Diabetes technology: past, present and future

Peter Hammond
Consultant Diabetologist

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“The Miracle of Insulin”

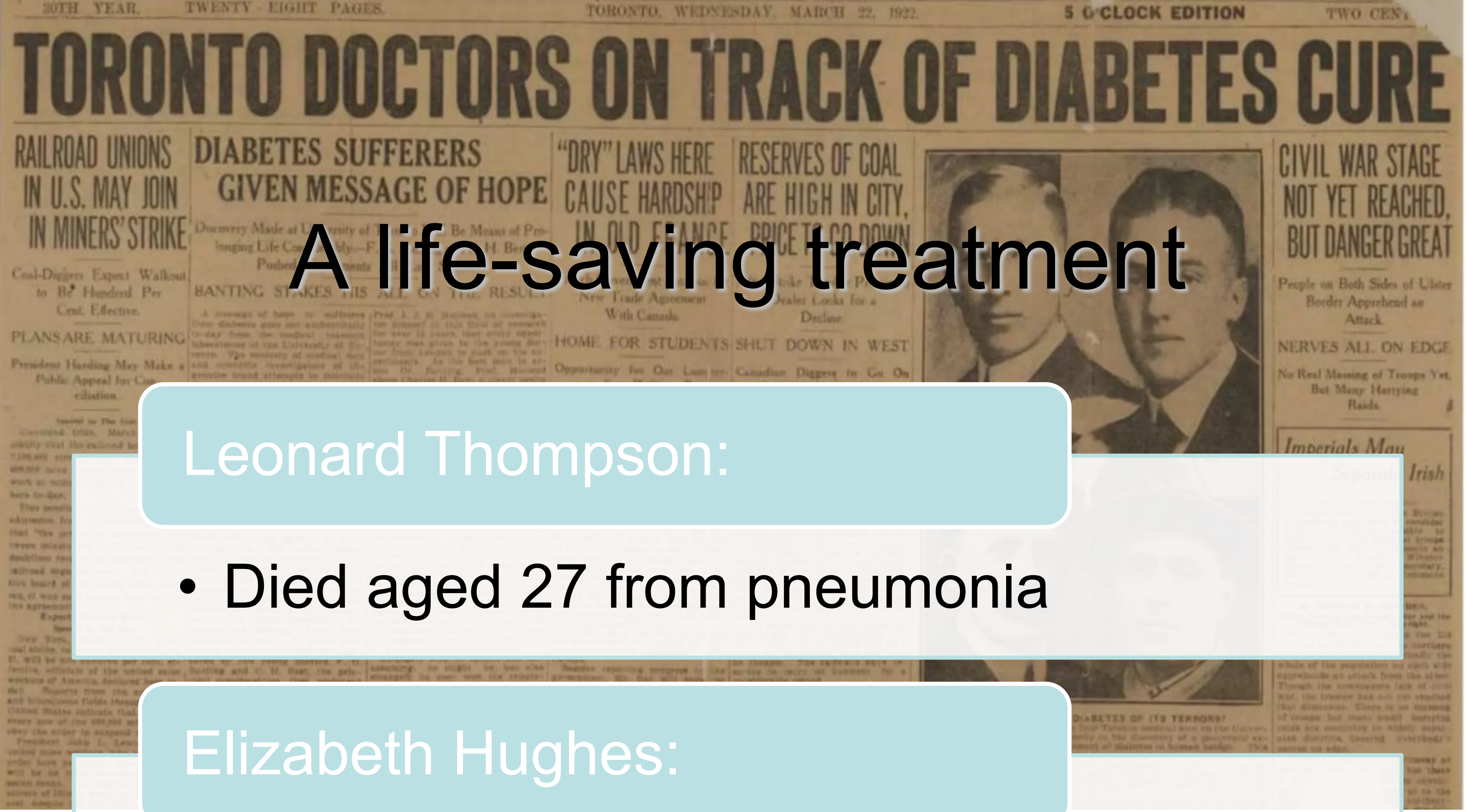
11th January 1922

…. But not a cure

- Frederick Banting, Nobel prize acceptance speech:

  “Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.”

A life-saving treatment


30TH YEAR. TWENTY-EIGHT PAGES. TORONTO, WEDNESDAY, MARCH 22, 1922. 5 O'CLOCK EDITION

TORONTO DOCTORS ON TRACK OF DIABETES CURE

RAILROAD UNIONS IN U.S. MAY JOIN IN MINERS' STRIKE

Coal-Diggers Expect Walkout to Be Hundred Per Cent. Effective.

PLANS ARE MATURING

President Harding May Make a Public Appeal for Conciliation.

DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

"DRY" LAWS HERE CAUSE HARDSHIP

New Trade Agreement With Canada

HOME FOR STUDENTS

RESERVES OF COAL ARE HIGH IN CITY,

Decline

SHUT DOWN IN WEST

CIVIL WAR STAGE NOT YET REACHED, BUT DANGER GREAT

People on Both Sides of Ulster Border Apprehend an Attack.

NERVES ALL ON EDGE

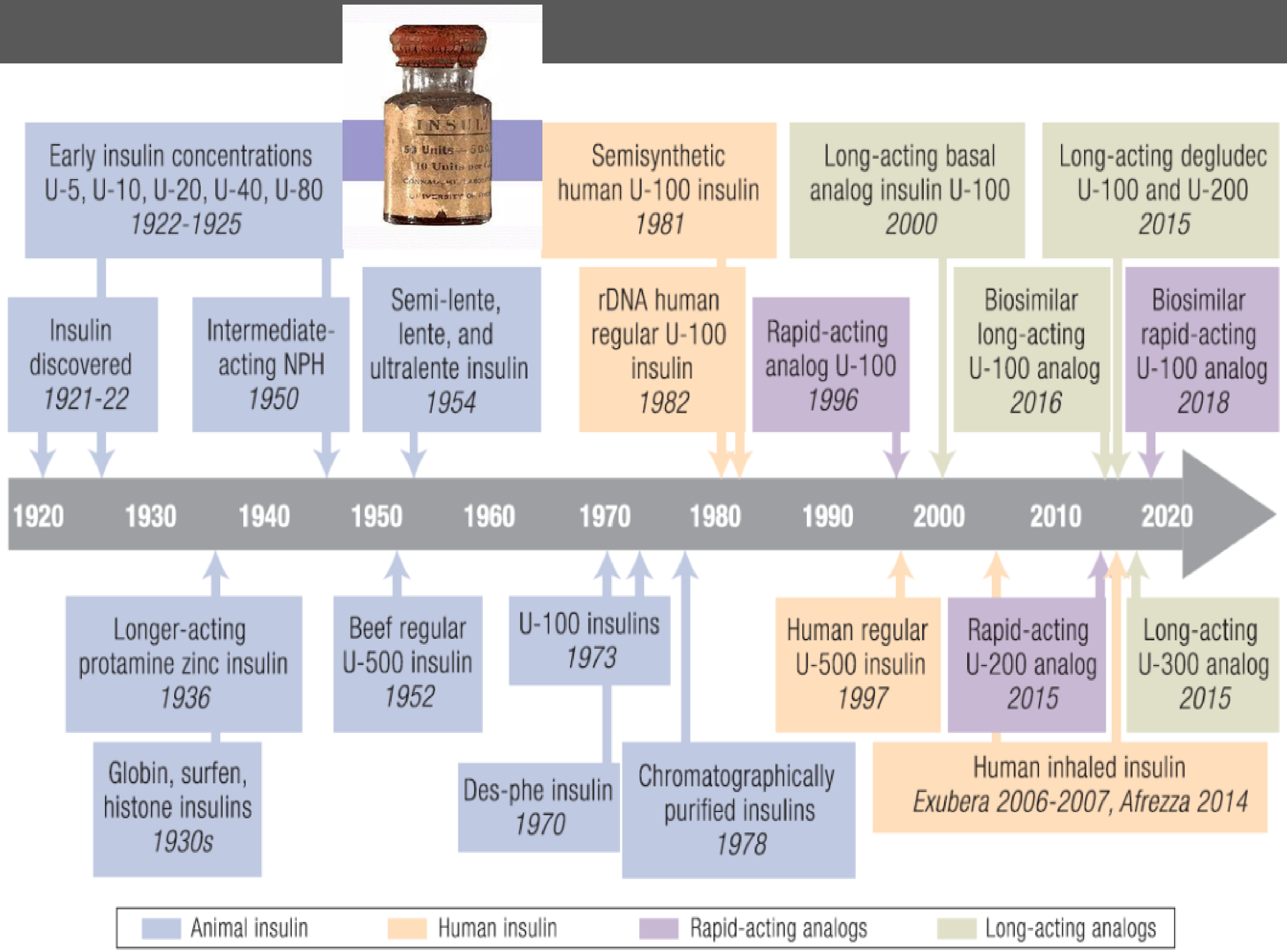
No Real Massing of Troops Yet, But Many Harrying Raids.

Leonard Thompson:

- Died aged 27 from pneumonia

Elizabeth Hughes:

- Started insulin aged 13, weighing 45 lbs and barely able to walk
- Died of “natural causes” aged 73



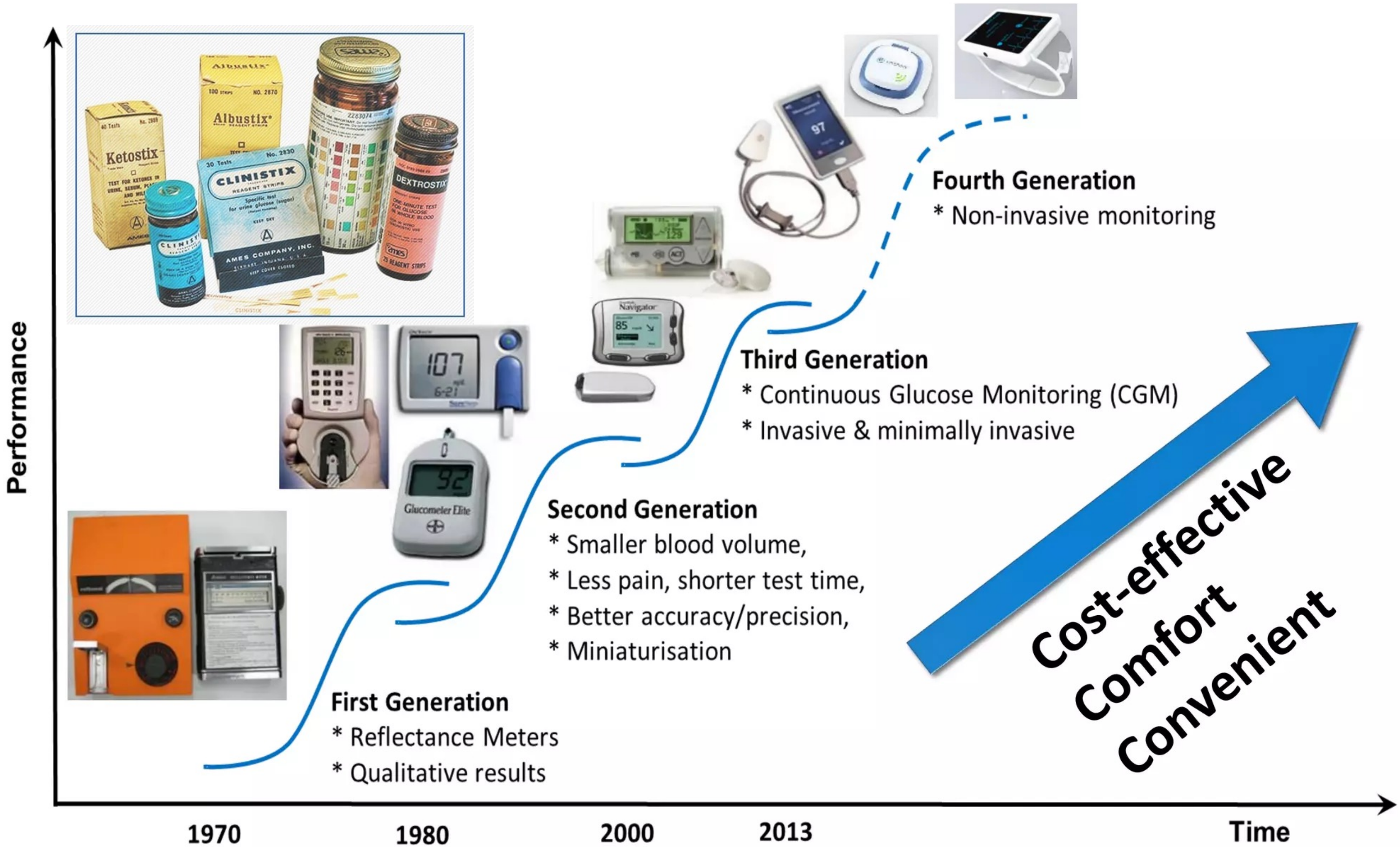
Early insulin concentrations U-5, U-10, U-20, U-40, U-80 1922-1925
INSULIN
Semisynthetic human U-100 insulin 1981
Long-acting basal analog insulin U-100 2000
Long-acting degludec U-100 and U-200 2015
Insulin discovered 1921-22
Intermediate-acting NPH 1950
Semi-lente, lente, and ultralente insulin 1954
rDNA human regular U-100 insulin 1982
Rapid-acting analog U-100 1996
Biosimilar long-acting U-100 analog 2016
Biosimilar rapid-acting U-100 analog 2018
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
Longer-acting protamine zinc insulin 1936
Beef regular U-500 insulin 1952
U-100 insulins 1973
Human regular U-500 insulin 1997
Rapid-acting U-200 analog 2015
Long-acting U-300 analog 2015
Globin, surfen, histone insulins 1930s
Des-phe insulin 1970
Chromatographically purified insulins 1978
Human inhaled insulin Exubera 2006-2007, Afrezza 2014
Animal insulin
Human insulin
Rapid-acting analogs
Long-acting analogs

Glucose testing

1941 Clinitest®

1956 Urine dip-stick

Blood glucose testing



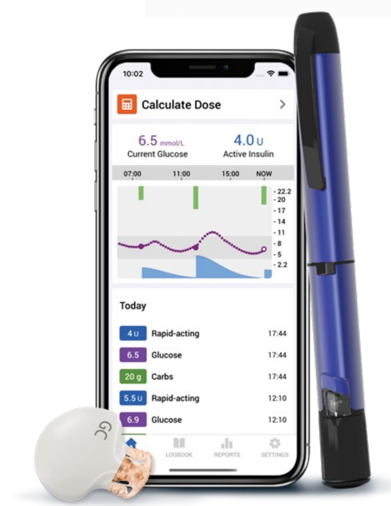
Insulin delivery devices: syringes

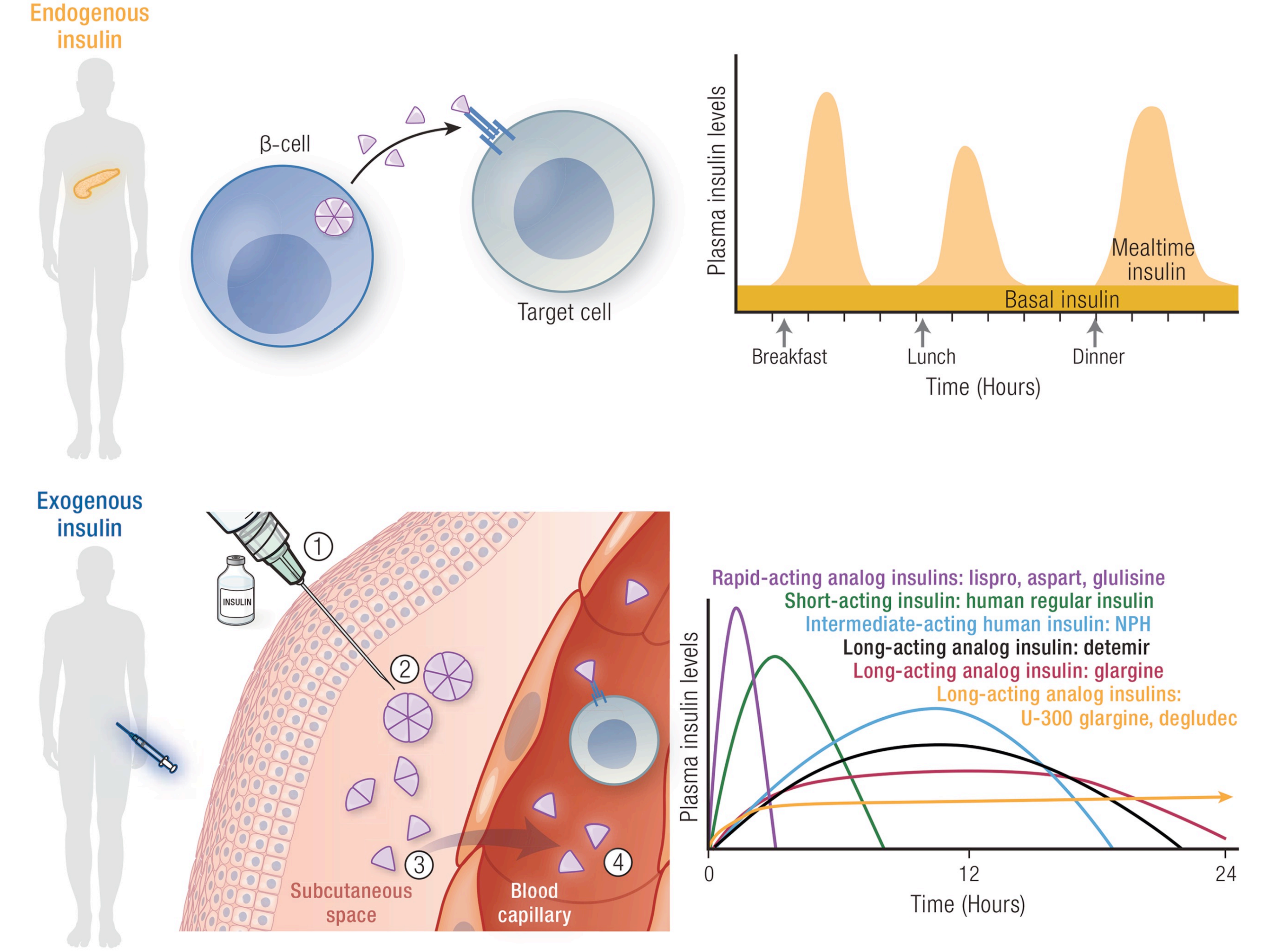
- 1924: First specialised insulin syringe (BD)
- 1954: First disposable glass syringe (BD)
- 1955: First disposable plastic syringe (Roche)

- 1983: U100 insulin syringes

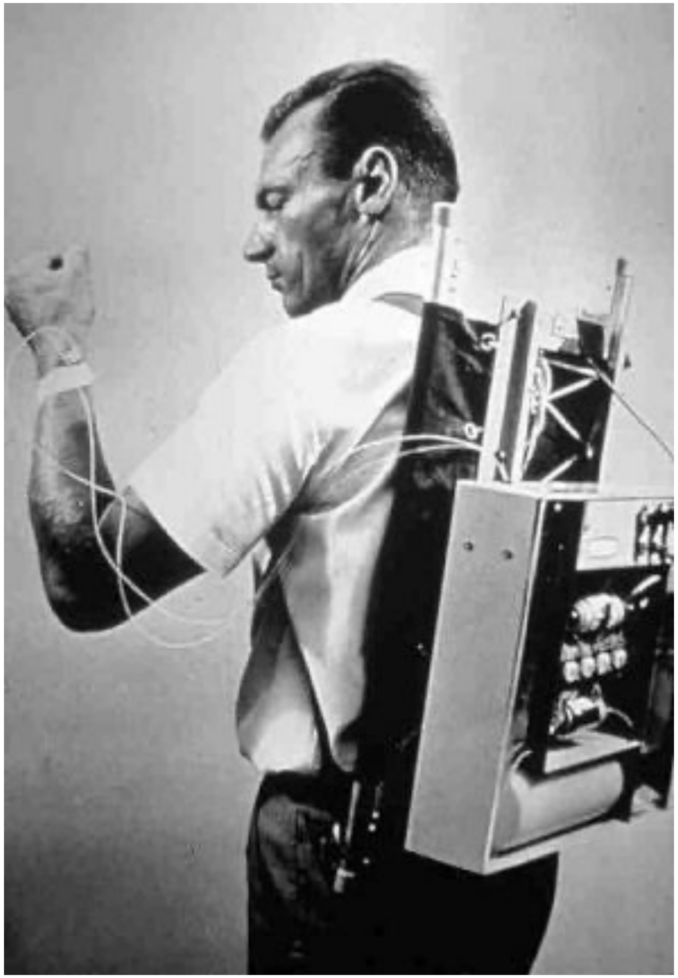
Insulin delivery devices: pens

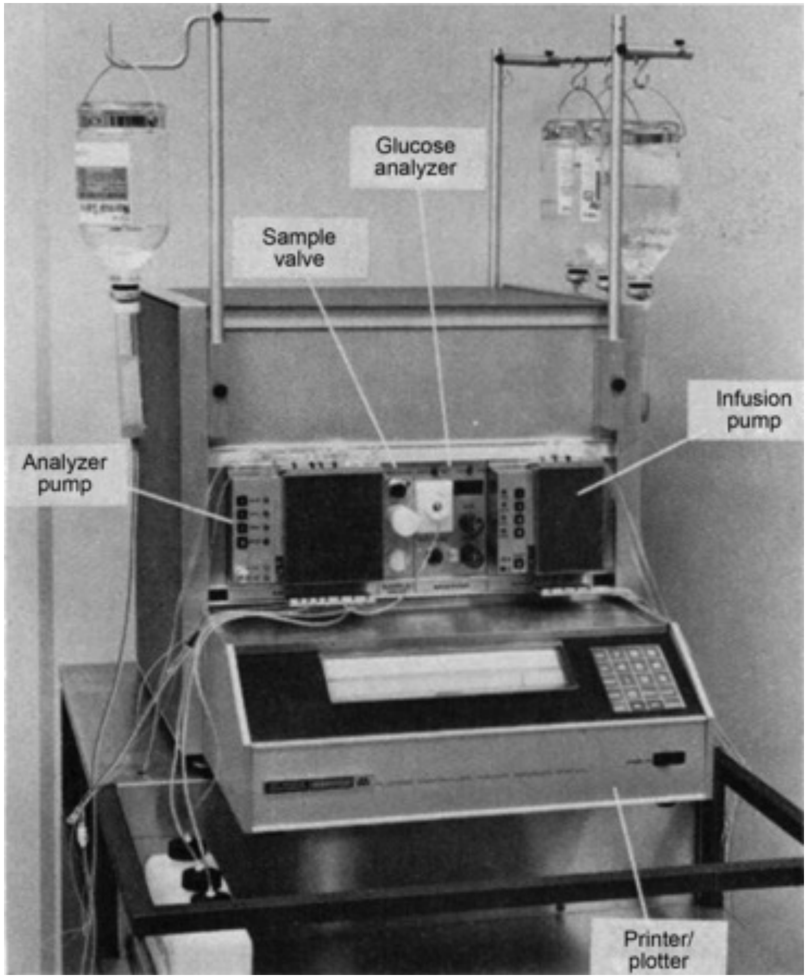
- 1985: Novopen launched
- Other manufacturer specific pens launched by Sanofi and Lilly, along with some generic pens
- 2007: Lilly launch Humapen Memoire
- 2017: First Smart Pen InPen launched



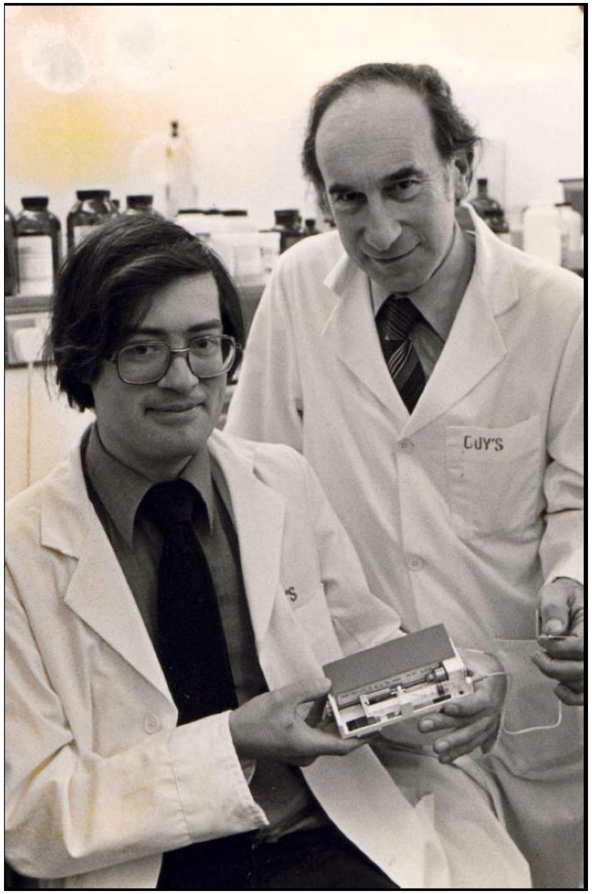


Endogenous insulin
β-cell
Target cell
Plasma insulin levels
Mealtime insulin
Basal insulin
Breakfast
Lunch
Dinner
Time (Hours)
Exogenous insulin
INSULIN
1
2
3
4
Subcutaneous space
Blood capillary
Rapid-acting analog insulins: lispro, aspart, glulisine
Short-acting insulin: human regular insulin
Intermediate-acting human insulin: NPH
Long-acting analog insulin: detemir
Long-acting analog insulin: glargine
Long-acting analog insulins: U-300 glargine, degludec
Plasma insulin levels
0
12
24
Time (Hours)





The Quest for the Holy Grail

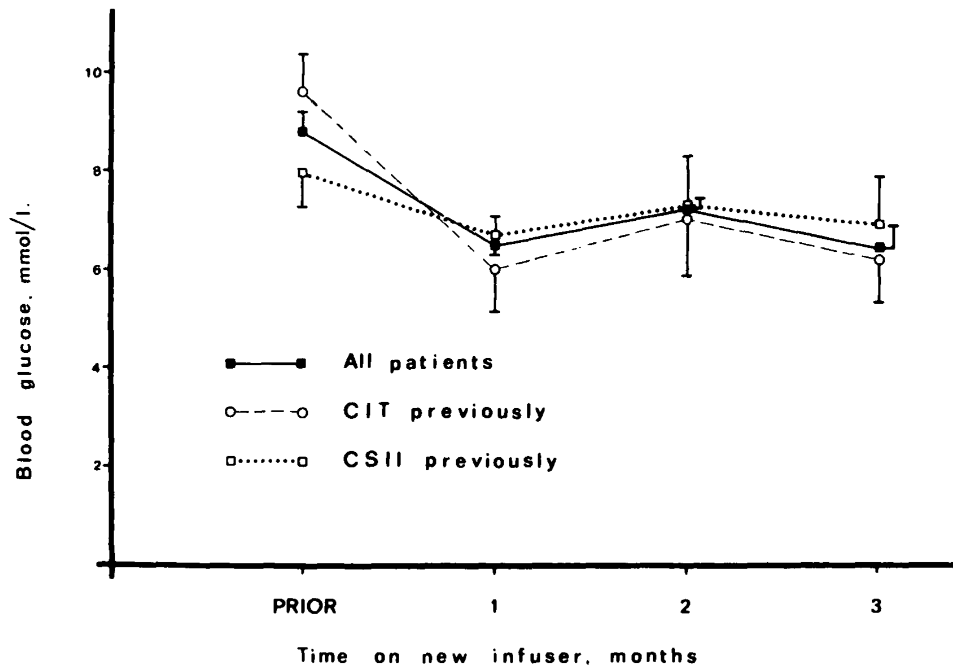


Insulin pumps – The Mill Hill Infuser

Meeting the Problems of First-Generation Insulin Infusion Pumps: Clinical Trial of a New Miniature Infuser

JEREMY J. BENDING, M.R.C.P., JOHN C. PICKUP, D.Phil., HARRY KEEN, M.D., DENIS ROTHWELL, M.A., AND IAN A. SUTHERLAND, Ph.D.

Case no.	Occupation	Age (yr)	Sex	Duration of diabetes (yr)
1	Health inspector	35	M	12
2	Research scientist	40	M	18
3	Machine engineer	38	M	19
4	Musician	24	M	20
5	Hygiene foreman	48	M	35
6	Housewife	37	F	19
7	Clerk	42	F	18
8	Student	21	F	4
9	Teacher	49	F	14



Diabetes Care 1983;6:452-8

… but is pump therapy safe

BRITISH MEDICAL JOURNAL VOLUME 291 10 AUGUST 1985 371

Severe hyperkalaemia and ketoacidosis during routine treatment with an insulin pump

GRAHAM KNIGHT, ADRIAN M JENNINGS, ANDREW J M BOULTON, STEPHEN TOMLINSON, JOHN D WARD

Abstract

During a feasibility study of the use of insulin pumps to treat diabetes ketoacidosis occurred at a rate of 0·14 episodes/patient/year in the first year but was lower in subsequent years. A case of cardiac arrest secondary to hyperkalaemia during ketoacidosis occurred in a patient treated with a pump. The mean (SD) serum potassium concentration on presentation to hospital with ketoacidosis was significantly higher in patients treated with a pump (5·7 (1·1) mmol(mEq)/l) than those treated with conventional injections of insulin (4·9 (0·9) mmol/l; $p<0·01$).

The high rate of ketoacidosis and raised serum potassium concentrations during treatment with the pump creates doubt about the use of this treatment as an alternative regimen for large numbers of patients in a busy diabetic clinic.

Introduction

Continuous subcutaneous infusion of insulin is increasingly considered for routine clinical use, in addition to its original role in clinical research.[1] A feasibility study of the use of continuous subcutaneous infusion of insulin in a busy diabetic clinic has been carried out in Sheffield to assess the practicality of the widespread

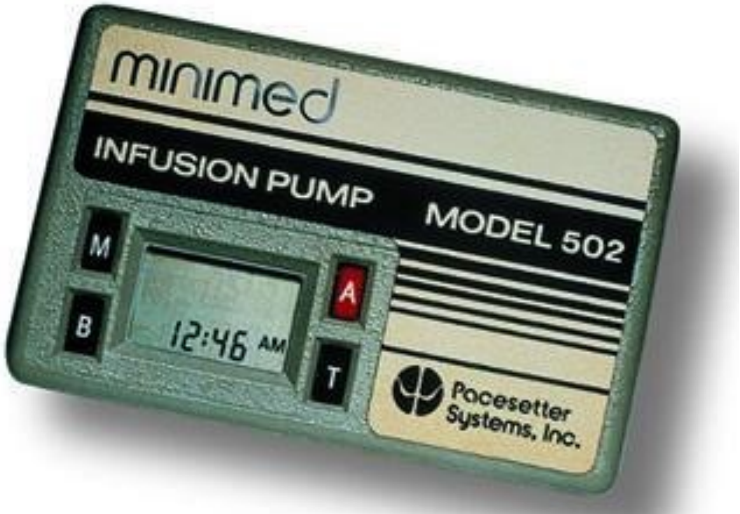
infusions of insulin; doctors could therefore be contacted at any time if patients encountered problems.

Initially, patients were taught individually by a doctor about the use of continuous subcutaneous infusions of insulin and verbal and written instructions were given. Instructions given to treat hyperglycaemia emphasised the importance of intensified monitoring of blood glucose concentrations at home, urinary ketone testing, and increased insulin dosage, usually by additional boluses but if necessary by increased basal infusion rate.

After four months rapid severe loss of metabolic control was clearly identified as a recurrent problem in those treated with continuous subcutaneous infusions of insulin; subsequently, this problem has been reported by other groups.[3,4] Consequently a protocol of more aggressive action was recommended to the patients when glycaemic control deteriorated, including precise extra dosages of insulin, timing of blood glucose and testing of urinary ketones, examination of the infusion system, and early contact by telephone to the diabetic unit. Diabetic ketoacidosis was defined as ketonaemia and hyperglycaemia with symptoms of nausea, thirst, malaise, vomiting, and serum bicarbonate concentrations ≤15 mmol (mEq)/l.

After the identification of severe hyperkalaemia as a potential problem in patients receiving continuous subcutaneous infusions of insulin who developed diabetic ketoacidosis the notes of all patients admitted to our unit since January 1982 with diabetic ketoacidosis were examined to assess clinical and biochemical features on admission. Measurements of emergency specimens of venous blood had been made with reference to the following

Insulin pumps: commercialisation

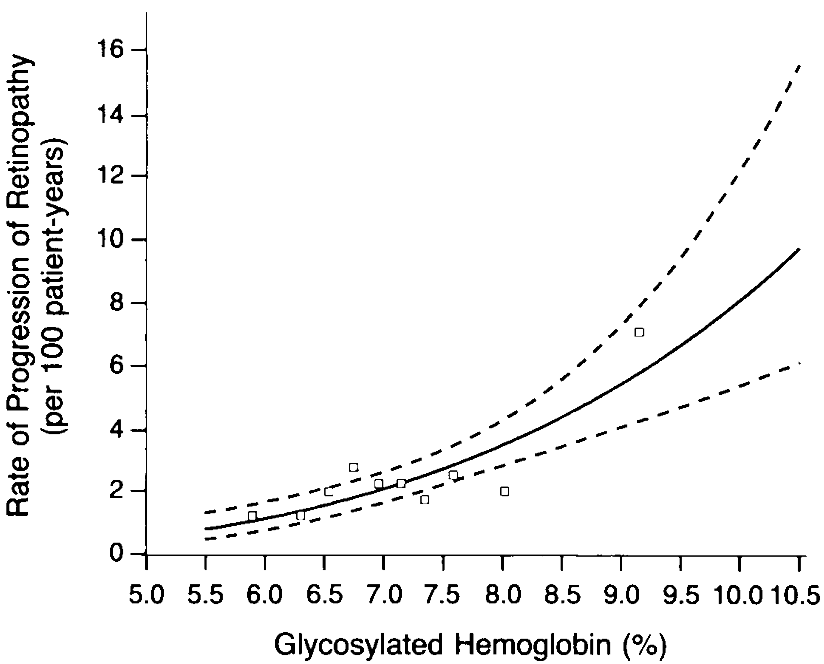


The New England
Journal of Medicine

Volume 329 | SEPTEMBER 30, 1993 | Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*



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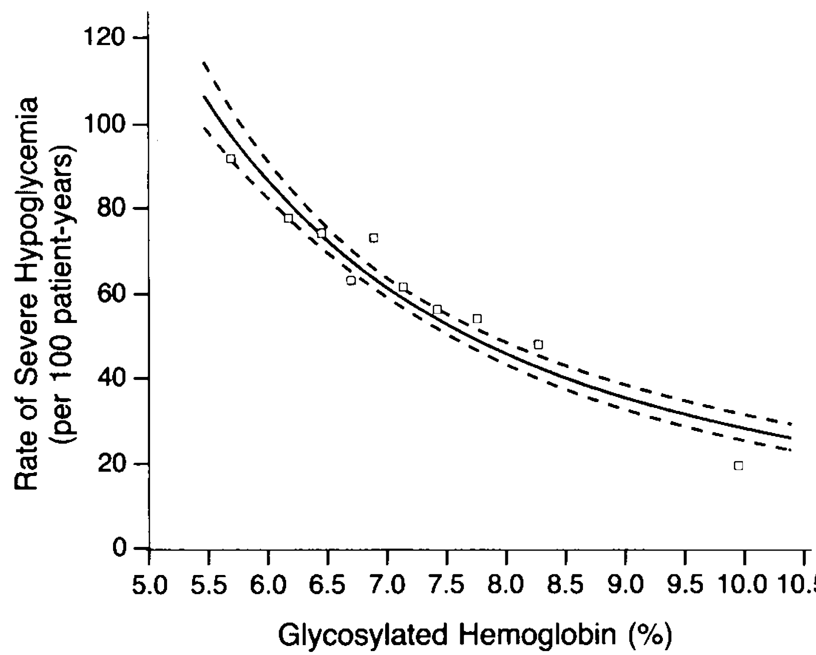

B


DISETRONIC
S
P
U/h
B
H-TRONplus V100


IDAHO
Susan Hessing
Photography

Insulin Pumps back in the UK

Risks with continuous subcutaneous insulin infusion can be serious

EDITOR—The editorial by Pickup and Keen about continuous subcutaneous insulin infusion is worrying in advocating this treatment, albeit for a comparatively small proportion of the diabetic population in Britain.[1] Pickup and Keen do not highlight adequately the serious risks associated with it for doctors considering introducing this treatment to their patients.

Pickup and Keen acknowledge high rates of ketoacidosis with subcutaneous insulin infusion but attribute it to lack of experience, unsuitable pump insulin, and the less reliable devices previously available. They identify that rates of ketoacidosis fell as physicians' experience with the treatment increased,[2] but they do not acknowledge that a new generation of diabetes physicians considering using subcutaneous insulin infusion will be unfamiliar with it, as will their support staff and patients.

Letters

Pickup and Keen emphasise the need to limit the availability of subcutaneous insulin infusion for use from specialist centres—although financial costs may not be comparatively high, the treatment is expensive in patient and professional time to ensure safety. Pickup and Keen do not define specialist centres—I suggest that physicians should avoid being coerced into dabbling in pump therapy by patients or pressure groups.

G Knight *consultant physician*
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1 Pickup J, Keen H. Continuous subcutaneous insulin infusion in type 1 diabetes. *BMJ* 2001;322:1262-3. (26 May.)
2 Bending JJ, Pickup JC, Keen H. Frequency of diabetic ketoacidosis and hypoglycaemic coma during treatment with continuous subcutaneous insulin infusion. *Am J Med* 1985;79:685-91.
3 Knight G, Jennings AM, Boulton AJM, Tomlinson S, Ward JD. Severe hyperkalaemia and ketoacidosis during routine treatment with an insulin pump. *BMJ* 1985;291:371-2.

	Disetronic H-tron plus	Animas Ping	Medtronic Paradigm Veo	Roche Accu-Chek Combo	Dana Diabecare R
Pump features					
Basal increment (range)	0.1 U (0.1-10)	0.025 U (0.025-25)	0.025 U (0.025-35)	0.01 U (0.05-50)	0.01 U
Basal change	60 minutes	30 minutes	30 minutes	60 minutes	60 minutes
Basal profiles	1	4	3	5	4
Bolus types	Standard	Standard, extended, dual	Standard, extended, dual	Standard, extended, dual	Standard, extended, dual
Bolus increments	0.5 U	0.1 U (max 35)	0.1 U (max 75)	0.1 U (max 50)	0.05 U
Calculator	No	Yes	Yes	Yes	Yes
Sensor +	No	Imminent	Yes	No	No

DM

DOI: 10.1111/j.1464-5491.2005.01738.x

Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial

R. P. L. M. Hoogma, P. J. Hammond*, R. Gomis†, D. Kerr‡, D. Bruttomesso§, K. P. Bouter¶, K. J. Wiefels**, H. de la Calle††, D. H. Schweitzer‡‡, M. Pfohl§§, E. Torlone¶¶, L. G. Krinelke*** and G. B. Bolli¶¶, on behalf of the 5-Nations Study Group[1]

Five Nations Study

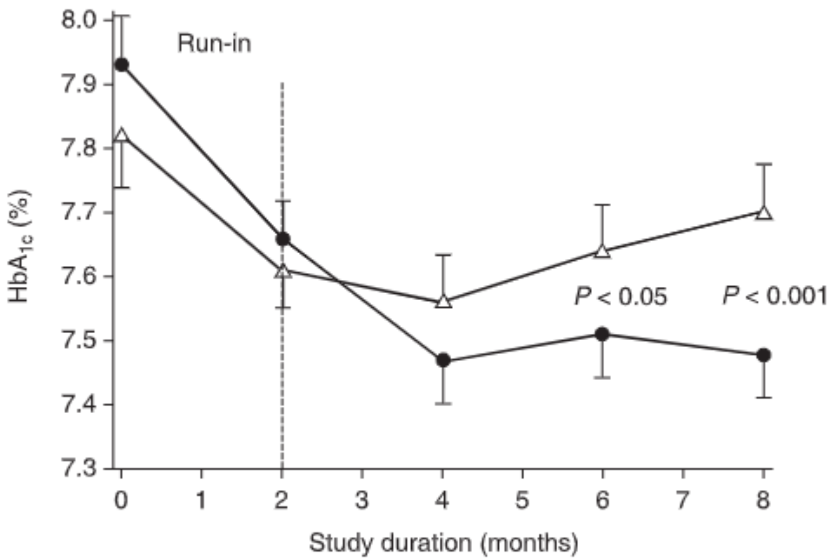


Figure 1 HbA_{1c} values (mean ± SEM) by type of treatment. The data represent both treatment periods in the crossover study design. (△) MDI, (●) CSII.

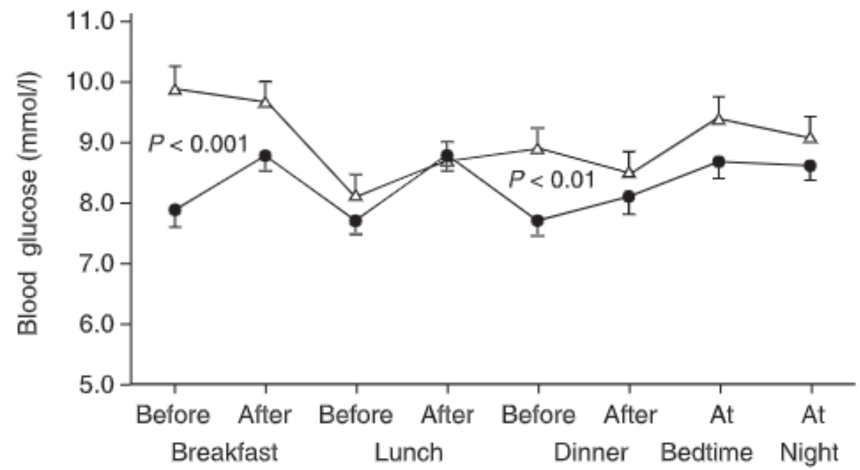


Figure 2 Blood glucose profiles (mean ± SEM) with the MDI (△) and CSII (●) regimens. The data represent both treatment periods in the crossover study design.

Hoogma et al, *Diabetic Medicine* 2006;23:141-148

National Institute for Health and Clinical Excellence

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (review of technology appraisal guidance 57)

Implementing NICE guidance

Evidence-based Clinical Practice

NICE technology appraisal guidance TA151

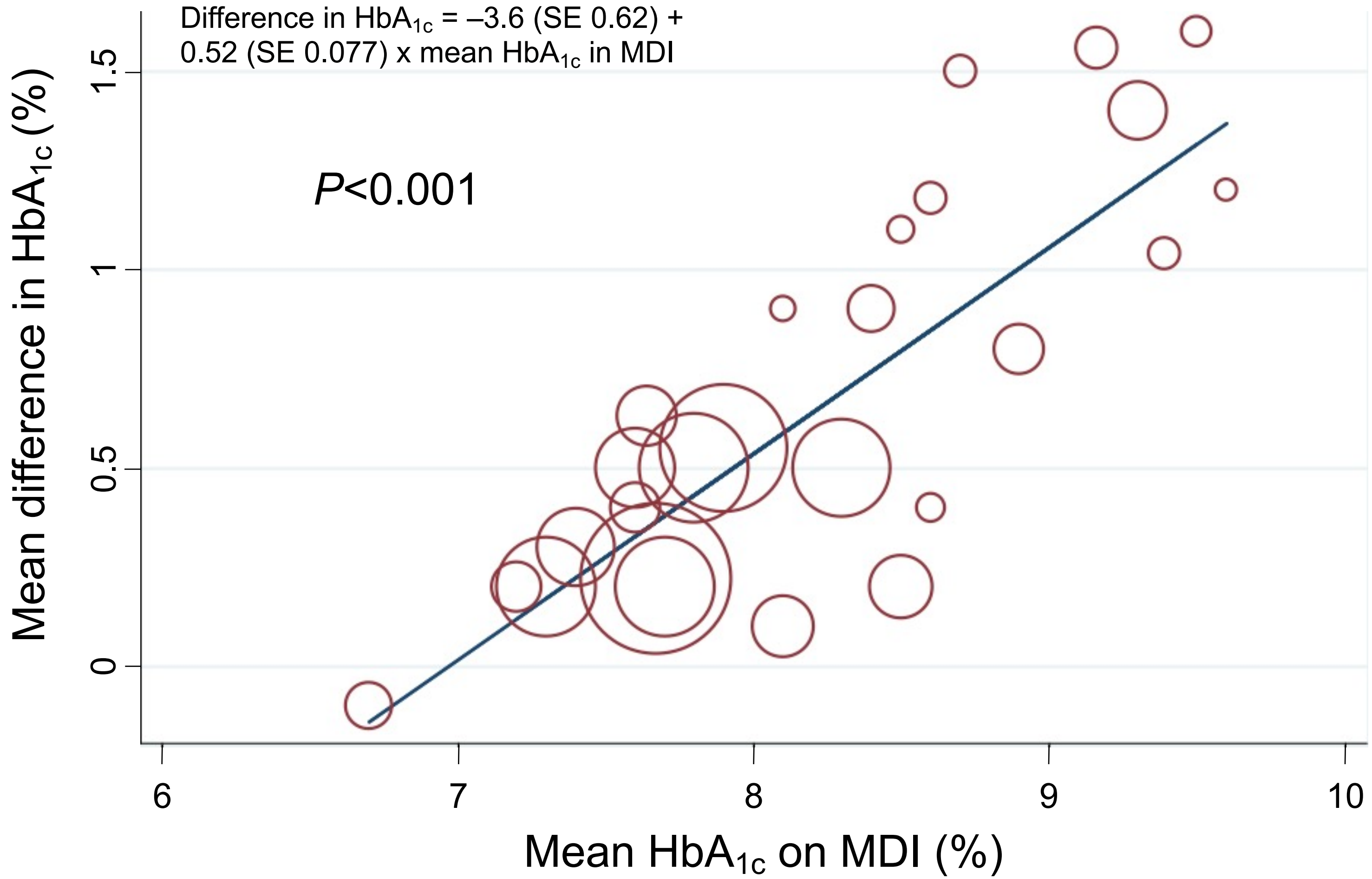
NICE TA 151

- CSII for adults and children (≥12 years) with T1DM after optimised MDI if:
  - Occurrence of “disabling hypoglycaemia”

    OR
  - HbA_{1c} persistently ≥8.5% (≥69 mmol/mol)
- CSII is recommended as a treatment option for children (<12 years) where MDI is considered inappropriate.
- Initiation should be by a trained specialist team.
- CSII therapy is not recommended for the treatment of people with type 2 diabetes mellitus.

NICE. *CSII for the treatment of diabetes mellitus. TA 151*.
London: NICE; 2008 (www.nice.org.uk)

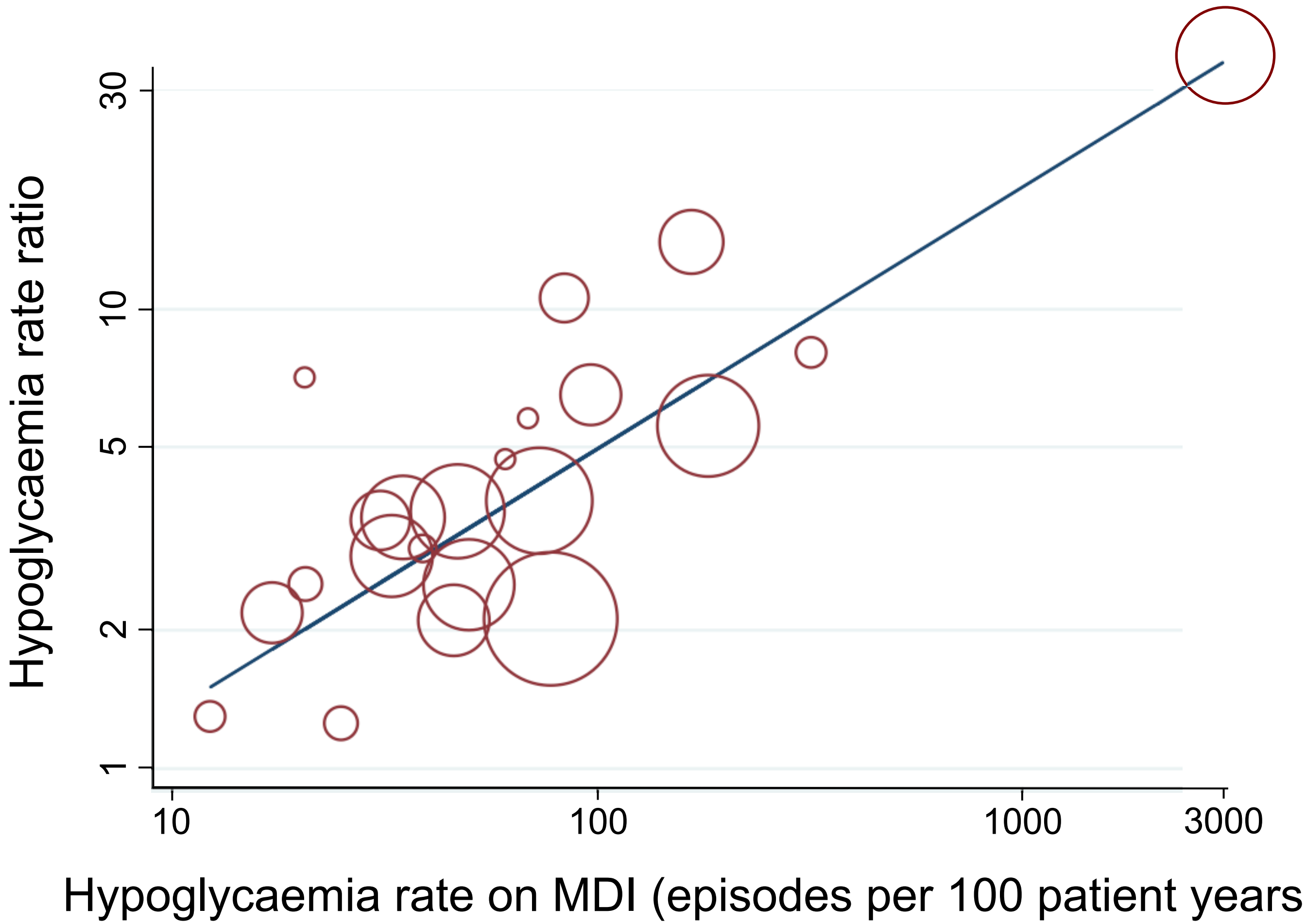
Meta-analysis CSII vs MDI: HbA_{1c}



CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections

Pickup JC, Sutton AJ (2008) *Diabetic Medicine* **25**: 765–74

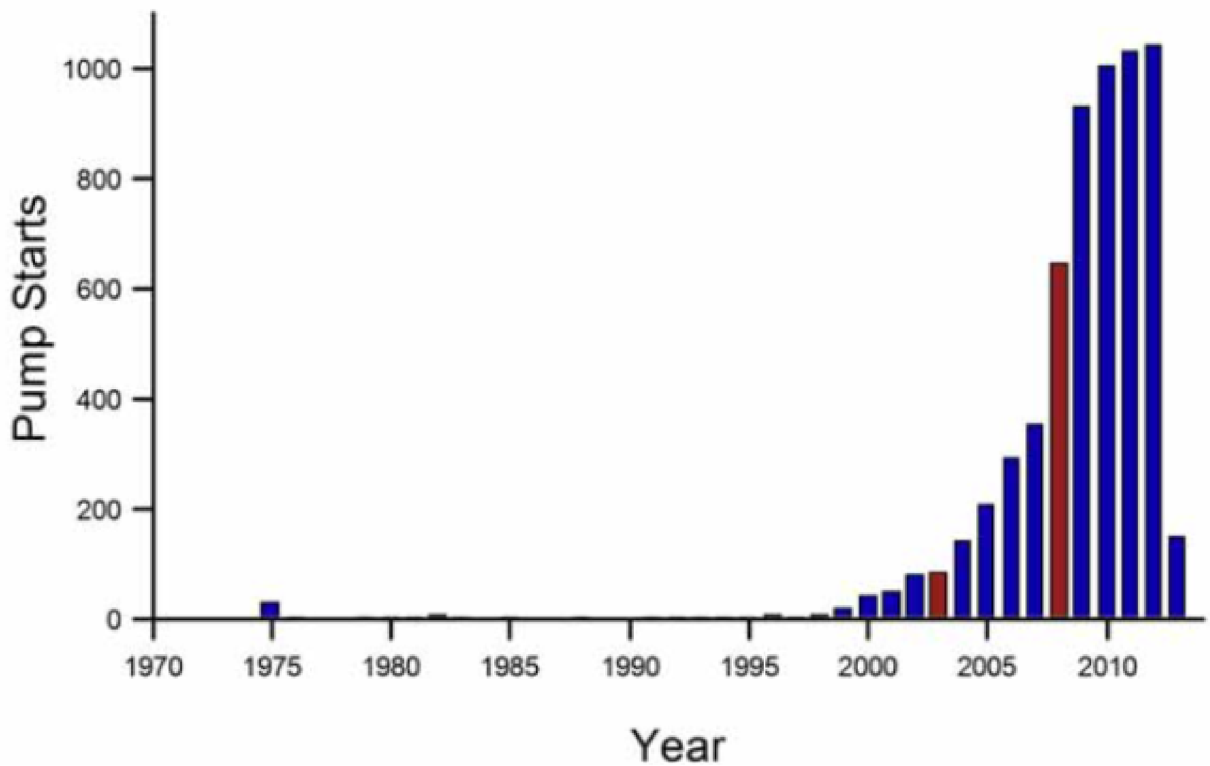
Hypoglycaemia: CSII vs MDI



CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections

Pickup JC, Sutton AJ (2008) *Diabetic Medicine* **25**: 765–74

Year starting pump therapy



How to get the best HbA1c?

HbA_{1c} group range (%, mmol/mol)	5–7.4, 31–57	7.5–8.9, 58–74	9.0–14, 75–129
Number (%) of subjects	38 (25.3)	67 (44.7)	45 (30.0)
HbA_{1c} (%, mmol/mol)	6.89*, 51.9*	8.15*, 65.5*	10.06, 86.6*
Age (years)	13.29	13.37	14.4
Number of boluses/day	7.26*	6.42*	4.19
Boluses delivered via bolus calculator	4.33†	4.13†	3.03
Total insulin (U/kg/day)	0.79	0.81	0.82
Per cent basal (of total daily insulin)	48%†	49%†	56%
Per cent bolus (of total daily insulin)	53%†	51%†	44%
Time of temporary basal use/day (min)	71.3	58.13	32.52
Time suspended/day (min)	47.74	51.88	44.05
Carbohydrates entered/day (gm)	202*	198†	148
Duration of diabetes (years)	6.42	7.23	7.67
Number of blood glucose checks/day	4.06*	3.15†	2.16

Statistical comparisons were performed using ANOVA.
Results represent the mean for each of the three groups.
*$P < 0.001$ compared with HbA_{1c} 9.0–14%, 75–129 mmol/mol.
†$P < 0.05$ compared with HbA_{1c} 9.0–14%, 75–129 mmol/mol.

Wilkinson J et al. Diabetic Med 2010;27:1174-7

How to get improvement in HbA1c?

Group	HbA_{1c} increase†		HbA_{1c} decrease‡	
	Initial	Final	Initial	Final
HbA_{1c} (%, mmol/mol)	7.6, 60	8.4, 68	9.3, 78	8.4, 68
Number of boluses/day	6.3	6.2	5.7	6.0
Total insulin/day (U/kg/day)	38.2	37.6	41.3	45.4*
Time of temporary basal use/day (min)	49.6	22.4	32.4	72.8
Per cent basal insulin/day (%)	51	52	50	48
Per cent bolus insulin/day (%)	49	48	50	52
Time of pump suspension/day (min)	36.1	39.8	51.8	55.4
Number of blood glucose checks/day	3.4	3.4	3.0	2.7
Carbohydrate intake entered/day (g)	185.3	170.1	197.0	212.1

Statistical analysis were carried out using the paired *t*-test.
$^*P = 0.02$ (in comparison with initial value).
†Includes the 24 subjects who had an increase in HbA_{1c} > 0.5%, 6 mmol/mol.
‡Includes the 24 subjects who had a decrease in HbA_{1c} > 0.5%, 6 mmol/mol.

Wilkinson J et al. Diabetic Med 2010;27:1174-7

Bolus frequency and control

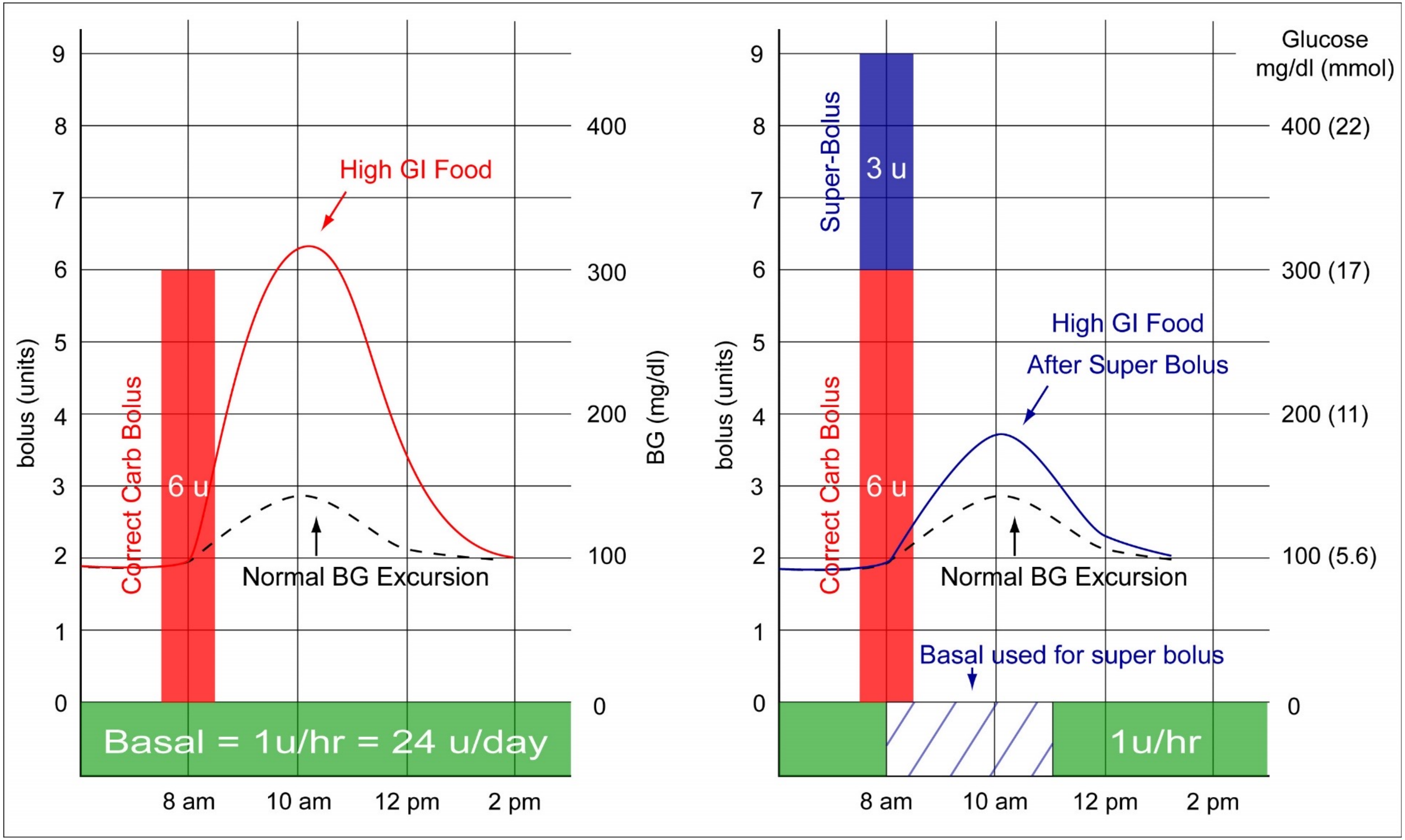
Table 2—*Parameters related to glycemic control*

	Experimental group			Control group		
	Baseline	3 months	6 months	Baseline	3 months	6 months
A1C (%)	9.32 ± 1.12	8.86 ± 1.10*	9.41 ± 1.16†	8.93 ± 1.04	8.67 ± 1.17	8.78 ± 1.17†
Number of missed meal boluses per week (7 days)	4.9 ± 3.7	2.5 ± 2.5*	3.3 ± 3.6*	4.3 ± 2.7	4.2 ± 3.9	3.6 ± 3.5
SMBG (% in range)	31.8 ± 15.1	35.4 ± 11.3	30.4 ± 10.6	31.0 ± 11.1	34.4 ± 11.6	34.0 ± 11.7
Mean difference in physician and subject estimates of missed boluses per week	1.29 ± 3.44	0.348 ± 4.57	1.05 ± 4.08*	0.667 ± 2.51	1.79 ± 3.24	−0.167 ± 3.99*

Data are means ± SD. *$P < 0.05$ for within-group difference from baseline. †$P < 0.05$ for preplanned contrast at 6 months.

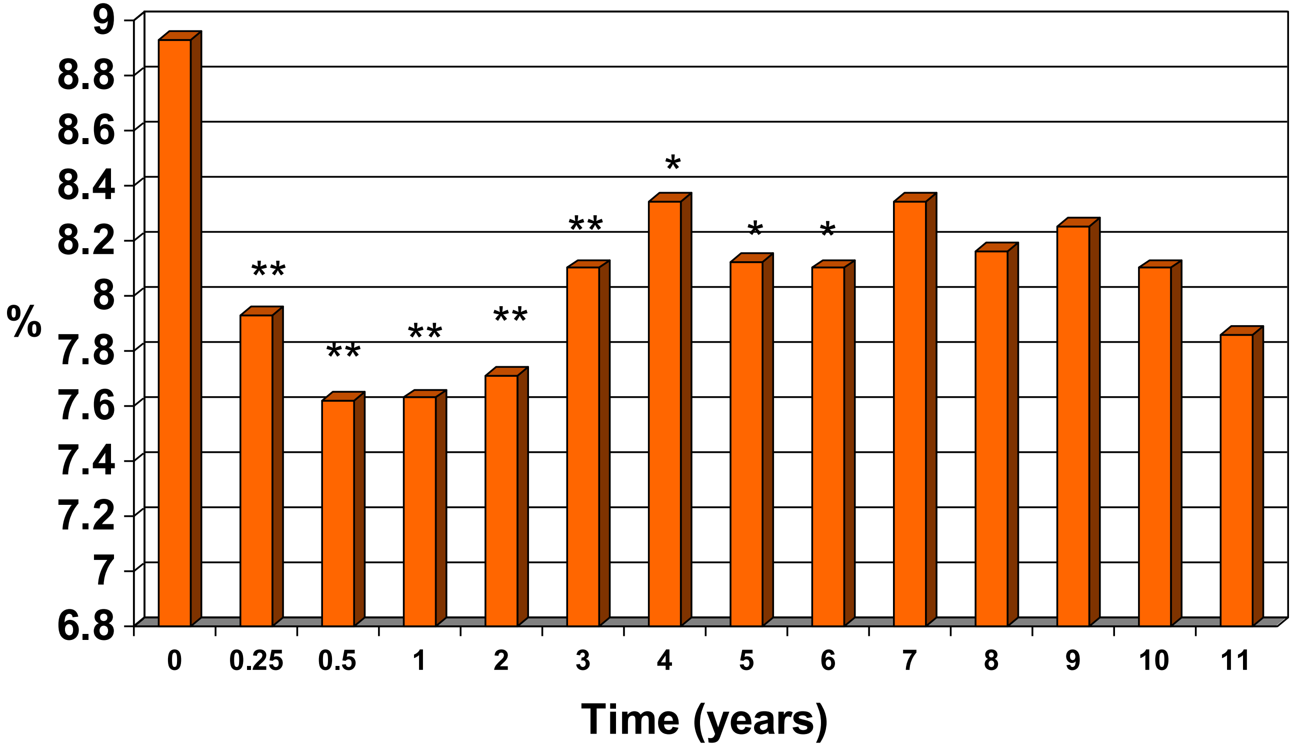
Chase et al, *Diabetes Care* 2006;29:1012-1015

"Super Bolus"



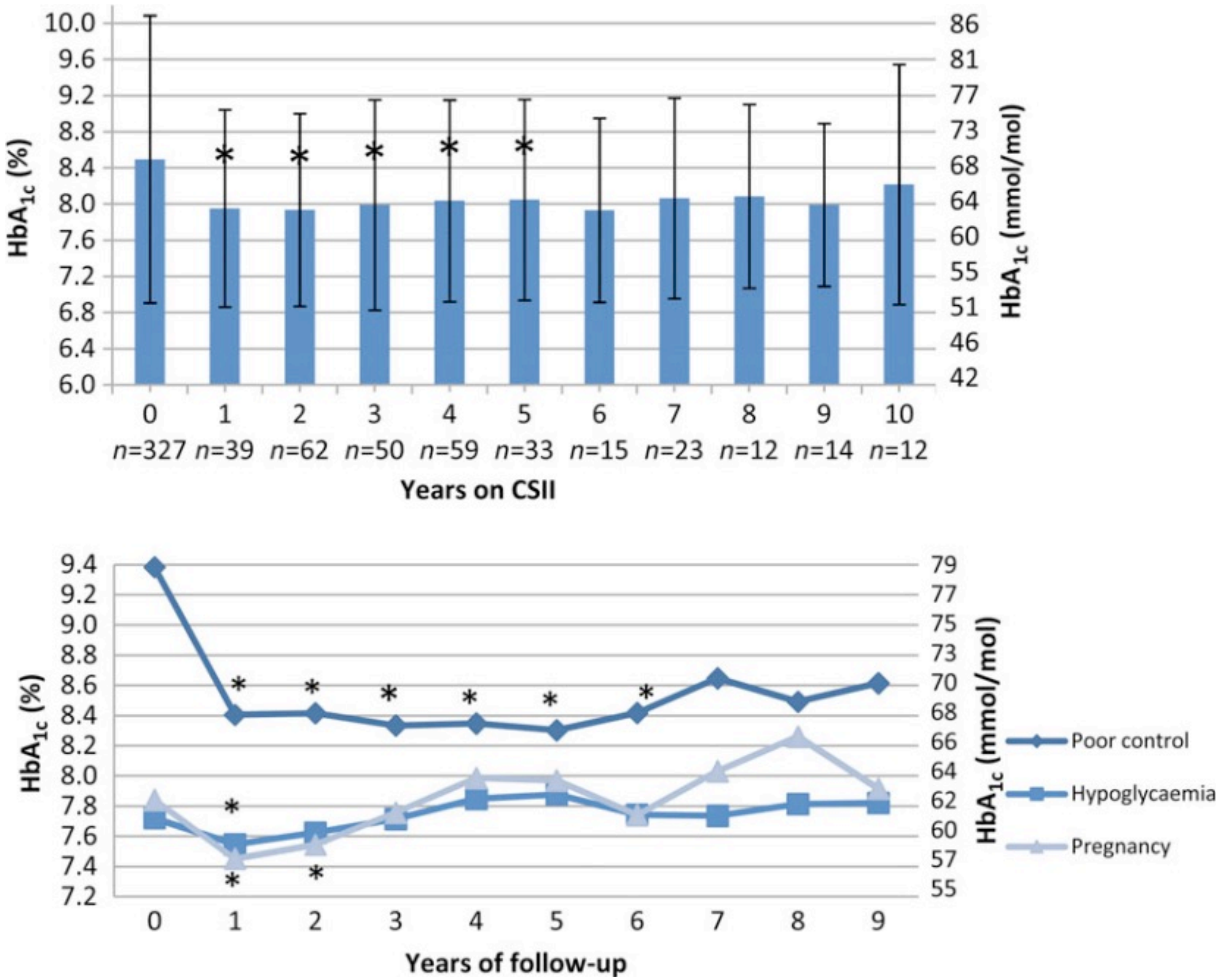
Walsh J & Roberts R, *Pumping Insulin* 4th Ed

Harrogate experience – HbA1c



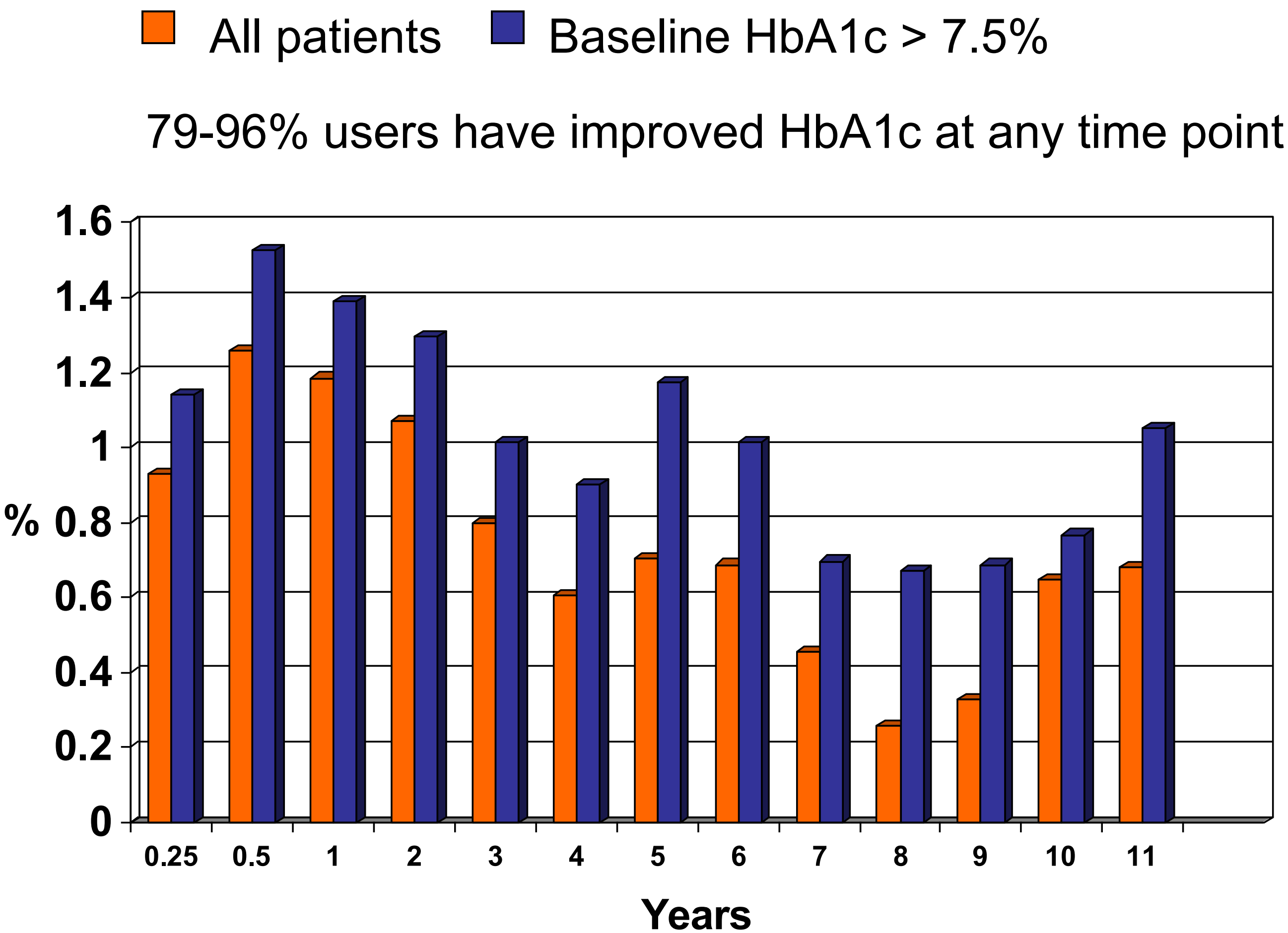
** p<0.005,
*p<0.05

CSII: sustained improvement

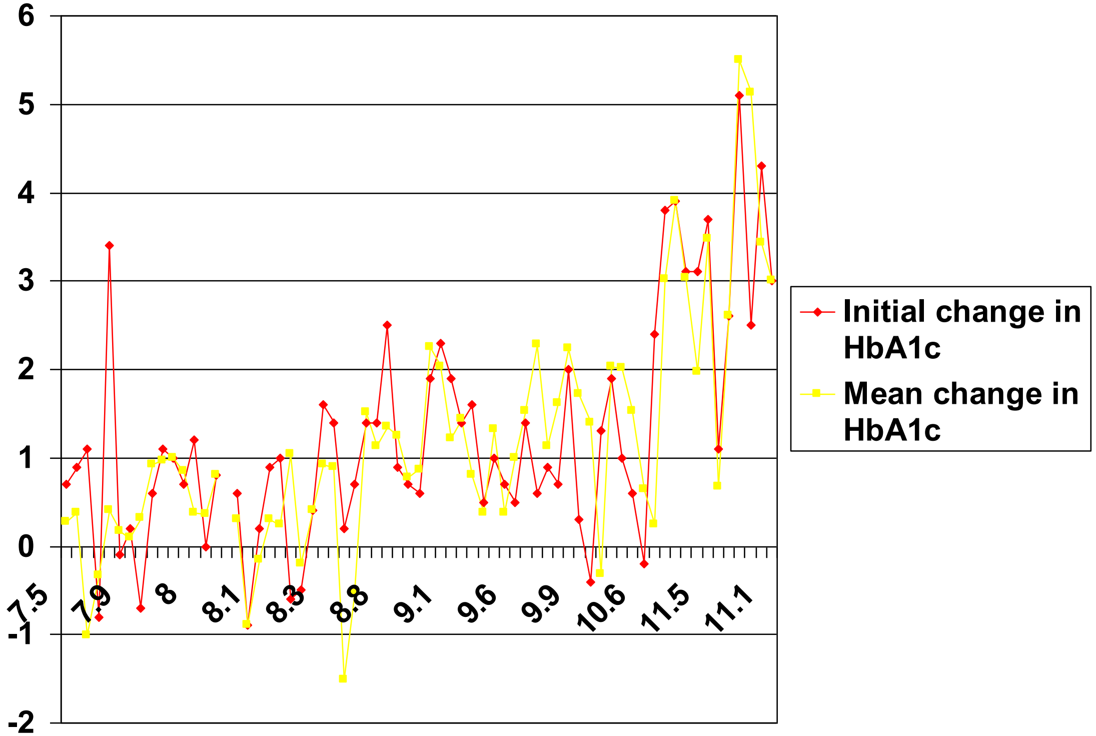


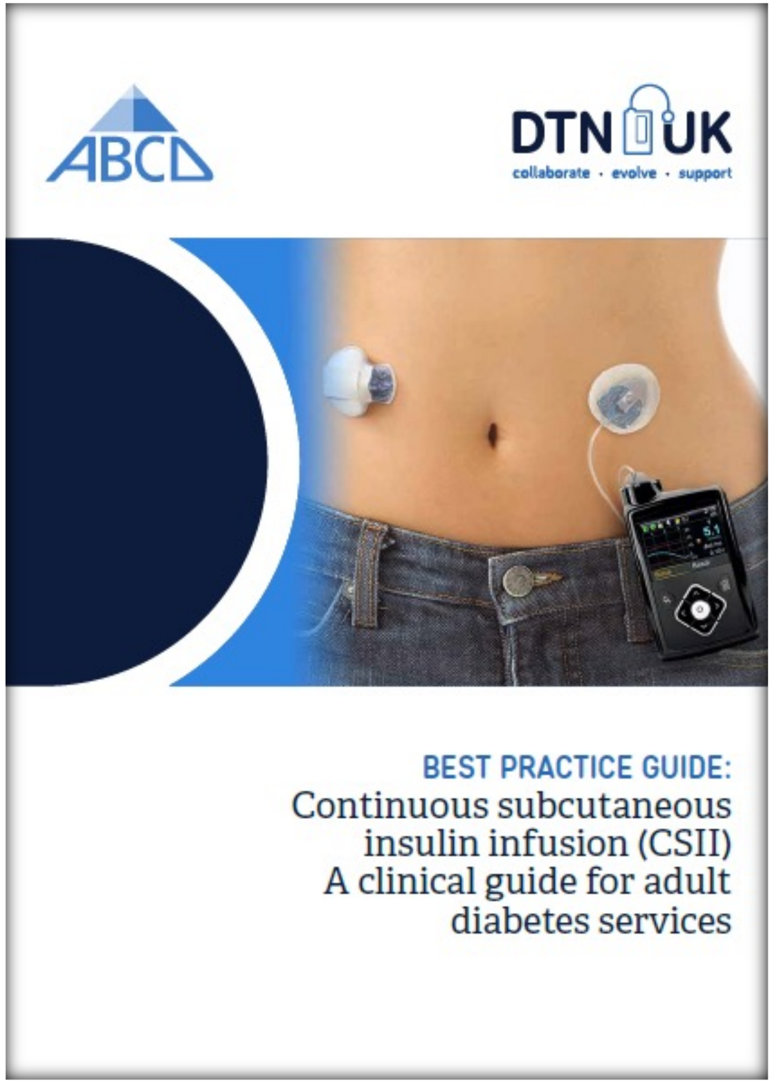
Beato-Vibora P et al. *Diabet Med.* 2015;Online first

Harrogate – improved HbA1c



What about the individual?




ABCD

DTN UK

collaborate · evolve · support

BEST PRACTICE GUIDE:

Continuous subcutaneous insulin infusion (CSII)
A clinical guide for adult diabetes services

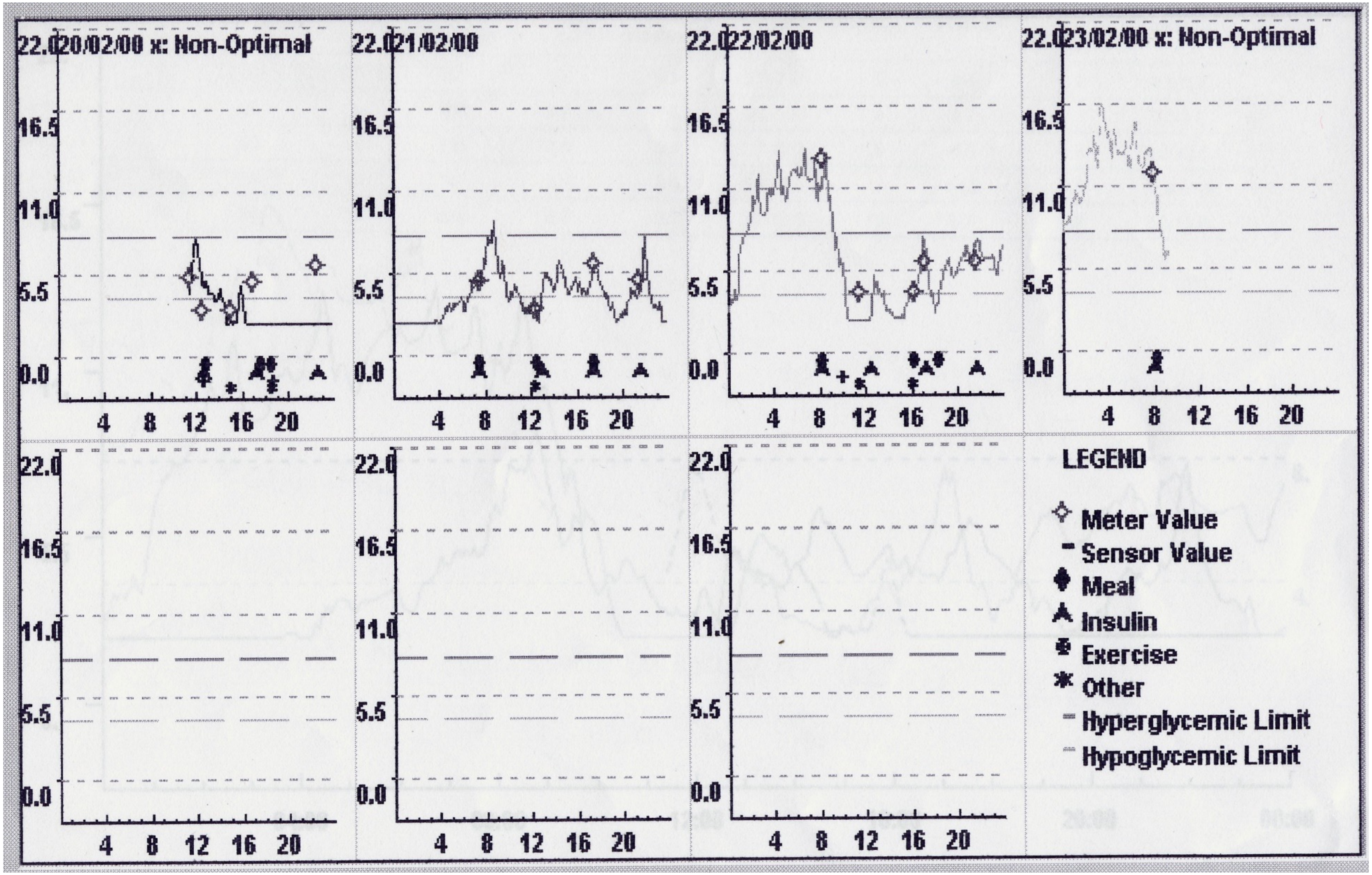
DTN UK

	Omnipod patch pump	Animas Vibe*	Medtronic 640G*	Roche Insight	CellNovo patch pump
Pump features					
Weight	25 g	105 g	96 g	122 g	30 g
Basal increment	0.05 U (0.05-30)	0.025 U (0.025-25)	0.025 U (0.025-35)	0.01 U (0.02-25)	0.05 U (0.05-30)
Basal rate/d	24 @ 30 min	12	48	24	24
Basal profiles	7	4	8	5	20
Basal deliver	0.05 u pulse	3 min	10m (0.2-60)	3 min	?0.05u pulse
Extended bolus	30 min steps up to 8 h	30 min steps up to 12 h	30 min steps up to 8 h	15 min steps up to 24 h	30 min steps up to 8 h
Bolus increments	0.05 U (max 30)	0.05 U (max 35)	0.1 U (max 75)	0.05 U (max 25)	0.05 U (max 30)
Occlusion alarm	?	1.5-3h	2-3.8h	< 2h	Max 16h
Insulin vol	200 u	200 u	180 u	160 u	170 u

*Sensor augmentation option

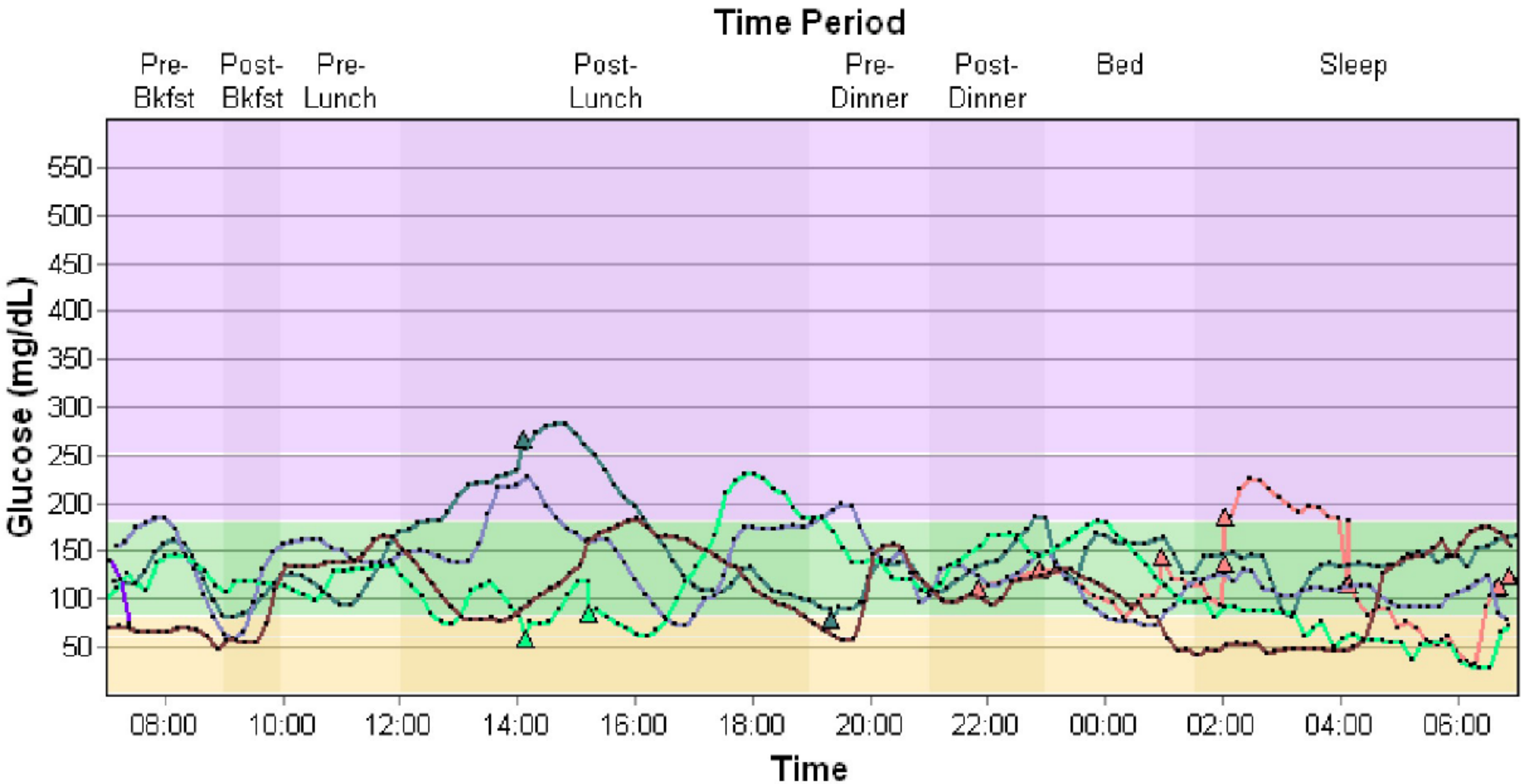
CGMS

Minimed – CGMS

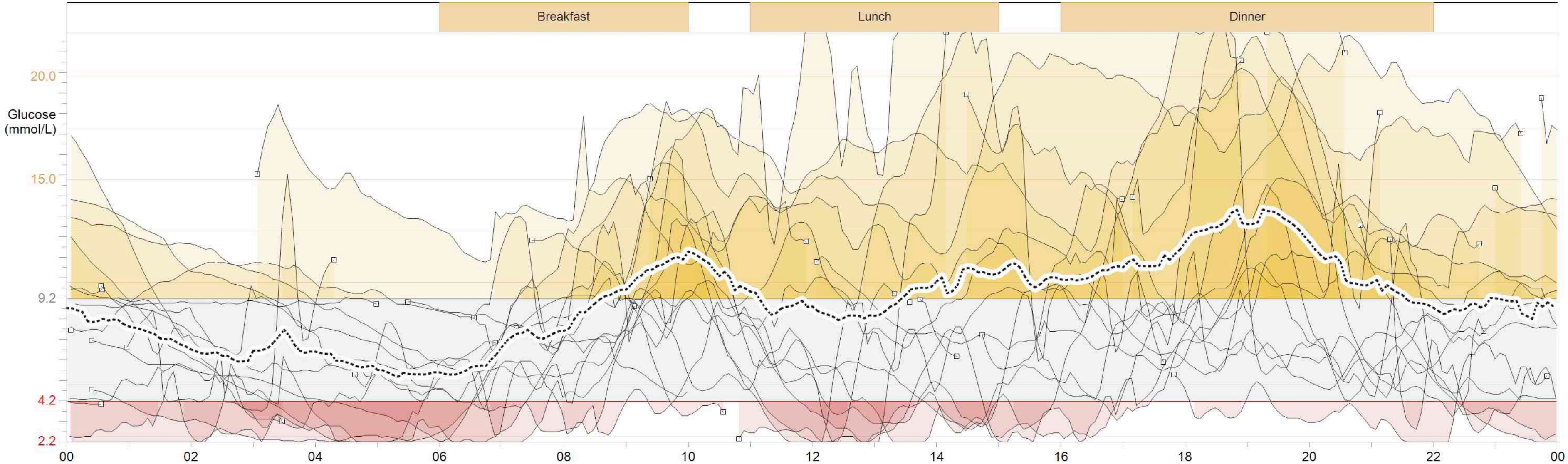


	Guardian RT	640G Smart guard	DexCom G4 Platinum	Freestyle Navigator II
				
Sensor life	6 days		7 days	5 days
Alarms	Multiple		1 high, low and trend	High, low and projected
Predictive	Yes		No	Yes
Trends	Yes		Yes	Yes
Rate change	Yes		No	Yes
Calibration	12 hrly		2h, then 12 hrly	1, 2, 10, 24, 72 h
MARD	13%		12.6%	11.8%

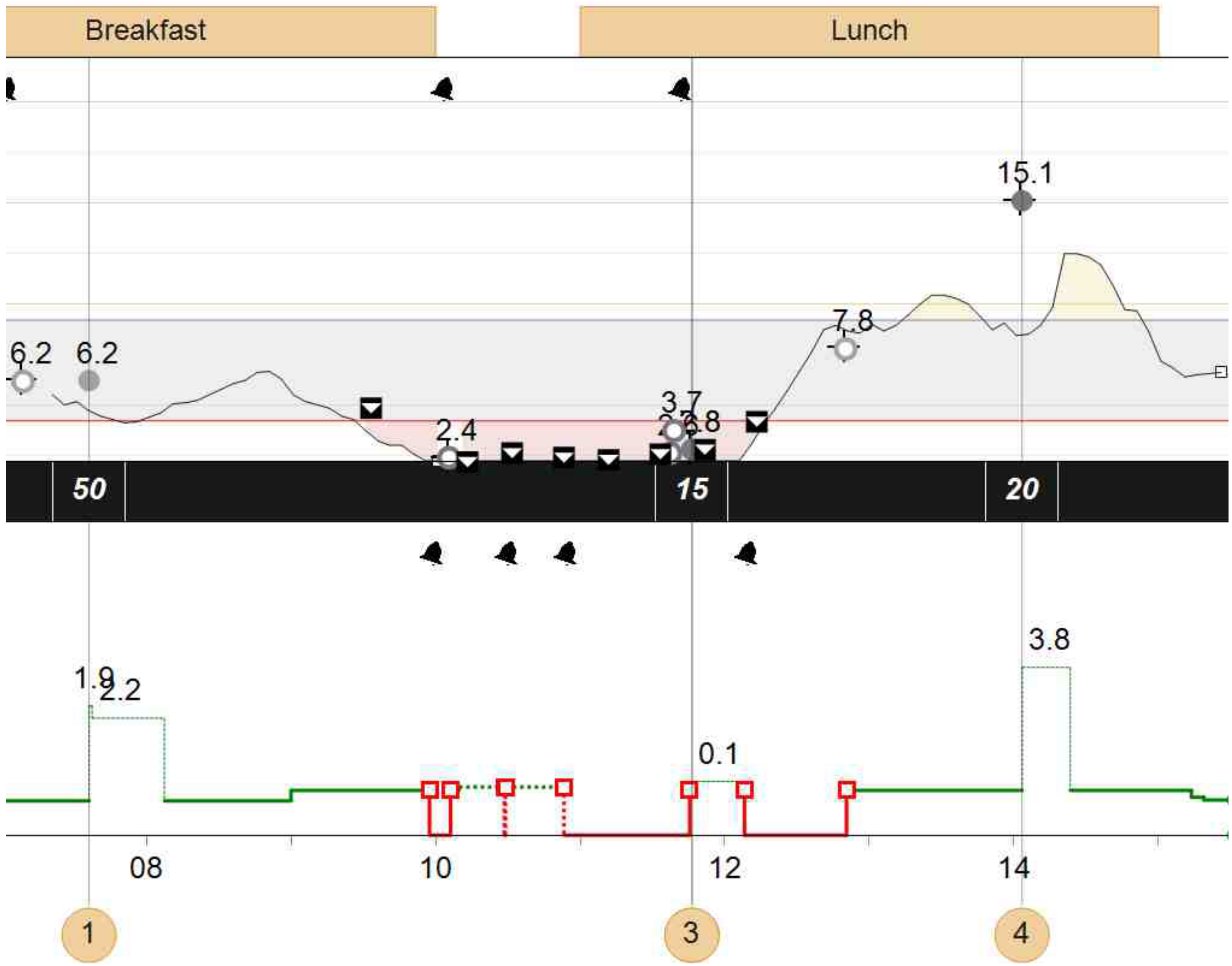
HW 32F Pregnant - Alarms



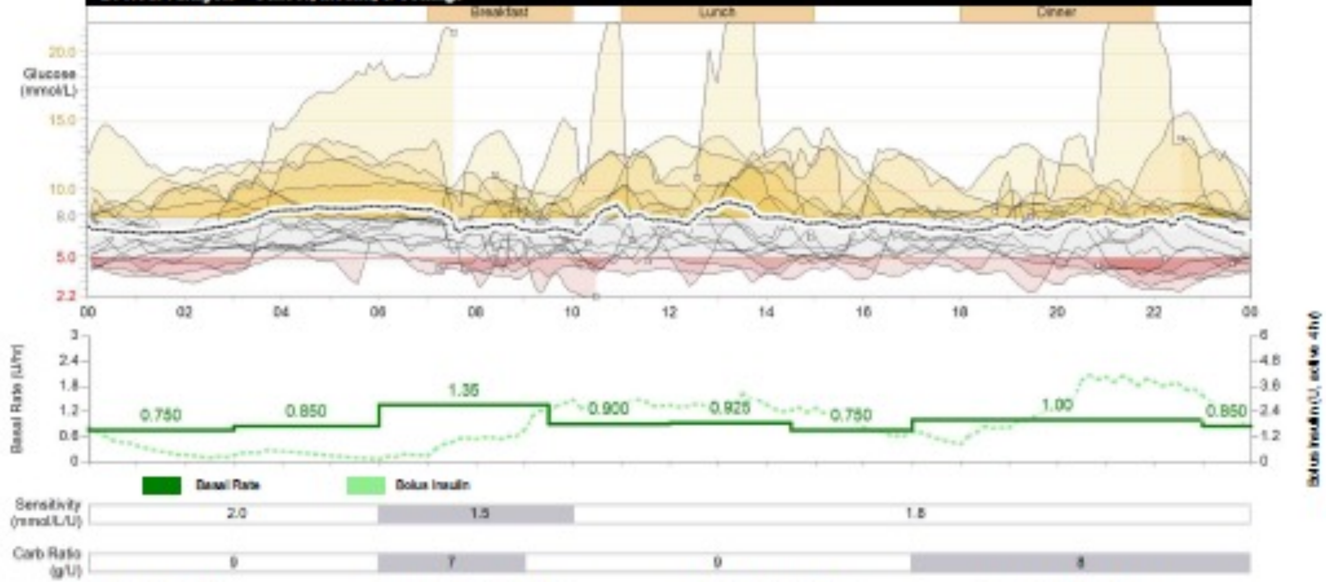
CR 40F Hypoglycaemia unawareness



CR 40F Man vs machine



24-Hour Analysis – Sensor, Insulin, & Settings



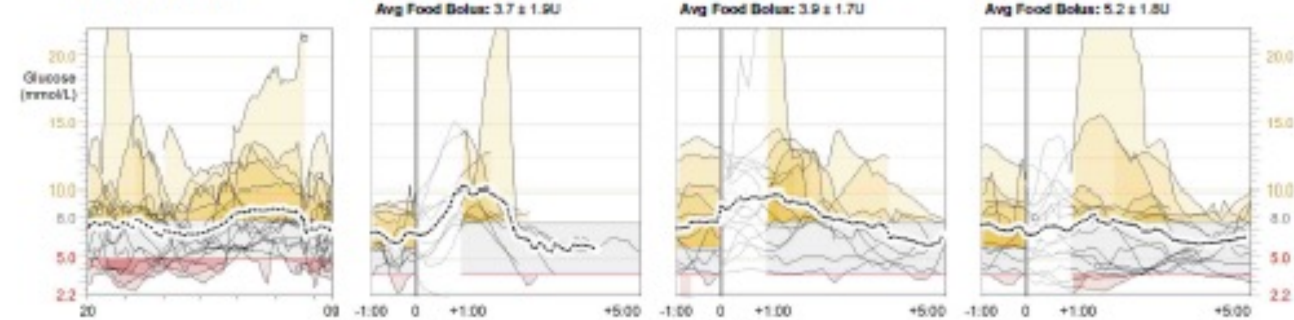
Bedtime to Wake-up

Bedtime: 20:00 - 00:00
Wake-up: 05:00 - 09:00

Breakfast: 07:00 - 10:00 (12)
Pre-meal SG Avg: 6.7 ± 1.8mmol/L
Post-meal SG Avg: 8.2 ± 2.8mmol/L
Avg Carbs: 31 ± 17g
Avg Food Bolus: 3.7 ± 1.9U

Lunch: 11:00 - 15:00 (19)
Pre-meal SG Avg: 7.4 ± 3.5mmol/L
Post-meal SG Avg: 9.3 ± 2.8mmol/L
Avg Carbs: 33 ± 14g
Avg Food Bolus: 3.9 ± 1.7U

Dinner: 18:00 - 22:00 (23)
Pre-meal SG Avg: 7.4 ± 2.5mmol/L
Post-meal SG Avg: 7.1 ± 2.5mmol/L
Avg Carbs: 42 ± 15g
Avg Food Bolus: 5.2 ± 1.8U



Statistics	
Avg BG	8.3 ± 3.3mmol/L
Estimated A1C	6.5%
BG Readings	5.5 per day
Carbs Entered	147 ± 57g per day

Hypoglycemic Patterns (1)	
	06:34-03:47 (26)
Time Period	

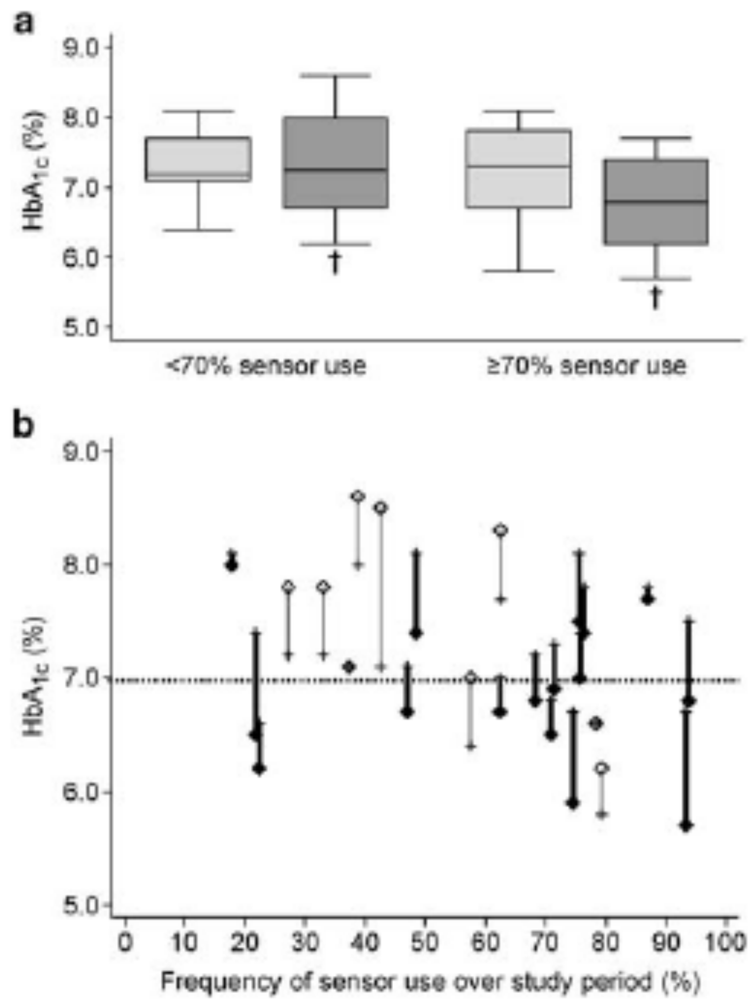
Hyperglycemic Patterns (3)	
	12:35-13:55
Time Period	03:30-07:30
	10:30-11:10

Pump Use	Per Day
Insulin TDD	43.8 ± 7.5U
Basal/Bolus Ratio	51 / 49
Manual Boluses	0.0U (0.0 boluses)
Bolus Wizard	21.3U (6.4 boluses)
Food	17.7U (4.3 boluses)
Correction	5.3U (2.4 boluses)
Override (+)	1.4U (1.1 boluses)
Override (-)	-0.1U (0.1 boluses)
Suspend Duration	20m per day
LGS Events	0.6 per day
Time	11m per day
Res./Site Change	Every 2.9 / 2.9 days

Sensor Use	
Avg SG	7.7 ± 3.0 mmol/L
Wear Duration	5d 15h per week
Low SG Alarms	2.6 per day
High SG Alarms	0.0 per day

Action Plan

Self-taught SAP vs CSII

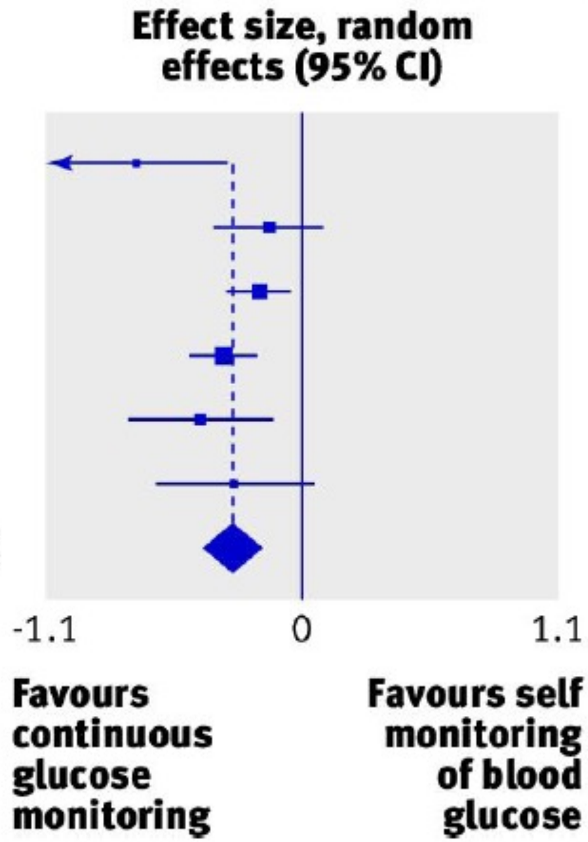


O'Connell MA et al. *Diabetologia* 2009;52:1250-1257

UC201101075EE

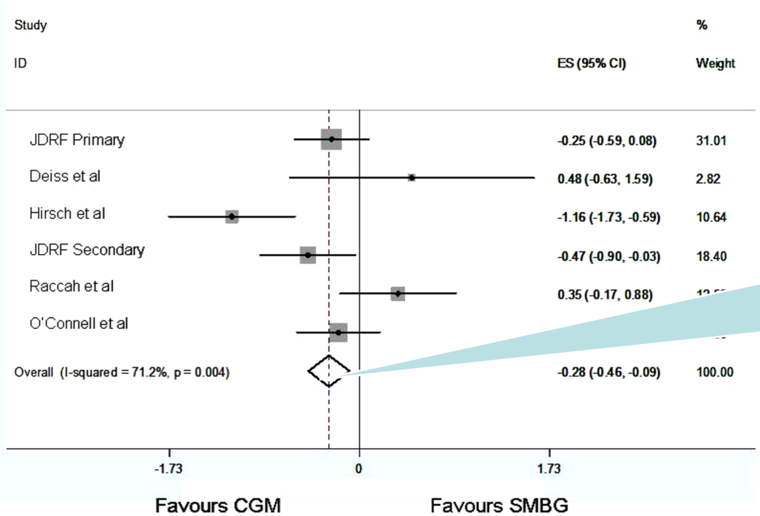
Meta-analysis: T1DM
Individual Patient Data: HbA1c

Study	Weight (%)	Effect size, random effects (95% CI)
Deiss et al 2006[3]	8.36	-0.71 (-1.10 to -0.32)
Hirsch et al 2008[4]	17.08	-0.13 (-0.37 to 0.10)
JDRF 2008 (primary)[5]	26.73	-0.19 (-0.32 to -0.05)
JDRF 2009 (secondary)[6]	25.57	-0.34 (-0.49 to -0.19)
O'Connell et al 2009[7]	11.85	-0.43 (-0.74 to -0.12)
Raccah et al 2009[8]	10.41	-0.29 (-0.63 to 0.05)
Test for overall effect: I^2=47.2%, P=0.092	100.00	-0.30 (-0.43 to -0.17)

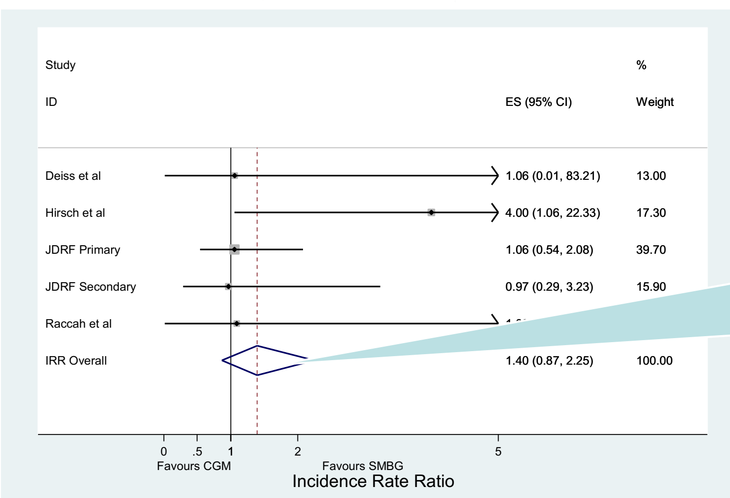


Pickup J et al. *BMJ* 2011;343:d3805

Meta-analysis: T1DM Individual Patient Data: Hypo



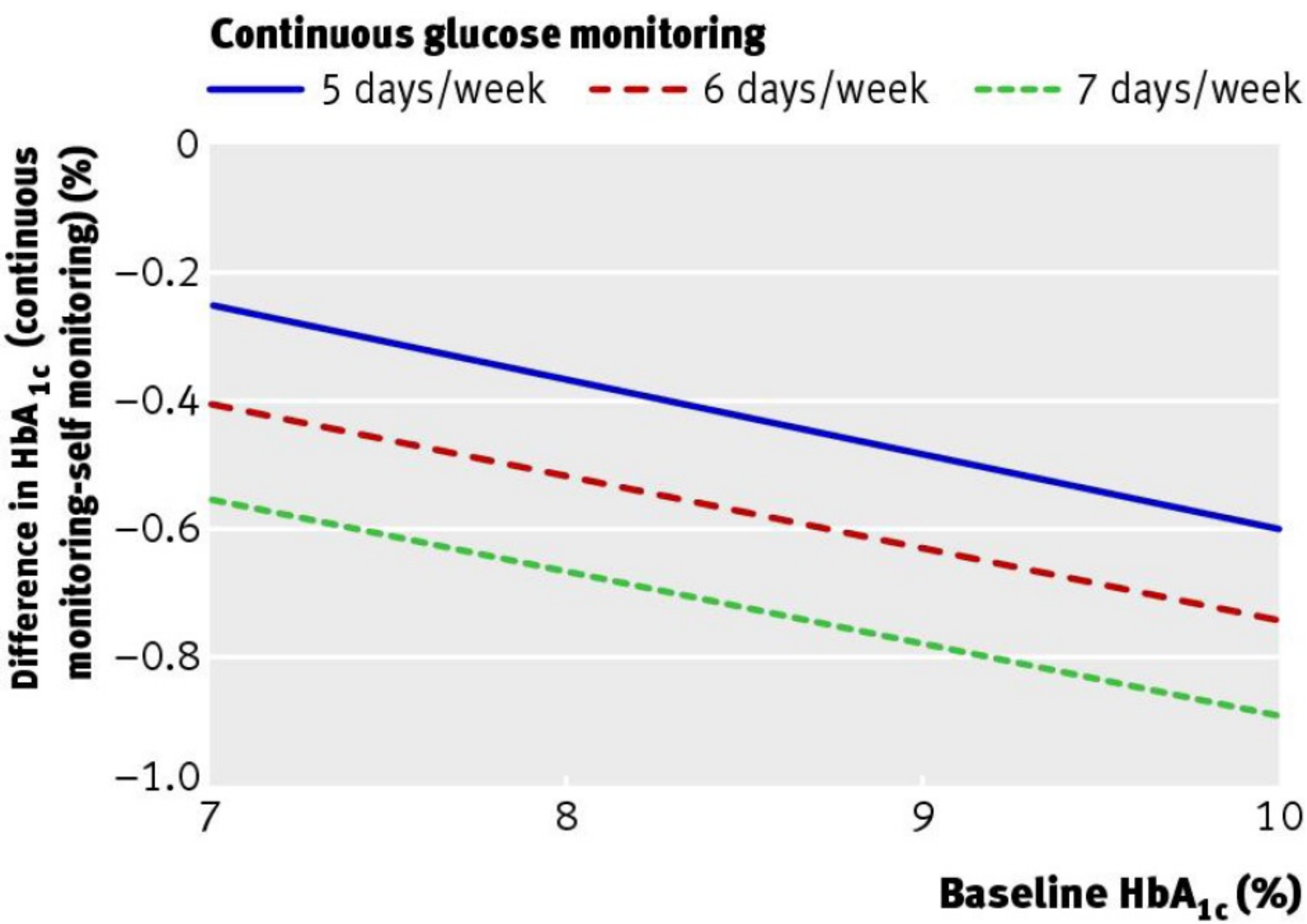
Overall mean AUC hypo difference -0.28 (-0.46, -0.09) (23% reduction in hypo exposure)



Severe hypo rate ratio CGM: SMBG ns

Pickup J et al. *BMJ* 2011;343:d3805

Meta-analysis: IPD Impact of variables



Pickup J et al. *BMJ* 2011;343:d3805

Insulin pump with low-glucose suspend

- CGM-linked insulin pump suspends for up to 2 hours if blood glucose falls below set threshold

- May help to prevent severity of hypoglycemia

NG17: CGM

- Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes.

- Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimised use of insulin therapy and conventional blood glucose monitoring:
  - More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause.
  - Complete loss of awareness of hypoglycaemia.
  - Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
  - Extreme fear of hypoglycaemia.
  - Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day (see recommendations 1.6.11 and 1.6.12). Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more

NICE clinical guideline NG17: Type 1 Diabetes in Adults

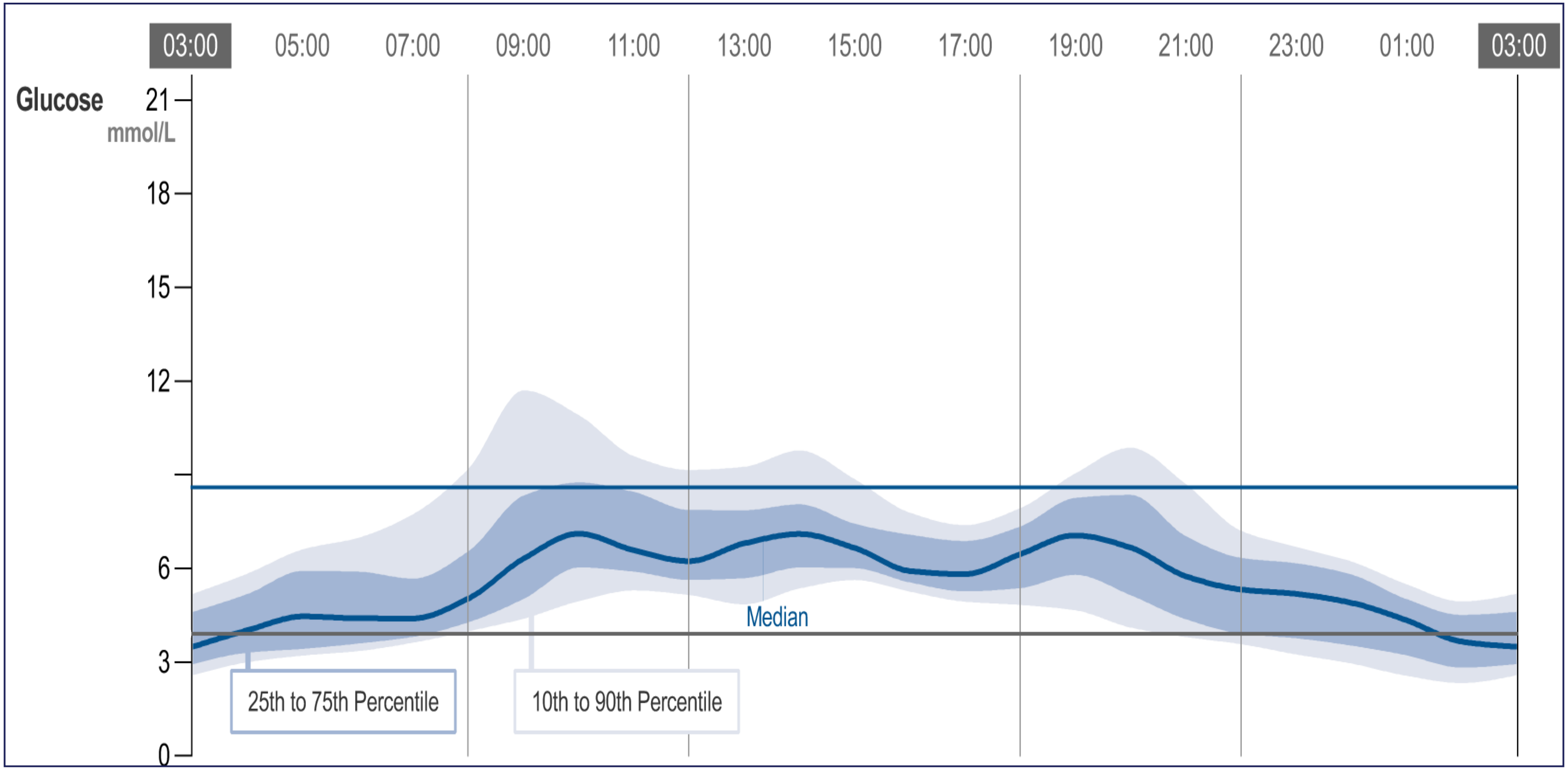
Flash glucose sensing: Freestyle Libre

The FreeStyle Libre sensor

The FreeStyle Libre software

The FreeStyle Libre reader

Ambulatory glucose profile (AGP)



Closed loop insulin delivery – “The Holy Grail”

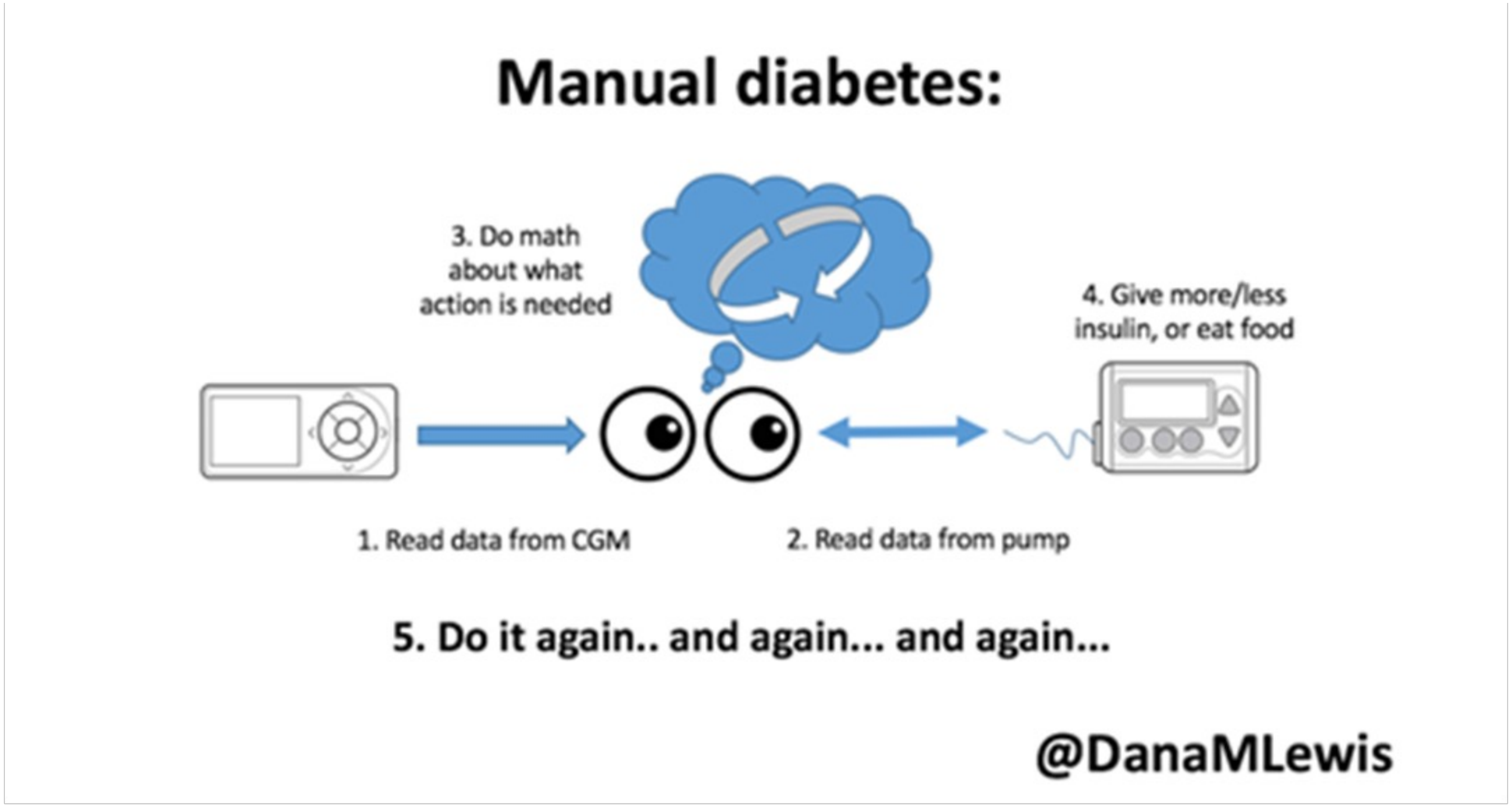


Figure taken with permission from Lewis D, Automated Insulin Delivery, ISBN 9781797763699, https://www.artificialpancreasbook. com Dana Lewis 2019

The Challenge in Type 1 Diabetes

Automated Insulin Delivery Systems

AIDS
APS –Artificial pancreas system
AID system
HCL – hybrid closed loop

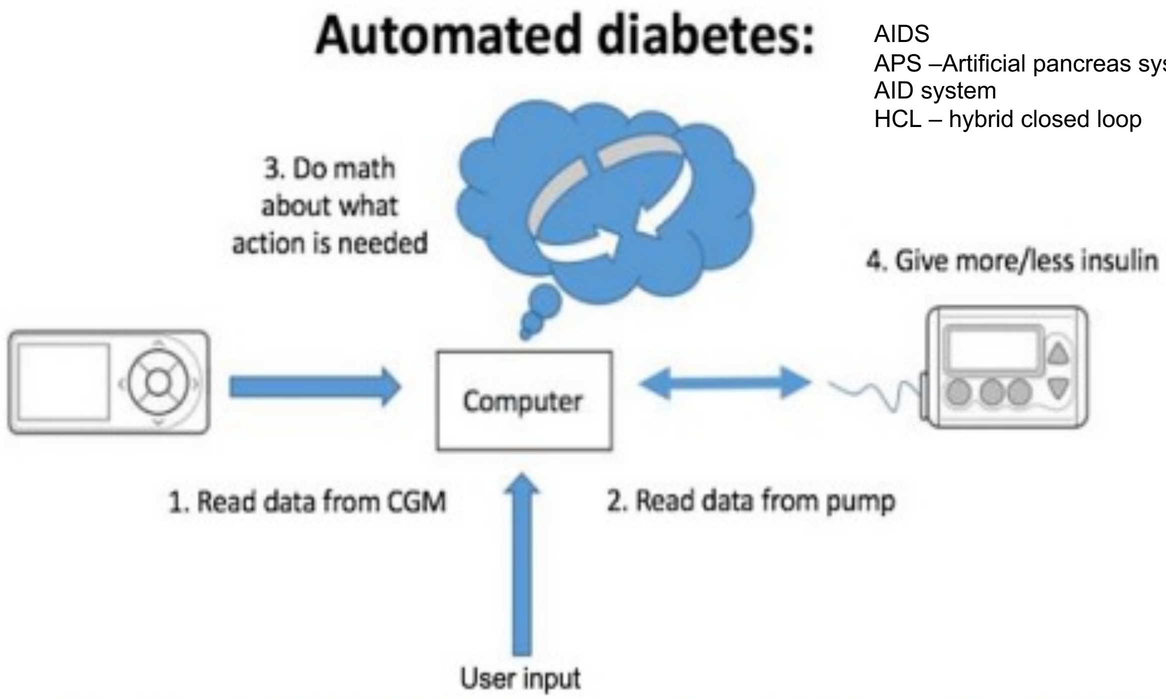
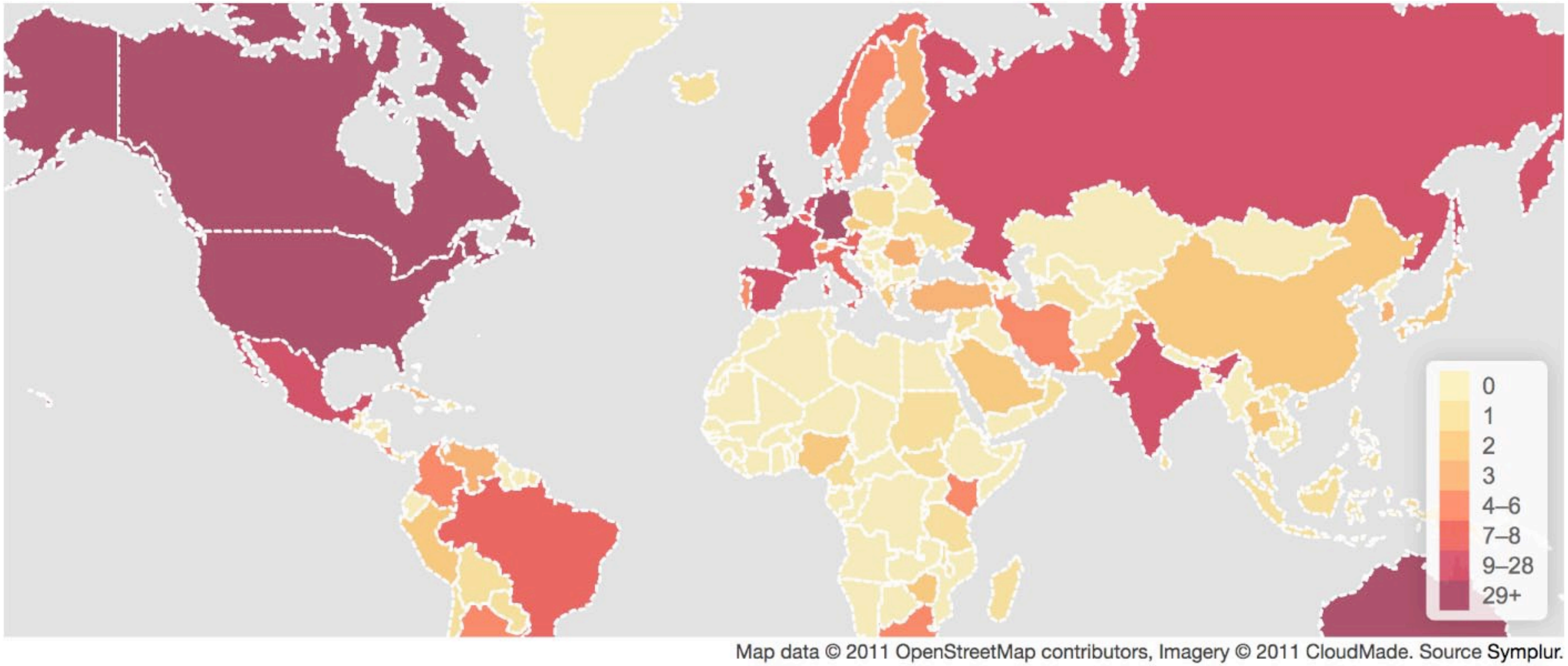


Figure adapted with permission from Lewis D, Automated Insulin Delivery, ISBN 9781797763699, https://www.artificialpancreasbook. com Dana Lewis 2019 and taken from Marshall, Holloway, Korer, Woodman, Brackenridge, Hussain, Diabetes Ther. 2019

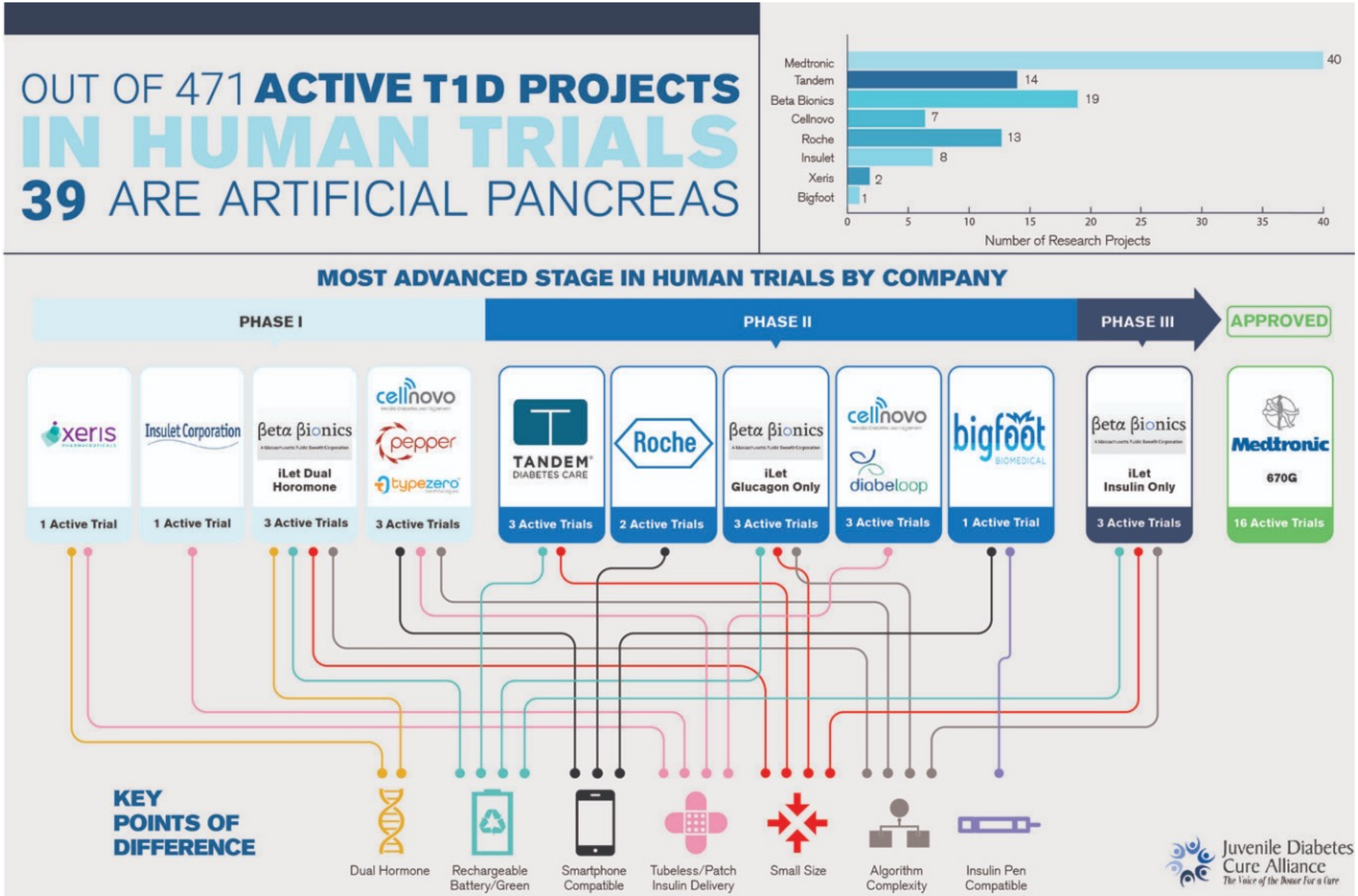
#WeAreNotWaiting

My insulin #Pump
(link: https://bionicwookiee.com/2018/10/12/my-insulin-pump/)
bionicwookiee.com/2018/10/12/my-… #AccuChek #Android #AndroidAPS #Dexcom #Diabetes #G5 #Looping #OpenAPS #OzDOC



Open APS twitter users

Litchman et al. *J Diabetes Sci Technol 2018:* ePub before print


OUT OF 471 ACTIVE T1D PROJECTS
IN HUMAN TRIALS
39 ARE ARTIFICIAL PANCREAS
Medtronic 40
Tandem 14
Beta Bionics 19
Cellnovo 7
Roche 13
Insulet 8
Xeris 2
Bigfoot 1
0 5 10 15 20 25 30 35 40
Number of Research Projects
MOST ADVANCED STAGE IN HUMAN TRIALS BY COMPANY
PHASE I
PHASE II
PHASE III
APPROVED
xeris
1 Active Trial
Insulet Corporation
1 Active Trial
Beta Bionics
iLet Dual Horomone
3 Active Trials
cellnovo
pepper
typezero
3 Active Trials
TANDEM DIABETES CARE
3 Active Trials
Roche
2 Active Trials
Beta Bionics
iLet Glucagon Only
3 Active Trials
cellnovo
diabeloop
3 Active Trials
bigfoot BIOMEDICAL
1 Active Trial
Beta Bionics
iLet Insulin Only
3 Active Trials
Medtronic
670G
16 Active Trials
KEY POINTS OF DIFFERENCE
Dual Hormone
Rechargeable Battery/Green
Smartphone Compatible
Tubeless/Patch Insulin Delivery
Small Size
Algorithm Complexity
Insulin Pen Compatible
Juvenile Diabetes Cure Alliance
The Voice of the Donor For a Cure

DTN UK

Hybrid Closed Loop Systems

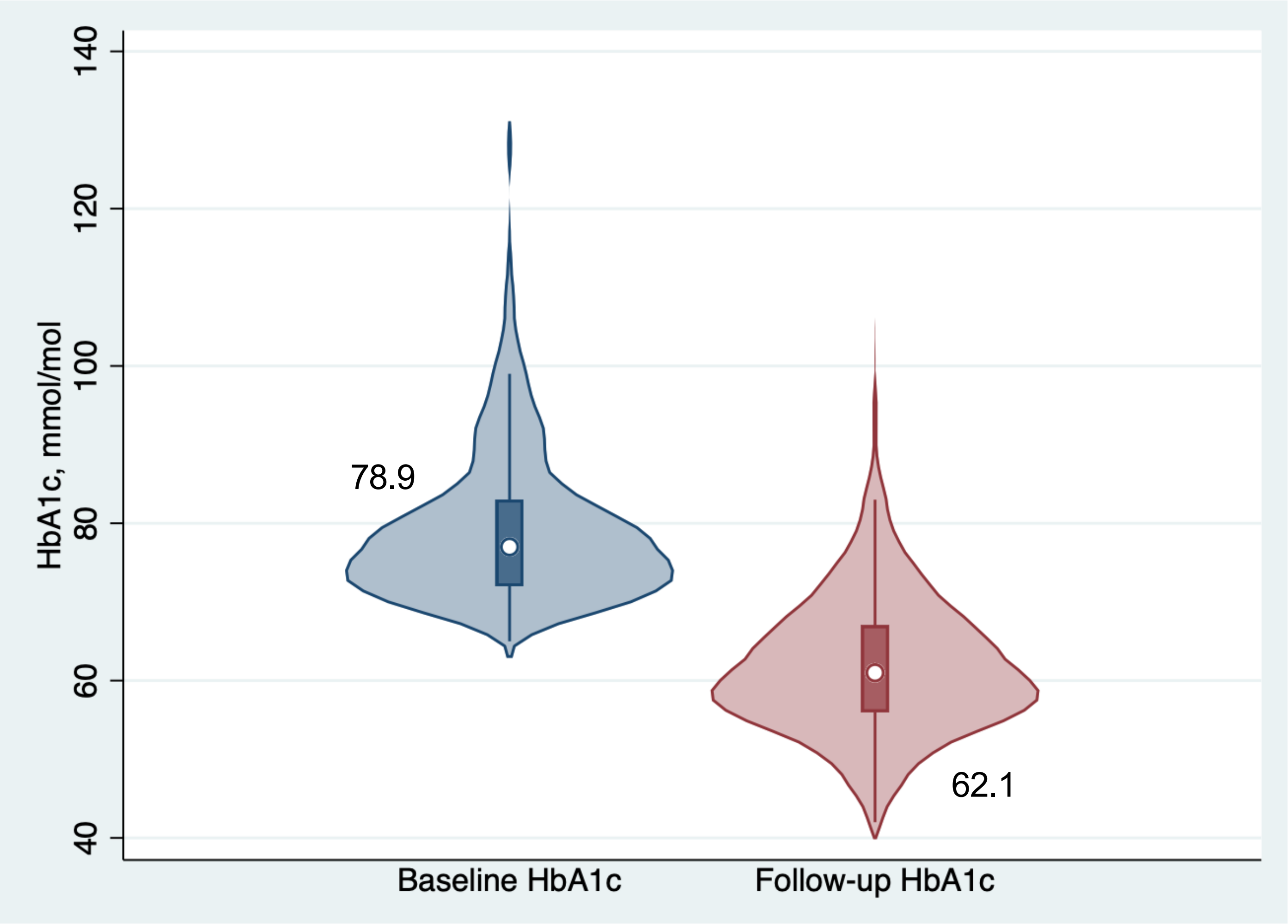
Harrogate and District NHS
NHS Foundation Trust

NHSE Pilot

- 570 pilot patients – 520 HCL users
- At baseline on CSII + FGM for at least 6 months and HbA1c $\geq$ 69 mmol/mol
- 69% female; 39% from 2 most deprived quintiles
- 46% Medtronic 780G
- 37% Tandem Control IQ
- 96% time spent in closed loop

Crabtree T et al. Diabetes Care 2023;46(10):1–8 | https://doi.org/10.2337/dc23-0635

NHSE Pilot – HbA1c



Crabtree T et al. Diabetes Care 2023;46(10):1–8 | https://doi.org/10.2337/dc23-0635

DTN-UK
Collaborate • Evolve • Support

Harrogate and District NHS
NHS Foundation Trust

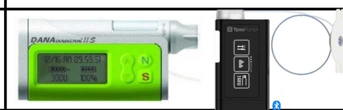
NICE National Institute for Health and Care Excellence

NICE guidance

Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes

Technology appraisal guidance
Published: 19 December 2023

Commercial Closed Loop Systems

	Medtronic 780G	Tandem Control IQ	Cam APS	Omnipod 5
Pump				
CGM				
Target	5.5 (default), 6.1 or 6.7 mmol/L	Range 6.3-8.9 mmol/L daytime; 6.3-6.7 mmol/L overnight; 7.8-8.9 mmol/L activity	Personalised target: 4.4-11.0 mmol/L – default 5.8 mmol/L	Personalised target: 6.1-8.3 mmol/L
Variables	Active insulin time I:C ratio	I:C ratio Insulin sensitivity factor Basal rates	I:C ratio Weight *Slowly absorbed meal* *Correction bolus*	Active insulin time I:C ratio ISF for manual correction
Insulin delivery	Basal insulin adjusted every 5 minutes	Basal insulin adjusted only if SG predicted to exit range	Basal insulin set to zero: extended bolus given every 10-12 minutes	Basal insulin adjusted every 5 minutes
Connectivity	Minimed Mobile and Carelink Connect App Carelink	Glooko-Diasend	CAMAPS FX Glooko-Diasend	Glooko-Diasend
CE license (age)	>7 years Pregnancy	>6 years	>1 years Pregnancy	>2 years

CGM in pregnancy: CONCEPTT

Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

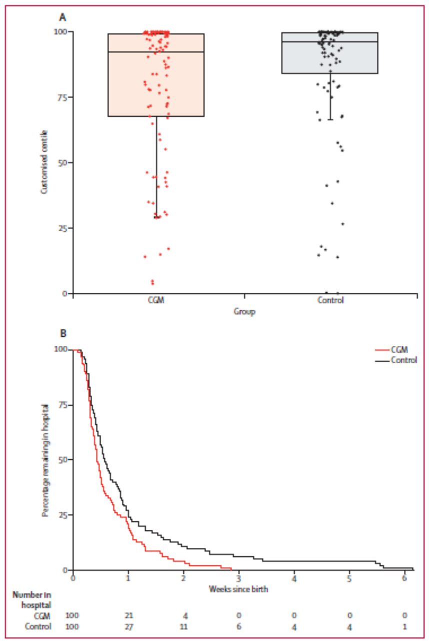


Figure 3: Neonatal outcomes of pregnancy trial participants
(A) Neonatal birthweight centiles are shown with box plots. The horizontal line in the middle of each box represents the median, and the lower and upper boundaries of the box represent the 25th and 75th percentiles, respectively. Whiskers are drawn to the smallest value that is within 1·5 x IQR below the 25th percentile. Values outside of the whiskers are drawn individually. These data are based on customised growth charts (gestation-related optimal weight) that adjust infant birthweight for maternal parity, ethnicity, height, and weight, and for infant sex and gestational age.[20] (B) The Kaplan-Meier plot shows infants' length of hospital stay from delivery until hospital discharge.

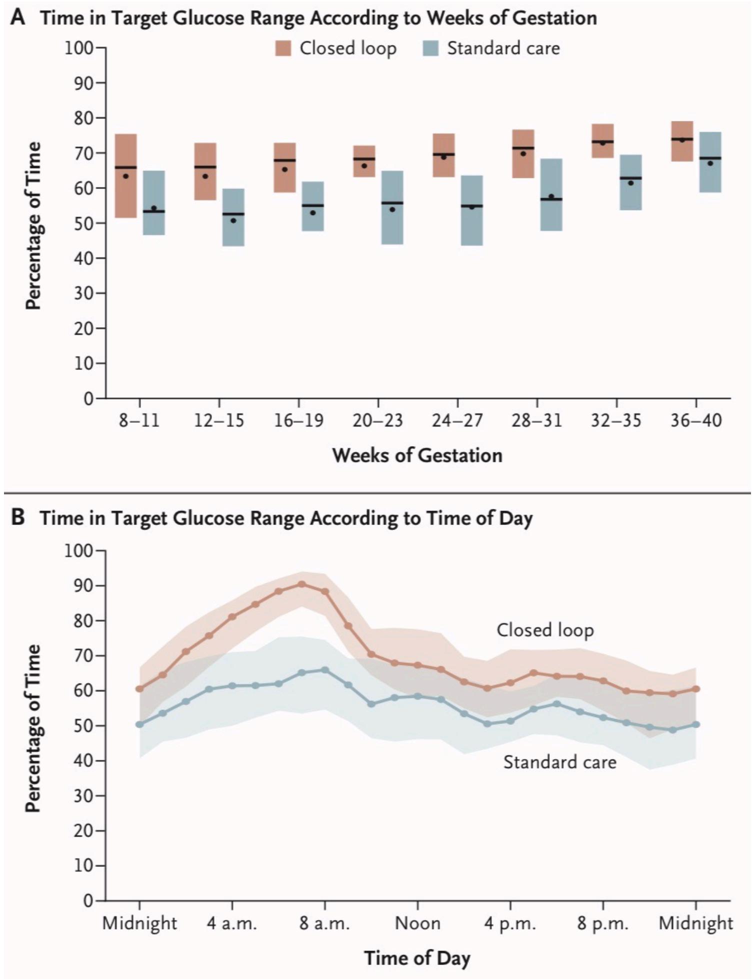
	CGM	Control	p value
Maternal outcomes			
Number assessed	100	102	..
Hypertensive disorders	18 (18%)	28 (27%)	0·13
Worsening chronic	2 (2%)	4 (4%)	0·68
Gestational	8 (8%)	9 (9%)	1·0
Pre-eclampsia	9 (9%)	18 (18%)	0·10
Caesarean section	63 (63%)	74 (73%)	0·18
Maternal weight gain (kg)*			
Entry to 34 weeks	13·1 (9·9–16·6)	13·7 (10·9–17·6)	0·22
From 16 to 34 weeks	8·9 (6·6–11·3)	9·7 (8·3–11·8)	0·09
Maternal length of stay (days)	3·5 (2·6–5·3)	4·2 (2·9–6·8)	0·10
Neonatal outcomes			
Number assessed	105	106	..
Pregnancy loss <20 weeks	5 (5%)	4 (4%)	1·0
Stillbirth	0	1	..
Termination	0	1	..
Congenital anomaly†	2	3	..
Preterm births			
Number assessed	100	102	..
Preterm <37 weeks	38 (38%)	43 (42%)	0·57
Early preterm <34 weeks	5 (5%)	11 (11%)	0·19
Gestational age at delivery‡	37·4 (36·7–38·1)	37·3 (36·0–38·0)	0·50
Birthweight			
Number assessed	100	100	..
Birthweight (g)	3545·4 (649·0)	3582·(777·0)	0·37
Median customised centile§	92 (68–99)	96 (84–100)	0·0489
Small for gestational age (<tenth centile)	2 (2 %)	2 (2%)	1·0
Large for gestational age (>90th centile)	53 (53%)	69 (69%)	0·0210
Extremely large for gestational age (>97·7th centile)	36 (36%)	44 (44%)	0·31
Macrosomia (≥4000 g)	23 (23%)	27 (27%)	0·62
Neonatal complications			
Number assessed	100	100	..
Birth injury	1 (1%)	0	1·0
Shoulder dystocia	1 (1%)	0	1·0
Neonatal hypoglycaemia requiring intravenous dextrose	15 (15%)	28 (28%)	0·0250
Hyperbilirubinaemia	25 (25%)	31 (31%)	0·43
Respiratory distress	9 (9%)	9 (9%)	1·0
High-level neonatal care (NICU) >24 h	27 (27%)	43 (43%)	0·0157
Infant length of hospital stay	3·1 (2·1–5·7)	4·0 (2·4–7·0)	0·0091
Composite neonatal outcome¶	45 (42·9%)	56 (52·8%)	0·17

Values are mean (SD) and median (IQR) as appropriate. CGM=continuous glucose monitoring. NICU=neonatal intensive care unit. *Entry weight was self-reported or recorded pre-pregnancy weight, or both. The weight from 16 to 34 weeks was measured. †Congenital anomalies were aortic stenosis and hypospadias grade 1 (CGM group) and hypoplastic right heart syndrome (termination of pregnancy), aberrant right subclavian artery, and bilateral hydronephrosis (control group). ‡Gestational age at delivery was calculated only for the 100 pregnancies in the CGM group and the 101 pregnancies in the control group that were ongoing after 24 weeks' gestation. §Based on gestation-related optimal weight customised growth charts. ¶Composite outcome comprises pregnancy loss (miscarriage, stillbirth, and neonatal death); birth injury; neonatal hypoglycaemia; hyperbilirubinaemia; respiratory distress; and high-level neonatal care for more than 24 h.

Table 4: Obstetric and neonatal health outcomes of pregnancy trial participants

Feig DS et al. *Lancet* 2017;390:2347-59

HCL in pregnancy: AIDAPT



Lee TTM et al. N Engl J Med 2023;389:1566-78.

Mean time in target:

68.2 +/- 10.5% HCL

55.6 +/- 12.5% Standard

P < 0.001

12 device adverse effects:

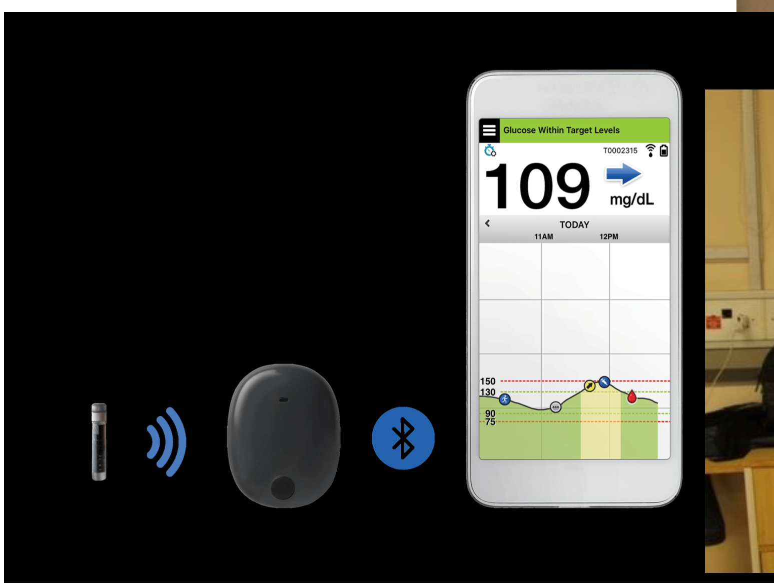
One severe hypo due to an incorrect bolus

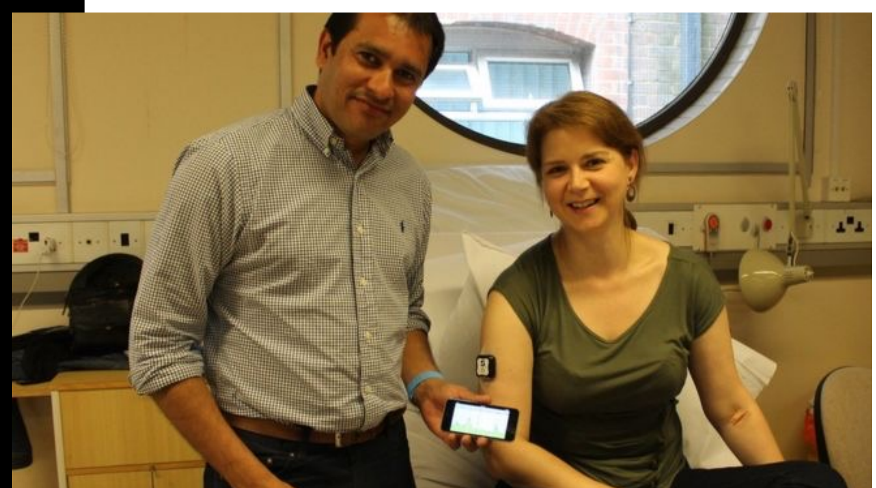
One hyperglycaemic event so stopped HCL

One moderate ketosis with O/N loss bluetooth

HCL Target:
5.67 +/- 0.11 mmol/L at start
5.17 +/- 0.28 mmol/L at end

Gone …. and forgotten?





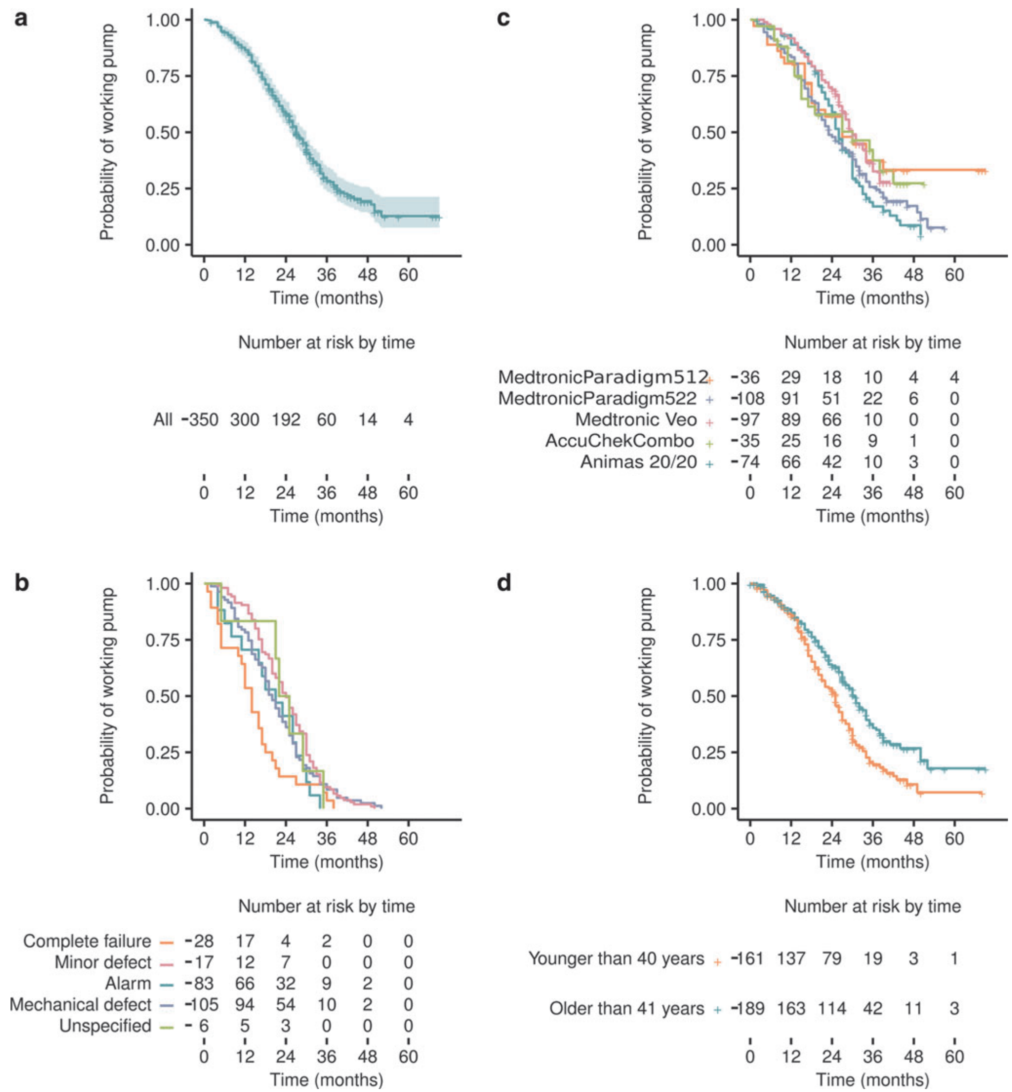
Thought for the year - 2017!

- The hybrid closed loop is within reach

BUT improvements are needed:

- Pump reliability
- Infusion set technology
- CGM accuracy
- Cyber security?!

Pump Failure Rates



Guenego et al.
Diab Tech Ther 2016;18:820-4

Time from catheter insertion

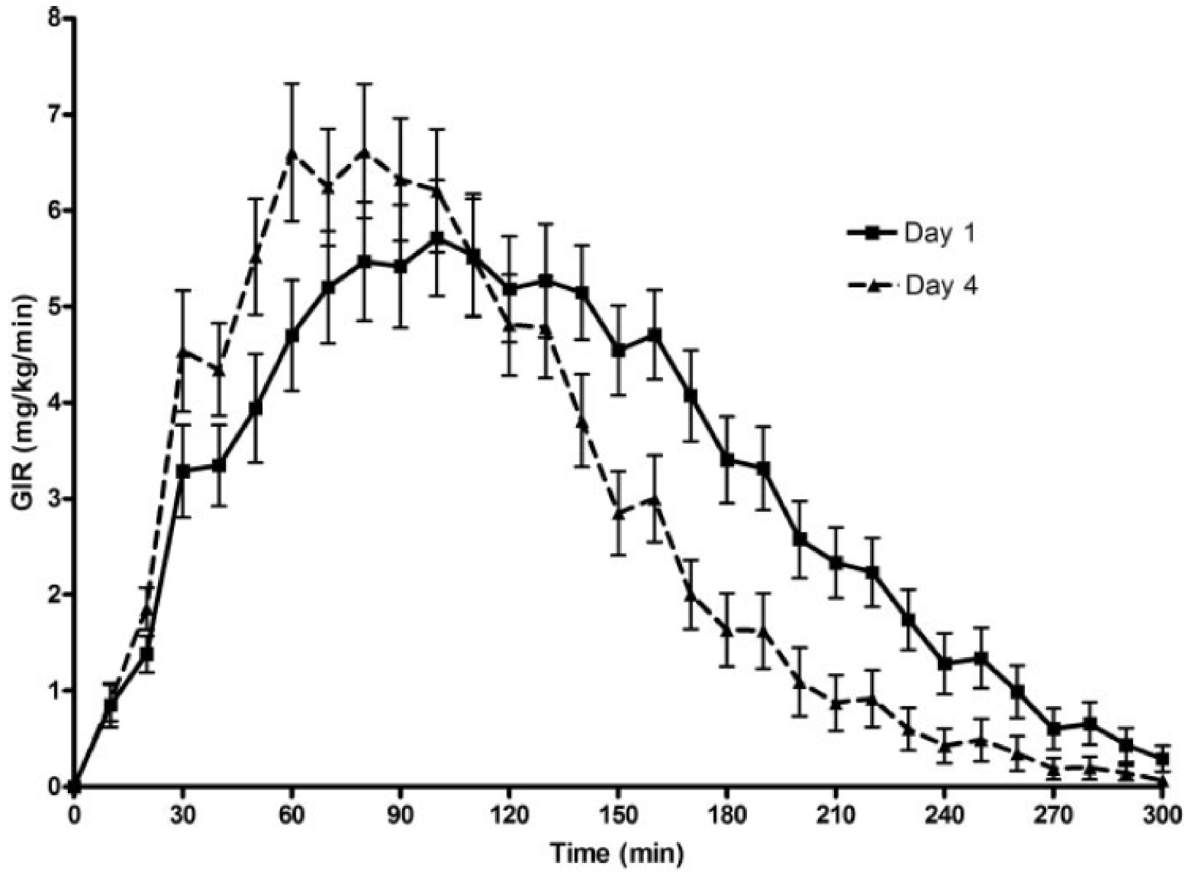


Figure 2—*Pharmacodynamic profiles for all subjects on day 1 versus day 4 of catheter site insertion. Insulin action, as expressed as GIR, required to maintain euglycemia after a standard bolus of 0.2 unit/kg insulin aspart or lispro. Data are presented as means ± SEM.*

Swan et al, *Diabetes Care* 2009;32:240-244

Infusion set failure

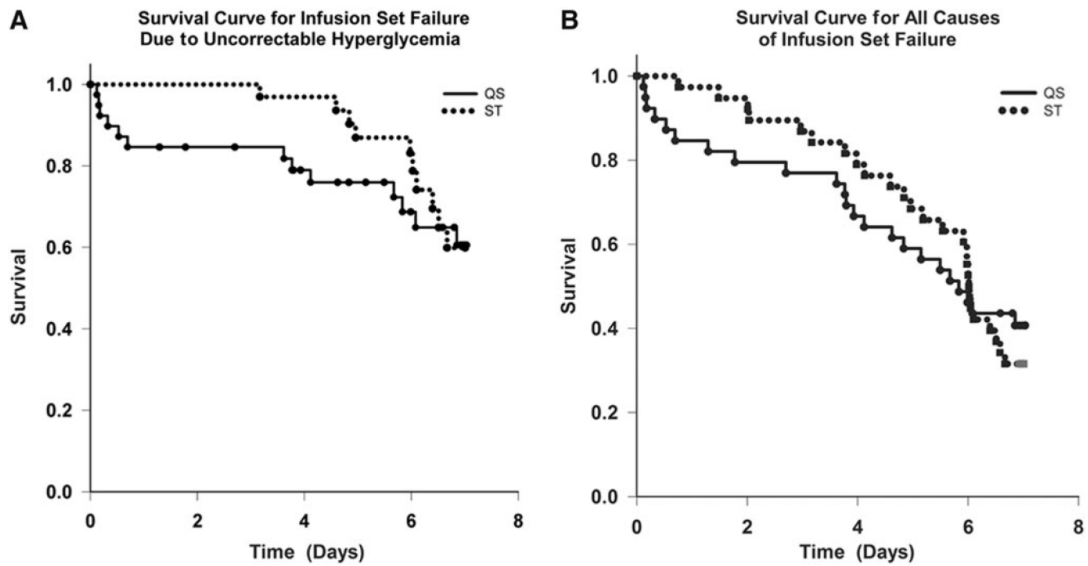


FIG. 1. Survival curves for infusion sets: **(A)** infusion set failure due to uncorrectable hyperglycemia (when the end point was hyperglycemia [>250 mg/dL] and the meter blood glucose level did not decrease by at least 50 mg/dL an hour after a correction bolus and/or blood ketone levels were greater than 0.6 mmol/L) and **(B)** for all causes of infusion set failure (uncorrectable hyperglycemia with or without ketonemia, pain, infusion set fell out [loss of adhesion], pulled out accidentally, erythema and induration, and infection). The solid line is the Teflon catheter (Quick-Set [QS]), and the dotted line is the steel needle catheter (Sure-T [ST]).

Patel P et al. *Diab Ther Tech* 2014;16:15-9

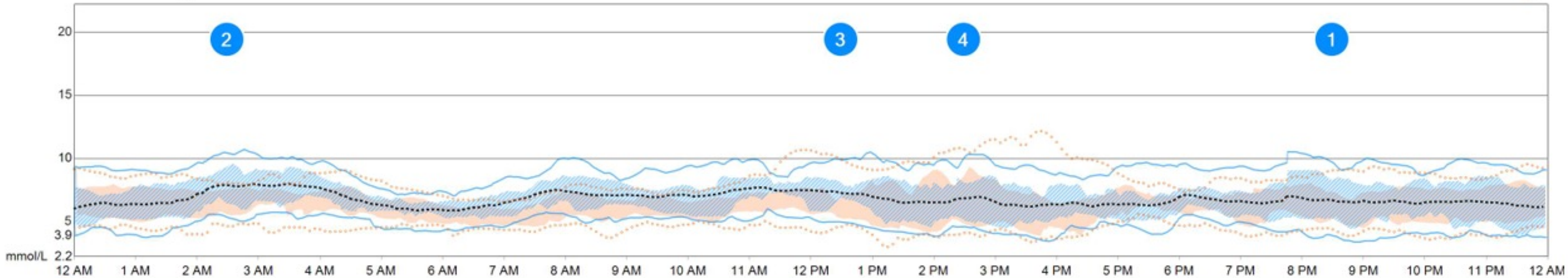
minimed (A) 22/10/2025 - 04/11/2025 (14 Days)
(B) 27/10/2024 - 09/11/2024 (14 Days)

PID: 421573

Data Sources: MiniMed 780G, MMT-1885 (NG2881744H)

Percentile comparison

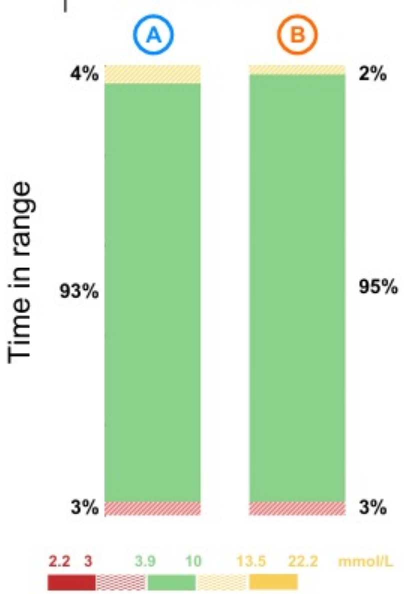
25-75% 5-95% Average (A)



Carb Ratio (g/U)
(A) 10.0 | 9.5 | 8.8
(B) 8.5

(A)

Hypoglycemic patterns (1)	# Episodes (per day): 0.4	Hyperglycemic patterns (3)	# Episodes (per day): 0.9
1 8:00 PM - 8:59 PM (2 occurrences)		2 2:00 AM - 2:59 AM (2 occurrences); 3 12:00 PM - 12:59 PM (2 occurrences); 4 2:00 PM - 2:59 PM (2 occurrences)	



3 Glucose Management Indicator
4 Manual mode 24hr programmed total from the active basal pattern

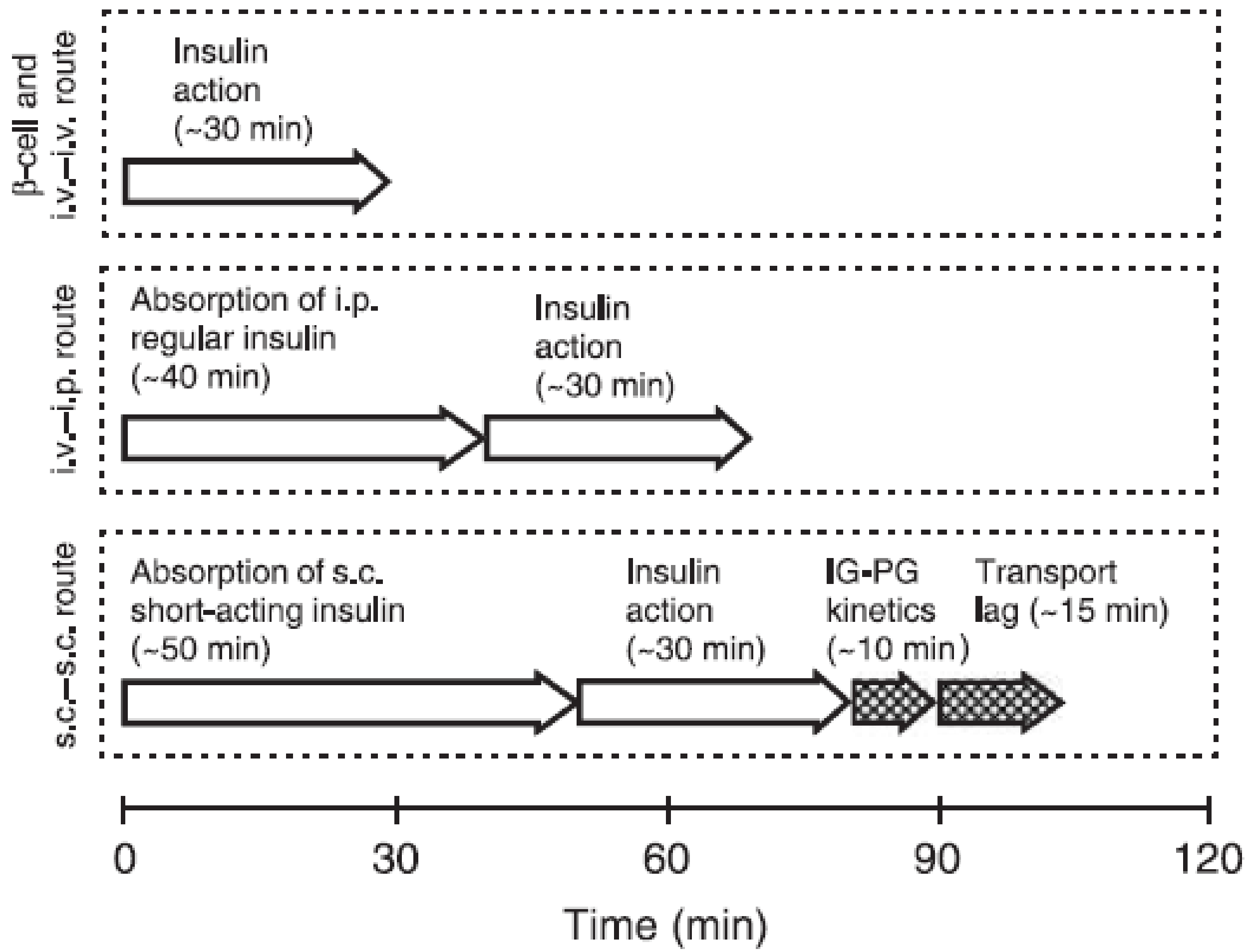
SmartGuard Exits

SmartGuard Exits	(A)	(B)
No Calibration	0	0
SmartGuard max delivery	0	0
SmartGuard min delivery	0	0
BG required for SmartGuard	0	0
Sensor Algorithm Underread	0	0
Sensor Updating	0	0
No SG values	0	0
Sensor Expired	0	0
SmartGuard disabled by user	0	0
Prolonged Suspend	0	0
SmartGuard Warm Up	0	0
Unidentified	• 1	0

Statistics

Statistics	(A)	(B)
SmartGuard (per week)	0% (00h)	100% (7d 01h)
Manual Mode (per week)	94% (6d 14h)	0% (00h)
Sensor Wear (per week)	92% (6d 11h)	99% (6d 22h)
Average SG ± SD	6.8 ± 1.7 mmol/L	6.3 ± 1.7 mmol/L
GMI³	6.2% (44.7 mmol/mol)	6.0% (42.5 mmol/mol)
Coefficient of Variation (%)	25.5%	26.2%
Low / High SG Alerts (per day)	7.9 / 2.9	8.1 / 1.7
Average BG	5.9 ± 2 mmol/L	5 ± 1.4 mmol/L
BG / Calibration (per day)	1.4 / 1.2	0.6 / 0.5
Total daily dose (per day)	21.1 units	18.4 units
Bolus amount (per day)	12.0U (57%)	10.1U (55%)
Auto Correction amount (per day)	--	1.1U (11%)
Auto Basal / Basal amount (per day)	9.1U (43%)	8.3U (45%)
Set / Reservoir Change	3.7 / 3.7 days	3.7 / 3.7 days
Carbs entered / Meal (per day)	88 ± 34 g / 2.8	93 ± 22 g / 3.1
Active Insulin time	2:00 hrs	2:00 hrs
24hr programmed manual basal ⁴	12.550U	13.800U
SmartGuard target	5.5 mmol/L	5.5 mmol/L

Technological limitations



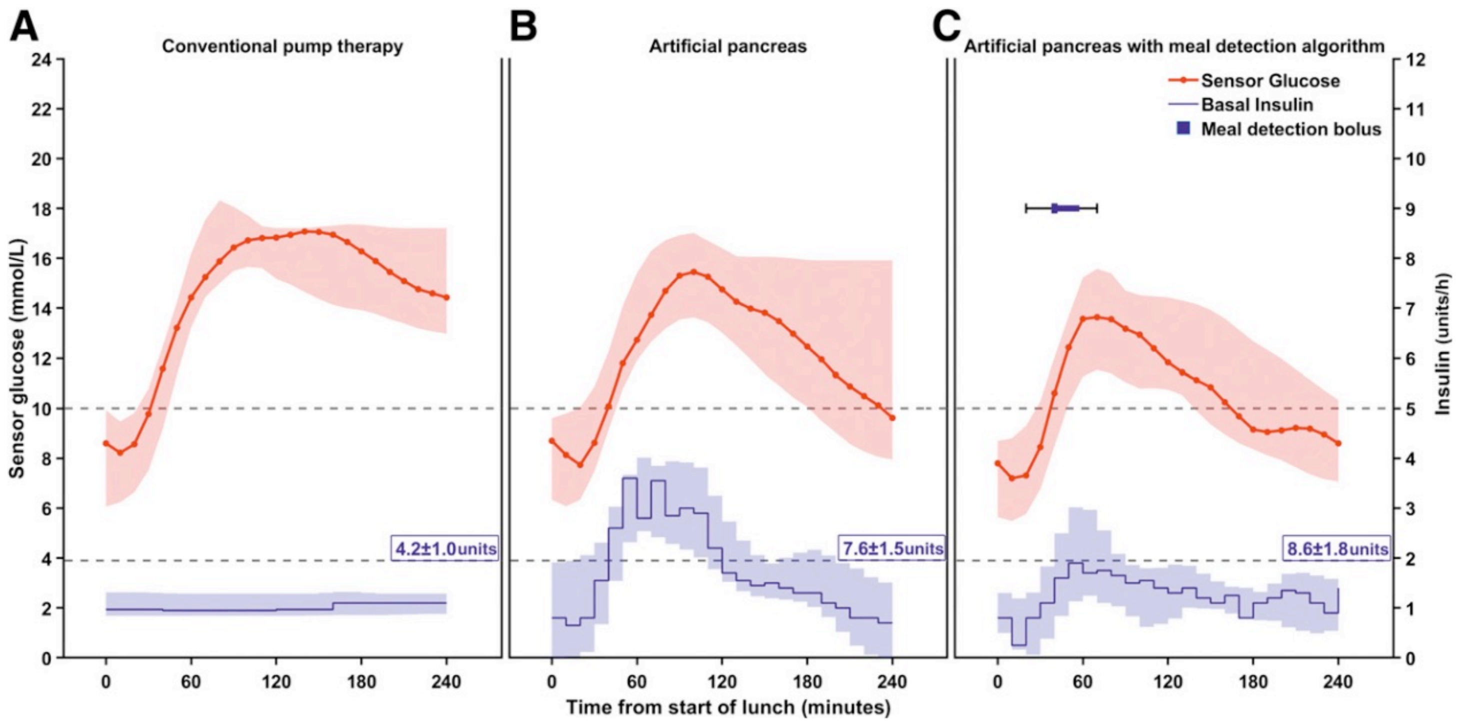
Hovorka R *Diabet Med* 2006;23:1-12

Improving HCL performance

- Form and function
- Interoperability
- Meal detection
- Activity detection
- Fully closed loop?
- Bihormonal systems?
- Variable active insulin time??!!

- Equity of access AND equity of outcome

Meal Detection Algorithm



Palisaitis E et al. Diabetes Care 2021;44:604-6

Closed loop with heart rate signal

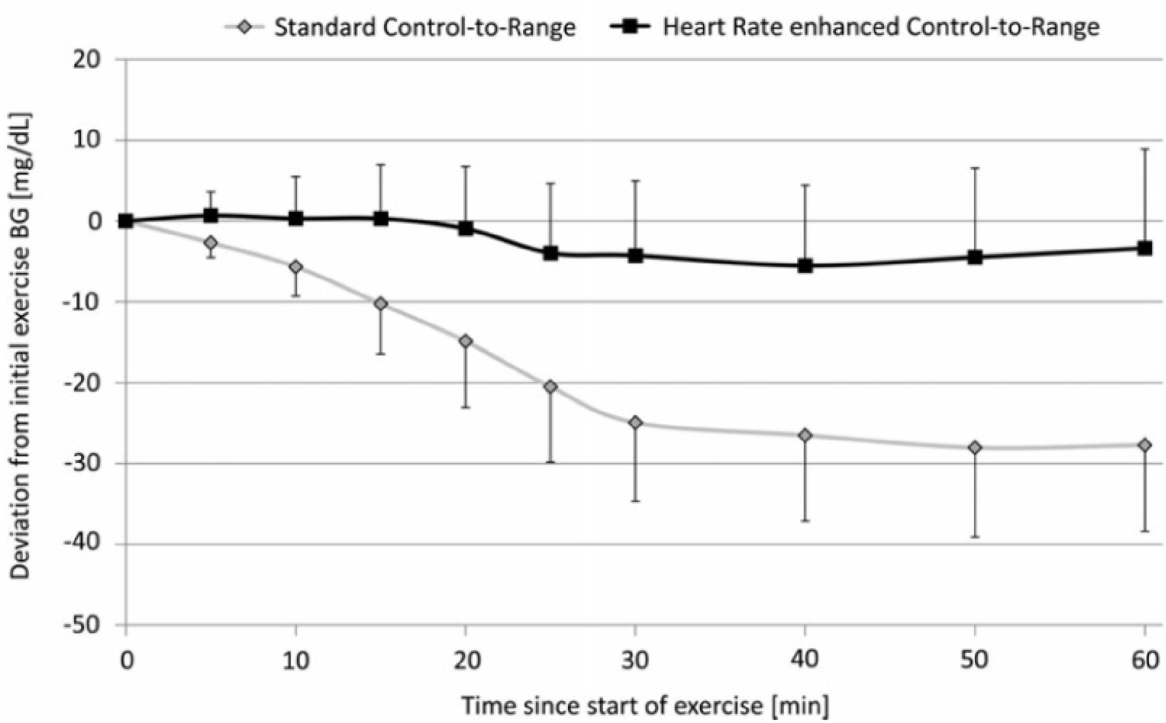
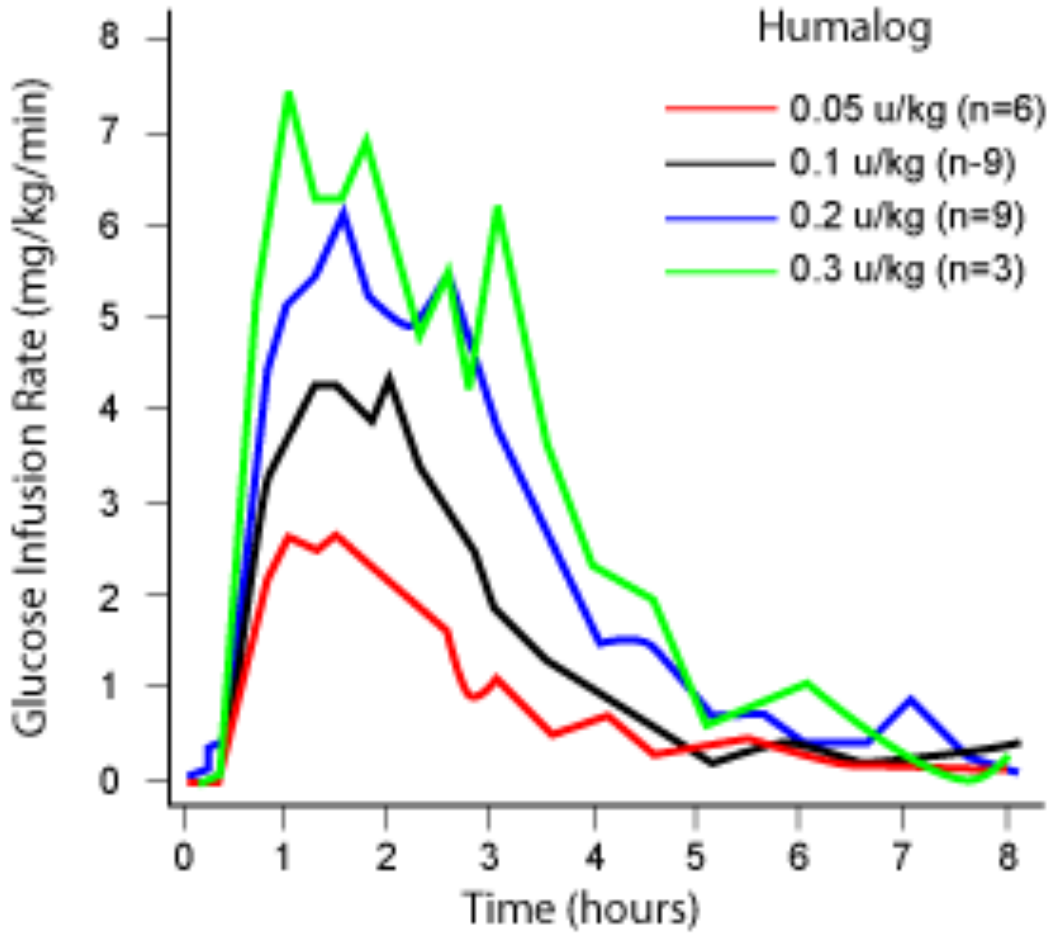


FIG. 3. On average, the plasma glucose level did not decline during exercise and only moderately afterward when using control-to-range plus heart rate (squares with black line). In contrast, under standard control-to-range the average plasma glucose decline was pronounced throughout the exercise bout and moderately amplified thereafter (diamonds with gray line). Maximum separation was achieved at min 60 after onset of exercise (-3.4 mg/dL vs. -27.7 mg/dL). BG, blood glucose.

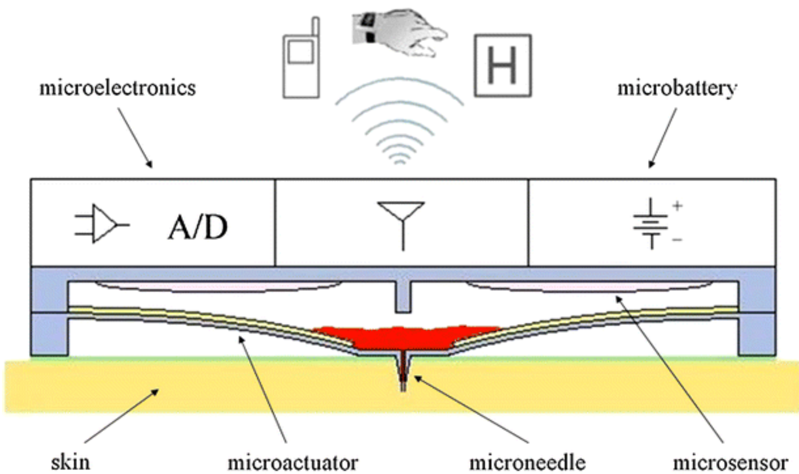
Breton MD et al. *Diab Tech Ther* 2014;16:506-11

Insulin action – dose-response curve



Woodworth et al. *Diabetes* 1993;42(Suppl. 1):54A

The e-mosquito



The contact lens

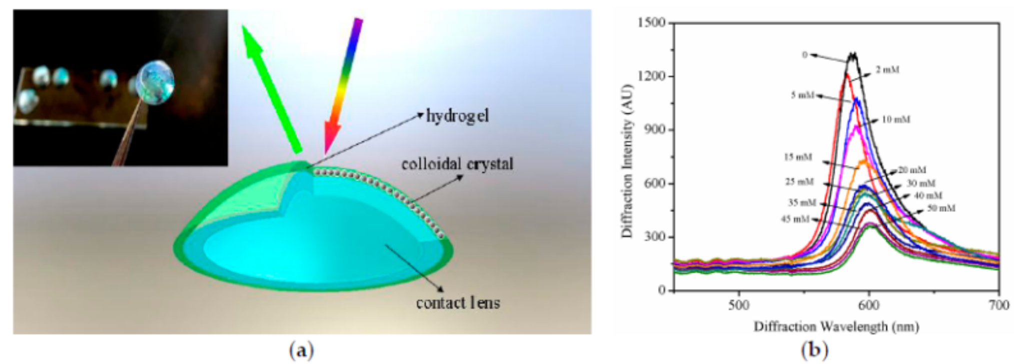


Figure 6. (**a**) Diagram and photograph (insert) of a physical hydrogel photonic crystal sensing lens; (**b**) Diffraction wavelength shifts with the variation of the glucose concentration in artificial tear solution.

Wang G et al. IEEE Transactions Biomed Circ Sys 2017;11:979-87

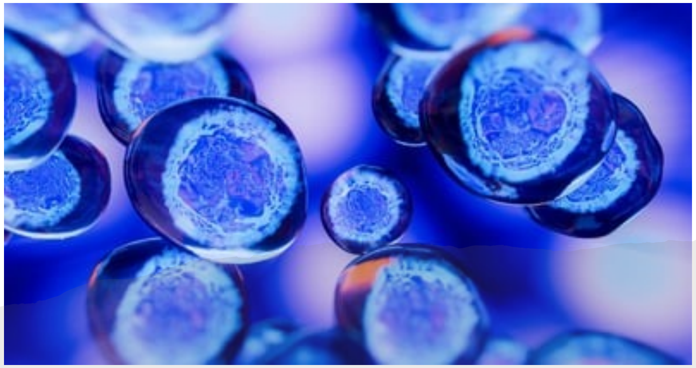
Chen C et al. *Sensors* 2017;17:182

The Future

- Further refinement of existing technologies

- The next “Holy Grail”
  - Stem cells
  - Transplantation
  - Gene Therapy
  - Immunotherapy
  - Gluco-responsive insulin

Type 1 Diabetes TrialNet



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