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# Update on biomarkers of bicuspid aortic disease: still a long road to run?

Alessandro Della Corte<sup>1,2</sup>, Federica Lo Presti<sup>1</sup>, Davide Pacini<sup>3</sup>

<sup>1</sup>Unit of Cardiac Surgery, Monaldi Hospital, Department of Translational Medical Sciences, University of Campania “L. Vanvitelli”, Naples, Italy; <sup>2</sup>Heart and Vessels Department, Casa di Cura San Michele, Maddaloni, Italy; <sup>3</sup>Division of Cardiac Surgery, IRCCS Azienda Ospedaliero-Universitaria di Bologna, S. Orsola Hospital, ALMA Mater Studiorum University of Bologna, Bologna, Italy

*Correspondence to:* Prof. Alessandro Della Corte, MD, PhD. Department of Translational Medical Sciences, University of Campania “L. Vanvitelli”, Unit of Cardiac Surgery, Monaldi Hospital, 80131 Naples, Italy. Email: aledellacorte@libero.it.

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## Introduction

Management criteria of patients with aortopathy are based mainly on dimensional parameters, namely aortic diameter and growth rate (1), with the rationale that elective treatment is aimed at preventing acute aortic events (AAEs), i.e., aortic dissection or rupture, and that the risk of AAEs is predicted by the aortic diameter. However, this principle has been questioned by some evidence: the majority of acute aortic dissections occurs at diameters well below the threshold for prophylactic surgery, and their number may be even underestimated since an acute increase in aortic diameter occurs as the aorta dissects (2).

The increase in size remains a very specific biomarker of the risk of aortopathy complications, yet with low sensitivity. Within this general scenario, the case of bicuspid aortopathy presents peculiar issues: although bicuspid aortic valve (BAV) patients do have a much higher risk of AAEs than the general population, aortic dissection occurs at greater diameters in the BAV population, yet at a younger age (3). Adjunctive parameters, including flow-related functional imaging biomarkers and circulating molecular biomarkers have, therefore, been proposed as potential tools for a more accurate risk stratification of BAV aortopathy (4).

## What is a circulating biomarker for in BAV aortopathy?

The ideal circulating biomarker should be a molecule

clearly belonging to the pathways involved in the pathobiology of the disease, its serum/plasma levels should be reliably measured and quantitatively related to its tissue expression, and its abnormalities should have clinical relevance (meaning that higher levels are detected in cases with more severe prognosis). Altered levels of the biomarker should not accompany the presence of simply measurable clinical hallmarks of the condition to detect, in the case of BAV aortopathy, a hypothetical biomarker whose levels increase with increasing aortic diameter would add very little in terms of risk prediction (4). Thus, previous studies finding a good correlation of some circulating molecules with the aortic diameter (5) have remained speculative, with poor translational impact. Further, it is not correct to use untargeted approaches [e.g., mass spectrometry (6)] to identify proteins reaching high circulating levels in patients with BAV-related aneurysm and then defining as “at risk” of aortopathy those patients with nonaneurysmal aorta but similarly high levels of those proteins. Such methods lack a verification of the causative link between the identified candidate biomarker and the development of aneurysm.

## In which subset of BAV aortopathy patients does a biomarker make sense?

Within the spectrum of anatomic-clinical forms of BAV aortopathy, the dilatation predominantly involving the aortic root, namely the “root phenotype”, represents an

uncommon but more severe form of disease. It usually affects younger patients, mostly male, with non-stenotic aortic valve, most frequently aortic insufficiency, sometimes with associated mitral prolapse. Given its demonstrated worse prognosis (faster progression, higher risk of AAEs), the latest consensus document on BAV aortopathy suggested a lower surgical threshold (50 mm diameter instead of 55 mm) in this patient subset (7). Dilatation of the tubular tract, i.e., “ascending phenotype”, is more common and presents heterogeneity in both clinical presentation and course: here it is where we really see space for better stratification, including circulating biomarkers.

### What class of biomolecules should be focused on in the search for BAV biomarkers?

In the setting of BAV aortopathy, investigators have so far mostly focused on circulating proteins –including matrix metalloproteinases (MMPs), alpha1-antitrypsin, soluble form of the receptor for advanced glycation end-products (sRAGE), asymmetric dimethylarginine, transforming growth factor-beta1 (TGF- $\beta$ 1), ratio of TGF- $\beta$ 1 to endoglin (ENG)–, or on small noncoding circulating RNA molecules, especially micro-RNAs (miRNA) [reviewed in (8,9)]. Among investigated proteins, none have been demonstrated to be an optimal candidate biomarker on their own, leading to the suggestion that only a combination of several biomarkers could reach good predictivity. Two studies stand out in this field: one found sRAGE to correlate with aortic wall degeneration independent of aortic diameter (10), another found the ratio of circulating TGF- $\beta$ 1 to the soluble form of its co-receptor ENG (T/E ratio) to correlate with increased MMP-2 and TGF- $\beta$ 1 gene expression in the non-aneurysmal aortic wall and with faster aortic growth over time (11).

Among miRNAs, miR-145 was linked to NOTCH1 mutations, miR-34a to deranged aortic wall properties [reviewed in (9)] and others [including miR-15b, miR-17, miR-20a, miR-106a (5)] have been shown to correlate with aortic diameter, thus representing markers of the presence - rather than prognostic predictors - of the aortopathy. Therefore, no miRNA appears as a promising candidate biomarker so far, inasmuch as we still ignore their unique role in BAV aortopathy pathobiology, and because no study has ever linked their alterations to significant clinical endpoints (12).

### What is the right direction to go for research on BAV aortopathy biomarkers?

The ideal study design would involve having access, either prospectively or retrospectively, to the natural history data of an adequate number of BAV patients (i.e., information on aneurysm development, surgery, or AAE occurrence) whose blood samples were collected at the beginning of the follow-up period: this is difficult to achieve in the clinical “real world”. The classical surrogate endpoint for imaging or bio-humoral risk-marker studies has been the fast growth of the aortic diameter, since harder endpoints are either rare, e.g. AAEs, or subjective, e.g. surgery for aortic dilatation, depending on the individual surgeon’s or center’s judgment/policy. Furthermore, either a very large number of patients must be included in such studies, thus being able to control for confounding factors (especially valve dysfunction, which can be per se associated with alteration of some bio-humoral levels), or patient subsets must be selected based on clinical phenotype [e.g., only BAV patients with aortic valve stenosis and ascending-type dilatation (11)]. Besides homogeneity of the study population, an adequate choice of the control subjects is key to a correct interpretation of the resulting evidence: the control group must be designed according to both the study population and the endpoint measures.

### Conclusions

Only by complying with the above methodology requirements will research of BAV aortopathy biomarkers produce evidence readily translatable to the clinical practice of risk stratification and treatment personalization.

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### Footnote

*Conflicts of Interest:* The authors declare no conflicts of interest.

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