Coiling and Aneurysm Rerupture: Incomplete Treatment Is a Causal Intermediate Not a Confounder

To the Editor:

The article by Johnston et al reporting an analysis of the predictors of aneurysm rupture after treatment in the Cerebral Aneurysm Rerupture After Treatment (CARAT) study1 captured our attention. The authors are to be commended for their large multicenter approach to this important question. We are concerned, however, that the analysis underemphasizes the relationship between coating and aneurysm rupture and that the probability values reported in the abstract regarding this relationship may be misleading.

First, the unadjusted probability value for the comparison of rerupture rates between coating and clipping (P=0.092) does not account for the high rate of retreatment reported previously by the investigators. Retreatment occurred in 35 of 299 (12%) patients undergoing coating versus 12 of 711 (2%) undergoing clipping.2 Because retreatment may alter the probability of rerupture, not censoring these patients could violate the fundamental assumptions of the log-rank test.3 Indeed, in the body of the article, the authors report that when patients that were retreated were censored, there was a significant relationship between rerupture and whether the aneurysm was treated by coating or clipping (P=0.02). This latter analysis should be included in the abstract.

Second and more importantly, the multivariable adjustment includes the degree of treatment because this is said to be a confounder. This results in the conclusion that coating and aneurysm rerupture are unrelated (P=0.83), contradicting prior studies indicating that the risk of rerupture is higher after coating than clipping.4 The reason for this is that the degree of treatment is a causal intermediate in the pathway from rupture to treatment to prevention of rerupture. If one adjusts for the intermediate factor, the treatment that preceded it becomes insignificant. The standard definition of a confounder is a variable related to both the intervention and the outcome, but not part of the putative causal pathway between the intervention and the outcome. Adjusting for a true confounder decreases bias in the estimate of treatment effect. Adjusting for even a partially causal intermediate will incorrectly remove a true association.5 The current study displays a relationship between degree of aneurysm occlusion and postprocedural rupture. It also emphasizes the relationship between coating and incomplete aneurysm treatment: the odds ratio for a residual neck and a residual aneurysm associated with coating are 11.2 (P<0.0001) and 5.9 (P<0.0001), respectively (contingency analysis of data in Table 2). From a pathophysiological perspective, residual aneurysm after treatment of a ruptured intracranial aneurysm seems like it should be considered a primary intermediate in the pathway between treatment and postprocedural rupture. As such, adjusting for this variable removes the significant relationship between coating and rerupture.

The CARAT study provides further evidence that coating is an effective and lasting treatment for ruptured intracranial aneurysm, particularly when complete treatment can be achieved. This study also demonstrates a significant association between coating and aneurysm rerupture that is mediated in part by a higher proportion of incomplete aneurysm occlusion.

Disclosures

None.

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