Chapter

# Ascending Aortic Aneurysm in Relation to Aortic Valve Phenotype

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## Abstract

Being born with a bicuspid aortic valve (BAV) is a significant risk factor for developing an ascending aortic aneurysm (AscAA). Research has uncovered different mechanisms influencing AscAA development in BAV-patients compared to those with normal tricuspid aortic valves (TAV). BAV-associated AscAA may result from intrinsic hemodynamic or genetic alterations, possibly even embryonic origins. During embryonic development, neural crest cells and the second heart field contribute to the ascending aorta's formation, with defective signaling potentially increasing susceptibility to aneurysm development. BAV can manifest with different phenotypes, impacting clinical outcomes. The degenerative AscAA in TAV-patients differs from BAV-associated AscAA, marked by fibrosis, smooth muscle cell loss, and inflammation. AscAA in TAV-patients rarely appears in those with aortic stenosis, suggesting a link between aortic valve disease and degenerative AscAA. This chapter aims to describe suggested molecular mechanisms driving aneurysm formation in BAV- and TAV-patients.

**Keywords:** ascending aortic aneurysm, bicuspid aortic valve, embryology, valvulogenesis, vascular inflammation, aortic stenosis, aortic regurgitation

## 1. Introduction

Ascending aortic aneurysm (AscAA), defined as a dilatation of the ascending aorta 1.5 times the expected diameter [1], is a silent, potentially fatal disease with regrettably little known of its underlying pathomechanisms. The condition is most often discovered incidentally during radiological examinations, and no screening for the disease is performed. AscAA in general has a reported incidence of 5 per 100,000 patient-years [2]. The most significant risk factor for developing AscAA, with 80 times increased risk compared to the general population [3], is the common congenital heart malformation, the bicuspid aortic valve (BAV) [4–6]. The embryonic development of the aortic valve and ascending aorta are spatiotemporally associated, and implications of this, aortic flow disturbances and/or genetics have been proposed for the cooccurrence of BAV and AscAA [7–9]. Notably, the ascending aortic media is structurally well preserved in patients with concomitant aneurysm and BAV [10] (**Figure 1A**). Contrastingly, an aneurysm of the ascending aorta in patients with normal tricuspid aortic valves (TAV) is characterized by marked degenerative insults and immune cell infiltration [11] and almost exclusively occurs in association with aortic

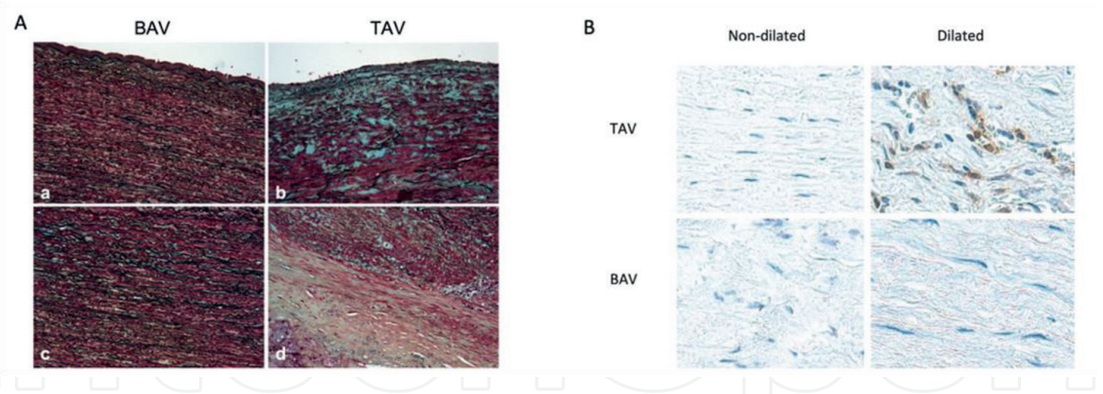


**Figure 1.**
*(A) Movat pentachrome stainings of dilated aortas from patients with BAV (a, c) and TAV (b, d). In TAV-associated aneurysm, clear signs of degeneration, fibrosis, smooth muscle cell loss, and extracellular matrix component deposition can be seen. Magnification x20. Adapted from Freiholtz et al. [10].*
*(B) Immunohistochemical stainings of CD4+ cells in ascending aortic tissue of BAV- and TAV-patients, magnification x40. Adapted from Folkersen et al. [11].*

valve regurgitation, not aortic valve stenosis [12]. In this chapter, we will describe the potential effects of aortic valve cuspidity and aortic valve disease on ascending aortic aneurysm formation and development.

## 2. A spatiotemporal embryonic association of the aorta and aortic valve

Valvulogenesis involves the initial formation of endocardial cushions in the atrioventricular canal and outflow tract via a process known as endocardial-to-mesenchymal transition. Specifically, delamination, endocardial cell migration, and remodeling events give rise to mesenchymal cells, subsequently forming the atrioventricular canal leaflets (mitral and tricuspid) and semilunar valves (aortic and pulmonary) [13]. However, lineage tracing studies in various animal models have demonstrated that the formation of semilunar valves is a more complex process involving other cell lineages, including cardiac neural crest cells as well as second heart field [14]. Interestingly, cardiac neural crest cells are crucial for arteriopulmonary septation and also give rise to vascular smooth muscle cells (VSMCs) of the ascending aorta and the aortic arch [15]. In the aortic root, the adluminal media is derived from neural crest cells, while the outer media/adventitia originates from second heart field [16, 17].

Evidently, there is a direct embryonic relationship of the adult ascending aorta and the aortic valve. During embryogenesis, various signaling pathways, such as Wnt/β-catenin, NOTCH, and transforming growth factor β (TGFβ), play a crucial role in regulating cell migration, proliferation, and extracellular matrix (ECM) deposition in the developing valves and ascending aortic wall [13, 18–22]. Defects in these signaling pathways may indeed lead to dysfunctional valvulogenesis and the formation of a BAV [15].

## 3. Embryonic origin of the bicuspid aortic valve: Impact on clinical manifestations of AscAA

BAV is the most common congenital malformation of the heart, with a prevalence of 1–2% in the general population [23]. It is characterized by the occurrence of two, as

opposed to the normal three, aortic valvular cusps, and its morphotype may be classified by the number of raphe – a fusion of the lanulae valvarum of the left-coronary (L), the right-coronary (R) or the noncoronary cusp (N) [24]. A fusion of two cusps, confers a type-I BAV where the most common variant is fusion of the R and L cusps, followed by R–N and L–N. A type II BAV entails fusion of two raphe, and type 0 BAV represents a BAV with only two valvular sinus. Interestlingly, studies investigating the involvement of cardiac progenitor cells in the development of different BAV phenotypes have suggested that the type 1 BAV fusions R–L and R–N (i.e., the most common BAV phenotypes) have separate developmental aberrations. In particular, the R–L fusion was shown to be associated with abnormal behavior of neural crest cells [15], whereas an eNOS mutation has been proposed as a cause for the R–N fusion and a predisposition to aortic dilatation and dissection [25, 26]. The latter finding may suggest a role of second heart field in the development of type 1 R–N BAV as eNOS is expressed by endocardial cells, cardiomyocytes, and VSMCs, all of which are derived from the second heart field [27].

A possible consequence of different cardiac progenitor cells conferring different BAV phenotypes could be that specific regions of the ascending aorta are affected depending on the individual's phenotype. Indeed, we and others have shown an association between BAV phenotype and different clinical manifestations [27, 28]. Furthermore, the R–L phenotype was associated with larger aortic root dimensions, which has been well-documented in echocardiography cohorts [29–32]. Additionally, patients with type 0 BAV tended to present clinically at an earlier age than those with other phenotypes, and a similar trend was observed in men in this study [28]. Interestingly there are trends showing that R–L and type 0 phenotypes are associated with a higher prevalence of ascending aortic dilatation at any segment compared with the R–N phenotype, which relation to aortopathy has historically been conflictingly [28]. For instance, a large study on a surgical cohort reported a lack of ascending aortic root dilatation in combination with R–N phenotype [33].

## 4. Characteristics of BAV-associated ascending aortopathy

As described above, an association between impaired embryonic signaling between different cardiac progenitor cells and the formation of a BAV has been suggested, likely contributing to aortopathogenesis. The cardiac progenitor cells involved in valvulogenesis migrate and populate the ascending aortic media [18]. The literature has as such focused on the aortic media as causative of aortopathy. The adult ascending aortic media is laminarly structured with VSMCs sandwiched between load-bearing elastin and collagen [34]. Albeit BAV has been known as a risk factor for disease since 1844 [35], it was first during 1984, in necropsy studies by Larson et al., that structural differences between BAV-associated aortopathy and degenerative ascending aortic aneurysm were proposed in light of vastly different rates of acute aortic syndromes [36]. Histologically, one can observe very small differences in the ascending aorta of BAV patients with or without aneurysm, i.e., the elastin is intact, there is VSMC apoptosis, although notably without mucoid extracellular matrix accumulation (MEMA), and the aortic intima-media exhibits few signs of inflammation [10]. Still, the nondilated aorta of individuals with BAV displays a seemingly thinner intima [37].

In past years, researchers have focused on the aortic media in BAV-associated aortopathy with findings of differential VSMC phenotypes in BAV and TAV aortopathies

[11, 38]. Not only have these cells been found to undergo apoptosis [39] without apparent MEMA [10], but BAV VSMCs also exhibit distinct morphology. In BAV patients, VSMCs are less differentiated, indicating a defect in the phenotypic switch process, leading to significantly lower expression of differentiated, contractile VSMC markers, such as smoothelin, calponin, and SM22alpha [40, 41]. Additionally, VSMC dissociated from aneurysmal tissue exhibit differences in proliferation and migration comparing BAV and TAV VSMC. Specifically, in an ORIS migration assay, TAV VSMCs showed a faster migration and a higher proliferation rate than BAV VSMCs [10]. Although these cells exhibit such characteristics and behavior in aneurysmal tissue, the less differentiated and immature VSMCs are observed in both nondilated and dilated BAV populations [40], leading the mind to wonder if this VSMC phenotype might itself not be driving aneurysm development.

Interestingly, we and others have observed a mesenchymal-like state of endothelial cells in the ascending aorta of BAV patients, even prior to aortic dilatation [7, 42, 43]. Moreover, the expression of the endothelial-specific marker CD31 is decreased in nondilated BAV aorta, indicating a less differentiated endothelial phenotype [10]. Also, there are signs of a compromised basal membrane, with decreased expression of laminin gamma 1 [10], the main monomer in laminin trimers of large artery basal membranes [44]. This, together with reports of alterations in endothelial junction protein expression in nondilated BAV, such as increased protein turnover of CDH5, decreased expression of CLDN5, and increased mRNA expression of *CDH2* with dilatation compared to TAV patients [45], indeed implicates dysfunctional endothelium in BAV. Electron microscopy further strengthens this observation with signs of junctional degradation and a less intact endothelium in nondilated BAV individuals compared with TAV [45]. The genetic variants and missense mutations of ROBO4 found to associate with BAV aortopathy further strengthen the role of the endothelium in the AscAA development of BAV patients [46], as ROBO4 is an arbiter of vascular integrity and endothelial barrier function [47, 48]. The study by Gould et al. demonstrates the endothelial barrier impairment by infiltration of albumin into the ascending aortic wall [46], but we, too, have observed this to be a general characteristic of BAV ascending aortas, no matter if they are dilated or not [10].

Thus, the endothelium, too, has a seemingly important role in the distinct aortic wall phenotype observed in BAV patients. This is further supported by numerous animal models with endothelial-specific mutations producing offspring with a higher prevalence of BAVs. Most notably, in regards to endothelial function, mice lacking eNOS result in 40% BAV progeny [25]. Mice with GATA5$^{-/-}$ (with 25% BAV progeny) indicate that dysfunctional endothelial phenotype, as they also display lower expression of endothelial-specific markers – CDH5, TIE2, and eNOS, is related to BAV [49]. However, a drawback of these studies is that the prevalence of, or propensity to develop, aortopathy was not investigated. Nonetheless, the endothelial-specificity of eNOS, and the fact that GATA5 is mostly restricted to the endocardium, disappearing at mid-gestation and is required for early differentiation of cardiac progenitors into endothelial/endocardial cells, suggests a connection between the BAV phenotype and disturbed endothelial function.

An observed consequence of impaired endothelial function related to BAV is increased permeability. Ascending aortas of nondilated and dilated BAV patients exhibit greater infiltration of albumin in the aortic intima-media compared to TAV patients, which in nondilated state have a normal functional endothelium [10, 46]. The infiltration of plasma proteins into the aortic wall of BAV patients and potential

consequences to VSMC phenotype thereof has to our knowledge, not been investigated. It is, however, a promising line of research in search of circulating biomarkers influencing the cellular phenotype of ascending aortas in BAV patients. One might speculate that such a biomarker might guide practices of surveillance and indications of ascending aortic surgery.

## 5. Genetics and hemodynamics in BAV aortopathy

Analyses of the genetic contribution to BAV and its associate aortopathy in a large family-based study suggested that genetics and the presence of BAV independently influence ascending aortic diameter [50]. These investigations highlight the first and oldest hypothesis of BAV-associated AscAA development, namely the hemodynamic hypothesis [51]. Indeed, several studies have suggested a contribution of BAV-associated impaired flow to aneurysm development [52, 53]. A plethora of radiological tools, such as low-sensitive cardiac magnetic resonance imaging with full volumetric coverage of the ascending aorta, have allowed multiple flow-specific investigations on BAV aortopathy in the previous decade. As such, it is clear that hemodynamic alterations are intrinsic to BAV, even in the absence of severe valve disease, by virtue of its anatomy. Hemodynamic alterations in the presence of a BAV include flow jets, eccentric helical flow, and increased ascending aortic wall-shear stress. Observations of increased wall-shear stress and intramural stresses underpin the hypothesis that these hemodynamic alterations indeed participate in AscAA development and progression [54]. Not only are disturbances in ascending aortic flow pathognomic of BAV, but signs of flow-dependent cellular and histological changes have also been observed. Grewal et al. have published data suggesting a jet-associated phenotypic switch of the inner ascending aortic media by virtue of hemodynamic alterations [55]. Similarly, in support of a hemodynamic component in ascending aortopathy is a spatial differential expression of matrix proteins and smooth muscle cell depletion compared to a more circumferentially homogenous Marfan-or TAV-associated aorta [56, 57]. Furthermore, aortic endothelial cells isolated from BAV patients exhibit differential expression of flow-related *KLF2, KLF4, PECAM1,* and *CDH5* compared with TAV ECs [58]. Still, as explored by Gauer et al., the expression of eNOS synthase does not differ between different ascending aortic regions in BAV, despite being subject to different hemodynamic forces and wall-shear stress [59]. Another topic obscuring the influence of hemodynamics on BAV aortopathy is the remedy of BAV through aortic valve repair and the possible progression of ascending aortic dilatation. There are conflicting reports on the pace at which the BAV aorta continues to dilate following aortic valve repair, showing both a faster growth and a normal rate of dilatation [60, 61]. There are still no investigations on transcatheter aortic valve replacement in BAV patients and the continued dilatation of the ascending aorta.

The second hypothesis of BAV development, i.e., the genetic hypothesis, is gaining more favor, and indeed genome-wide association studies are finding noncoding variants of genes like *GATA4* associating with BAV [62] Albeit GATA4 deletion hampers endothelial-to-mesenchymal transition in transfected cells, and are through this mechanism believed to influence BAV-development [62]. GATA4-variants and mutations, while not functionally investigated, are further implicated in BAV development by a well-described association with congenital heart defects [63–65]. While GATA4 is associated with the presence of a BAV, genetic variants of ROBO4 – a gene associated

with endothelial cell performance and function [47, 48], are also implicated in both BAV development and its associated aortopathy [46]. Even still, variants of SMAD6 are associated with BAV-associated aortopathy [66].

Of note, exploration of genetic causes of nonfamilial BAV aortopathy cannot be disentangled from the concomitant hemodynamic alterations, and as such, both genetic and an altered hemodynamic are likely to contribute to disease development. This way, the current state of the literature warrants an integration of genetic and molecular factors being investigated in association with hemodynamic factors.

## 6. Degenerative ascending aortic aneurysm

While degenerative AscAA manifests with the same clinical manifestation as the BAV-associated AscAA, i.e., a dilated aorta, it is histomorphologically vastly different [67]. A comprehensive global gene expression analysis was conducted on ascending aortic intima-media obtained from both nondilated and dilated ascending aortas of 131 patients with BAV and TAV (i.e., degenerative AscAA), showing significant molecular disparities in the underlying pathophysiology between BAV and TAV- aortopathy [11]. The degenerative form of AscAA is marked by fibrotic, inflammatory, and degenerative changes [7, 68]. The histopathology of degenerative AscAA was first described by Erdheim in 1929 as idiopathic cystic medial necrosis [69]. Although this descriptor of the changes has been abandoned by contemporary science, the changes describe the loss of VSMCs with the subsequent accumulation of ECM components. Cystic medial necrosis is, by the current histopathological consensus on degenerative thoracic aortic disease [70], instead described as MEMA, whereby dead VSMCs deposit primarily collagens and proteoglycans to the site of injury [71]. Furthermore, one of the main load-bearing proteins, elastin [72], which, together with the VSMCs, make up the lamellar units of the vascular media, appear fragmented and thinned out with disease progression [70]. Furthermore, there are multiple reports of low-grade inflammation and infiltrated leukocytes into the aortic intima-media of degenerative AscAA [11].

Although the main histopathological characteristics of degenerative AscAA are described in the pathological consensus, structured histopathological studies reveal a degree of heterogeneity in AscAA tissue from patients undergoing ascending aortic repair. The degree of inflammatory activity and location of infiltrated leukocytes, i.e., subintimal or mid-media, varies without known associations to patient characteristics [11]. Noteworthy is also the reported experience of surgeons treating aortic diseases, where degenerative AscAA differ significantly from descending aortic aneurysm or abdominal aortic aneurysms (AAA), in particular with respect to the absence of mural thrombi or macroscopic signs of atherosclerosis [73]. Taken together, this indicates, in our minds, that the degenerative changes described in the pathological consensus apply to most AscAA patients despite some reports of heterogeneity as pronounced inflammation or microscopic atherosclerotic lesions.

AscAA in patients with tricuspid aortic valves can manifest as part of monogenic syndromes, where inherited genetic mutations play a significant role in the development of aortopathy. Mutations in genes encoding ECM proteins, such as FBN1 in Marfan syndrome, COL3A1 in vascular Ehlers–Danlos syndrome, and TGFBR1 and TGFBR2 in Loeys–Dietz syndrome, disrupt the structural integrity of the aortic wall [74]. These mutations lead to abnormal ECM synthesis, impaired collagen and elastin assembly, and risk of ascending aortic dilatation.

In the absence of monogenic diseases, molecular drivers of degenerative AscAA development may be matrix metalloproteinsases (MMP), TGFβ signaling pathway disruptions, and inflammation [11, 75]. MMPs are a family of enzymes involved in the breakdown of ECM components. Excessive MMP activity has been observed in AscAA, particularly MMP-2 [76], –3 [77], –9 [78], –14, and – 19 [79]. Increased MMP expression and degraded ECM structures, such as elastin, induce VSMC death, weakening the aortic wall and promoting aneurysm formation [80]. Dysregulated TGFβ signaling is central in AscAA in monogenic conditions like Marfan syndrome and Loeys–Dietz syndrome [81, 82] but may too contribute to disease progression in polygenic contexts. The disruption of TGFβ signaling results in increased production of TGFβ ligands, which, paradoxically, can lead to defective TGFβ signaling and impaired ECM maintenance and turnover [83]. Altered TGF-β signaling disrupts the balance between ECM synthesis and degradation, consequently leading to aneurysm development. Inflammatory processes also play a role in degenerative AscAA pathogenesis. Macrophages and T lymphocytes infiltrate the aortic wall, releasing pro-inflammatory cytokines and chemokines with reports of upregulated inflammatory genes [84]. This immune system activation contributes to chronic inflammation, subsequent oxidative stress, and ECM remodeling, thereby exacerbating degenerative characteristics and aneurysm growth [85–88].

The clear difference between degenerative and BAV-associated AscAA strengthens the idea that these diseases are indeed separate. Instead, degenerative AscAA appears more similar to AAA at a molecular level, although genetic analyses have demonstrated a limited overlap [74, 89].

Atherosclerotic processes are often implicated in AAA, with accumulation of lipids, immune cells, and ECM components within the abdominal aortic wall [90]. Lipid deposition and macrophage infiltration contributes to the release of pro-inflammatory cytokines and the production of reactive oxygen species, resulting in chronic inflammation, endothelial dysfunction, and vascular degeneration [91, 92]. Oxidative stress further promotes inflammation, ECM degradation, and apoptosis of vascular cells, exacerbating AAA progression [93]. Moreover, proteolytic enzymes, such as MMPs (in particular MMP-1, –2, –3, –9, –12, and – 13) and elastases, are secreted by immune and vascular SMCs leading to increased degradation of ECM components and weakening the abdominal aortic wall [80, 94]. Of note, in the context of differential mechanisms driving aneurysm development, the abdominal aorta is subject to different hemodynamic forces than the ascending aorta, including flow disturbances, pulsatile flow, and increased wall-shear stress. These hemodynamic forces induce endothelial dysfunction, inflammation, and arterial wall remodeling, contributing to AAA formation [95]. Of note, intracranial aneurysms (IAs) are also influenced by hemodynamic forces, specifically in the context of formation and rupture [96]. Regions of disturbed flow, such as bifurcations and curvatures, are particularly vulnerable [96]. Also, similarly to AscAA and AAA, proteolytic enzymes (e.g., MMP-2 and -9) are involved in the pathogenesis of IA [97].

Genetic predisposition also plays a significant role in IA development. Mutations in genes encoding components of the ECM, such as collagen type IV alpha-1 and alpha-2, have been identified in familial cases of IA [98, 99]. These mutations hamper the structural integrity of the intracranial arterial wall, causing a propensity to IA formation. Inflammation and immune responses also contribute to IA pathogenesis. Inflammatory cells infiltrate the arterial wall, releasing cytokines and promoting oxidative stress [100–102]. This leads to ECM degradation, smooth muscle cell apoptosis, and arterial wall remodeling, ultimately contributing to aneurysm formation and growth (**Figure 2**).

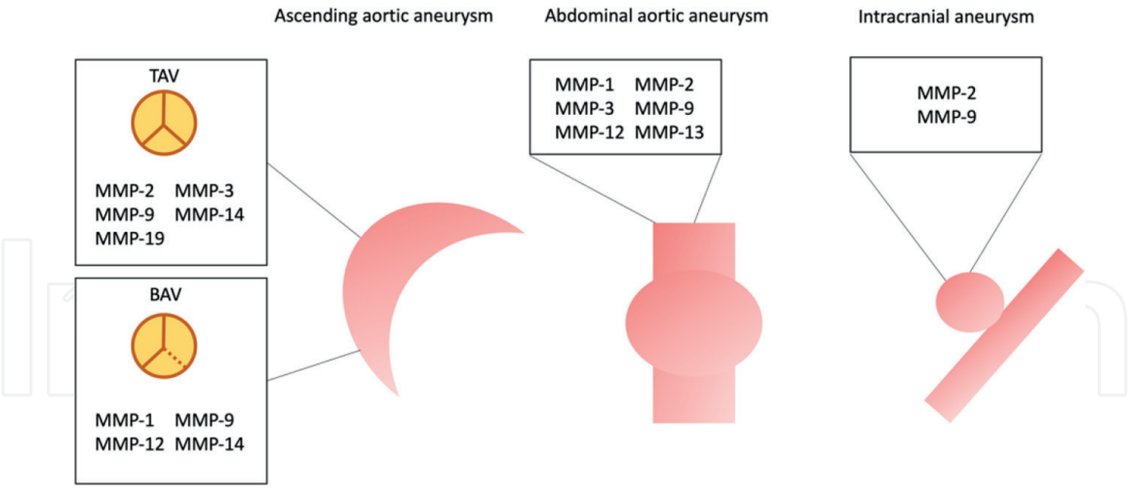


**Figure 2.**
*Matrix metalloproteinases associated with degenerative aneurysmal disease.*

It is important to note that while there are similarities in the molecular drivers between AscAA, IA, and AAA, there are also distinct differences. AscAA is often associated with monogenic connective tissue disorders or proteolytic enzyme degenerative effects, whereas IAs are more often influenced by polygenic genetic factors, hemodynamic forces, and inflammation [103]. AAA is influenced by atherosclerotic processes, proteolytic enzyme activity, oxidative stress, hemodynamic forces, inflammation, and ECM remodeling [74, 98]. It is important to note that while these molecular drivers are often associated with AscAA, IA, and AAA, there can be considerable heterogeneity in the underlying mechanisms between individual patients. Moreover, there may be overlapping molecular pathways and interactions, requiring further studies. Understanding the molecular drivers of aneurysmal disease is crucial for developing targeted therapies and interventions to prevent its progression and improve patient outcomes.

## 7. Implications of aortic valve disease on degenerative ascending aortic aneurysm

There are signs that degenerative AscAA is also associated with aortic valve disease when examining the surgical ASAP-cohort (described in detail elsewhere [12]); BAV-associated aortopathy has an equal prevalence of aortic stenosis (AS) and aortic regurgitation (AI). Contrastingly TAV-associated (degenerative) AscAA often associates with AI but very seldomly AS. This may imply that AS has protective effects on AscAA development, or the inverse, that AscAA patients are protected from AS.

The association of AI with degenerative AscAA may in part represent secondary causes of AI, i.e., disease of surrounding structures [104]. However, AI, combined with degenerative AscAA, was also prevalent in the absence of aortic root dilatation, as seen in the ASAP cohort, pointing toward a primary cause of AI to AscAA formation. Notably, AI is a well-known prognostic factor in clinical outcomes of patients undergoing ascending aortic repair [105]. A worse surgical outcome for AscAA/AI repair is reported in both BAV and TAV individuals [106].

Interestingly, further strengthening the association of AI to AscAA formation is the fact that degenerative changes are noted in ascending aortas of patients with

normal aortic diamters and AI. Specifically, elastin fragmentation, thinning and MEMA (indicative of VSMC death) have been observed in patients with AI but not AS [105, 107]. One apparent line of investigation not yet explored is whether this association can be observed in individuals with BAV without dilatation but with respective aortic valve disease [37]. Neither have implications of AI-associated ascending aortic degeneration been investigated as a possible player in AscAA formation.

## 8. Summary

In summary, the impact of aortic valve cuspidity on ascending aortic aneurysm is well-established. Specifically, BAV aortopathy has been associated with endothelial instability and endothelial-to-mesenchymal transition, possibly of embryonic origin. Moreover, different BAV fusion types may impose different mechanisms of aortopathy, with different aortic segments being affected. TAV-associated degenerative aneurysms, on the other hand, are molecularly more similar to AAA with clear medial degeneration and inflammation. Also, aortic valve disease may play a role in degenerative aneurysm formation, with aortic dilatation occurring almost exclusively in combination with aortic regurgitation. This is further supported by histopathological evidence.

As the aortic valve and ascending aorta are not only anatomically proximate but also embryonically associated and physiologically interacting, the impact of aortic valve cuspidity and disease on ascending aortopathy is warranted further research specifically to explore more patient-specific molecular mechanisms. An elucidation of the molecular underpinnings of AscAA development in different conditions of the aortic valve will help guide novel diagnosis and treatment strategies.

## Conflict of interest

The authors declare no conflict of interest.

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