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Review

Current status and future perspective of structural heart disease intervention

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ABSTRACT

Summary: Valvular heart diseases are one of the most frequent causes for heart failure. Degenerative diseases of the aortic and mitral valve as well as a dysfunctional tricuspid valve disease result in a worse clinical outcome if severe. Minimal-invasive, surgical and/or catheter-based structural heart disease (SHD) interventions have recently seen a dramatic increase. Transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) is a disruptive technology, and next generation devices and careful patient selection will minimize limitations of TAVI such as paravalvular leak, conductance disturbances, ischemic stroke, and vascular complications. The indication of TAVI continues to shift toward lower risk patients and patients with complex anatomy such as bicuspid AS or native pure aortic regurgitation. Successful clinical results in TAVI have generated considerable interest in further transcatheter technologies targeting mitral regurgitation (MR) and also toward tricuspid regurgitation (TR). The efficacy and safety of edge-to-edge with or without annuloplasty leaflet repair mimicking surgical repair will have to be confirmed by technical improvement, device development, and further emerging studies. Transcatheter mitral valve implantation might be an alternative strategy in patients with symptomatic severe MR and favorable anatomy. Possible interventional treatment approaches for TR have gained more attention. Improvement and development of SHD interventions have enabled more patients to receive minimally invasive heart valve interventions and these procedures have prolonged life and/or improved quality of life for many patients who were previously considered unsuitable for surgery. Continued technical and device improvements and accumulated evidence will expand its possibility and future of SHD interventions.

Contents

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Introduction

Valvular heart diseases (VHDs) are one of the most frequent causes for heart failure [1] and are associated with poor prognosis particularly among patients with conservative management [2,3]. Although degenerative disease of the aortic and mitral valve is most frequently seen, a dysfunctional tricuspid valve is often a bystander in cardiovascular disease and by itself results in a worse clinical outcome if severe. Minimal-invasive, surgical and/or catheter-based structural heart disease (SHD) interventions have recently seen a dramatic increase especially in aortic and mitral valve disease. Successful clinical results in transcatheter aortic valve implantation (TAVI) for aortic stenosis (AS) over the past decade have generated considerable interest in further transcatheter technologies targeting mitral regurgitation (MR) and also toward tricuspid regurgitation (TR). In this review, we aim to summarize current status and future perspective of SHD intervention with respect to TAVI, transcatheter mitral valve repair and replacement, and transcatheter tricuspid repair.

Transcatheter aortic valve implantation (TAVI)

AS is the most common valvular disease worldwide, ranging from 2 to 4% in patients older than 75 years old [4,5]. The progressive calcific degeneration caused by aging, congenital alterations, or rheumatic diseases [4] lead to left ventricular impairment and symptoms such as dyspnea, chest pain, and syncope, leading to sudden death. Therefore, a valve replacement treatment is necessary especially in symptomatic patients to improve patients' prognosis [5–7]. Currently, surgical aortic valve replacement (SAVR) or TAVI are the preferred treatment options depending on patients' comorbidities, preferences, and concomitant coronary artery disease and/or valve disease [7,8]. The transfemoral (TF) TAVI is the most commonly performed approach for TAVI [9].

Current indication for TAVI – from high to intermediate surgical risk patients

The landmark Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated equivalent survival rate after TAVI using the Edward Sapien balloon-expandable valve (Edwards Lifesciences Corp., Irvine, CA, USA) compared to SAVR [10,11], which was confirmed by the CoreValve US Pivotal trial demonstrating the safety, efficacy, and superior survival rates in patients undergoing TAVI using the Medtronic self-expanding valve (Medtronic Inc., Minneapolis, MN, USA) compared to SAVR [12,13]. These trial results in high-risk patients have shifted attention to applying TAVI to intermediate-risk patients, and many observational studies have shown comparable short- and mid-term mortality between TAVI and SAVR groups in intermediate-risk patients [14–16].

In 2016, results from the randomized PARTNER 2 trial were presented and TAVI using the Sapien XT valve system (Edwards Lifesciences Corp., Irvine, CA, USA) demonstrated similar event rates of all-cause death or disabling stroke at 2 years (19.3% vs. 21.1% for TAVI and SAVR) [17]. Using the Medtronic 14–16 Fr self-expanding valve system (CoreValve and Evolut R, Medtronic Inc., Minneapolis, MN, USA), the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial demonstrated that TAVI was non-inferior to surgery in intermediate surgical risk patients [18]. Further development and improvement of the first- and second-generation devices together with convincing data from the randomized and additional non-randomized studies have expanded indication of TAVI to intermediate surgical risk patients [19].

Current generation valves – toward lower rates of complications

The most current Edwards Sapien 3 valve system (Edwards Lifesciences Corp., Irvine, CA, USA) is a lower profile, balloon-expandable valve that is designed to further reduce paravalvular leak (PVL). It has improvement in geometry of the tri-leaflet bovine pericardial valve and is delivered through a 14–16 Fr expandable sheath that helps to overcome transvascular stenosis/kinking and may reduce vascular complications.

The Medtronic Evolut R and Evolut PRO system (Medtronic Inc., Minneapolis, MN, USA) are current generation devices, which allow recapturing and repositioning of the valve. The prosthesis has a supra-annular design resulting in low post-procedural gradients and large orifice areas. A pericardial skirt allows a secure seal against PVL. Head-to-head comparison of balloon-expandable vs. self-expanding transcatheter heart valves has shown comparable results in terms of outcomes [20].

The Boston Lotus system (Boston Scientific Corporation, Marlborough, MA, USA) is a mechanically expandable system with full recapture and repositionable properties and consists of tri-leaflet bovine pericardial tissue with an adaptive seal at the inflow segment. The Lotus Valve had received CE mark in Europe based on the initial results of the REPRISE study [21], with low rates of PVL, but pacemaker rates reported to range from 24.0% to 31.8% in published patient series [22–26]. The valve was taken off the market in 2016 due to technical issues involving the Edge series. A new version is expected to enter the European market again in 2019.

The self-expanding ACURATE neo prosthesis (Symetis/Boston, Ecublens, Switzerland) is a new-generation device. The prosthesis has specific design features which may be associated with lower conduction disturbances in early clinical trials and registries [27,28]. Its current transfemoral system has flexible stabilization arches allowing for axial self-alignment. In addition, the upper crown allows supra-annular anchoring and captures the native

leaflets, reducing the risk of coronary obstruction and PVL, while the lower crown has minimal left ventricular outflow tract protrusion, avoiding interference with the conduction system. A skirt system helps to seal against PVL [29]. The ACURATE neo prosthesis has supra-annular leaflets, which enable a large effective orifice area and low gradients. The Symetis ACURATE neo Valve Implantation Using Transfemoral Access (SAVI-TF) registry showed favorable 30-day [30] and 1-year outcomes [31]. However, randomized studies comparing against current transcatheter valves or SAVR are still missing.

Future valves of TAVI – more performance and lower complications

Next-generation TAVI devices include the Sapien 3 Ultra (Edwards Lifesciences Corp., Irvine, CA, USA), the CENTERA (Edwards Lifesciences Corp., Irvine, CA, USA), the ACURATE neo AS (Symetis SA, Ecublens, Switzerland), and the LOTUS Edge (Boston Scientific Corporation, Marlborough, MA, USA), the new transfemoral system of JenaValve (JenaValve technology, Munich, Germany) and the NVT Allegra (New Valve Technology, Hechingen, Germany).

The Sapien 3 Ultra with Axela Sheath (14Fr, expandable) is a further development of Sapien 3. A new on-balloon design removes the need for valve alignment before implantation. The positioning slider allows for single-handed control during valve positioning. Its taller skirt system leads to up to 50% more contact surface area with native anatomy aiming to prevent PVL. Study data are not available yet regarding the Sapien 3 Ultra.

The CENTERA is a next-generation self-expanding TAVI device, compatible with 14Fr e-Sheath. It is a repositionable and recapturable device and characterized by distal flex mechanism (trackability and coaxial alignment) and motorized handle (precise deployment control). Tchetche et al. have recently reported the initial clinical results of the CENTERA trial including 203 patients (unpublished data). Technical and device success were 97.5% and 96.4%, respectively, and clinical outcomes at 30 days revealed 1.0% mortality, 4.0% stroke, 6.4% major vascular complication, and 4.9% new permanent pacemaker. Only 0.6% of patients had moderate AR at 30 day, with 0.0% of severe AR (EuroPCR 2017, unpublished data).

The LOTUS Edge (Boston Scientific Corporation, Marlborough, MA, USA) with iSleeve Expandable Sheath (14Fr) is a new model of LOTUS, maintaining benefits of the first-generation system (e.g. adaptive seal, complete repositionability, no rapid pacing with precise placement, hemodynamic stability, and early valve function), combined with an improved low-profile delivery system and a more flexible catheter. Depth Guard technology aims at limiting depth of implantation, potentially leading to optimized deployment. The adaptive seal conforms to irregular anatomical surfaces to minimize PVL. The feasibility study reported by Walters et al. at ACC 2017 revealed 100% of technical success and 0.0% of moderate-severe PVL, with 11.8% of new permanent pacemaker implantation (ACC 2017, unpublished data).

ACURATE neo AS is an improved model of ACURATE neo with modified skirt material, expected to reduce PVL rates. Initial clinical results of the ACURATE neo AS (n = 30) showed that the rate of freedom from VARC 2 combined safety events was 96.7% (Möllmann H, EuroPCR 2017; unpublished data).

The next generation JenaValve is a transfemoral access device allowing for treatment of pure AR. The first report of TAVI using the JenaValve in patients with moderate or severe AR and high surgical risk showed that procedural success was achieved in all cases with no death or stroke at 30 day [32].

The NVT Allegra transcatheter heart valve is a self-expanding and repositionable TAVI prosthesis, which was designed to avoid hemodynamic compromise and facilitate correct positioning with three-step release mechanism and radiopaque markers. The specific design facilitates the access for possible percutaneous coronary intervention at a later stage. The first feasibility study showed a high rate of procedural success and short-term clinical and hemodynamic results [33].

Future indication of TAVI – direction to the low risk patients?

Rosato et al. recently reported a subgroup analysis of the Observational Study of Effectiveness of SAVR-TAVI Procedures for Severe Aortic Stenosis Treatment (OBSERVANT) registry investigating efficacy of TAVI using the self-expanding CoreValve and the balloon-expandable SAPIEN XT valves in low surgical risk patients. They found significantly higher 3-year survival rates in SAVR group compared with TAVI and concluded that the expansion of TAVI to low risk patients is not yet justified [34]. The Nordic Aortic Valve Intervention Trial (NOTION) is a randomized controlled trial to evaluate TAVI with the self-expanding CoreValve in low risk patients and found no statistically significant difference in the composite outcomes consisting of all-cause death, stroke, or myocardial infarction at 1 year between TAVI and SAVR patients [35]. Waksman et al. recently reported favorable results of TAVI in low-risk patients with low complication rates, short hospital length of stay, zero mortality, and zero disabling stroke at 30 days [36]. There may be currently insufficient data to justify TAVI in low-risk populations; however, clinical trials of TAVI in low-risk patients using 2nd generation valves of Sapien 3 and Evolut R are underway (NCT02675114; NCT02701283; NCT03042104; NCT02825134; NCT02628899). Moreover, TAVI technology has evolved rapidly improving clinical outcomes and reducing complications, and several other devices are under development to challenge current problems with TAVI [37,38]. Until future evidence emerges, careful assessment and strategies are necessary especially for low-risk patients; however, the indication of TAVI continues to shift toward lower risk patients.

Future strategies of TAVI – expansion to complex anatomies?

Bicuspid AS

Bicuspid aortic valve is the most frequent congenital heart defect and is often associated with aortic root dilatation [39]. TAVI in bicuspid aortic valve remains challenging because of the more elliptical annulus, enlarged anatomy of aortic root, asymmetrical and insufficient expansion of the prosthesis, and excessive calcification of aortic valvular complex, resulting in impaired hemodynamic outcomes [40]. Bicuspid valve morphology is classified into type 0, 1, and 2 based on the number of raphe, which can be evaluated well on high-resolution computed tomography [41]. SAVR has long been the gold standard for patients with bicuspid aortic valve, but growing experience, accumulated data, and technological development have led to the expanded use of TAVI also in bicuspid aortic valve patients [42]. A meta-analysis [43] of 13 observational studies showed that success rate of TAVI in bicuspid valve was 95% but the incidence of moderate to severe PVL was 12.2%, which is higher than that for tricuspid valve. Early event rates of all-cause mortality, stroke, life-threatening bleeding, major vascular complications, annulus rupture, or valve dysfunction were similar to tricuspid aortic valves, while rates of permanent pacemaker implantation were higher in TAVI for bicuspid valves. Technical adjustments such as modifications in sizing, a more cranial positioning, and adaptation of the valve type to the bicuspid anatomy might result in lower permanent pacemaker implantation rates, reduced PVL, and favorable hemodynamics [44]. Advanced techniques and newer-generation devices will be associated with improved success rates and lower rates of complications. At the same time, long-term durability and outcome data are warranted to expand TAVI to

bicuspid AS, considering higher prevalence of bicuspid AS in a younger population.

Pure aortic regurgitation?

Limited data exist for TAVI in pure aortic regurgitation (AR) patients. In contrast to AS, TAVI for pure AR is still challenging, because the absence of valvular calcification complicates anchoring of the transcatheter valve prosthesis within the annular plane [45]. Additionally, excessive stroke volume and the dynamic jet limits device control during positioning and release. Moreover, increased annulus width may exceed the range of commercially available prostheses.

There are reports of inoperable patients with pure AR undergoing TAVI [46–51]. A systematic review of TAVI for native pure AR including 237 patients has shown that self-expandable prostheses were used in 79% of patients and that TAVI for pure AR is feasible and associated with acceptable risk of early mortality [52]. The transfemoral JenaValve system targets patients with native pure AR. Although SAVR remains the gold standard for pure AR at the moment, larger studies and longer follow-up data as well as developments in device technology might expand TAVI indication to pure AR.

Lower ischemic stroke?

Ischemic stroke following TAVI is a serious complication associated with increased acute and long-term prognosis [53–56]. Ischemic stroke rates have been suggested to be up to 10.0% following TAVI [57,58] with recent studies indicating stroke rates around 3.4% after TAVI compared to 5.6% after SAVR [18]. Nonetheless, procedural strokes need to be limited to an absolute minimum due to its detrimental effects on the patient. The United States Food and Drug Administration (FDA) recently approved the Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, CA, USA) [59] after the randomized SENTINEL trial had shown a 44% reduction of lesion volume on cerebral magnetic resonance imaging with use of the dual-filter cerebral embolic protection device [60]. This is of high interest since the primary endpoint of the study was neutral and underlines the importance of the prevention of stroke. Seeger et al. recently analyzed patients from the SENTINEL US IDE trial [58], CLEAN-TAVI [57], and SENTINEL-Ulm [61] study on a patient level pooled analysis and reported a signify lower occurrence of procedural stroke with protection compared to unprotected procedures (1.88% vs. 5.44%, $p = 0.0028$) [62]. However, stroke rates within this study were higher compared to recently published randomized trials and the intrinsic stroke rate associated with protection device placement has not yet been systematically investigated.

Summary of future perspective of TAVI

Although there are still unmet needs as shown in Table 1, TAVI is a disruptive technology and next-generation devices will minimize the limitations of TAVI such as PVL, conductance disturbances, ischemic stroke, and vascular complications. Main contributors are dedicated devices (sheaths, wires, valves), lean procedures with limitation to the important procedural steps, and careful patient selection. The indication of TAVI continues to shift toward lower risk patients with further study data. Dedicated studies investigating complex anatomy with dedicated valves will demonstrate that TAVI may be feasible, reasonably safe, and efficacious in patients with bicuspid AS or native pure AR.

Table 1
Unmet needs in transcatheter aortic valve implantation.

• Challenging anatomy
Bicuspid
Annular and leaflet calcium
Horizontal aorta
Tortuous aorta
Femoral iliac access – narrow, calcified, tortuous
• Conduction disturbance
• Residual paravalvular leakage
• Coronary obstruction
• Cerebral embolization during TAVI
• More procedural performance
• TAVI for young and/or low-risk patients
• TAVI for asymptomatic patients
• TAVI for moderate aortic stenosis
• TAVI for aortic regurgitation
• Long-term outcome and durability after TAVI
• Cost-effectiveness

TAVI, transcatheter aortic valve implantation.

Transcatheter mitral valve repair and replacement

Mitral regurgitation (MR) is one of the most prevalent valvular diseases [63]. Mitral valve anatomy is more complex than aortic valve anatomy, and the clinical evidence is limited compared to TAVI. Surgical mitral valve repair or replacement remains the current gold standard. However, surgery is limited to active, low-to-intermediate risk patients and often not suitable for patients at high surgical risk. With the development of novel minimal-invasive surgical procedures, additional transcatheter technologies are already established or under development to mimic surgical repair and replacement strategies [transcatheter mitral valve repair (TMVR) and transcatheter mitral valve implantation (TMVI)].

Development and indication of MitraClip – mimicking surgical edge-to-edge repair

Secondary (functional) MR (FMR) results from left ventricular dilatation and dysfunction, left atrial dilatation, and mitral annulus dilatation [64–66]. In contrast, primary (degenerative) MR (DMR) is caused by structural disease of the mitral leaflets or the subvalvular apparatus. There is also another classification of ischemic and non-ischemic MR. Ischemic MR denotes the occurrence of MR in the presence of significant coronary artery disease, resulting from wall motion abnormality with papillary muscle dysfunction or from ischemic cardiomyopathy with global left ventricular dysfunction [67], while non-ischemic MR occurs in dilated cardiomyopathy. Echocardiography is the primary method to diagnose and quantify MR [66].

The initial efforts to treat DMR with catheter-based methods began with the MitraClip (Abbott Vascular, Santa Clara, CA, USA) device in 2003. The MitraClip was designed to mimic the surgical edge-to-edge repair in operable patients at high surgical risk with DMR. Initial experiences have been developed in patients with DMR [68], and subsequently, the MitraClip device has been used in tens of thousands of patients worldwide. Interestingly, despite the initial study design, most experience with the MitraClip system was generated in patients with FMR. Currently, edge-to-edge repair is the only treatment option mentioned in the guidelines for patients with significant and symptomatic DMR and FMR [66]. For FMR, optimal medical therapy is the first-line treatment [66]. Surgical mitral valve repair is recommended in patients with severe FMR undergoing coronary artery bypass graft, and mitral valve replacement should be considered if morphological risk factors for MR recurrence are present [66]. In patients without indication for revascularization and left ventricular ejection fraction (LVEF) >30%, either surgery or transcatheter repair may be considered, depending on the surgical risk and valve morphology. In patients with an LVEF <30%, the Heart Team of each institution should discuss therapeutic options.

Current status of edge-to-edge mitral valve repair – accumulating evidences for FMR

Edge-to-edge repair with the MitraClip technology has changed the landscape for symptomatic severe MR patients with already >60,000 performed procedures worldwide. The optimal outcome of MitraClip can be expected in patients with DMR between the A2/P2 scallops and with an expected reduction of MR to ≦2. Initial experiences in the USA showed that A2–P2 location was targeted in 78% of cases, with 37% of cases requiring >1 devices [69]. A MitraClip location in the A2/P2 segment was associated with higher success of MR grade ≦2 reduction (OR, 2.29; $p = 0.02$). In addition, A2/P2 location was favorably associated with composite outcomes of residual MR grade ≦2, no conversion to cardiac surgery, and no in-hospital mortality (OR, 2.36; $p = 0.008$) [69]. Residual valve disease is the major factor involved in MR recurrence, and Buzzatti et al. recently reported that a single clip was associated with an increased recurrence of MR compared with that of 2 clips, both in FMR and in DMR [70].

While the DMR etiology may be considered ideal for MitraClip, the most common clinical indication worldwide is FMR [71]. A recent meta-analysis showed that mitral re-intervention at 1 year was lower in FMR compared with DMR patients (4% vs. 10%, respectively; $p = 0.04$) without a significant difference in mortality between FMR and DMR ($p = 0.18$) [72]. Multiple ongoing trials, including a multicenter randomized control study are evaluating the role of MitraClip in FMR, and these trials compare the percutaneous edge-to-edge repair with optimal medical therapy (COAPT, RESHAPE, MITRA-FR [73]) or surgery (MATTERHORN) in FMR patients. The MITRA-FR trial was conducted in France and the COAPT trial in the USA. The MITRA-FR trial showed no significant difference between the device and optimal medical therapy group with respect to composite outcomes of all-cause death and unplanned hospitalization for heart failure at 1 year, while the COAPT trial showed a significantly lower rate of hospitalization for heart failure (a primary outcome) and all-cause mortality (a secondary outcome) at 2 years in the device group [74,75]. Baseline characteristics and the indexed left-ventricular end-diastolic volume were different in the two randomized controlled trials. These differences might have made the discordant results, and we should wait for the results of COAPT trial to be replicated for our decision-making for MitraClip in FMR patients. Further studies are needed to carefully evaluate the MitraClip system against medical and surgical therapy.

The second generation of MitraClip is the MitraClip NTR/XTR (Abbott Vascular), with design changes within the clip arms and grippers, leading to more effective grasping of leaflets also in cases with larger coaptation defects [76]. A new device for percutaneous edge-to-edge repair, the Edwards PASCAL transcatheter mitral valve repair system (Edwards Lifesciences Corp., Irvine, CA, USA) has recently been introduced and addresses several limitations of the MitraClip. This includes simplified navigation within the left atrium, further MR reduction by implementation of a central spacer, and independent leaflet grasping. A multi-center, prospective, observational, first-in-man study including FMR, DMR, and mixed MR etiologies showed that the implantation of at least one device was successful in all patients, resulting in procedural residual MR of grade 2+ or less in 96% of patients, despite the anatomical complexity of MR [77]. A multi-center, multi-national, prospective study (the CLASP Study) to assess the safety, performance, and clinical outcomes of the Edwards PASCAL is underway.

Other current devices for FMR – mimicking surgical ring annuloplasty

In clinical practice, the majority of patients undergoing interventional MR have functional mitral valve diseases [78,79]. The durability of interventional FMR repair with edge-to-edge repair is a matter of debate due to its limited approach by targeting the valve leaflets only. Therefore, interventional therapies mimicking the surgical gold standard for FMR, aiming at reducing annular dimensions might be the preferred treatment option. The initial ideas were based on coronary sinus annuloplasty (indirect annuloplasty) since that seemed to be relatively simple from a technical standpoint with the potential to mimic an established surgical procedure [80]. One coronary sinus annuloplasty device, the Carillon Mitral Contour System (Cardiac Dimensions Inc., Kirkland, WA, USA), has received CE approval [81], but others remain in the earliest stages [82,83].

Among various direct annuloplasty devices, the Cardioband™ (Edwards Lifesciences Corp., Irvine, CA, USA) most closely resembles a surgical annuloplasty ring. Based on the satisfactory device safety, the device obtained CE mark approval in September 2015. The device is delivered via transseptal atrial access and the ring is implanted directly at the atrial side of the mitral annulus. The first anchor is deployed in the lateral commissure and then the ring is extruded from a delivery catheter in small segments, each in turn anchored by a screw mechanism encompassing the posterior annulus until the last anchor is implanted in the medial commissure. The band can be tensioned to reduce the annular circumference and reduce the degree of MR. Nickenig et al. reported the 6-month outcomes of 31 patients enrolled in the Cardioband feasibility trial. It included patients with a mean age of 71.8 ± 6.9 years, a mean LVEF of 34% ± 11%, and a mean EuroSCORE II of 8.6% ± 5.9% [84]. A total 77.4% of the patients had severe (3–4+) MR and technical success was achieved in 93.6% of patients with no in-hospital deaths or major complications [84]. At 6-month follow-up, favorable reduction of MR and significant improvements in New York Heart Association (NYHA) classification, 6-min walk test, and quality of life were observed. The result of a multicenter trial recently demonstrated significant MR reduction in most of the patients with significant functional improvements at 1-year follow-up [85]. The Cardioband system results are in line with those of the MitraClip at its early phase and better than those currently reported for other annuloplasty devices [78,86,87]. The randomized controlled ACTIVE Trial (NCT03016975), which assesses the Cardioband treatment compared with medical therapy alone, is currently underway in the USA.

Other current devices-based strategies for DMR – artificial chord implantation

The transapical Off-Pump Mitral Valve Repair with Neochord Implantation (TOP-MINI) is a new TMVR option to implant artificial chords with a minimally invasive approach in patients with severe MR due to leaflet prolapse or flail [88–90]. The procedure is performed using the NeoChord DS1000 system (NeoChord, Inc., Eden Praire, MN, USA) under guidance of transesophageal echocardiography, implanting expanded polytetrafluoroethylene (e-PTFE) sutures as artificial neochordae without the need for cardiopulmonary bypass. A standard left lateral mini-thoracotomy under general anesthesia is performed to access the left ventricular apex. Since its first experience [91], the NeoChord has demonstrated favorable outcomes in reducing MR in patients with severe MR [90,92]. The rupture of implanted NeoChord is rare, though reported previously [76]. A multicenter study in Europe recently reported high procedural success rates with 98% of 1-year survival and 84% freedom from composite endpoints [93]. In the USA, a prospective, multicenter, randomized controlled clinical trial comparing the NeoChord procedure with conventional surgical mitral valve repair is underway (NCT02803957).

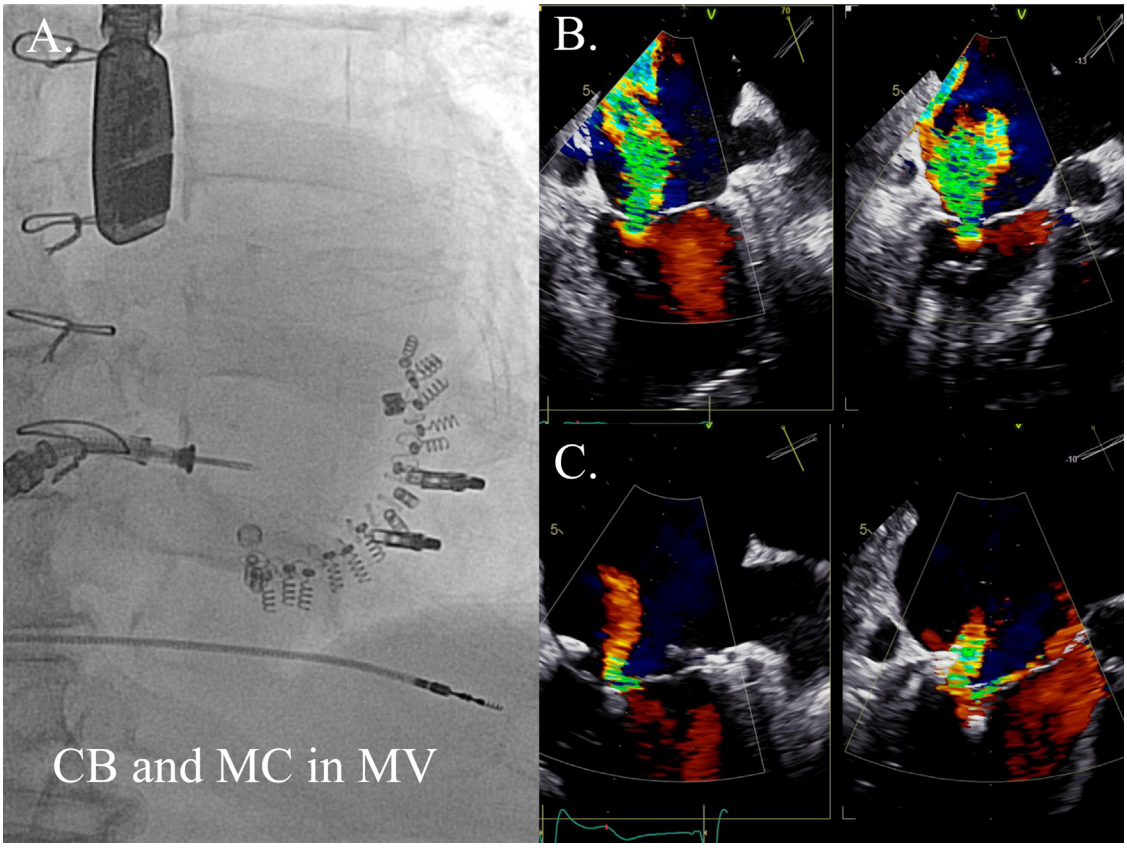

Fig. 1. A case example of the combination MR therapy of the Cardioband and the MitraClip. (A) Fluoroscopic view after direct annuloplasty by the Cardioband and edge-to-edge by the MitraClip. (B) Transesophageal intercommissural and LVOT view before treatment. (C) Transesophageal intercommissural and LVOT view after the Cardioband and the MitraClip. MR, mitral regurgitation; LVOT, left ventricle outflow tract.

Future strategies for severe MR

At present, our understanding of how to treat severe MR in patients at high surgical risks with minimal-invasive, transcatheter-based technologies is still limited. This is mainly due to the fact that mitral valve anatomy is complex, underlying etiologies of MR are highly variable, dedicated devices are limited, and durable surgical strategies of how to treat MR best are still under debate. Surgical evidence suggests that a combination of 'leaflet repair' with annuloplasty might be superior compared to a single-leaflet procedure or annuloplasty [94–97]. Very first experience with a combination of MitraClip and Cardioband (Case example in Fig. 1) show promising results [98]. In addition, some case reports describe the concomitant use of the Cardioband in combination with the transapical NeoChord repair [99].

However, evidence suggests that the long-believed superiority of mitral valve repair in surgery may be overcome by mitral valve replacement [100]. To date, transcatheter mitral valve implantation (TMVI) with TAVI valves has been performed in patients with valve-in-valve or valve-in-ring technique [101,102], and few cases of TAVI valves implantation in calcified native mitral valve have been reported [103,104]. Currently, several mitral valve replacement technologies are under development, both for transapical and transseptal approaches [105,106]. The early feasibility study with the Tendyne system (Tendyne Holdings, LLC, Roseville, MN, USA), was encouraging [107,108] and a pivotal randomized trial (SUMMIT; NCT03433274) is underway. Additional studies are undertaken with the TIARA (TIARA-I; NCT02276547) (Neovasc Inc., Richmond, BC, Canada), CardiAQ system (RELIEF; NCT02722551) (Edwards Lifesciences Corp., Irvine, CA, USA) and the Intrepid (APOLLO; NCT03242642) (Medtronic Inc., Minneapolis, MN, USA) systems [109–111]. Currently, major limitations are the anchoring of the device within the mitral valve, left ventricular outflow tract obstruction due to the valve design, and the need for a transapical, large bore access.

Table 2
Unmet needs in transcatheter mitral valve treatment.

[Edge-to-edge therapy]
• Optimal edge-to-edge strategy? (e.g. one or two clips, small or large clip?)
• Edge-to-edge or NeoChord in DMR patients with prolapse?
• How to predict MR reduction
• More evidence even in high-risk patients
• More evidence for FMR
• Long-term outcome and durability
[Annuloplasty therapy]
• Learning curve for procedure
• Edge-to-edge repair or annuloplasty for FMR patients?
• How to predict MR reduction
• More evidence even in high-risk patients
• Long-term outcome and durability
• Feasibility and safety of the combination of edge-to-edge and annuloplasty repair
[Mitral valve implantation]
• TMVR or TMVI especially for complex anatomy?
• Transvascular/transseptal or transapical?
• Lower peri-procedural complications
• Short-term feasibility and safety
• Long-term outcome and durability

MR, mitral regurgitation; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; TMVR, transcatheter mitral valve repair; TMVI, transcatheter mitral valve implantation.

Summary of future perspective of interventions for MR

Future perspective of interventions for MR is still speculative due to unmet needs as shown in Table 2. The efficacy and safety of edge-to-edge with or without annuloplasty leaflet repair mimicking surgical repair will have to be confirmed by technical improvement, device development, and further emerging studies. The edge-to-edge mitral repair is an option for edge-to-edge leaflet

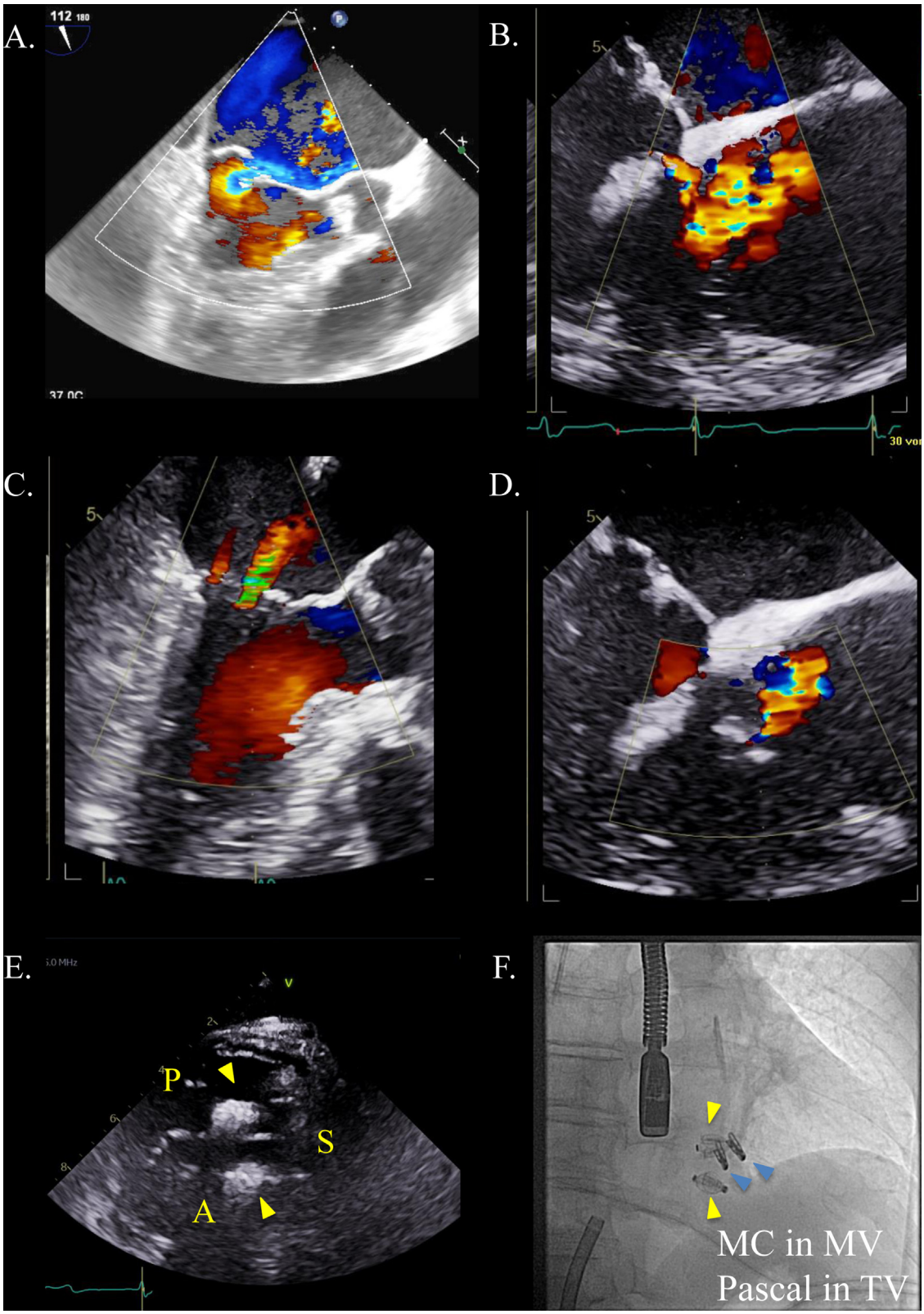

Fig. 2. A case example of the combination therapy of mitral and tricuspid valve by the MitraClip and PASCAL system. (A and B) Pre-procedural transesophageal echocardiography (TEE) showing a severe mitral and tricuspid regurgitation (MR and TR). (C–E) Following the MitraClip to mitral segment A2/P2 and PASCAL to tricuspid anterior-septum and posterior-septum leaflets, significant reductions of both MR and TR to grade I–II were observed.

repair for DMR in high-risk or inoperable patients. TMVI might be an alternative strategy in patients with symptomatic severe MR and favorable anatomy (e.g. low risk of left ventricular outflow tract obstruction, low degree of calcification) if randomized studies confirm initial results. Minimal invasive surgical repair will play a role in dedicated anatomies. Surgical repair and replacement will remain the standard therapy in low- to intermediate-risk patients until proven otherwise.

Current and future interventions for tricuspid regurgitation

Tricuspid regurgitation (TR) is a common valvular heart disease, and the prevalence of moderate or severe TR has been estimated to be approximately 1.6 million people in the USA [112]. Functional TR caused by left-sided heart pathologies is the most frequent etiology, which is characterized by annular dilatation and leaflet tethering with malcoaptation [113]. Organic causes of TR are less frequent and characterized by abnormal or damaged leaflets. Symptoms resulting from TR may be uncertain, particularly in the early stages, leading to a late referral. In the current European guidelines, the indication for surgery for symptomatic severe TR is generally accepted (Class I). With regard to treatment of moderate TR, there is a trend for intervention, especially during surgery for left heart valve diseases or in cases of significant dilatation of the tricuspid annulus (Class IIa) [114]. When untreated, TR commonly progresses to right ventricular failure, with impact on the patients' quality of life and prognosis [115]. However, the indication for surgery remains challenging given the complexity of the patients and the mortality rates [116].

Accordingly, there is a clinical need for the development of transcatheter strategies to address symptom severe TR, and at the same time, successful clinical results of TAVI and also of MitraClip procedures have gained cardiologists' attention to further develop transcatheter technologies for TR. All current transcatheter strategies aiming at the treatment of TR are still in their early stages [117]. Anatomical complexities include large annulus, deficiency of valve and/or annulus calcification, adjacency of the right coronary artery, and fragility of tissue. Current approaches include the edge-to-edge repair (with a dedicated tricuspid valve-adapted Clip system), annuloplasty with the Cardioband system, dedicated tricuspid systems (Forma), heterotopic caval transcatheter valve implantation, and valve replacement [118–120].

The MitraClip device has recently been used successfully for treating severe TR in very high-risk patients [121]. The transfemoral access has become the preferred route of access. Nickenig et al. recently reported promising 30-day outcomes in a series of 64 high-risk patients with severe TR treated with tricuspid clipping [119]. Functional TR was present in 88% and the degree of TR was severe or massive in 88% of patients. The MitraClip device was successfully implanted in the tricuspid valve in 97% of patients with significant TR reduction, no complications and significant improvements in NYHA classification and 6-min walking distance [119]. Recent evidence suggests that patients undergoing a MitraClip procedure for MR benefit less if concomitant TR is present [122,123], making it justifiable to treat both mitral and tricuspid valve, in one procedure (Case example in Fig. 2).

Severe TR is often due to a significant annular dilatation, making surgical annuloplasty the first procedure of choice in treating this condition. The Cardioband system is a surgical-like annuloplasty technique already in use for severe MR treatment. Preliminary results from the early feasibility trial in the tricuspid position have been recently presented by Kuck KH (EuroPCR 2017, unpublished data). Among 20 patients with severe functional TR treated to date, a 27% reduction in septolateral tricuspid annular

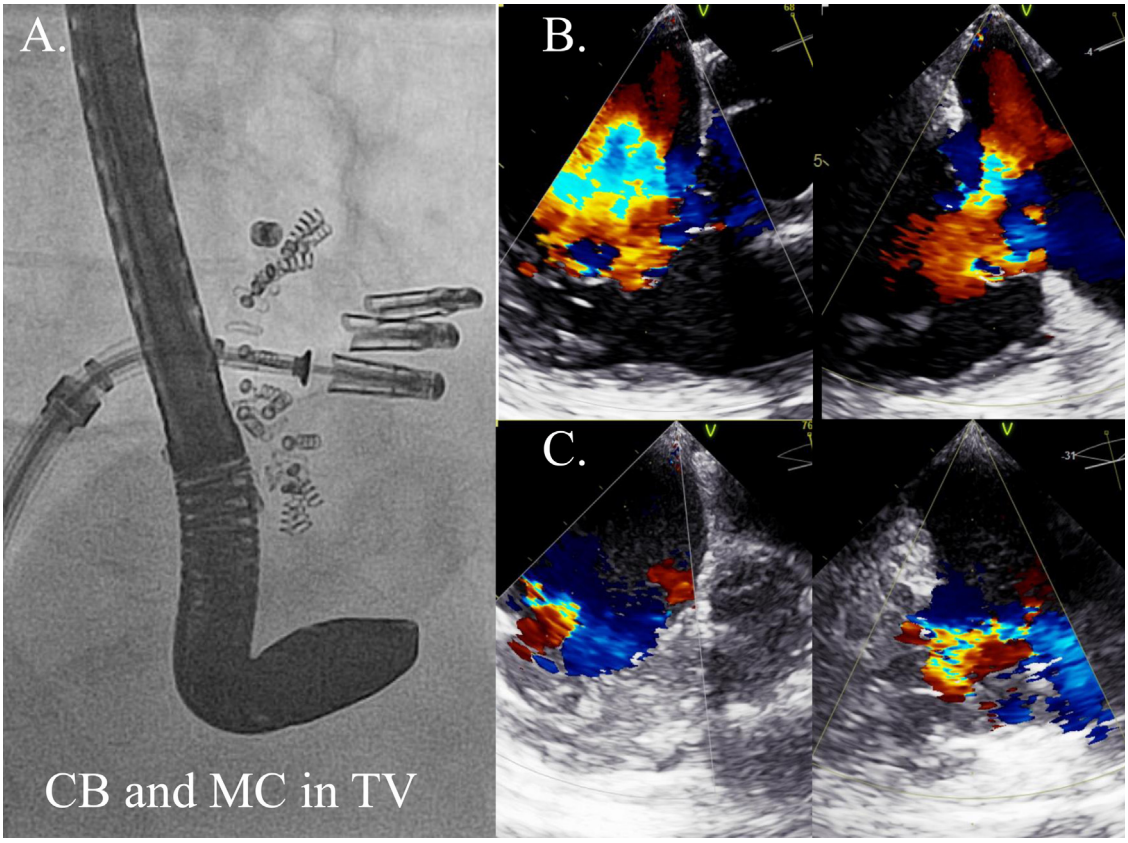

Fig. 3. A case example of the combination TR therapy of the Cardioband and the MitraClip. (A) Fluoroscopic view after direct annuloplasty by the Cardioband and edge-to-edge by the MitraClip. (B) Transesophageal mid-esophageal views before treatment. (C) Transesophageal views after the Cardioband and the MitraClip. TR, tricuspid regurgitation.

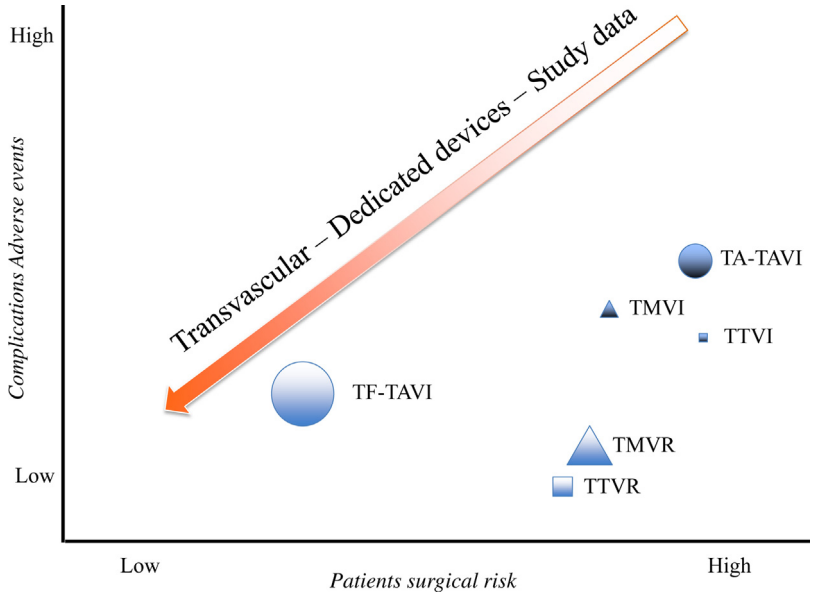

Fig. 4. Future of valve heart interventions. TF-TAVI data are available for patients with a mean STS score <4% [36], while TA-TAVI data for patients with low-intermediate risk are not yet available and TA-TAVI patients in the PARTNER trial had a mean STS score of 11.8% [126]. Recent data included patients at surgical risk of a median EuroSCORE II of 6.6% for the MitraClip [74], a mean STS score and EuroSCORE II score of 5% and 7% for the Cardioband [85], a mean STS score and EuroSCORE II score of 6.4 and 7.9% for TMVI [108], a mean STS score of 4.7% for TTVR [119]. Data for TTVI are still limited. Improvement and development of transvascular interventions, dedicated devices, and further study data will expand structural heart disease interventions toward lower complications, improved clinical outcome, and indication to lower surgical risk patients. The size of the symbol is an approximation of the strength of current evidence. TF, transfemoral; TA, transapical; TAVI, transcatheter aortic valve implantation; TMVR, transcatheter mitral valve repair; TMVI, transcatheter mitral valve implantation; TTVR, transcatheter tricuspid valve repair; TTVI, transcatheter tricuspid valve implantation; STS, Society of Thoracic Surgeons; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

dimension has been reported. At 30 days, core-lab adjudicated data showed a reduction of TR, with a significant improvement in symptoms and quality of life. First experiences include the combination therapy of edge-to-edge and direct annuloplasty (Case example in Fig. 3) resembling surgical technique [124,125].

Possible interventional treatment approaches for TR have gained more and more attention. Considering untreated TR causes progressive right ventricular dysfunction and annular dilatation, early intervention of TR is essential before TR is torrential, because coaptation defect becomes untreatable, right ventricular dysfunction becomes severe, and benefits for patients become limited. Further clinical studies and a combination of different approaches such as transcatheter annuloplasty and edge-to-edge repair might lead to superior procedural results and pronounced clinical benefit in patients with TR.

Conclusions

Improvement and development of SHD interventions have enabled more patients to receive minimally invasive heart valve interventions and these procedures have prolonged life and/or improved quality of life for many patients who were previously considered unsuitable for surgery. Continued technical and device improvements and accumulated evidence will expand its possibility and future of SHD interventions described as in Fig. 4.

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