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Comparison of the Overtime Fasting Plasma Glucose Between Patients Receiving Angiotensin Receptor Blocker (ARB) and Non-ARB Drugs

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Background: Previous studies have shown a relationship between renin angiotensin aldosterone system (RAAS) and insulin resistance. This in turn can delay the onset of diabetes mellitus (DM). The impact of angiotensin receptor blocker (ARB) on the fasting plasma glucose (FPG) level is not clear.

Objective: To compare the overtime FPG between ARB and non-ARB using.

Methods: A retrospective-longitudinal cohort study, data were collected from medical records of hypertensive patients who were not diagnosed DM in 2007 and 2008, each patient was followed up 10 years. The association between antihypertensive drugs and FPG by multilevel mixed-effects linear regression was evaluated. Multistate Markov chain model was used to evaluate the probability to become pre-DM or DM stage.

Results: Of 822 patients, 571 patients were excluded and 251 patients met criteria for analysis. From multilevel mixed-effects linear regression, ARB usage was associated with a nonsignificant decreased FPG when adjusted with visit (mean FPG change, -0.98; 95% CI, -2.65 to 0.69; $P = .25$) and with visit plus glomerular filtration rate (mean FPG change, -1.89, 95% CI, -4.88 to 1.19; $P = .24$). The probability of change in 10 years from normal to pre-DM stage was 0.41 and 0.38, normal to DM stage was 0.03 and 0.01, pre-DM to DM stage was 0.08 and 0.04, in non-ARB and ARB group, respectively.

Conclusions: ARB tended to decrease probability to become DM. Thus, physicians should prescribe ARB in hypertensive patients to prevent new-onset DM.

Keywords: Angiotensin receptor blocker, Fasting plasma glucose, Hypertension

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Introduction

Hypertension and diabetes mellitus (DM) are the most threatenable noncommunicating disease in Thailand. Thai health report 2009 found that 21.4% (9.9 million persons) became hypertension and 6.9% (3.2 million persons) become DM.[1] There was cost for outpatient unit about ฿1172 per person, inpatient unit about ฿10 217 per person, and total amount was ฿3984 million per year in Thailand.[2] The average cost of illness per DM patient was 21% of per capita gross domestic product of Thailand in 2008.[3] Hypertension is a major risk factor of DM, Thai-Clinical Practice Guideline for Diabetes 2017 suggested that hypertensive patients should be screening for DM.[4]

Antihypertensive drugs influence the patient's insulin sensitivity, which is responsible for the development of new-onset DM (NOD). Previous studies showed that β-blockers and diuretics increase NOD.[5] In addition, previous meta-analysis studies have found that both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) could reduce the incidence of NOD.[5-7] There are few studies about the relationship of antihypertensive and NOD conducted in Asian. Previous study in primary care unit of the university, Thailand, demonstrated that ARB was associated with increased risk of NOD.[8] The result was not consistent with the previous meta-analysis studies. The hypothesis of ARB results that different from previous meta-analysis studies is that study was single level analysis, non-evaluate the repeated measurement. Therefore, it is necessary to make a comprehensive comparison of the previous findings.

This study aimed to compare the overtime fasting plasma glucose (FPG) between ARB and non-ARB usage in primary care unit.

Methods

Participants

The calculated sample size was at least 181 persons by using R package (R Project for Statistical Computing) with long power package. Inclusion criteria were 1) patients who were diagnosed with hypertension or took antihypertensive drugs at primary care unit of Songklanagarind Hospital from 1 January 2007 to 31 December 2018; 2) age greater than or equal to 35 years; 3) FPG data from 1 January 2007 to 31 December 2019; and 4) patients who were not diagnosed with DM before 1 January 2007. Exclusion criteria were 1) patients who were followed up less than 2 visits in 10 years; 2) patients who had FPG results less than 2 times; and 3) duration between visits more than 1500 days.

Ethics

Ethical approval was gained from the Faculty of Medicine, Prince of Songkla University, certificate of approval No. REC.61-332-9-4.

Study Design

This longitudinal study was conducted to compare developing NOD between patients receiving each group of antihypertensive drugs. Each patient was followed up 10 years. Researcher would stop collecting data when found these end points: 1) receiving antiglycemic drugs or FPG greater than or equal to 126 mg/dL at once, to convert to millimoles per liter, multiply by 0.0555; 2) dead at Songklanagarind Hospital; and 3) loss follow-up until December 31, 2018. Data were recorded in case record form then inputted the data in KoBoCollect (KoBoToolbox).

Statistical Analysis

Mean, median, standard deviation (SD), interquartile range (IQR), and 95% confidence interval (CI) were used for describing continuous data (age, body weight, height, systolic blood pressure [SBP], diastolic blood pressure [DBP], FPG, creatinine, glomerular filtration rate [GFR], total cholesterol, triglyceride, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], uric acid, and microalbumin). As categorical data (sex, occupational, religion, use of antihypertensive drugs, and use of lipid lowering agents) were described with percentages and 95% CI. This study

evaluated the association between antihypertensive drugs and mean change of FPG by multilevel mixed-effects regression. Data were evaluated based on their significance level ($P < .05$). Multistate Markov chain model was used to evaluate the probability to become pre-DM or DM stage. Statistical analyses were done by using R statistical software version 3.6.0 (R Project for Statistical Computing).

Results

Total of 822 patients were diagnosed hypertension in 2007 and 2008, 546 patients were excluded because they came to follow-up less than 2 times, 16 patients were excluded because they had less than 2 results of FPG, and 9 patients were excluded because duration between visits more than 1500 days. Finally, there were 251 patients that were analyzed in the study. There were total 8924 visits. Median (IQR) of visits per person were 46 (40 - 52) visits in ARB and 42 (36 - 49) visits in non-ARB group, There were significantly more age, body weight, height, SBP, DBP, creatinine, and uric acid in ARB group more than non-ARB group ($P < .001$) (Table 1). There were significantly different in sex, occupational, religion, and medical insurance between ARB and non-ARB group ($P < .001$). There were significantly more spironolactone, furosemide, metoprolol, carvedilol, losartan, valsartan, hydralazine and doxazosin usage in ARB group more than non-ARB group ($P < .001$) (Table 2). From aggregate plot of mean FPG by number of visits, mean FPG trended to be decreased in ARB group (Figure 1).

Stepwise regression analysis model when adjusted by visits, ARB usage associated with decreased FPG with a nonsignificant (mean FPG change, -0.98; 95% CI, -2.65 to 0.69; $P = .25$). Whereas universal coverage scheme was associated increase in FPG compared with cash (mean FPG change, 5.02; 95% CI, 0.73 to 9.3; $P = .03$). Simvastatin usage was associated with a decrease in FPG (mean FPG change, -1.14; 95% CI, -2.26 to -0.01; $P = .05$). Regarding the results using stepwise regression analysis model was adjusted by visits and GFR, ARB usage was associated with decreased FPG (mean FPG change, -1.89; 95% CI, -4.88 to 1.19; $P = .24$). Social security scheme was associated with increased FPG compared with cash (mean FPG change, 14.02; 95% CI, 3.92 - 23.6; $P = .01$). GFR was also associated with an increased in FPG (mean FPG change, 0.09; 95% CI, 0.01 to - 0.17; $P = .03$) (Table 3).

The probability of change in 10 years by multistate Markov chain model from normal to pre-DM stage was 0.41 and 0.38; normal to DM stage was 0.03 and 0.01; pre-DM to DM stage was 0.08 and 0.04, in non-ARB and ARB group, respectively. DM state defined as FPG greater than or equal to 126 mg/dL at once, to convert to millimoles per liter, multiply by 0.0555 (Table 4).

Table 1. Clinical Characteristics of Patients

Demographic	Mean (SD)	Patient Group, Median (IQR) of Visits		*P* Value*
		ARB (n = 2670)	Non-ARB (n = 6254)	
Age, y	59.2 (10.9)	64 (55 - 72)	62 (55 - 70)	< .001
Body weight, kg	62.6 (14.8)	62 (54.7 - 71.6)	61 (55- 68.4)	< .001
Height, cm	156.3 (8.1)	156 (152 - 160)	155 (150 - 160)	< .001
SBP, mm Hg	135.6 (17.3)	137 (127 - 147)	133 (124 - 142)	< .001
DBP, mm Hg	85.3 (36.2)	80 (71 - 87)	79 (70 - 86)	< .001
FPG, mg/dL	102 (12.0)	100 (94 - 106)	100 (94 - 109)	.13
Cr, mg/dL	0.9 (0.3)	0.9 (0.7 - 1.2)	0.8 (0.7 - 1)	< .001
GFR, mL/min/1.73 m^2	77.3 (18.3)	72 (59 - 88)	81 (68.5 - 94)	< .001

Table 1. Clinical Characteristics of Patients (Continued)

Demographic	Mean (SD)	Patient Group, Median (IQR) of Visits		*P* Value*
		ARB (n = 2670)	Non-ARB (n = 6254)	
TC, mg/dL	215.2 (469.6)	199 (176 - 226)	205 (180 - 233)	.001
TG, mg/dL	127.2 (56.2)	111 (83 - 144)	120 (91 - 157)	< .001
HDL-C, mg/dL	57.6 (34.4)	54 (46.2 - 62)	55 (46 - 63)	.94
LDL-C, mg/dL	138.1 (44.6)	132 (111 - 158)	137 (112 - 162)	.12
Uric acid, mg/dL	6 (3.7)	6.2 (5.1 - 7.3)	5.7 (4.9 - 6.6)	< .001
Microalbumin, mg/L	45.6 (96.5)	15 (7 - 42)	14 (7 - 33)	.94

Abbreviations: ARB, angiotensin receptor blocker; Cr, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

SI conversion factors: To convert fasting plasma glucose to millimoles per liter, multiply by 0.0555; to convert creatinine to micromoles per liter, multiply by 88.4; to convert total cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259; to convert low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259; to convert uric acid to millimoles per liter, multiply by 0.0595.

* *P* value < .05 was considered statistically significant difference between 2 groups.

Table 2. Descriptive Data of Number of Visits of Patients

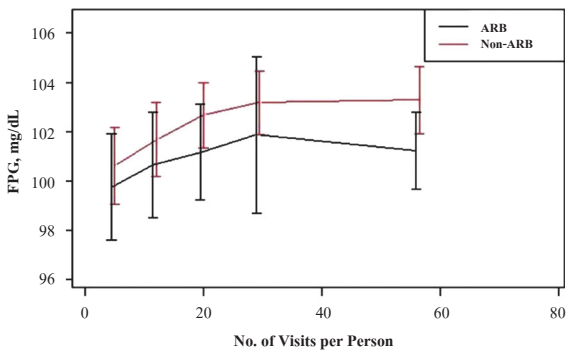
Demographic	Patient Group, No. (%) of Visits		*P* Value*
	ARB (n = 2670)	Non-ARB (n = 6254)	
Sex			
Male	995 (37.3)	1507 (24.1)	< .001
Female	1675 (62.7)	4747 (75.9)	
Occupational (N = 251)			
Government officer	868 (32.5)	1308 (20.9)	< .001
Own business/merchant	494 (18.5)	1110 (17.7)	
Employee/technicians	229 (8.6)	993 (15.9)	
Agribusiness/fisher	505 (18.9)	1038 (16.6)	
No occupation/student	574 (21.5)	1685 (26.9)	
Unknown occupations	0	120 (1.9)	
Religion			
Buddhism	2213 (82.9)	6114 (97.8)	< .001
Christianity	22 (0.8)	0	
Islam	435 (16.3)	140 (2.2)	

Table 2. Descriptive Data of Number of Visits of Patients (Continued)

Demographic	Patient Group, No. (%) of Visits		*P* Value*
	ARB (n = 2670)	Non-ARB (n = 6254)	
Medical insurance			
Cash	152 (5.7)	923 (14.8)	< .001
Government scheme (cash)	79 (3)	266 (4.3)	
Government scheme	1778 (66.6)	2724 (43.6)	
Universal coverage scheme	596 (22.3)	1949 (31.2)	
Social security scheme	43(1.6)	143 (2.3)	
Local government officer scheme	22 (0.8)	249 (4)	
Antihypertensive drugs			
Diuretics			
Hydrochlorothiazide	1014 (38)	2611 (41.7)	< .001
Amiloride	100 (3.7)	193 (3.1)	.11
Spironolactone	13 (0.5)	4 (0.1)	< .001
Furosemide	20 (0.7)	13 (0.2)	< .001
Calcium channel blockers			
Amlodipine	613 (23.0)	1947 (31.1)	< .001
Nifedipine	428 (16.0)	1145 (18.3)	.01
Manidipine	7 (0.3)	6 (0.1)	.06
Felodipine	22 (0.8)	72 (1.2)	.17
Beta-blockers			
Metoprolol	1088 (40.7)	1921 (30.7)	< .001
Propranolol	53 (2.0)	372 (5.9)	< .001
Carvedilol	14 (0.5)	0 (0.0)	< .001
Angiotensin converting enzyme inhibitors			
Enalapril	250 (9.4)	1758 (28.1)	< .001
Captopril	6 (0.2)	104 (1.7)	< .001
Losartan	1101 (41.2)	0	< .001
Valsartan	8 (0.3)	0	< .001
Others			
Hydralazine	16 (0.6)	0	< .001
Doxazosin	72 (2.7)	40 (0.6)	< .001
Simvastatin	980 (36.7)	2500 (40.0)	.004
Atorvastatin	9 (0.3)	41 (0.7)	.07
Rosuvastatin	11 (0.4)	13 (0.2)	.09

* *P* value < .05 was considered statistically significant difference between 2 groups.

Figure 1. Aggregate Plot of Mean FPG by Number of Visits per Person



Abbreviations: ARB, angiotensin receptor blocker; FPG, fasting plasma glucose.

SI conversion factors: To convert fasting plasma glucose to millimoles per liter, multiply by 0.0555.

Table 3. Stepwise Regression

Stepwise Regression	FPG Change, mg/dL	95% CI	*P* Value*
Stepwise Regression (adjusted by visits)			
ARB	-0.98	-2.65 to 0.69	.25
Body mass index	2.84	-1.27 to 7.19	.19
Own business/merchant	0.83	-3.62 to 5.31	.72
Agribusiness/fisher	2.07	-2.19 to 6.32	.36
No occupation/student	0.66	-3.52 to 4.87	.77
Unknown occupation	6.76	-7.74 to 21.26	.38
Government scheme (cash)	4.45	-3.33 to 12.27	.28
Universal coverage scheme	5.02	0.73 to 9.30	.03
Social security scheme	4.42	-5.19 to 14.03	.39
Local government officer scheme	1.2	-8.31 to 10.74	.81
University officer and relatives' scheme	0.69	-3.77 to 5.16	.77
Christianity	-7.96	-29.08 to 13.13	.48
Islam	4.62	-0.73 to 9.92	.10
Hydrochlorothiazide	0.41	-0.78 to 1.61	.51
Amlodipine	0.96	-0.26 to 2.18	.12
Simvastatin	-1.14	-2.26 to -0.01	.05
Atorvastatin	-0.77	-5.71 to 4.16	.76
Stepwise regression (adjusted by visits and GFR)			
ARB	-1.89	-4.88 to 1.19	.24
Body mass index	53.03	29.46 to 74.81	0
Own business/merchant	-1.85	-7.13 to 3.43	.52
Employee/technicians	-4.66	-10.23 to 0.96	.13
Agribusiness/fisher	-5.09	-10.2 to 0.17	.07

Table 3. Stepwise Regression (Continued)

Stepwise Regression	FPG Change, mg/dL	95% CI	*P* Value*
No occupation/student	0.3	-4.76 to 5.42	.91
Unknown occupation	9.06	-5.81 to 23.71	.26
Government scheme (cash)	4.74	-4.35 to 13.92	.34
Universal coverage scheme	2.71	-2.34 to 7.79	.33
Social security scheme	14.02	3.92 to 23.6	.01
Local government officer scheme	-4.14	-14.14 to 6.00	.45
Government scheme	-1.08	-6.39 to 4.27	.71
Islam	2.49	-4.21 to 9.19	.49
GFR	0.09	0.01 to 0.17	.03
Hydrochlorothiazide	2.28	-0.08 to 4.5	.06
Amlodipine	-0.22	-2.2 to 1.91	.84
Simvastatin	-0.77	-2.91 to 1.07	.45

Abbreviations: ARB, angiotensin receptor blocker; CI, confidence interval; GFR, glomerular filtration rate.

SI conversion factors: To convert fasting plasma glucose to millimoles per liter, multiply by 0.0555.

* *P* value < .05 was considered statistically significant difference between 2 groups.

Table 4. Probability of Becoming Diabetes by Multistate Markov Chain Model

Patient Group	Probability		
	Normal	Pre-DM	DM
Non-ARB group			
Normal	0.56	0.41	0.03
Pre-DM	0.43	0.50	0.08
DM	0	0	1.00
ARB group			
Normal	0.61	0.38	0.01
Pre-DM	0.35	0.61	0.04
DM	0	0	1.00

Abbreviations: ARB, angiotensin receptor blocker; DM, diabetes mellitus.

Discussion

This study was used longitudinal study because it took time to become DM. ARB usage tended to reduce FPG and have lower probability to become DM. These results are consistent with previous meta-analysis, showing the beneficial effects of ARB in preventing NOD.[7] Epidemiological evidence indicates that markers of low-grade inflammation is independent predictor of incident DM.[9, 10] A clear link between inflammation and DM is still missing but the RAAS adversely influences the fibrinolytic balance and vascular inflammation.

Various studies suggest favourable effects of ARB on the markers of vascular cell adhesion molecule-1 and C-reactive protein.[11] Thus, chronic blockade of the RAAS may decrease a subclinical inflammatory response, which could suppress pancreatic islet fibrosis, resulting in a reduced risk of incident DM.

The partial peroxisome proliferator-activated receptor gamma ($PPAR_{\gamma}$) agonist activity of ARB have been shown to improve insulin sensitivity in non-modulating hypertensive patients.[12, 13]

In stepwise regression model, universal coverage scheme was associated with increasing FPG compared with cash when adjusted by visits. Moreover, social security scheme was associated with increasing FPG compared with cash when adjusted by visits and GFR. The results should be by the theory in previous systematic review that patients with full-medication subsidies payment scheme (received medication at no cost) were found to have poor adherence to their medication especially in nonsevere disease.[14] GFR was significantly associated with increasing FPG. There is an evidence showed that the kidneys release glucose via gluconeogenesis in the postabsorptive state.

In the postprandial state, renal gluconeogenesis actually increases by approximately 2-fold.[15] Statin usage was significantly associated with decreasing FPG in this study when adjusted by visits. The result was different from the meta-analysis study that claims statins were one of the risk factors of NOD.[16] This can be supported by the theory of an improvement in the action of insulin by stronger inhibition of hepatic glucose output and glucose metabolic clearance rate.[17] However, statin usage was insignificantly associated with decreasing FPG in this study when adjusted by visits and GFR.

Strengths

There were 4 strengths of this study, firstly this study was long study period, a 10-year follow-up would be enough to show the association between the effect of ARB usage and FPG. Secondly, this study was a longitudinal cohort design, which is better than the previous cross-sectional study at primary care unit (PCU). Thirdly, the result that ARB tended to decrease NOD from multilevel mixed-effects regression was consisted with multistate Markov chain model result, so the results were more reliable. Finally, there was no conflict of interest in this study.

Limitations

This study was retrospective study, there are many confounders that we could not collect the data such as dietary record, exercise, family history. This study was collected data from PCU setting only. So, this might be aware the result if using in the specialist's unit. DM state defined as FPG greater than or equal to 126 mg/dL at once, the result of this study may be overestimated.

Conclusions

ARB tended to decrease probability to become diabetes mellitus. Thus, physicians should prescribe ARB in hypertensive patients to prevent new onset of DM. Future studies should be prospective double-blinded randomized controlled trials to confirm the importance of ARB in preventing new-onset diabetes.

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การเปรียบเทียบการเปลี่ยนแปลงระดับน้ำตาลในเลือดในผู้ป่วยที่ได้รับยาลดความดันโลหิตกลุ่ม Angiotensin Receptor Blocker (ARB) กับยากลุ่ม Non-ARB ในเวลาที่เปลี่ยนไป

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บทนำ: การศึกษาที่ผ่านมาพบความสัมพันธ์ระหว่างระบบ Renin angiotensin aldosterone system และภาวะดื้อต่ออินซูลิน ซึ่งเป็นปัจจัยที่ทำให้ชะลอการเกิดโรคเบาหวาน (Diabetes mellitus, DM) อย่างไรก็ตาม ยังไม่มีผลสรุปที่แน่ชัดถึงความสัมพันธ์ระหว่างการใช้ยากลุ่ม Angiotensin receptor blocker (ARB) กับระดับน้ำตาลในเลือด

วัตถุประสงค์: เพื่อเปรียบเทียบการเปลี่ยนแปลงระดับน้ำตาลในเลือดโดยการตรวจ Fasting plasma glucose (FPG) ในผู้ป่วยที่ได้รับยาลดความดันโลหิตกลุ่ม ARB กับยากลุ่ม Non-ARB ในเวลาที่เปลี่ยนไป

วิธีการศึกษา: การศึกษาย้อนหลังโดยเก็บข้อมูลจากเวชระเบียนของผู้ป่วยโรคความดันโลหิตสูงที่ไม่ได้เป็นโรคเบาหวานตั้งแต่ปีพ.ศ. 2550 - 2551 ติดตามผู้ป่วยแต่ละคนเป็นระยะเวลา 10 ปี เปรียบเทียบความสัมพันธ์ระหว่างการใช้ยากลุ่ม ARB กับ FPG ด้วยการวิเคราะห์ Multilevel mixed-effects linear regression และหาค่าความน่าจะเป็นของการเปลี่ยนเป็นระยะก่อนเบาหวาน (pre-DM stage) หรือระยะเบาหวาน (DM stage) ในระยะเวลา 10 ปี ด้วยการวิเคราะห์ Multistate Markov chain model

ผลการศึกษา: จากผู้ป่วยทั้งหมด จำนวน 822 คน มี 571 คน ถูกคัดออก จึงมี 251 คนที่อยู่ในการศึกษา พบว่า การใช้ยากลุ่ม ARB สัมพันธ์กับการลดลงของระดับ FPG ทั้งเมื่อถูกปรับด้วยจำนวนครั้งการมาโรงพยาบาล (mean FPG change, -0.98; 95% CI, -2.65 ถึง 0.69; $P = .25$) และเมื่อถูกปรับด้วยจำนวนครั้งการมาโรงพยาบาลร่วมกับค่าอัตราการกรองของไต (mean FPG change, -1.89; 95% CI, -4.88 ถึง 1.19; $P = .24$) ความน่าจะเป็นของการเปลี่ยนจากระยะปกติเป็นระยะ pre-DM เท่ากับ 0.41 และ 0.38 จากระยะปกติเป็นระยะ DM เท่ากับ 0.03 และ 0.01 และจากระยะ pre-DM เป็นระยะ DM เท่ากับ 0.08 และ 0.04 ในกลุ่ม non-ARB และกลุ่ม ARB ตามลำดับ

สรุป: การใช้ยากลุ่ม ARB มีแนวโน้มลดการเกิดโรคเบาหวาน ดังนั้นแพทย์ควรพิจารณาใช้ยากลุ่ม ARB ในผู้ป่วยโรคความดันโลหิตสูงเพื่อลดการเกิดโรคเบาหวาน

คำสำคัญ: ยาลดความดันโลหิตกลุ่ม Angiotensin receptor blocker ระดับน้ำตาลในเลือด โรคความดันโลหิตสูง

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