Drug Corner

Expert Opinion on Novel Fixed Drug Combination of Metformin Sustained Release and Vildagliptin Immediate Release for Type 2 Diabetes Mellitus Management in India

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Type 2 Diabetes Mellitus (T2DM) is a highly prevalent cardiometabolic disorder in India and is further projected to rise (10.4% by 2030). In newly diagnosed patients, maintaining HbA1c 6.5-7.0% and minimizing glycaemic exposure, particularly during the first year following diagnosis, may be crucial for preventing complications. Early treatment initiation with a synergistic combination of vildagliptin and metformin is one of the many possible combinations to manage type 2 diabetes mellitus. In view of emerging clinical evidence on early initiation of combination therapy than monotherapy with metformin, there is a need for expert consensus on the use of the current approved Fixed Dose Combination (FDC) of Metformin SR + Vildagliptin IR in newly diagnosed diabetic patients. Experts framed final consensus statements based on available scientiûc evidence, experience and collective clinical judgment from practical experience this FDC.

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Key words **: Type 2 diabetes mellitus, Fixed-dose combination, Metformin, Vildagliptin**

Introduction

Current Indian Scenario :

The age-adjusted prevalence of diabetes in India as per the Diabetes Atlas 2021 released by the International Diabetes Federation (IDF) is 9.6% (projected to increase by 10.4 by 2030)[1]. In a recent 2020 Indian study, the average HbA_{1C} in a newly diagnosed diabetic patient was reported to be 9.1 ± 2.3%, whereas the average HbA_{1C} was 8.3 ± 2.4% in a diabetic patient diagnosed during screening[2]. This suboptimal disease awareness and high average HbA1C at diagnosis, in addition to the fact that the onset of diabetes among Indians is about a decade earlier than the Western counterparts, highlights that diagnosis is delayed or missed in Indians.Indians have a higher overall disease burden with a longer duration spent in pre-detection, hence a longer untreated period than the Western population[3].

Early *versus* Late Intensification of Diabetic Therapy :

A 1% increase in HbA_{1c} concentration was associated with about a 30% increase in all-cause mortality and a 40% increase in cardiovascular mortality[4]. Risk of hospitalization for heart failure increases 8-32% per 1% unit increase in HbA_{1c}[5]. Hence, optimal glycemic control is one of the most important treatment goals.

For most patients with HbA1c 8.0-8.5% at diagnosis, metformin monotherapy does not lower HbA1c sufficiently to achieve target levels[6,7]. Delayed

- Early combination therapy could potentially alter the course T2DM, thereby providing longer periods with stable HbA_{1c} levels, delaying the need for therapy intensification, and reducing the risk of chronic complications.Initial combination therapy with Metformin Sustained Release (SR) and Vildagliptin Immediate Release (IR) Fixed Drug Combination (FDC) should be considered in:
  - Patients presenting with A1C levels 1.5-2.0% above target,
  - Patients with any one of the below comorbidities:
    - # Patients with diabetic end-organ damage manifestations
    - # Patients with Cardiac or renal risk factors.
    - # Elderly patient
    - # Obese patients and patients in whom weight gain is undesirable.

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treatment intensification after monotherapy failure, seen in real-world settings, results in more time spent in avoidable hyperglycemia, raising a crucial barrier to optimized care[8].

The INITIAL study demonstrated that vildagliptin and metformin combination therapy was associated with significant and clinically relevant HbA1c reduction in relatively young drug-naïve Asian patients with T2DM[9]. In newly diagnosed patients, maintaining HbA1c 6.5-7.0% and minimizing glycaemic exposure, particularly during the first year following diagnosis, may be crucial for preventing complications[10,11].

The VERIFY (Vildagliptin Efficacy in combination with Metformin for Early Treatment of Type 2 Diabetes) Trial :

The five year long VERIFY trial demonstrated that initial combination therapy is superior to sequential addition of medications for extending primary and secondary treatment failure. Newly diagnosed T2DM patients that received early combination therapy had a significant reduction in the relative risk for time to initial treatment failure compared to initial metformin monotherapy (HR 0.51, p<0.0001). Compared to initial metformin monotherapy, at 5 years, more than twice as many patients had an extended time with good glycaemic control after early combination therapy. The median time to loss of glycaemic control was almost doubled in patients that received early combination therapy compared to patients that received initial metformin monotherapy (61.9 months *versus* 36.1 months). Thus, extending the need to intensify treatment by more than 2 years. Furthermore, patients receiving early combination therapy had consistently lower glycaemic exposure for the entire study duration, compared with those on initial metformin monotherapy, with a greater proportion of patients attaining HbA1c target levels of <7%, <6.5%, or <6.0%[12]. Both groups showed similar safety and tolerability profiles, with no new safety findings, low rates of hypoglycaemic events, and comparable changes in body weight, despite the concurrent use of two OHAs in the combination treatment arm.

Besides delaying the time to primary treatment failure, early combination therapy also reduced the risk of time to secondary treatment failure by 26% (HR 0.74, p<0.0001). This suggests a 'legacy effect' in which only the early normalization of blood glucose can help to reduce diabetes progression[11,13].

Early treatment initiation with a synergistic combination of vildagliptin and metformin is one of the many possible combinations to manage T2DM. Results from the ongoing GRADE study comparing the durability of different agents in combination with metformin will add evidence to the proposed early combination treatment strategy[14].

Current Treatment Guidelines on Combination Therapy for Diabetes :

(1) Global Guidelines :

The American Diabetes Association (ADA) 2021 states that more intensive early treatment has some clinical benefits, and it should be evaluated as part of a collaborative decision-making process with patients. Furthermore, since the absolute effectiveness of most oral hypoglycemic agents (OHAs) rarely exceeds 1%, initial combination therapy should be considered in patients with HbA_{1C} levels 1.5- 2.0% above the target. Treatment intensification recommendations for patients not meeting treatment goals should not be delayed. The choice of OHA added to metformin is based on the patient's clinical condition[3].

The American Association of Clinical Endocrinology (AACE) 2020 guidelines recommend dual combination therapy when HbA1c is ≥7.5% at diagnosis15.

(2) Indian Guidelines :

The latest Research Society for the Study of Diabetes in India (RSSDI) guidelines 2020 recommends initiating combination therapy early if the HbA1c >1.5% above the target[16].

Rationality of Metformin SR + Vildagliptin IR Fixed Drug Combination (FDC) :

The Metformin SR + Vildagliptin IR FDC consists of antidiabetic with complementary modes of action. Metformin helps with insulin sensitization and Vildagliptin with glucose-dependent beta-cell stimulation. Furthermore, both drugs reduce hepatic glucose production[17].

A survey showed that patients and providers both cited gastrointestinal side effects as the primary barrier to metformin use[18]. The once-daily metformin (Met-XR) formulation allows a more gradual release of metformin in the upper gastrointestinal tract compared to the immediate release of metformin (Met-IR)[19]. An open-label, prospective 24-week study showed that patients who switched to metformin XR observed the same clinical and metabolic benefits as for standard metformin but with fewer gastrointestinal side effects, reduced dosage, and a greater sense of well-being and satisfaction on medication[20].

Benefits of metformin hydrochloride sustained release (SR) and vildagliptin immediate release (IR) combination therapy have been summarised in Fig 1[19,20].

Need for Expert Opinion

In view of emerging clinical evidence on early

Assessment of key criterias of Metformin XR + Vildagliptin IR

HbA_{1c} control	Yes
Risk of hypoglycemia	No
Convenient to use	Yes
Risk of weight gain	No
Side effects (diarrhea, nausea, vomiting and abdominal pain)	Reduced compared to Met-IR
Ease of dose titration	Yes
Reduced pill burden	Yes
Usage in T2D patients at high CV risk	Safe
Better adherence and compliance	Yes

Fig 1 — Assessment of Treatment Satisfaction Criterion
CV: Cardiovascular; HbA_{1c}: Glycated haemoglobin; IR: Immediate release; XR: Extended release; T2D: Type 2 diabetes.

initiation of combination therapy than monotherapy with metformin, we need expert opinion on the use of the current approved FDC of Metformin SR + Vildagliptin IR in newly diagnosed diabetic patients.

Methodology

110 diabetologists from India convened for 10 advisory board meetings between June 2021 to August 2021 to discuss the use of Metformin SR + Vildagliptin IR in current practice. All meetings were conducted on a virtual platform. The experienced endocrinologists were selected based on their seniority (over at least 10 years of experience in field of diabetes management).Experts framed statements based on available scientific evidence, experience and collective clinical judgment from practical experience with this combination. Objectives and specific topics relating to metformin and vildagliptin combination were discussed, and each expert shared their views, which led to group discussions. The consensus was formed if the agreement to the statement was more than 80% within the group.

Consensus statements introduced for panel discussion :

- In India, diagnosis of type 2 diabetes is delayed.
- In India, the average HbA_{1C} at the time of diagnosis is higher than the west.
- In practice, treatment should be individualised for patients including shared decision making for early initiation of combination therapy early in newly diagnosed diabetics.
- In practice, Metformin sustained release (SR) has better tolerance than Metformin immediate release (IR).
- It is important to identify patient profiles who could benefit from Metformin SR + Vildagliptin IR combination therapy.

Expert Opinion

In the light of the above information, a panel of experts discussed the following topics to help arrive at final expert consensus statements.

Diagnosis of Type 2 Diabetes is Delayed in India

All experts agreed that only 50% of the patients with diabetes are diagnosed and only 50% of the diagnosed patients are on treatment. There is suboptimal disease awareness and limited accessibility to regular health care.

The average HbA_{1C} at the time of diagnosis is higher in India compared to the West

Most of the experts reported that the average HbA_{1C} at the time of diagnosis in their practice ranges between 8-10%.

Monotherapy has Limitations when used for the Treatment of T2DM Patients

Metformin monotherapy, which primarily controls fasting plasma glucose, is preferred, especially when the HbA1C is 7.5-8% at the time of diagnosis. Treatment failure to Metformin monotherapy is usually noticed at an average of 3 months. A trial with monotherapy is done for a maximum of 8-12 weeks before switching to combination therapy based on Hb1AC values at follow-up. Usually, a maximum dose of Metformin Monotherapy is needed to achieve an average of 1% drop in HbA1C. Monotherapy does not provide long-term stable glycaemic control, requiring up-titration of dose or initiation of combination therapy.

In Clinical Practice, Shared Decision-making should be for Early Initiation of Combination Therapy in Newly Diagnosed Diabetics

Experts believe that considering the unique challenges faced by Indian patients, the “Hit it hard” strategy is necessary. Early combination therapy using OHAs with complementary mechanisms of action can alter the course of the disease, allowing for more extended periods of stable HbA1c levels, delaying the need for treatment intensification, and lowering the risk of chronic complications.

Patients with high HbA1c (9-10%) at diagnosis need dual therapy or a Fixed-dose Combination (FDC). Experts also report that it is better to switch to combination therapy rather than increasing the drug dose used in the initial monotherapy. Dual therapy with two different classes of medication provides the benefit

of complementary action. FDCs are known to increase adherence to therapy and reduce pill burden. Patients also achieve glycemic control at lower doses of individual components of the combination. One of the drawbacks of combination therapy is the higher cost to the patient, therefore shared decision-making is critical. To facilitate shared decision-making in India, where the time spent with each patient is limited.It is helpful to have an algorithm (Fig 2) to help facilitate discussion.

Identify Patient Profiles who could benefit from Metformin SR + Vildagliptin IR Combination Therapy

Most experts agreed that Metformin SR + Vildagliptin FDC therapy benefits patients with baseline HbA1c 1.5-2.0% above target with any of the following comorbidities: (a) diabetic end-organ manifestations, (b) cardiac or renal risk factors, (c) elderly patients d) obesity or undesirable weight gain. The experts also agreed that patients with T2DM who practice fasting during Ramadan or Navratra would benefit from this combination therapy. Patients with T2DM at high risk of hypoglycemia or intolerant to Metformin IR formulations can be given this combination therapy, according to experts. Finally, the experts agreed that patients with T2DM on Metformin and Vildagliptin combination therapy can also be switched to Metformin SR + Vildagliptin IR FDC therapy.

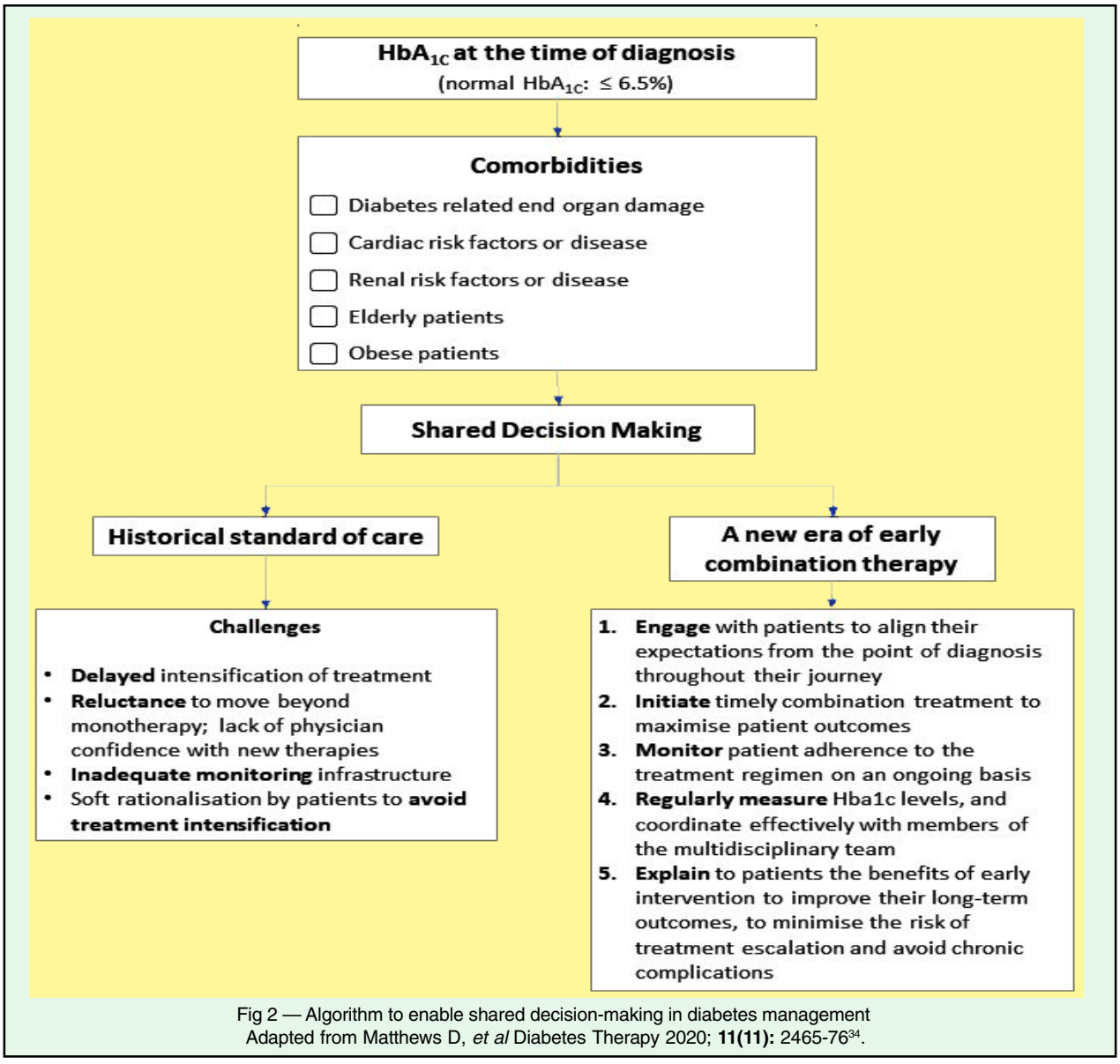

Fig 2 — Algorithm to enable shared decision-making in diabetes management
Adapted from Matthews D, *et al* Diabetes Therapy 2020; **11(11):** 2465-76[34].

Final Expert Opinion

- Combination therapy is required for sustained glycemic control in patients with type 2 diabetes mellitus.
- Early combination therapy could potentially alter the course T2DM, thereby providing longer periods with stable HbA_{1c} levels, delaying the need for therapy intensification, and reducing the risk of chronic complications.
- Initial combination therapy with Metformin Sustained Release (SR) and Vildagliptin Immediate Release (IR) Fixed Drug Combination (FDC) should be considered in:
  - Patients presenting with A1C levels 1.5– 2.0% above target,
  - Patients with any one of the below comorbidities:
    - # Patients with diabetic end-organ damage manifestations
    - # Patients with Cardiac or renal risk factors.
    - # Elderly patient
    - # Obese patients and patients in whom weight gain is undesirable.
- Diabetic patients who can be started or switched to Metformin SR + Vildagliptin IR Fixed Drug Combination (FDC):
  - Practice fasting during Ramadan or Navratra
  - Are at high risk for hypoglycemia
  - Are intolerant to Metformin IR formulations
  - Patients on Metformin and Vildagliptin combination therapy can also be switched to FDC.

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