Preventing Acute Aortic Dissections: The Power of Familial Screening and Risk Assessment

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The natural history of aortic aneurysms involving the root and/or ascending aorta is to progressively and asymptotically enlarge over time. If aneurysms are not diagnosed, progressive growth over time often leads to an acute type A dissection that requires emergent surgical repair or results in sudden death. However, if at-risk individuals are identified before dissections occur, ascending aortic aneurysms can be repaired to prevent dissection-related mortalities. In patients with heritable thoracic aortic conditions like Marfan syndrome, timely diagnosis has proven effective in reducing the prevalence of acute aortic dissection by enabling tailored medical management and surgical intervention. However, the optimal strategy for identifying individuals in the general population with increased risk of thoracic aortic disease (TAD) remains a challenge.

The impact of family history data to inform care was demonstrated by Abbasciano et al. in 2018, who found an increased burden of thoracic aortic aneurysms and sudden death in first-degree relatives (FDRs) of NS-TAD probands compared with a control group. These data were supported by studies from an independent group, which showed that up to 20% of NS-TAD probands have a family history of TAD. We found an increased burden of thoracic aortic aneurysms and sudden death in first-degree relatives (FDRs) of NS-TAD probands compared with a control group. These data were supported by studies from an independent group, which showed that up to 20% of NS-TAD probands have a family history of TAD.

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See Article by Abbasciano et al.
extended further by 2 studies that demonstrated patients with family history of TAD are at higher risk for aortic events at younger ages, show more rapid aneurysm growth, and have a higher likelihood of surgical reintervention.5,9 Highly penetrant forms of thoracic aortic disease in individuals with or without syndromic features, collectively termed heritable thoracic aortic disease (HTAD), can be identified by molecular genetic testing, family history analysis, and phenotypic evaluation. HTAD is a genetically heterogeneous condition, associated with 11 clinically actionable genes to date.10 Professional guidelines and practice statements support genetic testing to confirm molecular diagnosis, tailor aortic surveillance and surgical management, and identify at-risk relatives.1 However, pathogenic variants in these genes only account for only ≈30% of HTAD, with more diagnoses confirmed in syndromic families compared with nonsyndromic families.11 The likelihood of identifying a pathogenic variant in an HTAD gene is closer to 10% in patients ≤56 years with sporadic aortic dissection.3 If a pathogenic variant is identified, predictive “cascade” genetic testing can be used to definitively determine TAD risk in relatives. However, when the causative gene cannot be identified in patients with TAD, thoracic aortic imaging is the only way to diagnose aneurysms in at-risk family members.

Despite professional society guidelines and expert opinion that recommend thoracic aortic imaging for at-risk relatives, additional data are needed to determine the optimal timing to initiate imaging, the preferred imaging modality, and impact of screening programs on health outcomes.12,13 Results from the largest cross-sectional aortic surveillance study of 581 at-risk relatives of NS-TAD probands yielded 216 new TAD diagnoses with management implications, including 42 patients with aortic root/ascending diameters >50 mm.14 Although the cost-effectiveness of familial screening programs for TAD has not been investigated, Tessler et al. recently showed that echocardiography was a cost-effective strategy to screen FDRs of patients with bicuspid aortic valve (BAV).15 The success of screening programs also relies on communication with at-risk relatives and the relatives’ willingness to pursue screening. A retrospective study of pediatric patients with BAV and/or thoracic aortic aneurysm called attention to screening barriers as only 38.7% of the 150 at-risk siblings pursued aortic imaging.16 In addition to evaluating the clinical utility and sustainability of aortic screening programs moving forward, there is a critical need to assess screening implementation barriers.

In this issue of the Journal of the American Heart Association (JAHA), Abbasciano et al. investigated the feasibility of a multifaceted TAD screening program that integrated thoracic aortic imaging for at-risk relatives of NS-TAD probands, exome sequencing for TAD probands, and psychological and quality of life assessments.17 This study included 16 probands with NS-TAD (8 familial; 8 sporadic) and 54 FDRs and second-degree relatives who underwent thoracic aortic imaging via transthoracic echocardiogram (n=54) and magnetic resonance imaging (n=43). Approximately 62% of the probands were male with median ages of 68.5 and 67.5 years in the familial and sporadic groups, respectively. All 16 probands were hypertensive and several had additional TAD or atherosclerosis risk factors (eg, aortic valve dysfunction, renal disease, smoking history). Notably, the median age of probands in the familial group and burden of hypertension are more typical of patients with sporadic TAD who have an average disease onset closer to 65 years.6,18 The preponderance of hypertension and older age of disease onset in the familial group could be due to several factors (eg, small sample size, heterogeneity of proband phenotype, how familial disease was defined) and is important to consider when interpreting the clinical implications of this study.

This study identified dilatation of the aortic root or ascending aorta in 13 of the 54 at-risk FDRs and second-degree relatives, conferring a 24% overall yield, which is consistent with the familial TAD burden in other studies. Six of the newly diagnosed relatives were from the familial group (21%) and 7 from the sporadic group (27%). These findings emphasize the importance of aortic imaging for relatives of patients with sporadic TAD, which is often overlooked in clinical practice. It was surprising that the burden of TAD was higher in the sporadic group compared with the familial cohort, which highlights an issue in that the authors did not define how they classified familial disease (eg, number of affected relatives, aneurysm/dissection location, age diagnosed). Additionally, 5 probands with aneurysmal disease had either aortic stenosis or prior aortic valve repairs, yet only 1 proband was reported with BAV. The study summary data indicate 4 total BAV diagnoses suggesting that other probands or relatives had BAVs, which are a major risk factor for TAD and can be inherited in an autosomal dominant fashion with and without ascending aneurysms.19 Lastly, it is worth noting that the authors reported the sensitivity and specificity of echocardiogram and magnetic resonance imaging for diagnosing ascending dilatation, which are key metrics for evaluating screening modalities. Although discordant results were reported for 3 individuals and magnetic resonance imaging revealed additional data on distensibility and tortuosity, the clinical implications of these findings are limited given the small number screened and insufficient detail regarding the discrepancies in aortic dimension.

In addition to aortic imaging, exome sequencing was pursued for the 16 probands with NS-TAD to detect pathogenic variants that could be used for
predictive cascade genetic testing in relatives and to identify variants of uncertain significance that may prompt additional phenotyping or segregation studies. After filtering variants by allele frequency and predicted functional impact, they identified 14 variants (9 variants of uncertain significance, 5 benign) in 32 genes included on the National Institutes of Health Genomic Medicine Service Aortopathy Panel. No pathogenic or likely pathogenic variants were identified. Notably, only 4 of the 9 variants of uncertain significance were detected in an established HTAD gene (FBN1, MYH11, MYLK), whereas the other 5 were found in genes not yet validated to cause HTAD. This is relevant for clinical interpretation of genetic testing as we need sufficient evidence to support the association between genes and TAD for data to be clinically meaningful. Additional clinical phenotyping pursued for individuals with variants of uncertain significance in this study did not yield evidence to support variant pathogenicity.

This study by Abbasciano et al. further confirms the significant burden of TAD in at-risk FDRs and second-degree relatives. Additionally, they integrated other critical components of TAD risk assessment including genetic variant analysis, clinical risk factor assessment, psychological well-being, and quality of life. When genetic or clinical risk factors such as hypertension are identified in at-risk relatives, secondary prevention strategies can be implemented to reduce aortic dissection risk. This current study emphasizes the utility of aortic surveillance for at-risk relatives of all patients with TAD, regardless of known family history and age of onset. To date, TAD screening programs have focused on imaging at-risk relatives to identify asymptomatic aneurysms after a family member is diagnosed with an aneurysm, has an acute dissection, or dies suddenly. However, we are still challenged to investigate approaches for TAD risk stratification in the general population. Up to 80% of aortic dissection is sporadic in nature and likely driven by interactions between more than 1 genetic risk variant in combination with environmental and lifestyle factors. In these cases, family history and physical syndromic features cannot be used to signal individuals who are at increased risk. Moving forward, studies aimed at identifying novel environmental and lifestyle risk factors and how they interact with genetic risk variants, will be crucial for stratifying risk in the general population to determine who would benefit most from aortic surveillance, risk-reducing intervention, and lifestyle modification.

ARTICLE INFORMATION

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Disclosures
None.

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