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Original Article

Long-Term Probucol Treatment Prevents Secondary Cardiovascular Events: a Cohort Study of Patients with Heterozygous Familial Hypercholesterolemia in Japan

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Aim: The POSITIVE study assessed whether long-term treatment with probucol, a potent anti-oxidant and cholesteryl ester transfer protein (CETP) activator, is associated with a lowered risk of cardiovascular events in a very high-risk population: familial hypercholesterolemia (FH).
Methods: The study cohort included 410 patients with heterozygous FH, diagnosed between 1984 and 1999 by cardiovascular and metabolic experts at fifteen centers. Traceable patients were screened using predefined eligibility criteria. The primary outcome measure for comparison between probucol exposure and non-exposure was the time to the first cardiovascular event involving hospitalization.
Results: Analysis revealed significant differences in baseline characteristics and follow-up treatment between exposure and non-exposure. An observed indication bias was the use of probucol in more severe FH at diagnosis, both for primary and secondary prevention. When the multivariate Cox regression procedure was used after adjustment for possible confounding factors, probucol lowered the risk (hazard ratio [HR], 0.13; 95% confidence interval [CI], 0.05–0.34) in secondary prevention ($n=74$) and was statistically significant ($p<0.001$), although not significant (HR, 1.5; 95% CI, 0.48–4.67; $p=0.49$) in primary prevention ($n=233$). Safety assessment found no specific difference between exposure and non-exposure.
Conclusion: Long-term probucol treatment may prevent secondary attack in a higher cardiovascular risk population of heterozygous FH.

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Key words; Atherosclerosis, Antioxidants, CETP activator, Dyslipidemia

Introduction

Cardiovascular (CV) diseases, including coronary heart disease and stroke, are the leading cause of death in Japan. Prevention of fatal CV events is therefore the final goal as well as the rationale of cholesterol-lowering therapy.

Probucol, a conventional cholesterol-lowering drug, originated with the report by Barnhart in 1970 [1]. The drug has been used clinically in Japan since 1985. Nearly 60,000 Japanese patients still take probucol; western countries discontinued probucol use after

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the original manufacturer's withdrawal notice to the United States FDA in 1995 after 18 year's use of the drug. Probucol's cholesterol-lowering mechanism has not yet been clearly established, but it is thought to increase catabolic excretion of cholesterol into bile[2]. Later studies[3-5] have described new mechanisms of probucol, including anti-atherogenic and anti-oxidant actions. Another controversial and anti-atherogenic feature of probucol is its paradoxical effect of lowering high-density lipoprotein cholesterol (HDL-C). This action reflects, most likely, its molecular mechanisms: promoting cholesterol efflux, and enhancing reverse cholesterol transport by activation of cholesteryl ester transfer protein (CETP)[6-8] and class B type 1 scavenger receptor[9, 10]. Matsuzawa and his colleagues reported an observed close correlation between the extent of regression in Achilles' tendon xanthoma and probucol-induced decrease in HDL-C levels in patients with familial hypercholesterolemia (FH)[11].

No large-scale, randomized, double blind comparative study has been conducted to justify the use of probucol in the prevention of CV events or diseases. However, clinical studies as well as pre-clinical data have been accumulating evidence of the clinical worth of probucol in arteriosclerotic diseases. Numerous clinical results, including a reduction in Achilles' tendon xanthoma thickness after long-term treatment for FH[12, 13], reduced rates of restenosis after angioplasty[14-16], and a decrease in carotid artery intima-media thickness[17, 18] support the therapeutic and preventative effects of probucol on arteriosclerotic lesions and plaque. To evaluate the risk and benefit of long-term probucol treatment, we conducted a cohort study to determine whether probucol treatment is associated with the risk reduction of CV events in patients with heterozygous FH, a very high-risk population.

Methods

Study Cohort

We registered patients with FH who received treatment between January 1, 1984 and December 31, 1999 at 15 centers specializing in CV and metabolic diseases, including FH, nationwide. Patients were traceable by medical record and met the diagnostic criteria for heterozygous FH under the Japan Atherosclerosis Society Guidelines (2002) for the Diagnosis and Treatment of Atherosclerotic CV Diseases[19]. Definite heterozygous FH was defined as having at least two of the major features: total cholesterol (TC) of 260 mg/dL and above; tendon xanthoma or xanthoma tuberosum; reduced or abnormal receptor activity noted by LDL receptor analysis. Probable heterozygous FH was defined as having at least one each of the major (as above) and minor features: palpebral xanthoma; arcus juvenilis (<50 years); juvenile (<50 years) ischemic heart disease. For other eligibility criteria, we excluded patients with possible homozygous FH or with severe ventricular arrhythmias (polymorphic premature ventricular contractions). Possible homozygous FH was defined as having any one of the clinical features: defect of homozygous or hetero-polymeric LDL receptors confirmed by gene analysis; no LDLR activity observed by receptor analysis, severe elevation of plasma TC higher than 500 mg/dL; xanthoma or atherosclerotic vascular lesions including symptoms of juvenile ischemic heart disease; hypercholesterolemia confirmed in both parents; history of ischemic heart disease confirmed in both parents; or poor response to any 3-hydroxy-3methyl-glutaryl-coenzyme A reductase inhibitor (statin).

During the study period between June, 2004 and September, 2005, we collected anonymous case report forms with the patients' baseline data, including medical history, findings at clinical examination, medication data, and laboratory data. The investigators transcribed the data onto case report forms (identified by a code) from the stored medical charts of the patients. The observation period was the period for which each patient's clinical course could be traced. The longest observation period exceeded 20 years for patients on stable doses of probucol.

We required a sample size of 200 in both the probucol exposure and non-exposure groups, supposing a difference of 10% in the incidence of CV events for 5 years (15% in exposure and 25% in non-exposure). At least 400 subjects were needed to detect the difference with 80% power and a type I error of 5% at the 5% significance level with two-sided log-rank test based on normal approximation. The study protocol was approved through the process of ethics committee or institutional review board at each center.

Definitions and Endpoints

The primary outcome measure was the time to the first CV event, defined as acute myocardial infarction (MI), angina pectoris (AP), heart failure (HF), stroke, transient ischemic attack (TIA) or arteriosclerotic peripheral artery diseases (PAD) leading to hospitalization or death as well as sudden death within 24 hours of an observed intrinsic event. The obtained baseline data at the first visit of each patient included demographic characteristics: sex, date of diagnosis at the participant medical center, age, height, weight, and habits of smoking and drinking. Body mass index (BMI) was calculated as weight in kilograms divided

by the square of height in meters. The other collected characteristic factors at diagnosis were the presence of xanthoma and its location, prior CV event, onset date if any prior CV event, treatment for the event, and other possible risk factors for CV events, including the presence of hypertension, diabetes, ventricular arrhythmia, and PAD. We collected data on cholesterol-lowering therapy (with or without probucol) and other concomitant therapy with anti-platelet, antihypertensive or diabetic drugs. Dates of drug initiation, discontinuation, re-administration, and termination were entered as elemental information. Treatment period was defined as the length from initiation until medication termination, or until the occurrence of the defined CV event, whichever came first. A lipid profile of TC, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and HDL-C, blood pressure, level of fasting blood sugar (FBS), hemoglobinA_{1c} (HbA_{1c}), and thickness of tendon xanthoma in both feet were variables of interest, seen as potential predictors of CV events. We obtained measurements of those variables on a yearly basis after each patient was diagnosed. LDL-C levels were calculated from TC and HDL-C measurements with the Friedewald formula in TG <400 mg/dL. For TG of 400 mg/dL and more than 400 mg/dL, the expression of 0.16 X TG was applied in stead of 0.2 X TG[20]. Most patients had fasted compliantly at periodic checkups of their lipid levels. We set a follow-up period of 10 years for the measurements.

Statistical Analyses

The primary objective of analysis was a comparison between probucol exposure and non-exposure to evaluate whether treatment with probucol (500 mg to 1,000 mg daily) for FH provided CV benefits. The analysis was based on intent-to-treat principles. The secondary objective was to assess whether changes in the lipid profile after probucol treatment predicted CV events in the cohort. Event-free survival, defined as the time from diagnosis to the first CV event, was determined as a response variable. Statistical analysis was performed to evaluate clinical outcomes separately for secondary and primary prevention groups; that is, patients with or without a history of CV events at diagnosis.

Baseline characteristics of each group were explored to detect risk factors for CV events because potential confounders, including indication bias, were anticipated. For baseline comparison, Wilcoxon's rank sum test and Fisher's exact test were used for continuous variables and categorical variables respectively. For detection of risk factors, univariate Cox proportional hazards regression with a baseline variable as covariate was used as a screening step to determine the relationship with CV events. Variables that achieved significance at the level of 20% in univariate analysis were subsequently included in a multivariate Cox proportional hazards regression using backward variable selection. Variables proving significant at the 10% significance level were selected as risk factors to be adjusted. Consequently, probucol treatment effect was evaluated using the multivariate Cox model with adjustment for the selected baseline variables. Finally, the other observed treatment factors: cholesterol-lowering drugs other than probucol, LDL-apheresis, anti-platelet drugs, anti-hypertensive drugs, and diabetic drugs were entered into that model to assess their effects.

For the association between changes in lipid profile after probucol treatment and the risk of CV events, pre-treatment values of TG, LDL-C, HDL-C as well as TC, and each lipid reduction ratio after treatment were used as covariates. Multivariate analyses of time from probucol start to the first CV event used multivariate Cox's proportional hazards models. Statistical analysis was performed with SAS version 8.2.

Results

Patient Characteristics

We collected data from the medical records of 541 patients, and excluded the data of 131 patients that did not meet eligibility predefined in the protocol.

The flow diagram (**Fig. 1**) gives reasons for the exclusion. A substantial fraction of probucol-exposed patients, 80.0% and 93.2%, took probucol within two years after diagnosis in primary and secondary prevention groups, respectively. Baseline characteristics at diagnosis are given for each group (**Table 1, 2**). The secondary prevention group (**Table 2**) had prior diseases of AP, MI, stroke, HF, and TIA. This group was found to have significant higher proportions of men (60.2%, $p<0.01$), smokers (50.0%, $p<0.01$), hypertension (40.9%, $p<0.001$) diabetes (15.9%, $p=0.02$), and older median age (52 years, $p=0.01$) than the primary prevention group. Moreover, the group tended to have hypo-HDL cholesterolemia of median 42 (20-90) mg/dL, and to receive combined treatments with anti-platelet drugs (56.8%), anti-hypertensive drugs (53.4%), and LDL-apheresis (14.8%).

Comparison between probucol-exposed and non-exposed groups revealed significant differences in some baseline characteristics and treatments, which showed a confounding indication that patients with more severe FH took probucol. For baseline characteristics, the exposed group for primary prevention had more

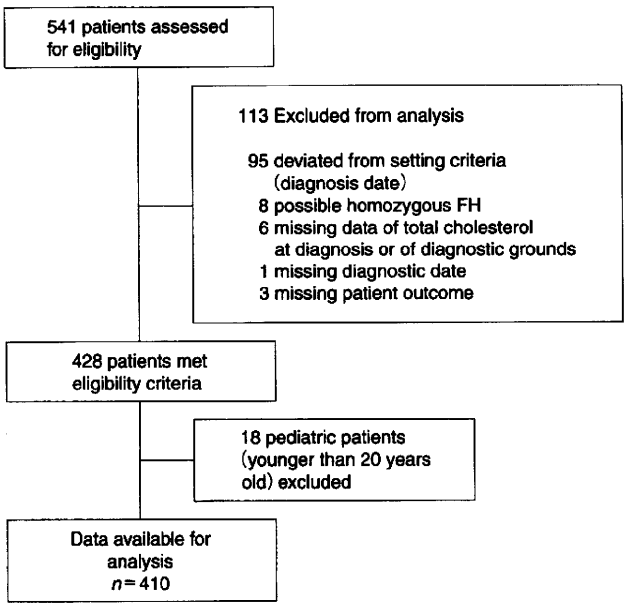


Fig. 1. Patient Flowchart.

We collected data from the medical records of 541 patients, and excluded the data of 131 patients who did not meet the eligibility predefined in the protocol. The flow diagram gives reasons for the exclusion.

palpebral xanthoma (13.4%, $p=0.05$), thicker median measurement of tendon xanthoma (12.5 mm, $p<0.01$), higher median HbA_{1c} (5.8%, $p=0.03$), and more use of antihypertensive drugs (25.3%, $p<0.01$). Their lipid profile was more severe with a higher median baseline TC (325 mg/dL, $p=0.001$), a higher median LDL-C level (253 mg/dL, $p<0.001$), and a lower HDL-C level (47 mg/dL, $p<0.001$) than the unexposed group. The exposed group for secondary prevention had a higher prevalence of post-MI (44.6%, $p<0.01$) than the unexposed group. Observed medications were also significantly different between the exposed and unexposed groups. The exposed group used anti-hypertensive drugs concomitantly at a higher rate (25.3% vs. 11.2%, $p<0.01$) for primary prevention.

Descriptive analysis of baseline characteristics and treatments during observation implies that in both primary and secondary prevention, the exposed groups tended to include patients with more severe FH at diagnosis. Arguably, patients considered more severe at diagnosis would receive more intensive treatment, including probucol.

Outcomes

We present the absolute number of CV events requiring hospitalization by prevention group with details of the events (**Table 3**). The incidence of CV events without consideration of confounding factors was 11.6% in the exposed group and 4.5% in the unexposed group for primary prevention. For secondary prevention, the incidence was 27.0% in the exposed group and 64.3% in the unexposed group. The event-free survival curve of the secondary prevention group is given (**Fig. 2**).

To identify risk factors for CV events, we determined the relationship between the incidence and every baseline variable using univariate Cox regression at a significant level of 20%. Variables proving significant at the 10% significance level in multivariate Cox regression were selected as risk factors to be adjusted. We estimated the effect of treatment after adjusting the selected risk factors. We calculated hazard ratios (HRs) with 95% confidence interval (CI) for binary variables, BMI ≥25 vs BMI <25, drinking vs no drinking, for example, and the indicated HRs corresponded to a 1 standard deviation increase for continuous variables, including TC. Estimated results are given (**Table 4**).

In the primary prevention group, significant variables were BMI ≥25 (HR 1.86, 95% CI 0.87-3.98; $p=0.11$), drinking (HR 2.17, 95% CI 1.02-4.63; $p=0.05$), tendon xanthoma (HR 2.17, 95% CI 0.76-6.23; $p=0.15$), prior diseases other than CV events (HR 1.87, 95% CI 0.87-3.99; $p=0.11$), PAD (HR 5.23, 95% CI 0.70-39.2; $p=0.11$), diabetes (HR 2.27, 95% CI 0.79-6.50; $p=0.13$), TC (HR 1.37, 95% CI 0.99-1.89; $p=0.06$), HDL-C (HR 0.75, 95% CI 0.50-1.12, $p=0.16$), SBP (HR 1.48, 95% CI 1.00-2.18; $p=0.05$), and the thickness of tendon xanthoma (HR 1.50, 95% CI 1.06-2.14; $p=0.02$). Three of these variables, drinking, TC, and PAD were selected for adjustment at the 10% significance level as a result of a multivariate Cox regression with backward variable selection. After adjustment for these three baseline variables, we found no significant effect by probucol at the 5% significant level. The estimated hazard ratio of probucol use for CV events was 1.50 (95% CI 0.48-4.67; $p=0.49$).

In the secondary prevention group, significance variables were drinking (HR 1.74, 95% CI 0.80-3.79; $p=0.17$), presence of palpebral xanthoma (HR 5.34, 95% CI 2.26-12.61, $p<0.001$), TIA (HR 4.16, 95% CI 0.54-32.21; $p=0.17$), history of coronary artery bypass graft (HR 0.31, 95% CI 0.11-0.90; $p=0.03$), hypertension (HR 0.58, 95% CI 0.26-1.28; $p=0.18$), diabetes (HR 2.89, 95% CI 1.30-6.42; $p<0.01$), and fasting blood sugar (HR 1.31, 95% CI 0.91-1.89; $p=0.15$). Two of these variables, palpebral xanthoma and diabetes, were selected for adjustment at the 10% sig-

Table 1. Baseline characteristics of patients in primary prevention group[†]

Characteristics	Primary prevention No. (%) of patients All n=322	Exposed n=233 (72.4)	Unexposed n=89 (27.6)	p
Age, mean (range)	49 (27-74)	50 (20-74)	47 (20-72)	0.18
Men, No. (%)	134 (41.6%)	96 (41.2%)	38 (42.7%)	0.90
BMI ≥25	71 (22.5%)	49 (21.4%)	22 (25.6%)	0.45
Smoker	99 (33.2%)	74 (34.1%)	25 (30.9%)	0.68
Drinker	124 (42.2%)	93 (43.7%)	31 (38.3%)	0.43
Xanthoma	259 (80.7%)	190 (81.9%)	69 (77.5%)	0.43
Tendon xanthoma	245 (76.3%)	181 (78.0%)	64 (71.9%)	0.30
Nodular xanthoma	28 (8.7%)	22 (9.5%)	6 (6.7%)	0.51
Palpebral xanthoma	36 (11.2%)	31 (13.4%)	5 (5.6%)	0.05
PAD	4 (1.2%)	1 (0.4%)	3 (3.4%)	0.07
Hypertension	54 (16.8%)	40 (17.2%)	14 (15.7%)	0.87
Diabetes	22 (6.9%)	17 (7.3%)	5 (5.6%)	0.81
Lipid profile, mg/dL				
TC[§]	320 (188-493)	325 (188-493)	307 (194-464)	0.001
TG[§]	120 (28-1289)	121 (34-1068)	120 (28-1289)	0.96
HDL-C[§]	49 (20-108)	47 (20-90)	52 (27-108)	<0.001
LDL-C[§]	244 (45-425)	253 (98-425)	223 (45-403)	<0.001
Blood Pressure, mmHg				
SBP[§]	129 (82-190)	128 (82-190)	131 (90-190)	0.57
DBP[§]	0 (48-120)	80 (48-120)	80 (56-120)	0.91
FBS (mg/dL)[§]	95 (63-276)	94 (63-140)	95 (81-276)	0.41
HbA_{1c} (%)[§]	5.7 (4.1-12.4)	5.8 (4.1-9.7)	5.3 (4.3-12.4)	0.03
Tendon xanthoma thickness (mm)[§]	12.1 (7.5-49.0)	12.5 (7.5-49.0)	10.5 (8.0-20.0)	<0.01
Treatment				
Cholesterol-lowering drugs (non-probucol)	302 (93.8%)	219 (94.0%)	83 (93.3%)	0.80
LDL-apheresis	7 (2.2%)	6 (2.6%)	1 (1.1%)	0.68
Anti-platelet drugs	49 (15.2%)	41 (17.6%)	8 (9.0%)	0.06
Anti-hypertensive drugs	69 (21.4%)	59 (25.3%)	10 (11.2%)	<0.01
Diabetic drugs	15 (4.7%)	12 (5.2%)	3 (3.4%)	0.37

[†]Continuous variables compared by Wilcoxon's rank sum test, distribution of categorical variables by Fisher's exact test. [§]Data are median (range). All data are number (%) unless otherwise indicated. Each percentage shown is related to the total number with measurement data. BMI, body mass index; PAD, peripheral artery disease; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA_{1c}, hemoglobin A_{1c}. LDL-C was calculated with the Friedewald formula.

nificance level as a result of multivariate Cox regression analysis using a backward variable selection. After adjustment for these two baseline variables, the hazard ratio of probucol use for CV events was estimated to be 0.13 (95% CI 0.05-0.34) and significant ($p<$ 0.001). In sensitivity analyses, we also obtained similar estimation results on probucol for various sets of baseline covariates for adjustment.

The lipid levels of TC, LDL-C and HDL-C were lowered after probucol treatment both in primary and secondary prevention. In the primary prevention group, the median (range) levels of TC, TG, LDL-C and HDL-C closest to before treatment were respectively 305 (165-493), 119 (35-1068), 228 (107-425) and 48 (25-96) mg/dL, and those at 10-year treatment were, respectively, 222 (141-371), 94 (43-335), 157 (91-311) and 39 (17-81) mg/dL. In the secondary prevention, the median levels of TC, TG, LDL-C and HDL-C closest to before treatment were, respectively, 320 (191-469), 129 (37-636), 240 (117-381) and 44 (24-90) mg/dL, and those at 10-year treatment were, respectively, 211(135-305), 71 (48-475),

Table 2. Baseline characteristics of patients in secondary prevention group

Characteristics	Secondary prevention No. (%) of patients			*p*
	All *n*=88	Exposed *n*=74 (84.1)	Unexposed *n*=14 (15.9)	
Age, mean (range)	52 (23-71)	51 (29-70)	53 (23-71)	0.62
Men, No. (%)	53 (60.2%)	46 (62.2%)	7 (50.0%)	0.55
BMI ≥25	21 (25.3%)	17 (24.3%)	4 (30.8%)	0.73
Smoker	42 (50.0%)	38 (53.5%)	4 (30.8%)	0.23
Drinker	39 (46.4%)	33 (46.5%)	6 (46.2%)	1.00
Xanthoma	75 (85.2%)	63 (85.1%)	12 (85.7%)	1.00
Tendon xanthoma	71 (80.7%)	61 (82.4%)	10 (71.4%)	0.46
Nodular xanthoma	7 (8.0%)	6 (8.1%)	1 (7.1%)	1.00
Palpebral xanthoma	8 (9.1%)	5 (6.8%)	3 (21.4%)	0.11
PAD	2 (2.3%)	2 (2.7%)	0 (0.0%)	1.00
Hypertension	36 (40.9%)	30 (40.5%)	6 (42.9%)	1.00
Diabetes	14 (15.9%)	9 (12.2%)	5 (35.7%)	0.04
Lipid profile, (mg/dL)				
TC†	332 (191-469)	334 (191-469)	322 (229-444)	0.41
TG†	128 (37-636)	128 (37-636)	136 (63-318)	0.85
HDL-C†	42 (20-90)	42 (20-90)	39 (26-73)	0.91
LDL-C†	249 (117-381)	256 (117-381)	245 (138-354)	0.57
Blood Pressure, mmHg				
SBP†	129 (90-180)	128 (96-180)	136 (90-166)	0.97
DBP (mmHg)†	80 (52-114)	80 (52-114)	78 (60-104)	0.33
FBS (mg/dL)†	96 (72-252)	97 (72-197)	94 (79-252)	0.96
HbA1c (%)†	5.8 (4.1-10.6)	5.5 (4.1-8.1)	6.4 (5.3-10.6)	0.06
Tendon xanthoma thickness (mm)†	14.5 (5.8-25.0)	15.0 (5.8-25.0)	10.0 (8.5-18.8)	0.09
Prior CV events				
Angina Pectoris	45 (51.1%)	36 (48.6%)	9 (64.3%)	0.39
Myocardial Infarction	34 (38.6%)	33 (44.6%)	1 (7.1%)	<0.01
Stroke	7 (8.0%)	4 (5.4%)	3 (21.4%)	0.08
Heart failure	2 (2.3%)	2 (2.7%)	0 (0.0)	1.00
TIA	2 (2.3%)	1 (1.4%)	1 (7.1%)	0.29
Treatment				0.08
Cholesterol-lowering drugs (non-probucol)	81 (92.0%)	70 (94.6%)	11 (78.6%)	
LDL-apheresis	13 (14.8%)	11 (14.9%)	2 (14.3%)	1.00
Anti-platelet drugs	50 (56.8%)	44 (59.5%)	6 (42.9%)	0.38
Anti-hypertensive drugs	47 (53.4%)	42 (56.8%)	5 (35.7%)	0.24
Diabetic drugs	6 (6.8%)	3 (4.1%)	3 (21.4%)	0.05

†Data are the median (range). All data are numbers (%) unless otherwise indicated. Each percentage is related to the total number with measurement data. TIA indicates transient ischemic attack.

147 (124-197) and 33 (17-70) mg/dL. Sub-analysis of changes in the lipid profile after probucol treatment detected significant three predictors of CV event risk: higher baseline TC (HR 2.74, 95% CI 1.05-7.16; p= 0.04) in the primary prevention group; reduction in TG (HR 0.22, 95% CI 0.06-0.86; p=0.03); and reduction in LDL-C (HR 0.17,95% CI 0.03-0.90; p=0.04) after treatment in the subset of the secondary prevention group on stable doses of probucol. Neither TC nor HDL-C after treatment was associated with CV event risk in the probucol-exposed group, which indicates that reduction of the HDL-C level after probucol treatment is not related to CV event risk for probucol-exposed patients.

We evaluated the safety of probucol for all collected data from 541 patients, and found 56 adverse

Table 3. Incidence of cardiovascular events

		Cardiovascular Event	No event	Total	*p*
Primary prevention (n=322)	Exposed (n=233)	27 (11.6%)	206	233	
	MI	4			
	AP	18			
	Str.	3			
	TIA	1			
	PAD	1			0.058
	Unexposed (n=89)	4 (4.5%)	85	89	
	AP	1			
	Str.	2			
	TIA	1			
Secondary prevention (n=88)	Exposed (n=74)	20 (27.0%)	54	74	
	MI	6			
	AP	12			
	HF	1			
	Str.	1			0.012
	Unexposed (n=14)	9 (64.3%)	5	14	
	MI	2			
	AP	6			
	Str.	1			

MI, myocardial infarction; AP, angina pectoris; HF, heart failure; Str., stroke; TIA, transient ischemic attack; PAD, peripheral artery disease.
[1]One of the 4 patients died after 12 months of probucol termination.

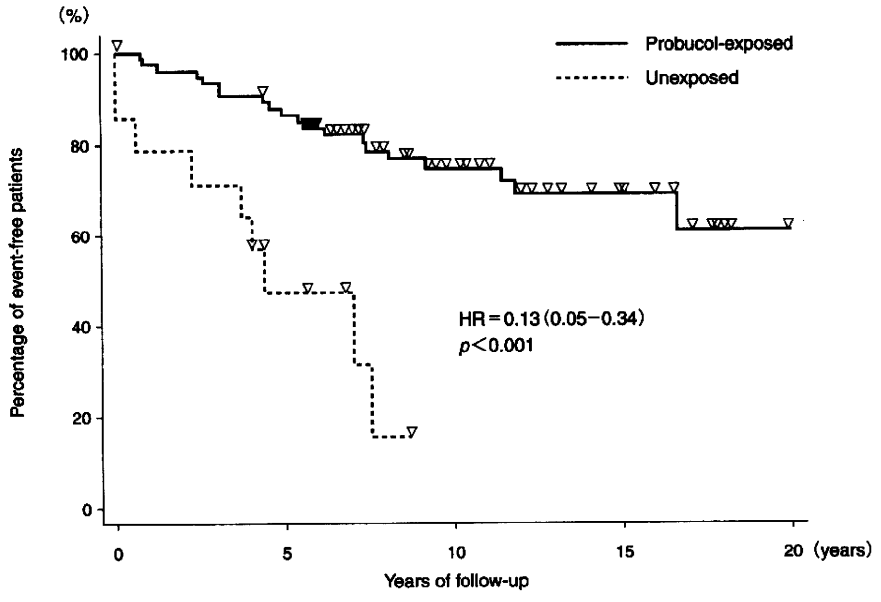
events in 18 patients. Malaise, pruritus, macrocytic anemia and pain in the extremities were recorded as adverse drug reactions associated with probucol. We noted and reported gastric cancer stage III immediately to the Ministry of Health and Welfare as an unexpected serious event, because of an unknown drug relation due to many concomitant drugs, although probucol was found to be non-carcinogenic alone[21]. Six deaths were observed in the population not taking probucol or stopping probucol. There was no other difference in the incidence of adverse events, including serious events, between probucol exposure and non-exposure.

Discussion

Many data from large-scale randomized controlled trials have overwhelmingly demonstrated the clinical benefits of lowering cholesterol with statins[22, 23], yet the rapid and extensive prophylactic use of cholesterol-lowering drugs remains controversial. Few studies have addressed the clinical risks and benefits of long-term treatment of hyperlipidemia among women[24] or elderly patients[25]. The safety of long-term cholesterol-lowering therapy, including the issue of associated cancer risk or benefit, remains inconclusive because of conflicting clinical evidence[26]. More importantly, conclusions from the results of randomized controlled trials are limited by their relatively short follow-up periods (generally less than 5 years) in the analyzed studies.

In long-term treatment for FH, probucol was used with other cholesterol lowering drugs in over 80% of the secondary prevention group–those with a more severe clinical outlook than the primary prevention group: a higher prevalence of hypertension and diabetes, significant thicker tendon xanthoma, more combined therapy with LDL-apheresis, anti-platelet drugs, and anti-hypertensive drugs. The high rate of probucol use in FH was surprising, different from expected. This might partly reflect the prescription behavior of experts with the result that intractable patients responded to the regimen.

In the secondary prevention, the higher-risk group, probucol exposure was associated with a reduction in the risk of cardiovascular events (HR 0.13; 95% CI 0.05–0.34) with high significance ($p<0.001$), while it was not significant in the primary prevention group. This result was also contrary to our expectation that probucol exposure would likely be associated with increased event risk due to a confounding indication–that patients considered more severe at diagnosis would receive more treatment, including probucol. We did not collect the details of non-probucol drugs



Number at risk

Years	0					5					10					15					20
Exposed	74	71	70	68	66	62	54	50	42	38	34	30	25	19	17	13	12	8	3	1	0
Unexposed	14	11	11	10	9	5	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0

Estimates of event-free rates are according to whether patients received probucol. The cumulative probability of remaining without events was higher in patients treated with probucol ($p<0.001$; log-rank test).

Fig. 2. Kaplan-Meier Estimates of Event-free Rate.

For secondary prevention, the incidence of cardiovascular events was 27.0% in the exposed group and 64.3% in the unexposed group. An event-free survival curve for the secondary prevention group is given.

Table 4. The results of multivariate analysis using Cox regression procedure

Factor	Primary prevention			Secondary prevention		
	HR	95% CI	*p*	HR	95% CI	*p*
Baseline variables						
Total cholesterol	1.58	1.06–2.33	0.02	–	–	–
Drinking	2.43	1.09–5.44	0.03	–	–	–
Peripheral artery disease	5.27	0.51–54.63	0.16	–	–	–
Palpebral xanthoma	–	–	–	2.94	1.02–8.47	0.05
Diabetes	–	–	–	2.58	0.76–8.76	0.13
Treatment in follow-up						
Probucol use	1.50	0.48–4.67	0.49	0.13	0.05–0.34	<0.001
Anti-platelet drug use	–	–	–	2.48	1.00–6.17	0.05

to simplify the study procedure. However, we would likely exclude underused statins because of the reduced use of non-probucol drugs from the possible factors of the higher event rate in the unexposed group, because statins were available when all of the 9 recurrent patients (**Table 3**) started and the patients continued on cholesterol-lowering drugs. We suppose, therefore, that the reasons for this unanticipated great risk reduction include some antioxidant and anti-atherogenic actions[3, 4, 27] of probucol. The finding in second prevention may be suggested by the report[27] that probucol significantly decreased *in vitro* LDL oxidizability measured under typically strong oxidative conditions, and that long-term treatment with probucol had an

anti-atherogenic effect in Watanabe Heritable Hyperlipidemic rabbits. From the observation that the baseline lipid profile was not different between the two groups of exposure and non-exposure in secondary prevention, the drug might exhibit greater effectiveness in post-cardiovascular disease patients, in possibly advanced lipid accumulation and inflammation, which are associated with the circulation of oxidized LDL[28].

In primary prevention, we observed an almost significant increase of events in the exposed group (**Table 3**), and an apparently increased risk (HR 1.5), although not statistically significant after adjustment (**Table 4**). We suppose, however, that the ideal effects of probucol might be concealed by the following factors noted in primary prevention. The exposed group had a worse lipid profile (TC, LDL-C and HDL-C levels), higher HbA_{1c}, and thus definitely a higher risk than the unexposed group. Furthermore, 8 (nearly 30%) of the 27 patients experiencing cardiovascular events in the exposed group discontinued probucol when they had events. This was consistent with the different finding between primary and secondary preventions in the exposed group: less than half of the patients (113 of 233) in primary prevention continued on probucol, while 53 (72%) of 74 patients continued in secondary prevention. This estimation might be conservative.

The controversial and paradoxical action of probucol- lowering HDL-C- level was not associated with the risk of CV events in the cohort, therefore, the association between low levels of HDL-C and an increased risk for CV events or death indicated by the early Framingham Heart Study[29] may not be extrapolated to probucol-treated patients. This proposition is consistent with recent findings that a lowered HDL-C level is not always atherogenic, but that the quality or function of HDL-C is more important than the HDL-C levels[30]. In fact, increased levels of HDL-C with torcetrapib, a CETP inhibitor, were not associated with a significant clinical benefit in patients with coronary disease[31], FH[32] or mixed dyslipidemia[33].

We speculate that enhanced reverse cholesterol transport by CETP activation as a result of probucol treatment also contributed to the detected risk reduction in the cohort. The observed positive outcome of probucol, a CETP activator, might be a mirror image of the negative clinical trial results for the CETP inhibitor[34]. Reports[35, 36] of increased coronary heart disease in CETP deficiency despite increased HDL-C levels, and the molecular approach to review CETP deficiency[37] support our hypothesis, at least in Japanese genealogy. Interestingly, a recent basic research reports that human CETP expression enhances the mouse survival rate in an experimental systemic inflammation model[38], indicating for the first time a role for CETP in the defense against the exacerbated production of proinflammatory mediators.

For the safety evaluation, we found no cardiotoxic adverse drug reaction including QT/QTc prolongation or torsade de pointes, in this study, although probucol can cause them[16, 39, 40].

We obtained these results from an observational study with no control for inaccuracy, unexpected bias or confounding factors. We could not assure the precision of the baseline measurements due to unrecorded data. The participant centers were major hospitals for FH, but not all hospitals in Japan, because the study was conducted as part of a post-marketing study by a pharmaceutical manufacturer within the framework of the Japanese government regulations. Some restrictions on collecting data might have resulted in unexpected small numbers in the unexposed group in secondary prevention, although we think that the study cohort represents nearly a nationwide population of heterozygous FH in Japan. The results derived from patient data in Japan can not necessarily be generalized to patients in western countries.

Despite these limitations of the study, however, we could evaluate the outcome of long-term probucol treatment in the medical practice setting for FH, a high-risk population, for as long as 20 years in Japan. The significant risk reduction of CV events observed in the secondary prevention group holds clinical significance and suggests some beneficial therapeutic actions of this drug in arteriosclerotic diseases. The hypothesis from the findings warrants a randomized controlled trial for verification of the secondary prevention, and needs further research into the molecular mechanisms or roles of CETP in pathogenesis.

Author Contributions

Dr. Yamashita had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Matsuzawa, Kita, Saito, Fukushima, Matsui. Acquisition of data: Yamashita, Bujo, Arai, Harada-Shiba, Saito, Kita, Matsuzawa. Analysis and interpretation of data: Yamashita, Bujo, Arai, Harada-Shiba, Matsui, Saito, Fukushima, Kita, Matsuzawa.

Drafting of the manuscript: Yamashita, Bujo, Arai, Harada-Shiba, Matsui, and Fukushima. Critical revision of the manuscript for important intellectual content: Yamashita, Matsui, Fukushima, Kita, Saito,

and Matsuzawa. Statistical analysis: Matsui and Fukushima. Administrative, technical, or material support: Fukushima, Matsui, Kita, Saito, and Matsuzawa. Study supervision: Yamashita, Fukushima, Matsui, Kita, Saito, and Matsuzawa.

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Disclosures

From the formerly Daiichi and Otsuka, Dr. Matsui, Dr. Fukushima, Dr. Matsuzawa, and Dr. Kita received fees and expenses for meetings related to protocol design, statistical and clinical interpretation of the data; Dr. Bujo, Dr. Arai, Dr. Harada-Shiba received honoraria and travel expenses for lectures, Dr.Yamashita, Dr. Bujo, Dr. Arai received fees and travel expenses for a meeting related to clinical interpretation of the data. Dr. Yamashita received consultancy fees from Otsuka. Dr. Matsuzawa is contracted as a short-term adviser to Otsuka in medical science. Dr. Saito received travel expenses only.

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Safety Aspects of Statins: Which Factors Create the Adverse Effects of Statins

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Abstract: Statins have been shown to have beneficial effects on myocardial infarction, revascularization, stroke, and cardiovascular mortality in numerous clinical trials. Seven kinds of statins are available today and have different characteristics in their efficacy of LDL-lowering, their metabolism and their adverse effects including hepatic injury, muscle disease, renal injury and neurologic injury. Muscle disease is the most discussed adverse effect with the use of statins including rhabdomyolysis, the most serious one. Hepatic injury with high dose statin use should be mentioned, although the incidence is low. Statins are well-tolerated and have been extremely well studied all over the world. As the contribution of statins in preventing cardiovascular events has already been proven, physicians should not hesitate to prescribe statins to patients not only with hypercholesterolemia, but also to those with high risks.

Key Words: Statin, myopathy, rhabdomyolysis, drug interaction, cytochrome P-450 system.

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INTRODUCTION

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have been demonstrated in numerous clinical trials to have beneficial effects on myocardial infarction, revascularization, stroke, and cardiovascular mortality. Therefore, current guidelines unequivocally advocate statin therapy for high-risk individuals, and encourage lower low-density lipoprotein cholesterol (LDL-C) goals that effectively broaden the pool of individuals eligible for statin therapy. The third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) identified an LDL-C goal < 100 mg/dl for high risk patients (those with clinical cardiovascular disease, diabetes, or 10-year coronary heart disease risk > 20%) [1]. A subsequent 2004 report from the NCEP suggested an optional LDL-C goal < 70 mg/dl for those with the highest risk including those with established cardiovascular disease, as well as additional high risk characteristics: diabetes mellitus, multiple cardiovascular risk factors of metabolic syndrome, or severe or poorly controlled risk factors, especially cigarette smoking [2]. Today, seven statins are available in most parts of the world including lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin. Cerivastatin was approved in 1998 but was withdrawn in 2001 because of a high incidence of rhabdomyolysis [3]. Statins have different characteristics in their efficacy of LDL-C-lowering, their metabolism and their adverse effects (Table 1). Trials using simvastatin doses of 40- 80 mg have been shown to reduce LDL-C by 29–35% [4-6]. A 40 mg dose of pravastatin has been shown to consistently reduce LDL-C by 25-34% in various trials [7-11]. Fluvastatin, at doses of 40-80 mg has reported reductions in LDL-C of 27-33% [12-14]. Atorvastatin doses ranging from 10-80 mg have observed reductions in LDL-C of 35-42% [15-19]. Therefore, for each statin, the dose required to achieve a specific LDL-C reduction varies. Generally, statins are well tolerated. Controlled trials and clinical practices have demonstrated that statins are generally safe; in fact, the incidence of clinically significant side effects is quite low. However, adverse effects of statin such as hepatic injury, myopathy, and rhabdomyolysis are sometimes quite serious. Indeed, concern over the safety of statins followed the worldwide withdrawal in 2001 of cerivastatin and further concern followed documentation of the hazards of rosuvastatin after regulatory approval by the US Food and Drug Administration (FDA) and marketing [20]. These also suggest that there might be a measurable difference in the incidence of adverse events among each statin. The aim of this review is to describe the rate and characteristics of various adverse effects of statins including the difference between each statin.

Table 1. Efficacy and Metabolism of Statins

	Dose Range (Percent of LDL-C Reduction by Each Statin)	Drug Metabolism
Lovastatin	20-80 mg/day	CYP3A4
	30% with 40 mg	
Simvastatin	5-80 mg/day	CYP3A4
	41% with 40 mg	
Pravastatin	5-80 mg/day	Sulphation, biliary and urinary excretion
	34% with 40 mg	
Fluvastatin	20-80 mg/day	CYP2C9
	23% with 40 mg	
Atorvastatin	5-80 mg/day	CYP3A4
	38% with 10 mg	
Rosuvastatin	2.5-40 mg/day	CYP2C8 (minor)
	45% with 10 mg	CYP2C9 (minor), lactonisation and biliary excretion
Pitavastatin	1-4 mg/day	Unclear
	42% with 2 mg	

MUSCLE DISEASE

Disorders to muscle tissue, ranging in severity from an asymptomatic creatine kinase (CK) elevation to rhabdomyolysis, are among the most discussed adverse effects with the use of statins. Myopathy is defined as muscle symptoms including pain and weakness accompanied by a CK elevation more than ten times the upper limit of the normal range. Rhabdomyolysis is a severe form of myopathy with symptoms of muscle break down and myoglobin release which causes brown urine and renal failure. Rhabdomyolysis can be diagnosed by a serum concentration of CK > 10,000 U/L and detection of myoglobin. Rhabdomyolysis may occur at any time an individual is taking a statin. Therefore incidence (the rate of occurrence) rather than prevalence (the proportion affected by a certain disease at a given time) is the appropriate measure. The

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cohort based on the UK General Practice Research Database (GPRD), which contains medical information entered by family practitioners in the United Kingdom since 1988, includes information on 2.5 million persons aged 25-75 years for the decade of 1990-1999. Only 1 case among the 52,000 persons in the cohort who took lipid-lowering drugs had rhabdomyolysis. The Japanese cohort, of the 51,000 persons taking simvastatin with 175,000 person-years of follow-up, recorded no case of rhabdomyolysis under the dose of simvastatin, in this cohort the dose of simvastatin given to patients was relatively low (5 mg/day) [21]. Analysis of administrative claims data from diverse regions in United States showed that the risk of hospitalization due to myopathy increased 5.13 times in the presence of hypertension and 6.01 times in the presence of the coadministration of CYP3A4 inhibitors [22]. A previous report on drug specific cohorts of statin and fibrate in the United States, showed that the incidence increased to 5.98 (95%CI, 0.72-216.0) per 10,000 person-years for combined therapy of atorvastatin, pravastatin, or simvastatin with fibrate, and to 1035 (95%CI, 389-2117) for combined cerivastatin-fibrate use, compared with monotherapy [23]. Fibrates rarely cause myopathy, but combinations of statins with some fibrates increase the risk by inhibiting glucuronidation of statins and increasing their serum concentration [24, 25]. Renal impairment, hypothyroidism, old age (those older than 80 years) and serious debility can increase the risk of rhabdomyolysis with statins [26]. Therefore, it is important for physicians to pay attention to a patient's characteristics when they prescribe statins, even though the incidence of rhabdomyolysis in patients taking statins is very low.

The incidence of rhabdomyolysis may be different among statins. Cziraky *et al.* reported on the incidence of rhabdomyolysis caused by each statin using an analysis of a large administrative database [22]. This report showed that the incidence of myopathy cases requiring hospitalization in patients treated with monotherapy ranged from 1.58 with fluvastatin to 10.59 with cerivastatin per 10,000 person-years. The incidence of myopathy cases requiring hospitalization after treatment with cerivastatin was significantly greater than other statins. There were no significant differences among other statins with respect to the incidence of myopathy events requiring hospitalization. Another report showed that the notification rate of rhabdomyolysis to the FDA Adverse Event Reporting System was about 4 times higher for monotherapy with lovastatin, simvastatin, and atorvastatin (mean rate 0.73; 95%CI, 0.64-0.82 per million prescriptions) than for monotherapy with pravastatin and fluvastatin (mean rate, 0.15; 95%CI, 0.09-0.24 per million prescriptions) [27]. Uncontrolled trials and post-marketing surveillance suggested that the highest dosage (80 mg/day), now withdrawn, caused rhabdomyolysis significantly more frequently than lovastatin, simvastatin, and atorvastatin, but with a lower dosage ($\leq$ 40 mg/day) the incidence rate is similar [20]. Thus there seems to be little difference in the incidence of rhabdomyolysis among each statin (the incidence of rhabdomyolysis by pravastatin and fluvastatin might be lower than that by simvastatin, lovastatin, and atorvastatin). However, it is unclear if this advantage of fluvastatin and pravastatin should make them the preferred choice in clinical use, since generally they need a higher dose to achieve their target cholesterol level than the other statins.

Statins cause myopathy as well as rhabdomyolysis. Myopathy is defined as diffuse muscle symptoms (pain, tenderness, weakness) with elevated CK. The incidence of myopathy in persons taking statins was estimated from the UK General Practice Research Database. Adjusting for incidence in the untreated group, these rates are equivalent to a mean incidence of 11 (95%CI, 4-27) per 100,000 person-years in people taking statins other than cerivastatin [27]. Four randomized trials recorded the number of participants with minor degrees of muscle pain, and found the incidence of such pain was similar in both treated and placebo groups on average. Therefore minor muscle pain attributable to statins, if it occurs, may be uncommon.

Little is known about the mechanisms by which statins produce myopathy as a side effect. Inhibition of HMG-CoA reductase by statins decreases not only synthesis of cholesterol, but also other products of mevalonate such as coenzyme Q10 (CoQ10) known as ubiquinone which is a central component of mitochondrial membrane required for oxidative phosphorylation [28, 29]. More than 50% of serum CoQ10 is derived from endogenous synthesis. Under statin treatment, reduction of serum and muscle CoQ10 is reported [30-32]. Exogenous CoQ10 supplementation was reported to prevent ubiquinone reduction induced by statins. It needs to be elucidated whether the administration of CoQ10 can prevent the adverse effect of statins. Recently, atrogin-1, a key gene involved in skeletal muscle atrophy, has been reported to be a critical mediator of the muscle damage induced by statins [33].

HEPATIC INJURY

Generally, drugs are important cause of liver disease, because most of the drugs are metabolized by the liver. Drug-induced hepatotoxicity may mimic almost any type of hepatobiliary disease from fulminant liver failure to chronic liver disease with cirrhosis. In pooled data from 3 randomized trials of pravastatin, recording 45,000 person-years follow-up of both statin-treated and placebo groups, both gall bladder disorders (1.9% vs. 2.1%) and other hepatobiliary disorders (0.7% vs. 0.9%) were less common in patients treated with statin than in participants who received a placebo [34]. In the 4S study, there was no significant difference in the elevation of transaminase between the simvastatin group and the placebo group over 5 years [35]. In a retrospective analysis of the safety of fluvastatin based on the data from 1815 patients who received fluvastatin at daily doses of $\geq$ 20 mg compared with a placebo, AST and ALT elevation were only 0.2% and 0.7%, respectively [36]. Thus, the evidence indicates that liver disease attributable to statins is rare, although there are some case reports of liver disease in patients taking statins [37]. In the FDA Adverse Event Reporting System, 38 cases of liver failure in patients taking statins were reported up to the end of 1999 (8 cases where other causes of liver failure were also present and 30 cases with no other recognized causes) [38]. This is equivalent to a notification rate of about 0.1 per 100,000 person-years of use. Hepatic injury with statin use is an extremely low incidence that is less or no greater than the risk of liver failure in general population among persons not taking statins [38]. However, clinicians need to pay attention to hepatic injury caused by the use of high dose statin, since the rate of persistent hepatic transaminase elevation of high dose atorvastatin or simvastatin is significantly higher than the use of a moderate dose [39]. Clinicians also need to be mindful of hepatic injury when they treat hypertensive or diabetic patients with statins, since analysis using administrative claims data from diverse regions in the United States showed that the risk of hospitalization due to a hepatic event increased 2.55 times in the presence of hypertension and 1.84 times in the presence of diabetes[22].

RENAL INJURY

The Renal Expert Panel finds no evidence that statins cause acute renal failure or renal insufficiency not associated with rhabdomyolysis. Combined data from 3 trials of pravastatin showed that renal failure or other renal diseases designating a serious adverse event occurred in 0.5% of the participants allocated pravastatin and 0.8% of those allocated a placebo [34]. In New Drug Applications data, rosuvastatin 80 mg/day was associated with an increased incidence of proteinuria, when compared with a placebo, lower doses of rosuvastatin, and other statins [40]. On the analysis of prescription data obtained from IMS Health, the rate of proteinuria of rosu-

vastatin was not significantly different from simvastatin and pravastatin but was significantly higher than what was observed with atorvastatin [41]. In meta-analyses of 13 trials of lipid-lowering drugs in patients with renal disease including 10 statin trials, there was a lower rate of decline in glomerular filtration rate in treated participants than in controls [42]; the difference in favor of treatment was equivalent to about 3% of the baseline glomerular filtration rate per year. In the Assessment of Lescol in Renal Transplantation (ALERT) trial of fluvastatin in renal transplant recipients, the incidence of either graft loss or doubling of serum creatinine did not significantly differ among the participants allocated fluvastatin or a placebo [43]. There is no indication that any statin at any currently marketed dose causes renal disease. However, analysis using administrative claims data from diverse regions in the United States showed that the risk of renal events requiring hospitalization increased over 7-fold in patients with hypertension and 2.8-fold in patients with diabetes [22].

NEUROLOGIC INJURY

In the analysis of cohort studies of serum cholesterol and stroke that can be distinguished by thromboembolic and hemorrhagic stroke, a lower LDL-C level was associated with a higher risk of hemorrhagic stroke [44]. On the other hand, the randomized trials of serum cholesterol reduction did not show an increase in hemorrhagic stroke in treated patients [44]. Thus the evidence is insufficient to demonstrate that low cholesterol level causes hemorrhage stroke. Furthermore, no mechanism underlying the association between low cholesterol level and hemorrhage stroke is apparent. Therefore these should not affect the use of statins to prevent cardiovascular disease since the possible excess of hemorrhage stroke is greatly outweighed by the protective effect against coronary artery disease and thrombolic stroke [44]. However, patients who have had a hemorrhage stroke should not be given cholesterol lowering drugs including statin.

Peripheral neuropathy in patients taking statins have been identified by published case reports [45]. The symptoms generally developed 1-2 months after the start of therapy, and usually resolved after discontinuation of the statins. On the other hand, in one large trial, 11 participants treated with statin and 8 participants with placebo manifested peripheral neuropathy, suggesting that there was no association [5]. Therefore, if statins cause peripheral neuropathy, the attributable risk seems to be minimal.

DRUG INTERACTIONS BETWEEN STATINS AND OTHER DRUGS

The effective doses of statins are rarely associated with significant adverse events. However, combining other drugs that have an interaction with statins, the risk of adverse events can be significantly increased. Generally, drug interactions may be effected by a change in the concentration of either or both drugs in the body (pharmacokinetic interaction) or by a change in the relation between the concentration of the drug and the response of the body to the drug (pharmacodynamic interaction) [46]. The mechanism for most statin drug interactions are associated with the cytochrome P-450 system which is involved in the metabolism of most drugs. The cytochrome P-450 system makes it relatively easy to predict which drugs may interact; however, it makes it difficult to predict the probability of a drug interaction in a given patient owing to individual differences in sensitivity to increased statin drug levels [46]. Clinically, significant drug interactions with statins are thought to be resulted from altered pharmacokinetics, primarily metabolism, as these drugs are highly selective inhibitors of HMG-CoA reductase with no known effects on other receptors, making pharmacodynamic interaction less likely. However, fibrates and niacin can cause myopathy, when added to statin therapy, an increased additive risk may be anticipated [25].

Approximately 80% of drugs require biotransformation into hydrophilic metabolites for renal elimination, with about 50% of these drugs undergoing metabolism by the CYP3A4 isoenzyme, which is the major liver microsomal (60%) and interstitial (70%) isoenzyme of the cytochrome P-450 system [47]. Concomitant administration of compounds metabolized by this system can result in inhibition of enzyme activity by an inhibiting drug or compound with an increased plasma level of the substrate drug and increased potential for adverse drug reactions. In addition to an inhibition of the liver P-450 system, other sites of potential statin drug interactions include inhibiting metabolism by intestinal P-450 isoenzymes, and preventing P-glycoprotein transfer across the intestinal wall.

Drug specific interactions with each statin are dependent on the metabolic pathway of the statin. Lovastatin, simvastatin, and atorvastatin are metabolized *via* the cytochrome P450 3A4 (CYP3A4) pathway [46] (Table **1**). Drug metabolism studies show simvastatin and lovastatin to be especially sensitive to inhibiting effects on CYP3A4. *In vitro* studies of the potent CYP3A4 inhibitors including erythromycin and verapamil demonstrated that simvastatin levels increased 4~5-fold, and more potent inhibitors such as itraconazole increased simvastatin concentration by 10~20-fold [48-50]. Similar results have been shown with lovastatin and CYP3A4 inhibitors [50]. Fluvastatin which is metabolized by the CYP2C9 has been shown to increase the concentration of diclofenac significantly [46]. Warfarin and phenytoin, which are known to be metabolized by CYP2C9, both increased their effect when co-administered with fluvastatin. Pravastatin and rosuvastatin are not significantly metabolized by the CYP pathway, however gemfibrozil and cyclosporine can increase the concentration of these statins by possibly blocking their biliary excretion [51]. Gemfibrozil also inhibits glucuronidation, which affects primarily the acid form of statins [24]. Concentrations of lovastatin and simvastatin increase 3-fold and rosuvastatin increase 2-fold, when these statins are combined with gemfibrozil. Table **2** shows the profiles of reports of rhabdomyolysis associated with statins [52].

SAFETY OF HIGH DOSE STATIN USE

The third report of NCEP identified an LDL-C goal < 100 mg/dl for high risk patients (those with clinical cardiovascular disease, diabetes, or 10-year CHD risk > 20%) [1]. A subsequent 2004 report from the NCEP suggested an optional LDL-C goal < 70 mg/dl for those the highest risk including those with established cardiovascular disease plus additional high risk characteristics: diabetes mellitus, multiple cardiovascular risk factors of metabolic syndrome, or severe or poorly controlled risk factors, especially cigarette smoking [2]. Therefore, high risk patients should be treated with high dose statin. Indeed, in the TNT (Treating to New Targets) trial, based on the standard deviation of LDL at baseline, it can be estimated that approximately 90% of subjects in the atorvastatin 80 mg group had an LDL-C < 100 mg/dl, whereas approximately 50% of patients had an LDL-C >100 mg/dl in the atorvastatin 10 mg group [19].

Overall, high dose statins were reasonably well tolerated in clinical trials using several statins, there was evidence of a higher rate of adverse effects leading to their discontinuation. In the long term event trials of atorvastatin 80 mg, the discontinuation rate due to unspecified drug related adverse events was consistently higher in the patients with high dose aims (7% to 10%) than those with moderate dose aims (4% to 5%) over the approximately 5 years of observation. Though no additional risk of myopathy was reported in the higher dose group, the effect on transaminases seemed to be dependent on the statin dose in some statins (Table **3**). In the A to Z trial, simvastatin 80 mg had a slightly higher rate of treatment discontinuation due to muscle side effects (1.8%) than the simvastatin 20 mg group (1.5%) [4].

Table 2. Profiles of Reports of Rhabdomyolysis Associated With Statins

Statin	Frequency of Reports/Unique Cases	No. of Cases Associated with Potentially Interacting Drugs* (n)	
Simvastatin	321/215	Mibefradil (48) Fibrates (33) Cyclosporine (31) Warfarin (12) Macrolide antibiotics (10) Digoxin (9)	Azole antifungals (4) Chlozoxazone (2) Nefazodone (2) Niacin (2) Tacrolimus (1) Fusidic acid (1)
Cerivastatin	231/192	Fibrates (22) Digoxin (7) Warfarin (6) Macrolide antibiotics (2) Cyclosporine (1) Mibefradil (1)	
Atorvastatin	105/73	Mibefradil (45) Fibrates (10) Macrolide antibiotics (13) Warfarin (7) Cyclosporine (5) Digoxin (5) Azole antifungals (2)	
Pravastatin	98/71	Fibrates (6) Macrolide antibiotics (6) Warfarin (5) Cyclosporine (2) Digoxin (2) Mibefradil (1) Niacin (1)	
Lovastatin	51/40	Cyclosporine (12) Macrolide antibiotics (11) Azole antifungals (6) Fibrates (5) Mibefradil (3)	Digoxin (2) Nefazodone (2) Niacin (1) Warfarin(1)
Fluvastatin	11/10	Fibrates (4) Warfarin (2) Digoxin (1) Mibefradil (1)	

*Each case may be associated with one or more potentially increasing drugs. Adapted from reference No.35.

Table 3. Safety Data from Randomized Controlled Trials of Intensive Statin Therapy. (Adapted from Reference No.20)

Trials	Statin Comparison Higher vs Lower	Characteristics of Participants	Alanine Transaminase 3 Times Upper Limit of Normal Higher vs Lower	Creatine Kinase 10 Times Upper Limit of Normal, or Myopathy Higher vs Lower	Rhabdomyolysis Higher vs Lower	Non-Vascular Death Higher vs Lower
PROVE-IT	A 80 mg vs P 40 mg	Acute coronary syndrome	69(3.3%) vs 23(1.1%)	2(0.1%) vs 3(0.15%)	0(0%) vs 0(0%)	17(0.8%) vs 27(1.3%)
A to Z trial	S 80mg vs S 20 mg	Acute coronary syndrome	19(0.9%) vs 8(0.4%)	9(0.4% vs 1(0.04%)	3(0.1%) vs 0(0%)	21(0.9%) vs 21(0.9%)
TNT	A 80 mg vs A 10 mg	Stable CHD	60(1.2%) vs 9(2%)	(0.0%) vs (0.0%)	2(0.04%) vs 3(0.06%)	158(3.2%) vs 127(2.5%)
IDEAL	A 80 mg vs S 20-40 mg	Stable CHD	43(0.97%) vs 5(0.11%)	6(0.14%) vs 11(0.25%)	2(0.05%) vs 3(0.07%)	143(3.2%) vs 156(3.5%)
SPARCL	A 80 mg vs placebo	Post stroke or TIA	51(2.2%) vs 11(0.5%)	7(0.3%) vs 7(0.3%)	2(0.1%) vs 3(0.1%)	117(4.9%) vs 94(3.9%)

To improve patient outcome, clinicians need to be aware of patient characteristics. Special attention should be given to those who have renal impairment, hypothyroidism, serious debility, or those who are over 80 years old, especially when considering the use of high dose statin.

CONCLUSION

Previous analyses based on cohort and trial database demonstrated that the incidence of rhabdomyolysis is low under available statins use, that is, pravastatin, simvastatin, fluvastatin, atorvastatin, lovastatin, pitavastatin, and rosuvastatin. Incidence of adverse effects including hepatic injury or renal injury is also quite low under various statins. Therefore, physicians should not hesitate to prescribe statins to patients with hypercholesterolemia or patients that have high risk to prevent cardiovascular diseases. However, several drugs increase the risk of adverse effects of statins because of drug interaction with statins, and patients with hypertension, diabetes, and older age are also at high risk of having an adverse event to a statin. Statins are well-tolerated and have been extremely well stud-