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CONTEMPORARY REVIEW

Mitral Valve Prolapse and Its Motley Crew-Syndromic Prevalence, Pathophysiology, and Progression of a Common Heart Condition

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ABSTRACT: Mitral valve prolapse (MVP) is a commonly occurring heart condition defined by enlargement and superior displacement of the mitral valve leaflet(s) during systole. Although commonly seen as a standalone disorder, MVP has also been described in case reports and small studies of patients with various genetic syndromes. In this review, we analyzed the prevalence of MVP within syndromes where an association to MVP has previously been reported. We further discussed the shared biological pathways that cause MVP in these syndromes, as well as how MVP in turn causes a diverse array of cardiac and noncardiac complications. We found 105 studies that identified patients with mitral valve anomalies within 18 different genetic, developmental, and connective tissue diseases. We show that some disorders previously believed to have an increased prevalence of MVP, including osteogenesis imperfecta, fragile X syndrome, Down syndrome, and Pseudoxanthoma elasticum, have few to no studies that use up-to-date diagnostic criteria for the disease and therefore may be overestimating the prevalence of MVP within the syndrome. Additionally, we highlight that in contrast to early studies describing MVP as a benign entity, the clinical course experienced by patients can be heterogeneous and may cause significant cardiovascular morbidity and mortality. Currently only surgical correction of MVP is curative, but it is reserved for severe cases in which irreversible complications of MVP may already be established; therefore, a review of clinical guidelines to allow for earlier surgical intervention may be warranted to lower cardiovascular risk in patients with MVP.

Key Words: Ehlers-Danlos syndrome ■ heart failure ■ Loeys-Dietz syndrome ■ Marfan ■ MASS phenotype ■ mitral regurgitation ■ mitral valve prolapse

Mitral valve prolapse is a common heart condition that is estimated to affect 2% to 3% of individuals.[1] The defining finding in mitral valve prolapse (MVP) is myxomatous degeneration of the mitral valve leaflets,[2] which eventually leads to structural incompetence and superior displacement of one or both mitral leaflets into the left atrium (LA) during systole.[3] Though it is recognized as a highly prevalent heart condition, the question of whether it is benign has been hotly disputed over the years.[1,4-6] After initially being described as a risk factor for several diseases including heart failure, atrial fibrillation, stroke, mitral regurgitation, and others,[4,7] an analysis of the Framingham Heart Study offspring cohort in 1999 disputed these findings, arguing that many of these associations were made in hospital-based cohorts, and therefore patients were sicker and more likely to have comorbid disease.[1] Subsequently, a community study of asymptomatic patients with mitral valve prolapse disputed these findings, and reported that the clinical course was much more heterogeneous than described in the Framingham study.[8]

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Nonstandard Abbreviations and Acronyms

ADPKD	autosomal dominant polycystic kidney disease
BDCS	Boronne Dermato-Cardio-Skeletal syndrome
DZIP1	DAZ interacting protein 1
ECM	extracellular matrix
EDS	Ehlers-Danlos syndrome
IE	infective endocarditis
LDS	Loeys-Dietz syndrome
MASS	mitral, aorta, skeleton, and skin
OI	osteogenesis imperfecta
SCD	sudden cardiac death
SH3PXD2B	SH3 and PX domains 2B
TGF-β	transforming growth factor-beta

Despite the controversy, it is now well recognized that mitral valve prolapse poses a significant disease burden and is a major contributor to cardiovascular morbidity and mortality. Based on the prevalence estimates at 2% to 3%, it is hypothesized that >7.8 million people in the United States, and >176 million people worldwide, are living with MVP.[3] Another study published in 2020 estimates that prevalence worldwide of degenerative mitral valve disease, defined as myxomatous degeneration of the mitral valve leading to hemodynamically moderate or severe mitral regurgitation, is 18.1 million people (95% uncertainty interval [UI], 17.6 million to 18.6 million) and that the mortality rate from degenerative mitral valve disease in 2017 was 35 700 people (95% UI, 30 500–42 500).[9] The discrepancy in prevalent cases between these 2 studies is likely attributable to a more stringent definition of degenerative mitral valve disease, which excludes patients with myxomatous degeneration who have mild or absent regurgitation. Further, it is unclear from the published data whether the mortality associated with degenerative mitral valve disease is a direct result of the valvular dysfunction itself, or as a result of recognized nonvalvular complications of mitral valve disease. Greater than 90 000 mitral valve surgeries occur each year making it the fastest growing cardiovascular intervention in the United States.[10] Further, no Food and Drug Administration approved medical treatments exist for MVP, meaning surgical or percutaneous correction is the only treatment available to patients.

The purpose of this review was to summarize and analyze the current understanding of comorbid conditions with MVP. MVP has been identified as a component of many genetic syndromes,[11] and genome-wide association studies have identified primary loci thought to be important for MVP pathogenesis. Further, both cardiac and non-cardiac diseases have been associated with MVP. An important consideration is that most, if not all, of the publications cited in this manuscript use Barlow disease and MVP interchangeably. There is an important distinction between these 2 types of mitral valve disease. Barlow disease is characterized by pronounced annuluar dilatation, bileaflet prolapse and/or billowing, hooding, and the presence of thick, spongy leaflets because of excessive myxomatous tissue proliferation with or without calcification. The terminology of Barlow does not apply to all cases of MVP, especially in terms of single leaflet prolapse. As these distinctions are generally not well documented in the literature, we will use the more encompassing term of MVP. The following review will focus on analyzing the shared pathophysiology between MVP and other diseases, and the unique pathways that exist in MVP.

CLINICAL CHARACTERISTICS OF MVP

A diagnosis of MVP is not reliably made using clinical symptoms. In fact, patients with MVP appear to exhibit symptoms that have been previously attributed to MVP (dyspnea, chest pain, and electrocardiographic abnormalities) at an equivalent rate to patients without any identifiable prolapse.[1] Even patients with quite severe regurgitation as a result of prolapse may be asymptomatic.[8] As such, symptoms should not be used to diagnose MVP, although the presence of symptoms warrant further investigation. Physical exam findings that are associated with MVP include a lower body mass index and a mid-systolic "click" heard best at the apex on cardiac auscultation.[12,13] A late systolic or holosystolic murmur may be appreciated as well, and suggests the presence of mitral regurgitation.[14] Thoracic, or bony abnormalities, as well as other extra-cardiac findings may suggest the presence of MVP as part of a syndrome.[15] Physical exam findings should also not be used to diagnose MVP, as the presence of any of these findings are not sensitive or specific enough to accurately make a diagnosis.[12] Echocardiography is the gold standard for diagnosis, as it provides a high-resolution and dynamic view of the three-dimensional mitral valve, can quantify leaflet involvement, and is able to detect and quantify characteristics of more severe disease, such as annulus dilation, flail leaflet because of chordal rupture, and severity of regurgitation.[4] Cardiac magnetic resonance imaging may also have a place in the MVP workup, as it is exquisitely sensitive and specific, and is able to uniquely detect and quantify fibrosis in patients with MVP by measuring

late gadolinium enhancement.[16] Electrocardiography or 24-hour Holter monitoring may also provide utility in the workup of MVP, as both atrial and ventricular arrhythmias may arise in these patients. Patients who experience an increased burden of premature ectopic beats (such as premature ventricular contractions [PVCs]) are at an increased risk of developing more severe, even life-threatening arrhythmias.[17,18] Many studies have reported a high PVC burden in patients with MVP. In a recent review of patients with MVP who experienced sudden cardiac death, 92% experienced PVCs on Holter monitoring,[19] and in another electrophysiologic study, PVCs were identified as a trigger for more complex, life threatening arrhythmias in patients with MVP.[20] As such, there is an opportunity to risk stratify patients with MVP using Holter monitoring, to identify subsets of patients who are at an increased risk for sudden cardiac death.

PRIMARY MVP

MVP has been found to follow 2 inheritance patterns: X-linked and, more commonly, autosomal dominant, but age and sex penetrance combined with phenotypic heterogeneity have made the genetics largely elusive.[21-23] In recent years there has been significant progress in finding genes associated with nonsyndromic autosomal dominant MVP. It was suggested very early on that variations in a collagen gene were to blame since MVP is a common comorbidity of connective tissue disorders, including Marfan Syndrome, and pathological evidence points to an extracellular matrix (ECM) defect.[24] However, this idea was discredited in 1989 and no evidence has been found to support it.[25,26] Pedigree linkage studies first demonstrated the immense genetic heterogeneity associated with MVP, identifying 3 loci linked to non-syndromic autosomal dominant MVP.[27-29]

Further investigation into the locus on chromosome 11 associated with MVP led to the discovery of the first gene known to cause nonsyndromic autosomal dominant MVP in humans, *DCHS1* (dachsous cadherin-related 1), which codes for a protein within the cadherin family expressed in fibroblasts.[30] Mice with decreased levels of *DCHS1* have enlarged mitral leaflets and a missense mutation within *DCHS1* segregates with MVP in a large family pedigree.[30] However, how decreased *DCHS1* expression affects mitral valve development to cause MVP remains unknown.

Significant progress was made in 2015 with the first population-based genome wide association study of nonsyndromic autosomal dominant MVP.[31] This meta-analysis of 2 GWAS (Genome-wide association study) for MVP discovered 6 new loci and 2 functional candidate genes, Tensin 1 (*TNS1*) and LIM and cysteine rich domains protein 1 (*LMCD1*).[31] *TNS1* knockout mice have abnormal mitral valves, including thicker posterior mitral leaflets and signs of myxomatous degeneration.[31] LMCD1 acts as a co-regulator of transcription and has been exhibited as a repressor of GATA6 (GATA binding protein 6) a transcriptional regulator important for cardiac development.[32] In fact, both *TNS1* and *LMCD1* are involved in cellular proliferation and migration during valvular development, and it is thought that mutations in these genes cause MVP by affecting embryonic valvulogenesis.[31] To date, no additional studies connecting these 2 genes to nonsyndromic autosomal dominant MVP have been done.

Recently, a cilia gene, *DZIP1*, which encodes DAZ interacting zinc finger protein 1, was identified as a causal gene for nonsyndromic autosomal dominant MVP in humans. A deleterious missense mutation in *DZIP1* segregates with MVP in a large family pedigree. Mice with a similar missense mutation knocked in to their *DZIP1* locus develop functional MVP with evidence of defects in ciliogenesis during development.[33] Population burden tests using previously performed GWAS data sets revealed a bias towards primary cilia genes as contributing to disease phenotype.[32]. Together, these findings implicate MVP as originating from development defects as well as the disease being considered a ciliopathy. However, because of its genetic and clinical heterogeneity, additional studies need to be done to determine how many cases of MVP are a result of impaired ciliogenesis.

SYNDROMIC MVP

Marfan Syndrome

Marfan syndrome is a rare autosomal dominant connective tissue disorder that affects that affects 1 in 5000 patients.[34] Manifestations of Marfan syndrome are diverse, and tend to affect the ocular, musculoskeletal, and cardiovascular systems.[35,36] As a result of its pleiotropic presentation, the diagnosis of Marfan syndrome is made using a clinical assessment known as the Ghent criteria, a specific test which scores the likelihood that a patient has Marfan syndrome over other, similar connective tissue disorders.[37] Advances in molecular and genetic testing have further allowed for confirmation of patients who are suspected of having Marfan syndrome and who score positive on the Ghent criteria.[38,39] As a result, extensive clinical analysis of the phenotypic presentation of genetically confirmed patients with Marfan syndrome exists in the literature. Cardiovascular complications represent the main cause of death in Marfan syndrome, with

the majority of fatal events occurring because of aortic pathology including aneurisms, and dissections.[40] In addition, large numbers of patients diagnosed with Marfan have coexistent MVP; our analysis found a median prevalence of 56.7% (range, 21.9%–100%, Figure S1).[41-67] Indeed, the presence of MVP is considered a minor feature of Marfan syndrome within the most recent Ghent criteria, and is included within the scoring criteria.[37]

Fibrillin-1 (*FBN1*) mutations have been implicated as the major disease-causing variants within patients with Marfan Syndrome, although other mutations within fibrillin-2 have been shown to cause Marfan Syndrome.[68] Fibrillins are a high molecular weight ECM protein that possesses both structural and nonstructural functions. Structurally, fibrillins are a component of microfibrils, which are complexes of multiple ECM proteins including elastin, that provide mechanical and elastic support to the connective tissues.[69] Nonstructurally, fibrillins have been shown to play a role in the regulation of cell signaling, and possess structural similarity to LTBPs (latent transforming growth factor beta binding proteins).[68] LTBPs bind transforming growth factor-beta (TGF-β) and regulate its ability to interact with its receptors, thereby decreasing TGF-β signaling when present. Fibrillin mutations decrease the ability for the fibrillin protein to act as an LTBP, and decrease sequestration of the large, latent TGF-β complex, thereby exposing TGF-β more easily to cell surface receptors.[70] This leads to increased TGF-β–mediated cell signaling, through canonical and noncanonical TGF-β signaling pathways, the proliferation of valve interstitial cells, and activation of these cells to secrete ECM proteins.[71,72] TGF-β signaling has been shown to be a critical driver of MVP within Marfan syndrome, and inhibition of TGF-β signaling using antibodies is able to stop the progression of MVP in mice.[71] More recently, inflammatory cells have been implicated as drivers of MVP progression in Marfan syndrome, though to what extent the immune system is involved in disease initiation remains unanswered.[73]

Mitral Aorta Skeleton and Skin Phenotype

The mitral, aorta, skeleton, and skin (MASS) phenotype is a marfanoid syndrome that consists of phenotypes involving MASS, but that doesn't meet the Ghent criteria for Marfan syndrome. As would be expected, MVP is seen at a high prevalence in patients with MASS phenotype. Our analysis shows a median prevalence of 74.3% of MVP in patients diagnosed with the MASS phenotype (Figure S1).[44,74,75] The genetic basis of MASS phenotype is currently unknown, although some patients who presented with MASS had identifiable *FBN1* mutations, leading some researchers to believe that this condition is a milder form of Marfan syndrome.[44] As such, it is likely that aberrant TGF-β signaling drives the progression of MVP in patients with MASS, though this has not been investigated.

Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) is a rare autosomal recessive connective tissue disorder caused by aberrant TGF-β signaling. It is most often caused by mutations in the TGF-β receptor 1 and 2 genes, though mutations in mothers against decapentaplegic homolog 3(*SMAD3*), as well as *TGFB2*, and *TGFB3* have also been reported to cause LDS.[76,77] Mild forms of the disease may resemble Marfan syndrome, whilst very severe disease can result in death in childhood as a result of aggressive arterial aneurisms.[78] As in Marfan syndrome, MVP is enriched in patients with LDS, although to a lesser extent than is seen in Marfan. Our analysis found a median prevalence of 25% in studies that assessed prevalence of MVP in LDS (Figure S1).[41,53,76] It seems counterintuitive that a more aggressive marfanoid syndrome would cause a lower prevalence of MVP. Why fewer patients with LDS get prolapse is not well understood.

As with Marfan syndrome, excessive TGF-β signaling has been implicated as the stimulus for the development of MVP in both Marfan and LDS.[76] In LDS, it has been observed that although mutations in the TGF-β receptor would in theory decrease downstream signaling, a paradoxical increase in *SMAD2* phosphorylation is observed in these patients, along with an increase in connective tissue growth factor, a TGF-β responsive, SMAD-dependent growth factor, suggesting that mutations result in an increase in signaling.[76] This suggests that perhaps TGF-β is signaling through a different receptor, though it is not known what other receptors may be hyperactivated in this disease state. Furthermore, these recent data seem to dispute other studies that have found that TGF-β receptor mutations cause a decrease in not only the production of mature receptor, but also a decrease in activation, turnover, and downstream signaling.[79] Multiple theories have been proposed to try and rectify the discrepancy, including a loss of canonical TGF-β–dependent negative feedback leading to excessive noncanonical TGF-β signaling, and cell-dependent effects of loss of TGF-β.[80] Nonetheless, more rigorous interrogation of how canonical TGF-β pathway disruption leads to MVP are required.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) refers to a heterogeneous group of connective tissue disorders that share some common clinical phenotypes, including joint hypermobility, tissue fragility, and skin hyperextensibility.[81]

Currently, 13 subtypes of EDS have been identified. Most subtypes of EDS are diagnosed using genetic testing, however, hypermobile EDS, the most common EDS subtype, has no identified genetic cause.[81] Hypermobile EDS is therefore diagnosed using clinical criteria, which may obfuscate more mild cases and prevent a definitive diagnosis.[81] Although initial discoveries implicated mutations in fibrillar collagen as the cause, subsequent studies on patients with EDS have identified many genes that cause different subtypes of EDS, and are important for collagen biosynthesis and processing, proteoglycan synthesis, and innate immunity. Thus, EDS, though often taught to be a disorder of impaired collagen production to medical students, is significantly more diverse and mechanistically much more complicated.

In addition to many musculoskeletal, autonomic, neurologic, gastrointestinal, and psychiatric manifestations that are seen in patients with EDS, cardiac and vascular manifestations may also be seen. Cardiovascular manifestations are common with subtypes of EDS, in particular vascular EDS, a hallmark of which is brittle vasculature, putting patients at risk of arterial rupture.[82] Furthermore, a report identified a cardiac valvular subtype of EDS, in which a series of patients with a collagen type 1 alpha 2 chain mutation were diagnosed with EDS or other similar connective tissue disorders, all of whom had cardiac valvular involvement.[83] Cardiac involvement in most other subtypes of EDS is thought to be uncommon, but has been reported in previous literature.[84-88] MVP is mildly enriched in patients with EDS compared with the general population; in studies included in this review, the median prevalence of MVP was 6.2% (range, 2.6%–66.7%) in patients with a diagnosis of EDS with no further classification of subtype (Figure S1).[84-88]

The pathophysiology of MVP in patients with EDS is currently not well understood. Most of the genes that are known to cause EDS are associated with the biosynthesis, processing, and turnover of ECM components such as collagen which are important for connective tissue stiffness and strength. It could be hypothesized that less abundant, or less organized collagen causes decreased stiffness and increased flexibility of the connective tissue which results in an increased amount of biomechanical tension within the valve in response to the high pressures exerted on the valve during systolic contraction of the LV. This increase in biomechanical tension may stimulate biomechanical signaling within the valve, activating valve interstitial cells to increase production of glycosaminoglycans and other ECM proteins within the valve; indeed increasing biomechanical forces on valve interstitial cells has been shown to increase the synthesis of ECM proteins.[89] Analytical studies of the mitral valve architecture in patients with EDS would be illuminating to better understand how mutations in collagen genes affect valve structure and function.

Ebstein Anomaly

Ebstein anomaly is a developmental heart defect characterized by inferior displacement of the proximal attachments of the tricuspid valve leaflets from the atrioventricular valve ring, resulting in an “atrialized” portion of the right ventricle.[90,91] Ebstein anomaly occurs in ≈1 in 14 000 live births, and has been associated with other cardiovascular defects, including MVP.[90-97] In studies included in this review, we found the median prevalence of MVP was 11.4% in patients who were born with Ebstein anomaly (Figure S1).[90,92-98] The precise mechanism of MVP development in Ebstein anomaly is not known, but that is unsurprising since the precise cause of Ebstein anomaly is also not known. Lithium, a mood stabilizer used to treat bipolar disorder, was originally thought to be a major causative factor in Ebstein anomaly, and was thought to affect cardiovascular development during the first trimester, although more recent studies dispute this finding.[99,100] In addition, family studies have shown several genes that are associated with Ebstein anomaly.[101-103] The future will hopefully shed light on the precise mechanism of development of Ebstein anomaly.

Familial Myxomatous Valvular Degeneration

Familial myxomatous valvular degeneration, also called familial cardiac valvular dystrophy, is a heterogeneously defined group of disorders characterized by myxomatous degeneration in multiple heart valves.[104,105] The median prevalence of MVP in patients with familial myxomatous valvular degeneration is 38.1% in studies that our analysis identified (Figure S1).[104,105] Mutations in the Xq28 gene encoding filamin A has been found to cause familial myxomatous valvular degeneration.[104,105] In animal studies, knockout of Filamin A was demonstrated to cause enlargement of the mitral valve in the fetal period that progressed to MVP by 2 months of age.[106] Further, filamin A mutations were found to disrupt the interactions between filamin A and PTPN12, a tyrosine phosphatase that is a key regulator of cell-ECM crosstalk, in a yeast 2-hybrid screen.[107] Loss of this interaction appears to disrupt integrin-mediated adhesion and endothelial cell migration in the developing mitral valve, leading to a structurally weak mitral valve. Further, mechanical stress on the mitral valve has been shown to affect the affinity of filamin A to its binding partners, though no study has specifically looked at the filamin A-PTPN12 interaction in the context of mechanical stress.[108] One recent study also highlights a potential interaction between components of the serotonergic signaling cascade. This may be

relevant in light of carcinoid mitral valves, which stem from hyperstimulation of serotonin system on valve endothelial cells.[106] Taken together, filamin A disrupts cell behaviors during heart development, and provides a developmental substrate for hemodynamically induced myxomatous degeneration of the mitral valve.

Fragile X Syndrome

Fragile X syndrome is the leading inherited form of intellectual disability. It is a trinucleotide repeat disorder caused by an increase in CGG repeats in the fragile X mental retardation protein translational regulator 1 (*FMR1*) gene to >200, at which point FMR1 becomes silenced. This gene is critically important for gene transcription, particularly for formation of neuronal synapses; as such, inactivation leads to a decrease in neural connectivity and neuroplasticity, which leads to intellectual disability. In addition to intellectual disability, fragile X is associated with other developmental defects, including (wide set ears, macroorchidism, and cardiac anomalies, including MVP). In our analysis, a median of 37.8% of patients who had fragile X syndrome were found to have coexistent MVP (Figure S1).[109-114] An important caveat to this analysis should be made—nearly all studies that assess the prevalence of MVP within fragile X syndrome patients were conducted before the revision of clinical guidelines for the diagnosis of MVP, and as such, prevalence is likely overestimated. However, the biological pathway responsible for MVP as a result of *FMR1* gene silencing has yet to be identified.

Juvenile Polyposis Syndrome

MVP has been reported in juvenile polyposis syndrome. A family study of 4 patients with juvenile polyposis syndrome found that half also had MVP, demonstrating an enrichment for this phenotype, though larger scale analysis of patients with juvenile polyposis syndrome needs to be done to assess the true prevalence of MVP.[115] Mutations in *SMAD4*, a co-SMAD that complexes with phosphorylated *SMAD2* as part of the TGF-β signaling pathway, has been identified as the cause of juvenile polyposis syndrome, aortopathy, and mitral valve features in these patients. This once again demonstrates the importance of TGF-β signaling in the mitral valve.[115]

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a connective tissue disorder characterized by abnormally brittle bones and an increased risk of fractures that is apparent in early infancy or even prenatally.[116] There are 4 subtypes of OI that differ in level of severity; type 1, the most common, is typically a milder form of disease, type 2 is frequently lethal at birth, and types 3, and 4 are of varying severity.[117] Most subtypes of OI are caused by mutations in the procollagen subunits, that cause abnormal truncation of 1 of the 3 subunits, which leads to abnormal triple helix formation, and subsequent intracellular or extracellular degradation before it can be incorporated into the collagen fibers.[117] As with many connective tissue disorders, MVP has been reported at increased frequency in OI patients. However, our analysis identified only a mildly increased prevalence; a median of 5.4% of patients with OI had MVP in 4 studies (Figure S1).[118-121] It has been theorized that MVP is not seen at an increased frequency in patients with OI; MVP was over-diagnosed through the use of M-mode echocardiography before guideline revisions came into effect in the early 2000s, and studies before that had proposed that the prevalence of MVP in the general population was similar to that seen in patients with OI.[119] As a result, no studies have looked into how MVP occurs in OI.

Mucopolysaccharidosis

Mucopolysaccharidosis is a family of disorders that occur because of mutations in lysosomal enzymes that degrade glycosaminoglycans.[122] There are 11 different enzyme deficiencies that give rise to 7 different identifiable subtypes of mucopolysaccharidosis. Deficiencies of these enzymes leads to accumulation of glycosaminoglycan substrates, which results in end organ dysfunction that can be more mild or more severe depending on the amount of residual enzyme activity.[123] Cardiovascular manifestations are common in mucopolysaccharidosis, and include thickening of the interventricular septum, asymmetric septal hypertrophy, and valvular issues, including MVP.[122] Our analysis of 3 studies that were comprised of patients with all 6 different types of mucopolysaccharidosis found that the median prevalence of MVP was 11.5% (Figure S1).[122,124,125] Importantly, all studies analyzed found that mucopolysaccharidosis type III, also called Sanfilippo syndrome, was associated with a lower risk of MVP compared with other types of mucopolysaccharidosis.[122,124,125] It is thought that decreased metabolism of glycosaminoglycans leads to an accumulation of dermatan sulfate in the cardiac valvular tissue, causing valve thickening which, over time, can cause further enlargement, mechanical incompetence, and the development of cardiac valve pathology.[122]

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is a heritable connective tissue disorder characterized by calcification of elastin fibers of the skin, arteries, and retina that eventually causes loss of skin elasticity, arterial insufficiency, and macular degeneration.[126] Patients with

Pseudoxanthoma elasticum have characteristic yellowing, grouped papules, and plaques present on the skin of flexural areas of the body.[127] Cardiovascular complications are common in Pseudoxanthoma elasticum, and typically are related to premature atherosclerotic calcification, and loss of elasticity of the arteries.[127] In addition, MVP has been reported. Our analysis found that a median of 43.4% of patients with Pseudoxanthoma elasticum had MVP, though the 2 studies that assessed prevalence had significantly divergent findings, and were conducted before the adaptation of new diagnostic guidelines for MVP (Figure S1).[127,128] The precise mechanism linking Pseudoxanthoma elasticum to MVP is not known; theories have suggested that abnormal degeneration of collagen, destruction of elastin, or myocardial ischemia and subsequent chordal rupture could all be the shared pathway between the 2 disorders.[127,128]

Stickler Syndrome

Stickler syndrome is an autosomal dominant disorder of collagen connective tissue that results in ocular, skeletal, otologic and joint abnormalities.[129] Mutations in the genes that encode type II and type XI collagen have been identified as causative for Stickler syndrome.[129] To our knowledge, 2 studies assessed MVP prevalence in patients with Stickler syndrome.[129,130] The first study, conducted in 1986, found a nearly 50% prevalence of MVP in affected patients, while the second study, which used more current echocardiographic diagnostic criteria, found 0 of 78 patients analyzed had MVP.[129,130] As such, it is suggested that Stickler syndrome is not in fact associated with an increase in MVP prevalence.

Down Syndrome

Down syndrome, also called trisomy 21, is a chromosomal abnormality that results from meiotic non-disjunction of chromosome 21, Robertsonian translocation of a large part of chromosome 21, or a somatic nondisjunction event early in embryologic life that causes 3 copies of chromosome 21 to be present in the majority of cells. Cardiovascular manifestations are common in Down syndrome and include MVP, which has a median prevalence of 31.4% in the 7 studies analyzed for this review (Figure S1).[131-138] The precise cause of MVP in Down syndrome is unclear. However, it is known that patients with Down syndrome have joint and ligament laxity, and it has been further shown that there is a decrease in collagen density and abnormal protein structure in the tendons of patients with Down syndrome.[135] Furthermore, the 21st chromosome has genes that encode 2 of the subunits of collagen VI that both map to the downs obligate region of chromosome 21, and are expressed in human fetal heart tissue.[139] Taken together, abnormalities in connective tissue synthesis as a result of chromosomal abnormalities appear to cause MVP in Down syndrome, but a precise mechanism has not yet been clearly delineated.

Larsen-Like Syndrome

MVP is one of the several heart malformations that occur as a result of mutations in beta-1,3-glucuronyltransferase 3, which cause a subtype of Larsen-like syndrome. Mutations cause decreased production of glucuronosyltransferase-1, a Golgi apparatus enzyme responsible for the initial step in the synthesis of glycosaminoglycan side chains for the proteoglycans dermatan sulfate, heparin sulfate, and chondroitin sulfate. This results in a partial deficiency of these 3 proteoglycans, disrupting the ECM, and causing the MVP phenotype in affected patients. In a family enriched for this gene mutation, 4 of 5 children that were homozygous for the mutation had MVP, in addition to various other heart, craniofacial, and skeletal abnormalities.[140] Further study of Larsen-like syndrome are needed however, as only 1 paper which analyzed 5 patients has actually assessed cardiovascular traits in Larsen-like syndrome.

Syndrome With Sinus Node Dysfunction, Arrhythmias, Left Ventricular NonCompaction

A series of recent studies reported several families that suffered from a mutation in a cardiac ion channel that, in addition to having electrophysiologic abnormalities, had structural heart abnormalities, and MVP.[141-143] Mutations in hyperpolarization activated cyclic nucleotide-gated potassium channel 4, cause dysfunction of hyperpolarization-activated cyclic nucleotide channel 4, an important contributor to the pacemaker current of sinoatrial node cells.[143] Patients with this mutation exhibit sinus bradycardia, as well as left ventricular noncompaction, a cardiomyopathy characterized by noncompacted left ventricular myocardial layer with many trabeculations and deep intertrabecular recesses.[141] MVP was also identified in 3 of 15 patients described in a recent study of this gene mutation.[142] It is unclear why patients with an ion channelopathy develop MVP or abnormalities in the ventricular myocardium.[141] A few theories have emerged: in the first, loss of hyperpolarization activated cyclic nucleotide-gated potassium channel 4, which is involved in early heart in addition to its role in the developed sinoatrial node, causes atypical signaling in pathways important for ventricular wall maturation and compaction, with resultant hypertrabeculated myocardial tissue and prolapse.[143] In the second,

hyperpolarization activated cyclic nucleotide-gated potassium channel 4 itself acts as a signaling molecule, and decreased expression of hyperpolarization activated cyclic nucleotide-gated potassium channel 4 in the cardiac progenitor cells that eventually form the LV directly causes improper compaction. In the third, left ventricular noncompaction is an acquired compensatory feature that results to improve stroke volume and cardiac output in the patient with bradycardia.[142] None of the authors speculate specifically about how MVP develops in these patients; perhaps abnormal trabeculation of the LV allows for retrograde movement of the mitral valve during systole attributable to abnormal mechanics through the chordae tendineae, or atypical development around the mitral valve annulus causes disjunction, and abnormal valve prolapse.

Borrone Dermato-Cardio-Skeletal Syndrome

Borrone Dermato-Cardio-Skeletal syndrome (BDCS syndrome) is characterized by skin, skeletal, and cardiac abnormalities, including MVP, which is seen in an average (median) of 62.5% of patients analyzed across 6 studies (Figure S1).[144-149] A recent linkage analysis of a consanguineous family with a child diagnosed with BDCS syndrome found homozygous mutations in 2 different genes, *BDCS1* and *BDCS3*. These genes encode the protein SH3PXD2B (SH3 and PX domains 2B). Mutation results in a truncated protein, and complete loss of SH3PXD2B in affected patient fibroblasts. SH3PXD2B is an adapter protein required for formation of podosomes, which are actin-rich membrane protrusions involved in cellular adhesion, migration, and ECM remodeling. SH3PXD2B is highly expressed in the heart during development, and may cause MVP through diminished recruitment of matrix metalloproteases and impaired ECM remodeling during valve development, ultimately leading to a structurally incompetent mitral valve.[145] SH3PXD2B missense and frameshift mutations are also responsible for ≈50% of patients with another similar autosomal recessive condition called Frank-Ter-Haar syndrome[147]; in fact, as a result of recent studies, the BDCS and Frank-Ter-Haar syndrome are now thought to represent the same disease entity,[145] with pleiotropic effects being responsible for the phenotypic differences between the 2 conditions.

Williams-Beuren Syndrome

Williams-Beuren syndrome (sometimes referred to as Williams syndrome) is a rare autosomal dominant disease that is characterized by cardiovascular connective tissue, and central nervous system abnormalities, as well as mild mental retardation and extroverted personality.[150] MVP is reported to be among the most common cardiovascular abnormalities in this condition, with a median prevalence of 22.3% across 10 studies (Figure S1).[151-160] The causal mutation is a recurrent 7q11.23 contiguous gene deletion, which contains the elastin gene within the deleted region.[161] This results in abnormal vascular stiffness in the major elastic arteries of the body, causing progressive arterial stenosis most commonly in the aorta and pulmonary trunk.[150] The precise mechanism linking Williams-Beuren syndrome to MVP is not known, though it can be theorized that abnormal connective tissue structure, and decreased elastic properties of the mitral valve because of elastin deficiency contribute to myxomatous degeneration and the development of prolapse. Furthermore, defects in the structure of elastin are seen in Marfan syndrome, as fibrillin is a component of elastic microfibrils. Mutated fibrillin is known to affect sequestration of latent TGF-β, increasing signaling through that pathway, and causing excessive myxomatous matrix production. Therefore, it may be possible that a driving force behind myxomatous valve degeneration in Williams-Beuren syndrome is an increase in TGF-β signaling.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most commonly observed hereditary conditions, and is estimated to affect almost 1 in 400 to 1000 people.[162] The disease is characterized by the age-related development and enlargement of renal cysts, stemming from the tubular epithelium. Extrarenal involvement of multiple other tissues has been shown in patients with ADPKD, including liver, spleen, pancreas, blood vessels, and the heart.[163] MVP is enriched in patients with ADPKD compared with the general population; in the 8 studies analyzed for the current review, we found the mean prevalence of MVP was 21.4% in patients with ADPKD (Figure S1).[164-171]

Two genes, *PKD1* and *PKD2*, have been implicated in the vast majority of ADPKD cases.[172-174] These genes encode for integral membrane proteins called polycystins 1 and 2, which are found in the plasma membranes and primary cilia of renal tubular epithelial cells, as well as in hepatic bile ductules, and pancreatic ducts.[175] Defects in these genes impair their ability to localize to primary cilia, and are thought to affect mechanosensing of the primary cilia, and structural organization of the epithelial cells, which leads to the formation of cysts, which enlarge over time.[176] Genes involved in primary ciliogenesis are also associated with MVP outside of syndromes as well. In 2019, the cilia gene, *DZIP1* was identified as a causative gene in idiopathicnonsyndromic MVP.[33] It is therefore hypothesized that defects in the organization, assembly, and maintenance of primary cilia underlie the mitral valve involvement in ADPKD.

CARDIAC ASSOCIATIONS OF MVP

Mitral Regurgitation

A study estimated that MVP related complications occur in patients at a rate of ≈1.0 per 100 patient years, or about 1%. The most common complication observed in patients were prosthetic mitral valve implantation or mitral valve repair attributable to severe mitral regurgitation, which occurred in 3.5% of the population over the course of the entire study. Further, baseline presence of a holosystolic murmur, thought to indicate more severe mitral regurgitation, was strongly associated with fatal and nonfatal complications.[177]

Mitral regurgitation is a natural consequence of MVP.[178,179] It is thought that regurgitation develops in patients with MVP through 2 distinct, albeit related pathways—in the first pathway, changes in valve geometry that occur as a result of the myxomatous degeneration process underlying MVP cause separation of the anterior and posterior mitral leaflets, which decreases valve coaptation and allows for retrograde blood flow through the mitral valve during systole.[180-183] Regurgitation that develops in this way gradually worsens as the valve geometry changes and valve coaptation decreases.[184] Eventually, a cyclical pattern develops (Figure), where worsening regurgitation causes an increase in volume overload, which further increases the annulus diameter and further worsens the amount of regurgitation.[184] The annual rate of progression of the regurgitant volume in patients was estimated to be ≈5.9 mL/year.[184] In the second pathway, mechanical stressors on the chordae tendineae leads to degeneration and rupture,[185-187] which causes a flail leaflet that is untethered to the papillary muscle (Figure). This causes a much more rapid progression of mitral regurgitation; the annual increase in regurgitant volume in this group was 18.4 mL/year, >3 times higher compared with patients without flail leaflet.[184] Mitral regurgitation can also develop in the setting of ischemia, and occurs as a result of diminished contractility of the LV, with subsequent papillary muscle displacement, which, as a result of tethering to the valve leaflets, diminishes valve coaptation and increases regurgitation.[188]

The estimated prevalence of regurgitation in patients with MVP has been discussed in several populations, both community-based,[1,15,189,190] and hospital-based cohorts.[8,191] In a series of publications on the Framingham Heart Study, there was a greater degree of mitral regurgitation in patients with MVP compared with controls without prolapse, but the amount of regurgitation seen was, on average, mild.[5] Further, the rate of severe regurgitation, defined as having an area of the regurgitant jet >40% of the area of the LA, was 7% when compared cross-sectionally at baseline.[1] It is worth noting, however that the primary goal of this study was to examine the prevalence of MVP in the community, and the examination of comorbidities performed was on small numbers of MVP positive patients and was done in a cross-sectional manner. Subsequent longitudinal analysis on the Framingham cohort has demonstrated that the rate of patients with MVP at baseline progressing to severe mitral regurgitation (MR) requiring surgery is 25% over a follow-up period of 3 to 16 years.[182]

In a second study comprised of 833 asymptomatic patients with MVP defined by echocardiography at baseline, the presence of comorbidities was analyzed longitudinally. In this cohort, 7.6% were determined to have an MVP-related event, defined as death, heart failure related to MVP, endocarditis, or mitral surgery in 10 years of follow-up. Further, severity of mitral regurgitation at baseline was the strongest risk factor for cardiovascular morbidity.[8] In the Strong Heart Study, patients with MVP had a significantly higher prevalence of both mild mitral regurgitation (28.1% versus 18.9%) and moderate-to-severe mitral regurgitation (8.8% versus 2.1%) compared with patients without MVP. Whilst the above studies make it clear that MVP is not as benign of a disease as was originally thought, more work needs to be done to understand why some patients have a more severe disease course, while others do not.

MVP is the most common cause of severe mitral regurgitation requiring surgery.[192-194] By one estimate, ≈0.2% to 3.5% of patients with prolapse will require surgery for their condition at some point in their lifetime, depending on their demographics.[195] Mitral valve surgery, carries significant risks,[196] but is highly effective at preventing mortality in patients with severe regurgitation.[197] Moreover, less invasive percutaneous catheter-based procedures have been developed, are available for patients who are not ideal candidates for surgery, and have been shown to improve quality of life, reduce rehospitalizations, and promote favorable ventricular remodeling, although they were not shown to improve survival at 1 year.[198]

Atrial Fibrillation

Rates of atrial fibrillation (AF) appear to be low in patients with MVP without significant amounts of regurgitation.[1] However, as the degree of mitral regurgitation increases, so does the prevalence of AF,[199-206] suggesting that the AF incidence seen in patients with MVP occurs as a secondary result of the increasing regurgitation.[204] Estimates of the prevalence of AF in patients with severe regurgitation have ranged from 20% to 55%[202,205,207] depending on the type of cohort analyzed (eg, symptomatic, asymptomatic, surgical, etc). Most recently, a multicentered prospective study of 2425 patients with severe regurgitation because of flail leaflets found that ≈30% had coexistent AF.[200]

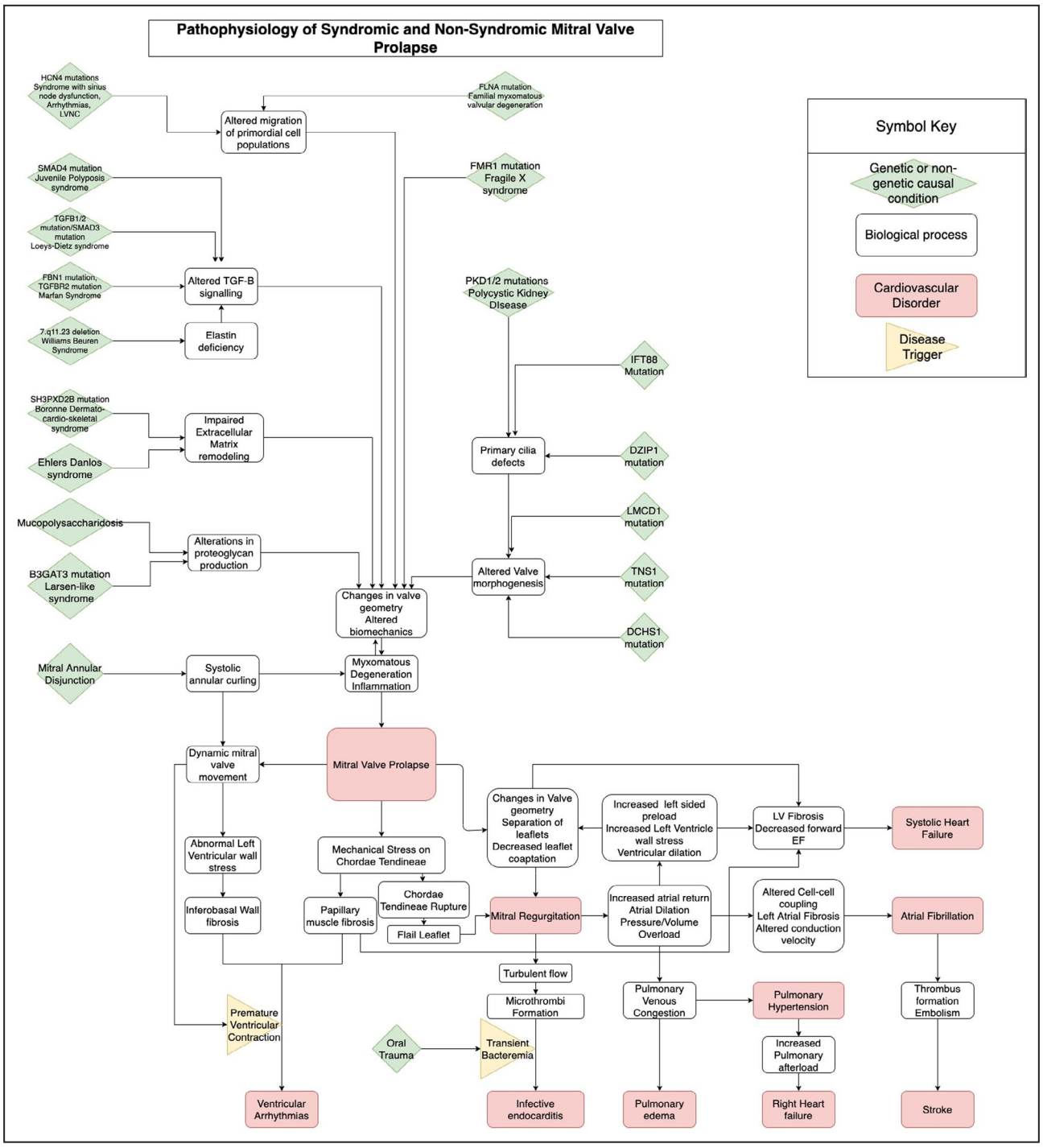

Figure 1. Flowchart showing the inter-relatedness of pathophysiology of syndromic vs nonsyndromic mitral valve prolapse. B3GAT3 indicates beta-1,3-glucuronyltransferase 3; DCHS1, dachsous cadherin-related 1; DZIP, DAZ interacting protein 1; EF, ejection fraction; FLNA, filamin A; FMR1, fragile X mental retardation protein 1; HCN4, hyperpolarization activated cyclic nucleotide-gated potassium channel 4; IFT88, intraflagellar transport 88; LMCD1, LIM and cysteine rich domains protein 1; LV, left ventricle; LVNC, left ventricular noncompaction; PKD, polycystic kidney disease; SH3PXD2B; SH3 and PX domains 2B; SMAD3, mothers against decapentaplegic homolog 3; SMAD4, mothers against decapentaplegic homolog 4; TGFBR2, TGF-beta receptor 2; TGF-β, transforming growth factor beta; and TNS1, tensin 1.

Though MVP is not the only etiology of a flail leaflet, as we have previously discussed it is the most common etiology.[185,186] Further, in a smaller scale study conducted by the same group in 2002, the results demonstrated that the incidence of AF in patients with regurgitation who were medically managed was similar

whether a patient had regurgitation because of simple MVP or a flail leaflet.[206] Taken together, the presence of regurgitation of increasing severity appears to drive the development of AF, and the prevalence of AF in patients with severe regurgitation is high.

Despite its prevalence a paucity of data is present to support a mechanistic link of regurgitation to AF. However, previous studies have compiled a rough understanding of how this might occur based on observations in other diseases that affect the hemodynamics of the mitral valve. Mechanistically, regurgitation of blood through the mitral valve returns blood to the LA, which increases the amount of blood the LA has to accommodate, causing pressure and volume overload.[199] Reflecting this, clinical studies have previously shown that LA volume can predict the development of AF in patients with severe MR.[208] The mechanical stress seen in LA volume overload appears to alter cell-cell coupling of atrial cardiomyocytes, cause tissue fibrosis, and affect the conduction velocity of the atrial tissue, causing currents to travel at differing velocities through conduction pathways in the atria.[209-211] This in turn increases the propensity for reentrant circuits to develop, thus, providing the substrate for AF (Figure).

The interplay between surgical treatment, AF, and regurgitation attributable to MVP has been controversial over the years. It has been well established that patients who have AF at the time of MR surgery have worse outcomes compared with patients without AF.[200,201,206,212,213] However, surgery has previously been associated with an increase in the incidence of AF,[213,214] though more recent data argue that medical management produces worse outcomes than surgical intervention irrespective of whether a patient is in sinus rhythm, has paroxysmal AF, or persistent AF.[200] In addition, one study that found that even though there was an increase in the incidence of AF in patients who were treated surgically compared with conservative treatment, the risk of death from cardiac causes was lower, and the incidence of congestive heart failure was also lower.[213] Others have further argued that concomitant ablation has the ability to decrease the incidence of AF in patients who are undergoing mitral valve surgery.[212] Though current American Heart Association/American College of Cardiology guidelines recommend waiting to perform MR surgery until a patient has new onset AF, these recent studies demonstrating that this waiting approach will lead to worse outcomes has increased calls to amend the guidelines to intervene earlier.[199,200,202]

Ventricular Arrhythmias and Sudden Cardiac Death

The estimated annual risk of sudden cardiac death in patients with MVP ranges from 0.2% to 1.9% depending on the patient characteristics of the study.[215,216] Despite this heterogeneity, what is clear is that MVP appears to be a significant player in the development of sudden cardiac death (SCD) in certain patients. A report in 2001 found that isolated MVP was the suspected cause of SCD in 12% of all cases of SCD in the study population, making it the third leading cause of SCD behind arrhythmogenic right ventricular cardiomyopathy (14%), and premature atherosclerosis (21%).[217] Subsequent analysis of 650 young (<40) patients with SCD performed by the same group found MVP to be implicated in 7% of young patients with SCD. It is important to note that this population has a systematic government-implemented electrocardiography screening protocol that is used to prevent exercise-associated SCD attributable to cardiomyopathies and ion channelopathies,[218] thus the incidence of SCD attributable to MVP in this population is likely high compared with other populations; studies on other populations implicate MVP in ≈1.7% of SCD cases.[219]

Although we have long appreciated the association between MVP with significant regurgitation and the development of ventricular arrhythmias,[216,220] it is becoming evident that regurgitation does not have to be present or severe to increase the risk for SCD. Several recent studies have identified a subset of patients with MVP that have little to no regurgitation, but have a significantly elevated incidence of ventricular arrhythmias, including sudden death.[221-223] The patients described in these reports display a remarkably similar phenotype; young, female, bileaflet MVP without significant regurgitation, a mid-systolic click on cardiac auscultation, presence of mitral annulus disjunction, signs of cardiac fibrosis observed on cardiac magnetic resonance imaging, a high burden of premature ventricular contractions, and increased rates of nonsustained and sustained ventricular tachycardia, ventricular fibrillation, and cardiac arrest.[215]

A proposed mechanism for this "arrhythmogenic mitral valve prolapse syndrome" has begun to emerge.[215] The baseline finding is mitral annulus disjunction, which is an echocardiographic and morphologic finding characterized by increased distance between the atrial mitral valve attachment and the left ventricular attachment.[215,224,225] This abnormality allows for increased mechanical stress on the annulus and leads to irregular curling motion of the mitral valve annulus during systole, in turn increasing the mitral valve annulus diameter during systole.[224] Myxomatous degeneration, in combination with these abnormal stressors on the annulus, leads to increases in mechanical stress on the inferobasal myocardial wall, as well as on the papillary muscles through the chordae tendineae.[225] These stressors increase fibrogenesis in the myocardium,[16] providing the substrate for ventricular arrhythmogenesis through the well documented effects on

cardiomyocyte electrical conduction in the context of fibrosis.[226] At the same time, an increase in the observance in PVCs are seen in patients with MVP.[227,228] Electrophysiologic mapping in these patients has demonstrated that these originate most frequently in the papillary muscles, as well as the fascicles, and the left ventricular outflow tract.[20,228-230] Purkinje tissue in these zones appears to be the trigger for ventricular ectopic beats,[231] and has been theorized to result from either mechanical stretch of the cells as a result of direct mechanical forces from the mitral leaflet on the myocardium, or because of aberrant electrical activity in damaged cells as a result of abnormal calcium handling and the evocation of delayed afterdepolarizations.[222] Together, these provide the substrate (fibrosis and altered electrical conductivity of the myocardium), and trigger (PVCs) for reentrant circuits to develop, causing malignant ventricular arrhythmias.

Treatment for malignant ventricular arrhythmias in patients with MVP follows the standard of care for all patients who experience life threatening ventricular arrhythmias. Ablation procedures have been used successfully to treat ventricular arrhythmias in patients with MVP, but recurrent ventricular arrhythmias can re-emerge in patients treated with this technology.[230] Internal cardioverter defibrillator implantation is often used in these patients for additional prophylaxis, and has been shown to successfully manage subsequent ventricular arrhythmias in some, but not all patients.[228] However, these therapies only work in patients who survive out-of-hospital cardiac arrest, of which only 8.4% of patients do, on average.[232] More work needs to be done to better understand why some patients with hemodynamically benign MVP are at high risk for ventricular arrhythmias and SCD.

Infective Endocarditis

It is estimated that patients with MVP have a 3- to 8-fold increased risk of developing infective endocarditis (IE), although the estimated annual risk is still quite low, at 0.02%.[233] Nonetheless, endocarditis is a pernicious complication of MVP when it does occur. Mortality rates in patients with infective endocarditis are between 10% and 30%, even in spite of advances in diagnosis and surgical/antibiotic treatment.[234,235] Proposed risk factors for endocarditis in patients with MVP are the presence of mitral regurgitation as suggested by a systolic murmur, increased age, male sex, and leaflet thickening/redundancy.[233]

According to studies documenting the etiology of IE in MVP, dental procedures are the most common cause,[233,236,237] although in a recent study of patients with IE who had underlying MVP, an identifiable portal of entry was only seen in 37% of cases.[235] An oral source of the infection is further supported when we consider the organisms implicated in IE. Viridans group Streptococci (which are known to colonize the oral mucosa[238]), in addition to other normal flora of the oral microbiota, accounted for >85% of IE cases in a recent study of patients with MVP.[235] This is in line with previous studies that implicate Viridans group Streptococci as the major cause of infective endocarditis in patients with MVP.[239,240] Based on these findings, it can be hypothesized that in many of the cases of IE without a portal of entry, traumatic inoculation of bacteria during chewing, or brushing may be the stimulus that is responsible for the increased rate, although this has not been tested. Dental procedures or oral trauma allow for oral microbes to enter the bloodstream, causing a transient bacteremia, and providing a trigger for patients to develop endocarditis. Other causes of bacteremia, including gastrointestinal and genitourinary procedures, surgery, indwelling catheters, and intravenous drug use, are further implicated as trigger agents for the development of endocarditis, though to a lesser extent than dental work in patients with MVP.[235]

This leads to an important question: Why then do patients with MVP develop endocarditis at increased rates compared with patients without valve abnormalities? Studies have theorized changes in ECM components as a result of myxomatous degeneration, though this still remains unproven.[240] Other studies have further implicated turbulent flow through the mitral valve,[233] and microthrombi formation on the mitral valve leaflets as promoters of microbial adhesion to the surface of the mitral valve, which is accomplished through complex interactions between microbial surface components recognizing adhesive matrix molecules, (Such as adhesins, dextrans, fructans, and other microbial surface components), and ECM ligands including fibronectin, collagen, laminin, fibrinogen, vitronectin, thrombospondin, elastin, and bone sialoprotein.[241,242] In turn, virulent organisms are capable of activating platelets,[241] and binding coagulation cascade proteins,[242] facilitating growth of the vegetation, which in turn facilitates the adhesion of additional bacteria, forming a cyclical growth pattern that results in enlargement of the vegetation.[242] Another option is that in MVP, the endothelium may become compromised or broken and thereby provide a niche for bacteria to colonize. Bacterial-mediated destruction of the mitral valve, chordal rupture, septic emboli, hemodynamic instability, organ failure, and death can then result.

Though endocarditis is seen at increased rates in patients with MVP, and despite calls to use prophylaxis in all patients with MVP who have evidence of regurgitation,[233] MVP is currently defined as an intermediate risk cardiac condition for endocarditis, and as such, antibiotic prophylaxis for this condition is not recommended.[69] Historically, this has been a controversial

issue.[239] Assuming 2% to 3% of the population are living with MVP, this would mean putting millions of patients on antibiotic prophylaxis, which would be a significant economic burden and, an enormous cost to the healthcare system, and a burden for patients, in addition to the problematic effects such a strategy would have on emerging antibiotic resistance. Nonetheless, since the changes in guidelines in 2007, the prevalence of endocarditis attributable to streptococcal species has been rising.[243] Studies have identified subgroups that would benefit more from prophylaxis; restricting antibiotic prophylaxis to patients with a systolic murmur, for example, is estimated to provide cover to ≈90% of patients likely to develop infective endocarditis.[237] Further, recent studies have suggested that restricting antibiotic prophylaxis to patients with MVP undergoing dental procedures could be of benefit, given that the vast majority of bacteria causing IE in patients with MVP originate from the mouth.[235] Nonetheless, current guidelines find insufficient evidence that antibiotic prophylaxis would be effective in preventing infective endocarditis in MVP.[244]

Heart Failure

Heart failure occurs when the heart is unable to pump sufficient blood to meet the physiologic demands of the rest of the body. In the literature, heart failure is defined heterogeneously, and can be established as a diagnosis in multiple different ways based on the presence of symptoms, as well as based on objective measurements of heart function observed through cardiac imaging.[245,246] MVP without regurgitation was conventionally not considered to directly cause heart failure.[247] Instead, MVP was thought to cause heart failure through worsening mitral regurgitation, which causes hyperdynamic LV function, volume overload, and eventual decompensation.[248] However, this viewpoint is changing in light of recent data which implicate MVP in the development of left ventricular fibrosis even when mild to no regurgitation is present.[249,250] In a study that compared patients with MVP and regurgitation to matched patients with regurgitation but no prolapse, a third of patients with MVP had established cardiac fibrosis compared with just 3% of patients with isolated regurgitation.[251] Furthermore, even in patients with clinically mild regurgitation, presence of MVP was significantly associated with increased LV dimensions and remodeling independent of the amount of regurgitation.[252] Perhaps most significantly, 1 in 5 patients who receives corrective surgery to treat MVP will develop an acute decline in their LV dysfunction, even though echocardiographic parameters before their surgery are normal.[253] These findings taken together suggest that, while there are no doubt changes in volume handling as a result of regurgitation play a role in the progression of heart failure, isolated mechanical effects as a direct result of a prolapsing leaflet is also likely contributory.

When mitral regurgitation becomes heart failure is also heterogeneously defined in the literature. For the purposes of discussion here, and based on our interpretation of the guidelines, the development of heart failure in a patient with mitral regurgitation would hinge on the development of the clinical symptoms of heart failure (eg, dyspnea, exercise intolerance), which is denoted "Severe symptomatic mitral regurgitation" by the 2014 American Heart Association/American College of Cardiology guidelines on the management of patients with valvular heart disease executive summary.[254] Indeed, many studies that describe the outcomes of patients with severe mitral regurgitation describe the severity of symptoms using the New York Heart Association functional criteria for heart failure.[255-257] This of course makes it difficult to delineate the 2 disorders from one another.

Because heart failure is defined in many ways, and as a result of the inter-relatedness of heart failure and mitral regurgitation, it is difficult to estimate the risk of developing heart failure in patients with MVP; nonetheless studies have tried to do so. In the Olmstead study of 833 patients with asymptomatic MVP, 5.7% developed heart failure that was determined to be a result of their disease. In the same study, however, 66 patients had mitral valve surgery, which may demonstrate additional patients who initially developed symptoms of heart failure, but who met criteria for surgery.[8] In another cohort of patients with mitral regurgitation that that met criteria for valve surgery, a third of patients went on to develop heart failure within 10 years, but in the same cohort, 370 out of 576 patients, or nearly 2 in 3 patients, had a diagnosis of heart failure before their surgery,[213] presumably because of the presence of symptoms of heart failure. In an editorial in 2018, Gillam et al further highlighted the problems with using presence of symptoms as a tool for diagnosis of symptomatic mitral regurgitation/heart failure. They argue that it can be difficult to differentiate the patient with severe regurgitation who is "at risk" for heart failure (meaning in New York Heart Association class 1, but without symptoms) from someone who meets criteria for a diagnosis of heart failure because patients with mild exercise intolerance will subconsciously curtail the amount of physical activity they engage in.[258] In a nationwide hospital-based registry study, Andell et al found that 39.3% of patients with a diagnosis of mitral regurgitation had a coexistent diagnosis of heart failure, yet they also point out that this is a 2-way street; primary MR reduces effective stroke volume and causes heart failure, but mitral regurgitation can also result from annular dilation secondary to left ventricular dilation in heart failure or ischemic heart disease.[207] For the purposes of this review, we focused primarily on

the mechanisms through which primary regurgitation can cause worsening left and right heart function, and eventually cause heart failure.

Patients can present with symptoms of heart failure (eg, dyspnea, exercise intolerance) as a result of MVP through several different pathophysiologic mechanisms. First, as MVP worsens, higher amounts of biomechanical tension are applied to the LV through the chordae tendineae.[259] In addition, mitral annulus disjunction contributes to increased biomechanical forces experienced by the basal LV.[224] These locations of increased tension correlate with regions of left ventricular fibrosis, and suggest that increasing tension applied to the myocardium as a result of prolapse is causing left ventricular fibrosis.[225,228] Fibrosis in turn increases the stiffness of the myocardium, and impairs contractility, which ultimately causes worsening systolic and diastolic heart function until the symptoms of heart failure develop.[260] LV fibrogenesis caused by increases in chordal tugging forces as a result of a prolapsing valve are independent of mitral regurgitation, which further demonstrates the role of biomechanical tension as an initiator in driving pathogenesis.[251] In addition, a recent study that performed hybrid cardiac magnetic resonance imaging and positron emission tomography scanning of patients with MVP found that regions of myocardial fibrosis exhibited increased fluorodeoxyglucose uptake, demonstrating a hypermetabolic state of the fibrous zones, and suggesting that there is subclinical myocardial inflammation occurring in response to increased mechanical tension.[261] How tension causes regionalized fibrosis and the role of myocardial inflammation in this process is not well understood and will be the subject of much interesting work in the future.

Second, MVP can also cause left ventricular dysfunction, and systolic heart failure.[262-264] Although patients with severe regurgitation, may have a completely "normal" ejection fraction, this doesn't reflect the true underlying hemodynamic alterations that are occurring. To do a quick calculation, in severe regurgitation (defined in the Framingham Heart Study as regurgitant jet area >40% of the volume of the LA[1]), assuming a normal left atrial volume index of ≈41 mL/m^2 for a male patient, ≈16 mL of blood would be regurgitated with each beat of the ventricle. Assuming a normal ventricular stroke volume index of 65 mL/m^2, ≈25% of the blood ejected from the heart each beat is flowing from LV to LA. This implies that only 75% of the blood ejected with each beat makes it to systemic circulation, and therefore, the cardiac output has to increase 33% to pump enough blood in the forward direction to meet the body's metabolic demands. The initial response by the LV is a compensatory increase in left ventricular end-diastolic volume and force of contraction supported by the frank starling mechanism,[265] but chronically, this volume overload causes increased LV wall stress, LV hypertrophy, fibrosis, increases in LV afterload, and a gradually worsening systolic function.[264,265] The best evidence that ventricular systolic dysfunction exists in patients with severe mitral regurgitation is the acute decline in ejection fraction that occurs in patients just after mitral valve surgery.[201,266-268] Even further, patients with impaired preoperative ejection fraction had a much more drastic reduction in ejection fraction with their operation, and patients with a more significant reduction in ejection fraction carried a worse prognosis.[266] In a prospective study of asymptomatic patients with severe mitral regurgitation, immediate surgical correction was compared with a conventional treatment strategy that waited to perform surgery until they developed symptoms (exertional dyspnea), or they experienced a declination in ejection fraction (<60), an increase in LV end systolic diameter (>45 mm), AF, or pulmonary hypertension (pulmonary arterial pressure >50 mm Hg). In follow-up, conventional management resulted in an estimated actuarial 7-year cardiac mortality rate of 5%, compared with 0% with immediate surgery.[197] As such, the 2017 American Heart Association/American College of Cardiology focused update on the management of valvular heart disease guidelines state that surgical intervention in a patient with a normal ejection fractionF (>60%) who has increasing LV size or worsening ejection fractionF is reasonable, since an ejection fractionF <60% indicates these patients are already in LV dysfunction.

Third, as regurgitation through the mitral valve worsens, increasing amounts of blood are expelled into the LA instead of through the aorta, causing left atrial pressure and volume overload.[269] This results in left atrial enlargement, and may cause AF, as has been discussed in our section on AF.[208] At the same time, worsening regurgitation has been associated with increases in pulmonary arterial pressures,[184,270] likely as a result of pulmonary congestion because of the regurgitant blood and left atrial volume overload.[271] Even in asymptomatic patients with severe regurgitation, 34% had elevated pulmonary systolic pressures during exercise, suggesting that these patients may have subclinical pulmonary congestion that has not yet progressed to symptomatic pulmonary hypertension.[271] In another study of patients with left ventricular dysfunction (defined by an EF <50%), severity of mitral regurgitation was found to independently predict pulmonary arterial pressure.[272] These findings suggest that regurgitation drives the onset of pulmonary hypertension independent of left ventricular dysfunction. Worsening pulmonary hypertension, in turn, increases right ventricular afterload, and causes right ventricular remodeling and hypertrophy, but this is ultimately insufficient to overcome the increase in pulmonary afterload, and right-sided heart failure develops.[273] Severity

of pulmonary hypertension in patients with mitral regurgitation is associated with worse outcomes. In a study of 1318 patients with severe mitral regurgitation attributable to myxomatous degeneration, an elevated right ventricular systolic pressure (>35 mm Hg) was seen in 77% of patients who died, and there was a positive trend that showed the higher your baseline right ventricular systolic pressure, the higher your mortality risk.[274] Despite the risks of pulmonary hypertension on adverse outcomes in MR patients, current American Heart Association/American College of Cardiology guidelines recommend avoiding surgical intervention on patients with regurgitation until the development of pulmonary hypertension, when their right ventricular systolic pressures reach 50 mm Hg.[254] As such, current guidelines may wait too long to intervene in patients with mildly elevated right ventricular systolic pressures, and delay care that may be associated with a more favorable outcome.[274]

Finally, regurgitation can develop abruptly as a result of papillary muscle, or chordal rupture. As was previously discussed, changes in valve geometry and myxomatous enlargement of the leaflets causes an increase in mechanical stress on the chordae tendineae, which eventually may rupture.[185,186] Mitral regurgitation develops abruptly and without appropriate compensation by the LA. This leads to acute left atrial volume overload, and causes pulmonary edema and symptoms of respiratory distress.[275] Mechanistic studies in dogs have nicely demonstrated these effects, showing that when mitral regurgitation was acutely induced through chordal severance, massive increases in LA volumes and pressures are seen, as well as a significant rise in left ventricular end diastolic pressure, a marker of preload.[276] Further, this study found a decrease in the LV systolic pressure with acute regurgitation, consistent with a decrease in effective afterload on the LV, as well as forward cardiac output to the systemic circulation. In support of this, administration of isoproterenol (a beta-adrenergic agonist that may decrease peripheral resistance through its effects on β2 receptors) as well as nitroprusside (an antihypertensive that decreases peripheral resistance through production of nitric oxide) decreased left ventricular end-diastolic pressure, findings that demonstrate administration of these drugs increases forward flow, decreases left ventricular preload, in turn decreasing effective regurgitant orifice size and regurgitant fraction, and reducing LA volume overload.[276] Early surgery is recommended in patients with mitral regurgitation because of flail leaflets, and is associated with a good outcome.[277-279]

"NONCARDIAC" ASSOCIATIONS

The association between MVP and stroke has long been debated. Early case reports and case-control studies that found an association between MVP and stroke in young patients are criticized for using older, less stringent MVP specifications which led to an overdiagnosis and consequently an over association.[280-284] These MVP disease criteria were redefined in the late 1980s, and a prominent case-control study was then published in 1999 that contradicted the previous reports of an association between MVP and stroke in young patients.[285] However, one group disagrees with the power of case-control studies and in 2003 conducted a community-based study, which they say takes away bias in picking cases and controls, increases sample number, and allows for long-term follow-up. This paper reported that individuals over the age of 50 years with MVP have increased risk of stroke possibly because of AF and increased valvular surgery.[280] The controversy around the association between MVP and stroke will remain until there is knowledge of the pathophysiology that connects the 2.

Left atrial myxomas are noncancerous tumors found in the LA of the heart.[286] They have been loosely associated with MVP, with a handful of case reports documenting them as comorbidities.[287-291] However, no case-control studies have been conducted to determine the association between left atrial myxomas and MVP.

The association between cardiovascular disease and erectile dysfunction has been established for a number of years.[292,293] The link between the 2 is thought to be systemic inflammation, a symptom that has been known to cause MVP.[294,295] Despite this, little is known about the association between erectile dysfunction and MVP specifically. The first study to determine that this association exists was published just last year in 2019. Using data from the Taiwan National Health Insurance Research Database, these researchers found that people currently suffering from erectile dysfunction were more likely to have previously been diagnosed with MVP than controls.[296] While the exact mechanisms that cause MVP are still being resolved, these researchers hypothesize that the link between MVP and erectile dysfunction may come from shared features such as oxidative stress and endothelial dysfunction that affects blood flow.[296]

Many studies have found that MVP is significantly associated with lower body mass index as compared with controls.[297-300] However, the underlying link between these 2 physical characteristics remains unknown. It is interesting to point out the patients with anorexia nervosa have been shown to develop MVP and then recover while receiving therapy and treatment.[301] It has been suggested that this occurs because of the "ventriculo-valvular disproportion," meaning that patients with anorexia nervosa lose cardiac muscle but not valve tissue and these disproportionally large valves are more likely to prolapse.[302,303]

Whether or not this phenomenon is true for people with just lower body mass indexes is to be determined.

THE FUTURE: NONSURGICAL THERAPY FOR MVP

Mitral valve surgery or percutaneous intervention is the only currently available treatment for MVP, and because of the invasive nature and significant risks associated with these procedures, it is reserved for patients with severe disease.[244] Although surgery is effective at preventing many of the complications of MVP,[193,197,213,274,277-279] it is not always curative. Long-term follow-up of patients with mitral valve repair found that re-repair of the valve or recurrent nontrivial mitral regurgitation may develop in 4% to 35% of patients,[304-308] demonstrating that although valve repair does provide a benefit to the patient, it doesn't necessarily stop the underlying pathophysiology.

A growing interest in the field is the development of nonsurgical pharmacologic treatments to MVP. MVP is observed in 70% of small breed dogs,[309-311] with macroscopic and microscopic pathological findings consistent with primary MVP in humans.[312-314] Drugs commonly prescribed to affected dogs include angiotensin-converting enzyme inhibitors,[315] diuretics,[316] vasodilators,[317] β-adrenergic receptor blockers (β-blockers),[318,319] and inotropes.[320-322] Angiotensin-converting enzyme inhibitors promote a reduction in cardiac after-load by decreasing arterial pressure, thus, reducing mitral regurgitation.[315,323] Loop diuretics, such as furosemide and torsemide, promote natriuresis, reducing cardiac preload by decreasing total blood volume.[316] In addition, torsemide produces vasodilation; enhances cardiac function, and abrogates aldosterone-induced cardiac remodeling.[324-331] Vasodilators, such as nitroglycerin and angiotensin-converting enzyme inhibitors, decrease cardiac preload and afterload, leading to a reduction in systemic vascular resistance. Medical management with vasodilators lends to a reduction in mitral regurgitation in patients with severe mitral valve disease.[332] β-blockers promote negative inotropic and chronotropic effects, decreasing cardiac demand, and oxygen demand.[318,319] While β-blockers have not been proven to reduce mitral regurgitation in the setting of human or canine MVP, a reduction in the incidence of heart palpitations and arrhythmias is observed.[333] Additionally, β-blockers are purported to prevent deleterious cardiac remodeling by preventing adrenergic over-activation.[334] Lastly, positive inotropic agents, such as the cardiac glycoside digoxin, are used to enhance cardiac contractility and to treat AF in canines with severe MVP.[320,335] In addition to digoxin, the calcium sensitizer and phosphodiesterase 3 inhibitor pimobendan is used in canines because of its positive inotropic and dilatory effects.[336] In the EPIC (Evaluation of Pimobendan in dogs with Cardiomegaly caused by preclinical mitral valve disease) trial, dogs treated with pimobendan experienced 15 more months of symptom-free life than did dogs treated with placebo.[321,322] Despite the plethora of medications used to provide moderate symptomatic relief in canines, there are no drugs available that target disease initiating pathways associated with deleterious myxomatous degeneration.

Dysregulation of the TGF-β1 (transforming growth factor beta 1) pathway contributes to the pathogenic myxomatous valvular remodeling seen in MVP, making TGF-β receptor 1 an attractive anti-target.[337-340] Furthermore, activation of the TGF-β1 signaling pathway in MVP induces valvular interstitial cell differentiation into contractile myofibroblasts, contributing to ECM remodeling.[339] A study by Ng et al demonstrated that TGF-β antagonism in vivo rescued the valve phenotype in a mouse model of Marfan syndrome,[341] suggesting aberrant TGF-β signaling contributes to cell proliferation and survival in MVP.[342] Losartan, an angiotensin receptor type II blocker, reduces TGF-β levels and may represent an avenue to modulate the pathological progression of MVP.[343-346] Similar to angiotensin-converting enzyme inhibitors, losartan decreases cardiac afterload, leading to a reduction in left ventricular end-systolic wall stress and mitral regurgitation.[347] Finally, following the discovery of increased inflammatory cells within myxomatous valves, as well as data that show that deficiency of circulating monocytes inhibits progression of MVP, immunomodulating drugs may be of interest, although these carry significant side-effect profiles.[73,348] Future directions should include the use of unbiased genetic screening approaches to identify novel druggable targets in the setting of MVP, as well as targeted therapeutics that can decrease systemic administration of agents while increasing drug concentrations within the mitral valve. Safe and effective therapies, if identified, could slow the rate of myxomatous degeneration, potentially delaying the need for surgery and improving outcomes.

CONCLUSIONS

Our review of the literature found that while MVP is enriched in several genetic and syndromic disorders, many disease associations that have previously been reported either do not have enough data available to assess the true prevalence of disease, or were reported before the adaptation of new clinical diagnostic guidelines for MVP that took the saddle shape of the mitral valve annulus into account. As such, diseases such as osteogenesis imperfecta, fragile X syndrome, Down syndrome, and Pseudoxanthoma elasticum, which have all been previously associated with MVP, may be over-reporting the prevalence of MVP. Finally, MVP may be a phenotype present in other genetic

syndromes not discussed within this paper, but that have not been well documented in the literature. Additional studies, which use up-to-date diagnostic criteria for MVP, will be important to assess whether MVP is truly associated with these conditions.

Our review further demonstrates the shared pathways through which MVP can develop in a heterogeneous group of conditions. First, the vast majority of mutations that have been identified that cause syndromic and nonsyndromic MVP cause alterations in valve geometry through either increases in ECM production, impaired ECM remodeling, or altered cell migration and valve morphogenesis. Second, the new, novel role for primary cilia as a master regulator of valve morphogenesis and major cause of MVP has shed new light on how disruptions in early cardiac valve development may "prime" patients to develop worsening MVP by altering their valve architecture early on in their lifetime. Finally, the role of TGF-β dependent cell signaling highlights the importance of cell signaling, proliferation, and activation in driving MVP pathophysiology. Taken together, we propose a model in which changes in valve geometry, and subsequent alterations in valvular dynamics during the cardiac cycle, create a feed forward cycle that, through altered cell signaling, interstitial cell activation, and ECM production and remodeling, drives myxomatous degeneration and the development of MVP. A prolapsing valve then drives the further development of cardiovascular disorders through changes in biomechanics and hemodynamics (Figure).

Over the past 20 years, our understanding of MVP has evolved considerably. Precise definition of the disorder has allowed for large, population level studies to occur which have shown that even though MVP is a common and often benign entity, the lifetime cardiovascular risk of patients with MVP is both substantial and diverse. Through the hard work of many clinical and basic science researchers, genetic causes of MVP have been identified, and animal models of MVP have been developed which allow in-depth investigation of the molecular drivers of mitral valve enlargement, myxomatous tissue formation, and prolapse.[30-33,73,104] With these tools, future investigations can focus on how MVP progresses beyond the valve, to the ventricle, and whether new studies may inform revised clinical guidelines or application of rationale remedial therapies to blunt disease progression or severity.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Figure S1

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SUPPLEMENTAL MATERIAL

Figure S1. Type of MVP-associated disease analyzed, study population size, prevalence, sex, year of study and journal of publication

Disease	Year	# screened patients	# included patients	Mean Age	Percent female	Number of MVP cases	Percentage prevalence of MVP, median (range)	Recruitment method	Study design	**Notes/ Reference** Number
Population Prevalence Studies					**56.2**	**256**	**2.1 (1.7-2.7)**			
	2004	N/A	972		48	27	2.7	Patients were members of three ethnic groups in canada and were enrolled as part of the Study of Health Assessment and Risk in Ethnic groups (SHARE) study	Cross sectional population based cohort	Multiracial cohort (189)
	1999	3736	3491	56.7/55.4 classic/nonclassic MVP	52.9	84	2.4	Subjects were prospectively recruited as offspring of original Framingham cohort	Prospective cohort	Framingham cohort- caucasian (1)
	2001	3630	3340	60	62.2	57	1.7	Subjects were recruited based on geographic location or membership to a native american tribe	geographic population based prospective cohort	American Indian cohort (strong heart study) (190)
	1999	5081	5063	N/A		88	1.7	Subjects were recruited based on geographic location to participate in a prospective heart study.	Prospective cohort	African American cohort (Jackson heart study)- data obtained from JHS website, not published in a journal. Link: lhttps://www.jacksonheartstudy.org/Portals/0/pdf/DataBook_Exam1/ECHA.pdf
Marfan syndrome					**46.3**	**2856**	**56.7 (21.9-100)**			
	2019	236	101	23.8	45.54	55	54.46	Subjects were referred based on clinical suspicion	Descriptive study	57
	2019	166.0	83.0	34	48	48	57.8	Subjects were recruited as controls for a retrospective comparison with LDS patients	retrospective, observational case-matched cohort	41
	2017	381	139.0	11.4		61	43.9	Subjects were recruited based on positive clinical diagnosis of MFS	retrospective study	No sex data listed. Abstract for an oral presentation (42)
	2017	65	22.000	35.4	45.5	14	63.6	Subjects from a previous study of MFS were recruited for a clinical trial	Prospective double-blind, randomized placebo-controlled trial	43
	2016	125	81.0	35	58	75	92.6	Medical Record Screening	retrospective longitudinal observational study	44
	2015	73	73.0	32	29	15	21.9	Subjects included in study all underwent cardiovascular surgical procedure at Bejing Anzhen hospital; all had echocardiography	Retrospective study	45
	2013	1367	608.0	11.2 ±6.3	40	229	37.7	Subjects 6 months-25 years of age who met original ghent criteria and had a BSA-adjusted aortic root diameter z-score>3 were included.	Randomized clinical trial	Numbers not provided, our numbers are an estimate based on percentages reported in the paper (47)
	2014	119	31	11.5	48.4	20	64.5	Subjects were Included based on clinical diagnosis of marfan syndrome at a single hospital	Cross-sectional study	46
	2014	304	134.0	35±16	55	85	56.7	Database analysis that included subjects based on a diagnosis of MFS who underwent dural MRI	Cross sectional study	58
	2013	316	234.0	32±13		166	70.9	Subjects were Included if enrolled in the AVOOMP study and had an available preoperative echocardiogram	Retrospective study	Unclear # of men- 93 males had MVP, but unclear how many out of total cohort were men (48)

2013	155	84.0	9±5.7	56	26	31.7	Subjects under 18 subjected to a standardized diagnostic problem between 1998 and 2011 and who met the Ghent Criteria, or who had a confirmed FBN1 mutation	Prospective study	49
2011	668	256	34±15	56.3	112	43.75	Subjects with clinical features of marfan syndrome were screened and patients were included in the study if they were both diagnosed with Marfan syndrome and Mitral valve prolapse with moderate or less mitral regurgitation (n=112)	population based cohort study	50
2010	1191	965.0	22 (11-34 quartile)	47	743	77.0	Subjects were members of the Universal Marfan database. Patients were excluded if there was insufficient data to conduct their analysis, or if they were diagnosed with neonatal marfan syndrome, had 2 mutations on th same FBN1 gene, or had compound heterozygousity for FBN1.	Retrospective study	51
2010	549	204.0	31.2±16.4	47	82	40.2	Only Subjects who fulfilled the criteria of classic marfans syndrome and lived within the 180km area around the hamburg clinic	population based cohort study	67
2010	166	114.0	ɤr children, 32.5±9	53.5	70	61.4	Subjects were recruited if they had a clinical diagnosis of Marfan Syndrome and presented to the clinic with dyspnea, chest pain, syncope, tachycarduam cardiac murmur, or a pulsatile neck mass.	Cross Sectional study	59
2009	90	90	29±14	50	25	28	Subjects were enrolled based on definitive diagnosis of marfan syndrome based on standardized criteria with or without genetic testing, and referral to Massachusetts General Hospital for Transthoracic echocardiography	Cross Sectional study	52
2009	243	232.0	36.5±16.5		105	45.3	Subjects were included in the MFS group if they had an identified FBN1 mutation	Cross Sectional study	53
2009	1191	320.0	6.5 (3-11)	45	198	61.9	Subjects were identified based on registration within the universal marfan database as having a FBN1 mutation, and were included if they were under 18 years of age.	Retrospective study	60
2006	77	53	33±10.9	53	35	66	Subjects were included in the MFS group if they fulfilled the ghent criteria for MFS and were adults	Case-control study	54

2005	N/A	83.0	37±17	34.9	23	27.7	Included subjects were diagnosed with marfan syndrome and fulfilled strict ghent criteria, and underwent aortic root surgery between 1971 an 2001	Retrospective study	55
2004	N/A				179	78.9			61
2003	N/A	70.0	median, birth-52 ye	51.4	34	48.6	Subjects were diagnosed with Marfan syndrome and were followed in the subspecialty cardiology clinic of a single institution	Observational study	62
2003	128	36.0	26 (10-54)	36.1	18	50.0	Subjects met the ghent criteria for marfan's syndrome but had no or only mild aortic and mitral valve regurgitation noted on the first complete echocardiogram recorded at the study institution	Cross sectional study	66
2002	513	513.0	31.7 (0.1-81)	41.5	247	48.1	Subjects were diagnosed with Marfan syndrome and were seen as inpatients or outpatients at a single hospital between 1989 and 1997, and identified through medical records review (inpatient) or chart review (outpatient)	Retrospective, hospital-based study	63
2001	223	68.0	7.9 (1.0-16)	52	46	88.5	Subjects were identified through a search of all datafiles of the pediatric department at the study institution.	retrospective cohort study	64
1983	171	166	(males) 11.0±0.6 (I	49.4	113	68	Study subjects met diagnostic criteria of Marfan syndrome and had at least one M-mode echocardiographic syudy performed before the age of 22 at a single institution.	Retrospective study	used previous diagnostic criteria for MVP-likely overestimated (65
1975	35	35	20.9 (3-61)	33	32	91	Subjects diagnosed with marfan syndrome were elgible for this study	Cross sectional study	used previous diagnostic criteria for MVP-likely overestimated (65)
MASS phenotype				**29.2**	**107**	**74.3 (40.2-100)**			
2016	N/A	15	30±11	73	15	100	included subjects had a clinical diagnosis of MASS identified through a patient records screen at two institutions. No included patients had an identifiable FBN1 mutation.	Retrospective longitudinal observational study	73
2012	N/A	92.0	16.4	14	37	40.2	Subjects all had a diagnosis of pectus excavatum and were identified through a medical records screen, then assessed for MASS phenotype severity using a numerical scoring system	Retrospective study	Majority of study patients (72%) had a clinical diagnosis of MASS, though based on the text this study may not have included only MASS patients in their workup. (74)
1989	161	138.0	23.3	39.1	55	74.3	Included subjects had been referred to a medical genetics clinic due to clinical suspicion of a heritable connective tissue disorder between january 1986 and may 1987, were white, had available medical records, and were diagnosed with an HCDT.	Retrospective Case-Control study	75

Loeys dietz syndrome					**45.7**	**47**	**25 (22.7-33.7)**		
	2019	166	83.0	34	48.2	28	33.7	Retrospective, observational case-matched comparison with Marfan syndrome	retrospective, observational case-matched cohort	41
	2009	243	33.0	33		15	22.7	Subjects were Identified through Marfan clinic	Cross Sectional study	53
	2005	34	16.0	15	33	4	25.0	Referral from doctor	Family study	76
Ehlers Danlos syndrome					**77.2**	**47**	**6.2 (2.6-66.7)**		
	2020	532	95.0	13.4		11	11.6	Subjects were recruited based on EDS diagnostic criteria during retrospective review of electronic medical records	Retrospective chart review	84
	2018	518	209.0	31	87.6	13	6.2	Subjects were identified through a Medical record screening	Retrospective chart review	88
	2014	N/A	28.0	37.8	85.7	18	66.7	Subjects were selected from clinics for heritable connective tissue disorders	Case-control study	87
	2011	302	252.0	median age 14	67	15	6.0	Chart review of children with EDS seen at Cincinnati Children's Hospital Medical Center between 1995 and 2006	cross-sectional study	85
	2006	N/A	38.0	36	81.6	1	2.6	Recruited based on EDS diagnosis from previous heritable connective tissue disorders study	cross-sectional study	86
Ebsteins anomaly					**66.53466981**	**54**	**23.3 (2.3-100)**		
	2008	N/A	104.0	31	57	14	13.5	Subjects were recruited based on tricuspid valve replacement surgery	Cross sectional study	92
	2006	700	12.0	10.5	42	2	16.7	All subjects had an chocardiographic diagnosis of Ebstein's anomaly	Retrospective study	98
	2005	115	106.0	32	60.4	16	15.1	All subjects had an echocardiographic diagnosis of Ebstein's anomaly	Retrospective study	97
	2001	1	1	27	100	1	100	One patient was included in this case report	Case Report	93
	1993	N/A	19.0	4.5	57.9	11	57.9	Morphological collections from Royal Brompton and National Heart Hospital, Killingbeck Hospital, and personal collection of LMG	Retrospective study	leaflet anomalies, including "dysplasia, excessive number of leaflets, thickening, calcification, fusion, funneling, and muscular arcade. Not specifically prolapse (94)
	1994	N/A	220.0	23 adults >18y/o, 15 adolescents 10-17y/o, 50 children 2-10y/o, 132 <2y/o	55	5	2.3	Ebstein's anomoly records from 5 London hospitals	Retrospective study	23 adults >18y/o, 15 adolescents 10-17y/o, 50 children 2-10y/o, 132 <2y/o (90)
	1981	N/A	10.0	its <1y/o, 5 averag	60	3	30.0	Necropsy	Descriptive study	Necropsy study- not diagnosed using currently established guidelines (95)
	1976	NA	2.0	26.5	100	2	100.0	n/a	Case report	96
Familial myxomatous valvular degeneration					**67.1**	**27**	**38.1 (37.8-38.5)**		
	2007	176	45.0	37.2	68.9	17	37.8	Subjects were recruited based on referral from doctor due to family history of valve disease	family study	104
	2000	87	26.0	36.9	65.4	10	38.5	n/a	family study	105

Fragile X syndrome						**45**	**38.4 (5.9-100)**			
	2007	35	22.0	8.5	0	3	13.6	Molecular DNA analysis	Descriptive study	only echo data from 22/24 patients (109)
	1993	32	17.0	8.3	6	1	5.9	Subjects had a diagnosis of fragile X from patient data from CCDD	Descriptive study	110
	1990	52	13.0	15.0	38	10	76.9	Subjects were hospitalized at a single institution, suffered from Fragile-X syndrome (martin-bell syndrome) and underwent clinical and instrumental cardiac evaluation.	Case-Control study	111
	1989	28	23.0	51	0	5	21.7	Prospective survey	Descriptive study	severe disease (114)
	1986	105	40	16.5	15	22	55	Subjects all had Fragile X diagnosis at Childrens Hospital of Denver between 1981-1985	Cross-sectional study	Diagnosed using outdated criteria (112)
	1984	N/A	4	25.75	25	4	100	Subjects were referred to the study center for workup following a diagnosis of fragile X syndrome	Case series	diagnosed using outdated criteria (113)
Juvenile polyosis syndrome						**2**	**50**			
	2011	5	4	20.75		2	50	Included subjects were family members of a patient with an identified SMAD4 mutation that had echocardiographic workup.	Family study	115
Osteogenesis Imperfecta					**60**	**6**	**5.9 (3.4-20.0)**			
	2013	N/A	5.0	50.4	0	1	20.0	subjects were identified if they had a diagnosis of osteogenesis imperfecta and underwent valve surgery at a single institution.	Case series	121
	1989	N/A	58.0	9 (1-16)		2	3.4	subjects were affected with either type I, type III, or unclassefied Osteogenesis imperfecta	Cross sectional study	118
	1986	N/A	29.0	27 (1-75)		2	6.9	Subjects had been referred to one of three clinical centers for genetic counseling, and subsequently were diagnosed with osteogenesis imperfecta based on clinical symptoms and radiographic findings. Of these patients, 29 had adequate studies to assess MVP.	Cross sectional study	119
	1983	N/A	20.0	40.2	75	1	5.0	Included subjects were referred to a regional metabolic bone disease clinic for diagnosis or treatment, and had a diagnosis of osteognesis imperfecta	Cross sectional study	120
Mucopoly-saccharidosis					**38.88288288**	**27**	**11.5 (8.0-36.7)**			

	2019	26	26.0	7.4 (1.8-26.5)	46	3	11.5	All subjects with a diagnosis of MPS III and available echocardiographic data were reviewed for this study.	Retrospective, uncontrolled study	Mucopolysaccharidosis III (all 3 subtypes) (124)
	2018	25	25.0	6.8±2.8	48	2	8.0	subjects were enrolled at a single center and all had a diagnosis of MPS III.	Prospective study	Mucopolysaccharidosis III (125)
	2014	N/A	60.0	21.0±6.3	32	22	36.7	All subjects diagnosed with MPS at a single center between Jan 2000 and December 2012 were included.	Retrospective study	all 6 mucopolysacchardidoses (122)
Pseudoxanthoma elasticum					**50**	**14**	**43.4 (15.4-71.4)**			
	1982	N/A	14.0	43.1	50	10	71.4	Subjects were diagnosed with pseudoxanthoma elasticum and confirmed with a punch biopsy of characteristic skin lesions.	Cross sectional study	Used outdated criteria for MVP diagnosis (M Mode) (127)
	1982	28	26.0	43.3 (13-71)		4	15.4	All subjects had a diagnosis of Pseudoxanthoma elasticum.	Cross sectional study	128
Stickler syndrome					**16**	**26**	**22.8 (0-45.6)**			
	2003	115	78	Not specified		0	0	subjects were identified from the vitreoretinal service database at a single institution, and diagnosed clinically using established criteria, with subsequent validation using molecular genetic means	Cross sectional study	129
	1986		57.0	(4-60)	39	26	45.6	Included subjects met the diagnostic criteria for sticker syndrome.	Cross sectional study	130
Down syndrome (Trisomy 21)					**39.9**	**117**	**31.4 (2.7-57.1)**			
	1999	N/A	37.0	0		1	2.7	Subjects were all diagnosed with down syndrome between jan 1987 and dec 1996, and underwent echocardiography either between 6 and 12 months, or earlier if an anomaly was suspected based on clinical suspicion or ECG results taken at 48 hours.	Prospective study	138
	1998	N/A	30.0	33.2±8.8 (20-49)	46.7	8	26.7	Subjects were included if they were diagnosed with down's syndrome, had no cardiac symptoms, and did not have a previous diagnosis of congenital heart disease	Case-Control study	133
	1994	52	36.0	(20-32)	58	13	36.1	All subjects who had a diagnosis of down syndrome, were 20 years of age or older, and who had not previously undergone cardiac surgery were invited to participate in the study.	Cross sectional study	135

	1993	N/A	35.0	20±4.2	37	16	45.7	All subjects followed at 2 institutions with down syndrome, who were aged 12 years or older, who had no congenital heart disease based on previous physical examination, and no previous intracardiac surgery, were included in the study.	Cross sectional study	132
	1988	N/A	83.0	29.5 (9-55)	48.2	41	49.4	Study subjects were a group of noninstitutionalized patients with Down's syndrome who were not prescreened for clinical evidence of heart disease, and were drawn as a random sample of patients either visiting a local physician or a dentist for care.	Cross sectional study	136
	1988	N/A	131	41±11	37	18	13.7	For this case-control study, patients with down syndrome were compared to patients of a comparably retarded population of patients without down syndrome at the same institution.	Case control study	131
	1987	35	35.0	26±8	29	20	57.1	Study cohort consisted of asymptomatic, noninstitutionalized adults with down's syndrome who all underwent cardiac examination.	Cross sectional study	137
Larsen like syndrome					**40**	**4**	**80**			
	2011	N/A	5	13.2	40	4	80	Study subjects were identified within a consanguineous family through clinical assessment, and confirmed to have the mutation with genetic testing.	genetic linkage study	140
Syndrome with sinus node dysfunction, arrhythmias, LVNC					**34**	**6**	**59.3 (18.8-100)**			
	2014	39	16	45.9	31	3	18.8	Subjects were identified based on symptoms, were members of one of 3 families, and had an identified HCN4 mutation	genetic linkage study	142
	2014	N/A	3	34.75	50	3	100	Living patients from an identified family with an HCN4 mutation (n=3) were clinically assessed for presence of structural heart disease.	genetic linkage study	143
Borrone dermato-cardio-skeletal syndrome/FTH syndrome					**24.9**	**28**	**62.5 (5.9-100)**			
	2019	N/A	20	not reported		11	55	this study assessed all clinical features of documented patients who have a SH3PXD2B mutation in the published literature	Literature review	144

	2014	N/A	10	11.7	20	7	70	Affected subjects were identified through linkage analysis of 3 families with the BCDS phenotype, and from 7 families with FTHS	genetic linkage study	145
	2012	13.0	13	not reported	23	5	38.5	3 subjects with an SH3PXD2B mutation, as well as 10 patients diagnosed with FTH were included for this study	Case series	146
	2010	N/A	17	Not reported	35	1	5.9	Study subjects were members of 12 unrelated families and had a diagnosis of FTHS	family study	Several patients were reported to have a mitral valve anomaly, but only one was listed as definitively having mitral valve prolapse. (147)
	2007	N/A	2	18	0	2	100	Included subjects were brothers who had a constellation of symptoms that resembled BDCS syndrome	Case report	148
	1993	N/A	2	N/A	0	2	100	Subjects were 2 brothers affected by the same constellation of symptoms	Case report	149
Williams-Beuren syndrome					**49.1**	**120**	**22.3 (1.3-42.9)**			
	2019	N/A	80	1.0 (0-17.3)	43.8	18	22.5	Subjects were included if they were confirmed diagnosis of willams syndrome and had a follow up duration of more than 5 years.	Retrospective study	151
	2012	70	45	4.6±3.1	40	10	22.0	diagnosed by a medical genetecist and confirmed with fluorescence in situ hybridization, and had regular follow up	Retrospective study	152
	2011	N/A	27	11.6 (1.1-25.7)	66.7	9	33.3	Subjects were identified through a review of an echocardiographic database at the study institution over a 10 year period	Cross sectional study	153
	2010	N/A	270	3.3±5.9	50.4	40	14.8	Subjects were included if they were diagnosed with a medical geneticist and subsequently evaluated by a pediatric cardiologist	Retrospective study	154
	2007	N/A	21	6 (0-17)	33	9	42.9	Subjects were diagnosed at a single tertiary center between 1995 and 2005	Retrosective study	155
	2006	N/A	29	12.8 (2-23)	58.6	9	31.0	Subjects were diagnosed with williams syndrome by clinical diagnosis and haplotype analysis	Retrospective case series	156
	2003	N/A	53	3.6±4.0	38	12	22.6	Subjects were included if they were diagnosed with williams syndrome at the study institution between 1980 and 2002.	Cross sectional study	157
	2003	20	16	5.9 (.7-10.7 years)	45	3	18.8	Subjects were included if they were diagnosed with williams beuren syndrome at the study center and had follow up data that assessed mitral valve prolapse	Retrospective study	Poorly reported data (158)
	2002	N/A	75	22.7 (0.3-76)	55	1	1.3	Subjects were identified after screening and diagnosis at the study centers between 1974 and 2000	Retrospective follow up study	159

	1988	N/A	66	9.8 (.6-29)	53	9	15.0	Subjects were all members of he infantile hypercalcaemia foundation and enrolled with parent consent	cross sectional study	160
Autosomal dominant polycystic kidney disease					**50.1**	**165**	**21.4 (4.3-33.3)**			
	2008	N/A	56	47±14.5	28.6	10	17.9	Subjects identified through medical record search of patients diagnosed with ADPKD between 1997 and 2003 using strict clinical criteria	Retrospective study	164
	2001	182	109	44±1	54	28	26	Subjects were members of 16 families and had a PKD1 mutation	Case-control study	165
	2001	130	130	3.4/64.3 (± 8.5, 12.!	51.3	6	4.3	Subjects were identified through the nephrology service at a hospital.	Cross sectional study	169
	1995	N/A	30	45±10.1	57	5	16.7	Study subjects were identified if they attended the renal clinic at one saudi arabian hospital	Prospective study	171
	1995	149	83	9.6±0.5	51	10	12	Subjects were identified as minors whose parents were enrolled in an ongoing ADPKD study. Subjects were included if any renal cysts were identified on examination, or if they had gene linkage analysis that yielded a high probability of being affected.	Prospective, single blinded study	170
	1992	N/A	21	50 (20-78)	52.4	7	33.3	Included subjects were followed in the renal service at a single institution and had previously underwent abdominal untrasound which had identified the presence of more than 5 renal cysts bilaterally.	Case-Control study	2 control groups-unaffected family members and patients affected by an unrelated nephropathy. (166)
	1992	374	228	39±3	47.8	57	25	Recruited study participants were members of a large family with ADPKD, and were included if they had a clinical diagnosis based on presence of bilateral renal cysts totalling 5 or more in numbers, or if a diagnosis was suspected based on presence of less than 5 cysts total, or unilateral cysts.	Family study	167
	1988	163	163	40±1	55	42	25.8	Subjects were identified from a signle institutions registry of affected ADPKD patients	Prospective study	168

*red text denotes study was conducted prior to implementation of current AHA screening guidelines for MVP diagnosis