SGLT2 Inhibitors – Review of options and practicalities

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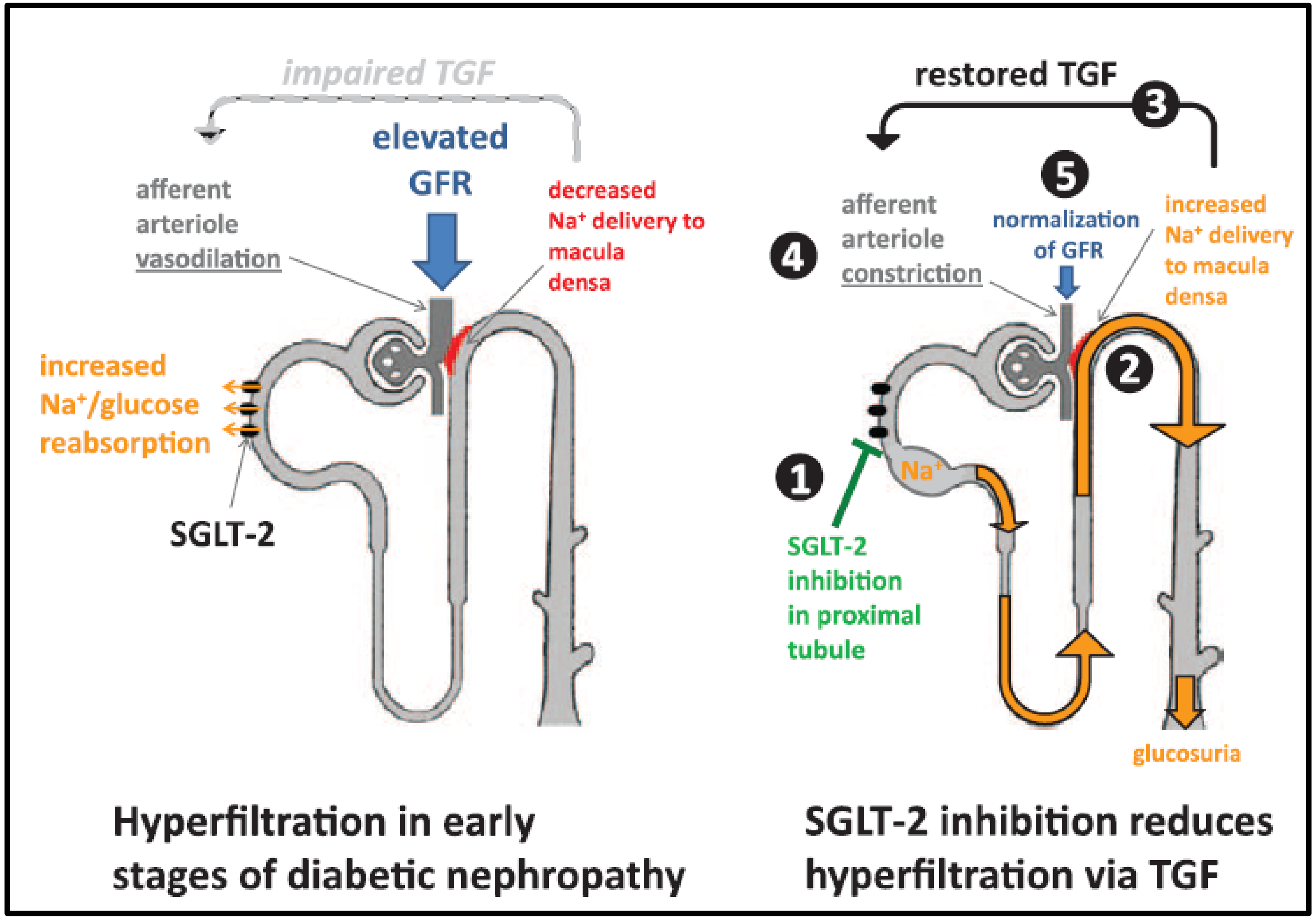
SGLT-2 Inhibitors



GFR, glomerular filtration rate; TGF, tubuloglomerular feedback;
SGLT2, sodium-glucose co-transporter-2.

Cherney et al. Circulation 2014.

SGLT-2 Inhibitors

Renal effects

Renal glucose excretion

Glucosuria

- Risk of UTI/thrush, particularly in girls. Counsel on good genital hygiene.
- Only excretes glucose if it is above the renal threshold. Incapable of causing hypoglycaemia.
- Will test positive for glucose on urine dipsticks. This is normal.

Osmotic diuresis

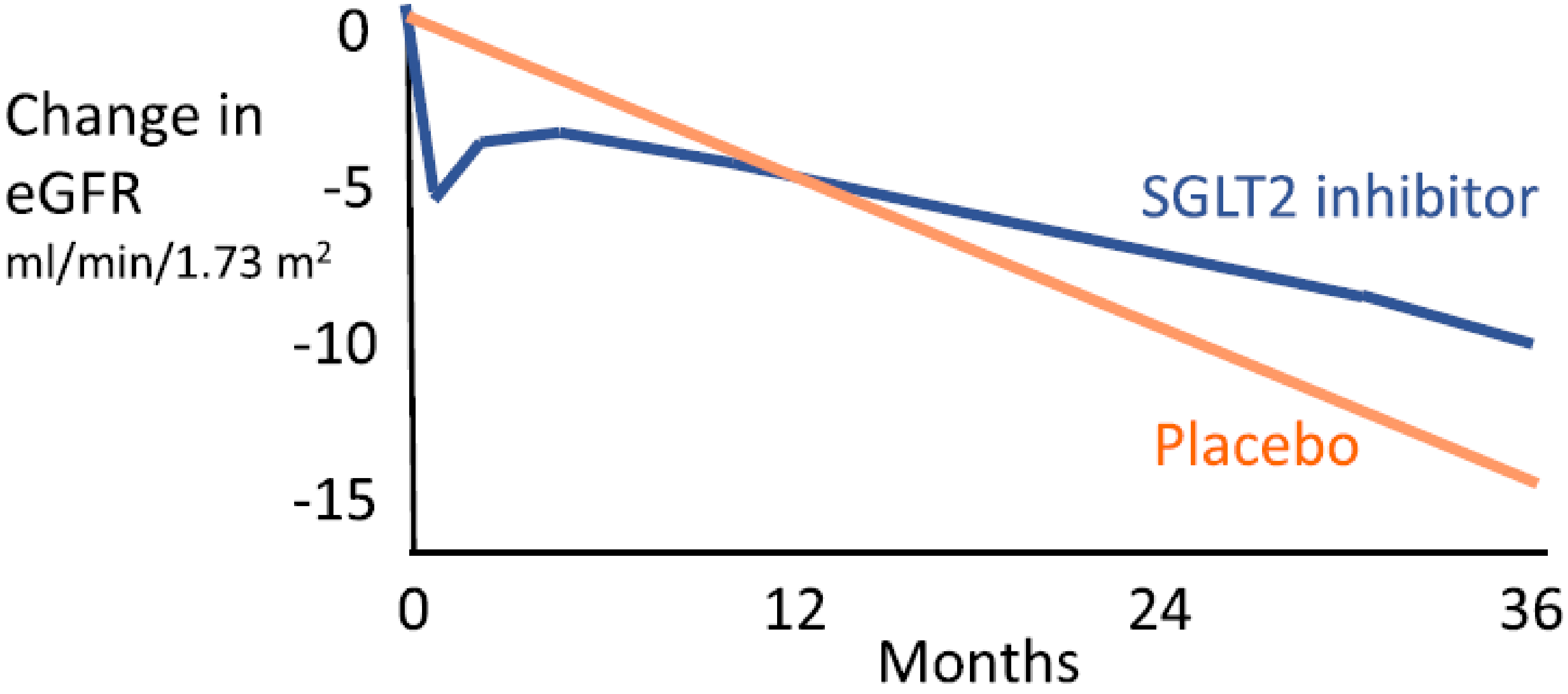
- Some reduction in blood pressure (particularly if very hyperglycaemic). Often a beneficial side effect.
- Volume depletion (dehydration, dizziness) was not seen in children. But potential risk if severe illness or at risk of dehydration.

Reducing hyperfiltration

- Transient drop in renal function (raised creatinine).
- Do not check renal function in early weeks of treatment.
- Renoprotective in long-term.

SGLT-2 Inhibitors

Renal effects



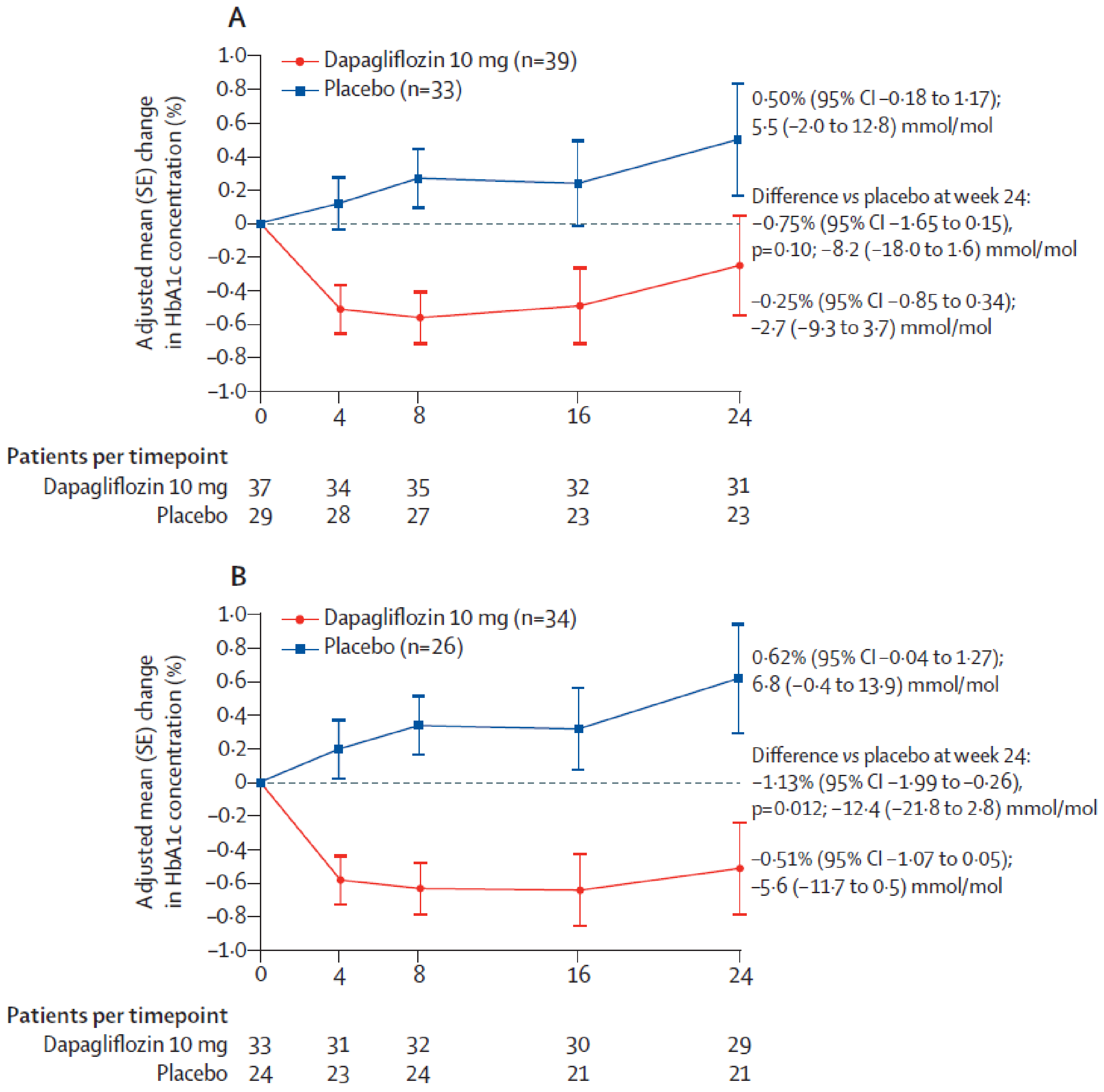
Bailey et al. Current Diabetes Reports 2022

SGLT-2 Inhibitors

Key trial – dapagliflozin

Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study

William V Tamborlane, Lori M Laffel*, Naim Shehadeh, Elvira Isganaitis, Michelle Van Name, Jayantha Ratnayake, Cecilia Karlsson, Ensio Norjavaara*



- *N=72 (53 age 10-17y; 19 age 18-24y)*
- *Add-on to metformin and/or insulin*

- ***HbA1c reduction 1.1% (12mmol/mol)*** *when excluding non-adherence*

- *No cases of DKA*
- *Hypoglycaemia – children were also on insulin*
- *No significant weight loss*

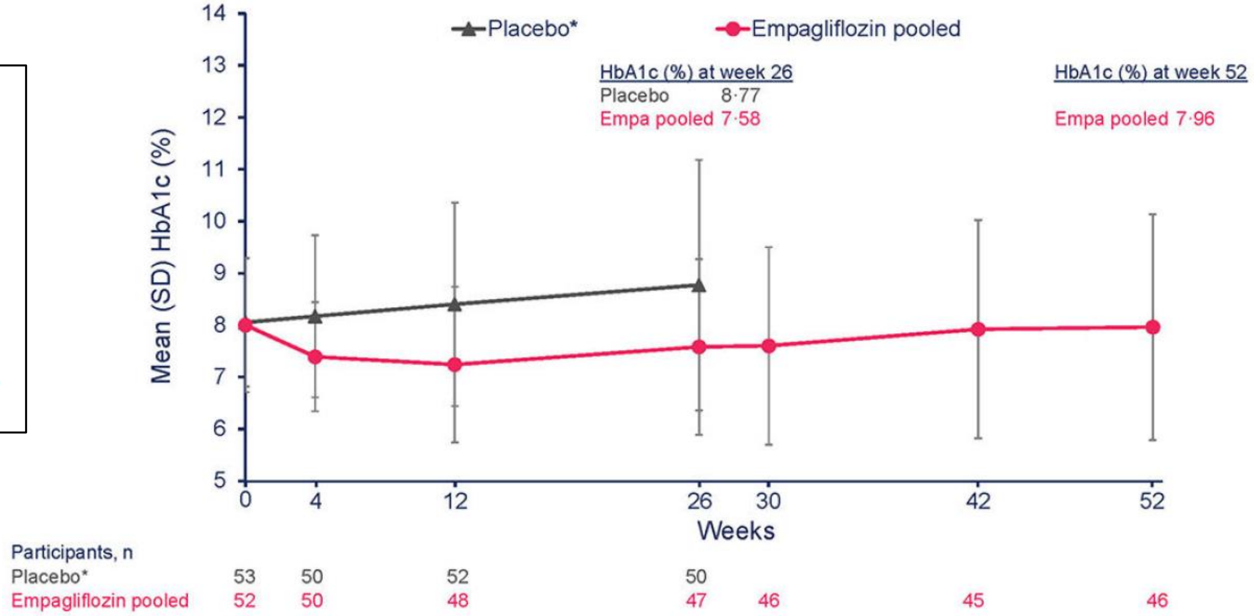
Tamborlane et al. Lancet Diabetes Endocrinol 2022

SGLT-2 Inhibitors

Key trial – empagliflozin

Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in youth with type 2 diabetes: a multicentre, randomised, double-blind, parallel group, phase 3 trial

Lori M. Laffel, MD[1] [Prof], Thomas Danne, MD[2] [Prof], Georgeanna J. Klingensmith, MD[3] [Prof], William V. Tamborlane, MD[4] [Prof], Steven Willi, MD[5] [Prof], Philip Zeitler, MD[6] [Prof], Dietmar Neubacher, Dipl Stat[7], Jan Marquard, MD[8] DINAMO Study Group



- *N=262 (10-17y)*
- *Add-on to metformin and/or insulin*

- ***Empagliflozin HbA1c reduction 0.84% (9.2 mmol/mol)***

- *No cases of DKA*
- *No cases of severe hypoglycaemia*
- *Small reduction in weight and BP, but not statistically significant.*

Laffel et al. Lancet Diabetes Endocrinol 2023

SGLT-2 Inhibitors

Formulations

Dapagliflozin

- *Always start with 10mg daily.*

Empagliflozin

- *Start with 10mg daily. Increase to 25mg if tolerated.*

- *No need to take at certain time of day or in relation to food.*
- *No risk of hypoglycaemia.*

SGLT-2 Inhibitors

Formulations

Dapagliflozin/Metformin

5mg/850mg, 5mg/1000mg

Empagliflozin/Metformin

5mg/850mg, 5mg/1000mg, 12.5mg/850mg, 12.5mg/1000mg

- *Less useful in practice:*
  - *Require twice-daily dosing.*
  - *Metformin is <u>standard-release</u> formulation. More likely to get GI side effects.*

SGLT-2 Inhibitors

Side effects & counselling

UTI (6%) and thrush (2%)

- *Particularly in girls. Managed with hydration or OTC treatment in most cases.*
- *Counsel on good genital hygiene.*
- *Does not correlate with dose (i.e., no benefit in reducing dose if this is experienced).*

Hypoglycaemia

- **Not** a risk if not on insulin. No glucose monitoring necessary.
- If on insulin: consider insulin dose reduction after starting SGLT-2 inhibitor.

Euglycaemic DKA

- *Rare complication. Not reported in children.*
- *Counsel on recognising signs of DKA (even if normoglycaemic).*
- *If acutely unwell:*
  - *Hospital: check ketones on admission + daily (even if normoglycaemic). Consider suspending therapy.*
  - *Home: **sick day rules**. Hold treatment if D&V, fever, severe infection, dehydrated.*

Pregnancy

- *Effect on foetus is not known. Girls recommended to use appropriate contraception.*

Guidelines

		ACDC 2023, UK Consensus 2024	NICE 2023	ISPAD 2024
At diagnosis	**HbA1c <70 mmol/mol (8.5%)**	Metformin	Metformin	Metformin
At diagnosis	**HbA1c ≥70 mmol/mol (8.5%) or symptomatic**	Metformin + Insulin	Metformin + Insulin (If ketotic: basal-bolus insulin)	Metformin + Insulin (If ketotic: basal-bolus insulin)

Second line	○ Liraglutide ○ Dapagliflozin	○ Liraglutide/dulaglutide ○ Empagliflozin (if GLP1 not tolerated)	○ GLP1 ○ SGLT2 ○ TZD
Third line	○ Insulin ○ Basal up to 1.5 unit/kg/day, then start basal-bolus	○ Insulin	○ Add GLP1/SGLT2/TZD ○ HbA1c ≥70mmol/mol (8.5%): add/increase insulin
When to wean insulin?	At 4 weeks if HbA1c < 48 mmol/mol	HbA1c ≤ 48 mmol/mol (or FBG 4-7mmol/L or postprandial glucose 5-9mmol/L)	At 4 weeks if autoantibody negative

GLP1, glucagon-like peptide-1 agonist; SGLT2, sodium-glucose transporter-2 inhibitor; TZD, thiazolidinedione.

ACDC 2023, White et al. BMC Medicine 2024, NICE 2023, Shah et al. Horm Res Pediatr 2024

NPDA Data 2023/24

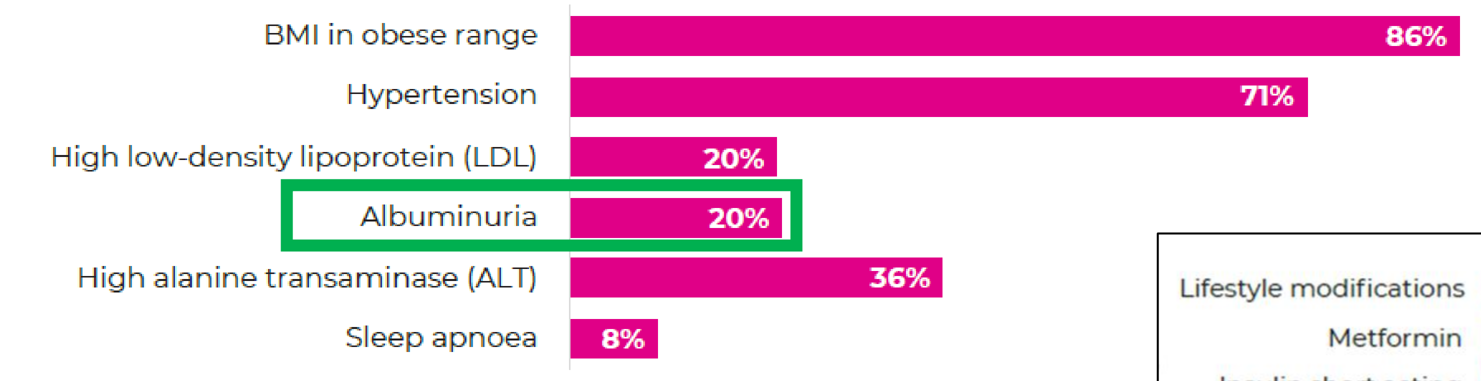
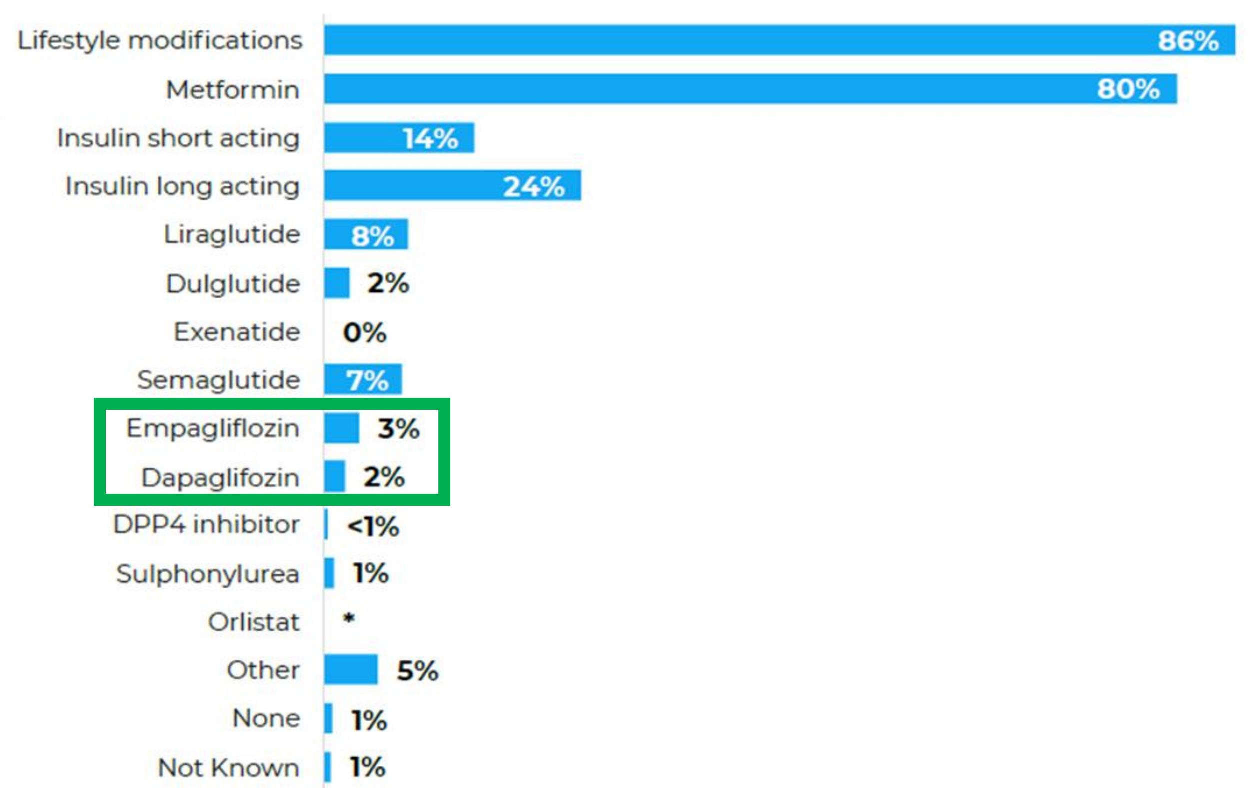


Figure 7: Percentage of CYP with Type 2 diabetes and abnormal health checks.



NPDA Type 2 Diabetes Spotlight Audit 2023/24. RCPCH Audits 2025.

Case Study

10 year old girl admitted to hospital with coryza, sore throat, fever.

- *Incidental finding of glucose 12.7 mmol/L. No polydipsia, polyuria, fatigue, weight loss.*
- *Acanthosis nigricans around neck.*
- *South Asian ethnicity. Family history of (?type 2) diabetes – mother, father, five paternal uncles*
- *HbA1c 97 mmol/mol, C-peptide 933 pmol/L*
- *Weight 55kg (98th centile), BMI SDS +2.2*

Diagnosis (Feb 2019):

- *Start metformin 250mg BD + Lantus*

May 2019:

- *HbA1c 79 mmol/mol, triple antibody negative*
- *Increase metformin to 500mg BD*
- *Add Novorapid TDS*

Case Study

Family not engaging as was hoped for; not perceiving diabetes as a significant diagnosis (many family members are affected); language barrier; child left to self-manage.

Feb 2022 (age 13.5 years):

- *HbA1c 74 mmol/mol (8.9%), weight 67.6 kg (91-98th centile)*
- *On basal-bolus insulin regimen*
- *Decision to admit to behavioural support unit for 2 weeks:*
    - *Start semaglutide + dietetic input*
    - *Wean insulin to stop over next 2 months*

Case Study

HbA1c steadily dropped and Lantus was stopped.

August 2022:

Frequent vomiting (binge eating). Semaglutide reduced to 0.25mg.
HbA1c rose to 81 mmol/mol and Lantus restarted.

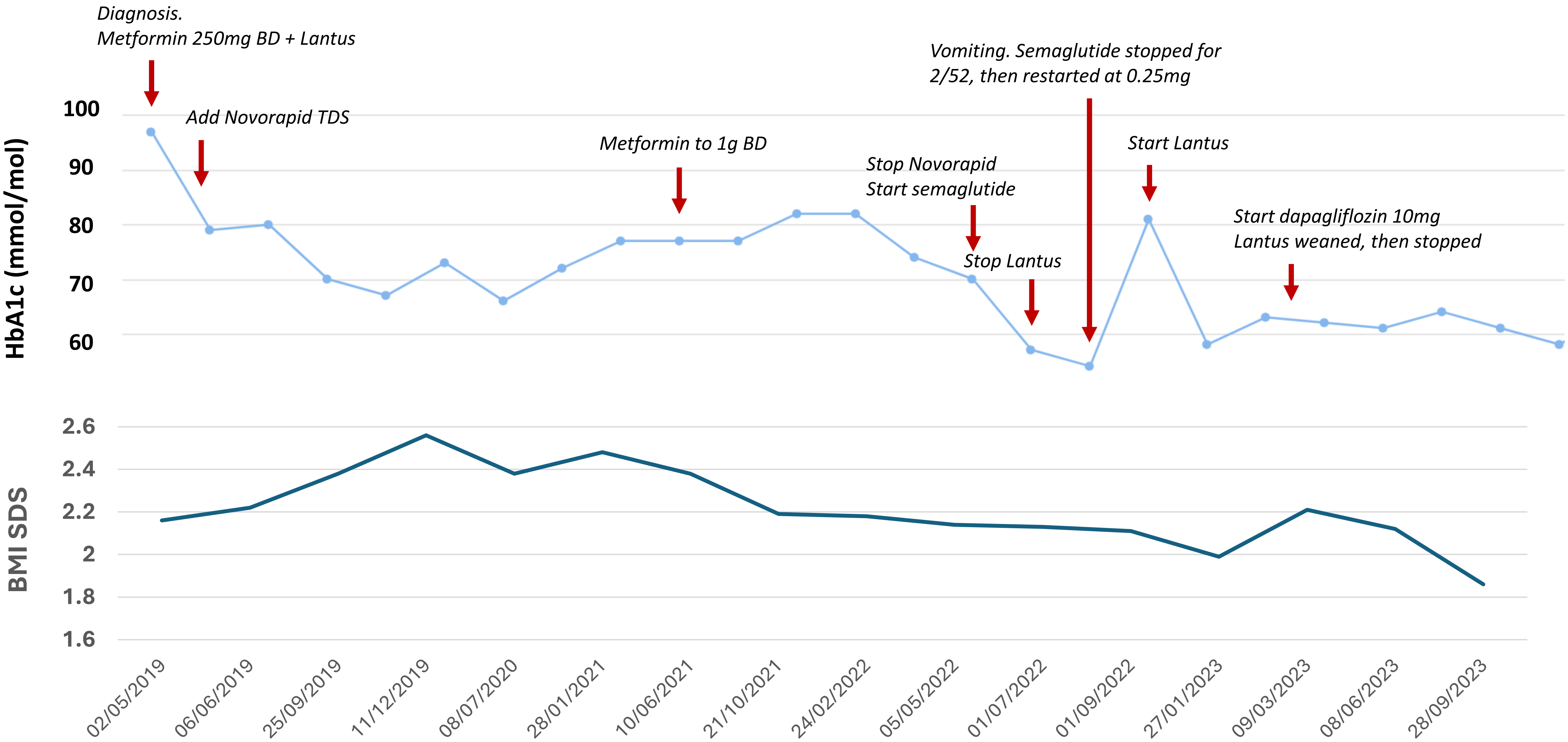
Mar 2023:

HbA1c 62 mmol/mol, BMI SDS +2.21.
Unable to tolerate higher semaglutide doses.
Start dapagliflozin and wean Lantus to stop.

Sept 2023:

HbA1c 58 mmol/mol, BMI SDS +1.86

Case Study



Diagnosis.
Metformin 250mg BD + Lantus
Add Novorapid TDS
Metformin to 1g BD
Stop Novorapid
Start semaglutide
Stop Lantus
Vomiting. Semaglutide stopped for 2/52, then restarted at 0.25mg
Start Lantus
Start dapagliflozin 10mg
Lantus weaned, then stopped
HbA1c (mmol/mol)
100
90
80
70
60
BMI SDS
2.6
2.4
2.2
2
1.8
1.6
02/05/2019
06/06/2019
25/09/2019
11/12/2019
08/07/2020
28/01/2021
10/06/2021
21/10/2021
24/02/2022
05/05/2022
01/07/2022
01/09/2022
27/01/2023
09/03/2023
08/06/2023
28/09/2023

Case Study

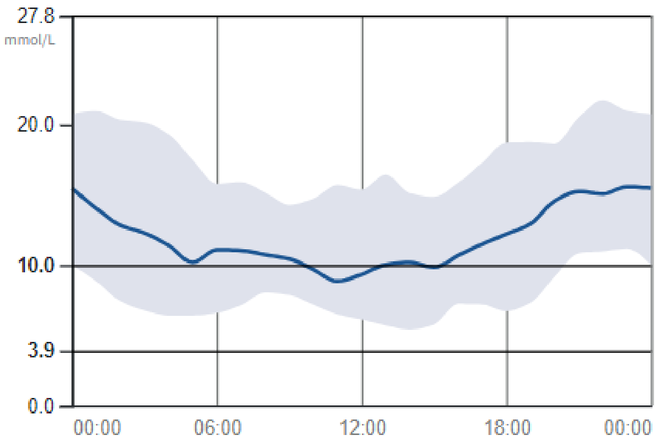
28 March 2023 – **10 April 2023**

FreeStyle Libre 3
SN: 53ddc77c-b352-4fda-a6bc-77399df49d71

12.1 mmol/L
Average Glucose

86%
Days of Data

0
Hypo events



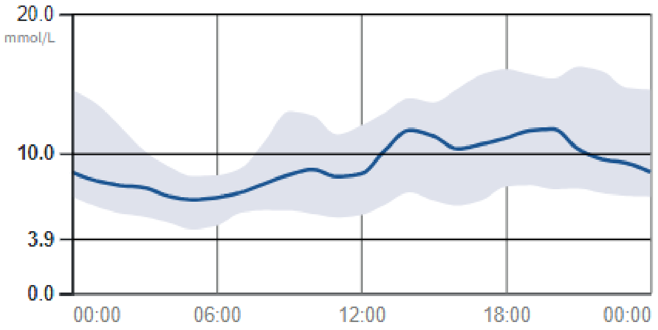
6 June 2023 – **19 June 2023**

FreeStyle Libre 3
SN: 53ddc77c-b352-4fda-a6bc-77399df49d71

9.3 mmol/L
Average Glucose

86%
Days of Data

0
Hypo events



Thank you