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ORIGINAL RESEARCH

Transapical Mitral Valve Replacement

1-Year Results of the Real-World Tendyne European Experience Registry

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ABSTRACT

BACKGROUND Early studies of the Tendyne transcatheter mitral valve replacement (TMVR) showed promising results in a small selective cohort.

OBJECTIVES The authors present 1-year data from the currently largest commercial, real-world cohort originating from the investigator-initiated TENDER (Tendyne European Experience) registry.

METHODS All patients from the TENDER registry eligible for 1-year follow-up were included. The primary safety endpoint was 1-year cardiovascular mortality. Primary performance endpoint was reduction of mitral regurgitation (MR) up to 1 year.

RESULTS Among 195 eligible patients undergoing TMVR (median age 77 years [Q1-Q3: 71-81 years], 60% men, median Society of Thoracic Surgeons Predicted Risk of Mortality 5.6% [Q1-Q3: 3.6%-8.9%], 81% in NYHA functional class III or IV, 94% with MR 3+/4+), 31% had "real-world" indications for TMVR (severe mitral annular calcification, prior mitral valve treatment, or others) outside of the instructions for use. The technical success rate was 95%. The cardiovascular mortality rate was 7% at 30 day and 17% at 1 year (all-cause mortality rates were 9% and 29%, respectively). Reintervention or surgery following discharge was 4%, while rates of heart failure hospitalization reduced from 68% in the preceding year to 25% during 1-year follow-up. Durable MR reduction to ≤1+ was achieved in 98% of patients, and at 1 year, 83% were in NYHA functional class I or II. There was no difference in survival and major adverse events between on-label use and "real-world" indications up to 1 year.

CONCLUSIONS This large, real-world, observational registry reports high technical success, durable and complete MR elimination, significant clinical benefits, and a 1-year cardiovascular mortality rate of 17% after Tendyne TMVR. Outcomes were comparable between on-label use and "real-world" indications, offering a safe and efficacious treatment option for patients without alternative treatments. (Tendyne European Experience Registry [TENDER]; NCT04898335)
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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

IFU = instructions for use

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

MAC = mitral annular calcification

MR = mitral regurgitation

MV = mitral valve

PROM = Predicted Risk of Mortality

STS = Society of Thoracic Surgeons

TMVR = transcatheter mitral valve replacement

TR = tricuspid regurgitation

Transcatheter mitral valve replacement (TMVR) offers a treatment option for patients with symptomatic mitral valve (MV) disease unsuitable for transcatheter repair or at high or prohibitive risk for surgery.[1-4] The Tendyne prosthesis (Abbott Structural) is the only commercially available TMVR device with >1,400 implantations to date. The early feasibility study of the Tendyne prosthesis (global feasibility study), including 100 selected patients, showed very promising mid-term results (NCT02321514).[5-7] The reduction in mitral regurgitation (MR), alleviation of symptoms, and reduction in rehospitalization rate were sustained through 2 years.[6]

Surgical MV treatment in the presence of severe mitral annular calcification (MAC) remains a high-risk intervention leading to a considerable proportion of symptomatic patients being untreated.[8] Severe MAC is also highly challenging in TMVR because of more challenging valve anchoring, potential frame compression, and risk for paravalvular leak. The Tendyne feasibility study excluded patients with severe MAC as defined by the instructions for use (IFU) of the prosthesis. Smaller studies, though, have reported promising early and mid-term outcomes.[9-11]

The TENDER (Tendyne European Experience) registry is an ongoing investigator-initiated retrospective multicenter registry enrolling surgical high-risk symptomatic patients at 31 European high-volume heart valve centers. It currently includes the largest real-world, commercial cohort of patients treated with the Tendyne prosthesis, aiming to investigate outcomes in a nonselected cohort in a European multinational and multicenter setting. This includes the whole spectrum of patients with native valves as well as severe MAC and prior MV treatment, who were excluded from the feasibility study. We recently reported data from TENDER on procedural and 30-day outcomes among 108 patients.[12] At early clinical follow-up, MR reduction was sustained, and heart failure symptoms decreased significantly.

In the present study, we present 1-year outcomes focusing on mortality and MR reduction in patients who were treated on-label according to the manufacturer's IFU as well as "real-world" indications beyond the IFU.

METHODS

STUDY DESIGN AND PATIENTS. The TENDER study is an ongoing investigator-initiated, prospective, multicenter trial registry that currently includes >265 patients from 31 high-volume centers throughout

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Europe (Germany, Austria, Belgium, France, Italy, Spain, Switzerland, and the United Kingdom). All consecutive patients undergoing commercial Tendyne TMVR at the participating centers have been enrolled in the registry, starting with the launch of European commercial availability in January 2020. For 1-year outcome analysis, patients from the TENDER cohort implanted between January 2020 and December 2021 who were eligible for 1-year follow-up (defined as ≥270 days postimplantation) (Figure 1) were included.

Preinterventional diagnostics have been described in detail.[12] In short, MR severity was graded from 0+ (none) to 4+ (severe), and concomitant tricuspid regurgitation (TR) from 0+ (none) to 5+ (torrential).[13,14] Severe MAC was defined by a Guerrero score of ≥7 points on computed tomography.[15]

Data on patients' medical histories, imaging work-up, procedural data, in-hospital courses, and 30-day and 1-year follow-up were collected in an anonymized fashion. The study was approved by the lead ethics committees in Mainz and Munich and additionally by the respective local ethics committees of the trial centers and was registered with ClinicalTrials.gov (NCT04898335).

On-label treatment was defined according to the manufacturer's IFU as treatment of the native MV without prior MV intervention in patients with MR ≥3+, left ventricular ejection fraction (LVEF) ≥30%, and left ventricular (LV) end-diastolic diameter ≤70 mm, in the absence of severe MAC, and with primary MR with LV end-systolic diameter >30 mm.

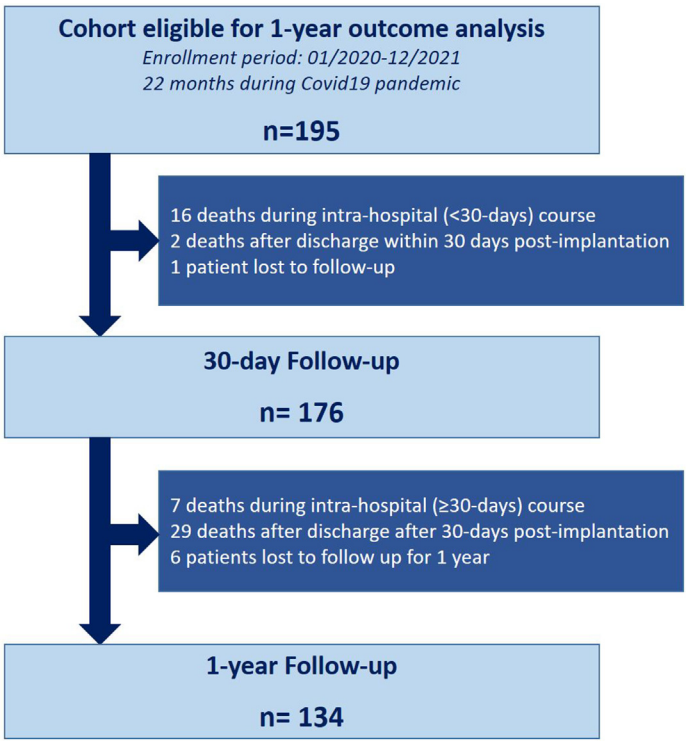
ENDPOINTS AND FOLLOW-UP. The primary safety endpoint of the study was 1-year cardiovascular mortality. The primary performance endpoint was reduction of MR severity up to 1-year follow-up. Clinical endpoints were defined according to Mitral Valve Academic Research Consortium criteria.[16]

Thirty-day and 1-year follow-up visits included clinical and echocardiographic work-up. If patients were unavailable to keep their appointments at the tertiary center, reports from private practice cardiologists or structured telephone interviews were used.

For 1-year data analysis, only follow-up visits after 365 ± 90 days postimplantation were accepted. For echocardiographic outcome analysis, the latest available echocardiography report after implantation was applied.

The observed-to-expected 30-day mortality ratio was derived by dividing the observed mean 30-day mortality after TMVR by the expected mean 30-day mortality as estimated by the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM).[17]

FIGURE 1 Study Flowchart



Patient flowchart over the 1-year follow-up period presenting number of patients treated and followed in the study and deaths or exits.

IMPLANTATION OF THE TENDYNE MV SYSTEM. The Tendyne MV system is a dedicated transapical TMVR system with an implantation procedure previously described in detail.[18] For antithrombotic management, vitamin K antagonist or, in isolated cases, non-vitamin K antagonist anticoagulant therapy was initiated after the procedure with or without additional antiplatelet therapy, as site reported.

STATISTICAL ANALYSIS. Statistical analysis was performed using SPSS Statistics 23 (IBM). Continuous variables are expressed as mean ± SD when normally distributed and otherwise as median (Q1-Q3). Categorical variables are presented as frequencies and percentages, unless otherwise specified. The Shapiro-Wilk test was used to assess normality for continuous data. Statistical significance was assessed using Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. The Fisher exact test or chi-square test was used to compare categorical variables as appropriate. Baseline and follow-up parameters were compared using the paired Student's *t*-test or the Wilcoxon signed rank test for continuous variables and the

TABLE 1 Baseline Characteristics

	All	On-Label Use	"Real-World" Indications	*P* Value
Baseline characteristics	(n = 195)	(n = 135)	(n = 60)	
Age, y	77 (71-81)	77 (72-81)	76 (70-82)	0.570
Male	116 (59.5)	80 (59.3)	36 (60.0)	0.923
EuroSCORE II, %	5.7 (3.5-11.6)	5.5 (3.5-11.6)	6.5 (3.3-11.2)	0.922
STS PROM, %	5.6 (3.6-8.9)	5.5 (3.7-9.0)	5.8 (3.2-8.9)	0.993
Prior HF hospitalization	130/191 (68.1)	92/132 (69.7)	38/59 (64.4)	0.469
NYHA functional class III or IV	158/194 (81.4)	107/134 (79.9)	51/60 (85.0)	0.394
BNP, pg/mL (n = 57)	555 (300-1,360)	467 (199-1,093)	651 (504-1,547)	0.068
NT-proBNP, pg/mL (n = 117)	3,840 (1,903-8,232)	3,737 (1,898-8,232)	4,296 (1,947-9,192)	0.495
Comorbidities	(n = 195)	(n = 135)	(n = 60)	
GFR < 50 mL/min	115 (59.0)	79 (58.5)	369 (60.0)	0.846
Diabetes mellitus	56 (28.7)	38 (28.1)	18 (30.0)	0.792
Coronary artery disease	111 (56.9)	80 (59.3)	31 (51.7)	0.323
Prior CABG	49 (25.1)	36 (26.7)	13 (21.7)	0.458
Prior MV surgery	11 (5.6)	0 (0)	11 (18.3)	
Prior MV intervention (device placed)	7 (3.6)	0 (0)	7 (11.7)	
Prior edge-to-edge repair (device placed)	5 (2.6)	0 (0)	5 (8.3)	
Prior transcatheter annuloplasty	2 (1.0)	0 (0)	2 (3.3)	
Prior unsuccessful MV intervention attempt (no device left)	12 (6.2)	11 (8.1)	1 (1.7)	0.082
PM/ICD	49 (25.1)	29 (21.5)	20 (33.3)	0.078
Prior stroke	27 (13.8)	18 (13.3)	9 (15.0)	0.756
Baseline MV and echocardiographic characteristics	(n = 195)	(n = 135)	(n = 60)	
MR etiology	(n = 191)	(n = 133)	(n = 58)	0.155
Primary	79 (41.4)	49 (36.8)	30 (51.7)	
Secondary	74 (38.7)	56 (42.1)	18 (31.0)	
Mixed	38 (19.9)	21.1 (28)	17.2 (10)	
MR grade 3+/4+	183 (93.8)	135 (100)	48 (80.0)	<0.001[a]
MV gradient >5 mm Hg	34/179 (19.0)	11/122 (9.0)	23/57 (40.4)	<0.001[a]
Estimated neo-LVOT (systole), cm^2	393 (318-480)	386 (316-468)	413 (341-554)	0.129
Severe MAC (grade 3)	20 (10.3)	0 (0)	20 (33.3)	
Left ventricular ejection fraction, %	50 (38-57)	48 (38-56)	50 (39-59)	0.504
Severe TR (>3+)	44 (22.6)	27 (20.0)	17 (28.3)	0.199
sPAP (estimated), mm Hg	49 (40-61)	52 (40-61)	45 (40-60)	0.557

Values are median (Q1-Q3) or n (%). [a]$P < 0.05$.

BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; GFR = glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVOT = left ventricular outflow tract; MAC = mitral annular calcification; MR = mitral regurgitation; MV = mitral valve; NT-proBNP = N-terminal pro-brain natriuretic peptide; PM = pacemaker; PROM = Predicted Risk of Mortality; sPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TR = tricuspid regurgitation.

McNemar test for categorical variables. Kaplan-Meier analysis with the log-rank test was applied to generate survival estimates for freedom from all-cause mortality. A binomial logistic regression was performed to determine the effects of gender, age, kidney function STS score, European System for Cardiac Operative Risk Evaluation score, and LV function (univariate analysis) and gender, age, and kidney function (multivariate analysis) on mortality. All statistical tests were 2 sided, and *P* values <0.05 were considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. Among the >265 patients enrolled in the TENDER registry, 195 patients underwent Tendyne TMVR between January 2020 and December 2021 and were eligible for 1-year outcome analysis. Patient enrollment per center ranged from 1 to 19 patients (mean 6, median 5) AT the 31 participating centers. The mean screening failure rate was 55.2% ± 19.5%, due mainly to a too small estimated neo-LV outflow tract (LVOT) and either a too large or a too small MV annulus. The median age was 77 years (Q1-Q3: 71-81 years), 59.5% were men, and the median STS PROM was 5.6% (Q1-Q3: 3.6%-8.9%) (Table 1). All patients were symptomatic, with 81.4% of patients in NYHA functional class III or IV. More than two-thirds of patients (68.1%) had been previously hospitalized for heart failure in the 1-year period prior to intervention. MV surgery or intervention with remaining implanted device had been performed in 18 patients (9.2%), of whom 11 (5.6%) had previous surgical repair (chordal

TABLE 2 Short-Term Outcomes and Site-Reported Anticoagulation or Antiplatelet Regimen

	All	On-Label Use	"Real-World" Indications	*P* Value
Procedural	(n = 195)	(n = 135)	(n = 60)	
Technical success	185 (94.9)	129 (95.6)	56 (93.3)	0.500
MR none/mild	192/194 (99.0)	132/134 (98.5)	60/60 (100)	1.000
Paravalvular leakage more than trace	3/194 (1.5)	3/134 (2.2)	60/60 (0)	0.554
Periprocedural valve retrieval	8 (4.1)	5 (3.7)	3 (5.0)	0.703
Device migration	1 (0.5)	0 (0)	1 (1.7)	0.308
Conversion to open heart surgery	3 (1.5)	2 (1.5)	1 (1.7)	1.000
Procedural mortality	2 (1.0)	1 (0.7)	1 (1.7)	0.522
In-hospital	(n = 195)	(n = 135)	(n = 60)	
Periprocedural cardiovascular mortality	12 (6.2)	8 (5.9)	4 (6.7)	0.638
Periprocedural all-cause mortality	23 (11.8)	15 (11.1)	8 (13.3)	1.000
Disabling stroke	3/182 (1.6)	3/125 (2.4)	0/57 (0)	0.553
Major bleeding (BARC type 2, 3, or 5)	27/193 (14.0)	22/134 (16.4)	5/59 (8.5)	0.143
Acute renal insufficiency requiring dialysis	17/191 (8.9)	12/132 (9.1)	5/59 (8.5)	0.890
Sepsis	29/192 (15.1)	21/133 (15.8)	8/59 (13.6)	0.691
Myocardial infarction	3/193 (1.6)	3/134 (2.3)	0/59 (0)	0.554
New-onset atrial fibrillation	16/192 (8.3)	12/133 (9.0)	4/59 (6.8)	0.780
Ventricular arrhythmia	11/193 (5.7)	7/134 (5.2)	4/59 (6.8)	0.739
30-d mortality	(n = 193)	(n = 134)	(n = 59)	
Cardiovascular mortality	13 (6.7)	9 (6.7)	4 (6.7)	1.000
All-cause mortality	18 (9.3)	11 (8.2)	7 (11.7)	0.443
Anticoagulation/antiplatelet regimen	(n = 172)	(n = 120)	(n = 52)	0.777
VKA only	91 (52.9)	62 (51.7)	29 (55.8)	
VKA plus antiplatelet therapy	52 (30.2)	38 (31.7)	14 (26.9)	
DOAC only	16 (9.3)	10 (8.3)	6 (11.5)	
DOAC plus antiplatelet therapy	13 (7.6)	10 (8.3)	3 (5.8)	

Values are n (%) or n/N (%). Periprocedural mortality according to the consensus document from the Mitral Valve Academic Research Consortium includes all deaths occurring within 30 days of the intervention or beyond 30 days if the patient is not yet discharged.[16]

BARC = Bleeding Academic Research Consortium; DOAC = direct oral anticoagulant agent; MR = mitral regurgitation; VKA = vitamin K antagonist.

repair and annuloplasty rings from 36 to 40 mm), 5 (2.6%) transcatheter edge-to-edge repair, and 2 (1.0%) transcatheter annuloplasty. An additional 6.2% of patients underwent prior transcatheter repair attempts without implanted devices.

MR 3+ or 4+ was present in 93.8% of patients, with secondary or mixed pathology in 58.6%. Baseline mean MV gradients >5 mm Hg were measured in 19.0% of patients (median 3 mm Hg; Q1-Q3 2-5 mm Hg). The median LVEF was 50% (Q1-Q3: 38%-57%). The median systolic pulmonary artery pressure was 49 mm Hg (Q1-Q3: 40-61 mm Hg). Severe MAC was present in 10.3% of patients. The cohort included 30.8% of patients with "real-world" indications extending the manufacturer's IFU.

For anticoagulation and antiplatelet regimen post-TMVR, 83.1% of patients of the discharged patients were prescribed vitamin K antagonist and 16.9% non-vitamin K antagonist anticoagulant therapy. Additional antiplatelet therapy was applied in 37.8% of patients.

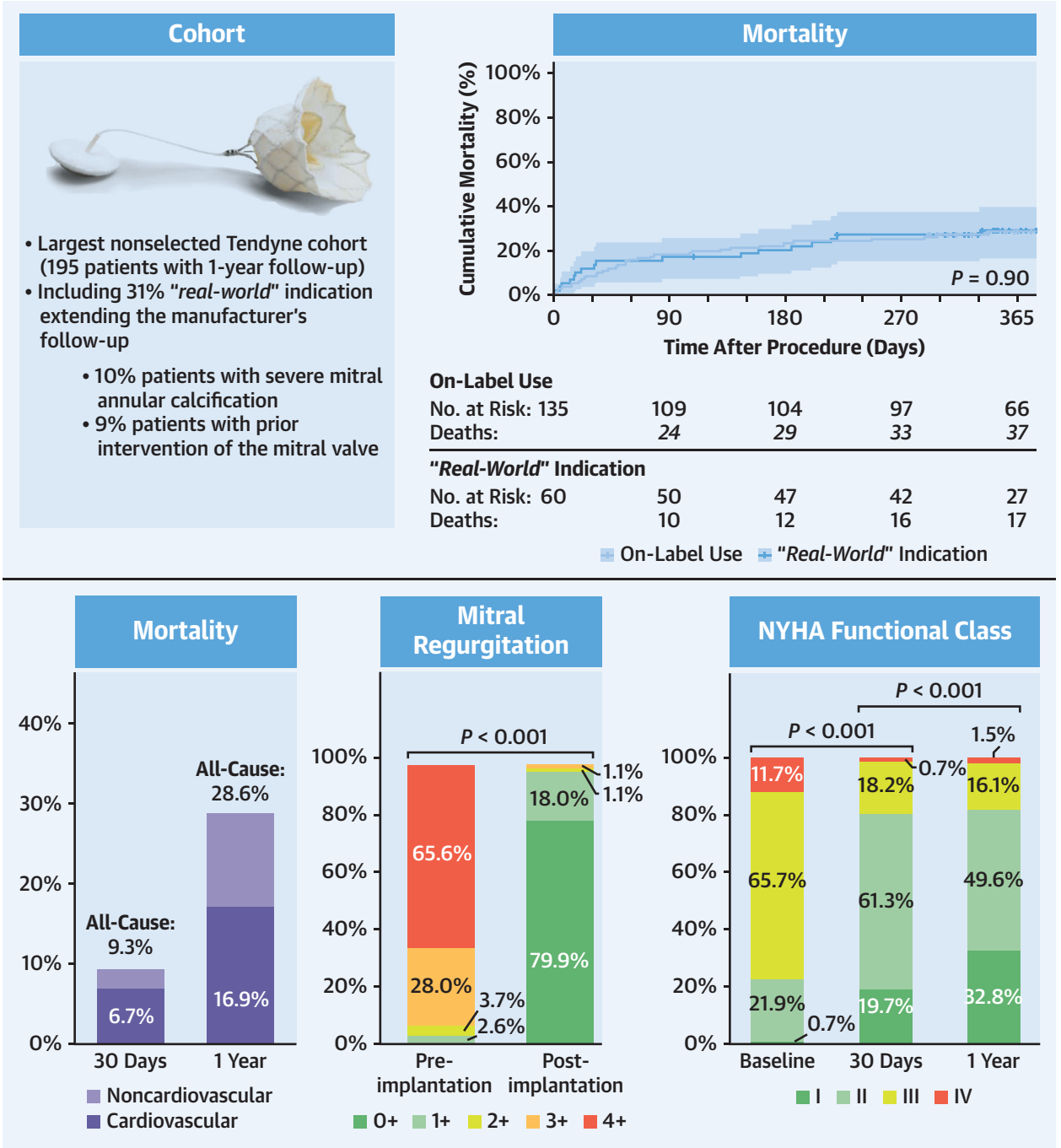
SHORT-TERM OUTCOMES. Table 2 presents procedural and short-term outcome data. Technical success was achieved in 94.9% of patients. One patient required retensioning because of severe paravalvular leak during the intrahospital course (day 20 post-implantation). Cardiovascular mortality was 6.7% at 30 days, and all-cause mortality was 9.3% at 30 days. The observed-to-expected 30-day mortality ratio was 1.0 for cardiovascular mortality and 1.4 for all-cause mortality.

1-YEAR OUTCOMES. Among 195 patients eligible for 1-year follow-up, 1 patient (0.5%) was lost to follow-up directly after discharge, and 6 patients (3.0%) did not complete 1-year follow-up, resulting in a follow-up rate of 96.4%. Among the latter, 5 patients had mid-term follow-up of at least 100 days. An overview of patient flow is provided in Figure 1.

The primary safety endpoint, 1-year cardiovascular mortality, occurred in 16.9%, and the primary performance endpoint, reduction of MR to mild or less, in 97.9% of patients (Central Illustration, Table 3).

All-cause mortality at 1 year was 28.6% (Central Illustration, Table 3). Median time to death during the 1-year follow-up period was 53 days (Q1-Q3: 19-167 days) (cardiovascular mortality, 68 days [Q1-Q3: 14-176 days]). The majority of deaths (all-cause, 68.2%; cardiovascular, 59.4%) occurred within the

CENTRAL ILLUSTRATION **Tendyne Transcatheter Mitral Valve Replacement: Mid-Term Outcomes From the TENDER Registry (N = 195)**



- High technical success, durable and substantial MR elimination, and significant clinical benefits of Tendyne TMVR in this nonselected cohort
- No difference in mortality and major adverse events between on-label use and real-world indications up to 1 year

Hell MM, et al. J Am Coll Cardiol Intv. 2024;■(■):■-■.

(Top left) The Tendyne prosthesis. (Top right) One-year mortality curves for strict on-label vs "real-world" indication treatment. For the total cohort, 30-day and 1-year mortality (bottom left), reduction in mitral regurgitation (MR) (bottom middle), and improvement in functional status according to NYHA functional classification (bottom right). TENDER = Tendyne European Experience Registry; TMVR = transcatheter mitral valve replacement.

TABLE 3 One-Year Follow-Up: Mortality and Major Adverse Events

	Total Cohort	On-Label Use	"Real-World" Indications	*P* Value
Mortality				
1-y mortality	(n = 189)	(n = 131)	(n = 58)	
Cardiovascular mortality	32 (16.9)	21 (16.0)	11 (19.0)	0.620
All-cause mortality	54 (28.6)	37 (28.2)	17 (29.3)	0.881
Further adverse events				
HF hospitalization	43/169 (25.4)	32/117 (27.4)	11/52 (21.2)	0.393
MV reintervention or surgery (only postdischarge)	7/172 (4.1)	5/120 (4.2)	2/52 (3.8)	1.000
MV reintervention or surgery (in-hospital and postdischarge)	8/173 (4.6)	5.0 (6/121)	2/52 (3.8)	1.000
Disabling stroke (only postdischarge)	4/168 (2.4)	1/117 (0.9)	3/51 (5.9)	0.084
Disabling stroke (in-hospital and postdischarge)	7/169 (4.1)	4/118 (3.4)	3/51 (5.9)	0.432
Myocardial infarction	2/160 (1.3)	1/113 (0.9)	1/47 (2.1)	0.503
Myocardial infarction (in-hospital and postdischarge)	5/162 (3.1)	4/115 (3.5)	1/47 (2.1)	1.000
New-onset atrial fibrillation (only postdischarge)	9/168 (5.4)	7/117 (6.0)	2/51 (3.9)	0.724
New-onset atrial fibrillation (in-hospital and postdischarge)	23/168 (13.7)	17/116 (14.7)	6/52 (11.5)	0.809
New conduction disturbances (only postdischarge)	2/169 (1.2)	0/117 (0)	2/52 (3.8)	0.093
New conduction disturbances (in-hospital and postdischarge)	6/172 (3.5)	3/118 (2.5)	3/54 (5.6)	0.380
Specific device adverse events				
Valve thrombosis	5/167 (3.0)	4/118 (3.4)	1/49 (2.0)	1.000
Valve migration	1/167 (0.6)	0/119 (0)	1/48 (2.1)	0.287
Paravalvular leak more than mild	9/172 (5.2)	8/117 (6.8)	1/55 (1.8)	0.275

Values are n (%) or n/N (%).
Abbreviations as in Tables 1 and 2.

first 90 days, and the predominant causes of death were noncardiovascular infection or sepsis (n = 8) and refractory heart failure (n = 6) (Supplemental Table 1, Supplemental Figure 1). A Kaplan-Meier curve of 1-year mortality is presented in Figure 2A.

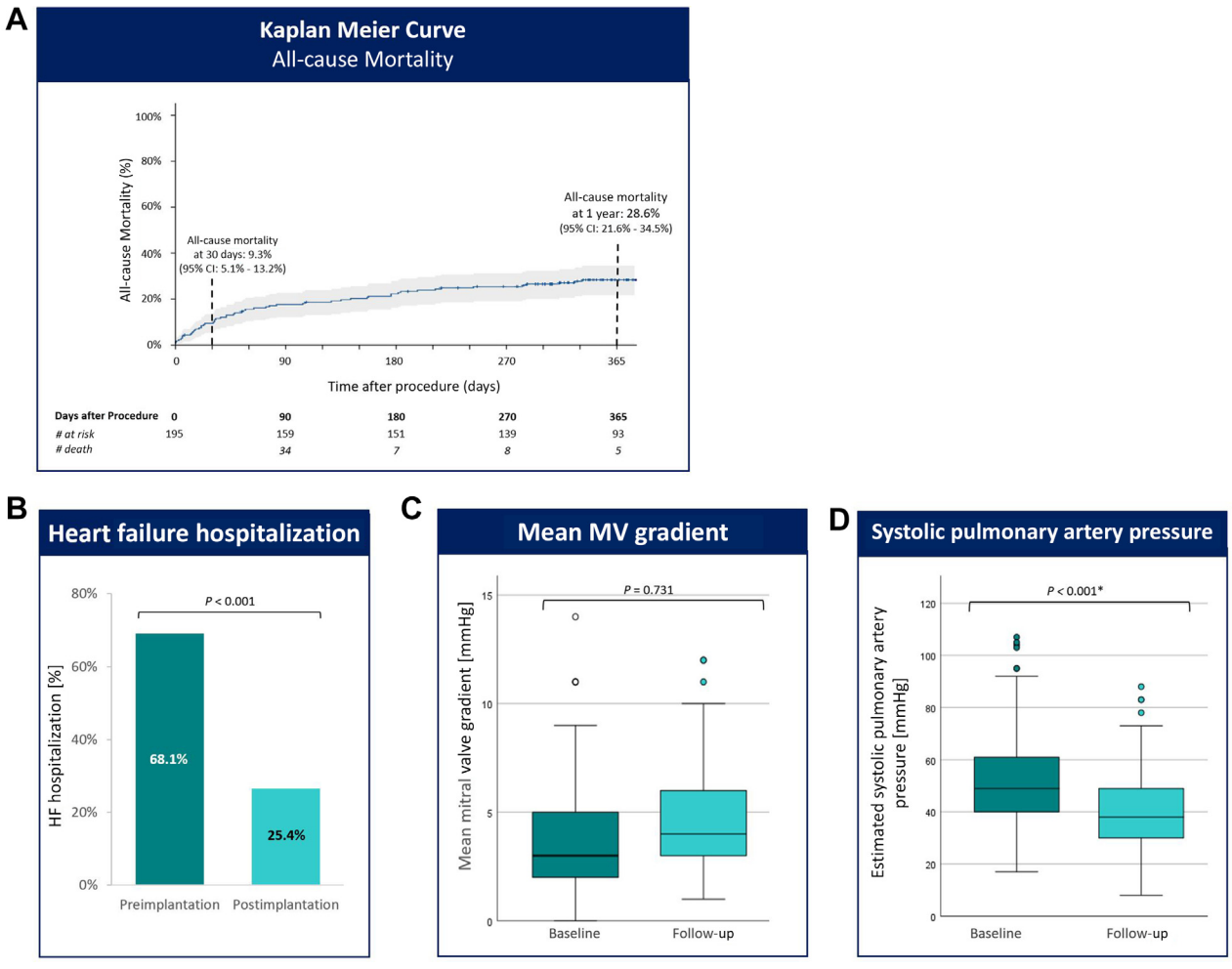
Heart failure hospitalization significantly decreased from 68.1% in the year prior to the procedure to 25.4% in the 1-year postprocedure period ($P < 0.001$) (Figure 2B).

Major adverse events within the 1-year follow-up period after discharge included disabling stroke in 2.4% and myocardial infarction in 1.3% of patients (Table 3). New-onset atrial fibrillation occurred in 5.4% of patients and new conduction disturbances in 1.2% within the 1-year period after discharge. Device-specific events included valve thrombosis in 3.0%, valve migration in 0.6%, and paravalvular leak >1+ in 5.2% of patients. We found no association between anticoagulation or antiplatelet regime (vitamin K antagonist only vs vitamin K antagonist plus antiplatelet therapy vs direct oral anticoagulant agent only vs direct oral anticoagulant agent plus antiplatelet therapy) and valve thrombosis ($P = 0.170$) or major bleeding ($P = 0.341$). Reintervention or surgery postdischarge was necessary in 7 patients (4.1%). In 2 patients, open heart MV surgery was required because of late valve endocarditis (postimplantation days 124 and 272). One patient required a new apical pad for evidence of an apical false aneurysm secondary to apical pad suture dysfunction (day 209). Retethering because of relevant paravalvular leakage was necessary in 3 patients (days 81, 86, and 127). One patient required surgery for thoracic access-site infection (day 189).

Paired comparisons showed significant improvement in NYHA functional class at 1 year, with 82.5% of patients in NYHA functional class I or II compared with 22.6% prior intervention (n = 137; $P < 0.001$) (Central Illustration, Table 3). Paired analysis of echocardiographic parameters was available in 167 patients (median follow-up time to echocardiography 272 days; Q1-Q3: 43-383 days) (Table 4). Reduction of MR to ≤1+ was achieved in 97.9% of patients ($P < 0.001$) (Central Illustration). Elevated mean MV gradient (>5 mm Hg) was observed in 16.8% of patients after intervention (Figure 2C). Systolic pulmonary artery pressure significantly decreased from 49 mm Hg (Q1-Q3: 40-61 mm Hg) preoperatively to 38 mm Hg (Q1-Q3: 30-50 mm Hg) on follow-up ($P < 0.001$) (Table 4, Figure 2D). There was a reduction in severe TR (≥3+) after intervention compared with baseline (from 22.9% to 15.7%; $P = 0.028$) (Table 4). LV systolic function postoperatively declined compared with baseline (LVEF from 50% [Q1-Q3: 38%-56%] to 48% [Q1-Q3: 35%-55%]; $P < 0.001$).

BASELINE PARAMETERS INFLUENCING MORTALITY AND MAJOR ADVERSE EVENTS. Patients with estimated neo-LVOTs in the lowest (<318 mm^2) and highest (>480 mm^2) quartiles showed a higher rate of intraprocedural valve retrieval (7.2% vs 1.0%; $P = 0.035$), with a trend toward a lower technical

FIGURE 2 **Clinical and Survival Outcomes of the TENDER 1-Year Cohort**



(A) Kaplan-Meier estimate of all-cause mortality to 1 year after Tendyne transcatheter mitral valve (MV) replacement. (B) Heart failure hospitalization preimplantation and postimplantation. (C) Mean MV gradient at baseline and follow-up. (D) Decrease in systolic pulmonary pressure from baseline to follow-up. TENDER = Tendyne European Experience Registry.

success rate (91.8% vs 98.0%; $P = 0.058$) and a higher rate of conversion to open heart surgery (3.1% vs 0%; $P = 0.079$) and valve thrombosis (5.9% vs 0%; $P = 0.059$) compared with patients with estimated neo-LVOTs in the second and third quartiles (318-480 mm^2). Patients with predicted neo-LVOTs in the highest quartile (>480 mm^2) had significant higher baseline LV end-diastolic diameters (median 61 mm; Q1-Q3: 55-67 mm) and lower LVEFs (40%; Q1-Q3: 30%-50%) compared with patients with predicted neo-LVOTs ≤480 mm^2 (53 mm [Q1-Q3: 47-60 mm] and 51% [Q1-Q3: 41%-59%], respectively).

Patients with impaired baseline renal function (estimated glomerular filtration rate [eGFR] <50 mL/min/1.73 m^2) had a significantly higher mortality rate compared with those with preserved renal function (30-day all-cause mortality, 14.0% vs 2.5% [$P = 0.006$]; 1-year all-cause mortality, 37.8% vs 15.4% [$P = 0.001$]). On univariate analysis, 1-year cardiovascular mortality was significantly associated with eGFR (OR: 0.97; 95% CI: 0.95-0.99; $P = 0.006$) and age (OR: 1.08; 95% CI: 1.02-1.15; $P = 0.013$) and 30-day cardiovascular (OR: 0.95; 95% CI: 0.92-0.99; $P = 0.010$), 30-day all-cause (OR: 0.96; 95% CI: 0.93-0.99; $P = 0.007$), and 1-year all-cause (OR: 1.05; 95% CI: 1.01-1.10; $P = 0.028$) mortality with eGFR. Multivariate analysis assessing for eGFR, age, and gender revealed significant associations of 1-year cardiovascular mortality with eGFR (OR: 0.97; 95% CI: 0.95-1.00; $P = 0.018$) and age (OR:

1.07; 95% CI: 1.01-1.14; $P = 0.028$) and of 30-day cardiovascular (OR: 0.96; 95% CI: 0.92-0.99; $P = 0.019$), 30-day all-cause (OR: 0.96; 95% CI: 0.94-0.99; $P = 0.009$), and 1-year all-cause (OR: 0.97; 95% CI: 0.95-0.99; $P < 0.001$) mortality with eGFR. Furthermore, impaired renal function at baseline resulted in a lower rate of NYHA functional class improvement to class I or II at follow-up (72.9% vs 92.5%; $P = 0.002$).

FOCUS ON PATIENTS WITH "REAL-WORLD" INDICATIONS FOR TMVR. The TENDER registry includes 60 patients (30.8%) who would have been excluded from implantation according to the manufacturer's IFU: the predominant causes were severe MAC (20 patients [10.3% of total cohort]) and previous MV treatment with implanted device (18 patients [9.2%]) (Figure 3). Baseline characteristics (except prior MV treatment) did not significantly differ between the cohorts. Procedural and in-hospital outcomes were similar, with a technical success rate of 93.3% and MR grade ≤ 1+ in 100% for the "real-world" cohort (Table 2). All-cause mortality rates were also similar (30-day mortality 8.2% vs 11.9% [$P = 0.443$] and 1-year mortality 28.2% vs 29.3% [$P = 0.881$] for on-label vs "real-world," respectively) (Table 3, Figure 4A). The observed-to-expected 30-day mortality ratios in the on-label cohort were 1.0 for cardiovascular mortality and 1.3 for all-cause mortality and in the real-world cohort were 1.0 and 1.7, respectively. A Kaplan-Meier curve of 1-year mortality for both cohorts is presented in the Central Illustration. Further adverse events, including stroke, heart failure hospitalization, and valve thrombosis or migration, did not significantly differ between the cohorts.

The primary performance endpoint, reduction to MR ≤1+ on echocardiographic follow-up, was achieved in 97.7% of patients in the on-label cohort and 98.3% in patients with "real-world" indications ($P = 0.630$) (Figure 4B). NYHA functional class significantly improved in both groups, with the percentage of patients in NYHA functional class I or II increasing from 25.0% at baseline to 79.2% at 1 year in the on-label cohort and from 17.1% to 90.2% in the "real-world" indication cohort ($P = 0.118$ between cohorts) (Figure 4C, Table 5). No significant increase was observed regarding mean MV gradient on follow-up for both cohorts (Table 5, Figure 5A). Systolic pulmonary artery pressure significantly decreased in the on-label cohort ($\Delta = -13.6 \pm 17.8$ mm Hg; $P < 0.001$) (Table 5, Figure 5B), whereas in the "real-world" cohort, the decrease did not reach statistical significance ($\Delta = -6.8 \pm 22.5$ mm Hg; $P = 0.057$).

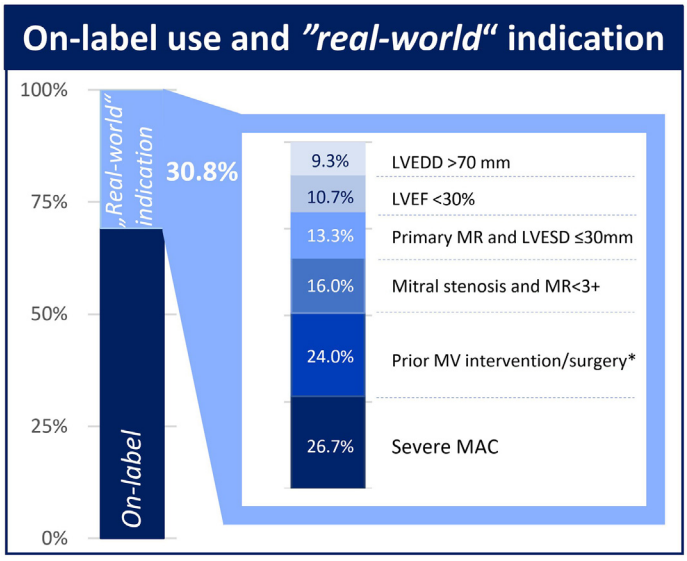
TABLE 4 Paired Comparison of 1-Year NYHA Functional Status and Latest Echocardiographic Parameters With Baseline

	Baseline	Follow-Up	Change	*P* Value
NYHA functional class (n = 137)				<0.001[a]
I	1 (0.7)	45 (32.8)		
II	30 (21.9)	68 (49.6)		
III	90 (65.7)	22 (16.1)		
IV	16 (11.7)	2 (1.5)		
I or II	31 (22.6)	113 (82.5)	59.9%	<0.001[a]
LVEF, % (n = 167)	50 (38-56)	48 (35-55)	−2.5 ± 10.0 −2 (−9 to 2)	<0.001[a]
MR severity (n = 189)				<0.001[a]
0	0	151 (79.9)		
1+	5 (2.6)	34 (18.0)		
2+	7 (3.7)	2 (1.1)		
3+	53 (28.0)	2 (1.1)		
4+	124 (65.6)	0 (0)		
Mild or less (≤1+)	5 (2.6)	185 (97.9)	95.2%	<0.001[a]
Mean mitral gradient, mm Hg (n = 167)	3 (2-5)	4 (3-5)	−0.1 ± 3.1 0 (−2 to 2)	0.731
>5 mm Hg	33 (19.8)	28 (16.8)	−3.0	0.446
TR grade (n = 166)				0.013[a]
0	6 (3.6)	12 (7.2)		
1+	68 (41.0)	69 (41.6)		
2+	54 (32.5)	59 (35.5)		
3+	23 (13.9)	17 (10.2)		
4+	13 (7.8)	7 (4.2)		
5+	2 (1.2)	2 (1.2)		
Less than severe (<3/5)	128 (77.1)	140 (84.3)	−7.2%	0.028[a]
sPAP (estimated), mm Hg (n = 129)	49 (40-61)	38 (30-50)	−11.2 ± 19.7 −10 (−23 to 2)	<0.001[a]

Values are n (%), median (Q1-Q3), or mean ± SD. NYHA functional class was assessed at 1-year follow-up. Echocardiographic parameters are from latest echocardiographic follow-up (median follow-up time to echocardiography 272 days; Q1-Q3: 43-383 days). [a]$P < 0.05$.

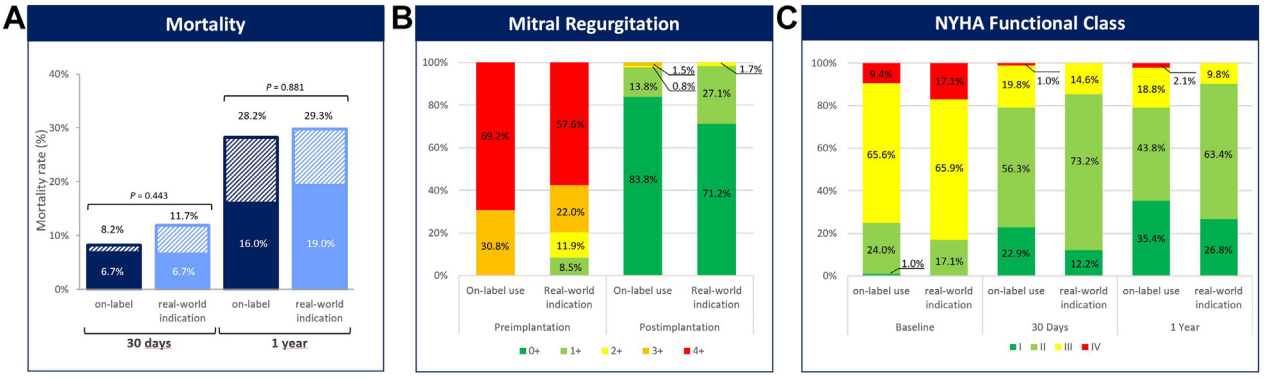
LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

FIGURE 3 Reasons for "Real-World" Indication in the TENDER Cohort



Multiple criteria can be present in the same patient. *Prior MV intervention or surgery with remaining device. 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; TENDER = Tendyne European Experience Registry.

FIGURE 4 Clinical and Survival Outcomes in Patients With On-Label Use and "Real-World" Indications for Tendyne Implantation



(A) 30-day and 1-year mortality of the TENDER (Tendyne European Experience Registry) cohort. (B) Reduction in mitral regurgitation from baseline to follow-up. (C) Improvement in functional status according to NYHA functional classification from baseline to 30-day and 1-year follow-up.

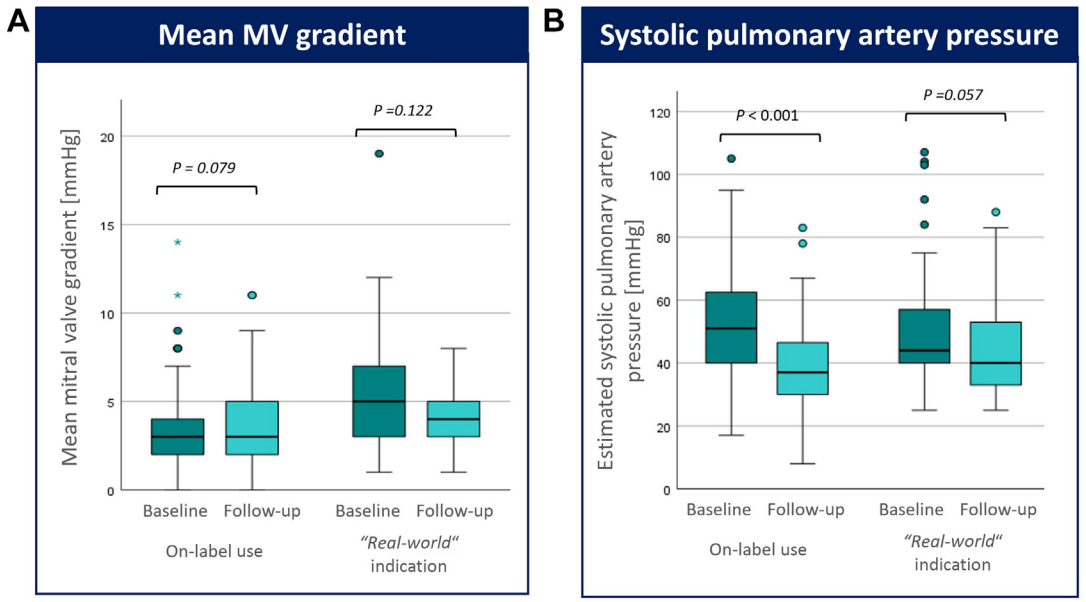
TABLE 5 Paired Comparison of NYHA Functional Class and Echocardiographic Parameters in Patients With On-Label Use and Real-World Indications at Baseline and 1-Year (NYHA Functional Class) or Latest Echocardiographic Follow-Up

	On-Label Use					"Real-World" Indications				
	n	Baseline	Follow-Up	Change	*P* Value	n	Baseline	Follow-Up	Change	*P* Value
NYHA functional class	96				<0.001	41				<0.001
I		1.0	35.4				0	26.8		
II		24.0	43.8				17.1	63.4		
III		65.6	18.8				65.9	9.8		
IV		9.4	2.1				17.1	0		
I or II		25.0	79.2	54.2	<0.001		17.1	90.2	73.2	<0.001
LVEF, %	113	48 (38-56)	48 (36-55)	−1.7 ± 9.9 −1 (−6 to 2)	0.046	54	52 (40-60)	50 (35-55)	−4.3 ± 10.2 −5 (−12 to −2)	0.003
MR severity	130				<0.001	59				<0.001
0		0	83.8				0	71.2		
1+		0	13.8				8.5	27.1		
2+		0	0.8				11.9	1.7		
3+		30.8	1.5				22.0	0		
4+		69.2	0				57.6	0		
Mild or less (≤1+)		0	97.7	97.7	<0.001		8.5	98.3	89.8	<0.001
Mean mitral gradient, mm Hg	114	3 (2-4)	3 (2-5)	0.3 ± 2.8 1 (−1 to 2)	0.079	53	5 (3-7)	4 (3-5)	−1.0 ± 3.6 −1 (−2 to 2)	0.122
>5 mm Hg	114	9.6	14.0	4.4	0.275	53	41.5	22.6	−18.9	0.033
TR grade	113				0.071	53				0.082
0		4.4	8.0				1.9	5.7		
1+		42.5	43.4				37.7	37.7		
2+		32.7	33.6				32.1	39.6		
3+		13.3	10.6				15.1	9.4		
4+		6.2	3.5				11.3	5.7		
5+		0.9	0.9				1.9	1.9		
Less than severe (<3/5)		79.6	85.0	5.3	0.157		71.7	83.0	11.3	0.083
sPAP (estimated), mm Hg	84	51 (40-63)	37 (30-47)	−13.6 ± 17.8 −13 (−25 to −1)	<0.001	45	44 (40-57)	40 (33-53)	−6.8 ± 22.5 −4 (−13 − 5)	0.057

Values are %, median (Q1-Q3), or mean ± SD. NYHA functional class was assessed at 1-year follow-up. Echocardiographic parameters are from latest echocardiographic follow-up (median follow-up time to echocardiography 272 days; Q1-Q3: 43-383 days).

Abbreviations as in Tables 1 and 4.

FIGURE 5 **Mitral Valve Gradient and Secondary Right Heart Outcomes in Patients With On-Label Use and "Real-World" Indications for Tendyne Implantation**



(A) Mean mitral valve gradient at baseline and follow-up. (B) Decrease in systolic pulmonary pressure from baseline to follow-up.

Among the 20 patients with severe MAC, all-cause 30-day mortality was 10.0% (n = 2 of 20), and all-cause 1-year mortality was 21.1% (n = 4 of 19, 1 lost to follow-up). Cardiovascular mortality at 30 days and 1 year (2 patients were lost to follow-up) was 0%. Periprocedural device retrieval was necessary in 2 patients because of incomplete unfolding and device migration. There was no intraprocedural need for conversion to open heart surgery. Periprocedural and 1-year outcomes regarding disabling stroke, valve migration, MV reintervention or surgery, and paravalvular leak more than mild did not differ from patients without severe MAC.

DISCUSSION

This is the largest investigator-initiated retrospective multicenter TMVR registry recording the use of Tendyne TMVR in a real-world scenario. The main findings can be summarized as follows: 1) TMVR is a feasible treatment option in high-risk patients with adequate procedural safety, and TMVR decreases MR with low transvalvular gradients; 2) there was a significant and sustained improvement in functional status at 1 year; 3) there was a similar 1-year mortality rate compared with previously reported TMVR cohorts[6,7,19]; and 4) outcomes were comparable between patients treated with "real-world" TMVR indications and those with on-label indications.

The TENDER registry comprises fewer selected patients who were excluded from the early feasibility trial because of severe MAC, prior MV surgery or intervention with remaining device, a severe dilated left ventricle, predominant MV stenosis with MR ≤2+, severe LV dysfunction, and primary MR with a small left ventricle.[5-7] These real-world anatomies account for 31% of the TENDER cohort.

Severe MAC is a frequently prohibitive condition for surgical therapy because of common significant comorbidities and technically difficult suture-based fixation leading to paravalvular regurgitation or fatal atrioventricular groove disruption.[20] With the pioneering off-label use of balloon-expandable prostheses in patients with MAC,[11] there are now promising data available for the dedicated Tendyne TMVR device. Sorajja et al[9] reported acute procedural success with no residual MR in all 9 enrolled patients, durable amelioration of MR in all patients, and no cardiovascular death at 1 year. In the study by Gössl et al[10] including 20 patients with severe MAC and MR, all-cause mortality at 30 days and 1 year was 5% and 40%, respectively, and the rate for heart failure rehospitalization was 30%. These patients were treated either on a compassionate-use basis or as part

TABLE 6 Comparison of TENDER and Initial Feasibility Study

	Tendyne Feasibility Study[6,7] (n = 100)	TENDER 1-Year Outcome (n = 195)
Age, y	75 ± 8	76 ± 8
Male	69	60
STS PROM, %	7.8 ± 5.7	6.7 ± 4.4
Coronary artery disease	74	57
Previous CABG	47	25
Previous MV intervention/surgery	0	18
NYHA functional class III/IV	66	81
LVEF ≤30%	0	4
MR ≥3+	99	94
Severe TR	0	23
sPAP (estimated), mm Hg	44 ± 11	51 ± 18
Severe MAC	0	10
Secondary/mixed MR	89	59
30-d all-cause mortality	6	9
30-d cardiovascular mortality	4	7
1-y all-cause mortality	26	29
1-y cardiovascular mortality	22	17
1-y PVL	8	5
1-y HF hospitalization	31	25
1-y disabling stroke	3	4
1-y MV reintervention	6	5
1-y valve thrombosis	6	3
1-y NYHA functional class I/II	89	83
1-y MR ≤1+	100	98

Values are % or mean ± SD.

PVL = paravalvular leak; TENDER = Tendyne European Experience Registry; other abbreviations as in Table 1.

of the feasibility study of Tendyne in MAC (NCT03539458). Promisingly, there was no prosthetic dysfunction, and MR remained absent in all patients at 1 year.

In the present study, we included 20 patients with severe MAC, accounting for 10.3% of the cohort. Although presumed to be at risk for a higher rate of complications, these patients were similar in terms of mortality and residual regurgitation. There was only 1 case of intraprocedural device migration and 1 case with incomplete device stent unfolding, both of which could be solved by interventional retrieval of the device without conversion to open heart surgery. Compared with the study by Gössl et al,[10] all-cause 1-year mortality (22% vs 40%) and the rate of rehospitalization (17% vs 30%) was lower in the present analysis and did not significantly differ from patients without MAC in the TENDER cohort.

The present investigation demonstrates that TMVR allows safe and durable treatment in patients with both strict on-label indications and "real-world" indications. The global feasibility study, including 100 patients with on-label Tendyne indications according to the IFU, showed similar cardiovascular and all-cause mortality rates at 30 days (4% and 6%, respectively) and 1 year (22% and 26%, respectively) as observed in the present analysis.[5,7] Important baseline characteristics and 1-year outcome data of TENDER and the global feasibility study are compared in Table 6. In terms of baseline characteristics, the feasibility study included a more male-predominant cohort (69%), with a similar age (75 ± 8 years vs 76 ± 8 years) and high surgical risk profile (mean STS PROM 7.8% ± 5.7% vs 6.7% ± 4.4%). The TENDER registry included more symptomatic patients (NYHA functional class III or IV in 81% vs 66%). Patients with common conditions such as prior aortic valve surgery, severe TR, and severe pulmonary hypertension were not represented in the feasibility study. The TENDER registry included almost 4 times more patients with primary MR compared with the feasibility study (41% vs 11%). This trend has been accelerated by a larger MAC cohort and the later availability of low-profile Tendyne valves.

TMVR is an emerging field offering an alternative therapeutic option for an unmet need in patients with severe symptomatic MR when transcatheter MV repair is not feasible or is suboptimal because of anatomical constrains.[1,4,21] In terms of clinical benefit, we observed a significant reduction in MR and, likewise, sustained improvement in functional capacity according to NYHA functional classification at 1-year follow-up (Central Illustration). We observed a significant reduction for heart failure hospitalization during the first postprocedural year compared with the year prior to TMVR. The clear improvement in the patients' clinical situation is in line with previous findings demonstrating that TMVR is a valid option for this challenging patient group.[6,7,19] The CHOICE-MI registry investigated the outcomes of patients undergoing screening for TMVR because of ineligibility for standard treatment. Among 746 retrospectively included patients, 31% underwent TMVR using 10 different dedicated MV prostheses. The recently published 1-year data showed promising results for the TMVR approach. Mortality at 30 days was 9.6%, and all-cause mortality at 1 year was 28.1%, comparable with the results of the TENDER trial follow-up.[19] Valve thrombosis after TMVR remained low at 3% compared with 6% in previous studies.[7] This may be related to high use of oral anticoagulation.

STUDY LIMITATIONS. The nature of these prospectively collected data with retrospective single-treatment arm analysis has some inherent

limitations. There was no echocardiography or computed tomography core laboratory, and patients were selected for TMVR on the basis of local heart team decisions. All computed tomographic and echocardiographic scans were, however, centrally reviewed by the industry product specialists prior to each intervention.

Optimal medical treatment regarding heart failure and anticoagulation regime were executed at high-volume centers with real-world guideline adherence. Follow-up of patients regarding mortality was almost complete, but registry limitations in the rate of echocardiography and functional outcome documentation apply. Additionally, TENDER is an observational registry, and the findings from this cohort need to be confirmed in adequately powered trials.

CONCLUSIONS

This large real-world analysis shows a similar 1-year mortality rate and a lower cardiovascular mortality rate compared with previous studies. We observed a durable clinical benefit and significant elimination of MR, with MR ≤1+ in 98% of patients at 1 year. Our cohort for the first time demonstrates no differences in survival, outcomes, or major adverse events between patients treated with strict on-label IFU indications compared with "real-world" indications for TMVR, considered by local heart teams in selected patients without other treatment options. Accordingly, the present findings imply that TMVR using the Tendyne device might offer safe and efficacious treatment strategies for patients who cannot be treated with MV surgery or mitral transcatheter edge-to-edge repair in daily clinical practice.

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PERSPECTIVES

WHAT IS KNOWN? Early Tendyne TMVR trials showed promising results but were limited to early operator experience in a small selective cohort excluding patients with severe MAC, prior MV treatment, and other exclusion criteria.

WHAT IS NEW? Transapical TMVR achieves a sustained and significant elimination of MR and clinical benefit with a feasible safety profile for both on-label and "real-world" indications. This applies for both primary and secondary MR in native anatomy, including patients with severe mitral annular calcification and after previous MV treatment.

WHAT IS NEXT? The encouraging results observed in the TENDER registry up to 1 year support the extended use of a dedicated MV prosthesis in more real-world anatomies, potentially to be supported by the upcoming single-arm trials of TMVR in MAC.

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KEY WORDS mitral annular calcification, mitral regurgitation, mitral valve, transcatheter mitral valve replacement

APPENDIX For a list of TENDER registry investigators, a supplemental table, and a supplemental figure, please see the online version of this paper.