A Comparative Analysis of Mitraclip Versus Mitral Valve-In-Valve Replacement for High-Risk Patients With Severe Mitral Regurgitation After Transcatheter Aortic Valve Replacement

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Introduction

Patients with severe aortic stenosis frequently have mitral regurgitation. In the Placement of AoRTic TraNscathetER Valve (PARTNER) trial, severe mitral regurgitation was observed in 21% of surgical (SAVR) and 20% of transcatheter (TAVR) aortic valve replacement. Improvement in mitral regurgitation was reported in 69% of SAVR and 58% TAVR patients at 30 days.[1,2] The impact on mitral regurgitation on the outcome of TAVR or SAVR is unclear. Mortality rates of about 10% have been reported for combined aortic and mitral surgery as compared to 3% for standalone SAVR.[3,4] With PARTNER2 trial now allowing patients with both high and intermediate risk to be eligible for TAVR, interval or concomitant transcatheter management of the mitral regurgitation is emerging as an important need for cardiac intervention in high-risk surgical patients with combined aortic stenosis and mitral regurgitation. This option provides an alternative solution for these patients as the challenges of transcatheter mitral valve (MV) repair/replacement (TMVR) are further minimized.

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Transcatheter Mitral Valve-in-Valve (TMV-I-V) and Percutaneous Mitral Valve Repair (PMVR/MitraClip) have emerged as novel treatment strategies for severe mitral regurgitation (MR).[5,6] We sought to compare the safety and efficacy of combined transcatheter therapy in patients with severe aortic stenosis who received TAVR followed by either PMVR or TMV-I-V for severe MR.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews recommended by the Cochrane Collaboration was followed in this study.

Studies including case reports, case series, and original articles published between 2012 and 2017 were identified with a systematic electronic search using SCOPUS, EMBASE, MEDLINE, and the PubMed. Only studies reporting data on demographic and procedural characteristics, management and follow-up outcomes were analyzed. A Boolean search was performed combining the following keywords: "transcatheter aortic valve replacement" or "transcatheter aortic valve implantation" and "percutaneous mitral valve replacement" or "TMV-I-V."

No language restriction was applied. We scanned the bibliographies of all included articles and relevant review articles to identify additional studies. Only studies reporting data on demographic, procedural characteristics, management, and follow-up were included. To obtain missing data, the primary investigators of the included studies were contacted. All publications were limited to those involving human subjects. Conference presentations, ongoing studies, editorials, reviews, and expert opinions were excluded. Statistical analysis was done using CMA Version 3.3.070 (Bio Stat Inc., Englewood, NJ). The authors screened and retrieved reports and excluded irrelevant studies. Any uncertainty about the eligibility of any included study was resolved by group consensus.

Data were analyzed using the SPSS version 23 (SPSS Inc., Chicago, IL). Statistical significance was taken as $P = 0.05$.

Results

Baseline Characteristics

Seventeen publications describing 60 patients who underwent both TAVR and PMVR and 7 patients who underwent TAVR and TMV-I-V were identified. Mean age, mean logistic EuroSCORE (European System

for Cardiac Operative Risk Evaluation) was essentially similar in the 2 groups and the NYHA class (>3) were similar in both groups (P= 0.55, 0.7, and 0.5, respectively). All patients had moderate to severe, symptomatic MR, on post-TAVR assessment and pre-MV intervention. Besides coronary disease, hyperlipidemia was more prevalent in the PMVR group, there was no significant difference between both groups (Table 1).

Procedural Characteristics

The preferred access site was transfemoral in the PMVR group (83%) while transapical access was preferred in the TMV-I-V group (100%; P= 0.001). Twenty-six of the 41 patients received Medtronic Core valve (Table 1).

Clinical Outcomes

Device success in the PMVR group was 88% and 100% in the TMV-I-V group (P= 1.0). Median discharge time was 10.5 days in PMVR and 15 days in TM-V-I-V. Mean discharge time was 14 ± 11.3 days in PMVR and 18.25 ± 12.8 days in TM-V-I-V (P= 0.59) 76% of the PMVR and 80% of the MV-I-V group were in NYHA Class ≤2 postprocedure (P= 1.0; Table 2).

After a median follow-up of 7 months (interquartile range 3-11) in the PMVR group and 3 months (interquartile range 1-6) in the MV-I-V group, 30-day stroke was 2.4% in PMVR vs 0% in MV-I-V group (P= 1.0). Thirty-day all-cause mortality was 7.7% vs 14.2% in the PMVR and TMV-I-V, respectively (P=0.49; Table 2).

Discussion

MR of greater than mild severity is seen in over 20% of patients that undergo SAVR or TAVR. The prognostic implication of this is not clearly delineated. With higher mortality associated with double valve surgery compared to isolated SAVR and the broadening acceptance of TAVR to the intermediate surgical risk patients, transcatheter therapy is increasingly becoming the preferred modality of treatment of these high-risk patients with severe aortic stenosis and moderate to severe MR.

TMVR is emerging on the forefront of structural interventions but the experience is still at a relatively early stage compared to TAVR.[7,8] The complex mitral valve structure including its oval shape, bulky subvalvular apparatus and interaction with the adjacent structures including the left ventricle outflow tract and the aortic valve poses a great deal of challenge

TABLE 1. . Baseline demographic and procedural characteristics

	PMVR (60)	MVIV (7)	*P* value
Age	79.3 ± 6.5	80.8 ± 4.7	0.93
Male sex	28	4	0.7
EuroSCORE	32 ± 20.5 (59)	41.49 ± 6.23 (2)	0.93
MR type (40)			
Functional	18	NR	
Mixed	6	NR	
Degenerative	16	1	
NYHA ≥ 3	29/41	4/6	1.0
HTN	12/18	3/7	0.37
HLD	9/16	0/7	0.02
AF	17/28	4/7	1
COPD	8/27	2/7	1
PCI	18/30	3/7	0.43
CAD	26/31	3/7	0.04
ACS	13/28	2/7	0.67
CABG	13/28	2/7	0.67
DM	9/27	1/7	0.64
LVEF	39.78 ± 12.6 (17)	52.6 ± 6.8 (4)	0.63
MR ≥ 3 post-TAVR, pre-PMVR or MVIV	40/41	7/7	1.0
Access			
TF	34/41	0	0.038
Trans apical	5/41	7/7	<0.0001
Trans SC	1/41	0	1
Direct aortic	1/41	0	1
Valve type			
Edwards sapien XT	8	7	
Edwards Sapien 3	1	0	
Core Valve	26	0	
Evolut R	1	0	
Edward Sapien	5	0	
TAVR Pre PMVR	41/42		
TAVR pre MVIV		6/7	
Number of Clips			
1 Clip	28		
2 Clips	9		
3 Clips	3		

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

to the development of a uniform technology for TMVR. This is further complicated by the broader etiology of mitral valve pathology that ranges from stenosis and regurgitation from several mechanisms that adds to the difficulties in designing a uniform device to be used in TMVR. Most importantly, these patients usually have multiple comorbidities including

TABLE 2. Postprocedural outcomes

	PMVR	MVIV	RR (CI)	*P* value
MR post-TAVR (SAM)	2	NR		
MR postclip				
1	28	6		
2	9	1		
3	3	0		
4	1	0		
MR postclip $\geq$ 3	4/41	0/7	1.5 (0.09-26.3)	0.76
NYHA postprocedure				
1	12	1		
2	19	3		
3	8	0		
4	1	0		
NYHA $\geq$ 3 postprocedure	9/40	0/7	3.7 (0.24-57.4)	0.35
Post-TAVR + MC CVA	2/40	0/7	0.9 (0.05-18.4)	0.98
Length of F/U (months) median	7	3		
D/C time (days) median	10.5	15		
D/C time (SD) (days)	14 $\pm$ 11.3 (5)	18 $\pm$ 12.8 (5)		0.82
30-Day mortality	3/39	1/7	0.5 (0.06-4.4)	0.56
1-Year mortality	15/39	NR		

Abbreviations: CVA, cerbrovascualr accident; D/C, discharge; F/U, follow-up; SD, standard deviation.

severe left ventricular dysfunction and pulmonary hypertension that can impact outcomes. Over the last few years, progress has been made with TMVR; however it would be most prudent to develop strategies that ensure optimal outcomes especially when multiple valvular pathologies exist.

Randomized trials investigating and comparing these modalities are still unavailable and several questions regarding the timing or staging of such interventions still exist. Due to lack of guideline-based recommendations, treatment strategies have to be individualized based on lessons learned from large randomized TAVR trials, valvular pathology, and comorbidities that define patients' procedural risk.In the PARTNER trial, patients with moderate to severe MRs benefited from TAVR more than those without. Significant improvement in MR has been reported after TAVR or SAVR due to reverse left ventricular remodeling and improved left ventricular function. [9-12] This improvement may be more prominent in patients with secondary MR and those without severe pulmonary hypertension and atrial fibrillation. Improvement in MR shortly after TAVR has been attributed to improved mitral leaflet tethering.[13] Studies suggest that greater improvement in MR is seen in patients that undergo TAVR with balloon expandable when compared to self-expandable transcatheter valves.[14] This also then brings into question the timing of the transcatheter therapy for the 2 valves.

The success of the combined or bivalvular approach of TMVR performed at the time of TAVR has been reported as case reports or series thereof. These mitral procedures have included edge-to-edge repair with MitraClip. Percutaneous mitral annuloplasty can be accomplished with either direct annuloplasty with a Cardioband through transseptal approach or using the Carillon Mitral Contour system that is implanted within the coronary sinus to reduce the severity of MRs by indirect annular placation. Finally, transcatheter mitral valve replacement TMVR in high-risk patients with valve-in-valve, valve-in-ring, and valve-in-native ring all now reported,[15-18] randomized trials are awaited to validate their role and outcome benefit in patients with severe MR and especially in patients who have undergone TAVR.

Our analysis shows that transcatheter treatment of high-risk patients with severe MR post-TAVR is feasible with either PMVR (MitraClip) or MV-I-V replacement. Both groups showed high device success, symptom reduction, and low stroke rates. PMVR showed a trend toward lower 30-day mortality compared to the MV-I-V.

While randomized trials for this subgroup of bi-valvular disease will await results of large trials and the refinement of the TMVR, especially in the native valve that is impacted by several more anatomical challenges than TAVR, we recommend using the lessons learned from large TAVR trials thus far. As significant improvement in severity of MR has been reported after TAVR, a staged approach should be pursued. TAVR followed by guideline-based heart failure therapy and multidisciplinary reassessment of the MR should direct the possible need for TMVR, which should be reserved only for patients that remain symptomatic after a successful TAVR and persistent moderate to severe MR. Randomized trials are awaited to guide therapeutic modalities and timing thereof in this very complex and high-risk group of patients.

Conclusion

Patients with concomitant aortic stenosis and MR present as a unique cohort. There is a component of secondary MR that is a result of hemodynamic impact of the severe aortic stenosis in this group. Due to the heterogeneity and complexity of mitral disease in these patients, we recommend that an individualized multispecialty team assessment with imaging and hemodynamic assessment be employed. As significant improvement in the severity of MR as well as hemodynamic state has been demonstrated by several randomized TAVR trials, we recommend that TAVR only followed by interval assessment for staged TMVR if

needed will improve patient outcomes in patients with such bi-valvular disease. The results of ongoing trials are awaited to define the benefit of TMVR vs aggressive heart failure treatment in TAVR patients with concomitant MR.

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