Clinical News and Innovation in Type 1 Diabetes and Technology

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- Adjunctive therapy to insulin
- Accurate diagnosis of T1D
- Early intensive treatment
- Technology
  - Glucose sensing
  - Insulin delivery with sensor augmentation
  - Artificial pancreas
- The post code lottery that is T1D care in the UK
- Suggested way forward

Adjunctive therapy to insulin

Getting to target in T1D?

|	Type 1		
	Under 40	**40 to 64**	**65 to 79**
HbA$_{1c}$ <48mmol/mol (6.5%)[a]	7.7%	6.7%	8.6%
HbA$_{1c}$ ≤58mmol/mol (7.5%)[a]	24.8%	26.0%	35.5%
HbA$_{1c}$ ≤86mmol/mol (10.0%)[a]	77.5%	84.4%	91.4%
BP ≤140/80[b]	78.1%	70.3%	71.7%
Cholesterol <4mmol/L	22.3%	28.4%	41.6%
Cholesterol <5mmol/L	64.1%	70.4%	81.5%
Meet all treatment targets[c]	14.7%	14.7%	22.4%

National Diabetes Audit

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level and Renal Disease Status, Model 3.*

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)

Lind 2014

Options for glucose lowering agents (other than insulin) in T1D

Currently licensed	Not licensed but promising	Not licensed but potential in selected patients
Exercise Metformin Pramlintide (not licensed in UK)	**SGLT inhibitors** GLP1 agonists	Pioglitazone Acarbose Bariatric surgery DPP IV inhibitors

Tahrani et al 2013
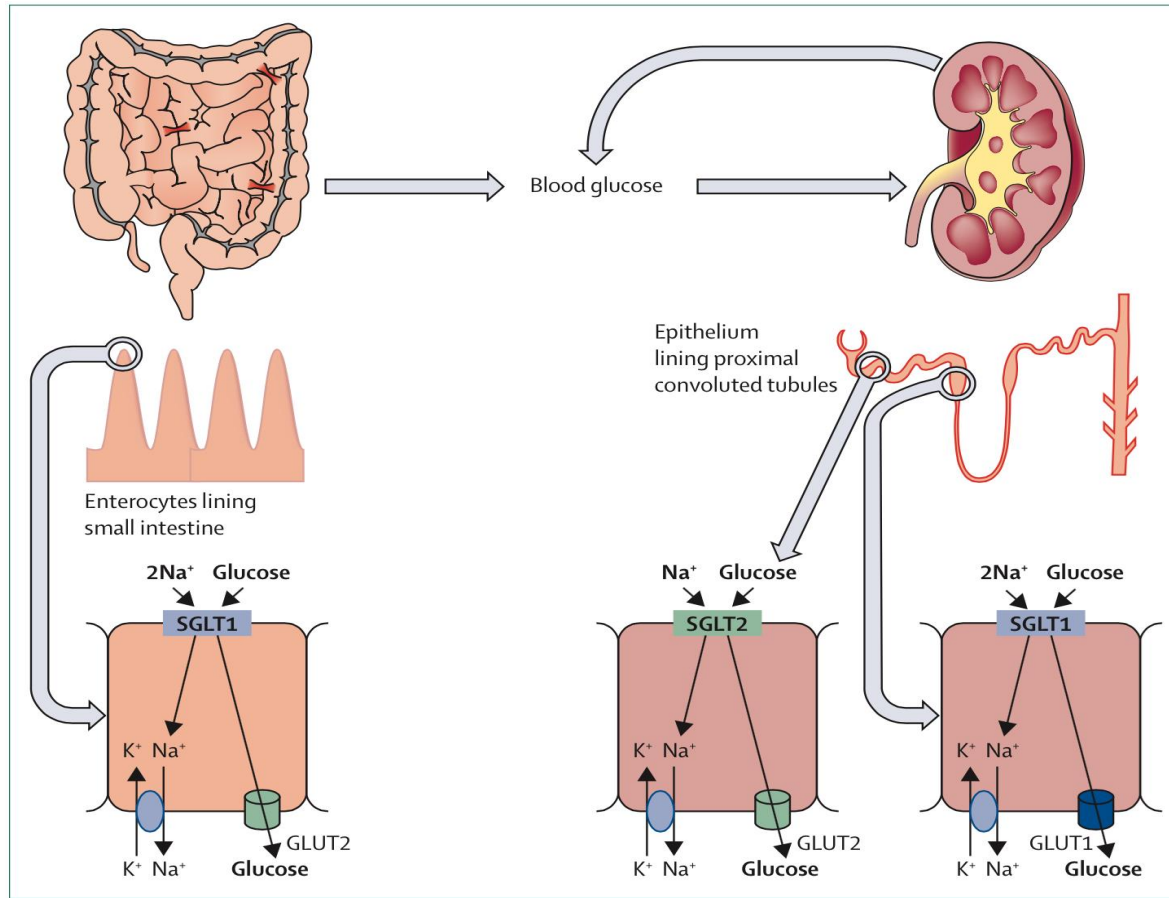
Effect of 10mg Dapagliflozin in a T1D patient
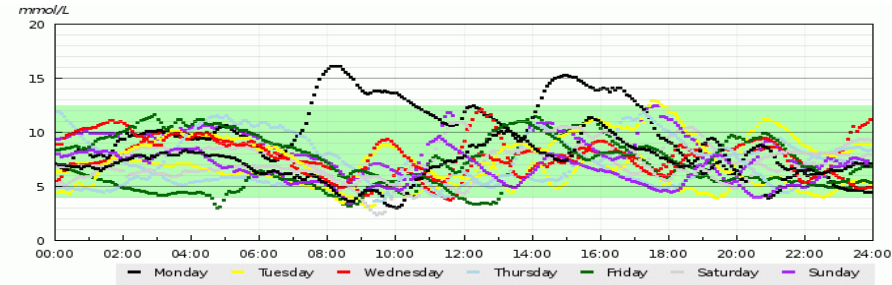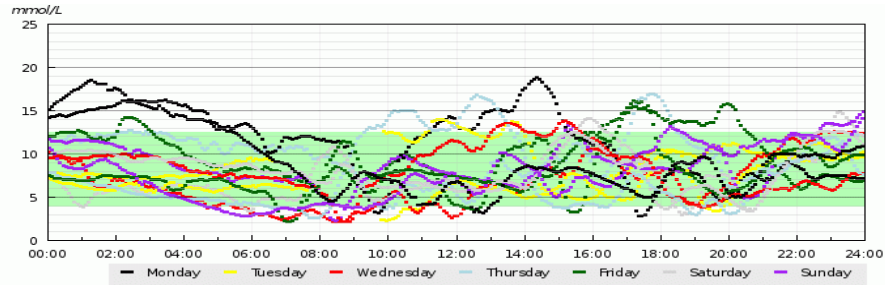
	Pre - DAPA	During DAPA
Range	2.2 - 18.8 mmol/L	2.2 – 16.1
% High	12%	2%
% Low	7%	2%
Num high periods	17	4
Num low periods	25	14
CGM Std Dev	3.2 mmol/L	2.2 mmol/L
Insulin TDD	43.6 U	33.9 U

DEPICT 1 (Dapagliflozin)

HbA1c reduction: 0.4-0.5%

Daily insulin: 10%

Body weight: 3Kg

SBP 3-6

SH – NS

DKA - NS

GU infection 4x

Global inTandem3 (Sotagliflozin)

HbA1c reduction: 0.5%

Daily insulin: 9%

Body weight: 3Kg
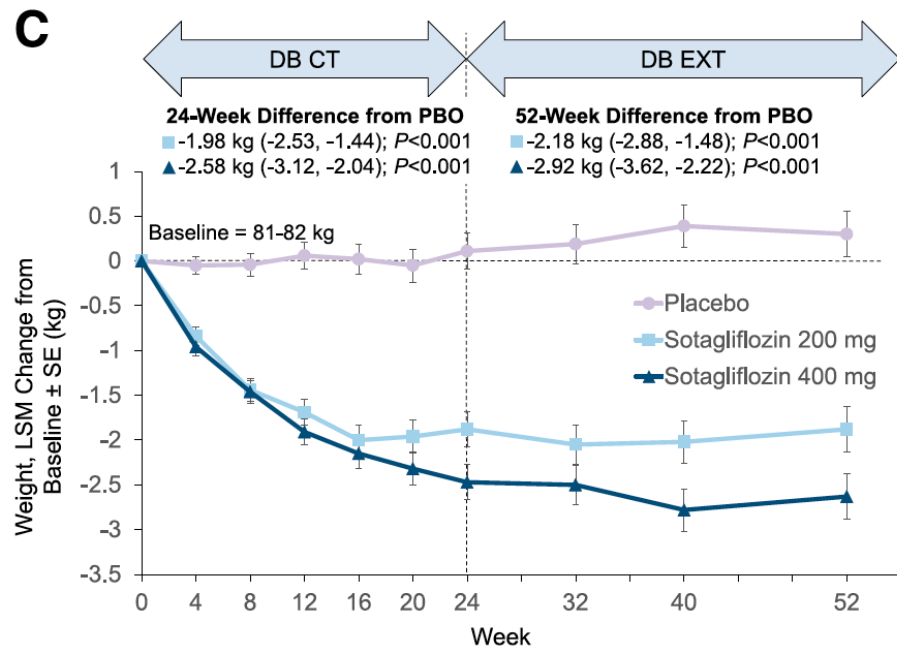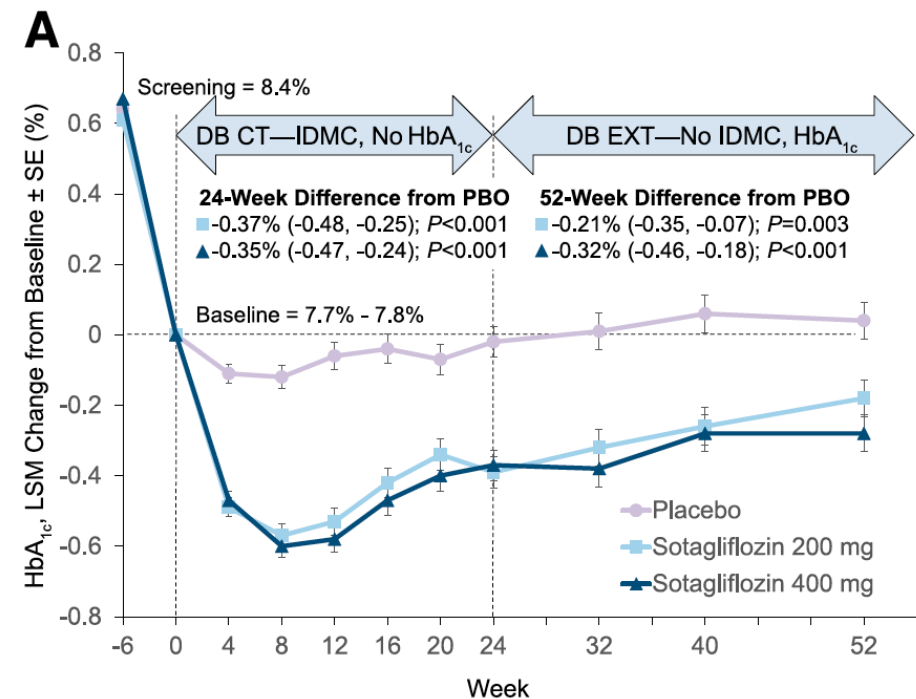
SBP 3.5

SH – NS

DKA 5x

GU infection 3x

Dapa T2D
HbA1c: 0.5%   Weight: 2Kg
SBP: 4mmHg   DBP: 2mmHg

European and Israeli **inTandem2**

A

HbA$_{1c}$, LSM Change from Baseline ± SE (%)

Screening = 8.4%

DB CT—IDMC, No HbA$_{1c}$ → DB EXT—No IDMC, HbA$_{1c}$

24-Week Difference from PBO
■ -0.37% (-0.48, -0.25); *P*<0.001
▲ -0.35% (-0.47, -0.24); *P*<0.001

52-Week Difference from PBO
■ -0.21% (-0.35, -0.07); *P*=0.003
▲ -0.32% (-0.46, -0.18); *P*<0.001

Baseline = 7.7% – 7.8%

Placebo
Sotagliflozin 200 mg
Sotagliflozin 400 mg

Week

C

Weight, LSM Change from Baseline ± SE (kg)

DB CT → DB EXT

24-Week Difference from PBO
■ -1.98 kg (-2.53, -1.44); *P*<0.001
▲ -2.58 kg (-3.12, -2.04); *P*<0.001

52-Week Difference from PBO
■ -2.18 kg (-2.88, -1.48); *P*<0.001
▲ -2.92 kg (-3.62, -2.22); *P*<0.001

Baseline = 81–82 kg

Placebo
Sotagliflozin 200 mg
Sotagliflozin 400 mg

Week

782 participants, DKA 2-3%

Current state of play

AZ Dapagliflozin for T1D

EMEA decision late 2018?

NICE decision mid 2019?

Sanofi Sotagliflozin for T1D

EMEA decision late 2018?

If licensed

Who prescribes?
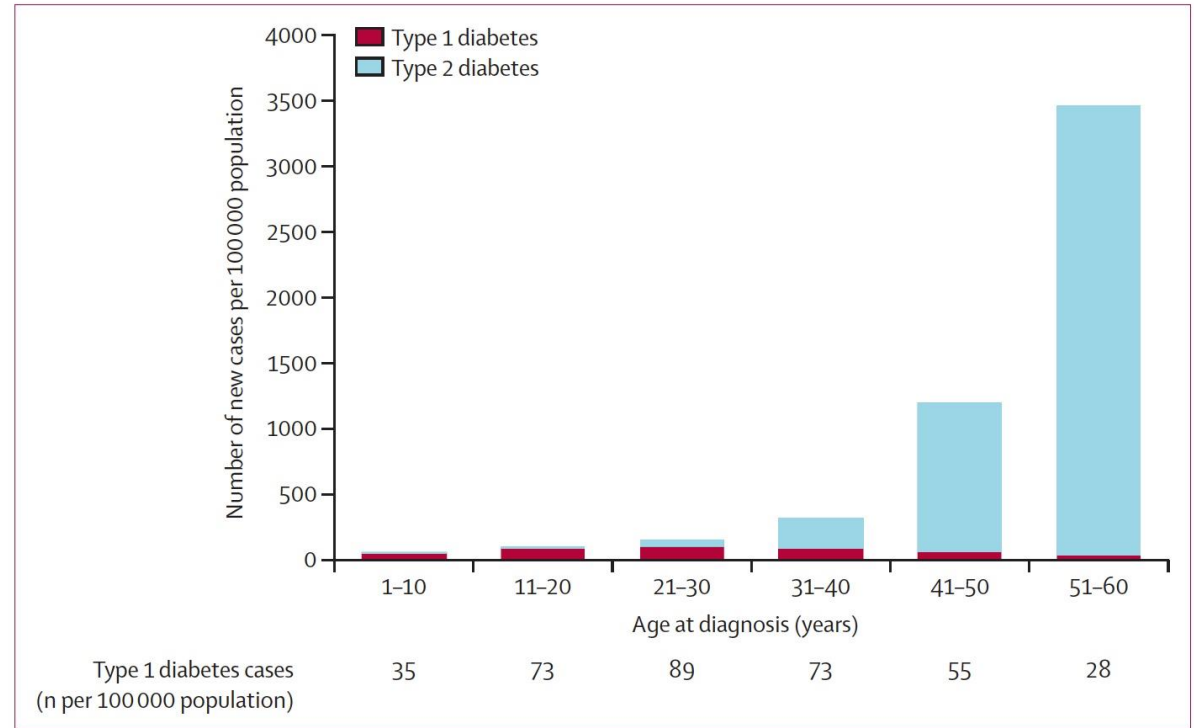
The importance and practicalities of education

DKA risk subgroups: females? CSII?

DKA risk does not decline with therapy duration

Accurate diagnosis of T1D

Differentiating between T1D and T2D is challenging

- 86% accurate in white European
- 70% accurate in south Asian

Hope 2016, Thomas 2018

NICE guidelines NG17

Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults.

Consider further investigation in adults that involves measurement of C-peptide and/or diabetes-specific autoantibody titres if:

type 1 diabetes is suspected but the clinical presentation includes some atypical features

or

type 1 diabetes has been diagnosed and treatment started but there is a clinical suspicion that the person may have a monogenic form of diabetes

or

classification is uncertain, and confirming type 1 diabetes would have implications for availability of therapy

Clinical cases can be challenging

- 20yr old South Asian
- Strong family history of T2D
- Diagnosed with 'T1D' whilst on holiday in Pakistan
- Ab negative
- C peptide high
- Not taking insulin for 3 weeks: glucose 7-12mmol/L without ketones
- **T1D in Honeymoon?**
- **T2D?**

StartRight
Getting The Right Classification And Treatment From Diagnosis Of Diabetes

Primary objective

- To establish diagnostic performance of biomarkers including islet autoantibodies, C-peptide and a genetic risk score in identifying patients with rapid requirement for insulin, alone and in combination with clinical features.

Secondary objectives

- To prospectively validate a clinical prediction model developed from cross sectional datasets in predicting rapid insulin requirement in young onset diabetes.

- To integrate discriminative and additive biomarkers into the clinical prediction model.

- To establish a bio resource for future biomarkers discovery and assessment.

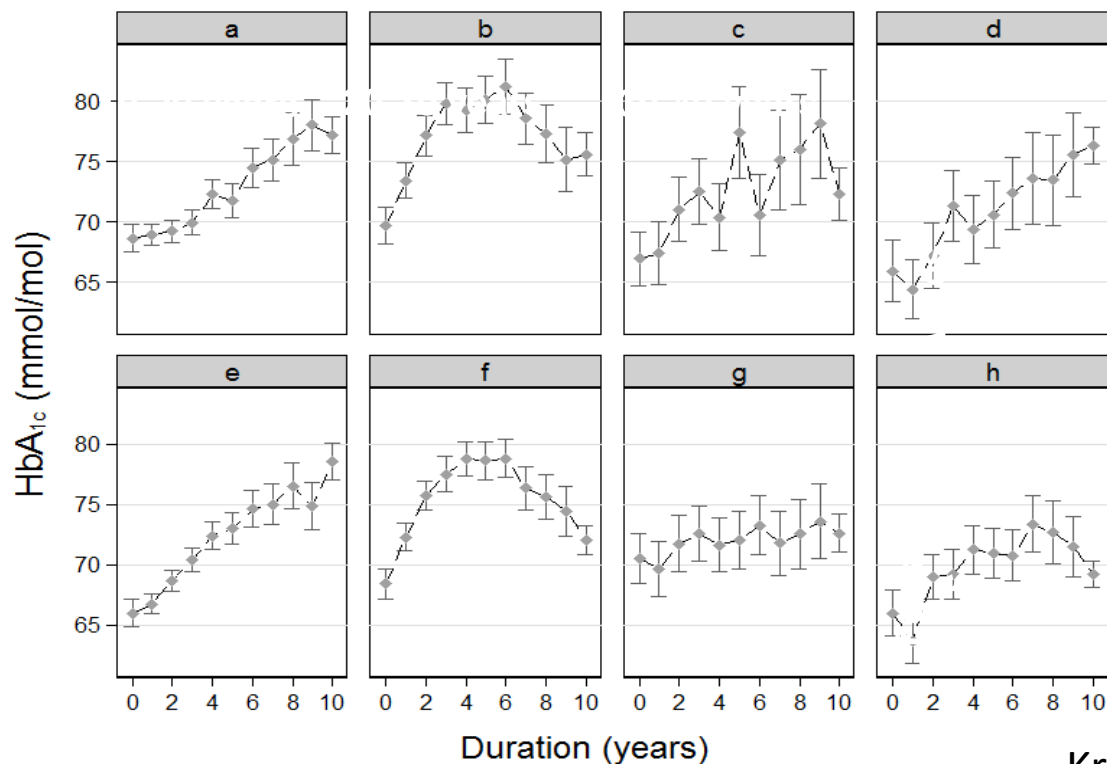# Early intensive treatment for T1D

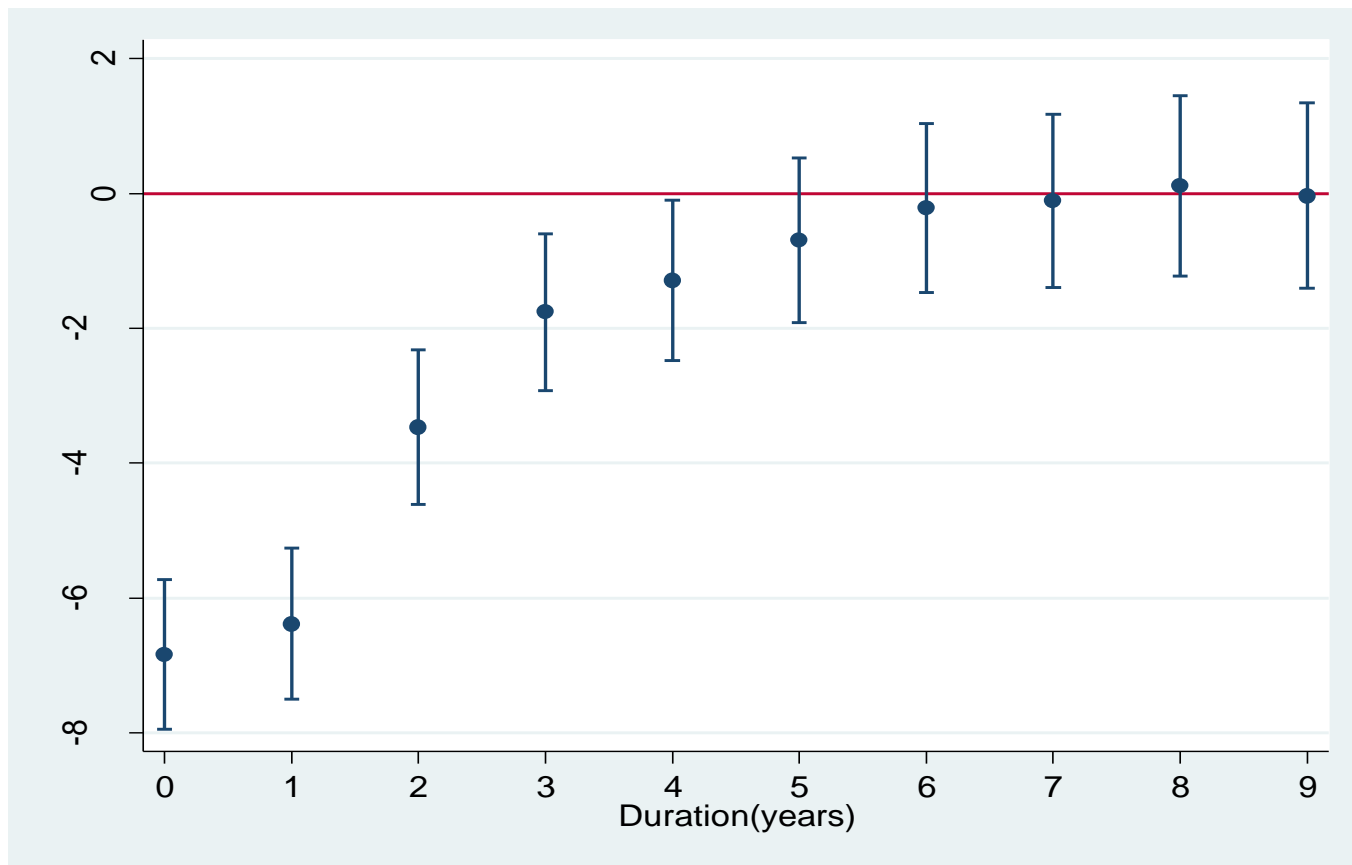# Glycaemic tracking and importance of early intensive treatment

(4,500 incident cases of UK T1D)
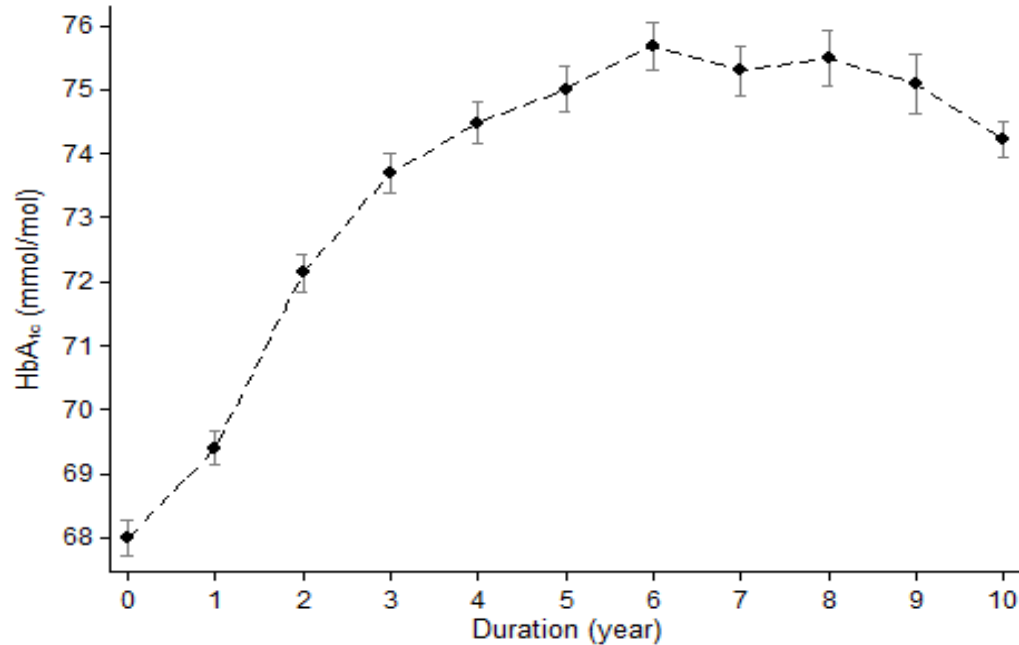
Krishnarajah et al 2018

Exploratory plots - stratified by sex and age

Krishnarajah et al 2018

Krishnarajah et al 2018

Conclusions

- Individuals with type 1 diabetes, glycaemic control measured by HbA_{1c} settles onto a long-term 'track'

- Tracking occurs on average at 4-5 years following diagnosis

- Age at diagnosis modifies both the rate at which individuals settle into their track and the absolute HbA_{1c} tracking level

- Early targeted intervention may impact on long term outcomes

Krishnarajah et al 2018

Technology

Emerging recognition of the value of continuous glucose feedback in the day to day management of glucose

- Flash glucose sensing
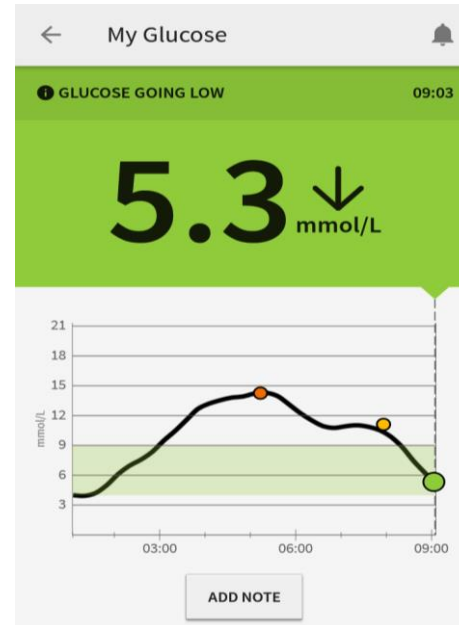- Continuous glucose monitoring

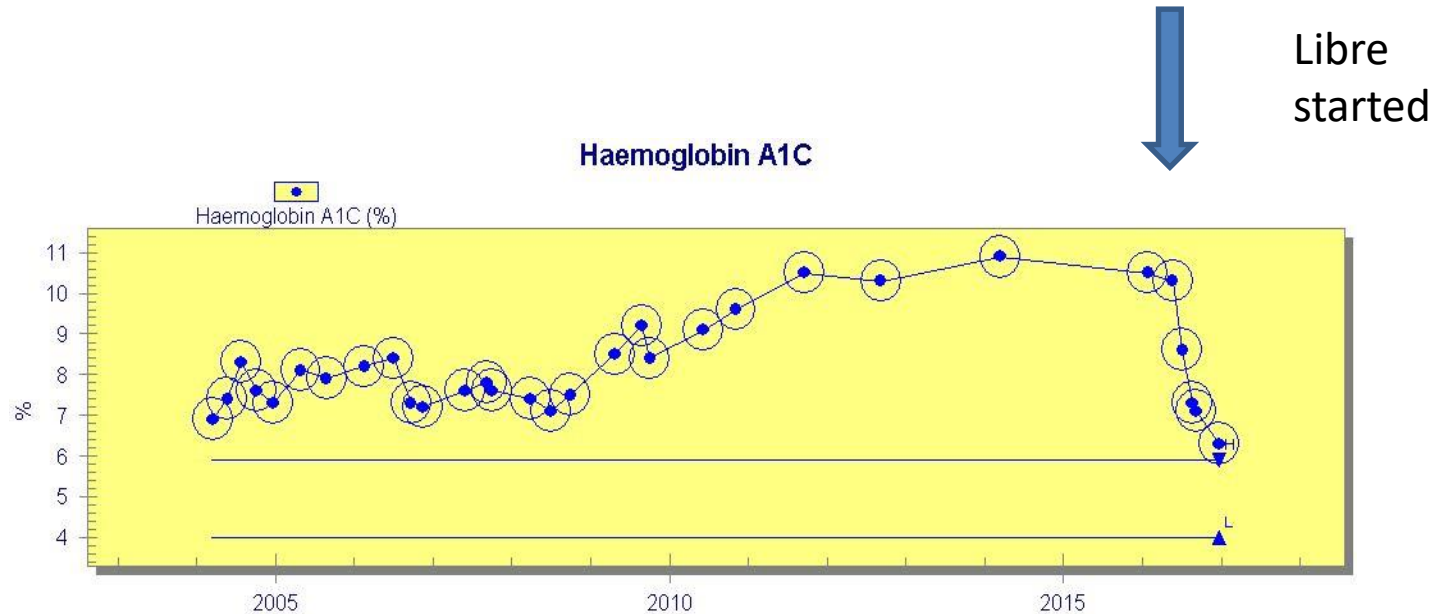# Freestyle Libre

Impact on decision making
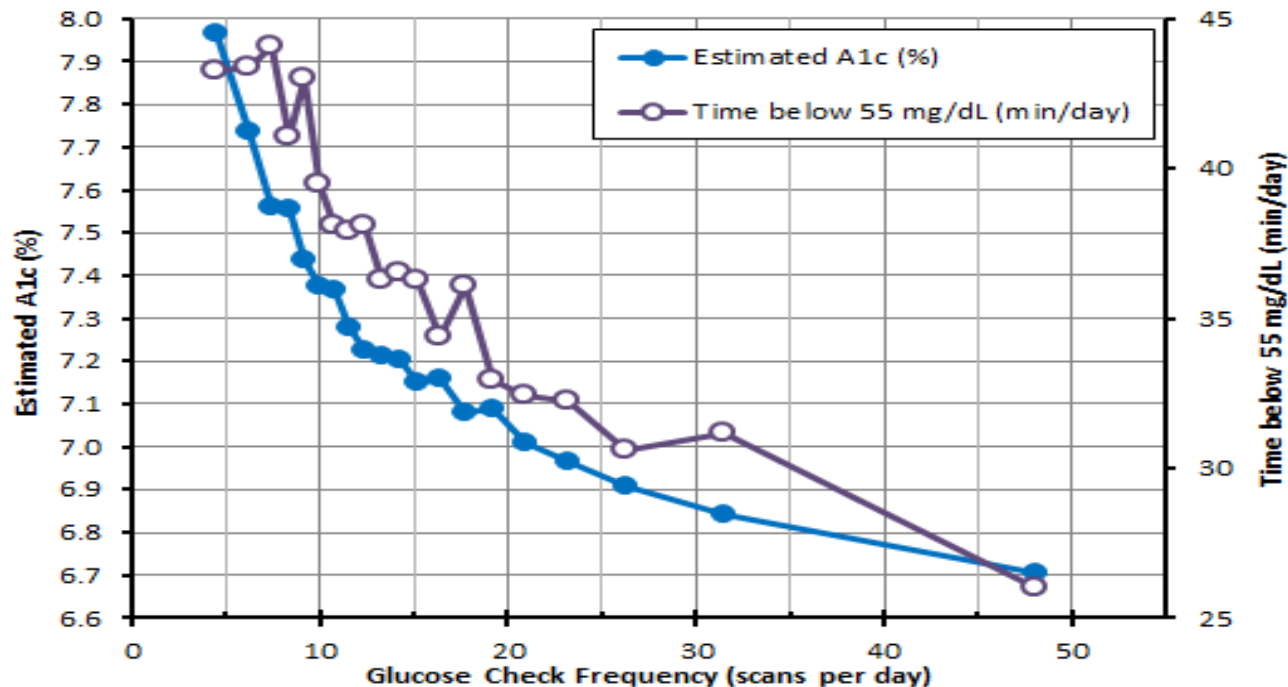
- Response to this….   ….very different to….

Example of how continuous feedback can help
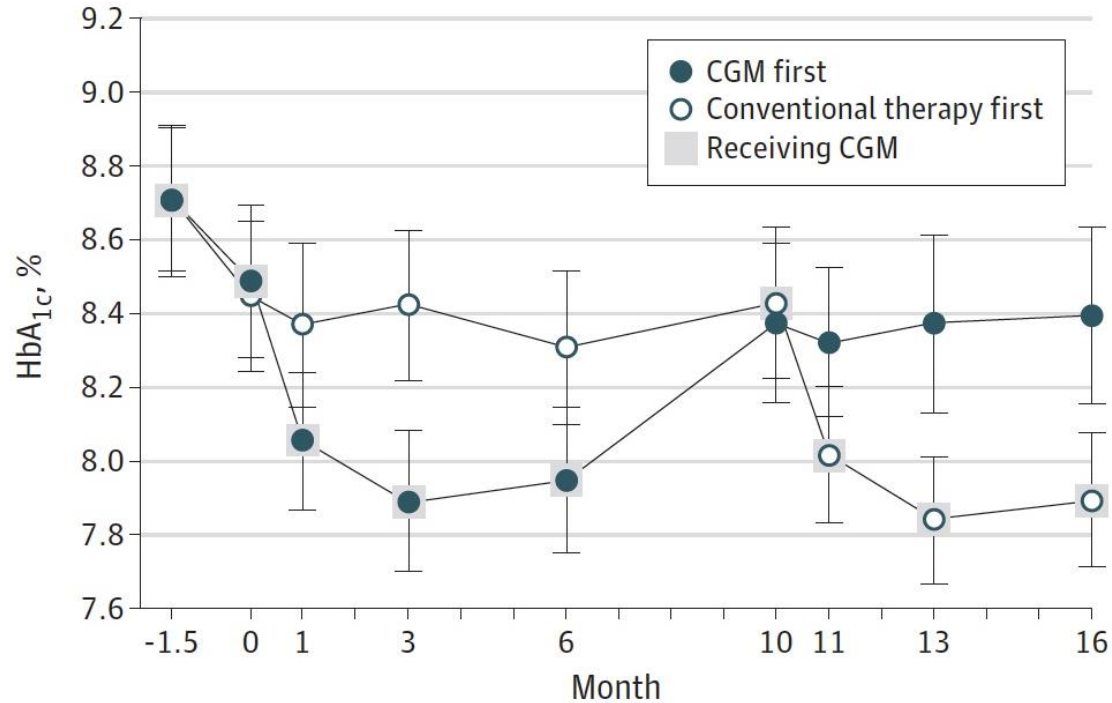

Libre
started

Courtesy of Emma Wilmot

Real world Libre data

- **51K readers, worldwide**

- **Average 16 scans/day**

CGM is useful in people on MDI (as well as pumps)

Lind 2017

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

Denice S Feig, Lois E Donovan, Rosa Corcoy, Kellie E Murphy, Stephanie A Amiel, Katharine F Hunt, Elisabeth Asztalos, Jon F R Barrett, J Johanna Sanchez, Alberto de Leiva, Moshe Hod, Lois Jovanovic, Erin Keely, Ruth McManus, Eileen K Hutton, Claire L Meek, Zoe A Stewart, Tim Wysocki, Robert O'Brien, Katrina Ruedy, Craig Kollman, George Tomlinson, Helen R Murphy, on behalf of the CONCEPTT Collaborative Group*

- HbA1c improved by 0.19%
- TIR increased from 61% to 68%

- Significant improvement in neonatal outcomes
  - Large for gestational age – 69 to 53%
  - Neonatal hypoglycaemia requiring IV dextrose – 28 to 15%
  - Need for ICU – 43 to 27%
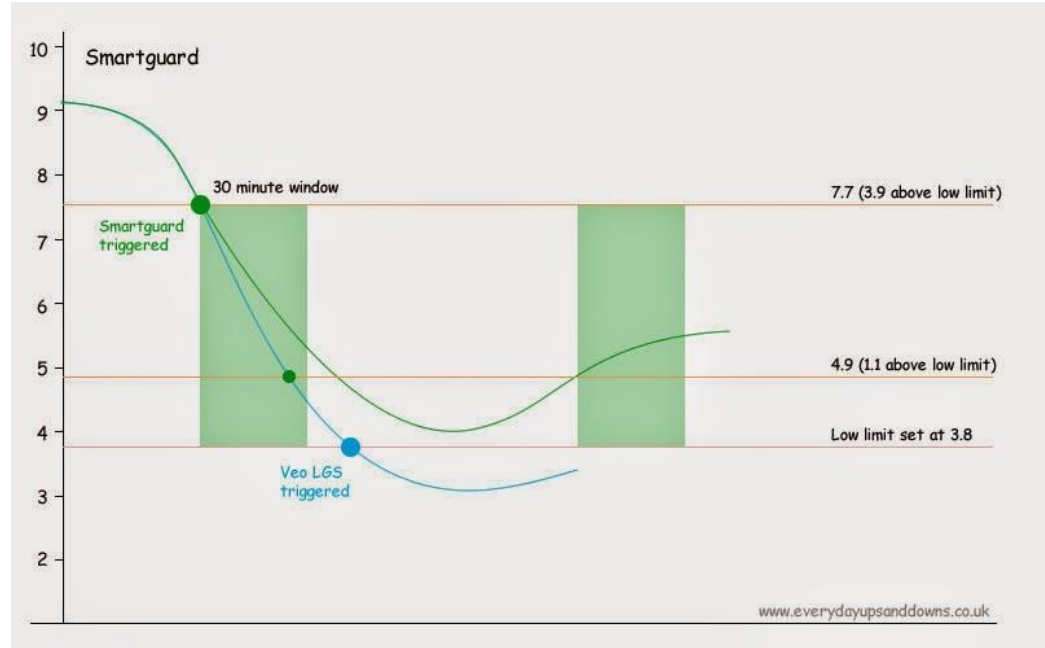 - 1 day less in hospital

Glucose sensing/monitoring

- Libre – Libre like
- Real time CGM: Dexcom G6, Enlite 3, Medrum
- Implantable sensors: Senseonics

Low Glucose Suspend

The **dynamic suspend** feature is based on certain criteria: sensor glucose must be within 3.9mmol/L of the low limit and predicted to be 1.1mmol/L above the low limit within 30 minutes AND the pump must not be in the refractory period.

The **dynamic resume** feature is based on certain preset criteria: sensor glucose must be 1.1mmol/L above the preset low limit and predicted to be 2.2mmol/L above within 30 minutes AND insulin must have been suspended for at least 30 minutes.

Smartguard

10	
9	
8	30 minute window — 7.7 (3.9 above low limit)
7	Smartguard triggered
6	
5	4.9 (1.1 above low limit)
4	Veo LGS triggered — Low limit set at 3.8
3	
2	

www.everydayupsanddowns.co.uk

Other low glucose suspend systems

t:slim X2™
Insulin Pump

NEW! Predicts and helps prevent lows with Basal-IQ™ Technology

Tandem pump and Dexcom sensor

FDA approves first automated insulin delivery device for type 1 diabetes

US release March 2017
UK release planned Autumn 2018

Real world data from ADA
Lower mean BG
Increased time in range

|	Manual Mode	After Auto Mode start
Patients, N	13,906	
Auto Mode Use, %	–	80.05%
Mean SG, mg/dL	163.53	154.87
SD SG, mg/dL	54.22	51.04
Percentage of time in SG ran		
<50	0.38%	0.31%
<54	0.60%	0.49%
<70	2.59%	2.05%
70–180	63.16%	71.35%
>180	34.24%	26.60%

Other potential hybrid closed loops

- What is a hybrid closed loop?
- Omnipod Insulet hybrid closed loop
- Diabeloop DBLG1
- Dual hormone (insulin and glucagon)

A way forward

The post code lottery that is T1D care in the UK
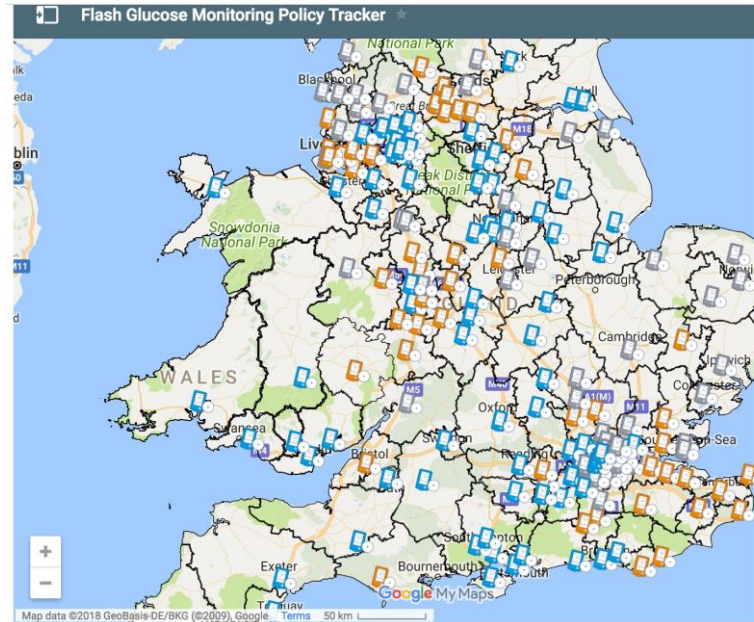
- Flash Glucose sensing
- CGM
- Psychology
- Emerging technology

Keeping up with emerging technology

A way forward?

- Offer participation in research
- Structured education
- Glucose download facilities
- Transition service
- Pregnancy care
- Flash
- Insulin pumps
- CSII
- Sensor augmented pumps
- Closed loop pumps
- Other approaches to insulin delivery (IP)
- Beta cell replacement

All T1D centres

Regional T1D Hubs
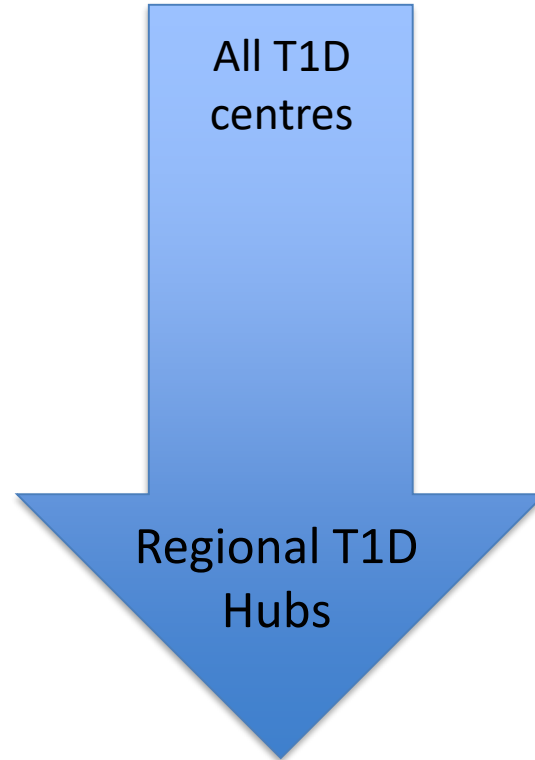
- KPI

- Referral centre for the more complicated patient

- Responsibilities for teaching and training local centres

- Hubs would meet to discuss more difficult patients