LETTERS TO THE EDITOR

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Erythropoiesis-stimulating agents in heart failure: no proof of effectiveness or proof of no effectiveness?

The editorial by Kleijn et al.\(^1\) provides an exhaustive update on the controversy surrounding the use of erythropoietin-stimulating agents (ESAs) in heart failure (HF). Several small studies and one meta-analysis\(^2\) had previously suggested a beneficial effect, but the recent large-scale trial\(^3\) found no benefit, given that both the composite endpoint and all-cause mortality were not affected by ESAs. The editorial therefore concludes that ‘anaemia may […] be a marker of disease severity rather than a therapeutic target in patients with HF, and ESA treatment for the correction of anaemia is therefore not recommended.’

One might argue whether a single large-scale trial, as opposed to numerous previous small studies, can be sufficient to settle this controversy. We have therefore addressed this question by applying trial sequential analysis (TSA).\(^4\) The main advantage of TSA is that this technique helps in interpreting controversial findings by classifying results according to four mutually exclusive categories (superiority, inferiority, futility, or inconclusive).

Our TSA had the purpose of re-examining, based on all-cause mortality, the 10 trials studied in the meta-analysis by Kotecha et al.\(^5\) In particular, we added to these trials the results of Swedberg et al.\(^6\) thus obtaining a data set of 11 studies (3042 patients). We assumed two-sided testing, type-1 error = 5%, power = 80%, event frequency for controls = 14.8%, and anticipated a relative risk reduction of 50%. A cumulative Z-curve graph was constructed (with boundaries for superiority, inferiority, or futility according to the O’Brien-Fleming alpha-spending function).

The results of our TSA (Figure 1) clearly indicate futility of ESA treatment, i.e. proof of no effectiveness. This is more informative than the mere conclusion of no proof of effectiveness.\(^7\)

In summary, our results fully support the conclusion by Kleijn et al.,\(^1\) and the main implication of our TSA is that further trials on this issue are not recommended.

Conflict of interest: none declared.

References

Figure 1 Trial sequential analysis of 11 randomized trials. In the z-curve (represented in blue), individual trials correspond to individual segments: trials are plotted in chronological order (from left to right). The x-axis indicates the cumulative number of patients; the starting point of the z-curve is at x = 0, i.e. inclusion of no trials. After estimating that 4078 patients would be needed to reach a conclusion, the curve crosses the red boundaries at the cumulative number of 3042 patients (those of the 11 trials) and permits the conclusion of futility. The graph was plotted according to TSA software (User Manual for TSA. Copenhagen Trial Unit 2011, www.ctu.dk/tsa). Abbreviations and symbols: green lines are the boundaries for superiority or inferiority while red lines are the boundaries for futility; T, treatment; C, controls.
testing in patients with acute decompensated heart failure (ADHF), employing the spectral method, provides sorely needed information regarding the incremental value of this modality in predicting mortality in this burgeoning clinical population which confronts us. The study is important because it reflects a ‘real-world' scenario, in terms of the response of the patients to the invitation to be studied, their eligibility, and the results of TWA testing of an unselected consecutive patient cohort of 1003 patients recently hospitalized with ADHF. From this original cohort, 64.6% consented to the study, and 32.9% were eligible to undergo testing, with results of TWA in this subpopulation being 30% positive, 24% negative, and 46% indeterminate. Ineligibility was due to inability to exercise, atrial fibrillation, or pacemaker dependency. At a mean 3.1 year follow-up, the ineligible patients had statistically significant higher mortality than eligible patients (48% vs. 35%), and univariate and multivariate analyses of TWA testing results did not have a bearing on mortality, while a paradoxical finding of a negative, as opposed to a non-negative, result being an independent predictor of death was detected. It appears that it will be difficult to improve on what has been accomplished by this study, which showed that the spectral TWA testing did not predict mortality, and is associated with high (51%) ineligibility rates in patients with recently diagnosed ADHF. Where can we go from here? Before abandoning TWA testing as a predictor of mortality in patients with ADHF, we should resort to testing, employing the modified moving average time domain method (TWA-MMA), based on Holter ambulatory ECG monitoring, as the authors hinted. One wonders about the optimal testing time for such a technology to be implemented. Perhaps using the present study as a model, a large cohort of patients with ADHF (and with the improved eligibility expected) can undergo a 24 h TWA-MMA testing, starting upon their hospital discharge, with a repeat TWA-MMA testing 1 month later, or on the first post-hospital discharge clinic appointment. This approach will be the most cost-effective way of finding out whether TWA-MMA is of any use, as a predictor of mortality, and what is the optimal time for clinical application of this technology, since this study design will ensure that the enrolled patients will be ‘their own controls'. Perhaps the authors of this important study may be our colleagues who will ‘finish the job', and provide us with the answers in this important area of scientific inquiry.

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Reference

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