

## Indexed Aortic Area in Bicuspid Valve Disease An Important Step Toward a More Personalized Approach to Risk Prediction and Clinical Decision Making

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*Never put off until tomorrow what you can do the day after tomorrow.*

—Mark Twain

The decision to undertake thoracic aortic repair in patients with progressive aortic dilation in the setting of bicuspid aortic valvular disease remains a point of much discussion and continuing investigation. The ongoing work to find an optimal cutoff value for intervention that balances surgical risk and risk of dissection or rupture to optimize patient care is perhaps best reflected in the most recent American College of Cardiology/ American Heart Association guidelines (2014) that recommended a 5.5 cm threshold for surgery in regard to patients with bicuspid valves.<sup>1</sup> This is a notable change from the 2010 guidelines which cited a 5 cm threshold.<sup>2</sup> These thresholds have informed clinical decisions for decades but are inherently limited because they do not adjust for patient size (body surface area or height) or sex. Growing awareness of the limitations of unadjusted 2-dimensional measurements of the aorta has driven a desire for further refinement of noninvasive risk assessment leading to the introduction of the concept of the ratio of aortic area:height. Importantly, a threshold of  $>10$  cm<sup>2</sup>/m has been shown to be strongly prognostic on a large tricuspid aortic stenosis population but has not been formally evaluated in bicuspid valvular disease on a large scale inclusive of assessment of prognostic use for mortality.<sup>3,4</sup>

### See Article by Masri et al

In this issue of *Circulation: Cardiovascular Imaging*, Masri et al<sup>5</sup> from the Cleveland Clinic provide data as to the clinical use of indexed aortic area for risk stratification in a population of 969 bicuspid aortic valve (BAV) patients followed for a median of 10.8 years (Interquartile Range, 9.6–12.3). Using either aortic root or ascending aorta area:patient height ratio, the authors report an increased hazard for cardiovascular death and the downstream surgical intervention. Importantly, no association was seen with the nonindexed aortic diameter using a cutoff of  $\geq 5.0$  cm. In

doing so, they provide the field with the first large-scale analysis of BAV patients indexed in this manner thereby confirming its prognostic use in the BAV patient population and effectively building on their past work in analysis of tricuspid aortic valve patients with dilated ascending aortas.<sup>3</sup>

These data suggest that traditional 2-dimensional diameter evaluation of aortic size may be insufficient to understand patient-specific risk related to aortic dilatation. While an important advancement, this work highlights the need to delve even more deeply into mechanisms of risk in bicuspid valve associated aortic disease. There remain many unanswered questions in this field. In particular, as we move toward more individualized medicine, will even an adjusted measure of aortic size be sufficient to evaluate patient-specific risk? Does the pattern of BAV type play a role? Can the same threshold of aortic area:height ratio be used across all of the patterns of bicuspid valve morphology? Moreover, the underlying pathology of the aorta will almost certainly need to be considered to understand risk. BAV patients have long been known to have aortic medial degeneration, characterized by elastic fiber fragmentation and changes in vascular smooth muscle cells and endothelium and collagen and elastin disruption.<sup>6,7</sup> However, recent papers continue to identify aspects of BAV-associated aortopathies, including increased levels of matrix metalloproteinases 2 and 9 with concomitant decline in their inhibitors and dysregulation of cardioprotective signaling molecules that thereby establish a milieu promoting pathology within the aortic wall.<sup>8–10</sup> Such cellular changes inevitably lead to pathological changes in overall aortic physiology and altered biomechanics that are reflected in studies showing reduced aortic elasticity and increased stiffness in BAV and associated with poor cardiovascular outcomes.<sup>11–13</sup> How to directly assess such physiological and cellular changes through imaging remains in development. Although such goals may seem far out of reach, the potential for using magnetic resonance imaging with specific contrast agents targeting key structural components of the aortic wall or some combination of imaging with risk stratification based on genetics associated with BAV aortopathy or the use of circulating biomarkers that have been recently reviewed and proposed for BAV aortopathy prediction exists.<sup>14,15</sup> Although the maturation of such techniques and subsequent integration into mainstream practice holds promise, the current analysis by Masri et al<sup>5</sup> allows the field to move forward toward better risk prediction, thereby enabling more informed clinical decisionmaking. Ultimately though, for these data to be truly impactful, adjusted aortic area to guide surgical intervention needs to be validated prospectively in a randomized multicenter trial showing improved clinical outcomes when compared with the traditional approach of using nonindexed aortic.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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## Disclosures

Dr Leipsic serves as a consultant for Edwards Lifesciences, and provides core lab services for Edwards Lifesciences, Medtronic, Tendyne, and Neovasc. The other authors report no conflicts.

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