Diabetes medications: what to recommend and why?

PITstop for Diabetes

@PITstopDiabetes

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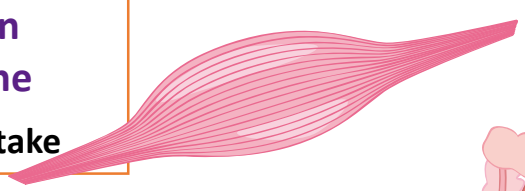
Declaration of interest:

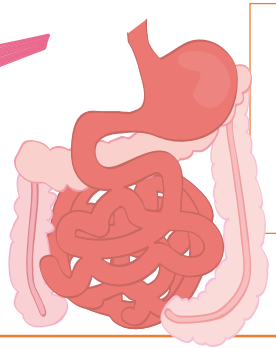
I have:

- acted as a paid speaker for Astra Zeneca, Janssen and Sanofi.
- developed educational resources for Astra Zeneca.
- received an educational grant to complete my insulin masters module from Lilly.
- participated in an expert working group for Sanofi
- attended conferences and workshops sponsored by Astra Zeneca, Boehringer Ingelheim, Janssen, Lilly, Napp, Novo Nordisk and Sanofi.

Treatment options for Type 2 diabetes

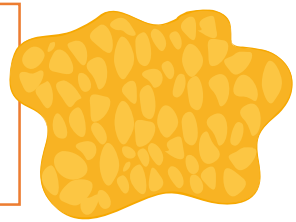
Metformin
Pioglitazone
↑ glucose uptake





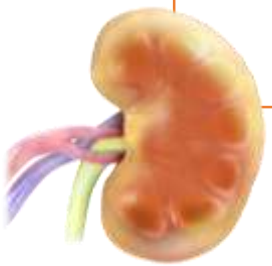
Acarbose
(α-glucosidase inhibitor)
Inhibit carbohydrate breakdown

Pioglitazone
↑ glucose intake
↓ Free fatty acid release



GLP-1 agonists
Slow gastric emptying

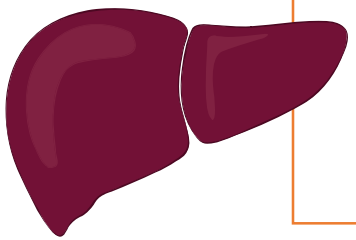
Sulphonylureas and short-acting insulin secretagogues
Stimulate insulin secretion



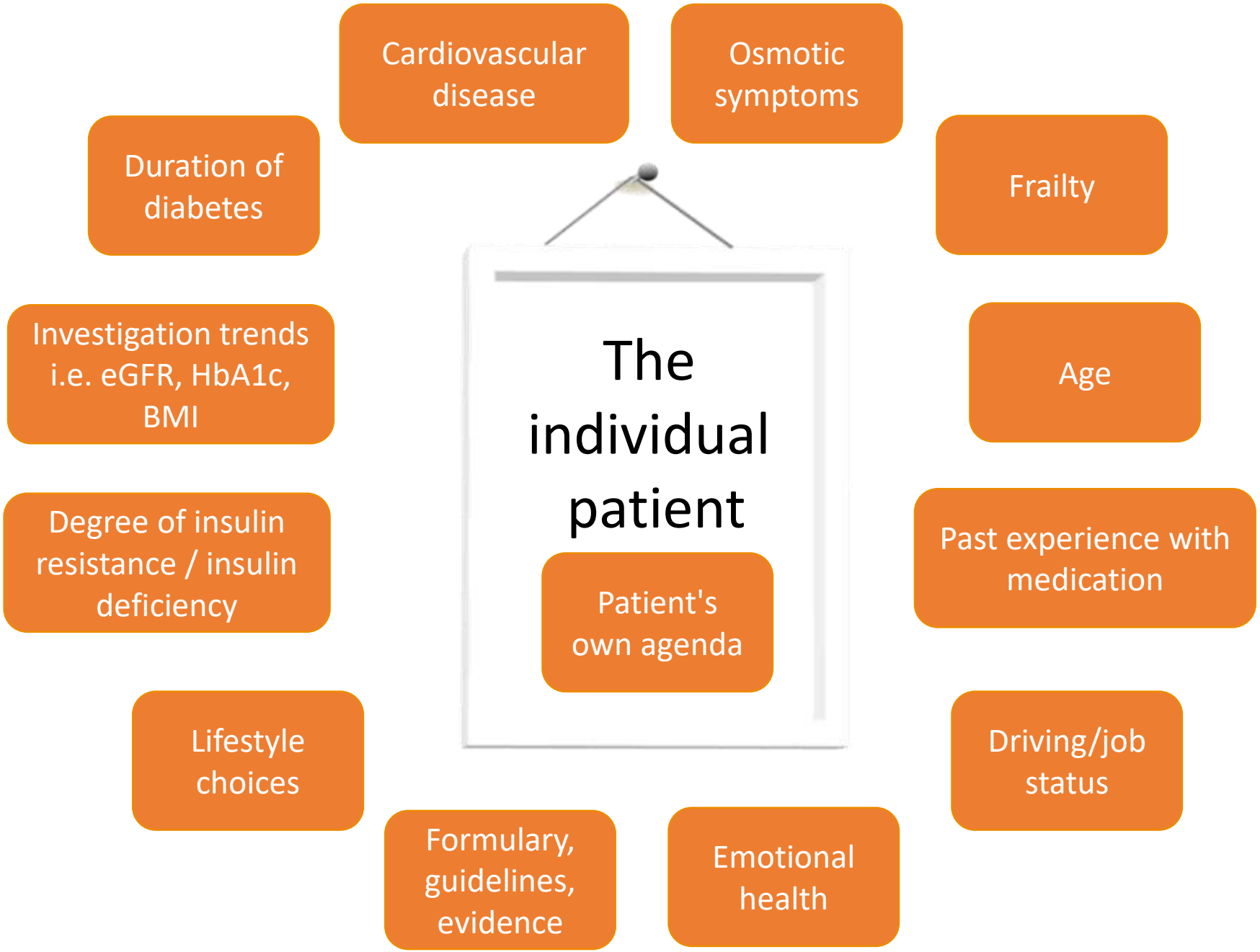
SGLT-2 Inhibitors
Glucose excretion
Caloric loss

Insulin
Insulin replacement

GLP-1 agonists
DPP-4 inhibitors
↑ insulin secretion
↓ glucagon secretion



Metformin
Pioglitazone
Decrease hepatic glucose output


Cardiovascular disease
Osmotic symptoms
Duration of diabetes
Frailty
Investigation trends i.e. eGFR, HbA1c, BMI
Age
The individual patient
Degree of insulin resistance / insulin deficiency
Past experience with medication
Patient's own agenda
Lifestyle choices
Driving/job status
Formulary, guidelines, evidence
Emotional health

Debbie, age 48

Type 2 diabetes for 14 months (diagnostic HbA1cs 55/54mmol/mol). Attended structured education. Agreed target HbA1c 48mmol/mol

HbA1c after 14 months 53mmol/mol. Debbie is requesting more time before starting medication.

BMI was 37kg/m², now 36.6kg/m²

Renal and liver function function normal

Has tried every diet and hates discussing her weight. Agreed to self-refer to Psychological Therapies to explore her relationship with food.

Cardiovascular disease

Osmotic symptoms

Duration of diabetes

Frailty

Investigation trends i.e. eGFR, **HbA1c, BMI**

Age

Insulin resistance / insulin deficiency

Past experience with medication

Debbie's own agenda

Lifestyle choices

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Emotional health

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2, **and** for whom insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
  - an SGLT-2ib instead of a DPP-4i if an SU or pioglitazonea is not appropriate
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

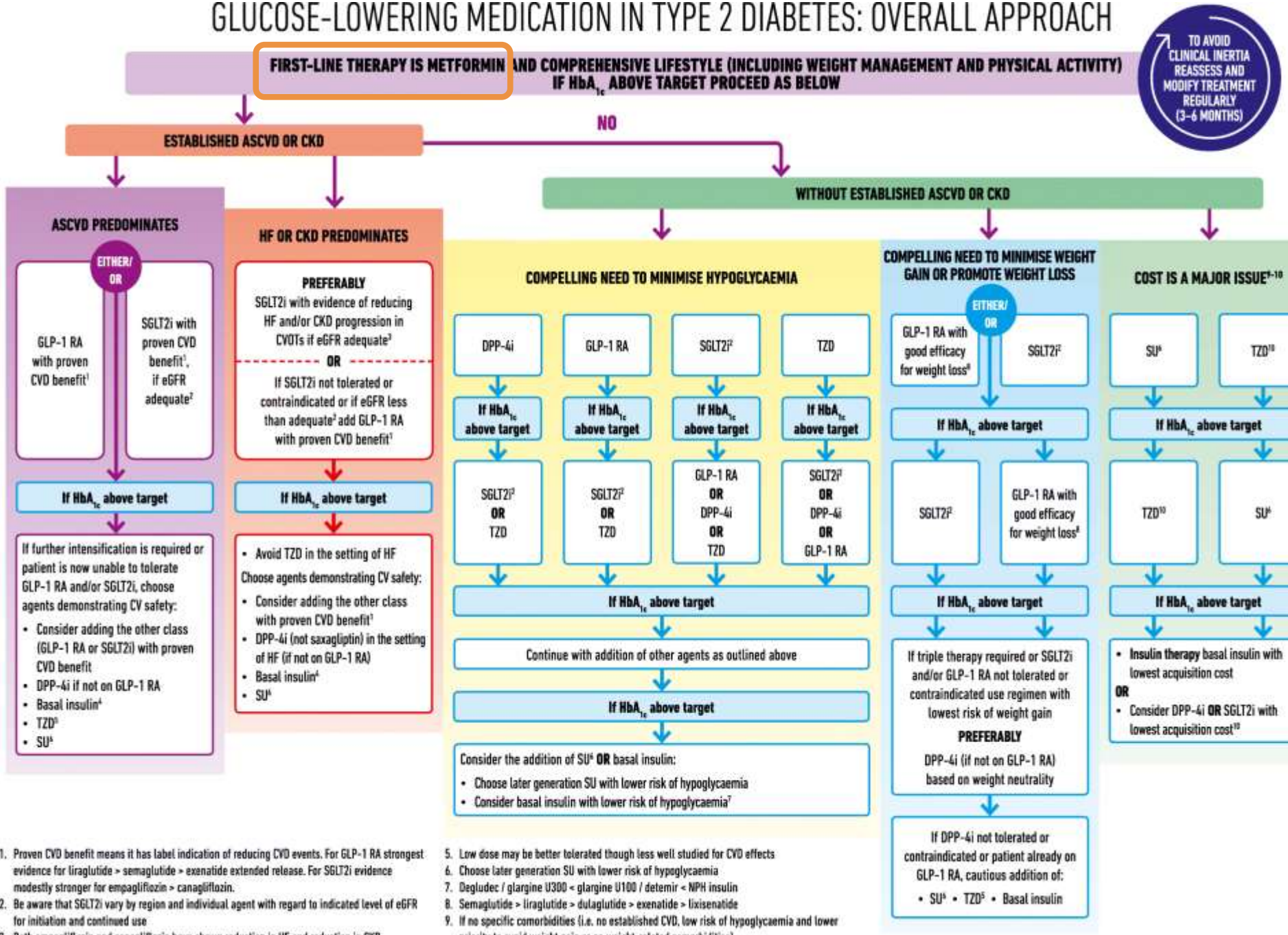
- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargineg if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include shortacting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option*[b].

Abbreviations: [DPP-4i]Dipeptidyl peptidase-4 inhibitor, [GLP-1]Glucagon-like peptide-1, [SGLT-2i]Sodium–glucose cotransporter 2 inhibitors, [SU]Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

See footnotes on reverse

'Type 2 diabetes in adults: management', NICE guideline NG28. Published December 2015, last updated April 2017.

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more

Davies et al, Diabetes Care, 2018 Sep; dci180033

Considerations: remaining on diet only

Insulin resistance will continue to cause:

- compensatory over production of basal insulin
- stunted post meal insulin production.

Delaying the treatment pathway in the presence of insulin resistance may lead to further beta cell dysfunction (50% beta cell function is lost at the time of diagnosis).

Debbie

Aim: preserve/improve her beta cell function

Explain: HbA1c trend compared to target

Explain: the mechanisms involved with insulin resistance and the importance of achieving a negative calorie balance to reduce insulin resistance

Explain: the role of Metformin

Agree: a plan for Metformin……..start low and go slow. It can always be stopped if insulin sensitivity improves

Proactive treatment escalation

Audit recommendation:
search HbA1c > 48mmol/mol, on no diabetes medication, date of diagnosis, age, eGFR, BMI, level of frailty

Nicholas, age 66

Type 2 diabetes 7 years with HbA1cs 52-58mmol/mol. BMI 34.4kg/m²

On Ramipril 5mg, Atorvastatin 20mg Metformin 1g twice daily

Recent MI and diagnosed with heart failure (ECHO ejection fraction 32%)

Aspirin 75mg and Isosorbide mononitrate 60mg added. Atorvastatin increased to 80mg

Metformin discontinued

At his annual review, 5 months later, HbA1c 72mmol/mol, eGFR 62mL/min/1.73 m^2 (3 last results 64-72 mL/min/1.73 m^2)

Treatment options

a. Restarting Metformin
b. Adding a Sulphonylurea
c. Adding Pioglitazone
d. Adding a DPP-4 inhibitor (Gliptin)
e. Adding an SGLT-2 inhibitor (Gliflozin)
f. Adding a GLP-1 Receptor Agonist (GLP-1 RA)
g. Adding insulin

Cardiovascular (CV) safety studies

Medication	Group	Study (& population detail)	Medication
Sitagliptin	DPP-4 i	TECOS[1]	Non inferiority in **MACE outcomes: CV death, non-fatal MI, non-fatal stroke**
Saxagliptin	DPP-4 i	SAVOR-TIMI 53[2]	Non inferiority in MACE outcomes Increase admissions heart failure (HF) (sig.)
Alogliptin	DPP-4 i	EXAMINE[3]	Non inferiority in MACE outcomes Increased admissions HF failure (non sig.)
Linagliptin	DPP-4 i	CARMELINA[4] CAROLINA[5]	Non inferiority in MACE outcomes No increased CVD when compared to Glimepiride
Empagliflozin	SGLT-2 i	EMPA-REG[6] 99% established CV disease	Reduction in MACE outcomes, mainly CV mortality, MI & also death from any cause 35% reduction admissions for HF
Canagliflozin	SGLT-2 i	CANVAS[7] 65% established CV disease CREDENCE[8] (renal specific)	Reduction in MACE similar to EMPA-REG (14% compared to 15%), HF results similar Significant reduction in MACE by 20%
Dapagliflozin	SGLT-2 i	DECLARE-TIMI 58[9] 40% established CV disease	Non inferiority in MACE outcomes Lower rate of CV death, due to reduction in HF

1. Green J et al. NEJM, 2015;373:232–242 **2.** Scirica B et al. NEJM, 2013;369:1317-1326. **3.** White W et al. Am Heart J 2011 Oct;162(4):620-626 **4.** Rosenstock J et al. JAMA, 2019;321(11):69-79 **5.** Rosenstock K et al. JAMA, 2019;322(12):1155-1156 **6.** Zinman B et al. NEJM, 2015;373:2117-2128. **7.** Neal B et al. NEJM, 2017;377: 644-657 **8.** Perkovic V et al. 2019;380:2295-2306 **9.** Wiviott S et al. NEJM, 2019;380:347-357

Nicholas

Nicholas' own agenda

Lifestyle choices

Investigation trends i.e. **eGFR, HbA1c, BMI**

Metformin → SGLT-2 i → ?

Formulary, guidelines, **evidence**

Cardiovascular disease

Nicholas

The same as before **but**

eGFR 50 mL/min/1.73 m^2 (3 last results 54-59 mL/min/1.73 m^2)

Treatment options

a. Restarting Metformin
b. Adding a Sulphonylurea
c. Adding Pioglitazone
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f. Adding a GLP-1 RA
g. Adding insulin

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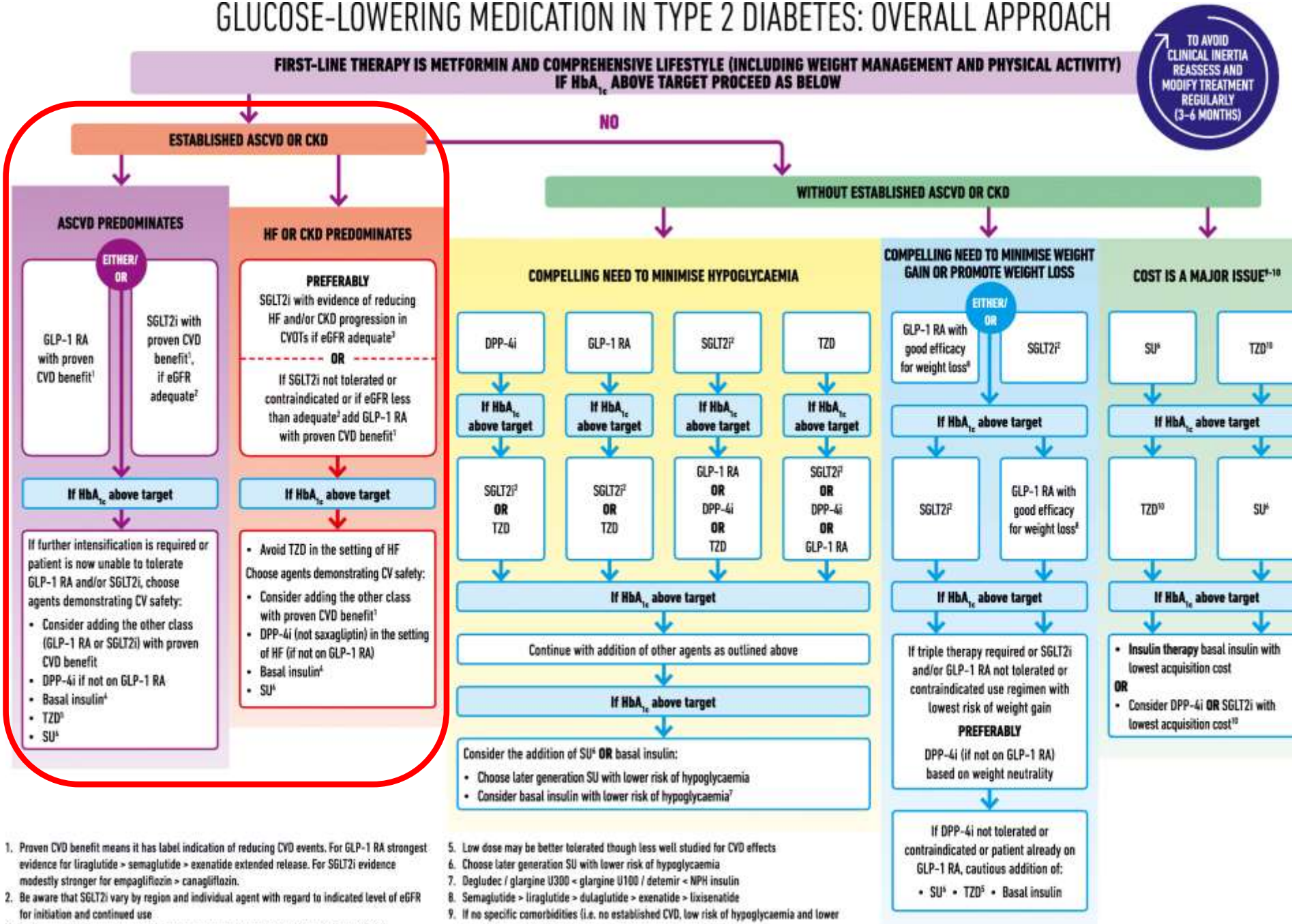

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9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Davies et al, Diabetes Care, 2018 Sep; dci180033

GLP-1 CV safety studies

Medication	Study	Medication
Albiglutide	HARMONY[1] 100% established CV disease	Significant reduction in CV events but not deaths
Dulaglutide (Trulicity)	REWIND[6] 31.5% established CV disease	Significant reduction in non-fatal stroke aided primary MACE outcome, with or without previous CV event
Exenatide once weekly (Bydureon)	EXSCEL[2] 73% established CV disease	Non inferiority in MACE outcomes
Liraglutide (Victoza)	LEADER[3] 81% established CV disease	Significant reduction in MACE, CV mortality & death from any cause.
Lixisenatide	ELIXA[4] Recent acute cardiac event	Non inferiority in CV events
Semaglutide (Ozempic®▼)	SUSTAIN-6[5] 83% established CV disease	Significant reduction in non-fatal stroke and MI aided primary MACE outcome

1. Hernandez A. et al for the HARMONY investigators, The Lancet, 2018 392:10157:1519-1529 2. Holman R. for the EXSCEL investigators, NEJM, 2017 28;377(13):1228-1239 3. Marso P. et al., for the LEADER investigators, NEJM, 2016;375:311-22 4. Pfeffer M, for the ELIXA investigators, NEJM, 2015; 373: 2247-2257 5. Marso S. et al. for the SUSTAIN 6 investigators, NEJM, 2016; 375:1834-1844 6. Gerstein HC et al for the REWIND investigators, Lancet 2019; 394

Ray, age 56

Type 2 diabetes for 2.5 years

Normally active lifestyle, 30 minute dog-walk daily, shop worker – on his feet most of the working day, works shifts with an erratic eating pattern.

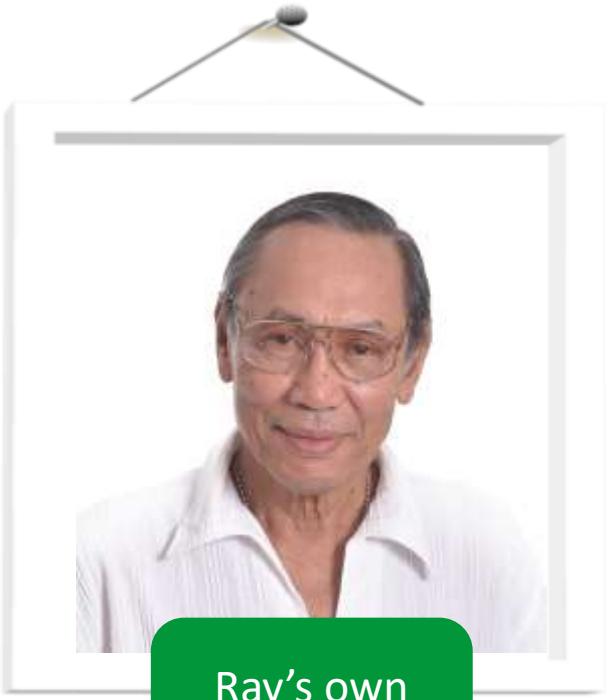
Found working difficult over the last two months

- BMI 21.2kg/m^2
- HbA1c 77mol/mol (9.2%). Symptomatic: lethargy, polyuria, polydipsia
- eGFR 67mL/min/1.73 m^2
- blood ketones 0.4mmol/l (normal < 0.6mmol/l)
- LFTs within normal range
- On Metformin slow release 1g daily (does not tolerate more)

What will Ray's treatment pathway include?

a. Sulphonylurea (Gliclazide or Glimepiride)
b. Short-acting insulin secretagogues (Repaglinide)
c. Pioglitazone
d. DPP-4 inhibitor
e. SGLT-2 inhibitor
f. GLP-1 RA
g. Insulin

Ray



Ray's own agenda

Lifestyle choices

Investigation trends i.e. eGFR, **HbA1c, BMI**

Metformin mr 1g → Sulfonylurea / DPP-4i → Basal NPH Insulin

Osmotic symptoms

Degree of insulin resistance / **insulin deficiency**

Proactive treatment escalation

Audit recommendation:
search HbA1c > 58mmol/mol, on Metformin, date of diagnosis, age, eGFR, BMI, level of frailty

Leonard, age 84

Type 2 diabetes for 31 years. He enjoys a daily walk and still drives from Kent to Leicester to visit family

Takes Metformin 500mg three times daily, Gliclazide 120mg twice daily, Sitagliptin 100mg once daily

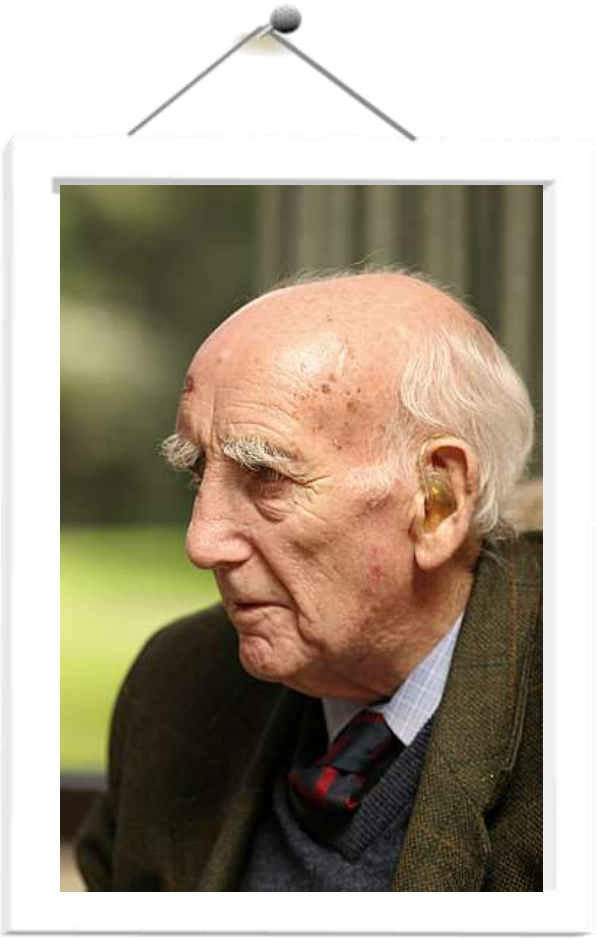
eGFR 36mL/min/1.73 m^2

Moderate frailty

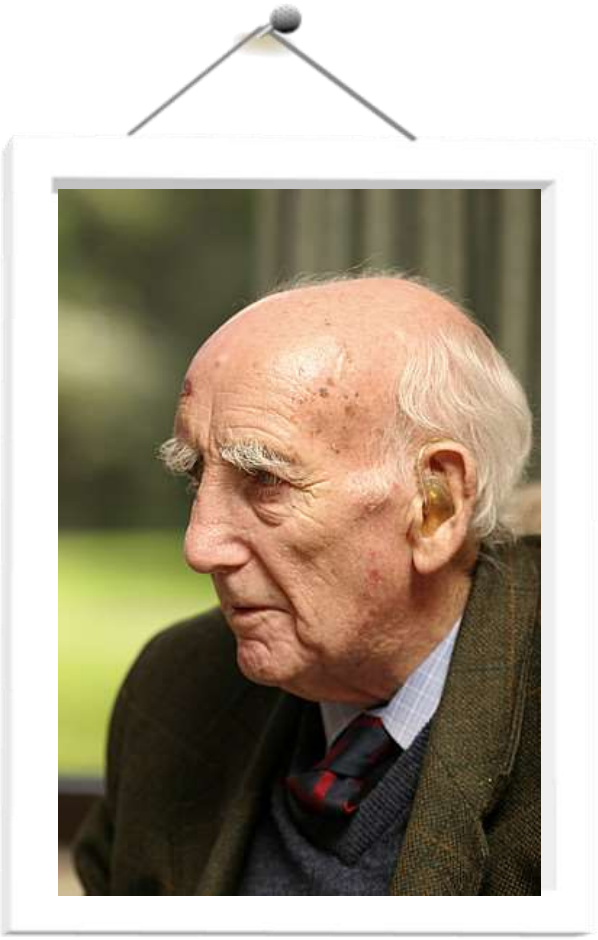
HbA1c 40mmol/mol (5.8%), was 44mmol/mol (6.2%) 18 months ago

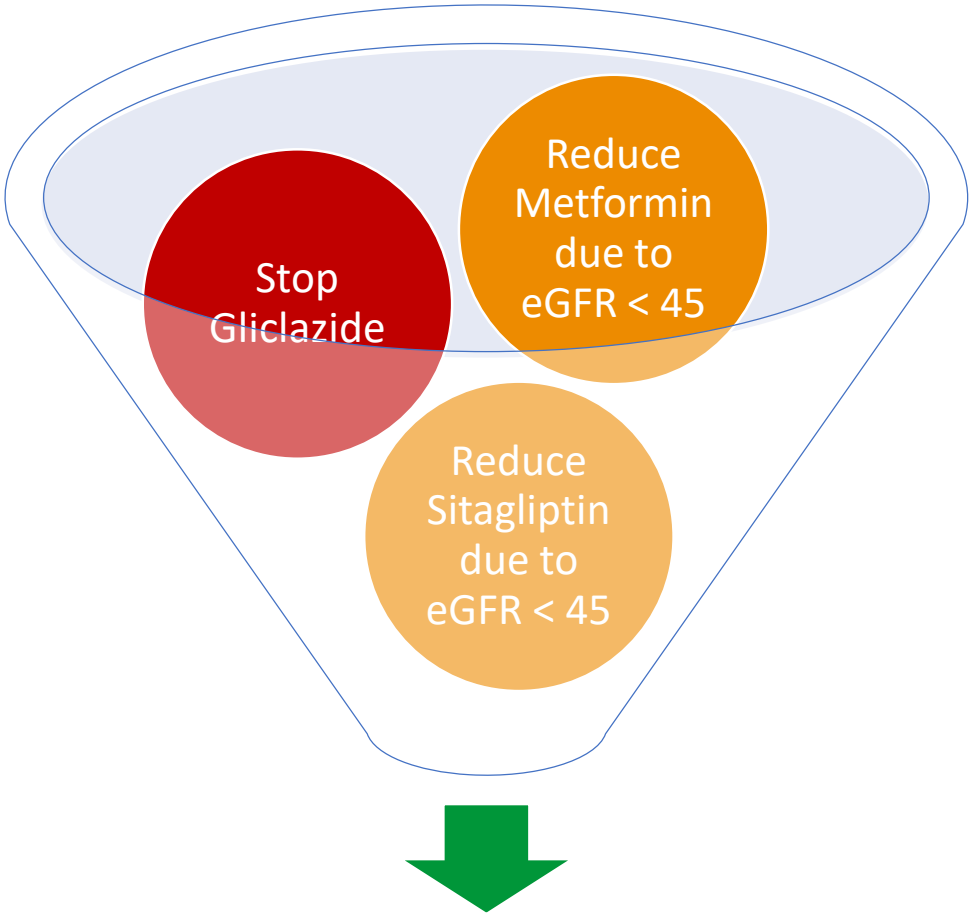
BMI 29kg/m^2

No prescription request for blood glucose monitoring strips for over 12 months



Leonard





Recheck HBA1c in 3 months and compare to agreed target. Then review need for further de-escalation

De-escalation of treatment

Audit recommendation:
search HbA1c < 53mmol/mol, on a Sulfonylurea or insulin, moderate or high frailty, age, eGFR, BMI

PrePITstop for Diabetes

PITstop for Diabetes

CPD PITstop for Diabetes

Thank you

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