many of these studies excluded diabetic patients from their study populations (9,22–24). Diabetic patients are known to be at greater risk for CVD than nondiabetic subjects (21), and it has been suggested that MetS is responsible for the increased prevalence of coronary heart disease (CHD) seen in diabetic patients (20). Therefore, it is important to evaluate the predictive value of MetS on incident CVD in diabetic patients in long-term, prospective studies. To the best of our knowledge, there have been four cohort studies specifically targeting diabetic patients to determine the relative risk of MetS on the incidence of CVD (12,15,16) and mortality due to CVD (17). Although these studies involved only white European subjects and used only the WHO definition of MetS, most of them (12,15,16) demonstrated, as expected, that the presence of MetS is associated with at least a severalfold increase in the risk of CVD. The above findings notwithstanding, it remains unclear *1*) whether such predictive values of MetS are also applicable to diabetic patients of other ethnicities, *2*) which features of MetS are the best predictors of CVD and should become the critical therapeutic targets for the optimal management of CVD risk in diabetic patients (28), and *3*) whether the commonly used NCEP definition of MetS (3) possesses the same predictive value for CVD as the WHO definition in diabetic patients.

The incidence of CVD in Asian subjects is known to be much less than in white subjects in general (29) and in diabetic populations in particular (30). In addition, the degree of obesity is very different between white and Asian diabetic patients (31,32), and the impact of obesity on CHD risk is known to be entirely different between whites and Asians (33,34). These differences could affect the apparent clinical significance of MetS (35,36), so that it is questionable whether the overall concept of MetS itself and the diagnosis of MetS under the present definitions based on data from mostly European and American patients are applicable to the evaluation of CVD risk in Asian diabetic patients. Therefore, in this long-term, prospective study of Japanese diabetic patients with no history of CVD, we determined the prevalence of MetS and analyzed its individual features and predictive value for incident CVD using the two most widely used definitions of MetS (2,3). Such comparisons are helpful in possibly establishing a global definition of MetS (10,37) and are also warranted to determine if there is heterogeneity in the power of individual MetS components to predict CVD (28).

RESEARCH DESIGN AND METHODS

— The Japan Diabetes Complications Study (JDCS) is a nationwide, multicenter, prospective study of type 2 diabetic patients (38). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels >6.5% were recruited and registered. The eligibility criteria for participating patients has been previously described (38). The duration of the study was 8 years. Of the 2,205 patients, the present study focused on 1,424 patients (771 men and 653 women) who had a complete set of data, including those parameters necessary to satisfy the WHO (2) and NCEP (3) criteria for the definition of MetS at baseline. The JDCS protocol, which is in accordance with the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutes and was undertaken in accordance with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare. All of the study participants gave written informed consent.

Both the WHO (2) and the NCEP (3) definitions were used to diagnose MetS in this study. However, because the original cut-off for abdominal obesity in the NCEP definition (waist circumference ≥102 cm for men and ≥89 cm for women) has previously been shown to be inappropriate for Asian populations (35,37) and the number of subjects who met these criteria was extremely low, the cut-off limit was adjusted according to the criteria proposed by the Japan Society for the Study of Obesity (≥85 cm for men or ≥90 cm for women), which were based on the risk of obesity-related disorders in a Japanese population (39). The WHO criteria for obesity were adopted because the waist-to-hip ratio (WHR) was used rather than waist circumference. The criteria used for analysis in this study are shown in Table 3. Because all of the study subjects were diabetic, those who fulfilled two or more of criteria 1a, 2a, 5, or 6 were classified as having WHO-MetS and those who fulfilled two or more of criteria 1b, 2b, 3, or 4 were diagnosed as having NCEP-MetS, using a modified NCEP definition (Table 3). For comparisons with other traditional risk factors for CVD, we also evaluated high LDL cholesterol levels, cigarette smoking, and excessive alcohol intake (40). Medication use, including agents for hypertension and hyperlipidemia, were not considered when diagnosing MetS in this study.

Waist and hip circumferences were measured at the umbilicus and trochanter level, respectively. A baseline dietary survey, comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information regarding cigarette smoking was collected using a standardized questionnaire. All laboratory tests were undertaken using the standard methods of each of the participating institutes, apart from the HbA_{1c} assays, which used a common standard, with 5.8% as the upper normal limit. Plasma LDL cholesterol was calculated using Friedewald's equation, except for triglyceride levels >400 mg/dl, in which case the LDL cholesterol data were treated as "missing." To estimate insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was used (41). Plasma insulin levels and the HOMA-IR were not evaluated in patients treated with insulin.

Patients were assessed for CHD and stroke at baseline and yearly thereafter. In all subjects, a 12-lead electrocardiogram (ECG) was recorded at each assessment. Fatal and nonfatal CHD and stroke events identified during follow-up were certified by at least two members of the experts' committee who were masked as to risk factor status and the other member's diagnosis. With regard to CHD, myocardial infarction was defined according to the WHO Monitoring of Trends and Determinants in Cardiovascular Disease criteria (42) and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by using nitroglycerine, as validated by exercise-positive ECG and/or angiography. Stroke events were defined as a constellation of focal or global neurological deficits of sudden or rapid onset and for which there was no apparent cause other than a vascular accident, as determined by a detailed history, a neurological examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were

classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (43). No cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were included. Only "first-ever" CHD or stroke events during the study period were counted for the analysis; if a patient had both CHD and stroke events, each event was counted separately.

Data are presented as means ± SD or as a proportion, unless otherwise specified. To compare the distributions of baseline characteristics between groups, Wilcoxon's rank-sum test or Fisher's exact test was used. Incidence rates in the two groups were assessed by a score test under the Poisson assumption. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI) of MetS risk factors with CHD, stroke, or both. Statistical analyses were performed separately by sex. The SAS software package (Version 8.0, Cary, NC) was used for all analyses. $P < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics and prevalence of the metabolic syndrome

The baseline characteristics of the study subjects are shown in Table 1. In all, 51% of male and 53% of female subjects met WHO criteria for MetS, whereas 45% of male and 38% of female subjects met NCEP criteria for MetS. Plasma insulin levels and HOMA-IR were significantly higher in patients with MetS (both definitions) than in those without MetS; however, there were no significant differences in HbA_{1c} or the frequency of oral hypoglycemic agent use. Insulin usage was significantly lower in women with MetS by either definition and in men with NCEP-MetS. Blood pressure and serum triglycerides were significantly higher and HDL cholesterol was significantly lower in MetS patients, despite the fact that the use of medications for both hypertension and hyperlipidemia was much more common than in patients without MetS. Daily energy intake did not differ between patients with and without MetS (data not shown).

Incidence of cardiovascular disease during follow-up

During the 8-year study period, the total number of CVD events was 117, comprised of 62 CHD and 59 stroke events. The combined incidence (per 1,000 patient-years) of CHD and/or stroke was significantly greater in patients with MetS (except in female patients with NCEP-MetS) than in those without MetS (Table 2).

Hazard ratios of the metabolic syndrome and its individual components for coronary heart disease and stroke

HRs were calculated to determine which definition of MetS was the better predictor of CVD and which of the individual MetS components (or other classic risk factors) could most efficiently predict CVD events in our subjects (Table 3). In male patients, WHO-MetS was not significantly associated with an increased risk for either CHD or stroke separately, but was associated with the combination of both (HR = 1.6). Triglyceride, LDL cholesterol (both for CHD), and blood pressure (≥140/90 mmHg) levels (for stroke) showed higher HRs. NCEP-MetS was a significant predictor of CHD in male patients, although its HR (1.9) was lower than that for triglycerides (2.9) or LDL cholesterol (2.1). Thus, neither definition of MetS was a substantially better predictor of CVD than the component parts in male patients. In contrast, in the female patients, WHO-MetS was a significant and strong predictor of CHD (HR = 2.8), stroke (HR = 3.7), and both CHD and stroke (HR = 3.2). In female patients, none of the individual elements nor the other classic risk factors showed significant increases in HRs, with the exception of hypertension (≥140/90 mmHg) for stroke, although its HR (2.4) was still lower than that for WHO-MetS. NCEP-MetS was not a significant risk factor for CHD or stroke in female patients (Table 3).

To examine the clustering effects of the individual components of MetS, the association between CVD risk and the number of MetS components fulfilled (other than diabetes) was analyzed (Table 3). Increasing the cut-off component number for the diagnosis of NCEP-MetS from ≥2 to ≥3 in male subjects did not dramatically improve the HR but did greatly reduce the number of patients diagnosed as having MetS, from 45 to 14.5% (Table 3). In female patients, changing the diagnostic cut-off component numbers was not particularly beneficial in improving the prognostic value of WHO-MetS (Table 3).

CONCLUSIONS — The prevalence of MetS in our diabetic patients who were free from CVD was not as high as that reported in previous studies that included patients with previous CVD (12–20) but was nevertheless relatively high (38–53%). Although we did not have age-matched nondiabetic control subjects, the prevalence of MetS was much higher than that reported in Japanese general population workers, namely 19.5% in men and 7.9% in women (33). Hypertension and dyslipidemia are much more common in diabetic patients than in nondiabetic subjects (21), and it has been speculated that the features of MetS more easily aggregate, even in the absence of current or previous CVD, leading to the observed increase in the prevalence of MetS. On the other hand, the prevalence of NCEP-MetS in the U.S. general population age 50 years and older is 44% (20), which is relatively close to that in our Japanese diabetic patients. However, even in the U.S. (excluding Asian Americans), the prevalence of MetS in those who have a BMI range equivalent to that of Japanese subjects is not >10% (44). This implies that in the U.S., obesity has a potent impact on the prevalence of MetS, as has also been shown in a recent study (45). This is in contrast to findings in Japan, where diabetes rather than obesity may have the greater influence on the prevalence of MetS, as Japanese diabetic patients are not obese by comparison with white diabetic patients or nondiabetic Japanese subjects (31,32).

The clinical importance of MetS is related to its putative impact on CVD morbidity and mortality. Among Italian patients with type 2 diabetes, the risk for CVD was 4.9 (CI 1.2–20.7) times higher in patients with WHO-MetS than in those without it (16), which was a higher rate than that seen in our male (1.6 [CI 1.0–2.6] times) and female (3.2 [CI 1.6–6.5] times) patients. These results suggest that the clinical impact of MetS on diabetic patients varies by ethnic group. Comparing cardiovascular risk factors in our Japanese patients to those in patients in the U.K. Prospective Diabetes Study (UKPDS) (46,47), hypertension is a common

Table 1—*Baseline characteristics of study subjects, grouped by metabolic syndrome status*

	Total	WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
		Without	With	*P*	Without	With	*P*
n							
Men	771	376 (48.8)	395 (51.2)	—	424 (55.0)	347 (45.0)	—
Women	653	310 (47.4)	343 (52.6)	—	405 (62.0)	248 (38.0)	—
Age (years)							
Men	58.2 ± 7.4	57.4 ± 7.6	58.9 ± 7.2	0.01	58.0 ± 7.6	58.4 ± 7.2	0.50
Women	58.7 ± 7.4	57.9 ± 7.7	59.5 ± 7.0	0.01	58.4 ± 7.4	59.4 ± 7.2	0.11
Diabetes duration (years)							
Men	10.9 ± 7.6	11.0 ± 7.6	10.9 ± 7.6	0.66	11.5 ± 7.8	10.2 ± 7.4	0.01
Women	10.1 ± 6.7	10.7 ± 7.3	9.5 ± 6.0	0.10	10.6 ± 7.0	9.4 ± 6.0	0.07
BMI (kg/m^2)							
Men	22.9 ± 2.6	22.0 ± 2.4	23.7 ± 2.6	<0.01	21.8 ± 2.3	24.2 ± 2.4	<0.01
Women	23.4 ± 3.3	22.3 ± 3.0	24.3 ± 3.3	<0.01	22.6 ± 3.1	24.6 ± 3.3	<0.01
Waist circumference (cm)							
Men	82.3 ± 7.7	79.0 ± 7.1	85.3 ± 7.0	<0.01	78.4 ± 6.4	87.0 ± 6.5	<0.01
Women	76.5 ± 9.8	72.4 ± 8.3	80.1 ± 9.7	<0.01	74.1 ± 8.6	80.4 ± 10.4	<0.01
Waist-to-hip ratio							
Men	0.89 ± 0.07	0.86 ± 0.05	0.92 ± 0.06	<0.01	0.87 ± 0.06	0.92 ± 0.06	<0.01
Women	0.83 ± 0.08	0.80 ± 0.06	0.86 ± 0.07	<0.01	0.82 ± 0.07	0.86 ± 0.08	<0.01
Blood pressure (mmHg)							
Men	132 ± 16/78 ± 10	124 ± 13/74 ± 9	139 ± 15/81 ± 10	<0.01	127 ± 16/75 ± 9	137 ± 15/81 ± 9	<0.01
Women	132 ± 17/76 ± 10	124 ± 13/73 ± 9	139 ± 16/79 ± 11	<0.01	128 ± 17/74 ± 10	138 ± 14/80 ± 10	<0.01
HbA_{1c} (%)							
Men	7.61 ± 1.36	7.53 ± 1.42	7.67 ± 1.30	0.05	7.54 ± 1.36	7.68 ± 1.36	0.18
Women	8.05 ± 1.45	8.07 ± 1.51	8.04 ± 1.40	0.79	8.09 ± 1.47	7.99 ± 1.42	0.41
Fasting plasma glucose (mmol/l)*							
Men	8.3 (7.2–10.0)	8.2 (7.0–9.7)	8.6 (7.4–10.4)	<0.01	8.2 (7.1–9.8)	8.6 (7.4–10.3)	0.02
Women	8.6 (7.3–10.2)	8.6 (7.2–10.2)	8.6 (7.3–10.2)	0.74	8.6 (7.2–10.3)	8.5 (7.4–9.9)	0.77
Fasting plasma insulin (pmol/l)*‡							
Men	6.2 (0.5–1.9)	5.4 (0.5–1.9)	7.2 (0.5–1.9)	<0.01	5.2 (0.5–1.9)	7.7 (0.5–1.9)	<0.01
Women	7.1 (0.5–1.9)	5.9 (0.5–1.9)	8.3 (0.6–1.8)	<0.01	6.2 (0.5–1.9)	8.7 (0.5–1.9)	<0.01
HOMA-IR‡							
Men	3.1 ± 3.1	2.6 ± 2.6	3.6 ± 3.4	<0.01	2.4 ± 2.1	3.9 ± 3.8	<0.01
Women	3.3 ± 2.6	2.8 ± 2.2	3.8 ± 2.8	<0.01	2.9 ± 2.1	4.1 ± 3.1	<0.01
Serum total cholesterol (mmol/l)							
Men	5.01 ± 0.90	4.93 ± 0.84	5.09 ± 0.94	0.01	4.97 ± 0.82	5.07 ± 0.98	0.16
Women	5.44 ± 0.85	5.38 ± 0.84	5.50 ± 0.86	0.05	5.41 ± 0.83	5.50 ± 0.89	0.28
Serum HDL cholesterol (mmol/l)							
Men	1.34 ± 0.39	1.42 ± 0.39	1.27 ± 0.38	<0.01	1.48 ± 0.38	1.18 ± 0.34	<0.01
Women	1.47 ± 0.44	1.57 ± 0.45	1.37 ± 0.41	<0.01	1.65 ± 0.43	1.17 ± 0.26	<0.01
Serum triglycerides (mmol/l)*							
Men	1.2 (0.6–1.6)	1.0 (0.7–1.5)	1.5 (0.6–1.6)	<0.01	1.0 (0.7–1.5)	1.6 (0.6–1.6)	<0.01
Women	1.1 (0.6–1.7)	0.9 (0.6–1.6)	1.4 (0.6–1.6)	<0.01	9 (0.7–1.5)	1.6 (0.6–1.6)	<0.01

Current smoker (%; men/women)	43.9/8.7	46.6/8.1	41.3/9.2	0.08/0.38	44.7/7.1	42.9/11.3	0.33/0.049
Excessive alcohol intake (%; men/women)§	12.4/0.2	8.2/0.0	16.4/0.3	<0.01/0.51	7.7/0.3	18.4/0.0	<0.01/0.62
OHA use (without insulin) (%; men/women)	72/77	72/76	73/78	0.38/0.33	72/75	72/79	0.50/0.20
Insulin use (with or without OHA) (%; men/women)	16/20	18/24	15/16	0.16/0.01	20/22	11/15	<0.01/0.02
Medication for hypertension (%; men/women)	22/29	12/17	32/40	<0.01/<0.01	16/23	30/40	<0.01/<0.01
Medication for hyperlipidemia (%; men/women)	15/35	11/30	19/39	<0.01/<0.01	10/32	21/40	<0.01/0.02

Data are *n* (%), means ± SD, *median (interquartile range), or †geometric means (1 SD). ‡Patients with insulin therapy were excluded. §Excessive alcohol intake was defined as more than three drinks (38 g ethanol) per day. OHA, oral hypoglycemic agent.

and potent risk factor for stroke (Table 3) (46). By contrast, HDL cholesterol levels, hypertension, and smoking, all of which were identified as significant risk factors for CHD in UKPDS patients (47), were not associated with a significant elevation of HRs in our Japanese patients (Table 3). Instead, triglyceride levels, which were not significant in UKPDS patients (47), were a strong predictor for CHD in male Japanese patients. These findings imply that the critical therapeutic targets among the components of MetS for preventing cardiovascular complications (28) may need to be modified according to a patient's ethnic group.

Most of the previous studies evaluating the predictive power of MetS for CVD calculated the HRs by including sex as one of the independent variables for statistical adjustment, and very few studies have analyzed CVD risk separately by sex (24). Sex is reportedly an independent predictor for CVD, with an odds ratio of 2.6, which is larger than that of age, HbA_{1c}, and even of MetS itself in type 2 diabetic patients (16). Our results revealed drastic differences in the HRs between sexes. In our female patients, WHO-MetS presented an increased risk for CVD events to a greater degree than could be predicted by the sum of the individual components (Table 3), whereas, in contrast, in our male patients, WHO-MetS was not even a significant risk factor for CVD. At baseline, obvious sex differences were observable in the proportion of subjects who smoked or consumed excessive alcohol, both of which were much higher in male patients. Of particular interest, the proportion of male subjects with excessive alcohol intake was at least twice as high in male patients with MetS than in those without MetS, whereas the proportion of current smokers did not differ in patients with and without MetS (Table 1). It can be speculated that excessive alcohol intake could be closely associated with MetS in male Japanese diabetic patients. Moreover, moderate alcohol intake, which has been shown to be beneficial for preventing CHD in U.S. and European diabetic patients, is not beneficial for Japanese patients (40).

Few studies have applied both the WHO and NCEP definitions of MetS to the same subjects to compare the prevalence of MetS or its predictive value for CVD. It has been reported that the prevalence of WHO-MetS is generally higher than that of NCEP-MetS in both sexes (7,12). This was confirmed in our Japanese diabetic subjects, although the difference in prevalence was not great. Regarding the predictive value of MetS, in subjects without diabetes or other cardiovascular risks, Hunt et al. (27) reported that the NCEP-MetS tended to be more predictive for cardiovascular mortality than the WHO-MetS, whereas Lakka et al. (9) reported a contrary result. In our diabetic patients, the NCEP guidelines, even modified for optimal use by Japanese subjects, were not more predictive than the WHO guidelines in female patients nor did they show excellent clinical usefulness in male patients. One possible explanation for this difference in our patients could be the hypertension cut-off used, with 140/90 mmHg in the WHO defini-

Table 2—*Incidence of coronary heart disease and/or stroke (per 1,000 patient-years) among study subjects grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total (%)	Without (%)	With (%)	*P*	Without (%)	With (%)	*P*
Incidence among							
Men							
CHD	9.8	8.4	11.3	0.34	7.0	13.5	0.04
Stroke	7.7	5.1	10.3	0.05	6.6	9.1	0.35
CHD and/or stroke	17.1	12.7	21.6	0.03	13.0	22.6	0.02
Incidence among							
Women							
CHD	5.5	2.9	8.0	0.04	4.4	7.3	0.27
Stroke	7.2	2.8	11.2	<0.01	6.2	8.8	0.38
CHD and/or stroke	12.6	5.7	19.0	<0.01	10.7	15.6	0.22

Table 3—*Patient prevalence at baseline and hazard ratios for coronary heart disease, stroke, or both in Japanese study subjects grouped by metabolic syndrome status*

	Prevalence at baseline		Hazard ratios for CHD		Hazard ratios for stroke		Hazard ratios for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
Criteria of individual components								
1a. BMI >30 or WHR >0.90 (men) or >0.85 (women)	39.4	37.5	1.3 (0.7–2.5)	1.2 (0.5–3.0)	1.3 (0.7–2.6)	1.1 (0.5–2.3)	1.4 (0.8–2.2)	1.2 (0.6–2.1)
1b. Waist circumference ≥85cm (men) or ≥90 cm (women)	36.7	9.6	1.7 (0.9–3.0)	1.0 (0.2–4.4)	0.90 (0.4–1.9)	1.1 (0.3–3.7)	1.3 (0.8–2.1)	1.1 (0.4–2.8)
2a. SBP ≥140 or DBP ≥90 mmHg	38.9	38.9	0.8 (0.4–1.6)	1.0 (0.4–2.6)	2.1 (1.1–4.3)	2.4 (1.1–5.5)	1.3 (0.8–2.1)	1.8 (1.0–3.2)
2b. SBP ≥130 or DBP ≥85 mmHg	60.7	62.2	0.9 (0.5–1.6)	0.9 (0.4–2.2)	1.4 (0.7–2.9)	1.8 (0.7–4.5)	1.1 (0.6–1.7)	1.2 (0.7–2.4)
3. Triglycerides ≥150 mg/dl	24.8	21.0	2.9 (1.6–5.3)	1.7 (0.6–4.4)	1.1 (0.5–2.4)	0.7 (0.2–1.9)	2.0 (1.2–3.2)	1.1 (0.5–2.2)
4. HDL cholesterol ≤40 mg/dl	19.3	36.3	1.8 (0.9–3.5)	1.5 (0.6–3.6)	1.0 (0.4–2.5)	1.3 (0.6–2.9)	1.6 (0.9–2.6)	1.3 (0.7–2.4)
5. Triglycerides ≥150 mg/dl or HDL cholesterol <35 mg/dl	28.5	27.0	2.8 (1.6–5.2)	1.8 (0.7–4.5)	0.9 (0.4–1.9)	1.6 (0.7–3.5)	1.8 (1.1–2.9)	1.6 (0.9–2.9)
6. Urinary albumin excretion >30 μg/g creatinine	51.2	57.7	1.2 (0.6–2.3)	2.9 (0.9–8.7)	1.8 (0.9–3.8)	1.1 (0.5–2.4)	1.4 (0.9–2.3)	1.6 (0.8–3.0)
7. LDL cholesterol ≥120 mg/dl	45.1	65.2	2.1 (1.1–3.9)	1.2 (0.5–3.2)	0.9 (0.5–1.8)	0.6 (0.3–1.3)	1.4 (0.9–2.3)	0.8 (0.4–1.4)
8. Current smoker	43.9	8.7	1.4 (0.7–2.5)	0.6 (0.1–4.3)	0.9 (0.4–1.8)	2.5 (0.8–7.3)	1.2 (0.7–1.9)	1.6 (0.6–4.1)
9. Alcohol intake >3 drinks/day*	12.4	0.2	0.7 (0.3–2.1)	0.0 (0.0–0.0)	1.0 (0.4–2.8)	0.0 (0.0–0.0)	0.9 (0.4–1.8)	0.0 (0.0–0.0)
Number of components comprising WHO-MetS other than diabetes (i.e., among 1a, 2a, 5, and 6)								
0	18.6	16.4	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	81.5	83.6	1.7 (0.7–4.5)	3.9 (0.5–28.4)	1.0 (0.4–2.5)	2.3 (0.5–9.7)	1.2 (0.7–2.4)	2.8 (0.9–9.0)
≥2 (vs. <2; i.e., WHO-MetS)	51.2	52.5	1.3 (0.7–2.4)	2.8 (1.0–7.9)	2.0 (0.9–4.1)	3.7 (1.4–9.9)	1.6 (1.0–2.6)	3.2 (1.6–6.5)
≥3 (vs. <3)	21.8	20.7	1.8 (0.9–3.5)	1.3 (0.5–3.7)	2.1 (1.0–4.4)	1.1 (0.4–2.7)	1.9 (1.2–3.2)	1.2 (0.6–2.4)
Number of components comprising NCEP-MetS other than diabetes (i.e. among 1b, 2b, 3, and 4)								
0	20.1	21.6	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	79.9	78.4	1.9 (0.7–4.9)	1.6 (0.4–5.6)	1.0 (0.4–2.2)	6.4 (0.9–46.7)	1.3 (0.7–2.4)	2.7 (0.9–7.7)
≥2 (vs. <2; i.e., NCEP-MetS)	45.0	38.0	1.9 (1.0–3.6)	1.7 (0.7–4.0)	1.4 (0.7–2.8)	1.3 (0.6–2.8)	1.8 (1.1–2.8)	1.4 (0.8–2.5)
≥3 (vs. <3)	14.5	11.5	2.5 (1.3–4.9)	0.9 (0.2–3.7)	0.9 (0.3–2.4)	0.3 (0.0–2.2)	1.8 (1.0–3.2)	0.5 (0.2–1.7)

Data are percent or hazard ratios (95% CIs) and are grouped according to individual and combined cardiovascular risk factors mostly comprising the metabolic syndrome as defined by the World Health Organization or the National Cholesterol Education Program. *Equivalent to 38 g ethanol/day. DBP, diastolic blood pressure; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

tion being a significant predictor for stroke, whereas 130/85 mmHg in the NCEP definition is not.

The strengths of our study were that *1*) it is the first prospective study to determine the predictive value of MetS on CVD in Asian subjects, 2) the two most widely used definitions of MetS were applied to the same cohort for the evaluation of their clinical usefulness, and *3*) the follow-up was mainly carried out in university or large general hospitals, which facilitated the reliable assessment of follow-up data and event diagnosis/records. Nevertheless, we acknowledge that the study had certain limitations: *1*) Our study subjects were hospital-based patients with diabetes of a relatively long duration; therefore, we cannot make inferences beyond a similar group. 2) We analyzed both intervention (lifestyle modification through diabetes self-management care) and control (continuance of conventional care) groups of the JDCS together, although mild intervention produced only limited differences in glycemic control (0.1–0.2% in HbA_{1c}) as well as a lack of significant differences in known classical cardiovascular risk factors, as previously reported (38). *3*) We did not consider medication use in the diagnosis of MetS in this study. *4*) Mortality was not analyzed because we did not have sufficient occurrences at this stage of the study.

In conclusion, we found a high prevalence of MetS among diabetic patients with no history of CVD. For Japanese female patients with type 2 diabetes, WHO-MetS but not NCEP-MetS was predictive for CVD. In male patients, although both WHO-MetS and NCEP-MetS were somewhat predictive for CVD, hyperlipidemia or hypertension had equivalent or higher HRs for CVD and seemed to be sufficient for the prediction of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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APPENDIX

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References

1. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
2. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Ge-

neva, World Health Organization, 1999
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
4. Balkau B, Charles MA, Drivsholm T, Borch-Johnsen K, Wareham N, Yudkin JS, Morris R, Zavaroni I, van Dam R, Feskins E, Gabriel R, Diet M, Nilsson P, Hedblad B, European Group for the Study of Insulin Resistance: Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabete Metab* 28:364–376, 2002
5. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB: The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 163: 427–436, 2003
6. Meigs JB, Wilson PW, Nathan DM, D'Agostino RB Sr, Williams K, Haffner SM: Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. *Diabetes* 52:2160–2167, 2003
7. Cameron AJ, Shaw JE, Zimmet PZ: The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 33:351–375, 2004
8. Simmons D, Thompson CF: Prevalence of the metabolic syndrome among adult New Zealanders of Polynesian and European descent. *Diabetes Care* 27:3002–3004, 2004
9. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
10. Ford ES, Giles WH: A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care* 26:575–581, 2003
11. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M: Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck study. *Diabetes Care* 26:1251–1257, 2003
12. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
13. Ilanne-Parikka P, Eriksson JG, Lindstrom J, Hamalainen H, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Rastas M, Salminen V, Aunola S, Sundvall J, Valle T, Lahtela J, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study Group: Prevalence of the metabolic syndrome and its components: findings from a Finnish general population sample and the Diabetes Prevention Study cohort. *Diabetes Care* 27:2135–2140, 2004
14. Relimpio F, Martinez-Brocca MA, Leal-Cerro A, Losada F, Mangas MA, Pumar A, Astorga R: Variability in the presence of the metabolic syndrome in type 2 diabetic patients attending a diabetes clinic: influences of age and gender. *Diabetes Res Clin Pract* 65:135–142, 2004
15. Gimeno Orna JA, Lou Arnal LM, Molinero Herguedas E, Boned Julian B, Portilla Cordoba DP: Metabolic syndrome as a cardiovascular risk factor in patients with type 2 diabetes. *Rev Esp Cardiol* 57:507–513, 2004 (in Spanish)
16. Bonora E, Targher G, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Gemma L, Santi L, Bonadonna RC, Muggeo M: Metabolic syndrome is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabet Med* 21:52–58, 2004
17. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P, Casale Monferrato Study: Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. *Diabetes Care* 27:2689–2694, 2004
18. Costa LA, Canani LH, Lisboa HR, Tres GS, Gross JL: Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in type 2 diabetes. *Diabet Med* 21: 252–255, 2004
19. Lee YJ, Tsai JC: ACE gene insertion/deletion polymorphism associated with 1998 World Health Organization definition of metabolic syndrome in Chinese type 2 diabetic patients. *Diabetes Care* 25:1002–1008, 2002
20. Alexander CM, Landsman PB, Teutsch SM, Haffner SM, Third National Health and Nutrition Examination Survey (NHANES III), National Cholesterol Education Program (NCEP): NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 52:1210–1214, 2003
21. Ekoe JM, Zimmet P, Williams R: *The Epidemiology of Diabetes Mellitus*. West Sussex, U.K., Wiley, 2001
22. Klein BE, Klein R, Lee KE: Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care* 25:1790–1794, 2002
23. Girman CJ, Rhodes T, Mercuri M, Pyorala K, Kjekshus J, Pedersen TR, Beere PA, Gotto AM, Clearfield M, 4S Group, AFCAPS/TexCAPS Research Group: The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol* 93:136–141, 2004
24. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K, the DECODE Study Group: Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in non-diabetic European men and women. *Arch Intern Med* 164:1066–1076, 2004
25. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, Williams GR: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 110: 1239–1244, 2004
26. Ford ES: The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis* 173: 309–314, 2004
27. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP, San Antonio Heart Study: National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation* 110: 1251–1257, 2004
28. Golden SH, Chong R: Are there specific components of the insulin resistance syndrome that predict the increased atherosclerosis seen in type 2 diabetes mellitus? *Curr Diab Rep* 4:26–30, 2004
29. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D: The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world: Seven Countries Study Research Group. *N Engl J Med* 342:1–8, 2000
30. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M: Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. *Diabetologia* 44 (Suppl. 2):S3–S13, 2001
31. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N, Japan Diabetes Complication Study Group: Obesity and type 2 diabetes in Japanese patients (Letter). *Lancet* 361: 85, 2003
32. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N, Japan Diabetes Complications

Study Group: Energy intake and obesity in Japanese patients with type 2 diabetes. *Lancet* 363:248–249, 2004
33. Anuurad E, Shiwaku K, Nogi A, Kitajima K, Enkhmaa B, Shimono K, Yamane Y: The new BMI criteria for Asians by the regional office for the Western Pacific region of WHO are suitable for screening of overweight to prevent metabolic syndrome in elder Japanese workers. *J Occup Health* 45:335–343, 2003
34. WHO Expert Consultation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 363:157–163, 2004
35. Tan CE, Ma S, Wai D, Chew SK, Tai ES: Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 27:1182–1186, 2004
36. Ota T, Takamura T, Hirai N, Kobayashi K: Preobesity in World Health Organization classification involves the metabolic syndrome in Japanese. *Diabetes Care* 25:1252–1253, 2002
37. Jorgensen ME, Borch-Johnsen K: The metabolic syndrome. Is one global definition possible? *Diabet Med* 21:1064–1065, 2004
38. Sone H, Katagiri A, Ishibashi S, Abe R, Saito Y, Murase T, Yamashita H, Yajima Y, Ito H, Ohashi Y, Akanuma Y, Yamada N, the Japan Diabetes Complications Study Group: Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and three year-interim report. *Horm Metab Res* 34: 509–515, 2002
39. Examination Committee of Criteria for "Obesity Disease" in Japan, Japan Society for the Study of Obesity: New criteria for "obesity disease" in Japan. *Circ J* 66:987–992, 2002
40. Sone H, Yamada N, Mizuno S, Aida R, Ohashi Y, the Japan Diabetes Complications Study (JDCS) Group: Alcohol use and diabetes mellitus. *Ann Intern Med* 141:408–409, 2004
41. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Cacciatori V, Santi L, Targher G, Bonadonna R, Muggeo M: HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care* 25:1135–1141, 2002
42. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A: Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 90:583–612, 1994
43. Aho K, Harmsen P, Hatano S: Marquardsen J, Smirnov VE, Strasser T, on behalf of the participants in the WHO Collaborative Study on the Control of Stroke in the Community: Cerebrovascular disease in the community: results of a WHO Collaborative Study. *Bull World Health Organ* 58: 113–130, 1980
44. St-Onge MP, Janssen I, Heymsfield SB: Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. *Diabetes Care* 27:2222–2228, 2004
45. Huang TT, Kempf AM, Strother ML, Li C, Lee RE, Harris KJ, Kaur H: Overweight and components of the metabolic syndrome in college students. *Diabetes Care* 27:3000–3001, 2004
46. Davis TM, Millns H, Stratton IM, Holman RR, Turner RC: Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. *Arch Intern Med* 159:1097–1103, 1999
47. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 23. *BMJ* 316:823–828, 1998

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Increased Risk for Cardiovascular Outcomes and Effect of Cholesterol-Lowering Pravastatin Therapy in Patients with Diabetes Mellitus in the Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE)

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ABSTRACT

Background: The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE) was the first large-scale, prospective clinical trial to show that cholesterol-lowering therapy with pravastatin is effective in reducing the risk for cardiovascular events (CVEs) in elderly (aged ≥60 years) patients with hypercholesterolemia. PATE also included a subgroup of patients with diabetes mellitus (DM).

Objective: The aim of this post hoc analysis was to assess the effects of long-term pravastatin therapy on cardiovascular outcomes in the subgroup of patients with DM compared with a subgroup without it.

Methods: PATE was conducted at 50 hospitals, universities, and clinics across Japan. Patients were randomly allocated to 1 of 2 treatment groups: low-dose pravastatin (5 mg PO QD; L group) or standard-dose pravastatin (in Japan, 10 mg PO QD; S group). Treatment was given for 3 to 5 years. Serum cholesterol levels were measured and the prevalence of CVEs was determined. The primary end point of the study was the S:L risk ratio for fatal or nonfatal CVEs. The secondary end point was the effect of diabetic patients' glycemic control on CVEs.

Results: A total of 665 patients (527 women, 138 men; mean [SD] age, 72.8 [5.7] years) were followed up for a mean of 3.9 years (range, 3–5 years). Among these, 199 patients had DM; 104 patients with DM were allocated to the L group and

*The PATE Investigators are listed in **Appendix I**.

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95 to the S group. Four hundred sixty-six patients did not have DM (L group, 230 patients; S group, 236 patients). Overall, between 3 months and 3 years after the initiation of treatment, patients in the L group (mean dose, 4.5 mg/d) experienced reductions from baseline total cholesterol level of 11% to 13%. Those in the S group (mean dose, 8.3 mg/d) experienced reductions from baseline of 15% to 17%. Decreases in low-density lipoprotein cholesterol (LDL-C) levels were 17% to 20% and 23% to 26% in the L and S groups, respectively. Statistically similar reductions were noted between patients with DM and those without it in response to either dose. The DM subgroup experienced 32 CVEs (L group, 17; S group, 15) compared with 39 CVEs (L group, 25; S group, 14) in the subgroup without DM. The S:L CVE risk ratio (primary end point) was 0.94 (95% CI, 0.46–1.92) in patients with DM and 0.54 (95% CI, 0.28–1.05) in those without DM; the differences between the treatment groups were not statistically significant. The risk for CVEs in patients with DM whose glycosylated hemoglobin concentrations were <8.0% and ≥8.0% were, respectively, 1.87-fold (95% CI, 1.09–3.20; $P = 0.02$) and 3.79-fold (95% CI, 1.92–7.48; $P < 0.01$) higher than that in patients without DM.

Conclusions: In this post hoc analysis of the effects of long-term cholesterol-lowering therapy (low- and standard-dose pravastatin) on cardiovascular outcomes in elderly patients with DM, dose had no effect on the risk for CVEs in these patients as it did in those without DM. Poorer glycemic control in patients with DM was related to a higher risk for CVEs. The lack of pravastatin efficacy found in the subgroup with DM may have been attributable to the small differences in LDL-C levels found between the 2 treatment groups and/or the small sample size of the study. (*Curr Ther Res Clin Exp.* 2005;66:48–65) Copyright © 2005 Excerpta Medica, Inc.

Key words: PATE study, elderly patients, pravastatin, hyperlipidemia, diabetes mellitus, prospective interventional trial.

INTRODUCTION

The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE)[1] was the first large-scale, prospective clinical trial specifically designed to investigate the effects of lowering serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) on the risk for cardiovascular events (CVEs) in elderly patients with hypercholesterolemia. Based on a MEDLINE search (key terms: *hypercholesterolemia, intervention*, and *elderly people*; years, 1980–2000), PATE was the first such study.

Briefly, the study included male and female Japanese patients aged ≥60 years with and without cardiovascular disease (CVD) and with hypercholesterolemia. Patients were randomly allocated to 1 of 2 treatment groups: low-dose pravastatin (5 mg PO QD; L group) or standard-dose pravastatin (in Japan, 10 mg PO QD; S group). Treatment was given for 3 to 5 years. The primary end point of PATE was the prevalence of CVEs, including ischemic heart disease, cerebrovascular disease, peripheral vascular disorder, and sudden cardiac death.

Because all of the patients in the study were at risk for CVEs due to their age and TC levels, no placebo group was included. The hypothesis of the study was that pravastatin would lower patients' TC and LDL-C levels. Because elderly patients commonly have reduced drug tolerance and their physicians often prescribe lower drug doses compared with younger patients, the rationale behind the study design was assessment of the effects of low- versus standard-dose therapy on clinical outcome.

A total of 665 patients were enrolled (527 women, 138 men; mean [SD] age, 72.8 [5.7] years; mean [SD] serum TC level, 253 [15] mg/dL; mean [SD] serum LDL-C level, 165 [24] mg/dL; L group, 334 patients; S group, 331 patients). Mean follow-up was 3.9 years. The mean pravastatin doses in the L and S groups were 4.5 and 8.3 mg/d, respectively.

Overall, between 3 months and 3 years after the initiation of treatment, the mean (SD) serum TC levels decreased 11% to 13% (from 253 [15] to 218 [28] mg/dL) in the L group and 15% to 17% (from 253 [15] to 211 [27] mg/dL) in the S group (both, $P < 0.01$). In the same period, the mean (SD) LDL-C levels decreased 17% to 20% (from 164 [23] to 131 [27] mg/dL) in the L group and 23% to 26% (from 166 [25] to 127 [27] mg/dL) in the S group (both, $P < 0.01$). Forty-two CVEs occurred in the L group and 29 in the S group; the difference was statistically significant ($P = 0.046$).

In addition to cholesterol lowering in reducing cardiovascular risk, evidence shows that diabetes mellitus (DM) may be associated with a markedly increased risk for CVEs,[2-6] and it is widely recognized that established risk factors for CVEs (eg, dyslipidemia, hypertension, obesity) are common in patients with DM.[7] Diabetic dyslipidemia in particular appears to be strongly linked to CVD.[8] Impaired glucose tolerance—an independent risk factor for CVD and an intermediate stage in the pathogenesis of type 2 DM[9,10]—has been associated with the insulin resistance syndrome, which includes hypertension, a low high-density lipoprotein cholesterol (HDL-C) level, and an elevated serum triglyceride (TG) level.[11,12] An elevated TG level has been shown to decrease LDL-C particle size[13] (which, in turn, has been shown to increase the atherogenicity of LDL-C[14,15]) and to increase platelet release of plasminogen activator inhibitor 1[16] (which has been shown to contribute to enhanced thrombosis[17]). Thus, it is of considerable interest to ascertain the effects of lowering TC and LDL-C on the occurrence of macrovascular abnormalities in DM.

In a subanalysis[18] of 586 patients aged 21 to 75 years with DM and impaired glucose tolerance included in the Cholesterol and Recurrent Events (CARE) trial,[19] pravastatin therapy was associated with a lower prevalence of recurrent CVEs after myocardial infarction (MI) in this population compared with placebo ($P = 0.05$). The Scandinavian Simvastatin Survival Study (4S)[20] showed a similarly reduced risk in patients with elevated fasting plasma glucose levels or DM after cholesterol-lowering therapy in the setting of secondary prevention compared with placebo ($P < 0.01$).[21] The Heart Protection Study[22] also showed a decreased prevalence of CVEs in patients with DM with and without a history

of coronary heart disease or MI after cholesterol-lowering therapy with simvastatin compared with placebo ($P < 0.05$).

PATE included 199 patients with DM. The present report is a post hoc analysis of the effects of long-term (at least 3 years) pravastatin therapy on cardiovascular outcomes in this subgroup of patients compared with a subgroup without it.

PATIENTS AND METHODS

Study Design

The design and major findings of PATE have been reported elsewhere.[1] PATE was conducted at 50 hospitals, universities, and clinics across Japan. Patients were randomly allocated to the L or S group using an adaptive balancing method (biased coin minimization). History of CVD (MI, angina pectoris [AP], cerebrovascular disease, or arteriosclerosis obliterans), TC level, and study site were balancing factors.

Because the study was conducted before the International Conference on Harmonisation, Good Clinical Practice guidelines were established, verbal informed consent was obtained from eligible patients and was recorded in the medical records, and institutional review board approval of the study protocol was not sought at all of the study sites. However, the ethical aspects of the study were continually examined by the Monitoring Committee of the PATE Investigators. Although this trial was open-label, assessment of the end points was performed under investigator-blinded conditions.

Patients with familial or secondary hypercholesterolemia and/or malignant neoplasia were excluded from the study.

Patients who had confirmed DM or were receiving antidiabetic drugs at enrollment constituted the subgroup with DM; DM was diagnosed according to the criteria of the Japan Diabetes Society (**Appendix II**[23]). Primary care physicians' patient interviews and clinical examination of results were used to determine whether the patients met the criteria for inclusion in the DM subgroup. All other patients recruited in PATE constituted the subgroup without DM. Registration forms and records from follow-up indicated that patients with types 1 and 2 DM were included in the study, although all but 3 of these patients had type 2 DM.

All antihyperlipidemic drugs, except for the study agent, were to be discontinued at least 3 months before the study. Other concomitant drugs (eg, antidiabetic drugs) were allowed. Twelve-hour fasting serum lipid levels (TC, HDL-C, and TG), blood pressure, and body weight were measured at baseline (month 0); at 1, 3, and 6 months of pravastatin therapy; and every 6 months thereafter until study end. LDL-C levels were calculated using the Friedewald formula[24] unless the TG level was ≥400 mg/dL. *Hypertension* was defined as systolic/diastolic blood pressure ≥160/≥90 mm Hg[25] and/or the use of antihypertensive drugs. Routine physical examinations and laboratory analyses, including peripheral blood cell count, and biochemistry (including hepatic and renal func-

tion tests and creatine kinase activity), were conducted by primary care physicians at intervals of no more than 6 months.

During the follow-up period, physicians contacted patients by mail every 3 months to determine compliance with pravastatin therapy. If a patient had discontinued therapy, his or her physician was to record the discontinuation date and the reason(s) for it.

Primary care physicians provided general instructions for diet and exercise before the study. However, no further detailed instructions were given after the start of the study, and patients' diet and exercise habits were not investigated.

The primary end point of PATE was the S:L risk ratio for fatal or nonfatal CVEs, including cerebrovascular disease, ischemic heart disease, peripheral vascular disease, and sudden cardiac death. Cerebrovascular disease included cerebral infarction, cerebral hemorrhage, transient ischemic attack, and subarachnoid hemorrhage. Ischemic heart disease included MI, AP, congestive heart failure due to ischemic heart disease, and arrhythmia requiring pharmacologic treatment. A patient was diagnosed with AP if he or she had chest pain or discomfort with all of the following characteristics: (1) it included any level of the sternum; (2) it occurred during exertion or stress and usually lasted at least 30 seconds; (3) on most occasions it resolved within 10 minutes of stopping or decreasing the intensity of exertion; and (4) it was usually relieved within 2 to 5 minutes after receiving nitroglycerine, if nitroglycerine was used. All outcome variables were assessed based on the end point defined in the appendix of the original PATE study.[1]

The effect of the extent of glycemic control on the risk for CVEs (secondary end point) was assessed by measuring the prevalence of CVEs in patients with DM whose glycosylated hemoglobin (HbA_{1c}) concentration was ≥8.0% versus that in patients whose concentration was <8.0%. HbA_{1c} concentration 8.0% was selected as the cutoff point because it is generally considered indicative of uncontrolled DM.

Potential end points were reviewed and classified by the members of a Case/Event Evaluation Committee of the study investigators. Members of this committee were blinded to the identities and treatment assignments of the patients. In cases in which the first reporting by the physicians of a CVE was inadequate, additional information required to determine whether an event was a CVE (eg, electrocardiography, brain computed tomography, coronary angiography) was requested by the Case/Event Evaluation Committee.

Statistical Analysis

Analyses were performed on an intent-to-treat basis. Baseline characteristics were compared between groups using the Wilcoxon, Kruskal-Wallis, or chi-square test. Changes in serum lipid levels before and after the initiation of pravastatin therapy were assessed with the least squares means calculated using general linear models. Differences between patients with and without DM and between the 2 treatment groups were assessed using repeated-measures analysis of variance.

For the primary end point in patients with and without DM and overall, the Cox regression analysis was used to assess the effectiveness of standard-dose pravastatin compared with low-dose pravastatin adjusted for age, sex, DM, smoking history, hypertension, and history of CVD. Cardiovascular risk in patients with DM was also assessed using the Cox regression analysis adjusted for treatment group, age, sex, smoking history, hypertension, and history of CVD.

$P < 0.05$ (2-sided) was considered statistically significant. All statistical analyses were performed using SAS software version 6.12 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient Population

A total of 703 patients were enrolled in the original PATE.[1] After randomization, 38 patients were excluded for the following reasons: no attendance at hospital after registration (19 patients), withdrawal of informed consent (6), another cholesterol-lowering regimen in use at the start of pravastatin treatment (4), duplicate entry (3), active malignancy (3), familial hypercholesterolemia (2), and secondary hypercholesterolemia due to hypothyroidism (1). The remaining 665 patients (527 women, 138 men; mean [SD] age, 72.8 [5.7] years) were followed up (**Table I**). The L group contained 334 patients (104 with DM, 230 without it); the S group, 331 patients (95 with DM, 236 without it). The numbers of patients with and without DM were statistically similar between the 2 treatment groups.

No significant differences in age, HbA_{1c} concentration, or presence of cardiovascular risk factors (eg, hypertension, history of CVD, smoking) were found between the 2 treatment groups. Mean (SD) HbA_{1c} concentrations in the patients with DM were 6.9% (1.2%) (range, 4.8%–10.6%) in the L group and 6.9% (1.1%) (range, 5.1%–10.1%) in the S group. The percentages of patients with DM and a history of CVD were 26.9% (28/104) and 17.9% (17/95) in the L and S groups, respectively. The percentage of S-group female patients without DM was higher than those with DM ($P = 0.049$).

The clinical profile of the patients with DM (n = 199), including their concomitant drug regimens (eg, antihypertensive drugs, nitrites, antidiabetic drugs) is shown in **Table II**. Major DM complications present in these patients included diabetic nephropathy (L group, 1.9% [2/104]; S group, 2.1% [2/95]) and diabetic retinopathy (L group, 0; S group, 1.1% [1/95]). A total of 44.2% (46/104) of patients with DM in the L group and 45.1% (43/95) in the S group were receiving antihypertensive drugs. The numbers of patients receiving antihypertensive drugs were statistically similar between the L and S groups. The proportions of patients receiving hydrochlorothiazide were 1.9% (2/104) and 1.1% (1/95) in the L and S groups, respectively.

During the follow-up period, the mean pravastatin doses were 4.5 and 8.3 mg/d in the L and S groups, respectively. Patients who discontinued treatment were

Table I. Baseline demographic and clinical characteristics of patients in the Pravastatin Anti-atherosclerosis Trial in the Elderly.

Characteristic	Patients with DM		Patients Without DM		All Patients[1]	
	L Group (n = 104)	S Group (n = 95)	L Group (n = 230)	S Group (n = 236)	L Group (n = 334)	S Group (n = 331)
Demographic						
Age, mean (SD), y	72.5 (5.4)	72.5 (5.3)	72.6 (5.5)	73.2 (6.1)	72.6 (5.5)	73.0 (5.9)
Sex, no. (%)						
Female	76 (73.1)	73 (76.8)	178 (77.4)	200 (84.7)*	254 (76.0)	273 (82.5)
Male	28 (26.9)	22 (23.2)	52 (22.6)	36 (15.3)	80 (24.0)	58 (17.5)
Clinical						
BMI, mean (SD), kg/m^2	23.6 (3.1)	23.2 (2.9)	22.9 (3.2)	23.4 (3.3)	23.2 (3.2)	23.3 (3.2)
Lipid levels, mean (SD)						
TC, mg/dL	254 (16)	254 (15)	253 (15)	253 (16)	253 (15)	253 (15)
HDL-C, mg/dL	56 (15)	58 (15)	55 (16)	54 (14)	55 (15)	55 (15)
LDL-C, mg/dL	160 (24)	162 (25)	166 (23)	168 (25)	164 (23)	166 (25)
TG, mg/dL	161 (87)	147 (69)	149 (69)	155 (104)	153 (75)	152 (95)
HbA_{1c}, %	6.9 (1.2)	6.9 (1.1)	–	–	–	–
Risk factors						
HTN, no. (%)†	50 (48.1)	46 (48.4)	121 (52.6)	121 (51.3)	171 (51.2)	167 (50.5)
History of CVD, no. (%)	28 (26.9)	17 (17.9)	67 (29.1)	65 (27.5)	95 (28.4)	82 (24.8)
Smokers, no. (%)‡	12/104 (11.5)	6/95 (6.3)	21/226 (9.3)	18/234 (7.7)	33/330 (10.0)	24/329 (7.3)

DM = diabetes mellitus; L = low-dose pravastatin; S = standard-dose pravastatin; BMI = body mass index; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = glycosylated hemoglobin; HTN = hypertension; CVD = cardiovascular disease.

*$P < 0.05$ versus patients with DM.

†*Hypertension* was defined as systolic/diastolic blood pressure ≥160/≥90 mm Hg[25] and/or the use of antihypertensive drugs.

‡Data were unavailable in 12 patients.

Table II. Diabetes mellitus (DM) type, complications, and concomitant drug use in patients (no. [%]) in the Pravastatin Antiatherosclerosis Trial in the Elderly.*

Variable	L Group (n = 104)	S Group (n = 95)
DM type		
1	1 (1.0)	2 (2.1)
2	103 (99.0)	93 (97.9)
Complications		
Diabetic nephropathy	2 (1.9)	2 (2.1)
Diabetic retinopathy	0 (0.0)	1 (1.1)
Drug use		
Antihypertensive drugs		
CCB	34 (32.7)	36 (37.9)
ACEI	13 (12.5)	9 (9.5)
Beta-blocker	4 (3.8)	4 (4.2)
Hydrochlorothiazide	2 (1.9)	1 (1.1)
Alpha-blocker	1 (1.0)	5 (5.3)
Alpha- and beta-blocker	1 (1.0)	3 (3.2)
Sulfonylureas	45 (43.3)	35 (36.8)
Nitrites	4 (3.8)	1 (1.1)
Insulin	3 (2.9)	8 (8.4)

L = low-dose pravastatin; S = standard-dose pravastatin; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor.
*No significant between-group differences were found.

included in the calculation of the mean dose given in the S group (8.3 mg/d). The total discontinuation rate was 23.9% (L group, 21.3%; S group, 26.5%).

Total DM patients and total non-DM patients showed similar percent reductions in serum TC and LDL-C levels (**Figure 1A, B**). Furthermore, both DM and non-DM patients experienced similar reductions in TC and LDL-C in response to either low- or standard-dose pravastatin (**Figure 1C–F**). A significant difference ($P < 0.01$) between the L and S groups was seen in DM patients (**Figure 1C, D**) and non-DM patients (**Figure 1E, F**).

At the end of follow-up, in the L group of patients with DM, the mean (SD) serum TC level decreased from 254 (16) to 217 (27) mg/dL, and LDL-C from 160 (24) to 131 (26) mg/dL. In the S group, the mean (SD) TC level decreased from 254 (15) to 208 (28) mg/dL, and LDL-C from 162 (25) to 125 (25) mg/dL. LDL-C decreased to ≤100 mg/dL in 8.7% (9/104) of patients with DM receiving the low dose, and 13.7% (13/95) of patients with DM receiving the standard dose.

The subgroup with DM experienced 32 CVEs compared with 39 CVEs in the subgroup without DM. In the subgroup with DM, 17 CVEs occurred in patients receiving the low dose, and 15 CVEs in patients receiving the standard dose.

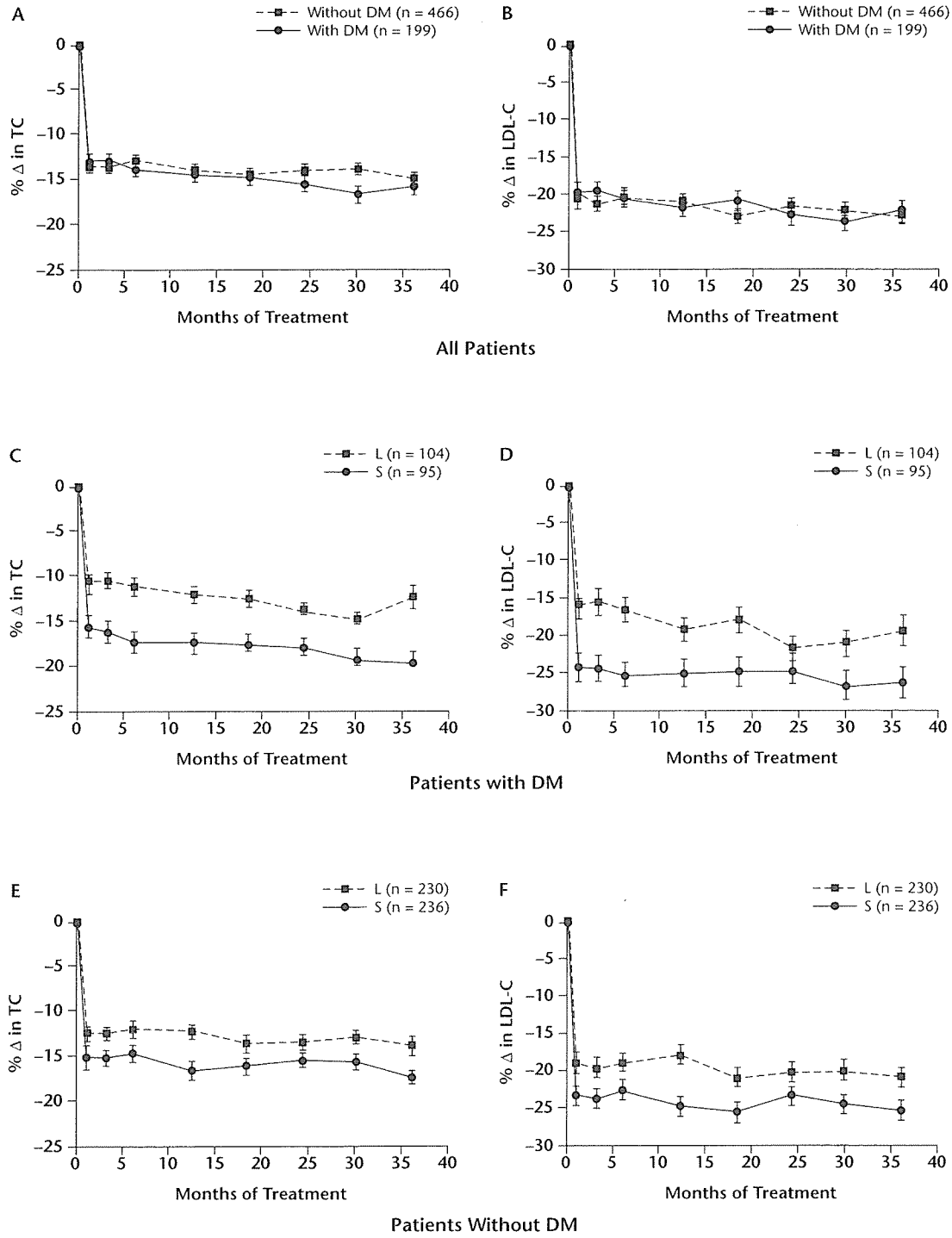

Figure 1. Least squares mean (SE) percentage changes in total cholesterol (TC) (A, C, E) and low-density lipoprotein cholesterol (LDL-C) (B, D, F) over time in patients in the Pravastatin Anti-atherosclerosis Trial in the Elderly.[1] DM = diabetes mellitus; L = low-dose pravastatin; S = standard-dose pravastatin. C–F, significant difference ($P < 0.01$) between the L and S groups.

In the subgroup without DM, 25 and 14 CVEs occurred in patients receiving the low and standard doses, respectively.

The S:L CVE risk ratio for the prevalence of fatal or nonfatal CVEs was 0.94 (95% CI, 0.46–1.92) in the subgroup with DM and 0.54 (95% CI, 0.28–1.05) in the subgroup without DM. The S:L risk ratio for the overall population was 0.70 (95% CI, 0.43–1.12) (**Figure 2**). For the combined prevalence of MI, AP, and death from any cause, the S:L risk ratios were 0.54 (95% CI, 0.18–1.63) and 0.79 (95% CI, 0.24–2.55) in the subgroups with and without DM, respectively. None of the differences were statistically significant. In patients with DM and a history of CVD, the S:L hazard ratio was 0.35 (95% CI, 0.06–1.93), whereas in patients with DM and without a history of CVD, the S:L hazard ratio was 1.23 (95% CI, 0.05–2.85).

The relative risk (RR) for CVEs in the DM subgroup, adjusted for dose group, age, sex, and CVD risk factors, was 1.87-fold (95% CI, 1.09–3.20; $P = 0.02$) higher in patients with HbA_{1c} <8.0% and 3.79-fold (95% CI, 1.92–7.48; $P < 0.01$) higher in patients with HbA_{1c} ≥8.0% than that observed in the subgroup without DM (**Figure 3**). When the risk for CVEs in patients with neither DM nor a history of CVD was assigned a reference value of 1, the RR in patients with DM but without a history of CVD (calculated in the same manner) was 3.34 (95% CI, 1.77–6.31; $P < 0.01$). In patients without DM but with a history of CVD, the RR was 3.57 (95% CI, 1.88–6.78; $P < 0.01$). In patients with DM and a history of CVD, the RR was 3.73 (95% CI, 1.57–8.86; $P < 0.01$).

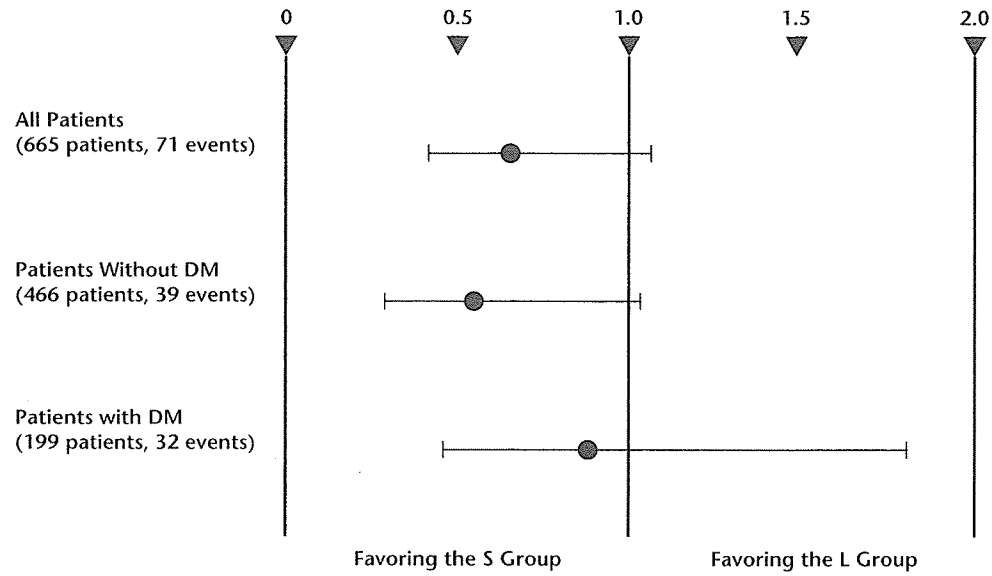

Figure 2. Risk ratios (95% CI) for the prevalence of fatal and nonfatal cardiovascular events (primary end point) in the Pravastatin Anti-atherosclerosis Trial in the Elderly.[1] Risk ratios were calculated using Cox regression analysis adjusted for age, sex, diabetes mellitus (DM), smoking history, hypertension, and history of cardiovascular disease. S = standard-dose pravastatin; L = low-dose pravastatin. No significant between-group differences were found.

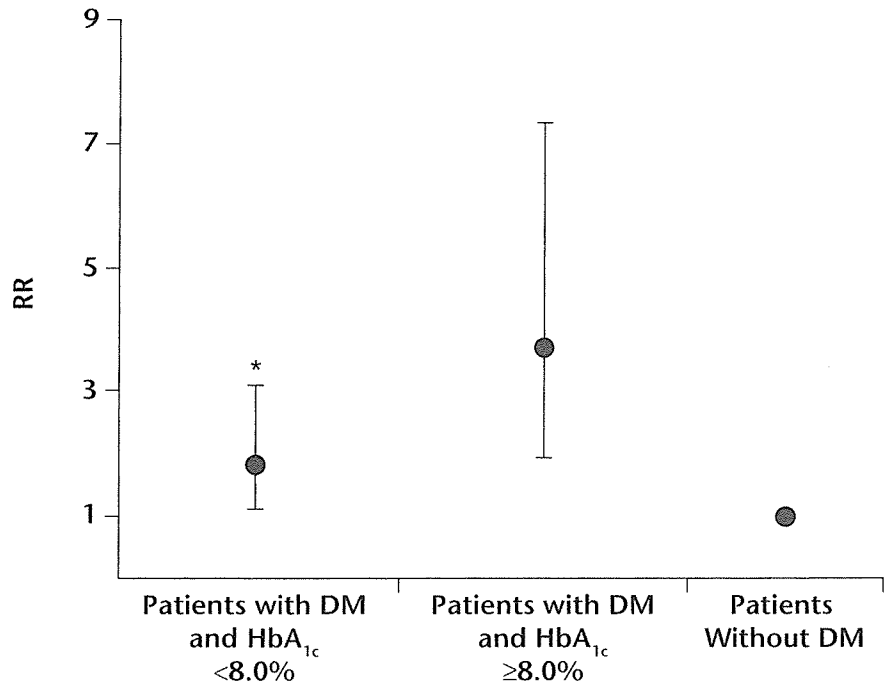

Figure 3. Risk ratios (RRs) (95% CI) for cardiovascular events.[1] Glycosylated hemoglobin (HbA_{1c}) concentrations were measured on enrollment. RRs were calculated from Cox regression analysis adjusted for group, age, sex, smoking history, hypertension, and history of cardiovascular disease. *P = 0.02 versus patients without diabetes mellitus (DM); †P < 0.01 versus patients without DM.

Table III shows the baseline characteristics of 2 subsets of patients with DM (ie, HbA_{1c} <8.0% vs HbA_{1c} ≥8.0%) compared with patients without DM. Because their baseline HbA_{1c} concentrations were not measured, 7 patients with DM were excluded from the analysis of the effect of the extent of glycemic control on CVE prevalence. No significant within-group differences in age or serum lipid levels were observed.

Tolerability

In PATE,[1] the prevalence of adverse events other than CVEs and malignant disease was similarly low in the L group (19 events in 5.4% [18/334] of patients) and the S group (26 events in 6.0% [20/331] of patients). The most common adverse drug reactions observed in the study were a slight elevation in creatine kinase activity (6 cases in the L group; 12 in the S group) and gastrointestinal symptoms (5 cases in the L group; 6 in the S group). Forty-two of 45 adverse events were mild, but 3 events were moderate (L group, decreased peripheral leukocyte count [from 3900 to 2400 cells/μL in 1 patient]; S group, increased blood urea nitrogen [from 20 to 27 mg/dL in 1 patient; from 21 to 29 mg/dL in 1 patient). All 3 of the moderate adverse events resolved on continuation of drug therapy. No serious adverse events were reported in PATE. The prevalence of adverse drug reactions was statistically similar between the groups with and without DM.

Table III. Baseline demographic and clinical characteristics of patients in the Pravastatin Anti-atherosclerosis Trial in the Elderly.

Characteristic	Patients with DM*		Patients Without DM (n = 466)
	HbA_{1c} <8.0% (n = 152)	HbA_{1c} ≥8.0% (n = 40)	
Pravastatin dose, no. (%)			
Low	78 (51.3)	24 (60.0)	230 (49.4)
Standard	74 (48.7)	16 (40.0)	236 (50.6)
Demographic			
Age, mean (SD), y	72.5 (5.4)	72.9 (5.4)	72.9 (5.8)
Sex, no. (%)			
Female	116 (76.3)	30 (75.0)	378 (81.1)
Male	36 (23.7)	10 (25.0)	88 (18.9)
Clinical			
Lipid levels, mean (SD), mg/dL			
TC	254 (15)	251 (15)	253 (15)
HDL-C	57 (15)	57 (16)	55 (15)
LDL-C	162 (24)	160 (25)	167 (24)†
TG	152 (80)	160 (74)	152 (88)
HbA_{1c}, %	6.5 (0.8)	8.7 (0.7)	–
Risk factors, no. (%)			
HTN‡	74 (48.7)	17 (42.5)	242 (51.9)
History of CVD	28 (18.4)	11 (27.5)	132 (28.3)
Smokers	14 (9.2)	4 (10.0)	39/460§ (8.5)

DM = diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HTN = hypertension; CVD = cardiovascular disease.
*Seven patients with DM were excluded from this analysis because their baseline HbA_{1c} levels were not measured.
†$P = 0.03$ versus patients with DM.
‡*Hypertension* was defined as systolic/diastolic blood pressure ≥160/≥90 mm Hg[25] and/or the use of antihypertensive drugs.
§Data were unavailable in 6 patients.

DISCUSSION

DM is a significant risk factor for CVEs in elderly patients with hypercholesterolemia.[5] The results of the present analysis suggest that patients with DM have a similar risk for CVEs as those with a history of CVD. The risk was higher when glycemia was poorly controlled. Although the duration of DM in patients in PATE was not recorded, it has been shown to be proportional to the risk for CVEs.[5] Thus, glycemic control is important in reducing the risk for CVD in elderly patients.