BEMS Reports, 2025; 11(1):14-17.
https://www.bemsreports.org

Brief Report

Unravelling the Role of Sphingosine-1-Phosphate Signaling in Promoting Aortic Stenosis

Arun HS Kumar

School of Veterinary Medicine, University College Dublin, Belfield, Dublin, IRELAND.

ABSTRACT

Aortic Stenosis (AS) is one of the most common life-threatening cardiovascular conditions, particularly among the aging population. AS is characterized by the progressive narrowing of the aortic valve due to calcific degeneration, leading to increased left ventricular workload, heart failure, and ultimately, mortality if left untreated.[1,2] Historically, AS has been considered a passive degenerative disease associated with aging and mechanical stress. However, recent research has shed light on the active molecular and cellular mechanisms that drive its progression.[1,3] One such emerging pathway of interest is Sphingosine-1-Phosphate (S1P) signalling, which has been identified as a crucial modulator of osteogenic differentiation and valvular calcification. The recent study offers critical insights into the mechanistic role of S1P signalling in AS and proposes a potential therapeutic avenue for intervention.[3]

Keywords: Sphingosine-1-Phosphate, Network pharmacology, Calcification, Valves, Hemodynamics.

Correspondence
Dr. Arun HS Kumar
School of Veterinary Medicine, University College Dublin, Belfield, Dublin-04, IRELAND.
Email: arun.kumar@ucd.ie

Received: 07-01-2025;
Revised: 21-02-2025;
Accepted: 14-03-2025.

INTRODUCTION

The current treatment options for patients with AS depend on the severity of the condition, symptoms, and the patient's overall health.[4,5] The relative clinical efficacy of each of these approaches used for clinical management of AS depends on patient characteristics, disease severity, and long-term outcomes (Table 1). The current options available are: Surgical Aortic Valve Replacement (SAVR), Transcatheter Aortic Valve Replacement (TAVR), and Balloon Valvuloplasty, along with medical management considerations.

Treatment options for aortic stenosis

Monitoring and Medications (For Mild to Moderate Cases)

The regular monitoring of patients with mild aortic stenosis who may not need immediate surgical intervention involves periodic echocardiograms. In addition, medications (Beta-blockers, Diuretics, ACE inhibitors or ARBs and/or Statins) are used to manage the symptoms and associated conditions.[6,7] This approach is only supportive and does not treat the underlying valve narrowing. It is the best option for patients with mild-to-moderate AS or those who are not candidates for surgery. This option alone cannot prevent disease progression. Eventually, most patients will require valve replacement with median survival for symptomatic severe AS without intervention being 2-3 years. The limitations in the pharmacological based management of AS is largely due to our lack of understanding of the AS pathophysiology.

Aortic Valve Replacement (For Severe Cases)

Here two options are used i.e.,

Surgical Aortic Valve Replacement (SAVR) by Open-heart surgery to replace the narrowed valve with a mechanical or biological valve. SAVR is the gold standard for low-to-intermediate risk surgical candidates with severe AS.[8,9] The Operative mortality is reported to be ~1-3% (varies by patient risk profile), with mechanical valves lasting for >20 years, while biological valves last for 10-15 years. SAVR achieves excellent symptom relief, restores normal life expectancy in many patients improving the overall Quality of Life (QoL). SAVR is best suited for younger (<65 years) low-risk patients and those needing concurrent open-heart surgery (e.g., CABG). The major limitation of SAVR approach is it requires open-heart surgery with longer recovery time.

Transcatheter Aortic Valve Replacement (TAVR) performed by a minimally invasive procedure where a catheter is used to implant a new valve without open-heart surgery. TAVR is usually the preferred option for high-risk or elderly patients. TAVR is similar or superior to SAVR in high-risk and elderly patients.[10,11] The symptomatic relief and restoration of normal life expectancy is comparable to SAVR but with faster recovery time. It is best suited for older adults (≥65-80 years), high-risk

OPEN ACCESS
Manuscript TECHNOMEDIA

DOI: 10.5530/bems.11.1.3

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

surgical patients, or those with contraindications to open surgery. Some of the limitations of TAVR are higher risk of paravalvular leak, requirement of pacemaker, and limited long-term durability (~10+ years). While the 30-day mortality rate is comparable or lower than SAVR, the 5-year survival rate is similar to SAVR among intermediate- and high-risk patients. A recent trial (PARTNER 3) has reported TAVR to be non-inferior or superior to SAVR in low-risk patients.[12]

Balloon Aortic Valvuloplasty (BAV)

A catheter with a balloon is inserted into the narrowed valve and inflated to improve blood flow. BAV only offers a temporary relief and is not a definitive treatment.[13,14] It is often used in paediatric AS patients and as a bridging therapy in adults before TAVR/SAVR could be performed. BAV is also used during palliative care for non-surgical candidates. BAV has high restenosis rate (within 6-12 months), requiring repeat procedures.

The Paradigm Shift: Aortic Stenosis as an Active Pathobiological Process

The classical view of AS describing it as a degenerative disease has been increasingly challenged by evidence demonstrating that active inflammatory, fibrotic, and osteogenic pathways contribute to its pathogenesis. Valvular Interstitial Cells (VICs), which are majority of the cells within the aortic valve and play a central role in the progression of aortic stenosis.[3] Under pathological conditions, VICs undergo osteogenic differentiation, leading to the deposition of hydroxyapatite crystals and subsequent valve stiffening (Figure 1). Additionally, chronic inflammation and lipid deposition further exacerbate this cycle, promoting disease progression.[3]

S1P, a bioactive sphingolipid, has been widely studied in the context of immune signalling, vascular homeostasis, and fibrosis. However, its role in valvular disease remained largely unexplored until recent investigations began uncovering its involvement in VIC transformation and calcification. The recent study provides compelling evidence that S1P signalling is a critical mediator of the osteogenic phenotype in VICs, thereby contributing to AS progression.[3] This study demonstrates that S1P exerts its effects on VICs through activation of specific S1P receptors (S1PR), particularly S1PR1 and/or S1PR2, which are known to regulate various cellular processes including proliferation, migration, and differentiation. This study utilized a combination of *in vitro* and *in vivo* models to elucidate the molecular mechanisms underlying S1P-induced VIC calcification. The key findings from this study include:

Table 1: Summary of current treatment options for aortic stenosis.

Treatment	Durability	Survival Benefit	Recovery Time	Best for	Risks
Medical Therapy	Supportive only.	No impact on progression.	N/A	Mild AS or non-candidates.	No disease reversal.
SAVR	Best (~15-20 years).	Excellent (restores near-normal life expectancy).	Long (weeks-months).	Younger, low-risk, multi-procedure patients.	Open-heart surgery risks.
TAVR	Good (~10+ years).	Comparable to SAVR (in high/intermediate risk).	Short (days-weeks).	Older, high-risk, or inoperable patients	Paravalvular leak, pacemaker need
BAV	Poor (~6-12 months).	Temporary benefit only.	Short	Temporary/palliative cases.	High restenosis rate.

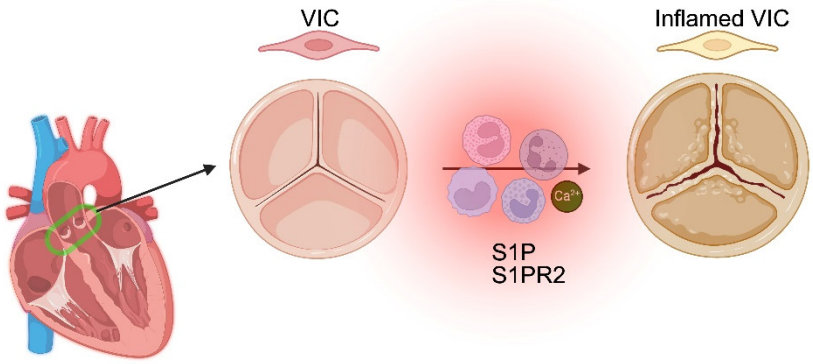

Figure 1: Valvular Interstitial Cells (VICs) are the major cell types within the aortic valve and play a central role in aortic stenosis via the activation of S1P Receptors (S1PR), particularly S1PR2 subtype.

- S1P promotes VIC osteogenic differentiation: The study shows that exposure to S1P enhances the expression of osteogenic markers such as RUNX2, BMP2, and alkaline phosphatase, which are essential for bone-like matrix deposition in calcifying valves.
- S1P receptor signalling drives pathological calcification: The study identifies that S1P1 and S1P2 activation leads to downstream signalling cascades, including ERK1/2 and AKT pathways, which are instrumental in VIC transformation into an osteogenic phenotype.
- Therapeutic targeting of S1P signalling mitigates AS progression: Using pharmacological inhibition of S1P2 receptors, the researchers observed a significant reduction in VIC calcification in a rodent model, suggesting that blocking S1P signalling could serve as a novel therapeutic strategy to prevent or slow down AS progression.

A new frontier for aortic stenosis therapy

Currently, the only definitive treatment for severe AS is Surgical or Transcatheter Aortic Valve Replacement (SAVR/TAVR). However, these interventions are invasive, costly, and not suitable for all patients, particularly those with multiple comorbidities or for those patients at a very early stage of disease development. The lack of pharmacological treatments to halt or slow AS progression represents a major unmet clinical need. The findings from this preclinical study open the possibility of targeting S1P signalling as a therapeutic strategy. If future translational studies and clinical trials confirm the efficacy and safety of S1P2 receptor inhibitors, they could potentially serve as a non-invasive treatment option for patients in the early stages of AS. Such an approach could delay the need for surgical intervention, improve long-term outcomes and reduce complications associated with disease progression.

While the study provides valuable insights into the role of S1P in AS, several questions remain unanswered. Most of the findings are based on preclinical models, and it remains to be seen whether S1P-targeting therapies will be effective in human patients with AS. Since S1P is involved in numerous physiological processes, broad inhibition could lead to unintended side effects, such as immune dysregulation, GI and vascular dysfunction. The development of highly selective S1P modulators will be crucial to ensure therapeutic efficacy without off-target effects. For this understanding the network associations of S1P, its receptors and its modulators will be crucial. Given the growing recognition of AS pathology as an active disease process, identifying circulating biomarkers linked to S1P signalling could help stratify patients at risk and facilitate early intervention. Since AS is a multifactorial disease involving inflammation, fibrosis, and calcification, a combined approach targeting multiple pathways (e.g., S1P signalling and inflammation) may prove more effective in preventing disease progression.

The discovery of S1P signalling as a critical driver of aortic valve calcification represents a much-needed advancement in the field of cardiovascular research. By shifting the focus from a purely mechanical view of AS to a systematic understanding of its molecular drivers, we are entering an era of precision medicine where targeted therapies may soon become a reality. If validated in clinical settings, S1P-targeting drugs could offer a much-needed pharmacological alternative to valve replacement, potentially transforming the management of AS and improving patient outcomes.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

S1P: Sphingosine-1-phosphate; **S1PR:** S1P receptors; **AS:** Aortic stenosis; **SAVR:** Surgical Aortic Valve Replacement; **TAVR:** Transcatheter Aortic Valve Replacement; **ACE:** Angiotensin converting enzyme; **ARB:** Angiotensin receptor blocker; **QoL:** Quality of Life; **CABG:** Coronary artery bypass graft; **BAV:** Balloon Aortic Valvuloplasty; **VIC:** Valvular interstitial cells; **GI:** Gastro intestinal.

REFERENCES

1. Willner N, Prosperi-Porta G, Lau L, Nam Fu AY, Boczar K, Poulin A, *et al.* Aortic stenosis progression: a systematic review and meta-analysis. JACC Cardiovasc Imaging. 2023;16(3):314-28. doi: 10.1016/j.jcmg.2022.10.009, PMID 36648053.
2. Zheng KH, Tzolos E, Dweck MR. Pathophysiology of aortic stenosis and future perspectives for medical therapy. Cardiol Clin. 2020;38(1):1-12. doi: 10.1016/j.ccl.2019.09.010, PMID 31753168.
3. Benkhoff M, Barcik M, Mourikis P, Dahlmanns J, Kahmann P, Wollnitzke P, *et al.* Targeting sphingosine-1-phosphate signaling to prevent the progression of aortic valve disease. Circulation. 2025;151(4):333-47. doi: 10.1161/CIRCULATIONAHA.123.067270, PMID 39429140.
4. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, *et al.* Aortic valve replacement versus conservative treatment in asymptomatic severe aortic stenosis: the AVATAR trial. Circulation. 2022;145(9):648-58. doi: 10.1161/CIRCULATIONAHA.121.057639, PMID 34779220.
5. Khanji MY, Ricci F, Galusko V, Sekar B, Chahal CA, Ceriello L, *et al.* Management of aortic stenosis: a systematic review of clinical practice guidelines and recommendations. Eur Heart J Qual Care Clin Outcomes. 2021;7(4):340-53. doi: 10.1093/ehjqcco/qcab016, PMID 33751049.
6. Shah SM, Shah J, Lakey SM, Garg P, Ripley DP. Pathophysiology, emerging techniques for the assessment and novel treatment of aortic stenosis. Open Heart. 2023;10(1):e002244. doi: 10.1136/openhrt-2022-002244, PMID 36963766.
7. Sen J, Chung E, Neil C, Marwick T. Antihypertensive therapies in moderate or severe aortic stenosis: a systematic review and meta-analysis. BMJ Open. 2020;10(10):e036960. doi: 10.1136/bmjopen-2020-036960, PMID 33020089.
8. Blankenberg S, Seiffert M, Vonthein R, Baumgartner H, Bleiziffer S, Borger MA, *et al.* Transcatheter or surgical treatment of aortic-valve stenosis. N Engl J Med. 2024;390(17):1572-83. doi: 10.1056/NEJMoa2400685, PMID 38588025.

9. Sharma T, Krishnan AM, Lahoud R, Polomsky M, Dauerman HL. National trends in TAVR and SAVR for patients with severe isolated aortic stenosis. J Am Coll Cardiol. 2022;80(21):2054-6. doi: 10.1016/j.jacc.2022.08.787, PMID 36122626.
10. Cannata F, Chiarito M, Pinto G, Villaschi A, Sanz-Sánchez J, Fazzari F, *et al.* Transcatheter aortic valve replacement in aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis. ESC Heart Fail. 2022;9(5):3188-97. doi: 10.1002/ehf2.13876, PMID 35770333.
11. Vincent F, Ternacle J, Denimal T, Shen M, Redfors B, Delhaye, v C, *et al.* Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. Circulation. 2021;143(10):1043-61. doi: 10.1161/CIRCULATIONAHA.120.048048, PMID 33683945.
12. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, *et al.* Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380(18):1695-705. doi: 10.1056/NEJMoa1814052, PMID 30883058.
13. Kleczynski P, Kulbat A, Brzychczy P, Dziewierz A, Trebacz J, Stapor M, *et al.* Balloon aortic valvuloplasty for severe aortic stenosis as rescue or bridge therapy. J Clin Med. 2021;10(20):4657. doi: 10.3390/jcm10204657, PMID 34682783.
14. Bularga A, Bing R, Shah AS, Adamson PD, Behan M, Newby DE, *et al.* Clinical outcomes following balloon aortic valvuloplasty. Open Heart. 2020;7(2):e001330. doi: 10.1136/openhrt-2020-001330, PMID 32907920.

Cite this article: Kumar AHS. Unravelling the Role of Sphingosine-1-Phosphate Signaling in Promoting Aortic Stenosis. BEMS Reports. 2025;11(1):14-7.