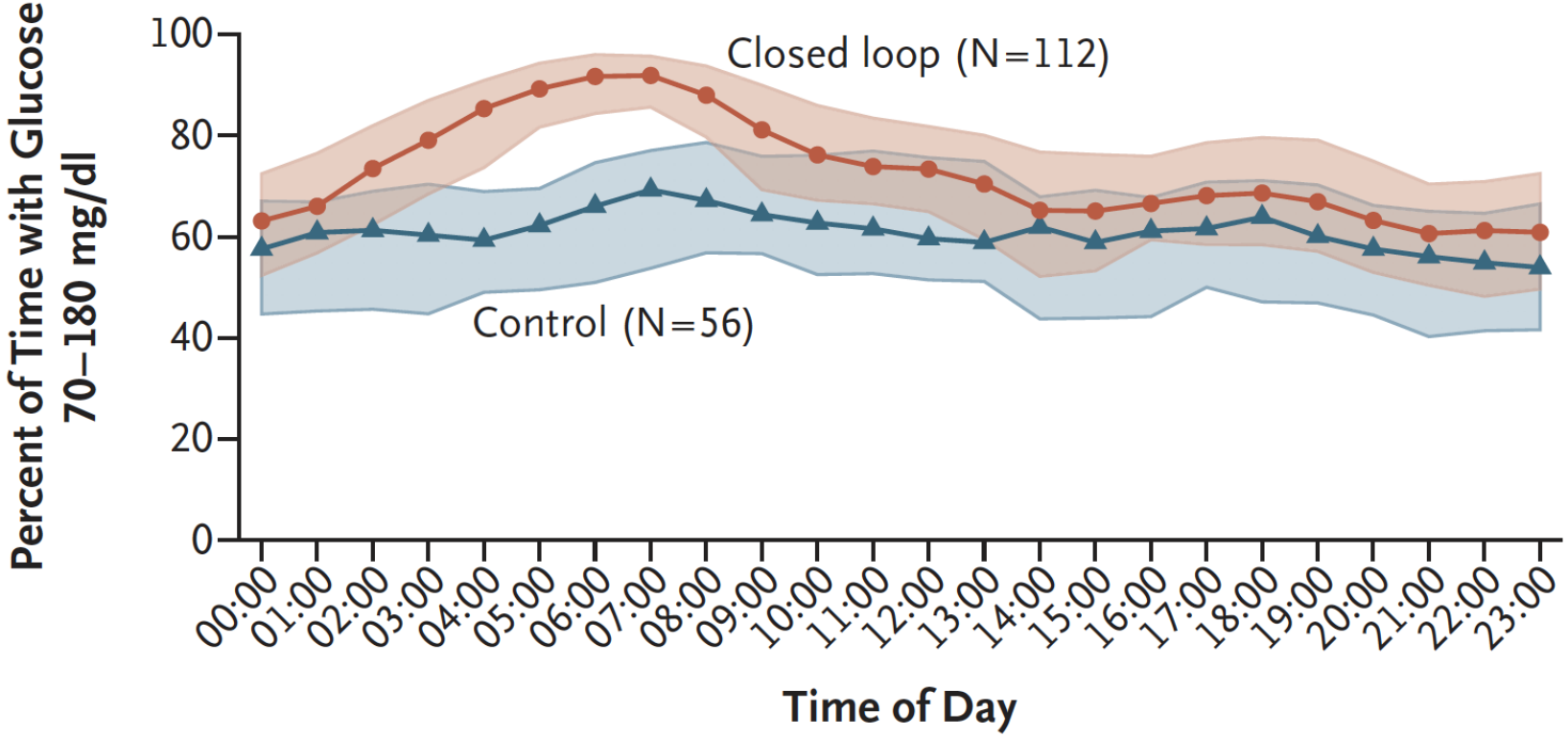
Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes

S.A. Brown, B.P. Kovatchev, D. Raghinaru, J.W. Lum, B.A. Buckingham, Y.C. Kudva, L.M. Laffel, C.J. Levy, J.E. Pinsker, R.P. Wadwa, E. Dassau, F.J. Doyle III, S.M. Anderson, M.M. Church, V. Dadlani, L. Ekhlaspour, G.P. Forlenza, E. Isganaitis, D.W. Lam, C. Kollman, and R.W. Beck, for the iDCL Trial Research Group*

Hybrid Closed Loop

- 6-month randomized, multicenter trial
- 2:1 randomisation to closed-loop system (closed-loop group) or a sensor-augmented pump (control group)
- N =168 (112 closed-loop; 56 control group)
- 14 to 71 years
- HbA1c 5.4 to 10.6%

Hybrid Closed Loop



Mean adjusted difference, 11 percentage points; 95% confidence interval [CI], 9 to 14; P<0.001

Summary

Pumps	CGM	Flash
Reduced HbA1c	Reduced HbA1c with pump or pens	Reduced hypoglycaemia in some
Reduced hypoglycaemia	Reduced hypos with pump or pens	Reduced HbA1c in some data
Improved quality of life	Reduced hypoglycaemia fear	Fingerprick replacement
Reduced glucose variability	Reduced glucose variability	Cost pressure in most users
Weight neutral	Reduced hospital admissions	
Cost effective	Can share data with carers	
Can talk to CGM	Cost effective in high risk	
	Can talk to pumps	