

Effectiveness of ACE inhibitors and ARBs among
hemodialysis patients with heart failure reduced ejection fraction:
a retrospective cohort study

by

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Abstract

Background: The burden related to heart failure and chronic kidney disease has been increasing rapidly in Japan. Contrary to this current trend, there is dearth of evidence related to medical treatment for heart failure with reduced ejection fraction (HFrEF) especially these patients with renal failure. This study examined the effectiveness of ACE inhibitors and ARBs for the prognosis of HFrEF among hemodialysis patients.

Methods: This study was based on a retrospective cohort study design using electronic medical record data from St. Luke's International Hospital from 2005 to 2019. The cohort was assembled with HFrEF patients with ejection fraction (EF) 40% or less who have been receiving hemodialysis regularly. The primary outcome was death due any cause, and secondary outcomes were the frequency and total duration of hospitalizations due to any cause. Outcomes were compared between patients who had received ACE inhibitors or ARBs before the events of interest and patients who never received them. Cox proportional hazard models, Poisson regression and linear regression models were used to estimate the association after adjusting for confounders.

Results: The mean follow-up periods were 595.69 (\pm 831.37) and 194.86 (\pm 488.75) days in the treatment and control groups, respectively ($P < 0.001$). There were 19 deaths in the treatment group during 324.77 person-years of follow-up (5.85 %) and 16 deaths during 35.21 person-years of follow-up in the control group (45.44 %). After adjusting for confounders which include age, receiving calcium channel blockers and antiplatelet agents, hazard ratio of treatment with ACE inhibitors or ARBs did not differ significantly than controls (hazard ratio (HR)=0.73, 95% CI 0.32-1.64, $P=0.446$). Also, frequency and total

duration of hospitalizations did not differ significantly between these two groups

Conclusion: Although not statistically significant, there was a tendency toward reduced mortality and total hospitalized duration among HFrEF patients with hemodialysis who received ACE inhibitors or ARBs compared with controls.

Keywords: Heart failure with reduced ejection fraction (HFrEF), Heart failure, hemodialysis, Renin-angiotensin-aldosterone system (RAAS) inhibitors, ACE inhibitors, ARBs, Mortality

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List of abbreviations

HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
CKD	Chronic kidney disease
eGFR	Estimated glomerular rate
RAAS inhibitors	Renin-angiotensin-aldosterone system inhibitors
ACE inhibitors	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers

1. INTRODUCTION

1.1. Background Information

The number of patients with heart failure has been increasing rapidly in Japan due to increased incidence of ischemic heart disease and growing older age people in Japan. It is also called “heart failure pandemic” and it is one of the leading public health problems in Japan. It is estimated that the number of outpatients with left ventricular dysfunction is expected to increase rapidly from 979,000 persons in 2005 to 1,300,000 persons by 2030 [1]. A study in the United States has reported that the incidence of chronic heart failure among people in their 50s was 1 %, while the incidence was 10 % among people over 80 years old. Using this data, over 350,000 people would newly develop heart failure in 2025 among elderly population over 65 years old [2].

The etiology of heart failure due to systolic dysfunction, generally called HFrEF, can be broadly classified into nonischaemic dilated cardiomyopathy and ischemic cardiomyopathy. In patients with these diseases, the sympathetic nervous system and the renin-angiotensin-aldosterone (RAA) system are activated. These phenomena can result in progressive left ventricular enlargement, reduced contractility and then remodelling, which later lead to events such as death and worsening heart failure [3]. Therefore, inhibition of the neuroendocrine system to suppress left ventricular remodelling and improve the prognosis of heart failure has become the standard treatment for chronic heart failure patients. One of the standard medical treatments is inhibitors against RAA system which includes ACE inhibitors and angiotensin II receptor blockers (ARBs).

The effects of ACE inhibitors on the prognosis and incidence of various cardiovascular events among HFrEF patients have been widely examined by large clinical trials such as CONSENSUS trial and SOLVD trial [4, 5]. It is considered that there is dose-response

relationship and the higher doses are more effective with regard to death or hospitalization based on the result of the ATLAS trial [6]. Therefore, this class of medication was attempted to increase the dose as long as it is tolerated. The major side effects include cough, hypotension and hyperpotassaemia. The results of large clinical trials indicate that ARBs are as effective as ACE inhibitors in terms of reducing cardiovascular events among HFrEF patients. Therefore, ARBs are used in patients who cannot tolerate ACE inhibitors.

Similar to heart failure, incidence of patients with end-stage kidney disease (ESKD), and dialysis has been increasing over the period of time. 2020 Annual Dialysis Data Report in Japan indicated the prevalence of dialysis patients was 2,754.3 per million people in 2020, which means that 1 in 363.1 people in Japan are on dialysis. According to the United State Renal Data System, Japan has the second highest prevalence of dialysis patients in the world after Taiwan. The most common cause of death among dialysis patients has been heart failure since 1983. In the 2020 survey, the proportion of cardiovascular deaths, which includes heart failure, cerebrovascular disease, and myocardial infarction, mounted to 32.0 % [7].

Heart failure patients are often complicated by renal dysfunction, while renal dysfunction is the most important prognostic factor in both acute and chronic heart failure [8]. Heart disease and renal disease are closely related, and, currently, the importance of the cardio-renal syndrome has been emphasized. In fact, according to a report based on the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), more than 70 % of the population of heart failure have kidney dysfunction, which is stated as $\text{eGFR} < 60.0 \text{ mL/min/1.73m}^2$, and 3.1 % patients treated with dialysis [9]. Compared to the prevalence in the general population around the time of this report was published, 10.6 % of people had $\text{eGFR} < 60.0 \text{ mL/min/1.73m}^2$ and 0.2% of people received dialysis [10]. It is obvious that there is a higher prevalence of CKD among heart failure patients.

Contrary to this current trend, the evidence level of medical treatment to HFrEF is still

low once the cases are complicated with renal failure. Many large clinical trials have been conducted in acute and chronic heart failure, but many of them have excluded patients with impaired renal function. In general, CKD stage 3 cases, which is stated as eGFR 30 to 59 mL/min/1.73m², can be considered to treat almost as same as those without CKD complications. However, there is extremely little evidence for patients with CKD stages 4: eGFR 15 to 29 mL/min/1.73m² and stage 5: eGFR < 15 mL/min/1.73m², including dialysis patients. Some post-hoc studies and clinical observational studies based on effectiveness of ACE inhibitors among chronic heart failure patients with kidney dysfunction have been published [11, 12]. However, none of these studies were based on Japanese population. Therefore, the choice of appropriate treatment for each individual case of HFrEF patients with CKD stage 4 to 5 depends on physicians' preference in the current clinical setting.

Another drawback of the related published studies is that studies' results are not completely applicable to Japanese patients because of the dosage problem. For example, the universally accepted target dose of enalapril, which is the most widely prescribed medicine among ACE inhibitors, is 10 to 20mg twice daily based on the large trials. However, Japanese guideline recommended dose is 5-10mg once daily. Japanese dose is based on a clinical trial at the time of approval in Japan which was conducted in 1990s with a follow up period of 12 weeks among 144 patients to confirm the "general improvement" for the primary end point [13]. The detailed information is not publicly available now, but it probably does not mean mortality or other solid objective indicators like the ones universal big trial used.

According to a published registry study in Asia, only 5% of Japanese patients achieved universally established target dose of ACE inhibitors or ARBs in spite of the fact that around 80 % Japanese heart failure patients, regardless of EF value, received these medicines [14]. Even though it is considered to have dose-dependent effects among these medicines, this tendency of underdosing was revealed. It could be also associated with the Japanese aging

population and comorbidity problem. Hyperpotassaemia is well known adverse effects among ACE inhibitor and ARBs users, following hypotension. It usually makes difficult to increase the dosage of these medicines especially among CKD patients, who are with difficult electrolyte regulation.

Therefore, we believe that research results about these medicines from other countries are not appropriate to extrapolate to the Japanese patients. There are several reports based on HFrEF patients with CKD in Japan, but none included dialysis patients.

1.2. Objectives

The objective of this study was to examine the effectiveness of ACE inhibitors and ARBs for the prognosis of HFrEF patients with hemodialysis.

2. METHODS

This study was based on a retrospective cohort study design using electronic medical record data.

2.1. Data sources

This study used data was from St. Luke's International Hospital from 2005 to 2019: before the approval of Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors and Angiotensin Receptor Neprilysin Inhibitor (ARNI) in Japan which are new medicines for heart failure.

2.2. Patients

The cohort was assembled with criteria of HFrEF patients, whose ejection fraction is less than 40 and on regular hemodialysis. The definition of HFrEF followed Japanese heart failure guideline from The Japanese Circulation Society (JCS) and Japanese Heart Failure Society (JHFS). Because St. Luke's International Hospital is an acute care hospital, this study was targeted to those who regularly received hemodialysis as outpatients. Patients who withdrew ACE inhibitors and/or ARBs before the follow-up period were excluded.

2.3. Outcomes

The primary outcome was death due to any cause during the follow-up period. The secondary outcomes were the frequency and duration of hospitalization during follow-up period.

The follow-up period was defined for each subject started from the day when the criteria

were met. The last day of follow-up was considered the day after 7 days of the last hemodialysis or the end of the study period. Follow-up days in the exposure group were limited to the duration of exposure period: the period taking ACE inhibitors or ARBs, in the exposure group.

2.4. Statistical analysis

For the primary outcome of all-cause mortality, Cox proportional hazard model was used to estimate the hazard ratio after adjusting for possible confounders with using STATA/BE 17.0. To maintain the power of 0.80, needed total number of participants would be 3,330 based on the expected probability of the primary end point, which is death due to any cause, in treatment group and comparison group are 0.80 and 0.90 respectively. This sample size is difficult to achieve for this population in a single center, so this study was considered as a pilot study before conducting a multicenter study.

For the secondary outcome, Poisson regression model and linear regression model were used to examine the association between the exposure and secondary outcomes.

2.5. Ethical approval

All procedures were performed in accordance with the “Declaration of Helsinki” and “Ethical Guidelines for Medical and Health Research Involving Human Subjects”. The study was reviewed and approved by the institutional review board of St. Luke’s International Hospital. Since this is an observational study based on electronic medical records without using samples taken from the human body, informed consent was obtained from all participants through the opt-out method on our hospital website.

3. RESULTS

During the study period, 326 patients met the inclusion criteria. Sixty-one patients were excluded because they stopped taking ACE inhibitors and/or ARBs before the follow-up period. Finally, 265 patients were eligible for the analysis. Among them, 199 patients had the prescription record of ACE inhibitor and/or ARBs for certain period during the follow-up. Rest of the patients (n=66) were considered as control group in this study. For the medication group, 110 patients (55.3 %) had history of receiving ACE inhibitors and 137 patients (68.8%) receiving ARBs during the study period.

3.1. Patients Characteristics

Table 1 compares the baseline characteristics of 265 patients by the receipt of ACE inhibitors and/or ARBs. Patients in the medication group were a bit younger than the control group (66.5 ± 12.1 years vs 69.5 ± 14.0 years, $P=0.044$). The distribution of gender was similar between the two groups. The frequency of LVEF are also similar at the baseline (31.7 ± 7.0 vs 31.2 ± 7.4 , $P=.619$).

In the cohort, there were several differences between the medication group and the control group. Patients treated with ACE inhibitors and/or ARBs were more likely to receive other medication for heart failure including beta blockers, and also antithrombotic agents. These patients were also more likely to have several comorbidities such as hypertension, dyslipidemia, diabetes and ischemic heart disease. The variables which caused more than 10% changes in the hazard ratio (HR) were considered as confounders in the final analytic model.

Table 1: Patients characteristics by receipt of RAAS inhibitors: ACE inhibitors, ARBs

	RAAS inhibitors n = 199 (75.1 %)	No RAAS inhibitors n = 66 (24.9 %)	P-value
Demographics			
Age	66.5 (± 12.1)	69.5(± 14.0)	.044
Gender			
Male	155 (77.9 %)	47 (71.2 %)	.269
Female	44 (22.1 %)	19 (28.8 %)	
Clinical			
BMI			
<18.5	24 (12.1 %)	9 (13.6 %)	.717
>=18.5 and <25	105 (52.8 %)	31 (47.0 %)	
>=25	70 (35.2 %)	26 (39.4 %)	
LVEF	31.7 (± 7.0)	31.2 (± 7.4)	.619
Comorbidities			
Hypertension	176 (88.4 %)	31 (47.0 %)	<.001
Dyslipidemia	126 (63.3 %)	9 (13.6 %)	<.001
Diabetes	127 (63.8 %)	24 (36.4 %)	<.001
Atrial fibrillation	41 (20.6 %)	10 (15.2 %)	.330
Atrial flutter	2 (1.0 %)	1 (1.5%)	.734
Chronic obstructive pulmonary disease	4 (2.0 %)	0 (0.0%)	.246
Ischemic heart diseases	129 (64.8 %)	24 (36.4 %)	<.001
Malignant tumor	41 (20.6 %)	6 (9.1 %)	.034
Medication			
Beta blockers	174 (87.4 %)	38 (57.6 %)	<.001
Mineralocorticoid receptor antagonists	82 (41.2 %)	7 (10.6 %)	<.001
Calcium channel blockers	168 (84.4 %)	29 (43.9 %)	<.001
Digoxin	14 (7.0 %)	2 (3.0 %)	.237
Antiplatelet agents	178 (82 %)	38 (57.6 %)	<.001
Anticoagulant agents	114 (57.3 %)	20 (30.3 %)	<.001
Anti-arrhythmic agents	51 (25.6 %)	7 (10.6 %)	.011
Nitrate / Hydralazine	98 (49.3 %)	12 (18.2 %)	<.001

3.2. Primary Outcome

The primary outcome was all-cause mortality during the follow-up period. The mean follow-up periods were 595.69 (\pm 831.37) and 194.86 (\pm 488.75) days in the treatment and control groups, respectively ($P < 0.001$). There were 19 deaths in the treatment group during 324.77 person-years of follow-up (5.85 %) and 16 deaths during 35.21 person-years of follow-up in the control group (45.44 %). Kaplan-Maier survival curve shows (Figure 1) that unadjusted survival rate was significantly lower in the treatment group than in the control group based on log-rank test ($P < 0.001$).

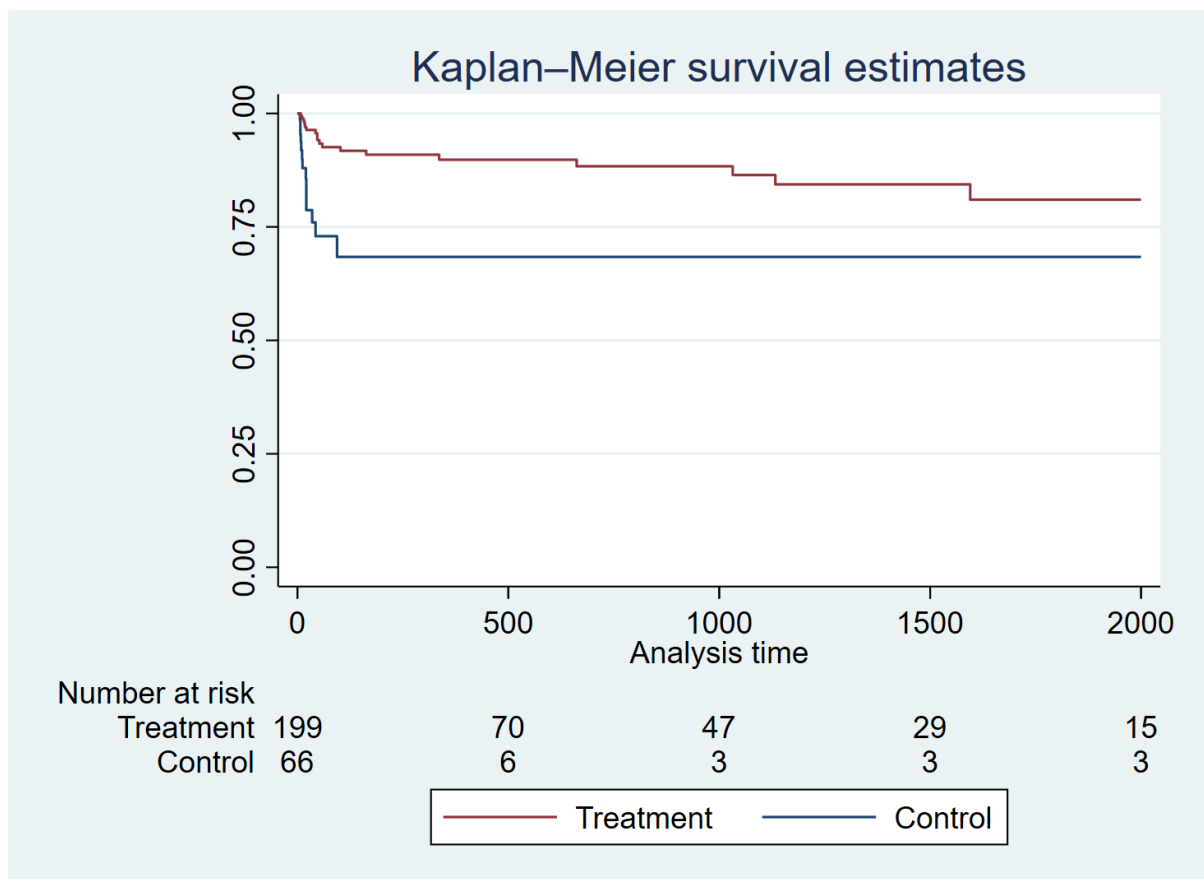


Figure 1: Kaplan-Meier curve for all-cause mortality

However, after adjusting with confounders including age, receiving calcium channel blockers and antiplatelet agents, HR of treatment with ACE inhibitors and/or ARBs was not

significant based on Cox-proportional hazard regression as shown in Table 2.

Table 2: Cox proportional hazard regression for all-cause mortality

Variables	HR	95% CI	P-value
ACE inhibitors / ARBs	0.73	0.32 – 1.64	0.446
Calcium channel blockers	0.19	0.09 – 0.41	<.001
Antiplatelet agents	0.22	0.10 – 0.49	0.096
Age	1.03	1.00 – 1.06	1.002

Table 3 shows the interaction effect between RAAS inhibitors and calcium channel blockers. HR decreased as receiving both of RAAS inhibitors and calcium channel blockers more than only receiving of calcium channel blockers.

Table 3: Analysis of interaction effect between Calcium channel blockers and RAAS inhibitors: ACE inhibitors, ARBs

Variables	HR	95% CI	P-value
ACE inhibitors / ARBs and Non-Calcium channel blockers	0.71	0.27 – 1.86	0.489
Non-ACE inhibitors / ARBs and Calcium channel blockers	0.18	0.05 – 0.66	0.009
ACE inhibitors / ARBs and Calcium channel blockers	0.14	0.06 – 0.34	<0.001
Antiplatelet agents	0.22	0.10 – 0.49	0.096
Age	1.03	1.00 – 1.06	1.002

3.3. Secondary outcome

The secondary outcomes were the frequency and duration of hospitalization during the follow-up period. The result of Poisson regression analysis with the secondary outcome as frequency of hospitalization during the follow-up period is shown in Table 4. After adjusting with confounders, the incidence rate of hospitalization tended to increase by about 6% as

patients received the medication of RAAS inhibitors. However, it did not achieve statistical significance. However, the results of deviance goodness-of-fit test and Pearson goodness-of-fit test were significant ($P<.001$).

Table 4: Poisson regression for times of hospitalization

Variables	IRR	95% CI	P-value
ACE inhibitors / ARBs	1.06	0.75 – 1.50	0.740
Calcium channel blockers	1.51	1.13 – 2.01	0.005
Antiplatelet agents	5.17	2.87 – 9.31	<.001
Anticoagulant agents	1.40	1.14 – 1.72	0.001
Nitrate / Hydralazine	1.58	1.29 – 1.93	<.001
Hypertension	2.30	1.63 – 3.25	<.001
Diabetes	1.33	1.08 – 1.64	0.007
Age	0.97	0.97 – 0.98	<.001
Sex	0.67	0.52 – 0.87	0.002

The result of linear regression analysis with the secondary outcome of the total duration of hospitalized days during the follow-up period is shown in Table 5. After adjusting with confounders, the model showed that the duration of hospital stay tended to decrease by around 8 days as patients received the medication of RAAS inhibitors. However, this association was not significant. However, the R-squared of the model was 11.15 % and the model was not fitted well in this study. Moreover, the result of Breusch–Pagan/Cook–Weisberg test for heteroskedasticity was significant ($P<.001$). It means variance was not homoscedastic in this model.

Table 5: Linear regression for total duration of hospitalized days

Variables	Coefficient	95% CI	P-value
ACE inhibitors / ARBs	-10.77	-39.02 – 17.48	0.453
Calcium channel blockers	5.41	-19.55 – 30.37	0.670
Antiplatelet agents	19.69	-9.84 – 49.22	0.190
Anticoagulant agents	12.15	-8.86 – 33.17	0.256
Nitrate / Hydralazine	20.44	-1.53 – 42.42	0.068
Anti-arrhythmic agents	28.35	3.45 – 53.26	0.026

Hypertension	14.12	-14.09 – 42.33	0.325
Dyslipidemia	0.95	-23.28 – 25.18	0.939
Diabetes	17.87	-3.82 – 39.56	0.106
Ischemic heart diseases	-8.88	-32.50 – 14.74	0.460
Age	-0.84	-1.65 – -0.02	0.044
Sex	-5.12	-28.37 – 18.12	0.665

4. DISCUSSION

Based on the result of this study, the medication with ACE inhibitors and/or ARBs decrease all-cause mortality but it did not achieve statistical significance. It is not possible to determine that there is no association because this study did not have sufficient sample size. As long as there is a trend toward the reduction, further researches with enough sample size are needed to shed more light on this association.

According to the result of Cox-proportional hazard regression analysis for the primary outcome, the interaction effect of calcium channel blockers was observed. This tendency was also reported in another study from Taiwan which also examined the effectiveness of ACE inhibitors and/or ARBs among long-term hemodialysis patients who had heart failure [15]. There is no consensus that calcium channel blockers improve long-term prognosis among heart failure patients, so it is not included in the standard medication for heart failure even among general population who do not have CKD. However, calcium channel blockers are likely to prescribe for hypertension management among hemodialysis patients because these types of medicines are not removed during hemodialysis in contrast to ACE inhibitors. This tendency of strong interaction might also be examined in future studies.

Regarding the secondary outcome, both Poisson regression and linear regression analyses were not well-fitted in this study. As a result, the interpretation of the results needs caution. Although not statistically significant, a trend toward an increase in the number of hospitalizations and a decrease in the number of days of hospitalized duration was observed. The results were conflicting, and the information on the reasons for hospitalization is essential. More concrete results might be obtained if the analysis was conducted with hospitalizations limited to CVD events that would benefit from these medicines. Another problem is that the study used single-center data and did not include the information on patients who were hospitalized or died at other hospitals. This would be a limiting point for a

retrospective single-center study.

4.1. Limitations

The biggest limitation of this study is the lack of appropriate sample size and the small number of events. According to Japanese statistical report, 5 years, 10 years and 15 years survival rate among hemodialysis patients regardless of their comorbidity were 60.8 %, 35.9 % and 23.5 %, respectively [16]. This study used the data of 15 years: 2009 to 2015, the background mortality rate within the follow-up period was set at 80%, referring also to the results of previous studies. However, the actual mortality rates are much less than expected. The big reason for that is the shorter follow-up period than expected, which were around 20 months and 6 months for the treatment and control group, respectively. The problem of the length of follow-up period may be the limitation of acute hospitals. The fewer incident rate influenced the results do not represent well-controlled effects of confounding factors due to the limited number of variables which could be added into the models. Even though long-term hemodialysis patients have various comorbidity problems, the influences of residual or unmeasured factors could not be excluded. Either way, the lack of sample size was presented in this study, so that the possibility of detecting smaller statistical differences was limited. However, this study was designed as a pilot study to find preliminary evidence, which might guide the future studies. Since the trend to reduce mortality was observed, the further investigations are needed.

4.2. Conclusions

Although no significant results were observed in this study, there was a trend toward reduced mortality and total hospital stay. It implicates the needs of further investigation with

a larger sample size. This study can be considered as one of the studies to provide the hypotheses for future large cohort studies or randomized trials.

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