High blood pressure at old age : The Leiden 85 plus study

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Chapter 3

Prospective study of the effect of blood pressure on renal function in old age; The Leiden 85-plus Study

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Abstract

High blood pressure is associated with decline of renal function. Whether this is true for very old people largely is unknown. Therefore, the study assessed the effect of blood pressure on creatinine clearance over time in very old participants. A total of 550 inhabitants (34% men) of Leiden, The Netherlands, were enrolled in a population-based study at their 85th birthday and followed until death or age 90. Blood pressure was measured twice at baseline and at age 90 years. Creatinine clearance was estimated annually (Cockcroft-Gault formula). The mean creatinine clearance at baseline was 45.4 ml/min (SD 11.5). Systolic blood pressure was not associated with changes in creatinine clearance during follow-up. Those with diastolic blood pressure below 70 mmHg had an accelerated decline of creatinine clearance (1.63 ml/min/year) compared with those with diastolic blood pressures between 70 and 79 mmHg (1.21 ml/min/year; $P = 0.01$), 80 to 89 mmHg (1.26 ml/min/year; $P = 0.03$), and higher than 89 mmHg (1.38 ml/min/year; $P = 0.32$). Participants with a decline in systolic blood pressure during follow-up had an accelerated decline of creatinine clearance compared with yhose with stable blood pressures (1.54 ml/min/year [SE 0.09] versus 0.98 ml/min/year [SE 0.09]; $P < 0.001$). Similar results were found for a decline in diastolic blood pressure (1.54 ml/min/year [SE 0.10] versus 1.06 ml/min/year [SE 0.08]; $P < 0.001$). In the oldest individual, high blood pressure is not associated with renal function. In contrast, low diastolic blood pressure is associated with an accelerated decline of renal function. The clinical implications of these findings have to be studied.

Introduction

An old age, renal function will be compromised as a result of progressive loss of glomeruli and decline in renal blood flow [1], especially in those with persistent high blood pressure [2]. Because blood pressure increases with age, this implicates a possible double strike for creatinine clearance in the oldest individual [3].

In contrast with younger populations, in the oldest individuals, the association among high blood pressure, mortality and renal function is not straightforward. The available data suggest that blood pressure lowering above 80 years does not lower overall mortality [4,5]. Data on the effect of blood pressure on morbidity such as renal function are relatively scarce in the oldest individuals [6-8]. One longitudinal report associated blood pressure and renal function in a considerable group of very old Japanese individuals [7]. In that report, high blood pressure was related to an excess decline of serum creatinine. However, an important drawback was the use of serum creatinine for estimation of renal function. In addition, selection bias could have been induced as a result of exclusion of 40% of the participants, who did not attend the reexamination after 3 years.

Although blood pressure lowering in individuals over 80 years might not lower mortality, it is unknown if a high blood pressure might be deleterious for renal function. To investigate whether high blood pressure still is a risk factor for decline in renal function in the oldest individuals, we prospectively studied the effect of blood pressure on changes of creatinine clearance over time in a population-based study of the general population of the oldest individuals.

Materials and Methods

Study population

The Leiden 85-plus Study is a prospective population-based study of all 85-year-old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously [9,10]. In short, between September 1997 and September 1999 all 705 members of the 1912 to 1914-birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. Participants were followed until death or the age of 90. At baseline and yearly thereafter, 85-year-old participants were visited at their place of residence. During these visits, participants were weighed, blood pressure was measured, a venous blood sample was drawn, an electrocardiogram was recorded and face-to-face interviews and performance tests were conducted. Information on the medical history was obtained by standardized interviews of the participant's treating physicians. In addition, information on the use of medication was obtained from the participant's pharmacist. Participants gave informed consent; for people who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Commission of Leiden University approved the study.

Blood pressure

At baseline and at age 90 years, blood pressure was measured twice, with a mean intervening period of 2 weeks. Blood pressure was measured, using a mercury sphygmomanometer, in the seated position after at least 5 min of rest and no vigorous exercise the preceding 30 min. The systolic value was measured at Korotkoff sound 1, and the diastolic value was measured at Korotkoff sound 5. For the analysis of blood pressure, we used the mean of the measured systolic and diastolic values. For the analysis of pulse pressure, we used the mean systolic minus the mean diastolic blood pressure. Data are presented according to four strata of systolic blood pressure (<140, 140 to149, 150 to 159, and ≥ 160 mmHg), four strata of diastolic blood pressure (<70, 70 to 79, 80 to 89, and ≥ 90 mmHg), and quartiles of pulse pressure. The change of systolic and diastolic blood pressure between ages 85 and 90 was categorized into 3 groups: Declining (≥ 10-mmHg decrease), stable (<10-mmHg increase or <10-mmHg decrease) and increasing (≥ 10-mmHg).

Creatinine clearance

At entry and at yearly intervals thereafter, both the serum creatinine concentration and bodyweight were measured. Creatinine was fully automatically measured according to the Jaffé method (Hitachi 747; Hitachi, Tokyo, Japan). The creatinine clearances were estimated yearly with the Cockcroft-Gault formula as follows [11]:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine } (\mu\text{mol/l})} \times (0.85 \text{ if female})$$

Demographic and clinical characteristics

At baseline, a research nurse collected information concerning the demographic characteristics. The presence of cardiovascular disease was defined as a previous history of cerebrovascular accident, angina pectoris, myocardial infarction, peripheral vascular disease (including a history of arterial grafting, endarterectomy and angioplasty) or an electrocardiogram revealing myocardial ischemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [12]. The presence of chronic disease was defined as a history of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, osteoarthritis, or malignancies. Antihypertensive drugs were classified as usage of angiotensin converting enzyme inhibitor, angiotensin-1 receptor blocker, thiazid diuretic, dihydropyridin calcium channel blocker or β-blocker with the exclusion of Sotacor. We had data on use of anti-hypertensive medication at the ages of 85 and 86.

Statistical analyses

Data were presented as percentages for clinical characteristics and as the mean with standard deviation for continuous variables. The differences in mean creatinine clearances between the categories of blood pressure at baseline were compared with independent *t* test. The associations over time between creatinine clearance (ml/min) and categories of diastolic and systolic blood pressure were analyzed with a linear mixed model. The creatinine clearance was the dependent factor. The outcome was the effect on the change in creatinine clearance of the interaction between time and categories of blood pressure. This analysis models the change over time by computing the rate of change for each participant on the basis of all data for that individual adjusted for gender and other possible confounders.

Then the rate of changes for the entire group and the individual deviation from the group rate are computed. This model analyzes the unique effects of individual predictors adjusted for all other fixed and random predictors, accounts for the correlation among repeated measurements on the same participant, and is unaffected by randomly missing data. To investigate the effects of missing data due to mortality, we repeated all analyses with exclusion of participants who died within the first year of follow-up and repeated all analyses with inclusion only of surviving participants who participated up to age 90 years.

An additional analysis was done to examine the effect of a decline in systolic and diastolic blood pressure between ages 85 and 90 on the decline of creatinine clearance in participants who were alive at age 90. The associations between the groups of blood pressure and creatinine clearance were analyzed with a linear mixed model. All analyses were done with software SPSS version 12.0 (SPSS, Inc. Chicago, IL).

Results

Of the 705 eligible participants, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants (87 % response). Only one blood pressure measurement was available for 27 participants, serum creatinine at baseline was missing in 11 participants and body weight in 11 participants. Thus, in these analyses we included 550 participants (Table 1). During follow up, 34 participants declined further participation and 243 participants died (Figure 1). At age 86, 36 participants had started antihypertensive medication and 54 had stopped antihypertensive medication. There were no significant associations between the categories of diastolic and systolic blood pressure and changes of use of antihypertensive medication between ages 85 and 86 years (data not shown).

Table 1: Baseline characteristics of 550 participants aged 85 years.

Females		363 (66%)
History of hypertension		218 (40%)
Antihypertensive treatment		201 (37%)
Mean diastolic blood pressure (mmHg [SD])		76.9 (9.4)
Mean systolic blood pressure (mmHg [SD])		155.6 (18.4)
Mean pulse pressure (mmHg [SD])		78.7 (15.2)
Number of cardiovascular disease[a]	0	203 (37%)
	1	210 (38%)
	2	105 (19%)
	>=3	32 (6%)
No history of chronic diseases[b]		227 (41%)
Diagnosis of diabetes		87 (16%)

[a] Including history of peripheral vascular disease, cerebrovascular accident, angina pectoris, myocardial infarction, or an electrocardiogram revealing myocardial ischemia or infarction, [b] History of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, osteoarthritis, or malignancies.

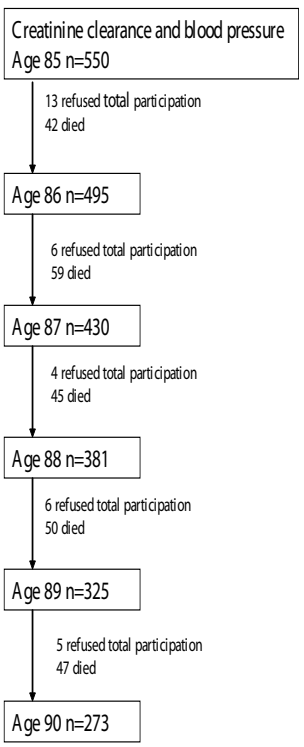

Figure 1: Number of participants during the study period.

At baseline the mean creatinine clearance was 45.4 ml/min (standard deviation [SD] 11.5 ml/min). Females had a 2.19 ml/min (standard error [SE] 1.04 ml/min) lower creatinine clearance compared with men ($P < 0.035$). During follow-up, the overall decline in creatinine clearance was 1.31 ml/min per year (SE 0.06, $P < 0.001$). At baseline, four participants had end-stage renal failure, defined as a creatinine clearance less than 15 ml/min. During follow-up, three participants progressed to end-stage renal failure: Two at age 89 years and one at age 90 years.

At baseline, creatinine clearance was correlated with the presence of cardiovascular disease. For every additional cardiovascular disease, creatinine clearance was 2.05 ml/min (SE=0.54, $P < 0.001$) lower. During follow-up, creatinine clearance declined with an extra 0.21 ml/min per year (SE 0.07, $P = 0.002$) over the normal annual decline for every additional manifestation of cardiovascular disease. A history of hypertension and diabetes (Table 2) was not associated with the decline of renal function either at baseline or during follow-up.

At baseline, creatinine clearance was not dependent on systolic blood pressure or pulse pressure (all comparisons between groups, $P > 0.18$). In contrast, diastolic blood pressure at baseline was significantly associated with creatinine clearance: Creatinine clearances were significantly lower in the two lowest categories (<70 and 70 to 79 mmHg) of diastolic blood pressure (43.8 ml/min [SE 0.98], 44.7 ml/min [SE 0.77]) compared with the two highest categories (80 to 89 and ≥90 mmHg) of diastolic blood pressure (47.5 ml/min [SE 0.97], 46.5 ml/min [SE 1.61]; $P = 0.005$). The associations among systolic, diastolic blood pressure and pulse pressure versus creatinine clearance were similar in men and women (data not shown).

Table 2: Additional change in creatinine clearance (ml/min) per year during follow-up until death or the age of 90, according to the number of cardiovascular diseases, the history of hypertension, and the history of diabetes at baseline in 550 participants[a].

	Crude model		Adjusted model	
	ml/min (SE)	P-value	ml/min (SE)	P-value
Number of cardiovascular diseases[b]	- 0.21 (0.07)	0.002	- 0.21 (0.07)	0.002
History of hypertension[c]	-0.12 (0.12)	0.31	-0.12 (0.12)	0.30
History of diabetes mellitus[c]	-0.18 (0.17)	0.27	-0.18 (0.17)	0.27

[a]Analyses with linear mixed model with estimates plus Standard Errors (SE) of the mean. Crude model: adjusted for gender. Adjusted model: adjusted for gender and use of antihypertensive medication at age 85 and 86.
[b]Change per additional number (range: 0 to 5) of cardiovascular diseases present.
[c]Change according to positive history versus negative history of hypertension and diabetes.

Relations between baseline blood pressure and changes in renal function over time were similar to those observed at the cross-sectional analyses. There was no association between baseline systolic blood pressure or pulse pressure and the annual decline of creatinine clearance (Figure 2). However, baseline diastolic blood pressure lower than 70 mmHg was associated with a significantly accelerated decline of creatinine clearance during follow-up when compared to higher diastolic blood pressures (Figure 2). These findings remained similar after exclusion of 42 participants who died within the first year of follow-up. The restricted analyses for 273 surviving participants who participated up to 90 years did also not change the significant association between low diastolic blood pressure and an accelerated decline of creatinine clearance. The yearly decline in creatinine clearance was –1.58 ml/min for 53 participants with baseline diastolic blood pressure < 70 mmHg (reference group), -1.13 for 70 to 79 mmHg (n = 112, P = 0.006), -1.13 for 80 to 89 mmHg (n = 82, P = 0.01), and –1.30 (n = 26, P = 0.24) for > 89 mmHg.

During follow-up a low diastolic blood pressure was consistently associated with an accelerated decline of creatinine clearance in those with and those without cardiovascular disease at baseline (data not shown). Stratification according to the median of creatinine clearance at baseline did not reveal a different effect of blood pressure on creatinine clearance over time (data not shown).

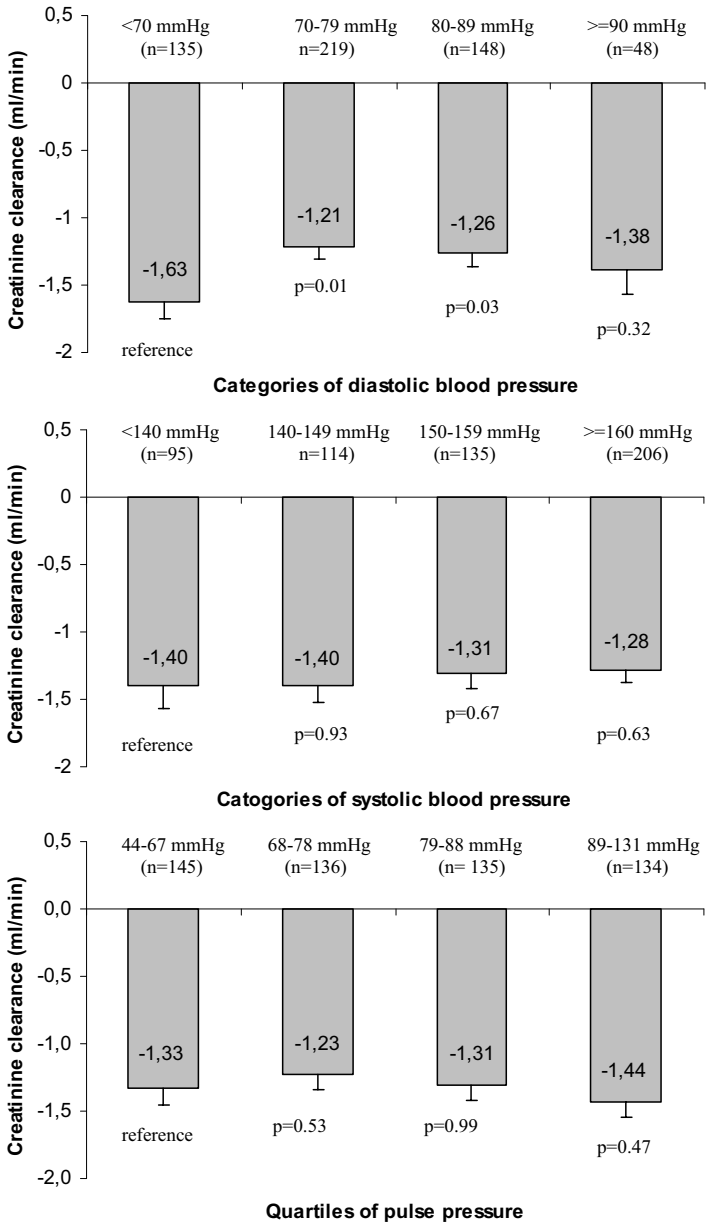

Figure 2. Yearly decline of creatinine clearance depending on categories of blood pressure and pulse pressure. Analyses with linear mixed model with estimates plus standard errors of the mean. Adjusted for gender, cardiovascular disease, chronic disease and use of antihypertensive medication at age 85 and 86 year. Diastolic blood pressure was adjusted for systolic blood pressure and vice versa. P-values reflecting the differences in additional annual decline compared to the reference category.

Figure 3 presents the annual decline of creatinine clearance in survivors up to 90 year according to the change of blood pressure from age 85 up to 90. Those with a decline in systolic blood pressure had an accelerated decline of creatinine clearance -from age 85 up to 90- compared with those with a stable systolic blood pressure (1.54 ml/min/year [SE 0.09] versus 0.98 ml/min/year [SE 0.09]; $P < 0.001$). Those with a decline in diastolic blood pressure had an accelerated decline of creatinine clearance –from age 85 up to 90- compared with those with a stable diastolic blood pressure also (1.54 ml/min/year [SE 0.10] versus 1.07 ml/min/year [SE 0.08]; $P < 0.001$). There were no associations between the presence of chronic disease, cardiovascular disease, history of hypertension or usage of antihypertensive medication at baseline and a decline versus an increase in systolic or diastolic blood pressure between 85 and 90 year (data not shown).

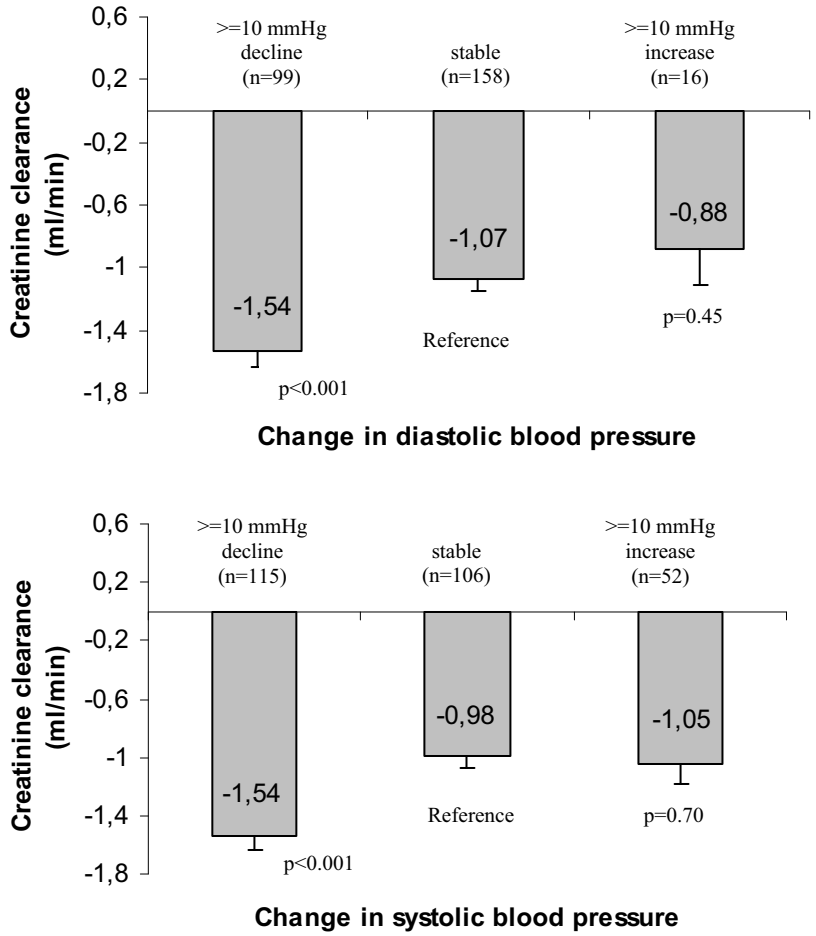

Figure 3: Annual decline of creatinine clearance in 273 survivors up to 90 year depending on a decline, stable or increase in systolic and diastolic blood pressure in-between age 85 to age 90. Analyses with linear mixed model with estimates plus standard errors of the mean. Adjusted for gender and use of antihypertensive medication at age 85 and 86. P-values reflecting the differences in additional annual decline compared to the reference category.

Discussion

In our prospective, population based study of the oldest individuals, we found no association between high systolic blood pressure and decline of creatinine clearance during follow-up. Strikingly, a diastolic blood pressure below 70 mmHg preceded an accelerated decline of creatinine clearance during follow-up. Moreover, a decline in systolic and diastolic blood pressure from ages 85 up to 90 was related to an accelerated decline of creatinine clearance.

In younger age groups, the deleterious effect of elevated diastolic and systolic blood pressure on renal function is beyond doubt [13]. Up to an average age of 72 year, harmful effects of systolic blood pressure on renal function has been reported [14]. Intervention trials have shown that blood pressure lowering prevents renal failure, independently of renal function at baseline [15]. Therefore, it is surprising that we could not find an association between elevated blood pressure (diastolic and systolic) and creatinine clearance in our elderly participants. To date, only one published longitudinal study with a considerable amount of very old participants has shown that high blood pressure was associated with a decline of creatinine clearance [7]. However, renal function was estimated with two measurements of serum creatinine three years apart. In older people, serum creatinine is less reliable as an estimate for renal function due to progressive loss of muscle mass [1,16]. In addition, only 60% of the participants who attended the first examination were reexamined after three years, possibly inducing selection bias. We did find an annual decline of renal function of 1.3 ml/min/year and also gender differences in creatinine clearances, both in line with the literature [17-20]. In addition, a strong association with cardiovascular disease and creatinine clearance existed at baseline and during follow-up [21]. Therefore, we do think that our data are reliable and representative for the oldest individuals.

How can we explain the effect of a low diastolic blood pressure on creatinine clearance over time and the accelerated decline in creatinine clearance that is associated with a decline in blood pressure? Possibly, a low diastolic blood pressure in the ninth decade is a reflection of a decline in blood pressure in the years before. The underlying mechanism of the accelerated decline of creatinine clearance might be chronic hypoperfusion of the kidneys. The vulnerability of the

kidney in the elderly could be related due to an impaired autoregulatory response of the renal arteries in the presence of atherosclerosis.
Different from in middle age, high blood pressure in elderly has been associated with an increased, equal, or even decreased mortality [22-24]. Within our prospective cohort study, high blood pressure was not related to an increased mortality risk after age 85 years [25]. In addition, it is not established whether hypertension should be treated in the very old. A meta-analysis of treated participants of 80 years and older included in hypertension trials had inconsistent results [5]. A placebo-controlled trial for treatment of hypertension in people above 80 year is still running [26]. The pilot study did not show a survival benefit for treatment; even worse, a non-significant trend towards excess mortality was found in the treated group [4]. However, some beneficial effect was seen on the reduction of strokes. Given these considerations, our finding that an elevated blood pressure is not a risk factor for decline of renal function in the oldest old is of interest.

Because our data are from a prospective population-based study with a high response rate and virtually no dropouts during follow-up, we were able to observe the impact of blood pressure on renal function of the oldest individuals in the population at large. Another strength is that we measured blood pressure twice and assessed the creatinine clearance yearly for a period of 5 years. Although the estimation of creatinine clearance with the Cockcroft-Gault formula is not the gold standard to measure renal function, this is a very widely used and validated method for estimation of the creatinine clearance [11,16,17,19]. Because we did not have reliable data on clinical heart failure, this might have influenced our results. The linear mixed model that was used is an accurate model that can handle at random missing data. Participants who die probably will not die at random. However, our results remained similar in the additional analyses without the participants who died within the first year and also in the restricted analyses for survivors up to age 90 years. These additional analyses show that our results are unlikely to be influenced by underlying survivor bias.

In contrast with younger age groups, elevated systolic and diastolic blood pressure did not influence the annual decline in renal function in the oldest individuals. A diastolic blood pressure lower than 70 mmHg and a decline in systolic or diastolic

blood pressure between ages 85 and 90 was related to an accelerated decline of creatinine clearance over time. Clinical implications of these findings have to be studied more in depth.

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