Erythropoietin in Patients With Acute Myocardial Infarction: No Proof of Effectiveness or Proof of No Effectiveness?

To the Editor:

In patients who have experienced a myocardial infarction (MI), the treatment with erythropoietin (EPO) does not seem to be beneficial. There is not, however, complete agreement on this point. On the one hand, after examining the data of 10 randomized placebo-controlled studies, a recent meta-analysis found no significant improvement in left ventricular ejection fraction (LVEF) (absolute improvement of 0.33% with the 95% confidence interval from −1.24% to 1.90%, \( P = 0.68 \)). Likewise, no improvement was found in other relevant end points. On the other hand, further studies on this treatment are being undertaken, and a query of clinicaltrials.gov (run on June 5, 2013) indicates that 5 trials registered on this Web site are presently under way.

The statistical question addressed by the aforesaid meta-analysis was whether or not the 10 randomized vs placebo-based trials evaluating EPO showed superiority on the end point of LVEF, and the conclusion was no proof of effectiveness (ie, no proof of superiority).

Trial-sequential analysis (TSA) is a relatively new statistical technique that improves the interpretation of meta-analyses, particularly those generating negative results. One merit of TSA is that when appropriate, a more informative conclusion can be provided in terms of proof of no effectiveness (otherwise denoted as futility). In fact, TSA aims to classify each nonsignificant meta-analysis into 1 of 2 mutually exclusive categories: futility or inconclusive result.

We applied TSA to reexamine the 10 randomized studies evaluated by Gao et al. Our analysis considered the end point of LVEF. Our main assumptions included 2-sided testing, risk of type 1 error = 5%, and power = 80%. For LVEF, the intervention effect was set at an anticipated absolute improvement of at least 3%. As usual, the main result of TSA was expressed through the graph of a cumulative Z-curve. With reference to this graph, the boundaries for concluding superiority or inferiority or futility were calculated according to the O'Brien-Fleming \( \alpha \)-spending function. Our analysis employed specific statistical software (User Manual for TSA, Copenhagen Trial Unit 2011; www.ctu.dk/tsa).

Figure 1. Trial sequential analysis: analysis of 10 randomized placebo-controlled trials. In the Z-curve (represented in blue), individual trials correspond to individual segments. Trials are plotted in chronological order (from left to right) with the x-axis indicating the cumulative number of patients; the starting point of the Z-curve is at \( x = 0 \) (ie, inclusion of no trials). At the cumulative number of 1275 included patients, the curve has already crossed the red boundaries and is in the futility area. Green lines are the boundaries for superiority or inferiority, whereas red lines are the boundaries for futility. Abbreviations: C, controls; T, treatment.

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The Figure 1 shows our results. Applying TSA to these 10 randomized trials indicated futility, i.e., proof of no effectiveness. This result is more informative than the mere conclusion of no proof of effectiveness. Furthermore, our TSA estimated that the optimal information size would be 1426 patients, but at the cumulative number of 1275 patients, the results were already sufficient to reach the conclusion of futility. It is noteworthy that the final part of the Z-curve was far beyond the boundary of futility. Futility was confirmed by other TSAs that we ran to test other values of the anticipated LVEF improvement (data not shown).

Because our TSA provided the proof of no effectiveness of EPO for improving LVEF after MI, undertaking new trials in this area seems to make little sense. Our evaluation is also a practical example of the idea that TSA can play to integrate the results of traditional meta-analyses.

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References


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