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# Data Supplement. TAD/VHD Guideline Clarification Statement—Surgery for Aortic Dilatation in Patients With Bicuspid Aortic Valves

| **Study** | **Aim of Study** | **Study Type** | **Study Size (N)** | **Inclusion Criteria** | **Exclusion Criteria** | **Endpoints** | **Study Limitations and Adverse Events** | **Conclusions** |
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| Svensson LG, et al., 2008  (1)  [18083364](http://www.ncbi.nlm.nih.gov/pubmed?term=18083364) | Expert consensus document on treatment of descending TAD using endovascular stent grafting. | Expert consensus | N/A | N/A | N/A | In older pts, ascending aorta growth rate-0.07 cm/y.  Descending aorta growth rate-0.19 cm/y.  For ascending and descending aorta;  Non-dissected aorta growth rate-0.09 cm/y,  Dissected aorta growth rate-0.14 cm/y.  Ascending aorta hinge point at the diameter of 6 cm (34% risk of rupture or dissection)  Descending aorta hinge point at the diameter of 7cm (43% risk of rupture and dissection). | Most databases have fewer patients with diameter in 5.0–5.5 cm size. | Surgical treatment recommended at 5.5 cm diameter for ascending and 6.5 cm for descending aorta to prevent complications. For Marfan’s syndrome or a BAV, 15% of dissections occur at ascending aorta diameter of 5.0 cm. Dividing the ascending aorta maximal cross-sectional area by pt height and using threshold of 10 recommended for indication of operation. At high experience facilities, it has been suggested for asymptomatic pts (with connective tissue disorders, chronic aortic dissection with increased growth rate) to use <5 cm for ascending and <6 cm for descending aorta and thoracoabdominal aorta as criteria.  No evidence that asymptomatic aneurysms <5.5 cm benefit from repair. |
| Svensson LG, et al., 2003  (2)  [14502185](http://www.ncbi.nlm.nih.gov/pubmed/?term=14502185) | Investigate relationship between risk of aortic dissection and aortic cross-sectional area size-to-height ratio in pts with BAVs. | Observational | 430 pts with BAV (40 acute aortic dissection) | Pts who underwent surgical intervention for BAVs and ascending aorta with or without aortic arch repair; CT, MRI and ECG studies used to determine aorta size, pre-replacement | N/A | Of the group with aortic dissection, 35% had aortic diameters ≤5.5 cm and 12.5% <5 cm. | This study looks at pts with symptomatic disease, and it does not inform us about the majority of pts with BAV who are asymptomatic and undergoing surveillance imaging. | Aortic dissection can occur at a smaller size than generally perceived. Authors suggest indexing the cross-sectional area of aneurysms to the pt height to more accurately determine dissection risk, and more aggressive treatment for asymptomatic aortic aneurysms as well as repair for symptomatic BAVs if aorta >4.5 cm or cross-sectional: height ratio is >10. |
| Kouchoukos NT, et al., 1997  (3)  [9197217](http://www.ncbi.nlm.nih.gov/pubmed/?term=9197217) | To review existent diagnostic and management plans for acquired diseases of thoracic aorta and whether the treatments improve outcomes | Review article | Ascending Aorta:  1. Marfan’s and cystic medical degenerative disease: elective replacement of ascending aorta and aortic sinuses when the greatest diameter of the aorta >5.0–5.5 cm;  2. Significant AR-surgery may be recommended before it reaches that diameter;  3. Degenerative aneurysms within the ascending aorta with sx; graft replacement when diameter of aorta >5.0–5.5 cm | Aortic Arch:  Elective surgery only for aneurysms that are more than 5.5–6.0 cm in diameter (due to risk of neurologic injury) | Descending Aorta: with degenerative or chronic aneurysm with sx, elective resection if the aneurysm  >5 to 6 cm | Thoracoabdominal Aorta: asymptomatic and aneurysm or chronic dissection >5–6 cm diameter, elective surgery. With existent techniques postoperative outcomes have improved. | Review article | As rupture of aneurysms is very common cause of death, surgical approach may be appropriate in asymptomatic pts with aneurysms that are ≥6 cm diameter. Periodic postoperative evaluation is critical. |
| Elefteriades JA, et al., 2002  (4)  [12440685](http://www.ncbi.nlm.nih.gov/pubmed/?term=12440685) | To understand natural history of TAA | Prospective database analysis | 1,600 | TAA pts |  | **Growth rate**: avg. 0.10 cm/y (0.07 for ascending and 0.19 for descending).  **Genetic analysis:** 21% of probands with TAA have first-order family members with arterial aneurysm. | **Critical sizes:** for rupture or dissection of aortic aneurysm were 6.0 cm for the ascending aorta and 7.0 cm for the descending. At these sizes, likelihood of rupture or dissection was 31% for the ascending and 43% for the descending aorta.  **Yearly event rates:** At 6 cm, the yearly rates of serious AEs: rupture (3.6%), dissection (3.7%), death (10.8%), rupture, dissection, or death (14.1%).  **Surgical risks**: risk of death from surgery: 2.5% for the ascending and arch and 8% for the descending and thoracoabdominal aorta | **a.** Surgery in asymptomatic patients for the following cases was recommended:  -ascending aorta at 5.5 cm  -descending aorta at 6.5 cm.  **b.** Surgery for Marfan’s disease or  familial TAA:  -ascending at 5.0 cm  -descending at 6.0 cm.  **c.** Symptomatic aneurysms must be resected regardless of the size. |
| Tzemos N, et al.,  2008  (5)  [18799444](http://www.ncbi.nlm.nih.gov/pubmed/?term=18799444) | To determine the frequency and predictors of cardiac outcomes (and disease progression) in a large consecutive series of adults with BAVs | Cohort study | 642 consecutive ambulatory adults | BAV documented on TTE | Complex congenital cardiac defects; referral for cardiac surgery, catheter-based treatment, obstetric care | Mortality (28 deaths; 17 cardiac-related) and cause of death; 161 pts had ≥1 primary cardiac events including cardiac death (17; 12 HF, 2 aortic dissection, 3 cardiac surgery post-op), intervention on the aortic valve or ascending aorta (142), aortic dissection or aneurysm (11), or congestive heart failure requiring hospital admission (16). Independent predictors of primary cardiac events were age >30 y (HR: 3.01; CI: 2.15–4.19); moderate or severe aortic stenosis (HR: 5.67; CI: 4.16–7.80); and moderate or severe aortic regurgitation (HR: 2.68; CI: 1.93–3.76). | Risk estimates derived from retrospectively identified population and baseline extent of ascending aortic dilation could not be defined in most pts. Mortality ratios compared to the general population were not adjusted for various risk factors (smoking, socioeconomic status, or ethnicity). | Age, severity of aortic stenosis, and severity of aortic regurgitation were independently associated with primary cardiac events (survival rates of this cohort were not statistically different from general population estimates). 25% with BAV experienced a primary cardiac event during a mean follow-up of 9 y. |
| Michelena HI, et al.,  2011  (6)  [21917581](http://www.ncbi.nlm.nih.gov/pubmed/?term=21917581) | To evaluate aortic complications in BAV pts | Retrospective cohort study | 416 pts followed for an average of 16 y |  |  | Type A and type B aortic dissection, ascending AA, and aortic surgery.  Of the 416, 2 had aortic dissections (1 type A and 1 type B) with most recent aortic diameters of 52 and 50 mm, respectively, yielding a risk of dissection of 0.5% over 25 y, or an incidence of 3.1 cases per 10,000 pt y; RR compared to the rest of the population of 8.4.  32 pts with aortic aneurysm and 14 subsequently had surgery (including the 2 dissections). Of the 384 without initial aneurysm, 49 developed an aortic aneurysm(p<.001 compared with general population)  25 y risk of aortic surgery was 25%. | Limited number of dissections observed.  Authors make 2 somewhat opposing statements: a) observations support elective aortic surgery for ascending aortic aneurysms according to the 2006 ACC/AHA VHD guidelines (≥5.0 cm); b) aortic dissection is not exclusively a matter of absolute size. | Incidence of aortic dissection in BAV pts is low and is not comparable to pts with Marfan syndrome.  Many of the pts with aortic aneurysms (almost one-half) underwent elective aortic surgery. |
| Davies RR, et al.,  2002  (7)  [11834007](http://www.ncbi.nlm.nih.gov/pubmed/?term=11834007) | To estimate yearly rupture or dissection rates for TAA (asymptomatic) | Prospective Database analysis | 304 (dissection free at presentation).  Followed from 1985-2000. | Aortic size at least 3.5 cm and >6 y, absence of congenital aortic malformations, and at least 1 size dimension before referral for surgical repair | Preexisting dissection | Dissection, rupture, and death (or various combinations), 92 pts with endpoints. (55 deaths, 13 documented ruptures, and 24 documented new, acute aortic dissections)  Aneurysms >6 cm: Rupture-3.7%/ y,  Rupture or dissection: 6.9%/y,death:11.8%/y, all outcomes together: 15.6%/y.  OR increased 27 fold (p=0.002) | Larger sample size required for studies of risk factors for complications. The question for 5-6 cm sizes still remains unanswered, when risk is so clear for ≥6cm in this study. | Aortic size strong predictor of dissection, rupture and death.  Elective surgery brings life-expectancy to normal. Risk of specified outcomes from all causes: 6.5% for 5.0-5.9 cm; 14.1% for ≥6.0 cm. |
| Braverman AC, et al., 2005  (8)  [16129122](http://www.ncbi.nlm.nih.gov/pubmed/?term=16129122) | Review of BAV including timing for ascending aorta replacement | Review | (NA) | (NA) | (NA) | Risk of complications: ascending aorta is 6 cm for all pts, and possibly closer to 5.5 cm for aneurysms associated with BAVs. Biomechanical testing for aortic wall stress was found to be 1-cm increase in aortic diameter for a 26 mm Hg rise in BP. | Review article | Risk of aortic wall rupture or dissection associated with aneurysm size, pt age, and BP.  For ascending AA resection in pts with BAV, the authors recommended to use the following criteria (1) aortic diameter  >5.0 to 5.5 cm; (2) rapid enlargement (>3 -5 mm in 1 y); (3) sx of aneurysm (4) large sinus of Valsalva aneurysm.  Ascending AA >4.5cm should undergo replacement ascending aorta with AVR |
| Svensson LG, et al, 2011  (9)  [21292285](http://www.ncbi.nlm.nih.gov/pubmed/21292285?dopt=Citation) | To evaluate whether pre-emptive BAV surgery with ascending aorta repair improve outcomes | Prospective Cohort registry study | 1,989 with BAV surgery (1,449 with BAV surgery alone and 361 had surgery with aortic repair) |  |  | 30 d in-hospital survival (98.8% with valve alone vs 98.9% with aortic repair)  10 y survival for valve alone (75% vs 85%, p=.0001) but matched cohort survival was identical.  Freedom from late aortic events high in both groups (99% valve alone vs 97% with aortic repair at 10 y and similar in matched cohort. | No aortic imaging performed for postoperative follow up and echo was performed at the cardiologist discretion. | There is no additional risk and improved late survival for simultaneous aortic repair for the aortic size >4.5 cm or the cross sectional area/height ration >8-10.  More aggressive approach is not reasonable. |
| McKellar SH, et al.,  2010  (10)  [21094365](http://www.ncbi.nlm.nih.gov/pubmed/21094365?dopt=Citation) | To evaluate long-term risk of aortic events following AVR in pts with BAV | Observational database analysis | 1286 AVRs with BAV from 1960-95 (normal aorta-779; enlarged aorta 507) | AVR pts with BAV | Marfan’s, Ehler-Danlos syndrome | Composite “aortic events”, overall mortality and cardiac mortality.  160 aortic events in 1,286 pts with 12 y follow up. 13 aortic dissections (1%), 11 aortic replacements (0.9%), and 127 progressive aortic enlargements.  Predictors of all-cause mortality by MVR analysis included age 60 y at AVR (HR: 2.5, 95% CI: 2.1–2.9, p=0.001), DM (HR: 2.1, 95% CI: 1.6–2.7, p=0.001), CABG at AVR (HR: 1.3, 95% CI: 1.1–1.6, p=0.003), and use of a tissue prosthesis (HR: 1.3, 95% CI: 1.1–1.5, p=0.006). Aortic size was not predictive of mortality.  Cardiac mortality predictors were diabetes (HR: 2.7, 95% CI: 1.7–4.3, p=0.001), age 60 years (HR: 2.1, 95% CI: 1.6–2.7, = 0.001), interval AVR (HR: 1.8, 95% CI: 1.2–2.5, p=0.002), and HTN (HR: 1.3, 95% CI: 1.0–1.7, p=0.03). | Aortic enlargement documentation for the study complicated by the imaging advancement during the progress of the study. | Aortic rupture or dissection rates in AVR pts with BAV are low thus surgery risks for prophylactic repair of ascending aorta must be low. |
| Borger MA, et al.,  2004  (11)  [15514594](http://www.ncbi.nlm.nih.gov/pubmed/15514594?dopt=Citation) | To determine the diameter at which ascending aorta be replaced in BAV pts. | Computerized database analysis | 201 | BAV pts undergoing AVR followed for 10 y on average | Aortic root replacement or supracoronary replacement of ascending aorta, BAV pts with severe dilation >5.0 cm underwent AVR were excluded. | 22 pts had long-term ascending aorta complications (18 for aneurysm and thus underwent replacement, 1 for aortic dissection, 3 for SCD). 43 (21%) died during follow up. “15 freedom from ascending aorta–related complications was 86%, 81%, and 43% in pts with an aortic diameter of <4.0 cm, 4.0 to 4.4 cm, and 4.5 to 4.9 cm, respectively (p=.001)” | Retrospective study.  No exact measurements of ascending aorta available for earlier years of the study. | BAV pts undergoing operations should be considered for concomitant replacement of the ascending aorta if the diameter is ≥4.5 cm. |

ΔPmean indicates mean transaortic systolic pressure gradient; AF, atrial fibrillation; AR, Aortic Regurgitation; AS, aortic stenosis; Ascending AA , ascending aorta aneurysm; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; AVR, aortic valve replacement; BAV, Bicuspid Aortic Valve; BNP, brain natriuretic peptide; BSA, Body surface area; BP, Blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CR, contractile reserve; DM, Diabetes Mellitus; DSE, dobutamine stress echocardiography; HF, heart failure; HTN, Hypertension; LFLG, low-flow/low-gradient; LF, low flow; LG, low gradient; N/A, not applicable; pts, patients; Rx, prescription; LVEF, left ventricular reduced ejection fraction; MVR, multivariate regression analysis; SAVR, surgical aortic valve replacement; SV, stroke volume; SVi, stroke volume indexed to body surface area; sx, symptoms; TAA, Thoracic aortic aneurysms; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography; SCD, sudden cardiac death; and TAA, thoracic aortic aneurysm.

**References**

1. Svensson LG, Kouchoukos NT, Miller DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. Ann Thorac Surg. 2008;85:S1-41.

2. Svensson LG, Kim KH, Lytle BW, et al. Relationship of aortic cross-sectional area to height ratio and the risk of aortic dissection in patients with bicuspid aortic valves. J Thorac Cardiovasc Surg. 2003;126:892-3.

3. Kouchoukos NT, Dougenis D. Surgery of the thoracic aorta. N Engl J Med. 1997;336:1876-88.

4. Elefteriades JA. Natural history of thoracic aortic aneurysms: indications for surgery, and surgical versus nonsurgical risks. Ann Thorac Surg. 2002;74:S1877-S1880.

5. Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. JAMA. 2008;300:1317-25.

6. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA. 2011;306:1104-12.

7. Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg. 2002;73:17-27.

8. Braverman AC, Guven H, Beardslee MA, et al. The bicuspid aortic valve. Curr Probl Cardiol. 2005;30:470-522.

9. Svensson LG, Kim KH, Blackstone EH, et al. Bicuspid aortic valve surgery with proactive ascending aorta repair. J Thorac Cardiovasc Surg. 2011;142:622-9, 629.

10. McKellar SH, Michelena HI, Li Z, et al. Long-term risk of aortic events following aortic valve replacement in patients with bicuspid aortic valves. Am J Cardiol. 2010;106:1626-33.

11. Borger MA, Preston M, Ivanov J, et al. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? J Thorac Cardiovasc Surg. 2004;128:677-83.