Anatomical or Functional Assessment of Coronary Artery Disease in Aortic Stenosis: Haven't We Been Down This Road Before?

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In patients with symptomatic severe aortic stenosis undergoing surgical aortic valve replacement, concomitant coronary artery bypass grafting for severe coronary artery disease (CAD; diameter stenosis ≥50–70%) is recommended by societal guidelines.[1,2] However, the safety and efficacy of this widely accepted approach has never been formally tested in a prospective clinical trial. Instead, expert consensus (level of evidence C) and perhaps common-sense reasons for avoiding the risks and costs inherent in future percutaneous coronary intervention (PCI) or coronary artery bypass grafting justify the higher short-term risk of the simultaneous valve and coronary intervention. It is somewhat surprising, however, that this strategy has not been tested, given the fact that concomitant coronary artery bypass grafting is performed in 4 of 10 patients undergoing surgical aortic valve replacement.[3]

The prevalence of obstructive CAD in patients undergoing transcatheter aortic valve implantation (TAVI) is thought to be greater than that reported in surgical series; the older age and constellation of comorbid conditions of the TAVI population account for this difference. In randomized trials of intermediate- and high-risk patients, more than two thirds of TAVI candidates had CAD.[4,5] Importantly, it is not clear that CAD negatively affects clinical outcomes of TAVI after adjustment of coexisting comorbidities.[6] Moreover, percutaneous treatment of CAD before TAVI has not been associated with lower in-hospital or 1-year mortality or improved symptoms during follow-up.[7] Therefore, current guidance recommends that PCI before TAVI should be limited to significant stenoses of proximal major coronary arteries.

Among the potential explanations for the absence of clinical benefit from PCI in TAVI patients could be that the stented lesions are not prognostically significant or perhaps even that nonhemodynamically significant coronary lesions have been treated. Functional assessment of CAD using fractional flow reserve (FFR) or resting indexes, such as the instant wave-free ratio, are validated diagnostic tools that clarify the clinical impact of individual coronary stenoses[8]; however, the diagnostic accuracy of these indexes in the setting of a pressure-loaded left ventricle is unclear. Severe aortic stenosis increases left ventricular pressure, and compensatory left ventricular hypertrophy can increase myocardial compressive forces throughout the cardiac cycle and thus affect physiological indexes.[9] Prior work by the Verona group suggests that FFR, in particular, may underestimate the severity of intermediate coronary stenoses.[10] In contrast, the impact of aortic stenosis on lesion assessment appears to be less variable with the instant wave-free ratio.[11]

In this context, the study by Lunardi et al in this issue of the *Journal of the American Heart Association* (*JAHA*) is timely and adds to our understanding of which coronary lesions should be treated before TAVI.[12] This new single-center, retrospective, observational analysis examined the incidence of major adverse cardiac and cerebral events (MACCE) in patients with combined CAD and severe aortic stenosis who received TAVI. At 2-year follow-up in per-protocol analysis, MACCE-free survival in the FFR-guided group was 92.6% (7 events in 94 patients) compared with 82% (22 events in 122 patients) in the angiography-guided group (P=0.035; hazard ratio: 0.4; 95% CI, 0.2–1.0). Kaplan–Meier event curves dissociate from the outset because of a numerical increase of periprocedural type 4a myocardial infarction (MI; 3 MIs for 31 PCIs in 24 patients with FFR guidance versus 7 MIs for 54 PCIs in 122 patients with angiographic guidance). Of note, a rather conservative definition of periprocedural type 4a MI was used, requiring the occurrence of new ischemic symptoms or signs in addition to elevation of cardiac biomarkers (peak value exceeding 15× as the upper

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reference limit for troponin or 5× for creatine kinase myocardial band) ≤72 hours after the index procedure.

The most striking observation was that FFR guidance resulted in PCI deferral in the majority of lesions (78.2%, 111/142 lesions) in view of preserved FFR>0.8. Likewise, the deferral rate was high in the group with angiographic guidance (70.7%, 130/184 lesions; NS (*P* value not significant) versus FFR group), much higher than reported in trials and registries obtained in patients with CAD but without associated aortic valvular disease. Similar to earlier observations in CAD patients, outcomes in deferred patients were quite good, once again indicative of the fact that when it comes to outcome benefit of stented angioplasty, "less is more." In other words, restricting stented angioplasty to hemodynamically significant stenoses spares inappropriately "treated" patients the risk of periprocedural MI.

The authors conclude that the current study shows "proof of concept" evidence that FFR guidance might provide superior clinical outcomes in this context and that the concept should be tested prospectively in a randomized trial. The study also confirms that hyperemia can be induced safely via intracoronary adenosine injection in patients with severe aortic stenosis. Surprisingly, not a single side effect was reported.

Indeed, the time seems right for randomized evaluation of different treatment options in patients with combined coronary and valvular heart disease. Whether MACCE is the proper end point for such trials is debatable. In an attempt to minimize the limitations of the retrospective analysis, the authors performed sequential analysis of 2 consecutive periods: (1) between March 2010 and December 2014, all revascularization decisions were made using coronary angiography alone, and (2) between January 2015 and December 2018, revascularization decisions were based largely on FFR but also on angiography in some patients. This selection bias is an important confounder that could have affected clinical outcomes. For instance, many more patients included in the FFR-guided group had prior history of MI (96% versus 27%, $P<0.001$). Although overall difference in MACCE was of borderline significance, none of the individual elements of the composite end point were significantly different between groups. Numerical differences were largest for periprocedural MI, as mentioned, and for disabling stroke at 2 years: 1.1% (1 event) with FFR guidance versus 4.9% (6 events) with angiographic guidance. It is difficult to envisage why stroke rates would be different if not a play of chance or perhaps a

Table. Planned and Ongoing Trials in the Functional Assessment of CAD in TAVI Candidates

Study Name	ClinicalTrials.gov Identifier	Status	Patients, N	Description	Completion Date
FAVOR IV-QVAS (Quantitative Flow Ratio [QFR] Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease)	NCT03977129	Recruiting	792	Randomized comparison of QFR- and angiography-guided revascularization; primary end point at 30 d: all death, nonfatal MI, stroke, unplanned revascularization, new kidney disease requiring dialysis	2022
NOTION-3 (Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation)	NCT03058627	Recruiting	452	Routine FFR-guided complete revascularization with PCI compared with conservative management in TAVI candidates	2025
FAITAVI (Functional Assessment In TAVI)	NCT03360591	Recruiting	320	Comparison of clinical outcome of patients with severe AS and associated significant CAD treated with TAVI and PCI guided by an angiographic vs physiologic strategy	2021
TCW (The Transcatheter Valve and Vessels Trial)	NCT03424941	Recruiting	328	FFR-guided PCI and TAVI in severe AS and multivessel CAD vs CABG and SAVR for a composite primary end point of all-cause mortality, stroke, MI, coronary or valve reintervention, and life-threatening or disabling bleeding at 1 y	2021
FORTUNA (Evaluation of fractional flow reserve calculated by computed tomography coronary angiography in patients undergoing TAVI)	NCT03665389	Planned	25	Comparison of FFR derived from coronary computed tomography angiography before TAVR and FFR after TAVI	2022
A Prospective Study of Fractional Flow Reserve Assessment of Intermediate Coronary Stenoses in Severe Aortic Stenosis	NCT03442400	Recruiting	50	Comparison of pre- and post-TAVI iFR/FFR values and assessment of short-term outcomes	2019

AS indicates aortic stenosis; CABG, coronary artery bypass grafting; CAD, coronary artery disease; FFR, fractional flow reserve; iFR, instant wave-free ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio (fractional flow reserve computed from coronary angiography); SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement.

sign of increased site experience and/or enhanced procedure safety over nearly a decade. The observed reduction in MACCE is thus probably unrelated to FFR guidance. Caution should be exercised when designing future randomized studies, with respect to the anticipated benefit and estimation of study power and size.

Ultimately, the question as to whether coronary revascularization is beneficial in patients undergoing TAVI will be answered only by large enough prospective randomized trials. Foremost among these studies is the ACTIVATION (Assessing the Effects of Stenting in Significant Coronary Artery Disease Prior to Transcatheter Aortic Valve Implantation) trial, an open-label noninferiority trial of 310 patients randomized to treatment of significant CAD by PCI (test arm) or no PCI (control arm).[13] Patients undergoing TAVI with ≥1 coronary stenosis of ≥70% are eligible for inclusion. The composite primary outcome is 12-month mortality and rehospitalization. Further prospective investigation is required to clarify the role of physiological indexes in the assessment and decision-making of CAD in TAVI patients. Table highlights a number of studies that will shed light on this important topic. It is also likely that the availability of image-based methods for FFR computation will facilitate adoption of combined angiographic and functional assessment in this setting, as will be the case in the FAVOR IV-QVAS (Quantitative Flow Ratio [QFR] Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease) trial. The use of computational computed tomography–derived FFR in the assessment of CAD in TAVI candidates is particularly appealing because all TAVI patients require multislice computed tomography to evaluate suitability for and planning of TAVI.

How should clinicians treat CAD in TAVI candidates until prospective data are available? The important work undertaken by the Verona group to date on this topic demonstrates that FFR-guided revascularization is feasible and safe and results in deferral of stenting in a large proportion of patients and may have the potential to reduce MACCE. We would support the liberal use of functional assessment of CAD in this often elderly and frail patient group. Haven't we been down this road before?

Disclosures

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