# High Blood Pressure and Its Association With Incident Diabetes Over 10 Years in the Korean Genome and Epidemiology Study (KoGES)

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## OBJECTIVE

**No prospective, community-based cohort studies have investigated the association between blood pressure and diabetes in Asian ethnicity. We investigated this issue in a 10-year prospective, community-based study of Koreans.**

## RESEARCH DESIGN AND METHODS

**We studied whether high blood pressure was associated with the development of diabetes in a population-based cohort, where we sampled ~5,000 random subjects each from rural and urban areas (age range 40–69 years) during 2001–2010. Among 10,038 subjects, 8,359 without diabetes at baseline were categorized into normal (*n* = 4,809), prehypertension (*n* = 2,141), stage 1 hypertension (*n* = 804), and stage 2 hypertension (*n* = 605) groups, according to their blood pressure readings of <120/80 mmHg, 120–139/80–89 mmHg, 140–159/90–99 mmHg, and ≥160/100 mmHg, respectively. The development of diabetes was defined as a fasting glucose concentration of ≥126 mg/dL or a postload glucose concentration of ≥200 mg/dL, based on a 75-g oral glucose tolerance test, or the use of antidiabetic medication.**

## RESULTS

**During the 10-year follow-up period, diabetes developed in 1,195 subjects (14.3%). The incidence of diabetes increased from 11.1% in the normal group to 17.0% in the prehypertension group, 17.7% in the stage 1 hypertension group, and 25.8% in the stage 2 hypertension group (*P* < 0.001). After adjusting for anthropometric factors; family history of diabetes; biochemical parameters including C-reactive protein, A1C, and fasting glucose and postload 2-h glucose levels; and the use of lipid-lowering medications, the hazard risks of diabetes development were 1.23 (95% CI 1.06–1.42), 1.26 (1.04–1.54), and 1.60 (1.30–1.96), respectively, in the prehypertension, stage 1 hypertension, and stage 2 hypertension groups.**

## CONCLUSIONS

**Our findings indicate a grade association of baseline blood pressure with the development of diabetes in Korean individuals.**


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Historically, a relationship between hyperinsulinemia and hypertension has been recognized (1,2). Subsequently, several studies (3,4) have shown that insulin resistance (IR) and insulin levels at baseline are associated with a higher risk of incident hypertension.

IR and compensatory hyperinsulinemia could be primary events in the time sequence of the diabetes-hypertension relationship. Enhanced sympathetic activity and diminished adrenal medullary activity may be important links between defective insulin activity and the development of hypertension. Thus, IR and compensatory hyperinsulinemia play major roles in the regulation of blood pressure in susceptible subjects with a predisposition to hypertension.

In a different context, it is conceivable that high blood pressure with enhanced sympathetic activity and diminished adrenal medullary activity may contribute to defective insulin activity, the development of diabetes, and associated metabolic abnormalities (5). Regardless of any causal inferences, which remain speculative, most risk scores for diabetes in mainly Western populations include hypertension or blood pressure as a predictor (6–8).

However, a few studies (9–12) have investigated how blood pressure might affect diabetes. Twenty years ago, it was reported (13) that high blood pressure was associated with the incidence of non-insulin–dependent diabetes in men after adjusting for age and BMI in subjects of European descent. A study with male employees of a gas company in Japan (10) showed that high normal blood pressure and hypertension are associated with an increased risk of the development of diabetes. In a representative population sample in Germany, hypertension was significantly associated with incident diabetes in men and women (11). In the Atherosclerosis Risk in Communities Study (14), the presence of hypertension was associated with an increased risk of diabetes. However, the researchers focused mainly on antihypertensive medication and found that the use of β-blockers increased the risk of diabetes (14).

To the best of our knowledge, no prospective community-based cohort studies have investigated this issue in Asian ethnic groups. In this study, therefore, we investigated the association between blood pressure and the development of diabetes in a large community-based cohort of Koreans.

## RESEARCH DESIGN AND METHODS

### Study Population

In 2001, two communities in South Korea were selected for the Korean Genome and Epidemiology Study (KoGES). The Ansung cohort represented a rural community, and the Ansan cohort was an urban community. KoGES is an ongoing prospective study, which involves a biennial examination. Details of KoGES and the methods used have been described previously (15,16). In brief, 10,038 subjects aged 40–69 years were recruited (5,020 from a farming community for Ansung and 5,018 from an urban community for Ansan). Of these 10,038 subjects, the total number of patients with diabetes was 1,298 (12.9%). Among the remaining 8,740 subjects, 381 subjects (4.4%) who were taking one or more antihypertensive medications (calcium channel blockers: $n$ = 141, 37.0%; angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: $n$ = 83, 21.8%; diuretics: $n$ = 47, 12.3%; β-blockers: $n$ = 42, 11.0%; and unknown: $n$ = 116, 30.4%) were further excluded from the study (Supplementary Table 1). Finally, 8,359 subjects (3,930 men and 4,429 women) were enrolled in the current study.

All subjects participated in the study voluntarily, and informed consent was obtained in all cases. The study protocol was approved by the Ethics Committee of the Korean Health and Genomic Study at the Korea National Institute of Health.

### Measurement of Anthropometric and Biochemical Parameters

The height, body weight, and waist and hip circumference were measured using standard methods in light clothes. The BMI was calculated as the weight divided by height squared (kg/m$^2$). The body fat and lean body mass were measured by tetrapolar bioelectrical impedance analysis (InBody version 3.0; InBody, Seoul, Republic of Korea). Bioelectrical impedance analysis measures two parameters, fat and lean tissue, using empirically derived formulae, which were validated in earlier studies (17,18) and were found to correlate well with underwater weighing, except with extremely obese subjects. Smoking status was divided into three categories: current smokers, ex-smokers, and never smokers. Alcohol intake was assessed based on the frequency and quantity of the intake of beer, distilled spirits, and fermented wine during the previous 12 months. Alcohol intake, measured in in kcal of alcohol per week, was divided into the following two categories: moderate (<420 kcal/week) and heavy intake (≥420 kcal/week). Physical activity was classified into the following three categories: none, irregular (≤2 episodes/week), and regular (≥3 episodes/week) exercise. One episode of exercise was defined as exercising for at least 30 min.

After fasting overnight for 12 h, the plasma concentrations of glucose, total cholesterol, triglyceride, and HDL cholesterol were measured enzymatically using a 747 Chemistry Analyzer (Hitachi, Tokyo, Japan). The level of LDL cholesterol (in milligrams per deciliter) was calculated using the following equation (all in milligrams per deciliter): total cholesterol − HDL cholesterol − triglyceride/5 (19). The fasting plasma insulin concentrations were determined by a radioimmunoassay kit (Linco Research, St. Charles, MO). The glycosylated hemoglobin (A1C) level was measured by high-performance liquid chromatography (VARIANT II; Bio-Rad Laboratories, Hercules, CA). The hsCRP concentration was measured by immunoradiometric assay (ADVIA 1650; Bayer Diagnostics, Tarrytown, NY). Hepatic enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase, were measured using a Hitachi 747 Automated Analyzer.

### Definition of Hypertension and Antihypertensive Medications

Blood pressure was recorded three times between 7:00 A.M. and 9:00 A.M. after the subjects had been in a relaxed state for at least 10 min in a sitting position; there was a 5-min resting period between each measurement. Subjects were asked to refrain from smoking for 24 h and from consuming alcohol for 7 days before blood pressure was measured. Mercurial sphygmomanometers were used (CK-101; CHIN KOU Medical Instrument Co. Ltd., Taipei, Taiwan). The arithmetic mean value of the blood pressure readings was used to define

the blood pressure status (systolic blood pressure [SBP]/diastolic blood pressure [DBP]): <120/80 mmHg for the normal group; 120–139/80–89 mmHg for the prehypertension group; 140–159/90–99 mmHg for the stage 1 hypertension group; and ≥160/100 mmHg for the stage 2 hypertension group (based on the study by Joint National Committee 7 [20]). The higher category was used when a person's SBP and DBP belonged to different categories.

### Definition of Diabetes and Evaluation of IR and Pancreatic β-Cell Function

In the current study, we excluded patients with previous antidiabetic medication usage and those with newly detected diabetes. A 75-g oral glucose tolerance test (OGTT) was conducted to diagnose diabetes. Diabetes was defined as a fasting glucose concentration of ≥126 mg/dL or a postload glucose concentration of ≥200 mg/dL after the 75-g OGTT based on the World Health Organization criteria (21). Excluding the patients with known diabetes and subjects who had started to take antidiabetic medication since their previous visit, all of the remaining subjects underwent a 2-h 75-g OGTT at each follow-up visit, and the same standard definition was used to define new cases of diabetes.

To evaluate IR, a HOMA-IR index was produced using the following equation: fasting plasma insulin (in micro international units per milliliter) × fasting plasma glucose (in milligrams per deciliter)/405 (22). The insulinogenic index (IGI), which is an estimate of early insulin secretion, was calculated by dividing the increase in insulin during the first 60 min by the increase in glucose during the same period, as follows: 60–0 min insulin (in international units per milliliter)/60–0 min glucose (in millmoles per liter) (23).

### Statistical Analysis

All of the data were expressed as the mean and SD or as the number and percentage. The ALT, triglycerides, insulin, HOMA-IR index, IGI, and hsCRP values were highly skewed, so their values were normalized by logarithmic transformation before all analyses. Comparisons of the baseline variables with respect to the presence or absence of incident hypertension were analyzed using the Student *t* test for continuous variables. Categorical variables were analyzed using the $\chi^2$ test.

We calculated the hazard ratios (HRs) for incident diabetes using the following Cox proportional hazards models with potential confounding variables: model A, adjusted for age, sex, and center; model B, model A plus smoking status, exercise habits, alcohol intake, family history of diabetes, and waist circumference; model C, model B plus A1C level, HOMA-IR index, IGI, HDL cholesterol level, triglyceride level, ALT level, hsCRP level, and the use of lipid-lowering agent medication; and model D, model C plus fasting and postload 2-h glucose levels. The analyses were performed using SPSS Statistics for Windows version 18.0 (IBM, Armonk, NY). For all tests, $P < 0.05$ was considered to be a statistically significant difference.

## RESULTS

The anthropometric and biochemical characteristics of the subjects according to their blood pressure status are shown in Table 1. The mean age, BMI, waist circumference, and percentage of body fat increased with the baseline blood pressure categories. There were statistically significant trends for an increase in the A1C levels and the fasting and postload 2-h glucose concentrations with respect to the blood pressure categories. The fasting and postload 2-h insulin concentrations and HOMA-IR index also had similar increasing trends. The total cholesterol, triglyceride, and LDL cholesterol levels increased.

Of 8,359 subjects, diabetes developed in 1,195 (14.3%) during the 10-year follow-up period. The biannual incidence of diabetes is shown in Table 2. The probability of the development of diabetes increased with blood pressure in the study subjects compared with those with normal blood pressure ($P < 0.05$) (Fig. 1).

Using the Cox proportional hazards model, we also investigated the independent risk of high blood pressure for the development of diabetes during the follow-up period (Table 3). Participants with high blood pressure had a higher risk of diabetes in a model adjusted for age, sex, and center. Additional adjustments for smoking status, exercise habits, alcohol intake, family history of diabetes, and waist circumference also maintained a significant association between high blood pressure and incidence of diabetes. The HR for stage 2 hypertension was 2.53 (95% CI 2.07–3.10, $P < 0.01$). Further adjustments for A1C level, HOMA-IR index, IGI, HDL cholesterol level, triglyceride level, ALT level, hsCRP level, and the use of lipid-lowering agents attenuated the association slightly (HR for stage 2 hypertension 2.11 [95% CI 1.72–2.58], $P < 0.01$). Additional adjustment for fasting and postload 2-h glucose levels further attenuated the association (HR for stage 2 hypertension 1.60 [95% CI 1.30–1.96], $P < 0.01$). Older age, rural area, current smoking status, large waist circumference, a family history of diabetes, high A1C level, high fasting and postload 2-h glucose levels, low HDL cholesterol level, high triglycerides level, and high ALT level were all significantly associated with the incidence of diabetes in the final model (Supplementary Table 2). Use of lipid-lowering medications was not associated with the development of diabetes in the final Cox proportional hazards model.

## CONCLUSIONS

In this large prospective, community-based cohort study of Korean adults, we found that prehypertension, stage 1 hypertension, and stage 2 hypertension (SBP/DBP ≥160/100 mmHg or use of antihypertensive medication) were associated with 1.23-, 1.26-, and 1.60-fold higher risks of the development of diabetes after adjusting for a comprehensive panel of factors that are known to either affect glucose metabolism or be related to its subsequent risk, including adiposity and baseline glycemic measures.

There have been several studies (9–12) that investigated the association of blood pressure with diabetes. However, most of them were conducted with whites (11,13,14). A study (10) based on health check-up data with male employees of a Japanese gas company showed that high normal blood pressure and hypertension are associated with an increased risk of the development of diabetes: the relative risk was 1.39 in men with high blood pressure (95% CI 1.14–1.69) and 1.76 in men with hypertension (1.43–2.16). In the other study (24) with a health screening population in Taiwan, there was positive association between hypertension (SBP/DBP ≥140/90 mmHg or use antihypertensive therapy) and incident diabetes. But these studies were not

**Table 1—Baseline characteristics according to blood pressure status**

| | Normal ($n$ = 4,809) | Prehypertension ($n$ = 2,141) | Stage 1 hypertension ($n$ = 804) | Stage 2 hypertension ($n$ = 605) | $P$* |
|---|---|---|---|---|---|
| Age (years) | 49.2 ± 7.2 | 53.4 ± 8.7 | 54.0 ± 8.4 | 58.1 ± 7.9 | <0.001 |
| Male sex | 2,139 (44.5) | 1,135 (53.0) | 418 (52.0) | 238 (39.3) | <0.001 |
| SBP (mmHg) | 104.7 ± 9.0 | 124.4 ± 6.9 | 139.9 ± 9.8 | 142.6 ± 21.3 | <0.001 |
| DBP (mmHg) | 67.7 ± 7.6 | 80.1 ± 5.7 | 89.7 ± 5.8 | 88.4 ± 13.0 | <0.001 |
| BMI (kg/m$^2$) | 24.1 ± 2.9 | 24.8 ± 3.1 | 25.3 ± 3.2 | 25.8 ± 3.4 | <0.001 |
| Waist circumference | 80.3 ± 8.2 | 84.1 ± 8.4 | 85.6 ± 8.4 | 87.4 ± 8.7 | <0.001 |
| Body fat (%) | 26.1 ± 7.1 | 26.5 ± 7.1 | 27.6 ± 7.0 | 29.9 ± 7.0 | <0.001 |
| Center: Ansung | 1,973 (41.0) | 1,233 (57.6) | 486 (60.4) | 514 (85) | <0.001 |
| Family history of diabetes | 579 (12.0) | 188 (8.8) | 67 (8.3) | 38 (6.3) | <0.001 |
| Current smoker | 1,216 (25.3) | 572 (26.7) | 213 (26.5) | 102 (16.9) | <0.001 |
| Alcohol intake (≥420 kcal/week) | 943 (19.6) | 564 (26.3) | 235 (29.2) | 107 (17.7) | <0.001 |
| Current drinker | 2,425 (50.4) | 1,174 (54.8) | 438 (54.5) | 262 (43.3) | <0.001 |
| Regular exercise | 1,768 (36.8) | 681 (31.8) | 241 (30.0) | 169 (27.9) | <0.001 |
| AST (mg/dL) | 26.4 ± 14.9 | 28.3 ± 12.1 | 30.6 ± 25.0 | 27.8 ± 24.1 | <0.001 |
| ALT (mg/dL) | 24.5 ± 21.8 | 27.5 ± 17.8 | 30.4 ± 34.2 | 26.5 ± 19.7 | <0.001 |
| A1C (%) | 5.3 ± 0.4 | 5.4 ± 0.4 | 5.4 ± 0.4 | 5.5 ± 0.5 | <0.001 |
| A1C (mmol/mol) | 34.6 ± 4.1 | 35.6 ± 4.2 | 35.7 ± 4.2 | 36.2 ± 5.0 | <0.001 |
| Fasting glucose (mg/dL) | 83.9 ± 8.5 | 85.6 ± 9.4 | 86.8 ± 9.6 | 86.6 ± 10.0 | <0.001 |
| Postload 2-h glucose (mg/dL) | 116.4 ± 29.6 | 120.2 ± 32.7 | 123.1 ± 32.7 | 129.4 ± 32.7 | <0.001 |
| Fasting insulin (μIU/mL) | 7.3 ± 4.5 | 7.7 ± 5.1 | 8.1 ± 4.2 | 8.7 ± 4.1 | <0.001 |
| Postload 2-h insulin (μIU/mL) | 26.9 ± 24.7 | 28.4 ± 27.3 | 31.7 ± 29.2 | 35.5 ± 34.2 | <0.001 |
| HOMA-IR index | 1.51 ± 0.96 | 1.64 ± 1.10 | 1.76 ± 0.96 | 1.87 ± 0.95 | <0.001 |
| IGI | 13.2 ± 30.6 | 13.5 ± 34.5 | 11.5 ± 25.5 | 10.9 ± 15.8 | 0.422 |
| Total cholesterol (mg/dL) | 189.7 ± 33.4 | 195.4 ± 35.5 | 197.1 ± 36.7 | 197.8 ± 37.1 | <0.001 |
| Triglyceride (mg/dL) | 140.5 ± 91.8 | 161.9 ± 91.4 | 178.9 ± 116.6 | 175.1 ± 102.2 | <0.001 |
| HDL cholesterol (mg/dL) | 46.9 ± 10.7 | 46.0 ± 10.8 | 46.1 ± 10.9 | 46.2 ± 11.9 | 0.316 |
| LDL cholesterol (mg/dL) | 117.1 ± 32.1 | 119.6 ± 34.1 | 119.3 ± 38.3 | 120.4 ± 36.0 | 0.001 |
| hsCRP (mg/L) | 0.19 ± 0.36 | 0.24 ± 0.43 | 0.28 ± 0.80 | 0.30 ± 1.03 | <0.001 |

Data are reported as the mean ± SD or $n$ (%), unless otherwise indicated. HOMA-IR = fasting plasma insulin (μIU/mL) × fasting plasma glucose (mg/dL)/405; IGI = 60–0 min insulin (μIU/mL)/60–0 min glucose (mmol/L). AST, aspartate aminotransferase. *ANOVA was used for comparison between categories.

community-based cohort studies, and OGTTs were not performed in all subjects. Furthermore, important indices reflecting IR or β-cell function were also not included in their analyses. In this way, our study is perhaps one of the most comprehensive to address an association between blood pressure and incident diabetes.

Several mechanisms may underlie the association between high blood pressure and impaired glucose metabolism (25), although one must accept that a direct causal link has not been established. The altered endothelial permeability and diminished peripheral blood flow caused by high blood pressure may limit insulin delivery and promote IR in metabolically active tissues (26). The oxidative stress associated with high blood pressure is postulated to play a critical role in pancreatic β-cell dysfunction (27,28). Cytokines related to oxidative stress, such as interleukin-1, interleukin-6, and tumor necrosis factor-α, can potentially modify the glucose and lipid metabolism (29). Thus, the systemic vascular resistance

**Table 2—Incidence of diabetes during the follow-up study**

| Year range | Follow-up | $n$ | Diabetes cases ($n$) | Diabetes incidence rate (/2 years) |
|---|---|---|---|---|
| 2001–2002 | Baseline | 8,359 | | |
| 2003–2004 | 2 years | 7,218 | 300 | 4.2 |
| 2005–2006 | 4 years | 6,191 | 285 | 4.6 |
| 2007–2008 | 6 years | 5,679 | 243 | 4.3 |
| 2009–2010 | 8 years | 5,527 | 215 | 3.9 |
| 2011–2012 | 10 years | 5,417 | 101 | 1.9 |

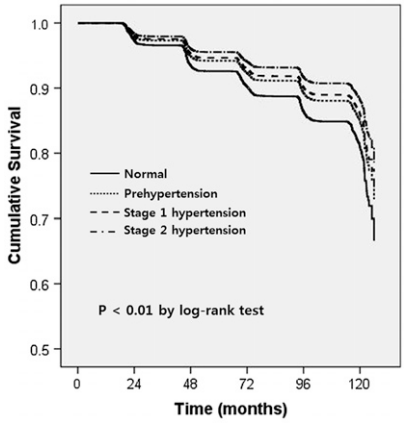


**Figure 1**—Diabetes-free survival over 10 years.

**Table 3—Association of blood pressure with the incidence of diabetes in the Cox proportional hazards models**

| | Normal* (*N* = 4,809) | Prehypertension† (*N* = 2,141) | | Stage 1 hypertension‡ (*N* = 804) | | Stage 2 hypertension§ (*N* = 605) | |
|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Model A | 1 | 1.48 (1.28–1.70) | <0.01 | 1.91 (1.58–2.29) | <0.01 | 2.99 (2.46–3.62) | <0.01 |
| Model B | 1 | 1.36 (1.17–1.57) | <0.01 | 1.59 (1.31–1.92) | <0.01 | 2.53 (2.07–3.10) | <0.01 |
| Model C | 1 | 1.33 (1.15–1.54) | <0.01 | 1.43 (1.17–1.74) | <0.01 | 2.11 (1.72–2.58) | <0.01 |
| Model D | 1 | 1.23 (1.06–1.42) | <0.01 | 1.26 (1.04–1.54) | <0.05 | 1.60 (1.30–1.96) | <0.01 |

Model A: adjusted for age, sex, and center; model B: adjusted for model A plus smoking status, exercise habits, alcohol intake, family history of diabetes, waist circumference; model C: adjusted for model B plus A1C level, HOMA-IR index, IGI, HDL cholesterol, triglyceride, ALT, hsCRP, and use of lipid-lowering agent medication; model D: adjusted for model C plus fasting glucose and postload 2-h glucose levels. *HR reference value; 533 events (11.1%). †364 events (17.0%). ‡142 events (17.7%). §156 events (25.8%).

that accompanies oxidative stress and inflammation leads to the activation of signaling molecules, such as nuclear factor-κB, and other mediators of stress-sensitive pathways, all of which could conceivably increase IR and lead to the development of diabetes (30).

Recent studies (31,32) have shown that statin treatment, particularly at high doses, increases the risk of diabetes. However, lipid-lowering medications were not associated with the incidence of diabetes in our study, though power was again limited in this context.

The current study has several strengths. First, the subjects were from a well-defined heterogeneous population with a single ethnic group, and all were 40–69 years of age (16,33). Second, the current study used dynamic indices for pancreatic β-cell function and IR, which are not easily captured in clinical practice. Third, the grade of blood pressures was used to investigate its diabetes risk. Finally, the analyses used in the current study were adjusted for various important factors that may affect glucose homeostasis, such as age, sex, waist circumference, smoking status, alcohol consumption, lipid profiles, inflammatory marker levels, liver enzyme levels, use of antihypertensive medication, use of lipid-lowering agent medication, A1C level, and fasting and postload 2-h glucose concentrations.

Our study also had limitations. First, anthropometric parameters such as BMI and waist circumference were used for obesity in this study. However, these parameters cannot distinguish between visceral and subcutaneous fat. Thus, the assessment of abdominal visceral fat using expensive imaging techniques would be required to better inform on the associations between regional adiposity and metabolic disorders (34). Second, the exact classes of lipid-lowering agents were not available in this study.

To the best of our knowledge, this is one of the largest community-based longitudinal cohort studies to report the risk of hypertension for the further occurrence of diabetes in an Asian population. Our findings support a strong and graded association between high blood pressure and incident diabetes in a Korean population, and further emphasize that a common link between these two disorders appears to be prevalent across many ethnic groups.

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**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** N.H.C. and S.L. had the idea for and designed the study; collected, analyzed, and interpreted the data; wrote the first draft and revised later drafts of the article; and obtained funding for the study. K.M.K., S.H.C., K.S.P., H.C.J., S.S.K., and N.S. analyzed and interpreted the data, performed the statistical analysis, revised the article, and obtained funding. S.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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