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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Coronary Artery Disease and Transcatheter Aortic Valve Replacement

JACC State-of-the-Art Review

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ABSTRACT

About one-half of transcatheter aortic valve replacement (TAVR) candidates have coronary artery disease (CAD), and controversial results have been reported regarding the effect of the presence and severity of CAD on clinical outcomes post-TAVR. In addition to coronary angiography, promising data has been recently reported on both the use of computed tomography angiography and the functional invasive assessment of coronary lesions in the work-up pre-TAVR. While waiting for the results of ongoing randomized trials, percutaneous revascularization of significant coronary lesions has been the routine strategy in TAVR candidates with CAD. Also, scarce data exists on the incidence, characteristics, and management of coronary events post-TAVR, and increasing interest exist on potential coronary access challenges in patients requiring coronary angiography/intervention post-TAVR. This review provides an updated overview of the current landscape of CAD in TAVR recipients, focusing on its prevalence, clinical impact, pre- and post-procedural evaluation and management, unresolved issues and future perspectives. (J Am Coll Cardiol 2019;74:362–72)

This review provides an updated overview of the current landscape of coronary artery disease (CAD) in transcatheter aortic valve replacement (TAVR) recipients, focusing on its prevalence, clinical impact, pre- and post-procedural evaluation and management, unresolved issues, and future perspectives.

EPIDEMIOLOGY

The prevalence of CAD has been ~50% (1), and it has decreased from 81% to 15% in randomized controlled trials along with the progressive reduction in mean age and surgical risk of enrolled patients (**Figure 1**) (2–9), with a much lower prevalence of CAD in low-risk patients compared with intermediate- and high-risk patients. About one-half of TAVR candidates with CAD exhibit multivessel disease (10), and a mean Syntax score (SS) of ~14 was recently reported in a series including 4,000 TAVR recipients with CAD, with the involvement of the left main and left anterior descending artery in 11% and 50% of patients, respectively (11).

CLINICAL IMPACT OF CAD IN TAVR RECIPIENTS

Controversial results have been reported in many observational studies evaluating the clinical impact of CAD in patients undergoing TAVR

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HIGHLIGHTS

- The impact of CAD in TAVR recipients remains controversial, and no definite data exist on the most appropriate revascularization strategy in these patients.
- The use of CTA and hemodynamic assessment to guide pre-TAVR revascularization will likely increase in the coming years.
- The management of coronary events occurring after TAVR (including coronary access) requires further investigations.

(Online Table 1). The results of these studies can be grouped into 3 categories: 1) studies showing an association between the presence of CAD (and its severity) and patient prognosis; 2) studies failing to show such a relationship; and 3) studies showing no association between the presence of CAD and clinical outcomes, but a significant negative effect of severe CAD. Two recent meta-analyses showed contradictory results regarding the association between CAD and clinical outcomes post-TAVR (11,12). A significant heterogeneity between studies may explain such discordant results. First, the definition of CAD was very variable, with only a minority of studies relying on an objective measurement of coronary lesion severity (quantitative coronary angiography). Second, a hemodynamic assessment with fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) was rarely used to evaluate the severity of CAD. Third, revascularization completeness was generally left at the discretion of operator/heart team of each center, which may have introduced a significant bias and contributed to the differences between studies. Finally, the definition of composite clinical endpoints was variable, and the SS cut-off for defining CAD severity also varied across studies. The presence of CAD and its severity are often associated with other comorbidities and high surgical risk scores, and the impact of CAD on the prognosis frequently disappears after adjustment. Thus, it appears that the presence of CAD and its severity may be markers of comorbidity and increased risk status rather than independent factors of poorer outcomes. However, it has to be noted that most studies had a limited follow-up (usually <2 years), and longer time periods may be needed to determine the real impact of CAD on clinical outcomes post-TAVR.

CAD ASSESSMENT

Coronary angiography (CA) remains the standard examination for determining the presence and severity of CAD in TAVR candidates. However, recent studies evaluated the use of noninvasive coronary imaging techniques, such as computed coronary angiography (CTA), as well as coronary pressure wire measurements for determining coronary stenosis severity in the context of TAVR, with promising preliminary data (13–25).

COMPUTED TOMOGRAPHY ANGIOGRAPHY.

Some authors proposed to perform CA pre-TAVR only in a selected group of patients according to the results of pre-procedural electrocardiogram-gated synchronized cardiac CTA findings. Chieffo et al. (13) showed the feasibility and potential clinical relevance of this strategy, with CA performed in only 24% of TAVR candidates based on CTA results (those cases with an obstructive coronary stenosis identified on the CTA), and no negative clinical impact associated with the avoidance of CA on the basis of CTA results.

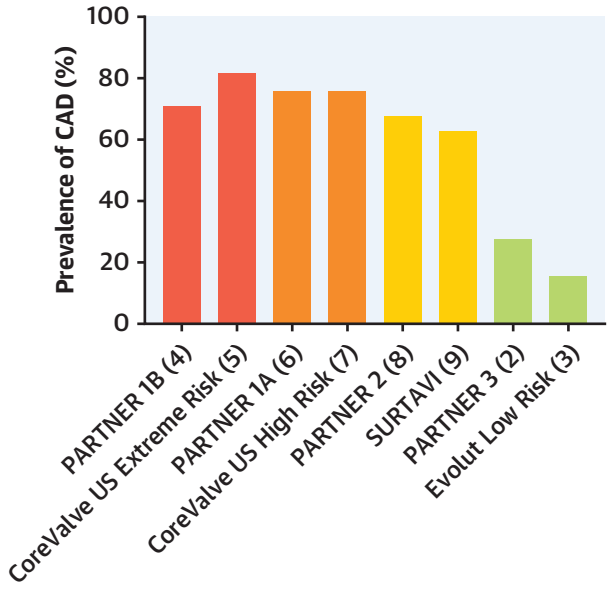
Several studies have compared the performance of coronary CTA with CA for the detection of significant coronary stenosis during the pre-TAVR work-up. All studies found an excellent CTA performance in terms of negative predictive value, at the cost of a relatively poor specificity (**Table 1**) (14–20). Compared with coronary CTA in patients without aortic stenosis (AS), similar sensitivity (95% vs. 99%) but a lower specificity (65% vs. 88%) and a higher contrast volume have been associated with coronary CTA during the pre-TAVR work-up (26,27). Evaluation of a previously stented coronary segment was feasible in 69% to 92% of cases with a good diagnostic performance (14–16,18), whereas heavy calcifications generally resulted in an increase of false positive results. Finally, it appears that using CTA as a gatekeeper for CA in the TAVR work-up could decrease the number of coronary angiographies by 37% (26). This percentage would likely increase in younger patients, with a much lower probability of CAD and a lower degree of coronary artery calcification (28).

In summary, CTA has emerged as a reasonable alternative to CA for the evaluation of CAD pre-TAVR, and it may become an important tool in the stratification of CAD in TAVR candidates, particularly with the increasing number of lower-risk patients. Two ongoing studies will provide further important

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
CA = coronary angiography
CABG = coronary artery bypass graft
CAD = coronary artery disease
CTA = computed tomography angiography
FFR = fractional flow reserve
iFR = instantaneous wave free ratio
NSTEMI = non-ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
rSS = residual Syntax score
SAVR = surgical aortic valve replacement
SS = Syntax score
TAVR = transcatheter aortic valve replacement

FIGURE 1 Coronary Artery Disease in Randomized Trials



Trends in CAD prevalence in randomized trials. CAD = coronary artery disease; PARTNER = Placement of Aortic Transcatheter Valves; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation.

information regarding the exact role of coronary CTA in this context (Table 2).

FFR AND iFR. In the presence of a coronary lesion without evidence of ischemia in the corresponding myocardial territory, it is recommended that revascularization should be guided by hemodynamic functional assessment (29,30). Considering that noninvasive ischemia testing is rarely available before CA in the TAVR work-up, hemodynamic assessment of coronary lesions should ideally be performed to guide coronary revascularization in such cases. However, scarce data exist on the functional evaluation of coronary lesions in TAVR candidates (Table 3).

Stanojevic et al. (31) demonstrated the safety and good tolerance of intravenous adenosine in this population, and several studies have used boluses of intracoronary adenosine without any signal of poor tolerance or side effects (21–25) (Table 3). However, left ventricular hypertrophy induced by AS may alter the coronary flow reserve, potentially tampering the final results obtained by FFR. Ahmad et al. (21) showed that systemic and hyperemic coronary flow increased significantly after TAVR (compared with the values pre-TAVR). These results suggested that FFR may underestimate coronary stenosis severity in patients with severe AS, whereas coronary flow during the wave-free period of diastole did not change post-TAVR, suggesting that iFR was not influenced by the effect of the stenotic aortic valve. However, Pesarini et al. (22) showed that the mean FFR prior to TAVR did not significantly differ from the mean FFR immediately after the TAVR. Yet, the mean FFR decreased after TAVR in the subgroup of pathological FFR, whereas the average FFR increased in the normal FFR subgroup. Of note, this variation in FFR changed the therapeutic strategy (according to the 0.80 threshold) in a minority (6%) of patients.

The iFR may be of interest in this population, because it does not require the administration of a vasodilator. However, the common threshold of 0.89 (32) for determining lesion severity may not be valid in this population. In fact, it was shown that, in a population of patients with severe AS, a threshold value of 0.93 excluded negative FFR (>0.80) with a negative predictive value of 98.4%, and a threshold of 0.83 identified positive FFR (≤0.80) with a positive predictive value of 91.3%. Using a hybrid strategy with FFR only when iFR values were between 0.83 and 0.93, the authors suggested that 63% of patients can be assessed without adenosine while maintaining 97% overall agreement with FFR lesion severity classification (23). However, the same authors reported significant and mostly erratic individual variations in iFR pre- and post-TAVR and concluded that caution is still advisable in the interpretation of iFR in the presence of AS (24). Finally, Yamanaka et al. (25) showed, in a population of 95 patients with severe AS and intermediate coronary lesions previously assessed by myocardial perfusion scintigraphy, that there was a good correlation between FFR and iFR, as well as between iFR and the presence of ischemia on scintigraphy (area under the curve of 0.89 and 0.84, respectively), using a cut-off of 0.82 for indicating a positive FFR and the presence of myocardial ischemia on scintigraphy findings. Currently available

TABLE 1 Diagnostic Value of the Electrocardiogram-Gated CTA for the Detection of Significant Stenosis (>50%) Versus Coronary Angiography (Gold Standard)

First Author, Year (Ref. #)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Pontone et al., 2011 (14)	89	88	91	85
Andreini et al., 2014 (15)	90	91	95	81
Hamdan et al., 2015 (16)	96	73	96	72
Harris et al., 2015 (17)	99	58	94	87
Opolski et al., 2015 (18)	98	37	94	67
Matsumoto et al., 2017 (19)	92	58	91	60
Rossi et al., 2017 (20)	91	55	90	59

CTA = computed tomography angiography; NPV = negative predictive value; PPV = positive predictive value.

TABLE 2 Summary of Ongoing and Future Studies on CAD Evaluation and Management in TAVR Recipients

Study	Study Design	Population	Sample Size	Intervention	Primary Endpoint
CT-CA (NCT03291925)	Randomized open-label trial (pilot study)	Patients with symptomatic severe AS eligible for TAVR	200	Selective invasive angiography based on CT/coronary CTA imaging vs. systematic invasive angiography	Number of patients enrolled in the study of all those that are eligible
FORTUNA (NCT03665389)	Prospective open-label registry (exploratory)	Patients with moderate stenotic lesions (30%-<70%) or severe stenotic lesions on CTA who are candidates for PCI following TAVR	25	Measurement of iFR before TAVR, FFRct before TAVR and FFR + iFR after TAVR	FFRct before TAVR
TCW (NCT03424941)	Randomized open-label noninferiority trial	Patients age ≥70 yrs with severe AS feasible for treatment by both TF or TSc approach TAVR as well as conventional SAVR, and ≥2 de novo coronary lesions ≥50% diameter stenosis on main artery or side branch >2 mm or single LAD lesion >20 mm length or involving a bifurcation, feasible for treatment with CABG as well as PCI	328	FFR-guided PCI and TAVR vs. CABG and SAVR	Composite of all-cause mortality, myocardial infarction, disabling stroke, unscheduled clinically-driven target vessel revascularization, valve reintervention, and life threatening or disabling bleeding at 1 yr
FAITAVI (NCT03360591)	Randomized open-label trial	Patients with severe AS with the indication of TAVR and at least one coronary stenosis >50% at angiography	320	Physiologically-guided strategy (PCI of lesions with FFR ≤0.80) vs. angiographically guided strategy (PCI of all lesions >50% by visual estimation of major branches >2.5 mm)	Composite of all-cause death, myocardial infarction, stroke, major bleeding and target vessel revascularization at 1 yr
ACTIVATION (ISRCTN75836930)	Randomized trial	Patients with symptomatic severe AS accepted for TAVR, and ≥1 proximal stenosis of ≥70% in a major epicardial artery deemed suitable for PCI	310	Pre-TAVR PCI vs. no pre-TAVR PCI	Mortality and rehospitalization at 1 yr
NOTION-3 (NCT03058627)	Randomized open-label trial	Patients with severe aortic stenosis selected for TAVR and at least one coronary stenosis with FFR ≤0.80 or diameter stenosis >90% in a coronary artery ≥2.5 mm	452	TAVR only vs. TAVR + FFR-guided complete revascularization	All-cause mortality, myocardial infarction, or urgent revascularization at 1 yr

ACTIVATION = Assessing the effects of stenting in significant coronary artery disease prior to transcatheter aortic valve implantation; AS = aortic stenosis; CABG = coronary artery bypass graft; CT = computed tomography; CTA = computed tomography angiography; CT-CA = Primary Non-invasive Cardiac Computed Tomography Versus Routine Invasive Angiography Prior to TAVI; FAITAVI = Functional Assessment in TAVI: FAITAVI; FFR = fractional flow reserve; FORTUNA = Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVR; iFR = instantaneous wave-free ratio; LAD = left anterior descending; NOTION-3 = Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TCW = The TransCatheter Valve and Vessels Trial; TF = transfemoral; TSc = trans-subclavian.

evidence suggests the use of FFR with the usual 0.80 cut-off and a threshold of 0.89 or less for iFR for the evaluation of CAD severity in TAVR candidates. Nevertheless, these data remain preliminary, and the level of evidence is low. Future studies with a larger number of patients and further validation with clinical events should determine the optimal FFR and iFR cut-off values to be used in TAVR candidates. Preliminary data showed a very low rate of coronary events at midterm follow-up among those patients who had FFR and/or iFR evaluation pre-TAVR (22,23,31) (**Table 3**). However, long-term follow-up data will be needed to confirm the clinical validity of this strategy.

Overall, preliminary clinical data with the use of FFR/iFR in TAVR candidates are promising, and this functional evaluation of coronary lesions, already well established in stable CAD patients without AS, should probably be implemented in the evaluation of such patients. Two ongoing randomized clinical trials will further determine the role of invasive functional assessment of coronary lesions pre-TAVR (**Table 2**).

CORONARY REVASCULARIZATION PRE-TAVR

The clinical relevance of percutaneous coronary intervention (PCI) performed during the TAVR work-up remains to be determined. Indeed, randomized trials failed to demonstrate a clear beneficial effect of PCI in stable CAD patients (33,34), and current guidelines state that performing PCI in the presence of a coronary artery stenosis >70% in proximal coronary segments during the pre-TAVR work-up lacks scientific evidence (35,36).

Numerous observational studies have shown the lack of differences in clinical outcomes in patients

TABLE 3 Summary of Studies Evaluating the Use of FFR During the Pre-TAVR Work-Up

First Author, Year (Ref. #)	Population	FFR Measurement Protocol	Related Side Effects	Treated Lesions	Follow-Up
Stanojevic et al., 2016 (31)	82 lesions (n = 72)	Peripheral intravenous infusion of 140 μg/kg/min adenosine for up to 4 min (infusion terminated earlier than this time frame if a value <0.80 was attained, or if hemodynamic alterations resulting in adverse symptoms were noted)	1 AV block No symptomatic hypotension resulting in cessation of adenosine infusion	PCI performed for 37 of 82 lesions	At a median follow up of 19 ± 14 months after TAVR: 4 ACS, no TVR or TLR
Pesarini et al., 2016 (22)	133 lesions (n = 54)	Intracoronary bolus of 150 to 250 μg adenosine without nitroglycerin administration	None	PCI performed for 19 of 133 lesions (n = 17)	At 30 days: No sustained angina or hypotension, myocardial infarction, or heart failure
Scarsini et al., 2018 (23)	141 lesions (n = 62)	Intracoronary bolus of 150 to 250 μg adenosine without nitroglycerin administration	None	PCI performed for 19 of 141 lesions (n = 17)	At 30 days: No death or new coronary revascularization
Ahmad et al., 2018 (21)	30 lesions (n = 28)	Intracoronary bolus of 150 μg adenosine	None	Missing information	Missing information
Yamanaka et al., 2018 (25)	116 vessels (n = 95)	Intravenous infusion of adenosine at a dose of 140 μg/kg/min via a central or large antecubital vein	Systolic blood pressure fluctuations of more than 40 mm Hg in 12 of 116 vessels Maximal systolic blood pressure fluctuation of 90 mm Hg in 1 of 116 vessels 1 intermittent AV block No ventricular arrhythmias, bronchospasm, thrombus formation or coronary dissection	Missing information	Missing information

ACS = acute coronary syndrome; AV = atrioventricular; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 2.

undergoing TAVR + PCI versus isolated TAVR (Online Table 2), and a recent meta-analysis showed that PCI pre-TAVR was not associated with any increase in 1-year mortality (10). These results have generally been interpreted as a proof of the feasibility and safety of PCI in this context. Also, several studies have examined the completeness of coronary revascularization in TAVR candidates with CAD, most often using the residual Syntax score (rSS) (Online Table 3). Interestingly, many studies have shown the negative impact of incomplete coronary revascularization and/or high rSS, and this negative impact remained significant after adjustment for potential confounders. These results are further supported by 2 recent meta-analyses confirming that patients with high rSS have a higher mortality after TAVR (11,37). However, the selection of which coronary lesions to treat and the completeness of revascularization was usually left to the discretion of the operator/heart team of each center and may have been influenced by other factors (e.g., angina or decreased left ventricular ejection fraction), leading to a large variability on PCI strategies across studies that may indeed have had an impact on clinical outcomes.

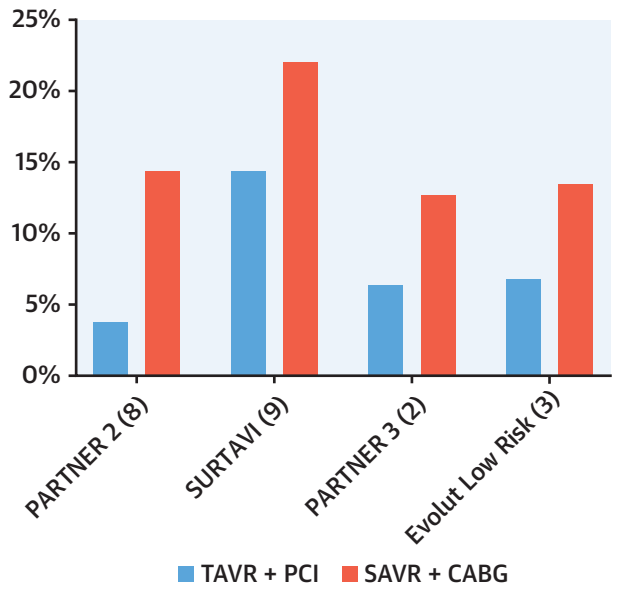
Randomized trials comparing TAVR and surgical aortic valve replacement (SAVR) for the treatment of low- to intermediate-risk patients with severe symptomatic AS have included patients with CAD (2,3,8,9). All CAD patients included in these trials were eligible for either PCI or coronary artery bypass graft (CABG), and those allocated to TAVR received PCI within the weeks prior to the procedure, whereas those allocated to SAVR underwent concomitant CABG. About 12% (range 4% to 22%) of patients included had coronary revascularization (either by PCI or CABG) in addition to TAVR or SAVR (2,3,8,9) (**Figure 2**). The global results of all randomized trials showed either the noninferiority or superiority of TAVR versus SAVR for the combined endpoint of mortality or stroke at midterm follow-up (1 to 2 years). Although patients with CAD requiring revascularization represented a minority, these results indirectly supported the strategy of TAVR + PCI versus SAVR + CABG in the treatment of AS and CAD. Unfortunately, specific data on patients receiving coronary revascularization (PCI or CABG) was provided only in the recently published PARTNER 3 (The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis) trial, showing the lack of differences between TAVR + PCI (n = 32) and SAVR + CABG (n = 58). Thus, the rate of the combined endpoint of mortality/stroke/rehospitalization was 9.4% in the TAVR + PCI group versus 12.1% in the SAVR + CABG group (hazard ratio: 0.77; 95% confidence interval: 0.20 to 2.98) (2). However, it should be noted that no data on periprocedural (PCI)

myocardial infarction were available. In addition, patients with complex CAD (including left main coronary artery or with an SS >22 or 32) were excluded from randomized trials. Chakravarty et al. (38) recently provided reassuring data on the safety of left main PCI in TAVR candidates, and some teams have reported the feasibility of using mechanical support (such as Impella, Abiomed, Danvers, Massachusetts; or TandemHeart, TandemLife, Pittsburgh, Pennsylvania) (39,40) or performing balloon aortic valvuloplasty (41) prior to complex PCI in patients with severe AS. Future studies are needed to determine the clinical outcomes in patients with complex CAD undergoing PCI + TAVR.

Two ongoing randomized trials are trying to determine the usefulness of coronary revascularization with PCI (vs. no revascularization) in patients with CAD undergoing TAVR (**Table 2**).

Although ticagrelor is considered a potential choice for high-risk PCI in stable patients (29), no data exist on the potential risk of increased bleeding events in the periprocedural TAVR period in patients under ticagrelor treatment. While waiting for additional data, we consider that the combination of aspirin + clopidogrel should be prioritized in these patients, with a dual antiplatelet therapy duration that should be individualized between 1 and 6 months (29,42).

FIGURE 2 Coronary Revascularization in Randomized Trials



Percentage of patients who underwent TAVR + PCI and SAVR + CABG in randomized trials. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

TIMING OF CORONARY REVASCULARIZATION PRE-TAVR

When a PCI indication is established, it is usually performed upstream of TAVR. However, a staged PCI prior to TAVR is inevitably associated with an additional vascular puncture, repeated injection of contrast media, and dual antiplatelet therapy, which may increase the complication rates following TAVR. Thus, the optimal timing of PCI prior to TAVR remains unclear.

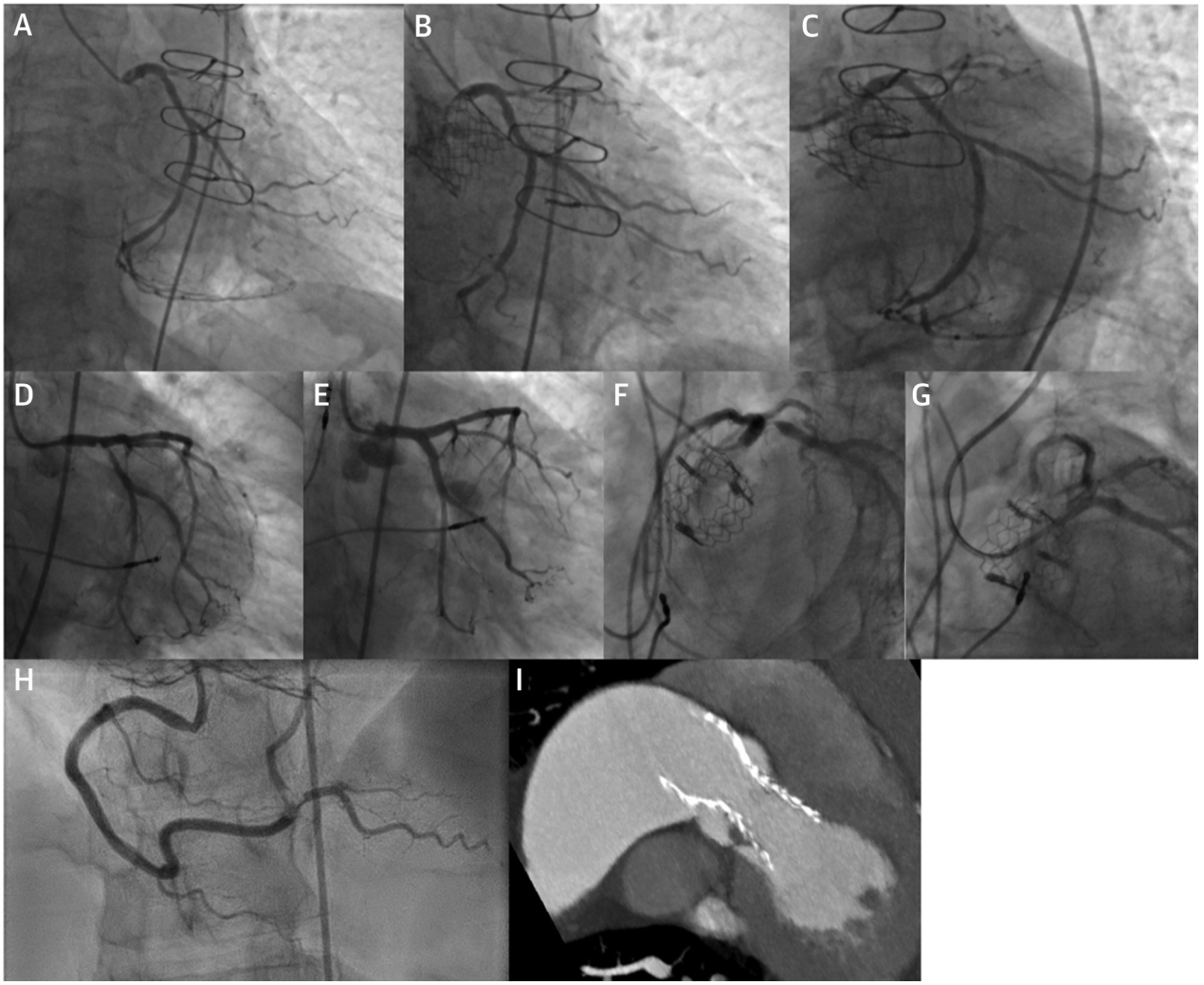
van Rosendael et al. (43) compared the clinical outcomes of patients undergoing PCI within 30 days or >30 days before TAVR and failed to show significant differences between groups in overall mortality after a median follow-up of 2 years. However, a significant increase in minor vascular injury and bleeding complications after TAVR was observed in the group who had PCI performed within 30 days before TAVR. Singh et al. (44) showed that patients who underwent PCI during the same hospitalization as the TAVR procedure had a higher in-hospital mortality. Finally, several studies have shown the feasibility and safety of TAVR and concomitant PCI (45–50). Although this strategy has the advantage of avoiding multiple procedures and can potentially reduce the risks associated with obtaining vascular access at different time points, it increases the amount of contrast media administered at the time of the TAVR procedure and could potentially increase the risk of contrast nephropathy, particularly in patients with complex CAD.

In summary, no definite data exist on the timing of PCI in TAVR candidates with significant CAD. While staging the PCI and TAVR procedures remains the most common strategy, controversial data exist on the most appropriate (minimum) delay between PCI and TAVR. In the absence of further data, no specific timing strategy can be recommended in this setting. However, the presence of both complex CAD and risks factors for contrast nephropathy (e.g., history of chronic kidney injury) should probably be considered when establishing a minimum delay between procedures.

CORONARY EVENTS AFTER TAVR

EPIDEMIOLOGY AND PATHOPHYSIOLOGY. AS and CAD share some common risk factors, and some studies have suggested a similar pathophysiological process for both entities (51). However, little data is available on the incidence of coronary events after

FIGURE 3 Examples of Coronary Events Post-TAVR



Case 1: **(A)** Pre-TAVR coronary angiogram. **(B)** De novo stenosis at the distal left circumflex artery revealed by a NSTEMI (8 months after TAVR). **(C)** PCI result. Case 2: Pre-TAVR coronary angiogram before **(D)** and after **(E)** PCI. In-stent restenosis at the proximal left circumflex artery revealed by a NSTEMI (9 months after TAVR) before **(F)** and after **(G)** PCI. Case 3: **(H)** Coronary angiogram showing a thrombus located on the crux cordis revealed by a NSTEMI (13 months after TAVR). **(I)** Computed tomography angiography showing an external partial thrombosis of the TAVR bioprosthesis. NSTEMI = non-ST-segment elevation myocardial infarction; other abbreviations as in Table 2.

TAVR. Vilalta et al. (52) reported, in a cohort of 779 TAVR recipients, an incidence of acute coronary syndrome (ACS) of 10% after a median follow-up of about 2 years after TAVR. Up to 36% of the ACS events consisted of non-ST-segment elevation myocardial infarction (NSTEMI) type 2, followed by unstable angina (35%), NSTEMI type 1 (28%), and STEMI (1%). Finally, only 39% of the patients benefited from PCI. Of note, the prognosis of ACS occurring after TAVR was poor, with an all-cause mortality of 37% after a median follow-up of 21 months post-ACS.

The majority of coronary events occurring after TAVR are likely related to an atherothrombotic mechanism, either by the progression of CAD, or the failure of a PCI performed before the TAVR (Figure 3). Moreover, some authors have hypothesized other potential mechanisms, such as impaired coronary flow dynamics and coronary hypoperfusion related to the TAVI bioprosthesis (53), a coronary embolism related to subclinical leaflet thrombosis in bioprosthetic aortic valves thrombosis (54) (Figure 3), a late valve migration occluding a coronary ostia

TABLE 4 Summary of Studies on the Feasibility of PCI After TAVR

First Author, Year (Ref. #)	Population	Devices and Results	Conclusions
Blumenstein et al., 2015 (58)	35 patients who underwent CA or PCI after TAVR	Sapien XT: 19 of 19 selective CA; 8 of 8 successful PCI CoreValve: 3 of 10 selective CA, 6 of 10 nonselective CA, 1 of 10 nondiagnostic CA; no PCI Symetis: 2 of 4 selective CA, 2 of 4 nonselective CA; 1 of 1 successful PCI Jena: 1 of 1 selective CA; no PCI Portico: 1 of 1 nonselective CA; 1 of 1 successful PCI	Selective CA and PCI in patients with prior TAVR is generally feasible. Depending on stent frame type, the procedure can be challenging or even unfeasible.
Allali et al., 2016 (59)	24 PCI procedures in 17 patients with CoreValve bioprosthesis	4 of 24: difficult ostium intubation and suboptimal stability 23 of 24 procedural success (1 procedural death)	PCI after implantation of the self-expanding CoreValve is mostly feasible and safe. Selective intubation of the native coronary may be challenging.
Chakravarty et al., 2016 (38)	9 LM PCI: 4 patients with CoreValve and 5 with Edwards	9 of 9 successful PCI	LM PCI was feasible with self-expandable and balloon expandable TAVR bioprosthesis.
Chetcuti et al., 2016 (60)	190 CA and 113 attempted PCI in 169 patients with CoreValve bioprosthesis	186 of 190 successful CA 103 of 113 successful PCI	CA and PCI are possible in nearly all patients with CoreValve bioprosthesis.
Zivelonghi et al., 2016 (61)	66 patients who underwent CA or PCI after TAVR	Evolut R: 24 of 25 successful CA (of which 4 semiselective) and 6 of 6 successful PCI Sapien 3: 41 of 41 successful CA (of which 2 semiselective) and 13 of 13 successful PCI	Catheterization of the coronary ostia after TAVR with balloon or self-expandable valves is safe and feasible in almost all cases.
Boukantar et al., 2017 (62)	16 patients with CoreValve	9 of 16 adequate coronary opacification 6 of 7 successful PCI	CA after CoreValve TAVR are feasible but challenging.
Htun et al., 2017 (63)	43 CA in 28 patients with CoreValve or Evolut R	42 of 43 selective LMCA engagement 29 of 32 selective RCA engagement 29 of 29 successful PCI	CA and PCI after TAVR are feasible and safe with supra-annular self-expandable valve.
Tanaka et al., 2019 (64)	40 patients with CoreValve or Evolut R	16 of 32 RCA angiography success 28 of 32 LCA angiography success 28 of 30 PCI success	CA and PCI following CoreValve TAVR is safe and feasible in most cases. Success rate of selective RCA angiography is relatively low.

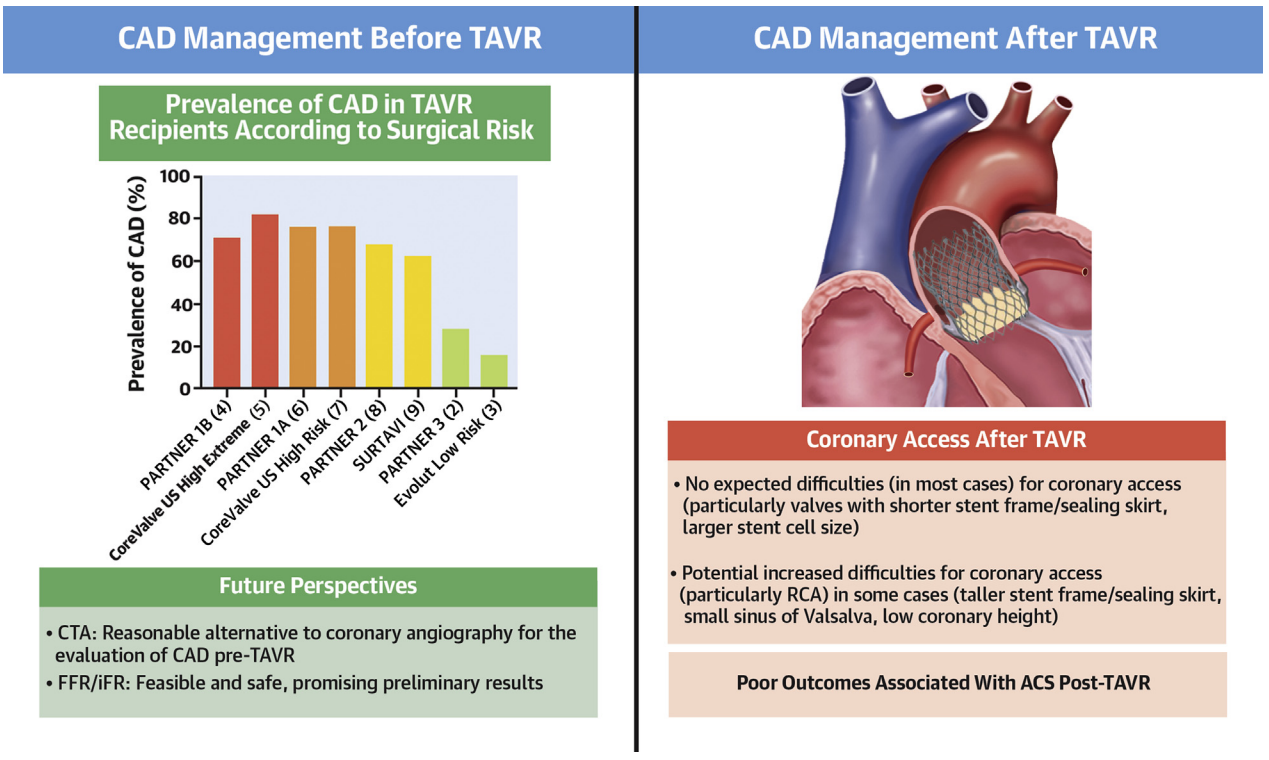
CA = coronary angiogram; LCA = left coronary artery; LM = left main stem; RCA = right coronary artery; other abbreviations as in Table 2.

initially partially covered but not occluded (55,56), and a hypersensitivity reaction against metal anions present into the device (Kounis syndrome) (57). Future studies are needed to better categorize the type and frequency of coronary events post-TAVR, and further investigate the factors determining the occurrence and poor outcomes of patients experiencing such events.

CORONARY ACCESS AFTER TAVR. Irrespective of the mechanisms leading to a coronary event post-TAVR, obtaining appropriate images of the coronary arteries by selective CA is frequently mandatory for establishing an appropriate diagnosis and therapeutic strategy. The presence of a TAVR bioprosthesis could potentially make the selective catheterization of coronary ostia difficult or even impossible. Although it seems obvious that the type of transcatheter valve (and its geometry) may have an effect on coronary access, no studies have yet shown differences in coronary access and CA and PCI feasibility according to transcatheter valve type. Available data are related to isolated cases and small series globally, including 190 reports of CA and/or PCI in patients with a TAVR bioprosthesis (Table 4), with rates of successful selective CA ranging from 50% to 100% (38,58-64).

Yudi et al. (65) recently proposed a catheter selection algorithm depending on the type of bioprosthesis (CoreValve, Medtronic, Minneapolis, Minnesota; or Sapien, Edwards, Irvine, California), the type of procedure (CA or PCI), and the position of the transcatheter valve commissure with respect to the coronary ostium. Also, the authors recommended the systematic use of 6-F catheters, as well as selecting a femoral or left radial approach for patients with a Medtronic CoreValve system, and a femoral or radial (left or right) approach for patients with an Edwards Sapien valve. Data from our experience (unpublished) including 41 patients with a SAPIEN or SAPIEN XT valve undergoing repeat CA or PCI showed no increased difficulties (number of catheters used, procedural time, contrast volume) with respect to pre-procedural CA/PCI. In about two-thirds of the cases, the procedure was performed with no need for crossing through the struts of the stent valve frame (coronary ostia were frequently located at the level or above the top of the stent frame). Thus, we consider that no particular changes in catheters (size or type) or approach (right radial) would be required in such cases. On the other hand, although not definitely proven, there is increased concern regarding coronary

CENTRAL ILLUSTRATION **Coronary Artery Disease Management Before and After Transcatheter Aortic Valve Replacement**



Faroux, L. et al. J Am Coll Cardiol. 2019;74(3):362–72.

Current evidence and future perspectives of CAD management before and after TAVR. ACS = acute coronary syndrome; CAD = coronary artery disease; CTA = computed tomography angiography; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention; RCA = right coronary artery; TAVR = transcatheter aortic valve replacement.

access in the presence of some self-expanding valves due to the taller valve frame and supra-annular valve. In particular, catheterization of the right coronary artery can be particularly challenging in these cases, and we agree with the main recommendations from Yudi et al. (65) in this context. Also, the use of the Barbeau curve catheter (with a slightly larger secondary curve with respect to the Judkins right catheter) may be helpful in some cases. Future studies will need to validate these recommendations and further determine the feasibility and failure rates regarding selective CA/PCI for each transcatheter valve type.

CONCLUSIONS AND FUTURE PERSPECTIVES

CAD remains one of the most frequent comorbidities among TAVR candidates (Central Illustration). While controversial results have been reported regarding its clinical impact, revascularization (PCI) pre-TAVR of lesions located in the proximal-mid coronary segments remains the most common practice worldwide. Ongoing randomized trials should determine the efficacy of this strategy (vs. no revascularization) in the coming years. Also, the most appropriate timing of PCI pre-TAVR remains undetermined, and the possibility of a combined procedure (PCI at the time of TAVR) merits further evaluation, particularly in patients with no complex CAD or kidney dysfunction. The use of noninvasive methods like coronary CTA in the pre-TAVR work-up, and a more accurate evaluation of coronary lesion severity with coronary pressure wire measurements have shown to be associated with good preliminary results and will likely increase in the coming years; several ongoing studies are going to clarify the exact role of these technologies in the TAVR field. Finally, scarce data exist on the

occurrence, impact, and management of coronary events post-TAVR. Apart from better understanding the pathophysiology and establishing the most appropriate treatment strategy in such cases, more data is urgently needed regarding the coronary access (feasibility and failure rate) across different transcatheter valve types (**Central Illustration**). The fact that many patients with a coronary syndrome post-TAVR are treated in centers with no TAVR experience further highlights the importance of establishing clear recommendations regarding selective CA and PCI in these cases. The recent publication of 2 randomized trials with positive results for TAVR in a low-risk AS population has provided definite evidence for extending this treatment toward younger and lower-risk patients. However, a better understanding of the diagnosis, prognosis, and management of CAD pre- and post-procedure will be needed in the process of the final expansion of TAVR.

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KEY WORDS coronary artery disease, coronary computed tomography angiography, fractional flow reserve, TAVR

APPENDIX For supplemental tables, please see the online version of this paper.