Journal of Clinical Nephrology & Kidney Diseases

Review Article
Published: 22 Mar, 2021

SGLT2 Inhibitors Use in Non-Diabetic Patients: A Narrative Review

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Abstract

We conducted a thorough review of the effects of SGLT2 inhibitors on cardiorenal protection in diabetic and non-diabetic patients in randomized controlled trials and controlled observational studies. PubMed, NCBI database, uptodate.com and ClinicalTrials.gov were searched with date restriction until December 28th, 2020. The medical subject headings included the terms: "sodium-glucose transporter 2" in combination with "Heart failure", "cardiovascular disease", "CKD", "renal failure" and "non-diabetic". This retrospective search evaluated pertinent data and allowed for a thorough review of literature on the usage of SGLT-2 inhibitors in non-diabetic patients. The search was not limited to say study designs. JA and JP first independently screened titles and abstracts of all articles and reviewed full texts of the potentially relevant studies and cases for use in this article. SM wrote the review of literature alongside conducting a thorough evaluation on the current research available.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a widespread disease across the United States and accounts for approximately 10% of the population according to the CDC. This statistic does not account for prediabetic patients which lead to diabetes if not managed efficiently. Diabetes has become more prevalent in the states in the past decade which has inevitably leaded to more research on a new line of treatment. One of the drug classes that was recently developed are the Sodium-Glucose Co-Transporter-2 inhibitors (SGLT2 inhibitors). As a 3rd line treatment for diabetes, their usage is predominantly dependent on individualized patient treatment plans and the comorbidities. While the SGLT-2 inhibitors are not the drug of choice as the first-line treatment for DM, current research has elucidated that patients with various existing conditions have shown proven benefits on their comorbidities but not on their respective diabetic profiles. So, why not utilize said treatment in non-diabetic patients with those other medical conditions like Chronic Kidney Disease (CKD), Heart Failure (HF) or Cardiovascular Diseases (CVD)? One out of three people with T2DM have underlying cardiovascular disease, and over 50% of people with T2DM die from a cardiovascular cause. In addition, approximately a third of people with long standing diabetes have CKD, and according to the CDC around 160 people with diabetes begin treatment for CKD every day. Interestingly the most common cause of CKD is diabetes and the second most common is Hypertension (HTN), henceforth, a drug improving both glycemic control and decreasing blood pressure would be more than welcome in the treatment of CKD. T2DM treatment classically focuses on insulin availability or sensitivity, delaying absorption of glucose in the gastrointestinal tract or reducing blood glucose by increasing glucose excretion through the kidneys. Increasing comorbidities in this population forces the scientific community to observe the mechanism of action of relevant diabetic drugs on other dilatory conditions associated with diabetes like HF or CKD.

Background

SGLT2 inhibitors act on the sodium glucose co-transporter present in the proximal convoluted tubules of the kidneys. By blocking reabsorption of 90% of the glucose excreted, they cause a mild disposal of glucose. They are not associated with hypoglycemia since that glycemic control is metabolically balanced by the plasma concentration of glucose. They also cause osmotic diuresis by enhancing excretion of sodium by the kidneys which eventually adversely affects the heart. This last statement is the main narrative behind their specific benefit on the heart and kidneys.

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Received Date: *25 Feb 2021*
Accepted Date: *16 Mar 2021*
Published Date: *22 Mar 2021*

Citation:
Audet J, Pagé J, Moten S, Rauf A. SGLT2 Inhibitors Use in Non-Diabetic Patients: A Narrative Review. J Clin Nephrol Kidney Dis. 2021; 6(1): 1029.

Since the effects of SGLT2 inhibitors on plasma glucose are mild, they are not considered the first line therapy for diabetes [1]. The health care professional must evaluate the patient on a multi-factorial platform, particularly in the presence of other comorbidities such as heart failure, or history of chronic kidney disease. The usage of SGLT-2 inhibitors on said population is particularly intreaging as the inhibitor has the ability to affect the comorbidities rather than the diabetes itself. SGLT2 inhibitors compared to a placebo decrease the risk of major cardiovascular outcomes (MI and stroke), cardiovascular death or heart failure. The decreased risk is observed in patient with a known history of Cardiovascular Disease (CVD), but controversial in patients with known multiple risk factors of CVD. In addition, SGLT2 inhibitors were compared to placebo and were found to slow down the progression of kidney function decline, reducing renal events and reducing mortality in patients with T2DM.

In that light, use of SGLT2 inhibitors in patient with CKD, CVD, HF or major risk factor for CVD but with no known history of diabetes mellitus are a possibility in modern cardiology and nephrology intervention. Various institutions are studying and closely monitoring the effects of SGLT2 inhibitors on HF and CKD on both, diabetic and non-diabetic patients. In this paper, we discuss that key factors of EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, EMPA-REG OUTCOME, CREDENCE, CANVAS and DAPA-CKD, and correlate the conclusion of given studies to the mechanism of action of SGLT2 inhibitors to attempt basic guidelines of usage and treatment.

CKD

Kidney disease is the 8th leading cause of death in the US, according to the CDC. Kidney disease is a silent disease, meaning that a vast majority of patients do not experience any symptoms in the early stages of the disease. The most common cause of CKD is diabetes followed closely by HTN; hence a drug improving glycemic control and decreasing blood pressure is a logical step in the line of treatment for CKD. If diagnosed early, CKD can be managed by mitigating unhealthy lifestyles and through implementing pharmacologic treatment. The management of CKD is based on slowing the progression of the disease to avoid Renal Replacement Therapy (RRT) *via* intensive blood pressure control. Currently, the standard care for preventing that progression includes blood pressure and glycemic control alongside the use of Angiotensin-Converting Enzyme inhibitors (ACE inhibitors). It is the first line therapy and it consists in giving patients with diabetic and non-diabetic CKD an ACE or Angiotensin-Receptor Blocker (ARB) until the maximal tolerated dose is reached. The choice between the two medications is based on evidence of benefits and the patient's tolerance to side effects. Unfortunately, in non-diabetic patients, the use of ACE inhibitors is the only pharmacologic treatment that has shown prevention of kidney failure in CKD. This increases the demand for new add on treatment when the first line is no longer enough. Second-line treatment consists of diuretics. The American Society of Nephrology suggests that the potential to use either thiazides or loop diuretics should be based on the patient's metabolic and blood profile. SGLT2 inhibitors were first introduced for patients as a diabetes management drugs because they acted on glucose reabsorption in the kidneys. It has now been shown that they slow the progression of kidney disease by decreasing the rate of function decline irregardless of the status of the patient's diabetes. The CREDENCE trial showed a clear benefit in CKD management in T2DM patients, but what about non-diabetic CKD patients? With the promising effects, physicians and clinicians deduced that the SGLT2 inhibitors could be integrated in the treatment regimen of CKD whether or not it is being used to manage a diabetic kidney. The DAPA-CKD trial answer was able to answer that question. The DAPA-CKD trial showed that the use of SGLT2 inhibitors (specifically dapagliflozin) have beneficial effects on renal function and mortality in patients with CKD, independent of their diabetes status. They found that the risk of "a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo" [2,3].

Rate of renal replacement therapy

Patients with long standing uncontrolled CKD will inevitably end up in end-stage renal disease and require Renal Replacement Therapy (RRT) if not adequately managed. The goal of RRT is to replace the non-endocrine kidney function in patients with renal failure. The forms of RRT consist of dialysis: Hemodialysis or peritoneal dialysis, and kidney transplant. In the EMPA-REG outcome trial, there was a significant risk reduction of RRT in 55% in patients treated with empagliflozin *vs.* placebo (0.45; 95% CI: 0.21 to 0.97; P=0.04). The CANVAS trial also showed a 40% reduction in their renal outcome, which included the need for RRT or mortality from any renal causes (HR: 0.60; 95% CI: 0.47 to 0.77) [4-7]. This risk reduction for RRT in patients is associated with an increase in quality of life of the patients, since majority of the RRT are time consuming and require a higher level of care and medications.

Effects on renal function

Life expectancy becomes markedly reduced when a patient's kidney function declines. The effect of the SGLT2 inhibitor on the maintenance of the glomerular filtration rate has been shown in various studies. The benefits of SGLT2 inhibitors come from its principal mechanism of action, which takes place in the proximal convoluted tubule of the nephron, blocking the reabsorption of glucose and sodium causing glucosuria and enhanced natriuresis. It has been proposed that the increase in the urinary concentration of glucose along with sodium is sensed by the macula densa, and thus restores the tubuloglomerular feedback and causing vasoconstriction of the afferent arteriole. This in turn decreases intraglomerular pressure, and hyperfiltration- a frequent pathophysiological problem in chronic kidney disease caused by diabetes. The pathophysiology of diabetic hyperfiltration is seen due to the high urinary glucose load causing SGLT2 activation, therefore causing an increase in glucose and sodium reabsorption. This diminished delivery of sodium in the renal tubules is sensed by the macula densa, which reduces the tubuloglomerular feedback, resulting in a dilation of the afferent arteriole and a concomitant efferent arteriole constriction, causing the hyperfiltration. Long term effects of this consist of damage of the kidney's selective glomerular barrier and lead to a net decrease of renal function and albuminuria. Albuminuria is also a key feature seen in patient with CKD without diabetes. Hence, SGLT2 inhibitors were expected to have a role in the primary prevention of diabetic and non diabetic kidney disease *via* attenuation of this mechanism [8]. The afferent arteriolar vasoconstriction would explain the initial reduction in the eGFR seen with the usage of SGLT2 inhibitors (EMPA-REG outcome trial, CANVAS) but the studies also have shown it was followed by a stabilization in renal functions compared to a marked decline in patients receiving the placebo (EMPA-REG OUTCOME: 0.19 mL/min/1.73 m^2 in empagliflozin group *vs.*

1.67 mL/min/1.73 m^2 in placebo [p<0.001]) [4,5,9,10]. Since these protective changes were seen independent of glycemic control, the DAPA-CKD trials evaluated the therapeutic potential in non diabetic patients with CKD. It was found that regardless of diabetic status, the risk of a marked decline in GFR, ESRD occurrence, and death from renal or cardiovascular cause with dapagliflozin *vs.* placebo was measured. The results showed a significant decreased risk in their composite outcome (sustained decline in the estimated GFR of at least 50%, end-stage kidney disease or death from renal causes) with a hazard ratio of 0.56, 95% CI: 0.45 to 0.68; p<0.001 [2,3].

Fibrosis

When a cell has a high intracellular glucose concentration it can induce the expression of specifics inflammatory cytokines, fibrotic mediators, and growth factors which may lead to the production of reactive oxygen species. This is often seen in diabetic patients with the activation of SGLT2 by the extensive filtered glucose load. The SGLT2 inhibitor via this intracellular glucose concentration reduction has been shown to decrease interstitial fibrosis [11]. The combined effects of inhibition of renal inflammation, with a reduction in TNFR1, IL-6, MMP7 and FN1, and reduction in oxidative stress alongside changes in glomerular hemodynamics are believed to be the main hypothetical processes in the reduction of renal fibrosis [12,13]. There has been some talk about using SGLT2 inhibitors for organ protection in the recent COVID-19 pandemic. The anti-inflammatory, antifibrotic effects and the reversal of renal hypoxia is believed to be translated to potential pulmonary injuries and has been studied in preclinical trials. Since the risk-benefit balance during this COVID-19 is still very uncertain, the favorable efficacy profile of SGLT2 inhibitor in preserving kidney functions and reducing the burden of heart failure is being considered in very severe cases of COVID-19 to try to increase survival rates [13].

Heart Failure (HF)

Management and treatment of Heart Failure with reduced Ejection Fraction (HFrEF) focuses on improving symptoms, reducing hospitalization, and increasing survival. Main line of treatment is classically composed of ACE, ARB or an Angiotensin Receptor Neprilysin Inhibitor (ARNI) with concomitant use of a beta-blocker. As a second-line approach, spironolactone is given in resistant HFrEF to a patient who presents with a GFR over 30 ml/min/1.73 m^2 and serum potassium under 5 mEq/L. The third-line management for refractory and persistent symptomatic HFrEF is composed of SGLT2 inhibitors or hydralazine with nitrate. The selection of either is contingent upon the patient's clinical presentation and evidence of the benefits outweighing the risks. SGLT2 inhibitors are the preferred medication in patients with DM-II but also demonstrate great effects in non-diabetic patients. SGLT2 inhibitors reduce the rate of hospitalizations of patient with heart failure and increase survival [11]. Heart failure is a condition usually part of a complicated array of diseases including diabetes mellitus. SGLT2 inhibitors have proven to help in heart failure with reduced ejection fraction in diabetic patients and in non-diabetic patients (hazard ratio: 0.72 [95% CI 0.60 to 0.87] and 0.78 [95% CI 0.64 to 0.97], respectively, interaction P=0.57) [14]. In patients with concurrent diabetes, SGLT2 inhibitors are adjuvant to treat hyperglycemia and diabetic kidney. The mechanism of action of these drugs is the culprit to understanding their effect in a heart failure population. Of note, none of these treatments are proven efficient in Heart Failure with preserved Ejection Fraction (HFpEF), further discussed in a later section.

Improvement of cardiovascular factors

Mechanisms of action of SGLT2 inhibitors on the cardiovascular system are mainly indirect *via* the renal system. They improve the cardiovascular profile by their effects on the nephron primarily. By the blockade of SGLT2 protein in the proximal tubule of the nephron, SGLT2 inhibitors reduces reuptake of glucose and sodium by the kidneys [15]. The latter causes a daily urinary loss of glucose which improves glycemic control in diabetic patients. Consistent use therefore improves HbA1C and contributes to a better cardiovascular profile. Interestingly, the loss of excess glucose also produces a calorie deficit which promotes weight loss and a better metabolic profile. Moreover, a significant loss of sodium and glucose causes an osmotic diuresis which is favorable to a healthier blood pressure. This enhanced natriuresis and glucose mediated diuresis, diminishes the cardiac preload by consistently reducing the plasma volume [16]. The enhanced natriuresis increases the delivery of sodium to the macula densa and by the tubuloglomerular feedback; this phenomenon causes vasoconstriction of the afferent arteriole to the nephron diminishing hyperfiltration, which again is a favorable mechanism of action in CKD. A decrease in body weight, reduction in blood pressure and a normal HbA1C are all contributing factors to a healthy cardiovascular profile. Of note, those outcomes are targeted goals by many therapies in heart failure.

Fasting mimicry and improved energy metabolism and anti-inflammatory properties

SGLT2 primarily causes a state of glucosuria which promotes a shift towards ketone metabolism, a more energy efficient state. In the case of heart failure, the heart preferentially uses ketone bodies as energy fuel, and therefore would be an advantage by this hypothetical effect of SGLT2 inhibitors [17]. This model has only been proven on rat models and has some contradictions since ketone metabolism also promotes glomerular hyperfiltration, diabetic nephropathy and kidney fibrosis [18]. Any glucosuric agent should then have similar cardiorenal effect which has not been demonstrated. SGLT2 inhibitors have now been postulated to induce cell response to starvation by activation of the SRT1/AMPK pathway. SGLT2 protein activation and SIRT1/AMPK are inversely proportional in their action [19]. Therefore, the blockade of SGLT2 protein would promote the activation of this respective pathway. SIRT1 mute oxidative stress and enhance antioxidant activity in cells therefore diminish any inflammatory processes. On the other hand, AMPK senses the balance between ATP and AMP in cells to preserve mitochondrial function and reduce inflammatory factor in the instance of starvation in addition to sense cell stress factors like hypoxia, injured organelles, etc. These classes of kinases are critical in the maintenance of cell homeostasis, survival, which promotes both cardiovascular and renal protection.

Direct cardiovascular effect of SGLT2 inhibitors: Ongoing studies

SGLT2 inhibitors could influence cardiac remodeling and fibrosis by modulating macrophage phenotypes. SGLT2 inhibitors would down-regulate a reactive oxygen and nitrogen species specific pathways and therefore diminishes cardiac fibrosis in post-infarcted rats [20]. Other ongoing hypotheses regarding SGLT2 inhibitors are to improve endothelial function by increasing flow-mediated dilation of vessels [21]. This effect has only been observed with the concomitant use of metformin. Moreover, this study has been conducted on a Japanese population and should, therefore, be evaluated in different ethnic backgrounds for its validity on a larger and more diverse

population.

What about HFpEF?

HFpEF is characterized by inflammation of the myocardium, adipose tissue deposit, and cardiac fibrosis. This results in a thickened ventricular wall and small cardiac chambers. Despite relative ejection fraction preservation, the stiffened ventricular chambers result in increased cardiac filling pressures and exertional dyspnea. Combined with distorted renal function, which is primarily the case in T2DM, this condition can have deleterious effect on the lifespan and quality of life in patients. HFpEF is predicted to have an increased prevalence in the US population in the upcoming decades due to the constantly aging population, and low death rates [22]. Since the treatment options are limited, more research and advancement is needed in order to efficiently create a more dynamic form of treatment. Currently, first-line treatment is solely based on management of fluid overload with diuretics, systolic and diastolic hypertension control with antihypertensive agents (choices of which is dependent on the specific condition of the patient) and risk factor modulations. Given that neurohormonal systems have deleterious effect on the heart in HFpEF, those systems are usually targeted in treatment and have proved to reduce morbidity and mortality [23]. SGLT2 inhibitors are shown to have significant impact in improvement of outcomes in HFrEF patients. This study shows that the use of empagliflozin in mice with impaired diastolic relaxation and increased left ventricular pressure could have beneficial effects on cardiac remodeling, plasma fluid balance and improvement of glomerular filtration; this has shown promising effects in HFpEF and has been conclusive in rat models [24]. Empagliflozin improved glycemic indices, diastolic function, left ventricular hypertrophy and improved fibrosis state ($P<0.05$) without any change in blood pressure ($P>0.05$). These findings and the conclusive effects of SGLT2 inhibitors on HFrEF serves as the major narrative in the EMPEROR-preserved trial [25]. Given the lack of current specific therapy in HFpEF, this trial could have major unknown impacts on clinical cardiology, and so, the independent results in diabetic and non-diabetic population should be further explored.

Discussion

Our review highlights that the use of SGLT2 inhibitors can be extended outside the diabetic only use. Though this pharmacological treatment was originally developed to mediate glycemic control, it has shown cardiac and reno-protective effects independent of glucose regulation as well as has positive metabolic effects. The control of blood pressure *via* the enhanced natriuresis, among others, is a key factor that helps prevent the worsening of CKD and paves the way towards a healthier cardiovascular profile. The use of SGLT2 inhibitors are associated with a decrease in body weight, reduction in blood pressure, slower eGFR decline, reduction in hyperfiltration, albuminuria, and a decrease in HbA1C - all of which are targets in the management of HF and CKD. The DAPA-CKD trial clearly showed the renal protective effects of the SGLT2 inhibitors outside the diabetic population to a larger population with CKD. These conclusions are a big step towards a robust treatment for patient with CKD without diabetes, particularly for whom only ACE inhibitors were shown to help prevent the progression towards end stage renal disease, and inevitably kidney failure. Various studies on SGLT2 inhibitors have underline minimal adverse effects in diabetic populations which are also expected to manifest in a non-diabetic population. Some precautions can further be implemented to prevent some of the most concerning side effects: AKI, hypotension, increased risk of Urinary Tract Infection (UTI), increase risk of bladder cancer, increase risk of fractures and Diabetic Ketoacidosis (DKA). The most alarming side effect was the increased risk of Acute Kidney Injury (AKI), which is believed to be caused by hypovolemia induced by the SGLT2 inhibitors. However, it was later proven in a systematic review, that the odds of suffering of AKI was reduced in patients receiving the SGLT2 inhibitors (OR: 0.40 [95% CI: 0.33 to 0.48], $p<0.001$) [26]. Another review of literature assessed adverse effects related to a reduced intravascular volume causing hypotension. The incidence of hypotension (orthostatic or postural dizziness) or other events related to volume reduction was small, and the difference was not statistically significant when contrasting the subjects given canagliflozin to the placebo group. It is also relevant to mention that a majority of the study's participant were also concomitantly taking some form of anti-hypertensive medication, mostly ACE inhibitors [27]. The increase risk of UTI appeared to be the most common complication and biggest threat to their use. This is unlikely, because after pondering on the EMPAREG OUTCOME, one learns that the overall occurrence of UTI was 18% and 18.1% in the 2 groups and the occurrence of UTI with complications was 1.7% and 1.8% in the empagliflozin *vs.* placebo groups. In CANVAS, the incidence of UTI with canagliflozin and placebo was 40 *vs.* 37 per 1000 patient-years, respectively ($p=0.38$). Those results were later reinforced with a meta-analysis concluding there was no significant difference in the risk of UTI in patients using SGLT2 inhibitors *vs.* placebo (RR: 1.03, 95% CI 0.96 to 1.11). There was some discussion regarding dapagliflozin having a statistically significant increase risk in the drug specific analysis, but it was later found to be dose specific to 10 mg daily and not to 5 mg daily [28]. This should be taken into account in their future use. Another side effect that was a major concern in the studies was the increase risk of bladder cancer. In clinical trials with dapagliflozin, safety signals have risen about bladder cancer but most of these patients already had hematuria at baseline, which could indicate preexistent cancers, but this still cannot eliminate the possibility that enhanced glycosuria can cause damage to the urinary tract [29]. The FDA recommended a post-marketing surveillance studies for this reason. Further on a meta-analysis published in 2016 assessed the risk of bone fracture with use of three different SGLT2 inhibitors and found that "compared with placebo, canagliflozin (OR: 1.15, 95% CI 0.71 to 1.88), dapagliflozin (OR: 0.68, 95% CI 0.37 to 1.25) and empagliflozin (OR: 0.93; 95% CI 0.74 to 1.18) were not significantly associated with an increased risk of fracture". Future safety monitoring should continue in post marketing to ensure bone health is warranted [30]. A concerning adverse event from SGLT2 inhibitor use is the increased risk of DKA. In a study comparing SGLT2 inhibitors *vs.* DPP-4 inhibitors, SGLT2 inhibitors, especially canagliflozin, were associated with increased risk of DKA with a hazard ratio of 2.85 (95% CI; 1.99 to 4.08) [31]. There is a more alarming type of DKA associated with SGLT2 inhibitor called "euglycemic" DKA since it is harder to recognize due to the absence of hyperglycemia [32,33]. This type of DKA was seen in type 1 diabetes (T1DM) patients but can also be observed in T2DM. The guidelines for future reference should be to measure serum ketones level in any patient experiencing nausea, vomiting, or malaise while they are on SGLT2 inhibitors. If acidosis is confirmed, the medication should be immediately discontinued to avoid further complications. This specific side effect was seen in studies on T1DM patients and there was a 5.8 increase fold of developing DKA. The high unmet need for treatment of T1DM brought the emergence of studies on the use of SGLT2 inhibitors in combination with insulin

therapy. The risk/benefit ratio doesn't seem to be positive enough to move forward with the use of SGLT2 inhibitor as adjuvant therapy for now. Hence, our recommendation would be to avoid use with T1DM patients. None of the side effects mentioned should cause further questioning in usage in a non-diabetic population. Monitoring and close surveillance should be similar to diabetic patients.

Conclusion

SGLT2 inhibitor is a current treatment in patient with T2DM with concurrent comorbidities. Promising discovery on cardio-renal outcome made their usage in non-diabetic patient the center of discussion in modern nephrology and cardiology. With a minimal effect on blood glucose level, their usage can be further questioned in non-diabetic patients. Studies showed positive effect on HFrEF, CKD and overall cardio-renal health panel. Ongoing studies are present in HFpEF, a field where common line of treatment is not efficient to control the disease consequences. In studies like CANVAS and EMPOROR, the side effect profile is similar in diabetic and non-diabetic patients. The use of SGLT2 inhibitors as an add on therapy to ACE inhibitors will be more widespread in the nephrology field for CKD patients in the years to come. From 3rd line therapy in HFrEF to an ongoing discussion about their positive effect profile, SGLT2 inhibitors could be used in combination with current therapy in heart failure patients. Overall, this class of medication shows promising effects on multifactorial levels that improves cardiovascular and renal outcomes. With the previously discussed factors, in addition to weight loss, further studies about their usage in obesity and metabolic syndrome are awaited. SGLT-2 inhibitors are very promising in the realm of medicine, particularly in non-diabetic patients; therefore further analysis is needed to demonstrate the use of this multi-fasceted drug.

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