Predicting optimal drug choice for glucose lowering in type 2 diabetes

Routinely available clinical information can be used to optimise the choice of glucose-lowering therapy in type 2 diabetes, according to this five-drug prediction model developed and validated by the MASTERMIND consortium, presented at the Diabetes UK Professional Conference in February 2025 and published simultaneously in the *Lancet*. The model uses nine readily available parameters (age, sex, duration of diabetes, baseline HbA_{1c}, BMI, eGFR, HDL and total cholesterol, and alanine aminotransferase [ALT]), as well as current glucose-lowering therapies, to predict which add-on therapy will optimise glucose lowering over the next 12 months. The model was developed using data from more than 100 000 drug initiations in the UK Clinical Practice Research Datalink and then validated with data from three separate trials. Those receiving the model-predicted therapy not only had lower HbA_{1c} at 12 months compared with those initiating other therapies, but also had a lower risk of drug failure (HbA_{1c} rising to ≥69 mmol/mol, requiring addition of further therapy), and a lower 5-year risk of some diabetes complications such as major adverse cardiovascular events, heart failure, renal progression and other microvascular events.

The model is available at: https://www.diabetesgenes.org/t2-treatment

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Glycaemic control is important in the prevention of the microvascular and macrovascular complications of diabetes. In recent years, we have been reminded of the short- and long-term benefits of ensuring tight glycaemic control early in the course of type 2 diabetes, as illustrated by long-term data from the UK Prospective Diabetes Study.

In people with type 2 diabetes who do not have established cardiovascular disease (CVD), high risk of CVD, heart failure or chronic kidney disease, current guidelines do not offer specific recommendations on the choice of glucose-lowering therapy, rather encouraging clinicians to individualise the therapy choice and glycaemic target. This can be challenging for those less experienced in choosing therapy to optimise glycaemia and are time-consuming for all clinicians, as multiple drug classes have to be considered.

The MASTERMIND Consortium has been developing a model to assist clinicians in choosing therapies to optimise glucose lowering for many years, and their tool has now been validated, particularly in the UK, allowing them to share it for clinician use. The model and its validation study were presented at the Diabetes UK Professional Conference in Glasgow in February, and were simultaneously published in the *Lancet* (Dennis et al, 2025).

The model

The model uses nine readily available data parameters about individuals with type 2 diabetes (*Box 1*) to predict the HbA_{1c}-lowering efficacy over 12 months of the five common classes of drugs used as add-ons to metformin. Drugs already in use can be removed from the options.

The model was developed using data from drug initiations in more than 100 000 people with type 2 diabetes in England, using the Clinical Practice Research Datalink (CPRD) Aurum database from 2004 to 2020. It was validated using data from this and other databases.

The prediction model is available open-access at: https://www.diabetesgenes.org/t2-treatment

Results of validation study

From 212 166 initiations in the CPRD cohort, 15.2% of initiations were of the optimal drug

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Box 1. Parameters used in the model to predict effectiveness of add-on glucose-lowering therapy.

- Age
- Sex
- Duration of diabetes
- Baseline HbA_{1c}
- BMI
- eGFR
- HDL and total cholesterol
- Alanine aminotransferase (ALT)
- Therapies already in use (in addition to metformin):
  - DPP-4 inhibitors
  - GLP-1 receptor agonists
  - SGLT2 inhibitors
  - Sulfonylureas (gliclazide)
  - Thiazolidinediones (pioglitazone)

Note: the model is not designed for people who are already on insulin therapy.

class recommended by the model, and these were compared with people receiving alternative agents, matched for major comorbidities. The two groups were compared up to 5 years.

A mean HbA_{1c} reduction of 5.3 mmol/mol was observed in those treated with the model-recommended drug class compared with matched controls. There was also a 38% reduction in the 5-year risk of "glycaemic failure" (i.e. HbA_{1c} increasing to ≥69 mmol/mol and additional glucose-lowering therapy being required). Although both groups had a similar 5-year risk of all-cause mortality, those who received the model-recommended therapy had a lower risk of major adverse cardiovascular events or heart failure (15% lower), renal progression (29% lower) and microvascular complications (14% lower), likely to be mainly due to use of GLP-1 receptor agonist and SGLT2 inhibitor use.

In the CPRD cohort, 33.4% of recommendations for optimal glucose lowering were for GLP-1 RAs, 28.9% for SGLT2 inhibitors, 27.6% for sulfonylureas, 10.0% for thiazolidinediones and only <0.01% for DPP-4 inhibitors, a drug class still commonly initiated for glucose lowering in the UK. Interestingly, sex influenced the therapies recommended by the model, with GLP-1 RAs recommended for 71.9% of females but less than 10% of males, whereas SGLT2 inhibitors and sulfonylureas were most likely to be recommended for males. DPP-4 inhibitors appeared less effective in those with higher BMIs, as had previously been demonstrated by this group in the TriMaster trial (Shields et al, 2023). Notably, even in recent years (since 2019), only 17.8% of initiations in the CPRD cohort were for drug classes recommended by the model.

The study differentiated between predictive factors (the nine factors used in the prediction model), which predict the effectiveness of the individual drug classes for glucose-lowering, versus prognostic factors, which were deemed to influence glycaemic effectiveness irrespective of choice of treatments. Prognostic factors included the number of current and previously prescribed glucose-lowering factors, ethnicity, Index of Multiple Deprivation quintile and smoking status.

The authors conclude that, since the model uses readily available data, it should be easy to achieve these benefits in people with type 2 diabetes in routine care. However, there were limited data in those aged ≥80 years, so clinicians need to use individual judgement in agreeing therapies in these groups.

Implications for practice

With rapidly expanding numbers of people with type 2 diabetes in our practice, it can be both time-consuming and challenging to ensure we individualise the advice we give on glucose-lowering therapy. NICE guidelines for those with type 2 diabetes who have established or high risk of CVD, or who have heart failure or renal disease, are clear on the benefits of use of SGLT2 inhibitors or GLP-1 RAs. However, for other people with type 2 diabetes but without these risk factors, the guidelines recommend a range of glucose-lowering therapies which can be used at each stage, and clinicians are encouraged to individualise the choice of drug based on what is perceived to be safe, likely to be effective and which is acceptable to the person with diabetes.

Knowing which drug is likely to optimise glucose lowering in individuals is difficult even for experienced clinicians. Shortages of GLP-1 RAs over the last 18 months or so have resulted in increased use of sulfonylureas despite their risks of hypoglycaemia and weight gain, and we are now reassessing optimal glucose-lowering therapy for these people.

This model, carefully developed using UK data and then validated using data from UK clinical practice and other studies over many years, offers useful support to new and well-established prescribers alike, helping us optimise glucose-lowering therapy to achieve both short- and long-term benefits.

To use the model, we will need to add ALT to routine bloods for type 2 diabetes reviews. Where I practise, our local laboratory can measure this without full liver function tests, but clinicians will need to check this with their local laboratory.

When implementing the calculator to assist with decision-making in practice, many of the recommendations for optimal glucose-lowering therapy, particularly in females with type 2 diabetes, will involve GLP-1 RAs, which may not otherwise be recommended by guidelines such as NICE. Clinicians will, therefore, have to carefully document reasons for the drug choice.

As with all tools, and indeed all guidelines, we need to continue to use our clinical judgement to help people with type 2 diabetes choose therapies that are right for them. This model should assist us in this important role. ■

Dennis JM, Young KG, Cardoso P et al; MASTERMIND Consortium (2025) A five-drug class model using routinely available clinical features to optimise prescribing in type 2 diabetes: A prediction model development and validation study. *Lancet* **405**: 701–14

Shields BM, Dennis JM, Angwin CD et al; TriMaster study group (2023) Patient stratification for determining optimal second-line and third-line therapy for type 2 diabetes: The TriMaster study. *Nat Med* **29**: 376–83

A five-drug class model using routinely available clinical features to optimise prescribing in type 2 diabetes: a prediction model development and validation study

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