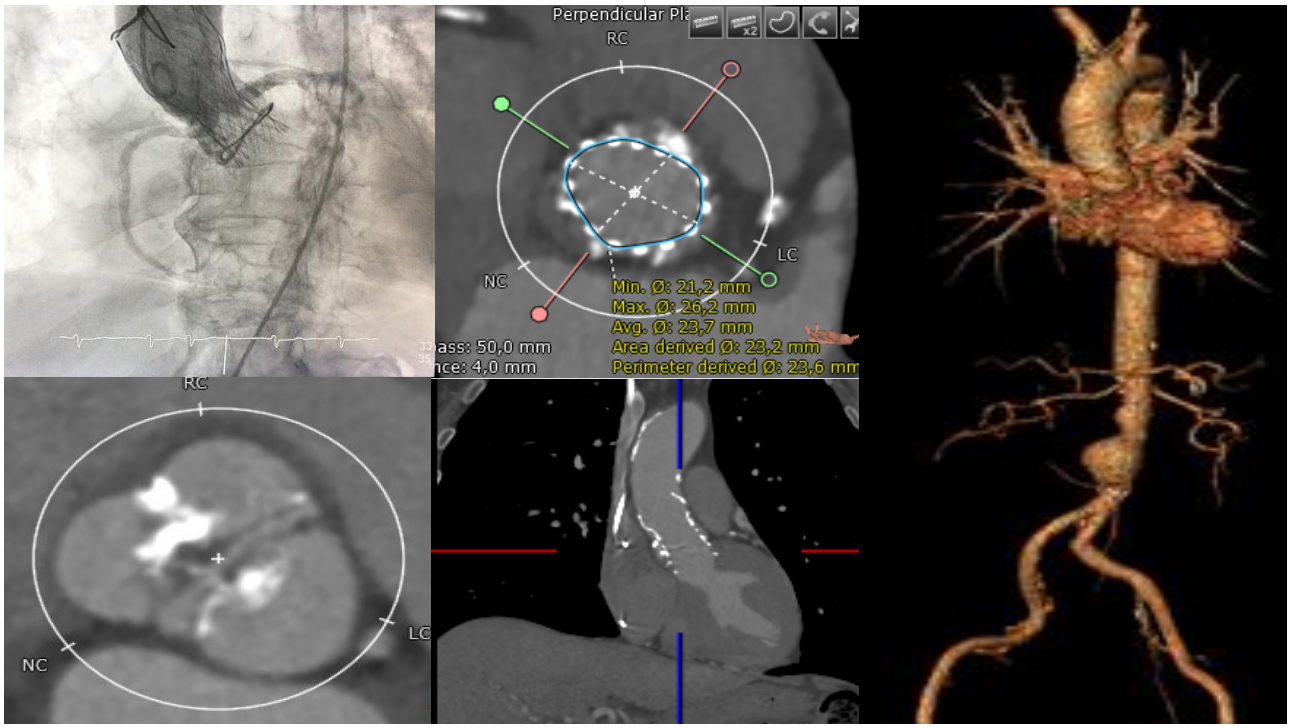
International PhD program in Cardiovascular Pathophysiology and Therapeutics - CardioPaTh



New perspectives for transcatheter aortic valve implantation: the *"coup d'essai"* of bicuspid aortic valves

PhD thesis

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New perspectives for transcatheter aortic valve implantation: the *"coup d'essai"* of bicuspid aortic valves

PhD Thesis

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It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change.

Charles Darwin

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Chapter 1

General introduction and outline of the thesis

Transcatheter aortic valve implantation (TAVI) for aortic disease is a robust alternative to surgery in intermediate to high-risk patients with symptomatic aortic stenosis (AS) [1-7]. Sixteen years have elapsed since the first TAVI, and the procedure has now been widely adopted. The first time the procedure was performed, the patient was under conscious sedation with local anaesthesia for an antegrade trans-septal procedure [8]. The pioneering team in Rouen published a series of case reports for patients treated via a transfemoral route using a conscious sedation/local anaesthesia policy. The outcome in this cohort was excellent, with a low 30-day mortality and conversion to general anaesthesia required in only 3.3% of the cases [9]. However, in the vast majority of the early cases, general anaesthesia and transoesophageal guidance were used as routine. The main reasons for this were the need for surgical cutdown, because of the large bore sheaths that were used at the time; the need for a thorough assessment of residual aortic regurgitation post-TAVI and the need for early identification of complications. When the procedure was first in use, we had to deal with multiple potential complications including vascular injuries, aortic annulus rupture, moderate-to-severe paravalvular regurgitation, the need for a permanent pacemaker and stroke [10]. Using a general anaesthetic was a safe way to quickly identify life-threatening complications and bail out of the procedure.

Nowadays more than 300,000 TAVIs have been performed worldwide in more than 70 countries across the globe [11]. Introducer sheaths of 20–24 Fr are no longer used, and have been replaced by smaller ones thanks to new devices that are 14–16 Fr compatible, reducing rates of vascular complications [12]. Transcatheter heart valves (THV) have definitely improved, allowing more predictable deployment and preventing paravalvular regurgitation. Transfemoral access is used in more than 90% of cases in centres where the procedure is carried out regularly. The large and rapid expansion of TAVI has led to constant improvement in techniques and clinical outcomes for patients,

requiring, anyway, to treat more patients in a more efficient way, with shorter procedures and shorter hospital stays, while maintaining excellent outcomes. The cost-effectiveness of TAVI has been demonstrated in several studies with various types of THV, at least for transfemoral access, even if significant variations in cost can be identified in different countries' healthcare systems. Efficient TAVI has become a contemporary challenge.

The recently published European Society of Cardiology (ESC) guidelines for valvular heart disease provide a valuable framework for defining patients that are eligible and would benefit from a TAVI procedure [13]. However the debate between percutaneous or open surgery treatment is still open in specific settings, according to cardiac and extra-cardiac characteristics of patients, the risk of procedure as calculated from the different available scores assessed by the Heart Team and the experience of the physician, considering some limitations of TAVI procedure. Despite favourable results of TAVI, data concerning long-term durability are lacking. Moreover there are still key issues that must be addressed in order for TAVI recommendations to be expanded to younger and lower risk patients, like pace-maker implantation rate, residual paravalvular leak, intra- and peri- procedural stroke, vascular complications and challenging anatomical settings like the bicuspid aortic valves (BAV).

In particular, BAV represents a big challenge for percutaneous treatment due to anatomical specificities. BAV can be distinguished in two basic categories, congenital and functional when the native aortic valve 'functions' as a bicuspid. Therefore it is a condition encountered in young adults as well as elderly patients. BAV is the most common congenital valvular abnormality occurring in 0.5 % to 2% of the general population, in 2% to 6% of patients with severe AS and up to 20% of octo-nonagenarians undergoing surgery [14, 15]. When compared to patients with tricuspid aortic valve, BAV patients are younger with a male predominance of 3:1. BAV may combine a large annulus, heavily calcified leaflets, and dilated ascending aorta [16]. The presence of BAV has regularly been considered a contraindication to TAVI because of a high risk of malpositioning and potentially accelerated leaflet degeneration [17]. Indeed BAV anatomic features can negatively impact the optimal

interaction between the native valve and the TAVI prosthesis leading to high rates of paravalvular regurgitation, device under expansion, and the need for a second THV [18]. The dilated aorta may predispose to aortic dissection [19]. These potential suboptimal procedural outcomes translate into worse long-term outcomes [20]. Thus, BAV has been regarded as a relative contraindication to TAVI and has been excluded from major randomized clinical trials. However, recent registries demonstrated the feasibility of TAVI in this specific anatomical setting, in particular with new-generation THV [21-24].

New-generation prostheses offer better positioning and alignment, repositionability, and sealing properties with more accurate deployment and low paravalvular leak rate in tricuspid aortic valves [12]. Recently published retrospective registries demonstrated the safety of TAVI in BAV using second-generation prostheses, with clinical outcomes comparable to TAVI in tricuspid aortic valves [23, 25, 26].

Despite encouraging clinical outcomes, correct sizing for BAV remains controversial and debatable. Multidetector computed tomography (MDCT) is the preferred sizing modality for TAVI in both tricuspid and bicuspid aortic valves [20, 27-30]. Current sizing practices in patients with BAV employ two different methodologies: a standard annular-based sizing and a supra-annular sizing, at the level of the leaflets or the commissures. Sizing options for BAV patients undergoing TAVI with second-generation devices across European centres represent the final topic of this thesis, with a focus on MDCT as the "gold standard" imaging modality in pre and post TAVI to better understand THV geometry and expansion in the bicuspid setting.

Outline of the thesis

The thesis is divided in four parts.

Part I: Aortic valve disease and innovation in percutaneous treatment by transcatheter aortic valve implantation. In this first section of the thesis we present some research projects published in

the field of transcatheter aortic valve replacement in general population, describing the progress of this percutaneous technique during the past years until nowadays practice. In this section there are some considerations about TAVI in particular scenarios and procedural settings requiring dedicated technical adjustments.

Part II: TAVI in a complex anatomical setting: Bicuspid Aortic Valve management and percutaneous treatment. In this second section we collected research papers focused on the challenging anatomy of bicuspid aortic valves (BAV) undergoing TAVI treatment for aortic stenosis (AS). In contemporary TAVI practice BAV anatomy still represents a challenge for percutaneous treatment. This section is the real focus of the three years of PhD research, since the complexity of the topic and the time required for data collection and analysis. Moreover, this part represents the result of an International collaboration and knowledge sharing among renowned centres for the percutaneous treatment of aortic disease.

Part III: Imaging for TAVI in Bicuspid Aortic Valve. This section includes research papers investigating the role of imaging, in particular of multi-sliced computed tomography (MSCT), in BAV patients undergoing TAVI procedure, considering the lack of standardized protocols for sizing and device choice in this complex aortic valve anatomy.

Part IV: Discussion and Conclusions. The last part of the thesis is a discussion of the presented topics with some conclusions.

Part I

Aortic valve disease and innovation in percutaneous treatment by transcatheter aortic valve implantation

Chapter 2

Optimizing TAVI could make it even more effective!

Transcatheter aortic valve implantation (TAVI) celebrated the fifteenth anniversary since the first procedure sixteen years ago: more than 200.000 procedures have been performed worldwide with a dramatic increase in the recent years. An overwhelming and enthusiastic literature has established TAVI as a real breakthrough. In parallel to continuous technology refinements, we observed a decrease of the risk-profile of patients undergoing TAVI in our institutions. Several steps led to the wide acceptance of TAVI. One of the hurdles to overcome was mortality. Initially quite high and related to the patients' comorbidities, a regular improvement in thirty days and one-year survival has been observed, correlated to better transcatheter heart valves (THV) and increased operators' experience. Apart from the Nordic Aortic stenosis (NOTION) trial, ongoing randomized studies will try to demonstrate the non-inferiority of TAVI in comparison to surgical aortic valve replacement (SAVR) for all-comers low risk patients. The economic context in western countries precludes any larger adoption of TAVI, partly because of concerns about its cost-effectiveness. In this issue of the journal, Geisler et al. present an interesting Dutch perspective of TAVI cost-effectiveness, based on the CoreValve High risk pivotal trial. Cost-effectiveness has been the focus of few studies among which, a 2012 sub-analysis of the PARTNER IA trial, comparing TAVI with a balloon-expandable valve and SAVR in high-risk patients. In this trial, after stratification of the results by access route, transfemoral TAVI was associated to slightly lower 12-month costs and slightly increased quality-adjusted life years (QALY). At an incremental cost-effectiveness ratio <$50,000/QALY, transfemoral TAVI was economically attractive in 70.9% of bootstrap replicates, in comparison to only 7.1% of replicates in the transapical cohort. From a United Kingdom perspective, a cost-utility analysis based on the National Institute of Clinical Excellence (NICE) reference case design for technology and TAVI/SAVR effectiveness from the PARTNER IA trial confirmed these findings in 2013. The cost-effectiveness acceptability curve indicated that at a NICE £20,000 willingness to pay threshold per

QALY gained, TAVI had a 64.6% likelihood of being cost-effective, compared with 35.4% for SAVR. Most of the analyses were derived from a trial evaluating a balloon-expandable platform. As there are technical and outcome differences between balloon-expandable and self-expanding devices, dedicated economic study focusing on the latter type of THV are lacking. The work of Geisler and colleagues is the first analysis with a self-expanding device, in a European country. The authors confirmed the cost-effectiveness of a transcatheter approach: TAVI was projected to add 0.41 (3.69 vs. 3.27) QALY at an increased cost of €9,048, resulting in an incremental cost- effectiveness ratio of €21,946 per QALY gained. The probability of TAVI being cost-effective was 71%. Further cost reduction of approximately €5,400 would be associated to a "lean" scenario and make TAVI the predominant option.

One of the main findings from this study is that optimizing TAVI could make it even more cost-effective as compared to SAVR. This simplification results from optimizing the number of operators and nursing staff, decreasing procedural time to reducing hospital stay with early discharge for selected patients. Indeed, in the UK NICE analysis, despite greater procedural costs and THV prices, TAVI was cost-effective compared with SAVR over a 10-year model horizon. The reasons were greater postsurgical costs and hospital stay. Even though meticulous and coherent, a limitation of the analysis from Geisler et al. is the lack of integration of rehospitalization in their economic model. Indeed, about 17% of TAVI patients are re-admitted within 30 days in the ACC STS/TVT registry.

In conclusion, as it is now obvious, to any heart team across the globe, that TAVI is superior to medical therapy in inoperable patients, at least equal to SAVR in high-risk patients and comparable to SAVR at to 2 years in intermediate-risk ones, TAVI cost-effectiveness should not be questioned anymore. Simplification and optimization of TAVI pathway are key for future enhancement of its cost-effectiveness. We can be confident and anticipate continuous improvements in THV costs, clinical outcomes and hospital stay. However, before making TAVI the dominant therapy, durability needs to be assessed thoroughly.

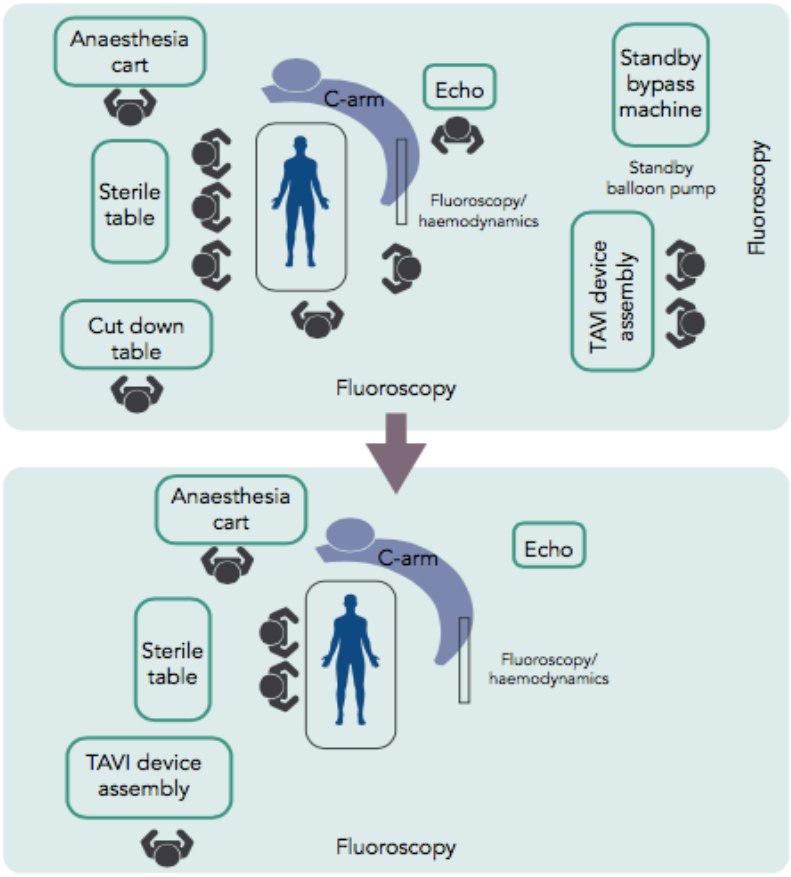
Chapter 3

How to Make the TAVI Pathway More Efficient

As there has been a rapid expansion transcatheter aortic valve implantation (TAVI) produres, there is a need to optimise TAVI programmes to ensure efficiency. In this article, we discuss the reasons why clinicians need to make the TAVI pathway more efficient and describe the most important steps to take from screening to early discharge, including procedural optimisation.

The core idea behind an efficient TAVI programme is to be able to treat all patients who need the procedure by including optimisation of the screening phase, a minimalist approach during the procedure and early discharge without compromising clinical outcomes, as efficient TAVI should aim to eliminate complications. Optimising the screening phase is potentially the most important part of an efficient TAVI programme. It should quickly provide the heart team with all the necessary elements for a multidisciplinary discussion: transthoracic echocardiography, multisliced computed tomography (MSCT) of the aortic root and peripheral vasculature, coronary angiogram (according to local practice) and blood tests. A dedicated TAVI coordinator in charge of scheduling the screening tests during a 2–3-day hospitalisation, gathering all the results for the heart team, scheduling the TAVI procedures and preparing the mode of discharge of the patients after the procedure would simplify the screening phase. This enables the team to screen all eligible patients.

Making the procedure more efficient means avoiding steps that are inessential. The contemporary trend for transfemoral TAVI is to reduce the team to two main operators, an anaesthesiologist, a perioperative nurse to prepare the THV and a circulating nurse to cover logistics in the operating room.



Cath-lab organisation to improve TAVI procedure. Two main operators, an anaesthesiologist, a perioperative nurse to prepare the THV and a circulating nurse to cover logistics in the operating room, fluoroscopic guidance, a transthoracic echography machine in the operating room in order to quickly identify complications.

Conscious sedation is the gold standard for transfemoral TAVI because general anaesthesia can be harmful, particularly in older people. For femoral access, the most popular closure devices are Prostar and ProGlide, which are similar and carry low rates of major vascular complications. However, new closure devices are being introduced that may simplify and further secure femoral closure for early ambulation. Many teams are moving to the use of a single femoral access and a radial access as the secondary arterial access to reduce the rate of vascular complications. Given the accuracy of positioning of current THV and their efficiency in mitigating paravalvular regurgitation, the use of transoesophageal echocardiography is no longer necessary. Fluoroscopic guidance has proven its feasibility since the early days in Rouen and it is becoming the rule in most institutions. However it is generally recommended to have a transthoracic echography machine in the operating room in order to quickly identify complications; at least to verify the absence of pericardial effusion after the THV has

been deployed.

The last aspect of an efficient TAVI programme is early ambulation and early discharge, usually within two days. This will ensure an adequate turnover of uncomplicated patients. Local rules have to be determined to make sure that every patient can be safely discharged, particularly without an increased risk of delayed atrioventricular block and with an adequate follow-up. baseline renal impairment or geriatric assessment. There are also indications for general anaesthesia, such as a need for a ‘zero contrast’ procedure with transoesophageal echocardiography guidance. In some cases there will also be a need for a longer period of post-operative surveillance, such as high risk of AV block, depressed renal function, vascular complications or the need for blood transfusion.

Chapter 4

Local Anesthesia-Conscious Sedation: The Contemporary Gold Standard for Transcatheter Aortic Valve Replacement

To date, more than 300,000 transcatheter aortic valve replacement (TAVR) procedures have been performed worldwide. This rapid adoption reflects the enthusiasm surrounding that breakthrough therapy. The standardization of TAVR procedures makes them more reproducible and predictable outcome-wise. General anesthesia (GA) has been mainly performed for transesophageal echocardiography guidance. This imaging modality may be useful to guide transcatheter heart valves (THV) deployment, appreciate the degree of residual aortic regurgitation, and quickly identify life-threatening complications such as annular rupture or cardiac tamponade. However, in contemporary practice, the technological refinements of second- generation THV enable 30-day mortality rates of approximately 1% to 2%, major vascular complications and moderate-severe residual aortic regurgitation rates under 10%, and extremely rare cases of tamponade or annular rupture. Thus, the systematic use of transesophageal echocardiography is questionable. With the expansion of the indications for TAVR, physicians and hospitals are facing new challenges. How do we treat more TAVR patients while guarding against increased health care costs and protecting against adverse clinical events? Several levers can be activated to achieve that goal. Shortening procedure duration and hospital stay, alongside early discharge, remain central among the possibilities. We have seen in recent years the development of various strategies aimed at simplifying or streamlining TAVR procedures, at least trans- femoral procedures, which represent more than 90% of the cases in most institutions. Indeed, local anesthesia-conscious sedation (LACS), percutaneous access with closure devices, direct THV implantation without balloon valvuloplasty, and minimizing cases of left ventricle pacing, are strategies recently adopted by many heart teams. By combining these various time-saving strategies, up to 7 TAVR procedures can be performed daily in some high-volume institutions. Simple evidence to support TAVR under LACS is the first-in man case that was performed in this manner over 15 years

ago. The pioneering team in Rouen promoted that technique and was the first to demonstrate the safety of this LACS approach for transfemoral TAVR, legitimizing the expansion of this strategy. Another small study demonstrated that GA could be associated with an increased risk of post-operative delirium and subsequent late death. The need for a surgical cut down for femoral ac- cess has been opposed as an argument for GA, but it can be performed without precluding LACS use. The theoretical benefits of LACS include a reduction of intraoperative instability, shorter procedures, better recovery, and shorter hospital stays. However, data on the real impact of LACS are conflicting and mainly represent the early experience of some centres.

Chapter 5

Embolic Events Post-Transcatheter Aortic Valve Replacement: Time to Protect the Brain

The use of cerebral protection devices (CPD) during transcatheter aortic valve replacement (TAVR) is still a matter of debate. It brings to mind the initial conversations between partisans of balloon-expandable transcatheter heart valves (THVs) and self-expanding valves. This confrontation mainly reflected the limited experience at that time with a single type of THV. In a contemporary and mature practice, the community now agrees that both types of THVs are complementary and carry clear advantages in specific anatomies. As an analogy, the actual divergence of opinion about CPD opposes users and nonusers of the technology, in other words physicians with different levels of experience with it. What does the available research tell us? The first thing we know is that stroke remains frequent post-TAVR, about 3% to 5% at 1 year, with 50% of events occurring within 3 days and being procedure related. Stroke post-TAVR is probably underreported, and its real frequency in- creases when a neurologist is involved in patient assessment. Half of strokes are covert events and could have a delayed impact on depression, cognitive function, and quality of life. Another important point to be gleaned from published studies is that every TAVR procedure generates micro- and macroscopic debris to the brain. Indeed, between 75% and 99% of analyzed filters, from the pioneer experience of Van Mieghem et al. to the most recent SENTINEL randomized trial, contain debris up to 4 mm in size. This debris is independent of operators' experience and inherent to the procedure itself. Histopathologic analysis finds, non- exhaustively, thrombus-surrounding emboli, aortic wall fragments, aortic leaflet material, ventricular components, calcium nodules, and plastic debris from the delivery catheters. The SENTINEL trial could not demonstrate a statistically significant difference in overall stroke rates with CPDs during TAVR, mostly because of a lack of power. However, an absolute reduction of 63% in the number of events occurring within 3 days was observed.

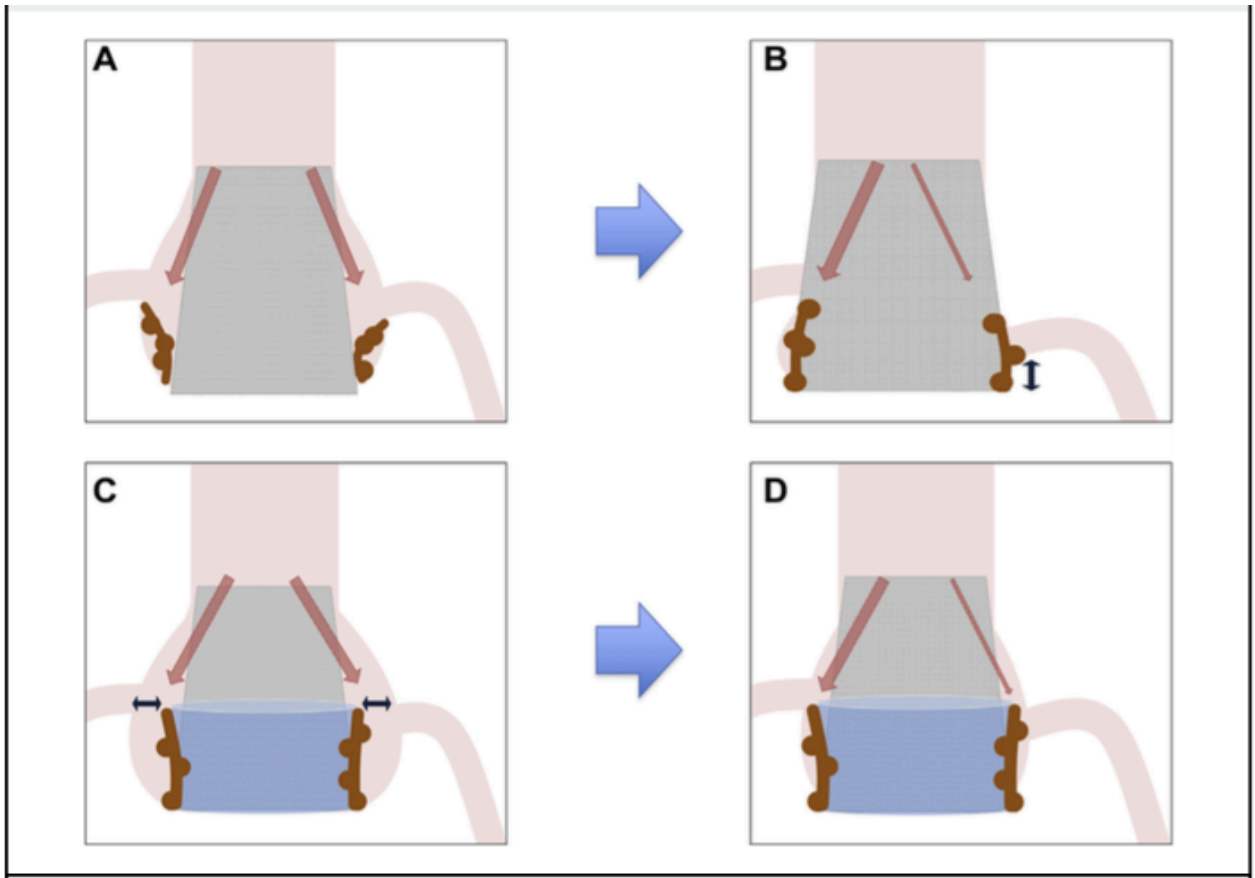
Chapter 6

Chimney Stenting for Coronary Occlusion During TAVR: Insights From the Chimney Registry

The aim of this study was to determine the safety and efficacy of chimney stenting, a bailout technique to treat coronary artery occlusion (CAO).

Background: CAO during transcatheter aortic valve replacement (TAVR) is a rare but often fatal complication.

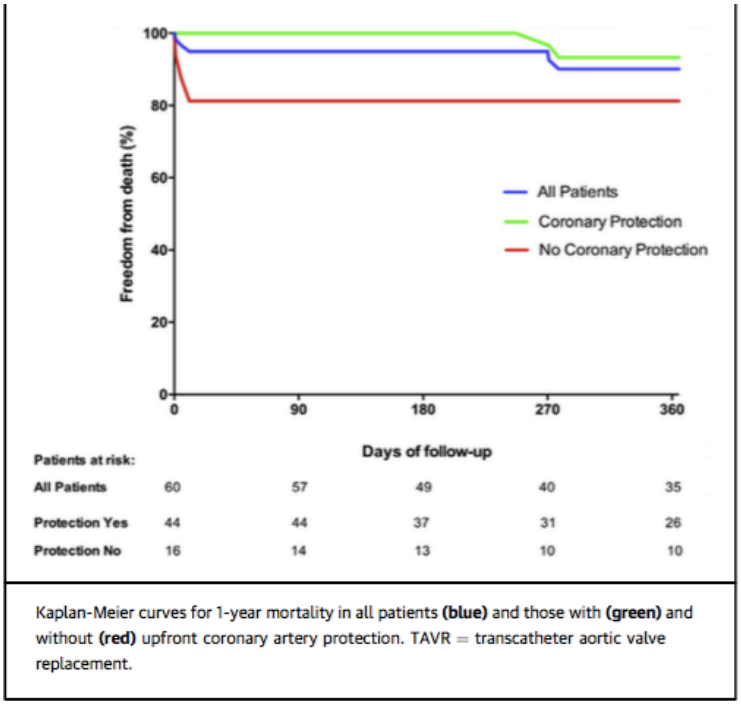
Methods: In the international Chimney Registry, patient and procedural characteristics and data on outcomes are retrospectively collected from patients who underwent chimney stenting during TAVR.



(A) Normal coronary flow after transcatheter aortic valve replacement (TAVR). **(B)** Coronary artery occlusion (CAO) with low coronary height **(black arrow)** or shallow sinuses of Valsalva and/or sinotubular junction. **(C,D)** TAVR for degenerated surgical bioprosthesis (valve-in-valve): surgical bioprosthesis with externally mounted leaflets or a short distance between the coronary ostia and the anticipated final position of the displaced bioprosthetic leaflets after transcatheter heart valve implantation **(black arrows)** are the main determinants of CAO.

Results: To date, 16 centers have contributed 60 cases among 12,800 TAVR procedures (0.5%). Chimney stenting was performed for 2 reasons: 1) due to the development of an established CAO (n 1⁄4 25 [41.6%]); or 2) due to an impending CAO (n 1⁄4 35 [58.3%]). The majority of cases (92.9%) had 1 or more classical risk factors for CAO. Upfront coronary protection was performed in 44 patients (73.3%). Procedural and in-hospital mortality occurred in 1 and 2 patients, respectively. Myocardial infarction (52.0% vs. 0.0%; $p < 0.01$), cardiogenic shock (52.0% vs. 2.9%; $p < 0.01$), and resuscitation (44.0% vs. 2.9%; $p < 0.01$) all occurred more frequently in patients with established CAO compared with those with impending CAO. The absence of upfront coronary protection was the sole independent risk factor for the combined endpoint of death, cardiogenic shock, or myocardial infarction. During a median follow-up time of 612 days (interquartile range: 405 to 842 days), 2 cases of stent failure were reported (1 in-stent restenosis, 1 possible late stent thrombosis) after 157 and 374 days.

One-Year All-Cause Death After TAVR With Chimney Stenting



Kaplan-Meier curves for 1-year mortality in all patients **(blue)** and those with **(green)** and without **(red)** upfront coronary artery protection. TAVR = transcatheter aortic valve replacement.

Conclusions: Chimney stenting appears to be an acceptable bailout technique for CAO, with higher event rates among those with established CAO and among those without upfront coronary protection.

Chapter 7

Transcatheter Aortic Valve Replacement in Pure Native Aortic Valve Regurgitation

This research aimed to create an International multicenter registry of transcatheter aortic valve implantation (TAVI) in pure native aortic regurgitation (AR) and evaluate procedural and clinical outcomes taking into consideration the technological developments of transcatheter valves.

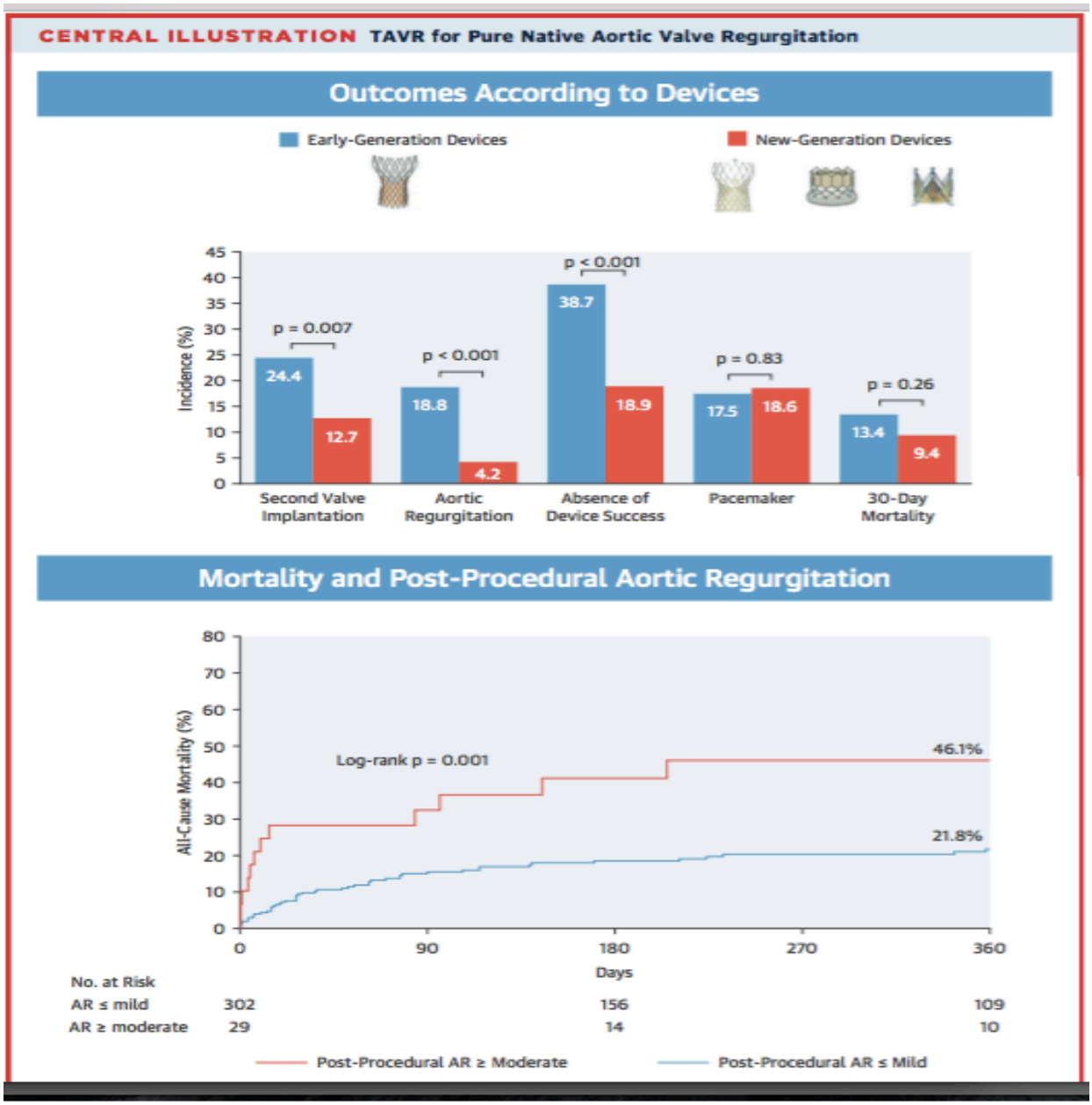
Background: Limited data exist about safety and efficacy of transcatheter aortic valve replacement (TAVR) in patients with pure native AR.

Objectives: This study sought to compare the outcomes of TAVR with early- and new-generation devices in symptomatic patients with pure native AR.

Methods: From the pure native AR TAVR multicenter registry, procedural and clinical outcomes were assessed according to VARC-2 criteria and compared between early- and new-generation devices.

Results: A total of 331 patients with a mean STS score of 6.7 ` 6.7 underwent TAVR. The early- and new-generation devices were used in 119 patients (36.0%) and 212 patients (64.0%), respectively. STS score tended to be lower in the new- generation device group (6.2 ` 6.7 vs. 7.6 ` 6.7; p 1⁄4 0.08), but transfemoral access was more frequently used in the early- generation device group (87.4% vs. 60.8%; p < 0.001). Compared with the early-generation devices, the new-generation devices were associated with a significantly higher device success rate (81.1% vs. 61.3%; p < 0.001) due to lower rates of second valve implantation (12.7% vs. 24.4%; p 1⁄4 0.007) and post-procedural AR moderate (4.2% vs. 18.8%; p < 0.001). There were no significant differences in major 30-day endpoints between the 2 groups. The cumulative rates of all-cause and cardiovascular death at 1-year follow-up were 24.1% and 15.6%, respectively. The 1-year all-cause mortality rate was significantly higher in the patients with post-procedural AR $ moderate compared with those with post-procedural AR # mild (46.1% vs. 21.8%; log-rank p 1⁄4 0.001). On multivariable analysis, post-procedural AR moderate was

independently associated with 1-year all-cause mortality (hazard ratio: 2.85; 95% confidence interval: 1.52 to 5.35; p 1⁄4 0.001).



Incidences of second valve implantation, post-procedural aortic regurgitation (AR) $ moderate, device success, new permanent pacemaker insertion, and 30-day mortality following transcatheter aortic valve replacement (TAVR) for patients with pure native AR using the early- and new-generation devices are shown (top). The cumulative 1-year all-cause mortality rates in patients with post-procedural AR $ moderate (orange line) and those with post-procedural AR # mild (blue line) after TAVR in pure native AR are shown (bottom).

Conclusions: Compared with the early-generation devices, TAVR using the new-generation devices was associated with improved procedural outcomes in treating patients with pure native AR. In patients with pure native AR, significant post-procedural AR was independently associated with increased mortality.

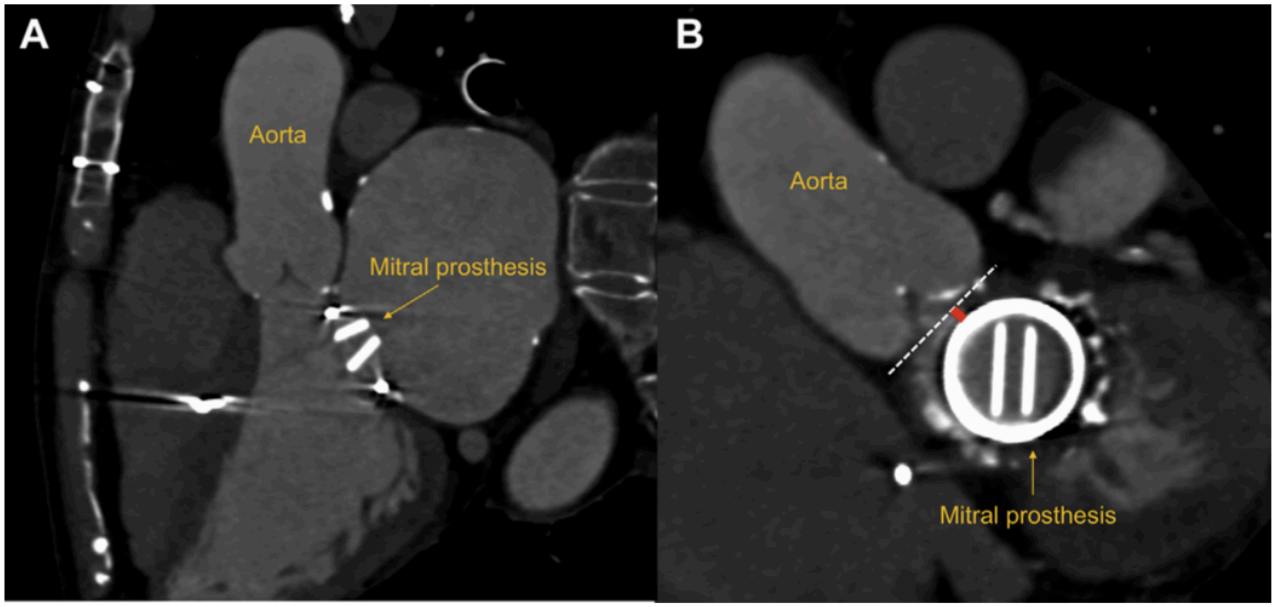
Chapter 8

Outcome of Patients Undergoing Transcatheter Implantation of Aortic Valve With Previous Mitral Valve Prosthesis

(OPTIMAL) Study

The aim of this study is to describe real- world procedural and early outcomes of patients with previous MV prostheses undergoing TAVR at high-volume centres

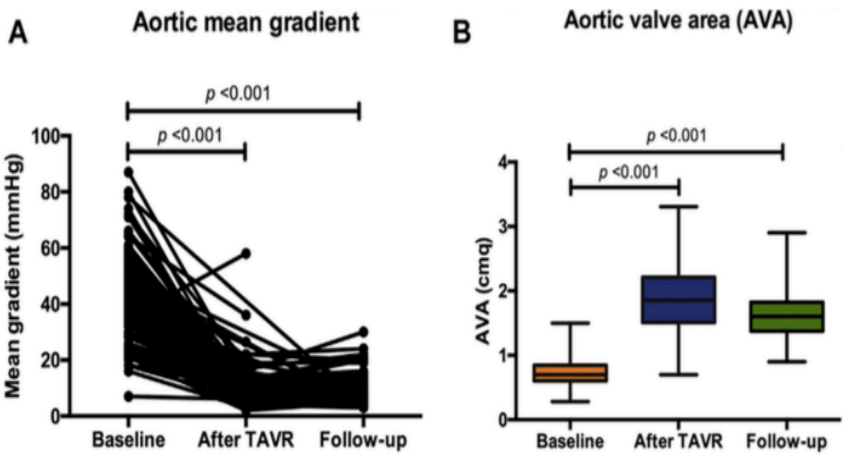
Background: Transcatheter aortic valve replacement (TAVR) is the gold standard for severe valvular aortic stenosis in patients at high/ prohibitive surgical risk. This procedure has also been used in patients with previous mitral valve (MV) prostheses, with contrasting outcomes reported. The aim of this study is to describe procedural and early outcomes of patients with previous MV prostheses undergoing TAVR.



Mitroaortic distance. The virtual basal ring is identified by multiplane reconstruction (A, B). Then, the mitroaortic distance (red line) is calculated as the perpendicular segment between the virtual basal ring plane (white dashed line) and the closest point of the MV prosthesis cage (B).

Methods: This is a retrospective registry of 154 patients with previous MV prostheses who underwent TAVR across high-volume medical centres at a mean of 11.7 ± 8.4 years after mitral surgery.

Results: Mean mitroaortic distance at computed tomography was 9.7 ± 4.8 mm. Procedural success was achieved in 150 (97.4%) patients, with reduction of aortic gradients (42.6± 14.2 to 10.0 ± 7.0 mm Hg; P < 0.001). Device success was achieved in 133 (86.3%) patients. MV prosthesis interference by the TAVR device was observed in 2 patients; in both, the mitroaortic distance was <5 mm, with 1 complicated by TAVR prosthesis embolization. Periprocedural complications included 4 (2.6%) cerebrovascular accidents, 10 (6.6%) major vascular complications, 22 (14.4%) severe bleedings, 1 (0.7%) myocardial infarction, and 5 (3.2%) in-hospital deaths (all cases cardiovascular or procedure related). At a median follow-up of 13.5 (interquartile range 1.0 to 36.0) months, 26 (16.9%) deaths occurred; 15 (9.7%) were cardiac related. Late fatal mitral prosthesis thromboses occurred in 2 patients. We recorded a case of fatal hemorrhagic stroke; hospital readmission was observed in 25 (16.2%) patients due to worsening heart failure.



TAVR performance at follow-up. Mean aortic gradient (A) and AVA (B): the favourable hemodynamic profile after TAVR was maintained at long-term follow-up.

Conclusions: TAVR in patients with previous mitral prostheses appears to be safe and feasible, with good hemodynamic results at 30-day and at longer-term follow-up.

Chapter 9

Aortic Valve Replacement in Oncology Patients With Severe Aortic Stenosis

The authors sought to collect data on contemporary practice and outcome of transcatheter aortic valve replacement (TAVR) in oncology patients with severe aortic stenosis (AS).

Background: Oncology patients with severe AS are often denied valve replacement. TAVR may be an emerging treatment option.

Cancer Characteristics at TAVR Day (n 222)

Cancer stage	
I	60 (28)
II	46 (21)
III	23 (11)
IV	86 (40)
Metastasis	68 (31)
Antineoplastic therapy at baseline	59 (29)
Treatment goal	
Palliative	78 (37)
Curative	117 (55)
Undecided	17 (8)
Indication for surgery, oncological	55 (26)
Cancer type	
Gastrointestinal	49 (22.1)
Prostate	36 (16.2)
Hematological	35 (15.8)
Breast	34 (15.3)
Lungs	25 (11.3)
Urinary bladder	12 (5.4)
Renal	9 (4.1)
Melanoma	5 (2.3)
Thyroid	4 (1.8)
Upper respiratory tract	3 (1.4)
Ovary	3 (1.4)
Meningioma	2 (0.9)
Parotid	1 (0.5)
Testes	1 (0.5)
Adenocarcinoma	1 (0.4)
Leiomyosarcoma	1 (0.5)
Liposarcoma	1 (0.5)

Methods: A worldwide registry was designed to collect data on patients who undergo TAVR while having active malignancy. Data from 222 cancer patients from 18 TAVR centres were compared versus 2,522 "no-cancer" patients from 5 participating centres. Propensity-score matching was performed to further adjust for bias.

Results: Cancer patients' age was 78.8 ` 7.5 years, STS score 4.9 ` 3.4%, 62% men. Most frequent cancers were gastrointestinal (22%), prostate (16%), breast (15%), hematologic (15%), and lung (11%). At the time of TAVR, 40% had stage 4 cancer. Periprocedural complications were comparable between the groups. Although 30-day mortality was similar, 1-year mortality was higher in cancer patients (15% vs. 9%; $p < 0.001$); one-half of the deaths were due to neoplasm. Among patients who survived 1 year after the TAVR, one-third were in remission/cured from cancer. Progressive malignancy (stage III to IV) was a strong mortality predictor (hazard ratio: 2.37; 95% confidence interval: 1.74 to 3.23; $p < 0.001$), whereas stage I to II cancer was not associated with higher mortality compared with no-cancer patients.

Conclusions: TAVR in cancer patients is associated with similar short-term but worse long-term prognosis compared with patients without cancer. Among this cohort, mortality is largely driven by cancer, and progressive malignancy is a strong mortality predictor. Importantly, 85% of the patients were alive at 1 year, one-third were in remission/cured from cancer.

Chapter 10

What are the remaining limitations of TAVI?

This review aims to face the debated subject of limitations of transcatheter aortic valve implantation (TAVI) in nowadays-clinical practice, outlining the controversial indications, complications and long-terms outcomes of the percutaneous treatment for aortic stenosis.

TAVI is a recognized therapy for patients with symptomatic severe aortic stenosis (AS). TAVI resulted superior to medical therapy for mortality in extreme-risk patients, non-inferior or superior to surgery in high-risk patients and non-inferior to surgery in intermediate-risk patients. However, several limitations affect outcomes after TAVI. Adverse events related to this procedure, like vascular complications, need for pacemaker implantation, paravalvular regurgitation, can be factors limiting TAVI treatment in younger patients at lower risk, as well as uncertainties regarding valve durability. This review tries to figure out some of the main complications still unsolved after TAVI.

Pacemaker implantation: The conduction disturbances after TAVI is still one of the most frequent complications of this technique, potentially limiting the treatment in younger and lower risk patients. The new-onset of left bundle branch block (LBBB) or of high-degree atrio-ventricular (AV) block requiring permanent pacemaker implantation (PPI) are still high (above 13%) and usually occur in the periprocedural period or within 24-48 hours from the procedure.

Thus, predictive factors and preventive strategies have been investigated in an attempt to decrease pacemaker implantation. The mechanical interaction between the prosthesis and the conduction system is the main subject of matter, because of the amount of calcium in proximity with the conduction system that is compressed during valve deployment. In addition, there are several clinical factors predicting conductance abnormalities or definitive PPI, including aortic valve calcification, previous coronary artery by-pass grafting (CABG), diabetes and above all, base- line right-brunch bundle block (RBBB). This last rep- resents the strongest pre-procedural predictor for pace- maker implantation. The intraprocedural predictors are the device implantation depth in the left ventricle outflow tract

(LVOT), the presence of heart block during device implantation and the use of a self-expandable prosthesis. Indeed, the PPI rate was higher when a self-expandable CoreValve was implanted as compared to balloon-expandable ed- wards Sapien/Sapien XT devices. The risk of PPI was higher with first generation devices and proper valve size is imperative as the incidence of pacemaker implantation increases with prosthesis oversizing. Even with some of the new-generation devices the PPI risk has not been significantly reduced, and data available up to date do not show any improvement in definitive PPI rate, still up to 10% even with reposition- ing/retrievability characteristics of newer delivery systems. Data concerning the association between the PPI rate and mortality remain ambiguous but the possible reduction of left ventricular function induced by permanent right ventricle-based pacing should be taken into ac- count before referring patients at intermediate to low risk for TAVI procedures. Strategies to prevent the PPI have been proposed, including the higher device implantation, balancing the risk of valve embolization/migration and the occurrence of paravalvular leak (PVL), and reduced prosthesis length, in order to reduce the implantation depth in the LVOT (device depth inferior to 25% of LV OT). PPI indications are even controversial and sometimes not properly recognized, with an excess of post implantation related complications. Special attention should be given to patients presenting new-onset LBBB with Qrs longer than 160 milliseconds, because of their in- creased risk of sudden cardiac death and overall mortality. Nevertheless, prophylactic implantation in new- onset LBBB lacks of solid and reliable evidence. In case of new high degree AV block, an observational period with 7-day electrocardiographic monitoring should be performed to determine the disturbance persistence (*2017 ESC/EACTS Guidelines for the management of valvular heart disease* -Class I, level of evidence C). This observational period could be shortened in case of persisting AV block for 48 hours, considering that pro- longed observation can lead to bed rest for temporary pacemaker related risks. The majority of patients usually receive pacemaker implantation within 3 days after the procedure. Nevertheless, PPI performed the same day of TAVI procedure could be a safe option, achieving earlier discharge timing without long-terms complications; on the opposite, PPI during TAVI may result in an increase of periprocedural complications such as

pneumothorax or pocket hematoma. Data from the on-going prospective observational study "ambulatory electrocardiographic Monitoring for the detection of high-degree Atrio-ventricular Block in Patients With New-onset Persistent Left Bundle Branch Block after Transcatheter aortic Valve implantation (the Mare study) (ClinicalTrials.gov identifier: NCT02153307) may shed light to this controversial subject and clarify/modify our strategy for implantation of pacemaker after TAVI procedures. Additional technical advances, new strategies and further studies with longer follow-up need to address this matter in order to reduce the rate of PPI in the era of TAVI indications expanding towards younger patients.

Paravalvular aortic regurgitation: Paravalvular leak (PVL) represents one of the principal drawbacks of the concept of transcatheter aortic valves. Moderate-severe PVL can be related to suboptimal device implantation, valve under sizing, or to the huge amount of calcium in the aortic root.[40] The presence of those significant PVL is detrimental for patient since it is associated to worse hemodynamic outcome and impaired survival. Unknown is the potential impact of mild PVL on the durability of TAVI devices. Significant PVL was more frequent after first generation devices implantation, where moderate or severe PVl rate was 10% to 11% after both balloon-expandable Edwards Sapien XT or self-expandable Medtronic Core-Valve. With new-generation devices the PVL incidence has been drastically reduced, thanks to the improvement in device sealing characteristics of new-generation valves. As reported in previous studies, the incidence of severe and moderate PVL was respectively "none" and be- low 4% after new-generation self-expandable Medtronic Evolut R and balloon-expandable Edwards Sapien 3, thanks to dedicated sealing skirts of these devices and also better understanding of sizing requirements of each type of valve. Operator's experience and new device technologies can help to minimize this unfavourable consequence after TAVI procedure.

Vascular complications: Transfemoral access represents the usual vascular ac- cess in TAVI procedures.[47-49] The risk of vascular complications is related to puncture performance, sheath outer diameter, closure device failure or incorrect pre- closing strategy. But even after new prosthesis

delivery-system downsizing and proper vessel selection by multi-sliced computed tomography (MSCT) analysis, vascular complications still occur and are always associated with higher morbidity and mortality. Vascular complications and bleedings are classified following the Valve academic research Consortium (VARC)-2 consensus document for TAVI endpoints.

Predictors of vascular injury have been investigated in previous papers, including the "sheath to femoral artery ratio" (SFAR), the vascular calcifications and the centre experience. In particular, an SFAR cut-off value of 1.05 correlated to better TAVI-related outcomes. In addition, female gender can be an independent determinant of both major vascular complications and bleeding. Bleeding complications associated to vascular injury represent additional predictor of worse patient outcome. As reported from a multicenter analysis, bleeding after TAVI are frequent, are usually related to access site complications and often require blood trans- fusion. This last one represents an independent predictor of increased 1-year mortality, acute kidney injury and stroke after TAVI.

New strategies have been proposed to reduce vascular complications and bleeding. Sheath smaller outer diameter, better profile and performance are of paramount importance to reduce vessel injury, while preclosing device strategy can minimize the bleeding from vascular access. Left radial artery as second vascular access would help to reduce contralateral femoral bleeding. Innovation on puncture assessment, as the echo-guided puncture and preclosing device deployment, showed significant lower rate of major vascular complication after transfemoral TAVI. However, the majority of vascular complications and bleeding are still related to closure device complications including vessel dissection, occlusion of femoral artery, major bleeding and device failure in calcified arteries. Thus, further vascular closure devices could help reducing the burden of access-site related complications.

Stroke: Despite operator expertise improvement and improved delivery systems and devices, stroke or transient ischemic attack (TIA) remain potential complications after TAVI. The risk of stroke is equal or rather lower after TAVI when compared to surgery, but it is significantly higher within 90 days from TAVI when compared to the risk of the general population. The majority of acute ischemic strokes are caused by athero or thrombo embolic events generated during the crossing of the aortic

arch, during aortic balloon valvuloplasty or device deployment, and above all during valve postdilation. Late predictor for cerebrovascular event is the presence at baseline or the new-onset of atrial fibrillation that increases the risk of stroke of 4.4 fold. In addition, baseline aortic regurgitation can represent an independent predictor for postprocedural stroke. Cerebral protection devices as filters or deflectors can represent a good strategy to prevent embolic risk above all in highly calcified aortic root. Some of them are un- der evaluation for their real efficacy during TAVI. The SENTINEL Trial outlined that in the 99% of TAVI cases filters were useful to gather debris made of non-thrombotic material. This would be in favour of the potential embolic risk during TAVI suggesting that antithrombotic therapy cannot prevent alone embolization risk. a re- cent meta-analysis and 4 randomized studies about the use of cerebral protection device during TAVI reported lower incidence of new cerebral ischemic lesions. Anyway, even the preponderance of data showing the safety of these protection devices, there are still no evidence of efficacy from RCTs and the debate is still open if younger patients would really benefit from routinely use of embolic protection devices.

Antithrombotic therapy and valve thrombosis: Latest guidelines do not report any conclusive data about a definite strategy for antithrombotic therapy after TAVI. Empirical combination of low-dose of aspirin and a thienopyridine (dual antiplatelet therapy-DAPT) are usually administrated during the three months following TAVI in patients not requiring further anticoagulation. Anyway further studies suggest that single antiplatelet therapy would be even safer.[68, 69] Triple therapy (DAPT and vitamin K antagonist-VKA) should be carefully evaluated according to the ischemic and bleeding risk of patients, since antiplatelet agents can increase the major bleeding risk when added to anticoagulation. Valve thrombosis is a rare event that can happen af- ter TAVI (subclinical leaflet thrombosis occur in the 13%).[71-73] in this setting, anticoagulation therapy demonstrated better reduction of subclinical device thrombosis after TAVI when compared to DAPT. VKA or un-fractioned heparin (UFH) are anyway the first-line treatment in any case of device thrombosis. Ongoing randomized trials will improve current limited knowledge on optimal antithrombotic treatments showing results even for

new-oral-anticoagulants efficacy in the TAVI setting: GALILEO (rivaroxaban), ATLANTIS (apixaban), ENVISAGE TAVI (edoxaban).

Bicuspid aortic valves: TAVI treatment for AS in bicuspid aortic valve (BAV) is still controversial due to specific anatomical characteristics of this subset of patients. BAV can be encountered in both young and elderly patients and represent the 2% to 6% of patients with severe as. BAV usually present asymmetric cusps, highly calcified valve, larger annulus and ascending aorta aneurysm when compared to tricuspid aortic valve. The anatomical complexity can lead to procedural complications, such as device mal-positioning/embolization or significant residual PVL. For these reasons bicuspid has been considered as relative contraindication to TAVI and BAV patients are not included in major RCTs. Nonetheless, recent registries report the safety and the feasibility of percutaneous aortic valve replacements even in these complicated aortic roots. New-generation devices showed better outcome in BAV patients when compared to old-generation devices. data at follow-up for mortality and PVL resulted comparable to patients with tricuspid aortic valve undergoing TAVI. Anyway further RCTs on correct sizing and dedicated de- vice still need to validate the percutaneous treatment in BAV patients.

Low-surgical risk patients: TAVI procedure lacks of strong evidence from RCTs in patients at low-surgical risk, defined as patients with society of Thoracic surgeons risk for mortality (STS) <4 and logistic European system for Cardiac operative risk evaluation (EUROSCORE) <10%. A recent paper outlines that elderly patients at low-risk undergo TAVI as routinely practice in many European centres while for younger low-risk patients TAVI indication is still controversial. The main controversy is represented by unclear TAVI device durability, with the possibility of valve-in-valve need or rather surgical valve repair at long-term. Available data on mortality up to now reflect the advanced age and comorbidities of population treated more than the prosthesis failure. Anyway the shorter life expectancy of population represents a bias. Some hypothesis on leaflet crimping, incomplete expansion, asymmetric leaflet opening or major shear stress let assuming that TAVI device durability can be shorter compared to surgical bio-prosthesis, even if outcomes are comparable for TAVI or

surgery at 5 years follow-up. Two RCTs on younger low-risk patients (PARTNER 3 and Evolut R-low risk) are on- going in order to obtain longer follow-up data in this specific setting.

Durability: TAVI devices can degenerate similar to surgical bio- prosthesis valves. Prosthesis failure can be related to several clinical factors, including age as main determinant, infections, renal failure, and to some technical factors as valve malposition for severe calcifications. Since patients referred to the TAVI treatment are old and high-risk patients, life expectancy of this population in- deed influence the device durability. The novelty of the TAVI devices does not permit having long-term FU similar to 10 years FU of surgical bioprosthesis (TAVI CE Mark approval was obtained in 2007 while FDA approval in 2011). However some data on first generation TAVI devices have been extrapolated from the PARTNER Trial, reporting freedom from valve deterioration at the 5 years from the index procedure. For the Sapien valve the 9.7% of patients surviving at 5 years showed device failure nor requiring re-intervention, while for the CoreValve device the percentage of failure at 5 years were of 1.4%, requiring re-intervention in two cases. A recent meta-analysis including 70 publications re- ports 87 cases of transcatheter device failure related to specific complications as endocarditis, structural failure, thrombosis, compression and late-embolization. These two latter complications are specifically related to transcatheter procedure and never re- ported for surgical bioprosthesis in the literature. So far there are no reliable data on TAVI devices at long-term FU and TAVI durability has not been yet established. Data on TAVI device durability are anyway of paramount importance in the new setting of lower risk or younger patients and larger registries with longer FU are required to really qualify and quantify the TAVI device deterioration.

Conclusions: TAVI procedure can be the optimal strategy in some categories of patients not suitable for surgery or in which surgery is not mandatory. Anyway, further data from RCTs and on-going technological or pharmacological refinements are needed to minimize the remaining limitations of this technique in order to provide safety even in lower-risk population. New-generation devices, data on medical therapy and operator's expertise need to achieve this goal.

Part II

TAVI in a complex anatomical setting: Bicuspid Aortic Valve management and percutaneous treatment

Chapter 11

Contemporary management of severe symptomatic bicuspid aortic valve stenosis: the BiTri registry

In this research paper we sought to evaluate the contemporary frequency and pre interventional management of symptomatic patients with severe BAV stenosis.

Background: A greater number of patients with bicuspid aortic valves (BAV) may be identified and treated as indications for transcatheter aortic valve implantation (TAVI) is expected to expand to younger patients. We evaluated the contemporary frequency and management of symptomatic patients with stenotic BAV in a multicenter European registry.

Methods: Between November 2017 and February 2018, all consecutive patients admitted for symptomatic aortic stenosis (AS) across six high-volume European hospitals were prospectively enrolled in the BiTri registry.

Results: Of the 832 patients, 17% (n=138) had a BAV. The most frequent BAV phenotypes were type 1 (left-right coronary cusps fusion-64%) and type 1 (right-non coronary cusps fusion-17%). Type 0 and type 2 accounted for 12% and 2%, respectively. When compared with tricuspid patients (n=694), BAV patients were younger, with lower surgical risk. The transthoracic echocardiography (TTE) identified BAV in 64% of patients. Multi-sliced computed tomography (MSCT) additionally completed the diagnosis in 20% of patients. Surgical inspection finally identified remaining undiagnosed 16% of BAV. A combination of TTE and MSCT was the most common diagnosis method for BAV. Surgical aortic valve replacement (SAVR) was the predominant therapeutic option for BAV (70%) whilst TAVI was performed in 26%.

Aortic stenosis treatment

	Bicuspid (N=138)	*Tricuspid (N=694)*	*P*
Medical Therapy	5 (4)	13 (2)	0.20
SAVR	97 (70)	328 (47)	**<0.001**
TAVI	36 (26)	351 (51)	**<0.001**

SAVR: surgical aortic valve replacement; TAVI: trans-aortic valve implantation.

Aortic stenosis mode of diagnosis

A – Distances between Bicuspid Valve diagnosed and First Mode of Diagnosis

	First Mode	*Distance*
Bicuspid Valve	**Surgical inspection**	**0.87**
Bicuspid Valve	MSCT	0.99
Bicuspid Valve	Echography	1.40

B – Distances between Bicuspid Valve diagnosed and Modes of Diagnosis

	Modes	*Distance*
Bicuspid Valve	**Echography & MSCT**	**0.20**
Bicuspid Valve	Surgical inspection only	0.22
Bicuspid Valve	MSCT & Surgical inspection	0.34
Bicuspid Valve	Echography & MSCT & Surgical inspection	0.34
Bicuspid Valve	MSCT only	0.34
Bicuspid Valve	Echography & Surgical inspection	0.47
Bicuspid Valve	Echography only	2.29

C – Distances between Bicuspid Valve diagnosed and Last Mode of Diagnosis

	Last Mode	*Distance*
Bicuspid Valve	**MSCT**	**0.17**
Bicuspid Valve	Surgical inspection	0.22
Bicuspid Valve	Echography	2.27

MSCT: multi-sliced computed tomography

Conclusions: BAV is frequently observed in symptomatic patients with AS. These patients are younger, have a lower risk profile and are predominantly treated with SAVR as compared to tricuspid patients. However, TAVI is performed in almost one third of BAV patients in contemporary European practice. TTE combined with MSCT identified 84% of BAV.

Chapter 12

Aortic valve anatomy and outcomes after transcatheter aortic valve implantation in bicuspid aortic valves

In this paper we aimed at comparing the anatomical characteristics and clinical outcomes of patients with bicuspid or tricuspid aortic valves undergo- ing TAVI for severe AS in our centre.

Purpose: Aortic stenosis (AS) in bicuspid aortic valve (BAV) remains a challenge for transcatheter aortic valve implantation (TAVI). BAV is a condition encountered in young adults as well as elderly patients. Frequently we face in clinical practice elderly patients with BAV and severe AS, but there is little evidence concerning TAVI in this population. The aim of our study was to compare anatomic features and outcomes of bicuspid and tricuspid patients with AS undergoing TAVI.

Methods: 83 consecutive BAV patients undergoing TAVI were matched, in a 1:2 ratio, to 166 tricuspid patients. Multi-detector computed tomography (MDCT) and transthoracic echocardiogram (TTE) were assessed at base- line. Primary endpoint was all-cause mortality and early safety at 30 days according to Valve Academic Research Consortium criteria 2 (VARC-2). Secondary endpoint included device success.

Results: BAV patients presented more aortic root calcifications, smaller diameter of left ventricular outflow tract (LVOT) and dilated aorta. We did not observe any statistically significant difference concerning all-cause mortality and early safety at 30 days. However higher intra-procedural TAV-in-TAV bailout procedure was observed in the BAV cohort, with consequent reduction of device success rate.

In-hospital and 30-days follow-up

In Hospital	*N*	Tricuspid ($N = 166$)	Bicuspid ($N = 83$)	P
VARC-2 endpoints				
All-cause mortality n. (%)	249	4/166 (2)	3/83 (3)	0.68
All-stroke n. (%)	248	2/166 (1)	1/83 (0.5)	1
Device success n. (%)	249	155/166 (93)	61/83 (73)	<0.01
Additional results				
New Pacemaker n. (%)	249	17/166 (10)	12/83 (14)	0.4
PVL n. (%)	249	84/166 (52)	35/83 (46)	0.48
– Moderate–severe PVL n. (%)		4/166 (2)	3/83 (3)	
Mean trans-aortic gradient (mm Hg)	249	10 ± 4	9.8 ± 4.5	0.1
Hospital stay (day)	249	6.8 ± 2.4	8.2 ± 4.1	<0.01
30 Days	*N*	Tricuspid ($N = 166$)	Bicuspid ($N = 83$)	P
VARC-2 endpoints				
All-cause mortality n. (%)	249	5/166 (3)	4/83 (5)	0.47
All-stroke n. (%)	249	1/166 (0.6)	0/83	1
Early safety n. (%)	249	142/166 (85)	59/83 (71)	0.32
Additional results				
New pacemaker n. (%)	249	3/166 (2)	1/83 (1)	1
PVL n. (%)	249	88/166 (60)	35/83 (42)	0.47
– Moderate–severe PVL n. (%)		5/166 (3)	4/83 (5)	
Mean trans-aortic gradient (mm Hg)	249	10.4 ± 5.6	9.7 ± 4.8	0.44
Mean follow up timing (day)	249	39.1 ± 19.9	42.6 ± 23.2	0.24

Conclusions: Patients with BAV present more complex anatomy at baseline as compared to tricuspid AS patients. These anatomical features lead to more frequent TAV-in-TAV bailout procedure and lower device success rate, but are not associated with higher mortality rate at 30 days. Our findings support the feasibility of TAVI in BAV, but larger studies with longer follow-up and a focus on sizing are required.

Chapter 13

Balloon Versus Self-Expandable Valve for the Treatment of Bicuspid Aortic Valve Stenosis: Insights From the BEAT International Collaborative Registry

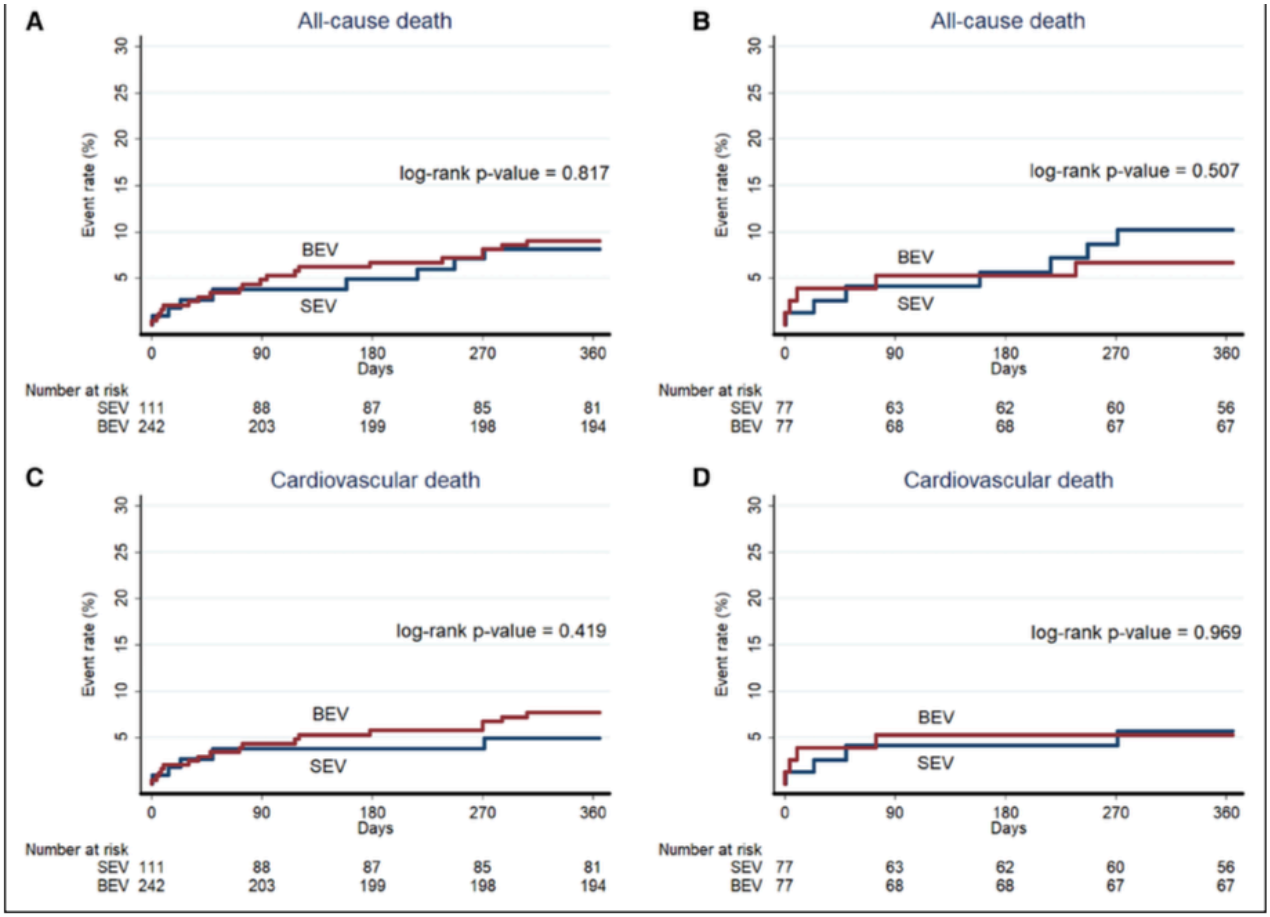
The aim of our international registry is to compare the procedural and clinical outcome of patients treated with the balloon- expandable Sapien 3 valve (Edwards Lifesciences, Irvine, CA) with those treated with the self-expandable Evolut R/ PRO valve (Medtronic, Minneapolis, MN).

Background: Large data comparing the performance of new-generation self-expandable versus balloon-expandable transcatheter heart valves in bicuspid aortic stenosis are lacking. We aim to compare the safety and performance of balloon- expandable and self-expandable transcatheter heart valves in the treatment of bicuspid aortic stenosis.

Methods: The BEAT (balloon versus self-expandable valve for the treatment of bicuspid aortic valve stenosis) registry included 353 consecutive patients who underwent transcatheter aortic valve implantation using new-generation Evolut R/PRO or Sapien 3 valves in bicuspid aortic valve.

Results: A total of 353 patients (n=242 [68.6%] treated with Sapien 3 and n=111 [68.6%] treated with Evolut R (n=70)/ PRO [n=41]) were included. Mean age was 77.8±8.3 years and mean Society of Thoracic Surgeons Predicted Risk of Mortality was 4.4±3.3%. Valve Academic Research Consortium-2 device success was similar between Sapien 3 and Evolut R/ PRO (85.6% versus 87.2%; P=0.68). In the Sapien 3 group, 4 patients experienced annular rupture whereas this complication did not occur in the Evolut R/PRO group. After propensity score matching, Valve Academic Research Consortium-2 device success was similar between both groups (Sapien 3=85.7% versus Evolut R/Pro=84.4%; P=0.821). Both in the overall and in the matched population, no differences in the rate of permanent pacemaker implant were observed. At 1-year follow-up, the rate of overall death and cardiovascular death were similar between the 2 groups. In the unmatched population, the 1-year echocardiographic

follow-up demonstrated similar rate of moderate-to-severe paravalvular aortic regurgitation (Evolut R/PRO 10.5% versus Sapien 3 4.2%, P=0.077); however, after propensity matching, the rate of moderate-to-severe paravalvular leak became significantly higher among patients treated with self-expandable valves (9.3% versus 0%; P=0.043).



One-year outcome according to all cause of death and cardiovascular deaths in both matched and unmatched populations. BEV indicates balloon-expandable valves; and SEV, self-expandable valve.

Conclusions: Our study confirms the feasibility of both Sapien 3 and Evolut R/PRO implantation in bicuspid aortic valve anatomy; a higher rate of moderate-severe paravalvular aortic regurgitation was observed in the Evolut R/PRO group at 1-year follow-up in the matched cohort, although patients treated with balloon-expandable valve had a higher rate of annular rupture.

Chapter 14

Transcatheter treatment of bicuspid aortic valves with the Evolut platform: the BIVOLUT-X registry

The aim of our prospective registry is to evaluate the clinical impact of the new Evolut PRO/XL prostheses (Medtronic, Minneapolis, Minnesota) in bicuspid aortic valve (BAV) and evaluate sizing methods for TAVI in BAV.

Objectives: Primary endpoint of the registry is to explore the 30 days and 1year outcomes post TAVI implantation using the Evolut PRO or Evolut XL devices via transfemoral approach in BAV patients. Secondary endpoint is to understand the implications of two sizing algorithms for BAV patients: annular-based sizing, supraannular-based sizing or combined sizing.

Study design: This is one of the first investigator initiated, international, multicenter, and prospective registry enrolling 14 centres across Europe and Canada. 151 consecutive patients undergoing TAVI for BAV with the Evolut Pro (23-26-29) or Evolut R 34 THVs were finally included. The indication for TAVI was under local Heart Team decision. As per local institution's regulatory policy, each patient provided a written informed consent for the TAVI procedure, anonymous data collection and analysis. All data were collected in an electronic clinical report form (eCRF).

Sample Size Calculation: No formal sample size calculation has been performed. This study is exploratory in nature.

Investigational Transcatheter Heart Valve: Evolut PRO™ (Medtronic, Minneapolis, MN, USA) is the latest iteration of the Medtronic CoreValve® Evolut R. It is a nitinol THV with a trileaflet porcine pericardium valve in a supra-annular position. The self-expanding nitinol stent frame integrates an architecture in three levels of function: inflow portion with a high radial force for anchoring within the aortic annulus, mid portion with a constrained structure for preservation of the coronary flow and outflow portion with a high hoop strength for coaxiality with the aortic root. As compared to Evolut

R™, Evolut PRO contains an external porcine pericardial wrap at the inflow level, designed to enhance the surface of contact with the patient annulus and LVOT, thus mitigating perivalvular regurgitation. The prosthesis is fully repositionable and retrievable before final detachment of the hooks and is available in three sizes (23, 26, 29) covering aortic annuli from 18 to 26 mm. The Enveo™ R delivery system and Enveo Inline™ sheath, compatible with the Evolut Pro 23-26-29 and the Evolut R 34, represent a 16F design with a modified intuitive handle, a reinforced nitinol capsule for resheathing and an integrated sheath (See figure). It is also possible to insert Evolut Pro or XL THV through a 20F femoral arterial sheath. It is up to the operator's discretion to use either the Enveo Inline sheathless insertion technique or a conventional sheath.

Evolut Pro and Evolut R XL were respectively CE-marked on January 13 2017 and July 27 2017.

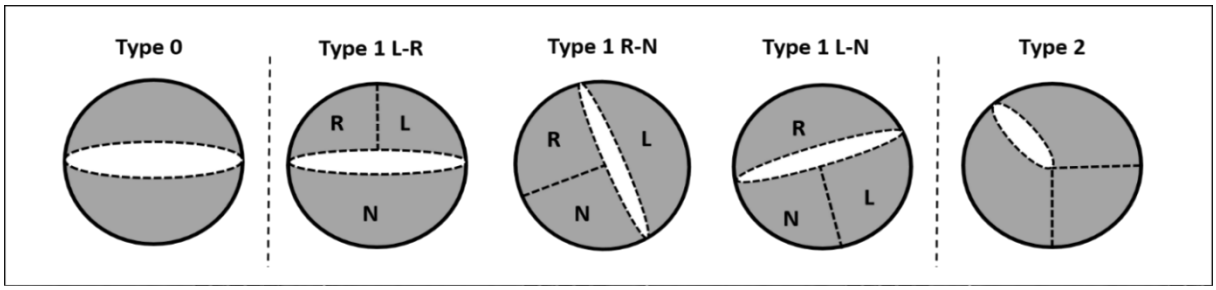
Evolut R 34 and Evolut Pro platforms

Sizing Based on Multislice Computed Tomography (MSCT): As per standard of care, the following recommendations apply for MSCT acquisition:

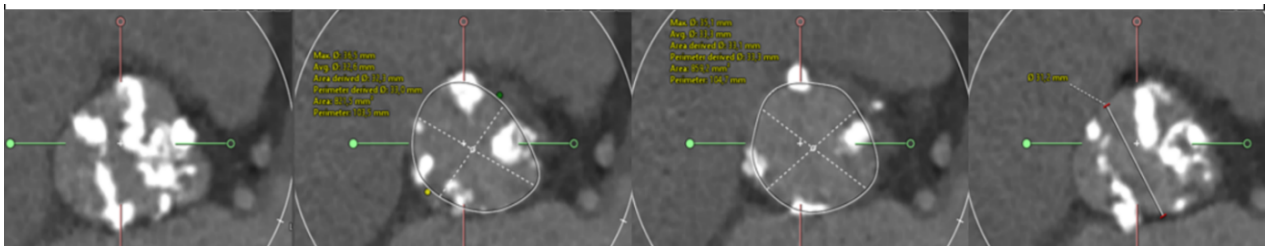
- ECG-assisted data acquisition for the aortic root
- Retrospective ECG-gating (full current and entire cardiac cycle)
- Prospective ECG-triggering centred in systole
- Smallest available slice thickness (0.6-0.8 mm)
- Mid-systole phase: 25-45% RR are considered for reconstruction

The BAV type was characterized according to Sievers et al. classification: Type 0 has no raphe, type 1 has one raphe and Type 2, two raphes.

Sievers Classification of BAV



The aortic annulus is determined by the virtual basal ring linking the hinge points of the aortic leaflets. The perimeter and perimeter-derived diameter of the aortic annulus are the dimensions considered for THV size selection. The intercommissural distance (ICD) or the supraannular periemeter-derived were measured at 4 mm above the aortic annulus, in an effort of standardization. The presence of a raphe and its length were measured together with the calcium load.



Various measurements at the level of the aortic. From left to right: sinus of Valsalva, aortic annulus, LVOT and ICD at 4 mm

Transcatheter Aortic Valve Implantation Procedure: TAVI procedures were performed according to the local standards of care. The transfemoral access could be fully percutaneous with closure devices or surgical cutdown. Heparin was provided to achieve an ACT about 250 sec. Balloon valvuloplasty was performed to prepare for THV insertion almost sistematically. Balloon size should not exceed the minimal diameter of the aortic annulus at baseline. THV deployment was performed as the current best practices with a final implant depth about 3-5 mm below the aortic annulus. If necessary, THV postdilatation was performed, based on the final hemodynamics and aortic

regurgitation assessment. Balloon size did not exceed the mean perimeter-derived diameter of the aortic annulus at baseline.

Follow-up: In hospital clinical and echographic monitoring were realized according to local policy. A transthoracic echocardiography (TTE) was performed, as per guidelines.

At 30 days, a physical examination was performed combined to TTE if not performed at discharge. Post-TAVI MSCT was sistematically performed to better appreciate THV shapes. At one-year follow-up, a physical examination coupled to TTE represent the target for the long-term outcome.

Results :

- **30 days clinical outcomes:**

Clinical outcomes	N = 151	Annular sizing N = 78	Combined sizing N = 73
All-cause death, n (%)	**5 (3.3)**	3 (3.8)	2 (2.7)
Cardiovascular death (n,%)	**3 (1.9)**	2 (2.5)	1 (1.4)
Disabling stroke, n (%)	**5 (3.3)**	3 (3.8)	2 (2.7)
Non-disabling stroke, n (%)	1 (0.7)	1 (1.3)	0(0)
Major bleeding, n (%)	7 (4.6)	2 (2.6)	5(7)
Life-threatening bleeding, n (%)	4 (2.6)	3 (3.8)	1 (1.4)
Acute kidney injury, n (%)	3 (2.0)	3 (3.9)	0 (0)
Major vascular complication, n (%)	**7 (4.6)**	4 (5,1)	3 (4.1)
Pacemaker implantation, n (%)	**29 (19.6)**	13 (16.7)	16 (21.2)

No significant p value between sizing strategies

- **30 days echographic outcomes:**

	Overall N = 151	Annular sizing N = 78	Combined sizing N = 73	P value
LVED, mm (IQR)	51 (45-56)	51 (44-56)	52 (44.8-55.2)	0.9
LVEF, %, median (IQR)	62 (52-65)	62 (50.5-65)	62 (53-65)	0.6
AVA, cm2, median (IQR)	**2.1 (1.8-2.7)**	2.2 (1.7-2.8)	2.0 (1.8-2.5)	0.1
AVA index, cm2/m2, median (IQR)	1.2 (0.9-1.5)	1.3 (1-1.6)	1.1 (0.9-1.5)	0.2
Mean aortic gradient (mmHg), median (IQR)	**7.3 (5.5-9.6)**	7.8 (5.7-10.4)	6.8 (5-9)	0.09
Paravalvular regurgitation, n(%)	85 (74.6)	46 (74.2)	39 (75)	1
Trivial	28 (34.1)	12 (27.3)	16 (42.1)	0.4
Mild	47 (57.3)	29 (65.9)	18 (47.4)	
Mild-Moderate	5 (6.1)	2 (4.5)	3 (7.9)	
Moderate	**3 (2)**	1 (2.3)	1 (2.6)	
Moderate-Severe	**0 (0)**	0 (0)	0 (0)	
Severe	**0 (0)**	0 (0)	0 (0)	
Prosthesis-patient mismatch, n (%)	**15 (10.5)**	**5 (6.4)**	**10 (13.7)**	**0.17**
Moderate 0.85-0.65 cm2/m2	5 (3.3)	1 (1.3)	4 (5.47)	
Severe < 0.65 cm2/m2	**2 (1.34)**	1 (1.3)	1 (1.36)	

- **Valve performance at 30 days :** Mean aortic valve gradient < 20 mm Hg or peak velocity < 3 m/s and no moderate or severe AR are reported in 98 % of the population, without significant difference according to sizing strategy (annular or combined sizing).
- **VARC2 device success :** device success is reported in 96 % of patients of the population**,** without significant difference according to sizing strategy or type 0/1 BAV.
- **Ellipticity index :** Mean ellipticity after THV implantation is 1.22 (1.14-1.35), without significant difference according to sizing strategy. This value do not differ significantly from the ellipticity index at baseline.

Conclusions: BIVOLUT X is one of the first prospective registries on BAV with a robust academic setting. An annular-based or combined sizing strategy is efficient for TAVI in BAV. The Evolut Pro and XL platforms demonstrate large EOAs, low gradients and minimal AR in type 0 and type I BAV, without an excess of ellipticity at the annular level. Systematic pre and tailored postdilatation may help in preventing greater ellipticity. The repositioning capability of the Evolut Pro/XL platform is of particular utility in TAVI for BAV.

Part III
Imaging for TAVI in Bicuspid Aortic Valve

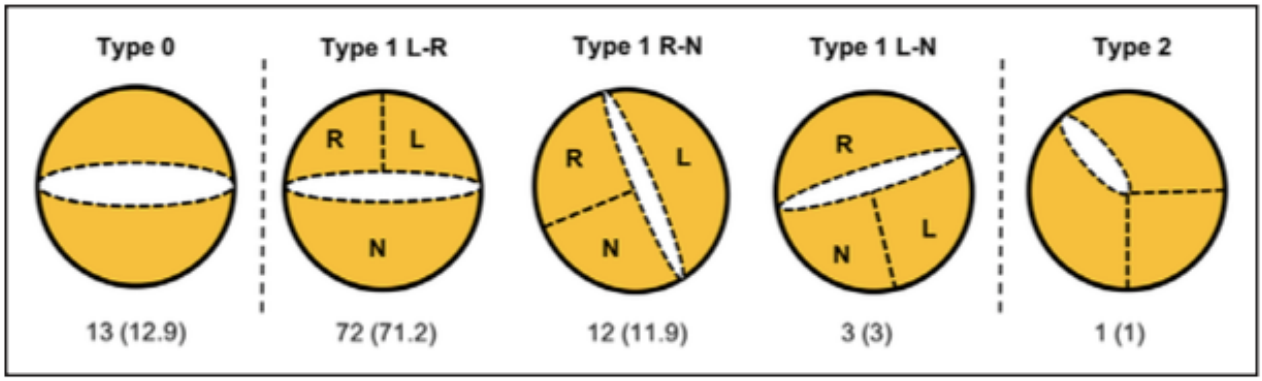
Chapter 15

Bicuspid Aortic Valve Anatomy and Relationship With Devices: The BAVARD Multicenter Registry

A European Picture of Contemporary Multidetector Computed Tomography Sizing for Bicuspid Valves

The aim of our retrospective registry is to capture the sizing ratios used in European and Israeli centers for BAV patients undergoing TAVI with second-generation prostheses, when using MDCT as the imaging modality, and also to analyze by postprocedural MDCT the prostheses geometry, in situ.

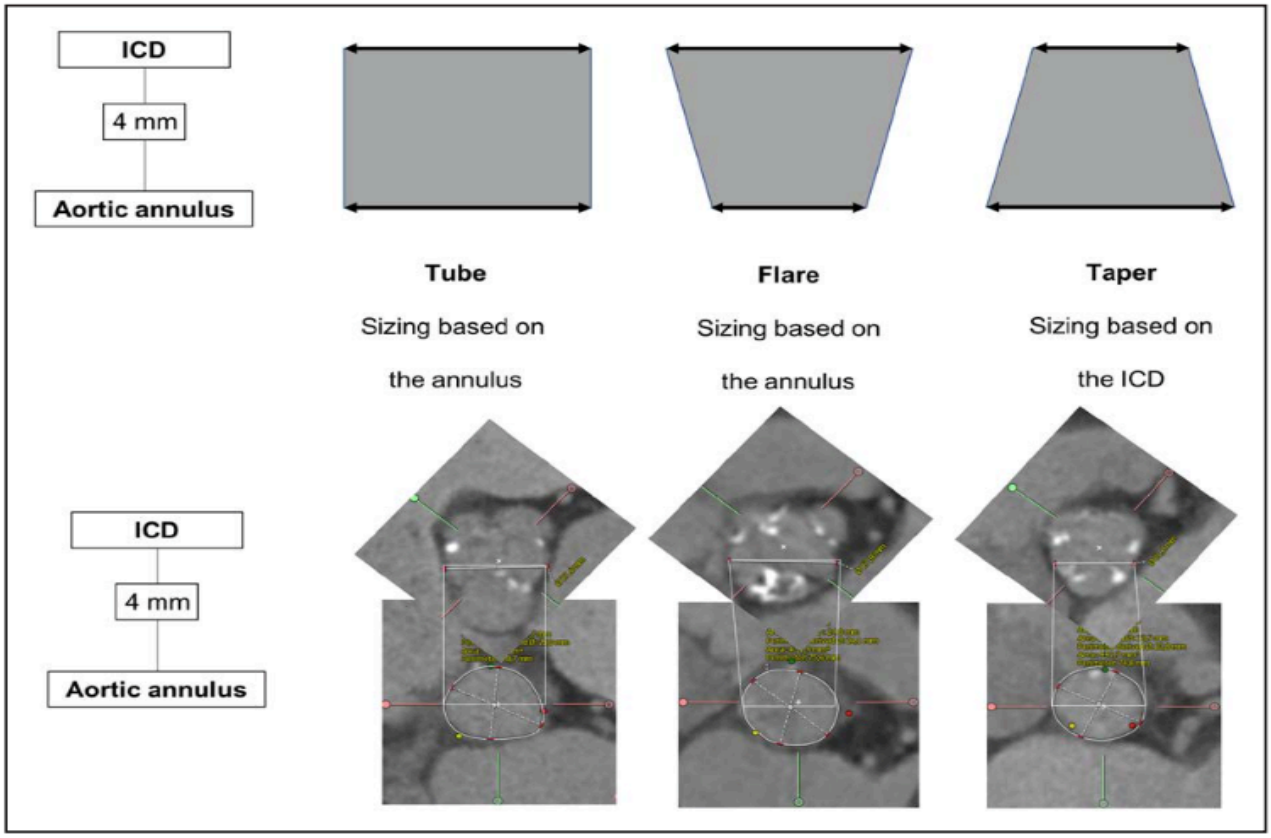
BAV type according to Sievers Classification



Background: Sizing for transcatheter aortic valve implantation in bicuspid aortic valves (BAV) remains controversial.

Methods and Results: The aim of the BAVARD (Bicuspid Aortic Valve Anatomy and Relationship With Devices) retrospective registry is to capture the sizing ratios used for transcatheter aortic valve implantation in BAV and analyze the second-generation prostheses geometry postimplantation. About 101 patients with BAV along with available pre- and post-transcatheter aortic valve implantation multidetector computed tomography were compared with 88 tricuspid aortic valves (TAV) patients. Preprocedural MDCT diagnosed type 0 and type 1 BAV in, respectively, 12.9% and 86.1 % of BAV. At baseline, the ellipticity index was similar between BAV and TAV patients: 1.2±0.1 versus 1.2±0.1, P=0.09. The mean annular oversizing was, respectively, 1.14±0.04 and 1.04±0.04, P<0.001, in TAV

and BAV patients. The mean prosthesis intercommissural distance, ratio was 1.03±0.1. The mean diameter of the prostheses at the annulus matched the mean perimeter- derived diameter of the aortic annulus at baseline with TAV (23.3±2.2 versus 23.6±1.9, P=0.4) and was smaller with BAV (24±2.8 versus 26.8±3.1, P<0.01), confirming 11% underexpansion in BAV. Finally, in situ, prosthesis diameter and ellipticity followed the same pattern, with stable values from the distal edge to 12 mm above, in both groups.



Various configuration of the landing zone in bicuspid patients and simplified sizing algorithm. ICD indicates intercommissural distance.

Conclusions: Second-generation prostheses similarly reshape the aortic annulus in TAV and BAV. Prostheses keep consistent diameters from distal edge to 12 mm in TAV and BAV. Prosthesis underexpansion is constantly observed in BAV. Annular-based sizing is accurate in BAV with minimal oversizing. The intercommissural distance, 4 mm above the annulus, could be integrated in gray zones.

Chapter 16

Supra-annular sizing for prediction of THV expansion in bicuspid aortic valves: a MSCT study

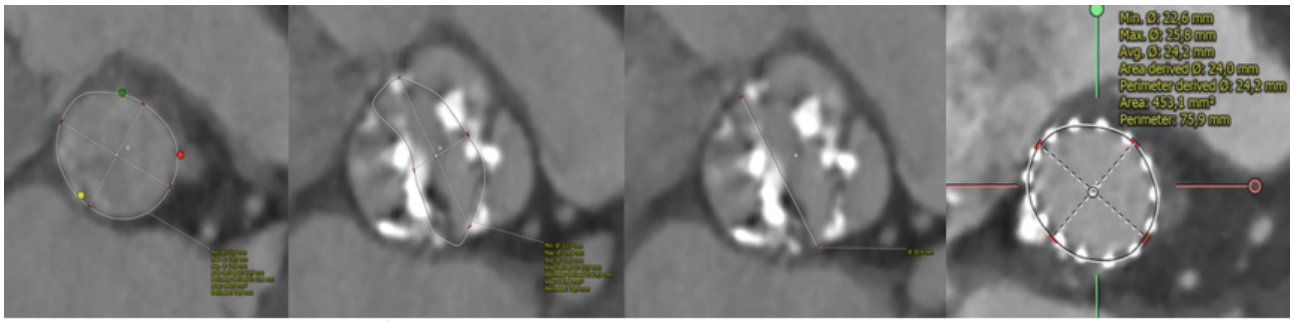
This paper aims to identify which of these dimensions best predicts the geometry (dimension and ellipticity) of THVs in BAV patients undergoing TAVI for symptomatic AS.

Objectives: This study aimed to identify baseline multislice computed tomography (MSCT) measurement that could predict the geometry of transcatheter heart valve (THV) in bicuspid aortic valve (BAV) patients undergoing transcatheter aortic valve implantation (TAVI) for symptomatic aortic stenosis (AS).

Background: MSCT is the most common sizing method for TAVI in BAV. It is unclear whether annular and supra-annular dimensions could predict final prosthesis diameter and expansion.

Methods: 102 BAV patients undergoing TAVI for AS were included in this observational, retrospective, single-center study. Pre and post TAVI MSCT were compared. On pre and post MSCT, means of perimeter derived diameter (PdD) and ellipticity indexes were measured at annular plane, 4 mm and 8 mm above, intercommissural distance (ICD) at 4 and 8 mm.

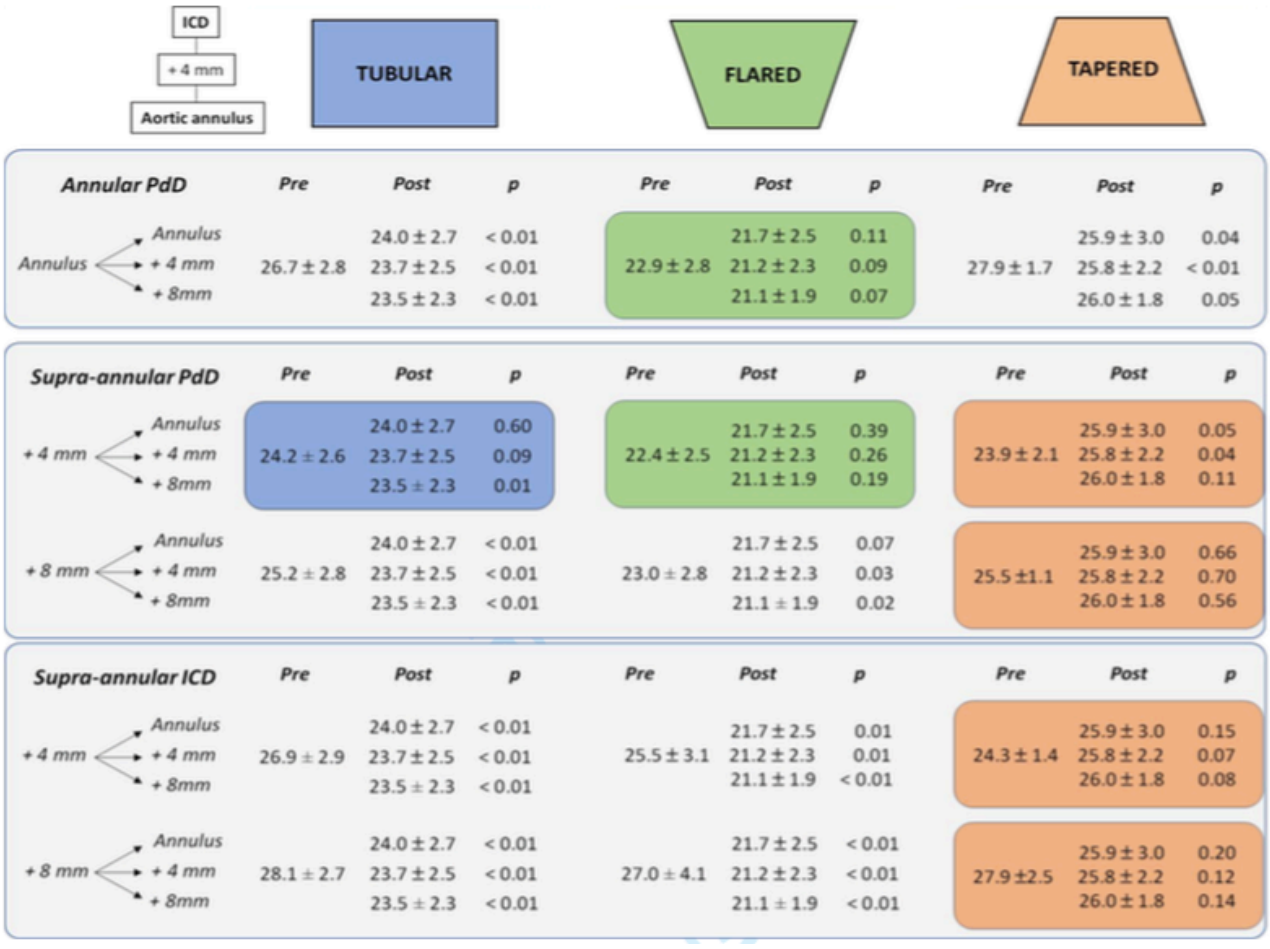
MSCT annular and supra-annular measurements



Annular measurement | Supra-annular measurement | ICD measurement | Annular measurement post TAVI

Results: Comparison of pre and post TAVI PpDs at 3 levels showed that pre TAVI PdD at +4 mm was correlated to post TAVI PdD at annulus (24.2 ± 2.6 mm vs. 24.0 ± 2.7 mm; p= 0.87) and at +4 mm (24.2 ± 2.6 mm vs. 23.7 ± 2.5 mm; p= 0.16). All other comparisons showed significant difference between pre and post dimensions, with reduction in post TAVI THV dimensions, as compared to baseline measurements, suggesting underexpansion. Pre and post TAVI ellipticity indexes comparison showed significant reduction in post TAVI ellipticity indexes at 3 levels, suggesting a more circular THV geometry.

Annular and supra-annular comparison in BAVARD landing zone configuration



		Tubular Pre	Tubular Post	Tubular p	Flared Pre	Flared Post	Flared p	Tapered Pre	Tapered Post	Tapered p
Annular PdD										
Annulus	Annulus	26.7 ± 2.8	24.0 ± 2.7	< 0.01	22.9 ± 2.8	21.7 ± 2.5	0.11	27.9 ± 1.7	25.9 ± 3.0	0.04
	+ 4 mm		23.7 ± 2.5	< 0.01		21.2 ± 2.3	0.09		25.8 ± 2.2	< 0.01
	+ 8mm		23.5 ± 2.3	< 0.01		21.1 ± 1.9	0.07		26.0 ± 1.8	0.05
Supra-annular PdD										
+ 4 mm	Annulus	24.2 ± 2.6	24.0 ± 2.7	0.60	22.4 ± 2.5	21.7 ± 2.5	0.39	23.9 ± 2.1	25.9 ± 3.0	0.05
	+ 4 mm		23.7 ± 2.5	0.09		21.2 ± 2.3	0.26		25.8 ± 2.2	0.04
	+ 8mm		23.5 ± 2.3	0.01		21.1 ± 1.9	0.19		26.0 ± 1.8	0.11
+ 8 mm	Annulus	25.2 ± 2.8	24.0 ± 2.7	< 0.01	23.0 ± 2.8	21.7 ± 2.5	0.07	25.5 ±1.1	25.9 ± 3.0	0.66
	+ 4 mm		23.7 ± 2.5	< 0.01		21.2 ± 2.3	0.03		25.8 ± 2.2	0.70
	+ 8mm		23.5 ± 2.3	< 0.01		21.1 ± 1.9	0.02		26.0 ± 1.8	0.56
Supra-annular ICD										
+ 4 mm	Annulus	26.9 ± 2.9	24.0 ± 2.7	< 0.01	25.5 ± 3.1	21.7 ± 2.5	0.01	24.3 ± 1.4	25.9 ± 3.0	0.15
	+ 4 mm		23.7 ± 2.5	< 0.01		21.2 ± 2.3	0.01		25.8 ± 2.2	0.07
	+ 8mm		23.5 ± 2.3	< 0.01		21.1 ± 1.9	< 0.01		26.0 ± 1.8	0.08
+ 8 mm	Annulus	28.1 ± 2.7	24.0 ± 2.7	< 0.01	27.0 ± 4.1	21.7 ± 2.5	< 0.01	27.9 ±2.5	25.9 ± 3.0	0.20
	+ 4 mm		23.7 ± 2.5	< 0.01		21.2 ± 2.3	< 0.01		25.8 ± 2.2	0.12
	+ 8mm		23.5 ± 2.3	< 0.01		21.1 ± 1.9	< 0.01		26.0 ± 1.8	0.14

ICD: intercommisural distance; PpD: perimeter derived diameter.
*Configurations: Flared: ICD at +4 mm larger than PpD at annulus (greater than 10% absolute difference); Tapered: PdD at annulus larger than the ICD +4 mm (greater than 10% absolute difference); Tubular: similar PpD at annulus and ICD at +4 mm (less than 10% absolute difference).

Conclusion: Based on our findings, we may conclude than on top of the annular PdD, +4 mm PdD may be integrated for sizing in type 0-1 BAV of tubular and flared landing zones configurations, as it better predicted the final THV diameter, suggesting leaflet sealing at this level. The supra-annular PdD +8 mm could be the main element for THV sizing in tapered configurations. A systematic underexpansion of THV, as compared to baseline annular dimensions, is observed, advocating the avoidance of excessive oversizing in BAV. A constant reshaping of the landing zone, with improved circularity, was achieved post TAVI in BAV.

Clinical perspectives

What is known: TAVI is feasible in bicuspid aortic valves, despite several anatomical challenges. MSCT based sizing is the gold standard for accurate THV selection before TAVI. The debate on the most appropriate sizing for BAV between annular and supra-annular measurements is still ongoing.

What is new: Our study provides an analysis of baseline anatomical dimensions at MSCT that could predict THV expansion in BAV patients undergoing TAVI for AS. The mean perimeter- derived diameter measured 4 mm above the annulus seems a valuable dimension.

What is next: We need standardized methods for sizing in BAV.

Part IV

Discussion and conclusions

Discussion

Part I: Aortic valve disease and innovation in percutaneous treatment by transcatheter aortic valve implantation

TAVI procedure can definitely represent the optimal strategy in some categories of patients not suitable for surgery or in which surgery is not mandatory. Anyway, further data from rCTs and ongoing technological or pharmacological refinements are needed to minimize the remaining limitations of this technique in order to provide safety, above all if indications to TAVI move to lower-risk population. Up-to date it is obvious, to any heart team across the globe, that TAVI is superior to medical therapy in inoperable patients, at least equal to SAVR in high-risk patients and comparable to SAVR at to two years in intermediate-risk patients. Thus, TAVI cost-effectiveness should not be questioned anymore [4, 6, 31, 32]. Simplification and optimization of TAVI pathway are key for future enhancement of its cost-effectiveness. However, before making TAVI the dominant therapy, durability needs to be assessed thoroughly. New-generation devices, data on medical therapy and operator's expertise need to achieve this goal.

TAVI safety, efficacy, and clinical outcomes were investigated in the paper focused on patients with pure native AR. The major findings of this study report that TAVI in pure native AR was associated with relatively high rates of procedural complications, particularly when using the early-generation device. However, new-generation devices were associated with improved procedural outcomes with lower rates of second valve implantation and of moderate post-procedural AR. Moreover post-procedural moderate AR moderate resulted associated with increased all-cause mortality and rehospitalization.

Indeed the majority of currently available transcatheter devices are designed for treating calcified aortic stenosis, relying on the fixation of the transcatheter valve within an extensively calcified annulus. In case of pure native AR, the large aortic annulus with minimal calcification challenges the anchoring of the prosthesis. Therefore, patients with predominant AR are not indicated for TAVR

according to the current guidelines [2]. However, accumulated experience and advancement of device technology lead to the increased off-label use of TAVI for untreated patients with significant valvular disease other than severe aortic stenosis [33]. New-generation devices possess new specific features: namely, retrievability and repositioning capacity, an external sealing cuff, and a unique anchoring mechanism with clipping of the native aortic valve cusps. Recently, several studies demonstrated the acceptable clinical outcomes of TAVR using the new-generation devices in patients with pure native AR [34-36]. However, these studies were limited in sample size, type of device, and follow-up period. Furthermore, limited data exist about the impact of the absence of sufficient aortic valve calcification and dilation of ascending aorta on outcomes of TAVR in pure native AR. Therefore, the possibility of valve dislocation and subsequent need for second valve implantation should be considered during the planning process. Given the relatively high rates of complications, general anesthesia and intraprocedural echocardiography assessment of post-procedural AR would help to optimize the procedural results. In terms of device sizing, a relatively higher degree of device oversizing was associated with a reduction in post-procedural AR rates when using the self- expanding valves, which confirms the importance of pre-procedural computed tomography assessment in this population as well. Further studies are required to evaluate the optimal sizing for other valves in treating pure native AR. Although new-generation devices were associated with relatively high rates of second valve implantation in patients with a larger annulus, it should be noted that the second valve implantation was not associated with increased 1-year all-cause mortality. More importantly, the technological advancement of transcatheter valves succeeded in eliminating or reducing post-procedural AR in the pure native AR popula- tion. Given the significant impact of post-procedural AR on long-term mortality, this advantage of the new-generation devices should be highlighted. The impact of post-procedural AR on increased mortality, which is well recognized in the aortic stenosis population [37], was consistently observed in the pure native AR population. The advantage of new-generation devices over the early-generation devices was observed in 1-year cardiovascular mortality, which may be due to decreased post-procedural AR as well as fewer baseline comorbidities in the new-generation device

group. Baseline characteristics of patients with pure AR included had reduced left ventricular ejection fraction, and one-third of patients had significant mitral regurgitation and/or pulmonary hypertension, which may render patients with pure native AR more vulnerable and contribute to the relatively higher short- and mid-term mortality than is observed in aortic stenosis patients. Furthermore, due to lack of randomized studies in pure native AR, the findings in the present study need cautious interpretation. TAVR in pure native AR should be considered for patients deemed high surgical risk after consultation with the multidisciplinary heart team, and the generalization of this procedure should be recommended only after further investigation.

TAVI procedure was investigated even in the setting of previously implanted mitral prostheses, since raising specific safety and efficacy concerns. Possible pitfalls include higher risk of bleeding due to concomitant anticoagulation therapy for MV prostheses, risk of interference of TAVI valve with MV prosthesis stent or mobile elements and vice versa, choice of ideal access route for TAVI deployment, choices between balloon expandable (BE) or self-expanadable (SE) TAVI devices, and choices between older vs newer retrievable/repositionable devices. The high rate of procedural success observed in our paper (97.4%) supports the notion of the feasibility of TAVR in this specific subset of patients. TAVI was performed after approximately 12 to 14 years from MV surgery. Two out of three patients with fatal or life-threatening complications resulted to be on combined OAC and antiplatelet therapy. This finding raises the question of optimal antithrombotic regimens after TAVR in this setting. Although the presence of mechanical prostheses mandates OAC, addition of antiplatelet drugs may be associated with excess bleeding. Further studies are warranted to define the best antithrombotic treatment in such patients. Of note, there was a higher proportion of BE valves implanted in the cohort of patients with biologic mitral prostheses. This may reflect the preference for a device with lower stent height to avoid interference with the biologic MV prostheses, which usually have higher commissural stent struts profiles. In 1 case of interference of the TAVI device with the MV prosthesis, multiple retrievals were necessary to restore a normal MV valve function and a proper TAVI positioning. It is conceivable that new, repositionable, or completely retrievable devices could be

particularly suitable for this particular clinical setting. A safe mitroaortic distance cut-off of 7 to 8 mm has traditionally been proposed to identify high-risk anatomies. In patients with mitroaortic distances < 7 mm, implantation of BE or SE devices performed equally. However, interference or embolization during deployment were observed only in patients with SE devices; it is conceivable that the lower stent profile of BE valves might be preferred to reduce the risk of interference with MV prostheses in very low mitroaortic distances. Taken together, these findings highlight the role of pre- procedural CT imaging for intervention planning and risk stratification. Finally, safety and efficacy of TAVI procedures in the population of patients with previous MV prostheses were confirmed; at follow-up, the good hemodynamic performance of TAVR devices was maintained, and no cases of TAVI-related MV dysfunction were observed.

TAVI efficacy and safety were further investigated in oncology patients with severe AS. Throughout the years, the portion of cancer patients among TAVR recipients increased, with the most prevalent malignancies including gastrointestinal, prostate, breast, hematologic, lung, and urinary tract. Compared with patients without cancer, oncology patients were more frequently frail, even though they were younger, had lower STS risk, and had fewer CV comorbidities. TAVI seemed safe in oncology patients, with similar short-term mortality and periprocedural complication rates as in patients without cancer. However 1 year mortality was higher among cancer patients, in the majority of cases cancer related while among the 85% patients who survive 1 year after the TAVR, one-third entered remission or were cured of cancer. The transformative innovation of TAVR has provided a tremendous opportunity to treat many patients with severe AS, but also raised awareness for important futility questions which needs to be further stressed when addressing patients with cancer. One should bear in mind that untreated severe symptomatic AS is a malignant disease by itself in terms of its dreadful prognosis. In patients with cancer, AS creates a greater misfortune, as it may interfere with optimal antineoplastic therapy. The European Society of Cardiology position paper on cancer treatments and CV toxicity [38] recommend afterload reduction (using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) for attenuation of left ventricular dysfunction and heart

failure induced by anthracyclines and other antineoplastic therapies. In AS patients, afterload reduction is only possible by aortic valve intervention. Balloon valvuloplasty has repeatedly failed to improve survival in AS patients and is associated with limited efficacy, complications, and high early restenosis rates [39, 40]. Although surgical aortic valve replacement has been shown to improve survival in cancer patients with severe AS compared with conservative management, it was associated with increased perioperative mortality and morbidity compared with patients without cancer [41, 42]. Additionally, the invasive nature of open heart surgery and cardiopulmonary bypass make surgical replacement less suitable for many "real life" cancer patients [43]. TAVR may be an optimal treatment strategy in selected oncology patients with severe AS. At least theoretically, TAVR may address many of the concerns associated with open heart surgery in cancer patients, such as increased risk for bleeding and infections, and the suspension of anticancer therapy during the post-surgical recovery window. In addition, TAVR may allow a more aggressive and optimal cancer treatment soon after the procedure. In addition to survival, a question remains whether TAVR improves symptoms and quality of life in cancer patients, because their symptoms may at times be multifactorial, less specific, and overlapping with paraneoplastic symptoms. Both at 1 month and 1 year, cancer patients experienced a significant and persis- tent symptomatic benefit with regard to NYHA functional class, albeit less pronounced compared with no-cancer patients. Consequently, whether a correlation exists between cancer state and symptomatic benefit remains unknown. Irrespective of this, one should bear in mind that AS symptoms may indeed be more multifactorial in cancer patients and not merely caused by the stenotic valve. The data on TAVR in oncological patients are scarce. Our study collected a larger number of patients from a designated registry of 18 centers worldwide, thus supports better validation and allows a more comprehensive data analysis.

The last complicated TAVI field investigated is represented by patients requiring ostia angioplasty before/during TAVI device implantation for the potential high risk of coronary occlusion. Our study represents data from patients undergoing chimney stenting during TAVR. The salient findings of this registry show that chimney stenting is infrequently required in contemporary practice, accounting for

0.5% of all cases and that in the majority of cases (93%), 1 or more classical anatomic risk factors for CAO were present. Coronary protection is an important strategy, facilitating rapid restoration of coronary flow, and was associated with lower risk for cardiogenic shock, myocardial infarction, and death. Clinical outcomes suggest that chimney stenting is a successful bailout strategy for treating iCAO or eCAO, but there are some concerns around late stent failure (3.5% at 1 year). Left main stenting following this chimney stenting technique as a bailout for acute CAO during TAVI was first described in 2013 by Chakravarty et al. (14). Our data suggest that chimney stenting is performed not only for the acute treatment of complete obstruction of coronary flow but also applied when pre procedural imaging reveals partial obstruction of the coronary ostium or reduced coronary blood flow and possible complete CAO. Alternatives for the treatment of acute CAO include snaring and removal of the THV or referral for urgent surgical coronary artery bypass grafting. More recently, a novel technique was developed for the prevention of CAO in at risk patients. The BASILICA (bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction) technique uses electrocauterization to split a bioprosthetic or native heart leaflet that could obstruct coronary arteries after displacement by TAVI, thus maintaining blood flow into the coronary sinuses [44, 45]. BASILICA has been associated with encouraging early results, but it remains a relatively complex procedure that is not yet widely practiced outside expert centers. BASILICA has advantages over chimney stenting, including the avoidance of placing a coronary stent in the aorta and the consequent risks for reaccessing the coronary arteries, restenosis, and thrombosis. Familiarity with both BASILICA and chimney stenting is advised for those performing TAVI in cases at risk for CAO. However, the efficacy of chimney stenting in patients at risk for CAO is unknown. In the study, 7% of patients did not present “classical risk factors” for CAO on the basis of MSCT analysis or characteristics of the failing bioprosthetic valve for VIV cases. Additional risk factors, such as bulky calcification or thickened leaflets, can heighten CAO risk, and new risk models and tools to better predict CAO are required [46, 47]. The vogue for coronary protection in contemporary TAVR practice stems from the difficulty encountered when trying to cross the struts of a THV in the setting of acute

eCAO and the dismal outcomes reported from eCAO (mortality up to 50%) [48]. In the present study, which included only successful chimney stenting procedures, the technical feasibility appeared to be greatly facilitated and more expedient when coronary protection was used upfront. Indeed, we observed higher rates of myocardial infarction (43.8% vs. 13.6%; p 1⁄4 0.03), cardiogenic shock (62.5% vs. 9.1%; p < 0.01), and in- hospital death (18.8% vs. 0%; p 1⁄4 0.02) in those without coronary protection. The multivariate analysis suggests that the absence of upfront coronary protection is an important risk factor for adverse outcomes. Although this analysis is limited by its small sample size, we encourage upfront coronary protection in all at-risk cases. As with any coronary or structural intervention, the result of a chimney stenting pro- cedure should be optimized. Angiographic under-expansion of the chimney stent frequently necessitated high-pressure post-dilatation (50%) or even a second stent (double stent layer; 18.3%) to improve the angiographic appearance. The thrombotic or restenosis risk of a double layer of chimney stent is unknown. Invasive coronary angiography was performed in only 4 cases during follow-up, and selective intubation of the coronary arteries was feasible in 3 of 4 cases via the chimney stent. Whether future access to the coronary circulation for the management of coronary syndromes is as difficult as predicted requires further study. Persistent turbulent flow across the THV and the coronary stent, local inflammatory pro- cesses, and galvanic corrosion between both metallic frames have been proposed as potential mechanisms of chimney stent failure, including the risk for chim- ney stent thrombosis [44]. The optimal antiplatelet or anticoagulant strategy after TAVI is unclear. When chimney stenting is performed, a greater emphasis on dual-antiplatelet therapy is appropriate. Current guideline recommendations of 3 to 6 months of dual-antiplatelet therapy post-TAVI may not be applicable to patients with proximal coronary stenting and with a substantial proportion of the stent protruding into the ascending aorta, which is unlikely to undergo endothelialization [49]. Nevertheless, the bleeding risk in this population is considerable, and careful case-by-case management of the antiplatelet strategy is mandatory after chimney stenting. According to these considerations, the median intended duration of antiplatelet or anticoagulant therapy in our cohort was 7.5 months (IQR: 6 to 12 months). Further data require to understand the

mechanisms and frequency of these late events. Until longer-term data on the incidence of stent failure are available, chimney stenting should be considered only as a bailout option for impending or eCAO.

Part II: TAVI in a complex anatomical setting: Bicuspid Aortic Valve management and percutaneous treatment

BAV represents a challenge for diagnosis and treatment strategies in contemporary clinical practice. BAV frequency in general European population, methods of diagnosis and contemporary treatment were investigated in the BiTri registry. This European multicenter registry identified BAV in 17% of patients treated for severe, symptomatic aortic stenosis. Patients with BAV were predominantly males, younger, with had fewer cardiovascular risk factors, and a lower surgical risk profile. These findings are consistent with previous analyses showing a younger BAV population, with a male predominance when compared to patients undergoing TAVI for tricuspid AS [50]. The epidemiology may probably influence the mode of presentation and the treatment of European bicuspid patients. Diagnosing BAV remains difficult, especially in severe calcified valves. The use of multimodality imaging may facilitate the diagnosis of bicuspid disease [51]. Our data suggest that the most reliable imaging modality for BAV diagnosis and phenotyping is MSCT, followed by a combination of TTE and MSCT. These findings confirm what prior studies have shown about the strength of MSCT in identifying bicuspid aortic valves anatomy [28, 29]. Transthoracic echocardiography being the first imaging modality, at least for the diagnosis of aortic stenosis, for the vast majority of the patients, it could be systematically combined with MSCT when suspecting BAV. Given the expected expansion of the indications for TAVI toward patients at lower surgical risk, we may witness a paradigm shift: suitability for transfemoral TAVI may become the main element for decision-making. TTE and MSCT may therefore be systematically associated, in the future, for any single patient entering the screening process for AS. Within the entire BAV cohort, less than 45 was treated by medical treatment while the 26% of patients underwent TAVI. These patients treated with TAVI were older, had more comorbidity, and were at higher surgical risk when compared to BAV patients who underwent SAVR.

This is consistent with the current guidelines recommending TAVI for patients at increased surgical risk or inoperable ones with acceptable life-expectancy [13]. With potential expansion of TAVI indications, younger patients may be offered TAVI, including more BAV patients. There are still issues associated to TAVI in BAV, including the management of aortic aneurysms and unclear device durability. So far, patients with BAV have been excluded from the major registries and randomized trials, although such evidence is needed to justify TAVI to younger patients with severe, symptomatic BAV stenosis.

In the comparison between patients with tricuspid and bicuspid aortic valve with severe aortic stenosis in a TAVI setting we investigated also procedural outcomes (device success), all-cause mortality and safety concerns at 30 days. Baseline anatomy of BAV resulted in more complex procedures as compared to tricuspid patients. BAV patients had major aortic root calcifications and larger diameter of ascending aorta. These features are concordant to previous analysis [21]. In the BAV group the need for valvuloplasty was bigger mainly for "opening the way" for the endoprosthesis. Even though the percentage of valvuloplasty was not similar, it is a procedure that is considered safe and in accordance with published data we do not consider it to have an impact on clinical outcomes of our patients [52-54]. However BAV group had more incidents concerning malpositioning, severe aortic regurgitation and bailout TAV-in-TAV procedures. As a result the TAVI procedures in the BAV group were more complex with longer procedural duration and at the end had lower device success rate. Indeed the lower device success rate was mainly related to the second device implantation need (TAV-in TAV) since nor PVL or mean gradient and mortality rate were significantly different. The particular anatomy of the bicuspid valve may be the reason for this but surely more data are required to validate our hypothesis. Despite intra procedural complications, there was no statistically significant difference for all-cause mortality at 30 days follow-up between our two groups. It may be more difficult to perform a TAVI procedure in a patient with a BAV but the procedure is safe and with similar short-term clinical outcomes. MDCT was performed in all patients since it is considered the gold standard to assess aortic annulus dimensions and device size [28, 29]. Proper measurements are necessary to prevent PVL and

PPM. Sizing strategy included measurement of MDCT diameter at annulus level and the inter-commissural distance 4 mm above the annulus. When the anatomy was suitable we opted for the new-generation balloon-expandable Sapien 3 valve. Especially for patients with BAV balloon-expandable device had better sealing and lower incidence of PVL, as this is correlated with an increase in mortality rate. Balloon expandable valves implantation is supported by some data, configuring lower incidence of PVL when new-generation devices were implanted. BAV patients treated with Sapien-3 reported a favorable outcome in terms of low PVL rate and better device success rate when compared to old generation devices [25, 55-57]. In this BAV population only one patient experienced aortic annulus rupture after Sapien 3 implantation, complication that can be mitigated by pre-procedural imaging. One very interesting finding regarding the balloon-expandable valve is that it seemed to expand to a more circular shape at MDCT scanner control post TAVI. It appears to "respect" the bicuspid annulus geometry that tends to be less elliptical than the tricuspid one [22]. On the other hand self-expandable devices showed even less incidence of aortic injury and lower rate of oversizing [58, 59]. As to the self-expanding devices we noticed a non-circular expansion at annulus level but greater adaptation to irregular bicuspid orifice [60, 61].

Since the lack of well-powered studies comparing balloon- vs. self- expanding devices in BAV patients, the BEAT registry focused the attention on this specific comparison. The BEAT international registry is the first study comparing the most commercially utilized THVs belloon-expandable valve (BEV) Sapien 3 vs. self-expandable valve (SEV) EvolutR/PRO in BAV anatomy. VARC-2 device success was obtained in 86.7% of patients, without significant differences after SEV and BEV both in the entire population and in the PS-matched cohort. The rate of moderate-severe PAR after TAVI was acceptable (4%) in the entire cohort, however it was higher after SEV implantation both in the overall and PS-matched populations. Residual mean AV gradient was higher in the BEV group, however the rate of mean gradient ≥20 mmHg was not different after BEV or SEV implantation (either in the overall cohort and in the PS-matched cohort); At 30-day follow-up, the two groups of treatment showed comparable rates of clinical events both in the entire cohort and in the PS-matched population.

The large Bicuspid AS TAVI multicenter registry has recently compared clinical outcomes of patients undergoing TAVI for bicuspid vs. tricuspid aortic stenosis and a subsequent analysis of the same multicenter registry focused on the type of THV implanted, comparing TAVI with early- vs. new-generation devices in patients with BAV and reporting a lower rate of moderate-severe regurgitation and a higher rate of device success with the new-generation group. Favourable outcomes with the Sapien 3 THV were also reported in a recent single-arm study, showing a 0% rate of moderate-severe PAR among 51 BAV patients treated with this new-generation BEV device [26]. Despite this early evidence supporting the use of new-generation THVs for the treatment of bicuspid aortic stenosis, there is not a direct comparison between different new-generation devices and available studies included a relatively low number of patients treated with Sapien 3, without any data for Evolut R/PRO in BAV population. The Sapien 3 BEV is a low profile valve with an outer skirt and a higher radial force able to minimize the risk of PVL; the Evolut R/PRO SEVs are higher profile valves with less radial force. The Evolut PRO THV has an adjunctive pericardial wrap that increases valve sealing, thus theoretically reducing the risk of PVL; however real-world experiences have demonstrated that Evolut R and PRO have similar results in terms of device success [62]. The supra-annular design of SEVs can mitigate the effect of valve asymmetry and under-expansion, thus minimizing the risk of high transvalvular gradients. However, these data need to be carefully confirmed in larger and prospective studies to evaluate the possible clinical impact that residual high gradients have on valve durability. The high rate of PVL observed in bicuspid anatomies in the SEV group could be justified by the low radial force of this prosthesis that does not guarantee an optimal sealing in the pericommissural zone. The highly calcified raphes and leaflets can hamper a complete SEV expansion. As matter of fact, SEV required more frequently pre-dilatation and post-dilatation to be optimally implanted and to achieve a satisfactory result. A high rate of post-dilation was similarly observed for another SEV, the Acurate *neo* device (Boston Scientific, Marlborough, USA), when implanted in bicuspid anatomies: among 54 patients treated with such THV, the rate of post-dilatation increased proportionally according to the degree of annular calcifications [63].

The Bicuspid Aortic Stenosis With Evolut Platform International Experience (BIVOLUT X) international registry (Clinical trial identifier: NCT03495050) enrolling 151 BAV treated with Evolut PRO or Evolut R XL gave more definite answers in a preliminary data analysis presented al last digital version of EuroPCR 2020. In this prospective registry enrolling 14 centers across Europe and Canada, results at 30 days were really promising. The Evolut Pro and XL platforms demonstrated large EOAs, low mean gradients (< 10 mmHg) and minimal AR in type 0 and type I BAV, without an excess of ellipticity at the annular level at 30-days follow-up. Systematic predilation and tailored postdilatation were performed, thus preventing greater ellipticity and guarantying better sealing. Moreover, the repositioning capability of these new-generation platforms is of particular utility in TAVI for BAV.

Part III: Imaging for TAVI in Bicuspid Aortic Valve

The BAVARD (Bicuspid Aortic Valve Anatomy and Relationship With Devices) registry is the largest registry addressing TAVI in BAV with contemporary prosthesis platforms and pre and post procedural MDCT analysis. This study aimed to capture the sizing ratios used for TAVI in BAV in contemporary European practice and analyze the configuration of TAVI prostheses in BAV. Given the bicuspid type of the study patients, our findings mostly apply to type 0 and type 1 BAV. BAVARD was not focused on clinical outcomes. However, we observed similar the Valve Academic Research Consortium-2 criteria outcomes in TAV and BAV patients. In a recent report, Yoon et al. already demonstrated the improved safety of TAVI with second-generation prostheses in bicuspid anatomies as compared with first-generation devices [64].

MDCT analysis was the main focus of our registry. Given the final prosthesis depth of implantation in TAV and BAV patients, the MDCT region of interest ex- tended from 4 mm below the annulus to 8 mm above. At baseline, as compared with TAV patients, the aortic annulus in BAV patients was larger but not more elliptical. These findings echo the conclusions from Son et al.22 Watanabe et al23 compared the outcomes in TAV and BAV patients post-TAVI with first-generation pros- theses:

patients with BAV had higher gradients, larger annulus perimeters, and more calcified valves. Higher postprocedural gradient and valve underexpansion were frequently observed.

In TAV patients, we observed that the aortic annulus influenced the final diameter of the TAVI devices. In the region of interest, the most frequently used second-gen- eration devices (S3, ER, and Lotus) matched the aortic annulus mean diameter, remained cylindrical, with con- stant diameters and ellipticity indexes. With BAV, the prostheses trended to be slightly more elliptical but overall exerted the same cylindrical pattern. The only and important difference with BAV was prostheses evident underexpansion, underscored by mean diameters being constantly smaller than the mean aortic annulus diam- eter and the ICD. This finding highlights potential points of constraints throughout the aortic root. This underex- pansion in BAV is of utmost importance as it may po- tentially hamper prosthesis durability or even promote leaflet thrombosis. It stresses the need for refined siz- ing policies, to select the appropriate prosthesis size, and procedural technique modification to obtain the max- imum expansion achievable in a given bicuspid anatomy.

The stability of both prosthesis diameters and ellip- ticity from 0 to 12 mm attests to the high radial force and the ability of second-generation devices to reshape the surrounding structure in both TAV and BAV. In some patients, with self-expanding or mechanically expanded devices, that reshaping may be facilitated by an adequate postdilatation. Second-generation prostheses conserve stable diameters and ellipticity when they meet a point of high resistance, with similar patterns in both TAV and BAV. In TAV patients that point of re- sistance is usually located in the aortic annulus, while in BAV patients it could be positioned above the aortic annulus, at the level of the commissures and leaflets. In a MDCT analysis of 41 BAV patients treated with S3, Kawamori et al. found lesser expansion and greater ellipticity in BAV patients as compared with TAVI [65]. One possible explanation for that discrepancy with our find- ings, could be difference in sizing, with bigger prosthe- ses used in their series and devices potentially failing to achieve their maximal diameter and circularity in a relatively too constrained landing zone. In our series, minimal oversizing was applied (3%–4%), when using the mean perimeter-derived aortic annulus diameter, for sizing in BAV. In patients with

TAV, the landing zone usually integrates the aortic annulus and the left ventricular out- flow tract, 4 mm below it. As an analogy, given the location of constraint points, the landing zone in BAV patients could run from the aortic annulus to 4 mm above it. That explains, in an effort of simplification, our proposal of integration of the ICD at 4 mm above the annulus for sizing in BAV patients, at least type 0 and type 1 variations. Several configurations can be identified. In a tubular configuration, the mean aortic annulus diameter matches the ICD and can be used for sizing with an average oversizing of 3% in our cohort. In a flared configuration, in which the mean aortic annulus diameter is smaller than the ICD, it could also be used as the reference for sizing. In a tapered configuration (mean perimeter-derived diameter of the annulus greater than ICD), the ICD could be inte- grated, with a 0.9–1/1 ratio because prostheses were systematically smaller than the ICD in our BAV patients. Importantly, annulus-based sizing was appli- cable to 88% of our BAV patients (Table I in the Data Supplement). Even though rare, it remains important to identify a tapered configuration. In such anatomy, an annular-based sizing would result in selecting a device potentially too large for the patient, with inherent risks of aortic root rupture or greater device underexpansion. The calcium burden is likely a major player in the final expansion of TAVI prostheses and it should be quantified and integrated in the sizing process [30, 66].

Our last MSCT focused study showed that supra-annular sizing, and in particular the baseline mean PdD 4 mm above the annulus, closely matched the final THV diameter at annulus and up to 8 mm above. In contrast, annular PdD was not correlated to final THV PdD all across the landing zone (annulus to 8 mm above). This suggests constant THV under expansion and less accuracy of annular measurements to predict final THV diameters. The sub analyses for balloon-expandable Sapien 3 and self-expandable Evolut (R/PRO) valves demonstrated comparable findings. If we use the supra-annular tracing instead of the ICD, when considering the BAVARD configurations, the baseline PpD at +4 mm was the most reliable to predict the final THV dimensions in Sievers type 0-1 BAV with tubular configurations; in flared configurations both annular and +4 mm PdDs closely matched post TAVI dimensions. Focus may be necessary for tapered configurations in which the PdD 8 mm above

the annulus could be more predictive of final THV dimensions. Flared and tapered configurations only occurred in 5% of our cohort. Thus, these findings suggest that in most BAV, whatever the device, the baseline PpD at +4 mm is linked to the final THV expansion, finally suggesting a supra-annular leaflet sealing in BAV. Even if these results are consistent with the presence of a restricted area above the annulus that constrains the THV expansion and probably serves as the main anchor point, they need to be validated in a larger population.

Conclusions

In this long and interesting experience of research and knowledge-sharing we investigated: a) the improvement of percutaneous treatment of aortic valve disease, underlying new potential horizons for TAVI in challengig settings; b) the TAVI role in the complex anatomy of the bicuspid aortic valves; c) the importance of a dedicated and standardized MSCT guided sizing to improve THV performance in BAV patients.

We tried to get some answers to some unsolved questions by a translational research activity, collaborating and sharing knowledge with multiple international centres for structural heart interventions. TAVI confirms to be a validated option for treatment of aortic stenosis in patients at intermediate to high mortality risk. Our findings supported the possibility to move TAVI indications through lower risk patients, even if with challengig anatomy. This is the case of patients with symptomatic aortic stenosis and BAV undergoing aortic valve treatment. BAV patients are younger and have a lower risk profile as compared to patients with tricuspid aortic valves. An appropriate imaging modality for BAV diagnosis and anatomy definition seems to be the combination of TTE and MSCT. BAV patients are predominantly treated by surgical aortic valve replacement but TAVI is performed in almost one third of cases. Indeed these patients present with more complicated baseline anatomy as compared to patients with tricuspid valves. These anatomical features lead to higher TAV-in-TAV procedure rate. However this does not translate into increase in mortality rate at 30 days follow-up but rather correlate to a lower device success rate. Thus TAVI in BAV patients seem to be safe and feasible. In particular, second-generation TAVI prostheses similarly reshape the aortic annulus in tricuspid and bicuspid aortic valves. On average prostheses were deployed 3.4 mm below the aortic annulus, in the BAVARD registry, with excellent clinical outcomes. Devices keep consistent diameters from distal edge to 12 mm above. However, prosthesis underexpansion is constantly observed in BAV. Annular-based sizing seems to be accurate in type 0 and type 1 bicuspid valves with minimal oversizing, but a supra-annular evaluation should be integrated in the sizing process for gray

zones. Our findings and simplified sizing algorithm need to be validated in larger prospective registries, ideally evaluating the different types of prostheses separately. This sizing algorithm will be part of the BIVOLUT X prospective registry final paper.

List of abbreviations

AR: aortic regurgitation

AS: aortic stenosis

AV: aortic valve

BASILICA: bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction

BAV: bicuspid aortic valve(s)

BEV: balloon expandable valve

CABG: coronary artery bypass grafting

CAO: coronary artery occlusion

COPD: chronic obstructive pulmonary disease

eCAO: established coronary artery occlusion

iCAO: impending coronary artery occlusion

ICD: intercommissural distance

IQR: interquartile range

LMS: left main stem

MI: myocardial infarction

MDCT: multi-detector computed tomography

MSCT: multi-sliced computed tomography

NYHA: new york heart association

PAR: paravalvular aortic regurgitation

PpD: perimeter derived diameter

PCI: percutaneous coronary intervention

PVL: paravalvular leak

PS: propensity score

RCA: right coronary artery

SAVR: surgical aortic valve replacement

SEV: self expandable valve

STS: society of thoracic surgery

TAV-in-TAV: transcatheter aortic valve in transcatheter aortic valve

TAVI: transcatheter aortic valve implantation

TAVR: transcatheter aortic valve replacement

TEE: transesophageal echocardiogram

THV: transcatheter heart valve

TTE: transthoracic echocardiogram

VARC 2: Valve Academic Research Consortium 2

VIV: valve in valve

VTC: virtual transcatheter valve–to–coronary ostium

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Curriculum vitae

Personal Information

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Date of Birth : 21/09/1987
Nationality : Italian

Work Experiences

2018 – Present

Interventional cardiologist
- Caronary, carotid and peripheral artery angiography,
- Coronary Angioplasty
- Transthoracic echocardiography
- Excercise stress test

PhD « Cardiovascular Pathophisiology and Theraputics-CardioPaTh »
« Federico II » University of Naples (Italy) in collaboration with Clinique PASTEUR, Toulouse (France) under Dr. Didier Tchètchè supervision.

2016 - 2018

Fellow in interventional cardiology at Clinique PASTEUR, Toulouse (France)
- Research projects on bicuspid aortic valve undergoing TAVI
- Caronary, carotid and peripheral artery angiography (indipendent)
- Coronary Angioplasty (indipendent)
- TAVI (assisted)

Education

2012 - 2016

Cardiology training at « Federico II « University of Naples (Italy)
- Transthoracic echocardiography
- Excercise stress test
- Holter ECG
- Clinical research at « OLV » hospital in d'Aalst (Belgique)

2009 - 2011

Student on medical training at « Federico II » University of Naples (Italy)
- Clinical and laboratory research at Advanced Biomedical Sciences at « Federico II » University of Naples (Italy)
- Medical degree e (110/110 cum laude)
- Thesis in Interventional Cardiology

Publications

2020

"Procedural and clinical outcomes of type 0 versus type 1 bicuspid aortic valve stenosis undergoing trans-catheter valve replacement with new generation devices: Insight from the BEAT international collaborative registry"
Ielasi A, Tchétché D, **De Biase C**, et al.
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"Optimizing TAVI Could Make It Even More Cost-Effective"
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2015

"Early stent thrombosis with bivalirudin in patients undergoing percutaneous coronary intervention. A meta-analysis of randomised clinical trials"
Piccolo R, **De Biase C,** D'Anna C, Trimarco B, Piscione F, Galasso G1.
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2012

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"Long-term clinical outcomes following sirolimus eluting stent implantation in patients with acute myocardial infarction. A meta-analysis of randomized trials"
Piccolo R, Cassese S, Galasso G, Niglio T, De Rosa R, **De Biase C**, Piscione F.
Clin Res Cardiol.2012 Nov;101(11):885-93

Main Research Project

Sub-investigator of the BIVOLUT-X registry
Transcatheter treatment of bicuspid aortic valves with the Evolut platform: the BIVOLUT-X registry

Languages

Italian : Mother Tongue
English : C2
French : C2

Computer Skill

Microsoft Office suite
SPSS

List of publications

BOOK CHAPTERS

- "TAVI in special scenarios: valve-in-valve; valve-in-ring". Nicolas Dumonteil, Chiara De Biase. Part II – Therapeutic procedures, book "PERCUTANEOUS CARDIAC INTERVENTIONS TEXTBOOK-TIPS AND TRICKS OF NEW TECHNIQUES BEYOND STENTING" *under press*.

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Clin Res Cardiol.2012 Nov;101(11):885-93.

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