High serum total cholesterol levels is a risk factor of ischemic stroke for general Japanese population: the JPHC study

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Running Title: Total cholesterol levels and ischemic stroke

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Background: High serum total cholesterol levels represent a risk factor of ischemic stroke in Western countries. However, this association has not been thoroughly investigated in Asian populations where the incidence of stroke is high.

Methods: Participants were 11,727 men and 21,742 women aged 40-69 years, all free of cardiovascular disease and cancer at baseline. During the median 12-year follow-up, we documented 612 ischemic stroke (293 lacunar infarction, 107 large-artery occlusive infarctions, and 168 embolic infarctions).

Results: Excess risk of ischemic stroke was observed in men with serum total cholesterol levels of ≥6.21 mmol/L than those with the lowest category (<4.65 mmol/L), but not in women. The multivariable hazard ratios (HRs) and 95% confidence interval (95%CI) were 1.63(1.14-2.35) for men and 1.03(0.69-1.55) for women. The corresponding HRs of large-artery occlusive infarction were 2.86(1.31-6.27) for men and 0.75(0.28-2.01) for women. Serum total cholesterol levels were not associated with risk of lacunar or embolic infarction for either sex.

Conclusions: High serum total cholesterol is a risk factor of ischemic stroke, specifically large-artery occlusive infarction for Japanese men.

Key words: Cholesterol ■ Ischemic stroke ■ Epidemiology ■ Follow-up study

1. Introduction

Associations of high serum total cholesterol levels with increased risk of ischemic stroke have been reported for Americans [1], Europeans [2], and Japanese-American men [3]. As for ischemic stroke subtypes, the positive association with total cholesterol levels was confined to atherothrombotic infarction according to another study of Americans men and women [4]. Only one study in Japan reported that serum total cholesterol levels was positively associated with increased age-adjusted risk of atherothrombotic infarction for Japanese women aged ≥40 years but not for men [5]. In that study, however, the multivariable-adjustment was not performed probably due to the limited number of cases [5]. No other studies of Asian populations found a positive association between high serum total cholesterol levels and risk of ischemic stroke [6-10].

The aim of the current study was to examine the relation between serum total cholesterol levels and risk of ischemic stroke subtypes in a large Japanese cohort. According to a national survey conducted in Japan, mean serum total cholesterol levels increased from 4.81mmol/L in 1980 to 5.17mmol/L in 2000 for men and from 4.94 to 5.38mmol/L for women aged ≥30 years [11]. The levels in 2000 were not significantly different from those for US adults aged ≥20 years in 1999-2000 reported by the National Health and Nutrition Examination (NHANES) survey: 5.23mmol/L for men and 5.29mmol/L for women [12]. In addition, the prevalence of serum total cholesterol ≥6.21mmol/L increased from 6% to 12% for men and from 9% to 17% for women from the 1980s to the 2000s in Japan [11].

It is therefore important to conduct a thorough investigation of the associations

between serum total cholesterol levels and risk of ischemic stroke in a large Japanese cohort. The Japan Public Health Center based prospective (JPHC) study, which is a community-based study of cardiovascular disease in one of the largest Asian cohorts.

2. Methods

2.1. Surveyed populations

The JPHC study consisted of cohort I, conducted in 1990 with a population aged 40-59 and cohort II, conducted in 1993-1994 with a population aged 40-69 at 11 public health center areas throughout Japan. A total of 113,461 subjects participated in the JPHC study (overall response rate: 81%) and the health checkup data were collected from 34% of the subjects [13]. Two public health center areas from Tokyo and Osaka were excluded from this study because stroke incidence data were not available. Data regarding lifestyle, serum total cholesterol and high-density lipoprotein (HDL) cholesterol, blood pressure, height in stocking feet and weight in light clothing were obtainable for 34,780 subjects (12,195 men and 22,585 women). These subjects participated in the health checkup examinations during the same year as the baseline survey. We excluded the subjects who self-reported coronary heart disease, stroke or cancer at baseline. This left a total of 33,469 subjects (11,727 men and 21,742 women) who were used for the analyses. The study protocol was approved by the human ethics review committees of the National Cancer Center and Osaka University Graduate School of Medicine.

2.2. Baseline Questionnaire and Health Check-up Examination

A self-administered questionnaire was administered at baseline and covered med-

ical history, smoking habit and alcohol consumption. The amount of ethanol per week was estimated based on the weekly frequency of drinking. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or antihypertensive medication use. Persons who smoked ≥1cigarette/day were defined as current smokers. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2).

Data for serum total cholesterol and HDL- cholesterol in non-fasting state were available. Serum total cholesterol was measured by using an enzymatic method at 23 laboratories. According to the Osaka Medical Center for Health Science and Promotion, a member of the US Cholesterol Reference Method Laboratory Network [14], the precision and accuracy of the cholesterol measurements at all laboratories were satisfactory, with a mean coefficient of variation of 0.78% for precision and a mean percentage bias versus the target value of ±0.30%. Non HDL-cholesterol (mmol/L) was calculated by total cholesterol (mmol/L) minus HDL cholesterol (mmol/L).

2.3. Confirmation of Stroke Incidence

A total of 78 hospitals were registered in the sampling areas of the JPHC cohort. They were all major hospitals where acute stroke cases would be admitted. All medical records of strokes were reviewed by hospital physicians, public health center physi-

cians, or research physicians who were blinded to the baseline data, using standard format of registry. Stroke events were registered during the baseline survey and January 1, 2005.

To complete the surveillance for fatal stroke, we also conducted a systematic search of death certificates. For all fatal strokes was determined based on the codes I60-I69 of the International Classification of Diseases, 10th Revision (ICD-10), and that had been listed on the death certificate but not registered. Medical records at the registered hospitals were reviewed by hospital workers, research physician, and epidemiologists.

For non-fatal strokes, we asked by letter or telephone about the onset of stroke and for permission to review the medical records of those who had reported a history of non-fatal stroke on the 5th- and 10th-year follow-up questionnaire but had not been registered as stroke cases. Again, all these medical records were reviewed by hospital workers, research physicians, or epidemiologists. Stroke was confirmed based on medical records and meeting the criteria of the National Survey of Stroke [15], which requires a constellation of neurological deficits of sudden or rapid onset lasting at least 24 hours or until death. Strokes were classified as ischemic stroke (lacunar, large-artery occlusive, embolic and unclassified infarctions) and hemorrhagic stroke (intracerebral or subarachnoid hemorrhage) and stroke of undetermined type, primarily

based on computed tomography (CT), magnetic resonance imaging (MRI) or autopsy findings [16]. Infarcts ≤1.5 cm in diameter at based ganglion and/or pons on brain imaging were classified as lacunar infarction, while infarcts >1.5 cm involing cortical areas to be of large-artery occlusive infarction. Definite of embolic infarction required the same criteria as ischemic infarction, plus either a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain or medical record evidence of a possible source of embolus. A stroke case that was diagnosed clinically but showed no lesions on CT, MRI or autopsy was classified as stroke of undetermined type.

2.4. Statistical Analyses

Statistical analyses were based on incidence rates of stroke during the median 12 years of follow-up from 1990 in cohort I and from 1993-1994 in cohort II to the end of 2004. For each person-years of follow-up were calculated from baseline survey until whichever stroke or coronary heart disease came first, death (6.1% of the participants), emigration (4.2% of the participants) or January 1, 2005. The cut-off points of serum total cholesterol based on the combination of clinical criteria from the adult treatment panel III (4.14, 5.17 and 6.21mmol/L) [17] and the Japan Atherosclerotic Society Guideline (5.69 mmol/L) [18]. We added 4.65 mmol/L as an additional cut-off because there was a large number of participants with serum total cholesterol of 4.14-4.64 mmol/L. The

categorioes of serum total cholesterol <4.14 mmol/L and 4.14-4.64 mmol/L were combined because of the small number of incident cases in the category of serum total cholesterol <4.14 mmol/L. Consequently, the HRs and 95%CI of stroke and stroke subtypes were defined as the incidence of these outcomes for the categories of serum total cholesterol, 4.65-5.16 (180-199), 5.17-5.68 (200-219), 5.69-6.20 (220-239), and ≥6.21mmol/L (240mg/dL), divided by that for the reference category of <4.65mmol/L (180mg/dL).

The sex-specific age-adjusted differences in baseline risk characteristics among the categories of serum total cholesterol levels were deteremined with the analysis of covariance and chi-square test. Sex-specific HRs and 95%CI of stroke and its subtypes were calculated after adjusting for age and other potentially confounding factors by using the Cox proportional hazards model. We also analyzed the data with the time-dependent covariate Cox proportional hazards model using the additional data of lipid profiles for 13,243 persons (40% of the participans) who had undergone examination of blood lipids twice.

Potentially confounding factors selected for adjustment were baseline values of age (year), BMI (quartiles), systolic blood pressure (mmHg), serum HDL-cholesterol levels (quartiles), smoking status (never, ex- and current smoking 1-19, 20-29, and ≥30 cigarattes/day), alcohol consumption status (never, ex- and current drinking: ethanol

intake <150, 150-299, 300-449, ≥450g/week), diabetes (yes/no), medication use for hypertension (yes/no) and hyperlipedemia (yes/no), and study area (9 public health center areas).

All *p* values for statistical tests were two-tailed and *p* value <0.05 was regarded as statistically significant. SAS (version 9.13) was used for all statistical analyses.

3. Results

Table 1 shows the population characteristics at baseline examination for the five categories of serum total cholesterol levels. Compared to persons with serum total cholesterol levels <4.65 mmol/L, persons with levels of ≥6.21 mmol/L had higher mean values of BMI, systolic and diastolic blood pressure levels, HDL-cholesterol levels, and were more likely to be hypertensive, have diabetes mellitus and use medication for hyperlipidemia. These associations held true for both men and women, but the men with higher total cholesterol levels were younger and smoked less while such women were older. The subjects with cholesterol values were 3 to 4 years older than those without it for either sex (not shown in Table). However, there were no substantial differences in means of BMI or proportion of history of hypertension and diabetes at baseline except for the proportion of current smoking (men: 45% vs. 55%, women: 3% vs. 8%).

During the median 12-year follow-up of 11,727 men and 21,742 women aged 40-69 years, we documented 622 total strokes for men, composing of 207 hemorrhagic strokes, 354 ischemic strokes (156 lacunar infarctions, 66 large-artery occlusive and 104 cardioembolic infarctions, as well as 28 unclassified ischemic strokes) and 61 stroke of undermined type. The corresponding numbers for women were 563, 263 and 258 (137, 41, 64, and 16) and 42.

Age-adjusted risks of ischemic stroke and large-artery occlusive infarction were higher for men with serum total cholesterol levels of ≥6.21 mmol/L than those with serum levels <4.65 mmol/L but women did not show such associations (Tables 2 and 3). After adjustment for other cardiovascular risk factors, these associations did not

change substantially. The multivariable HRs (95%CI) of ischemic stroke and large-artery occlusive infarction for serum total cholesterol levels of ≥6.21 mmol/L versus <4.65 mmol/L were 1.63(1.14-2.35) and 2.86(1.31-6.27) respectively for men, and 1.03(0.69-1.55) and 0.75(0.28-2.01) for women. The respective multivariable HRs (95%CI) for 1 mmol/L increment of total cholesterol levels were 1.14(1.02-1.28) and 1.30(1.04-1.63) for men, and 1.05(0.92-1.21) and 0.88(0.62-1.24) for women. These associations did not change substantially when they were analyzed with the time-dependent covariate Cox proportional model. The resultant corresponding HRs (95%CI) were 1.84(1.33-2.54) and 2.44(1.05-5.70) for men, and 0.96(0.63-1.47) and 0.87(0.35-2.21) for women. The respective multivariable HRs (95%CI) for 1 mmol/L increment of total cholesterol levels were 1.14(1.03-1.27) and 1.24(0.97-1.58) for men, and 1.04(0.90-1.19) and 1.06(0.76-1.47) for women.

Non HDL-cholestrol levels were also associated with risk of ischemic stroke; the multivariable HRs (95%CI) of ischemic stroke for 1mmol/L increment of non HDL-cholesterol were 1.14(0.99-1.32) for men, 1.16(0.98-1.37) for women, and 1.11(1.00-1.24) for men and women (not shown in Table).

The association of high total cholesterol levels with risk of ischemic stroke tended to be stronger for men aged 40-59 years than for the older men, but an opposite trend was observed for women, the multivariable HR (95%CI) of ischemic stroke for 1 mmol/L increment of total cholesterol levels was 1.22(1.05-1.41) for men aged 40-59 years and 1.06(0.89-1.27) for those aged 60-69 years, p for interaction=0.10; and 0.97(0.80-1.17) and 1.19(0.97-1.47), p for interaction=0.94 respectively for women (not shown in Table).

4. Discussion

As a result of the median 12-year follow-up of middle-aged Japanese, we found that men with serum total cholesterol levels of ≥6.21 mmol/L had a 1.7-fold higher risk of ischemic stroke than those with serum total cholesterol <4.65 mmol/L. Our finding is consistent with the results of previous studies: the multivariable HR for serum total cholesterol <4.14 versus ≥6.21 mmol/L was 1.8 for American men [1], and that for serum total cholesterol <4.91 versus ≥6.21 mmol/L was 1.4 for Japanese-American men [3].

This report constitutes the first evidence of the excess risk of ischemic stroke for men with high serum total cholesterol levels in an Asian population. The appearance of this excess risk may be due to an increase in levels of serum total cholesterol among Japanese during the past several decades [11,19]. While some studies have reported that serum total cholesterol is more strongly associated with non-embolic than with other types of infarction [3,20], we found that the association of excess risk associated with high serum total cholesterol levels held true primarily for large-artery occlusive infarction among men with a HR (95%) of 1.30 (1.04-1.63) per 1mmol/L increment of serum cholesterol levels. In support of this finding, the ARIC study of 14,448 men and women aged 45-64 years reported that a 1 mmol/L increment in serum cholesterol levels was associated with a 1.13 (1.02-1.26) higher risk of large-artery occlusive infarction [4]. In addition, a pathologic study of Japanese men provided evidence that serum total cholesterol levels were higher among fatal cases of large-artery occlusive infarction [21]. High serum total cholesterol levels may thus play an important role in the development of atherosclerotic lesions of basal and large cerebral arteries. In the

present study, a 1 mmol/L increment of non HDL-cholesterol levels was associated with the higher risk of ischemic stroke with HR of 1.11(1.00-1.24) for men and women combined. This result was consistent with that of a mata-analysis of 68 prospective studies, showing the corresponding HR were 1.12 (1.04-1.20) [22].

On the other hand, we found the lack of association between total cholesterol levels and risk of ischemic stroke in women, although the sex interaction did not reach statictical significance (p for interaction = 0.14). Our finding may be due to the shorter incubation period for the exposure to higher cholesterol levels primarily after menopause compared with men [23] and the smaller number of incident ischemic stroke. The result of age-stratified analysis for women a positive association of borderline statistical significance between serum total cholesterol levels and risk of ischemic stroke among women aged 60-69, supports this interpretation.

The strengths of our prospective cohort study are that it has a large population base with a low pecentage of losses to follow-up and uses serum total cholesterol measurements standardized by the US cholesterol reference method laboratory network [14]. These advantages have resulted in a more realistic estimation of the association between serum total cholesterol and stroke incidence. Moreover, more than 98% of the stroke incidence was confirmed by findings of CT, MRI or autopsy. These study characteristics enabled us to conduct analyses for subtypes of ischemic stroke as well.

As for a limitation, the data of serum total cholesterol at baseline was available for only 34% of the study analysis. However, there was no significant difference in baseline characteristics between persons who had the cholesterol data and those

without the data, except for age and smoking. Second, the data of serum total cholesterol at baseline was used for the analysis, so that there is a possibility of intra-individual variability of cholesterol levels, which have may have attenuated the actual associations. However, the associations of high serum total cholesterol levels with risk of ischemic stroke did not alter when the time-dependent covariate Cox proportional model was applied.

In conclusion, our study established that high serum total cholesterol is associated with risk of ischemic stroke, specifically large-artery occlusive infarction, for Japanese men.

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Disclosure:

The authors declared no conflict of interest.

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Table1. Age-adjusted mean values and prevalence of risk factors according to serum total cholesterol category

	Serum total cholesterol categories				
Range, mmol/L (mg/dL)	<4.65 (180)	4.65-5.16 (180-199)	5.17-5.68 (200-219)	5.69-6.20 (220-239)	≥6.21 (240)
Men					
Number	4,166	2,899	2,205	1,405	1,052
Age, year	54.5	54.5	54.7	53.9*	53.6†
HDL-cholesterol, mmol/L	1.35	1.43‡	1.45‡	1.49‡	1.50‡
Body mass index, kg/m^2	23.0	23.6‡	23.6‡	24.0‡	24.3‡
Systolic blood pressure, mmHg	131.4	132.9**	133.3‡	135.0‡	136.6‡
Diastolic blood pressure, mmHg	79.2	80.4‡	81.1‡	81.6‡	82.7‡
Alcohol intake, g/week	294.7	299.9	293.9	283.1	318.6
Current smokers,%	50.2	45.3‡	43.8‡	40.3‡	36.6‡
Hypertension, %	36.8	42.2‡	41.9**	46.1‡	51.8‡
Diabetes mellitus, %	6.1	5.9	6.2	6.1	8.5*
Hyperlipidemia medication use, %	0.6	1.1	1.2*	1.6†	3.4‡
Women					
Number	5,095	4,731	4,801	3,627	3,488
Age, year	51.1	53.4‡	54.3‡	55.8‡	56.2‡
HDL-cholesterol, mmol/L	1.39	1.48‡	1.52‡	1.53‡	1.54‡
Body mass index, kg/m^2	23.2	23.4†	23.7‡	24.0‡	24.3‡
Systolic blood pressure, mmHg	127.5	128.4*	130.4‡	130.6‡	132.1‡
Diastolic blood pressure, mmHg	75.4	76.3‡	77.8‡	78.0‡	79.0‡
Alcohol intake, g/week	69.2	84.8	99.4†	98.3*	79.4
Current smokers,%	3.5	3.3	3.5	2.9	3.3
Hypertension, %	28.9	31.0*	34.8‡	35.8‡	38.9‡
Diabetes mellitus, %	2.5	2.4	2.8	3.0	3.3*
Hyperlipidemia medication use, %	0.9	1.1	1.9†	2.8‡	5.9‡

*p<0.05, †p<0.01,‡p<0.001, compared with serun cholesterol <180mg/dL category.

Table 2. Hazard ratios (HR) and 95% confidence intervals of stroke and stroke subtypes according to serum total cholesterol levels

	Serum total cholesterol categories					HR for 1mmol/L increment
Range, mmol/L (mg/dL)	<4.65 (180)	4.65-5.16 (180-199)	5.17-5.68 (200-219)	5.69-6.20 (220-239)	≥6.21 (240)	
Men						
Person years	51,854	36,139	27,573	17,619	13,028	
Total stroke	217	159	117	67	62	
Age- adjusted HR	1.00	1.05(0.86-1.29)	1.00(0.80-1.26)	0.93(0.71-1.23)	1.20(0.91-1.59)	1.03(0.95-1.12)
Multivariable HR	1.00	1.09(0.88-1.34)	1.04(0.83-1.31)	0.99(0.75-1.31)	1.24(0.92-1.65)	1.07(0.98-1.17)
Hemorrhagic stroke	65	59	45	21	17	
Age- adjusted HR	1.00	1.30(0.92-1.85)	1.29(0.89-1.89)	0.96(0.59-1.58)	1.07(0.63-1.83)	1.06(0.92-1.24)
Multivariable HR	1.00	1.26(0.88-1.80)	1.29(0.88-1.89)	0.93(0.57-1.54)	0.99(0.57-1.71)	1.05(0.90-1.23)
Ischemic stroke	121	89	61	41	42	
Age- adjusted HR	1.00	1.05(0.80-1.38)	0.94(0.69-1.27)	1.03(0.72-1.46)	1.47(1.04-2.09)*	1.09(0.97-1.22)
Multivariable HR	1.00	1.13(0.86-1.49)	1.00(0.73-1.37)	1.16(0.81-1.67)	1.63(1.14-2.35)†	1.14(1.02-1.28)*
Women						
Person years	66,400	60,666	61,276	45,711	43,939	
Total stroke	110	128	107	110	108	
Age- adjusted HR	1.00	1.09(0.84-1.41)	0.86(0.65-1.12)	1.08(0.72-1.40)	1.08(0.83-1.42)	1.04(0.95-1.15)
Multivariable HR	1.00	1.05(0.81-1.36)	0.79(0.61-1.04)	0.99(0.76-1.30)	0.95(0.72-1.25)	1.00(0.91-1.10)
Hemorrhagic stroke	58	62	52	46	45	
Age- adjusted HR	1.00	1.05(0.73-1.51)	0.84(0.58-1.23)	0.94(0.63-1.39)	0.94(0.64-1.40)	0.96(0.84-1.10)
Multivariable HR	1.00	1.00(0.70-1.44)	0.79(0.54-1.15)	0.89(0.59-1.32)	0.86(0.57-1.29)	0.93(0.81-1.07)
Ischemic stroke	45	56	49	55	53	
Age- adjusted HR	1.00	1.12(0.75-1.66)	0.91(0.61-1.36)	1.22(0.82-1.80)	1.21(0.81-1.80)	1.12(0.98-1.28)
Multivariable HR	1.00	1.11(0.75-1.65)	0.85(0.56-1.28)	1.13(0.76-1.69)	1.03(0.69-1.55)	1.05(0.92-1.21)

*p<0.05, †p<0.01, ‡p<0.001 compared with lowest serum total cholesterol category.

Multivariable adjusted for age, BMI, systolic blood pressure, HDL-cholesterol, smoking status, alcohol consumption status, diabetes, medication use for hypertension and hyperlipidemia, and study area.

Table 3. Hazard ratios (HR) and 95% confidence intervals of ischemic stroke subtypes according to serum total cholesterol levels

	Serum total cholesterol categories					HR for 1 mmol/L increment
Range, mmol/L (mg/dL)	<4.65 (180)	4.65-5.16 (180-199)	5.17-5.68 (200-219)	5.69-6.20 (220-239)	≥6.21 (240)	
Men						
Person years	51,854	36,139	27,573	17,619	13,028	
Lacunar infaction	51	39	32	19	15	
Age- adjusted HR	1.00	1.09 (0.72-1.66)	1.16 (0.75-1.81)	1.13 (0.67-1.91)	1.25 (0.70-2.22)	1.07(0.90-1.28)
Multivariable HR	1.00	1.20 (0.79-1.84)	1.29 (0.82-2.02)	1.35 (0.78-2.31)	1.48 (0.82-2.68)	1.16(0.97-1.38)
Large-artery occlusive infaction	18	20	8	9	11	
Age- adjusted HR	1.00	1.59 (0.84-3.01)	0.82 (0.36-1.90)	1.52 (0.68-3.38)	2.60 (1.23-5.51)*	1.29(1.01-1.64)*
Multivariable HR	1.00	1.72(0.90-3.28)	0.88 (0.38-2.04)	1.71 (0.76-3.88)	2.86 (1.31-6.27)†	1.30(1.04-1.63)*
Embolic infarction	39	22	18	13	12	
Age- adjusted HR	1.00	0.81 (0.48-1.36)	0.85 (0.49-1.49)	1.02 (0.54-1.90)	1.32 (0.69-2.53)	1.05(0.85-1.31)
Multivariable HR	1.00	0.82 (0.48-1.39)	0.85 (0.48-1.50)	1.04 (0.55-1.99)	1.26 (0.65-2.48)	1.06(0.85-1.32)
Women						
Person years	66,400	60,666	61,276	45,711	43,939	
Lacunar infaction	20	30	28	25	34	
Age- adjusted HR	1.00	1.33 (0.75-2.34)	1.15 (0.65-2.04)	1.22 (0.68-2.20)	1.70 (0.98-2.97)	1.21(1.01-1.46)*
Multivariable HR	1.00	1.34 (0.76-2.37)	1.11 (0.62-1.98)	1.17 (0.65-2.13)	1.55 (0.88-2.74)	1.17(0.97-1.40)
Large-artery occlusive infaction	9	12	3	9	8	
Age- adjusted HR	1.00	1.22 (0.51-2.89)	0.28 (0.08-1.05)	1.03 (0.41-2.61)	0.94 (0.36-2.45)	0.95(0.67-1.35)
Multivariable HR	1.00	1.26 (0.54-3.00)	0.27 (0.07-1.01)	0.93 (0.36-2.39)	0.75 (0.28-2.01)	0.88(0.62-1.24)
Embolic infarction	14	14	17	10	9	
Age- adjusted HR	1.00	0.90 (0.43-1.89)	1.02 (0.50-2.07)	0.72 (0.32-1.62)	0.66 (0.29-1.54)	0.92(0.69-1.21)
Multivariable HR	1.00	0.93 (0.44-1.96)	0.99 (0.48-2.02)	0.68 (0.30-1.56)	0.57 (0.24-1.35)	0.87(0.65-1.16)

*p<0.05, †p<0.01, ‡p<0.001 compared with lowest serum total cholesterol category.
Multivariable adjustment variables were the same shown in Table 2.