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Original Research Paper

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# COMBINE AND CONQUER:FIXED COMBINATION OF EMPAGLIFLOZIN AND LINAGLIPTIN TO EXISTING TYPE 2 DIABETES TREATMENT

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**ABSTRACT** The treatment of the most prevalent disease, Type 2 diabetes mellitus (T2DM), usually starts with monotherapy. Metformin is the most commonly preferred medication while starting the therapy. It is generally combined with lifestyle changes like dietary modifications and inclusion of physical activities in routine life to improve the Quality-of-Life of patients. However, many patients do not achieve the goal of glycemic control with monotherapy. Therefore, new medications are added to the therapy to gain better control over their blood sugar level and stop the disease's progression. Drugs with a newer mechanism of action and better safety profile are being developed. Linagliptin (Lina) and Empagliflozin (Empa) were approved for clinical use in adult T2DM patients in 2011 and 2014, respectively. Add-on therapy of these molecules to the existing monotherapy has shown improvements. When fixed-dose combination (FDC) of these two drugs was tested clinically, it was found to have several benefits like improved glycemic control, better weight management, fewer incidences of hypoglycemia, and overall improvement in Quality-of-Life of adult T2DM patients. The topic of initial combination therapy is an area of growing interest, and therefore several clinical trials are being conducted in various parts of the world. This review highlights the clinical findings of such clinical trials concerning the efficacy, safety, and tolerability parameters, which will help foster the new therapeutic regimen for better health outcomes in T2DM patients.

**KEYWORDS :** Type 2 diabetes mellitus, Metformin, Fixed-dose combination, Sodium-glucose co-transporter type 2 (SGLT2) inhibitor

## BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic disease prevalent worldwide, and its prevalence increases with age. [1] American Diabetes Association, together with the European Association for the Study of Diabetes, recommend a stepwise approach for T2DM treatment. Initial pharmacotherapy of T2DM starts with only one oral antidiabetic drug to achieve or maintain glycemic goals and lifestyle changes. [2] Metformin is the drug of choice while starting a pharmacotherapy for T2DM. [3] Although metformin is the most popular monotherapy drug for T2DM, some patients need add-on therapy as the second line of treatment. Patients often cannot tolerate thiazolidinedione or sulfonylurea type of drugs, or these drugs may be contraindicated. Some adult T2DM patients do not achieve the goal of glycemic control with single-drug treatment. Therefore, clinicians want to modify the treatment and add more drugs to the therapeutic regimen to arrest disease progression and prevent complications from worsening the disease.

Thus, clinicians often prefer dual or triple-drug combination therapy to achieve better glycemic control. [4] In such cases, randomized clinical trials are essential to provide the highest level of evidence in real-life settings with respect to safety, tolerability, and therapeutic efficacy. However, there is a possibility of variations in observations as considerable heterogeneity exists in the diabetes population. Therefore, it is desirable to review the data available worldwide before clinicians can start prescribing such combination therapy for a chronic disease. Generally additional one new drug will be introduced in the monotherapy and will be monitored for therapeutic outcomes. Sometimes, clinician's inertia to avoid change in therapy may delay the progress leading to the failure of monotherapy and prolonged hyperglycemia. [5] This may lead to increased risk of microvascular complications and reduction in patient's Quality-of-Life. [4]

Considering these facts, a new trend in the treatment pattern is using two-drug combinations in fixed-dose amounts with complementary mechanisms of action. This helps reduce the risk of hypoglycemic incidences and gives better control over the therapy.

Empagliflozin (Empa) and linagliptin (Lina) fixed-dose combination (FDC) is approved in the United States and Europe for the treatment of T2DM. [6] Empa is a sodium-glucose co-transporter type 2 (SGLT2) inhibitor. Therefore it inhibits the reabsorption of glucose into the systemic circulation and facilitates its excretion. Lina is a dipeptidyl peptidase (DPP)-4 inhibitor and stimulates insulin release. Being complementary mechanisms of action, these two drugs are used in combination. [2] Additionally, this add on therapy is very convenient as it needs only once-day administration. [2]

### Evidence-Based Benefits

Since the introduction of Empa-Lina-FDC as an adjunct therapy in the management of T2DM, several clinical trials have been carried out worldwide to evaluate the pharmacological efficacy and tolerability. This review summarises the clinical findings of these studies. This will help clinicians to understand the clinical effects and the metabolic risk factors for prescription purposes.

### Clinical Trial In Indian Patients

A study in a T2DM population of the Indian outpatient setting

was retrospectively evaluated. A total of 986 patients was screened for recruiting in the study. Only 347 patients (Male: 49%, Female: 51%, mean age:57.8 years, and average body weight: 79.8kgs). [7] These patients took Empa 25 mg and Lina 5 mg for more than a month. They were monitored for three months for various blood biochemistry and other health parameters.

Over three months, there was a significant lowering in mean values of HbA1c (-1.1 mg/dl), fasting blood glucose level (-47.11 mg/dl), postprandial glucose level (-71.32 mg/dl), body weight (-2.64 kg), and blood pressure (systolic BP -7.68 and diastolic -3.16) from baseline. The estimated glomerular filtration rate was improved and sustained over the study duration. This study did not analyze safety and tolerability outcomes as an additional outcome measure. [7]

### Clinical Trials In Japanese Patients

A study was performed at 40 sites in Japan that compared the therapy of Empa and Lina FDC (10 and 5 mg) with a combination of Lina (5 mg) and placebo in T2DM patients. [8] This study measured efficacy, safety, and tolerability. More patients with HbA1c < 7.0% and more significant decreases in fasting plasma glucose, body weight, and systolic blood pressure were seen in the Empa and Lina FDC group. The treatment was well tolerated, although few adverse events were observed which were known to be associated with Empa. No diabetic ketoacidosis events or lower limb amputations were reported in this study. This study supported the FDC of Empa and Lina as a therapeutic option for Japanese T2DM patients. [8]

Another placebo-controlled trial in Japanese patients with T2DM showed that adding Lina 5 mg to Empa 10 or 25 mg as an FDC formulation resulted in significantly more significant decreases in HbA1c after six months compared to monotherapy, and this effect was sustained for a year. [6]

### Global Clinical Trials

In a multicentre randomized trial at 90 different sites in 10 countries, including Australia, Brazil, Canada, France, Korea, New Zealand, Norway, Spain, Taiwan, and the U.S. [9] This study compared the efficacy and safety of Empa in patients (n = 333) taking Lina and metformin and having poor glycemic control. Empa was tested at two dose levels, 10 and 25 mg, for six months and showed statistically significant and clinically relevant improvements in mean HbA1c and fasting blood glucose levels. [9] Patients received benefits of weight loss and a low risk of hypoglycemia. The triple-drug therapy was well tolerated, and few adverse events were reported in patients who received a higher dose of Empa (25 mg). The addition of Empa to Lina and metformin provides a valuable treatment option as add-on therapy for patients with inadequate glycemic control with dual drug therapy. [9]

Another study was conducted in 197 centers in 22 countries to evaluate the efficacy and safety of a once-daily Empa and Lina FDC as an add-on to metformin in T2DM patients (n=686).

In the case of polytherapy, adherence of the patient to the prescribed regimen is a significant predictor of clinical outcomes. Generally, patients' compliance to the therapy decreases when they have to take more medications. A study of T2DM patients showed that patients were less satisfied and were four times less likely to adhere to the prescribed therapy as the number of tablets increased. Such noncompliance results in failure of treatment. [10] Therefore, a clinical trial was carried out in which three drugs were combined in one tablet. The therapy of these combined tablets was compared with that of individual drug tablets given separately. The medications were given to healthy adult male and female human volunteers in a two-way cross-over design. Results indicated that the formulations were bioequivalent as observed from the pharmacokinetic data, and also, there were no safety concerns raised. This study signifies the importance of combining multi-drugs in a single formulation to improve patient compliance without compromising the pharmacokinetic profiling. [11] However, a similar analysis should also be performed in T2DM patients to get real-time data.

To summarise, the retrospective analysis of data obtained from several randomized controlled trials indicated many potential benefits with add-on FDC with initial metformin therapy over metformin monotherapy. Figure 1 summarizes the benefits of add-on FDC therapy to monotherapy in the case of T2DM patients.

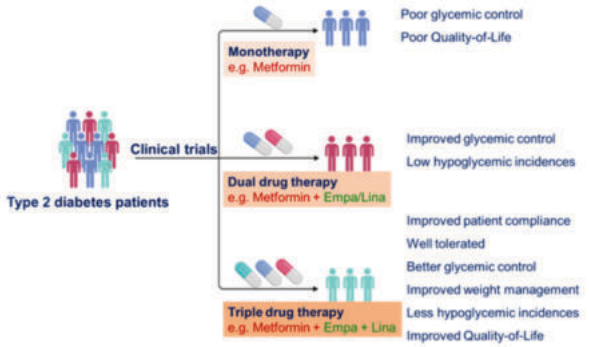


**Figure 1.** Benefits of add-on FDC of Empa and Lina to monotherapy for managing T2DM (triple-drug therapy).

## CONCLUSIONS

Unfortunately, despite the plethora of effective and safe antidiabetic medicines, almost half of adult T2DM patients fail to achieve control over their blood sugar levels. The problem can be easily overcome by using the FDC of Empa and Lina as an add-on therapy to metformin. It has been observed that such add-on therapy is generally well tolerated and also reduces the risk of frequent hypoglycemia. But there is always inertia from both patients and clinicians due to concerns related to efficacy, safety, fear of side effects, and cost of therapy. Therefore, there is a need to demonstrate a paradigm shift in the management of T2DM by long-term clinical trials comparing various initial combination therapies with the traditional stepwise approach. Several local and global clinical trials in T2DM patients have proved that add-on therapy provided sustained control over the blood sugar levels and HbA1c. Patients also get the additional benefits of reduction in extra body weight. Combination therapy has also provided some cardiovascular and renal benefits. In terms of adverse events, the incidences were similar to those observed with the individual drug therapy when given as a monotherapy.

Therefore, promoting a new pharmacotherapy strategy that includes the use of FDC will make treatment of T2DM more simple and will also contribute to improving clinical outcomes and will also help improve the Quality-of-Life of T2DM patients.

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