Title	Early combination therapy delayed treatment escalation in newly-diagnosed young-onset type 2 diabetes – a sub-analysis of VERIFY study
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ABSTRACT

We analysed glycaemic durability (sustained glycaemic control) with early combination therapy (metformin plus vildagliptin) versus metformin monotherapy, among patients with type 2 diabetes diagnosed before (young-onset [YOD]) and after (late-onset [LOD]) the age of 40 years, enrolled in the VERIFY trial. The primary endpoint was time to initial treatment failure (TF), defined as HbA1c ≥7.0% at two consecutive scheduled visits after randomisation. The time to secondary TF was assessed when both groups were receiving and failing on the combination. A total of 186 (9.3%) patients had YOD and 1815 (90.7%) had LOD with a mean age difference of 20.4 years. Compared with metformin monotherapy, early combination reduced the risk of time to initial TF for both YOD (48%, $p<0.0006$) and LOD (46%, $p<0.0001$). With early combination, risk for time to secondary TF was reduced by 48% ($p<0.0035$) in YOD and 24% ($p<0.0009$) in LOD. Both treatment approaches were well-tolerated with no unexpected safety concerns. In treatment-naïve patients with YOD (HbA1c 6.5-7.5%), early combination strategy improved attainment of glycaemic target with durability and delayed treatment escalation compared with initial metformin monotherapy.

INTRODUCTION

The majority of people with type 2 diabetes (T2D) are middle-aged and elderly (≥65 years). An estimated 16% of the total global adult population with T2D have young-onset diabetes (YOD), diagnosed before the age of 40 years.[1] Long disease duration and suboptimal control of cardiometabolic risk factors puts patients with YOD at high risk for premature complications and increased mortality.[2, 3] Pivotal clinical trials assessing impact of blood glucose-lowering drugs on cardiovascular outcomes have predominantly included elderly patients (age ≥60 years).[4] The lack of long-term efficacy and safety data of pharmacological interventions may contribute towards the delayed treatment initiation and intensification in patients with YOD. [5] Apart from causing long-term complications, the burden of hyperglycaemia can accelerate beta-cell failure leading to early treatment escalation including insulin, plausibly increasing treatment complexity. [2, 6, 7]

The VERIFY (The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) [8] study focused on early detection and intervention using early combination

therapy of metformin plus vildagliptin versus metformin monotherapy in newly-diagnosed adult patients with T2D aged 18–70 years. This recruitment strategy enabled us to evaluate the efficacy and safety of early combination treatment approach in patients with YOD versus those with late-onset diabetes (LOD).

METHODS

Study design and patients

VERIFY[8] was a randomised, double-blind, multinational, multi-ethnic, two-arm parallel-group study exploring the clinical benefits of early combination therapy (metformin plus vildagliptin) versus sequential intensification of metformin monotherapy for up to 5 years. Key inclusion criteria were glycated haemoglobin (HbA1c) level of 6.5–7.5% and body-mass index (BMI) of 22–40 kg/m². Patients went through an individualised metformin up-titration treatment phase (receiving a stable daily dose up to 1000, 1500 or 2000 mg metformin) for a 3-week run-in period. Individuals who were able to tolerate a total daily dose of at least 1000 mg of metformin during this run-in phase were randomly assigned to the early combination or monotherapy group in a 1:1 ratio without age-related stratification. Patients randomised to the early combination group received vildagliptin (50 mg twice-daily) on top of metformin while the monotherapy group received a placebo (Period 1) followed by the addition of vildagliptin (50 mg twice-daily) only after a confirmed initial treatment failure (transferring the patients to Period 2) (for details see Outcomes).

In Period 2, all patients received metformin plus vildagliptin combination therapy, independent of their initial treatment assignment. After a confirmed secondary treatment failure in Period 2, (open-label) insulin could be initiated as add-on to the combination therapy based on physician's discretion following the local diabetes treatment guidelines (Period 3). Patients whose therapy was intensified with blood glucose-lowering drugs other than insulin were discontinued from the study. Reasons for intensifying treatment with other anti-diabetic treatment could have been due to (but not limited to) patient unwillingness to initiate insulin therapy or insulin not being recommended according to local diabetes treatment guidelines.

Outcomes

In this pre-outlined[9] analysis, we stratified the study population into YOD and LOD with a cut-off age of 40 years and evaluated the time-dependent effects of the two treatment strategies from randomisation to 1) initial treatment failure (HbA1c ≥7.0%) at two consecutive visits, 13 weeks apart, and 2) secondary failure as confirmed by HbA1c ≥7.0% (on combination therapy) at two consecutive visits 13 weeks apart. In Period 1, the 6-month time-point was the earliest for initial treatment failure and the 12-month visit for secondary treatment failure in Period 2 indicating insulin requirement, with patients initiated on insulin therapy being transferred to Period 3. We compared the clinical profiles, rates of primary and secondary treatment failures, proportions of patients with HbA1c <7.0% and changes in body-weight and urinary albumin/creatinine ratio throughout the study period between the two treatment groups, stratified by YOD and LOD.

Safety

Treatment-emergent adverse and serious adverse events were recorded throughout the study period along with their severity and relationship with study drug. Incidences of pregnancy were also recorded. Hypoglycaemic events were separately reported. All patients were provided with a home blood glucose monitor. At the first visit, patients were trained to monitor their blood glucose as well as detect and report hypoglycaemia. Apart from typical symptoms of hypoglycaemia, a capillary whole blood glucose level of <50mg/dL (<2.8mM), corresponding to a plasma glucose level of <56mg/dL (<3.1mM), was considered as a hypoglycaemic event. Confirmed hypoglycaemic events were also classified based on their severity, i.e. those necessitating assistance were considered to be of Grade 2 severity.

Analysis

Detailed methods of statistical analyses have been reported earlier.[8] Here, we estimated the effect of treatment strategies on time to treatment failures using a Cox proportional hazards regression model. Cumulative probabilities of treatment failure over time in both the groups were assessed using Kaplan-Meier estimates. Adverse events were summarised as number and proportions of patients having any adverse event by treatment group and classified by each primary system organ class. A *p* value of 0.05 (2-sided) was considered significant. The statistics program used was SAS (versions 9.2 and 9.4; Cary, NC, USA).

RESULTS

Baseline characteristics

Amongst 2001 enrolled patients, [8] 186 (9.3%) had YOD and 96 of whom received early combination; 1815 (90.7%) had LOD, 902 of whom received early combination. There was a mean age difference of 20.4 years with 49.5% females in YOD and 53.3% females in LOD. The YOD group had lower median (interquartile range ([IQR]) body-weight than the LOD group (80.6 [68.6–95.0] kg versus 84.6 [72.7–97.0] kg), with YOD patients being predominantly from Asia than from other regions (34.9% vs 17.0%). Relatively, fewer patients with YOD completed the study than those with LOD (68.8 % vs 81.0%) (Supplementary Table 1).

Primary endpoint

In the YOD group, 50.5% (n=47) of the early combination versus 73.3% (n=66) of the monotherapy group attained the primary endpoint (p=0.0006). The respective figures were 42.9% (n=382) and 61.0% (n=548) in the LOD group (p<0.0001). In the YOD group, the median (IQR) time to treatment failure was 41.9 (23.9, non-evaluable [NE]) months in the early combination group compared to 26.9 (8.7, 53.9) months in the monotherapy group. The respective figures were 61.9 (30.1, NE) and 38.5 (18.0, NE) months in the LOD group. The reduction in risk for time to initial treatment failure with early combination versus monotherapy was similar between YOD (hazard ratio [HR] 0.52 [95% confidence interval: 0.36–0.76]; p=0.0006) and LOD patients (0.54 [0.48–0.62]; p<0.0001) (Figure 1).

Other endpoints

After 5 years, 35.5 % (n=33) patients with YOD of the early combination versus 58.9 % (n=53) patients in the monotherapy group had secondary treatment failure (p=0.0035) and the respective figures for the LOD group were 30.2 % (n=269) and 36.0 % (n=324; p=0.0009). The reduction in risk of secondary treatment failure with early combination was greater in the YOD (HR 0.52 [0.34–0.81]; p=0.0035) than the LOD group [HR 0.76 [0.65–0.89]; p=0.0009] (Figure 2).

Amongst patients with YOD who had a confirmed secondary treatment failure, the investigators decided to initiate insulin for 25 patients each from the early combination and monotherapy group. In the LOD group, 106 patients with early combination and 104 patients with monotherapy treatment received insulin after secondary failure.

Throughout the study period, YOD patients randomised to early combination were more likely to maintain HbA1c <7.0% than those treated with initial monotherapy (54.8% vs 33.3%), whereas the proportions were similar in the LOD group (63.7% versus 59.0%, respectively). In both YOD and LOD groups, urinary albumin/creatinine ratio and body-weight remained stable with both treatment approaches.

Safety

Both treatment approaches within each age group had similar safety and tolerability profiles with no unexpected safety findings. Six women became pregnant whilst on study drugs with five from the YOD group (two in early combination and three in monotherapy group). In the early combination group, three patients with YOD and two with LOD reported a single hypoglycaemic

event with one of the events reported during insulin treatment. All events were mild and considered as unrelated to the study drugs. None of these events led to treatment discontinuation.

DISCUSSION

In this sub-analysis of VERIFY study, early combination treatment with metformin plus vildagliptin improved glycaemic durability in patients with YOD and LOD compared with metformin monotherapy followed by sequential combination treatment. While early combination treatment conferred 50.0% risk reduction in primary treatment failure in both age groups, patients with YOD had 48.0% risk reduction in secondary failure compared with 24.0% in the LOD group.

The secondary treatment failure in the VERIFY study marked the threshold for need of additional glucose-lowering agents including insulin. In this study, the decision and time point for insulin initiation was arbitrary and left at the investigator's discretion. In this double-blinded randomised clinical trial, avoidance of glycaemic deterioration was a primary objective. However, after reaching the secondary treatment failure with combination therapy, not all patients were initiated on insulin therapy despite progressive worsening of glycaemia. This could be the reason why despite the higher rate of secondary treatment failure in the group treated with monotherapy followed by sequential combination, the actual number of patients treated with insulin did not differ between the two treatment approaches. Factors such as free access to or subsidy for insulin treatment, social and cultural norms for initiation and acceptance of insulin

could influence the rate of insulin usage in this multinational study. Although indication for insulin initiation was likely following the failure of combination therapy, in the VERIFY study, this could not be used as a hard endpoint to evaluate success or failure of a therapeutic strategy. Rather, we adopted the rate of confirmed secondary failure as a more accurate predictor for future need of insulin initiation in clinical practice.[10]

A higher proportion of patients in the YOD group required additional treatment compared with the LOD group throughout the 5-year study period. However, the YOD patients treated with early combination treatment were more likely to attain HbA1c <7.0% than their peers receiving sequential treatment. These results highlighted the efficacy of early combination treatment especially in newly-diagnosed patients with YOD who benefited proportionally more showing better glycaemic durability and delayed treatment escalation.

In the VERIFY study, nearly 1 in 10 patients was diagnosed before the age of 40 with more patients coming from Asia. This might explain the lower BMI in the YOD than the LOD group. In this clinical trial, for various reasons including but are not limited to addition of other non-insulin medications, 1 in 3 patients with YOD discontinued the study compared to 1 in 5 in the LOD group. In real-world practice, patients with YOD often experienced many challenges including adherence to self-management, follow-up visits and use of medications including insulin due to personal or work reasons.[5, 11] In an integrated system with health records of 32,137 adult patients in the United States, 26.4% patients were aged 21–44 years. Compared with their older counterparts, they had higher HbA1c (7.8% versus 7.4%) and were less likely to

visit their doctors or adhere to their medications.[11] In another territory-wide diabetes database including over 0.8 million adults with diabetes in Hong Kong, during 2001–2016, there was an increasing incidence of YOD despite a stable or declining trend in the older age groups.[12] Despite a 50%–70% decline in death rate during the same period, the age-adjusted mortality ratio in patients with YOD remained 5-fold higher than their counterparts without diabetes.[3] In patients with YOD, mental illness was a major cause of hospitalisation during their earlier years, being one of many unmet needs.[13]

Reduced early phase insulin secretion and non-suppression of glucagon are hallmarks in T2D, which can be corrected by incretin-based therapies. Once glucotoxicity sets in, beta-cell failure may accelerate, making early intervention an important strategy to reduce the glycaemic burden.[2, 14] Early use of metformin combined with other glucose-lowering drugs has shown an improved glycaemic control superior to metformin monotherapy in patients with HbA1c >7.5% and aged >50 years.[15] VERIFY is the first study to show the long-term benefits of this treatment approach in newly-diagnosed patients with HbA1c 6.5–-7.5% and a broad range of age.

Most practice guidelines advocate personalised treatment goals, strategies and targets, taking into consideration the clinical profiles, personal needs and comorbidities of the patient. A combination regimen was recommended if the diagnostic HbA1c is 1.5% above the individualised target with initial monotherapy combined with lifestyle and dietary restrictions.[16] The marked benefits of early combination strategy in maintaining glycaemic durability and delaying treatment escalation in newly diagnosed patients with HbA1c 6.5–7.5% shown in the

VERIFY study has catalysed the update of major guidelines which now include initial combination treatment in the treatment algorithm of newly-diagnosed T2D.[17] Although the statement within the American Diabetes Association Standards of Care 2020 update indicates that "Early combination can be considered in some patients at diagnosis",[18] our initial analysis did not show heterogeneity in glycaemic response and durability among all the explored, pre-defined sub-groups in the VERIFY study.[8] In the present sub-analysis, we observed equally durable glycaemic outcomes in both YOD and LOD groups, with an incremental improvement in secondary treatment failure favouring the YOD group. These results add to the array of evidence indicating that newly-diagnosed patients benefitted from early combination treatment irrespective of age at diagnosis.

Among many healthcare and treatment-related factors, weight gain and hypoglycaemia have been identified as key contributors to poor medication adherence impeding optimal glycaemic control.[5] Although clinical trials have confirmed the benefits of novel glucose-lowering drugs with fewer side effects in improving outcomes, there remain major care gaps especially amongst young patients and in women.[7] This sub-analysis of the VERIFY Study revealed that in these young patients, early combination treatment delayed glycaemic deterioration and treatment escalation compared with sequential treatment. Given the long disease duration, the high likelihood of insulin requirement and lifetime risk of complications in these young patients, the favourable effects of early combination treatment is expected to reduce the glycaemic burden, which, if sustained, will translate into long-term benefits.[19]

Despite these encouraging results, the small sample size of patients with YOD and the lower range of baseline HbA1c in the VERIFY study are some of the limitations to consider. Definitive clinical trials comparing early intensive blood glucose-lowering strategy versus stepwise treatment in this high-risk group are warranted. In addition, the limited number of patients treated with insulin and the pragmatic design of the study, did not allow any multivariate analysis for identification of the definitive predictors of insulin treatment among the treatment approaches within these patient groups. The over-representation of Asians in the YOD group is in accordance with the inter-ethnic differences reported earlier in terms of clinical course and treatment responses between Asian and non-Asian patients with T2D.[20, 21] This will require more focused evaluation regarding the benefits of combination treatment in this population.

CONCLUSIONS

In patients newly-diagnosed with YOD with HbA1c of 6.5−7.5%, early combination strategy of metformin plus vildagliptin improved attainment of glycaemic targets with durability and delayed treatment escalation compared with sequential treatment of metformin followed by addition of vildagliptin.

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DISCLOSURES

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DATA SHARING

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The criteria and process for trial data availability are described online at https://www.clinicalstudydatarequest.com/

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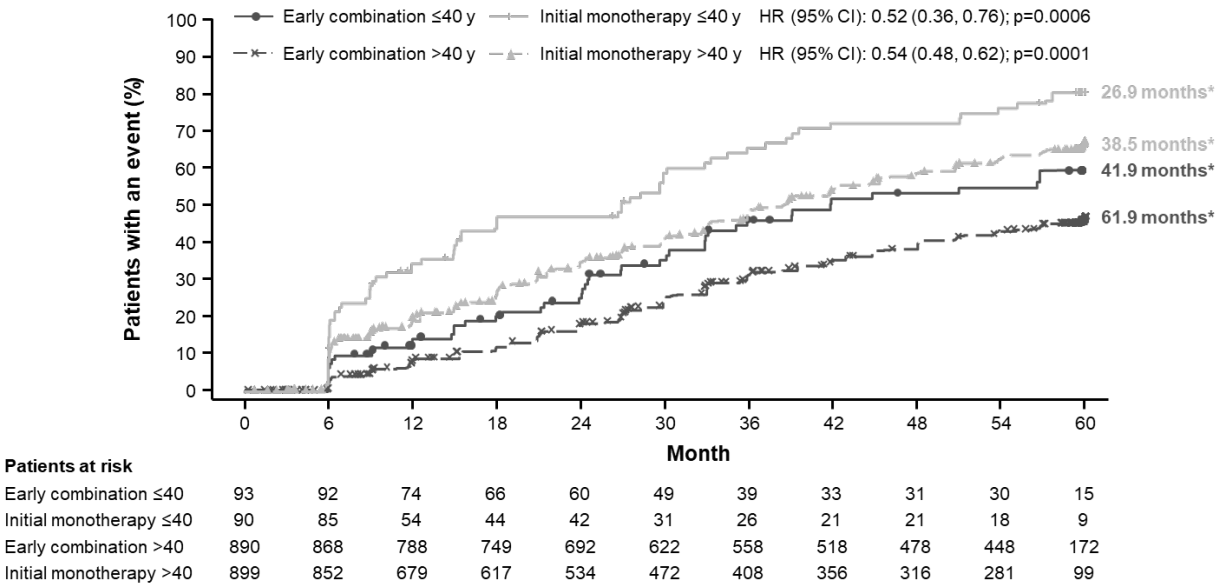
Figures

Figure 1: Primary treatment failure* among patients with young- and late-onset type 2 diabetes, randomised to early combination therapy of vildagliptin and metformin versus initial metformin monotherapy followed by addition of vildagliptin with glycaemic worsening



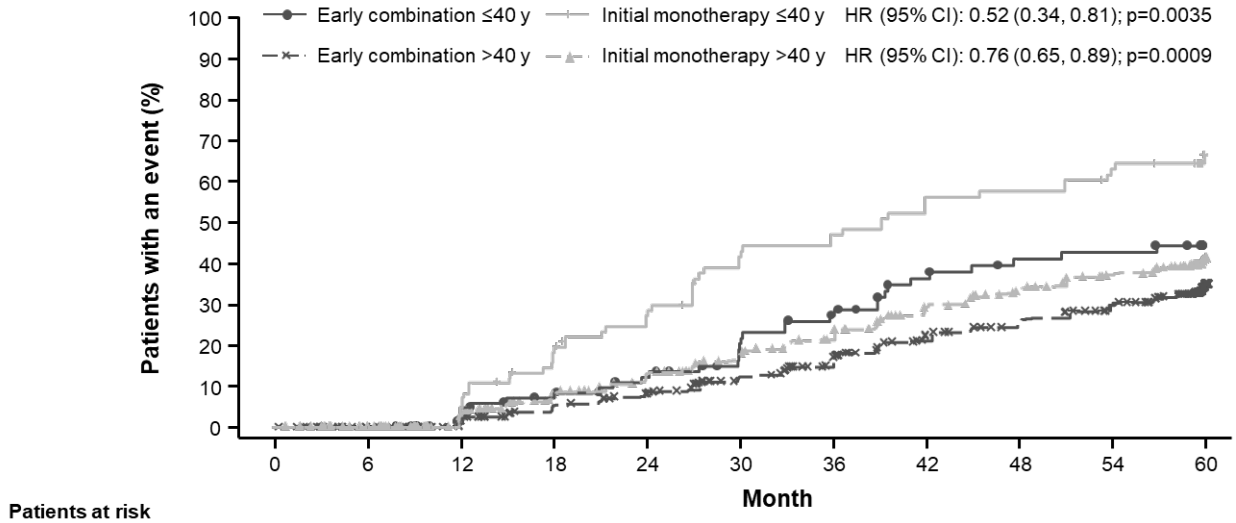
CI: confidence interval; HR: hazard ratio

*Primary treatment failure is defined as HbA1c ≥7.0% at two consecutive scheduled visits, starting from 13 weeks after randomisation. The time to initial treatment failure is the time from randomisation to the second consecutive scheduled visits with HbA1c ≥7.0%. Patients who discontinued the study for any reason during Period 1 were censored at the date of discontinuation. Patients with HbA1c <7.0% (or whose measurement ≥7.0% was not confirmed at next scheduled visit) were censored at the date of last study visit. The Kaplan Meier estimates were performed for patients who had received at least one randomised medication and one post-randomisation efficacy parameter assessed.

Note: Patients were stratified to young-and late-onset diabetes groups, by the age of diagnosis of 40 years

Figure 2: Secondary treatment failure* among patients with young- and late-onset type 2 diabetes, randomised to early combination therapy of metformin and vildagliptin versus

initial metformin monotherapy followed by addition of vildagliptin with glycaemic worsening.



Patients at risk											
Early combination ≤40	93	93	81	75	68	58	51	41	36	35	18
Initial monotherapy ≤40	90	89	79	66	57	44	40	33	32	27	15
Early combination >40	890	873	837	795	762	710	664	603	566	530	203
Initial monotherapy >40	899	879	818	755	704	654	603	542	499	463	164

CI: confidence interval; HR: hazard ratio

*Secondary treatment failure is defined as two consecutive scheduled visits with HbA1c ≥7.0% during Period 2 (i.e., after Period 1 comparing metformin monotherapy versus early combination therapy with metformin and vildagliptin and up to end of Period 2 when both groups are on combination therapy after primary treatment failure. The time to secondary treatment failure is the number of days from randomisation to the second confirmed HbA1c ≥7.0% during consecutive scheduled visits, three months apart, in Period 2. The Kaplan Meier estimates were performed for patients who had received at least one randomised medication and one post-randomisation efficacy parameter assessed. Patients who had no event and discontinued the study for any reason during Period 1 or Period 2 were censored at the date of discontinuation. Patients who entered Period 3 from Period 1 were censored to last study visit prior to start of Period 3. Two-sided *p* value was obtained from a Cox proportional hazards model containing terms for treatment approach. Baseline HbA1c was the value

obtained on Day 1, or the value obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement was missing.

Note: Patients were stratified to young-and late-onset diabetes groups, by the age of diagnosis of 40 years