

Management of Elevated Cholesterol in the primary prevention Group of Adult Japanese (MEGA) Study assists the view that a fasting plasma glucose level ≥ 100 mg/dL increases cardiovascular risk

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ABSTRACT

Aims/Introduction: To evaluate the relationship between fasting plasma glucose (FPG) level and cardiovascular disease in patients with hypercholesterolemia, and to evaluate the effect of pravastatin on risk reduction in a *post-hoc* analysis of the large-scale Management of Elevated Cholesterol in the primary prevention Group of Adult Japanese (MEGA) Study.

Materials and Methods: A total of 7832 patients were randomized to diet alone or diet plus low-dose pravastatin (10–20 mg/day, average 8.3 mg during follow-up periods) and followed for >5 years. In this analysis, the relationship between FPG and risk of cardiovascular disease events over 5 years were studied in 6673 patients with recorded baseline FPG levels by using the multivariable Cox proportional hazards model with the restricted quadratic spline based on three knots for FPG quartiles.

Results: The spline curve showed an obvious sharp increased risk from a FPG of ≥ 100 mg/dL. The spline curve in the diet plus pravastatin group was consistently lower than in the diet group, regardless of the FPG level.

Conclusions: The risk of cardiovascular disease appears to increase when FPG is ≥ 100 mg/dL, with a sharp increased risk found above this level in patients with hypercholesterolemia. Statin treatment seems to be beneficial to reduce cardiovascular disease risk in this population. This trial was registered with ClinicalTrials.gov (no. NCT00211705). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00121.x, 2011)

KEY WORDS: Fasting plasma glucose, Cardiovascular risk, Randomized controlled trial

INTRODUCTION

Accumulated epidemiological evidence shows that diabetes is highly associated with an increased risk of cardiovascular disease (CVD)^{1–4}. Furthermore, diabetes continues to be detected as a strong risk factor for CVD in people with hypercholesterolemia; the magnitude of the risk in diabetic patients is 2.59-fold higher than in non-diabetic Caucasian patients with hypercholesterolemia⁵; similarly, CVD risk is threefold higher in hypercholesterolemic Japanese patients with abnormal fasting glucose⁶.

The relationship between high fasting plasma glucose (FPG) and CVD risk in hypercholesterolemia is frequently reported in various populations. For example, the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), and the Diabetes Epidemiology Collaborative analysis of Diagnostic criteria in Europe

(DECODE) Study showed that impaired fasting glucose (IFG) is associated with increased CVD risk in the general population^{7,8}. Furthermore, the multiethnic meta-analysis showed that high fasting blood glucose is an independent predictor of vascular outcomes among individuals without diabetes in the multiethnic cohort⁹. However, the level at which CVD risk begins to increase is not well documented.

The current study therefore examined the relation between FPG and the incidence of CVD in patients in the Management of Elevated Cholesterol in the primary prevention Group of Adult Japanese (MEGA) Study. In addition, the effect of pravastatin according to the FPG level was evaluated using the MEGA Study data^{10,11}.

METHODS

The details of the MEGA Study have been described elsewhere^{10,11}. A total of 8214 men and postmenopausal women aged 40–70 years with hypercholesterolemia whose total cholesterol levels ranged from 220 to 270 mg/dL without a history of

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coronary heart disease (CHD) and stroke, and who provided written informed consent, were randomly assigned to the US National Cholesterol Education Program step I diet¹² alone (diet alone group) or to the step I diet plus 10–20 mg/day of pravastatin (diet plus pravastatin group). The average dose during follow-up periods was 8.3 mg. Major exclusion criteria included familial hypercholesterolemia, a history of CVD, a current diagnosis of malignancy, and secondary hyperlipidemia. Patients were evaluated by their attending physicians at 1, 3 and 6 months after the start of follow up, and every 6 months thereafter. Health checks at each clinic visit included biochemical tests and assessment of patients' compliance with dosing. For each event, detailed information was obtained from physicians and evaluated by the blinded Endpoints Committee according to established criteria¹⁰. The lipid values were centrally measured at the same laboratory using methods standardized by the US Centers for Disease Control and Prevention (Atlanta, GA, USA). Low-density lipoprotein cholesterol (LDL-C) level was estimated by Friedewald's formula. Other laboratory values were measured in each institution. The main analysis was carried out for 7832 patients after excluding 382 patients according to the intention-to-treat principle. In the present subanalysis, the 6673 patients in the main analysis who had FPG values measured within 12 months from the start of follow-up were analyzed. The FPG values after the occurrence of a CVD event were not included in this analysis.

In the current study, the relationship between the average FPG values for the first 12 months and the occurrence of CVD events, including myocardial infarction, angina pectoris, cardiac and sudden death, a coronary revascularization procedure, stroke, transient ischemic attack, and arteriosclerosis obliterans, were investigated over a 5-year period. In addition, coronary events and stroke were assessed independently. Event rates during 5 years of follow up were compared for eight categories of

FPG levels (<72, 72–<81, 81–<90, 90–<99, 99–<108, 108–<117, 117–<126 and ≥126 mg/dL). The relationship between FPG and risk of cardiovascular events was evaluated using the multi-variable Cox proportional hazards model with the restricted quadratic spline¹³ based on three knots for FPG quartiles. Additionally, for the sensitivity analysis, the spline curves with two and four knots for FPG tertiles and quintiles, or three knots for 90, 100 and 110 mg/dL of FPG were compared. The multi-variable models were simultaneously adjusted by treatment arm, sex, age, baseline LDL-C, baseline high-density lipoprotein cholesterol (HDL-C), hypertension and smoking. Additionally, the spline curves were compared according to treatment arm.

RESULTS

Of the 7832 hypercholesterolemic patients in the intention-to-treat analysis, 6673 with recorded baseline FPG levels were analyzed in the present *post-hoc* analysis. Baseline characteristics are shown in Table 1: 68% were women; the HDL-C level was proportionally high (57.4 mg/dL); body mass index (BMI) was approximately 24 kg/m², which is relatively overweight compared with the general Japanese population¹⁴; nearly a quarter were hyperglycemic; and 42% had hypertension. Of the patients with hypertension, 12.4% were taking a renin–angiotensin system (RAS) inhibitor. A total of 231 CVD events, including 133 CHD and 87 stroke events, occurred during the 5-year follow up (Table 2). The analysis population included 88 diabetic patients (1.3%) with FPG < 99 mg/dL and 104 non-diabetic patients (1.6%) with FPG ≥ 126 mg/dL; 61.8% of patients with FPG ≥ 126 mg/dL and 8.1% of patients with FPG < 126 mg/dL took an oral hypoglycemic agent (data not shown).

The spline curve increased from the level of 100 mg/dL FPG in the restricted quadratic spline curves for CVD using the 25th percentile value of 92 mg/dL FPG as the reference (Figure 1a). Similar shapes were observed if using the other knot patterns

Table 1 | Baseline characteristics of the patients

Variable	Control	Pravastatin	All
Age (years)	58.4 ± 7.2	58.2 ± 7.2	58.3 ± 7.2
Women (%)	67.8	67.5	67.7
BMI (kg/m ²)	23.8 ± 3.1	23.8 ± 3.2	23.8 ± 3.1
Diabetes (%)	24.1	24.0	24.1
Hypertension (%)	42.0	41.6	41.8
Current smoking (%)	14.6	16.1	15.4
TC (mg/dL)	242.6 ± 12.2	242.6 ± 12.0	242.6 ± 12.1
LDL-C (mg/dL)	156.7 ± 17.3	156.9 ± 17.4	156.8 ± 17.3
HDL-C (mg/dL)	57.4 ± 14.9	57.4 ± 14.6	57.4 ± 14.7
TG (mg/dL)*	127.0 (40.5, 1322.5)	127.0 (34.5, 759.3)	127.0 (34.5, 1322.5)
FPG (mg/dL)	108.2 ± 30.6	108.7 ± 31.9	108.4 ± 31.3
Anti-diabetic agent (%)	13.7	13.9	13.8
RAS inhibitors (%)	12.8	12.0	12.4

BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; RAS, renin–angiotensin system.

*Mean ± SD. Triglyceride concentration was median (maximum, minimum). Diabetes and hypertension defined by physician diagnosis.

Table 2 | Incidence of cardiovascular disease in relation to fasting plasma glucose level*

FPG (mg/dL)	All		Diabetes		Non-diabetes	
	Events/patients	Incidence (/1000 py)	Events/patients	Incidence (/1000 py)	Events/patients	Incidence (/1000 py)
<72	1/23	9.7	0/1	0	1/22	9.7
72–<81	1/167	1.3	1/3	75.2	0/164	0
81–<90	23/1023	5.0	1/17	15.7	22/1006	4.9
90–<99	44/2008	4.9	5/67	17.7	39/1941	4.5
99–<108	44/1364	7.3	7/125	13.1	37/1239	6.7
108–<117	24/623	8.5	12/190	14.1	12/433	6.1
117–<126	16/368	9.7	9/210	9.5	7/158	10.1
≥126	78/1097	16.2	73/993	16.7	5/104	11.1
Total	231/6673	7.8	108/1606	15.3	123/5067	5.4

FPG, fasting plasma glucose; py, patient years.

*FPG data at 1 year were used. The incidences were over 5 years.

with four knots for FPG quintiles, or three knots for FPG 90, 100 and 110 mg/dL (Figure 1b–d). Similar curves were observed for CHD; however, a somewhat different pattern was observed for stroke (Figure 2). The spline curves for the diet plus pravastatin group were consistently lower than those for the diet alone group, regardless of the FPG level (Figure 3).

DISCUSSION

It is well known that the risk of CVD in established diabetes is extremely high, and that the association between elevated plasma glucose and atherosclerotic change appears to begin from the stage of impaired glucose tolerance (IGT)^{3,4}. In 2003, the American Diabetes Association (ADA) recommended not to carry out the oral glucose tolerance test (OGTT), but to use FPG criteria to identify persons with elevated plasma glucose. The ADA defined IFG as a FPG of 100–126 mg/dL or less, and diabetes as a FPG of >126 mg/dL¹⁵. The Japan Diabetes Society also established a FPG of 100 mg/dL as the cut-off for high normal glycemia¹⁶. In the ADA's 2010 standards of medical care in diabetes, the new criteria for the diagnosis of diabetes included glycated hemoglobin (HbA_{1c})¹⁷. Although the usefulness of the HbA_{1c} measurement was shown, no gold-standard single assay to define diabetes was identified¹⁷. Therefore, it is still meaningful to evaluate cardiovascular risk using the FPG level, because of the sparse data for the relationship between HbA_{1c} and cardiovascular risk.

In the present analysis, a significant increase in CVD risk was found for patients with FPG ≥ 126 mg/dL. An increased risk for CVD events was observed for patients with a FPG between 100 and 126 mg/dL, but because of the small sample size, this did not reach a statistically significant level. However, the spline curves showed that the risk for CVD began to increase from <100 mg/dL FPG. Furthermore, a similar trend was shown by the spline curves using several different knot patterns, which were carried out as a sensitivity analysis. The increase in CVD events that began at a level <100 mg/dL FPG is similar to the

data from the DECODE-Study⁸, which showed that CVD risk is increased slightly in relation to the increase in FPG level, regardless of the presence or absence of hypercholesterolemia. In addition, Levitan *et al.* clearly showed in a meta-analysis a linear increase in cardiovascular risk from fasting glucose of ≥100 mg/dL. These results show that patients with a FPG level between 100 and 110 mg/dL should be considered at risk for CVD, regardless of their background.

The risk of CHD also increased from a level <100 mg/dL FPG. For stroke, however, there was a V-shaped curve with the bottom at the 95–100 mg/dL FPG level. Some epidemiological data also showed a V-shaped or U-shaped curve for the relationship between ischemic stroke and fasting glucose, similar to the present results^{18,19}. Further investigation is warranted to determine the relationship between a low FPG level and the risk of stroke, because of the limited data from this analysis as a result of the small number of strokes in the MEGA Study.

Comparisons of CVD risk across categories of continuous values, such as levels of plasma glucose or blood pressure, typically assume a constant magnitude of risk within the category, and therefore might not define the actual risk. Furthermore, a change in the actual risk in relation to an increase or decrease in a level within a category might be obscured when observed events are smaller or larger than the events that will be observed as actual risk. For example, in the DECODE Study, the hazard ratio (HR) for CVD for a FPG of 135 mg/dL was estimated to be lower than the HR for the previous or next category of FPG⁸. This might be a biased interpretation resulting from the arbitrary setting of cut-points for each category, leading to different results. To address this issue, statistical models have been developed to more accurately estimate risk in relation to continuous values, such as plasma glucose. Well-established and accepted models include the moving average, the kernel methods²⁰ and the local likelihood estimation²¹. The restricted quadratic spline method is also an accepted smoothing model and it can be used in the Cox model²². The spline model has been

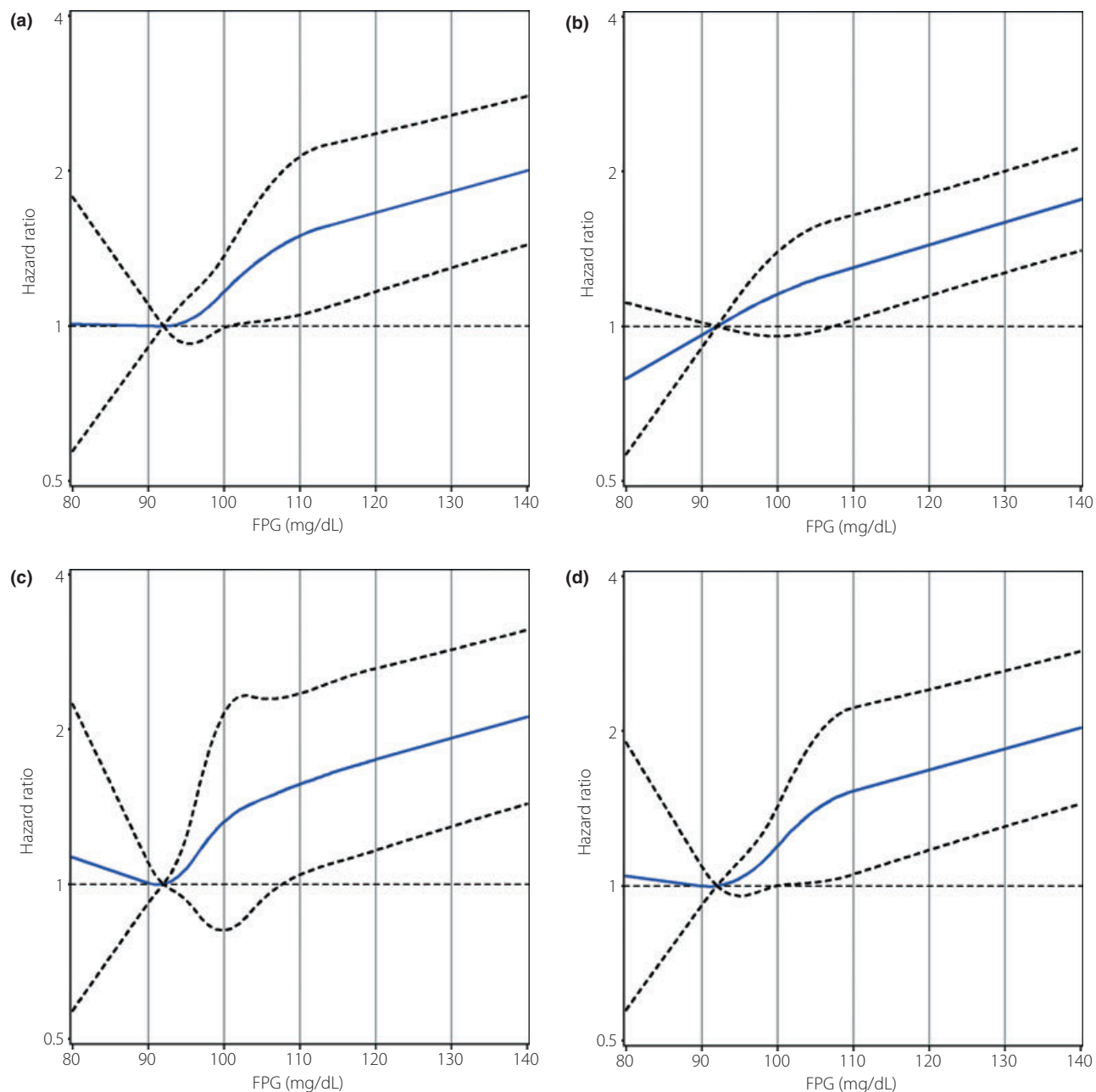


Figure 1 | (a) The restricted quadratic spline curve for cardiovascular disease according to levels of fasting plasma glucose (FPG), based on three knots for FPG quartiles. (b–d) Sensitivity analysis: (b) two knots by tertile points, (c) four knots by quintile points, and (d) three knots by FPG 90, 100 and 110 mg/dL. Dashed lines, corresponding 95% confidence intervals.

used to show the usefulness of percutaneous transluminal coronary angioplasty (PTCA) and the relationship between age and PTCA outcomes²³. The Hong Kong Diabetes Registry showed a relationship between CVD risk and a V-shaped curve with its bottom at the level of BMI 26 kg/m², HDL-C 1.15 mmol/L (44 mg/dL) and white blood cells 6.25/ μ L²⁴. Thus, the spline method allows the visual expression of the relationship between disease risk and continuous values. The results of the present analysis support the need to consider the importance of contin-

uous risk change when we develop risk assessment criteria or treatment guidelines.

Several clinical trials have shown an approximately 30% reduction in CVD risk with pravastatin for primary and secondary prevention, including the present MEGA Study^{25–28}. Furthermore, subgroup data and *post-hoc* analyses from these trials and a large meta-analysis have shown that a similar risk reduction can be expected with pravastatin in patients with diabetes^{29–33}. We recently reported a CVD risk reduction with

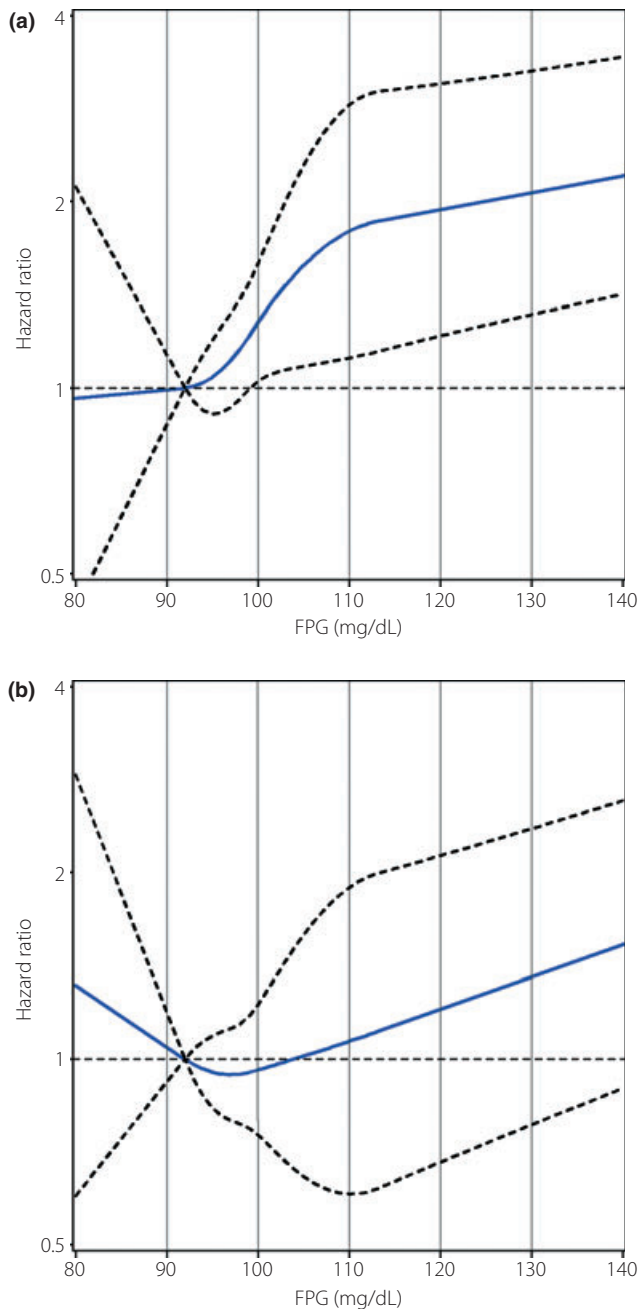


Figure 2 | The spline curves for (a) coronary heart disease and (b) stroke according to fasting plasma glucose (FPG). The knots are quartiles of the FPG in the whole group.

pravastatin in patients with abnormal fasting glucose in a *post-hoc* analysis of the present MEGA Study⁶. It showed the significant risk reduction of CVD by 32% by pravastatin treatment in the patients with abnormal fasting glucose. It also showed lower incidences of CVD by 29, 48 and 29% in the diabetes mellitus, impaired fasting glucose and non-diabetes mellitus groups, respectively. Although the 95% confidence interval in both treatment groups overlapped because of the small

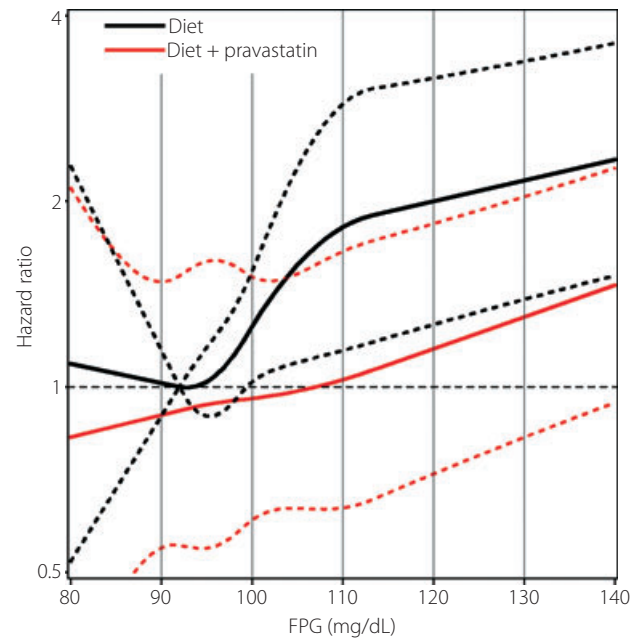


Figure 3 | The spline curves for cardiovascular disease according to levels of fasting plasma glucose (FPG) for each treatment arm. The knots are the quartiles of the FPG in the whole group. Black lines are the diet group and red lines are the diet plus pravastatin group (solid lines). Dashed lines, corresponding 95% confidence intervals.

number of events, the spline curves from the present analysis support the findings in our previous *post-hoc* analysis. However, further investigation, with more events, is required to confirm the relationship between FPG level and effect of a statin.

There are some limitations for interpreting the results of the present analysis. Most importantly, spline analysis was carried out for all patients, combining data from diabetic and non-diabetic patients to show the relationship between FPG and CVD. We believe that using data from a combined population was the best way to show the relationship between FPG and CVD risk in our analysis. Only a few diabetic patients and non-diabetic patients had FPG < 108 mg/dL and ≥ 126 mg/dL, respectively; only 8.1% of patients with FPG < 126 mg/dL were taking hypoglycemic agents; and all patients in the present study were on diet therapy according to the study protocol, irrespective of whether or not they had diabetes. Another important limitation was our interpretation of the shape of the spline curves by visual assessment, because smoothers such as splines are a useful tool to visually describe the relationship between exposures and outcomes³⁴. Therefore, the interpretation of the shape of the curves allows for some subjective interpretation. Another limitation was the small number of events, which might affect the accuracy of the spline method. Therefore, the analysis of the data for CHD alone or stroke alone and for age, sex, hypertension, HDL-C, LDL-C and treatment group was exploratory. The 12-month average of the FPG values was used as an explanatory factor to increase the size of the population to

produce more robust results. In the present study, patients in both groups received the diet intervention after entering the trial. Therefore, FPG possibly could have dropped in all groups after study entry. However, the FPG value was stable during, before and after starting the study, perhaps because of the fact that many patients might undertake basic lifestyle modification, because outpatients were the target population. Therefore, we believe the diet intervention did not significantly influence the results.

In conclusion, patients with hypercholesterolemia and a FPG level of ≥ 100 mg/dL should be carefully monitored, because of the sharply increased risk for CVD from this FPG level. Statin treatment might be effective to reduce CVD risk in this population. The beneficial effect of diet plus pravastatin treatment to reduce CVD risk in relation to FPG levels was visually confirmed in patients with hypercholesterolemia in the present analysis.

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