Management Strategies in Aortic Dilation Among Pediatric Cardiology Patients in a Tertiary Heart Center

Lerraughn Morgan[1], Brian Harvey[2], Nathan Rubin[2], Jamie Lohr[2], and Shanthi Sivanandam[2]

[1]Valley Children's Hospital
[2]University of Minnesota

April 28, 2020

Abstract

Background: Limited information is available to guide therapy for aortic dilation (AoD) in the absence of genetic syndromes. Our aim was to identify aortic diameters that prompted intervention. Methods: We performed a single center retrospective chart review of patients from birth to 30 years between 2011 and 2017. Advanced imaging [magnetic resonance (MR)/computed tomography (CT)] and echocardiographic diameters at the sinuses of Valsalva (SoV) and ascending aorta (AAo) were reviewed. We identified patients on pharmacotherapy and those who underwent aortic surgery. Results: Data from 47 patients was analyzed (74% male) and included bicuspid aortic valve (BAV, 40%), Marfan syndrome (MFS, 28%), isolated aortic dilation (21%), Turner syndrome (TS, 4%), and Loeys-Dietz syndrome (LDS, 4%). Family history of AoD, aortic dissection, or vascular aneurysm was identified in 40%. Medication was initiated at a median echo diameter of 34 mm at the SoV and 32 mm at the AAo. Patients with genetic conditions (MFS, LDS, TS) were started on medication earlier in the course of SoV dilation by echocardiography. Patients with BAV were started on medication at a larger AAo diameter compared to patients with genetic diagnoses and isolated AoD. Five patients underwent aortic surgery at a median age of 20 years (two patients were < 20 years old at surgery). Conclusion: Patients with genetic conditions were started on medications at an earlier stage of AoD compared to BAV and those with isolated AoD. Over a third of patients had a significant family history of AoD, aortic dissection, or vascular aneurysm.

Introduction

Aortic dilation (AoD) at the aortic root and ascending aorta have been identified in isolation and with genetic anomalies, particularly connective tissue disorders (CTD) [1, 2]. Despite the advances in imaging technology and aortic disease management, there is a paucity of literature regarding imaging choice, medical therapy, and appropriate timing for surgical intervention in patients with isolated AoD.

Guidelines do exist to aid clinicians in pharmacotherapy management and surgical intervention in patients with CTD [3]. Additionally, CTD patients are likely to have aortic root repair or replacement [4] and early initiation of pharmacotherapy. Identifying patients early with aortopathy and appropriately intervening with medical therapy to slow the progression of AoD or surgery to prevent aortic dissection is the goal.

Establishing defined ranges of aortic dimensions for which intervention is necessary would be beneficial to clinicians for guiding imaging choices, medication initiation, and patient counseling. A variety of imaging modalities have been utilized for measurements of the aorta including two-dimensional echocardiography, computed tomography (CT), and magnetic resonance (MR) imaging [5]. Currently CT is the gold standard for aortic visualization and ruling out significant aortic pathology [6]. Clinicians have utilized two-dimensional echocardiography as a screening tool for aortic pathology, such as AoD, however the literature has shown low sensitivity when attempting to detect AoD [7].

Information is limited regarding pharmacotherapy initiation or surgical intervention in patients with isolated AoD, especially when there is discrepancy between echocardiographic and advanced imaging modality measurements. Studies have compared aortic root size by advanced imaging and echocardiography and have demonstrated underestimation of the aortic root size by echocardiography and a general trend for the difference to become greater as the aortic root size increases [8]. Family history of AoD or aortic dissection may prompt clinicians to monitor patients more closely, obtain advanced imaging as an adjunct to echocardiography, and when appropriate establish a follow-up program for them [9]. Set diameter cutoffs have been established for various conditions with respect to when to consider intervention in the setting of AoD [3]. When patients experience progressive AoD despite pharmacologic therapy or in the presence of significant family history of aortic dissection, surgical intervention is typically necessary. From a surgical standpoint, aortic root replacement has been established as a method to prevent aortic dissection and in a majority of cases be performed in a fashion that preserves the aortic valve (David procedure) [4, 10]. In regards to patients with CTD (e.g. Ehlers-Danlos syndrome [EDS], Loeys-Dietz syndrome [LDS], or Marfan syndrome [MFS]), they are more likely to require aortic root replacement surgery compared to patients with other clinical conditions associated with AoD [11]. The purpose of this study was to describe a single center experience in identification of aortic dimensions, by multiple modalities, which prompted medical or surgical intervention. We also describe relationships between each modality at various points of measure of the aortic root.

Methods

A single center descriptive retrospective chart review for patients age birth to 30 years old was conducted from 2011 to 2017. The records were obtained using an institution managed academic health center data shelter. This study was reviewed and approved by the University of Minnesota Institutional Review Board and the study protocol conforms to the ethical guidelines of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Inclusion criteria included patients on medication for AoD, surgical intervention for AoD, and patients who had both echocardiogram and advanced imaging (MR/CT). International Classification of Diseases (ICD)-9 and ICD-10 codes were used to identify all patients with AoD and who were prescribed beta-blockers, Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II Receptor Blockers (ARB) in addition to patients who underwent surgery for AoD. Medical records were reviewed for demographic information and clinical course. Exclusion criteria included patients with conotruncal defects, absent medication start dates, and when echocardiogram and advanced imaging was performed more than 6 months apart.

Statistical Methods

Demographic information and absolute imaging diameters at the level of the sinuses of Valsalva (SoV) and ascending aorta (AAo) were obtained. All echocardiogram Z-scores were either obtained directly from the reports or calculated [12, 13]. For advanced imaging where bi-orthogonal measurements were obtained, the largest diameter was used in the analysis. Data was also analyzed by dividing the patients into two groups: birth -16 years of age and 17-30 years of age (Tables 5-6). Genetics diagnoses were obtained from laboratory reports or documentation from the cardiac geneticist or primary cardiologist (Table 2). Echocardiographic aortic dimensions were analyzed using median and interquartile ranges. Pearson correlation was used to compare echocardiography and advanced imaging aortic dimensions and p-values calculated using R[?] (R Project for Statistical Computing, version 3.5.1). Bland-Altman (B-A) analysis plots [14] were created to compare differences of measurements between echo and advanced imaging at the SoV and AAo using R[?].

Results

Eighty patients were identified with AoD. Table 1 presents population characteristics of the forty-seven (47) patients with complete data who met inclusion criteria. Thirty-five patients (74%) who were started on medication were male and White/Caucasian. A BAV was diagnosed in 40%, MFS was diagnosed in 28%, isolated AoD in 21%, TS in 4%, and LDS in 4%.

Thirty patients had genetic testing, of which 20 (67%) had a genetic anomaly identified (Table 2). Family history was significant in 40% of patients including AoD, aortic dissection, or vascular aneurysm.

Majority of patients were started on Losartan (51%), Atenolol (32%), Metoprolol (13%), and Lisinopril (4%). Four patients (9%) had a documented diagnosis of hypertension at the time of initiation of medication for AoD. Only one patient was not on medication at the time they underwent surgery.

IMAGING

There were 47 patients with echo and advanced imaging data. Thirty patients (64%) had AoD at the level of the sinuses of Valsalva by echocardiography. Thirty-seven patients (77%) had MR and 11 patients (23%) had CT performed. BAV (n=19) were started on medications at a diameter of 35mm [IQR: 29, 42] at the SoV and 34.5 mm [IQR: 30, 44] at the AAo. The median Z-score for patients with BAV at the SoV was 2.77 [IQR: 1.9, 4.3] and at the AAo was 5.38 [IQR: 3.4, 6.6]. Patients with genetic syndromes (MFS [n=13], LDS [n=2], TS [n=2]) were started on medication at the median diameter of 32 mm [IQR: 28, 36] at the SoV and 27 mm at the AAo [IQR: 25, 30]. The median Z-score for patients with genetic syndromes at the SoV was 2.96 [IQR: 1.9, 4.9] and at the AAo was 1.95 [IQR: 0.8, 3.7]. Patients without a genetic diagnosis and isolated AoD (n=10) were started on medications at a diameter of 34 mm [IQR: 31, 37] at the SoV and 27 mm [IQR: 24, 33] at the AAo. The median Z-score for patients with isolated AoD at the SoV was 3.13 [IQR: 2.2, 4.8] and at the AAo was 1.75 [IQR: -0.1, 2.6].

Based on Pearson correlation coefficient analysis, diameters between echocardiography and MR were relatively well correlated at the SoV and AAo. Echocardiographic and CT diameters at the SoV were also well correlated (Table 3). Echo SoV and AAo Z-scores were plotted by age and diagnosis at initiation of medication (Figures 1). The Kruskal-Wallis test show that the median Z-score differed by diagnosis for AAo ($p = 0.013$), but not for SoV ($p = 0.604$). A Dunn's post-hoc test revealed that the BAV group had significantly higher AAo Z-scores than MFS ($p = 0.045$). B-A analysis and distribution plots were used to compare diameters obtained by echocardiography and advanced imaging modalities. Thirty-six (36) patients were included in B-A analysis for Echo vs. MR at the SoV and nineteen (19) patients were included for Echo vs. MR at the AAo. Ten (10) patients were included in the B-A analysis for Echo vs. CT at the SoV (Figures 2).

SURGICAL PATIENTS

Five patients underwent surgical intervention with a median age at surgery of 20 years (range 10-22). The median diameters at the time of surgery by echocardiography at the SoV was 47 mm (median Z-score: 7.2), and at the AAo was 36 mm (median Z-score: 6.4). Three out of the five patients underwent valve sparing aortic root surgery, one had aortic valve and root replacement, and one patient underwent Ross procedure. The two patients with MFS with aortic root dilation underwent valve sparing aortic root replacement. Three patients had BAV with aortic root dilation and AI. One patient with BAV underwent valve sparing aortic root replacement, one underwent Ross procedure, and the last patient had aortic valve and root replacement.

Discussion

In our study, we found that patients with a genetic diagnosis (MFS, LDS, TS) were started on medications at lower severity of AoD at the SoV compared to patients without a genetic diagnosis. Patients with BAV were started on medication at a larger AAo diameter compared to patients with genetic diagnoses and isolated AoD. Additionally, over a third (40%) of patients in our study had family members with AoD, aortic dissection, or vascular aneurysm. Only two patients with genetic diagnoses (1 TS, 1 MFS) had documentation of family members with aortic aneurysms during the study period. Our cohort represents a limited number of patients with both echocardiography and advanced imaging. From this data, there were similar findings across each modality with good correlation coefficients and reasonable 95% limits of agreement on the B-A plot analyses. There were no patients identified with aortic dissection in our study population.

The incidence of isolated AoD in the pediatric population is low and those patients requiring intervention,

whether medically or surgically, is dependent on the aortic diameter, progression of AoD, associated genetic conditions, and family history [15]. Aortic dissection in children and young adults is even rarer [16, 17]. Even among patients with CTDs, aortic dissection is rare in the pediatric population. However, progressive AoD can occur at any period in time, even outside the years of normal growth in children and adolescence. In the study by Wozniak-Mielczarek et al., they compared children and adults with MFS and they found that the largest aortic diameters were identified between ages 18 and 29 years [18]. Monitoring patients with AoD becomes crucial to ensure appropriate management and education regarding modification of cardiovascular risk factors, including hypertension and smoking.

In a recent study by Bon et al. investigating screening for aortic pathology in patients [?] 15 years of age, a large percentage of patients (60%) had a family history of thoracic aortic pathology. They also found that close to 20% had a suspicion of a syndrome associated with aortic pathology [7]. This also raises the topic of which patients should be screened and once AoD is identified how should each patient be followed and managed. Even in MFS, there has been limited data looking at patients who develop rapid AoD. In recent literature evaluating patients who met Ghent criteria for MFS, there were no prolific findings that would predict rapid aortic root dilation that could be used to indicate which patients would need referral for aortic surgery [19]. This information further emphasizes the importance of obtaining an extended family history in patients with a diagnosis of AoD.

Based on clinical documentation and excluding genetic syndromes, factors that influenced the decision to initiate medication in our cohort included family history, concern for CTD, or progression of AoD. Risk factors (smoking and hypertension) were limited in our cohort and no patients in our analysis experienced aortic dissection. Close to two-thirds of patients in our study had genetic testing performed if there was concern for a genetic anomaly or CTD. It is well known that several genes associated with aortopathy exists and have significant familial inheritance [20–23]. Interestingly, we identified several patients with genetic results of unknown clinical significance in our study. Patel et al. in an abstract yielded similar findings and showed that 10 out of 25 patients with aortic root dilation and phenotypic findings in their study had mutations of unknown clinical significance [24]. Although rare, some patients are diagnosed with aortic dissection at relatively small aortic dimensions especially in very specific conditions such as Ehlers-Danlos syndrome [25]. In these patients it is imperative to manage them conservatively and maintain a low index of suspicion for aortic dissection. Clinicians must be mindful that aortopathy is a dynamic process, where aortic tissue is structurally weakened and the association between AoD and cystic medial necrosis/degeneration has been demonstrated [26]. Additionally, even if some patients with AoD do not meet clinical criteria or have a genetic diagnosis consistent with CTD, they may fall in the category of familial aortic aneurysm syndrome [27].

Due to the variety of etiologies and presentations of pediatric patients with AoD, there has been literature detailing algorithms and proposed strategies for evaluating patients with AoD [11]. Echocardiography serves as a cost-effective first line screening for AoD in suspected individuals. In some conditions, such as TS and EDS, MRI has been the imaging modality of choice especially when evaluating other cardiovascular abnormalities [28]. Several studies have compared aortic dimensions obtained by echocardiography and advanced imaging in TS and reasonable agreement between echocardiographic and MRI measurements has been shown. Literature also shows overestimation of aortic dimensions at the aortic root and underestimation at the level of the ascending aorta by echocardiography [28, 29]. When examining patients with BAV, the pattern of aortic valve cusps fusion will determine the geometry of AoD [30], which could influence the diameter reported depending on the angle and level of interrogation by echocardiogram. Advanced imaging does address the issues of angle and level of interrogation by utilizing bi-orthogonal measurements. Unfortunately, the factors of patient cooperation, exposure to radiation, and sedation does determine which type of advanced imaging modality is used (CT or MR). Shorter scanning protocols and reduction of ionizing radiation exposure has made advanced imaging a more feasible modality for evaluating younger patients, especially when considering candidacy for surgery.

Surgical intervention is performed for patients that have progressive AoD despite appropriate medical man-

agement or who meet published recommendations for intervention due to an increased risk of aortic dissection. There was a relatively small percentage of patients who met inclusion criteria and underwent surgical intervention in our study. In a study by Ono et al. the authors reported the indications for surgery were maximal diameter of 200% of normal for isolated aneurysms, and 160% of normal in case of associated aortic valve dysfunction or patients who were symptomatic [15]. In a recent study of MFS patients age 6 months-25 years of age, a change in aortic root Z-score of 0.72 SD units/year had 42% sensitivity and 92% specificity for predicting referral for aortic surgery. The same study demonstrated that a change in aortic root diameter of 0.34 cm/year had 38% sensitivity and 95% specificity for predicting referral for aortic surgery, however no new predictors of rapid AoD or referral to surgery were found [19]. This data emphasizes that surgery should be employed for those at highest risk for aortic dissection based on risk factors, clinical diagnosis, and family history.

Limitations

There were several limitations to our study. First, this was a retrospective study in a single center and there were patients who did not have complete information available for analysis and were excluded, incurring potential sampling bias.

Secondly, not all patients had both SoV and AAo dimensions measured, in which case only the measurement available was documented. In regard to imaging, there is an inherent difference in the methods used to measure aortic diameters between echocardiography and advanced imaging modalities. This problem is further compounded by inter-reader variability and technique in both echocardiographic and advanced imaging interpretation. Aortic diameters were not re-measured by the authors since the original measurements were used by clinicians during their decision-making process. Furthermore, the comparison and correlation between advanced imaging, including CT and MR, and echocardiographic measurements has been thoroughly investigated in the literature [8, 31–34].

Lastly, our study population was relatively homogenous in terms of ethnicity and a more diverse sampling could aid in defining patterns of AoD. A well-designed, multi-center prospective study evaluating AoD at the time of diagnosis, initiation of medication, and surgery could provide a greater yield of data in determining imaging strategies among patients and circumvent some of these limitations.

Conclusions

Based on this retrospective descriptive analysis, we observed that patients with a genetic diagnosis (including MFS, LDS, TS) were started on medications at lower severity of AoD at the SoV compared to patients without a genetic diagnosis or isolated AoD. Patients with BAV were started on medication at a larger AAo diameter compared to patients with genetic diagnoses and isolated AoD. Although echocardiographic aortic dimensions were relatively comparable to advanced imaging measurements in our study, multimodality imaging should be utilized especially when guiding decisions for AoD intervention. Genetic evaluation should be considered in patients with isolated AoD, family history of AoD, or clinical suspicion of CTD despite absence of clinical or phenotypic findings. Additional prospective studies may aid in further understanding progression of AoD in patients with and without genetic abnormalities and significant family history.

Author Contributions:

Drs. Morgan, Lohr, and Narasimhan contributed to the concept/design, data collection, data analysis/interpretation, statistical analysis, drafting article, critical revision and approval of article. Mr. Harvey contributed to the concept/design, data collection, data analysis/interpretation, statistical analysis, review and approval of article. Mr. Rubin data collection, data analysis/interpretation, and statistical analysis, review and approval of article.

References

1. Yetman AT, Graham T (2009) The Dilated Aorta in Patients With Congenital Cardiac Defects. JACC 53:461–467. https://doi.org/10.1016/j.jacc.2008.10.035

2. Kaddourah A, Uthup S, Madueme P, et al (2015) Prevalence and predictors of aortic dilation as a novel cardiovascular complication in children with end-stage renal disease. Clin Nephrol 83:262–271. https://doi.org/10.5414/CN108489

3. Hiratzka LF, Bakris GL, Beckman JA, et al (2010) 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease. Circulation 121:266–369. https://doi.org/10.1161/CIR.0b013e3181d4739e

4. Carrel T, Berdat P, Pavlovic M, et al (2003) Surgery of the dilated aortic root and ascending aorta in pediatric patients: techniques and results. Eur J Cardiothorac Surg 24:249–254. https://doi.org/10.1016/S1010-7940(03)00302-6

5. Jin-Sun Park, MD, Yong-Woo Choi, MD, Jeoung-Sook Shin, MD, Hyoung-Mo Yang M, Hong-Seok Lim, MD, PhD, Byoung-Joo Choi, MD, So-Yeon Choi, MD P, Myeong-Ho Yoon, MD, PhD, Gyo-Seung Hwang, MD, PhD,Seung-Jea Tahk, MD, PhD and Joon-Han Shin M (2011) Validation of Three-Dimensional Echocardiography for Quantification of Aortic Root Geometry: Comparison with Multi-Detector Computed Tomography. J Cardiovasc Ultrasound 19:128–133. https://doi.org/10.4250/jcu.2011.19.3.128

6. Erbel R, Aboyans V, Boileau C, et al (2014) 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. Eur Heart J 35:2873–2926. https://doi.org/10.1093/eurheartj/ehu281

7. Bons LR, Uchoa de Assis L, Dekker S, et al (2018) Screening for thoracic aortic pathology: Clinical practice in a single tertiary center. Congenit Heart Dis 13:988–996. https://doi.org/10.1111/chd.12663

8. Arevalo A, Haddad L, Johnson J, et al (2016) Aortic root size by echocardiogram compared with computed tomography in adolescents with pectus excavatum. J Thorac Imaging 31:163–167. https://doi.org/10.1097/RTI.000000000000

9. Hannuksela M, Stattin E-L, Johansson B, Carlberg B (2015) Screening for Familial Thoracic Aortic Aneurysms with Aortic Imaging Does Not Detect All Potential Carriers of the Disease. Aorta 03:1–8. https://doi.org/10.12945/j.aorta.2015.14-052

10. Birks E, Webb C, Child A, et al (1999) Early and Long-Term Results of a Valve-Sparing Operation for Marfan Syndrome. Circulation 100:II–29–Ii–35. https://doi.org/https://www.ahajournals.org/doi/full/10.1161/circ.100.supp 2.Ii-29

11. Zarate YA, Sellars E, Lepard T, Carlo WF (2015) Aortic dilation in pediatric patients. Eur J Pediatr 174:1585–1592. https://doi.org/10.1007/s00431-015-2575-8

12. Sluysmans T, Colan SD (2009) Structural Measurements and Adjustment for Growth. In: Lai WW, Cohen MS, Geva T ML (ed) Echocardiography in Pediatric and Congenital Heart Disease: from fetus to adult, 1st ed. Wiley-Blackwell, West Sussex, UK, pp 51–62

13. Colan SD (2009) Appendix 1: Normal Values for Cardiovascular Structures. In: Lai WW, Cohen MS, Geva T ML (ed) Echocardiography in Pediatric and Congenital Heart Disease: from fetus to adult, 1st ed. Wiley-Blackwell, West Sussex, UK, pp 765–785

14. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 327:307–10. https://doi.org/10.1016/S0140-6736(86)90837-8

15. Ono M, Goerler H, Boethig D, et al (2009) Current surgical management of ascending aortic aneurysm in children and young adults. Ann Thorac Surg 88:1527–33. https://doi.org/10.1016/j.athoracsur.2009.06.036

16. Youngmin Eun L, Kyu Cho D, Hyeong Cho Y, Hyun Byun K (2011) Aortic dissection and rupture in an 11-year-old child: A case report. J Cardiol Cases 3:46–49. https://doi.org/10.1016/j.jccase.2010.08.001

17. Fikar CR, Fikar R (2009) Aortic dissection in childhood and adolescence: An analysis of occurrences over a 10-year interval in New York State. Clin Cardiol 32:23–26. https://doi.org/10.1002/clc.20383

18. Wozniak-Mielczarek L, Sabiniewicz R, Drezek-Nojowicz M, et al (2019) Differences in Cardiovascular Manifestation of Marfan Syndrome Between Children and Adults. Pediatr Cardiol 40:393–403. https://doi.org/10.1007/s0024
018-2025-2

19. Hoskoppal A, Menon S, Trachtenberg F, et al (1916) Predictors of Rapid Aortic Root Dilation and Referral for Aortic Surgery in Marfan Syndrome on behalf of Pediatric Heart Network Investigators. 39:1453–1461. https://doi.org/10.1007/s00246-018-1916-6

20. Pyeritz RE (2014) Heritable thoracic aortic disorders. Curr Opin Cardiol 29:97–102. https://doi.org/10.1097/HCO.000000

21. Regalado E, Medrek S, Tran-Fadulu V, et al (2011) Autosomal dominant inheritance of a predisposition to thoracic aortic aneurysms and dissections and intracranial saccular aneurysms. Am J Med Genet Part A 155:2125–2130. https://doi.org/10.1002/ajmg.a.34050

22. Boileau C, Guo DC, Hanna N, et al (2012) TGFB2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nat Genet 44:916–921. https://doi.org/10.1038/ng.234

23. Reinstein E, Frentz S, Morgan T, et al (2013) Vascular and connective tissue anomalies associated with X-linked periventricular heterotopia due to mutations in Filamin A. Eur J Hum Genet 21:494–502. https://doi.org/10.1038/ejhg.2012.209

24. Patel S, Noble J, Suarez W, Vincent S (2016) Identifying Aortic Aneurysm Syndromes in Pediatric Patients with Aortic Root Dilation. JACC 67:2284. https://doi.org/10.1016/S0735-1097(16)32285-9

25. Mortani Barbosa EJ, Pyeritz RE, Litt H, Desjardins B (2011) Vascular Ehlers-Danlos syndrome presenting as rapidly progressive multiple arterial aneurysms and dissections. Am J Med Genet Part A 155:3090–3094. https://doi.org/10.1002/ajmg.a.34332

26. Kostich ND, Opitz JM (1965) Ullrich-Turner Svndrome Associated with Cystic Medial Necrosis of the Aorta and Great Vessels. Am J Med 38:943–50. https://doi.org/10.1016/0002-9343(65)90014-8

27. Isselbacher EM (2005) Thoracic and abdominal aortic aneurysms. Circulation 111:816–828. https://doi.org/10.1161/01.CI

28. Wong SC, Cheung M, Zacharin M (2014) Aortic dilatation and dissection in Turner syndrome: What we know, what we are unclear about and what we should do in clinical practice? Int J Adolesc Med Heal 26:469–488. https://doi.org/10.1515/ijamh-2013-0336

29. Lanzarini L, Larizza D, Prete G, et al (2007) Prospective Evaluation of Aortic Dimensions in Turner Syndrome: A 2-Dimensional Echocardiographic Study. https://doi.org/10.1016/j.echo.2006.08.028

30. Campion EW, Verma S, Siu SC (2014) Aortic Dilatation in Patients with Bicuspid Aortic Valve. N Engl J Med 370:1920–1929. https://doi.org/10.1056/NEJMra1207059

31. Park JY, Foley TA, Bonnichsen CR, et al (2017) Transthoracic Echocardiography versus Computed Tomography for Ascending Aortic Measurements in Patients with Bicuspid Aortic Valve. J Am Soc Echocardiogr. https://doi.org/10.1016/j.echo.2017.03.006

32. Saliba E, Sia Y, collaboration with Annie Dore I, El Hamamsy I (2015) The ascending aortic aneurysm: When to intervene? Int J Cardiol Hear Vasc 6:91–100. https://doi.org/10.1016/j.ijcha.2015.01.009

33. Freeman LA, Young PM, Foley TA, et al (2013) CT and MRI Assessment of the Aortic Root and Ascending Aorta. Am J Roentgenol 200:W581-92. https://doi.org/10.2214/AJR.12.9531

34. Goldstein SA, Evangelista A, Abbara S, et al (2015) Multimodality Imaging of Diseases of the Thoracic Aorta in Adults: From the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28:119–182. https://doi.org/10.1016/j.echo.2014.11.015

Table 1. Summary of Patient Characteristics

	n (%)
Sex	
Male	35 (74.5)
Female	12 (25.5)
Race	
White/Caucasian	35 (74.5)
Asian	4 (8.5)
Hispanic	3 (6.4)
African American	2 (4.3)
Unknown	3 (6.4)
Diagnosis	
BAV	19 (40.4)
MFS	13 (27.7)
Isolated AoD	10 (21.3)
TS	2 (4.3)
LDS	2 (4.3)
Anatomic Site of AoD	
Aortic root	31 (66.0)
AAo	7 (14.9)
Aortic root & AAo	9 (19.1)
Medication	
Losartan	24 (51.1)
Atenolol	15 (31.9)
Metoprolol	6 (12.8)
Lisinopril	2 (4.3)
Family History	
Aortic dissection	7 (14.9)
BAV	5 (10.6)
AoD	8 (17.0)
MFS	4 (8.5)
Vascular aneurysm	4 (8.5)

Table 2. Genetic Anomalies Identified in Cohort

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
1	F	AAo	TS Hypertension	Mildly dilated AAo and BP control. Patient was switched from HCTZ to Metoprolol.	Chromosome analysis: Female karyotype with Monosomy X	-
2	M	Aortic Root	BAV AS AI	FH of sudden death due to aortic dissection in father (47 yo). Pt did not meet Ghent criteria for MFS. Possibly has one of the familial thoracic aortic aneurysm and dissection syndromes	TAAD Panel: Hemizygous for FNLA gene splice variant of unknown clinical significance (c.116-3 C>A, Variant IVS1-3 C>A)	Father (Aortic dissection)
3	M	Aortic Root	Suspicion for CTD	Aortic dimensions above the 95th percentile for BSA; Father died of thoracic aortic dissection (38 yo)	SMAD 3 analysis: c.394A>G transition in exon 4 of SMAD3 gene of unknown clinical significance Negative TGFBR2, FBN1, MYH11	Father (Aortic dissection)

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
4	M	Aortic Root	AI	FH and concern for genetic abnormality	CGH: heterozygous deletion of one FBN1 allele; Copy Number LOSS in 15q21.1 - q21.3	Father (AoD - SoV 47 mm); Father's cousin died during weight lifting from "rupture of some sort"
5	F	Aortic Root	MFS	Aortic root dimension at the 95th percentile for BSA ; started due to aortic root size and mitral regurgitation	1 base pair deletion in the fragment containing axon 44 and flanking sequences of FBN1 gene	-
6	M	Aortic root	MFS	MFS	FBN1 gene c.2054G>A transition in exon 16	-
7	M	Aortic Root	MFS Atrial Tachycardia	SoV greater than the 95th percentile for BSA	FBN1 exon 11 mutation	Father (MFS)
8	M	Aortic Root	MFS Hypertension	MFS	FBN1 Exon 41 c.5071_-5073delAGA (heterozygous)	Mother, Sister (MFS)

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
9	M	Aortic root	Suspicion of CTD	Concern for possible CTD. Aortic root size in the upper normal limits, also dilation of the proximal descending aorta	SMAD 3 Exon 4 sequencing analysis: SMAD3 variant of unknown significance at c.394A>G (mother and brother with same variant)	Father (Aortic dissection) Brother (AoD) Mother, Brother (Same genetic mutation variant as pt)

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
10	M	Aortic root AAo	BAV AI	FH concerning for a potential genetic etiology for cardiac findings, at risk for progression of AoD given FH	CGH: 7q31.3 copy number loss; Adams-Oliver syndrome and Aarskog-Scott syndrome, which were negative by next-generation sequencing of FDG1 and NOTCH1; TAAD panel pending; WAS, DOCK8, GATA1, STAT3 and WIPF1: negative; ASXL1p.P1137L variant (unknown significance); KMT2Cp.R1095g variant (unknown significance)	Maternal GF (BAV, Aortic root aneurysm requiring surgery) Maternal great GF (brain aneurysm) Paternal uncle deceased at 1 day of age (CHD)

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
11	F	Aortic Root	MFS History of VT and Palpitations treated with Sotalol (Discontinued when started on Losartan)	MFS, SoV increased by 1 mm in 6 months	Heterozygous likely pathogenic missense variant detected in the FBN1 gene; c.6569G>T (p.Cys2190Phe), heterozygous, exon 54	-
12	M	Aortic Root	Suspicion for CTD	Concern for MFS (Aortic root increased from 30 to 37 mm in 2 years)	TAAD panel: Heterozygous FBN2 c.1644 T>G, pAsp548Glu (D548E), variant of unknown significance. Negative FBN1, TGFBR1 and TGFBR2. Plasma homocysteine: normal	Brother (Pectus abnormality) Father (high arch palate)
13	M	Aortic Root	Hypertension	aortic root dilation, BP control	CGH: Copy number gain within 16p13.11; 16p13.1 duplication, including MYH11 gene	-

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
14	M	Aortic Root	MFS	MFS	FBN1 & TGFBR2 analysis: FBN1 gene mutation exon 25 c.3146G>A	-
15	M	Aortic Root	-	FH, echocardiogram with aortic root dimensions above the 95th percentile for BSA, decrease rate of growth of aortic sinuses	TAAD Panel: Variants of unknown significance COL3A1 c.203A>G, pAsp68Gly (D68G), Heterozygous COL5A2 c.3316C>T, pArg1106Trp (R1106W), Heterozygous	Father (severe aortic regurgitation, AAo aneurysm with dissection s/p mechanical aortic valve, hypertension) Brother (BAV)
16	F	Aortic Root AAo	BAV AS AI	Aortic dimensions above the 95th percentile for BSA	FBN1 & TGFBR2 analysis: FBN1 negative; TGFBR2 exon 4 c.610G>A transition (unknown significance, most likely polymorphism)	Unknown, Adopted

Pt	Sex	Anatomic Site of AoD	Associated Diagnoses	Stated Indication for Initiation of Medication	Genetic Findings	Family History of aortic pathology/connective tissue disorder/CHD
17	F	Aortic Root AAo	BAV TS	MRA confirmed AoD, patient started on medication	Chromosome analysis: 45,X (Monosomy X)	Maternal GF (Aortic Aneurysm) Maternal uncle (MVP) Maternal cousin (BAV/AI)
18	F	Aortic Root	MFS	MFS, considered to have mild aortic root enlargement	FBN1 & TGFBR2 analysis: FBN1 exon 23 c.2849G>C; TGFBR2 negative	Maternal aunt (MVP) Brother (SVT)
19	M	Aortic Root	LDS Type 4	LDS	Level 2 sequencing: TGFB2 c.1210G>A (p.Ala404Thr) variant, heterozygous	-
20	F	Aortic Root	LDS Type 2	LDS	Next Generation Sequencing: TGFBR2 1336G>A (p.Asp446Asn) variant, heterozygous (Mutation in mosaic state in father)	Father (Genetic mutation)

AI = Aortic insufficiency; AS = Aortic stenosis; BSA = Body surface area; CGH = Comparative genomic hybridization; CHD = Congenital heart disease; FH = Family History; HCTZ = Hydrochlorothiazide; Pt = Patient; SVT = Supraventricular tachycardia

Table 3. Correlation between Echo and Advanced Imaging

Comparison	N	r	*p*-value	Median difference (mm)	IQR

Comparison	N	r	*p*-value	Median difference (mm)	IQR
Echo-MR SoV	36	0.90	<0.001	1.0	-0.25, 2.25
Echo-CT SoV	10	0.82	0.004	0	-0.75, 1
Echo-MR AAo	18	0.91	<0.001	1.0	0, 2
Echo-CT AAo	4	0.99	0.006	-0.3	-1, 0.55

p -value is in reference to correlation coefficient "r"

Figure 1. Echo SoV and AAo Z-scores by Age and Diagnosis at Initiation of Medication (see attached file)

Figure 2. Bland-Altman Analyses of Echo and Advanced Imaging (see attached file) –

Dotted lines Represent 95% CI of Bias

Table 4. Operative Details

Operative Patient Details	Operative Patient Details	Operative Patient Details	Operative Patient Details	Operative Patient Details	Operative Patient Details
Age at surgery (years)	**Diagnoses**	**Level of aortic dilation**	**Aortic diameters by echo (mm) at Surgery**	**Surgery**	**Family History**
22	MFS	Aortic root	SoV 55 (Z-score: 6.2)	Valve sparing aortic root and ascending aorta replacement	MFS
21	BAV Moderate AI	Aortic root	SoV 53 (Z-score: 8.2)	Valve sparing aortic root replacement and aortic valve repair	-
20	BAV Mild AS Moderate AI	Aortic root	SoV 40 (Z-score: 4.5) AAo 48 (Z-score: 8.1)	Ross procedure and replacement of ascending aorta	-
14	BAV Severe AS Mild AI	Ascending aorta	AAo 36 (Z-score: 4.7)	Aortic valve, root, and ascending aorta replacement	-
10	MFS	Aortic root	SoV 41 (Z-score: 9.4)	Valve-sparing aortic root replacement	-

AI = Aortic insufficiency; AS = Aortic stenosis

Table 5. Percentage of Diagnosis by Age Group

	Age Group	Age Group	
Diagnosis	**0 - 16 (N = 10)**	**17 - 30 (N = 37)**	**Total (N = 47)**
Isolated AoD	**Isolated AoD**	**Isolated AoD**	**Isolated AoD**
	2 (20.0%)	8 (21.6%)	10 (21.3%)
BAV	**BAV**	**BAV**	**BAV**
	5 (50.0%)	14 (37.8%)	19 (40.4%)
LDS	**LDS**	**LDS**	**LDS**
	2 (20.0%)	0 (0.0%)	2 (4.3%)
MFS	**MFS**	**MFS**	**MFS**
	1 (10.0%)	12 (32.4%)	13 (27.7%)
Concern CTD	**Concern CTD**	**Concern CTD**	**Concern CTD**
	1 (10.0%)	7 (18.9%)	8 (17.0%)
TS	**TS**	**TS**	**TS**
	1 (10.0%)	1 (2.7%)	2 (4.3%)

Table 6. Echo Aortic Dimensions (Median and IQR) at Initiation of Medication

	Age Group	Age Group	
	0 - 16 (N = 10)	**17 - 30 (N = 37)**	**Total (N = 47)**
Echo BSA			
Median (IQR)	1.1 (1.0, 1.3)	1.7 (1.5, 1.9)	1.6 (1.3, 1.8)
Echo SBP			
Median (IQR)	106.0 (98.2, 109.0)	114.0 (104.0, 119.2)	109.5 (101.8, 118.0)
Echo DBP			
Median (IQR)	65.0 (62.2, 72.5)	70.5 (64.0, 78.2)	70.0 (63.2, 77.8)
Echo SoV (mm)			
Median (IQR)	27.0 (26.0, 29.8)	35.0 (31.0, 39.5)	34.0 (29.0, 38.2)
Echo SoV (Z-score)			
Median (IQR)	2.9 (2.7, 4.3)	2.9 (1.9, 4.5)	2.9 (2.0, 4.4)
Echo STR (mm)			
Median (IQR)	23.7 (21.0, 25.5)	27.0 (24.5, 29.0)	26.0 (24.0, 28.8)
Echo STR (Z-score)			
Median (IQR)	2.5 (2.1, 3.5)	2.3 (1.6, 3.6)	2.4 (1.7, 3.6)
Echo AAo (mm)			
Median (IQR)	29.5 (27.0, 33.5)	33.0 (27.0, 34.8)	32.0 (27.0, 35.0)
Echo AAo (Z-score)			
Median (IQR)	3.4 (2.9, 5.4)	2.5 (1.0, 4.5)	3.3 (1.2, 4.6)