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RESPONSE TO LETTER TO THE EDITOR

Response by Gentile et al to Letters Regarding Article, "Clinical and Prognostic Significance of Anomalous Origin of a Coronary Artery in Adults"

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In Response:

We are sincerely grateful to the authors of the accompanying letters[1,2] for their careful appraisal of our work[3] and for their thoughtful, balanced, and constructive observations. Their comments provide an important opportunity to clarify the scope of our study and to further contextualize our findings within the broader and evolving literature on anomalous aortic origin of coronary arteries (AAOCA).

First, we fully agree that our investigation was conducted in a predominantly middle-aged adult population referred for coronary computed tomography angiography and that our results should not be extrapolated to pediatric cohorts, adolescents, or competitive athletes.[3] The pathophysiological substrate, clinical triggers, and risk profile of AAOCA in young individuals are fundamentally different from those of adults undergoing evaluation for suspected coronary atherosclerotic disease (CAD).[4] In younger populations, the association between specific anatomical patterns (notably, interarterial or intramural courses of the left main or left anterior descending artery) and sudden cardiac death has been well documented.[4] In contrast, our cohort was characterized by a high prevalence of traditional cardiovascular risk factors and a significant burden of concomitant obstructive CAD.[3] Accordingly, our conclusions apply to adults evaluated in a coronary computed tomography angiography setting and should be interpreted within that clinical framework.

We also acknowledge the important points raised regarding ischemia assessment. Functional testing was performed in a subset of patients according to clinical indication, reflecting real-world practice but inevitably introducing heterogeneity and potential verification bias. In an adult cohort with substantial CAD burden, distinguishing ischemia attributable to the anomalous vessel from that related to epicardial CAD or microvascular dysfunction is intrinsically challenging. Although we carefully recorded whether perfusion defects were judged to correspond to the AAOCA territory, we agree that more standardized attribution criteria and sensitivity analyses adjusting for CAD burden would further strengthen mechanistic inferences. Notwithstanding these limitations, the principal signal emerging from our data was that obstructive CAD, rather than anatomical subtype or inducible ischemia per se, was associated with adverse outcomes during follow-up.[3]

With regard to anatomical heterogeneity, we agree that not all left-sided anomalies are equivalent. In our cohort, anomalous left circumflex arteries with a retroaortic course represented the most frequent variant, whereas anomalous left main/left anterior descending were less prevalent. From a pathophysiological perspective, retroaortic left circumflex is generally considered benign, whereas left main or left anterior descending anomalies with interarterial/intramural courses have been associated with sudden cardiac death in younger individuals.[4,5] In our dataset,[3] although absolute event rates were numerically higher in case of an anomalous origin of left main/left anterior descending compared with left circumflex, the total number of events within each subtype was small. While this may reflect a survival bias toward less malignant phenotypes, any further stratified analysis would be underpowered and potentially misleading. We deliberately avoided overinterpretation of unstable estimates derived from limited events. We agree, however, that aggregating all left-sided anomalies may attenuate subtype-specific relevance, and we acknowledge this as an inherent limitation of single-center studies of rare congenital conditions.

These considerations underscore the central message discussed in both the letters[1,2] and in our original manuscript: multicenter, collaborative registries are essential to refine risk stratification across specific AAOCA phenotypes.[3] Adequately powered datasets would allow more granular analyses of subtypes, anatomical course, plaque burden distribution, and management strategies. They would also enable age-stratified assessments to clarify how the relative contributions of

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congenital anatomy and acquired CAD evolve across the lifespan.

Finally, we appreciate the concern that our Clinical Perspective statement (ie, that high-risk anatomical features and inducible ischemia were not associated with adverse clinical events) could be misinterpreted as implying uniform benignity. This was not our intent. Rather, in the specific context of adults referred for coronary computed tomography angiography, concomitant obstructive CAD emerged as the predominant determinant of poor outcomes. In younger individuals without significant CAD, anatomical features may have a greater prognostic role.[4,5] An individualized, context-specific, and age-sensitive approach therefore remains paramount.

In conclusion, we thank the authors of the letters[1,2] for their insightful contributions. We fully agree that our findings pertain primarily to adults undergoing coronary computed tomography angiography evaluation, that subtype-specific analyses in our cohort are limited by statistical power, and that collaborative multicenter efforts are needed to delineate the prognostic implications of distinct AAOCA phenotypes.[3] We hope that this dialogue will stimulate further research and promote a more nuanced, patient-tailored understanding of anomalous coronary anatomy.

ARTICLE INFORMATION

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Disclosures

None.

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