Bicuspid aortic valve syndrome and fibrillinopathies: potential impact on clinical approach

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Abstract

Bicuspid aortic valve (BAV) is a common heterogeneous disorder whose natural history is determined by hemodynamic valvular impairment and/or increased prevalence of aortic abnormalities ranging from dilatation to aneurysm and dissection. BAV-related aortopathy is frequently associated with relevant aortic pathologic changes leading to structural alterations, characteristic degenerative lesions and histological changes of the aorta very similar to those identified and described in patients with Marfan syndrome (MFS), an inherited connective tissue disorder associated with mutations in fibrillin 1 (\textit{FBN1}) gene in more than 90\% of patients. Recently, a 4-fold increase in the prevalence of BAV in MFS patients has been reported. Subsequently, pathogenetic \textit{FBN1} mutations in patients with BAV and aortic dilatation/aneurysm in whom MFS and other more severe type 1 fibrillinopathies were clinically excluded have been identified. In this review we discuss how this evidence, together with that of the wide heterogeneity in pathogenetic mechanisms of BAV-related aortopathy, may impact the clinical management of BAV.

Key words: bicuspid aortic valve, genetics, fibrillin-1, Marfan syndrome, clinical approach

Introduction

Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation with an estimated prevalence between 0.5\% and 2\% and a strong male predominance (M:F=3:1). BAV is a multifaceted, heterogeneous disorder (Figure 1). Its natural history is determined by hemodynamic valvular impairment (present at birth or, more commonly, acquired by aging), and/or by increased prevalence of aortic abnormalities ranging from reduced aortic elasticity to aortic dilatation/aneurysm/ dissection\textsuperscript{11-12}.

Each of the above features can be found in patients with isolated BAV or, in association with multiple congenital heart diseases (e.g. hypoplastic left heart syndrome, aortic coarctation, patent ductus arteriosus, ventricular septal defect), either in a syndromic (e.g. Turner’s syndrome, Williams syndrome) or in non-syndromic fashion. The familial clustering of BAV and/or its related aortopathy has been documented in up to 20-30\% of patients with isolated BAV supporting the notion of a relevant genetic background in BAV. Moreover, BAV can be detected in relatives of individuals with congenital abnormalities of the left ventricular outflow tract. This evidence has highlighted the need for screening first-degree relatives of BAV patients for aortic valve abnormalities, anomalies of the left ventricular outflow tract, and thoracic aortic wall alterations. Nonetheless, while multiple studies have searched for gene mutations and association with different chromosomal loci, the genetic bases of BAV, to date, are poorly defined\textsuperscript{11-12}.

Due to the high prevalence of isolated BAV, the perceived burden of thoracic aortic complications, namely aneurysm and dissection, has led many authors to an early indication to prophylactic aortic surgery in individuals with BAV in comparison with subjects with three-leaflet aortic valve\textsuperscript{16,17}. This position has been also supported by the presence of multiple reported similarities between BAV and Marfan syndrome (MFS)\textsuperscript{18}. Recently, however, two large, long-term, retrospective cohort studies of BAV patients \textsuperscript{19,20}, while confirming the absolute increased risk of aortic dissection in BAV in comparison with the general population, reported a low number of events. These findings have raised concerns \textsuperscript{21,22} on the application of surgical criteria adopted in Marfan (MF) patients to those with BAV and thoracic aortic aneurysm (TAA), resulting in more conservative and individualized recommendations for the repair of the aortic sinuses or replacement of the ascending aorta in BAV patients by the 2014 AHA/ACC valvular heart disease guidelines\textsuperscript{23}.

Pathogenesis

Despite the high prevalence, the pathogenetic mechanisms underlying the development of BAV are yet to be entirely clarified.

Embryology

According to many studies, the major factor involved in BAV pathogenesis is represented by the fusion of the two cusps occurring in the earlier stages of valvulogenesis during fetal development. One of the first theories assumed that failure in
cusps separation is the result of an abnormal blood flow across the developing valves. More recently, it has been suggested that other mechanisms, such as cell migration, signalling pathways, and genetic susceptibility may be involved. These mechanisms, together with abnormal neural crest migration, might lead to isolated or combined defects of the ascending aorta and aortic valve 24-26. Aortic, cervicocephalic and intracranial aneurysms all originate from the neural crest and are documented to have a higher incidence in BAV population 27. Furthermore, it has been shown that different embryological mechanisms are responsible for BAV with different spatial orientations of the cusps 28. Moreover, newer experimental models have found alternative embryological pathways leading to BAV formation 29. Other theories suggest that extracellular matrix proteins, which are involved in cell differentiation and cusp formation during the process of valvulogenesis, might play a pivotal role in BAV development. Endothelial nitric oxide is a key factor involved in the process of vascular and valve formation during embryogenesis. Lee and colleagues observed that knockout mice, lacking endothelial nitric oxide synthase, had a predisposition in developing BAV. This result supports the hypothesis that inadequate levels of this protein or its abnormalities may be involved in cell signalling alteration during valvulogenesis in mammalian heart 30. However, all these findings suggest that aortic valve dysfunction in BAV is the result of a combination of the altered biochemical, mechanical and morphological factors involved in late valve development by regulating the processes of valve tissue remodelling and leaflet architecture.

Clinical features associated with BAV

Aortic stenosis, a common complication of BAV (occurring in up to 50% of BAV patients), represents a result of premature fibrosis and calcification due to hemodynamic shear stress, an active process in which endothelium dysfunction takes place by involving inflammation, lipoprotein deposition, calcification, and ossification of the aortic side of the valve leaflets 31. Aortic regurgitation has a lower prevalence in BAV than stenosis (7-20%) and represents the predominant functional complication in young age 32,33. The pathogenesis of aortic regurgitation in BAV patients is complex: it can occur as an isolated functional abnormality due to fibrosis and retraction of the commissural margins of the leaflets or cusp prolapse.
Alternatively, it can also originate in combination with external factors such as aneurysmal enlargement of the root and valve annulus or valvular destruction secondary to endocarditis. Aortic regurgitation can also lead to an increased risk of heart failure, endocarditis and arrhythmia\(^4\). Recently, Benedik and colleagues evaluated the histological and mechanical characteristics of the aortic wall in patients who underwent aortic stenosis or regurgitation surgery and showed that the latter group had a worse quality and a superior thickness of the ascending aorta than the former\(^35\). Roberts and colleagues observed, in histological sections of ascending aortas, only a minimal loss of medial elastic fibers in the aortic media of patients with aortic stenosis compared to severe elastic fibers damage reported in patients with aortic regurgitation\(^36\).

Aortic dilation (mainly involving the ascending aorta) is one of the most common non-valvular findings in BAV occurring in 35-80% of adult patients\(^33,37,38\). It is mainly asymptomatic and often precedes aortic dissection or rupture. The considerable incidence of aortic dilation in BAV patients suggests a correlation between the aortic disease and the congenital malformation. Earlier studies, conducted by Larson and Edwards\(^39\), reported a 9-fold increased risk of aortic dissection in BAV patients and an 18-fold higher risk in unimissural aortic valve compared with controls. These findings suggested that the valve malformation may act as an independent risk factor for aortic dissection. However, the pathogenesis, as well as the cellular and molecular mechanisms underlying the development and progression of aortic dilation in BAV, is not clearly understood and remains controversial. Some mechanisms have been proposed so far that could take part in the pathogenesis of BAV-associated aortic aneurysms. According to the “Hemodynamic theory”, the altered hemodynamics in BAV, represented by a severe turbulence in blood flow, post-stenotic to the “Hemodynamic theory”, the altered hemodynamics in BAV, the pathogenesis of BAV-associated aortic aneurysms. According to the “Hemodynamic theory”, the altered hemodynamics in BAV, represented by a severe turbulence in blood flow, post-stenotic aortic dilation, and increased stroke volume, is the most common causative factor of root and ascending aorta segment dilation\(^4\).

Aortic dilation leads, as a consequence, to a greater expansion of the lumen, a reduction of wall thickness and a generalized increase of wall tension (Laplace law). These abnormalities may eventually result in aortic dissection or frank rupture. Vergara and colleagues\(^40\) have recently succeeded in supporting the hemodynamic hypothesis according to which the critical blood flow dynamics in the ascending aorta of BAV patients were responsible for the development and progression of aneurysm. In this study, a surface model of ascending aorta was obtained from magnetic resonance imaging (MRI) and numerical simulations of ascending aorta hemodynamics with different configurations of orifice area and valve orientation were performed in order to investigate the resulting wall shear stress (WSS) distributions and the asymmetry of the blood flow. High WSS-based indices (introduced to evaluate quantitatively the influence of valve geometry on magnitude of WSS in the ascending aorta) were found at the mid-ascending aorta, at the sinus of Valsava and at the sinotubular junction. These data confirm that the higher risk of developing aneurysm in BAV patients is related to the peculiar geometry of BAV and, consequently, to the abnormality of the blood flow. Conti and colleagues found a 36% increase in voltage at the wall of the longitudinal curvature of the ascending aorta in patients with BAV compared with TAV in tricuspid aortic valve (TAV) patients\(^41\). In 2011, Girdauskas further confirmed the role of altered hemodynamics as the main cause of aortopathy development in BAV despite the presence of a congenital defect\(^42\).

**Common features underlying BAV and Marfan patients**

The structural histological aortic pathology described above have been shown to be very similar to those identified and described in MF patients. MFS is an inherited connective tissue disorder associated with mutations in the fibrillin-1 (FBN1) gene in more than 90% of patients, and in transforming growth factor beta receptor 2 and 1 (TGFBR2 and TGFBR1) genes in less than 5%\(^43\). The common degenerative lesions and histological changes include degeneration of the aortic media with extracellular fragmentation and disorganization of elastic lamellae, high rate of vascular smooth muscle cell loss and accumulation of mucopolysaccharides\(^4,5,12,43\). Several studies demonstrated that vascular complications observed in MFS are a result of the impairment and weakness of the connective tissue due to the reduction of fibrillin-1. This glycoprotein represents the main component of the microfibril structures of the extracellular matrix, which has a crucial role in connecting vascular smooth muscle cells to elastin and collagen and, consequently, in maintaining tissue elasticity\(^6-8\). In 2003, Fedak and colleagues hypothesized that the mechanism of vascular matrix reorganization and remodelling, that contributes to aortopathy associated with BAV, might be the result of fibrillin-1 deficiency\(^9\). Indeed, their data demonstrated a significant reduction in fibrillin-1 glycoprotein content in the aortic media of a subset of patients with congenital BAV. They also observed that the abundance of fibrillin-1 was equivalent in patients with normal valves and in those with TAV disease, suggesting that the reduction of the protein was specific to the presence of the congenital BAV and it wasn’t the result of a valve dysfunction. Moreover, the deficiency of fibrillin-1 may result in an alteration of TGF-β signalling similar to that found in MFS\(^5\). Sakai and colleagues observed that fibrillin-1 is homologous with the family of latent transforming growth factor β (TGF-β) binding proteins (LTBPs), which serve to hold TGF-β in an inactive complex in various tissues, including the extracellular matrix\(^52\). The researchers showed that fibrillin-1 can bind TGF-β and LTBPs\(^51,52\). On the basis of these data, Dietz and co-workers hypothesized that abnormal fibrillin-1 or reduced levels of fibrillin-1 in connective tissue, might result in an excess of active TGF-β. They managed to prove this hypothesis and to demonstrate that blocking TGF-β with neutralizing antibodies led to the normalization of lung development in affected mice\(^53\). Data by Loeyes and colleagues\(^40\), together with those from studies involving mouse models of fibrillinopathies, showed that Marfan phenotype results mostly from perturbed TGF-β signalling\(^54,55\). Therefore, the aortic dilation in BAV may be the result of an underlying congenital defect caused by a mutation in FBN1, TGFBR1 or TGFBR2 genes.

**Genetics of BAV**

BAV has an autosomal dominant pattern of inheritance with incomplete penetrance. Recent studies demonstrated that BAV may be due to mutations in different genes\(^56\). The transcriptional regulator NOTCH1 gene (chr 9q34.3), encoding a single-pass transmembrane receptor and functioning in a highly conserved pathway, has been associated with the development and acceleration of calcium deposition in nonsyndromic BAV in humans\(^57\) (Table 1). The Notch signaling pathway plays a critical role in cell fate determination and differentiation during organogenesis and it regulates osteogenesis\(^58\). However, a consistent contribution of NOTCH1 gene variants to the development of BAV is yet to be clearly defined. Genome wide marker-based linkage analysis demonstrated a linkage of BAV to loci on chromosomes 18q, 5q and 13q in families with autosomal dominant inheritance of the disease\(^52\) (Table 1). These regions are likely to contain genes whose mutations result in BAV and/or associated cardiovascular manifestations, suggesting their potential role in valvulogenesis and cardiac development. Recently, the essential role of GATA5 (GATA-binding protein 5) in aortic valve morphogenesis and endocardial cell differentiation\(^59\) (Table 1) has been reported. BAV has also been associated
Table 1: Genes involved in BAV in human and animal models

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<th>Genes Involved</th>
<th>Non-syndromic BAV</th>
<th>Syndromic BAV</th>
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<td><strong>BAV IN HUMANS</strong></td>
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<td><strong>NOTCH1</strong></td>
<td>(missense and frame shift mutations)</td>
<td>Thoracic aortic aneurysm and dissection syndrome TAAD (ACTA2)</td>
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<tr>
<td><strong>GATA5</strong></td>
<td>(missense mutations)</td>
<td>Marfan syndrome (FBN1)</td>
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<td>Linkage to loci on:</td>
<td>Chr 5q</td>
<td>Loeys-Dietz syndrome (TGFBR1/2)</td>
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<td>Chr 15q</td>
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<td>Chr 18q</td>
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<td><strong>UFD1L</strong></td>
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<td>Turner syndrome (45X0 karyotype)</td>
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<td><strong>AXIN1/PDIA2</strong></td>
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<td>William Beuren syndrome (deletion of 1.5Mb region - q11.23 of chromosome 7 including more than 25 genes. CLIP2, ELN, GTF2i, GTF2IRD1, and LIMK1 are among the genes)</td>
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<td><strong>BAV IN ANIMAL MODELS</strong></td>
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<td><strong>Nos3 (eNOS)</strong></td>
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<td><strong>Nkx 2.5</strong></td>
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<td><strong>Gata 5</strong></td>
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with a reduced **UFD1L** (ubiquitin fusion degradation 1-like) gene expression (Table 1). The **UFD1L** gene encodes a component of a multi-enzyme complex involved in the degradation of ubiquitin fusion proteins during embryogenesis and its down-regulation, probably due to an abnormal behavior of neural crest cells, may lead to reduced degradation activities. These results highlight the important role of the **UFD1L** gene in the development of ectoderm-derived structures, including neural crest cells in aortic leaflets formation, supporting the hypothesis of a genetic background in the pathogenesis of BAV. Other genes have been associated with BAV. Wooten and colleagues demonstrated an association between BAV and a locus containing **AXIN1** and **PDIA2** genes in a cohort of 68 BAV probands and 830 control subjects (Table 1). **AXIN1** (AXIsInhibitor 1) is a critical member of the Wnt pathway and acts as a crucial regulator of both heart valve formation and cardiac neural crest development. It also influences TGF-β signaling. The potential role of **PDIA2** (Protein Disulfide Isomerase family A, member 2) in heart valve formation is unknown. Further genotyping is required to determine the relative contribution of **AXIN1** and **PDIA2** variants to BAV. About 12% of BAV/TAA patients carry mutations in **ACTA2** (Actin, alpha 2, smooth muscle, aorta; chr. 10q), a distinct subgroup characterized by livedo reticularis on lower limbs, and iris flocuill. Regarding TGFBR1 and TGFBR2 genes analyses, no mutations were detected in BAVs with aortic dilatation except for one incomplete clinically depicted patient carrying a TGFBR2 mutation. Animal studies have also been performed to identify genetic bases of BAV disease (Table 1). In mice, in particular, an association between BAV and the homozgyous deletion of the endothelial nitric oxide synthase gene (Nos3) has been demonstrated, and haploinsufficiency in the cardiac homeobox gene Nk2-5, is linked to a higher incidence of BAV.

**Marfan Syndrome, BAV and FBN1 mutations**

Recently, we demonstrated a 4-fold increase in the prevalence of BAV in a large cohort of unrelated MFS patients with respect to the general population screened by echocardiography (Figure 2). Indeed, out of the 257 unrelated MF patients [151 males (58%)], BAV was unequivocally identified in 12 (4.7%) MF patients [10 males (83%)]. Only 3 patients accepted to undergo mutation screening analysis. Previously described mutations were detected in 2 out of 3 patients, they involved conserved cysteine residues and are thought to be causative because they alter fibrillin-1 structure (Figure 2). These findings are consistent with data showing decreased **FBN1** mRNA or protein content in a subgroup of BAV patients, which suggest that **FBN1** may be one of the genes associated with BAV. Interestingly, most of MFS/BAV patients were males, a more common finding in BAV patients. Moreover, the association between the two disorders seems to cause a more severe involvement of the aorta with a higher percentage of TAA requiring surgery. Finally, our MFS/BAV did not present further congenital heart diseases, aortic valve calcification or livedo reticularis. Interestingly, Z score was 2 in all our adult patients. Moreover, ectopia lentis, dural ectasia, myopia and striae distense were common in our MFS/BAV, while they presented mostly minor skeleton criterion. Noteworthy, all 12 MFS/BAV patients satisfied the clinical diagnostic criteria for MFS also according to the newly revised Ghent criteria. Although a reduced **FBN1** content has been reported in the aortic media of BAV patients, it has been stated that in multiple clinical disorders associated with **FBN1** alterations there is no propensity for congenital aortic valve malformations. Our data challenged this consideration, prompting the need for the mutation screening analysis of BAV patients not fulfilling the clinical criteria for MFS. Moreover, from the practical point of view, the paper of Nistri et al. underscored the need to optimize the visualization of aortic valve morphology in MFS patients and the importance of a comprehensive clinical evaluation of BAV patients to detect clinical features suggestive for inherited connective tissue disorders.

Subsequently, our group performed a study aimed to screen for **FBN1** mutations in ten patients with BAV and thoracic aortic dilatation, not fulfilling the clinical criteria for MFS (Figure 2). Mutation analysis was performed on 8 of the 10 patients and **FBN1** mutations were detected in two. One patient had a c.1586G>A, p.Arg529Gln amino acid substitution which represents a basic to polar neutral charge change in exon 12 (cbEGF-like 03 domain). In the other patient, a double mutation was detected: a c.1906A>G change (p.Arg636Gly basic to apolipoprotein substitution) and a c.8176C>T mutation (p.Arg2726Trp causing a basic to apolipoprotein change); the first located in exon 15 (cbEGF-like 06 domain), the second in exon 64 (COOH unique region) (Figure 2).

This was the first study reporting pathogenetic **FBN1** mutations in patients with BAV and aortic dilatation/aneurysm in whom MFS and other more severe type 1 fibrillinopathies were clinically excluded. The mutations detected in the two unrelated studied patients are arginine substitutions. The Arg529Gln mutation detected in one patient was also reported at the UMD-FBN1 database in a male proband of France geographic origin with an incomplete MFS phenotype. Moreover, a single nucleotide substitution in the same codon, causing a preterminal stop codon, was previously described in a Norwegian patient displaying a classic MF phenotype with ectopia lentis, thoracic aorta dilatation and systemic features. The other patient
showed two mutations, one (Arg2726Trp) was previously associated with variable clinical phenotypes, including mitral valve prolapse (MVP) and myopia [3], isolated skeletal features [3], combined skeletal and ocular manifestations [4], mild skeletal abnormalities [5]; and a family in which the mutation displayed incomplete penetrance [6]. This mutation was reported in one chromosome of the 1000Genomes and NHLBI Exome Variant Server databases as rs61746008 (http://www.1000genomes.org/ and http://evs.gs.washington.edu/EVS/). The second mutation (Arg636Gly) has never been reported in literature, although another single nucleotide substitution, responsible for a different amino acid change at the same codon (Arg636ile) in a MF patient with aortic root dilation, ectopia lentis and minor involvement of skeleton, was previously described [4]. According to “Sorting Tolerant From Intolerant” (SIFT, http://sift.jcvi.org) both the Arg2726Trp and Arg636Gly mutations act decreasing protein stability as evaluated in silico by MuPro (http://www.igb.uci.edu/~baldig/mutation.html). It is unknown at present if the two FBN1 mutations of the second patient are in cis on the chromosome or in trans. The detection of FBN1 point mutations in patients with BAV/TAA without MFS, adds to the striking clinical heterogeneity of both BAV and type I fibrillinopathies showing that aortic dilation/aneurysm may develop in a subgroup of BAV patients as a manifestation of an inherited connective tissue disorder. Noteworthy, the two patients carrying the mutations were male, one displayed a family history of TAA, another had MVP, without systemic features which were otherwise prevalent in the remaining patients. Moreover, both had aortic aneurysm size attaining the threshold for surgery according to old American and current European Guidelines [7,8], notwithstanding the young age, with the largest diameter localized at the level of the sinuses of Valsalva, a pattern of aortic dilation, specifically addressed as “root phenotype” by Della Corte et al [9], and considered to be an independent predictor of fast progression [10] (Figure 3). Interestingly, 8 out of our 10 patients displayed this phenotype, in association with a certain degree of systemic features typical of connective tissue disorders [11]. Finally, the 2 patients bearing FBN1 mutations had significant aortic regurgitation, which is a powerful predictor of loss of aortic medial elastic fibers in patients with ascending aortic aneurysms and aortic valve disease [12,13]. These findings call for greater focus on the BAV-related cardiovascular abnormalities rather than on the MFS-like systemic features, which may well coexist and warrant investigation in BAV patients in general, but are not associated with the FBN1 mutations identified in the present study. On the other hand, these FBN1 mutations do not completely fulfill the definition of the major criterion for MFS according to the revised Ghent criteria since they have never been detected in Marfan patients with TAA [14]. Therefore, our two BAV/TAA patients did not achieve the diagnosis of MFS.

FBN1 gene has been previously associated with various conditions [15,16,17]. The interfamilial clinical heterogeneity at the FBN1 locus is further characterized by a striking intrafamilial variability (OMIM*134797). Contrasting data have been reported regarding the genetic background of BAV-related aortopathy. A decrease in FBN1 mRNA and protein has been demonstrated in some BAV patients suggesting a possible involvement of FBN1 with BAV [18]. Moreover, single nucleotide polymorphisms (SNPs) spread in the area of the FBN1 gene, which predispose to TAA, have been reported [19]. On the other hand, other investigators have screened BAV patients for mutations in FBN1, TGFBR2, and TGFBR1 genes and failed to detect any mutation, concluding that FBN1 gene is not, or only rarely, associated with BAV [20]. More recently, a mutation in TGFBR2 gene was reported in a patient classified as aortic dilation/aneurysm but otherwise not well clinically defined [21]. Another recent study, comparing gene expression in subjects with BAV and TAV, reported an increase of FBN1 mRNA only in the subjects with TAV [22]. Thus, it is conceivable that BAV represents the phenotypic manifestation of many distinct clinical outliers underlined by genetic, molecular, and structural anomalies that do not follow a common path [23]. At present, we cannot exclude a coincidence of a common trait such as BAV in males and a rare trait like MFS in our patients.

Conclusions

Recent improvements in knowledge regarding the natural history of the aortopathy in BAV [17,24] have raised concerns regarding the direct application of surgical criteria adopted in MFS patients to those with BAV and aortic dilation/aneurysm [25,26], although multiple similarities have been shown between MFS and BAV patients. Due to the prevalence of BAV and of associated dilatation/aneurysm of the ascending aorta, the increase in relative risk for aortic dissection in BAV patients could result into a disproportionately high indication for prophylactic aortic surgery by implementing criteria adopted for MFS and related disorders. Despite the 7-10 fold-increase in risk of dissection, the incidence of aortic dissection/rupture remains low (3-4/10,000 patient-years) [27-29]. Moreover, data regarding a threshold of aortic size portending an absolute increase in risk of dissection in BAV, such to warrant aortic surgery (when aortic valve replacement is not indicated based on the severity of aortic stenosis or regrigation) are limited. On the other hand, cardiovascular events are considerable in patients with FBN1 mutations and remain so throughout life, with men appearing to be at higher risk for an aortic event than women [30]. Our findings may thus have potential clinical implications, if confirmed by larger studies. Although sample size of our study and its retrospective design did not propose surgical implications, our data support the need of future studies aimed at characterizing BAV patients with aortic dilation/aneurysm according both to valvular and aortic phenotype (including rate of increase in aortic size), family history of aortic dissection and systemic clinical stigmata of connective tissue disorders, eventually performing genetic testing when appropriate, in order to promote individualized approach to these patients [31]. Whether such an approach would result in a different outcome, potentially affecting therapeutic choices in patients with BAV and aortic dilation/aneurysm, should be a pivotal target of such research [32]. A further implication for the discovery of the presence of FBN1 mutations in BAVs with and without systemic manifestations of MFS, is the need of a multidisciplinary approach (including internal medicine, medical genetics, cardiology, ophthalmology, cardiovascular surgery, orthopaedic, and molecular biology experts) for a comprehensive global assessment and, possibly, management of patients with BAV. While a number of studies [33,34] underscore the relevance of a more detailed phenotyping of BAV and its related aortic aneurysm, our data address the potential role of a generalized phenotypic approach aimed at detecting and possibly graduating the systemic manifestations of connective tissue disorders. In this perspective, a clinically oriented utilization of genetic testing, may be useful for the recognition of a responsible gene mutation to identify syndromic features, to confirm a clinical diagnosis, and to evaluate relatives who are at risk for the condition. However, a cautionary word regarding use and interpretation of genetic tests is needed, and genetic counselling should be included with its use.

Notwithstanding a great interest [35,36], there is no proven medical therapy shown to delay or reduce the rate of progression of
aortic size in BAV patients. Indeed, the classic pathophysiology of aortopathy in MFS founded the basis for the use of β-blockers, whose effectiveness in preventing aortic dissection in a great proportion of a large cohort of MFS patients has been recently shown. Moreover, the novel interpretation of the pathophysiology of MFS-related aortopathy based on TGF-β signaling, has resulted in researches evaluating the potential of TGF-β-antagonism by ACE-inhibitors and angiotensin II receptor blockers (ARBs). Prospective, randomized, controlled trials, indicating a beneficial effect of losartan treatment on aortic root dilation rate in adults with MFS, have been reported. However, since specific therapeutic data in BAV patients are lacking, no recommendation can be withdrawn, beyond that of treatment of systemic arterial hypertension. It is conceivable that the identification of specific genetic backgrounds and signalling pathways might theoretically support the utilization of specific medical approaches, in the future, tailored on individual patients. Finally, considering the specific natural history of patients with FBN1 mutations in the general population the finding of such genetic etiology in BAV patients might justify an aggressive surgical approach in a subgroup of BAV individuals, but also support the recent indication of more conservative thresholds for aortic surgery in patients in whom such mutations are not detected.

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