



Concomitant cardiovascular malformations in isolated bicuspid aortic valve disease: a retrospective cross-sectional study and meta-analysis

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Background: Congenital bicuspid aortic valve affects up to 2% of the general population. It occurs in complex congenital heart defects or in syndromes such as Turner, Marfan, or Loeys-Dietz. However, the majority of bicuspid aortic valves are considered to manifest as isolated malformations.

Methods: We aimed to assess retrospectively associated cardiovascular malformations in 200 individuals with bicuspid aortic valve considered to occur as an isolated manifestation. All individuals underwent transthoracic echocardiography, 164 thoracoabdominal tomographic imaging, and 84 coronary artery imaging. In addition, we also performed a meta-analysis of data from the literature to assess the occurrence of associate malformations.

Results: In our retrospective cross-sectional study collective, the mean age was 45±15 years, 154 (77%) individuals were male. Anatomy of bicuspid aortic valve according to Schaefer was type 1 in 142 (71%), type 2 in 35 (18%), type 3 in 2 (1%), unicuspid in 6 (3%), and unclassified in 15 (8%) individuals. Coarctation of the aorta had 4.2% of individuals, 3.6% had coronary anomalies. No individual had a patent ductus arteriosus, 0.5% had atrial and ventricular septal defect each, 1.5% mitral valve prolapse. No individual had a tricuspid valve prolapse. Our meta-analysis identified in cohorts with isolated bicuspid aortic valve 11.8% (95% CI: 7.7–16.0%) individuals with aortic coarctation, 3.7% (95% CI: 1.2–6.1%) with coronary anomalies, 3.3% (95% CI: 0.0–6.7%) with patent ductus arteriosus, 5.9% (95% CI: 1.3–10.5%) with ventricular septal defect and 1.6% (95% CI: 1.1–2.1%) with mitral valve prolapse.

Conclusions: Individuals with isolated bicuspid aortic valve may exhibit a variety of associated cardiovascular malformations and therefore screening for associated malformations may be warranted.

Keywords: Bicuspid aortic valve disease; associate malformations; aortic coarctation

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Introduction

The bicuspid aortic valve is the most frequent congenital heart defect in the general population. In echocardiographic and autopsy studies, the incidence of bicuspid aortic valve ranges from 0.16% in Asian (1) to 2% in the Western populations (2,3), and is more frequent in males (4). The abnormal architecture of the valve makes the leaflets susceptible to haemodynamic stress, leading to valvular thickening, calcification, and increased rigidity and narrowing of the aortic orifice (5). Independent of the cuspidity of the valve, women tend to present more often with moderate or severe aortic stenosis compared with men (4). Preventive measures, such as physical activity (6) and medicaments can't decrease the risk of severe aortic valve stenosis, therefore aortic valve surgery is currently the only treatment to increase life expectancy and quality. Bicuspid aortic valve diagnosed in children often occurs in complex congenital heart defects or in syndromes such as Turner, Marfan, or Loeys-Dietz (7). In contrast, the coincidental finding of bicuspid aortic valves in healthy and asymptomatic adolescents and adults, frequently associated with dilation of the proximal aorta (8), are usually considered to occur as isolated cardiovascular manifestation. However, in such "isolated bicuspid aortic valve disease" the prevalence of other associated cardiovascular malformations has not been assessed systematically (9-11).

According to the literature, aortic coarctation may be the most common associated cardiovascular malformation in bicuspid aortic valve disease (12). More than half of the individuals with aortic coarctation (13), about 14% with anomalous coronary arteries (14), 8% with patent ductus arteriosus (15), and 8.5% with ventricular septal defects (16) had a concomitant bicuspid aortic valve. About 1% of adults with atrial septal defect (17) and 3% with mitral valve prolapse also had a bicuspid aortic valve (17,18), and even in individuals with tricuspid valve prolapse, a bicuspid aortic valve may be present simultaneously (19). However, there is no study that systematically reports imaging results for all associated cardiovascular malformations.

In our outpatient section for individuals with isolated bicuspid aortic valve, we routinely perform comprehensive imaging for associated cardiovascular malformations. Our first aim was to assess the prevalence of associated cardiovascular malformations such as aortic coarctation, coronary anomalies, patent ductus arteriosus, ventricular septal defect, atrial septal defect, mitral valve prolapse, and tricuspid valve prolapse in our study collective of

200 individuals, in a retrospective, observational manner. Our second aim was to assess the prevalence of these malformations in individuals assumed to have isolated bicuspid aortic valve disease by performing a systematic review of literature data followed by a meta-analysis. We applied STROBE as guideline for retrospective observational study quality (20) and PRISMA for meta-analysis (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-22-112/rc>).

Methods

Individuals included in our retrospective study collective

We conducted a retrospective observational cross-sectional study of 200 consecutive individuals (154 males and 46 females), who presented to the adult cardiology outpatient department of the University Heart and Vascular Center in Hamburg with an isolated bicuspid aortic valve between January 2013 and December 2019. The indication for their visit comprised incidental finding of a bicuspid aortic valve for further clinical risk evaluation in 37%, symptomatic valve dysfunction including severe regurgitation or stenosis in 63%, and of these, indication for surgery for bicuspid aortic valve dysfunction or severe aneurysm in 40%. Individuals with complex cardiovascular malformations or with a known genetic aortic disease did not present to us as those are followed up in an adult congenital heart disease center or at a specialty consultation for genetic aortic disease. We collected anonymized patient data. According to German federal regulations, an approval for a retrospective study with anonymous data collection is not necessary. Our study complied with the Declaration of Helsinki (as revised in 2013). The study was approved by regional ethics committee of 2022_300194-WF.

Clinical manifestations in our retrospective study collective

We analyzed patient charts to assess age at first and final contact at our center. We documented the morphology and function of the aortic valve in all individuals. Morphologically, we distinguished bicuspid aortic valve type 1 with fusion of the right and the left coronary cusp; type 2 with right and non-coronary fusion; and type 3 with left and non-coronary fusion valves, according to Schaefer (21), or as "unknown" if not specified. We classified aortic valves exhibiting only one commissure as unicuspid. According to our clinical routine, we described aortic valve stenosis as at

least moderate if the valve orifice area was less than 1.5 cm² and considered regurgitation as at least moderate if the width of the vena contracta exceeded 3 mm, the pressure half time was below 500 ms or effective orifice area above 10 mm² according to the current European echocardiography guidelines (22). We gathered information about surgery of the aortic valve and distinguished between aortic valve repair and aortic valve replacement with a biological or mechanical valve prosthesis, or pulmonary autograft known as Ross procedure (23).

In accordance with the current European Society of Cardiology guidelines for aortic disease, we considered the presence of root or ascending aortic dilation with diameters exceeding 40 mm (24) and described it as proximal aortic dilation. We measured aortic diameters by echocardiography using the end-diastolic leading-edge-to-leading-edge convention as this method showed accurate and reproducible values (25,26). Additionally, we assessed the aortic diameters using computed tomography or magnetic resonance imaging as recommended in current European Society of Cardiology guidelines for aortic disease (24).

Imaging methods used in our retrospective study collective

All 200 individuals underwent at least one transthoracic echocardiographic examination. In addition, 89 individuals underwent a transesophageal echocardiography. Indications for transesophageal echocardiography comprised evaluation of the aortic root anatomy prior to surgery or assessment of the severity of aortic valve dysfunction identified on transthoracic views. We performed tomographic examination of the aorta in 164 individuals, which comprised computed tomography in 34 individuals and magnetic resonance imaging tomography in 130 individuals. The tomographic imaging at baseline evaluation was aimed to map the entire aorta for aortic pathology including aneurysm, coarctation, or patent ductus arteriosus. We applied current diagnostic imaging criteria and technology as specified recently (27,28). Eighty-four individuals underwent coronary artery imaging with invasive coronary angiography performed in 75 and coronary computed tomography angiography in 10 individuals. Cardiac magnetic resonance imaging additionally was performed in 32 individuals. All examinations were performed to diagnose or rule out progressive coronary artery or ischemic heart disease for preoperative evaluation.

Identification of associated malformations in our retrospective study collective

We documented associated cardiovascular malformations according to charts as assessed during our clinical routine as follows:

Aortic coarctation, defined as local narrowing of the aortic lumen, based on reported findings on tomographic imaging (29), and in the case of two individuals based on description of surgical correction of aortic coarctation.

Coronary anomalies using at least one of the following imaging modalities for assessing coronary artery anatomy: coronary angiography, cardiac computed tomography, cardiac magnetic resonance. We described and included in our statistics any deviations from normal coronary anatomy as defined by Angelini (30).

Patent ductus arteriosus, a persistent vessel between aorta and pulmonary artery based on reported findings on tomographic imaging.

Atrial and ventricular septal defects with demonstration of a transseptal jet on color flow Doppler echocardiography. Small septal defects, such as patent foramen ovale, requiring contrast echocardiography, were excluded from our statistical analysis.

Mitral valve and tricuspid valve morphology by echocardiography as stated by the guidelines of the European Association of Echocardiography (31,32) with criteria of mitral valve prolapse as described previously (32).

We calculated the competing risk for surgeries for associated malformations and for the bicuspid aortic disease. The group with surgeries for associated malformations included corrections of aortic coarctation, atrial and septal defects or mitral valve prolapse. The group of surgeries for the bicuspid aortic disease involved all surgeries on the proximal aorta, either for valve dysfunction, root or aorta ascendens aneurysms.

Meta-analysis of literature data

We performed a systematic review of the literature to assess published frequencies of malformations associated with non-syndromic bicuspid aortic valve disease (*Figure 1*). Two reviewers screened PubMed independently for the keyword “bicuspid aortic valve” up to 31 December 2019. We considered all studies published in English with inclusion of individuals of all ages with known bicuspid aortic valve. We excluded case reports, editorials, reviews,

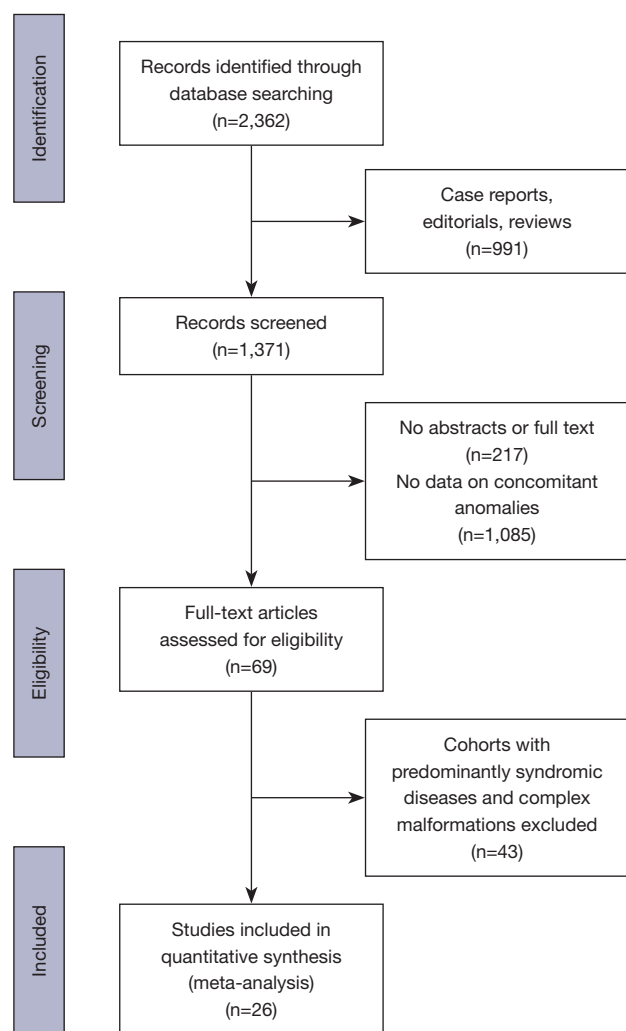


Figure 1 PRISMA 2009 flow diagram according to Moher and colleagues (33). Systematic review of the literature to assess published frequencies of malformations associated with non-syndromic bicuspid aortic valve disease.

articles without abstracts or full text available online. We looked for the completeness of information about associated malformations and study population characteristics. We removed articles without information on concomitant malformation. The remaining articles included at least one of the following terms in the abstract or, if the abstract was not available, in the manuscript: aortic coarctation, ventricular septal defect, atrial septal defect, patent ductus arteriosus, mitral valve prolapse. We excluded reports with less than 5 individuals or with collectives that included predominantly individuals with syndromic diseases or complex malformation. Furthermore, we excluded reports

not quantifying the frequency of the occurrence of concomitant malformations in a collective of individuals with bicuspid aortic valves. Two reviewers read thoroughly the studies appropriate for our meta-analysis and collected data on the frequency of malformations, primary imaging modalities and demographic parameters of the study group.

We assessed the risk of bias in individual studies by two independent raters. We graded the selection bias in the studies as low, intermediate, or high. Low, if the study population was close to the general population (for example asymptomatic individuals with incidental finding of a bicuspid aortic valve). On the other hand, we assumed a high bias in patient collectives presented in tertiary hospitals for surgeries. In case of different assessments of the two raters, we established a consensus.

Statistical methods

Unless otherwise specified, we expressed continuous data as means \pm standard deviation and categorical data as absolute numbers with respective percentages in parentheses. A surgery performed on the aortic root, ascending aorta, or the valve itself was considered for statistical analysis as surgery for bicuspid aortic disease.

To compare the mean age at first surgery for associated malformations and at surgery on the proximal aorta including the aortic valve, we performed a *t*-test for independent samples. All tests were performed in an explorative manner, rather than testing a hypothesis postulated in advance, therefore we did not adjust for multiple testing.

Time to surgery (either associated malformations or proximal aorta) was performed with a competing risk survival analysis. In the meta-analysis we used a random effects model to compute the summary estimates.

The forest plots show the individual estimates and 95% confidence intervals, as well as of the summary estimates. We report I^2 and τ^2 as measures of heterogeneity. We used the statistics software R version 4.1.0 (34) for all statistical tests and plots, including the R-package survival version 3.2-3 (35) and R-package metafor version 2.4-0 (36).

Results

Baseline characteristics of individuals in our retrospective study collective

The mean age of individuals at initial contact at our center was 45 ± 15 years (range, 14–80 years) and 77% were males.

Table 1 Baseline characteristics

Variable	Number of individuals with findings (N=200), n (%)
Sex	
Male	154 (77.0)
Female	46 (23.0)
Bicuspid aortic valve morphology according to Schaefer	
Type 1	142 (71.0)
Type 2	35 (17.5)
Type 3	2 (1.0)
Unicuspid	6 (3.0)
Unknown	15 (7.5)
Aortic valve surgery performed, type	
No surgery	100 (50.0)
Repair	17 (8.5)
Biological valve	64 (32.0)
Mechanical valve	18 (9.0)
Ross procedure	1 (0.5)
Aortic valve dysfunction (at least moderate)	
None	68 (34.0)
Stenosis	47 (23.5)
Regurgitation	73 (36.5)
Stenosis and regurgitation	12 (6.0)
Proximal aorta diameter >40 mm	102 (51.0)
Proximal aortic surgery	63 (31.5)

Table 2 Associated malformations in individuals with bicuspid aortic valve

Variable	No. of Individuals with findings (N=200*)
Aortic coarctation	7/166 (4.2%)
Coronary artery anomaly	3/84 (3.6%)
Patent ductus arteriosus	0/164
Atrial septal defect	1 (0.5%)
Ventricular septal defect	1 (0.5%)
Mitral valve prolapse	3 (1.5%)
Tricuspid valve prolapse	0

*, if less than total, we present the number of individuals with available information behind a slash.

The most frequent bicuspid aortic valve morphology was type 1 according to Schaefer. Aortic valve surgery was performed in 100 individuals at 47 ± 13 years (range, 21–75 years). At least moderate aortic valve dysfunction occurred in 132 (66.0%) individuals (*Table 1*). A total of 102 (51.0%) individuals had proximal aortic diameters exceeding 40 mm, of which 24 (12.0%) had aneurysms of the aortic root. We did not observe any statistically significant differences in aneurysm frequencies between the groups with different bicuspid aortic valve types. Aortic surgery was performed in 31.5% of these individuals at an age of 50 ± 12 years (range, 21–77 years).

Bicuspid aortic valve—associated malformations in our retrospective study collective

The most frequent malformation in our collective was coarctation of the aorta (*Table 2*). This associated malformation occurred in 7 (4.2%) of our individuals and was corrected in all individuals. Four individuals had type 1, two individuals type 2 bicuspid aortic valve, in one individual the valve type was not known. Surgical correction was performed at an age of 11 ± 10 years (range, 4 months to 31 years). One individual underwent an initial correction at an age of 4 months and a second surgical correction at an age of 20 years. Coronary anomalies occurred in three (3.6%) individuals as an incidental finding. Two individuals had type 1, one individual type 2 bicuspid aortic valve. These anomalies were: persistent left superior vena cava draining into coronary sinus, high ostium of the left coronary artery plus persistent left superior vena cava draining into coronary sinus, and abnormal origin of the right coronary artery from the left sinus. Surgical correction of the anomaly was not required before replacement of the valve or proximal aorta. None of the individuals had a patent ductus arteriosus. One individual with bicuspid aortic valve type 1 (0.5 % of all individuals) had a previous surgery due to atrial septal defect at the age of 7 years. One other individual, also with type 1 bicuspid aortic valve (0.5 % of all individuals) had a ventricular septal defect, corrected at the age of 5 years. Mitral valve prolapse was identified in three (1.5%) individuals. All of these individuals had a bicuspid aortic valve type 1. Two individuals had a mild prolapse of the anterior leaflet without a relevant insufficiency and one individual had a prolapse of the posterior leaflet. This individual underwent surgical correction of the valve at the age of 35 years because of high grade insufficiency. There was no individual with tricuspid valve prolapse in our study

collective. We did not observe a correlation between the bicuspid aortic valve type and occurrence of malformations.

Bicuspid aortic valve—associate malformations according to the literature

Our search of the literature yielded a total of 2,362 results (*Figure 1*). After exclusion of case reports, editorials, and reviews, we reviewed all 1,371 articles by title and abstract. We excluded 217 articles without abstract or full text available and further 1,085 with no concomitant malformations reported. From the remaining 69 full text articles we excluded 43 reports with small cohorts or with collectives that included predominantly individuals with syndromic diseases or complex malformation.

The systematic review includes a total of 26 studies that qualified for inclusion in the meta-analysis. We rated the selection bias for the study collectives as predominantly low-to intermediate (*Table S1*). The age of study individuals and primary imaging modalities are presented in the *Table 3*.

Our meta-analysis documented a pooled prevalence of 11.8% for aortic coarctation (95% CI: 7.7–16.0%), 3.67% for coronary anomalies (95% CI: 1.23–6.10%), 3.34% for patent ductus arteriosus (95% CI: 0.0–6.69%), 5.93% for ventricular septal defect (95% CI: 1.32–10.54%), and 1.6% for mitral valve prolapse (95% CI: 1.13–2.06%) (*Figure 2*). We found only one study which showed a prevalence of atrial septal defect with 7.5% (95% CI: 5.83–9.22%) in individuals with bicuspid aortic valve (*Table 3*). Therefore, a pooled prevalence could not be assessed.

Competing risks of surgeries for associated malformations versus bicuspid aortic valve disease in our retrospective study collective

Surgeries for associated malformations were performed at a significantly younger age 12.2 ± 11.8 years (range, 0.3–35 years) than those required for the bicuspid aortic valve disease, 48.0 ± 13.2 years (range, 21–77 years), $P < 0.001$.

The risk for surgeries for associated malformations increases before adolescence, whereas the risk for surgery for aortic valve or proximal aortic pathology starts to increase after 20 years of age (*Figure 3*).

Discussion

Our study reports results from comprehensive imaging in adolescents and adults with a bicuspid aortic valve that

was considered as isolated cardiovascular malformation. Our investigation documents that bicuspidality of the aortic valve may indeed be associated with concomitant cardiovascular malformations. The meta-analysis of the literature supports these findings. Pooling of our data and those from the literature document aortic coarctation in 11.8%, coronary anomalies in 3.7%, patent ductus arteriosus in 3.3%, ventricular septal defect in 5.9%, atrial septal defect in 4.0%, and mitral valve prolapse in 1.6% of individuals with a bicuspid aortic valve.

Aortic coarctation has a worldwide reported prevalence of 0.034% (3.4/10,000 live births) (60). We found a noticeably higher rate of coarctation in bicuspid aortic valve disease. Our meta-analysis revealed considerable variability in the reported prevalence of aortic coarctation in bicuspid aortic valve disease. We explain these highly variable frequencies with heterogeneous study groups. For example, the cohort with the highest reported rate of 34.2% (39) included mostly children, 4.2% with a syndromic disease. In contrast, two other studies reported a prevalence ranging between 20% and 25% for aortic coarctation in bicuspid aortic valve, but did not provide information on the frequency of underlying syndromic conditions (50,51). Interestingly, even in the three studies, which strictly excluded syndromic anomalies, the rate of concomitant aortic coarctation was high with 31.4% (41), 24.8% (40), and 22.2% (43) in adults with bicuspid aortic valve disease. In line with our findings, these studies suggest an association of aortic coarctation and non-syndromic bicuspid aortic valve disease.

Coronary anomalies occur with a prevalence of 0.2–2.3% in the general population (61). The highest prevalence was reported with usage of magnetic resonance angiography, most likely because other imaging modalities may be less sensitive (62). With about 3.6% of individuals with bicuspid aortic valve in our study group and 3.7% in the meta-analysis exhibiting an anomaly of the coronary anatomy, we noted a slightly higher prevalence than in the general population. Indeed, a direct comparison of groups with bicuspid versus tricuspid aortic valves revealed a more frequent occurrence of coronary anomalies in the bicuspid valve group (7.2% in bicuspid *vs.* 2.8% in tricuspid aortic valve group) (54).

A persistent ductus arteriosus is diagnosed in 0.009% (0.87/10,000 live births) worldwide (60). Although none of the individuals in our study group had a persistent ductus arteriosus, our meta-analysis identified a rate of 3.3% in bicuspid aortic valve disease. However, the number of children was high in studies that support a high prevalence

Table 3 Meta-analysis of literature for malformations associated with bicuspid aortic valve disease

First author, year of publication	Age (years)		Males (%)	Primary imaging modality
	Median (range)	Mean ± SD		
Coarctation of the aorta				
Roberts 1970 (37)	46 (15 to 79)	n.a.	72	Necropsy
Pachulski 1993 (38)	36 (21 to 67)	n.a.	78	TTE
Nistri 2005 (9)	n.a.	18±1	100	TTE
Ciotti 2006 (39)	5 (0 to 37)	n.a.	70	TTE
Tzemos 2008 (40)	n.a.	35±16	68	TTE
Thanassoulis 2008 (41)	n.a.	33±14	72	TTE
Schaefer 2008 (21)	n.a.	BAV 1: 46±14; BAV 2: 43±15	70	TTE
Michelena 2008 (42)	n.a.	32±20	65	TTE
Oliver 2009 (43)	32 (18 to 51)	n.a.	68	TTE
Yuan 2010 (44)	n.a. (16 to 85)	56±15	77	TTE
Michelena 2011(45)	n. a.	35±21	69	TTE
Roberts 2012 (46)	n.a. (23 to 89)	55±15	77	Necropsy
Lee 2013 (1)	n.a.	56±9	92	TTE
Koenraadt 2016 (47)	n.a. (18 to 85)	48±15	70	TTE
Koenraadt 2016 (48)	n.a.	51±14	79	TTE
Masri 2016 (49)	n.a.	50±14	75	TTE
Niaz 2017 (50)	12 (0 to 22)	n.a.	67	TTE
Tripathi 2018 (51)	5 (0 to 17)	n.a.	61	TTE
Ram 2018 (52)	n.a.	42±14	94	TTE
Koenraadt 2019 (53)	n.a.	42±15	76	CT scan
Own data	45 (14 to 80)	45±16	77	TTE
Coronary anomalies				
Roberts 2012 (46)	n.a. (23 to 89)	55±15	77	Necropsy
Naito 2018 (54)	61±13	(1 to 85)	72	TTE
Michałowska 2016 (55)	n.a.	58±14	n.a.	CT and CT-angiography
Own data	45 (14 to 80)	45±16	77	TTE
Patent ductus arteriosus				
Roberts 1970 (37)	46 (15 to 79)	n.a.	72	Necropsy
Ciotti 2006 (39)	5 (0 to 37)	n.a.	70	TTE, paediatric
Niaz 2017 (50)	12 (0 to 22)	n.a.	67	TTE
Ram 2018 (52)	n.a.	42±14	94	TTE
Own data	45 (14 to 80)	45±16	77	TTE

Table 3 (continued)

Table 3 (continued)

First author, year of publication	Age (years)		Males (%)	Primary imaging modality
	Median (range)	Mean ± SD		
Atrial septal defect				
Niaz 2017 (50)	12 (0 to 22)	n.a.	67	TTE
Own data	45 (14 to 80)	45±16	77	TTE
Ventricular septal defect				
Roberts 1970 (37)	46 (15 to 79)	n.a.	72	Necropsy
Pachulski 1993 (38)	36 (21 to 67)	n.a.	78	TTE
Lamas 2000 (56)	n.a.	39±9	100	TTE
Nistri 2005 (9)	n.a.	18±1	100	TTE
Ciotti 2006 (39)	5 (0 to 37)	n. a.	70	TTE
Lee 2013 (1)	n.a.	56±9	92	TTE
Niaz 2017 (50)	12 (0 to 22)	n.a.	67	TTE
Tripathi 2018 (51)	4.7 (0 to 17)	n.a.	61	TTE
Own data	45 (14 to 80)	45±16	77	TTE
Mitral valve prolapse				
Roberts 1970 (37)	46 (15 to 79)	n.a.	72	Necropsy
Lamas 2000 (56)	n.a.	39±9	100	TTE
Lad 2009 (57)*	(21 to 74)	51±15	86	TTE
Van Rensburg 2017 (58)	44 (1 to 9)	n.a.	60	TTE
Padang 2018 (59)	n.a.	51±16	81	TTE
Own data	45 (14 to 80)	45±16	77	TTE

*, the age range and percentage of males refers to the 29 individuals with MVP. Three individuals with MVP had a Marfan Syndrome. SD, standard deviation; n.a., not available; TTE, transthoracic echocardiography; BAV, bicuspid aortic valve; CT, computed tomography; MVP, mitral valve prolapse.

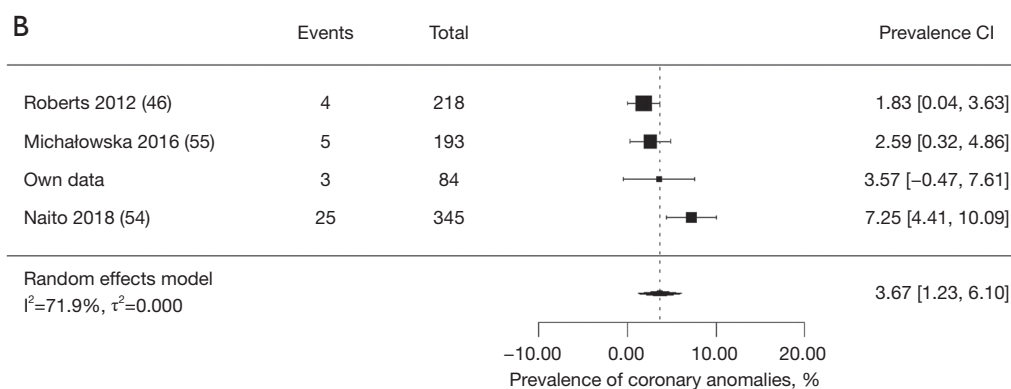
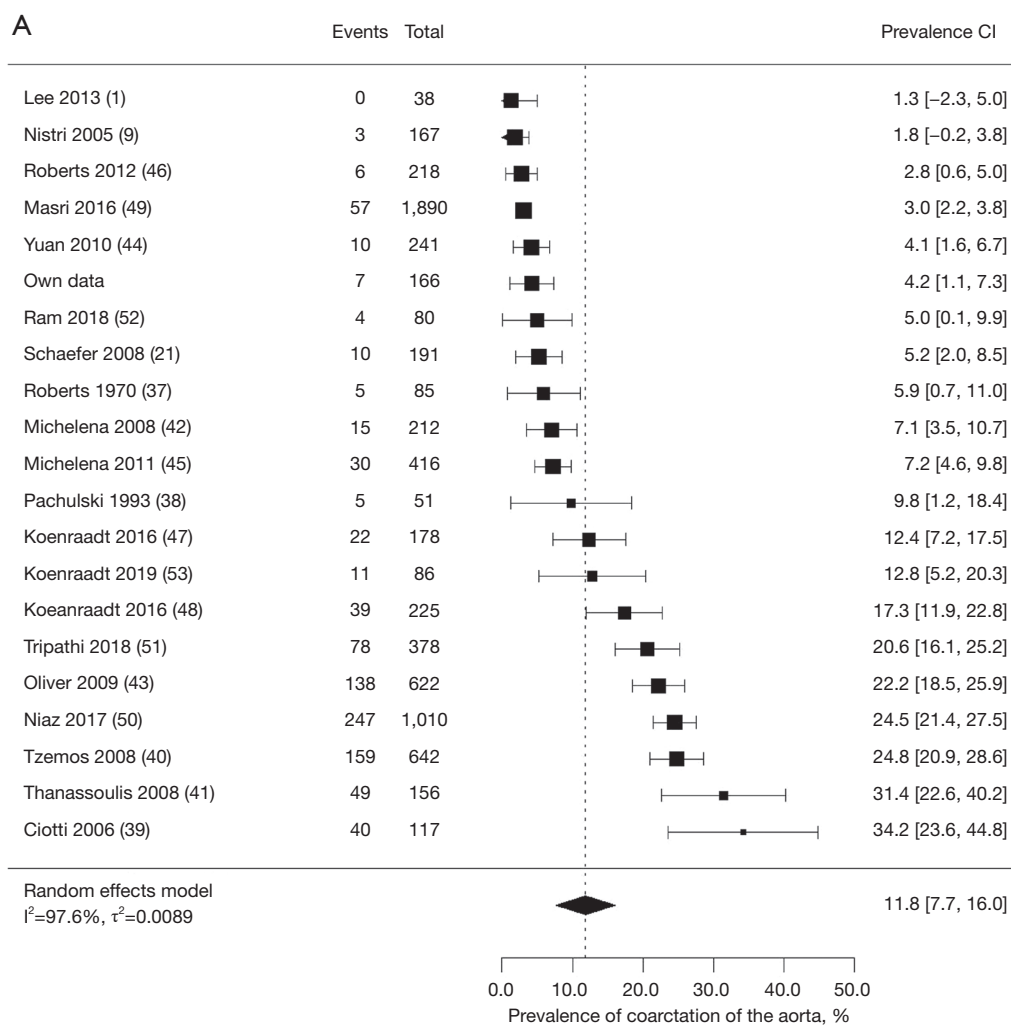
of persistent ductus arteriosus (39,50), whereas collectives with age ranges similar to ours showed a prevalence of 1.3% (37,52).

Atrial septal defect is diagnosed with a 0.016% prevalence (1.64/10,000 live births) worldwide (60). We identified only one individual (0.5%) with this anomaly. Our review of the literature included one study that assessed the occurrence of atrial septal defect in a group of predominantly children with bicuspid aortic valve disease. Here, the prevalence of atrial septal defect was 7.4%. However, complex cardiovascular anomalies were included in this study group.

Ventricular septal defect has a prevalence of 0.026% (2.62/10,000 live births) (60). Our study identified 0.5% of individuals with concomitant ventricular septal defect. Our meta-analysis revealed a pooled prevalence of 5.9%, where

cohorts with more children exhibited a higher frequency of this congenital defect than those with more adults (3.8–20.6% *vs.* 0–6%) (39,51).

The prevalence of mitral valve prolapse in the general population is about 2.4% (84/3,491) and is more common in women (63). It ranges from 0.4% (5/1,382) among male to 1.3% (9/690) among female teenagers (64) and shows an up to 2.1% (34/1,646) prevalence in male and 2.7% (50/1,845) in female adults (32). Mitral valve prolapse was present in 1.5% of individuals in our study group, predominantly comprising male individuals with bicuspid aortic valves, and in 1.6% of individuals according to our meta-analysis. Thus, we found that mitral valve prolapse occurred with similar frequencies in bicuspid aortic valve disease and in the general population. Indeed, another study showed a



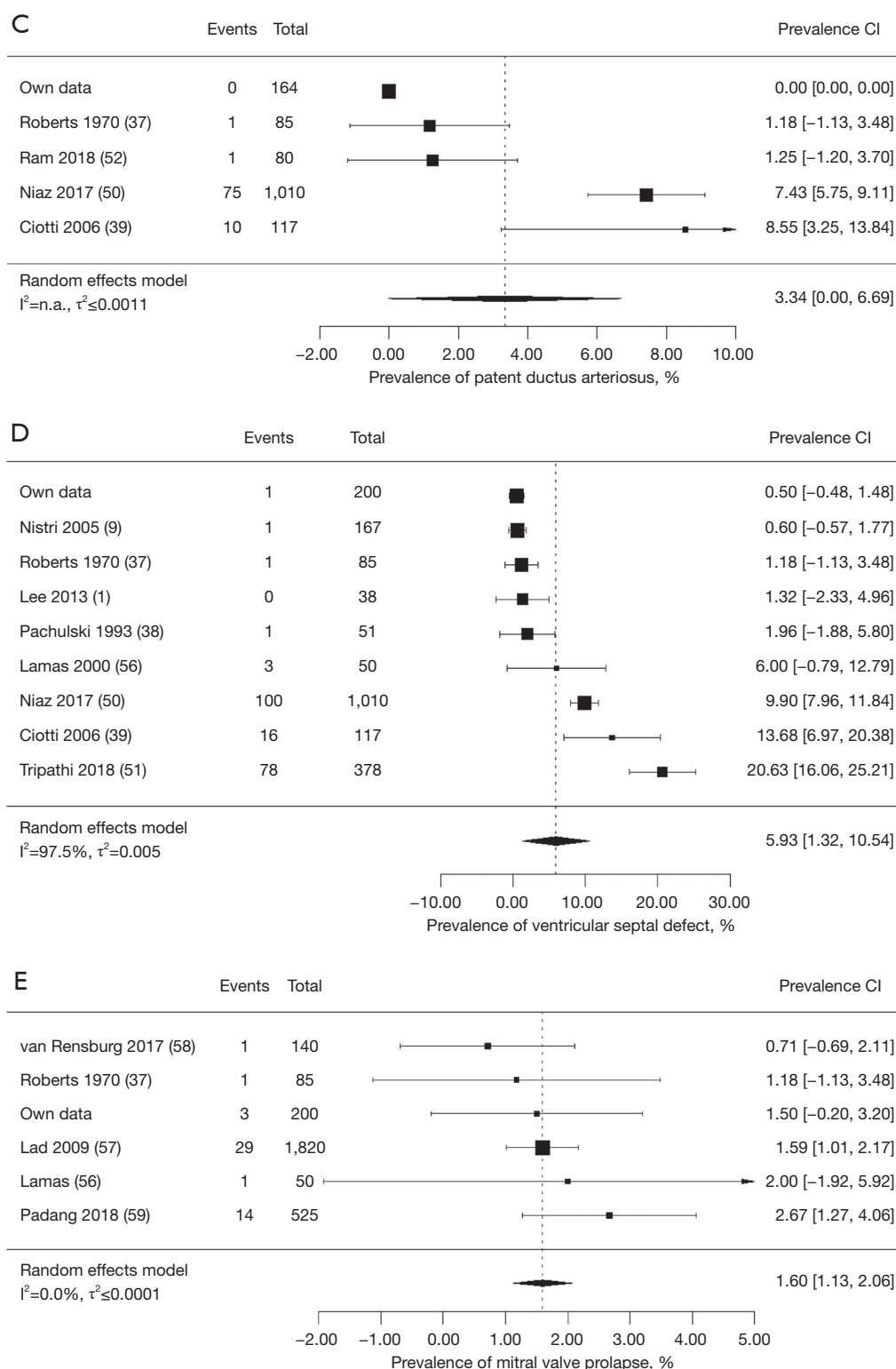


Figure 2 Meta-analysis of the literature for prevalences of associated cardiovascular malformations. (A) Aortic coarctation; (B) coronary anomalies; (C) patent ductus arteriosus; (D) ventricular septal defect; (E) mitral valve prolapse. CI, confidence interval.

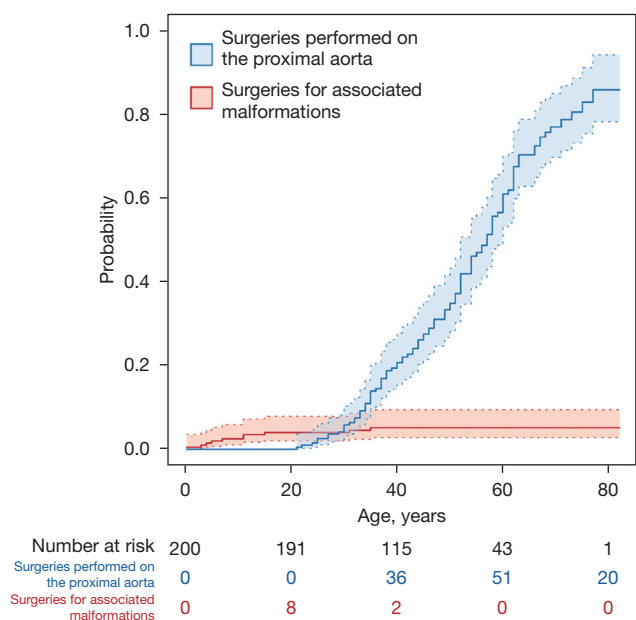


Figure 3 Competing risk for surgeries required for associated malformations *vs.* bicuspid aortic valve disease. The red line indicates the probability of surgeries for associated malformations (aortic coarctation, ventricular septal defect, atrial septal defect and mitral valve prolapse). The blue line shows all surgeries performed on the proximal aorta (valve, root and aorta ascendens). The shaded areas denote the confidence intervals.

comparable frequency of mitral valve prolapse in bicuspid (2.7%) and tricuspid (3.4%) aortic valves (63). Padang *et al.* describe elongated and at least slightly prolapsed anterior mitral valve leaflets and thereby suggest a specific mitral valve phenotype in bicuspid aortic valve disease rather than a more frequent occurrence of a prolapse (63).

Tricuspid valve prolapse is a far less common valve anomaly. Ong *et al.* (65) found a prevalence of 0.03% (20/63,472) in adults. Interestingly, tricuspid valve prolapse exclusively occurred in those individuals with a concomitant mitral valve prolapse. Given this small prevalence in the general population, we did not identify any individual with this anomaly in our study group and study data on the prevalence of tricuspid valve prolapse in bicuspid aortic valve disease are missing in the literature.

Competing risk of surgeries for associated malformations is the highest in childhood and decreases with age. These congenital defects tend to be symptomatic and thus require correction at a younger age. In contrast, the risk of surgery due to a pathology of the bicuspid aortic valve itself or a

concomitant bicuspid aortopathy seems to increase with age. A possible explanation might be a progressive valve degeneration and dilatation of the aorta with increasing age.

Study limitations

Given the retrospective design of our study, all presented data have to be considered with caution. In many cases, we relied on patient charts regarding associated malformations diagnosed in childhood. Therefore, asymptomatic ventricular and septal defects with spontaneous closure may not have been considered. As we did not routinely perform bubble tests, we may also have missed some asymptomatic atrial septal defects. Only individuals with clinical indication underwent coronary artery imaging. This might have led to underestimation of asymptomatic coronary anomalies especially in young individuals with no risk factors for coronary artery disease.

We did not detect all the cardiovascular malformations listed as associates of bicuspid aortic valve disease, which may be explained by our comparatively small study group. Furthermore, we did not assess the frequency of aneurysms of brain vessels, another known malformation associated with bicuspid aortic disease (66).

In general, we found lower prevalences for malformations associated with bicuspid aortic valve disease in our own study collective than in our meta-analysis. We exclusively included individuals aged at least 14 years, whereas the meta-analysis also included neonates and children. If an associated malformation is diagnosed early, the individual tends to be followed up in an adult congenital heart center rather than in our cardiac outpatient department. Since some cohorts included in the meta-analysis are from specialized centers, a selection bias cannot be excluded. The overall prevalence in the general population might be slightly lower.

To gain a better insight into the prevalence of associated malformations in bicuspid aortic disease, population-based multicenter studies with a prospective design are needed.

Conclusions

In conclusion, individuals with isolated bicuspid aortic valve may exhibit a variety of associated cardiovascular malformations. In order to prevent later cardiac or intraoperative complications, screening for associated malformations may be warranted.

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Table S1 Bias meta-analysis

Meta-analysis study	Selection bias rating
Roberts 1970	Low
Pachulski 1993	Low-intermediate
Nistri 2005	Low
Ciotti 2006	Low-intermediate
Tzemos 2008	Low-intermediate
Thanassoulis 2008	Intermediate
Schaefer 2008	Low-intermediate
Michelena 2008	Low
Oliver 2009	Low-intermediate
Yuan 2010	Intermediate-high
Michelena 2011	Low
Roberts 2012	Low
Lee 2013	Low
Koenraad 2016	Low-intermediate
Koenraad 2016	Low-intermediate
Masri 2016	Low-intermediate
Niaz 2017	High
Tripathi 2018	Low
Ram 2018	Intermediate-high
Koenraad 2019	Intermediate
Naito 2018	Intermediate
Michalowska 2016	Low-intermediate
Lamas 2000	Intermediate-high
Lad 2009	Intermediate-high
Van Rensburg 2017	Low-intermediate
Padang 2019	Low-intermediate