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ORIGINAL ARTICLE

An Exploratory Study of Dapagliflozin for the Attenuation of Albuminuria in Patients with Heart Failure and Type 2 Diabetes Mellitus (DAPPER)

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Abstract

Background and Aims Sodium-dependent glucose transporter-2 (SGLT-2) inhibitors, which are anti-diabetic drugs, reportedly decrease the incidence of cardiovascular events in high-risk patients with cardiovascular diseases, and thus chronic heart failure (CHF). SGLT-2 inhibitors also decrease albuminuria in patients with type 2 diabetes mellitus (T2D). Since albuminuria is a biomarker of not only chronic kidney disease but also cardiovascular events, we hypothesized that, among T2D patients with CHF, SGLT-2 inhibitors will decrease the extent of albuminuria and also improve CHF concomitantly.

Methods DAPPER (UMIN000025102) is a multicenter, randomized, open-labeled, parallel-group, standard treatment-controlled study, which is designed to evaluate whether dapagliflozin, one of the SGLT-2 inhibitors, decreases albuminuria in T2D patients with CHF and exerts cardioprotective effects on the failing heart. The patients are randomized to either of the dapagliflozin (5 or 10 mg, once daily orally) or control group (administration of anti-diabetic drugs administered other than SGLT 2 inhibitors). The estimated number of patients that need to be enrolled is 446 in total (223 in each group). The primary objective is the changes in the urinary albumin-to-creatinine ratio from the baseline after 2-year treatment. The key secondary objectives are (1) the safety of dapagliflozin and (2) the cardiovascular and renal efficacies of dapagliflozin.

Conclusion and Perspectives DAPPER study investigates whether dapagliflozin decreases albuminuria and exerts beneficial effects on the failing heart in T2D patients. (UMIN000025102).

Keywords Dapagliflozin · Type 2 diabetes mellitus · Chronic heart failure · Urinary albumin-to-creatinine ratio · Cardiovascular protection

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Introduction

Many studies targeting therapeutic strategies for chronic heart failure (CHF) have demonstrated the effectiveness of the medications including beta-blockers, angiotensin converting enzyme inhibitors, and mineral corticoid receptor blockers, which has culminated in guidelines for the treatment of CHF [1, 2]. However, further efforts are needed for the effective treatment for CHF because the number of CHF patients has continued to rise with increase in the prevalence of lifestyle-related diseases such as diabetes [3], hypertension [4], and dyslipidemia [5]. These lifestyle-related diseases simultaneously impair renal and cardiac functions, and renal dysfunction further deteriorates cardiac function, which is known as "cardio-renal syndrome" [6]. Therefore, the development of drugs that target lifestyle-related diseases and chronic kidney disease (CKD) are theoretically effective for the

treatment of CHF. Type 2 diabetes mellitus (T2D) is associated with lifestyle-related diseases, CKD and CHF. Among the many anti-diabetic drugs currently available, the administration of empagliflozin, a sodium-dependent glucose transporter-2 (SGLT-2) inhibitor, resulted in marked reductions in cardiovascular (CV) mortality (38%), hospitalization for heart failure (35%), and death from any cause (32%) in T2D patients at high risk of CV events in the EMPA-REG OUTCOME trial [7]. Empagliflozin has also been associated with the slower progression of kidney disease and lower rates of clinically relevant renal events [8, 9]. These findings support the potential of SGLT-2 inhibitors to ameliorate the pathophysiologies of T2D, CKD, and CHF. An observational study reported that a 52-week treatment with dapagliflozin, another SGLT-2 inhibitor, decreased the urine albumin-to-creatinine ratio (UACR) in Japanese patients with T2D [10]. Another randomized clinical trial (RCT) showed that the administration of 5 or 10 mg dapagliflozin for 104 weeks improved the category of UACR in T2D patients with moderate renal impairment [11]. Since sub-analyses of large RCTs recruiting CHF patients revealed that UACR is one of the risk factors for higher mortality [12], dapagliflozin appears to improve UACR and decreases in CV events in T2D patients. However, this may not be the case for CHF patients with T2D.

Therefore, we intended to investigate whether dapagliflozin attenuates albuminuria, and thus has a CV impact in T2D patients with CHF.

Methods and Design

Purpose

The purpose of the present study is to evaluate whether dapagliflozin, a SGLT-2 inhibitor, delays or prevents the deterioration of albuminuria in T2D patients with CHF along with the cardioprotective effects.

Study Setting

DAPPER is a multicenter, randomized, open-labeled, parallel-group, standard treatment-controlled study.

Endpoint

The primary endpoint is the changes in UACR from the baseline after a 2-year observation.

The secondary endpoints are the following:

1. The proportion of the number of patients presenting with an albuminuria category shift in each group (dapagliflozin group and control group).
   Improvement test
   A shift to a better category
   Prevention test
   No shift to a worse category
   Categories
   Category 1 (less than 30 mg/g Cr)
   Category 2 (from 30 to 299 mg/g Cr)
   Category 3 (more than 300 mg/g Cr)
2. Changes of eGFR during a 2-year period.
3. The proportion of the number of patients presenting with an eGFR category shift in each group.
   Improvement test
   A shift to a better category
   Prevention test
   No shift to a worse category
   Categories
   Category 1 (more than 90 ml/min/1.73 m^2)
   Category 2 (from 89 to 60 ml/min/1.73 m^2)
   Category 3 (from 59 to 45 ml/min/1.73 m^2)
4. The changes of urinary kidney injury molecule-1 (KIM-1) from the baseline after a 2-year observation.
5. The changes in the plasma aldosterone concentration, plasma NT-proBNP concentration, serum FGF23 concentration, and plasma alpha-Klotho concentration from the baseline after a 2-year observation.
6. The composite endpoint, which is defined as CV death or hospitalization for CV events in a 2-year observation.
7. The composite endpoint, which is defined as CV death or the hospitalization for HF in a 2-year observation.
8. The onset of CV events in a 2-year observation.
9. Hospitalization for CV events in a 2-year observation.
10. Hospitalization for HF in a 2-year observation.
11. Death from all causes in a 2-year observation.
12. Hospitalization for all causes in a 2-year observation.
13. An additional change in prescriptions for HF in a 2-year observation.
14. The changes in echocardiographic parameters, including left ventricular end-diastolic and end-systolic dimensions, the left atrial volume index, left atrial dimension, fractional shortening, and ejection fraction.
15. The category of the New York Heart Association (NYHA) classification in a 2-year observation.

Patient Selection

The following eligibility criteria were designed for the DAPPER trial. Inclusion criteria are as follows:

1. Patients with T2D who are ≥ 20 years old and ≤ 85 years old at the time of informed consent.
2. Patients needing to start treatment using anti-diabetic agent(s) or to change anti-diabetic agent(s).
3. Patients with plasma HbA1C levels < 10% with or without anti-diabetic agent(s).
4. Patients with any of the following items are defined as those with CHF:
    1. NYHA Functional Class II, III, or IV within 3 months before informed consent;
    2. Plasma BNP levels of ≥ 100 pg/ml or plasma NT-pro BNP levels of ≥ 400 pg/ml within 3 months before informed consent; or previous diagnosis of CHF that was treated with medical or non-medical therapy.
5. eGFR > 45 ml/min/1.73 m^2.
6. Agreement of written informed consent.

Exclusion Criteria

Exclusion criteria are as follows:

1. Patients treated with insulin.
2. Patients with an allergic history of dapagliflozin.
3. Patients with a history of severe diabetic ketoacidosis, diabetic coma, or pre-coma.
4. Patients using mechanical circulatory support devices.
5. Patients waiting for heart transplant.
6. Patients waiting for cardiac surgery.
7. Patients who may easily develop dehydration, including a history of dehydration, highly frequent changes in diuretics, and extreme thinness.
8. Patients with hepatic dysfunction with AST or ALT 3-fold of the upper limit of normal (ULN) at screening. However, if increased AST or ALT is attributable to cardiac diseases, patients do not meet this exclusion criterion as long as total bilirubin levels are < 3.0 mg/dl.
9. Patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney.
10. Patients in a serious clinical condition and who are expected to live for < 3 years.
11. Patients with possible alcohol or drug abuse.
12. Patients who are pregnant or possibly pregnant.
13. Patients who are breast feeding.
14. Patients who have been enrolled in other clinical studies at the same time as this study (excluding observational studies such as registry studies).
15. Patients who are judged by the investigator or sub-investigators to not be suitable for participation in the study.

Registration

Participants will be randomly assigned to the control (diabetic drugs administered other than SGLT 2 inhibitors) or dapagliflozin group with a 1:1 allocation as per a computer-generated randomization schedule stratified by site using permuted blocks of random sizes. Block sizes will not be disclosed, in order to ensure concealment.

Assessments regarding cardiac events will be conducted by an independent Clinical Events Committee (CEC) blinded to treatment allocation. Due to the nature of the intervention, neither participants nor staff may be blinded to the allocation, but are strongly instructed not to disclose the allocation status of the participant in follow-up assessments. People outside the research team will feed data into a computer on separate datasheets, thereby allowing researchers to analyze data without having access to information about the allocation.

Sample Size

The sample size was calculated based on the primary hypothesis. In a previous Phase III study (NCT01294436) conducted in Japan, monotherapy with dapagliflozin or in combination with other anti-diabetic agents in patients with T2D resulted in a greater reduction in microalbuminuria over a 52-week treatment, with the median reduction in microalbuminuria from baseline to the end of the 52-week treatment being − 3.0 mg/g Cr (interquartile range (IQR), 13.0) in the dapagliflozin combination treatment group and − 2.0 mg/g Cr (IQR, 10.0) in dapagliflozin monotherapy, respectively. Based on this finding, the present study is designed to detect a difference in median change from baseline between the two groups of − 3.0 with common standard deviations of 9.64 (roughly equivalent to IQR of 13.0), with 90% power at a 2.5% significance level of the one-sided test. In addition, the study includes one interim analysis for efficacy or futility stopping, in which critical values for both efficacy and futility are both assessed by the O'Brien-Fleming type boundary using Lan-DeMets error-spending method [13] with equally sized increments of information. Therefore, the two groups will require 223 participants in each group of the trial (Table 1) (East version 6.4, Cytel Inc.).

Treatment Methods

Dapagliflozin Group

In patients starting diabetic treatment for the first time, treatment with dapagliflozin was initiated at 5 mg/day and titrated to 10 mg/day as required. In patients with a necessity to reconsider resuming for anti-diabetic treatment, 5 mg of dapagliflozin up to 10 mg once a day is added to their

Table 1 The basis of sample size calculation

Difference in median change	Standard deviation	Power (%)	Fixed sample design	Group-sequential (2 analyses)	
				For efficacy only	For efficacy and futility
−2.0	9.64	80	365	367	386
−2.0	10.0	80	393	394	415
−3.0	9.64	80	163	163	172
−3.0	10.0	80	175	176	185
−2.0	9.64	90	489	490	501
−2.0	10.0	90	526	528	539
−3.0	9.64	90	217	218	*223*
−3.0	10.0	90	234	235	240

resumption or in change to (1) the other SGLT2 inhibitors and/or (2) other anti-diabetic drug(s).

Control Group

In patients starting diabetic treatment, anti-diabetic drugs other than SGLT-2 inhibitors are administered. In patients with a necessity to reconsider their resuming anti-diabetic treatment, anti-diabetic drugs other than SGLT-2 inhibitors are added to their resumption or in change to other anti-diabetic drug(s).

Concomitant Medications

Any concomitant medication/therapies except for prohibited medication may be used during the study. The addition of other drugs or dose increases in current medications (particularly medications for cardiac diseases such as angiotensin converting enzyme inhibitor, angiotensin type 1a receptor blocker, and mineralocorticoid receptor blocker) is discouraged. However, the new onset of lifestyle-related diseases needs to be treated following respective Japanese guidelines. For example, when systemic blood pressure becomes equal to or more than 140/90 mmHg after the entry, drugs for hypertension need to be added (calcium channel blocker, for instance).

Treatment Strategy of T2D

In both groups, patients need to be encouraged to follow the standard treatment for T2D, conduct appropriate exercise for 15–30 min more than three times a week, and restrict their calorie intake depending on their physical activity. Patients need to be treated to keep the guidelines of plasma glucose levels (Guidelines for diabetic treatment published by the Japanese Diabetes Society). After enrolling into this study, the patients need to be treated by drugs other than SGLT2 inhibitors for diabetes mellitus as HbA1C levels become less than 7.0%.

Follow-up

All patients are followed up with scheduled examinations, including body weight, blood pressure, pulse rate, NYHA class, physical findings, blood and biochemical testing, urinary biochemical testing, echocardiography, and electrocardiography. Central blood and biochemical testing is performed at baseline, and 48 and 96 weeks after the start of the study. Central urinary biochemical testing is performed at baseline, and 8 and 96 weeks after the start of the study. Echocardiography and electrocardiography are performed before and 96 weeks after the start of the study. The schedule of this trial is shown in Figs. 1 and 2.

Statistical Method

Analyses will be performed based on the intention-to-treat (ITT) principle, considering all patients as randomized regardless of whether they received the randomized treatment.

A per-protocol-based analysis will be conducted to assess the robustness of the conclusion from the ITT-basis analyses. The dapagliflozin group will be compared against the control group for all primary analysis. Patient demographic data will be analyzed descriptively; categorical variables will be

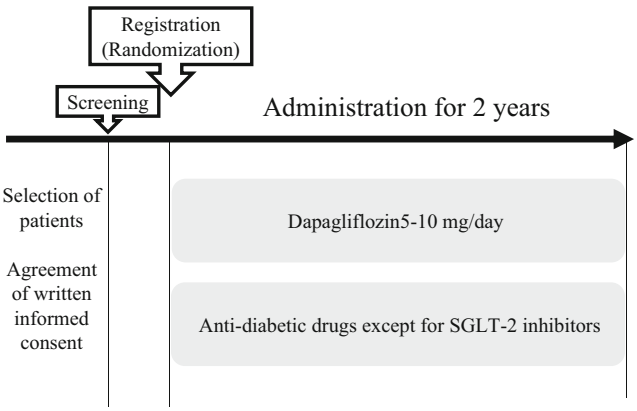

Fig. 1 Study protocol of the present study

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	screening	Baseline 0 week	8 weeks	24 weeks	48 weeks	72 weeks	At the end of the study/ premature termination 96 weeks
Acceptable range			4-12 weeks	20-28 weeks	40-56 weeks	64-80 weeks	88-104 weeks
Informed consent	○						
Background	○						
Body height	○						
Body weight	○	○	○	○	○	○	○
Blood pressure/Pulse rate	○	○	○	○	○	○	○
NYHA class	○	○	○	○	○	○	○
Physical findings	○	○	○	○	○	○	○
Cause of heart failure	○						
Blood and biochemical test (each institute)	X	X	X	X	X	X	X
Blood and biochemical test (central)		●			●		●
Urinary biochemical test (central)		△	△				△
Echocardiogram		○					○
12-lead electrical cardiogram	○						○
Concomitant medications	-	○	-	-	○	-	○
Clinical endpoint		←	—	—	—	—	→
Investigational drugs		←	—	—	—	—	→
Treatment compliance		○	○	○	○	○	○
Adverse events		←	—	—	—	—	→

Fig. 2 Multiplication sign of the blood and biochemical test = ordinary blood sampling for lipids, liver function, kidney function, plasma glucose levels, serum HbA1c levels, plasma BNP levels, and RBC/WBC/Hb levels. Filled circle of the blood and biochemical test = the serum NT-pro BNP concentration, serum FGF 23 concentration, plasma α-Klotho concentration, and plasma aldosterone concentration. Empty triangle of the urinary biochemical test = urinary albumin, creatinine, and KIM-1 levels Abbreviations: NYHA, New York Heart Association; Hb, hemoglobin; BNP, B-type natriuretic peptide; RBC, red blood cell; WBC, white blood cell; FGF, fibroblastic growth factor; KIM-1, kidney injury molecule-1

assessed with the chi-squared test or Fisher's exact test, whereas continuous variables will be assessed with the Student's *t* test or Wilcoxon rank-sum test, as appropriate. Analysis of covariance (ANCOVA) is used for primary endpoint, and the model includes baseline microalbuminuria as a covariate.

We will calculate an adjusted mean difference with corresponding 95% confidence intervals. In subgroup analyses, we will use the regression methods with appropriate interaction terms (respective subgroup × treatment group). Regarding binary outcomes, we will use the chi-squared test or Fisher's exact test followed by the multivariable logistic regression analysis. We will calculate the odds ratio (OR) with corresponding 95% confidence intervals. Regarding timed endpoints such as cardiac events or death, we will use the Kaplan-Meier survival analysis followed by multivariable Cox's proportional hazards model to adjust for baseline variables (if necessary). We will calculate hazard ratios (HR) with corresponding 95% confidence intervals. *p* values will be reported to four decimal places with *p* values less than 0.0001 being reported as $p < 0.0001$.

While the analysis of the secondary endpoint (cardiac events) will be based on a Log-rank test and, therefore, not affected by patient withdrawal (as they will be censored) provided that dropping out is unrelated to prognosis; other outcomes, such as the primary outcome, i.e., the microalbuminuria at 52 weeks post-randomization, may be missing for patients who withdraw from the trial. We will report reasons for withdrawal for each randomization group and compare the reasons qualitatively. The effect that any missing data may have on the results obtained will be assessed via sensitivity analysis of augmented data sets. Dropouts (essentially participants who withdraw consent for continued follow-up) will be included in the analysis by modern imputation methods for missing data.

Up-to-date versions of SAS (Cary, NC, USA) will be used to conduct analyses. In all tests, we will use two-sided *p* values with $p < 0.05$ level of significance.

Centralized Monitoring and the Data and Safety Monitoring Committee

Centralized monitoring is performed under the responsibility of the monitoring director to ensure that this study is properly conducted based on the execution facility. The Data and Safety Monitoring Committee (DSMC) will independently review the report of trial monitoring regarding efficacy and safety data derived from this study. The DSMC may consider the early termination of a treatment regimen based on the

monitoring results. Protocol compliance, safety, and on-schedule study progress are also monitored by the DSMC.

Participating Institutions

The participating institutions in the study are Hokko memorial clinic, National Center for Global Health and Medicine, The Sakakibara Heart Institute of Okayama, Nagasaki University Hospital, Osaka Medical College Hospital, Miura Central Clinic, Nishinomiya-Watanabe Cardiovascular Center, Sakurabashi Watanabe Hospital, Yokohama Rosai Hospital, Tokai University School of Medicine, Saiseikai Matsuyama Hospital, Fujita Health University School of Medicine, Sumi Clinic, Tachi Heart Clinic, Abo Clinic, Nagoya Circulatory and Medical Clinic, Kani Clinic, Konan Kosei Hospital, Hyogo Brain and Heart Center, Kimitsu Chuo Hospital, Minamiosaka Hospital, Sasebo City General Hospital, Tsukuba Memorial Hospital, and Sapporo Cardiovascular Center.

Availability of data and materials In order to avoid bias of the analysis, the dataset supporting the conclusions of this article will not be available until the final report of this trial is published.

Discussion

In T2D patients, increases in urinary albumin excretion reflect elevations of capillary pressure in renal glomeruli and is an early diagnosis of diabetic nephropathy [14, 15]. Furthermore, since an increase in urinary albumin excretion is a predictor of not only end stage renal failure [14], but also the onset of CV disease [16] and CV death [17], one of the aims of treating T2D to prevent CV disease is to prevent or reduce urinary albumin excretion [18, 19]. In epidemiological investigations, the urinary albumin excretion rate is known to be higher in CHF patients than in healthy subjects [20], and a recent study revealed that an increase in urinary albumin excretion is also a predictive factor of the prognosis of CHF patients [12, 21]. Therefore, it is extremely important to examine the excretion of urinary albumin in T2D patients with CHF, because it is a predictor of the onset and worsening of CHF as well as a marker of CKD in T2D patients.

SGLT2 inhibitors influence renal hemodynamics and are known to exert renal protective effects by suppressing glomerular hyperfiltration [22]. Furthermore, since SGLT2 inhibitors suppress Na^+ and glucose reabsorption in the proximal renal tubule and the reabsorption of Cl^- ions is maintained, Cl^- ion concentrations at the Henle loop become low. These considerations led us to speculate that the activity of the resorption mechanism via Henle loop's $Na^+/K^+/2Cl^-$ co-transporters declines and the natriuretic effect occurs [23]. Therefore, SGLT2 inhibitors are expected to provide a different class effect from other diabetic drugs. In the EMPA-REG OUTCOME trial, it was reported that empagliflozin reduced hospitalization rates due to CHF more than the placebo group [7]. However, the subjects in the EMPA-REG OUTCOME trial were T2D patients with mostly high-risk CV disease, in the presence of only 10.1% of CHF cases [24], suggesting that SGLT2 inhibitors are mostly effective for preventing the deterioration of renal dysfunction and onset of cardiac dysfunction in T2D patients without CHF. However, we currently do not know whether these beneficial effects on renal or cardiac function also occur in patients with CHF.

CHF activates the renin-angiotensin and sympathetic systems [6], which may reduce renal function in T2D patients. Furthermore, low cardiac output and renal congestion may further deteriorate the renal function [6]. In CHF, the beneficial effects of SGLT2 inhibitors on renal dysfunction may be enhanced. In contrast, CHF patients are typically treated with diuretics and ACE inhibitors; diuretics may weaken the natriuretic effects of SGLT2 inhibitors, and ACE inhibitors may also improve glomerular hyperfiltration, suggesting that the effects of SGLT2 inhibitors on renal function in T2D patients may be blunted more by the pathophysiological status of CHF than in those without CHF. Therefore, the clinical question as to whether SGLT2 inhibitors exert renal protective effects in T2D patients with CHF needs to be clarified, which is the major reason for planning this study.

The other issue is that SGLT2 inhibitors can correct the cardiorenal syndrome. Based on the diverse mechanisms of the pathophysiology of HF, the functions of the heart and kidneys are closely and complementarily interconnected, and the communication between these two organs through bidirectional pathways results in pathological changes in both organs. It is widely known that renal impairments in patients with CHF are common, due to renal ischemia following low cardiac output [6] and renal congestion [6], resulting in general edema. Renal dysfunction is being increasingly recognized as an independent risk factor for morbidity and mortality in patients with CHF [25]. In the viewpoint of the cardiorenal syndrome, it is of interest and importance that SGLT2 inhibitors prevent vicious cycles between renal and cardiac dysfunctions in the clinical setting. Since albuminuria is the most sensitive biomarker for renal dysfunction and a predictive biomarker for CV events, we set albuminuria for the primary endpoint and subsequent CV events as the secondary endpoint. Therefore, this study may successfully demonstrate whether SGLT2 inhibitors prevent cardiorenal syndrome in patients with both T2D and CHF.

A large-scale clinical trial on DAPA-HF (NCT03036124) to test whether dapagliflozin decreases the severity of CHF regardless of T2D is now ongoing, and our study may have an impact and provide an interpretation of the DAPA-HF clinical trial.

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Authors' Contributions MK conceived of the study and FY, TH, MK wrote the manuscript. MI, SI, KH, YY, KM, MW, and MA conceived of and coordinated the study. TH and HY performed statistical analyses and provided the biostatistical study design. SY and TA conceived of and supervised the study. MK conceived of and supervised the study and is the grant holder. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflict of Interest FY and MK report grants and personal fees from AstraZeneca Plc. and Ono Pharmaceutical Co., LTD, during the conduct of the study.

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Ethics Approval and Consent to Participate The final protocol was approved by the National Cerebral and Cardiovascular Center Ethics Committee (approval ID M28-059) and each Institutional Review Board of all participating centers and patient enrollment began in April 2017. This study complies with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent will be obtained from all patients before recruitment. Personal information about potential and enrolled participants will remain confidential and data will be never identified using participant's number. This trial has been registered in the UMIN Clinical Trials Registry as UMIN000025102 (http://www.umin.ac.jp/ctr/index-j.htm).

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