MEDICO RESEARCH CHRONICLES
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2022.9.2.586
Contents available at www.medrech.com

EMPAGLIFLOZIN, LINAGLIPTIN, AND METFORMIN IN A TRIPLE FIXED-DOSE COMBINATION FOR INDIVIDUALS WITH TYPE 2 DIABETES

Dr. C. B Prasad[1], Dr. Deepak Mahendru[2], Dr. Ganesh Dahiwal[3], Dr. Jugal Bihari Gupta[4], Dr. Jom Jacob Nellisserry[5]

1. General Physiscian, Hospital Road, Sitamadhi 843302, Darbhanga
2. General Physician, Kalyani Hospital, Yamunanagar,135001
3. Consultant Physician, Plot no 25 Nandigram Colony,Gajnan Maharaj Mandir, Essar Petroleum Pundlik, Nagar Road Garkheda, Aurangabad -431009
4. General Medicine. Plot No 53, Jawahar Colony, Tonk Road, Jaipur -302015
5. Daibetologist, Bishop Alappatt Mission Hospital Kattoor, Thrissur 680702

ARTICLE INFO | **ABSTRACT** | **ORIGINAL RESEARCH ARTICLE**

Article History
Received: March 2022
Accepted: April 2022

Corresponding author
Dr. C. B. Prasad*

2022, www.medrech.com

INTRODUCTION

As per the International Diabetes Federation (IDF), the percentage of patients with type 2 diabetes mellitus (T2DM) is increasing globally. [1]

Tight glycemic control is a crucial aspect of the management of T2DM due to the progressive nature of the disease. Evidence advises that aggressive glycemic control is beneficial not only for the short-term but also for the long-term well-being of patients. Due to the progressive nature of T2DM, first-line therapy often fails to provide effective glycemic control, necessitating the addition of add-on therapy. Hence, FDCs can play a crucial role in achieving glycemic targets effectively. Also, patients who are unable to 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 to enhance treatment efficacy. [1]

The initiation of triple FDCs can offer numerous advantages, like targeting multiple pathophysiological factors, improved glycemic control, reduced pill burden, and thus improved compliance. [1,2]

Combination of Empagliflozin and Metformin Therapy

The administration of empagliflozin plus metformin as initial combination therapy in patients with T2DM has been assessed in a

dedicated clinical trial, in addition to numerous studies of empagliflozin administration as an add-on to metformin, either alone or in addition to other agents as summarized in Table 1. [2]

The FDA approved the single-pill combination of empagliflozin, and metformin was based on pharmacokinetic analyses in healthy subjects that compared the single-pill combination with coadministration of individual tablets of empagliflozin and metformin. [2]

In a phase 3 study, the efficacy and safety of initial combination therapy was assessed versus the monotherapies in drug-naïve patients with HbA1c >7.5% to ≤12.0%. At week 24, adjusted mean reductions in HbA1c from baseline were significantly greater for patients receiving empagliflozin/metformin twice daily compared to those receiving either empagliflozin once daily ($P < .001$) or metformin twice daily ($P < .01$). At week 24, significantly greater proportions of patients treated with combination therapy reached HbA1c <7.0% versus patients who received either agent alone ($P < .05$ for all comparisons). The reduction in adjusted mean body weight from baseline to week 24 in the empagliflozin/metformin groups was greater than that achieved with either agent alone ($P < .001$ for all combination groups vs both metformin dose groups). Additionally, empagliflozin/metformin significantly reduced both systolic BP (SBP) and diastolic BP (DBP) versus metformin alone (adjusted mean differences in changes from baseline for the combination vs metformin alone: −2.8 to −4.0 mm Hg for SBP and −1.9 to −2.3 mm Hg for DBP; all comparisons $P < .05$), but not compared with empagliflozin alone. Hence, combination therapy was well tolerated, and the improvements in glycemic control vs monotherapies were achieved without significant increases in the risk of hypoglycemia. [3]

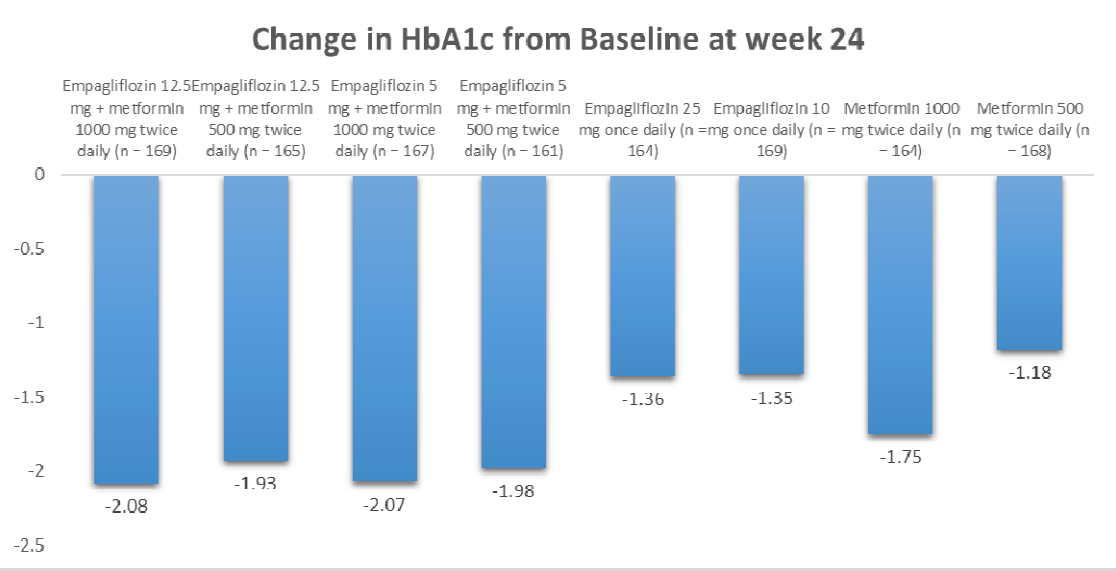
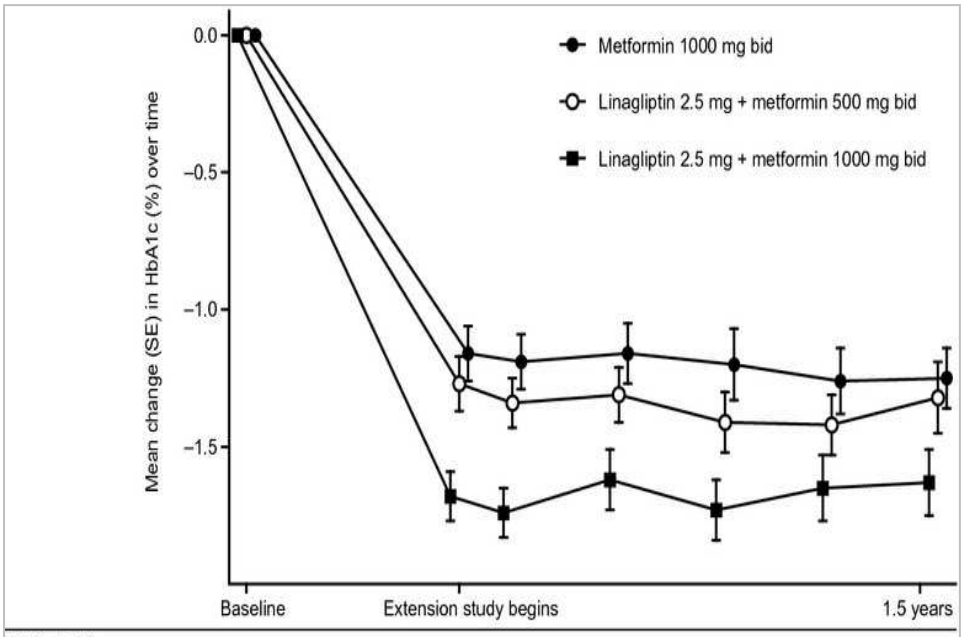


Figure 1 : Change in HbA1c from Baseline to week 24

Combination of Linagliptin and Metformin

1-year randomised, double-blind study that was the extension of a 6-month randomised controlled trial was carried out, in adults with type 2 diabetes in which patients received one of six treatment regimens (linagliptin 2.5 mg plus metformin 500 mg bid, linagliptin 2.5 mg plus metformin mg 1000 bid, metformin 1000 mg bid, metformin 500 mg bid, linagliptin 5 mg qd or placebo). In the extension, patients in the first three treatment groups continued their regimen (non-switched group, n = 333) whereas the metformin 500 mg bid, linagliptin 5 mg qd, and placebo groups were re-randomized to one of the three continuing regimens (switched group, n = 233). [4]

All three non-switched groups maintained reductions in glycosylated haemoglobin (HbA1c; mean ± standard deviation reductions across the 1.5-year period: linagliptin 2.5 + metformin 1000 bid, –1.63 ± 1.05%; linagliptin 2.5 + metformin 500 bid, –1.32 ± 1.06%; metformin 1000 bid, –1.25 ± 0.91%) while the switched groups reported additional HbA1c reductions. During the extension, there were no clinically meaningful changes in body weight in any group. Adverse event rates were similar between groups, with most events being mild or moderate, and the incidence of investigator-defined hypoglycemia was low, with no severe events. [4]



Patients (*n*)							
Met 1000 mg	109	105	102	90	81	74	66
Lina 2.5 mg + met 500 mg	113	113	103	92	81	73	66
Lina 2.5 mg + met 1000 mg	111	111	108	95	87	84	78

Figure 2 : Mean change in HbA1c in the non-switched set. Bid, twice daily; lina, linagliptin; met, metformin; SE, standard error.

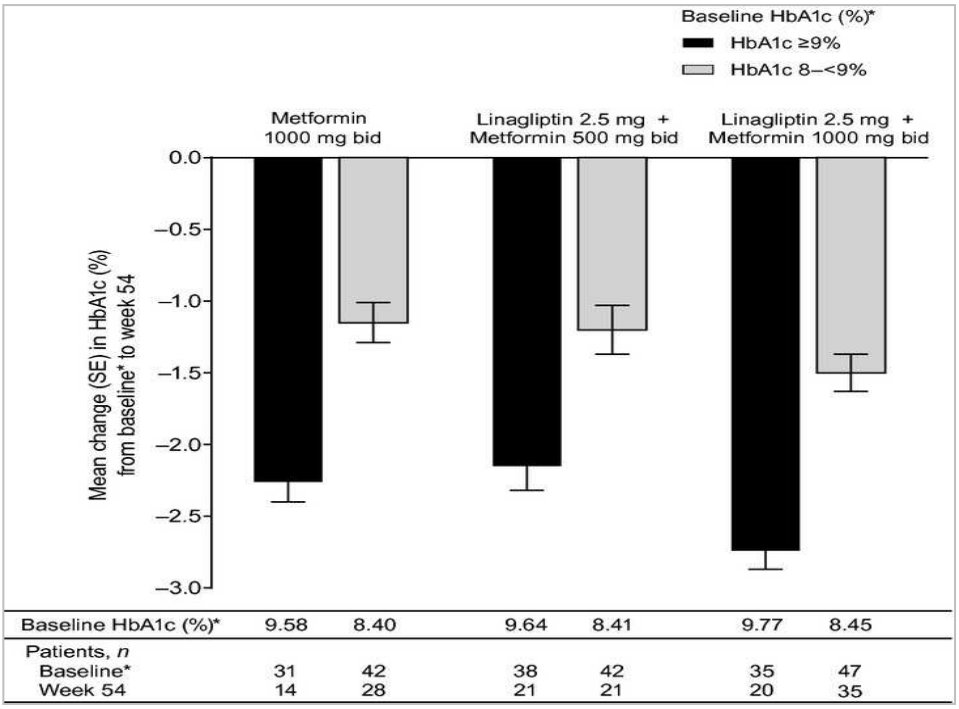


Figure 3: Mean change in HbA1c at week 54 by baseline HbA1c in the non-switched set. Bid, twice daily; SE, standard error.

Hence, initial combination of linagliptin and metformin was well tolerated over the 1-year extension period, with low risk of hypoglycaemia, as well as improved glycaemic control vs. metformin alone. [4]

Initial combination therapy may be beneficial in treating T2DM, as it targets the numerous pathophysiologic defects early. In a 24-week study, 791 patients were randomized to one of the six treatment regimens: (1) linagliptin 2.5 mg plus metformin 500 mg BID, (2) linagliptin 2.5 mg BID plus metformin 1000 mg BID, (3) metformin 1000 mg BID, (4) metformin 500 mg BID, (5) linagliptin 5 mg QD, or (6) placebo. Mean placebo-corrected reductions in HbA1c were -1.7% (linagliptin + high-dose metformin), -1.3% (linagliptin + low-dose metformin), -1.2% (high-dose metformin), -0.8% (low-dose metformin), and -0.6% (linagliptin). Hence, initial combination therapy with linagliptin plus metformin was superior to metformin or linagliptin monotherapy with respect to efficacy and had a comparable safety profile. Subgroup analyses of placebo-corrected HbA1c change by baseline HbA1c. [5]

Table 1. Adjusted placebo-corrected mean change in HbA1c at week 24 by hba1c category at baseline in randomized patients and open-label arm patients

HbA_{1c}	MEAN CHANGE IN HbA_{1c}, % (n)					
	LINA 5 mg QD	MET 500 mg BID	MET 1000 mg BID	LINA 2.5 mg + MET 500 mg BID	LINA 2.5 mg + MET 1000 mg BID	OPEN-LABEL ARM*
<8.5%	−0.37 (66)	−0.75 (68)	−1.01 (74)	−1.18 (63)	−1.47 (66)	–
8.5% to <11%	−0.77 (69)	−0.78 (73)	−1.37 (64)	−1.49 (74)	−1.93 (74)	–
≥11%	–	–	–	–	–	−3.7 (66)

Notes: *Patients in the open-label arm were

treated with linagliptin 2.5 mg + metformin 1000 mg BID: observed cases (n = 48). Abbreviations: bid, twice daily; hba1c, glycated hemoglobin; lina, linagliptin; Met, metformin; Qd, once daily

Triple fixed-dose combination empagliflozin, linagliptin, and metformin for patients with type 2 diabetes

A new FDC of extended-release metformin (metformin XR) plus an SGLT2 inhibitor, empagliflozin, and a DPP-4 inhibitor, linagliptin, has recently been assessed and approved by the FDA for the treatment of T2D. These agents are desirable choices for patients needing glucose lowering with multiple agents, in line with recommended treatment options for treatment intensification for T2DM. [6]

Two recently completed studies evaluated the bioequivalence of the highest and lowest doses of the FDC tablets in relation to the corresponding free combinations of tablets. Studies have previously been published to demonstrate the safety and efficacy of the combination of empagliflozin, linagliptin, and metformin in patients with T2DM.[6]

Two randomized, open-label, two-way crossover studies were conducted in healthy adults compared: 2 FDC tablets of empagliflozin 5 mg/linagliptin 2.5 mg/metformin XR 1000 mg (Study 1; N = 30), 1 FDC tablet of empagliflozin 25 mg/linagliptin 5 mg/metformin XR 1000 mg (Study 2; N = 30) versus corresponding dose of free combinations. Subjects received study medication under fed conditions; washout was ≥35 days between treatments. [6]

The studies reported that the evaluated doses of empagliflozin/linagliptin/metformin XR FDC tablets were bioequivalent to the corresponding free combinations. Based on these two bioequivalence studies and existing phase 3 data, the FDA has recently approved this triple FDC to improve glycemic control in adults with T2D. [6]

Four different tablet strengths of the FDC tablet have recently been approved by the FDA (January 2020).

Table 2. Approved doses of FDCs of empagliflozin/linagliptin/metformin XR

	Dose (mg)			
FDC	Empagliflozin	Linagliptin	Metformin XR	Recommended administration
1	25	5	1000	One tablet daily
2	12.5	2.5	1000	Two tablets daily
3	10	5	1000	One tablet daily
4	5	2.5	1000	Two tablets daily

FDC = fixed-dose combination.

A study of 333 patients with T2D evaluated empagliflozin as add-on therapy to linagliptin plus metformin over 24 weeks. Participants with inadequate glycemic control on metformin plus open-label linagliptin for 16 weeks were randomized to receive an FDC of empagliflozin 10 mg/linagliptin 5 mg, an FDC of empagliflozin 25 mg/linagliptin 5 mg, or placebo/ linagliptin 5 mg, as add-on therapy to metformin. The addition of either dose of the FDC of empagliflozin/linagliptin to metformin was associated with significant improvements ($p < 0.001$) from baseline in HbA1c at Week 24 compared with those who received placebo/linagliptin plus metformin, and the treatment was well tolerated.

At week 24, empagliflozin significantly reduced HbA1c (mean baseline 7.96–7.97% [63–64 mmol/mol]) compared to placebo; the adjusted mean differences in the change from baseline with empagliflozin 10 and 25 mg versus placebo were −0.79% (95% CI –1.02, –0.55) (−8.63 mmol/mol [–11.20, –6.07 mmol/mol]) and −0.70% (95% CI –0.93, –0.46) (−7.61 mmol/mol [–10.18, –5.05 mmol/mol]), respectively (both P < 0.001). Fasting plasma glucose and weight were significantly reduced in both empagliflozin groups compared to placebo (P < 0.001 for all comparisons). More patients receiving placebo than empagliflozin 10 and 25 mg demonstrated adverse events during double-blind treatment (68.2%, 55.4%, and 51.8%, respectively).

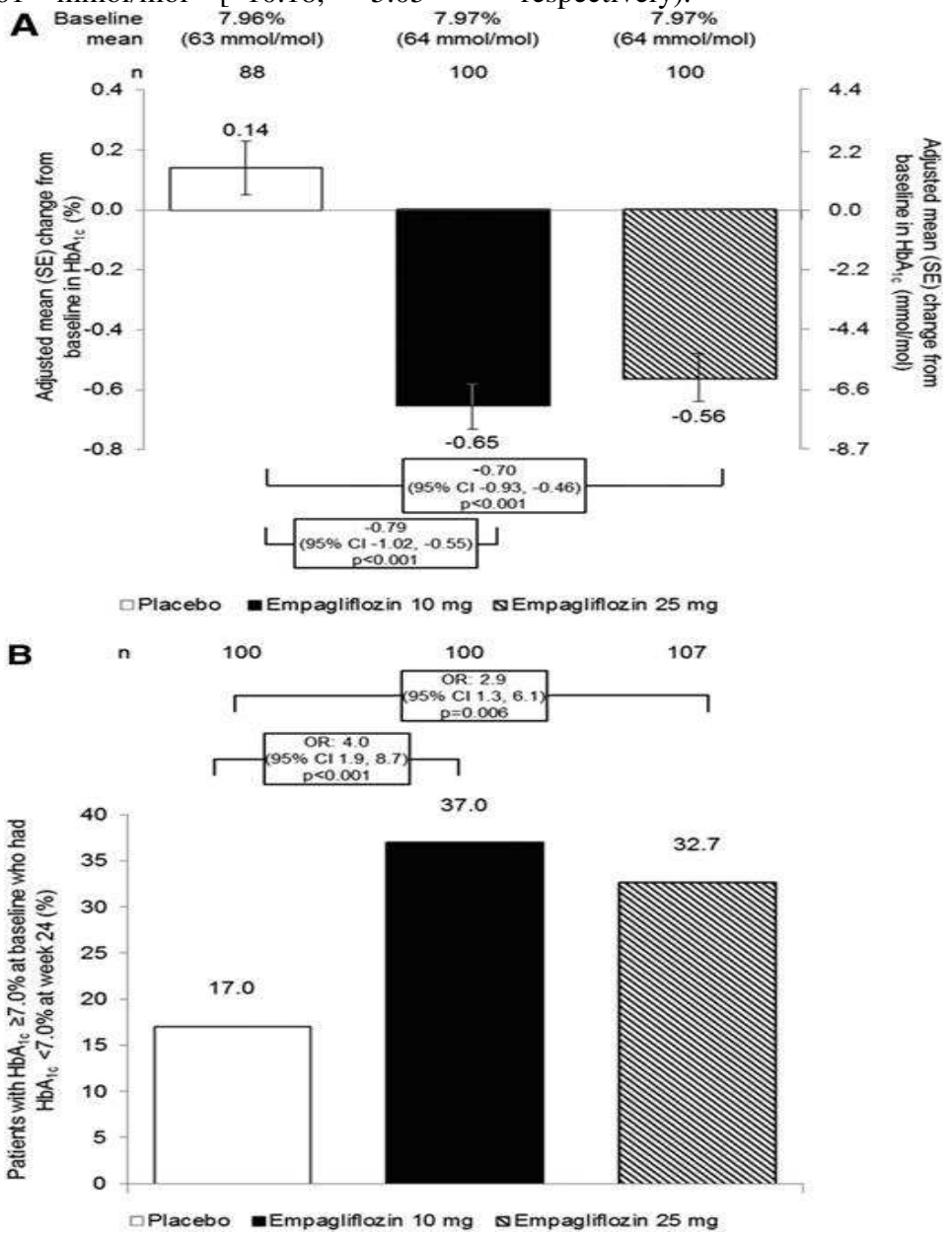


Figure 4: Efficacy parameters: HbA1c. A: Change from baseline in HbA1c at week 24 (MMRM in FAS using OC). B: Patients with HbA1c ≥7.0% (≥53 mmol/mol) at baseline who reached HbA1c <7.0% (<53 mmol/mol) at week 24 (logistic regression analysis in FAS using non-completers

considered failure). Data are adjusted mean ± SE or percentage. n, number of patients with data at week 24. Treatment differences and odds ratios (ORs) are presented as empagliflozin compared with placebo.

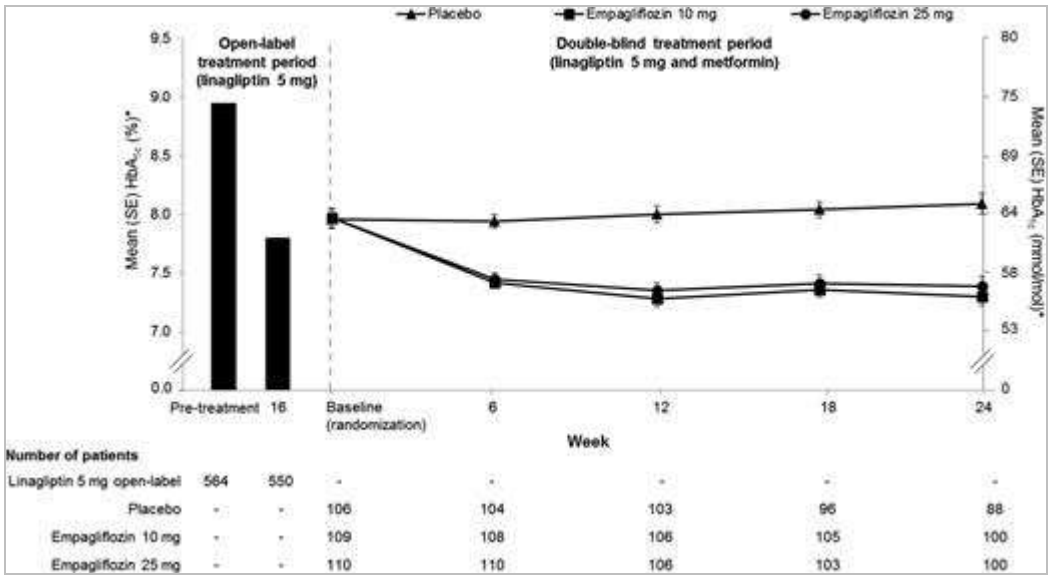


Figure 5 : HbA1c over time (mixed-model repeated measures (MMRM) in full analysis sets (FAS) using observed cases (OC)). *Data are adjusted mean ± SE, except for linagliptin open-label data, which are unadjusted mean. n, number of patients with data at week 24. Hence, empagliflozin treatment for 24 weeks improved glycemic control as well as weight versus placebo as an add-on to linagliptin 5 mg and metformin and was well tolerated.

SUMMARY

The triple FDC may be an apt option across a range of patients, including those with established ASCVD or indicators of high risk, established Heart Failure, or Chronic Kidney Disease due to the tolerability of the combination in addition to the potential benefits of empagliflozin on CV and renal outcomes, and no increased risk of heart failure with either agent. Patients with T2D may be at risk of nonadherence due to the complexity of treatment with multiple medications for the condition, in addition to the need for treatments for comorbid conditions, and the requirement for self-care activities (i.e., diet, exercise, foot care, blood glucose monitoring), the use of an FDC therapy could simplify individual treatment regimens for T2D and reduce the risk of nonadherence. Hence, this approach has the potential to increase the number of patients adhering to treatment and achieving their glycemic targets, which could translate into a lower long-term risk of complications of T2D, including micro-and macrovascular disease.

REFERENCES

1. Kalra S, Das AK, Priya G, Ghosh S, Mehrotra RN, Das S, et al. Fixed-dose combination in the management of type 2 diabetes mellitus: Expert opinion from an international panel. J Family Med Prim Care 2020; 9:5450-7.
2. Böhm AK, Schneider U, Aberle J, Stargardt T. Regimen simplification and medication adherence: Fixed-dose versus loose-dose combination therapy for type 2 diabetes. PLoS One. 2021;16(5):e0250993. Published 2021 May 4. doi: 10.1371/journal.pone.0250993
3. Goldman JD. Combination of Empagliflozin and Metformin Therapy:

A Consideration of its Place in Type 2 Diabetes Therapy. Clinical Medicine Insights: Endocrinology and Diabetes. January 2018. doi:10.1177/1179551418786258

4. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. The initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomized, double-blind 1-year extension study. Int J Clin Pract. 2013;67(12):1283-1293. doi:10.1111/ijcp.12308
5. Haak. Combination of linagliptin and Metformin for the Treatment of Patients with type 2 diabetes. Clinical Medicine Insights: Endocrinology and Diabetes 2015:8 1–6 doi:10.4137/CMED.S10360.
6. Lingvay, I., Beetz, N., Sennewald, R., Schuler-Metz, A., Bertulis, J., Loley, C.,Terada, D. (2020). Triple fixed-dose combination of empagliflozin, linagliptin, and metformin for patients with type 2 diabetes. Postgraduate Medicine, 1–9. doi:10.1080/00325481.2020.1750228
7. Søfteland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial. Diabetes Care. 2017 Feb;40(2):201-209. doi: 10.2337/dc16-1347. Epub 2016 Dec 2. PMID: 27913576.