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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Degenerative Severe Aortic Stenosis and Concomitant Coronary Artery Disease: What Is Changing in the Era of the "Transcatheter Revolution"?

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Abstract

Purpose of Review To summarize epidemiology, pathophysiology, prognostic relevance, and treatment options of coronary artery disease (CAD) when coupled with severe aortic stenosis (SAS). In regard to treatment options, we focused on the most recently adopted therapeutic approaches and on the future perspectives in light of the latest percutaneous and surgical technical improvements in the field of both CAD and SAS management.

Recent Findings Nowadays, SAS is the most common valve disease requiring intervention, either surgical or percutaneous. On the other side, CAD is one of the leading causes of death in the developed countries. CAD and degenerative SAS share several predisposing factors and are often concurrently found in clinical practice. Despite in the last years the transcatheter aortic valve replacement (TAVR) has been deeply changing the therapeutic approach to SAS, the correct management of patients with concomitant CAD remains controversial due to limited and heterogeneous data in the literature.

Summary Coronary revascularization is often performed in patients with concomitant CAD and SAS. Complete surgical approach is still the standard of care according to international guidelines. However, in light of the recent results of TAVR trials, the therapeutic approach is expected to change. To date, percutaneous coronary intervention performed before TAVR is safe and feasible even if the optimal timing for revascularization remains debated. Due to the great complexity of the patients affected by SAS and CAD and until unquestionable truths will come from large randomized trials, the role of the Heart Team in the decision-making process is of primary importance to guarantee the best tailored therapeutic strategy for the single patient.

Keywords Aortic stenosis · Coronary artery disease · Transcatheter aortic valve replacement · Surgical aortic valve replacement · Percutaneous coronary intervention · Coronary artery bypass graft

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Introduction

Degenerative severe aortic stenosis (SAS) is to date the most common valve disease requiring intervention (either surgical or percutaneous) in the Western world, and its prevalence increases with age [1]. At the same time, coronary artery disease (CAD) is the leading cause of death in the developed countries and is on its way to becoming the most common cause of death worldwide. Since the prevalence of both CAD and SAS augments with age and considering that atherosclerosis and aortic valve degeneration share some etiological factors, these conditions often coexist.

Despite in the last years the introduction of the transcatheter aortic valve replacement (TAVR) has been deeply changing the therapeutic approach to SAS, the optimal management of patients with concomitant CAD remains controversial. In this review we principally focus on (1) the incidence of CAD in patients with SAS undergoing invasive treatments, (2) the prognostic implications of CAD when coupled with SAS, and (3) the current treatment options in light of the latest percutaneous and surgical technical improvements.

Methodology

We searched on the PubMed Web site using the following terms: "coronary artery disease" AND "severe aortic stenosis" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve intervention" OR "surgical aortic valve replacement," and retrieved all published studies in English from February 1981 to October 2019. Using manual reading and screening, relevant literature (including reviews, meta-analyses, and original researches if deemed to have been designed, conducted, and reported with rigorous approach) on the topic was selected. Key features from the selected literatures researches were extracted and tabulated, with descriptive aims. All reviewing activities were performed independently by two expert reviewers (M.P. and C.L.), with divergences solved after consensus. Furthermore, the reference lists from the relevant publications were used to identify additional studies.

Epidemiology and Etiology

The high prevalence of CAD in patients with SAS has been clearly demonstrated, despite a wide heterogeneity of data probably due to diverse definitions of CAD and/or different studies' design and patients' selection (Fig. 1) [2]. The reported quote of significant CAD overlapped to SAS ranges from 25 to 50% [2]. The absolute prevalence of both diseases is expected to rise in the next years driven by the aging population phenomenon, being old age a common risk factor for atherosclerosis and degenerative aortic valve disease [3, 4]. In fact, it is esteemed that approximately 5% of the population between 75 and 86 years old is affected by moderate to severe aortic valve obstruction [1].

A large prospective Swedish study including about 2300 SAS patients undergoing surgical aortic valve replacement (SAVR) reported an overall 39% prevalence of CAD [5]. In detail, Kvidal showed as the rate of concomitant coronary artery bypass grafting (CABG) increased with patients' age in a stepwise fashion from the 7% in the subpopulation younger than 50 years, through the 30% in the 51–60 decade, up to the 51% in patients older than 71 years [5]. This keeps true despite the prevalence of CAD in patients less than 50 years old was probably underestimated because preoperative coronary angiography [CA] was, in this category, not mandatory and performed only if otherwise indicated. These data are in line with other evidences that reported severe CAD in 41 to 65% of patients older than 80 years and submitted to SAVR [6, 7].

In coeval "real-world" registries focused on TAVR, the prevalence of CAD was similar and estimated around 40–75% [8]. Epidemiology data from TAVR literature need, nevertheless, to be handled with caution: in these trials the prevalence of concomitant CAD over the last years progressively decreased from 81 to 15% due to an overtime change in patients' risk profile from very high at the beginning to low-intermediate in the last studies [9••]. A summary of the prevalence and prognostic impact of CAD coupled with SAS in the largest studies, both randomized and real-world registries, is shown in Table 1 [10–24].

The association of SAS and CAD is not driven by patients' age only: histological studies revealed that in the early phase of aortic valve degeneration, the aortic cusps share structural and cellular features with atherosclerotic lesions. In particular, lipid deposition and macrophage and inflammatory cell infiltration have been demonstrated in the early phase of aortic degeneration [25–28]. Moreover, some risk factors notoriously involved in the atherosclerosis pathogenesis such as male sex, hypertension, smoking, and LDL cholesterol levels have been shown to be also predictors of aortic sclerosis and stenosis [1].

Prognostic Implications of Concomitant CAD in Patients Addressed to SAVR and TAVR

The presence of CAD increased the procedural risk of SAVR in several studies [29, 30]. Moreover, long-term mortality seemed higher in concomitant CABG+SAVR than in SAVR alone [31]. What is nevertheless controversial is the actual prognostic role of CAD compresence, which can alternatively be considered an innocent bystander marker of high risk. In support of the latter hypothesis, in a large observational study, after propensity matching for several comorbidities and risk

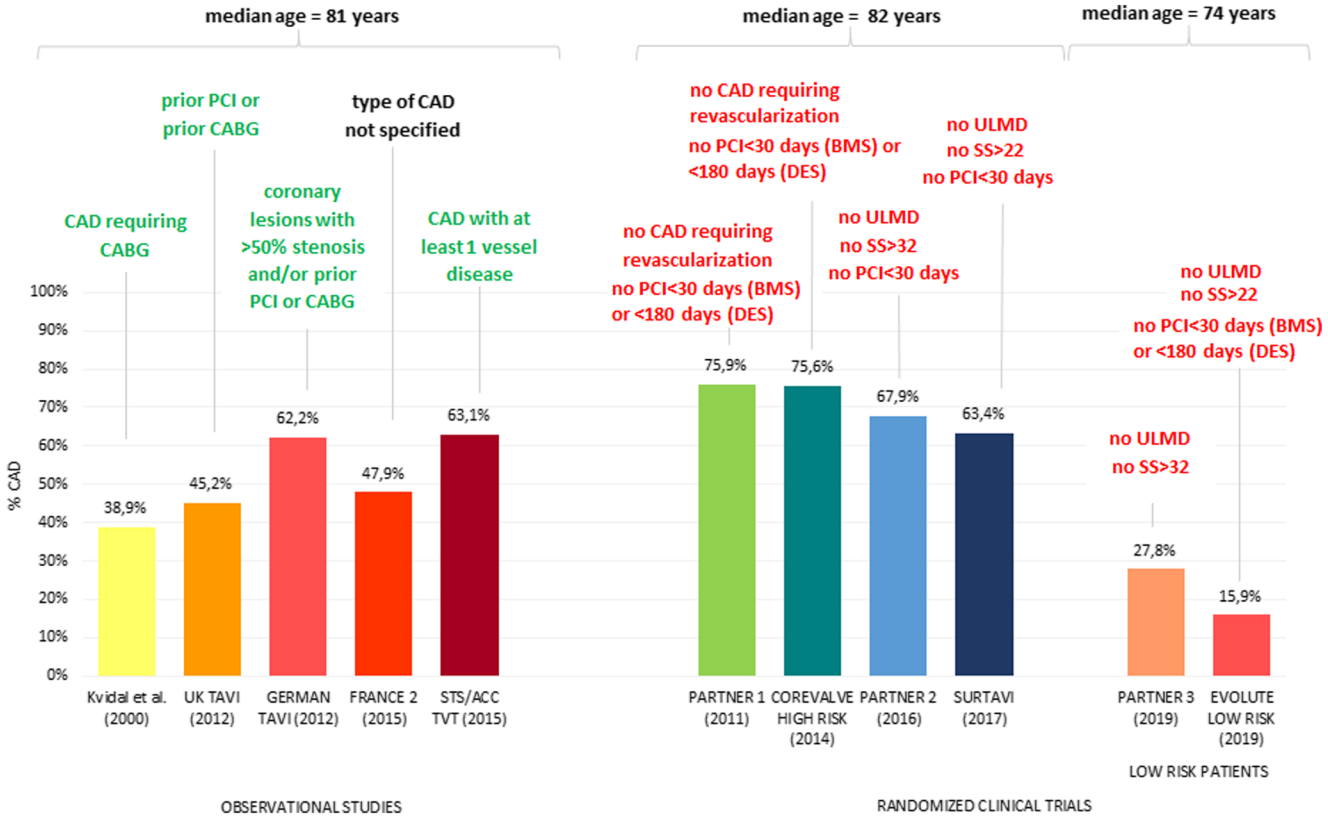

Fig. 1 Prevalence of CAD in SAS patients from both observational studies and randomized clinical trials in view of deeply different CAD definitions and median age. BMS bare metal stent, CABG coronary artery bypass graft, CAD coronary artery disease, DES drug eluting stent, PCI percutaneous coronary intervention, SAS severe aortic stenosis, SS sintax score, ULMD unprotected left main disease

factors, long-term survival resulted similar between patients undergoing SAVR+CABG or SAVR alone [32].

Since TAVR has emerged as a valid alternative option for the treatment of SAS, many studies have addressed the prognostic impact of concomitant CAD in the setting of TAVR. In early studies, CAD resulted not associated with worse prognosis; in particular, in an observational study including 240 patients referred for TAVR with a very high incidence of concomitant CAD, the survival rate was not different in patients with and without CAD [33]. Similar conclusions were drawn from a meta-analysis including more than 2400 patients from several TAVR registries: the presence of CAD (found in more than 50% of patients) did not show to affect mid-term outcome [34]. These results are in line with other evidences, coming from both randomized and observational trials, which support the presumption that CAD is not associated "per se" with higher post-TAVR mortality rate [10–24]. As strictly regards the intraoperative risk, the procedural induced ischemia (especially during rapid pacing) has been one of the most debated topic as a potential threat for patients with non-revascularized CAD. However, the rate of death within 24 h post-TAVR was globally low and showed not to be worsened by coexisting CAD [10–17].

More recent works tried to address the hypothesis that not the presence of CAD itself but the severity of CAD could influence the prognosis. In a recent large multicenter study, CAD severity showed to be a strong predictor of post-TAVR mortality [35]. This result was confirmed by a meta-analysis including 13 studies and more than 8000 TAVR patients in which the presence of CAD alone did not affect short-term mortality, while severe CAD defined as syntax score (SS) > 22 was conversely associated with higher 1-year mortality [36•].

Diagnosis

Angina is often present in patients with SAS, even in the absence of significant CAD, due to the chronic increase of left ventricle afterload and hypertrophy. In this setting, angina has, therefore, a low positive predictive value for CAD. On the other hand, in patients with SAS and asymptomatic for angina, left main stenosis or three-vessel disease is reported in about 14% of cases [37]. Considering the low specificity of non-invasive stress tests in SAS, CA remains the gold standard for CAD assessment.

Coronary computed tomography angiography (CTA) has been recently proposed as possible alternative to CA. In the context of percutaneous aortic valve replacement, CTA has the potential advantage of concurrently providing information about aortic annulus anatomy, peripheral arterial access, and CAD. Coronary CTA in patients with SAS, when compared to

Table 1 Summary of the epidemiological data from the largest randomized clinical trials and observational registries evaluating patients with severe aortic stenosis coupled with coronary artery disease undergoing TAVR or SAVR

Study	Design	Enrollment time	Population	Sample size	%CAD	% Prior PCI	% Prior CABG	% Prior AMI
PARTNER 1* [10–12]	RCT	May 2007 to August 2009	High surgical risk	Overall: 699 TAVR: 348 SAVR: 351	Overall: 526/693 (75.9%) TAVR: 260/347 (74.9%) SAVR: 266/346 (76.9%)	Overall: 226/679 (33.3%) TAVR: 116/341 (34.0%) SAVR: 110/338 (32.5%)	Overall: 299/689 (43.4%) TAVR: 147/345 (42.6%) SAVR: 152/344 (44.2%)	Overall: 195/648 (30.1%) TAVR: 92/343 (26.8%) SAVR: 103/343 (30.0%)
COREVALVE HIGH RISK* [13]	RCT	February 2011 to September 2012	High surgical risk	Overall: 747 TAVR: 390 SAVR: 357	Overall: 565/747 (75.6%) TAVR: 294/390 (75.4%) SAVR: 271/357 (75.9%)	Overall: 267/747(35.5%) TAVR: 133/390 (34.1%) SAVR: 134/357 (37.5%)	Overall: 226/747 (30.3%) TAVR: 115/390 (29.5%) SAVR: 111/357 (31.1%)	Overall: 189/747 (25.3%) TAVR: 99/390 (25.4%) SAVR: 90/357 (25.2%)
PARTNER 2* [14]	RCT	December 2011 to November 2013	Intermediate surgical risk	Overall: 2032 TAVR: 1011 SAVR: 1021	Overall: 1379 (67.9%) TAVR: 700 (69.2%) SAVR: 679 (66.5%)	Overall: 556 (27.4%) TAVR: 274 (27.1%) SAVR: 282 (27.6%)	Overall: 500 (24.6%) TAVR: 239 (23.6%) SAVR: 261 (25.6%)	Overall: 364 (17.9%) TAVR: 185 (18.3%) SAVR: 179 (17.5%)
SURTAVI* [15]	RCT	June 2012 to June 2016	Intermediate surgical risk	Overall: 1660 TAVR: 864 SAVR: 796	Overall: 1052(63.4%) TAVR: 541 (62.6%) SAVR: 511 (64.2%)	Overall: 353 (21.3%) TAVR: 184 (21.3%) SAVR: 169 (21.2%)	Overall: 275(16.5%) TAVR: 138 (16.0%) SAVR: 137 (17.2%)	Overall: 236 (14.2%) TAVR: 125 (14.5%) SAVR: 111 (13.9%)
PARTNER 3* [16]	RCT	March 2016 to October 2017	Low surgical risk	Overall: 950 TAVR: 496 SAVR: 454	Overall: 264/948 (27.8%) TAVR: 137/494 (27.7%) SAVR: 127/454 (28.0%)	–	–	Overall: 54/987(5.5%) TAVR: 28/495 (5.7%) SAVR: 26/452 (5.8%)
EVOLUTE LOW RISK * [17]	RCT	March 2016 to November 2018	Low surgical risk	Overall: 1403 TAVR: 725 SAVR: 678	–	Overall: 190 (13.6%) TAVR: 103 (14.2%) SAVR: 87 (12.8%)	Overall: 32 (2.3%) TAVR: 18 (2.5%) SAVR: 14 (2.1%)	Overall: 81 (5.8%) TAVR: 48 (6.6%) SAVR: 33 (4.9%)
OBSERVANT [18]	Multicenter prospective TAVR vs SAVR registry	December 2010 and June 2012	All-comers	Overall: 5468 TAVR: 1391	–	Overall: 621(11.4%) TAVR: 365 (26.3%) SAVR: 256 (6.6%)	–	Overall: 447 (8.2%) TAVR: 216 (15.7%) SAVR: 231 (5.8%)

Table 1 (continued)

Study	Design	Enrollment time	Population	Sample size	%CAD	% Prior PCI	% Prior CABG	% Prior AMI
				SAVR: 4077				
FRANCE 2 [19]	Nationwide multicenter prospective TAVR registry	January 2010 to October 2011	All-comers	3195	1483/3093 (47.9%)	–	564/3093 (18.2%)	508/3093 (16.4%)
UK TAVI [20]	Nationwide multicenter prospective TAVR registry	2007–2012	All-comers	3980	1698/3760 (45.2%)	841/3964 (21.2%)		892/3964 (22.5)
GERMAN TAVI [21]	Nationwide multicenter prospective TAVR registry	January 2009 to June 2010	All-comers	1382	859 (62.2%)	485 (56.6%)	254 (29.6%)	196 (22.9%)
STS/ACC TVT [22]	Multicentre prospective TAVR registry	November 2011 to December 2014	All-comers	26,414	63.1% 1 vessel disease: 19.6% 2 vessels disease: 16.1% 3 vessels disease: 27.4% LMCA disease: 10.8%	35.6%	31.4%	25.3%
GARY [23]	Nationwide multicenter prospective TAVR vs SAVR registry	January 2012 to December 2014	Intermediate surgical risk all-comer patients	Overall: 7613 TAVR: 6469 SAVR: 1144	–	Overall: 1922 (25.3%) TAVR: 1770 (27.4%) SAVR: 152 (13.3%)	–	Overall: 925 (12.2%) TAVR: 827 (12.8%) SAVR: 98 (8.6%)
POL-TAVI [24]	Nationwide multicenter prospective TAVR registry	January 2009 to December 2015	All-comers	896	462 (51.6%)	294 (32.8%)**	294 (32.8%)**	138 (30%)

AMI acute myocardial infarction, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *LMCA* left main coronary artery, *PCI* percutaneous coronary intervention, *RCT* randomized clinical trial, *SAVR* surgical aortic valve replacement, *TAVR* transcatheter aortic valve replacement

*Modified intention-to-treat analysis

**Prior PCI/CABG

the remaining population, demonstrated similar sensitivity but lower specificity (about 65%), being the augmented false positive rate due to higher presence of heavily calcified coronary lesions [38]. In any case the strategy of performing coronary CTA before TAVR was shown to be safe and not associate with negative prognostic implications, and to allow avoiding CA in 75% of cases [39]. A randomized trial exploring the possibility of performing coronary CTA before TAVR, on a regular basis and in place of CA, is ongoing [40].

Treatment

Despite the latest improvements in percutaneous and surgical techniques for both valvular and coronary interventions, unequivocal evidences about the best therapeutic approach in coexisting SAS and CAD are still lacking. The 2018 ESC/EACTS Guidelines on myocardial revascularization underline the central role of the Heart Team to guarantee a tailored approach by carefully weighing the risk/benefit ratio of each alternative possibility [41]. Nevertheless, many unresolved issues look for unquestionable answers.

Is Revascularization Necessary?

A clinically relevant and still debated topic is whether coronary revascularization is associated with improved outcomes in patients undergoing surgical or percutaneous aortic replacement. Despite the lack of adequate randomized controlled trials comparing CABG+SAVR with SAVR alone in the presence of significant CAD, from many observational studies, it emerges that combining SAVR and CABG is associated with higher postoperative and long-term major adverse cardiovascular events (MACEs) [42–44]. Reliability of these findings is nevertheless poor, since a worse risk profile in patients with concomitant CAD represents a relevant selection bias. A small study from the early 80s demonstrated, in a relatively small population, that even in presence of concomitant significant CAD, SAVR alone did not hinder either short- and long-term outcomes in comparison with patients undergoing also CABG; the main limitation of the study was nonetheless that most of patients had a single vessel disease [45]. On the other hand, in a more recent large observational study, CABG performed at the time of SAVR showed to reduce late mortality by more than one third without increasing operative risk [46]. Thanks to the most up-to-date improvements of the surgical techniques, Sakakura et al. demonstrated similar short- and long-term outcome in patients submitted to concomitant SAVR and CABG with complete coronary revascularization if compared to a cohort of patients with isolated SAVR, despite a higher surgical and cardiopulmonary bypass time [47].

CABG has been for decades the first-choice revascularization strategy in SAS patients eligible for SAVR; in the last years, inoperable patients with SAS have found in the TAVR a lifesaving alternative to medical treatment, known as ineffective [48, 49]. In this scenario, percutaneous coronary intervention (PCI) has attained a role in patients with SAS [50]. Yet, the potential prognostic impact of coronary revascularization during or before TAVR is still controversial. In a recent meta-analysis involving 1270 patients undergoing TAVR, severe CAD defined as SS > 22, and incomplete revascularization (assessed as residual SS > 8) were both associated with increased 1-year mortality [35]. Conversely, other studies failed to demonstrate that residual SS could influence post-TAVR mid- to long-term outcome [51, 52]. These contradictory findings can be explained by different study designs, selection biases due to the lack of randomization, variable completeness and modality (staged or concomitant) of revascularization strategies, discrepancies in the definitions of CAD whose prognostic impact can be assumed to be different according to the involved vessel, atherosclerotic disease extension, and patient's comorbidities. Overall, what seems unquestionable is that PCI in TAVR candidates has proven to be safe. In light of these considerations, current guidelines, even if with low evidence level, state that PCI should be considered in patients with a primary indication for TAVR and coronary artery diameter stenosis > 70% in proximal segments (class IIa, level of evidence C) [53]. The ACTIVATION trial is an ongoing randomized clinical trial that enrolled patients candidate to TAVR with severe CAD (including patients with left main coronary artery disease) aiming to compare in this setting the prognostic impact of preprocedural PCI vs medical therapy [54].

The few available randomized clinical trials comparing TAVR and SAVR naturally included also patients with CAD, addressed to either PCI or CABG if allocated to the TAVR or SAVR group, respectively; nevertheless, with exception of the PARTNER 3 Trial, no specific subanalyses on the CAD subpopulations were presented. Moreover, the most complex coronary scenarios such as unprotected left main disease, SS > 32, or recent previous percutaneous coronary procedures represented exclusion criteria. As shown in Table 2, despite comparable proportion of CAD in both groups, the quote of patients undergoing PCI in addition to TAVR (3.9 to 14.5%) was smaller compared to that of patients treated with SAVR+CABG (12.8 to 22.1%). This trend reflects the approach currently recommended by the abovementioned guidelines: to handle only proximal lesions in TAVR patients. However, the noninferiority or superiority of TAVR versus SAVR for the global composite primary endpoint (mostly death and stroke) was demonstrated in all trials.

Completely Percutaneous Versus Completely Surgical Treatment

The 2017 ESC/EACTS Guidelines for the management of valvular heart diseases indicate in patients with SAS and

Table 2 Summary of randomized clinical trials comparing undergoing TAVR vs SAVR

Study	Design	Enrollment time	Population	Sample size	TAVR	SAVR	%CAD	%CAD in TAVR	%CAD in SAVR	%PCI in TAVR	%CABG in SAVR	Composite primary endpoint	Follow-up (months)	Exclusion criteria	Results
PARTNER 1 [10–12]	RCT	May 2007 to August 2009	High surgical risk	ITT: 699	ITT: 348	ITT: 351	ITT: 526/693 (75.9%)	ITT: 260/347 (74.9%)	ITT: 266/346 (76.9%)	–	–	All-cause death	60	Significant CAD requiring revascularization Any PCI or PTA with a BMS within 30 days or DES within 180 days prior to randomization	All-cause death was similar in the TAVR and SAVR group (67.8% vs 62.4%, p 0.76).
COREVALVE HIGH RISK [13]	RCT	February 2011 to September 2012	High surgical risk	ITT: 995 mITT: 747	ITT: 394 mITT: 390	ITT: 401 mITT: 357	ITT: 603/795 (75.9%) mITT: 565/747 (75.6%)	ITT: 297/394 (75.4%) mITT: 294/390 (75.4%)	ITT: 306/401 (76.3%) mITT: 271/357 (75.9%)	–	–	All-cause death	12	Significant CAD requiring revascularization Any PCI or PTA with a BMS within 30 days or DES within 180 days prior to randomization	All-cause death was lower in the TAVR group than in the SAVR group (14.2% vs 19.1%; p 0.04 for superiority).
PARTNER 2 [14]	RCT	December 2011 to November 2013	Intermediate surgical risk	ITT: 2032	ITT: 10-11	ITT: 10-21	ITT: 1379 (67.9%)	ITT: 700 (69.2%)	ITT: 679 (66.5%)	39/994 (3.9-%)	137/944 (14.5%)	All-cause death or disabling stroke	24	Unprotected LMCA disease SS > 32 Any PCI within 30 days prior to randomization (unless part of planned strategy for concomitant treatment of CAD)	Primary endpoint was similar in the TAVR and SAVR group in both the IIT analysis (19.3% vs 21.1%; p 0.25) and mITT analysis (18.9% vs 21.0% p 0.18).
SURTAVI [15]	RCT	June 2012 to June 2016	Intermediate surgical risk	ITT: 1746 mITT: 1660	ITT: 879 mITT: 864	ITT: 867 mITT: 796	ITT: 1105 (63.3%) mITT: 1052 (63.4%)	ITT: 549 (62.5%) mITT: 541 (62.6%)	ITT: 556 (64.1%) mITT: 511 (64.2%)	125 (14.-5%)	176 (22.1%)	All-cause death or disabling stroke	24	Unprotected LMCA disease SS > 22 Any PCI or PTA within 30 days prior to randomization	Primary endpoint was similar in the TAVR and SAVR groups in both the mIIT analysis (12.6% vs 14.0%; 95% CI for difference − 5.2 to 2.3%) and ITT analysis (13.2% vs 14.1%; 95% CI for difference − 4.7 to 2.7%).
PARTNER 3 [16]	RCT	March 2016 to October 2017	Low surgical risk	ITT: 1000 mITT: 950	ITT: 503 mITT: 496	ITT: 497 mITT: 454	264/948 (27.8%)	137/494 (27.7%)	127/454 (28.0%)	32/496 (6.5-%)	58/454 (12.8%)	All-cause death, stroke or rehospitaliza-tion	12	Unprotected LMCA disease SS > 32	Primary endpoint was similar in the TAVR and SAVR groups in both the IIT analysis (8.5% vs 21.1%; p 0.25) and mITT analysis (18.9% vs 15.1%; p 0.001 for superiority and $p < 0.0014$ for noniferiority) In the TAVR+PCI vs SAVR+CABG subanalysis primary endpoint occurred in 9.4% of patients in TAVR+PCI group

Table 2 (continued)

Study	Design	Enrollment time	Population	Sample size	TAVR	SAVR	%CAD	%CAD in TAVR	%CAD in SAVR	%PCI in TAVR	%CABG in SAVR	Composite primary endpoint	Follow-up (months)	Exclusion criteria	Results
															vs 12.1% in SAVR+CABG group.
EVOLUTE LOW RISK [17]	RCT	March 2016 to November 2018	Low surgical risk	ITT: 1468 mITT: 1403	ITT: 734 mITT: 725	ITT: 734 mITT: 678	Prior PCI: 190 (13.5%) Prior CABG: 32 (2.3%) Prior AMI: 81 (5.8%)	Prior PCI: 103 (14.2%) Prior CABG: 18 (2.5%) Prior AMI: 48 (6.6%)	Prior PCI: 87 (12.8%) Prior CABG: 14 (2.1%) Prior AMI: 33 (4.9%)	50 (6.9-%)	92 (13.6%)	All-cause death or disabling stroke	24	Unprotected LMCA disease SS > 22 Any PCI or PTA with a BMS within 30 days or DES within 180 days prior to randomization	Primary endpoint was 5.3% in the TAVR group (95% CI for difference 3.3 to 8.0%) and 6.7% in the SAVR group (95% CI for difference 4.4 to 9.6%). The criterion for noninferiority was met (95% CI, − 4.9 to 2.1; posterior probability of noninferiority, > 0.999)

AMI acute myocardial infarction, *BMS* bare metal stent, *CI* confidence interval, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *DES* drug-eluting stent, *ITT* intention-to-treat analysis, *mITT* modified intention-to-treat analysis, *LMCA* left main coronary artery, *PCI* percutaneous coronary intervention, *PTA* percutaneous transluminal angioplasty, *RCT* randomized clinical trial, *SS* syntax score, *SAVR* surgical aortic valve replacement, *TAVR* transcatheter aortic valve replacement

concomitant > 70% coronary stenoses a combined SAVR+CABG as the first-choice treatment [53]. However, as suggested by the low level of evidence (LOE C), randomized data on the topic are lacking. Moreover to date, the quick and widespread expansion of TAVR poses the need for randomized clinical trials comparing a strategy of SAVR+CABG versus TAVR+PCI in patients with coexisting CAD and SAS.

So far, a variable rate of concomitant CAD patients was present in all the randomized trials comparing TAVR to SAVR, and overall, about 12% of them underwent any coronary revascularization (CABG or PCI) [16, 17, 55, 56]. The recently published PARTNER 3 randomized trial showed, in low-risk patients, an overall non-significant difference of MACE between TAVR and SAVR at 1 year. In both groups, 28% of coexisting CAD was found and concomitant revascularization was performed in 6.5% and 12.8% of patients in the TAVR and SAVR groups, respectively. Despite the low number of patients (32 in the TAVR+PCI and 58 in the SAVR+CABG arm), no differences between the two revascularization strategies in terms of death/stroke/rehospitalization at 1 year were noticed [16].

Recently, in a post hoc analysis of the OBSERVANT registry including 1719 patients with CAD and SAS (1420 treated with SAVR and 299 with TAVR) undergoing also coronary revascularization, Barbanti et al. found that the strategy of TAVR and PCI (prior or simultaneous) had similar 3-year mortality, stroke, myocardial infarction, and unplanned revascularization if compared to SAVR and CABG. However, a trend toward increased mortality and cumulative MACE rate was found in the TAVI group, probably due to the lower rate of complete revascularizations [57]. As it is known, the extension of CAD assessed by SS is a reliable tool to predict in-hospital and long-term survival in patients submitted to coronary revascularization [58]. Unfortunately, in the published randomized clinical trials, high SS (i.e., > 22 for Reardon et al. or > 32 for the other trials) or unprotected left main disease were exclusion criteria; further studies are thus strongly advocated to investigate the weight of coronary disease severity.

Which Is the Best Timing of Revascularization?

In case of planned surgical coronary revascularization, concomitant SAVR+CABG represents the only option. When conversely a PCI is the chosen revascularization strategy, the intervention can be performed before, after, or at the time of TAVR. Clear evidences on this topic are missing. A strategy of PCI performed within 10 days before TAVR proved to be safe and feasible, and not associated with increased intraprocedural, 30-day or 6-month adverse events if compared to patients without CAD [59]. In opposition, a comparison of PCI performed within 30 days versus > 30 days before TAVR highlighted that when revascularization was executed closer to TAVR significant more minor vascular and minor bleeding complications occurred during TAVR [60].

Overall, several prospective studies showed that in patients with concomitant CAD and SAS, percutaneous revascularization performed before or concomitantly with TAVR is equally feasible and safe at long-term follow-up [61, 62]. To date, a staged PCI before TAVR is the most frequently chosen strategy in the real-world, despite the lack of conclusive data about the optimal PCI/TAVR delay. Concomitant PCI during TAVR may be potentially indicated in particularly unstable patients or in presence of difficult vascular accesses, allowing to perform both procedures from the same route. This choice, on the other hand, implies higher procedural and radiation times and higher contrast medium load.

Finally, in selected cases, in presence of intermediate coronary stenoses not functionally evaluated, deferring PCI after TAVR could be an option because aortic stenosis treatment is sometimes associated with myocardial perfusion improvement. The appropriate selection of valve prosthesis is paramount in this setting in order to allow easy coronary ostia engagement. An accurate catheter selection algorithm depending on the type of implanted bioprosthesis has been recently proposed [63••].

Hybrid Approach: Percutaneous and Surgical

The hybrid approach represents the very last possible combination therapy for treating concurrent SAS and CAD. Despite unexpected only few years ago, in patients ineligible for surgical treatment of SAS, but in presence of highly calcified and tortuous vessels so that PCI is deemed at high risk, a hybrid treatment with TAVR+CABG can be considered. Baumbach et al. recently shared their single-center experience comparing the "pure" surgical approach (SAVR+CABG), the "pure" percutaneous approach (TAVR+PCI), and a hybrid approach (TAVR+off-pump CABG or minimally invasive direct CABG) [64]. At 12 months, mortality and rehospitalization rates were higher in the "hybrid" and percutaneous groups than in the surgical one. Of note, due to the non-randomized nature of the trial, the logistic EuroSCORE and comorbidities were in disfavor of the TAVR groups. Despite only hypothesis generating, this report suggests another possible way out for extremely challenging cases.

Which Role for "Physiological" Coronary Stenosis Assessment?

One crucial weakness of the available literature on CAD complicating SAS is the extremely indefinite definition of CAD, mostly based on angiographic parameters. The sole visual estimation has been proven to be often inaccurate to define the functional severity of coronary stenoses, in particular in patients whose arteries are prone to be calcified and tortuous.

Despite the role of coronary physiology is well recognized by international guidelines with a high level of evidence, the reliability of both hyperemic and non-hyperemic indices in the context of SAS is still debated. To date, we have clear evidence that both fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are safe and well-tolerated in patients with SAS [65•, 66]. However, little data are available about the trustworthiness of physiological assessment in this setting. In SAS, the impaired hyperemic response and the baseline coronary microvascular vasodilatation due to the left ventricular hypertrophy could potentially impair the results. Pesarini et al. confirmed that coronary hemodynamics change with the removal of SAS, but functional variations are minor and responsible for switch in the decision to treat or not to treat in only 6% of patients [65•]. Being independent of vasodilation, iFR could theoretically play an important role in the context of severe hypertrophy secondary to SAS. However, in the presence of SAS, conventional iFR cutoff demonstrated lower diagnostic agreement with FFR classification of coronary lesions; iFR accuracy seemed lower, especially in the left coronary artery territory, and a different ischemic threshold of 0.83 (instead of 0.89) has been proposed to achieve higher positive predictive value [67]. One explanatory hypothesis could be that severe hypertrophy and intrinsic compensatory microcirculatory vasodilatation may influence the resting flow and alter early diastole pressure-flow relationship, and therefore iFR assessment [68]. Even though underpowered to define the best cutoff for physiological indices in the setting of SAS, a recent paper by Scarsini et al. compared intracoronary physiological assessments with single-photon emission computed tomography (SPECT) founding that lower cutoffs for both iFR (0.82) and FFR (0.78) better associate with stress SPECT [69]. As a consequence, a "hybrid" approach with iFR as first choice and FFR assessment only for iFR values between 0.83 and 0.93 has been proposed and showed to avoid adenosine administration in 63% of patients maintaining a high agreement with FFR [70].

Overall, despite data come from small non-randomized trials, FFR and/or iFR use in SAS candidates should be considered safe [65•]. The interest on the topic is such high that several randomized clinical trials are ongoing to deeply comprehend the role of physiological measurements in this context [9••].

Limitations

The present review should be interpreted in the light of some limitations. Firstly, the prognostic implications of myocardial revascularization in patients with CAD and SAS cannot unquestionably defined, due to the lacking of randomized trials comparing CABG+SAVR strategy versus SAVR alone or TAVR+PCI strategy versus TAVR alone. Secondly, when revascularization is decided no clear and solid data on the comparison between completely percutaneous and completely surgical treatment (i.e., CABG+SAVR versus TAVR+PCI) are available: indeed, the only data at our disposal come from observational studies, affected by several selection biases, or from small randomized trials in which the downside is the

exclusion of the most complex coronary scenarios. Finally, one should bear in mind that little data are available about the management of coronary stenoses angiographically defined as "intermediate" since the reliability of physiological assessment (both hyperemic and non-hyperemic) in the context of SAS is still debate.

Future Directions

The confirmation of comparable results between TAVR and SAVR across different risk profile populations opens to promising therapeutic opportunities whose potential benefits need stronger proofs. The open questions to be addressed in the proximal future are as follows: is the completely surgical approach (SAVR+CABG) still "good for all seasons"? Is it time to switch to an "all percutaneous" strategy in every-day clinical practice, especially in "low-risk" patients? Is there any room for hybrid approaches? Are the current data on physiological (FFR and iFR) or imaging (IVUS or OCT) methods for coronary stenoses assessment adequate to guide myocardial revascularization in the context of SAS?

Randomized controlled trials are needed to determine the indication, the nature, the timing, and the prognostic implications of revascularization in patients with significant CAD undergoing aortic valve replacement.

Conclusions

CAD and degenerative SAS are often concurrently found in clinical practice; when coronary revascularization is decided, a completely surgical approach is still considered the standard of care by the international guidelines. However, in light of the recent results of TAVR trials in patients with intermediate to low surgical risk, the therapeutic approach is expected to change. To date, PCI performed before TAVR is considered safe and feasible.

Due to the great complexity of these patients contextually affected by SAS and CAD and until unquestionable truths will come from large randomized trials, the role of the Heart Team in the decision making process is of paramount importance to guarantee the best tailored therapeutic strategy for the single patient.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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