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STATE-OF-THE-ART PAPERS

Severe Aortic Stenosis and Coronary Artery Disease—Implications for Management in the Transcatheter Aortic Valve Replacement Era

A Comprehensive Review

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Management of coronary artery disease (CAD) in patients with severe aortic stenosis (AS) referred for transcatheter aortic valve replacement (TAVR) is posing challenges. Due to limited and heterogeneous data on the prevalence and clinical impact of CAD on the outcomes of TAVR and the management strategies for CAD in patients undergoing TAVR, we performed a comprehensive review of the literature. Significant CAD is present in 40% to 75% of patients undergoing TAVR. The impact of CAD on outcomes after TAVR remains understudied. Based on existing data, not all patients require revascularization before TAVR. Percutaneous coronary intervention (PCI) should be considered for severely stenotic lesions in proximal coronaries that subtend a large area of myocardium at risk. Ongoing studies randomizing patients to surgical or percutaneous management strategies for severe AS will help provide valuable data regarding the impact of CAD on TAVR outcomes, the role of PCI, and its timing in relation to TAVR. (J Am Coll Cardiol 2013;62:1–10) © 2013 by the American College of Cardiology Foundation

Risk factors for aortic stenosis (AS) have been shown to be similar to atherosclerosis (1). Consequently, coronary artery disease (CAD) is often found concurrently in patients presenting with severe symptomatic AS. The prevalence of significant CAD ranges from 25% to 50% in patients with severe AS (2–5). Surgical aortic valve replacement (SAVR) and concomitant coronary artery bypass grafting (CABG) has been the standard management strategy for patients with severe symptomatic AS and CAD (6). Recently, transcatheter aortic valve replacement (TAVR) has emerged as a less invasive and feasible treatment option in patients at high risk for conventional SAVR (7,8). More than 50,000 TAVRs have been performed around the world to date; however, there is no consensus on the management of severe CAD in this setting. We reviewed the available published data to understand: 1) the prevalence of CAD in patients with severe AS; 2) clinical impact of CAD on the outcomes of TAVR; and 3) the management options for CAD in patients with severe AS undergoing TAVR.

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Prevalence of CAD in Patients With Severe AS

CAD in SAVR patients. At the time of SAVR, the prevalence of significant CAD requiring concomitant CABG has been shown to increase with age. Studies have shown that in the age group of 61 to 70 years, 40% of patients required concomitant CABG, whereas in patients over the age of 80 years, >65% had concomitant CABG (9,10). Several surgical databases have shown that CABG increases operative and short-term mortality with SAVR (11–14). Similarly, concomitant CABG appears to have an adverse effect on long-term outcomes after SAVR (9,15). However, there are no randomized controlled trials of CABG+SAVR compared with SAVR alone in the presence of significant CAD. It is possible that the increase in short- and long-term mortality in patients undergoing concomitant CABG and SAVR compared with SAVR alone might be a reflection of more severe and diffuse atherosclerosis in the former group, which renders this population sicker and direct comparisons with those undergoing SAVR difficult to interpret (16). In a study comparing the outcomes of SAVR patients with severe AS and no CAD versus severe AS and CAD where CABG was not performed, short- and long-term outcomes were not found to be different (17). That study, however, is notable for a small number of patients (n = 55) who did not undergo CABG with SAVR in addition to most patients having single vessel CAD. In other

Abbreviations and Acronyms

AS = aortic stenosis
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CK = creatine kinase
DES = drug-eluting stent
DMJS = Duke Myocardial Jeopardy Score
EF = ejection fraction
MB = myocardial band
MI = myocardial infarction
PCI = percutaneous coronary intervention
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement
VARC = Valve Academic Research Consortium

larger studies, leaving significant CAD unrevascularized at the time of SAVR was associated with increased risk of adverse short- and long-term outcomes (15,18). Therefore, CABG is recommended along with SAVR in the presence of significant CAD (>50% to 70% stenosis) (6). This includes bypassing moderately severe lesions (i.e., 50% to 70%), which might or might not be clinically significant.

Prevalence of CAD in TAVR population. As shown in Table 1, in concurrence with SAVR published data, significant CAD is present in 40% to 75% of patients undergoing TAVR (7,8,19–34). In the FRANCE 2 (French Aortic National CoreValve and Edwards 2) registry, the largest published multicenter study of 3,195 TAVR patients, 48% patients had CAD (33). Significant numbers of patients undergoing TAVR also have prior history of myocardial infarction (MI) (12% to 51%) and prior percutaneous (16% to 34%) or surgical revascularization (14% to 48%) (Table 1). Most of these studies have not reported data on the burden of unrevascularized severe CAD before undergoing TAVR. The only randomized TAVR study, the PARTNER (Placement of AoRTic TraNscathetER Valve) trial excluded patients with untreated clinically significant CAD requiring revascularization (7,8); however, in the real world, patients being referred for TAVR often have concomitant significant CAD (35–37). Management of concomitant significant CAD in TAVR registries and nonrandomized studies thus far has been variable and of considerable emerging interest, raising issues around safety of performing TAVR in patients with unrevascularized CAD and also those related to performing percutaneous coronary intervention (PCI) in patients with AS who will later need TAVR, as discussed in the following.

Impact of CAD on Outcomes of TAVR

Procedural and short-term outcome. Most patients with significant unrevascularized CAD were excluded from the randomized PARTNER trial. Many patients undergoing TAVR have previously undergone PCI on the most significant coronary lesions before TAVR. Nevertheless, with the substantial selection criteria used in the currently published data, Table 1 shows that the risk of procedural death or death within 24 h post-TAVR is low. Second, as shown in Table 1, the risk of MI within 30 days after TAVR has ranged from 0% to 4.6%, except for a high rate of 15% described in the study by Svensson et al. (25), which was the initial feasibility study of transapical TAVR. Of note, most of these studies did not use a standardized definition for MI, as recently suggested by the Valve Academic Research Consortium (VARC) (38). There are significant differences in the threshold of peri-procedural cardiac biomarker elevation for the diagnosis of MI in these studies. For example, in the feasibility study by Svensson et al., MI was defined as development of new Q waves in 2 or more contiguous leads with creatine kinase (CK) or CK-myocardial band (MB) levels elevated above normal, and non–Q-wave MI was defined as CK elevation to twice normal (25). From a subsequent study by Rodes-Cabau et al. (39), it is now known that even patients without CAD undergoing TAVR have some elevation in cardiac biomarkers; hence a modest elevation of CK or CK-MB above normal range should not be used to define a coronary-related MI. It is hoped that with VARC definitions, all post-TAVR endpoints will be standardized, leading to easier interpretation and comparison of outcomes in future TAVR studies.

Long-term outcome. Few studies have directly evaluated and reported the impact of CAD on outcomes of patients after TAVR (Table 2) (40–46). Dewey et al. (40) were the first to report the impact of CAD as defined by prior CABG or prior PCI in 171 patients undergoing TAVR. In that study, patients with CAD had higher 30-day (13.1% vs. 1.2%, $p = 0.002$) and 1-year mortality (35.7% vs. 18.4%, $p = 0.01$) compared with patients without CAD. Patients with CAD were 10 times more likely to die within 30 days after TAVR compared with those without CAD (95% confidence interval: 2.1 to 174.8) (40). Lack of data on the degree of CAD and its physiological burden were the main limitations of this study. In contrast, a study by Masson et al. (41) evaluated the impact of CAD on outcomes of TAVR stratified by the extent of CAD, as characterized by the Duke Myocardial Jeopardy Score (DMJS). The DMJS is a well-validated prognostic marker in patients with CAD that takes into account the area of myocardium at risk and is more accurate at prediction of outcomes compared with the number of diseased coronary arteries (47). In contrast to the study by Dewey et al. (40), the study by Masson et al. (41) did not find a statistically significant difference in the 30-day mortality post-TAVR in patients with CAD compared with those without CAD (11.5% vs. 6.3%). However, given the almost 2-fold higher risk, it is possible that these results would have been significant in a larger number of patients. The other notable finding in that study is that 15 of 136 patients (11%) underwent PCI before TAVR, which reduced the DMJS by a median of 2 points (41). A recent study by Gautier et al. (42) also evaluated the impact of CAD on the outcomes of TAVR in 145 patients. They found no difference in the outcomes of 30-day or 1-year post-TAVR mortality in patients with and without CAD. Again, similar to the study by Masson et al. (41), 11 of 83 patients with CAD (17%) in their study underwent PCI before TAVR. This was mainly clinically driven on the basis

Table 1 Prevalence of CAD and Outcomes in Major Published TAVR Studies

	Prevalence of CAD				Outcomes				
First Author (Ref. #)	CAD	Prior MI	Prior CABG	Prior PCI	Procedural/24-H Death	30-Day/ In-HospitalMI	1-Yr MI	30-Day/ In-HospitalDeath	1-Yr Death
Leon et al. (7) n = 179	67.6%	18.6%	37.4%	30.5%	1.1%	0	0.6%	4.5%* 5.0%	19.6%* 30.7%
Eltchaninoff et al. (19) n = 244	41.3%	22.5%	25.4%		0.4%			12.7%	
Rodes-Cabau et al. (20) n = 339	69.0%	51.0%	34.2%	29.2%	1.7%	1.2%		10.4%	
Thomas et al. (21) n = 1,038	51.9%		22.6%				1.4%	8.5%	23.9%
Himbert et al. (22) n = 75	61.0%	20.0%	31.0%	22.0%	4.0%			9.0%* 10.0%	22.0%
Lefevre et al. (23) n = 130	60.0%	20.8%	31.5%	24.6%	0.8%	4.6% 0.8%†	6.9% 0.8%†	13.8%	36.9%
Walther et al. (24) n = 168	49.0%	18.0%	14.0%	16.0%		1.0%	4.0%	15.0%	37.0%
Svensson et al. (25) n = 40		27.5%	47.5%	45.0%	7.5%	15.0%		17.5%	
Grube et al. (26) n = 136	59.5%	25.7%	30.1%		2.2%	2.2%	2.2%	12.5%	18.4%
Petronio et al. (27) n = 514	50.4%	22.0%	16.3%	29.0%	0.8%	0.6%		5.4%	
Piazza et al. (28) n = 646	56.8%	11.9%	20.1%	28.9%	1.7%*	0.6%		5.8%* 8.0%	
Zahn et al. (29) n = 697	60.2%		20.6%	34.2%				12.4%	
Smith et al. (8) n = 348	74.9%	26.8%	42.6%	34.0%	0.9%	0	0.4%	3.4% 3.2%*	24.2% 14.3%*
Moat et al. (31) n = 870	47.6%					1.3%		7.1%	21.4%
Tamburino et al. (30) n = 663	48.3%	21.6%	15.7%	28.5%	0.9%		1.2%	5.9%	15.0%
Wenaweser et al. (32) n = 257		18.3%	21.0%	22.6%		0.4%	1.6%	6.6%	17.1%
Gilard et al. (33) n = 3,195	48.0%	16.0%	18.0%					9.7%	24.0%
Beckman et al. (34) n = 3,875	55.0%							5.1%	7.7%

*Cardiovascular; †coronary obstruction.
CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; TAVR = transcatheter aortic valve replacement.

of angina and/or severe ostial or proximal coronary stenoses subtending a large area of myocardium at risk (5 of 11 patients had proximal left anterior descending coronary artery stenosis). In this study, 16 of 83 (19%) patients in the CAD group were free of residual significant coronary stenosis (42). The recently published U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) registry had a 14% rate of PCI (55 of 410 patients) in patients undergoing TAVR (31), similar to the rates of PCI in the TAVR studies by Masson et al. (1) and Gautier et al. (42). In another study reporting outcomes of TAVR in 256 patients, Wenaweser et al. (43) compared the outcomes of 59 patients with significant CAD and a mean DMJS of 5.0, who underwent PCI (23%) before TAVR, with 197 patients who did not undergo PCI (mean DMJS 1.2) before TAVR. They found, although of marginal statistical significance, a 2-fold higher risk of 30-day post-TAVR mortality in patients who underwent PCI before TAVR compared with those who had TAVR alone (10.2% vs. 5.2%, p = 0.24). These findings raise concerns about the adverse impact of CAD on outcomes of TAVR, similar to surgical published data as discussed in the preceding text, although they do not advise on whether to revascularize by PCI before TAVR. It can be summarized that a select group of patients with CAD, ranging from 11% to 23%, have undergone PCI before TAVR (31,41–43), although it is not conclusive about how and when that should be performed.

Cause of death post-TAVR. In the inoperable cohort of the PARTNER trial, the 1-year mortality in the TAVR arm was 30.7% versus 49.7% in the standard medical therapy arm (7). There were a total of 71 deaths at 1 year in the TAVR arm, of which 27 (38%) were classified as cardiovascular death, 27 (38%) were non-cardiovascular and in 17 (24%) the cause of death was unknown. Similarly, in the SOURCE (Edwards SAPIEN Aortic Bioprosthesis European Outcome) registry, of the 179 deaths between 30 days and 1 year, 45

Table 2 Impact of CAD on TAVR Outcomes

First Author (Ref. #)	CAD Definition	STS, Log EuroScore	30-Day Mortality	1-Yr or Follow-Up Mortality	Conclusions
Dewey et al. (40) (n = 171)	Prior CABG or PCI				CAD patients had increased risk of 30-day mortality, OR: 10.1 (95% CI: 2.1–174.8, p = 0.009) and overall mortality, OR: 20.3 (95% CI: 2.4–172.3, p = 0.006)
CAD, 84 (49%)		14.5, 36.6	13.1%	35.7%	
No CAD, 87 (51%)		9.9, 27.5	1.2%	18.4%	
Masson et al. (41) (n = 136)	DMJS, ≥50% stenosis		14%	22.1%	No risk of increased 30-day mortality (p = 0.56) or 1-yr mortality (p = 0.63) in patients with CAD and without CAD
DMJS					
0, No CAD, 32 (23%)		7.1, 21.5	6.3%	18.8%	
0, CAD, 41 (30%)		9.4, 25.0	14.6%	28.8%	
2, 28 (21%)		9.0, 33.5	7.1%	35.7%	
4, 18 (13%)		9.7, 32.5	5.6%	11.1%	
6–12, 17 (13%)		11.3, 40.0	17.7%	29.4%	
			11.5%		
15 of 136 (11%) patients underwent PCI before TAVR					
Gautier et al. (42) (n = 145)	Prior MI, CABG, PCI or ≥70% stenosis (≥50% for LMT)				No risk of increased 30-day mortality (p = 0.37) or 1-yr mortality (p = 0.28) in patients with and without CAD
CAD, 83 (57%)		NA, 29	10%	24.0%	
No CAD, 62 (43%)		NA, 24	15%	29.0%	
PCI was performed in 11 of 83 (17%) patients before TAVR					
Wenaweser et al. (43) (n = 256)	DMJS, SYNTAX score				No risk of increased 30-day mortality in patients undergoing TAVR alone (55% with CAD) compared with those undergoing revascularization with PCI followed by TAVR
PCI + TAVR, 59 (23%) (Mean DMJS 5.0)		7.6, 28.6	10.2%		
TAVR alone, 197 (77%) (Mean DMJS 1.2)		6.1, 24.2	5.6%		
			(p = 0.24)		
Khawaja et al. (45) (n = 164)	≥70% stenosis				CAD patients had increased 30-day and 12-month mortality, OR: 2.92 (95% CI: 1.34–6.35, p = 0.007)
CAD, 54 (33%)	(≥50% for LMT) on pre-TAVR LHC	NA, 23.5	16.7%	31.5%	
No CAD, 110 (67%)		NA, 21.4	3.8%	14.4%	
10 of 54 (19%) patients underwent PCI before TAVR			(p = 0.005)	(p = 0.01)	
Ussia et al. (44) (n = 659)					No risk of increased 1-yr mortality in patients with and without CAD, adjusted HR: 0.74 (95% CI: 0.40–1.36, p = 0.3)
CAD, 251 (38%)	Prior PCI or CABG	NA, 28.6	6%	14.5%	
No CAD, 303 (62%)		NA, 21.4	5.9%	15.9%	
Wendler (46) (n = 2,307)	Prior CABG				No risk of increased mortality in patients with and without history of prior CABG
CABG + 502 (22%)		NA, 35.2	10.2%	23.5%	
CABG −1,805 (78%)		NA, 23.6	9.3%	23.5%	

Values are n (%), unless otherwise indicated.

CI = confidence interval; DMJS = Duke Myocardial Jeopardy Score; EuroScore = European System for Cardiac Operative Risk Evaluation; HR = hazard ratio; LHC = left heart catheterization; LMT = left main trunk; OR = odds ratio; STS = Society of Thoracic Surgeons; other abbreviations as in Table 1.

(25%) were cardiac, 88 (49%) were noncardiac, and in 46 (26%) patients the cause of death was unknown (21). Among the deaths of unknown cause in the SOURCE registry, 18 (39%) were classified as sudden death, which according to the new VARC definitions would be classified as cardiac deaths (48). In fact, the authors of the SOURCE registry note that a number of these patients were actually "found dead in bed" (21). It remains to be seen whether, in addition to the procedural and in-hospital outcomes, revascularization of significant CAD will have an impact on the long-term outcomes of these high-risk patients undergoing TAVR who have a very high 1-year risk of cardiovascular mortality, as noted in the PARTNER trial and SOURCE registry.

Difficulties in Interpreting Outcome Data in Patients With CAD Undergoing TAVR

As noted in the preceding text and in Table 2, studies comparing outcomes of TAVR in patients with and without CAD have used different definitions for CAD, there is

significant heterogeneity with regard to data on the anatomic and physiological burden of CAD, and a variable number of patients (11% to 23%) have already undergone PCI before TAVR on the basis of clinical evaluation by the managing team of physicians and the area of myocardium felt to be at risk. These factors make it difficult to interpret the direct impact of CAD on the short- and long-term outcomes of TAVR. Future studies should clearly define the coronary characteristics of patients in terms not only of anatomy on the pre-TAVR coronary angiogram and the number of unrevascularized coronary territories but also of an assessment of the physiological burden in some form, such as the DMJS. There are limited data directly comparing TAVR with SAVR, the concomitant CAD management strategies, and the completeness of revascularization with each approach. In a recently published study, Wenaweser et al. (32) compared the outcomes of patients with severe AS according to whether they underwent SAVR, TAVR, or medical therapy. They found that 44% of patients with severe AS and CAD who underwent SAVR had concomitant total coronary revascularization by CABG, whereas only 23% of patients with severe AS and CAD who underwent TAVR had total revascularization by PCI. This is partly because all coronary lesions $\geq$50% are bypassed at the time of SAVR; however, with PCI, the indication for revascularization tends to be more conservative and performed when the stenosis exceeds 70% or functional ischemia is more certain. Future randomized studies of SAVR and TAVR that include data on completeness of revascularization should help guide selection of patients for percutaneous revascularization before TAVR.

Management Options for CAD in Patients With Severe AS Being Considered for TAVR

The following considerations arise when evaluating patients with severe AS and CAD for TAVR: 1) hemodynamic alterations during TAVR in presence of unrevascularized CAD; 2) need for revascularization; 3) mode of revascularization—PCI or surgical; 4) safety of performing PCI in patients with severe AS; 5) timing of PCI in relation to TAVR; and 6) type of stent and management of antiplatelet regimen.

One of the procedural concerns during TAVR is the risk of inducing ischemia and hemodynamic instability in patients with significant unrevascularized CAD, especially during rapid ventricular pacing and balloon inflation, which are both part of the TAVR procedure. This real risk of this potential problem is unknown. In the Multicenter Canadian TAVR study, Rodes-Cabau et al. (20) showed that need for hemodynamic support during TAVR with intra-aortic balloon counter-pulsation or extracorporeal circulation due to severe sustained hypotension or hemodynamic collapse was an independent predictor of early as well as late mortality after TAVR. Even though it is unproven, intuitively this risk might potentially be higher in patients with unrevascularized severe CAD. As briefly mentioned in the preceding text, in the study evaluating the incidence and prognostic value of myocardial injury in the form of cardiac enzymes after TAVR, the same group showed that elevated CK-MB and troponin levels post-TAVR were associated with less improvement in left ventricular ejection fraction (EF) and higher cardiac mortality at follow-up (39). However, they did not find the presence of CAD or the presence of unrevascularized CAD to be a predictor of elevated cardiac enzymes post-TAVR (39). Transapical TAVR and baseline renal dysfunction were found to be predictive of greater increase in cardiac biomarkers post-TAVR in that study. These findings suggest that not all patients with significant CAD require revascularization before TAVR, in concurrence with the current clinical practice in the aforementioned TAVR studies (31,41–43). Pending randomized studies addressing this issue, it is likely that the patients most likely to derive benefit from PCI before or with TAVR are those with a large area of myocardium at risk, such as that subtended by a severe ostial or proximal stenosis in a large epicardial coronary artery. Fractional flow reserve–guided PCI has been shown to be beneficial compared with conventional angiography-guided PCI in patients with multivessel CAD, without significant valve disease (49). Similarly, fractional flow reserve might have a role in assessing hemodynamic significance of coronary stenoses during pre-TAVR coronary angiography and guiding revascularization; however, this has not been validated in patients with severe AS.

Mode of revascularization: percutaneous or surgical. In patients with severe left main disease or 3-vessel CAD, particularly in those with diabetes mellitus, outcomes after CABG have been shown to be superior to PCI (50,51). Patients with severe symptomatic AS with severe multivessel CAD or left main disease, who are at low or intermediate risk for surgery, should be considered for CABG and SAVR instead of percutaneous approach for treating both severe AS and CAD.

Safety of PCI in patients with severe AS. Historically, PCI has not been performed commonly in patients with severe AS. Therefore the outcomes of PCI in patients with severe AS have remained under-studied (52,53). Occasionally, patients with severe AS undergo PCI—such as those at high risk of morbidity and mortality from SAVR or those with temporary contraindications for SAVR, such as acute coronary syndromes or when symptoms are felt to be mainly from CAD. We recently published our experience with PCI in 254 patients with severe AS over an 11-year period, comparing the short-term outcomes after PCI with a propensity-matched group of 508 patients without AS who underwent PCI during the same time period (54). We found no difference in the risk of procedural complications or 30-day post-PCI mortality in patients with severe AS and the propensity-matched control subjects (4.3% vs. 4.7%, hazard ratio: 0.93, 95% confidence interval: 0.51 to 1.69, $p = 0.2$). However, patients with severe AS and EF $\leq$30% and those

with Society of Thoracic Surgeons (STS) score ≥10% were found to be at the highest risk of 30-day mortality after PCI (15.4% and 10.4%, respectively) in our study, whereas mortality risk was low in patients with EF >30% and those with STS score <10 (1.2% and 0%, respectively). Progressive cardiac and multi-organ failure was the cause of death in 9 of 11 (82%) patients with severe AS who died within 30 days after PCI. The findings of our study indicate that PCI can be performed in patients with severe AS without an increased risk of short-term mortality compared with a propensity-matched population with significant CAD but without AS. Nevertheless, a 30-day post-PCI mortality of 4.3% is a sobering finding, and patients with severe AS should be considered a high-risk group when being considered for PCI. This underscores the importance of patient selection for PCI before TAVR and weighing the risks and benefits of performing PCI before TAVR versus performing TAVR in the presence of unrevascularized significant CAD. There might also be a role for balloon aortic valvuloplasty, particularly if TAVR is not possible or feasible in a timely fashion after PCI, because most deaths in the 30 days after PCI in our study were related to progressive cardiac and multi-organ failure, which is likely an outcome of untreated severe symptomatic AS. Because patients with left ventricular EF ≤30% and STS score ≥10% were at a high risk of 30-day mortality after PCI in our study, balloon aortic valvuloplasty might have a role in these patients either as a staged procedure or concomitantly with PCI, although the available data are limited with these approaches (55,56).

Timing of revascularization of severe CAD in patients with severe AS undergoing TAVR. As stated in the preceding text, there are 2 key questions in the management of high-risk patients with severe AS and concomitant significant CAD. First, is the CAD significant enough to warrant an intervention? Second, if a PCI is deemed necessary, what is the best timing for PCI? It is still unclear which patients should undergo PCI before TAVR. However, it is logical, partly on the basis of the aforementioned studies, that severe coronary lesions that subtend a large area of myocardium such as proximal epicardial lesions should be considered for PCI before TAVR. The PCI can be performed before TAVR or concomitantly as a single-stage procedure with TAVR or be staged after TAVR. There are pros and cons to consider with each approach. Studies reporting outcomes of PCI before or concomitantly with TAVR are summarized in Table 3.

PCI before TAVR. The potential advantages of this approach are: 1) simplified access to the coronaries before TAVR; 2) less risk of ischemia and hemodynamic instability during rapid pacing and balloon inflation during subsequent TAVR; and 3) minimizing the contrast load by giving it at 2 separate points in time, thus minimizing the risk of contrast nephropathy. There are 2 potential issues with this approach: 1) dual antiplatelet therapy after PCI and its impact on bleeding outcomes after subsequent TAVR, especially via non-transfemoral approach; and 2) the safety of performing PCI in the presence of severe AS. As discussed earlier, we found that PCI can be performed without an increased risk of short-term mortality in patients with severe symptomatic AS, compared with a propensity-matched group of patients without AS (54). In concurrence with our findings with regard to safety of PCI in patients with severe AS, Abdel-Wahab et al. (57) found that PCI before TAVR in 55 patients (median duration between PCI and TAVR was 10 days) was not associated with worse 30-day (Fig. 1) and 6-month outcomes compared with 70 patients undergoing TAVR alone. Nevertheless, one has to be careful while selecting patients with severe AS for PCI before TAVR, because we found a high 30-day post-PCI mortality in patients with severe AS and low EF (<30%) and those with a high STS score (>10). Even though there was no risk of increased bleeding between the 2 groups in the study by Abdel-Wahab, this deserves further study, especially because previous data by Byrne et al. (58) suggest that PCI followed by valve surgery (median duration 10 days) is associated with a significantly increased risk of bleeding. A hybrid procedure where PCI is performed immediately before minimally invasive SAVR is also being proposed; however, the risk of postoperative bleeding with dual antiplatelet agents merits further evaluation.

PCI with TAVR as combined procedure. Some groups have proposed performing PCI on the most significant coronary lesions at the time of TAVR as a single staged procedure (59). Pasic et al. (60) reported their experience with this approach in 46 of 419 (11%) patients undergoing TAVR. They performed PCI on significant coronary lesions that subtended a large area of myocardium, such as proximal or mid left anterior descending coronary artery stenosis ≥90%, proximal or mid stenosis ≥90% in dominant right coronary artery or left circumflex coronary artery, or left main trunk stenosis ≥50%. There were 2 deaths (4.3%) within 30 days post-PCI+TAVR in this study—1 patient died after developing severe transvalvular regurgitation, and the other died after re-thoracotomy due to hematoma in the pleural space followed by multi-organ failure. Technical success was achieved in all patients in this study. The authors concluded that combined PCI and TAVR procedure is safe and feasible, and they suggest this approach in all patients when PCI is felt necessary. The limitation of this study is that there was no control arm consisting of patients undergoing isolated TAVR or staged PCI followed by TAVR. The potential advantages of this combined approach are: 1) treatment of both pathologies at the same time with elimination of potential morbidity and mortality after PCI while awaiting definitive management (i.e., TAVR for severe AS); 2) 1 arterial access for PCI and TAVR on the same day, with potential reduction in the risk of vascular access site complications and bleeding; and 3) possible reduction in the risk of inducing ischemia and hemodynamic instability while performing TAVR—this might be true if PCI is performed just before TAVR. This was not the case, however, in the study by Pasic et al.—they recommend

Table 3 PCI Staged or Combined With TAVR

First Author (Ref. #)	PCI Criteria	STS, Log EuroScore	30-Day Mortality	Follow-Up Mortality	Conclusions
Abdel-Wahab et al. (57) (n = 125)	All major vessels ≥50% stenosis			6 months	PCI before TAVR is not associated with worse 30-day or 6-month outcomes
PCI + TAVR, 55 (44%)		NA, 25.1	2.0%	9.0%	
TAVR alone, 70 (54%)		NA, 23.6	6.0%	14.0%	
52 had PCI before TAVR, 3 had single stage PCI+TAVR			p = 0.27	p = 0.42	
Pasic et al. (60) (n = 419)	LMT >50% ≥90% prox/mid LAD, RCA, LCX			Months 12 12.9% 24 30.3%	Combined TAVR+PCI is safe and feasible
TAVR+PCI, 46 (11%)		23, 40	4.3%	36 30.3%	
Wenaweser et al. (43) (n = 256)					PCI is safe in TAVR patients as staged or concomitant procedure
Staged PCI +TAVR, 23 (9%)	DMJS, SYNTAX score	8.2, 30.3	10.2%		
PCI+TAVR, 36 (14%)		7.3, 24.5			
TAVR alone, 197 (77%)		6.1, 24.2	5.6% p = 0.24		
Conradi et al. (61) (n = 179)					Staged PCI or concomitant PCI and TAVR feasible. Higher risk of renal failure in concomitant approach
Staged PCI+TAVR, 21 (12%)		9.3, 26.8	7.1%		
PCI+TAVR, 7 (4%)					

Values are n (%), unless otherwise indicated.
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; prox = proximal; RCA = right coronary artery; other abbreviations as in Tables 1 and 2.

performing TAVR first followed by PCI during the same procedure. Their rationale is that severe AS is the main lesion, and treating it first can potentially improve myocardial perfusion to a certain extent, even in the presence of a significant coronary stenosis. With this combined approach there is also a potential increased risk of contrast nephropathy secondary to the additional dye load during the same procedure. Wenaweser et al. (43) performed concomitant PCI+TAVR by performing PCI first, followed by TAVR in the same session, in contrast to the approach of Pasic et al. They also compared outcomes between patients undergoing concomitant PCI and TAVR versus those undergoing staged PCI followed by TAVR (after a mean of 34 days) (Fig. 1) (43). In that study, there was a statistically nonsignificant trend toward higher incidence of major access-related complication and life-threatening bleeding in the staged PCI and TAVR group compared with the concomitant PCI and TAVR group. In a study by Conradi et al. (61), there was a higher risk of renal failure in patients undergoing concomitant PCI and TAVR. Future studies evaluating the merits and demerits of both these approaches are required.

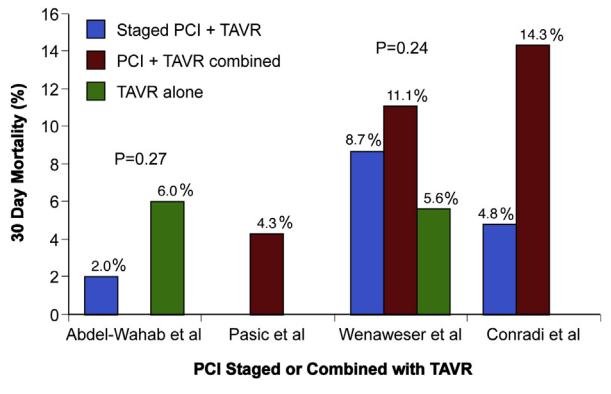

Figure 1 Staged or Combined PCI With TAVR

30-day mortality in published studies (43,57,60,61) including patients undergoing staged or combined percutaneous coronary intervention (PCI) with transcatheter aortic valve replacement (TAVR).

PCI after TAVR. There are a few case reports on PCI after TAVR; however, this approach is of some concern due to access issues (62,63). The valve struts could interfere with cannulation of coronaries, and catheter manipulation could potentially even dislodge the valve, although this is unlikely. As the TAVR experience continues to grow, ongoing studies will shed more light on whether PCI after TAVR might be a safe and feasible option in cases where the need for coronary revascularization arises post-TAVR.

Type of stent—drug-eluting or bare-metal—and interval between PCI and TAVR. In the absence of large-scale studies evaluating the outcomes of drug-eluting stent (DES) versus bare-metal stent in patients undergoing TAVR, this decision should be made on an individual basis

by the heart team, depending upon the perceived risk of bleeding and restenosis of the patient. For example, in patients with atrial fibrillation, the risk of bleeding with warfarin and long-term dual antiplatelet therapy should be weighed against the risk of restenosis with bare-metal stent. For other patients, DES might be suitable. The other issue relates to the time interval between PCI and TAVR. The ideal interval remains undefined and again should be individualized on the basis of the specific clinical situation. Dual antiplatelet therapy in patients with DES is not an issue in case of transfemoral TAVR. However, it has implications for patients being randomized to the SAVR arm in future studies or non-transfemoral TAVR where patients are placed in the studies after DES has already been implanted. Such patients with recent (<6 months) DES implantation should be excluded from randomization unless SAVR or TAVR (in case of non-transfemoral access) can be performed without interruption of dual antiplatelet therapy.

Future Directions

The ongoing ACTIVATION trial (Percutaneous coronary intervention prior to transcatheter aortic valve implantation: a randomized controlled trial), which is randomizing patients with CAD to pre-TAVR PCI and no pre-TAVR PCI, will help answer the question of whether pre-TAVR PCI has favorable impact on outcomes after TAVR. Other ongoing randomized trials such as SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) and PARTNER II are including patients with severe AS and significant CAD requiring revascularization. The SURTAVI trial is designed to compare TAVR with the CoreValve system (Medtronic, Minneapolis, Minnesota) with SAVR in intermediate risk patients (STS risk score 4 to 10). Similarly, the PARTNER II trial has been designed to compare TAVR with the Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California) with SAVR in intermediate-risk (STS score 4 and higher) patients. In both these ongoing randomized TAVR studies, patients with concomitant severe CAD will be randomized for percutaneous or surgical treatments. It is important to note that management strategies (i.e., TAVR with or without PCI) will be compared with SAVR with or without CABG. These are not trials to compare the PCI with CABG, but they are trials to compare percutaneous strategy for the treatment of AS and CAD with surgical strategies. The decisions with regard to targets for revascularization are defined before randomization for each strategy. Revascularization before randomization in the study will be discouraged unless patients present with acute coronary syndrome (non–ST-segment elevation MI or ST-segment elevation MI) requiring urgent PCI. Such patients can still be randomized to SAVR or TAVR arm depending on stent type and required duration of dual antiplatelet therapy. The need for revascularization in stable CAD patients will be determined by the heart team on an individual basis. Aforementioned factors with regard to DES use will need to be considered while considering elective PCI. Complex CAD such as unprotected left main trunk and multivessel CAD with SYNTAX score ≥33 will be excluded in both trials. Completeness of revascularization might differ in the 2 arms. For example, a chronic total occlusion of a well-collateralized right coronary artery will likely be left alone in the TAVR arm; however, a bypass graft if feasible during SAVR will be performed. Data from ongoing studies should provide valuable information with regard to the impact of CAD on TAVR outcomes and the role of revascularization with PCI and its timing in patients undergoing TAVR.

Conclusions

Significant CAD is commonly encountered in patients with severe symptomatic AS being evaluated for TAVR. The impact of CAD on short- and long-term outcome after TAVR remains understudied and should be rigorously evaluated in future studies. As experience with TAVR evolves, evidence-based management strategies for patients with severe AS and CAD will guide clinicians taking care of these high-risk patients. Revascularization should be considered for severe coronary stenoses in proximal epicardial coronary vessels that subtend a large area of myocardium at risk. A PCI can be safely performed in patients with severe AS without an increased risk of short-term adverse outcomes, particularly in those with preserved left ventricular function. Patients should undergo TAVR without a long delay after PCI. The choice of stents and the time interval between PCI and TAVR should be individualized. Patients with complex coronary disease involving major coronary arteries, especially in diabetic patients, should be considered for surgical revascularization and SAVR when appropriate. The concept of "heart team" in decision making, including those related to coronary revascularization, is critical in optimizing TAVR outcomes.

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