Fixed-dose combination in management of type 2 diabetes mellitus: Expert opinion from an international panel

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Type 2 diabetes mellitus (T2DM) is a progressive disease with multifactorial etiology. The first-line therapy includes monotherapy (with metformin), which often fails to provide effective glycemic control, necessitating the addition of add-on therapy. In this regard, multiple single-dose agents formulated as a single-dose form called fixed-dose combinations (FDCs) have been evaluated for their safety, efficacy, and tolerability. The primary objective of this review is to develop practice-based expert group opinion on the current status and the causes of concern regarding the irrational use of FDCs, in Indian settings. After due discussions, the expert group analyzed the results from several clinical evidence in which various fixed combinations were used in T2DM management. The panel opined that FDCs (double or triple) improve patient adherence, reduce cost, and provide effective glycemic control and, thereby, play an important role in the management of T2DM. The expert group strongly recommended that the irrational metformin FDC’s, banned by Indian government, should be stopped and could be achieved through active participation from the government, regulatory bodies, and health ministry, and through continuous education of primary care physicians and pharmacists. In T2DM management, FDCs play a crucial role in achieving glycemic targets effectively. However, understanding the difference between rational and irrational FDC combinations is necessary from the safety, efficacy, and tolerability perspective. In this regard, primary care physicians will have to use a multistep approach so that they can take informed decisions.

**Keywords:** Fixed-dose combination, metformin, sulfonylureas, thiazolidinediones, type 2 diabetes

**Introduction**

As per the International Diabetes Federation (IDF), the percentage of people with type 2 diabetes mellitus (T2DM) is increasing globally.[1] Tight glycemic control is an important aspect of management of T2DM due to the progressive nature of the disease. Evidence suggests that aggressive glycemic control is beneficial not only for short-term, but also for the long-term well-being of patients.[2] Patients who do not tolerate metformin or who experience side effects of metformin monotherapy receive fixed-dose combinations (FDCs) of various other oral antidiabetic agents (OAD) including sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase (DPP-4) inhibitors, thiazolidinediones (TZDs), sulfonylureas (SUs), glucagon-like peptide-1 (GLP-1) antagonist, and basal insulin. The addition of the third agent can also be considered in order to enhance treatment efficacy.[3]

**Methodology**

At a two-day international meeting held in Delhi on 13th and 14th of April 2019, India, experts reviewed literature evidence, that was available from PubMed and Google Scholar and discussed the importance of the rational use of FDCs in the management of diabetes mellitus. The experts discussed the availability and status of FDCs in the US, Europe, and India. The key discussion points of the experts covering the clinical approach to FDCs in the management of T2DM, recommendations for using combination therapy in T2DM management, evidence on efficacy of FDCs in T2DM management, and measures to promote rational FDCs are summarized under ‘Panel Recommendations’. This document will provide guidance to primary care physicians for choosing rational combinations for persons with T2DM.

**Results**

**Rationale for use of fixed-dose Combination in type 2 diabetes mellitus management**

To achieve the glycemic target without side effects or tolerability issues, it is important to consider certain aspects of drug interactions when two drugs are administered as FDCs. The concurrent use of two or more drugs can affect the efficacy of one, or both. The outcome could be better than anticipated, or worse than expected or can result in an unanticipated toxicity too. The potential drug interactions can be described in different terms, such as summation, additive effect, synergism, and antagonism.[4]

The FDCs should be selected or combined based on three important aspects as indicated in Box 1.[5]

- **Box 1: Rationale for choosing fixed-dose combinations**[2][4]:
  - Drugs in combination should have different mechanisms of action.
  - The pharmacokinetics of drugs must not be too different from each other.
  - The combination should not have additives that can induce supra-additive toxicity.
  - The combination can be chosen based on the recommendations of treatment guidelines: whether the guidelines support its use or have raised any concerns.

FDC: Fixed-dose combination

**Merits and demerits of fixed-dose combinations**

In India, many clinicians recommend patients newly diagnosed with T2DM to start with FDCs for their multiple advantages. The regimen offers low pill burden, low risk of side effects, low cost, good patient compliance, thereby, contributes to improved efficacy. While appropriate use of FDCs is associated with several advantages, inappropriate use may lead to serious adverse effects. Advantages and disadvantages of FDCs are listed in Table 1.[7][8]

**Government regulations on fixed-dose combinations in India**

In India, FDCs are widely used and many such combinations are considered to be irrational. Many FDCs were produced without government approval. Many times, international drug regulators...
expressed concerns about the quality of FDC drugs in India. Box 2 lists some of the causes of concerns for the irrational use of FDCs in India.

### Banned fixed-dose combinations in India

The Health Ministry of Government of India banned 328 FDCs in 2018 to stop their irrational use. As per the list, 23 combinations that contained the antidiabetic drug metformin were banned in India [Table 2].

In order to avoid the irrational use of FDCs, a systematic clinical approach should be followed before initiating FDCs in T2DM management. We will discuss some important aspects of initiating combination therapy in India in the next section.

#### Clinical Approach to Fixed-Dose Combinations in Management of Patients with Type 2 Diabetes Mellitus

**Treating early and effectively with combination therapy**

Traditionally, T2DM is managed in a stepwise approach, which includes lifestyle modification, followed by a single-agent OAD, and then combination therapy. However, this approach has a number of limitations: (1) delays in achieving and maintaining glycemic targets; (2) difficulty in implementing this regimen in routine practice; and (3) delays in switching from monotherapy to combination therapy. These result in hypoglycemic episodes and increased risk of microvascular and macrovascular complications. Hence, a more proactive, early, and aggressive

### Table 1: Merits and demerits of FDCs

| Merits of FDCs                        | Demerits of FDCs                         |
|--------------------------------------|-----------------------------------------|
| Simpler dosage improves therapy     | No dosing flexibility                    |
| adherence and treatment outcome      |                                         |
| Reduced pill burden                  | Risk of drug interactions leading to     |
|                                     | altered therapeutic effect               |
| Reduced medication error             | Incompatible pharmacokinetics of        |
|                                     | individual components                    |
|                                     | (if the FDC is irrational)               |
| Allows drugs with synergistic        | Need to discontinue if a patient is     |
| combination                          | allergic to even one component of the   |
|                                     | FDC                                      |
| Low manufacturing and other costs    | FDCs may sometimes become               |
|                                     | expensive than single-dose tablets      |
| Simplified dosing with only one      |                                         |
| expiry date                          |                                         |

FDC: Fixed-dose combination.

### Table 2: Banned FDCs for diabetes

| 1. Metformin 1000 mg/1000 mg/500 mg/500 mg + pioglitazone 7.5 mg/7.5 mg/7.5 mg/7.5 mg + glimepiride ½ mg/½ mg |
| 2. Gliclazide 80 mg + metformin 325 mg |
| 3. Voglibose + metformin + chromium picolinate |
| 4. Pioglitazone 7.5 mg/7.5 mg + metformin 500 mg/1000 mg |
| 5. Glimepiride 1 mg/2 mg/3 mg + pioglitazone 15 mg/15 mg/15 mg + metformin 1000 mg/1000 mg/1000 mg |
| 6. Glimepiride 1 mg/2 mg + pioglitazone 15 mg/15 mg + metformin 850 mg/850 mg |
| 7. Metformin 850 mg + pioglitazone 7.5 mg + glimepiride 2 mg |
| 8. Metformin 850 mg + pioglitazone 7.5 mg + glimepiride 1 mg |
| 9. Metformin 500 mg/500 mg + glimepiride (sustained release [SR]) 30 mg/60 mg + pioglitazone 7.5 mg/7.5 mg |
| 10. Voglibose + pioglitazone + metformin |
| 11. Metformin + bromocriptine |
| 12. Metformin + glimepiride + methylcobalamin |
| 13. Pioglitazone 30 mg + metformin 500 mg |
| 14. Glimepiride + pioglitazone + metformin |
| 15. Glimepiride 2.5 mg + metformin 400 mg |
| 16. Pioglitazone 15 mg + metformin 850 mg |
| 17. Metformin (extended-release) + Gliclazide (modified release) + Voglibose |
| 18. Chromium polynicotinate + metformin |
| 19. Metformin + glimepiride + pioglitazone + chromium polynicotinate |
| 20. Metformin + glimepiride + chromium polynicotinate |
| 21. Glibenclamide + metformin (SR) + pioglitazone |
| 22. Metformin (SR) 500 mg + pioglitazone 15 mg + glimepiride 3 mg |
| 23. Metformin (SR) 500 mg + pioglitazone 5 mg |
Timing of administration of fixed-dose combinations with varying mode of action and adverse effects

In a bibliographic analysis, standard textbooks of pharmacology, endocrinology, and diabetology were reviewed to assess the details regarding the timings of administration, frequency, and dose of various oral and injectable antidiabetic drugs. The analysis highlighted the uniformity pertaining to information related to glipizide and glibenclamide in most of the books; however, conflicting suggestions with regard to the frequency of dosage of glimepiride was noted in the review. The timing of administration of glimepiride was not mentioned in many books. Leading Indian textbooks on diabetes mellitus, recommend prescribing all sulfonylureas 20–30 minutes before meals. Lack of consensus was observed about the maximum dosage of glimepiride prescribed in clinical practice; some books mentioned 8 mg while others suggested 6 mg of glimepiride as maximum dose.[12]

Sola D et al. suggests that sulfonylureas should be taken 30 minutes before meals to optimize their absorption; however, the prescribing information of various SUs suggests differently.[13]

A randomized, pilot study by Hashimoto Y et al. showed that taking metformin 30 minutes before meals improved postprandial hyperglycemia. Evidence from other studies suggest that the intake of metformin before meals reduces the quantity of insulin needed and improves early prandial GLP1. However, to avoid gastrointestinal adverse effects, metformin is advised during or post meals.[14] In a randomized, cross-over study, Rosak C et al. reported a significant increase in blood glucose levels, when acarbose was taken 30 minutes before meals and the smallest increment in blood glucose levels was noted when acarbose was taken at the beginning or 15 minutes after meals. Therefore, for better glycemic control, acarbose should be taken with meals.[15]

Evidence suggests the beneficial effects of FDC of acarbose and glibenclamide as it has an additive blood glucose-lowering effect and results in decreased hypoglycemia. The study compared the efficacy of the combination therapy of acarbose and glibenclamide with acarbose and glibenclamide monotherapy with regard to postprandial blood glucose, serum insulin, and C-peptide levels and the risk of developing hypoglycemia. The treatment was administered before breakfast. The treatment with the combination therapy of acarbose and glibenclamide was associated with significant reduction in postprandial blood glucose levels, serum insulin, and C-peptide levels vs. treatment with monotherapy. The reduced risk of hypoglycemia associated with combination therapy could be attributed to modification of glibenclamide-induced insulin secretion by acarbose.[16]

Pattern of prescription of fixed-dose combination therapy in India

An observational study conducted by Vyas et al. was based on the information collected on the prescriptions for FDCs for antihypertensive and antidiabetic drugs. The descriptive analysis indicated that combination therapy was recommended in about 91% of patients with diabetes. Around 76% of prescriptions favored two-drug therapy, while 15% were in favor of three-drug therapy. A high percentage of patients receiving combination therapy were indicative of uncontrolled glycemic levels, likely due to monotherapy. Also, the study reported that irrespective of single or combination therapy, biguanides were recommended to most patients.[17]

Recommendations for Using Combination Therapy in Type 2 Diabetes Mellitus Management

- IDF 2017 Recommendations for Dual and Triple Therapy
  The IDF has provided specific recommendations (2017) for dual therapy in T2DM management. As per the IDF recommendations[18):
  - A second glucose-lowering drug (GLD) should be added if monotherapy with metformin (or its replacement) is not sufficiently effective to reach the glycated hemoglobin A1c target or fails afterwards.
  - The best choice of add-on is an SU (except glibenclamide/glyburide), a DPP-4 inhibitor, or an SGLT-2 inhibitor. An alpha-glucosidase inhibitor can be used as well. A GLP-1 receptor agonist can be used if weight loss is a priority and the drug is affordable.
  - The primary care physician may consider the patient’s profile (age, body weight, complications, and duration of disease) when choosing the best GLD to add (Box 3).

- American Diabetes Association (ADA) 2020 Recommendations for Combination Therapy

  For triple therapy in diabetes, the International Diabetes Federation recommendations (2017) are as follows[19]:
  - A third GLD should be added if a combination of a GLD with metformin is not sufficiently effective to reach or maintain the HbA1c target.
  - The most common choice to add to two oral GLDs is basal insulin. A GLP-1 receptor agonist can be added instead, if weight loss has been insufficient.
  - Triple therapy with three oral GLDs may be effective before adding an injectable.
The American Diabetes Association (2019) recommendations detail that if the glycated HbA1c target is not achieved after approximately three months and the patient does not have atherosclerotic cardiovascular disease (CVD) or chronic kidney disease (CKD), a combination of metformin and any one of the following preferred six treatment options must be considered:

- Sulfonylurea
- Thiazolidinedione
- Dipeptidyl peptidase-4 inhibitor
- Sodium–glucose linked transporter-2 inhibitor
- Glucagon-like peptide-1 receptor agonist
- Basal insulin

Whereas, in case of T2DM patients with established CVD, the antihyperglycemic regimen should contain SGLT-2 inhibitors, or GLP-1 receptor agonists with demonstrated cardiovascular disease benefit; however, after evaluating drug-specific and patient-related factors.

**Availability and Status of Fixed-Dose Combinations**

Metformin is the most common component of FDCs for T2DM management. Commonly available dual FDCs contain metformin along with either of the drugs, such as glyburide, pioglitazone, rosiglitazone, sitagliptin, saxagliptin, and repaglinide. However, some dual combinations (rosiglitazone plus glimepiride) do not contain metformin [Table 3]. Commonly prescribed triple FDCs contain metformin, SU, and voglibose or pioglibose [Table 3]. The initiation of triple FDCs can offer several advantages, such as targeting multiple pathophysiological factors, improved glyemic control, reduced pill burden, and thus improved compliance.

**Available fixed-dose combinations in US and Europe**

The FDCs available in the management of T2DM are listed in Table 3.

**Evidence on Efficacy of Fixed-Dose Combinations in Type 2 Diabetes Mellitus Management**

We will review the clinical evidence on the safety and efficacy of FDCs in the management of T2DM.

**Efficacy of double fixed-dose combinations in type 2 diabetes mellitus management**

In the START study, the safety and efficacy of metformin in combination with glimepiride or sitagliptin in patients with T2DM was evaluated. This was an open-label, randomized, comparative, and multicenter study, which included a total of 305 patients with T2DM who were either drug-naïve or uncontrolled on metformin. The patients were randomized to receive glimepiride 1 mg or 2 mg/SR metformin 1000 mg once daily (glimepiride group, n = 202) or sitagliptin 50 mg/metformin 500 mg twice daily (sitagliptin group, n = 103) for 12 weeks. At 12 weeks, the mean reduction in HbA1c from baseline was significantly greater in the glimepiride group (2.2%) than in the sitagliptin group (1.2%).

**Table 3: Metformin containing fixed-dose combinations for type 2 diabetes management**

| Dual fixed-dose combinations of metformin and SU | Dual fixed-dose combinations of metformin and AGI |
|-----------------------------------------------|-----------------------------------------------|
| Metformin + SU (gliclazide, glipizide, glibizide, glimepiride) | Metformin + SU (glimepiride) + AGIs (voglibose) |
| DPP-4 (sitagliptin, linagliptin, saxagliptin, gemigliptin, tenviglipitin) | Metformin + SU (glimepiride) + glitazones (pioglitazone, rosiglitazone) |
| SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin) | DPP-4 (linagliptin) + SGLT2-inhibitor (empagliflozin) |
| Glitazones (pioglitazone, rosiglitazone) | |
| AGIs (voglibose, acarbose) | |
| DPP-4 (linagliptin) + SGLT2-inhibitor (empagliflozin) | |

**Triple fixed-dose combinations**

| Triple fixed-dose combinations of metformin, SU, and AGI |
|-------------------------------------------------------|
| Metformin + SU (glimepiride) + AGIs (voglibose) | Metformin + SU (glimepiride) + glitazones (pioglitazone, rosiglitazone) |

DPP-4: Dipeptidyl peptidase-4; FDC: Fixed-dose combination; GLP-1: Glucagon-like peptide-1; SU: Sulfonylurea; AGIs: Alpha-glucosidase inhibitors; SGLT2: Sodium–glucose cotransporter-2.
group (0.42%) vs. sitagliptin group (0.30%) (p = 0.001). Additionally, significant reduction was observed in FPG and PPG in the glimepiride group. The study concluded that the combination of glimepiride and metformin achieved better glycemic control vs. the sitagliptin and metformin combination.26

In a retrospective study by Mamza J et al., time to treatment failure between different classes of OADs was compared when used as second-line (add-on) treatments to metformin monotherapy at HbA1c ≥ 7.5%. Data on 20,070 patients who were newly treated with either of the OADs (SU, DPP4-inhibitor, or TZD) following metformin therapy failure were included in the study. The primary outcome evaluated the risk of dual therapy failure between treatment groups.27 The survival analysis (without adjusting for baseline covariates) showed that the incidence of failure of dual therapy at one year was the highest for patients who received DPP4-inhibitor (23%) followed by with SU (15%) and with TZD (8%). Moreover, there was an increase in the corresponding failure rates (26%, 38%, and 12%, respectively) at two years.27 Sulfonylurea added to metformin resulted in a 0.3% to 0.5% greater reduction in HbA1c vs. DPP4-inhibitor added to metformin, whereas TZD showed an irregular pattern of HbA1c reduction. The study concluded that in routine medical practice, a combination of DPP4-inhibitor and metformin needed early treatment intensification vs. metformin in combination with either SU or TZD.27

### Efficacy of triple fixed-dose combinations in type 2 diabetes mellitus management

In a nonrandomized, open-labeled, noncomparative, single-center, post-marketing surveillance study, the safety and efficacy of triple FDC of voglibose (0.2 mg), glimepiride (0.5 mg), and metformin (500 mg SR) were evaluated in 50 patients with T2DM. The patients were advised twice-daily administration of triple FDC after major meals for three months. Glycemic parameters, including HbA1c, FPG, and PPG, were assessed at baseline and after three months of treatment.28 The use of triple FDC of voglibose, glimepiride, and metformin in T2DM patients resulted in a significant reduction in HbA1c from baseline to three months after completion of treatment (10.62 ± 1.31 [baseline] to 6.62 ± 0.45 [three months after treatment], P < 0.0001). Furthermore, triple FDCs significantly reduced the glycemic parameters (FPG, PPG) from baseline to three months after treatment (FPG 208.30 ± 29.01 mg/dL vs. 118.10 ± 14.15 mg/dL, P < 0.0001) and PPG [360.10 ± 68.18 mg/dL vs. 168.40 ± 18.80 mg/dL, P < 0.0001].28

In an open-label, prospective, multicenter, randomized controlled, two-treatment arm clinical study, Bell et al. compared the efficacy of triple-FDC containing glimepiride (1 mg or 2 mg), metformin (500 mg sustained release), and pioglitazone (15 mg) with human insulin (70/30 mix), and 500 mg sustained release metformin in insulin-naïve Indian patients. One hundred and one patients were randomized to receive either of the regimen for 12 weeks. Glycemic parameters, including HbA1c, FPG, and PPG, were assessed at baseline and assessed by the end of the treatment.29 The primary endpoint showed a trend toward lower levels of HbA1c by week 12 in patients receiving triple FDC vs. insulin plus metformin (-1.33% vs. -0.83%; P = 0.059). Additionally, the number of patients achieving reduction in HbA1c by > 1% were significantly higher in the triple-FDC group (72.5%) vs. insulin group (22%) (p = 0.0001). The

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**Table 4: Fixed-dose combinations available in US and Europe in management of T2DM**

| Drug Class | Generic component: dose (mg); frequency | Availability in US (timing of administration of SUs) | Availability in Europe |
|------------|----------------------------------------|-----------------------------------------------|-----------------------|
| Metformin + sulfonylurea | Glyburide/metformin IR: 1.25/250, 2.5/500, 5/500; twice daily Glipizide/metformin IR: 2.5/250, 2.5/500, 5/500; twice daily | Available (Glyburide should be taken with breakfast or first main meal) (Glipizide should be administered approximately 30 minutes before a meal) | Not available |
| Metformin + meglitinide | Repaglinide/metformin IR: 1/500, 2/500; twice daily | Available | Not available |
| Metformin + DPP-4 inhibitor | Sitagliptin/metformin IR: 50/500, 50/1000; twice daily Saxagliptin/metformin XR: 5/500, 5/1000, 2.5/1000; once daily | Available | Available |
| Metformin + TZD | Pioglitazone/metformin IR: 15/500, 15/850; divided doses with meals Pioglitazone/metformin XR: 15/1000, 30/1000; once daily Rosiglitazone/metformin IR: 2/500, 4/500, 2/1000, 4/1000; divided doses with meals | Available | Available |
| TZD + sulfonylurea | Rosiglitazone/glimepiride: 4/1, 4/2, 4/4, 8/2, 8/4; once daily Pioglitazone/glimepiride: 30/2, 30/4; once daily | Available (Glimepiride should be taken with breakfast or the first main meal) | Available (Glimepiride should be taken shortly before or during a meal) |

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DPP-4: Dipeptidyl peptidase-4; FDC: Fixed-dose combination; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; IR: Immediate-release formulation; TZD: Thiazolidinedione; XR: Extended-release formulation.
reduction in PPG and FPG was significant but similar between both the groups (p = 0.05). The study concluded that triple FDC resulted in statistically superior reductions in HbA1c and participants stated that the combination was more tolerable than insulin and metformin regimen.

Measures to Promote Rational Fixed-Dose Combinations

Although the estimated number of FDCs available in India is over 6000, several reports, studies, and editorials have pointed out inadequate data as the reason for not being able to establish the safety and efficacy of these FDCs. Additionally, we do not have an authorized up-to-date database that can provide information on the efficacy, merit, sales turnover, and usage pattern. Hence, choosing the right FDCs can be equated to ‘a needle in a haystack.’ A multistep and multistakeholder approach is necessary to improve the rationality of prescribing FDCs. It is necessary to ensure good pharmacovigilance, a rationale to develop FDCs, good prescribing and pharmacy practices, active enforcement by regulators, and continuing medical education of medical and pharmacy students with regard to drug information.

Panel Recommendations

In the light of the above information, a panel of experts analyzed the results from various clinical evidence in which various fixed combinations were considered and the expert group arrived at a consensus to curb the irrational use of FDCs.

- Rationality of FDCs can be based on treatment guidelines for/against their use in the concerned disease(s).
- In 2013, the Central Drugs Standard Control Organization, Government of India, has set the policies for the approval of FDCs in India.
- The Health Ministry of Government of India banned 329 FDCs in 2018. As per the list, 27 combinations contained the antidiabetic drug metformin.
- The global average HbA1c level in patients with diabetes is 9.5%. The key reason for this uncontrolled HbA1c is the reluctance to increase ‘pill burden,’ because patients are concerned about the increased cost, change in convenience, and potential side effects that may be associated with increased pill burden.
- Combination therapy is a useful strategy in diabetes management. The addition of a low-dose noninsulin antidiabetic drug to monotherapy can improve drug efficacy by 80%.
- Fixed-dose combination has some advantages over individual therapy, such as increased patient adherence due to reduced complexity of dosing, greater efficiency, and, most importantly, cost advantages.
- Double FDCs, such as metformin and glimepiride combination provide better glycemic control with good durability vs. metformin and sitagliptin combination.
- Triple FDCs offer reduced pill burden, improved compliance, and better glycemic control.
- Triple FDC of metformin, SU, and voglibose targets fasting plasma glucose and postprandial glucose, and, thereby, improves all five components of the glycemic pentad.
- A multistep approach is required to prevent the authorization of irrational FDCs.

Conclusion

Because of the progressive nature of T2DM, first-line therapy often fails to provide effective glycemic control, necessitating the addition of add-on therapy. In this regard, FDCs can play a crucial role in achieving glycemic targets effectively. However, understanding the difference between rational and irrational combinations is necessary from the safety, efficacy, and tolerability perspective. Indian clinicians will have to use a multistep approach so that they can take informed decisions.

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