Author's response to reviews

Title: The Risk of Paradoxical Embolism (RoPE) Study: Developing risk models for application to ongoing randomized trials of percutaneous patent foramen ovale closure for cryptogenic stroke.

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Version: 2 Date: 12 July 2011

Author's response to reviews: see over
Dear Editors:

We appreciate the positive comments and helpful criticisms from the reviewer of our initial submission. We have made changes in response to Dr Bonnett’s suggestions, including:

1. We have significantly restructured the manuscript so that the Design/Methods section is organized according to the 5 aims and each aim includes its own analytic section. We have included a flow diagram, based on a modified version of that suggested by Dr Bonnett.
2. We have spelled out all abbreviations.
3. We have clarified that all our analyses in aim 2 and aim 3 will be stratified by trial. For model 1, our approach is to separately examine effects across each trial, test for heterogeneity between trials and finally use a generalized linear mixed model that includes a random effect term for study to get final parameter estimates with their corresponding standard errors. For model 2, a similar approach is used and the final Cox models be run including the study as a stratification factor to control for potential between-study differences in baseline survival functions when estimating hazard ratios of potential risk factors.
4. We have defined calibration as comparing observed versus expected outcomes across equal-sized quantiles (typically deciles) based on predicted probabilities.
5. We have not changed the description of our “internal validation.” We have used the terms “evaluate” and “assess” model performance, which will be done on the entire RoPE databases and on the individual components. “Internal validation” (to us) typically implies some resampling procedure, such as bootstrap or jackknife, which is unlikely to add much to our analysis. We will have the opportunity to externally validate the recurrence risk models on the medical arms of the RCTs, as now indicated in aim 5.
6. In testing for an interaction between treatment and the composite index, aim 5 represents the simultaneous external validation of each of the two predictive models, the Bayesian transformation of the PFO propensity and the method by which the two models are combined, as well as the concept that this index will correlate with the probability of benefit from closure. (Failure of this model to validate in this way may arise from problems at any of these steps.) Model 1 cannot otherwise be validated in this population, since only PFO patients are included in the trials and validation of PFO probability predictions requires patients with and without PFO. To aim 5, we have added that Model 2 (recurrence risk) will be externally validated on the pooled medical therapy arms of the trials. Validation of Model 2 in isolation is, however, clearly of secondary importance, and we were therefore brief in describing this.

We include both a clean copy and a copy with track changes.

Again, thank you for considering this manuscript.

Sincerely,

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