Response to Letter Regarding Article, “Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study”

In their comments, Drs Noda and Iso focus on the concluding sentence of my editorial without reference to the preceding discussion that stressed the complex relationship between cholesterol and brain hemorrhage.

It is worthwhile to apply standardized criteria when assessing potential causal relationships. Although imperfect, the Bradford Hill considerations are frequently used for this purpose. These considerations evaluate several domains: (1) strength (stronger associations are more likely to be causal than weaker associations), (2) consistency (the observation is found in different settings), (3) specificity (the effect is specific to an outcome or group), (4) temporality (the exposure must occur before the outcome), (5) biological gradient (dose–response relationship between the factor and the outcome), (6) plausibility (there is a plausible biological mechanism to explain the effect), (7) coherence (the association should be consistent with existing knowledge), (8) experiment (causality is more likely if supported by data from a randomized experiment), and (9) analogy (causality for a specific factor is more likely if causality has been established for a similar factor).

To apply these considerations, the strength of the association between low total cholesterol and hemorrhagic stroke risk is not readily assessable on the basis of epidemiological studies, inasmuch as many do not evaluate stroke subtypes. For a usual total cholesterol of 4.5 mmol/L, however, the Prospective Studies Collaboration meta-analysis reported a hazard ratio of 1.29 for hemorrhagic stroke deaths compared with a hazard ratio of 1.25 for the Multiple Risk Factor Intervention Trial (MRFIT). This suggests that the strength of the association is at least mild to moderate. Other studies with relevant data, including that reported by Dr Noda et al., are reasonably consistent in finding an association between lower usual cholesterol and brain hemorrhage, as are the few that report a similar association with low low-density lipoprotein cholesterol. Although these studies generally control for other factors that may lead to brain hemorrhage, the outcome (brain hemorrhage) is not specific to low cholesterol. In epidemiological studies, having low cholesterol levels temporally precedes the outcome event. Whether there is a gradient in risk is less clear, inasmuch as many studies compare only the highest and lowest quartiles of cholesterol levels. The Prospective Studies Collaboration found no gradient in the effect of usual total cholesterol on the risk of hemorrhagic stroke death (hazard ratio 1.29 for 4.5 mmol/L, 1.00 for 5.25 mmol/L, 0.93 for 5.75 mmol/L, and 0.93 for 6.75 mmol/L)—results similar to their analysis of data from MRFIT. There remains no widely accepted mechanism underlying the association between low usual cholesterol and the risk of brain hemorrhage, although potential explanations have been offered. For example, noting this relationship in another Japanese cohort, other investigators proposed that low cholesterol might contribute to the fragility of the walls of cerebral vessels, thereby predisposing to hemorrhage. Whether a causal relationship between low cholesterol and brain hemorrhage is coherent with other data might be debated, and there is no similar analogous factor. Therefore, some but not all of these Bradford Hill considerations have been met.

The ultimate Bradford Hill consideration in support of causality, however, is evidence from a randomized experiment. Although the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was specifically cited as providing this evidence, the actual analysis found that the risk of brain hemorrhage was independent of achieved cholesterol levels. The latest meta-analysis, including data from 10 trials with 83,205 patients, found that the relative risk of brain hemorrhage with statin treatment was 1.03 (95% confidence interval 0.75–1.41), despite profound lowering of cholesterol levels in several studies. There may be a variety of reasons for the lack of relationship between therapeutically lowered cholesterol levels and the risk of brain hemorrhage, many of which are discussed by Drs Noda and Iso in their letter, but it remains that such data in support of causality do not exist.

If the association between low usual cholesterol levels and the risk of brain hemorrhage is not causal, how else might the association be explained? Persons in the general population with low cholesterol levels may have unmeasured genetic or other characteristics associated with their low levels that is causally related to their risk of brain hemorrhage (ie, it is the unmeasured factor that is associated with low cholesterol rather than the low cholesterol that is causally related to hemorrhage risk). I certainly concur with the assertion of Drs Noda and Iso that “we need to carefully weigh results from both observational and intervention studies in order to draw causal inferences.”

Sources of Funding
Dr Goldstein’s work is supported in part by an American Stroke Association–Bugher Foundation Grant for Stroke Prevention Research grant.

Disclosures
Dr Goldstein is a member of the SPARCL trial steering committee (supported by Pfizer) and a consultant for Pfizer.

Larry B. Goldstein, MD
Duke Stroke Center
Center for Clinical Health Policy Research
Duke University and Durham VA Medical Center
Durham, NC

References
Response to Letter Regarding Article, "Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study"
Larry B. Goldstein

Circulation. 2009;120:e281
doi: 10.1161/CIRCULATIONAHA.109.900399

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/22/e281

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/