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CORONARY ACCESS AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

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To my family

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ABSTRACT

Coronary artery disease (CAD) and aortic stenosis (AS) often coexist in the same patient. While the clinical impact of CAD on subjects with AS undergoing transcatheter aortic valve replacement (TAVR) is controversial, current guidelines suggest revascularization of proximal severe coronary artery stenoses before TAVR, despite the paucity of data on the topic. This recommendation is mainly based on concerns about the possibility to reaccess the coronary arteries once the transcatheter prosthesis is in place. In fact, previous case series report challenges in cannulation of coronary ostia after TAVR, particularly with self-expandable devices. These aspects are of particular importance as indication to TAVR is moving towards younger patients, who are more likely to undergo coronary angiography, giving the progressive nature of CAD and their longer life expectancy.

The first objective of our research was to assess the incidence of coronary access (CA) after TAVR at long-term follow up in our high-volume center, evaluating safety and feasibility of coronary angiography and percutaneous coronary intervention (PCI) after TAVR with different types of prosthesis. At a median follow up over 3 years, incidence of CA after TAVR was 5.3%. In one out of three patients the indication to re-access the coronaries was an acute coronary syndrome, and PCI was performed in over half of the cases. Independent predictors of CA after TAVR were younger age, previous PCI and CABG. CA of both vessels was feasible in all patients with an intra-annular THV, while the right coronary artery was not engaged in two patients with a supra-annular THV. PCI was successful in all but one case. All-cause mortality tended to be higher for patients needing CA for acute coronary syndrome.

Secondly, we evaluated advantages and pitfalls of CA after TAVR in the presence of bicuspid aortic valve stenosis. We performed post-TAVR 3-dimensional computed tomography evaluation in patients with bicuspid aortic valve stenosis treated both with balloon-expanding and self-expandable prostheses. In this particular

anatomical setting, CA after TAVR as advantages and pitfalls. For instance, the potential asymmetrical prosthesis expansion when the rafe is located between the left and right coronary cusp generates a larger free space between the valve frame and the coronary ostia, thereby simplifying CA. On the contrary, the higher implantation of the prosthesis in the setting of bicuspid aortic valve, aimed at the raphe rather than on the virtual basal ring, represents a potential challenge for CA.

Finally, we aimed to assess the feasibility of CA after TAVR-in-TAVR. In fact, as TAVR indication is moving towards younger patients with longer life expectancy, transcatheter prosthesis degeneration will be increasingly common. TAVR-in-TAVR is an appealing therapeutic option in this setting, but concerns have been raised about the risk of acute coronary obstruction and the possibility to re-access the coronaries once the second prosthesis is in place. In fact, when the second THV is implanted, the leaflets of the first prosthesis are displaced vertically, creating a cylindric cage which will impair coronary cannulation and possibly coronary flow. Consequently, there is a risk plane under which the first valve frame will not be crossable after TAVR-in-TAVR. We therefore developed a novel, imaging-based pre-procedural algorithm to predict possible coronary access impairment after TAVR-in-TAVR, based on the way CA is gained after the index TAVR and on the distance between the prosthesis frame and the aortic wall under the level of the RP. Furthermore, we tested our hypothesis by performing coronary angiography after TAVR in 137 consecutive patients. According to our algorithm, CA after TAVR-in-TAVR might be impaired in almost one third of patients currently treated by TAVR. This risk appears to be less frequent with intra-annular SAPIEN 3/Ultra as compared to supra-annular Evolut R/Pro and Acurate Neo prosthesis. Implantation of a supra-annular device, female gender and small sino-tubular junction dimensions are independent predictors of possible CA impairment after TAVR-in-TAVR. These results, which will need to be confirmed by larger studies with extensive use of computed tomography evaluation and validated in clinical practice by collecting

redo-TAVR procedures performed in non-selected cohorts of patients, are important for patient counseling and prosthesis selection in subjects with longer life expectancy.

1. EPIDEMIOLOGY AND CLINICAL IMPACT OF CORONARY ARTERY DISEASE IN PATIENTS UNDERGOING TAVR

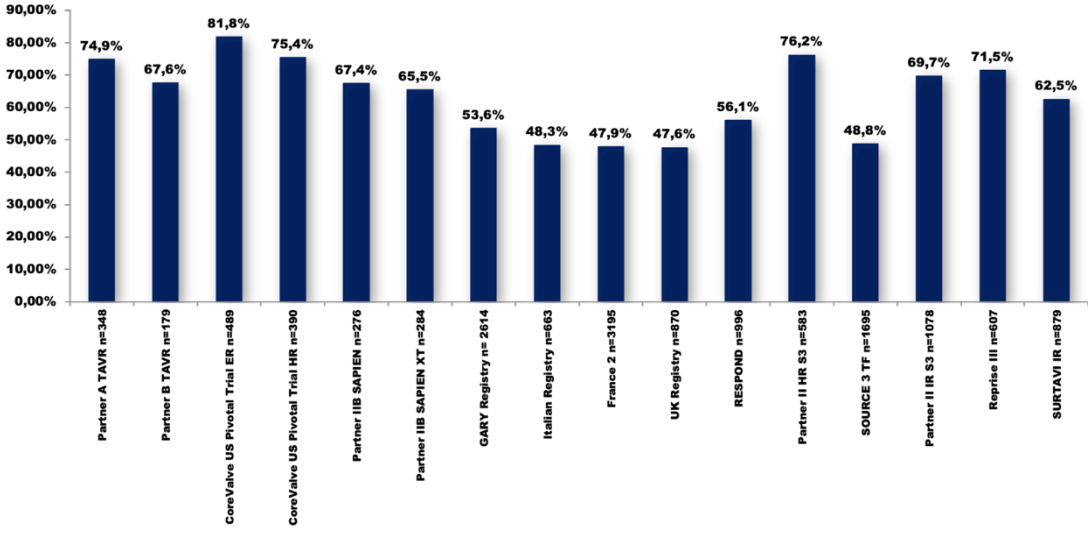
"Why CAD matters more in today's and tomorrow's TAVI population"

Tommaso Fabris, MD, Luca Nai Fovino, MD, Giuseppe Tarantini, MD, PhD, FESC.

Cardiac Interventions Today 2019 (In press)

Coronary artery disease (CAD) and severe aortic stenosis (AS) coexist in approximately 40-75% of patients referred for transcatheter aortic valve replacement (TAVR).[1] In particular, the prevalence of significant CAD in patients undergoing TAVR has been shown to increase with age,[1] in accordance with studies in patients with severe AS undergoing surgical aortic valve replacement (SAVR).[2,3] The presence of CAD has been clearly demonstrated to impair clinical outcomes after SAVR.[4,5] Accordingly, current guidelines recommend coronary revascularization of all significant lesions in patients undergoing SAVR.[6,7] Conversely, studies on the prognostic impact of CAD on short- and long-term outcomes after TAVR showed contrasting results,[8,9] suggesting that CAD alone might not significantly increase the risk of TAVR in the majority of cases as compared to patient without CAD undergoing

Figure 1. Coronary artery disease prevalence in major TAVR trials and registries .



TAVR. Such controversial clinical relevance of CAD in TAVR population, as well as overestimation of CAD prevalence itself, might be explained by the substantial heterogeneity in the definition of CAD among the historical trials and registries.[8,9]

The management of significant CAD in patients with concomitant indication to TAVR is complex.[1] It is crucial to answer these two key questions: 1) Is CAD significant enough to excessively increase the TAVR procedure risk if not treated? 2) If a percutaneous coronary intervention (PCI) is deemed necessary, which is the best timing of PCI in relation to TAVR? In patients with significant non-revascularized CAD, one of the procedural concerns during TAVR is the risk of inducing ischemia and hemodynamic instability, especially during rapid ventricular pacing and balloon inflation. Concerning the timing for PCI, it can be performed before TAVR or in the same setting or be staged after TAVR. There are pros and cons to consider with each approach (Table 1), and the decision to perform PCI should be balanced on single patient's risk profile, clinical condition, particular anatomy, and operator experience.

When TAVR devices were first introduced in Europe, the most common practice was that significant CAD had to be treated percutaneously before TAVR. Today TAVR is commonly performed as a stand-alone procedure, and variable degrees of concomitant CAD are tolerated without prior PCI.[10] Although PCI after TAVR has been reported to be feasible, the presence of a TAVR bioprosthesis could potentially make the selective catheterization of coronary ostia difficult or even impossible.[11-16] In particular, the potential of performing this procedure routinely, including in cases of acute coronary syndrome (ACS) and complex PCI, has not been widely evaluated. There are a few data on the incidence of coronary events after TAVR.

Table 1. Advantages and disadvantages of timing for PCI in relation to TAVR.

Timing of PCI	Pro	Cons
PCI before TAVR	• Free access to coronaries • May increase hemodynamic stability and procedural safety of TAVR • Reduced contrast use compared with concomitant PCI and TAVR	• Committed to DAPT prior to TAVR • Repeated vascular access, large bore if BAV performed • Less convenient
PCI at the time of TAVR	• Free access to coronaries • May increase procedural safety of TAVR • Avoiding repeated vascular access • Improved resource utilization	• More lengthy procedure • Increased contrast use in single setting • Loss of reimbursement for PCI
PCI after TAVR	• Re-evaluation without SAS • May increase hemodynamic stability and procedural safety of PCI • Reduced contrast use compared with concomitant PCI and TAVR	• Not free access to coronaries • Repeated vascular access

PCI=percutaneous coronary intervention; TAVR= transcatheter aortic valve replacement; DAPT= dual antiplatelet theraphy; BAV= balloon aortic valvuloplasty; SAS= severe aortic stenosis.

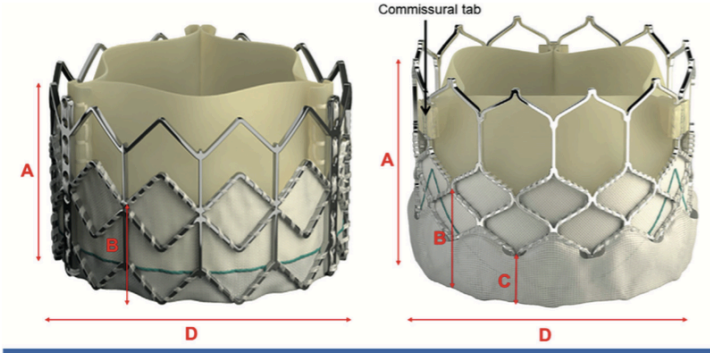
Recently, Vilalta et al.[17] reported, in a cohort of 779 TAVR recipients, an incidence of ACS of 10% after a median follow-up of about 2 years after TAVR. Up to 36% of the ACS events consisted of non–ST-segment elevation myocardial infarction (NSTEMI) type 2, followed by unstable angina (35%), NSTEMI type 1 (28%), and STEMI (1%). Of note, only 39% of the patients benefited from PCI. As the indications for TAVR expand towards low risk and younger patients, who may require coronary angiography (CA) or PCI in the future due to the progressive nature of CAD or the development of ACS, the ability to reaccess coronary ostia after TAVR is a major concern.

Factors that may influence coronary access after TAVR are either anatomical, such as coronary height, sinus of Valsalva height and width and sino-tubular junction dimensions, and device/procedural, such as sealing skirt height, implantation depth and orientation of commissural tabs.[18] Accordingly, it is crucial to know the technical specifics of each transcatheter heart valve (THV) and to understand the 3-dimensional interaction between the THV, coronary ostia and aortic root. This will guide prosthesis selection and procedural planning, in order to minimize the risk of

acute coronary artery occlusion and preserve future coronary access. In theory, all commercially available devices, which include balloon-expandable (BE) and self-expanding (SE) valves, allow access to the coronaries. Although, no studies have yet shown significant differences in coronary access rate for CA and PCI according to THV type, specific technical challenges, due to their different designs, have to be considered.

Balloon-expandable valves including Edwards SAPIEN XT and SAPIEN 3 (Edwards Lifesciences) have an intra-annular and sub-coronary design, with a low-profile stent frame consisting of 12 open cells at the upper portion, which may allow for coronary access in the majority of cases. Occasionally, long and bulky leaflets may extend beyond the inner skirt, especially in the presence of shallow sinuses, or the commissural tabs may end in front of the coronary ostia, hampering the co-axial and co-aligned engagement with the catheters.

Figure 2. Balloon-Expandable Edwards Sapien XT and Sapien 3: Features and Dimensions

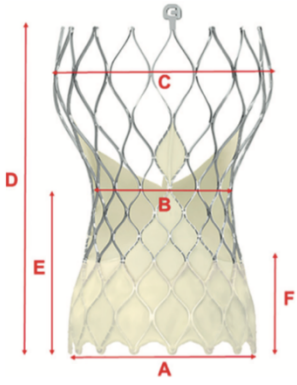


	23 mm Sapien XT	26 mm Sapien XT	29 mm Sapien XT	20 mm Sapien 3	23 mm Sapien 3	26 mm Sapien 3	29 mm Sapien 3
A. Frame Height	14 mm	17 mm	19 mm	15.5 mm	18 mm	20 mm	22.5 mm
B. Inner Skirt Height	6.7 mm	8.7mm	11.6 mm	7.9 mm	9.3 mm	10.2 mm	11.6 mm
C. Outer Skirt Height	N/A	N/A	N/A	5.2 mm	6.6 mm	7.0 mm	8.1 mm
D. Valve Diameter	23 mm	26 mm	29 mm	20 mm	23 mm	26 mm	29 mm

Adapted from Yudi et al[18]

Conversely, with the SE Corevalve and Evolut series (Medtronic), which have a supra-annular and supra-coronary stent design that extends above the coronary ostia, coronary access necessarily occurs through the prosthetic valve cells, which become "more closed" nearby the inflow portion. Importantly, in no case will coronary access feasible through the sealing skirt, whose height doubles at level of commissural posts. If a commissural post randomly ends up directly in front of a coronary ostium, the catheter necessitates entering through the valve only from a cell superior and/or lateral, making a co-axial and co-aligned engagement very challenging.[19,20]

Figure 3. Self-Expanding Medtronic Evolut R/PRO valves: Features and Dimensions



	23mm Evolut R / PRO	26 mm Evolut R / PRO	29mm Evolut R / PRO	34mm Evolut R
A. Inflow Diameter	23 mm	26 mm	29 mm	34 mm
B. Waist Diameter	20 mm	22 mm	23 mm	24 mm
C. Outflow Diameter	34 mm	32 mm	34 mm	38 mm
D. Frame height	45 mm	45 mm	45 mm	46 mm
E. Commissure Height	26 mm	26 mm	26 mm	26 mm
F. Skirt Height	13 mm	13 mm	13 mm	14 mm

Adapted from Yudi et al[18]

Due to the growing numbers of patients undergoing TAVR, many patients with an ACS post-TAVR are treated in centers with no TAVR experience. Consequently, we are dealing with the importance of establishing clear recommendations regarding selective CA and PCI after TAVR. Yudi et al.[18] recently proposed a catheter selection algorithm depending on the type of THV, the type of procedure (CA or PCI), and the position of the transcatheter commissural post with respect to the coronary ostium.

Finally, treatment of a failing THV by TAVR-in-TAVR procedure will be increasingly common with the expansion of TAVR indication to low-risk younger subjects with a life-expectancy over 10 years,[22,23] posing challenges in terms of preserving future coronary access. Goals for future should include a better understanding of the diagnosis, prognosis, and management of CAD pre- and post-TAVR, a continuous

improvement in THV design, and the ability to reach a commissure-to-commissure alignment with the native aortic valve, also with the perspective of future need for TAVR-in-TAVR procedures.[24]

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2. CORONARY ACCESS AFTER TAVR IN A HIGH-VOLUME CENTER

"Incidence and feasibility of coronary access after transcatheter aortic valve replacement"

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Manuscript currently under review

ABSTRACT

Background. Incidence of coronary access (CA) after transcatheter aortic valve replacement (TAVR) at long-term follow-up remains unknown. CA and percutaneous coronary intervention (PCI) after TAVR might present technical challenges, particularly with supra-annular devices.

Methods. Patients undergoing CA after being treated with TAVR at our Institution were included in the study. Coronary interventions for coronary obstruction during TAVR procedure were excluded. Incidence, feasibility and outcomes of CA after TAVR were analyzed.

Results. Out of 912 patients aged 80±7 years treated with TAVR at our Institution between 2007 and 2018, 48 (5.3%) underwent CA at a mean follow up of 1023±848 days. Twenty-one had received a SAPIEN XT, 15 a SAPIEN 3, 6 a Corevalve, 2 an Evolut Pro, 2 a JenaValve and 2 a Lotus THV. PCI was indicated in 26 (54%) cases. Seventeen (35%) procedures were performed for acute coronary syndromes (ACS). Independent predictors of CA after TAVR were younger age, previous PCI and CABG. CA of both vessels was feasible in all patients with an intra-annular THV, while the right coronary artery was not engaged in two patients with a supra-annular THV. PCI

was successful in all but one case. All-cause mortality trended to be higher for patients needing CA for ACS.

Conclusions. In this high-risk AS population, incidence of CA after TAVR at long-term follow-up was rather low. CA and PCI were safe and successful in most cases, with a lower rate of selective CA for supra-annular devices. Coronary access for ACS was associated with higher mortality.

INTRODUCTION

Coronary artery disease (CAD) is a frequent comorbidity among patients undergoing transcatheter aortic valve replacement (TAVR) for severe symptomatic aortic stenosis (AS), with a prevalence ranging between 60 and 80% in major high- and intermediate-risk trials[1]. The real impact of CAD on outcome after TAVR is controversial[2,3] and current guidelines recommend staged pre-TAVR revascularization of proximal severe coronary artery stenosis (Class IIa, Level of Evidence C)[4,5]. Few data exist on the incidence of coronary access (CA) after TAVR outside the peri-procedural period. In fact, previous reports focused on peri-procedural management of acute coronary obstruction during TAVR deployment[6] or on technical feasibility of PCI with a single TAVR device[7-10]. Due to the extension of TAVR indications towards patients who are younger and at lower risk[11-13] with the possibility of CAD progression, the ability to reaccess the coronary ostia for angiography and potentially to perform PCI after TAVR will become of paramount importance. With this study we aimed to characterize the incidence of CA after TAVR at long-term follow up, evaluating safety and feasibility of coronary angiography and PCI with different types of THVs.

METHODS

Study population. All patients undergoing TAVR at our Institution between June 2007 and November 2018 were considered for this study. Baseline clinical characteristics and procedural data were prospectively collected in a dedicated database. All patients underwent invasive coronary artery evaluation before TAVR. Decision to perform staged percutaneous revascularization of severe coronary lesions (defined as ≥70% stenosis in an epicardial artery, ≥50% in the left main) before TAVR was made on the basis of Heart Team consensus. In general, only severe lesions involving proximal coronary artery segments were treated. Revascularization was defined complete if all severe lesions in vessels with a diameter ≥2 mm were treated before TAVR. After PCI, patients were treated with dual antiplatelet therapy for at least 1 month after bare-metal and 6 months after drug-eluting stent implantation. Indications for TAVR, approach and type of prosthesis were decided by the local Heart Team. All patients were discharged after TAVR on aspirin plus clopidogrel for 3-6 months, followed by aspirin lifelong. Patients with an indication to anticoagulation were treated with warfarin or a novel oral anticoagulant agent plus clopidogrel for 6 months. Clinical follow-up was performed by outpatient visit or telephone interview at 1, 3, 12 months and yearly thereafter. Outcomes were defined according to the Valve Academic Research Consortium-2 criteria[14]. Informed patient consent was obtained to undergo TAVR and following diagnostic coronary angiography/PCI and for the collection and analysis of the anonymized data. The study was approved by the local ethics committee.

Coronary access. Need for CA was defined as indication to invasive evaluation of coronary artery anatomy after TAVR. Indications for CA were acute coronary syndromes, effort angina, acute heart failure and decrease in left ventricular systolic function. All patients undergoing coronary angiography and/or PCI after being treated with TAVR at our Institution were included. Procedures performed during index hospitalization because of acute TAVR complications such as coronary artery

obstruction by valve frame or leaflets were excluded. All angiographic images were independently reviewed by two experienced interventional cardiologists (L.N.F. and G.T.). If coronary intervention was not performed at our Institution, images were acquired from referring hospitals. Coronary access was defined selective if successful intubation of the coronary ostium was achieved, non-selective if the coronary artery could be displayed and adequately evaluated without full intubation, unfeasible when the coronary artery could not be displayed. Visualization of coronary arteries with aortic root angiography was considered an unsuccessful CA. PCI was defined successful when angiographic success was achieved without complications including valve dislodgment, fracture, coronary dissection or perforation. If a patient underwent multiple CA after TAVR, only the first procedure was considered.

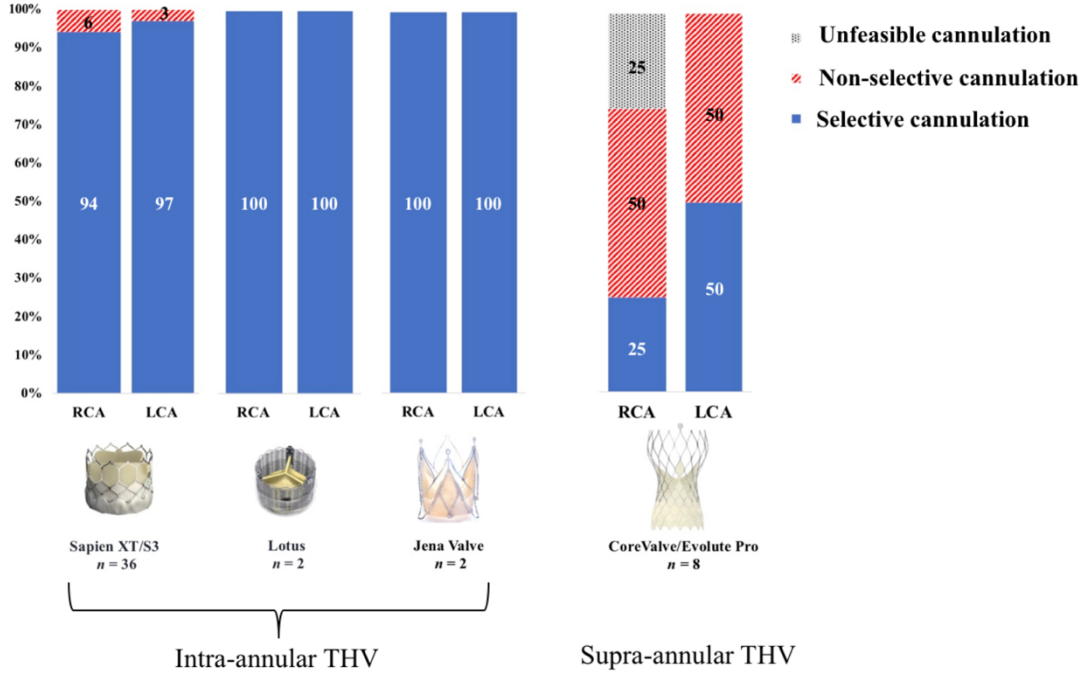
Statistical analysis. Baseline characteristics are described with mean ± standard deviation (SD) [or medians and 1st and 3rd interquartile ranges (IQRs)] for continuous variables and percentages for discrete variables. Comparisons were performed with Student's t test or Mann–Whitney or Wilcoxon tests, as appropriate. Categorical variables (as frequencies or percentage) were compared with $\chi 2$ test or the Fisher exact test. Kaplan–Meier method was used to evaluate event-free survival during follow-up and comparisons were made by log-rank test (Cox–Mantel test). The significant variables ($P<0.05$) at univariate Cox proportional hazards regression models were included in the multivariable Cox hazards regression. Statistical significance was defined by a p value of <0.05. The results of such analysis are presented as hazard ratios (HR) and 95% confidence intervals (CI). Statistical analyses were performed using SPSS 24.0.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Incidence and reasons for CA after TAVR. Out of 912 patients with a mean age of 80±7 years undergoing TAVR at our Institution, 48 (5.3%) underwent coronary angiography after a mean follow up of 1023±848 days. Of these, 26 (54%) had an

indication for PCI. Reasons for CA after TAVR were acute coronary syndrome (ACS) (35%; ST-elevation myocardial infarction in 6%), stable CAD (17%), acute heart failure (25%), worsening of left ventricular systolic function (23%). Among patients with ACS, 8 (47%) patients experienced another admission for ACS with a second CA during subsequent follow up. Coronary angiography after TAVR was performed at our Institution in 92% of cases. More than half of subjects underwent CA beyond one year after TAVR procedure (Figure 2, Panel A).

Figure 1. Histogram depicting selectivity of coronary cannulation of left and right coronary artery, according to transcatheter prosthesis type.



CA=coronary access; TAVR=transcatheter aortic valve replacement; RCA=right coronary artery; LCA=left coronary artery

Baseline characteristics of patients undergoing CA after TAVR. Clinical characteristics of patients undergoing CA after TAVR are outlined in Table 1. Compared to the rest of the population, patients with CA were more frequently male (67 vs. 44%, p=0.004), younger (mean age 75.5±8.5 vs. 80.0±6.6 years, p<0.001), with higher prevalence of dyslipidemia (73 vs. 57%, p=0.034), CAD (83 vs. 51%, p<0.001) and prior PCI (50 vs. 25%, p<0.001) or CABG (33 vs. 10%, p<0.001). Of note, among patients with CA, 29% had received incomplete revascularization before TAVR. Forty

patients (83.3%) were treated with an intra-annular THV (21 Edwards SAPIEN XT, 16 Edwards SAPIEN 3, 2 JenaValve, 2 Boston Lotus), 8 (16.7%) with a supra-annular THV (6 Medtronic Corevalve, 2 Medtronic Evolut Pro). In 2 patients CA was performed after a TAVR-in-TAVR procedure, in one case with implantation of two Corevalve prostheses, in the other of two SAPIEN XT.

Table 1. Baseline characteristics

Clinical Characteristics	**CA (48)**	**No-CA (864)**	***p-value***
Age (years)	75.5±8.5	80±6.6	**<0.001**
Male	32(67)	377(44)	**0.004**
EuroSCORE II (%)	6.3±4.5	5.7±5.9	0.486
STS (%)	8±8.3	7.7±7.4	0.601
Hypertension	42(87.5)	700(81)	0.540
Dyslipidemia	35(73)	492(57)	**0.034**
Current smoker	4(8)	33(4)	0.146
Diabetes Mellitus	15(31)	238(27.5)	0.899
Chronic Renal Failure	17(35)	345(40)	0.345
COPD	13(27)	167(19)	0.223
Porcelain Aorta	10(21)	69(8)	**0.002**
Coronary artery disease	40(83)	443(51)	**<0.001**
1 vessel	7(15)	171(20)	
2 vessels	13(27)	133(15)	
3 vessels	20(42)	139(16)	
Previous Myocardial Infarction	12(25)	133(15)	0.093
Previous PCI	24(50)	218(25)	**<0.001**
Previous CABG	16(33)	88(10)	**<0.001**
Complete revascularization	35(73)	629(73)	0.986
Previous Stroke	2(4)	49(6)	0.618
Congestive Heart Failure	21(44)	309(36)	0.660
Syncope	6(12.5)	104(12)	0.996
LV-EF (%)	53.5±11	55±12	0.401
Atrial Fibrillation	9(19)	275(32)	0.051
Pacemaker	4(8)	72(8)	0.952

STS=Society of Thoraci Surgery Score; COPD= chronic obstructive pulmonary disease; PCI= percutaneous coronary intervention; CABG=coronary artery bypass grafting; LVEF=left ventricular ejection fraction.

As shown in Table 2, at multivariate analysis younger age (HR 0.93 [0.90-0.96], p<0.001), previous PCI (HR 1.69 [1.26-2.28], p=0.001) and previous CABG (HR 2.53 [1.35-4.74], p=0.004) were found to be independently associated with the need for CA after TAVR.

Table 2. Multivariate analysis on coronary access after TAVR

	Cox regression adjusted HR (95% CI)	**p value**
Age	0.93 (0.90-0.96)	<0.001
Male	1.74 (0.92-3.28)	0.091
Previous PCI	1.69 (1.26-2.28)	0.001
Previous CABG	2.53 (1.35-4.74)	0.004

PCI= percutaneous coronary intervention; CABG=coronary artery bypass grafting

Procedural characteristics of CA after TAVR. Angiographic characteristics and procedural details of CA procedures are depicted in Table 3. Left coronary artery (LCA) was selectively cannulated in 90% of cases (97.5% of intra-annular and 50% of supra-annular devices); in the remaining subjects, the coronary vessel was displayed non-selectively (Figure 1). Right coronary artery (RCA) was selectively cannulated in 83% of patients (95% of intra-annular, 25% of supra-annular devices). With the exception of two patients with a supra-annular device for whom CA was unfeasible, in all other subjects a non-selective evaluation was possible. A mean of 1.2±0.2 catheters was necessary to selectively cannulate the LCA, a mean of 1.8±0.7 for the RCA, with the most frequent successful being Judkins left 4 (73%) and Judkins right 4 (83%) (Cordis Corporation, Freemont, CA, USA). Forty-two percent of procedures were conducted with a radial approach. When indicated, PCI was successfully performed in all but one case. The most frequently treated vessels were left anterior descending artery (n=11), followed by left main (n=9), RCA (n=4) and left circumflex artery (n=4). Nineteen (39.5%) lesions involved coronary ostium, 15 (31%) a bifurcation. In all but one patient at least one bare metal or drug-eluting stent was implanted (mean stent per patient 1.25±0.8). PCI was performed for restenosis of a previously implanted stent in 7 (27%) cases, for de novo lesions in 73% of patients.

PCI was not feasible in one patient previously treated with TAVR-in-TAVR with two Corevalve prostheses for device malpositioning, who finally underwent coronary artery bypass grafting. All other PCI were performed without complications. In fact, no case of coronary dissection, valve frame rupture or dislodgment, catheter/wire entrapment nor coronary stent dislodgement was recorded in our series.

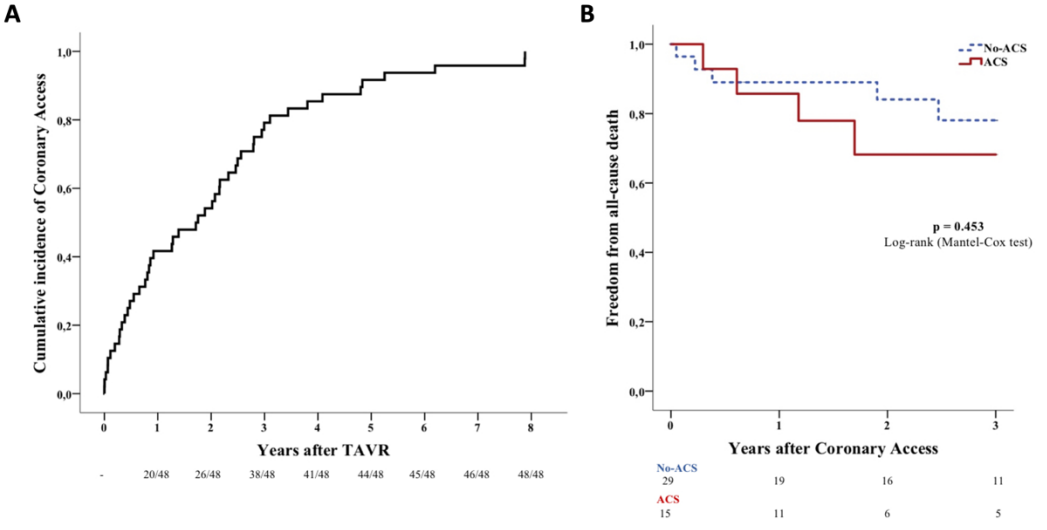
Table 3. Procedural characteristics

Coronary Angiography	**48**	**Percutaneous Coronary Intervention**	**26 (54)**
Days to CA after TAVR	748±719	Number of lesions treated	
Reason for coronary reaccess		1 lesion	16(61.5)
STEMI	3(6)	2 lesions	8(31)
NSTEMI / UA	14(29)	3 lesions	2(8)
SCAD	8(17)	Vessel treated	
Heart Failure	12(25)	LM	9 (35)
Worsening of LVEF	11(23)	LAD	11 (42)
Valve type		LCx	4 (15)
Edwards	36	RCA	4 (15)
Medtronic	8	Bypass graft	-
Lotus	2	Revascularization strategy	
Jena Valve	2	Plain Old Balloon Angioplasty	1(4)
TAVR in TAVR	2(4)	Stent implantation	24(92)
Access site		Coronary artery bypass grafting	1(4)
Radial	25(52)	De novo lesions	19(73)
Femoral	23(48)	In stent-restenosis	7(27)
Vessel diseased		Stent-thrombosis	0
0 vessel	10(21)	Guidewires	1.45±0.5
1 vessel	11(23)	Number of stents implanted	
2 vessel	8(17)	1 stent	13(50)
3 vessel	19(39.5)	2 stents	8(31)
Chronic Total Occlusion	10(21)	3 stents	2(8)
Ostial lesions	19(39.5)	4 stents	1(4)
Bifurcation lesions	15(31)	Total stents lenght, mm	31±20
LCA selective cannulation	43(90)	Type of stent used	
Intra-annular devices	39(97.5)	BMS	6
Supra-annular devices	4(50)	DES	33

RCA selective cannulation	40(83)	Microcatheter	-
Intra-annular devices	38(95)	Selective injection achieved	23(88)
Supra-annular devices	2(25)	Intracoronary evaluation	
Number of used catheters for LCA	1.2±0.2	iFR / FFR	1(2)
Number of used catheters for RCA	1.8±0.7	IVUS	3(6)
Successful catheter for LCA		Procedural duration, min	52±24
JL4	35(73)	Fluoroscopy time, min	17±10
XB 3.5 or 4	12(25)	Contrast amount, ml	202±99
AR1LBT	1(2)	Procedural success	25(96)
Successful catheter for RCA		Intraprocedural complications	0
JR4	40(83)	Coronary dissection/perforation	-
AL1 or 2	6(12.5)	Prosthesis rupture/dislodgment	-

CA=coronary access; TAVR=transcatheter aortic valve replacement; STEMI=ST elevation myocardial infarction; NSTEMI=non ST elevation myocardial infarction; UA=unstable angina; SCAD=stable coronary artery disease; LM=left main; LAD=left anterior descending artery; LCx=left circumflex; RCA=right coronary artery; JL=Judkins left; AR=Amplatz right; XB=extra backup; AL1=Amplatz left 1; BMS bare metal stent; DES=drug eluting stent; iFR=instantaneous wave free ratio; FFR=fractional flow reserve; IVUS=intravascular ultrasound

Figure 2. Panel A) Time to CA after TAVR. Panel B) Kaplan-Meier estimated for all-cause mortality post-CA after TAVR because of acute coronary syndrome (red, continuous line) vs. other clinical indications (blue, dotted line).



CA= coronary access; TAVR=transcatheter aortic valve replacement;

Outcomes of patients undergoing CA. In hospital mortality after CA was 2%. As shown by Kaplan Meier curves (Figure 2, Panel B), patients undergoing CA for ACS

trended to have higher all-cause mortality as compared to patients needing CA for other reasons (p=0.453).

DISCUSSION

The main findings of this study, the first to focus on CA after TAVR outside the peri-procedural period, are as follows: 1) In this high-risk population, the incidence of CA at long-term follow up was rather low. 2) Coronary access was safe and feasible in all cases with different types of THVs. However, selective cannulation was more frequently achieved with intra-annular than with supra-annular devices. 3) PCI was successfully performed in all cases except in one patient after TAVR-in-TAVR with two supra-annular THVs. 4) All-cause mortality was higher for patients undergoing CA for ACS.

TAVR is rapidly becoming the treatment of choice for severe AS not only in high but also in intermediate and low risk patients[11]. The optimal treatment of concomitant CAD, a frequent finding among AS patients, is still a matter of debate. In fact, two recent meta-analyses have shown contradictory results about the impact of CAD on clinical outcomes after TAVR[2,3]. To date very few data exist on the real incidence of CA after TAVR (both for ACS and other clinical indications), particularly at long-term follow up. In our population, the need for CA after TAVR outside the peri-procedural period at a mean follow up of about 3 years was 5.3%. Differently from previous reports, we collected information about CA also from referring hospitals, thereby minimizing the risk of underreporting. The low incidence of CA after TAVR may have two possible explanations. Firstly, a Heart team based pre-TAVR revascularization approach of proximal severe coronary stenoses seems effective in reducing future coronary events[15]. In fact, the proportion of patients with incomplete revascularization was identical in patients with and without CA (27 vs. 27%, p=0.986). Secondly, we cannot exclude that the multiple comorbidities of our patients influenced the rate of invasive strategy in the management of ACS. In fact, about 30%

of patients with an ACS in our TAVR population did not undergo coronary angiography, consistently with a recent report by Vilalta et al[16]. Our low rate of CA access after TAVR should not be generalized to younger subjects with longer life expectancy. In fact, as TAVR indication shifts towards lower risk and possibly even to asymptomatic patients [11,17,18], the need for CA and potentially PCI after TAVR is expected to increase, giving the progressive nature of CAD. To this regard, it should be noted that just 27% of PCI after TAVR in our population were due to in-stent restenosis, while over 73% were performed for de novo lesions and therefore secondary to disease progression.

Increasing interest exists on potential challenges in CA for patients needing coronary angiography or intervention after TAVR. In fact, unlike for surgical aortic valve replacement, where the prosthesis is sutured under direct vision in order to match the prosthesis to the native aortic valve commissures, during TAVR valve orientation is random and therefore a commissural post can end up directly in front of the coronary ostium, making CA difficult[19,20]. Few experiences on the feasibility of coronary angiography and/or PCI after TAVR have revealed mixed results, with challenges reported primarily with the self-expanding supra-annular THVs[8,21,22]. In our study, CA of both coronary vessels was possible in all cases with an intra-annular THV. These findings can be explained by the design of both types of valves. In fact, while JenaValve has a self-orientating implantation mechanism that allows the neo-commissures to rest away from the coronary ostia, Lotus, SAPIEN XT and SAPIEN 3 have a low frame height, which allowed easy CA from above the prosthesis in 95% of our patients. In two patients with a narrow sino-tubular junction treated with a SAPIEN 3 valve, CA was gained through the open cells in the upper part of the frame. This is important in perspective for TAVR-in-TAVR procedures, which will be feasible only if CA after the first TAVR can be gained from above the stent frame[23]. With supra-annular devices (CoreValve and Evolut Pro), selective coronary cannulation was possible in 50% of cases for LCA and only 25% for RCA. Self-expandable prostheses of

the Corevalve family extend over the coronary ostia so that CA is possible only through the diamond-shaped cells of the frame. However, commissural posts are 26 mm high and selective CA can be challenging if they are in overlap with a coronary ostium, particularly in case of high THV implantation[21,24,25]. The lower success rate in CA of the RCA with self-expandable THVs in our study could be partially explained by the fact that both patients in whom RCA cannulation was unfeasible had the LCA as culprit vessel. Therefore, the operator could have been less interested in gaining full information about the other coronary artery. To this regard, no additional supporting guidewire nor microcatheter was used by to achieve selective cannulation.

PCI was feasible in all but one case (a patient with prior TAVR-in-TAVR procedure with two Corevalve prostheses, as previously described) and was successfully performed in an emergency setting in 35% of patients. Of note, over 90% of cases were performed at our Institution by experienced operators familiar with TAVR procedure and therefore with the design of different THVs. Accordingly, these high rates of successful CA and PCI after TAVR might not be reproducible by non-structural interventionalists.

Finally, our results are reassuring in terms of the safety of CA and PCI after TAVR, as we did not experience any procedural complication. As shown by our results, the relevant all-cause mortality after CA seems not related to CA itself, but rather to the underlying reason for coronary angiography/PCI. In fact, our data confirm previous findings[16] reporting high mortality for patients experiencing an ACS after TAVR.

We should acknowledge that our study (as those previously published) was not powered to detect statistically significant differences in CA among different types of THVs, and therefore – in the absence of randomized trials - our findings should be considered hypothesis-generating only. However, our results are consistent with previous reports in the literature[10,22,26] and confirm greater challenges in CA with self-expandable supra-annular devices, particularly for RCA. Accordingly, these aspects

should be taken into account for device selection in younger patients with concomitant CAD and high likelihood of future coronary events. Future device iterations should take into account the need for CA, perhaps allowing the operator to orientate the valve so to avoid neo-commissures to be placed in front of the coronary ostium.

LIMITATIONS

The present work has the inherent limitations of an observational single-center study. Despite being a retrospective analysis, data of all consecutive patients undergoing TAVR at our institution are prospectively inserted in a dedicated database. Furthermore, adverse events were not adjudicated by an independent clinical event committee. Given the high baseline surgical risk of the study population, our results should not be extended to lower-risk, younger TAVR subjects. Moreover, our low incidence of CA may not reflect the findings of other institutions with different pre-TAVR revascularization strategies. Finally, considering the low number of patients undergoing CA, our study was not powered detect statistically significant differences among different prosthesis types in terms of selective CA.

CONCLUSIONS

In this retrospective single-center study, long-term incidence of CA after TAVR in a high-risk population was low. Diagnostic coronary angiography and PCI after TAVR were safe and successful in all patients with an intra-annular and in most subjects with a supra-annular THV. Patients undergoing CA for ACS had higher all-cause mortality. Further studies are needed to confirm these findings in younger and lower risk patients.

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3. CORONARY ACCESS AFTER TAVR IN BICUSPID AORTIC VALVE

"Coronary access after transcatheter aortic valve replacement in patients with bicuspid aortic valve: lights and shades"

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JACC Cardiovascular Interventions. 2019 Jun 24;12(12):1190-1191

Given the progressive nature of coronary artery disease, coronary access (CA) after transcatheter aortic valve replacement (TAVR) will become increasingly common as we move towards younger patients. In parallel, the prevalence of bicuspid aortic valve (BAV) in TAVR patients is expected to rise (1). Accordingly, CA in patients treated with TAVR in the setting of BAV will be frequently encountered in the future. An extensive knowledge of BAV-related anatomy and transcatheter heart valves (THV) design is essential to predict the geometric interaction between THV, native aortic valve leaflets and coronary ostia.

Three BAV morphologies have been identified (2): tri-commissural (also called "functional or acquired" BAV), bi-commissural raphe and non-raphe type. The importance of this classification lies in the different resistance opposed by the raphe to THV expansion, being higher in bi-commissural than in tri-commissural BAV (and than in tricuspid aortic valves). If, as in the majority of cases, the raphe is located between left and right coronary cusps, the asymmetrical prosthesis expansion generates a free space between valve frame and coronary ostia, which simplifies CA (Figure). Other potentially favorable BAV-related anatomical characteristics for CA post-TAVR are the wider sinuses of Valsalva and sino-tubular junction.

On the contrary, the higher prosthesis implantation in the setting of BAV represents a technical challenge to CA, especially in the presence of low coronary take-off. In fact, at least for bi-commissural BAV with raphe, THV sizing and positioning should be aimed at the raphe level rather than at the virtual basal ring. Balloon-expandable

valves (Edwards Sapien XT and Sapien 3) have an intra-annular/sub-coronary design and a lower frame height, which may allow for easier CA from above the prosthesis or through the open cells in the upper part of the frame. In no case CA will be feasible through the sealing skirt. Self-expanding valves of the CoreValve series have a supra-annular/supra-coronary design and extend beyond the coronary ostia jailing the coronary sinuses, but have a constrained central portion, which allows CA through the valve frame cells. Importantly, commissural posts are twice as high as the sealing skirt. This aspect has to be taken into account in the setting of a high TAVR implant, as in BAV. In fact, unlike for surgical aortic valve replacement, during TAVR valve orientation is random, and therefore a commissural post can end up directly in front of coronary ostium, making co-axial and co-aligned CA challenging. The self-expanding ACURATE Neo valve, despite having a supra-annular design, carries a “free access” architecture to the coronary ostia, with very high commissure posts and a lower sealing skirt profile. In conclusion, CA after TAVR in BAV carries potential advantages (such as larger free space in front of the coronary ostia in case of asymmetrical prosthesis expansion), but also pitfalls (mostly related to higher THV implantation) compared to TAVR in tricuspid aortic valve. As we start treating younger patients, this aspect should guide current choice of prosthesis and design of next generation THVs, also with the perspective of future need for valve-in-valve procedure.

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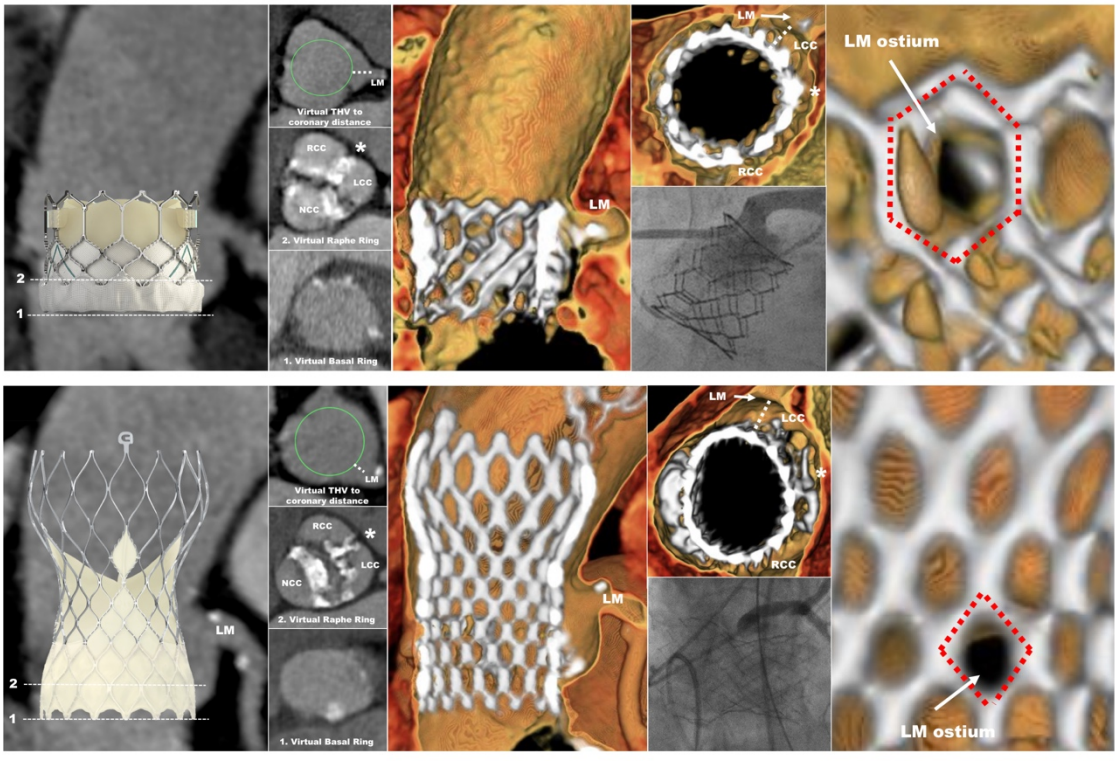
*Figure. Pre- and post-TAVR computed tomography imaging in two patients with severe bi-commissural raphe type bicuspid aortic valve stenosis treated with balloon-expandable (upper panel) and self-expanding (lower panel) transcatheter heart valve (THV). Note the distance between the asymmetrically expanded prosthesis and the coronary ostium (dashed line) and high implant of both THVs. * indicates the position of the raphe.*



LM: left main; RCC: right coronary cusp; LCC: left coronary cusp; NCC: non-coronary cusp.

4. FUTURE CHALLENGES: CORONARY ACCESS AFTER TAVR-IN-TAVR

"TAVR-in-TAVR and coronary access: the importance of pre-procedural planning"

A novel algorithm to predict feasibility of coronary access after redo-TAVR

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Manuscript currently under review

Transcatheter heart valve (THV) degeneration will be increasingly common with the expansion of transcatheter aortic valve replacement (TAVR) indication to low-risk younger subjects with longer life-expectancy(1-6). Treatment of structural THV degeneration with the implantation of a second THV is feasible(7), but data on this subject are scant. In particular, there are concerns about the risk of coronary artery obstruction and the possibility to access the coronary ostia in case percutaneous coronary artery intervention will be needed in the future(8).

Factors that influence coronary access after TAVR are both device-related, such as implantation depth, sealing skirt height and orientation of commissural tabs, and patient-related, such as coronary height, height and width of sinus of Valsalva and sino-tubular junction (STJ)(9,10). Accordingly, it is crucial to understand the 3-dimensional interaction among the degenerated THV, the coronary ostia and the aortic root to guide pre-procedural planning of TAVR-in-TAVR with the aim to minimize the risk of acute coronary artery occlusion and preserve future coronary access. In fact, the implantation of a second THV will tilt up the leaflets of the previously implanted device, thereby creating a covered cylindric stent tall as the commissural posts. We define *risk plane* (RP) the level under which the passage of a coronary catheter will be impossible after the second THV is implanted (Supplementary Figure). The current viewpoint aims to offer a pragmatic, computed tomography (CT) and coronary angiography-based approach for the prediction of acute coronary occlusion and feasibility of future coronary access after TAVR-in-

TAVR. We will primarily focus on Sapien XT/3 (Edwards Lifesciences, Irvine, California) and Evolut R/Pro (Medtronic, Galway, Ireland) THVs, the most widely used THVs for which the need for TAVR-in-TAVR is more likely in the years to come.

DEGENERATION OF INTRA-ANNULAR BALLOON-EXPANDABLE THV

Balloon-expandable (BE) prostheses Sapien XT and Sapien 3 (Edwards Lifesciences, Irvine, California) have an intra-annular design, low frame profile (frame height 14-19 mm for the Sapien XT, 15.5-22.5 mm for the Sapien 3) and an upper row of open cells (with a diameter of 4.4-6.8 mm in the Sapien 3, approximately 40% smaller in the Sapien XT). Commissural tabs and leaflet attachment are located in 3 of these 12 open cells. Therefore, the RP for Sapien XT and Sapien 3 THVs is located approximately 1 mm below the upper margin of the valve frame.

When planning the implantation of a second THV for the treatment of a failing BE prosthesis, it is important to assess by CT the relationship between RP and coronary ostia. Then, by attempting selective coronary angiography, it is crucial to understand how the coronaries can be cannulated with the first THV in place (Figure 1).

1) **Coronary ostia *above* the risk plane (Type 1).**

   When the RP lays below the coronary ostia, either because of high coronary origin or low THV implantation, coronary access can be gained from above the RP. In this case, TAVR-in-TAVR with a second intra-annular THV (avoiding high implantation) will not impede subsequent coronary cannulation. Implantation of a self-expandable (SE) supra-annular Medtronic Evolut R/Pro inside the first THV is also possible.

2) **Coronary ostia *below* the risk plane (Type 2)**

   When the coronary ostia are low or the first THV is implanted high, the origin of one or both coronaries will be below the RP. In this situation, CT analysis is

important to assess the valve-to-aorta distance (VTA), defined as the distance between the prosthesis frame at the level of the RP and the aortic wall. A free space of >2mm is necessary to navigate a 6 French catheter behind the prosthesis struts and engage the coronary ostium(11). Coronary angiography after index TAVR will characterize how coronary access can be achieved. Accordingly, we can single out two different scenarios.

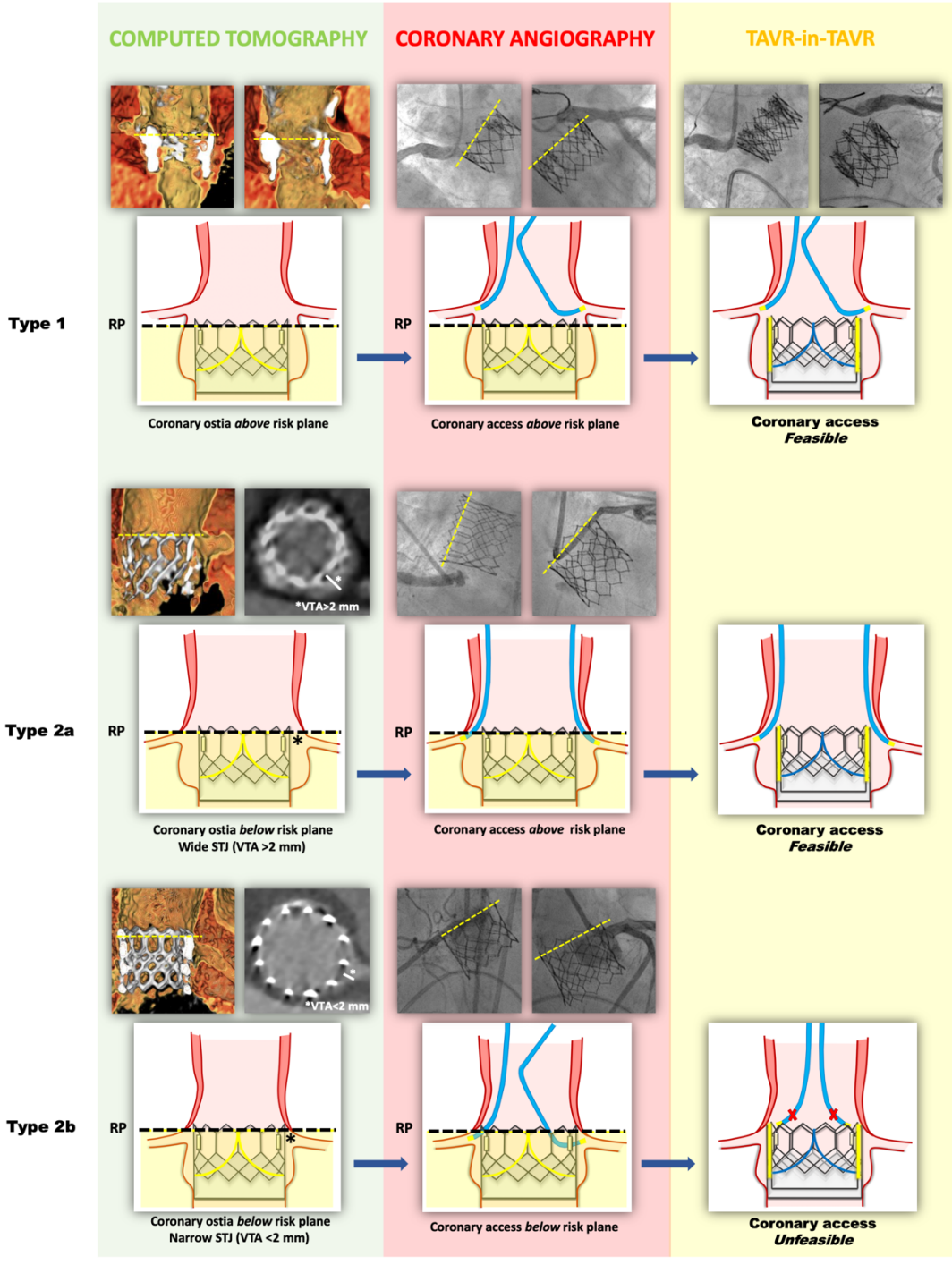
a) Coronary access from *above* the risk plane (Type 2a)

In patients with wide STJ and a CT-assessed VTA >2 mm, coronary access from above the RP outside the valve frame needs to be confirmed by selective coronary angiography. In this case, TAVR-in-TAVR with a second BE device is feasible, but excessive oversizing and post-dilation should be avoided in order not to flare the superior part of the THV and preserve the VTA. The use of a SE device with taller commissural posts for TAVR-in-TAVR is also possible, but coronary cannulation might be more challenging because of the closed cell design and the possibility to place a no-commissure in front of the coronary.

b) Coronary access from *below* the risk plane (Type 2b)

If the STJ is narrow and VTA is <2 mm, coronary cannulation will be possible only through the upper row cells of the THV frame. Since the leaflets of the first BE THV will form a cylinder when tilted up by the new BE or SE THV, coronary access after TAVR-in-TAVR will be unfeasible with the risk of coronary occlusion. According to a recent study based on aortic angiogram after TAVR, this unfavorable anatomical scenario could be found in up to 20% of patients treated with a Sapien 3 THV(11). However, considering that coronary cannulation was not attempted, we cannot exclude over- or underestimation of this situation.

Figure 1. TAVR-in-TAVR for a degenerated BE prosthesis.



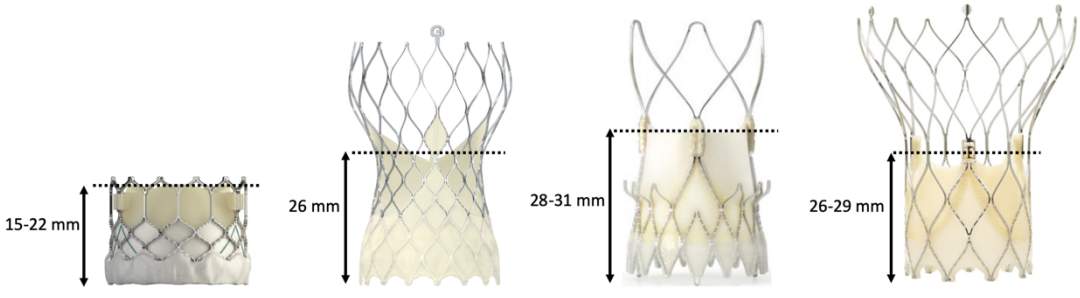
TAVR=transcatheter aortic valve replacement; CT=computed tomography; BE=balloon-expandable; RP=risk plane; VTA=valve-to-aorta distance; STJ=sino-tubular junction

DEGENERATION OF SUPRA-ANNULAR SELF-EXPANDABLE EVOLUT R/PRO THV

Self-expandable (SE) Evolut R and Pro devices (Medtronic, Galway, Ireland) have a supra-annular design, a taller frame (45-46 mm) and a commissure height of 26 mm. The risk of coronary obstruction with this type of prosthesis is minimized by their narrow waist and the possibility to be recaptured after partial deployment in case of coronary flow impairment. To cannulate the coronary, a catheter needs to pass through one of the diamond-shaped cells of the stent frame.

As for BE devices, pre-procedural planning of TAVR-in-TAVR with SE Evolut R/Pro THV should include both CT evaluation and selective coronary angiography. Given commissural post height, the RP of supra-annular Evolut R/Pro devices will be considerably higher compared to BE intra-annular THVs. In the current review we will not discuss other SE supra-annular devices without FDA approval, such as Acurate Neo THV (Boston Scientifics, USA), which have even higher commissural posts (28-31 mm) and, consequently, taller RP. Moreover, we will not focus on self-expandable intra-annular devices such as Portico (Abbott, USA), for which the RP is located 26 to 29 mm from the lower edge of the frame (*Supplemental Figure*).

Supplementary Figure. Risk plane of Sapien 3 (Edwards Lifesciences), Evolut Pro (Medtronic), Acurate Neo (Boston Scientifics) and Portico (Abbott) THVs.



1) **Coronary ostia *above* the risk plane (Type 1).**

This situation is extremely uncommon with correctly implanted supra-annular devices. In fact, Evolut R/Pro THV have 26 mm high commissures, that invariably expand above the coronary ostia. Accordingly, the RP is almost always above the coronaries, and coronary access from above the RP is feasible just in anecdotical cases with very high coronary origin or inappropriately low THV implantation. Even though TAVR-in-TAVR with a second Evolut R/Pro device is feasible, selective coronary engagement will be very challenging or impossible. In fact, given the impossibility to precisely orientate the THV during implantation, the two stent layers above the RP might overlap leaving insufficient room to permit the passage of a coronary catheter. The use of a self-expanding intra-annular device such as Portico (Abbott, USA – not FDA approved) would lead to a similar situation. On the contrary, implantation of a SE supra-annular Acurate Neo THV with its open cell architecture in the upper part of the frame would reduce the risk of struts overlap. To note, TAVR-in-TAVR with a low implanted lower-frame intra-annular BE device might not achieve complete vertical displacement of the degenerated leaflets of the first supra-annular SE device.

2) **Coronary ostia *below* the risk plane (Type 2) (Figure 2)**

This scenario is by far the most common with supra-annular SE devices. Once again, it is crucial to measure by CT the VTA at the RP and to evaluate by coronary angiography how coronary access is gained with respect to RP.

a) Coronary access from *above* the risk plane (Type 2a)

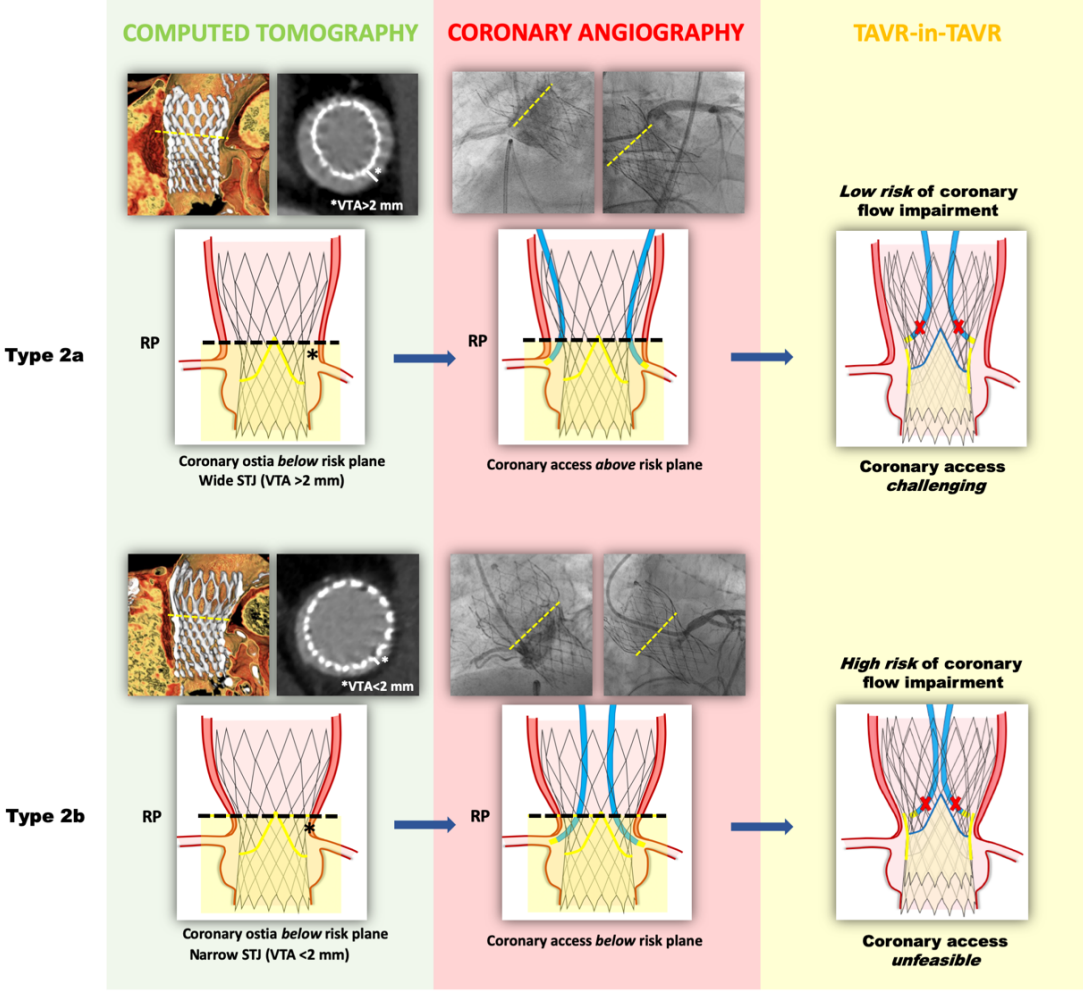
Coronary access from above the RP, although potentially challenging, is feasible only if the VTA is >2mm. In this situation, TAVR-in-TAVR is possible with the same caveats of the aforementioned Type 1 scenario.

b) Coronary access from *below* the risk plane (Type 2b)

In patients with narrow STJ, the VTA at RP might be <2mm. Accordingly, coronary cannulation is possible just through a cell located below the RP. When

the leaflets of the first SE THV are tilted up after the implantation of the second prosthesis, there will be a 26 mm tall barrier in front of the coronary ostia. Subsequent coronary access will be impossible and TAVR-in-TAVR will likely cause coronary artery obstruction, regardless of the type of prosthesis used.

Figure 2. TAVR-in-TAVR for supra-annular SE prosthesis degeneration. Given the high position of valve leaflets, coronary ostia will be almost always under the RP (Type 2).

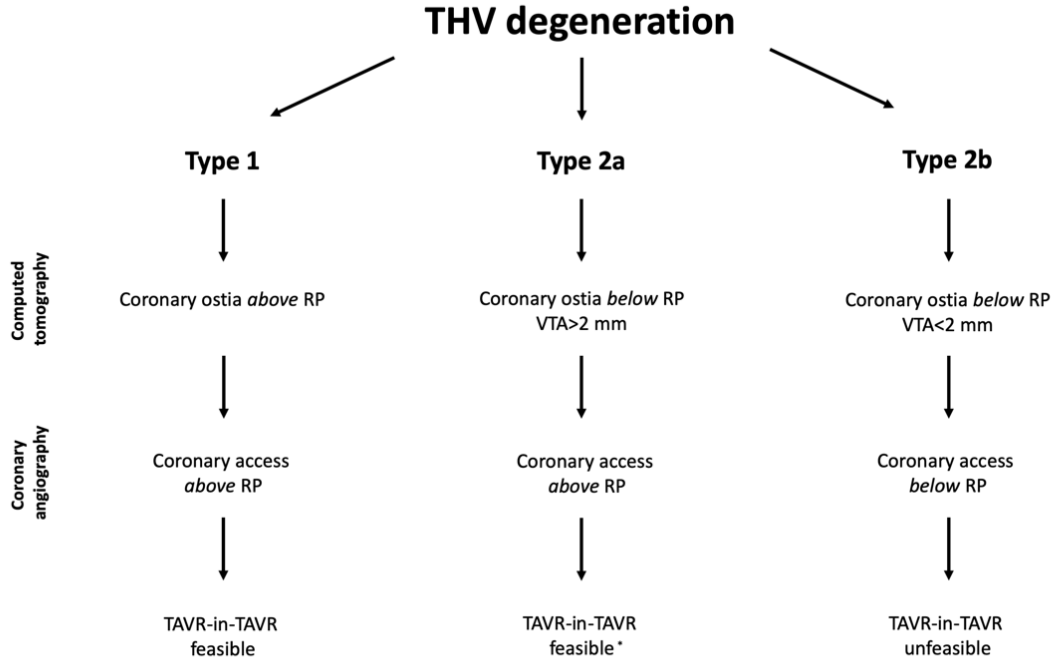


TAVR=transcatheter aortic valve replacement; SE=self-expandable; RP=risk plane; VTA=valve-to-aorta distance; STJ=sino-tubular junction

Percutaneous treatment of a failing THV poses challenges in terms of preventing acute coronary obstruction and preserving future coronary access. Unlike TAVR in surgical aortic valves, novel leaflet splitting techniques such as BASILICA may be less effective when THV neo-commissures are not aligned to those of the native aortic

valve. In our opinion, CT analysis and coronary angiography are important and complementary for a correct pre-procedural planning of the procedure (Central Figure). Coronary access after TAVR-in-TAVR will be feasible with type 1 (coronary ostia and coronary access above the RP) and type 2a scenarios (coronary ostia below the RP, VTA >2mm, coronary access above the RP). On the contrary, in patients with type 2b (coronary ostia and coronary access below the RP, VTA<2mm) TAVR-in-TAVR will carry high risk of coronary artery obstruction. Given their different design and their higher risk plane, supra-annular devices are more likely to impede coronary access after TAVR-in-TAVR.

Central Figure. Pre-procedural algorithm including computed tomography and coronary angiography assessment for evaluation of feasibility of coronary access after TAVR-in-TAVR.



**coronary access challenging if TAVR-in-TAVR with two Evolut R/Pro devices.*

These aspects should be considered when selecting the THV to implant in younger patients with longer life expectancy who are likely to need TAVR-in-TAVR in the future. Further studies are needed to assess the prevalence of these different

scenarios in the contemporary TAVR population and therefore to predict the percentage of patients potentially suitable (and unsuitable) for TAVR-in-TAVR.

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5. FEASIBILIY OF CORONARY ACCESS AFTER TAVR-in-TAVR

"Coronary angiography after TAVR to evaluate the risk of coronary access impairment after TAVR-in-TAVR"

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Manuscript currently under review

ABSTRACT

Background. TAVR-in-TAVR is a possible treatment for transcatheter heart valve (THV) degeneration. However, the displaced leaflets of the first THV will create a risk plane (RP) under which the passage of a coronary catheter will be impossible.

Objectives. To evaluate potential risk of impaired coronary access (CA) after TAVR-in-TAVR.

Methods. We prospectively performed coronary angiography after TAVR in 137 consecutive patients, looking where the catheter crossed the valve frame. If coronary cannulation was achieved from below the RP, the distance between valve frame and aortic wall (VTA) was measured by aortic angiography. CA after TAVR-in-TAVR was defined feasible if the catheter passed above RP, theoretically feasible if under RP with VTA>2mm, unfeasible if under RP with VTA≤2mm.

Results. Seventy-two (53%) patients received SAPIEN 3, 26 (19%) Evolut Pro/R, 39 (28%) Acurate Neo THV. CA after TAVR-in-TAVR was considered feasible in 40.9% (68.1 vs. 19.2 vs. 5.1%, p<0.001), theoretically feasible in 27.7% (8.3 vs. 42.3 vs. 53.8%, p<0.001), unfeasible in 31.4% (23.6 vs. 38.5 vs. 41.1%, p=0.116). Independent predictors of impaired CA after TAVR-in-TAVR were female gender (OR 3.99, 95% CI

1.07-14.86, p=0.040), sino-tubular junction (STJ) diameter (OR 0.62, 95% CI 0.48-0.80, p<0.001) and implantation of a supra-annular THV (OR 6.61, 95% CI 1.98-22.03, p=0.002).

Conclusions. CA after TAVR-in-TAVR might be unfeasible in over 30% of patients currently treated with TAVR. Subjects with small STJ and those who received a supra-annular THV are at highest risk of potential CA impairment with TAVR-in-TAVR.

INTRODUCTION

As transcatheter aortic valve replacement (TAVR) indication is moving towards younger patients with longer life expectancy(1-5), transcatheter aortic valve (THV) degeneration will be increasingly common. In this setting, TAVR-in-TAVR seems an appealing alternative to conventional surgery, although data are scant. Concerns have been raised about the risk of acute coronary obstruction and the possibility to re-access the coronaries once the second prosthesis is in place(6,7). In fact, when the second THV is implanted, the leaflets of the first prosthesis are displaced vertically, creating a cylindric cage which will impair coronary cannulation and possibly coronary flow. Accordingly, it is possible to identify a risk plane (RP) under which the first valve frame will not be crossable after TAVR-in-TAVR.

With the present study we prospectively performed coronary angiography after TAVR with different types of devices, aiming to evaluate the risk of possible coronary access (CA) impairment after the implantation of a second THV.

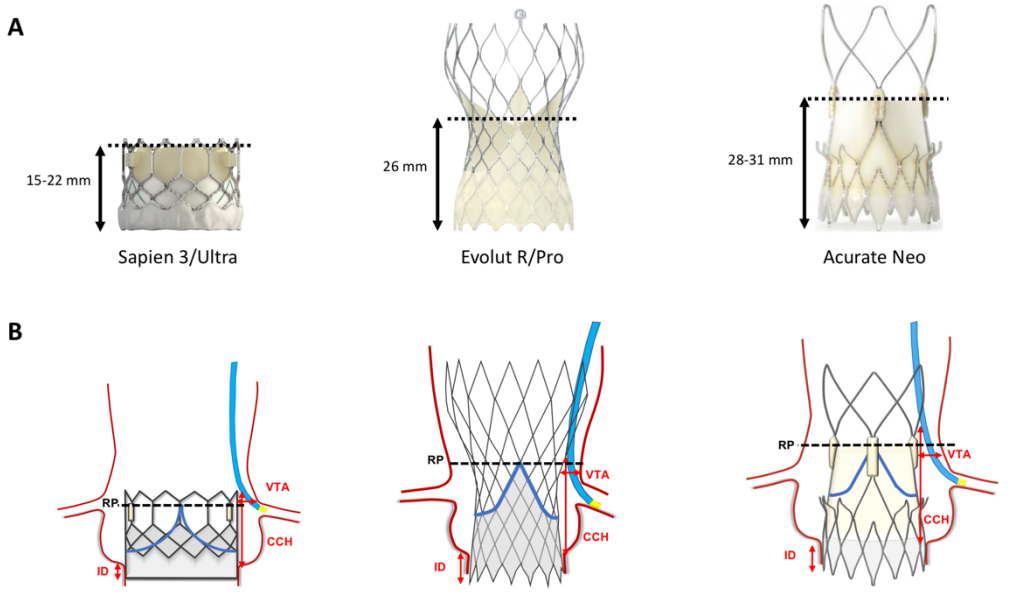
METHODS

Study population. Patients undergoing TAVR for severe symptomatic aortic stenosis at our center from November 2018 to August 2019 were considered for this study. Selective cannulation of both right (RCA) and left coronary artery (RCA) was attempted directly after THV implantation. Patients treated for surgical aortic

bioprosthesis degeneration (i.e. valve-in-valve) and those without device success defined according to VARC-2 criteria(8) were excluded. Indications for TAVR, approach and prosthesis choice were based on Heart Team decision. All patients underwent coronary angiography and multidetector computed tomography evaluation prior TAVR. All subjects gave their informed consent for both for TAVR and coronary angiography.

Risk plane of different THVs. Transcatheter heart valves used were intra-annular Sapien 3 and Ultra (Edwards Lifesciences, USA), supra-annular Evolut R and Pro (Medtronic, Ireland) and Acurate Neo (Boston Scientifics, USA). The RP was defined, according to manufacturer's instruction, as the level under which the stent frame of the first THV would be covered after its leaflets are displaced vertically with the implantation of a second TAVR device (Figure 1, Panel A)(9,10).

Figure 1. A) Risk plane level for Sapien 3/Ultra (Edwards Lifesciences), Evolut R/Pro (Medtronic) and Acurate Neo (Boston Scientifics) THVs. B) Angiographically acquired measurements with the first THV in place.



TAVR=transcatheter aortic valve replacement; CCH=coronary cannulation height; RP=risk plane; VTA=valve-to-aorta distance; ID=implantation depth

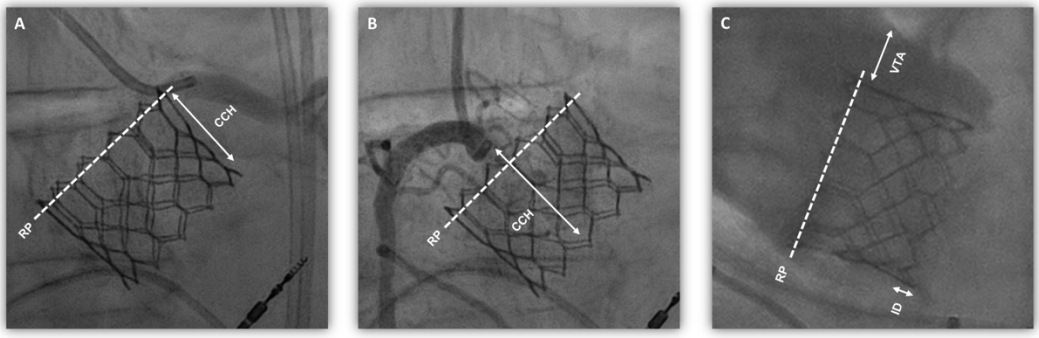
Intra-annular balloon-expandable Edwards Sapien 3 and Ultra have a low frame height (15.5-22.5 mm, according to valve size) and an upper row of open cells, where commissural posts are located. Accordingly, the RP is found approximately 1 mm below the upper part of the prosthesis frame.

Supra-annular self-expanding Evolut R and Pro's frame extends beyond the coronary ostia jailing the coronary sinuses, and has a constrained central portion. Coronary access (CA) is possible through the prosthesis frame cells. Importantly, the height of commissural posts, and therefore of the RP, is 26 mm from the bottom part of the THV.

Supra-annular self-expanding Acurate Neo valve has a commissural post height (and therefore a RP) of 28-31 mm according to valve size, but carries an open cell architecture in the upper part of the frame which allows easier access to the coronary ostia.

Coronary access after TAVR. Coronary angiography after TAVR was performed in all cases through the transfemoral approach. A first attempt was made to cannulate the coronaries from above the RP with standard diagnostic catheters (Judkins Right and Left – Cordis, USA). If cannulation from above the RP was unsuccessful, CA was attempted from below the RP (with the same catheter or with an Amplatz Left/Right diagnostic catheter or an Extra backup guiding catheter, if coronary cannulation with a standard diagnostic catheter was impossible). CA was defined selective if successful intubation of the coronary ostium was achieved, non-selective if the coronary artery could be displayed and adequately evaluated without full intubation, unfeasible when the coronary artery could not be displayed. All angiographic images were independently reviewed by two experienced interventional cardiologists (L.N.F. and G.T.).

Supplementary Figure. Dedicated angiographic views for LCA, RCA and aortogram measurements, optimized to eliminate valve frame parallax. Similar views were obtained for all types of THV.

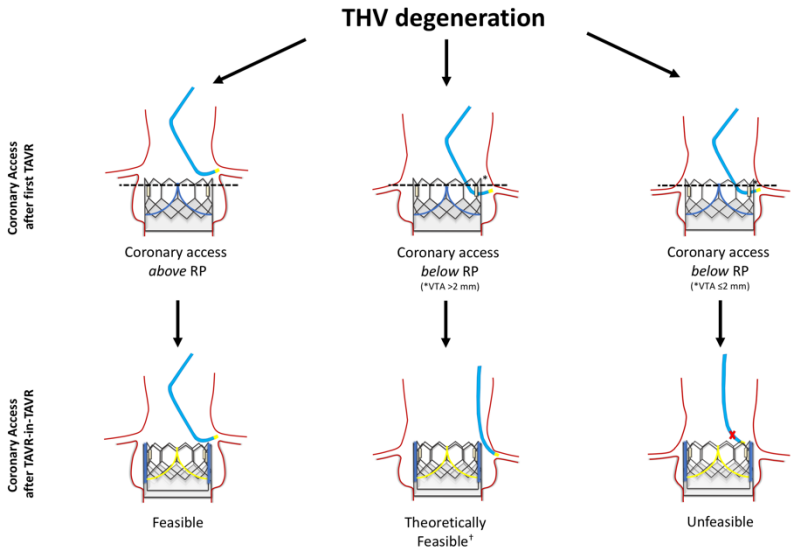


LCA=left coronary artery; RCA=right coronary artery; CCH=coronary cannulation height; RP=risk plane; VTA=valve-to-aorta distance; ID=implantation depth

Angiographic measurements. Aortic, left (LCA) and right coronary artery (RCA) angiograms directly after TAVR were obtained and analyzed in multiple optimized views aiming for elimination of prosthesis frame parallax (Supplementary Figure). Measurements acquired are summarized in Figure 1, Panel B. Coronary cannulation height (CCH) was measured as the distance between the aortic valve and the level at which the catheter crossed the prosthesis frame. Valve-to-aorta (VTA) distance was measured as the minimum distance between the prosthesis frame and the aortic wall under the RP level. A VTA >2 mm was considered necessary for a 6 French catheter to theoretically navigate behind the frame struts and engage the coronary ostia(7).

Feasibility of coronary access after TAVR-in-TAVR. Three possible scenarios are conceptualized in Figure 2 based on type of CA after index TAVR and VTA. CA after TAVR-in-TAVR was considered feasible when coronary cannulation after the first TAVR was possible from above the RP. When coronary cannulation was achieved below the RP, VTA was assessed. CA after TAVR-in-TAVR was considered theoretically feasible if VTA >2 mm, unfeasible if VTA $\leq$2 mm. Feasibility of CA was first evaluated on the basis of LCA cannulation. All feasible and theoretically feasible cases where then reviewed with regard to RCA engagement.

Figure 2. Proposed algorithm for assessment of coronary access (CA) feasibility after TAVR-in-TAVR. If coronary cannulation after index TAVR is achieved from above the RP (dashed line), CA after TAVR-in-TAVR is considered feasible. If the catheter crosses the valve frame below the RP, engagement of coronary ostia is considered theoretically feasible in the presence of a VTA>2mm (asterisk). On the contrary, in the presence of a VTA≤2mm TAVR-in-TAVR will impede future CA and possibly cause acute coronary obstruction.



TAVR=transcatheter aortic valve replacement; THV=transcatheter heart valve; VTA=valve-to-aorta distance. †coronary access challenging in case of TAVR-in-TAVR with two Evolut R/Pro THVs

Statistical analysis. Baseline characteristics are described with mean ± standard deviation (SD) [or medians and 1st and 3rd interquartile ranges (IQRs)] for continuous variables and percentages for discrete variables. Comparisons were performed with Student's t test or Mann–Whitney or Wilcoxon tests. Categorical variables (as frequencies or percentage) were compared with $\chi 2$ test or the Fisher exact test, as appropriate. Logistic regressions were used to estimate the independent effect of multiple independent variables on the risk of TAVR-in-TAVR unfeasibility. Only the covariates that were significantly associated with the risk of unfeasibility at univariate analysis ($p<0.05$ for model inclusion and $p>0.10$ for exclusion) and those considered clinically relevant were included, and the convention of limiting the number of independent variables to 1 for every 10 events was followed. Hosmer and Lemeshow (H-L) and c-statistic tests were used to assess the goodness of fit for logistic regression models and the predictive model discriminatory power,

respectively. The results of such analysis are presented as odds ratios (OR) and 95% confidence intervals (CI). For all analyses, a two-sided $p < 0.05$ was considered to be significant. Statistical analyses were performed using SPSS 24.0.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics. A total of 137 patients (48% female) with a mean age of 79.1±7.0 years and mean logistic Euroscore II of 4.1±3.0 were included in the study. Seventy-two (53%) received a Sapien 3, 26 (19%) an Evolut R/Pro and 39 (28%) an Acurate Neo THV. Baseline demographic characteristics were similar among valve groups (Table 1). Computed tomography-acquired aortic valve and root measurements are depicted in Table 1. Most parameters were comparable between groups. Patients receiving an intra-annular device had higher aortic valve area (425±84 vs. 401±117 vs. 395±62 mm^2, p=0.005), while subjects treated with an Evolt R/Pro tended to have lower LCA origin (14.6±3.3 vs. 12.7±3.2 vs 14.1±2.1 mm, p=0.033). Notably, sino-tubular junction (STJ) diameter was similar (28.2±3.3 vs. 28.9±5.2 vs 26.9±2.8 mm, p=0.087) among THV groups.

Table 1. Baseline characteristics and procedural data per THV

Clinical Characteristics	**Sapien 3/Ultra (72)**	**Evolut R/Pro (26)**	**Acurate Neo (39)**	**Total (137)**	***p-value***
Age (years)	77.9±7.9	80.4±6.4	80.3±5.1	79.1±7.0	0.148
Female	46% (33)	35% (9)	61.5% (24)	48% (66)	0.088
Euroscore II	4.5±3.6	3.8±2	3.5±2.2	4.1±3.0	0.214
Hypertension	86% (62)	88% (23)	87% (34)	87% (119)	0.951
Dyslipidemia	65% (47)	80% (21)	74% (29)	71% (97)	0.359
Diabetes Mellitus	31% (22)	31% (8)	31% (12)	31% (42)	0.989
COPD	26.5% (19)	8% (2)	15% (6)	20% (27)	0.105
Coronary artery disease	62.5% (45)	58% (15)	59% (23)	60.5% (83)	0.894
Previous PCI	30.5% (22)	31% (8)	31% (12)	31% (42)	0.953
Previous CABG	15% (11)	0%	13% (5)	12% (16)	0.136
Atrial Fibrillation	30% (21)	27% (7)	15% (6)	25% (34)	0.276

Prior pacemaker	10% (7)	4% (1)	5% (2)	7% (10)	0.256
LV-EF (%)	54.2±11.4	56.7±13.1	57.6±11.1	55.6±11.6	0.313
CT baseline					
Annulus area	450±84	401±117	395±62	425±84	**0.005**
Annulus perimeter	76.8±7.2	74.5±13.3	73.7±4.8	75.4±8.4	0.233
STJ mean diameter	28.2±3.3	28.9±5.2	26.9±2.8	27.9±3.7	0.087
Left sinus height	20.4±3.7	19.8±3.1	19.7±2.4	20.0±3.2	0.497
Right sinus height	20.9±4.0	21.3±5.9	19.5±3.4	20.5±4.3	0.215
Non coronary sinus height	20.7±3.4	21.6±4.4	19.4±2.8	20.4±3.5	**0.042**
LCA height	14.6±3.3	12.7±3.2	14.1±2.1	14±2.9	**0.033**
RCA height	15.6±3.6	15.7±5.3	14.8±3.2	15.4±3.8	0.518
Intercommissural (left)	30.4±3.6	31.2±5.5	28.1±2.7	29.8±4	**0.004**
Intercommissural (right)	29.4±3.2	30±5.3	27.3±2.7	28.8±3.7	**0.007**
Intercommissural (non coronary)	30.9±3.3	31±6.1	28.8±2.9	30.2±4	**0.027**
Procedural data					
Transfemoral access	76% (55)	100% (26)	97% (38)	87% (119)	**0.001**
THV size					
23 mm	19% (26)	6% (8)	5% (7)	30% (41)	
25 mm	-	-	17% (23)	17% (23)	
26 mm	24% (33)	3% (4)	-	27% (37)	
27 mm	-	-	7% (9)	7% (9)	
29 mm	9% (13)	3% (4)	-	12% (17)	
34 mm	-	7% (10)	-	7% (10)	
Oversizing	15.6±13	33±14.5	26.8±12.8	23.2±18.2	**<0.001**
Post-dilatation	6% (4)	37.5% (10)	33% (13)	20% (27)	**<0.001**
Implantation depth	3.5±0.8	4.9±1.7	4.3±0.9	4.0±1.2	**<0.001**
Risk Plane	14.6±2.1	22.2±2.7	24.7±2.2	19.1±5.1	**<0.001**
VTA above RCA*	1.4±0.9	2.3±2.9	2.2±1.4	2.1±2	0.097
VTA above LCA*	1.3±1.1	2.6±3.1	2.6±1.7	2.2±2.1	0.057
RCA cannulation height	16.9±1.9	17.5±3.2	19.1±4.8	17.7±3.4	**0.004**
LCA cannulation height	15.5±1.9	16.9±2.9	16.8±2.8	16.2±2.5	**0.011**

*for patients with theoretically feasible or unfeasible CA

COPD = chronic obstructive pulmonary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; LV-EF = left ventricular ejection fraction; CT= computed tomography; STJ = sinotubular junction; LCA = left coronary artery; RCA = right coronary artery; THV = transcatheter heart valve; VTA = valve-to-aorta distance

Procedural characteristics and outcomes. In 87% of patients TAVR was performed through the transfemoral approach. Mean implantation depth was 3.5±0.8 mm for Sapien 3/Ultra vs 4.9±1.7 for Evolut R/Pro vs 4.3±0.9 for Acurate Neo THV (p<0.001). Post-dilation was more often performed with Evolut R/Pro and Acurate Neo (37.5 and 33.3%) as compared to Sapien 3 (6%, p<0.001). No complication related to coronary cannulation was registered. According to inclusion criteria, intraprocedural mortality was 0%, no patient experienced annular rupture, device embolization, acute coronary obstruction, moderate/severe paravalvular leakage. Twelve (8.7%) patients underwent new pacemaker implantation before discharge.

Table 2. Baseline characteristics and procedural data per CA feasibility

Clinical Characteristics	**Feasible (56)**	**Theoretically Feasible (38)**	**Unfeasible (43)**	**Total (137)**	***p-value***
Age (years)	78.6±7.6	80.4±5.0	78.6±7.8	79.1±7.0	0.424
Female	41% (23)	42% (16)	63% (27)	48% (66)	0.068
Euroscore II	4.4±3.8	3.4±1.6	4.3±2.7	4.1±3.0	0.276
Hypertension	89% (50)	89.5% (34)	81% (35)	87% (119)	0.435
Dyslipidemia	61% (34)	76% (29)	79% (34)	71% (97)	0.129
Diabetes Mellitus	34% (19)	34% (13)	23% (10)	31% (42)	0.560
COPD	21% (12)	18% (7)	19% (8)	20% (27)	0.897
Coronary artery disease	59% (33)	66% (25)	58% (25)	60.5% (83)	0.822
Previous PCI	25% (14)	30% (11)	39.5% (17)	31% (42)	0.343
Previous CABG	10% (6)	10.5% (4)	14% (6)	12% (16)	0.773
Previous Stroke	12% (7)	8% (3)	14% (6)	12% (16)	0.746
Atrial Fibrillation	36% (20)	21% (8)	14% (6)	25% (34)	0.073
Prior pacemaker	9% (5)	10.5% (4)	2% (1)	7% (10)	0.334
LV-EF (%)	54.7±11.5	56.0±10.7	56.5±12.8	55.6±11.6	0.758
CT baseline					
Annulus Area	448±75	426±77	390±91	425±84	**0.013**
Annulus perimeter	76.9±7.2	76.9±9.5	72.0±8.4	75.4±8.4	**0.021**
STJ mean diameter	28.7±3.2	29.4±4.1	25.5±2.3	27.9±3.7	**<0.001**
Left sinus height	20.8±3.4	20.5±2.9	18.8±2.9	20.0±3.2	**0.009**
Right sinus height	21.3±3.8	21.3±4.6	18.9±4.0	20.5±4.3	**0.020**
Non coronary sinus height	21.3±3.2	20.8±3.7	19.1±3.3	20.4±3.5	**0.016**

LCA height	14.73±3.1	13.9±2.5	13.3±3.0	14.0±2.9	0.080
RCA height	15.5±3.6	15.7±4.4	14.8±3.6	15.4±3.8	0.539
Intercommisural (left)	30.6±3.7	30.2±4.8	28.5±3.1	29.8±4	**0.049**
Intercommisural (right)	29.6±3.1	29.5±4.7	27.2±2.9	28.8±3.7	**0.005**
Intercommisural (non coronary)	30.8±3.3	31±4.5	28.7±4.1	30.2±4	**0.025**
Procedural Data					
Transfemoral access	77% (43)	92% (35)	95% (41)	87% (119)	**0.013**
THV size					
23 mm	13% (18)	4% (6)	12% (17)	30% (41)	
25 mm	-	9% (13)	7% (10)	17% (23)	
26 mm	19% (26)	4% (5)	4% (6)	27% (37)	
27 mm	1% (2)	3% (4)	2% (3)	7% (9)	
29 mm	5% (7)	5% (5)	5% (5)	12% (17)	
34 mm	2% (3)	4% (5)	1% (2)	7% (10)	
Oversizing	15.8±15.4	27.9±18.7	29.9±18.1	23.2±18.2	**0.001**
Supra-annular THV	11% (6)	84% (32)	60.5% (26)	47% (64)	**<0.001**
Post-dilatation	9% (5)	29% (11)	25.5% (11)	20% (27)	**0.029**
Implantation depth	3.9±1.3	4.2±0.9	4.0±1.3	4.0±1.2	0.357
Risk Plane	15.4±3.6	23.3±3.7	20.2±4.6	19.1±5.1	**<0.001**
RCA VTA	-	3.6±0.8	0.8±0.7	2.1±0.9	**<0.001**
LCA VTA	-	3.8±2.2	0.9±0.6	2.2±2.1	**<0.001**
RCA cannulation height	17.9±2.6	19.5±4.3	15.9±2.3	17.7±3.4	**<0.001**
LCA cannulation height	17.0±2.9	16.6±2.0	14.8±1.7	16.2±2.5	**<0.001**

*for patients with theoretically feasible or unfeasible CA

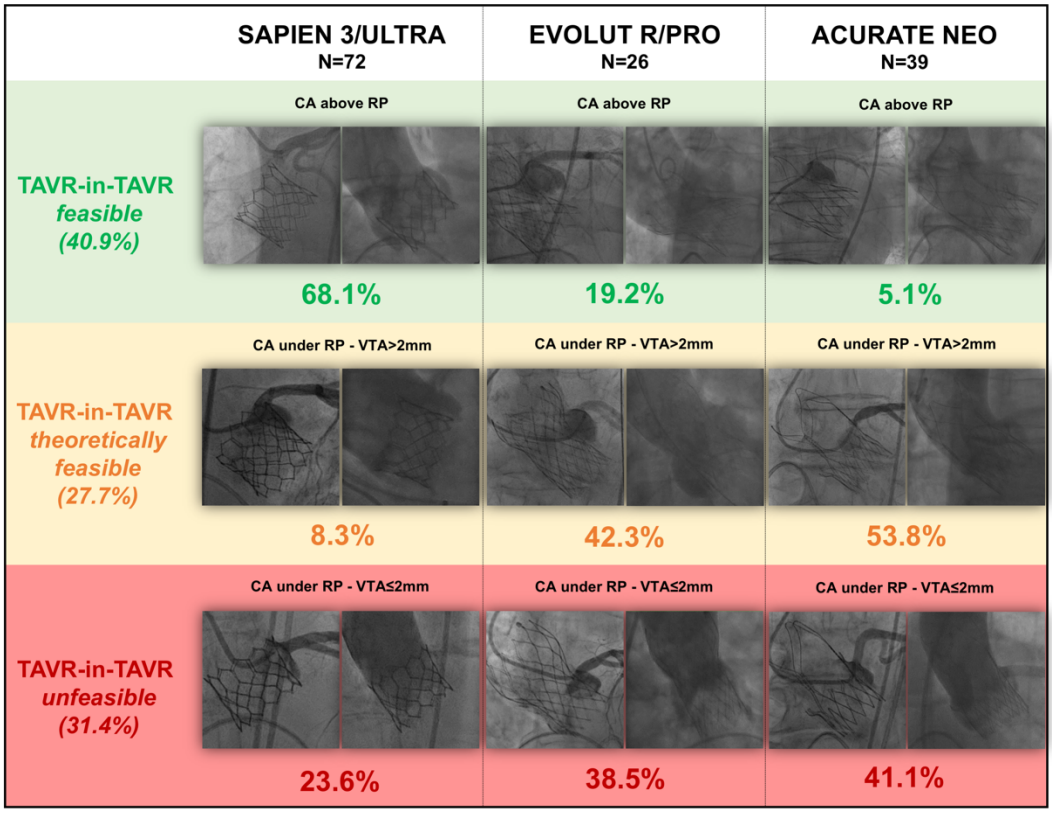
COPD = chronic obstructive pulmonary artery disease; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; LV-EF = left ventricular ejection fraction; CT= computed tomography; STJ = sinotubular junction; LCA = left coronary artery; RCA = right coronary artery; THV = transcatheter heart valve; VTA = valve-to-aorta distance

Coronary cannulation after TAVR. Cannulation of RCA and LCA was feasible in all patients (selective in 88.3%). The RP distance from the aortic valve, as measured by fluoroscopy, was significantly lower (mean 14.6±2.1 mm) in patients who received a Sapien 3 compared to Evolut R/Pro and Acurate neo THV (mean 22.2±2.7 and 24.7±2.2, p<0.001). Left and right CCH were also lower for Sapien 3/Ultra as compared to other THVs (p=0.001 and p=0.004, respectively). Consequently, in over 2/3 of patients with an intra-annular device coronary engagement was achieved

from above the RP, while this proportion was significantly lower in patients treated with an Evolut R/Pro or Acurate Neo (68.1 vs. 19.2 vs. 5.1%, p<0.001). Among patients with coronary cannulation under the RP, mean VTA was 2.2±2.1 mm for LCA and 2.1±0.9 mm for RCA, with no difference between THV groups. Twelve (8.7%) subjects also underwent computed tomography evaluation after TAVR. Visual inspection of Bland-Altman plots showed good agreement between computed tomography and angiography measurements of VTA and RP in this small subgroup of patients.

Feasibility of coronary access after TAVR. According to our classification algorithm, CA after TAVR-in-TAVR was deemed unfeasible in 31.4% of our TAVR population (Central Illustration). This unfavorable situation trended to be more frequent among patients with Evolut R/Pro or Acurate Neo (38.5 and 41.1%) as compared to Sapien 3 (23.6%, p=0.116). On the contrary, TAVR-in-TAVR was found to be more frequently feasible in patients with an intra-annular THV (68.1 vs. 19.2 vs. 5.1%, p<0.001). In about 27.7% of patients TAVR-in-TAVR was considered theoretically feasible, given the presence of a VTA>2 mm despite CA was achieved from below the RP. Notably, all feasible and theoretically feasible TAVR-in-TAVR based on LCA cannulation were confirmed after assessment of RCA measurements. Compared to the rest of the study population, subjects with predicted impaired CA after TAVR-in-TAVR had smaller annulus, narrower STJ and lower sinuses. Notably, LCA and RCA ostium heights were not different among groups. With regard to procedural characteristics, patients with unfeasible TAVR-in-TAVR had higher rates of post-dilation, lower risk plane and lower CCH (Table 2).

Central Illustration. Incidence of predicted CA impairment after TAVR-in-TAVR according to THV type.



TAVR=transcatheter aortic valve replacement; THV=transcatheter heart valve

Predictors of CA unfeasibility after TAVR-in-TAVR. Multiple potential predictors were tested (sex, mean aortic gradient at echocardiography, coronary ostium and coronary sinus height, sinus and STJ diameter, annular and LVOT area, perimeter and diameter, prosthesis size and oversizing, supra-annular design, CCH). At multivariate analysis (Table 3), female gender (OR 3.99, 95% CI 1.07-14.86, p=0.040), STJ diameter (OR 0.62, 95% CI 0.48-0.80, p<0.001), implantation of supra-annular THV (OR 6.61, 95% CI 1.93-22.03, p=0.002) and left CCH (OR 0.52, 95% CI 0.37-0.74, p<0.001) were found to be independent predictors of impaired CA after TAVR-in-TAVR (c-statistic 0.89, H-L test 0.6).

Table 3. Multivariate analysis of coronary access unfeasibility after TAVR-in-TAVR

Predictor variable	Predictor variable in Unfeasible vs. Feasible	OR (95% CI)	p value	c-Stat	H-L test
Female	41% vs. 22.5%	3.99 (1.07-14.86)	**0.040**	0.89	0.6
Supra-annular design	41% vs. 23%	6.61 (1.98-22.03)	**0.002**		
STJ mean diameter	25.5±2.3 vs. 29±3.6	0.62 (0.48-0.80)	**<0.001**		
Left CCH	14.8±1.7 vs. 16.8±2.6	0.52 (0.37-0.74)	**<0.001**		

OR = odds ratio; CI = confidence interval; H-L test = Hosmer-Lemeshow test; STJ = sinotubular junction; CCH=coronary cannulation height

DISCUSSION

The main findings of this study, the first to investigate potential unfeasibility of CA after TAVR-in-TAVR, are as follows: 1) According to our novel coronary angiography-based algorithm, almost one third of TAVR patients might be unsuitable for TAVR-in-TAVR; 2) Patients treated with intra-annular Sapien 3/Ultra THV are at lower risk of CA impairment after TAVR-in-TAVR as compared to subjects receiving supra-annular Evolut R/Pro and Acurate Neo; 3) Female gender, presence of a small STJ and implantation of a supra-annular device are independent predictors of possible impaired CA after TAVR-in-TAVR.

Given the positive results of recent low-risk trials(1,2), TAVR is being increasingly offered to younger patients, with the perspective of undergoing re-do TAVR in case they will outlive their THV. However, data on TAVR-in-TAVR are restricted to single case reports(11). Possible high risk of coronary obstruction and impossibility to re-access the coronary ostia after the leaflets of the first THV are displaced vertically by the implantation of the second device have been suggested(6). However, as yet, feasibility of CA after TAVR with different THVs has never been comprehensively addressed.

Feasibility of TAVR-in-TAVR. Our results suggest that in one every three subjects redo-TAVR might cause impairment in CA and possibly acute coronary obstruction.

In this situation, patients might experience the paradox of needing surgical aortic valve replacement after being treated with TAVR. A recent study based on aortic angiogram suggested that 21.3% of patients treated with SAPIEN 3 might be unsuitable for TAVR-in-TAVR(7). Interestingly, our data confirm these findings, with 23.6% intra-annular devices at high risk of CA impairment after TAVR-in-TAVR based on the proposed algorithm. In the same report, Tang et al proposed a novel aortic root classification, which – although useful – is not applicable to supra-annular prosthesis.

Procedural predictors of TAVR-in-TAVR unfeasibility. TAVR-in-TAVR with intra-annular SAPIEN 3/Ultra will not interfere with future coronary access in over 2/3 of subjects, while this percentage is considerably lower (<20%) in patients with supra-annular devices. These results can be explained by the lower frame of intra-annular THVs, whose design is more similar to surgical bioprostheses. On the contrary, supra-annular THVs invariably extend above the coronary ostia, and coronary cannulation after index TAVR is achieved under the RP with 80.8% of Evolut R/Pro and 94.9% of Acurate Neo devices. Nevertheless, in a consistent proportion of patients with large STJ (VTA>2mm) redo-TAVR is theoretically feasible, given the possibility for a coronary catheter to navigate between the valve frame and the aortic wall after the leaflets have been vertically displaced. However, CA in this situation will be challenging and operators will likely need differently shaped catheters or even the help of coronary guidewires or microcatheters to achieve coronary cannulation. Moreover, since in our study CA in the theoretically feasible group was achieved from below the RP, we cannot exclude that in some of these patients CA will eventually be unfeasible. This might be more likely if the coronary ostia are low or if TAVR-in-TAVR is performed with two Evolut R/Pro THVs. In fact, given the impossibility to orientate the THV(12), it is possible that the two frames above the RP would not perfectly align leaving insufficient room for a coronary catheter to cross the two overlapping stent layers. This issue might be mitigated by the open cell design of

Acurate Neo THV. If a supra-annular valve is implanted first and then TAVR-in-TAVR is performed with a Sapien 3/Ultra THV, the leaflet of the original valve might not be displaced in a completely vertical position making CA potentially easier, as long as a commissural post does not lie in front of the coronary ostium. Notably, novel leaflet splitting techniques such as BASILICA may be less effective in preventing coronary obstruction with TAVR-in-TAVR as compared to TAVR in surgical aortic valves, since the neo-commissure of the first prosthesis might not be aligned to those of the native aortic valve and potentially lying in front of a coronary ostium.

In our study most THVs were implanted quite higher (mean implantation depth 4.0±1.2 mm), resulting in a pacemaker implantation rate of 8.7%, comparable to other recent TAVR series(1,2). It could be speculated that a strategy of lower THV implantation would increase feasibility of CA after redo-TAVR by lowering the RP. However, this would likely happen at the cost of higher rates of pacemaker implantation(13,14), an undesirable complication particularly in younger patients(15,16).

Anatomic predictors of TAVR-in-TAVR unfeasibility. The major anatomic predictor of potential TAVR-in-TAVR unfeasibility is the presence of a narrow STJ. Being the tightest part of the aortic root, the STJ is the level at which the prosthesis frame is in closest proximity to the aortic wall and often represents the bottom neck where the catheter is not able to further navigate towards the coronary ostium. On the contrary, coronary sinus and coronary ostium height do not seem to predict CA impairment after TAVR-in-TAVR, possibly because the RP of correctly implanted supra-annular devices is almost always above the coronary sinuses even in the presence of a very high STJ.

The results of the present study should be considered hypothesis generating, and the proposed algorithm needs to be validated in clinical practice by collecting redo-TAVR procedures performed in non-selected cohorts of patients. However, based on

these findings, patients with longer life expectancy might be considered for implantation of a lower frame, intra-annular THV to preserve CA in case TAVR-in-TAVR is needed in the future. Recognition of anatomic features such as a narrow STJ potentially impairing CA after redo-TAVR is important for correct patient counseling in younger subjects proposed for TAVR. Choosing the first THV while considering future TAVR-in-TAVR highlights how far we have progressed in the field of transcatheter treatment of aortic stenosis. Particularly when small valves are required in younger patients, the potential advantages of better hemodynamics and lower patient-prosthesis mismatch rates with a supra-annular design need to be balanced with risk of CA unfeasibility after TAVR-in-TAVR.

LIMITATIONS

The main limitation of the current study is the lack of routine computed tomography evaluation after index TAVR. In fact, although coronary angiography and aortography were acquired in dedicated optimized fluoroscopic views to minimize valve frame parallax, VTA could have been underestimated(7). However, in the small subgroup of patients who underwent computed tomography after TAVR, the two measurements showed good agreement. Nevertheless, validation of our findings with routine integration of coronary angiography and 3-dimensional computed tomography reconstruction needs to be the focus of further research. Moreover, we cannot exclude that in some cases with a VTA >2 mm but coronary cannulation from below the RP (i.e. theoretically feasible TAVR-in-TAVR), CA could have been achieved from above the RP with the use of differently shaped coronary catheters or the help of a guidewire or microcatheter. At the same time, we also cannot exclude that in some of these patients CA might eventually be unfeasible, even if VTA is larger than 2 mm. Our results should not be extended to other devices, such as intra-annular Portico (Abbott) and Lotus (Boston Scientifics) THV(17), which were not investigated. Moreover, they should not be generalized to patients with bicuspid aortic valve stenosis, for which THV implantation is usually higher(10,18). Finally, this study was

conducted in a single high-volume TAVR center without core-laboratory validation of angiographic findings.

CONCLUSIONS

Coronary access after TAVR-in-TAVR might be unfeasible in approximately one third of patients currently treated by TAVR. Subjects who received a supra-annular THV are at higher risk of CA impairment as compared to those implanted with an intra-annular device. Female gender and small STJ dimensions are also independent predictors of impaired CA after TAVR-in-TAVR. Our findings are important for correct patient counseling and prosthesis selection in subjects with longer life expectancy. These results need to be confirmed by larger studies with integration of computer tomography evaluation and, most importantly, by collection of a larger number of redo-TAVR procedures in non-selected patients.

PERSPECTIVES

An increasing number of younger patients with severe aortic stenosis is currently being treated with TAVR. Many of these subjects are likely to live sufficiently longer to see their prosthesis degenerate. According to our results, TAVR-in-TAVR, an attractive therapeutic option for structural transcatheter valve degeneration, might be unfeasible in one every three patients currently undergoing TAVR, based on the potential risk of CA impairment. The findings of this study should guide patient counseling and prosthesis selection in subjects with longer life expectancy.

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