Original Article

Relationships between Family Histories of Stroke and of Hypertension and Stroke Mortality: NIPPON DATA80, 1980–1999

Aya KADOTA[1),2)], Tomonori OKAMURA[3)], Atsushi HOZAWA[4)], Takashi KADOWAKI[1)], Yoshitaka MURAKAMI[1)], Takehito HAYAKAWA[5)], Yoshikuni KITA[1)], Akira OKAYAMA[6)], Yasuyuki NAKAMURA[7)], and Hirotsugu UESHIMA[1)], for the NIPPON DATA80 Research Group*

A family history of stroke seems to be related with increased risk of stroke although the relationship is not always significant. Increased risk of stroke is strongly associated with hypertension, which might be also associated with family history. However, investigations into the relationship between family history of hypertension and stroke mortality are scarce. We investigated whether a family history of stroke and that of hypertension evaluated using a simple questionnaire could predict stroke mortality in Japanese. We obtained parental histories of stroke and of hypertension from 8,037 randomly selected general Japanese without history of cardiovascular disease and followed them for 19 years. The multivariate adjusted hazard ratios (HRs) for total stroke mortality, intra-cerebral hemorrhage mortality and for cerebral infarction mortality according to family history were estimated using the Cox proportional hazards model. The prevalences of family histories of stroke and of hypertension were 20.6% and 31.1%, respectively. A family history of stroke was not related to total stroke mortality, intra-cerebral hemorrhage mortality or to cerebral infarction mortality. Meanwhile, a family history of hypertension was positively related to total stroke mortality among women aged less than 60 years and men aged 60 or more years (women: HR=3.41, 95% confidence interval [CI]: 1.49–7.81; men: HR=1.50, 95% CI: 1.00–2.24) even after adjustment for systolic blood pressure. In conclusion, a family history of stroke could not predict total stroke mortality. However, a family history of hypertension might predict an increased risk for total stroke. (*Hypertens Res* 2008; 31: 1525–1531)

***Key Words*: family history, stroke, hypertension, stroke mortality, epidemiology**

From the [1)]Department of Health Science and [2)]Department of Internal Medicine, Shiga University of Medical Science, Otsu, Japan; [3)]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan; [4)]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; [5)]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; [6)]The First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo, Japan; and [7)]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan.

*Members of the Research Group are listed in the reference *6*.

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Address for Reprints: Aya Kadota, M.D., Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu 520–2192, Japan. E-mail: ayakd@belle.shiga-med.ac.jp

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Introduction

One of the simplest ways to determine whether individuals have a potential genetic risk for diseases, even in developing countries, is to collect information about their family history. The 2002 American Heart Association guidelines for primary prevention of cardiovascular disease and stroke recommend regularly updating family histories for coronary heart disease (*1*).

Stroke is strongly affected by hypertension, which may also be associated with family history (*2*). Thus, knowledge of the family history of hypertension might also provide potential predictability for stroke. Nevertheless, the relationship between stroke mortality and a family history of stroke and of hypertension remains unclear except for the relationship between subarachnoid hemorrhage and a family history(*3*, *4*).

Although stroke mortality and incidence has remained still higher in Japan than in Western countries (*5*), very few prospective studies have examined the association between family history and stroke mortality in the general Japanese population. NIPPON DATA80 is a large cohort study of individuals selected randomly from all over Japan who were followed up for 19 years. We investigated whether a simple questionnaire about family histories of stroke and of hypertension could predict stroke mortality among the general Japanese population.

Methods

Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged). The present study analyzed data from NIPPON DATA80, in which baseline surveys were performed in 1980. Details of this cohort have been reported elsewhere (*6*).

A total of 10,546 residents (4,640 men and 5,906 women, aged ≥30 years) from 300 randomly selected districts participated in the survey and were followed up until November 1999. The overall population of residents over 30 years of age in all districts was 13,771, and the participation rate in the survey was 76.6%. Accordingly, these participants were considered to be representative of the Japanese population. Of the 10,546 participants, 2,509 were excluded due to incomplete residential access information at the first survey (n=908), a history of coronary heart disease or stroke (n=697), or missing information in baseline survey (n=904). The present study analyzed data from the remaining 8,037 participants (3,586 men and 4,451 women). The prevalences of family histories of stroke and of hypertension did not differ between those who were followed up and those who were not.

Follow-Up Survey

The underlying causes of death in the National Vital Statistics which we obtained from the Ministry of Health, Labour and Welfare were coded according to the 9th International Classification of Diseases (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the start of 1995 until the end of 1999. The details of these classifications are described elsewhere (*1*). Codes 430–438 in ICD-9 and I60–I69 in ICD-10 were defined as death from total stroke, which included death from cerebral infarction (codes 433, 434, 437.7a and 7b in ICD-9, I61 and I69.1 in ICD-10) and from intra-cerebral hemorrhage (codes 431–432 in ICD-9, I63 and I69.3 in ICD-10).

The Management and Coordination Agency of the Government of Japan provided permission to use the National Vital Statistics and the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000) approved this study.

Baseline Examination

Public health nurses obtained information about parental family histories of stroke and of hypertension (none, both parents, only paternal, only maternal). We defined a participant as "family history positive" if he or she reported that one parent had such a history. Public health nurses also obtained information about smoking, alcohol consumption, and medical history. Trained observers obtained baseline blood pressure values using a standard mercury sphygmomanometer placed on the right arm of seated participants. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Non-fasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan) for blood measurements. Plasma glucose was measured using the cupric-neocuproine method and converted to the value of the glucose oxidase method (*7*). Total cholesterol was also measured enzymatically as standardized by the Centers for Disease Control/National Heart, Lung, and Blood Institute (CDC-NHLBI) Lipids Standardization Program (*8*).

We defined high blood pressure as systolic blood pressure of ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the administration of antihypertensive agents, or any combination of these. We divided participants into five categories of smokers (never-smoked; ex-smoker; current smoker, <21 cigarettes/d, ≥21 cigarettes/d and ≥41 cigarettes/d) and four categories of drinking (never-drinker; ex-drinker; current drinker, occasionally and daily).

Table 1. Means and Prevalence of Baseline Characteristics of 3,586 Men and 4,451 Women Aged 30 Years and Older (NIPPON DATA80, 1980)

Baseline risk characteristics	Family history							
	Men				Women			
	Stroke		Hypertension		Stroke		Hypertension	
	No	Yes	No	Yes	No	Yes	No	Yes
A: Age less than 60								
Number of participants	2,199	559	1,183	875	2,676	719	2,348	1,047
Family history of stroke (%)	0.0	100.0	14.4	32.8*	0.0	100.0	14.8	35.4*
Age (years)	44.47±8.43	44.47±8.44	44.34±8.46	44.73±8.38	44.54±8.62	44.49±8.48	44.63±8.65	44.30±8.45
BMI (kg/m^2)	22.81±2.80	22.62±2.77	22.80±2.78	22.72±2.81	22.86±3.27	22.82±3.34	22.82±3.25	22.91±3.38
SBP (mmHg)	134.52±18.70	134.63±18.39	134.06±18.79	135.59±18.26	129.24±19.15	129.18±19.11	129.35±19.07	128.97±19.29
DBP (mmHg)	83.21±12.13	82.56±12.41	82.78±12.03	83.72±12.50	78.27±11.64	79.28±11.67	78.22±11.36	79.07±12.27
Total cholesterol (mg/dL)	188.15±33.31	185.77±32.23	187.67±32.96	187.66±33.41	187.28±32.69	186.42±35.06	186.81±32.52	187.76±34.69
Blood glucose (mg/dL)	100.34±32.17	98.73±25.33	99.52±29.61	101.07±33.52	98.17±26.65	96.06±19.53	98.63±27.77	95.70±18.56
High blood pressure (%)	35.1	37.6	34.5	37.9	25.1	26.6	25.2	25.9
Medication for hypertension (%)	7.1	6.8	7.3	6.5	7.8	9.0	7.7	8.9
Drinking (%)								
Non-drinker	21.8	19.3	21.6	20.7	78.4	78.4	77.8	79.9
Occasional-drinker	29.1	27.4	29.3	27.8	19.0	19.2	19.3	18.4
Current-drinker	49.1	53.3	49.1	51.5	2.6	2.4	2.9	1.7
Smoking (%)								
Non-smoker	33.7	34.7	33.4	35.2	92.0	91.8	92.4	91.1
Current smoker (<21 cigarettes/d)	37.2	35.8	38.0	34.7	7.3	7.4	7.0	8.0
Current smoker (≥21 cigarettes/d)	29.1	29.5	28.6	30.1	0.7	0.8	0.6	0.9
B: Age 60 and more								
Number of participants	654	174	559	269	852	204	749	307
Family history of stroke (%)	0.0	100.0	15.0	33.5*	0.0	100.0	15.1	29.6*
Age (years)	69.06±6.35	68.54±6.04	68.67±6.05	69.12±6.75	68.71±6.29	69.01±6.87	68.66±6.20	69.03±6.87
BMI (kg/m^2)	21.78±2.91	21.77±3.09	21.74±2.90	21.86±3.03	22.77±3.54	22.78±3.53	22.79±3.54	22.74±3.51
SBP (mmHg)	150.24±20.87	150.22±20.94	150.32±22.49	150.06±22.45	147.32±22.59	144.85±22.61	147.64±22.78	144.88±22.09
DBP (mmHg)	85.12±12.67	84.89±11.64	84.81±12.33	85.61±12.72	82.65±12.32	81.53±11.86	82.58±12.33	82.06±12.03
Total cholesterol (mg/dL)	182.57±31.72	185.70±32.46	184.39±31.98	180.81±31.60	201.52±34.43	195.63±30.05	200.90±33.00	199.12±35.36
Blood glucose (mg/dL)	111.50±40.45	106.04±28.31	110.28±40.45	110.50±33.36	110.04±35.33	110.88±31.05	109.86±33.53	111.03±36.91
High blood pressure (%)	67.4	72.4	67.8	69.9	63.6	61.8	64.9	59.3
Medication for hypertension (%)	26.9	31.0	26.7	30.1	29.1	30.4	29.9	28.0
Drinking (%)								
Non-drinker	35.9	32.8	36.3	33.1	84.6	82.8	84.6	83.4
Occasional-drinker	20.6	17.2	18.8	22.3	11.3	12.7	11.2	12.4
Current-drinker	43.4	50.0	44.9	44.6	4.1	4.5	4.2	4.2
Smoking (%)								
Non-smoker	43.3	48.3	44.5	43.9	88.7	91.2	89.2	89.3
Current smoker (<21 cigarettes/d)	45.3	40.2	44.7	43.1	10.3	8.3	9.9	10.1
Current smoker (≥21 cigarettes/d)	11.4	11.5	10.8	13.0	1.0	0.5	0.9	0.6

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. High blood pressure was defined as SBP≥140 mmHg and/or DBP≥90 mmHg and/or medication. "Non-drinker" represents never-drinker and ex-drinker. "Non-smoker" represents never-smoked and ex-smoker. *$p<0.05$.

Statistical Analysis

Continuous variables were compared using the analysis of variance and dichotomized variables were compared using the χ^2-test to determine differences in the baseline characteristics according to family history categories. The multivariate adjusted hazard ratios (HRs) of stroke mortality were estimated by three Cox proportional hazards models with the following adjustments: Model 1, age; Model 2, age, total cholesterol, blood glucose, smoking, and drinking category; Model 3, systolic blood pressure was added to Model 2. All confidence intervals were estimated at the 95% level. All statistical tests were two-sided and significance was defined as $p<0.05$. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 11.0J, Tokyo, Japan) was used to perform all analyses.

Results

The prevalences of family histories of stroke and of hypertension were 20.6 and 31.1%, respectively. Table 1 shows the baseline characteristics of the study participants stratified by gender and age according to family histories. In both gender- and age-specific groups, participants with a family history of hypertension more often had a family history of stroke. We did not find any significant difference according to family history in mean values of age, BMI, blood pressure, total cholesterol, or blood glucose. In addition, the prevalences of hypertension, frequency of medication for hypertension, smoking, or alcohol consumption did not significantly differ.

Total person-years of follow-up were 140,340 and the mean follow-up period was 17.5 years. During this period, 1,570 participants died of all causes and 261 participants died of total stroke (152 of ischemic stroke, 58 of intra-cerebral hemorrhagic stroke and 51 of other conditions).

Table 2 shows gender specific analyses. The number of stroke deaths, multiple adjusted HRs and 95% confidence intervals (CIs) for stroke mortality according to family histories of stroke and of hypertension are listed. A family history of stroke was not related to stroke mortality in either gender. A family history of hypertension was positively and significantly related to cerebral infarction mortality in men (Table 2; total stroke, Model 2: HR=1.38, 95% CI: 0.97–1.96, cerebral infarction, Model 2: HR=1.68, 95% CI: 1.08–2.60). On the other hand, a family history of hypertension did not predict stroke mortality in women.

Table 3 shows gender- and age-group-specific analyses. A family history of stroke was not related to stroke mortality in either gender or any age specific group. A family history of hypertension did not relate to total stroke mortality in younger men aged <60 years but significantly increased total stroke mortality in elderly men aged ≥60 years (Table 3: men B; Model 2: HR=1.52, 95% CI: 1.02–2.27). Conversely, in women, a family history of hypertension significantly increased total stroke mortality in younger group aged <60 years (Table 3: women A; Model 2: HR=3.06, 95% CI: 1.37–6.86). Among elderly women aged ≥60 years, we did not find any relationship between family history of hypertension and stroke mortality (Table 3: women B). We calculated all HRs using the three models and found that adjustment for systolic blood pressure did not alter these findings.

Discussion

The present study found that a family history of stroke could not predict stroke mortality in the general Japanese population. However, a family history of hypertension significantly related to stroke mortality among elderly men aged 60 or more years and younger women aged less than 60 years.

In previous epidemiologic investigations including studies of twins and the Framingham Study, a family history of stroke seemed to increase the risk of stroke although some studies did not find a significant relationship (*4*, *9–16*). Floßmann *et al*. systematically reviewed the genetic epidemiology of ischemic stroke. Their meta-analyses identified a positive family history of stroke as a moderate risk factor for ischemic stroke in both case-control (odds ratio [OR]: 1.76; 95% CI, 1.7–1.9) and cohort (OR: 1.3; 95% CI, 1.2–1.5) studies (*4*). Although possible confounding factors were not adjusted for, a prospective Japanese study showed that a family history of stroke increased the risk of intra-cerebral hemorrhage but not of cerebral infarction (*11*). Based on these findings, the American Heart Association/American Stroke Association Stroke Council noted that both paternal and maternal histories of stroke are associated with increased risk of stroke through many mechanisms, including 1) genetic heritability of stroke risk factors, 2) inheritance of susceptibility to the effects of such risk factors, 3) familial sharing of cultural/environmental and lifestyle factors, and 4) interaction between genetic and environmental factors (*3*).

On the bases of this information, we initially postulated that participants with a family history of stroke might have higher blood pressure, other unfavorable risk factors and consequently a higher HR for stroke mortality than those without such a family history. However, we did not identify any significant associations. One possible explanation for the absence of a relationship between family history of stroke and stroke mortality might be the very high historical stroke mortality rate in Japan. Although the genetic pool of Japanese has not changed, the age-adjusted stroke mortality rate has significantly decreased during the past half-century (*17*). This suggests that environmental factors in the past, such as especially higher salt intake which lead to increased blood pressure or malnutrition, strongly contributed to the stroke incidence, especially that of cerebral hemorrhage (*18*). Furthermore, since infectious disease was frequent cause of death during the lifetimes of respondents' parents, there were also some possibilities that a positive family history of stroke in the present study included the parents who were afflicted with stroke because they simply lived longer. Thus, a family his-

Table 2. Multiple Adjusted Hazard Ratios and 95% Confidence Intervals According to the Family History by Gender in 3,586 Men and 4,451 Women Aged 30 Years and Older (NIPPON DATA80, 1980–1999)

	Family history							
	Men				Women			
	Stroke		Hypertension		Stroke		Hypertension	
	No	Yes	No	Yes	No	Yes	No	Yes
Number of participants	2,853	733	2,442	1,144	3,528	923	3,097	1,354
Person-years	48,805	12,550	41,926	19,378	62,799	16,237	55,044	23,992
All stroke								
Number of death	115	24	85	54	95	27	82	40
HR (95% CI)*	1.00	0.70 (0.45–1.10)	1.00	1.40 (0.99–1.99)	1.00	1.27 (0.82–1.95)	1.00	1.11 (0.75–1.62)
HR (95% CI)**	1.00	0.73 (0.47–1.15)	1.00	1.38 (0.97–1.96)	1.00	1.32 (0.85–2.04)	1.00	1.08 (0.73–1.59)
HR (95% CI)***	1.00	0.73 (0.47–1.15)	1.00	1.36 (0.96–1.93)	1.00	1.38 (0.89–2.14)	1.00	1.13 (0.77–1.66)
Intra-cerebral hemorrhage								
Number of death	28	6	22	12	18	6	13	11
HR (95% CI)*	1.00	0.77 (0.31–1.88)	1.00	1.19 (0.58–2.44)	1.00	1.26 (0.49–3.23)	1.00	1.93 (0.85–4.37)
HR (95% CI)**	1.00	0.77 (0.31–1.90)	1.00	1.16 (0.56–2.39)	1.00	1.36 (0.52–3.51)	1.00	1.87 (0.82–4.26)
HR (95% CI)***	1.00	0.78 (0.32–1.94)	1.00	1.13 (0.55–2.32)	1.00	1.47 (0.57–3.82)	1.00	1.82 (0.80–4.18)
Cerebral infarction								
Number of death	72	14	49	37	52	14	49	17
HR (95% CI)*	1.00	0.61 (0.34–1.10)	1.00	1.69 (1.10–2.61)	1.00	1.35 (0.74–2.45)	1.00	0.76 (0.44–1.33)
HR (95% CI)**	1.00	0.64 (0.35–1.15)	1.00	1.68 (1.08–2.60)	1.00	1.41 (0.78–2.57)	1.00	0.74 (0.42–1.29)
HR (95% CI)***	1.00	0.63 (0.35–1.14)	1.00	1.65 (1.07–2.56)	1.00	1.48 (0.81–2.69)	1.00	0.77 (0.44–1.36)

HR, hazard ratio; CI, confidence interval. Estimated by Cox proportional hazard model adjusted for: *age (Model 1); **age, blood glucose, total cholesterol, smoking habits and drinking habits (Model 2); and ***age, systolic blood pressure, blood glucose, total cholesterol, smoking habits and drinking habits (Model 3).

Table 3. Multiple Adjusted Hazard Ratios and 95% Confidence Intervals According to the Family History by Gender and Age Specific Group in 3,586 Men and 4,451 Women Aged 30 Years and Older (NIPPON DATA80, 1980–1999)

	Family history							
	Men				Women			
	Stroke		Hypertension		Stroke		Hypertension	
	No	Yes	No	Yes	No	Yes	No	Yes
A: Age less than 60								
Number of participants	2,199	559	1,883	875	2,676	719	2,348	1,047
Person-years	40,085	10,144	34,412	15,817	49,918	13,300	43,811	19,407
All stroke								
Number of death	26	8	22	12	20	5	11	14
HR (95% CI)*	1.00	1.19 (0.53–2.69)	1.00	1.10 (0.54–2.27)	1.00	0.74 (0.27–2.00)	1.00	3.18 (1.42–7.11)
HR (95% CI)**	1.00	1.30 (0.57–2.96)	1.00	1.03 (0.50–2.14)	1.00	0.72 (0.26–1.95)	1.00	3.06 (1.37–6.86)
HR (95% CI)***	1.00	1.31 (0.57–3.00)	1.00	1.04 (0.50–2.16)	1.00	0.65 (0.24–1.78)	1.00	3.41 (1.49–7.81)
B: Age 60 and more								
Number of participants	654	174	559	269	852	204	749	307
Person-years	8,720	2,355	7,514	3,561	12,881	2,937	11,233	4,585
All stroke								
Number of death	89	16	63	42	75	22	71	26
HR (95% CI)*	1.00	0.58 (0.34–1.00)	1.00	1.50 (1.01–2.23)	1.00	1.42 (0.88–2.30)	1.00	0.81 (0.52–1.28)
HR (95% CI)**	1.00	0.58 (0.34–1.01)	1.00	1.52 (1.02–2.27)	1.00	1.54 (0.95–2.50)	1.00	0.76 (0.48–1.20)
HR (95% CI)***	1.00	0.58 (0.34–1.00)	1.00	1.50 (1.00–2.24)	1.00	1.57 (0.97–2.57)	1.00	0.77 (0.49–1.23)

HR, hazard ratio; CI, confidence interval. Estimated by Cox proportional hazard model adjusted for: *age (Model 1); **age, blood glucose, total cholesterol, smoking habits and drinking habits (Model 2); and ***age, systolic blood pressure, blood glucose, total cholesterol, smoking habits and drinking habits (Model 3).

tory of stroke assessed using the reports to a simple questionnaire in the present study could not predict stroke mortality in Japan. Differentiation of family history of stroke and age of stroke onset among afflicted parents might be important to understand the influence of a family history of stroke on stroke mortality (*16*).

Hypertension is one of the main risk factors for stroke, which is also supposed to be affected by family history (*2*, *19*). Several genetic epidemiologic studies have revealed that gene polymorphisms are related to hypertension (*19–21*). Some studies have also found an aggregation of hypertension and stroke in family histories and medical histories, suggesting a close association between these diseases (*22*, *23*). We also found an aggregation of both diseases in family histories in the present study. However, studies on the relationship between a family history of hypertension and stroke mortality are still scarce and the results are not concordant. Floßmann *et al*. mentioned the difficulty of diagnosing family history of hypertension in the past in their review (*4*). Okada *et al*. reported the prevalence of family history of hypertension was 5.4% (224/4,186) in 1976 (*11*), which was much lower than that observed in the present study. Recall for parental hypertension may be difficult to confirm because of less frequent opportunity for measuring blood pressure or different criteria of hypertension when their parents were young and alive and of so-called "recall bias." Thus, further study should be warranted. In our present findings, we observed the relationship between family history of hypertension and stroke mortality was evident with a significant HR greater than 3.0 among younger women than elder women and men. This suggests that some genetic influences are involved in the pathogenesis of hypertension and stroke (*14*, *15*), although HR of elder men was around 1.5 with statistical significance. We primarily hypothesized that the relation between family history of hypertension and stroke mortality was stronger in younger than that in elderly because the effect of environmental cardiovascular risk factors might be evident in the elderly and numbers of risk factors would increase with age (*24*), which attenuated the effect of family history due to genetic background. This hypothesis is consistent with our findings for women. Since the awareness of hypertension was reported to be lower in men than in women (*25*), lower accuracy of family history of hypertension in men might have lead to the low HR in younger men.

In conclusion, a simple questionnaire designed to assess a family history of stroke could not be an index of potential genetic risk predicting stroke mortality in this study. More specific information with regard to parental history of stroke or more specific genetic exploration might be required to assess the genetic risk of stroke mortality. Whereas a family history of hypertension obtained from a simple questionnaire might have the potential to predict an increased risk of total stroke mortality. For individuals who reported family history of hypertension, other cardiovascular risk factors and the risk factors for future hypertension such as salt intake (*26*), should be managed to prevent stroke.

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