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Planning the next prescribing step with the individual: Practical case studies

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Declaration of interests

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Bear in mind that
there are no
“right” or “wrong”
answers, and we
value your
thoughts and
ideas

Please do
participate in
these case
discussions



Case 1

Mrs Begum






Mrs Begum

- 42 years old
- Always fast during Ramadan

- Diagnosed with of type 2 diabetes 12 months ago
 - Completed Urdu XPERT session 4 months previously
 - Tries to Walk each morning in the local park with a group of women after they have dropped their children off at school.
 - Has lost 3kg since commencing the XPERT course
- Blood glucose monitoring one day per week pre- meals
 - Blood glucose levels tends to be 7–10 mmol/L
- Started on metformin 500 mg once daily post evening meal titrated to 1gram post breakfast and evening meal
 - Tolerates metformin well and concordance improved since switched to BD treatment from TDS

- HbA_{1c} 59 mmol/mol
- BMI 29 kg/m²
- eGFR >90 mL/min/1.73 m²

What would your HbA1c Target be for Mrs Begum

-  <48mmol/mol
-  48-50mmol/mol
-  51-55mmol/mol
-  <59mmol/mol
-  Happy with current HbA1c (59mmol/mol)

Target HbA1c

- **“Legacy effect” of glucose control**
 - Importance of early, tight control of HbA_{1c} highlighted in the UKPDS¹
 - At 39, Mrs Begum is young – her current HbA_{1c} level of 59 mmol/mol is above target.
 - NICE recommends target of 48 mmol/mol when treated with mono therapy

UKPDS=UK Prospective Diabetes Study

1. Holman RR et al (2008) *N Engl J Med* 359: 1577–89

Blood-glucose lowering therapy - Therapeutic choices

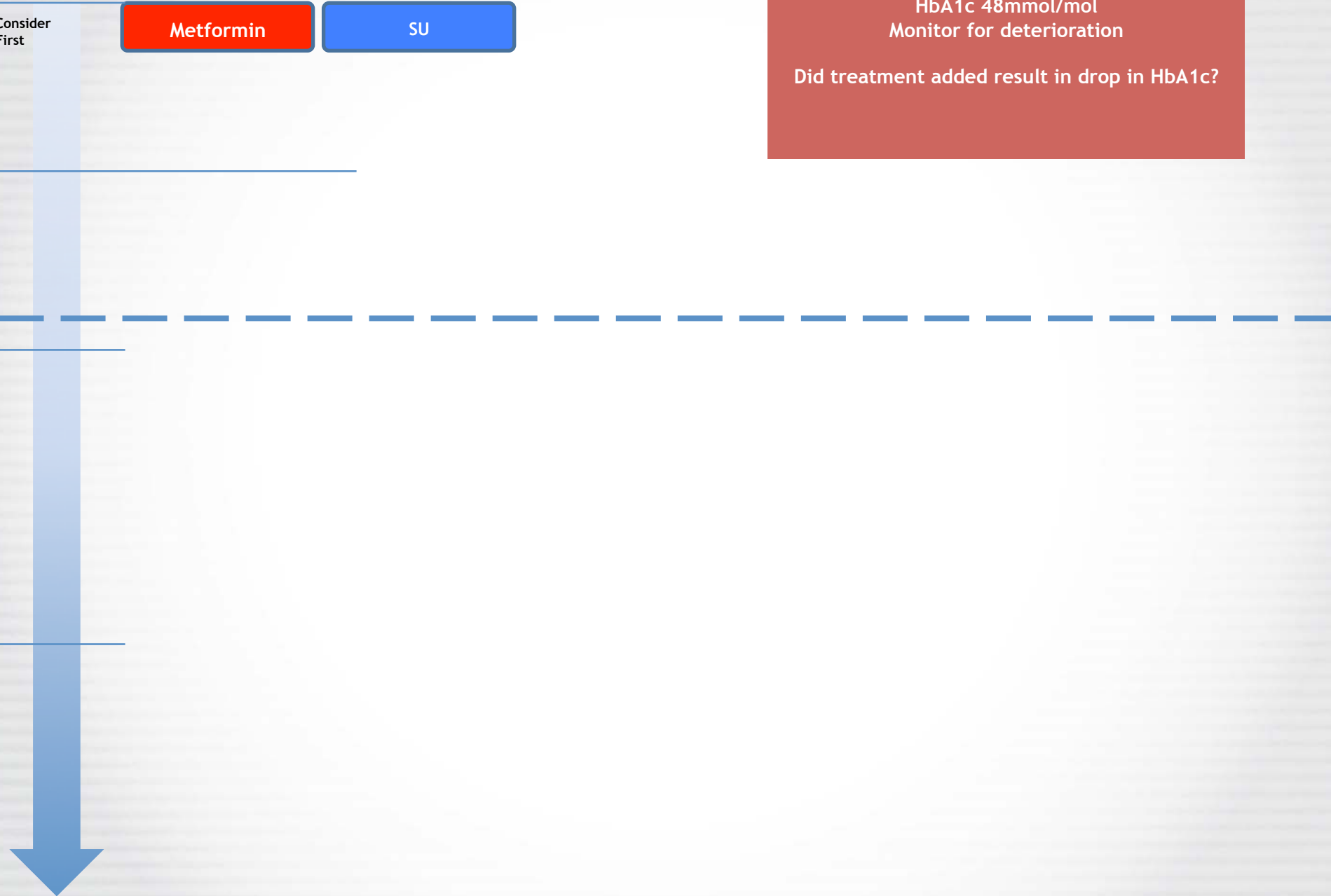
Consider First

Metformin

SU

HbA1c 48mmol/mol
Monitor for deterioration

Did treatment added result in drop in HbA1c?



Ref: Speaker's interpretation of BNF Guidance (2014).

Blood-glucose lowering therapy - Therapeutic choices DUAL

Consider First

Metformin

SU

HbA1c 48mmol/mol
Monitor for deterioration

Consider Second

SU

PIOGLITAZONE

DPP4 inhibitor

SGLT2

Add to Met
Add to SU

Add to Met
Add to SU

Add to Met
Add to SU

Insulin resistance
Driver

Hypoglycaemia a concern
Driver
Elderly
Consider eGFR

Weight an issue
eGFR > 60
Under 75
No Thrush
No UTI
No Diuretics
No postural hypotension

What would you do next?

- Refer to dietitian
- Add sulphonylurea
- Add DPP-4 inhibitor
- Add Pioglitazone
- Add SGLT2 inhibitor
- Add insulin
- Something else

Discussion points

- **Dietitian referral would be sensible¹**
 - In addition to prescribing a second glucose-lowering therapy?
 - The additional therapy could be discontinued if sufficient improvement in glycaemia is observed
- **Sulphonylurea is the usual second-line therapy recommended by NICE² and SIGN³**
 - The majority of dual therapy treatment is metformin plus a sulphonylurea ^{4,5}

1. NICE (2011) *Diabetes in adults quality standard*. Available at: <http://bit.ly/1bbFunM> (accessed 02.02.2014); 2. NICE (2009) *Type 2 Diabetes. The Management of Type 2 Diabetes. NICE Clinical Guideline 87*. Available at: <http://bit.ly/1cTYLVX> (accessed 22.03.2014); 3. SIGN (2010) 116. *Management of Diabetes. A National Clinical Guideline*. Available at: <http://bit.ly/1mJYmuX> (accessed 25.01.2014); 4. Morgan CL et al (2012) *J Clin Endocrinol Metab* 97: 4605–12; 5. NICE (2011) *NICE implementation uptake report: The management of type 2 diabetes*. Available at: <http://bit.ly/1qHGxQV> (accessed 15.04.2014)

More discussion points

- **Other considerations**

- What roles for goal-setting, care planning and structured education?
- How many people with type 2 diabetes have access to structured education?
- How important are hypos?
- Should this lady be home blood glucose monitoring?

- **Ramadan**

- The majority of Muslim patients will choose to fast during Ramadan
- The current length of fast creates a high risk of hypoglycaemia if on treatment that has a hypoglycaemic risk
- Many patients will stop treatment to enable fasting rather than not fast
- Ramadan management should not only be addressed in the weeks immediately prior to Ramadan.

Decision and outcome

- Mrs Begum chooses to start a DPP-4 inhibitor, as she is keen not to gain the weight she has managed to lose.
- 8 months later:
 - HbA_{1c} 56 mmol/mol (previously 59mmol/mol)
 - Weight unchanged (BMI still 29 kg/m²)
 - Feels well

Questions

- Is this outcome “good enough”?

Yes

No

- Should the DPP-IV be stopped?

Yes

No

- Would you consider a SGLT2

Yes

No

Blood-glucose lowering therapy - Therapeutic choices DUAL

Consider First

Metformin

SU

Consider Second

SU

PIOGLITAZONE

DPP4 inhibitor

SGLT2

Add to Met
Add to SU

Add to Met
Add to SU

Add to Met
Add to SU

HbA1c <58mmol/mol
Could be 48mmol/mol if no Hypo risk
Monitor for deterioration

Did treatment added result in drop in HbA1c?

Discussion points

- **Current DPP-4 inhibitor therapy**
 - Should sitagliptin therapy be continued?
 - NICE: Only continue DPP-4 inhibitor if reduction in HbA_{1c} of at least 6mmol/mol (0.5 %) in 6 months¹
 - SIGN: continue if individualised target achieved or HbA_{1c} falls >5.5 mmol/mol (>0.5%) in 3–6 months²

DPP-4=dipeptidyl peptidase-4

1. NICE (2009) *CG87 Type 2 diabetes - newer agents (a partial update of CG66)*. Available at: <http://nice.org.uk/cg87> (accessed 14.04.2014)
2. SIGN (2010) *116. Management of Diabetes. A National Clinical Guideline*. Available at: <http://bit.ly/1mJYmuX> (accessed 14.04.2014)

What would you do next – has your choice changed?

- Refer to dietitian
- Add sulphonylurea
- Add DPP-4 inhibitor
- Add GLP-1 receptor agonist
- Add SGLT2 inhibitor
- Insulin
- Other



Case 2

Mr Smith

- 82 years old
- Lives alone with support from Son and Daughter
- Diagnosed with of type 2 diabetes 4 years
- Current treatment Metformin 500mg BD
- HbA_{1c} 62 mmol/mol- (previously 52-60mmol/mol)
- BMI 26 kg/m²
- eGFR 40 mL/min/1.73 m²

What would your HbA1c Target be for Mr Smith

- 48-50mmol/mol
- 51-55mmol/mol
- <59mmol/mol
- 60-65mmol/mol
- <70mmol/mol

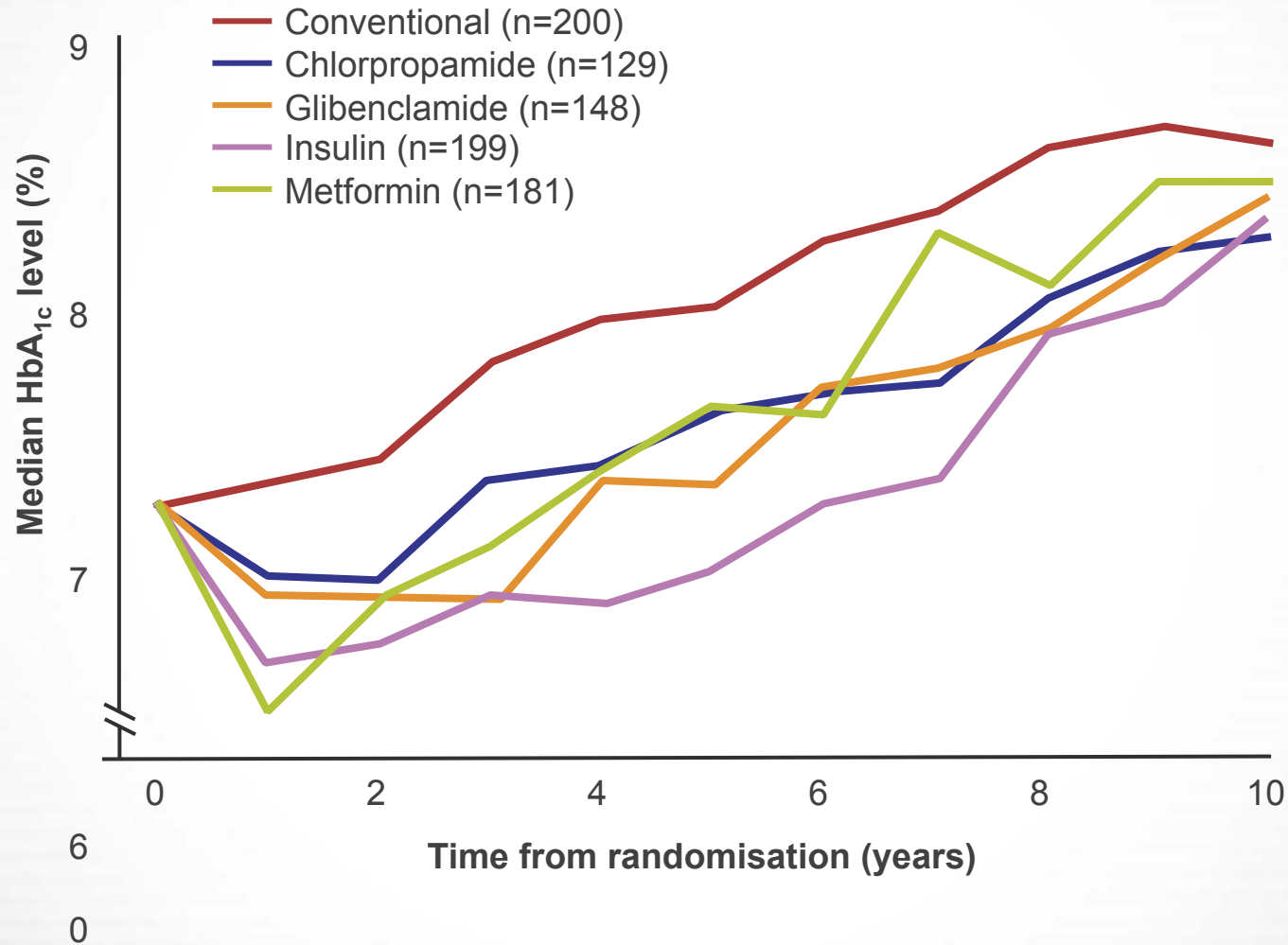
What would you do next?

- Refer to dietitian
- Add sulphonylurea
- Add DPP-4 inhibitor
- Add Pioglitazone
- Add SGLT2 inhibitor
- Add insulin
- Do Nothing

What would you do next?

- Increase Metformin Dose- eGFR 40 so current dose maximum recommended dose
- Add Sulphonylurea- not ideal in an elderly person living alone due to Hypo risk
- Add DPP-4 inhibitor- **An option** – correct dose based on eGFR **MUST** be given
- Add Pioglitazone- No suggestion Insulin resistance the issue as previous good control so not indicated
- Add SGLT2 inhibitor- eGFR 40 so contraindicated
- Do Nothing- **An option**- elderly lives alone HbA1c <65 mmol/mol probable appropriate

Type 2 diabetes is typically associated with progressive loss of glycaemic control



Median change in HbA_{1c} levels in cohorts followed up to 10 years by assigned treatment.
UKPDS Group (1998) *Lancet* **352**: 854–65

Points to bear in mind when managing older people with type 2 diabetes

- As many as 1 in 4 older people in residential and nursing care will have diabetes¹
- In a survey of health professionals' attitudes to managing older people with diabetes:¹
 - 50% of respondents considered an HbA_{1c} of <53 mmol/mo to be indicative of good glycaemic control
 - 16% considered an HbA_{1c} of <42 mmol/mol to be good glycaemic control!
- These attitudes do not take into account the increased risk of hypoglycaemia with older age (and renal disease, which is commonly seen older

1. Institute of Diabetes for Older People (2011) *Current IDOP research activity*. Available at: <http://bit.ly/1eIYHjQ> (accessed 16.04.2014)
2. Kirkman M et al (2012) *J Am Geriatr Soc* 60: 2342–56



Case 3

Mr Green

Mr Green

- 37years old
- Car Salesman





- Type 2 diabetes diagnosed 3 years ago
- Current therapies on repeat prescription
 - Metformin 850mg TDS
 - Glimepiride 2mg twice daily
 - Has never blood glucose monitored

- HbA_{1c} 84 mmol/mol, 86 mmol/mol 12 months ago,
79 mmol/mol 2 years ago

- Total cholesterol 3.8 mmol/L, BP 138/90 mmHg, eGFR > 90 mL/min/1.73 m²
- BMI 33 kg/m² (95.7kg)
- Has stopped glimepiride due to hypo symptoms and concerns expressed by employers insurance company.

eGFR=estimated glomerular filtration rate BP = Blood pressure

What would you your HbA1c Target be Mr Green

-  <48mmol/mol
-  48-50mmol/mol
-  51-55mmol/mol
-  <59mmol/mol

What would you do next?

- Refer to dietitian
- Increase Metformin Dose
- Add Sulphonylurea
- Add DPP-4 inhibitor
- Add Pioglitazone
- Add SGLT2 inhibitor
- Something else

What happened next

- Metformin changed to Metformin MR 2 grams post evening meal as admitted rarely remembered lunch time dose and omitted morning dose if not having breakfast.
 - One to one education session covering Healthy Eating role of Physical Activity
 - SBGM once a week pre- meals
 - Pioglitazone 15mg commenced post evening meal and increased to 30 mg after 8 weeks as SBGM remained unchanged at >15 mmols/l
-
- **6 months later**
 - HbA1c 66mmol/mol (down 18mmol/mol)
 - Weight 96.3kg (up 0.6kg)
 - Fast BG levels 7-9mmols
 - BP 130/92 mmhg

Discussion points

- **Physical activity**
 - has made some changes to physical activity but feels a more structured approach maybe helpful
- **Driving**
- **Pioglitazone**
 - What side effects might we expect?

Blood-glucose lowering therapy - Therapeutic choices

Consider First

Metformin

SU

HbA1c \leq 58mmol/mol
 Monitor for deterioration
 Did treatment added result in drop in HbA1c?

Consider Second

SU

PIOGLITAZONE

DPP4 inhibitor

SGLT2

Add to Met

Consider Third

SU

NPH Insulin

Other Insulin

PIOGLITAZONE

DPP-4 inhibitor

Canagliflozin
Empagliflozin

GLP 1

Add to Met + PIO
 or
 Add to Met + SGLT2
 or
 Add to Met + Gliptin

Add to Met + SU

Long-acting analogue - as an alternative to starting NPH
 Or
 Premix insulin

Add to Met + SU
 Or
 Add to Met + DPP-4 inhibitor

Add to Met + SU
 or
 Added to Met + Pio

Add to Met + SU
 Added to Met + Pio

Add to Met + SU
 or
 Add to Met + Pio



What would you do next

- Refer to dietitian
- Refer to exercise on prescription
- Add sulphonylurea
- Add DPP-4 inhibitor
- Add GLP-1 receptor agonist
- Add SGLT2 inhibitor
- Insulin

More discussion points

- **GLIPTIN**
 - What reduction in HbA_{1c} might we expect?
- **GLP-1 receptor agonist**
 - What reduction in HbA_{1c} might we expect?
- **SGLT2 inhibitor**
 - What outcome might we expect?
- **Insulin**
 - Risk of hypos?
 - Blood glucose monitoring requirements?

Which SGLT2 inhibitor

Considerations relevant to Mr Green ?

Table lists eGFR cut-offs only, but drug SPCs also provide creatinine clearance cut-off values.

eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter 2 SPC=summary of product characteristics.

1. *Dapagliflozin summary of product characteristics*; 2. NICE (2013) *Dapagliflozin in combination therapy for treating type 2 diabetes*. Available at: <http://bit.ly/17MEpQn> (accessed 25.03.2014); 3. *Canagliflozin summary of product characteristics*; 4. NICE (2014) *Diabetes (type 2) - canagliflozin: appraisal consultation document*. Available at: <http://bit.ly/1diNhCl> (accessed 25.03.2014) 5. NICE (2015) *Empagliflozin in combination therapy for treating type 2 diabetes* <https://www.nice.org.uk/guidance/ta336/resources/guidance-empagliflozin-in-combination-therapy-for-treating-type2diabetes-pdf> accessed 27.2.15

Decision and outcome

- **After discussion with the care team, the following was agreed:**
 - Continue with Metformin MR 2 grams and Pioglitazone 30 mg post evening meal.
 - Referred to exercise on prescription team
 - Canagliflozin 100mg commenced

4 months later

- HbA_{1c} has reduced to 49 mmol/mol (↓ 17 mmol/mol)
- Weight 94.6 (↓ 2kg)
- Blood pressure 125/78mmhg (↓ 13/15 mm/hg)
- Has joined the gym through exercise on prescription scheme

10 months after SGLT2 started

- HbA_{1c} maintained at 49mmol/mol
- Weight Static at 94kg
- Blood pressure 116/86



Case 3






Mrs White

Mrs White

- Age 60
- High carbohydrate intake and reluctant to make changes to diet.
- Diagnosed with type 2 diabetes 8years ago
- Medication
 - Metformin 1 g twice daily
 - HumalogMix 50 40 units TDS
 - Trail with Liraglutide prior to insulin being commenced but HbA1c increased
- HbA_{1c} 83 mmol/mol Weight 119kg
 - HbA1c 80–123 mmol/mol since diagnosis 9 years ago (glimepiride stopped when switched to TDS insulin)
 - HbA1c reduced from 128 to 83 mmols/mol since starting insulin 2 years ago
 - Weight increased from 95 to 119kg since insulin commenced 2 years ago
- BMI 44 kg/m²
- eGFR >60 mL/min/1.73 m²

eGFR=estimated glomerular filtration rate; BMI= body mass index

What would you your HbA1c Target be Mrs White

-  • <48mmol/mol
-  • 48-50mmol/mol
-  • 51-55mmol/mol
-  • <59mmol/mol
-  • Accept current HbA1c as not willing to change diet

What would you do next?

- Refer to weight management clinic
- Add DPP-4 inhibitor
- Add GLP-1 receptor agonist
- Add SGLT2 inhibitor
- Increase insulin dose
- Change insulin regime
- Do nothing as Mrs White not willing to change her diet

What happened Next

- Canagliflozin 100mg once daily add to current treatment

4 months later

- HbA1c 63 mmol/mol (↓ 20mmol/mol)
- Weight 118kg (↓ 1kg)
- Insulin doses reduced by 2units each injection to 38units TDS

What would you do next?

- Refer to weight management clinic
- Intensify SGLT2dose
- Increase insulin dose
- Change insulin regime
- Do nothing as Mrs White not willing to change her diet

What happened Next

- Canagliflozin increased to 300mg

3 months later

- HbA1c 66 mmol/mol (↓ 20mmol/mol)
- Weight 118kg (↓ 1kg)
- Insulin doses reduced by 10 units to 28 units at lunchtime due to afternoon hypoglycaemia

What would you do next?

- Continue Canglifoazin 300mg dose
- Reduce back to Canagliflozin 100mg
- Change insulin doses

CONCLUSION

- Need an Individualised target HbA1c
- Need to plan full treatment pathway
- If treatment ineffective stop- make not ineffective to avoid being used again at a later date
- Think about underlying problem and treatment options to address these.

Diabetes Decision Making Tree

Type 2 Diabetes

Insulin Resistance

Body does not respond to insulin normally

Metformin

Pioglitazone

Beta cell failure

Pancreas unable to produce enough insulin

Gliptins

SU

GLP1's
Injection

Insulins
Injection

Kidney

Encouraged to excrete glucose

Flozin

SGLT2

Treatment Algorithm for the Management of Type 2 diabetes with Oral Therapy

Lifestyle advice focusing on Healthy eating and increased physical activity to be explored at diagnosis
Referral to structured education programme and Dietitian to be discussed

First line	Metformin If BMI >25 or 23 if South Asian (SA) , eGFR >45 and If HbA1c >48mmol/mol 3 months post diagnosis 500mg once daily post main meal titrating to maximum tolerated dose or 2 grams daily over 4 weeks. Modified release to be used if concordance or side effects an issue		SU (Glimepiride) If Symptomatic (no ketonuria) or BMI< 25 (23 if south asian) or Metformin Contraindicated SBGM to be commenced to facilitate dose titration and detect hypoglycaemia			
Second line HbA1c >48mmol/mol after 3 months treatment	Glimepiride or Metformin		Gliptin eGFR related dose	Pioglitazone 15mg once daily to be increased to 30mg after 3 months if no impact on HbA1c	SGLT2 Inhibitor	Insulin
Indications	NICE guidance recommends Which ever not commenced first line SBGM with glimepiride for drivers		Hypoglycaemia avoidance Driver	Insulin resistance South Asian Driver	Facilitates Weight loss Hypoglycaemia avoidance	Persistent Symptoms or minimal response to SU
Contraindications Cautions	Glimepiride Hypoglycaemia	Metformin eGFR<45 max dose 1gram eGFR < 30 Contraindicated	Pancreatitis	Congestive cardiac failure History of Ca Bladder Osteoporosis or Osteomalacia	eGFR<60 History of thrush/UTI Over 75 Postural Hypotension Fluid depletion	
<p>Review HbA1c 3months after commencing a new treatment If no change or rise in HbA1c Stop Giptin or SGLT2 inhibitor. Increase dose of Pioglitazone to 30mg. Increase Glimepiride dose and commence SBGM to facilitate further dose titration.</p> <p>Review HbA1c at 6 months if HbA1c has not reduced by > 6mmol/mol</p> <p>STOP GLIPTIN, SGLT2 INHIBITOR and PIOGLITAZONE(45mg not indicated if no response to 30mg)</p>						
Third line HbA1c>59mmol/mol or individualised target	Glimepiride if not previously tried Commence SBGM	Pioglitazone Add to Metformin and Cana/Empa Metformin and Gliptin	Gliptin Add to Metformin and Glimepiride Metformin and pioglitazone	Canagliflozin or Empaglifozin Add to Metformin and pioglitazone Metformin and glimepiride	Insulin Refer Commence Blood Glucose Monitoring	GLP1 Refer Commence Blood Glucose Monitoring

If HbA1c >59mmol /mol or above individualised target after 6 months on triple therapy refer for injectable therapy

Preferred Treatment plan

First line incl. target Hba1c

Second line incl. target Hba1c

Third line incl. target Hba1c

Type 2 diabetes due to?

Can't have

Could use