

[ORIGINAL ARTICLE]

The Influence of Eicosapentaenoic Acid to Arachidonic Acid Ratio on Long-term Cardiovascular Events Following Percutaneous Coronary Intervention

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Abstract:

Objective The relationship between cardiovascular disease and the serum polyunsaturated fatty acid parameters has been reported. The aim of the present study was to investigate the association between the eicosapentaenoic acid and arachidonic acid (EPA/AA) ratio and long-term cardiovascular events in patients with coronary artery disease.

Methods We identified a total of 831 patients who underwent percutaneous coronary intervention and whose EPA/AA ratio was available. The patients were divided into two groups according to their serum EPA/AA ratio (median, 0.29; interquartile range 0.19-0.47): those in the lower quartile of EPA/AA ratios (Low EPA/AA group; n=231) and all other subjects (High EPA/AA group; n=600). The primary endpoints included a composite of cardiovascular death, myocardial infarction, and ischemic stroke.

Results Patients in the Low EPA/AA group were significantly younger (66.0 ± 12.6 years vs. 69.9 ± 9.3 years, $p < 0.001$), current smokers (33.3% vs. 22.7%, $p = 0.002$), and had a history of myocardial infarction (20.3% vs. 12.3%, $p = 0.003$). During the follow-up (median, 1,206 days; interquartile range, 654-1,910 days), the occurrence of the primary endpoint was significantly higher in the Low EPA/AA group than in the High EPA/AA group. Of note, the rate of cardiovascular death was significantly higher in the Low EPA/AA group, and the rates of myocardial infarction and stroke tended to be higher.

Conclusion A low EPA/AA ratio was associated with long-term adverse cardiovascular events in Japanese patients with coronary artery disease.

Key words: EPA/AA ratio, coronary artery disease, cardiovascular event

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Introduction

Fish oil intake is known to be associated with a reduced risk of cardiovascular disease (1-4). Among the omega-3 polyunsaturated fatty acids (PUFAs) contained in fish oil, eicosapentaenoic acid (EPA) has been shown to play important roles in preventing cardiovascular disease (5). Omega-3 PUFAs constitute an important component of the human cell

membranes and regulate the inflammatory response through the production of lipid mediators (6). In contrast, arachidonic acid (AA), an omega-6 PUFA, seems to have the opposite effect to that of EPA. Therefore, the EPA/AA ratio has appeared to be a potential predictor of cardiovascular disease/events in the clinical setting (7, 8). It has been reported that a lower serum EPA/AA ratio is associated with an increased risk of cardiovascular disease. However, the clinical significance and influence of the EPA/AA ratio on

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long-term clinical events have not yet been fully elucidated, and the distribution and the implication of EPA/AA values could be different among various populations. The purpose of this study was to investigate the distribution of the EPA/AA ratio and the association between the values and long-term cardiovascular events in Japanese patients with coronary artery disease.

Materials and Methods

This study was a single-center observational study. Among the patients who underwent PCI between December 2009 and September 2017 at Nagoya University Hospital, 831 patients whose serum EPA/AA levels at the time of the PCI procedure were available were identified and enrolled in the first procedure during the study period. Data regarding the patient characteristics, medications, laboratory and other examination results, and PCI procedures were obtained from medical records. This study was approved by our institutional ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Measurement of the EPA/AA ratio

The serum levels of EPA and AA in fasting blood samples on admission were analyzed at an external laboratory (LSI Medience, Tokyo, Japan), and the EPA/AA ratio was calculated. In this study, a low EPA/AA ratio was defined as having an EPA/AA ratio in the lowest quartile among the included subjects.

Clinical outcomes and other definitions

The primary composite endpoint was the occurrence of cardiovascular death, non-fatal myocardial infarction, and ischemic stroke. Cardiovascular death was defined as any death due to cardiovascular causes (e.g., acute myocardial infarction, heart failure, stroke, and cerebrovascular hemorrhage), sudden death, and death of unknown cause (9). Myocardial infarction was defined based on the fourth universal definition of myocardial infarction (type 1) (10). Stroke was defined as a neurological deficit of cerebrovascular origin lasting longer than 24 hours and was confirmed using computed tomography or magnetic resonance imaging (11). Clinical follow-up was performed in routine clinical visits or telephone interviews.

The estimated glomerular filtration rate (eGFR) was calculated using the revised Japanese equation: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum Cr}^{-1.094} \times \text{age}^{0.287} \times 0.739$ (in female patients) (12).

Statistical analysis

Continuous data are expressed as the mean \pm standard deviation or median (interquartile range). Categorical data are expressed as numbers and percentages. Continuous data were compared using the unpaired *t*-test or Mann-Whitney *U* test, and categorical data were compared using the chi-

square or Fisher's exact test. The cumulative event rates were analyzed using the Kaplan-Meier method, and the rate differences between groups were estimated using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated for each variable using the Cox univariate analysis. The Cox multivariate regression analysis was performed to determine independent predictors of the incidence of the primary endpoint after including all variables with $p < 0.1$ according to a univariate analysis. All statistical analyses were performed using SPSS version 25 (IBM, Armonk, USA). All *p* values reported are two-sided, and $p < 0.05$ was considered to be statistically significant.

Results

The distribution of the EPA/AA ratio among the 831 studied patients (mean age, 68.8 ± 10.5 years; 81.5% male) is shown in Fig. 1. The median EPA/AA ratio was 0.29 (interquartile range 0.19-0.47). The patients were divided into two groups according to their serum EPA/AA ratio: those with a low EPA/AA ratio, defined as having a ratio in the lowest quartile of obtained EPA/AA ratios (low EPA/AA group, $n = 231$), and those with a higher ratio (high EPA/AA group, $n = 600$).

The baseline characteristics are shown in Table 1. The patients in the Low EPA/AA group were significantly younger, more frequently current smokers, and had a history of myocardial infarction. The rate of acute coronary syndrome was significantly higher in the Low EPA/AA group. No significant difference was observed in the left ventricular ejection fraction between the two groups. The triglyceride levels were significantly higher in the Low EPA/AA group. The low-density lipoprotein cholesterol levels tended to be higher and the high-density lipoprotein cholesterol levels tended to be lower in the Low EPA/AA group; however, the difference was not significant.

The median patient follow-up was 1,206 days (interquartile range, 654-1,910 days). Kaplan-Meier event curves for the primary endpoint of cardiovascular death, myocardial infarction, and stroke and each component are presented in Fig. 2 and Table 2. The occurrence of the primary endpoint of cardiovascular death, myocardial infarction, and stroke was significantly higher in the Low EPA/AA group than in the High EPA/AA group (Fig. 2a). Notably, the occurrence of cardiovascular death (Fig. 2b) was significantly higher in the Low EPA/AA group, and the rates of myocardial infarction (Fig. 2c) and stroke (Fig. 2d) tended to be higher, respectively.

According to a multivariate analysis, a low EPA/AA ratio (HR, 1.92; 95% CI, 1.22-3.02; $p = 0.005$) and $eGFR < 60 \text{ mL/min/1.73 m}^2$ (HR, 2.41; 95% CI, 1.52-3.82; $p < 0.001$) were found to be predictors of the composite primary endpoint of cardiovascular death, myocardial infarction, and stroke (Table 3).

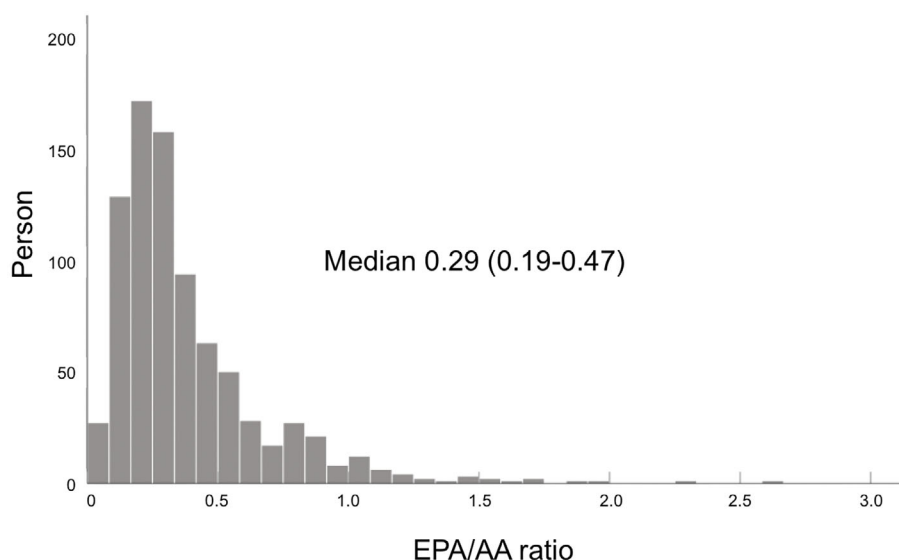


Figure 1. The distribution of the EPA/AA ratio among the studied patients. The median EPA/AA ratio was 0.29 (interquartile range 0.19-0.47).

Discussion

The main findings of this study are: 1) The EPA/AA ratio had a median value of 0.29 among the PCI population, which is relatively low when considering the values in prior Japanese reports of the general population. 2) Patients with a low EPA/AA ratio had a significantly higher occurrence of cardiovascular events, including cardiovascular death, myocardial infarction, and stroke. 3) Low EPA/AA and eGFR < 60 mL/min/1.73 m² were independent predictors of long-term cardiovascular events.

So far, only limited data have been available regarding the distribution of the EPA/AA ratio (8, 13-16), and the values vary widely among reports from 0.1 to 7. It is well known that the EPA/AA ratio is quite high in Greenlandic Inuit who consume a lot of fish (1, 13). The EPA/AA ratio has been shown to be low in Western populations (13-15). In Japan, the Hisayama study reported an average EPA/AA of 0.40 in the general population (8). In this study, the EPA/AA ratio had a median of 0.29 among the Japanese PCI population, which is relatively low when referring to prior limited reports. This result might suggest that patients with coronary artery disease generally have lower EPA/AA levels than those in the general population. The distribution of the EPA/AA values could thus be different among the various populations depending on race, lifestyle, food, and comorbidities, among other factors. Further accumulation of data regarding the distribution of the EPA/AA ratio is needed to reveal its clinical significance and recommended target levels among each population (13); this study provides a landmark for future studies.

Some cross-sectional studies have shown an association between low EPA/AA levels and cardiovascular disease (8). The EPA/AA ratio was shown to be lower among patients

with major cardiovascular diseases, including myocardial infarction and cerebral infarction (17, 18). We also previously reported a reverse association between the EPA/AA ratio and carotid atherosclerosis in hemodialysis patients (19). However, there have been only a few cohort studies with a clinical follow-up (16, 20-22). One previous report showed that the EPA/AA ratio was an independent predictor of cardiac death during a mean follow-up period of about 2 years in patients with decompensated heart failure (20).

Other reports showed that a lower EPA/AA ratio was associated with in-hospital fatal arrhythmic events among patients with acute myocardial infarction (21, 22). Domei et al. conducted a study with 284 consecutive patients who underwent elective PCI. During the mean follow-up period of 1.5 years, a lower serum EPA/AA ratio was associated with a higher incidence of major adverse cardiac events, including cardiac death, acute coronary syndrome, PCI for de novo lesions, and coronary artery bypass grafting (16). Our study might have some advantages; the study was conducted with a relatively large number of patients and long-term follow-up (approximately 3.3 years), and the endpoints consisted of only hard cardiovascular events, including cardiovascular death, myocardial infarction, and stroke. These results suggest that a lower EPA/AA ratio could be a useful marker for future cardiovascular events among patients with coronary artery disease. However, as described above, the clinical significance of the EPA/AA ratio might be different among each population; therefore, further accumulation of data is needed to verify and adopt the interpretation among various populations.

Our study showed that a low EPA/AA ratio could be a useful marker for the occurrence of cardiovascular events; however, it does not mean that EPA/AA is a suitable treatment target. It remains controversial whether the administration of EPA can improve the clinical outcomes. Some prior

Table 1. Baseline Patient Characteristics.

	All patients n=831	High EPA/AA n=600	Low EPA/AA n=231	p value
Age, years	68.8±10.5	69.9±9.3	66.0±12.7	<0.001
Male, n (%)	677 (81.5%)	488 (81.3%)	189 (81.8%)	0.87
Body mass index, kg/m ²	23.7±3.7	23.7±3.6	23.8±3.9	0.98
Diabetes mellitus, n (%)	379 (45.6%)	267 (44.5%)	112 (48.5%)	0.3
Dyslipidemia, n (%)	616 (74.1%)	443 (73.8%)	173 (74.9%)	0.79
Hypertension, n (%)	612 (73.6%)	446 (74.3%)	166 (71.9%)	0.47
Current smoker, n (%)	193 (23.2%)	126 (21.0%)	67 (29.0%)	0.01
Prior myocardial infarction, n (%)	120 (14.4%)	74 (12.3%)	46 (19.9%)	0.005
Prior PCI, n (%)	183 (22.0%)	134 (22.3%)	49 (21.2%)	0.73
Prior CABG, n (%)	63 (7.6%)	43 (7.2%)	20 (8.7)	0.47
Dialysis, n (%)	38 (4.6%)	30 (5.0%)	8 (3.5%)	0.34
Left ventricular ejection fraction, %	63.6 (56.0-69.1)	63.6 (57.2-69.2)	63.4 (51.1-69.1)	0.19
<i>Clinical presentation</i>				
Acute coronary syndrome	276 (33.2%)	180 (30.0%)	96 (41.6%)	0.002
<i>Medication</i>				
Statins n (%)	593 (71.4%)	439 (73.2%)	154 (66.7%)	0.06
Fibrates, n (%)	7 (0.8%)	6 (1.0%)	1 (0.4%)	0.68
EPA, n (%)	60 (7.2%)	55 (9.2%)	5 (2.2%)	<0.001
EPA+DHA, n (%)	6 (0.7%)	6 (1.0%)	0 (0%)	0.19
<i>Laboratory data</i>				
Total cholesterol, mg/dL	168 (143-196)	167 (143-194)	170 (142-202)	0.36
Triglycerides, mg/dL	115 (82-166)	113 (79-160)	123 (86-175)	0.048
HDL cholesterol, mg/dL	43 (36-52)	44 (37-53)	42 (36-50)	0.12
LDL cholesterol, mg/dL	97 (78-121)	96 (77-117)	100 (78-129)	0.07
Creatinine, mg/dL	0.88 (0.73-1.07)	0.87 (0.73-1.06)	0.90 (0.73-1.08)	0.62
eGFR, mL/min/1.73m ²	64.2 (51.4-77.5)	64.5 (51.4-77.2)	63.8 (51.1-79.9)	0.85
eGFR<60 mL/min/1.73m ² , n (%)	341 (41.0%)	238 (39.7%)	103 (44.6%)	0.20
HbA1c, %	6.1 (5.8-6.8)	6.1 (5.8-6.8)	6.0 (5.7-6.8)	0.40
Hemoglobin, mg/dL	13.2 (11.8-14.6)	13.1 (11.8-14.5)	13.4 (11.7-14.9)	0.17
Albumin, g/dL	3.9 (3.5-4.3)	4.0 (3.5-4.3)	3.8 (3.4-4.2)	0.02
EPA/AA	0.29 (0.19-0.47)	0.37 (0.27-0.56)	0.14 (0.11-0.17)	<0.001
EPA, µg/mL	47 (31-73)	59 (43-84)	25 (19-33)	<0.001
AA, µg/mL	162 (128-199)	153 (124-186)	188 (149-236)	<0.001

Continuous data are expressed as mean±standard deviation or median (interquartile range). Categorical data are expressed as numbers (percentages).

PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, DHA: docosahexaenoic acid, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, EPA: eicosapentaenoic acid, AA: arachidonic acid

studies failed to demonstrate any effect of EPA administration on the clinical outcomes. In the ORIGIN Clinical Trials, the purified EPA intake had no effect on the reduction of cardiovascular events during the median follow-up of 6.2 years in patients with diabetes or impaired glucose tolerance (23). In the VITAL trial, in middle-aged and older adults, a purified EPA intake failed to show a significant reduction in cardiovascular events during a median follow-up of 5.3 years (24). However, other trials demonstrated EPA to have a significant effect. In the JELIS study conducted in Japan, patients with dyslipidemia were treated with purified EPA in addition to statins, and the risk of cardiovascular events was significantly reduced by 19% when compared with that in the control group (25). In the recently published REDUCE-IT trial, a total of 8,179 patients were enrolled

and followed for a median of 4.9 years. The primary endpoint event, including cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina, was significantly lower in the EPA group than in the placebo group (HR, 0.75; 95% CI, 0.68-0.83) (26). The JELIS and REDUCE-IT trials used higher doses of EPA, which might partially explain the differences in the results. Furthermore, the effect might be influenced by various other factors, including the baseline EPA/AA ratio and the population. Further investigations are therefore required to clarify this issue.

EPA has been reported to have multifaceted effects primarily against inflammation through multiple pathways (6, 27, 28). EPA is also known to increase the secretion of adiponectin, which can be beneficial for insulin re-

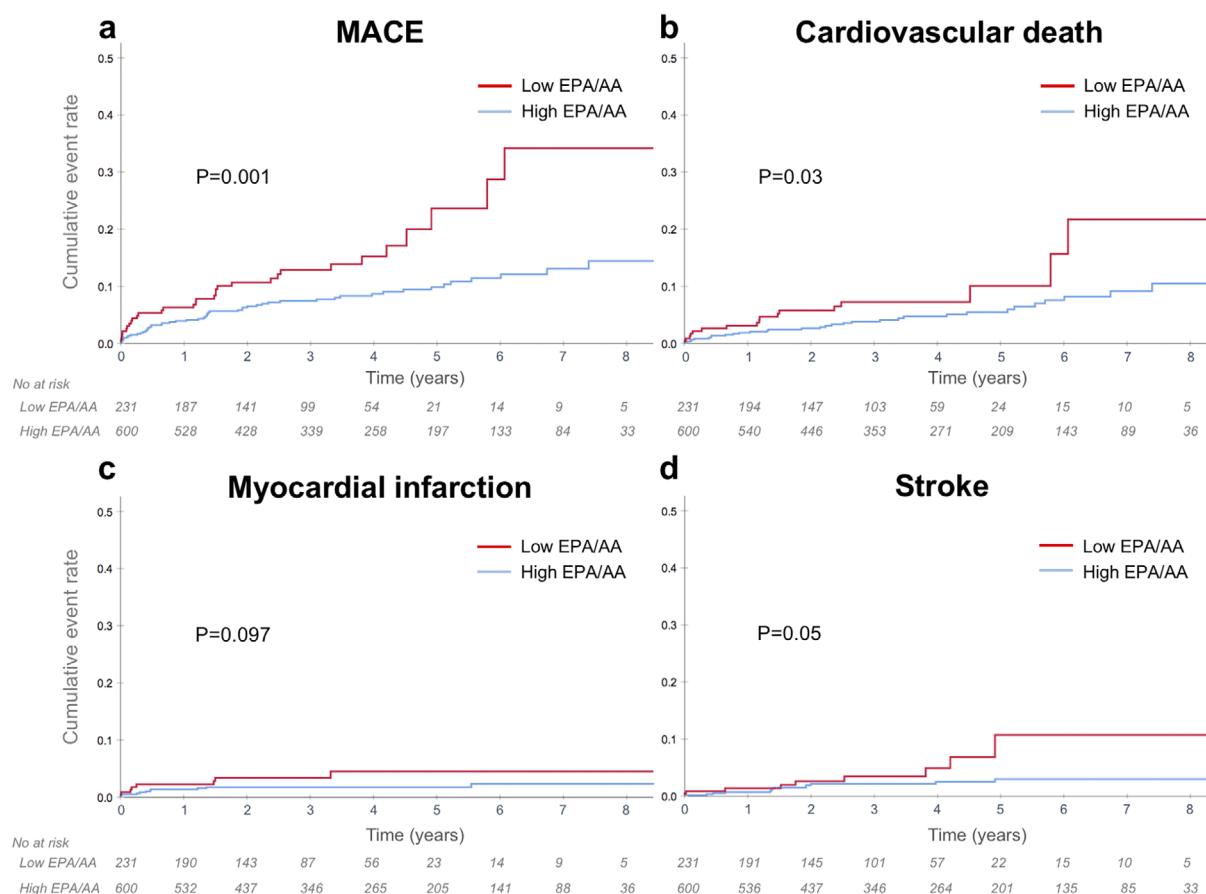


Figure 2. Kaplan-Meier curves in both groups for (a) cardiovascular death, myocardial infarction, and stroke (b) cardiovascular death, (c) myocardial infarction, (d) stroke. The occurrence of the primary endpoint of cardiovascular death, myocardial infarction, and stroke was significantly higher in the Low EPA/AA group than in the High EPA/AA group (a). Notably, the occurrence of cardiovascular death (b) was significantly higher in the Low EPA/AA group, and the rates of myocardial infarction (c) and stroke (d) tended to be higher, respectively.

Table 2. Clinical Events during Clinical Follow-up.

	All patients n=831	High EP/AAA n=600	Low EPA/AA n=231
MACE, n	85	53	32
Cardiovascular death	49	32	17
Myocardial infarction	19	11	8
Stroke	22	13	9

MACE: major adverse cardiovascular event

sistance (6, 27) Furthermore, EPA seems to have beneficial effects on the endothelial function, oxidative stress, and foam cell formation, which might prevent plaque formation, progression, and rupture (28-31). However, AA has been reported to counteract the effects of EPA (6). These mechanisms might support the clinical significance of the EPA/AA ratio and the possible use of EPA administration.

There are several limitations associated with the present study. First, this was a single-center observational study. Second, detailed data regarding diet were not available, which might have affected the results. Third, this study in-

cluded PCI patients within a relatively long study period, therefore the follow-up terms varied greatly. Fourth, this study could not determine the cut-off value of EPA/AA ratio for the study population. Further accumulation of data among various populations is therefore required to determine the specific cut-off values for use in clinical practice.

Conclusion

In conclusion, a low EPA/AA ratio was associated with long-term adverse cardiovascular events following PCI. The

Table 3. Univariate and Multivariate Cox Regression Analyses for Primary Endpoint.

Variables	Univariate			Multivariate		
	HR	95%CI	p value	HR	95%CI	p value
Age	1.02	1.00-1.05	0.04	1.01	0.99-1.03	0.38
Male	1.26	0.71-2.23	0.44			
Body mass index	0.94	0.89-1.00	0.06	0.96	0.89-1.02	0.18
Diabetes mellitus	1.5	0.98-2.31	0.06	1.40	0.91-2.15	0.13
Dyslipidemia	0.66	0.42-1.04	0.07	0.71	0.45-1.12	0.15
Hypertension	1.51	0.88-2.61	0.14			
Current smoker	0.92	0.55-1.55	0.75			
Prior myocardial infarction	0.97	0.53-1.78	0.92			
Prior PCI	0.77	0.45-1.33	0.35			
Prior CABG	1.57	0.79-4.29	0.20			
eGFR<60 mL/min/1.73m ²	2.76	1.78-4.29	<0.001	2.41	1.52-3.82	<0.001
Acute coronary syndrome	1.2	0.77-1.87	0.41			
Low EPA/AA	2.04	1.31-3.18	0.002	1.92	1.22-3.02	0.005

EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid

EPA/AA ratio can therefore be a useful marker in patients with coronary artery disease. Further investigations are needed to reveal its clinical significance and recommended target levels among various populations.

Author's disclosure of potential Conflicts of Interest (COI).

Hideki Ishii: Honoraria, Astellas Pharma, Astrazeneca, Daiichi-Sankyo Pharma and MSD. Toyoaki Murohara: Honoraria, Bayel Pharmaceutical, Daiichi-Sankyo, Dainippon Sumitomo Pharma, Kowa, MSD, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Sanofi-aventis and Takeda Pharmaceutical.

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