

Sodium Glucose Co-transporter 2 Inhibitors

By Christos Argyropoulos

Reducing the human and financial burden of progressive diabetic kidney disease (DKD) and ESKD stalled after the landmark trials of renin-angiotensin system inhibitors (RASi) in the early 2000s. The recent introduction of sodium glucose co-transporter 2 inhibitors (SGLT-2i) appears to reverse 20 years of stagnation in this area. This short review summarizes the key findings in this emerging suc-

cess story of nephrology therapeutics.

Of rodents ...

According to the Brenner hypothesis (1), hyperfiltration drives nephrons to glomerulosclerosis and eventually leads to chronic kidney disease (CKD) and ESKD. Reducing hyperfiltration has been the major paradigm for slowing the progression of CKD through RASi. How-

ever, the actual mechanisms of hyperfiltration in DKD remained poorly defined until the seminal report that a phlorizin, a naturally occurring SGLT-2i found in the unripe apple, inhibited glomerular hyperfiltration in the diabetic rat (2). The hypothesis was put forward that stimulation of tubular glucose/sodium transport through the SGLT-2 system reduced tubuloglomerular feedback, decreasing hyperfiltration in DKD. Subsequent micro-puncture studies provided evidence in support of this hypothesis under long-term SGLT-2i administration and in diabetic mice lacking the SGLT-2 transporter (3, 4). In similar studies, SGLT-2i prevented changes in BP, glomerular size, and markers of inflammation (5).

... and humans

The U.S. Food and Drug Administration (FDA) approved the first SGLT-2i in early 2013, followed by the report of the mandatory cardiovascular outcomes safety trials (Table 1) (6–9). Overall, the trials reported to date show that SGLT-2i do not raise cardiovascular risk. Two of the SGLT-2i (canagliflozin and empagliflozin) are associated with clinically meaningful reductions in major cardiovascular events and cardiovascular death. All-cause mortality was reduced by empagliflozin, and all three SGLT-2i safety trials reported reductions in congestive heart failure (CHF). In these trials, there was an impressive reduction in the risk for hard renal endpoints (ESKD, need for dialysis or doubling of serum creatinine [DSC], or death), with relative risk reductions between 40% and 24%. These reductions, along with the effects of SGLT-2i on cardiac outcomes, are much larger than those obtained with RASi (Table 1). However, renal endpoints were either secondary or exploratory in these cardiovascular safety trials, requiring further confirmation.

The first dedicated renal endpoint, double-blind, randomized trial was recently reported for canagliflozin (CRE-DENCE) (10). This trial enrolled patients with estimated GFR (eGFR) between 30 and 90 mL/min per 1.73 m², on a background of RASi therapy. The composite endpoint of ESKD/DSC or renal death was lowered by 34%, and the relative risk of ESKD was lower by 32%. The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke and CHF (Table 1). Importantly, there were no differences in rates of amputation or fracture, safety signals that had been reported in previous studies.

Examination of the slope of the eGFR over time shows that the SGLT-2i conform to the pattern anticipated from the Brenner hypothesis and verified in the RASi era: An initial decline over the first couple of months of therapy is followed by dramatically reduced loss of eGFR over time (10, 11). Viewed as a class, SGLT-2i also reduce BP by 2.46 mm Hg

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INDICATION AND USAGE

AURYXIA is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL as compared with 13 (9%) of patients treated with active control.

Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdosage in Children Due to Accidental Ingestion:

Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Advise patients of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hyperphosphatemia in Chronic Kidney Disease on Dialysis

A total of 289 patients were treated with AURYXIA and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with AURYXIA for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with AURYXIA; dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA.

Adverse reactions reported in more than 5% of patients treated with AURYXIA in these trials included diarrhea (21%), discolored feces (19%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week, active-control period, 61 patients (21%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 21 patients (14%) in the active control arm. Patients who were previously intolerant to any of the active control treatments (calcium acetate and sevelamer carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing AURYXIA (14%).

DRUG INTERACTIONS

Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above

There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1-mice and Wistar-rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20% respectively.

Clinical Considerations

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy.

Lactation:

Risk Summary

There are no human data regarding the effect of AURYXIA in human milk, the effects on the breastfed child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 292 subjects aged 65 years and older (104 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant intravenous iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient on dialysis administered intravenous iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Instruct patients to take AURYXIA as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be dosed apart from AURYXIA. Advise patients not to chew or crush AURYXIA because tablets may cause discoloration of mouth and teeth.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician.

Accidental Ingestion: Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.

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(systolic) and 1.46 mm Hg (diastolic) while also reducing body weight by 1.88 kg and waist circumference by 2.89 cm (12).

SGLT-2i in nephrology practice

The American Diabetes Association (ADA) guidelines (13) recommend that SGLT-2i with documented cardiovascular benefit (to date, empagliflozin and canagliflozin) should be the second agent added after metformin in patients with type 2 diabetes (T2D) and CKD or CHF. This recommendation is in alignment with the FDA-approved indications for these two agents (Table 2). Currently four

SGLT-2i have been approved in the United States (Tables 2 and 3); they are similar in many regards but also different in others (e.g., status of completed trials, heterogeneity in renal and cardiovascular outcomes, dosing recommendations, intrarenal handling, and an emerging, highly technical literature about off-target effects).

A suggested pragmatic approach to how these agents may be introduced into nephrology practice follows: The ADA guidelines (a live document updated throughout the year) should be consulted for the currently approved indications for SGLT-2i. As nephrologists, we want to reduce cardiorenal risk in our patients, not just lower the

hemoglobin A1c, so SGLT-2i with proven benefit should be prescribed, not merely recommended, by our specialty first (Table 2). Nevertheless, the inclusion of drugs in formularies does not always follow the clinical evidence, and the clinician will often have to choose between any SGLT-2i or no SGLT-2i at all. In these situations, one should opt for the SGLT-2i whose more robust evidence the insurance will cover and the patient can afford the copay for. For optimal effect, these agents should be added on the background of RASi therapy (CREDESCENCE), yet, even RASi-intolerant patients can benefit, as shown in the large subgroup (20%) of the cardiovascular safety trials who

Table 1. Composite renal and cardiovascular safety outcomes of the approved (May 2019) SGLT-2 inhibitors reported in cardiovascular safety (EMPAREG, CANVAS program, DECLARE-TIMI-58) and dedicated renal outcomes trials (CREDESCENCE) against ACEi and ARBs in patients with diabetes

Angiotensin receptor blockers		SGLT-2 inhibitors		
Composite renal outcome				
Irbesartan (IDNT)	Losartan (RENAAL)	Canagliflozin (CREDESCENCE CANVAS program)	Dapagliflozin (DECLARE-TIMI-58) ⁹	Empagliflozin (EMPA-REG) ^{7,11}
0.80 (0.66–0.97)	0.84 (0.72–0.98)	0.66 ¹⁰ (0.53–0.81) 0.60 ⁸ (0.47–0.77)	0.76 (0.67–0.87)	0.61 (0.53–0.70)
ESKD / Need for Renal Replacement Therapy (RRT)/DSC				
All ARB	0.78 ¹⁴ (0.67–0.91)	0.68 ¹⁰ (0.54–0.82)	0.76 (0.67–0.87)	0.45 (0.40–0.75)
All ACEi	0.60 ¹⁴ (0.39–0.93)			
MACE 3 outcome (cardiovascular death, myocardial infarction, ischemic stroke)				
All ARB	0.94 ¹⁵ (0.85–1.01)	0.80 ¹⁰ (0.67–0.95)	0.93 (0.84–1.03)	0.86 (0.74–0.99)
All ACEi	0.86 ¹⁵ (0.77–0.95)	0.86 ⁸ (0.75–0.97)		
Dapagliflozin				
Death of any cause				
All ARB	0.94 ¹⁵ (0.82–1.08)	0.83 ¹⁰ (0.68–1.02)	0.93 (0.82–1.04)	0.68 (0.57–0.82)
All ACEi	0.87 ¹⁵ (0.78–0.98)	0.87 ⁸ (0.74–1.01)		
Cardiovascular death				
All ARB	1.21 ¹⁵ (0.81–1.80)	0.78 ¹⁰ (0.61–1.00)	0.98 (0.82–1.17)	0.62 (0.49–0.77)
All ACEi	0.83 ¹⁵ (0.70–0.99)	0.87 ⁸ (0.74–1.01)		
Congestive heart failure				
All ARB	0.70 ¹⁵ (0.59–0.82)	0.61 ¹⁰ (0.47–0.80)	0.73 (0.61–0.88)	0.65 (0.50–0.85)
All ACEi	0.81 ¹⁵ (0.71–0.93)	0.67 ⁸ (0.52–0.87)		

Outcomes as reported in cardiovascular safety (EMPAREG, CANVAS program, DECLARE-TIMI-58) and dedicated renal outcomes trials (CREDESCENCE) against ACEi and ARBs in patients with diabetes. The definitions of the composite renal outcomes differed among trials : IDNT and RENAAL (development of ESKD), Doubling of Serum Creatinine (DSC) or death from any cause, CREDESCENCE (ESKD, DSC, or death from renal or cardiovascular causes), CANVAS (40% reduction in eGFR, need for renal replacement therapy (RRT) or death from renal causes), EMPAREG (progression to macroalbuminuria, DSC, RRT, renal death, and incident albuminuria; this composite outcome was not prespecified in EMPA-REG but need for RRT was), DECLARE-TIMI-58 (40% reduction in eGFR, ESKD, or death from renal or cardiovascular causes). Data on ACEi/ARB from studies in patients with both type 1 and 2 diabetes, whereas all SGLT-2i studies are in patients with diabetes type 2.

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; DSC = doubling of serum creatinine; eGFR = estimated GFR; RRT = renal replacement therapy; SGLT-2i = sodium glucose cotransporter-2 inhibitor.

Diabetic Kidney Disease

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were not receiving RASi.

In contrast to the antiglycemic effect, the cardiorenal benefit appears to be dose independent, so the lowest dose of all drugs should be used. Dosing in relation to eGFR is likely to evolve over time, so the prescribing information should be consulted. The guidelines in Table 3 are likely to be modified to allow continuation of drugs even when the eGFR declines after CREDENCE. As with RASi, kidney function should be monitored periodically because these drugs have been associated with acute kidney injury (AKI). However, AKI should be clearly distinguished from the expected initial drop in kidney function, which, as with RASi, may signal a long-term benefit.

Patients should be warned about potential side effects, especially euglycemic ketoacidosis in patients already receiving insulin, and fungal genital infections. Common-sense clinical measures that may reduce the frequency (such as drying the genital area), prevent or reduce severity (instituting “sick-day” rules), or allow the early detection of these complications (e.g., providing urinary ketone strips) should be discussed with our patients. Despite the reassuring follow-up data about amputations, a thorough discussion of the risk-versus-benefit ratio should be undertaken in patients with pre-existing peripheral vascular disease.

Going forward, additional studies will report kidney and cardiac efficacy, dosing, and safety data about rare, yet sensational, side effects (e.g., amputations or Fournier gangrene) about all SGLT-2i. Given the magnitude of benefit seen in the existing trials, waiting for these future

studies to conclude before we use these agents in patients with type 2 diabetes and CKD implies that we forego the opportunity to improve the care of our patients today. ■

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Table 2. Indications for and pharmacologic properties of the approved (May 2019) SGLT-2 inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Antiglycemic indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Cardiovascular indication	To reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established CVD		To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established CVD	
Bioavailability	65%	72%	78%	~100%
Peak plasma time	1–2 hours	2 hours (fasting) to 3 hours (fatty meal)	1.5 hours	1 hour (fasting) to 2 hours (after meal)
Protein binding	99%	91%	86.2%	93.6%
Volume of distribution	119 L	118 L	73.8 L	85 L
Half-life	10.6 hours (100 mg) to 13 hours (300 mg)	12.9 hours	12.4 hours	16.6 hours
Total body clearance	192 mL/min	207 mL/min	177 mL/min	187 mL/min
Hepatic route	>50%	21%	41.2%	40.9%
GI recovery of parent compound	41.5%	15%	>35%	33.8%
Renal route	~33%	75%	54%	50.2%
Renal recovery of parent drug	<1%	<2%	~20%	1.5%

Hepatic and renal routes of elimination refer to the recovery of radioactive labeled parent drug either as the parent drug or as one of its metabolites. None of the metabolites of the currently approved SGLT-2 inhibitors are pharmacologically active. CYP metabolism of all SGLT-2i is also minimal.

Abbreviations: CVD = cardiovascular disease; GI = gastrointestinal.

Table 3. Renal dosage adjustments for the approved (May 2019) SGLT-2 inhibitors

eGFR range	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
>60 mL/min per 1.73 m ²	100–300 mg/day	5–10 mg/day	10–25 mg/day	5–15 mg/day
45–60 mL/min per 1.73 m ²	Not to exceed 100 mg/day	5–10 mg/day	10–25 mg/day	Not recommended
<45 mL/min per 1.73 m ²	Do not initiate	Not recommended	Do not initiate	Not recommended
<30 mL/min per 1.73 m ²	Contraindicated	Contraindicated	Do not initiate	Contraindicated

Abbreviation: eGFR = estimated GFR.

Emergence of GLP-1 Receptor Agonists as a Therapy for Diabetic Kidney Disease

By Radica Z. Alicic, Emily J. Cox, and Katherine R. Tuttle

A multitude of clinical effects beyond glycemic control have placed glucagon-like peptide-1 (GLP-1) receptor agonists front and center in the fields of diabetology, cardiology, and nephrology. These incretin-based antihyperglycemic agents reduce the risk of new or worsening kidney disease and decrease the risk of cardiovascular death and atherosclerotic events (1–5). In the wake of these findings, the American Diabetes Association Standards of Care for treatment of hyperglycemia in type 2 diabetes now state that GLP-1 receptor agonists with proven cardiovascular benefits (liraglutide > semaglutide > exenatide extended release) should be added to the therapeutic regimen if glycemic targets are not achieved with metformin, particularly in patients with atherosclerotic cardiovascular disease (6). GLP-1 receptor agonists currently approved by the United States Food and Drug Administration are liraglutide (Victoza, Saxenda), semaglutide (Ozempic), lixisenatide (Adlyxin), exenatide (Byetta) and exenatide extended-release (Bydureon, Bydureon, BCise), and dulaglutide (Trulicity). Approved combination therapies are insulin glargine/exenatide (Soliqua 100/33) and insulin degludec/liraglutide (Xultophy 100/3.6).

Evidence supporting the kidney and cardiovascular benefits of the GLP-1 receptor agonists comes from large clinical trials enrolling patients with type 2 diabetes, cardiovascular disease, chronic kidney disease (CKD), or a combination of these conditions (Figure 1).

The dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate to severe CKD (AWARD-7) clinical trial was the first to be conducted in patients with moderate to severe CKD; nearly a third of enrolled patients had stage 4 CKD (4). Dulaglutide outperformed insulin glargine, the active comparator, in achieving glycemic control in patients with type 2 diabetes and a mean estimated GFR (eGFR) of 38 ± 13 mL/min per 1.73 m². Over 1 year, the average eGFR decline was –3.3 mL/min per 1.73 m² in the insulin-treated group and –0.7 mL/min

per 1.73 m² in both the higher-dose (1.5 mg weekly) and lower-dose (0.75 mg weekly) dulaglutide-treated groups (4). Among AWARD-7 patients with macroalbuminuria (urine-to-albumin creatinine ratio >300 mg/g) at high risk for progression of kidney disease, attenuation of mean eGFR decline was maintained (–5.5 mL/min per 1.73 m² in the insulin glargine group compared with –0.7 mL/min per 1.73 m² and 0.5 mL/min per 1.73 m² in the dulaglutide 0.75-mg and 1.5-mg groups, respectively). Notably, fewer patients in the higher-dose dulaglutide group reached the composite endpoint of ESRD or >40% eGFR decline in comparison with the insulin glargine group (5.2% vs. 10.8%, *p* = 0.038) (7).

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial and the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) clinical trial, treatment with liraglutide or semaglutide compared with placebo resulted in fewer patients experiencing a composite cardiovascular outcome and decreased risk of CKD development and progression—benefits mainly driven by the reduction in new-onset macroalbuminuria (2, 3, 5). Similarly to AWARD-7, in patients with albuminuria as well as those with eGFR <60 mL/min per 1.73 m², the LEADER trial demonstrated reduction of a composite of new-onset macroalbuminuria, doubling of serum creatinine, requirement for kidney replacement therapy, and death due to kidney causes (2). Importantly, the reduction of cardiovascular events and all-cause mortality was greater in LEADER participants with eGFR <60 mL/min per 1.73 m² than in those with eGFR ≥60 (8). In patients with type 2 diabetes and a recent acute coronary syndrome, the addition of lixisenatide to usual care moderately reduced albuminuria, even though the rates of cardiovascular events were unaffected (1).

The mechanism by which GLP-1 receptor agonists reduce the risk of macroalbuminuria and slow eGFR decline in patients with type 2 diabetes remains to be fully elucidated. These agents favorably affect major CKD risk factors by improving control of hyperglycemia, hypertension, and excess body weight (9–11). In addition to modifying CKD risk factors, GLP-1 signaling directly promotes antioxidant, anti-inflammatory, and antifibrotic effects in the diabetic kidney (12, 13).

GLP-1 receptor agonists fill longstanding unmet needs: antihyperglycemic agents that can be used safely and effectively in patients with moderate to severe CKD, and agents that will slow eGFR decline in patients with eGFR <30 mL/min per 1.73 m². The encouraging results from the AWARD-7 and cardiovascular outcome trials provide hope that the GLP-1 receptor agonists will join a growing menu of agents available to tackle the burgeoning problem of CKD in type 2 diabetes. ■

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