

## Introduction

High cholesterol levels are recognized as a major cause of atherosclerosis. However, for more than half a century some have challenged this notion. But which side is correct, and why can't we come to a definitive conclusion after all this time and with more and more scientific data available? We believe the answer is very simple: for the side defending this so-called cholesterol theory, the amount of money at stake is too much to lose the fight. The issue of cholesterol is one of the biggest issues in medicine where the law of economy governs. Moreover, advocates of the theory take the notion to be a simple, irrefutable 'fact' and self-explanatory. They may well think that those who argue against the cholesterol theory—actually, the cholesterol 'hypothesis'—are mere eccentrics. We, as those on the side opposing the hypothesis, understand their argument very well. Indeed, the first author of this supplementary issue (TH) had been a very strong believer and advocate of the cholesterol hypothesis up until a couple of years after the Scandinavian Simvastatin Survival Study (4S) reported the benefits of statin therapy in *The Lancet* in 1994. To be honest with the readers, he used to persuade people with high cholesterol levels to take statins. He even gave a talk or two to general physicians promoting the benefits of statins. Terrible, unforgivable mistakes given what we came to know and clearly know now.

In this supplementary issue, we explore the background to the cholesterol hypothesis utilizing data obtained mainly from Japan—the country where anti-cholesterol theory campaigns can be conducted more easily than in any other countries. But why is this? Is it because the Japanese researchers defending the hypothesis receive

less support from pharmaceutical companies than researchers overseas do? Not at all. Because Japanese researchers are indolent and weak? No, of course not. Because the Japanese public is skeptical about the benefits of medical therapy? No, they generally accept everything physicians say; unfortunately, this is also complicated by the fact that physicians don't have enough time to study the cholesterol issue by themselves, leaving them simply to accept the information provided by the pharmaceutical industry. Reading through this supplementary issue, it will become clear why Japan can be the starting point for the anti-cholesterol theory campaign. The relationship between all-cause mortality and serum cholesterol levels in Japan is a very interesting one: mortality actually goes down with higher total or low density lipoprotein (LDL) cholesterol levels, as reported by most Japanese epidemiological studies of the general population. This relationship cannot be observed as easily in other countries, except in elderly populations where the same relationship exists worldwide. The mortality from coronary heart disease in Japan has accounted for around just 7% of all-cause mortality for decades; a much lower rate than seen in Western countries. The theory that the lower the cholesterol levels are, the better is completely wrong in the case of Japan—in fact, the exact opposite is true. Because Japan is unique in terms of cholesterol-related phenomena, it is easy to find flaws in the cholesterol hypothesis. Based on data from Japan, we propose a new direction in the use of cholesterol medications for global health promotion; namely, recognizing that cholesterol is a negative risk factor for all-cause mortality and re-examining our use of cholesterol medications accordingly. This, we be-

lieve, marks the starting point of a paradigm shift in not only how we understand the role cholesterol plays in health, but also how we provide cholesterol treatment.

The guidelines for cholesterol are thus another area of great importance. Indeed, the major portion of this supplementary issue (from Chapter 4 onward) is given over to our detailed examination and critique of guidelines published by the Japan Atherosclerosis Society. We dedicate a large portion of this work to these guidelines because they are generally held in high regard in Japan, and the country's public health administration mechanism complies with them without question. Physicians, too, tend to simply obey the guidelines; their workloads often don't allow them to explore the issue rigorously enough to learn the background truth and they are afraid of litigation if they don't follow the guidelines in daily practice. These chapters clearly describe some of the flaws in the guidelines—flaws which are so serious that it becomes clear that times must change and the guidelines must be updated.

Our purpose in writing this supplementary issue is to help everyone understand the issue of cholesterol better

than before, and we hope that we lay out the case for why a paradigm shift in cholesterol treatment is needed, and sooner rather than later. We would like to stress in closing that we have received no funding in support of writing or publishing this supplementary issue, and our conflicts of interest statements are given in full at the end.

#### *A Note on the Units Used in This Issue*

We use two unit systems to report blood cholesterol and triglyceride concentrations: mmol/l and mg/dl. This is because Japanese researchers (and probably American researchers) are not well accustomed to using the mmol/l system. If the original papers we cite used the mmol/l system, we use that system first followed by mg/dl, and vice versa. The following equations are used in this supplementary issue for most of the part:  $1 \text{ mmol/l} = 38.67 \text{ mg/dl}$  for cholesterol and  $1 \text{ mmol/l} = 89 \text{ mg/dl}$  for triglycerides (we use two significant digits for the coefficient for triglycerides because it depends on fatty acid species).

## Chapter 1 Cholesterol and Mortality

**Summary:** All-cause mortality is the most appropriate outcome to use when investigating risk factors for life-threatening disease. Section 1 discusses all-cause mortality according to cholesterol levels, as determined by large epidemiological studies in Japan. Overall, an inverse trend is found between all-cause mortality and total (or low density lipoprotein [LDL]) cholesterol levels: mortality is highest in the lowest cholesterol group without exception. If limited to elderly people, this trend is universal. As discussed in Section 2, elderly people with the highest cholesterol levels have the highest survival rates irrespective of where they live in the world.

### (1) Cholesterol and All-Cause Mortality in Japan

All-cause mortality is the most appropriate outcome for both interventional and epidemiological studies to use when investigating risk factors for life-threatening disease. As shown in table 1, the PDQ<sup>®</sup> Levels of Evidence for Adult and Pediatric Cancer Treatment Studies (National Cancer Institute) classify total mortality (i.e., overall survival from a defined time) as the most important outcome to patients, the most easily defined, and the least subject to investigator bias [1]. The table was originally created for cancer treatment studies, but points A-D can be seen to apply to any life-threatening disease. If focus is placed on cause-specific mortality instead of

all-cause mortality, the following paradoxical situation might result.

Suppose that A is a potentially life-threatening disease and that B is a risk factor for A, then people who are at the best end of the risk factor B continuum in terms of all-cause mortality are probably the healthiest and last to be treated for risk factor B. This simple principle should be respected across the board, otherwise many of us will be treated with unnecessary medicines. It is highly unfortunate, then, that this is the case for cholesterol in Japan, and probably in all advanced countries. This section discusses the relationship between cholesterol levels and all-cause mortality in Japan, and you may find that what you learned about cholesterol is not actually the case.

Fig. 1-1 shows the relationship between all-cause mortality and LDL cholesterol levels in Japan, as determined by the largest epidemiological study—the Ibaraki Prefecture Health Study—carried out in Japan in recent years [2]. Men and women (n = 91,219) aged 40–79 years with no history of stroke or coronary heart disease (CHD) were followed for 10.3 years. The hazard ratio (HR) of all-cause mortality adjusted for age and many potential confounding factors was calculated according to LDL cholesterol levels and revealed that all-cause mortality was essentially inversely correlated with LDL cholesterol levels in both men and women.

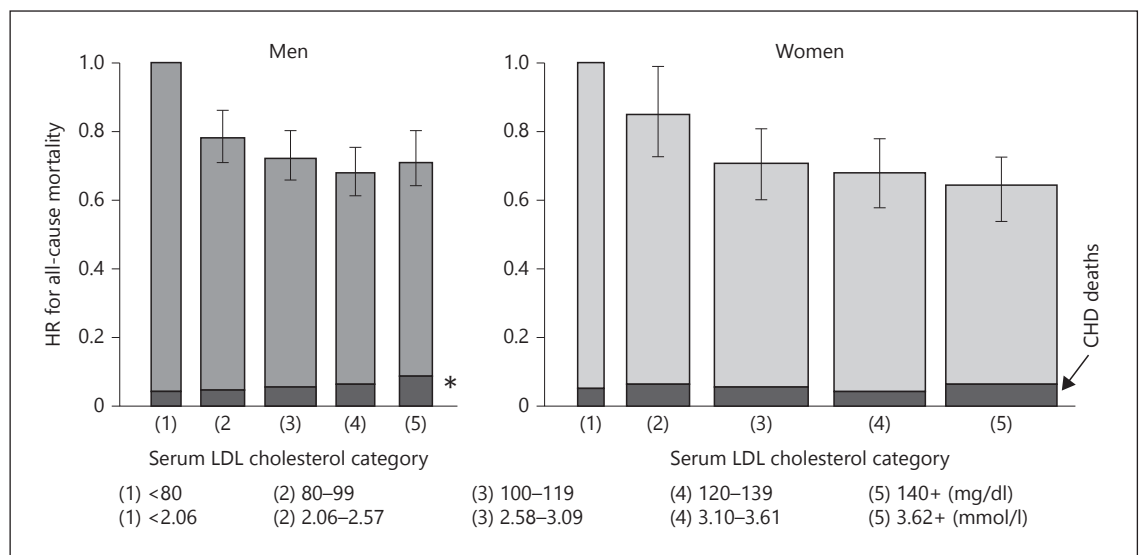
The first reaction of well-informed advocates of the cholesterol theory to the findings of this Japanese study

**Table 1.** Strength of endpoints

Commonly measured endpoints for adult and pediatric cancer treatment studies are listed below in descending order of strength:

- A. Total mortality (or overall survival from a defined time).  
This outcome is arguably the most important one to patients and is also the most easily defined and least subject to investigator bias.
- B. Cause-specific mortality (or cause-specific mortality from a defined time).  
Although this may be of the most biologic importance in a disease-specific intervention, it is a more subjective endpoint than total mortality and more subject to investigator bias in its determination. This endpoint may also miss important effects of therapy that may actually shorten overall survival.
- C. Carefully assessed quality of life.  
This is an extremely important endpoint to patients. Careful documentation of this endpoint within a strong study design is therefore sufficient for most physicians to incorporate a treatment into their practices.
- D. Indirect surrogates.
  - i. Event-free survival.
  - ii. Disease-free survival.
  - iii. Progression-free survival.
  - iv. Tumor response rate.These endpoints may be subject to investigator interpretation. More importantly, they may, but do not automatically, translate into direct patient benefit such as survival or quality of life. Nevertheless, it is rational in many circumstances to use a treatment that improves these surrogate endpoints while awaiting a more definitive endpoint to support its use.

This list can be found in PDQ® Levels of Evidence for Adult and Pediatric Cancer Treatment Studies [1].



**Fig. 1-1.** Relationship between serum low density lipoprotein (LDL) cholesterol level and the hazard ratio (HR) for all-cause mortality: the Ibaraki Prefecture Health Study [2]. A total of 30,802 men and 60,417 women were followed for a median 10.3 years. HRs were adjusted for age and potential confounding factors (blood pressure categories, anti-hypertensive medication use, diabetes mellitus, lipid medication use, body mass index, gamma-glutamyl transferase, smoking status, alcohol consumption, kidney dysfunction, and high density lipoprotein cholesterol and triglyceride categories). Dark gray shading represents coronary heart dis-

ease (CHD) deaths. The height of the bar for CHD deaths is set according to the ratio between the numbers of CHD deaths and all-cause deaths in the respective groups. The width of each column is proportional to the number of participants in that group. The vertical lines represent 95% confidence intervals. HRs for all-cause mortality for each standard deviation increment of LDL cholesterol were 0.88 (0.85–0.91) and 0.90 (0.86–0.93) for men and women, respectively. \* Significantly different from reference group (<80 mg/dl) with regard to CHD deaths.

would be that this kind of phenomenon can be easily explained by the presence of participants with an as yet sub-clinical serious disease (e.g., hidden cancer) where some of them who had lower cholesterol levels died during the study period (reverse causality). To exclude this possibility of reverse causality, the authors of the study re-analyzed the data excluding deaths that occurred within the first 2 years after baseline measurement and, interestingly, found that their initial results were not substantially changed [2].

Fig. 1-1 also shows the relationship between LDL cholesterol levels and CHD mortality by sex. In men, the hazard ratio of CHD mortality is significantly higher than that of the lowest group. However, in women, no differences were observed between any groups. Fig. 1-1 is a good representation of the situation in Japan with regard to cholesterol. This relationship between cholesterol and CHD mortality is not linked to genetic differences between Western and Japanese populations. Japanese emigrants to Hawaii, where Japanese culture is still preserved to a certain degree, had CHD mortality rates intermediate between those of Japanese men living in Japan and those of Japanese American men living in San Francisco, where the latter group had CHD mortality similar to the general population in San Francisco [3].

It seems, then, that cholesterol is not necessarily a deleterious substance after all, and may actually be a marker of healthy life and healthy organs.

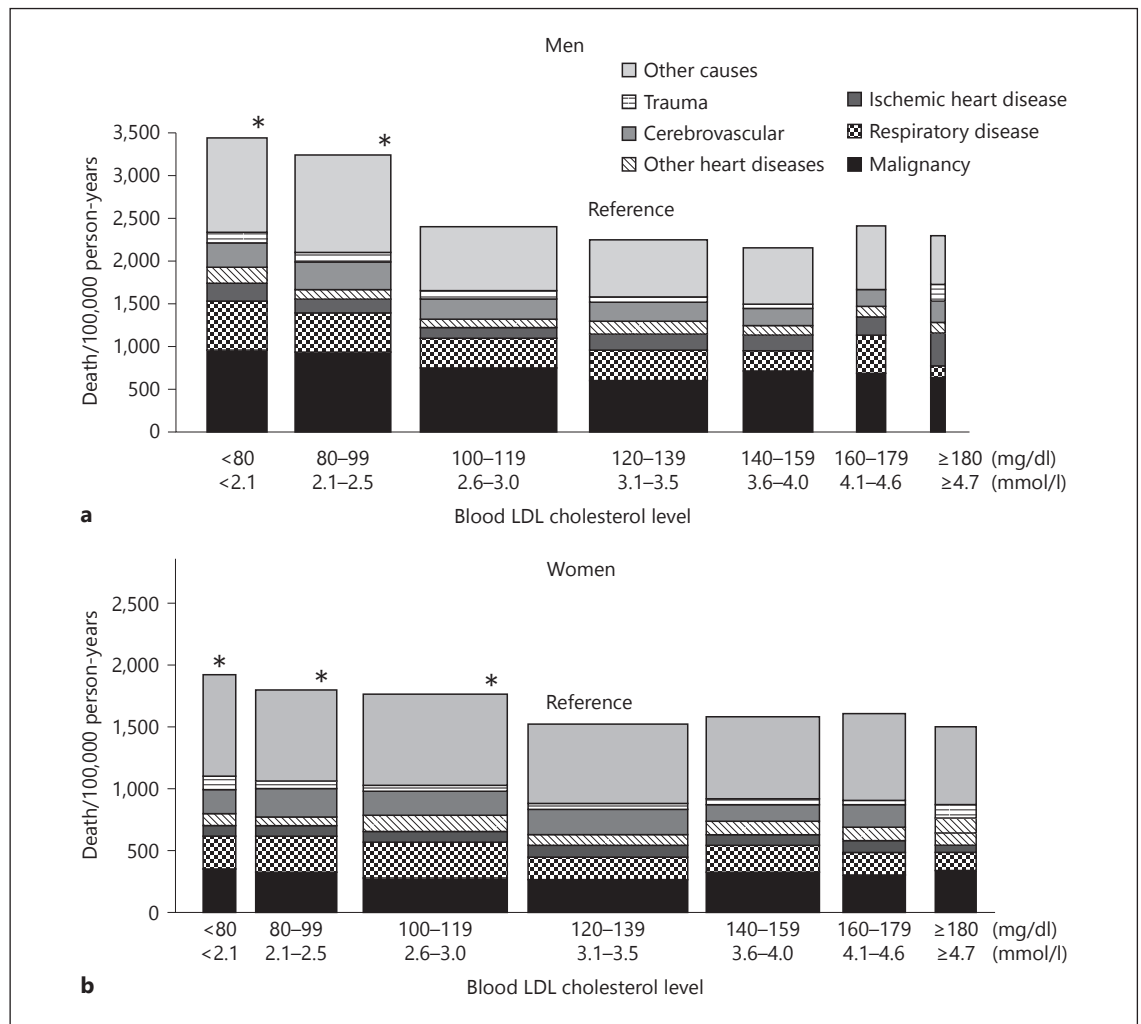
Another large-scale epidemiological study conducted in Japan is the Isehara Study, which analyzed data collected from the annual checkups of residents in Isehara City (population: about 100,000) between 1994 and 2004 [4]. During the study period, Japanese citizens aged  $\geq 40$  years were eligible for annual health checkups provided by local governments in accordance with the Health Care Act for the Elderly (1982; succeeded by new legislation in 2007). The final database containing data on 8,340 men (aged  $64 \pm 10$  years) and 13,591 women ( $61 \pm 12$  years) was compiled after applying the following exclusion criteria: death within 1 year of baseline, incomplete lipid data, attended single check-up only, and serum triglyceride levels beyond the Friedewald equation limits (400 mg/dl or 4.5 mm; 198 men, 126 women). Mean blood LDL cholesterol levels were calculated for individuals from all available LDL cholesterol values except their last checkup. Mean follow up for all subjects in the final database was 7.1 years (6.7 years for men, 7.3 years for women). LDL cholesterol levels were divided into 7 groups at 20-mg/dl (0.5-mmol/l) intervals. LDL cholesterol was again

found to be a negative risk factor for all-cause mortality (fig. 1-2). Of note, the mortality rates due to cancer in men and to respiratory disease without cancer (mostly pneumonia) in men and women were lowest in the highest cholesterol groups.

In 2007, Kirihara et al. performed a meta-analysis of the relationship between total cholesterol levels and all-cause mortality in Japan [5]. Because Japanese diets have been changing for decades, reports published before 1995 were not included, leaving 5 for analysis. As shown in fig. 1-3, the results indicate that total cholesterol levels  $\geq 240$  mg/dl ( $\geq 6.22$  mmol/l) should not in fact be regarded as a lipid disorder. The issue of familial hypercholesterolemia (FH) will be discussed separately below.

One of the most recent, large epidemiological studies in Japan is the Jichi Medical School Cohort Study, a community-based cohort study conducted in 12 rural areas in Japan [6]. The study participants were 12,334 healthy adults aged 40–69 years who were followed for a mean 11.9 years. As shown in fig. 1-4, HRs for all-cause mortality were significantly higher in the lowest cholesterol groups than in the reference groups for both men and women. Even the exclusion of deaths within 5 years of baseline did not change the relationship between low cholesterol levels and high mortality. The same case was apparent when deaths due to liver disease were excluded. This finding is incompatible with the notion that association between low cholesterol and high mortality might be due to the presence of participants with liver disease in the lowest cholesterol group. We will discuss liver disease specifically in later chapters (Chapter 2, Section 4 and Chapter 5, Section 1).

All-cause mortality in men is U-shaped. In the Jichi Medical School Cohort Study, the effects of the presence of participants with FH tended to be exaggerated in the highest cholesterol group; in other words, more participants with FH were concentrated in the highest cholesterol group. This phenomenon tends to appear when the participants' age range is rather low (none aged  $\geq 70$  at baseline) and when there are many recruiting areas. For example, if there is only one recruiting area, the more participants that are recruited, the closer the ratio of participants with FH to all participants becomes to the general ratio of FH in Japan (0.2%). However, if there are many recruiting areas, selection bias of participants with FH may raise the FH ratios to much higher than 0.2% and all-cause mortality in the highest cholesterol group may increase as a consequence. We will return to this important issue of the proportion of subjects with FH later (Chapter 3, Section 3). At any rate, what we can say already is that



**Fig. 1-2.** Low density lipoprotein (LDL) cholesterol and mortality in (a) men and (b) women: the Isehara Study [4]. Over 11 years (1994–2004), 8,340 men (aged  $64 \pm 10$  years) and 13,591 women ( $61 \pm 12$  years) were followed in Isehara City, Japan. Deaths during the first year of follow up were excluded. Mean follow-up period

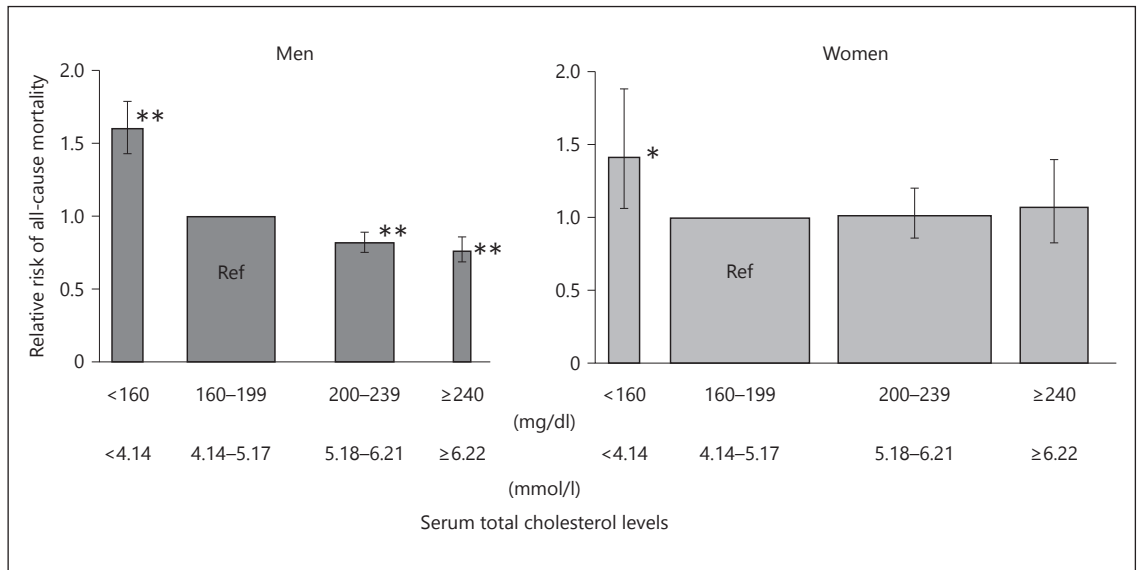
was 7.1 years. Cox's proportional hazards regression analysis was employed to calculate age-adjusted relative risks in both men and women. \*  $p = 0.001$ , Cox's proportional hazard regression analysis with Bonferroni adjustment. The width of each column is proportional to the number of participants in that group.

high cholesterol levels are not a risk factor for all-cause mortality.

We will finish this section by briefly mentioning the findings of another Japanese epidemiological study, NIPPON DATA80 [7]. They are of particular interest because this is the only epidemiological study performed in Japan that has ever found high cholesterol levels to be a significant risk factor for all-cause mortality. Describing the precise picture of this study warrants an entire chapter (Chapter 5), but for now it is suffice to say that the study is of considerable interest because the most important part of the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases

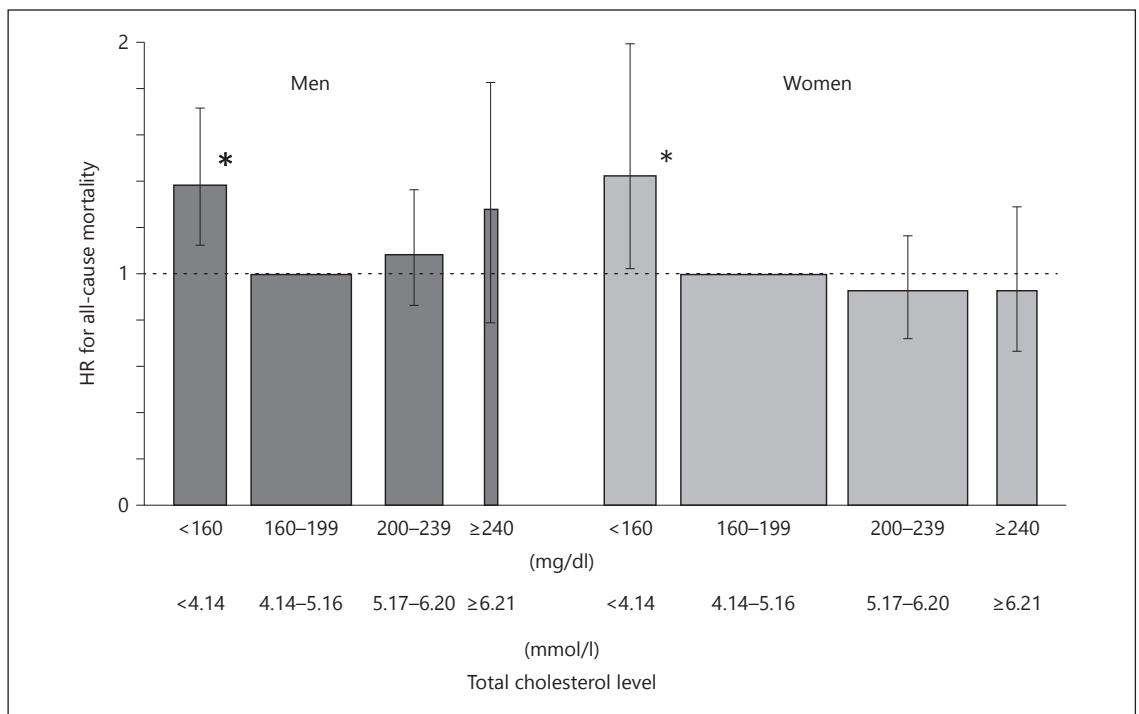
2012 (JASG2012) [8], which was published in June 2012, depends almost exclusively on NIPPON DATA80 for the risk calculation of CHD death.

To sum up, almost all Japanese epidemiological studies show that high cholesterol levels are a good marker of longevity. Unfortunately, however, many Japanese doctors try to reduce patients' cholesterol levels without due consideration of these overall findings. The Japan Atherosclerosis Society (JAS) first published the Guidelines for Diagnosis and Treatment of Atherosclerotic Diseases in 1997 and has revised them several times since. However, optimal cholesterol or LDL cholesterol levels in terms of all-cause mortality have not been given as yet.



**Fig. 1-3.** Cholesterol and all-cause mortality in Japan: meta-analysis [5]. This meta-analysis included five reports and excluded reports published before 1995, those based on a cohort <5,000 subjects, and those with no information on the number of deaths in

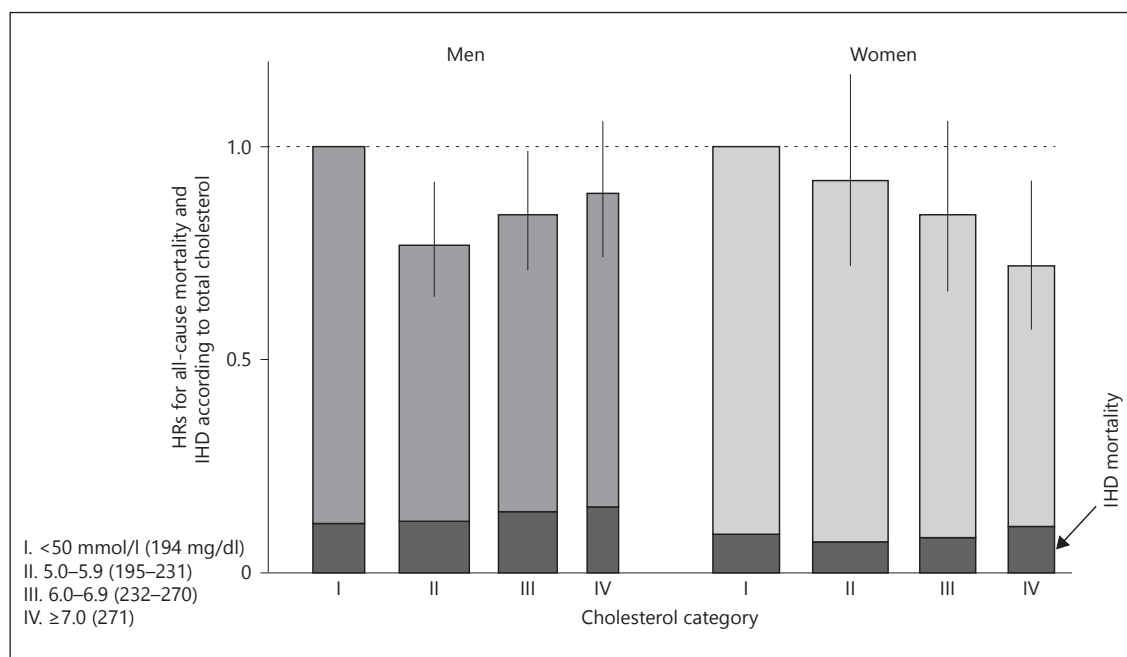
each cholesterol group. The width of each column is proportional to the number of participants in that group. Total number of subjects: 173,539. \*  $p = 0.02$ , \*\*  $p = 0.0001$ .



**Fig. 1-4.** Total cholesterol and all-cause mortality: Jichi Medical School Cohort Study [6]. More than 12,000 men and women aged 40-69 years in 12 different areas in Japan were followed for a mean 11.9 years. Cox's proportional hazards model was employed with adjustment for age, systolic blood pressure, high density lipoprotein cholesterol, smoking, drinking, and body mass index. The re-

lationship between low cholesterol levels and increased mortality did not change even after excluding deaths due to liver disease or deaths within 5 years of baseline. The width of each column is proportional to the number of participants in that group. \* Significantly different from reference group (160-199 mg/dl, 4.14-5.16 mmol/l). HR = Hazard ratio.





**Fig. 1-5.** Hazard ratios (HRs) for all-cause mortality and ischemic heart disease (IHD) according to total cholesterol level in Norway: HUNT 2 Study [9]. A total of 52,087 Norwegians aged 20–74 years were followed to calculate cause-specific mortality for 10 years. HRs were adjusted for age, smoking, and systolic blood pressure. The height of the black bar denoting IHD deaths is set according to the ratio between the numbers of IHD deaths and all-cause

deaths within the same column. HRs for IHD mortality in cholesterol categories II to IV were not significantly different from those in cholesterol category I in men or women. The width of each column is proportional to the number of participants in that group. The HR increments for 1 mmol/l (39 mg/dl) of cholesterol were 0.98 (0.93–1.03) for men and 0.94 (0.89–0.99) for women.

## (2) Elderly People with High Cholesterol Levels Live Longer Irrespective of Where They Live

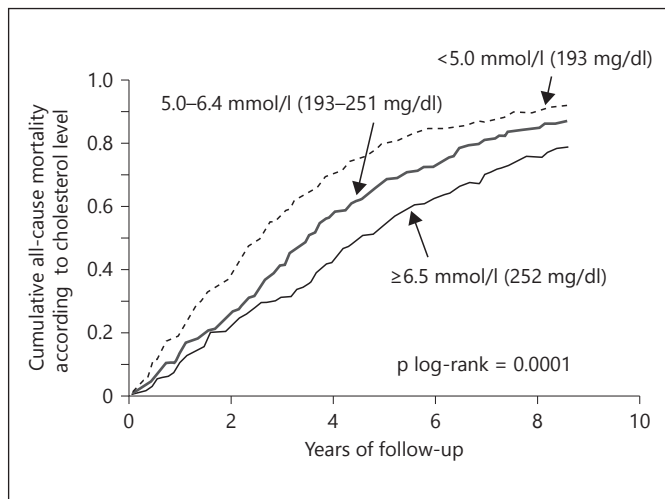
Before describing the relationship between all-cause mortality and serum total or LDL cholesterol levels in elderly people, let's start by discussing it in the general population. In well-developed countries, the relationship does not look like that found in Japan, where, as discussed in Section 1, the higher the cholesterol levels, the lower the mortality rate. However, according to Petursson et al, a phenomenon similar to that seen in Japan exists in the general population of Norway [9]. In their Nord-Trøndelag Health Study (HUNT 2, 1995–1997), 52,087 Norwegians aged 20–74 years were followed for cause-specific mortality over 10 years. As shown in fig. 1-5, the higher the total cholesterol levels, the lower the mortality rate in women. Interestingly, the results for both men and women are almost identical to those of the Jichi Medical School Study (fig. 1-4).

In their report, Petursson et al. indicated possible errors in the cardiovascular disease risk algorithms of many clinical guidelines [9]. They concluded that, if their find-

ings were generalizable, clinical and public health recommendations on the 'dangers' of cholesterol should be revised; this would be especially true for women, for whom moderately elevated cholesterol (by current standards) might prove to be not just harmless, but even beneficial.

Turning our focus now to elderly people, for the data we currently have available, the situation is perfectly uniform across the world: the higher the total cholesterol levels, the lower the all-cause mortality rate. Fig. 1-6 shows mortality in three groups of the oldest residents in the Leiden 85-Plus Study, conducted in Leiden, the Netherlands [10]. Total cholesterol concentrations were measured in 724 participants with a median age of 89 years, and mortality risks were calculated over 10 years of follow up. Participants with the highest total cholesterol levels ( $\geq 6.5$  mmol/l) had a lower mortality risk than those with the middle range of total cholesterol levels (5.0–6.4 mmol/l, middle risk) or those with the lowest range ( $< 5.0$  mmol/l). The latter group had the highest risk. Mortality risks were adjusted for age, sex, and cardiovascular risk factors, and the highest total cholesterol group owed its longevity to lower mortality from cancer and infection.



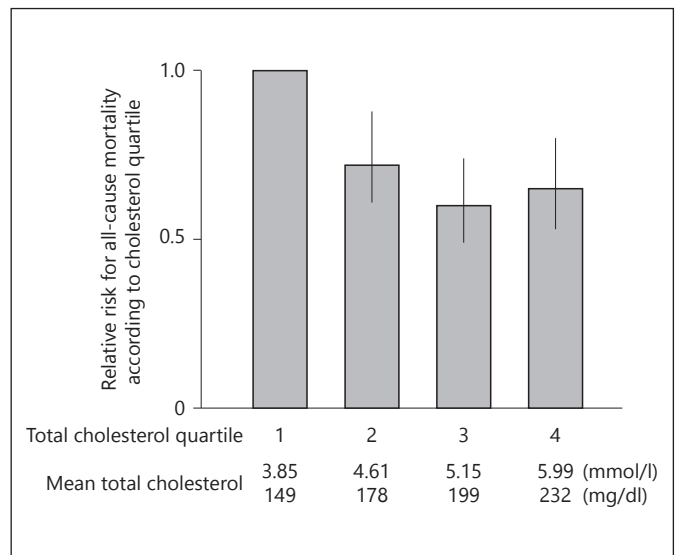


**Fig. 1-6.** All-cause mortality of residents aged  $\geq 85$  years according to total cholesterol level: Leiden 85-Plus Study [10]. A total of 724 residents in Leiden, the Netherlands, were followed for nearly 10 years. There were 203, 350, and 171 participants in the low, middle, and high cholesterol groups, respectively. Mortality risks were adjusted for age, sex, and cardiovascular risk factors (history of diabetes mellitus, myocardial infarction, cerebrovascular accident, smoking, and hypertension) with Cox's multivariate proportional hazards model. (Remade with permission from the publisher.)

As part of the Honolulu Heart Program, serum total cholesterol concentrations were measured in 3,572 Japanese-American men aged 71–93 years (between 1991 and 1993) [11]. A total of 727 deaths were registered between baseline and the end of 1996. Compared with the first (lowest) quartile of total cholesterol, the relative risks for all-cause mortality adjusted for age were significantly low in the other quartiles, with the third quartile being safest, followed by the fourth and second quartiles (fig. 1-7).

In another study, the Vorarlberg Health Monitoring and Promotion Programme conducted in Austria, 67,413 men and 82,237 women aged 20–95 years underwent various examinations over a 15-year period (1985–1999), and relations between measured variables and death were analyzed [12]. Cox's proportional hazards models were used to assess the age-adjusted associations between total cholesterol levels and mortality. In both men and women in the 50–64 and  $\geq 65$  age groups, total cholesterol concentrations were a negative risk factor for all-cause mortality (fig. 1-8).

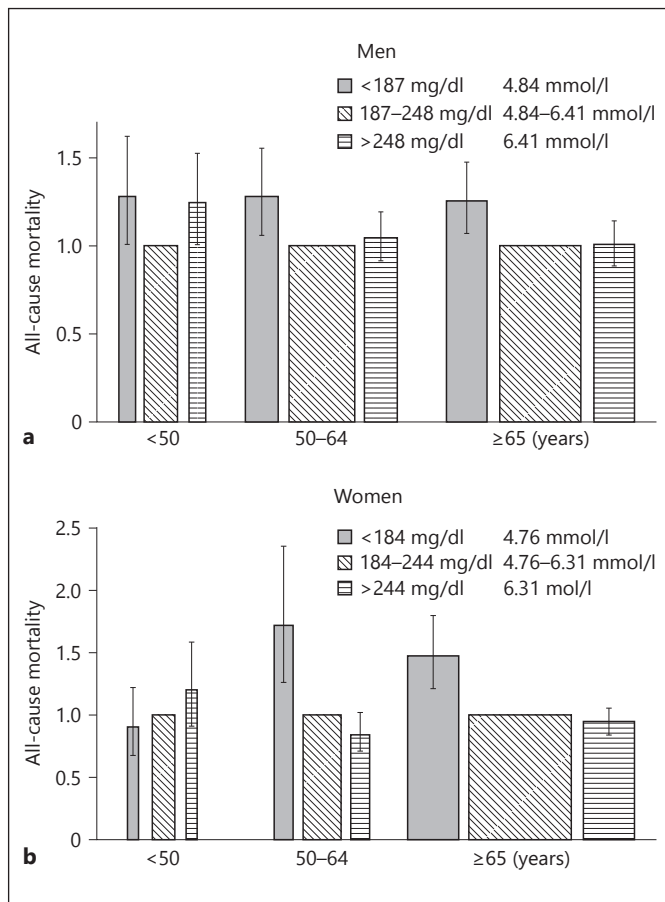
Charach et al. investigated the association between LDL cholesterol levels and clinical outcomes in 297 patients with severe heart failure (mean age  $71 \pm 11$  years, men 73%) in Israel [13]. Mean follow up was 3.7 years (8 months–11.5 years). The patients were grouped ac-



**Fig. 1-7.** Age-adjusted relative risk for all-cause mortality by serum cholesterol quartile: part of the Honolulu Heart Program [11]. A total of 3,572 Japanese-American men aged 71–93 years were followed from baseline (1991–1993) to the end of 1996. There were 727 deaths (20% of the total) over the study period. Exclusion of the deaths during the first year (106 deaths) did not markedly change the results.

ording to baseline plasma LDL tertiles:  $\leq 89$ ,  $>89$  to  $\leq 115$ , and  $>115$  mg/dl ( $\leq 2.30$ ,  $>2.30$  to  $\leq 2.97$ , and  $>2.97$  mmol/l). Patients with the highest baseline LDL cholesterol levels had significantly better outcomes, while those with the lowest LDL cholesterol levels had the highest mortality. The same trend was also observed in those taking statins (fig. 1-9). Low LDL cholesterol levels predicted less favorable outcomes in patients with heart failure whether they were taking statins or not.

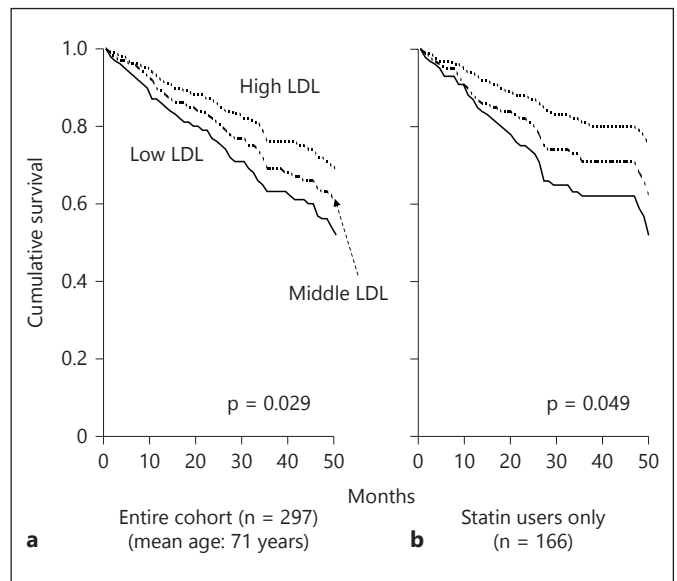
In a prospective cohort study with a 6-year follow-up period conducted in Kuopio, Finland, Tuikkala et al. investigated the association between total cholesterol levels and all-cause mortality in 490 home-dwelling elderly persons (aged  $\geq 75$  years, men 28%) who did not use lipid-modifying agents [14]. In a propensity score-adjusted model using total cholesterol  $<5$  mmol/l ( $<193$  mg/dl, the lowest tertile) as a reference, HRs for all-cause mortality became lower with increasing cholesterol tertiles (fig. 1-10). The inverse association between serum total cholesterol and mortality is often interpreted to be due to confounding by chronic diseases, but mortality in this study was found not to be associated with the following concomitant diseases or health status: history of hypertension, current hypertension, heart disease, stroke, obstructive pulmonary disease, history of cancer, and de-



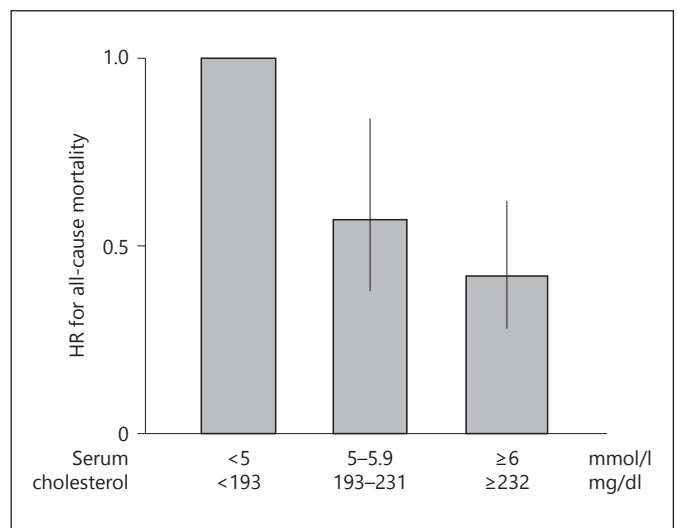
**Fig. 1-8.** Fifteen-year follow up of (a) 67,413 men and (b) 82,237 women aged 20–95 years in Vorarlberg, Austria: Vorarlberg Health Monitoring and Promotion Programme [12]. The width of a column is proportional to the number of participants. The left column in each age group represents the lowest total cholesterol quartile, the middle column represents the reference group containing the second and third quartiles combined, and the right column represents the highest cholesterol quartile. Adjusted for age (Cox’s proportional hazards model).

mentia. The decreasing HR pattern across cholesterol tertiles did not markedly change between participants with any one of the conditions listed above and participants without any one of them.

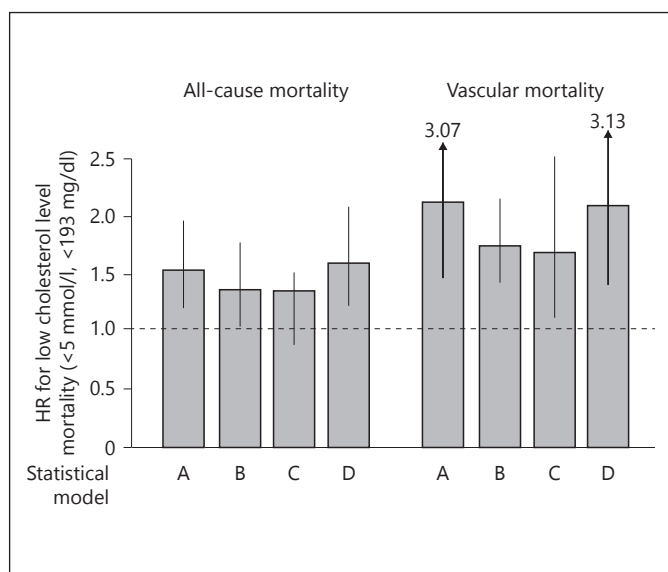
In another Finnish study, baseline examinations including serum cholesterol were performed in 1990 in persons selected from the census register in Helsinki (n = 623, aged ≥75 years) who were randomly selected from the birth cohorts of 1904, 1909, and 1914, and all persons were followed for 17 years [15]. Low cholesterol was found to be associated with poor health and multi-morbidity. Cholesterol <5.0 mmol/l (193 mg/dl) was associated with accelerated all-cause mortality and vascular



**Fig. 1-9.** Cumulative survival rate of patients with severe heart failure according to baseline cholesterol level: study in Israel [13]. A total of 297 patients with severe heart failure were followed for a mean 3.7 years. (a) Survival rates were compared according to tertiles of low density lipoprotein cholesterol with adjustment for age, sex, left ventricular ejection fraction, New York Heart Association functional class, creatinine clearance, diabetes, and hypertension. (b) Exactly the same trend was observed even if compared between patients with ischemic heart disease only (n = 227, p = 0.039). (Remade with permission from the publisher.)



**Fig. 1-10.** Hazard ratio for all-cause mortality according to total cholesterol tertile among participants in a home-dwelling elderly population: study in Kuopio, Finland [14]. A total of 490 home-dwelling residents were followed for 6 years, and cumulative survival was calculated in a propensity score adjusted model. HR = Hazard ratio.



**Fig. 1-11.** Cholesterol level <5 mmol/l (193 mg/dl) as a predictor of all-cause and vascular mortality: study in Helsinki, Finland [15]. A total of 623 elderly participants (aged  $\geq 75$  years, men 26%) were followed for 17 years. Model A: adjusted for age and sex. Model B: adjusted for age, sex, smoking, hypertension, body mass index, history of myocardial infarction, Mini-Mental State Examination score, and need of care. Model C: adjusted for age, sex, global health (visual analogue scale score), and three frailty indicators (weight loss, serum albumin, and physical fatigue). Model D: adjusted for age, sex, lathosterol, and sitosterol. See the text for details. HR = Hazard ratio.

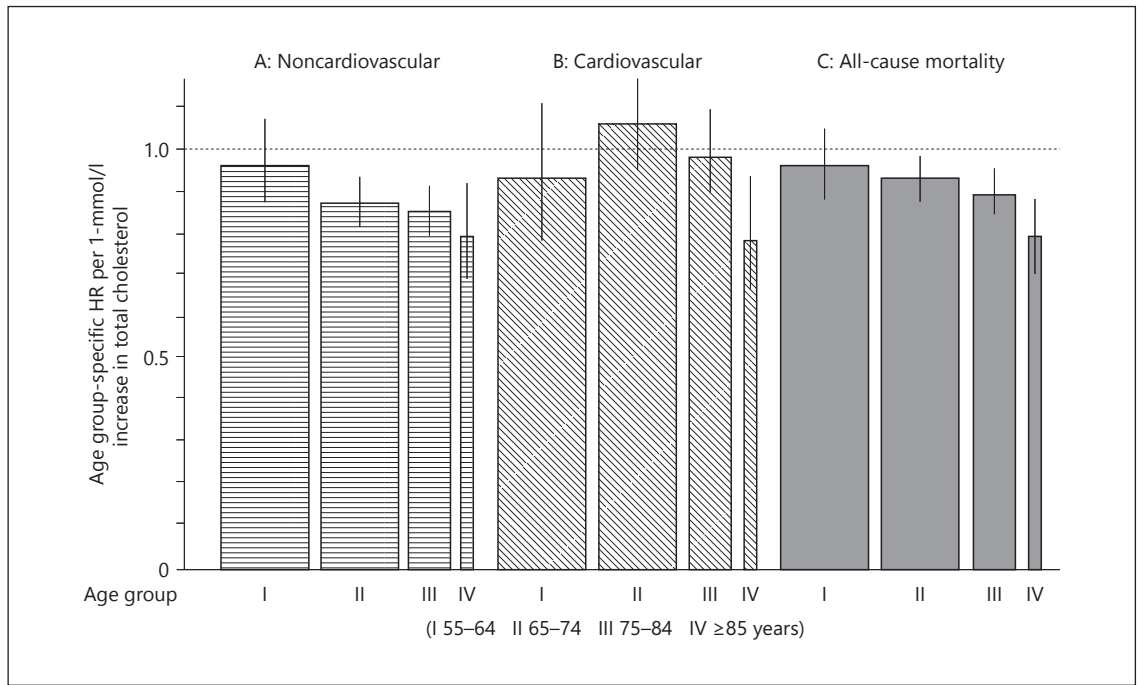
mortality in all statistical models except for model C for all-cause mortality (fig. 1-11). One of the items for adjustment in model C was serum albumin. This is probably why the significance of all-cause mortality in Model C did not reach significance; cholesterol and albumin levels in serum correlate well, and adjustment for albumin cancels the favorable effects of cholesterol (for a discussion of albumin, see Chapter 5, Section 1). Death certificates were collected for the first 9 years of follow up and of the 346 deaths recorded, 180 were caused by vascular disease. Among vascular deaths, 97 cases of acute myocardial infarction were classified as the immediate cause of death. Interestingly, total cholesterol had no predictive significance in this subgroup. Also, baseline Clinical Dementia Rating (CDR) scores (adjusted for age and sex) were inversely associated with total cholesterol levels: participants with CDR scores of 0–0.5 ( $n = 443$ ), 1–2 ( $n = 90$ ), and 3–4 ( $n = 64$ ) had mean cholesterol levels of 6.40 mmol/l (247 mg/dl), 6.24 (241), and 5.80 (224), respectively.

Participants in a study conducted in Rotterdam, the Netherlands, were evaluated for total cholesterol and fol-

lowed for mortality for a median of 13.9 years [16]. Cox's regression analyses were conducted for the total sample and within age groups (55–64, 65–74, 75–84, and  $\geq 85$  years). In the total sample, age- and sex-adjusted analyses showed that each 1-mmol/l (39-mg/dl) increase in total cholesterol was associated with an approximately 12% lower risk of noncardiovascular mortality. Age group-specific analyses demonstrated that this association reached significance after the age of 65 and increased in magnitude each subsequent decade (fig. 1-12, panel A). This was largely driven by non-high density lipoprotein (HDL) cholesterol (HR: 0.89, 95% CI: 0.85–0.93,  $p < 0.001$ ) and was partly attributable to decreased cancer mortality. Even cardiovascular mortality was significantly decreased with each 1-mmol/l (39-mg/dl) increase in total cholesterol in the  $\geq 85$  age group (fig. 1-12, panel B). Changes in all-cause mortality according to age (fig. 1-12, panel C) were similar to those in noncardiovascular mortality. The protective effects of cholesterol according to age are beautifully illustrated in this study. Unfortunately though, the HRs were adjusted for serum albumin levels. As described in the previous paragraph, adjustment for serum albumin obscures the real picture. Without albumin adjustment, the results illustrated in fig. 1-12 would be more prominent.

Lastly, the TMIG-LISA Study followed 1,048 Japanese individuals aged 65–85 years living at home in Tokyo or Akita Prefecture for 8 years [17]. As shown in fig. 1-13, the survival rate was lowest for the lowest quartile of total cholesterol and highest in the highest quartile (without any adjustment). As is apparent from the figure, the relationship between survival rates and cholesterol levels does not markedly change with the exclusion of deaths that occurred during the first 3 years. The multivariate HR for all-cause mortality for the 1st quartile of total cholesterol was 1.51 compared with the reference (4th quartile) after adjustment for 15 possible confounding factors including grip power and usual walking pace.

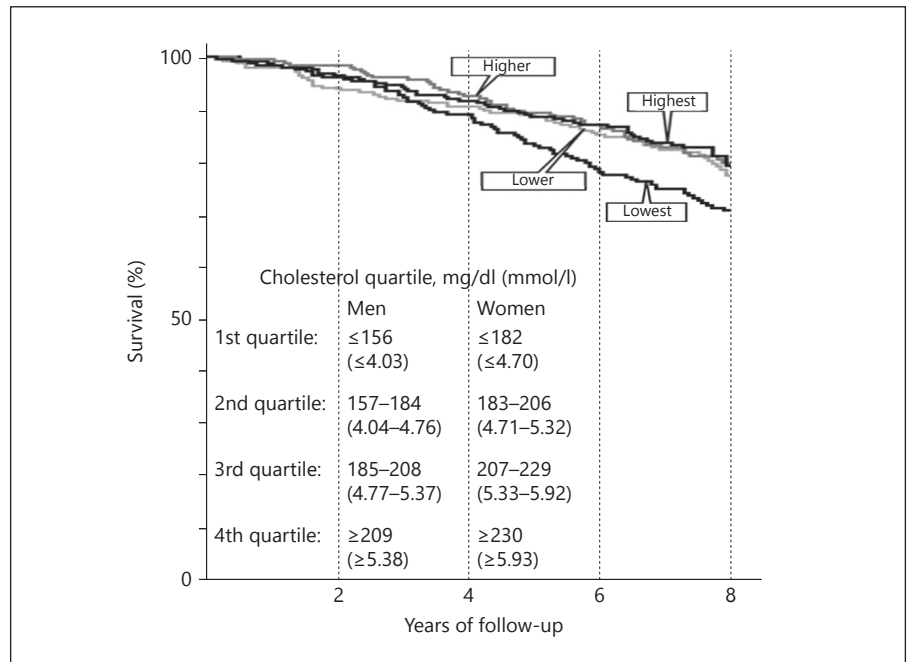
A new report was just published on the relationship in a very old Japanese population between all-cause mortality and serum cholesterol levels [18]. 207 participants aged 85 in Fukuoka Prefecture were followed for 10 years. The mortality rates according to serum total cholesterol levels were 77.4%, 62.5%, and 50% in the bottom ( $\leq 175$  mg/dl,  $\leq 4.52$  mmol/l), middle (176–208 mg/dl, 4.53–5.37 mmol/l), and top ( $\geq 209$  mg/dl,  $\geq 5.38$  mmol/l) tertiles, respectively. A multivariate Cox proportional hazards regression model, with adjustment for gender, smoking, alcohol intake, history of stroke or heart disease, serum albumin concentration, BMI, and systolic BP, revealed that



**Fig. 1-12.** Age group-specific association between total cholesterol and (A) noncardiovascular, (B) cardiovascular, and (C) all-cause mortality: study in Rotterdam, The Netherlands [16]. A total of 5,750 participants aged 55–99 years were evaluated for total cholesterol and followed for mortality for 13.9 years in Rotterdam. Cox’s regression analyses were conducted within the four age groups shown. Data were adjusted initially for age and sex, and

subsequently for education, cardiovascular risk factors (body mass index, smoking, diabetes mellitus, systolic and diastolic blood pressure, antihypertensive medication, and family history of early-onset CVD), and albumin. The vertical axis shows the hazard ratio (HR) and 95% confidence interval for every 1-mmol/l (39 mg/dl) increase in total cholesterol. The width of each column is proportional to the number of participants. See the text for details.

**Fig. 1-13.** Survival curve according to cholesterol quartile in Japanese elderly people: TMIG-LISA Study [17]. A total of 1,048 elderly participants were followed for 8 years. Survival rates are depicted according to cholesterol quartiles. No adjustment was performed. The hazard ratio for the 1st quartile was 1.51 compared with that of the 4th quartile after adjustment for 15 factors. (Courtesy of Dr. Shoji Shinkai, with slight modifications.)



the total mortality in the bottom tertile was 1.7-fold higher than that in the top tertile. Without albumin adjustment, the difference might have been larger (see Chapter 5, Section 1 for albumin discussion).

We have seen in this section that survival rate is definitely better in elderly people with high total or LDL cholesterol levels than in those with low levels. The proportion of people with FH or similar conditions among the elderly population is much smaller than that among younger populations, which explains why an inverse correlation between total cholesterol (or LDL cholesterol) and all-cause mortality becomes prominent with age in all countries (see fig. 3-4 in Chapter 3).

High LDL cholesterol levels might also be related to better cognitive function. The memory function of 193 functionally independent and community-dwelling elderly participants aged  $\geq 80$  years was cross-sectionally examined in the Key to Optimal Cognitive Aging (KOCO) Project, a prospective study undertaken in Okinawa, Japan [19]. High LDL cholesterol levels and low triglyceride/HDL cholesterol ratios were associated with high Scenery Picture Memory Test scores after adjustment for many confounding factors. When viewed together with the data presented above on cholesterol and longevity, it seems clear that high cholesterol levels should not be considered unhealthy especially in elderly people.

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## Chapter 2 Cholesterol and Disease

**Summary:** This chapter discusses relationships between diseases and cholesterol levels in the Japanese population, focusing on four main relationships. (1) Some association exists between mortality from coronary heart disease (CHD) and cholesterol only in men, although it is mostly explained by the presence of familial hypercholesterolemia in the cohorts studied to date. In women, there is even a study showing an inverse association between CHD mortality and cholesterol. In regard to stroke, it is more difficult to find a positive association with cholesterol, and inverse associations are found very easily. (2) Cancer mortality is inversely associated with cholesterol, and only a small proportion of this inverse association can be explained by reverse causality (i.e., the presence of subclinical participants whose cholesterol levels are low at baseline). (3) Mortality from infection is low in subjects with high cholesterol levels. This is because low density lipoprotein (LDL) and other lipoprotein particles stick to bacteria (and their toxic fragments) and viruses, decreasing their toxicity. (4) Liver disease seems to show the most marked association with cholesterol. Liver cancer incidence, liver cirrhosis mortality, and liver disease mortality have been found to be null in subjects with the highest cholesterol levels. Reverse causality cannot really explain this association. Competition between hepatitis C virus (HCV) and LDL at LDL receptors, which also happen to be the receptors for HCV, partly explains the protective effects of LDL.

### (1) Cholesterol and Mortality from Cardiovascular Disease

In a nutshell, what is known about the relationship between cholesterol and mortality from cardiovascular disease is that there is some association between cholesterol and CHD mortality in men but probably no clear association in women. In the case of stroke, cholesterol is known to be a negative risk factor.

Before discussing this relationship in detail, we should mention the issue of control groups, or reference groups. In epidemiological studies, reference groups should not have extreme values of the parameter being studied—in our case, cholesterol levels. Rather, they should contain subjects with median cholesterol values or they should be the largest groups closest to the median groups, because extreme groups may contain large proportions of people with disorders that could affect the mortality and incidence of the disease in question. For example, essentially all participants with familial hypercholesterolemia (FH) are included in the highest cholesterol groups, and if these groups were to serve as reference groups, the mortality and incidence of CHD may be lowered significantly in the other groups. As discussed in Chapter 1, groups with the lowest cholesterol levels have the highest all-cause mortality, with cancer accounting for the highest mortality (see Section 2 below). But what about mortality in patients with low cholesterol levels? Let's take the situation



where a death certificate must be issued for someone whose cholesterol levels were very low. The physician must decide what caused the patient's death. Say the patient had long been living with lung cancer, widespread metastasis had been found very recently, and on top of that the patient had had an acute myocardial infarction (AMI) 1 week before his death. The physician likely considers lung cancer or AMI as the likely cause of death, but which one exactly? In Japan, this kind of diagnostic dilemma occurs more frequently with patients in the lowest cholesterol group because more Japanese people in this group have cancer. In such cases, we could be underestimating the mortality from AMI in the lowest cholesterol group. There is also the possibility that people in the very low cholesterol groups do not survive long enough to suffer from CHD later. At any rate, we should not use extreme groups as reference groups.

In our review of the relationship between cholesterol and mortality from cardiovascular disease, let's look first at some epidemiological reports from Japan (written in English before 1990). Akita Prefecture, in northern Japan, used to have the highest death rate from stroke in Japan. An epidemiological survey of cardio- and cerebrovascular diseases in farming villages had been running in the prefecture since 1963, and during an 8-year follow-up period, 94 new stroke cases were observed among 1,814 subjects who were aged 40–69 years at the time of initial examination [1]. Multiple logistic function analysis using eight variables—age, sex, systolic blood pressure, obesity index, urinary sugar, urinary protein, serum total cholesterol, and total protein—revealed that hypertension was the most important risk factor for stroke. Multivariate analysis also showed that both men and women with low serum total cholesterol levels were more prone to cerebral hemorrhage, but that serum cholesterol levels had no weight as a risk factor for cerebral infarction. These results corresponded well with the then observed phenomena that stroke incidence and stroke mortality in Japan were higher in populations with a high prevalence of hypertension and low concentration of cholesterol [2], and that mortality from cerebral hemorrhage declined with increments in serum total cholesterol levels and the Westernization of diet. Data on the relation between all-cause mortality and cholesterol are not available in this particular study [1].

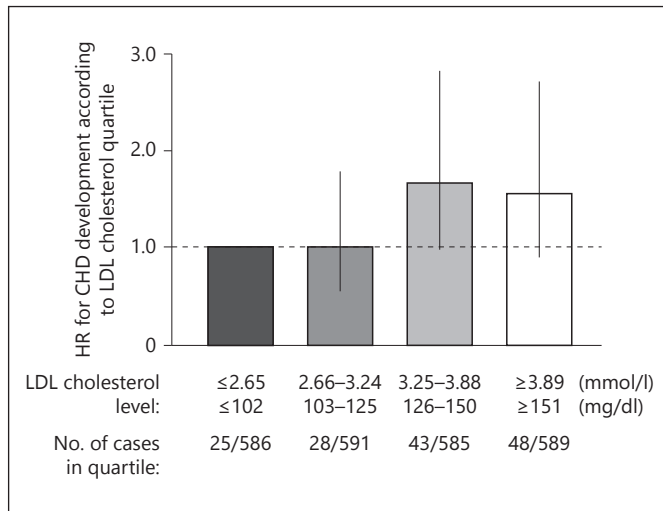
In a study of a rural community on Shikoku Island, men ( $n = 772$ ) and women ( $n = 901$ ) aged  $\geq 40$  without a history of stroke were followed for 10 years, from July 1967 through June 1977 [3]. The incidence of all strokes was 10.5 and 6.4 per thousand person-years for men and

women, respectively. The following risk factors were found to be statistically significant: age, male sex, elevated blood pressure, electrocardiographic abnormalities, and funduscopic abnormalities, with mean arterial pressure being the best predictive measure. Among all stroke cases, 26% involved cerebral hemorrhage, a proportion twice as high as that reported in comparable studies in the United States (12–15%) [3]. An inverse relationship was observed between serum cholesterol levels and cerebral hemorrhage incidence but not cerebral infarction incidence. Data on the relation between all-cause mortality and cholesterol are not available.

A subsequent study in Akita Prefecture did reveal some interesting relationships. Over two decades, between 1964 and 1983, disease surveillance and population surveys of risk characteristics were carried out in a rural community to investigate risk factor trends for CHD and stroke [4]. During this period, the incidence of CHD did not change significantly among men or women aged 40–69 years. The incidence of all stroke declined about 60% for both men and women, with significant decreases in cerebral hemorrhage for both sexes and in cerebral infarction for men. In the periods 1963–1966 and 1980–1983, significant upward shifts occurred in the means and distributions of serum total cholesterol in the 40–69 age group (22 mg/dl or 0.57 mmol/l for men, 29 mg/dl or 0.75 mmol/l for women, age-adjusted) and those of serum total protein in every age and sex group, primarily during the first decade. Animal fat intake doubled in men aged 40–59, from 4.5% of daily calories in 1969 to 9.6% in 1980–1983. Most of this increase occurred between 1969 and 1972–1975. Mean systolic and diastolic blood pressure levels declined for all age and sex groups. Two cohorts of men and women aged 40–69 at baseline were followed for disease incidence; an early cohort ( $n = 2,257$ ) was followed from 1963–1966 to 1973 and a later cohort ( $n = 2,711$ ) was followed from 1972–1975 to 1983. Serum cholesterol was found to be inversely associated with cerebral hemorrhage in the early cohort but not in the later one. This reduced association in the later cohort might be due in part to the marked upward shift in means and distributions of serum cholesterol between the two periods [4].

So, taken together, the findings of these early studies, conducted three or more decades ago, indicate that low cholesterol levels are a significant risk factor for hemorrhagic stroke in Japan.

Moving now to studies published after 1990 in Japan, one study was performed during a major shift toward more Western lifestyles (particularly during the period of



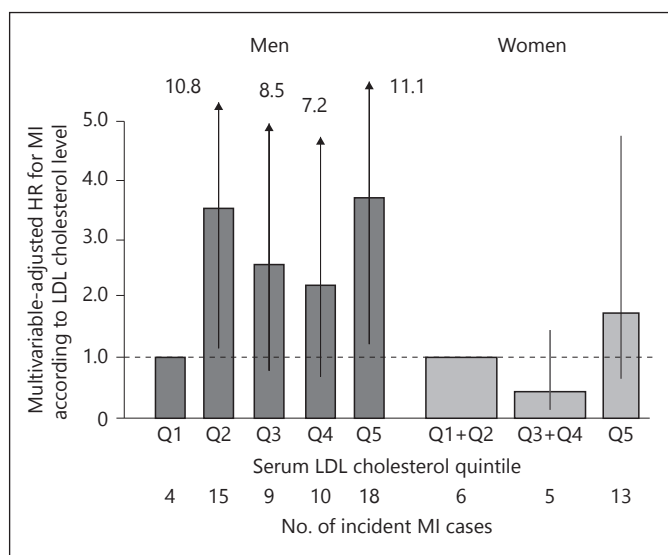
**Fig. 2-1.** Multivariate-adjusted hazard ratio (HR) for the development of coronary heart disease (CHD) according to low density lipoprotein (LDL) cholesterol quartile: Hisayama study [6]. A total of 2,351 residents (991 men, 1,360 women) aged  $\geq 40$  years in Hisayama Town, Fukuoka, were followed for 19 years. The participation rate of residents before exclusion of 197 residents for various reasons was 80.7% of the total population of this age group. During follow up, 144 participants developed CHD. The results were multivariate adjusted for age, sex, high density lipoprotein cholesterol, triglycerides, systolic blood pressure, electrocardiogram abnormalities, fasting blood glucose, body mass index, current drinking, current smoking, and regular exercise. CHD death data or those of sex-differentiated data according to LDL cholesterol levels were not available in the original paper. P for trend = 0.03, but the HR per 1-mmol/l increase in LDL cholesterol was 1.15 (0.95–1.39).

high economic growth around 1960 to 1975) when stroke frequency and the distribution of risk factors were dynamically altered in the Japanese population [5]. A cohort of 2,302 residents aged  $\geq 40$  in Shibata City, Niigata Prefecture, were followed from 1977 for 15.5 years. Crude incidence rates per 1000 person-years for all strokes were 5.22 for men (64 cases) and 4.36 for women (78 cases). Multivariate analyses performed with Cox's proportional hazard model confirmed the most traditional risk factors were operating, such as blood pressure and related organ diseases. However, serum total cholesterol was found to have essentially no effect on any stroke type. The relative risk for all strokes was 0.87 (0.66–1.15) and 0.99 (0.75–1.30) in men and women, respectively, for a 1 SD increment in total cholesterol (1.21 mmol/l, 47 mg/dl).

Another study, the Hisayama Study, is a well-known, long-term, prospective cohort study and one of the longest cohort studies conducted in Japan. It started in 1961 in Hisayama, a suburb of Fukuoka City in southern Japan,

and over 99% of the residents have been followed. Many reports have been published on this cohort, especially those on stroke, which was the main cause of death in Japan when the study started. One of these reports, published in 2009, discussed a relationship found between blood cholesterol levels and the incidence CHD overall as well as that of specific stroke types [6]. From a total of 2,351 residents aged  $\geq 40$  with no history of stroke or myocardial infarction (MI) who were followed for 19 years, 144 developed CHD [6]. Fig. 2-1 depicts the relationship between serum total cholesterol levels and CHD development. CHD in this study included silent MI, AMI, sudden cardiac death, coronary angioplasty, and bypass grafting. Unfortunately, data for both sexes were combined and data on CHD mortality, for which diagnosis is not easily biased, are not available. The results for stroke are discussed later in Chapter 5 (see table 5-C).

The Suita Study, a cohort study of cardiovascular disease, was started in 1989 with the urban residents of Suita City, Osaka. Men and women ( $n = 4,694$ ) aged 30–74 with no history of CHD or stroke were selected randomly from city records and followed for a mean 11.9 years [7]. During follow up, there were 80 incident cases of MI and 139 incident cases of stroke (23 intracerebral hemorrhages, 85 cerebral infarctions, and 31 other stroke types). The hazard ratio (HR) for MI was highest in the top quintile of LDL cholesterol (HR: 3.03, 95% confidence interval [CI]: 1.32–6.96, compared with the bottom quintile) when data for men and women were combined. However, mortality or incidence of MI should not be combined for men and women because women's data are very different from men's, especially in Japan. In fact, only a small number of epidemiological studies have shown a significant association between MI mortality and total or LDL cholesterol levels in women (see table 6-A in Chapter 6). Fig. 2-2 shows the sex-specific relations between the HRs for MI and LDL cholesterol [7]. Note the findings for men in particular: the incidence of MI in the lowest quintile of LDL cholesterol is somehow very low (only 4 incident cases). In other words, the chart does not indicate that high cholesterol levels are associated with MI. This returns to the point we made about control groups at the beginning of this section. The participants included in the lowest cholesterol groups always have the highest risks for all-cause mortality, so these groups must be regarded as groups very different from the rest and should not, therefore, be used as reference groups. In women, the highest cholesterol group does not show significantly higher HRs for MI than the lowest 2 LDL cholesterol quintiles combined (reference data). In addition, there were too few



**Fig. 2-2.** Multivariable-adjusted hazard ratio (HR) for myocardial infarction (MI) according to serum low density lipoprotein (LDL) cholesterol quintile: Suita Study [7]. A total of 4,694 residents were followed for 11.9 years, and 80 cases of incident MI were found. The HRs for MI are shown according to quintiles of LDL cholesterol levels. In the case of women, the bottom two quintiles and Q3 and Q4 were combined. The HRs were adjusted for age, body mass index, diabetes, high density lipoprotein cholesterol, cigarette smoking category, and alcohol intake categories by Cox's proportional hazard model. p values for trend were 0.08 for men and 0.14 for women. It is difficult to regard high cholesterol levels as a risk factor for MI from this figure. Quintiles for men (mmol/l, mg/dl), Q1 <2.54 (99); Q2 = 2.54–3.03 (99–117); Q3 = 3.04–3.43 (118–132); Q4 = 3.44–3.90 (133–150); Q5  $\geq$ 3.91 (151). Quintiles for women: Q1+Q2 <3.21 (124); Q3+Q4 = 3.21–4.22 (124–163); Q5  $\geq$ 4.23 (164). See the text for details.

incident cases of MI to obtain meaningful data in women. Unfortunately, no data are available on CHD mortality alone. If CHD mortality alone had been calculated in women or even in men, the results would have more accurately represented the situation in Japan (the number of fatal CHD cases is too small for epidemiological study in Japan). Lastly, the study found no association between the incidence of any subtypes of stroke and LDL cholesterol.

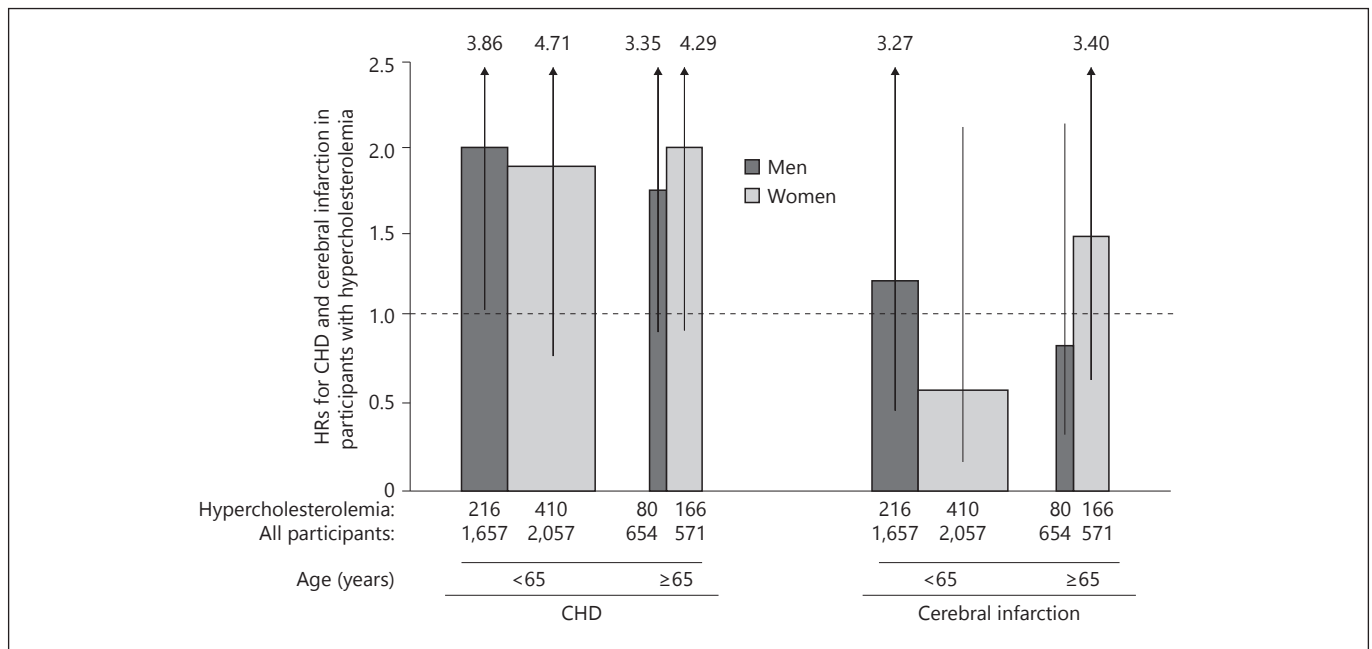
Another report in the Suita Study series recently reported HRs for CHD and LDL cholesterol [8]. Almost the same cohort as mentioned in the previous paragraph (but now 4,939, up from 4,694) was followed for 13 years. Participants with a history of coronary artery disease (CAD) or stroke or who were taking lipid-lowering drugs were excluded. During follow up, there were 155 cases of CAD (also interchangeably described as CHD in the report): 51

definite MIs, 62 probable MIs, 39 coronary interventions (coronary artery bypass or angioplasty), and 3 sudden deaths. There were also 204 cases of stroke: 118 ischemic strokes, 43 intracerebral hemorrhages, 22 subarachnoid hemorrhages, and 21 unclassified cases. Fig. 2-3 shows the HRs for CHD and cerebral infarction of participants with hypercholesterolemia, defined as LDL cholesterol level  $\geq$ 4.14 mmol/l (160 mg/dl). As can be seen, the HR for CHD was significantly higher only in men aged <65 years. However, the abstract states that serum LDL cholesterol levels were associated with an increased risk of CAD in men irrespective of age group. The report also does not provide any mortality data.

Coronary intervention depends partly on the subjective decisions of doctors, and it is likely that intervention is more aggressive than medication alone in those whose cholesterol levels are very high. In that sense, coronary intervention is not a bias-free measure, and without such an endpoint, the results might look different.

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), which was started in 1988–1990, analyzed data on 110,792 individuals (46,465 men, 64,327 women, aged 40–79) living in 45 areas across Japan who participated in municipal health screening examinations and completed self-administered questionnaires about their lifestyles and medical histories of previous cardiovascular disease and cancer [9]. This study, published in 2001, is highly regarded in the reference section of the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012 (JASG2012). However, the study's results on cholesterol have been overlooked in the guidelines, despite the fact that the relationships between cholesterol and mortality from stroke and CHD are clearly described in a later JACC Study published in 2007 [10].

The 2007 JACC Study reported 345 deaths from total strokes (including 76 intraparenchymal hemorrhages) and 150 deaths from CHD over 10 years of follow up (fig. 2-4). The corresponding control groups (n = 345 and 150, respectively) were matched for a number of variables (see fig. 2-4 figure legend for details). Serum total cholesterol levels were significantly lower in cases of total stroke than in the matched controls (5.10 vs. 5.30 mmol/l, 197 vs. 205 mg/dl, respectively) as well as more specifically in cases of intraparenchymal hemorrhage than in the controls (4.98 vs. 5.34 mmol/l, 193 vs. 206 mg/dl, respectively). Interestingly, serum total cholesterol levels did not differ significantly between cases of CHD and the controls (5.49 vs. 5.30 mmol/l, 212 vs. 205 mg/dl, respectively). Fig. 2-4 shows multivariable odds ratios (ORs) for



**Fig. 2-3.** Hazard ratios (HRs) for coronary heart disease (CHD) and cerebral infarction in participants with hypercholesterolemia: Suita Study [8]. The results shown here were obtained from essentially the same cohort as the study shown in Fig. 2-2. During 13 years of follow up, there were 155 cases of incident CHD and 204 cases of incident stroke. Hypercholesterolemia was classified as

low density lipoprotein cholesterol levels  $\geq 4.14$  mmol/l (160 mg/dl). The HRs were multivariable-adjusted for age, smoking, and alcohol drinking. The width of each column is proportional to the number of participants with hypercholesterolemia. No mortality rates for CHD or stroke are given in the original paper. See the text for details.

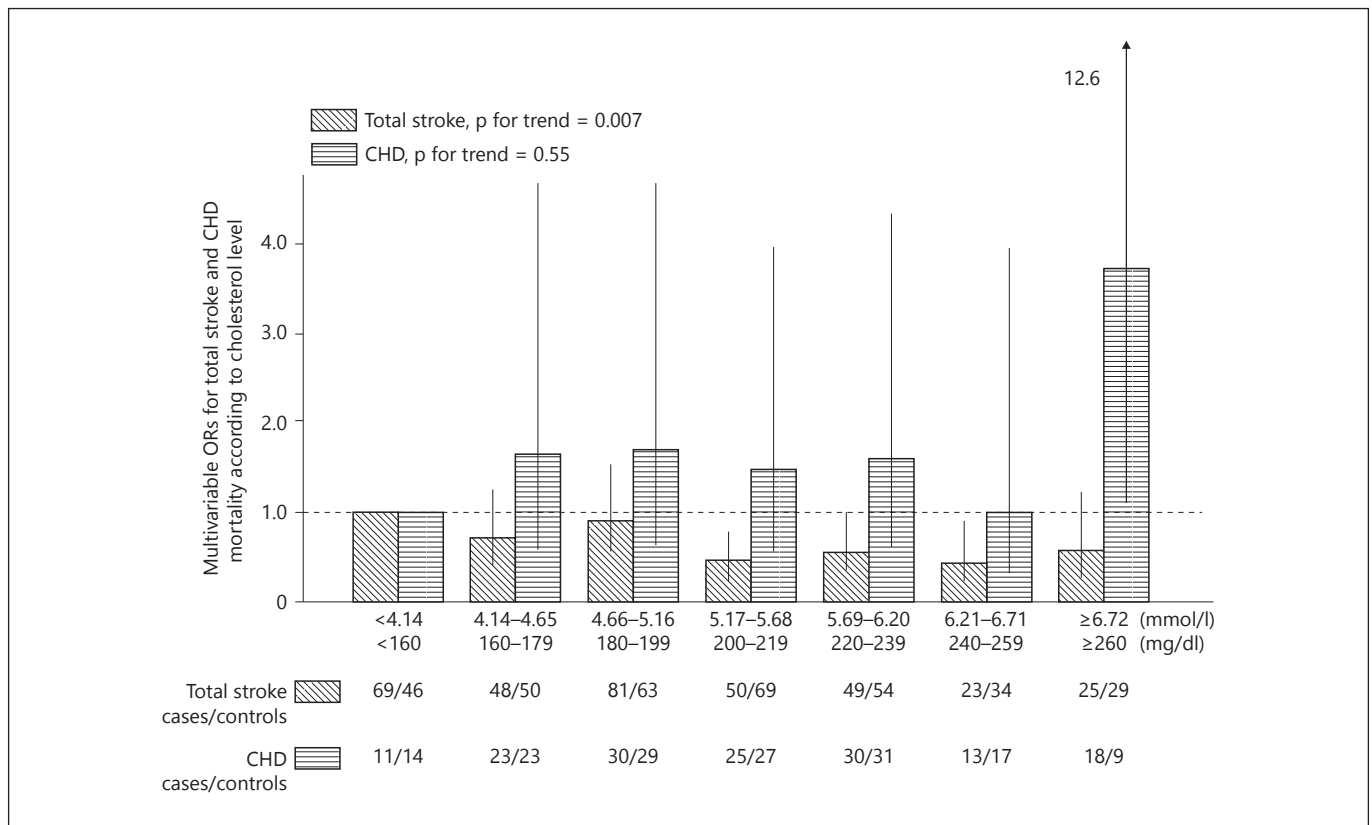
stroke and CHD according to total cholesterol values. The OR for CHD in the cholesterol range of  $\geq 6.72$  mmol/l (260 mg/dl) is significantly higher than that in the reference group ( $< 4.14$  mmol/l,  $< 160$  mg/dl). However, this is most likely due to the presence of patients with FH. Also, the reference groups should be somewhere in the middle, such as 5.17–5.68 mmol/l (200–219 mg/dl); if they were, there would no longer be any significantly different groups. Another interesting point with regard to CHD mortality is that it was lowest in two ranges (OR = 1.00 in both): one in the reference range ( $< 4.14$  mmol/l,  $< 160$  mg/dl) and the other in the range 6.21–6.71 mmol/l (240–259 mg/dl). The latter is actually recognized as one of the very dangerous zones in the JASG2012 chart (see fig. 5-5 in Chapter 5, the most important figure in JASG2012). All data were adjusted for sex, which is unfortunate because there is little evidence that mortality from CHD in women increases with serum cholesterol levels in Japan, so stratification by sex is in fact necessary.

The Japan Standard Stroke Registry Study (JSSRS) is the largest of the Japanese acute stroke studies. Cases of acute stroke ( $n = 47,782$ ) were registered between 1998 and 2007 [11]. To avoid the effects of medication, 16,850

cases (mean age,  $67.4 \pm 14.3$  years, men 61%) free from medication for hyperlipidemia, hypertension, or diabetes were extracted. This sample was composed of 12,162 cases with cerebral infarction ( $69.5 \pm 13.5$  years, men 64%), 3,238 with intraparenchymal hemorrhage ( $63.8 \pm 14.9$ , men 60%), and 1,450 with subarachnoid hemorrhage ( $58.2 \pm 13.9$ , men 37%). The clinical indices of stroke—modified Rankin Scale (mRS), Japan Stroke Scale (JSS), and National Institute of Health Stroke Scale (NIHSS)—were assessed at admission and discharge according to stroke type and the presence or absence of hyperlipidemia [12], which was most likely diagnosed based on the 1997 [13] and 2007 [14] JAS guidelines in use during the study period, namely, LDL cholesterol  $\geq 140$  mg/dl (3.62 mmol/l) or total cholesterol  $\geq 220$  mg/dl (5.69 mmol/l) in the case of [13], and/or triglycerides  $\geq 150$  mg/dl (1.69 mmol/l). Mortality at discharge was also similarly examined.

Patients with hyperlipidemia accounted for 19.0%, 13.6%, and 7.3% of patients in the cerebral infarction, intraparenchymal hemorrhage, and subarachnoid hemorrhage groups, respectively. These rates are actually quite low compared with the general Japanese pop-





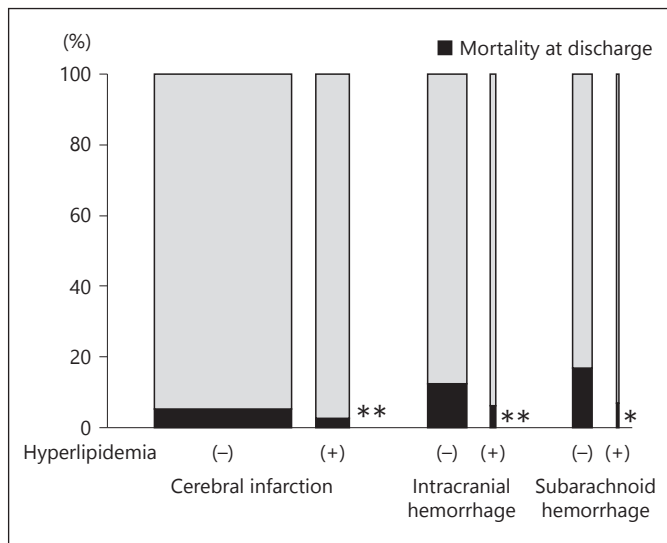
**Fig. 2-4.** Multivariable odds ratios (ORs) for total stroke and coronary heart disease (CHD) according to serum total cholesterol level: JACC Study [10]. This nested case-control study was performed as part of the JACC study. A total of 39,242 participants aged 40–79 years entered the study between 1988 and 1990. Over 10 years of follow up, there were 345 deaths from total strokes and

150 deaths from CHD. The control participants were matched for sex, age, community, and year of serum storage, and further adjusted for systolic blood pressure, high density lipoprotein cholesterol, ethanol intake, smoking, and diabetes. The width of each column is not proportional to the number of participants. See the text for details.

ulation, given that 41.3% of subjects had hyperlipidemia in a general Japanese population free from lipid-lowering medication when matched for sex and age with JSSRS cases [15]. Patients who had cerebral infarction or intraparenchymal hemorrhage and hyperlipidemia showed significantly better clinical scores at both admission and discharge than those without hyperlipidemia ( $P < 0.001$ ) irrespective of the clinical index used (mRS, JSS, or NIHSS). Similarly, patients who had subarachnoid hemorrhage and hyperlipidemia had better clinical scores with all three indices than those without hyperlipidemia, but the differences were not significant due to the small number of patients with hyperlipidemia. Fig. 2-5 shows mortality at discharge. For each stroke type, mortality was significantly smaller in the group with hyperlipidemia than in the group without it. The ORs for mortality at discharge adjusted for age and sex were 0.53 (95% CI: 0.40–0.71,  $p < 0.001$ )

for cerebral infarction, 0.48 (95% CI: 0.32–0.71,  $p < 0.001$ ) for intraparenchymal hemorrhage, and 0.33 (95% CI: 0.15–0.73,  $p < 0.01$ ) for subarachnoid hemorrhage. This study had some methodological limitations because of its cross-sectional nature. However, given the lower mortality at discharge seen for patients with hyperlipidemia (fig. 2-5), it seems highly unlikely that many patients with hyperlipidemia had died before admission.

A very recent study from Sweden reported 3-month, 1-year, and 5-year survival rates for 190 consecutive patients after acute ischemic stroke [16]. All three survival rates were significantly better in patients with high admission cholesterol levels ( $>4.6$  mmol/l,  $>177$  mg/dl) than in those with low ones ( $\leq 4.6$  mmol/l). Neither statin treatment at discharge nor newly initiated statins during hospital stay was independently associated with mortality.



**Fig. 2-5.** Mortality at discharge of 16,850 patients with acute stroke: Japan Standard Stroke Registry Study [12]. A total of 16,850 acute stroke patients who were free from medication for hyperlipidemia, hypertension, and diabetes were studied. Black bars: mortality at discharge depicted according to stroke type and the presence/absence of hyperlipidemia. (Details of hyperlipidemia are not clear.) For each stroke type, mortality at discharge was significantly higher in the normolipidemic group than in the hyperlipidemic group. Gray bars: alive at discharge. The width of each column is proportional to number of patients in that group. The ratio of patients with hyperlipidemia in each group was much lower than that in the general Japanese population (41.3%). See the text for details. \*  $p < 0.01$ , \*\*  $p < 0.001$  compared with respective normolipidemic counterparts.

It would seem then, taking all the above results together, that hyperlipidemia diagnosed based on the 1997 and 2007 JAS Guidelines is a negative risk factor for stroke.

The Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combined (JALS-ECC) is, as its name suggests, a combined cohort study. A total of 22,430 Japanese men and women (aged 40–89 years) without a history of cardiovascular events, from 10 community-based cohorts, were followed for a mean 7.6 years [17]. During that time, 104 individuals experienced AMI and 339 experienced stroke. The incidence of MI was positively associated with total cholesterol levels in both men and women (fig. 2-6). The point to note here is that the number of cases of MI was very small. Besides, the number of fatal cases was not reported. Look at the women's data (right side of fig. 2-6). There was only 1 MI in the lowest quartile of total cholesterol. The issue of control groups appears again: which group should be referred to as the control group? In Japan, it is very difficult to find a posi-

tive association between MI and cholesterol levels, particularly in women. In this combined cohort study, total cholesterol levels were not associated with any stroke subtype (or total stroke).

In Chapter 1, Section 1, we introduced the Ibaraki Prefecture Health Study [18]. The baseline survey was completed in 1993 and a total of 91,219 participants were followed through 2003. Fig. 2-7 shows the relation between cholesterol levels and the HR for stroke mortality. The relation is a very simple one: low cholesterol levels constitute a risk factor for stroke mortality, while mid to high cholesterol levels constitute a low risk. This was largely due to significantly lower hemorrhagic stroke mortality in the higher LDL cholesterol groups [19].

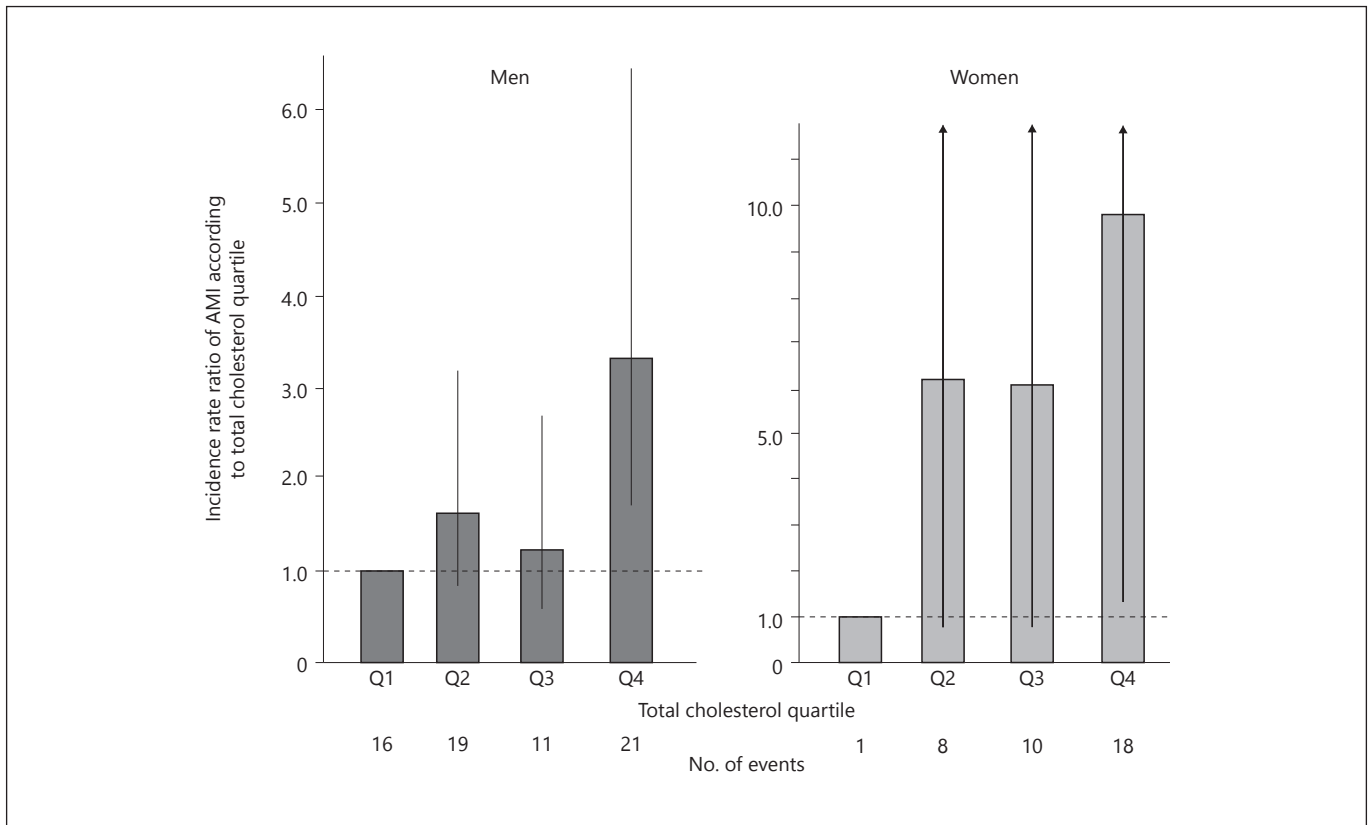
Also in Chapter 1, Section 1, we introduced the results for all-cause mortality in the Jichi Medical School Cohort Study [20]. Here, fig. 2-8 shows the relationship between total cholesterol levels and mortality from myocardial infarction (panel A) and stroke (panel B) in that study. No significant differences in mortality were found between the cholesterol categories in cases of MI or stroke. However, we believe this study, like many others on cholesterol, has some fundamental problems.

Let us explain. A total of 12,334 healthy participants aged 40–69 years were followed for a mean 11.9 years. The outcome was total mortality according to sex and cause of death. Actually, HRs were calculated for mortality from stroke (hemorrhagic and ischemic), heart disease (MI and heart failure excluding MI), and cancer according to four cholesterol level categories—I:  $<4.14$  mmol/l ( $<160$  mg/dl); II: 4.14–5.16 mmol/l (160–199 mg/dl); III: 5.17–6.20 mmol/l (200–239 mg/dl); and IV:  $\geq 6.21$  mmol/l ( $\geq 240$  mg/dl). These four cholesterol level categories were used throughout the whole paper except in one particular area [20]: the HRs for women's MI in the higher cholesterol categories (categories III and IV, shaded areas in fig. 2-8).

Table 3b in the Jichi Medical Cohort Study report [20] gives the number of deaths from various diseases during the follow-up period. In women, there were 3 MI deaths in cholesterol category I, 15 in category II, 9 in category III, and 0 in category IV. The fact that there was not even 1 case for cholesterol levels  $\geq 6.21$  mmol/l ( $\geq 240$  mg/dl) over the entire 11.9 years clearly argues against the notion of the lower the cholesterol levels, the lower the mortality'.

However, in table 5, arguably the most important table in the report [20], the authors for some reason do not show that the HR for MI was zero in women with category IV total cholesterol because they further divided the

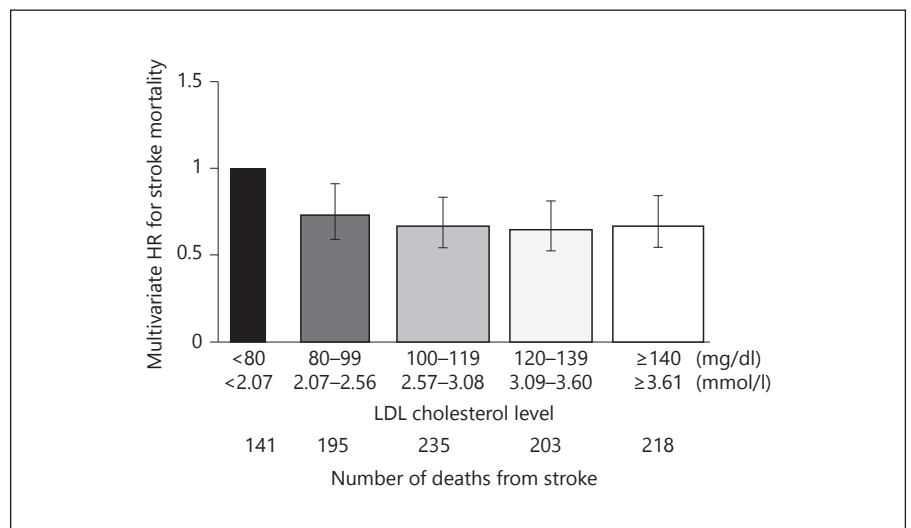


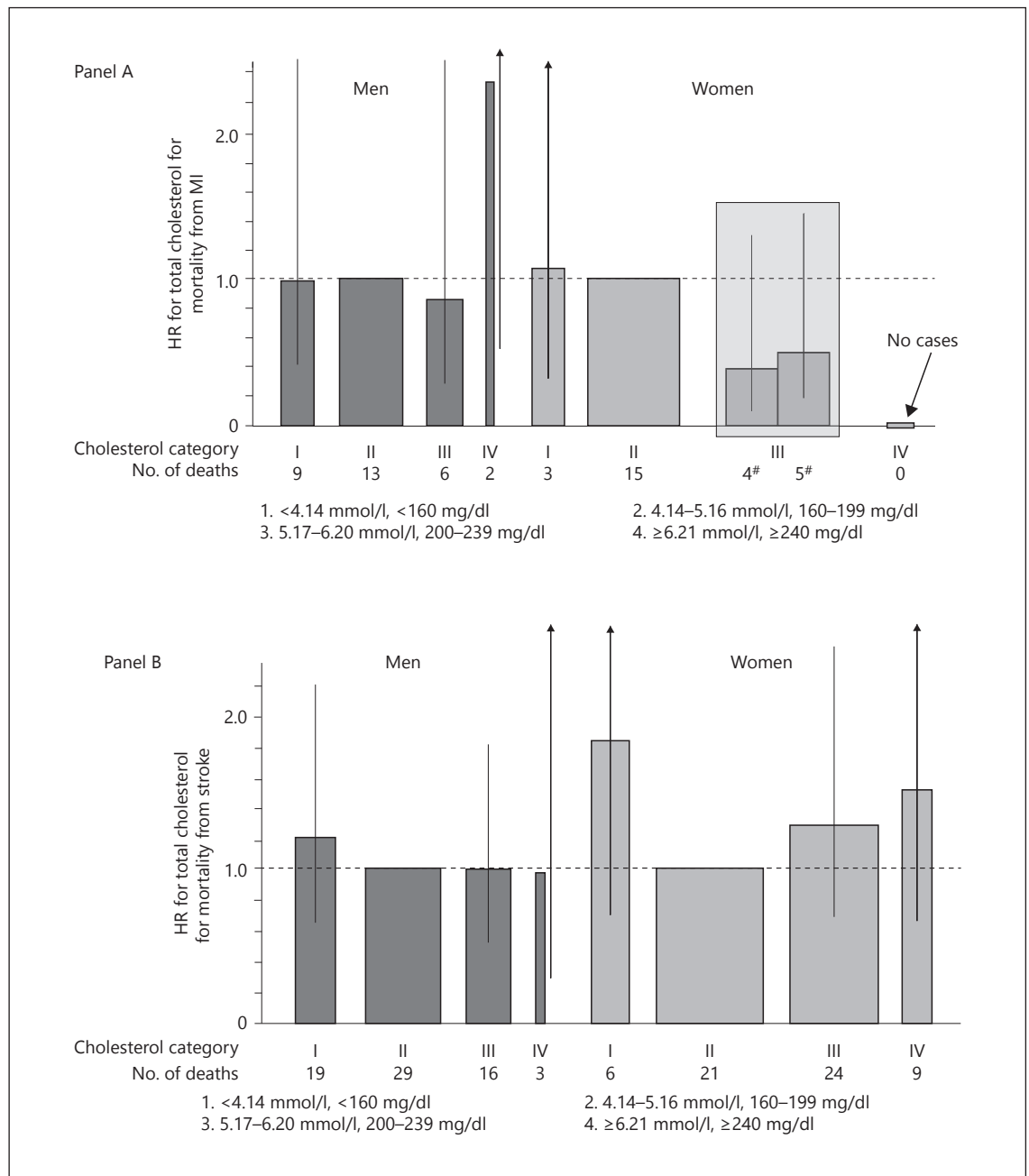


**Fig. 2-6.** Multivariable-adjusted incidence rate ratio of acute myocardial infarction (AMI) according to total cholesterol quartile: JALS-ECC study [17]. A total of 22,430 Japanese men and women aged 40–89 years with no history of cardiovascular events were followed for a mean 7.6 years. The incidence rate ratios of AMI were adjusted for sex, age, body mass index, serum high density lipopro-

tein cholesterol, blood pressure, diabetes, and current smoking status. The quartiles of cholesterol are Q1  $\leq 175$  mg/dl (4.54 mmol/l), Q2 = 176–198 (4.55–5.14), Q3 = 199–223 (5.15–5.78), and Q4  $\geq 224$  (5.79). Note that there was only one event in women’s Q1. See the text for details.

**Fig. 2-7.** Relationship between low density lipoprotein cholesterol and stroke mortality: Ibaraki Prefecture Health Study [19]. A total of 91,219 participants aged 40–79 years with no history of stroke or coronary heart disease were surveyed in Ibaraki Prefecture in 1993 and followed through 2003. The multivariable hazard rate (95% confidence interval) was adjusted for age, sex, and other cardiovascular risk factors. The width of each column is proportional to the number of participants in that group. HR = Hazard ratio; LDL = low density lipoprotein cholesterol.





**Fig. 2-8.** Mortality from (A) myocardial infarction and (B) stroke and relation with total cholesterol: Jichi Medical School Cohort Study [20]. More than 12,000 men and women were followed for 11.9 years. Hazard ratios (HRs) were calculated using Cox's proportional hazards model with adjustment for age, systolic blood pressure, high density lipoprotein cholesterol, smoking, drinking, and body mass index. (A) No significant differences in HRs were observed between any cholesterol groups in men or women. Note that there were only 2 cases in the highest category in men and none in the highest category in women. Two vertical lines (95% confidence intervals) are provided next to the columns for clarity.

The width of each column is proportional to the number of participants in that group, except for two cholesterol groups in women (shaded box in category III). The exact numbers of participants in these two groups are not available, but they are tentatively given as one half the number of participants in category III. The two columns represent the two cholesterol categories: left, 5.17–5.68 mmol/l (200–219 mg/dl) and right, 5.69–6.20 (220–239). The number of deaths in the two combined was 9 (respective numbers are not available). 4<sup>#</sup> and 5<sup>#</sup> are our estimates. See the text for the reasons why category III in the shaded box was divided into two.

**Table 2-A.** Multivariable hazard ratios and 95% confidence intervals for fatal and non-fatal coronary heart disease according to low density lipoprotein cholesterol category: Circulatory Risk in Communities Study [21]

mg/dl mmol/l	LDL cholesterol level					HR per 30-mg/dl (0.77-mmol/l) increment
	<80 <2.06	80–99 2.06–2.57	100–119 2.58–3.09	120–139 3.10–3.61	≥140 ≥3.62	
No. of participants (men and women)	1,774	1,899	1,949	1,302	1,207	Total: 8,131
Total CHD						
No. of cases	23	29	35	31	37	Total: 155
Multivariable HR* (95% CI)	1.0	1.35 (0.77–2.36)	1.66 (0.96–2.86)	2.15 (1.22–3.81)	2.80 (1.59–4.92)	1.30 (1.11–1.49)
Non-fatal CHD						
No. of cases	13	23	24	26	29	Total: 115
Multivariable HR* (95% CI)	1.0	1.95 (0.98–3.90)	2.06 (1.03–4.13)	3.25 (1.61–6.53)	4.07 (2.02–8.20)	1.36 (1.16–1.58)
Fatal CHD						
No. of cases	10	6	11	5	8	Total: 40
Multivariable HR* (95% CI)	1.0	0.57 (0.20–1.64)	1.04 (0.41–2.60)	0.72 (0.23–2.28)	1.24 (0.44–3.47)	1.16 (0.87–1.55)

HR = Hazard ratio, CI = confidence interval, LDL = low density lipoprotein, CHD = coronary heart disease.

A total of 8,131 men and women were followed for a median period of 21.9 years. Note that the HRs for non-fatal CHD increased with LDL cholesterol levels, but the HRs for fatal CHD, which was relatively easy to diagnose accurately, did not. Probably non-fatal CHD was overdiagnosed in groups with higher LDL cholesterol levels. See the text for details. \* HR adjusted for sex, age, blood pressure category, antihypertensive medication use, glucose category, body mass index, smoking status, alcohol intake category, lipid lowering medication use, categories of high density lipoprotein cholesterol and triglycerides, fasting status, year of entry to study, and study area. (Remade with permission from the publisher.)

data for category III (9 AMI deaths) into the two subcategories of 5.17–5.69 mmol/l (200–219 mg/dl) and ≥5.70 (≥220) and assigned the data for these two subcategories to original categories III and IV, respectively. If we look at the values in cholesterol category IV in their table, we see ‘0.52 (0.18–1.46)’ instead of ‘ - ’. These values actually refer to 5.70–6.20 mmol/l (220–239 mg/dl) and not to category IV. This can be easily overlooked because this re-assignment is explained only in the table footnote, with a very small superscript notation in the table itself [20].

The available data, when interpreted carefully, appears to tell us that the Japanese have high cholesterol levels, yet their mortality from AMI is very low—a kind of ‘Japanese paradox’ if you will.

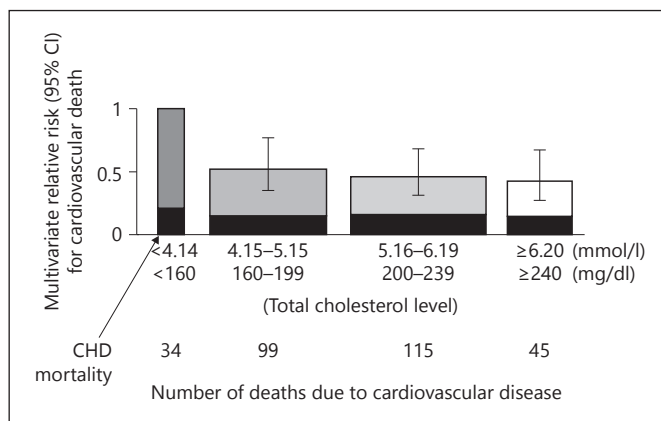
The Circulatory Risk Communities Study (CIRCS) was designed to examine the association between serum LDL cholesterol levels and risk for CHD among the Japanese [21]. Serum LDL cholesterol levels in casual blood samples were evaluated among residents from four Japanese communities participating in the study. A total of 8,131 men and women aged 40–69 years with no history of stroke or CHD completed baseline risk factor surveys between 1975 and 1987. By 2003, 155 cases of incident CHD (MI, angina pectoris, and sudden cardiac

death) had been identified. The median follow-up period was 21.9 years. Table 2-A shows the HRs for total, non-fatal, and fatal CHDs adjusted for sex, age, and other possible confounding factors. What table 2-A shows us is that in non-fatal CHD the HRs increased with LDL cholesterol levels, but did not do so for fatal CHD, which is relatively easy to diagnose accurately. According to the CIRCS report [21]p.382), ‘*Definite myocardial infarction was diagnosed as typical severe chest pain (lasting for ≥30 min) together with the appearance of new abnormal and persistent Q or QS waves, consistent changes in cardiac enzyme levels, or both. Probable myocardial infarction was indicated by typical chest pain, but for which no electrocardiographic findings or findings related to enzyme activity were available. Myocardial infarction was considered present if either definite or probable myocardial infarction was diagnosed*’ (emphasis added). CHD in the CIRCS also included angina pectoris, the diagnosis of which is also notoriously inaccurate because it can be diagnosed without any objective findings. It is highly possible that non-fatal CHD was overdiagnosed in groups with higher LDL cholesterol levels. The study’s use of the group with the lowest cholesterol levels as the reference group also has its problems. It would seem, then, that the CIRCS suffers some bias and does

not prove any association between high LDL cholesterol levels and CHD.

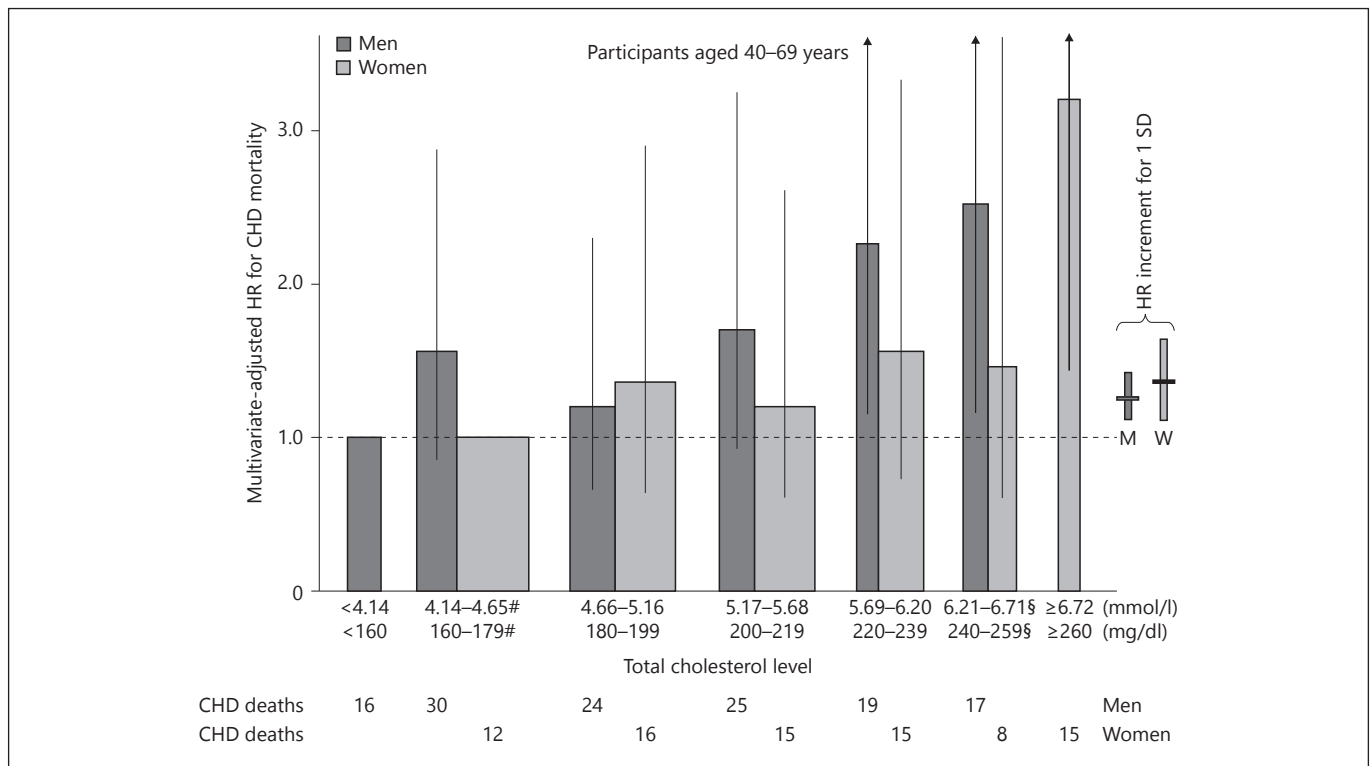
Tsuji followed 16,461 men and women for a mean 10.9 years in Moriguchi City, Osaka [22]. All participants were without any health problems and had not had regular health check-ups. As shown in fig. 2-9, CHD mortality (black bars) has no clear relation with total cholesterol levels. This leads us now to ask the important question we have been working up to: Is it actually necessary to lower cholesterol levels in the general population?

In the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan: EPOCH-JAPAN study, Nagasawa et al. reported a relationship between total cholesterol levels and cardiovascular disease by analyzing a pooled data set from 10 cohort studies involving a total of 65,594 men and women aged 40–89 years (mean age, 57 years, women 60%) and free from cardiovascular disease at baseline [23]. Three cohorts were nationwide and the other seven were from single prefectures. The participants were followed for a mean 10.1 years. They were divided into two age groups, middle-age (40–69 years) and elderly (70–89 years), and the respective multivariate-adjusted HRs of CHD mortality are shown in fig. 2-10 and 2-11. Among the elderly participants (fig. 2-11), only the HR for men with cholesterol levels  $\geq 6.21$  mmol/l ( $\geq 240$  mg/dl) was significantly different from that for the control group ( $< 4.14$  mmol/l,  $< 160$  mg/dl). This significant difference in men is completely dependent on the choice of the control group—a crucial issue we highlighted right at the start of this chapter. A range around 5 mmol/l (200 mg/dl) should be chosen as the reference range, at least in Japan. With this in mind, let's look again at fig. 2-10 and 2-11. We can start to see a different picture emerging. If the largest subgroup (4.66–5.17 mmol/l, 180–200 mg/L) is taken as the reference group, the chart for men aged 40–69 years may now indicate highly deleterious effects of cholesterol. The same is the case with elderly men (fig. 2-11). As can be seen from these figures, the columns for the control groups for women are rather wide: this is because they are composed of the two lowest cholesterol groups. We wonder why it is necessary to combine these two groups for women but not for men. One reason may be to increase participant numbers sufficiently to obtain significant results. In men, the columns for the two highest cholesterol groups are likewise combined. The reason for combining two columns becomes clear only when showing the column widths as proportional to the numbers of participants. The width of a column is an important factor to consider when interpreting results.



**Fig. 2-9.** Relationship between total cholesterol level and cardiovascular mortality in Moriguchi City, Osaka [22]. A total of 16,461 men and women (three-fourths women) were followed for 10.9 years in Moriguchi City. The relative risks were adjusted for age, sex, current smoker, hypertension, diabetes, drinking habit, and history of cardiovascular disease, using proportional hazards regression analysis. Black bars: relative risk for coronary heart disease (CHD) mortality, depicted according to the ratio between the number of CHD deaths and cardiovascular deaths within the same cholesterol groups. The width of each column is proportional to the number of participants in that group. CI = Confidence interval.

However, somewhat surprisingly, the EPOCH-JAPAN study does not mention the very important issue of all-cause mortality. In addition, the data set is not really representative of Japanese epidemiological studies since it does not include the two largest studies conducted thus far, the Ibaraki Prefecture Health Study [18] and Isehara Study [24] (see Chapter 1, Section 1). These two studies found no association between mortality from CHD or IHD and LDL cholesterol levels at all in women. Finally, the number of deaths in each cholesterol class is very small. The cholesterol categories with significantly higher HRs for CHD in fig. 2-10 have less than 20 CHD deaths, which are very small numbers compared with the 5600 total deaths we roughly estimate for the study period. (The total number of deaths is not given in the study, but we arrived at the estimation of 5,600 by dividing the total stroke deaths, 875, by a factor of 0.155, which was the average ratio of deaths from stroke among all-cause deaths between 1990 and 1995 in Japan [25]). Fig. 2-12 shows the relation with mortality from stroke according to total cholesterol levels reported by the study [23]. As can be seen, total cholesterol is a negative risk factor for stroke. The HR decreased to 0.93 (0.826–0.997) for each 1-SD increment in total cholesterol (0.98 mmol/l, 38 mg/dl).



**Fig. 2-10.** Multivariate-adjusted hazard ratios (HRs) for coronary heart disease (CHD) mortality according to total cholesterol level in participants aged 40–69 years: EPOCH-JAPAN [23]. A pooled data set of 65,594 individuals aged 40–89 years from 10 cohort studies in Japan (10.1 years of follow up) was analyzed. This figure shows the results for participants aged 40–69 years. The numbers of CHD deaths are given at the bottom of the figure for men and women. The HR increment for 1 SD of cholesterol is shown to the

right. The width of each column is proportional to the number of participants. # In women, participants with total cholesterol <4.14 mmol/l (160 mg/dl) are also included. \$ In men, participants with total cholesterol ≥6.72 mmol/l (260 mg/dl) are also included. This kind of manipulation (# and \$) raises some concerns. The control groups should be the third or fourth dark column (from the left) and the second or third light column. See the text for details.

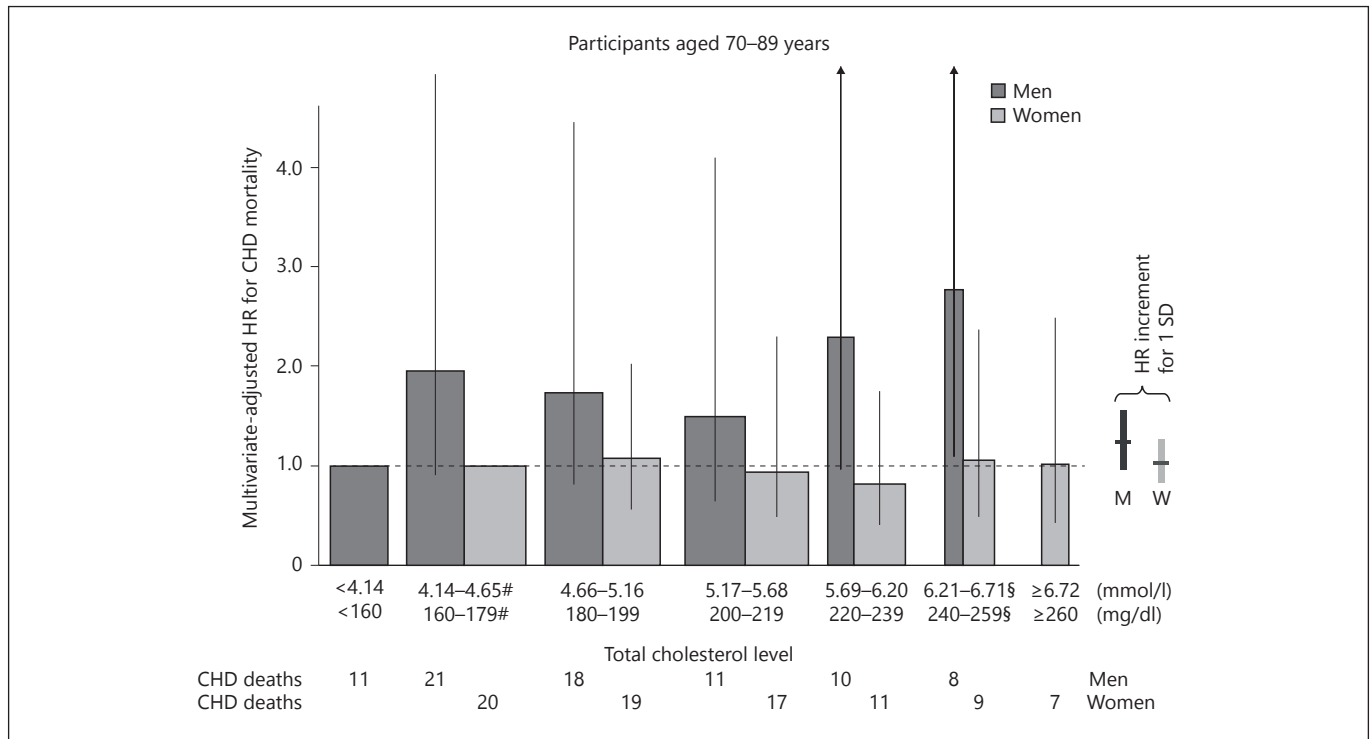
When we look at the results of most epidemiological studies, they indicate three general trends in CHD mortality. First, in men, the highest CHD mortality is found in the group with the highest cholesterol levels, irrespective of significance. This can be explained by the presence of participants with FH in the highest cholesterol category. Second, in women, there is no strong evidence of a relationship between CHD mortality and cholesterol levels. And third, cholesterol is more or less a negative risk factor for stroke.

## (2) Cholesterol and Cancer

One of the biggest contributors to the inverse correlation between the lowest cholesterol levels and the highest all-cause mortality is cancer mortality. In this section, we focus on the relationship between cholesterol and cancer.

We'll begin by introducing some epidemiological findings on cholesterol and cancer and then explore the relationship between cholesterol and liver cancer among other liver diseases.

In the Japan Public Health Center-based Prospective (JPHC) Study conducted in 9 public health center areas, 33,368 Japanese men and women aged 40–69 years who were free of prior diagnosis of cancer and cardiovascular disease undertook serum total cholesterol measurement between 1990 and 1994, and were followed to ascertain incident total and major sites of cancer until the end of 2004 (n = 2,728 incident cancers) [26]. Sex-specific associations between cholesterol and cancer risk were calculated. Serum total cholesterol levels were inversely associated with risk for total cancer in men (n = 1,434, see fig. 2-13) but not women, and showed strong inverse associations with stomach cancer in men and liver cancer in both sexes.



**Fig. 2-11.** Multivariate-adjusted hazard ratio for coronary heart disease mortality according to total cholesterol level in participants aged 70–89 years: EPOCH-JAPAN [23]. See the legend for Fig. 2–10 for details. This figure shows the results for participants aged 70–89 years. # In women, participants <4.14 mmol/l (160 mg/dl)

are also included. § In men, participants ≥6.72 mmol/l (260 mg/dl) are also included. The control groups should be the third or fourth dark column (from the left) and the second or third light column. See the text for details. HR = Hazard ratio; CHD = coronary heart disease.

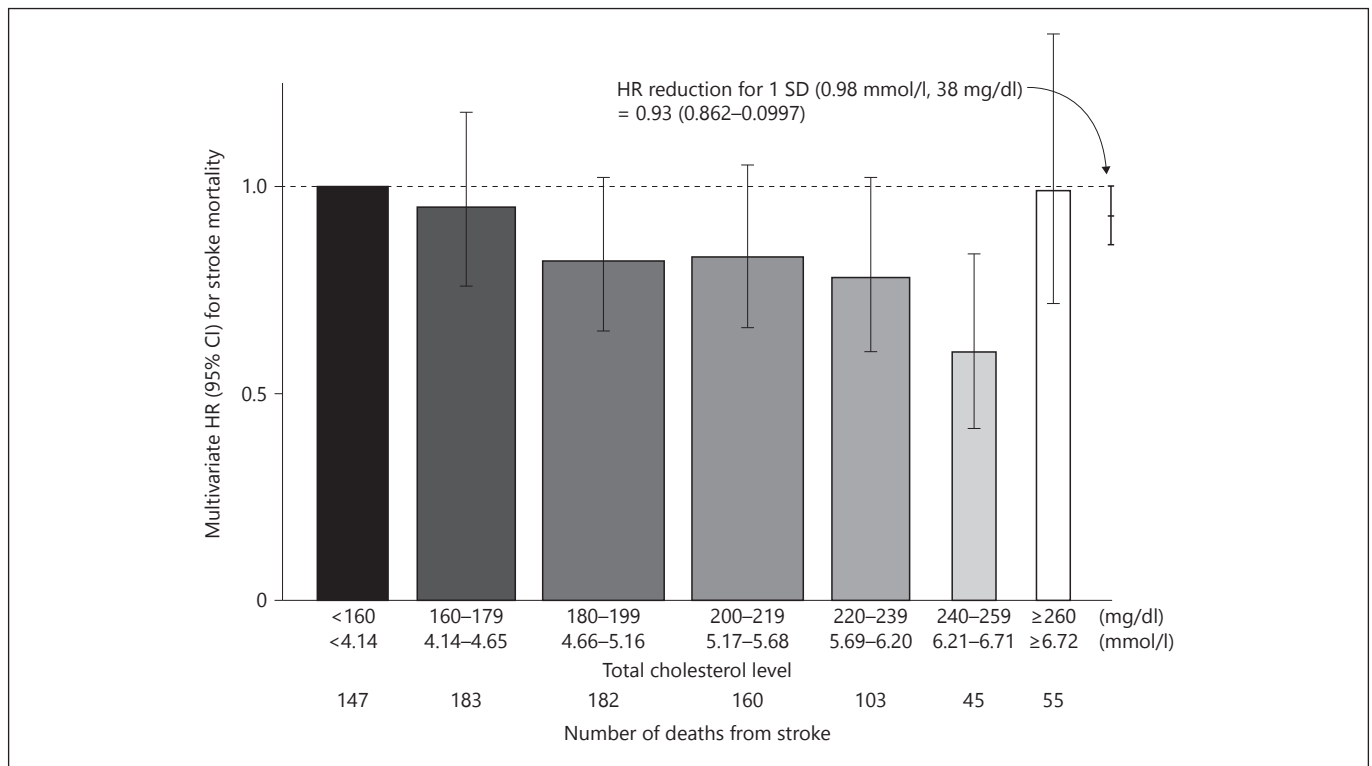
To avoid the possibility of reverse causality where some participants might have had subclinical cancer at baseline, which might decrease serum cholesterol levels, the authors of the study calculated multivariable HRs in men after excluding incident cancer cases that arose in the first 3 years of the study. This procedure slightly diminished the inverse association but not to a non-significant level: the HR reduction per 1 SD increment before such exclusion was 0.91 (0.86–0.96,  $p = 0.007$ ), which was increased only to 0.92 (0.87–0.98,  $p = 0.01$ ) after the exclusion. After further exclusion of advanced cases with metastasis, the inverse associations were no longer significant for total cancers or female stomach cancer but remained significant for liver cancer in both sexes. However, the change from significant to non-significant findings in total incident cancer cases in men was not due to the nature of this procedure itself (i.e., the exclusion of advanced cases, which might further reduce the possibility of subclinical cancer cases when baseline data were assessed); rather it was due to the reduction in the number of cancer cases (1,210 to 765 in men). Actually, after

further exclusion of advanced cases with metastasis, the HR for total incident cancer per 1-SD increment in total cholesterol in men was 0.93 (0.86–1.00,  $p = 0.06$ ,  $n = 765$ ). The two HR values, 0.92 after exclusion of first 3 years of incident cancer cases and 0.93 after further exclusion of advanced cases, were almost identical. Consequently, the loss of significance after the further exclusion was due to a reduction in the number of cancer cases only. This loss of significance seems to be the major reason for the authors' conclusion in the abstract that '*...our findings do not support that low serum total cholesterol levels increase risks of total cancer and other major [cancer] sites.*'

### (3) Cholesterol and Infectious Disease

LDL and the other lipoproteins are the nonspecific frontline against a wide variety of infectious agents. Lipoproteins have long been known to bind to and inactivate bacteria, bacterial fragments (lipopolysaccharides, LPS), and viruses. Ravnskov et al. nicely summa-





**Fig. 2-12.** Multivariate-adjusted hazard ratio for stroke mortality in both men and women according to total cholesterol level: EPOCH-JAPAN [23]. A total of 65,594 men and women aged 40–89 years were followed for a mean 10.1 years. See the legend to Fig.

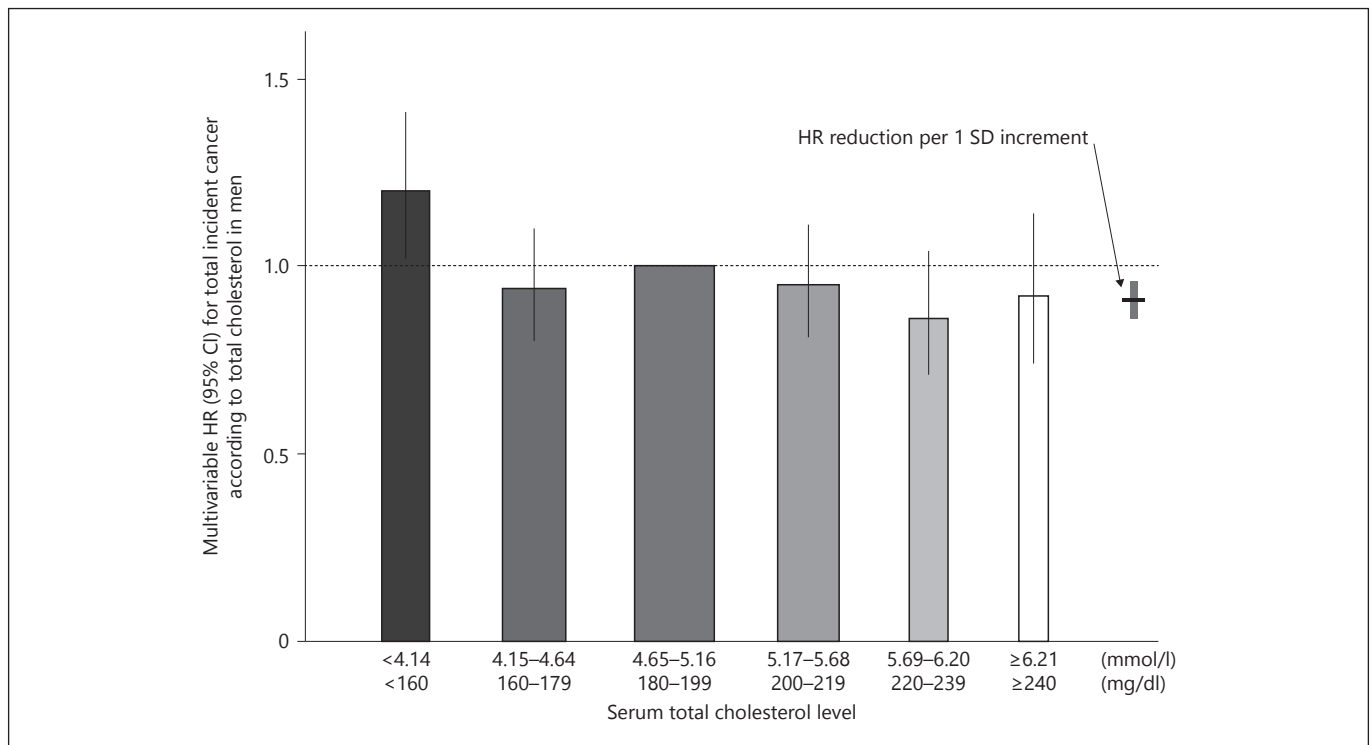
2–10 and the text for details. The width of each column is proportional to the number of participants. HR = Hazard ratio; CI = confidence interval.

alized the effects of lipoproteins (table 2-B) [27]. The body can handle the entire phase of infection with a safety margin if lipoproteins neutralize a considerable proportion of toxic agents in blood. Without the buffer of lipoproteins, however, the immune system needs to deal with all the infection-related materials directly. Although the following results are from an animal experiment, they are very suggestive. Genetically engineered LDL receptor-deficient mice (LDLR<sup>-/-</sup>, an animal model for homozygote FH) were challenged with various doses of LPS, and survival rates were compared with the results of wild C57Bl/6J mice (LDLR<sup>+/+</sup>) [28]. Plasma total cholesterol levels were  $9.55 \pm 1.11$  mmol/l ( $369 \pm 43$  mg/dl) and  $2.25 \pm 0.45$  ( $87 \pm 17$ ) in the LDLR<sup>-/-</sup> and wild mice, respectively. The median lethal dose, LD<sub>50</sub>, of LPS was 2.0 and 0.25 mg/mouse, respectively, which was 8-fold higher in the LDLR<sup>-/-</sup> mice. The plasma concentrations of tumor necrosis factor (TNF) and interleukin (IL)-1 $\alpha$  were measured after intravenous injection with 1 mg LPS (the lethal dose for wild mice). Significant decreases in TNF (90 min post-challenge)

and IL-1 $\alpha$  (4 h post-challenge) were seen in LDLR<sup>-/-</sup> mice when compared with control mice. These results help explain why the survival of people with FH was better than that of the general population in the Netherlands before 1900 [29], when infection was the major killer (see fig. 3-5 in Chapter 3).

In a multiethnic cohort of 55,300 men and 65,271 women that was followed for 15 years (1979–1993), Iribarren et al. examined the association between total cholesterol and risk of infections (other than respiratory and HIV) diagnosed in the in-patient setting [30]. Cholesterol was found to be inversely related to various infections, including all infections, in both sexes. The reduction of risk for all infections according to a 1-SD increase in total cholesterol was 8% in both sexes. This significant inverse association with all infections persisted after excluding cases from the first 5 years of follow up.

These findings are mirrored in the Leiden 85-Plus Study (see Chapter 1, Section 1) where total cholesterol concentrations were measured in 724 participants with a median age of 89 years and the mortality risk from infectious dis-



**Fig. 2-13.** Association between cancer incidence and serum cholesterol level in men: JPHC Study [26]. A total of 33,368 Japanese men and women aged 40–69 years were followed for more than 10 years (140,506 person-years for men alone). The following variables were adjusted for: age, body mass index, pack-years of smoking, ethanol intake, hypertension, diabetes, hyperlipidemia medication use, total vegetable intake, coffee intake, and participant’s

public health center area.  $p$  for trend = 0.0045; hazard ratio (HR) reduction per 1 SD increment (0.89 mmol/l, 35 mg/dl) = 0.91 (0.86–0.96),  $p$  = 0.007. There were no significant associations in women, with a HR reduction per 1 SD increment of 1.00 (0.94–1.06). The width of each column is proportional to the person-years of that group. See the text for details. CI = Confidence interval.

ease was calculated over 10 years of follow up [31]. The higher the total cholesterol levels were, the lower the mortality from infectious disease. All-cause mortality of this study is described in Chapter 1, Section 2 (fig. 1-6).

Let’s also return to fig. 1-2 in Chapter 1 from the Isehara Study [24] where the second block from the bottom of each column represents death from respiratory (lung) disease. Note that lung cancer would be covered by the first block ‘malignancy’, which would presumably leave this second block mostly to pneumonia. In men (panel A), deaths from respiratory disease are around one third in the highest LDL cholesterol group compared with the mean deaths from respiratory disease in the other groups. In women (panel B), mortality from respiratory disease is not as low as it is in men in the highest LDL cholesterol group but is still lower than in any other groups in women.

In the intensive care unit (ICU), controlling infection is literally of life-or-death importance. What if the cho-

lesterol levels of seriously ill patients in ICU were intentionally lowered? Considering the findings stated in this section so far, we would likely assume that the results would be opposite to those for the abovementioned mouse experiment. And indeed, this was found to be the case in a randomized, placebo-controlled, double-blind, parallel-group study involving 26 ICUs that was performed between January 2010 and March 2013 in France [32]. The researchers conducting this trial planned to enroll 1,002 patients requiring invasive mechanical ventilation for >2 days and having suspected ventilator-associated pneumonia, the most common infection in the ICU. Participants were randomized to receive 60 mg of the hypolipidemic drug simvastatin or placebo on the same day as antibiotic therapy. The primary endpoint was mortality at day 28. Unfortunately, the trial was stopped for futility at the first scheduled interim analysis after the enrollment of 300 patients. Day-28 mortality (95% CI) was 21.2% (15.4–28.6) in the simvastatin group and 15.2%

**Table 2-B.** Binding of and protection from microbial products by lipoproteins

Authors	Journal Publication year; volume: pages	Microbial product	Lipoprotein				Lipoprotein source	Method used to demonstrate inactivation and/or binding of microbial products by lipoproteins
			LDL	HDL	VLDL	All		
Humphrey JH, et al.	Br J Exp Pathol 1949; 30: 365–375	Streptolysin S				++	human	Inhibition of streptolysin S
Stollerman GH, et al.	J Clin Invest 1950; 29: 1636–1645	Streptolysin S	++	++			human	Inhibition of streptolysin S
Skarnes RC, et al.	J Bacteriol 1968; 95: 2031–2034	LPS; <i>S. enteritides</i>				++	rodents	Immunodiffusion
Shortridge KF, et al.	Southeast Asian J Trop Med Public Health 1975; 6: 461–466	<i>Togavirus</i>	++	+	+++		human	Inhibition of hemagglutination
Whitelaw DD, et al.	FEMS Microbiology Letters 1978; 3: 335–339	<i>S. aureus</i> δ-hemolysin	++	++			human	Inhibition of δ-hemolysin
Freudenberg MA, et al.	Infect Immun 1978; 19: 875–882	<i>S. abortus equi</i> <i>S. minnesota</i>	0	++	0		rat rat	Crossed Immunoelectrophoresis
Ulevitch RJ, et al.	J Clin Invest 1981; 67: 827–837	LPS; <i>S. minnesota</i>	0	++	0		rabbit	Binding of LPS to apoA1
Bhakdi S, et al.	J Biol Chem 1983; 258: 5899–5904	<i>S. aureus</i> α-toxin	++	0			human	Hemolytic titration; EM
Seganti L, et al.	Microbiologica 1983; 6: 91–99	<i>Rhabdovirus</i>	++	(+)	++		human	Inhibition of hemagglutination
Van Lenten BJ, et al.	Proc Natl Acad Sci USA 1986; 83: 2704–2708	LPS; <i>E. coli</i>	++	++	++		human, rabbit	Inhibition of scavenger receptor
Huemer HP, et al.	Intervirology 1988; 29: 68–76	<i>Herpes simplex</i>	++	++	++		human	EM
Flegel WA, et al.	Infect Immun 1989; 57: 2237–2245	LPS; <i>E. coli</i>				++	human	Inhibition of endotoxin activation of human monocytes
Cavaillon JM, et al.	Infect Immun 1990; 58: 2375–2382	LPS; <i>E. coli</i>	++	+	++		rabbit	Inhibition of cytokine-response of human monocytes
Northoff H, et al.	Beitr Infusionsther 1992; 30: 195–197	LPS(?)	++	++	0		human	Inhibition of cytokine-response of human monocytes
Superti F, et al.	Med Microbiol Immunol 1992; 181: 77–86	SA <i>Rotavirus</i>	++	++	++		human	Inhibition of viral hemagglutination and replication; EM
Weinstock C, et al.	Arterioscler Thromb 1992; 12: 341–347	LPS; <i>S. typhi</i>	++				human	Inhibition of endotoxin production
Flegel WA, et al.	Infect Immun 1993; 61: 5140–5146	LPS; <i>S. typhi</i>	++	(+)	0		human	Inhibition of endotoxin production
Feingold KR, et al.	Infect Immun 1995; 63: 2041–2046	LPS; <i>E. coli</i>				++	human	Endotoxin sensitivity
Netea MG, et al.	J Clin Invest 1996; 97: 1366–1372	LPS; <i>E. coli</i>				++	mouse	LD50 after experimental infection

The binding and inhibitory effects of LDL, HDL, and VLDL on various microbes and bacterial toxins. In 5 studies, the total effects of all lipoproteins together were examined. EM = Electron microscopy, LD50 = lethal dose 50%, LPS = lipopolysaccharide, ApoA1 = apolipoprotein A1 of HDL. (Remade from a review paper [27] with permission from the publisher; slightly modified.)

(10.2–22.1) in the placebo group ( $p = 0.10$ ). Although the difference was not significant, the results mean that for every 17 such patients treated with a statin in the ICU, 1 would die. If limited to statin-naive patients only (statin-naive ratios: 7% in the simvastatin group, 11% in the placebo group), day-28 mortality was 21.5% (15.4–29.1)

with simvastatin and 13.8% (8.8–21.0) with placebo ( $p = 0.054$ ).

A similar trial on acute respiratory distress syndrome (ARDS) has been published recently [33]. This multi-center trial randomly assigned patients with sepsis-associated ARDS to receive either enteral statin (rosuvastatin)

or placebo in a double-blind manner. The primary outcome was mortality in a health care facility to day 60. The study was stopped because of futility after 745 of the planned 1,000 patients had been enrolled. There were 108 deaths (28.5%) among the rosuvastatin patients and 91 deaths (24.9%) among the placebo patients ( $p = 0.21$ ). Compared with placebo, rosuvastatin therapy was associated with fewer days free of renal failure to day 14 ( $10.1 \pm 5.3$  vs.  $11.0 \pm 4.7$ ,  $p = 0.01$ ) and fewer days free of hepatic failure to day 14 ( $10.8 \pm 5.0$  vs.  $11.8 \pm 4.3$ ,  $p = 0.003$ ).

Taken together, the findings discussed in this section provide further support of the notion that high total cholesterol or LDL cholesterol levels directly affect longevity.

#### (4) Cholesterol and Liver Disease

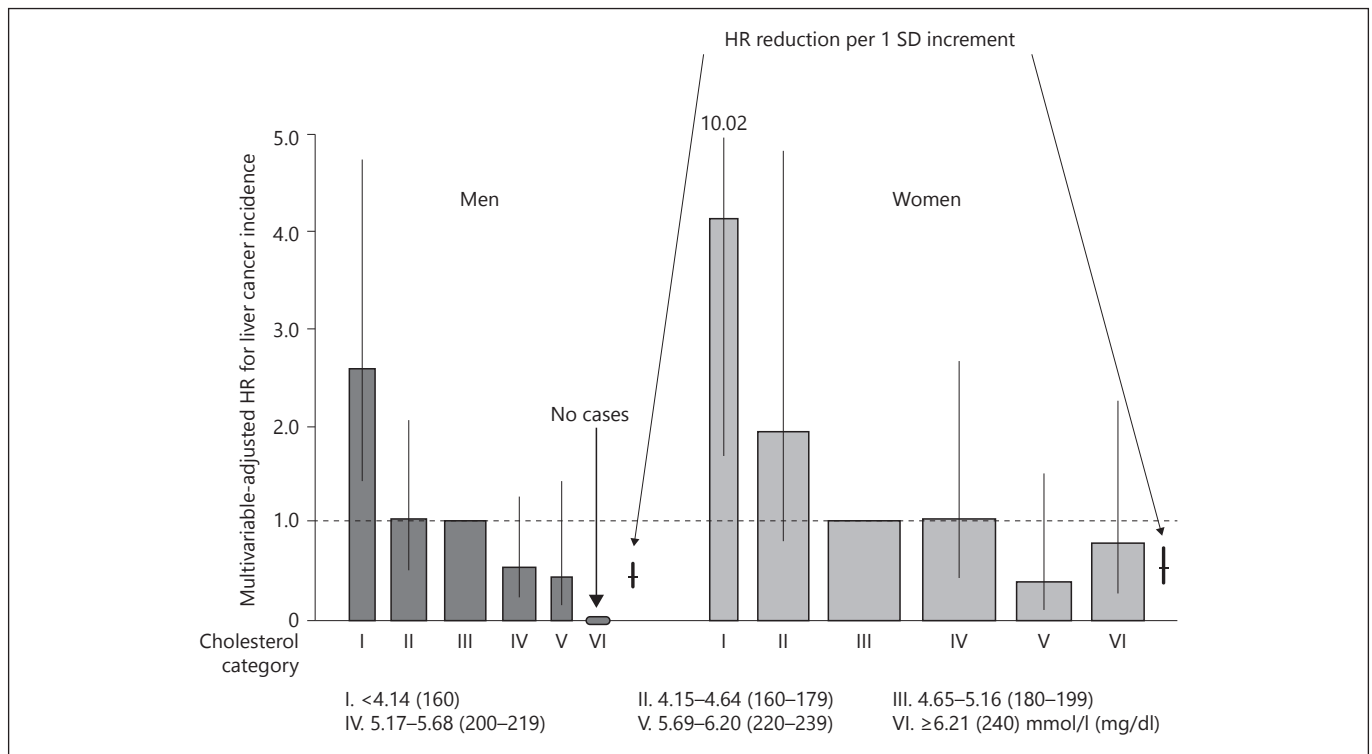
This section discusses the association between cholesterol levels and various liver diseases, and discusses the findings of the studies published to date. We'll start with the relationship found in the JPHC Study that was mentioned in the previous section [26]. Fig. 2-14 shows the multivariable-adjusted HRs for incident liver cancer cases according to serum total cholesterol levels: the results are shown in full without any exclusions (i.e., including both the cases from the first 3 years and advanced cases with metastasis). The multivariable HRs per 1-SD increment in total cholesterol for liver cancer were 0.45 (0.35–0.59,  $n = 75$ ,  $p < 0.0001$ ) in men and 0.54 (0.39–0.75,  $n = 50$ ,  $p = 0.0002$ ) in women, and after exclusions of both cases from the first 3 years and advanced cases with metastasis, the HRs were further reduced to 0.42 (0.27–0.65,  $n = 28$ ,  $p = 0.0001$ ) and 0.43 (0.26–0.69,  $n = 23$ ,  $p = 0.0006$ ), respectively. Interestingly, no liver cancer cases were reported in men with cholesterol  $\geq 6.21$  mmol/l ( $\geq 240$  mg/dl), with the total number of men with incident liver cancer being 75. The robust inverse association between liver cancer and cholesterol was maintained regardless of incidence time, stage, viral infection, and drinking habit. Similarly, the HR per 1-SD increment in total cholesterol for male stomach cancer after both exclusions was 0.86 (0.74–0.99,  $n = 220$  men,  $p = 0.04$ ).

The study also found a relationship between cholesterol and HCV. Participants with the antibody against HCV had lower age- and sex-adjusted mean total cholesterol values than participants without the antibody ( $4.93 \pm 0.03$  mmol/l [SE] vs.  $5.28 \pm 0.01$ , respectively,  $p < 0.001$ ) [26]. This difference was not observed in participants with hepatitis B virus (HBV) infection.

When Moriya et al. compared total cholesterol levels in 100 patients with histologically proven non-cirrhotic chronic hepatitis (F1 or F2) – 50 HCV-RNA positive and 50 HBsAg positive – matched for age, sex ratio (men to women, 30:20), body mass index, alanine aminotransferase levels, albumin levels, and prothrombin time, they found HCV positive patients had markedly lower total cholesterol levels ( $167.4 \pm 37.7$  mg/dl,  $4.33 \pm 0.97$  mmol/l vs.  $195.6 \pm 38.3$ ,  $5.06 \pm 0.99$ ,  $p < 0.0005$ , respectively) [34]. Compared to the general population's total cholesterol levels of  $198 \pm 35$  mg/dl ( $5.12 \pm 0.91$  mmol/l) in men and  $206 \pm 36$  ( $5.32 \pm 0.93$ ) in women (which are taken as mean total cholesterol levels  $\pm$  SD reported by the National Health and Nutrition Survey, 2003 [35] published in the same year of Moriya et al.'s study), the levels for HBV patients were little different. The difference in total cholesterol levels observed between the HCV and HBV patients can be explained by the fact that, apart from HBV, HCV infects hepatocytes through LDL receptors [36]. Consequently, it is highly likely that, if there are abundant LDL particles available, HCV infection can be prevented through competitive inhibition [37]. HCV and other *Flaviviridae* viruses enter cells via LDL receptors [36].

An association between low LDL cholesterol levels and liver cancer mortality was recently reported by the Ibaraki Prefectural Health Study group in its 2013 report [38]. (See fig. 1-1 for the association between all-cause mortality and serum LDL cholesterol levels found in a much larger cohort study.) A total of 16,217 participants (5,551 men, 10,666 women) aged 40–79 years at baseline in 1993 were followed until 2008. During a mean follow-up period of 14.1 years, 66 deaths from liver cancer or cirrhosis were recorded. Fig. 2-15 shows the HRs for the four categories of LDL cholesterol levels that were calculated for liver cancer mortality with adjustment for confounding factors. Exclusion of cases in the first 5 years slightly changed the trend as follows: 3.08 (1.22–7.80), 1.23 (0.49–3.04), 1.0, and 0.38 (0.17–0.86) for the four LDL cholesterol categories shown in fig. 2-15, respectively ( $p$  for trend  $< 0.01$ ). It is important to note that the HRs for both the lowest and highest LDL groups were significantly different (in opposite directions) from those for the reference group (LDL cholesterol 100–119 mg/dl, 2.58–3.08 mmol/l).

Another important point to note from this study is that there were no deaths from liver cirrhosis reported in the LDL cholesterol range  $\geq 120$  mg/dl (3.09 mmol/l) [38]. The HRs for death from liver cirrhosis for the four LDL cholesterol categories shown in fig. 2-15 were 7.01 (1.59–30.89,  $n = 6$ ), 3.86 (0.95–15.76,  $n = 6$ ), 1.0 ( $n = 3$ ), and 0 ( $n = 0$ ), respectively ( $p$  for trend  $< 0.01$ ), with



**Fig. 2-14.** Multivariable-adjusted hazard ratio for liver cancer incidence according to serum total cholesterol level: JPHC study [26]. See the legend to Fig. 2-13 and the text for details. The trends

shown here were not markedly changed even after exclusion of the first 3-year incident cases or further exclusion of advanced cases. HR = Hazard ratio.

adjustment for the same items stated in the legend to fig. 2-15.

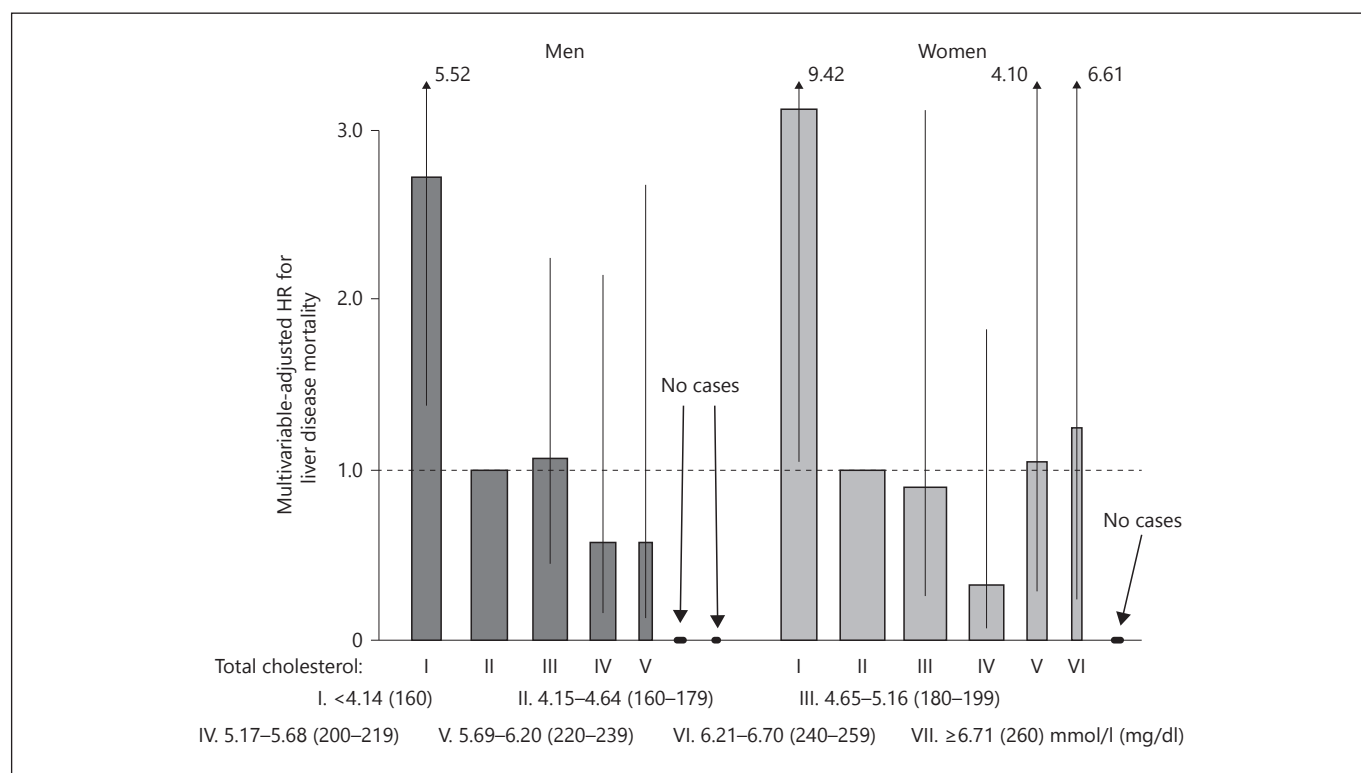
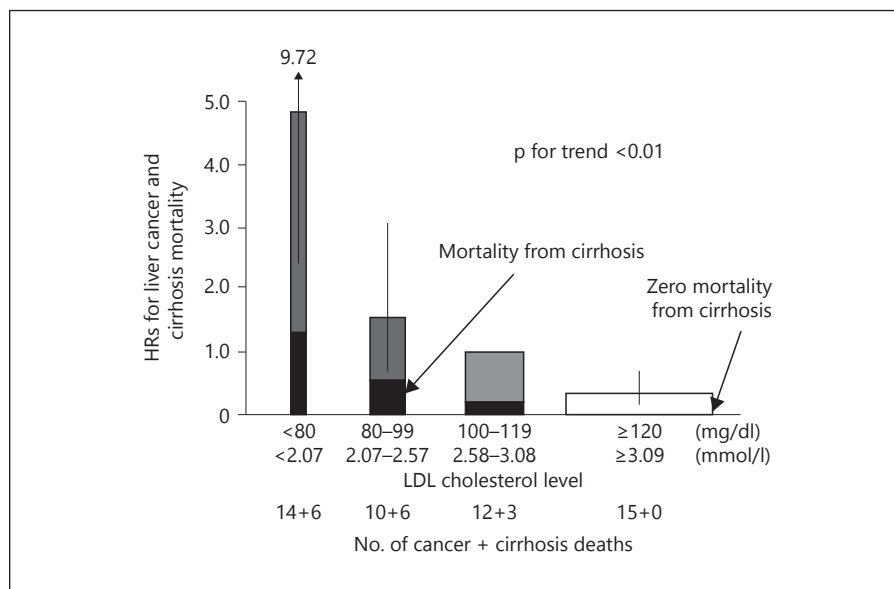
Let's look now at the results of the NIPPON DATA80 study in regard to cholesterol levels and mortality from liver disease [39]. While we believe this epidemiological study has a number of serious flaws in methodology and presentation of results (see Chapter 5 for a detailed discussion), its results on mortality from liver disease are very similar to those of other epidemiological studies. During the 17.3-year follow up of 9,216 participants, 85 deaths occurred from liver disease. In both sexes, the HRs for mortality from liver disease decreased according to increasing cholesterol levels (fig. 2-16). These decreasing trends can be partly explained by competition for LDL receptors between LDL particles and HCV.

Because the liver is the major organ that synthesizes cholesterol, its dysfunction may reduce the available supply of cholesterol for hepatocyte reconstruction. If cholesterol is abundant in the blood from the beginning of liver disease, secondary damage to the liver due to cholesterol insufficiency might be avoided. Also, with >2 g of cholesterol intake per day, the liver is freed from produc-

ing any cholesterol at all, allowing the liver to rest from the more than 20 enzymatic steps it needs to go through to produce cholesterol. This mechanism may be at work in any kind of liver disease. Therapy aimed at increasing serum cholesterol might also deserve serious consideration, particularly given that the highest cholesterol groups in the NIPPON DATA80 study [26] showed no incidence of liver cancer in men (fig. 2-14) and no deaths from liver cirrhosis (fig. 2-15) or liver disease (fig. 2-16) in either sex.

Very similar findings have been reported in Korea by the Korean Cancer Prevention Study [40]. Korean adults (n = 1,189,719) aged 30–95 years enrolled in the National Health Insurance Corporation were followed up for 14 years until cancer diagnosis or death. Total cholesterol was found to be inversely associated with all-cancer incidence in both men and women in the highest cholesterol group (≥240 mg/dl, 6.21 mmol/l) compared with the lowest cholesterol group (<160 mg/dl, 4.14 mmol/l) (men's HR: 0.84, 0.81–0.86 p for trend <0.001; women's HR: 0.91, 0.87–0.95, p trend <0.001). The HR in men remained significantly below unity even after exclusion of liver cancer

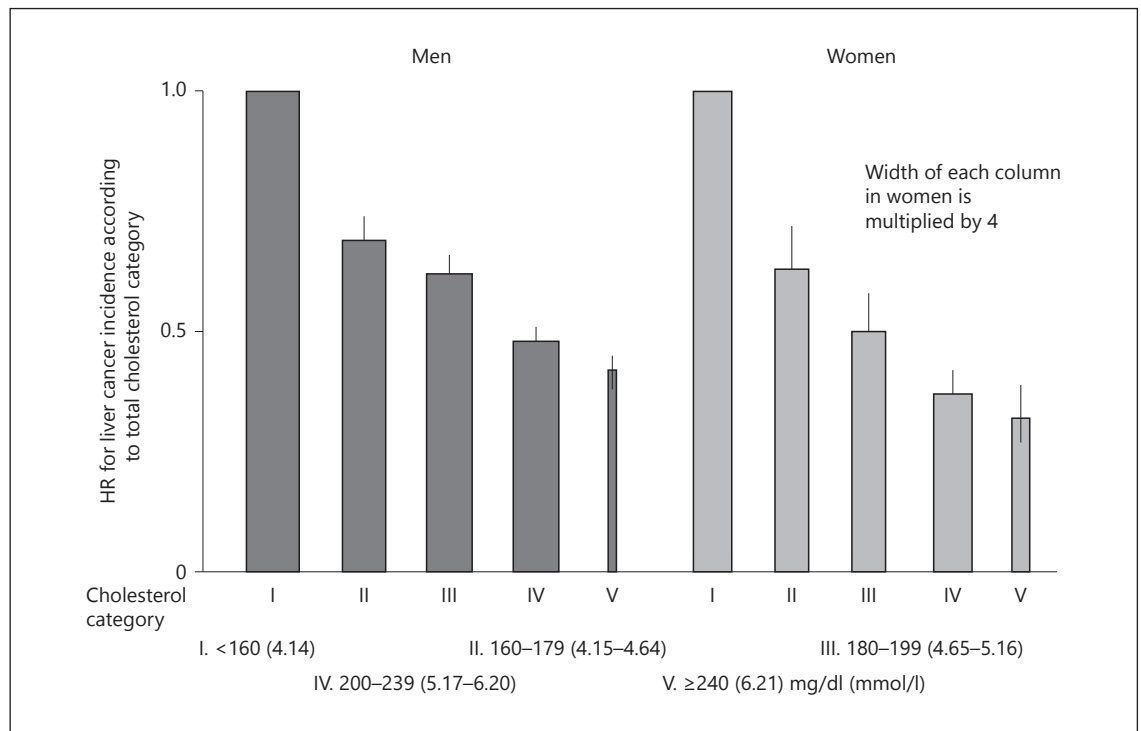
**Fig. 2-15.** Hazard ratios (HRs) for liver cancer and cirrhosis mortality according to low density lipoprotein (LDL) cholesterol level: Ibaraki Prefectural Health Study [38]. A total of 16,217 participants aged 40–79 years (men: 34%) were followed for 14.1 years. The HRs for liver cancer and cirrhosis mortality were calculated using a multivariable Cox proportional hazards model. Covariates were age, sex, alanine transaminase, body mass index, alcohol intake, and smoking status. The height of the black bar denoting liver cirrhosis mortality is set according to the ratio between the numbers of cirrhosis deaths and total cancer + cirrhosis deaths. The width of each column is proportional to the number of participants. Note that zero mortality from liver cirrhosis was found in the group with LDL cholesterol  $\geq 120$  mg/dl ( $\geq 3.09$  mmol/l). See the text for details.



**Fig. 2-16.** Multivariable-adjusted hazard ratio (HR) for liver disease mortality according to serum total cholesterol level: NIPPON DATA80 study [39]. See the legend to Fig. 5-1 for an explanation of the NIPPON DATA80 study. Briefly, 9,216 participants aged  $\geq 30$  years were followed for 17.3 years. HRs for liver disease mortality are depicted according to sex and serum total cholesterol

levels. HRs were adjusted for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking category, and alcohol intake category. The width of each column is proportional to person-years of the group. Note that zero mortality was found in men with cholesterol levels  $\geq 6.21$  mmol/l (240 mg/dl) and in women  $\geq 6.71$  mmol/l (260 mg/dl). See the text for details.





**Fig. 2-17.** Hazard ratio (HR) for liver cancer incidence according to total cholesterol level in Korea: NHIC study in Korea [40]. A total of 1,189,719 Korean adults enrolled in the National Health Insurance Corporation who underwent biennial medical examinations from 1992 through 1995 were observed for 14 years until cancer diagnosis or death. Cox's proportional hazards models with attained age as the underlying time metric were used to calculate HRs with adjustment for smoking, alcohol consumption, body

mass index, physical activity, hypertension, and fasting serum glucose. The width of each column is proportional to the number of participants of that group; however, because of a limited number of women, the width of women's columns is multiplied by 4. The trends in HRs for both sexes did not lose significance even after excluding cases during the first 10 years of observation. See the text for details.

(HR: 0.95, 0.91–0.98,  $p$  trend <0.001), but this was not the case for women (HR: 0.98, 0.94–1.03,  $p$  trend = 0.32). As can be seen in fig. 2-17, higher total cholesterol levels were associated with lower incidence of liver cancer in both sexes. These inverse associations for liver cancer are maintained even after excluding cases during the first 10 years of follow up (men's HR: 0.59, 0.51–0.58,  $p$  for trend <0.001;

women's HR: 0.44, 0.31–0.64,  $p$  for trend <0.001); such exclusion had to be robust enough to exclude those whose cholesterol levels at baseline were influenced by liver disease that would lead to clinical liver cancer after  $\geq 10$  years.

When the above findings on liver disease and cholesterol are seen together, they all point to the fact that high cholesterol levels prevent liver disease.

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## Chapter 3 **Familial Hypercholesterolemia: The Key to Solving the Cholesterol Myth**

**Summary:** Familial hypercholesterolemia (FH) is the key to the argument that cholesterol is the cause of coronary heart disease (CHD). However, mean cholesterol levels do not differ between individuals with heterozygous FH who develop CHD and those who do not develop CHD. When we consider homozygous FH specifically, similar cholesterol levels in heterozygous type cannot be explained by the ceiling effect. Instead, an abnormality of the hemostatic system in FH might explain the high CHD incidence. The most recognized low density lipoprotein (LDL) apheresis intervention study performed in Japan has a number of limitations and the results must be interpreted with care. The association between high cholesterol levels and CHD mortality in Japanese men is most likely due to the presence of individuals with FH in very high cholesterol groups. The association between CHD mortality and cholesterol levels decreases with age: this phenomenon can be explained by the decreasing proportion of FH subjects, some of whom die prematurely from CHD, as the cohort ages. Based on the historical fact that individuals with FH in the Netherlands lived longer than the general population before 1900 when infection was the primary cause of death, those with FH may well survive future major pandemics with unknown infectious agents.

### **(1) Is the Hypothesis Correct That the Lower the Cholesterol Levels, the Better?**

The mainstay argument for the cholesterol hypothesis is FH, and we therefore devote the entire chapter to discussing this genetic disorder. FH is characterized by very high LDL cholesterol values due to LDL receptor defects. About three decades ago, CHD mortality in Japan was calculated to be 11 times higher in subjects with heterozygous FH than in the general population [1]. But should this by itself establish that hypercholesterolemia is the reason for CHD vulnerability in individuals with FH?

When advocates of the cholesterol hypothesis are challenged by the notion that cholesterol is not the cause of atherosclerosis and that hypercholesterolemia is in fact an epiphenomenon—that is, it is induced by another factor such as psychological stress which increases the risk of coronary heart disease and cholesterol levels—some come back by asking why it is that patients with FH very often have CHD. They may also add that hypercholesterolemia is simply caused by genetic defects and not by psychological stress, and that the only difference between patients with FH and the general population is cholesterol levels. We believe we need to revisit whether cholesterol is actually the primary causal factor. If cholesterol is to blame, then patients with FH and CHD

**Table 3-A.** Comparison of cholesterol values in patients with heterozygous familial hypercholesterolemia (FH) between those with and without coronary heart disease (CHD)

Authors Investigation method	Publication year/ reference number	Endpoint	Measured items (mmol/l)	Cholesterol values in FH patients with CHD or artery disease	Cholesterol values in FH patients without CHD or artery disease (controls)	Significance	Blood sampling condition (follow-up period)
Miettinen TA, et al. <b>Prospective</b>	1988 [2]	CHD death started between 68 and 70	Total cholesterol	12.0±0.6 n = 26	12.1±0.3 n = 66	-	Before treatment (15 years)
Hill JS, et al. Cross-sectional	1991 [9]	CHD Men	LDL cholesterol	<b>7.13±1.5</b> n = 47	6.51±1.4 n = 68	+	Before treatment
		CHD Women	LDL cholesterol	7.25±2.0 n = 26	7.01±1.6 n = 147	-	
Ferrières J, et al. Cross-sectional	1995 [10]	CHD Men	LDL cholesterol	7.29±1.28 n = 54	7.11±1.26 n = 62	-	Before treatment
		CHD Women	LDL cholesterol	<b>7.85±1.71</b> n = 35	7.00±1.51 n = 112	+	
Kroon AA, et al. Cross-sectional	1995 [11]	Peripheral artery obstruction	LDL cholesterol	8.73±2.08 n = 21	9.19±2.09 n = 47	-	Before treatment
Hopkins PN, et al. Cross-sectional	2001 [12]	CHD	LDL cholesterol (mg/dl)	178±69 n = 68	<b>213±62</b> n = 194	+ (reverse)	Sampled >3 weeks after stopping lipid-reducing agents
Jansen AC, et al. Cross-sectional	2004 [13]	CHD	LDL cholesterol	7.45±2.18 n = 782	7.37±1.84 n = 1618	-	Sampled >6 weeks after stopping lipid-reducing agents

7 mmol/l = 270 mg/dl; 8 mmol/l = 309 mg/dl; 12 mmol/l = 463 mg/dl  
Significantly larger values are highlighted in bold font.

A similar data set was also reported from Japan. The complication rates of IHD in patients with heterozygous FH in Japan were not associated with their TC levels [5] (see fig. 3-2).

should have higher cholesterol levels than those with FH and no CHD yet—which would back up the widely held view that the lower the cholesterol levels, the better. So, let's take a look at whether currently available data supports this or not.

Table 3-A summarizes the findings of six studies on differences in cholesterol levels in patients with heterozygous FH between those with CHD and those without CHD. On the whole, there are no marked differences between the groups. The most important aspect to note is that this was also the finding of Miettinen et al's prospective study [2]. So, the claim that the lower the cholesterol levels, the better does not hold weight. Also, the cholesterol hypothesis itself does not seem to fit either. Let's look at this from another aspect of the discussion: that there might be a ceiling effect with regard to cholesterol levels (i.e., above certain cholesterol levels, the 'deleterious effects' of cholesterol stop increasing). However, this idea of the ceiling effect can be easily re-

futed if we consider the homozygous type of FH. Patients with homozygous FH have much higher cholesterol levels and CHD mortality than those with heterozygous FH, which indicates there is no ceiling effect at all.

It would seem difficult, then, to attribute CHD to high cholesterol levels even in FH, the symbol of hypercholesterolemia. But if high cholesterol levels are not behind the development of CHD in FH, what is? The following mechanisms have been proposed.

1. Certain hemostatic factors including fibrinogen may be increased in patients with FH [3].

2. Because of the reduced availability of LDL receptors in patients with FH, endothelial cells in arteries, for example, do not obtain sufficient nutrients contained in LDL particles via these receptors. LDL particles are the major vehicles that transport cholesterol and phospholipids (both of which are the most important building blocks of cell membranes) to cells. LDL particles also

transport triglycerides (TG), which serve mainly as an energy source, lipid soluble vitamins, anti-oxidants, and essential polyunsaturated fatty acids. Arterial malnutrition may lead to marked defects in arterial maintenance.

3. Arterial deficiency in cholesterol may up-regulate HMG-CoA reductase, the rate-limiting enzyme for cholesterol synthesis. This up-regulation increases the cellular contents of prenyl intermediates (the intermediate products of cholesterol) that are necessary for anchoring rho and ras to the cell membranes and may activate inflammation and proliferation.

## **(2) Has Low Density Lipoprotein Apheresis Proven Effective in Japan?**

Mabuchi et al. [4] conducted the largest control trial of LDL apheresis with patients with heterozygous FH in Japan. All participants had clinically significant coronary artery stenosis. They treated 43 FH heterozygotes with LDL apheresis combined with cholesterol-lowering drugs and 87 heterozygous patients with intensive drug therapy. Serum total cholesterol levels before treatment were significantly higher in the LDL apheresis group ( $9.28 \pm 1.71$  mmol/l,  $359 \pm 66$  mg/dl) than in the drug therapy group ( $7.94 \pm 1.24$ ,  $307 \pm 48$ ). This difference in total cholesterol levels between the two groups is unlikely to affect the incident cases of CHD because cholesterol levels are similar between FH heterozygotes with CHD and those without CHD in epidemiological studies (see table 3-A). As Mabuchi et al. stated, the patients were not randomized. In fact, smoking rates were higher in the control drug therapy group (26%) than in the apheresis group (9%). The endpoints were total mortality, major coronary events consisting of coronary deaths, definite nonfatal acute myocardial infarction, and coronary revascularization procedures—either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. These two procedures are decided on by the physician. The participating physicians might have been biased toward these interventions if they found patients with very high cholesterol levels in the control group compared with those in the apheresis group. Six years after treatment, the rate of total coronary events was significantly lower in the LDL apheresis group than in the drug therapy group (10% vs. 36%, respectively). (These figures did not markedly change even after excluding smokers.) However, on top of the possible biases described above, patients in the LDL apheresis group must

have been much freer in terms of time; at the least they were able to spare a few hours for apheresis sessions every 2 weeks. This circumstance in itself provides a healthy environment for the prevention of CHD. Moreover, their attitude toward treatment must have been very positive; they even had arteriovenous shunts constructed in their arms. Two deaths were recorded during the trial: 1 of 80 control patients and 1 of 41 apheresis patients. Taken as a whole, it is not possible from the results of this trial—or of the other very small Japanese trials of LDL apheresis, all of which had fundamental methodological limitations—to prove that LDL apheresis was effective.

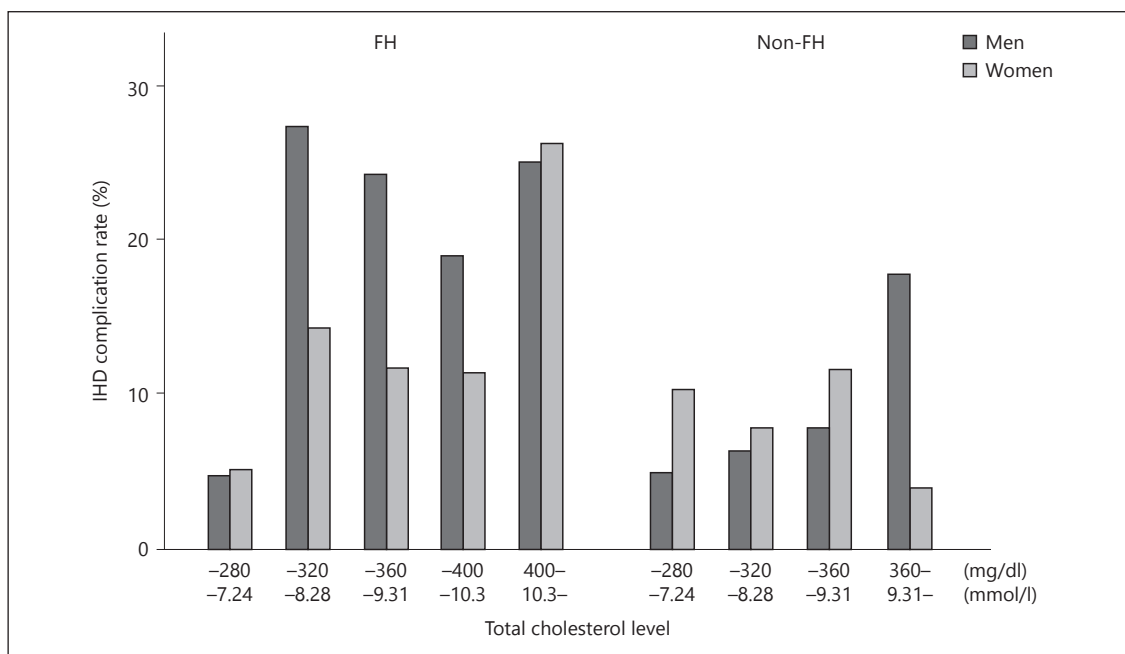
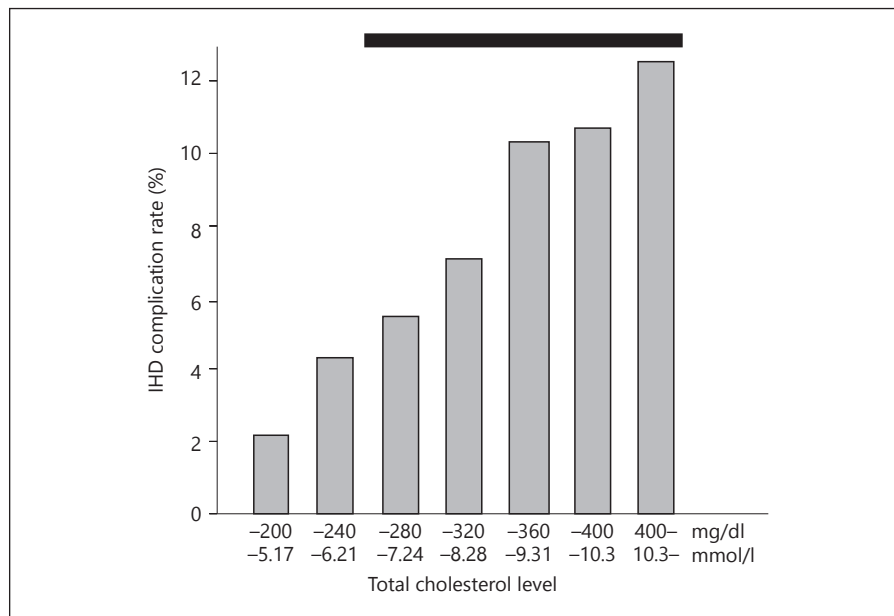
## **(3) The Proportion of Subjects with Familial Hypercholesterolemia in Cohorts Is the Key Issue**

One of the most comprehensive and oldest studies on hyperlipidemia in Japan is reported by the Research Group for Primary Hyperlipidemia, supported by the Ministry of Health and Welfare of Japan [5]. Subjects with high total cholesterol ( $>5.69$  mmol/l,  $>220$  mg/dl) or high TG ( $>1.69$  mmol/l,  $>150$  mg/dl) ( $n = 10,313$ ) were recruited from the research group members' hospitals and their complication rates for ischemic heart disease (IHD) were cross-sectionally investigated. Of those subjects, 388 (3.8%) were patients with FH. As shown in fig. 3-1, total cholesterol levels were strongly positively associated with IHD. The IHD complication rates were higher in patients with FH (22.2% men, 14.7% women) than in those with non-FH type II hyperlipidemia (6.4% men, 9.1% women). Also, the rates were markedly higher in FH than in non-FH even when total cholesterol was adjusted for, which means that something other than hypercholesterolemia is increasing the IHD rates in patients with FH. Moreover, the rates for patients with FH alone were not associated with total cholesterol levels (fig. 3-2, left).

A couple of important points can be drawn from these results. First, it is unlikely that hypercholesterolemia is the primary cause of IHD. The finding that cholesterol levels did not correlate with IHD incidence cannot be explained by the ceiling effect, as mentioned in the previous section. Second, the proportion of FH cases included in this study was 19 times higher than in the Japanese general population (0.2%), and the proportion of FH in the subgroup with total cholesterol  $>6.72$  mmol/l (260 mg/dl) was 27%, which is  $>130$  times higher than in the general Japanese population. By increasing the proportion of FH



**Fig. 3-1.** Relationship between total cholesterol level and ischemic heart disease (IHD) complication rate: Research Group for Primary Hyperlipidemia [5]. For 10,313 participants with hyperlipidemia, the IHD complication rate was calculated according to total cholesterol level in this cross-sectional study. There were 1,440 subjects with total cholesterol >6.7 mmol/l (>260 mg/dl), indicated by the black bar. Of them, 388 (27%) were patients with familial hypercholesterolemia (FH). This proportion of FH is more than 130 times higher than that in the general Japanese population. The figure shows that it is highly likely that the proportion of FH cases is increasing along with total cholesterol values. The number of subjects allocated to each column is not available.

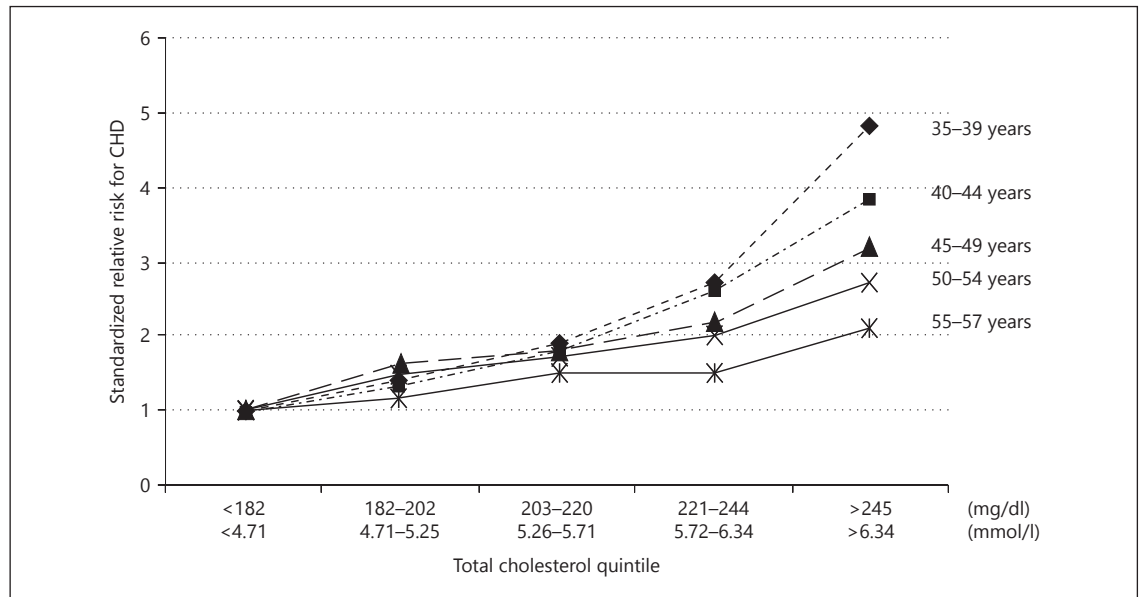


**Fig. 3-2.** Relationship between total cholesterol level and ischemic heart disease (IHD) complication rate in patients with familial hypercholesterolemia (FH) and those with non-FH type II hyperlipidemia: Research Group for Primary Hyperlipidemia [5]. See the legend to Fig. 3-1 for details. (Left) The IHD complication rate was

calculated for 388 patients with FH according to their total cholesterol level. (Right) A similar calculation was made for participants with non-FH hyperlipidemia. It is highly likely that high cholesterol levels in patients with FH are not the primary cause of IHD. The number of subjects allocated to each column is not available.

cases, we can get a beautiful figure like that of fig. 3-1. The positive associations observed between cholesterol values and CHD events simply reflect the proportion of FH in the study cohort, making it the key issue in the interpretation of research findings.

The right side of fig. 3-2 shows the IHD complication rates according to total cholesterol levels in patients with non-FH hyperlipidemia. It is likely that no statistical calculation was done and that no definite conclusion was derived from these findings. Neverthe-



**Fig. 3-3.** Age-specific relative risk for coronary heart disease mortality by total cholesterol quintile: MRFIT study [6]. The original cohort of 325,384 Caucasian male participants aged 35–57 years in the MRFIT study were followed for 6 years. Standardized relative

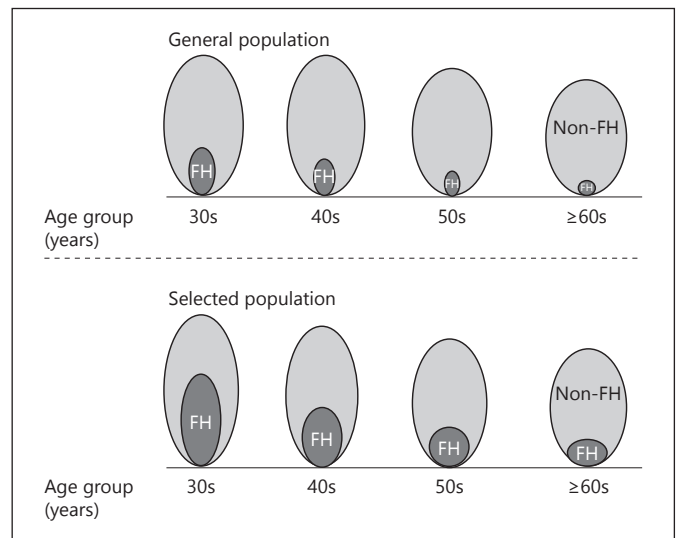
risk was calculated using figure 2 presented in the MRFIT study report [6] with the group with total cholesterol <182 mg/dl (4.71 mmol/l) as the reference group (Cholesterol Guidelines for Longevity, 2010 [17]). CHD = Coronary heart disease.

less, we can say that, at the very least, cholesterol had no involvement in IHD in women with non-FH hyperlipidemia.

#### (4) Effects of Age on the Relationship Between Coronary Heart Disease Mortality and Cholesterol Levels

The Multiple Risk Factor Intervention Trial (MRFIT) was a large-scale randomized controlled trial with participants at high risk of CHD. The original screening of 325,384 Caucasian men aged 35–57 years allowed detailed (e.g., age-specific) examination of the relationship of risk factors with CHD mortality rates. The strength of the association of each of the risk factors with CHD and all-cause mortality rates diminished with increasing age, although the number of excess deaths associated with the risk factors increased because of higher death rates among older men [6]. Fig. 3-3 illustrates the effect of aging on the relative risk for CHD.

The number of patients with FH decreases faster with age than that of the general population without FH because of the shorter survival rates for FH overall. Fig. 3-4 schematically illustrates the relationship between the proportion of patients with FH in a cohort and age. There



**Fig. 3-4.** Schematic illustration of the relative proportions of familial hypercholesterolemia (FH) to total and selected populations according to age [17]. Because there are still many surviving patients with FH or other similar genetic diseases in the young generations, the apparent association between cholesterol and mortality can be easily observed especially in the selected populations. The best example of selected populations is shown in fig. 3-1 (Taru, et al's report). Other examples are the MRFIT study (fig. 3-3) and NIPPON DATA80 study [18] (see Chapter 5). This illustration is taken from figure 8 of the Cholesterol Guidelines for Longevity, 2010 [17], with slight modifications.

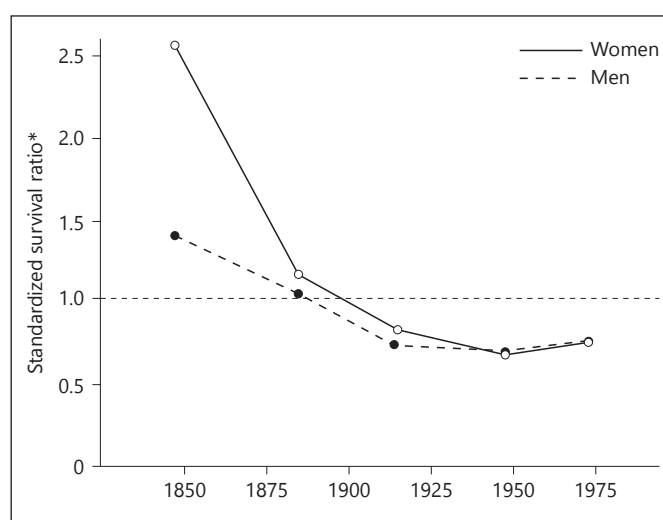
**Table 3-B.** Relative risks for coronary heart disease (CHD) between high and low total cholesterol levels reported by large-scale follow-up studies

Study name	Study				
	MRFIT	Framingham	Vorarlberg		Oxford PSC
Participant age (years)	35–57	31–65	20–95		40–89
Person x Year	8 million	0.13 million	2.2 million		11.6 million
Subjects	Selected population	General population	General population		General population?
Author	Kannel, et al.	Anderson, et al.	Ulmer, et al.		Prospective Studies
Publication year	1986	1987	2004		Collaboration, 2007
Reference	[6]	[14]	[15]		[16]
Age group			Men	Women	
30s	4.9	1.6	1.3	10.2*	
40s	3.9	1.5			14.7**
	3.1				
50s	2.8	1.1	1.2	1.07	6.26
	2.1				
60s		1.2	1.1	0.70	3.28
70s					2.37
80s					2.19
Age groups used	35–39, 40–44, 45–49, 50–54, 55–57	31–39, 40–47, 48–55, 56–65	<49, 50–64, >65		40–49, 50–59, 60–69, 70–79, 80–89

Relative risks for CHD mortality were calculated between the highest and lowest cholesterol groups within each study. The grouping methods were different from study to study, so a horizontal comparison of similar age groups between studies is not meaningful. Instead, compare the risk values vertically. \* This very high value was possible because there were only 2 cardiovascular (not CHD) deaths in the lowest cholesterol level (calculated using the reference [15]). \*\* To the best of our knowledge, no published data are available for this extraordinarily high value.

are only negligible proportions of patients with FH in the oldest groups. This is the reason why cholesterol comes to lose its meaning as a risk factor for CHD in elderly people. Examples of such cases, including the results of fig. 3-3, are summarized in table 3-B. The fact that the effects of cholesterol on CHD mortality decrease with age strongly suggests that high cholesterol is not a causative factor of CHD, and that high CHD mortality in the high total cholesterol groups reflects only their high proportion of FH cases. This interpretation is known as Okuyama's theory [7]. Without this theory, it would be very difficult to explain why positive associations between cholesterol levels and CHD mortality have been found only rarely in elderly populations around the world (table 3-B).

Recently one of the present authors (Y.O.) found that older cohorts had smaller gaps between mean and median cholesterol levels than younger cohorts, which indicates that the proportion of patients with FH in a cohort decreases as it ages (unpublished data; see Chapter 5, Section 1 for a description of part of these data).



**Fig. 3-5.** Survival ratio of people with the familial hypercholesterolemia (FH) pedigree according to sex and time, in the Netherlands [8]. The mortality of 250 persons with 0.5 probability of carrying V408M, a mutation for FH, was compared with the mortality in the general Dutch population standardized for age, sex, and calendar period. \* Standard survival ratio = 1/standard mortality ratio. (Re-made with permission from the publisher, with modifications.)

## (5) Will Familial Hypercholesterolemia Help Survival in Future Pandemics?

Up until more than a century ago, the survival ratio of Dutch people with FH seems to have been more favorable than that of the general population [8]. When the survival ratio of the general population during the 19th and early 20th centuries was compared with that of all individuals with the FH pedigree aged >20 years with a 0.5 probability of carrying V408M, a mutation for FH, the latter group's survival was not lower; it did, however,

drop after 1915 (fig. 3-5). One of the major reasons is likely to be the protective effects of very high LDL levels against many kinds of infection, since infection was the major cause of death before 1900.

With today's increasingly global lifestyles, which raise the possibility of greater numbers of worldwide pandemics, people with FH may have a better chance of surviving because of their very high LDL levels. Their high cholesterol levels may confer an advantage that benefits the longevity of the human race.

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## Chapter 4 Japan Atherosclerosis Society (JAS) Guidelines

**Summary:** The Japan Atherosclerosis Society (JAS) has issued guidelines on serum lipids several times since 1997. In this chapter, we discuss some of our concerns about the guidelines and discuss the implications of applying these guidelines to the diagnosis and treatment of hyperlipidemia. The most important figure contained in the very first edition published in 1997 was created to reflect the findings—in whole or part—of six epidemiological studies, most of which we consider had some notable methodological flaws. The figure presents a clearly positive relationship between coronary heart disease and cholesterol levels; however, we feel that it does not, in fact, accurately reflect the available data. Moreover, the treatment target recommended by the JAS guidelines started with total cholesterol levels and later changed to low density lipoprotein (LDL) cholesterol levels seemingly without scientific basis, but it is not clear in any edition of the guidelines why LDL levels constitute a better target than total cholesterol levels. The 2013 edition of JAS's Treatment Guide for Dyslipidemia is the first of the society's publications to contain conflict of interest (COI) statements.

### (1) Previous Japan Atherosclerosis Society Guidelines

The first edition of the JAS guidelines for the diagnosis and treatment of hyperlipidemia was published in 1997 (JASG1997) [1]. The Research Committee outlined their

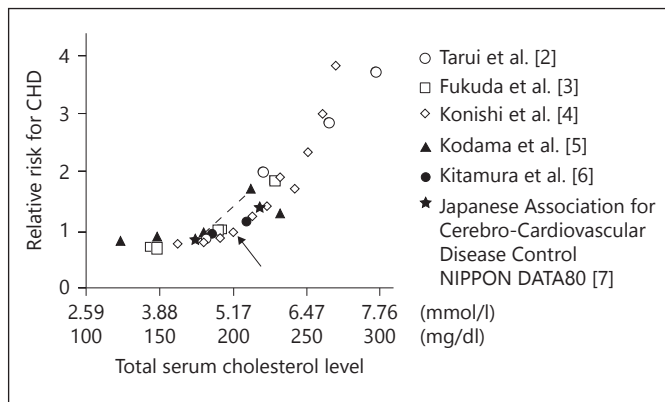
aims in producing the guidelines on page 2: they had sought to compile evidence-based guidelines, rather than experience-based ones, according to the thinking of the time, also to ascertain the standard (lipid) values based on published (Japanese) data, and to utilize meta-analytical techniques to apply to data collected as widely and in as balanced a manner as possible.

The first, and probably the most important, figure that appears in JASG1997 is a rather complicated one and is very difficult to digest in detail. We have therefore redrawn it here as fig. 4-1 to illustrate the contents more clearly.

According to JASG1997 [1] (pp.4–5), only a few epidemiological data sets were available from Japan to determine the appropriate ranges of serum lipids. The guidelines state, 'figure 1 [fig. 4-1] shows the relative risks of coronary heart disease (CHD) according to serum cholesterol levels in Japan, assigning a relative risk of unity to CHD incidence or complication rates at the serum total cholesterol level of 200 mg/dl (5.18 mmol/l).' The figure was created using six data sets [2–7], and the data were combined together as a whole without any meta-analytical techniques (see table 4-A for a summary of the studies from which data were used to create fig. 4-1).

When we look closely, however, the rule of unity for the serum total cholesterol level of 200 mg/dl was applied by only one of the studies [4]. In the other five studies, some values more than unity were assigned to 200 mg/dl (or to ranges including that value, for example, 180–220). In this way, relative risk values were inflated and the pic-





**Fig. 4-1.** Relationship between total cholesterol serum level and relative risk for coronary heart disease (CHD) in Japan: JASG1997 [1]. This figure is one we have redrawn from the original, highly complex figure 1 in JASG1997. We have not changed the relative ratios between the depicted values so that the symbol denoting each study and the relative relationship between the studies is easier to understand than in the original figure. The JASG1997 Investigation Committee assigned unity (relative risk of 1 for CHD) at the serum cholesterol level of 200 mg/dl (5.17 mmol/l) for each study. This was 100% correct in the study represented by open diamonds [4] as shown by the arrow. However, the other five studies did not follow this rule, and the relative risks for CHD incidence in these five studies are clearly above unity; for example, the closed triangles indicating Kodama, et al.'s findings [5]. We have added a broken line between the two triangles near the cholesterol level of 200 mg/dl (5.17 mmol/l), which is clearly well above the open diamond indicated by the arrow for the study with unity. Many values are likewise inflated. For clarity, the left black star was moved slightly to the left. When we exclude the open symbols (i.e., open circles, squares, diamonds) that are scientifically not valid in one way or another, the figure as a whole does not make sense. See the text for details.

ture for cholesterol looked worse than it really was. Usually this kind of data manipulation is easy to spot, but figure 1 is much too complicated to detect it without the very detailed and lengthy examination we undertook.

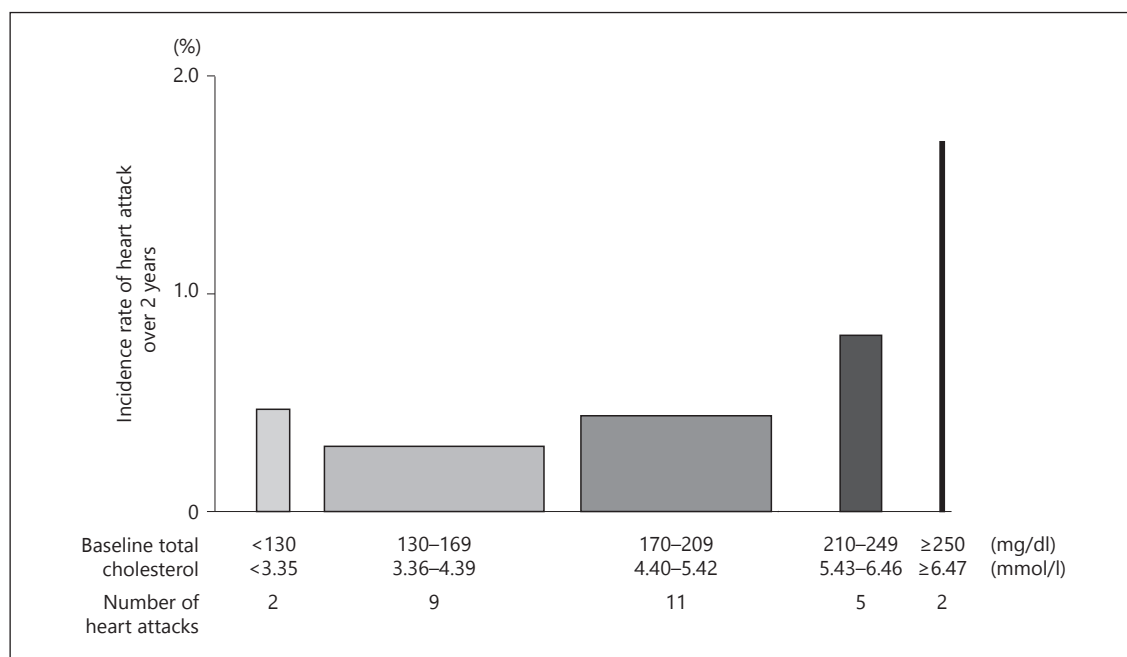
Let's direct our attention now to each of the six component studies that were used to create figure 1 in JASG1997 and our redrawn fig. 4-1 here. The first is the study by Tarui and the Research Group for Primary Hyperlipidemia [2], which we introduced in Chapter 3 (fig. 3-1). The main problem we see with this study is the proportion of patients with familial hypercholesterolemia (FH): 27% of all participants with total cholesterol levels >260 mg/dl (6.73 mmol/l) were patients with FH. This is about 130-fold that found in the general Japanese population, and these data should not, therefore, be included in the figure. Such inclusion is misleading. Tarui et al.'s original report shows the complication rates of ischemic heart

disease (IHD) across the whole range of total cholesterol levels at seven points (see fig. 3-1 in Chapter 3). Because JASG1997 deleted the highest three columns from Tarui et al.'s original figure (cf. fig. 3-1), only four points (open circles) remain in the JASG1997's figure (fig. 4-1).

The second study, by Fukuda et al. [3], is limited by its very small number of subjects who had a heart attack. The study followed 11,800 participants (possibly all men, age not known as not described) for 10 years after baseline measurement in 1962–64, and incidence data for stroke and heart attack (type not described) were collected every 2 years. Over the entire 10 years, only 29 participants had a heart attack. The relationship between total cholesterol levels and the incidence of heart attack is shown in fig. 4-2. The estimated number of heart attacks is given at the bottom of the figure. The incidence data for the highest and lowest cholesterol categories in fig. 4-2 (<130 and ≥250 mg/dl) are not represented in fig. 4-1 so that the J-curve shown in fig. 4-2 can be transformed to a simple curve to fit the general trend in fig. 4-1. The number of heart attacks in the three cholesterol ranges used in fig. 4-1 (middle three columns of fig. 4-2) are only around 10.

In the third study, Konishi et al. [4] recruited 8,294 men aged 35–54 years with no history of stroke or IHD from office workers who had health checkups in Osaka Prefecture between 1975 and 1986. During the mean follow-up period of 6 years from baseline, they found 50 cases of IHD: 26 of acute myocardial infarction (MI) and 24 of angina of effort. They also recruited >4,000 participants from farming villages in Akita Prefecture but did not include the data from this sample because the number of IHD cases in Akita was very small (n = 7) and were reported in a separate paper on this cohort [8]. According to this other paper, there was no association between cholesterol and IHD and none of the 7 participants with MI or angina pectoris had total cholesterol values ≥220 mg/dl (5.70 mmol/l) [8]. This decision to exclude data is a questionable practice. Leaving this point aside for now, let's examine the data from their study [4] that was used in JASG1997.

The relative risk for CHD according to cholesterol level is generally calculated by comparing between the CHD risk for a certain cholesterol range (e.g., 200–239 mg/dl, 5.17–6.20 mmol/l) and that for the control cholesterol range (e.g., 160–199 mg/dl, 4.14–5.16 mmol/l). However, Konishi et al. used a different method, which actually exaggerated the risk at higher cholesterol levels. When determining CHD risk at 200 mg/dl (5.17 mmol/l; they defined this value of 200 as the cut-off point), they first determined the IHD incidence of participants with



**Fig. 4-2.** Relationship between total cholesterol level and incidence of heart attack [3]. During follow up of 11,800 participants over 2-year intervals for a total of 10 years, 29 had a heart attack. This figure was redrawn from figure 2 in the original paper (originally log-scaled) [3]. It is most likely that JASG1997 adopted the all-age group that included both normotension and hypertension, although this information is not given in the 1997 JAS Guidelines

(JASG1997). We calculated the actual number of heart attacks (shown at the bottom of the figure) according to cholesterol level using the percentage shown in the figure and the number of participants. JASG1997 used the values for the three middle columns only when creating figure 1 in JASG1997 (our fig. 4-1). The width of each column is proportional to the number of participants in that group.

**Table 4-A.** Summary of methodological issues with the reference studies for which data was taken to create fig. 4-1 and the treatment of such data by the 1997 JAS guidelines for the diagnosis and treatment of hyperlipidemia

First author (year)		Problems						
Symbols used in fig. 4-1		exclusion of some data by JASG1997	unity set at 200 mg/dl, 5.17 mmol/l	<10 cases in certain cholesterol ranges	men's data only	follow-up, years	type of participants	heart disease studied by the study
□	Fukuda, et al. 1985 [3]	Y	N	Y	ND	2	ND	Specified only as 'heart attack'
○	Tarui, et al. 1987 [2]	Y	N	ND	N	Cross-sectional	Patients with hyperlipidemia	IHD
◇	Konishi, et al. 1987 [4]	Y (for the sake of simplicity)	Y	Y	Y	6	Office workers	IHD
▲	Kodama, et al. 1990 [5]	Y	N	Y	Y	26	A-bomb survivors	CHD
●	Kitamura, et al. 1994 [6]	Y	N	Y	Y	7.7	Urban company workers	CHD
★	Ueshima, et al. 1995 [7]	Y	N	Y	Y	14	General Japanese* NIPPON DATA80	Death due to IHD

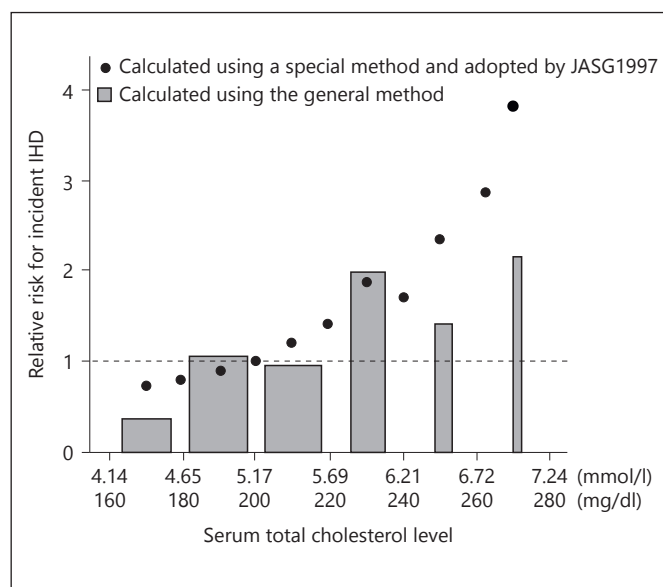
ND = Not described; IHD = ischemic heart disease; CHD = coronary heart disease.

\* The study population contained a sizable amount of patients with familial hypercholesterolemia (see Chapter 4, Section 1 regarding the NIPPON DATA80 study).

cholesterol levels  $\geq 200$  mg/dl (1.6 persons/1000 person-years) and that of participants with cholesterol levels  $< 200$  mg/dl (0.6 person/1000 person-years) and then calculated the ratio between them ( $1.6/0.6 = 2.6$ ). Konishi et al. calculated this 'relative risk' similarly at 15 cholesterol cut-off points from 160 to 300 mg/dl (4.14 to 7.76 mmol/l) at 10-mg/dl (0.26-mmol/l) intervals. Some of the results were as follows: at 160 mg/dl (4.14 mmol/l), the IHD risk was 1.3; at 200 mg/dl (5.17 mmol/l), it was 2.6; at 240 mg/dl (6.20 mmol/l), it was 3.2; and at 270 mg/dl (6.98 mmol/l), it was 6.7. The relative risk at 270 mg/dl compared with that at 200 mg/dl is  $6.7/2.6 = 2.6$ . In this way, they managed to create a data set of 15 relative risks for IHD from just 50 IHD cases only. However, the JASG1997 Research Committee chose not to include the division process for the incidence rates below the cut-off points. This calculation method served to inflate the relative risk at 270 mg/dl to 3.8 from 2.6 (Konishi et al.'s method) and 2.2 (the general method). Let's check this inflation of risk.

Fig. 4-3 shows differences between the data obtained using the JASG1997 calculation method (black circles) and the data obtained using the general method explained in the previous paragraph (bars). In the case of the general method, the IHD incidence curve is not smooth, but the JASG1997 method irons out the curve's ups and downs as well as exaggerates the data at higher cholesterol levels by 68% and 75% in the case of the third highest and top black circles (fig. 4-3), respectively. Because there were no upper limits for the cholesterol values, the presence of participants with FH exerted an effect at all cholesterol points; moreover, this effect is gradually concentrated toward the highest cholesterol levels (cut-off points). This is where the exaggeration comes from and why the curve of black circles is so smooth. In the general method (bars), the presence of participants with FH does not affect any data except for the highest cholesterol levels. It really is unfortunate that the data for these 15 IHD risk values occupy the most important positions in fig. 4-1 (see open diamonds); there are 11 of these diamonds, the most abundant and one of the most important symbols in the figure.

As the fourth study, Kodama et al. reported one of the longest cohort studies in Japan [5]. They recruited around 20,000 A-bomb survivors in Hiroshima and Nagasaki and followed them for 26 years. After excluding participants with a history of MI or angina pectoris, they calculated the age-adjusted CHD incidence rate for around 16,000 participants whose baseline measures were obtained in 1958–60. The results are shown in table 4-B. Only the men's data are used in fig. 4-1 (the most impor-



**Fig. 4-3.** Comparison of relative risks for ischemic heart disease (IHD) calculated by two different methods [4]. From a total of 8,294 men aged 35–54 years who were followed for a mean 6 years, 50 cases of IHD were recorded. Bars show the relative risks for incident IHD calculated using the general method. The number of participants in each cholesterol category was calculated through reading out the percentage of participants in each category (data for the years 1975 and 1985 were averaged) in figure 2 in the original report [4]. The number of cases in each category was calculated from table 4 in the report. Unity on the Y-axis was set midway between the height of the second and third columns (from left). The width of each column is proportional to the number of participants in that category. Black circles denote the relative risks and these values were used by 1997 JAS Guidelines. Black circles: risks at 200 mg/dl (5.17 mmol/l) calculated as the incidence rate for the participants with cholesterol levels  $\geq 200$  mg/dl; that at 210 mg/dl was similarly calculated using data from participants with cholesterol levels  $\geq 210$ ; and so on. Risks were compared with that of 200 mg/dl (relative risk = 1). In this way, the relative risk was exaggerated by 75% in the higher cholesterol range. These exaggerated data are used in our Fig. 4-1. See the text for details. No adjustment was done for either method. JASG1997: 1997 JAS Guidelines.

tant figure, in JASG1977). According to the text of JASG1997, unity was set at cholesterol level 200 mg/dl (5.18 mmol/l) for each study. However, the reference group was that of cholesterol range 4 (160–179 mg/dl, 4.12–4.63 mmol/l). Because cholesterol range 5 had the same relative risk (1.0), JASG1997 combined both ranges 4 and 5 to create the reference range, which means that the JASG1997 Research Committee used 180 mg/dl (4.64 mmol/l) as the actual reference value. As an aside, the black triangles denoting data from the study by Kodama et al. [5] were also shifted to the left, exaggerating the as-

**Table 4-B.** Age-adjusted coronary heart disease incidence rate according to baseline cholesterol level in men and women: Hiroshima/Nagasaki study [5]

Serum cholesterol range	1	2	3	4 (reference)	5	6	7	8
mmol/l	<3.11	3.11–3.60	3.61–4.11	4.12–4.63	4.64–5.15	5.16–5.67	5.68–6.19	≥6.20
mg/dl	<120	120–139	140–159	160–179	180–199	200–219	220–239	≥240
<b>Men</b>								
No. of cases	8	26	35	33	21	21	7	6
Person-years	6,080	9,957	11,842	9,365	5,973	3,330	1,505	832
Rate (per 1,000 person-years)	1.5	2.7	3.1	3.4	3.3	5.7	4.2	6.9*
Relative risk	0.4	<b>0.8</b>	<b>0.9</b>	<b>1.0</b>	<b>1.0</b>	<b>1.7</b>	<b>1.3</b>	2.0
<b>Women</b>								
No. of cases	5	8	23	29	32	22	8	10
Person-years	8,973	17,031	22,057	20,806	13,752	8,027	3,645	2,915
Rate (per 1,000 person-years)*	0.9	0.6	1.1	1.3	1.9	2.1	1.6	2.3*
Relative risk	0.7	0.5	0.9	1.0	1.4	1.5	1.2	1.7

Around 16,000 A-bomb survivors with no history of myocardial infarction or angina pectoris were followed for 26 years. Relative risk for CHD was calculated with cholesterol range 4 as the reference range. Only the bold values were used in fig. 4-1. In JASG1997 figure 1, cholesterol ranges of 4 and 5 were combined. \* p <0.001.

**Table 4-C.** Age- and multiple-adjusted risks for coronary heart disease in workers in Osaka Prefecture [6]

Serum total cholesterol (quartiles)					
mmol/l		<4.50	4.50–5.06	5.07–5.63	≥5.64
mg/dl		<174	174–195	196–217	≥218
No. of cases		5	7	9	25
Age-adjusted rate (per 1,000 person-years)		0.46	0.58	0.71	2.02
Multiple-adjusted relative risk*		1.00	<b>1.48</b>	<b>1.93</b>	4.89**

A total of 6,408 male workers aged 40–59 were followed for 7.7 years from baseline. \* Adjusted for age, high density lipoprotein cholesterol, systolic blood pressure, body mass index, number of cigarettes/day, and alcohol intake. Only the bold values were used in fig. 4-1, with unity set at the second lowest quartile. \*\* p = 0.001 compared with the lowest quartile. (Remade with permission from the publisher.)

sociation between cholesterol and CHD incidence at higher cholesterol levels. Moreover, the JASG1997 Research Committee did not use cholesterol range 8, probably to remove an outlier. They did not use women's data at all (lower part of table 4-B). The original purpose of Kodama et al's study [5] was not related to cholesterol because all participants were A-bomb survivors, so it might have been unwise to use this cohort in the creation of cholesterol guidelines since radiation might have exerted some effects on the incidence of CHD.

The fifth study referred to in JASG1997 is that by Kitamura et al. [6], who followed 6,408 male workers aged 40–59 years with no history of CHD or stroke at baseline in 13 industrial urban companies in Osaka Prefecture. They participated in cardiovascular risk surveys between 1979 and 1986 and were followed for 7.7 years.

During the follow-up period, 46 participants developed CHD. The relative risks for CHD according to serum total cholesterol quartiles are shown in table 4-C. We wonder why JASG1997 adopted only two points (bold values in table 4-C) from Kitamura et al.'s whole data set. Again unity is set not at 200 mg/dl (5.17 mmol/l) but at the second lowest cholesterol quartile (4.50–5.06 mmol/l, 174–195 mg/dl; in fig. 4-1, a closed circle denotes the middle of this range). In addition, the number of CHD cases in the second and third quartiles was 7 and 9, respectively.

The last data set included in fig. 4-1 is from the NIPPON DATA80 study (represented by black stars) [7]. Baseline data were obtained in 1980 and follow-up data were collected 14 years later. The NIPPON DATA80 report was based on the analysis of data from 9,457 participants from



**Table 4-D.** Age-adjusted relative risk for mortality from ischemic heart disease according to cholesterol level in men: NIPPON DATA80 study [7]

Serum total cholesterol	<4.14	4.14–5.17	5.18–6.20	≥6.21
mmol/l	<160	160–199	200–239	≥240
mg/dl	<160	160–199	200–239	≥240
Participants aged 30–60 at baseline	0	<b>1.0</b>	<b>1.3</b>	4.3
Participants aged >61 at baseline	0.8	<b>1.0</b>	<b>1.5</b>	3.7

Data were calculated from figure 2-21 in reference paper [7]. A total of 9,457 participants were followed for 14 years. Only the bold values were used in fig. 4-1, with unity assigned to the second cholesterol level. It is apparent that the simple mathematical mean values of 1.3 and 1.5 were used for the cholesterol range 200–239.

300 areas in Japan with 983 definitive all-cause deaths. There were 34 IHD deaths during follow up, but deaths during the first 5 years were excluded. The relationship between mortality from IHD and cholesterol levels in men is shown in table 4-D. Although participants were divided into two age groups in the study—30–60 and >61—it appears that JASG1997 used only the simple mean value of data obtained from 30–60 and >61. In the latest version of the JAS Guidelines (JASG2012), NIPPON DATA80, with its longer follow-up period, is used as the most important prospective study.

So, taking all of the above together, we can see that fig. 4-1 contains too many exaggerations generated from too few CHD cases. JASG1997 [1] (p.5) states that, ‘*The relative risk at 220 mg/dl (5.69 mmol/l) of CHD is increased 1.5 times compared with that at 200 mg/dl (5.17 mmol/l).*’ In the next version of the guidelines published, JASG2002 [9], the same errors appeared, with the same diagnostic criteria apparently referencing the same figure, fig. 4-1. It is unfortunate that the JAS guidelines had a number of limitations from the outset.

## (2) Moving from Total Cholesterol to Low Density Lipoprotein Cholesterol

JASG1997 [1] (p.6) states the following: ‘*Regarding the relationship with CHD, LDL cholesterol is supposed to be a closer index than total cholesterol, and it is necessary to emphasize this in the present Guidelines.*’ However, no citations appear alongside this statement and we can find no empirical studies in Japan reporting the superiority of LDL cholesterol over total cholesterol as a predictor for CHD. As described in Chapter 2, Section 1 particularly, many Japanese studies have failed to show a relationship between cholesterol levels and CHD incidence/mortality,

especially in women. The question is not which index is better, LDL cholesterol or total cholesterol, but whether cholesterol is related to CHD in Japan in the first place. All epidemiological findings in Japan in support of a significant relationship between cholesterol levels and CHD can be explained by (1) the presence of subjects with FH in the highest cholesterol groups, (2) the use of a reference group that has the highest all-cause mortality, and/or (3) the inclusion of unreliable CHD cases such as angina pectoris diagnosed without any hard evidence.

JAS revised the guidelines again in 2007 (JASG2007) [10] and entirely moved away from total cholesterol to LDL cholesterol in that version, and no description of total cholesterol appears in the summary of JASG2007. The guidelines actually state, in the footnote of table 2, that the diagnostic criterion for hyper-LDL cholesterol-emia is ≥140 mg/dl (3.62 mmol/l), with the measurement method given as follows: in the case of triglycerides values <400 mg/dl (4.52 mmol/l), LDL cholesterol levels should be directly measured or calculated according to the Friedewald equation [LDL cholesterol = total cholesterol – HDL cholesterol – 1/5 triglycerides (all in mg/dl)]; in the case of triglycerides ≥400 mg/dl (4.52 mmol/l), LDL cholesterol should be directly measured. This footnote later caused some considerable problems and revealed a lack of preparedness in creating JASG2007: in 2010, the top JAS board members including the JASG2007 Research Committee chairperson convened a press conference [11] and warned against measuring LDL cholesterol values directly because a wide range of measurement errors could ensue, and instead recommended that the values be measured using the Friedewald equation only. It was the JASG2007 Research Committee that recommended the direct measurement of LDL cholesterol, and this error forced it to admit quality control problems with the most im-



**Table 4-E.** List of epidemiological studies cited in JASG2007 [10] in support of the cholesterol risk stated for Japan

Name of study	First author publication year	Data given on LDL cholesterol and CHD	Type of study	Other comments	Peer-reviewed report
NIPPON DATA80	Ueshima H 1995	None	Cohort study	See table 4-D	N
Hiroshima/Nagasaki Study	[7] Kodama K 1990	None	Cohort study	See table 4-B	Y
Tarui Report*	Tarui S 1987	None	Cross-sectional study	see fig. 3-1	N
3M Study	Hirobe K 2002 2003	Yes, but very limited data**	Case control study	Two papers [12] and [13] are cited for 3M Study in JASG2007, but they are essentially the same papers	N N
Okinawa Cohort Research	Wakugami K 1998	None	Cohort study	Baseline measurement and AMI registration were performed by different bodies	Y
Ehime Epidemiological Investigation	Kukita H 1991	Yes, but very limited data with no statistical significance***	Cohort study	Statistical methods were not described in the report [14]	N

AMI = Acute myocardial infarction; LDL = low density lipoprotein; CHD = coronary heart disease.

\* Ministry of Health and Welfare Japan-specified diseases: Research report by the Research Group for Primary Hyperlipidemia in fiscal year 1986.

\*\* A case-control study with 252 men with AMI and sudden cardiac death. Data on LDL cholesterol and CHD from the entire data set were only as follows: odds ratio for LDL cholesterol  $\geq 140$  (3.62 mmol/l) = 5.56 (4.15–7.45) by univariate analysis,  $p < 0.0001$ , and 4.92 (3.48–6.97) by multivariate analysis,  $p < 0.0001$ .

\*\*\* Mean baseline LDL cholesterol level of all participants ( $n = 1,110$ ) was 120 mg/dl (3.10 mmol/l) and that for patients with CHD ( $n = 19$ ; mostly angina pectoris,  $n = 16$ ) was 136 mg/dl (3.52 mmol/l), which 'tended to be higher' [14].

portant measurement in JASG2007—the measurement of LDL cholesterol.

We decided to look into what scientific evidence was available to the JASG2007 Research Committee to prompt the switch from total cholesterol to LDL cholesterol. JASG2007 introduces several Japanese epidemiological studies in support of the claim that the relative risk for CHD increases with LDL cholesterol or total cholesterol levels. These epidemiological studies are shown in table 4-E. As a matter of fact, four of the seven cited papers do not give any LDL cholesterol data at all. In addition, the 3M Study (a case-control study) is described in two of the seven papers [12, 13], although both give the same results and an essentially identical picture of LDL cholesterol (see table 4-E and footnote\*\*). Moreover, neither of these 3M Study reports [12, 13] compares LDL cholesterol levels between CHD cases and controls. The Ehime Epidemiological In-

vestigation [14] does mention something about LDL cholesterol: the mean LDL cholesterol level for all participants ( $n = 1,110$ ) was 120 mg/dl (3.10 mmol/l) and that for participants with CHD was 136 mg/dl (3.52 mmol/l), probably with no significant difference between the groups because their report reads '[LDL levels of] patients [with CHD] tended to be higher' (p.554), although no description of the statistical methods used was given [14]. The 3M Study and Ehime Epidemiological Investigation reports were not peer-reviewed reports, however, which means that their results cannot be claimed to be scientifically valid.

The JASG2007 Research Committee might argue that some intervention studies endorsed the validity of LDL cholesterol as the major marker, but there have been no such intervention studies in Japan to date (we will return to this issue later in Chapter 7). Why, then, did the committee make this switch without first conducting a valid-

ity analysis of direct LDL cholesterol measurement? Because they had to switch to LDL cholesterol as soon as possible.

In the JASG2002 version [9], the Research Committee stated, *'...we do not have enough data indicating at which serum total cholesterol levels all-cause mortality is lowest'* (p.5). By the time JASG2007 was published, however, this argument for the paucity of epidemiological data no longer held. Plenty of epidemiological results dealing with total cholesterol were available by 2007, especially given that in 2008 even a meta-analysis was published on the relationship between all-cause mortality and total cholesterol levels in Japan [15]. However, by switching to LDL cholesterol, the Committee could use the same excuse again: *'...we do not have enough data indicating at which serum LDL cholesterol levels all-cause mortality is lowest'* (emphasis added). This is likely one of the reasons why the switch to LDL cholesterol occurred. Nevertheless, there were no valid epidemiological data showing LDL cholesterol was in fact a better marker for CHD. This hasty introduction of LDL cholesterol ultimately ended up with the introduction of another new marker, non-HDL cholesterol, in the latest version of the JAS guidelines, JASG2012 [16].

As we discuss in detail in the next chapter, the JASG2012 Research Committee had to officially introduce non-HDL cholesterol as a new surrogate marker seemingly as a way of repairing the damage caused by recommending inaccurate direct methods to measure LDL cholesterol levels and by the absence of any good methods to estimate LDL cholesterol levels when triglyceride levels were very high ( $\geq 400$  mg/dl, 4.52 mmol/l). JASG2012 states, *'But in the case that triglyceride levels are so high ( $\geq 400$  mg/dl, 4.52 mmol/l) or that it is hard to obtain to fasting blood samples, non-HDL cholesterol should be a target marker for control'* [16] (p.25). This is even more concerning to us though, because the validity of non-HDL cholesterol as a marker is not described in any of the cited works in JASG2012 and the term 'non-HDL cholesterol' does not even appear in the index.

### (3) Conflicts of Interest

We would like to point out next one very important aspect about the creation of official guidelines, namely, COI disclosures for the participant authors. The Research Committee members for the various versions of JASG have yet to disclose any COIs, which is clearly an issue that needs to be resolved. (We should interject that JAS has, however, included COI statements in its recent publication, the Treat-

ment Guide for Dyslipidemia (2013) [17]. An overview of these COI statements is given in Chapter 11, Section 1.)

The Japanese journalist Hiroshi Hasegawa interviewed the two most important figures on the JASG2012 Research Committee, Professor Toru Kita, then Chairperson of JASG Board, and Professor Tamio Teramoto, JASG2012 Research Committee Chairperson, to see if they were willing to disclose their COIs. According to Hasegawa's article published in the Japanese weekly journal *AERA* on September 24, 2012 [18], Professor Kita had told him with respect to forming a committee for COI within JAS, *'...we have been trying to set the COI rules.'* Professor Teramoto replied to the question of whether the guidelines were created for the promotion of statins, *'Almost all experts on the JASG2012 Research Committee have been involved in pravastatin development. We are very happy to have taken part in statin development. Of course, without drugs for treatment, these guidelines would be impossible [to compile]. But research funds are necessary to develop new drugs. [Consequently,] it is not necessary to hide [the receipt of research funds from drug companies]. We are right now setting rules for COI disclosure'* (pp. 54–55). Although many years behind the world standard on guideline COIs, we welcome the fact that JAS are now looking to address this important issue.

Hasegawa also compared JASG2012 with the Cholesterol Guidelines for Longevity (CGL) published by the Japan Society for Lipid Nutrition in 2010 [19]. He points out that the contents of the CGL, for which we (the present authors) are participating authors, were the direct opposite of the JAS guidelines. We provide the preface to CGL in its entirety [18] (p.3) below as it clearly illustrates the differences between two sets of guidelines.

*JAS and other bodies have already published guidelines for hyperlipidemia. The goal levels for so-called bad cholesterol, LDL cholesterol, are set at  $\leq 140$  mg/dl (3.62 mmol/l), or  $\leq 220$  mg/dl (5.69 mmol/l) in the case of total cholesterol.*

*However, because up to now the guidelines have included a number of serious flaws, [we consider that] they were not valid. Not only lay people but also medical professionals really want to know how all-cause mortality is affected by high cholesterol levels. However, the data on all-cause mortality has never been described in the previous guidelines. If, contrary to what seems intuitive—that the mortality of people with higher cholesterol levels is lower—it becomes necessary to reconsider our commonly held belief that cholesterol is bad.*

*As we show from several lines of evidence in our guidelines, all-cause mortality in Japan is reduced when total or*

LDL cholesterol values are high. That is to say, people with high cholesterol levels live longer. This fact has been known by researchers for more than 10 years. Why have the general public not been told of this important fact?

Our guidelines, compiled with support from the Japan Society for Lipid Nutrition, present many facts that the general public will not be aware of until now. This situation has been made possible simply because almost all editorial committee members [of CGL] do not receive any research grants from pharmaceutical companies. As shown on page 6, detailed conflict of interest statements for the [CGL] committee members are disclosed. The very least that committee members involved in the creation of any guidelines must do from the outset is to disclose COI information. Previous [JAS] guidelines have never disclosed such information.

In 2008, two news sources (one newspaper and one weekly journal) reported that many of the JASG committee members received large research grants, ranging from tens to hundreds of million yen (hundreds of thousands to millions US\$), from pharmaceutical companies. The amounts received by researchers working in private universities are not known. Is it possible to compile fair guidelines in such a situation?

The sales of statins that decrease cholesterol levels have expanded to 250 billion yen (2.5 billion US\$). Related medical costs are roughly 3 times that amount. A sizable part of that amount is covered by tax.

The present guidelines are prepared in order to summarize really necessary information and to prevent inutile and sometimes harmful medical care.

Tomohito Hamazaki  
Japan Society for Lipid Nutrition  
Committee on Cholesterol Guidelines for Longevity

Hasegawa concluded that the COI issue was now pretty much covered in CGL and declared the CGL's claims that cholesterol-lowering medication is not necessary—and not JASG2012's claim that it is necessary—as the winner. This issue in the United States has already been discussed by Dr Jerome P. Kassirer, who resigned as Editor-in-Chief of the *New England Journal of Medicine* in 1999 following a dispute with the journal's publisher over its plan to use the journal's name to brand and market other sources of healthcare information. On August 1, 2004, he wrote in an article for the *Washington Post* entitled 'Why should we swallow what these studies say?' [20]. In it he argued that physicians and scientists with financial ties to the pharmaceutical industry should not just have to disclose conflicts, they shouldn't be permitted to issue guidelines at all. This argument is impeccable in its simplicity.

Major bodies responsible for dyslipidemia guidelines overseas have a track record of disclosing COI information. For example, in America, the members of the working group for the Adult Treatment Panel III 2004 published their financial ties with industry [21]. All members except one declared ties with industry. The European Society of Cardiology and European Atherosclerosis Society issued their guidelines in 2011 [22] and, likewise, in their declaration of COIs [23], of the 18 task force members and additional contributors, only one declared no relationship with industry and the others all had rather close ties with large pharmaceutical companies producing statins. It is essential to know what COIs may exist in the issuance of guidelines, and we are hopeful that COI statements will be contained in forthcoming JASG versions.

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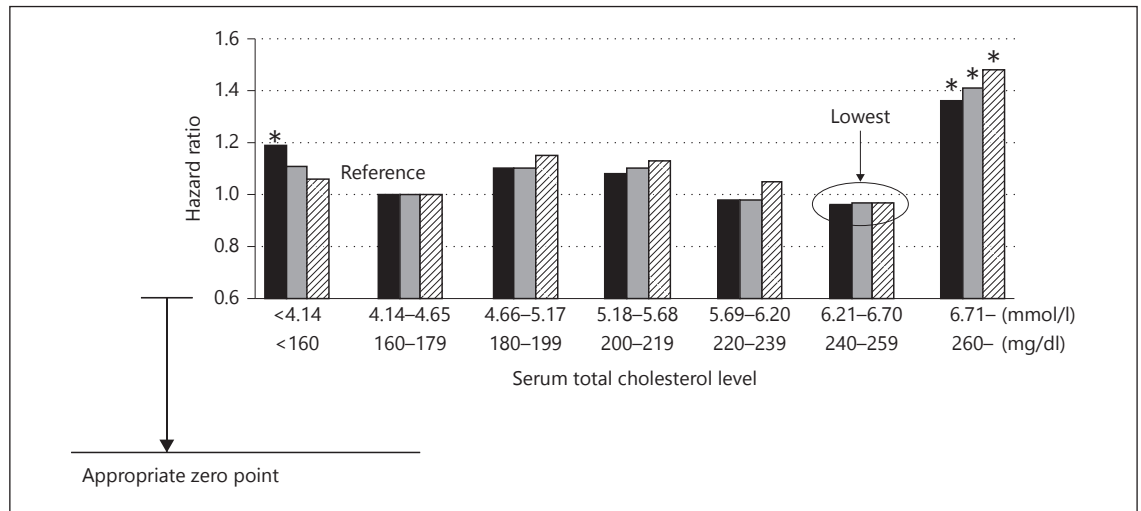
## Chapter 5 The Latest Edition of the the 2012 JAS Guidelines Part I: The Most Important Figure and Table

**Summary:** The most recent, 2012 edition of the Japan Arteriosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases (JASG2012) uses part of the absolute risk charts for coronary heart disease (CHD) mortality that appeared in one of the NIPPON DATA80 study reports. NIPPON DATA80 is unique in that it is the only epidemiological study in Japan to have found that all-cause mortality is highest in the highest cholesterol group. According to the study's CHD risk charts, high cholesterol levels are a risk factor for men only. The part of the chart used by JASG2012 for men concerns absolute 10-year mortality ranging from <0.5% to 5–10% (a difference of >10). Mortality is calculated according to four factors: smoker or non-smoker, three age groups, five blood pressure levels, and six cholesterol levels. Consequently, there are 180 risk boxes. However, the total number of CHD deaths contained in these 180 boxes is estimated to be just 35, too small a number to scientifically calculate and fill 180 risk boxes. In addition, stroke mortality is slightly inversely associated with cholesterol levels in NIPPON DATA80, but JASG2012 makes no mention of this finding on stroke risk.

### **(1) The NIPPON DATA80 Study Alone Reports All-Cause Mortality Is Highest in the Highest Cholesterol Group in Japan**

As we discussed in previous chapters, all epidemiological studies conducted in Japan that followed >10,000 participants over >10 years have shown that all-cause mortality in groups with the highest total cholesterol or low density lipoprotein (LDL) cholesterol levels was lower than in most of the other groups. The only exception is NIPPON DATA80—the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980—one of the longest cohort studies undertaken in Japan [1]. A total of 10,546 community dwellers (4,640 men, 5,906 women) aged  $\geq 30$  years from 300 districts across the country participated in the National Cardiovascular Survey in 1980. These districts were randomly selected from all 47 prefectures of Japan. After excluding 1,330 participants including those with past history of CHD or stroke ( $n = 280$ ), data from the remaining 9,216 participants (4,035 men, 5,181 women) were analyzed. Fig. 5-1 illustrates the findings reported by the NIPPON DATA80 study group after 17.3 years





**Fig. 5-1.** Hazard ratio (HR) of all-cause mortality according to serum total cholesterol level: NIPPON DATA80 study, 17.3 years of follow up [1]. In this study, 9,216 participants were followed for 17.3 years. HRs of all-cause mortality were adjusted for sex, age, serum albumin levels, body mass index, hypertension, diabetes, smoking, and drinking (black bars). Gray bars: HRs for all-cause mortality after excluding deaths from liver disease during the entire follow-up period. Hatched bars: HRs for all-cause mortality after further excluding all-

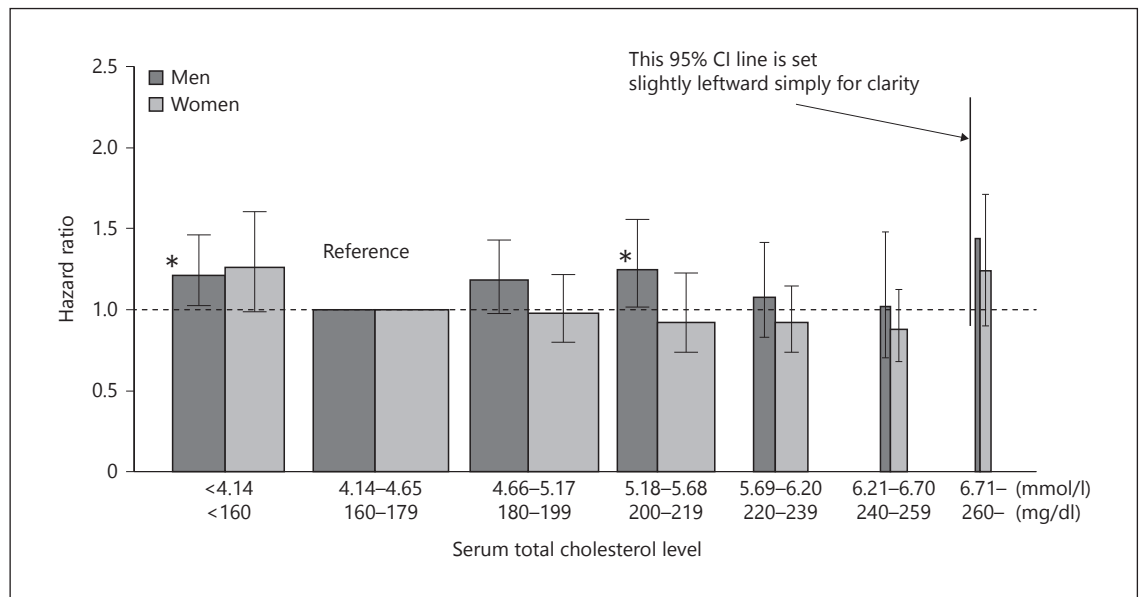
cause deaths within the first 5 years of follow up. Whatever technique the authors of the NIPPON DATA80 study report [1] might have used to emphasize the risk of hypercholesterolemia, participants in the cholesterol range 6.21–6.70 mmol/l (240–259 mg/dl) show the lowest risk. \* Significantly different from the reference group,  $p < 0.05$ . See the text for details. (Remade with permission from the publisher, with slight modifications.)

of follow up: the group of participants with the highest total cholesterol levels had the highest all-cause mortality [1]. We believe, however, that this finding needs to be re-examined as the presentation of the results suffers from several important flaws.

We'll begin our re-examination by looking in detail at fig. 5-1. First, let's focus on the black bars representing hazard ratios (HRs) for all-cause mortality according to baseline total cholesterol levels over the 17.3 years of follow up (hereinafter referred to as ND80-17.3 [1]). The ratios were adjusted for age, sex, serum albumin levels, body mass index, hypertension, diabetes, smoking, and drinking. At a glance, all-cause mortality in the highest cholesterol group looks to be about twice that of the reference group. However, closer examination reveals this is not actually the case because the authors of ND80-17.3 cut short the bars at a HR of 0.6, not the appropriate zero point that we have added to the figure. Let's look now at the gray bars representing HRs after excluding participants who died from liver disease. The caption for the original figure 1 in ND80-17.3 reads, '*Multivariable-adjusted hazard ratios (HR) for all-cause mortality grouped according to serum total cholesterol after adjustment for gender, age, serum albumin levels...*' (emphasis added) [1] (p.221). However, this caption misrepresents the findings, because without

the deaths from liver disease, the figure would no longer show all-cause mortality. The authors of ND80-17.3 state in their discussion [1] (PP.221–222): '*The prevalence of hepatitis C virus (HCV) infection in Japanese residents born before World War II has been estimated to be approximately 5–7% ... [around five lines deleted for simplicity]. It has recently been revealed that a low serum cholesterol level in individuals with chronic HCV infection is a predictor of both liver fibrosis [2] and liver cancer [3]. Another study indicated that subjects with genotype 1b HCV infection (the most common genotype of the HCV in Japan) had significantly lower serum cholesterol levels than those infected with hepatitis B virus or genotype 2a HCV, even in the precirrrosis period [4]... [omitted for simplicity] Low serum [total cholesterol] may be a response to liver dysfunction caused by progressive fibrotic changes rather than a primary cause of liver fibrosis. We believe these findings may partly explain the relationship we observed between low total cholesterol and all-cause death in Japan.*' However, they forget to mention that HCV enters hepatic cells via LDL receptors (see Chapter 2, Section 4).

Second, the adjustment for sex and serum albumin levels in ND80-17.3 seriously distorts the data. We have redrawn fig. 5-1 as fig. 5-2 to illustrate the same results reported in ND80-17.3 [1]. The bars showing the HRs of



**Fig. 5-2.** Black bars from Fig. 5-1 [1] presented in a different way. See the legend to Fig. 5-1. Hazard ratios (HRs) are shown according to sex. The zero line is clearly shown in this figure. Note that if the data were not adjusted for albumin, the HRs for the highest

cholesterol groups would become lower and the HRs for the lowest cholesterol groups would become higher. The width of the column of each group is proportional to the number of participants in that group.

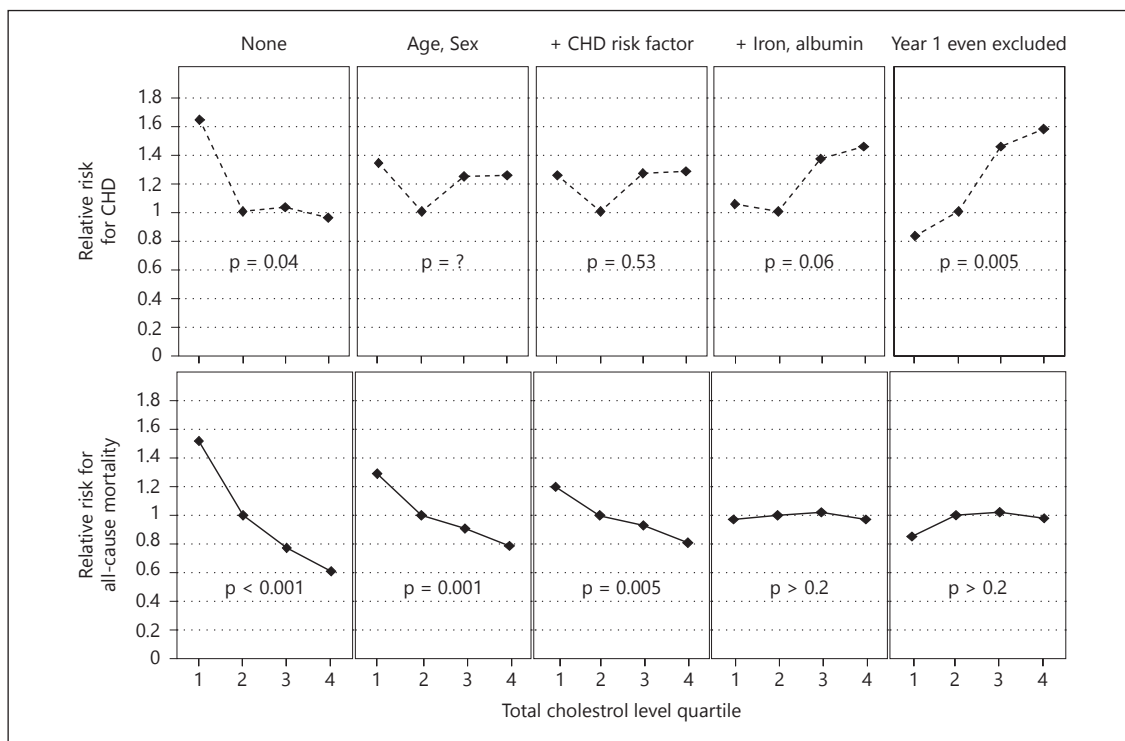
all-cause mortality in the two figures differ in that our fig. 5-2 clearly shows the appropriate zero point line, the width of each bar proportional to the number of participants in the group, and data expressed according to sex (not adjusted for sex). At first impression, the two figures are very different from each other. Without adjusting for sex, all-cause mortality in the group with the highest total cholesterol levels ( $\geq 6.71$  mmol/l,  $\geq 260$  mg/dl) is no longer significantly higher than that in the reference group for either men or women. It becomes clear that fig. 5-1 emphasizes the apparently unfavorable effects of cholesterol, whereas our accurately drawn fig. 5-2 does not.

In a separate study by one of the present authors (Y.O.), serum albumin levels were found to be positively associated with total cholesterol levels across generations in a sample of >200,000 participants [5]. As the liver is the only organ that synthesizes albumin and is practically the only one that synthesizes cholesterol, with the synthesis of both heavily dependent on nutrition, it is not surprising that serum cholesterol levels correlate well with albumin. Thus, the adjustment made in the ND80-17.3 for albumin (a negative risk factor for all-cause mortality) cancels the positive aspects of total cholesterol (or LDL cholesterol). This adjustment is a prime example of overfitting (over-adjustment) in epidemiological calculation. In fact, Corti et al. showed how, through a series of ana-

lytical adjustments, a negative relationship between cholesterol levels and CHD mortality could be changed to a positive one [6]. As shown in fig. 5-3, the biggest change in the correlation occurs when data are adjusted for serum albumin/Fe levels.

Because the entire ND80-17.3 data set is not available, we were not able to redraw fig. 5-2 without the original adjustment for albumin levels. However, by showing the correlation between serum total cholesterol and albumin levels in both male and female ND80-17.3 participants in fig. 5-4, we can give some idea of how the original data were distorted in the ND80-17.3 report. Serum albumin levels (age-adjusted) and total cholesterol levels are beautifully correlated in ND80-17.3. Yet, no other Japanese large-scale epidemiological study has adjusted for albumin when calculating the relationship between CHD incidence or mortality and cholesterol levels. Indeed, if no adjustment for albumin had been made in ND80-17.3, the height of the bar for the highest cholesterol levels ( $\geq 6.71$  mmol/l,  $\geq 260$  mg/dl) in fig. 5-2 would have been lower and that for the lowest cholesterol levels would have been higher.

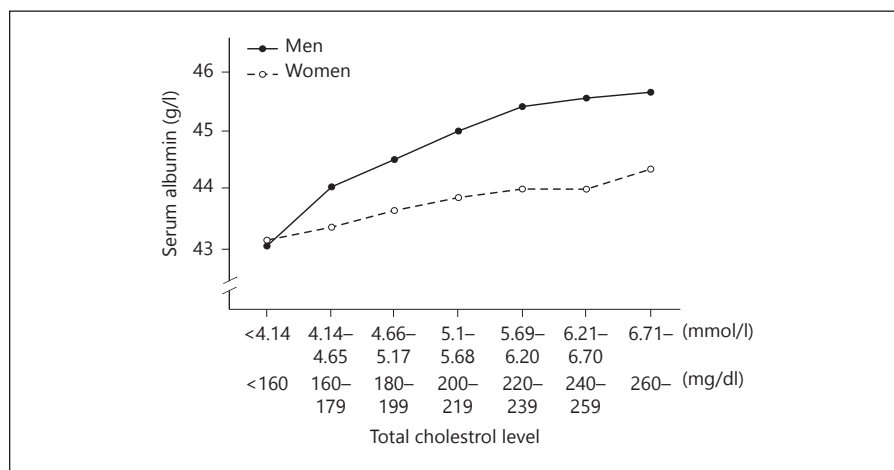
Compared with the reference group shown in fig. 5-2, the all-cause mortality of participants with the lowest cholesterol levels (<4.14 mmol/l, <160 mg/dl) was 1.21 (95% confidence interval [CI], 1.01–1.45) in men and



**Fig. 5-3.** Relative risks for coronary heart disease (CHD) mortality (upper panel) and all-cause mortality (lower panel) according to total cholesterol quartile in elderly persons, as an exemplar of the effects of adjustment factors in analysis [6]. Men and women from three communities in America (n = 4,066, aged >65 years) were followed for 5 years. Baseline measurements were performed in 1988. The correlation of mortality (of CHD in particular) with to-

tal cholesterol level can be seen to change from negative to positive through a series of analytical adjustments. Total cholesterol level quartiles: 1 = ≤4.15 mmol/l, ≤160 mg/dl, 2 = 4.16–5.19, 161–200, 3 = 5.20–6.19, 201–240, 4 = ≥6.20, ≥241. Both upper and lower panels are taken from figures 11 and 15, respectively, of the Cholesterol Guidelines for Longevity, 2010 [19].

**Fig. 5-4.** Age-adjusted mean albumin level according to total cholesterol level at baseline: NIPPON DATA80 study [1]. See the legend to Fig. 5-1 for NIPPON DATA80 study details (follow-up period, 17.3 years). Age-adjusted albumin levels are shown for seven total cholesterol categories. All the SDs in these categories were between 2.3 and 2.9 g/l but are not shown here for the sake of simplicity. Because albumin level is associated with longevity, adjustment for albumin mathematically decreases the good aspects of cholesterol. See the text for details. Both men and women, p < 0.001 (analysis of covariance).



1.26 (0.99–1.60) in women [1]. It is reasonable, therefore, to imagine that all-cause mortality in participants with the lowest cholesterol levels with adjustment for sex would fall between these two values of 1.21 and 1.26. However, this is not the case. The calculated mortality

adjusted for sex turned out to be 1.19 (1.03–1.37) [1], looking safer than for men or women alone. This kind of nonsensical result is known to result when a few conditions are met [7]; in this case, the adjustment for sex is not appropriate at all. Ultimately, then, cholesterol is not dan-

gerous in Japan, as it probably is not anywhere in the world.

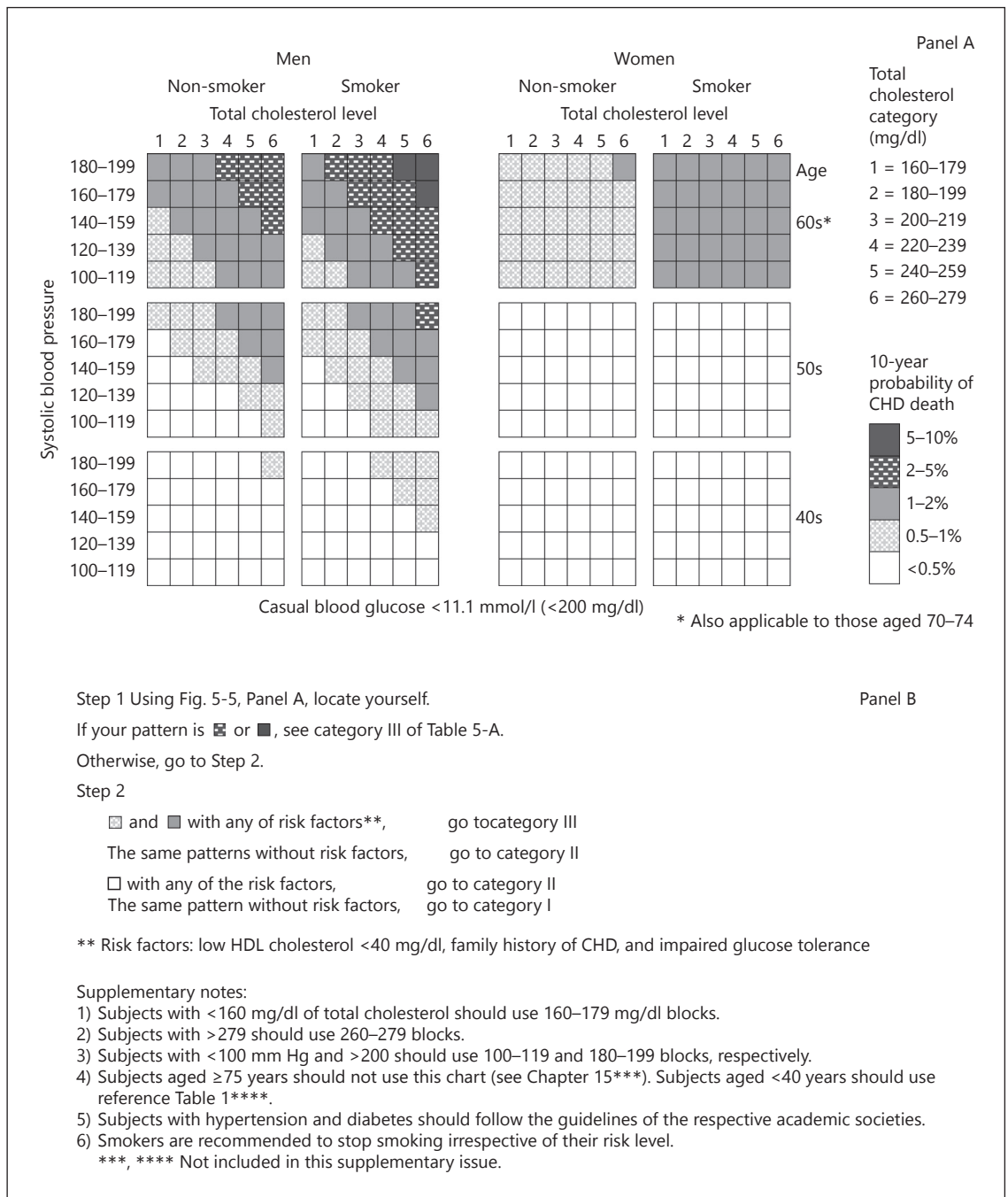
Third, the NIPPON DATA80 series of studies included a higher proportion of participants with familial hypercholesterolemia (FH) than included in the general Japanese population [8], which exaggerated the risk that total cholesterol poses. One of the merits of conducting large-scale epidemiological studies on circulatory disease in a single area is that the ratio of participants with FH to all participants approaches 0.2%; that is, the proportion of FH in the general population. Theoretically it would be 0.2% if all of the residents in one area participated in such a study. Differently, multi-area studies are apt to have more participants with FH especially when they are planned for circulatory disease—as was NIPPON DATA80 that clearly states its circulatory disease-oriented purpose in the study name [9]—because participants with FH are more likely to participate in such studies than those without FH. NIPPON DATA80 also recruited participants from 300 districts across Japan, meaning there were only 35 participants on average in each district. Although the NIPPON DATA80 results may be free from an area-related bias, it may have a serious bias in relation to the proportion of participants with FH. Those with FH might have been initially selected and encouraged to remain in the cohort because of their high cholesterol levels. This would have been doable for individual study superintendents in charge of a district because the number of participants in each district was rather small. Actually, the existence of such participants with high cholesterol levels is mentioned in one NIPPON DATA80 report [9] (p.269): ‘*The median value [of total cholesterol in all participants] is naturally lower than the mean value; presumably, some participants with extremely high values are present among our participants*’ (our translation). The exact differences in the mean and median values are 3 and 2 mg/dl (0.078 and 0.052 mmol/l) in men and women in their 50s, respectively ([9], table 2, p.280). Compared with the general population, these differences are nearly 3 times higher in men and about 1.5 times higher in women. To be precise, the differences in men aged 50–54 and 55–59 are 1.5 and 0.6 mg/dl (0.038 and 0.016 mmol/l), respectively, and those in similarly aged women are 1.9 and 0.8 mg/dl (0.049 and 0.021 mmol/l), respectively (unpublished data for about 57,000 men and 41,000 women aged 20–80 years from Y.O.). The proportion of participants with FH reported in NIPPON DATA80 is reasonably estimated to be 3-fold higher than that in the general population in male participants and 1.5-fold higher in female participants. This higher proportion of FH in the study cohort beautifully explains why all-

cause mortality is seen to be significantly increased in the highest cholesterol group in fig. 5-1 or insignificantly increased in fig. 5-2.

## **(2) The Major Figure and Table in the 2012 JAS Guidelines are Largely Derived from NIPPON DATA80 Findings**

Arguably the most important figure in JASG2012 (figure 2 and identical figure 7 in JASG2012, Chapters 1 and 4, respectively [10]) is shown here as fig. 5-5. Fig. 5-5 depicts the absolute risk for CHD death according to the following risk factors: sex, smoking status, age, systolic blood pressure, and total cholesterol level. People can first find their risk color (actually risk tone—dark gray to white—in this supplementary issue) in Panel A of the figure, then go to Panel B to find their treatment category, and finally go to table 5-A (which represents the most important table in JASG2012, table 2 and identical table 13 in JASG2012, Chapters 1 and 4, respectively [10]) to find their treatment goal for serum lipids. Putting aside for the moment the relevance of treating dyslipidemia, this system is apparently able to categorize patients with dyslipidemia. Unfortunately, fig. 5-5 has some fundamental problems.

Figure 2 (and figure 7) in JASG2012 (fig. 5-5) are derived from two charts that appear in one of the NIPPON DATA80 reports, which had a follow-up period of 19 years (hereinafter referred to as ND80-19) [11]. The part relating to men in the two charts in ND80-19 is shown in fig. 5-6. According to ND80-19, the final analysis was performed on data from 9,353 participants, 4,098 men (mean age, 50.3 years) and 5,255 women (mean age, 50.8 years). There were 132 CHD deaths (67 men, 65 women) recorded during the 19-year follow-up period. Because of a lack of detailed information available on these 132 CHD deaths and some baseline information about all participants in the ND80-19 report [11], we refer to two previous NIPPON DATA80 papers, ND80-17.3 [1] and ND80-13.2 [12], which essentially followed the same cohort. ND80-17.3 recorded 128 CHD deaths (65 men, 63 women) over 17.3 years, only 4 fewer (2 men, 2 women) than ND80-19 over 19 years. Consequently, it is reasonable that some pertinent data found in ND80-17.3 was used to substitute for missing data in ND80-19, although it should be noted that the number of participants in the ND80-17.3 and ND80-13.2 cohorts was slightly smaller ( $n = 9,216, 4,035$  men, 5,181 women) than that in the ND80-19 cohort ( $n = 9,353$ ). However, we do not investigate this difference in participant numbers because the difference



**Fig. 5-5.** Absolute risk chart for coronary heart disease (CHD), which was recreated from identical figures 2 and 7 in the 2012 JAS Guidelines [10] (with permission from the Japan Atherosclerosis Society, with slight modifications). Readers can first find their risk tone—dark gray to white—in Panel A, then go to Panel B to find their treatment category, and finally go to table 5-A shown below to find their treatment goal for serum lipids. A total of 9,353 par-

ticipants were followed for 19 years and there were 132 CHD deaths during follow up. Absolute risk for CHD death was calculated according to sex, smoking status, age, systolic blood pressure, and total cholesterol level. See the text for details. Cholesterol levels (mmol/l) 1 to 6: 1 = 4.14–4.64, 2 = 4.65–5.16, 3 = 5.17–5.68, 4 = 5.69–6.20, 5 = 6.21–6.71, 6 = 6.72–7.23. (Remade with permission from the publisher, translated.)



**Table 5-A.** Table 13 in JASG2012: Treatment goal for lipids according to risk level [10]

Principal treatment	Category	Treatment goals of lipids, mg/dl (mmol/l)			
		LDL cholesterol	HDL cholesterol	Triglycerides	non HDL cholesterol
<b>Primary prevention:</b> Improve lifestyle first, then consider drug treatment	Category I	<160 (4.14)			<190 (4.91)
	Category II	<140 (3.62)			<170 (4.40)
	Category III	<120 (3.10)	≥40 (1.03)	<150 (1.69)	<150 (3.88)
<b>Secondary prevention:</b> Consider both lifestyle change and drug treatment	Past history of coronary heart disease	<100 (2.59)			<130 (3.36)

LDL: low density lipoprotein, HDL: high density lipoprotein

**Supplementary notes:**

1. Refer to Chapter 9\* for familial hypercholesterolemia.
2. Refer to Chapter 15\* for subjects aged ≥75 years.
3. Refer to reference table 1\* for young subjects and other subjects with low risk.
4. The listed values above are only goals to strive for.
5. The goal for LDL cholesterol may be set 20–30% below the starting level.
6. The goal for non-HDL cholesterol is the secondary goal after reaching the goal of LDL cholesterol levels in patients with hypertriglyceridemia. Non-HDL cholesterol should be used when triglyceride levels are ≥400 mg/dl or when blood is sampled after a meal.
7. In any category, the principal goal to reach is lifestyle improvement.
8. In category I, drugs are administered only when LDL cholesterol levels are ≥180 mg/dl (4.65 mmol/l)

Comments from the present authors: Diet and lifestyle improvement can decrease total cholesterol only a few percent. Thus, JASG2012 does little more than recommend drug treatment from the outset. \* Chapters 9 and 15, and reference table 1 are not shown here. (Translated and remade with permission from the publisher.)

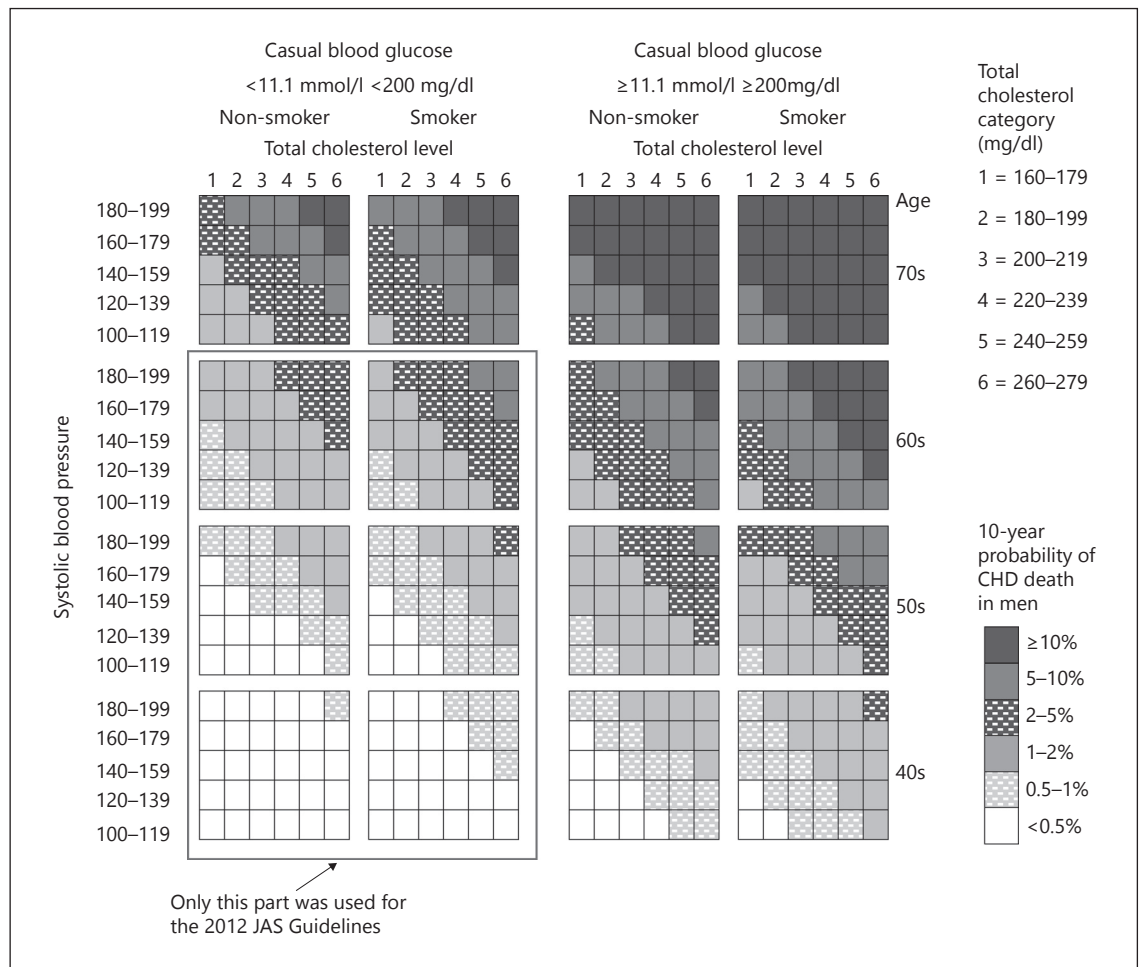
is small and irrelevant to the following discussion. Also, because cholesterol is not a risk factor for CHD death in women at all (fig. 5-5, right), we focus solely on the men's data from the NIPPON DATA80 series in the following re-examination of the most important figure and table in JASG2012.

The original charts showing absolute risk for CHD death given in ND80-19 included two higher risk groups, participants aged 70–79 years and participants with diabetes [11]. However, these two groups are not included in figure 2, the absolute risk chart for CHD, in JASG2012 (Fig. 5-5 and 5-6). As fig. 5-5 shows, there are five risk levels indicated by five different tones (from dark gray to white) and four borderlines in men. So let's start our re-examination by investigating whether dividing the men into five risk groups is evidence based or not.

The number of CHD deaths in the group aged ≥70 years can be estimated to around 23. Note that the group of participants with casual high blood glucose levels ≥11.1 mmol/l (≥200 mg/dl; defined as diabetes) is not included in fig. 5-5. This group of participants with diabetes com-

prised 1.61% of all male participants [11]. If we assume that NIPPON DATA80 participants with diabetes had about a 5-fold higher risk for CHD death than those without diabetes, the number of CHD deaths in this diabetic group (if limited to participants aged <70 years) is probably at least 3 (see fig. 5-7 for easy understanding and Appendix 1 for the detailed calculation). Furthermore, CHD deaths in the group with the lowest cholesterol levels (<4.14 mmol/l, <160 mg/dl, n = 10, see table 5-B) in ND80-17.3 have also been excluded from fig. 5-5. Because 4 deaths belonged to the group aged ≥70 years, another 6 CHD deaths (10–4=6, see Appendix 1) have probably been excluded from fig. 5-5.

Consequently, fig. 5-5 is created based on 35 CHD deaths only [33 (65–23–3–6) + 2 (difference in CHD deaths between ND80-19 and ND80-17.3)]. Yet, there are 180 boxes with five different CHD mortality risk tones, and the difference in mortality between the highest (dark gray) and lowest (white) is >10-fold. This raises the question of how four borderlines can be drawn between 180 boxes with just 35 deaths. This is not the end of the story, however.



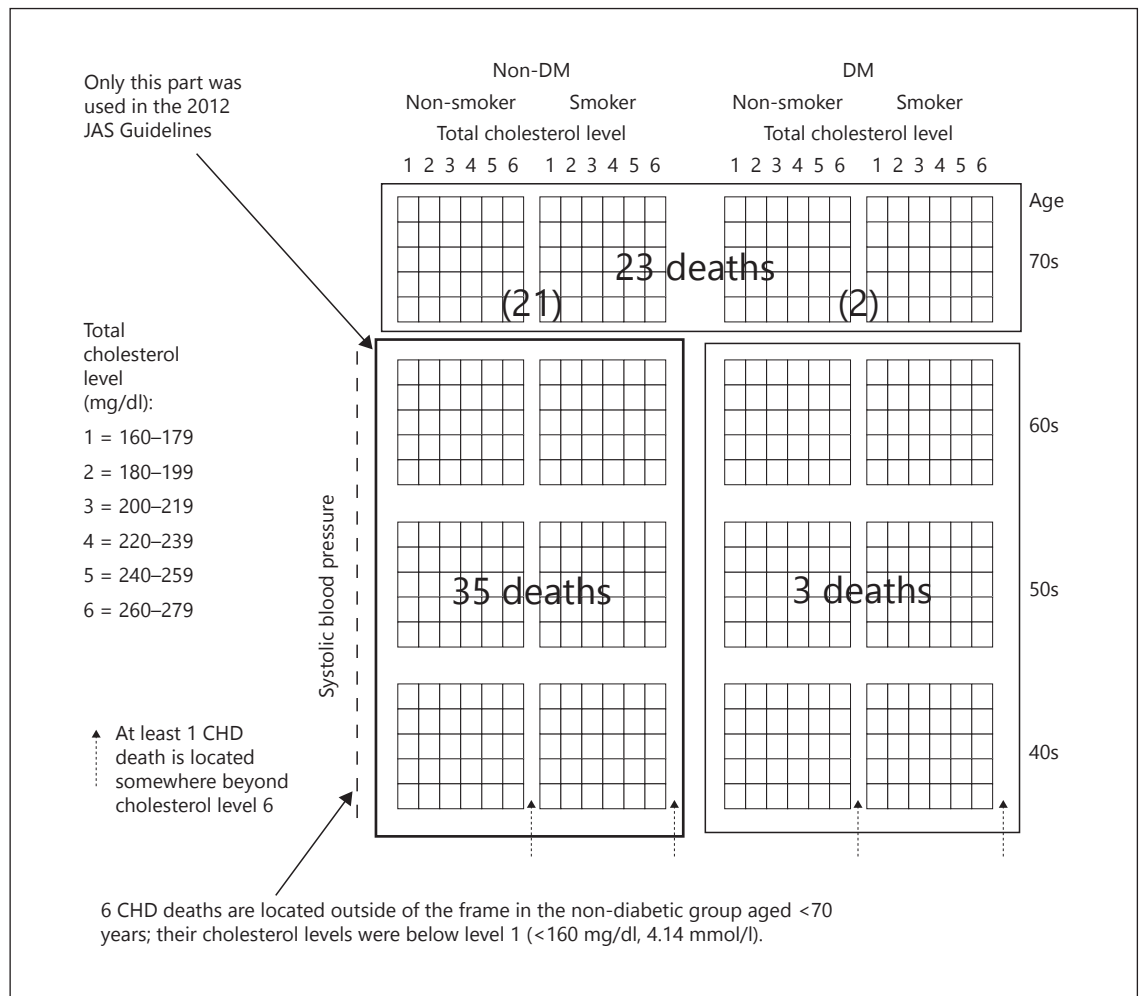
**Fig. 5-6.** Risk assessment chart for 10-year probability of death due to coronary heart disease (CHD) in men: NIPPON DATA80 study [11]. The 10-year probability of death was calculated based on individual risk assessment using sex, age, systolic blood pressure, serum total cholesterol, serum glucose, and smoking habit. Only the data included in the bold gray frame were used to create the

most important figure in the 2012 JAS Guidelines. Note, the number of CHD deaths on the right-hand side (participants with diabetes) is only 4 or 5 (see the text for details). Cholesterol level categories 1 to 6 (mmol/l): 1 = 4.14–4.64, 2 = 4.65–5.16, 3 = 5.17–5.68, 4 = 5.69–6.20, 5 = 6.21–6.71, 6 = 6.72–7.23. (Remade with permission from the publisher, with slight modifications.)

Details about the 67 male CHD deaths in this chart (fig. 5-5) are not available in ND80-19 [11]. However, data for 65 of the 67 CHD male deaths are available in ND80-17.3 [1]. Table 5-B shows these 65 CHD deaths according to total cholesterol levels. Cholesterol class 6 in ND80-17.3 (the highest class of  $\geq 260$  mg/dl,  $\geq 6.72$  mmol/l with a stratum mean of 282 mg/dl, 7.30 mmol/l; no upper limits) had only 3 deaths (ND80-17.3). The highest cholesterol level in fig. 5-5 is between 260–279 mg/dl (6.72–7.23 mmol/l), which means that the stratum mean is outside this range; in other words, at least one death is not included in this range and is located in a higher class than cholesterol class 6 in fig. 5-5,

leaving only 2 deaths at most in class 6. The important part of fig. 5-5 pertaining to cholesterol classes 4, 5, and 6 had only 9, 7, and  $\leq 2$  deaths, respectively, for men (see table 5-B). There are as many as 30 boxes in each cholesterol class. Although 2 more deaths may need to be added to some classes (the difference between 67 and 65), the actual number of deaths shown for men (fig. 5-5) should be reduced by nearly 40% because about 26 male CHD deaths are included in the oldest group and/or diabetic group that do not appear in the chart, as described earlier.

We'll continue by looking at the original chart from which fig. 5-5 derives (see fig. 5-6). This chart contains the



**Fig. 5-7.** Number of male coronary heart disease (CHD) deaths estimated from the NIPPON DATA80 series of papers. See the legend to Fig. 5-6 for an explanation of this figure. Note that the NIPPON DATA80 chart for men was created from only 67 CHD deaths. The part used for 2012 JAS Guidelines contained only 35

CHD deaths. In the diabetes group, there were 5 deaths (3 in the 40s to 60s age range and 2 in the 70s age range). The 23 CHD deaths in the 70s age range contains 4 deaths in the 80s age range for the sake of simplicity (see Appendix 1). See also the text for explanation.

absolute CHD mortality in men for both elderly participants in their 70s and participants with diabetes. Diabetes mellitus was defined as a serum glucose concentration  $\geq 200$  mg/dl ( $\geq 11.1$  mmol/l) in ND80-19 [11]. The right side of this chart shows mortality in participants with diabetes. To keep the story short, we simply present the results here. Only 5 deaths are noted in that right part of the chart for participants with diabetes (fig. 5-6, see Appendix 1). There are 6 levels (dark gray to white tones) of 10-year CHD mortality with 5 borderlines in the right part. The difference in probability between the highest probability ( $\geq 10\%$ ) of 10-year CHD deaths to the lowest ( $< 0.5\%$ ) is  $> 20$ . Nevertheless, there were only 5 deaths in that part.

So how did the authors of ND80-19 draw the chart in the first place? The answer is that it was just through mathematical calculation, the method for which is given in Appendix 2 at the end of this section.

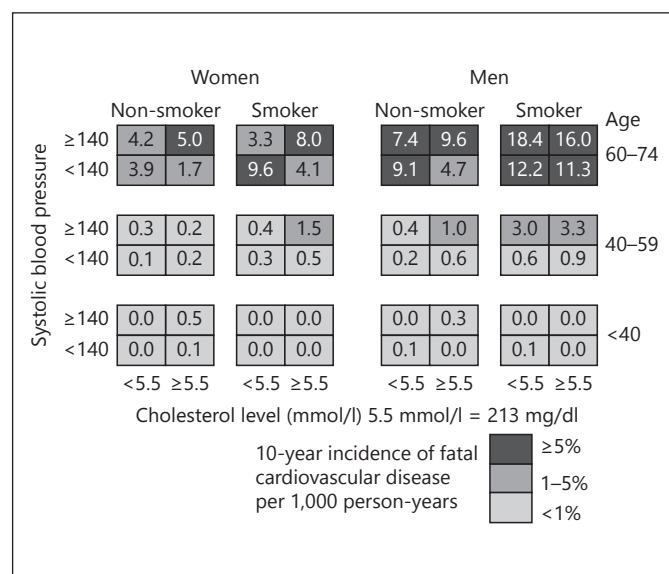
We would just like to add two short comments on JASG2012 as we conclude this section. (1) JASG2012 depends exclusively on NIPPON DATA80 with regard to deciding the 10-year probability of CHD death. (2) The 2007 JAS Guidelines included the entire chart (fig. 5-6) in their reference data section, but JASG2012 used only part of it.

And, as a final point on the importance of accurately presenting data, we would like to show what the data can

**Table 5-B.** Number of deaths and multivariable-adjusted hazard ratios for coronary heart disease (CHD) mortality in men: NIPPON DATA80 study [1]

Cholesterol class shown in the chart (fig. 5-5)	Not shown in the chart*	1	2	3	4	5	6	
Baseline serum total cholesterol levels with stratum mean (mmol/l) (mg/dl)	<4.14 3.74 <160 144	4.14–4.65 4.39 160–179 169	4.66–5.17 4.91 180–199 190	5.18–5.68 5.41 200–219 209	5.69–6.20 5.90 220–239 228	6.21–6.71 6.41 240–259 247	≥6.72** 7.30 ≥260** 282	Total
No. of persons	851	1,000	937	648	354	167	78	4,035
No. of CHD deaths	<b>10</b>	<b>12</b>	<b>12</b>	<b>12</b>	<b>9</b>	<b>7</b>	<b>3</b>	<b>65</b>
Hazard ratio	1.07	1.00	1.21	2.11	2.17	3.74	3.77	
95% confidence interval	0.46, 2.51		0.54, 2.71	0.92, 4.84	0.89, 5.25	1.44, 9.76	1.02, 13.9	

A total of 4,035 men aged ≥30 years were followed for a period of 17.3 years and 65 CHD deaths were registered. Essentially the same data were used for the chart in JASG2012 (fig. 5-5). However, 2 more deaths were added while followed for up to 19 years (and/or while the number of men starting in the cohort increased from 4,035 to 4,098). Deaths in the following groups were excluded from the chart in JASG2012: group of participants aged ≥70 years (about 23 deaths), group of participants with diabetes (about 3 deaths), and group of participants with baseline cholesterol levels <4.14 mmol/l (<160 mg/dl; n = 10). \* Data in this column were excluded from the NIPPON DATA80 chart (fig. 5-6). \*\* Different from fig. 5-5 and 5-6, there are no upper limits here. (Remade with permission from the publisher, with slight modifications.)



**Fig. 5-8.** A modest presentation of scientific findings: HUNT 2 study, Norway [13]. The 10 year-mortality from cardiovascular disease was calculated using Cox's proportional hazard models. A total of 52,087 Norwegians aged 20–74 years with no established cardiovascular disease at baseline (HUNT 2, 1995–1997) were followed for cause-specific mortality over a 10-year period. There were 776 deaths from cardiovascular disease (486 men, 290 women) and 347 deaths from ischemic heart disease (231 men, 116 women). The association between total cholesterol and all-cause mortality is shown in Fig. 1-5. See the text for details. (Remade with permission from the publisher, with slight modifications.)

look like when scientists represent their findings modestly. When we compare fig. 5-6 from NIPPON DATA80 and fig. 5-8 from a Norwegian study, we see a more modest representation of risk in the latter. Petursson et al. showed the association between total cholesterol and cause-specific mortality in a Norwegian cohort they followed for 10 years in the Nord-Trøndelag Health Study (HUNT 2, 1996–1997 [13]; see Chapter 1). During the course of the study, 2,490 deaths (1,447 men, 1,043 women) were recorded, 776 from cardiovascular disease (486 men, 290 women) and 347 from ischemic heart disease (IHD; 231 men, 116 women). Among women, cholesterol had an inverse association with all-cause mortality (see fig. 1-5 in Chapter 1). The large number of deaths from cardiovascular disease and IHD as well as the small number of risk level-indicating frames in HUNT 2 (one-tenth of those used in NIPPON DATA80) make for a striking contrast with NIPPON DATA80.

## Appendix 1: Calculating the Number of CHD Deaths

### Number of CHD Deaths in Men Aged ≥70 Years

The NIPPON DATA80 report (ND80-19) that contains the original chart (shown here as fig. 5-6) [11] does not have any age distribution information of participants. However, another NIPPON DATA80 paper (ND80-13.2) [12] that followed essen-



tially the same cohort (4035 men, 5181 women) does give a chart of age distribution. According to that distribution chart, the number of male participants aged 70–79 and 80–89 years are 323 and 60, respectively, for a total of 383. The ratio between CHD deaths and all-cause deaths can be estimated as 0.066 from tables 2 and 3 in ND80-17.3 [1]. Almost 100% of participants aged 80–89 ( $n = 60$ ) and about 90% of those aged 70–79 years presumably died during the 19 years of follow up. Because CHD deaths comprised about 0.066 of all-cause deaths, the number of CHD deaths in these two elderly groups are estimated to be 4 in the group aged 80–89 and 19 in the group aged 70–79 (for a total of 23).

### *Number of CHD Deaths in Men with Diabetes*

Diabetes mellitus was defined as a casual serum glucose concentration of  $\geq 200$  mg/dl ( $\geq 11.1$  mmol/l) in ND80-19 [11]. Prevalence of diabetes mellitus was 1.61% in men (ND80-19). Sixty-seven CHD deaths were registered (ND80-19), and the risk for CHD is probably increased in patients with diabetes by a factor of about 5 at most. Therefore, the number of CHD deaths in participants with diabetes in ND80-19 can be estimated as 5 [ $67 \times 0.0161 \times 5 / (0.9839 + 0.0161 \times 5)$ ]. Because the percentage of CHD deaths in the group aged  $\geq 70$  is 34% (23/67, see above), the number of CHD deaths in the group of diabetes  $< 70$  is 3 ( $5 \times 0.66$ ).

The number of CHD deaths in the group with the lowest cholesterol levels ( $< 4.14$  mmol/l,  $< 160$  mg/dl) was 10 (see table 5-B). The ratio of CHD deaths in the group aged  $\geq 70$  in ND80-17.3 was  $23/65 = 0.354$ . If this ratio was also the case for the group with cholesterol levels  $< 4.14$  mmol/l (160 mg/dl), 4 of these 10 deaths would be calculated to belong to the 70s age group. We speculate that the number of diabetic cases in these 10 cases ( $< 4.14$  mmol/l) was negligible because the number of participants with diabetes mellitus was so small.

### **Appendix 2: Drawing the Chart Shown in Fig. 5-6 Mathematically**

The absolute risk for CHD was calculated by the NIPPON DATA80 Study Group [14] using Cox's proportional hazard model. Calculated first is the 10-year survival probability of a standard person who has mean values for every measured item (i.e., blood pressure, cholesterol level, diabetic or not, smoker or not, and age). The probability was calculated as 0.9974 in the case of ND80-19. When calculating a certain person's probability, the difference (D) in each item from the mean is calculated and then  $\Sigma$  (D multiplied by the regression coefficient of the item) is calculated across all items, which gives the survival probability as  $0.9974^{\text{Exp } \Sigma}$ . The probability of death is expressed by the difference from 1.0000 ( $1.0000 - 0.9974^{\text{Exp } \Sigma}$ ). Using this calculation method, it is possible to mathematically evaluate the probability of death even if there are only a few deaths in the diabetes mellitus group. The problem is that neither p values nor 95% CIs are shown in ND80-19 or the paper explaining the calculation method [14].

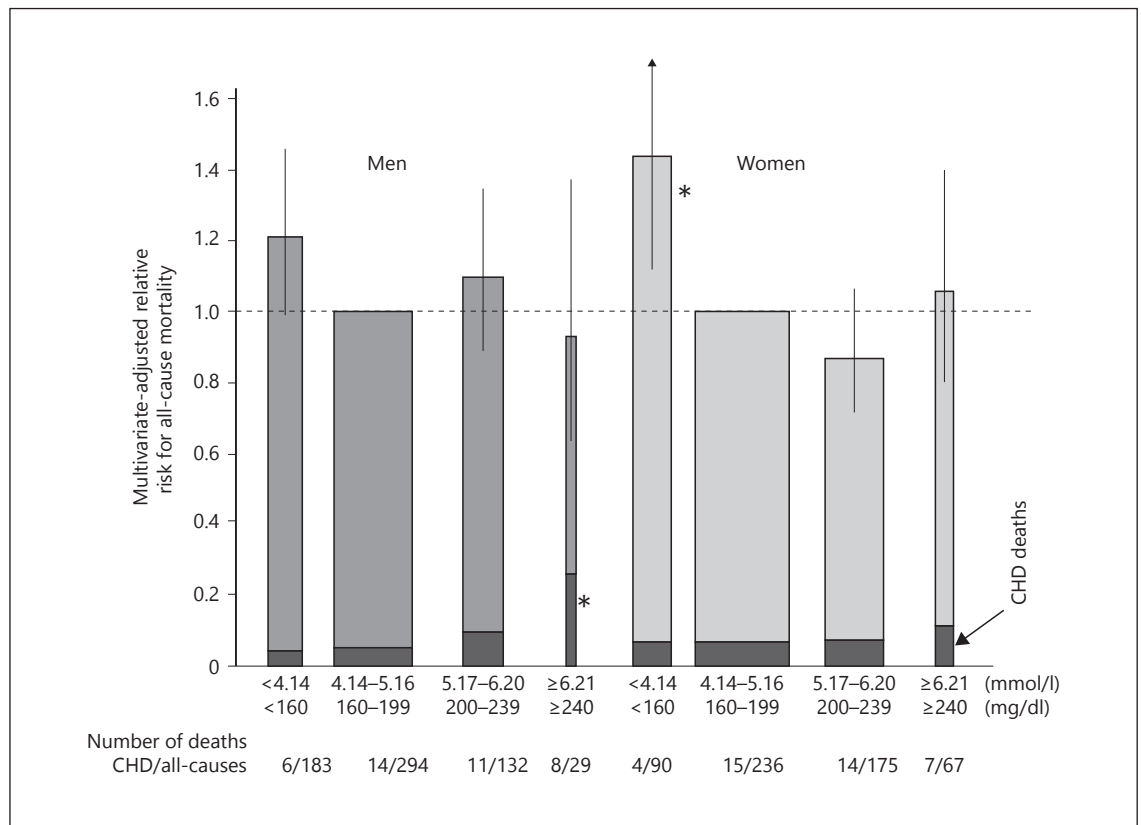
### **(3) Relationship Between Cardiovascular Mortality and Cholesterol in the NIPPON DATA80 Study**

In this section, we describe a few other important results from the NIPPON DATA80 studies. One of the earliest, most important English-language papers presenting NIPPON DATA80 is the abovementioned ND80-13.2, which was published in 2003 [12]. Over the 13.2 years of follow up, 1,206 deaths were recorded among 9,216 community dwelling participants with no past history of cardiovascular disease. These deaths included 462 due to cardiovascular disease and 79 due to CHD. High total cholesterol levels ( $> 6.21$  mmol/l,  $> 240$  mg/dl) were associated with significantly high mortality from CHD in men (relative risk [RR]: 4.76, 95% CI: 1.91–11.9) but not in women. Cholesterol levels were not associated with mortality from total stroke; however, low cholesterol levels ( $< 4.14$  mmol/l,  $< 160$  mg/dl) were associated with mortality from cerebral hemorrhage (RR: 2.70, 95% CI: 1.09–6.68). Also mortality from liver cancer was highest in the lowest cholesterol levels ( $< 4.14$  mmol/l,  $< 160$  mg/dl) if both sexes were combined (RR: 2.40, 95% CI: 1.11–5.18, compared with the reference group of 4.14–5.16 mmol/l, 160–199 mg/dl). (See also fig. 2-16 in Chapter 2 showing the later results of liver disease mortality at 17.3 years in the ND80-17.3 study [1].)

Fig. 5-9 shows the associations between total cholesterol levels and all-cause and CHD mortality in ND80-13.2. The significantly enhanced RR for CHD mortality in men (black bar indicated by an asterisk) suggests the presence of a higher than usual number of participants with FH in the NIPPON DATA80 cohort. At any rate, fig. 5-9 does not at all support the idea that the lower the cholesterol level, the better. Moreover, the RR in this figure was calculated with adjustment for albumin concentration, which served to reduce—unjustifiably, we believe—the good aspect of cholesterol.

The next NIPPON DATA80 paper to be published was ND80-17.3, reporting the 17.3-year follow-up data [1]. We described the results for all-cause mortality according to cholesterol levels earlier in this chapter, so here we focus on mortality from CHD. As shown in fig. 5-10, even women had significantly higher HRs for CHD mortality. This is one of only two cases when limited to single cohort studies and not multi-cohort studies in Japan. The other case showing a relationship between CHD and cholesterol in women is the EPOCH-JAPAN study (see fig. 2-10 in Chapter 2) [15]. In the EPOCH-JAPAN study, we believe that data went through a series of adjustments to obtain significant results, as we discussed in Chapter 2, Section 1. If we look closely at fig. 5-10, the groups of par-





**Fig. 5-9.** Multivariate-adjusted relative risk for all-cause mortality according to total cholesterol level: NIPPON DATA80 study, 13.2 years of follow up [12]. A total of 9,216 community dwelling participants aged  $\geq 30$  years were followed over a 13.2-year period and 1,206 deaths were recorded. Those included 79 deaths from coronary heart disease (CHD). Relative risks were adjusted for age, serum albumin, body mass index, hypertension, diabetes, cigarette

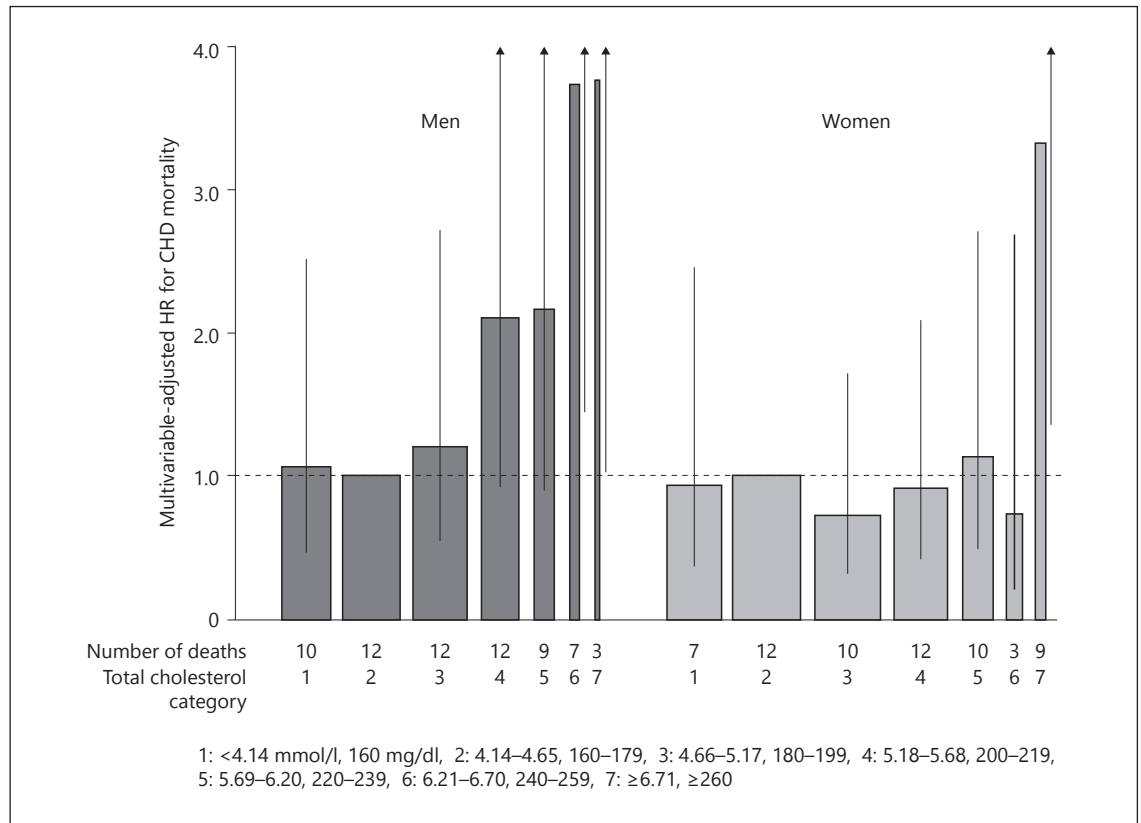
smoking, and alcohol intake. The width of each column is proportional to the number of participants in that group. Black columns represent relative risks for CHD death. The height of a CHD column is proportional to the ratio between the number of CHD deaths and all-cause deaths. \* Significantly different from the reference group (4.14–5.16 mmol/l, 160/199 mg/dl).

participants whose HRs for CHD mortality were significantly higher are just small groups (thin columns). Moreover, there were  $< 10$  deaths in each of these groups. This finding represents the actual situation in Japan: not so many CHD deaths occur. Note also that the HRs for mortality from stroke did not markedly change along with cholesterol values in men or women.

#### (4) The 2012 JAS Guidelines Make No Mention of the Protective Effects of Cholesterol on Stroke

In Section 3 of the summary chapter of JASG2012 describes the stratification (grouping) of absolute risk, as outlined in Section 1 of this chapter. The absolute risk that JASG2012 chose to use was the risk of CHD mortality. JASG2012 explains the decision as follows: ‘*The Na-*

*tional Cholesterol Education Program-Adult Treatment Panel III regards those whose risk of the combined mortality from CHD and morbidity of nonfatal AMI is  $\geq 20\%$  in 10 years as the high risk group. On the other hand, the guidelines in Europe regard those whose risk of mortality from atherosclerotic disease (the sum of cerebrovascular disease, CHD etc.) is  $\geq 5\%$  as the high risk group. Considering the paucity of evidence on the relation of hypercholesterolemia with cerebrovascular disorders [in Japan], we decided that the present Guidelines regard those whose risk of mortality from CHD is  $\geq 2\%$  in 10 years as the high risk group...*’ (emphasis added) [10] (p.15). So, the JASG2012 Research Committee did not actually describe the relationship between cholesterol and mortality from cerebrovascular disease at all. Yet, the phrase indicated in bold is absolutely wrong as we discuss below. Even the most important database that JASG2012 is based on (i.e.,



**Fig. 5-10.** Multivariable-adjusted hazard ratio (HR) for coronary heart disease (CHD) mortality according to serum total cholesterol level: NIPPON DATA80, 17.3-year follow up [1]. The same cohort as shown in Fig. 5-9 was followed for 17.3 years. There were 128 deaths from CHD. With regard to all-cause deaths, see Section 1 of this chapter. HRs were adjusted as for Fig. 5-9. The number of CHD deaths in the highest cholesterol groups (categories 6 and 7)

were <10 in both sexes. It is likely that significance would disappear in the high cholesterol categories if the adjustment for albumin was not included (see Fig. 5-3). The width of each column is proportional to the number of participants in that group. In some groups, the 95% confidence interval lines are not within their columns just for clarity.

the NIPPON DATA80 database) has sufficient data about mortality from stroke. NIPPON DATA80 showed that mortality from stroke tends to be low when serum total cholesterol levels are high. As a matter of fact, mortality from cerebrovascular disease is important because it was higher than that from CHD (10.3% vs. 6.6%, respectively) in 2010 in Japan [16]. The phrase in bold would be better if reworded as follows: ‘Considering there is practically no evidence for the deleterious effects of hypercholesterolemia on stroke as a whole...’ If JASG2012 had presented the data for CHD and stroke combined, then it would be clear to everyone that cholesterol is no longer the enemy in Japan it has been portrayed as.

Nevertheless, JASG2012 tries to emphasize in Chapter 14 on cerebrovascular disorders that hypercholesterolemia is a disadvantage for cerebrovascular disorders by citing one of the Hisayama Study papers [17]. The

Hisayama Study started in 1983, and a total of 2,351 Hisayama residents aged ≥40 years with no history of stroke or myocardial infarction were followed for 19 years. During follow up, 271 participants developed stroke. After multivariate adjustment, LDL cholesterol levels were found to be positively associated with the risks of atherothrombotic infarction and CHD (p for trend = 0.02 for atherothrombotic infarction and 0.03 for CHD), whereas LDL cholesterol levels were inversely associated with cardioembolic stroke (p for trend = 0.03), although the number of cases was small (table 5-C). JASG2012 made no mention of this inverse association of LDL cholesterol levels with cardioembolic stroke. Fig. 2-1 in Chapter 2 shows the CHD data for the Hisayama Study [17].

Finally, another Hisayama Study reported the incidence of first-ever cerebral infarction including its sub-

**Table 5-C.** Age-, sex-, and multivariate-adjusted hazard ratio (HRs) and 95% confidence intervals (CIs) for the development of cerebrovascular disease according to low density lipoprotein (LDL) cholesterol quartile: Hisayama study [17]

	LDL cholesterol level quartile				p for trend	
	mmol/l mg/dl No. of participants	≤2.65 ≤102 586	2.66–3.24 103–125 591	3.25–3.88 126–150 585		≥3.89 ≥151 589
Total stroke <sup>#</sup>						
No. of events		56	62	74	79	
HR (95% CI) <sup>  </sup>		1.0	0.94 (0.64–1.38)	1.15 (0.79–1.67)	1.23 (0.84–1.81)	0.16
Atherothrombotic						
No. of events		9	12	9	21	
HR (95% CI) <sup>  </sup>		1.0	1.35 (0.54–3.35)	1.19 (0.45–3.17)	2.84 (1.17–6.93)*	0.02
Lacunar						
No. of events		14	21	25	33	
HR (95% CI) <sup>  </sup>		1.0	1.19 (0.57–2.50)	1.14 (0.69–2.89)	1.69 (0.83–3.43)	0.11
Cardioembolic						
No. of events		14	14	12	6	
HR (95% CI) <sup>  </sup>		1.0	0.75 (0.34–1.63)	0.59 (0.25–1.38)	0.44 (0.12–0.96)*	0.03
Hemorrhagic stroke						
No. of events		19	15	27	19	
HR (95% CI) <sup>  </sup>		1.0	0.71 (0.35–1.47)	1.41 (0.75–2.65)	1.01 (0.50–2.05)	0.53
CHD		See fig. 2-1				

A total of 2,351 inhabitants in Hisayama Town in southern Japan were followed for 19 years. During follow up, 271 participants developed stroke and 144 developed CHD. Adjusted HRs are shown according to LDL cholesterol quartile. <sup>#</sup> Some other subtypes of stroke are not shown here because there was no association between incidence and LDL cholesterol level. <sup>||</sup> HR was adjusted for age, sex, high density lipoprotein cholesterol, triglycerides, systolic blood pressure, fasting blood glucose, body mass index, current smoking, and regular exercise. \* p < 0.05. (Remade with permission from the publisher, with slight modifications.)

**Table 5-D.** Age-adjusted relative risks and 95% confidence intervals of total cholesterol levels for cerebral infarction and its subtypes: Hisayama study [18]

Cerebral infarction n = 144/154 (m/w)	Lacunar n = 81/86	Atherothrombotic n = 29/33	Cardioembolic n = 31/25
		Men	
1.1 (0.9–1.4)	1.2 (1.0–1.5)	1.1 (0.7–1.6)	1.0 (0.7–1.5)
		Women	
1.1 (1.0–1.3)	1.2 (1.0–1.5)	1.4 (1.0–1.9)	0.6 (0.4–0.9)*

Stroke-free subjects (n = 1,621) aged ≥40 years were followed for 32 years from 1961. During this period, 298 cerebral infarctions were recorded. Age-adjusted relative risks were calculated for an increase of 1 mmol/l (39 mg/dl). \* p < 0.05. (Remade with permission from the publisher, with slight modifications.)

types and their risk factors [18] before the abovementioned report [17]. Stroke-free subjects (n = 51,621) aged ≥40 years were followed up for 32 years from 1961. During follow up, 298 cerebral infarctions occurred (167 lacunar, 62 atherothrombotic, 56 cardioembolic, and 13 undetermined subtypes of infarction). Total

cholesterol levels were not markedly associated with these subtypes except for an inverse association with cardioembolic infarction in women (table 5-D). This study [18] was much larger than the previously mentioned one [17], but JASG2012 also neglected to cite this report.

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## Chapter 6 The Latest Edition of the JAS Guidelines (2012) Part II: Other Risk Factors Besides Cholesterol for Coronary Heart Disease

**Summary:** The target levels for low density lipoprotein (LDL) cholesterol in the 2012 JAS Guidelines (JASG2012) are more stringent for smokers than non-smokers. This recommendation probably comes from the assumption that the deleterious effects of smoking on the heart can be mitigated or cancelled out by decreasing cholesterol levels. However, there is no clinical evidence to back up this assumption. In addition, it is not clear why JASG2012 sets target levels for cholesterol in the case of women, given that the absolute risk chart for coronary heart disease (CHD) mortality for women in the NIPPON DATA80 study, which JASG2012 relies heavily on, shows that cholesterol is not a risk factor for CHD mortality. A very clear risk factor for CHD is age. As discussed earlier in Chapter 3, the relationship between CHD mortality and cholesterol levels seems to decrease with age, so we question why the target cholesterol levels become more stringent with age in JASG2012. The issues of statins and the risk factor of diabetes are discussed in detail in Chapter 9.

### **(1) The Risk of Smoking Can Be Reduced by Stopping Smoking Only, Not by Lowering Cholesterol Levels**

Taking up half a page, JASG2012 describes the risk of smoking in Chapter 5, Section 3 and includes the following text [1] (p.46): ‘*Furthermore, it has been shown that [high density lipoprotein] cholesterol levels were increased up to non-smokers’ levels after cessation of smoking [2], and [therefore] smoking directly affects lipid metabolism.*’ The section continues by stating that smoking additively increases the risks for incident CHD and cerebral infarction if one also has metabolic syndrome [3, 4]. However, it makes no mention of an additive relationship of the effects of LDL cholesterol and smoking on cardiovascular disease, despite going on to recommend more stringent target levels for LDL cholesterol for smokers than non-smokers. The additive effects of smoking are shown only in figure 2 (and identical figure 7) in JASG2012 (see fig. 5-6 in Chapter 5 of this supplementary issue), but, as we discussed in the previous chapter, there are a number of serious short-



comings with this figure, chiefly because too few CHD deaths in the derivative NIPPON DATA80 study [5] were used to construct figure 2 (see fig. 5-7 in Chapter 5). JASG2012 presumably gives the more stringent target levels for smokers based on the assumption that the deleterious effects of smoking on the heart can be mitigated or cancelled out by decreasing cholesterol levels. However, we argue that there is no empirical evidence that smokers should have more stringent LDL cholesterol level targets than non-smokers (see fig. 5-5 and table 5-A in Chapter 5 for how JASG2012 calculates the absolute risk for CHD death). Moreover, JASG2012 provides no citations to support this recommendation either. We advocate instead that if patients are current smokers, the best thing for them to do to reduce their risk for incident CHD is to stop smoking. Reducing their cholesterol levels is not the answer.

## **(2) The 2012 JAS Guidelines Give Target Levels for Low Density Lipoprotein Even for Women**

Table 6-A summarizes the results of Japanese cohort studies examining the association between cholesterol levels and CHD in women [5–14]. On the whole, there is no definitive evidence that hypercholesterolemia in women is a risk factor for CHD. If we focus on CHD mortality (upper half of the table), which is more reliable than CHD incidence (bottom half), we can see that cholesterol has nothing to do with CHD mortality. As an exception, however, among the NIPPON DATA80 series of studies, the study with a follow-up period of 17.3 years showed that high cholesterol levels were a risk factor for CHD death even in women [6]; however, there were in fact only 9 CHD deaths in the highest cholesterol category (total cholesterol  $\geq 6.71$  mmol/l,  $\geq 260$  mg/dl) (fig. 5-10 in Chapter 5 in this supplementary issue). If we look at the right side of fig. 5-5 (panel A, see Chapter 5), we again see that we need not worry about cholesterol in women. From this summary of Japanese cohort study results in table 6-A, the main point of interest is shown by the results of the Jichi Medical School Cohort Study [9]: CHD mortality is most likely to be significantly inversely correlated with total cholesterol levels, although no p value calculation for this relationship is given.

The results on CHD incidence in the bottom half of table 6-A look somehow different from those on CHD mortality, and this is chiefly because the former is not as reliable a measure as the latter—sometimes physicians' subjective decisions are important in determining incidence, whereas mortality can be determined easily and

confirmed by a third party. Two out of the four studies on CHD incidence showed a positive association with total or LDL cholesterol levels. One of these two studies, the JALS-ECC Study, is a combination of 10 cohorts [12]. With so many cohorts, complete compliance with the study protocol in every research group might have been difficult. Moreover, selection bias might have occurred. The second study, the Japan Diabetes Complication Study, analyzed patient data collected from 59 medical institutes [14] and similarly was likely to have suffered from selection bias. The mean number of patients was only about 30 per medical institute, so researchers in those institutes might have selected those patients who were cooperative with medical staff and study coordinators. Thus, we should interpret the results for CHD incidence more carefully than we may think at first glance.

On the whole, JASG2012 encourages physicians to prescribe more lipid-lowering agents, and statins in particular. But in certain areas of medicine, treatment does more harm than good, and we believe that hypercholesterolemia is just such an area. For women with no history of cardiovascular disease, the association between high cholesterol levels and CHD mortality has not actually been established. By raising this issue, we hope that JASG2012's recommendation for these women to receive lipid-lowering agents will be revisited and ultimately withdrawn.

## **(3) The 2012 JAS Guidelines Give More Stringent Target Levels for Low Density Lipoprotein Cholesterol with Age**

The relationship between age and atherosclerosis is described in Chapter 5, Section 4 of JASG2012 as follows: '*Aging is a strong risk factor for atherosclerotic disease not only in Europe and the United States but also in Japan ... (a few lines on epidemiological studies are deleted for the sake of simplicity) mortality and morbidity of atherosclerotic disease clearly increase from the age of 45 and 55 in men and women, respectively.*' We agree that aging is a clear risk factor for atherosclerosis. However, JASG2012 does not cite any evidence for why it gives more stringent target cholesterol levels for the elderly than for younger people (see fig. 5-5 and table 5-A in Chapter 5 in this supplementary issue). Let's return to fig. 3-4 in Chapter 3. The relative proportion of people with familial hypercholesterolemia and other similar genetic disorders who have high mortality from CHD gets smaller and smaller with age because these people

**Table 6-A** Summary of the relationship between cholesterol level and coronary heart disease (CHD) in Japanese women (cohort studies)

Name of study	Publication year and reference	Figure or table in this issue	Endpoint	No. of female participants	Follow-up years	Remarks (measured cholesterol)
<b>CHD mortality</b>						
NIPPON DATA80 (19 years)	2006 [5]	Fig. 5-5 Panel A (R)	CHD death	5,255	19	Apparently no relationship (total cholesterol)
NIPPON DATA80 (17.3 years)	2007 [6]	Fig. 5-10	CHD death	5,181	17.3	Positive. HR for levels $\geq 6.71$ mmol/l ( $\geq 260$ mg/l) was 3.33 (1.35–8.18) (total cholesterol)
Isehara Study	2008 [7]	Fig. 1-2 (B)	IHD death	13,591	11	No relationship (LDL cholesterol)
Ibaraki Prefecture Health Study	2010 [8]	Fig. 1-1	CHD death	60,417	10.3	No relationship (LDL cholesterol)
Jichi Medical School Cohort Study	2011 [9]	Fig. 2-8	AMI death	7,495	11.9	Most likely a significant inverse correlation. See the legend to fig. 2-8 (total cholesterol)
EPOCH-JAPAN	2012 [10]	Fig. 2-10 Fig. 2-11	CHD death	38,540 10 cohorts	10.3	Positive trend for aged 40–69 years. No relationship for 70–89 years (total cholesterol)
<b>CHD incidence</b>						
JPHC Study	2009 [11]	none	CHD	21,685	>10	No relationship (total cholesterol), but positive in men (1.34; 1.17–1.53, per 1-SD increment of cholesterol)
JALS-ECC	2010 [12]	Fig. 2-6	AMI incidence	13,477 10 cohorts	7.6	Positive trend. However, there was only 1 case in the reference group (lowest total cholesterol). Mortality data were not available
Suita Study*	2011 [13]	Fig. 2-3	CHD event**	2,628	13	High LDL cholesterol levels ( $\geq 4.14$ mmol/l, 160 mg/dl) were not associated with CHD events in either age group, <65 or $\geq 65$ years
Japan Diabetes Complications Study	2012 [14]	none	CHD incidence	1,771 diabetics 59 institutes	8	Positive trend. LDL cholesterol was $3.31 \pm 0.79$ mmol/l for women without CHD and $3.64 \pm 0.79$ for women with CHD. No CHD mortality data were available

IHD = Ischemic heart disease; AMI = acute myocardial infarction; HR = hazard ratio; LDL = low density lipoprotein.

In the case of CHD mortality, only a limited number of studies showed a positive relationship with cholesterol. CHD incidence studies are not as reliable as CHD mortality studies because diagnosis of nonfatal CHD partly depends on physicians' subjective judgments.

\* See fig. 2-2 for another data set from the Suita Study, with a mean follow-up period of 11.9 years. No relationship was observed between myocardial infarction incidence and LDL cholesterol level. \*\* Coronary artery disease and CHD were interchangeably used in the original report.

may die at an early age. This fact in itself suggests that the association between cholesterol levels and CHD mortality becomes weaker and weaker as a cohort ages. And indeed this is the case, as is beautifully illustrated in fig. 3-3 in Chapter 3 (see table 3-B for a summary). We can see that age is not at all a factor to consider in making the cholesterol level treatment goals more stringent.

It is just the opposite. As we age and become elderly, we probably need to increase our cholesterol levels, since people with high cholesterol levels have better longevity than those with low cholesterol levels.

In fact, reference ranges of cholesterol levels for Japanese women were very recently revealed to be completely opposite to the recommendation by JASG2012 in which

**Table 6-B.** Reference values for low density lipoprotein cholesterol obtained from healthy people, issued by the Japan Society of Ningen Dock [15]

Men		Women		Previous reference values, mg/dl (mmol/l)
age, years	mg/dl (mmol/l)	age, years	mg/dl (mmol/l)	
30–80	72–178 (1.86–4.60)	30–44	61–152 (1.58–3.93)	60–119 (1.55–3.08)
		45–64	73–183 (1.89–4.73)	
		65–80	84–190 (2.17–4.91)	

Note that the reference values in women increase with age.

target cholesterol levels decrease with age. The Japan Society of Ningen Dock, a society for medical workers in charge of health check-ups, issued a preliminary report on reference values of the items assessed in health check-ups [15]; the report was compiled as joint research with the National Federation of Health Insurance Societies. These completely new reference values were obtained from a group of 10,000–15,000 super-healthy subjects as follows: from data on 1,500,000 subjects who took a health check-up, 340,000 healthy subjects were extracted using a standard method [16], then one-seventh were randomly selected and further screened using Ichihara's method [17], and the ranges of these supposedly healthy values were then calculated. These preliminary values were reported to the Ministry of Health, Labour and Welfare of Japan as well as released to the media. Table 6-B shows the relevant

part of the reported material. The important point is that the supposedly healthy ranges of LDL cholesterol values proposed by the Japan Society of Ningen Dock are much broader than those given by JASG2012, and these values do increase with age in the case of women, which is completely opposite to what is stated in JASG2012. There is also the possibility that these reference LDL cholesterol values are somewhat lower than they should be because individuals with a body mass index (BMI)  $\geq 25$  were not included in their calculation for LDL cholesterol. Interestingly, their calculated reference BMI values are 18.5–27.7 for men and 16.8–26.1 for women [15]. If they had included men with BMI 25–27.7 and women with BMI 25–26.1, who are likely to have higher cholesterol levels than those who have BMI  $< 25$ , the calculated reference values for cholesterol would probably have been higher.

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# Chapter 7 The Latest Edition of the JAS Guidelines (2012)

## Part III: Cholesterol-lowering Drugs and Diets

**Summary:** The most influential statin trial in Japan, the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, unfortunately had some serious flaws. For example, the diet recommended to both the statin plus diet group and the diet alone group is now known to be harmful, having more trans fatty acids and less n-3 fatty acids, and was, in fact, coronary heart disease (CHD) inducing. Also, the statin plus diet group did not likely stick to the diet because they and their doctors knew that their cholesterol levels were decreasing and probably attributed this to the statins. However, the control participants did stick to the actually harmful diet (as this was the only major intervention recommended to them to reduce their risk for CHD) and had a higher occurrence of CHD than the statin plus diet group. Other intervention studies with statins were also flawed. Among them, the Japan Lipid Intervention Trial (J-LIT), the most cited study in the 2012 JAS Guidelines (JASG2012), did not have its own control group. JASG2012 cited it as a cohort study and made no mention of the increased all-cause mortality that J-LIT found in participants whose cholesterol levels decreased markedly. Ingesting a diet rich in saturated fatty acids has not been shown to be harmful in Japan—actually the reverse is the case—but JASG2012 recommend a diet lower in saturated fatty acids. We close the chapter by discussing whether the evidence currently available supports this recommendation.

### (1) Serious Flaws in the MEGA Study

The MEGA Study, often billed as the most influential statin trial in Japan, was designed as a prospective randomized, open-labeled, blinded-endpoint (PROBE) study [1]. As mentioned later, however, randomization appears to have been broken due to a protocol violation. According to the index of JASG2012 [2], these guidelines cite the MEGA Study nine times, making it the third most cited study after the J-LIT [3] (see the next section for details) and NIPPON DATA80 (see Chapter 5). Because J-LIT is described as a cohort study in JASG2012, the MEGA Study is essentially the only clinical trial with a seemingly valid control group (only half-valid, though, as discussed below) that JASG2012 refers to. Consequently, the MEGA Study holds great meaning in any discussion of JASG2012 and warrants a close look at all aspects.

Let's start with the study protocol. Men and postmenopausal women weighing  $\geq 40$  kg, aged 40–70 years, and with total cholesterol values of 5.69–6.98 mmol/l (220–270 mg/dl) were enrolled between February 1994 and March 1999. Note that this period is of critical importance in understanding the nature of the then diet, as we discuss in subsequent paragraphs. Individuals with familial hypercholesterolemia (FH) or a history of coronary heart disease (CHD) or stroke were excluded.



Participants were randomized to either treatment with diet alone ( $n = 3,966$ ) or diet plus the statin pravastatin (10–20 mg/day,  $n = 3,866$ ). The follow-up period was initially scheduled for 5 years, but ‘on the basis of recommendations from the data and safety monitoring committee, the study was continued for an additional 5 years to increase the number of events’ [1]. This means that the committee considered there were too few events to obtain significant results—this extension of the study, as we see it, is a clear protocol violation. Participants in both groups were counseled to follow the National Cholesterol Education Program step I diet<sup>1</sup> compiled in the United States [4]. In the diet group alone, intervention involved following the step I diet throughout the study period. Physicians could prescribe mild hypolipidemic drugs (e.g.,  $\gamma$ -oryzanol, riboflavin butyrate, and pantothenic acid) if they deemed that such treatment would be useful to prevent dropout. In the diet plus pravastatin group, intervention was started at pravastatin 10 mg daily. Data were gathered every 3–6 months, and the primary composite endpoint was the first occurrence of CHD, which included fatal and non-fatal myocardial infarction (MI), angina, cardiac sudden death, and a coronary revascularization procedure. (While we’re talking about the endpoint, we should mention that the last two letters of ‘PROBE’ stands for ‘blinded endpoint’; however, in the case of intervention studies with a composite endpoint, such as the MEGA Study, the term ‘blinded’ endpoint isn’t really appropriate because its primary composite endpoint contains almost every event related with CHD.)

The results of the MEGA Study are shown in fig. 7-1 and table 7-A. At first glance, there are fewer CHD events in the diet plus pravastatin group than in the diet alone group, but this is not the exact picture when we look at the study more closely.

First, a check of the mathematics raises some questions. If we look at the straight part of the solid curve in fig. 7-1, it seems very long for intervention studies of this scale; that is, no CHD events occurred over >13 months

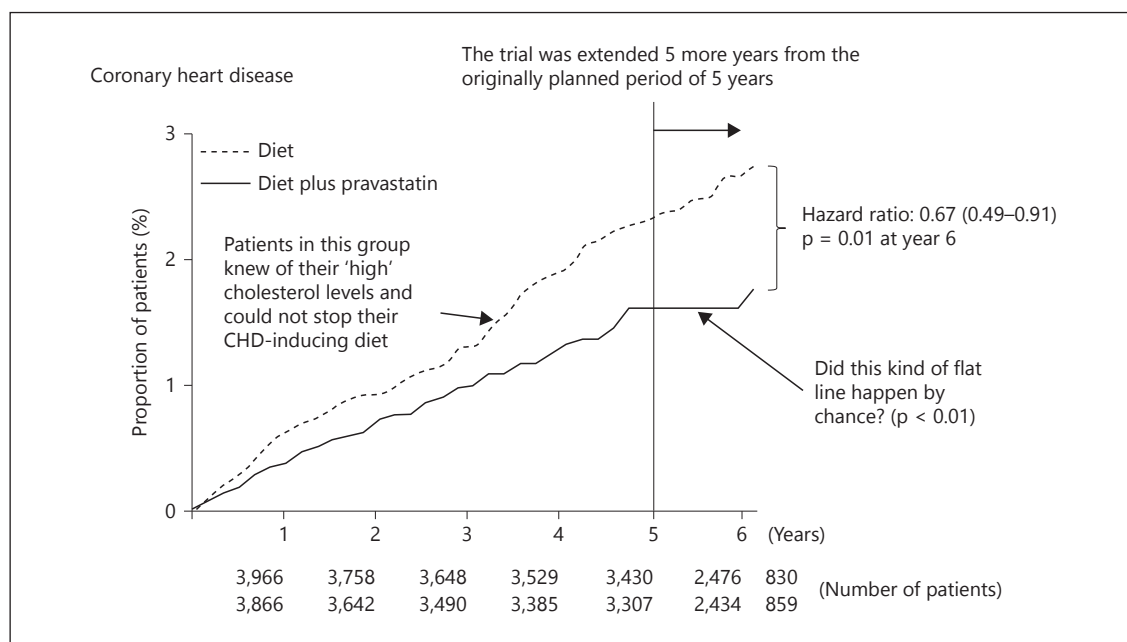
<sup>1</sup> This step I diet was not popular outside of the trial among the general public or even among the study’s participating physicians and dietitians. Briefly, the dietary education provided in the MEGA Study consisted of calorie restriction (25–30 kcal/kg of body weight, 105–125 J/kg of body weight), calorie intake from fat between 20–25%, restriction of cholesterol intake below 300 mg/day, and increased intake of polyunsaturated fatty acids (concretely, linoleic acid) rather than saturated acids. It was recommended that butter be replaced with margarine and that fatty fish be avoided because it was rich in cholesterol.

in the diet plus pravastatin group. We thought this needed further evaluation and decided to calculate how often this type of phenomenon appears. We found that it would have a <1% probability of occurring by chance alone; in other words, only once in every 100 plus studies (see Appendix 3 at the end of this section for how we obtained this result of  $p < 0.01$ ). The hazard ratio for CHD in the diet plus pravastatin group of 0.67 (0.49–0.91,  $p = 0.01$ ) indicates that this did not happen just by chance though. However, the authors of the MEGA Study insist that the straight line indicated by the bold arrow in fig. 7-1 happened just by chance even though the  $p$  value was even smaller than that for the hazard ratio difference ( $p < 0.01$  vs.  $p = 0.01$ ). It seems likely that randomization of this study was broken at the start point of that straight line.

Second, this study was an open-label study and participating physicians were presumably pro-statin, otherwise they wouldn’t have participated in the study. Therefore, the differences in angina and revascularization events between the two participant groups should be discounted. Both of these events were dependent on physicians’ subjective judgment (Chapter 2, Section 1 and Chapter 6, Section 2), especially if the physicians viewed those patients who were not receiving the statin to be at higher risk for CHD than those receiving it. If we discount these two events that are open to subjective bias, there would have been no significant difference between the two groups (see the numbers in bold in table 7-A).

Third, total cholesterol levels decreased by only 1–3% over the first 5 years of intervention in the diet alone group, compared to a decrease of 12% in the diet plus pravastatin group. Naturally, participants in the diet alone group, with encouragement from their physicians, tried hard to stick to the diet to decrease their cholesterol levels. Unfortunately though, the diet they were recommended according to the thinking of that time was not appropriate nutritionally for CHD prevention. Butter was replaced with margarine containing a lot of linoleic acid and/or trans fatty acids, and fatty fish was avoided because of high cholesterol content. In fact, this diet was CHD *inducing*. Participants in the diet plus pravastatin group, however, did not stick to the diet because they already knew that their cholesterol levels were decreasing and probably attributed this to the statin. This is one of the reasons for the lower occurrence of CHD in the pravastatin group.

Fourth, the ratio of participants who could *not* be confirmed to be alive was significantly higher in the



**Fig. 7-1.** Kaplan-Meier curves for the primary endpoint of first occurrence of coronary heart disease (CHD): MEGA Study [1]. Patients with hypercholesterolemia without any history of CHD or stroke were randomly assigned to the diet or diet plus pravastatin 10–20 mg group. The mean follow-up period was 5.2 years. CHD was significantly lower in the diet plus pravastatin group than in the diet alone group (66 versus 101 events,  $p = 0.01$ ). In the diet alone group, patients could not easily stop their CHD-inducing

diet because their total cholesterol levels decreased by 1–3% only, whereas those in the diet plus pravastatin group decreased by their levels 12% during intervention. Patients in the latter group might not have stuck to the diet as strictly as in patients in the diet alone group as they knew their levels were decreasing. See also the footnote of table 7-A and the text for details. (Remade with permission from the publisher, with slight modifications.)

**Table 7-A.** Results of the MEGA Study [1]

Endpoints	No. of events (per 1,000 person-years)		Hazard ratio (95% CI)	p-value
	diet group	diet plus pravastatin group		
Coronary heart disease	101 (5.0)	66 (3.3)	0.67 (0.49–0.91)	0.01
Myocardial infarction	33 (1.6)	17 (0.9)*	0.52 (0.29–0.94)	0.03
Fatal	3 (0.1)	2 (0.1)	–	–
Non-fatal	30 (1.5)	16 (0.8)	–	–
Cardiac sudden death	10 (0.5)	5 (0.2)	0.51 (0.18–1.50)	0.21
Angina	<b>57 (2.8)</b>	<b>46 (2.3)</b>	0.83 (0.56–1.23)	0.35
Coronary revascularization	<b>66 (3.2)</b>	<b>39 (2.0)</b>	0.60 (0.41–0.89)	0.01

CI = Confidence interval.

Incidence of coronary heart disease was significantly lower in the diet plus pravastatin group than in the diet alone group. However, the biggest difference between the two groups was found in coronary revascularization (66–39 = 27). At least 57% [(101–33–10)/101] and 67% [(66–17–5)/66] of the primary endpoint events were either angina or revascularization in the diet alone group and diet plus pravastatin group, respectively. These two events (bold values) were influenced by physicians' subjective judgments, and we speculate that they occurred more in the diet alone (control) group than in the diet plus pravastatin group because almost all participating physicians in this trial were pro-statin physicians who believed patient prognosis was better with statins. See the text for details. \* The value 17 is written according to the original paper [1], but must be 18. (Remade with permission from the publisher, with slight modifications.)

pravastatin plus diet group than in the diet alone group. Hama et al. collected relevant data from published papers about the MEGA Study and from the study's website (<http://www.mega-study.jp/mega-study.html>) and also obtained a Japanese version of a slide set on the MEGA Study presented at the American Heart Association Scientific Sessions, 2005 [5]. According to the Japanese slides, 13.5% of participants in the pravastatin plus diet group compared to 11.9% of participants in the diet alone group could not be confirmed to be alive (odds ratio: 1.16, 1.01–1.33,  $p = 0.031$ ). These data were not included in the most important MEGA Study report, however [1]. Moreover, participants who were diagnosed with cancer within the first 6 months of the study were excluded from the analysis—this is stated only in the Safety Section of the Results on the study's website and in the Japanese slides. It's unclear to us why details about these excluded cancer patients were not reported and why was it necessary to exclude them from the analysis.

It would seem, then, that there is little real evidence for the effectiveness of pravastatin reported by the MEGA Study given, for example, the issues with the study protocol, the unsuitable diet recommended, and the likely break in randomization. Regrettably, JASG2012 viewed the MEGA Study findings as the most important evidence for patients with dyslipidemia to receive statin treatment, and ultimately this means that JASG2012, too, has no hard evidence for recommending statins.

### **Appendix 3: Detailed Method for Calculating the Probability of There Being No Events Within >13 Months in the Diet Plus Pravastatin Group**

The absence of events in this >13 month period are denoted by the straight black line, indicated by the bold arrow, in Fig. 7-1.

First, the mean period between two consecutive events and its SD were calculated in the diet plus pravastatin group during the first 57.5 months of the study (the straight line started appearing at 57.5 months). The mean was 0.9 months [57.5 months/65 cases (66 cases—the last case at the end of study)]. The SD was calculated from the values collected for all periods between two consecutive events using the MEGA Study's original figure (downloaded from the study website and enlarged). A slightly modified figure is presented as fig. 7-1 here. This procedure for SD calculation is not free from error, so we added a safety margin<sup>2</sup> of 50% and  $SD = 0.9$  was obtained. Then the mean  $\pm$  SD ( $0.9 \pm 0.9$ ) was divided by the prod-

<sup>2</sup> 'Safety margin' here means that calculations were conservative; in other words, they were performed such that the final  $p$  value was higher.

uct of  $859^3/3,596^4$ , the ratio between the numbers of participants in the diet plus pravastatin group at the end of the study (6 years) and during its first 4 years, and  $3.8 \pm 3.8$  was obtained.

Then the probability of the occurrence of a straight line 13.1 months' long was calculated under the assumption that the next CHD event would occur at an interval of  $3.8 \pm 3.8$  months and that this occurrence was normally distributed. The probability was calculated as  $<0.01$  using a normal distribution table.

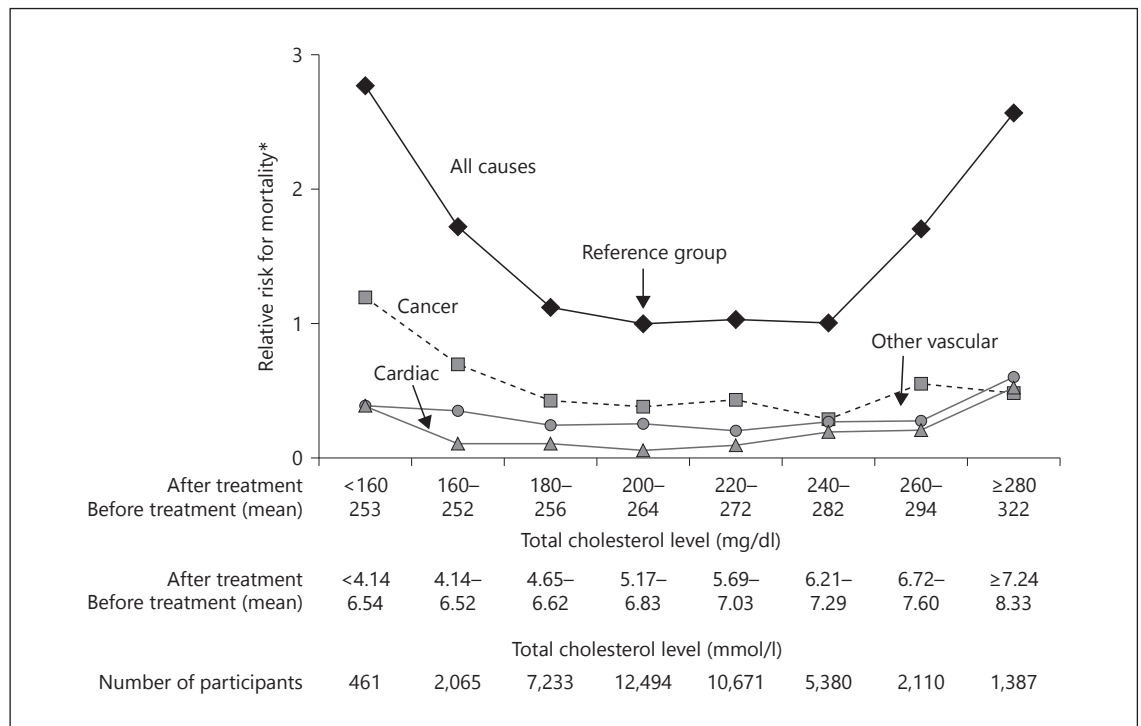
Strictly speaking, the calculation methods used above may have some errors, but the safety margin introduced during calculation should be sufficiently large.

### **(2) The 2012 JAS Guidelines Cite J-LIT, an Intervention Study, as a Cohort Study**

J-LIT including its sub-analyses is cited 13 times in JASG2012, making it the most cited study according to the JASG2012 index [3, 6]. As indicated by its name, J-LIT was a standard intervention trial. However, JASG2012 made use of its data referring to it only as a kind of cohort study. J-LIT, the largest statin trial ever performed in Japan, was a 6-year, nationwide (cohort) study of 47,294 patients aged 35–70 years who had serum total cholesterol levels  $\geq 220$  mg/dl (5.69 mmol/l). All patients were treated with open-label simvastatin (5–10 mg/day). The aim of the study was to determine the relationship between CHD occurrence and serum lipid concentrations during low-dose simvastatin treatment. fig. 7-2 shows the relative mortality due to all-causes, cancer, cardiac disease, and other cardiovascular disease in 41,801 participants with no history of CHD. Because all of the participants were treated with simvastatin, it is not really appropriate to extrapolate these results to the general population not taking any lipid-lowering agents. However, JASG2012 used data from subgroup analyses in this cohort to indicate the risk posed by high cholesterol levels in individuals with diabetes (JASG2012, p.35, 87, and 93), individuals with a family history of CHD (similarly, p.47), and elderly individuals (similarly, p.103 and 104). Using data from another subgroup analysis in this cohort, JASG2012 claims that the relative risk for cerebral infarction in women with low density lipoprotein (LDL) cholesterol levels  $\geq 160$  mg/dl (4.14 mmol/l)

<sup>3</sup> Instead of the number of patients at the end of the study, the mean number of patients during the 6th year might be better, but the mean number was not available. So, again to provide a large safety margin, the smaller number of 859 was used.

<sup>4</sup> The mean number of patients in the first 4 years in the statin group:  $(3866+3642+3490+3385)/4 = 3,596$  (see the lower part of fig. 7-1).



**Fig. 7-2.** Relationship between serum total cholesterol level and mortality during simvastatin therapy: J-LIT Study [3]. A total of 41,801 subjects aged 35–70 years with no history of coronary heart disease (cholesterol levels  $\geq 220$  mg/dl, 5.69 mmol/l) were treated with simvastatin 5–10 mg/day for 6 years. The group of patients with cholesterol levels 200–219 mg/dl (5.17 and 5.68 mmol/l) served as a reference group. \* The relative risk for all-cause mortal-

ity was adjusted for age at baseline, sex, hypertension, diabetes mellitus, and smoking habit. Relative risks of death due to cancer, cardiac disease, and other vascular disease were calculated as follows: (relative risk for all-cause mortality in each cholesterol group)  $\times$  (ratio of number of deaths due to specific disease and all-causes in the same group).

is two-fold higher than in women with LDL cholesterol levels  $< 120$  mg/dl (3.10 mmol/l) (similarly,  $p = 1.09$ ). These statements in JASG2012 based on the J-LIT subgroup analyses indicate how little evidence the authors of JASG2012 had at hand.

The proportion of patients with FH in the primary prevention cohort was 2.5% [6], which is  $> 12$  times higher than the general population. This is one of the reasons why all-cause mortality showed a U-shaped curve. Fig. 7-2 suggests to us that subjects with total cholesterol values  $< 260$  mg/dl (6.72 mmol/l) should not be treated because all-cause mortality below that value increased with treatment.

There are a couple of very important reasons (biases) why mortality from cardiovascular disease ('cardiac' and 'other vascular' in fig. 7-2) was increased in those with high cholesterol levels during treatment. Table 7-B shows the reduction rates of total cholesterol in each cholesterol category shown in fig. 7-2. Both absolute and relative reductions by statin treatment decreased as cholesterol lev-

els, whether measured at baseline or during treatment, increased. It is likely that compliance with treatment in participants with higher total cholesterol levels, either at baseline or during treatment, were poor. Relative reductions in total cholesterol were very low in the highest cholesterol levels; namely 0.11, 0.08, and 0.07 in the order of increasing levels of cholesterol in the highest three groups. The higher incidence of cardiovascular disease in these highest cholesterol groups can be partly explained by low compliance, which most likely correlated with compliance with other treatment such as smoking cessation and increased exercise. Although ignoring dietary advice was actually healthier sometimes before 2000, the year that the J-LIT findings were reported (see Section 1 above and also below), because all J-LIT participants were receiving statin treatment, dietary advice was anyway probably not rigorously provided.

There is another important aspect we should note. As described above, this 'cohort' was composed of 2.5% of patients with FH ( $> 1,000$  participants). The numbers of



**Table 7-B.** Change in total cholesterol (TC) level in the primary prevention cohort of J-LIT according to level during treatment [3]

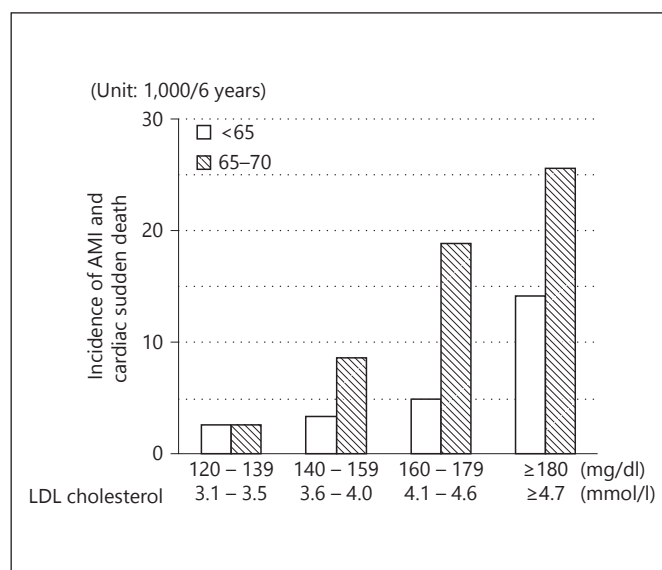
(A)	Grouping according to TC level during treatment	(mg/dl) (mmol/l)	<160 <4.14	160–179 4.14–4.65	180–199 4.66–5.17	200–219 5.18–5.68	220–239 5.69–6.20	240–259 6.21–6.71	260–279 6.72–7.23	≥280 ≥7.24
(B)	Mean baseline TC level	(mg/dl) (mmol/l)	253 6.54	252 6.52	256 6.62	264 6.83	272 7.03	282 7.29	294 7.60	322 8.33
(C)	Estimated mean TC level during treatment	(mg/dl) (mmol/l)	145 3.75	170 4.40	190 4.91	210 5.43	230 5.95	250 6.47	270 6.98	298 7.71
(D)	Absolute reduction (B–C)	(mg/dl) (mmol/l)	<b>108</b> 2.79	<b>82</b> 2.12	<b>66</b> 1.71	<b>54</b> 1.40	<b>42</b> 1.09	<b>32</b> 0.83	<b>24</b> 0.62	<b>24</b> 0.62
(E)	Relative reduction (D/B)		<b>0.43</b>	<b>0.33</b>	<b>0.26</b>	<b>0.20</b>	<b>0.15</b>	<b>0.11</b>	<b>0.08</b>	<b>0.07</b>

See the legend to fig. 7-2 for an explanation. The mean TC level during treatment (item C) was set at the middle of each cholesterol category [item (A)]. With regard to TC categories <160 and ≥280, mean values were estimated by extrapolation using the values in items (D) and (E). Note that both absolute and relative reductions in TC levels [items (D) and (E), respectively] decreased according to cholesterol level during treatment, which suggests that compliance to statins was not good in the high cholesterol groups. (Remade with permission from the publisher, with slight modifications. Items D and E are our calculations.)

participants with the highest and second highest cholesterol levels were only 1,387 and 2,110, respectively, so the proportion of patients with FH was very likely high in both of these groups: this high proportion is one of the most important reasons why their relative risk for cardiovascular disease was high (fig. 7-2). So, the reason for their high relative risk was not their high cholesterol levels, but the high proportion of participants with FH among them.

The findings of J-LIT have also been utilized by a statin manufacturer in its promotional literature. Fig. 7-3 appears in the manufacturer's sales promotion brochure, but is actually only part of a figure from one of the J-LIT study reports (figure 1, panels A and B, in [7]). The original figure (panel A for participants aged <65 years and panel B for those aged 65–70 years) is a kind of modified version of fig. 7-2 in that total cholesterol has been changed to LDL cholesterol. What's important to note is that the brochure presents only the most impressive part of the entire original figure (i.e., the right side of panels A and B in [7]) and in doing so exaggerates the relationship between cholesterol and CHD incidence. The figure seems to show a 10-fold difference in CHD incidence between the highest and lowest LDL cholesterol groups. What we find most concerning is that the leaflet was produced under the supervision of the chief editor of JASG2012.

Another point to mention about J-LIT was that it did not have its own control group. So, to collect reference data, Yoshiike et al. followed a reference cohort with no history of acute myocardial infarction (AMI) for 6 years in the Area-matched Control Study for the Japan Lipid

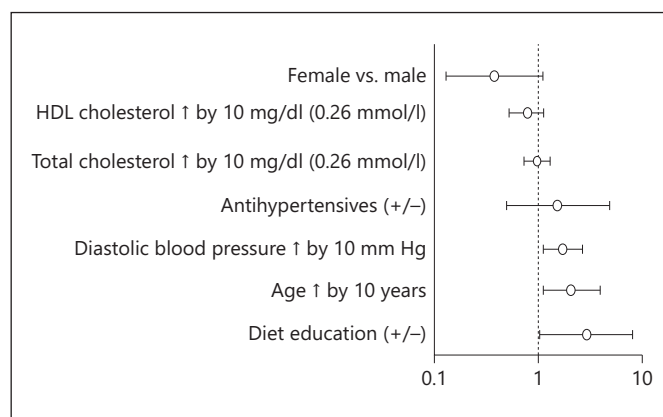


**Fig. 7-3.** Rough reproduction of the important part of a cholesterol campaign brochure published by Daiichi-Sankyo Company, Ltd. The original of this figure appeared in a sales promotion leaflet for pravastatin, a statin produced by Daiichi-Sankyo Company, Ltd. The original data come from one of the J-LIT Study reports (figure 1, panels A and B) [7]. However, note the start point of the X-axis is 120–139 mg/dl (3.1–3.5 mmol/l): the left part of both original panels was deleted in the figure shown here, because the major coronary events were slightly increased in the LDL cholesterol ranges <100 mg/dl (0.26 mmol/l) and 100–119 (2.6–3.0) in the elderly group aged 65–70 years. The all-cause mortality is not shown in the leaflet either. See the text and table 7-B for more problems with this leaflet. The important point for us here is that the Chief Editor of the 2012 JAS Guidelines supervised the making of this leaflet. AMI = Acute myocardial infarction; LDL = low density lipoprotein.



Intervention Trial [8]. They originally hoped to perform a case-control study, but it turned out to be impossible because of a paucity of cases. Their reference cohort comprised 4,918 participants aged 35–79 years who had high cholesterol levels (220–299 mg/dl, 5.69–7.75 mmol/l). When this cohort was established, the following four factors were matched to create a similar cohort as J-LIT's: location, sex, age (in 5-year age brackets), and serum total cholesterol level (6 categories). During the 6-year follow-up period, 26 cases of AMI, 6 cases of suspected AMI, and 4 sudden deaths were registered. The incident rate of AMI+sudden deaths was 1.24/1,000 person-years [8], which is slightly higher than the rate of 0.91 found by J-LIT [3]. Unfortunately, the matching described above was not well balanced enough: the reference cohort comprised 44% men compared with 32% men in J-LIT [6] and the percentage of participants with diabetes was 4.4% in men and 2.9% in women in the reference cohort compared with 15% in J-LIT [3, 8]. Moreover, cases of suspected AMI were also counted as AMI in the reference cohort. All-cause mortality was 2.4/1,000 person-years in the reference cohort (all-cause deaths/1,000 person-years) [8] and estimated to be 3.7 in J-LIT (all-cause deaths/6 years/all participants—those excluded for various reasons) [3]. While it is possible that statin has some toxicity in terms of all-cause mortality, it is not prudent to conclude anything from these results. Nonetheless, there is a very interesting point to be made about this reference cohort study as we discuss next.

The hazard ratios (HRs) for AMI and sudden deaths ( $n = 36$ ) are shown in fig. 7-4. There are two important things to note in this figure. First, total cholesterol level was not the determining factor for AMI. This is borne out by the fact that cholesterol levels were not associated with AMI in the reference cohort as shown in fig. 7-4; details for AMI incidence according to total cholesterol levels are shown in table 7-C. Second, of all the risk factors, dietary education was the biggest risk factor for AMI. This cohort comprised participants with high cholesterol levels and naturally the dietary education they received concerned how to reduce blood cholesterol levels. Thus, given what we learned above about older dietary advice not necessarily always being appropriate, the reason why dietary education was significantly associated with AMI may simply be because the participants with higher cholesterol levels in the reference cohort—who might well have greater opportunities to receive such education because of their higher levels—had higher risk for imminent AMI. When the study was performed, the prevailing concept for re-



**Fig. 7-4.** Hazard ratios for acute myocardial infarction (AMI), including suspected cases, and sudden death: area-matched control study for J-LIT [8]. A total of 4,918 participants aged 35–70 years with high cholesterol levels (220–299 mg/dl, 5.69–7.75 mmol/l) were followed for 6 years. In a multivariate model, hazard ratios were calculated with adjustment for age, sex, systolic and diastolic blood pressure, and receipt of dietary education. The risk associated with diet education was 2.87 (95% confidence interval, 1.03–7.96): diet education at that time actually increased the risk for AMI. HDL = High density lipoprotein.

ducing blood cholesterol levels was to have a higher intake of linoleic acid and a lower intake of cholesterol. It was very unfortunate for the participants that fatty fish, which contains a lot of cholesterol, was to be avoided and they lost the chance for a good intake of eicosapentaenoic acid and docosahexaenoic acid.

Taken together then, we do not think that this reference cohort study [8] really worked as a reference for J-LIT at all, but the finding of a positive relationship between ‘older’ dietary education and CHD is very important when interpreting the results of MEGA Study [1] we discussed in the previous section..

### (3) Flaws in Other Japanese Intervention Studies

#### *The PATE Trial*

The problem we encounter most with Japanese intervention trials is the absence of valid control groups. Furthermore, no double-blind procedures are adopted in long-term trials. One such example is the Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE) trial, which evaluated the efficacy of pravastatin in an elderly population [9]. The trial compared two doses of pravastatin, 5 mg/d and 10–20 mg/d, for a mean period of 3.9 years. The

**Table 7-C.** Number of cases of acute myocardial infarction (AMI) and sudden death cases during the follow-up period of the Area-matched Control Study for J-LIT [8]

	Total cholesterol		No. of participants	AMI + sudden death	
	mg/dl	mmol/l		no. of cases	incidence rate*
Men	220–239	5.69–6.20	1,193	13	1.89
	240–259	6.21–6.71	623	6	1.64
	260–279	6.72–7.23	272	2	1.21
	280–299	7.24–7.75	83	1	1.97
	Subtotal		2,171	22	1.73
Women	220–239	5.69–6.20	1,379	7	0.86
	240–259	6.21–6.71	794	4	0.85
	260–279	6.72–7.23	416	0	0.00
	280–299	7.24–7.75	158	3	3.15
	Subtotal		2,747	14	0.86
Total			4,918	36	1.24

A total of 4,918 participants were followed for 6 years. Those receiving dietary education were 10.5% of men and 18.8% of women. Interestingly, dietary education was the biggest risk factor for AMI and sudden death (see fig. 7-4). When the data in this table are taken into account, the risk of dietary education cannot simply be explained by a possible combination of a very high AMI incident rate and a possible high dietary education rate in participants with hypercholesterolemia. Cholesterol level had nothing to do with AMI (fig. 7-4). Rather it seems that the recommended diet at that time was unsuitable; butter was replaced with margarine, saturated fats were replaced with linoleic acid, fatty fish was replaced with lean fish, etc. \* No. of cases/1,000 person-years. (Remade with permission from the publisher, with slight modifications.)

participants were men and women recruited from 52 participating institutions. As shown in table 7-D, they were all aged  $\geq 60$  years, with or without a history of previous cardiovascular disease, and had serum total cholesterol levels of 220–280 mg/dl (5.69–7.24 mmol/l). They were allocated to either group by the biased-coin minimization method, using history of disease, total cholesterol levels, and research institution as balancing factors. Unfortunately, randomization was not successful with regard to the male to female ratio between the groups, and there was also a significantly higher proportion of men in the low-dose group (24.0%) than in the standard-dose group (17.5%) (table 7-D). Because the primary endpoint of the trial was the combined incidence of any type of fatal and nonfatal cardiovascular events—including angina pectoris, which is highly dependent on the subjective decision of participating physicians—and because the trial was not double-blind, the significantly lower incidence in the standard-dose group than low-dose group should be interpreted with caution (see the bottom half of table 7-D). In fact, the number of cases of angina pectoris in the low-dose and high-dose groups were 10 and 6, respectively (table 7-D) compared with 6 and 8 total number of deaths (the most reliable diagnosis of a cardiovascular event), respectively.

Moreover, this significant difference in primary endpoint was observed in the situation where the proportion of men was 37% higher (6.5% in absolute terms) in the low-dose group than in the high-dose group. Although the study authors performed very complicated subgroup analyses, the value of the results is limited in our view because these subgroup analyses included cases with angina pectoris.

### *The KLIS Study*

We mention this study because the Japan Atherosclerosis Society committees responsible for creating guidelines have referred to the results of KLIS's subgroup analyses a few times in the past, including once in JASG2012. However, we have a number of concerns about the robustness of its findings.

The Kyushu Lipid Intervention Study (KLIS) was originally planned as a randomized control trial to investigate the effects of pravastatin (10–20 mg/day) on the primary prevention of coronary events and cerebral infarction in Japanese men aged 45–74 years with serum total cholesterol levels of 220–299 mg/dl (5.69–7.75 mmol/l) [10]. The follow-up period was 5 years on average. Participants

**Table 7-D.** Participant characteristics at baseline and results in the PATE trial [9]

		Low dose group	Standard dose group
<i>Baseline characteristics</i>			
No. of participants		334	331
Men/women		80/254	58/273*
(men)		<b>(24.0%)</b>	<b>(17.5%)</b>
Total cholesterol (mg/dl)		253±15	253±15
(mmol/l)		6.54±0.39	6.54±0.39
Complications		95 (28%)	82 (25%)
	Myocardial infarction	11 (3%)	11 (3%)
	Angina pectoris	33 (10%)	31 (9%)
	Cerebrovascular disease	48 (14%)	38 (11%)
	Arteriosclerosis obliterans	2 (1%)	3 (1%)
<i>Results: No. of events (deaths)</i>			
Classification of events			
Cardiovascular disease			
	Cerebrovascular disease		
	Cerebral hemorrhage	2	0
	Cerebral infarction	15 (1)	11 (2)
	Transient ischemic attack	1	1
	Subarachnoid hemorrhage	1 (1)	0
	Cardiac disease	7 (3)	4 (3)
	Myocardial infarction	7 (3)	4 (3)
	Angina pectoris	<b>10</b>	<b>6</b>
	Cardiac failure	0	1 (1)
	Arrhythmia	2	2
	Peripheral vascular disorders		
	Arteriosclerosis obliterans	2	2
	Dissecting aortic aneurysm	0	1 (1)
	Left upper limb thrombosis	1	0
	Sudden death	1 (1)	1 (1)
	Total cardiovascular events (deaths)	42 ( <b>6</b> )	29 ( <b>8</b> )**
	Deaths due to other causes	14	6
	Total number of deaths	20	14

A total of 665 participants aged  $\geq 60$  years ( $73 \pm 6$  years) with serum cholesterol levels of 220–280 mg/dl (5.69–7.24 mmol/l) were randomly allocated to either to the low-dose pravastatin (5 mg/dl) group or standard-dose pravastatin (10–20 mg/dl) group and followed for 3–5 years (mean: 3.9 years). It appears difficult to conclude from these results that the higher statin dose was better than the low dose (see the text for details). \*  $p = 0.049$ , Chi-square test; \*\*  $p = 0.046$ , generalized Wilcoxon test, but  $p = 0.096$ , log-rank test. (Remade with permission from the publisher, with slight modifications.)

with primary hypercholesterolemia ( $n = 5,640$ ) were allocated to either the pravastatin group or conventional treatment group. The conventional treatment included lifestyle changes and hypolipidemic medications other than statins (i.e., probucol and bezafibrate). Unfortunately, in this study too, it seems that randomization was not successful. Allocation was performed by the envelop method. Each study physician received at least one set of 4 sealed, numbered envelopes: the first envelope was to be opened only for the first of the physician's eligible patients and the instructions provided in the envelope followed accordingly; the second envelope was to be opened only for the second eligible patient, and so on. In this way, equal numbers of patients were planned to be randomly allocated to two groups. However, it would appear that

this did not go as planned, as can be seen from the fact 3,061 patients were allocated to the pravastatin group and 2,579 to the conventional treatment group, with respective baseline total cholesterol levels of  $259 \pm 26$  and  $246 \pm 20$  mg/dl ( $6.69 \pm 0.70$  and  $6.35 \pm 0.52$  mmol/l,  $p = 0.001$ ) [11]. This suggests that physicians preferred to treat their patients with statins, especially those with very high cholesterol levels, and so often put aside the envelopes for conventional treatment until they reached the envelopes for pravastatin treatment. In addition, we note that originally 5,640 patients were allocated to the two groups, but before data analysis, nearly one third were excluded for various reasons. One of the reports presenting the study results [10], but not the study design paper itself [11], explains this exclusion was made because there were very

few patients with serum total cholesterol  $\geq 300$  mg/dl (7.76 mmol/l) in the conventional treatment group, so they were excluded to secure comparability between the two groups. The statistical analysis section of the paper states: 'As the KLIS was an observation study, a protocol-based analysis was employed with adjustment for coronary risk factors at baseline.' [10] (p.112). We don't really understand what this sentence means, given that the 'I' in the study name stands for 'Intervention'.

### *The MUSASHI-AMI Trial*

The Multicenter Study for Aggressive Lipid-lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction (MUSASHI-AMI) trial [12] is a typical example of a Japanese intervention trial that had weaknesses due to its open-label design. Eligible consecutive patients with AMI (n = 486) who were admitted to 54 medical centers in 28 prefectures in Japan were randomly allocated either to the statin group (standard therapy with open-label treatment with statins) or to the non-statin group (standard therapy) within 96 hours of AMI onset. Those who had used lipid-reducing agents during the previous 3 months and those with FH were excluded. Patients were followed for 24 months, with a mean follow-up period of 416 days. The primary endpoint was a combination of cardiovascular death, nonfatal AMI, recurrent symptomatic myocardial ischemia with objective evidence for emergent rehospitalization, congestive heart failure requiring emergent rehospitalization, and nonfatal stroke. Participant characteristics at baseline and the results are shown in table 7-E. The combined primary endpoint events were 15 and 29 in the statin and non-statin groups, respectively, the absolute risk difference of which was reported 5.2% (p = 0.0433 by log rank test) [12]. The biggest problem with this trial is that the number of nitrate users, which is seriously related to the primary endpoint, in the statin group was significantly lower than in the non-statin group. The absolute difference between them was 11% (94/244–65/237 = 0.11), exceeding double that of the primary outcome (5.2%), and not adjusted for. Another problem is that one of the most important contributors to this 5.2% difference—heart failure requiring emergency rehospitalization (table 7-E)—was not evidence-based. Because this investigation was an open-label trial, physicians' judgment to rehospitalize patients might have been easily biased. The same concern applies to the event of symptomatic myocardial ischemia requiring emergent rehospitalization. Here, 'symptomatic' means that partici-

pating physicians were able to make a subjective decision as to whether their patients had myocardial ischemia, without needing objective evidence. Also, judging the need for 'rehospitalization' is subjective. There is a significant discrepancy between physicians' subjective judgment (events requiring emergent rehospitalization) and objective endpoints (cardiovascular death, nonfatal AMI, and stroke). The number of subjective events was 7 in the statin group and 26 in the nonstatin group, and the corresponding number for objective events was similarly 8 and 3 (p = 0.0018, Chi-square test done by us). Somewhat ironically, this is the most significant result of the MUSASHI-AMI Trial except for changes in cholesterol levels between the groups. If we discount the subjective judgments, the trial would have found no significant findings. Interestingly, the authors of the trial conclude in the abstract of the study report that 'early lipid-lowering therapy with statins decreases recurrent cardiovascular events, in particular, congestive heart failure' [12] (p. 1165).

An important finding in this trial is that, without including patients with FH and users of lipid-reducing agents, the mean total cholesterol value in consecutive patients with AMI was 207 mg/dl (5.35 mmol/l) (see table 7-E); this value is rather low. Assuming that cholesterol values are normally distributed when FH patients are excluded, we estimate from table 7-E that 78% of all patients who had AMI in this trial had total cholesterol levels  $< 220$  mg/dl (5.69 mmol/l). This finding indicates that the anti-cholesterol campaign does not work in Japan: the majority of AMI cases occurred in the so-called normolipidemic range. Data on all-cause mortality in the two groups are not available.

### **(4) Should Saturated Fatty Acids Be Reduced?**

The recommendations for lipid intake described in the section on diet in Chapter 7 of JASG2012 [2] can be summarized as follows: reduce the intake of saturated fatty acids (SFAs), cholesterol, and trans fatty acids and increase the intake of n-3 fatty acids in fish. But is there any reliable evidence for reducing SFA intake in the Japanese population? The answer is 'No'. Researchers in Japan have never succeeded in reducing CHD by limiting SFA intake. This notion is more or less applicable the world over [13]. Even though some slight positive effect was seen decades ago in Western countries for replacing SFAs with vegetable oil containing polyunsaturated fatty acids (PUFAs), the beneficial effects of the replacement can be explained by the treatment of n-3 PUFA deficiency with  $\alpha$ -linolenic acid (an



**Table 7-E.** Participant characteristics at baseline and results in the MUSASHI-AMI Investigation [12]

Characteristics and primary events	Statin group	Nonstatin group	p-value
<i>Baseline characteristics</i>			
No. of participants	237	244	
Men	190 (80)*	193 (79)	
Total cholesterol (mg/dl)	208±17	206±17	
(mmol/l)	5.38±0.44	5.33±0.44	
Previous myocardial infarction	10 (4)	15 (6)	
Hypertension	149 (63)	142 (58)	
Current smoking	131 (55)	130 (53)	
Diabetes mellitus	83 (35)	61 (25)	
ST-segment elevation myocardial infarction	208 (88)	219 (90)	
Appearance of new Q wave	161 (68)	180 (74)	
Nitrates	65 (27)	94 (39)	p < 0.05**
<i>Results: primary endpoint events</i>			
No. of participants	237	244	
Cardiovascular death	2	1	
Nonfatal acute myocardial infarction	3	0	
Symptomatic myocardial ischemia requiring emergent rehospitalization	6	17	
Heart failure requiring emergent rehospitalization	1	9	
Stroke	3	2	
Total	15	29	p = 0.0433***

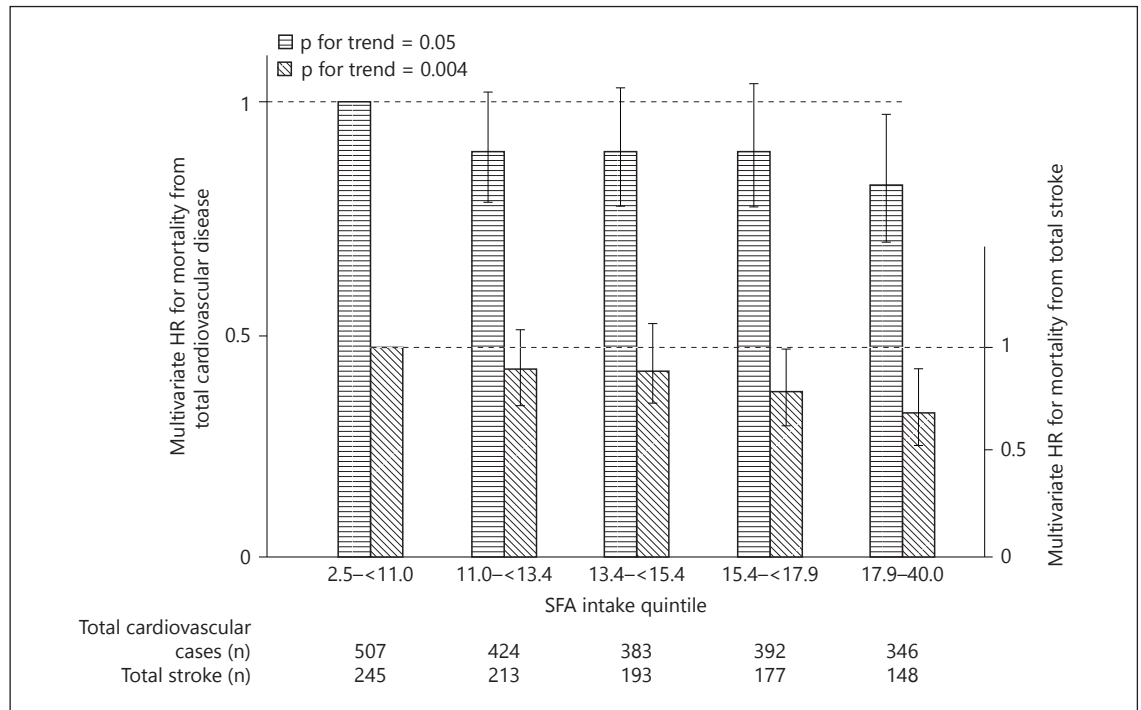
The MUSASHI-AMI Trial was a prospective, randomized, open-label trial examining the effect of statins in Japanese patients with acute myocardial infarction (AMI). Patients were randomly assigned to receive any available statin (n = 241) within 96 hours of AMI onset or no statin (n = 245) and were followed for 24 months. The primary endpoint was a composite of cardiovascular death, nonfatal acute myocardial infarction, recurrent symptomatic myocardial ischemia, congestive heart failure, and stroke. There is a discrepancy between the event rates of objective endpoints (cardiovascular deaths and nonfatal AMI) and nonobjective events depending on physicians' judgement (rehospitalization due to heart failure that did not have any objective evidence). \* Percentage in parentheses. \*\* p = 0.012 by Fisher's exact test; odds ratio = 0.60 (95% CI: 0.41 to 0.89) according to our calculation. \*\*\* Note the absolute differences: 11% for nitrate users at baseline and 5.2% for primary outcome. (See the text.) (Reproduced with permission from the publisher, with slight modifications.)

n-3 PUFA, which can be desaturated and elongated to longer n-3 PUFAs, namely, eicosapentaenoic and docosahexaenoic acids in the liver) contained in vegetable oil [13]. Given that people in Western countries ingested only 0.3–0.5 energy percent as  $\alpha$ -linolenic acid and very little fish before and around the year 2000 [13] and that the daily requirement of  $\alpha$ -linolenic acid was estimated to be 0.2–0.3 energy percent in patients with long-term total parenteral nutrition in Norway [14], a considerable proportion (at least 20% in our estimation) of people suffered from n-3 PUFA deficiency or  $\alpha$ -linolenic acid deficiency in Western countries at that time. In fact, vegetable oil consumption in 1961–63 in many Western countries, around the time when many trials replacing SFA with PUFAs were conducted, was only half that in 2000–02 [15]. Consequently, it is highly likely that there are no reliable intervention studies indicating that SFAs should be reduced.

Moreover, there is a possibility that important data from some intervention trials have not been reported,

data which might go against the notion that SFA replacement with PUFAs is good for the heart, especially in the case of linoleic acid selective replacement. As a case in point, Ramsden et al. [16] recently reevaluated the Sydney Diet Heart Study conducted between 1966 and 1973 with newly found data and updated a meta-analysis on the efficacy of such replacement. The Sydney Diet Heart Study, involving 458 men aged 30–59 years with a recent coronary event, recommended the men in the dietary group replace dietary saturated fats (from animal fats, common margarines, and shortenings) with linoleic acid (from safflower oil and safflower oil polyunsaturated margarine). The control group received no specific dietary instruction or study foods. All non-dietary aspects were designed to be equivalent in both groups. The replacement diet actually increased the rates of death from all causes (HR: 1.62, 1.00–2.64), coronary heart disease (HR: 1.74, 1.04–2.92), and cardiovascular disease (HR: 1.70, 1.03–2.80). Ramsden et al's updated meta-analysis





**Fig. 7-5.** Multivariate hazard ratios (HRs) for mortality from total cardiovascular disease and total stroke according to saturated fatty acid (SFA) intake quintile: Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) [17]. A total of 58,453 Japanese men and women were followed up for 14.1 years. HRs were adjusted for age, sex, history of hypertension and diabetes, smoking

status, alcohol consumption, body mass index, mental stress, walking, sports, educational level, and dietary intakes of total energy, cholesterol, n-3 and n-6 polyunsaturated fatty acids, vegetables, and fruit. Vertical scales on both sides are proportional to the total numbers of cases (n = 2,052 for total cardiovascular disease, n = 976 for total stroke).

of linoleic acid intervention trials showed no evidence of cardiovascular benefit, and replacement of SFAs selectively with linoleic acid might even be a risk factor for death from CHD (HR: 1.33, 0.99–1.79) [16]. The point of Sydney Diet Heart Study, an intervention study, is that the safflower oil used in the study contained essentially no  $\alpha$ -linolenic acid and did not ameliorate n-3 PUFA deficiency but rather deteriorated (increased) the ratio of n-6 PUFAs to n-3 PUFAs.

An interesting cohort study in Japan has shown the beneficial effects of higher SFA intake. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) included 58,453 Japanese adults (23,024 men, 35,429 women) aged 40–79 years at baseline (1988–1990) who completed a food-frequency questionnaire [17]. The participants were followed for 14.1 years, during which time 976 cases with stroke were registered. Associations of energy-adjusted SFA intake with mortality from stroke and heart disease were examined with adjustment for age, sex, cardiovascular disease risk, and dietary factors. SFA intake was observed to be significantly inversely associ-

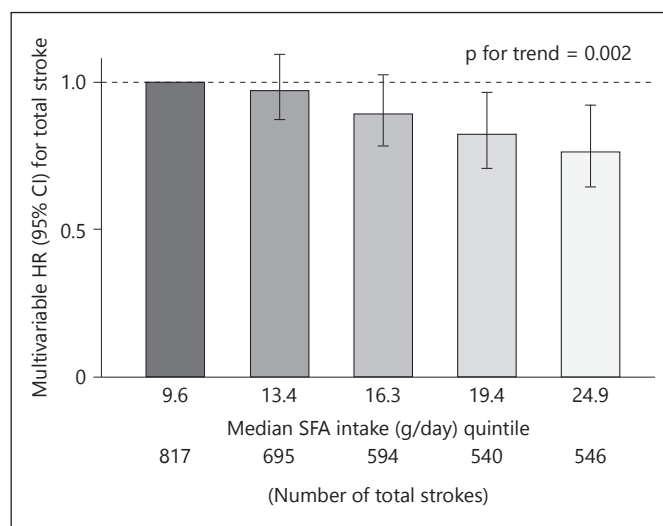
ated with mortality from total stroke (fig. 7-5). Heart disease was not found to be associated with SFA intake (multivariable HR for the highest vs. lowest SFA intake quintiles: 0.89, 0.68–1.15, n = 836). There was a trend for lower mortality from cardiovascular disease with increasing SFA intake (p for trend = 0.05) (fig. 7-5).

More recently, the Japan Public Health Center-based prospective (JPHC) Study published a new report [18]. After excluding participants such as those with a history of MI, angina pectoris, stroke, or cancer, data were analyzed for a total of 81,931 adults (38,084 men, 43,847 women) aged 56.7 years at baseline who were followed for a mean 11.1 years. HRs were determined for incident total stroke (ischemic stroke, intraparenchymal hemorrhage, and subarachnoid hemorrhage), MI, and sudden cardiac death across dietary SFA quintiles (assessed by a food frequency questionnaire). Significant inverse associations were observed between SFA intake and total stroke (fig. 7-6). According to the report, a positive association was observed between SFA intake and MI primarily in men (multivariable HR for the highest vs. lowest quintiles: 1.39,

0.93–2.08,  $p$  for trend = 0.046). However, sudden cardiac death showed a trend for an inverse association with SFA intake (HR: 0.39, 0.15–0.99,  $p$  for trend = 0.06). Although sudden cardiac deaths amounted to only 16% of total CHD events (CHD was defined as MI or sudden cardiac death in the methods section of the study report [18]), a significantly lowered HR for sudden cardiac death in the highest SFA quintile would have nullified the significance ( $p = 0.046$  for MI) if both MI and sudden cardiac death had been combined to make up total CHD events as defined (table 7-F). It would seem as if the authors of this report were hesitant about showing the safety of SFA intake. Actually in the discussion section, the authors state, ‘Therefore, a recommendation to increase SFA intake cannot [be] made in Japan [at this time], since both SFA intake and coronary heart disease incidence rate are increasing among urban Japanese men.’ In addition, we find it strange that while the title of the report, ‘Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: the JPHC Study’, includes the phrase ‘coronary heart disease’, nowhere in the report is the multivariable HR for CHD given.

Next, we’d like to mention a 14-year (on average) prospective epidemiological study by Iso et al. that ended in 1997 in Japan and was published in 2003 [19]. Their study offers reasonable support for SFA intake—intake that should not be avoided especially for the prevention of cerebral hemorrhage. The relation between low intake of saturated fat (and animal protein) and risk for intraparenchymal hemorrhage was examined in 4,775 Japanese aged 40–69 years from 5 communities who undertook a single 24-hour dietary recall. Of the 5 communities, 2 were in a northeast rural area, 1 in a western urban suburb, 1 in a southwest rural area, and 1 in central Japan. As shown in fig. 7-7, SFA intake was linearly associated with decreased multivariate relative risks for incident intraparenchymal hemorrhage ( $p$  for trend = 0.005). Intake of animal protein tended to correlate inversely with risk. Although the  $p$  for trend was 0.25, multivariate relative risk was inversely associated with cholesterol intake (relative risk: 1.0, 0.98, 0.74, and 0.71 for increasing cholesterol intake quartiles). Unfortunately, the report does not mention the relative risks for the other types of stroke. Because this study was conducted between the 1970s and 1990s, SFA intake was still low compared with that found in more recent studies.

Lastly, we should discuss the findings of Adult Health Study (AHS), which evaluated SFA intake particularly in respect to death from cerebral infarction [20]. The participants were a clinical study sub-cohort from the Life Span Study [21]. The LSS is a cohort of 120,000 persons (93,000



**Fig. 7-6.** Multivariable hazard ratio (HR) for incident stroke according to saturated fatty acid (SFA) intake quintile: JPHC Study [18]. A total of 38,084 men and 43,847 women with no history of cardiovascular disease or cancer were followed for a mean period of 11.1 years. HR was adjusted for age, sex, energy intake, cohort, cigarette smoking status, alcohol intake, body mass index, sports (during leisure time, walking, and standing time), perceived mental stress, and energy-adjusted dietary intakes of carbohydrate, protein, cholesterol, vegetables, fruit, and calcium. SFA intake was energy-adjusted. See also table 7-F for the HRs for incident myocardial infarction, sudden death, and total cardiovascular disease. CI = Confidence interval.

atomic bomb survivors and 27,000 unexposed individuals) who were residents of Hiroshima and Nagasaki in the early 1950s. A prospective study involving 3,731 Japanese men and women aged 35–89 years was conducted from 1984 to 2001. Food intake was estimated at baseline by a 24-hour diary. During the follow-up period, 60 deaths from cerebral infarction were recorded. High intakes of animal fat and cholesterol were significantly associated with a reduced risk of death from cerebral infarction (fig. 7-8). A high intake of SFA was linearly associated with low mortality from cerebral infarction, but the trend was not significant. Age- and sex-stratified and multivariate-adjusted relative hazards (95% confidence intervals) were 1.00, 0.85 (0.46–1.54), and 0.58 (0.28–1.20) for increasing SFA intake tertiles ( $p = 0.14$ ), with mean SFA intakes (g/day) of 7, 12, and 21, respectively. Unsurprisingly, animal protein intake was inversely associated with cerebral infarction deaths; the respective relative hazards were 1.00, 0.54 (0.28–1.03), and 0.45 (0.23–0.89) in the order of increasing animal protein intake tertiles ( $p = 0.018$ ).

This section posed the question of whether SFA intake should be reduced in the Japanese population, and we have

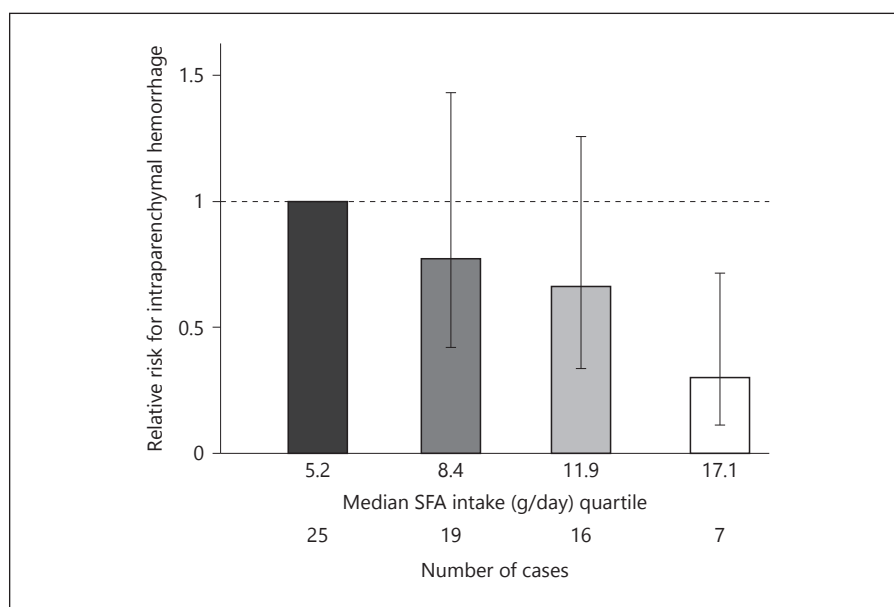
**Table 7-F.** Multivariable hazard ratios (95% confidence intervals) for total cardiovascular disease, incident myocardial infarction, and sudden cardiac death according to saturated fatty acid (SFA) intake quartile: JPHC Study [18]

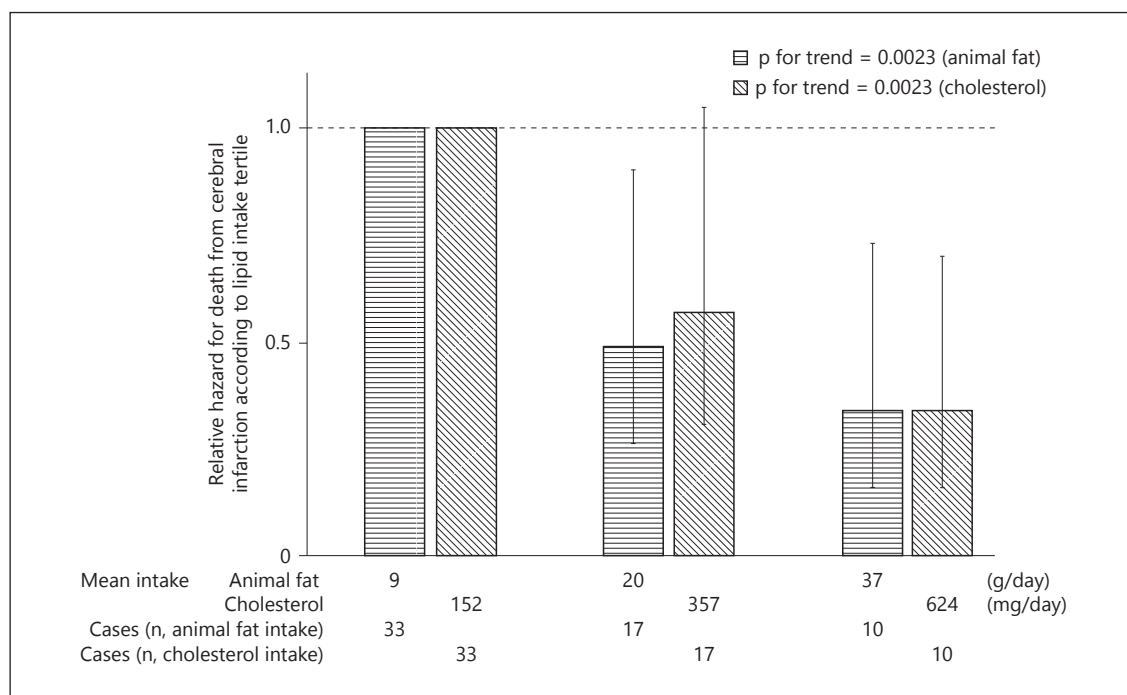
Median SFA intake quartile (g/day)	Q1 9.6	Q2 13.4	Q3 16.3	Q4 19.4	Q5 24.9	p for trend
<i>Total cardiovascular disease</i>						
No. of cases	996	812	724	664	671	
Multivariable HR	1.0	0.94	0.91	0.86	0.82	p = 0.01
95% CI		0.85–1.05	0.81–1.03	0.75–0.98	0.69–0.96	
<i>Myocardial infarction</i>						
No. of cases	142*	104	125	115	124	
Multivariable HR	1.0	0.90	1.24	1.24	1.39	p = 0.046
95% CI		0.68–1.18	0.93–1.67	0.88–1.75	0.93–2.08	
<i>Sudden cardiac death</i>						
No. of cases	43	24	13	19	17	
Multivariable HR	<b>1.0</b>	<b>0.53</b>	<b>0.29</b>	<b>0.42</b>	<b>0.39</b>	p = 0.06
95% CI		0.30–0.93	0.14–0.60	0.19–0.92	0.15–0.99	
<i>Coronary heart disease**</i>						
No. of cases	185	128	138	134	141	
Multivariable HR			Not available			Most probably not significant
95% CI						

HR = Hazard ratio; CI = confidence interval.

See the legend to fig. 7-6 and the text for an explanation of this table. The possible risk of high SFA intake is found only for incident myocardial infarction (MI). The point is that MI did not include sudden cardiac death. Unfortunately, multivariable HRs for coronary heart disease (CHD), which is defined in the study paper itself as constituting MI or sudden cardiac death [18], cannot be found in any figures, tables, or supplemental data for this study. Because the HR for sudden cardiac death was significantly lower in the fifth SFA intake quintile than in the first (see values in bold), the combination of MI and sudden cardiac death (i.e., total CHD) must have been unrelated to SFA intake. \* No. of cases is highest here, but the HRs for the third, fourth, and fifth quintiles are >1.0. This means that the first quintile for MI is an outlier and cannot serve as the reference value. \*\* MI + sudden cardiac death. (Remade with permission from the publisher, with slight modifications.)

**Fig. 7-7.** Relative risk for intraparenchymal hemorrhage according to dietary saturated fatty acid (SFA) quartile: a study in Japan [19]. A total of 4,775 Japanese aged 40–69 years were followed for 14 years on average. They undertook a single 24-hour dietary recall. The relative risk for incident intraparenchymal hemorrhage was calculated according to SFA intake quartile after adjustment for age, sex, community, total energy intake, and known cardiovascular risk factors. Vertical bars show 95% confidence intervals. p for trend = 0.005.





**Fig. 7-8.** Relative hazard (95% confidence intervals) for death from cerebral infarction according to lipid intake tertile: Adult Health Study [20]. Participants in the Adult Health Study consisted of a clinical study sub-cohort of the Life Span Study, which included atomic-bomb survivors. A prospective study with 3,731 Japanese

men and women aged 35–89 years was conducted from 1984 to 2001. Relative hazards were stratified by sex and age, and adjusted for radiation dose, city, body mass index, smoking status, alcohol habit, and medical history of hypertension and diabetes.

provided evidence to support our answer that it shouldn't. However, JASG2012 completely neglects to cite the above-mentioned findings from Japan. Maybe the JASG2012 Committee would argue that these studies were conducted a couple of decades ago when Japanese people did not have a high SFA intake. We would counter that, as shown in the JPHC Study published in 2013 [18], SFA is still a negative risk factor for stroke and is not a risk factor for CHD at all if sudden cardiac death is counted as CHD. So the notion

that we should limit our intake of animal protein and fat, especially SFAs, has lost its scientific basis. Moreover, in contrast to JASG2012, the evidence from Japan indicates that we should actually increase our SFA intake. We close by pointing out that SFA intake and cerebral infarction incidence were inversely associated ( $p = 0.002$ ) even in one of the most famous studies, the Framingham Heart Study [22], where middle-aged American men had higher intake of animal fats than the average Japanese citizen.

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## Chapter 8 The Latest Edition of the JAS Guidelines (2012) Part IV: The Adverse Effects of Statins

**Summary:** Descriptions of the adverse effects of lipid-lowering drugs, especially statins, are very limited in the 2012 JAS Guidelines (JASG2012) and are not improved over those in the previous 2008 guidelines (JASG2008). Important adverse effects involving the nervous system, even though they occur infrequently, are not mentioned in JASG2012. Nor is the carcinogenicity or diabetogenicity of statins. Breast cancer was recently reported to increase more than two-fold after 10 years of statin administration compared with non-use among participants with a history of high cholesterol levels only. Other adverse effects of statins include teratogenicity, depressed sexual pleasure, peripheral neuropathy, cataract, musculoskeletal disturbance, and liver dysfunction.

### (1) The 2012 JAS Guidelines Have Limited Descriptions of the Adverse Effects of Lipid-Lowering Drugs

In JASG2012, the title of Chapter 7B is ‘Treatment Method B, Drug treatment’, and the characteristics and selection criteria of various drugs are listed in Section 3. However, the first paragraph of the chapter states, ‘...with regard to the concrete dosage, health insurance, and safety [of various drugs for dyslipidemia], please refer to the ‘Treatment Guide for Dyslipidemia 2008’’, another JAS publication. This would suggest that the JASG2012 com-

mittee members considered no new information of importance had been published on drug safety or side effects during the 4 year period between the 2008 and 2012 guidelines. Yet, this is clearly not the case, as we discuss below. The authors of JASG2008 described the side effects of lipid-lowering agents in just 1.3 pages and those for rhabdomyolysis in 1 page. The following in italics is our summary of the important points given in the 1.3-page description:

*The side effects that need special care are presented in table 10-2. (There is only one line for statins in that table: Statins – rhabdomyolysis, gastrointestinal symptoms, liver disorders, etc.)*

*Most of those side effects are mild and reversible. A possible serious side effect is rhabdomyolysis (the details of which they presented on the following 1 page). Statins and fibrates induce this side effect more often in kidney patients. Prescribing fibrates and statin at the same time is contraindicated in kidney patients.*

*Most of the lipid-soluble statins are metabolized through cytochrome P450 (CYP), and therefore caution should be exerted when inhibitors or competitors (of CYPs) are used together (with statins). (Metabolic competitors for CYPs of statins are listed in table 10-3 of this section on side effects in JASG2008.)*

***Fibrates and statins are contraindicated in pregnant women.*** (Bold-faced type is written in red in the original.)

The description of statin side effects is similarly rather limited in JASG2012 (Chapter 7B). In addition to refer-

ring to the previous 2008 guidelines outlined above, in the part on statins it reads:

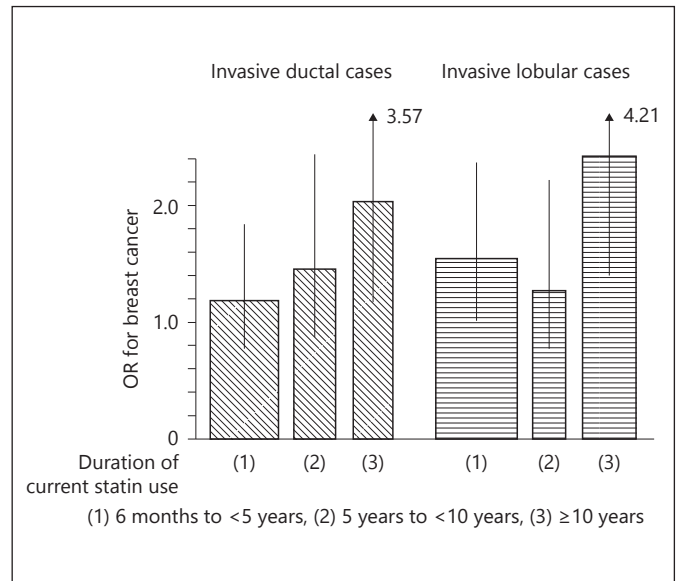
*Liver dysfunction, myopathy-like symptoms with increased CPK values or lassitude [are noticed] as side effects, and furthermore, rhabdomyolysis characterized by a myoglobin increase in blood and urine have been reported extremely rarely as side effects. This risk is increased with simultaneous prescription with fibrates, nicotinic acid derivatives, cyclosporine, erythromycin, etc.*

*Also, teratogenicity [associated with statins] was suspected in cases in which statins happened to be taken during the early stage of pregnancy [1]. Accordingly, it is considered that statin must not be prescribed to those who are planning to become pregnant or, needless to say, to women in the early stage of pregnancy.’ (This mention of pregnancy is not written in red this time.)*

So we can see that there is little difference between the two sets of guidelines on the side effects of statins, despite a 4-year period between their publication. We ask ourselves what other popular drugs that are teratogenic are currently on the market and so widely prescribed (see Section 4 below for a detailed discussion of the teratogenicity of statins). Moreover, they are very likely to be carcinogenic, as we discuss in the next section. We also discuss some other important side effects in Sections 3 and 4 below, side effects that JASG2012 largely omit.

## (2) The Carcinogenic Nature of Statins

There is accumulating evidence for the carcinogenicity of statins. Let’s start by looking at the case for breast cancer. Inconsistent results have been found by epidemiological studies on statin use and breast cancer risk, and comprehensive investigations on long-term statin use in breast cancer patients are scarce. Only a couple of long-term studies have been published so far. The first, a population-based case-control study of invasive breast cancer comparing statin users obtained by telephone interview, was published in 2008 and involved 3,859 cases and 4,761 controls [2]. The study found no overall breast cancer risk in current statin users (odds ratio [OR]: 1.0, 0.8–1.2) or in current statin users with  $\geq 10$  years of use. In fact, the OR for those with long-term use (25 cases, 37 controls) adjusted for 10 confounding factors was 0.8 (0.5–1.4). However, a second population-based case-control study recently reported entirely different results. Current statin users with  $\geq 10$  years of use had a two-fold higher risk for breast cancer than controls [3]. Although overall there were smaller numbers of all cases (1,927) and controls (877) than in the first study mentioned [2],



**Fig. 8-1.** Odds ratios (ORs) for invasive ductal or lobular breast cancer in statin users with different durations among those having a history of high cholesterol levels [3]. A population-based case-control study of breast cancer was conducted in three counties in the Seattle-Puget Sound metropolitan region of the United States. Between 2000 and 2008, 916 patients with invasive ductal carcinoma and 1,068 patients with invasive lobular carcinoma (aged 55–74 years) were diagnosed, and the results compared with those for 902 control women. All participants were interviewed in person, and data on cholesterol levels and all episodes of lipid-lowering medication use were collected using a structured questionnaire. ORs for breast cancer were adjusted for reference year, reference age, county of residence, and hormone replacement therapy. The numbers of cases were 273, 286, and 320 for controls, ductal cases, and lobular cases, respectively (regardless of years of statin use). This figure shows the findings restricted to participants with a history of high cholesterol levels. The width of each column is proportional to the numbers of cases.

there were larger numbers of breast cancer cases (50 ductal cases, 60 lobular cases) and controls (31 cases) who were current users with  $\geq 10$  years of statin use. If limited to participants with high cholesterol levels, ORs were more than 2 (fig. 8-1). The carcinogenesis of statin for ductal breast cancer in this study was time dependent.

More recently, one of the reports from the Women’s Health Initiative (WHI) assessed the relationship between statins and breast cancer risk, although it did not look at statin use for  $>10$  years [4]. The study population consisted of 154,587 postmenopausal women aged 50 to 79 years who were enrolled in an observational study or one or more of four WHI clinical trials (hormone therapy, dietary modification, calcium, or vitamin D). In total,

7,430 pathologically confirmed cases of breast cancer were identified over an average of  $10.8 \pm 3.3$  years. Various analyses were performed but, overall, statins were not associated with breast cancer risk. The results might have been different if participants taking statins for  $\geq 10$  years were the focus. We eagerly await results into the future.

In a recent study, Nielsen et al. [5] concluded that statin use in patients with any of 13 types of cancer was associated with reduced cancer-related mortality. However, we believe the results should be interpreted with caution. The study assessed mortality in patients from the entire Danish population who had been diagnosed with cancer between 1995 and 2007 and were followed until December 31, 2009. Among patients aged  $\geq 40$  years, 18,721 had used statins regularly before their cancer diagnosis and 277,204 had never used statins. Multivariable-adjusted hazard ratios (HRs) for statin users, as compared with never users, were 0.85 (0.83–0.87) for death from any cause and 0.85 (95% confidence interval [CI]: 0.82–0.87) for death from cancer. The reduced cancer-related mortality among statin users as compared with that of never users was observed for each of the 13 cancer types. While this study would seem to show the association between statin use and cancer prevention beautifully, there are a few very important aspects that Nielsen et al. missed [6]. HRs were adjusted for many confounding factors but unfortunately not for baseline cholesterol levels. Low cholesterol levels are associated with the occurrence of cancer even decades later in Western populations [7, 8], and although not decades later, similar trends have been found in Japan, in men particularly (e.g., see fig. 1-2 in Chapter 1 and fig. 2-13 in Chapter 2, and the Jichi Medical School Cohort Study [9]). It is highly likely in Nielsen et al.'s study that the statin cohort had, for decades before treatment, elevated cholesterol levels that provided protection from cancer. If the confounding factor of the difference in cholesterol levels before treatment were controlled for, we believe we would find that statins induce cancer, as shown in fig. 8-1. Ravnskov et al. pointed out several important confounding factors when interpreting cohort cancer studies [10]; the discussion above exemplifies just one of these.

Another important point to consider, although not directly associated with the effects of statins, concerns how we interpret the findings of cohort studies that were started before the statin era. The clofibrate trial run by the World Health Organization (WHO) showed that cancer was an adverse effect of clofibrate [11]. However, as Ravn-

skov et al. [10] pointed out, some participants of the WHO study who had high cholesterol levels at baseline, which were measured before the statin era, may well have had prior treatment with clofibrate, the most popular drug then. This confounding factor likely increased cancer incidence in participants with high cholesterol levels and diminished the difference in cancer incidence and mortality between individuals with high and low cholesterol levels.

In Japan, Iwata et al. [12] also showed a relationship between statins and cancer, reporting an increased OR for lymphoid malignancy with statin use (mostly pravastatin). The cases were 221 consecutive incident cases (lymphoma and myeloma) admitted to the Department of Hematology of Toranomon Hospital, Tokyo, between 1995 and 2001. Two control groups, comprising 442 and 437 inpatients without malignancy from the Departments of Orthopedics and Otorhinolaryngology of the same hospital, respectively, were selected to test association. They were matched individually with cases for age, sex, and year of admission. Patients with lymphoid malignancy had a higher frequency of statin use than both control groups (adjusted OR: 2.11 [1.20–3.69,  $p = 0.009$ ] compared with orthopedic patients, adjusted OR: 2.59 [1.45–4.65,  $p = 0.001$ ] compared with otorhinolaryngology patients).

A few clinical trials have also indicated the carcinogenic nature of statins. According to Ravnskov et al., if the findings of the first two simvastatin trials, the 4 S and HPS trials, were combined, taking statins significantly increased the incidence of non-melanoma skin cancer (256/12,454 vs. 208/12,459,  $p < 0.028$ ) [10]. In the CARE trial, 12 cases of breast cancer were found among 286 women in the pravastatin group but only 1 case was found among 290 women in the placebo group at follow up ( $p = 0.002$ ) [13]. In the PROSPER trial involving elderly individuals receiving pravastatin or placebo, the difference in cancer cases was significant at 4 years (245/2891 in the pravastatin group vs. 199/2913 in the placebo group,  $p = 0.02$ ) [14]. And in the SEAS trial, 39/944 in the simvastatin/ezetimibe group had cancer at follow up compared to only 23/929 in the placebo group ( $p = 0.05$ ) [15].

When considering the relationship between statins and cancer development, we have a few more points of evidence. Animal experiments showing statin carcinogenesis have comparable findings to clinical and epidemiological studies reporting a positive relationship. Newman et al. determined the carcinogenesis of hypolipidemic drugs in rodents by analyzing the data avail-

able in the Physicians' Desk Reference (PDR) and its Supplement A [16]. Various tumors occurred in rodents receiving lovastatin, pravastatin, simvastatin, and fluvastatin (recent statins were not available before 1994 when the PDR was published) and the effects of their exposure were not markedly different from those in humans. Relative exposure in terms of area under the curve of blood concentrations compared with data when the maximum dose was administered to humans was 0.5–45. Eight out of 10 tumors were induced by relative exposure <10. If we take a 10-fold safety margin for interspecies difference (rodents to humans) and another 10-fold safety margin for intraspecies difference (among humans), a relative exposure of 0.5–45 is of significant clinical concern. Newman et al. [16] also provided a very valuable table containing data on reference drugs and antihypertensive drugs created from information in the PDR that showed very few malignant tumors were found with various kinds of antihypertensive drugs. This is an astonishing contrast to the situation with statins. It flags only too clearly that statin administration must be approached with caution so that physicians and patients don't potentially regret their use later in life.

### (3) Statins and Nervous System Disorders

#### *Peripheral Neuropathy*

Using a population-based patient registry, Gaist et al. identified 166 first-time-ever cases of idiopathic polyneuropathy over the 5-year period 1994–1998 [17]. They also randomly selected 25 age-, sex- and calendar time-matched control subjects for each case from the background population. Exposure to statins was examined by analyzing data from a prescription database, and the ORs for statin use—ever use and current use—for idiopathic polyneuropathy were calculated compared with controls. ORs for statin use were 14.2 (95% CI: 5.3–38.0) for definite cases (n = 35) and 3.7 (95% CI: 1.8–7.6) for all cases; when limited to current statin users, the respective values were 16.1 (5.7–45.4) and 4.6 (2.1–10.0). For patients with statin use  $\geq 2$  years, the OR for definite idiopathic polyneuropathy was 26.4 (95% CI: 7.8–45.4). The time dependency indicates a probable causal relationship. Although idiopathic polyneuropathy is not a common disease, these findings suggest that a very large number of long-term statin users could be suffering from mild polyneuropathy.

#### *Amyotrophic Lateral Sclerosis-Like Central Nervous System Disorders*

Using Vigibase, the database of the WHO Programme for International Drug Monitoring, Edwards et al. summarized reports of a disproportionate number of upper motor neuron lesions [18], a rare adverse event to drugs. From a total of 172 individual case safety reports on upper motor neuron lesions, 43 were related to statins, and Edwards et al. further investigated 40 of these. All but 1 case was reported as amyotrophic lateral sclerosis (ALS). A statin was the sole reported suspected drug in 34 of the 40 reports. A similar data mining signal was found in the spontaneous adverse event reporting system run by the US Food and Drug Administration (FDA); however, a retrospective analysis of 41 statin clinical trials did not reveal an increased incidence of ALS in subjects treated with a statin compared with placebo [19]. Edwards et al. concluded that statins should be discontinued in trial participants with serious neuromuscular disease, such as ALS-like syndrome, given their poor prognosis and the possibility that progression of the disease may be halted or even reversed by the discontinuation [18].

#### *Diminished Sexual Pleasure*

More than 1,000 adults with high levels of low density lipoprotein (LDL) cholesterol without heart disease were randomly assigned to either a statins group (simvastatin and pravastatin) or a placebo group and were followed for 6 months. Patients who took simvastatin had the largest LDL cholesterol decrease, but men in that subgroup experienced a nearly 50% reduction in sexual pleasure over the study period [20, 21]. Women were somewhat better off. While pravastatin, the other statin tested, reduced LDL cholesterol somewhat less, patients did not experience a significant decrease in sexual pleasure. This suggests that diminished sexual pleasure may not be because of increased age but because of statin use.

Why would statins impair sexual pleasure? The sex-driving hormone testosterone is composed of cholesterol, the synthesis of which in the genital organs and adrenal glands is reduced by statins. The answer is probably this simple. Moreover, sexual pleasure is heavily dependent on functions of the peripheral and central nervous systems. Damage to the peripheral system by statins was briefly described at the beginning of this section. But what



about the brain? Lipid soluble statins penetrate the brain and can reduce substrate levels for steroid hormone synthesis there [22]. Moreover, even sex hormones are synthesized in the brain [23] (see the next subsection ‘Memory Impairment’). So, it is entirely possible that statins reduce sexual pleasure in the brain, too.

### *Memory Impairment*

One rather shocking case reported in 2006 highlights the dangers that statins pose to memory function [24]. Duane Graveline, a former astronaut, aerospace medical research scientist, flight surgeon, and family doctor, was started on atorvastatin for high cholesterol levels. Six weeks later he suffered transient global amnesia (TGA). One year later he resumed the drug at half dose and 8 weeks later lost his memory again, but with more severe symptoms this time, forgetting everything after high school. He warns what the outcome might be if the same were to happen to public transportation operators (e.g., airplane pilots). Much more recently in 2014, consumer health information published by the FDA warned that ‘reports about memory loss, forgetfulness and confusion span all statin products and all age groups’ [25].

So, in what ways do statins deteriorate memory. The brain contains nearly 25% of all unesterified cholesterol in the body, which means that the concentration of unesterified cholesterol in the brain is about 15-fold that for other organs. Although the half-life of the bulk of cholesterol is estimated to be at least 5 years, the turnover rate of unesterified cholesterol that is not integrated in the cell membranes is thought to be much shorter. And this short turn means the cholesterol fractions are ready for important steroid hormone synthesis. Probably because of the brain’s structural needs for cholesterol (since cholesterol is the most abundant single molecule in the cell membranes) and its functional needs for cholesterol (for steroid hormone synthesis), the brain synthesizes all cholesterol by itself without depending on other organs (including the mother during fetal development)(see Björkhem et al. for a review [26]). Recently, sex hormones were found to be synthesized in the hippocampus—the memory center—and to play an important role in memory [23]. Statin-induced reductions in the amounts of cholesterol available for hormone synthesis in the hippocampus and for cell membrane synthesis throughout the brain likely deteriorates memory function.

### **(4) Teratogenicity Associated with Statins**

Statin exposure during pregnancy can cause severe defects of the central nervous system as well as limb anomalies and reproductive disorders [1]. Cholesterol is required for myelin sheath formation, and in fact sonic hedgehog signal protein, which plays a crucial role in organogenesis [27], requires covalent modification with cholesterol, and any such impairment of this process can lead to monophthalmos. In postnatal and adult hippocampal neurons, the hedgehog protein is involved in determining presynaptic terminal size, ultrastructure, and function in hippocampal neurons [28].

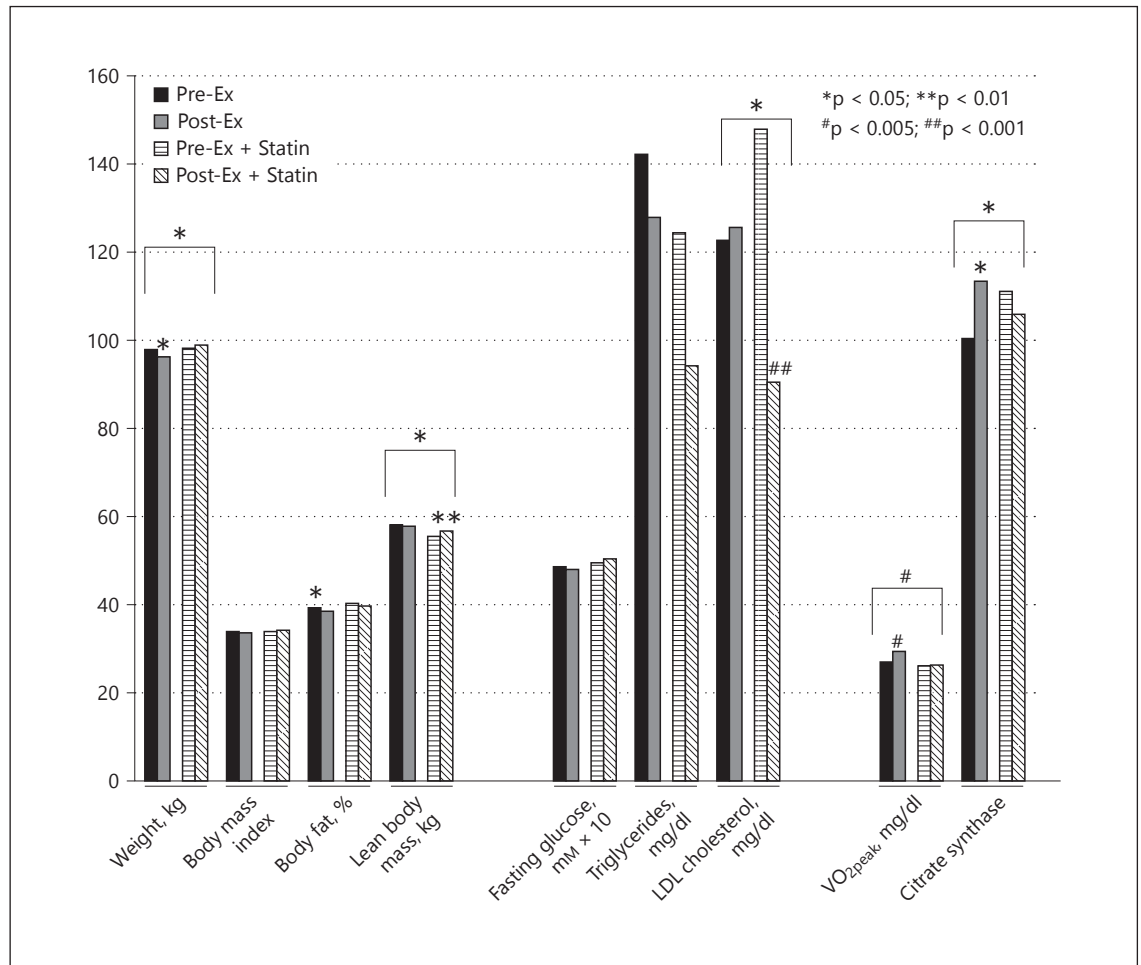
### **(5) Other Organ Dysfunction Caused by Statins**

#### *Musculoskeletal Disorders*

We discuss here one of the most prominent adverse effects of statins, namely, muscle disorders. This type of adverse effect is probably the most important to discuss in terms of preventing cardiovascular disease because, if musculoskeletal damage reduces exercise in those trying to prevent such disease, statins are then in fact having just the opposite effect than intended. We believe that patients on statins must have considerable muscle damage. We say this given the results of, for example, a study in professional athletes with familial hypercholesterolemia who received statins [29]. Around 80% of them could not tolerate statin treatment because of muscular problems. As all participants were top athletes and very focused on the condition of their muscles, it is likely they readily detected muscle problems, suggesting underreporting of this side effect by the general population on statins because of less focused attention on muscle condition.

Mikus et al. recently investigated the effects of simvastatin on changes in cardiorespiratory fitness and the mitochondrial content of skeletal muscle in response to aerobic exercise training [30]. Sedentary overweight or obese adults with at least two metabolic syndrome risk factors were randomized to 12 weeks of aerobic exercise training alone (n = 19) or to exercise in combination with simvastatin 40 mg daily (n = 18). Cardiorespiratory fitness (peak oxygen consumption,  $VO_{2peak}$ ) was increased by 10% ( $p < 0.05$ ) in response to exercise training alone, but was blunted by the addition of simvastatin, resulting in only a 1.5% increase ( $p < 0.005$ , Group  $\times$  Time interaction; fig. 8-2). Similarly, skeletal muscle mitochondrial content





**Fig. 8-2.** Changes in cardiorespiratory fitness, muscle mitochondrial content, etc. after exercise alone or exercise plus statin for 12 weeks [30]. Sedentary overweight or obese adults were randomized to 12 weeks of aerobic exercise training or to exercise in combination with simvastatin 40 mg daily. Cardiorespiratory fitness (peak oxygen consumption; VO<sub>2peak</sub>) and skeletal muscle mitochon-

chondrial content (citrate synthase activity) were measured. Filled black and gray bars: before (Pre) and after (Post) 12 weeks of supervised aerobic exercise training (Ex), respectively. Hatched black and gray bars: similarly before and after combined exercise plus statin therapy (Ex + Statin), respectively. See the text for details.

(citrate synthase activity determined from biopsied vastus lateralis muscle tissue) was increased by 13% in the exercise alone group ( $p < 0.05$ ), but was decreased by 4.5% in the simvastatin plus exercise group ( $p < 0.05$  for group by time interaction). Thus, simvastatin attenuated the benefit obtained through exercise in overweight or obese patients at risk of metabolic syndrome.

It is likely that statins damage not only muscles, but also joints and connective tissue. Mansi et al. performed a retrospective cohort study involving active-duty soldiers (17.1% of the sample) and veterans and their families (82.9%) between October 2003 and March 2010 [31]. The participants were divided into two groups, statin us-

ers (received a statin for at least 90 days,  $n = 6,967$ ) and matched nonusers (did not receive a statin throughout the study period,  $n = 6,967$ ). Baseline data were collected during the first 2 years of the study and the participants were followed thereafter. Among the matched pairs, statin users had higher ORs for all musculoskeletal diseases (1.19, 95% CI: 1.08–1.30), injury-related diseases (dislocation, sprain, strain, 1.13, 95% CI: 1.05–1.21), and drug-related musculoskeletal pain (1.09, 95% CI: 1.02–1.18); the OR for arthropathies and related diseases was 1.07 (95% CI: 0.99–1.16,  $p = 0.07$ ).

Golomb et al. conducted an RCT to test whether statins worsened exertional fatigue and/or energy [32].

They randomized a total of 1,016 subjects (692 men, 324 nonprocreative women) aged  $\geq 20$  years with screening LDL cholesterol levels of 115–190 mg/dl (2.97–4.91 mmol/l) and no cardiovascular disease or diabetes equally to one of three groups: simvastatin 20 mg, pravastatin 40 mg, or placebo. The groups took identical blinding capsules for 6 months. Single-item self-ratings of change from baseline in ‘energy’ and ‘fatigue with exertion’ were rated on a 5-point scale from ‘much less’ (–2) to ‘much more’ (+2) than baseline and reassessed at a 6-month follow-up visit. They found that energy and exertional fatigue significantly worsened during treatment with all statins compared with placebo, and that each statin contributed to this worsening (significant for simvastatin only). Women were disproportionately affected. This significant difference for women receiving simvastatin compared with those receiving placebo (–0.4 points) would have arisen if 4 in 10 treated women reported worsening in either energy or exertional fatigue or if 2 in 10 reported both factors as ‘worse’ or ‘much worse’. Clearly, then, these adverse effects are formidable and definitely reduce exercise undertaken.

### *Cataract*

Leuschen et al. retrospectively compared the risks for cataract development in a propensity score-matched cohort of statin users and nonusers from October 2003 to March 2010 [33]. Statin users were defined as those who received at least a 90-day supply of statin. In total, they identified 13,626 statin users and 32,623 nonusers. For their primary analysis, they matched 6,972 pairs of statin users and nonusers and found a higher risk for cataract among the statin users (OR: 1.09, 1.02–1.17). In secondary analyses of patients with no comorbidities determined according to the Charlson Comorbidity Index, the incidence of cataract with adjustment for identified confounders was higher in statin users than in nonusers (OR: 1.27, 1.15–1.40). The analyses above were not adjusted for baseline cholesterol levels as usual in this type of study. This might have made it the most important confounding factor, especially if high cholesterol were a risk factor for cataract; however, this is not the case, and probably the opposite is actually true [34]. In fact, the lens membrane contains the highest cholesterol content of any known membrane [34].

Lai et al. conducted a retrospective cohort study in Taiwan using data from the Longitudinal Health Insur-

ance Database 2005 that were randomly sampled from the National Health Insurance Research Database [35]. They analyzed data from a total of 50,165 adults aged 65–90 years in 1998 without records of statin therapy or diagnosis of cataracts between July and December 1997 and identified 17,670 individuals with an incident lens extraction during a median follow-up period of 10.7 years. The incidence of cataract surgery was 49.7/1,000 person-years in the statin use period compared with 38.5/1,000 person-years in the statin non-use period. The adjusted HR for cataract surgery was 1.20 (1.14–1.27,  $p < 0.001$ ) for statin users compared with nonusers after adjustment for age and propensity score. The important point to note about this study is that shortening the follow-up duration from 12 to 6 years extinguished the association between statin use and cataract surgery (adjusted HR: 1.05, 0.95–1.18), which suggests that statin effects are more likely than the confounding factors at baseline.

Clinical studies, on the other hand, have shown either harmful or protective effects of statins for cataract. It usually takes a long time for cataract to develop—anywhere between 10 and 20 years—so clinical trials of 5–6 year’s duration would not anyway be able to determine if there were any deleterious effects of statins in the case of cataract.

Lastly, in experiments with dogs, dosages of various statins that were high enough to decrease serum cholesterol levels by 40% to 60% resulted in the development of subcapsular lenticular opacity [36].

### *Liver Dysfunction*

We close this chapter on the adverse effects of statins by looking at their effect on the liver. Almost all drugs induce liver dysfunction as a side effect, but statin-induced liver dysfunction has special meaning. As described in Chapter 2, Section 3 (and Appendix 1 at the end of the section), high cholesterol levels are beneficial for severe liver disease. If liver damage by statins is serious, cholesterol levels may be markedly decreased by a compounding effect, namely, reduced cholesterol synthesis through the primary pharmacological effect of statins and liver damage, which also decreases cholesterol synthesis, as a side effect. And this compounding effect may start a vicious cycle. Consequently, liver dysfunction by statins is not as simple as liver dysfunction induced by other kinds of drugs.

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## Chapter 9 **Are Statins Effective for Preventing Coronary Heart Disease in Type 2 Diabetes Mellitus in Japan, as the 2012 JAS Guidelines Recommend?**

**Summary:** The 2012 JAS Guidelines (JASG2012) recommend the most stringent control of cholesterol in patients with diabetes for the primary prevention of coronary heart disease (CHD) and the use of statins for this purpose, despite the fact that statins raise blood levels of glucose and glycated hemoglobin (HbA1c) and increase incident diabetes. Statins impair glucose tolerance through (1) disintegrating the lipid raft where insulin receptors are located and cholesterol is enriched, (2) damaging the musculoskeletal system and consequently decreasing glucose consumption, and (3) harming mitochondria by reducing synthesis of the important mitochondrial components heme A and CoQ. They also reduce some other important cellular components. In this way, statins can impair any cells containing mitochondria. Recent clinical studies failed to show any benefits of statins for patients with diabetes.

### **(1) Background to the Relationship Between Diabetes and Hypercholesterolemia**

CHD is a major complication of type 2 diabetes. JASG2012 recommends more stringent control of cholesterol in patients with diabetes than in any other patient groups. According to table 5-A in JASG2012, in Category

III (the most stringent control group for patients without CHD), the target level for low density lipoprotein cholesterol in diabetes is <120 mg/dl (3.1 mmol/l). Dietary intervention to achieve this goal is usually unsuccessful in patients with diabetes who have already tried a diet, and statins eventually become necessary. However, statins enhance blood glucose and HbA1c levels [1, 2]. In 2012, a description to this effect became mandatory in statin package inserts in Western countries [3]—the drug administration agencies in Western countries did not ban statins altogether for patients with diabetes as they accepted the argument put forward by statin experts that these disadvantages of statins (i.e., deterioration of glucose metabolism) were outweighed by their benefits for CHD prevention. However, we argue that while statins lower cholesterol levels, they do not prevent CHD disease, as we stated in the Japan Society for Lipid Nutrition's 'Cholesterol Guidelines for Longevity, 2010' [4].

### **(2) First and Foremost, Statins Increase Incident Diabetes**

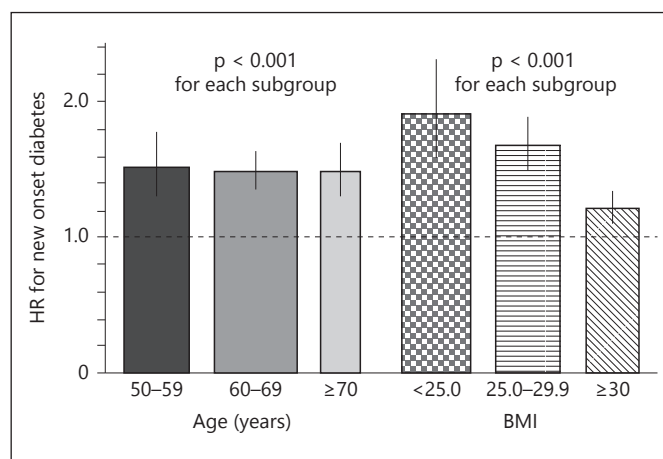
A number of studies have shown that, among the various disadvantages of statins, they increase incident diabetes. The JUPITER (Justification for the Use of

Statins in Primary Prevention) trial showed just such an increase with rosuvastatin, with new-onset diabetes (physician diagnosed) comprising 3.0% of the active group compared with 2.4% in the placebo group ( $p = 0.01$ ) [1]. In an analysis of three intervention trials—TNT, IDEAL, and SPARCLE—Waters et al. concluded that treatment with high-dose atorvastatin was associated with an increased risk for new-onset type 2 diabetes (hazard ratio [HR]: 1.37, 95% confidence interval [CI]: 1.08–1.75) [2].

In a retrospective cohort study performed using an Irish database [5], from 1,235,671 individuals who had received any medication between January 2001 and January 2009, 239,628 were newly treated with statins between January 2002 and January 2007 and 38,503 were newly treated with antidiabetic medication. Statin use was associated with an increased risk for new-onset treated diabetes (HR: 1.18, 95% CI: 1.15–1.22), and was specifically found with rosuvastatin (HR: 1.41, 95% CI: 1.31–1.52), atorvastatin (HR: 1.23, 95% CI: 1.19–1.27), and simvastatin (HR: 1.15, 95% CI: 1.05–1.25). There were significant overall dose and duration effects for all statins except fluvastatin, which demonstrated a duration effect only. The HR would have been higher still if new-onset diabetes treated with dietary intervention alone (without antidiabetic medication) had also been included.

Similarly, another population-based study, which was conducted in Ontario, Canada, found a possible association between higher potency statins, especially atorvastatin and simvastatin, and increased risk for new onset diabetes [6]. Data from the Ontario Drug Benefit database was analyzed for all patients identified to be without diabetes, aged  $\geq 66$  years, and newly started on statins at some point between 1997 and 2010. Compared with pravastatin (the reference drug in all analyses), there was a significantly increased risk for incident diabetes with atorvastatin (HR: 1.22, 95% CI: 1.15–1.29), rosuvastatin (HR: 1.18, 95% CI: 1.10–1.26), and simvastatin (HR: 1.10, 95% CI: 1.04–1.17), but not for fluvastatin (HR: 0.95, 95% CI: 0.81–1.11) or lovastatin (HR: 0.99, 95% CI: 0.86–1.14). The absolute risks for incident diabetes were about 31, 34, and 26 events per 1,000 person-years for atorvastatin, rosuvastatin, and simvastatin, respectively. The control value with pravastatin was 23 outcomes per 1,000 person-years.

In the Women's Health Initiative study [7], 153,840 postmenopausal women without diabetes and aged 50–79 years were followed. At baseline, 7.0% reported taking statin medication. There were 10,242 cases of self-reported incident diabetes during the mean 6.5 years of follow-



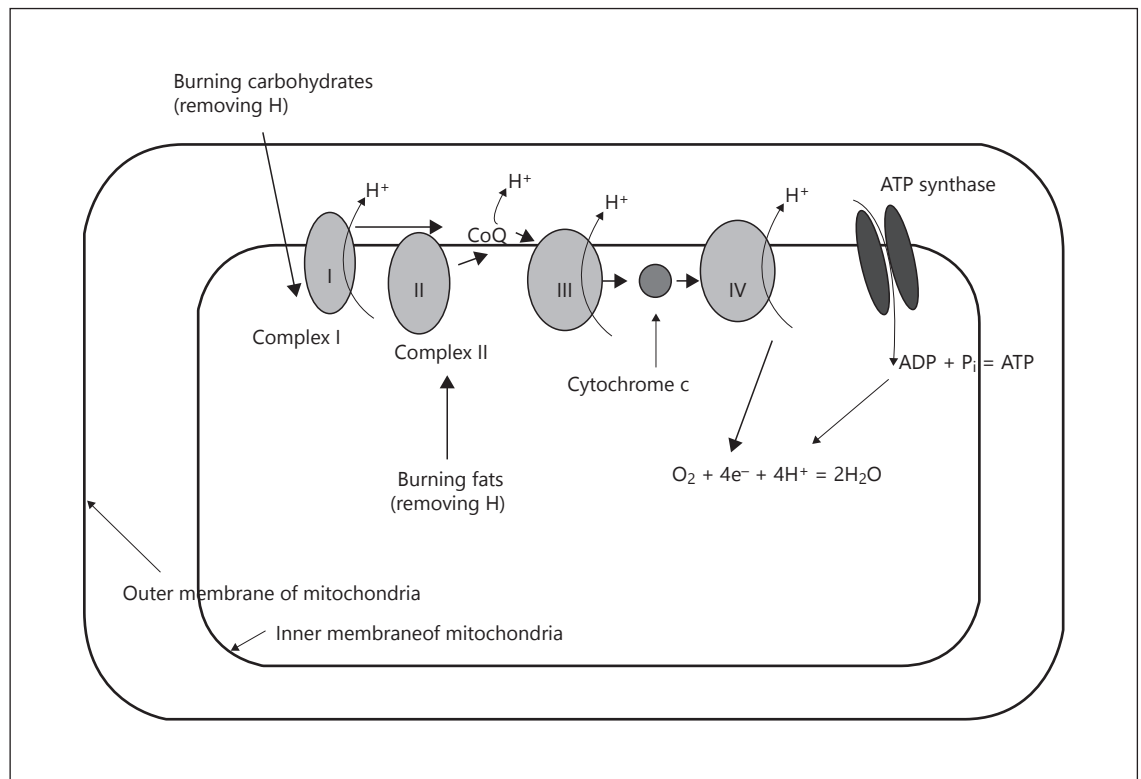
**Fig. 9-1.** Association between diabetes risk and statin use status at baseline, according to age and body mass index (BMI) subgroups in women: Women's Health Initiative [7]. A total of 153,840 postmenopausal women without diabetes aged 50–79 years were followed for a mean period of 6.5 years. Statin use at baseline was associated with incidence of new onset diabetes (multivariate adjusted hazard ratio: 1.48, 1.38–1.59). Adjusted for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of diabetes mellitus, hormone therapy, study arm (42% of participants were enrolled in clinical trials), and self-report of cardiovascular disease at baseline. Age and BMI were excluded in models for the age and BMI subgroups, respectively. The width of each column is proportional to the number of subgroup participants at baseline. HR = Hazard ratio.

up. Statin use at baseline was associated with significantly increased risk for diabetes, and this association remained even after adjusting for other potential confounders (multivariate adjusted HR: 1.48, 95% CI: 1.38–1.59) and was observed for all subgroups of age and BMI (as shown in fig. 9-1), and all types of statin medications (not shown in fig. 9-1).

### (3) How Statins Deteriorate Glucose Metabolism

In addition to incident diabetes increasing with statins, statins are associated with the impairment of glucose tolerance. This impairment can be considered from three aspects. First, mitochondrial membrane levels of cholesterol, which is one of the most important of the membrane's components, are lowered by statins. Any decrease in the cholesterol levels in cholesterol-rich lipid rafts on the plasma membranes can adversely affect the integrity of the rafts, and insulin receptors are localized on these rafts. Second, statins are very likely to result in reduced muscle strength and exercise





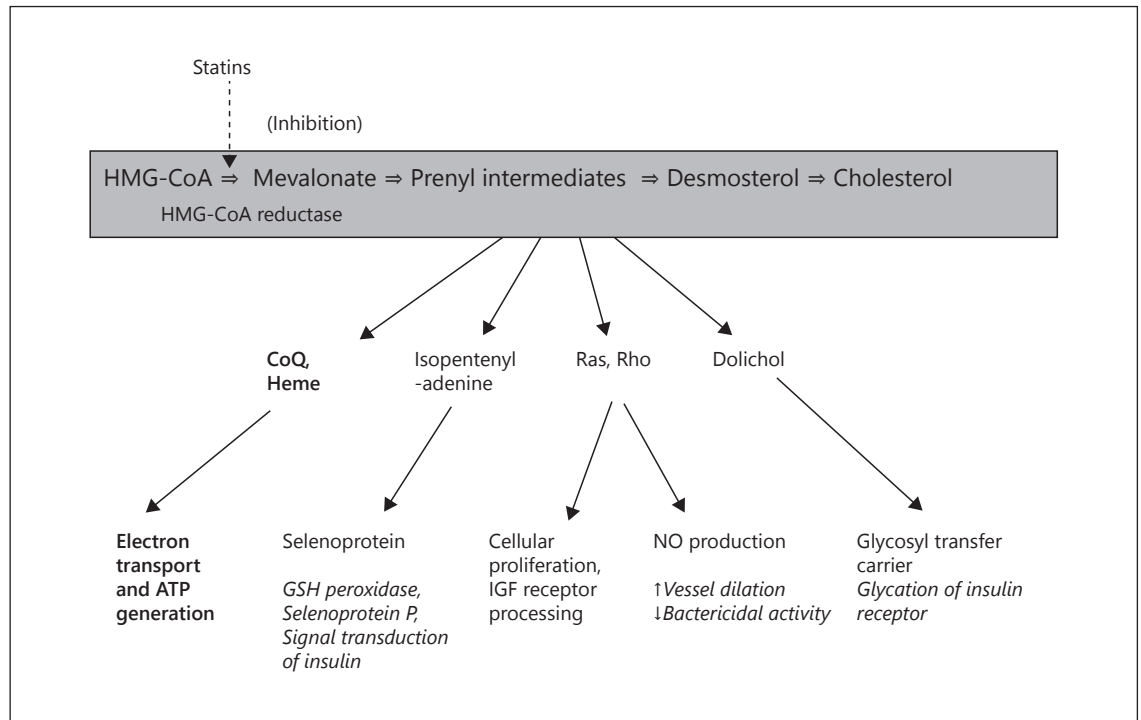
**Fig. 9-2.** Mitochondrial electron transport chain (big arrowheads) and the coupled oxidative phosphorylation system for adenosine triphosphate (ATP) synthesis. See the text for an explanation.

tolerance. Indeed, statins were recently reported to damage not only muscles, but also joints (see Chapter 8). These impairments ultimately reduce energy consumption and deteriorate glucose tolerance. The third point concerns prenyl intermediates, the production of which is depressed by statins, and we discuss this in detail next.

As shown in fig. 9-2, hydrogen extracted from the carbohydrates and fatty acids we ingest is separated into a proton (H<sup>+</sup>) and electron (e<sup>-</sup>) within the mitochondria. The electron is transferred to oxygen through Complex I or II, CoQ, Complex III, cytochrome c, and finally Complex IV. Water is synthesized with a proton that returns through adenosine triphosphate synthase.

As shown in fig. 9-3, heme A, an important component of Complex IV, and CoQ are synthesized from prenyl intermediates. In this sense, statins are considered to be toxins for mitochondria and thus affect every kind of tissue except for mature red blood cells, which are mitochondria free. Without healthy mitochondria, glucose cannot be metabolized normally.

Deterioration of glucose tolerance and an increase in insulin resistance have been reported by a few clinical trials. In one of these, 29 patients with type 2 diabetes mellitus were treated with gemfibrozil (1,200 mg/day) or simvastatin (10 mg/day) for 4 months in a double-blind, randomized crossover study. In both treatments the insulin concentration was increased during the major part of the intravenous glucose tolerance test and during the hyperinsulinemic euglycemic clamp [8]. In a second trial, medical records were reviewed for 72 patients with hyperlipidemia and impaired fasting glucose who were receiving rosuvastatin (10, 20, or 40 mg/day). The median follow-up period was 12.4 weeks. Data were compared between the first visit prior to rosuvastatin prescription and at the latest visit. Rosuvastatin was associated with a significant dose-dependent increase in homeostasis model assessment (HOMA) values, by 25.4%, 32.3%, and 44.8% at the dosages of 10, 20, and 40 mg/day, respectively, which were mirrored by a correspondent increase in plasma insulin levels [9]. A very recent study examined the effects of simvastatin on human skeletal muscle [10]. Glucose tolerance and



**Fig. 9-3.** The systems affected by statins. The pleiotropic effects of prenyl (isoprenyl) intermediates of cholesterol biosynthesis on diabetes mellitus. See the text for an explanation. ATP = Adenosine triphosphate synthase; IGF = insulin-like growth factor; GSH = glutathione.

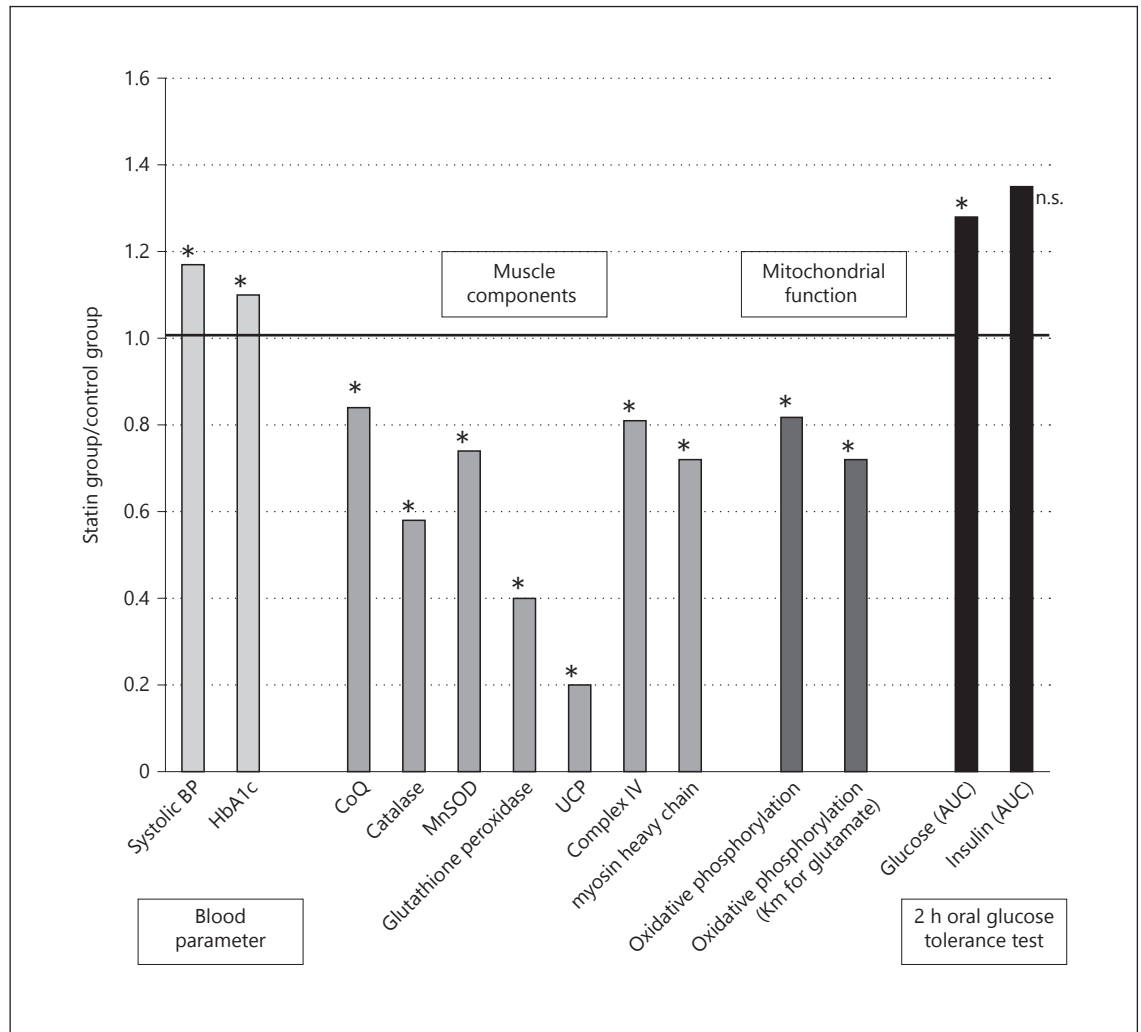
skeletal muscle CoQ10 content, mitochondrial density, and mitochondrial oxidative phosphorylation capacity were measured in 10 patients with high cholesterol levels (mean age 45 years) on simvastatin for a mean period of 5 years and in 9 well-matched control subjects. As illustrated in fig. 9-4, the simvastatin-treated patients had impaired glucose tolerance and a decreased insulin sensitivity index. Mitochondrial study revealed that CoQ10 content was reduced between the two groups ( $p = 0.05$ ), whereas mitochondrial content was similar. Oxidative phosphorylation capacity was significantly reduced in patients compared with controls ( $p < 0.01$ ).

#### **(4) Do the Benefits of Statins Outweigh the Risk for Incident Diabetes?**

Before we can answer the main question posed in this chapter—are statins effective for preventing CHD in patients with type 2 diabetes mellitus in Japan, as JASG2012 recommends?—we must first answer whether the benefits of statin use in patients with dyslipidemia outweigh

the risks for incident diabetes. In our attempt to answer this, we need to look at the situation around statin prescription in this patient population before and after a scandal was exposed in the pharmaceutical industry.

Late in the 20th century, the pharmaceutical industry started to exert powerful control over the evaluation of its prescription drugs by paying for clinical trials in their entirety and supporting all aspects of the work, including the logistics, data collection and analyses, and even ghost writing [11]. As a result, data manipulation and misleading and/or false statements, including the concealment of results, were found one after another in the medical literature. The Vioxx scandal prompted a change. In 2004, Merck withdrew the medication Vioxx (rofecoxib, a COX2 inhibitor) from the market because of concerns about increased risks for heart attack and stroke; however, the company had kept it on the market although it very likely had known about these risks for 5 years. In the settlement reached, Merck agreed to pay US \$4.85 billion [12]. In response to this, in 2004 the EU enacted new regulations for conducting clinical trials of investigational medicinal products, where contraventions can lead to criminal proceedings [13]. The Vioxx scandal was also a

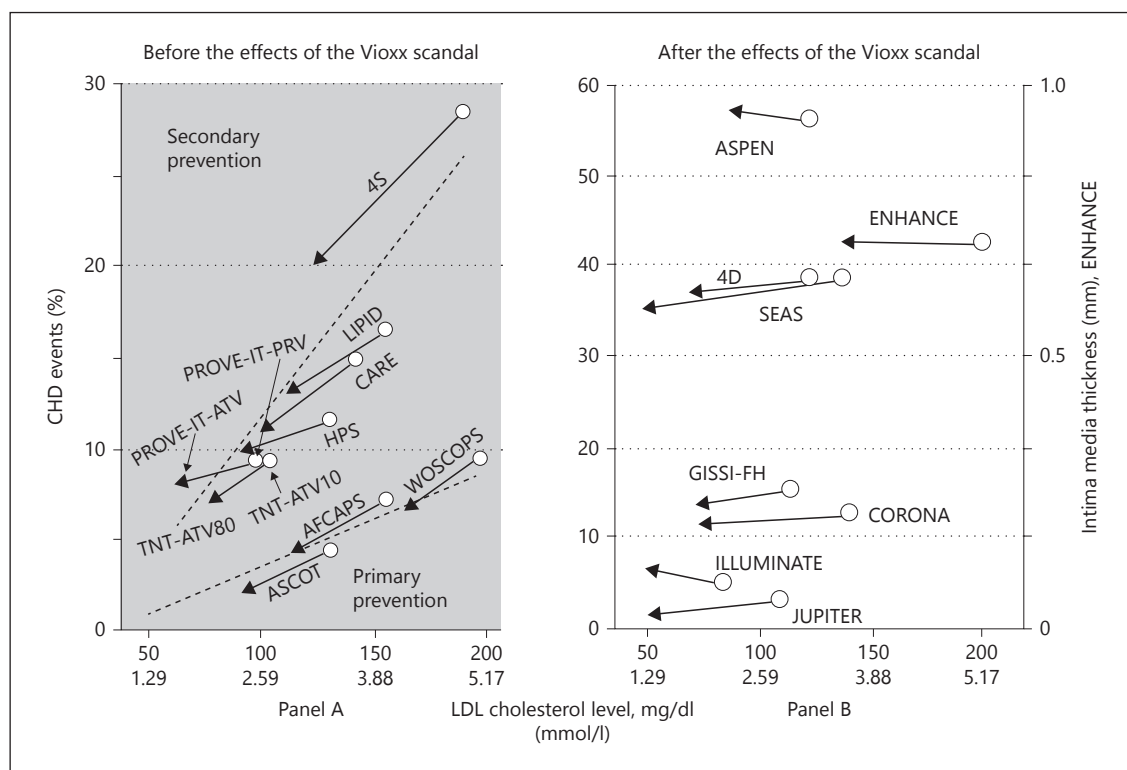


**Fig. 9-4.** Effects of simvastatin on human skeletal muscle [10]. Ten participants with high cholesterol levels took the statin for 5 years on average. The control group comprised 9 participants matched for age, sex, body weight, body mass index, body fat (%), and maximum oxygen intake. Participants reported to the laboratory at 8:00 AM after an overnight fast (10–12 h) on 2 separate days. On

day 1 blood samples were drawn, and on day 2 muscle biopsy was obtained from the vastus lateralis muscle for various measurements. Also see the text. \*  $p \leq 0.05$ . n.s. = Not significant; BP = blood pressure; HbA1c = glycated hemoglobin; MnSOD = manganese superoxide dismutase; UCP = uncoupling protein; AUC = area under the curve.

grave ethical as well as economic lesson for the pharmaceutical industry as a whole: withholding important clinical information could not only hurt patients, but also lead to huge settlements. These new regulations and lessons from the scandal worked to some extent [14]. Fig. 9-5 illustrates the difference in the effects of lipid-lowering drugs between studies published before and after this watershed year of 2004. As shown in panel B, after 2004 none of the trials conducted were able to prove the efficacy of lipid lowering drugs except for the JUPITER trial, which was, however, heavily criticized in a reappraisal by

de Lorgeril et al. [15]. Moreover, although some meta-analyses and re-analyses have concluded that statins exert positive influences on the heart or other organs, unfortunately they relied on data from clinical studies performed before 2004, when it was possible that pharmaceutical companies distorted these studies in one way or another. Pharmaceutical companies have continued to wield influence though, prompting Marcia Angell, a former editor of the *New England Journal of Medicine*, to write in 2008, 'Physicians can no longer rely on the medical literature for valid and reliable information' [16] and Peter



**Fig. 9-5.** Results of trials with lipid-lowering drugs before and after the effects of the Vioxx scandal. Arrowheads indicate the values after lipid-lowering drug intervention. Tails indicate control group values. Panel A: The chart that has often been used to ‘prove’ the notion that the lower the cholesterol levels are, the better. The statin trials shown here are mostly those performed before 2004 and under the influence of big pharma. Panel B: The statin trials (other kinds of cholesterol-reducing drugs also used) performed after 2004 when the new EU law regulating clinical trials came in effect. These trials are apparently independent of big pharma. Simvastatin + ezetimibe was used in ENHANCE and SEAS studies, while atorvastatin was used in ASPEN and 4D studies. Statins were not effective for the prevention of coronary events in any of the

trials except for JUPITER, the problems of which have been critically reviewed by de Lorgeril M, et al. [15]. The dal-OUTCOMES study published in 2012, which tested the effects of dalcetrapib (a cholesterol ester transfer protein inhibitor) in patients who had recently suffered acute coronary syndrome [28], is not shown in Panel B because low density lipoprotein levels changed only minimally (high density lipoprotein levels were increased markedly). The hazard ratio for the primary endpoint (a composite of cardiovascular events) in the dalcetrapib group was 1.04 (0.93–1.16) compared with the placebo group. Note: The Y-axis in panel A is enlarged by a factor of 2. CHD = Coronary heart disease; LDL = low density lipoprotein.

Gøtzsche in his recent book ‘*Deadly Medicines and Organised Crime*’ to unmask how big pharma has corrupted healthcare [17]. In face of the clear contrast between Panels A and B in fig. 9-5, there seems to be no strong evidence that taking statins confers an overall benefit given the risk for incident diabetes.

So, returning to our main question about whether statins are effective for preventing CHD in patients with type 2 diabetes mellitus in Japan, we have no clinical trials that can answer it because all the large-scale Japanese statin trials were irrecoverably flawed in some way, as we discussed in Chapter 7. Even the most important Japanese statin trial that JASG2012 refers to, the MEGA Study [18],

was a failure in dietary, mathematical, and methodological senses (see fig. 7-1 in Chapter 7 for just a couple of examples). There have been no large-scale, randomized control trials conducted with patients with type 2 diabetes mellitus in Japan at all, and instead JASG2012 depended mostly on sub-analyses from several clinical trials and on a meta-analysis by Cholesterol Treatment Trialists’ (CTT) Collaborators [19]. Sub-analyses do not provide evidence, however, just suggestions.

As an example of the sub-analyses referred to by JASG2012, its chapter on diabetes (Chapter 12) presents the finding of a sub-analysis from the ACCORD Study that actually had nonsignificant results for the efficacy of

statins and thus, we believe, overstates the importance of the result. The Accord Study examined the effects of a combination of open simvastatin plus masked fenofibrate or placebo in 5,518 patients with type 2 diabetes mellitus [20]. The primary outcome of the study was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Mean follow-up was 4.7 years. The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR: 0.92, 95% CI: 0.79–1.08,  $p = 0.32$ ). JASG2012 writes that the results of the sub-analysis of the risk for cardiovascular events might be reduced by fibrate addition even after statin administration in patients who had high triglyceride and low levels of high density lipoprotein cholesterol. However, this reduction was not significant ( $p = 0.057$ ). This inclusion of nonsignificant results from a sub-analysis is misguided and is not hard evidence for the efficacy of statins. Furthermore, in the main text, JASG2012 does not mention the nonsignificant results for the primary endpoints found in the ACCORD Study.

As for the meta-analysis by CTT Collaborators [19] that JASG2012 refers to, the findings are not completely reliable because it essentially examined trials performed before 2004. Some of them were prematurely terminated without pertinent medical justification—a procedure that is now well acknowledged to overestimate the reported benefits of any treatment [21]. The meta-analysis consisted of 14 trials, but the mean percentage of patients with diabetes was only 21%, with the CARDS trial being the only exception with 100% of participants having diabetes [22]. This means that the meta-analysis was composed of nonrandomized subgroups (except for CARDS). Moreover, it did not include the 4D [23] and ASPEN [24] trials in its analysis. These two studies were published in 2005 and 2006, respectively, and before the publication of the meta-analysis (2008). They were both performed without early termination and involved patients with type 2 diabetes only. Interestingly, their results showed no positive effect of statins on cardiovascular morbidity or mortality. It's unclear why these two studies were overlooked in the meta-analysis by CTT Collaborators, particularly as their addition would not have radically changed their results. But more importantly we feel, it's unclear why JASG2012 did not refer to them when they clearly provide the most reliable results.

Although the systematic review we discuss next included a study with fenofibrate, the results can help to directly answer the main question posed in this chapter. de Lorgier et al. [25] systematically reviewed the results of high-

quality double blind trials testing whether cholesterol-lowering drugs (statins and fibrates) reduce mortality and cardiovascular complications specifically in type 2 diabetics, and in their review they followed the PRISMA statements (Preferred Reporting Items for Systematic reviews and Meta-Analyses [26]). Trials with premature termination without pertinent medical justification or the use of nonrandomized subgroups of diabetic participants were excluded from the review. Only four trials met their predefined inclusion criteria. Among the 3 statin trials of the four trials in total, CARDS was discontinued 2 years before the anticipated end and in the absence of significant effect on either overall or cardiovascular mortality. The two other statin trials showed no significant effect on the primary endpoint or similarly on either overall or cardiovascular mortality. Finally, the fourth trial, the FIELD fibrate trial, conferred no significant benefit for primary endpoint or mortality [27]. Because of medical heterogeneity between the patients in the four trials that met de Lorgier et al's inclusion criteria, analysis in their systematic review had to be stopped at that stage. The results of their review did not, therefore, support the use of cholesterol-lowering drugs to reduce mortality or cardiovascular complications in those with type 2 diabetes.

To sum up, given the evidence presented above, the benefits of statins likely does not outweigh the risk for incident diabetes.

## **(5) Answering the Main Question Posed in This Chapter**

So, are statins actually effective for preventing CHD in type 2 diabetes mellitus in Japan, as the 2012 JAS Guidelines recommend? The answer is unfortunately 'No'. There are no such trials supporting the use of statins in patients with type 2 diabetes in Japan. High-quality double-blind trials using only patients with type 2 diabetes as subjects did not show any benefits of statins (Section 4). In fact, statins deteriorate glucose metabolism and increase incident diabetes (Section 2), and the pathophysiological mechanism of statin-induced glucose intolerance has actually been elucidated (Section 3). JASG2012 set much more stringent target levels of LDL cholesterol for patients with type 2 diabetes than for other subsets of individuals with high cholesterol, yet no trials comparing target LDL cholesterol levels in patients with diabetes have been conducted in Japan or elsewhere in the world to date. We actually consider that using statins is contraindicated for patients with type 2 diabetes.



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## Chapter 10    **Hypertriglyceridemia and Low Levels of High Density Lipoprotein Cholesterol: Are They Treatment Targets?**

**Summary:** On an examination of five publications cited in the 2012 JAS Guidelines (JASG2012) as evidence for the deleterious effects of high triglyceride levels on coronary heart disease (CHD) in Japan, we were concerned to find major weaknesses in each of the studies and that none of the data were adjusted for n-3 fatty acid consumption, which decreases both serum triglyceride levels and CHD incidence. Nor were the data adjusted for sugar intake or exercise. Two publications cited in JASG2012 on the deleterious effects of high triglyceride levels on health outcomes in stroke were similarly flawed, with no adjustment made for important lifestyle factors, and consequently they should not be relied on to help produce treatment guidelines. The most important factor determining both high density lipoprotein (HDL) cholesterol levels and cardiovascular outcome is exercise. JASG2012 lists the findings of six publications as evidence for the deleterious effects of low HDL cholesterol on cardiovascular disease, but none were adjusted for exercise. We conclude, then, that no valid data exist for the deleterious effects of hypertriglyceridemia or low HDL cholesterol on cardiovascular disease in the Japanese population.

### **(1) Hypertriglyceridemia: Should It Be Treated to Prevent Coronary Heart Disease?**

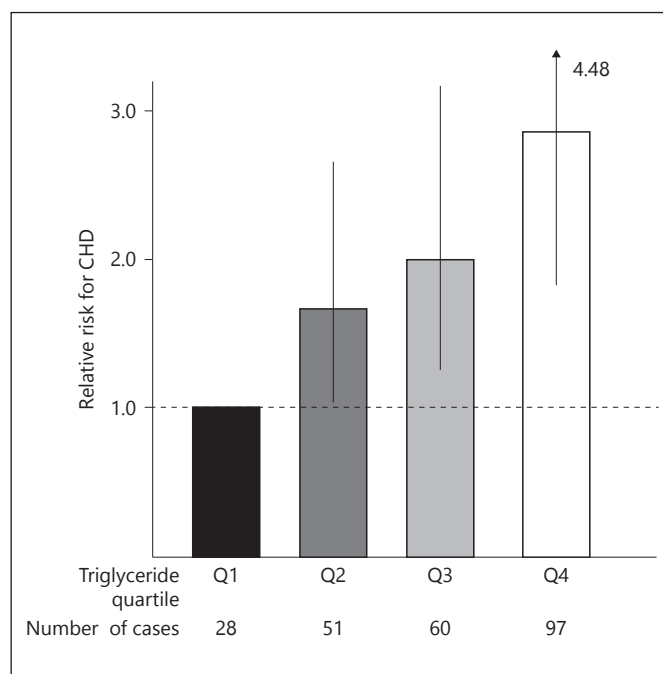
Hypertriglyceridemia is a treatment target in JASG2012 [1], with the treatment goal given as <150 mg/dl (1.7 mmol/l) in Chapter 1 of the guidelines and the deleterious effects of hypertriglyceridemia on CHD briefly described in Chapter 3. Here, we evaluate how valid the notion is of the deleterious effects of hypertriglyceridemia on CHD in Japan, as set out in JASG2012. If we exclude the findings from overseas studies that the guidelines cite, only five studies conducted with Japanese participants are presented in Chapter 3 in support of the notion [2–6].

Let's start by examining the oldest study in Japan on the epidemiology of triglycerides that JASG2012 cites. The study was published in the proceedings of the 5th Research Meeting on Triglycerides [2]. Male office workers aged 30–45 years (n = 1,110) were followed for 15 years. During follow up (1977–1992), 5 participants had acute myocardial infarction (MI; 3 fatal cases) and 25 had angina pectoris diagnosed when any of the following criteria were met: medicated for angina pectoris, chest pains

ameliorated with nitrate, ischemic electrocardiographic (ECG) changes at chest pain, positive ECG changes on exercise, and  $\geq 75\%$  stenosis in a coronary artery on angiography. Hypertriglyceridemia was defined as  $\geq 150$  mg/dl (1.7 mmol/l). A significant difference was found in the proportion of participants with hypertriglyceridemia at baseline between participants who subsequently had ischemic heart disease (IHD;  $n = 30$ ) and all participants ( $n = 1,110$ ;  $p < 0.001$ ); the actual proportions were not reported. The mean triglycerides value in the case group was 150 mg/dl (1.7 mmol/l) and that in all participants was 118 mg/dl (1.3 mmol/l) (no SD values were reported). There are three important points, then, to note about this study: no confounding factors were adjusted for; the diagnosis of angina pectoris was not reliable (Chapter 2, Section 1; Chapter 6, Section 2; and Chapter 7, Section 1) and the scale of the study was too small to draw generalized conclusions.

Of the five Japanese studies JASG2012 cites, that by Iso et al. provides the strongest evidence for JASG2012's recommendation to treat hypertriglyceridemia for the prevention of CHD [3]. Yet, only 51% of all participants had their HDL cholesterol levels measured. To examine the relationship between triglycerides and CHD in people with low mean total cholesterol levels, they conducted a 15.5-year prospective study that ended in 1997. Participants were 11,068 Japanese aged 40–69 years, from four communities, who were initially free of CHD and stroke: 4,452 men and 6,616 women with mean total cholesterol levels of  $4.73 \pm 0.88$  mmol/l ( $185 \pm 34$  mg/dl) and  $5.03 \pm 0.91$  mmol/l ( $195 \pm 35$  mg/dl), respectively. During the study period, there were 236 CHD events comprising 133 MIs, 68 angina pectoris events, and 44 sudden cardiac deaths. The incidence of CHD was greater in a dose-response manner across increasing non-fasting triglyceride quartiles (fig. 10-1). The trend was similar for MI, angina pectoris, and sudden cardiac death. The relationship between triglycerides and CHD was not directly associated with total cholesterol levels or HDL cholesterol levels. The multivariate relative risk associated with an increase in triglycerides of 1-mmol/l (89 mg/dl) was 1.29 (1.09–1.53,  $p = 0.004$ ) for men and 1.42 (1.15–1.75,  $p = 0.001$ ) for women. The multivariate relative risk for total mortality in the highest versus lowest triglyceride quartiles was 1.26 (0.90–1.77,  $p = 0.18$ ) for men and 1.50 (0.99–2.27,  $p = 0.05$ ) for women.

However, these results cannot be seen as strong evidence since they were not adjusted for some important lifestyle factors that are confounders. Intake or tissue values of n-3 polyunsaturated fatty acids are well recognized



**Fig. 10-1.** Relationship between serum triglyceride level and risk for coronary heart disease (CHD) [3]. A total of 11,068 Japanese men and women aged 40–69 years were prospectively followed for 15.5 years. Because the associations between non-fasting serum triglycerides and relative risk for CHD were very similar in both men and women, the combined data are shown here. Relative risks were adjusted for age, sex, body mass index quartiles, serum total cholesterol quartiles, cigarette smoking status, hypertensive status, alcohol intake category, serum glucose category, and time since last meal. However, n-3 fatty acid levels were not adjusted for (see the text). Triglyceride quartiles were  $<0.95$ ,  $0.95$ – $1.31$ ,  $1.32$ – $1.88$ , and  $\geq 1.89$  mmol/l ( $<85$ ,  $85$ – $116$ ,  $117$ – $167$ , and  $\geq 168$  mg/dl, respectively).

to be related with both serum triglyceride levels [7, 8] and CHD: without adjustment for n-3 fatty acids, the results from epidemiological studies on triglycerides cannot be deemed valid. Similarly, the other major confounding factors of exercise and sugar intake were not adjusted for in this study [3].

The third study cited by JASG2012 involved 6,966 male employees aged 33–59 years, from a single company in Hokkaido, who had no evidence of coronary artery disease (CAD) [5]. The participants were followed for 10 years. CAD was defined as acute myocardial infarction (AMI) or angina pectoris. During follow up, 111 participants had CAD (74 AMIs, 37 cases of angina pectoris). Baseline triglycerides levels differed significantly between the participants with and without CAD, at 157 (113–207, median with interquartile range) mg/dl [ $1.76$  ( $1.27$ – $2.33$ ) mmol/l] and 110 (78–159) mg/dl [ $1.24$

**Table 10-A.** Sex-specific multivariable-adjusted hazard ratios (HRs) for cardiovascular disease in participants with hypertriglyceridemia ( $\geq 1.69$  mmol/l, 150 mg/dl): Japan Public Health Center-based Study [4]

Sex	Hypertriglyceridemic participants	
	men	women
No. of participants	2,533	3,420
Ischemic heart disease		
No. of events	41	8
HR (95% CI)	<b>1.76 (1.10–2.81)</b>	0.70 (0.31–1.58)
Total stroke		
No. of events	101	68
HR (95% CI)	1.28 (1.00–1.65)	1.14 (0.85–1.52)
Ischemic stroke		
No. of events	69	44
HR (95% CI)	<b>1.42 (1.04–1.93)</b>	1.33 (0.91–1.95)
Hemorrhagic stroke		
No. of events	32	24
HR (95% CI)	1.07 (0.69–1.65)	0.91 (0.57–1.45)
Intraparenchymal hemorrhage		
No. of events	28	15
HR (95% CI)	1.15 (0.71–1.84)	0.97 (0.53–1.76)
Subarachnoid hemorrhage		
No. of events	4	9
HR (95% CI)	0.74 (0.23–2.38)	0.82 (0.39–1.76)

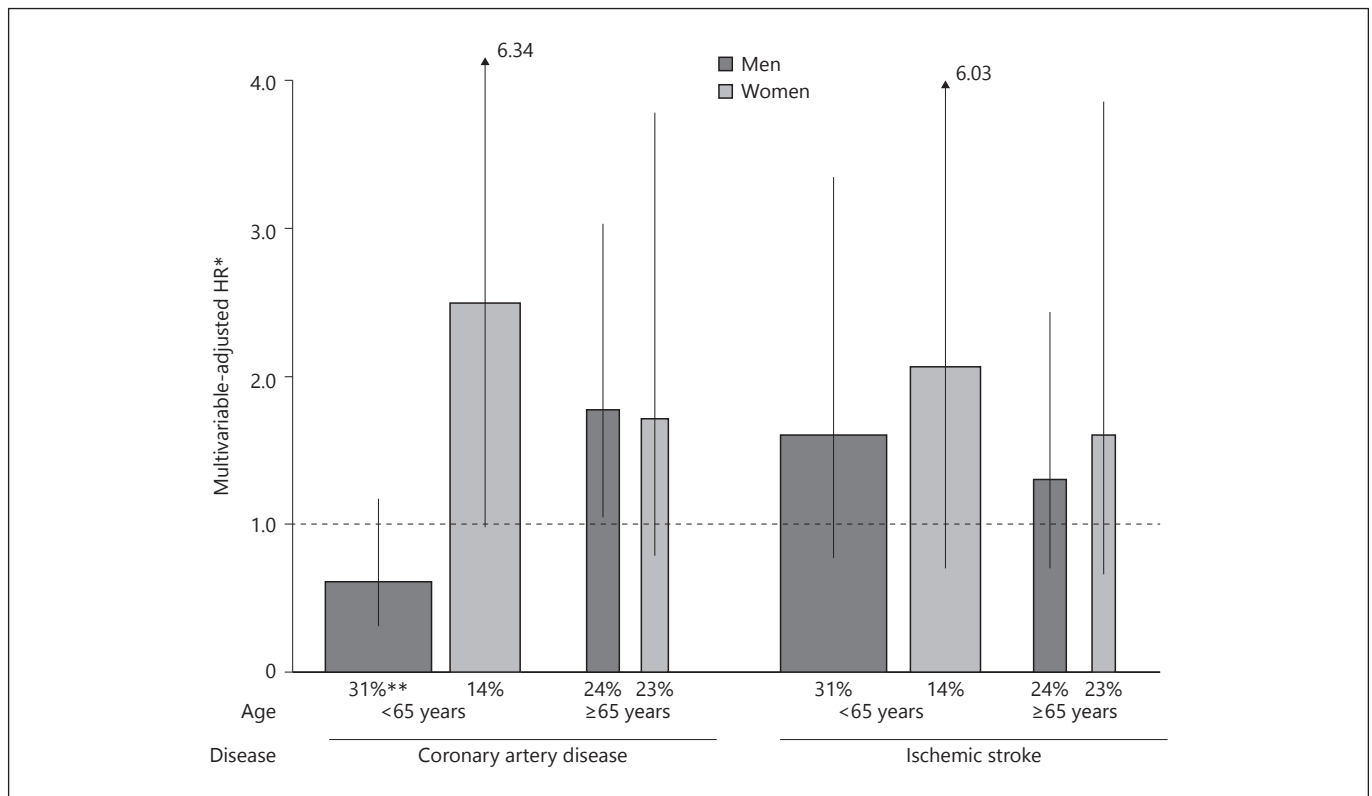
A total of 23,313 participants aged 40–69 years with no history of ischemic heart disease, stroke, or cancer were followed for a median period of 11 years. During follow up, 395 men and 298 women presented with cardiovascular disease as either ischemic heart disease (82 men, 401 women) or stroke (314 men, 258 women). Multivariable HR was adjusted for age, study area, time since last meal, total cholesterol level, smoking status, and ethanol intake. Significant findings are shown in bold. (Remade with permission from the publisher, with slight modifications.)

(0.88–1.79) mmol/l], respectively ( $p < 0.01$ ). The hazard ratio (HR) for CAD for a 1-log increase in triglyceride levels adjusted for 10 possible confounding factors, including total cholesterol and HDL cholesterol, was 3.07 (95% confidence interval [CI]: 1.01–9.35). However, again, the data were not adjusted for the important life-style factors of n-3 fatty acids, sugar intake, or exercise mentioned above.

The fourth study cited by the guidelines, the Japan Public Health Center-based Study, was planned to elucidate the impact of metabolic syndrome on the incidence of IHD and stroke in Japan, and it evaluated the components of metabolic syndrome, including triglyceride levels [4]. A total of 8,249 men and 15,064 women aged 40–69 years with no history of IHD, stroke, or cancer completed a risk-factor survey between 1993 and 1995. Systematic cardiovascular surveillance was carried out throughout 2003, and 693 events of IHD or stroke were identified. The HR for IHD was significantly increased in men with hypertriglyceridemia ( $\geq 1.69$  mmol/l, 150 mg/dl) compared with men without it (multivariable HR:

1.76, 95% CI: 1.10–2.81). However, the trend was the opposite for women (multivariable HR: 0.70, 95% CI: 0.31–1.58). With regard to stroke, only a marginally significant association was observed in men (multivariable HR: 1.28, 95% CI: 1.00–1.65), and no significant association was seen in women (multivariable HR: 1.14, 95% CI: 0.85–1.52). The results of this study seem not to support the notion advocated by JASG2012. And once more, the study had the same serious flaws discussed in previous paragraphs. Table 10-A shows the HRs for IHD and various types of stroke.

The last report cited in JASG2012 in support of the relationship between serum triglycerides and cardiovascular disease is the Suita Study, the original aim of which was also to investigate the relationship between metabolic syndrome and cardiovascular disease [6]. Briefly, in this study, 4,939 Japanese aged 30–79 years living in Suita City were followed for a period of 13 years. Fig. 10-2 shows the multivariable-adjusted HRs for cardiovascular disease in men and women with hypertriglyceridemia ( $\geq 1.7$  mmol/l, 150 mg/dl). The only significantly elevated



**Fig. 10-2.** Multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals for coronary heart disease (CHD) and ischemic stroke in participants with hypertriglyceridemia: Suita Study [6]. A total of 4,939 Japanese residents living in an urban area were followed for 13 years. The only significantly elevated HR compared with normotriglyceridemic participants was observed for CHD in men aged  $\geq 65$  years. During follow up, there were 204 incident cases of stroke, which consisted of 118 ischemic strokes, 43 intra-

cerebral hemorrhages, 22 subarachnoid hemorrhages, and 21 unclassified cases. No association was observed between serum low density lipoprotein cholesterol and ischemic stroke in any group stratified by sex and age  $\geq 65$  years. The study report gave no results for hemorrhagic stroke. \* Compared with normolipidemic participants. \*\* Percentage of hypertriglyceridemic participants in each group; there were 1,657 and 654 men in the groups aged  $<65$  and  $\geq 65$ , respectively, and 2,057 and 571 women, respectively.

HR compared with normotriglyceridemic participants was observed for CAD in men aged  $\geq 65$  years (multivariable HR: 1.77, 95% CI: 1.04–3.02). For this study too, the same comments for the previous four studies apply: the HR related with triglycerides is not a reliable result because no adjustments were made for the important lifestyle factors, particularly n-3 fatty acid intake. We also wonder why this study is not cited in JASG2012's section specifically on the relationship between hypertriglyceridemia and stroke.

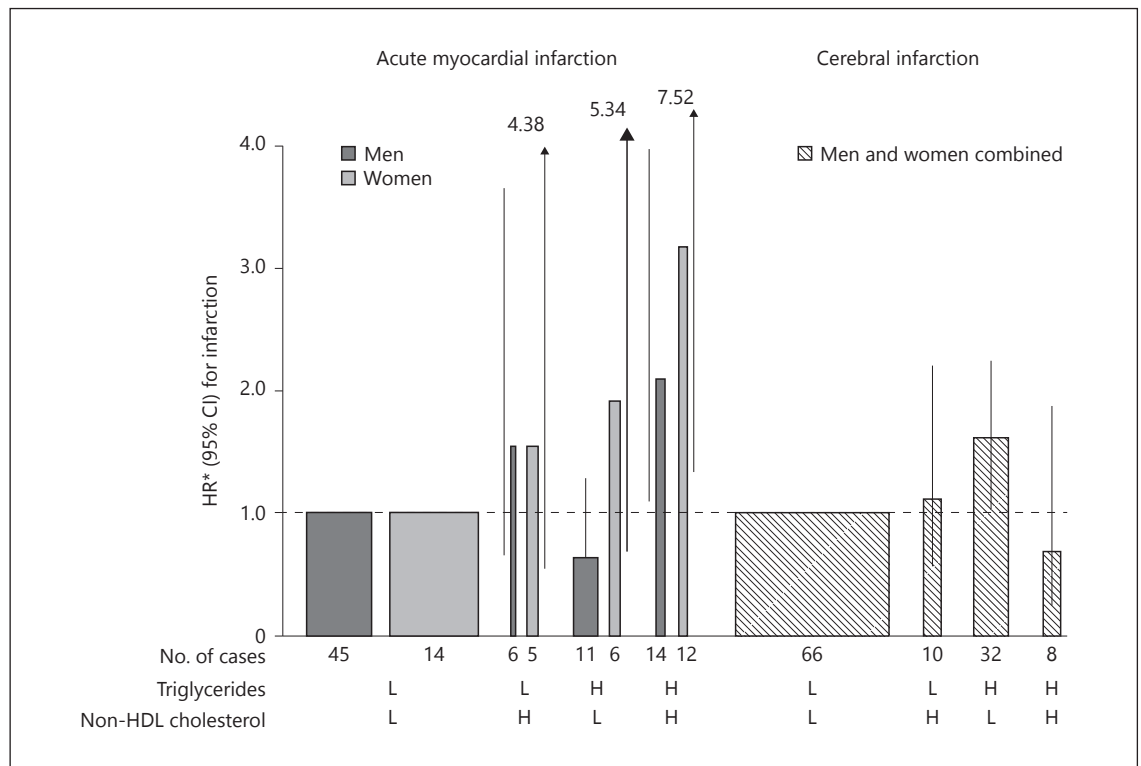
It would seem from our discussion so far that the evidence presented in JASG2012 for treating hypertriglyceridemia, at least in the case of preventing CHD, is tenuous. Let's now look at the hypertriglyceridemia guidelines for preventing stroke before drawing any firm conclusions about whether hypertriglyceridemia should be a treatment target in Japan

## (2) Hypertriglyceridemia: Should It Be Treated to Prevent Stroke?

According to Chapter 3 in JASG2012, 'There are also many reports which indicate that hypertriglyceridemia is a risk factor for cerebral infarction, although its association is weaker than that with CHD.' Let's look at the evidence behind this statement. JASG2012 cites just two epidemiological studies involving only Japanese participants [4, 9] in Chapter 3; the other studies involve either Asian-Pacific populations including Japanese or completely non-Japanese populations.

One of the two studies with a Japanese population is the Japan Public Health Center-based Study [4], which we introduced in the previous section. As shown in table 10-A, on the whole, stroke was barely associated with hypertriglyceridemia, with no significant association found in





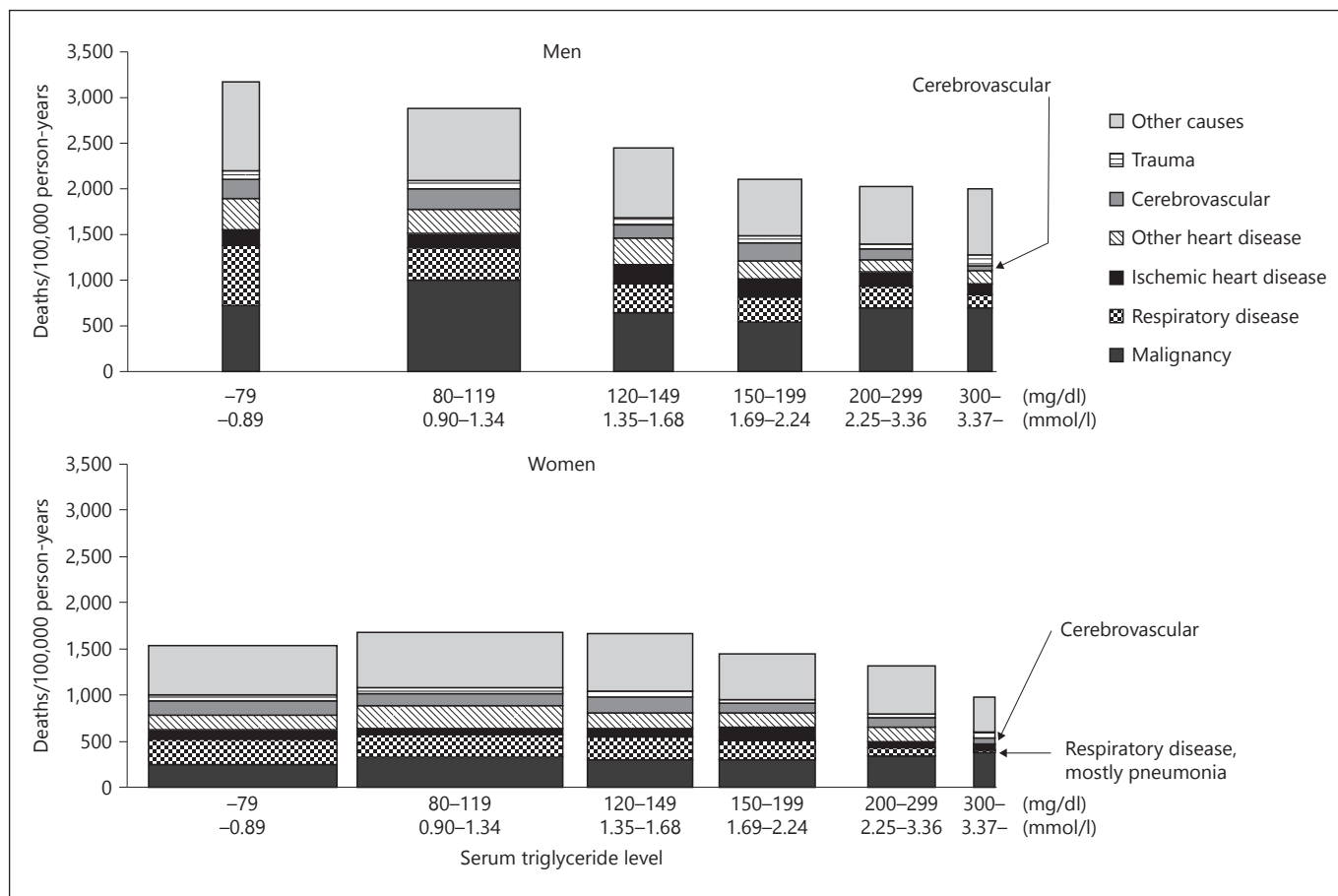
**Fig. 10-3.** Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals for acute myocardial infarction (AMI) and cerebral infarction stratified by triglycerides and non-high density lipoprotein (HDL) cholesterol level: Suita Study [9]. A total of 5,098 Japanese aged 30–79 years who were initially free of stroke or myocardial infarction were followed for a mean period of 11.7 years. HRs for AMI and cerebral infarction was determined after stratifying the participants by a combination of serum triglyceride levels and non-HDL cholesterol levels (four groups). Because of

the very small numbers of cerebral infarction cases, only the combined data for both sexes are depicted in this figure. High triglycerides and high non-HDL cholesterol were defined as  $\geq 1.7$  mmol/l (150 mg/dl) and  $\geq 4.9$  mmol/l (190 mg/dl), respectively. CI = Confidence interval. \* Adjusted for age, body mass index, hypertension, diabetes, HDL cholesterol, cigarette smoking, and alcohol intake by a Cox proportional hazard model; sex was also adjusted in the combined sexes model.

women. The other study cited is another report [9] by the Suita Study, which we also introduced in the previous section [6]. As a brief recap, the Suita Study showed no significant association between ischemic stroke and hypertriglyceridemia in terms of a significant hazard ratio [6]. However, this other Suita Study report [9], published 1 year earlier, had a somewhat complicated design. The study authors tried to elucidate the effects of triglycerides and non-HDL cholesterol levels on stroke and MI. The study methods are essentially the same as described above [6] except that 5,098 Japanese (a slightly larger number) aged 30–79 years and initially free of stroke or MI were followed for a mean period of 11.7 years (a shorter period). The relationship between serum lipid level and the risk for stroke or MI was determined by dividing the participants into four groups stratified by a combination of serum triglyceride levels and non-HDL cholesterol levels.

During follow up, there were 113 cases of AMI and 180 of stroke with the following subtypes: 116 cases of cerebral infarction, 28 cases of intracerebral hemorrhage, 21 cases of subarachnoid hemorrhage, and 15 unclassified cases. Compared with the low triglycerides/low non-HDL cholesterol group, the HR (95% CI) for AMI for men and women combined in the high triglycerides/high non-HDL cholesterol group was 2.55 (1.53–4.24) after adjusting for other cardiovascular risk factors. The HR for cerebral infarction in the high triglycerides alone group was 1.63 (1.03–2.56); however, the risk for cerebral infarction was not significantly increased in the other groups (fig. 10-3).

There was no association between triglycerides or non-HDL cholesterol with incidence of total stroke, intracerebral hemorrhage, or subarachnoid hemorrhage in either sex. When the participants were divided into two



**Fig. 10-4.** Relationship between serum triglyceride level and mortality: Isehara Study [10]. Over 11 years (1994–2004), 8,340 men (aged  $64 \pm 10$  years) and 13,591 women (aged  $61 \pm 12$  years) were followed in Isehara City, Japan. Deaths during the first year of follow up were excluded. Mean follow up was 7.1 years. The width of

each column is proportional to the number of participants in that group. See fig. 1-2 in Chapter 1 for the relationship between low density lipoprotein cholesterol and mortality from coronary heart disease in the Isehara City sample.

groups by age ( $<60$  and  $\geq 60$  years), the results for all the analyses listed above were similar in both age groups (no numerical data were given in the report [9]). Taking both the Suita Study reports together (fig. 10-2 [6] and fig. 10-3 [9]), we would caution that the Suita Study as a whole didn't actually prove any relationship exists between hypertriglyceridemia and cerebral infarction or total stroke.

Taken together, the findings discussed in this section do not constitute valid data in support of the deleterious effects of hypertriglyceridemia on cardiovascular disease. JASG2012 presents a figure similar to our fig. 10-1, but otherwise it does not present any other figures on the relationship between serum triglycerides levels and cardiovascular disease. JASG2012 cites the Suita Study with its very weak association between hypertriglyceri-

demia and cardiovascular disease (as seen from fig. 10-2 and 10-3) simply as 'evidence', without illustrating its results or explaining them fully. Fig. 10-4 shows the relationship between triglyceride levels and all-cause mortality as found by the Isehara Study [10] (see Chapter 1 for a detailed description of this study). Note that deaths from pneumonia (respiratory disease minus cancer) in women and deaths from cerebrovascular disease in both sexes are almost nonexistent in the highest triglyceride groups. These findings are consistent with the notion that serum high lipid levels are beneficial for surviving infections and stroke, yet JASG2012 does not cite the study.

Finally, from the evidence presented in both Sections 1 and 2, we conclude that there is no robust evidence currently available to recommend reducing triglyceride lev-

**Table 10-B.** Associations between cardiovascular disease and high density lipoprotein (HDL) cholesterol in Japan reported by the six studies cited in the 2012 JAS Guidelines

Authors publication year [reference]	Participants	Follow-up period (years)	No. of cases	Adjustment for: Activity Ethanol	Results	Stroke and HDL cholesterol
Kitamura A, et al. 1994 [13]	6,408 workers (men) in Osaka aged 40–59	7.7	CHD = 46 AMI = 21 Stroke = 33	(–) (+)	HR for CHD and definitive AMI was 3–4 times higher in the lowest HDL cholesterol quartile than in the highest	No association
Satoh H, et al. 2006 [14]	2,764 workers (men) aged 35–44 in Hokkaido (see also [5])	10	AMI = 25 Angina pectoris = 10	(–) (+)	HR for CHD at HDL cholesterol levels $\leq 39$ mg/dl (1.01 mmol/l) was 21.71 ( $p < 0.05$ )*	Not reported
Okamura T, et al. 2006 [15]	ND90, see the text (Chapter 9, Section 3).	9.6	All-cause deaths = 636 CHD deaths = 25	(–) (+)	HR for all-cause mortality was inversely associated with HDL cholesterol, but not HR for CHD death	Participants with low levels of HDL cholesterol had an increased HR for ischemic stroke
Maruyama K, et al. 2009 [16]	Male workers aged 35–65 in 76 companies	Case control study	MI = 241, Controls = 482	(–) (+)	Odds ratio for AMI per 1 SD increment of HDL cholesterol was 0.53 (0.38–0.75)	Not reported
Noda H, et al. 2009 [4]	See table 10-A	11	IHD = 82 men, 401 women	(–) (+)	Men, but not women, with low HDL cholesterol had an increased HR for ischemic heart disease	Participants with low levels of HDL cholesterol had an increased HR for ischemic stroke
Yokokawa H, et al. 2011 [17]	24,566 participants aged $\geq 18$ without cardiovascular disease	2.7	AMI = 35 men, 5 women Ischemic stroke = 114 men, 68 women	(–) (–)	HR for AMI in men was 0.20 ( $p = 0.03$ ) in the third HDL cholesterol quartile compared with the first	No association (ischemic stroke)

CHD = Coronary heart disease; AMI = acute myocardial infarction.

Multivariable-adjusted hazard ratios (HRs) or odds ratios are employed here. None of the studies were adjusted for daily activity. Some studies did not even adjust for ethanol intake. \* Values calculated against the reference group (HDL cholesterol  $\geq 60$  mg/dl, 1.55 mmol/l) where there was only 1 case of coronary artery disease.

els below 150 mg/dl (1.7 mmol/l) in the Japanese population. We urge JAS to reconsider its recommendations in JASG2012.

### (3) What Do Low Levels of High Density Lipoprotein Cholesterol Mean?

Low levels of HDL cholesterol are also a target for dyslipidemia treatment in JASG2012. The guidelines cite eight Japanese epidemiological studies [4, 11–17] to emphasize an inverse relationship between HDL cholesterol levels and CHD. (We omit mention of two reports on ‘cohorts’ [11, 12] from further discussion, because participants of both were all taking simvastatin.) In the next paragraph, we discuss the many problems with these remaining six epidemiological studies. They are

summarized in table 10-B. To cut a long story short, none of the six studies were robust enough to indicate significant associations between serum HDL cholesterol levels and CHD incidence or mortality.

HDL cholesterol levels are known to increase with a healthy lifestyle, especially with regular exercise [18]. One of the most important explanatory links between high HDL cholesterol levels and CHD prevention is probably the amount of daily exercise, yet none of the data listed in table 10-B were adjusted for daily exercise. Ethanol intake is also regarded as another explanatory link, although moderate intake may be a surrogate marker for enjoyment of life. Two of the studies listed in table 10-B did not even account for ethanol intake [14, 17]. Of the four remaining studies, first, Okamura et al.’s report on the NIPPON DATA90 and ND90 studies surprisingly showed a non-significant association

between HDL cholesterol levels and CHD mortality (see also Appendix 4 below) [15]. Second, one study was just a case-control study [16], and case-control studies should not be used for guidelines because they are far less reliable than prospective studies. The third study did not include women at all [13]. And the last study, which included women, actually found no significant association between HDL cholesterol levels and CHD mortality in women [4]. Although the last two studies reported a significant association between HDL cholesterol levels and incident CHD in men [4, 13], we argue that these results are not reliable because the statistical calculations didn't adjust for exercise.

Interestingly, there is evidence that HDL cholesterol is simply a surrogate marker for lifestyle. The administration of cholesteryl ester transfer protein (CETP) inhibitors, which serve to increase HDL cholesterol over 100%, have not shown any beneficial effects: early results from the ILLUMINATE trial with torcetrapib, the first CETP inhibitor, actually showed an increase in all-cause mortality [19]. Another CETP inhibitor, dalcetrapib, showed no benefits in patients who had recently suffered an acute coronary syndrome event [20].

So, in answer to our question of what do low levels of HDL cholesterol mean, we recommend that subjects with low HDL cholesterol levels focus on some-

thing other than HDL. Considering the lack of effectiveness of CETP inhibitors for CHD prevention, HDL cholesterol levels may just be a surrogate marker for a healthy lifestyle and so should not be manipulated by anything other than lifestyle management. Instead, exercise should be the first management strategy recommended.

#### Appendix 4: High Density Lipoprotein Cholesterol and All-Cause Mortality in Okamura et al's Report (ND90)

Okamura et al's report on the ND90 study [15] is described in JASG2012 in Chapter 3, Section 3 [1], where four short summary statements are given, one of which reads '*the incidence of CHD increases with decreasing HDL cholesterol.*' In the text of that section, the ND90 study is explained as follows: '*over 9.6 years of follow up, HDL cholesterol was significantly inversely correlated with not only all-cause mortality but also stroke mortality.*' This description is strange because the theme of the section is CHD, not all-cause or stroke mortality. This instance is the only description about all-cause mortality in JASG2012 as far as we are aware. This description about the association between HDL cholesterol and all-cause mortality seems to us to indicate that JASG2012 members were not able to find any positive associations between total or LDL cholesterol levels and all-cause mortality. As we mentioned in Chapter 1 right at the beginning of this supplementary issue, the opposite is in fact true.

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# Chapter 11 Japan Atherosclerosis Society Treatment Guide for Dyslipidemia (2013)

**Summary:** In 2013, JAS published its latest edition of the Treatment Guide for Dyslipidemia as a sister publication to the 2012 JAS Guidelines (JASG2012). In this treatment guide, JAS publishes conflict of interest (COI) statements for the editors for the first time, a move which everyone will welcome. However, there is still more work to be done as it is not completely clear who received what from whom. On a separate issue, the space allocated to the side effects of statins is very limited in the 2013 guidelines. They also do not recommend immediate cessation of statin use when creatine kinase (CK) levels increase 2–5 times the upper limit of normal. We raise these issues to encourage JAS to review both JASG2012 and the 2013 treatment guidelines and update them to state that statin treatment for dyslipidemia should be more carefully considered in the Japanese population, particularly in those with muscle symptoms and/or higher than normal CK levels.

## (1) Newly Presented Conflicts of Interests Statements

JAS published the latest version of its Treatment Guide for Dyslipidemia for the prevention of atherosclerotic diseases in 2013 [1]. The guide was specifically edited to focus on the treatment of dyslipidemia and it serves as a kind of sister publication to JASG2012, which we have been discussing throughout this supplementary issue. A very welcome addition to this latest edition of the treat-

ment guide is that the JAS Committee have given some information about the editors' COIs. However, we still believe the committee has not gone far enough to ensure complete transparency.

The 2013 treatment guide gives the COI statements on the very first page after the cover page, first briefly describing the rules of COI disclosure, which are said to follow the 'Policy of Conflict of Interest in Clinical Research' ([http://www.naika.or.jp/coi/shishin\\_english.html](http://www.naika.or.jp/coi/shishin_english.html)) of the Japanese Society of Internal Medicine and nine other related societies. The COI information is presented for only one calendar year starting from January 1, 2011, a rather unusual time frame. The section then lists 28 health product companies (mostly pharmaceutical ones) and one publisher as a means to disclose the COIs of the editors. This list is not, however, linked to any of the editor names, so the exact COIs are not clear. That said, we welcome the committee's new addition, although the information is still rather limited and unclear, and we hope that JAS will describe these COIs more fully and transparently at the earliest opportunity.

## (2) Side Effects of Lipid-Lowering Drugs, Such as Statins

The 2013 treatment guide states the side effects of statins in table 9-5 on page 51 [1]. The list is short enough to describe here: *rhabdomyolysis*, *myopathy-like symp-*

toms such as myalgia, lassitude, liver dysfunction, cognitive impairment, increment in fasting blood glucose levels and HbA1c, interstitial pneumonia, etc. The next table in the guide, table 9-6 on page 52, lists each statin available in Japan and its catabolism (i.e., the enzymes, CYP3A4 and CYP2C9, and excretion pathways involved). It also lists competitive drugs against the two CYPs.

On different pages of the guide (pp.54–55), rhabdomyolysis is separately reviewed. There, rhabdomyolysis is defined as a muscle symptom with a more than 10-fold increase over the upper limit of normal CK levels, increased serum creatinine levels, and typically dark brown urine with myoglobin. However, the guide focuses on emphasizing that rhabdomyolysis is a very rare side effect, indicating its zero incidence in the J-LIT series of studies—although the studies are not actually cited in the guide (see Chapter 7, Section 2 of this supplementary issue for our critique of the J-LIT studies)—and it essentially neglects to mention the muscle-related symptoms with a 2- to 9-fold increase over the upper limit of normal serum CK values. The last two sentences of the final para-

graph of the section entitled ‘What is rhabdomyolysis?’ is as follows (our translation):

*‘In fact there are symptomless cases where the CK levels increase to about 3- to 10-fold over the upper limit; when CK elevates to  $\geq 10$ -fold the upper limit, first consider [the possibility of] this side effect [rhabdomyolysis] and stop the drugs; then CK values should be followed up. Muscle exercise can markedly increase CK; so in the case of a 2- to 5-fold increase in CK over the upper limit of normal, it is possible that [the symptom] is **not necessarily** due to rhabdomyolysis, and careful follow-up is required’ (emphasis added).*

Our worry here is that these final two sentences do not clearly encourage physicians to stop statin therapy when patients present with any evidence of statin-related muscle side effects. How can patients be safely managed with CK values nearly 10-fold (or even 5-fold) above the upper limit of normal after the administration of statins? We would instead prefer to see a clear statement that if any muscle symptoms and/or increments in CK are above normal limits, the drugs should be stopped because such a situation is abnormal. We believe that the recommendation in any treatment guide should be that simple.

## Reference

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## Conclusion

In this supplementary issue, using data in large part from Japan where the mean life expectancy has been the longest in the world for decades, we have tried to show that cholesterol is not an enemy but a friend. The general Japanese population with high total cholesterol levels—or with high levels of low density lipoprotein (LDL) cholesterol—have very often been shown in cohort studies to have low all-cause mortality. This phenomenon cannot be explained by so-called reverse causality (i.e., where subjects with an as yet subclinical serious disease and lower cholesterol levels die earlier in a study because of that disease, so cholesterol levels have nothing to do with their longevity). And how do we know this? Because omitting deaths that occurred in the first couple of years of the studies does not markedly change the original results.

What about the most relevant disease with respect to cholesterol, coronary heart disease (CHD)? Some epidemiological studies have found an association between high cholesterol levels and CHD mortality in Japanese men. In Japanese women, however, this association has been found in just one study, the NIPPON DATA80 study with a 17.3-year follow up. In fact, other studies have shown that CHD mortality in Japanese women is not related to cholesterol levels at all or even has an inverse association with cholesterol levels. Closer examination of the studies reveals that the positive association between cholesterol levels and CHD mortality in men is largely explained by the presence of participants with familial hypercholesterolemia (FH); actually, the propor-

tion of FH participants in the NIPPON DATA80 study was about twice that in the general Japanese population. Moreover, the high CHD incidence and mortality rates seen in people with FH cannot really be explained by their cholesterol levels; these levels are essentially the same between people with heterogeneous FH who developed CHD and those who did not.

Cholesterol levels also have some association with cancer, infection, and liver disease: subjects with high cholesterol levels have lower incidence and mortality rates from these diseases. With regard to liver disease specifically, if cholesterol levels are high enough, serious liver disease does not develop. This association too cannot be explained by reverse causality.

Despite the many positive findings about cholesterol we have reviewed and restated in this supplementary issue, we have shown that the evidence the Japan Atherosclerosis Society (JAS) has relied on when creating guidelines is, unfortunately, very weak. One of the most serious problems with the latest version of the JAS Guidelines (JASG2012) is that it uses part of the NIPPON DATA80 risk chart for CHD mortality—the part for men that concerns 10-year absolute mortality for CHD that ranges from <0.5% to 5–10% (a difference of >10-fold). Mortality is calculated according to four factors: smoker or non-smoker, three age groups, five blood pressure levels, and six cholesterol levels. Consequently, there are 180 risk boxes. However, the total number of CHD deaths contained in these 180 boxes is estimated to be just 35 men,

too small a number to scientifically calculate and fill 180 risk boxes (see Fig 5-5 in Chapter 5). Other major issues we have raised include an overly brief description of the side effects of statins in both JASG2012 and the more recently published Japan Atherosclerosis Society Treatment Guide for Dyslipidemia (2013), the failure to recognize triglycerides as a risk factor for cerebrovascular disease, and the continued recommendation to use statins to control cholesterol levels. Based on the evidence we have presented in this issue, we believe it is time for a paradigm shift in the way we view and treat cholesterol.

And it does look like this is starting to happen. In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) released a new guideline for cholesterol [1]. Even if we disregard the fact that the new guideline will eventually increase the numbers of statin users on the order of millions if people are preventively treated for atherosclerotic cardiovascular disease exactly according to the guideline's risk calculator, which overestimates the risk by 50% [2]—and we should not in fact disregard this—the guideline states that ‘...the Expert Panel was unable to find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non-HDL-C levels, as recommended by Adult Treatment Panel III’ [3] (p.12). This statement by ACC/AHA in itself destroys the mainstay of JASG2012 of achieving target LDL-cholesterol levels (see Fig 5-5 in Chapter 5).

Our fervent wish is that, through this supplementary issue, people can see that the cholesterol hypothesis relies on very weak data—and sometimes considerably distorted data. Indeed, many studies in Japan actually show that cholesterol plays a very positive role in health. We hope

that JAS, and the government authorities that defer to JAS's recommendations, will move toward recognizing cholesterol as a friend not an enemy. In the meantime, we will continue pushing for acceptance of the anti-cholesterol hypothesis, to reverse what we see as the biggest mistake made by medical science in the previous century.

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‘Fat and Cholesterol are Good for You!’ by Uffe Ravnskov, 2009, GB Publishing, Sweden.

### Conflict of Interest

TH is a member of the Science Board of Aker BioMarine Antarctic and has received travel expenses. HO, YO, and RH have nothing to declare.

Our policy: To report if US\$ 5,000 or more was received during the four-year period from January 2011 to the date of publication from any organizations that may possibly influence the content of this supplementary issue.

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