REVIEW

Blood Cholesterol Level and Risk of Stroke in Community-based or Worksite Cohort Studies: A Review of Japanese Cohort Studies in the Past 20 years

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Evidence of the causal relationship between hypercholesterolemia and coronary artery disease (CAD) has been established worldwide. However, little attention has been paid to the relationship between hypercholesterolemia and stroke, despite stroke being the most common cardiovascular disease in Japan. We therefore reviewed cohort studies that investigated this relationship in the Japanese population over the past 20 years, and compared their findings with clinical trials and cohort studies in Western countries. Fourteen cohort studies were carried out in Japan during this period. The number of subjects in the studies ranged from 1621 to 91,219 and the mean follow-up period ranged from 7.6 to 32 years. The majority of studies showed no association between hypercholesterolemia and total stroke. However, one report showed a positive association between low-density lipoprotein cholesterol and atherothrombotic cerebral infarction. The relationship between hypercholesterolemia and cerebral infarction may be modified by the proportion of atherothrombotic infarctions in the population surveyed. Randomized controlled trials on statins have shown a substantial reduction in cerebral infarction, and so the discrepancy between cohort studies and clinical trials requires further study. However, some studies have reported that subjects with low blood cholesterol are more susceptible to intracerebral hemorrhage. Two hypotheses have been proposed to explain this association between low cholesterol and intracerebral hemorrhage. First, low blood cholesterol may induce angionecrosis, possibly in combination with hypertension, and second, low blood cholesterol may reflect a poor nutritional status. Either way, further continuous research in various fields of medical science is required to clarify the overall effect of blood cholesterol on stroke in humans. (Keio J Med 61 (3) : 79–88, September 2012)

***Keywords*: cholesterol, stroke, cohort studies, cerebral infarction, intracerebral hemorrhage**

Introduction

The causal relationship between coronary artery disease (CAD) and high serum levels of total cholesterol (TC) or low-density lipoprotein cholesterol (LDLC) is well established.[1–4] Serum cholesterol levels are therefore the main target for lipid management and prevention of atherosclerotic disease in the guidelines of the majority developed countries. Furthermore, some U.S. cohort studies have suggested that non-high-density lipoprotein cholesterol (non-HDLC) may be a better predictor of CAD.[5,6] Non-HDLC reflects the total cholesterol concentration of all atherogenic lipoproteins and is calculated by subtracting the level of high-density lipoprotein cholesterol (HDLC) from that of TC. The Health and Medical Service Law for the Elderly was enacted in 1982, and as

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a result, all Japanese citizens aged 40 years and over have had the opportunity to undergo screening for TC from 1986 and screening for HDLC from 1992. Citizens with dyslipidemia are also provided with health services such as health education to prevent CAD. For this screening system, the basis was changed from TC to LDLC in April 2008.

In contrast, little attention has been paid to the relationship between hypercholesterolemia and stroke, despite stroke being the most common cardiovascular disease in Japan.[7] There is evidence that the mean cholesterol level in the Japanese population has been lower than that in most Western countries for many decades and this is associated with a lower CAD mortality than in Western populations.[7] However, to clarify the relationship between hypercholesterolemia and stroke it is necessary to carry out original cohort studies. This review article focuses on a series of cohort studies performed in Japanese community-based or worksite populations. These studies provide evidence that partially establishes the long-held, but unconfirmed, belief that hypercholesterolemia is associated with stroke.

Overview of Japanese Cohort Studies Carried Out in the Past Two Decades

We performed a PubMed literature search of studies published between January 1991 and August 2011. We used the search terms "*cholesterol*" in combination with "*cerebrovascular disease* or *stroke*," "*Japan* or *Japanese*" and "*cohort studies*." Studies were selected using the following criteria: (1) reports were published in English, (2) studies were performed in Japan, (3) studies were of the prospective cohort type (including nested case–control studies), and (4) statistical analyses were carried out on the relationship between cholesterol levels (TC, LDLC, non-HDLC) and stroke endpoint (fatal and/or non-fatal stroke including its subtypes) adjusted at least for age and hypertension (including blood pressure levels). Finally, we selected potentially relevant articles based on the title and the abstract, and obtained the full text of these articles for detailed review.

Table 1 summarizes the cohort studies carried out on Japanese populations over the past 20 years, listed in chronological order of date of publication. Of the 14 studies,[8–21] 2 studies were on worksite populations[8,18] and the remaining 12 studies were on residents of various communities. All but one of the studies were cohort studies, the exception being a nested case–control study.[13] The number of subjects ranged from 1621 to 91,219, and the mean or median follow-up periods ranged from 7.6 to 32 years. In the cohort studies, the endpoint in eight studies was the first occurrence of stroke and/or its subtypes during the follow-up period,[8–10,14–16,18,19] and in six studies, the endpoint was death due to stroke and/or its subtypes.[11–13,17,20,21] Apart from two studies,[10,16] all the investigations also examined the relationship between TC (or LDLC or non-HDLC) and myocardial infarction (MI) or CAD. A positive association between hypercholesterolemia and CAD was shown in all but two of the studies[20,21] (data not shown in the table). In contrast, the majority of studies showed no association between hypercholesterolemia and total stroke events. Furthermore, some studies reported that community residents with low serum TC or LDLC levels were *more* likely to develop intracerebral hemorrhage.[11–13,17,21] Only one recent report from the Hisayama study showed a positive association between LDLC and atherothrombotic cerebral infarction.[15] Several of the above-mentioned studies are discussed in more detail below.

Summary of Key Studies

1. NIPPON DATA80

The cohort studies of the National Survey on Circulatory Disorders, 1980, Japan, are referred to as NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980).[11,12] The baseline surveys were performed in 1980. In 1980 approximately 10,000 community residents aged 30 years or older from 300 randomly selected districts participated in a survey. **Figure 1** shows the relationship between TC and death due to CAD in the 17.3-year follow-up period of NIPPON DATA80.[12] A positive, graded relationship was observed between the two parameters in men. Although a graded relationship was not observed in women, the group with the highest TC had a significantly increased risk of death from CAD. In contrast, there was no association between TC and the risk of stroke mortality (**Fig. 2**). Limited analysis showed there was also no association between TC and death due to cerebral infarction. However, this study had some limitations. The first is the possible misclassification of stroke diagnosis because the endpoints were determined from death certificates. The second is that TC includes HDLC, a protective factor for atherosclerosis. These issues were therefore addressed by other cohort studies.

2. The Suita study

The Suita study was established in 1989 and invited 12,200 Japanese urban residents of Suita City, Osaka, to participate. The participants were 30–79 years old and were selected randomly from the municipal population registry. Of these, 6485 men and women took part in a baseline medical examination at the National Cardiovascular Center between September 1989 and February 1994. The endpoints of this study were the first incidence of MI or stroke. In this study,[14] the relative risk for MI in the top quintile of LDLC (≥151 mg/dl in men and ≥164 mg/dl in

Table 1 Overview of community-based or worksite cohort studies investigating blood cholesterol levels and stroke in Japan published between January 1991 and August 2011*

Author	Study name	Publication year	Number of subjects	Follow-up years	Endpoints for stroke	Results concerning stroke
Kitamura A, et al.[8]	-	1994	6408 men (Worksite)	7.7	Incidence of total stroke.	TC and total stroke: No relationship.
Nakayama T, et al. [9]	Shibata Study	1997	2302 men and women (Community)	15.5	Incidence of total stroke, cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.	TC and all total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: No relationship.
Tanizaki Y, et al. [10]	Hisayama Study	2000	1621 men and women (Community)	32	Incidence of cerebral infarction and its subtypes: cardioembolic, lacunar, and atherothrombotic.	TC and cerebral infarction: No relationship. TC and lacunar type: No relationship. TC and atherothrombotic type: No relationship. TC and cardioembolic type: No relationship. in men and inverse relationship in women.
Okamura T, et al. [11]	NIPPON DATA80	2003	9216 men and women (Community)	13.2	Death due to total stroke, intracerebral hemorrhage, and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: Inverse relationship in men.
Okamura T, et al. [12]	NIPPON DATA80	2007	9216 men and women (Community)	17.3	Death due to total stroke, intracerebral hemorrhage, and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: Inverse relationship.
Cui R, et al. [13]	JACC Study	2007	345 cases and 345 controls from 39,242 men and women of a cohort study. (Community-based nested case–control study)	10	Death due to total stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction.	TC and total stroke: Inverse relationship. TC and intracerebral hemorrhage: Inverse relationship. TC and subarachnoid hemorrhage: No relationship. TC and cerebral infarction: No relationship.
Okamura T, et al. [14]	Suita Study	2009	4694 men and women (Community)	11.9	Incidence of total stroke and cerebral infarction.	LDLC and total stroke: No relationship. LDLC and cerebral infarction: No relationship. Non-HDLC and total stroke: No relationship. Non-HDLC and cerebral infarction: No relationship.
Imamura T, et al. [15]	Hisayama Study	2009	2351 men and women (Community)	19	Incidence of total stroke, cerebral infarction and its subtypes (cardioembolic, lacunar, and atherothrombotic) and hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage).	LDLC and total stroke: No relationship. LDLC and cerebral infarction: No relationship. LDLC and atherothrombotic type: Positive relationship. LDLC and lacunar type: No relationship. LDLC and cardioembolic type: Inverse relationship. LDLC and hemorrhagic stroke: No relationship.

Author	Study name	Publication year	Number of subjects	Follow-up years	Endpoints for stroke	Results concerning stroke
Ishikawa S, et al. [16]	JMS Cohort Study	2009	12,276 men and women (Community)	10.7	Incidence of total stroke and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship.
Noda H. et al. [17] **	Ibaraki Prefectural Cohort Study	2009	91,219 men and women (Community)	10.3	Death due to total stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction.	LDLC and total stroke: Inverse relationship. LDLC and subarachnoid hemorrhage: No relationship. LDLC and intracerebral hemorrhage: Inverse relationship. LDLC and cerebral infarction: No relationship.
Li Q, et al. [18]	YKK study	2010	1794 men (Worksite)	12	Incidence of total stroke.	TC and total stroke: No relationship.
Tanabe N, et al. [19]	JALS Study	2010	22,430 men and women (Community)	7.6	Incidence of total stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction.	TC and total stroke: No relationship. TC and cerebral infarction: No relationship. TC and intracerebral hemorrhage: No relationship. TC and subarachnoid hemorrhage: No relationship. Non-HDLC and total stroke: No relationship. Non-HDLC and cerebral infarction: No relationship. Non-HDLC and intracerebral hemorrhage: No relationship. Non-HDLC and subarachnoid hemorrhage: No relationship.
Nago N, et al. [20]	JMS cohort study	2011	12,334 men and women (Community)	11.9	Death due to total stroke, hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage), and cerebral infarction.	TC and total stroke: No relationship. TC and hemorrhagic stroke: No relationship. TC and cerebral infarction: No relationship.
Tsuji H, et al. [21]	-	2011	16,461 men and women (Community)	10.9	Death due to total stroke, hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage), and cerebral infarction.	TC and total stroke: Inverse relationship. TC and hemorrhagic stroke: Inverse relationship. TC and cerebral infarction: Inverse relationship.

* Although the nomenclatures of subtypes of stroke were not unified among the cohort studies, they are unified in this table for the reader's convenience.
**Serum LDLC levels in this cohort were calculated by the Friedewald formula, with the majority of serum samples being collected in the non-fasting state.
NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged; JACC Study: The Japan Collaborative Cohort Study; JMS Cohort Study, Jichi Medical School Cohort Study; JALS Study, Japan Arteriosclerosis Longitudinal Study.
TC, total cholesterol; LDLC, low-density lipoprotein cholesterol; non-HDLC, non-high-density lipoprotein cholesterol.

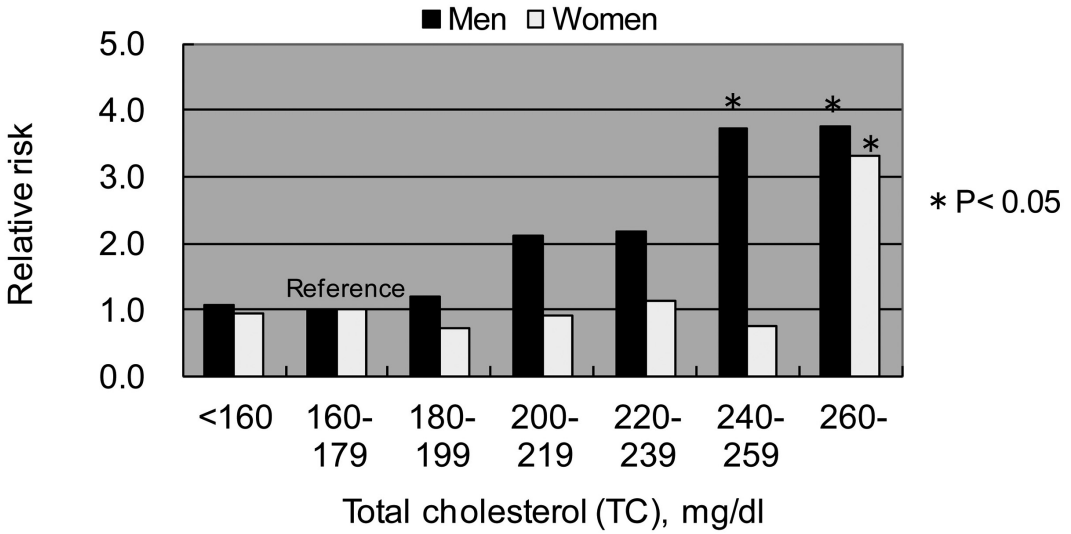

Fig. 1 Total cholesterol and coronary mortality data from NIPPON DATA80.
Multivariable-adjusted relative risk (RR) for coronary artery disease (CAD) mortality grouped according to serum total cholesterol (TC) after adjustment for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking, and alcohol intake. RR data are shown as black bars for men and white bars for women (from Okamura T, et al.[12]). *P< 0.05 vs. reference group.

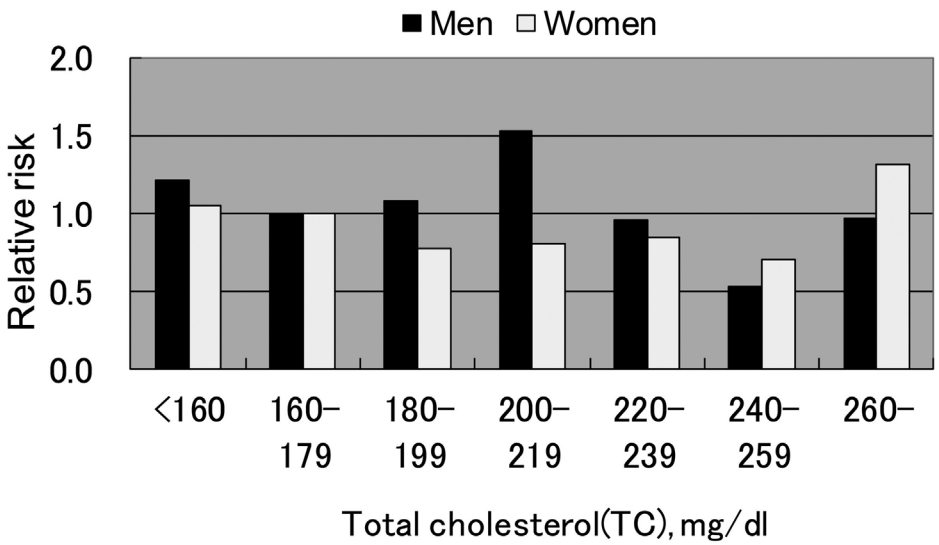

Fig. 2 Total cholesterol and stroke mortality data from NIPPON DATA80.
Multivariable-adjusted relative risk (RR) for stroke mortality grouped according to serum total cholesterol (TC) after adjustment for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking, and alcohol intake. RR data are shown as black bars for men and white bars for women (from Okamura T, et al.[12]). No group has significantly lower or higher RR than the reference group.

women) was approximately three times that in the lowest quintile (<98 mg/dl in men and <106 mg/dl in women). Similar results were also observed for non-HDLC. However, there was no correlation between the incidence of any subtype of stroke and either LDLC or non-HDLC.

The relationship between serum lipids and cerebral infarction warrants further investigation because the study did not evaluate the effect of serum LDLC or non-HDLC

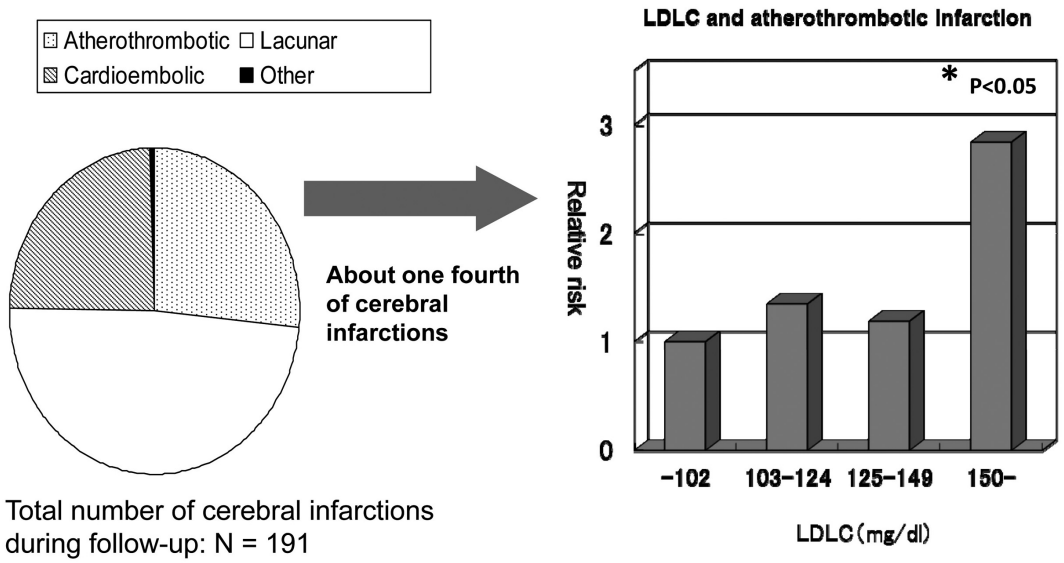

Fig. 3 Low-density lipoprotein cholesterol (LDLC) and atherothrombotic type cerebral infarction in the Hisayama study.
Pie chart (left) showing the proportion of each subtype of cerebral infarction detected during 19 years of follow-up in the Hisayama study. The bar graph (right) shows the relationship between LDLC and relative risk (RR) of atherothrombotic cerebral infarction. Each bar shows RR stratified by LDLC quartiles after adjustment for age, sex, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, ECG abnormalities, fasting blood glucose, body mass index, current drinking, current smoking, and regular exercise (from Imamura T, et al.[15]). *P< 0.05 vs. bottom quartile.

on each subtype of cerebral infarction due to the small number of stroke cases, especially for atherothrombotic cerebral infarctions.

3. The Hisayama study

A cohort study in the town of Hisayama in Fukuoka Prefecture has been ongoing since 1961 and is the most famous cohort study on cardiovascular disease in Japan. In this study, when stroke or CAD occurs or is suspected, physicians in the study team examine the subject and evaluate his/her detailed clinical information. Furthermore, when a subject dies, an autopsy is performed at the Department of Pathology of Kyushu University. In the reference study,[15] a total of 2351 residents were followed-up for 19 years. Analysis showed that the association between LDLC and the incidence of total stroke, cerebral infarction, or hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage) was not significant. However, the risk of atherothrombotic cerebral infarction, which represented about one-fourth of all cerebral infarctions, was increased significantly for the fourth quartile of LDLC compared with the first quartile (**Fig. 3**). In addition, this is the first study in a Japanese population to show an inverse association between LDLC and cardioembolic cerebral infarction. The only limitation in this cohort study is its small number of participants. However, a sufficient number of stroke events have been observed due to the long follow-up period of the study.

Cohort Studies in Western Populations

As described above, the majority of cohort studies in Japan failed to demonstrate a positive relationship between hypercholesterolemia and stroke. In contrast to the universally established evidence that hypercholesterolemia is associated with an increased risk of CAD, the effect of hypercholesterolemia on cerebral infarction remains controversial, even in Western populations. For example, a positive association between TC and cerebral infarction was observed in the multiple risk factor intervention trial (MRFIT) in the U.S.[22] and in the Copenhagen City Heart Study in Europe.[23] However, the Atherosclerosis Risk in Communities Study (ARIC study) showed that TC was not associated with increased risk of total cerebral infarction,[24] although hypercholesterolemia was associated with non-lacunar, non-embolic stroke (i.e., atherothrombotic stroke). Similar results were observed in the Hisayama study.[15] A very large meta-analysis of individual data from 61 prospective studies, most of which were car-

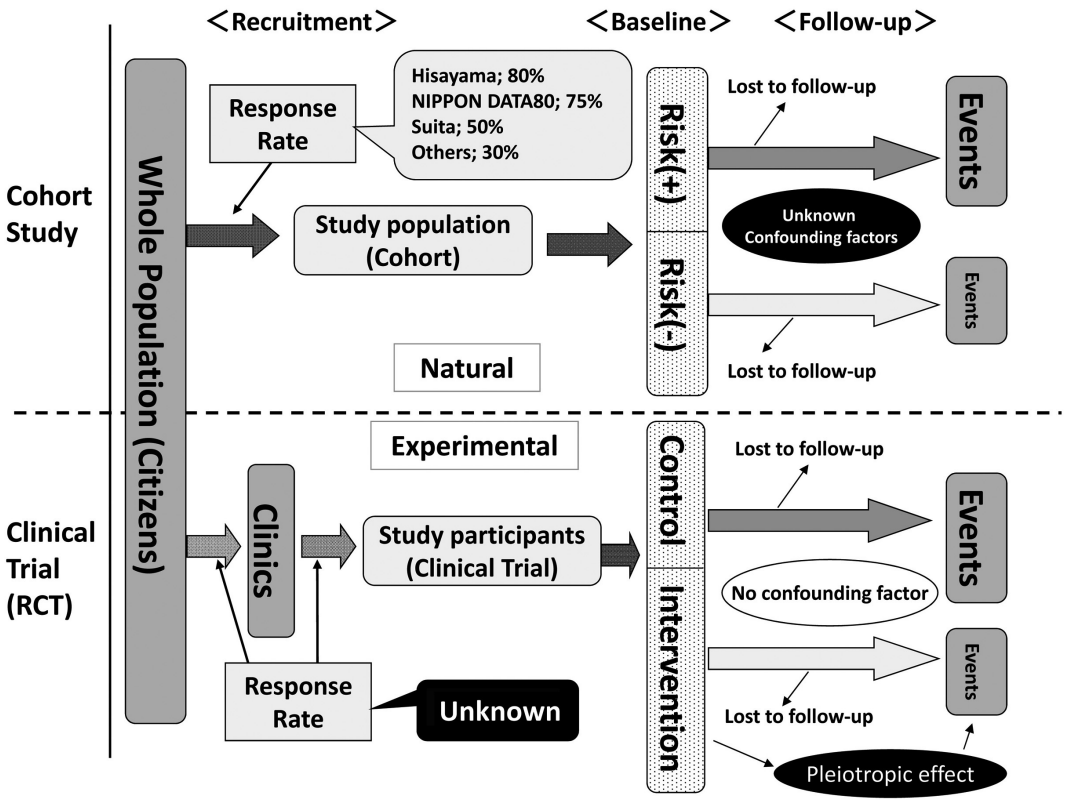

Fig. 4 Putative issues in study design for cohort studies and clinical trials [randomized controlled trials (RCTs)].
In RCTs, there is no information on whether the participants are representative of the parent population. Furthermore, clinical trials may be affected by pleiotropic or off-target effects of each medicine. In contrast, it is possible to accurately calculate the participation rate of the parent population in cohort studies, although theoretically, cohort studies cannot control for unknown confounding factors.

ried out in U.S. and European populations, showed no independent positive association between TC and ischemic and total stroke mortality.[25] Consequently, in cohort studies, the relationship between hypercholesterolemia and cerebral infarction may be modified by the proportion of atherothrombotic infarctions in the population surveyed. In a population or country with a low proportion of atherothrombotic cerebral infarctions, the relationship between hypercholesterolemia and cerebral infarction may be difficult to detect. However, from the viewpoint of patients and the general population, hypercholesterolemia should be thought of as a risk factor for stroke because it does seem to affect the risk of some types of stroke.

Randomized Controlled Trials

Recent randomized controlled trials (RCTs) have shown that statins used as either primary[26] or secondary prevention[27]substantially reduced levels of CAD and cerebral infarction. Statin therapy has also been shown to successfully decrease the risk of cerebral infarction or composite outcome of CAD or cerebral infarction in Japanese trials.[28,29] However, caution is needed when interpreting the results of these clinical trials. First, although there have been numerous clinical trials on statin therapy, the primary endpoint of these studies was CAD, with cerebral infarction usually being the secondary endpoint in the protocols. To our knowledge, only the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) was designed with stroke as the primary endpoint.[30] Second, statins have well-known pleiotropic effects that prevent cardiovascular disease. These include anti-inflammatory effects, an improvement in vascular endothelial function, and plaque stabilization. This may be a reason why we observed a significant discrepancy between the results of cohort studies and clinical trials.[31] However, a recent meta-analysis indicated that further reductions in LDLC result in further decreases in the incidence of cerebral infarction with no evidence of any lower threshold. [32] An ongoing clinical trial to examine whether the addition of ezetimibe to statin therapy improves cardiovascular outcomes compared with statin alone may provide in-

formation concerning the pleiotropic effects of statins. [33] Because both RCTs and cohort studies have fundamental limitations, it is important to take the findings from both study designs into account. The RCT design provides no information as to whether the participants are representative of the parent population, whereas this may be clear in cohort studies. In community-based or worksite cohort studies it is also possible to calculate the participation rate of the parent population. To examine weak associations suggested by cohort studies, such as that between hypercholesterolemia and stroke, it is necessary to use caution and prudence when interpreting the results of clinical trials, even those with an RCT design. The putative issues in both types of study design are summarized in **Figure 4.**

Risk of Low Blood Cholesterol Levels

Five out of 14 studies in **Table 1** observed an inverse relationship between serum TC (or LDLC) and hemorrhagic stroke, mainly intracerebral hemorrhage.[11–13,17,21] In 1990, a National Heart, Lung, and Blood Institute (NHLBI) Conference was held to discuss the associations between low blood cholesterol and non-coronary mortality.[34] The conference concluded that most of the inverse associations between cholesterol and non-coronary mortality, such as cancer, could be explained by reverse-causality such as pre-existing disease, unadjusted confounding factors, and socio-economic status. However, this report recommended that further studies should be undertaken on causal mechanisms linking low TC and hemorrhagic stroke. Several hypotheses have been proposed to explain the inverse association between cholesterol and intracerebral hemorrhage.[35] First, low blood cholesterol may induce angionecrosis, possibly in association with hypertension; however, experimental evidence of this effect is limited. Second, low blood cholesterol may reflect poor nutritional status, which is known to be related to death after onset of stroke, but not to onset *per se*. The inverse association between cholesterol and hemorrhagic stroke is most commonly observed when stroke mortality is the endpoint in cohort studies. Third, there may be some residual confounding factors. In the majority of clinical trials on statin therapy, it is very rare for an increase in intracerebral hemorrhage to be observed during trials. However, in the SPARCL study that used stroke as the primary endpoint, hemorrhagic stroke was more frequently observed in patients treated with statins, especially in those with a past history of hemorrhagic stroke or hypertension.[30] Further research is needed in various fields of medical science to validate these hypotheses and also to explain the findings of the SPARCL study.

The Hisayama study[15] and probably one other study[21] showed an inverse relationship between blood cholesterol and cardioembolic cerebral infarction. We are unaware of any known mechanisms to explain this relationship. One plausible explanation is that low blood cholesterol alone or low dietary magnesium in combination with low blood cholesterol may increase the risk of atrial fibrillation,[36,37] the main risk factor for cardioembolic infarction. However, there is little evidence to support this possibility at the present time.

Conclusions and Directions for Future Research

There have been few cohort studies on the relationship between serum cholesterol levels and cardiovascular disease in Japan. One reason for this is the low incidence in Japan of CAD, which is associated strongly with hypercholesterolemia. As described in this article, the association between hypercholesterolemia and cerebral infraction is weak, making it difficult to perform epidemiologic studies due to the need for large sample sizes to achieve sufficient statistical power.

Furthermore, there are some residual issues to be clarified in the cohort studies in Japan. Some cohort studies in Japan have shown an inverse relationship between HDLC and cerebral infarction or stroke.[38,39] The Suita study showed a positive relationship between serum triglycerides (TG) and cerebral infarction.[40] However, none of these studies showed any association between TC (LDLC) and the risk of cerebral infarction. From the viewpoint of the "lipid hypothesis," it is difficult to understand these findings. Because both HDLC and TG are strongly associated with metabolic syndrome and visceral fat accumulation, participants of cohort studies with abnormalities in these lipids may be affected by the new onset of hypertension during follow-up, which may be related to the incidence of stroke.[41] However, most cohort studies did not evaluate the longitudinal trend for each risk factor after the baseline survey. Accordingly, we need further research to address this concern.

The atherogenic effect of hypercholesterolemia is well established and is based on evidence from numerous epidemiological, pathological, and biological studies. Furthermore, the proportion of atherothrombotic cerebral infarctions may have recently increased in Japan, because this subtype currently accounts for approximately one third of cerebral infarctions in the Japan Standard Stroke Registry Study (JSSRS).[42] We should formulate a confirmed strategy for lipid management to prevent cerebral infarction. Toward this end, further long-term, prospective research needs to be undertaken to clarify the effect of blood cholesterol levels on stroke.

Acknowledgments

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