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COMMENTARY

# Effective Utilization of Oral Hypoglycemic Agents to Achieve Individualized HbA1c Targets in Patients with Type 2 Diabetes Mellitus

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## ABSTRACT

Type 2 diabetes is a progressive condition that may require the combination of three oral treatments to achieve optimal glycemic management to prevent microvascular and macrovascular complications whilst minimizing the risk of acute complications and side effects or adverse reactions to treatments. With the widening availability of treatment options and increasing importance of individualized treatment pathways, including personalized HbA1c targets, this article will explore the mode of action of currently available oral treatments, factors to consider when individualizing HbA1c targets, the relevance of estimated glomerular filtration rate assessment, and the importance of reviewing the clinical impact of all treatment decisions.

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## INTRODUCTION

Type 2 diabetes is a progressive life-long condition that, if poorly managed, results in significant morbidity as a result of micro- and macrovascular complications [1, 2]. Macrovascular or cardiovascular disease is the leading cause of mortality in individuals with type 2 diabetes, accounting for 54% of deaths [2]. Effective diabetes management to prevent the development of long-term complications requires intensive treatment of numerous risk factors, including hypertension, hypercholesterolemia, and hyperglycemia. In recent years, the treatment options to achieve optimum glycemic control have rapidly expanded. There are currently five groups of oral agents and two injectable therapies available (Fig. 1). The challenge for clinicians is determining which combination of treatment is most appropriate for an individual with type 2 diabetes, with the recommendation being that a maximum combination of three oral treatments are used [3].

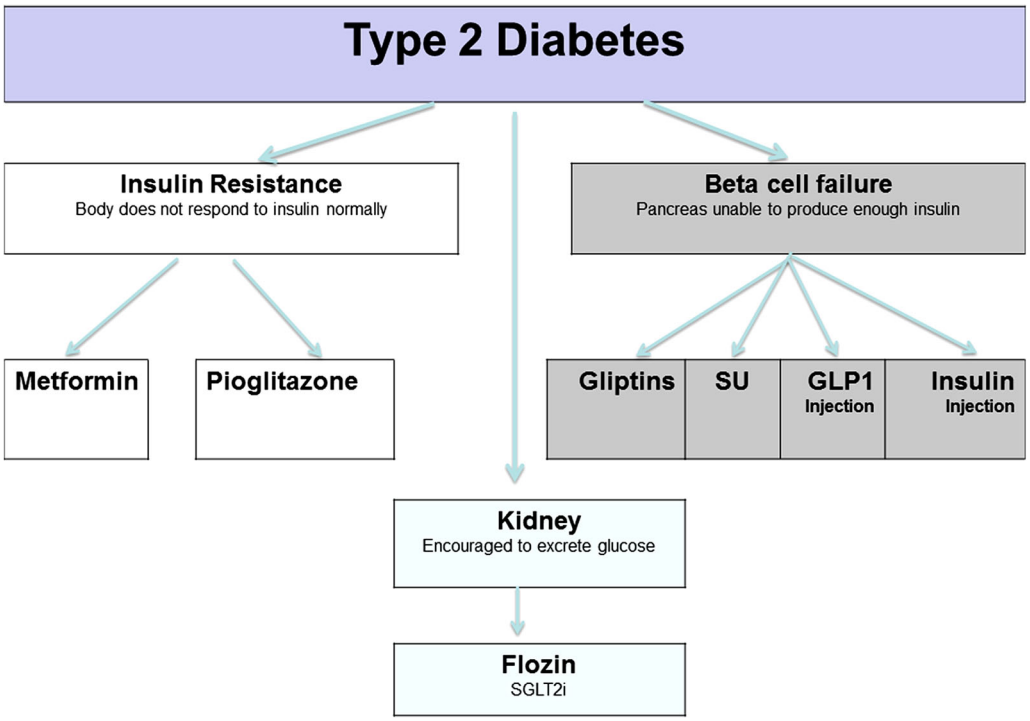


**Fig. 1** Diabetes treatment tree. *GLP1* glucagon-like peptide-1, *SGLT2i* sodium-glucose co-transporter-2 inhibitor, *SU* sulfonylurea

This article does not contain any new studies with human or animal subjects performed by any of the authors. Informed consent was received from all patients for inclusion in this article.

## PATHOPHYSIOLOGY

The number of people diagnosed with type 2 diabetes has escalated in the last decade, and is reaching epidemic levels worldwide [4]. In 2014, the worldwide prevalence of diabetes for 20–79 year olds was 387 million, with type 2 diabetes accounting for 90% of cases [2]. This rapid increase in the incidence of diabetes is linked partly to the significant increase in the worldwide population who are overweight or obese. The latter account for 80–85% of those at risk for developing type 2 diabetes [2], although the aging populations of, in particular, many westernized countries have also contributed to its increased incidence.

The primary pathophysiological abnormality in the majority of individuals that develop type 2 diabetes is insulin resistance. Insulin resistance develops when the insulin receptor on the surface of muscle and other cells change shape. This results in an inability of the insulin molecule to attach to the receptor opening the glucose channel, which prevents the uptake of glucose by the cells. Many ethnic groups have underlying insulin resistance which is significantly increased by any escalation in weight. Type 2 diabetes is six times more common in people of South Asian descent, and three times more common in those of African or African Caribbean origin [2].

As insulin resistance increases, the beta cells compensate by producing additional insulin which maintains blood glucose levels within

the normal range. However, with increasing insulin resistance and progressive beta cell failure, blood glucose levels become increasingly difficult to maintain within the normal range of 3.5–6.5 mmol/L. The high demand for insulin and the glucose toxicity that develops from increasing blood glucose levels results in the development of beta cell failure and a decline in insulin production. Type 2 diabetes is preceded by a period of impaired glucose regulation that can be corrected if the body's insulin requirements are reduced by a reduction in weight, increase in physical activity, or reduction in food intake, or a combination of all three. Type 2 diabetes develops when an individual's demand for insulin exceeds the amount they are able to produce, even though at the time of diagnosis they may have significant hyperinsulinemia. Beta cell failure is also linked to increasing age, and when type 2 diabetes develops in an elderly person with a healthy body mass index (BMI) the underlying cause is most likely beta cell failure.

Insulin release occurs in two phases. First-phase insulin release occurs 2–10 min following a rise in blood glucose level; this rapid release of insulin prevents the blood glucose level from rising too high. Second-phase insulin release is much more controlled. The amount and speed of insulin release is determined by the actual rise in blood glucose level and the rate that carbohydrate is digested. First-phase insulin release is stimulated by the hormone glucagon-like peptide-1 (GLP-1), which primes the beta cells in the pancreas to release insulin in response to a rise in the blood glucose level. GLP-1 is rapidly destroyed in the body by the enzyme dipeptidyl peptidase-4 (DPP4), and has a half-life of 2 min. First-phase insulin release is absent in type 2 diabetes as a result of low levels of the GLP-1 hormone.

In a healthy individual, glucose should not be present in the urine. As blood passes through the kidney, all glucose passes through the glomerulus into the nephric filtrate; 100% of glucose, 99% of water, and other essential electrolytes are reabsorbed through a process of selective reabsorption as the filtrate passes through the nephron. Glucose reabsorption occurs predominantly (90%) in the proximal tubule due to the action of the hormone sodium-glucose co-transporter 2 (SGLT2), which opens glucose channels in the wall of the tubule. A normal renal threshold enables 10 mmol/L of glucose to be reabsorbed with water reabsorption occurring through osmosis in the loop of Henle. If blood glucose levels in the filtrate exceed the renal threshold, glucose will remain in the filtrate and result in reduced water reabsorption and the presence of glucose in the urine.

## LITERATURE REVIEW

The publication of the UK Prospective Diabetes Study (UKPDS) [5] brought into question the importance of glycemic management in the prevention of macrovascular complications in type 2 diabetes. The impact of intensive glycemic control on the prevention of macrovascular disease, unlike in microvascular disease, did not reach statistical significance. The focus changed to intensive blood pressure management. However, the publication of the UKPDS follow-on study [1] demonstrated that the impact of intensive glycemic control on macrovascular complications does not become evident as early as in microvascular complications. Individuals who had participated in the intensive glycemic control

arms of the original UKPDS were noted to have statistically better outcomes in relation to myocardial infarction 10 years post completion of the study than those who had participated in the conventionally controlled arm, even though for the subsequent 10 years they had experience similar levels of control [1]. These findings have resulted in the development of the term "metabolic memory." This refers to the fact that good glycemic control in the early years post diagnosis protects against complications after 15–20 years of having type 2 diabetes, when achieving good glycemic control is more difficult due to declining insulin production as a result of beta cell failure.

This current evidence has returned the focus to optimum glycemic control in the management of type 2 diabetes, balanced against the potentially increased risk of hypoglycemia. Hypoglycemia, especially in individuals with existing macrovascular disease, has been linked to an increase in mortality [6].

Individualized HbA1c targets appropriate for the individual's age are actively encouraged (Table 1) [3, 7], and are supported by the development of treatment plans that utilize a combination of treatments which take into consideration age, occupation, and estimated glomerular filtration rate (eGFR) to achieve agreed individualized targets.

## Treatment Options

### *Biguanides*

Metformin is the only biguanide available, and one of the oldest treatments for diabetes, dating back to the 1960s. Metformin reduces gluconeogenesis in the liver, lessening the amount of glucose released by the liver, particularly overnight. Additionally it increases the sensitivity of muscle cells to insulin, improving peripheral glucose uptake and utilization. Due to its mode of action, metformin rarely causes hypoglycemia.

The National Institute for Health and Care Excellence [3] pathway for blood-glucose-lowering therapy for type 2 diabetes recommends that metformin is initiated as first-line therapy in asymptomatic patients with a HbA1c greater than 48 mmol/mol, or higher than an agreed individualized target despite changes to lifestyle. Metformin should be commenced with a starting dose of 500 mg once daily after food with active titration over a 4-week period to the maximum tolerated dose or maximum dose of 2 g daily. Adopting this approach reduces the common side effects of nausea, vomiting, diarrhea, and abdominal pain. Slow-release preparation of metformin could be trialed if side effects mean that standard release preparations cannot be tolerated.

If renal function declines below 45 mL/min/1.73 $m^2$ [8], a dose review should occur, with a maximum dose of 1 g being prescribed. Metformin should be discontinued in patients whose eGFR is less than 30 mL/min/1.73 $m^2$. Due to an increased risk of lactic acidosis if a sudden deterioration in renal function occurs, metformin should be withheld prior to general anesthesia, procedures requiring contrast medium, and episodes of acute deterioration in eGFR until the renal function normalizes. Dehydration increases the risk of deterioration in renal function; therefore, patients should be aware that they should stop taking metformin if they become unwell with diarrhea and vomiting.

### *Sulfonylureas*

Commonly prescribed sulfonylureas include glimepiride and gliclazide; their mode of

**Table 1** International Diabetes Federation HbA1c targets in the elderly (over 75 years old) [7]

| Category | Targets |
|---|---|
| Category 1: functionally independent | Living independently |
| | No impairment of ADLs |
| | Receiving none or minimal care-giver support |
| | **HbA1c target: 53–59 mmol/mol** |
| Category 2: functionally dependent | Due to loss of function, having impairment of ADLs |
| | Increased likelihood of requiring additional medical and/or social care |
| | **HbA1c target: 53–64 mmol/mol** |
| Subcategory A: frail | Combination of significant fatigue, recent weight loss, severe restriction in mobility and strength, increased propensity for falls, and increased risk of institutionalization |
| | A recognized condition, and accounts for 25% of older people with diabetes |
| | Clinical frailty scale or CSSHA 9-point scale (assessment tool) |
| | **HbA1c target: 60–70 mmol/mol** |
| Subcategory B: dementia | Degree of cognitive impairment leading to significant memory problems, a degree of disorientation or a change in personality, and unable to self-care |
| | Mini cognitive tool (easy-to-use assessment tool) |
| | **HbA1c target: 60–70 mmol/mol** |
| Category 3: end of life care | Significant illness or malignancy, and have life expectancy reduced to <1 year |
| | **Glycemic aim: hypo- and symptomatic hyperglycemia avoidance** |

*ADL* activity of daily living, *CSHA* Canadian Study of Health and Aging

action requires a degree of beta-cell function, as they stimulate the pancreas to increase insulin secretion and as a result have a significant risk of inducing hypoglycemia and can potentially cause weight gain. NICE 2015 [3] recommends their use as first-line therapy in symptomatic patients, and should be titrated weekly whilst osmotic symptoms are present based on blood glucose self-monitoring results. Prescribing sulfonylureas in the elderly population and in people who drive requires caution because of the associated risk of hypoglycemia.

### *Thiazolidinedione*

Pioglitazone is the only thiazolidinedione currently prescribable in Europe. It acts directly at the cellular level, increasing the sensitivity of the hepatic and muscle tissue to endogenous insulin, and is particularly efficacious in patients whose underlying pathophysiology is insulin resistance. As pioglitazone does not impact on insulin secretion, the hypoglycemia risk is low unless used in combination with a sulfonylurea or insulin. Pioglitazone should be initiated at 15 mg, increasing to 30 mg after 3 months if there has not been a response. Increasing to 45 mg would only be indicated if there was a reduction in HbA1c with 30 mg but the target HbA1c was not reached. If no additional response is noted with 45 mg, the dose should be reduced back to 30 mg [9]. If a 6 mmol/mol

drop is not achieved after 6 months on 30 mg it should be stopped. Due to an increased risk of fluid retention, which could exacerbate or precipitate heart failure, pioglitazone is contraindicated in patients with or a history of heart failure. Advice in relation to signs and symptoms of heart failure such as edema should be part of the patient consultation on initiating treatment, and treatment should be stopped if any symptoms develop. Liver function tests should be carried out prior to initiation and periodically thereafter due to a rare potential risk of liver toxicity. If the alanine aminotransferase (ALT) level remains more than three times the upper limit of normal, pioglitazone should be discontinued. Suggestions have been made that pioglitazone potentially increases the risk of bone fractures and bladder cancer in a recent multi-population pooled cumulative-exposure analysis; however, it showed that there was no association with the cumulative use of pioglitazone and the associated incidence of bladder cancer [10]. Recent studies in individuals without diabetes but with diagnosed insulin resistance and a history of ischemic stroke or transient ischemic attacks treated with pioglitazone showed a significant reduction in the relative risk of nonfatal heart attack or fatal and nonfatal stroke, suggesting that addressing insulin resistance though treatment with pioglitazone could improve cardiovascular outcomes [19].

### *DDP4 Inhibitors, Commonly Known as Gliptins*

There are five different DPP4 inhibitors currently on the market: alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. They work by inhibiting DPP4, which is an enzyme that destroys the hormone GLP-1. GLP-1 aids glucose-dependent insulin production, in particular first-phase insulin release. Due to the glucose-dependent mode of action, they are unlikely to cause hypoglycemia unless used concomitantly with a sulfonylurea or insulin. These groups of drugs are weight neutral which, combined with the low risk of hypoglycemia, means they are a suitable treatment option for the elderly and occupational drivers. If used as second-line therapy with metformin, patients are not required to undertake glucose self-monitoring due to the low risk of hypoglycemia. DPP4 inhibitors have the associated increased risk of pancreatitis and should be avoided in patients with high triglycerides. Patients require counseling on initiation about the signs and symptoms of pancreatitis, with instructions for when and how to seek urgent medical advice. The majority of DPP4 inhibitors are taken once daily and the doses need to be adjusted according to renal function, with the exception of linagliptin, which has no restriction based on eGFR as it is excreted in the bile. Post-surveillance trials have highlighted that DPP4 inhibitors can cause severe and disabling joint pain. It was found that when DPP4 inhibitors were stopped, the pain and symptoms resolved. Therefore, it would be appropriate to consider a trial without the DPP4 inhibitor if patients report joint pains [11]. Concerns relating to DPP4 inhibitors and increased heart failure risk have been raised in cardiovascular safety studies for a number of treatments. The SAVOR-TIMI 53 trial [12] found an increased risk of admission to hospital for heart failure with saxagliptin. The EXAMINE trial [13], which reviewed alogliptin, and the TECOS trial [14], which reviewed sitagliptin, did not identify any statistically significant effect on hospital admissions for heart failure. More recently, a further safety review from the US Food and Drug Administration [15] found that saxagliptin and

alogliptin may increase the risk of heart failure, especially in patients where heart failure or kidney disease is already present. Patients therefore should be warned of the signs and symptoms of heart failure and advised to seek urgent medical advice if concerned, and healthcare professionals should contemplate stopping the treatment if patients develop heart failure. Applying these findings to clinical practice would mean exercising caution when utilized in patients with type 2 diabetes with heart and kidney disease, paying particular attention to ensuring correct dosage based on a current eGFR result. Response to treatment initiation must be reviewed, and if the HbA1c has not reduced by 6 mmol/mol from when the treatment was initiated it should be discontinued [3].

### *SGLT2 Inhibitors*

These are the newest group of oral hypoglycemic agents, and include dapagliflozin, canagliflozin, and empagliflozin. SGLT2 is a protein which encourages glucose reabsorption in the proximal tubule in the kidney. The SGLT2 inhibitors block the receptor site, preventing activation of the glucose channel and glucose reabsorption, so the glucose remains in the renal filtrate and ultimately the urine. As the filtrate passes through the loop of Henle, water is reabsorbed by osmosis, but as a result of the elevated levels of glucose in the filtrate, reduced water reabsorption occurs, resulting in increased urine production. The loss of glucose in the urine and thus calories can result in weight loss. However, the side effects due to the glycosuria include increased risk of urinary tract infections and thrush/balanitis. For SGLT2 inhibitors to be effective, good renal function is required, and they should not be prescribed to patients whose eGFR is less than 60 mL/min/1.73 $m^2$. The increased diuresis that can result from glycosuria can potentially cause hypotension, and SGLT2 inhibitors should be used with caution in combination with a loop diuretic. The three SGLT2 inhibitors vary in their licensing guidance. Dapagliflozin is not licensed with pioglitazone, is not recommended in triple therapy, and should be stopped if eGFR drops below 60 mL/min/1.73 $m^2$. Canagliflozin and empagliflozin are both licensed for triple therapy and with pioglitazone. They can be continued at the lower prescribable dose even if eGFR drops below 60 mL/min/1.73 $m^2$ if a therapeutic benefit has been noted, but are stopped if eGFR drops below 45 mL/min/1.73 $m^2$. SGLT2 inhibitors are taken once daily, with canagliflozin and empagliflozin having the option of a titrating dose. If the HbA1c has not reduced by 6 mmol/mol following the initiation of treatment, it should be discontinued. Unless prescribed in combination with a sulfonylurea or insulin, then the risk of hypoglycemia is low.

As with all new diabetes oral therapies, they require the study of cardiovascular endpoints to assess safety. Empagliflozin, the most recent SGLT2 inhibitor on the market, was found to have added benefits of reducing the relative risk of cardiovascular death, nonfatal heart attack, or nonfatal stroke by 14% and a significant 38% relative risk reduction in cardiovascular death rate. These positive results come from the EMPA-REG OUTCOME trial [16], but it still needs to be determined if this relates to the class of drugs, as cardiovascular outcome studies are still in progress for canagliflozin and dapagliflozin.

A number of clinical concerns have been raised with this group of drugs. An increased risk of acidosis with euglycemia has been noted, particularly during the first 2 months of

treatment [17]. Whilst the case numbers were low and a third were identified as having type 1 diabetes, clear guidance has been issued that—particularly when used in combination with insulin or a sulfonylurea, where doses have been reduced—vigilance for ketosis must be high. Patients therefore should be informed of the signs and symptoms of diabetic ketoacidosis (DKA), and healthcare professionals still need to consider DKA in patients who present with the symptoms but whose glucose levels are within the normal range and, as with metformin treatment, should be suspended in patients hospitalized for major surgical procedures or acute medical illness and restarted once the patient's condition has stabilized.

Concerns in relation to an increased frequency of fractures with canagliflozin compared to placebo and links to reduced bone mineral density have resulted in changes to the drug label "warning and precaution" and "adverse reactions" [18]; further concerns have been highlighted in the CANVAS study in relation to increased amputation rates in those patients with a high cardiovascular risk, particularly those with a previous history of amputation [20]. In clinical practice, this requires healthcare professionals to be mindful of patient risk factors before commencing this treatment, and to consider if it actually the most appropriate treatment choice for that patient. Reporting side effects is an important way of establishing any adverse impacts from new drugs, and all healthcare professionals need to be involved in this process when appropriate. The importance of ensuring that patients maintain good levels of hydration when treated with SGLT2 inhibitors in order to minimize the risk of potential adverse outcomes is being increasingly being stressed [20].

## CASE STUDIES

The glycemic management of type 2 diabetes requires clinicians to identify the most therapeutic combinations of treatments, with a maximum of three oral treatments being prescribed. The choice of initial therapy is usually clear, with metformin being identified as first-line therapy in asymptomatic individuals and those with eGFR >45 mL/min/1.73 $m^2$, and a sulfonylurea in symptomatic patients.

The choice of second-line therapy is more complicated, with factors such as weight, hypoglycemic risk, occupation, and age to be taken into consideration. Third-line treatment would be required if HbA1c remains at 58 mmol/mol or greater, or above the agreed target [3]. Figure 2 was developed by one of the authors as a tool to facilitate treatment choices for patients with type 2 diabetes in response to local demands from healthcare professionals who wanted more guidance in oral hypoglycemic agents. Past experience has shown that some clinicians swap one treatment which was effective for another treatment and the HbA1c then declines. Figure 2 also indicates that HbA1c should be monitored after a new treatment has been

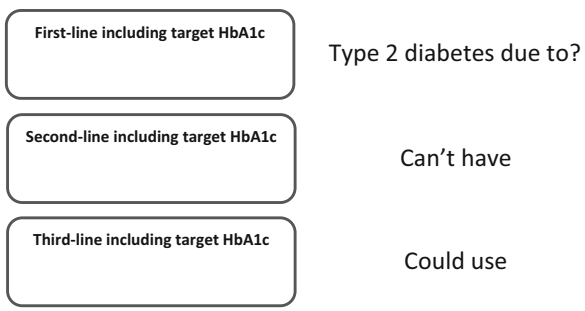


**Fig. 2** Preferred treatment plan

initiated and that treatments which have not had the therapeutic effect of a 6 mmol/mol reduction in HbA1c should be discontinued. With an estimated £10 billion annually spent by the National Health Service on diabetes, which equates to £1 million each hour [2], it is imperative that treatments are discontinued if they are not proving to be effective.

Case studies will be utilized in the following section to help illustrate how appropriate treatment decisions can be supported by utilizing the clinical information for individual patients and individualized HbA1c targets. A rationale will then be provided for each of the treatment decisions.

## Case Study 1

An 81-year-old female, who lives alone, mobilizes with a Zimmer frame, and has vascular dementia. Recent blood results show an eGFR of 49 mL/min/1.73 $m^2$ and a HbA1c of 76 mmol/mol, and her BMI is 24 kg/$m^2$. Current treatment is metformin 1 g twice daily.

### *Treatment Recommendation*

A DPP4 inhibitor. With an eGFR of 49 mL/min/1.73 $m^2$, alogliptin, saxagliptin, sitagliptin, and vildagliptin could be used at a reduced dose. Linagliptin would not need adjusting according to eGFR as the dose is not affected by eGFR results, so this could be used at the maximum dose. The eGFR would need to be closely monitored because the metformin dose would need halving if the eGFR drops below 45 mL/min/1.73 $m^2$.

Table 2 shows the treatment decisions and rationales for this patient.

## Case Study 2

An unemployed 45-year-old white male. His recent blood results show an eGFR > 90 mL/min/1.73 $m^2$ and a HbA1c of 64 mmol/mol, and his BMI is 36 kg/$m^2$. He has had type 2 diabetes for 4 years. Current treatment is metformin 1 g twice daily and pioglitazone 45 mg.

### *Treatment Recommendation*

An SGLT2 inhibitor. His eGFR is within the normal range. His weight is his main concern. Pioglitazone was shown to have a good therapeutic effect at 30 mg, and his HbA1c reduced by another 7 mmol/L when the dose was increased to 45 mg, so pioglitazone would be continued. Dapagliflozin is not licensed with pioglitazone so it would not be appropriate in

**Table 2** Treatment decision rationale for Case Study 1

| Treatment options | Decision | Rationale |
|---|---|---|
| HbA1c target | <70 mmol/mol | IDF guidance, category 2, subcategory B: dementia |
| Glimepiride | Unsuitable | Increased risk of hypoglycemia |
| SGLT2i | Contraindicated | eGFR <60 mL/min/1.73 $m^2$ |
| Pioglitazone | Unsuitable | Unlikely to have a therapeutic effect with a BMI of 24 kg/$m^2$; increased fracture risk |
| DPP4i | Suitable | No risk of hypoglycemia |

*BMI* body mass index, *DPP4i* dipeptidyl peptidase-4 inhibitor, *eGFR* estimated glomerular filtration rate, *IDF* International Diabetes Federation, *SGLT2i* sodium-glucose co-transporter-2 inhibitor

**Table 3** Treatment decision rationale for Case Study 2

| Treatment options | Decision | Rationale |
|---|---|---|
| HbA1c target | 58 mmol/mol | NICE 2015 (NG 28) |
| DPP4i | An option | May still have some beta-cell function but will not promote weight loss |
| Glimepiride | An option | May still have some beta-cell function; may increase weight |
| SGLT2i | An option | eGFR >60 mL/min/1.73 $m^2$; encourages weight loss |

*DPP4i* dipeptidyl peptidase-4 inhibitor, *eGFR* estimated glomerular filtration rate, *NICE* National Institute for Health and Care Excellence, *SGLT2i* sodium-glucose co-transporter-2 inhibitor

this case, but empagliflozin and canagliflozin would be an option for third-line therapy.

Table 3 shows the treatment decisions and rationales for this patient.

## Case Study 3

A 38-year-old male of Pakistani origin who works as a taxi driver. Recent blood results show an eGFR of 78 mL/min/1.73 $m^2$ and a HbA1c of 60 mmol/mol, and his BMI is 32 kg/$m^2$. He has had type 2 diabetes for 2 years. Current treatment is metformin modified release 2 g post main meal.

### *Treatment Recommendation*

Pioglitazone 15 mg (titrated to 30 mg at 3 months if HbA1c remains above target) or SGLT2 inhibitor. Insulin resistance is the primary pathology of type 2 diabetes in this patient due to his ethnic origin and raised BMI. Pioglitazone has the potential to improve his insulin sensitivity. A SGLT2 inhibitor will potentially result in weight loss, and a 5–10% weight loss would have a positive impact on insulin sensitivity. As the patient is an occupational driver with potentially erratic meal patterns, it is important to minimize the risk of hypoglycemia. Whichever treatment is commenced first should be agreed upon following discussion with the patient. The unused treatment should be added if triple therapy is indicated or the first choice is stopped due to lack of impact on control or side effects.

Table 4 shows the treatment decisions and rationales for this patient.

## Case Study 4

A 68-year-old female newly diagnosed with diabetes from a random blood glucose level of 15.3 mmol/L (no urinary or blood ketones), marked thirst, nocturia, and vulval thrush. Blood results show an eGFR of >90 mL/min/1.73 $m^2$ and a HbA1c of 76 mmol/mol, and her BMI is 22 kg/$m^2$.

### *Treatment Recommendation*

Glimepiride with blood glucose self-monitoring to facilitate dose titration. A sulfonylurea will have the quickest impact on symptoms, as it will stimulate increased insulin production if sufficient beta-cell function remains. Blood glucose self-monitoring will be required to facilitate rapid dose titration to correct high blood glucose levels and in turn resolve symptoms. If there is no response to glimepiride in the first couple of weeks, rapid referral to the specialist diabetes team for insulin therapy is indicated. Metformin could be added as second-line treatment if there is a

**Table 4** Treatment decision rationale for Case Study 3

| Treatment options | Decision | Rationale |
|---|---|---|
| HbA1c target | <53 mmol/mol | NICE 2015 (NG 28) |
| DPP4i | An option but may not improve control | Circulating insulin levels are likely to be high but ineffective due to insulin resistance |
| Glimepiride | Not an option as second-line therapy | Risk of hypoglycemia; drives for a living; will not target insulin resistance |
| Pioglitazone | An option | Will target Insulin resistance; no hypoglycemic risk |
| SGLT2i | An option | eGFR > 60 mL/min/1.73 $m^2$; encourages weight loss |

*DPP4i* dipeptidyl peptidase-4 inhibitor, *eGFR* estimated glomerular filtration rate, *NICE* National Institute for Health and Care Excellence, *SGLT2i* sodium-glucose co-transporter-2 inhibitor

**Table 5** Treatment decision rationale for Case Study 4

| Treatment options | Decision | Rationale |
|---|---|---|
| HbA1c target | <53 mmol/mol | NICE 2015 (NG 28) |
| DPP4i | Not an option | May not be therapeutically potent enough to resolve symptoms or achieve Hba1c target |
| Glimepiride | An option | Will have quickest impact on symptoms; NICE 2015 (NG 28) |
| Metformin | An option | NICE 2015 (NG 28) |
| Pioglitazone | Not an option | BMI <23 kg/$m^2$; insulin resistance not the primary problem |
| SGLT2i | Not an option | Already symptomatic, may make symptoms worse |

*BMI* body mass index, *DPP4i* dipeptidyl peptidase-4 inhibitor, *NICE* National Institute for Health and Care Excellence, *SGLT2i* sodium-glucose co-transporter-2 inhibitor

positive response to glimepiride but the HbA1c target is not achieved. Due to BMI, the third-line treatment should be insulin.

Table 5 shows the treatment decisions and rationales for this patient.

## CONCLUSION

Prevention of the long-term complications of type 2 diabetes is enhanced by optimum glycemic control, especially in the early years post diagnosis [1]. A maximum of three oral treatments may be required due to the progressive nature of type 2 diabetes. As more treatment options become available, it is essential that the correct treatments are used for each individual. By obtaining a thorough family, medical, and social history of the individual with diabetes and treating the most likely primary pathophysiology, in addition to having a clear HbA1c target and assessing the impact of all treatments commenced, good glycemic control is possible in most individuals with type 2 diabetes.

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***Compliance with Ethics Guidelines.*** This article does not contain any new studies with human or animal subjects performed by any of the authors. Informed consent was received from all patients for inclusion in this article.



## REFERENCES

1. Holman RR, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. 2008. http://www.nejm.org/doi/full/10.1056/NEJMoa0806470. Accessed 4 Jan 2016.
2. Diabetes UK. Diabetes facts and stats version 3. 2014a. https://www.diabetes.org.uk/Documents/About%20Us/Statistics/Diabetes-key-stats-guidelines-April2014.pdf. Accessed 4 Jan 2016.
3. NICE. Type 2 diabetes in adults: management NICE guidelines (NG28). 2015. https://www.nice.org.uk/guidance/ng28. Accessed 10 Dec 2015.
4. WHO. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. 2011. http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/. Accessed 4 Jan 2016.
5. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Br Med J. 1998;317:703–13.
6. Diabetes UK. Diabetes complications. 2014b. https://www.diabetes.org.uk/Guide-to-diabetes/complications/. Accessed 30 Dec 2015.
7. International Diabetes Federation. IDF global guideline for the managing older people with type 2 diabetes. 2013. http://www.idf.org/guidelines-older-people-type-2-diabetes. Accessed 4 Jan 2016.
8. BNF. Metformin hydrochloride. 2016. >https://www.evidence.nhs.uk/formulary/bnf/current/6-endocrine-system/61-drugs-used-in-diabetes/612-antidiabetic-drugs/6122-biguanides/metformin-hydrochloride. Accessed 2 May 2016.
9. EMA. European Medicines Agency clarifies opinion on pioglitazone and the risk of bladder cancer. 2011. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/10/news_detail_001368.jsp&mid=WC0b01ac058004d5c1. Accessed 2 May 2016.
10. Levin D, Bell S, Sund R, et al. Pioglitazone and bladder cancer risk: a multipopulation pooled, cumulative exposure analysis. 2015. http://link.springer.com/article/10.1007%2Fs00125-014-3456-9#page-1. Accessed 4 Jan 2016.

11. FDA. FDA drug safety communications: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. 2015. http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm. Accessed 4 Jan 2016.

12. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–26. http://www.nejm.org/doi/full/10.1056/NEJMoa1307684#t=articleTop. Accessed 09 Apr 2016.

13. Zannad F, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. 2015. http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(14)62225-X.pdf. Accessed 2 May 2016.

14. Green JB, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. 2015. http://www.nejm.org/doi/full/10.1056/NEJMoa1501352. Accessed 2 May 2016.

15. FDA. FDA drug safety communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. 2016. http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm. Accessed 09 Apr 2016.

16. Zinman B, Wanner C, John M. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.

17. Medicines and Healthcare Products Regulatory Agency. Drug safety update SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin): risk of diabetic ketoacidosis. 2015. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-canagliflozin-dapagliflozin-empagliflozin-risk-of-diabetic-ketoacidosis. Accessed 12 Apr 2016.

18. FDA. FDA drug safety communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 2015. http://www.fda.gov/downloads/drugs/drugsafety/ucm461790.pdf. Accessed 22 Mar 2016.

19. Kernan W, et al. Pioglitazone after ischemic stroke or transient ischemic attack. 2016. http://www.nejm.org/doi/full/10.1056/NEJMoa1506930. Accessed 16 Jun 2016.

20. MHRA. Canagliflozin: signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients. 2016. https://www.gov.uk/drug-safety-update/canagliflozin-invokana-vokanamet-signal-of-increased-risk-of-lower-extremity-amputations-observed-in-trial-in-high-cardiovascular-risk-patients. Accessed 16 Jun 2016.