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Total cholesterol and stroke mortality in middle-aged and elderly adults: A prospective cohort study

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ABSTRACT

Background and aims: The association between cholesterol and stroke has been inconsistent. This study aimed to examine the association between total cholesterol (TC) and mortality from total stroke and stroke subtypes.

Methods: 503,340 Korean adults aged 40–80 years without a history of heart disease or stroke participated in routine health examinations in 2002 and 2003, and were followed up until 2013. Adjusted hazard ratios (HRs) for stroke (I60-I69) mortality were calculated.

Results: Nonlinear associations for total stroke (U-curve) and hemorrhagic stroke (L-curve), especially intracerebral hemorrhage (ICH), but a linear association for ischemic stroke, were found. In the range <200 mg/dL, TC was inversely associated with stroke mortality (HR per 39 mg/dL [1 mmol/L] increase = 0.88 [95% CI = 0.80–0.95]), mainly due to hemorrhagic stroke (HR = 0.78 [0.68–0.90]), especially ICH (HR = 0.72 [0.62–0.85]). In the upper range (200–349 mg/dL), TC was positively associated with stroke mortality (HR = 1.09 [1.01–1.16]); ICH and subarachnoid hemorrhage mortality showed no inverse association. The associations were generally similar in middle-aged (40–64 years) and elderly (≥65 years) adults and, in the upper range, each 1 mmol/L (39 mg/dL) higher TC was associated with 11% higher mortality from stroke (95% CI = 2%–21%) in the elderly. Both middle-aged (39%) and elderly (23%) adults had higher ischemic stroke mortality associated with TC ≥240 mg/dL, compare to <200 mg/dL.

Conclusions: TC level around 200 mg/dL was associated with the lowest risk of overall stroke in the elderly and middle-aged adults. No stroke subtype including ICH, was inversely associated with TC in the range ≥200 mg/dL.

1. Introduction

Stroke imposes huge health and economic burdens worldwide [1,2]. The associations between cholesterol and stroke have been inconsistent. Randomized controlled trials have provided evidence that lowering cholesterol, particularly by statins, reduces the risk of stroke, except fatal stroke [3–6]. Accordingly, in the recent European guidelines, statin therapy is recommended for prevention of stroke [7]. Reviews and meta-analyses of prospective cohort studies, however, found no consistent graded association between cholesterol and stroke [8–10]. Furthermore, concerns persist that lowering cholesterol level may increase the risk of hemorrhagic stroke [11–13]. The fact that prospective cohort studies consistently showed inverse associations of cholesterol with hemorrhagic stroke, especially intracerebral hemorrhage (ICH) [10,14,15], fueled these concerns. These discrepancies between studies on the association of cholesterol with overall stroke and stroke subtypes increase the complexity of decision making in the clinical and public health settings, such as whether or when statins can be used in persons with, or at risk for, ICH, or for primary prevention for stroke

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in older adults.

Through a large prospective cohort study, we aimed to examine the association between total cholesterol (TC) and stroke mortality, and to elucidate whether inconsistencies between previous studies may be resolved. TC remains an integral part of risk prediction and prevention models for cardiovascular disease [16–18], and of public health initiatives, such as Healthy People 2020 [1,19], Therefore, precise estimates of association of TC below 140 mg/dL could help inform decision-making for stroke prevention and management, in the coming era of mean TC levels below 180 mg/dL, in populations with much higher TC levels decades ago [1,19].

2. Materials and methods

2.1. Data availability

Data are accessible to researchers by the National Health Insurance Service (NHIS) of Korea, when their study protocol is reviewed and approved by the NHIS [20].

2.2. Study population and follow-up

The NHIS provides compulsory health insurance to 97% of the Korean population [21]. The study cohort (n = 514,795) comprised a random sample of 10% of the 5.15 million NHIS beneficiaries aged 40–79 years in 2002, who underwent health examinations during 2002–2003. Of these subjects, 11,455 were excluded due to missing information on TC (n = 1710), fasting glucose, systolic blood pressure, and body mass index (BMI), due to a history of heart disease and stroke (n = 9693), or due to an extremely high BMI (≥50 kg/m^2, n = 52). For the remaining 503,340 subjects, follow-up on stroke deaths through December 31, 2013 was conducted via record linkage with national death records. The International Classification of Diseases-10th Revision was used to define death from total stroke (I60-I69), and the subtypes of stroke were classified into hemorrhagic stroke (I60-I62), subarachnoid hemorrhage (SAH, I60), intracerebral hemorrhage (ICH, I61-I62), and ischemic stroke (I63). In Korea, hospitals have routinely used computed tomography and/or magnetic resonance imaging for stroke diagnosis since the late 1990s; 89% of hospital admissions used those imaging techniques for stroke according to a nationwide survey in 2000 [22]. The NHIS can provide data without specific informed consent from participants according to the Korean law [20]. This study was approved by the Institutional Review Board of the Catholic Kwandong University, Republic of Korea. The NHIS provided authors with access to the anonymized data.

2.3. Data collection

TC and glucose were assayed using fasting serum samples by enzymatic methods. Systolic blood pressure (SBP) was measured in a seated position using a standard mercury sphygmomanometer. Weight and height were measured to the nearest kilogram and centimeter, respectively [21]. BMI was calculated by weight in kilograms divided by the square of height in meters (kg/m^2). Smoking history, alcohol use, and physical activity were assessed via a questionnaire. Health examination and data collection followed a standard protocol, the Health Examination Practice Guide, officially registered by the Ministry of Health and Welfare. The Korean Association of Quality Assurance for Clinical Laboratory supervised external quality assessment in clinical chemistry, such as TC measurements, for participating hospitals, and assessments of the quality of assays were regularly performed [23].

2.4. Statistical analysis

For analysis, TC levels were categorized into 8 groups (<140, 140–159, 160–179, 180–199 [reference], 200–219, 220–239, 240–259, and ≥260 mg/dL). The category with the lowest mortality was used as reference. Log risk was regressed on TC as a continuous variable within the range <200 mg/dL (termed “lower range”), 200–349 mg/dL (“upper range”), or <350 mg/dL (“full range”), yielding HRs per 39 mg/dL (1 mmol/L) increase in TC in each range. Analysis using a restricted cubic spline transformation of TC with 3 knots (150, 190, and 230 mg/dL) was also performed.

HRs for stroke mortality were calculated using Cox proportional hazards models stratified by age (years) at baseline (40–44, 45–54, 55–64, 65–74, and 75–80) after adjustment for age at baseline (continuous variable; within each age group), sex (when applicable), smoking status (current smoker, former smoker, never smoker, and missing information [n = 21,282]), alcohol use (frequency; monthly or less, 2 days/month to 2 days/week, 3–7 days/week, and missing information [n = 9458]), physical activity (at least once a week; yes, and no), beneficiary income status (deciles; below 4 [low income], 4–7, 8–10 [high income]), BMI (continuous variable), SBP (continuous variable), and fasting glucose (continuous variable). In a sensitivity analysis, lipid-lowering medication use (yes [n = 7742], and no) at baseline was further adjusted for.

The nonlinear associations of TC with stroke mortality were assessed with a likelihood ratio test, in which we compared the model with only the linear term to that with both the linear and the cubic spline terms. Subgroup analyses with varying categories of TC served as sensitivity analyses.

All p values were 2-sided. All analyses used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

During 5,223,381 person-years of follow-up of 503,340 people (45.7% women), 3383 individuals died from stroke: 1184 from hemorrhagic stroke; 354 from SAH; 830 from ICH; and 1044 from ischemic stroke. At baseline the mean age was 52.9 ± 9.7 years and the mean TC level was 200.4 ± 38.7 mg/dL (Table 1), and 14.5% of subjects had TC levels 240 mg/dL or higher. Persons with higher TC values were more likely to be women and current smokers, and were less likely to exhibit frequent alcohol use than those with lower levels. Higher TC levels were associated with older age and higher levels of systolic blood pressure, fasting glucose, and BMI (Table 1).

3.1. TC and stroke mortality

The associations between TC and total stroke mortality were nonlinear. Total stroke mortality showed U-curve associations with a nadir at 200–219 mg/dL (Fig. 1). Mortality from hemorrhagic stroke, especially ICH, was inversely associated with TC in the lower range <200 mg/dL, but not in the upper range (L-curve). Ischemic stroke was positively associated with TC, particularly in the upper range. After adjustment for other confounders, the associations generally did not substantially change (Supplementary Table1). Further adjustment for lipid-lowering medication use at baseline yielded no material change (Supplementary Table2).

In the restricted cubic spline analysis, the patterns of associations and TC values associated with the lowest stroke mortality were generally the same as in the categorical analysis of TC, and the nonlinear associations were statistically confirmed for total stroke and each subtype, except for SAH and ischemic stroke (Fig. 2).

Assuming a linear association below 200 mg/dL, TC was inversely associated with stroke mortality (Fig. 3; HR per 39 mg/dL

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