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Advances in the Treatment of Aortic Valve Disease: is it Time for Companion Diagnostics?

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Abstract

Purpose of the review—Aortic valve disease (AVD) is a growing public health problem, and the pathogenesis underlying AVD is complex. The lack of durable bioprostheses and pharmacologic therapies remain central needs in care. The purpose of this review is to highlight recent clinical studies that impact the care of children with AVD and to explore ongoing translational research efforts.

Recent findings—Clinical studies have evaluated the durability of bioprosthetics and surgical strategies, tested statins during early disease, and identified new predictive biomarkers. Large animal models have demonstrated the effectiveness of a novel bioprosthetic scaffold. Mouse models of latent AVD have advanced our ability to elucidate natural history and perform preclinical studies that test new treatments in the context of early disease.

Summary—Current priorities for AVD patients include identifying new pharmacologic treatments and developing durable bioprostheses. Multidisciplinary efforts are needed that bridge pediatric and adult programs, bring together different types of expertise and leverage network and consortium resources. As our understanding of the underlying complex genetics is better defined, companion diagnostics may transform future clinical trials and ultimately improve the care of patients with AVD by promoting personalized medicine and early intervention.

Keywords

genetics; biomarkers; clinical trials; bioprosthetic valves; pediatrics

Introduction

Aortic valve disease (AVD) is a progressive disease process that results in greater than 25,000 deaths annually in the US [1]. Aortic valve malformation, typically bicuspid aortic valve (BAV), is an independent risk factor the development of AVD and is present in the majority of cases at any age, suggesting a developmental etiology [2,3]. Increasing evidence suggests that AVD is not simply a degenerative process, and genetic and developmental

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abnormalities are involved in disease initiation and progression before established environmental factors contribute to pathogenesis [4,5]. The management of pediatric AVD is different from adult AVD for two basic reasons: the small size of the patient creates surgical considerations and the absence of comorbid cardiovascular diseases that are common in the adult patient with AVD.

Recently, the American Heart Association and American College of Cardiology revised the Guidelines for the management of patients with heart valve disease [6], and a working group from the National Heart and Lung and Blood Institute made recommendations outlining research priorities moving forward [7], including identification of genetic and clinical risk factors for early AVD, development of animal models that duplicate the natural history of AVD, and identification of pharmacologic-based therapies for early intervention. Currently, two fundamental gaps in the standard of clinical care for AVD are the need for drugs that directly treat early disease processes and the need for durable bioprosthetic valves.

The genetic basis of BAV is well established, but only a small number of genes have been associated with AVD. Mutations in NOTCH1 and SMAD6 account for approximately 2–3% of cases only [8–10]. Family based studies have determined that the inheritance of BAV is complex and polygenic [11]. Interestingly, family based studies have also suggested that while BAV is determined largely by genetic effects, the phenotypic variability of AVD is determined in part by non-genetic factors [12], underscoring the importance of distinguishing between early and late disease processes. The clinical utility of genetic testing in the context of cardiovascular malformation and disease has been carefully defined [13], and the advent of clinical and research exome testing promises to accelerate the discovery of causal and modifying variants, as well as clinically meaningful phenotype stratification [14,15].

The Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) project is an early example of the operational implementation of personalized medicine whereby genotype information (e.g. *CYP2C19* variants associated with reduced clopidogrel metabolism) was integrated into the electronic medical record and was shown to impact clinical decision making (which drug to prescribe) in an individual specific manner [16]. The Family Healthware Impact Trial has demonstrated the power of family history and patient empowerment by using a web-based tool to assess familial risk and provide a personalized prevention plan [17], which may be a practical and complementary tool. Since the US Food and Drug Administration (FDA) includes pharmacogenomics data in drug labels now, and clinical trials increasingly require genotype and biomarker information [18], companion diagnostics, or the use of specific diagnostic tests such as genotype and/or biomarker panels that can be used to identify a subset of patients that will benefit from a specific therapy or should not receive it [19], has gained favor, especially in oncology [20–22], as an effective way to improve patient care and advance the use of personalized medicine.

Herein, we review recent advances in the care of patients with AVD, especially children, as well as ongoing translational efforts that appear poised to impact clinical practice paradigms in the near future.

Bioprosthetic valves are increasingly used in young patients, but continue to lack durability

Aortic valve replacement procedures using mechanical prosthetic valves have demonstrated excellent long-term durability, but are associated with a number of significant complications including bleeding and thromboembolism related to the need for anticoagulation (Table). Aortic valve replacement in children is complicated further by the fact that children are growing, such that over time the child “outgrows” the prosthetic valve and requires replacement, often multiple surgeries. The increasing use of bioprosthetic valves in pediatric and young adult patients recognizes the emphasis patients place on avoiding the complications of anticoagulation, as well as activity restrictions or life style modifications [23,24]. There is substantial interest in developing bioprosthetic valves that grow with the patient and do not require re-intervention. Several recent studies have advanced our understanding of the durability of commonly used bioprosthetic valves.

Une et al reported the twenty-year durability of the aortic Hancock II bioprosthesis in young patients [25*]. While good long-term results have been demonstrated in older patients, there is limited information on durability beyond the first decade in young patients. Because younger age is a strong predictor of structural valve deterioration, the research group examined outcomes in “young patients” specifically. Over 300 patients aged 17–59 were studied, and a significant increase in valve failure was demonstrated in the second decade after implantation. Specifically, freedom from major adverse valve-related events decreased from 74% at 10 years to 17% at 20 years. Likewise, the freedom from re-operation decreased from 84% to 25%, and in the less-than-40 age subgroup this decreased further to 14%. Indeed, the strongest predictor of the need for re-operation was age ($p < 0.01$), but prosthesis-patient mismatch predicted need for re-operation as well ($p = 0.045$), suggesting surgical technique impacted a subset of cases, but also highlighting the possibility that smaller prostheses in younger patients are exposed to increased mechanical stresses that contribute to faster degeneration. Importantly, this cohort did not include pediatric patients and therefore does not address the potential issue of lack of valve growth.

Saleeb et al report their experience in a small series of pediatric patients using two types of bovine pericardial bioprostheses, the Mitroflow® LXA and the Magna®/Magna Ease® valves [26**]. Freedom from valve failure at 3 years among those patients with a Mitroflow® LXA valve was only 18% and progression to severe stenosis occurred over a median of only 6 months. Importantly, these patients were younger and smaller and received smaller valves (all known risk factors for valve failure) when compared to the Magna®/Magna Ease® group, but 40% of the Mitroflow® LXA valve failures occurred in fully grown young adults, suggesting these factors do not fully explain the failures. Of note, many of these patients had additional cardiovascular malformations, genetic syndromes and a history of infective endocarditis, confounding generalizability. Interestingly, failure in all cases was due to intrinsic calcification *without* inflammation that resulted in decreased effective orifice area and stenosis. The authors concluded that patients who have received a Mitroflow® LXA pericardial aortic bioprosthetic valve are at increased risk for rapid valve failure and recommended that those patients who have been implanted already undergo increased echocardiographic surveillance since rapid disease progression was not coincident with

symptomatology. Taken together, the findings from these two studies identify a continued need to improve the durability of bioprosthetic alternatives for pediatric patients.

Advances in catheter-based interventions promise increasing use of less invasive valve replacement procedures in the future

Catheter-based balloon valvuloplasty remains an effective way to treat aortic stenosis in children and postpone if not prevent the need for valve replacement; however, newer catheter-based procedures are delivering replacement valves and these procedures may be applicable to children. Transcatheter aortic valve replacement (TAVR) is increasingly becoming the preferred approach to intervention in a number of AVD patient subsets, including high-risk patients and those with prosthetics already in place using a valve-in-valve approach [27]. Most recently, Adams et al reported early findings using TAVR with a self-expanding prosthesis and demonstrated increased survival and decreased major cardiovascular and cerebrovascular events [28]. The Melody valve (Medtronic, Minneapolis MN), a bovine jugular vein sewn into a stent, has been used successfully for pulmonary valve replacement using a Humanitarian Device Exemption; the effectiveness of the device has not yet been demonstrated. In the context of lower right-sided heart pressures, anecdotal evidence has been positive, but attempts to use the Melody valve on the left-sided aortic valve have not been reported. Interestingly, the first report of successful percutaneous transcatheter Melody valve placement in the neo-aortic valve position of a patient with hypoplastic left heart syndrome who had undergone the Fontan procedure demonstrated tolerance of systemic pressures in the context of single ventricle physiology [29*], consistent with recent observations in the context of a systemic semilunar valve in various forms of complex cardiovascular malformation using surgical or hybrid approaches [30]. Taken together, these observations suggest the Melody valve may be a therapeutic option in pediatric patients with complex cardiovascular malformation to avoid additional surgery and potentially delay the need for heart transplantation, and should be tested in children and adults with isolated AVD.

AVD is often associated with aortopathy and this presents unique surgical challenges. Often the degree of AVD at the time of aortic root replacement does not indicate replacement and the surgeon must decide between an aortic valve sparing procedure or replacement of both the aortic root and aortic valve. Some patients with both these disease processes have connective tissue disorders such as Marfan syndrome. Coselli et al reported no differences in survival, valve related morbidity and major valve related events at one year when comparing pediatric patients with Marfan syndrome who underwent either aortic valve sparing or aortic valve replacing aortic root replacement. Of note, more bleeding complications occurred in the valve replacement group and nonstructural valve dysfunction was more common in the valve sparing group [31**], emphasizing the importance of interpreting one-year outcomes with caution and emphasizing the need for long term follow up. David et al recently reported their experience with valve sparing operations in 371 nonsyndromic patients and concluded that both reimplantation and remodeling approaches to valve sparing aortic root replacement results in excellent clinical outcomes, including 95% freedom from reoperation at 18 years despite a slow but progressive deterioration of valve function [32]. Importantly, the new

AHA/ACC Guidelines for Valve disease recognize the BAV-Aortopathy association and have initiated specific recommendations for this subgroup [6].

New therapies are needed to treat early AVD and biomarkers that identify those at risk are being identified

There are currently no pharmacologic therapies to directly treat underlying AVD processes, only symptoms of heart failure in the context of advanced disease. A recent study examining the larger Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study examined the use of statins in the context of asymptomatic patients with mild aortic stenosis and no comorbidities [33**]. The authors conclude that treatment with statins is not associated with a significant reduction in cardiovascular death, need for AVR, heart failure due to progression of AVD, or cardiovascular ischemic events at mild or moderate degrees of AVD, consistent with the primary outcome from the seminal study [34]. This interesting finding has been supported recently by a large-scale human genetics study that examined 1435 single nucleotide polymorphisms in 11 genes associated with cholesterol metabolism from 382 patients with AVD and found that these variants do not influence disease susceptibility and functional characteristics of cholesterol metabolism are not altered as they are in the context of coronary artery disease [35]. Taken together, these findings suggest that atherosclerosis related processes contribute to disease progression but other factors underlie the etiology of AVD and contribute to disease initiation.

Other large clinical studies have begun to explore the possibility of using circulation and imaging biomarkers. Linefsky et al examined the nearly 7000 participants of the Multi-Ethnic Study of Atherosclerosis (MESA) and showed that serum phosphate levels are associated with aortic valve calcification, but a number of phosphate metabolism pathway markers are not [36], identifying a potentially modifiable risk factor and a number of important future studies. Dusenbery et al analyzed young patients with congenital aortic stenosis by cardiac magnetic resonance measuring myocardial extracellular volume fraction. The authors found that the volume fraction is significantly elevated and associated with a greater number of aortic valve interventions and diastolic dysfunction, but not severity of stenosis, left ventricular mass or indexes of systolic dysfunction [37*]. While most of the patients studied had a normal extracellular volume fraction, this measure potentially represents a new non-invasive marker that may be clinically useful for risk stratification and monitoring the response to various therapies.

Ongoing efforts in translational research identify next steps

In an ovine model, a novel bioprosthetic tricuspid valve (CorMatrix Cardiovascular, Inc, Roswell, GA) constructed from non-cross-linked extracellular matrix derived from porcine small intestinal submucosa has been shown to adopt the appearance of a native valve by 4 months with normal valve function at one year [38**]. Importantly, histopathology was characterized by cell recruitment and constructive tissue remodeling with no evidence of inflammation. In a small series of patients requiring aortic valve repair, CorMatrix material was used with limited evidence of resorption and no evidence of tissue remodeling at <9 months [39]. One explanation for why the constructive remodeling was not reproduced may

be that only a small area of patch material was implanted, not a valve scaffold, limiting cell recruitment and therefore tissue remodeling.

Tissue engineered heart valves (TEHV) continue to be an area of active investigation due to their promise to be a permanent valve replacement. TEHV refers to the development of a completely biological heart valve in vitro by isolating the patient's own cells, including bone marrow, adipose and induced pluripotent stem cells, creating a scaffold and implanting this "living valve" construct back into the patient, providing the benefits of ongoing physiologic remodeling and growth. Despite the sensational failure of an early TEHV in children [40], there has been substantial interest in refining this approach. Since the primary cause of failure of TEHV in vivo has been attributed to contraction of the cusps due to the hypercontractile properties of the transplanted cells, which results in cusp shortening and ultimately valve regurgitation, Syendain et al examined the tensile properties of a scaffold developed from human neonatal dermal fibroblast cells and showed that both cell removal and complete recellularization was feasible without altering the matrix organization or structure [41*]. Additional studies have shown that TEHVs that fabricate native valve ECM organization (trilaminar structure) ex vivo promoted the deposition of valve interstitial cells [42], anisotropic scaffolds (where the fibers are uni-directionally oriented) resulted in matrix production of collagens and elastins and increased recovery of the physiologic valve interstitial cell phenotype [43], and the use of a specific hydrogel platform maintains quiescent valve interstitial cell phenotype [44]. Taken together, these advances suggest significant progress is being made that improves the stability of scaffolds and prevents the cells from damaging it, and therefore a viable TEHV may be developed in the near future.

Mutant mouse models have begun to focus on defining natural history as a way to identify early disease processes and test potential new therapies. The *eNOS*^{-/-} and *Notch*^{+/-} mice both show aortic valve tissue architectural changes and mild mineralization with small subsets of mutants demonstrating BAV without AVD [45,46]. Bosse et al created a double mutant that demonstrates a nearly completely penetrant BAV phenotype with AVD and shows that loss of endothelial nitric oxide regulates Notch signaling in aortic valves, which in turn accelerates calcification [47**]. Weiss et al. performed a preclinical study in *Ldlr*^{-/-}; *Apob*^{100/100} mice, a model of latent calcific AVD, to test the efficacy of Osteoprotegerin, a RANK signaling inhibitor that promotes demineralization [48]. They demonstrated attenuated calcification and inflammation but not fibrosis or AVD, suggesting Osteoprotegerin protects predisposed aortic valve tissue from developing calcific AVD and may be a useful therapy early in disease course. Wrigg et al. identified increased COX2 expression in *Klotho* deficient mice, a model of robust aortic valve calcification without inflammation [49*]. In addition to COX2's well-known role in inflammation, COX2 activity is known to contribute to bone differentiation and homeostasis. Both genetic loss of COX2 function and pharmacologic inhibition of COX2 using celecoxib result in partial rescue of calcific AVD, potentially identifying a new cardiovascular indication for this approved medication.

Our understanding of cell-matrix architecture in aortic valve tissue is critical to both identify new therapeutic targets. Wang et al carefully examined progenitor cell markers from porcine semilunar valves and identified subsets of resident valve interstitial cells (VICs) that are

more prone to calcification (ABCG2+) and may be the valve's resident myofibroblasts (OB-CDH+) [50**]. Myofibroblasts have been difficult to phenotype in valve tissue, but are generally thought to be critical for both repair and disease processes, and most importantly may provide key insights into mechanisms underlying disease progression. Recent efforts have demonstrated the importance of understanding dynamic patterns of protein expression in the context of healthy aortic valve tissue homeostasis. For example, Dupuis et al recently described comprehensive and elegant expression patterns for small leucine rich proteoglycans, small molecules with specialized roles in the cardiovascular extracellular matrix [51]. Balaoing et al identified differences in specific valve maintenance proteins secreted by valve endothelial cells with age, identifying some changes that may translate to age-associated risk and demonstrating the complex regulation of homeostasis [52]. Combining these types of studies with emerging proteomics initiatives [53] will allow a more comprehensive approach to understanding valve tissue homeostasis and developing therapeutics using protein engineering [54].

Conclusions

Outcomes of patients with AVD continue to improve, and the research community has a well-defined agenda for further progress. Translational research efforts appear to be on the verge of many important applications. Mutidisciplinary teams are required to combine the disparate expertise of cardiology, cardiothoracic surgery, human genetics, developmental biology, biomedical engineering and bioinformatics, among others. Valve Centers of Excellence that incorporate pediatric programs will create unique bridges that will enhance clinical and research efforts alike. Because Pharma is becoming more selective about drug discovery efforts [55,56] there appears to be an increased interest in “disease management,” including companion diagnostics [57–59], providing new reasons for focusing on innovation in partnership with Pharma.

As gene discovery accelerates and clinical genetic testing expands, the use of genetic information for the management of patients with cardiovascular disease, including AVD, will become commonplace [14]. Companion diagnostics for specific cardiovascular diseases will advance our ability to realize the promise of personalized medicine [60]. To this end, the pediatric cardiology research community is in an excellent position to leverage consortia that combine genomics with patient care [61]. The Pediatric Cardiac Genomics Consortium (PCGC) is linked to the Pediatric Heart Network (PHN) and therefore is in a position to apply combined genetic information and predictive biomarkers to new clinical trials. For example, companion diagnostics may provide a strategy to stratify the Kawasaki or Single Ventricle cohorts in clinically meaningful ways. Ultimately, more assertive care for early AVD processes using genetic and clinical information will significantly improve patient care.

Acknowledgments

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Key points

Aortic valve replacement using bioprosthetics are effective but improvements in durability are needed.

New circulating and imaging markers are being developed that predict AVD severity risk, which may be useful for the management of early AVD.

Preclinical large animal studies are testing new bioprostheses that may be more durable due to constructive remodeling that allows the bio prosthetic to recruit resident cells and transform the bioprosthetic construct into a native valve.

Preclinical studies in mouse models are elucidating the natural history and pathogenesis of AVD, and targeting developmental programs for new therapies.

Companion diagnostics may be feasible to advance personalized medicine for patients with early AVD as the underlying genetic causes and defined and predictive biomarkers are identified.

Table**Current Options for Aortic Valve Replacement (AVR) in Children**

AVR Method	Strengths	Weaknesses
Mechanical	Durable	Bleeding, thromboembolism, lifestyle modification
Bioprosthetic	No anticoagulation, limited impact on activity level	Limited durability
Autologous (Ross procedure)	Attractive alternative for children, potentially grows with the patient, and pregnant women	Limited durability, potentially creates second surgical problem
Homograft	Resistant to infection so preferred in cases of IE,	Limited durability, limited donor number, potential size mismatch
Transcatheter	Excellent early results on right side, "Valve-in-Valve" popular for first reoperation on left side	Utility on left side largely unknown, long term results unknown