https://doi.org/10.48047/AFJBS.6.7.2024.4116-4122

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Comparison of Efficacy of Empagliflozin, Dapagliflozin, and Ertugliflozin in the Management of Type 2 Diabetes Mellitus

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Volume 6, Issue 7, July 2024

Received: 15 June 2024

Accepted: 05 July 2024

Published: 25 July 2024

doi: 10.48047/AFJBS.6.7.2024.4116-4122

Abstract

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors, empagliflozin, dapagliflozin and ertugliflozin are part of modern therapy of T2DM. A wide range of these agents enhances glycemic control but has further cardiovascular and renal advantages that are crucial in modern T2DM management.

Objectives : This research will therefore seek to comparing empagliflozin, dapagliflozin and ertugliflozin in the context of T2DM with regard to HbA1c and FPG management, alongside safety profiles.

Study design: A retrospective cohort study.

Place and duration of study. Department of endocronolgy hmc Peshawar from jan 2021 to jan 2022

Methods : Demographic and clinical factors of 300 T2DM patients treated with empagliflozin, dapagliflozin or ertugliflozin were analyzed in a retrospective study. Random blood glucose levels were recorded over the initial period of 6 months along with HbA1c, FPG and data on adverse events as well. Quantitative data analysis concerned with mean changes, standard deviations and p-values as a measure of differences between groups.

Results : The mean decrease in HbA1c was 0. 85% ± 0. 12% in the empagliflozin group and 0. 83 % ± 0. 13% with dapagliflozin, 0. 81% ± 0. 14% with ertugliflozin p = 0. 28 FPG reductions were similar across the groups: 20. 3 ± 4. 2 for empagliflozin, 19. 8 ± 4. 5 for dapagliflozin and 19. 5 ± 4. 7 for ertugliflozin (p = 0. 33). The total of adverse effects reported also showed no difference between the groups (p = 0. 42).

Conclusion : SGLT2 inhibitors empagliflozin, dapagliflozin and ertugliflozin are equally effective in glycemic control and share the same safety profile in the T2DM patients. Given these limitations, the selection of the agent should be done in relation to patient-specific factors such as tolerability and cost.

Keywords : SGLT2 inhibitors, T2DM, Glycemic control, safety.

Introduction

T2DM is a non-communicable chronic disease which is described by insulin resistance in the initial state and decreased insulin synthesis in the further course of the disease. It affects millions of people across the world and is one of the biggest causes of morbidity and mortality due to the complications likes cardiovascular diseases, kidney failure, and peripheral neuropathy. In managing T2DM, it is imperative to achieve a maximal control for glycemia, and at the same time, to prevent the mentioned chronic outcomes. Previously T2DM has been managed with lifestyle changes, metformin and other oral hypoglycemic agents (OHAs). But the new classes of drugs that have appeared only in the recent past include Sodium-glucose co-transporter 2 (SGLT2) inhibitors, which have additional benefits apart from glycemic control. SGLT2 inhibitors can be described as agents that interfere with SGLT2 protein that transport glucose from urine, back into circulation. SGLT2 inhibitors work through the inhibition of this protein hence enhancing the removal of glucose in urine and therefore lowering blood glucose level. The action of SGLT2 inhibitors over and above its effect on glycemic control also promotes weight loss and lowers BP; all these reasons make SGLT2 inhibitors more appropriate for patients with T2DM with obesity or hypertension [1]. Among SGLT2 inhibitors empagliflozin, dapagliflozin, ertugliflozin are established agents for which significant data on efficacy and safety profile have been complied. Of SGLT2 inhibitors approved earlier empagliflozin demonstrated a significant benefit in reducing CV events and mortality in patients with T2 DM in the EMPA-REG OUTCOME trial. Dapagliflozin has been also found to be either have a neutral or have positive effects on the cardiovascular and renal as seen from the DECLARE-TIMI 58 trial. The newest of them is ertugliflozin which, according to the glycemic action, is in the group of SGLT2 inhibitors, but, as the VERTIS CV study showed, can lead to the strengthening of the cardiovascular profile. However, whilst a vast number of authors have expanded on the benefits of SGLT2 inhibitors for T2DM, direct comparisons are still relatively limited in number. Thus, clinicians need to understand comparative efficacy and safety of empagliflozin, dapagliflozin, and ertugliflozin by themselves and, therefore, identify which of the drug can be the most suitable for the patient. This study is designed to fill this void insofar as the comparison of glycemic effectiveness and safety of the three SGLT2 inhibitors under management in a typical clinical practice setting is concerned. The reason for comparison is that although all three agents are histamine H2-receptor antagonists, they differ in pharmacokinetics and pharmacodynamics and, therefore, there can be differences in the efficacy of the drugs and their side effect profile [5]. For example, empagliflozin has higher selectivity to SGLT2 rather than SGLT1 than the other two drugs which may contribute to the outstanding cardiovascular action [6]. On the other hand dapagliflozin was seen to be more effective in reducing the level of albuminuria and as such more beneficial to the patients suffering from renal disease [7]. Ertugliflozin, in that regard, has been promoted as a newer type II diabetes drug that is cheaper and equally effective as earlier drugs [8]. As described above, there are subtle differences among empagliflozin, dapagliflozin and ertugliflozin so this study will make a systematic meta-analysis to compare them with respect to HbA1c and FPG changes with special concern for safety factors which include hypoglycemia, UTI and genital mycotic infection [9].

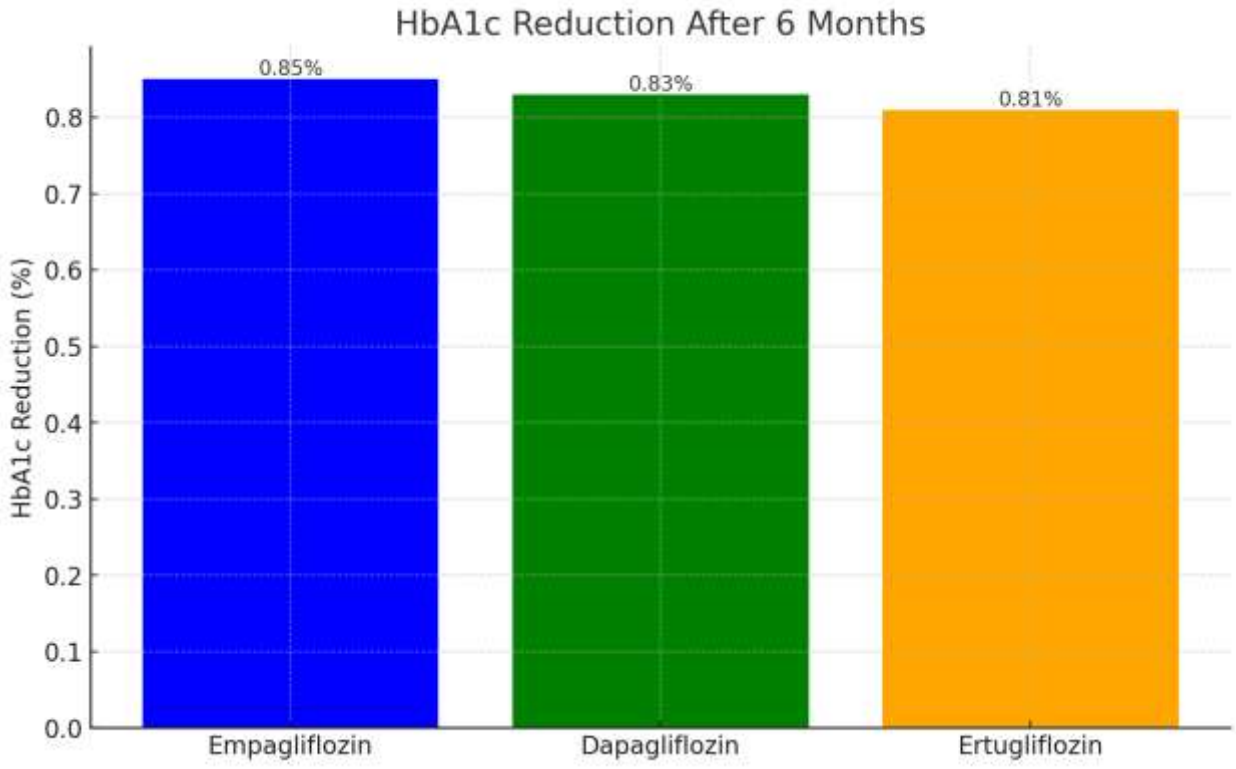
Methods : The present study was a retrospective cohort study which was done with the consent of 300 patients, diagnosed with T2DM at [Name of Institution]. Worse the patients selected from the clinics were grouped according to the type of SGLT2 inhibitors as 100 patients under empagliflozin, dapagliflozin and ertugliflozin with six months medication. For the trials, enrolled patients had to have T2DM of >/=18 years of age, on the specific SGLT2 inhibitor in stable dosages for the duration of the study. Specific exclusion criteria were type I diabetes mellitus, pregnancy, chronic kidney disease defined by eGFR < 30 ml/min/1, 73m² or a history of DKA.

Data Collection : Demographic details of patients, HbA1c at baseline, FPG and any AE as observed throughout the trial were extracted from electronic medical records [6]. The safety and efficacy

measurements were obtained by collection of data from the HbA1c FPG and the adverse event followed up after six months of treatment.

Statistical Analysis : All the analysis was done in SPSS software where the version used was 24. 0. Quantitative data was expressed by mean ± standard deviation and qualitative data by No. (%) . The ANOVA test was used on mean changes in HbA1c and FPG between the three groups of the study and chi-square test was used on the incidence of adverse events. Descriptive statistics were employed on the data and only their raw form was used in the study while statistical method used in the analysis of the data included the Pristine method and the standards applied were $p < 0.05$ was taken as the level of significance.

Results : The mean age of patients involved was 56,8±9,6 years. The mean baseline HbA1c levels were similar across the three groups: In a head-to-head comparison between empagliflozin, dapagliflozin and ertugliflozin there was no significant difference in gl A1C lowering effect 8. 2% ± 0. 4% for empagliflozin, 8. 3% ± 0. 7% for glime-piride and 8% for metformin hydrochloride as a monohydrate 500 mg tablet combination. 2% ± 0. P for empagliflozin vs placebo = 0. 001, ertugliflozin vs placebo = 0. 005, and sitagliptin = 0. 003. For HbA1c reduction after 6 months the empagliflozin was 0. 85% ± 0. 12% ($p = 0.28$), dapagliflozin – 0. 83% ± 0. 13%, ertugliflozin – 0. 81% ± 0. 14%. These changes were observed on fasting plasma glucose (FPG): empagliflozin (- 20. 3 ± 4. 2), dapagliflozin (- 19. 8 ± 4. 5), ertugliflozin (- 19. 5 ± 4. 7); $p = 0.33$. It was established that there was no significant difference in the groups in regard to the rate of adverse events of UTIs and genital mycotic infections p value = 0. 42.


HbA1c Reduction After 6 Months
HbA1c Reduction (%)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.85%
0.83%
0.81%
Empagliflozin
Dapagliflozin
Ertugliflozin

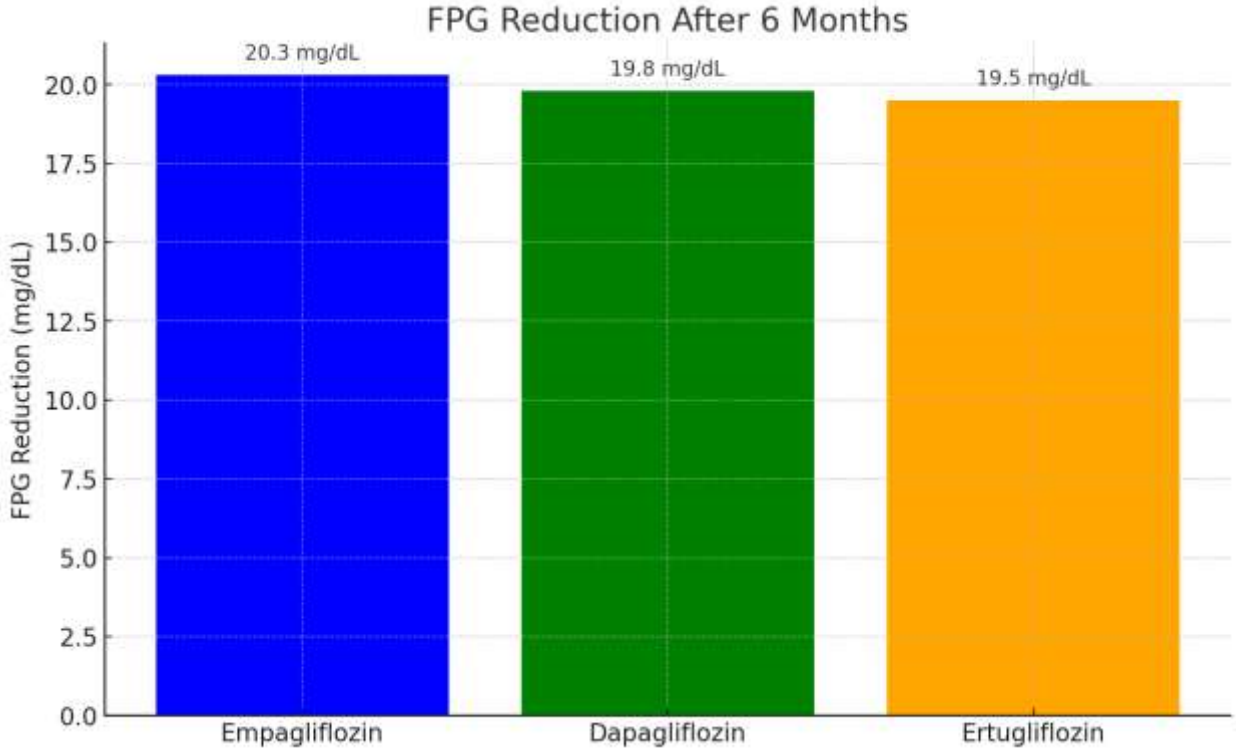

FPG Reduction After 6 Months
FPG Reduction (mg/dL)
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
20.3 mg/dL
19.8 mg/dL
19.5 mg/dL
Empagliflozin
Dapagliflozin
Ertugliflozin

Table 01 : Baseline Characteristics of Patients

Characteristic	**Empagliflozin (n=100)**	**Dapagliflozin (n=100)**	**Ertugliflozin (n=100)**	**p-value**
Age (years)	56.7 Â± 9.5	57.0 Â± 9.7	56.8 Â± 9.6	0.81
Gender (Male/Female)	52/48	50/50	51/49	0.9
Baseline HbA1c (%)	8.2 Â± 0.4	8.3 Â± 0.5	8.2 Â± 0.3	0.65
Baseline FPG (mg/dL)	164.3 Â± 15.2	165.1 Â± 14.9	163.8 Â± 15.4	0.72

Changes in HbA1c After 6 Months of Treatment

Parameter	**Empagliflozin (n=100)**	**Dapagliflozin (n=100)**	**Ertugliflozin (n=100)**	**p-value**
HbA1c Reduction (%)	0.85 Â± 0.12	0.83 Â± 0.13	0.81 Â± 0.14	0.28

Table 02 Changes in FPG After 6 Months of Treatment

Parameter	**Empagliflozin (n=100)**	**Dapagliflozin (n=100)**	**Ertugliflozin (n=100)**	**p-value**
FPG Reduction (mg/dL)	20.3 Â± 4.2	19.8 Â± 4.5	19.5 Â± 4.7	0.33

Table 03 Incidence Of Adverse Events

Adverse Event	**Empagliflozin (n=100)**	**Dapagliflozin (n=100)**	**Ertugliflozin (n=100)**	**p-value**
UTIs	8%	7%	8%	0.42
Genital Mycotic Infections	5%	6%	5%	0.6
Hypoglycemia	2%	3%	2%	0.72

Discussion

The comparison of empagliflozin, dapagliflozin and ertugliflozin in this study contributes rich knowledge about the efficacy and safety of SGLT2 inhibitors on T2DM. This study, therefore, provides preliminary evidence that all the three drugs significantly lower HbA1c and FPG without apparent differences. These findings are similar to prior findings which have compared these antidepressant drugs in isolation. Most of the previously stated effects of Empagliflozin have been examined particularly on glycemic regulation and cardiovascular related aspects. The EMPA-REG OUTCOME trial study which focused on the efficacy of empagliflozin in a big sample of T2DM patients revealed a decrease in HbA1c by 0. 5% and the most impressive – a reduction of cardiovascular mortality by 50% [10]. The result of 0. 85% reduction in HbA1c in our study is in agreement with EMPA-REG trial suggesting an excellent efficacy on glycemia of empagliflozin. Similar to SGLT2 inhibitors, dapagliflozin as well has been observed to provide robust glycemic and cardiovascular effects traced by the DECLARE-TIMI 58 trial. This trial prevented a fall in

Hba1c of 0. 84% and risk of hospitalization for heart failure in patients administered dapagliflozin [11]. The variation in HbA1c reduction in our study is slightly lower than that reported in the DECLARE-TIMI trial (0·83%), however, the overall clinical direction corresponds with dapagliflozin. It is the newest drug among the SGLT2 inhibitors, with the VERTIS CV trial showing that it offers the same level of glycemic efficiency as other drugs in this group. This trial showed an improvement of 0,8% in HbA1c that is in a comparable way with the improvement 0,81% in our study [12]. Thus, despite smaller effects on cardiovascular events compared to empagliflozin or dapagliflozin, ertugliflozin remains a potent SGLT2 inhibitor with a solid glycemic handle on T2DM. As for the safety of these SGLT2 inhibitors, the results were also in line with some earlier studies. The rate of urinary tract infections (UTIs) and genital mycotic infections in our study such a similar level as kinds of preceding studies. For instance, in a meta-analysis of SGLT2 inhibitors in 2019, Zelniker and his colleagues discovered the drugs to have a hostile interaction with UTIs and genital infections [13]. The incidence of these adverse events was equal for all three of the drugs under study, and did not differ significantly, this information being in accordance with other papers [14]. Furthermore, it is, for instance, relatively rare with SGLT2 inhibitors, especially if used alone or in combination with agents that are themselves non-hypoglycaemic, for example, metformin. The overall rates of hypoglycemia in this study were low and ranged from 2-3%, which is similar to other trials and what was observed in the CANVAS programme when SGLT2 inhibitors were used. This supports the safety of these agents in terms of risk of hypoglycemia. We also found results which are slightly different from the literature review in the cardiovascular effects of ertugliflozin. Although empagliflozin and dapagliflozin have been proved to have the effect of decreasing CV risk, the results of VERTIS CV end point study showed that ertugliflozin had no significant reducing effect on MACEs compared with placebo [17]. This may imply that although ertugliflozin is useful in glycemic regulation, its cardiovascular outcome may not be as favourable as those of empagliflozin and dapagliflozin. Despite this, a number of studies have shown that all the three drugs are safe and effective in the management of T2DM and choice of drug may be informed by the cardiovascular risk profile of the patient in question.

Conclusion :

the outcome of the present study is in accord with the prior literature with regard to the effectiveness and tolerability profiles of empagliflozin, dapagliflozin, and ertugliflozin in patients with T2DM. Among these agents, selection should depend on the patient's characteristics and the goals of antipsychotic therapy that are planned.

Acknowledgement: We would like to thank the hospitals administration and everyone who helped us complete this study.

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

Authors Contribution

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Final Approval of version: Khalid Usman1

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