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ORIGINAL ARTICLE

Nighttime *vs.* daytime blood pressure as a predictor of changes in left ventricular mass in hypertensive subjects

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Left ventricular hypertrophy (LVH) conveys an increased risk of cardiovascular morbidity and mortality. We aimed to compare the prognostic value of daytime and nighttime blood pressure (BP) on the changes in LVH status in newly diagnosed hypertensive subjects. Three hundred and five hypertensive, nondiabetic subjects (mean age 51.1 ± 10.2 years, 190 men) were prospectively studied for a mean period of 42 ± 17 months. At baseline and last follow-up visit, all patients underwent office and ambulatory BP monitoring, as well as echocardiographic assessment. We defined the following: LVH development/LVH persistence as the new-onset LVH at the end of follow-up or the presence of LVH at both baseline and the end of follow-up; left ventricular mass index (LVMI) reduction as a decline in LVMI at the end of follow-up of $\geqslant 15\%$ compared with the baseline value. Multivariate Cox regression analyses revealed that baseline nighttime systolic BP was a significant predictor of LVH development/LVH persistence during follow-up (hazard ratio = 1.066, $P = 0.02$), whereas baseline daytime systolic BP was not. Moreover, the reduction of nighttime systolic BP is related to an almost threefold increase in the probability of LVMI reduction, independently of daytime BP reduction. In conclusion, nighttime BP constitutes a better prognosticator of left ventricular mass alterations over time in treated essential hypertensive patients than does daytime BP.

INTRODUCTION

Left ventricular hypertrophy (LVH) conveys an increased risk of cardiovascular morbidity, including coronary heart disease, congestive heart failure and stroke, as well as of all-cause mortality.[1,2] In addition, its regression with the implementation of antihypertensive treatment has been associated with a reduced risk of future cardiovascular events.[3]

Although the superiority of ambulatory blood pressure (BP) monitoring (ABPM) over office BP measurements in the management of hypertension is well established,[1,4] the relative prognostic importance of diverse time-dependent components derived from ABPM, namely daytime and nighttime BP, is still controversial.[5–8] In this setting, the objective of the present study was to compare the prognostic value of daytime BP with nighttime BP on the changes in LVH status in newly diagnosed treated hypertensive subjects after a mean follow-up period of 3.5 years.

METHODS

Study population

A total of 700 consecutive, white subjects aged >18 and <85 years with untreated newly diagnosed (<2 years) hypertension, who were referred or self-referred to our outpatient hypertension unit, were recruited between January 2003 and January 2008. Exclusion criteria included stage III hypertension or secondary hypertension, white-coat hypertension (office BP $>140/90$ mm Hg and daytime BP $<135/85$ mm Hg), subjects working in nightshifts, history of coronary artery disease, cerebrovascular disease or congestive heart failure, atrial fibrillation, diabetes mellitus, overt proteinuria ($\geqslant 300$ mg g^{-1}) or renal dysfunction (estimated glomerular filtration rate (eGFR) according to the modification of diet in renal disease (MDRD) formula <60 ml min^{-1} 1.73 m^{-2}) and the presence of neoplastic or any other concurrent systemic disease. After the implementation of the exclusion criteria, 320 subjects with sustained essential hypertension stages I and II, confirmed by ABPM (daytime systolic/diastolic BP $\geqslant 135/85$ mm Hg),[1] were eligible for the analysis. Among those subjects, 305 completed the follow-up visits and were entered in the final analysis. From January 2008 to January 2009, last visit measures were registered.

Study design

This is a longitudinal prospective study. At baseline, according to the European Society of Hypertension guidelines,[1] a careful medical history was obtained and all patients underwent routine laboratory tests, office and ambulatory BP measurements and echocardiographic examination. Antihypertensive therapy was prescribed in line with the current guidelines.[1] All of the subjects were

periodically referred to the outpatient hypertensive unit of our institution, at least two times annually, for evaluation of BP control, and each participant had at least 1 year of follow-up. At the last follow-up visit, office BP evaluation, ABPM and echocardiographic examination were repeated, while registration of the treatment duration of each of the implemented antihypertensive drug category was done. The study protocol complies with the Declaration of Helsinki, it was approved by our local institutional Ethics Committee and all participants gave written informed consent.

Definitions

(a) LVH was defined as left ventricular mass indexed for body surface area $\geqslant 116 \mathrm{g} \mathrm{m}^{-2}$ in men and $\geqslant 96 \mathrm{g} \mathrm{m}^{-2}$ in women;[9] (b) LVH development was defined as new-onset LVH at the end of follow-up; (c) LVH persistence was defined as the presence of LVH at both baseline and end of follow-up; (d) LVMI reduction was defined as the decline of LVMI at the end of follow-up of $\geqslant 15\%$ with respect to the baseline value; (e) LVH regression was defined as the presence of LVH at baseline and the absence of LVH at the end of follow-up; and (f) LVH prevention was defined as the absence of LVH at both baseline and end of follow-up (Table 1). Moreover, we defined as daytime and nighttime systolic BP reduction, levels of daytime and nighttime systolic BP at end of follow-up <baseline daytime and nighttime systolic BP levels, respectively, and finally dipping status was defined as more than 10% fall in the average systolic BP recorded at night, from the average daytime systolic BP measurements.

Measurements

Office and ambulatory BP. Office BP was measured with the patient in the sitting position after a 5-min rest as the average of three consecutive measurements according to the recent guidelines.[1] Ambulatory BP was recorded over a working day (Monday through Friday) using the automatic Spacelabs units 90207 (Redmond, Washington, USA) that was set to obtain automatic heart rate and BP readings at 15-min intervals during daytime and at 30-min intervals during nighttime. In keeping with current practice, daytime and nighttime were defined using short fixed-clock time intervals, which ranged from 1000 to 2000 h and from 2400 to 0600 h, respectively, while automatic editing was used. Twenty-four-hour, daytime and nighttime systolic and diastolic BP values were the mean of the overall 24-h, daytime and nighttime recordings, respectively, after artifact editing.[1,6–8]

Echocardiographic study. The echocardiographic studies were conducted by an experienced senior echocardiographer who was blind to the clinical status of the examined subject, according to the recommendations of the American Society of Echocardiography,[10] using a Vivid 3 PRO ultrasound imager (General Electric, Milwaukee, WI, USA) equipped with a 2.5–5 MHz (harmonics) phased-array transducer. Left ventricular mass was calculated using the method of Devereux et al.[10] and normalized for body surface area to obtain LVMI.

Table 1 Definitions of the changes in LVH status

	Baseline	Follow-up	Change of values between baseline and follow-up visit	Main outcome variable
LVH development	No	Yes	NA	√
LVH persistence	Yes	Yes	NA	√
LVMI reduction	NA	NA	$\geqslant 15\%$	√
LVH regression	Yes	No	N/A	
LVH prevention	No	No	N/A	

Abbreviations: LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; NA, not applicable.

Statistical analysis

SPSS statistical package, release 16.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Categorical variables are presented as absolute frequencies and percentages, whereas the continuous variables are presented as means and s.d. The difference (Δ) between baseline and last value of each variable was defined as the baseline value minus the last-visit value. Comparisons between groups were performed by Student's t-test, paired samples t-test or chi-square test, where appropriate. Correlation analyses were performed using Pearson's correlation coefficient. Forward stepwise linear multiple regression models were used to examine the independent significant predictors of LVMI at last follow-up visit. The candidate explanatory (independent) variables entering the multiple regression model were age, sex, baseline body mass index, baseline glucose, baseline low-density lipoprotein cholesterol, baseline eGFR, baseline LVMI, baseline office systolic/diastolic BP, baseline daytime systolic/diastolic BP, baseline nighttime systolic/diastolic BP, Δ24-h systolic/diastolic BP and the duration of treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor 1 blockers (ARBs), calcium channel blockers (CCBs), diuretics and β-blockers. To validate our multiple linear regression models, we tested the normality and heteroscedasticity of the residuals produced. Any potential multicollinearity between the explanatory variables was tested by calculating the variance inflation factor (VIF) and tolerance (1/VIF). No multicollinearity was found, as tolerance values were higher than 0.1. Our multiple regression model had the highest adjusted R^2 value of all other models, explaining the variability of our dependent variable the best way possible. Cox proportional hazard models were used to assess the effect— presented as hazard ratios (HR) and 95% confidence intervals (CI)—of different determinants on LVH development/LVH persistence and on LVMI reduction. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 305 hypertensive, nondiabetic subjects (mean age 51.1 ± 10.2 years, 190 men, baseline office BP = 145/94 mm Hg) were prospectively studied for a period of 6 years (mean follow-up period of 42 ± 17 months).

The demographic, laboratory, BP and echocardiographic characteristics of the study population at both baseline and last visit are presented in Table 2. A decrease between baseline and last visit was observed in office systolic/diastolic BP by 14/10 mm Hg, in 24-h systolic/diastolic BP by 11/6 mm Hg, in daytime systolic/diastolic BP by 12/8 mm Hg and in nighttime systolic/diastolic BP by 9/7 mm Hg ($P < 0.01$ for all). Sixty-two percent of patients (189 patients) achieved office systolic/diastolic BP levels <140/90 mm Hg at the end of follow-up. Seventy-eight percent of patients (238 patients) presented nighttime systolic BP reduction between baseline and end of follow-up. Smoking status was decreased by 40.5% ($P < 0.01$). No difference was observed in glucose and creatinine levels, whereas low-density lipoprotein cholesterol levels were diminished by 11.2 mg dl^{-1}, $P < 0.01$.

During the follow-up period, LVMI decreased from 97.5 ± 22.8 to $93 \pm 18.4 \mathrm{g} \mathrm{m}^{-2}$, $P < 0.01$. The prevalence of LVH at baseline was 27.2% (83 patients). The prevalence of LVH development/LVH persistence was 17.7% (54 patients) at the end of follow-up (Table 2), whereas 63 patients (20.6%) presented LVMI reduction during follow-up. The duration of the implemented antihypertensive treatment during follow-up was as follows: 23 ± 9 months for ACE inhibitors, 30 ± 12 months for ARBs, 19 ± 8 months for CCBs, 22 ± 8 months for diuretics and 7 ± 3 months for β-blockers.

LVMI at the last follow-up visit was positively correlated to male sex ($r = 0.317$, $P < 0.01$), baseline body mass index ($r = 0.177$, $P < 0.01$), baseline office systolic BP ($r = 0.171$, $P < 0.01$), baseline office diastolic BP ($r = 0.139$, $P = 0.02$), baseline LVMI ($r = 0.693$, $P < 0.01$), baseline 24-h systolic BP ($r = 0.165$, $P < 0.01$), baseline daytime systolic BP ($r = 0.129$, $P = 0.03$) and baseline nighttime systolic BP ($r = 0.209$, $P < 0.01$).

Table 2 Demographic, blood pressure, laboratory and echocardiographic parameters of the study population

Parameter	Baseline (n = 305)	Follow-up (n = 305)	P-value
Age (years)	51.1 ± 10.2	54.6 ± 10.4	<0.01
Male sex, n (%)	190 (62.3)	190 (62.3)	—
Body mass index (kg m^{-2})	28.5 ± 4.7	28.5 ± 4.8	0.65
Smoking, n (%)	123 (40.3)	73 (24)	<0.01
Office SBP (mm Hg)	145 ± 14	131 ± 13	<0.01
Office DBP (mm Hg)	94 ± 9	84 ± 10	<0.01
Office HR (b.p.m.)	77 ± 9	73 ± 11	<0.01
24-h SBP (mm Hg)	132 ± 11	121 ± 11	<0.01
24-h DBP (mm Hg)	82 ± 9	76 ± 8	<0.01
24-h HR (b.p.m.)	74 ± 8	72 ± 9	<0.01
Daytime SBP (mm Hg)	137 ± 12	125 ± 12	<0.01
Daytime DBP (mm Hg)	86 ± 9	78 ± 9	<0.01
Nighttime SBP (mm Hg)	121 ± 15	112 ± 12	<0.01
Nighttime DBP (mm Hg)	74 ± 10	67 ± 8	<0.01
Dippers, n (%)	154 (50.5)	127 (41.6)	0.4
Serum creatinine (mg dl^{-1})	0.95 ± 0.28	0.94 ± 0.19	0.66
eGFR (ml min^{-1} 1.73 m^{-2})	84.6 ± 17.5	83.3 ± 16.9	0.29
Plasma glucose (mg dl^{-1})	98.4 ± 13.1	99.8 ± 15.5	0.19
Total cholesterol (mg dl^{-1})	218.4 ± 39.5	206.5 ± 34.9	<0.01
HDL- cholesterol (mg dl^{-1})	50.7 ± 13.2	51.1 ± 13	0.67
LDL-cholesterol (mg dl^{-1})	141.8 ± 35.8	130.6 ± 30.6	<0.01
Triglycerides (mg dl^{-1})	122.6 ± 57.6	124.6 ± 60.8	0.56
LVMI (g m^{-2})	97.5 ± 22.8	93 ± 18.4	<0.01
LVH n (%)	83 (27.2)	54 (17.7)	<0.01

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; SBP, systolic blood pressure.

Table 3 Baseline demographic, laboratory, BP and echocardiographic parameters for the study groups of LVH development/LVH persistence and LVH regression/LVH prevention

Parameter	LVH development/LVH persistence (n = 54)	LVH regression/LVH prevention (n = 251)	P-value
Age (years)	53.8 ± 10.2	50.1 ± 10.1	0.03
Male sex, n (%)	27 (50)	165 (65.7)	0.045
Body mass index (kg m^{-2})	29.4 ± 7.9	28.3 ± 3.8	0.35
Office SBP (mm Hg)	151 ± 17	144 ± 13	<0.01
Office DBP (mm Hg)	96 ± 11	94 ± 9	0.13
Office HR (b.p.m.)	78 ± 9	77 ± 9	0.87
24-h SBP (mm Hg)	135 ± 11	131 ± 12	0.03
24-h DBP (mm Hg)	87 ± 10	86 ± 9	0.42
24-h HR (b.p.m.)	74 ± 9	74 ± 9	0.99
Daytime SBP (mm Hg)	139 ± 11	137 ± 12	0.06
Daytime DBP (mm Hg)	87 ± 10	86 ± 9	0.45
Nighttime SBP (mm Hg)	125 ± 13	120 ± 15	0.02
Nighttime DBP (mm Hg)	74 ± 10	74 ± 10	0.77
Dippers, n (%)	27 (50)	142 (56.6)	0.48
eGFR (ml min^{-1} 1.73 m^{-2})	85.4 ± 19.7	84.8 ± 17.8	0.8
Plasma glucose (mg dl^{-1})	99 ± 16	99 ± 13	0.98
Total cholesterol (mg dl^{-1})	216 ± 39	217 ± 40	0.8
HDL cholesterol (mg dl^{-1})	50 ± 12	50 ± 13	0.94
LDL cholesterol (mg dl^{-1})	140 ± 35	141 ± 35	0.77
Triglycerides (mg dl^{-1})	120 ± 64	125 ± 63	0.5
LVMI (g m^{-2})	117.6 ± 24.6	92.9 ± 19.8	<0.01

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; LVMI left ventricular mass index; SBP, systolic blood pressure.

Multiple regression analysis revealed that independent determinants of LVMI at the last follow-up visit were as follows: baseline nighttime systolic BP ($\beta = 0.476$, $P < 0.01$), baseline LVMI ($\beta = 0.634$, $P < 0.01$) and male sex ($\beta = 0.199$, $P < 0.01$), whereas baseline daytime BP was not a predictor of LVMI.

Compared with patients with LVH regression/LVH prevention, patients with LVH development/LVH persistence were older at baseline (53.8 ± 10.2 vs. 50.1 ± 10.1 years, $P = 0.03$), exhibited higher levels of baseline office systolic BP (151 ± 17 vs. 144 ± 13 mm Hg, $P < 0.01$), baseline 24-h systolic BP (135 ± 11 vs. 131 ± 12 mm Hg, $P = 0.03$), baseline nighttime systolic BP (125 ± 13 vs. 120 ± 15 mm Hg, $P = 0.03$) and greater LVMI at baseline (117.6 ± 24.6 vs. 92.9 ± 19.8 g/m^2, $P < 0.01$), although there was a borderline difference regarding sex, with a greater percentage of men in the LVH regression/LVH prevention group. There was no difference between the two groups regarding baseline daytime BP values. Of note, the two groups did not differ with regard to the number of patients with a dipping pattern (Table 3).

Multivariate Cox regression analysis revealed that significant predictors of LVH development/LVH persistence during follow-up were baseline age (HR = 1.046; CI 95%, 1.005 to 1.088), baseline LVMI (HR = 1.028; CI 95%, 1.016 to 1.040) and baseline nighttime systolic BP (HR = 1.066; CI 95%, 1.004 to 1.132), whereas baseline daytime systolic BP was not a significant predictor (Table 4).

Furthermore, multivariate Cox regression analysis revealed that significant predictors of LVMI reduction during follow-up were baseline age (HR = 0.966; CI 95%, 0.938 to 0.995), baseline LVMI (HR = 1.025; CI 95%, 1.014 to 1.037), baseline nighttime systolic BP

Table 4 Multivariate Cox regression analysis for LVH development/LVH persistence during follow-up

Variables	Adjusted HR	P-value	95% CI for adjusted HR Lower	95% CI for adjusted HR Upper
Baseline age (years)	1.046	0.03	1.005	1.088
Baseline LVMI (g m^{-2})	1.028	<0.01	1.016	1.040
Baseline nighttime SBP (mm Hg)	1.066	0.02	1.004	1.132

Abbreviations: CI, indicates confidence interval; HR, hazard ratio; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
Adjustment for the following covariates: sex, baseline body mass index, baseline daytime systolic/diastolic BP, baseline nighttime diastolic BP and Δ24-h systolic/diastolic BP.

Table 5 Multivariate Cox regression analysis for LVMI reduction during follow-up

Variables	Adjusted HR	P-value	95% CI for Adjusted HR Lower	95% CI for Adjusted HR Upper
Baseline age (years)	0.966	0.02	0.938	0.995
Baseline LVMI (g m^{-2})	1.025	<0.01	1.014	1.037
Baseline nighttime SBP (mm Hg)	0.972	0.02	0.950	0.995
Nighttime SBP reduction	3.351	0.03	1.127	9.962

Abbreviations: CI, confidence interval; HR, hazard ratio; LVMI, left ventricular mass index; SBP, systolic blood pressure. Adjustment for the following covariates: sex, baseline body mass index, baseline daytime SBP, daytime SBP reduction and Δ24-h systolic/diastolic BP.

(HR = 0.972; CI 95%, 0.950 to 0.995) and nighttime systolic BP reduction (HR = 3.351; CI 95%, 1.127 to 9.962), whereas the reduction of daytime systolic BP was not a significant predictor (Table 5).

DISCUSSION

The novel finding of our study is that nighttime BP outweighs daytime BP in the prediction of LVH development/LVH persistence after a mean follow-up period of 3.5 years, in the setting of optimally treated essential hypertension. Moreover, the reduction only of nighttime but not of daytime BP over time was shown to be a potent prognosticator of LVMI reduction. Strengthening the above, nighttime hemodynamic load is a better determinant of future LVMI levels compared with daytime hemodynamic load, independently of body mass index, antihypertensive therapy and baseline left ventricular mass.

According to recent data, nighttime BP, either defined as absolute BP values during nighttime or as a categorical parameter according to the magnitude of BP drop during the night with respect to daytime BP (dipping phenomenon), seems to be a superior prognosticator of hard end points compared with daytime BP.[11–13] However, with regard to the intermediate end points in hypertension, such as left ventricular mass adaptations, the results from cross-sectional studies on surrogate markers of target organ damage are rather inconsistent, showing in some cases no statistical difference between daytime and nighttime BP as determinants of LVH,[14,15] whereas in others nighttime BP is favored.[16,17] Furthermore, prospective data aiming at the direct comparison of the prognostic role of ambulatory BP monitoring parameters are scarce. Results from the study on ambulatory monitoring of blood pressure and Lisinopril evaluation (SAMPLE) showed that in 206 essential hypertensive subjects with LVH, after 1 year of treatment the reduction in LVMI induced by treatment showed a similar correlation with the reduction in daytime and nighttime BP.[18] Moreover, Fagard et al.[19] have shown that in 44 patients with essential hypertension who were followed up for a short 6-month treatment period the correlation coefficients for relationships between the changes in left ventricular mass and BP were similar for daytime and nighttime BP. These findings are different from those in our study; however, we included a greater number of essential hypertensive subjects who were followed up for a longer time period, and we directly compared the prognostic value of ABPM parameters from a different perspective, applying cox-proportional hazard models including simultaneously both baseline daytime and nighttime BP values.

In the present study, the greater prognostic value of nighttime BP over daytime BP regarding the development/persistence of LVH during the follow-up period was proven independently of the presence of daytime BP in the cox model, as daytime BP failed to reach statistical significance. In a step further, the reduction in nighttime systolic BP levels between baseline and the end of follow-up is related to an almost threefold increase in the probability of LVMI reduction during the follow-up period, independently of the reduction in daytime BP. In addition to this, when different BP components were entered in the same multivariate regression model, only nighttime BP achieved independent statistical significance with future LVMI values. This further supports the view that nighttime BP is superior to daytime BP in the prediction of target organ damage independently of office BP values in a longitudinal basis. It is also important that the prognostic value of baseline nighttime BP regarding LVMI values at last follow-up visit be proven independently of the treatment implicated during the follow-up period.

The superiority of nighttime over daytime BP in the prediction of the change in LVH status could be explained by the fact that the absolute nighttime BP values express more accurately the real nocturnal hemodynamic load responsible in part for the hypertension-induced cardiac damage and better reflect the basal BP (that is, the minimal BP needed for sufficient perfusion of the peripheral organs and tissues in resting conditions).[20] Moreover, daytime BP is influenced by daytime confounders (that is, physical and mental activity, seasonality and so on).[21,22] By contrast, nighttime BP is unsusceptible to the influence of daytime-oriented factors and thus better standardized.[13,22]

Another interesting issue is that there was no difference in the number of dippers between those with LVH development/LVH persistence and those with LVH regression/LVH prevention. This result is in line with the view that the absolute nighttime BP values demonstrate a more constant association with cardiovascular and renal outcomes than dipping status,[12,23] partially attributed to the lower reproducibility that characterizes dipping pattern compared with the absolute nighttime BP values.[24]

Our results could reinforce the notion that antihypertensive treatment should focus on the reduction of BP over 24 h, targeting especially the sleep period. Chronotherapy seems to have a favorable effect on 24-h BP control, including the reduction of nighttime BP. In the HOPE (Heart Outcomes Prevention Evaluation) trial, the administration of ramipril at bedtime was beneficial with regard to cardiovascular morbidity and mortality in high-risk patients.[25] Of note, in a small substudy of HOPE trial, the 24-h systolic and diastolic BP levels were significantly reduced mainly because of a more pronounced BP reduction during nighttime.[26] In addition, the night-to-day BP ratio was significantly decreased in the subjects who received ramipril at bedtime.

Our study has certain limitations that should be considered. First, the study is conducted in white hypertensive patients; thus, findings may not be directly applicable to other ethnicities. Second, it included subjects with new diagnosis of hypertension without history of cardiovascular disease, rendering difficult the generalization of the findings to subjects with overt vascular disease burden. Moreover, no estimation of the effect of short-term BP changes during follow-up was made, given the emerging importance of BP variability on hypertensive sequelae.[27]

In conclusion, nighttime BP constitutes a better prognosticator of left ventricular mass alterations over time in treated essential hypertensive subjects than does daytime BP. Furthermore, these findings underscore the clinical importance of ambulatory BP measurement and highlight the predictive role of nighttime hemodynamic load for better estimation of hypertensive cardiac damage.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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