

Cite this article as: Girdauskas E, Disha K, Rouman M, Espinoza A, Borger MA, Kuntze T. Aortic events after isolated aortic valve replacement for bicuspid aortic valve root phenotype: echocardiographic follow-up study. *Eur J Cardiothorac Surg* 2015;48:e71–e76.



# Aortic events after isolated aortic valve replacement for bicuspid aortic valve root phenotype: echocardiographic follow-up study<sup>†</sup>

Evaldas Girdauskas<sup>a,\*</sup>, Kushtrim Disha<sup>a</sup>, Mina Rouman<sup>a</sup>, Andres Espinoza<sup>a</sup>,  
Michael A. Borger<sup>b</sup> and Thomas Kuntze<sup>a</sup>

<sup>a</sup> Department of Cardiac Surgery, Heart Center, Central Hospital Bad Berka, Bad Berka, Germany

<sup>b</sup> Cardiovascular Institute, Columbia University Medical Center, New York, USA

\* Corresponding author. Department of Cardiac Surgery, Central Hospital Bad Berka, Robert-Koch-Allee 9, 99437 Bad Berka, Germany. Tel: +49-3645851101; fax: +49-3645853510; e-mail: egirdauskas@web.de, evagird@centras.lt (E. Girdauskas).

Received 16 March 2015; received in revised form 14 June 2015; accepted 18 June 2015

## Abstract

**OBJECTIVES:** Various forms of bicuspid aortic valve (BAV) aortopathy exist, and the optimal treatment for the different subgroups is insufficiently defined. We aimed to analyse the risk of adverse aortic events after aortic valve replacement (AVR) for BAV insufficiency and concomitant mild-to-moderate dilatation of the aortic root (i.e. BAV root phenotype).

**METHODS:** A total of 56 consecutive patients (mean age  $47 \pm 11$  years, 95% men) with BAV insufficiency and a root diameter of 40–50 mm underwent AVR surgery from 1995 to 2008. All patients, as identified from our institutional BAV database, had a dilated aortic annulus (i.e. defined as valve prosthesis size  $\geq 27$  mm) without aortic stenosis (i.e. mean gradient  $\leq 20$  mmHg). Patients who underwent concomitant aortic surgery were excluded. Follow-up (622 patient-years) including echocardiography data was available for all patients. Aortic events were defined as the need for proximal aortic surgery, the occurrence of aortic dissection/rupture, echocardiographic evidence of increasing aortic root diameter/occurrence of late paravalvular leakage or sudden death during follow-up.

**RESULTS:** Actuarial survival was 90% at 10 years and 78% at 15 years. Adverse aortic events occurred in 19 (34%) study patients. Redo aortic surgery was performed in 6 patients (11%), 2 of which were for aortic dissection. Four patients (7%) suffered sudden cardiac death. Moreover, follow-up echocardiography revealed a significant, progressive enlargement of the aortic root diameter in 7 (13%) patients and occurrence of late *de novo* paravalvular leakage in 2 (3%) patients. The resultant freedom from aortic events was 81% at 10 years and 51% at 15 years.

**CONCLUSIONS:** Patients with a BAV root phenotype are at significant risk of aortic events after isolated AVR. Simultaneous root/ascending aortic surgery should be strongly considered in such patients.

**Keywords:** Aortic dissection • Bicuspid aortopathy • Aortic aneurysm

## INTRODUCTION

The bicuspid aortic valve (BAV) is the most common congenital abnormality of the human heart, affecting  $\sim 1$ –2% of the general population [1]. Moreover, BAV disease has been demonstrated to be a very heterogeneous disorder, and different forms of BAV-associated aortopathy (so-called BAV phenotypes) have been identified [2]. Tailored surgical strategies may be required to specifically treat these different forms of BAV-associated aortopathy. New management algorithms and recommendations may be required in order to take into account the heterogeneity of BAV disease and provide the best-tailored approach for such patients.

Considering the heterogeneity of BAV disease, clinical research should focus specifically on the distinct BAV phenotypes [3]. However, the clinical outcomes of distinct BAV subgroups have

not been analysed systematically. There are some data in the literature, indicating that the 'BAV stenosis' phenotype is predominantly secondary to haemodynamic effects of transvalvular flow and is associated with a very satisfactory long-term prognosis, once the stenotic BAV is replaced [4, 5]. In contrast, there are practically no systematic clinical outcome data on the BAV 'root' phenotype, which is associated with proximal aortic root dilatation and aortic insufficiency [6]. Therefore, we aimed to assess the long-term risk of adverse aortic events after isolated aortic valve replacement (AVR) for BAV insufficiency in the presence of mild-to-moderate dilatation of aortic root/ascending aorta.

## METHODS

We identified all BAV patients who underwent isolated AVR surgery for BAV insufficiency in the presence of concomitant aortic root dilatation (40–50 mm) from 1995 to 2008 from our

<sup>†</sup>Presented at the Valves in the Heart of the Big Apple VIII, New York, NY, USA, 8–10 May 2014.

institutional BAV database ( $n = 510$ ) at the Central Hospital Bad Berka, Germany. Our local ethics committee approved this retrospective study. Individual patient consent was waived.

Only patients with isolated/predominant BAV insufficiency were included in this study. Patients with aortic stenosis (i.e. mean transvalvular pressure gradient  $\geq 20$  mmHg) were excluded. Moreover, all study patients had a dilated aortic annulus (i.e. defined as aortic valve prosthesis size  $\geq 27$  mm) and aortic root dilatation with a diameter of 40–50 mm. Concomitant aortic surgery was performed for aortic root diameter of  $>50$  mm, and these BAV patients were excluded. Patients with Marfan syndrome and those without dilatation of the aortic annulus (i.e. patients receiving a prosthetic valve sized 25 mm or less) were also excluded. These inclusion criteria resulted in a total of 56 consecutive BAV patients (11% of total BAV cohort, mean age  $47 \pm 11$  years, 95% men) who served as our study cohort.

The end-point of current study was the cumulative risk of post-AVR aortic events in patients with BAV insufficiency and concomitant mild-to-moderate dilatation of aortic root (i.e. root phenotype). We defined aortic events as the need for redo aortic surgery, the occurrence of type A dissection, echocardiographic evidence of increasing aortic root diameter/occurrence of late paravalvular leakage or sudden cardiac death during the follow-up.

Based on our previous data [5], sample size calculation was performed and it was determined that the minimum of 36 patients would be required to detect the absolute difference of 20% in post-AVR aortic events between BAV stenosis versus BAV root phenotype cohorts with a power of 90% and the probability of type I error of 5%.

## Definitions and measurements

The definition of aortic valve morphology (i.e. BAV versus TAV) was described in our previous study [5]. Aortic valve insufficiency was quantified using the uniform and validated Doppler-based echocardiographic measurements [7]. All BAV patients with mean transvalvular pressure gradient  $>20$  mmHg and aortic insufficiency were qualified as having mixed lesions, and were not included in the current study. We used Sievers' classification for categorizing the bicuspid aortic valves [8].

Proximal aortic diameters were determined uniformly during the study period. The dimensions of the proximal aorta were assessed by preoperative transthoracic two-dimensional echocardiography and routine aortic angiography during cardiac catheterization. Multiple echocardiographic measurements were performed in end systole using the parasternal long-axis view. All patients with proximal aortic dimensions of  $\geq 40$  mm, as diagnosed by these screening examinations, underwent subsequent computed tomography (CT) or magnetic resonance angiography (MRA) of the thoracic aorta for exact quantification of the aortic diameters. If a proximal aortic diameter of  $>50$  mm was observed by CT or MRA, then simultaneous aortic surgery was performed. In all remaining patients with a proximal aortic diameter of 40–50 mm (i.e. based on CT/MRA measurements), isolated AVR was performed.

Progressive enlargement of aortic root diameter at follow-up echocardiography was defined as an increase in maximal aortic root dimensions  $\geq 5$  mm when compared with the corresponding measurements at preoperative transthoracic echocardiography.

The occurrence of post-AVR paravalvular leakage was determined as an adverse event only if it was diagnosed during the late postoperative course, and there was no evidence of paravalvular leakage at discharge echocardiography post-AVR surgery.

## Study population

Demographics and surgical parameters are summarized in Table 1. Our study cohort, consisting of young, predominantly male patients with pure BAV insufficiency, underwent an isolated AVR surgery. Arterial hypertension was present in 62% study patients, and was the most common comorbidity.

All 56 patients underwent standard isolated AVR surgery through a median or partial upper sternotomy, using cardiopulmonary bypass and mild systemic hypothermia. Mechanical valve prosthesis was used in 96% of patients. The labelled valve prosthesis was 27 mm in 59%, 29 mm in 39% and 31 mm in 2% of study patients. As stated above, patients without aortic annular dilatation (defined as those receiving an aortic valve prosthesis of 25 mm or less) were excluded from the current study.

## Follow-up

All hospital survivors were followed by means of clinical interview and echocardiographic surveillance. Follow-up transthoracic echocardiography data were obtained from patients' cardiologists or family physicians. A total of 22 (40%) patients underwent follow-up echocardiography in our institution. Hospital records of patients who died during follow-up were requested, and all operative reports of redo surgery were obtained. A total of 27 (48%) patients were treated in our hospital during the post-AVR course, and their medical records were included. In a total of 5 patients (9%) for whom no contact details were available, a telephone book-based search was performed. By means of telephone book-based search and an excerpt from resident's register, we were able

**Table 1:** Demographics and intraoperative variables

Variable	BAV root phenotype (N = 56)
Mean age (years)	47 $\pm$ 11 (19–71)
Male	53 (95)
BSA (m <sup>2</sup> )	1.98 $\pm$ 0.6
NYHA class III/IV	27 (48)
Aortic root (mm)	45 $\pm$ 4 (40–51)
Arterial hypertension	35 (62)
Diabetes	4 (7)
History of smoking	18 (32)
Peripheral arterial disease	0 (0)
COPD	3 (5)
Urgent/emergent surgery	3 (5)
CPB time (min)	69 $\pm$ 16 (40–139)
Cross-clamp time (min)	35 $\pm$ 8 (21–53)
Mean prosthesis size (mm)	27.6 $\pm$ 2 (27–31)
Mechanical prosthesis	54 (96)

Data presented as  $n$  (%) or as mean  $\pm$  SD (range).

BAV: bicuspid aortic valve; BSA: body surface area; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass.

to identify all 5 missing patients, who were contacted successfully thereafter.

## Statistics

Standard definitions were used for patient variables and outcomes. Categorical variables are presented as percentages, and continuous variables are expressed as mean  $\pm$  SD with range throughout the study. All statistical analyses were performed with the IBM SPSS 19.0 software (IBM Corp., New York, USA). Survival analyses (i.e. overall survival and freedom from aortic events) were performed according to the methods of Kaplan–Meier. Preoperative and follow-up aortic dimensions were compared for differences using the paired *t*-test. The impact of preoperative aortic diameters on the risk of adverse aortic events was analysed using Cox regression. All *P*-values of  $<0.05$  were considered statistically significant.

## RESULTS

### Survival

One patient (1.8%) died in hospital. This patient suffered sudden cardiopulmonary arrest on the surgical ward, and cardiopulmonary resuscitation was unsuccessful. An autopsy was performed and revealed acute type A aortic dissection with a pericardial tamponade. The maximal dimension of the ascending aorta was 43 mm in this patient. This adverse event occurred at the beginning of our series, and was one of the reasons why we chose to systematically analyse the long-term outcomes in this specific BAV cohort.

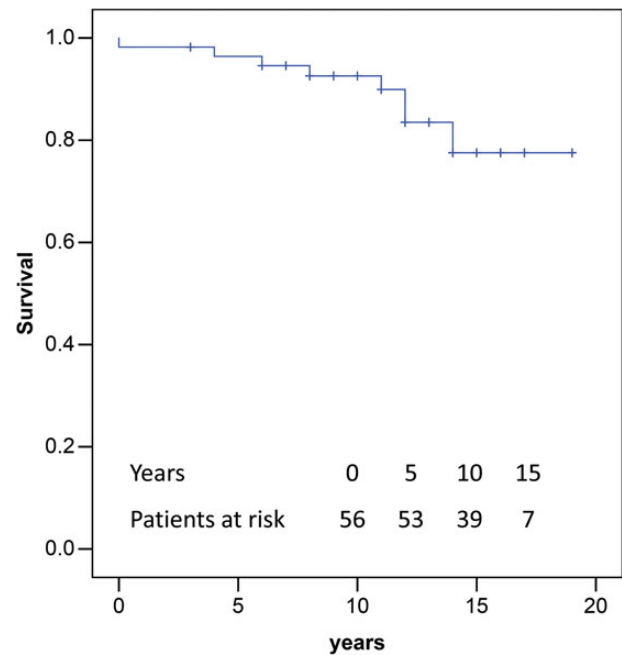
Follow-up data (i.e. 622 patient-years) were available for all surviving patients. The mean follow-up was  $11.1 \pm 3.6$  years (range 0–19 years). Eight patients (14%) died during follow-up, resulting in 10-year survival of  $90 \pm 4\%$  and 15-year survival of  $78 \pm 8\%$  (Fig. 1). A total of 88% of all late deaths were cardiac-related, and are presented in Table 2. Two patients died of documented type A aortic dissection, both of which occurred during the first postoperative year after AVR surgery. One patient suffered a non-cardiac death due to an end-stage pancreatic malignancy 7 years after AVR.

### Proximal aortic surgery

Redo aortic surgery was performed in 6 patients (11%), 2 of which were for type A aortic dissection. A progressive increase in aortic root dimensions was the most common indication for redo aortic surgery (Fig. 2). The median aortic root diameter at the time of aortic surgery was  $55 \pm 3$  mm. The mean period of time between AVR and proximal aortic surgery was  $4 \pm 2$  years. All 6 patients underwent a composite graft replacement, and survived the redo surgery uneventfully. One patient, who underwent emergent surgery for type A aortic dissection, died of multisystem organ failure after a prolonged postoperative intensive care unit (ICU) course complicated by visceral malperfusion.

### Follow-up echocardiography

The mean length of echocardiographic follow-up was  $10.3 \pm 3.6$  years (a total of 473 patient-years). The mean diameter of aortic



**Figure 1:** Overall survival (Kaplan–Meier) of BAV patients with a root phenotype. BAV: bicuspid aortic valve.

**Table 2:** Causes of late deaths (in BAV patients with a root phenotype)

Cause of death	N = 8
Cardiac death	7 (88%)
Aortic dissection	2
Valve-related	
Stroke	1
Haemorrhage	1
Sudden death	3
Non-cardiac death	1 (12%)
Total death	8 (100%)

BAV: bicuspid aortic valve.

root (i.e. measured at the level of the sinus of Valsalva) increased significantly from  $45.4 \pm 4.8$  mm preoperatively to  $49.8 \pm 6.3$  mm at the latest echocardiographic follow-up ( $P = 0.03$ ). Postoperative echocardiographic follow-up revealed a total of 7 (13%) patients with a significant, progressive enlargement of the aortic root diameter  $\geq 5$  mm. Elective redo aortic root surgery has been scheduled in 3 of these patients with a maximal aortic root diameter reaching 55 mm (i.e. patients on the surgical list and waiting for intervention). The remaining 4 patients (aortic root diameters in the range 50–53 mm) undergo continuous echocardiographic surveillance at 6-month intervals. Moreover, only 4 (7%) patients demonstrated ‘stable’ aortic root dimensions, without any change when compared with preoperative diameters. All remaining patients showed a mild progression of aortic root diameters at follow-up echocardiography, which was still less than 5 mm when compared with baseline.

Two (3%) patients had late *de novo* paravalvular leakage, which was probably caused by continuing dilatation of the aortic annulus and aortic root. These 2 patients had slightly increasing



**Figure 2:** Progressive aortic root enlargement at 9 years after an isolated AVR surgery in BAV patient with a root phenotype (maximal aortic root diameter at the time of AVR surgery was 42 mm). AVR: aortic valve replacement; BAV: bicuspid aortic valve.

aortic root diameters on serial aortic imaging, whereas paravalvular leakage was a relatively new finding at the time of latest echocardiographic follow-up. Owing to the mild degree of paravalvular insufficiency and the complete asymptomatic course, these patients were subjected to a regular echocardiographic surveillance.

### Cumulative aortic events

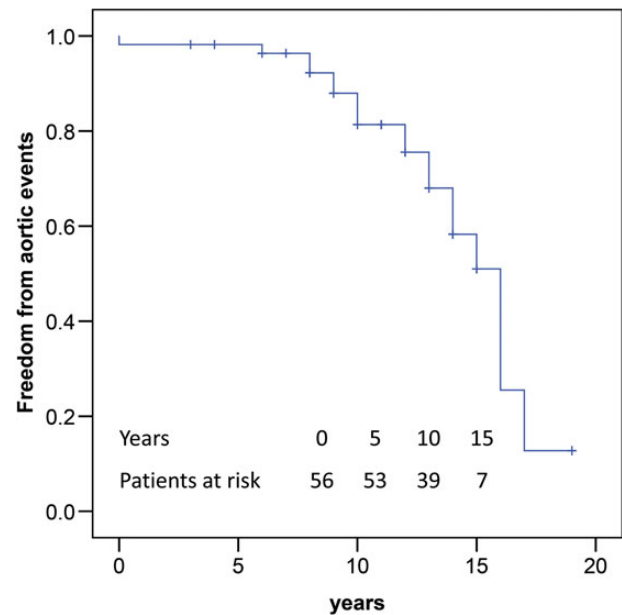
The composite end-point (i.e. aortic events) occurred in 19 of 56 patients (34%). Four patients (7%) died suddenly, one of them due to documented type A aortic dissection. Six patients (11%) required proximal aortic surgery, 2 of them due to type A aortic dissection. Echocardiographic progression of aortic root diameters  $\geq 5$  mm occurred in 7 (13%) patients. The remaining 2 patients were diagnosed with late *de novo* paravalvular leakage after AVR surgery. The resultant freedom from adverse aortic events was  $81 \pm 6\%$  at 10 years and  $51 \pm 11\%$  at 15 years (Fig. 3).

The mean preoperative aortic root diameter was  $44.9 \pm 4.4$  mm in the subgroup with adverse aortic events vs  $45.8 \pm 4.0$  mm in the subgroup without adverse events ( $P = 0.6$ ). The impact of preoperative aortic root diameter (mm) on the risk of post-AVR aortic events in the BAV root phenotype was analysed by means of Cox regression analysis. Of note, we found no significant impact of preoperative aortic root dimensions (i.e. in the range 40–50 mm) on the risk of adverse aortic events (HR 0.9, 95% CI 0.77–1.04,  $P = 0.1$ ). Moreover, maximal aortic root diameter  $>45$  mm (i.e. in the range 46–50 mm) was not predictive of adverse aortic events when compared with aortic root diameter  $\leq 45$  mm (i.e. in the range 40–45 mm; HR 1.3, 95% CI 0.71–1.62,  $P = 0.2$ ).

### DISCUSSION

Whether BAV-associated aortopathy is secondary to haemodynamic effects related to abnormal transvalvular flow patterns or a primary manifestation of a genetic disorder remains controversial. It has been shown that BAV is a heterogeneous disease, and this heterogeneity probably explains the marked variation in reported outcomes following isolated AVR in BAV patients [9, 10].

However, there are only limited data on the clinical outcomes of specific BAV phenotypes. The subgroup of young, predominantly male BAV patients with dilatation of the aortic root and aortic valve insufficiency (so-called root phenotype) has been described by several authors [6, 11]. This form of BAV aortopathy appears to be completely different from the haemodynamically-triggered aortopathy observed in patients with BAV stenosis and



**Figure 3:** Freedom from adverse aortic events in BAV patients with a root phenotype. BAV: bicuspid aortic valve.

concomitant asymmetric dilatation of the tubular ascending aorta [4, 5]. Some evidence exists that root phenotype may illustrate the predominantly genetic form of BAV disease, and mutations in the *TGFBR2* and *FBN1* genes have been demonstrated in families with such BAV-associated aortopathy [12–14]. Biner *et al.* [15] demonstrated that the congenital pattern of aortopathy observed in the first-degree relatives of BAV patients presented with aortic root dilatation. Another important study by Loscalzo *et al.* [16] revealed the association of BAV disease and familial thoracic aortic aneurysms in selected families. Patients with Turner syndrome, a genetic malformation associated with BAV disease, are known to have larger aortic root diameters in the presence of a BAV when compared with Turner patients with a tricuspid aortic valve [17]. Such evidence further supports the hypothesis that BAV root phenotype is a predominantly genetic disorder.

Transvalvular flow patterns have been shown to be very different in patients with BAV stenosis and asymmetrical dilatation of the tubular ascending aorta when compared with a BAV root phenotype [18]. Furthermore, the histological lesions in the proximal aortic wall have been shown to be significantly more severe in the BAV cohort with aortic valve insufficiency when compared with BAV stenosis patients [19, 20]. Another important study which included 60% BAV insufficiency patients demonstrated a high

prevalence of moderate/severe aortic medial lesions, even in the absence of clinically obvious aortopathy [21]. Moreover, a significant correlation was found between the severity of aortic medial lesions and aortic annular dimensions, which in turn indicates aortic root disease [21].

Despite these obvious differences between the two distinct forms of BAV-associated aortopathy, the clinical outcomes of specific BAV phenotypes have not been thoroughly analysed. In particular, long-term follow-up data on BAV root phenotype are lacking. Owing to our large institutional BAV database, we aimed to address this important entity of BAV patients in the current study. Because of the relative rarity of BAV root phenotype (i.e. only 10% of BAV patients were referred for AVR surgery), long enrolment period was required to obtain a sufficient number of root phenotype patients available for long-term post-AVR follow-up.

The most important finding of our study is the high prevalence of post-AVR aortic events in BAV patients with a root phenotype [i.e. 19 events in 56 patients (34%)]. To the best of our knowledge, this is the first clinical report which focused on post-AVR outcomes in BAV patients with a root phenotype. Only one half of our study patients were free from aortic events at 15 years post-AVR surgery (i.e.  $51 \pm 11\%$  at 15 years, Fig. 3). These results are quite different from the long-term outcomes, which had been reported for patients with a BAV stenosis and comparable dimensions of the proximal aorta [4–5].

Three patients with BAV root phenotype suffered a type A aortic dissection during follow-up, whereas none of the patients in our BAV stenosis subgroup suffered [5]. Moreover, 3 further patients with a root phenotype died suddenly during the late postoperative course. Although we cannot be sure of the cause of death in these 3 patients, because a post-mortem examination was not performed, an aortic-related death was very likely in these relatively young and otherwise healthy patients. Furthermore, post-AVR aortic root replacement was performed due to progressive aneurysmal disease in 11% of study patients. Echocardiographic surveillance of our study cohort revealed 7 further patients with a significant progression of aortic root dimensions during follow-up. Even more importantly, only 4 (7%) patients showed completely stable aortic root dimensions at follow-up echocardiography. This finding highlights the importance of continuous echocardiographic surveillance of patients with a BAV root phenotype after an isolated AVR surgery. Of note, preoperative aortic root diameter (i.e. in the range 40–50 mm) was not predictive of adverse aortic events, as demonstrated by our univariate and multivariate analyses.

Our current findings further support the hypothesis that patients with a BAV root phenotype may exhibit a ‘malignant’ form of genetically triggered BAV aortopathy, which is prone to life-threatening adverse aortic events, and should probably be treated in analogy to other well-known connective tissue disorders (e.g. Marfan syndrome). Simultaneous aortic root/ascending aortic surgery during the initial AVR procedure would have prevented all aortic events reported here, and therefore should be strongly considered in such BAV patients. Low perioperative risk and long-term efficacy of simultaneous aortic root replacement in BAV patients have been demonstrated in previous studies [22].

### Study limitations

Our study has some important limitations. It is a retrospective analysis with all known limitations of such a study design. Another

major limitation is the lack of data on the follow-up diameters of proximal aorta in the BAV stenosis subgroup. Therefore, a reasonable comparison of adverse aortic events after isolated AVR surgery in the BAV root phenotype versus BAV stenosis subgroup was not possible in the current study.

### CONCLUSIONS

In summary, patients with BAV insufficiency and a concomitant root dilatation of 40–50 mm (i.e. root phenotype) are at significant risk of post-AVR aortic events. Based on our observations, we strongly suggest simultaneous aortic root surgery in patients with BAV insufficiency and aortic root diameter >40 mm during their initial AVR procedure. Owing to the relative rarity of BAV root phenotype (i.e. only 10% patients undergoing AVR surgery for BAV disease), a multicentre prospective registry should aim at better characterization of the pathogenesis and clinical outcomes of patients with a BAV root phenotype.

**Conflict of interest:** none declared.

### REFERENCES

- [1] Williams DS. Bicuspid aortic valve. *J Insure Med* 2006;38:72–4.
- [2] Girdauskas E, Disha K, Secknus M, Borger M, Kuntze T. Increased risk of late aortic events after isolated aortic valve replacement in patients with bicuspid aortic valve insufficiency versus stenosis. *J Cardiovasc Surg (Torino)* 2013;54:653–9.
- [3] Girdauskas E, Borger MA. Bicuspid aortic valve and associated aortopathy: an update. *Semin Thorac Cardiovasc Surg* 2013;25:310–6.
- [4] Cotrufo M, Della Corte A. The association of bicuspid aortic valve disease with asymmetric dilatation of the tubular ascending aorta: identification of a definite syndrome. *J Cardiovasc Med (Hagerstown)* 2009;10:291–7.
- [5] Girdauskas E, Disha K, Raisin HH, Secknus MA, Borger MA, Kuntze T. Risk of late aortic events after isolated aortic valve replacement for bicuspid aortic valve stenosis with concomitant ascending aortic dilation. *Eur J Cardiothorac Surg* 2012;42:832–8.
- [6] Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M *et al.* Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. *Eur J Cardiothorac Surg* 2007;31:397–404.
- [7] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA *et al.* Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611–44.
- [8] Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg* 2007;133:1226–33.
- [9] Russo CF, Mazzetti S, Garatti A, Ribera E, Milazzo A, Bruschi G *et al.* Aortic complications after bicuspid aortic valve replacement: long-term results. *Ann Thorac Surg* 2002;74:S1773–6.
- [10] Goland S, Szer LS, De Robertis MA, Mirocha J, Kass RM, Fontana GP *et al.* Risk factors associated with reoperation and mortality in 252 patients after aortic valve replacement for congenitally bicuspid aortic valve disease. *Ann Thorac Surg* 2007;83:931–7.
- [11] Nistri S, Sorbo MD, Marin M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart* 1999;82:19–22.
- [12] Pepe G, Nistri S, Giusti B, Sticchi E, Attanasio M, Porciani C *et al.* Identification of fibrillin 1 gene mutations in patients with bicuspid aortic valve (BAV) without Marfan syndrome. *BMC Med Genet* 2014;24:15–23.
- [13] Girdauskas E, Schulz S, Borger MA, Mierzwa M, Kuntze T. Transforming growth factor-beta receptor type II mutation in a patient with bicuspid aortic valve disease and intraoperative aortic dissection. *Ann Thorac Surg* 2011;91:e70–1.
- [14] Prapa S, McCarthy K, Krex D, Gatzoulis M, Ho S; ESC Working Group on Development, Anatomy and Pathology. The aortic root phenotype in

- bicuspid aortic valve disease: evidence of shared Smad2 activation in aortic regions of distinct embryologic origin. *Cardiovasc Res* 2014;103 (Suppl 1):S16.
- [15] Biner S, Rafique AM, Ray I, Cuk O, Siegel RJ, Tolstrup K. Aortopathy is prevalent in relatives of bicuspid aortic valve patients. *J Am Coll Cardiol* 2009;53:2285-95.
- [16] Loscalzo ML, Goh DL, Loeys B, Kent KC, Spevak PJ, Dietz HC. Familial thoracic aortic dilation and bicommissural aortic valve: a prospective analysis of natural history and inheritance. *Am J Med Genet* 2007;143A: 1960-7.
- [17] Sachdev V, Matura LA, Sidenko S, Ho VB, Arai AE, Rosing DR *et al.* Aortic valve disease in Turner syndrome. *J Am Coll Cardiol* 2008;51:1904-9.
- [18] Girdauskas E, Rouman M, Disha K, Scholle T, Fey B, Theis B *et al.* Correlation between systolic transvalvular flow and proximal aortic wall changes in bicuspid aortic valve stenosis. *Eur J Cardiothorac Surg* 2014;46: 234-9.
- [19] Roberts WC, Vowels TJ, Ko JM, Filardo G, Hebler RF Jr, Henry AC *et al.* Comparison of the structure of the aortic valve and ascending aorta in adults having aortic valve replacement for aortic stenosis versus for pure aortic regurgitation and resection of the ascending aorta for aneurysm. *Circulation* 2011;123:896-903.
- [20] Girdauskas E, Rouman M, Borger MA, Kuntze T. Comparison of aortic media changes in patients with bicuspid aortic valve stenosis versus bicuspid valve insufficiency and proximal aortic aneurysm. *Interact CardioVasc Thorac Surg* 2013;17:931-6.
- [21] Leone O, Biagini E, Pacini D, Zagnoni S, Ferlito M, Graziosi M *et al.* The elusive link between aortic wall histology and echocardiographic anatomy in bicuspid aortic valve: implications for prophylactic surgery. *Eur J Cardiothorac Surg* 2012;41:322-7.
- [22] Etz CD, Homann TM, Silovitz D, Spielvogel D, Bodian CA, Luehr M *et al.* Long-term survival after the Bentall procedure in 206 patients with bicuspid aortic valve. *Ann Thorac Surg* 2007;84:1186-93.