Appendix 1. Websites for patients

The NHS Scotland interactive website

This well-constructed website has a wealth of resources for patients. For example, under their heading "My lifestyle"-there are three areas, where patients can read information, watch videos, or interact actively online. Go to this link:

http://www.mydiabetesmyway.scot.nhs.uk/

The Diabetes UK site is also well-reviewed and has large sections on prediabetes and "know your risk "score tools.

Go to this link: https://www.diabetes.org.uk/

Published November 2016

Appendix 2a. Medications and their mechanism of action

Metformin decreases hepatic glucose production and may improve peripheral glucose disposal while suppressing appetite and promoting weight reduction.

Metformin should be taken with or immediately after a meal. It should be introduced in low dose, with gradual escalation (e.g. 500 mg once daily for one week, 500 mg twice daily in week two, 500 mg thrice daily in week three, and 1 g twice daily in week four). Some individuals may not tolerate higher doses, in which case dose reduction is appropriate. Nausea, diarrhoea, and abdominal pain are the most common adverse effects. People should be informed that these side effects often improve after a few days of continued therapy, or with a small dose reduction.

A modified release preparation (metformin MR) is also available suitable for once daily dosing; some individuals otherwise intolerant of metformin may find this more acceptable, or may in some cases be able to take higher doses.

Metformin should usually be discontinued during a severe illness (e.g. myocardial infarction, pneumonia, severe infection and/or dehydration) as it may aggravate tissue hypoxia and accumulate when renal function is impaired. In these circumstances, it may be appropriate to use other glucose-lowering therapies, including insulin, in which case admission to hospital may be required.

As iodine-containing contrast media may cause acute deterioration of renal function, local arrangements should be in place for discontinuation of metformin prior to radiological investigations using >100 ml of contrast or where serum creatinine is raised.

NICE recommends that the dose should be reviewed if eGFR less than 45 mL/minute/1.73 m^2 and to avoid if eGFR less than 30 mL/minute/1.73 m^2. Metformin impairs B12 absorption so annual check of this needs to be performed and once a year injection considered to offset this in those affected.

[Expert reviewer's comment: Metformin tolerance by the gut may be partly genetically mediated. This can be enhanced by co-administration with common medications. For those who have to deal with this, I suggest looking at http://diabetes.diabetesjournals.org/content/58/6/1434.long .]

The ***sulphonylureas*** (glipizide, gliclazide, glibenclamide [glyburide], gliquidone, glyclopyramide, glimepiride) increase endogenous release of insulin from pancreatic β-cells. They act mainly by augmenting insulin secretion and thus are effective only when some residual pancreatic beta-cell activity is present.

Several sulfonylureas are available and choice is determined by side-effects and the duration of action as well as the patient's age and renal function. Glibenclamide, a long-acting sulfonylurea, is associated with a greater risk of hypoglycaemia; for this reason it should be avoided in the elderly, and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead.

All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital

Gliclazide is available in a modified release (MR) preparation. This permits once daily dosing even when higher doses are required. Prescribers should be aware that gliclazide MR 30 mg

is therapeutically equivalent to standard gliclazide 80 mg (maximum dose therefore 120 mg once daily rather than 160 mg twice daily).
People taking sulphonylureas should also be advised of their propensity to cause weight gain and therefore the need, if possible, to avoid calorie excess.

Dipeptidyl peptidase-4 (DPP-4) inhibitors include sitagliptin, vildagliptin, alogliptin and saxagliptin. They are oral agents which inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion. So far studies have shown them to be weight neutral.

They are generally well tolerated. However, questions remain about the possibility that they may predispose either to more frequent (usually minor) upper respiratory tract infections, and acute pancreatitis. People prescribed these agents should therefore be encouraged to report potentially serious symptoms, particularly severe abdominal pain, and, where in doubt, to discontinue DPP-4 inhibitors pending prompt further assessment. Also:

- reduce dose to 50 mg once daily if eGFR 30–50 mL/minute/1.73 m^2
- reduce dose to 25 mg once daily if eGFR less than 30 mL/minute/1.73 m^2.

Pioglitazone increases whole-body insulin sensitivity by activating nuclear receptors and promoting esterification and storage of circulating free fatty acids in subcutaneous adipose tissue.

When prescribing pioglitazone, exercise particular caution if there are high risk of the adverse effects of the drug, e.g. heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment. 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' and symptoms of heart failure should be actively assessed.

[Expert reviewer's comment: I think the bladder cancer link with pioglitazone has been largely refuted now. http://www.bmj.com/content/354/bmj.i3903.long .]

The ***meglitinides*** (repaglinide and nateglinide) act on the β-cell receptor to stimulate insulin secretion. The BNF advises that drivers on these drugs need to be particularly careful to avoid hypoglycaemia and should be warned to potential problems. They also need to be stopped during intercurrent illness e.g. MI, and on morning of planned surgery.

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 patient for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification (see flow-chart).

The ***Sodium-Glucose cotransporter-2 inhibitors (SGLT-2i)*** dapagliflozin, canagliflozin, empagliflozin act by reversibly inhibiting the sodium-glucose co-transporter-2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion. Thus they increase the finding of urine dipstick glucose at lower plasma glucose levels.

These medications should be avoided if e GFR is < 60 and renal function should be assessed prior to and throughout treatment.

Serious and life threatening ketoacidosis has been reported during administration with these medications and within short periods of stopping. Test for raised ketones in patients presenting with symptoms of DKA, even if plasma glucose levels are near-normal; omitting this test could

delay diagnosis of DKA, and patients should be advised on how to recognize the signs and symptoms of DKA so that they can seek prompt medical attention if these symptoms develop.

The ***Glucagon Like Peptide (GLP) -1 agonists*** exenatide and liraglutide amplify the secretion of insulin from pancreatic β-cells and inhibit inappropriate glucagon secretion. They also slow gastric emptying, resulting in slower absorption of glucose following meals, and reduce appetite.

Weight loss is a possible advantage of GLP-1 agonist therapy compared to insulin therapy and some oral glucose-lowering drugs.

Careful clinical judgement must be applied in relation to people with long duration of type 2 diabetes on established oral glucose-lowering drugs with poor glycaemic control (>10 years, these individuals being poorly represented in published studies) to ensure insulin therapy is not delayed inappropriately for the perceived benefits of GLP-1 agonists. NICE recommends review at 6 months and STOP treatment if HBa1c is not reduced by 11 mmol and weight loss of at least 3% of initiation body weight not achieved.

These agents require to be injected subcutaneously, like insulin. In keeping with the appetite-suppressant effect of these agents the most common adverse effects are nausea, vomiting and diarrhoea. Increased contact with the diabetes team is required particularly in the first weeks of use, usually with monitoring of therapeutic response – weight and HbA1c. Hypoglycaemia is much less frequent than with insulin, but may occur with GLP-1 agonists, particularly when administered in combination with a sulphonylurea. When a GLP-1 agonist is added to a sulphonylurea, a reduction in sulphonylurea dose should be considered.

As there is a small risk of acute pancreatitis with these agents, people receiving these agents should be encouraged to report any unexpected or severe abdominal symptoms. [Expert reviewer's comment: I would put this more strongly: a previous history of pancreatitis or inflammatory bowel disease is a contra-indication to these agents, so don't refer patients to us with this combined history, looking to start these drugs.]

As for oral agents, people taking exenatide or liraglutide may hold a regular (Group 1) driving licence without restriction.

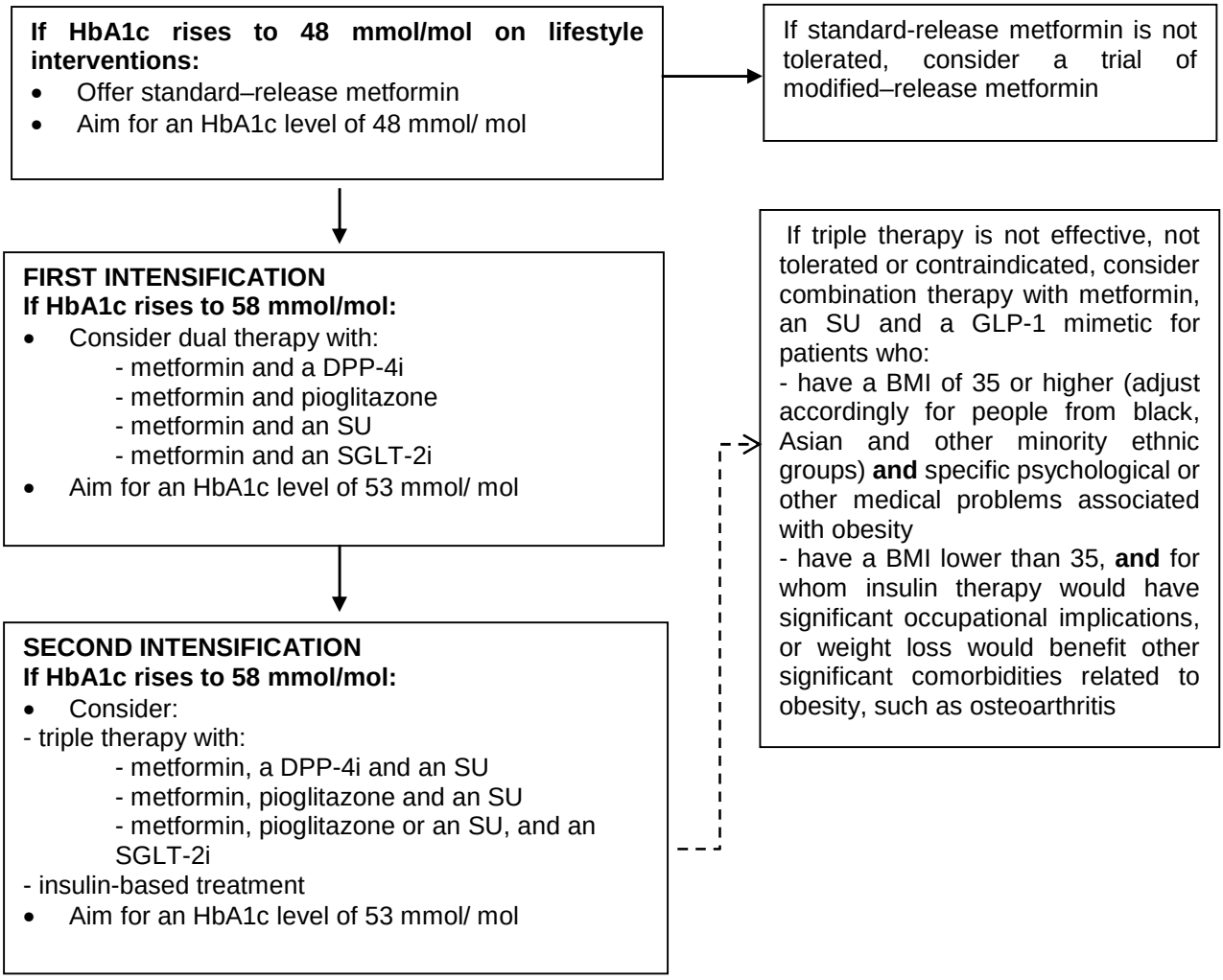
Appendix 2b: medication algorithm (NICE)

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

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.

PATIENTS WHO CAN TAKE METFORMIN



[Expert reviewer's comment: You have done an excellent job of streamlining the new NICE guidelines. Readers could consider the EASD-ADA algorithm also, which is good, particularly the beautiful coloured version of Figure 2 in the article below: http://care.diabetesjournals.org/content/38/1/140.figures-only

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol on lifestyle interventions:

- Consider one of the following: a DPP-4i, pioglitazone or an SU
- Aim for an HbA1c level of
    - 48 mmol/mol for people on a DPP-4i or pioglitazone
    - 53 mmol/mol for people on an SU

↓

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol:

- Consider dual therapy with:
  - a DPP-4i and pioglitazone
  - a DPP-4i and an SU
  - pioglitazone and an SU
- Aim for an HbA1c level of 53 mmol/mol

↓

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol:

- Consider insulin-based treatment
- Aim for an HbA1c level of 53 mmol/mol

Insulin-based treatment:

- When starting insulin use a structured programme, and continue metformin if tolerated. 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 or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine if
    - assistance to inject insulin is needed,
    - lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes
    - the patient otherwise needs 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 patient prefers injecting insulin immediately before a meal
    - hypoglycaemia is a problem
    - blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic in combination with insulin with specialist care advice.
- 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:

Treatment with combinations of drugs including SGLT-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 of the NICE guideline, 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.

Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol and a weight loss of at least 3% of initial body weight in 6 months).