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Original research

A SINGLE-CENTER, RETROSPECTIVE OBSERVATIONAL STUDY COMPARING THE EFFICACY OF EMPAGLIFLOZIN AND DAPAGLIFLOZIN AS ADD-ON THERAPY IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Objective: *This study aimed to compare the efficacy of dapagliflozin and empagliflozin as add-on therapies for type 2 diabetes mellitus (T2DM) over 6 months in a real-world setting, focusing on key metabolic parameters.*

Methods: *We conducted a single-center, retrospective observational study involving 74 T2DM patients receiving either dapagliflozin (10mg) or empagliflozin (25mg) as add-on therapy. Data from 843 patients's electronic medical records were collected at the Center for Endocrinology and Diabetes, Da Nang Family Hospital, between May 2021 and June 2023. Baseline data and data from the 3rd and 6th months of treatment were analyzed using SPSS software (version 20.0). Statistical significance was set at $p < 0.05$.*

Results: *The mean participant age was 58.8 years, with 54.1% females. Mean baseline HbA1c and fasting blood glucose were 8.18% and 9.1 mmol/L, respectively. After 6 months of SGLT2i treatment, both medications significantly improved glycemic control: HbA1c decreased from 8.18% to 7.3% ($p < 0.05$), and fasting plasma glucose dropped from 9.1 mmol/L to 7.4 mmol/L ($p < 0.05$). Systolic blood pressure also decreased significantly, from 130.7 mmHg to 126.5 mmHg ($p < 0.05$). Although a trend towards weight reduction (1.5 kg) was observed, it was not statistically significant ($p > 0.05$). Notably, empagliflozin led to a significantly greater decrease in fasting plasma glucose compared to dapagliflozin ($p < 0.05$). No other significant differences in metabolic parameters were observed between the groups at either 3 or 6 months.*

Conclusion: *Both dapagliflozin and empagliflozin demonstrated significant efficacy as add-on therapies for T2DM patients, improving glycemic control, reducing blood pressure, and potentially promoting weight loss. While empagliflozin showed slightly better BMI, body weight and fasting plasma glucose reduction after 3 months, further research is needed to confirm this finding and explore underlying mechanisms.*

Keywords: *Type 2 Diabetes, SGLT2i, metabolic parameters, empagliflozin, dapagliflozin.*

I. INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disorder, is increasing at an alarming rate worldwide. According to the International Diabetes Federation (IDF), the prevalence of DM is 8.3%, equivalent to 463 million people worldwide. IDF estimates this figure will increase to 578 million people by 2030 with type 2 diabetes mellitus (T2DM) accounting for 90% [1]. It has a significant impact on both morbidity and mortality, and poses an enormous economic burden. Diabetes are not only the leading cause of short and long-term health complications,

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but also one of the top deadly diseases worldwide [2]. Given the global burden of T2DM, there has also been significant progress in its treatment. While a definitive cure for diabetes remains elusive, therapeutic interventions and comprehensive self-management strategies empower diabetic individuals to achieve optimal glycemic control, mitigate the risk of complications, and lead long and fulfilling lives [3]. Oral antidiabetics, in addition to lifestyle modifications, are usually considered first-line therapy for type 2 diabetes [4, 5]. Sodium Glucose Co-Transporter-2 inhibitors (SGLT2i), one of seven groups of antidiabetic medications through a variety of mechanisms to control blood sugar are the latest antidiabetic drugs with a unique mechanism of action that differs from conventional antidiabetic agents [4]. They have been developed based on the antidiabetic action initiated by inhibiting renal glucose reabsorption, thereby increasing urinary glucose excretion [6].

SGLT-2i, a novel class of antidiabetic drugs, boast impressive efficacy, safety, and tolerability, as evidenced by numerous large-scale clinical trials like DECLARE-TIMI 58 and EMPA-REG OUTCOME [7, 8]. They do not cause hypoglycemia and have beneficial effects on body weight, blood pressure, dyslipidemia, and fatty liver [4, 10]. In patients with T2DM, SGLT2i treatments are now being considered as the first line of therapy in some guidelines because of their metabolic and cardio-renal benefits [11, 12].

DM presents a substantial burden on both individuals and healthcare systems in Vietnam. Urban centers witness a particularly alarming rise, experiencing annual increases in diabetes and prediabetes of approximately 6.23% and 16.17%, respectively [13]. Addressing this public health challenge necessitates prioritizing effective glycemic control strategies in our country. A recent study assessed the efficacy of SGLT-2i (dapagliflozin and empagliflozin) as add-on therapy in type 2 diabetic patients over a period of 6 months in primary care setting.

II. MATERIALS AND METHODS

2.1. Participants and study design

A retrospective study of 74 outpatients with type 2 diabetes was conducted at the Centre of Endocrinology and Diabetes, Danang Family hospital, Vietnam. Patients received either dapagliflozin (10mg) or empagliflozin (25mg) as add-on therapy for 6 months. The study analyzed medical records from May 2021 to June 2023.

Inclusion criteria A diagnosis of diabetes according to the 2023 American Diabetes Association criteria [14] and treatment with either dapagliflozin or empagliflozin as add-on therapy for at least 6 months. Sufficient medical history, anthropometric data, and blood test results at the initial time, 3 months, and 6 months after initiation of treatment.

Exclusion criteria: Type 1 diabetes mellitus; Insufficient medical history or missing blood test results for at least one of the three time points mentioned.

2.2. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Institutional Review Board of Danang Family hospital, Danang, Vietnam (No.: 013/QĐ-NCKH/FAMILY).

2.3. Data measurements

The patients were retrospectively selected and classified into two groups using ether empagliflozin (25mg) or dapagliflozin (10mg).

Variables: Socio-demographic information; Clinical features: Clinical information consisted of duration of living with DM, duration of hypertension, history of coronary artery disease, history of hypertension, history of hyperlipidemia, history of diabetic nephropathy, medications used, blood pressure, body weight, body mass index, fasting blood glucose level, lipid profile, HbA1c, creatinine, ure, and liver enzyme. Adverse events associated with the addition of SGLT2i were assessed at 3 and 6 months post-treatment and included female genital mycotic infections, urinary tract infections, increased urinary frequency, nausea, and constipation [14]. Baseline data, third and sixth months' data of treatment were reevaluated and recorded.

2.4. Data analysis

Statistical analysis was performed using SPSS version 20.0. Baseline characteristics were compared using appropriate t-tests or Whitney U tests. Changes in variables over time were assessed using a general linear model. A p-value of < 0.05 was considered significant.

III. RESULTS

The sample comprised 54.1% female with a mean age of 58.8 years (SD, 12.8). The average duration of diabetes mellitus and hypertension was 6.6 and 5.2 years, respectively. The prevalence of comorbidities among DM patients included coronary artery disease (32.4%), hypertension (75.7%), hyperlipidemia (28.4%), and diabetic nephropathy (11.1%). Initial clinical parameters revealed a mean systolic blood pressure of 130.7 mmHg, diastolic blood pressure of 75.6 mmHg, and body mass index (BMI) of 26.3 kg/m². Concomitant medications for DM included metformin (82.4%), dipeptidyl peptidase-4 (DPP-4) inhibitors (35.1%), sulfonylureas (SUs) (27.0%), and insulin (63.7%). Notably, no statistically significant differences were observed in these characteristics between the dapagliflozin and empagliflozin groups (Table 1).

Table 1: The initial demographic parameters of type 2 diabetes patients

	All patients (n = 74)	**Dapagliflozin treatment group (n = 32)**	**Empagliflozin treatment group (n = 42)**	**p**
Female/male (n)	40/34	19/13	21/21	0.48
Age (years)	58.8 ± 12.8	60.0 ± 15.3	57.9 ± 10.5	0.55
Diabetes duration (years)	6.6 ± 5.3	7.3 ± 6.4	6.1 ± 4.2	0.77
Hypertension duration (years)	5.2 ± 5.4	5.7 ± 6.7	4.8 ± 4.3	0.88
Coronary artery disease (n, %)	24 (32.4)	12 (37.5)	12 (28.6)	0.46
Hypertension (n, %)	56 (75.7)	22 (68.8)	34 (81.0)	0.27
Hyperlipidemia (n, %)	70 (94.6)	32 (100)	38 (90.5)	0.13
Renal disease (n, %)	21 (28.4)	10 (31.3)	11 (26.2)	0.79
Systolic pressure (mmHg)	130.7 ± 19.4	129.0 ± 18.3	132.0 ± 20.4	0.47
Diastolic pressure (mmHg)	75.6 ± 10.6	73.4 ± 10.7	77.3 ± 10.4	0.17
Metformin (n, %)	61 (82.4)	24 (75.0)	37 (88.1)	0.21
DPP-4 inhibitor (n, %)	26 (35.1)	12 (37.5)	14 (33.3)	0.81
Sulfonylurea (n, %)	20 (27.0)	7 (21.9)	13 (31.0)	0.43
Insulin (n, %)	33 (63.7)	12 (37.5)	11 (26.2)	0.22
ARB (n, %)	22 (29.7)	7 (21.9)	15 (35.7)	0.13
ACEi (n, %)	25 (33.8)	13 (40.6)	12 (28.6)	0.326
Statin (n, %)	56 (75.7)	23 (71.9)	33 (78.6)	0.37
Fibrate (n, %)	10 (13.5)	4 (12.5)	6 (14.3)	0.51
BMI (kg/m^2)	26.3 ± 3.7	25.7 ± 3.3	26.8 ± 3.9	0.33
Body weight (kg)	65.7 ± 11.9	63.4 ± 9.7	67.4 ± 14.1	0.33

The average HbA1c and fasting blood glucose levels were 8.18% (SD, 1.9) and 9,1 mmol/l (SD, 2.8), respectively. Of which, 18.9% of them had good HbA1c control and 24.3% had good fasting plasma glucose control according to American Diabetes Association 2022 criteria. At initial time, the mean of ALT, AST, ure and creatinine were 35.9 u/l, 29.5u/p, 5.6mmol/l and 80.9 micromol/l. These biochemical results were

not significant in group of dapagliflozin and empagliflozin treatment. No adverse events associated with the addition of SGLT2i were recorded at 3 and 6 months post-treatment in our patients (Table 2).

Table 2: The initial Biochemical results of type 2 diabetes patients

	All patients (n =74)	**Dapagliflozin treatment group (n = 32)**	**Empagliflozin treatment group (n = 42)**	**p**
Fasting plasma glucose (mmol/L)	9.1 ± 3.5	8.2 ± 2.7	9.8 ± 3.9	0.13
HbA1c (%)	8.18 ± 1.9	8.0 ± 1.6	8.3 ± 2.1	0.81
Total cholesterol (mmol/L)	4.45 ± 1.5	4.5 ± 1.4	4.4 ± 1.6	0.66
LDL cholesterol (mmol/L)	2.5 ± 1.3	2.5 ± 1.2	2.5 ± 1.5	0.63
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 0.3	1.1 ± 0.4	0.92
Triglyceride (mmol/L)	2.8 ± 1.9	2.5 ± 1.5	2.9 ± 2.2	0.51
Creatinine (micmol/L)	80.9 ± 59.8	84.7 ± 58.6	78.0 ± 61.2	0.25
Ure (mmol/L)	5.6 ± 2.8	5.8 ± 3.2	5.3 ± 2.6	0.54
ALT (U/L)	35.9 ± 17.5	32.7 ± 16.5	38.5 ± 28.6	0.07
AST (U/L)	29.5 ± 17.7	25.4 ± 11.2	32.7 ± 21.0	0.65
Good HbA1c control (n, %)	14 (18.9)	6 (18.8)	8 (19.0)	0.98
Good fasting glucose control (n, %)	18 (24.3)	10 (31.3)	8 (19.0)	0.22

Three and six months of SGLT2i treatment resulted in significant reductions in systolic blood pressure (130.7 mmHg to 126.5 mmHg, $p < 0.05$), fasting plasma glucose (9.1 mmol/L to 7.4 mmol/L, $p < 0.05$), and HbA1c (8.1% to 7.3%, $p < 0.05$). Additionally, triglycerides significantly decreased from 2.8 mmol/L to 2.2 mmol/L ($p < 0.05$). Body weight decreased by 1.5 kg at 6 months, but this change was not statistically significant ($p > 0.05$). No significant differences were observed in other clinical parameters, including diastolic blood pressure, BMI, other lipid profiles, creatinine, urea, or liver enzymes, at either 3 or 6 months ($p > 0.05$) (Table 3).

Table 3: Metabolic changes in Type 2 diabetes with SGLT-2i add-on.

	Initial time	**3 months after add-on**	**6 months after add-on**	**p**
Systolic pressure (mmHg)	130.7 ± 19.4	123.8 ± 15.6	126.5 ± 14.8	0.005
Diastolic pressure (mmHg)	75.6 ± 10.6	72.9 ± 10.4	73.7 ± 8.7	0.13
BMI (kg/m2)	26.3 ± 3.7	26.1 ± 5.2	25.8 ± 3.4	0.34
Body weight (kg)	65.7 ± 11.9	65.1 ± 16.3	64.2 ± 10.9	0.38
Fasting plasma glucose (mmol/l)	9.1 ± 3.5	7.4 ± 2.1	7.4 ± 2.5	0.0001
HbA1c (%)	8.18 ± 1.9	7.3 ± 1.3	7.2 ± 1.4	0.0001
Total cholesterol (mmol/L)	4.45 ± 1.5	4.6 ± 4.3	4.0 ± 1.2	0.38
LDL cholesterol (mmol/L)	2.5 ± 1.3	2.3 ± 1.1	2.3 ± 1.0	0.21

	Initial time	3 months after add-on	6 months after add-on	p
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	0.09
Triglyceride (mmol/L)	2.8 ± 1.9	2.0 ± 1.2	2.2 ± 1.6	0.004
Creatinine (mcmol/L)	80.9 ± 59.8	81.8 ± 56.7	82.9 ± 63.8	0.86
Ure (mmol/L)	5.6 ± 2.8	6.0 ± 2.9	6.1 ± 2.9	0.18
ALT (U/L)	35.9 ± 17.5	31.7 ± 26.1	49.9 ± 151.1	0.45
AST -GOT (U/L)	29.5 ± 17.7	27.4 ± 14.7	38.6 ± 103.2	0.40

Notably, fasting plasma glucose (FPG), body weight and BMI demonstrated a significantly greater reduction in the empagliflozin group compared to the dapagliflozin group at 3 months ($p < 0.05$). However, these differences is not statistically significant at 6 months ($p > 0.05$). No statistically significant differences were observed for any other metabolic parameters at either time point ($p > 0.05$) (Table 4).

Table 4: Comparison of metabolic effects between 2 groups following 3 and 6 months of SGLT2i add-on

	3 months after add-on vesus intial time		6 months after add-on vesus intial time		p3	p6
	Dapagliflozin (n=32)	Empagliflozin (n=42)	Dapagliflozin (n=32)	Empagliflozin (n=42)		
Systolic pressure (mmHg)	-5.8 ± 19.2	-7.8 ± 19.9	-2.6 ± 17.0	-5.5 ± 16.7	0.88	0.34
Diastolic pressure (mmHg)	-1.4 ± 12.2	-3.7 ± 10.6	-0.3 ± 11.8	-3.1 ± 9.3	0.47	0.52
BMI (kg/m^2)	0.7 ± 6.1	-1.0 ± 1.6	-0.3 ± 0.9	-0.8 ± 1.4	0.04	0.09
Body weight (kg)	2.3 ± 17.7	-2.8 ± 5.1	-0.6 ± 2.3	-2.1 ± 3.7	0.02	0.08
Fasting plasma glucose (mmol/l)	-0.6 ± 2.2	-2.6 ± 4.1	-0.5 ± 3.2	-2.5 ± 3.7	0.021	0.10
HbA1c (%)	-0.5 ± 1.2	-1.1 ± 1.8	-0.8 ± 1.4	-1.2 ± 1.9	0.114	0.34
Total cholesterol (mmol/l)	0.7 ± 6.5	-0.3 ± 1.6	-0.2 ± 1.5	-0.6 ± 1.4	0.83	0.21
LDL cholesterol (mmol/l)	-0.3 ± 1.2	-0.2 ± 1.3	-0.1 ± 1.4	-0.4 ± 1.3	0.59	0.40
HDL cholesterol (mmol/l)	0.1 ± 0.3	0.1 ± 0.5	0.1 ± 0.4	-0.1 ± 0.6	0.87	0.79
Triglyceride (mmol/l)	-0.4 ± 1.5	-1.0 ± 2.0	-0.4 ± 1.8	-0.6 ± 2.1	0.45	0.82

	3 months after add-on vesus intial time		6 months after add-on vesus intial time		p3	p6
	Dapagliflozin (n=32)	**Empagliflozin (n=42)**	**Dapagliflozin (n=32)**	**Empagliflozin (n=42)**		
Creatinine (mcmol/L)	-5.8 ± 46.9	5.9 ± 29.3	-3.7 ± 47.3	6.4 ± 33.8	0.21	0.68
Ure (mmol/L)	0.1 ± 2.5	0.8 ± 2.1	0.3 ± 2.6	0.6 ± 2.5	0.49	0.68
ALT (U/L)	-1.3 ± 25.7	-6.5 ± 25.1	7.8 ± 91.6	17.9 ± 184.8	0.06	0.19
AST (U/L)	1.7 ± 11.0	-5.1 ± 20.1	4.9 ± 46.5	11.8 ± 135.3	0.95	0.65

IV. DISCUSSION

Recent clinical evidence has positioned SGLT2 inhibitors as a valuable therapeutic option for T2DM patients with cardiorenal complications. Their cardiorenal protective benefits, acting on both the heart and kidney, have led to their inclusion in treatment guidelines [4, 8, 10]. Furthermore, some guidelines recommend the use of SGLT2 inhibitors beyond diabetes, in patients with heart failure and chronic kidney disease [9, 11, 15].

However, limited real-world data exists on key metabolic parameters within these groups in Vietnam, particularly within primary care settings. In this study, we evaluated our own real life data due to addion SGLT-2i in seventy four type 2 diabetic patients for improvement glycemic control. Approximately 63.7% of patients were receiving insulin in combination with other oral antidiabetic medications like metformin, sulfonylureas (SUs), and DPP-4 inhibitors. Remarkably, a very low percentage achieved glycemic control with baseline HbA1c and FPG values exceeding target goals. This highlights the need for additional therapeutic options like SGLT-2 inhibitors, such as empagliflozin and dapagliflozin, to improve metabolic control. Importantly, our study found no significant baseline differences in these characteristics between the empagliflozin and dapagliflozin groups.

Following 3 and 6 months of treatment with empagliflozin or dapagliflozin, statistically significant improvements were observed in several metabolic parameters, including systolic blood pressure, fasting plasma glucose (FPG), HbA1c, and triglycerides. Notably, the FPG reduction was significantly greater in the empagliflozin group compared to the dapagliflozin group ($p < 0.05$). No statistically significant differences were found between the two groups for any other measured parameters at either time point.

There are many previous studies showing the advantageous effects of SGLT2i group on weight, BMI, FPG and HbA1c. Matthaei S. et al study showed that after 6 months dapagliflozin addition, HbA1c, FPG, body weight, BMI, and systolic blood pressure in terms of 8 weeks and 6 months have been reported to improve significantly [16]. Kovacs et al study show empagliflozin once daily for 24 weeks as add-on reduced HbA1c, FPG and weight and were well tolerated in patients with T2DM [17]. According to meta-analysis results of Cai et al., the average weight loss between 1.3 kg - 2.24 kg and 1.84 kg - 1.93 kg has been shown in patients using Dapagliflozin and Empagliflozin [18]. In this study, it was shown there was a weight loss of 0.6 kg in the 3rd month and 1.5 kg in the 6th month, however these differences were not statiscally significant. Our findings deviate from previous observations. This discrepancy could be attributed to both the limitations inherent in this retrospective study's small sample size and the high proportion of participants receiving insulin therapy (63.7%). Also, studies have demonstrated that

SGLT2 inhibitors not only promote the excretion of glucose, but also increase urinary fluid and sodium excretion, ultimately leading to calorie deficit and subsequent weight loss [19]. However, insulin therapy commonly results in weight gain in type 2 diabetes [20]. This weight gain can be excessive, adversely affecting cardiovascular risk profile [21]. So, SGLT2i can help to limit weight gain from insulin therapy [22].

A 52-week prospective study by Ku EJ et al. compared Dapagliflozin 10 mg/day to Empagliflozin 25 mg/day in terms of weight, BMI, systolic blood pressure, FPG, and HbA1c changes. Interestingly, Empagliflozin demonstrated significantly greater efficacy for these parameters [23]. In contrast, our data suggest significant differences between Empagliflozin and Dapagliflozin about weight, BMI and FPG after only 3 months of treatment.

Evaluation of lipid profiles in all patient groups revealed a numerical decrease in triglyceride levels following treatment. HDL and LDL levels also increased numerically but did not reach statistical significance. This finding aligns with the mixed literature on the effects of SGLT2 inhibitors on lipid panels. For instance, Cha SA et al. observed similar numerical decreases in triglyceride and total cholesterol in a 24-week follow-up study, but without statistical significance, while HDL and LDL levels significantly increased [24]. Notably, a six-month observational study from Turkey reported significant reductions in total cholesterol, triglycerides, and LDL with dapagliflozin, but statin use was not reported [25]. In our study, statin and fibrate use were prevalent (75.7% and 13.5%, respectively), potentially contributing to the observed numerical increases in HDL ($p > 0.05$) alongside the decrease in triglycerides. These findings are consistent with the existing literature on SGLT2 inhibitor-mediated lipid panel changes.

This study has three main limitations. Firstly, this study was limited by its retrospective design, which may introduce bias due to unmeasured confounders. Secondly, the sample size was relatively small, limiting generalizability of the findings. Finally, detailed information on concomitant medications and lifestyle factors was not included, which could have influenced outcomes. Future research should address the limitations of this study by conducting larger, prospective trials to validate these findings and evaluate the long-term safety and efficacy of dapagliflozin and empagliflozin in T2DM patients. Mechanistic investigations are needed to understand the observed differential FPG reduction between these SGLT2i agents. Exploring their potential benefits in specific patient subgroups with comorbidities could offer valuable insights.

V. CONCLUSION

Both dapagliflozin and empagliflozin demonstrated significant efficacy as add-on therapies for T2DM patients, improving glycemic control, reducing blood pressure, and potentially promoting weight loss. Empagliflozin showed slightly better reductions in BMI, body weight, and fasting plasma glucose at 3 months, but these differences were no longer apparent at 6 months.

Disclosure

The authors report no other conflicts of interest in this work

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