Clinical Trial Subgroups
Challenges and Opportunities in Describing the Benefits of Therapy

John Spertus, MD, MPH

Heart disease is the leading cause of death in women in the United States.1 To combat this phenomenon, professional guidelines for primary and secondary prevention as well as sex-specific guidelines for women have been developed and promulgated.2–4 Despite these efforts, there remains some controversy surrounding the benefits of statin therapy in women,5 although a 2004 meta-analysis clearly demonstrated benefits for secondary prevention on nonmortal cardiovascular events.6 In light of these data, current secondary prevention guidelines endorse statin therapy as a class IA recommendation for all patients recovering from an acute coronary syndrome, not just men.7

Despite these recommendations for the use of statin therapy as an effective means for secondary prevention, it remains unclear whether the intensity of lipid-lowering therapy is important. In fact, the entire concept of treating patients to target lipid values, rather than treating on the basis of risk, has been questioned.8 In light of this concern, the current study by Truong et al9 in this issue of Circulation: Cardiovascular Quality and Outcomes, examines the sex-specific benefits of more-intensive statin therapy after acute coronary syndromes in women. Using data from the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial,10 the authors conducted a thorough analysis of outcomes stratified by sex and extended the existing literature by exploring treatment effects among women according to menopausal and estrogen replacement status. They found no evidence of any difference in the nonmortal benefits of more-potent statin treatment in women compared with men. In light of these findings, the study not only provides support to the absolute and relative risk reductions of more-intensive therapy in women (6.7% and 25%, respectively) were numerically greater than that observed in men (3.2% and 14%), the formal test for an interaction was not significant ($P=0.38$ in unadjusted analyses and $P=0.34$ in adjusted analyses). This nonsignificant interaction means that there was no statistically significant difference in the treatment benefits for men and women. Interaction tests formally examine whether the observed effect differs among the subgroups. Without formally testing and providing the interaction, one naturally would assume that the benefits of treatment were larger among women, whereas in reality, these are chance observations, and the overall benefit of intensive statin therapy is similar.

It is quite common for clinical trialists to provide subgroup analyses from their trials, despite well-articulated concerns about the dangers of subgroup analyses.13,14 One of the most notorious examples of the dangers of subgroup analyses was performed by the ISIS-2 (Second International Study of Infarct Survival) investigators, who compared aspirin, streptokinase, both, or neither in the setting of acute myocardial infarction.15 Although the investigators initially did not want to provide subgroup analyses, the editors insisted. So among the 40 subgroups that they provided, the authors also included patients’ zodiac sign and demonstrated a significant interaction between Geminis and Libras in deriving harm from treatment, whereas other astrological signs benefited substantially. The farcical nature of this comparison highlights the challenge of such subgroup analyses. However, such analyses continue to be routinely provided, and readers need to be cautioned about their interpretation. As Yusuf et al13 and Schultz and Grimes14 advised, if subgroup analyses are to be performed, they should be prespecified on the basis of a substantial biological hypothesis, include formal statistical interaction tests, be fully disclosed (including the number of subgroup analyses performed, even if all are not reported), and be interpreted with extreme caution.

Despite these sagely concerns about the use of subgroup analyses, there is 1 important analysis that rarely is provided in clinical trials and needs to become a much more routine part of clinical trial reporting.16,17 When comparing the benefits of a novel intervention, the relative risk reduction (1 minus the relative risk) of an adverse outcome often is reported as the primary analysis. However, if a treatment has a constant relative risk reduction across the population, then the greatest absolute risk reduction would be observed among those patients with the highest risk for an adverse outcome. Because the number of patients that need to be treated to prevent an adverse outcome (1 minus the absolute risk reduction) is smallest among those at the highest risk, more formal analyses of the risks of outcomes—and the interaction of treatment across these strata of risk—should be provided.
Thus, rather than perform subgroup analyses that examine only 1 patient characteristic at a time, we need to recognize that there are likely to be groupings of characteristics that better differentiate the risks and benefits of therapy. These groupings will be categorized most accurately through the use of multivariable models. For example, if one could stratify risk from <2% to >20%, and there was a constant relative risk reduction of 20%, then the number needed to treat in the lowest-risk group is >250, whereas it would be <25 in the highest-risk group. The need to prespecify these types of analyses, to formally build risk models of adverse outcomes, and to test the interaction of treatment across risk categories, as well as to use these data to better identify patients most likely to benefit, could greatly advance the application of trial results to those likely to have the greatest benefit and least risks from therapy.

This concept of using multivariable risk stratification to provide evidence-based estimates of treatment benefit can support individualized treatment recommendations that, in turn, can realize the Institute of Medicine’s goals for safer, more cost-effective care. They also can overcome a limitation of current efforts to create clinical practice guidelines. Guidelines summarize the results of clinical evidence, generally from randomized clinical trials, to support the translation of evidence into practice. Yet, when clinical trials report the mean effect of therapy on outcomes, it is not possible to appreciate the wide variations in benefit that occur as a result of patients’ individual risks. By reporting and underscoring these differences, guidelines will be able to supplement their current recommendations with insights about how best to tailor therapy to patients most likely to benefit. Adopting these strategies of limiting subgroup analyses to those most likely to demonstrate greater benefits, or harms, formally testing and reporting the results, and supporting the translation of such insights into practice, can elevate the insights from clinical trials to support safer, more cost-effective care.

Disclosures
None.

References

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