

**Coronary revascularization in patients undergoing aortic valve replacement for
severe aortic stenosis**

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Abstract:

Aortic stenosis (AS) and coronary artery disease (CAD) frequently coexist with up to two thirds of AS patients having significant CAD. Given the challenges when both disease states are present, these patients require a tailored approach diagnostically and therapeutically. This review article addresses the impact of AS and aortic valve replacement (AVR) on coronary hemodynamics and discusses the assessment of CAD and the role of revascularization in patients with concomitant AS and CAD.

Remodeling in AS increases the susceptibility of myocardial ischemia, which can be compounded by concomitant CAD. AVR can improve coronary hemodynamics and reduce ischemia. Assessment of the significance of coexisting CAD can be done using non-invasive and invasive metrics. Revascularization in patients undergoing AVR can benefit certain patients where CAD is either prognostically or symptomatically important. Identifying this cohort of patients is challenging and as yet incomplete.

Patients with dual pathology present a diagnostic and therapeutic challenge; both AS and CAD affect coronary hemodynamics, provoke similar symptoms, and their respective treatments can have an impact on both diseases. Decisions regarding coronary revascularization should be based on understanding this complex relationship, using appropriate coronary assessment and consensus within a multi-disciplinary team.

Key words: aortic stenosis, coronary artery disease, chronic coronary syndromes, revascularization, coronary hemodynamics

Word count: 7950

Introduction

Coronary artery disease (CAD) and aortic stenosis (AS) share similar etiologies and pathophysiologic mechanisms (1). Consequently, both diseases frequently co-exist; reported rates of significant CAD vary between 24-64% among patients with AS (2,3). Both diseases can also cause similar symptoms: angina and breathlessness (4) and both affect coronary hemodynamics. Ultimately, this presents a dilemma among patients with AS, regarding the relative contribution of co-existing CAD on symptoms and prognosis, the optimal method of assessing CAD severity and the best management strategy for revascularization.

Current guidelines, based on a level of evidence C, recommend concomitant revascularization in patients undergoing surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR), with an angiographically defined coronary stenosis of >50% or 70% (5,6). However, using this approach to guide revascularization has its limitations and a physiologically-guided strategy may improve outcomes (7,8).

This review article evaluates the complexities of coronary hemodynamics in patients with AS, strategies to assess CAD in this patient population, and examines the evidence for revascularization and its timing in the setting of AS. Based on best available evidence, we propose an algorithm for the investigation and management of CAD in patients undergoing aortic valve replacement.

Coronary hemodynamics in aortic stenosis

Alterations in coronary hemodynamics among AS patients are the result of an intimate relationship between the myocardium and its blood supply (**Figure 1**). AS increases left ventricular (LV) afterload, which in turn increases LV wall stress. The

myocardium adapts to overcome the afterload and normalize wall stress by undergoing cellular hypertrophy, which increases LV mass (1). These changes influence myocardial oxygen demand and supply. Demand is increased by the increase in LV mass (1). Supply is restricted due to capillary rarefaction (9) and perivascular/interstitial fibrosis (10), increased LV afterload and reduced diastolic perfusion time (11) and coronary flow reserve (CFR) (12,13).

In order to meet the increased myocardial oxygen demand at rest, patients with AS have lower microvascular resistance and greater resting vasodilatation and coronary blood flow than non-AS controls (11,13,14). Consequently, there is reduced capacity for additional vasodilation of the coronary vasculature with further increases in myocardial oxygen demand during exercise or adenosine-induced hyperemia. This accounts for the lower CFR among AS patients (13,14) and is believed to be one of the main reasons that AS patients without obstructive CAD develop exertional angina. Small coronary artery diameters and inadequate LV hypertrophy (LVH) may also contribute to angina (15). The latter exists when adaptive hypertrophy is insufficient for the degree of LV pressure, resulting in high wall stress, which is an important determinant of myocardial oxygen demand (16).

Higher LV afterload increases pressure on intramural vessels- more so in the subendocardium than the subepicardium, stopping or reversing coronary blood flow during systole. As LV pressure reduces during diastole, coronary flow rapidly increases. In AS, associated LVH and diastolic dysfunction attenuate this rapid increase in diastolic flow. Additionally, the reactive hyperemia associated with diastole causes vasodilatation of subepicardial vessels before subendocardial vessels, further limiting blood flow to the subendocardium (17). This is further compounded by perivascular fibrosis and capillary rarefaction (the result of LVH without an

equivalent increase in vasculature), which increases diffusion distances for oxygen, rendering the myocardium more susceptible to ischemia (18). This sets the stage for a vicious cycle, with ischemia leading to further fibrosis. While the majority of coronary flow and myocardial perfusion takes place during diastole, in AS, the fraction of the cardiac cycle spent in diastole is reduced compared to controls, as systole is prolonged by the time taken for blood to pass through a stenosed aortic valve (19). During exercise induced tachycardia, diastolic perfusion time is further reduced, compromising blood supply (15). Any “significant” epicardial CAD will compound this effect.

Assessment of coronary stenosis

The evaluation of an epicardial coronary stenosis involves considerations regarding the approach (anatomical vs. functional), the vessels involved (single vessel vs. multi-vessel), and the contribution of the microvasculature. Patients with AS often undergo several investigations, both invasive and non-invasive as part of their work-up prior to aortic valve replacement. Each of these can provide valuable data on coronary anatomy or the functional effect of CAD.

Non-invasive assessment of coronary stenosis

Data is limited to small studies that address the safety, feasibility and diagnostic accuracy of functional, non-invasive imaging. The potential risks of hypotension and arrhythmias with stress testing discourages studies in the field, which is consequently not recommended by guidelines (5). Among non-AS patients, revascularization of moderate to severe ischemia has not shown to improve outcomes compared to medical therapy (20). This casts doubt over the role of perfusion testing (stress

echocardiography, cardiac magnetic resonance (CMR) and myocardial perfusion scintigraphy) among AS patients, where myocardial hypoperfusion and inducible functional abnormalities can be due to AS-induced supply-demand mismatch (cellular hypertrophy, capillary rarefaction, changes in coronary hemodynamics), epicardial coronary stenosis or a combination. Differentiating between the two etiologies can be challenging (21).

Stress echocardiography in a study with AS (n=50) demonstrated a sensitivity of 85% and specificity of 96.5% to localize >50% stenosis on invasive coronary angiography (22). Single photon emission computed tomography (SPECT) has been shown to predict significant CAD (defined by angiographic stenosis of either >50 or 70%) with a sensitivity of 85-100% and specificity of 71-91%. However, these were small studies and validation in larger cohorts is required. Adverse events were minimal and in one study were similar to a control group. Overall, SPECT perfusion imaging was deemed to be safe (22–26). Positron Emission Tomography (PET) imaging has also been safely used in a small cohort of AS patients with CAD (27). Although stress CMR has been performed in patients with AS (28), and has been shown to be safe in a large study (29), its diagnostic accuracy for detecting obstructive CAD in patients with AS has not been evaluated. Studies evaluating outcomes based on perfusion (ideally combined with anatomical data) compared to anatomically-guided revascularization in patients undergoing AVR, are needed.

With increased availability and advances in cardiac computed tomography (CCT), many centers are changing their practice and using CCT as the primary screening tool for coronary disease in patients with AS, reserving invasive coronary angiography if CCT is inconclusive (30). This strategy can reduce invasive coronary angiography among a high risk population by up to 37% (31). The diagnostic accuracy of CCT can

reduce with higher coronary calcium burden, which is very common among patients with AS (32). Vasodilators and chronotropic medications that are often used for CT coronary angiography are often avoided due to safety concerns in patients with AS undergoing CCT, which can result in suboptimal imaging. However, a recent study (n=42) employing computed tomography derived fractional flow reserve (CT-FFR) has shown that sublingual glycerol trinitrate and beta-blockers/ivabradine can be administered without resulting in adverse events (33). CT-FFR is a promising imaging modality that has gained considerable adoption for the evaluation of CAD in non-AS patients, as it provides both anatomical and functional data (table 1). A prospective, single center study has demonstrated its safety and feasibility in patients with AS. 92% of the CCT data was interpretable for CT FFR analysis. Compared to invasive FFR, per-vessel analysis of CT-FFR demonstrated sensitivity, specificity, positive predictive value, negative predictive value of 73.9%, 78.4%, 68.0%, 82.9% respectively and a diagnostic accuracy of 76.7% (33). Larger, multi-center studies are needed to validate these findings.

Invasive assessment of coronary stenosis

There is substantial evidence to support the use of intracoronary measurements to determine the functional significance of a coronary lesion in non-AS patients and they are recommended to guide revascularization for intermediate lesions (34). Fractional flow reserve (FFR) and instantaneous wave free ratio (iFR) both measure the pressure gradient across a coronary lesion during hyperemia and the wave-free period of diastole respectively. The pressure difference across a coronary lesion is influenced by microvascular resistance, which changes during hyperemia. This raises two limitations of FFR, that need to be acknowledged. First, the effect of adenosine in

patients with AS is often blunted, calling into question whether true FFR values can be obtained in patients with AS (35). Secondly, there is uncertainty about the change in hyperemic microvascular resistance pre- and post-TAVR and hence FFR, with studies showing discrepant results. Some studies demonstrate a reduction (13,36–38), some an increase (39,40), and others minor to non-significant changes in post-TAVR FFR compared to pre-TAVR FFR values (40–43). Further studies are needed to clarify this. By contrast, iFR obviates the need for pharmacological hyperemia and recent studies have shown that iFR measurements remain similar pre and post-TAVR (41,44). This makes iFR a potentially attractive alternative to FFR (table 1) in patients with AS. Although, iFR has been compared to FFR among AS patients in a small study (44), larger studies with outcome-driven data are required to establish appropriate cut-off points for intervention. Among patients with borderline FFR or iFR values, small changes can reclassify the functional severity of lesions and caution is required when interpreting these values (40,42). Quantitative flow ratio (QFR) which assesses the functional significance of a coronary stenosis without the use of a pressure wire or drug-induced hyperemia is an alternative to FFR and iFR. It is based on computational assessment of the passage of contrast during diagnostic coronary angiography. One study in severe AS patients demonstrated that when compared to FFR, QFR has a good diagnostic ability for identifying functionally relevant coronary stenosis, with an accuracy of 81% and an area under the receiver operating characteristic curve of 0.88 (95% CI: 0.82-0.93) (45). These physiological metrics have been used with both SAVR and TAVR to evaluate the effect of AS and valve replacement on coronary hemodynamics and outcomes.

Effect of SAVR on coronary hemodynamics

Figure 1 illustrates the changes associated with relief of AS and their effects on coronary hemodynamics. Several studies have demonstrated normalization in coronary hemodynamics following SAVR. Coronary flow profiles improve one-week post SAVR as systolic forward flow begins earlier in systole accompanied by an increase in diastolic time. These improvements are associated with improvements in energetics, oxygenation and circumferential strain (46).

Myocardial blood flow in the subendocardium, which is reduced in AS, improves as early as 2 weeks post SAVR (47) due in part to the reduction in LV wall stress that accompanies the relief of AS. At 6 months post SAVR, CFR improves due to a reduction in resting blood flow, the increase in hyperemic myocardial blood flow, and the associated reduction in LVH (14). However, even at 30 months post-SAVR, CFR may not completely normalize as hyperemic blood flow can remain blunted (48).

Because CFR is dependent on diastolic perfusion time, severity of AS and LV afterload (11,49), the presence of hypertension after SAVR is an important consideration as it contributes to LV afterload, preventing structural and functional changes that would improve myocardial blood flow.

The type of prosthesis used, and the presence of patient-prosthesis mismatch (PPM) also affect CFR. Stentless biological prosthesis closely resemble physiological geometry and diastolic flow patterns and do not result in diastolic leakage flow.

Consequently, they can result in normalization of CFR values. Metallic prosthesis, on the other hand, result in less of an improvement in CFR. PPM can cause increased aortic flow turbulence and reduced coronary flow. However, compared to metallic prosthesis, CFR with stentless biological prosthesis is not adversely affected by PPM (50).

Effect of TAVR on coronary hemodynamics

TAVR results in reduced afterload and subendocardial compression, which subsequently increases systolic coronary flow at rest (18) and diastolic coronary flow during hyperemia (18,36,51). These hemodynamic changes are likely to account for the relief of angina in some patients immediately following TAVR (52). Figure 1 summarizes the changes associated with relief of AS and their effects on coronary hemodynamics.

There is uncertainty regarding normalization of CFR post-TAVR with some studies suggesting immediate improvement post-TAVR (13) and others suggesting it is a long term phenomenon (18,53). Improvement in CFR is predominantly driven by a decrease in hyperemic microvascular resistance, which increases vasodilatory capacity and hyperemic blood flow. Post-TAVR aortic regurgitation may play a detrimental role in these changes (13), as it is known to reduce CFR and change phasic coronary flow from predominantly diastolic to systolic in a severity-dependent manner (54). At rest, microvascular resistance and flow velocity remained unchanged immediately pre and post-TAVR as the driving forces- myocardial mass and capillary rarefaction are still present- requiring the compensatory vasodilatation at rest (13).

Given the overall improvements in coronary hemodynamics and in some cases angina post-TAVR, the significance of coexisting epicardial coronary stenosis needs to be carefully considered. A recent study sought to identify the ‘predominant lesion’ in patients with severe AS and coexisting coronary stenosis by comparing iFR in AS patients treated with TAVR to iFR in patients with coronary stenosis (without AS) treated with PCI. Their study was based on the concept that both AS and coronary stenosis independently affect microvascular resistance during the wave free period of diastole, such that low resistance indicates a higher severity of stenosis. In AS, resting

microvascular resistance was low and subsequently increased following TAVR, signifying the role of AS in reducing coronary flow. This increase was independent of the severity of coexisting coronary stenosis. TAVR achieved a similar increase in microvascular resistance as stenting a coronary stenosis with an iFR > 0.74. With an iFR ≤ 0.74, PCI achieved larger increases in microvascular resistance than TAVR, concluding that for any coronary stenosis with an iFR > 0.74, AS was the predominant lesion and TAVR achieved greater improvements in microvascular hemodynamics than PCI (37). This study highlights how dual pathology (severe AS and coronary stenosis) influences coronary hemodynamics and the importance and feasibility of assessing the effect of each lesion. However, further validation of these physiological assessment tools is required to guide management. Until trial data emerges, revascularization decisions have to be made on a case-by-case basis, with functional data contributing to this decision.

Revascularization in aortic stenosis

Guidelines for revascularization in non-AS patients make a distinction between revascularization for symptoms and prognosis depending on the site and extent of CAD (34). These have been clinically extrapolated into the AS population to guide revascularization. However, in this unique patient group it is key to understand the evidence available on the impact of revascularization in this cohort.

Revascularization with SAVR

A systematic review showed that CAD among patients undergoing SAVR increases the risk of early mortality, but this included a heterogeneous collection of studies. Unadjusted mortality was higher among patients undergoing SAVR and concomitant

coronary artery bypass grafting (CABG) compared to isolated SAVR (55). However, two studies have demonstrated that, after propensity matching, mortality was similar in both cohorts, suggesting the differences in reported unadjusted mortality rates can be accounted for by existing comorbidities (56,57). Furthermore, two observational retrospective studies involving patients with AS and coexisting CAD, treated with combined CABG and SAVR had significantly reduced early and late mortality compared to the SAVR-only group (58,59). The prognostic benefit was evident in both coronary stenosis >50% and >70% (59) (table 1).

PCI can also be performed safely as part of a hybrid procedure in patients undergoing SAVR without increasing the risk of short term mortality (60), providing an alternative to CABG and SAVR (61). Bleeding complications remain a concern with hybrid procedures due to the need for dual antiplatelet agents (60), however performing PCI on the day of or day prior to SAVR may reduce bleeding rates, potentially because platelets are not completely inhibited by the time of SAVR (62).

Revascularization with TAVR

With the rapid adoption of TAVR, the assessment and management of CAD is becoming increasingly important. A key advantage of TAVR over SAVR is that PCI with TAVR can be performed separately, whereas CABG needs to be performed at the same time as SAVR. Several non-randomized studies and a meta-analysis have demonstrated that CAD does not affect short and mid-term outcomes in patients undergoing TAVR, with similar outcomes among patients treated medically and those with PCI (63–71) (table 1).

In the short-term, post-TAVR myocardial injury, determined by serum biomarkers is independently influenced by significant CAD, with complex CAD having a greater

impact (72,73). However, revascularization even in patients with severe CAD (high SYNTAX scores) has not demonstrated an improvement in short-term outcomes, suggesting that it is not a pre-requisite pre-TAVR (70,74–76).

However, in the mid-term, some studies do suggest a mortality benefit with a selective revascularization strategy, especially among patients with a high SYNTAX score) (63–71). Studies addressing the completeness of revascularization have yielded conflicting results- with some demonstrating that incomplete revascularization is associated with increased cardiovascular events (70,76,77), whilst others demonstrating that it does not (64,71,74,75). Several of these studies were limited by low patient numbers, short follow-up and differences in cohorts based on lesion location, angiographic severity, atherosclerotic burden, comorbidities and the definition of incomplete revascularization. Further studies are needed to provide clarity on this.

Recent results from the ACTIVATION study, a randomized controlled trial evaluating the safety and efficacy of medical therapy to PCI in coronary vessels with >70% stenosis prior to TAVR, demonstrated similar short-term outcomes. Among 235 patients, (Canadian Cardiovascular Society (CCS) class 0-2), PCI compared to no PCI, had similar rates of mortality and rehospitalization at 1 year (41.5 vs 44%; $p=0.067$) and higher bleeding rates (44.5 vs 28.4%; $p=0.02$) (78). It should be noted that patients in this study had low symptom burden, the recruitment target ($n=310$) was not met and PCI was guided by angiographic stenosis severity.

Several studies have investigated the role of physiology-guided revascularization in patients with CAD and AS. In a single-center, observational study, FFR-guided PCI was shown to be superior to angiographically-guided PCI in patients undergoing TAVR. The authors reported better major adverse cardiac and cerebrovascular event–

free survival in the FFR-guided group compared to the angiography-guided group (hazard ratio 0.4; 95% confidence interval 0.2–1.0; p=0.035) at 2 years following TAVR (79). The NOTION-3 (80) and FAITAVR (81) trials are currently underway to assess the role of FFR in guiding revascularization upstream of TAVR (table 1).

Timing of revascularization

The section below discusses revascularization in patients with stable CAD. However, among patients who present acutely, the predominant lesion (AS vs CAD) needs to be identified in order to guide further management. This can be challenging as both acute decompensated aortic stenosis (ADAS) and acute coronary syndrome (ACS) can present with an increase in cardiac troponin, ECG changes and similar symptoms (82). Clinical evaluation, coronary angiography and echocardiography are all required to differentiate between the two presentations. If ACS is the predominant condition, PCI should be undertaken first. However, if ADAS is the predominant condition, valve replacement should be undertaken first, with studies supporting the feasibility of TAVR in ADAS (83,84). Figure 2 describes factors that support revascularization decisions either pre-, peri- or post-valve replacement

Peri-procedural revascularization

For surgical patients, CABG at the time of SAVR makes clear sense given the risks of reoperation. CABG has proven its prognostic superiority over PCI in patients with triple vessel and severe CAD (SYNTAX score>32) and should sway the decision away from percutaneous and towards surgical treatment (85,86). Among TAVR patients however the timing is less clear. Alternatively, PCI can be performed concomitantly with TAVR where there is the inherent benefit to the patient of a

‘single procedure’ and hospital admission. Timing considerations include the risk of acute kidney injury among patients with pre-existing renal function and should be individualized (87). In both settings, the need to withhold dual antiplatelet therapy (DAPT) in the event of TAVR-related bleeding or vascular complications can be potentially dangerous. Evidence from observational studies suggest that staging PCI at least 30 days pre-TAVR can reduce bleeding and vascular complications (88). A nationwide registry showed that performing concomitant TAVR and PCI during the same admission can increase mortality compared to TAVR alone (10.7% vs 4.6%; $p < 0.001$ respectively) (89).

Post-TAVR PCI

As aortic valve replacement often leads to symptom improvement (angina/dyspnea), among patients where equipoise/uncertainty remains, a strategy of initial valve replacement (at least in the case of TAVR), with revascularization deferred until after the TAVR if symptoms persist, may also be reasonable. This maybe more applicable to younger and lower risk patients. Supporting a post-TAVR PCI strategy is the evidence that neither CAD nor revascularization adversely affects TAVR short-term outcomes.

However, performing PCI after TAVR can be technically challenging as access to the coronary ostia can be partially obstructed by the native leaflets, the prosthetic valve’s commissural posts or skirt, especially in the case of a supra-annular self-expanding prosthesis (90–92). Although, more recent studies have reported high success rates for PCI post-TAVR (>95%), regardless of valve prosthesis type (93–95). Challenging cases may require modifications to PCI technique (90), and benefit from CT angiography to assist in planning PCI (95) and pre-TAVR simulation to assess the

effect of the prosthesis on coronary hemodynamics and its position relative to the coronary ostia (96). When performing TAVR, optimizing commissural alignment in order to maintain access to the coronary ostia is feasible with some valves and is especially important for supra-annular bioprosthesis (97). If there is a risk of coronary obstruction, electrosurgical laceration of the native or bioprosthetic valve leaflets can be performed using the BASILICA technique (98). Alternatively PCI can be performed pre-TAVR.

Pre-TAVR PCI

Although revascularization pre-TAVR can reduce the ischemic burden during rapid pacing for valve deployment (99,100), the evidence discussed above suggests that neither CAD nor revascularization affect hard procedural outcomes with TAVR.

Prognostic lesions that will require revascularization should be considered for PCI pre-TAVR, especially if there are any high-risk features present. PCI should also be considered pre-TAVR in patients with anatomical and procedural characteristics that may render PCI challenging post-TAVR.

Coronary access is an increasingly important issue in lower risk patients. As life expectancy exceeds valve durability, TAVR-in-TAVR or TAVR-in-SAVR is required, increasing the risk of coronary ostial obstruction by pinning the old bioprosthetic leaflets against the sinotubular junction with the new valve. This is more of a concern with the taller Corevalve/Evolut R/Pro valves than the Sapien 3 valves and among surgical bioprosthesis- stentless valves and valves with leaflets sutured on the outer side of the stent frame (101–103). In patients considered for the prosthesis mentioned above, PCI should be considered pre-TAVR or pre-TAVR-in-valve.

Additionally, PCI for complex coronary anatomy that requires extra support and

advanced techniques maybe easier without having to manipulate around a TAVR (104). Patients with short coronary ostial heights and narrow sinus of Valsalva may also benefit from pre-TAVR PCI (105,106).

Although, the safety and efficacy of PCI in patients with AS, including for complex coronary lesions, was similar to patients without AS in one study (107), the potential risk of hemodynamic instability still exists and needs to be carefully considered (108,109). Ostial left main stenosis is a recognized high-risk feature associated with coronary obstruction during TAVR requiring unplanned left main PCI. This is associated with increased mortality even if PCI is successful. These patients should be considered for pre-TAVR PCI or measures taken to protect the left main stem during TAVR (103). As discussed above, bleeding risk and the need to withhold DAPT in the setting of a TAVR-related complication needs to be considered with pre-TAVR PCI. Adopting a staged procedure with PCI preceding TAVR by several months can reduce the risk of stent thrombosis if DAPT need to be withheld (110).

Suggested management strategies

Based on current guidelines for revascularization and existing evidence, we have developed an algorithm to guide revascularization in patients undergoing valve replacement with coexisting CAD (**Figure 3**). Other factors, as indicated by guidelines, including comorbidities, procedure-related risks and patient preference should be considered concomitantly in order to formulate a management strategy (5). Initial coronary assessment with CT and/or invasive coronary angiography will identify the extent and severity of CAD. Those without significant CAD can proceed to aortic valve replacement without revascularization. Triple vessel disease or a SYNTAX score >32 should sway the decision towards surgical rather than

percutaneous intervention. Evidence from non-AS patients suggests that revascularization of left main stem and proximal CAD is prognostically beneficial. Non-proximal stenosis >90% is very often hemodynamically significant (34,111) and all three lesions can be revascularized with PCI, although CABG is also a reasonable option. Patients with a LMS stenosis <50%, an intermediate proximal stenosis (40-70%) or a non-proximal stenosis (50-90%) should have functional assessment- with the only existing, albeit limited evidence supporting the use of FFR and iFR (37,79). The timing of this evaluation and subsequent PCI if needed can be based on the presence of high risk features that would make PCI safer or easier pre-TAVR or ongoing symptoms post-TAVR (**figure 2**). Fundamental to all management decisions is an evaluation by the multi-disciplinary team, where findings can be discussed, benefits and risks weighed, and a joint management decision established. For those deemed appropriate for revascularization, a bleeding risk assessment is helpful in decision making. Although risk stratification tools have not been developed for TAVR patients, scores such as the HAS-BLED or PRECISION-DAPT scores can help gauge the bleeding risk (112,113). Where equipoise remains, performing valve replacement in the first instance, using a prosthesis that will permit future revascularization is a reasonable option.

Open Questions – need for further research

There remain many unanswered questions regarding the optimal strategy for assessing and managing epicardial coronary stenosis in the setting of AS and aortic valve replacement. Current guidelines recommend physiology-guided revascularization in non-AS patients with CAD. We now need prospective randomized studies evaluating the efficacy of FFR/iFR-guided revascularization in AS patients, of which several are

underway (table 2). Non-invasive imaging to guide revascularization within the context of AS is an attractive prospect with CT-derived FFR in particular, as a pre-procedural CT will be undertaken in almost all patients being considered for TAVR.

Conclusions

The coexistence of epicardial coronary artery disease among AS patients is common, however diagnostic and treatment alternatives remain ambiguous and highly debated. Physiological changes of AS on coronary hemodynamics challenge the physiologic ischemic assessment of concomitant coronary artery disease. Based on current evidence, we provide a detailed review and propose an algorithm for the management of coronary artery disease in patient with significant aortic stenosis.

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Conflicts of interest

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1 **Tables**

2

Study	Design	Patient population	Patients (n)	Follow-up	Outcome
Roberts et al	Retrospective observational single-centre	SAVR + CABG vs SAVR	871	10 years	Adjusted mortality of concomitant CABG: HR 1.01, 95% CI:0.74-1.34; p=0.976
Beach et al	Retrospective observational single-centre	Propensity matched SAVR + CABG vs SAVR	3923	Median: 4.7 years	Similar survival: 80% in matched groups
Thalji et al	Retrospective observational single-centre	Patients with AS and CAD having either SAVR + CABG vs SAVR alone	1308	Mean: 4.7 years	Adjusted mortality for concomitant CABG: HR 0.62, 95% CI: 0.49-0.79; p<0.001

Tjang et al	Qualitative systematic review	All patients with AS undergoing SAVR +/- CABG	106660	Early: <30 days or in-hospital mortality. Late: >30 days or post-discharge mortality	Inconclusive evidence whether concomitant CABG affects early or late mortality
Santana et al	Retrospective observational single-centre	Hybrid (PCI + minimally invasive SAVR) vs matched CABG + SAVR	117	In-hospital & 30 days	<ul style="list-style-type: none"> - In-hospital mortality for hybrid vs conventional group: 0 vs 3.8%; p=0.11 - Death, renal failure, stroke at 30 days for hybrid vs conventional group: 1.5 vs 28.8%; p=0.001
Brinster et al	Prospective cohort Single-centre	Hybrid (PCI + minimally invasive SAVR)	18	Mean: 19 months	1 post-operative death. No late mortality
Ussai et al	Prospective registry	TAVR in patients with previous	663	12 months	MACCE in CAD vs no CAD group: adjusted HR: 0.76, 95% CI: 0.42-1.36; p=0.353

	Multi-centre	revascularization vs TAVR alone			
Van Miegham et al	Retrospective observational single-centre	CR vs IR in TAVR patients	263	Median: 18 months	1 year mortality in CR vs IR: 79.9 vs 77.4%; p=0.85
D'Ascenzo et al	Meta-analysis	TAVR patients	2472	Median: 452 days	Mortality risk with CAD with multivariate approach: OR 1.0, 95% CI: 0.67-1.5; I ² 0%
Masson et al	Retrospective observational single-centre	TAVR patients divided according to Duke Myocardial Jeopardy Score	136	1 year	No mortality difference between groups (p=0.63)
Gasparetto et al	Prospective registry single- centre	TAVR patients with CAD (+/-	191	Mean: 12.9 months	No difference in all-cause and cardiovascular mortality (log-rank p=0.282 and 0.739 respectively)

		revascularization) vs without CAD			
Wenaweser et al	Prospective registry single-centre	TAVR vs TAVR + PCI and No CAD vs CR vs IR	256	Up to 2 years	<ul style="list-style-type: none"> - Mortality according to PCI status: Log-rank p=0.96 - Mortality according to CAD and revascularisation status: Log rank p=0.16
Stefanini et al	Prospective registry single-centre	No CAD vs low SS vs high SS among TAVR patients	445	Mean: 258 days	CV death: no CAD vs low SS vs high SS: 8.6 vs 13.6 vs 20.4% respectively; p=0.029
López Otero et al	Retrospective observational single-centre	CR (rSS=0) vs RCR (rSS 0-7) vs IR (rSS>7) among TAVR patients	349	Mean: 35.2 months	<ul style="list-style-type: none"> - MACE: log-rank p=0.866 - Death: log-rank p=0.605

Paradis et al	Retrospective observational 2-centre with angiographic core lab	No CAD vs low SS (1-22) vs intermediate SS (23-32) vs high SS (>32) among TAVR patients	377	1 year	Mortality, MI, stroke: log-rank p=0.688
Saia et al	Retrospective observational single-centre	No CAD vs CAD CR vs IR among TAVR patients	540	Median: 57.8 months	Survival free from CV death for: <ul style="list-style-type: none"> - no CAD vs CAD: 77.9 vs 79.6%; p=0.98 - CR vs IR: 84.3 vs 74.3%; p=0.25
Witberg et al	Meta-analysis	No CAD vs RCR vs IR among TAVR patients	3107	0.7-3 years	<ul style="list-style-type: none"> - Mortality for IR vs no CAD: OR 1.85, 95% CI: 1.42-2.40; p<0.01. - Mortality for IR vs RCR: OR 1.69, 95% CI: 1.26-2.28; p<0.001. - Mortality for RCR vs no CAD: OR 1.11, 95% CI: 0.89-1.39; p=0.33.

Landt et al	Retrospective observational single-centre	No CAD vs CR vs IR among TAVR patients	875	1 year	CV mortality in: - CR vs no CAD: 7.4 vs 9.0%; log rank p=0.537 - IR vs no CAD: 17.1 vs 9.0%; log rank p= 0.054 - CR vs IR: 7.4 vs 17.1%; p=0.042 Revascularization was beneficial in patients with multivessel CAD but not with single vessel CAD
Faroux et al	Retrospective observational multi-centre	IR vs CR among TAVR patients	1197	Median: 2 years	- Death, MI, stroke: log rank p=0.005. - CR vs IR in multivariate model: HR: 0.77, 95% CI: 0.63-0.95; p=0.014

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2 Table 1: Summary of studies evaluating the impact of peri- and pre-aortic valve replacement coronary revascularization. SS- SYNTAX score,

3 rSS- residual SYTAX score, MI- myocardial infarction, PCI- percutaneous coronary intervention, SAVR- surgical aortic valve replacement,

- 1 TAVR- transcatheter aortic valve replacement, MACCE- death, MI, stroke, conversion to open surgery, MACE- death, myocardial infarction
- 2 and further revascularization, CR- complete revascularization, IR- incomplete revascularization, RCR- reasonable complete revascularization,
- 3 HR- hazards ratio, OR- odds ratio, CV- cardiovascular, CI- confidence interval.
- 4

Physiological index	Mechanistic principle	Considerations in aortic stenosis
Coronary Flow Reserve (CFR)	Maximal blood flow during hyperemia compared to rest	<ul style="list-style-type: none"> - Requires adenosine induced hyperemia - CFR reduces in AS - Tends to underestimate blood flow in AS - Susceptible to changes in heart rate, blood pressure and cardiac contractility - Unable to differentiate between epicardial and microvascular contribution to blood flow
Fractional Flow Reserve (FFR)	Trans-stenotic pressure gradient during maximal hyperemia	<ul style="list-style-type: none"> - Requires adenosine induced hyperemia - Effect of adenosine maybe blunted in AS - FFR tends to underestimate lesion severity in AS
Instantaneous wave free ratio (iFR)	Trans-stenotic pressure gradient during the wave free period of diastole	<ul style="list-style-type: none"> - No change pre vs post-TAVR
Computed tomography Fractional Flow Reserve (CT-FFR)	Blood flow simulation on acquired coronary CT angiograms to calculate FFR	<ul style="list-style-type: none"> - Limited evidence in AS, especially among those with prior revascularization - Requires good quality CT imaging, which can be affected by high calcium burden and changes in coronary hemodynamics in AS - May overestimate trans-stenotic gradients compared to FFR

1 Table 1: Physiological indices of coronary artery assessment in patients with aortic
 2 stenosis.
 3

Study name	Study type	Primary endpoint	Completion date
FAVOR IV-QVAS Quantitative Flow Ratio (QFR) Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease NCT03977129	Multicenter, randomized control trial in patients undergoing primary valvular surgery with coexisting CAD (stenosis \geq 50%)	Composite endpoint: all cause death, non-fatal myocardial infarction, non- fatal stroke, unplanned coronary revascularization, new renal failure requiring dialysis at 30 days post- surgery	2022
NOTION 3 Revascularization in Patients Undergoing Transcatheter	Multicenter, open label, randomized controlled trial evaluating the effect of FFR- guided	Composite endpoint of all- cause mortality, myocardial infarction or urgent	2022

Aortic Valve Implantation NCT03058627	revascularization to conservative management in patients with CAD undergoing TAVR	revascularization at 1-year post-TAVR	
TAVI-PCI Optimal Timing of Transcatheter Aortic Valve Implantation and Percutaneous Coronary Intervention NCT04310046	Open label, randomized controlled trial evaluating the safety and efficacy of FFR-guided revascularization pre- or post-TAVR	Composite of all- cause death, non- fatal myocardial infarction, ischemia-driven revascularization, rehospitalization and bleeding	2023
FAITAVI Functional assessment in TAVI NCT03360591	Single center, open label, randomized control trial comparing FFR- guided PCI to angiographically- guided PCI in TAVR patients	Composite endpoint of all cause death, myocardial infarction, stroke, major bleeding, and target vessel revascularization at 12 months post- TAVR	2020

<p>TCW</p> <p>The transcatheter valve and vessels trial</p> <p>NCT03424941</p>	<p>Multicenter, international open label, randomized controlled, non-inferiority trial comparing FFR-guided PCI + TAVR to CABG + SAVR</p>	<p>Composite endpoint of mortality, myocardial infarction, disabling stroke, target vessel revascularization, valve reintervention at 1-year post-intervention</p>	<p>2021</p>
<p>FORTUNA</p> <p>Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVI</p> <p>NCT03665389</p>	<p>Single center open label study comparing CT based FFR pre-TAVR to FFR/iFR pre and post-TAVR</p>	<p>Evaluating the utility of CT derived FFR</p>	<p>2022</p>

1 Table 2: On-going studies assessing the efficacy of physiologically guided
2 revascularization in patients undergoing aortic valve replacement for AS.

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1 **Figure legends**

2 Figure 1: Myocardial remodeling changes related to aortic stenosis and reverse
3 remodeling related to aortic valve replacement. Myocardial remodeling and an
4 increase in afterload affect coronary demand and supply such that the myocardium (in
5 particular the subendocardium) becomes susceptible to ischemia. After aortic valve
6 replacement, afterload reduces and remodeling reverses to a certain extent, leading to
7 a beneficial change in coronary hemodynamics and thus a reduction in ischemic
8 susceptibility. Cross-sectional image of the heart obtained from www.vecteezy.com.

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11 Figure 2: Based on coronary, TAVR, SAVR and anatomical factors, the heart team
12 can decide on the timing of revascularization; either pre, peri or post-AVR.

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14

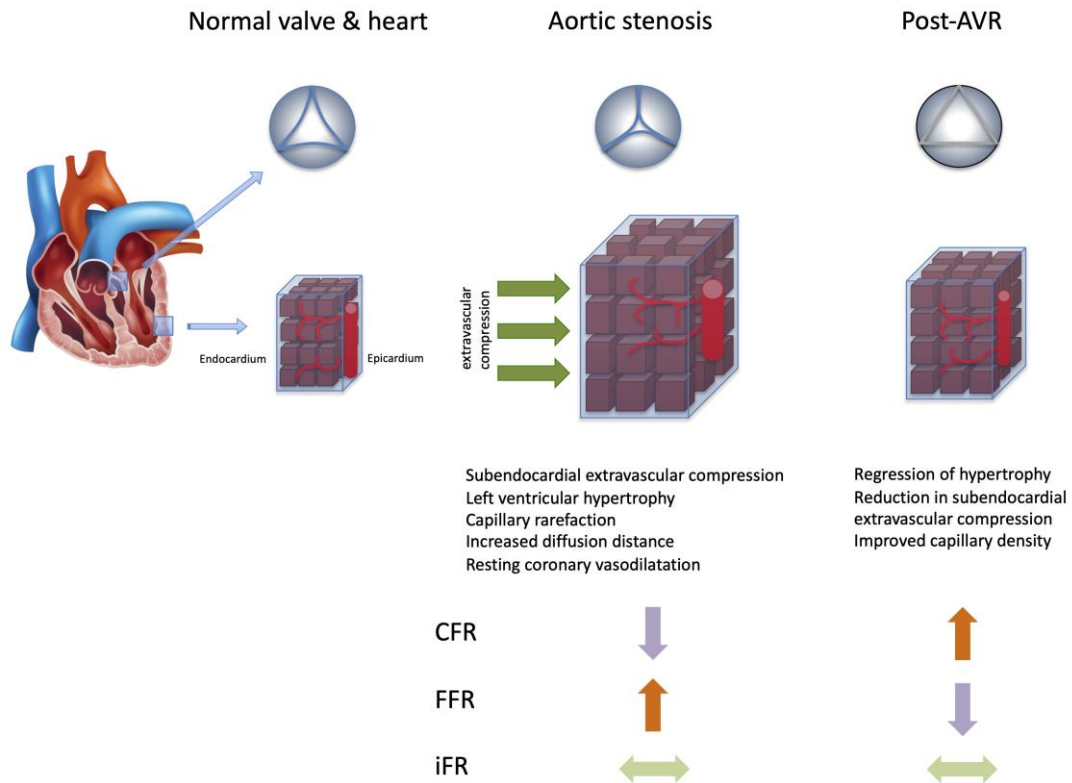
15 Figure 3: This proposed algorithm for revascularization among patients undergoing
16 valve replacement, considers current practices, expert opinion and existing evidence.
17 Among patients where further evaluation of their CAD is indicated, the bottom part of
18 the algorithm should be used. Figure 3 should be used in conjunction with figure 2 to
19 decide on the timing of revascularization for each subgroup.

20

21

22 Central illustration: Myocardial remodeling changes related to aortic stenosis and
23 reverse remodeling related to aortic valve replacement. Myocardial remodeling and an
24 increase in afterload affect coronary demand and supply such that the myocardium (in
25 particular the subendocardium) becomes susceptible to ischemia. After aortic valve

- 1 replacement, afterload reduces and remodeling reverses to a certain extent, leading to
- 2 a beneficial change in coronary hemodynamics and thus a reduction in ischemic
- 3 susceptibility. Cross-sectional image of the heart obtained from www.vecteezy.com.
- 4



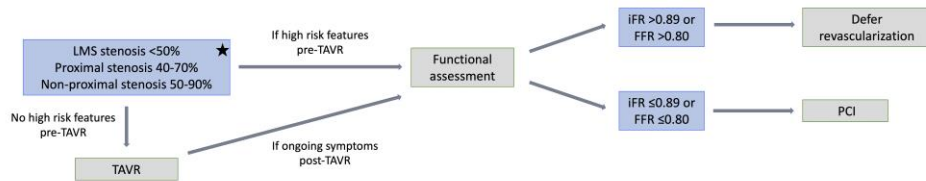
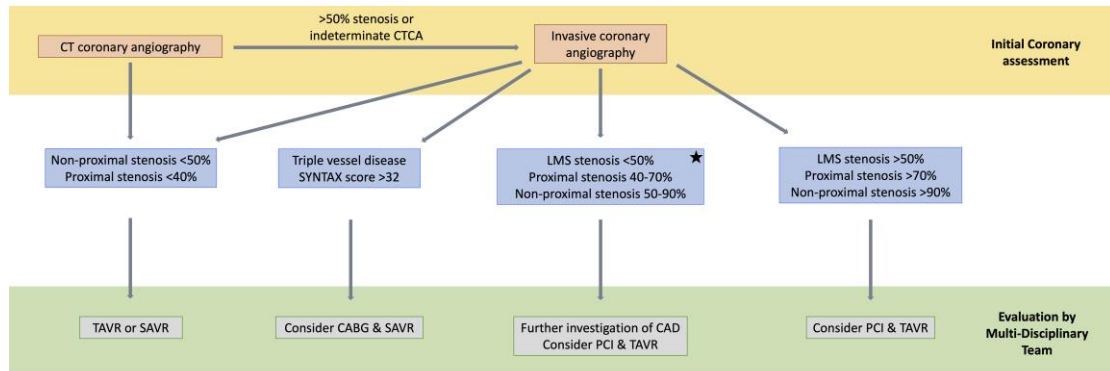
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2 Figure 1

<u>Pre-valve replacement</u>	<u>Peri-valve replacement</u>	<u>Post-valve replacement</u>
For PCI - Short coronary ostial heights - Supra-annular valve considered - Complex coronary lesions - For TAVR-in-valve - Ostial left main stem stenosis - Prognostically significant stenosis	For CABG - Triple vessel disease - Severe disease (SYNTAX score>32)	For PCI - Ongoing angina/dyspnea - Functionally significant stenosis
	For PCI - Non-complex single-vessel stenosis	

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4 Figure 2



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2 Figure 3