Recent advances in medical treatment and percutaneous, transapical and surgical interventions in aortic-valve stenosis
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Abstract
This review focuses on recent advances in the treatment of aortic-valve stenosis with special emphasis on medical treatment for preventing disease progression, and on novel surgical and percutaneous approaches.

Introduction and context
Aortic stenosis (AS) is the most common native valve disease at present. It is the third most common cardiovascular disease after hypertension and coronary artery disease.

The first epidemiologic study evaluating the prevalence of AS in Finland revealed the prevalence of severe AS (AVA ≤ 0.8 cm²) in 2.9% of elderly over 75 years of age, mild aortic valve calcification in 40% and severe calcification in 13% [1].

Currently, AS is also the second most common indication for cardiac surgery, and the most common indication for valve surgery. In the European registry for valvular heart disease it was found that AS constitutes 43% of all valve diseases [2]. There are two important reasons for this high prevalence: first, about 2% of the population is born with a bicuspid aortic valve; and second, the ageing population is reaching the stage where significant degenerative aortic valve disease is developing. Although AS is associated with substantial clinical consequences, until recently there was no effective therapy to treat it other than surgical aortic valve replacement.

Recent advances
Effect of statins on the progression of aortic valve stenosis
Recent advances in the pathophysiology of AS indicate that calcific AS is an active disease process that resembles atherosclerosis and shares the same risk factors. An active atherosclerotic-type pathophysiology involving oxidative stress, inflammation, and endothelial dysfunction in aortic valves has been induced in mice by hypercholesterolaemia, and inhibited by administering HMG-CoA reductase inhibitors (statins) [3]. Consequently, a hypothesis was developed proposing that AS could be a preventable disease, or at least that its progression could be slowed by medical interventions that are effective in slowing or reversing atherosclerosis. Several retrospective studies have suggested that statin therapy may slow the progression of AS as measured by the annual change per year in aortic valve area. Novaro et al. [4], for example, found that the decrease in aortic valve area for a group not treated with statins was 0.11±0.18 cm², compared to 0.06±0.16 cm² for those treated with statins (P = 0.030).

These findings and existing experimental data were the driving force to conduct prospective randomized studies to resolve this important question. In the past several years, three completed prospective studies on the effect of statin therapy on AS progression have been published. The first prospective (non-randomized), open-label
study was the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study [5]. In this study, echocardiographic, serum lipid, and inflammatory marker determinations were used at baseline and every 6 months for 18 months to evaluate outcomes in 121 patients with asymptomatic moderate to severe AS (aortic valve area 1.0-1.5 cm²) who were treated with or without rosvastatin. This study suggested that rosvastatin treatment slowed the progression of AS, including hemodynamic indices of progression. It was the first prospective study that showed the potential of medical treatment to slow progression of asymptomatic AS. However, this study was limited by being a non-randomized, observational study.

The second important study was the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) [6], a randomized, double blind, placebo-controlled trial with a median follow-up of 25 months. In this study, 155 patients with calcific AS and aortic jet velocity <2.5 m/s were treated with either atorvastatin 80 mg/day (n = 77) or placebo (n = 78). In contrast to the RAAVE study, it did not detect a short-term impact of statins on echocardiographic progression of AS or on aortic valve calcium score. The SALTIRE investigators concluded that intensive lipid-lowering therapy did not slow the progression of calcific AS or induce its regression. However, the investigators could not exclude a small reduction in the rate of AS progression or a significant reduction in major clinical endpoints. Also, nearly 25% of the study population in the atorvastatin group and 22% in the placebo group had severe AS to begin with and in these patients the disease stage may have been too advanced to be affected by statin therapy within the study's duration.

The third study, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study [7], was a randomized, double blind trial involving 1,873 patients with mild to moderate asymptomatic AS. The patients received either 40 mg simvastatin plus 10 mg ezetimibe or placebo daily. The primary outcome was a composite outcome of combined aortic-valve events and ischemic events. During a median follow-up of 52.2 months, simvastatin and ezetimibe did not reduce the composite outcome. Statin therapy reduced the incidence of ischemic cardiovascular events but not events related to AS. Interestingly, cancer occurred more frequently in the simvastatin-ezetimibe group.

**Apicoaortic conduit bypass surgery**

Conventional aortic valve replacement surgery mandates the use of cardiopulmonary bypass, ascending aortic crossclamping, aortotomy, debridement of the diseased valve, and cardioplegic cardiac arrest. An alternative surgical approach has been suggested in which a conduit containing a prosthetic valve relieves AS by shunting blood from the apex of the left ventricle to the descending thoracic aorta (apicoaortic conduit bypass surgery). This surgical approach has been applied sporadically to high-risk adult patients with acquired AS, with just over 100 reported cases in the literature [8]. Recently, Gammie et al. [9] described a series of 31 high-risk AS patients treated with apicoaortic conduit bypass surgery; 22 patients (71%) were undergoing re-operation with patent coronary bypass grafts, and five (16%) had a porcelain ascending aorta. Postoperative echocardiographic assessment demonstrated that a mean of 72% of cardiac output flowed through the bypass conduit. The relief of left ventricular outflow tract obstruction was commonly associated with a downgrading of the degree of mitral regurgitation and left ventricular function was preserved. Importantly, in this high-risk patient group, surgical complications were uncommon (only one patient required temporary postoperative hemodialysis and only one patient experienced stroke); however, median postoperative survival was only 870 days, similar to the natural history of unoperated symptomatic AS. This approach is an addition to the armamentarium of therapies for symptomatic AS patients with a high surgical risk and will be further examined in the future.

**Percutaneous aortic valve implantation**

As many as one-third of elderly patients with symptomatic AS are not referred for surgery, usually due to high surgical risk or patient refusal. Unfortunately, percutaneous balloon valvuloplasty is unsatisfactory with high recurrence rates. In 2002, Cribier performed the first percutaneous aortic valve implantation (PAVI), opening a new era in AS management [10].

Early implants were performed using Cribier-Edwards valves (Edwards Lifesciences, Irvine, California, USA), which are composed of three leaflets of animal pericardium sutured to a balloon-inflated stent 23 or 26 mm in diameter. Cribier et al. [11] described the first 27 patients treated by PAVI with the Edwards valve, 23 with the antegrade approach and four with the retrograde approach. All were elderly, with severe co-morbidities, and ineligible for conventional therapy (‘no-option’ patients). After the procedure, mean valve area increased to 1.7 cm², yielding a small but significant improvement in global function of the left ventricle. Importantly, there were no deaths directly related to the procedure. Afterwards, Webb et al. [12] reported the outcome of the first 50 high surgical risk severe symptomatic AS patients treated with the Edwards
valve implant in Vancouver, Canada, all with the retrograde approach. PAVI was successful in 86% of patients. On long-term follow-up of 1 year, and up to 2 years, there was not a single case of valve restenosis or malfunction. The mortality rate was 12% in the first month after the procedure, which was lower than the 28% predicted mortality according to the patients' preprocedural EuroSCOREs (European System for Cardiac Operative Risk Evaluation). Another important finding in the study of Webb et al. was the difference between patients treated at the beginning of the learning curve and those treated later in terms of procedural success (76 versus 96%) and 1-month mortality (16 versus 8%), indicating the importance of physician experience. Currently, more than 1,000 patients have been treated using the PAVI technique and the Cribier-Edwards valve, which was slightly modified and is now called the Edwards SAPIEN valve (Figure 1).

The CoreValve system for percutaneous aortic valve replacement (CoreValve Inc, Irvine, CA, USA), also called ReValving technology, is composed of a valve encircled by a 50–53 mm-long frame (depending on valve size) (Figure 2). The CoreValve is self-expandable and intended for mitigation of paravalvular leak and increased durability, although post implantation frame remodeling by means of balloon expansion during use is not uncommon [13]. The possibility to remodel the system after implantation may decrease the risk of perivalvular leak. Because of the self-expanding feature, the suggested use of the system might be extendable to patients who underwent prior surgical biologic valve replacement ('ReDo™ procedure) [14]. If physicians were able to effectively perform PAVI inside a degenerative implanted biologic valve, the use of biologic valves for aortic valve replacement may increase, because valve malfunction could be treated without the need for redoing surgery. The current (third generation) model has been significantly improved and its delivery catheter has a diameter of only 18Fr. The implantation results of the second- and third-generation systems in 86 patients in several centers in Germany and Canada have been published [15]. Most patients were women, selected because of the small size of the implanted valve, with a mean age of 82 years and a high mean EuroSCORE of 21.7%. The procedural success rate was 88%. There was a dramatic improvement in hemodynamic parameters, including an increase in valve area to 1.7 cm². Valve regurgitation worsened in only a minority of cases. In the first month after the procedure the mortality rate was 12%; half of these deaths occurred in the first 2 days. Stroke occurred in 10%. Furthermore, urgent cardiac surgery to release the device was necessary in 6% of patients. At the time of preparing the present review, more than 3,000 patients had been treated with the CoreValve framed valve. According to currently unpublished results, the procedural success rate for the 18Fr device is 98%, with only 0.7% of patients requiring aortic valve replacement surgery in the first post-procedural month.

The transapical approach requires a team consisting of cardiac surgeons and interventional cardiologists [16,17]. After a left anterolateral intercostal incision is made to expose the cardiac apex, the delivery system is inserted into the left ventricular cavity and the valve is implanted (Figure 3). This approach is more invasive than those discussed above. The transapical approach has several important advantages. First, there is no delivery of the system via the peripheral vessels, the ascending aorta, or several cardiac chambers, with attendant risks. Second, unlike conventional valve replacement, there is no need for cardiopulmonary bypass or manipulation in the ascending aorta, potentially decreasing the risk of periprocedural stroke. In a recent report on their experience with this method in patients with severe co-morbidity (EuroSCORE 31%), Walther et al. [18] described no procedural failures and excellent hemodynamics in all cases after several months' follow-up. There were no procedure-related deaths or strokes. Recently, Zierer et al. [19] reported on 26 patients treated with this approach. The EuroSCORE-predicted risk for mortality was 36.5%. All valves were successfully deployed at the target and there were only minor

![Figure 1. The Edwards SAPIEN transcatheter heart valve](image-url)

A bovine pericardial valve is sewn within a stainless steel frame. Image provided by Edwards Lifesciences, Irvine, California.
paravalvular leakages. Thirty-day mortality was 15% (n = 4). There were two cases of conversion to open surgery. In two patients, the left main stem was partially obstructed by the native valve and required stent angioplasty. During this past year, this approach has been used in several centers worldwide.

Implications for clinical practice

Effect of statins on the progression of aortic valve stenosis

Several retrospective and one non-randomized study (RAAVE) have suggested that statin therapy may slow the progression of AS, but the only two available large prospective randomized double blinded studies did not show any effect of high-dose statin therapy on AS progression. Therefore, the data we currently have are contradictory but tend to suggest that statin therapy has no significant effect on the natural history of AS. However, we should await the results of larger randomized studies (ASTRONOMER, AORTICA 1, STAAT and STOP-AS) with longer follow-up, which hopefully will resolve this important issue. Importantly, most of these studies were performed on patients with moderate or severe AS. It might be that statin therapy may be more effective if it is started at a very early stage of the disease when patients have only mild AS or even only non-obstructive aortic valve calcification.

Percutaneous aortic valve implantation

Although still in its early stages, and not yet sufficiently viable to replace conventional methods in low-risk patients, percutaneous treatment of AS holds promise for providing symptomatic relief and, possibly, longevity to patients who are ineligible for surgery due to their high surgical risk. Preliminary studies show that PAVI is both feasible and effective in elderly patients with AS in the short and medium term. However, the procedure is still associated with significant adverse effects and mortality, and the long-term results are still unknown. Therefore, the procedure is not yet ready to replace conventional surgical aortic valve replacement in low risk patients and at this time is reserved for high surgical risk candidates.

Abbreviations

AORTICA 1, Double Blind Randomized Phase IV Clinical Trial to Evaluate the Efficacy of Fluvastatin on Inflammatory Markers in the Haemodynamic Progression of Degenerative Aortic Stenosis; AS, aortic stenosis; ASTRONOMER, Aortic Stenosis Progression
Observation: Measuring Effects of Rosuvastatin; EuroSCORE, European System for Cardiac Operative Risk Evaluation; PAVI, percutaneous aortic valve implantation; RAAVE, Rosuvastatin Affecting Aortic Valve Endothelium; SALTIRE, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression; STAAI, Statin Therapy in Asymptomatic Aortic Stenosis; STOP-AS, Stop Aortic Stenosis.

Competing interests
The authors declare that they have no competing interests.

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