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STRUCTURAL

Impact of Transcatheter Edge-to-Edge Mitral Valve Repair on Guideline-Directed Medical Therapy Uptitration

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ABSTRACT

BACKGROUND Guideline-directed medical therapy (GDMT) optimization is mandatory before transcatheter edge-to-edge mitral valve repair (M-TEER) in patients with secondary mitral regurgitation (SMR) and heart failure (HF) with reduced ejection fraction (HFrEF). However, the effect of M-TEER on GDMT is unknown.

OBJECTIVES The authors sought to evaluate frequency, prognostic implications and predictors of GDMT uptitration after M-TEER in patients with SMR and HFrEF.

METHODS This is a retrospective analysis of prospectively collected data from the EuroSMR Registry. The primary events were all-cause death and the composite of all-cause death or HF hospitalization.

RESULTS Among the 1,641 EuroSMR patients, 810 had full datasets regarding GDMT and were included in this study. GDMT uptitration occurred in 307 patients (38%) after M-TEER. Proportion of patients receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists was 78%, 89%, and 62% before M-TEER and 84%, 91%, and 66% 6 months after M-TEER (all $P < 0.001$). Patients with GDMT uptitration had a lower risk of all-cause death (adjusted HR: 0.62; 95% CI: 0.41-0.93; $P = 0.020$) and of all-cause death or HF hospitalization (adjusted HR: 0.54; 95% CI: 0.38-0.76; $P < 0.001$) compared with those without. Degree of MR reduction between baseline and 6-month follow-up was an independent predictor of GDMT uptitration after M-TEER (adjusted OR: 1.71; 95% CI: 1.08-2.71; $P = 0.022$).

CONCLUSIONS GDMT uptitration after M-TEER occurred in a considerable proportion of patients with SMR and HFrEF and is independently associated with lower rates for mortality and HF hospitalizations. A greater decrease in MR was associated with increased likelihood for GDMT uptitration. (J Am Coll Cardiol Intv 2023;16:896-905) © 2023 by the American College of Cardiology Foundation.

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Secondary mitral regurgitation (SMR) is the most frequent valvular heart disease in patients with heart failure (HF) with reduced ejection fraction (HFrEF) and is associated with unfavorable outcomes.[1-3] COAPT (Cardiovascular Outcomes Assessment of the MitraClip in Patients with Heart Failure and Secondary Mitral Regurgitation) was the first prospective randomized trial demonstrating the symptomatic and prognostic benefit of transcatheter edge-to-edge mitral valve repair (M-TEER) in patients with chronic HFrEF.[4,5] Current European Society of Cardiology guidelines on the management of patients with HF recommend that M-TEER should be considered (Class IIa recommendation, Level of Evidence: B) in patients with characteristics similar to those of the patients enrolled in COAPT.[6] Notwithstanding, these patients must also undergo optimization of guideline-directed medical therapy (GDMT) before the evaluation for M-TEER.[6] Indeed, GDMT may improve mitral regurgitation (MR) severity in up to 40% of patients with HFrEF, whereas persistence of SMR despite GDMT is associated with an almost 2-fold increased relative risk of HF hospitalization or mortality.[7,8]

Recent registries have confirmed that GDMT is still underused and underdosed in a high percentage of patients with HFrEF, and this likely has an impact on clinical outcomes.[1,9-13] Hypotension and renal dysfunction are major causes of undertreatment of HFrEF patients.[13-15] It can be hypothesized that M-TEER, increasing systemic cardiac output, may improve hemodynamics with beneficial effects on blood pressure and renal function, which may enable to optimize GDMT.[14] In COAPT, administration of stable maximal doses of GDMT was a major inclusion criterion, but a further slight increase in GDMT doses occurred in the device group.[4] However, data on GDMT and outcomes may differ in routine clinical practice, and no data are available from observational prospective studies to date, to our knowledge.

Thus, the aim of this study was to investigate frequency and prognostic implications of GDMT uptitration after M-TEER in a large, real-world, unselected group of patients with SMR and HFrEF enrolled at 11 high-volume European centers and included in EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation; German Clinical Trials Register; DRKS00017428).[16]

METHODS

STUDY POPULATION. This is a retrospective analysis of prospectively collected data on patients with SMR who underwent M-TEER between November 2008 and January 2021 at 11 high-volume European centers included in the EuroSMR Registry. Patients received GDMT according to local judgment and expertise, and were considered eligible for M-TEER after a multidisciplinary heart team discussion. All patients gave their consent after explanation of the benefits and risks of the procedure. The study complied with the Declaration of Helsinki and was performed with the approval of local ethical committees. For the purpose of this analysis, only patients with HFrEF (left ventricular ejection fraction ≤40%) and complete data regarding GDMT at both baseline and 6-month follow-up were included.

GUIDELINE-DIRECTED MEDICAL THERAPY. Among patients with complete medication data at baseline and at 6-month follow-up, the following 3 drug classes were examined: 1) angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI); 2) beta-blockers; and 3) mineralocorticoid receptor antagonist (MRA). Of note, sodium-glucose cotransporter 2 inhibitors (SGLT2i) were not routinely implemented in clinical practice during the study period. Patients were stratified according to presence of GDMT uptitration, which was defined as initiation of a new HF drug class and/or increase in dose of at least 1 drug class previously prescribed without down-titration of any other drug class.

Further outcome analyses were performed stratifying the population in patients with up-titrated vs

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

M-TEER = transcatheter edge-to-edge mitral valve repair

MR = mitral regurgitation

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

SMR = secondary mitral regurgitation

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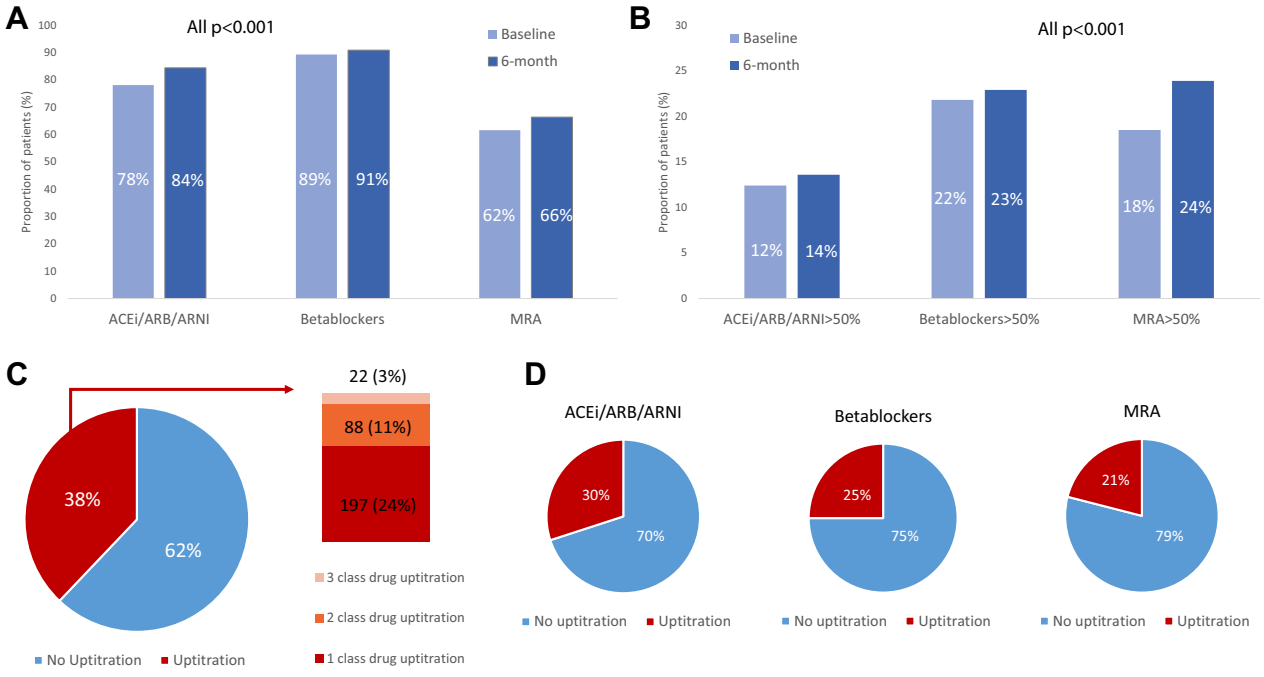
FIGURE 1 Changes in GDMT After M-TEER



Proportion of patients receiving angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonist (MRA) at baseline and 6 months after transcatheter edge-to-edge mitral valve repair (M-TEER) **(A)**. Proportion of patients receiving >50% of ACEi/ARB/ARNI, beta-blockers, and MRA doses at baseline and 6 months after M-TEER **(B)**. Proportion of patients undergoing uptitration or not uptitration of guideline-directed medical therapy (GDMT) 6 months after M-TEER. Among patients undergoing GDMT uptitration the rate of those receiving uptitration of 1, 2, or 3 drugs is reported **(C)**. Proportion of patients undergoing uptitration of ACEi/ARB/ARNI, beta-blockers and MRA 6 months after M-TEER **(D)**.

unchanged vs down-titrated dose of GDMT after M-TEER. Moreover, for each drug class, patient stratification in uptitration vs non-uptitration was explored. Drug doses were measured as percentage of the target dose recommended in current guidelines.[6,17] Accordingly, patients were also stratified into 5 groups as follows: not receiving medication, receiving ≤25%, 26% to 50%, 51% to 75%, and 76% to 100% of the guidelines-recommended target dose.

DATA COLLECTION AND OUTCOMES. Demographic, clinical, laboratory, and echocardiographic data were entered into a dedicated database using anonymized datasets. Six-month follow-up was performed at each site by clinical visits and included vital status, HF hospitalization, medications, symptoms assessed by New York Heart Association (NYHA) functional class, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement, as clinically indicated. Longer follow-ups were evaluated by clinical visits, phone calls, or hospital and civil record assessment, and included vital status and HF hospitalization.

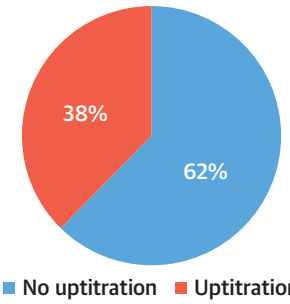
Outcomes of interest were all-cause mortality and the composite of all-cause mortality or HF hospitalization assessed at 3 years.

STATISTICAL ANALYSIS. Normal distribution of continuous variables was explored through the Shapiro-Wilk test. Continuous variables were presented as mean ± SD when normally distributed, and as median (IQR) when non-normally distributed. Categorical variables were presented as counts and percentages. To compare groups, unpaired Student's *t*-test or Mann-Whitney *U* test for continuous variables and the chi-square or Fisher exact tests for categorical variables were used, as appropriate.

Cumulative event-free survival estimates were obtained using the Kaplan-Meier method and compared with the log-rank test. The proportionality

CENTRAL ILLUSTRATION **Prevalence, Predictors, and Impact on Outcomes of Guideline-Directed Medical Therapy Uptitration After Mitral Transcatheter Edge-to-Edge Repair**

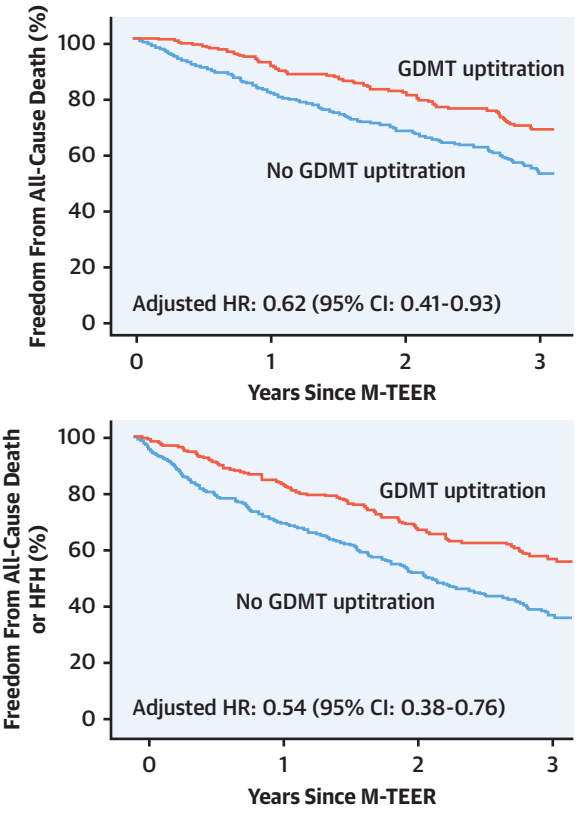
GDMT Uptitration After M-TEER



Predictors of GDMT Uptitration

Variables*	OR (95% CI)	*P* Value
NT-proBNP	1.16 (0.56-2.41)	0.695
Systolic pulmonary artery pressure	0.99 (0.97-1.02)	0.513
Previous myocardial infarction	0.81 (0.38-1.75)	0.593
Mean arterial blood pressure	1.00 (0.98-1.02)	0.868
Glomerular filtration rate	1.01 (0.99-1.02)	0.280
MR reduction of at least 3 grades	1.71 (1.08-2.71)	0.022
NYHA improvement (≥1 class)	0.66 (0.35-1.25)	0.200

Association Between GDMT Uptitration and Outcomes



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Prevalence of guideline-directed medical therapy (GDMT) uptitration, predictors of GDMT uptitration, and 3-year all-cause death as well as all-cause death or heart failure hospitalization (HFH) in patients undergoing GDMT uptitration as compared with those who did not, were reported. *N-terminal pro-B-type natriuretic peptide (NT-proBNP), systolic pulmonary artery pressure, mean arterial blood pressure, and glomerular filtration rate are intended as 1% increase. MR = mitral regurgitation; M-TEER = mitral transcatheter edge-to-edge repair; NYHA = New York Heart Association.

assumptions were checked by visual estimation after plotting the log cumulative hazard vs (log) time at follow-up after the index procedure and by applying a test for nonproportional hazards using Schoenfeld residuals, which failed to reject the null hypothesis that the clinical endpoint was affected by time. Univariable Cox regression analysis was used to evaluate associations between baseline characteristics and study outcomes. Variables with *P* values <0.05 in univariable logistic regression for outcomes and with missing data <10% were entered into the multivariable Cox model. The multivariable model included age, previous myocardial infarction, glomerular filtration rate, log NT-proBNP and TAPSE (tricuspid annular plane systolic excursion) at baseline and postprocedural MR. To investigate independent predictors of GDMT uptitration at 6-month follow-up after M-TEER, a hierarchical logistic regression model was constructed. All variables significantly associated with GDMT uptitration at univariable analysis were entered into this multivariable model. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software, version 21 (IBM Corp).

RESULTS

During the study period, a total of 1,641 patients underwent M-TEER for SMR, 1,159 of whom had HFrEF. After excluding patients without data regarding

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TABLE 1 Baseline Characteristics by Uptitration of GDMT

	All (N = 810)	No Uptitration (n = 503)	Uptitration (n = 307)	*P* Value
Clinical characteristics				
Age, y,	71.6 ± 10.2	71.6 ± 10.3	71.5 ± 10.4	0.821
Male	583 (72)	376 (75)	207 (67)	0.022
BMI, kg/m^2	26.4 ± 4.7	26.4 ± 4.6	26.4 ± 4.8	0.901
Mean arterial blood pressure, mm Hg	90 ± 17	88 ± 16	93 ± 19	0.001
Ischemic etiology	419 (55)	269 (56)	150 (54)	0.621
Previous myocardial infarction	263 (33)	179 (36)	84 (28)	0.018
Diabetes	266 (35)	167 (35)	99 (34)	0.704
Hypertension	506 (67)	319 (68)	187 (66)	0.640
Previous stroke	78 (10)	54 (11)	24 (8)	0.169
COPD	116 (14)	69 (14)	47 (15)	0.540
History of atrial fibrillation	478 (59)	298 (59)	180 (59)	0.734
Previous ICD	151 (31)	100 (31)	51 (29)	0.611
Previous CRT	219 (28)	149 (31)	70 (24)	0.052
Loop diuretic dose, mg	25 (10-50)	30 (15-60)	20 (10-40)	0.002
NYHA functional class I, II, III, IV	1, 94, 524, 187 (0, 12, 65, 23)	1, 56, 314, 129 (0, 11, 63, 26)	0, 38, 210, 58 (0, 12, 69, 19)	0.128
Laboratory findings				
GFR, mL/min/1.73 m^2	50 ± 23	48 ± 23	52 ± 23	0.017
Creatinine, mg/dL	1.2 (1.0-2.0)	1.4 (1.0-2.0)	1.1 (1.0-1.5)	0.022
NT-proBNP, ng/L	3,500 (1,794-7,362)	3,549 (1,831-8,284)	3,411 (1,578-6,599)	0.136
Urea, mg/dL	63 ± 49	66 ± 40	59 ± 50	0.093
Hemoglobin, g/dL	12.7 ± 2.0	12.6 ± 2.2	12.8 ± 1.7	0.496
Echocardiographic findings				
LVEDV, mL	204 ± 77	206 ± 78	200 ± 77	0.319
LVESV, mL	146 ± 64	148 ± 64	142 ± 63	0.285
LVEDD, mm	61 ± 20	61 ± 19	60 ± 20	0.477
LVESD, mm	51 ± 26	52 ± 31	49 ± 18	0.282
LVEF, %	29 ± 7	28 ± 7	29 ± 7	0.194
LAVI, mL/m^2	61 ± 29	62 ± 30	62 ± 28	0.844
TR grade 0-1, 2, 3-4	362, 288, 137 (46, 37, 17)	219, 175, 94 (45, 36, 19)	143, 113, 43 (48, 38, 14)	0.215
MR VC, mm	6.0 ± 2.8	6.0 ± 2.6	6.0 ± 3.1	0.985
MR EROA, cm^2	0.32 ± 0.20	0.33 ± 0.22	0.30 ± 0.15	0.092
MR RV, mL	42 ± 21	43 ± 21	42 ± 22	0.674
RVEDD (mid), mm	37 (31-42)	37 (31-43)	35 (30-41)	0.043
TAPSE, mm	16.9 ± 4.6	16.8 ± 4.6	17.0 ± 4.7	0.657
sPAP, mm Hg	46 (38-56)	47 (38-58)	45 (35-54)	0.018

Values are mean ± SD, n (%), or median (IQR).

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LAVI = left atrial volume indexed; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR EROA = mitral regurgitation effective orifice regurgitant area; MR RV = mitral regurgitation regurgitant volume; MR VC = mitral regurgitation vena contracta; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RVEDD = right ventricular end diastolic diameter; sPAP = systolic pulmonary artery pression; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

GDMT at both baseline and 6-month follow-up, 810 patients were finally included into this analysis (Supplemental Figure 1). Before M-TEER, 798 patients (98.5%) received GDMT, of whom 633 (78%) received ACE inhibitor/ARB/ARNI, 723 (89%) beta-blockers, and 499 (62%) MRA (**Figure 1A**). GDMT was largely underdosed with >50% target doses of ACE inhibitor/ARB/ARNI, beta-blockers, and MRA administered to only 12.4%, 21.8%, and 18.5% of the patients, respectively (**Figure 1B**, Supplemental Figure 2). At 6-month follow-up after M-TEER, 307 patients (38%) underwent GDMT uptitration, and 503 (62%) did not **Central Illustration**). The rate of patients receiving ACE inhibitor/ARB/ARNI, beta-blockers, and/or MRA increased compared with baseline (**Figure 1A**) as well as that of patients receiving 3 HF drug classes (47% at baseline and 51% at 6-month follow-up; $P < 0.001$) conversely to those receiving 1 HF drug class (14% at baseline and 10% at 6-month follow-up; $P < 0.001$) or 2 HF drug classes (38% at baseline and 37% at 6-month follow-up; $P = 0.010$). The proportion of patients on >50% target doses of ACE inhibitor/ARB/ARNI, beta-blockers, and MRA after M-TEER remained low, though increased compared with baseline (**Figure 1B**, Supplemental Figure 2).

Most of the patients undergoing uptitration of 1 drug class after M-TEER (**Figure 1C**). Rates of uptitration were 30.1% for ACE inhibitor/ARB/ARNI,

TABLE 2 Short-Term Outcomes by Uptitration of GDMT

	All (N = 810)	No Uptitration (n = 503)	Uptitration (n = 307)	*P* Value
NYHA functional class I, II, III, IV	122, 275, 181, 41 (20, 44, 29, 7)	50, 159, 111, 27 (14, 46, 32, 8)	72, 116, 70, 14 (26, 43, 26, 5)	0.002
Delta NYHA, improved >1 class, 0-1 class change, worsened	155, 419, 45 (25, 68, 7)	74, 241, 32 (21, 69, 9)	81, 178, 13 (30, 65, 5)	0.012
Loop diuretic dose, mg	25 (10 to 60)	30 (15 to 75)	20 (10 to 50)	0.001
Changes in diuretic dose	0 (−10 to 10)	0 (−5 to 5)	0 (−10 to 11.3)	0.747
NT-proBNP, ng/L	2,158 (937 to 5,580)	2,493 (1,090 to 6,025)	1,793 (717 to 4,599)	0.035
Changes in NT-proBNP, ng/L	−255 (−1,729 to 398)	−156 (−1,273 to 792)	−406 (−2,531 to +199)	0.043
MR degree 0-1, 2, 3-4	203, 156, 59 (49, 37, 14)	104, 91, 40 (44, 39, 17)	99, 65, 19 (54, 36, 10)	0.062
MR degree 0-1, 2-4	203, 2015 (49, 51)	104, 131 (44, 56)	99, 84 (54, 46)	0.046
Changes in MR 0-1 vs 2 vs 3-4	162, 180, 77 (39, 43, 18)	100, 103, 33 (42, 44, 14)	62, 77, 44 (34, 42, 24)	0.022

Values are n (%) or median (IQR).
MR = mitral regurgitation; other abbreviations as in Table 1.

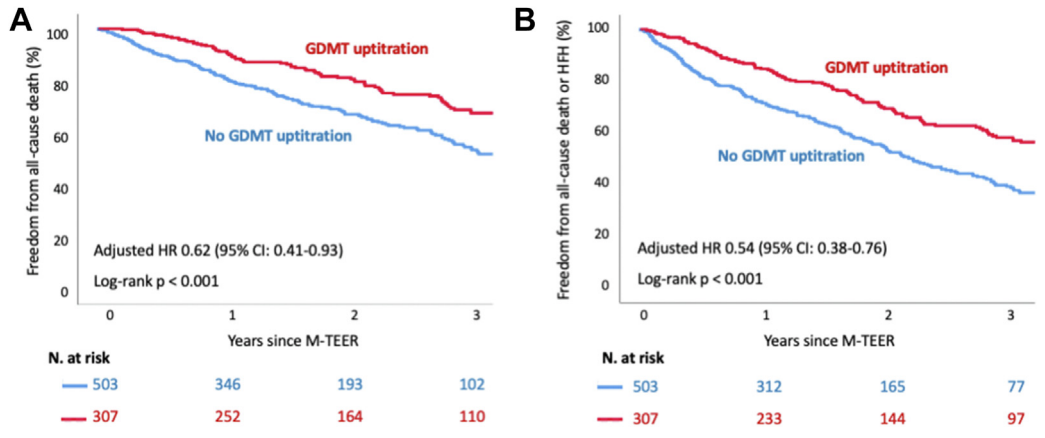
24.8% for beta-blockers, and 20.7% for MRA (Figure 1D).

BASELINE CHARACTERISTICS. Demographic, clinical, and baseline echocardiographic characteristics of the study population stratified according to GDMT uptitration after M-TEER are shown in Table 1. Patients who had GDMT uptitration after M-TEER were less likely to be males and to have a history of previous myocardial infarction. They also received lower doses of diuretic agents and had higher mean arterial blood pressure, better renal function, smaller right ventricular dimensions, and lower systolic pulmonary artery pressure at baseline.

OUTCOMES. From baseline to 6-month follow-up after M-TEER, a greater decrease in MR severity (3 or 4 degree vs 2, 1, or 0 degree), NYHA functional class, and NT-proBNP were observed in patients with vs those without GDMT uptitration in the absence of significant changes in diuretic dosage (Table 2).

At a median follow-up of 644 (364-1,127) days, 294 patients (36.3%) died and 195 (24.1%) were hospitalized for HF. All-cause death-free survival and all-cause death or HF hospitalization-free survival at 3-year follow-up was higher in patients with uptitration of GDMT after M-TEER compared with those without (67.7% vs 53.7%; log rank $P < 0.001$; and 57.1% vs 37.9%; log rank $P < 0.001$, respectively)

FIGURE 2 Kaplan-Meier Estimated Survival Rates by GDMT Uptitration After M-TEER



Kaplan-Meier curves of freedom from all-cause death at 3-year follow-up stratified by GDMT uptitration 6 months after M-TEER and adjusted relative risk of 3-year all-cause death **(A)**. Kaplan-Meier curves of freedom from all-cause death or heart failure hospitalization (HFH) at 3-year follow-up stratified by GDMT uptitration 6 months after M-TEER and adjusted relative risk of 3-year all-cause death or heart failure hospitalization **(B)**. Abbreviations as in Figure 1.

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TABLE 3 Multivariable Binary Logistic Regression Analysis for the Variables Associated With 6-Month GDMT Uptitration

	OR (95% CI)	*P* Value
Log NT-proBNP at baseline, 1% increase	1.16 (0.56-2.41)	0.695
Systolic pulmonary artery pressure, 1% increase	0.99 (0.97-1.02)	0.513
Previous myocardial infarction, 1% increase	0.81 (0.38-1.75)	0.593
Mean arterial blood pressure, 1% increase	1.00 (0.98-1.02)	0.868
Glomerular filtration rate, 1% increase	1.01 (0.99-1.02)	0.280
Mitral regurgitation improvement, 3 vs <3 grades	1.71 (1.08-2.71)	0.022
NYHA functional class improvement, 1 vs <1 class	0.66 (0.35-1.25)	0.200

All the variables included were significantly associated with GDMT uptitration at univariate analysis.

Abbreviations as in Table 1.

(Figure 2, Central Illustration). The lower risk of all-cause death and the composite endpoint in patients with uptitration of GDMT remained significant after adjustment for other variables at multivariable analysis (adjusted HR: 0.62; 95% CI: 0.41-0.93; $P = 0.020$ and adjusted HR: 0.54; 95% CI: 0.38-0.76; $P < 0.001$ for each event, respectively) (Figure 2, Supplemental Table 1). No differences in outcomes were noted between the patients who had GDMT down-titration vs those in whom GDMT dose remained unchanged, whereas the outcomes of both groups were worse compared with patients in whom GDMT uptitration was observed (Supplemental Figure 3). When patients were subdivided according to the class of drugs, ACE inhibitor/ARB/ARNI uptitration was associated with a significant benefit in reducing clinical events after M-TEER, whereas beta-blockers and MRA dose changes did not (Supplemental Figure 4). Of note, there were no differences in outcomes stratified by GDMT uptitration and according to site of enrolment after adjustment for possible confounders.

FACTORS ASSOCIATED WITH GDMT OPTIMIZATION. Degree of MR reduction (3 or 4 degrees vs <3 degrees) from baseline to 6-month follow-up was the only variable independently associated with the likelihood of GDMT uptitration after M-TEER (adjusted OR: 1.71; 95% CI: 1.08-2.71; $P = 0.022$) (Table 3, Central Illustration).

DISCUSSION

The main findings of this analysis of EuroSMR, the largest observational study of M-TEER in patients with SMR, are the following: 1) more than one-third of patients undergoing M-TEER underwent uptitration of GDMT after M-TEER, which consisted of the initiation or increase in dose of either ACE inhibitor/ARB/ARNI and/or beta-blockers and/or MRA after the procedure; 2) uptitration of GDMT after M-TEER was independently associated with a lower risk of all-cause death and of all-cause death or HF hospitalization; and 3) a reduction of at least 3 MR grades was the strongest factor associated with GDMT uptitration after M-TEER.

INCIDENCE OF GDMT OPTIMIZATION AFTER M-TEER. Current guidelines recommend optimization of GDMT before M-TEER.[6,17-19] Several studies showed that SMR may dynamically change after implementation of GDMT.[7,8,20-24] In this real-world EuroSMR cohort, the large majority of patients received GDMT before M-TEER, with 78%, 89%, and 62% patients on ACE inhibitor/ARB/ARNI, beta-blockers and MRA, respectively. However, only a minority of the patients received ≥50% of target doses of GDMT: 12.4% for ACE inhibitor/ARB/ARNI, 21.8% for beta-blockers, and 18.5% for MRA, respectively. These percentages are in line with those reported in a smaller Italian cohort.[25] Similar percentages of patients treated with each class of GDMT were also described in the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT trials, but without further information on different dosages.[4,26] These data are also consistent with the proportion of patients receiving GDMT and the doses administered in recent registries in patients with HFrEF.[1,9,12-14]

We observed a 38% incidence of GDMT initiation or uptitration of at least 1 evidence-based HF drug class, namely ACE inhibitor/ARB/ARNI, beta-blockers, and MRA, at 6-month follow-up after M-TEER. This rate was significantly higher compared with that observed in COAPT, where GDMT optimization within 1 year after M-TEER was noted in <10% of patients for each drug class. In COAPT, optimization of GDMT was mandated before patients' randomization and this may have decreased the likelihood of additional changes during follow-up.[4] In MITRA-FR, no information regarding changes in GDMT was reported during the follow-up.[26] However, our results are in line with a previous small study (N = 121) reporting that 34% of HFrEF patients with significant secondary MR (≥3+) undergoing M-TEER up-titrated GDMT at a median of 4 months after the procedure.[25]

In the present study, patients undergoing GDMT uptitration after M-TEER had lower pulmonary artery pressure, smaller right ventricular dimensions, higher mean arterial blood pressure measurements, better renal function, and need for lower diuretic dose

before the procedure, compared with those who did not, consistent with a less advanced stage of HF. Performance of M-TEER earlier in the clinical course of HF was associated with better clinical outcomes also in previous studies, and it might be that GDMT optimization also had a role in these patients.[27-30]

Another interesting finding is that ACE inhibitor/ARB/ARNI was the drug class more likely to be up-titrated. A possible explanation is that blood pressure levels may increase after M-TEER due to an increase in forward systemic cardiac output, allowing improvement in tolerance to ACE inhibitor/ARB/ARNI. Furthermore, in previous studies, M-TEER improved renal function in approximately 30% of patients, and this may allow a further optimization of therapy with ACE inhibitor/ARB/ARNI and/or MRA.[31,32]

UPTITRATION OF GDMT AFTER M-TEER IS ASSOCIATED WITH OUTCOME. Optimization of GDMT is a major goal in the management of HFrEF patients because it improves survival and reduces HF events. Uptitration of GDMT may have further beneficial effects in patients undergoing M-TEER, because left ventricular reverse remodeling induced M-TEER plus neurohormonal antagonists could lead to a better stabilization of mitral valve apparatus, adaptation of mitral valve clips and prevention of MR recurrence that is known to be associated with unfavorable outcome.[33]

This is the first large multicenter study evaluating changes in GDMT after M-TEER. Our results are consistent with the smaller study by Stolfo at al,[25] who described a 2.8-fold higher risk of death or heart transplantation in HFrEF patients undergoing M-TEER who had down-titration of GDMT at first follow-up, compared with those who had unchanged/up-titrated doses. However, differently from the present data, they also showed a similar outcome between the subgroups of patients with unchanged ($n = 40$) vs up-titrated GDMT ($n = 41$). This discrepancy may be explained by differences of the sample size as well as of the patient characteristics. Those included in the study by Stolfo et al[25] had more advanced HF, as shown by their larger left ventricular dimensions and higher pulmonary pressures, compared with those in the present study.

Notably, in our cohort, the association between GDMT uptitration and clinical events was higher for Consistently, ACE inhibitor/ARB/ARNI compared with other drug classes. ACE inhibitor/ARB, but not beta-blockers or MRA, were recently found to be associated with MR improvement after GDMT optimization in a large cohort of HF patients.[7] Sacubitril/valsartan was also reported as more effective than valsartan alone in reducing MR degree.[21] Finally, moderate or severe MR was recently shown to be a major variable associated with intolerance to ARNI.[15]

ROLE OF REDUCTION OF MR DEGREE. The hypothesis explored in this study is that M-TEER might lead to a further uptitration of GDMT due to improvement in hemodynamic conditions. As a proof of the concept, the extent of MR reduction from baseline to 6-month follow-up was associated with a 72% increased probability of GDMT uptitration after M-TEER independently from other relevant variables such as baseline blood pressure or renal function. Also, the improvement in NYHA functional class and NT-proBNP was greater in patients with vs without GDMT uptitration, despite no changes in diuretic doses.

Previous studies reported the role of CRT in leading to a further GDMT optimization (ie, beta-blockers) in patients with HF and wide QRS.[34,35] Similarly, in our study, MR reduction after M-TEER was associated with uptitration of GDMT in patients with SMR and HFrEF. These data may support the concept of "device therapies enabling medical therapies". Specifically, M-TEER and GDMT may act synergistically in patients with HFrEF rather than reflecting tools to be used at different stages of treatment. In other words, these findings may support an earlier treatment with M-TEER once patients have persisting SMR.

STUDY LIMITATIONS. First, this was a retrospective analysis of a prospective observational registry potentially leading to the common bias of different selection criteria and treatments. GDMT data at baseline and 6-month follow-up were not available in all patients enrolled, and there was not a comparable cohort of patients followed in the same centers not undergoing M-TEER to compare GDMT uptitration in those without M-TEER in a similar time frame. However, all patients underwent M-TEER after optimization of GDMT, and it is unlikely they could have had further changes without M-TEER. In addition, this retrospective analysis yielded the unique opportunity to observe further GDMT uptitration without the bias that may be introduced by a specific protocol design. It is therefore possible that both a reduction in clinical inertia as well as lower rates of hypotension and kidney dysfunction, that is, the major causes of undertreatment of HFrEF patients, caused the observed implementation of GDMT without the chance to assess their relative role with a post hoc analysis. However, the high proportion of patients

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who underwent uptitration of GDMT and its independent association with better outcomes point out that this may be a major mechanism of the effects of successful M-TEER on outcomes. Unfortunately, a possible increase in cardiac output after SMR correction, a major factor enabling GDMT uptitration, can only be speculated because of the lack of data regarding cardiac output or left ventricular function after M-TEER. Finally, SGLT2i could not be considered in the present analysis because it was not indicated for nondiabetic patients with HFrEF at the time of enrolment.

CONCLUSIONS

More than one-third of patients with HFrEF and SMR undergoing M-TEER received GDMT uptitration at 6 months after the procedure. GDMT uptitration after M-TEER was independently associated with a reduced risk of clinical events. Greater decrease in MR severity was a major factor associated with GDMT uptitration after M-TEER.

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PERSPECTIVES

WHAT IS KNOWN? GDMT is recommended before M-TEER because it may improve SMR. However, whether treatment of SMR may enable further GDMT uptitration is unknown.

WHAT IS NEW? Uptitration of GDMT occurred in more than one-third of patients undergoing M-TEER and is associated with better outcomes. Greater decreases in SMR are associated with higher likelihood of GDMT uptitration.

WHAT IS NEXT? Further research is needed to confirm our results and to clarify the mechanisms behind GDMT uptitration after M-TEER.

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APPENDIX For a supplemental table and figures, please see the online version of this paper.