# Paediatric Type 2 Diabetes – from 3 months after diagnosis

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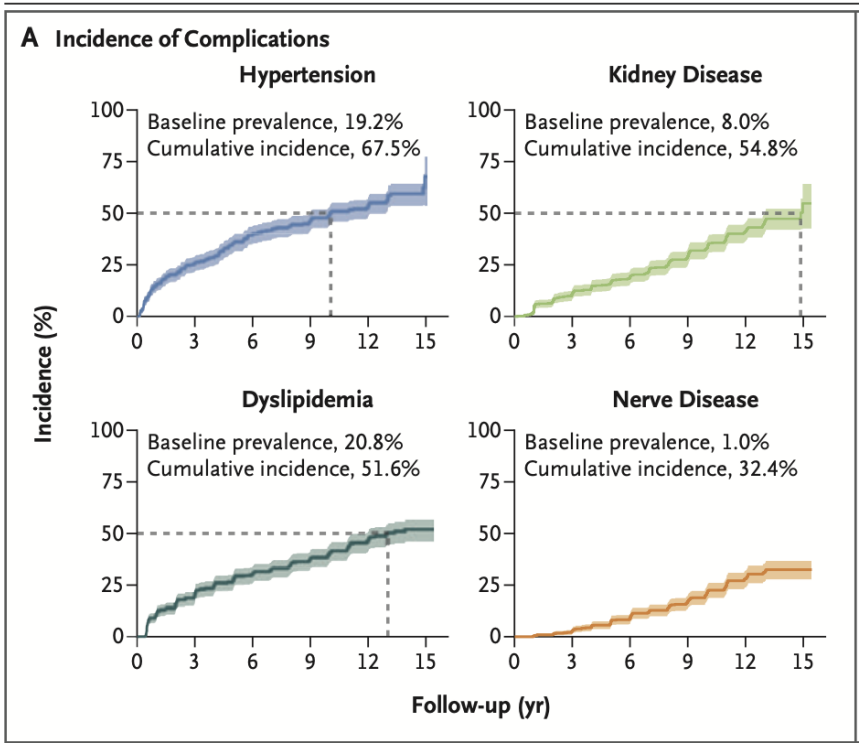
***Helping all children and young people with diabetes in East London to lead a healthy, happy life.***

Barts and The London
School of Medicine and Dentistry

# Outline

- Target HbA1c and BGs
- Escalation of treatment
- Available drugs and trial results
- Treatment of complications.
- NICE guideline

# Long term complications in T2D in TODAY study

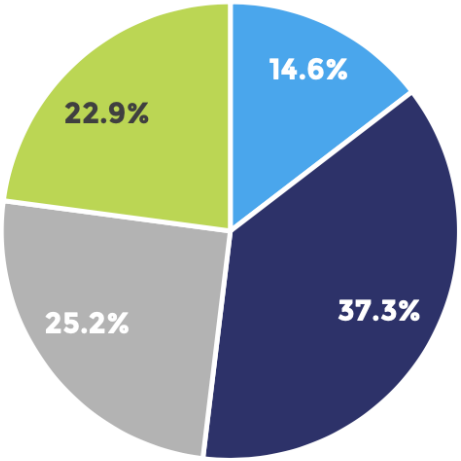


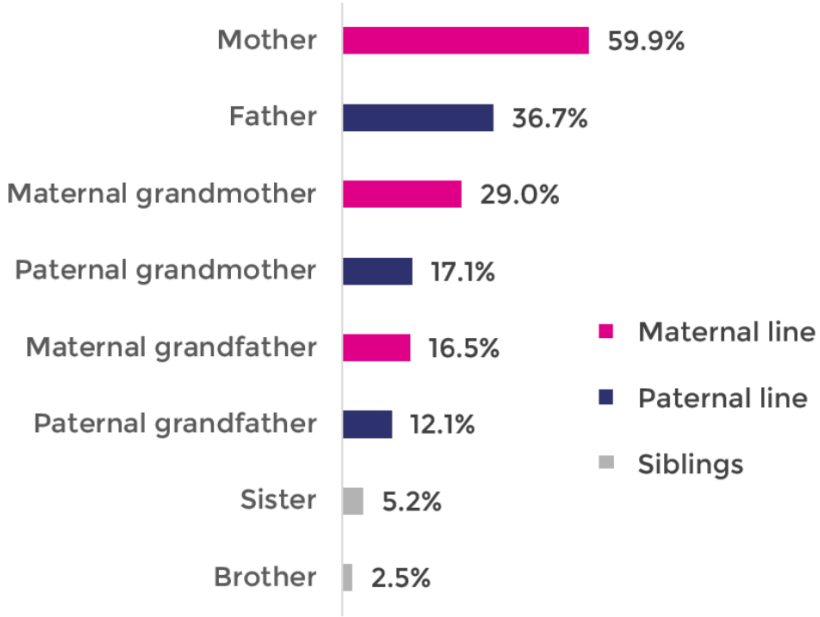

- Follow up of 500 CYP with T2D
- Previously in TODAY study (2004-2011)
- Age 26.4±2.8 years
- Mean time since diagnosis 13.3±1.8 yrs

- Conclusion: Complications increase with increased duration of T2D

Today Study Group, NEJM 2022

# Family history of T2D in 85%



# Aims in T2D management

- HbA1c: < 48 mmol/mol
- Glucose: Preprandial 3-7 (3.9-7 if on insulin), postprandial 4-9 mmol/L (NICE)
- Weight loss 5-10% and long term BMI < 85$^{TH}$ centile:
- Co-morbidity screening and treatment

# Recommendations (ACDC)

- HbA1c should be measured every 3 months in CYP with T2DM
- HbA1c targets should be individualised, noting the low risk of hypoglycaemia.
- Intensify treatment if HbA1c is not below 48mmol/mol (6.5%) at 3 months.
- Individualise HbA1c Target after the first 3 months but aiming to keep below 48mmol/mol (6.5%)

# Glucose testing

- ADA/ISPAD/NICE/ACDC: BG should be monitored in all patients with T2DM
- Frequency should be tailored to the individual based on treatment-factors.

- RLH:
- **If on MDI**: SMBG at least 5 times a day to adjust doses, give corrections and monitor for hypoglycaemia, similar to T1D
- **If stable, and not on MDI**:
  - When BG still often > 9 → test fasting BG and 2 hrs after each meal, and pre-meals if needed
  - When BG mostly < 9 → test once a week fasting BG and once a day post-meal

- **CGM/Flash**: if insulin dependent, or learning difficulties, severe/frequent hypoglycaemia, or BG testing > 8 x per day (**NICE guideline, 2023**).

# Hypoglycaemia

- Hypoglycaemia
  - if on insulin → BG <3.9 needs treating in same way as T1D
  - if on Metformin only → only BG <3.0 needs treating (hypoglycaemia not expected)

# Clinical case - I

- 11.5 yr old Asian boy, referred from gastro enterologist, fatty liver.
- Increase in weight at age 4 and again at age 10.  Four kg increase in last 6 months.
- No other history of note.
- Fam history: both parents T2D, diagnosed around 50 yrs of age, mother on insulin
- Height 153.6 cm, weight 104 kg, BMI 44.1 kg/m2. BP 98$^{th}$ centile.
- OGTT performed: BG  5 -- > 15.5 mmol/L. HbA1c 52. Anti GAD, IA2, ZnTF8 negative.
- C peptide 416, ALT 62, urine alb/creat 0.3, cholesterol 4.2 mmol/L, LDL 2.3 mmol/L
- Started Metformin 500 mg OD -- > BD → 1000 mg BD
- 1 month later: HbA1c 45, lost 1 kg. Sleep study: mild OSA.

# Clinical case - I

- 1 month later: HbA1c 51, weight 105 kg (+ 2 kg), random BG 9.6.
- Not on full dose Metformin. Advised BG testing and full dose Metformin.
- Referred to CAHMS.
- Dietitian: attempted phone call
- 3 months later: phone review due to pandemic. Not testing BGs
- Advised to take Metformin together with his mum and to do post meal BGs
- 3 months later (Oct 2020): weight – 8kg (98kg) , HbA1c 130, BG 16, ketones neg. ALT 241

- WHAT TO DO?

# Clinical case - I

WHAT TO DO ?

- A) Add basal insulin
- B) Add fast acting insulin for corrections
- C) Add fast acting insulin for meals
- D) Add Liraglutide
- E) A combination of the above

# Clinical case - I

- Admitted to assess BG profile, corrections if BG > 14 (required 3 x 2U overnight)
- Start Liraglutide sc OD 0.6 mg
- Added Tresiba 8 U
- Switched to slow release Metformin OD
- Psychologist re-introduced.
- Start Freestyle Libre
- Increased Liraglutide to 1.8 mg OD sc over next few weeks

# Medical management at 3 months

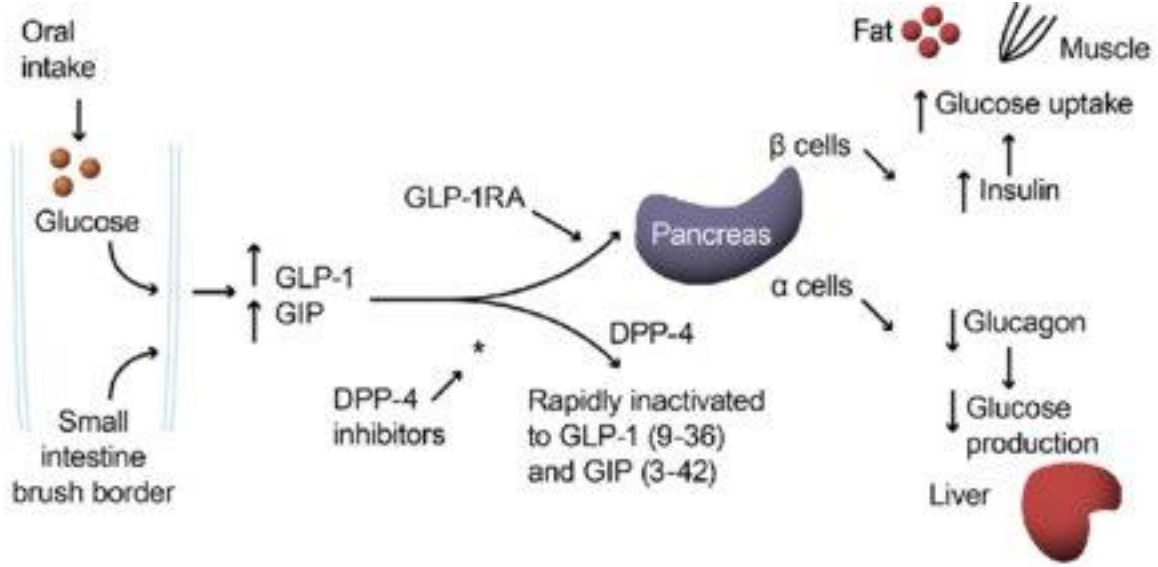
- Ensure taking Metformin 2000 mg per day (**Liquid or SR Metformin** if needed)
- **Ensure insulin is weaned as much as possible**

- If no further possibility to reduce insulin doses, or Metformin monotherapy not sufficient to reach target of hbA1c < 48, **start Liraglutide** 0.6 mg SC OD to max dose of 1.8 mg and wean insulin by 10% at a time when possible

- **Engagement:** keyworker, same D/D/N/P, family support worker, school, youth worker

# GLP1RA and DPP-4 inhibitors

- Glucagon like peptides: GLPs produced in small intestine, bind to receptors in the pancreas to increase insulin and decrease glucagon
- Di-peptyl peptidase 4 breaks down GLPs

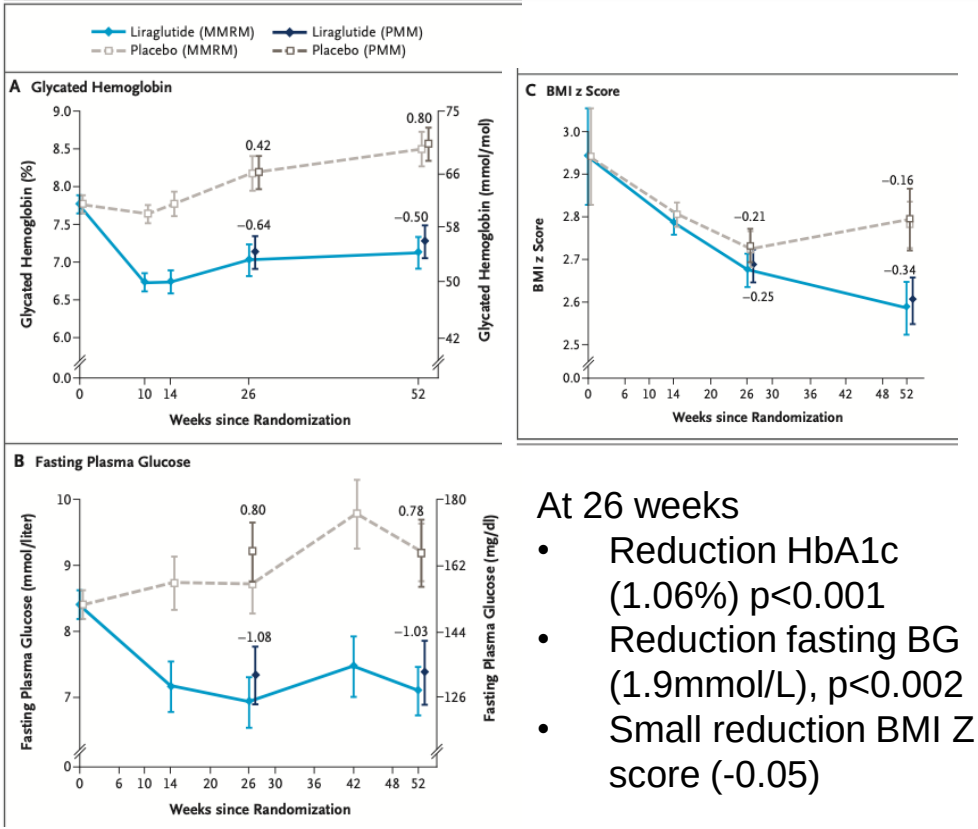


# Liraglutide (Victoza)

- Glucagon-like peptide 1 receptor agonist (GLP1-R agonist)
- Increases insulin secretin, suppresses glucagon secretion and slows gastric emptying
- Licence: T2D if existing treatment fails to achieve good glycaemic control in CYP from 10 yrs of age with BMI > 85$^{th}$ centile
- **Now recommended by NICE (2023) for paediatric T2 diabetes**

- Can be used as monotherapy, or with Metformin and/or insulin
- Once daily sc injections.
- Start 0.6 mg,  increase weekly or more slowly to 1.2 mg and max 1.8 mg OD
- Contra-indications: gastroparesis, IBD, pregnancy, previous pancreatitis (and MEN?)
- Drug interaction: lisinopril, not with OCP

# Liraglutide vs placebo for 26 weeks, OLE to 52 weeks




At 26 weeks

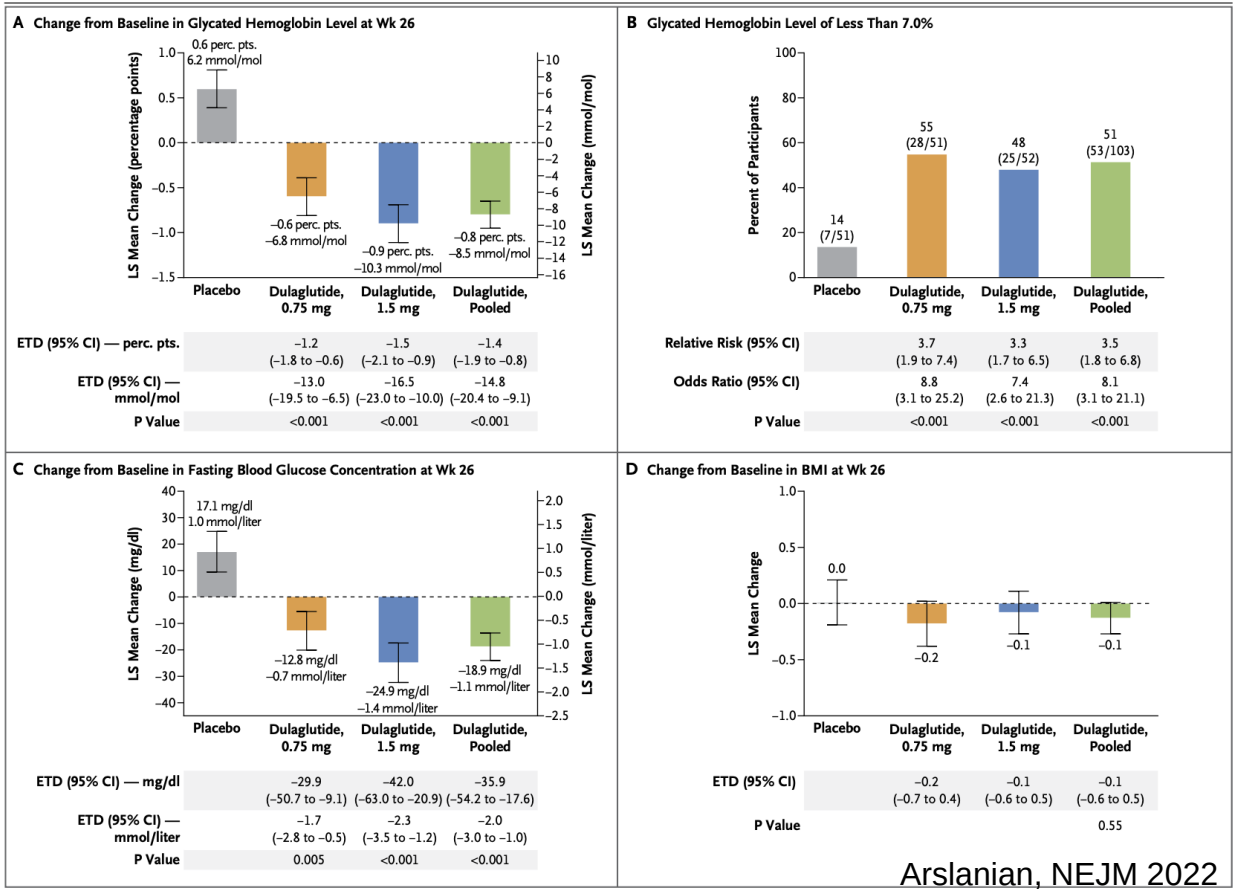
- Reduction HbA1c (1.06%) p<0.001
- Reduction fasting BG (1.9mmol/L), p<0.002
- Small reduction BMI Z score (-0.05)

**Side Effects Liraglutide vs placebo**

- Gastro-intestinal (nausea, diarrhea, vomiting, abdominal pain) – 20-25%
- 55% of patients at max dose in 3 weeks (not all patients required max dose)
- Hypoglycaemia 45% vs 25%, none severe
- Lipase higher in Liraglutide vs placebo (but in normal range)
- DKA (if insulin weaned to quickly), pancreatitis and thyroid disorder (BNF)
- Warn for signs of DKA and pancreatitis.

Tamborlane, NEJM 2019

# Dulaglutide 1.5 mg/ 0.75 mg/ placebo **once weekly** 26 weeks




Arslanian, NEJM 2022

Results vs placebo:

- HbA1c: - 0.8% vs +0.6% (p<0.001)
- HbA1c < 7.0%: 51% vs 14% (p<0.001)
- Fasting glucose: -1.1 mmol/L vs +1.0 mmol/L (P<0.001)
- BMI: -0.1 kg/$m^2$ vs 0.0 (non significant)
- 1.5 mg most effective

# Dulaglutide – adverse events

| | Placebo/ Dulaglutide 0.75 mg (N=51) | Dulaglutide 0.75 mg (N=51) | Dulaglutide 1.5 mg (N=52) | Pooled Dulaglutide (N=103) |
|---|---|---|---|---|
| **Patients with at least one adverse event, n (%)*** | | | | |
| Any adverse event | 40 (78.4) | 40 (78.4) | 42 (80.8) | 82 (79.6) |
| Serious adverse event | 3 (5.9) | 2 (3.9) | 1 (1.9) | 3 (2.9) |
| Adverse event leading to treatment discontinuation | 1 (2.0) | 1 (2.0) | 2 (3.8) | 3 (2.9) |
| Adverse events in at least 5% of patients | | | | |
| Diarrhea | 7 (13.7) | 9 (17.6) | 14 (26.9) | 23 (22.3) |
| Headache | 7 (13.7) | 10 (19.6) | 10 (19.2) | 20 (19.4) |
| Nausea | 5 (9.8) | 8 (15.7) | 12 (23.1) | 20 (19.4) |
| Vomiting | 6 (11.8) | 12 (23.5) | 9 (17.3) | 21 (20.4) |
| Abdominal pain upper+ | 6 (11.8) | 3 (5.9) | 9 (17.3) | 12 (11.7) |
| Upper respiratory tract infection | 7 (13.7) | 2 (3.9) | 6 (11.5) | 8 (7.8) |
| Nasopharyngitis | 6 (11.8) | 5 (9.8) | 5 (9.6) | 10 (9.7) |
| Abdominal pain^ | 3 (5.9) | 6 (11.8) | 2 (3.8) | 8 (7.8) |
| Allergic/hypersensitivity reaction events | 3 (5.9) | 3 (5.9) | 4 (7.7) | 7 (6.8) |
| Injection-site reactions | 6 (11.8) | 7 (13.7) | 5 (9.6) | 12 (11.7) |
| **Hypoglycemia, n (%)** | | | | |
| Severe | 0 | 0 | 0 | 0 |
| All with PG <54 mg/dL (<3.0 mmol/L) | 1 (1.0) | 2 (3.9) | 2 (3.9) | 4 (3.9) |
| Documented symptomatic PG<70 mg/dL (<3.9 mmol/L) | 6 (11.8) | 7 (13.7) | 5 (9.6) | 12 (11.7) |

- Gastro-intestinal side effects reported to be mostly mild and transient, and in first 4 weeks.
- No pancreatitis, but lipase and amylase levels higher in dulaglutide group
- 1 patient had to stop due to vomiting

Arslanian, NEJM 2022

# Other GLP1R agonists

- **Exenatide** for **T2D** in CYP (**from 10 yrs**), **once weekly SC injection**
  - o HbA1c decreased vs placebo (-0.36 vs +0.49%), no effect on BMI

- **Liraglutide (Saxenda)** for **obesity** (**from 12 yrs**), **OD SC, max 3.0 mg**
  - o **BMI reduction -4.7**% after 26 weeks, 44% vs 19% reduced BMI by >5%, weight loss -5.0%

- **Semaglutide** for **obesity (with or without T2D, from 12 yrs**), **once weekly SC, max 2.4 mg** (STEP-TEENS)
  - o **BMI reduction 16% vs +0.6%** after 68 wks, weight loss 15%
- **Adults: Semaglutide** for **T2D and obesity > 18 yrs**, **once weekly SC injection**
  - o Weight loss 15-17%

Kelly, NEJM 2020, Arslanian, NEJM 2022, Shankar Ped Diab 2022, Tamborlane, Diab Care 2022, Weghuber, NEJM 2022

# Clinical case – I

- Admission Oct 2020: HbA1c > 130, 98 kg, ALT 241, start Liraglutide
- Nov 2020: mother passes away due to COVID.
- Jan 2021: HbA1c 60 mmol/mol
- March 2021: HbA1c 68 mmol/mol, weight 104 kg
- June 2021: HbA1c 85 mmol/mol, weight 107 kg
- Oct 2021: Hba1c 116 mmol/mol, weight 105 kg, ALT 91, Tresiba increased
- Dec 2021: Hba1c 108, weight 102 kg
- March 2022: HbA1c 102, weight 108 kg, ALT 178, not scanning FS Libre, aim to admit, weekly updates
- **May 2022: ALT 202, admission for optimisation**..

# Clinical case - I

WHAT TO DO ?

- A) Change to weekly Dulaglutide
- B) Change to Saxenda
- C) Add SGLT2 inhibitor
- D) Add DPP4 inhibitor

# Clinical case – I

WHAT DID WE DO ?

- Changed to Saxenda (Liraglutide to 2.4 mg and then 3.0 mg OD)

Also:

- Changed to Metformin SR again.
- Increased Tresiba dose
- Started Dexcom.
- Repeated dietary and exercise advise

# Clinical case - I

- June 2022: HbA1c 89 mmol/mol , weight 108 kg, increase Saxenda to 3.0 mg OD
- Repeat pancreas antibodies: negative. DNA for obesity gene panel – not performed.
- Oct 2022: HbA1c 69 mmol/mol, weight 116 kg, agreed to gym.
- Dec 2022: HbA1c 79 mmol/mol, weight 113 kg, agreed to meal replacement shake OD
- Jan 2023: hbA1c 89 mmol/mol , weight 113 kg, BP 140/87 mmHg, not started MR, start lisinopril 5 mg od, Tresiba increased, agreed to gym, continuing psych input.
- March 2023: HbA1c 87 mmol/mol , weight 111 kg, BP 123/84, tried but stopped meal replacement drinks, going to gym twice a week, agreed to referral for bariatric surgery for information only, lisinopril not started, increased Liraglutide to 21 U.
- April 2023: HbA1c 99, weight 111 kg, BP 134/86. No MR shakes, not going to gym, refused lisinopril.

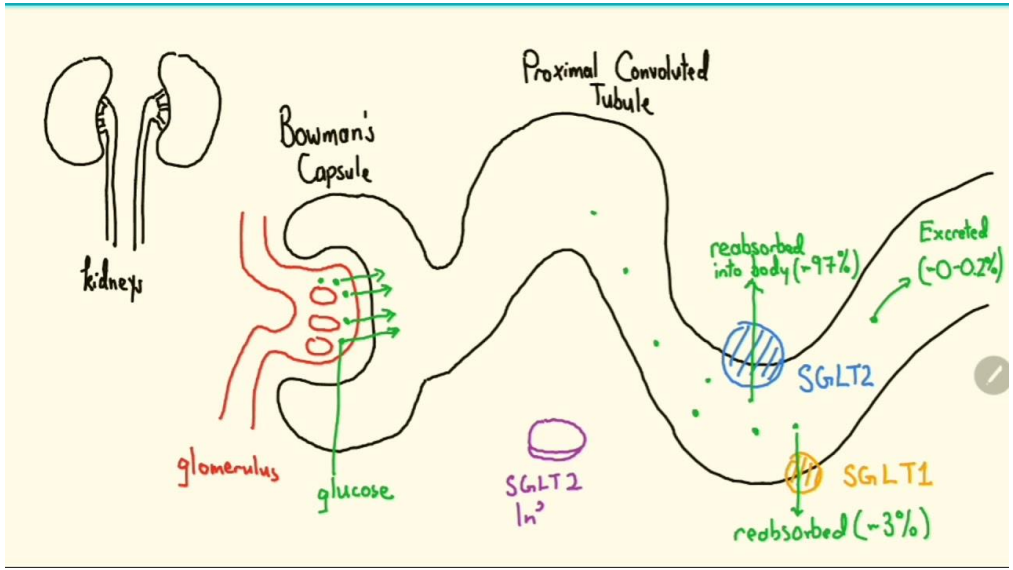
# Clinical case - I

WHAT TO DO ?

- A) Change to weekly Dulaglutide
- B) Increase Tresiba
- C) Add mealtime fast acting insulin
- D) Add SGLT2 inhibitor
- E) Add DPP4 inhibitor

# SGLT2 inhibitors

- inhibit SGLT2 (Na/glucose co transporter) in proximal renal tubule
- Increase urinary glucose concentration and thus lower blood glucose
- Oral tablets
- Extremely effective in adults with T2D, and may have additional cardiovascular effects



# SGLT2 inhibitors in T2 in CYP

- **SGLT2 inhibitors: inhibit SGLT2 (Na/glucose transporter) in proximal renal tubule, once daily tablets**
- - **Dapagliflozin** (10-24 yrs): (Astra Zeneca) (licensed)
    - o **no effect on HbA1C** in intention-to-treat analysis
    - o subanalysis of compliant patients Hba1c -0.51 vs +0.62%
  - **Empagliflozin**/Linagliptin: **HbA1c -0.84% vs placebo.** Linagliptin no effect (Boerhinger, DINAMO)
  - Dapagliflozin/Saxagliptin : no data available yet (Astra Zeneca T2NOW study)
  - Ertugliflozin: no data available yet (Merck VERTIS study)

- **Side effects SGLT2 inhibitors:** DKA (in Type 1 diabetes), genital infections, hypoglycaemia
- **Warning MHRA/BNF: stop when DKA suspected or when hospitalized with severe illness/trauma.**

Tamborlane, Lancet Diab Endocr 2022
Tahrani, Nat Rev Endo 2016; Laffel, Lancet Diab Endocr 2023

# DPP4 inhibitors

**Di-peptidyl peptidase inhibitors (oral)** → reduce degradation of GLP1

- **Sitagliptin** (Januvia/Janumet Merck)
  - no effect on HbA1c
- **Saxagliptin** (Onglyza, Astra Zeneca) :
  - no data available from Saxagliptin only study
  - T2NOW study: Saxagliptin with/without dapagliflozin
- **Linagliptin**: 1mg/5mg/placebo, 12 wks
  - 0.38% and 0.48% reduction in HbA1c (not significant)

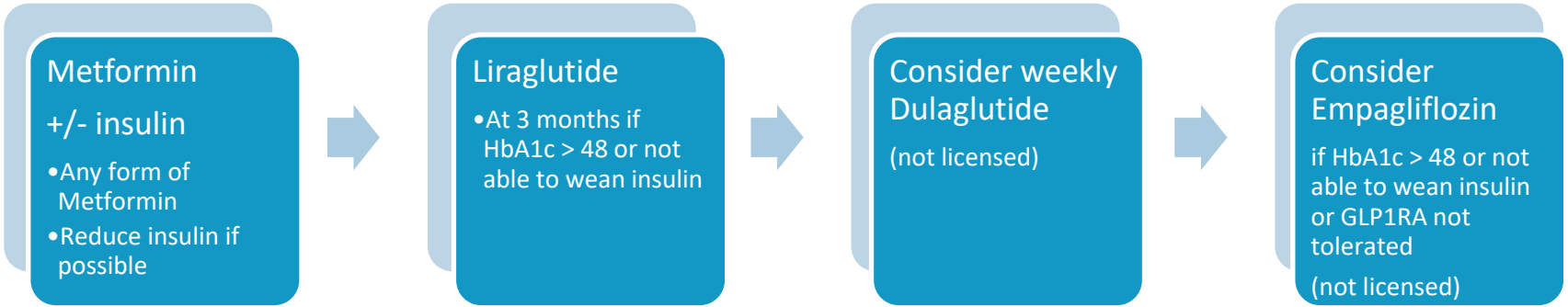
Shankar Ped Diab 2022, Jalaludin Paed Diab 2022
Tamborlane, Ped Diab 2017

# Sulfonylureas, thiazolinediones

- **Sulfonylurea: increase insulin secretion by binding SUR1 and closing K channels**
  - Gliclazide, glipizide, glibenclamide (adults): no data in children
- **(Thiazolinediones: PPAR-gamma agonists)**
  - Pioglitazone, Rosiglitazone: safety concerns and taken off the market

**No role in treatment of T2D in CYP**

# Algorithm for drug treatment in CYP with T2D




NICE guideline T1/T2D in CYP, 2023

# Treatment of complications (RLH/ACDC)

- **Hypertension**
  - BP > 95$^{th}$ centile for height and sex on 3 occasions, 24 hr BP if possible
  - First line: **focus on weight loss, exercise, and reduced salt intake**
  - Second line if after 6 months no effect: start **ACE inhibitor**
  - Aim for BP < 90$^{th}$ centile
- **Dyslipidaemia**
  - If abnormal, **focus on dietary modification and improvement of hyperglycaemia**
  - If after 6 months LDL still >3.4 mmol/L, **start statin**
  - Aim for LDL <2.6 mmol/L and increase statins accordingly 3 monthly or refer
  - If persistent hypertriglyceridaemia , consider fibrate treatment (with lipid specialist)

ACE inhibitors/statins – advice on contraception
Statins licenced from age 10

# Treatment of complications (RLH/ACDC)

- **NAFLD**
  - If fatty liver on US, **aim for weight loss and optimizing glycaemia**
  - Yearly US and consider referral gastro-enterologist if not improving
  - **Refer to gastro-enterologist** if ALT > 2-3x upper normal range
- **Albuminuria**
  - If spot urine albumen/creat ratio 3-30 mg/mmol, **repeat on 2 early morning samples** within 3-6 months
  - If continuing abnormal, despite lifestyle measures, **start ACE inhibitor** (lisinopril, enalapril)
  - Refer to nephrology, if urine alb/creat > 30 mg/mmol
- **Obstructive sleep apnoea**
  - Refer to respiratory sleep specialist

# Last but not least…

- Consider bariatric surgery

# Barts Health Paediatric Diabetes Team

**Type 2 focus group**
Evelien Gevers, consultant
Nicky Moore, Band 8 PDSN
Waseema Skogen, dietitian
Elizabeth Nash, psychologist
Nish Patel, database manager
Yasmin Khatun, database admin
Maggie Murphy, secretary

**Current consultants RLH**
Evelien Gevers (Lead T2)
Ruben Willemsen (Lead T1)
Claire Hughes
Pratik Shah
Rathi Prasad / Rosie Brungs

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# Proforma T2 clinic – for patient

Barts Health NHS
NHS Trust

**Type 2 Diabetes Clinic**

Name: Date:

**Is there anything you would like to discuss with the diabetes team today?**

.....

1. How confident have you felt with:
(1= not confident at all 5= very confident)

Managing Blood Glucose levels
1 2 3 4 5

Taking Medication
1 2 3 4 5

Achieving dietary goals
1 2 3 4 5

Achieving activity Goals
1 2 3 4 5

2. How are you coping with your diabetes and:
(1=very badly, 5 = really well);

School / Education / Work
1 2 3 4 5

Family Life:
1 2 3 4 5

Friends and Social Life
1 2 3 4 5

Activities and Hobbies
1 2 3 4 5

Barts Health NHS
NHS Trust

My **HbA1c** today is ..... previously it was ..... .....

| My Average Blood Glucose mmol/l Finger prick | HbA1c % Clinic 3 month old measurement | HbA1c mmol/mol Clinic 3 month new measurement |
|---|---|---|
| 6.2 | 5.5% | 37 |
| 7.8 | 6.5% | 48 |
| 8.2 | 6.75% | 50 |
| 8.6 | 7.0% | 53 |
| 9.5 | 7.5% | 58 |
| 10.1 | 8.0% | 64 |
| 11.0 | 8.5% | 70 |
| 12.5 | 9.5% | 80 |

**Food Goals**

Since last clinic I have.....

.....

My next goal is.....

.....

**Exercise Goals:**

Since last clinic I have.....

.....

My next goal is.....

.....

**Medication Goals**

Since last clinic I have.....

.....

My next goal is.....

.....

.....

**Family Goals**

Since last clinic I have.....

.....

My next goal is.....

.....

.....

# Proforma T2 clinic – for doctor

**Proforma T2 Diabetes clinic**

Name …… Date ……..

**At diagnosis:**

Weight …….kg BMI ……kg/m2

HbA1c ……. mol/mmol

**Established diagnoses:**

| | Yes | Maybe | No |
|---|---|---|---|
| T2D | | | |
| Hypertension | | | |
| Fatty liver | | | |
| Hyperlipidaemia | | | |
| Microalbuminuria | | | |
| Sleep apnoea | | | |

Other diagnosis: ……

Mental health diagnosis : ……..

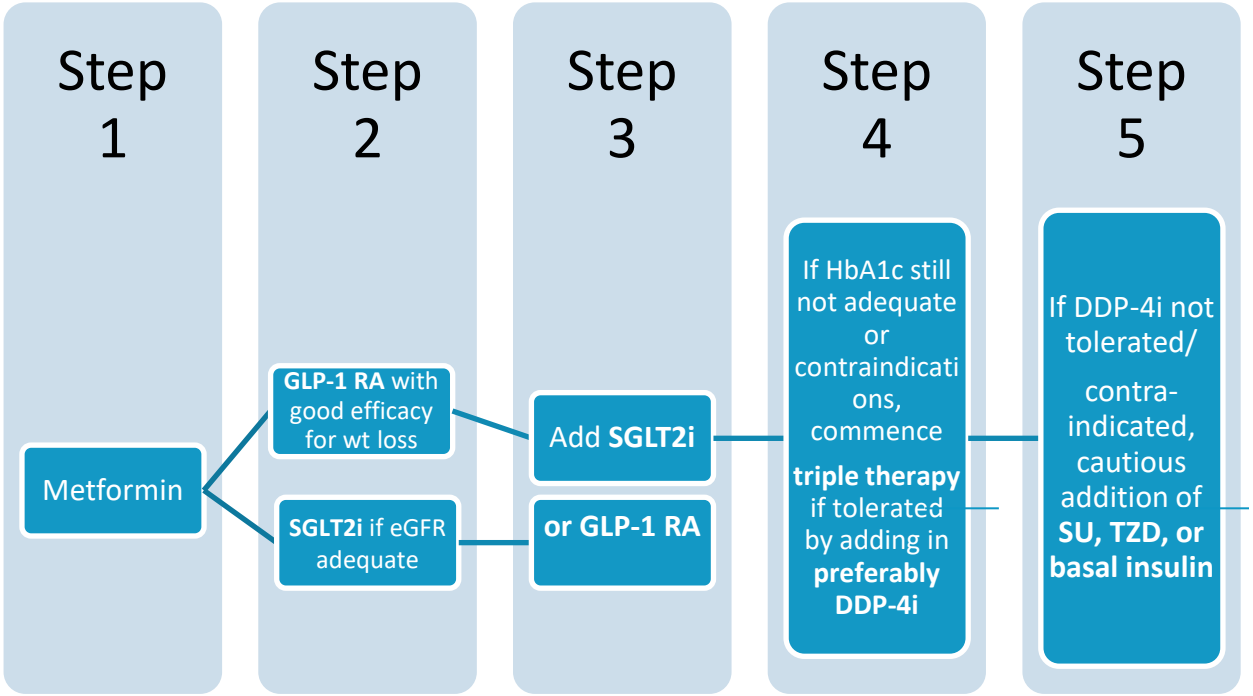
**Investigations:**

| | YES/NO | If abnormal | YES/NO |
|---|---|---|---|
| LFTs with GGT | | Abdo US | |
| | | Refer gastro if ALT > 2X ULN | |
| Random lipids | | Fasting lipids | |
| | | if fasting lipids abnormal, focus on lifestyle and then treat | |
| Blood pressure | | If > 95$^{th}$ centile for height, and sex despite lifestyle for 6 months, start treatment | |
| Urine ACR | | Abnormal if > 3. Repeat in first morning urine (2x). If > 30mg/mol creat, refer to paed nephrologist | |
| Sleep study | | To be decided by resp team. | |
| Psychol referral | | in house psychology | |

# SGLT2 inhibitors in adults

| | |
|---|---|
| **Mechanism of action** | • Inhibits SGLT2 (sodium/glucose cotransporter 2) in the proximal tubule, blocking reabsorption of filtered glucose (leading to osmotic diuresis) |
| **Examples ( _ gliflozin)** | • Empagliflozin (Jardiance®) - Best risk/benefit ratio of the three<br>• Dapagliflozin (Forxiga®)<br>• Canagliflozin (Invokana®) |
| **Major advantages** | • Weight loss (~2-3kg)<br>• Empagliflozin and canagliflozin ↓ CV mortality in high risk patients with T2D + atherosclerotic heart disease<br>• All 3 ↓ heart failure hospitalizations and progression of nephropathy |
| **Contraindications** | eGFR < 30 mL/minute/1.73 $m^2$ (for first initiation of use) |
| **Common side effects and important toxicities** | • AKI (likely from hypovolemia)<br>• GU infections (e.g. UTIs, vulvovaginal candidiasis)<br>• Euglycemic diabetic ketoacidosis (DKA)<br>• Canagliflozin ↑ risk of lower limb amputation and bone fractures |

# Algorithm for adults with T2D




**Combination of NICE guidance and ADA and EASD consensus statements**