ORIGINAL ARTICLE

Glucose intolerance, insulin resistance and metabolic syndrome in patients with stable angina pectoris. Obesity predicts coronary atherosclerosis and dysglycemia

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KEY WORDS

coronary angiography, coronary artery disease, diabetes, insulin resistance, oral glucose tolerance test

ABSTRACT

INTRODUCTION Disturbances of glucose regulation and other metabolic disorders, as part of metabolic syndrome, are important risk factors for atherosclerosis. Abnormal glucose metabolism is commonly observed in patients with acute coronary syndrome. However, there is no consistent evidence for subjects with stable angina.

OBJECTIVES To investigate the prevalence of glucose metabolism in patients with stable coronary artery disease (CAD) documented angiographically and to assess correlations of metabolic profile and extent of atherosclerotic lesions.

PATIENTS AND METHODS 100 consecutive non-diabetic patients with stable CAD referred to coronary angiography were studied. Total cholesterol and its fractions, triglycerides, uric acid and fasting insulin levels were determined. Oral glucose tolerance test (OGTT) and then coronary angiography were performed. All patients were divided into groups according to glucometabolic and coronary status and insulin resistance. The sum of all lesions in coronary vessels was calculated for each patient (CAD score).

RESULTS After OGTT, 44% of patients presented disturbed glucose metabolism: 9% of patients had newly diagnosed diabetes and 35% patients were in the prediabetic state. There was no correlation between glycemic status and insulin resistance, and severity of coronary heart disease. Obesity, reflected by **body mass index, waist circumference and waist-to-hip ratio, was a major metabolic disorder** and independent predictor of the extent of coronary atherosclerosis and glucose intolerance.

CONCLUSIONS Abnormal glucose regulation is very common in patients with stable CAD. Only obesity was the independent predictor of coronary atherosclerosis and dysglycemia. Other metabolic risk factors are target for prevention and treatment.

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INTRODUCTION Cardiovascular diseases (CVD) are the major cause of death in adults and the elderly in the majority of developed and in many developing countries. In nearly all Europe, cardiovascular mortality represents about 40% of all deaths before the age of 74 years.[1] Risk factors, such as hypertension, atherogenic dyslipidemia, insulin resistance, glucose intolerance, abdominal obesity – as part of metabolic syndrome (MS) – play an important role in initiating and accelerating the complex process of atherosclerosis.[2] Constellation of interrelated risk factors of metabolic origin appear to directly promote the development of atherosclerotic CVD and type 2 diabetes.[3]

Diabetes mellitus (DM) and impaired glucose tolerance (IGT), a precursor stage of diabetes, are a strong risk factor for all manifestations of atherosclerotic vascular disease: coronary artery disease (CAD), cerebrovascular and peripheral vascular

TABLE 1 Clinical characteristics and laboratory results by glucose tolerance

Parameter	All individuals	Normal glucose tolerance	Prediabetic state	Diabetes
n (%)	100 (100)	56 (56)	35 (35)	9 (9)
Age (years)	60.7 ±9.2	60.0 ±9.2	60.3 ±9.3	66.9 ±7.3[a]
Female/Male	28/72	12/44	12/23	4/5
%	28/72	21.4/78.6	34.3/65.7	44.4/55.6
BMI (kg/m^2)	27.3 ±3.3	26.4 ±2.9[a]	28.4 ±3.6	28.6 ±2.9
WHR	0.96 ±0.08	0.95 ±0.07	0.96 ±0.08	0.93 ±0.1
Blood pressure RR>140/90 mm Hg (%)	60	51.7[a]	62.8	100
CAD score	315 ±171	322 ±192	291 ±128	366 ±180[b]
Drugs at admission (%)				
Acetylosalicylic acid	96	92.9	100	100
Statin	55	57.1	54.3	33.3[b]
ACE inhibitor	72	66.1[b]	80	77.8
β-blocker	76	69.6	82.9	88.9
Diuretic	22	25	13.3	44.5
Nitrates	63	64.3	68.6	33.3
LM stenosis (% of patients)	6	3.6	8.6	11.1
FPG (mmol/l)	4.91 ±0.68	4.73 ±0.55[c]	5.02 ±0.74[d]	5.72 ±0.64[c]
2-hPG (mmol/l)	7.53 ±2.23	6.01 ±1.06[c]	8.8 ±1.22[c]	12.07 ±1.0[c]
Lipid profile (mmol/l)				
total cholesterol	5.41 ±1.11	5.52 ±1.15	5.31 ±1.12	5.15 ±0.81
HDL cholesterol	1.36 ±0.34	1.37 ±0.31	1.41 ±0.39	1.11 ±0.17[a]
LDL cholesterol	3.77 ±1.06	3.89 ±1.1	3.62 ±1.06	3.57 ±0.86
triglycerides	1.9 ±0.79	1.84 ±0.74	1.88 ±0.88	2.32 ±0.73
Fasting insulinemia (μIU/ml)	5.83 ±2.55	5.52 ±2.49	6.07 ±2.45	6.82 ±3.21[b]
HOMA-IR	1.28 ±0.58	1.17 ±0.55	1.34 ±0.54	1.73 ±0.77[a]
Uric acid (μmol/l)	366.5 ±89.9	370.1 ±81.3	371.1 ±90.3	326.8 ±134.1

a $p < 0.05$
b not significant
c $p < 0.001$
d $p < 0.01$ vs. NGT group

Abbreviations: ACE – angiotensin converting enzyme, BMI – body mass index, CAD – coronary artery disease, FPG – fasting plasma glucose, HDL – high-density lipoprotein, HOMA-IR – homeostasis model assessment of insulin resistance, LDL – low-density lipoprotein, LM – left main artery, NGT – normal glucose tolerance, WHR – waist-to-hip ratio

disease.[4] Mortality among diabetic patients after myocardial infarction (MI) is 2- to 4-fold higher than in the non-diabetic group, and is predicted by age, previous heart failure and the severity of the glycometabolic state on admission.[5,6] Subjects with asymptomatic hyperglycemia (IGT or newly diagnosed non-insulin dependent DM) also tend to have an increased prevalence of coronary heart disease (CHD).[7] A 10-year biennial observation of the Framingham Study population showed that casual glucose levels below the threshold range for diabetes are independent predictors of CVD.[8] Non-diabetic degrees of fasting plasma glucose (FPG) and postprandial hyperglycemia are associated with CHD and that dysglycemia is a cardiovascular risk factor.[9] Abnormal glucose metabolism is frequently observed in patients with acute MI. However, there is no consistent evidence for subjects with stable angina. In the GAMI study, less than 35% of patients had normal glucose tolerance 3 months after MI.[10] The Euro Heart Survey on diabetes and the heart study demonstrated that normal glucose regulation is less common than abnormal in patients with CAD.[11] Other studies reported the prevalence of glucose disturbances from 43 to even 78% of patients with stable angina.[12-15] For more than 40 years there has been a controversy about the oral glucose tolerance test (OGTT), and now the discussion embraces the question of the best glucose level and method (OGTT vs. FPG) to predict an increased risk of future diabetes and CVD.[16] Most observations, assessing the cardiovascular risk due to glucose tolerance, are epidemiology studies. Few data are available on the relation between glucose intolerance, insulin resistance and other metabolic factors, and angiographic evidence of coronary atherosclerosis.[17-26]

The purpose of this study was to reveal the impaired glucose regulation, insulin resistance and other metabolic disorders, as part of MS, in patients with stable CHD, and to assess correlations of their metabolic profile and extent of atherosclerotic lesions.

TABLE 2 Clinical characteristics and laboratory results by coronary angiography

Parameter	Group 0	Group 1	Group 2	Group 3
n (%)	11	36	23	30
Age	64.9 ±11.8	58.8 ±8.4[a]	57.5 ±10.1[a]	64.0 ±7.2
Female/Male	7/4	11/25	3/20	7/23
%	63.6/36.4[b]	30.6/69.4	13/87	23.3/76.7
BMI (kg/m^2)	27.6 ±3.5	27.7±3.6	27.1 ±3.6	26.9 ±2.6
WHR	0.89 ±0.06[b]	0.95 ±0.08	0.97 ±0.07	0.97 ±0.08
Blood pressure RR>140/90 mmHg (%)	27.3	30.6	30.4	30
CAD score	148 ±45[c]	205 ±83	308 ±78	514 ±141
LM stenosis (%)	0	0	8.7	13.3
FPG (mmol/l)	5.04 ±0.61	4.88±0.75	4.95 ±67	4.9 ±0.67
2-hPG (mmol/l)	8.24 ±2.5	7.58±2.23	7.38 ±1.99	7.34 ±2.36
Lipid profile (mmol/l)				
total cholesterol	5.0 ±0.94	5.48 ±1.13	5.48 ±1.15	5.42 ±1.15
HDL cholesterol	1.62 ±0.47[b]	1.34 ±0.3	1.31 ±0.3	1.32 ±0.34
LDL cholesterol	3.22 ±0.82	3.89 ±1.07	3.87 ±1.13	3.75 ±1.07
triglycerides	1.35 ±0.66[d]	2.0 ±0.77	2.2 ±0.95[e]	1.75 ±0.62
Fasting insulinemia (µIU/ml)	5.32 ±1.7	6.18 ±3.04	5.9 ±2.61	5.54 ±2.13
HOMA-IR	1.19 ±0.4	1.36 ±0.68	1.29 ±0.63	1.2 ±0.48
Uric acid (µmol/l)	287.8 ±64.2[b]	394.1 ±95.9	367.6 ±79.8	361 ±83.1

a $p < 0.05$ – vs. group 1 and 3
b $p < 0.05$ – vs. other groups
c not significant – vs. group 1
d $p < 0.01$ – vs. other group
e $p < 0.05$ – vs. group 3

Abbreviations – see **TABLE 1**

PATIENTS AND METHODS

A total of 100 consecutive patients (male and female) with stable angina referred to elective coronary angiography at the Department of Cardiology in a Provincial Specjalist Hospital in Bytom from May to December 2005 were studied. All subjects gave their informed consent, and the study protocol was approved by the Bioethical Committee of Silesian Physicians Board in Katowice.

Patients with: acute coronary syndrome in the last 3 months, previously diagnosed DM or receiving hypoglycemic treatment, and with admission plasma glucose >200 mg/dl were excluded from the study. The other exclusion criteria were: severe heart failure in NYHA III or IV class; hepatic, renal, endocrine or lung dysfunction. Demographic variables including: age, weight, height, waist and hip circumferences, and other information concerning patient's medical history, smoking status and concomitant medications, were recorded.

After an overnight fast blood samples were drawn for measurement of fasting glucose, fasting insulin, total cholesterol and its fractions, triglycerides and uric acid. A 75-g load of glucose was then administered and blood samples were drawn at 120 min. to determine postprandial glucose level (2h-PG). The plasma insulin concentration was measured by standard radioimmunoassay (BioSource Inc.) and other biochemical parameters were determined with the standard laboratory method using commercial kits (Randox Lab). Insulin resistance was estimated by a homeostasis model assessment of insulin resistance (HOMA-IR).[27]

Coronary angiography was performed by the Judkins or Sones technique in multiple standard projections. Internal luminal narrowing in one major epicardial artery (left anterior descending, circumflex and right coronary artery) or its major branches, greater than 70% was considered significant, except for left main artery (LM) – significant stenosis greater than 50%. Angiographic measurements were performed using computer-assisted quantitative analysis (QCA) and the data were assessed by an experienced cardiologist, who was blind to the glucose tolerance status. Patients were classified according to the number of stenosed major vessels. The sum of all lesions in coronary vessels was calculated for each patient (CAD score).[18]

Statistical analysis All the data are expressed as the mean ± standard deviation or n (%). Differences were examined by Student t-test or Mann-Whitney U-test for continuous variables. Percentages of categorical variables were tested by χ^2 analysis with Yate's correction. The relationship between the metabolic parameters and glucose regulation abnormalities, a number of involved vessels and insulin resistance were assessed by Spearman's rank correlation and multiple

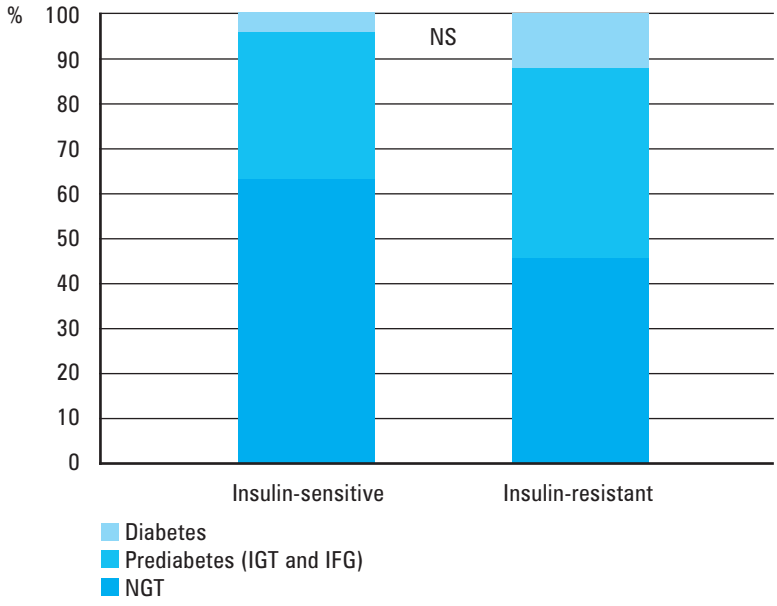

FIGURE 1 Effect of insulin resistance on glucose metabolism disorders
Abbreviations: IFG – impaired fasting glucose, IGT – impaired glucose tolerance, NGT – normal glucose tolerance, NS – not significant

stepwise regression. Statistical significance was defined as a p value <0.05.

RESULTS According to result of the OGTT patients were divided into 3 groups: normal glucose tolerance group (NGT) (FPG <5.6 mmol/l and 2-hPG <7.8 mmol/l) – 56 patients; prediabetes group: impaired fasting glucose (IFG) (FPG 5.6–6.9 mmol/l) – 3 patients, IGT (FPG <7.0 mmol/l and 2-hPG 7.8–11.0 mmol/l) – 32 patients; DM group (FPG ≥7.0 mmol/l or 2-hPG ≥11.0 mmol/l) – 9 patients.

Clinical characteristics and laboratory results are shown in TABLE 1. There were no differences in pharmacological treatment between groups according to glucose tolerance, coronarography and insulin resistance. Patients with newly diagnosed diabetes were significantly older, and patients with NGT had lower body mass index (BMI) and blood pressure. In all groups mean total and low-density lipoprotein (LDL) cholesterol were above current norms; high-density lipoprotein (HDL) cholesterol was significantly lower in diabetes group and those patients were more insulin resistant expressed by HOMA-IR. FPG positively correlated with body mass ($R = 0.3$, $p < 0.01$), BMI ($R = 0.26$, $p < 0.01$), waist and hip circumference ($R = 0.2$, $p < 0.05$). We also observed a significant correlation between 2-hPG, and age ($R = 0.23$, $p < 0.05$) and BMI ($R = 0.23$, $p < 0.01$). The multiple stepwise regression analysis revealed that only waist circumference ($\beta = 0.27$, $R^2 = 0.1$, $p < 0.01$) and HOMA-IR ($\beta = 2.07$, $R^2 = 0.3$, $p < 0.01$) were independently associated with degree of glucose disregulation.

Based on results of coronary angiography, patients were divided into 4 groups: group 0 – no significant stenosis; group 1 – 1-vessel disease; group 2 – 2-vessel disease; group 3 – 3- or multivessel disease (TABLE 2). Patients with 1- and 2-vessel disease were significantly younger, in group 0 there were more women than in other groups. Higher HDL cholesterol and lower values of triglycerides and uric acid were observed by patients with no significant stenosis. Both FPG and 2-hPG, and fasting plasma insulin and HOMA-IR were not statistically different among groups – glucose metabolism disturbances and insulin resistance did not predict coronary atherosclerosis. Correlation analysis did not show any association between the sum of lesions in coronary arteries and metabolic parameters (FPG, 2-hPG, cholesterol and its fractions, uric acid, fasting insulin and HOMA-IR). The multiple stepwise regression analysis suggested that factors independently associated with number of involved vessel were only waist-to-hip ratio (WHR) ($\beta = 2.27$, $R^2 = 0.06$, $p < 0.05$) and waist circumference ($\beta = 3.72$, $R^2 = 0.14$, $p < 0.05$) and BMI ($\beta = 0.63$, $R^2 = 0.11$, $p < 0.05$).

After determination of fasting insulin level, the insulin resistance index HOMA-IR was calculated. Patients with HOMA-IR in the 4th quartile were assessed as insulin resistant and compared to patients with HOMA-IR in the 1st quartile (insulin sensitive). Insulin resistant patients had higher BMI and WHR, and more atherogenic profile (high levels of triglycerides and low HDL cholesterol). Insulin resistance was not related to the severity of coronary atherosclerosis nor glucose disturbances (FIGURE 1 and FIGURE 2).

Analysis of correlations showed significant associations between insulin levels and HOMA-IR as well as weight, BMI, waist and WHR ($p < 0.01$), HDL cholesterol and triglycerides ($p < 0.05$). In multiple stepwise regression analysis the association of insulin and HOMA-IR with these parameters was not significant.

DISCUSSION The current study indicates that glucose intolerance is an important diagnostic and therapeutic problem. Patients, both women and men, with stable CAD documented angiographically, presented an abnormal glucose regulation in 44%, and this finding is more meaningful than those described in the latest large trials, like the EUROASPIRE I and II.[34] In the current study, compared with the results presented in other reports[12-15], the prevalence of glucose metabolism disturbances was significantly higher than in the general population[28]. According to Wascher et al., impaired glucose metabolism is present even in 78% of CAD patients without previously known diabetes.[13] Those findings show that these subjects are especially exposed to glucose intolerance, and cardiovascular risk factors with concomitant metabolic disorders comprised in metabolic syndrome, may affect the development of glucose intolerance.[30]

Many studies demonstrated substantial discrepancies between the classification of the diabetes category based either on fasting or the 2-h glucose level, and differences in estimation of cardiovascular risk related to dysglycemia (graded relation or threshold effect).[31-33]

Current criteria for NGT seem to be not suitable for patients with CHD. According to Bartnik et al., when the glucometabolic classification

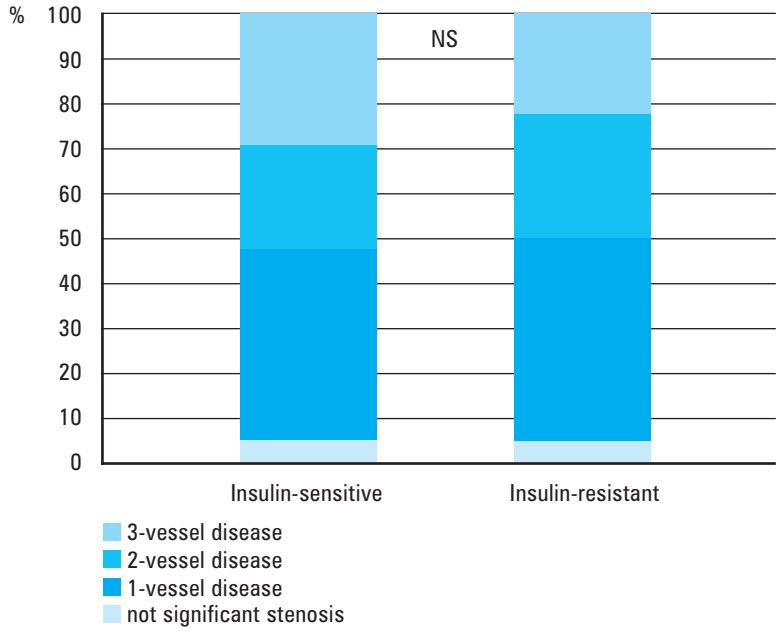

FIGURE 2 Effect of insulin resistance on coronary atherosclerosis Abbreviations: see FIGURE 1

was assessed only by fasting glucose, the percentage of patients with dysglicemia was lower than when OGTT was considered.[11] Lankish et al. postulate considering OGTT for all patients with FPG greater than 4.9 mmol/l – otherwise about 80% of the patients with undiagnosed diabetes would be missed.[15] In the current study only 14% of patients presented elevated FPG, and OGGT fully disclosed glucose disturbances.

According to Qiao et al., the 2-h post-load glucose in OGTT was a stronger predictor of the risk of future CVD events than FPG.[33] And even the most recent change in diagnostic criteria, in which the threshold for IFG was lowered to 5.55 mmol/l, still misses the increased CHD risk associated with IGT, as IGT can be undetected.[29]

A dominant disturbance in the current study was IGT. It is a more sensitive indicator for predicting progression to diabetes than IFG.[35] Data by Hu et al. suggest that cardiovascular risk begins to increase long before overt diabetes develops and it may dominate in subjects with IGT in the prediabetic group.[36] This evidence supports the "ticking clock" hypothesis by Haffner – prediabetic subjects have the cardiovascular risk pattern, which may be present for many years and may contribute to the risk of CVD as much as the duration of overt diabetes.[37]

Both conditions (diabetes and large-vessel atherosclerosis) have common genetic and environmental antecedents – they spring from a "common soil".[38] It is important to develop a sensitive screening strategy for diabetes and pre-diabetes category, and OGTT is a feasible tool to disclose the glucometabolic status and should be diagnostic routine and integral part of the care of patients with clinically established CAD (recommendation of ESC and EASD 2007).[44]

In our study glucose tolerance was predicted by obesity (reflected by weight, BMI, WHR and waist circumference), age and insulin resistance. Similarly, BMI and WHR, independently of other parameters, determined coronary atherosclerosis. In a group with not significant stenosis in coronary arteries, WHR was significantly lower than in other groups, with comparable BMI, which strongly correlated with dysglicemia. Data from long-term observations of Framingham population and other studies suggest that obesity is a risk factor for CHD, independently of standard risk factors including: atherogenic dyslipidemia, insulin resistance, a proinflammatory and prothrombotic state.[39] Growing clinical evidence suggests that abdominal obesity, assessed by waist circumference or WHR, is a stronger predictor of adverse cardiovascular outcome than BMI, and it increases the risk of developing CHD or the MS, respectively, at each level of BMI.[40] Accumulation of intra-abdominal fat, which promotes increased secretion of a range of metabolites and of biologically active substances (glycerol, free fatty acids, inflammatory mediators), is better revealed by waist circumference or WHR than BMI, which depends on skeletal muscles mass rather than adipose tissue.[41] Otherwise, McGill et al. reported a strong relationship of obesity, defined by BMI, and accelerated coronary atherosclerosis in adolescent and young adult men.[42]

The latest data suggest that even adolescent overweight will increase rates of CHD among future young and middle-aged adults, resulting in substantial morbidity and mortality. And aggressive treatment with now available therapies to reverse obesity-related risk factors could mitigate, though not eliminate, the increase in CHD events.[43]

In our study, we did not show the effect of glucose intolerance on severity of CAD. Neither fasting nor the 2h-postload glucose level correlated with the number of affected coronary vessels or the extent of atherosclerotic lesions. No correlations between the cholesterol level and its fraction, insulin and HOMA-IR, and the severity of CHD were observed, only in group 0 (patients with no significant stenosis) significantly lower uric acid and triglycerides and higher HDL-cholesterol levels were examined. Similarly, the study of Seiback et al. did not demonstrate differences in coronary angiography findings between subgroups according to glucose tolerance and insulin levels.[22] In turn, Katoka et al. reported that diffuse vessel narrowing develop not only in the diabetes groups but also in patients with IGT, and that morphological lesions are strongly associated with postprandial hyperglycemia.[24]

The study by Sasso et al. revealed that even in normoglycemic patients the glucose parameters, especially postload glycemia and glycated hemoglobin, are not equally distributed but are significantly higher in those with more severe CAD.[21]

We used 2 scoring systems: the number of significantly stenosed vessels and CAD score. Many studies exploring the relation between metabolic parameters, and the extent and severity of CAD, classify patients only according to the number of affected arteries (1-, 2- or 3-vessel disease).

A number of "jeopardy scores" were found to quantitate the plaque burden and predict morbidity and mortality in patients with CAD (Califf score, Gensini score, Candell-Riera score). However, the differences between these systems are more related to distinct terminology than possibility to obtain an unique prognostic value.[45] Only intravascular ultrasound (IVUS), especially with option virtual histology (IVUS-VH) represents a technique to explore the vessel walls and to observe its histological properties. The IVUS-VH is the first diagnostic tool that allows direct assessment of the composition of the atherosclerotic plaque burden and lesion site remodeling in the coronary artery.[46]

The knowledge of existing disturbances of glucose metabolism should favorably affect the prognosis for patients with CHD. Glucose control alone is not sufficient to significantly reduce macrovascular disease. Additional aggressive treatment for hypertension, dyslipidemia, obesity and smoking habits would be required to reduce rates of CHD.

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