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ORIGINAL ARTICLE

Nocturnal non-dipping pattern in untreated hypertensives at different cardiovascular risk according to the 2003 ESH/ESC guidelines

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Abstract
Aim. To evaluate in a large population of untreated, uncomplicated essential hypertensives the relationship between alterations in nocturnal blood pressure (BP) profile, i.e. non-dipping pattern, and total cardiovascular risk. *Methods.* A total of 580 consecutive patients with grade 1 or 2 hypertension, referred to our outpatient clinic, underwent the following procedures: (i) clinical and routine laboratory examinations; (ii) 24-h ambulatory BP monitoring; (iii) 24-h collection for microalbuminuria; (iv) echocardiography; and (v) carotid ultrasonography. Cardiovascular risk was assessed according to the stratification scheme suggested by the 2003 ESH/ESC guidelines. *Results.* According to this classification, 16.2% of the 580 patients were considered at low added risk, 42.4% at medium added risk and 41.4% at high added risk; 38.5% of the overall population was classified in the high-risk stratum because of at least one manifestation of target organ damage (TOD) and 6.3% for the presence of three or more risk factors. The prevalence rates of a non-dipping pattern (decrease in BP at night $\leqslant 10\%$ compared with the average daytime values) were 28.5% in low-risk, 32.6% in medium-risk and 42.2% in high-risk patients, respectively. *Conclusions.* Our findings show that the prevalence of a non-dipping profile is significantly greater in patients stratified at high compared with those at low and medium added risk.

Key Words: *Ambulatory blood pressure monitoring, cardiovascular risk, hypertension, non-dipper*

Introduction

Two points should be considered in the management of subjects with elevated blood pressure (BP): first of all, cardiovascular risk in patients with arterial hypertension is not only related to BP levels but also (and more importantly in many cases), to the presence of other modifiable or not modifiable factors contributing to the total risk (1–4). Secondly, a more comprehensive approach in defining BP status than that based on a few clinic BP measurements is recommended; irrefutable evidence exists that 24-h ambulatory BP monitoring (ABPM), and probably home-BP, is superior to clinic BP in the diagnosis and prognostic evaluation of hypertensive subjects, by providing a large number of readings taken during habitual daily activity and sleep (5–7). In addition, ABPM may provide the pattern of arterial pressure variation at different times of the day and night; in particular in most essential hypertensives a large dip in BP during sleep can be demonstrated (dippers), whereas in a minority of patients this nocturnal fall in BP may be scarce or even absent (non-dippers)(8–10).

A large body of evidence indicates that individuals with a non-dipper circadian pattern exhibit a greater cardiac [left ventricular hypertrophy (LVH), diastolic dysfunction and prolonged ventricular repolarization; 11,12] and extracardiac (renal dysfunction, carotid atherosclerosis and silent cerebrovascular disease) target organ damage (TOD) than subjects with a dipper circadian rhythm (13–15). The lack of nocturnal decline in BP has been also

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related to an increase in cardiovascular events (5,16,17).

To date no information is available on the association between abnormalities in circadian BP rhythm and total cardiovascular risk in essential hypertension. The present study was designed to investigate in a large population of never-treated uncomplicated hypertensive patients the relationship between alterations in nocturnal BP profile and cardiovascular risk defined according to the 2003 ESH/ESC algorithm.

Methods

Study population

A total of 580 consecutive, never-treated hypertensive patients referred to our outpatient hospital clinic were included in the study. They met the following inclusion criteria: (i) grade 1 and 2 hypertension (clinic BP values 90–109 for diastolic or 140–179 mmHg for systolic) confirmed during the first visit at our outpatient clinic; (ii) the absence of secondary hypertension and diabetes mellitus (anti-diabetic treatment or blood glucose >126 mg/dl on two separate occasions); (iii) the absence of associated clinical conditions according to the definition of the 2003 ESH/ESC guidelines (4). After their informed consent had been obtained during the initial visit, all patients were subjected to the following procedures within 1–3 weeks: (i) medical history and physical examination; (ii) repeated clinic BP measurements; (iii) routine examinations; (iv) 24-h urine collection for microalbuminuria; (v) 24-h ABPM; (vi) echocardiogram; (vii) carotid ultrasonography.

Clinic BP measurement

BP was measured at two different visits in the outpatient clinic by a physician with a mercury sphygmomanometer [first and fifth phases of Koroktoff sounds for systolic (SBP) and diastolic (DBP), respectively] after the subjects had rested for 5 min in the sitting position. Three measurements were taken at 1-min intervals, and the average was used to define clinic SBP and DBP.

ABPM

Twenty-four-hour ABPM was carried out on the non-dominant arm using a Spacelabs 90207 device (Spacelabs Inc. Richmond, Washington, USA) after validation of its readings against those of a mercury sphygmomanometer by means of a Y tube. The device was set to obtain BP readings at 15-min intervals during the day (07.00–23.00 h) and at 20-min intervals during the night (23.00–07.00 h). The time of application (± 1 h), and the type of device were the same in all patients. The patients were instructed to attend their usual day-to-day activities but to keep still at the time of measurements; all were asked to go to bed no later than 23.00 h and arise not before 07.00 h. The recording was then analysed to obtain 24-h, daytime and night-time average SBP, DBP and heart rate. Nocturnal dipping was defined as a reduction in the average SBP and DBP at night greater than 10% compared with the daytime values (11). An average 24-h ABP of 125/79 mmHg was considered as the upper limit of normality, according to the results of the PAMELA study (18).

Echocardiography

Technical details have been reported previously (19). In brief, M-mode, two-dimensional and Doppler echocardiographic examinations were performed with commercially available instruments (ATL HDI 3000 or 5000, Bothell, Washington, USA). Left ventricular mass (LVM) was estimated from end-diastolic left ventricular internal diameter (LVIDd), interventricular septum (IVSd) and posterior wall thickness (PWTd) by Devereux's formula (20) and indexed to body surface area. LV systolic function was assessed by endocardial fractional shortening [(LVIDd–LVIDs/LVIDd]. LV filling was assessed by recording mitral flow with standard pulsed Doppler technique. The following parameters were considered: early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and their ratio (E/A).

Carotid ultrasonography

Technical details have been reported previously (19). In brief, images of the extracranial carotid artery walls (common, bifurcation and internal carotid arteries) were obtained in several projections by a high resolution, linear array 7.5–10 MHz probe (ATL HDI 3000 or 5000). Plaques were sought in the near and far walls of the entire extracranial carotid tree based on the presence of a focal wall thickening. Intima-media thickness (IMT) was measured in the posterior wall of both common carotids (5, 10, 15, 20 and 25 mm caudally to the bifurcation)(21). To obtain a mean value of common carotid IMT, all five measurements were averaged.

Microalbuminuria

The 24-h urinary concentration of albumin was measured using a high sensitive commercially available radioimmunoassay kit (Sclavo SPA, Cinisello Balsamo, Italy). The detection limit of the method was 0.5 mg/l. Microalbuminuria was defined as a urinary albumin excretion >30 mg/24-h and 300 mg/24-h.

Stratification of patients by absolute level of cardiovascular risk

The level of total risk of each patient was defined according to the criteria suggested by the 2003 ESH/ESC guidelines (3). The estimate of future cardiovascular risk was based on risk factors as age, gender, current smoking, dyslipidaemia, abdominal obesity, family history of premature cardiovascular disease, the presence of TOD and history of accompanying cardiovascular or renal disease. Detection of usual cardiovascular risk factors and diagnosis of cardiovascular or renal disease were accomplished by a careful medical history and by routine examinations as recommended by the ESH/ESC guidelines. The detection of TOD was accomplished by the routine examinations with the addition of echocardiographic, carotid ultrasonographic examination and microalbuminuria.

Detection of TOD

TOD by routine examinations was defined by the presence of slight elevation of plasma creatinine concentration (1.3–1.5 mg/dl in men and 1.2–1.4 mg/dl in women) and electrocardiographic signs of LVH according to the Sokolow–Lyon voltage (sum of amplitude of S wave in V1 and R wave in V5 or V6 >38 mm). Microalbuminuria (30–300 mg/24 h) has been recently added to other recommended tests (echocardiography and carotid ultrasonography) by the 2003 ESH/ESC guidelines. Regarding ultrasound data, LVH was defined as LVMI$\geqslant$125 g/m^2 in men and $\geqslant$110 g/m^2 in women (3). The presence of diffuse IM thickening or of at least one carotid atherosclerotic plaque was taken as evidence of vascular alterations. Diffuse IM thickening was diagnosed when common carotid wall thickness exceeded 0.8 mm (0.9–1.3 mm); a plaque was defined as a focal thickening greater than 1.3 mm in any segment of either carotid artery (3).

Statistical analysis

Statistical analysis was performed by the SAS System (version 6.12; SAS Institute Inc., Cary, North Carolina, USA). Values were expressed as means $\pm$ SD or as percentages. Means were compared by the Student's *t*-test for independent samples. Analysis of categorical data was carried out with the χ^2 test or Fischer's exact test when appropriate. The differences within groups were tested using analysis of variance (ANOVA). The limit of statistical significance was set at $p<0.05$.

Results

Clinical characteristics

Recruitment of patients began in March 1999 and ended in June 2005. The screening process involved 670 consecutive untreated patients with grade 1 and 2 hypertension. Of these, 30 were excluded because of secondary hypertension, 24 for diabetes mellitus, 15 for valvular disease, 11 due to unwillingness to participate or miscellaneous reasons. Thus, 590 hypertensive subjects met the inclusion criteria, 580 of them completed the study having echocardiographic and carotid ultrasonographic examinations of good technical quality.

The overall characteristics of the population are shown in Table I. Of the 580 patients included in the study, 61.2% were men. Mean age was 45.9 years (range 16–79 years) The prevalence of isolated clinic hypertension (mean 24-h BP $<125/80$ mmHg with clinic BP$\geqslant$140 and/or $\geqslant$90 mmHg) was 7.4%. Table II indicates the prevalence rates of the various risk factors and TOD. In 86 patients (14.9%) LVH,

Table I. Demographic and clinical characteristics of the total study population (n=580).

Variable	Value
Age (years)	45.9 $\pm$ 11.9
Gender (M/F)	355/225
Body mass index (kg/m^2)	25.4 $\pm$ 3.7
Body surface area (m^2)	1.84 $\pm$ 0.20
Clinic blood pressure (mmHg)	146 $\pm$ 11/97 $\pm$ 7
Grade 1 hypertension (%)	74.9
Clinic heart rate (beats/min)	74 $\pm$ 10
24-h Ambulatory blood pressure (mmHg)	136 $\pm$ 10/87 $\pm$ 7
Day-time ambulatory blood pressure (mmHg)	141 $\pm$ 10/92 $\pm$ 8
Night-time ambulatory blood pressure (mmHg)	123 $\pm$ 11/76 $\pm$ 8
Known duration of hypertension (years)	2.1 $\pm$ 3.0
Prevalence of isolated clinic hypertension (%)	7.4
Fasting serum glucose (mg/dl)	93.6 $\pm$ 11.6
Total serum cholesterol (mg/dl)	216.4 $\pm$ 40.2
HDL cholesterol (mg/dl)	46.8 $\pm$ 15.4
Triglycerides (mg/dl)	125.3 $\pm$ 78.4
Serum creatinine (mg/dl)	0.87 $\pm$ 0.17

Data are reported as means $\pm$ SD, absolute numbers or percentages. HDL, high-density lipoprotein.

Table II. Prevalence of associated risk factors and target organ damage in the total study population (n=580).

Variable	%
Age >55 years (men)	12.1
Age >65 years (women)	3.1
Family history of premature cardiovascular disease	9.2
Dyslipidaemia	57.7
Current smoker	24.1
Abdominal obesity	20.8
Presence of three or more risk factors	6.3
Metabolic syndrome (ATP III criteria)	26.3
Left ventricular hypertrophy (echo criteria)	14.9
Increased serum creatinine	0.9
Microalbuminuria	7.6
Carotid wall thickening	14.2
Carotid plaques	19.2
Carotid thickening and/or plaques	27.3
Overall target organ damage	38.1

as defined by echocardiographic criteria was present; one or more carotid plaques were present in 111 patients (19.2%) and common carotid thickening (IMT$\geqslant$0.9 mm) was found in 82 patients (14.2%). Overall, carotid involvement, defined as the presence of at least one plaque in any segment of arterial tree and/or common carotid thickening, was detected in 158 patients (27.3%). Approximately 9% of the patients showed renal TOD, as suggested by microalbuminuria and a slight increase in plasma creatinine concentration. On the whole, 220 patients had at least one manifestation of cardiac, carotid or renal damage.

Risk stratification

The distribution of patients in the different risk strata according to the 2003 ESH/ESC algorithm was as follows: 16.2% were classified as low added risk, 42.4% medium added risk and 41.4% high added risk. The major determinant in the identification of high-risk patients was represented by cardiac and extracardiac TOD, in fact only a small fraction of subjects were stratified at high added risk because of three or more concomitant risk factors. Table III shows demographic and clinical characteristics of these subgroups of patients: high-risk subjects were older than their counterparts, had a greater body mass index, higher clinic and ambulatory BP values. As reported in Table IV, absolute LVM, LVIDd, end-diastolic septal and posterior wall thickness, left atrial diameter, aortic root dimension and LVM indexed either to body surface area or height$^{2.7}$ were all significantly higher in the high-risk group. A stepwise increase in the IMT of the far wall of the both common carotid arteries and the carotid internal diameters occurred from patients in the low-risk group to patients at medium and high cardiovascular risk.

Nocturnal BP

Of the 580 study participants, 372 (64.1%) showed a fall in SBP/DBP>10% during night-time sleep and were categorized as dippers, while the remaining 202 showed a fall of $\leqslant$10% and were categorized as non-dippers.

Table III. Demographic and clinical characteristics in patients classified at low, medium and high cardiovascular risk according to the 2003 ESH/ESC guidelines.

	Value		
Variable	Low risk	Medium risk	High risk
Prevalence (%)	16.2	42.4	41.4**
Age (years)	40.4±11.3	42-6±10.8	52.0±10.5*
Gender (% M)	53.8	63.8	61.6
Body mass index (kg/m^2)	24.4±3.6	25.2±3.7	26.2±3.6*
Clinic blood pressure (mmHg)	140±10/92±7	145±12/97±7	151±14*/97±9**
Clinic heart rate (beats/min)	75.5±10.4	75.6±11.1	78.1±9.3
24-h ambulatory BP (mmHg)	132±7/84±7	136±9/88±7	139±11**/88±8***
Day-time BP (mmHg)	138±8/89±7	141±9/93±8	144±12**/93±8***
Night-time BP (mmHg)	120±8/73±7	122±10/77±8	128±12/78±8***
Known duration of HT (years)	2.3±3.3	2.4±3.1	2.0±2.5
Prevalence of ICH (%)	15.3	5.4	6.8***
Metabolic syndrome (%)	8.1	16.9****	37.8*
Fasting blood glucose (mg/dl)	89.7±8.6	92.1±10.4	97.1±13.2***
Total cholesterol (mg/dl)	200.2±31.1	217.2±43.4	223.4±38.5**
HDL cholesterol (mg/dl)	52.1±13.8	47.9±14.8	47.3±15.8
Serum creatinine (mg/dl)	0.84±0.17	0.88±0.17	0.87±0.18

BP, blood pressure; HT, hypertension; ICH, isolated clinic hypertension; HDL, high-density lipoprotein. *p<0.01 high risk vs medium and low risk; **p<0.01 high risk vs low risk; ***p<0.05 high risk vs low risk; ****p<0.05 medium risk vs low risk.

Table IV. Cardiac and ultrasonographic parameters in patients classified at low, medium and high cardiovascular risk according to the 2003 ESH/ESC hypertension guidelines.

	Value		
Variable	Low risk	Medium risk	High risk
LV end-diastolic diameter (mm)	47.6±4.5	47.5±3.9	48.6±4.3*
IVS thickness (mm)	9.4±1.0	9.7±1.0	10.4±1.1*
LV posterior thickness (mm)	8.6±0.8	8.9±0.8	9.5±0.9*
Left atrium (mm)	34.6±3.8	35.1±4.6	36.6±4.4*
Aortic root (mm)	31.7±3.0	32.4±3.7	33.7±3.5*
LV mass (g)	168.0±39.9	178.7±38.9	204.5±49.1*
LV mass index (g/m^2)	91.9±14.3	95.6±15.2	110.0±22.0*
LV mass index ($g/h^{2.7}$)	39.7±6.6	41.5±7.6	49.2±10.1*
E/A ratio	1.29±0.3	1.26±0.3	1.10±0.4*
LCC IMT (mm)	0.58±0.1	0.62±0.1	0.75±0.2*
RCC IMT (mm)	0.57±0.1	0.62±0.1	0.73±0.2*
LCC diameter (mm)	5.6±0.5	5.7±0.7	6.0±0.7***
RCC diameter (mm)	5.7±0.5	5.8±0.8	6.2±0.8***

LV, left ventricular; LCC, left common carotid; RCC, right common carotid; IMT, intima-media thickness. *$p<0.01$ high risk vs medium and low risk; ***$p<0.05$ high risk vs low risk.

The percentage nocturnal SBP decrease was greater in patients classified at low and medium risk compared with the high-risk ones. Furthermore, when nocturnal BP data were analysed in a categorical way according to the presence or absence of non-dipping pattern, the prevalence rates of this BP profile was significantly lower in low (28.5%) and medium-risk patients (32.6%) than in high-risk individuals (42.2%)(Table V).

Discussion

Our study analysed for the first time the relationship between nocturnal BP profile and total cardiovascular risk, defined according to the algorithm recommended by the 2003 ESH/ESC hypertension guidelines, in a large cohort of uncomplicated, never-treated, essential hypertensive patients. The results of the present study show that: (i) patients classified at high added risk have a reduced fall in nocturnal BP and consequently a greater prevalence of non-dipping pattern compared with patients at low and medium added risk; (ii) a non-dipping profile, however, was present also in a notable fraction (approximately 30%) of patients stratified at low and medium risk. The following aspects of these findings deserve to be discussed. First, more than 40% of grade 1 and 2 hypertensive patients referred to an hospital outpatient clinic were classified at high added risk, using the risk stratification scheme recommended by the ESH/ESC guidelines. The classification of patients in the high added risk stratum was almost exclusively due to the presence of preclinical TOD mainly detected by echocardiography, carotid ultrasonography and microalbuminuria assessment. Only 6% of hypertensive patients could be classified at high risk because of the presence of three or more additional risk factors. Among the various markers of TOD, subclinical signs of cardiac, carotid and renal involvement occurred in approximately 15%, 27% and 8% of the patients, respectively. Prevalence of any TOD is obviously influenced by the cut-off values used to define TOD in a categorical way; in this study the

Table V. Percent decrease in nocturnal systolic and diastolic blood pressure and prevalence of non-dipping pattern in patients classified at low, medium and high cardiovascular risk according to ESH/ESC hypertension guidelines.

	Value		
Variable	Low risk	Medium risk	High risk
Mean decrease in SBP (%)	13.1±4.1	13.0±5.1	10.0±5.9*
Mean decrease in DBP (%)	17.9±6.1	17.5±6.6	16.0±6.0
Non-dipping pattern (%)	28.5	32.6	42.2**,****
Dipping pattern (%)	71.5	67.4	57.8**,****

SBP, systolic blood pressure; DBP, diastolic blood pressure. *$p<0.01$ high risk vs medium and low risk; **$p<0.01$ high risk vs low risk; ****$p<0.05$ high risk vs medium risk.

values suggested in the ESH/ESC guidelines were chosen (3), i.e. for LVH a LVMI $\geq$125 g/m^2 in men and 110 g/m^2 in women, for vascular damage a common carotid IMT > 0.8 mm or the presence of plaques and microalbuminuria > 30 mg/24 h. These cut-offs may have excluded moderate cardiac and vascular alterations detectable with more sensitive and liberal criteria; however, they represent a well recognized and balanced threshold for TOD categorization in non-obese populations. Second, the greater prevalence of non-dippers among high-risk patients may be explained in terms of elevated prevalence of cardiac and extracardiac TOD. Several studies demonstrated that the non-dipping status was associated with greater prevalence of LVH or LV remodelling and LV diastolic abnormalities, increased carotid structural alterations such as IM thickenings and carotid plaques (11,14,22); other studies, however, failed to demonstrate any significant difference in cardiovascular structure among dippers and non-dippers (23,24). Despite these conflicting results, it is reasonable to think that hypertensives with a persistent elevated BP in the night develop more extensive cardiovascular damages than those with a marked BP reduction during sleeping hours. On the other hand, the presence of structural vascular alterations may contribute to blunt the nocturnal BP fall (25). It has been suggested that BP can be fully lowered by the suppression of pressor regulatory systems during sleep only when cardiovascular structure is unimpaired, whereas the development of TOD blunts the vasodepressor influence of sleep (26). Third, an interesting finding of our study is that approximately one-third of patients classified at low or medium added risk, who by definition were free of any cardiac, vascular and renal manifestation of TOD, were non-dippers. This piece of evidence underlines the complexity of the mechanism(s) involved in the circadian variations of BP, as a blunted fall in nocturnal BP occurred in a significant fraction of patients with normal cardiac and vascular structural features, as assessed by ultrasonographic examinations. The lack of any relation between non-dipping pattern and TOD in low- and medium-risk patients may be explained by the numerous factors other than TOD influencing nocturnal BP decrease, such as autonomic nervous system activity, vasoactive hormones, haematological and renal variables, sex, ethnicity, age, quality of sleep, emotional state, physical activity, diet (caffeine and alcohol consumption) and smoking habit (11,27–30). However, it is also possible that a non-dipping pattern in these patients could be a clinical trait predisposing to development of TOD.

Finally, it should be pointed out that the classification of hypertensive patients into dippers and non-dippers on the basis of a single ABPM has a limited reproducibility over time both in the presence and the absence of antihypertensive treatment. Omboni et al. (31) have shown that about 40% of the 170 patients included in the SAMPLE study (Study of Ambulatory Monitoring of Pressure and Lisinopril Evaluation) classified into dippers and non-dippers according to the first session of ABPM changed their pattern when studied after 1 year of treatment. Manning et al. (32) investigated the long-term variability in the nocturnal BP profile in 79 subjects (69 untreated hypertensives and 10 normotensives) and observed that the initial night-time pattern was maintained in only half of their patients. More recently, Tsioufis et al. (33) found that in approximately one-third of 106 untreated patients with grade I and II hypertension, a nocturnal fall in BP was not reproducible. According to these findings, the assumption that one single ABPM can provide a reliable classification of the patients into dippers or non-dippers should be accepted with caution.

Some other points deserve to be discussed. First, we failed to demonstrate significant differences in nocturnal BP pattern in patients at low risk as compared with those at medium risk, this finding may be related to the similar demographic characteristics and to the absence of TOD in both groups. Second, a stepwise increase in the prevalence of the metabolic syndrome, as defined according to the ATP III criteria (34), occurred from the group at low risk to those at medium and high risk. These are in line with previous reports showing that in patients with the metabolic syndrome alterations in cardiac and vascular structure are more frequent (19,35). Third, to avoid potential methodological problems, in the present study we chose: (i) to include only untreated hypertensive patients, as previous reports have shown an increased prevalence of non-dippers among patients receiving antihypertensive treatment, probably due to the lack of therapeutic coverage for the 24 h of the day (30); (ii) to define the night-time interval as the effective bed-rest period of 8 h. Certain limitations of our study should be recognized. The study population included uncomplicated patients with grade 1 and 2 hypertension; thus our findings should not be generalized to different clinical categories, such as elderly, diabetics or patients with severe hypertension or more advanced TOD. In this analysis, we classified dippers and non-dippers on the basis of a single 24-h ABPM; potentially, a repetition of the ABPM sessions within a period of few weeks or

months may have provided a more accurate classification of nocturnal BP patterns.

In conclusion, the present study performed in a large sample of uncomplicated never-treated essential hypertensive patients indicates that a blunted fall in nocturnal BP is more frequently found in subjects classified at high added risk, because of the presence at least a manifestation of subclinical TOD, according to the 2003 ESH/ESC scheme stratification, than in those at low or medium risk. However, the presence of this pattern, with a potential adverse prognostic significance, in a notable fraction of low and medium risk patients, indicates that a reduced fall in BP at night, defined on the basis of a single ABPM session, may frequently occur in hypertensive individuals free of any sign of TOD or accompanying risk factors, suggesting that numerous variables other than TOD and traditional risk factors influence circadian variations in BP.

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