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COMMENTARY

Insights from VERIFY: Early Combination Therapy Provides Better Glycaemic Durability Than a Stepwise Approach in Newly Diagnosed Type 2 Diabetes

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ABSTRACT

The treatment aims for type 2 diabetes are to prevent complications and premature mortality, and improve quality of life. Glycaemic control is central to these aims; clinical guidelines have sought to achieve this with a stepwise approach starting with lifestyle measures and metformin, adding further medications once glycated haemoglobin (HbA_{1c}) levels rise above a predefined threshold. However, treatment intensification can be delayed when HbA_{1c} levels increase, and HbA_{1c} levels become inadequately controlled in many patients. Clinical inertia can result in sustained elevated levels of HbA_{1c}; when combined with a late diagnosis, this negatively impacts patients' prognosis. Early combination therapy using medications with complementary modes of action could achieve optimal glycaemic targets and alter the course of the disease more than metformin alone. The multinational VERIFY study (clinicaltrials.gov NCT01528254) provided evidence accrued over 5 years, demonstrating the potential of early combination therapy: time to loss of

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glycaemic control was nearly doubled, and more than twice the number of patients experienced extended glycaemic control, with a vildagliptin–metformin combination therapy versus metformin alone. The study also showed a delay in secondary treatment failure in patients receiving the combination. Early combination therapy therefore offers a different trajectory to the stepwise approach. Translating these findings into clinical practice will require early detection and diagnosis of type 2 diabetes plus a shift in disease management. Nonetheless, the potential benefits of sustained and continuous disease control that early combination therapy offers represent the start of a new era in early diagnosis and intensive management, to achieve the treatment aims of type 2 diabetes.

PLAIN LANGUAGE SUMMARY

Blood glucose progressively increases over time in type 2 diabetes and is currently treated in a stepwise fashion, with more medications added when a single treatment fails. The VERIFY trial studied people with newly or recently diagnosed type 2 diabetes. Treating people early with two glucose-lowering drugs given together could slow the worsening of blood glucose levels, compared with starting with metformin first and then adding a second treatment later. Taking the two treatments together was as well tolerated as taking the single treatment alone. Starting treatment with two glucose-lowering drugs given together lengthened the time before insulin was needed, compared with starting with metformin and then adding a second treatment later. This is important to people with diabetes, as early treatment is straightforward but becomes increasingly complicated in later stages. The long-term benefits of this early combination treatment are awaited. In the meantime, the VERIFY trial has shown that combination therapy given at the start of treatment with medication can improve blood glucose levels and delay the need for insulin.

Keywords: Combination therapy; Glycaemic control; Type 2 diabetes; VERIFY; Vildagliptin

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Key Summary Points

The aim of type 2 diabetes management is to improve quality of life and prevent chronic complications and premature mortality. Glucose management is an important part of this strategy and is usually approached in a stepwise fashion, where a single therapy is initially given alongside lifestyle measures and followed by intensification of treatment when blood glucose levels rise.

However, this stepwise approach is associated with delay in adding new treatments when blood glucose levels rise. When this is combined with a late diagnosis and late treatment initiation, the patient's prognosis is negatively impacted.

In 2019, the multinational study, VERIFY, provided the most compelling evidence accrued over 5 years to guide treatment optimisation in type 2 diabetes. In this study, initiating combination therapy with two drugs in patients with newly diagnosed type 2 diabetes led to superior and more durable control of blood glucose levels than using the stepwise approach.

Early combination treatment strategies represent the beginning of a new era of early detection, diagnosis and intervention for patients with type 2 diabetes, with the potential of preventing the progressive deterioration of glucose control and the increasing need for additional treatments.

DIGITAL FEATURES

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STEPWISE TREATMENT INTENSIFICATION TO AVOID CLINICAL INERTIA

In type 2 diabetes, the goals of treatment are to prevent or delay chronic complications and maintain the patient's quality of life, which requires control of glycaemia and managing cardiovascular risk factors [1]. Treating to target glycated haemoglobin (HbA_{1c}) levels is therefore fundamental to achieving disease control and preventing chronic complications and premature mortality [2, 3]. The standard of care for first-line drug therapy has been metformin monotherapy with lifestyle measures (e.g. nutrition and exercise) followed by stepwise treatment intensification to achieve HbA_{1c} targets (e.g. $HbA_{1c} < 7.0\%$, < 53 mmol/mol; Fig. 1) [1, 4–7]. Yet, for most patients with $HbA_{1c} > 8.0$–8.5% at diagnosis, metformin monotherapy will not lower HbA_{1c} sufficiently to achieve target levels [8, 9]. Furthermore, once diagnosed, many patients with diabetes may experience one treatment failure after another, often due to delayed intervention. In a substantial number of newly diagnosed patients, their treating physicians fail to intensify therapy within 6 months of failure of metformin monotherapy [10]. This inability to achieve target glycaemic control is multifactorial. The person with diabetes often has difficulties in completely understanding the importance of glycaemic control. They can have the unrealistic expectation that the condition will resolve spontaneously, rather than progressively worsening over decades [11, 12]. The 'wait and see' approach of the stepwise treatment approach also creates uncertainties for the physician who may therefore become indecisive. This clinical inertia—a failure to initiate or intensify treatment in a timely manner—is common and may expose patients to long-term elevation of HbA_{1c} that can negatively impact their prognosis [11].

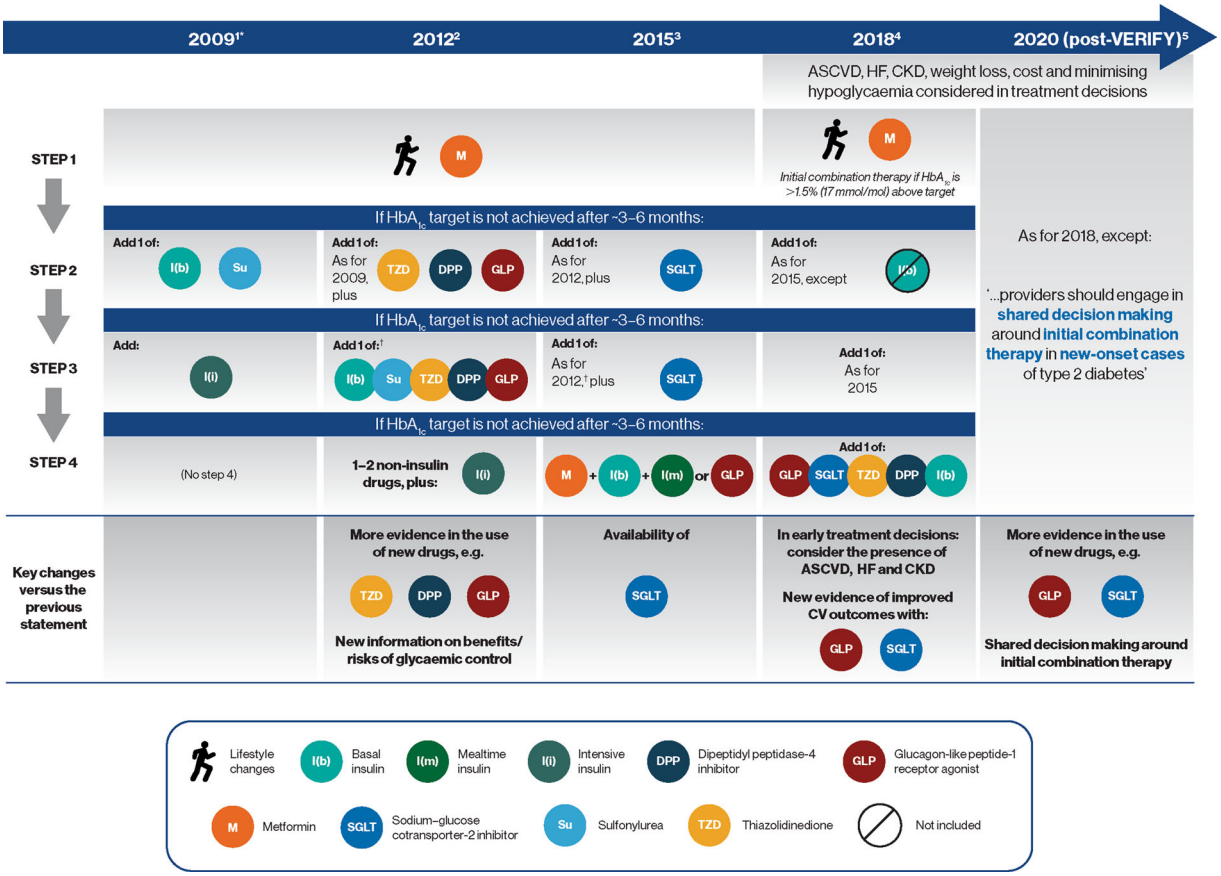

Fig. 1 An abbreviated overview of ADA and EASD recommendations over the last decade for stepwise therapy for patients with type 2 diabetes. [1]Nathan DM, et al. Diabetologia 2009;52:17–30 [4]. [2]Inzucchi SE, et al. Diabetologia 2012;55:1577–96 [6]. [3]Inzucchi SE, et al. Diabetologia 2015;58:429–42 [5]. [4]Davies MJ, et al. Diabetologia 2018;61:2461–98 [1]. [5]Buse JB, et al. Diabetologia 2020;63:221–8 [7]. *Well-validated core therapies. †GLP-1 receptor agonist not to be used with either a DPP4 inhibitor or an SGLT2 inhibitor. ADA American Diabetes Association, ASCVD atherosclerotic cardiovascular disease, CKD chronic kidney disease, CVD cardiovascular disease, EASD European Association for the Study of Diabetes, HbA_{1c} glycated haemoglobin

ADVENT OF AN EARLY COMBINATION STRATEGY IN TYPE 2 DIABETES

The paradox of diabetes management is that early drug treatment is considerably less complex than late intervention. However, the lack of symptoms at the early stage often leads to complacency for both patients and physicians [11]. Progressive decline in beta cell function and relentlessly increasing blood glucose are hallmarks in type 2 diabetes. In all likelihood, combination therapy, using two drugs with complementary modes of action targeting different physiological abnormalities, will be required to achieve optimal glycaemic targets, prevent or slow beta cell failure and provide more durable glycaemic control than metformin alone [9]. However, until recently, practice guidelines suggested that initial combination therapy was only indicated for those newly diagnosed patients who were presenting with HbA_{1c} levels more than 17 mmol/mol (> 1.5%) above their target (i.e. HbA_{1c} > 8.5%) [1].

Another aspect of early combination therapy is the potential for disease modification, an

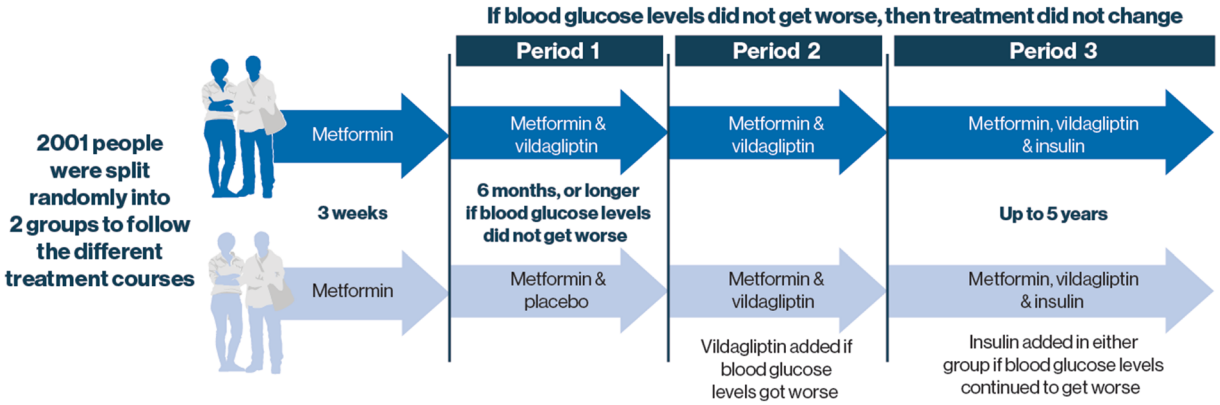

Fig. 2 The VERIFY study design. Adapted from Del Prato S, et al. Diabet Med. 2014;31;1178–84 [16]

altering of the progressive clinical course often seen in many patients with type 2 diabetes [13]. The UK Prospective Diabetes Study (UKPDS) has shown that monotherapy does not provide long-term stable glycaemic control, requiring addition and combination of glucose-lowering agents [9]. So, early combination therapy using agents with complementary modes of action holds the promise of altering the course of disease, thereby providing longer periods with stable HbA_{1c} levels, delaying the need for therapy intensification and reducing the risk of chronic complications.

The multinational VERIFY (vildagliptin efficacy in combination with metformin for early treatment of type 2 diabetes) study (clinicaltrials.gov NCT01528254), published in the *Lancet* in 2019 [14], provides the most compelling evidence accrued over 5 years to guide treatment optimisation in type 2 diabetes [15]. The question posed by VERIFY was simple: Would initiating treatment in newly diagnosed patients with combination therapy—in this case metformin plus vildagliptin—lead to durable glycaemic control over 5 years, compared with an initial metformin standard of care protocol? The trial outline [16] is shown in Fig. 2. The metformin–vildagliptin combination was selected for its established safety profile [17–19] and the complementary modes of action of its two components (glucose-dependent beta-cell stimulation by vildagliptin [20, 21] and insulin sensitisation by metformin [9, 22], with both drugs reducing hepatic glucose production [9, 22, 23]). VERIFY enrolled patients aged 18–70 years with a body mass index of 20–40 kg/m^2 who were in a relatively early stage of disease (diagnosed with type 2 diabetes within 24 months; HbA_{1c} levels 6.5–7.5%; no prior diabetes treatment or maximum of 4 weeks of metformin). The study was notable for its ethnic, gender, regional and socioeconomic diversity—40% of the recruited patient population were non-Caucasian and over half were female [16]. The study protocol was approved by the local ethics committees of all study sites and all patients provided written informed consent for participation in the study. The study was designed and carried out in accordance with International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice and according to the ethical principles of the Declaration of Helsinki, and was overseen by an independent data monitoring committee [14].

STRATEGY FOR INITIAL EARLY SUCCESS

Rather than waiting to lose control under the stepwise treatment intensification approach, diabetes management should aim at achieving and maintaining control early. The expectation of the patient should not be 'Will I be able to control my disease?', but instead 'How quickly can I expect to control my disease? And how long will this take and ultimately, last?' The possibility of controlling diabetes from the point of diagnosis introduces 'remission' as an

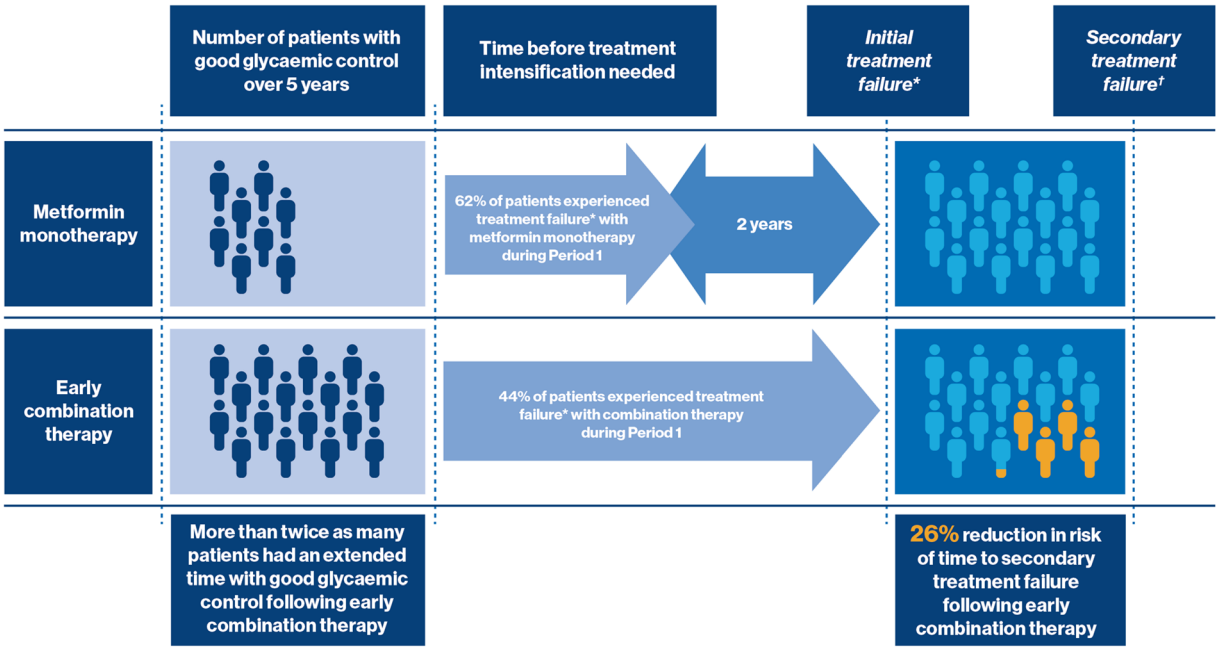

Fig. 3 A 26% reduction in risk of time to secondary treatment failure following early combination therapy in the VERIFY study [14]; i.e. approx. 1 in 4 patients treated and initially experiencing failure with early combination treatment did not require addition of a third treatment (usually insulin), versus delayed combination therapy. *Defined as loss of glycaemic control: two consecutive values of $HbA_{1c} \geq 53$ mmol/mol (7.0%). †Defined by the need to maintain glycaemic control with a third treatment (usually insulin) in patients receiving combination therapy, according to local diabetes treatment guidelines and as per investigators discretion

achievable concept [24]. In newly diagnosed patients, maintaining $HbA_{1c} < 6.5/7.0\%$ (< 48/53 mmol/mol) and minimising glycaemic exposure, particularly during the first year following diagnosis, may be crucial for the prevention of later complications [25, 26].

As the first large-scale prospective study of its kind, VERIFY offered a unique opportunity to examine the benefits of initial early success in the type 2 diabetes setting [15]. Over 5 years, early combination therapy significantly reduced the relative risk for time to initial treatment failure ($HbA_{1c} \geq 7.0\%$ at two consecutive scheduled visits) by 49% (hazard ratio [HR] [95% confidence interval (CI)] 0.51 [0.45, 0.58]; $P < 0.0001$) compared with initial metformin monotherapy. At 5 years, more than twice as many patients had an extended time with good glycaemic control following early combination therapy, compared with initial metformin monotherapy (Fig. 3). The median time to loss of glycaemic control was nearly doubled in the early combination group, compared with initial metformin monotherapy (61.9 months vs 36.1 months, respectively), extending the need to intensify treatment by more than 2 years (Fig. 3). Glycaemic exposure was consistently lower for the entire duration of the VERIFY study for patients receiving early combination therapy, compared with those on initial metformin, with a greater proportion attaining HbA_{1c} target levels of < 7%, < 6.5% or < 6.0%. Treatment arms exhibited similar safety and tolerability profiles, with no unexpected safety findings and low rates of hypoglycaemic events and comparable changes in body weight, despite the concurrent use of two glucose-lowering agents in the combination treatment arm [14].

IMPORTANCE OF MAINTAINING GLYCAEMIC CONTROL

Early glycaemic control can mitigate the risk of disease progression and reduce patient

susceptibility to cardiovascular and other complications of diabetes [25], but only if it is maintained. It is important that physicians resist the temptation to de-escalate treatment or initiate 'drug holidays' following a reduction in HbA_{1c} to pre-diabetic or close to normoglycaemic levels. To use the analogy of weight loss, once a person achieves their target weight, they should not automatically revert to the lifestyle habits that prompted their decision to lose weight in the first place.

In the VERIFY study, all patients who initially received metformin monotherapy went on to receive combination therapy with metformin and vildagliptin following their first treatment failure. Apart from delaying the time to primary treatment failure, early combination therapy also reduced the risk of time to secondary treatment failure by 26% (HR [95% CI] 0.74 [0.63, 0.86], $P < 0.0001$) in VERIFY (Fig. 3). This suggests a 'legacy effect' by which only the early normalisation of blood glucose can help to attenuate diabetes progression [15, 25]. It remains to be seen whether this will translate into a long-term reduction in cardiovascular and microvascular outcomes, but the delayed requirement for insulin during the study period is encouraging.

WHAT HAVE WE LEARNED AND WHAT REMAINS TO BE DONE?

The VERIFY study has shown that early combination treatment in patients with early-stage type 2 diabetes provides increased glycaemic durability of target HbA_{1c} levels with less frequent interventions for treatment intensification over time. These benefits were achieved without added tolerability issues versus the monotherapy approach. The combination strategy was equally well accepted with no weight gain and only a few cases of mild hypoglycaemia.

Further investigation is warranted in a number of areas. A limitation of the VERIFY study was that only one treatment combination was assessed. Mechanistically, studying the effects of other dipeptidyl peptidase 4 inhibitors (DPP4i) in combination with metformin or other oral agents, based on a rational consideration of mode of action, will provide further insight into the pathophysiological processes in early type 2 diabetes. The amelioration of glucotoxicity due to early versus later lowering of hyperglycaemic load in newly diagnosed patients, and the impact of an early combination strategy on the preservation of pancreatic beta-cell function [9], is an important topic. Assessment of long-term clinical benefits of early combination treatment strategy in patients with higher baseline HbA_{1c} levels is also of interest, given that a limitation of VERIFY is that it was conducted within a narrow and low HbA_{1c} range (HbA_{1c} 6.5–7.5%). Adequately powered dedicated cardiovascular follow-up studies in a primary prevention population will help establish whether early intervention confers protection against cardiovascular events. Importantly, cost-effectiveness studies and real-world data are needed before this early combination strategy can be translated into clinical practice.

A final question to be answered is whether the observations made during the early combination treatment of the DPP4i, vildagliptin, and metformin also hold true for other combinations. For each individual class, perhaps even each agent, this question should be investigated, as risk–benefit ratios will differ in different combinations, thus altering clinical conclusions.

HOW CAN AN EARLY COMBINATION STRATEGY BE APPLIED IN CLINICAL PRACTICE?

Early combination treatment offers people newly diagnosed with type 2 diabetes a different trajectory to the current treatment paradigm. The VERIFY study suggests that early combination is acceptable, beneficial and easily administered by the physician. Putting this into practice will require a change in approach across all aspects of diabetes management, from early case finding and diagnosis to treatment initiation and continuing follow-up (Figs. 4, 5) [10–12].

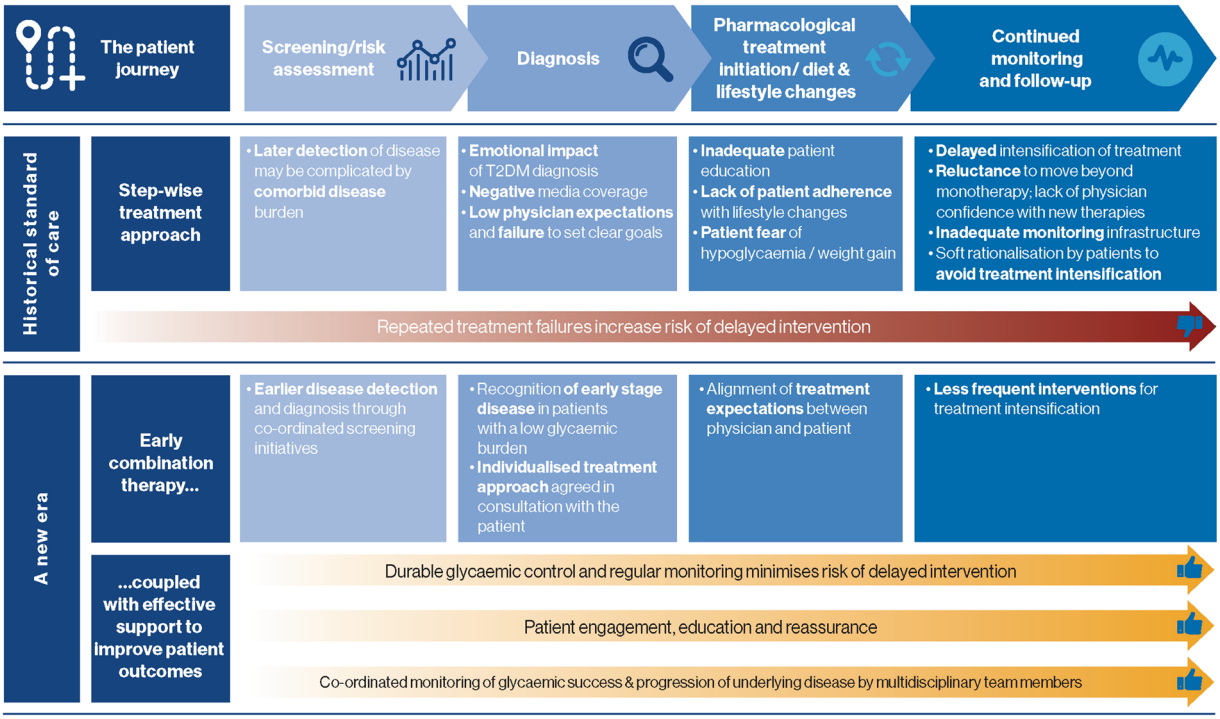

Fig. 4 Early combination strategy and evolution of the patient journey from early diagnosis of type 2 diabetes. Adapted from Reach G, et al. Diabetes Metab. 2017;43:501–11, Strain WD, et al. Diabetes Res Clin Pract. 2014;105:302–12 and Pantalone KM, et al. Diabetes Care. 2016;39:1527–34 [10–12]

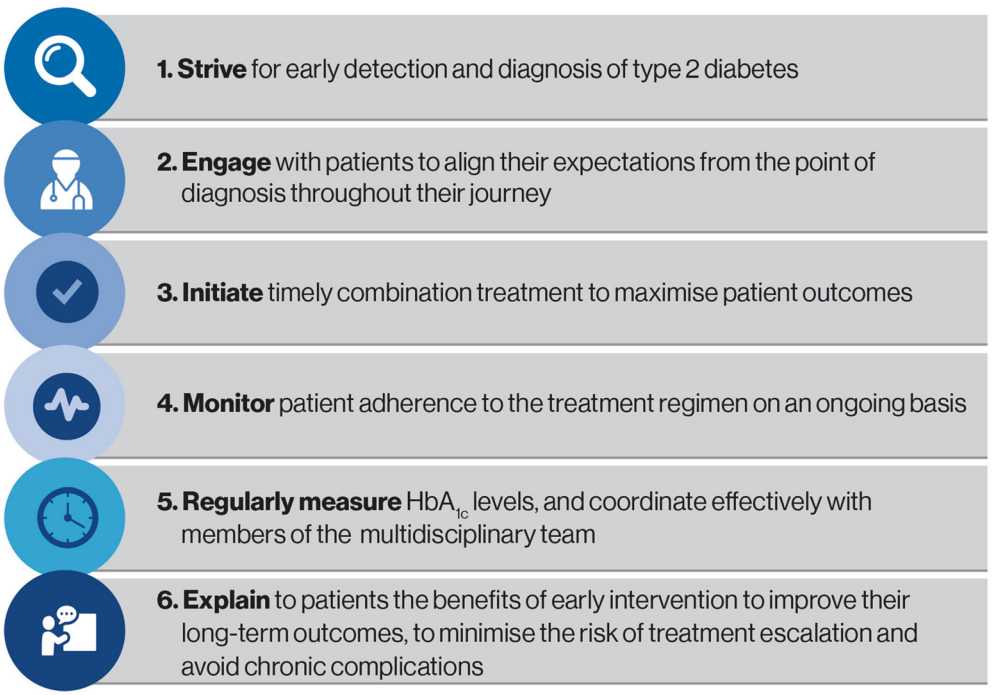

Fig. 5 Guiding principles: the six most important actions for the physician in an early combination strategy

An early combination strategy will require timely detection of type 2 diabetes, in order to maximise the long-term clinical benefits of combination therapy. Procedures will need to be put into place that facilitate early disease detection and diagnosis. The answer may lie in designing and implementing integrated screening programmes with coordination and awareness across all members of the multidisciplinary diabetes management team, acknowledging that the pathway to diagnosis in patients with early stage disease will differ substantially to that followed by patients with more advanced disease and who carry a higher glycaemic burden. Pragmatically, healthcare providers may face challenges in justifying continuation of a treatment regimen when glycaemic control has been achieved and diabetes remission is apparent. Combination therapy also has higher initial costs than stepwise therapy, although improved glycaemic control with combination therapy could reduce costs associated with disease complications in the long-term and thereby offset the higher initial costs [27]. In addition, newer antidiabetic medications such as DPP4i have been shown to be cost-effective compared with insulin, sulfonylureas and thiazolidinediones [28]. Increasing awareness of the benefits of sustained and continuous disease control is essential to align expectation amongst patients, physicians, payers and policymakers.

CONCLUSION

Early combination treatment strategies represent the beginning of a new era of early detection, diagnosis and intensive management in patients newly diagnosed with type 2 diabetes. Evidence from the VERIFY study has led to the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) suggesting that healthcare providers engage their patients in making shared decisions around using initial combination therapy when type 2 diabetes is diagnosed [7, 29]. This evidence, together with changes in management guidelines, will help physicians and multidisciplinary teams take the next steps in evolving the management of type 2 diabetes, whilst further study of this approach is being pursued.

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Compliance with Ethics Guidelines. The VERIFY study protocol was approved by the local ethics committees of all study sites and all patients provided written informed consent for participation in the study. The study was designed and carried out in accordance with International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice and according to the ethical principles of the Declaration of Helsinki, and was overseen by an independent data monitoring committee. The article is a commentary on a previously conducted study previously published that does include human participants. The authors of this commentary were authors of the original manuscript and/or investigators of the study that was previously published.

Data Availability. 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: https://www.clinicalstudydatarequest.com/

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