VERIFY the role of initial combination therapy in patients with type 2 diabetes

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Treatment of patients with recent onset of type 2 diabetes with early combination of glucose-lowering agents or with sequential intensification is still an open question. Position statements by the American Diabetes Association and the European Association for the Study of Diabetes and by the American Association of Clinical Endocrinologists and American College of Endocrinology recommend sequential intensification therapy for patients recently diagnosed with diabetes and mild hyperglycaemia.[1,2] A recent meta-analysis[3] of 15 randomised controlled trials showed that early combination therapies were associated with greater reduction of glycaemia; however, there was heterogeneity in basal glycated haemoglobin (HbA_{1c}) levels and median duration of follow-up was short. Therefore, the long-term clinical benefits of early combination therapy are still not clear.

In *The Lancet*, David R Matthews and colleagues[4] report the results of the VERIFY trial, which compared the efficacy and safety of early combination therapy of metformin plus dipeptidyl peptidase-4 inhibitor vildagliptin with metformin monotherapy. VERIFY was a 5-year, multicentre, randomised, double-blind study in 2001 patients with newly diagnosed type 2 diabetes with mild hyperglycaemia (HbA_{1c} 48–58 mmol/mol or 6·5–7·5%). Patients were randomly assigned to receive either the early combination treatment with metformin (1000 mg, 1500 mg, or 2000 mg) and vildagliptin 50 mg twice daily, or initial metformin monotherapy (1000 mg, 1500 mg, or 2000 mg) and placebo twice daily. The primary efficacy endpoint was the time from randomisation to initial treatment failure, defined as HbA_{1c} measurement of at least 53 mmol/mol (7·0%) at two consecutive scheduled visits, 13 weeks apart. If the initial treatment did not maintain HbA_{1c} below 53 mmol/mol (7·0%), patients in the metformin monotherapy group received vildagliptin 50 mg twice daily in place of the placebo and entered a second phase of the study, in which all patients received the combination therapy.

A significant reduction in the relative risk (RR) for time to initial treatment failure was observed in the early combination treatment group compared with the monotherapy group over the 5-year study duration (hazard ratio 0·51 [95% CI 0·45–0·58]; p<0·0001). The incidence of initial treatment failure during the first phase of the study was 429 (43·6%) patients in the combination treatment group and 614 (62·1%) patients in the monotherapy group. The median observed time to treatment failure in the monotherapy group was 36·1 (IQR 15·3–not reached [NR]) months, while the median time to treatment failure for those receiving early combination therapy could only be estimated to be beyond the study duration at 61·9 (29·9–NR) months. Strikingly, the RR for time to second treatment failure (defined as two further consecutive values of HbA_{1c} of at least 53 mmol/mol [7·0%]) during the second phase of the study was also significantly reduced in the combination treatment group compared with the monotherapy group. Collectively, early combination therapy with metformin and vildagliptin seems superior to sequential intensification of metformin in patients with recent onset of diabetes with mild hyperglycaemia, as evidenced by increased glycaemic durability and probable attenuation of the progression of diabetes over time.

The VERIFY trial is, to our knowledge, the largest, long-term prospective trial testing the effects of early combination treatment on glycaemic durability. The study reassures that combination treatment with metformin and vildagliptin is well tolerated, safe, and effective. The finding that early combination treatment

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reduced the probability of initial treatment failure is expected when combining medications with additive anti-hyperglycaemic effects such as metformin, which increases insulin sensitivity, and vildagliptin, which enhances β-cell function. However, the effect of early combination treatment on glycaemic control and risk of secondary treatment failure strengthens the notion that early combination therapy could have long-term clinical benefits regarding glycaemic durability.

Which are the mechanisms underlying the beneficial effects of early combination treatment on glycaemic durability? The UK Prospective Diabetes Study[5] showed that diabetes is progressive and that worsening of glycaemia over time correlates with declining β-cell function. This can be attributed to deleterious effects of chronic hyperglycaemia, and probably other environmental, genetic, and epigenetic factors. Previous studies[6] have shown that near normalisation of blood glucose by insulin in patients with newly diagnosed type 2 diabetes can improve β-cell function, leading to sustained improvement of glycaemia. Possibly, more effective reduction of glycaemia by the combination treatment better preserves β-cell function. A post-hoc analysis of the SAVOR-TIMI 53 trial showed that the dipeptidyl peptidase-4 inhibitor saxagliptin was better than placebo in maintaining β-cell function and glycaemic control, further suggesting that saxagliptin might attenuate the decline of β-cell function.[7] β-cell function has not yet been reported in the VERIFY trial; therefore, it is not clear whether the beneficial effect of early combination treatment is indeed mediated via improved β-cell function.

Whether early combination treatment strategy should be applied to all patients with type 2 diabetes requires further consideration. The findings of the VERIFY study suggest that early normalisation of blood glucose has a beneficial legacy effect that attenuates diabetes progression. Other studies[8] have shown that normalisation of blood glucose during the first year after diagnosis was associated with decreased risk of microvascular and macrovascular complications. In clinical practice, treatment intensification is often delayed, resulting in exposure to prolonged hyperglycaemia. Early combination therapy with two or more glucose-lowering agents might become an effective strategy to prevent clinical inertia.[9] However, combination treatment can potentially increase the risk of side-effects and is more costly. Additional studies are needed to confirm that early combination treatment indeed halts the progression of diabetes. In the VERIFY study, 40% of patients receiving metformin monotherapy had no treatment failure within 5 years. Initiation of dual treatment at diagnosis would expose such patients to unnecessary overtreatment. In the emerging era of precision medicine, better stratification of the individual risk factors for diabetes progression and complications will be required for personal tailoring of treatment. Large trials showed that newer glucose-lowering agents, mainly GLP-1-RA and SGLT2i, have cardiovascular and renal benefits,[10,11] and the place of metformin as the first drug for all patients with type 2 diabetes is questioned.[12] Further studies to assess the effects of different combination therapies on glycaemic durability and more importantly on the risk of late complications are necessary.

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1 Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; **41:** 2669–701.
2 Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2019 executive summary. *Endocr Pract* 2019; **25:** 69–100.
3 Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab* 2014; **16:** 410–17.
4 Matthews DR, Paldánius PM, Proot P, Chiang YT, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet* 2019; published online Sept 18. https://doi.org/10.1016/S0140-6736(19)32131-2.
5 UK Prospective Diabetes Study Group. UK Prospective Diabetes Study 16: overview of 6 years' therapy of type ii diabetes: a progressive disease. *Diabetes* 1995; **44:** 1249–58.
6 Raz I, Mosenzon O. Early insulinization to prevent diabetes progression. *Diabetes Care* 2013; **36** (suppl 2)**:** S190–97.
7 Leibowitz G, Cahn A, Bhatt DL, et al. Impact of treatment with saxagliptin on glycaemic stability and β-cell function in the SAVOR-TIMI 53 study. *Diabetes Obes Metab* 2015; **17:** 487–94.
8 Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). *Diabetes Care* 2019; **42:** 416–26.

9 Abul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab* 2015; **17:** 268–75.

10 Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; **393:** 31–39.

11 Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; published online Aug 14. http://dx.doi.org/10.1016/S2213-8587(19)30249-9.

12 Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2019; published online Aug 31. DOI:10.1093/eurheartj/ehz486.