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Original Article

Effectiveness Assessment of Dapagliflozin as an Add-on to Sitagliptin, Vildagliptin and Metformin in Patients with Different Demographic Parameters in Type II DM

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ABSTRACT

Objectives: The study's goal is to examine the efficacy of various newer anti-diabetic drug combinations that include SGLT2 inhibitors (dapagliflozin), DPP-4 inhibitors (sitagliptin and vildagliptin) and metformin. **Materials and Methods:** Patients with diabetes who had blood glucose levels that were managed (as per the established guidelines), as indicated by Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS), met the inclusion criteria for this study. Only a person's medical history, medicines and glycemic control are taken consideration in this study. A sample size of 90 samples was included in the study and equally divided among three treatment groups, each of which received a certain treatment option. Each group is once again examined based on gender and the age ranges of 30 to 50 and 51 to 70 years. **Results and Discussion:** Total 90 samples are considered in the study and divided into 3 group consist of 30 sample size Visit 1 is significant than Visit 2 and Visit 3 and Visit 2 is significant than Visit 3 (p value≤.000). In comparison to the other group, Group 1 achieved a better control of FBS and PPBS levels from Visit 1 to Visit 3, followed by the pharmacological therapy of Dapagliflozin and Sitagliptin. **Conclusion:** The current study establishes for the first time that dapagliflozin, when used in combination with sitagliptin, vildagliptin and metformin, has comparable advantages for improving blood glucose control. When choosing a medicine combination to be used as the first line of treatment for people with type 2 diabetes, it is crucial.

Keywords: Combination drug therapy, Dapagliflozin, Type II Diabetes, Glycemic control.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is the more frequent form of this diverse chronic metabolic disease, which is characterised by hyperglycemia, brought on by abnormalities in the release of insulin and use and is influenced by biological, environmental and immunological factors.[1]

Asian nations in particular have noticed a sharp increase in the prevalence of people with Type 2 Diabetes Mellitus (T2DM) as the worldwide burden of diabetes increases.[2]

In terms of diabetes epidemiology globally, India comes in second. Over 90% of all cases of diabetes in India are T2DM. Estimates indicate that over 74 million Indians had diabetes in 2021 and by 2045, that figure is predicted to reach over 124 million.[3]

For all of these reasons, managing T2DM can be essential to helping affected individuals live better lifestyles and keeping them that way. But selecting a successful treatment plan is still a difficult choice. More recently, there have been more reports suggesting that administering a combination therapy of Oral Antidiabetic Medications (OADs) with different mechanisms of action early in the development of T2DM may be more beneficial than a pharmacological regimen that progressively increases the dosage of one or more agents. Patients with type 2 diabetes are now being treated with tremendous success thanks to the advancement and enhancement of medical technology.[4,5]

A sensible and effective Fixed-Dose Combination (FDC) of diabetic medications might be an excellent choice. Combination therapy with two medications can assist patients in achieving their desired glycemic control in addition to lowering dosage burden and enhancing compliance. Combination therapies are beneficial because they target many diseases pathophysiologic functions that have a mutually beneficial or complementary impact on glucose levels.[6]

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Metformin is the first-line treatment for people with T2DM; however, if metformin alone is unable to control a patient's blood sugar levels, a combination therapy is required. For individuals whose glycemic control remains inadequate with a combination of metformin and a Dipeptidyl Peptidase-4 inhibitor (DPP-4i), adding an SGLT2 inhibitor (SGLT2i) is a beneficial alternative. The FDC of Sodium-Glucose Cotransporter type 2 inhibitor (SGT2i) and Dipeptidyl Peptidase-4 inhibitor (DPP-4i) present a novel approach.[3,7]

Type 2 diabetics can choose from a variety of treatment options. Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors are oral hypoglycemic medications that lower blood sugar levels without the use of insulin by preventing glycosuria and inhibiting renal reabsorption. Additionally, they lower the risk factors for cardiovascular disorders, including high blood pressure, adipose tissue mass, uric acid, triglyceride and high-density lipoprotein levels. In patients with type 2 diabetes, both those with and without preexisting atherosclerotic cardiovascular disease, SGLT2 inhibitors have demonstrated positive outcomes.[7]

A highly effective and selective SGLT2i, dapagliflozin is >1400 times more selective for SGLT2 than SGLT1, which is the main transporter in charge of absorbing glucose in the stomach. Dapagliflozin successfully reduced body weight, Blood Pressure (BP) and blood sugar levels in numerous carefully planned clinical investigations. Dapagliflozin is a vital choice for treating a wide range of patients due to its cardioprotective and potentially renoprotective qualities as well as its typically favourable tolerability profile.[6]

Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists are not linked to weight gain or hypoglycemia, but evaluation of long-term use is required. Additional therapies are also required to address some of the more general metabolic problems associated with diabetes without relying solely on β-cell function and to avoid unwanted effects.[13]

Sitagliptin helps to inhibit DPP-4 (Dipeptidyl Peptidase) competitively. GLP-1 and GIP, two gastrointestinal hormones that are generated in response to food, are broken down by this enzyme. They are able to boost insulin secretion and decrease glucagon release by the pancreatic beta cells by blocking the breakdown of GLP-1 and GIP. As the blood sugar level becomes closer to normal.[8]

Vildagliptin causes persistent enzyme inhibition by forming a covalent bond with the catalytic site of Dipeptidyl Peptidase-4 (DPP-4). This increases levels of intact Glucagon-Like Peptide-1 (GLP1) both after meals and during a fast. In a glucose-dependent way, it has been demonstrated to increase insulin secretion and decrease glucagon secretion.[3]

Objective of the study is to compare the effectiveness of different newer antidiabetic drug combination of SGLT2 inhibitors (dapagliflozin) with the DPP-4 inhibitors (sitagliptin and vildagliptin) and metformin for a better therapeutic management of diabetes.

MATERIALS AND METHODS

Study Design and Data Source

The period from January 2023 to July 2023 was used for an independent cross-sectional study. The study, used clinical data from clinical practitioner is based on observation of prescription. In this study inclusion criteria as were diabetic patients with blood glucose levels that were managed or nearly controlled (as per the recommended standards) as determined by Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS). Consecutively enrolled T2DM patients were those who had been monitored at the same centre. Only type II diabetes patients are the intended target population for the current report. If a patient was pregnant, under 30 years old, with chronic liver disease, or psychiatric illnesses, were excluded from the study. This study only considers a person's medical background, medication and glycemic control by observing their prescriptions. The total sample size of 90 samples were included in the study according to the above criteria and equally divided into three treatment group for a specific treatment option to each group. Each group is again analysed according to gender basis and age group 30≤50 year and 51≤70 year.

Ethical Statement

The study had the approval of Institutional Ethics committee KIDS Hospital, Bhubaneswar, Odisha, India.

Patient Consent

Informed consent was obtained from each patient.

Statistics analysis

The analysis was done using SPSSV20 statistical software. Paired T test was used to analyse the data and significance was found out by comparing the calculating t value at 95% confidence interval ($p \leq 0.005$). p value was considered to be significant.

RESULTS

The result depicted in the Table 1 represents 90 samples equally divided into three treatment group. Group 1, 2 and 3 consider male age group of 52.43, 54.07, 50.93 year out of 14 in each group and female of 53.19, 54.81, 52.38 year out of 16 in each group. At the same time the duration of diabetes was 5.79, 7.57, 5.79 year and 4.69, 6.56, 5.50 year with respect to male and female diabetic subject. However, the average age of the diabetic subject was observed as 52.83, 54.47, 51.70 years and the duration of diabetes was 5.20, 7.03, 5.63 years out of 30 diabetic subjects in each treatment group considered in this study.

Table 1: The demographic and clinical characteristics of patients with Type II DM.

	Group 1 (*n*=30)			Group 2 (*n*=30)			Group 3 (*n*=30)		
	Sample (n)	Age (Year)	DOD (Year)	Sample (n)	Age (Year)	DOD (Year)	Sample (n)	Age (Year)	DOD (Year)
Total	30	52.83±10.8	5.20±3.0	30	54.47±12.0	7.03±4.6	30	51.70±8.7	5.63±2.4
Male	14	52.43±9.8	5.79±3.5	14	54.07±13.9	7.57±5.8	14	50.93±8.2	5.79±2.6
Female	16	53.19±11.9	4.69±2.5	16	54.81±10.6	6.56±3.4	16	52.38±9.3	5.50±2.3

DOD: Duration of Diabetes, Values are expressed in terms of Mean±SD.

Table 2: Basic parameter of three treatment group with Type II Diabetic subjects according to Age Group.

	Age Group (30 ≤ 50 years)			Age Group (51 ≤ 70 years)		
	Group 1 (*n*=11)	Group 2(*n* =11)	Group 3 (*n*=14)	Group 1 (*n*=19)	Group 2 (*n*=19)	Group 3 (*n*=16)
Age (Year)	40.64±4.4	42.45±4.0	44.29±5.2	59.89±5.9	61.42±9.3	58.19±5.2
Male (%)	45.5	45.5	57.1	47.4	47.4	37.5
Female (%)	54.5	54.5	42.9	52.6	52.6	62.5
DOD (Year)	4.18±3.7	5.09±3.3	4.64±2.4	5.79±2.5	8.16±5.0	6.50±2.3

DOD: Duration of Diabetes, Values are expressed in terms of Mean±SD.

Table 3: Clinical characteristics of three treatment group with Type II Diabetic Subjects according to their Antidiabetic Treatment.

Visit	Group 1 (*n*=30)		Group 2 (*n*=30)		Group 3 (*n*=30)	
	FBS (mg/dL)	PPBS (mg/dL)	FBS (mg/dL)	PPBS (mg/dL)	FBS (mg/dL)	PPBS (mg/dL)
V1	218.00±45.8	291.30±67.0	229.03±67.1	312.40±94.3	234.10±54.7	313.73±66.6
V2	172.23±29.4	229.00±43.2	173.37±31.4	226.27±36.4	173.53±29.3	215.60±23.9
V3	136.07±25.1	182.23±22.3	141.93±21.4	187.70±19.0	133.87±17.7	169.40±24.2

Values are expressed in terms of Mean±SD.**FBS:** Fasting Blood Sugar Level; **PPBS:** Post-Prandial Blood Sugar Level.In Group 1 V1 is significant than V2 and V3 and V2 is significant than V3 (p value ≤ .000).In Group 2 V1 is significant than V2 and V3 and V2 is significant than V3 (p value ≤ .000).In Group 3 V1 is significant than V2 and V3 and V2 is significant than V3 (p value ≤ .000).While all are analysing by the Paired Sample *T*-Test.

Each group is followed by a specific treatment i.e., specific combination for the management of glycemic management. Group 1 followed Dapagliflozin 10 mg and Sitagliptin 100 mg, Group 2 with Dapagliflozin 10 mg and Vildagliptin 100 mg and Group 3 with Dapagliflozin 10 mg and Metformin 500 mg administered to evaluate the efficacy.

The result depicted in the Table 2 represents three treatment group divided into two age groups of 30≤50 years and 51≤70 years. Age group (30≤50 years) considered to Group 1, 2 and 3 sample size of 11, 11, 14 while mean ages of 40.64, 42.45, 44.29 years, at the same time the duration of diabetes was 4.18, 5.09, 4.64 years. Considering age group (51≤70 years) Group 1, 2 and 3 sample size of 19, 19, 16 and mean ages of 59.89, 61.42, 58.19 years at the same time the duration of diabetes was 5.79, 8.16, 6.50 years respectively.

The result depicted in the Table 3 represents three treatments Group 1, 2 and 3 showing different visits in which blood sugar level is monitored by specific combination therapy to each group. Group 1 consider to specific combination of Dapagliflozin and Sitagliptin which results in FBS in visit 1, 2 and 3 is 218.00, 172.23 and 136.07 mg/dL while PPBS value is 291.30, 229.00 and 182.23 mg/dL respectively. Considering Group 1 there is significant change in FBS as well as PPBS that is p value of .000 when compared to Visit 1 FBS and PPBS with Visit 2 and 3. Group 2 followed to the treatment combination of Dapagliflozin and Vildagliptin the sugar level monitored as FBS value in Visit 1, 2 and 3 is 229.03, 173.37 and 141.93 mg/dL at the same time PPBS value is 312.40, 226.27 and 187.70 mg/dL respectively. Group 2 shows significant change that is p value of .000 when compared to Visit 1 FBS and PPBS with Visit 2 and 3. Lastly Group 3 followed to the treatment group of Combination therapy of Dapagliflozin and Metformin which monitored as FBS in Visit 1, 2 and 3 is 234.10, 173.53 and 133.87 mg/dL and PPBS value is 313.73, 215.60 and 169.40 mg/dL respectively. Group 3 also showing significant change i.e, p value of .000 when compared to Visit 1 FBS and PPBS with visit 2 and 3.

The result depicted in Table 4 represents gender basis differentiation, i.e., male and female and different age groups, 30≤50 years and 51≤70 years.

Considering male patients in each study parameter, Group 1 showed the FBS in visits 1, 2 and 3 was 206.93, 171.50 and 131.71 mg/dL, while the PPBS registered 276.93, 224.29 and 181.57 mg/

Table 4: Clinical characteristics of three treatment group with Type II Diabetic Subjects observed by Gender basis and Age group.

Treatment Group	Visit	Male		Female		Age Group (30 ≤ 50 years)		Age Group (51 ≤ 70 years)	
		FBS (mg/dL)	PPBS (mg/dL)	FBS (mg/dL)	PPBS (mg/dL)	FBS (mg/dL)	PPBS (mg/dL)	FBS (mg/dL)	PPBS (mg/dL)
Group 1	V1	206.93±46.3	276.93±55.8	228.25±44.3	303.88±74.9	219.55±48.7	284.55±48.8	217.11±45.4	295.21±76.5
	V2	171.50±33.5	224.29±31.0	172.88±26.4	233.13±52.3	173.27±30.9	228.09±29.5	171.63±29.3	229.53±50.2
	V3	131.71±33.2	181.57±27.3	139.88±15.3	182.81±17.8	143.45±28.5	188.09±16.2	131.79±22.6	178.84±25.0
Group 2	V1	216.43±54.6	313.57±108.4	240.06±76.5	311.38±83.7	229.18±81.1	298.55±87.8	228.95±60.0	320.42±99.3
	V2	172.36±34.2	234.21±42.5	174.25±29.8	219.31±29.8	170.36±26.1	228.09±29.4	175.11±34.6	225.21±40.7
	V3	137.29±18.9	182.71±18.1	146.00±22.6	192.06±19.4	139.45±17.5	187.27±23.7	143.37±23.2	187.95±16.5
Group 3	V1	236.64±55.8	295.21±66.4	231.88±44.9	329.94±64.5	237.00±68.8	305.00±74.5	231.56±40.8	321.38±60.3
	V2	174.43±33.2	215.43±27.1	172.75±26.4	215.75±21.7	171.57±30.0	211.86±25.6	175.25±29.5	218.88±22.7
	V3	136.79±22.9	170.64±24.3	131.31±11.8	168.31±24.8	130.64±15.7	165.79±23.8	136.69±19.5	172.56±24.9

Values are expressed in terms of Mean±SD.**FBS:** Fasting Blood Sugar Level; **PPBS:** Post-Prandial Blood Sugar Level.In Group 1 V1 is significant than V2 and V3 and V2 is significant than V3 (p value ≤ .000).In Group 2 V1 is significant than V2 and V3 and V2 is significant than V3 (p value ≤ .000).In Group 3 V1 is significant than V2 and V3 and V2 is significant than V3 (p value ≤ .000).While all are analysing by the Paired Sample T-Test.

dL, respectively. Group 2 showed the FBS in visits 1, 2 and 3 was 216.43, 172.36 and 137.29 mg/dL and the PPBS were 313.57, 234.21 and 182.71 mg/dL, respectively. In Group 3, monitored FBS in visits 1, 2 and 3 is 236.64, 174.43 and 136.79 mg/dL, at the same time PPBS is 295.21, 215.43 and 170.64 mg/dL, respectively.

While focusing on female patients in Group 1, registered in visits 1, 2 and 3 FBS is 228.23, 172.88 and 139.88 mg/dL, at the same time PPBS is 303.88, 233.13 and 182.81 mg/dL, respectively. Group 2 monitored in visits 1, 2 and 3 FBS is 240.06, 174.25 and 146.00 mg/dL, at the same time PPBS is 311.38, 219.31 and 192.06 mg/dL respectively. In Group 3, shown in visits 1, 2 and 3 FBS is 231.88, 172.75, 131.31 mg/dL while PPBS is 329.94, 215.75, 168.31 mg/dL respectively.

Generally concentrating on the age group of 30≤50 years in Group 1 the FBS is monitored through visits 1, 2 and 3 is 219.55, 173.27 and 143.45 mg/dL while the same time PPBS is 284.55, 228.09, 188.09 mg/dL respectively. Group 2 showed in visits 1, 2 and 3 FBS is 229.18, 170.36, 139.45 mg/dL in the same manner, PPBS is 298.55, 228.09, 187.27 mg/dL respectively. Group 3 indicates in visits 1, 2 and 3 that FBS is 237.00, 171.57, 130.64 mg/dL in the same way that PPBS is 305.00, 211.86, 165.79 mg/dL respectively.

While observing the age group of 51≤70 years in Group 1, the FBS shown in visits 1, 2 and 3 is 217.11, 171.63, 131.79 mg/dL, while the PPBS is 295.21, 229.53, 178.84 mg/dL respectively. In Group 2 registered in visits 1, 2 and 3 the FBS is 228.95, 175.11, 143.37 mg/dL and PPBS is 295.21, 229.53 and 178.84 mg/dL respectively. Considering Group 3 visits 1, 2 and 3 the range of FBS is 231.56, 175.25, 136.69 mg/dL at the same time PPBS is 321.38, 218.88, 172.56 mg/dL respectively.

Considering the age group of 30≤50 years, the Group 3 treatment group showed more effective control of FBS and PPBS from visits 1-3 by Dapagliflozin and Metformin combined drug therapy than the other two groups. At the same time, the age group of 51 ≤ 70 years showed the most effective treatment in Group 1, followed by Dapagliflozin and Sitagliptin, by observing the FBS and PPBS values from visits 1-3 when compared to the other two groups.

DISCUSSION

Notably, metformin has a favourable safety profile, making it the first-line therapy for diabetes. Several innovative anti-diabetic drugs have been explored in diabetic animal models and diabetic people during the last several decades. Because both SGLT-2 inhibitors and DPP-4 inhibitors are widely used in clinical practise, comparing the effects of these drugs is therapeutically important.[9]

Combination medications were formerly often combined sequentially and administered as separate pills. FDC medicines, on the other hand, are increasingly being used in clinical settings to treat type II diabetes. One advantage of FDC therapy versus separate tablet delivery is improved adherence, which has been related to better glycemic control and less medication waste. Both SGLT-2 inhibitors and DPP-4 inhibitors are widely used in clinical practice and both medications examined in this study proved their positive effects on blood glucose management. Because Type II DM is progressive and complicated, many diabetic patients struggle to attain effective glucose control with monotherapy alone. As a result, the use of a combination is suggested.[6,10]

Our study includes each group is followed by a specific treatment i.e., specific combination for the management of glycemic management. Group 1 followed by Dapagliflozin 10 mg and Sitagliptin 100 mg, Group 2 with Dapagliflozin 10 mg and Vildagliptin 100 mg and Group 3 with Dapagliflozin 10 mg and Metformin 500 mg for consecutive three visit to evaluate the efficacy.

While analysing male patients through different treatment groups, it would be noticed that Group 1, followed by the drug therapy of Dapagliflozin and Sitagliptin, showed the maximum control in FBS and PPBS levels from visit 1 to visit 3, compared to the other group. While considering female patients, Group 3 drug therapy of Dapagliflozin and Metformin controls more FBS and PPBS levels from visits 1 to 3 than the other two groups. At the same time, the mean age of male and female patients in Group 1 is 52.43 and 53.19 years, respectively and the duration of diabetes is 5.79 and 4.69 years. In Group 2, the mean age is 50.93 and 52.38 years and the duration of diabetes is 5.79 and 5.50 years, which shows males are affected more quickly than females at a younger age in the two effective treatment groups. In comparison to women, men are more susceptible to risk factors such as stress, alterations in lifestyle, such as smoking and drinking and irregular eating patterns. Diabetes is impacting both men and women more than ever before because stress-related factors produce reactive free radicals. Using pancreatic beta cells, aortic smooth muscle cells and endothelial cells in cell culture experiments, it has been shown that diabetes is linked to an increase in the production of Reactive Oxygen Species (ROS). It has been shown that oxidative stress suppresses the promoter activity and mRNA expression of the insulin gene, reducing insulin gene expression in cell lines and isolated pancreatic islet cells. Also strongly thought to be a contributing factor to insulin resistance brought on by chronic hyperglycemia is oxidative damage.[11]

Due to the retrospective nature of the inquiries, information on the patients' diet and physical activity was not accessible in this study. When taken in combination with a DPP-4 inhibitor, dapagliflozin considerably improved the glycemic control of type 2 diabetes patients, according to the findings of this study. The authors also suggested that using dapagliflozin as an adjunct medication might be a suitable option for individuals who are hesitant to take insulin therapy. Notably, the co-administered diabetes medicines had no significant comparative effect among the three groups. Dapagliflozin was not used as a single agent in the current study.[12,13]

It has also been proposed that dapagliflozin could protect pancreatic β cells by lowering plasma insulin levels, which might be a key component in long-term type II diabetes treatment. Given these considerations, we believe that when selecting medications to act as first-line medications for patients with type II diabetes, it is critical that the agent has a good glucose-lowering effect, does not cause hypoglycemia or weight gain, protects pancreatic β cells and is highly tolerable, particularly in elderly diabetes patients. Furthermore, it is critical to decrease cardiovascular events, particularly heart failure.[14]

Our study considers to specific combination of Dapagliflozin and Sitagliptin which results in effective lowering FBS and PPBS level. The complementary mechanisms of action of SGLT2i and DPP4i may explain these advantages of the combinations. As a result, combining them in an FDC product can provide benefits such as reduced tablet load and improved glycemic control.

CONCLUSION

The present investigation demonstrates for the first time that dapagliflozin, an add-on to sitagliptin, vildagliptin and metformin, has equivalent benefits for enhancing blood glucose control when used together. It's essential when selecting combination drugs to be used as first-line drugs for people with type 2 diabetes that the drug has a beneficial glucose-lowering effect without resulting in hypoglycemia or increasing body weight, protects pancreatic beta cells and is extremely tolerable, especially in elderly diabetes patients. Though the study shows dapagliflozin and sitagliptin are more effective than dapagliflozin added to vildagliptin and metformin, Dapagliflozin and vildagliptin show better control of diabetes when the duration is longer than in the other groups.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **SGLT2 inhibitors:** Sodium-glucose co-transporter2 inhibitors; **DPP-4 inhibitors:** Dipeptidyl Peptidase IV Inhibitors; **FBS:** fasting blood sugar; PPBS: Postprandial blood sugar; **OADs:** Oral antidiabetic medications; **FDC:** Fixed-dose combination.

SUMMARY

Diabetes mellitus is becoming an increasingly complex metabolic illness due to the consequences associated with persistent hyperglycemia. The purpose of the research is to look at the efficacy of several modern anti-diabetic medication combinations, such as SGLT2 inhibitors (dapagliflozin), DPP-4 inhibitors (sitagliptin and vildagliptin) and metformin. Patients with diabetes, who had blood glucose levels that were controlled as measured by Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS), satisfied the inclusion criteria for this research. This new research proves for the primary period that dapagliflozin has comparable advantages for improving blood glucose control when combined with sitagliptin, vildagliptin and metformin. It is vital when considering an oral combination to be used as the first line of treatment for persons with type 2 diabetes.

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