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Response by Murthy et al. to Letter Regarding Article, "Restarting Anticoagulant Therapy After Intracranial Hemorrhage: A Systematic Review and Meta-Analysis"

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In Response:

We thank Barco et al for taking interest in our study.[1] The authors highlight important limitations of our study, which though acknowledged in detail are critical to the generation of new knowledge for intracranial hemorrhage (ICH) and stroke prevention, and therefore worth re-emphasis. We would like to reiterate that our aim was to perform the most rigorous possible evaluation of the existing data using meta-analysis guidelines. Given the absence of large, randomized clinical trials, it is clear we need more data to develop firm scientific ground for decision making around: 1) location of bleed (lobar versus deep), 2) differential cardiovascular risk (atrial fibrillation, mechanical valve, venous thromboembolism), and 3) competing risk of ICH, ischemic disease, and ICH-related mortality. Each of these populations may carry different risks of bleeding and ischemia altering the risk/benefit balance. While emerging data from Biffi et al suggest that anticoagulation after ICH appears to be safe regardless of the location of the ICH[2], further research is needed to resolve the gaps in our current understanding of resumption of anticoagulation therapy after ICH.

We concur with the authors that inclusion of patients with both cardiac and non-cardiac indications for resumption of anticoagulation may have influenced the findings of our meta-analysis. However, current studies failed to provide details of outcomes stratified by the indication for anticoagulation. Additionally, lack of consistency of data on recurrent venous thromboembolism and mortality (ICH-related or all-cause) across the studies precluded the use of these measures as secondary endpoints in our analyses.

In regards to the event rates in the study by Nielsen et al, the apparent discrepancy stems from our need to use consistent methods across all the included studies. Not all the studies described the exact person-years of follow-up in both the anticoagulated and non-anticoagulated groups, and we therefore had to use the crude numbers of events and patients to ensure homogeneity across studies. We therefore used the crude 5-year numbers, which are available in their supplemental material.[3] Even if we use Nielsen et al's reported 5-year hazard ratio based on the exact person-years of follow-up in each group (hazard ratio, 0.79; 95% CI, 0.52-1.19), there is no significant association between anticoagulation and recurrent

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ICH across the eligible studies (pooled risk ratio, 1.16; 95% CI, 0.77-1.66). This is not surprising given that we had already reported in our paper an analysis in which we excluded the two largest studies, including the one by Nielsen et al, and found similar results (pooled risk ratio, 1.18; 95% CI, 0.83-1.70).[1]

Taken together, the existing observational data suggest that reinstatement of anticoagulation therapy after ICH may have a favorable risk-benefit profile, but such a hypothesis must be tested in at least one large, randomized clinical trial, hopefully with sufficient power to fully explore each of the important sub-populations with potentially different risk.

Acknowledgments

Disclosures

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