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ORIGINAL RESEARCH

# What Next After Metformin in Type 2 Diabetes? Selecting the Right Drug for the Right Patient

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## ABSTRACT

***Introduction***: Metformin is the recommended initial treatment in type 2 diabetes mellitus (T2DM), but when this does not give adequate glucose control the choice of which second-line drug to use is uncertain as none have been found to have a better overall glycaemic response. In this real-world study dipeptidyl peptidase 4 inhibitors (DPP4i), sulphonylureas (SU), thiazolidinediones (TZD) and sodium glucose co-transporter 2 inhibitors (SGLT2i) were compared for their effectiveness in lowering glycated haemoglobin (HbA1c) levels for a particular individual based on their clinical characteristics.

***Methods***: A retrospective analysis was undertaken of electronic health records of people with T2DM prescribed metformin alongside a DPP4i, SU, TZD or SGLT2i at second-line. Regression modelling was used to model the changes in HbA1c from baseline at month 6 and month 12 for the individual therapies, adjusting for demographic and clinical characteristics.

***Results***: There were 7170 people included in the study. Treatment at second-line with SUs, DPP4i, TZDs and SGLT2i resulted in similar percentages of people achieving the recommended HbA1c target of $< 7.5\%$ (58 mmol/mol) at both 6 and 12 months. For those receiving SGLT2i and SUs, the greatest improvement in HbA1c was observed in relatively younger and older people, respectively. Trends were detected between other baseline characteristics and HbA1c improvement by drug class, but they were not statistically significant. Non-adherence rates were low for all drug classes. People with a higher medication possession ratio ($\geq 80\%$) also had greater improvements in HbA1c at 12 months.

***Conclusion***: This study identified patients' phenotypic characteristics that may have the potential to influence individual treatment response. Accounting for these characteristics in

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clinical treatment decisions may facilitate individualised prescribing by being able to select the right drug for the right patient.

**Keywords:** Dipeptidyl peptidase 4 inhibitor; Glycaemic control; Second-line therapy; Sodium-glucose transporter 2 inhibitor; Sulphonylurea; Thiazolidinedione; Type 2 diabetes mellitus

**Key Summary Points**

**Why carry out this study?**

Metformin is the recommended initial treatment in type 2 diabetes mellitus (T2DM), and when this does not give adequate glucose control the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines provide second-line therapy recommendations based on the presence of established chronic kidney disease, heart failure or atherosclerotic cardiovascular disease.

The majority of people with T2DM do not have these comorbidities, and for these people there is uncertainty within the clinical community around the optimal choice of second-line treatment, as none have been found to have a better overall glycaemic response.

In this study, the real-world efficacy profiles of dipeptidyl peptidase 4 inhibitors (DPP4i), sulphonylureas (SU), thiazolidinediones (TZD) and sodium glucose co-transporter 2 inhibitors (SGLT2i) following metformin monotherapy were examined in terms of glycaemic control as a function of baseline phenotypic characteristics at second-line initiation.

**What was learned from the study?**

The study found little difference in the glycaemic effects of the different drug classes at 6 and 12 months.

However, patients' age may have the potential to influence treatment response. In addition, other phenotypic characteristics such as gender, body mass index, estimated glomerular filtration rate (eGFR) and duration of T2DM may also be associated with HbA1c response but further research is required to examine these trends.

Accounting for specific demographic and clinical characteristics in clinical treatment decisions will enable better targeting of second-line regimens according to a person's individual profile to achieve optimal clinical outcomes.

## INTRODUCTION

Type 2 diabetes (T2DM) is characterised by insulin resistance, progressive decline in β-cell function and associated hyperglycaemia. Glycated haemoglobin (HbA1c) remains the gold standard for monitoring glycaemic control, albeit with the limitations that it only measures average glucose concentration and cannot report glycaemic excursions or frequency of hypoglycaemia [1]. Recent cardiovascular outcome trials (CVOTs) have focused on macrovascular complications in later diabetes; however, microvascular complications, present in approximately 54% of the total population with diabetes [2], also represent a significant clinical burden [3]. Microvascular complications such as blindness, renal failure and diabetic foot disease are associated with poor quality of life [4] and are amongst the greatest concerns for people with T2DM [5–7]. Optimised glycaemic control to the recommended HbA1c target of 7% (53 mmol/mol) [8, 9] remains the optimum strategy for minimising the risk of these microvascular complications as well as limiting progression of some macrovascular complications (notably stroke, congestive heart failure, peripheral vascular disease) [10–12].

Large randomised trials and prospective observational studies have demonstrated that