Author's response to reviews

Title: Investigation of 95 variants identified in a genome-wide study for association with mortality after acute coronary syndrome

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We again thank the reviewers for their time, expertise, careful reading of our manuscript, and helpful suggestions. Our specific replies to comments appear below.

Reviewer: Jan Bressler
Reviewer's report:
Morgan et al. have submitted a revised version of their manuscript in which they examined the association between 95 polymorphisms identified in a genome-wide association study of premature myocardial infarction and post acute coronary syndrome (ACS) mortality within 3 years. The report is now framed as a negative result since the statistically significant association between ACS and a MTHFDIL variant (rs6922269) first found in a discovery sample of 811 white individuals was not replicated in 3 additional independent cohorts. My previous concerns have been addressed; some suggestions for minor revisions of the current paper are listed below:

Minor Essential Revisions:
1. Results, fifth paragraph: The association between the A/A genotype and all-cause mortality in the combined group of patients is said to be shown in Figure 2. Figure 2 was not included with the manuscript for review.

2. Table 4: The abbreviation “IQR” should be defined.

3. Table 5: The referent genotype for the Cox proportional hazards analysis should be indicated.

4. Appendix: There are several incomplete or missing references which should be provided. Additional information concerning genotyping quality control and call rates for the Cleveland Clinic GeneBank and Emory Cardiology Biobank validation cohorts would be helpful for assessment of these association studies.

Reviewer: Aaron Isaacs
Reviewer's report:
Morgan et al. made numerous substantial improvements to this manuscript and, generally, addressed all of my concerns. A few minor outstanding points:

Minor Essential Revisions
It would be nice to reduce the number of tables. In particular, Table 3 might be
better as a supplement. Tables 4, 5, 6, and 7 could be combined into fewer tables plus some text.

A more informative presentation of the rs6922269 data would be as a meta-analysis and forest plot.

The y-axis on Figure 1 is labeled as expected beta, while the figure title says it depicts p-values.

Discretionary Revisions
The initial data for rs6922269 appears to fit a dominant genetic model. It might be of interest to test such a model.