Ischemic Stroke Subtypes and Risk Factors: The Probable Bias Arisen From the Classification Style Across Studies

Response:
We thank Dr Tuttolomondo et al for their interest regarding our recent article. In their comments, they address the issue of selecting a precise ischemic stroke classification system to evaluate the relationship between ischemic stroke subtype and diabetes mellitus. An attempt to classify ischemic stroke had been initiated to serve different purposes, including therapeutic decision-making in day-to-day clinical practice, accounting for patients' characteristics in clinical trials, phenotyping of patients in genetic studies, or classifying patients in epidemiological studies. The method of classification depended on the extent of information available for the stroke events, and this itself is highly dependent on the purpose of the study. Clinical trials or hospital-based clinical case series will generally have extensive information available for the stroke events. Apart from these types of studies, community-based surveillance studies for stroke also have been initiated for the purpose of disease detection, assessment of trends, identification of service needs for program and policy development, or research in specific populations. These studies use existing administrative health service data for their purposes, and thus detailed information on the stroke events in these circumstances are often somewhat limited. For our study, which is based on continuous stroke surveillance in an entire community population over a prolonged period of time, we had to depend on health service administrative data sources for case identification and event information. In our methods section, we gave a detailed description of the scheme that we used to classify ischemic stroke subtypes. We classified the ischemic stroke according to criteria adapted from the Atherosclerosis Risk in Communities study, which also used available documentation for the registered stroke events to classify ischemic strokes into different subtypes. It is likely that Dr Tuttolomondo et al misapprehended the scheme that we used to classify ischemic stroke into different subtypes, which the reviewers obviously did not. We described the method of identifying cerebral infarction as the first step, and then we described the method of subclassifying these identified cerebral infarctions. An ischemic stroke without evidence of infarction on imaging was classified as a lacunar event in the presence of symptoms suggestive of lacunar syndrome.

A potential limitation of our study, similar to other studies that used predominantly administrative health data sources for case findings and event registration, is that the subtype classification was made by a review of medical records and neuroimaging reports rather than direct examination of patients or images. Thus, the possibility of misclassification cannot be entirely ignored. Similar to other studies, we also had to define the presence of diabetes based on the history of diabetes before the stroke or elevated blood glucose on admission. We could not distinguish among known diabetes, newly diagnosed diabetes, or stress-induced hyperglycemia. Therefore, there is likelihood that this may have affected the estimation of the impact of diabetes on ischemic stroke subtypes. However, it is not surprising that there was no significant effect of diabetes on lacunar infarction when comparing ischemic stroke subtypes, because diabetes is a risk factor for cerebral infarction and all of the infarction subtypes, as well. Although Tuttolomondo et al raises an issue about the use of TOAST for evaluation of ischemic stroke subtypes and their relation with diabetes, a recent systematic review and meta-analysis by Jackson and Sudlow suggest that the controversial assertion that diabetes is associated with lacunar infarction might have arisen almost entirely from the classification bias when assessing differences in risk factor profiles among ischemic stroke subtypes. This was predominantly suggested for the TOAST classification system, which uses history of risk factors in the ischemic stroke subtype definitions. The apparent excess of diabetes among lacunar infarction disappeared when studies using risk factor-free classification were examined. In another study by Schulz and Rothwell, who performed a meta-analysis of population-based stroke incidence studies, it was reported that there was no association between small vessel stroke and diabetes. On the contrary, as Tuttolomondo et al have mentioned, there are studies that have reported fairly clear association of diabetes mellitus with lacunar infarctions. The population-attributable fraction of diabetes was almost twice as great for lacunar as for nonlacunar stroke, although the cause of this distinction between ischemic stroke subtypes could not be inferred from the data. However, differences between studies in risk factor definitions and in risk factor prevalence are a possible source of bias. Although diabetes was defined differently among studies, this should not have led to any major bias in the results of the meta-analysis, because meta-analysis of within-study estimates is methodologically valid even when the studies use different definitions of diabetes. In the context of the current debate, more data, ideally pooled individual patient data from cohort studies, are required to determine the association between risk factors and ischemic stroke subtypes more reliably.

Regarding the study of Kubo et al, Tuttolomondo et al implied that we did not mention the study in our article. However, we have definitely cited and mentioned this study in our text and references.

Sources of Funding

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(Stroke. 2011;42:e11-e12.)
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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.110.603167
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Stroke. 2011;42:e11-e12; originally published online December 9, 2010;
doi: 10.1161/STROKEAHA.110.603167
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/1/e11