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RESEARCH ARTICLE

Transapical mitral valve implantation for treatment of symptomatic mitral valve disease: a real-world multicentre experience

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Aims Transcatheter mitral valve implantation (TMVI) is a new treatment option for patients with symptomatic mitral valve (MV) disease. Real-world data have not yet been reported. This study aimed to assess procedural and 30-day outcomes of TMVI in a real-world patient cohort.

Method and results All consecutive patients undergoing implantation of a transapically delivered self-expanding valve at 26 European centres from January 2020 to April 2021 were included in this retrospective observational registry. Among 108 surgical high-risk patients included (43% female, mean age 75 ± 7 years, mean STS-PROM 7.2 ± 5.3%), 25% was treated

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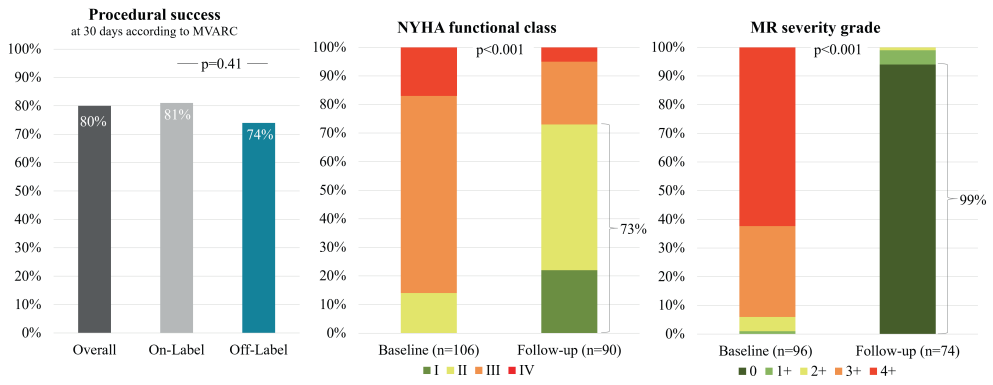
for an off-label indication (e.g. previous MV intervention or surgery, mitral stenosis, mitral annular calcification). Patients were highly symptomatic (New York Heart Association [NYHA] functional class III/IV in 86%) and mitral regurgitation (MR) was graded 3+/4+ in 95% (38% primary, 37% secondary, and 25% mixed aetiology). Technical success rate was 96%, and MR reduction to ≤1+ was achieved in all patients with successful implantation. There were two procedural deaths and 30-day all-cause mortality was 12%. At early clinical follow-up, MR reduction was sustained and there were significant reductions of pulmonary pressure (systolic pulmonary artery pressure 52 vs. 42 mmHg, $p < 0.001$), and tricuspid regurgitation severity ($p = 0.013$). Heart failure symptoms improved significantly (73% in NYHA class I/II, $p < 0.001$). Procedural success rate according to MVARC criteria was 80% and was not different in patients treated for an off-label indication (74% vs. 81% for off- vs. on-label, $p = 0.41$).

Conclusion In a real-world patient population, TMVI has a high technical and procedural success rate with efficient and durable MR reduction and symptomatic improvement.

Graphical Abstract



Procedural success at 30 days (according to MVARC), functional outcome (NYHA class) and MR severity at baseline and follow-up. M R, mitral regurgitation; MVARC, Mitral Valve Academic Research Consortium; NYHA, New York Heart Association.

Keywords Mitral valve disease • Mitral regurgitation • Transcatheter mitral valve implantation • Tendyne

Introduction

Transcatheter mitral valve implantation (TMVI) has been proposed as an alternative treatment for patients with symptomatic mitral valve (MV) disease ineligible or at high risk for conventional MV surgery. Treatment of the MV has long been exclusively based on surgical valve repair or replacement. However, a substantial proportion of patients could not benefit from this approach, owing to high surgical risk because of advanced age or significantly impaired left ventricular function.[1] Over the last years, several minimally invasive percutaneous solutions have been introduced into clinical practice to bridge this therapeutic gap and expand treatment options. They can be classified into techniques for valve repair (mitral transcatheter edge-to-edge repair [M-TEER] or annuloplasty devices) and valve replacement. While M-TEER has evolved rapidly over the last years and is already an integral part of the MV treatment armamentarium, the field of TMVI is still developing.

The Tendyne Mitral Valve System (Abbott Vascular, Roseville, MN, USA) was the first TMVI system to obtain commercial approval in Europe (CE mark) in January 2020 for use in patients with clinically relevant mitral regurgitation (MR) who are ineligible for surgery. The initial feasibility study included 100 selected patients at high or prohibitive surgical risk treated for primary or secondary MR. Despite the high-risk profile of the patient population, procedural safety and technical success were high, and 1-year survival was 72%. Symptom relief was observed in the majority of patients (New York Heart Association [NYHA] functional class I or II in 89% at 1-year follow-up), as well as significant improvement of 6-min walking distance and quality of life score.[2,3] The recently reported 2-year follow-up showed sustained MR reduction, lower hospitalization rate in the second year, and a 2-year all-cause mortality of 39%.[4]

However, many open questions remain regarding TMVI, including optimal patient selection, particularly in patients with off-label

indications for TMVI, including previous MV surgical repair or intervention, mitral annular calcification (MAC), or mitral stenosis. The aim of this retrospective study was to investigate procedural and 30-day outcomes in a non-selected real-world patient cohort treated on-label as well as off-label with the Tendyne Mitral Valve System in a multicentre setting.

Methods

Study design and patients

The TENDyne European expeRience registry study (TENDER) is a retrospective and prospective observational registry and the current data analysis included data from 26 tertiary care centres throughout Europe (Germany, Austria, Belgium, France, Italy, Spain, Norway, Switzerland, and United Kingdom). In this analysis, all consecutive patients undergoing commercial implantation of a Tendyne Mitral Valve System at the participating centres from January 2020 to April 2021 were included. Patients were symptomatic despite optimal guideline-directed medical therapy, and were deemed high-risk for conventional MV surgery, but eligible for TMVI by the local Heart Team. Anatomical suitability was assessed by transthoracic (TTE) and transesophageal echocardiography (TEE), and by cardiac computed tomography (CT). Grading of MAC in mild, moderate and severe was performed by the central screening core laboratory based on current recommendations for multi-slice CT-based analysis. Severe MAC was defined by a Guerrero score of seven points or greater.[5] MR was graded by an integrative echocardiographic approach according to the current guidelines of the American Society of Echocardiography from 0+ (none) to 4+ (severe).[6] Concomitant tricuspid regurgitation (TR) was reported on a five-grade scale from mild (1+) to torrential (5+).

Data on the patients' medical history, heart failure symptoms, medication, risk evaluation, imaging parameters, procedural data, hospitalization and 30-day follow-up were collected retrospectively in an anonymized fashion. The study was approved by the respective local ethics committees and was registered with ClinicalTrials.gov (NCT04898335).

Endpoints and follow-up

The primary endpoint of the study was procedural success as defined by the Mitral Valve Academic Research Consortium (MVARC)[7] assessed at 30 days, defined as device success and absence of major device- or procedure-related serious adverse events such as death, stroke, life-threatening bleeding, major vascular or cardiac structural complications, acute kidney injury stage 2 or 3, myocardial infarction, severe heart failure and valve-related dysfunction including migration, thrombosis or other complication requiring surgery or reintervention.

Secondary endpoints included technical success according to MVARC,[7] all-cause and cardiovascular mortality, cerebrovascular events, myocardial infarction, bleeding complications, new-onset arrhythmia or conduction abnormality, acute kidney injury, repeated MV surgery or intervention, rehospitalization for heart failure, as well as functional status according to NYHA functional class. Major adverse cardiac events were defined as cumulative endpoint of non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality.

Clinical follow-up with concurrent TTE was usually performed at 30 days. In patients with prolonged duration of the index hospitalization, the first outpatient visit was used for evaluation of early follow-up. On-label treatment was defined according to the instructions for use as treatment of the native MV in patients with MR ≥3+, left ventricular ejection fraction (LVEF) ≥30%, left ventricular end-diastolic diameter ≤70 mm, in the absence of severe MAC, and additionally, patients with primary MR with a left ventricular end-systolic diameter >30 mm.

The Tendyne Mitral Valve System

The Tendyne Mitral Valve System is a dedicated transapical MV implantation system consisting of a self-expanding trileaflet porcine valve prosthesis sutured to a double nitinol frame. Multiple sizes and different profiles (standard and low) are available, chosen according to individual patient's anatomy assessed by TTE, TEE and CT. The procedure is performed under general anaesthesia using a left lateral minithoracotomy. The prosthesis is placed in the native MV annulus under echocardiographic and fluoroscopic guidance and then retained by a tether connected to an epicardial pad fixed on the apex according to the counter-pull principle. The amount of tension applied to the tether is calculated individually according to the systemic pressure conditions. The prosthesis can be repositioned and retrieved if positioning is not optimal, i.e. in case of left ventricular outflow tract obstruction (LVOTO). Patients usually follow an antithrombotic management with warfarin or less frequently non-vitamin-K antagonist oral anticoagulants (NOACs) after the procedure.

Statistical analysis

Continuous variables were expressed as mean with standard deviation and compared using a paired *t*-test. Categorical variables were displayed as counts and percentages and compared using the Wilcoxon signed rank test. Predictors for procedural success were identified using a logistic regression model. Parameters showing $p < 0.1$ in a univariate analysis were included into the multivariate model. Results are presented as odds ratio (OR) with 95% confidence interval (CI) and *p*-value. Independent samples were compared using the Mann–Whitney U test. For all statistical tests, a two-sided *p*-value of 0.05 was defined as significance threshold. Statistical analysis was performed with IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

From January 2020 to April 2021, 108 consecutive patients (43% female, mean age 75 ± 7 years) underwent implantation of a Tendyne bioprosthesis at 26 participating European sites. The mean European System for Cardiac Operative Risk Evaluation II score was 8.4 ± 6.1% and the Society of Thoracic Surgeons predicted risk of mortality for MV replacement was 7.2 ± 5.3%. Baseline characteristics of the study cohort are summarized in *Table 1*. Prevalence of coronary artery disease (63%), atrial fibrillation (70%) and chronic renal failure (78%) was high; in addition, 16% of patients had undergone previous MV surgical or transcatheter intervention. More than two thirds of patients (70%) had been previously hospitalized for heart failure and the majority of patients (86%) were in NYHA functional class III or IV.

Echocardiographic baseline data are shown in *Table 2*. Left ventricular function was impaired (LVEF <50%) in 44% of patients, and echocardiographically estimated systolic pulmonary

Table 1 Baseline clinical characteristics (n =108)

Female sex	46 (43)
Age, years	75 ± 7
BMI, kg/m^2	26 ± 5
EuroSCORE II, %	8.4 ± 6.1
STS-PROM, %	7.2 ± 5.3
Comorbidities	
Coronary artery disease	68 (63)
Previous myocardial infarction	27 (25)
Previous PCI	42 (39)
Previous CABG	32 (30)
Previous TAVI	24 (22)
Previous AV surgery	18 (17)
Previous MV intervention	14 (13)
Previous MV surgery	3 (3)
History of atrial fibrillation	76 (70)
Oral anticoagulation	77 (71)
COPD	19 (18)
Previous stroke	17 (16)
GFR, ml/min	46 ± 22
Renal failure (GFR < 60 ml/min)	84 (78)
Heart failure severity and treatment	
NYHA functional class	
II	15 (14)
III	73 (69)
IV	18 (17)
Previous hospitalization for heart failure	76 (70)
NT-proBNP, pg/ml	9334 ± 17 333
ACE-inhibitors/ARB	77 (71)
Beta-blocker	95 (88)
Diuretics	95 (88)
Cardiac resynchronization therapy	10 (9)

Values are given as n (%) or mean ± standard deviation.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, aortic valve; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MV, mitral valve; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Table 2 Baseline echocardiographic and computed tomography characteristics

Echocardiographic characteristics (n = 104)	
LVEF, %	48 ± 12
LVEF 31%–49%	33 (32)
LVEF ≤30%	12 (12)
LVEDD, mm	56 ± 8
TAPSE, mm	17 ± 4
sPAP (estimated), mmHg	53 ± 18
sPAP >35 mmHg	67 (65)
TR ≥3 (severe)	20 (19)
MR severity	
1+	1 (1)
2+	5 (4)
3+	34 (33)
4+	64 (62)
EROA (PISA), cm^2	0.43 ± 0.22
MR aetiology	
Degenerative	40 (38)
Functional	38 (37)
Mixed	25 (25)
Mitral stenosis (transvalvular gradient >5 mmHg)	16 (15)
Severe stenosis (>10 mmHg)	3 (3)
CT characteristics (n = 94)	
Predicted neo-LVOT, mm^2	418 ± 129
<300 mm^2	18 (19)
MV annular diameter, antero-posterior, mm	31 ± 4
MV annular diameter, intercommissural, mm	40 ± 4
MV annular perimeter, mm	119 ± 17
Mitral annular calcification	
None	49 (51)
Mild/spotty	28 (30)
Moderate	12 (13)
Severe	7 (6)

Values are given as n (%) or mean ± standard deviation.
CT, computed tomography; EROA, effective regurgitant orifice area; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MV, mitral valve; PISA, proximal isovelocity surface area; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

artery pressure was elevated (>35 mmHg) in 65%. MR was moderate-to-severe (grade 3+) or severe (grade 4+) in 95% of patients with a mean effective regurgitant orifice area (EROA) of 0.43 ± 0.22 cm^2. Mitral stenosis (mean transvalvular gradient >5 mmHg) with or without concomitant MR was present in 16 patients (15%). Aetiology of MV disease was classified as primary/degenerative in 38%, secondary/functional in 37%, and mixed in 25% of patients.

The mean predicted neo-left ventricular outflow tract (LVOT) assessed using valve simulation on CT images was 418 ± 129 mm^2 (<300 mm^2 in 18 patients [19%]; <200 mm^2 in none). Baseline CT parameters are displayed in *Table 2*. Moderate or severe MAC was present in 19 patients (20%).

According to the instructions for use criteria, one quarter of patients (25% [n = 27]) were treated for an off-label indications (*Figure 1*) owing to previous MV treatment with a device in place (*Figure 2A,B*), left ventricular function or dimension, predominant mitral stenosis or presence of severe MAC (*Figure 2C*). Off-label patients were more symptomatic (NYHA functional class IV in 30% vs. 13%, p = 0.041), whereas on-label patients more frequently had a history of atrial fibrillation (75% vs. 45%, p = 0.015) (online supplementary *Table S1*). The majority of patients (89% [n = 93/104]) was classified ineligible for an M-TEER-based approach. Detailed reasons are depicted in *Table 3*.

Procedural and in-hospital outcomes

Procedural outcomes are summarized in *Table 3*. Technical success was achieved in 96% (104 patients). Half of the patients (52%) received a low-profile valve to avoid LVOTO according to the CT-based anatomical evaluation. MR at the end of the procedure was none/trace (grade 0) in 96% and ≤1+ in all patients. The

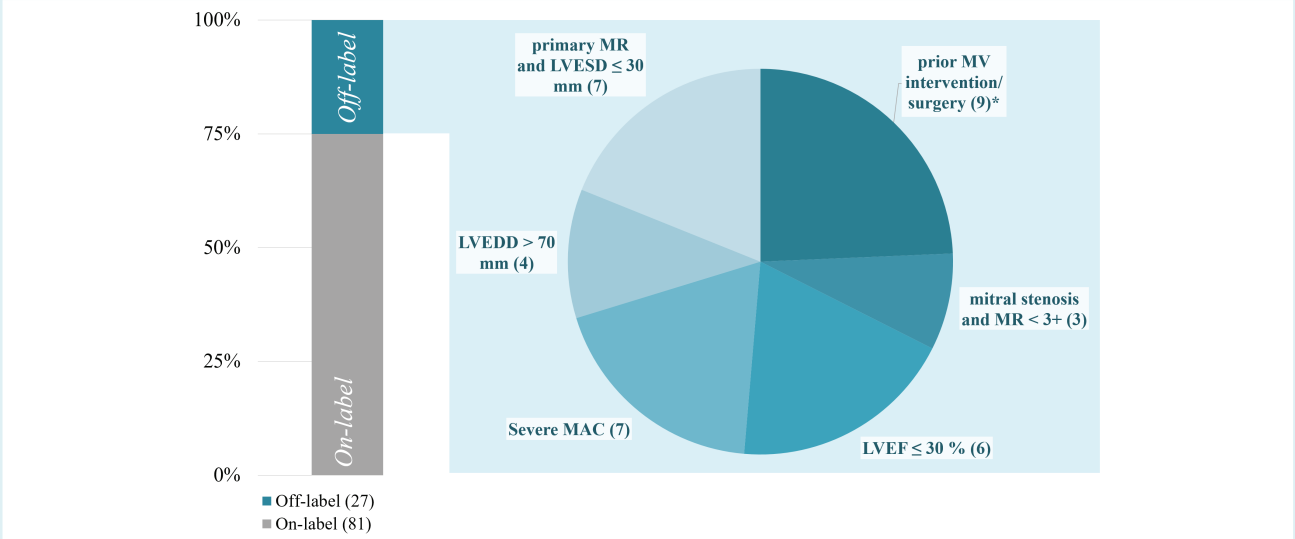


Figure 1 On-/off-label use according to instructions for use criteria. *Prior MV intervention/surgery with remaining device. Multiple criteria can be present in the same patient. LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MAC, mitral annular calcification; MR, mitral regurgitation; MV, mitral valve.

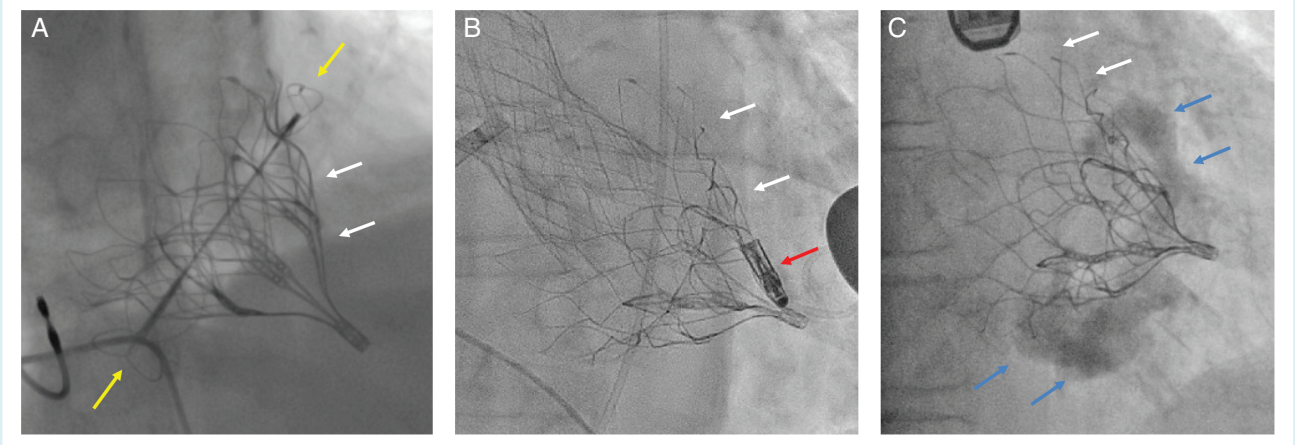


Figure 2 Examples of off-label cases after Tendyne implantation. (*A*) Previous transcatheter indirect annuloplasty device (yellow arrows). (*B*) Previous edge-to-edge repair (red arrow). (*C*) Severe mitral annular calcification.

mean transprosthetic gradient was 3.8 ± 1.5 mmHg. Paravalvular leak (PVL) occurred in ten patients (9%), and was graded mild in all 8. There were four patients with valve retrieval. In two of them, one due to incomplete unfolding and one due to dislocation into the left ventricle, a successful attempt was made to reposition the same valve, whereas in another patient the valve had to be fully retrieved and a second valve implanted because of interaction with an existing annuloplasty device. In a fourth patient, the valve was fully retrieved due to haemodynamic instability following LVOTO, and the patient was converted to open-heart surgery following installation of extracorporeal membrane oxygenation. In another patient, transient LVOTO during the procedure was solved by valve repositioning. In two other patients, conversion to open-heart surgery was performed following major apical access site bleeding and ventricular rupture, leading to intra-procedural death in both (2%).

The median length of stay on the intensive care unit was 3 days (interquartile range 1–5.3 days; five patients were directly transferred to standard care ward), whereas the median total length of hospitalization was 12 (interquartile range 9–19.5 days). In-hospital mortality was 8% (n = 9), including the two procedural deaths. During hospital stay, two patients (2%) experienced a disabling stroke (one peri-procedural), five patients (5%) acute kidney failure requiring dialysis, and five patients (5%) presented with ventricular arrhythmia. Major bleeding events (BARC 2, 3a or 5) during the hospitalization occurred in 12 patients (11%), requiring blood

Table 3 Procedural and in-hospital outcomes ($n = 108$)

Procedural	
M-TEER ineligibility, reason	93 (89)
Short leaflet with/without restricted movement	51 (53)
Relevant calcification/s	36 (36)
Small MVA	22 (23)
Attempted M-TEER, high gradient	12 (12)
Previous MV intervention/surgery with device in situ	7 (7)
Thickened leaflet/s	4 (4)
Large leaflet prolapse	5 (5)
Technical success	104 (96)
MR grade at the end of procedure (in implanted patients)	
0	101 (96)
1+	4 (4)
Paravalvular leak	
Mild	9 (8)
Moderate	1 (1)
Peri-procedural valve retrieval	4 (4)
LVOT obstruction	2 (2)
Major apical access site complication	2 (2)
Conversion to open-heart surgery	3 (3)
Procedural mortality	2 (2)
Procedure time, min	130 ± 41
In-hospital	
In-hospital mortality	9 (8)
Cerebrovascular event	3 (3)
Major bleeding (BARC 2, 3 or 5)	12 (11)
Acute kidney failure	23 (21)
Requiring dialysis	5 (5)
Sepsis	11 (10)
Ventricular arrhythmia	5 (5)
New pacemaker implantation	2 (2)
Valve thrombosis	1 (1)
Discharge ($n = 97$)	
Home	64 (66)
Other hospital	11 (12)
Rehabilitation facility	22 (23)

Values are given as *n* (%) or mean ± standard deviation. For M-TEER ineligibility multiple choices were possible.
BARC, Bleeding Academic Research Consortium; LVOT, left ventricular outflow tract; MR, mitral regurgitation; M-TEER, mitral transcatheter edge-to-edge repair; MV, mitral valve; MVA, mitral valve area.

Table 4 Outcomes at 30 days ($n = 108$)

Procedural success	86 (80)
All-cause mortality	13 (12)
Cardiovascular mortality	9 (8)
Rehospitalization for heart failure	14 (13)
MV reintervention or surgery[a]	0 (0)
Myocardial infarction[a]	0 (0)
Evidence of haemolysis[a]	2 (2)
Evidence of valve thrombosis[a]	0 (0)
Valve migration/embolization[a]	1 (1)
NYHA functional class ($n = 90$)	
I	20 (22)
II	46 (51)
III	20 (22)
IV	4 (5)
Echocardiographic outcomes ($n = 74$)	
LVEF, %	46 ± 14
LVEDD, mm	56 ± 9
MR severity	
0	68 (95)
1+	3 (4)
2+	1 (1)
Transvalvular gradient, mmHg	4 ± 2
>5 mmHg	8 (11)
>10 mmHg	0 (0)
Paravalvular leak more than trace	7 (10)
sPAP (estimated), mmHg	40 ± 19
TAPSE, mm	16 ± 5
TR ≥3+ (severe)	6 (8)

Values are given as *n* (%) or mean ± standard deviation.
LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.
[a]Events following hospital discharge.

transfusions in all and surgical intervention (evacuation of a thoracic haematoma) in one patient (1%). Owing to higher grade atrioventricular block, two patients (2%) underwent pacemaker implantation. One patient (1%) showed early subclinical valve thrombosis detected by an elevated mean gradient of 6 mmHg 5 days after the procedure (post-procedural mean gradient 2 mmHg) and confirmed by CT detection of a hypo-attenuated leaflet thickening. Oral anticoagulation was switched from NOAC to warfarin, and CT at follow-up showed complete resolution of the thrombus. The overall rate of in-hospital major adverse cardiac events was 9% ($n = 10$).

The majority of the patients were discharged home (66% [$n = 64$]) or to a rehabilitation facility (23% [$n = 22$]), whereas 12% ($n = 11$) were transferred to another hospital for further treatment. At 30 days, one patient was still hospitalized at the intermediate unit. Most patients (80% [$n = 76$]) followed an antithrombotic regime with a vitamin-K antagonist, and 20% ($n = 19$) with a NOAC.

Follow-up outcomes

Clinical follow-up at 30 days was obtained for all patients. Results are shown in *Table 4*. The overall rate of procedural success according to the MVARC definition[7] was 80% ($n = 86$). Procedural success in on-label and off-label treated patients was 81% and 74%, respectively, without statistically significant difference ($p = 0.41$) (*Graphical Abstract*). In a univariate logistic analysis, none of the baseline or echocardiographic parameters was identified as predictor for procedural success (online supplementary *Table S2*). Regarding a potential learning curve, we did not identify any statistical relationship between the centre's TMVI volume and the rate of procedural success.

At 30-day follow-up, there were four additional deaths. Two patients (2%) died of cardiovascular cause, and two patients (2%) of non-cardiovascular causes (COVID-19 pneumonia; urosepsis).

There was no patient with new stroke, myocardial infarction, or MV reintervention. Thus, among patients discharged, the rate of major adverse cardiac events was 3% ($n = 3$), the overall 30-day mortality was 12% ($n = 13$), and cardiovascular mortality 8% ($n = 9$). Regarding valve function, two patients (2%) developed haemolysis, of which one occurred in the context of mild valve migration towards the atrium leading to a moderate PVL. Valve re-tensioning 3 months after the index procedure successfully resolved PVL and haemolysis. In six other patients, a mild PVL was detected without clinical relevance.

Reduction of MR was sustained in all but one patient having MR ≤1+ ($p < 0.001$ as compared to baseline; *Graphical Abstract*). Left ventricular function and dimension remained unchanged (LVEF [59 paired values] 47% vs. 46%, $p = 0.179$; left ventricular end-diastolic diameter [58 paired values] 57 vs. 56 mm, $p = 0.310$), whereas pulmonary pressure (systolic pulmonary artery pressure [48 paired values] 52 vs. 42 mmHg, $p < 0.001$) and TR severity (64 paired values, $p = 0.013$) decreased significantly. The transprosthetic gradient was elevated >5 mmHg in 8 patients (11%) at follow-up, but overall remained stable as compared to discharge ([51 paired values] 3.7 vs. 3.6 mmHg, $p = 0.746$).

NYHA functional class was available for 90 patients of whom 73% were in NYHA functional class I or II ($p < 0.001$; *Graphical Abstract*) at early clinical follow-up (median 50 days, interquartile range 32–79 days).

Discussion

The salient findings of this real-world experience with transapical valve implantation for symptomatic MV disease can be summarized as follows: (i) technical success was achieved in 96% and MR was reduced to ≤1+ in all patients; (ii) mortality was 8% during hospitalization (including two intra-procedural deaths) and 12% at 30-day follow-up; (iii) functional status according to NYHA class was significantly improved at follow-up and MR reduction was sustained; (iv) procedural success at 30 days according to MVARC criteria was 80% and was not different for patients treated off-label; and (v) transmitral gradients, as well as the rate of LVOTO, and thrombotic complications were low.

Several transcatheter treatment options have emerged over the last decade to address the growing therapeutic need for MV disease. Compared to M-TEER, a well-established technique with proven safety and efficacy,[8,9] TMVI is a rather young, but emerging treatment option in the spectrum of percutaneous MV treatment. Specific challenges, including LVOTO, as well as thrombotic and ventricular complications have slowed its development in comparison to transcatheter aortic valve implantation. Nevertheless, possible advantages of TMVI over M-TEER are the standardized approach with predictable resolution of MR, which might translate in a better durability of MR reduction and later outcome benefits. The cumulative evidence of current TMVI techniques shows a post-procedural reduction to MR ≤1+ in 97% of patients (252/260 patients),[10] whereas similar MR reduction with M-TEER can only be achieved in 77%–80% of patients and is highly anatomy-dependent.[11–16]

There are numerous anatomical features complicating MV treatment using M-TEER like leaflet calcifications or thickening, small MV area, concomitant or predominant mitral stenosis, short or immobile posterior leaflet, and last but not least device failure or MR recurrence after previous transcatheter or surgical MV repair without option for another clip-based approach. Complex anatomy has been shown to negatively impact procedural result and prognosis after M-TEER.[17] In TENDER, the majority of patients was classified ineligible for an M-TEER-based approach. However, despite the anatomical challenges, MR reduction to ≤1+ was achieved in all patients and to none/trace in 96% of patients. The technical success rate of 96% in TENDER is similar to the reported data of the initial feasibility study (IFS),[3] although 25% of patients in this cohort have been treated off-label or would have been excluded from the IFS. Procedural success was not different in patients treated on-label (*Graphical Abstract*), and on-label treatment could not be identified as a predictor for procedural success in a logistic regression model (online supplementary *Table S2*). Similarly, patients with severe pulmonary hypertension or TR ≥ grade 3+ have been excluded from the IFS, while they accounted for 14% and 19% of TENDER patients, respectively. Important baseline characteristics, and procedural as well as early clinical follow-up data of TENDER and the IFS are compared in *Table 5*. In the present study, conversion to open-heart surgery and procedural mortality was 3% and 2%, respectively, and also 30-day mortality was substantially higher (13% compared to 6% in the IFS, and also higher than hitherto real-world M-TEER experience).[18] This is most likely due to major differences in terms of patient selection of a real-world cohort as opposed to a highly selected patient cohort in a feasibility study. However, overall adverse events were comparably low in the TENDER cohort and in particular, there was no patient with MV reintervention, myocardial infarction and a low rate of major bleeding complications. Although a considerable proportion of patients (17%) were highly symptomatic at baseline (NYHA functional class IV), symptomatic improvement at early follow-up among survivors was comparable with 73% and 78% of patients being in functional class I or II in TENDER and the IFS, respectively.

Although the treatment of patients with MAC with the Tendyne prosthesis has been shown to be feasible and safe,[19] our study reports the largest cohort of MAC patients treated with the system so far. Compared to valve-in-MAC, we report a much lower rate of mortality and adverse events using a dedicated system. In particular, there was no case of conduction disturbances requiring new pacemaker implantation or relevant PVL in this subgroup of patients.

Although TMVI allows the treatment of a wider range of anatomies than M-TEER, it is noteworthy that still a considerable proportion of patients is rejected during the screening process for various reasons. Preliminary results from the CHOICE-MI study reported a rate of screening failure of 70% in nearly 750 patients included (Ali W.B., unpublished data). The availability of different valve sizes, including low-profile valves, might overcome some anatomical limitations like too small or too large MV annulus and left ventricular dimensions. However, the risk of potential LVOTO remains a challenge and might occur despite meticulous screening.[20] In TENDER, there was one patient with LVOTO leading to

Table 5 Comparison of TENDER and initial feasibility study

	TENDER ($n = 108$)	IFS ($n = 100$)
Female sex	46 (43)	31 (31)
Age, years	75 ± 7	75 ± 8
STS-PROM, %	7.2 ± 5.3	7.8 ± 5.7
Coronary artery disease	68 (63)	74 (74)
Previous CABG	32 (30)	47 (47)
Previous MV intervention/surgery	17 (16)	0 (0)
NYHA functional class IV	18 (17)	4 (4)
LVEF ≤30%	12 (11)	0 (0)
MR ≥3+	97 (96)	99 (99)
Primary aetiology of MV disease	35 (38)	11 (11)
LVEDD ≥70 mm	6 (6)	0 (0)
sPAP ≥70 mmHg	14 (13)	0 (0)
TR ≥3 (severe)	15 (16)	0 (0)
Severe MAC	7 (6)	0 (0)
Procedural outcome		
Technical success	104 (96)	96 (96)
MR none/trace[a]	103 (95)	87 (99)
Device retrieval	4 (4)	3 (3)
Major apical access site complications	2 (2)	1 (1)
Conversion to open-heart surgery	3 (3)	0 (0)
Procedural mortality	2 (2)	0 (0)
30-day outcome		
All-cause mortality	14 (13)	6 (6)
Cardiovascular mortality	9 (8)	4 (4)
Disabling stroke	2 (2)	2 (2)
Major bleeding (BARC 2, 3 or 5)	12 (11)	20 (20)
Myocardial infarction	0 (0)	2 (2)
Rehospitalization for heart failure	14 (13)	12 (12)
MV reintervention	0 (0)	1 (1)
Device-related adverse events	3 (3)	4 (4)

Values are given as *n* (%), or mean ± standard deviation.
BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; IFS, initial feasibility study; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; TR, tricuspid regurgitation.
[a]Measured at the end of the procedure for TENDER and at discharge for IFS.

haemodynamic instability and conversion to open-heart surgery. New transcatheter techniques to reduce the risk of LVOTO like the intentional anterior mitral leaflet laceration (LAMPOON)[21] or alcohol septal ablation for neo-LVOT modulation[22] could further expand the population of patients eligible for TMVI. Patients with heart failure with mildly reduced ejection fraction or reduced ejection fraction made up nearly half of the TENDER patient population. Whereas other TMVI systems rely only on annular anchoring of a valve prosthesis, and therefore mainly target primary MR patients,[23] the tensioning mechanism of the Tendyne Mitral Valve System also allows treatment of patients with secondary MR with very low risk of valve migration or embolization.

However, a potential limitation of many TMVI systems, including the Tendyne Mitral Valve System, is the transapical approach. This became apparent in our cohort with two patients experiencing of major apical access site bleeding and ventricular rupture ultimately causing procedural death. Furthermore, this approach may lead to longer intensive care unit and hospital stay due to longer recovery time. However, the majority of bleeding events during hospitalization were treated conservatively in TENDER and only required a reintervention (evacuation of a thoracic haematoma) in one patient. There were no major bleeding events in the further clinical course after hospital discharge. Facing the limitations of the transapical access, the transfemoral-transseptal approach may become the default strategy in the future, but currently there is no dedicated system commercially available and clinical experience is limited. On the other hand, the transapical approach enables a precise positioning of the valve prosthesis as well as safe anchoring via apical pad.

The anticoagulation regimen remains another field of uncertainty in TMVI and is not yet defined for patients after implantation of a Tendyne prosthesis. In the present study, more than 70% of patients were previously treated with oral anticoagulation with either vitamin K antagonist or NOAC for other indications (e.g. atrial fibrillation). At discharge all patients were prescribed an oral anticoagulation, in 40% combined with an antiplatelet therapy. We observed one patient with early subclinical valve thrombosis which occurred under NOAC treatment and resolved at early follow-up under treatment with a vitamin K antagonist. In summary, our findings underline the current recommendation of anticoagulation after TMVI, although the specific medication and duration of treatment require further investigation.

Limitations

There are inherent limitations of the present study due to its retrospective nature. Follow-up schedules and content were not pre-specified and only observational data were included. Defined study endpoints according to MVARC might be difficult to implement in this setting since due to longer hospital stay most patients do not attend a 30-day follow-up visit and the median early follow-up time period in our study was almost 2 months. Also, some clinical endpoints such as new conduction disturbances or minor bleeding events not requiring any medical intervention might not have been accurately documented compared to a prospective study.

Conclusion

In a real-world high-risk population, primarily considered ineligible for M-TEER, TMVI results in a high technical success. Despite high anatomical variability and complexity, technical success rate was high and MR was successfully reduced to mild or even trace in all patients. At early follow-up, we observed significant symptomatic improvement and sustained MR reduction. The main TENDER results appear to be comparable to the IFS study results, despite a less selective patient inclusion and a very low TMVI site experience. TENDER demonstrates that the Tendyne system expands the catheter-based treatment options for patients who are no candidates for conventional MV surgery or M-TEER.

Finally, the results of this study might encourage expansion of TMVI indications.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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