Core stepped approach in diabetes

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

Berkwest CCGs Area Prescribing Committee

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NHS Newbury and District Clinical Commissioning Group
NHS North and West Reading Clinical Commissioning Group
NHS South Reading Clinical Commissioning Group
NHS Wokingham Clinical Commissioning Group
Berkshire West Area Prescribing Committee (BWAPC)

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		METFORMIN CONTRAINDICATED OR NOT TOLERATED
If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions: * Offer standard–release metformin, 500mg od. Titrate to 1g bd. Consider continuing at lower dose if GI side-effects. * 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	**If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:·** *Consider one of the following[1]: - SU (gliclazide), DPP-4i (**alogliptin** 25mg od) or pioglitazone *Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i 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 with: - metformin and an SU (usually gliclazide 80mg od. Titrate to max 160mg bd if required. - metformin and a DPP-4i (**alogliptin**) - metformin and pioglitazone - metformin and an SGLT-2i (**empagliflozin** (**empa**)) * 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 (**lixisenatide**) for adults with type 2 diabetes who:- have a BMI of 35 kg/m2 or higher (adjust accordingly for people from black, Asian and other minority ethnic	**FIRST INTENSIFICATION** **If HbA1c rises to 58 mmol/mol (7.5%):·** *Consider dual therapy with: - a DPP-4i and pioglitazone - a DPP-4i and an SU (gliclazide) - pioglitazone and an SU (gliclazide) *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.
- 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 glargine 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 short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a

Abbreviations: DPP-4iDipeptidyl peptidase-4 inhibitor, GLP-1Glucagon-like peptide-1, SGLT-2iSodium–glucose cotransporter 2 inhibitors, SUSulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.b. Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months).d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification. e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

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SECOND INTENSIFICATION **If HbA1c rises to 58 mmol/mol (7.5%):·** *****Consider:- A)Triple therapy with: -metformin, a DPP-4i (**alogliptin**) and an SU (gliclazide) -metformin, pioglitazone and an SU (gliclazide) -metformin, pioglitazone or an SU, and an SGLT-2i (**empa**) B) Insulin-based treatment * Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)	→	groups) and specific psychological or other medical problems associated with obesity or- have a BMI lower than 35 kg/m2, and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities	**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%)	problem or blood glucose levels rise markedly after meals. • Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team. • 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.

Notes by Dr Gallen 5th January 2016

[1] Guidelines adapted from NICE guidelines NG 28 http://www.nice.org.uk/guidance/ng28

[2] In some patients, a lower target might be appropriate but consideration should be given to the intensity of treatment. It would be inappropriate to aim for a lower target in patients with longstanding poor control. Intensive management of HbA1C in the elderly is not appropriate because of the risk of hypoglycaemia precipitating serious events in these patients.

[3] Consider immediate treatment with Metformin if HbA1c >85 mol/mol

[4] Consider **MR Metformin** if poorly tolerated

[5] **Pioglitazone**
Tablet with proven cardiovascular safety, but usually some weight gain.
Renal impairment: OK.
Side effects: weight gain, fluid retention.
Contraindications: heart failure, haematuria, risk of osteoporosis.

[6] **DPP-4 inhibitors (alogliptin, or linagliptin, (others sitagliptin, vildagliptin, *saxagliptin do not use risk of CCF*)**
Tablet with no weight gain and few side effects, but long-term benefit not proven. Do not use Saxagliptin. Use linagliptin when with reduced eGFR).

[7] Average HbA1c reduction is about 11 mmol/mol with newer drugs, but may be individual variation, and some patients do show a greater response.

[8] When HbA1c is very high, you will usually not achieve good control by adding one of these drugs. Insulin is preferred for patients with very poor control.

[9] **Insulin should be the usual option after metformin and sulphonylurea.**
The newer drugs are aggressively marketed, but insulin remains a valuable therapy for type 2 diabetes and we have a huge amount of experience with it.
Insulin is "cleaner" and should be used in significant renal or hepatic impairment.
Insulin choice Humulin I, or Humulin M3. **Do not use analogue basal or biphasic insulin** without advice from diabetes team.

[10] **GLP-1 analogues (Preferred agents Lixisenatide or dulaglutide)**. .
NICE: only if BMI>30, unless psychological or occupational reasons to avoid insulin. Lixisenatide 10mcg increasing to 20mcg. Substitute dulaglutide 1.5mg every week if weekly treatment is preferred or if side effects/suboptimal response to lixisenatide. Weight reduction – average 2-4kg, though significant individual variation. Renal impairment: OK if eGFR >30. Side effects: nausea, bloating. Contraindications: risk of pancreatitis, bowel surgery.