Biochemical Efficacy of Sodium–Glucose Cotransporter 2 Inhibitors by Cardiovascular Risk Profile and Volume Status in a Real-World Diabetic Population

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Abstract: Despite large-scale randomized clinical trials (RCTs) highlighting a consistent prognostic benefit of sodium–glucose cotransporter 2 inhibitors (SGLT2is) both in diabetic patients at high cardiovascular risk and in those with heart failure, there is relative paucity of data on their biochemical effects in a real-world setting. We performed a retrospective analysis on consecutive diabetic patients who were prescribed a SGLT2i in a tertiary referral center and completed at least 1 year of treatment. Changes in glycated hemoglobin, weight, and hematocrit were compared across 2 cardiovascular risk categories, defined through the inclusion criteria of 3 large RCTs. Of the 459 patients screened, 312 completed 1 year of treatment (68.0%), 92 interrupted the treatment prematurely (20.0%), and 55 were lost to follow-up (12.0%). The most common cause of drug discontinuation was genital or urinary tract infections (9.4%). At 1 year, reduction in glycated hemoglobin concentration (−0.7 ± 1.5%, P < 0.001) and body weight (2.4 ± 4.6 kg, P < 0.001) was comparable between patients at high versus low cardiovascular risk, while hematocrit increase (2.3 ± 3.3%, P < 0.001) was more marked in patients with high cardiovascular risk and low baseline hematocrit. In a real-world population of diabetic patients, SGLT2is were well-tolerated at 1 year and led to improved glycemic control and weight loss. Hematocrit increase was more consistent in patients with high cardiovascular risk and signs of fluid overload, indicating euvolemic restoration as a potential cardioprotective mechanism mediated by these compounds.

Key Words: SGLT2 inhibitors, diabetes at high cardiovascular risk, HFpEF, hematocrit

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INTRODUCTION

Type 2 diabetes mellitus is a leading cause of morbidity and mortality worldwide, affecting nearly 10% of adults in high-income countries.1 Cardiovascular diseases are a major prognostic determinant in diabetic patients as this condition is associated with both an exponentially higher risk of atherosclerotic vascular complications and a faster heart failure (HF) onset and progression.2,3

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) are a relatively novel class of antidiabetic medications, which inhibit glucose reabsorption in the nephron thereby causing glycosuria. In addition to the well-established blood glucose–lowering effect, a series of large randomized clinical trials (RCTs) has suggested that SGLT2is have a strong prognostic impact on both diabetic patients at high cardiovascular risk and patients with heart failure with reduced ejection fraction (HFpEF), leading to their inclusion among first-line medications in the 2021 ESC guidelines.4–7 Moreover, empagliflozin was recently demonstrated to reduce HF hospitalizations across patients with heart failure with preserved ejection fraction (HFpEF), therefore becoming the first medication with proved prognostic benefit for this disease.8

In contrast with growing evidence from clinical trials, SGLT2is are still underused in routine clinical practice.9 This is at least in part because of the drug-related safety issues, such as recurrent urinary and genital tract infections, acute kidney injury, and ketoacidosis, which have been widely reported since their introduction on the market as antidiabetic medications.10,11 Furthermore, the mechanisms underlying
cardiovascular benefits are still unknown, and none of the various hypotheses proposed solely justifies the strong mortality reduction observed in RCTs.1,2

The aim of our registry was to provide real-world evidence on the safety profile of SGLT2is in diabetic patients referred to a tertiary care center and to compare their metabolic effects across different cardiovascular risk categories.

METHODS

This single-center, retrospective observational registry was conducted at IRCCS Humanitas Research Hospital (Rozzano, Milan, Italy) from March 2015 to June 2020. This study was approved by the institutional review board and conforms with the principles outlined in the Declaration of Helsinki. The investigators were responsible for all data extraction, collection, and analysis. When clinical data were uploaded on the electronic records during routine clinical visits, all patients were assigned a numeric code so that the extracted data were anonymized. As such, informed consent for study enrolment was waived.

Consecutive diabetic patients who were prescribed a SGLT2i at the local diabetology clinic were screened and those who continued the treatment for at least 1 year were included in the final analysis. Patients with stage ≥4 chronic kidney disease (estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m² using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation13) and those with a diagnosis of type 1 diabetes mellitus were not eligible for SGLT2i use based on the prior guidelines and were therefore excluded. After the enrolment visit (T0), all patients had follow-up clinical visits scheduled at high-risk into high-risk with low Htc, if baseline Htc was lower than the first tertile, and high-risk with medium–high Htc, if baseline Htc fell into the second or third tertile.

Statistical Analysis

Continuous variables were reported as mean and SD, based on the normality assumption for large sample sizes. Categorical variables were reported as absolute number and percentage. Multiple imputation (R package “mice”; 5 imputed data sets) was used to handle missing values of the variables of interest. Both baseline and follow-up variables (see full list in the Supplemental Digital Content, http://links.lww.com/JCVP/A821) were included in the multiple imputation model, to increase the accuracy of point estimates.15 The percentage of missing values for each baseline variable is reported in the Appendix (see Table 3, Supplemental Digital Content, http://links.lww.com/JCVP/A821); for follow-up variables, there were no missing data. HbA1c, eGFR, Htc, hemoglobin (Hb), and weight at T0, T1, and T2 were compared using the paired samples Student’s t test. Between-group differences for baseline values, delta values, and percent delta values were assessed using independent samples Student’s t test. Between-group differences for baseline variables, delta values, and percent delta values were assessed using independent samples Student’s t test, if 2 groups were compared, or through the analysis of variance with Bonferroni adjustment, in case of multiple (>2) groups. Analysis of variance with Bonferroni adjustment was used to compare rates of medications at T0, T1, and T2. Association between mH2FpEF score, as the independent variable, and baseline Htc, as the dependent variable, was evaluated through a linear regression model.

All reported P values were 2-sided, and a P < 0.05 was considered statistically significant. Statistical analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 17 (StataCorp, College Station, TX).

RESULTS

From March 2015 to June 2020, 459 diabetic patients were prescribed a SGLT2i. Of these, 92 (20.0%) interrupted the treatment before 1 year, 55 (12.0%) were lost to follow-up (Fig. 1), and 312 (68.0%) were adherent to the drug at 1 year and were therefore considered as the study population. The most common cause of discontinuation was urinary (UTI) or genital tract infections, occurring in 43 patients (9.4%). Twenty-three patients (5%) had to switch antidiabetic treatment before 1 year because of poor glycemic control. Based on prior guidelines indication, SGLT2is were suspended because of worsening renal function and homoconcentration at periodic blood examinations in 5 (1.1%) and 3 (0.7%) patients, respectively. In 25 patients (5.4%), adverse events which did not lead to drug discontinuation were observed. In particular,
14 patients (3.1%) had urinary or genital tract infections which were deemed nonsevere by the treating physicians, and 3 patients (0.7%) had a myocardial infarction.

The baseline characteristics of the study population are summarized in Table 1. One hundred eighty-five of the 312 included patients (59.3%) were male. The mean age was 62.92 \pm 10.65 years, and 44 patients (14.1%) were aged 75 years or older. The mean diabetes duration was 10.85 \pm 8.40 years. The most commonly prescribed SGLT2i was empagliflozin (165/312 patients, 52.9%), followed by dapagliflozin (122/312, 39.1%) and canagliflozin (25/312, 8.0%). Most patients suffered from hypertension (250/312, 80.1%). The mean body mass index (BMI) was 32.02 \pm 5.74 kg/m², and 186 patients (59.6%) were obese as defined by a BMI \geq 30 kg/m². A history of coronary artery disease (CAD) was recorded in 98 patients (31.4%), while 35 (11.2%) and 17 (5.4%) patients had significant carotid artery disease and peripheral artery disease (PAD), respectively. Seventeen patients (5.4%) had a concomitant diagnosis of HFpEF.

Supplemental Digital Content (Figure 1S, http://links.lww.com/JCVP/A821) shows the distribution of the mH2FpEF score in the study population, after having excluded patients with HFpEF (n = 295). One hundred fifty-six patients (52.9%) had a score \geq 3, reflecting a \geq 50% probability of having underlying HFpEF.

Median follow-up duration was 6 months for T1 and 12 months for T2. Supplemental Digital Content (see Table 4, http://links.lww.com/JCVP/A821) shows the rates of cardiovascular and antidiabetic medications usage at the 3 time points. Two hundred sixty-six patients (85.3%) had metformin at baseline while 122 (39.1%) had prescribed insulin. Most of the patients also used angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) (222/312, 71.2%) and beta blockers (169/312, 54.2%).

Mean values of the main biochemical parameters at baseline, 6 months, and 12 months of follow-up were compared (Fig. 2). Mean percentage HbA1c values at baseline (8.0 \pm 1.7 mg/dL) were significantly higher than at T1 (7.2 \pm 1.1, P < 0.001) and T2 (7.3 \pm 1.3, P < 0.001), while no differences between T1 and T2 were present. Similarly, a

| TABLE 1. Baseline Characteristics |
|-------------------------------|
| N                             | 312 |
| Age (yr) (mean \pm SD)        | 62.92 \pm 10.65 |
| Age 75 y or older [n [%]]     | 44 (14.1) |
| Female sex [n [%]]            | 127 (40.7) |
| Race [n [%]]                  |         |
| White                         | 297 (95.2) |
| African American              | 2 (0.6)  |
| Others                        | 13 (4.2)  |
| Body mass index (kg/m²) (mean \pm SD) | 32.02 \pm 5.74 |
| Obesity (body mass index \geq 30 kg/m²) [n [%]] | 186 (59.6) |
| Smoking [n [%]]               |         |
| Current                       | 68 (21.8) |
| Former                        | 94 (30.1) |
| Never                         | 150 (48.1) |
| Hypertension [n [%]]          |         |
| Yes, treated with only 1 medication | 58 (18.6) |
| Yes, treated with at least 2 medications | 185 (59.3) |
| Yes, untreated                | 7 (2.2)  |
| No                            | 62 (19.9) |
| eGFR (CKD-EPI creatinine equation—categorized) [n [%]] | |
| \(\geq 90\) mL/min/1.73 m²     | 143 (45.8) |
| 60–89.9 mL/min/1.73 m²        | 132 (42.3) |
| 45–59.9 mL/min/1.73 m²        | 31 (9.9)  |
| 30–44.9 mL/min/1.73 m²        | 6 (1.9)   |
| Family history of cardiovascular disease [n [%]] | 71 (22.8) |
| Chronic obstructive pulmonary disease [n [%]] | 37 (11.9) |
| Obstructive sleep apnea syndrome [n [%]] | 21 (6.7) |
| Carotid artery disease [n [%]] |         |
| \(\geq 50\)% stenosis         | 27 (8.7)  |
| Prior thromboendarterectomy    | 8 (2.6)   |
| Other peripheral artery disease [n [%]] |         |
| \(\geq 50\)% stenosis         | 10 (3.2)  |
| Prior intervention             | 7 (2.2)   |
| Prior transient ischemic attack or stroke [n [%]] | 18 (5.8) |
| History of coronary artery disease [n [%]] | 98 (31.4) |
| Prior myocardial infarction [n [%]] | 75 (24.0) |
| Prior coronary revascularization [n [%]] |         |
| Percutaneous coronary intervention | 65 (20.8) |
| Coronary artery bypass grafting | 16 (5.1)  |
| Both                          | 12 (3.8)  |
| History of atrial fibrillation [n [%]] | 29 (9.3) |
| History of heart failure with reduced ejection fraction [n [%]] | 17 (5.4) |
| Diabetes duration (yr) (mean \pm SD) | 10.85 \pm 8.40 |
| SGLT2 inhibitor [n [%]]       |         |
| Empagliflozin                 | 165 (52.9) |
| Dapagliflozin                 | 122 (39.1) |
| Canagliflozin                 | 25 (8.0)  |
significant weight reduction was observed from T0 (87.6 ± 17.2 kg) to both T1 (85.2 ± 16.9 kg, Δ = -2.4 ± 4.1, P < 0.001) and T2 (85.2 ± 17.1 kg, Δ = -2.4 ± 4.6, P < 0.001), while mean weight values at T1 and T2 were comparable. Estimated glomerular filtration rates at T0 (85.1 ± 19.4 mL/min/1.73 m²), T1 (84.5 ± 21.4 mL/min/1.73 m²), and T2 (84.9 ± 21.8 mL/min/1.73 m²) were comparable (P > 0.05 for all comparisons). The mean hematocrit was 41.4 ± 4.0% at T0, 43.7 ± 4.6% at T1 [Δ (T1 - T0) = 2.3 ± 3.2%, P < 0.001] and 43.7 ± 4.4% [Δ (T2 - T0) = 2.3 ± 3.3%, P < 0.001] at T2.

When applying the inherent simplified inclusion criteria (see Table 2, Supplemental Digital Content, http://links.lww.com/JCVP/A821), the percentage of high cardiovascular risk patients in our population was 39.1% for EMPA-REG OUTCOME (122/312), 76.6% (239/312) for CANVAS, and 75.6% (236/312) for DECLARE-TIMI 58. The mean ΔHbA1c in the overall group was −0.7 ± 1.5%, and no significant differences between patients at high versus low cardiovascular risk according to the 3 trials definitions were encountered (Fig. 3 and see Table 5, Supplemental Digital Content, http://links.lww.com/JCVP/A821). Baseline hematocrit was

![Glycated hemoglobin (%)](image1)

**FIGURE 2.** Biochemical alterations at 6 months and 1 year. Mean values (with SD) of glycated hemoglobin concentration (A), glomerular filtration rate (B), body weight (C), and hematocrit (D) at baseline, 6 months, and 1 year are displayed, alongside with the relative deltas.
FIGURE 3. Changes in glycated hemoglobin, hematocrit, and weight at 1 year based on cardiovascular risk profile. Mean values of delta (T2 – T0) glycated hemoglobin concentration (upper panel), hematocrit (middle panel), and weight (lower panel) in patients at high cardiovascular risk (red) and low cardiovascular risk (green), as defined by the inclusion criteria of 3 large scale randomized clinical trials (EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58) are displayed.
higher among patients at low risk (see Table 4, Supplemental Digital Content, http://links.lww.com/JCVP/A821), while there were no significant differences in ΔHtc and %ΔHtc.

Supplemental Digital Content (Table 6, http://links.lww.com/JCVP/A821) shows the comparison of baseline, delta, and percent delta values across different subgroups. ΔHbA1c was greater in patients who had insulin (−0.95 ± 1.65 vs. −0.50 ± 1.32, $P = 0.009$), who also had higher HbA1c at baseline (8.84 ± 1.84 vs. 7.41 ± 1.33, $P < 0.001$). Obese patients had a significantly greater ΔWeight (−2.89 ± 4.80 vs. −1.80 ± 4.32, $P = 0.042$) as well as those with no history of CAD (−2.90 ± 4.54 vs. −1.46 ± 4.72, $P = 0.010$).

ΔHtc was always significantly greater in patients with high cardiovascular risk and low baseline Htc compared with those at low risk or at high risk with medium–high Htc ($P < 0.001$ for all comparisons), as shown in Figure 4. At linear regression analysis, higher mH2FpEF scores were associated with lower baseline Htc values ($β$: −0.3, $P = 0.026$).

DISCUSSION

The main results of this real-world registry of diabetic patients treated with SGLT2is are listed as follows: (1) overall, SGLT2is were well-tolerated with an adherence of 68% at 1 year; however, one out of 5 patients discontinued the drug before 1 year, mainly driven by urinary or genital tract infections in almost 10% and by scarce blood glucose control in 5% of patients; (2) among those who were adherent, SGLT2is on top of other guideline-recommended antidiabetic and cardiovascular medications led to significantly improved glycemic control (−0.7% decrease in HbA1c) and weight loss (−2.4 kg), with no effects on renal function; (3) these biochemical changes were consistent regardless of baseline cardiovascular risk; and (4) hematocrit increase at 1 year (+2.3%) was more pronounced in patients with high cardiovascular risk and fluid overload, reflected by a lower baseline Htc.

By causing glycosuria, SGLT2is exert a glucose-lowering effect which is different from most other antidiabetic drug classes, and in fact, since they have been brought into the market, continuous concerns about their safety and efficacy have emerged. Our registry confirms a not negligible incidence of adverse events leading to discontinuation, early after the beginning of the treatment, with an overall 20% incidence. This was mainly driven by a combined 9.4% rate of urinary and genital infections; of note, an additional 3.1% of patients experienced similar infections to a milder degree, not leading to drug discontinuation. The latter findings are in line with previous reports from both clinical trials and nationwide cohorts, in which UTIs and genital fungal infections affected more than 10% patients per year among those treated with SGLT2is. Although there is a biological plausibility for SGLT2is causing UTIs, most of these infections are not severe, and the rates of associated urosepsis and pyelonephritis are in the range of 1/500–1/1000 patients; in fact, none of the patients in our cohort had a complicated UTI. It is expectable that with growing awareness of benefits and side effects of these medications, clinicians will be more likely to prevent and manage nonsevere UTIs than to discontinue SGLT2is.

SGLT2is were proved to have a consistent glucose-lowering effect in this study, with only 5% of patients switching to other antidiabetic medications because of poor glycemic control, and a mean HbA1c decrease of −0.8% at 6 months and −0.7% at 1 year from an average baseline level of 8% across the adherent patients. Such decrease is comparable with that described in a meta-analysis of placebo-controlled studies of SGLT2is. In addition, the trend toward a greater HbA1c reduction in the first weeks with steady levels from 6 months to 1 year had already been reported in CANVAS and EMPA-REG and reflects the mechanism of

**FIGURE 4.** Hematocrit changes at 1 year based on baseline cardiovascular risk and volume status. Mean values of delta hematocrit and relative standard deviations (error bars) are displayed. After applying the simplified high cardiovascular risk definitions of 3 large randomized clinical trials (EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58), patients were classified into 3 groups: low-risk (yellow), high-risk and medium–high baseline hematocrit (if baseline hematocrit fell into the second or third tertile—orange), high-risk and low baseline hematocrit (if baseline hematocrit fell into the first tertile—red).
action of SGLT2is, whose ability to lower blood glucose and HbA1c levels is limited by the filtered load of glucose, which falls as plasma glucose levels fall.4,5,19 For the same reason, these drugs cannot directly cause hypoglycemia, which we observed in only 1 patient who was concomitantly treated with a sulfonylurea.19 The complimentary antidiabetic effect compared with insulin sensitizers and secretagogues also underlies the unchanged rate of metformin, insulin, thiazolidinediones, and sulfonylureas prescriptions across the 3 time points. Therefore, SGLT2i improved glycemic status on top of other antidiabetic medications.20 Finally, although empagliflozin was the agent of choice in more than half of the patients, there were no differences in the degree of HbA1c reduction when compared with dapagliflozin and canagliflozin, confirming the well-known drug class effect.21

As expected, SGLT2is displayed an optimal renal safety, as indicated by no significant changes in eGFR at 6 months and 1 year, on this population of diabetic individuals with relatively normal baseline kidney function (only 1.9% of those included had an eGFR < 45 mL/min/1.73 m², and none had eGFR < 30 mL/min/1.73 m²). Consistently, only 5 of the 459 screened patients (1.1%) had to interrupt the treatment because of worsening renal function.

Weight reduction (~2.4 kg) was also consistent with findings from a prior meta-analysis showing a ~2.1 kg weight loss compared with placebo, while the plateau from 6 to 12 months is probably due to compensatory caloric intake after the first weeks of treatment.12,22 Body mass reduction is believed to be one of the main players of SGLT2i-associated cardiovascular benefit, and 2 theories have been proposed. At first, urinary glucose excretion can induce osmotic diuresis and natriuresis with extracellular fluid loss; second, metabolic alterations caused by SGLT2is promote a reduction in visceral adipose tissue.23,24 Overall, up to 3 quarters of the total weight loss is believed to be from body fat and only 15%–35% from interstitial water.25 The prominent role of adipose fat depletion seems to be confirmed by the fact that there were no differences in AWeight between patients with and without HFrEF in our cohort, with a numeric trend toward those presenting no history of HF.

Increasing hematocrit levels (+2.3% at 1 year in the present cohort) have been observed in all major trials of SGLT2is in diabetic patients at high cardiovascular risk and were in great part attributed to enhanced diuresis with plasma and extracellular volume contraction.26,27 In a mediation analysis of EMPA-REG OUTCOME trial, changes in hematocrit and hemoglobin were the 2 strongest predictors of the reduced risk of cardiovascular death with empagliflozin versus placebo.28 When performing a subgroup analysis by applying to our population, the high cardiovascular risk definitions used to include patients in EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58,4-6 patients with high cardiovascular risk had a numerically higher increase in hematocrit than those at low risk. More importantly, patients experiencing greater hematocrit increase at 1 year were those with more consistent fluid overload, thereby presenting high cardiovascular risk and low baseline hematocrit. This finding is hypothesis generating for 2 reasons. As first, because hematocrit is a direct marker of volume status, it suggests SGLT2is reduce fluid retention and improves systemic congestion.29 A recently published post hoc analysis of the EMPAREG-OUTCOME trial observed a similar cardiovascular efficacy of SGLT2is in patients with or without volume overload; however, an unstandardized definition of fluid overload, based only on clinical evaluation, was adopted, and this might have generated significant selection bias.30 Second, about half of the included patients had a high clinical likelihood of having underlying HFpEF, as indicated by the mHF2PEF score distribution.

Because clinical signs and symptoms of congestion were not routinely investigated in the diabetology clinic, cardiological evaluation and echocardiography were often not prescribed to these patients, thus not allowing to pose a proper HFpEF diagnosis. Indeed, HFpEF is notably underdiagnosed in clinical practice because of many patients being asymptomatic or only mildly symptomatic at rest, while isolated diastolic dysfunction represents the earliest stage of diabetic cardiomyopathy.14,31–33 HFpEF is also associated with water and sodium retention and fluid overload, and in fact, we observed a significant negative correlation between baseline hematocrit values and mHF2PEF score.34 It is therefore likely that if HFpEF had been considered in the diagnostic assessment of these patients, SGLT2is would have been proven to provide more efficacious euvoletic restoration among those with HFpEF and systemic congestion.

Increased hematocrit also indicates increased blood viscosity, which has been yield responsible of some ischemic complications reported for SGLT2is, mainly stroke and lower-limb amputations.35,36 Across the study population, however, the rate of ischemic adverse events was limited: 4 patients (0.8%) had a myocardial infarction (of whom only 1 discontinued the treatment), 1 had a stroke (0.2%) and 2 (0.4%) underwent PAD progression.

Limitations

This study has several limitations, most of which are inherent to its single-center retrospective design. First, there was a selection bias because patients who were not taking the drug at 1 year, including those in whom SGLT2is were interrupted because of poor glycemic control, had to be excluded. This might have overestimated SGLT2i efficacy especially for HbA1c reduction; however, a relatively small percentage of the overall cohort (5%) fell into this category. Second, the decision to interrupt or to continue the treatment was based on clinicians’ discretion, and no standardized definitions of adverse events severity were provided. Third, the relatively short follow-up duration might limit the generalizability of our findings on adherence and side effects, while most of SGLT2i-related biochemical alterations notably occur within the first weeks from initiation.12 Fourth, in the analysis of patients at high versus low cardiovascular risk, we used some simplified inclusion criteria for the 3 RCTs; our aim was to obtain a surrogate definition of cardiovascular risk, while this study should not be intended as an eligibility analysis. Fifth, a not negligible even if acceptable proportion of patients (12%) were lost to follow-up.
CONCLUSION

In a population of diabetic patients treated with SGLT2 inhibitors and referred to a tertiary care center, SGLT2 inhibitors showed a good safety profile, with over two-thirds of patients tolerating the drug at 1 year. A good glycemic and metabolic control was achieved at 6 months and 1 year, as indicated by glycated hemoglobin and body mass lowering. Euvolemic restoration, expressed through an increase in hematocrit, was more pronounced in patients with high cardiovascular risk and signs of volume overload and might be a key determinant for the prognostic benefits offered by SGLT2is.

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