Management of type 2 diabetes: now and the future

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There are about 4.7 million people living with diabetes mellitus in the UK and 90% have type 2 diabetes mellitus (T2DM). This burden will only get worse as there are currently about 12.3 million more at risk of T2DM. Moreover, up to 30% of diagnosed patients already have eye, foot, kidney or nerve complications. This impacts the NHS considerably as it spends about £10 billion annually on diabetes (80% on complications alone). Atherosclerotic cardiovascular disease (ASCVD), the leading cause of death in diabetes, contributes significantly to this. Therefore, there is significant emphasis on the prevention of T2DM especially in at-risk groups with the setting up of initiatives like the Diabetes Prevention Programme. When prevention fails, it is essential to commence glucose-lowering agents to reduce the burden of disease, prevent associated complications and improve quality of life.

A patient-centred approach is required to ensure efficacy of treatment strategies and the presence of co-morbidities such as cardiovascular and renal disease should be considered.

Introduction

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A patient-centred approach is required to ensure efficacy of treatment strategies and the presence of co-morbidities such as cardiovascular and renal disease should be considered.

Key points

The UK prevalence of type 2 diabetes mellitus (T2DM) is rising and costing the NHS significantly.

Optimising glycaemic control promptly can confer long-lasting protection from microvascular complications.

Metformin remains the first-line glucose-lowering agent in T2DM.

Sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 agonists have benefit in atherosclerotic cardiovascular disease and heart failure and confer renal protection.

These agents should be added to metformin promptly in at-risk groups with patient-specific glycated haemoglobin targets set.

Keywords: Type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, heart failure, glucose-lowering agents
Cardiovascular and renal protection. We would suggest the addition of either a sodium-glucose co-transporter-2 inhibitor (SGLT-2i) or glucagon-like peptide-1 (GLP-1) receptor agonist with proven evidence of cardiovascular and renal benefit. These agents can also promote weight loss, which would also be beneficial. However, patient preference and cost effectiveness of medication should be considered when choosing glucose-lowering agents.

We would therefore suggest introducing empagliflozin 10 mg or dapagliflozin 10 mg once daily to his medication and he should have a repeat HbA1c in 3 months to assess the efficacy of treatment as well as monitoring of his renal function.

Discussion: glucose-lowering agents

The level of HbA1c is an estimate of mean blood glucose over a 3 month period. HbA1c targets have been set by different national and international guidelines to determine when to optimise treatment. These targets should be patient centred and treatment individualised to ensure success. This is important because there is evidence showing that if glycaemic control is optimised especially around the time of diagnosis, the effects in preventing microvascular complications can be long lasting.5

The choice of glucose-lowering agent used in T2DM is dependent on a number of factors including patient preference, drug efficacy, presence of co-morbidities and side effect profile (eg weight gain or hypoglycaemia).6 Traditionally, due to the close association of T2DM and obesity, medication that are either weight neutral or those that promote weight loss are preferred (see Table 1 for commonly used glucose-lowering agents).

Reviewing the case illustration, the patient is obese with ASCVD, early stage renal impairment and sub-optimal glycaemic control. Optimising his glucose-lowering medication should factor all these and the most clinical and cost-effective agent should be selected using evidence based medicine.

There is now evidence showing that certain SGLT-2i and GLP-1 receptor agonists have beneficial cardiovascular protection in ASCVD and heart failure (HF) and can reduce the progression of chronic kidney disease (CKD).

Empagliflozin has shown a 38% risk reduction in cardiovascular deaths (reduced hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.49–0.77; p<0.001) in people with T2DM and established ASCVD.7 Also, canagliflozin demonstrated a reduction in three-point major adverse cardiovascular events (MACE; HR 0.86; 95% CI 0.75–0.99; p=0.02).8 Furthermore, dapagliflozin was proven to reduce cardiovascular death and hospitalisation due to heart failure (HR 0.83; 95% CI 0.73–0.95; p=0.005).9 This effect might be related to blood pressure lowering or effects on vascular endothelium as it occurred irrespective of improvement in HbA1c.

It should be noted that there was no significant reduction in cardiovascular death or hospitalisation due to heart failure in patients without established ASCVD. One could argue that if the patient in the illustrated case did not have ASCVD, then a dipeptidyl peptidase-4 inhibitor (DPP-4i) may have been an appropriate addition to his medication.

Furthermore, liraglutide and semaglutide have both shown statistically significant reduction in three-point MACE with the former reducing CV death and the latter reducing non-fatal strokes, respectively.10,11 Canagliflozin and semaglutide reduce the

Table 1. Common glucose-lowering agents. Data derived from meta-analyses and British National Formulary

<table>
<thead>
<tr>
<th>Drug class (example)</th>
<th>Glycated haemoglobin reduction</th>
<th>Effect on weight</th>
<th>Side effects</th>
<th>Cardiovascular benefit</th>
<th>Renal benefit</th>
<th>Monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide (metformin)</td>
<td>0.8–1.0% (9–12 mmol/mol)</td>
<td>Neutral</td>
<td>Gastrointestinal</td>
<td>Yes</td>
<td>N/A</td>
<td>£3.20 or £4.26</td>
</tr>
<tr>
<td>Sulphonylurea (glicazide, glibenclamide)</td>
<td>0.8–1.1% (9–22 mmol/mol)</td>
<td>Weight gain</td>
<td>Hypoglycaemia</td>
<td>N/A</td>
<td>N/A</td>
<td>£1.63 or £3.27</td>
</tr>
<tr>
<td>Thiazolidinedione (pioglitazone)</td>
<td>0.5–0.7% (6–8 mmol/mol)</td>
<td>Weight gain</td>
<td>Fluid retention</td>
<td>No</td>
<td>N/A</td>
<td>£1.84</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin)</td>
<td>0.4% (5 mmol/mol)</td>
<td>Neutral</td>
<td>Cough</td>
<td>N/A</td>
<td>No</td>
<td>£26.60–£33.26</td>
</tr>
<tr>
<td>Sodium-glucose co-transporter-2 inhibitor (canagliflozin, a dapagliflozin, a emagliflozin, a ertugliflozin)</td>
<td>0.4% (5 mmol/mol)</td>
<td>Loss</td>
<td>Urinary tract infections</td>
<td>Yes</td>
<td>Yes</td>
<td>£36.59–£39.20</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 receptor agonists (dulaglutide, a exenatide, lixisenatide, semaglutide)</td>
<td>0.5–0.7% (6–8 mmol/mol)</td>
<td>Loss</td>
<td>Gastrointestinal</td>
<td>Yes</td>
<td>Yes</td>
<td>£73.25</td>
</tr>
</tbody>
</table>

a = evidence of cardiovascular benefit; b = evidence of renal benefit.

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either a DPP-4i, pioglitazone or a sulphonylurea (SU) instead. It is relatively well tolerated, weight neutral and is unlikely to cause hypoglycaemia. Although there are some instances when its use is not appropriate such as in advanced CKD or intolerance due to gastrointestinal side effects. NICE guidelines then recommend appropriate such as in advanced CKD or intolerance due to metformin as first-line but suggest including an SGLT-2i or GLP-1 agonist as second-line treatment if metformin does not achieve target HbA1c and a GLP-1 agonist as third-line. GLP-1 agonist use may be limited because they are given via subcutaneous injections and cost more than standard oral treatment.

In contrast to NICE and SIGN, ADA and EASD recommend starting treatments with proven efficacy in ASCVD, CKD and HF in at-risk groups sooner.13 The ADA/EASD guidelines advice metformin as first-line but suggest including an SGLT-2i or GLP-1 even if patients are at HbA1c target. This would involve reviewing patient specific targets to ensure they receive the added cardiovascular and/or renoprotective benefits without compromising their glycaemic control. Therefore, it may be appropriate to add an SGLT-2i to the case patient’s medication even if his HbA1c was 51 mmol/mol (6.8%) due to the cardiovascular and renal benefits conferred. These agents have been shown to be cost effective and would help lessen the economic burden on the NHS in the long term.16

We suggest that NICE consider implementing ADA/EASD recommendations to introduce SGLT-2i and GLP-1 agonists sooner in patients with T2DM and ASCVD, CKD or HF when it is appropriate. Rather than focusing on HbA1c targets and optimising treatment only when glycaemic control is above target, patient-specific treatment plans should involve their cardiovascular and renal co-morbidities.

Conclusion

Type 2 diabetes is a complex entity that can be associated with multiple end-organ complications if not adequately managed. Lifestyle modification in the form of reduced carbohydrate intake and increased physical activity is fundamental. However, if glucose-lowering treatment is required, metformin remains the first-line treatment but SGLT-2i or GLP-1 agonists should be instituted early in patients with ASCVD, HF or CKD with patient-specific HbA1c targets set. Using these agents appropriately has been shown to be both clinically and cost effective.

References


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Complex regional pain syndrome in adults
UK guidelines for diagnosis, referral and management in primary and secondary care

Published by the Royal College of Physicians, these guidelines concern the diagnosis and management of patients with complex regional pain syndrome (CRPS). They are designed for professionals working in the different health specialties who care for these patients.

Updated in 2018, and published in partnership with over 20 other medical organisations, the guidelines provide information on diagnosis, treatment, management and support for patients in a wide variety of clinical settings.

The report underlines the need for multidisciplinary support to manage CRPS and outlines the four pillars of care that underpin management:
> education
> pain relief
> physical rehabilitation
> psychological intervention.

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