Blood Pressure and the Progression of Carotid Atherosclerosis in Middle-Aged Men

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Abstract—Elevated blood pressure has consistently been associated with increased prevalence of preclinical atherosclerosis and with increased risk of clinical atherosclerotic cardiovascular disease (CVD). However, there is no prospective evidence of the association between blood pressure and the progression of preclinical atherosclerosis. We therefore investigated the relationships of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure to the 4-year increase in the measures of early carotid atherosclerosis, the mean and maximal common carotid intima-media thickness (IMT), assessed by B-mode ultrasonography, in 1026 men aged 42 to 60 years. Men with the SBP of <120, 120 to 126, 127 to 134, 135 to 143, and >143 mm Hg (fifths) had an increase in the mean IMT of 0.074, 0.090, 0.110, 0.136, and 0.158 mm per 4 years ($P<0.001$ for difference between groups, $P<0.001$ for linear trend) and in the maximal IMT of 0.212, 0.221, 0.279, 0.286, and 0.315 mm per 4 years, ($P<0.001$, $P<0.001$), respectively, adjusting for other atherosclerotic risk factors, including DBP. Also, pulse pressure, when adjusted for other risk factors including mean arterial pressure, was directly associated with the IMT increase. DBP was not independently related to the IMT increase. This is the first documentation to show that mildly elevated SBP and pulse pressure accelerate the progression of preclinical atherosclerosis. This study provides further evidence for the finding that systolic hypertension is a more important risk factor for atherosclerosis and consequent CVD than diastolic hypertension. Therefore, more attention should be paid to the level of SBP in the evaluation of CVD risk and in the treatment of hypertension. (***Hypertension.* 1999;34:51-56.**)

Key Words: atherosclerosis ■ ultrasonography ■ blood pressure ■ hypertension, mild ■ population studies ■ pulse pressure

Basic research has suggested that hypertension plays an important role in the pathogenesis of atherosclerosis.[1,2] Indeed, elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) have consistently been associated with increased risk of atherosclerotic cardiovascular disease (CVD) in prospective population studies.[3–5] Additional evidence for the role of hypertension as a predictor of CVD derives from randomized trials,[6–9] in which the treatment of elevated blood pressure (BP) with antihypertensive drugs has reduced CVD risk. Even mildly elevated SBP and DBP have been related to increased CVD risk in prospective population studies.[3–5] Support for this finding comes from randomized trials[6,9] that have shown a large cardiovascular benefit from the treatment of uncomplicated mild hypertension.

Decisions about the initiation of antihypertensive medication have usually been based on the level of DBP.[3,7] According to some prospective population studies,[4,5] however, systolic hypertension may be a more important CVD risk factor than diastolic hypertension. Consistently, elevated SBP but not elevated DBP has been associated with increased prevalence of early atherosclerotic manifestations, including carotid intima-media thickening, in cross-sectional studies.[10–13] Additional evidence for the role of systolic hypertension in CVD derives from a randomized trial, in which the treatment of elevated SBP with antihypertensive drugs slowed the progression of carotid stenosis[14] and reduced CVD risk[8] in older persons with isolated systolic hypertension. Some studies have also emphasized elevated pulse pressure as a risk factor for atherosclerosis[11–13] and consequent CVD.[15,16]

There are no previous reports from prospective population studies of the association between BP and the progression of preclinical atherosclerosis. We therefore investigated the relationships of SBP, DBP, and pulse pressure to the 4-year increase in the measures of early carotid atherosclerosis, the mean and maximal intima-media thickness (IMT) in the common carotid arteries (CCAs), in a population-based sample of middle-aged men from eastern Finland.

Methods

Subjects

The subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), which is an ongoing population study

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designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in men from eastern Finland.[17] The recruitment of the subjects has been explained in detail previously.[17] The KIHD was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each subject gave written informed consent to participate in the study. A total of 1229 men who had undergone ultrasound examination of the carotid arteries at the KIHD baseline between August 1986 and December 1989 were invited to participate in a 4-year follow-up study between March 1991 and December 1993. Of these men, 1038 (88.2%) participated, 107 refused, 52 could not participate because of death, severe illness, or relocation, and 32 could not be contacted. Average time to follow-up was 4.2 years (range 3.8 to 5.2 years). This study is based on data from the 1026 men who had complete information on BP and carotid atherosclerosis. Of these men, 73 had been in the pravastatin treatment group in the Kuopio Atherosclerosis Prevention Study (KAPS) for 3 years.[18] We included these men in the present study because the association between BP and atherosclerotic progression remained similar regardless of whether these men were included.

Measurement of BP

BP was measured with a random-zero mercury sphygmomanometer (Hawksley) between 8:00 and 10:00 AM. The measurement protocol included a supine rest of 5 minutes, then 3 measurements with subjects in the supine position, 1 measurement with subjects in the standing position, and 2 measurements with subjects in the seated position at 5-minute intervals. The mean of all 6 values was used as a measure of BP in the present study.

Assessment of Carotid Atherosclerosis

The extent and severity of carotid atherosclerosis was assessed by high-resolution B-mode ultrasonography of the right and left CCA of a 1.0- to 1.5-cm section at the distal end of the CCA proximal to the carotid bulb as explained in detail previously.[19] The mean and maximal IMT were used as the measures of carotid atherosclerosis in the present study. The mean IMT was calculated as the mean of ≈100 IMT estimates from the right and left CCA and was used as an overall measure of the atherosclerotic process. The maximal IMT was calculated as the average of the points of maximal thickness from the right and left CCA and was used as an indicator of the depth of intima-media protrusion into the lumen in this part of the CCA. The baseline ultrasonographic findings were classified into 4 categories according to their severity: (1) no atherosclerotic lesion, (2) intima-media thickening (a distance of >1.0 mm between the lumen/intima and the media/adventitia interfaces), (3) a nonstenotic plaque (a distinct area of mineralization or focal protrusion into the lumen), and (4) a large, stenotic plaque (obstruction of >20% of the lumen diameter).[19]

Assessment of Covariates

The examination protocol,[17] the assessment of medical history, medications, cigarette smoking, the dietary intake of iron and vitamin C, alcohol consumption,[20] maximal oxygen uptake ($\dot{V}O_{2\ max}$),[21] body mass index (BMI), waist-to-hip ratio,[22] and hair mercury content[20] have been described previously. The collection of blood specimens and the measurement of serum lipids,[20] blood glucose, serum insulin,[22] and plasma fibrinogen[20] have been explained previously.

Statistical Methods

The baseline associations of BP with covariates were investigated with univariate regression analysis. The strongest baseline risk factors for the IMT increase were determined by entering each variable individually into the multivariate regression model with the technical covariates (examination years, the zooming depth at baseline for right and left side, the baseline mean or maximal IMT, sonographer, follow-up time, and pravastatin treatment in the KAPS). The heterogeneity of the means of the IMT increase across the fifths of BP was examined with covariance analysis, and the linear trend was tested with multivariate regression analysis. All analyses included the technical covariates. Other covariates were selected based on their statistical significance ($P<0.20$) versus all variables shown in Table 1 and were entered into the same step-up multivariate regression model. These variables included age, treatment for dyslipidemia, cigarette smoking, iron and vitamin C intake, $\dot{V}O_{2\ max}$, hair mercury content, serum HDL cholesterol, and waist-to-hip ratio. All statistical analyses were conducted with procedures from SAS, version 6.09, installed on an IBM RS/6000.

TABLE 1. Baseline Characteristics of Subjects

Characteristic	Mean	SD	Range
Age, y	52.0	6.7	42.0–61.3
BMI, kg/m^2	26.7	3.4	18.8–40.3
Waist-to-Hip Ratio	0.94	0.06	0.75–1.51
SBP, mm Hg	131.8	16.1	88.7–211.7
DBP, mm Hg	87.4	10.2	58.7–129.0
Pulse pressure, mm Hg	44.4	10.9	22.7–111.7
Cigarette smoking, pack-years	7.6	15.3	0.0–117.0
Dietary intake of iron, mg/d	18.7	6.0	6.9–56.9
Dietary intake of vitamin C, mg/d	86.3	53.3	6.6–550.4
Hair mercury content,* μg/g	1.81	1.96	0.0–23.30
$\dot{V}o_2$max, L/min	2.49	0.62	0.47–5.46
Serum LDL cholesterol, mmol/L	3.86	0.93	0.68–8.46
Serum HDL cholesterol, mmol/L	1.30	0.30	0.58–2.78
Serum triglycerides, mmol/L	1.44	0.87	0.25–7.84
Serum apolipoprotein B, g/L	1.01	0.23	0.19–2.08
Fasting serum insulin, mU/L	10.8	5.9	1.0–50.0
Plasma fibrinogen, g/L	3.00	0.56	1.74–6.71
Mean common carotid IMT, mm	0.77	0.17	0.42–2.12
Maximal common carotid IMT, mm	0.95	0.24	0.54–2.71
Treated for hypertension, %	20.6%		
β-blockers, %	15.2%		
Diuretics, %	3.1%		
Treated for dyslipidemia, %	1.1%		
Type 2 diabetes, %	3.8%		
Advanced atherosclerosis, %*	31.0%		

*Defined as stenotic plaque (>20 percent of the lumen diameter obstructed) or nonstenotic plaque (distinct mineralization or focal protrusion into the lumen).

Results

BP and Other Baseline Characteristics

Baseline characteristics are shown in Table 1. SBP had unadjusted direct associations with BMI, waist-to-hip ratio, fasting serum insulin, serum triglycerides ($P<0.001$); the baseline mean IMT and type 2 diabetes ($P=0.001$); age ($P=0.005$); the baseline maximal IMT ($P=0.006$); and serum apolipoprotein B ($P=0.01$). SBP had inverse relationships with $\dot{V}O_{2\ max}$ ($P<0.001$) and treatment for dyslipidemia ($P=0.02$). DBP had unadjusted direct associations with BMI, waist-to-hip ratio, fasting serum insulin, serum triglycerides ($P<0.001$); and serum apolipoprotein B ($P=0.001$). DBP had inverse relationships with iron intake ($P=0.003$); $\dot{V}O_{2\ max}$ ($P=0.005$); treatment for dyslipidemia ($P=0.02$); vitamin C intake and baseline maximal IMT ($P=0.04$); and age ($P=0.05$).

TABLE 2. Strongest Baseline Risk Factors for a 4-Year Increase in Mean and Maximal CCA IMT

	Increase in Mean IMT (mm/4 y)			Increase in Maximal IMT (mm/4 y)		
	Multivariate Regression Coefficient			Multivariate Regression Coefficient		
Risk Factors	Original Units (95% CI)	Standardized	P	Original Units (95% CI)	Standardized	P
Hair mercury content (μg/g)	0.010 (0.006, 0.015)	0.136	<0.001	0.011 (0.005, 0.017)	0.107	<0.001
Pulse pressure (mm/Hg)	0.002 (0.0009, 0.002)	0.125	<0.001	0.002 (0.001, 0.003)	0.111	<0.001
Age (y)	0.003 (0.001, 0.004)	0.120	<0.001	0.002 (0.0004, 0.004)	0.077	0.02
$\dot{V}o_2$max (L/min)	−0.027 (−0.041, −0.013)	−0.113	<0.001	−0.039 (−0.059, −0.019)	−0.118	<0.001
Treatment for dyslipidemia (yes vs no)	0.150 (0.068, 0.233)	0.105	<0.001	0.166 (0.049, 0.282)	0.083	0.006
SBP (mm Hg)	0.001 (0.0004, 0.001)	0.100	<0.001	0.001 (0.0006, 0.002)	0.109	<0.001
Cigarette smoking (pack-years)	0.001 (0.0002, 0.001)	0.079	0.01	0.001 (0.0003, 0.002)	0.084	0.008
Plasma fibrinogen (g/L)	0.020 (0.005, 0.036)	0.076	0.01	0.029 (0.007, 0.051)	0.078	0.01
Dietary intake of iron (g/d)	0.002 (0.0003, 0.003)	0.069	0.02	0.002 (−0.0003, 0.004)	0.049	0.10
Waist-to-hip ratio	0.166 (0.020, 0.313)	0.068	0.03	0.252 (0.047, 0.457)	0.074	0.02

From linear forced regression models, including examination years, the zooming depth at baseline for right and left side, the baseline mean or maximal IMT, sonographer, follow-up time, and pravastatin treatment in KAPS.

Strongest Baseline Risk Factors for 4-Year Increase in the Mean and Maximal IMT

The strongest baseline risk factors for the IMT increase were high hair mercury content, elevated pulse pressure, high age, low $\dot{V}o_{2\ max}$, treatment for dyslipidemia, elevated SBP, cigarette smoking, increased plasma fibrinogen, high iron intake, and high waist-to-hip ratio (Table 2).

Baseline BP and 4-Year Increase in the Mean and Maximal IMT

SBP had a strong, direct, and graded association with the increase in the mean and maximal IMT when adjusted for other risk factors (Table 3). These relationships were even stronger after further adjustment for DBP. The difference in the increase in the mean IMT between the highest and lowest fifth was 57% adjusted for other risk factors and 114% after additional adjustment for DBP. The respective differences in the increase in the maximal IMT were 33% and 49%. DBP had a weak, direct association with the increase in the maximal IMT when adjusted for other risk factors but not after further adjustment for SBP (Table 3). DBP was not related to the increase in the mean IMT. SBP was associated directly with the increase in the mean and maximal IMT at each level of DBP, whereas DBP had no consistent relationship with the IMT increase at different levels of SBP (Figure). Pulse pressure was directly associated with the increase in the mean and maximal IMT when adjusted for other risk factors (Table 3). These relationships were slightly weaker after additional adjustment for mean arterial pressure. The difference in the increase in the mean IMT between the highest and lowest fifth was 64% when adjusted for other risk factors and 57% when also adjusted for mean arterial pressure. The respective differences in increase in maximal IMT were 30% and 22%.

Baseline IMT and the 4-Year Increase in BP

The mean IMT had an unadjusted direct association with the increase in SBP (P=0.005) and pulse pressure (P<0.001). Also, the maximal IMT had an unadjusted direct relationship with the increase in SBP (P=0.01) and pulse pressure (P<0.001). These associations disappeared after further adjustment for age. The IMT was not related to the change in DBP.

Discussion

This 4-year follow-up study in middle-aged men provides the first prospective evidence that mildly elevated SBP and pulse pressure accelerate the progression of preclinical atherosclerosis, quantified by the mean and maximal IMT in the CCAs. SBP had a strong, graded, and direct association with the IMT increase regardless of the level of DBP, whereas DBP had no relationship with the IMT increase when controlled for SBP. Intima-media thickening started to accelerate at the SBP of approximately 120 mm Hg and at the pulse pressure of ≈36 mm Hg. Interestingly, intima-media thickening was the most rapid in men with SBP of >140 mm Hg and DBP of <85 mm Hg.

Taken together with prospective studies of CVD events,[3–5] the present study shows that even mildly elevated BP is a risk factor for atherosclerosis and consequent CVD. Similar to the results of cross-sectional studies of early atherosclerotic manifestations[10–13] and prospective studies of CVD events,[4,5,15,16] our findings suggest that systolic hypertension is a more important risk factor for atherosclerosis and CVD than diastolic hypertension and that elevated pulse pressure also increases the risk of atherosclerotic CVD. Interestingly, some other studies have suggested that elevated SBP is also a risk factor for early atherosclerosis in populations with a high prevalence of hypertension but a relatively low prevalence of atherosclerosis and hypercholesterolemia, such as in the Japanese.[23] Our findings provide one explanation for the effectiveness of antihypertensive medication in reducing CVD risk in persons with uncomplicated mild hypertension[6,9] or isolated systolic hypertension.[8] They also are in agreement with the reduced treatment goals for hypertension recommended by the Joint National Committee[24] and the World Health Organization/International Hypertension Society.[25]

TABLE 3. Four-Year Increase in Mean and Maximal CCA IMT (in Fifths) of SBP, DBP, and Pulse Pressure

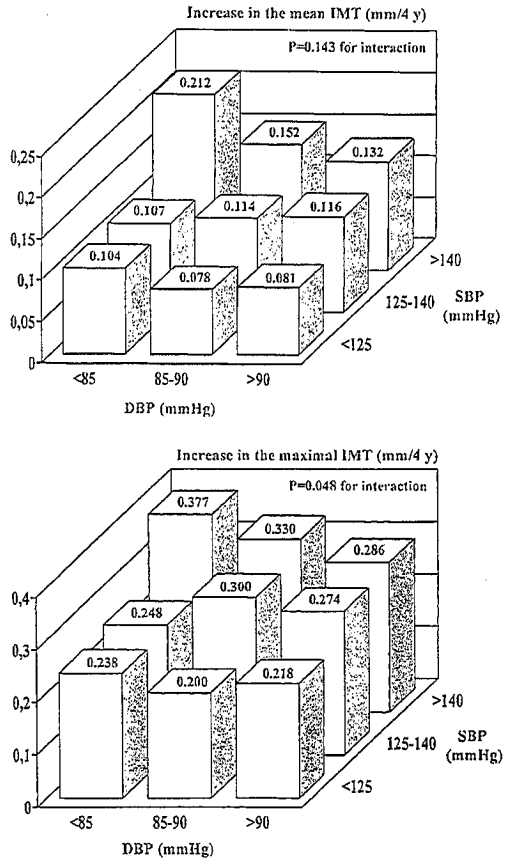
	Increase in Mean IMT(mm/4 y), mean (95% CI)		Increase in Maximal IMT (mm/4 y), mean (95% CI)	
SBP, mm Hg	Adjusted for covariates*	Adjusted also for DBP	Adjusted for covariates*	Adjusted also for DBP
<120	0.090 (0.072, 0.112)	0.074 (0.072–0.112)	0.226 (0.203, 0.256)	0.212 (0.203–0.256)
120–126	0.097 (0.074, 0.116)	0.090 (0.074–0.116)	0.228 (0.190, 0.253)	0.221 (0.190–0.253)
127–134	0.110 (0.092, 0.123)	0.110 (0.092–0.123)	0.280 (0.254, 0.300)	0.279 (0.254–0.300)
135–143	0.129 (0.113, 0.146)	0.136 (0.113–0.146)	0.280 (0.254, 0.310)	0.286 (0.254–0.310)
>143	0.141 (0.118, 0.169)	0.158 (0.118–0.169)	0.300 (0.272, 0.335)	0.315 (0.272–0.335)
Difference between fifths	P=0.001	P<0.001	P<0.001	P<0.001
Linear trend	P<0.001	P<0.001	P<0.001	P<0.001
DBP, mm Hg	Adjusted for covariates*	Adjusted also for SBP	Adjusted for covariates*	Adjusted also for SBP
<79	0.100 (0.068–0.112)	0.121 (0.068–0.112)	0.227 (0.185–0.246)	0.255 (0.185–0.246)
79–85	0.115 (0.097–0.139)	0.122 (0.097–0.139)	0.260 (0.237–0.290)	0.270 (0.237–0.290)
86–90	0.112 (0.086–0.127)	0.114 (0.086–0.127)	0.275 (0.236–0.299)	0.277 (0.236–0.299)
91–96	0.124 (0.111–0.146)	0.116 (0.111–0.146)	0.290 (0.271–0.325)	0.281 (0.271–0.325)
>96	0.118 (0.107–0.145)	0.095 (0.107–0.145)	0.266 (0.249–0.297)	0.235 (0.249–0.297)
Difference between fifths	P=0.51	P=0.50	P=0.03	P=0.13
Linear trend	P=0.15	P=0.20	P=0.01	P=0.99
Pulse pressure, mm Hg	Adjusted for covariates*	Adjusted also for MAP	Adjusted for covariates*	Adjusted also for MAP
<36	0.088 (0.076–0.111)	0.090 (0.076–0.111)	0.231 (0.214–0.263)	0.239 (0.214–0.263)
36–41	0.111 (0.093–0.128)	0.112 (0.093–0.128)	0.261 (0.235–0.285)	0.264 (0.235–0.285)
42–45	0.108 (0.091–0.126)	0.108 (0.091–0.126)	0.253 (0.228–0.279)	0.254 (0.228–0.279)
46–51	0.117 (0.093–0.137)	0.116 (0.093–0.137)	0.269 (0.234–0.299)	0.266 (0.234–0.299)
>51	0.144 (0.115–0.165)	0.141 (0.115–0.165)	0.301 (0.265–0.328)	0.291 (0.265–0.328)
Difference between fifths	P=0.001	P=0.03	P=0.007	P=0.22
Linear trend	P=0.001	P=0.004	P=0.002	P=0.04

*From covariance models, including age, examination years, the zooming depth at baseline for right and left side, the baseline mean or maximal IMT, sonographer, follow-up time, pravastatin treatment in KAPS, treatment for dyslipidemia, cigarette smoking, dietary intake of iron and vitamin C, $\dot{V}o_2$max, hair mercury content, serum HDL cholesterol, and waist-to-hip ratio. MAP indicates mean arterial pressure.

Previous studies[11–13] have not been able to draw a conclusion about the time order of the relationship between BP and atherosclerosis due to their cross-sectional study design. In our prospective study, baseline SBP and pulse pressure were directly and independently associated with the IMT increase, which suggests that systolic hypertension and high pulse pressure are true atherosclerotic risk factors. However, baseline IMT was also associated directly with the increase in SBP and pulse pressure. Such a reciprocal relationship indicates a vicious cycle between baseline BP and IMT in the central conduit vessels. In other words, the increase in IMT and artery wall stiffness is associated with elevated SBP and pulse pressure at baseline due to the relative stiffness of the artery wall, and further stiffening would be related to a greater increase in BP. However, this phenomenon appears to occur mainly in older individuals, because the association between baseline IMT and the increase in BP disappeared when data were controlled for age.

In the Systolic Hypertension in the Elderly Program (SHEP),[14] the progression of carotid stenosis, quantified by blood flow velocity and extent of plaque, was slower in the diuretic and/or β-blocker group than in the placebo group, which suggests a causal association between systolic hypertension and atherosclerosis. The Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS)[26] did not, however, provide evidence for a causal relationship, because the carotid IMT increased less over the first 6 months of the trial in spite of a slightly higher SBP in the isradipine group than in the hydrochlorothiazide group. Ongoing trials[27] will provide further information about the effect of lowered BP on intima-media thickening.

Carotid IMT, assessed by ultrasonography, has been regarded as a valid indicator of generalized atherosclerosis, because it has been related to atherosclerotic risk factors, coronary and peripheral atherosclerosis, and the risk of coronary and cerebrovascular events.[19,28–30] However, it has been criticized as an indicator of atherosclerosis, because the intima cannot be discriminated from the media using ultrasonography. Thus, it is likely that the IMT increase observed in our study is not only due to atherosclerotic intimal thickening but also due to medial hypertrophy caused by the hemodynamic stimulation of a progressive increase in SBP, pulse pressure, or arterial diameter over time.



The 4-year increase in the mean and maximal CCA IMT according to SBP and DBP adjusting for examination years, the zooming depth at baseline for right and left side, the baseline mean or maximal IMT, sonographer, follow-up time and pravastatin treatment in the KAPS.

Hypertension could cause atherosclerosis through a number of plausible mechanisms, which have been reviewed in detail previously.[1,2] Briefly, hypertension has been associated with (1) impaired endothelium-dependent arterial relaxation, (2) enhanced monocyte and lymphocyte adherence to the endothelium and migration into the intima, (3) enhanced macrophage accumulation in the intima, (4) stimulated growth factor and cytokine expression, (5) stimulated smooth-muscle cell proliferation, (6) increased plaque cellularity, (7) increased susceptibility to intimal tears due to increased medial collagen synthesis and reduced arterial wall elasticity, (8) increased vascular oxidative stress and oxygen-free radical production by the arterial wall, and (9) increased hypoxia caused by increased diffusion distances due to intimal and medial thickening.

The results of the present study are important from both a clinical and public health viewpoint. This is the first documentation that mildly elevated SBP and pulse pressure accelerate the progression of preclinical atherosclerosis in middle-aged men with increased CVD risk. This study provides further evidence for the finding that systolic hypertension is a more important risk factor for atherosclerosis and consequent CVD than is diastolic hypertension. Therefore, more attention should be paid to the level of SBP in the evaluation of CVD risk and in the treatment of hypertension.

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