The Complex Relationship Between Cholesterol and Brain Hemorrhage

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In this issue of *Circulation*, Noda et al report an association between low levels of low-density lipoprotein cholesterol (LDL-C) and an increase in the risk of fatal intraparenchymal intracerebral hemorrhage in a Japanese population-based cohort. The relationship between lipid levels and stroke is complex. The Prospective Studies Collaboration conducted a meta-analysis evaluating the association between blood cholesterol and vascular mortality based on data from 61 prospective cohort studies including nearly 900,000 persons free of vascular disease at baseline (11.6 million person-years at risk). Lower levels of usual total cholesterol were strongly associated with lower risk of fatal ischemic heart disease; every 1 mmol/L lower cholesterol was associated with a 56% reduction (hazard ratio [HR], 0.44; 95% CI, 0.42 to 0.48) in those 40 to 49 years of age, a 34% reduction (HR, 0.66; 95% CI, 0.65 to 0.68) in those 50 to 69 years of age, and a 17% reduction (HR, 0.83; 95% CI, 0.81 to 0.85) in those 70 to 89 years of age. In contrast to death resulting from ischemic heart disease, there was only a weak relationship between usual total cholesterol and death caused by stroke in those 40 to 59 years of age (HR, 0.90; 95% CI, 0.84 to 0.97 for every 1 mmol/L lower cholesterol) and no relationship for older age groups after accounting for blood pressure. An analysis combining the data for the Prospective Studies Collaboration with data from the Multiple Risk Factors Intervention Trial (MRFIT) also found that lower usual total cholesterol was associated with a lower risk of fatal stroke in those 40 to 49 years of age (HR, 0.87; 95% CI, 0.76 to 1.00 per 1 mmol/L lower total cholesterol), with similar reductions in those 50 to 59 (HR, 0.91; 95% CI, 0.85 to 0.97) and 60 to 69 (HR = 0.93; 95% CI 0.89 to 0.97) years of age but no reductions in those >70 years of age.2 There was no relationship between non–high-density lipoprotein cholesterol and stroke risk at any age. Data for analyses based on stroke subtype were limited because many of the studies did not verify whether a stroke was due to ischemia or hemorrhage with neuroimaging. The MRFIT included an analysis of the relationship between total cholesterol and fatal brain hemorrhage.3 Intracranial hemorrhage was 3 times more common (P=0.05) in men with serum cholesterol levels <160 mg/dL compared with those with higher levels, whereas higher levels were associated with an increased risk of ischemic stroke (P=0.007). Although there were too few deaths for meaningful analysis, there was no apparent relationship between non–high-density lipoprotein cholesterol and stroke subtype.

The Prospective Studies Collaboration meta-analysis was based primarily on studies conducted in North America and Western Europe, and MRFIT was done in the United States. The study by Noda et al was carried out in Japan. The Asia-Pacific Cohort collaborators analyzed combined data from 29 regional studies.4 There was a 25% (95% CI, 13 to 40) increased risk of fatal ischemic stroke but a 20% (95% CI, 8 to 30) decreased risk of fatal hemorrhagic stroke for every 4.5-mg/dL increase in total cholesterol. Therefore, in both Western and Asian populations, the relationship between usual total cholesterol and overall stroke may be at least partially obscured by competing risks; higher levels of total cholesterol tend to be associated with an increased risk of ischemic stroke, with lower levels associated with an increased risk of hemorrhagic stroke.

Consistent with the previously cited reports, after multivariable adjustment, the present study identified a lower risk of parenchymal brain hemorrhage associated with higher total cholesterol (HR, 0.55; 95% CI, 0.33 to 0.91; P=0.02 for total cholesterol >240 versus ≤160 mg/dL) but, in addition, found a somewhat stronger relationship with LDL-C (HR, 0.45; 95% CI, 0.30 to 0.69; P<0.001 for LDL-C >140 versus ≤80 mg/dL). The 95% CIs for the point estimates based on these 2 lipid indexes overlap and therefore do not differ significantly. The observation suggesting a relationship between LDL-C and brain hemorrhage supports the findings from a pooled cohort of the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS).5 Multivariable analysis found that older age, black ethnicity, hypertension, lower LDL-C, and lower triglycerides were independently associated with an increased risk of intracerebral hemorrhage. Although uncontrolled hypertension was the strongest risk factor for hemorrhage, the relative rate for the highest compared with the lowest quartile of LDL-C was 0.52 (95% CI, 0.31 to 0.88; P=0.008). The relationship between low, usual LDL-C and brain hemorrhage is further supported by a Korean study using T2*-weighted gradient-echo magnetic resonance imaging to detect “micobleeds,” areas of old extravasation of blood thought to be associated with an increased risk of intracerebral hemorrhage.6 Both total cholesterol and LDL-C levels were lower in those with...
compared with those without such magnetic resonance imaging findings.

Although low, usual total cholesterol and LDL-C levels in persons free of cardiovascular disease or stroke appear to be associated with a higher risk of brain hemorrhage, this does not mean that treating patients with vascular disease with lipid-lowering medications increases risk. A meta-analysis of data from 90,056 participants in 14 randomized trials of statins found that treatment was associated with a 12% reduction in all-cause mortality per 1-mmol/L reduction in LDL-C (rate ratio [RR], 0.88; 95% CI, 0.84 to 0.91; P < 0.0001) and reductions in myocardial infarction or coronary death (RR, 0.77; 95% CI, 0.74 to 0.80; P < 0.0001) and in fatal or nonfatal stroke (RR, 0.83; 95% CI, 0.78 to 0.88; P < 0.0001). There was no increase in brain hemorrhage with treatment (RR, 1.05; 95% CI, 0.78 to 1.41). This is consistent with another meta-analysis that found no relationship between statin therapy and the risk of hemorrhagic stroke (n = 54,334; RR, 0.94; 95% CI, 0.68 to 1.30). The same lack of relationship between lipid lowering with statins and hemorrhagic stroke risk appears to be true in Japanese primary prevention populations. Even achieving very low levels of LDL-C (ie, < 40 mg/ dL or < 64 mg/dL) with statins in patients with coronary heart disease is not associated with an increased risk of brain hemorrhage.

The situation is somewhat more complicated in patients with a prior history of stroke. Secondary analysis of data from the subgroup of patients enrolled in the Heart Protection Study with prior cerebrovascular disease found a nonstatistically significant increase in hemorrhagic stroke in those treated with simvastatin 40 mg/d versus placebo (n = 21 [1.3%] versus n = 11 [0.7%]). There was, however, statistical heterogeneity between those with and without a prior stroke history for the risk of brain hemorrhage (P = 0.03). The Stroke Prevention With Aggressive Reduction of Cholesterol Levels (SPARCL) trial cited by Noda et al in their discussion was a pure secondary cerebrovascular prevention trial. Subjects with a stroke or transient ischemic attack within the preceding 1 to 6 months, an LDL-C between 100 and 190 mg/dL, and no known coronary heart disease were randomized to atorvastatin 80 mg/d or placebo. The overall treatment-related benefit in reducing the primary end point (fatal or nonfatal stroke; adjusted HR, 0.84; 95% CI, 0.71 to 0.99; P = 0.03; unadjusted P = 0.05) was partially attenuated by a treatment-related increase in brain hemorrhage (HR, 1.66; 95% CI, 1.08 to 2.55). Thus, the relationship between statin therapy and the risk of brain hemorrhage may be different in patients with a history of cerebrovascular disease (who overall still benefit from statin treatment) compared with those without such a history.

Noda et al write, “Although it is difficult to confirm the causality between low LDL cholesterol and increased risk of intraparenchymal hemorrhage through the present observational study only, the consistency of epidemiological and experimental evidence [referring to the SPARCL trial in which the average on-treatment LDL-C was 73 mg/dL] . . . supports a causal relationship” (p 2143).

Although the epidemiological data based on usual total cholesterol and LDL-C levels suggest an association between low levels and increased risk of brain hemorrhage, as reviewed above, there is no evidence of a relationship between cholesterol levels and bleeding risk in patients with coronary heart disease whose lipid levels have been lowered medically. Furthermore, exploratory analyses of SPARCL trial data found that the risk of hemorrhage was independently related to treatment assignment, age, sex, a baseline hemorrhage, and uncontrolled hypertension. The risk of hemorrhage was unrelated to LDL-C levels in statin-treated subjects. Regardless of treatment assignment, there were no increase in hemorrhagic stroke in those who had the greatest reductions in LDL-C (HR, 1.04; 95% CI, 0.61 to 1.78; P = 0.8864) and no LDL-C threshold below which the risk of brain hemorrhage was increased.

Establishing causality based on statistical associations from observational studies is always hazardous. In the general population, having low, usual total cholesterol and LDL-C appears to be associated with a higher risk of brain hemorrhage. In contrast, there is no evidence of a similar relationship in persons whose total cholesterol and LDL-C levels have been lowered therapeutically. This suggests no causal relationship between total cholesterol and LDL-C and bleeding risk.

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