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Coronary artery disease in patients undergoing transcatheter aortic valve implantation.

A single centre registry on prevalence, management and immediate clinical impact

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SOUHRN

Úvod: Prevalence ischemické choroby srdeční (ICHS) se u všech pacientů se stenózou aortální chlopně (aortic valve stenosis, AVS) pohybuje v rozmezí 30 % až 60 %. Dosud nebyla nalezena jednoznačná shoda ohledně optimálního způsobu léčby ICHS u pacientů s indikací k transkatétrové implantaci aortální chlopně (transcatheter aortic valve implantation, TAVI). Cílem této studie bylo stanovit prevalenci, určit způsob léčby i bezprostřední klinické důsledky ICHS u dané populace, se zvláštním zaměřením na proveditelnost a bezpečnost metody revaskularizace na základě fyziologických parametrů.
Metody a výsledky: Do analýzy byly zařazeny retrospektivní údaje o celkem 287 po sobě následujících pacientech indikovaných k TAVI na našem pracovišti. Nemocní s ICHS (123; 43 %) byli rozděleni do tří skupin podle léčebné strategie zvolené operatérem: optimální farmakoterapie (42 z oněch 123; 34 %), preventivní perkutánní koronární intervence (percutaneous coronary intervention, PCI) pro angiograficky významné koronární léze (34 ze 123; 28 %) a strategie s použitím fyziologických parametrů (47 ze 123; 38 %). V populaci pacientů s ICHS hodnota logistického EuroSCORE dosahovala hodnoty 31 ± 24, přičemž rizikový profil byl vyšší ve skupině s farmakoterapií. Úspěšnost výkonu při použití TAVI v celé populaci byla 96 %. Klinické výsledky po 30 dnech prokázaly vyšší incidenci závažných kardiovaskulárních příhod (major adverse cardiovascular event, MACE) ve skupinách s optimální farmakoterapií a s preventivní PCI (11,9 %, resp. 5,9 %); ve skupině s použitím fyziologických parametrů nebyly zaznamenány žádné příhody.
Závěry: Nejlepší způsob léčby ICHS při TAVI se stále ještě hledá. Přes poměrně omezenou velikost vzorku prokazují naše zjištění proveditelnost a bezpečnost revaskularizační léčby s použitím fyziologických parametrů. Potvrzení našeho zjištění a zhodnocení dlouhodobých klinických důsledků si vyžádá větší studie.

ABSTRACT

Introduction: Prevalence of coronary artery disease (CAD) ranges from 30% to 60% of all patients with aortic valve stenosis (AVS). At present, little is known about the best management of CAD in patients undergoing trans-catheter aortic valve implantation (TAVI). Aim of this study is to investigate the prevalence, management and the immediate clinical impact of CAD in this population, with a special focus on the feasibility and safety of a physiologically-guided revascularization strategy.

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Keywords:
Aortic valve stenosis
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Methods and results: A total of 287 consecutive patients undergoing TAVI in our centre were retrospectively included in the analysis. Those presenting CAD (123, 43%) were divided in three groups, according to the therapeutic strategy adopted by the operator: optimal medical therapy group (42 out of 123, 34%), preventive-PCI for angiographically significant coronary lesions (34 out of 123, 28%) and a physiologically-guided strategy (47 out of 123, 38%). The mean Logistic EuroSCORE was 31 ± 24 in the CAD population, with a higher risk profile in medical therapy group. TAVI procedural success in the overall population was 96%. Thirty-day clinical outcome showed a higher incidence of MACEs in the optimal medical therapy and the preventive PCI group (11.9% and 5.9%, respectively), with no occurrence of adverse events in the FFR-guided group.

Conclusions: The best management of CAD in TAVI is still under investigation. Despite a relatively limited sample size, our findings demonstrate the feasibility and safety of a physiologically-guided revascularization strategy. Larger trials are needed to confirm our observations and to assess the long-term clinical impact.

Introduction

The prevalence of coronary artery disease (CAD) ranges from 30% to 60% of all patients with aortic valve stenosis (AVS) [1]. Observational studies reporting outcomes of patients undergoing trans-catheter aortic valve implantation (TAVI) revealed a prevalence of CAD in the range of 40–75% [2–4]. Current guidelines state that myocardial revascularization at the time of surgical aortic valve repair (SAVR) is a class-I recommendation in the presence of coronary stenosis ≥70%, and a class-IIa recommendation for angiographic stenosis 50–70% [5] while the best management of CAD in TAVI candidates is unclear [6]. At present, there is no evidence of increased survival or symptoms relief with a full revascularization strategy, thus raising concerns about the real functional meaning of coronary lesions incidentally found in this specific subset during the routine diagnostic workout. Furthermore, it is unknown whether percutaneous coronary interventions (PCI) should be performed before or after valve implantation, or even if a physiological assessment of lesion severity, by means of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) should be adopted to guide myocardial revascularization. Recent studies from our institution have investigated the safety and feasibility of coronary angiography and intervention after TAVI [7], and a dedicated registry has more specifically explored the performance of FFR and iFR indexes before and after the percutaneous valve intervention [8].

The aim of the present analysis is to report the prevalence and clinical impact of CAD in a single centre population of patients undergoing TAVI. Furthermore, the feasibility and safety of CAD management guided by FFR after TAVI was explored and compared to a conservative strategy of optimal medical therapy, and the percutaneous interventions indicated on the visual angiographic estimation of the coronary lesions.

Methods

All consecutive patients undergoing TAVI for severe aortic stenosis in our centre have been included in the analysis. Severe symptomatic aortic stenosis was defined by the current ESC guidelines [9]. TAVI procedures were performed either by the percutaneous trans-femoral or by surgical trans-apical approach. As for the initial manufacturer's indications, vascular access was obtained with surgical approach in the first 20 patients and then percutaneous access was managed by pre-implantation of a Prostar closure device in the common femoral artery (Abbott Vascular, Santa Clara, CA, USA) in all trans-femoral cases. Cardiac surgeons managed access in trans-apical valve implantations. The choice of the aortic valve prosthesis was left to the operator's discretion. Both balloon-expandable Edwards SAPIEN (Edwards Lifesciences, Irvine, CA, USA) and self-expandable Medtronic CoreValve (Medtronic Inc., Minneapolis, MN, USA) and Lotus Edge (Boston Scientific, Natick, Massachusetts) prosthesis were implanted through the trans-femoral approach, while only the balloon-expandable device was adopted in the trans-apical group. Almost all patients underwent pre-TAVI imaging of the aortic root by means of contrast angiography and CT-scan. Coronary angiography was always performed before or during the TAVI procedure, at the operator's discretion. Patients presenting with CAD, defined as coronary obstruction ≥50% by visual estimation, have been further classified according to the therapeutic strategy adopted. Of note, myocardial revascularization has been consistently guided by functional assessment with FFR and iFR since January 2015, according to an internal research protocol whose features and results have been already published elsewhere [8]. Briefly, a pressure monitoring guide wire (PrimeWire, Volcano Therapeutics, Rancho Cordova, California, USA) was advanced distally to the coronary artery stenosis after normalization, hyperemia was obtained after administration of intra-coronary bolus of 150 to 250 mg adenosine. An FFR value ≤0.80 was considered pathologic while an FFR value >0.80 was considered 'negative', i.e. unlikely to induce reversible myocardial ischemia according to current recommendation. iFR was measured on-line using the Volcano iFR computational algorithm. An iFR cut-off value of 0.90 was considered equivalent to the 0.80 FFR value for the determination of ischemia-provoking stenosis, according to recent recommendation; in case of discordance between the two techniques, revascularization was based on FFR.

Clinical outcome was obtained by consultation of our outpatient clinic data and by phone call when no documentation was available in our archives. The measured clinical end-points were all-cause death, cardiac death, myocardial infarction (MI), ischemia-driven revascularization, stroke and the composite occurrence of these events at 30 days from the index procedure.

Statistical analysis

Summary descriptive statistics are reported as mean + standard deviation (SD), median (inter-quartile range) or counts (%), as appropriate; 95% confidence intervals (CI) are added, as appropriate. Correlation among variables was determined by Pearson or Spearman correlation tests, as appropriate and expressed as r-value. Comparisons between continuous variables were performed using the Student's *t* test or Mann-Whitney *U* test, as appropriate. Comparisons between categorical variables were evaluated using the Fisher's exact test or the Pearson's chi-square test, as appropriate. A probability value of $p < 0.05$ was considered statistically significant. All analyses were performed with SPSS 21.0 (IBM Inc., New York, USA).

Results

A total of 287 patients underwent TAVI between March 2010 and September 2016 and were included in the present analysis. Baseline clinical characteristics are shown in Table 1. A self-expandable CoreValve device was used in 69 cases, the Lotus one in 2 cases, and the Edwards Sapien in the remaining 216 patients. A trans-apical approach was adopted in 45 patients. Of the study population, 123 patients presented significant CAD at pre-procedural coronary angiography, and were further divided in those referred to an optimal medical therapy (OMT) strategy (42 out of 123, 34%), preventive-PCI strategy for the significant coronary lesions (34 out of 123, 28%) and an FFR-guided strategy (47 out of 123, 38%). The mean Logistic EuroSCORE was 31 ± 24 in the overall CAD population, with a significantly higher risk profile in those selected for OMT (36 ± 24.8%, $p = 0.03$).

TAVI procedural success was 97% in the global population, with no significant differences in the various sub-groups. Procedural results are shown in Table 2. The mean clinical follow-up was 17 ± 10 months for the overall population, with a global survival rate of 96.9% at 30 days and 89.6% at complete follow-up. Patients affected by CAD showed a trend towards worse clinical outcome when compared with those without CAD in terms of short-term survival (30 days all-cause death 4.8% vs 1.8%, $p = 0.33$, 30 days cardiac death 3.2% vs 0.6%, $p = 0.39$, Table 3).

Optimal Medical Therapy group

After percutaneous treatment of the valve disease, treatment for the CAD was left to optimal medical therapy in 51 patients, as per operator's choice. Patients of this group presented multi-vessel disease in 15 cases (36%), while the majority had a single vessel involvement (27 out of 51, 64%). Mean Logistic EuroSCORE in this population resulted 36 ± 24.8. These patients represented those initially referred to TAVI by the Heart Team, being at very high risk for conventional surgery. Dual antiplatelet therapy was continued for a minimum of 3 months in all these patients [3,10]. All-cause death at 30 days occurred in 5 patients (11.9%), 3 of which were due to car-

Table 1 – Clinical characteristics of the study population

Variables	Overall pop. (287)	CAD* (123)	OMT (42)	Preventive PCI (34)	FFR strategy (47)
Age, years	81.2 ± 7.8	81.1 ± 7.5	81 ± 7.8	77.7 ± 9.1	81.1 ± 7
Logistic EuroSCORE	28.6 ± 20.8	31.4 ± 24	36 ± 24.8	32.7 ± 22.4	24.5 ± 21
Male, n (%)	124 (43.2%)	61 (49.6%)	20 (47.6%)	20 (59%)	21 (44.7%)
BMI, kg/m^2	25.9 ± 4.6	26.4 ± 4.7	25.7 ± 4.8	27.9 ± 6.4	26.2 ± 4.3
Dyslipidemia, n (%)	173 (60.3%)	77 (62.6%)	28 (66.7%)	29 (85.3%)	20 (42.6%)
COPD, n (%)	65 (22.6%)	33 (26.8%)	10 (23.8%)	12 (35.3%)	11 (23.4%)
Diabetes, n (%)	85 (29.6%)	41 (33.3%)	14 (33.3%)	12 (35.3%)	15 (31.9%)
Hypertension, n (%)	244 (85%)	105 (85.4%)	33 (78.6%)	28 (82.4%)	44 (93.6%)
History of CAD, n (%)	123 (42.9%)	123 (100%)	42 (100%)	34 (100%)	47 (100%)
Previous AMI, n (%)	57 (19.9%)	39 (31.7%)	14 (33.3%)	17 (50%)	8 (17%)
Atrial fibrillation, n (%)	106 (36.9%)	44 (35.8%)	20 (47.6%)	4 (12%)	20 (42.6%)
Previous stroke, n (%)	20 (7%)	10 (8.1%)	4 (9.5%)	2 (6%)	4 (8.5%)
Previous CABG, n (%)	51 (17.8%)	26 (21.1%)	11 (26.2%)	10 (29.4%)	5 (9.6%)
Previous AVR, n (%)	8 (2.8%)	4 (3.3%)	3 (7.1%)	0	1 (2.1%)
Previous MVR, n (%)	6 (2.1%)	1 (0.8%)	1 (2.4%)	0	0
Valve in valve, n (%)	21 (7%)	8 (6.5%)	5 (11.9%)	1 (2.9%)	2 (4.3%)
Stable angina, n (%)	90 (31.4%)	44 (35.8%)	8 (19%)	23 (67.6%)	13 (27.7%)
Unstable angina, n (%)	20 (7%)	14 (11.4%)	2 (4.8%)	5 (14.7%)	7 (14.9%)
NYHA class III or IV, n (%)	228 (79.4%)	104 (85%)	37 (88%)	30 (88.2%)	37 (84%)

AMI – acute myocardial infarction; AVR – aortic valve replacement; BMI – body mass index; CABG – coronary artery bypass graft; CAD – coronary artery disease; COPD – chronic obstructive pulmonary disease; MVR – mitral valve replacement; NYHA – New York Heart Association; OMT – optimal medical therapy; PCI – percutaneous coronary intervention. * CAD: CAD (>50%) at time of TAVI.

Table 2 – Procedural details

Variables	Overall pop. (287)	CAD* (123)	OMT (42)	Preventive PCI (34)	FFR strategy (47)
Valve type					
Medtronic CoreValve, n (%)	67 (23.3%)	35 (28.5%)	13 (31%)	9 (26.5%)	13 (27.7%)
Edwards SAPIEN, n (%)	218 (76%)	87 (70.7%)	29 (69%)	25 (73.5%)	33 (70%)
Lotus, n (%)	2 (0.7%)	1 (0.8%)	0	0	1 (2.1%)
Approach					
Trans-apical, n (%)	44 (15.3%)	19 (15.4%)	8 (19%)	7 (20.6%)	4 (8.5%)
Trans-femoral, n (%)	240 (83.6%)	103 (0.8%)	34 (81%)	27 (79%)	42 (89%)
Trans-subclavian, n (%)	3 (1%)	1 (0.8%)	0	0	1 (2.1%)
Procedural success, n (%)	279 (97.2%)	118 (96%)	39 (93%)	32 (94%)	47 (100%)
Fluoroscopy time, min	21.4 ± 10.1	23.5 ± 9.5	22 ± 11	21.7 ± 8.4	28 ± 8.6
Procedural time, min	115.7 ± 46	132.9 ± 53.6	105 ± 45.6	130.8 ± 54	167.5 ± 42.3
Moderate PR, n (%)	18 (8.6%)	7 (6.7%)	2 (6.3%)	1 (3.6%)	3 (10%)
Conversion to CS, n (%)	1 (0.4%)	1 (0.8%)	0	0	1 (2.1%)
CAD extension					
Single vessel, n (%)	59 (20.6%)	59 (48%)	27 (64%)	15 (44.1%)	17 (36.2%)
Multi vessels, n (%)	64 (22.3%)	64 (52%)	15 (36%)	19 (55.9%)	30 (63.8%)
3 months DAPT, n (%)	n.a	73 (59.3%)	42 (100%)	0	25 (53.1%)
6 months DAPT, n (%)	n.a.	52 (42.3%)	0	34 (100%)	22 (46.9%)

CAD – coronary artery disease; CS – cardiac surgery; DAPT – double antiplatelet therapy; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; PR – prosthetic regurgitation.
* CAD: CAD (>50%) at time of TAVI.

Table 3 – Clinical events at 30 days

Variables	Overall pop. (287)	No CAD (164)	CAD* (123)	*p* value	OMT (42)	Preventive PCI (34)	FFR strategy (47)	*p* OMT vs PCI	*p* OMT vs FFR	*p* PCI vs FFR
Death, n (%)	9 (3,1%)	3 (1.8%)	6 (4.8%)	0.33	5 (11.9%)	1 (2.9%)	0	0.22	0.01	0.42
Cardiac death, n (%)	5 (1.7%)	1 (0.6%)	4 (3.2%)	0.39	3 (7.1%)	1 (2.9%)	0	0.18	0.03	0.42
MI, n (%)	1 (0.3%)	0	1 (0.8%)	0.4	0	1 (2.9%)	0	0.5	–	0.41
PCI, n (%)	1 (0.3%)	0	1 (0.8%)	0.4	0	1 (2.9%)	0	0.5	–	0.4
Stroke, n (%)	1 (0.3%)	1 (0.6%)	0	0.32	0	0	0	–	–	–
CE, n (%)	10 (3.5%)	3 (1.8%)	7 (5.7%)	0.11	5 (11.9%)	2 (5.9%)	0	0.45	0.01	0.17

CAD – coronary artery disease; CE – composite events of death, MI, PCI, and stroke; MI – myocardial infarction; OMT – optimal medical therapy; PCI – percutaneous coronary intervention. * CAD: CAD (>50%) at time of TAVI.

diac causes (7.1%). No spontaneous MI or percutaneous revascularizations were observed in this group in the first month after the procedure.

Preventive-PCI group

A "preventive-PCI" approach with last-generation DES implantation was adopted in 34 patients before the percutaneous treatment on the aortic valve. Patients of this group presented multi-vessel disease in 19 cases (56%), while only 15 had a single vessel involvement. Mean Logistic EuroSCORE was 32.7 ± 22.4%. The coronary percutaneous intervention was performed according to current standards of care, with adequate lesion pre-dilation before the stent deployment and final optimization with post-dilation when necessary. A total of 55 lesions were treated, with implantation of 63 DES. Dual antiplatelet therapy was continued for at least 6 months in all these patients. At 30 days, 1 cardiac death occurred (2.9%) and 1 spontaneous acute MI. The patient who suffered the acute MI underwent coronary angiography and a second PCI with DES implantation in a vessel different from that previously treated (non-target vessel revascularization). The composite event rate was therefore 5.9%, being not significantly different compared to the OMT group. The preventive PCI strategy was applied mostly on MVD patients between March 2010 and January 2015, before the routine implementation of FFR-guided PCI in TAVI patients in our centre.

FFR-guided strategy group

Physiological assessment of coronary lesion severity after TAVI procedure was consistently performed in the last

47 consecutive patients candidate to percutaneous valve treatment who presented CAD at pre-TAVI angiography. Of note, no cases of unsuccessful selective coronary catheterization after valve implantation were observed. The logistic EuroSCORE in this population resulted 24.5 ± 21%, as the effect of a larger adoption of percutaneous valve implantation technique in the most recent years. According to the results of FFR, revascularization was deferred in 25 patients, and performed in 22 patients with FFR determinations below 0.80 on 24 coronary stenosis. Also in these patients, PCI was performed according to the current standard of care, with last-generation DES implantation and DAPT was continued for a minimum of 6 months in those patients who underwent PCI (46.8%) and interrupted after 3 months in the remaining cases. No adverse clinical events were detected within 30 days in this group, as detailed in Table 3.

Death and the composite events rate showed a statistical significant reduction in the FFR-guided group as compared to the OMT group (11.9% vs 0%, $p = 0.01$), and a similar trend when compared to the preventive PCI group (5.9% vs 0%, $p = 0.17$).

Discussion

Coronary artery disease is a very frequent co-morbidity in patients with high-risk AVS undergoing TAVI. The prevalence observed in our series is comparable to previous studies [3,11–17], and confirms the importance of this clinical variable in the decision-making and strategic management of TAVI in high-risk patients.

Associated CAD strongly impacts the clinical prognosis of patients with AVS [18] and simultaneous myocardial revascularization at the time or SVR is strongly recommended despite a higher peri-operative risk, outweighed however by the long-term benefits of the combined coronary surgery when compared to the AVR alone [19].

Given the relatively recent implementation of TAVI as a therapeutic option for high-risk patients with AVS, there are no available recommendations as to the management of associated CAD. Recent reports have not demonstrated an improvement of the long-term survival or the symptomatic status with PCI performed either before or after TAVI and in some cases, the associated coronary procedure has been related to higher rates of complications [20]. As a consequence, there is no one accepted strategy that can be recommended over others, and it is common practice to perform PCI of bystander lesions in major coronary branches found during the diagnostic triage before TAVI, even in the absence of angina symptoms or documented instrumental ischemia as a preventive strategy before the valve implantation.

Our centre has been investigating the feasibility and reliability of obtaining FFR measurements in patients undergoing the diagnostic screening before TAVI, and consequently guiding PCI according to the physiologic relevance of the stenosis as indicated by a critical FFR value below 0.80 [8]. The clinical outcome of our TAVI experience and an accurate assessment of the learning curve have been previously reported [21]. The preliminary results of our experience related to the management of CAD in TAVI are reported in this article and despite a relatively limited sample size, they confirm the feasibility and safety of a physiologically-guided revascularization strategy. More specifically, our results suggest on the one hand, that deferring coronary lesions based on negative FFR results after TAVI has no consequences in terms of major adverse events in a short-time elapse. On the other hand, performing PCI according to the FFR evaluation of the stenosis severity caused no ischemic complications in the immediate post-procedural and post-discharge period.

Indeed, during the first years of our TAVI experience (2010–2014), most patients presenting a significant CAD of the main coronary arteries at the time of the diagnostic coronary angiogram before TAVI were treated with PCI using second-generation drug eluting stents in most cases. Such patients had a higher baseline clinical risk, a more frequent multi-vessel disease involvement (as assessed by the angiographic visual estimation), and more often presented with symptoms of suspected ischemic nature as compared to those left in medical therapy, that had predominantly a single vessel disease and were more frequently in chronic atrial fibrillation. The short-term mortality of these two groups was different, likely because of the higher baseline risk of the medically treated patients. Since 2015, FFR assessment of coronary lesions found during diagnostic coronary angiograms was systematically performed as mandated by a research protocol at our centre [8] and therefore, myocardial revascularization was guided by the physiologic data revealed after the valve implantation. FFR-guided patients had a much higher prevalence of multi-vessel coronary artery disease, but a lower baseline clinical risk as compared to the other two groups, a difference in part related to the extension of the clinical indications of TAVI towards a lower risk in the latest years, and to the inclusion criteria of our FFR study protocol [8].

This short-term clinical analysis demonstrates the safety of measuring FFR in TAVI patients and of performing physiologically-guided PCI during the same TAVI procedure. Whether the long-term clinical outcome of a physiologically-guided revascularization in TAVI patients will be in line with previous large studies demonstrating the advantages of a physiologically-guided PCI strategy as compared to the *"oculo-stenotic-induced stented PCI"* [22–24] is of great interest to the cardiologic community, and our long-term results might provide some valuable information in the next future.

Our observation, being novel is unique and so far cannot be compared with others. A dedicated multi-centre, randomized, Nation-wide Italian trial promoted by our Institution entitled *FAITAVI* (Functional Assessment In TAVI) will start in January 2017 and aims to investigate the clinical differences of an angiographically-guided versus a physiologically-guided PCI strategy in patients at low, intermediate and high clinical risk undergoing trans-femoral TAVI with the Edwards Sapien S3 trans-catheter valve.

Conflict of interest
Flavio Ribichini is a TAVI proctor for Edwards Lifescience and for Medtronic Inc. Other authors have no potential conflicts of interest.

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