Determining the Relationship between Triglycerides and Arterial Stiffness in Cardiovascular Risk Patients Without Low-Density Lipoprotein Cholesterol-Lowering Therapy
The Coupling Registry

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Summary
Data examining the relationship between arterial stiffness and triglyceride (TG) and other cardiovascular risk factors have remained to be sparse.

Of the 5,109 patients with any cardiovascular risk factors in the Cardiovascular Prognostic Coupling Study in Japan (the Coupling Registry), the data of 1,534 patients who had no history of cardiovascular disease and were without low-density lipoprotein cholesterol (LDL-C)-lowering therapy (average age 67.9 ± 12.0 years, 55% males) were analyzed. Arterial stiffness was evaluated using the cardio-ankle vascular index (CAVI).

Among the clinical and behavioral cardiovascular risk factors, the significant factors that constituted the CAVI value were smoking, diabetes, lower high-density lipoprotein cholesterol, and higher TG. After adjustment for age, sex, and body mass index (BMI), only TG (odds ratio [OR] per 1 standard deviation, 1.26 [95% confidence interval, 1.12-1.44]) and diabetes (OR, 1.52 [1.22-1.90]) were found to be associated with a risk of higher CAVI (≥ 9.0). TG (C-statistic, 0.80 [0.78-0.82]; \( P = 0.040 \)) and diabetes (C-statistic, 0.80 [0.78-0.82]; \( P = 0.038 \)) significantly improved the discrimination of the risk of a higher CAVI beyond the model that included age, sex, and BMI.

TG was associated with a risk of arterial stiffness, and its contribution was slight but almost the same as that of diabetes among patients who had cardiovascular risk without a history of cardiovascular disease and LDL-C-lowering therapy.

Key words: Atherosclerosis, Dyslipidemia, Cardiovascular disease, Cardio-ankle vascular index, Diabetes mellitus

Arterial stiffness, which involves structural and physiological changes in the arteries, has been identified to be associated with risk of cardiovascular disease (CVD) events.1,2) Although there are several established traditional cardiovascular risk factors such as age, male gender, smoking, hypertension, low-density lipoprotein cholesterol (LDL-C), diabetes, and chronic kidney disease (which all contribute as risk factors of arterial stiffness), the contribution of each risk factor to the risk of CVD events is different.3,5) In epidemiological studies, triglyceride (TG) has been recognized as an important marker of CVD events.5-9) However, the most recent trial using omega-3 fatty acid (which primarily lowers the body’s TG level) did not observe any significant reduction in statin-treated CVD events.10) The association between TG and CVD events has thus, remained in the modern era despite aggressive treatment with LDL-C-lowering therapy.

The cardio-ankle vascular index (CAVI), which is a noninvasive vascular function test, is widely used as a surrogate marker of both arterial stiffness and the risk of CVD.11-13) In several cross-sectional studies, the clinical and behavioral cardiovascular risk factors including TG have been determined as significant factors that constituted the CAVI.14-16) However, a part of those studies did not take LDL-C-lowering therapy into consideration.16) Most importantly, a majority of those studies did not compare the relationship between arterial stiffness and TG and other cardiovascular risk factors.

In this study, we investigated whether TG is associated with the CAVI in a modern cohort that consisted of a large Japanese population with cardiovascular risk. We also compared the risk discrimination of the CAVI between TG and other cardiovascular risk factors. We targeted individuals without lipid-lowering therapy to clearly test the association between TG and the CAVI; we have also extended the search for this association based on the specified threshold of LDL-C, speculating that the asso-
cation between TG and CAVI would be attenuated in the group with higher LDL-C level and might be more remarkable in the group with lower LDL-C level. These speculations were based on the strong evidence about the association between lipid-lowering statin therapy/LDL-C level and arterial stiffness.\textsuperscript{17-19}

**Methods**

**Subjects:** The protocol of the Cardiovascular Prognostic Coupling Study in Japan (the Coupling Registry) has been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) website under the trial number UMIN000018474.\textsuperscript{20} Briefly, the Coupling Registry is a nationwide multicenter prospective cohort study to determine CAVI values that are predictive of cardiovascular events in Japanese patients aged ≥ 30 years with any of the following cardiovascular risk factors observed at a clinic or hospital: diabetes, glucose tolerance disorder, dyslipidemia, high-normal normotension or grade I-III hypertension (> 130/85 mm Hg), current smoking, chronic kidney disease (estimated glomerular filtration rate < 60 mL/minute/1.73 m\textsuperscript{2} and/or positive proteinuria), and medical history of CVD (coronary artery disease, cerebrovascular disorder or non-cardiogenic cerebrovascular disorder, aortic dissection, peripheral artery disease, history of hospitalization by heart failure).

Patients with any of the following were excluded: chronic renal failure requiring hemodialysis; other serious illnesses (e.g., end-stage cancer, active connective tissue disease); alcohol or drug addiction; inability to attend hospital visits or provide informed consent; or other factors rendering them inappropriate as judged by the study physician.

This research was conducted in accordance with the Helsinki Declaration. The ethics committee of the internal review board of the Jichi Medical University School of Medicine approved the protocol. The Fujitsu Clinic Ethics Committee reviewed this study, and we obtained the approval of the Committee before conducting this study (Ethical Committee Approval No. 13). The study protocol was registered on the clinical trials registration site, i.e., the UMIN-CTR, under registration no. UMIN000018474. Written informed consent was obtained from all subjects enrolled in this study.

**Measurement of blood pressure:** Clinic blood pressure (BP) was measured after 5 minutes of rest as the average of 2 serial measurements taken by a physician or nurse using the same validated methods used in their clinical practice. We obtained each subject’s systolic and diastolic BP and pulse rate.\textsuperscript{21}

**Measurement of the CAVI:** The CAVI was measured using a VaSera VS-1000 device (Fukuda Denshi, Tokyo), with the subject in the recumbent position, and it was calculated automatically using a VaSera VS-Series Vascular Screening System (Fukuda Denshi). Measurement of the CAVI requires the placement of electrocardiogram electrodes on both wrists and a microphone for phonocardiography on the sternum in the second intercostal space. In addition, a BP cuff is wrapped around each of the 4 extremities. In this manner, the upper arm and ankle pulse waves, as well as BP, can all be measured using plethysmography. The CAVI value was calculated as the average of the right and left CAVI values. We defined a higher CAVI as ≥ 9.0, which was established as being associated with the progression of CVD events.\textsuperscript{12,22}

**Statistical analyses:** The data are expressed as the mean ± standard deviation (SD) or percentage. Correlations between parametric variables were analyzed using Pearson’s correlation coefficient. The difference in CAVI between males and females was analyzed using Mann-Whitney U-test. We performed a multiple regression analysis using the entire population to evaluate the association between each cardiovascular risk factor and the CAVI after adjustment for age, sex, and BMI. The predictive performance of each variable was calculated and compared with each other by a receiver operating characteristics analysis.

An optimized LDL-C level is the most important factor for preventing the progression of arteriosclerosis and the onset of CVD.\textsuperscript{1,4} Therefore, to dilute the effect of the LDL-C level on CAVI, we further performed a similar analysis for the association between TG and CAVI after dividing the subjects into 2 groups, that is, those with LDL-C ≥ 140 mg/dL and those with LDL-C < 140 mg/dL, according to the Japan Atherosclerosis Society definition of hypercholesterolemia,\textsuperscript{19} and then a similar analysis was performed. Statistical analyses were conducted using the JMP software program for Windows (ver. 10.0; SAS Institute, Cary, NC, USA) and STATA ver. 15.0 software (StataCorp, College Station, TX). Significant differences were defined at a $P$-value for the hazard ratio of < 0.05.

**Results**

**Background characteristics of the subjects:** The CAVI has been measured in 5,109 patients in the Coupling Registry. Of these patients, those missing LDL-C, high-density lipoprotein cholesterol (HDLC), or TG data ($n = 1,499$), those with a history of CVD ($n = 1,207$), and those with LDL-C-lowering therapy (i.e., those taking statins; $n = 2,393$) were excluded from analysis. Thus, in total, the data of the remaining 1,534 participants were analyzed (Figure 1). The average age and BMI were 67.9 ± 12.0 years old and 24.5 ± 4.1 kg/m\textsuperscript{2}, respectively. Of these, 850 (55%) were male. The average CAVI value was 8.8 ± 1.4. The prevalence and extent of other cardiovascular risk are shown in Table I. The distributions of TG and CAVI are illustrated in Figures 2, 3.

**Association between cardiovascular risk and CAVI:** Age ($r = 0.574$; $P < 0.001$) and BMI ($r = -0.327$; $P < 0.001$) were significantly associated with CAVI. Males had higher CAVI than females (8.9 ± 1.4 versus 8.6 ± 1.3, $P < 0.001$). In the multiple regression analysis adjusted for age, sex, and BMI, the presence of diabetes, current smoking, HDLC, and TG were associated with the CAVI,
while the presence of hypertension, chronic kidney disease, and LDL-C was not (model 1 in Table II). In the multiple regression analysis that included age, sex, BMI, and the significant risk factors in model 1, the presence of diabetes ($\beta = 0.12$ and $P < 0.001$), current smoking ($\beta = 0.04$ and $P = 0.030$), and TG ($\beta = 0.05$ and $P = 0.042$) were independently associated with the CAVI (Model 2 in Table II). In addition, 87 patients were determined to be taking fibrates (bezafibrate and fenofibrate), representing only 6% of the total patients. When we performed further analysis adding the use of fibrates as a covariate, the association between TG and CAVI remained the same in both model 1 ($\beta = 0.05$, $P < 0.001$) and model 2 ($\beta = 0.04$, $P = 0.49$).

We next investigated the association between cardiovascular risk factors and higher CAVI ($\geq 9.0$). After adjustment for age, sex, and BMI, we observed that TG (odds ratio [OR] per 1 SD, 1.26; 95% confidence interval [CI]: 1.12-1.44), the presence of diabetes (OR, 1.52; 95% CI: 1.22-1.90), and chronic kidney disease (OR, 1.93; 95% CI: 1.51-2.47) were associated with the risk of a higher CAVI ($\geq 9.0$), but the presence of hypertension, smoking, and LDL-C were not (Table III).

**Discrimination of cardiovascular risk for CAVI:** We assessed the discriminative performance of cardiovascular risk factors for a higher CAVI by using C-statistics. When each cardiovascular risk factor was added to the base model that included age, sex, and BMI, we observed that TG ($P = 0.040$) and diabetes ($P = 0.038$) significantly improved the model of discrimination of the risk of a higher CAVI, whereas chronic kidney disease did not (Table III).

**Association between cardiovascular risk and the CAVI stratified by LDL-C levels:** When we divided the subjects into a lower LDL-C group (< 140 mg/dL, $n = 1,232$) and a higher LDL-C group ($\geq 140$ mg/dL, $n = 302$), the results of a multiple regression analysis showed that the presence of diabetes, current smoking, HDL-C, and TG were associated with CAVI adjusted for age, sex, and BMI in the subjects with LDL-C < 140 mg/dL (model 1 in Table IV). In a multiple regression analysis that included age, sex, BMI, and significant risk factors from model 1, the presence of diabetes ($\beta = 0.13$ and $P < 0.001$), current smoking ($\beta = 0.05$ and $P = 0.046$), and TG ($\beta = 0.06$ and $P = 0.022$) were determined to be independently associated with the CAVI (model 2 in Table IV). In the subjects with LDL-C values $\geq 140$ mg/dL, only HDL-C ($\beta = -0.10$ and $P = 0.037$) was associated with CAVI (Table IV).

Table V showed the association between cardiovascular risk factors and a higher CAVI after the subjects are divided into with and without LDL-C values $\geq 140$ mg/dL. In the subjects with LDL-C $< 140$ mg/dL, after adjustment for age, sex, and BMI, the presence of diabetes,
chronic kidney disease, and TG were associated with the risk of a higher CAVI, whereas in the subjects with LDL-C values ≥ 140 mg/dL, this association was identified for hypertension and chronic kidney disease. Concerning the discrimination of cardiovascular risk factors for a higher CAVI, adding TG or diabetes to the base model that included age, sex, and BMI tended to improve the model of discrimination of the risk of a higher CAVI in the subjects with LDL-C < 140 mg/dL.
Table II. Multiple Linear Regression Analysis with Cardio-Ankle Vascular Index as Dependent Factor (n = 1,534)

| Variables | Model 1 | Model 2 |
|-----------|---------|---------|
|           | β       | P-value | β       | P-value |
| Diabetes (0 = no, 1 = yes) | 0.13    | < 0.001 | 0.12    | < 0.001 |
| Hypertension (0 = no, 1 = yes) | -0.02   | 0.268   | -       | -       |
| Smoking (no = 0, 1 = yes) | 0.05    | 0.008   | 0.04    | 0.030   |
| Chronic kidney disease (0 = no, 1 = yes) | -0.03   | 0.163   | -       | -       |
| LDL-C (1 mg/dL) | 0.00    | 0.992   | -       | -       |
| HDL-C (1 mg/dL) | -0.06   | 0.006   | -0.03   | 0.235   |
| TG (1 mg/dL) | 0.07    | < 0.001 | 0.05    | 0.042   |

In model 1, each variable was added separately to the baseline regression models, which included age, sex, and BMI. In model 2, each variable was added separately to the model, which included age, sex, BMI, and selected covariates that were significant in model 1 (diabetes, smoking, HDL-C, and TG).

Table III. Multiple Logistic Regression Analysis and Change in Model Discrimination with Cardio-Ankle Vascular Index ≥ 9 as Dependent Factor

|            | OR (95% CI) of each variable | P-value | C-statistic | P-value of change from base model |
|------------|-------------------------------|---------|-------------|-----------------------------------|
| Base model | -                             | -       | 0.79 (0.77, 0.81) | -                                 |
| + Diabetes (0 = no, 1 = yes) | 1.52 (1.22–1.90) | < 0.001 | 0.80 (0.78, 0.82) | 0.038                             |
| + Hypertension (0 = no, 1 = yes) | 1.33 (0.98–1.82) | 0.066 | 0.79 (0.77, 0.82) | 0.772                             |
| + Smoking (no = 0, 1 = yes) | 1.15 (0.83–1.62) | 0.396 | 0.80 (0.77, 0.82) | 0.296                             |
| + Chronic kidney disease (0 = no, 1 = yes) | 1.93 (1.51–2.47) | < 0.001 | 0.79 (0.77, 0.81) | 0.872                             |
| + LDL-C, per 1 SD | 1.03 (0.91–1.16) | 0.623 | 0.79 (0.77, 0.81) | 0.935                             |
| + HDL-C, per 1 SD | 0.88 (0.78–1.00) | 0.056 | 0.79 (0.77, 0.82) | 0.206                             |
| + TG, per 1 SD | 1.26 (1.12–1.44) | < 0.001 | 0.80 (0.78, 0.82) | 0.040                             |

The base model included age, sex, and BMI. One SD increment of each measure is as follows: LDL-C, per 28.7 mg/dL; HDL-C, per 17.1 mg/dL; TG, per 79.6 mg/dL.

Table IV. Multiple Linear Regression Analysis with Cardio-Ankle Vascular Index as the Dependent Factor in LDL-C < 140 mg/dL and LDL-C ≥ 140 mg/dL

| Variables | LDL-C < 140 mg/dL (n = 1,232) | LDL-C ≥ 140 mg/dL (n = 302) |
|-----------|-------------------------------|-------------------------------|
|           | Model 1 | Model 2 | Model 1 | Model 2 |
|           | β       | P-value | β       | P-value | β       | P-value |
| Diabetes (0 = no, 1 = yes) | 0.14    | < 0.001 | 0.13    | < 0.001 | 0.06    | 0.169   |
| Hypertension (0 = no, 1 = yes) | -0.04   | 0.067   | -       | -       | 0.05    | 0.275   |
| Smoking (no = 0, 1 = yes) | 0.06    | 0.014   | 0.05    | 0.046   | 0.05    | 0.315   |
| Chronic kidney disease (0 = no, 1 = yes) | -0.02   | 0.297   | -       | -       | -0.04   | 0.368   |
| LDL-C (1 mg/dL) | 0.00    | 0.987   | -       | -       | -0.07   | 0.129   |
| HDL-C (1 mg/dL) | -0.05   | 0.034   | -0.02   | 0.535   | -0.10   | 0.037   |
| TG (1 mg/dL) | 0.08    | < 0.001 | 0.06    | 0.022   | 0.02    | 0.638   |

In model 1, each variable was added separately to the baseline regression models, which included age, sex, and BMI. In model 2, each variable was added separately to the model, which included age, sex, BMI, and selected covariates that were significant in model 1 (diabetes, smoking, HDL-C, and TG).

Discussion

The findings of this study can be summarized as follows: in the patients aged ≥ 30 years with one or more cardiovascular risks who had no history of CVD and who had not taken LDL-C-lowering therapy, (1) the presence of diabetes, smoking, and TG were independently associated with the CAVI as a continuous variable. (2) As a categorical variable, only the addition of diabetes and TG improved the model discrimination for a higher CAVI, for which the contributions were slight but almost the same as that of diabetes. (3) These associations were marginally consistent in the subjects with LDL-C < 140 mg/dL, but not in those with LDL-C ≥ 140 mg/dL. **Hypertriglyceridemia and CAVI:** Our analyses revealed that TG had a significant positive effect on the CAVI in the entire cohort and in the LDL-C < 140 mg/dL group when adjusted for age, sex, and BMI in each group. Although there have been reports examining the association between hypertriglyceridemia and high CAVI values.
their results have been inconsistent.25-27) In a population
with uncontrolled mean LDL-C levels or without measured LDL-C data (174.4 mg/dL or no records), no signifi-
cant association was noted between hypertriglyceridemia and CA VI values.14-16) Our present findings support the results
of those studies, because the mean LDL-C level in this
study was relatively low (115.1 ± 28.7 mg/dL).

In studies examining the coronary artery disease risk
assessment using Mendelian randomization, TG was re-
garded as a significant positive risk factor, along with
LDL-C and non-fasting plasma glucose.28) In addition, al-
though high LCL-C levels are an important risk factor for CVD, lowering the LDL-C alone cannot sufficiently sup-
press the onset of CVD. Even though LDL-C in patients with metabolic syndrome was shown to be strongly re-
duced by statins, it was not possible to counteract cardio-
vascular risk factors other than LDL-C for the onset of CVD.29) In that report, TG remained as a significant factor
along with fasting plasma glucose as cardiovascular risks.29

There is also a meta-analysis demonstrating that fi-
brate use for hypertriglyceridemia reduced major CVD
events by 25% when limited to primary pre-
vention.30) Namely, next to hyper-LDL-cholesterolemia,
hypertriglyceridemia as a residual risk has been identified
to be vital (along with hyperglycemia) in efforts to sup-
press the onset of CVD.

However, we observed no significant association be-
 tween LDL-C levels and CAVI in this study. In earlier in-
vestigations, the association between the lipid profile and
CAVI has also shown inconsistent results. Although LDL-
C has been recognized as an established major risk factor for arteriosclerosis, several studies reported that there was no association between LDL-C and CAVI levels.31,32) The pathological processes in the early phase of atherogenesis are initiated by accumulation of LDL-C, followed by cell-
ular infiltration and foam cell formation.33) There is a pos-
sibility that initial lipidosis induced by infiltration of
LDL-C may soften the arterial wall.34) The effect of statins
on CAVI levels has been considered regarding this dis-
crepancy, but this has not been established.35,36) We thus,
include subjects who had not been treated with an LDL-
C-lowering therapy including statin, but our findings are
similar to those of the previous studies. Further research is
necessary to clarify the association between LDL-C and
CAVI.

Hypertriglyceridemia, diabetes mellitus, and cardiovas-
cular risk: Interestingly, in this study, the inclusion of
high TG level improved the model discrimination for a
higher CAVI, similar to diabetes. Although diabetes has
been established as an important risk factor for CVD,37)
the risk posed by TG for CVD has been debated as men-
tioned above. The TG level in Japanese subjects with type
2 diabetes is considered a major predictor of CVD, com-
parable to LDL-C.38) It is possible that our present find-
ings indicate that hypertriglyceridemia along with diabetes mellitus could pose a residual risk among lipid items.

There have been several investigations examining the
association between both TG and diabetes and the CAVI,
and the results of the majority of those investigations have
failed to determine whether the treatment of TG or diabe-
tes has greater clinically meaningful improvement that
would affect the risk of a high CAVI. In this study, we as-
essed this association with the use of C-statistics, and our
findings indicated that the TG level is clinically meaning-
ful for arterial stiffness, equal to incident diabetes.

**Study limitations:** The blood test data in this study were
analyzed without taking into account the time of the
blood collection. It has been acknowledged that there is
no difference in terms of LDL-C and HDL-C between
non-fasting and fasting conditions.39) In contrast, several
previous papers reported that TG was more predictive of
a CVD incident in non-fasting than in fasting blood collec-
tion.36,39) While other papers reported that TG was associ-
ated with CVD incidence irrespective of fasting condi-
tion.40) Thus, the debate remains about the ability of non-
fasting TG to predict the onset of CVD.34,41)

As a result, the effects of high TG levels and the use

### Table V. Multiple Logistic Regression Analysis and Change in Model Discrimination with CAVI ≥ 9 as Dependent Factor in LDL-C < 140 mg/dL and LDL-C ≥ 140 mg/dL

| Variables | LDL-C < 140 mg/dL (n = 1,232) | LDL-C ≥ 140 mg/dL (n = 302) |
|-----------|-------------------------------|-------------------------------|
|           | OR (95% CI) of each variable | P-value | C-statistic | OR (95% CI) of each variable | P-value | C-statistic |
| Base model | – | – | 0.79 (0.76, 0.81) | – | – | – |
| + Diabetes (0 = no, 1 = yes) | 1.46 (1.14–1.87) | 0.003 | 0.79 (0.77, 0.82) | 1.61 (0.95–2.74) | 0.076 | 0.82 (0.78, 0.87) |
| + Hypertension (0 = no, 1 = yes) | 1.16 (0.81–1.66) | 0.424 | 0.79 (0.76, 0.81) | 1.91 (1.02–3.73) | 0.044 | 0.82 (0.77, 0.87) |
| + Smoking (no = 0, 1 = yes) | 1.03 (0.70–1.49) | 0.890 | 0.79 (0.77, 0.81) | 1.24 (0.50–2.99) | 0.637 | 0.82 (0.77, 0.87) |
| + Chronic kidney disease (0 = no, 1 = yes) | 1.35 (1.50–2.56) | < 0.001 | 0.79 (0.76, 0.81) | 2.04 (1.06–3.97) | 0.033 | 0.82 (0.77, 0.87) |
| + LDL-C, per 1SD | 1.02 (0.90–1.17) | < 0.001 | 0.79 (0.76, 0.81) | 0.493 | 0.49 (0.20–0.94) | 0.018 | 0.83 (0.78, 0.87) |
| + HDL-C, per 1SD | 0.92 (0.80–1.05) | 0.213 | 0.79 (0.76, 0.81) | 0.451 | 0.72 (0.53–0.97) | 0.032 | 0.82 (0.78, 0.87) |
| + TG, per 1SD | 1.30 (1.13–1.50) | < 0.001 | 0.79 (0.77, 0.82) | 0.054 | 1.06 (0.75–1.48) | 0.730 | 0.82 (0.77, 0.87) |

The base model included age, sex, and BMI. One SD increment of each measure is as follows: LDL-C, per 22.1 mg/dL; HDL-C, per 17.7 mg/dL; TG, per 82.1 mg/dL in LDL-C < 140 mg/dL and LDL-C, per 13.7 mg/dL; HDL-C, per 14.3 mg/dL; TG, per 67.3 mg/dL in LDL-C ≥ 140 mg/dL.
of fibrates and antidiabetes/hypertension drugs on the CAVI levels were unclear in this study.

TG was not significantly associated with CAVI value in those with LDL-C ≥ 140 mg/dL, which may have been due to the insufficient sample size, because of the nature of subanalysis.

**Conclusion:** In this cohort, high TG was associated with a risk of arterial stiffness assessed using the CAVI, and its contribution was slight but almost the same as that of diabetes in the subjects who had cardiovascular risk with a history of CVD and LDL-C-lowering therapy. These findings were remarkable in the subjects with lower LDL-C. For the primary prevention of CVD events, hypertriglyceridemia may be a potential therapeutic target among dyslipidemias. It is necessary to prospectively examine whether CAVI-guided therapy in patients with cardiovascular risks can suppress the onset of CVD. It is also necessary to verify this with the Coupling Registry study.

**Disclosure**

**Conflicts of interest:** Kazuomi Kario has received research funding from Fukuda Denshi Co. All other authors have no conflicts of interest to declare.

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