Review Article

Treatment of Hyperlipidemia from Japanese Evidence

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The treatment of hyperlipidemia is aimed at preventing cardiovascular disease (CVD) and coronary heart disease (CHD). As the incidence of CHD in Japan is about one-third lower and that of stroke is two-fold higher compared to Western countries, and the doses of lipid-lowering drugs used in foreign randomized controlled clinical trials (RCTs) are much higher than in general use in Japan, it remains unclear whether the results of RCTs conducted in Western countries could be extrapolated to Japanese patients. Recently, two major large-scale, prospective, RCTs in Japanese hypercholesterolemic patients, the Management of Elevated Cholesterol in the Primary Prevention of Adult Japanese (MEGA) study and the Japan EPA Lipid Intervention Study (JELIS), have been reported. Japanese epidemiological studies and Japanese clinical studies are reviewed. The evidence suggests that hypercholesterolemia, hypertriglyceridemia, and low HDL-cholesterol are strongly associated with increased CHD risk. Lipid-lowering medication shows beneficial effects even in low-risk populations; however, the data did not support that lower cholesterol is better. The safety and efficacy of hyperlipidemia treatment in Japanese patients are discussed.

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Key words; Hyperlipidemia, Randomized controlled trial, Cardiovascular disease, Coronary heart disease, Epidemiological study, Lipid-lowering therapy

Introduction

It is well established that hyperlipidemia is a major cause of the development of atherosclerotic cardiovascular disease (CVD), especially coronary heart disease (CHD). Thus, hyperlipidemia treatment is aimed at preventing CVD and CHD. Current national and international guidelines identify the reduction of low-density lipoprotein-cholesterol (LDL-C) levels as the primary target for cardiovascular risk reduction therapy¹⁻³. Hyperlipidemia includes both hypercholesterolemia and hypertriglyceridemia, and the latter is often associated with a spectrum of other lipid abnormalities which have atherogenic potential of their own. The so-called atherogenic lipoprotein profile or ath-

erogenic dyslipidemia consists of elevated levels of triglyceride, low levels of high density-lipoprotein-cholesterol (HDL-C), and the predominance of small dense LDL⁴.

The National Cholesterol Education Program Adult Treatment Panel III (ATP-III) guidelines in the United States emphasize evidence based on a number of large epidemiological studies and many large, randomized, controlled clinical trials (RCTs)². Many RCTs in Western countries have shown that the reduction of LDL-C levels by lipid-lowering therapy such as HMG CoA reductase inhibitors (statins) reduces the major coronary events and CHD mortality⁵⁻¹⁴. Recent studies have shown that the benefit of LDL-C-lowering therapy is observed regardless of the baseline levels of LDL-C in high-risk patients such as patients with previous CHD, diabetic patients and patients with a clustering of risk factors¹². On the other hand, the incidence of CHD in Japan is about one-fourth to one-third lower and that of stroke is two-fold higher compared to Western countries¹⁵⁻¹⁸. In addition, the dose of lipid-lowering drugs used in for-

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eign RCTs is much higher than in general use in Japan. Thus, it remains controversial whether the results of clinical studies conducted in Western countries could be extrapolated to Japanese patients. There had been few RCTs with Japanese patients until two major large-scale, prospective, RCTs with statin and eicosapentaenoic acid (EPA) therapy in Japanese hypercholesterolemic patients were reported last November^{18, 19}. The purpose of the present document is to review the Japanese evidence of hyperlipidemia as a risk factor for CVD and to discuss the treatment of hyperlipidemia from the viewpoint of the Japanese evidence.

Epidemiological Studies in Japan

Hypercholesterolemia and CHD

A 26-year follow-up of the Hiroshima-Nagasaki study of a fixed population of 13898 subjects in Hiroshima and 6063 subjects in Nagasaki which was conducted in 1958-1960, demonstrated an almost linear increase in the age-adjusted incidence of CHD and the relative risk of CHD in relation to serum cholesterol levels in both men and women²⁰. The cohort of the Hiroshima-Nagasaki Study is the Japanese cohort of the NI-HON-SAN Study, a well-known migration study; middle-aged Japanese men living in Japan, Honolulu, and San Francisco had progressively higher serum total-cholesterol (TC) and CHD death rates as their lifestyle became progressively westernized, including a shift toward a diet higher in animal fat²¹. In the Seven Countries Study, a population-based survey of 16 cohorts of men aged 40-59 years between 1959 and 1964, the relative risk for 5-year and 10-year CHD incidence was positively associated with serum TC levels; however, the association was less clear in Japan and Mediterranean South Europe²². The Serum Lipid Survey in Japanese populations has shown gradual increases in serum TC levels from 1960 to 2000 due to the westernization of dietary habits²³.

In a number of epidemiological studies in Japan, NIPPON DATA 80 (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980) is a large prospective epidemiological study which reflects the Japanese population. This is a nationwide cardiovascular survey from 1980 and 10546 community-based subjects (4640 men and 5906 women) aged ≥ 30 years in 300 randomly selected health districts in all 47 prefectures participated. The 13.2-year prospective study of NIPPON DATA 80 showed a significantly positive relation of hypercholesterolemia (≥ 240 mg/dL) to CHD mortality and that the attributable risk percentage of hypercholesterolemia was 66% for CHD²⁴. The re-

cent analysis of 159293 person-years with a mean follow-up of 17.3 years has shown that the highest TC (≥ 6.71 mmol/L, 260 mg/dL) at baseline had an increased risk of CHD (hazard ration [HR] 3.81; 95% confidence interval [CI] 1.70-5.43) whereas the lowest TC (< 4.14 mmol/L, 160 mg/dL) had an increased risk of liver disease²⁵. After the exclusion of death due to liver disease during the entire follow-up period, increased HR in the lowest TC group disappeared and the HR for total mortality within the first 5 years of follow up in the highest TC group further increased (HR 1.48; 95%CI 1.12-1.96), mainly as a consequence of CHD. These results were similar in gender-specific analysis, and were in good agreement with the Okinawa cohort study where mortality from CVD is the lowest and life expectancy is the highest in Japan²⁶. On the other hand, hypercholesterolemia was not a risk factor for stroke, which is in good agreement with the Hisayama Study, an established cohort study²⁷, and the mortality from cerebral hemorrhage was even the highest in the lowest TC group in men (HR 3.77; 95% CI, 1.35-10.5). The recent risk assessment chart for death from CVD based on a 19-year follow-up NIPPON DATA 80 showed that the stroke chart was not graded by TC levels²⁸; therefore, hypercholesterolemia, especially higher than 260 mg/dL of TC and 160 mg/dL of LDL-C, has been shown to be positively associated with CHD mortality in Japan.

On the other hand, several epidemiological studies failed to show a positive relationship between serum TC and CHD incidence^{29, 30}. A 15.5-year rural community-based cohort study in Niigata, which was conducted in 1977, has shown no relationship between serum TC and the occurrence of myocardial infarction²⁹. There is a variation in the serum TC levels between rural and urban areas, and CHD mortality may be higher in the urban population than in the rural population^{30, 31}. Thus, it seems likely that lifestyle affects serum lipid levels, and the morbidity and mortality of CHD.

Hypertriglyceridemia, Low HDL-C and CHD

Although the association between elevated serum TC levels and the increased risk of CHD is well established, the mean serum TC levels in Japanese are still one of the lowest in the world and even in Asia³². A 15.5-year prospective study of 4452 men and 6616 women, aged 40-69 years, and free of CHD and stroke from 3 rural and one urban area demonstrated that non-fasting serum triglycerides are positively associated with the incidence of CHD in both men and women independently of TC and HDL-C³³. The significance of triglyceride as a risk factor for CHD was also

Fig. 1. Association between the usual levels of total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL), non-HDL-cholesterol, and the ratios of TC/HDL and TG/HDL, and death due to coronary heart disease, in Asian (dashed line), and Australia and New Zealand (solid line) cohorts. Analyses are adjusted by study and sex (as stratification variables), age, current smoking, and systolic blood pressure. The hazard ratio and 95% confidence interval for a one standard deviation (SD) higher level of TC, log TG, non-HDL, TC/HDL-C, log (TG/HDL-C), and a one SD lower level of HDL-C are shown. The *p* value for the heterogeneity of each association by region is also shown. 1 mmol/L (cholesterol) = 38.67 mg/dL, 1 mmol/L (triglyceride) = 88.57 mg/dL. Adapted from reference 35.

reported from international studies including Japanese cohorts³⁴. The Asia-Pacific Cohort Studies Collaboration (APCSC) is a meta-analysis of prospective cohort studies to provide reliable evidence about the determinants of risk factors for CVD in the Asia Pacific region, including not only Asian countries but also Australia and New Zealand. The APCSC includes a number of Japanese cohorts such as Hisayama, Ohasama, and Tanno/Soubetsu. Meta-analysis of 26 studies in APCSC with 96224 individuals and 796671 person-year follow-up have shown that increased baseline triglyceride levels are significantly associated with fatal and non-fatal CHD, and fatal and non-fatal cerebral infarction, independently of other major risk factors including HDL-C³⁴. Recent meta-analysis in comparison with risk factors between Asian and white populations (Australia) has demonstrated that high TC, high triglyceride, high non-HDL-C, and low HDL-C are each independent risk factors for CHD death in

both Asia and Australia (**Fig. 1**)³⁴. In addition, triglyceride and the triglyceride/HDL-C ratio were more informative predictors for CHD than TC³⁵.

Hypertriglyceridemia is often associated with low-HDL-C, both of which are integral components of metabolic syndrome^{36, 37}. Several case-control studies including ours³⁸⁻⁴¹ and a prospective observational study⁴² have shown that low-HDL-C and high triglyceride are important risk factors for CHD as well as hypercholesterolemia. Recent studies suggest that high triglyceride and/or low HDL-C are strongly associated with the predominance of highly atherogenic small dense LDL^{41, 43-45}. The Honolulu Heart Program, a population study of older Japanese-American men living in Oahu, demonstrated that the composite risk factor for small LDL, triglyceride and HDL-C is an increased risk for CHD independent of other risk factors⁴⁵. In addition, the recent Framingham study has shown that increased small LDL-C evaluated by NMR

spectroscopy is closely associated with metabolic syndrome⁴⁴). Atherogenic hypertriglyceridemia and/or low HDL-C should be an alternative target for the prevention of CVD.

Cohort Study of Hypercholesterolemic Patients with Statins

The Japan Lipid Intervention Trial (J-LIT) was the first nationwide 6-year cohort study of 41801 hypercholesterolemic patients without a prior history of CHD and 4599 hypercholesterolemic patients with CHD, aged 35 to 70 years in men and postmenopausal women aged under 70 years, with open-labeled simvastatin (5-10 mg daily) treatment to determine the relationship between the occurrence of CHD and serum lipid levels⁴⁶⁻⁴⁹). This study was designed in 1990 and 67% of the participants were women. Simvastatin reduced LDL-C levels by 27%. During the 6 years of simvastatin treatment, the incidence of CHD was much higher in the secondary prevention cohort than that in the primary prevention cohort (4.45 vs 0.91 per 1000 patient years, respectively). Although we could not conclude the evidence of risk reduction of CHD by simvastatin treatment because of no intervention trial, J-LIT showed the significance of a clustering of risk factors for CHD. Male patients had a 2.3-fold higher risk of CHD onset and a 2.6-fold higher risk of CHD recurrence compared with female patients. Diabetes was an increased risk in both primary and secondary prevention. Elderly patients aged older than 65 years, and patients with hypertension, a family history of CHD or smoking habit showed an increased risk of CHD onset. The onset and recurrence of coronary events were each positively and inversely associated with averaged concentrations of LDL-C and HDL-C in 6-year simvastatin treatment, respectively, whereas the averaged triglyceride levels did not correlate with the recurrence of CHD in secondary prevention. In addition, the recent sub-analysis of 41088 patients without a history of CHD and cerebrovascular disease showed that not cerebral hemorrhage but cerebral infarction was significantly associated with high TC (≥ 240 mg/dL), high LDL-C (≥ 160 mg/dL), high triglyceride (≥ 150 mg/dL) and low HDL-C (< 40 mg/dL)⁴⁹). Simvastatin was well tolerated and adverse side effects were reported in 3.2% over 6 years. No case of rhabdomyolysis was observed⁴⁶).

Review of Clinical Trials in Japan

As Japanese physicians rejected the determined rules of randomization, and placebo-controlled trials

are unethical, we had very few RCTs. **Tables 1, 2, and 3** compare Japanese clinical trials and major RCTs in the West. We have one observational study and three RCTs, all of which used pravastatin in hypercholesterolemic patients. It is very difficult to compare the results of Japanese RCTs to Western RCTs because of the different incidence of events, endpoints and clinical characteristics of the studied population. While most primary endpoints in Western RCTs are hard events such as all-cause death, CHD death and fatal or non-fatal myocardial infarction, the primary endpoints of Japanese RCTs are coronary events including angina pectoris, coronary revascularization, and/or unexpected or sudden death because of much lower CHD mortality compared with other countries.

Observational Study

The Kyushu Lipid Intervention Study (KLIS)

The KLIS was designed as the first large-scale RCT to investigate the effects of pravastatin in the primary prevention of CHD events and cerebral infarction in Japan. A total of 5640 Japanese men, aged 45 to 74 years with hypercholesterolemia (TC ≥ 220 mg/dL), were randomly allocated to either pravastatin (10 to 20 mg daily) or conventional treatment other than statins, probucol and bezafibrate⁵⁰); however, the participating physicians did not necessarily follow the instructions of the random assignment, and the number of patients and baseline lipid levels were quite different between pravastatin and conventional treatment groups. Thus, the results should be interpreted as an observational study. After a 5-year follow-up period, pravastatin reduced LDL-C by 20% while conventional therapy reduced LDL-C by 10%. The incidence of CHD including myocardial infarction, coronary revascularization procedure, and cardiac or unexpected death and/or cerebral infarction was 9.77 per 1000 patient years in the pravastatin group and 10.99 per patient years in the conventional therapy group. The risk of CHD and/or cerebral infarction was 19% lower ($p=0.08$) and the total mortality was 21% lower ($p=0.08$) in pravastatin treatment. When the pravastatin group was divided into two subgroups of poor and good compliance, the good-compliance pravastatin treatment reduced LDL-C by 10% and significantly reduced the risk of CHD and/or cerebral infarction by 27% ($p=0.04$) compared to conventional treatment. The recent sub-analysis of KLIS to compare the relation of serum lipid levels to CHD events between middle-aged (< 65 years) and elderly men (≥ 65 year) has shown that serum TC concentration during the follow-up period, not at the baseline, was related to an increased risk of CHD in elderly men⁵¹).

Table 1. Comparison of characteristics between Japanese clinical trials and major randomized controlled trials in Western countries

Trials (region)	Treatment Comparison (mg/day)	Number of patients (Men %)	Baseline characteristics			Mean duration (years)	Age Mean [SD], eligibility (M: men), (W: women)
			CHD/CVD	Diabetes	hypertension		
KLIS (Japan), non-RCT	P 10-20 Vs Usual care	3853 (100)	Non-CVD	23%	43%	5	58 [8], 45-74
PATE (Japan), RCT	P 10-20 Vs P 5	665 (21)	CVD 177	30%	51%	3.9	73 [6], ≥ 60
MEGA (Japan), RCT	P 10-20 Vs Diet therapy	7832 (32)	Non-CVD	21%	42%	5.3	58 40-70 (M) Postmenopause-70 (W)
JELIS (Japan), RCT	P 10 or S 5 Vs P 10 or S 5 + EPA 1800	18645 (45)	CHD 3664	23%	44%	5	61 40-75 (M) Postmenopause-75 (W)
WOSCOPS (Europe)	P 40 Vs placebo	6595 (100)	Non-CHD	1%	15%	4.8	55 [6], 45-64
AFCAPS/TextCAPS (North America)	L 20-40 Vs placebo	6605 (85)	Non-CHD	2%	22%	5.3	58 [7] 45-73 (M), 55-73 (W)
ASCOT-LLA (Europe)	A 10 Vs placebo	10305 (81)	Non-CHD	25%	100%	3.2	63 [9], 40-79
CARDS (Europe)	A 10 Vs placebo	2838 (68)	Non-CHD	100%	84%	3.9	62 [8], 40-75
PROSPER (Europe)	P 40 Vs placebo	5804 (48)	CVD 44%	11%	62%	3.2	75 [3], 70-82
4S (Europe)	S 20-40 Vs placebo	4444 (81)	CHD	5%	26%	5.2	58 [7] (M), 61 [6] (W) 35-70
HPS (Europe)	S 40 Vs placebo	20536 (75)	CVD 17907	29%	41%	5	40-80
CARE (North America)	P 40 Vs placebo	4159 (86)	CHD	14%	43%	4.8	59 [9], 21-75
LIPID (Australia, NZ)	P 40 Vs placebo	9014 (83)	CHD	9%	42%	5.6	62, 31-75
GREACE (Europe)	A 10-80 Vs Usual care	1600 (79)	CHD	20%	42%	3.0	A: 58 [12], Usual care 59 [14] <75

P 5-40: pravastatin 5 mg-40 mg, S 5-40: simvastatin 5 mg-40 mg, L 20-40: lovastatin 20 mg-40 mg, A 10-80: atorvastatin 10 mg-80 mg, U: usual care
 NZ = New Zealand, CHD = coronary heart disease, CVD = cardiovascular disease, M = men, W = women

The KLIS has shown that high serum TC levels with treatment are a significant risk for CHD in hypercholesterolemic elderly men.

Randomized Controlled Trials (RCTs)

The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE)

The PATE is the first prospective RCT in the world for only hypercholesterolemic elderly patients, aged ≥ 60 years. This study was started in 1990, and at that time, no large RCT had been reported. Six hundred and sixty-five hypercholesterolemic elderly men and women both with and without previous CHD randomly received either a low dose (5 mg/day) or standard dose (10-20 mg/day) of pravastatin⁵². Baseline TC levels were similar in the 2 groups ($253 \pm$

15 mg/dL); however, the proportion of women was significantly more in the standard-dose group than in the low-dose group. With treatment TC levels were 209 ± 2 mg/dL in the standard dose and 221 ± 2 mg/dL in the low dose. The decrease of TC and LDL-C, calculated using Friedewald's formula, and triglyceride, and the increase of HDL-C were significantly greater in the standard-dose group than in the low-dose group at all time points; however, the difference of TC was 10-14 mg/dL, which was smaller than that reported in the West. Nevertheless, the incidence of fatal and non-fatal cardiovascular events was significantly lower in the standard-dose group than in the low-dose group ($p=0.0046$, generalized Wilcoxon test; $p=0.096$, log-rank test) at a mean follow-up of 3.9 years. The risk reduction for cardiovascular events in

Table 2. Comparison of lipid levels between Japanese clinical trials and major randomized controlled trials in Western countries

Trials (region)	T-C		LDL-C		HDL-C		TG	
	Mean (Eligibility)	Net change	Mean (Eligibility)	Net change	Mean (Eligibility)	Net change	Mean (Eligibility)	Net change
KLIS (Japan), non-RCT	P 254, U 243 (≥220)	P -39 mg/dL, -15% U -19 mg/dL, -8%	P 169 U 160	P -37 mg/dL, -20% U -17 mg/dL, -10%	P 49 U 50		P 174, U 156	
PATE (Japan), RCT	253 (220-280)	P10 -38-42 mg/dL, -15-17% P5 -28-32 mg/dL, -11-13%	P10 166, P5 164	P10 -39-43 mg/dL -23-26% P5 -30-34 mg/dL -17-20%	55		P10 153, P5 152	
MEGA (Japan), RCT	243 (220-270)	-11.5%	157	-18.0%	58	5.8%	127	-8.1%
JELIS (Japan), RCT	275 (≥250)	-19%	182	49 mg/dL -26%				-4% (control) -9% (EPA)
WOSCOPS (Europe)	272 (≥252)	-20%	192 (≥155)	-26%	44	5%	164	-12%
AFCAPS/TexCAPS (North America)	221 (180-264)	-37 mg/dL -18.4%	150 (130-190)	-73 mg/dL -25.0%	36 (≤45) M 40 (≤47) W	3 mg/dL 6.0%	158 (≤400)	-15 mg/dL -15%
ASCOT-LLA (Europe)	213 (≤250)	-50 mg/dL	131	-41 mg/dL	50	0	146 (<400)	-33 mg/dL
CARDS (Europe)	207	-48 mg/dL* -26%*	117 (≤160)	-46 mg/dL* -40%*	54	0.8 mg/dL* 1%*	150 (≤600)	-35 mg/dL* -19%*
PROSPER (Europe)	221 (155-348)		147	-50 mg/dL -32%	50	5%	133 (<531)	-12%
4S (Europe)	260 (212-309)	-26%	188	-36%	46	7%	133 (≤221)	-17%
HPS (Europe)	228 (≥135)	-46 mg/dL	131	-39 mg/dL	41	1 mg/dL	186	-27 mg/dL
CARE (North America)	209 (<240)	-20%*	139 (115-174)	-42 mg/dL -32%, -28%*	39	5%*	155 (≤350)	-14%*
LIPID (Australia, NZ)	218 (155-271)	-39 mg/dL -18%*	150	-25%*	36	5%*	140 (<445)	-11%*
GREACE (Europe)	A 257, U 255	-92 mg/dL -32%	180 (>100)	-83 mg/dL -46%	39	3 mg/dL 7%	184 (<400)	-56 mg/dL -31%

* Compared to the placebo group. See Table 1 for abbreviations.

the standard-dose group was more striking in non-diabetic patients, patients aged less than 72 years, patients with TC levels less than 253 mg/dL or patients with triglyceride levels ≥133 mg/dL in comparison with each counterpart. However, cardiovascular event endpoints included various cardiovascular events including cerebral infarction, cerebral hemorrhage, transient ischemic attack, subarachnoidal hemorrhage, congestive heart failure due to ischemic heart disease, arrhythmia requiring pharmacological treatment, dissecting aortic aneurysm, and peripheral arterial thrombosis, which was quite different from other RCTs in the West. The prevalence of adverse events other than cardiovascular events was similarly low in both groups. This study demonstrated that pravastatin at the standard dose is safe and useful to prevent cardiovascular

disease than low-dose pravastatin even in elderly hypercholesterolemic Japanese patients who are at high risk for CHD and CVD.

The Management of Elevated Cholesterol in the Primary Prevention of Adult Japanese (MEGA) Study

The MEGA study is the first prospective RCT in Asia. In this study, 7832 hypercholesterolemic patients, men aged 40 to 70 years and postmenopausal women aged less than 70 years, TC levels 220-270 mg/dL and without any CVD, were randomly allocated to diet therapy or diet plus pravastatin (10 to 20 mg daily)¹⁸⁾. Of the patients, 68% were women, 42% had hypertension and 21% had diabetes. These subject types are commonly seen in clinical practice in Japan. The HDL-C level at baseline was 57.5 mg/dL, which was mark-

Table 3. Comparison of outcomes between Japanese clinical trials and major randomized controlled trials in Western countries

Trials (region)	Endpoints	Incidence of events (%)				Relative risk reduction	
		treatment		control		% (95% CI)	p
KLIS (Japan), non-RCT	1, Coronary events [†]	P 10-20	2.9	Usual care	2.9	14 (-20 to 39)	NS
	2, Coronary events, Cerebral infarction		4.9		5.3	19 (-4 to 39)	NS
	3, All-cause death		3.9		4.8	21 (-4 to 40)	NS
PATE (Japan), RCT	1, Cerebrovascular and cardiovascular disease [†]	P 10-20	8.8	P 5	12.6	33 (-7 to 55)	NS
	2, MI, AP		3.0		5.1		NS
	2, All-cause death		4.2		6.0		NS
MEGA (Japan), RCT	1, CHD (MI, AP, cardiac or sudden death, revascularization)	P 10-20	1.7	Diet	2.5	33 (19 to 51)	0.010
	2, CHD + Cerebral infarction		2.5		3.6	30 (10 to 46)	0.005
	3, All-cause death		1.4		2.0	28 (-1 to 49)	0.055
JELIS (Japan), RCT	1, Coronary events [§]	Statin +	2.8	Statin	3.5	19 (5 to 31)	0.011
	2, All-cause death	EPA	3.1		2.8	-9 (-28 to 8)	NS
WOSCOPS (Europe)	1, Non-fatal MI, coronary death	P 40	5.5*	Placebo	7.9*	31 (17 to 43)	<0.001
	2, CVD death		1.6*		2.3*	32 (3 to 53)	0.033
	2, All-cause death		3.2*		4.1*	22 (0 to 40)	0.051
AFCAPS/TexCAPS (North America)	1, fatal or non-fatal MI, sudden death, UAP	L 20-40	3.5	Placebo	5.5	37 (21 to 50)	<0.001
	2, Coronary revascularization		3.2		4.8	40 (17 to 57)	0.001
	2, Fatal or non-fatal MI		1.7		2.9	33 (15 to 48)	0.002
ASCOT-LLA (Europe)	1, Non-fatal MI, fatal CHD	A 10	1.9	Placebo	3.0	36 (17 to 50)	0.0005
	2, Total cardiovascular events including revascularization		7.5		9.5	21 (10 to 31)	0.0005
	2, Total coronary events		3.4		4.8	29 (14 to 41)	0.0236
CARDS (Europe)	2, All-cause death		3.6		4.1	13 (-6 to 29)	NS
	1, Acute coronary events, coronary revascularization, stroke	A 10	5.8	Placebo	9.0	37 (17 to 52)	0.001
	2, All-cause death		4.3		5.8	27 (-1 to 48)	0.059
PROSPER (Europe)	2, Acute hospital-verified cardiovascular events		9.4		13.4	32 (15 to 45)	0.001
	1, CHD death, non-fatal MI, stroke	P 40	14.1	Placebo	16.2	15 (3-26)	0.014
	2, CHD death, non-fatal MI		10.1		12.2	19 (6-31)	0.006
4S (Europe)	1, All-cause death	S 20-40	8.2	Placebo	11.5	30 (15 to 42)	0.0003
	2, Major coronary events		19.0		28.0	34 (15 to 41)	<0.00001
	3, Coronary revascularization		11.3		17.2	37 (26 to 46)	<0.00001
HPS (Europe)	1, All-cause death	S 40	12.9	Placebo	14.7	13 (6 to 29)	0.0003
	2, Any vascular death		7.6		9.1	17 (9 to 25)	<0.0001
	3, Non-fatal MI, CHD death		8.7		11.8	27 (11 to 33)	<0.0001
CARE (North America)	1, Fatal CHD, non-fatal MI	P 40	10.2	Placebo	13.2	24 (9 to 36)	0.003
	2, Coronary revascularization		14.1		18.8	27 (15 to 37)	<0.001
LIPD (Australia, NZ)	1, CHD death	P 40	6.4	Placebo	8.3	24 (12 to 35)	<0.001
	2, All-cause death		11.0		14.1	22 (13 to 31)	<0.001
GREACE (Europe)	1, All-cause death	A 10-80	2.9	Usual care	5	43	0.0021
	1, CHD death		2.5		4.8	47	0.0017
	1, Non-fatal MI		2.6		6.4	59	0.0001

Endpoint-1=primary endpoints, 2=secondary endpoints, 3=other principal endpoints. [†]KLIS coronary events=fatal and non-fatal MI, coronary revascularization procedure, cardiac death, sudden and unexpected death. [†]PATE primary events=cerebral infarction, cerebral hemorrhage, transient ischemic attack, subarachnoid hemorrhage, congestive heart failure due to ischemic heart disease, arrhythmia requiring pharmacological treatment, dissecting aortic aneurysm, ASO, dissecting aortic aneurysm, peripheral arterial thrombosis. [§]JELIS coronary events=fatal and non-fatal MI, unstable angina, coronary revascularization procedure, CHD death, sudden cardiac death, non-fatal coronary events, Major coronary events = coronary death, non-fatal acute MI, resuscitated cardiac arrest, and definite silent MI, AP=angina pectoris, UAP=unstable angina pectoris, *absolute % risk at 5 years, MI=myocardial infarction, See Table 1 for other abbreviations.

edly higher than other RCTs, suggesting a low-risk population. Pravastatin reduced LDL-C levels by 18% whereas LDL-C decreased by 3.2% in the diet group.

At a mean follow-up of 5.3 years, the onset of CHD defined as fatal or non-fatal myocardial infarction, sudden death, angina pectoris and coronary revascu-

Fig. 2. Kaplan-Meier curves for primary and secondary endpoints in the MEGA study. Adapted from reference 18.

larization procedure was reduced by 33% ($p=0.010$) (3.3/1000 patient years in the diet plus pravastatin group compared to 5.0/1000 patient years in the diet group), and the number needed to treat was 119 (**Fig. 2**). The onset of CHD and/or cerebral infarction fell with pravastatin therapy by 30% ($p=0.005$) and number needed to treat was 91. All cardiovascular events fell by 26% ($p=0.01$; number needed to treat, 91) and total mortality by 28% ($p=0.055$) with pravastatin therapy. No clinically significant difference was found between groups with severe adverse events or cancer. These results demonstrated that 10 to 20 mg pravastatin reduced the CHD risk in low-risk population the same as the primary prevention trials with 20 to 40 mg of pravastatin in the West. The benefit of pravastatin for the reduction of CHD incidence was more likely to be seen in men aged older than 60 years, and baseline LDL-C levels higher than 155 mg/dL compared with those counterparts. The MEGA study had the largest number of postmenopausal women in the primary prevention study with statins. Sig-

nificant risk reduction of stroke and CHD plus cerebral infarction was found in older women aged ≥ 55 years. In addition, the reduction of total mortality was found regardless of age, although pravastatin therapy could not achieve a significant risk reduction of the incidence of CHD in women. Further sub-analysis may prove the mechanism of reduced non-CHD death in women⁵³.

The Japan EPA Lipid Intervention Study (JELIS)

The JELIS is the first large scale, prospective RCT in Asia including both primary ($n=14981$) and secondary prevention strata. ($n=3664$) to test the hypothesis that treatment with highly purified ($>98\%$) EPA in addition to statin would be more effective than treatment with statin alone in reducing major coronary events in hypercholesterolemic patients. In this study, 7832 hypercholesterolemic patients, men aged 40 to 75 years and postmenopausal women aged under 75 years, TC levels ≥ 250 mg/dL were randomly allocated to statin therapy (pravastatin 10 mg daily

Fig. 3. Comparison of the incidence of coronary events among patients with diet therapy and with pravastatin plus diet in MEGA, and those with statin therapy and statin plus EPA therapy in JELIS. Based on references 18 and 19. The coronary events were defined as fatal or non-fatal MI, angina pectoris, cardiac or sudden death, and coronary revascularization.

or simvastatin 5 mg daily) or statin plus EPA (1800 mg daily)¹⁹. Measurement of the plasma fatty acid fraction revealed the EPA/arachidonic acid ratio from 0.63 at the baseline to 1.23 at 5 years in the EPA plus statin group and from 0.60 to 0.59 in the statin group. The HDL-C levels showed 5% and 3% increases by treatment with EPA plus statin and statin alone, respectively, at 5 years. On the other hand, significant reductions in LDL-C levels were 26% in both groups (133 mg/dL). At a mean follow-up of 4.6 ± 1.1 years, the composite incidence of sudden cardiac death, fatal and non-fatal myocardial infarction, unstable angina pectoris and coronary revascularization therapy was significantly 19% lower in the EPA plus statin group than the statin alone group (2.8% vs 3.5%, $p=0.0113$). **Fig. 3** compares the incidence of CHD in the first occurrence and recurrence of CHD in MEGA study and JELIS. The incidence of the first occurrence of CHD was similar between pravastatin-treated patients in MEGA and statin-treated patients in JELIS, regardless of the different LDL-C reduction and different baseline LDL-C levels. Significant risk reduction by supplemented EPA was observed in the secondary prevention stratum in JELIS (8.7% vs 10.7%, HR=0.810, 95%CI 0.657-0.998; $p=0.0476$). This study demonstrated that the addition of EPA to statin therapy provided further benefits in preventing major coronary events including coronary revascularization, unstable angina and non-fatal coronary events, regardless of no further reduction of LDL-C levels. Many epidemiological studies and secondary prevention

studies with fish intake and/or supplementary omega-3 polyunsaturated fatty acids have shown the beneficial effects of fish intake on CHD events and sudden death in the world; on the other hand, it remains controversial whether omega-3 fatty acid has beneficial effects for CHD prevention in the Japanese population living in Japan, where 95% of adults eat fish at least once a week and the average fish intake is around 100 g/day^{54, 55}. A 19-year follow-up prospective study of the NIPPON DATA 80⁵⁴ has failed to show beneficial effects of fish consumption for reducing all-cause and/or CVD death whereas the Japan Public Health Center-Based study with 41578 men and women aged 40 to 59 years has shown that a high fish intake (8 times a week or 180 g/day) is associated with the reduction of non-fatal coronary events compared with a modest fish intake of once a week or less than 23 g/day⁵⁵. The JELIS has indicated that elevated levels of plasma EPA by the addition of EPA to statin therapy has the beneficial effects of CHD prevention through non-LDL-C lowering.

Treatment for Hyperlipidemia from the Viewpoint of Japanese Evidence

Similar to Western countries, Japanese epidemiological studies have clearly shown that hypercholesterolemia, hypertriglyceridemia, and low HDL-C are strongly associated with increased CHD risk independently of each other. Furthermore, a clustering of risk factors further enhanced the increased CHD risk. Similar to ATP-III, the Japanese guidelines 2002 have shown that the lipid management goal is modified by the presence of other risk factors (**Table 4**). The recent ATP-III guidelines indicate that LDL-C levels of 100 mg/dL are the minimal goal for high-risk patients and recommend an optional therapeutic target of LDL-C less than 70 mg/dL in very high-risk patients such as those with acute coronary syndrome and diabetic patients with CHD. However, it remains controversial whether a threshold of LDL-C levels for CHD prevention really exists². As the lipid-lowering intensity of each statin has been shown to be dose-dependent⁵⁶, it is conceivable that aggressive lipid lowering by high-dose atorvastatin has shown more intensive LDL-C lowering. However, it remains to be determined whether beneficial effects of aggressive lipid-lowering therapy can be seen in primary prevention, in CHD patients with relatively low LDL-C levels (<125 mg/dL), and can result in the prevention of CHD death⁵⁷⁻⁵⁹. A recent meta-analysis of 10 RCTs with statins using the method of L'Abbé plot⁶⁰ demonstrated that the relative risk reduction of fatal CHD and non-fatal myo-

Table 4. Lipid management goals by patient category. Adapted from reference 1

Category	CHD history*	Major CHD risk factors other than LDL-C**	Lipid management goal (mg/dL)				
			T-C	LDL-C	HDL-C	triglyceride	
A	Absent	0	<240	<160	≥40	<150	
B1		1	<220	<140			
B2		2					
B3		3	<200	<120			
B4		4 or more					
C	Present		<180	<100			

*: Coronary heart disease (CHD) is defined as myocardial infarction and symptomatic angina pectoris. **: Major CHD risk factors other than LDL-C: age (≥ 45 for men, ≥ 55 for women); hypertension; diabetes mellitus or glucose intolerance; cigarette smoking; family history of CHD; low HDL-C. Diabetes mellitus is regarded as B3 risk equivalent. Cerebral infarction and arteriosclerosis obliterans are regarded as B4 risk equivalent.

cardial infarction is comparable ($\sim 25\%$) among pravastatin, simvastatin, and atorvastatin irrespective of their different doses and different risk populations. Another recent meta-analysis of data from 14 RCTs of statins⁶¹⁾ has shown an approximately linear relationship between the absolute reductions in LDL-C and the proportional reductions in CHD and other events, that is, the risk reduction by lowering LDL-C from 155 to 116 mg/dL is similar to that from 116 to 77 mg/dL, which suggests that achieving a substantial absolute reduction in LDL-C is more important than achieving particular target levels of LDL-C (**Fig. 4**). In the MEGA study, only 23 mg/dL reduction of LDL-C resulted in 33% risk reduction of CHD in a low-risk population, the same as about 40 mg/dL reduction of LDL-C did in Western RCTs. Similarly, PATE showed that a small reduction of LDL-C was enough to reduce the CHD risk in the Japanese older population. A necessary reduction in LDL-C to achieve beneficial risk reductions may differ between Western and Japanese populations with different lifestyles, body size, and genetics.

A meta-analysis of 97 RCTs to investigate the efficacy of different lipid-lowering interventions has shown that statins and omega-3 fatty acids offer favorable benefits by reducing the risk of cardiac and overall mortality (**Fig. 5**)⁶²⁾. The JELIS first indicated that the addition of omega-3 fatty acids to statins lead to further prevention of the incidence of major coronary events, especially unstable angina, mainly through LDL-C-independent mechanisms. This may be attributed to the inhibition of platelet aggregation, slight increase in HDL-C, modest decrease in triglyceride, and/or anti-inflammatory action^{63, 64)}. Thus, “the lower is better” may not be proved in Japanese hypercholesterolemic patients. Further sub-analysis may prove which

Fig. 4. Relation between proportional reduction in the incidence of major coronary events and mean absolute LDL-C reduction at 1 year. Square represents a single trial plotted against mean absolute LDL-C reduction with vertical lines above and below corresponding to one SE of unweighted event rate reduction. The overall incidence was reduced by 25% per 1 mmol/L (=38.46 mg/dL) reduction in LDL-C. The relative reduction of major coronary events in the MEGA study was placed above the line of the relationship between absolute LDL-C reduction and reduction of CHD events in 14 randomized clinical trials conducted in the West. Adapted from reference 61.

patients have more benefit of lipid-lowering drugs. Pharmacogenetic studies have shown that the lipid response and adverse effects of drugs may be related in part to genetic variations in individuals⁶⁵⁾; evidence for Caucasians is not always the same for Japanese, and evidence for pravastatin is not always the same for other statins. Further studies are required to deter-

Fig. 5. Summary estimates for cardiac mortality for different types of lipid-lowering interventions. The Cochrane Q test for heterogeneity.

N=number of trials available for analysis. n-3FA=n-3 fatty acid. Adapted from reference 62.

mine the effects of different statins in high-risk Japanese populations.

Adverse effects such as the elevation of liver enzyme and discontinuation of statins were more frequent in high-dose atorvastatin compared with others^{58, 59}. On the other hand, it remains controversial whether low LDL-C concentrations relate to an increased risk of cerebral hemorrhage and/or cancer mortality^{25, 47, 66-69}. Patients with low TC often had low LDL-C and/or low HDL-C. This may be attributed to not hyper-responders to statins but low lipid levels caused by underlying malignancy. Recent reports of meta-analysis of RCTs have shown that statins have a neutral effect on cancer and cancer death^{61, 67}. In the MEGA study and KLIS, incidences of adverse effects such as elevated serum liver enzymes and any type of cancer were similar between the pravastatin group and diet or conventional therapy group. Thus, the standard dose of pravastatin and simvastatin are safe for Japanese patients.

The intake of fat and incidence of obesity have been increasing with lifestyle westernization, and it is of great concern that both the mortality and morbidity of CHD may shift to increasing trends soon or later. It must be emphasized that all guidelines place a major emphasis on lifestyle modification such as diet therapy, weight loss for those overweight, cessation of smoking, and increased physical activity as essential therapy for hyperlipidemia¹⁻³. Lipid-lowering drug therapy has additive and/or synergistic beneficial effects in some patients, and the absolute benefit depends on the absolute risk. As adherence with drug treatment is very important, we should choose drugs proved as safe by evidence.

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