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Risk Factors for Valvular Calcification

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Abstract

Purpose of Review: Recent literature is examined to identify established and emerging risk factors for valvular calcification, specifically aortic valve disease and mitral annular calcification.

Recent Findings: Strong evidence implicates older age, male sex, cigarette smoking, elevated blood pressure, dyslipidemia, adiposity, and mineral metabolism as risk factors for calcific aortic valve disease. Emerging evidence suggests family history and lipoprotein(a) are additional risk factors. Recently, large-scale genome-wide analyses have identified robust associations for *LPA*, *PALMD*, and *TEX41* with aortic stenosis. Factors predisposing to mitral annular calcification are less well characterized. Older age, cigarette smoking, increased body mass index, kidney dysfunction, and elevated triglycerides are associated with greater risk of mitral annular calcification, but conflicting evidence exists for sex and C-reactive protein.

Summary: Established and emerging risk factors for calcific aortic valve disease, including some that overlap with atherosclerosis, may represent targets for pharmacological intervention. Mitral annular calcification is comparatively less well understood though some atherosclerosis risk factors do appear to increase risk.

Keywords

Calcific Aortic Valve Disease; Aortic Stenosis; Mitral Annular Calcification; Risk Factor; Genomics

Introduction

In calcific aortic valve disease (CAVD), valvular calcification is observed on the cusps of the aortic valve and ranges from aortic sclerosis, when calcific nodule formation and leaflet thickening are relatively mild and individuals are asymptomatic, to aortic stenosis, where substantial nodular development and stiffened leaflets lead to severe obstruction of blood

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Conflicts of Interest

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flow through the valve and individuals become symptomatic. Prognosis is poor: aortic sclerosis is associated with 68% higher risk of coronary events, 69% higher risk of cardiovascular mortality, and 36% higher risk of all-cause mortality (1), and without aortic valve replacement, less than one-third of patients with severe aortic stenosis survive beyond 5 years (2,3).

In developed nations, CAVD is the most prevalent valvular heart disease among the elderly (4). Aortic sclerosis afflicts between 2.3% and 51.7% of older individuals, with the prevalence of sclerosis increasing dramatically with age (1). Aortic stenosis is observed in 1.7% of individuals 65 years or older (5) but 12.4% of individuals greater than 75 years of age (6). The prevalence of aortic stenosis demonstrates a similar dependency on age (7) and is expected to more than double by the year 2040 and triple by the year 2060 (8) due to the ageing population. Healthcare costs are expected to increase in tandem and in the United States, the cost of medically-managed severe aortic stenosis is already estimated to be \$1.3 billion per year (2).

Mitral annular calcification (MAC) is a less common form of valvular calcification that occurs at the fibrous base of the mitral valve. It affects 9-20% of the population (9,10) and likewise increases in prevalence with age. MAC has been associated with 50% greater risk of incident cardiovascular disease, 60% greater risk of cardiovascular death, and 30% greater risk of all-cause death, adjusted for cardiovascular risk factors (11). Individuals with MAC are also more likely to have severe coronary artery disease (12) and to sustain a stroke (13).

Currently, no medical therapy exists for either CAVD or MAC. Epidemiological studies spanning the last three decades have implicated a number of risk factors which associate with valve calcification. Recent studies, including large-scale genome-wide studies, have identified novel risk factors. In this review, we discuss established and emerging risk factors for both CAVD and MAC.

Established Risk Factors for CAVD

Older Age—Due to the advanced ages of CAVD patients, the disease was thought to be a degenerative condition acquired due to ageing. Although this view has been overturned, age remains a strong risk factor for CAVD. Each 10-year increase in age among participants of the Cardiovascular Health Study (CHS) was associated with double the odds of CAVD (odds ratio [OR], 2.18; 95% confidence interval [CI], 2.15-2.20; $p<0.001$), adjusted for clinical factors (14). In the Multi-Ethnic Study of Atherosclerosis (MESA), the risk for aortic valve calcium (AVC) more than doubled per decade (risk ratio [RR], 2.19; 95% CI, 1.84-2.61; $p<0.001$) (15).

Male Sex—With the exception of Boon *et al* (16), male sex has been consistently associated with increased risk for AVC and aortic stenosis. Relative to women, men in the Framingham Offspring Study (FOS) had 56% higher odds of AVC (95% CI, 1.15-2.13; $p=0.005$) in models adjusted for atherosclerotic risk factors (9). Similarly, men were more likely than women to have aortic sclerosis or stenosis in the CHS (OR, 2.03; 95% CI, 1.7, 2.5; $p<0.001$), independent of other clinical factors (14).

Cigarette Smoking—Smoking has been strongly associated with increased risk of CAVD. In the FOS, greater cigarette use was associated with elevated odds for AVC (OR per standard deviation [SD] of cigarettes per day, 1.22; 95% CI, 1.06-1.39; $p=0.005$), adjusted for other cardiovascular factors (9). In the MESA, current smokers more than doubled their risk of incident AVC relative to never smokers independent of other clinical factors (RR, 2.49; 95% CI, 1.49-4.15; $p=0.001$), though smoking was not associated with the progression of calcification (15). Current smokers also had higher odds for aortic stenosis in the CHS (OR, 1.35; 95% CI 1.1-1.7; $p=0.006$) (14).

Blood Pressure and Vascular Stiffness—A number of studies have demonstrated an association between hypertension and CAVD. In the Helsinki Ageing Study, hypertension was associated with AVC independent of the effects of age and body mass index (OR, 1.74; 95% CI, 1.19-2.55; $p=0.005$) (17). A more modest effect was observed in the CHS, which accounted for additional clinical factors (OR, 1.23; 95% CI, 1.1-1.4; $p=0.002$). Within the MESA, a graded correlation was observed between the stages of hypertension, as defined by the Joint National Committee 7, and AVC: calcification was observed in 6% of normotensive individuals, 11% of borderline hypertensive individuals, 17% of individuals with stage I hypertension, and 16% of individuals with stage II hypertension. The association of hypertension with prevalent AVC was also modified by age (interaction $p=0.041$), such that hypertensive individuals doubled their odds of calcification, but only before 65 years of age (adjusted OR, 2.31; 95% CI, 1.35-3.94).

Hypertension has also been associated with more rapid progression of CAVD. Peak aortic jet velocity, a measure of aortic stenosis progression, increased more rapidly in hypertensive versus non-hypertensive individuals (annualized change in velocity, 0.26 ± 0.23 m/s versus 0.17 ± 0.20 m/s; $p<0.01$) in a retrospective, echocardiography study (18). Faster progression was also observed among individuals with systolic hypertension in the PROGRESSA study (2-year change in median [25th-75th percentile] AVC, 370 [126-824] versus 157 [58-303] among normotensives; $p=0.007$), and this association persisted following adjustment for clinical factors and baseline AVC (19).

In the MESA, a comparison of blood pressure measures and their association with prevalent AVC demonstrated that the largest effect was observed for pulse pressure (OR per 10 mmHg, 1.41; 95% CI, 1.21-1.64 among individuals <65 years old and 1.14; 95% CI, 1.05-1.23 among individuals ≥65 years old) (20). Pulse pressure is a measure of arterial stiffness and wave reflection, suggesting that abnormal hemodynamics may promote calcification. Consistent with this hypothesis, greater wave reflection, as represented by the augmentation index, was associated with elevated odds for moderate to severe diffuse AVC independent of demographic variables and glomerular filtration rate in the Cardiac Abnormalities and Brain Lesions cohort (OR per 1% increase in augmentation index, 1.08; 95% CI, 1.02-1.14; $p=0.005$) (21). Increased wave reflection leads to greater tensile stress on the cusps of the aortic valve, and exposure of porcine aortic valve interstitial cells to such stress initiates extracellular matrix remodelling (22), which precedes thickening and calcification of the aortic valve.

Dyslipidemia—Whether elevated low-density lipoprotein cholesterol (LDL-C) is a risk factor for CAVD remains controversial in light of apparently discrepant findings between observational studies and randomized controlled trials. An immunohistological study found that apolipoprotein B and apolipoprotein(a) co-localized with calcium in the lesions of stenotic valves, but neither apolipoprotein was detected in normal valves (23). The distribution of apolipoprotein B was also more diffuse than that of apolipoprotein(a), suggesting LDL-C is found in the diseased aortic valve in addition to lipoprotein(a) (see section on lipoprotein(a)). This finding was supported by observations in the CHS that higher levels of LDL-C were associated with greater odds of developing aortic sclerosis (OR, 1.00; 95% CI, 1.00-1.01; $p=0.002$) (24) and increased odds for prevalent aortic sclerosis or stenosis (OR per mg/dl, 1.12; 95% CI, 1.03-1.23; $p=0.008$) (14), adjusted for other clinical factors. In the FOS, levels of total cholesterol, which correlate highly with levels of LDL-C, in early adulthood strongly predicted the presence of AVC in later life (adjusted OR per SD, 1.81; 95% CI, 1.55-2.11; $p<0.0001$) (9). Retrospective studies have also shown that aortic stenosis patients treated with statins progressed less rapidly (25-27).

Building upon this body of evidence, three randomized controlled trials investigated the use of lipid-lowering therapies in delaying or reversing aortic stenosis progression. In the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE), 155 patients randomized to either atorvastatin (80 mg) or placebo were followed for a median of 25 months (28). The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial followed 1,873 patients with mild to moderate, asymptomatic aortic stenosis for a median of 52.2 months following randomization to simvastatin (40 mg) plus ezetimibe (10 mg) or placebo daily (29). In the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial, 269 patients were randomized to rosuvastatin (40 mg) or placebo daily and followed for a median of 3.5 years. No reductions in aortic stenosis progression were observed in any of these trials.

Although the results of these trials were disappointing, it would be premature to dismiss the therapeutic potential of statins for CAVD. In all three trials, patients had relatively advanced disease with elevated transaortic pressure gradients and mean aortic valve areas $>1.5 \text{ cm}^2$. Lipids may exert a larger influence on the initiation of the disease process and earlier intervention, perhaps among patients with aortic sclerosis, may be more effective. Mendelian randomization analysis performed in the Malmö Diet and Cancer Study demonstrated that genetically-elevated levels of LDL-C, reflecting a lifetime exposure to higher LDL-C, were causally associated with the incidence of aortic stenosis (hazard ratio [HR] per genetic risk score unit, 2.78; 95% CI, 1.22-6.37; $p=0.02$) (30). Moreover, individuals were not eligible to participate in the trials if they had clinical indications for cholesterol lowering, but these individuals would benefit most from intensive lipid-lowering therapies and their exclusion could underestimate the effectiveness of such regimens. While lipid-lowering therapies may be ineffective at delaying progression in advanced aortic stenosis cases, additional studies are warranted to assess the effectiveness of statins in early stage CAVD.

Adiposity—Several adiposity measures have been associated with greater risk for CAVD. In the MESA, metabolic syndrome and diabetes separately increased odds of developing AVC (OR, 1.67; 95% CI, 1.21-2.31 and 2.06; 95% CI, 1.39-3.06, respectively), adjusted for

clinical factors, but neither were associated with progression among participants with calcification at baseline (31). Diabetes was also associated with greater risk of incident aortic stenosis in the Cardiovascular Health in Ambulatory Care Research Team cohort, which featured a 13-year median follow-up period (HR, 1.49; 95% CI, 1.44-1.54; $p<0.001$) (32). Long-term mean of body mass index in adulthood was associated with the presence of AVC (OR per SD, 1.21; 95% CI, 1.05-1.40; $p=0.008$) in the FOS, adjusted for clinical factors. Being overweight or obese also conferred increased risk of incident aortic stenosis relative to normal weight (HR, 1.24; 95% CI, 1.05-1.48 and 1.81; 95% CI, 1.47-2.23, respectively). These findings indicate that increased adiposity confers risk for CAVD, but additional work is required to identify possible mechanisms, such as dysglycemia or dyslipidemia.

Kidney Dysfunction and Mineral Metabolism—CAVD is commonly observed among patients with renal failure, with AVC reported in 28% of individuals 70 years old with end stage renal disease (33). Kidney dysfunction has also been linked to more rapid progression of, and more severe, disease. Aortic stenosis patients undergoing dialysis progress more rapidly (change in valve area in cm^2/year , -0.19 ; range, -1.45 to 0.20 versus -0.07 ; range, -1.1 to 0.37 ; $p<0.001$), and dialysis remains an independent predictor of annualized changes in aortic valve area following adjustment for clinical variables (cm^2/year , -0.92 ; $p=0.02$) (34). Calcium, phosphate, and the calcium $\times$ phosphate product were elevated among end-stage renal disease patients with AVC (all $p<0.05$) (33). Among aortic stenosis patients treated with hemodialysis, greater serum calcium levels predicted faster progression (OR, 6.08; 95% CI, 1.28-28.8; $p=0.02$). In community cohorts, higher serum phosphate has also been associated with greater risk for AVC (RR per mg/dl , 1.3; 95% CI, 1.1-1.5; $p<0.001$) (35) as well as aortic sclerosis (OR per 0.5 mg/dl , 1.17; 95% CI 1.04-1.31; $p=0.01$) (36).

Emerging Risk Factors for CAVD

Family History—Recently, a few studies have suggested that aortic stenosis has a familial component. Using national registry data on 6.1 million Swedish siblings, including 13,442 cases of aortic stenosis, Martinsson and colleagues observed that 4.8% of aortic stenosis patients had a sibling with aortic stenosis, compared to 0.5% among the general population (37). Following adjustment for age, sex, family size, and comorbidities, individuals with a sibling history of aortic stenosis had more than three times the risk (HR, 3.41; 95% CI, 2.23-5.21). In contrast, having a spouse with aortic stenosis was associated with a smaller increase in risk (HR, 1.16; 95% CI, 1.05-1.28 for husbands and 1.18; 95% CI, 1.07-1.30 for wives), suggesting that shared environment in adulthood explains less risk than genetics. Using the Utah Population Database, which features linkage of genealogical records with death certificates, Horne and colleagues demonstrated that individuals who died of non-rheumatic aortic stenosis were on average more related than the average relatedness observed among matched controls (genealogical index of familiarity, 3.44 in cases versus 2.62 in controls; $p<0.001$) (38). When restricted to deaths before 65 years of age, the higher relatedness among cases was more pronounced, consistent with other partially heritable disorders (genealogical index of familiarity, 8.47 in cases versus 2.43 in controls; $p<0.001$). In regions of France with little population movement, the distribution of aortic stenosis cases

who undergo aortic valve replacement is heterogeneous and some families have a higher than expected disease prevalence (39,40), but these lines of evidence are weaker.

Lipoprotein(a)—A rapidly-growing body of evidence points to lipoprotein(a) as an important, potentially causal contributor to CAVD. A genome-wide association study (GWAS) performed in the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium associated a variant at the *LPA* locus, rs10455872, with both prevalent AVC (OR per G allele, 2.05; 95% CI, 1.66-2.53; $p=2.8\times 10^{-11}$) and incident aortic stenosis (HR per G allele, 1.68; 95% CI, 1.32-2.15; $p=3\times 10^{-5}$) (41). The association of this variant with aortic stenosis has since been robustly demonstrated in a number of cohorts (42-45). The *LPA* gene codes for apolipoprotein(a), and >90% of the variation in lipoprotein(a) levels has been attributed to genetic variation in *LPA* (46). The association of *LPA* with AVC and aortic stenosis therefore implicates elevated lipoprotein(a) as a risk factor for CAVD. Mendelian randomization studies have confirmed that this association is likely causal (41,43), pointing to lipoprotein(a) as a therapeutic target. Lipoprotein(a)-lowering agents are currently in development and randomized controlled trials have demonstrated remarkable reductions in lipoprotein(a) levels (47,48), paving the way for future trials investigating lipoprotein(a)-targeting therapeutics for arresting aortic stenosis progression.

Findings from Large-Scale Genetic Association Studies—Two large-scale GWAS for aortic stenosis have been reported in the years following the discovery of *LPA*. A study in the deCODE cohort and a transcriptome-wide association study in the QUEBEC-Cardiac Aortic Valve Stenosis cohort independently identified a variant in the *PALMD* locus as associated with aortic stenosis, with each copy of the risk allele conferring 20-28% greater odds for the disease (49,50). The genome-wide association study in deCODE additionally identified the *TEX41* variant rs1830321, which was associated with 15% greater odds for aortic stenosis per T allele (95% CI, 1.11-1.20; $p=1.8\times 10^{-13}$). Both the *PALMD* and *TEX41* variants were also associated with bicuspid aortic valves and atrial septal defects (all $p < 5.9\times 10^{-3}$), implicating congenital cardiac malformations as a mechanism for CAVD.

Risk Factors for MAC

Our understanding of the risk factors for MAC remains poor due to the relatively low prevalence of MAC in the general population leading to very few adequately-powered cohorts. As observed for CAVD, the most critical risk factor is older age. In the MESA, each 10-year increase was associated with 3.58 times the odds of MAC adjusted for clinical factors (95% CI, 3.18-4.03; $p<0.01$) (10). Body mass index and cigarette smoking also conferred elevated odds for MAC in both the MESA and the FOS, while diabetes was only associated in the MESA (adjusted OR, 1.58; 95% CI, 1.25-1.99) (9,10). In the FOS, chronic kidney disease was associated with 60% greater odds for MAC independent of clinical factors (95% CI, 1.03-2.5; $p<0.05$) (51).

Unlike CAVD, women may be more likely than men to have MAC. In the MESA, the odds were 41% higher for women (95% CI, 1.15-1.75) (10). However, female sex was not a predictor of MAC in the FOS (9). Conversely, C-reactive protein was associated with MAC in the FOS (adjusted OR per SD, 1.29; 95% CI, 1.10-1.52; $p=0.002$) but not in the MESA,

though it has not been associated with AVC in either cohort (9,15). Also notable was the lack of association for MAC with LDL-C. Rather, Mendelian randomization analyses supported a causal association with triglycerides in the Cohorts for Heart and Aging Research in Genomic Epidemiology cohort (OR per genetic risk score unit, 1.73; 95% CI, 1.24-2.41; $p=0.0013$) that persisted in sensitivity analyses accounting for genetic pleiotropy or the inclusion of Hispanic-Americans (52). This finding suggests that triglycerides may represent a new therapeutic target for the treatment or prevention of MAC.

Conclusion

Valvular calcification, manifesting as either CAVD or MAC, is particularly prevalent among the elderly. Strong evidence implicates atherosclerotic risk factors as increasing the risk of CAVD, and emerging evidence indicates family history, lipoprotein(a), and some genetic variants are also likely contributors. Risk factors for MAC overlap with those for CAVD, suggesting a shared aetiology, but female sex, C-reactive protein, and triglycerides may be more important for MAC. Among these are risk factors with potential for therapeutic targeting, though a better characterization of their contributions is warranted given the failure of statins in randomized controlled trials for aortic stenosis. Large-scale genetic analyses and Mendelian randomization may provide valuable insight in this regard.

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Abbreviations

AVC	Aortic Valve Calcium
CAVD	Calcific Aortic Valve Disease
CHS	Cardiovascular Health Study
CI	Confidence Interval
FOS	Framingham Offspring Study
HR	Hazard Ratio
LDL-C	Low-Density Lipoprotein Cholesterol
MAC	Mitral Annular Calcification
MESA	Multi-Ethnic Study of Atherosclerosis
OR	Odds Ratio
RR	Risk Ratio
SD	Standard Deviation

References

1. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. *J Am Coll Cardiol* 2014;63:2852–61. [PubMed: 24814496]
2. Clark MA, Arnold SV, Duhay FG et al. Five-year clinical and economic outcomes among patients with medically managed severe aortic stenosis: results from a Medicare claims analysis. *Circ Cardiovasc Qual Outcomes* 2012;5:697–704. [PubMed: 22949492]
3. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *Ann Thorac Surg* 2006;82:2111–5. [PubMed: 17126120]
4. Yutzey KE, Demer LL, Body SC et al. Calcific aortic valve disease: a consensus summary from the Alliance of Investigators on Calcific Aortic Valve Disease. *Arterioscler Thromb Vasc Biol* 2014;34:2387–93. [PubMed: 25189570]
5. Benjamin EJ, Virani SS, Callaway CW et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018;137:e67–e492. [PubMed: 29386200]
6. Osnabrugge RL, Mylotte D, Head SJ et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;62:1002–12. [PubMed: 23727214]
7. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. the Tromso study. *Heart* 2013;99:396–400. [PubMed: 22942293]
8. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: the AGES-Reykjavik study. *Int J Cardiol* 2014;176:916–22. [PubMed: 25171970]
9. Thanassoulis G, Massaro JM, Cury R et al. Associations of long-term and early adult atherosclerosis risk factors with aortic and mitral valve calcium. *J Am Coll Cardiol* 2010;55:2491–8. [PubMed: 20510217]
10. Kanjanathai S, Nasir K, Katz R et al. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2010;213:558–62. [PubMed: 20926076]
11. Fox CS, Vasan RS, Parise H et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003;107:1492–6. [PubMed: 12654605]
12. Atar S, Jeon DS, Luo H, Siegel RJ. Mitral annular calcification: a marker of severe coronary artery disease in patients under 65 years old. *Heart* 2003;89:161–4. [PubMed: 12527666]
13. Benjamin EJ, Plehn JF, D'Agostino RB et al. Mitral annular calcification and the risk of stroke in an elderly cohort. *N Engl J Med* 1992;327:374–9. [PubMed: 1625711]
14. Stewart BF, Siscovick D, Lind BK et al. Clinical factors associated with calcific aortic valve disease. *J Am Coll Cardiol* 1997;29:630–4. [PubMed: 9060903]
15. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD. Incidence and progression of aortic valve calcium in the Multi-ethnic Study of Atherosclerosis (MESA). *Am J Cardiol* 2010;105:701–8. [PubMed: 20185020]
16. Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. *Heart* 1997;78:472–4. [PubMed: 9415006]
17. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J* 1994;15:865–70. [PubMed: 7925504]
18. Capoulade R, Clavel MA, Mathieu P et al. Impact of hypertension and renin-angiotensin system inhibitors in aortic stenosis. *Eur J Clin Invest* 2013;43:1262–72. [PubMed: 24117162]
19. Tastet L, Capoulade R, Clavel MA et al. Systolic hypertension and progression of aortic valve calcification in patients with aortic stenosis: results from the PROGRESSA study. *Eur Heart J Cardiovasc Imaging* 2017;18:70–78. [PubMed: 26896413]
20. Linefsky J, Katz R, Budoff M et al. Stages of systemic hypertension and blood pressure as correlates of computed tomography-assessed aortic valve calcium (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol* 2011;107:47–51. [PubMed: 21146685]

21. Sera F, Russo C, Iwata S et al. Arterial wave reflection and aortic valve calcification in an elderly community-based cohort. *J Am Soc Echocardiogr* 2015;28:430–6. [PubMed: 25600036]
22. Balachandran K, Bakay MA, Connolly JM, Zhang X, Yoganathan AP, Levy RJ. Aortic valve cyclic stretch causes increased remodeling activity and enhanced serotonin receptor responsiveness. *Ann Thorac Surg* 2011;92:147–53. [PubMed: 21718840]
23. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb Vasc Biol* 1996;16:523–32. [PubMed: 8624774]
24. Novaro GM, Katz R, Aviles RJ et al. Clinical factors, but not C-reactive protein, predict progression of calcific aortic-valve disease: the Cardiovascular Health Study. *J Am Coll Cardiol* 2007;50:1992–8. [PubMed: 17996566]
25. Novaro GM, Tiong IY, Pearce GL, Lauer MS, Sprecher DL, Griffin BP. Effect of hydroxymethylglutaryl coenzyme A reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 2001;104:2205–9. [PubMed: 11684632]
26. Bellamy MF, Pellikka PA, Klarich KW, Tajik AJ, Enriquez-Sarano M. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. *J Am Coll Cardiol* 2002;40:1723–30. [PubMed: 12446053]
27. Rosenhek R, Rader F, Loho N et al. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation* 2004;110:1291–5. [PubMed: 15337704]
28. Cowell SJ, Newby DE, Prescott RJ et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;352:2389–97. [PubMed: 15944423]
29. Rossebø AB, Pedersen TR, Boman K et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343–56. [PubMed: 18765433]
30. Smith JG, Luk K, Schulz CA et al. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA* 2014;312:1764–71. [PubMed: 25344734]
31. Katz R, Budoff MJ, Takasu J et al. Relationship of metabolic syndrome with incident aortic valve calcium and aortic valve calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes* 2009;58:813–9. [PubMed: 19136658]
32. Yan AT, Koh M, Chan KK et al. Association Between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. *J Am Coll Cardiol* 2017;69:1523–1532. [PubMed: 28335833]
33. Maher ER, Young G, Smyth-Walsh B, Pugh S, Curtis JR. Aortic and mitral valve calcification in patients with end-stage renal disease. *Lancet* 1987;2:875–7. [PubMed: 2889080]
34. Perkovic V, Hunt D, Griffin SV, du Plessis M, Becker GJ. Accelerated progression of calcific aortic stenosis in dialysis patients. *Nephron Clin Pract* 2003;94:c40–5. [PubMed: 12845236]
35. Linefsky JP, O'Brien KD, Sachs M et al. Serum phosphate is associated with aortic valve calcification in the Multi-ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2014;233:331–7. [PubMed: 24530958]
36. Linefsky JP, O'Brien KD, Katz R et al. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. *J Am Coll Cardiol* 2011;58:291–7. [PubMed: 21737022]
- **37. Martinsson A, Li X, Zoller B et al. Familial Aggregation of Aortic Valvular Stenosis: A Nationwide Study of Sibling Risk. *Circ Cardiovasc Genet* 2017;10. National registry data were used to demonstrate that siblings of individuals with aortic stenosis are at high risk of aortic stenosis while spouses of aortic stenosis patients experience only a modest increase in their risk of the disease. This study highlights the large contribution of genetics to aortic stenosis risk, compared to a shared environment in adulthood.
38. Horne BD, Camp NJ, Muhlestein JB, Cannon-Albright LA. Evidence for a heritable component in death resulting from aortic and mitral valve diseases. *Circulation* 2004;110:3143–8. [PubMed: 15520309]
39. Le Gal G, Bertault V, Bezon E, Cornily JC, Barra JA, Blanc JJ. Heterogeneous geographic distribution of patients with aortic valve stenosis: arguments for new aetiological hypothesis. *Heart* 2005;91:247–9. [PubMed: 15657257]

40. Probst V, Le Scouarnec S, Legendre A et al. Familial aggregation of calcific aortic valve stenosis in the western part of France. *Circulation* 2006;113:856–60. [PubMed: 16461814]
41. Thanassoulis G, Campbell CY, Owens DS et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013;368:503–12. [PubMed: 23388002]
42. Arsenault BJ, Boekholdt SM, Dube MP et al. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. *Circ Cardiovasc Genet* 2014;7:304–10. [PubMed: 24704946]
43. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* 2014;63:470–7. [PubMed: 24161338]
44. Cairns BJ, Coffey S, Travis RC et al. A Replicated, Genome-Wide Significant Association of Aortic Stenosis With a Genetic Variant for Lipoprotein(a): Meta-Analysis of Published and Novel Data. *Circulation* 2017;135:1181–1183. [PubMed: 28320808]
- *45. Chen HY, Dufresne L, Burr H et al. Association of LPA Variants With Aortic Stenosis: A Large-Scale Study Using Diagnostic and Procedural Codes From Electronic Health Records. *JAMA Cardiol* 2018;3:18–23. [PubMed: 29128868] This paper describes how different combinations of genetic variation at the *LPA* locus confer increased odds of aortic stenosis in a large-scale cohort.
46. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest* 1992;90:52–60. [PubMed: 1386087]
47. Tsimikas S, Viney NJ, Hughes SG et al. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet* 2015;386:1472–83. [PubMed: 26210642]
48. Viney NJ, van Capelleveen JC, Geary RS et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet* 2016;388:2239–2253. [PubMed: 27665230]
49. Helgadóttir A, Thorleifsson G, Gretarsdóttir S et al. Genome-wide analysis yields new loci associating with aortic valve stenosis. *Nat Commun* 2018;9:987. [PubMed: 29511194]
50. Theriault S, Gaudreault N, Lamontagne M et al. A transcriptome-wide association study identifies PALMD as a susceptibility gene for calcific aortic valve stenosis. *Nat Commun* 2018;9:988. [PubMed: 29511167]
51. Fox CS, Larson MG, Vasan RS et al. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. *J Am Soc Nephrol* 2006;17:521–7. [PubMed: 16382018]
- **52. Afshar M, Luk K, Do R et al. Association of Triglyceride-Related Genetic Variants With Mitral Annular Calcification. *J Am Coll Cardiol* 2017;69:2941–2948. [PubMed: 28619195] Using Mendelian randomization techniques, this study demonstrated that genetic elevation of triglycerides may cause mitral annular calcification. This finding indicates that triglycerides may be a therapeutic target for mitral valve disease.

Key Points

- Atherosclerotic risk factors have been well established as increasing the risk of calcific aortic valve disease
- Emerging risk factors for calcific aortic valve disease include a family history of the disease, lipoprotein(a), and genetic variants
- Large-scale genetic analyses and Mendelian randomization studies have identified risk loci with strong evidence of association with aortic stenosis
- Current understanding of the risk factors for mitral annular calcification is limited. While a subset of atherosclerotic risk factors has been shown to increase mitral annular calcification risk, the evidence was inconsistent for some others and non-atherosclerotic risk factors have not been well studied

Table 1.

Summary of Evidence for Risk Factors for Calcific Aortic Valve Disease.

Risk Factor	Strength of Evidence	
	Observational Studies	Genetic Studies
Established Risk Factors		
Older Age	+++	n/a
Male Sex	+++	n/a
Cigarette Smoking	++	n/a
Blood Pressure and Vascular Stiffness	++	n/a
Dyslipidemia	^a +	+++
Adiposity	++	n/a
Kidney Dysfunction and Mineral Metabolism	++	n/a
Emerging Risk Factors		
Family History	+	n/a
Lipoprotein(a)	++	+++
Findings from Large-Scale Genetic Association Studies	n/a	++

+++ , strong evidence of increased risk; ++ , moderate evidence of increased risk; + , weak evidence of increased risk; n/a , not available.

^aDiscrepant findings between observational studies and randomized controlled trials.

Table 2.

Summary of Evidence for Risk Factors for Mitral Annular Calcification.

Risk Factor	Strength of Evidence	
	Observational Studies	Genetic Studies
Established Risk Factors		
Older Age	+++	n/a
Adiposity	+	n/a
Cigarette Smoking	++	n/a
Triglycerides	n/a	++
Emerging Risk Factors		
Kidney Dysfunction	+	n/a
Female Sex	+	n/a
C-Reactive Protein	+	n/a

+++ , strong evidence of increased risk; ++ , moderate evidence of increased risk; + , weak evidence of increased risk; n/a , not available.