

Observational Study

Relationship between coronary calcium score and high-risk plaque/significant stenosis

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Abstract

AIM

To investigate the relationship between coronary calcium score (CCS) and vulnerable plaque/significant stenosis using coronary computed tomographic angiography (CCTA).

METHODS

CCTA was performed in 651 patients and these patients were divided into the four groups (CCS 0, 1-100, 101-400 and > 400). We studied the incidence of high-risk plaque, including positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign, and significant stenosis in each group.

RESULTS

High-risk plaque was found in 1.3%, 10.1%, 13.3% and 13.4% of patients with CCS 0, 1-100, 101-400 and > 400, respectively ($P < 0.001$). The difference was only significant for patients with zero CCS. The incidence of significant stenosis was 0.6%, 7.6%, 13.3% and 26.9% for each patient group, respectively ($P < 0.001$), which represented a significant stepwise increase as CCS increased. The combined incidence of high-risk plaque and significant stenosis was 1.9%, 17.7%, 26.9% and 40.3% in each patient group, respectively ($P < 0.001$), again representing a significant stepwise increase with CCS. The rate of major coronary event was 0%, 4.0%, 7.9% and 17.2% in each patient group, respectively ($P < 0.001$), another significant stepwise increase as CCS increased.

CONCLUSION

Stepwise increased risk of coronary events associated with increasing CCS is caused by increasing incidence of significant stenosis, while that of high-risk plaque remains the same.

Key words: Coronary calcium score; Coronary stenosis; High-risk plaque; Low attenuation plaque; Napkin-ring

sign; Positive remodeling; Spotty calcification

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Core tip: Coronary computed tomographic angiography was performed in 651 patients and these patients were divided into the four groups according to coronary calcium score (CCS): 0, 1-100, 101-400 and > 400. The incidence of high-risk plaque was not significantly different among the three groups, except patients with zero CCS. The incidence of significant stenosis increased stepwise as CCS increased, as did the rate of major coronary event. Therefore, the stepwise increased risk of coronary events associated with increasing CCS is caused by an increasing incidence of significant stenosis, while that of high-risk plaque remains the same.

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INTRODUCTION

Coronary artery calcification represents the presence of coronary atherosclerosis and there is a strong relationship between the extent of coronary artery calcification and the total coronary plaque burden^[1-3]. Many studies demonstrate that coronary calcium score (CCS) is the powerful predictor of coronary events and provide incremental risk stratification beyond traditional risk scores^[4,5]. In contrast, patients with no calcium show a very low risk of coronary events^[6]. However the precise mechanism of this increased risk associated with increased CCS has not been fully elucidated. Generally, most coronary events are caused by significant stenosis or vulnerable plaque. Many studies have demonstrated that significant stenosis increases the risk of coronary events^[7,8]. In addition, recent studies demonstrate that 70%-80% of cardiac death and myocardial infarction are caused by rupture of vulnerable plaque, which often has non-significant stenosis^[9,10].

Thus, we hypothesized that both significant stenosis and vulnerable plaque were associated with increased coronary events as CCS increased. We investigated the relationship between CCS and vulnerable plaque/significant stenosis using coronary computed tomographic angiography (CCTA).

MATERIALS AND METHODS

Patients

From September 2010 through September 2014, 981 patients underwent CCTA. We excluded: (1) patients who underwent coronary revascularization before CCTA;

(2) patients who developed acute coronary syndrome before CCTA; (3) patients who have coronary artery disease (CAD); and (4) patients with inadequate image quality because of motion artifacts, blooming artifacts, or severe calcification. Finally, we studied 651 patients. Most patients underwent CCTA for the evaluation of CAD because of multiple risk factors and/or symptom of chest pain.

CCTA

For CCTA, we used a sixty-four multi-detector computed tomography (MDCT) scanner (SOMATOM Sensation 64 Cardiac, Siemens Medical Solutions, Erlangen, Germany). Before the scan, we administered 20 mg metoprolol if patients had a heart rate more than 70 beats/min. We administered sublingual nitroglycerin 0.8 mg for all patients.

We performed a scan without contrast dye to measure the coronary calcium burden. The detail of the CCTA procedure was reported in the previous study^[11].

CCTA image interpretation

For image analysis, we transferred CT data sets to a workstation (Aquarius NetStation, Terarecon Inc, San Mateo, CA, United States). We calculated total calcium score and expressed as Agatston score^[12]. We divided our patients into the four groups according to the usual CCS risk classification definitions: CCS 0, 1-100, 101-400 and > 400. We defined high-risk CCS as CCS > 400.

Two reviewers, who were blinded to the patients' clinical characteristics, evaluated the CCTA data, with maximum intensity and curved multiplanar reconstruction (CMPR) techniques. We regarded positive remodeling as the ratio of plaque site diameter divided by reference segment diameter more than 1.1^[13]. We regarded spotty calcification as its size less than 3 mm on CMPR images and one side occupied on cross-sectional images^[13]. We regarded low attenuation plaque as the lowest CT number less than 30 HU on axial images^[13]. We regarded napkin-ring sign as a ring of high attenuation around coronary artery plaque and CT attenuation of a ring higher than that of the adjacent plaque but no greater than 130 HU^[14]. We regarded high-risk plaque as the plaque with positive remodeling, low attenuation plaque, spotty calcification, or napkin ring sign. Percent aggregate plaque volume was measured according to Nakazato's method^[15]. Two reviewers identified coronary segments and these segments were classified into normal, non-significant stenosis, or significant stenosis. Normal segment was defined as smooth parallel or tapering borders. Non-significant stenosis was defined as luminal irregularities or % diameter stenosis less than 50%. Significant stenosis was defined as % diameter stenosis more than 50%.

Major coronary event

The duration of follow-up was 2.1 ± 1.3 years (median 1.9 years). Major coronary event was defined as cor-

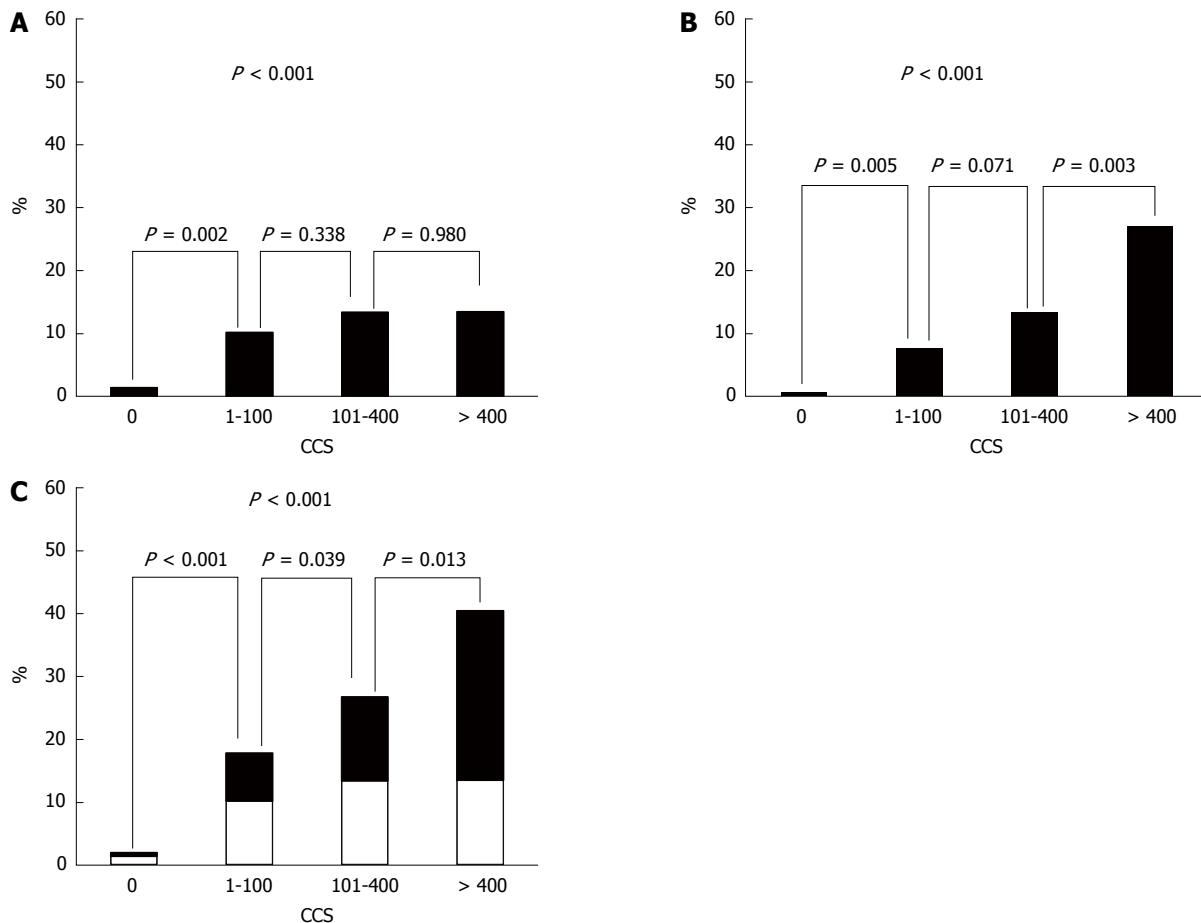


Figure 1 Prevalence of high-risk plaque and significant stenosis among the four groups. A: Prevalence of high-risk plaque; B: Prevalence of significant stenosis; C: Prevalence of combined high-risk plaque and significant stenosis. CCS: Coronary calcium score.

onary death, myocardial infarction, and coronary revascularization.

The Institutional Review Board of Okayama Kyokuto Hospital reviewed and approved this study. All patients provided informed consent.

Statistical analysis

We described continuous variables as mean \pm SD. We compared continuous variables by two group *t*-test between the two groups and by one-factor ANOVA among the four groups. We described discrete variables as counts or percentage. We compared discrete variables by the χ^2 or Fisher's exact test between the two groups and by the χ^2 test for independence among the four groups. We investigated predictors of high-risk plaque, significant stenosis, and high-risk CCS by a multiple logistic regression analysis, including age, sex, and all risk factors. A *P*-value < 0.05 was regarded as statistically significant. The biomedical statistician performed statistical review of this study.

RESULTS

The patients' clinical characteristics are shown in Table 1. Figure 1 shows the incidence of high-risk plaque and significant stenosis among the four groups. The high-risk

plaque was found in 1.3%, 10.1%, 13.3% and 13.4% of patients with CCS 0, 1-100, 101-400 and > 400 , respectively (Figure 1A). The difference was only significant for patients with zero CCS. The incidence of significant stenosis was 0.6%, 7.6%, 13.3% and 26.9% in each patient group, respectively (Figure 1B), which represented a stepwise increase as CCS increased. The combined incidence of high-risk plaque and significant stenosis was 1.9%, 17.7%, 26.9% and 40.3% in each patient group, respectively (Figure 1C), again representing a significant stepwise increase as CCS increased.

Table 2 shows the incidence of high-risk plaque among the four groups. Apart from patients with zero CCS, there were no significant differences in the incidence of high-risk plaque, positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring appearance among the three groups. In addition, the incidence of multiple high-risk plaques was not significantly different among the four groups. The percent aggregate plaque volume was not significantly different among the four groups. Table 3 shows the predictors of high-risk plaque, significant stenosis, and high-risk CCS by stepwise increased rate of major coronary event was observed. The rate of coronary revascularization also increased stepwise. The rate of coronary death and myocardial infarction was not significantly different among the four

Table 1 Clinical characteristics of studied patients *n* (%)

CCS	0	1-100	101-400	> 400	<i>P</i>
<i>n</i>	154	198	165	134	
Age	63.1 ± 11.7	68.2 ± 8.5	69.6 ± 9.8	71.5 ± 8.1	< 0.0001
Male sex	76 (49.4)	137 (69.2)	121 (73.3)	98 (73.1)	< 0.0001
Risk factor					
Hypertension	85 (55.2)	125 (63.1)	115 (69.7)	99 (73.9)	0.0045
Dyslipidemia	88 (57.1)	124 (62.6)	105 (63.4)	82 (61.2)	0.6484
Diabetes	53 (34.4)	76 (38.4)	65 (39.4)	76 (56.7)	0.0007
Stroke	36 (23.4)	58 (29.3)	58 (35.2)	58 (43.3)	0.0024
CKD	30 (19.5)	47 (23.7)	47 (28.5)	43 (32.1)	0.07
BMI (kg/m ²)	25.7 ± 3.7	24.4 ± 2.6	24.2 ± 3.7	23.8 ± 4.8	0.2514
Laboratory data					
HbA1c (mmol/mol)	46.1 ± 13.4	47.4 ± 14.5	48.5 ± 13.0	48.9 ± 12.0	0.3286
BS (mmol/L)	7.43 ± 2.37	7.73 ± 2.44	7.94 ± 2.39	8.52 ± 2.99	0.0333
TC (mmol/L)	5.24 ± 0.99	5.13 ± 0.99	4.95 ± 0.98	4.72 ± 0.87	0.0054
TG (mmol/L)	1.69 ± 1.12	1.63 ± 1.01	1.73 ± 0.94	1.72 ± 0.90	0.8925
HDL-C (mmol/L)	1.50 ± 0.51	1.47 ± 0.43	1.29 ± 0.30	1.41 ± 0.39	0.0084
LDL-C (mmol/L)	3.18 ± 0.86	2.93 ± 0.91	2.96 ± 0.85	2.68 ± 0.72	0.0023
Cr (μmol/L)	69.0 ± 28.3	73.4 ± 19.4	75.1 ± 17.7	78.7 ± 21.2	0.0481
Medication					
ARB/ACE-I	70 (45.5)	101 (51.0)	98 (59.4)	97 (72.4)	< 0.0001
CCB	53 (34.4)	98 (49.5)	96 (58.2)	95 (70.9)	< 0.0001
Diuretics	5 (3.2)	10 (5.1)	9 (5.5)	7 (5.2)	0.7883
Beta-blocker	3 (1.9)	5 (2.5)	3 (1.8)	4 (3.0)	0.9096
Aspirin	37 (24.0)	60 (30.3)	61 (37.0)	60 (44.8)	0.0013
Statin	85 (55.2)	119 (60.1)	100 (60.6)	79 (59.0)	0.7559
Oral diabetics	51 (33.1)	76 (38.4)	65 (39.4)	76 (56.7)	0.0004
Insulin	10 (6.5)	15 (7.6)	16 (9.7)	19 (14.2)	0.112

CCS: Coronary calcium score; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; BS: Blood sugar; CCB: Calcium channel blocker; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

Table 2 Incidence of high-risk plaque among the four groups *n* (%)

CCS	0	1-100	101-400	> 400	<i>P</i>
<i>n</i>	154	198	165	134	
High-risk plaque	2 (1.3) ^b	20 (10.1)	22 (13.3)	18 (13.4)	0.0171
Positive remodeling	2 (1.3) ^d	20 (10.1)	21 (12.7)	18 (12.7)	< 0.001
Low attenuation plaque	0 (0) ^e	7 (3.5)	4 (2.4)	1 (0.7)	0.0217
Spotty calcification	0 (0) ^h	13 (6.6)	11 (6.7)	8 (6.0)	< 0.001
Napkin-ring sign	0 (0) ⁱ	7 (3.5)	2 (1.2)	1 (0.7)	0.0474
Multiple plaques	0 (0)	4 (2.0)	3 (1.8)	3 (2.2)	0.166
%APV	30.5 ± 24.3	42.5 ± 9.0	44.8 ± 9.2	42.2 ± 7.8	0.2537

^b*P* = 0.0016 compared with group with CCS 1-100; ^d*P* = 0.0016 compared with group with CCS 1-100; ^e*P* = 0.0486 compared with group with CCS 1-100; ^h*P* = 0.0031 compared with group with CCS 1-100; ⁱ*P* = 0.0486 compared with group with CCS 1-100. CCS: Coronary calcium score; %APV: Percent aggregate plaque volume.

groups (Table 4).

DISCUSSION

Our results showed that the incidence of high-risk plaque was not significantly different among the three groups with CCS of 1-100, 101-400 and > 400. However, the incidence of significant stenosis increased stepwise as CCS increased. Thus, the combined incidence of high-risk plaque and significant stenosis increased significantly as

CCS increased. These results suggest that the stepwise increased risk of coronary events associated with increasing CCS would be due to an increasing incidence of significant stenosis, while the incidence of high-risk plaque remains the same except in patients who have zero CCS.

High-risk plaque

Recently, CCTA characteristics of vulnerable plaque are reported to be positive remodeling, low attenuation

Table 3 Predictors of high-risk plaque, significant stenosis, and high-risk coronary calcium score by multivariate analysis

	OR	95%CI	P
High-risk plaque factor			
Male	4.93	2.07-11.7	0.0003
Hypertension	2.2	1.13-4.28	0.0204
Significant stenosis factor			
Hypertension	2.66	1.44-4.89	0.0017
Dyslipidemia	2	1.15-3.47	0.0137
Diabetes	2.32	1.42-3.79	0.0008
High-risk CCS factor			
Age	1.06	1.03-1.08	0.00001
Male	1.54	1.02-2.34	0.0414
Diabetes	2.46	1.68-3.59	0.0001

CCS: Coronary calcium score.

plaque, and spotty calcification^[13]. In addition, the napkin-ring sign is regarded as another sign of vulnerable plaque^[14]. Thus, we regarded high-risk as the plaque with positive remodeling, low attenuation plaque, spotty calcification, or napkin-ring sign.

The incidence of high-risk plaque was 9.5% in our patients. Motoyama *et al.*^[16] detected positive remodeling and/or low attenuation plaque in 6.8%. Fujimoto *et al.*^[17] detected positive remodeling and low attenuation plaque in 6.3%. Their incidence is similar to our results.

In our study, the incidence of high-risk plaque was not significantly different among the three groups with CCS ≥ 1 . No previous studies demonstrated this association. Fujimoto *et al.*^[17] studied the incidence of positive remodeling and low attenuation plaque in 1139 patients without symptoms or with atypical symptoms. High-risk plaque was detected in 0%, 4.3% and 15.5% in the low-, intermediate- and high-risk Framingham scores groups, respectively. For patients of the intermediate-risk group, the incidence of high-risk plaque was 3.3%, 4.9%, 9.8% and 6.5% in patients who have CCS of 0, 1-250, 251-500 and > 500 , respectively. For patients of the high-risk group, it was 7.0%, 20.0%, 17.1% and 12.5% in the respective CCS groups. They found that the incidence of high-risk plaque was lower for CCS > 500 and > 250 in the intermediate- and high-risk groups, respectively. However, when we recalculated their results, we found that the incidence of high-risk plaque was 3.7%, 9.1%, 13.2% and 9.5% in the respective CCS categories. There were no significant differences apart from patients with zero CCS. These results are very similar to ours. Because extensive calcification appears at a later stage of atherosclerotic progression, the incidence of high-risk plaque may not increase in extensively calcified lesions.

Patients who have a high CCS may have multiple plaques compared to those with a modest CCS. Thus, we investigated the incidence of multiple plaques in each group, but there were no significant differences among the four groups. The percent aggregate plaque volume was also not significantly different among the 4 groups.

Significant stenosis

Our results also showed that the incidence of significant stenosis increased stepwise as CCS increased. Rosen *et al.*^[18] performed CCS measurement and coronary angiography and found a close association between baseline calcium mass score and stenosis severity in each coronary artery. Ho *et al.*^[19] performed CCS measurement and CCTA in 664 patients and found that the frequency of significant stenosis increased as CCS increased, being 7.9%, 8.3%, 14.5% and 27.2% in those with CCS of 1-100, 101-400, 401-1000 and > 1000 , respectively. These results are consistent with ours.

Zero CCS

Our study showed that, in patients who have zero CCS, the incidence of non-calcified plaque, high-risk plaque, and significant stenosis was 13.6%, 1.3% and 0.6%, respectively. Previously, we found non-calcified plaque in 11.1% of 224 asymptomatic low-risk patients with zero CCS^[20]. Hausleiter *et al.*^[21] detected non-calcified plaque in 15.9% of intermediate risk patients. The CONFIRM registry reported that the incidence of significant stenosis was 1.4% in patients with zero CCS^[22]. Their results are consistent with ours.

Predictors of high-risk plaque, significant stenosis, and high-risk CCS

In our study, multivariate analysis demonstrated that the predictors of high-risk plaque were male sex and hypertension, while those of significant stenosis were hypertension, dyslipidemia, and diabetes. Furthermore, the predictors of high-risk CCS were age, male sex, and diabetes. These predictors are conventional coronary risk factors.

Limitations

There are several limitations to our study. The number of patients was not large enough. We need a larger patient population to confirm our results. Although the rate of major coronary event differed significantly among the four groups, this difference was caused by the difference in coronary revascularization. We selected coronary revascularization only for patients with either moderate or severe ischemia by myocardial perfusion imaging or fractional flow reserve less than 0.75. Many studies demonstrate that these patients are at increased risk of coronary events, and benefit from coronary revascularization^[23,24]. We think that it is difficult to demonstrate differences in hard cardiac events among the 4 groups, because the number of patients and follow-up period were not sufficient. In addition, our patients are basically at low to intermediate risk for coronary events, because these patients have no known CAD, which means subclinical CAD. Moreover, we prescribed high-intensity statin therapy for patients with high-risk plaque. Therefore, we think that these are the reasons why there are too few events in our study.

Table 4 Major coronary event among the four groups *n* (%)

CCS	0	0-100	101-400	> 400	<i>P</i>
<i>n</i>	154	198	165	134	
MCE	0 (0)	8 (4.0) ^a	13 (7.9) ^c	23 (17.2) ^f	< 0.001
Coronary death	0 (0)	0 (0)	0 (0)	1 (0.8)	0.6345
Myocardial infarction	0 (0)	1 (0.5)	1 (0.6)	3 (2.2)	0.4584
Revascularization	0 (0)	7 (3.5) ^e	12 (7.3) ⁱ	19 (14.2) ^k	< 0.001

^a*P* = 0.0306 compared with group with CCS 0; ^c*P* = 0.1188 compared with group with CCS 1-100; ^f*P* = 0.0141 compared with group with CCS 101-400; ^e*P* = 0.0486 compared with group with CCS 0; ⁱ*P* = 0.1114 compared with group with CCS 1-100; ^k*P* = 0.0333 compared with group with CCS 101-400. CCS: Coronary calcium score; MCE: Major coronary event.

Our results demonstrate that the stepwise increased risk of coronary events in association with an increased CCS would be caused by an increasing incidence of significant stenosis, while the incidence of high-risk plaque remains the same, except patients with zero CCS. Thus, the combined incidence of high-risk plaque and significant stenosis increased stepwise as CCS increased.

COMMENTS

Background

Coronary calcium score (CCS) is the most powerful predictor of cardiac events beyond conventional risk factors. However, the precise mechanism of increased risk of coronary events associated with increasing CCS is not fully elucidated.

Research frontiers

Many studies have demonstrated that most cardiac death and myocardial infarction are caused by rupture of vulnerable plaque, which often has non-significant stenosis. Recent studies demonstrate that the characteristics of vulnerable plaque by coronary computed tomographic angiography, which is called high-risk plaque, are positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign.

Innovation and breakthroughs

The authors showed that stepwise increased risk of coronary events associated with increasing CCS is caused by increasing prevalence of significant stenosis, while that of high-risk plaque remains the same. There was each study which investigated the relationship between CCS and significant stenosis, and CCS and high-risk plaque, respectively. However, the authors comprehensively showed the relationship between CCS and high-risk plaque/significant stenosis.

Applications

The higher the CCS, the more the authors have a chance to find significant stenosis in these patients. For patients with significant stenosis, non-invasive stress test to detect myocardial ischemia is needed. The authors also must pay attention to high-risk plaque even for patients with low CCS.

Terminology

Napkin-ring sign is defined as the presence of a ring of high attenuation around certain coronary artery plaque and the CT attenuation of a ring presenting higher than those of the adjacent plaque and no greater than 130 HU.

Peer-review

Very nice and interesting study, well performed.

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