
First of all, we thank Drs Wehrum and Harloff for their timely comments and constructive criticism about our meta-analysis.2 We acknowledge that the 2 studies from the research group of Harloff et al14 were not included in our meta-analysis because of the restriction of our inclusion criteria in prospective cohort studies that reported the prevalence of complex atheromatous plaques in the ascending aorta (DAo) using the widely available and the (still considered) gold standard investigation of transesophageal echocardiography.2 The aforementioned studies14 used sophisticated MRI protocols to detect plaques and further analyze blood flow in the DAo, reporting considerably higher complex atheromatous rates in the DAo (43.6% and 52.4%, respectively) compared with the studies presented in the meta-analysis that used protocols more close to everyday clinical practice.2 The results of these pioneering studies were, however, mentioned in the introduction (reference 6) and in the discussion section of our article (reference 29), whereas a previous study published from the same group—which reported data on the prevalence of complex DAo plaques in transesophageal echocardiographic examination—was used in the quantitative synthesis (reference 15).2

Drs Wehrum and Harloff indicate that in the pivotal French study, the crude odds ratio (OR) for stroke was ≈4x greater for plaques ≥4 mm located in the distal arch/proximal DAo (crude OR, 5.5; 95% confidence interval, 2.8–10.6) compared with those located in the distal straight segment of the DAo (crude OR, 1.5; 95% confidence interval, 0.5–4.8).5 However, we note that in the same study the likelihood of cerebral ischemia was considerably higher for plaques ≥4 mm located in the ascending aorta or proximal arch (crude OR, 13.8; 95% confidence interval, 5.2–36.1) in comparison with plaques located in the distal arch/proximal DAo. In addition, the authors have provided adjusted OR according to the cause of stroke only for the ascending aorta or proximal arch plaques.5 Consequently, it is uncertain whether the unadjusted association between plaques located in the distal arch/proximal DAo and ischemic stroke would retain its statistical significance after adjustment for potential confounders. Nevertheless, we agree with the comment raised by Drs Wehrum and Harloff that the exact location of complex plaques in the DAo could be a potential moderator in the risk of cerebral embolism, but the available literature data are still insufficient to assess this assumption in a subgroup or a meta-regression analysis. Furthermore, we note that also in the study by Kim et al6 no precise definition of different aortic segments is provided. Consequently, this study that has been cited by Drs Wehrum and Harloff as a potential argument supporting their theory that atheromatous plaques in the DAo may cause cerebral ischemia via retrograde embolization suffers from the same methodological limitation as our meta-analysis.

Our article is a systematic review and meta-analysis of prospective observational studies, containing all the inherent limitations of the individual study protocols. We performed a systematic control for possible confounders and biases, presenting and discussing the results with brevity and clarity. Moreover, we acknowledged as the last and most important limitation of our study (in the Discussion section) that our analysis cannot evaluate a direct causal relationship between DAo atheromatous plaques and cerebral ischemia and that this association should be further investigated in future prospective cohort studies.2

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Disclosures
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Aristeidis H. Katsanos, MD
Department of Neurology
School of Medicine
University of Ioannina
Ioannina, Greece

Georgios Tsivgoulis, MD, PhD, MSc, FESO
Second Department of Neurology
Attikon Hospital
School of Medicine
University of Athens
Athens, Greece


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Aristeidis H. Katsanos and Georgios Tsivgoulis

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