Review

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Calcific aortic valve disease and atherosclerotic cardiovascular disease

Shared and distinct mechanisms and treatment strategies

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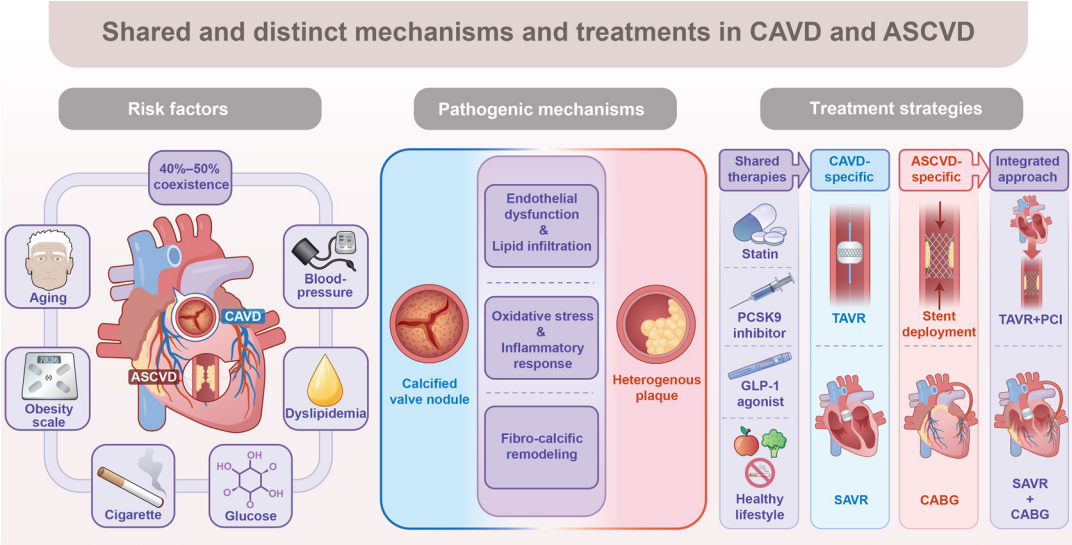
Graphical abstract



Abstract

Calcific aortic valve disease (CAVD) and atherosclerotic cardiovascular disease (ASCVD) represent two major cardiovascular disorders that frequently coexist and share overlapping risk factors and pathophysiological processes, yet also exhibit distinct features that shape their progression and management. This review synthesizes current evidence on their common mechanisms—including endothelial dysfunction, lipid infiltration, oxidative stress, and inflammatory activation—and highlights disease-specific pathways in CAVD versus ASCVD. Therapeutically, both conditions benefit from risk factor modification, diabetes control, and emerging agents such as glucagon-like peptide-1 receptor agonists. Divergent treatment strategies are defined by surgical or transcatheter valve replacement for CAVD, often integrated with percutaneous or surgical revascularization for concomitant ASCVD. This review underscores the need for mechanistically informed and integrative approaches to improve outcomes in patients burdened by these interrelated conditions.

Keywords: calcific aortic valve disease, coronary artery disease, pathogenic mechanisms, treatment strategies

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Highlights

- CAVD & ASCVD share endothelial dysfunction, lipid infiltration, and oxidative stress.
- Caveolin-1/FGF2 axis drives EndMT in valves and VSMC remodeling in arteries.
- CAVD uniquely involves osteogenic remodeling of valvular interstitial cells.
- Integrated TAVR and coronary revascularization optimize comorbid outcomes.

1. Introduction

Calcific aortic valve disease (CAVD) and atherosclerotic cardiovascular disease (ASCVD) are two prominent cardiovascular conditions that significantly contribute to morbidity and mortality worldwide.[1] The prevalence of these diseases is notably increasing, particularly in aging populations, and they share several common risk factors, including hypertension, dyslipidemia, and smoking. Studies indicate that up to 40%–50% of patients with CAVD have concomitant coronary artery disease (CAD), a comorbidity that is associated with higher rates of adverse cardiovascular events and poorer long-term outcomes.[2] This strong association is largely attributed to shared pathobiological mechanisms and risk factors, including age, hypertension, dyslipidemia, diabetes, obesity, smoking, and metabolic syndrome. It has been proposed that CAVD could serve as a marker of subclinical CAD, and vice versa. However, the clinical trajectories diverge, as valvular calcification progresses through osteogenic and fibro-calcific remodeling rather than plaque formation. Previous reviews have mainly focused on either the cellular and molecular mechanisms of each disease or on the shared risk factors between valvular and coronary atherosclerosis. The present review provides a comprehensive synthesis of the overlapping and distinct molecular pathways underlying CAVD and ASCVD, highlights novel regulatory axes, and discusses current and potential therapeutic approaches.

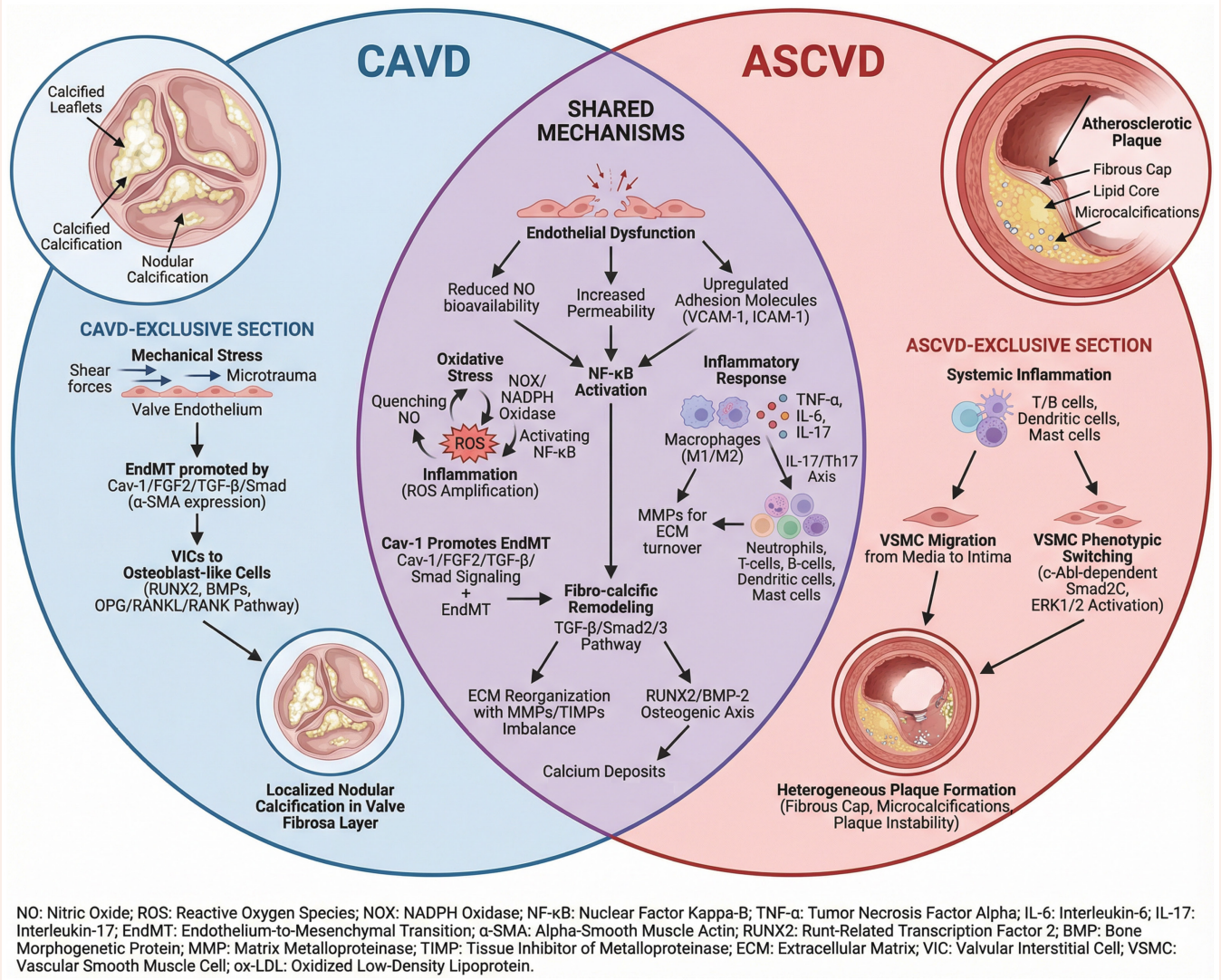
2. Common and divergent pathogenic mechanisms

The shared and disease-specific mechanisms underlying CAVD and ASCVD are summarized in Figure 1, including endothelial dysfunction and lipid infiltration, oxidative stress and inflammatory response, and fibro-calcific remodeling. Recent advances in multi-omics approaches, including bulk and single-cell transcriptomics, proteomics, and integrative epigenomic analyses, have substantially advanced our understanding of these processes by resolving cell-type-specific programs and molecular networks that drive the initiation and progression of CAVD.[3–5]

2.1. Endothelial dysfunction and lipid infiltration

Endothelial dysfunction is increasingly recognized as a pivotal event in the pathogenesis of both CAVD and CAD. This dysfunction is characterized by a series of alterations in endothelial cell function, including impaired vasodilation, increased permeability, and heightened inflammatory responses, which collectively contribute to the initiation and progression of these conditions.[6,7] For CAVD, abnormal mechanical forces exerted on the aortic valve caused by altered flow patterns result in microtrauma to the valvular endothelium, which promotes the build-up of lipids subendothelially.[8] Similarly, in ASCVD, altered shear stress at arterial branch points promotes endothelial activation and subendothelial lipid retention, which together drive the development of atherosclerotic lesions and the associated inflammatory response.[9] These changes in the integrity of the endothelium are mediated by oxidative stress and the downstream activation of inflammatory transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), which further amplify endothelial cell dysfunction.

At a molecular level, endothelial dysfunction manifests as a reduced bioavailability of nitric oxide (NO) and adhesion molecule upregulation, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).[10,11] In CAVD, the localized endothelial injury aligns with mechanical stress, triggering an endothelium-to-mesenchymal transition (EndMT) that is less prominent in the diffuse and laminar flow-associated vascular injury observed in ASCVD.[12] The spatially restricted biomechanical microenvironment of the aortic valve favors sustained activation of transforming growth factor-β (TGF-β)/small mothers against decapentaplegic (Smad) signaling and inflammatory mediators. In CAVD, caveolin-1 (Cav-1) has been shown to affect the bioavailability of fibroblast growth factor 2 (FGF2).[13] The dysregulation of this axis that regulates the regulates protein kinase B, extracellular signal-regulated kinase (ERK), and Smad pathways can lead to increased endothelial permeability and subsequent lipid infiltration, exacerbating the calcific process in the aortic valve. Zhu and Lai[14] demonstrated that Cav-1 promotes EndMT by facilitating FGF2 binding to its receptor and enhancing TGF-β/Smad signaling, which ultimately drives valvular interstitial cell (VIC) activation and valvular calcification. Similarly, in ASCVD, Cav-1 functions as a signaling scaffold for growth factor receptors and endothelin-1, integrating NADPH oxidase (NOX)-derived redox signaling and c-Abl–dependent phosphorylation events to modulate Smad2C and ERK1/2 activation in vascular smooth muscle cells (VSMCs), promoting vascular remodeling and plaque fibrosis.[15] Moreover, Cav-1 differentially regulates canonical and noncanonical TGF-β and epidermal growth factor receptor pathways, establishing it as a dynamic modulator of both fibrotic and proliferative signaling responses relevant to cardiovascular pathology.[16] Thus, while Cav-1–mediated signaling underlies endothelial dysfunction in both CAVD and ASCVD, the distinct mechanical and hemodynamic contexts determine the extent and outcome of EndMT activation, explaining its greater prominence in the valvular environment.



NO: Nitric Oxide; ROS: Reactive Oxygen Species; NOX: NADPH Oxidase; NF-κB: Nuclear Factor Kappa-B; TNF-α: Tumor Necrosis Factor Alpha; IL-6: Interleukin-6; IL-17: Interleukin-17; EndMT: Endothelium-to-Mesenchymal Transition; α-SMA: Alpha-Smooth Muscle Actin; RUNX2: Runt-Related Transcription Factor 2; BMP: Bone Morphogenetic Protein; MMP: Matrix Metalloproteinase; TIMP: Tissue Inhibitor of Metalloproteinase; ECM: Extracellular Matrix; VIC: Valvular Interstitial Cell; VSMC: Vascular Smooth Muscle Cell; ox-LDL: Oxidized Low-Density Lipoprotein.

Figure 1. Shared and divergent pathogenic mechanisms of calcific aortic valve disease and atherosclerotic cardiovascular disease.

Although they shared initiation of endothelial dysfunction and lipid infiltration, the microenvironment in the aortic valve exhibits distinct characteristics compared with the coronary arteries. In CAVD, the restricted and highly mechanical environment of the aortic valve predisposes the tissue to calcific remodeling through the activation of osteogenic signaling pathways in VICs. These cells, under stress conditions, express bone-related transcription factors such as runt-related transcription factor 2 (RUNX2) and bone morphogenetic proteins (BMPs) that drive calcification.[17,18] Conversely, the coronary arterial wall is more susceptible to diffuse infiltration by inflammatory cells and smooth muscle cell proliferation, which culminate in heterogeneous plaque formation and atheroma development.[8,9]

2.2. Oxidative stress and inflammatory response

Oxidative stress and inflammation are two core processes that interact with each other in the pathogenesis of aortic valve calcification and coronary artery atherosclerosis. A variety of mechanisms, such as mitochondrial dysfunction, inflammation, lipid peroxidation, etc., produce reactive oxygen species (ROS) and lead to endothelial dysfunction and smooth muscle cell proliferation. In the pathophysiology of CAVD, oxidative stress favors the osteogenic transition of VICs, resulting in ectopic calcification, and the presence of oxidized low-density lipoprotein (ox-LDL), which not only acts as a pro-inflammatory stimulus but also promotes the infiltration of macrophages into the injured site to maintain a vicious cycle of inflammation and oxidative damage. This inflammatory environment releases pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin (IL)-6, which exacerbate oxidative stress conditions and recruit more immune cells, leading to a vicious cycle that promotes both calcification and atherosclerosis.[19,20]

Macrophages exhibit distinct polarization states that significantly influence the progression of both diseases.

In CAVD, macrophages can adopt a pro-inflammatory M1 phenotype, which promotes fibrosis and calcification through the secretion of inflammatory cytokines and matrix metalloproteinases (MMPs). Conversely, the M2 phenotype, which is associated with tissue repair and remodeling, can also contribute to calcific processes by promoting fibroblast activation and osteogenic differentiation. This polarization is influenced by the local microenvironment, including the presence of ox-LDL and other inflammatory mediators that are prevalent in atherosclerotic plaques and calcified valves. Other key cells include neutrophils, dendritic cells, mast cells, and T/B-cells. The IL-17/Th17 axis operates as a shared inflammatory amplifier in both diseases: IL-17A activates endothelial cells and licenses neutrophil recruitment while reprogramming macrophages toward chemokine-high, protease-rich states, thereby priming MMP-driven extracellular matrix (ECM) turnover that links upstream endothelial/lipid disturbances to downstream fibro-calcific remodeling. In CAVD, human valves and primary valve cells express IL-17RA, and IL-17A augments inflammatory signaling in valve endothelium and promotes RUNX2-dependent osteogenic programming.[21] IL-17RA expression is elevated in leukocytes from patients with early-onset CAD, and its promoter region polymorphisms influence transcriptional levels, suggesting that the IL-17 system may exert a gene regulatory role in CAD pathogenesis.[22]

Subtle differences of inflammatory response between two diseases can be identified. In atherosclerosis, the inflammatory response tends to be systemic, with a complex crosslinking between a variety of immune cells, such as macrophages, T-cells, and B-cells, resulting in plaque formation and instability; in aortic valve calcification, the inflammatory response is localized, with VICs and the surrounding ECM undergoing pathological remodeling as the principal targets of pathological remodeling. This localized inflammation is driven by mechanical stress and hemodynamic changes that further increase oxidative stress and favor calcification.[11,23] The importance of oxidative stress as an intermediary linking inflammation to calcification is highlighted by reports showing how ROS can trigger signaling cascades that drive expression of osteogenic markers in VICs to encourage calcification. Inhibition of oxidative stress or regulation of inflammatory mechanisms may be potential avenues of treatment for both disorders, suggesting the necessity of targeted therapies aimed at addressing these two intertwined processes.[24,25]

2.3. Fibro-calcific remodeling

Fibro-calcific remodeling in CAVD and ASCVD emerges from a common inflammatory–stromal program. Within the valvular microenvironment, quiescent VICs are activated and acquire a myofibroblastic phenotype characterized by α-SMA upregulation through the TGF-β/Smad2/3 signaling axis. Under sustained inflammatory stimulation, particularly via IL-6 and tumor necrosis factor-α–induced NF-κB activation in cooperation with osteogenic mediators such as BMP-2 and RUNX2, these cells undergo osteoblast-like differentiation and deposit calcific nodules within the fibrosa layer. Concomitantly, EndMT and an imbalance between MMPs and their tissue inhibitors promote the reorganization of collagen type I and III fibers and the fragmentation of elastin, ultimately leading to an irreversible fibro-calcific remodeling loop.[17,26] In the arterial wall, VSMCs undergo phenotypic modulation from contractile toward synthetic and osteogenic states that shape fibrous-cap architecture and stability.[27] Imbalance of matrix metalloproteinases and their inhibitors promotes collagen and elastin reorganization and increases tissue stiffness, while apoptotic bodies and calcifying extracellular vesicles nucleate microcalcifications that can mature into macrocalcific deposits.

Although both diseases share IL-1β/IL-6/IL-17, NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3)–IL-18, RUNX2/BMP-2, and MMP-driven ECM remodeling, the cells that execute calcification and the surrounding microenvironment differ. In CAVD, fibrous tissue accumulates in the inflammatory valve microenvironment, where ECM remodeling promotes the transition of quiescent VICs into myofibroblasts that subsequently differentiate into osteoblast-like cells.[28] This transformation involves several osteogenic signaling cascades, including the osteoprotegerin/receptor activator of NF-κB (RANK)/receptor activator of NF-κB ligand (RANKL) pathway and TGF-β/Smad2/3 signaling, which together drive osteocalcification and the formation of discrete nodular calcifications within the fibrosa layer.[28,29] In contrast, atherosclerotic remodeling occurs primarily in the arterial wall, where VSMCs migrate from the medial layer into the intima in response to inflammatory and lipid cues. These VSMCs synthesize ECM components and contribute to fibrous-cap formation, while prolonged inflammatory stimulation induces their phenotypic modulation toward osteogenic or chondrogenic states, promoting microcalcification within the cap. Thus, valve disease reflects osteogenic transformation of myofibroblasts within an avascular, mechanically stressed leaflet, whereas atherosclerosis reflects migration and remodeling of smooth muscle cells in a lipid-rich, vascularized wall that shapes plaque stability.[27]

3. Treatment strategies

3.1. Common treatment strategies

Building upon the shared pathophysiological mechanisms discussed above, several molecular mediators act as converging nodes that link endothelial dysfunction, oxidative inflammation, and fibro-calcific remodeling in both CAVD and ASCVD. Table 1 summarizes these shared molecular mediators, their biological roles, and translational opportunities that provide a rationale for the subsequent therapeutic strategies.

3.1.1. Risk factor modification and lifestyle interventions. Weight control and diabetes management

Table 1

Shared molecular mediators linking CAVD and ASCVD and their translational implications.

Shared process	Molecular mediator/ pathway	Role across CAVD & ASCVD	Candidate interventions
Endothelial dysfunction & lipid infiltration	NO/eNOS	• Reduced NO impairs endothelial barrier and vasoprotection • Upregulates adhesion molecules and increases lipid permeability	eNOS activation; ACEi/ARB; GLP-1RA; exercise/shear-stress optimization
	VCAM-1/ ICAM-1	• Promote leukocyte adhesion and transendothelial migration • Early common event linking endothelium to inflammatory lipid entry	Antiadhesion/anti-inflammatory strategies
	EndMT	• Integrates mechanical cues with phenotypic switching • Bridges endothelial dysfunction to fibro-calcific remodeling	Anti-EndMT approaches; TGF-β/Smad modulation
	Caveolin-1/FGF2 axis	• Regulates endothelial transcytosis and permeability • Coordinates EndMT and lipid handling in valve and vascular beds	Target Cav-1/FGF2 interaction; fine-tune downstream signaling
	Ox-LDL → TLRs → NF-κB	• Oxidized lipids activate innate immune receptors • Converges lipid signals with inflammatory transcriptional programs	TLR antagonism; NF-κB modulators
Oxidative stress & inflammatory response	NOX-derived ROS	• Major source of ROS leading to NO quenching • Amplifies osteogenic and inflammatory signaling cascades	Selective NOX inhibitors; antioxidant strategies
	NF-κB hub (with IL-6/ TNF-α; IL-17/Th17 axis)	• Central transcriptional hub for oxidative–inflammatory amplification • Links innate/adaptive cytokines to tissue remodeling	IL-6R blockade; targeted anti-cytokine strategies; NF-κB modulation
Fibrotic remodeling	TGF-β/Smad2/3	• Master regulator of fibrosis integrating endothelial and mesenchymal programs • Drives transition toward osteogenic and collagen-rich states	Selective TGF-β/Smad modulation; anti-EndMT strategies
	RUNX2/BMP-2 osteogenic axis	• Terminal osteogenic program in VIC/VSMC • Promotes calcific nodule formation and mineralization	Downstream osteogenic inhibition; BMP pathway modulation
	MMPs/TIMPs	• Dysregulated ECM degradation and crosslinking • Contributes to leaflet stiffening and cap vulnerability	Selective MMP inhibition; ECM-protective strategies
	OPG/RANK/ RANKL	• Bone-like differentiation and calcific nodule pathways • Shared osteo-immunomodulatory signaling	RANKL inhibition

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; ASCVD = atherosclerotic cardiovascular disease; BMP = bone morphogenetic protein; Cav-1 = caveolin-1; CAVD = calcific aortic valve disease; ECM = extracellular matrix; EndMT = endothelial-to-mesenchymal transition; eNOS = endothelial nitric oxide synthase; FGF2 = fibroblast growth factor 2; GLP-1RA = glucagon-like peptide-1 receptor agonists; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; MMPs = matrix metalloproteinases; NF-κB = nuclear factor kappa-B; NO = nitric oxide; NOX = NADPH oxidase; OPG = osteoprotegerin; ox-LDL = oxidized low-density lipoprotein; RANK/RANKL = receptor activator of nuclear factor κB (ligand); ROS = reactive oxygen species; RUNX2 = runt-related transcription factor 2; Smad = small mothers against decapentaplegic proteins; TGF = transforming growth factor-β; Th17 = T helper 17 cells; TIMPs = tissue inhibitors of metalloproteinases; TLRs = Toll-like receptors; TNF-α = tumor necrosis factor-α; VCAM-1 = vascular cell adhesion molecule-1; VIC = valvular interstitial cell; VSMC = vascular smooth muscle cel.

are pivotal in mitigating the risks associated with CAVD and CAD. Obesity is linked to increased inflammation and metabolic dysregulation, which can accelerate the progression of both diseases. Therefore, lifestyle interventions aimed at weight loss, including dietary modifications and increased physical activity, are recommended. Additionally, managing diabetes effectively is crucial, as hyperglycemia has been associated with an increased risk of aortic valve calcification. Strategies such as continuous glucose monitoring and individualized diabetes care plans can help optimize glycemic control and reduce the risk of cardiovascular complications.[30]

Furthermore, the role of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the management of CAVD and CAD is gaining attention. These agents not only aid in glycemic control but also exhibit cardiovascular benefits, including weight loss and improved lipid profiles. Recent studies have shown that GLP-1RAs can reduce the risk of major cardiovascular events in patients with type 2 diabetes, which may extend to those with CAVD and CAD. Their multifaceted effects on the cardiovascular system make them a promising therapeutic option in this patient population.[31]

3.1.2. Lipid-lowering therapies. Statin therapy has been a fundamental part of ASCVD treatment for decades, as it has been shown to decrease LDL cholesterol levels as well as cardiovascular events. Statins exert multiple effects through improving endothelial function, decreasing oxidative stress, and inhibiting inflammatory pathways.[32] In ASCVD, these effects translate into significant clinical benefits, including plaque stabilization and regression, which have been reinforced by multiple randomized controlled trials. However, while the biochemical rationale suggests that statins might similarly benefit patients with CAVD, clinical trials have repeatedly demonstrated that aggressive LDL-cholesterol (LDL-C) lowering does not notably slow the progression of aortic valve calcification.[17] Trials such as Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) have highlighted the paradox in which the dramatic lowering of LDL-C

with statin therapy does not correlate with improvements in outcome on the valve, implying that the mechanism underlying CAVD is more complex than the accumulation of lipids.[33] New lipid-lowering agents such as PCSK9 inhibitors have further enriched the toolbox for ASCVD by further lowering LDL-C and reducing cardiovascular event rates.[34] For aortic stenosis, randomized trials Simvastatin and Ezetimibe in Aortic Stenosis (SEAS), and Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) consistently demonstrated no benefit.[35] However, recent evidence indicates that within the aortic valve microenvironment, PCSK9 functions not only as a regulator of lipid metabolism; its overexpression in VICs enhances calcium deposition and upregulates osteogenic markers, indicating that PCSK9 exerts a direct pro-calcific effect.[36] Furthermore, *in vitro* studies demonstrate that silencing or neutralizing PCSK9 attenuates pro-calcification responses.[37] Retrospective real-world cohorts suggest that evolocumab use is associated with significantly slower hemodynamic progression in patients with moderate aortic stenosis, aligning with the aforementioned molecular and cellular evidence.[38] Prospective results from trials such as Evaluation of PCSK9 Inhibition in Subjects with Elevated Lipoprotein(a) for Aortic Valve Disease (EPISODE) are anticipated. Therefore, the role of PCSK9 inhibitor in CAVD is still pending, and evidence for a role in altering valve calcification awaits further definition. This difference likely reflects key biological distinctions between vascular and valvular disease. In CAVD, lipid accumulation triggers early inflammation that gradually progresses to irreversible fibro-calcific remodeling, often beyond the stage where statins can provide benefit. In addition, differences in patient selection, disease severity, and timing of treatment across trials, as well as the unique characteristics of the aortic valve, such as low lipid turnover, high mechanical stress, and osteogenic activation of VICs, may further explain the limited effect of statins. These factors highlight the need for mechanism-based therapies, including PCSK9 inhibitors or anti-inflammatory agents, that can act earlier and more specifically on the molecular pathways driving valve calcification. Consequently, though lipid-lowering strategies are a common area of treatment, the varying responses in ASCVD and CAVD emphasise divergent pathobiological dependencies on cholesterol management.

3.1.3. Anti-inflammatory approaches. The recognition that inflammation plays a central role in the progression of both ASCVD and CAVD has spurred interest in anti-inflammatory therapies. In ASCVD, agents such as colchicine have been integrated into treatment protocols based on evidence from clinical trials demonstrating reductions in cardiovascular events through modulation of inflammatory pathways. Additionally, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial provided compelling evidence that targeted anti-IL-1β therapy reduces recurrent cardiovascular events in postmyocardial infarction patients, thereby establishing inflammation as a discrete and modifiable therapeutic target.[39] Although similar inflammatory mediators are involved in CAVD, anti-inflammatory strategies have not yet been rigorously evaluated in clinical trials for valve disease. Preclinical data suggest that agents capable of modulating macrophage activation and cytokine release may reduce valvular calcification, yet the translation of these results into the clinical arena remains preliminary.[40] Analysis of 578 patients revealed that the IL6 rs1800795 polymorphism is significantly associated with calcific aortic stenosis, with CC genotype carriers exhibiting markedly elevated circulating IL-6 levels (23.5 vs. 10.5 pg/mL), implicating IL-6 signaling in disease susceptibility.[41] This genetic evidence supports the exploration of IL-6 pathway inhibition, potentially via selective receptor blockade, as a promising anticalcific intervention pending preclinical validation in valve models. In parallel, according to the pathology of TGF-β/Smad signaling axis in CAVD, inhibition of TGF-β1 or partial loss of Smad3 significantly reduced valvular calcification and osteogenic gene expression in murine models, confirming the causal role of canonical TGF-β signaling in disease progression.[42] Multi-omics analyses further identified TGF-β1 as an epigenetically regulated driver of inflammatory and fibrotic pathways in human CAVD. At the post-transcriptional level, noncoding RNAs help regulate TGF-β signaling. CircANKRD36 suppresses TGF-β/Smad pathway activation and reduces VIC calcification, whereas miR-21-5p promotes calcification by inhibiting the TGF-β–induced gene TGFBI.[43] Additional early-phase or preclinical avenues include NOD-, LRR-, and NLRP3 inflammasome inhibitors and GLP-1 receptor agonism, which have shown anti-inflammatory or antiosteogenic effects in relevant cardiovascular settings but remain to be established in valve disease.[31,44] Novel therapeutic interventions aimed at these pathways hold promise for preventing the progression of valvular fibrosis and calcification toward irreversible remodeling.

3.2. Divergent treatment strategies

The management of CAVD in conjunction with CAD has evolved significantly, particularly with the advent of transcatheter aortic valve replacement (TAVR) and its combination with percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG). TAVR alone has demonstrated clinical efficacy in patients with CAVD and CAD, providing a less invasive alternative to surgical aortic valve replacement (SAVR). SAVR remains the gold standard for patients with severe aortic stenosis, particularly in those with low surgical risk and anatomical suitability for traditional surgical approaches. Studies indicate that TAVR can improve hemodynamics and alleviate symptoms in patients with severe aortic stenosis, even in those with concomitant CAD, leading to favorable outcomes in terms of mortality and quality of life.[45,46] However, the presence of CAD complicates the treatment landscape, necessitating careful consideration of the timing and type of intervention.

When comparing TAVR combined with PCI in patients with CAVD and CAD, studies have demonstrated that this combined approach can offer significant advantages. In selected high-risk patients, combining TAVR with PCI may be associated with improved outcomes compared with either strategy alone. The rationale of the combination is that the correction of both valvular and coronary pathologies can maximize the hemodynamic condition and minimize the risk of adverse cardiovascular events.[47] However, the optimal timing for these interventions remains a matter of debate, with some studies suggesting that performing PCI before TAVR may reduce the risk of complications.[48] In complex cases where patients present with significant comorbidities and anatomical challenges, the combination of TAVR and CABG may be necessary. The feasibility of this approach has been supported by emerging evidence, demonstrating that patients undergoing TAVR followed by CABG can achieve satisfactory outcomes, although careful patient selection is crucial.[49] Ultimately, the choice between TAVR, SAVR, and their combinations with PCI or CABG should be individualized, taking into account the patient's specific clinical scenario, preferences, and the multidisciplinary heart team's recommendations. The surgical team must weigh the risks of simultaneous procedures against the potential benefits of comprehensive treatment, considering factors such as the patient's overall functional status, the extent of CAD, and the anatomical characteristics of the aortic valve and coronary arteries.

4. Future perspectives

Emerging advances in circulating biomarkers, imaging technologies, and artificial intelligence (AI) are transforming the early detection and precision management of both CAVD and CAD. Biomarkers such as fetuin-A, oxidized high-density lipoprotein, and specific microRNAs such as miR-21-5p and miR-126-3p have been linked to inflammatory activation, offering potential for early diagnosis and prognostic stratification in CAVD.[50,51] In CAD, biomarkers such as high-sensitivity troponin, matrix Gla protein, and acetate have been linked to arterial calcification and metabolic remodeling. Advanced imaging modalities such as ^{18}F-sodium fluoride positron emission tomography/computed tomography (^{18}F-NaF PET/CT) and 4D flow magnetic resonance imaging now enable *in vivo* assessment of valvular inflammation, wall shear stress, and early calcific activity, while coronary CT angiography and AI-enhanced PET/CT improve characterization of vulnerable plaques.[52,53] Deep learning-based models applied to coronary CT angiography can automatically quantify plaque burden and stenosis severity, improving the prediction of major adverse cardiac events beyond traditional clinical risk factors.[54] These developments illustrate the shared potential of AI to enhance early detection of fibro-calcific remodeling and microvascular dysfunction across both diseases. The clinical translation of AI-based models into standardized workflows, regulatory frameworks, and outcome-driven trials remains an essential next step to fully realize their impact in both CAVD and CAD management.

5. Conclusion

Although CAVD and CAD are clinically very different, their risk factors and pathogenesis are highly similar. Endothelial dysfunction, oxidative stress, inflammation, and immune response are common driving factors, but the different remodeling mechanisms of diseases separate the aortic valve osteogenic calcification and coronary artery fibroatherosclerosis. Current treatment of valve disease is therefore still largely surgical, with TAVR and SAVR being the cornerstones of care, frequently with PCI or CABG in the presence of CAD. Looking beyond these procedures, mechanistic studies and translation of preclinical findings to targeted therapies will be crucial to inform procedural approaches and enhance long-term outcomes. Integration of emerging biomarkers, imaging tools, and AI-driven models into clinical workflows may accelerate early detection and precision management, bridging the gap between experimental discovery and real-world application.

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Ethics statement

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Date availability statement

Data sharing is not applicable to this article as all data discussed are derived from previously published studies.

Author contributions

Conceptualization: Tong Tan and Hao Cui.

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