

Review Article

Percutaneous Transcatheter Therapy of Non-Coronary Structural Cardiac Disease

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During the last few years, adult cardiovascular medicine has witnessed the continuous development of novel non-coronary percutaneous transcatheter interventions aiming at the treatment of structural heart disorders (valvular and congenital).¹⁻³ Structural heart disorders now amenable to percutaneous treatment include valvular diseases (calcific degenerative aortic valve stenosis, bioprosthetic aortic valve degeneration, mitral stenosis, mitral regurgitation, pulmonic valve stenosis, prosthetic paravalvular leak) and non-valvular congenital and non-congenital disorders (interatrial septal defect, ventricular septal defect, arterial-venous fistulae, left atrial appendage occlusion, septal ablation in obstructive hypertrophic cardiomyopathy, balloon pericardiotomy for chronic pericardial effusions, patent *ductus arteriosus*, aortic coarctation, etc.). The present paper provides an overview of the indications, guidance and procedural issues involved in treating degenerative aortic stenosis, mitral regurgitation, interatrial septal defect and paravalvular leak, which are currently amenable to percutaneous transcatheter treatment.

Transcatheter aortic valve implantation for degenerative aortic valve stenosis

Degenerative aortic stenosis is a progressive disorder, and the prognosis is unfav-

orable after the appearance of symptoms.⁴ Medical treatment does not effectively decelerate the progression of the disease. Until recently, aortic valve replacement (AVR) was the only reliable treatment for severe symptomatic degenerative aortic stenosis. Percutaneous treatment was limited to aortic valvuloplasty, which is considered a temporary/palliative treatment rather than a definitive treatment, due to the high rates of valve restenosis and the limited long-term durability.⁵ In contrast, aortic valvuloplasty is the gold-standard treatment in younger patients who have severe congenital aortic stenosis without severe calcification.

Transthoracic echocardiography is a valuable tool for the diagnosis of severe aortic stenosis. A mean transvalvular gradient >40 mmHg and a valve area index <0.6 cm²/m² are the cornerstones of the diagnosis. In the case of impaired left ventricular contractility, low transvalvular gradient and low estimated valve area, echocardiography after a low-dose dobutamine challenge may differentiate between true severe aortic stenosis and pseudo-severe stenosis secondary to low transvalvular flow. In patients with true severe aortic stenosis, a severely hypertrophied left ventricle, and impairment of relaxation, an estimated low valve area is occasionally associated with a moderately elevated mean gradient, due to the low stroke volume.⁵

Transcatheter aortic valve implantation (TAVI) is a new percutaneous treatment of severe aortic stenosis that was first applied in humans in 2002.⁵⁻⁸ Since then, with the significant technological improvements and accumulating experience, TAVI has emerged as a reliable alternative therapy to surgery in patients who have severe symptomatic aortic stenosis with high risk or contraindications for surgery. High risk for AVR surgery is defined when a logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) is >20% or a Society of Thoracic Surgeons (STS) score is >10%. Contraindications for surgery are conditions such as chest radiation or porcelain aorta.^{6,7}

The technology around TAVI continues to evolve; currently there are two approved prosthetic valves for TAVI and many more valves are under evaluation. The two valve systems now used in clinical practice are the CoreValve (Medtronic, Inc.) and the Sapien (Edwards Life Sciences, Inc.). The CoreValve is a self-expanding valve, and consists of three leaflets made of porcine pericardium, which are mounted in a nitinol frame (the self-expanding component). The Sapien is a balloon-expandable valve consisting of three leaflets made of bovine pericardium, which are mounted in a stent made of stainless steel. The common femoral, common carotid and subclavian artery can be used as access sites for the CoreValve, whereas the Sapien valve can be introduced through the common femoral artery or via the transapical approach. Both valves can be inserted through the transaortic route in patients without appropriate arterial access.^{6,7}

TAVI is associated with a clinical benefit in properly selected individuals with severe aortic stenosis. Using the Sapien valve, the PARTNER trial showed that TAVI is superior to the conventional conservative approach (including medical therapy and balloon aortic valvuloplasty) in patients who are not suitable for AVR, whereas it is equivalent to AVR in patients who are considered high risk candidates for surgery.^{9,10} The 2012 ESC guidelines on the management of valvular heart disease recommend TAVI for patients with severe symptomatic aortic stenosis who are not suitable for AVR as assessed by a “heart team”, provided they are expected to gain improvement in their quality of life and to have a life expectancy of more than 1 year, after consideration of their comorbidities (Class I, level of evidence B). Additionally, the ESC guidelines suggest that TAVI should be considered in patients with severe symptomatic aortic stenosis who may still be suitable, but who are at

high risk for surgery, provided that the consideration of comorbidities, individual risk profile and anatomic characteristics by the “heart team” favors TAVI (Class IIa, level of evidence B).⁵

Appropriate patient selection and meticulous pre-procedural screening are key components of TAVI. The candidate should have severe symptomatic aortic stenosis, should be at high risk for AVR or inoperable, and should have a life expectancy >1 year, based on comorbidities, while an improvement in quality of life must be expected with TAVI. In addition to the above, certain anatomical conditions must be fulfilled, and careful assessment of the anatomy and function of the heart, as well as the anatomy of the aortic valve, root, ascending aorta, coronaries and peripheral arteries to be used for arterial access is of utmost importance.^{6,7}

A careful assessment of the severity of aortic stenosis must be performed in the first instance. In the case of severe obstruction, it is imperative to confirm that the obstruction is located at the valvular level and not at the left ventricular outflow tract. Then, the aortic annulus must be accurately sized. This is a crucial step in the screening process, as correct sizing is essential for procedural success: a small implanted valve may cause paravalvular regurgitation or even device instability, whereas a larger implanted valve may be associated with an underexpanded frame (with transvalvular gradient and functional stenosis), and even aortic rupture.⁶⁻⁸ Sizing of the aortic annulus is often a challenge, as it usually has an elliptical/oval rather than a round shape, with a major and a minor diameter. There is no gold standard method for its measurement. Transthoracic echocardiography (TTE) is the most commonly used modality, and transesophageal echocardiography (TEE) is used when an accurate measurement is not feasible with TTE, especially when a borderline annulus size questioning the feasibility of TAVI is derived by TTE. Computed tomography also contributes significantly to acquiring the anatomical information needed to plan a TAVI, including annulus size. It not only estimates the exact shape of the annulus, but also, in case of a severely elliptical shape, it can calculate the mean diameter by measuring the annular perimeter. Other anatomical characteristics, such as the diameters of the ascending aorta and sinotubular junction, the height of the coronary ostia from the valve leaflets, and the height of the sinotubular junction from the valve leaflets, are also important.⁶⁻⁸ In the case of a mitral valve prosthesis, the distance between the aortic annulus and the superior part of the mitral

prosthesis is crucial, in order that the implanted aortic bioprosthesis will not interfere with the function of the prosthetic mitral valve.

TEE may play some role in the positioning of the Sapien bioprosthesis, especially when a transapical approach is employed. On the other hand, implantation of the CoreValve is guided by fluoroscopy. TAVI is usually performed under conscious sedation through the common femoral artery and percutaneous closure is performed using a closure device, such as a preloaded Prostar XL suture device. After crossing the stenosed valve and prior to prosthesis implantation, balloon valvuloplas-

ty is often (but not always) performed with a balloon under rapid ventricular pacing (Figure 1). Then, the deployment procedure is initiated. The CoreValve prosthesis is advanced retrogradely over a stiff guidewire and deployed across the aortic annulus. Deployment of the prosthetic valve consists of three stages. During the first stage, the operator has full control of the valve expansion, without being forced to deploy the valve rapidly, since the valve is deployed under the patient's native rhythm. During the second stage, the partially deployed prosthesis obstructs the aortic valve flow, blood pressure may be compromised, and the operator deploys the prosthesis in

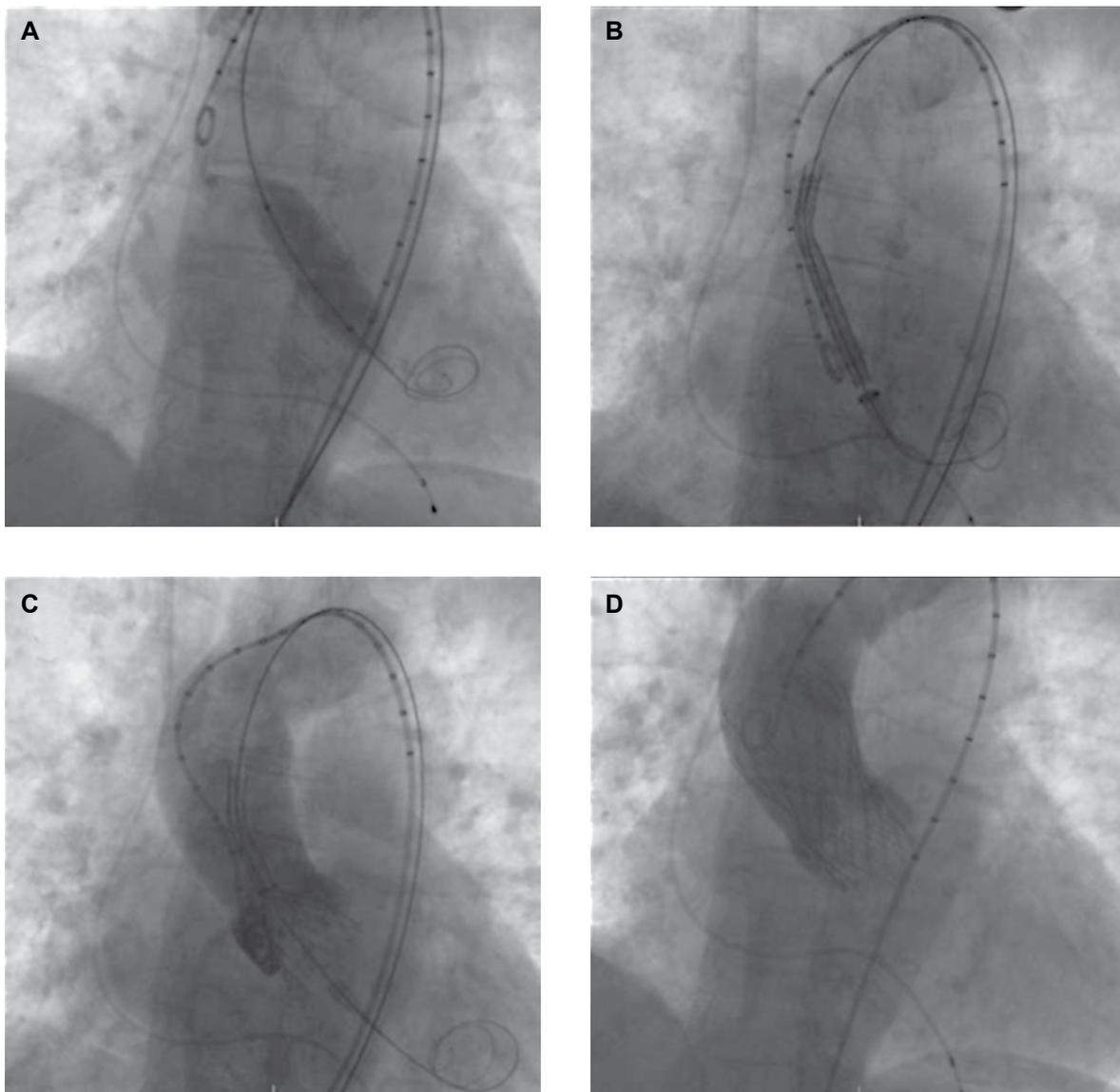


Figure 1. Balloon valvuloplasty performed with a balloon under rapid ventricular pacing (A). Positioning of the CoreValve prosthesis across the aortic annulus (B). Deployment of the CoreValve (initial phase) (C). Aortography after deployment confirms correct positioning and absence of aortic regurgitation (D). From the authors' personal data.

an uninterrupted mode until blood pressure returns to baseline. The third step (full deployment) is then completed, without any need for hurry, since sufficient blood flow is maintained through the deployed valve (Figure 1). Proper prosthesis placement is assessed serially by aortograms.

Post-implantation paravalvular aortic regurgitation is usually evaluated using aortography and measurement of aortic and left ventricular hemodynamics. TTE is a valuable tool for identifying transvalvular gradients and aortic regurgitation after the procedure. TTE is also valuable for the evaluation of ventricular function, transvalvular gradient, aortic valve area, and aortic regurgitation during the long-term follow up.

A recent large European registry showed very good results with TAVI (in-hospital mortality 7.4%, stroke 1.8%, myocardial infarction 0.9%, and major vascular complications 3.1%), with similar outcomes for both the Sapien valve and CoreValve.¹¹ Mortality was lower for the transfemoral route than for other routes, whereas advanced age, a high logistic EuroSCORE, and pre-procedural mitral regurgitation grade ≥ 2 were independent predictors of mortality.¹¹

Post-implantation paravalvular aortic regurgitation is not unusual after TAVI. It is attributed to inadequate expansion of the bioprosthesis or to excessive calcification that does not allow the valve apparatus to seal within the annulus. Recent data suggest that moderate or severe paravalvular aortic regurgitation is an independent predictor for both periprocedural and long-term mortality.¹² For these reasons, moderate or severe paravalvular aortic regurgitation should be addressed aggressively and treated with the commonly used post-dilation using a balloon. In case of a low implantation leading to significant paravalvular aortic regurgitation, the snare repositioning technique or the balloon withdrawal technique can be employed.^{13,14}

Transcatheter mitral valve repair for severe mitral regurgitation

The cause of primary or organic severe mitral regurgitation (MR) is primary leaflet abnormality, as in severe mitral prolapse or Barlow's disease. In contrast, in functional or ischemic MR, regurgitation is due to severe left ventricular dilatation or to abnormalities of ventricular contraction secondary to ischemia or infarction.

Severe MR results in left ventricular overload, ventricular dilatation and pulmonary hypertension, and at later stages left ventricular systolic dysfunction ensues. Unless treated, patients with severe MR de-

velop symptoms of heart failure and have increased mortality.¹⁵⁻¹⁷

Medical therapy alone is not an efficient treatment for severe MR. In selected cases of severe functional MR, cardiac resynchronization therapy can improve functional capacity and reduce the severity of MR. Although the aim of resynchronization therapy is to improve the functional capacity and life expectancy of heart failure patients, and not to improve the functional MR *per se*, the functional MR can be improved due to reverse remodeling. So far, the definitive treatment for symptomatic patients with severe MR or patients with asymptomatic severe MR and evidence of an abnormal ejection fraction ($< 60\%$ but $> 30\%$) or left ventricular dilation has been mitral valve surgery.¹⁵⁻¹⁷ Today, mitral valve repair is considered as the optimal surgical approach in patients with severe MR, compared to mitral valve replacement. Mitral valve repair results in lower perioperative and long-term morbidity and mortality, and better preservation of left ventricular function.¹⁸ However, not all patients with severe MR are suitable candidates for mitral valve repair, and not all cardiovascular surgeons have adequate experience with mitral repair. Notably, a significant number of patients with severe MR needing surgery do not undergo any operation, due to the high surgical risk of mitral valve surgery or significant comorbidities.

In an attempt to decrease the risk of mitral valve surgery, or to treat inoperable patients with severe MR, percutaneous approaches aiming at treating MR have been developed. A few years ago, a technique employed the implantation of a metallic rim in the coronary sinus, but the clinical results were not favorable.¹⁹ The MitraClip device is a recently developed device that is implanted percutaneously in the 2 mitral cusps and may shorten the distance between the mitral leaflets.²⁰⁻²² Its efficacy was recently evaluated in the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) trial, which compared the MitraClip with classical mitral valve surgery (repair or replacement) in patients with moderate to severe or severe MR.²³ After 1 year, the primary composite efficacy endpoint (death, surgery for mitral valve dysfunction, and grade 3+ or 4+ MR) occurred at a significantly higher rate in patients in the MitraClip group (45%) than in the surgical group (27%). This difference was driven by the higher risk of surgery for MV dysfunction in the MitraClip group. The MitraClip was safer than MV surgery (major adverse events at 1 month 15% vs. 48%). After 1 year,

functional class and quality of life improved in both groups.²³ The EVEREST II Trial showed that, despite not being as efficient as MV surgery in reducing MR immediately post-intervention, MitraClip implantation is a safe procedure that is associated with a significant reduction in MR and an improvement in functional status during long-term follow up.²³ Recently, the 4-year results of the EVEREST-II Trial were published. These data show that, after the first year and until the fourth year of follow up, very few patients required surgery for residual MR after either percutaneous or surgical treatment, and that there was no difference in the prevalence of moderate or severe MR or mortality at four years.²⁴ The

ACCESS EU cohort evaluated patients with severe functional MR who were treated with the MitraClip. At 6 months, patients with an ejection fraction lower than 30%, a group with significant perioperative mortality if treated with MV surgery, had a similar reduction of MR, similar functional improvement and similar mortality compared with patients with an ejection fraction greater than 30%.²⁵

Meticulous patient selection is a crucial step for the implantation of the MitraClip. As strict anatomical criteria need to be met, TEE is of utmost importance for correct patient selection. In order for a patient with severe mitral regurgitation to be eligible for MitraClip, the coaptation length must be ≥ 2 mm, the coaptation

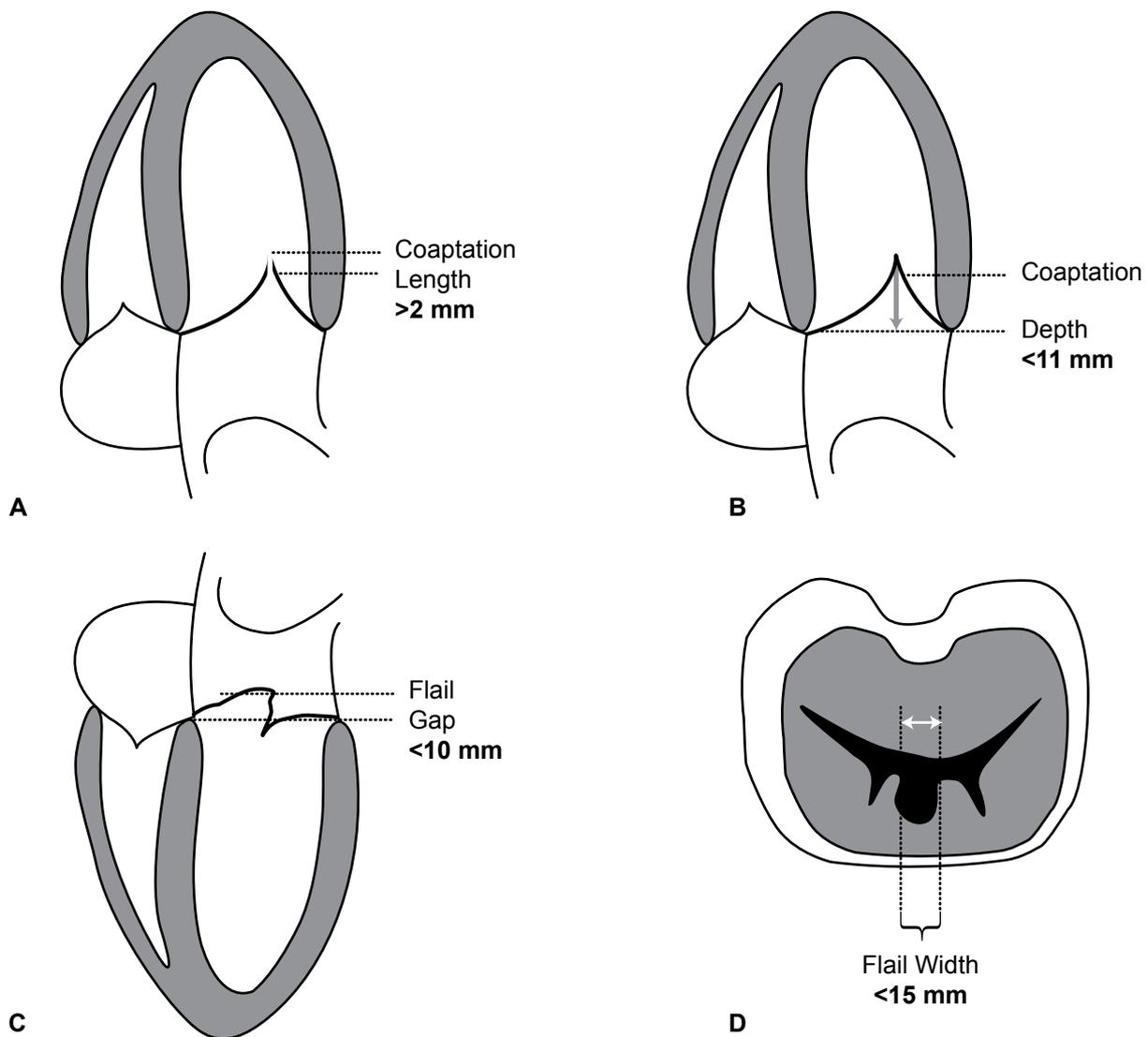


Figure 2. Meticulous patient selection is crucial before MitraClip implantation. Eligible patients should have a coaptation length ≥ 2 mm (A), a coaptation depth < 11 mm (B), a flail gap < 10 mm (C) and a flail width < 15 mm (D). Modified from Contaldi C et al, Cardiovasc Ultrasound 2012; 10: 16. (ref. #2). Originally published by BioMed Central.

depth must be <11 mm, the flail gap must be <10 mm and the flail width must be <15 mm.^{20,21,23} (Figure 2)

The percutaneous MitraClip intervention involves the placement of a 4-mm wide cobalt chromium device that grasps the mitral leaflets, in a manner which is analogous to the surgical edge-to-edge Alfieri repair. Transseptal puncture is an essential step of the procedure, which needs guidance by TEE.^{20,21,23}

Transcatheter atrial septal defect closure

Atrial septal defect (ASD) is a common congenital heart disease that, if left untreated, may result in right ventricular volume overload, pulmonary hypertension, and in extreme cases, Eisenmenger's syndrome. In the case of pulmonary hypertension and transient right-to-left shunt, paradoxical embolism may occur.²⁶ Among the different forms of ASD, only *secundum* ASD is amenable to transcatheter closure.

Transcatheter ASD closure is indicated in the case of right ventricular dilation and volume overload, significant left-to-right shunt with a Qp/Qs ratio ≥ 1.5 , or on the occurrence of a paradoxical embolism. It is contraindicated in the presence of a large defect with a diameter of greater than 38-40 mm, when there is no adequate septal rim, and when there is severe pulmonary hypertension with right-to-left shunt. In the presence of additional congenital cardiac abnormalities, it may be preferable to refer the patient for surgery.²⁶

TTE is a valuable tool that can be used to diagnose ASD, calculate the shunt flow, and evaluate its effects on right chamber volumes and the pulmonary circulation. However, once transcatheter closure has been decided upon, TEE is mandatory in order to accurately quantify the dimensions of the defect, to evaluate the presence of adequate rims, and to diagnose any coexistent congenital heart abnormality.

TEE is also a useful tool for guiding the placement of the ASD closure device. The use of TEE is not mandatory, however, as intracardiac echocardiography is a reliable alternative that does not require general anesthesia. To date, there are several types of device dedicated for ASD closure. Most devices comprise two disks that cover the two surfaces of the interatrial septum (left and right atrial surface), while a waist between the two disks seals the defect. In brief, the defect is crossed initially with a regular wire through a multipurpose catheter. Then the regular wire is exchanged for a stiff wire, a balloon is in-

flated across the defect until no flow is detected and the diameter of the defect is measured using fluoroscopy and echocardiography (Figure 3). However, the use of a sizing balloon is optional. Then, an appropriately sized occlusion device is deployed against the interatrial septum, covering the defect. The correct position of the occlusion device and its stability are confirmed using both fluoroscopy and echocardiography (TEE or intracardiac). If the position or size of the device is unsatisfactory, it may be retrieved and redeployed. If available, three-dimensional TEE can be useful for evaluating the shape of the ASD and guiding the procedure.²⁷ It has been shown that three-dimensional TEE sizes an ASD more accurately than two-dimensional TEE; in the case of complex ASDs, the latter may underestimate its area, and this may drive the placement of an undersized closure device, resulting in residual shunting.²⁸

Transcatheter percutaneous ASD closure is a beneficial procedure in patients with ASD and appropriate indications for closure, as it improves exercise capacity and halts right heart failure.²⁹ Late device erosion is a rather uncommon but potentially disastrous complication.³⁰

In recent years, percutaneous closure of a patent *foramen ovale* (PFO) has been recommended in patients with ischemic—especially cryptogenic—stroke and PFO, in order to prevent recurrent stroke. However, the prevalence of PFO is high in the general population; thus, the association between PFO and ischemic stroke is sometimes incidental and not etiological. Recent randomized studies (CLOSURE 1, RESPECT, PC Trial) have failed to show a clear clinical benefit of percutaneous closure of PFO compared with medical treatment,³¹ and accordingly, the enthusiasm for PFO closure has declined considerably.

Transcatheter closure of paravalvular leaks

A paravalvular leak (PVL), meaning the presence of regurgitant flow between the ring of the prosthetic valve and the annulus, is an adverse complication encountered in patients with prosthetic valves. Prosthetic valve endocarditis and calcification of the native annulus are conditions that may result in PVL. The clinical significance of a PVL may vary from a mild, trivial regurgitation without hemodynamic compromise, to severe regurgitation with volume overload and congestive heart failure or severe hemolysis.³²

TTE is a valuable tool for identifying and quantifying PVL. However, in most cases, especially with

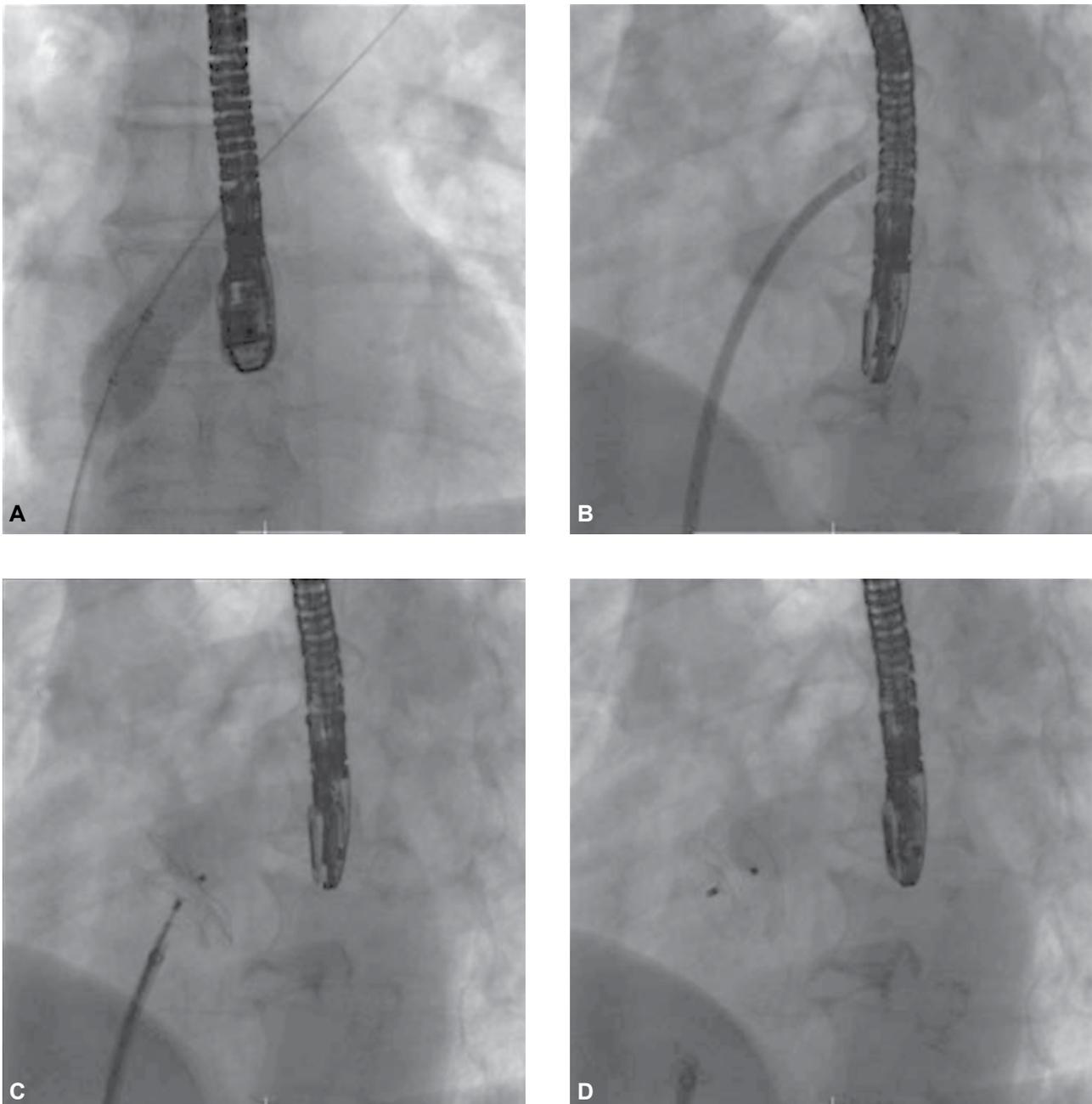


Figure 3. After crossing the atrial septal defect (ASD), a balloon is inflated across the defect until no flow is detected and the size of the defect is measured using fluoroscopy and transesophageal echocardiography (A). The delivery sheath is across the ASD (B). Both disks of the closure device are deployed (C). The deployed closure device is released from its delivery system (D). From the authors' personal data.

mitral prostheses that do not allow adequate penetration of ultrasound and imaging of the regurgitant flow, TEE is necessary. TEE may provide all required information (position, shape and size of the PVL) to allow sufficient planning for transcatheter PVL closure.³²

Although surgery is the gold standard treatment for PVL, it requires a new thoracotomy, and this is

associated with a high periprocedural mortality. In properly selected patients with a PVL in need of correction and an unacceptably high risk for surgery, transcatheter PVL closure offers a reliable alternative. The procedure is contraindicated in the presence of endocardiac infection with vegetations, intracardiac thrombus, and an unstable prosthetic valve. Due to the complex and largely unexpected anatomy, TEE

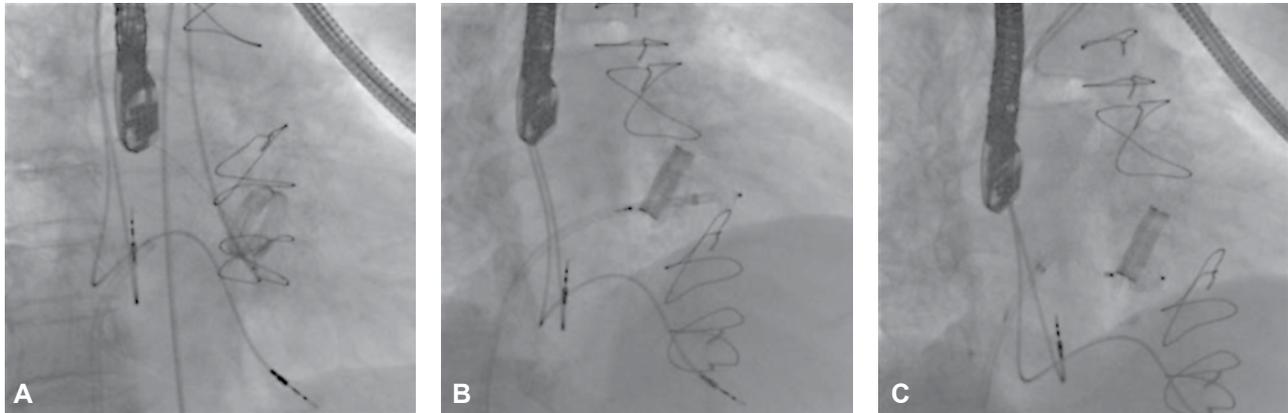


Figure 4. A mitral prosthesis paravalvular leak (PVL) has been crossed retrogradely (the tip of the guidewire is located in the left atrium) (A). After a transseptal puncture and placement of a delivery sheath via the femoral vein route across the PVL, one disk of the umbrella-type occluder has been successfully deployed in the left ventricle (B). Once the second disk has been deployed in the left atrium, the deployed closure device is released from its delivery system (C). From the authors' personal data.

is routinely used for guidance, and is generally preferred over intracardiac echocardiography.^{32,33} For the same reasons, 3-dimensional TEE is the key to correctly characterizing the location, size, and shape of the defect, and is currently considered mandatory for the guidance of PVL closure.³⁴

Depending on the exact position of the mitral PVL in relation to the mitral annulus, the PVL can be approached/crossed either retrogradely (through the aorta and the left ventricle) or antegradely (through the left atrium after a transseptal puncture). Mitral PVLs can also be crossed retrogradely using the transapical route, especially in medially located defects.³⁴ Aortic PVLs are approached/crossed retrogradely. Once the leak is properly crossed with a wire, a device selected using TEE imaging is deployed to seal the defect (Figure 4). As there are no specific devices dedicated to PVL closure, vascular plugs, coils or umbrella-type occluders can be used, based on the anatomical characteristics of the defect. Before releasing the closing device, it is necessary to confirm correct position, adequacy of regurgitant flow discontinuation and absence of interference with the function of the prosthetic valve (Figure 4).

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