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 “one-variable-at-a-time” 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 consistently 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 unadjusted 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 thrombolitics 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.

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