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STATE-OF-THE-ART REVIEW

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 patients with AS having significant CAD. Given the challenges when both disease states are present, these patients require a tailored approach diagnostically and therapeutically. In this review the authors address the impact of AS and aortic valve replacement (AVR) on coronary hemodynamic status and discuss 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 hemodynamic status and reduce ischemia. Assessment of the significance of coexisting CAD can be done using noninvasive and invasive metrics. Revascularization in patients undergoing AVR can benefit certain patients in whom 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 hemodynamic status, they 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 multidisciplinary team. (J Am Coll Cardiol Intv 2021;14:2083–2096) © 2021 by the American College of Cardiology Foundation.

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

Current guidelines (Level of Evidence: C) recommend concomitant revascularization in patients undergoing surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR), with

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ABBREVIATIONS AND ACRONYMS

ADAS = acute decompensated aortic stenosis

AS = aortic stenosis

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CT = computed tomography

CFR = coronary flow reserve

DAPT = dual-antiplatelet therapy

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

LV = left ventricular

LVH = left ventricular hypertrophy

PCI = percutaneous coronary intervention

PPM = patient-prosthesis mismatch

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

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).

In this review we evaluate the complexities of coronary hemodynamic parameters in patients with AS and strategies to assess CAD in this patient population, and we examine the evidence for revascularization and its timing in the setting of AS. On the basis of the best available evidence, we propose an algorithm for the investigation and management of CAD in patients undergoing aortic valve replacement.

CORONARY HEMODYNAMIC STATUS IN AS

Alterations in coronary hemodynamic parameters among patients with AS are the result of an intimate relationship between the myocardium and its blood supply (**Central Illustration**). 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 because of capillary rarefaction (9) and perivascular or interstitial fibrosis (10), increased LV afterload, and reduced diastolic perfusion time (11) and coronary flow reserve (CFR) (12,13).

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 control subjects without AS (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 patients with AS (13,14) and is believed to be one of the main reasons patients with AS 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).

HIGHLIGHTS

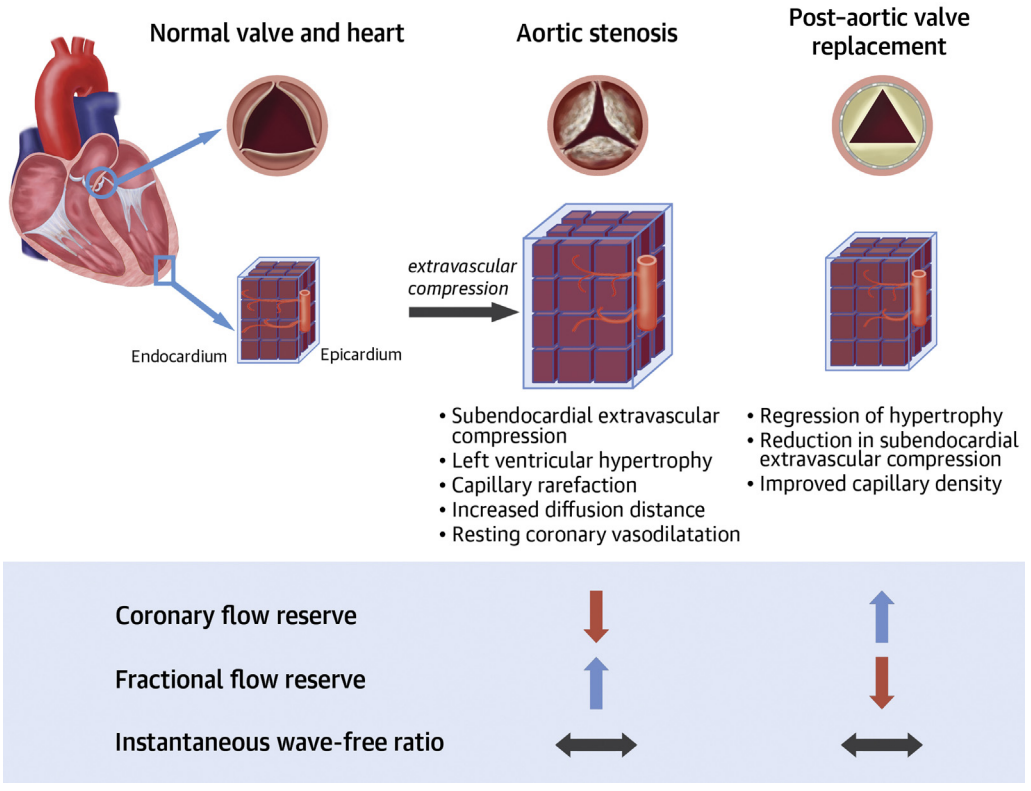
- The coexistence of epicardial CAD among patients with AS is common.
- Diagnostic and treatment alternatives remain ambiguous and highly debated.
- Physiological changes of AS on hemodynamic status challenge assessment of concomitant CAD.
- Studies evaluating the efficacy of revascularization in patients with AS are needed.

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. Although the majority of coronary flow and myocardial perfusion takes place during diastole, in patients with AS, the fraction of the cardiac cycle spent in diastole is reduced compared with control subjects, 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 multivessel), and the contribution of the microvasculature. Patients with AS often undergo several investigations, both invasive and noninvasive, 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.

CENTRAL ILLUSTRATION **Myocardial Remodeling Changes Related to Aortic Stenosis and Reverse Remodeling Related to Aortic Valve Replacement**



Patel, K.P. et al. J Am Coll Cardiol Intv. 2021;14(19):2083–2096.

Myocardial remodeling and an increase in afterload affect coronary demand and supply such that the myocardium (in particular the subendocardium) becomes susceptible to ischemia. After aortic valve replacement, afterload reduces and remodeling reverses to a certain extent, leading to a beneficial change in coronary hemodynamic status and thus a reduction in ischemic susceptibility.

NONINVASIVE ASSESSMENT OF CORONARY STENOSIS. Data are limited to small studies that address the safety, feasibility, and diagnostic accuracy of functional, noninvasive imaging. The potential risks for hypotension and arrhythmias with stress testing discourage studies in the field, and stress testing is consequently not recommended in guidelines (5). Among patients without AS, revascularization of moderate to severe ischemia has not shown to improve outcomes compared with medical therapy (20). This casts doubt over the role of perfusion testing (stress echocardiography, cardiac magnetic resonance, and myocardial perfusion imaging) among patients with AS, in whom myocardial hypoperfusion and inducible functional abnormalities can be due to AS-induced supply-demand mismatch (cellular hypertrophy, capillary rarefaction, changes in coronary hemodynamic status), epicardial coronary stenosis, or a combination. Differentiating between the 2 etiologies can be challenging (21).

Stress echocardiography in a study of AS (n = 50) demonstrated sensitivity of 85% and specificity of 96.5% to localize >50% stenosis on invasive coronary angiography (22). Single-photon emission computed tomography (CT) has been shown to predict significant CAD (defined by angiographic stenosis of either >50 or 70%) with sensitivity of 85% to 100% and specificity of 71% to 91%. However, these were small studies, and validation in larger cohorts is required. Adverse events were minimal and in one study were similar to those observed in a control group. Overall, single-photon emission computed tomographic perfusion imaging was deemed to be safe (22-26). Positron emission tomographic imaging has also been

safely used in a small cohort of patients with AS with CAD (27). Although stress cardiac magnetic resonance 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 on the basis of perfusion (ideally combined with anatomical data) compared with anatomically guided revascularization in patients undergoing aortic valve replacement are needed.

With increased availability and advances in cardiac CT, many centers are changing their practice and using cardiac CT as the primary screening tool for coronary disease in patients with AS, reserving invasive coronary angiography if findings on cardiac CT are inconclusive (30). This strategy can reduce invasive coronary angiography among a high-risk population by up to 37% (31). The diagnostic accuracy of cardiac CT 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 computed tomographic coronary angiography are often avoided because of safety concerns in patients with AS undergoing cardiac CT, which can result in suboptimal imaging. However, a recent study (n = 42) using CT-derived fractional flow reserve (FFR) showed that sublingual glycerol trinitrate and beta-blockers or ivabradine can be administered without resulting in adverse events (33). CT-derived FFR is a promising imaging modality that has gained considerable adoption for the evaluation of CAD in patients without AS, as it provides both anatomical and functional data (**Table 1**). A prospective, single-center study demonstrated its safety and feasibility in patients with AS. Ninety-two percent of the cardiac computed tomographic data were interpretable for CT-derived FFR analysis. Compared with invasive FFR, per-vessel analysis of CT-derived FFR demonstrated sensitivity, specificity, positive predictive value, and negative predictive value of 73.9%, 78.4%, 68.0%, and 82.9%, respectively, and diagnostic accuracy of 76.7% (33). Larger, multicenter 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 patients without AS, and they are recommended to guide revascularization for intermediate lesions (34). 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 2 limitations of FFR that must 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). Second, there is uncertainty about the change in hyperemic microvascular resistance pre- and post-TAVR and hence FFR, with studies showing discrepant results. Some studies demonstrated reductions (13,36-38), some increases (39,40), and others minor to nonsignificant changes in post-TAVR FFR compared with pre-TAVR FFR values (40-43). Further studies are needed to clarify this. In contrast, iFR obviates the need for pharmacologic 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 with FFR among patients with AS 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, 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 patients with severe AS demonstrated that compared with FFR, quantitative flow ratio has a good diagnostic ability for identifying functionally relevant coronary stenosis, with 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 hemodynamic status and outcomes.

EFFECT OF SAVR ON CORONARY HEMODYNAMIC STATUS

The **Central Illustration** depicts the changes associated with relief of AS and their effects on coronary hemodynamic status. Several studies have demonstrated normalization of coronary hemodynamic status following SAVR. Coronary flow profiles improve 1 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).

TABLE 1 Physiological Indices of Coronary Artery Assessment in Patients With AS

Physiological Index	Mechanistic Principle	Considerations in Aortic Stenosis
CFR	Maximal blood flow during hyperemia compared with rest	• 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
FFR	Trans-stenotic pressure gradient during maximal hyperemia	• Requires adenosine-induced hyperemia • Effect of adenosine may be blunted in AS • FFR tends to underestimate lesion severity in AS
iFR	Trans-stenotic pressure gradient during the wave-free period of diastole	• No change pre- vs post-TAVR
(CT FFR	Blood flow simulation on acquired coronary CT angiography to calculate FFR	• Limited evidence in AS, especially among patients 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 with FFR

AS = aortic stenosis; CFR = coronary flow reserve; CT = computed tomographic; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; TAVR = transcatheter aortic valve replacement.

Myocardial blood flow in the subendocardium, which is reduced in AS, improves as early as 2 weeks post-SAVR (47), in part because of the reduction in LV wall stress that accompanies the relief of AS. At 6 months post-SAVR, CFR improves because of 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 prostheses 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 prostheses, in contrast, result in less of an improvement in CFR. PPM can cause increased aortic flow turbulence and reduced coronary flow. However, compared with metallic protheses, CFR with stentless biological prostheses is not adversely affected by PPM (50).

EFFECT OF TAVR ON CORONARY HEMODYNAMIC STATUS

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). The **Central Illustration** summarizes the changes associated with relief of AS and their effects on coronary hemodynamic status.

There is uncertainty regarding normalization of CFR post-TAVR, with some studies suggesting immediate improvement post-TAVR (13) and others suggesting that it is a long-term phenomenon (18,53). Improvement in CFR is driven predominantly 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 compensatory vasodilatation at rest (13).

Given the overall improvements in coronary hemodynamic status 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 patients with AS treated with TAVR with iFR in patients with coronary stenosis (without AS) treated with percutaneous coronary intervention (PCI). Their study was based on the concept that both AS and coronary stenosis independently affect microvascular resistance

TABLE 2 Summary of Studies Evaluating the Impact of Coronary Revascularization, Peri- and Pre-Aortic Valve Replacement

First Author	Design	Patient Population	Patients	Follow-Up	Outcome
Roberts et al	Retrospective observational single center	SAVR + CABG vs SAVR	871	10 y	Adjusted mortality of concomitant CABG: HR: 1.01; 95% CI: 0.74-1.34; $P = 0.976$
Beach et al	Retrospective observational single center	Propensity-matched SAVR + CABG vs SAVR	3,923	Median 4.7 y	Similar survival: 80% in matched groups
Thalji et al	Retrospective observational single center	Patients with AS and CAD undergoing SAVR + CABG vs SAVR alone	1,308	Mean 4.7 y	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	106,660	Early: <30 d or in-hospital mortality Late: >30 d or postdischarge mortality	Inconclusive evidence whether concomitant CABG affects early or late mortality
Santana et al	Retrospective observational single center	Hybrid (PCI + minimally invasive SAVR) vs matched CABG + SAVR	117	In-hospital and 30 d	• In-hospital mortality for hybrid vs conventional group: 0% vs 3.8% ($P = 0.11$) • Death, renal failure, stroke at 30 d for hybrid vs conventional group: 1.5% vs 28.8% ($P = 0.001$)
Brinster et al	Prospective cohort single center	Hybrid (PCI + minimally invasive SAVR)	18	Mean 19 mo	1 postoperative death; no late mortality
Ussai et al	Prospective registry multicenter	TAVR in patients with previous revascularization vs TAVR alone	663	12 mo	MACCE in CAD vs no-CAD group: adjusted HR: 0.76; 95% CI: 0.42-1.36; $P = 0.353$
Van Miegham et al	Retrospective observational single center	CR vs IR in TAVR patients	263	Median 18 mo	1-y mortality in CR vs IR: 79.9% vs 77.4% ($P = 0.85$)
D'Ascenzo et al	Meta-analysis	TAVR patients	2,472	Median 452 d	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 center	TAVR patients divided according to Duke myocardial jeopardy score	136	1 y	No mortality difference between groups ($P = 0.63$)
Gasparetto et al	Prospective registry single center	TAVR patients with CAD (± revascularization) vs without CAD	191	Mean 12.9 mo	No difference in all-cause and cardiovascular mortality (log-rank $P = 0.282$ and $P = 0.739$, respectively)
Wenaweser et al	Prospective registry single center	TAVR vs TAVR + PCI and no CAD vs CR vs IR	256	Up to 2 y	• Mortality according to PCI status: log-rank $P = 0.96$ • Mortality according to CAD and revascularization status: log-rank $P = 0.16$
Stefanini et al	Prospective registry single center	No CAD vs low SS vs high SS among TAVR patients	445	Mean 258 d	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 center	CR (rSS = 0) vs RCR (rSS = 0-7) vs IR (rSS > 7) among TAVR patients	349	Mean 35.2 mo	• MACE: log-rank $P = 0.866$ • Death: log-rank $P = 0.605$
Paradis et al	Retrospective observational 2-center with angiographic core laboratory	No CAD vs low SS (1-22) vs intermediate SS (23-32) vs high SS (>32) among TAVR patients	377	1 y	Mortality, MI, stroke: log-rank $P = 0.688$
Saia et al	Retrospective observational single center	No CAD vs CAD CR vs IR among TAVR patients	540	Median 57.8 mo	Survival free from CV death: • No CAD vs CAD: 77.9% vs 79.6% ($P = 0.98$) • CR vs IR: 84.3% vs 74.3% ($P = 0.25$)

Continued on the next page

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

TABLE 2 Continued

First Author	Design	Patient Population	Patients	Follow-Up	Outcome
Witberg et al	Meta-analysis	No CAD vs RCR vs IR among TAVR patients	3,107	0.7-3 y	• 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 center	No CAD vs CR vs IR among TAVR patients	875	1 y	CV mortality: • 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 those with single-vessel CAD
Faroux et al	Retrospective observational multicenter	IR vs CR among TAVR patients	1,197	Median 2 y	• Death, MI, stroke: log-rank $P = 0.005$ • CR vs IR in multivariate model: HR: 0.77; 95% CI: 0.63-0.95; $P = 0.014$

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CR = complete revascularization; CV = cardiovascular; IR = incomplete revascularization; MACCE = major adverse cardiac and cerebrovascular event (death, MI, stroke, conversion to open surgery); MACE = major adverse cardiac event (death, MI, and further revascularization); MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RCR = reasonable complete revascularization; rSS = residual SYTAX score; SAVR = surgical aortic valve replacement; SS = SYNTAX score; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Table 1.

than TAVR, suggesting that for any coronary stenosis with an iFR >0.74, AS was the predominant lesion and TAVR achieved greater improvements in microvascular hemodynamic status than PCI (37). This study highlights how dual pathology (severe AS and coronary stenosis) influences coronary hemodynamic status 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 emerge, revascularization decisions must be made on a case-by-case basis, with functional data contributing to this decision.

REVASCULARIZATION IN AS

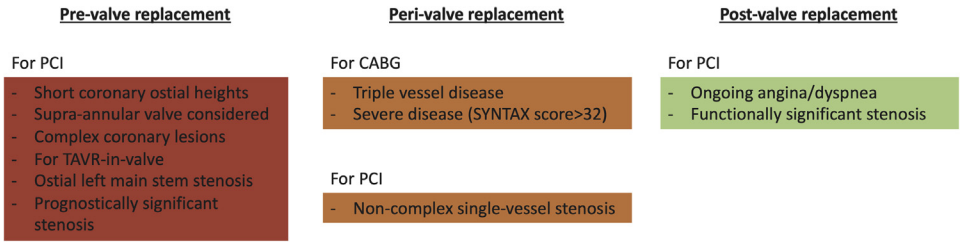
Guidelines for revascularization in patients without AS make a distinction between revascularization for symptoms and prognosis depending on the site and extent of CAD (34). These have been clinically extrapolated into the AS population to guide revascularization. However, in this unique patient group 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 for 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 with isolated SAVR (55). However, two studies have demonstrated that after propensity matching, mortality was similar in both cohorts, suggesting that the differences in reported unadjusted mortality rates can be accounted for by existing comorbidities (56,57). Furthermore, 2 observational retrospective studies involving patients with AS and coexisting CAD treated with combined CABG and SAVR demonstrated significantly reduced early and late mortality compared with the SAVR-only group (58,59). The prognostic benefit was evident for both coronary stenosis >50% and >70% (59) (**Table 2**).

PCI can also be performed safely as part of a hybrid procedure in patients undergoing SAVR without increasing the risk for short-term mortality (60), providing an alternative to CABG and SAVR (61). Bleeding complications remain a concern with hybrid procedures because of the need for dual antiplatelet agents (60), but 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 must be performed at the same time as SAVR. Several nonrandomized 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 2**).

FIGURE 1 Timing of Revascularization



On the basis of coronary, transcatheter aortic valve replacement (TAVR), surgical aortic valve replacement, and anatomical factors, the heart team can decide on the timing of revascularization: before, during, or after aortic valve replacement. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

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 [Synergy Between PCI With Taxus and Cardiac Surgery] scores) has not demonstrated an improvement in short-term outcomes, suggesting that it is not a prerequisite 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 high SYNTAX scores (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) and others demonstrating no association (64,71,74,75). Several of these studies were limited by small patient numbers, short follow-up, and differences in cohorts on the basis of lesion location, angiographic severity, atherosclerotic burden, comorbidities, and the definition of incomplete revascularization. Further studies are needed to provide clarity on this.

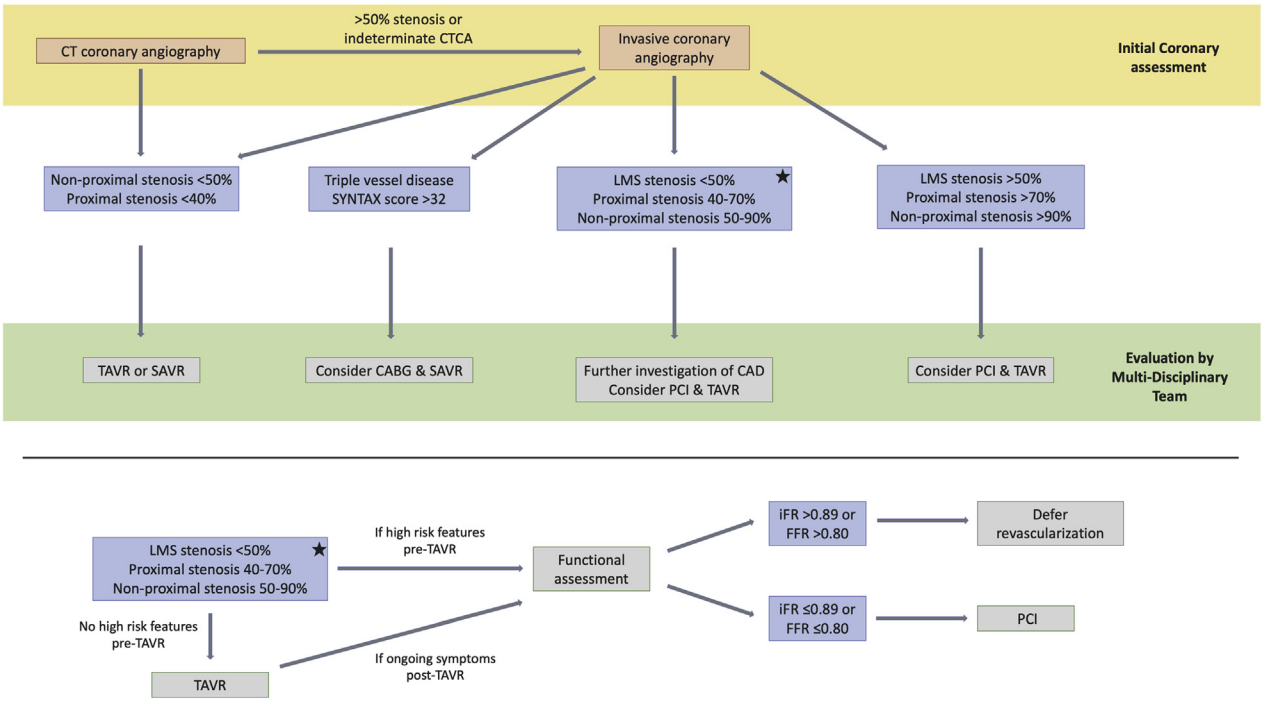
Recent results from the ACTIVATION (Percutaneous Coronary Intervention Prior to Trans-Catheter Aortic Valve Implantation; ISRCTN75836930), a randomized controlled trial evaluating the safety and efficacy of medical therapy to PCI in coronary vessels with >70% stenosis prior to TAVR, demonstrated similar short-term outcomes. Among 235 patients, (Canadian Cardiovascular Society class 0-II), PCI and non-PCI groups 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%; $P = 0.02$). 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 investigators reported better major adverse cardiac event-free and major adverse cerebrovascular event-free survival in the FFR-guided group compared with the angiography-guided group (HR: 0.4; 95% CI: 0.2-1.0; $P = 0.035$) at 2 years following TAVR (78). The NOTION-3 (Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation; NCT03058627) and FAITAVI (Functional Assessment in TAVI; NCT03360591) trials are currently under way to assess the role of FFR in guiding revascularization upstream of TAVR (**Table 3**).

TIMING OF REVASCULARIZATION

In this section we discuss revascularization in patients with stable CAD. However, among patients who present acutely, the predominant lesion (AS vs CAD) must be identified to guide further management. This can be challenging, as both acute decompensated AS (ADAS) and acute coronary syndrome can present with an increase in cardiac troponin, electrocardiographic changes, and similar symptoms (79). Clinical evaluation, coronary angiography, and echocardiography are all required to differentiate between the 2 presentations. If acute coronary syndrome 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

FIGURE 2 Proposed Algorithm for Revascularization Among Patients Undergoing Valve Replacement



This proposed algorithm for revascularization among patients undergoing valve replacement considers current practices, expert opinion, and existing evidence. Among patients in which further evaluation of their coronary artery disease (CAD) is indicated, the bottom part of the algorithm should be used. Figure 2 should be used in conjunction with Figure 1 to decide on the timing of revascularization for each subgroup. The **top star** indicates that if a patient fits into this category, the algorithm at the **bottom with a star**, should be used. High-risk features refer to those that would make PCI safer or easier pre-TAVR (Figure 1).
CT = computed tomographic; CTCA = computed tomographic coronary angiography; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LMS = left main stem; SAVR = surgical aortic valve replacement; other abbreviations as in Figure 1.

(80,81). Figure 1 describes factors that support revascularization decisions before, during, or after valve replacement.

PERIPROCEDURAL REVASCULARIZATION. For surgical patients, CABG at the time of SAVR makes clear sense given the risks of reoperation. CABG has proved its prognostic superiority over PCI in patients with triple-vessel and severe CAD (SYNTAX score >32), which should sway the decision away from percutaneous and toward surgical treatment (82,83). Among TAVR patients, however, the timing is less clear. Alternatively, PCI can be performed concomitantly with TAVR, in which there is the inherent benefit to the patient of a "single procedure" and hospital admission. Timing considerations include the risk for acute kidney injury among patients with preexisting renal function, and timing should be individualized (84). 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 suggests that staging PCI at least 30 days pre-TAVR can reduce bleeding and vascular complications (85). A nationwide registry showed that performing concomitant TAVR and PCI during the same admission can increase mortality compared with TAVR alone (10.7% vs 4.6%; $P < 0.001$) (86).

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

However, performing PCI after TAVR can be technically challenging, as access to the coronary ostia can be partially obstructed by the native leaflets or the prosthetic valve's commissural posts or

TABLE 3 Ongoing Studies Assessing the Efficacy of Physiologically Guided Revascularization in Patients Undergoing Aortic Valve Replacement for AS

Study Name	Study Type	Primary Endpoint	Completion Date
FAVOR IV-QVAS (NCT03977129)	Multicenter, randomized control trial in patients undergoing primary valvular surgery with co-existing CAD (stenosis ≥50%)	Composite endpoint: all cause death, nonfatal myocardial infarction, nonfatal stroke, unplanned coronary revascularization, new renal failure requiring dialysis at 30 d postsurgery	2022
NOTION 3 (NCT03058627)	Multicenter, open-label, randomized controlled trial evaluating the effect of FFR-guided revascularization vs conservative management in patients with CAD undergoing TAVR	Composite endpoint of all-cause mortality, myocardial infarction, or urgent revascularization at 1 y post-TAVR	2022
TAVI-PCI (NCT04310046)	Open-label, randomized controlled trial evaluating the safety and efficacy of FFR-guided revascularization pre- or post-TAVR	Composite of all-cause death, nonfatal myocardial infarction, ischemia-driven revascularization, rehospitalization and bleeding	2023
FAITAVI (NCT03360591)	Single-center, open-label, randomized control trial comparing FFR-guided PCI with angiographically guided PCI in TAVR patients	Composite endpoint of all-cause death, myocardial infarction, stroke, major bleeding, and target vessel revascularization at 12 mo post-TAVR	2020
TCW (NCT03424941)	Multicenter, international open-label, randomized controlled, noninferiority trial comparing FFR-guided PCI + TAVR with CABG + SAVR	Composite endpoint of mortality, myocardial infarction, disabling stroke, target vessel revascularization, valve reintervention at 1 y postintervention	2021
FORTUNA (NCT03665389)	Single-center open-label study comparing CT-based FFR pre-TAVR with FFR/iFR pre- and post-TAVR	Evaluating the utility of CT-derived FFR	2022

CT = computed tomography; FAITAVI = Functional Assessment in TAVI; FAVOR IV-QVAS = Quantitative Flow Ratio (QFR) Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease; FORTUNA = Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVI; NOTION-3 = Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation; TAVI-PCI = Optimal Timing of Transcatheter Aortic Valve Implantation and Percutaneous Coronary Intervention; TCW = The Transcatheter Valve and Vessels Trial; other abbreviations as in Tables 1 and 2.

skirt, especially in the case of a supra-annular self--expanding prosthesis (87-89). However, more recent studies have reported high success rates for PCI post-TAVR (>95%) regardless of valve prosthesis type (90-92). Challenging cases may require modifications to PCI technique (87) and benefit from computed tomographic angiography to assist in planning PCI (92) and pre-TAVR simulation to assess the effect of the prosthesis on coronary hemodynamic status and its position relative to the coronary ostia (93). When performing TAVR, optimizing commissural alignment to maintain access to the coronary ostia is feasible with some valves and is especially important for supra-annular bioprosthesis (94). If there is a risk for coronary obstruction, electrosurgical laceration of the native or bioprosthetic valve leaflets can be performed using the BASILICA (bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction) technique (95). 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 (96,97), the evidence discussed previously suggests that neither CAD nor revascularization affects hard procedural outcomes with TAVR. Prognostic lesions that will require revascularization should be considered for PCI pre-TAVR, especially if any high-risk features are 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 for 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, and Evolut PRO valves than the SAPIEN 3 valve and among surgical bioprostheses, stentless valves, and valves with leaflets sutured on the outer side of the stent frame (98-100). In patients considered for the prostheses mentioned previously, PCI should be considered pre-TAVR or pre-TAVR-in-valve. Additionally, PCI for complex coronary anatomy that requires extra support and advanced techniques may be easier without having to manipulate around a TAVR (101). Patients with short coronary ostial heights and narrow sinus of Valsalva may also benefit from pre-TAVR PCI (102,103).

Although the safety and efficacy of PCI in patients with AS, including for complex coronary lesions, was similar to those in patients without AS in 1 study (104), the potential risk for hemodynamic instability still exists and needs to be carefully considered (105,106). 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 (100). As discussed previously, bleeding risk and the need to withhold DAPT

in the setting of a TAVR-related complication must be considered with pre-TAVR PCI. Adopting a staged procedure with PCI preceding TAVR by several months can reduce the risk for stent thrombosis if DAPT needs to be withheld (107).

SUGGESTED MANAGEMENT STRATEGIES

On the basis of current guidelines for revascularization and existing evidence, we have developed an algorithm to guide revascularization in patients undergoing valve replacement with coexisting CAD (**Figure 2**). Other factors, as indicated by guidelines, including comorbidities, procedure-related risks, and patient preference should be considered concomitantly 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 toward surgical rather than percutaneous intervention. Evidence from patients without AS suggests that revascularization of the left main stem and proximal CAD are prognostically beneficial. Nonproximal stenosis >90% is very often hemodynamically significant (34,108), and all 3 lesions can be revascularized with PCI, although CABG is also a reasonable option. Patients with left main stem stenoses <50%, intermediate proximal stenoses (40%-70%), or nonproximal stenoses (50%-90%) should undergo functional assessment, with the only existing, albeit limited, evidence supporting the use of FFR and iFR (37,78). 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 1**). Fundamental to all management decisions is an evaluation by the multidisciplinary team, so that findings can be discussed, benefits and risks weighed, and a joint management decision established. For patients 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 HAS-BLED and PRECISION-DAPT can help gauge the bleeding risk (109,110). 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 patients without AS with CAD. We now need prospective randomized studies evaluating the efficacy of FFR- and iFR-guided revascularization in patients with AS, of which several are under way (**Table 3**). Noninvasive imaging to guide revascularization within the context of AS is an attractive prospect with CT-derived FFR in particular, as preprocedural CT will be undertaken in almost all patients being considered for TAVR.

CONCLUSIONS

The coexistence of epicardial CAD in patients with AS is common, but diagnostic and treatment alternatives remain ambiguous and highly debated. Physiological changes of AS on coronary hemodynamic status challenge the physiological ischemic assessment of concomitant CAD. On the basis of current evidence, we provide a detailed review and propose an algorithm for the management of CAD in patients with significant AS.

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