Clinical update

Aortic stenosis and coronary artery disease: What do we know? What don’t we know?
A comprehensive review of the literature with proposed treatment algorithms

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Received 3 November 2013; revised 7 May 2014; accepted 26 May 2014; online publish-ahead-of-print 26 June 2014

Aortic valve stenosis is the most common form of valvular heart disease in the elderly population and occurs frequently in conjunction with coronary artery disease (CAD). Compelling epidemiological and histopathological data suggest that degenerative calcific aortic stenosis (AS) is an active and multifaceted disease process that resembles both atherosclerosis and elastocalcinosis. Furthermore, risk factors for AS have been shown to be similar to those for atherosclerosis and CAD. It is therefore not surprising that significant CAD is often present in patients with severe AS. The prevalence of CAD also increases with age, such that it is present in more than 50% of patients with AS over 70 years of age and 65% of patients with AS over 80 years of age. The standard treatment option for patients with AS and CAD has been surgical aortic valve replacement (SAVR) and concomitant coronary artery bypass grafting (CABG). However, over the last 10 years, treatment paradigms have shifted due to the availability of transcatheter aortic valve replacement (TAVR) for high-risk patients. However, in the setting of this less-invasive approach, the appropriate management of coexistent significant CAD still remains unclear. This article, which includes a comprehensive review of the literature and seeks to describe the actual knowledge on the topic of aortic stenosis and concomitant coronary artery disease.

Keywords
Coronary artery disease • Aortic stenosis • Percutaneous coronary intervention • Transcatheter aortic valve replacement • Surgical aortic valve replacement

Introduction

Aortic valve stenosis is the most common form of valvular heart disease in the elderly population and occurs frequently in conjunction with coronary artery disease (CAD). Compelling epidemiological and histopathological data suggest that degenerative calcific aortic stenosis (AS) is an active and multifaceted disease process that resembles both atherosclerosis and elastocalcinosis. Furthermore, risk factors for AS have been shown to be similar to those for atherosclerosis and CAD. It is therefore not surprising that significant CAD is often present in patients with severe AS. The prevalence of CAD also increases with age, such that it is present in more than 50% of patients with AS over 70 years of age and 65% of patients with AS over 80 years of age. The standard treatment option for patients with AS and CAD has been surgical aortic valve replacement (SAVR) and concomitant coronary artery bypass grafting (CABG). However, over the last 10 years, treatment paradigms have shifted due to the availability of transcatheter aortic valve replacement (TAVR) for high-risk patients. However, in the setting of this less-invasive approach, the appropriate management of coexistent significant CAD still remains unclear. This article, which includes a comprehensive review of the literature, seeks not only to describe the actual knowledge on the topic of AS and concomitant CAD, but also to identify the unanswered questions, especially those emerging in the era of TAVR.

Aortic valve calcification and prevalence of coronary artery disease

The prevalence of CAD in patients undergoing surgical aortic valve replacement has been shown to increase with both age and the presence of valve calcification. This was demonstrated in a large
Coronary flow in aortic stenosis

The coronary flow reserve (CFR) is defined as the maximal increase in myocardial blood flow above its resting level for a given perfusion pressure when coronary vasculature is maximally dilated. It therefore represents an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation. Narrowing of the epicardial coronary arteries or dysfunction of the coronary circulation may lead to an abnormal CFR even in the absence of angiographically proven atherosclerotic disease. Patients with AS and angiographically normal coronary arteries have been shown to have decreased CFR, which limits the capacity of the coronary circulation to increase flow to match myocardial oxygen demand. This impairment of CFR is certainly one of the key elements responsible for myocardial ischaemia in AS patients and may contribute to the development of symptoms, LV dysfunction, and adverse outcomes. The mechanisms underlying the reduction of CFR in patients with AS remains unclear. Concentric LV hypertrophy was previously believed to be the major cause of the reduction in CFR in patients with AS, but recent data suggest that the abnormally high LV workload induced by AS may be the key factor. In fact, reduced CFR correlates better with haemodynamic indexes of AS severity (valve effective orifice area and transvalvular pressure gradient) than with LV mass. Additionally, it has been demonstrated that coronary microcirculation is impaired in ventricles suffering from long-term pressure load. It stands to reason that these functional alterations of intramyocardial coronary arterioles may be the cause of the reduction in CFR in patients with severe AS.

Fractional flow reserve (FFR) has been shown to be a valuable tool for physiology-guided lesion assessment, and routine FFR in addition to coronary angiography has improved the outcome of percutaneous coronary intervention (PCI). In patients with AS, evaluation of induced myocardial ischaemia is controversial and in fact, exercise testing is contraindicated in severe AS. Nevertheless, a recent case series showed the safety and benefits of FFR assessment in patients with severe AS and concomitant CAD. Likewise, in another study, dipyridamole myocardial perfusion tomography has been demonstrated to be of high diagnostic value (sensitivity 100%, specificity 91%) and safe in the detection of CAD in patients with severe AS.

Symptoms and coronary artery disease in patients with aortic stenosis

The presence of symptoms is of limited utility in detecting CAD in patients with AS because angina pectoris is the most common presenting symptom in both disease states. Various series have demonstrated that the prevalence of CAD in patients with AS is similar in those with (43%) and without (29%) angina. In one study, the sensitivity, specificity, positive predictive value, and negative predictive value of angina in identifying coronary disease was 68, 46, 43, and 71%, respectively. Studies have consistently reported that about half of patients with AS and angina pectoris have angiographically significant CAD. In patients with AS and angina but without CAD, it has been postulated that diminished CFR leads to an imbalance between myocardial oxygen supply and demand resulting in angina. Given the poor discriminatory capacity of angina for predicting CAD in patients with AS, coronary angiography is recommended in the following: symptomatic patients before AVR in men older than 35 years; pre-menopausal women older than 35 years with coronary risk factors, as well as asymptomatic men older than 45 years; women older than 55 years; and those with two or more coronary risk factors (Table 1).

Impact of coronary artery disease on the outcomes of surgical aortic valve replacement

The presence of CAD has been demonstrated to increase the procedural risk of surgical aortic valve replacement, and coronary revascularization is generally recommended at the time of surgery.
The American College of Cardiology and American Heart Association guidelines on valvular heart disease advocate, as a Class 1 recommendation, that patients undergoing AVR with significant stenoses (greater than or equal to 70% reduction in luminal diameter) in major coronary arteries should be treated with bypass grafting. The European Society of Cardiology guidelines also recommend complete revascularization in patients with severe AS undergoing SAVR to improve long-term outcomes. However, interventions combining AVR and coronary artery bypass grafting are associated with higher post-operative mortality than AVR alone. Data from 10,000 patients undergoing heart surgery from the New York Cardiac Surgery Reporting System showed that mortality for isolated valve surgery was 4.4% compared with 8.9% for valve surgery and CABG. This is supported by a recent, large observational study showing no differences between those with and without AS with respect to 30-day mortality (4.3 vs. 4.7%, HR 0.51–1.69, P = 0.2). The high short-term mortality rate observed in both groups is a testament to the high-risk nature of this patient population. Subgroup analysis of the patients with severe AS showed that patients with a low EF (≤30%) or a high STS score (>10) had a significantly higher 30-day post-PCI mortality. Other short-term complications of PCI, including procedural death, haemodynamic compromise during PCI, peri-procedural MI, coronary dissection, coronary perforation, cardiac tamponade, access site haematoma, retroperitoneal bleed, and contrast nephropathy, did not differ significantly between groups. From these data, the authors concluded that PCI could be performed in patients with severe AS without increased risk of short-term mortality or procedural complications compared with similar patients without concomitant AS. With respect to long-term outcomes, at a mean follow-up of 3.7 years, 29% of patients with severe AS had undergone SAVR with a mean duration of 15.5 months between PCI and SAVR, and CABG was performed with SAVR in 71% of these patients. Long-term mortality was 42.5% in AS patients who underwent SAVR compared with 68% in AS individuals who did not undergo SAVR and 46.7% in the control group without AS. In the multivariable analysis incorporating SAVR as a time-dependent covariate, independent predictors of long-term mortality for patients with severe AS undergoing PCI were age, ejection fraction <30%, chronic kidney disease, diabetes mellitus, and chronic obstructive pulmonary disease.

The study has several limitations worth mentioning. Most importantly, it was an observational, single-centre study and consequently prone to bias. Also, only about 22% of patients in each group underwent PCI with drug eluting stents (DES), making this largely a bare metal stent (BMS) study.

### Outcomes of percutaneous coronary intervention in patients with severe aortic stenosis

Because surgical AVR and CABG has been considered the preferred treatment option for patients with concomitant AS and CAD, PCI has been performed infrequently in this population. The outcomes data for PCI in patients with severe AS and CAD is therefore limited to observational studies.

### Outcomes of hybrid procedures with surgical aortic valve replacement and percutaneous coronary intervention

As noted earlier, the traditional treatment for severe AS with concomitant CAD has been combined AVR and CABG. This combined...
Combining PCI with surgical valve replacement as treatment for concomitant CAD was first investigated by Byrne et al. in a single-centre retrospective study of 26 patients who underwent PCI either for ACS (24 patients) or for a complex re-operative valve surgery (two patients) followed by aortic or mitral valve surgery using either a minimally invasive or traditional approach. With valve replacement (58% primary, 42% re-operative) occurring a median of 5 days after PCI, operative mortality was 3.8%, which was significantly lower than the STS-predicted mortality of 22%. Of note, there was an extremely high rate of blood transfusion (85%), likely due to the requirement for dual anti-platelet therapy following PCI. Survival at 1, 3, and 5 years was 78, 56, and 44%, respectively. While this study was limited by its small sample size and heterogeneous patient population, it demonstrated the feasibility of performing PCI prior to AVR.

The idea of combining AVF with PCI was revisited by Brinster et al. in a prospective observational series of 18 patients who underwent PCI to date, Santana et al. studied 65 consecutive patients with CAD and either aortic (47.7%), mitral (36.9%), or combined aortic and mitral (15.4%) valvular disease who underwent planned PCI followed by valve surgery within 60 days. This cohort was compared with 52 matched controls that underwent simultaneous CABG and conventional valve surgery. The median number of days between PCI and valve surgery was 24 (interquartile range, 2.5–37). There were no in-hospital deaths in the PCI group compared with two (3.8%) in the matched control group (P = 0.11), and the combined endpoint of 30-day death, renal failure or stroke occurred in 1 (1.5%) of the PCI group compared with 15 (28.8%) of the control group (P = 0.001). Length of ICU and total hospital stay were less in the AVR/PCI group and the average amount of blood transfusions did not differ significantly between the groups. While this study showed the potential promise of combined PCI and valvular surgery, it is important to note that it was a retrospective observational study of a heterogeneous group of patients with follow-up limited to 30 days. The MI-AVR group and control group also differed in regards to the time period when the procedures were performed with the patients who underwent PCI selected from 2009 to 2011 compared with the conventional AVR/CABG patients who were treated from 2005 to 2011.

Overall, the available studies demonstrate the feasibility of a hybrid approach to the treatment of AS and CAD with staged or single setting PCI and AVR. An important issue is the timing of the procedures and management of anti-platelet therapies. Future studies, including randomized trials are necessary to clarify the clinical utility of this treatment strategy, particularly with respect to long-term outcomes. While awaiting further confirmatory data, Figure 2 summarizes the treatment algorithm used at Columbia University Medical Center.

Transcatheter aortic valve replacement

According to a recent EuroHeart survey, as many as one-third of all potential surgical AVR candidates do not undergo surgery. This may be due in part to prohibitive surgical risk in these patients. The estimated operative risk may be higher due to advanced age, comorbid medical conditions, or the need for combined valve and coronary surgery.

Over the past several years, TAVR has emerged as an attractive therapeutic option in patients with severe symptomatic AS who are inoperable or high-risk candidates for surgical AVR. Multiple studies and registries have demonstrated that the prevalence of CAD in patients undergoing TAVR ranges from 47.6 to 74.9%. Coronary angiography is therefore strongly recommended in the assessment of eligibility for TAVR, although the optimal management of CAD in the context of TAVR has not yet been established.

Myocardial infarction after transcatheter aortic valve replacement

Excluding the initial feasibility study of transapical TAVR, which showed a rate of MI of 15%, studies have shown the rate of peri-procedural MI after TAVR to be between 0 and 4.6%. However, the available studies have used non-uniform definitions of MI with different thresholds of cardiac biomarker elevation. One study by Rodes-Cabau et al. demonstrated that a greater degree of myocardial injury was associated with less improvement in LVEF and higher cardiac mortality at follow-up. Further research is required to definitively establish the clinical impact of peri-procedural MI after TAVR.

Impact of coronary artery disease on the outcomes of transcatheter aortic valve replacement

The few published studies evaluating the impact of concomitant CAD on procedural outcomes and long-term survival after TAVR have yielded conflicting results (Table 3). Dewey et al. demonstrated a trend towards more MI-AVR.
Table 2  Summary of the main studies on the ‘hybrid approach’ combining percutaneous coronary intervention and surgical aortic valve replacement

<table>
<thead>
<tr>
<th>Study-Author</th>
<th>Date of study</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>LVEF (%)</th>
<th>STS score (%)</th>
<th>Logistic Euroscore (%)</th>
<th>Indication for PCI</th>
<th>Time between PCI and surgery</th>
<th>Rate of DES implantation, %</th>
<th>Type of surgery</th>
<th>Rate of reoperation for bleeding, %</th>
<th>Blood transfusion requirements</th>
<th>Short-term mortality (In-hospital-30 day mortality), %</th>
<th>Mid-long-term mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrne26</td>
<td>September 1997–August 2003</td>
<td>26</td>
<td>Median: 72</td>
<td>Median: 22</td>
<td>n/a</td>
<td>UA = 50% AMI = 42% Prior to complex re-operative valve surgery = 8%</td>
<td>PCI 5 days before (median)</td>
<td>12</td>
<td>Re-operative valve surgery = 42% (mitral = 8 pts, aortic = 3 pts) Primary valve surgery = 58% (mitral = 13 pts, aortic = 1 pt, double = 1 pt)</td>
<td>8</td>
<td>Rate of any post-operative blood transfusions: 85%</td>
<td>3.8</td>
<td>1, 3, 5 year mortality was 22, 44, and 56, respectively</td>
<td></td>
</tr>
<tr>
<td>Brinster27</td>
<td>May 2003 to February 2006</td>
<td>18</td>
<td>Median: 75</td>
<td>Median: 55</td>
<td>n/a</td>
<td>n/a</td>
<td>PCI &lt; 24 h before</td>
<td>100</td>
<td>Mi-AVR</td>
<td>0</td>
<td>Rate of any post-operative blood transfusions: 38.9%</td>
<td>5.5 (1 early post-operative mortality form a colonic perforation)</td>
<td>5.5 [at a mean follow-up of 19 months (no late mortalities)]</td>
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<tr>
<td>Santana28</td>
<td>February 2009 to June 2011 (study group) Historical control March 2005–June 2011</td>
<td>65</td>
<td>Mean: 75.4</td>
<td>Mean: 53.9</td>
<td>10</td>
<td>n/a</td>
<td>PCI 24 days before (median)</td>
<td>55.5</td>
<td>Mi-AVR</td>
<td>1.5</td>
<td>Mean number of transfusion: 1.6</td>
<td>0</td>
<td>n/a</td>
<td></td>
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</tbody>
</table>

PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; LVEF, left-ventricular ejection fraction; STS, Society of Thoracic Surgeons; DES, drug eluting stent; n/a, not available; UA, unstable angina; AMI, acute myocardial infarction; pts, patients; Mi-AVR, minimally invasive aortic valve replacement.
analysed the impact of CAD requiring prior CABG or PCI in 201 high-risk patients undergoing TAVR (161 transfemoral and 40 transapical). In this study, patients with CAD had higher rates of important medical comorbidities, higher EuroSCORE (35.8 vs. 26.1%), lower ejection fraction (EF) (48 vs. 54%), and were more frequently treated by the TA access. Overall mortality after TAVR was significantly higher among the CAD group (35.7 vs. 18.4%), and logistic regression analysis found that patients with CAD were 10.1 times more likely to die (95% CI 2.1–174.8) within 30 days of TAVR. However, there was no indication in the analysis that a history of either CABG or PCI directly led to an increased risk of mortality. Several limitations of this study are worth noting. The study represents the earliest experience with TAVR in both the USA and Europe, and techniques and devices have since been refined. Also, CAD was defined simply as prior revascularization (CABG or PCI), and there was no information about ischaemic burden or completeness of revascularization. Finally, the populations were unmatched, and there were significant differences in terms of comorbidities and risk profiles, so it is possible that CAD in this study was simply a marker of higher risk patients rather than a cause of adverse outcomes.

In contrast, a study by Masson et al. of 136 patients who underwent TAVR between 2005 and 2007, showed similar survival rates in quintiles stratified by the extent of CAD, as assessed by the Duke Myocardial Jeopardy Score (DMJS). The groups were similar with respect to baseline risk factors except for peripheral vascular disease, which was more common in the groups with higher DMJS. The authors concluded that, in this cohort of patients, the presence of CAD or non-revascularized myocardium was not associated with an increased risk of adverse events. However, the sample size of this study was small, and 15 patients underwent revascularization with PCI prior to TAVR, which may have impacted the results.

Figure 2 Algorithm used at Columbia University Medical Center to treat patients with severe aortic stenosis (PART 1: selected treatment option: SAVR). *For re-operative patients, the clopidogrel loading dose is given via the nasogastric tube at the time of aortic cross-clamping. AS, aortic stenosis; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; CAD, coronary artery disease; CABG, coronary artery bypass grafting; LAD, left-anterior descending coronary; PCI, percutaneous coronary intervention; OR, operating room.
### Table 3  Influence of coronary artery disease on outcomes after transcatheter aortic valve replacement

<table>
<thead>
<tr>
<th>Study-Author</th>
<th>Date of study</th>
<th>Study groups (n)</th>
<th>Age (years)</th>
<th>LVEF (%)</th>
<th>STS score</th>
<th>Logistic Euroscore</th>
<th>Definition of CAD</th>
<th>In-hospital/30-day mortality, %</th>
<th>Mid-long-term mortality (1-year or at follow-up), %</th>
<th>Conclusion</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dewey10</td>
<td>December 2005 to February 2008</td>
<td>CAD = 84     No CAD = 87</td>
<td>Overall = 85.1 Median = 60.0 Overall population = 9.1</td>
<td>Overall population = 29.0</td>
<td>Presence of prior revascularization or any coronary lesion of ≥50% in severity by visual assessment. Stratified into groups based on DMJS</td>
<td>A = 6.3 B = 14.6 C = 7.1 D = 5.6 E = 17.7 (P = 0.56)</td>
<td>CAD = 13.1 No CAD = 1.2 (P = 0.002)</td>
<td>CAD = 35.7 No CAD = 18.4 (P = 0.01)</td>
<td>Coexisting coronary artery disease negatively impacts procedural outcomes and long-term survival in patients undergoing TAVR.</td>
<td>CAD was defined as prior revascularization (CABG or PCI) with no information on ischaemic burden.</td>
<td>(i) Small sample size (ii) PCI performed prior to TAVR in 15 patients</td>
</tr>
<tr>
<td>Masson18</td>
<td>January 2005 to December 2007</td>
<td>Group A: no CAD (32) Group B: CAD with DMJS 0 (41) Group C: CAD with DMJS 2 (28) Group D: CAD with DMJS 4 (18) Group E: CAD with DMJS ≥6 (17)</td>
<td>Overall = 82.8 Overall = 48 Overall = 16 Overall = 28 CAD = 81.0 CAD = 45 CAD = 17 CAD = 31 No CAD = 83.0 No CAD = 53 No CAD = 14 No CAD = 24</td>
<td>History of prior MI or coronary revascularization or significant coronary stenosis on screening angiography (epicardial artery with ≥70% luminal diameter measured in the “worst view” angiographic projection or ≥50% for the left main stenosis)</td>
<td>CAD = 10 No CAD = 15 (P = 0.37)</td>
<td>1-year mortality rates: CAD = 23.6 No CAD = 29.4 (P = 0.28)</td>
<td>The presence of CAD or non-revascularized myocardium was not associated with an increased risk of adverse events.</td>
<td>CAD had a limited impact on both decision to perform TAVR as well as both short and mid-term prognosis. (ii) It supported a selective revascularization strategy with only 17% of patients with new or residual CAD found on TAVR evaluation undergoing PCI and inclusion of many subsets of patients (i.e. SAVR, TAVR, medical treatment only)</td>
<td>Small sample size (ii) PCI performed prior to TAVR in 15 patients</td>
<td></td>
<td></td>
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<tr>
<td>Gautier19</td>
<td>October 2006 – October 2009</td>
<td>CAD = 144     (TAVR = 83) No CAD = 86 (TAVR = 62)</td>
<td>Overall = 81.2 Overall = 46 Overall = 16 Overall = 28 CAD = 81.0 CAD = 45 CAD = 17 CAD = 31 No CAD = 83.0 No CAD = 53 No CAD = 14 No CAD = 24</td>
<td>CAD group with critical stenosis = 48.3 CAD group without critical = 31.7</td>
<td>Previous PCI or surgical revascularization.</td>
<td>CAD = 6.0 No CAD = 5.9 (P = 0.61)</td>
<td>1-year mortality rates: CAD = 14.5 No CAD = 15.9 (P = 0.33)</td>
<td>Coexisting CAD does not impact procedural outcomes and mid-term incidence of MACCE and survival in elderly patients</td>
<td>CAD was defined based on historical revascularization and not based on the significance of coronary stenosis at follow-up</td>
<td>Continued</td>
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## Table 3

<table>
<thead>
<tr>
<th>Study/Author Date of study</th>
<th>Group</th>
<th>Study group (n)</th>
<th>Age (years)</th>
<th>Left ventricular ejection fraction (LVEF) (%)</th>
<th>STS score</th>
<th>Logistic Euroscore</th>
<th>Definition of CAD</th>
<th>In-hospital/30-day mortality, %</th>
<th>Mid-long-term mortality, % (1 year or at follow-up), %</th>
<th>Mid-long-term mortality, % (2 years or at follow-up), %</th>
<th>Mid-long-term mortality, % (3 years or at follow-up), %</th>
<th>Conclusion</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Van Mieghem et al. [52]</td>
<td>CAD</td>
<td>124</td>
<td>80.3</td>
<td>Overall = 0%</td>
<td>53.1</td>
<td>Overall = 50.5</td>
<td>47.2</td>
<td>40.2</td>
<td>22.2</td>
<td>20.5</td>
<td>17.63 Previous PCI or CABG</td>
<td>Residual CAD found on TAVR evaluation undergoing PCI. This study showed that CAD had limited impact on the decision to perform TAVR as well as the short- and mid-term prognosis. It supported a selective revascularization strategy with only 17% of patients with new or residual CAD found on TAVR evaluation undergoing PCI. This study was limited by a lack of long-term outcome data and the inclusion of many subsets of patients (i.e. AVR, TAVR, medical treatment only) instead of a homogenous patient population. The very small sample size of patients undergoing PCI prior to or concomitant with TAVR limits the ability of meaningful conclusions to be made about such strategies. Recently, a meta-analysis of adjusted observational results of seven studies and 2472 patients also supported the finding that CAD does not affect TAVR outcomes after a median follow-up of 452 days. Indeed, in the multivariable analysis, the diagnosis of CAD had no influence on the risk of all cause death (OR 1.0, 95% CI: 0.67–1.50).</td>
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<tr>
<td>Gautier et al. [49]</td>
<td>No CAD</td>
<td>88</td>
<td>Overall = 80.3</td>
<td>Overall = 50.5</td>
<td>47.2</td>
<td>Overall = 50.5</td>
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These results were supported by two prospective studies of the impact of CAD on AS in the TAVR era. The first was published by Gautier et al. [49] in 2011, in which 240 high-risk patients with severe AS were consecutively enrolled from 2006 to 2009. Of the 230 patients with known coronary status, 63% had CAD which was defined as a history of prior myocardial infarction, coronary revascularization, or significant angiographic coronary stenosis (epicardial artery with ≥70% diameter stenosis or left main ≥50%). Among the study population, 63% underwent TAVR, 13% underwent surgical AVR, and 24% were treated medically. CAD did not lead to denial of intervention in any patient, and only one patient underwent surgical treatment due to CAD (unprotected left main stenosis). Among those with CAD who underwent TAVR, the decision to proceed with PCI was clinically driven and restricted to patients who presented with angina or had threatening ostial or proximal coronary lesions with a large area of myocardium at risk. Of the 83 patients with CAD who underwent TAVR, 16 (19%) were found to be free of any residual significant coronary stenosis at evaluation for TAVR. Among the remaining 67 patients with ≥1 coronary stenosis, 56 (83%) did not undergo revascularization prior to TAVR. Survival rates were similar in the CAD and non-CAD groups at 30 days (90 vs. 85%, P = 0.37) and 1 year (76 vs. 71%, P = 0.28). Functional status was also similar in both groups at 1 year. This study showed that CAD had limited impact on the decision to perform TAVR as well as the short- and mid-term prognosis. It supported a selective revascularization strategy with only 17% of patients with new or residual CAD found on TAVR evaluation undergoing PCI. This study was limited by a lack of long-term outcome data and the inclusion of many subsets of patients (i.e. AVR, TAVR, medical treatment only) instead of a homogenous patient population. The very small sample size of patients undergoing PCI prior to or concomitant with TAVR limits the ability of meaningful conclusions to be made about such strategies. Recently, a meta-analysis of adjusted observational results of seven studies and 2472 patients also supported the finding that CAD does not affect TAVR outcomes after a median follow-up of 452 days. Indeed, in the multivariable analysis, the diagnosis of CAD had no influence on the risk of all cause death (OR 1.0, 95% CI: 0.67–1.50).
Aortic stenosis and coronary artery disease

Timing of percutaneous coronary intervention in patients undergoing transcatheter aortic valve replacement

Similar to revascularization strategies, the optimal timing of revascularization remains uncertain in patients undergoing TAVR. The sections below review the existing experience with different PCI timing strategies (Table 4).

Before transcatheter aortic valve replacement

Percutaneous coronary intervention before TAVR in patients with significant CAD has the potential to reduce the procedural risk of TAVR as well as the need for revascularization after TAVR. Gasparetto et al. assessed the safety and efficacy of a selective percutaneous revascularization strategy before TAVR. This single-centre, prospective registry (PUREVALVE Registry) included 191 consecutive patients with severe AS referred for TAVR. The presence of CAD was defined as any previous percutaneous or surgical coronary revascularization or the presence of any coronary stenosis of at least 50%. Percutaneous coronary intervention was performed only for lesions involving proximal-to-mid segments of major coronary branches. Chronic total occlusions (CTO) and lesions in small vessels (reference diameters <2.5 mm) were not considered for revascularization. Interventions were performed only on lesions that were deemed clinically relevant after consideration of symptoms, the extent of myocardium at risk, proven ischaemia by invasive or non-invasive testing, and technical feasibility of PCI. Of the 191 patients who underwent TAVR, CAD was present in 113 (59.2%) and PCI was performed before TAVR in 39 (20.4%). A total of 78 stents were implanted in 66 lesions and BMSs were used in 56.4% of cases. Overall 30-day mortality did not differ significantly between patients with or without CAD (5.7 vs. 2.9%, P = 0.32), although there were numerically higher rates of myocardial infarction (4.4 vs. 0%, P = 0.08) and major stroke (2.7 vs. 0%, P = 0.14) in the CAD group. These results suggest that a selective, clinically driven coronary revascularization strategy before TAVR can lead to outcomes similar to those observed in patients without CAD.

In another study by Abdel-Wahab et al., patients who underwent PCI before TAVR with the Medtronic CoreValve prosthesis were compared with 70 patients who underwent TAVR alone. Thirty-day mortality, major bleeding, major vascular complications, VARC defined combined safety endpoint, symptom improvement, and adverse events at 6 months were comparable between the two groups, again suggesting that PCI before TAVR is safe and effective.

In another single-centre study, TAVR combined with PCI within 12 months produced at least equivalent results for in-hospital mortality in 59 high-risk patients presenting with AS and concomitant CAD compared with 184 high-risk patients undergoing SAVR and CABG surgery.

Concomitant with transcatheter aortic valve replacement

Some authors have proposed performing PCI and TAVR during a single procedure. Potential advantages of this approach may include enhanced resource utilization, patient convenience, safety due to use of the same arterial access for both PCI and TAVR. A small case series of 28 inoperable patients who underwent PCI and TAVR between 2008 and 2010 was the first to demonstrate that concomitant PCI and TAVR was feasible and safe. Twenty-one patients underwent staged PCI and TAVR, with PCI on average 14.3 days prior
### Table 4 Summary of the main studies on percutaneous coronary intervention and transcatheter aortic valve replacement

<table>
<thead>
<tr>
<th>Study</th>
<th>Study groups (n)</th>
<th>Study type/patient population</th>
<th>Definition of CAD</th>
<th>Decision to perform PCI</th>
<th>Characteristics of intervention</th>
<th>BMS vs. DES, %</th>
<th>Anatomically complete revascularization (definition, % of cohort obtained)</th>
<th>Antiplatelet therapy</th>
<th>Follow-up</th>
<th>30-day outcomes</th>
<th>Mid/Long-term Outcomes</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>Gasparetto&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Prior to TAVR</td>
<td>Total population: 191 patients, 113 pts with CAD</td>
<td>Previous PCI or surgical coronary revascularization and/or presence of any coronary stenosis of at least 50% in diameter of the epicardial coronary arteries by visual assessment</td>
<td>Driven first by symptoms, then evaluation of the extent of myocardium at risk, non-invasive/invasive tests, technical feasibility of PCI. CTO and lesions in small vessels (reference diameter &lt; 2.5 mm) were not considered for revascularization</td>
<td>PCI performed 27 days prior to PCI (median)</td>
<td>BMS: 56.4</td>
<td>Defined as complete revascularization of all stenotic coronary vessels ≥2.5 mm, 33.6</td>
<td>ASA 100 mg, Clopidogrel 75 mg for 3 months after TAVR for patients with BMS and 12 months for patients with DES</td>
<td>12.9 months</td>
<td>(i) PCI was performed prior to TAVR in 29.4% of patients with no adverse events. (ii) All-cause mortality was 4.2% and cardiovascular mortality was 3.7%, with no difference between CAD and non-CAD patients.</td>
<td>Overall mortality at follow-up was 14.8% without significant differences between CAD and non-CAD groups</td>
<td>A selective strategy of treating CAD with PCI prior to TAVR is safe and has short- and mid-term outcomes similar to patients without CAD</td>
</tr>
<tr>
<td>Abdel-Wahab&lt;sup&gt;14&lt;/sup&gt;</td>
<td>PCI + TAVR: 55 patients Isolated TAVR: 70 patients</td>
<td>Single-centre retrospective study</td>
<td>Presence of lesions with ≥50% diameter stenosis on angiogram and/or previous MI, PCI, or CABG</td>
<td>All significant (&gt;50%) lesions in the major epicardial coronary vessels</td>
<td>PCI performed 10 days before TAVR (median)</td>
<td>DES: 71</td>
<td>n/a</td>
<td>n/a</td>
<td>Up to 3 years</td>
<td>All-cause mortality: PCI + TAVR: 2% Isolated TAVR: 6% (P = 0.27)</td>
<td>All-cause mortality at up to 3 years: PCI + TAVR: 16.1% Isolated TAVR: 16.1% (P = 0.36)</td>
<td>PCI before TAVR appears feasible and safe</td>
</tr>
<tr>
<td>Wendt&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Group 1: SAVR and CABG: 184 patients Group 2: PCI + TAVR: 59 patients</td>
<td>Non randomized, single-centre study</td>
<td>The indication for PCI was discussed in a consensus conference (heart team)</td>
<td>PCI performed 82 +/− 93 days before TAVR</td>
<td>BMS: 70</td>
<td>DES: 30</td>
<td>n/a</td>
<td>n/a</td>
<td>Up to 6 years</td>
<td>30-day mortality was similar in the two groups: 12.5% in Group 1 compared with 11.5% in Group 2</td>
<td>Freedom from cardiac reintervention was similar in the two groups</td>
<td>PCI (within 12 months) and TAVR produce similar results for in-hospital mortality compared with high-risk patients undergoing SAVR + CABG</td>
</tr>
<tr>
<td>Conrad&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Total population: 28 patients Group 1: PCI prior to TAVR (21 patients) Group 2: PCI concomitant with TAVR (7 patients)</td>
<td>Retrospective single-centre study</td>
<td>n/a</td>
<td>Group 1: PCI 14 days prior to procedure (on average) Group 2: PCI performed immediately before TAVR</td>
<td>BMS: 65.9</td>
<td>n/a</td>
<td>All patients received a loading dose of 300 mg of Clopidogrel either before the initial PCI in the staged approach or before the combined single-stage</td>
<td>(i) No peri-procedural MI or stroke in any patient. (ii) Overall in-hospital and 30-day mortality was identical at 7.1% (n = 2 of 28). (iii) The two deaths occurred in Group 2 (peri-procedural)</td>
<td>n/a</td>
<td>Concomitant PCI and TAVR procedure is feasible and safe. Higher risk of renal failure with the concomitant strategy</td>
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</table>
Aortic stenosis and coronary artery disease

Wenaweser et al.24 Total population: 256 pts
Group 1: PCI prior to TAVR (23 pts)
Group 2: PCI with concomitant TAVR (36 pts)
Group 3: TAVR alone (197 pts)

Prospective single-centre registry

History of PCI or CABG or stenosis of >50% in at least one coronary artery during coronary angiography

 Operators used DMJS and SYNTAX score. CTO and distal segments or side branches with a small area at risk were left untreated.

Staged PCI performed at 34 ± 26 days of TAVR. Concomitant PCI performed immediately before TAVR.

Group 1: 47.8% of BMS
Group 2: 11.4% of BMS

DMJS < 1.49

- For pts undergoing PCI + TAVR: Aspirin at least 100 mg daily, 600 mg plavix load prior to PCI
- Up to 2 years
- Clinical outcomes at 30 days were similar for patients undergoing isolated TAVR compared with TAVR combined with PCI in terms of death (5.6 vs. 10.2%, P = 0.24), major stroke (4.1 vs. 3.4%, P = 1.00), and combined safety endpoint from the VARC (31.0 vs. 23.7%, P = 0.33).

No difference between overall mortality in patients with or without CAD up to 2-year follow-up

(i) Staged or concomitant PCI are both safe and feasible treatment options in select patients undergoing TAVR.

(ii) Complete or incomplete revascularization does not appear to adversely impact mid-term survival.

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PCI after TAVR

Pasic et al.40 Total population: 419 subjects with 46 patients undergoing PCI immediately after the TA-TAVR

Retrospective single-centre study

Only significant CAD was reported

(i) LM >50%

(ii) Coronary stenosis of ≥90% in the proximal or mid-LAD or proximal or mid RCA, if right dominant or proximal or mid left circumflex (if dominant)

(iii) The coronary lesions above were amendable to straightforward PCI with a very high probability of success

PCI performed immediately after TA-TAVR

n/a

ASA 100 mg, clopidogrel 75 mg daily for at least 6 months. Patients undergoing combined PCI and TAVR received additional loading dose of 300 mg of clopidogrel.

3 years

(i) Technical procedural success was achieved in 100% of patients, without any need for conversion to open heart surgery.

(ii) 30 day mortality rate was 4.3%.

In the TA-TAVR and PCI group, survival at 12, 24, and 36 months was 87.1, 69.7, and 69.7%, respectively.

Simultaneous treatment of the most significant CAD with PCI immediately after TA-TAVR is safe and feasible.

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PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; BMS, bare metal stent; DES, drug-eluting stent; CAD, coronary artery disease; CTO, chronic total occlusion; MI, myocardial infarction; CABG, coronary artery bypass grafting; DMJS, Duke myocardial jeopardy score; VARC, valve academic research consortium; TA, trans-apical; LM, left main; LAD, left anterior descending coronary; RCA, right coronary artery; pts, patients.
to TAVR, while seven were treated in a single procedure. In this small retrospective study, the overall 30-day mortality was 7.1%, which is comparable to the rates reported in multiples studies and registries.

The question of feasibility and safety of concomitant PCI and TAVR was further addressed by a study of the BERN TAVI registry,36 which prospectively enrolled 256 patients undergoing TAVR. In this study, CAD was defined as an angiographic stenosis of >50% in at least one coronary artery or a history of PCI or CABG. In patients with CAD, the amount of myocardium at risk was assessed using the DMJ. Of the 165 patients with CAD, 59 underwent PCI either prior to TAVR (n = 23) or in a single-stage procedure (n = 36). Of the remaining 108 patients with CAD, 53 had been completely revascularized prior to TAVR, and 55 had an incomplete revascularization status (DMJS ≥ 1). In this study, CTO and distal segments or side branches with a small area at risk were left untreated. Clinical outcomes at 30 days were similar for patients undergoing isolated TAVR or concomitant TAVR and PCI in terms of death (5.6 vs. 10.2%, P = 0.24), major stroke (4.1 vs. 3.4%, P = 1.00), and VARC combined safety endpoint (31.0 vs. 23.7%, P = 0.33). Limitations of this study include its observational nature, the limited number of patients, and the possibility of selection bias (the treatment strategy was left to the discretion of the operator). Nevertheless, it appears to demonstrate that revascularization with PCI can be safely performed either before TAVR or as a single-stage procedure with TAVR.

### After transcatheter aortic valve replacement

Investigators have also explored the possibility of performing PCI immediately after TAVR, but this strategy poses certain, unique procedural risks.38-39 These include the possibility that the prosthetic valve struts may interfere with cannulation of the coronary arteries and that catheter manipulation may potentially dislodge the prosthetic valve.25 Pasic et al.40 analysed the outcomes of 419 patients who underwent TA-TAVR between 2008 and 2011. In this cohort, single-stage PCI was performed immediately after TAVR in 46 patients (11%). Only the most significant lesions that were amenable to straightforward PCI were treated. Technical procedural success was achieved in 100% of patients, without any need for conversion to open surgery. In the TA-TAVR and PCI group, survival at 12, 24, and 36 months was 87.1, 69.7, and 69.7% respectively. The authors’ rationale for this approach was the view that severe AS could be viewed as the ‘most proximal coronary artery stenosis’ and treating AS with TAVR would decrease myocardial oxygen demand, leaving the patient less vulnerable to possible intra-procedural complications of PCI. While this study demonstrated that this single-stage approach may be feasible and safe at least for selected patients undergoing TA-TAVR, it remains unclear if these findings will be broadly applicable.

### Unanswered questions

In the TAVR era, there remain more questions than answers with respect to CAD and AS. The only randomized study in the literature, the Placement of AoRTic TraNstheter Valves (PARTNER) trial, excluded patients with unvascularized, obstructive CAD and did not demonstrate any interaction between CAD or prior coronary revascularization and mortality.30 Robust data are still lacking on numerous aspects regarding both the management and the impact of CAD in patients with AS. Table 5 summarizes some of the unanswered questions. Further studies are needed to address some of these issues. Indeed, no large studies have demonstrated the superiority of one type of stent over the other in patients undergoing PCI and TAVR. Therefore, taking into account the risk of bleeding as well as the risk of restenosis, the decision to implant a BMS or DES should be individualized by the heart team. The access route might also have an influence on the type of stent selected by the heart team since the longer mandatory dual antiplatelet therapy with DES may increase the bleeding risk for patients scheduled for an approach other than transfemoral TAVR. Larger trials will also be needed to resolve the matters of the best antithrombotic antiplatelet regimen for patients undergoing PCI and TAVR, as well as the concern of the impact of those procedures on the quality of life.

### Upcoming studies

PARTNER 2A and SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) are large, randomized, controlled...
trials that will include patients with CAD requiring revascularization and will compare AVR with and without CABG vs. TAVR with and without PCI.

**PARTNER 2A trial**
The PARTNER 2A trial is a prospective, multicentre, randomized trial comparing safety and efficacy of SAVR vs. TAVR with the Edwards SAPIEN XT THV with NovaFlex delivery system in intermediate risk surgical candidates. Enrolment will consist of up to 2000 patients at intermediate risk for surgical AVR. The study excludes patients with complex coronary disease, defined as an unprotected left main lesion or a SYNTAX score >32. However, patients with CAD that requires revascularization are randomized to undergo TAVR and PCI or SAVR and CABG with the exact timing of the PCI left to operator discretion.

**SURTAVI trial**
The Medtronic CoreValve® SURgical Replacement And Transcatheter Aortic Valve Implantation (SURTAVI) trial is a prospective, multicentre, randomized trial comparing safety and efficacy of SAVR vs. TAVR with the Medtronic CoreValve System in intermediate risk surgical candidates (STS score ≥4% and ≤10%). Every patient undergoes a heart team evaluation, which includes an assessment for significant CAD and the need for revascularization. If there is significant CAD with intended revascularization, the patient is then randomized and will undergo either TAVR + PCI or SAVR + CABG. If there is no intended revascularization, the patient is randomized between TAVR only or SAVR only. Up to 2500 patients will be included in the trial and followed through 5 years. Clinical endpoints will be reported and adjudicated according to Valve Academic Research Consortium (VARC) standard endpoint definitions.

**ACTIVATION trial**
The percutAneous Coronary inTerventlon prior to transcatheter aortic VAle implantATION: a randomized controlled trial (ACTIVATION), will be the first randomized trial to specifically address the impact of coronary revascularization by PCI for significant CAD prior to TAVR. This study will be conducted at a number of European centres and will randomize 310 patients with severe AS and at least one proximal coronary stenosis of ≥70% to undergo PCI and TAVR vs. TAVR alone. Important endpoints will include 30-day and 1-year mortality and re-hospitalization. Hopefully, from these studies, a clearer understanding of the best PCI strategy in various clinical scenarios will emerge. Until then, a case

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**Figure 3** Algorithm used at Columbia University Medical Center to treat patients with severe aortic stenosis (PART 2: selected treatment option: TAVR). AS, aortic stenosis; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; CAD, coronary artery disease; CTO, chronic total occlusion; LM, left main; pLAD, proximal left-anterior descending artery; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; BAV, balloon aortic valvuloplasty; pLVAD, percutaneous left-ventricular assist device; IABP, intra-aortic balloon pump; BMS, bare metal stent; DES, drug eluting stent.
by case approach should be used by the heart team to guide selection of patients for percutaneous revascularization prior to TAVR. The risks and benefits of performing TAVR in the presence of unrevascularized CAD should be weighed against the risk-benefit ratio of doing a PCI prior to TAVR. Figure 3 shows the algorithm used in our high volume TAVR centre. In our algorithm, as it is the case for the PARTNER 2A trial and for the SURTAVI study, the heart team (consisting of at least one interventional cardiologist and at least one cardiac surgeon) has to agree on a treatment strategy for AS and also for concomitant coronary disease. During the initial evaluation, if the coronary disease is diffuse and complex, we tend to favour a surgical approach. Although there is no established cut-off, the SYNTAX score should be calculated to guide the decision-making process. For example, in the PARTNER 2A and the SURTAVI trials, patients were excluded if their SYNTAX score was >32 and >22, respectively. At Columbia University Medical Center, lesions located in small vessels, distal lesions, chronic total occlusions, or very complex lesions that will require a large iodine load for the PCI in patients with severe chronic renal failure all tend to be treated medically. Moreover, it is important to mention that in the PARTNER 2A and the SURTAVI trials, patients with unprotected left main coronary disease are excluded. However, in our centre, those left main cases are carefully reviewed but may still be considered for a left main PCI followed by a TAVR, especially if the coronary disease is located at the ostium of the left main. Furthermore, in patients selected for a TAVR approach, our tendency is to proceed with a PCI prior to TAVR if the lesion is located in a vessel perfusing a significant territory, if the initial mode of presentation is an acute coronary syndrome (especially with dynamic ST changes or with hemodynamic instability), or if there is clinical evidence of ischaemia (for example, a positive stress-echocardiogram or a nuclear stress test showing significant ischaemia in the territory of the index lesion). To minimize the iodine contrast load and reduce the risk of acute kidney injury in patients with impaired renal function, we usually favour proceeding with PCI a few weeks before TAVR. Prior to PCI, a right heart catheterization is nearly always performed. Depending on thefilling pressures and the complexity of the coronary intervention, we then consider the following options: (i) performing a balloon aortic valvuloplasty; (ii) placing an intra-aortic balloon pump; or (iii) placing a left-ventricular assist device. As previously mentioned, the decision to implant a BMS or a DES should also be individualized.

Conclusion

For many decades, surgical aortic valve replacement has been considered the standard treatment for symptomatic severe AS. The high prevalence of CAD in this patient population has been well documented and was classically treated in a combined AVR/CABG procedure. With TAVR emerging as a reasonable alternative for patients deemed inoperable or at high risk for surgery, the question of how to manage concomitant CAD is currently being revisited. Recent studies point to a treatment paradigm shift from SAVR and CABG to TAVR and PCI or even a hybrid approach. However, the lack of robust randomized data is striking and many questions remain unanswered. Ongoing studies, like PARTNER 2A and SURTAVI, will analyse the outcomes of TAVR in lower risk populations, and will scrutinize the impact of percutaneous or surgical revascularization strategies.

In this context, while awaiting more definitive data, the collaborative efforts of the heart team remain crucial to appropriately managing and optimizing the outcomes of patients with AS and CAD.

Conflicts of interest: M.W. and S.K. have received consulting fees from Edwards Lifesciences. M.B.L. is a non-paid member of the Scientific Advisory Board of Edwards Lifesciences and Medtronic Vascular. The other authors do not have any disclosures.

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