Aortic Valve Replacement for Aortic stenosis and Concomitant Coronary Bypass: An Updated Overview

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Introduction

Aortic stenosis (AS) and coronary atherosclerosis can independently cause myocardial ischemia and the sequelae of myocardial ischemia, including angina, myocardial infarction (MI), and death. A review of the results of combined aortic valve replacement (AVR) and coronary artery bypass grafting (CABG) in several centersshow more variable mortality than after isolated AVR. **[1].**Patients treated for severe AS constitute a heterogeneous population ranging from young patients with isolated bicuspid valve disease to elderly patients with degenerative disease complicated by multiple comorbidities. The most common comorbidity,most importantly influencing outcomes after AVR, affecting a third of patients and half of those above age 70, is coronary artery disease (CAD) **[2].**When CAD is present in AVR patients, early- and long-term survival rates have been found to be worse without CABG. On AVR-CABG, however, there is conflicting evidence. Some reports demonstrated higher rates of early mortality. **[3].**Whereas other reports showed no significant difference with concomitant AVR-CABG. **[4].**When indicated, a single session, concomitant CABG with aortic valve surgery is comparatively harmless with satisfactory early outcomes and complications. CABG, when combined with double valve replacement, increases the risk of postoperative morbidities and mortality. **[5].**

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Co-presentation with both CAD and valve diseases increases as the age of patients referred for CABG surgery rises. If AS is severe or the patient is symptomatic, single-stage AVR-CABG should be carried out. For patients with combined valvular and CAD, AVR-CABG is an acceptable surgical intervention. Even though there are some contradictory conclusions in the literature, most authors approve that performing CABG with AVR marginally increases long-term survival, even in the high-risk population. **[6].**In recent years, the range of treatment options, non-surgical as well as surgical, has increased, and so requires reliable assessment of relative risks associated with those options. Outcomes have improved with developments in surgical techniques, myocardial protection, and perioperative management, and the present study was intended to contribute data on the risks of AVR with and without CABG.

Aortic Stenosis (AS)

AS is a narrowing of the aortic valve (AV) that leads to decrease blood flow to all parts of the body. It is estimated to be prevalent in up to 7% of the population over the age of 65. It is also more likely to affect males more than females as 80% of adults with symptomatic AS are males. After the onset of symptoms, patients with severe AS have a survival rate as low as 50 % at 2 years and 20% at 5 years without AVR. **[7]**.

Etiology of AS:

AS is primarily caused by rheumatic fever (RF), the most common pathogenesis today is an active inflammatory process with some features that are similar to atherosclerosis. Because of this shift, the age at onset of severe AS has changed from the sixth decade to the eighth decade in most individuals today. The onset of symptoms remains a key

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determinant of outcome, although the later age at onset may make it difficult to detect if AS or other age-related comorbidities is the cause of the symptoms. Once symptoms of AS develop, life expectancy is shortened to around 3 years unless the mechanical obstruction to left ventricular outflow is relieved by AVR. **[8]**

Among the acquired etiologies of AS, rheumatic valvular AS (Figure 1) and senile calcific degeneration of AV are the most common causes in developing and developed world respectively. **[9].**

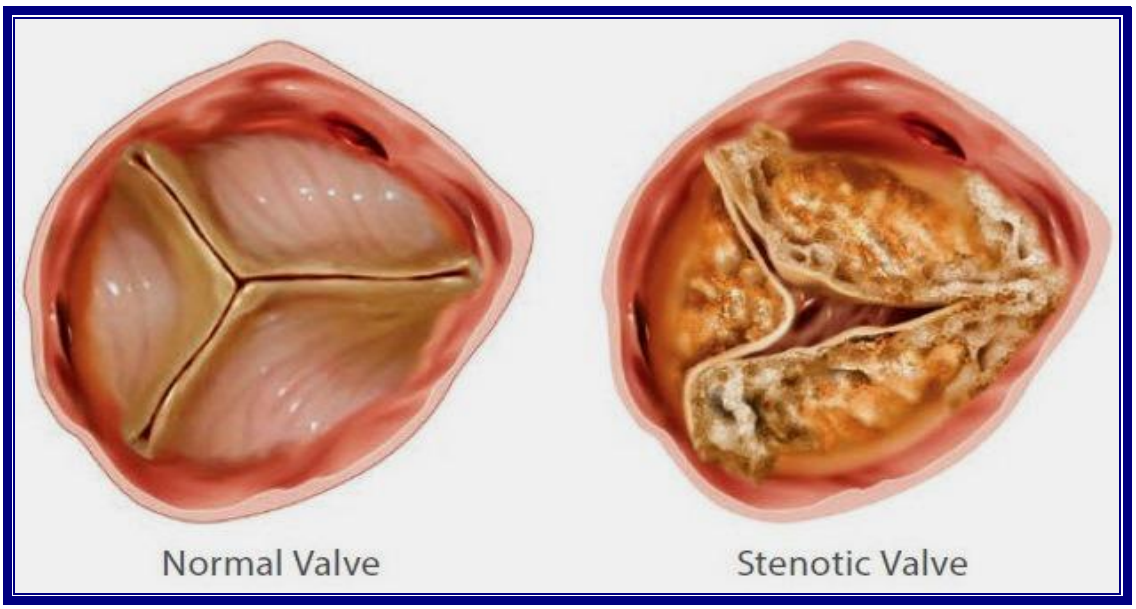

Figure (1): 3D picture of normal Aortic valve and Rheumatic Aortic stenosed valve**[10].**

Prevalence of AS

An estimated 4.2 to 5.6 million adults in the United States have some form of clinically important valve disease. There were approximately 40 million persons aged 65 and older in 2010, but this number increased to 55 million in 2020 and expected to be 72 million in 2030. Because the common forms of valve diseases are linked to aging, this demographic shift will increase the number of patients with AS. The Helsinki Aging Study, an echocardiographic screening study, provided further evidence of increased calcification and degeneration of the AV with increasing age.**[11].**

The prevalence of critical AS increased with age from between 1% and 2% in persons aged 75 to 76 years to 6% in those aged 85 to 86 years. Similarly, the Euro Heart Survey on Valvular Heart Disease prospectively surveyed 5001 individuals from 92 centres in 25 countries. Among incident native left-sided valve disease, AS was the most frequent and was severe in a substantial number of affected individuals. **[12].**

Pathophysiology

AS has a prolonged latent period, during which progressive worsening of left ventricular outflow (LVOT) obstruction leads to compensatory hypertrophic changes in the Left ventricle (LV) myocardium. LV hyper-trophy may also lead to diastolic dysfunction and increased resistance to LV filling. So, left atrial contraction may be needed to provide enough LV diastolic filling and to support adequate stroke volume. As the severity of AS worsens, these adaptations become inadequate to overcome the outflow obstruction and maintain systolic function. **[13].**

Impaired systolic and diastolic dysfunction may lead to clinical heart failure. The same manifestations may occur if the atrial kick is lost and diastolic filling time shortens, as in

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atrial fibrillation (AF) with a rapid ventricular response. Progressive LV hypertrophy from AS may also result in increased myocardial oxygen needs. Myocardial LV hypertrophy may compress the intramural coronary arteries as they carry blood toward the myocardium. These changes, along with reduced diastolic filling of the coronary arteries, may cause angina, even in the absence of CAD. In addition, as AS becomes severe, the cardiac output becomes fixed withexercise. In this setting, a drop in systemic vascular resistance (SVR) with exertion may lead to syncope. **[13]**.

Patients treated for severe AS constitute a heterogeneous population ranging from young patients with isolated BAV to elderly patients with degenerative disease complicated by comorbidities. The most common comorbidity,most importantly influencing outcomes after AVR, affecting a third of patients and half of those above age 70, is CAD. **[2].**

Calcific AS is the most common valve disease in high-income countries and is set to become a major healthcare burden in elderly patients**[14].**

It is characterized by fibrocalcific remodelling of the valve leaflets, resulting in progressive stenosis of the AV opening and a hypertrophic response of the LV, which may lead to heart failure, syncope, angina, and ultimately death. Although the associated risk factors for AS incidence are similar to atherosclerosis, treatment with statins has failed to slow AS progression in 3 randomized controlled trials.

AS was long considered a degenerative disease in which “wear and tear” over the years resulted in gradual calcium deposition in the AV leaflets. AS is instead the result of actively regulated and complex cellular processes coordinated by valve interstitial cells (VICs) **[15].**

The pathophysiology of AS occursin two phases: the initiation phase, similar to atherosclerosis and characterized by endothelial damage, lipid infiltration, and inflammation; and the propagation phase, in which VICs assume an osteoblast-like phenotype and drive a vicious cycle of valve calcification with similarities to skeletal bone formation **[16].**

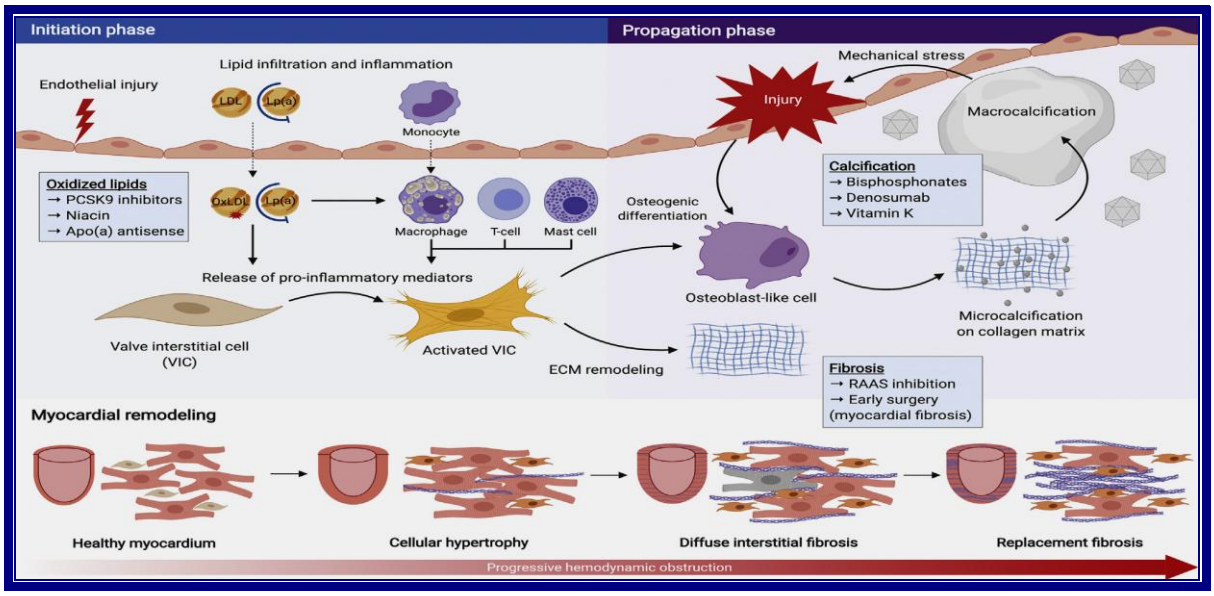

Figure (2): Pathogenesis of AS**[17].**

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Symptoms of AS:

The cardinal symptoms of severe AS are exertion-related angina, congestive heart failure or syncope. Dyspnea is due to either increased left ventricular filling pressure or inability to increase cardiac output with exercise. In most patients, symptoms appear with normal LVEF; however, in some patients there is a reduction in systolic myocardial function and inability of the LV to develop pressure and shorten against a load (afterload mismatch) before the onset of symptoms.**[18]**.

Angina can be caused by increased myocardial oxygen demand due to myocardial hypertrophy, compression of intramyocardial coronary arteries, impaired coronary flow reserve, and/or reduced diastolic coronary perfusion time during tachycardia. Earlier series reported significant CAD in 25% to 50% of patients and that it was a function of age. Surgical series have found that in the age group 61 to 70 years, 40% of patients require concomitant CABG, whereas in patients older than 80 years, more than 65% require concomitant CABG.**[19]**.

Correlation between onset of symptoms and severity of stenosis is not clear. The onset of symptoms may be early with coexistent aortic regurgitation or delayed in some patients even with critical stenosis. However, symptoms generally appear in patients with normal ejection fraction when the AS is severe and can be vague, such as tiredness or fatigue. In symptomatic patients, event-free survival is only 30% to 50% at 2 years, underscoring the need for frequent monitoring for progression**. [20]**.

Sudden death, an important consideration and a complication of severe AS, is more common in patients with symptomatic AS but can occur without preceding symptoms at a rate of 1% per year. Patients with moderate AS may exhibit similar symptoms, but other etiologies for these symptoms should be carefully considered before attributing symptoms to AS. For example, dyspnea can be a symptom of cardiomyopathy, chronic lung disease, anaemia, renal failure, or coexisting CAD. Similarly, angina can manifest CAD; arrhythmias and heart block in the elderly can lead to presyncope and syncope. However, once a diagnosis of severe AS is firmly established, careful attention should be paid to even mild cardiac symptoms because symptom onset is associated with an average survival without valve replacement of only 2 to 3 years, and there is an increased risk of sudden death**. [21].**

Diagnosis and Evaluation of AS:

An AVA of 1 cm2 or less is considered severe AS (normal, 3-4 cm2), and the hemodynamic severity of AS is best characterized by a transaortic peak velocity of 4 m/s or more or a mean gradient of 40 mm Hg or more. Greater importance is attached to the peak velocity and means gradient, and if the hemodynamic threshold for severe AS is met, then severe AS is considered to be present regardless of the aortic valve area. Recent recommendations on the echocardiographic assessment of AS from the European Association of Cardiovascular Imaging and the American Society of Echocardiography recognize the importance of the entity of low gradient AS when the AVA is small (<_1 cm2), but the hemodynamics are discordant with a peak velocity of less than 4 m/s or a mean gradient of less than 40 mm Hg**. [22]**.

Reasons for discordance include measurement error, elevated blood pressure at the time of echocardiography, or low forward flow (stroke volume index <35 mL/m2) because flow influences gradient. Flow gradient patterns in AS can be categorized as normal flow-high gradient, low flow-high gradient, normal flow-low gradient, and low flow-low gradient, with preserved (>_50%) or reduced (<50%) LVEF**. [22].**

The high-gradient pattern categories indicate classic severe AS; patients with the low flow-low gradient pattern appear to have worse outcomes with medical management than those with classic AS; patients with the

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normal flow-low gradient pattern have clinical outcomes more similar to those with moderate AS. These flow gradient AS categories are in line with the AHA/ACC guideline on the management of patients with valve disease and are part of the continuum in the stages of AS**. [23]**.

Echocardiography:

The primary test for diagnosis and management decisions in patients with AS is echocardiography. A transthoracic echocardiogram (TTE) delineates aortic valve anatomy (number of cusps, extent of calcification, leaflet excursion), and valve hemodynamics to confirm severity, its consequences on left ventricle function, pulmonary hypertension, and concomitant valvular heart disease, and ascending root dilation. TTE is indicated in patients with signs or symptoms of AS or a bicuspid valve for accurate diagnosis of the cause, hemodynamic severity, left ventricular size, and systolic function and for determining prognosis and timing of valve intervention**[23].**

Cardiac catheterization:

Cardiac catheterization is recommended when there is discordance between the clinical and echocardiographic evaluations, when non-invasive methods are nondiagnostic, or when coronary angiography needs to be obtained as a part of the work-up or treatment. According to the AHA/ACC guideline for the management of patients with valvular heart disease, coronary angiography is indicated before valve intervention in patients with symptoms of angina, objective evidence of ischemia, decreased left ventricular systolic function, history of CAD, or coronary risk factors (including age >40 years in men and postmenopausal status in women).**[23]**.

Indications to proceed with a coronary angiogram before surgical AVR:

- Symptomatic men older than 35 years.
- Asymptomatic men older than 45 years.
- Pre-menopausal women older than 35 years with coronary risk factors.
- Women older than 55 years or post-menopausal.
- Patients with two or more coronary risk factors.
- Patients with a history of coronary artery disease.
- Patients are undergoing cardiac catheterization to clarify the severity of the valve disease.

Treatment Overview:

Medical Treatment:

Hypertension

Hypertension results in serially increased afterload and are associated with higher mortality rates and ischemic cardiovascular events. Hypertension is common in patients with AS, and its treatment should follow the guidelines. Hypertensive patients with asymptomatic AS had a 56% higher rate of ischemic cardiovascular events and a 2-fold increased mortality ratecompared with normotensive patients with AS. Systemic hypertension in low-gradient severe AS with preserved ejection fraction (stage D3) is associated with increased left ventricular filling pressures and pulmonary hypertension, and treatment of hypertension with vasodilator therapy results in symptom improvement. **[24]**.

Lipid-Lowering Therapy

Three randomized trials failed to demonstrate the usefulness of statins to prevent the progression of calcific AS. In a randomized, double-blind controlled trial, a combination of simvastatin and ezetimibe in 1873 patients with mild to moderate AS did not reduce primary outcomes of cardiovascular death, AVR, nonfatal myocardial infarction, hospitalization for unstable angina, heart failure, CABG, percutaneous coronary intervention, and non-hemorrhagic stroke during a median follow-up of 52.2 months. Current AHA/ACC guidelines do not

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recommend statins to prevent the hemodynamic progression of AS; however, statins are important for patients with associated CAD to lower ischemic endpoints.**[25]**.

Vasodilator Therapy

Vasodilator therapy is a cornerstone in managing patients with left ventricular dysfunction but was historically contraindicated in patients with severe AS. It was previously believed that cardiac output across a fixed stenotic aortic valve and vasodilatation from vasodilator therapy would reduce the systemic vascular resistance without a compensatory increase in the cardiac output that will result in severe hypotension. However, smaller studies have documented the beneficial effects of vasodilatation in asymptomatic patients with severe AS.**[26].**

Aortic Balloon Valvuloplasty

Percutaneous aortic balloon valvoplasty is balloon inflation across the AV to reduce the severity of AS. The mechanism by which reduction in AV gradient and improvement in symptoms with valvuloplasty occurs is yet unknown, but fracture of the calcific deposits, separation of commissures, or stretching of the aortic annulus may play a part. Its current role is mainly as a part of the TAVR procedure or sometimes as a bridge to more definitive therapy. **[27].**

Surgical AVR (SAVR):

Indications of SAVR:

European Society of Cardiology guidelines on the management of valvular heart disease.

- AVR is indicated in patients with severe symptomatic AS (class 1 recommendation, level of evidence B) and also asymptomatic patients with LV systolic dysfunction (class 1 recommendation, level of evidence C).
- In patients with symptomatic severe AS who are inoperable or at high surgical risk for SAVR, TAVI should be considered, after detailed assessment by the “Heart team”.
- A STS score >10% (preferably) or Euro score>20% have been suggested to identify patients who may be suitable for TAVI, owing to high operative risk for SAVR.
- Patients with operative risk lower than the above, may also be suitable for TAVI in certain situations; frail, porcelain aorta, patent coronary artery bypass grafts, or history of chest radiation.
- However, currently, no risk score is perfect,, and the assessment should be based on the clinical judgment of the “Heart team”.
- Suitable patients with concomitant severe AS and CAD should undergo combined CABG and SAVR, despite increased mortality of the combined procedure.
- More data are required before firm recommendations can be made regarding the hybrid procedures and performing percutaneous coronaryimplantation (PCI) with TAVI in patients with severe AS and CAD.
    - **Indications and Timing of Replacement in Asymptomatic Patients.**

Patients with asymptomatic AS have low rates of sudden death (<1% per year) and therefore require only regular monitoring for the progressionthe of disease or development of symptoms, which is unavoidable in these patients. Moderate or severe aortic valve calcification, peak aortic velocity, and progression of peak aortic velocity have been correlated with mortality and the need for AVR.**[28]**.

Asymptomatic severe AS is divided into two categories, C1 (normal ejection fraction) and C2 (reduced ejection fraction). Patients with C2 disease benefit from AVR. Depressed ejection fraction results from afterload mismatch that improves following AVR or CAD

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and prior MI . AVR is also recommended in asymptomatic patients with severe AS who are undergoing cardiac surgery for other indications such as CABG (class I indication) and in asymptomatic low-risk patients with very severe AS (aortic velocity >_5 m/s or mean pressure gradient >_60 mm Hg) because these patients have more rapid progression of AS and symptom onset is inevitable (class IIa indication).**[23]**.

Choice of Intervention:

AVR is indicated for survival benefit, improvement in symptoms, and improvement in left ventricular systolic function in patients with severe, symptomatic AS. The choice of intervention (surgical vs transcatheter) rests on the risk of operation, frailty, and comorbid conditions.Surgical AVR is considered primarily in low or intermediate-risk patients and in patients with severe multivessel CAD. All patients should be evaluated by a multidisciplinary heart valve team, and the suitability of the surgical vs transcatheter approach should be determined. TAVR is considered primarily in patients with prohibitive, high or intermediate surgical risk based on current guidelines. No valve replacement is recommended for patients with a life expectancy of less than 1 year. **[29]**.

Aortic valve calcification and prevalence of CAD

The prevalence of CAD in patients undergoing SAVR has been shown to increase with both age and the presence of valve calcification. This was demonstrated in a large Swedish registry where CABG occurred simultaneously with AVR in 7.2% of patients aged ≤50 years, 30.2% of patients aged between 51 and 60 years, 41.2% of patients aged 61–70 years, and 51.2% of patients aged ≥71 years. **[30]**.

Impact of CAD on the outcomes of SAVR

The presence of CAD has been demonstrated to increase the procedural risk of SAVR, and coronary revascularization is generally recommended at the time of surgery **[31].**

The ACC and AHA guidelines on valvular heart disease advocate, as a Class 1 recommendation, that patients undergoing AVR with significant stenoses (greater than or equal to70% reduction in luminal diameter) in major coronary arteries should be treated with bypass grafting. **[23].**

Outcomes of PCI in patients with severe AS

Because AVR-CABG has been considered the preferred treatment option for patients with concomitant AS and CAD, PCI has been performed infrequently in this population. The outcomes data for PCI in patients with severe AS and CAD is therefore limited to observational studies. In the largest study to date comparing patients with and without severe AS who underwent PCI, Goel et al. analyzed the short-term outcomes of 254 patients with severe AS and CAD who were treated with PCI over a 10-year period. **[32]**.

From these data, the authors concluded that PCI could be performed in patients with severe AS without increased risk of short-term mortality or procedural complications compared with similar patients without concomitant AS. With respect to long-term outcomes, at a mean follow-up of 3.7 years, 29% of patients with severe AS had undergone SAVR with a mean duration of 15.5 months between PCI and SAVR, and CABG was performed with SAVR in 71% of these patients. Long-term mortality was 42.5% in AS patients who underwent SAVR compared with 68% in AS individuals who did not undergo SAVR and 46.7% in the control group without AS. **[33].**

Outcomes of hybrid procedures with surgical AVR and PCI

As noted earlier, the traditional treatment for severe AS with concomitant CAD has been combined AVR and CABG. This combined procedure carries a mortality rate nearly double that of isolated AVR (4.4 vs 9%). Combined AVR/CABG is also less favorable in patients with poor or limited conduit vessels, patients presenting with ACS, and patients requiring valve reoperation. For these reasons, it has been proposed that some

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patients may benefit from a hybrid procedure in which PCI is combined with SAVR**. [34].**

It is worthwhile to note that studies examining hybrid procedures have included both minimally invasive AVR (MI-AVR) as well as traditional AVR via median sternotomy with a trend towards more MI-AVR.**). [34]**.

The prognostic impact of concomitant AVR-CABG

CAD is identified in almost half of the patients undergoing AVR and if left unmanaged, may negatively impact early and late postoperative outcomes. Previous iterations Of AHA/ACC guidelines considered CABG indicated (class I) for 'significant'' CAD (>70% stenosis) at time of AVR, and reasonable (class IIa) in patients with ''moderate'' CAD (50%-70% stenosis) level of evidence: C). **[35].**

This finding is echoed by various studies demonstrating an association between concomitant CABG and differing short-term outcomes. However, these survival estimates were derived by comparing patients with isolated AS undergoing AVR only versus those with coexistent AS and CAD undergoing AVR with CABG. A detailed analysis by Beach and colleagues recently highlighted that early postoperative risks incurred by patients with AS plus CAD (having AVR with CABG) are largely a function of baseline CAD rather than CABG per se**. [4]**

Indeed, our results coincide with historical reports as we demonstrate that among patients with CAD, early operative mortality rates are not augmented by the addition of CABG at AVR. This is also in keeping with more recent data attesting to the safety of coronary revascularization at AVR, even in high-risk elderly patients.**[36].**

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