

Dual versus single oral therapy following type 2 diabetes diagnosis

Achieving and sustaining target HbA_{1c} levels is fundamental in the management of type 2 diabetes. A recently published article aimed to assess whether initial dual oral therapy with a sodium–glucose cotransporter-2 (SGLT2) inhibitor outperforms monotherapy in reaching glycaemic targets in individuals with treatment-naïve or early-stage type 2 diabetes (Kelly et al, 2026).

Since the late 1990s, metformin has been the preferred first-line pharmacotherapy in the UK, Europe and numerous other regions globally (unless contraindicated because of renal impairment [eGFR ≤ 30 mL/min/1.73 m²] or not tolerated because of gastrointestinal side effects), paired with comprehensive lifestyle interventions, including dietetic advice, regular physical activity and behavioural modification (UK Prospective Diabetes Study Group, 1998; BNF, 2026; NICE, 2026). However, recent NICE guidance recommends that an SGLT2 inhibitor should be considered as first-line treatment alongside modified-release metformin for most adults with newly diagnosed type 2 diabetes (NICE, 2026). This is particularly relevant given that dapagliflozin is now available in a generic formulation in the UK.

Monotherapy with metformin consistently fails to achieve target HbA_{1c} levels in many cases, with success rates dropping below 30% among those with baseline HbA_{1c} values $\geq 8.0\%$ (64 mmol/mol; Fernandes et al, 2020). Failure to achieve rapid glycaemic control in type 2 diabetes may be compounded by therapeutic inertia, which delays timely intensification of therapy, allowing hyperglycaemia to persist (Khunti et al, 2018). Prolonged exposure to chronic hyperglycaemia worsens pancreatic beta-cell dysfunction and insulin resistance, making subsequent glucose control increasingly difficult and less responsive to treatment (Saisho, 2015).

Other advantages of SGLT2 inhibitors as first-line options include their ability to reduce rates of

heart failure hospitalisation, delay progression of kidney disease and lower cardiovascular mortality (Mavrakanas et al, 2023), with the understanding that candidal infections can be a side effect.

What was found

The systematic review and meta-analysis synthesised evidence from 21 parallel-group randomised controlled trials, involving 37 independent treatment arms, to assess whether initiating dual oral pharmacotherapy with metformin and an SGLT2 inhibitor at the time of type 2 diabetes diagnosis results in better HbA_{1c} target achievement, at thresholds of $\leq 7.5\%$ (58 mmol/mol), $\leq 7.0\%$ (53 mmol/mol), and $\leq 6.5\%$ (48 mmol/mol), compared to monotherapy approaches.

Combination therapy could involve any two oral agents from predefined classes (biguanides, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, bile acid sequestrants or traditional Chinese medicines). Studies were excluded if they were extension trials or had treatment durations shorter than 12 weeks. Injectable therapies were not included in the meta-analysis. Across the 21 randomised controlled trials included in the meta-analysis, there were 37 treatment arms and 11 478 participants.

In analyses focusing specifically on regimens combining metformin with an SGLT2 inhibitor, dual therapy with metformin plus SGLT2 inhibitor was consistently superior to metformin monotherapy across all three HbA_{1c} thresholds. For a target HbA_{1c} $\leq 6.5\%$ (≤ 48 mmol/mol), the estimated proportions achieving target were 37.5% with metformin alone versus 43.7% with metformin plus SGLT2 inhibitor ($P=0.030$). For target HbA_{1c} $\leq 7.0\%$ (≤ 53 mmol/mol), the corresponding proportions were 62.8% versus 71.3% ($P\leq 0.001$), and for target HbA_{1c} $\leq 7.5\%$ (≤ 58 mmol/mol), they were 80.8% versus 87.6% ($P\leq 0.001$).

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“This paper suggests that dual therapy facilitates more rapid achievement of target HbA_{1c}, potentially addressing therapeutic inertia that often delays treatment intensification, and supports the recent NICE guidance on the management of type 2 diabetes.”

Why this is important

These findings in people with newly or recently diagnosed type 2 diabetes provide compelling evidence that initial combination pharmacotherapy is superior to monotherapy, alongside lifestyle measures, for optimising HbA_{1c} control. Across 21 randomised controlled trials comprising 37 arms, dual therapy with metformin and an SGLT2 inhibitor achieved HbA_{1c} ≤7.5% (58 mmol/mol) in 88% of participants, compared with 82% with metformin monotherapy (odds ratio [OR], 1.33 [95% confidence interval, 1.20–1.47; *P*=0.002]). This rapid and consistent attainment of targets may help to reduce therapeutic inertia. These benefits were observed across trial durations of 12–52 weeks and baseline HbA_{1c} levels ranging from 48 mmol/mol (6.5%) to 97 mmol/mol (11.0%), including among participants with significant pre-treatment hyperglycaemia, for whom monotherapy often proves less effective.

Dual therapy with metformin plus any additional agent was significantly more effective than metformin monotherapy for achieving HbA_{1c} ≤7.5% (58 mmol/mol; OR, 1.39; *P*=0.002), highlighting the limitations of metformin as a sole initial treatment, especially at higher baseline HbA_{1c} levels. Notably, combinations involving metformin and an SGLT2 inhibitor demonstrated the greatest efficacy relative to monotherapy, achieving superiority at all HbA_{1c} thresholds: ≤7.5% (58 mmol/mol), 88% vs 81% (OR, 1.55; *P*≤0.001); ≤7.0% (53 mmol/mol; OR 1.47, *P*≤0.001; ≤6.5% (48 mmol/mol; OR, 1.29; *P*=0.030).

In interpreting these findings, it is important to note that the authors treated SGLT2 inhibitors as a uniform class, rather than evaluating individual agents separately. Dapagliflozin is currently the only generic SGLT2 inhibitor available in the UK, hence it now being recommended as the first line SGLT2 inhibitor in England as the lowest priced agent in the class.

These findings align with and expand upon prior systematic reviews and meta-analyses reporting glycaemic and weight reduction-related advantages of early combination therapy (Phung et al, 2014; Cai et al, 2018; Milder et al, 2019). Unlike earlier analyses, this study provides a detailed quantification of SGLT2 inhibitor strategies across

multiple clinically relevant HbA_{1c} thresholds, incorporates data through to December 2025 and remained robust after excluding rosiglitazone-containing trials.

The randomised trials included in the review generally enrolled adults with newly diagnosed or early type 2 diabetes and excluded individuals with extreme hyperglycaemia, overt catabolic symptoms or suspected type 1 diabetes. In routine practice, patients who present with marked hyperglycaemia, osmotic symptoms, weight loss or ketosis risk are often better served by initial insulin based regimens to restore metabolic stability, with metformin and SGLT2 inhibitors introduced or optimised subsequently. In such cases, the potential risk of ketoacidosis associated with SGLT2 inhibitors in susceptible phenotypes should be carefully considered. A limitation for the paper is that we have not here addressed the role of SGLT2 inhibitors in relation to cardiorenal risk reduction and management of cardiorenal disease. The focus of this meta-analysis was specifically on glycaemia as an outcome, which is an integral part of wider cardiometabolic outcomes.

The authors recommended that SGLT2 inhibitors, alone or in combination with metformin, can be considered as initial therapy for individuals with newly diagnosed or early type 2 diabetes, without evidence of significant insulin deficiency or acute metabolic decompensation.

Type 2 diabetes constitutes a growing global health crisis and is associated with microvascular, macrovascular and renal complications (World Health Organization, 2024). This paper suggests that dual therapy facilitates more rapid achievement of target HbA_{1c}, potentially addressing therapeutic inertia that often delays treatment intensification, and supports the recent NICE guidance on the management of type 2 diabetes (NICE, 2026).

Conclusion

This systematic review and meta-analysis provides robust evidence for nurses, doctors and other prescribers that initial dual oral therapy with metformin and an SGLT2 inhibitor achieves superior glycaemic control compared to monotherapy with metformin alone across several HbA_{1c} target thresholds in treatment-naïve

individuals with early type 2 diabetes, with an SGLT2 inhibitor plus metformin emerging as the most effective combination evaluated. ■

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None of the authors have any conflicts of interest to declare.

AH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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