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Evaluation and management of coronary artery disease in patients undergoing transcatheter aortic valve implantation

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Abstract

Significant coronary artery disease (CAD) and severe aortic stenosis (AS) are frequent findings in patients who undergo transcatheter aortic valve implantation (TAVI). With the extension of TAVI in patients who have intermediate and even low surgical risk, the optimal evaluation and management of concomitant CAD needs to be determined. Both pre-TAVI evaluation of CAD and indications for revascularization remain a matter of debate. In this review, we provide an updated overview of the prevailing landscape of CAD in patients undergoing TAVI with a focus on its prognostic impact, diagnostic evaluation pre-procedure, indications for revascularization, optimal timing of revascularization, and future directions.

Keywords: Coronary artery disease, aortic stenosis, transcatheter aortic valve implantation, revascularization, percutaneous coronary intervention

INTRODUCTION

Aortic stenosis (AS) and obstructive coronary artery disease (CAD), which is defined as at least one coronary artery with ≥ 50% stenosis, are common conditions frequently seen in the same patient, especially in Western countries[1]. CAD's prevalence in patients with AS undergoing transcatheter aortic valve implantation (TAVI) has varied widely in different randomized controlled trials. The highest prevalence

was noted in CoreValve US High Risk trial at 81%, and the lowest prevalence was noted in the Evolut Low Risk trial at 15%[2,3]. In a prospective study from the German Aortic Valve Registry of 15,964 patients from 2011-2013, the prevalence of CAD was 55% in the patients undergoing TAVI in a relatively older and high-risk population[4].

Per American College of Cardiology/American Heart Association guidelines, TAVI is preferred for surgical aortic valve replacement in patients aged > 80 years, patients with a life expectancy < 10 years, or patients who are at high surgical risk[5]. However, as TAVI has been extended to low-risk patients - given patient preference and improved safety - TAVI is becoming the preferred treatment in younger patients who are at intermediate and even low surgical risk for aortic valve replacement[6,7]. These patients have a longer life expectancy and are more likely to develop obstructive CAD or have a progression of underlying CAD that may not have been significant at the time of TAVI. In elderly patients, TAVI can be safely performed in the presence of stable CAD without revascularization, and the role of revascularization is uncertain. Thus, the appropriate diagnosis and management of CAD in patients undergoing TAVI remains unclear.

There is a lack of randomized trials comparing surgical aortic valve replacement with Coronary Artery Bypass Graft Surgery (CABG) to TAVI and Percutaneous Coronary Intervention (PCI) in patients with severe aortic stenosis and significant left main and/or multivessel CAD. These patients who are low or intermediate risk for surgery should have surgical AVR and CABG.

The aim of this article is to review the management of CAD in TAVI patients, with a focus on the prognostic role of CAD, its evaluation and management before and after TAVI, discuss unresolved issues, and provide future perspectives.

DISCUSSION

Prognostic role of CAD in patients undergoing TAVI

The impact of CAD on the outcomes of TAVI patients remains uncertain. This has led to differences in the management of CAD in TAVI patients. There are conflicting results in major studies, with differences in how CAD is defined and its management, short-duration follow-up data, and less frequent use of fractional flow reserve (FFR) for physiologic assessment during invasive coronary angiography[8].

A meta-analysis of 15 studies comprising a total of 8,013 patients published in 2017 addressed the prognostic risk of CAD in TAVI patients[9]. At 30 days post-procedure, no significant difference in the cumulative odds ratio for all-cause mortality between patients with CAD and without CAD who underwent TAVI was noted. However, 1-year mortality was higher in the CAD group with a cumulative odds ratio of 1.21. The major limitation of this study was that only a few studies reported all of the secondary endpoints, including cardiovascular mortality at 30 days, myocardial infarction at 30 days, stroke at 30 days, major bleeding at 30 days, vascular complications at 30 days, cardiovascular mortality at 1 year, myocardial infarction at 1 year, and stroke at 1 year. The SYNTAX score, a grading tool to estimate CAD burden, complexity, and preprocedural risk accounting for complex lesions including bifurcations, chronic total occlusions, thrombus, calcification, and small diffuse disease[10], was not utilized in this meta-analysis. The separate role of left main coronary artery disease was also not evaluated in this study.

Data from the FRANCE-2 registry showed that only significant lesions in the LAD had an association with higher 3-year mortality post-TAVI, and neither the presence nor extent of any other CAD was associated with higher mortality[11].

In another meta-analysis performed in 2018, comprising 13 studies and 8,334 patients treated with TAVI[12], there was no difference in 30-day or 1-year mortality comparing the presence or absence of CAD. Subgroup analysis based on low (< 16), intermediate (16-22), and high (> 22) SYNTAX scores was also performed. In the specific subgroup of patients with CAD and an intermediate or high SYNTAX score, there was an increased 1-year mortality with an odds ratio of 1.71. The impact of percutaneous coronary intervention (PCI) and residual SYNTAX score (rSS, the remaining SYNTAX score post-revascularization) on outcomes was also studied, and an rSS of < 8 was associated with lower 1-year mortality with an odds ratio of 0.34.

Regarding the role of revascularization with PCI and TAVI, another systematic review and meta-analysis of 6 studies with 3,107 patients looked at the prognostic role of incomplete revascularization (ICR) and *reasonable* ICR[13]. ICR was defined as an rSS of > 8 in a majority of the studies, and *reasonable* ICR was defined as an rSS of ≤ 8. There was significantly increased mortality in patients with ICR, with an odds ratio of 1.69 compared to patients with *reasonable* ICR. Significant limitations of this study were that it included observational studies prone to reporting the results without adjustment. This could result in confounding by major comorbidities and, thus, could account for the increased mortality in the incomplete revascularization group. In addition, incomplete revascularization was defined differently in different studies.

Given these studies and other observational and retrospective studies, it does appear that the presence of CAD is associated with worse outcomes in some subgroups of TAVI patients with complex CAD and high SYNTAX scores[14,15], and revascularization with PCI does improve intermediate and long-term mortality. However, the benefit of PCI needs to be individualized. CAD is a highly diversified disease, and a more stratified approach with guidelines on evaluation and management is currently not available.

Diagnostic evaluation of CAD prior to TAVI

Anginal chest pain and dyspnea on exertion are symptoms of both obstructive CAD and severe AS. Distinguishing which symptom is related to either or both diseases can be difficult[1]. Symptomatic patients with severe AS are referred for TAVI, and an assessment of CAD is recommended prior to performing the procedure[5].

Historically, invasive coronary angiography (ICA) has been performed in almost all patients undergoing TAVI prior to performing the procedure or at the time of the procedure[1]. Patients also receive a gated cardiac computed tomography angiography (CTA) of the chest, abdomen, and pelvis as a part of a pre-TAVI work-up for preprocedural planning including valve sizing and access approach, which usually does not include imaging of the coronary arteries. With the increasing popularity of coronary CTA, simultaneous cardiac and coronary CTA offers an alternative to traditional CTA. One of the major limitations of this is that coronary CTA protocols often require the use of IV nitroglycerin or IV beta-blockers, which may not be safe for patients with severe AS[1]. In spite of this, as TAVI is being offered and even preferred in lower-risk, relatively young patients who are less likely to have significant obstructive CAD, coronary CTA has reasonable negative predictive value to exclude CAD, and decreases the chance of needing ICA[16]. The extent of coronary calcification on CT scan also provides further information.

A single-center, retrospective study in the United Kingdom of 491 patients assessed the utility and outcomes of coronary CTA in patients undergoing TAVI. 76.3% of patients only received coronary CTA, and 21.7% who had either a suspicious lesion on coronary CTA or an inability to assess coronary anatomy due to severe coronary calcifications or motion artifacts also underwent ICA[17]. Thus, coronary CTA was able to avoid ICA in more than two-thirds of patients. Of the patients who received both coronary CTA and ICA,

only 21.5% needed PCI, which was performed before, concomitantly, or after TAVI. Thirty-day and 1-year major cardiovascular and cerebrovascular events post-TAVI were similar in patients who only received coronary CTA compared to both CTA and ICA.

In a meta-analysis of 7 studies totaling 1,275 patients treated with TAVI, an attempt was made to evaluate the performance of coronary CTA for accurate detection of CAD[18]. Sensitivity was noted to be 95%, with a negative predictive value (NPV) of 94%. Specificity was poor at 65%. However, given the high NPV, the routine use of coronary CTA could reduce the need for pre-TAVI ICA by 37%.

Another retrospective study in 1,060 patients validated these results by showing that pre-TAVI coronary CTA excludes > 50% stenosis with a sensitivity of 96.4% and a NPV of 98%[19]. For > 70% stenosis, it offers a sensitivity of 96.7% and NPV of 99%. It was suggested that coronary CTA would reduce the need for ICA by 52%-70%, depending on the severity of stenosis used to define CAD.

The addition of fractional flow reserve to CT with FFR-CT provides the additional advantage of obtaining physiologic in addition to anatomic assessment of CAD. FFR-CT uses the coronary CTA to perform segmentation of the coronary arteries, providing the coronary flow dynamics, and allowing physiological information about the stenotic lesion[20]. A prospective study assessing CT-FFR to invasive FFR in 42 patients with severe aortic stenosis found sensitivity, specificity, positive predictive, and negative predictive values for physiologically significant CAD to be 76.5%, 77.3%, 72.2%, and 81.0%, respectively, with a 76.9% diagnostic accuracy[21]. These results are similar to patients who have CT-FFR without aortic stenosis. In another study in 296 patients with stable angina and with intermediate to high pre-test likelihood of CAD, Peper *et al.* reported a similar sensitivity of 81.2%, specificity of 83.3%, positive predictive value of 84.1%, and negative predictive value of 80.2%, with an overall diagnostic accuracy of 82.2%[22]. Thus, it is possible for FFR-CT to become a first-line test for CAD evaluation in aortic stenosis patients, at least in young patients with a lower pre-test likelihood of CAD.

However, there are major limitations to coronary CTA imaging. In patients with prior PCI and significant CAD, coronary CTA is less likely to provide adequate imaging due to stent artifact or severe coronary artery calcifications[23]. In these patients, ICA still remains the first line and gold standard test for CAD evaluation.

Catheterization and ICA offer additional benefits that cannot be obtained with coronary CTA. Hemodynamic assessment of the severity of AS can be determined invasively prior to TAVI[24]. When the severity of CAD is intermediate, ICA offers options to obtain a functional physiological assessment of the lesion and decide whether PCI is indicated and potentially beneficial. Pre-procedure ICA may also better help identify whether SAVR + CABG may be more beneficial than TAVI + PCI. However, for patients who are not surgical candidates for AVR, or who are elderly with a low probability of CAD or need for PCI, it is reasonable to avoid CAD assessment pre-TAVI and proceed directly to TAVI.

Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) with ICA provide invasive physiologic assessment of CAD. A retrospective study by Stanojevic *et al.* assessed the safety of IV adenosine during FFR evaluation of intermediate CAD in patients who had severe AS[25]. The study demonstrated good tolerance of adenosine without any significant adverse events.

However, the interpretation of FFR and iFR in the setting of severe AS remains debatable[26]. Patients with severe AS have left ventricular hypertrophy, which has the potential to alter coronary blood flow and thus affect FFR results. A prospective study of 28 patients by Ahmad *et al.* demonstrated that systolic and

hyperemic coronary blood flow increased significantly post-TAVI, and FFR was noted to decrease significantly post-TAVI[27]. Thus, FFR may underestimate the significance of CAD pre-TAVI. However, another prospective observational study of 133 lesions in 54 patients with severe aortic stenosis assessed FFR pre- and post-TAVI[28]. This study showed that even though there were significant variations pre- and post-TAVI in positive and negative pre-TAVI FFR values, overall, the variations were minor, and changed the indication to treat coronary stenosis with PCI in only a small number of patients (6%) post-TAVI when PCI was not indicated pre-TAVI.

In the study by Ahmed *et al.*, during diastole, wave-free period flow did not show any significant change post-TAVI, and thus, iFR did not change pre- and post-TAVI, suggesting that it may be more accurate for assessing CAD severity in patients with severe AS[27]. iFR does not require the administration of adenosine, so it may be the better modality for physiologic assessment of CAD in severe AS patient[16]. However, the conventional iFR threshold of < 0.89 to determine significant lesion severity might not be accurate in these patients[29]. In a prospective observational study, Scarsini *et al.* report an iFR value of > 0.93 to have a NPV of 98.4% to exclude FFR non-significant stenosis and a value of < 0.83 to have a PPV of 91.3% to diagnose FFR significant stenosis[30]. They recommended the use of FFR only when iFR ranges between 0.83-0.93. This allowed 63% of patients to avoid FFR with adenosine, and still reproduced results which had 97% overall agreement with FFR. Although further research is needed to validate the cut-offs of FFR and iFR for physiologically significant CAD in the severe AS subset, based on current data, it is reasonable to continue with traditional cut-offs of ≤ 0.80 for FFR and ≤ 0.89 for iFR to guide revascularization.

Revascularization of stable CAD in patients undergoing TAVI

Patients with acute coronary syndrome and unstable angina or NSTEMI who are candidates for TAVI should undergo PCI pre-TAVI. However, robust, conclusive, and randomized clinical evidence for the management of stable ischemia and CAD pre-TAVI is lacking[16]. Current guidelines recommend PCI in patients with stable CAD with > 70% stenosis in the proximal coronary segments as a part of the pre-TAVI work-up[24,31]. However, these recommendations are based on single-center observational studies, retrospective studies, and meta-analyses[32]. These studies have limitations, with the majority being observational with no defined criteria for revascularization, and with complete *vs.* incomplete revascularization decided at the discretion of the proceduralist.

The benefits of PCI pre-TAVI for stable ischemia remain uncertain. A meta-analysis of 9 studies comprising 3,858 patients studied the outcomes of patients who underwent TAVI with and without PCI[33]. Patients who underwent TAVI after PCI had a higher rate of major vascular complications with an odds ratio of 1.86 and a higher 30-day mortality with an odds ratio of 1.42. No differences were noted between the groups in other outcomes, including myocardial infarction, acute kidney injury, stroke, and 1-year mortality. The increased bleeding and vascular complications and probably the higher preoperative risk in the PCI cohort contributed to the higher early 30-day mortality which was not seen at 1 year. However, another meta-analysis of 11 studies with 5,580 patients noted no difference in 30-day or 1-year all-cause mortality in the patients who underwent TAVI with or without PCI prior[34].

These results in patients with severe aortic stenosis and stable CAD mirror the ISCHEMIA trial in 5,179 patients with stable CAD and moderate or severe ischemia on stress testing (but no aortic stenosis) randomized to ICA and PCI *vs.* medical therapy. For stable CAD in ISCHEMIA, there was no difference in the composite outcome of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest in patients randomized to invasive *vs.* initial conservative strategy[35].

The ACTIVATION trial is the only randomized controlled trial that compared elective, pre-TAVI PCI *vs.* no PCI in patients with TAVI with significant CAD. Significant CAD was defined as ≥ 1 lesion of ≥ 70% severity in a major epicardial vessel or 50% in a vein graft or protected left main lesion[36]. Two hundred and thirty-five patients were randomized to PCI *vs.* no PCI arms. No difference was noted in mortality or major adverse cardiovascular and cerebrovascular events between the two groups. However, the PCI group was noted to have a higher incidence of bleeding[37].

In AS patients with complex CAD and high-risk anatomy, when PCI is deemed necessary, residual SYNTAX SCORE (rSS) has been a marker for effective revascularization, and various meta-analyses have demonstrated a low rSS to be associated with better outcomes. In a prospective study by Stefanini *et al.* in 445 patients with AS and CAD with an intermediate risk SYNTAX score of > 22, less complete revascularization was associated with worse clinical outcomes at 1 year[14]. In another study by Witberg *et al.* in 1,270 consecutive patients, it was noted that severe CAD with a SYNTAX score of > 22, and ICR as defined by rSS of > 8, were both associated with increased mortality after a median follow-up of 1.9 years, with hazard ratios of 2.09 and 1.72 respectively[38].

A meta-analysis of 13 studies comprising 8,334 patients showed that patients with CAD and SYNTAX score of > 22 had higher 1-year mortality, and a low rSS of < 8 post-revascularization was associated with decreased mortality[12]. In another study, 287 consecutive patients by Witberg *et al.* showed that patients with rSS of < 8 post-revascularization had similar outcomes compared to patients who did not have CAD[12,39].

Thus, in AS patients who are treated with PCI, more complete revascularization appears to have better outcomes. This mirrors results from the recent randomized FIRE trial showing that physiology-guided complete revascularization in patients aged above 75 years with MI with CAD was associated with a lower risk of death, stroke, myocardial infarction, or ischemia-driven revascularization at 1 year[40].

Given these results, there remains a need for a stratified approach to managing stable CAD in TAVI patients based on symptoms, physiologic severity and extent of the disease, and coronary artery anatomy. The current guidelines stating PCI should be considered in patients undergoing TAVI with a coronary artery diameter stenosis of > 70% need revision. These guidelines were framed when TAVI was mainly performed in patients > 75 years of age. With an increase in TAVI in the < 75-year-old population, extrapolation of these guidelines may not be appropriate. Patients who are asymptomatic and have single vessel CAD may not need to be revascularized pre-TAVI, even if they have > 70% proximal stenosis. Revascularization would commit the patient to dual antiplatelet therapy (DAPT) pre-TAVI, increasing bleeding risks in addition to possible higher vascular complications during TAVI. On the other hand, if involvement includes left main (LM) with ≥ 50% stenosis or left anterior descending (LAD) with > 70% proximal stenosis, it may be reasonable to pursue PCI with TAVI.

Revascularization with CABG needs to be considered along with SAVR in younger lower-risk patients despite the extension of TAVI in this population. The prognostic value of PCI (especially with multivessel disease) in stable CAD is less clear, whereas CABG has shown consistent benefit[35,41]. Thus, despite TAVI being extended to younger patients, in patients with comorbid stable CAD, the option of SAVR with CABG should be considered. The ongoing TransCatheter Valve and Vessels Trial (NCT 03424941) - randomized FFR-guided PCI and TAVI *vs.* CABG and SAVR - will answer the question of whether PCI and TAVR are noninferior to CABG and SAVR.

Optimal timing of revascularization: before, during, or after TAVI?

The optimal timing of PCI in patients who undergo TAVI remains uncertain. When the decision is made to pursue PCI, it is usually performed prior to TAVI[32]. This offers the advantages of improving coronary flow prior to TAVI and thus preventing ischemia during rapid pacing and times of hypoperfusion during the TAVI procedure[42]. PCI potentially reduces the risk of periprocedural myocardial infarction or ischemic arrhythmias. However, there is concern about the risk of hemodynamic instability during complex PCI before the treatment of severe AS[43], and dual antiplatelet therapy required post-PCI increases the bleeding risk during TAVI.

Van Rosendael *et al.* assessed the impact of the timing of planned PCI on TAVI outcomes[44]. Patients either received PCI within 30 days pre-TAVI or greater than 30 days pre-TAVI. Results showed an increased incidence of bleeding and vascular complications in the group that received PCI < 30 days prior to TAVI. No other major differences were reported.

Concomitant PCI and TAVI offers the benefit of avoiding multiple vascular punctures, avoiding pre-procedure DAPT, and lowering the cost of the procedures[45]. However, this approach is associated with the use of more contrast, risking acute kidney injury (AKI)[1]. In a retrospective study of 22,344 patients from the Nationwide Inpatient Sample database of the United States by Singh *et al.*, 21,736 (97.3%) patients underwent isolated TAVI and 608 (2.7%) patients underwent simultaneous TAVI and PCI. There were significantly higher rates of mortality, vascular injury requiring surgery, and respiratory and infectious complications in patients who received simultaneous TAVI and PCI compared to isolated TAVI[46].

However, a prospective study of 604 patients by Barbanti *et al.* reported that patients undergoing TAVI and PCI simultaneously had similar mortality and morbidities of stroke, transient ischemic attack, life-threatening bleeding, major bleeding, need for permanent pacemaker, and AKI in comparison to patients who had TAVI without CAD or TAVI with CAD left untreated[47]. A meta-analysis by Bao *et al.* showed similar findings of non-significant differences in 30-day all-cause mortality, 30-day cardiovascular mortality, 1-year mortality, stroke, bleeding, and vascular complications in patients treated with isolated TAVI *vs.* concomitant TAVI and PCI[48]. A prospective study by Ochiai *et al.* also showed no difference in 2-year major cardiovascular and cerebrovascular events irrespective of whether PCI was performed before, concomitantly, or after TAVI[49].

Thus, most data show simultaneous PCI with TAVI is safe, but it is still not recommended, given the potential increased procedure risk and risk for contrast AKI.

PCI after TAVI may be safer and more beneficial. Persistent symptoms of angina or dyspnea post-TAVI would be clear indications for revascularization of obstructive CAD. Functional assessment of CAD with invasive FFR appears more accurate post-TAVI, allowing more appropriate decision-making regarding revascularization. High-risk PCI would be better tolerated in patients post-TAVI, and DAPT is avoided pre-TAVI, helping reduce bleeding complications with TAVI[16]. Recent data from a retrospective study by Rheude *et al.* of 1,603 patients from the REVASC-TAVI registry noted significantly decreased 2-year mortality in patients who received PCI post-TAVI (6.7%) compared to patients who received PCI pre-TAVI (20.1%) and PCI concomitantly with TAVI (20.6%)[50]. However, coronary access post TAVI through valve struts, especially for the self-expanding CorValve with its taller frame, may be difficult. Dislodgement of the transcatheter heart valve (THV) is also a concern[51]. Despite these concerns, deferring PCI for stable ischemia with the benefit of avoiding DAPT has become more accepted, since the most recent data support stable CAD need not be revascularized pre-TAVI. 3D models can also be used for planning future coronary

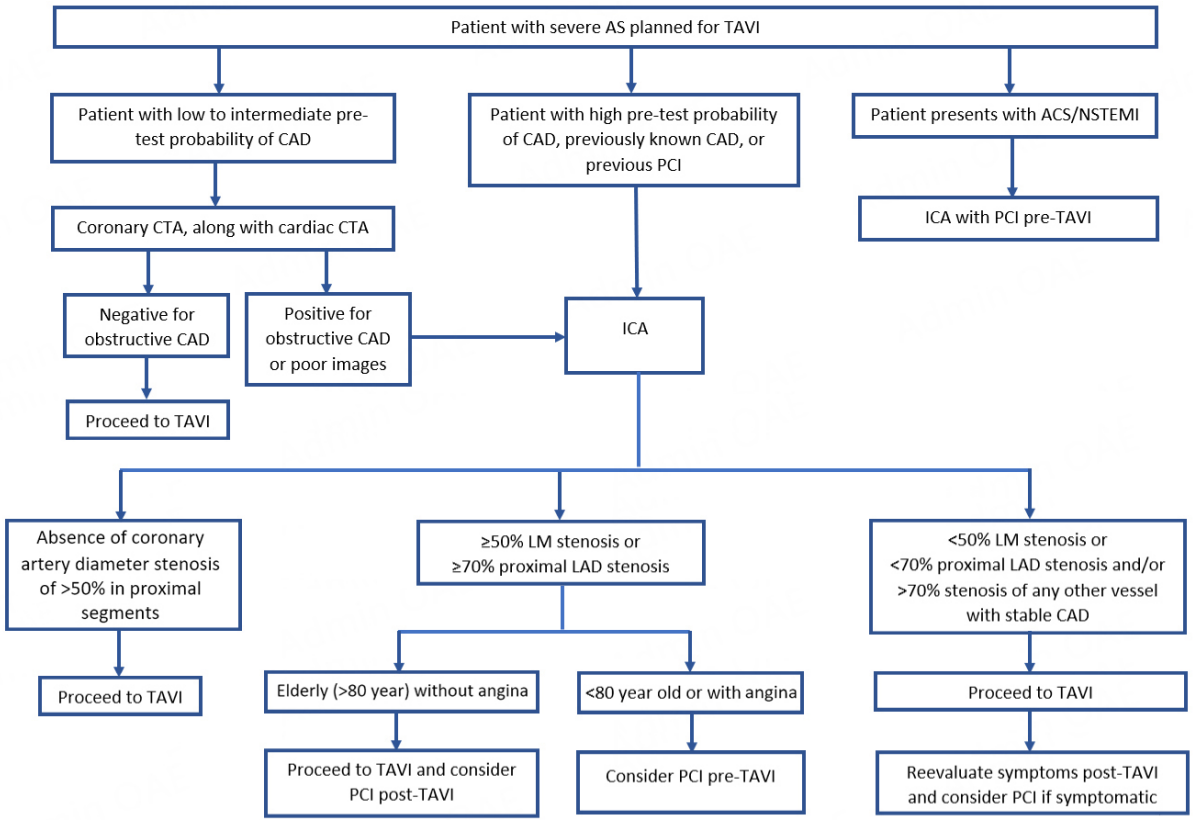

Figure 1. Approach to diagnostic evaluation and management of CAD in patients undergoing TAVI. CAD-coronary artery disease, TAVI-transcatheter aortic valve implantation, AS-aortic stenosis, PCI-percutaneous coronary intervention, ACS-acute coronary syndrome, NSTEMI-non-ST elevation myocardial infarction, CTA-computed tomography angiography, ICA-invasive coronary angiography, LM-left main artery, LAD-left anterior descending artery.

access in patients with complex anatomy, especially with valve-in-valve TAVI[52]. We use the algorithm, as shown in Figure 1, to guide decision-making regarding the evaluation and management of CAD in patients undergoing TAVI.

In summary, the question remains whether patients with stable obstructive CAD either benefit from PCI pre- or post-TAVI or even benefit from PCI compared with guideline-directed medical therapy. There are two randomized trials investigating the role of PCI in TAVI-treated patients in stable CAD. The primary objective of the TAVI PCI Trial (ClinicalTrials.gov: NCT04310046) is to compare iFR-guided complete revascularization performed within 45 days pre-TAVI or within 45 days post-TAVI in patients treated with the Edwards Sapien Transcatheter heart valve who have severe aortic stenosis and concomitant CAD. The COMPLETE TAVR Trial (ClinicalTrials.gov: NCT04634240) will determine whether a strategy of complete revascularization of all suitable lesions with staged PCI post-TAVI with the Edwards Sapien valve is superior to a strategy of medical therapy alone for CAD in reducing the composite outcome of cardiovascular death, new MI, ischemia driven revascularization, or hospitalization for unstable angina or heart failure.

CONCLUSION

Concomitant CAD and AS are frequently seen in clinical practice. Evaluation and management of CAD in patients with severe AS undergoing TAVI continues to remain an area needing further research. In

choosing to treat CAD with severe AS, the institutional structure and availability of close follow-up must be taken into consideration. ICA is the gold standard for CAD evaluation pre-TAVI; however, it is not always necessary. In younger patients with a low pre-test probability of CAD, coronary CTA provides a useful alternative. In older patients, the gated non-coronary CTA used for TAVI evaluation alone may be sufficient to exclude CAD in the left main or proximal vessels. When ICA is indicated, the use of FFR and iFR is recommended for indeterminant stenotic CAD, but the interpretation of the results needs caution. After ICA, if the need for PCI is identified, it is reasonable to pursue PCI pre-TAVI to avoid issues with future coronary access, but may lead to increased bleeding complications with TAVI. If post-TAVI PCI is planned, the selection of a transcatheter heart valve should be made with the preservation of coronary access in mind. Ultimately, a personalized approach depending on the anatomy and clinical profile is needed. Adequately powered randomized controlled studies are needed to determine whether significant stable CAD needs PCI in TAVI patients and to assess the optimal timing for PCI.

DECLARATIONS

Author's contribution

Conceptualization, methodology, investigation, resources, writing original draft, writing - review and editing, visualization, project administration: Raval M, Gordon PC
Software: Raval M
Supervision: Gordon PC

Availability of data and materials

This is a review article and all data mentioned in the article can be obtained from the appropriate citation.

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Not applicable.

Consent for publication

Not applicable.

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