Optimizing the treatment of newly diagnosed type 2 diabetes mellitus with combination of dipeptidyl peptidase-4 inhibitors and metformin: An expert opinion

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ABSTRACT

The expanding burden of Type 2 Diabetes Mellitus (T2DM) in today’s world, with respect to incidence, prevalence, and cost incurred, is an existential risk to society. Various guidelines recommend individualization of treatment. This expert opinion aims to review the recent evidences and reach a consensus on the preferable combination therapy for use in newly diagnosed Indian T2DM patients with HbA₁c > 7.5%. The core committee included seventeen diabetes specialists. Three statements were developed, discussed, and rated by specialists and recommendations were noted. Specialists were requested to rate the statements using a 9-point Likert's scale with score of 1 being "Strongly Disagree" and 9 being "Strongly Agree". Statement-specific scores of all the specialists were added and mean score of ≥7.00 was considered to have achieved a consensus. Statements used to meet the consensus were: Statement 1. Majority of newly-diagnosed Indian diabetics have HbA₁c > 7.5%; Statement 2. Patients with HbA₁c > 7.5% may be initiated with dual therapy of dipeptidyl peptidase-4 inhibitors (DPP4Is) + Metformin; and Statement 3. In Indian patients with HbA₁c > 7.5% at diagnosis, DPP4Is + Metformin may be considered as a first-line therapy. Literature review revealed that HbA₁c level at the time of diagnosis in majority of Indian T2DM patients is > 7.5%. Consensus was reached that dual anti-diabetic therapy should be initiated in patients with HbA₁c > 7.5%. DPP4Is + Metformin is the preferred cost-effective option and may be considered as a first-line therapy in Indian T2DM patients with HbA₁c > 7.5% at diagnosis.

Keywords: Combination therapy, DPP4 inhibitors, HbA₁c, Metformin, T2DM

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Received: 03-12-2020  Revised: 20-02-2021
Accepted: 09-07-2021  Published: 27-12-2021

How to cite this article: Das AK, Gandhi P, Saboo B, Reddy S, Chawla R, Zargar AH, et al. Optimizing the treatment of newly diagnosed type 2 diabetes mellitus with combination of dipeptidyl peptidase-4 inhibitors and metformin: An expert opinion. J Family Med Prim Care 2021;10:4398-409.
Introduction

Diabetes mellitus (DM) is considered as one of the major health challenges for the 21st century and expanding burden of DM possesses a pragmatic risk to society.[8] Estimates of International Diabetes Federation (IDF) Diabetes Atlas show that India is a significant contributor to global burden of Type 2 DM (T2DM), as suggested by a tenfold rise in prevalence over past four decades.[2] It is evident from Global Burden of Disease data illustrating prevalence of 26 million in 1990, which increased to 65 million in 2016.[3] This figure is anticipated to rise to 134.3 million by 2045.[2,4] The ICMR-INDIAB study, involving 15 Indian states, reported overall prevalence of diabetes to be 7.3%, with prevalence being higher in urban (11.2%) than rural areas (5.2%), and significantly higher in mainland (8.3%) than North-Eastern states (5.9%).[5]

According to American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2018 consensus statement,[6] American Diabetes Association (ADA) 2018 consensus report,[7] and Research Society for the Study of Diabetes in India (RSSDI) 2017 guidelines,[8] Metformin is first line therapy for newly diagnosed T2DM patients, based on baseline HbA1c at diagnosis. If Metformin is contraindicated or not tolerated, other alternative oral anti-diabetics (OADs) can be considered as first line therapy, which include Dipeptidyl Peptidase-4 Inhibitors (DPP4Is), Glucagon-like Peptide 1 (GLP-1) Agonists, Sulfonylureas (SUs), Thiazolidinediones (TZD), Alpha-glucosidase Inhibitors (AGIs), Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2Is), and Glinides [Figures 1-3].[1,6,7] If HbA1c at diagnosis is higher (>7.5%), initial dual OAD combination therapy can be considered.[8] RSSDI guideline (2017) states, first line dual therapy is considered, if single agent is not able to achieve glucose targets.[1]

Aim of this expert opinion was to deliver important and reasonable proposals for management of T2DM with dual therapy of DPP4Is and Metformin, as an initial OAD combination therapy, if entry HbA1c is >7.5%. It will form a significant decision-making tool for clinicians in various Indian healthcare settings. In this expert opinion, we review glycemic, metabolic effects, and cardiovascular outcomes, and provide rationale for recommendation of combination of DPP4Is + Metformin.

Methodology and Approaches for Developing the Expert Opinion

The core committee of subject experts for framing expert opinion included 17 specialists. Position statements (2012, 2015) and consensus statement (2018) given by ADA/ESAD,[10] AACE/ACE (2018),[8] and RSSDI guidelines (2017)[7] were used as reference points. Thorough review of literature was directed towards evaluating efficacy and safety of combinations involving DPP4Is + Metformin and existing treatment algorithms. Subject specialists assessed underlying draft proposals and provided pertinent recommendations to reach at an agreement and then proposals were consolidated, as deemed appropriate. This expert opinion has been framed using available evidences and where strong reinforce did not exist, by utilizing experience and knowledge of specialists and extensive review by additional experts.

Key principles of expert opinion

These important principles incorporate elements of managing T2DM with combination of DPP4Is + Metformin which include:

- All therapeutic decisions should be based on comprehensive assessment and risk stratification.
- A clear focus on available evidence on efficacy and safety of DPP4Is + Metformin.

We hope that this expert opinion forms a platform for all clinicians, as part of renewed emphasis on explicit management approaches to T2DM with combination of DPP4Is and Metformin.

Expert Opinion: Use of DPP4Is + Metformin as first line therapy in patients with HbA1c >7.5%.

Purpose of the Expert Opinion

Management of hyperglycemia in T2DM is highly intricate with an augmented cluster of available pharmacological agents. However, there is an apprehension regarding their possible adverse events (AEs) and ambiguity regarding actual advantages of tight glycemic control on macrovascular complications.[11] The expert opinion aims to -

- Provide an improved and up-to-date understanding on management of T2DM from context of Indian diabetic patients.
- Identify key treatment algorithms in T2DM patients, based on baseline HbA1c.
- Address key inquiries on initial combination of therapy, to help clinical practice.
- Discuss combination therapy using DPP4Is + Metformin: Highlighting its mechanism, rationale, and clinical evidences to provide clinical recommendations categorically in Indian patients with entry HbA1c >7.5%.
- To discuss out-of-all available options, the preferred choice of DPP4Is from context of Indian diabetic patients.

Developing an expert opinion through modified Delphi method

Eligible specialists having related background and experience concerning target issue were considered and invited for discussion. These specialists could contribute and were willing to give decisions in order to reach consensus.

The meeting was initiated by Working Group Members, and 17 Indian specialists were involved in discussion. The expert opinion context was set as:
DPP4Is + Metformin may be used as 1st line therapy in Indian diabetic patients with HbA$_{ic}$ >7.5% at the diagnosis.

The modified Delphi method was used for developing expert opinion by drafting statement related questions and circulating to all specialists. There were three statements and each specialist was requested to rate statements using a 9-point Likert’s scale, with a score of 1 being “Strongly Disagree” and 9 being “Strongly Agree”. For each statement, scores of all specialists were added and then mean score was derived.\[9\]

Reaching the consensus

Statements achieving mean score of ≥7.00 were considered to have achieved consensus; mean score of ≥6.50 were considered to have achieved a near consensus; and statements achieving mean score of <6.50 were considered to have achieved no consensus.

Following statements were used to develop consensus among specialists for use of dual therapy containing DPP4Is and Metformin:

Statement 1. Majority of newly diagnosed Indian diabetic patients (NDIDP) have HbA$_{ic}$ >7.5%

In a retrospective analysis (CINDI 2) of 1500 Indian patients with newly diagnosed young onset diabetes (YOD), mean HbA$_{ic}$ was found to be 9.86 ± 2.43% at the time of diagnosis.\[10\] Another study reported overall prevalence of patients with a mean HbA$_{ic}$ of 7.5 ± 0.33% and above to be 10.4%, in Newly Diagnosed Diabetics (NDD).\[11\]

Wani et al. reported that T2DM patients with HbA$_{ic}$ >7.5% had more microvascular complications (neuropathy, nephropathy, and retinopathy) than patients with HbA$_{ic}$ in the range of 6.5-7.5% demonstrating an association between raised HbA$_{ic}$ and increased risk of microvascular complications.\[12\]

Based on available evidences and individual clinical experience, majority of specialists agreed that majority of NDIDPs have HbA$_{ic}$ >7.5%. Mean consensus score achieved on the Likert’s scale was 7.76 ± 0.60 (Mean ± SEM) and hence, this statement was accepted.

Statement 2. Patients with entry HbA$_{ic}$ >7.5% may be initiated on dual therapy of DPP4Is + Metformin

Glycemic management and monitoring in newly diagnosed T2DM

Combination therapy

T2DM is a progressive disease generally ascribed to steady decline in insulin secretion and rise in insulin resistance. Gradual loss of beta cell secretion significantly affects glycemic control with monotherapy. This theory is supported by report of ADA-EASD (2018) which endorses step-wise addition of anti-hyperglycemic agents, and also considers initiating a dual therapy in patients with newly diagnosed T2DM who have HbA$_{ic}$ ~ 1.5% (17 mmol/mol) above their glycemic target.\[13\]

AACE/ACE (2018) consensus statement algorithm considered Metformin as first line drug and second line drugs recommended are SUs, DPP4Is, GLP1-RA, SGLT2Is, AGIs, TZDs, and Glidines. It states that patients with HbA$_{ic}$ >7.5% at diagnosis should be prescribed Metformin + another agent and addition of any second-line agent is generally associated with further decrease in HbA$_{ic}$ by ~ 0.5 to 1%.\[14\] Latest ADA-EASD consensus report recommends, considering cardiovascular and renal risk when initiating second line drugs after Metformin, wherein, SGLT2I and GLP1As are recommended because of their established cardio-renal benefits.\[15\] However, there are limitations for usage of SGLT2Is and GLP1As, due to adverse events. Various publications have pointed out adverse events mainly associated with SGLT2Is,\[16\] GLP1RAs\[17,18\] and sulfonylureas.\[19\] Compared to other OADs, considering efficacy, safety, and cost, DPP4Is are preferred add-on oral therapies to Metformin.\[20\] Moreover, current trend is to initiate therapy with combination of drugs rather than sequential addition.\[21\]

Rationale for combining DPP4Is with Metformin

DM is characterized by impaired secretion of insulin, insulin resistance, and glucagon hypersecretion. Metformin acts by decreasing hepatic glucose yield and enhances insulin sensitivity, while DPP4Is act by stimulating insulin secretion and inhibiting glucagon hypersecretion. Hence, additive or synergistic activity is predicted through possibly enhanced distinctive mechanism. Moreover, Metformin increases GLP-1 levels which would be potentially additive to action of DPP4Is.\[22\] Thus, combined use of these two classes of drugs is justified.

Clinical evidence of combination therapy of DPP4Is and Metformin

Initial combination therapy

A 24-week randomized trial (RT) showed maximum reduction in HbA$_{ic}$ (2.1%), fasting glucose (3.8 mmol/l), and post-prandial glucose (15.9 mmol/l) in patients receiving initial combination therapy of Sitagliptin (50 mg) + Metformin (1000 mg) twice daily with 66% patients achieving HbA$_{ic}$ <7.0%.\[23\]

A study by Haak et al. evaluated efficacy and safety of Linagliptin + Metformin as an initial combination therapy in patients with inadequate glycemic control through 24 weeks double-blind, RT in 791 patients. Mean change in HbA$_{ic}$ from baseline was significantly (p < 0.001) higher in combination arms compared to their respective monotherapy arms.\[24\]

In 12-week controlled trial of newly diagnosed T2DM patients with severe hyperglycemia, significant reduction of HbA1c was observed in patients receiving Saxagliptin + Metformin combination therapy as compared with Glipizide monotherapy.\[25\]

The post-trial observations of UKPDS and DCCT trials have suggested the importance of early tight glycemic control for the prevention of future complications of diabetes. These post-trial
observations have been called legacy effects or metabolic memory (Laiteerapong N, et al., 2019).

VERIFY study, assessed glycemic durability of an early initial combination therapy with Vildagliptin and Metformin versus Sequential Metformin monotherapy in newly diagnosed T2DM patients. Treatment failure incidence was comparatively lesser in combination group (43.6%) than monotherapy group (62.1%), concluding that early intervention with combination therapy provides significant long-term benefits compared with initial metformin monotherapy.[23]

Thorough literature search revealed, initial treatment of severe hyperglycemia with DPP4Is + Metformin in newly diagnosed patients with HbA1c >7.5% resulted in significant change in HbA1c and this combination therapy was effective [Table 1].[22,26‑30]

Sequential addition of anti-hyperglycemic agents DPP4Is + Metformin vs Monotherapy:

In a clinical study on T2DM, addition of DPP4I LAF237 (50 mg o.d.) to Metformin (1,500–3,000 mg/day) resulted in reduction of HbA1c by 0.6 ± 1% in 12 weeks.[31]

Numerous studies have revealed better improvements in glycemic control with combination of DPP4Is and Metformin [Table 2].[32‑37]

DPP4Is + Metformin vs Metformin + Other agents:

Various studies demonstrated that addition of DPP4I to Metformin monotherapy is non-inferior to combination of Metformin with other OAD agents. Comparable reduction in mean HbA1c was observed. Moreover, when adverse effects (hypoglycemia, GI disturbances, and weight gain) were considered, DPP4I was better tolerated [Table 3].[34,38‑41]

Currently, approved indications of DPP4Is and Metformin combination are:

- Adjunctive to diet and exercise, to enhance glycemic control in T2DM patients with insufficiently controlled diabetes with Metformin hydrochloride alone.[42,43]
- As triple combination therapy, in insufficiently controlled T2DM patients with Metformin and Sulfonylureas, in addition to diet and exercise.[43]
- An add-on to Insulin, to improve glycemic control, when adequate doses of Insulin and Metformin do not result in enough glycemic control.[42]

Patient-focused perspectives

Route of administration, adverse event profile, patient preference, and cost of therapy are factors considered for choosing adjunctive therapy. Considering safety, DPP4Is + Metformin combination is associated with minimal or no risk and thus effective in achieving better glycemic control and minimizing pill burden in T2DM.[44]

Pharmacoeconomic profile of DPP4Is compared to other second-line agents

As second-line therapy in T2DM, long-term cost-effectiveness of DPP4I + Metformin was compared with SU + Metformin and incremental cost-effectiveness ratio (ICER) was estimated using Markov model. Incremental cost of DPP4I + Metformin was found to be $11,849 with 0.61 incremental life-years gained compared to SU + Metformin resulting in an ICER of $19,420 per life-year gained.[45]

Other similar studies also demonstrated cost-effectiveness of DPP4Is as second-line therapies.[46‑49]

From the evidences, DPP4Is are preferred hypoglycemic agent for patients who are uncontrolled on Metformin monotherapy. Safety profile and cost-effectiveness analysis of DPP4Is + Metformin

| Study Drug | Baseline HbA1C | Mean diabetes duration | No. of patients (n) | Mean change from baseline (%) | Ref. no. |
|------------|----------------|------------------------|---------------------|-----------------------------|----------|
| Metformin 1,000 mg b.i.d. + Sitagliptin 100 mg b.i.d | 11.2% | 4.5 years, 4.5 years, | 117 | HbA1C reduction by -2.9% | [22] |
| Linagliptin 2.5 mg + Metformin 1,000 mg b.i.d. | 11.8% | ≤1 years 23, >1-5 years 23, >5 years 20 | 66 | HbA1C reduction by -3.7% | [26] |
| Metformin 500-2,000 mg b.i.d. + Saxagliptin 5-10 mg | ≥9.0% | 1.7-2.0 years, 1.7-2.0 years, 1.7-2.0 years, | 991 | HbA1C reduction by -1.7 to -2.5% | [27] |
| Sitagliptin/Metformin 50/500, 50/1000 mg bid, Metformin 500 mg bid | 9.9% | 3.3 years, 3.3 years, 3.3 years, | 1250 | HbA1C reduction by -2.4% for sitagliptin/metformin | [28] |
| Sitagliptin 100 mg once and Metformin 500 mg twice daily | 8.7% | 6.1 years, 6.1 years, 6.1 years, | 150 | HbA1C reduction by -1.5% for metformin | [29] |
| Tenegliptin 20 mg + Metformin 1000 mg | 8.0% | - | 450 | HbA1C reduction after 12 weeks -1.2%, after 24 weeks -1.6%, after 48 weeks -1.0% | [30] |
are comparable with other dual combination therapies. Combination of DPP4Is and Metformin results in reduction of HbA1c level below 7.5% in T2DM. Thus, specialists agreed that Indian patients with HbA1c >7.5% at diagnosis may be initiated on dual therapy of DPP4Is + Metformin. Mean consensus score achieved on the Likert’s scale was 7.00 ± 0.61 (Mean ± SEM) and hence, this statement was accepted.

Statement 3. In Indian diabetic patients having HbA1c > 7.5% at diagnosis, DPP4Is + Metformin may be considered as a 1st line therapy

RSSDI (2017) guidelines state dual combination therapy of DPP4Is + Metformin is more effective in reducing HbA1c (1%) than metformin monotherapy.[7] Moreover, ICMR (2018) guidelines for management of T2DM states, DPP4Is are first choice after SU and preferred over other OAD agents, when treating asymptomatic individuals with HbA1c >9%.[51,52]

DPP4Is are divided into peptidomimetics (Vildagliptin, Saxagliptin, and Teneligliptin) and non-peptidomimetics (Sitagliptin, Alogliptin, and Linagliptin).[81,82] Various DPP4Is + Metformin combinations, as dual therapy, are widely used and are available in India [Table 4].[53-56] A survey questionnaire involving 502 physicians and endocrinologists reported that 59.9% physicians preferred DPP4Is + Metformin. Additionally, DPP4Is (54%) are preferred choice of drugs than other OADs in T2DM patients not controlled on combination of SU + Metformin.[57]

DPP4Is + Metformin: FDC versus co-administered dual therapy: Efficacy and compliance

Bajaj et al. assessed HbA1c change in Fixed-dose combination (FDC) versus co-administered dual therapy (CDT) of DPP4Is + Metformin. Switching to FDC of DPP4 + Metformin was associated with significant improvement in HbA1c especially in patients with high pill burden.[58] American College of Physicians (ACP) practice guideline updated recommendation states that, combination treatment is superior to Metformin alone for decreasing A1c levels, weight, and blood pressure in T2DM.[17]

Comparison among various DPP4Is in terms of efficacy and selectivity

A study by Agrawal et al. observed no significant difference between Teneligliptin and other DPP4Is. Teneligliptin was equally efficacious to other available DPP4Is in maintaining HbA1c levels.[59]

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**Table 2: Clinical studies on DPP-4 Inhibitors + Metformin vs monotherapy**

| Study Drug | Baseline HbA1C/| Mean diabetes | Study duration | Key efficacy results | Ref. no. |
|------------|---------------|---------------|---------------|---------------------|----------|
|            | Fasting glucose | duration |           |                      |          |
| Vildagliptin 50 mg OD added to Metformin 2.1 g daily | 8.4%/9.7 mmol/l | 6 years | 24 weeks | HbA1C reduction by in Metformin alone - 0.2% Vildagliptin alone - 0.5% Combination - 0.9% Fasting glucose, Metformin alone - increased by 0.7 mmol/l Vildagliptin alone - reduced by 0.8 mmol/l Combination - reduced by 1.7 mmol/l Significant reduction in GI adverse events with combination | [32] |
| Sitagliptin 100 mg OD added to Metformin >1.5 g daily | 7.7%/8.4 mmol/l | 6.6 years | 4 weeks | Fasting glucose reduced by, Metformin alone - 0.4 mmol/l Combination - 1.3 mmol/l | [33] |
| Sitagliptin 100 mg OD or Placebo added to Metformin >1.5 g daily | 8.0%/9.5 mmol/l | 6.2 years | 24 weeks | Target HbA1C <7% reached by, 47% in combination group 18.3% in Metformin alone group | [34] |
| Sitagliptin 50 mg BD + Metformin 1,000 mg BD or Sitagliptin 50 mg BD + Metformin 500 mg BD or Metformin 1,000 mg BD or Metformin 500 mg BD or Sitagliptin 100 mg q.d. | 8.7% | - | 54 weeks (788 patients) | HbA1C reduction by, 1.7% in group 1 1.4% in group 2 1.3% in group 3 1.1% in group 4 1.2% in group 5 | [35] |
| Sitagliptin 100 mg + Metformin 500 mg BD (titrated to 50/1000 mg BD) vs Pioglitazone 15 mg (titrated to max. 45 mg daily) | 9.0% | - | 40 weeks (f/b extension of 50 weeks 517 patients) | Change in HbA1C from baseline to 40 weeks, Sitagliptin/Metformin: -1.7% Pioglitazone: 1.4% Proportion of patients achieving HbA1C <7% and <6.5% were, 55% with combination 31.2% with Pioglitazone | [36] |
| Sitagliptin 100 mg + Metformin OR Placebo + Metformin | 9.2%/200 mg/dl | - | 30 weeks | Patients on combination were more likely to achieve HbA1C <7% at week 18 and week 30 (p=0.012 and p<0.001) | [37] |
Figure 1: Glycemic Control Algorithm by AACE/ACE 2018 (Adapted from AACE/ACE 2018)
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Jayanthi et al. evaluated glycemic, non-glycaemic effects of Teneligliptin versus Sitagliptin. Statistically significant (p < 0.001) decrease in FBS and PPBS at week 8, week 12, and reduction in HbA1C, LDL-CH, TC from baseline in Teneligliptin group, as compared to Sitagliptin group was observed.[60]

In a study, Teneligliptin co-administered with Metformin monotherapy demonstrated dose-related and statistically significant (p < 0.001) reductions in HbA1C after 24 h, increased proportion of responders achieving HbA1C < 7.0% and maintenance of response throughout 28 weeks with Teneligliptin (20 mg).[61]

Data from real-world, retrospective study (Treat-India) suggests that Teneligliptin significantly (p < 0.001) improves glycemic control in T2DM patients, when prescribed either as monotherapy or in combination with Metformin compared with SU combination therapy.[62,63]

Cardiovascular safety of DPP4Is

Cardiovascular (CV) safety is the major focus of anti-diabetic therapy and it was mandated by USFDA in 2008 to establish cardiovascular safety of newer OADs. CV safety of DPP4Is is proved in several clinical trials. They reduce CV risk factors (weight gain and hypoglycemia).[64]

Multiple clinical trials (SAVOR-TIMI 53, EXAMINE, TECOS, CARMELINA) have evaluated the CV safety and efficacy of DPP4Is in patients with T2DM and reported improved glycemic control with DPP4Is and favorable CV safety as compared to placebo or other OAD agents.[65-69]

Safety profile of DPP4Is in T2DM patients with respect to QTc prolongation

Multiple studies have demonstrated significant reduction in FPG, PPBG and HbA1C with no significant effects on QT/QTc interval prolongation by Teneligliptin.[70,71]

A thorough QT/QTc study has shown no clinically significant QTc interval prolongation with 40 mg dose of teneligliptin as per data submitted to Pharmaceuticals and Medical Devices Agency, Japan.[72]

Pharmacoeconomic profile of various DPP4Is

Choice of DPP4Is is based on clinical characteristics of patient, inclination, insurance or paying capacity of patient, and existing co-morbidities. Cost of drugs and affordability of overall therapy are basis for decision making while selecting proper treatment option.[73] Average cost per day for DPP4Is was reduced to INR 9 after switching to Teneligliptin as observed in a cost effectiveness study.[79]
Table 4: DPP4Is plus Metformin dual combinations currently available and marketed in India

| Drug Combination | Brand Name   | Company Name               | Dose           | Ref. no |
|------------------|--------------|----------------------------|----------------|---------|
| Vildagliptin + Metformin | Galvus Met     | Novartis India (Mumbai, Maharashtra, India) | 50 mg + 500-1000 mg | [42]    |
| Sitagliptin + Metformin | Janumet XR | MSD Pharmaceuticals (Mumbai, Maharashtra, India) | 100 mg + 1000 mg | [43]    |
| Alogliptin + Metformin | Kazano       | Takeda Pharmaceutical Company (Mumbai, Maharashtra, India) | 12.5 mg + 500 mg | [53]    |
| Linagliptin + Metformin | Jentadueto   | Boehringer Ingelheim and Lilly (Mumbai, Maharashtra, India) | 2.5 mg + 500-1000 mg | [54]    |
| Saxagliptin + Metformin | Kombiglyze XR | Bristol Myers Squibb India Private Limited (Mumbai, Maharashtra, India) | 5 mg + 1000 mg | [55]    |
| Teneligliptin + Metformin | Zita Met Plus | Glenmark Pharmaceuticals (Mumbai, Maharashtra, India) | 20 mg + 500 mg | [56]    |

Based on these evidences, Teneligliptin is the most preferred DPP4I used in combination with Metformin in newly diagnosed T2DM patients as per efficacy, safety, and cost-effectiveness.

Based on results of various studies, DPP4Is co-administered with Metformin produce significant reductions in HbA1c (<7.5%) in T2DM without increasing risk of hypoglycemia and thus,
specialists agreed that this combination may be considered as first line therapy. Mean consensus score achieved on the Likert's scale was 7.09 ± 0.41 (Mean ± SEM) and hence, this statement was accepted.

**Advantages of Using Combination of DPP4Is and Metformin in T2DM**

- With distinct advantages of oral administration, weight neutrality, and no hypoglycemia, DPP4Is are recommended as second-line therapy, and as an alternative first line therapy when Metformin is contraindicated or not tolerated.[5,7]
- DPP4Is are also recommended as an add-on therapy to Metformin and as an add-on therapy to SU and Metformin, TZD and Metformin, Metformin plus Insulin and Insulin monotherapy in patients not adequately controlled on monotherapy or dual therapy.[8,6,7,43]
- DPP4Is carry an insignificant risk of hypoglycemia, when used as either monotherapy or combination therapy with Metformin.[9]
- DPP4Is and Metformin do not affect the pharmacokinetics of each other.[10]
- FDC of DPP4Is and Metformin allows physicians to modify treatment regimens of patients with inadequately controlled glucose levels without increasing pill burden.[44]
- DPP4Is + Metformin treatment is cost-effective as compared to SU + Metformin, as long-term second-line therapy in treatment of T2DM.[45]
- Availability of extended/sustained release FDC of Metformin with Teneligliptin results in fewer gastrointestinal adverse events and improved compliance as compared to immediate release metformin FDC formulations.[46,54,55,56]

**Conclusion**

Evidence from various studies revealed that majority of Indian T2DM patients have HbA1c level >7.5% at diagnosis. This expert opinion provides a comprehensive summary of existing clinical trials and best evidence for managing T2DM using a combination of DPP4Is + Metformin. The consensus was reached amongst specialists that at time of diagnosis, dual oral anti-diabetic therapy in the form of DPP4Is + Metformin needs to be initiated in patients with HbA1c >7.5%. Moreover, DPP4Is + Metformin is preferred option and may be considered as a 1st line therapy in Indian T2DM patients with HbA1c >7.5% at diagnosis. The consensus reached among specialists depicts best professional judgment and is based on currently available evidence and practical experience of specialists.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Davies MJ, D’Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, 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. International Diabetes Federation. Diabetes Atlas. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.
3. India State-Level Disease Burden Initiative Diabetes Collaborators. The increasing burden of diabetes and variations among the states of India: The Global Burden of disease study 1990-2016. Lancet Glob Health 2018;6:e1352-62.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. American diabetes association (ADA); European association for the study of diabetes (EASD). Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care 2012;35:1364-79.
5. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, et al. Prevalence of diabetes and prediabetes in 15 states of India: Results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol 2017;5:585-96.
6. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm-2018 executive summary. Endocr Pract 2018;24:91-120.
7. Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. Int J Diabetes Dev Ctries 2018;38(Suppl 1):1-115.
8. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American diabetes association and the European association for the study of diabetes. Diabetes Care 2015;38:140-9.
9. Yoshida S. Approaches, tools and methods used for setting priorities in health research in the 21st century. J Glob Health 2016;6:010507.
10. Sosale B, Sosale AR, Mohan AR, Kumar PM, Saboo B, Kandula S. Cardiovascular risk factors, micro and macrovascular complications at diagnosis in patients with young onset type 2 diabetes in India: CINDI 2. Indian J Endocrinol Metab 2016;20:114-8.
11. Nair M, Prabhakaran D, Venkat Narayan KM, Sinha R, Lakshmy R, Devanesanpathy N, et al. HbA (1c) values for defining diabetes and impaired fasting glucose in Asian Indians prim care diabetes. Prim Care Diabetes 2011;5:95-102.
12. Wani FA, Kaul R, Raina AA, Nazir A, Maqbool M, Bhat MH, et al. Prevalence of microvascular complications in newly diagnosed type-2 diabetes mellitus. Int J Sci Stud 2016;3:102-5.
13. Avogaro A, Delgado E, Lingvay I. When metformin is not enough: Pros and cons of SGLT2 and DPP-4 inhibitors as a second line therapy. Diabetes Metab Res Rev 2018;34:e2981.
14. U.S. Food and Drug Administration. FDA drug safety
communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR) [article online], 2016. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm505860.htm. [Last accessed 2018 Aug 11].

15. Brown DX, Evans M. Choosing between GLP-1 receptor agonists and DPP-4 inhibitors: A pharmacological perspective. J Nutrition Metab 2012;2012, Article ID 381713, 10 pages. https://doi.org/10.1155/2012/381713

16. Tran S, Retnakaran R, Zimman B, Kramer CK. Efficacy of glucagon-like peptide-1 receptor agonists compared to dipeptidyl peptidase-4 inhibitors for the management of type 2 diabetes: A meta-analysis of randomized clinical trials. Diabetes Obes Metab 2018;20:68-76.

17. Practice Guidelines. Type 2 diabetes mellitus: ACP releases updated recommendations for oral pharmacologic treatment. Ann Intern Med 2017;96:472-3.

18. Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: Is one approach more successful or preferable than the other? Int J Clin Pract 2014;68:557-67.

19. Ahren B. Novel combination treatment of type 2 diabetes DPP-4 inhibition+metformin. Vasc Health Risk Manag 2008;4:383-94.

20. Herman GA, Bergman A, Yi B, Kipnes M. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase 4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. Curr Med Res Opin 2006;22:1939-47.

21. Liu Y, Hong T. Combination therapy of dipeptidyl peptidase-4 inhibitors and metformin in type 2 diabetes: Rationale and evidence. Diabetes Obes Metab 2014;16:111-7.

22. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptide-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007;30:1979-87.

23. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linaclotide and metformin improves glycemic control in type 2 diabetes: A randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2012;14:565-74.

24. Amblee A, Liou S, Fogfeldt L. Combination of saxagliptin and metformin is effective as initial therapy in new-onset type 2 diabetes mellitus with severe hyperglycemia. J Clin Endocrinol Metab 2016;101:2528-35.

25. Matthews DR, Palaidius PM, Proot P, Chiang YT, Stumvoll M, Prato SD. 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;394:1519-9.

26. Haak T. Initial combination with linaclotide and metformin in newly diagnosed type 2 diabetes and severe hyperglycemia. Adv Ther 2012;29:1005-15.

27. Jazdinsky M, Pfutzner A, Paz-Pacheco E, Xu Z, Allen E, Chen R. Saxagliptin given in combination with metformin as initial therapy improves glycemic control in patients with type 2 diabetes compared with either monotherapy: A randomized controlled trial. Diab Obes Metab 2009;11:611-22.

28. Reasner C, Oalansky L, Seck TL, Williams-Herman DE, Chen M, Terranella L, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diab Obes Metab 2011;13:644-52.

29. Lim S, An JH, Shin H, Khang AR, Lee Y, Ahn HY, et al. Factors predicting therapeutic efficacy of combination treatment with sitagliptin and metformin in type 2 diabetic patients: The COSMETIC study. Clin Endocrinol (Oxf) 2012;77:215-23.

30. Chudasama DB, Saboo BD, Panchal D, Patel F, Saiyed M, Hasnani D, et al. The efficacy of teneligliptin with metformin in Drug-Naive type 2 subjects. Diabetes 2018;67(Supplement 1). doi.org/10.2337/db18-1205-P.

31. Ahren B, Gizris R, Standl E, Mills D, Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care 2004;27:2874-80.

32. Bosi E, Camisasca RP, Collober C, Rochette E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes in adequately controlled with metformin. Diabetes Care 2007;30:890-5.

33. Braze R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptide-4 inhibitor, to metformin on 24-h glycaemic control and β-cell function in patients with type 2 diabetes. Diabetes Obes Metab 2007;9:186-93.

34. Charbonnel B, Karasik A, Liu J, Wu M, Meiningen G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638-43.

35. Williams-Herman D, Johnson J, Teng R, Golm G, Kaufman KD, Goldstein BJ, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab 2010;12:442-51.

36. Pérez-Monterverde A, Seck T, Xu L, Lee MA, Sisk CM, Williams-Herman DE, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naive patients with type 2 diabetes. Int J Clin Pract 2011;65:3930-8.

37. Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, et al. Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin 2008;24:537-50.

38. Scott R, Loeys T, Davies MJ, Engel SS. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2008;10:959-69.

39. Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A, Gause-Nilsson I. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adults patients with type 2 diabetes mellitus. Diabetes Metab Res Rev 2010;26:540-9.

40. Bergenstal RM, Wysham C, Macconnell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. Lancet 2010;376:431-9.
noninferiority trial. Diabetes Obes Metab 2007;9:194-205.

42. G alv um e t® (V il dal glipt in/Me tfor m in Hydrochloride) [package insert]. Australia: Novartis Pharmaceuticals; 2018.

43. J anum et® XR (s itagliptin and metformin HCl extended-release) [package insert]. USA: Merck and Co., Inc. 2012.

44. St O nge E, Miller S, Clements E. Sitagliptin/ Metformin (janumet) as combination therapy in the treatment of type-2 diabetes mellitus. PT 2012;37:699-708.

45. Lorenzoni V, Baccetti F, Genovese S, Torre E, Turchetti G. Cost-consequence analysis of sitagliptin versus sulfonylureas as add-on therapy for the treatment of diabetic patients in Italy. Clinicoecon Outcomes Res 2017;9:699-710.

46. Bergenheim K, Williams SA, Bergeson JG, Stern L, Srirpasant M. US cost effectiveness of saxagliptin in type 2 diabetes mellitus. Am J Pharm Benefits 2012;4:20-8.

47. Kwon CS, Seoane-Vazquez E, Rodriguez-Monguio R. Cost-effectiveness analysis of metformin-dipeptidyl peptidase-4 inhibitors vs. metformin-sulfonylureas for treatment of type 2 diabetes. BMC Health Serv Res 2018;18:78.

48. Pérez A, Raya PM, de Arellano AR, Briones T, Hunt B, Valentine WJ. Cost-effectiveness analysis of incretin therapy for type 2 diabetes in Spain: 1.8 mg liraglutide versus sitagliptin. Diabetes Ther 2015;6:61-74.

49. Oishi TS, Ali NSS, Wingate LT. A cost-effectiveness analysis of dapagliflozin in comparison to dipeptidyl peptidase-4 inhibitors using a meta-analysis. Value Health 2015;18:A61.

50. ICMR Guidelines for Management of Type 2 Diabetes. New Delhi, 2018. p. 1-70.

51. Sharma SK, Panneerselvam A, Singh KP, Parmar G, Gadge P, Swami OC. Teneligliptin in management of type 2 diabetes mellitus. Diabetes Metab Syndr Obes 2016;9:347-53.

52. Gupta V, Kalra S. Choosing a gliptin. Indian J Endocrinol Metab 2011;15:298-308.

53. KAZANO (Alogliptin and Metformin HCl) [package insert]. Takeda Pharmaceuticals America, Inc.; 2013.

54. JEN TADUETO® (linagliptin and metformin hydrochloride) [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2017.

55. Kombiglyze XR. (Saxagliptin and Metformin HCl Extended-Release). NJ: Bristol-Myers Squibb Company Princeton; 2012.

56. Patil M, Jani HD, Khoja SS, Pirani NA, Khoja S. A review on chemistry and pharmacological activity of metformin hydrochloride and teneligliptin hydrobromide hydrate in combined dosage form. Pharma Tutor 2017;5:24-30.

57. Kumar PKM, Ingole S, Tamboli T, Bain R. Management of type 2 diabetes mellitus: Insights into prescribing trends. Int J Res Med Sci 2017;5:1306-11.

58. Bajaj HS, Ye C, Jain E, Venn K, Stein E, Aronson R. Glycemic improvement with a fixed-dose combination of DPP-4 inhibitor+metformin in patients with type 2 diabetes (GIFT study). Diabetes Obes Metab 2018;20:195-9.

59. Agrawal P, Gautam A, Purnsani N, Maheshwari PK. Teneligliptin: An economic and effective DPP-4 inhibitor for the management of type-2 diabetes mellitus: A comparative study. J Assoc Physicians India 2018;66:67-9.

60. Jayanthi CR, Subash A, Raveendra KR. Comparison of efficacy and safety of teneligliptin versus sitagliptin as add on to metformin in type 2 diabetes mellitus at a tertiary care hospital. Int J Res Pharmacol Pharmacothe 2017;6:208-17.

61. Bryson A, Jennings PE, Deak L, Pavliju FS, Lawson M. The efficacy and safety of teneligliptin added to ongoing metformin therapy in patients with type 2 diabetes: A randomized study with open label extension expert opin. Pharmacother 2016;17:1309-16.

62. Ghosh S, Trivedi S, Sanyal D, Modi KD, Kharb S. Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA study). Diabetes Metab Syndr Obes 2016;9:347-53.

63. Gadke PV, Gadke RP, Paralkar ND. Patients characteristics associated with better glycemic response to teneligliptin and metformin therapy in type 2 diabetes: A retrospective study. Int J Adv Med 2018;5:424-8.

64. Corneli S. Type 2 diabetes treatment recommendations update: Appropriate use of dipeptidyl peptidase-4 inhibitors. J Diabetes Metab 2014;5:8.

65. Mosenzon O, Raz I, Scirica BM, Hirshberg B, Stahre CI, Steg PG, et al. Baseline characteristics of patient population in the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus (SAVOR)-TIMI 53 trial. Diabetes Metab Res Rev 2013;29:417-26.

66. White WB, Heller SR, Cannon CP, Howitt H, Khunti K, Bergenstal RM. Alogliptin in patients with type 2 diabetes receiving metformin and sulfonylurea therapies in the EXAMINE trial. Am J Med 2018;131:813-9.e5.

67. Green JB, Bethel MA, Armstrong PW, Buse JB, Engsl SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42.

68. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA randomized clinical trial. JAMA 2019;321:69-79.

69. Seong JM, Choi NK, Shin JY, Chang Y, Kim YJ, Lee J, et al. Differential cardiovascular outcomes after dipeptidyl peptidase-4 inhibitor, sulfonylurea, and pioglitazone therapy, all in combination with metformin, for type 2 diabetes: A population-based cohort study. PloS One 2015;10:e0124287.

70. Erande S, Sawardekar S, Desai B, Suryawanshi S, Barkate H, Rathod A. QT/QTc safety and efficacy evaluation of teneligliptin in Indian type 2 diabetes mellitus patients: The thorough QT/QTc and RDQUO; study (Q-SET study). Diabetes Metab Syndr Obes 2019;12:961-7.

71. Mitra A, Ray S. Evaluation of the safety and efficacy of teneligliptin at a higher dose in Indian type 2 diabetes patients: A retrospective analysis. Cureus 2020;12:e6812.

72. Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare: Tenedia Tablets 20 mg; 2012. https://www.pmda.go.jp/files/000153594.pdf. [Last accessed 2020 Apr 4].

73. Munir KM, Lamos EM. Diabetes type 2 management: What are the differences between DPP-4 inhibitors and how do you choose? Expert Opin Pharmacother 2017;18:839-41.

74. Garber AJ, Handelsman Y, Grunberger G, Einhorn D, 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–2020 executive summary, Endocr Pract 2020;26:107-39.

75. Yang J, Tian Q, Tang Y, Shah AK, Zhang R, Chen G, et al. Effect of dipeptidyl peptidase 4 inhibitors used in combination with insulin treatment in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Ther 2020;11:2371-82.