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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