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ORIGINAL RESEARCH

STRUCTURAL

Guideline-Directed Medical Therapy and Survival After TEER for Secondary Mitral Regurgitation With Right Ventricular Impairment

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ABSTRACT

BACKGROUND Right ventricular impairment is common among patients undergoing transcatheter edge-to-edge repair for secondary mitral regurgitation (SMR). Adherence to guideline-directed medical therapy (GDMT) for heart failure is poor in these patients.

OBJECTIVES The aim of this study was to evaluate the impact of GDMT on long-term survival in this patient cohort.

METHODS Within the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) international registry, we selected patients with SMR and right ventricular impairment (tricuspid annular plane systolic excursion ≤17 mm and/or echocardiographic right ventricular-to-pulmonary artery coupling <0.40 mm/mm Hg). Titrated guideline-directed medical therapy ($GDMT_{tit}$) was defined as a coprescription of 3 drug classes with at least one-half of the target dose at the latest follow-up. The primary outcome was all-cause mortality at 6 years.

RESULTS Among 1,213 patients with SMR and right ventricular impairment, 852 had complete data on medical therapy. The 123 patients who were on $GDMT_{tit}$ showed a significantly higher long-term survival vs the 729 patients not on $GDMT_{tit}$ (61.8% vs 36.0%; $P < 0.00001$). Propensity score–matched analysis confirmed a significant association between $GDMT_{tit}$ and higher survival (61.0% vs 43.1%; $P = 0.018$). $GDMT_{tit}$ was an independent predictor of all-cause mortality (HR: 0.61; 95% CI: 0.39-0.93; $P = 0.02$ for patients on $GDMT_{tit}$ vs those not on $GDMT_{tit}$). Its association with better outcomes was confirmed among all subgroups analyzed.

CONCLUSIONS In patients with right ventricular impairment undergoing transcatheter edge-to-edge repair for SMR, titration of GDMT to at least one-half of the target dose is associated with a 40% lower risk of all-cause death up to 6 years and should be pursued independent of comorbidities. (J Am Coll Cardiol Intv 2024;17:1455–1466) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor neprilysin inhibitor

BB = beta-blocker

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

GDMT = guideline-directed medical therapy

$GDMT_{tit}$ = titrated guideline-directed medical therapy

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

MRA = mineralocorticoid receptor antagonist

RV = right ventricular

RVI = right ventricular impairment

RVPAc = right ventricular-to-pulmonary artery coupling

SMR = secondary mitral regurgitation

sPAP = systolic pulmonary artery pressure

TAPSE = tricuspid annular plane systolic excursion

TEER = transcatheter edge-to-edge repair

Secondary mitral regurgitation (SMR) affects about one-third of heart failure (HF) patients, worsening their prognosis.[1] Transcatheter edge-to-edge repair (TEER) is a therapeutic option with significant prognostic benefit in selected subgroups of patients.[2-4] However, the long-term mortality of SMR patients undergoing TEER remains poor.[5] Several echocardiographic parameters predict outcomes after TEER for SMR.[6,7] The ratio of tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure (sPAP) at echocardiography, a proven noninvasive surrogate of right ventricular-to-pulmonary artery coupling (RVPAc),[8] has prognostic value in various HF types[9] and after TEER for SMR.[7,10,11] Because a reduction in TAPSE/sPAP may occur in the presence of normal TAPSE and vice versa, the presence of an abnormality in either index may indicate the presence of right ventricular impairment (RVI). Patients with SMR and RVI are under-represented in clinical trials,[3,4] and their management is particularly challenging.[12]

Guideline-directed medical therapy (GDMT) is recommended before TEER for SMR.[2,13] The benefits of GDMT on 2-year clinical outcomes were previously reported both in patients with new-onset HF with reduced TAPSE and in patients with a reduced RVPAc.[12,14] However, few data are available on the longer-term impact of GDMT in general, namely its administration at target doses. The issue of drug dosage is of particular relevance because uptitration of triple GDMT is often prevented or discouraged by arterial hypotension, chronic kidney disease (CKD), hyperkalemia, and bradycardia, which are commonly found in chronic HF and TEER candidates.[14-16] In this study, we aimed to assess GDMT prevalence and its impact on long-term survival in SMR patients with RVI in the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry.

METHODS

STUDY POPULATION. The EuroSMR registry is an international, prospective registry including patients undergoing TEER for SMR using the MitraClip device (Abbott Structural Heart) in 14 European centers.[10] SMR was diagnosed as significant mitral regurgitation (MR) with a structurally normal mitral valve graded according to European recommendations.[17] SMR phenotype was defined as "ventricular functional" in the presence of either global left ventricular (LV) dilation and dysfunction or wall motion abnormalities with relatively preserved global systolic function.[17] For the present analysis, we included patients with a prevalent ventricular functional phenotype associated with RVI. Considering the overestimation of left ventricular ejection fraction (LVEF) because of severe MR, we included only patients with LVEF below normal, which was defined as <54% for women and <52% for men.[18]

Based on the available literature, we defined RVI as the presence of a TAPSE value ≤17 mm[18] and/or an echocardiographic RVPAc value <0.40 mm/mm Hg.[8,11] The choice of the latter threshold was also supported by maximization of log-rank statistics performed within the entire EuroSMR patient population.

DATA COLLECTION. Patient demographics and echocardiographic and procedural data were collected at each site. The methodology of echocardiographic assessment was previously described.[10] Patients were followed up in their respective hospitals as per local practice. The available follow-up data included survival status, functional class, medical therapy, and echocardiographic assessment through outpatient visits or by telephone interviews. Data collection was performed with the approval of the local ethical committee.

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DEFINITIONS AND OUTCOMES. Information on medical therapy, prescribed at the physician's discretion, was collected before TEER and at the last available follow-up. Medical therapy at follow-up was categorized as follows: "GDMT" was defined as the coprescription of beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)/angiotensin receptor neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRA); "on-titrated guideline-directed medical therapy ($GDMT_{tit}$)" was defined as the coprescription of all 3 classes at a dose ≥ one-half of the target dose for each drug (Supplemental Table 1); and "non-$GDMT_{tit}$" was defined either by the lack of any of the 3 drug classes or by the prescription of those at a dose less than one-half of the target dose. The primary outcome was all-cause mortality at long-term follow-up.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or as median (IQR), as appropriate, and were compared using the Student's *t*-test or the Mann-Whitney *U* test, respectively. Categoric variables are reported as counts and percentages and were compared using the chi-square or Fisher exact test. Cumulative survival rates were estimated with the Kaplan-Meier method, and the differences between groups were calculated using the log-rank test. We used maximization of log-rank statistics to define the optimal cutoff values of continuous variables according to their discriminatory value for long-term mortality. To account for differences regarding baseline and procedural characteristics between on-$GDMT_{tit}$ and non-$GDMT_{tit}$ patients, propensity score-based matching was used. Propensity scores were calculated using a logistic regression model based on age, sex, baseline NYHA functional class IV, LVEF, and estimated glomerular filtration rate (eGFR). A 1:1 optimal matching algorithm with Mahalanobis distance and caliper of 0.2 was applied. Absolute standardized mean differences <0.2 were considered as the indicator of adequate bias reduction. Cox proportional hazards regression models were used to identify predictors of all-cause mortality. Multivariable models were adjusted for covariates based on the literature and clinical experience.[14,15,19] The factors selected for the multivariable model are represented in a directed acyclic graph (Supplemental Figure 1). Given the complexity of interactions, to prevent overfitting, we developed 2 Cox models, the first one adjusting for clinical variables and the second adjusting for biomarkers and echocardiographic variables. The proportionality of hazards was assessed using Schoenfeld residuals. Results were expressed as HRs and corresponding 95% CIs. Sensitivity analyses were performed by means of Cox regression analysis within subgroups of patients defined by cutoff values of continuous variables. To evaluate the association between on-$GDMT_{tit}$ and all-cause death relative to the components of GDTM, we used category-free event net reclassification improvement.

A 2-sided *P* value <0.05 was considered statistically significant. All analyses were performed using SPSS version 28 (SPSS Inc).

RESULTS

BASELINE CHARACTERISTICS AND CHANGES IN MEDICAL THERAPY. Between November 2008 and March 2021, a total of 2,268 patients were enrolled in EuroSMR. Complete baseline echocardiographic data were available for 1,905 patients; of these, 1,648 patients had ventricular functional SMR and 1,213 ventricular functional SMR associated with RVI. After excluding 361 patients with incomplete data regarding medical therapy at baseline and/or follow-up, the study population consisted of 852 patients (Supplemental Figure 2). The baseline patient profile is described in **Table 1**. Of note, the mean LVEF was 33% ± 10%, the mean TAPSE was 15 ± 4 mm, and the median RVPAc was 0.30 mm/mm Hg (IQR: 0.24-0.36 mm/mm Hg). At baseline, most patients received BBs, ACEIs/ARBs/ARNIs, or MRAs, but only 42.8% (365/852) received all 3 drug classes; in particular, only 13.8% (118/852) received ≥50% target doses and 1.5% (13/852) full target doses (Supplemental Tables 2 and 3). At the last available follow-up, the proportion of patients receiving BBs, ACEIs/ARBs/ARNIs, and MRAs increased slightly compared to baseline (Supplemental Tables 2 and 3), with 372 of 852 patients (43.7%) receiving all 3 classes, 123 of 852 (14.4%) receiving ≥50% target doses, and 27 of 852 (3.2%) receiving full target doses. However, at the patient level, changes in medical therapy were not infrequent, with 17% (146/852) of patients swapping between on-$GDMT_{tit}$ and non-$GDMT_{tit}$ (Supplemental Table 4). The 123 patients receiving $GDMT_{tit}$ showed significant differences in baseline and procedural characteristics compared to non-$GDMT_{tit}$ patients (**Table 1**). On-$GDMT_{tit}$ patients were significantly younger, more often carried an implantable defibrillator, less frequently were in NYHA functional class IV, and had higher eGFR and lower LVEF. No significant differences in right ventricular (RV) function and procedural results were observed.

TABLE 1 Baseline and Postprocedural Characteristics of the Overall Population and of Patients Receiving (On-GDMT$_{tit}$) or Not Receiving (Non-GDMT$_{tit}$) Titrated Doses of Guideline-Directed Medical Therapy at the Latest Follow-Up

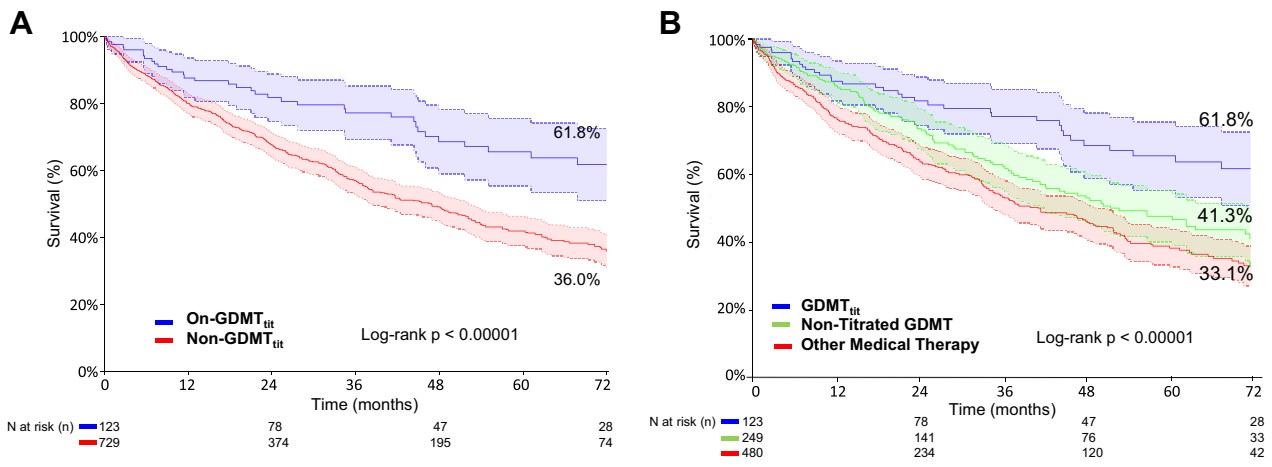
	Overall Population (N = 852)	On-GDMT$_{tit}$ (n = 123)	Non-GDMT$_{tit}$ (n = 729)	*P* Value
Baseline				
Male	589 (69)	93 (76)	496 (68)	0.10
Age, y	73 ± 10	70 ± 11	74 ± 10	0.00001
Body surface area, m^2	1.89 ± 0.22	1.96 ± 0.21	1.88 ± 0.21	0.0001
Diabetes mellitus	315 (37)	53 (43)	262 (36)	0.16
History of stroke	90 (11)	11 (9)	79 (11)	0.52
Chronic obstructive pulmonary disease	149 (17)	19 (15)	130 (18)	0.54
History of atrial fibrillation	558 (65)	74 (60)	484 (67)	0.17
Previous ICD implantation	259 (30)	48 (39)	211 (29)	0.05
Previous CRT implantation	188 (22)	26 (21)	162 (22)	0.84
NYHA functional class IV	199 (23)	19 (15)	180 (25)	0.02
Ischemic etiology of heart failure	491 (58)	70 (57)	421 (58)	0.84
MAP, mm Hg	86 (77-97)	89 (77-100)	86 (77-97)	0.11
NT-proBNP, pg/mL	3,315 (1,562-7,227)	2,951 (1,056-6,352)	3,411 (1,609-7,314)	0.15
eGFR, mL/min/1.73 m^2	50 ± 22	61 ± 21	48 ± 22	<0.00001
Stages of CKD[a]				0.001
CKD I-III	685 (80)	114 (93)	573 (79)	<0.0001
CKD IV	143 (17)	9 (7)	132 (18)	0.003
CKD V	24 (3)	0 (0)	24 (3)	0.04
EuroSCORE II	6.4 (4.1-10.9)	5.1 (3.7-10.4)	7.1 (4.2-11.8)	0.06
LV ejection fraction, %	33 ± 10	31 ± 10	33 ± 10	0.02
LV ejection fraction >40%	207 (24)	20 (16)	187 (26)	0.02
LV end-diastolic volume, mL	185 ± 81	204 ± 76	182 ± 81	0.004
MR severity: 2+	68 (8)	7 (6)	61 (8)	
3+	453 (53)	62 (50)	391 (54)	0.53
4+	331 (39)	54 (44)	277 (38)	
TAPSE, mm	15 ± 4	15 ± 3	15 ± 4	0.81
sPAP, mm Hg	53 ± 15	52 ± 14	54 ± 15	0.28
RVPAc, mm/mm Hg	0.30 (0.24-0.36)	0.30 (0.24-0.37)	0.30 (0.24-0.36)	0.89
Right atrium area, cm^2	25 ± 8	25 ± 8	25 ± 8	0.58
TR severity ≥2+	508 (60)	76 (62)	432 (59)	0.57
Postprocedure				
MR severity: 0/1+	554 (65)	86 (70)	468 (64)	0.23
2+	235 (28)	26 (21)	209 (29)	
3+	48 (6)	9 (7)	39 (5)	
4+	15 (2)	2 (2)	13 (2)	
MV mean gradient, mm Hg	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.08
TR severity ≥2+	437 (51)	66 (54)	371 (51)	0.60

Values are n (%), mean ± SD, or median (IQR). [a]CKD I-III: eGFR <30 mL/min/1.73 m^2; CKD IV: eGFR 15 to 29 mL/min/1.73 m^2; and CKD V: eGFR <15 mL/min/1.73 m^2.

CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; GDMT$_{tit}$ = titrated guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; LV = left ventricle; MAP = mean arterial pressure; MR = mitral regurgitation; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RVPAc = right ventricular-to-pulmonary artery coupling; sPAP = pulmonary arterial systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

LONG-TERM SURVIVAL (UP TO 6 YEARS). The median follow-up time was 25 months (IQR: 11-49 months); 91 patients died within 6 months of TEER, and an additional 303 died during follow-up. The cumulative long-term survival rate was significantly higher among on-GDMT$_{tit}$ vs non-GDMT$_{tit}$ patients (61.8% vs 36.0%; 95% CI: 51.0%-72.6% vs 95% CI: 31.3%-40.7%; $P < 0.00001$) (Figure 1A). Moreover, on-GDMT$_{tit}$ patients displayed better long-term outcomes compared to patients receiving GDMT at doses < one-half of the target dose and to those not receiving a coprescription of BBs, ACEIs/ARBs/ARNIs, and MRAs (61.8% vs 41.3% vs 33.1%; 95% CI: 51.0%-72.6% vs 95% CI: 33.1%-49.5% vs 95% CI: 27.3%-38.9%; $P < 0.00001$) (Figure 1B). Propensity score matching identified 117 matching pairs among on-GDMT$_{tit}$ and non-GDMT$_{tit}$ patients. The 2 groups showed no statistically significant differences in

FIGURE 1 Kaplan-Meier Estimated Survival Rates by Medical Therapy



Kaplan-Meier curves of freedom from long-term all-cause death (A) stratified by titrated guideline-directed medical therapy (GDMT$_{tit}$) at the latest follow-up and (B) stratified by GDMT$_{tit}$ vs nontitrated guideline-directed medical therapy (GMDT) vs other medical therapy schemes.

clinical, echocardiographic, or procedural data between them (**Table 2**) but did show more favorable clinical characteristics (eg, younger age, higher blood pressure, and better renal function) compared to patients not included in the propensity-matched populations (Supplemental Table 5). In the propensity-matched population, on-GDMT$_{tit}$ patients showed a significantly higher long-term survival rate vs non-GDMT$_{tit}$ patients (61.0% vs 43.1%; 95% CI: 49.9%-72.1% vs 95% CI: 31.8%-54.4%; $P = 0.018$) (**Figure 2**).

PREDICTORS OF LONG-TERM MORTALITY. The cut-off values with the highest discriminatory value for long-term mortality were 7,937 pg/mL for N-terminal pro-B-type natriuretic peptide, 1,374 pg/mL for B-type natriuretic peptide, 30% for LVEF, 46 mL/min/1.73 m^2 for eGFR, 13% for EuroSCORE II, and 0.274 mm/mm Hg for RVPAc. Through a multivariable Cox regression model based on clinical characteristics, we identified the following independent predictors of all-cause mortality: older age (HR per 5-year increase: 1.21; 95% CI: 1.12-1.30; $P < 0.0001$), previous cardiac resynchronization therapy or implantable cardioverter-defibrillator insertion (HR: 1.61; 95% CI: 1.24-2.08; $P < 0.0001$), baseline NYHA functional class IV (HR: 1.53; 95% CI: 1.16-2.01; $P = 0.003$), and ischemic etiology (HR: 1.33; 95% CI: 1.01-1.74; $P = 0.04$). In the model based on biomarkers and echocardiographic characteristics, higher levels of natriuretic peptides (HR: 1.83; 95% CI: 1.34-2.48; $P < 0.0001$) and postprocedural MR ≥3+ (HR: 1.84; 95% CI: 1.12-3.02; $P = 0.02$) were associated with overall mortality; in contrast, higher baseline LVEF (HR per 10% absolute increase: 0.82; 95% CI: 0.71-0.95; $P = 0.008$) was a predictor of survival. In all the models, on-GDMT$_{tit}$ was independently associated with overall survival (HR: 0.60; 95% CI: 0.37-0.96; $P = 0.03$; HR: 0.61; 95% CI: 0.39-0.93; $P = 0.02$) (**Figure 3**). Similar results were observed when replacing eGFR with stages of CKD and TAPSE with RVPAc (Supplemental Table 6). Importantly, the combination of TAPSE ≤17 mm and/or RVPAc <0.40 mm/mm Hg was an independent predictor of long-term all-cause mortality among the entire cohort of 1,648 patients with ventricular functional MR in EuroSMR (adjusted HR: 1.27; 95% CI: 1.004-1.608; $P = 0.047$) (Supplemental Table 7), with an estimated long-term overall survival of 34.2% vs 42.9% (95% CI: 39.5%-46.3% vs 95% CI: 30.8%-37.6%; $P = 0.0001$) (Supplemental Figure 3).

SENSITIVITY ANALYSES. EuroSCORE II wase excluded from Cox regression analysis because of multicollinearity issues. As sensitivity analysis, we investigated the prognostic role of on-GDMT$_{tit}$ with respect to RVPAc stratified by a cutoff value of 0.274 mm/mm Hg[10] and EuroSCORE II stratified by a cutoff value of 13%. On-GDMT$_{tit}$ remained a significant predictor of all-cause mortality in all subgroups, with $P_{interaction} = 0.72$ for RVPAc and $P_{interaction} = 0.69$ for EuroSCORE II (**Figure 4**). Further sensitivity analyses were performed within subgroups of LVEF and eGFR.

TABLE 2 Baseline and Procedural Characteristics of Patients Receiving $GDMT_{tit}$+ or Not Receiving ($GDMT_{tit}$−) Titrated Doses of Guideline-Directed Medical Therapy at the Latest Follow-Up After Propensity Score Matching

	Propensity Score–Matched Population		
	On-$GDMT_{tit}$ (n = 117)	Non-$GDMT_{tit}$ (n = 117)	*P* Value
Baseline			
Male	87 (74)	84 (72)	0.66
Age, y	70 ± 11	70 ± 9	0.69
Body surface area, m^2	1.95 ± 0.21	1.91 ± 0.20	0.13
Diabetes mellitus	49 (42)	47 (40)	0.67
History of stroke	10 (9)	12 (10)	0.65
Chronic obstructive pulmonary disease	17 (15)	19 (16)	0.74
History of atrial fibrillation	70 (60)	69 (59)	0.89
Previous ICD implantation	46 (39)	42 (36)	0.66
Previous CRT implantation	25 (21)	32 (27)	0.31
NYHA functional class IV	19 (16)	19 (16)	0.99
Ischemic etiology of heart failure	67 (57)	69 (59)	0.75
MAP, mm Hg	90 (78-100)	90 (80-100)	0.71
NT-proBNP, pg/mL	2,969 (1,257-6,391)	2,973 (1,493-4,869)	0.95
eGFR, mL/min/1.73 m^2	61 ± 22	58 ± 20	0.22
Stages of CKD[a]			0.42
I-III, %	108 (92)	111 (95)	
IV, %	9 (8)	6 (5)	
V, %	0 (0)	0 (0)	
EuroSCORE II	5.1 (3.7-10.4)	6.5 (3.5-9.7)	0.54
LV ejection fraction, %	31 ± 10	30 ± 10	0.70
LV ejection fraction >40%	19 (16)	19 (16)	1.00
LV end-diastolic volume, mL	204 ± 77	197 ± 82	0.48
MR severity: 2+	7 (6)	11 (9)	
3+	58 (50)	56 (48)	0.62
4+	52 (44)	50 (43)	
TAPSE, mm	15 ± 3	15 ± 4	0.83
sPAP, mm Hg	52 ± 14	53 ± 14	0.43
RVPAc, mm/mm Hg	0.30 (0.24-0.36)	0.31 (0.23-0.36)	0.94
Right atrium area, cm^2	25 ± 8	25 ± 7	0.99
TR severity ≥2+	74 (63)	69 (59)	0.67
Postprocedure			
MR severity: 0/1+	82 (70)	76 (65)	0.69
2+	25 (21)	32 (28)	
3+	8 (7)	6 (5)	
4+	2 (2)	3 (2)	
MV mean gradient, mm Hg	3.0 (2-4)	3.3 (2-5)	0.06
TR severity ≥2+	61 (52)	60 (51)	0.84

Values are n (%), mean ± SD, or median (IQR). [a]CKD I-III: eGFR <30 mL/min/1.73 m^2; CKD IV: eGFR 15 to 29 mL/min/1.73 m^2; and CKD V: eGFR <15 mL/min/1.73 m^2.

Abbreviations as in Table 1.

On-$GDMT_{tit}$ confirmed its prognostic role among patients with LVEF ≥30% or <30% ($P_{interaction} = 0.33$) and with eGFR ≥46 mL/min/1.73 m^2 or <46 mL/min/1.73 m^2 ($P_{interaction} = 0.75$) (**Figure 4**) as well as among patients with LVEF ≤40% (Supplemental Figure 4). We then performed net reclassification improvement analysis to investigate the association between on-$GDMT_{tit}$ and all-cause death relative to the main components of on-$GDMT_{tit}$. The categorization of medical therapy as on-$GDMT_{tit}$ was superior or similar to all of its components in predicting the risk of all-cause mortality (on-$GDMT_{tit}$ vs a prescription of titrated BBs and ACEIs/ARBs/ARNIs: $P = 0.007$; on-$GDMT_{tit}$ vs titrated BBs alone: $P = 0.41$; on-$GDMT_{tit}$ vs titrated ACEIs/ARBs/ARNIs alone: $P = 0.02$; on-$GDMT_{tit}$ vs titrated MRAs alone: $P = 0.54$; on-$GDMT_{tit}$ vs a coprescription of all 3 classes at any dose: $P = 0.027$) (Supplemental Table 8). Finally, we analyzed the role of BB therapy alone and found that patients receiving titrated BBs showed a significantly higher survival rate vs nontitrated BBs ($P = 0.036$), being in turn superior to a lack of BB therapy ($P = 0.015$) (Supplemental Figure 5). Titrated BB therapy also proved to be an independent predictor of long-term survival (Supplemental Table 9).

ECHOCARDIOGRAPHIC FOLLOW-UP. Among the 789 patients with postprocedural MR ≤2+, follow-up measurement of TAPSE and RVPAc was available in 389 and 318 patients, respectively. A mild but significant improvement in TAPSE and RVPAc was observed ($P < 0.0001$) independent of $GDMT_{tit}$ prescription (Supplemental Figure 6).

DISCUSSION

The EuroSMR registry is a large, multicenter, prospective registry enrolling patients undergoing TEER for SMR. In the present retrospective analysis, we investigated the association between $GDMT_{tit}$ and long-term survival in the largest population of patients with RVI undergoing TEER for ventricular functional SMR with the longest follow-up ever reported from a multicenter registry. The main findings were as follows (**Central Illustration**):

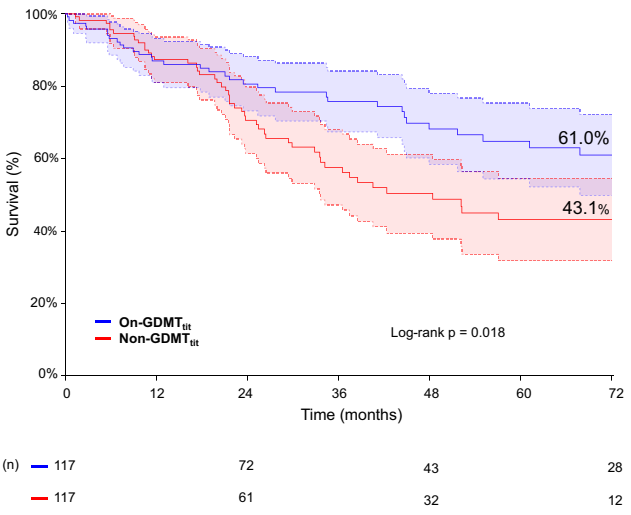
- The proportion of patients receiving a coprescription of any dose of BBs, ACEIs/ARBs/ARNIs, and MRAs was 43.7% (372/852), with only 14.4% (123/852) receiving ≥50% target doses and 3.2% (27/852) full target doses.
- Patients who received a coprescription at follow-up of ACEIs/ARBs/ARNIs, BBs, and MRAs at ≥50% target doses (on-$GDMT_{tit}$) showed a significantly higher long-term survival rate (up to 6 years) compared to those who did not; this benefit was confirmed in the propensity score–matched population.
- $GDMT_{tit}$ was an independent predictor of long-term survival, with an adjusted HR of 0.60 for all-cause death.
- The prognostic benefit of $GDMT_{tit}$ was confirmed at sensitivity analyses performed in subgroups of patients with different values of LVEF, RVPAc, eGFR, and EuroSCORE II.

SMR results from imbalances in closing and tethering forces, often caused by LV dysfunction, either from global LV dilation and dysfunction or wall

motion abnormalities with relatively preserved LVEF. In this context, RVI is common and is associated with poor prognosis after TEER.[6,20] Echocardiographic parameters such as TAPSE, tissue Doppler imaging's peak systolic velocity, and RV fractional area change predict outcomes after TEER.[6] RV afterload also plays a role in load-dependent measures of RV function. Indeed, RVPAc estimation is a strong predictor in SMR patients.[9,21] In particular, TAPSE/sPAP shows a tight association with invasive measurement of RVPAc[8] and improves mortality prediction in patients undergoing TEER for SMR.[10] However, severe tricuspid regurgitation and reduced RV stroke volume may lead to low values of sPAP and hence overestimated RVPAc values, even in the presence of a severely deranged RV physiology.[11] Based on the available literature, we defined RVI as the presence of reduced TAPSE (≤17 mm) and/or reduced RVPAc (TAPSE/sPAP <0.40 mm/mm Hg). Normal values of TAPSE/sPAP in healthy subjects range from 0.7 to 2.0 mm/mm Hg.[22] Different TAPSE/sPAP thresholds for predicting outcomes were identified according to the underlying disease.[8-11] However, given the heterogeneity of patients' characteristics and the different follow-up duration, these values cannot be easily extrapolated to other populations. In the present analysis, we chose the cutoff value of RVPAc <0.40 mm/mm Hg, which was associated with a worse prognosis in patients with HF.[8,9] Importantly, our definition of RVI, combining TAPSE ≤17 mm and/or RVPAc <0.40 mm/mm Hg, independently predicted all-cause mortality in the entire ventricular functional MR patient cohort in EuroSMR.

Reducing RV afterload is crucial in treating RVI associated with left heart disease.[23] In SMR, successful TEER (MR <1+) decreases left atrial pressure, providing significant prognostic benefits in patients with severely deranged RVPAc (<0.274 mm/mm Hg).[24] However, the impact of $GDMT_{tit}$ on long-term survival remains understudied. A previous analysis of EuroSMR reported that patients with RVPAc <0.274 mm/mm Hg receiving GDMT at the time of TEER displayed a higher 2-year survival.[14] Recent EuroSMR analysis showed reduced all-cause mortality and HF hospitalizations in SMR patients optimizing GDMT within 6 months after TEER.[15] Considering that almost 50% of patients experienced changes in drug dosage in the first months after TEER,[15] in the present analysis, we categorized medical therapy based on drug prescription at the latest available follow-up. On the other hand, most of the changes previously reported were minor variations in drug dosage, not affecting the overall category of medical therapy;[15] indeed, in our population, optimization from non-$GDMT_{tit}$ to on-$GDMT_{tit}$ during follow-up occurred only in 8% of patients, whereas 8% experienced a downgrading of GDMT. Hence, we can assume that medical therapy remained stable after initial adjustments, allowing us to assess its impact on long-term survival based on the latest prescriptions.

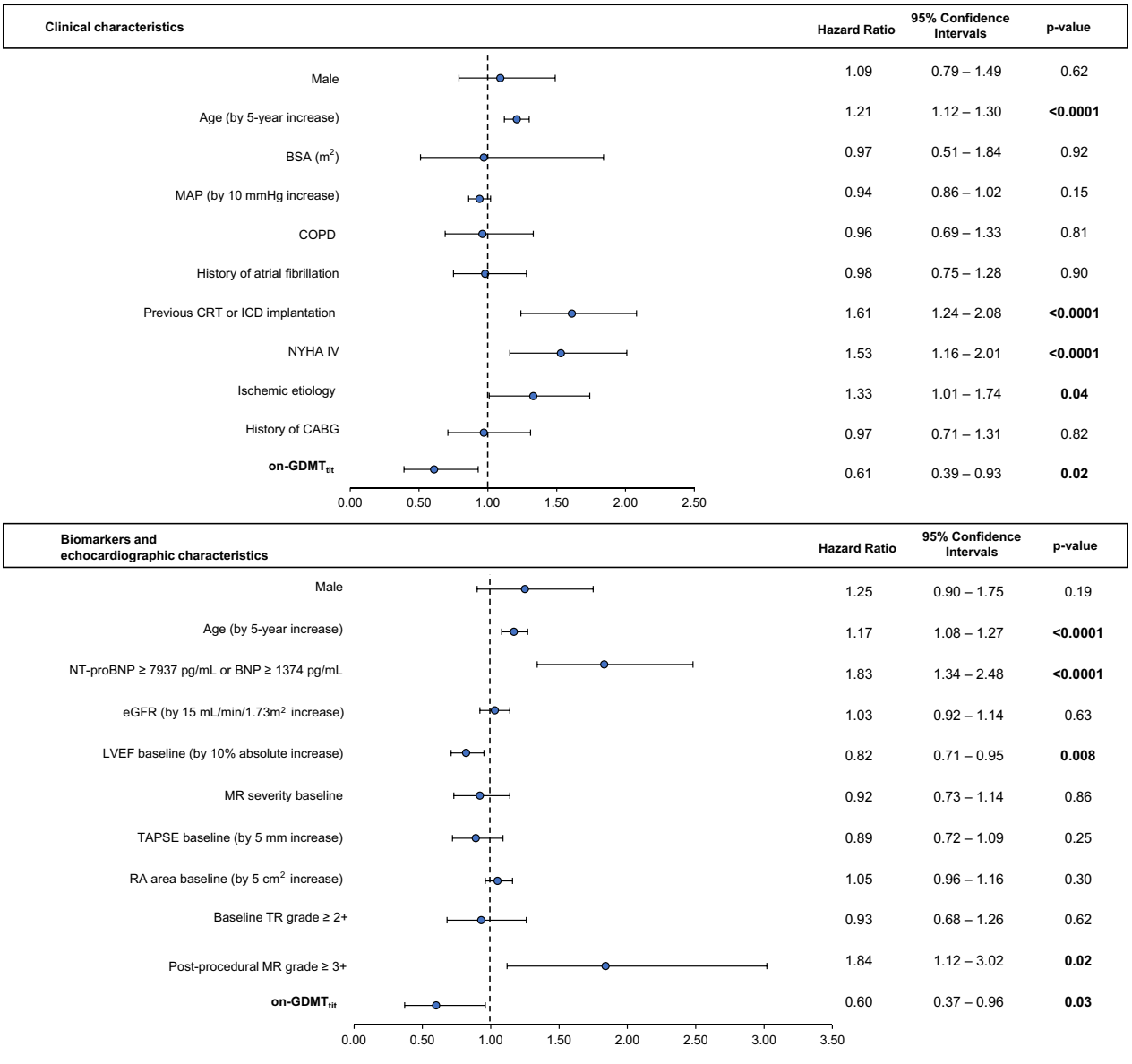
FIGURE 2 Kaplan-Meier Estimated Survival Rates by Medical Therapy in the Propensity-Matched Population



Kaplan-Meier curves for long-term all-cause death stratified by titrated guideline-directed medical therapy ($GDMT_{tit}$) among 117 propensity score–matched pairs of patients.

GDMT is still largely underprescribed and underdosed in HF patients, mainly because of hypotension and CKD,[25] particularly among patients with RVI;[12] <1% of patients have been reported to receive all life-prolonging treatments at trial-proven doses.[26] Accordingly, in our population, the proportion of patients receiving a coprescription of BBs, ACEIs/ARBs/ARNIs, and MRAs at full target doses was 1.5% at baseline and 3.2% at follow-up. This is mainly because of concerns about undesirable effects on blood pressure, kidney function, and electrolyte levels that prompt clinicians to settle for medium-range below-target doses; their prognostic benefit remains unclear.[26] Importantly, we found that a prescription of GDMT at ≥50% target dose was associated with a striking increase in overall survival, even after accounting for differences in baseline characteristics through propensity score matching. As expected, propensity score matching selected patients with more favorable clinical characteristics because titration of GDMT is more common among patients with younger age, higher blood pressure, and better renal function. However, even among patients with fewer

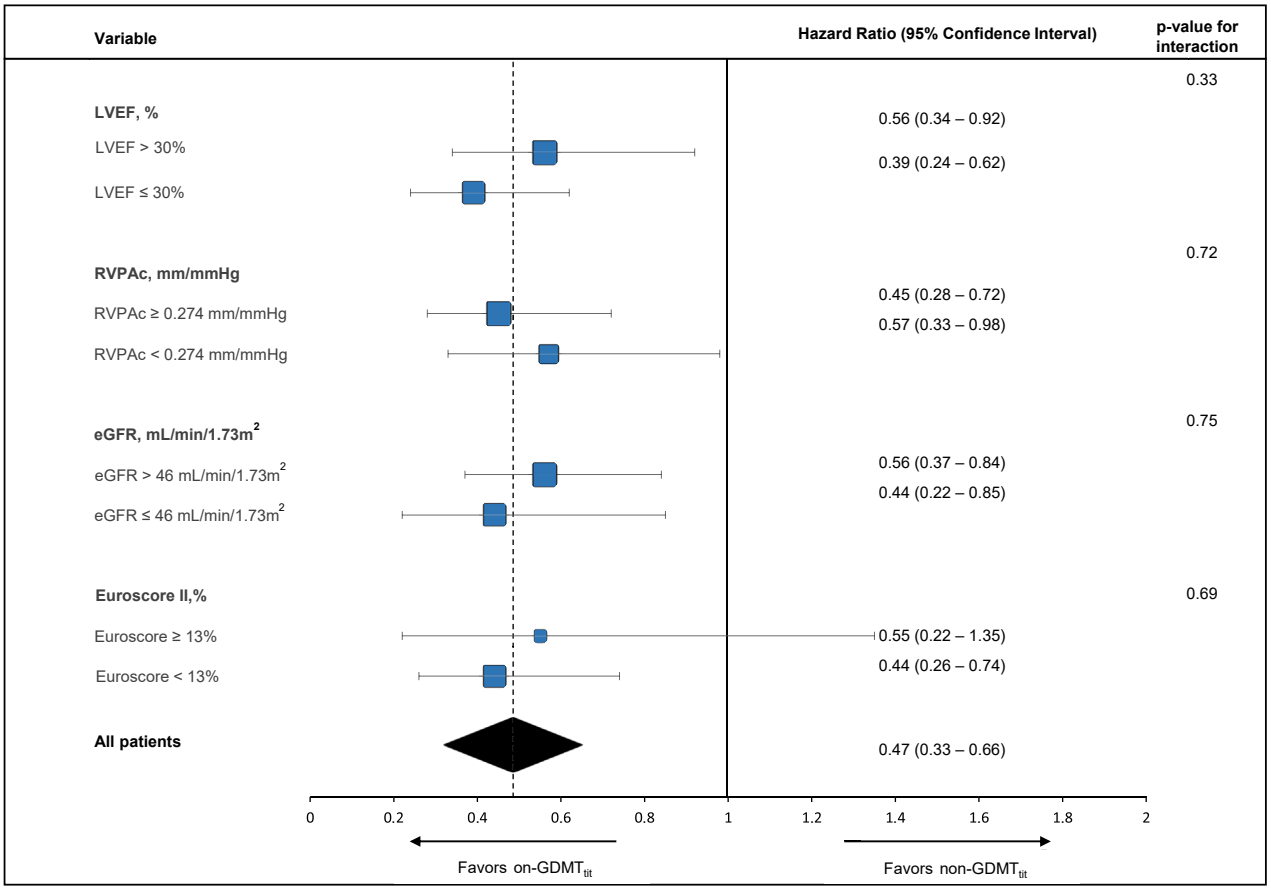
FIGURE 3 Multivariable Cox Regression Models for Predictors of All-Cause Death



BNP = B-type natriuretic peptide; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; $GDMT_{tit}$ = titrated guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RA = right atrium; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

comorbidities, $GDMT_{tit}$ confirmed its independent prognostic value. Moreover, $GDMT_{tit}$ offered a significant benefit also in comparison with GDMT at <50% target dose, underlining the need to repeatedly verify the possibility of uptitrating GDMT throughout follow-up. Of note, although target doses of all 3 classes are achieved in a minimal proportion of HF patients, in our population, a dose ≥50% of the target was reached in 14% of patients. The attainability in clinical practice of these doses together with their benefit on overall survival warrant efforts toward uptitration of GDMT. In addition, $GDMT_{tit}$ was associated with a noticeable 60% survival rate up to 6 years after TEER in SMR patients with RVI, supporting the effectiveness of TEER in this specific population. Moreover, although the prognostic benefit of

FIGURE 4 Post Hoc Subgroup Analyses for All-Cause Death



RVPAc = right ventricular-to-pulmonary artery coupling; other abbreviations as in Figure 3.

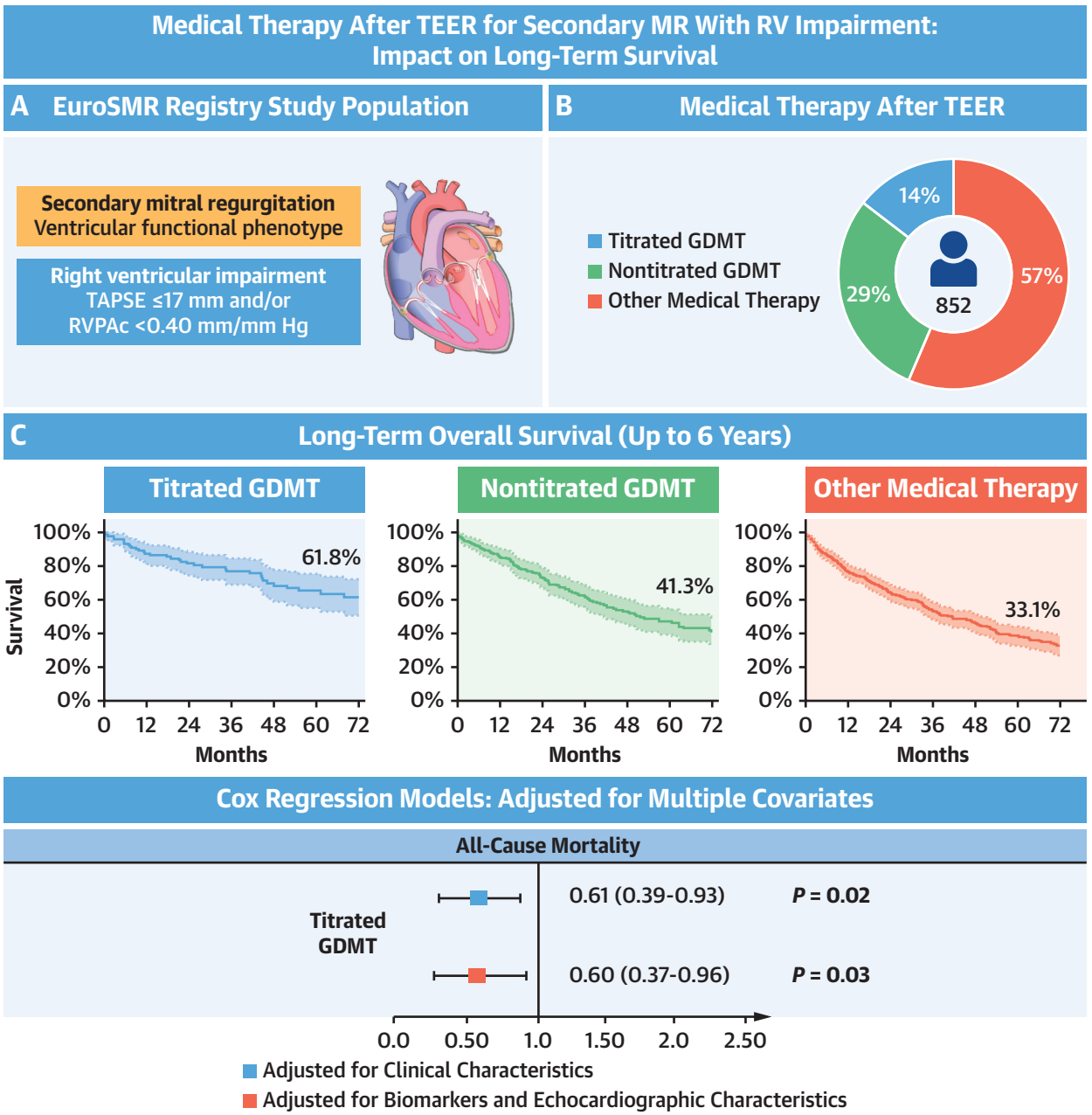
triple GDMT in patients with functional MR undergoing TEER has been previously demonstrated,[19] even in the presence of RVD,[14] our study is the first to report details on drug dosages and their relationship with long-term clinical outcomes.

In the context of medical therapy for HF, the role of BB therapy in RVD remains controversial because BBs may counteract compensatory adrenergic mechanisms. However, in patients with RVD caused by chronic pulmonary arterial wedge pressure increase, the blocking of adrenergic overdrive may enhance LV function, prevent progressive dilation, and positively affect filling pressures.[23] Accordingly, in our study, patients with a BB dose ≥50% of the target had higher long-term survival than those with lower doses or no BB therapy, even after adjusting for covariates.

Consistent with prior research,[14,24] older age, NYHA functional class IV at baseline, higher natriuretic peptide levels, and moderate or worse residual MR were independent predictors of all-cause mortality. Despite previous studies suggesting the impact of TAPSE and RVPAc on medium-term outcomes, we did not find a significant impact on long-term survival.[14,24] A few factors may underly these findings. First, all our patients had baseline RVI, making it harder to discern survival differences related to RV parameters in our population. Second, the negative effects of severely reduced RVPAc on short- and mid-term prognosis[7,10] may have lessened over the extended follow-up, especially considering that most patients with low RVPAc improved soon after TEER.[7]

This study showed the benefits of $GDMT_{tit}$ on long-term survival across eGFR, LVEF, RVPAc, and EuroSCORE II subgroups. It supports prior findings of GDMT benefit in advanced CKD patients.[14] However, despite the absence of a significant interaction between GDMT and EuroSCORE II, within the subgroup

CENTRAL ILLUSTRATION **Guideline-Directed Medical Therapy and Long-Term Survival After Transcatheter Edge-to-Edge Repair in Secondary Mitral Regurgitation With Right Ventricular Impairment: Impact on Long-Term Survival**



Mazzola M, et al. J Am Coll Cardiol Intv. 2024;17(12):1455–1466.

Among patients with secondary mitral regurgitation and RV impairment (A), only 14% were on titrated GDMT (B). Titrated GDMT was associated with higher long-term survival vs nontitrated GDMT and vs other medical therapy (61.8% vs 41.3% vs 33.1%, respectively; $P < 0.00001$), even after adjustment for multiple covariates (C). GDMT = guideline-directed medical therapy; RV = right ventricular; RVPAc = right ventricular–to-pulmonary artery coupling; TAPSE = tricuspid annular plane systolic excursion; TEER = transcatheter edge-to-edge repair.

with EuroSCORE II ≥13%, GDMT did not reach significance presumably because of the small sample size. We also highlight advantages in patients with RVPAc ≥0.274 mm/mm Hg and LVEF >30%, in contrast to previous EuroSMR analysis.[14] Although guidelines recommend triple GDMT for LVEF ≤40%, it may also be considered for those with LVEF between 40% and 50%.[13] Moreover, the beneficial effect of triple GDMT has been recently observed across the spectrum of LV systolic dysfunction.[27] Thus, our findings emphasize the importance of focusing on optimizing GDMT prescription and therapeutic adherence across all patient categories.

STUDY LIMITATIONS. Our study has the following limitations: varying selection criteria and treatments across centers introduced bias in the retrospective analyses, incomplete GDMT data raised uncertainty about consistent medical therapy, sodium glucose cotransporter 2 inhibitor use and ARNI therapy details were unavailable, our definition of "titrated" GDMT (≥50% of target dose) was arbitrary, RVPAc and TAPSE cutoffs for RVI were also arbitrary because of the lack of consensus on the thresholds, and freedom from hospitalization could not be assessed because of incomplete timing data. Moreover, the data regarding GDMT were not collected at prespecified time points.

The inclusion of patients with mildly reduced LVEF in the present analysis may appear questionable given the weak evidence on triple GDMT in this patient subgroup. Nevertheless, analyses of randomized controlled trials and echocardiographic registries suggested that the LVEF cutoff of 50% may be inadequate to identify LV dysfunction in MR patients, proposing higher thresholds. Additionally, the prognostic benefit of $GDMT_{tit}$ was confirmed in our population after excluding patients with LVEF >40%.

Another limitation of our study is the absence of blood pressure and renal function data at follow-up. During follow-up, hypotension and renal impairment may have prevented $GDMT_{tit}$ prescription. Thus, patients tolerating GDMT uptitration at follow-up may have had a higher blood pressure/pulse pressure (thereby intrinsic myocardial contractility) and a better renal function, which might be responsible for the superior survival in this group.

CONCLUSIONS

In RVI patients undergoing TEER for ventricular SMR, a coprescription of 3 HF drug classes at ≥ one-half the target dose is associated with a 40% reduction in the risk of all-cause death at long-term follow-up. Although the ability to tolerate GDMT uptitration may per se select patients with better prognosis, our findings support repeated attempts to uptitrate GDMT during follow-up in all patient subgroups and not settling for medium-range suboptimal doses.

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Dr Pfister is a consultant for Edwards Lifesciences; and has received speaker honoraria from Edwards Lifesciences and Abbott Vascular. Dr Iliadis is a consultant for Abbott and Edwards Lifesciences. Dr Kalbacher has received personal fees from Abbott, Edwards Lifesciences, and Pi-Cardia Ltd. Dr Metra has received consulting/speaker fees from Amgen, Livanova, Vifor Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? GDMT for HF is frequently underprescribed and underdosed, and its effectiveness in patients undergoing TEER for SMR has been poorly investigated, particularly among those with RVI.

WHAT IS NEW? Our findings demonstrate that a prescription of GDMT at doses at least equal to half of the target dose dramatically improves long-term survival in patients with RVI regardless of renal function, LV systolic function, and surgical risk profile.

WHAT IS NEXT? Adequately powered randomized trials are needed to confirm the benefits of TEER on top of GDMT in patients with SMR and RVI.

REFERENCES

1. Goliasch G, Bartko PE, Pavo N, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J*. 2018;39:39-46.

2. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561-632.

3. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307-2318.

4. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297-2306.

5. Stone GW, Abraham WT, Lindenfeld J, et al. Five-year follow-up after transcatheter repair of

secondary mitral regurgitation. *N Engl J Med*. 2023;388:2037–2048.

6. Italia L, Adamo M, Lupi L, Scodro M, Curello S, Metra M. Percutaneous edge-to-edge mitral valve repair: beyond the left heart. *J Am Soc Echocardiogr*. 2021;34:1038–1045.

7. Adamo M, Inciardi RM, Tomasoni D, et al. Changes in right ventricular-to-pulmonary artery coupling after transcatheter edge-to-edge repair in secondary mitral regurgitation. *J Am Coll Cardiol Img*. 2022;15:2038–2047.

8. Tello K, Wan J, Dalmer A, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. *Circ Cardiovasc Imaging*. 2019;12:e009047.

9. Guazzi M, Dixon D, Labate V, et al. RV Contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: stratification of clinical phenotypes and outcomes. *J Am Coll Cardiol Img*. 2017;10:1211–1221.

10. Karam N, Stolz L, Orban M, et al. Impact of right ventricular dysfunction on outcomes after transcatheter edge-to-edge repair for secondary mitral regurgitation. *J Am Coll Cardiol Img*. 2021;14:768–778.

11. Brener MI, Lurz P, Hausleiter J, et al. Right ventricular-pulmonary arterial coupling and afterload reserve in patients undergoing transcatheter tricuspid valve repair. *J Am Coll Cardiol*. 2022;79:448–461.

12. Ansari Ramandi MM, van Melle JP, Gorter TM, et al. Right ventricular dysfunction in patients with new-onset heart failure: longitudinal follow-up during guideline-directed medical therapy. *Eur J Heart Fail*. 2022;24:2226–2234.

13. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24:4–131.

14. Higuchi S, Orban M, Adamo M, et al. Guideline-directed medical therapy in patients undergoing transcatheter edge-to-edge repair for secondary mitral regurgitation. *Eur J Heart Fail*. 2022;24:2152–2161.

15. Adamo M, Tomasoni D, Stolz L, et al. Impact of transcatheter edge-to-edge mitral valve repair on guideline-directed medical therapy uptitration. *J Am Coll Cardiol Intv*. 2023;16:896–905.

16. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018;72:351–366.

17. Lancellotti P, Pibarot P, Chambers J, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. *Eur Heart J Cardiovasc Imaging*. 2022;23:e171–e232.

18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233–270.

19. Varshney AS, Shah M, Vemulapalli S, et al. Heart failure medical therapy prior to mitral transcatheter edge-to-edge repair: the STS/ACC Transcatheter Valve Therapy Registry. *Eur Heart J*. 2023;44:4650–4661.

20. Adamo M, Fiorelli F, Melica B, et al. COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing MitraClip implantation. *J Am Coll Cardiol Intv*. 2021;14:15–25.

21. Brener MI, Grayburn P, Lindenfeld J, et al. Right ventricular-pulmonary arterial coupling in patients with HF secondary MR: analysis from the COAPT trial. *J Am Coll Cardiol Intv*. 2021;14:2231–2242.

22. Gargani L, Pugliese NR, De Biase N, et al. Exercise stress echocardiography of the right ventricle and pulmonary circulation. *J Am Coll Cardiol*. 2023;82:1973–1985.

23. Houston BA, Brittain EL, Tedford RJ. Right ventricular failure. *N Engl J Med*. 2023;388:1111–1125.

24. Higuchi S, Orban M, Stolz L, et al. Impact of residual mitral regurgitation on survival after transcatheter edge-to-edge repair for secondary mitral regurgitation. *J Am Coll Cardiol Intv*. 2021;14:1243–1253.

25. Greene SJ, Fonarow GC, DeVore AD, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;73:2365–2383.

26. Packer M, Metra M. Guideline-directed medical therapy for heart failure does not exist: a nonjudgmental framework for describing the level of adherence to evidence-based drug treatments for patients with a reduced ejection fraction. *Eur J Heart Fail*. 2020;22:1759–1767.

27. Vaduganathan M, Claggett BL, Inciardi RM, Fonarow GC, McMurray JJV, Solomon SD. Estimating the benefits of combination medical therapy in heart failure with mildly reduced and preserved ejection fraction. *Circulation*. 2022;145:1741–1743.

KEY WORDS guideline-directed medical therapy, heart failure, right ventricle dysfunction, right ventricular–to–pulmonary artery coupling, secondary mitral regurgitation, transcatheter edge-to-edge repair

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