Letters to the Editor

Stroke welcomes Letters to the Editor and will publish them, if suitable, as space permits. They should not exceed 750 words (including references) and may be subject to editing or abridgment. Please submit letters in duplicate, typed double-spaced. Include a fax number for the corresponding author and a completed copyright transfer agreement form (published in every issue).

Differences in Response to Reperfusion Therapies in Acute Stroke Between Men and Women: Mediated by Sex or by Chance?

To the Editor:

Drs. Sandercock and Lewis remind us of some of the very real hazards of subgroup analysis. Performing multiple “one-variable-at-a-time” subgroup analyses will inevitably yield spurious results.1,2 This problem of spurious false-positive results, however, is not one that is directly addressed by increased sample size or statistical power, as they imply. Further, they seem to argue that the proper response to the risk of spurious false-positive results is to cease all analyses on variation in the effect of thrombolysis in stroke until the IST-3 Trial is completed. We respectfully disagree.

Although multiple “one-variable-at-a-time” subgroup analyses may sometimes yield misleading results, for treatments with both risks and benefits such as recombinant tissue plasminogen activator for stroke, reporting only the summary result is also likely to be misleading, because the average effect might not even reflect the risk-benefit trade-offs seen in typical patients within the trial.1–3 This is a true dilemma, and we believe that both terms of this dilemma deserve respect (because patients are harmed by type II as well as by type I error). Although completely satisfactory solutions to this dilemma may not be possible, one approach that we believe has promise is the use of extant databases to develop multivariate risk-benefit models.1–3 These models, informed in part by subgroup analyses such as ours, can then be used to explore treatment-effect heterogeneity when future randomized clinical trial data become available. Hypothesis-generating analyses on “old data” can guide a priori hypothesis-driven analyses on new data (as Sandercock and Lewis appear to implicitly concede at the very end of their editorial).

Regarding specifically our “inappropriate” analyses on the influence of gender on treatment effect, in the pooled analysis of the intravenous recombinant tissue plasminogen activator trials, because we had no a priori expectation of finding this effect, our primary hypothesis, as noted in the discussion, was that the effect arose by chance. Since uncovering this effect, there have been some confirmatory signals, which suggest the results might not be spurious. Perhaps, the most important of these is the relatively consistent finding that women with ischemic stroke do substantially worse than men in the absence of therapy.4–9 A finding confirmed by a recent (and entirely appropriate) subgroup analysis of the International Stroke Trial to which Dr. Sandercock contributed.10 At the same time, no such effect is seen among lytic-treated patients, either in the combined trial database (n=1069, odds ratio for good outcome in men 0.92 [0.72 to 1.18]) or in CASES (n=1135, odds ratio 1.05 [0.82 to 1.24] [M.D.H., unpublished data, 2001]). The presence of a gender effect among the untreated and its absence among the treated implies a treatment-effect interaction of precisely the kind we found.

Additionally, the previous analysis by Kent et al was an adjusted analysis; outcomes in subgroups were presented in unadjusted form just for clarity and transparency. Both unadjusted and adjusted analyses are also reported in the PROACT-2 analysis. The choice for modified Rankin Scale ≤2 for the PROACT-2 analysis was based on the fact that this was the primary outcome for the study, and appropriate for the severe stroke severity of enrollees. Selecting the modified Rankin Scale ≤1, which is reported in our analysis as a secondary analysis, could have been justified on other grounds (eg, consistency with the “inappropriate” analysis of the intravenous trials) and using this outcome would not have uncovered a treatment-effect interaction, as Sandercock and Lewis correctly point out.

Despite appearances to the contrary, we think the methodological disagreements between ourselves and the editorialists are more superficial than they seem. We agree that sorting out which patients benefit from thrombolysis in stroke will require new trials like the IST-3 and ECASS-3. Indeed, multivariate risk-benefit stratification may be most appropriate for interventions informed by a redundancy of prior clinical trials and subgroup analyses.11,12 Thus, we believe that the pending trials present us with more reasons, not less, to torture the old data.

Disclosures

None.

David M. Kent, MD, MS
Institute for Clinical Research and Health Policy Studies
Tufts-New England Medical Center
Boston, Mass

Michael D. Hill, MD, MS
Foothills Hospital
Calgary, Alberta, Canada


Differences in Response to Reperfusion Therapies in Acute Stroke Between Men and Women: Mediated by Sex or by Chance?
David M. Kent and Michael D. Hill

Stroke. 2006;37:2878-2879; originally published online October 19, 2006;
doi: 10.1161/01.STR.0000248166.30486.4f
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
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/37/12/2878

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at:
http://stroke.ahajournals.org//subscriptions/