

Guideline-directed medical therapy after transcatheter edge-to-edge mitral valve repair

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ABSTRACT

Objective A sizeable proportion of patients with secondary mitral regurgitation (SMR) do not receive guideline-directed medical therapy (GDMT) for heart failure (HF). We investigated the association between the use of GDMT and mortality in patients with SMR who underwent transcatheter edge-to-edge repair (TEER).

Methods We retrospectively analysed patients with SMR and a left ventricular ejection fraction of <50% who underwent TEER at three centres. According to current HF guidelines, GDMT was defined as triple therapy consisting of beta-blockers, renin–angiotensin system (RAS) inhibitors and mineralocorticoid receptor antagonists (MRAs). Patients were divided into two groups: GDMT and non-GDMT groups. We calculated the propensity scores and carried out inverse probability of treatment weighting (IPTW) analyses to compare 2-year mortality between the two groups.

Results Of 463 patients, 228 (49.2%) were treated with GDMT upon discharge. IPTW-adjusted Kaplan–Meier curve showed patients with GDMT had a lower incidence of mortality than those without GDMT (19.8% vs 31.1%, $p=0.011$). In IPTW-adjusted Cox proportional hazards analysis, GDMT was associated with a reduced risk of 2-year mortality (HR: 0.58; 95% CI: 0.35 to 0.95; $p=0.030$), which was consistent among clinical subgroups. Moreover, patients with GDMT had a higher rate of left ventricular reverse remodelling at 1 year after TEER than those without GDMT.

Conclusion GDMT, defined as triple therapy consisting of beta-blockers, RAS inhibitors and MRAs, was associated with a reduced risk of 2-year mortality after TEER for SMR. Optimisation of medical therapy is crucial to improve clinical outcomes in patients undergoing TEER for SMR.

INTRODUCTION

Secondary mitral regurgitation (SMR) is associated with an impaired prognosis in patients with heart failure (HF).¹ SMR is mainly attributed to underlying left ventricular (LV) systolic dysfunction,^{2,3} and the use of neurohormonal antagonists based on the HF guidelines is an initial treatment for SMR. Recently, transcatheter edge-to-edge mitral valve repair (TEER) is an emerging treatment option for symptomatic SMR. Based on the results of the COAPT trial,⁴ the current guidelines recommend TEER for patients with SMR and LV ejection fraction (LVEF) of 20%–50% who

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Guideline-directed medical therapy (GDMT) is an essential treatment for secondary mitral regurgitation (SMR) and impaired left ventricular systolic function; however, in clinical practice, there is a sizeable proportion of patients with SMR who do not receive GDMT.

WHAT THIS STUDY ADDS

⇒ In this study including 463 patients with SMR and a left ventricular ejection fraction of <50% who underwent transcatheter edge-to-edge repair (TEER), we used inverse probability of treatment weighting methodology and showed that use of GDMT, defined as triple therapy consisting of beta-blockers, renin–angiotensin system inhibitors, and mineralocorticoid receptor antagonists, was associated with a reduced risk of 2-year mortality after TEER. Furthermore, patients with GDMT had a higher rate of left ventricular reverse remodelling following TEER compared with those without GDMT.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underline that there is a crucial need for using optimal GDMT to improve clinical outcomes after TEER in patients with SMR.

continued to be symptomatic despite the maximally tolerated medical therapy.⁵ However, in clinical practice, there is a sizeable proportion of patients with SMR who do not receive optimal medical therapy as recommended by the HF guidelines.^{6,7} Beneath these observations, the clinical relevance of guideline-directed medical therapy (GDMT) after TEER needs to be elucidated.

We sought to evaluate the association between the use of GDMT and all-cause mortality after TEER in patients with SMR and an LVEF of <50%.

METHODS

Study population

This study was designed as a retrospective analysis of data from a multicentre, prospective, observational registry of symptomatic patients with MR

who underwent a MitraClip procedure (Abbott Vascular, Santa Clara, California, USA) from October 2011 to September 2018 at three German high-volume centres (University Hospitals of Bonn, Cologne and Düsseldorf). The patients all agreed to participate in our registry.

Consecutive patients with an LVEF of <50% and SMR who underwent TEER were enrolled in this study. All patients had moderate-to-severe or severe MR accompanied by symptomatic HF despite medical therapy and were considered as inoperable or at high surgical risk. Patients who died during the index hospitalisation ($n=22$) and those without available information about their medical therapy ($n=19$) were excluded from the present analysis. The final study population consisted of 463 patients (online supplemental figure 1).

The indication for TEER was evaluated by the interdisciplinary heart team of each centre, including HF specialists. The heart teams optimised medical therapy based on the guidelines and decided to perform TEER, considering MR severity, cardiac function, symptoms, comorbidity and life expectancy of the patient. A titration of the medical therapy was performed by the heart team during the index hospitalisation and was left up to the discretion of the treating physicians after discharge.

The medical therapy of each patient was evaluated at discharge after TEER. Based on the 2021 European Society of Cardiology (ESC) HF guidelines,⁸ GDMT was defined as triple therapy consisting of beta-blockers, renin-angiotensin system (RAS) inhibitors (ACE inhibitors, angiotensin receptor blockers, or angiotensin receptor/neprilysin inhibitor) and mineralocorticoid receptor antagonists (MRAs). In contrast, patients with a lack of the triple therapy were recognised as non-GDMT group. Sodium-glucose co-transporter 2 (SGLT2) inhibitors were not included in the definition of GDMT, because the use of SGLT2 inhibitors was still rare in this registry. For each patient, the percentage of the optimal dosage of beta-blockers and RAS inhibitors was calculated and stratified based on the recommended target dose in the 2021 ESC HF guidelines (0%, 1%–24%, 25%–49%, 50%–99% and 100%), and the dose of loop diuretics was expressed as a standardised furosemide equivalent.⁹

Echocardiographic parameters

We assessed the echocardiographic parameters that were collected at baseline and discharge, according to the current guidelines.¹⁰ The severity of MR was graded as follows: grade 0, none; 1+, mild; 2+, moderate; 3+, moderate to severe; 4+, severe. LV volumes and ejection fraction were calculated using the apical biplane views, including two-chamber and four-chamber views. Also, post-procedural echocardiographic assessments were collected at 1 year after TEER. LV reverse remodelling was defined as a reduction in the LV end-systolic volume of $\geq 10\%$ from baseline to the 1-year follow-up.¹¹ All measurements were reviewed by an independent cardiologist dedicated to echocardiographic evaluation at each centre.

Clinical follow-up

The primary endpoint was all-cause mortality within 2 years after TEER. Follow-up data and the occurrence of clinical events were collected from admission and outpatient medical records or telephone interviews with the patients' general practitioners or families.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analysis

Continuous variables are presented as the mean \pm SD or medians with an IQR for normally and non-normally distributed variables, respectively. Continuous variables were compared using t-tests or the Mann-Whitney test. Proportions of categorical data were presented as percentages and compared using the χ^2 test or Fisher's exact test.

Treatment effects were examined in two ways. First, to minimise confounding by patient factors for GDMT, we calculated propensity scores and carried out inverse probability of treatment weighting (IPTW)-adjusted analyses.¹² Multiple imputation using chained equations was performed to handle missing values in baseline variables that were required for estimation of the propensity score and subsequent analyses, and we generated 20 imputed data sets by using a sequential regression model.¹³ The number of missing records per baseline variable is summarised in online supplemental table 1. In all subsequent analyses, Rubin's rules were applied to unify the effect estimates and variances from the 20 different analyses across multiple imputed data sets. A propensity score was separately calculated in each imputed data set using multiple logistic regression that estimated the propensity toward belonging to GDMT. The dependent variables were age, sex, body mass index, prior myocardial infarction, coronary artery disease, diabetes mellitus, atrial fibrillation, estimated glomerular filtration rate (eGFR), haemodialysis, New York Heart Association class, cardiac implantable electronic device, cardiac resynchronisation therapy, chronic obstructive pulmonary disease, N-terminal pro-B-type natriuretic peptide, Logistic European System for Cardiac Operative Risk Evaluation, systolic blood pressure, heart rate, site of intervention, LVEF, LV end-diastolic volume, MR severity grade, effective regurgitation orifice area, systolic pulmonary artery pressure, tricuspid annular plane systolic excursion (TAPSE), severity of tricuspid regurgitation and dose of loop diuretics. Each patient was weighted by the inverse probability of treatment: patients who received GDMT were weighted by the reciprocal of the propensity score, and those who did not receive GDMT were weighted by the reciprocal of 1 minus the propensity score; the weights were then stabilised by the proportion of patients in each group.¹⁴ Covariate balance was evaluated by using the standardised differences approach and Kernel density plots. Absolute standardised differences $\leq 10\%$ were considered acceptable. IPTW-adjusted Kaplan-Meier curves were depicted to compare 2-year mortality between groups. We further conducted an IPTW-adjusted Cox proportional hazards regression model to calculate the weighted HRs, which allowed for adjustment for any covariate that remained unbalanced after IPTW. In addition, we conducted a stratified analysis to examine heterogeneity of treatment effects according to age, eGFR, site of intervention, LVEF, TAPSE, residual MR and post-procedural LVEF by testing the interaction terms within the IPTW-adjusted Cox proportional hazards models.

Second, as a sensitivity analysis, we fitted multivariable Cox proportional hazards regression models to assess the effect of GDMT on 2-year mortality in the non-weighted population, in which covariates that showed significance ($p < 0.10$) in the univariate analysis were included. We tested for collinearity in the multivariable models using a variance inflation factor, and the variables had low variance inflation factors (< 2).

Table 1 Baseline patient characteristics

	All n=463	GDMT n=228	Non-GDMT n=235	P value
Age, years	74±9	73±10	75±8	0.010
Male, %	72.6	76.8	68.5	0.048
BMI, kg/m ²	26.2±4.7	25.9±4.7	26.4±4.7	0.241
Diabetes, %	34.1	35.1	33.2	0.667
Hypertension, %	77.8	76.8	78.7	0.611
CAD, %	67.4	65.4	69.3	0.360
Prior MI, %	42.5	43.4	41.7	0.708
Prior CABG, %	35.6	31.6	39.6	0.073
COPD, %	17.9	18.0	17.9	0.975
CIED, %	55.5	59.7	51.5	0.078
CRT, %	19.2	23.7	14.9	0.017
NYHA class III/IV, %	81.9	83.8	80.0	0.290
Atrial fibrillation, %	62.1	57.0	67.0	0.017
Systolic BP, mm Hg	119±22	117±20	121±18	0.038
Systolic BP <100 mm Hg, %	11.1	14.9	7.6	0.028
Diastolic BP, mm Hg	70±17	69±12	70±12	0.626
HR, bpm	74±14	74±14	74±13	0.868
HR <60 bpm, %	10.4	8.4	12.1	0.227
Logistic EuroSCORE, %	19.9 (10.9–34.0)	21.0 (11.0–35.3)	19.5 (10.9–31.6)	0.280
Site of intervention				0.089
University Hospital Bonn, %	41.5	38.2	44.7	
University Hospital Düsseldorf, %	30.7	29.4	31.9	
University Hospital Cologne, %	27.9	32.5	23.4	
eGFR	44.6 (31.6–60.6)	48.7 (35.1–62.9)	40.6 (29.0–58.1)	0.005
>60 mL/min/m ² , %	25.5	29.6	21.6	0.001
30–60 mL/min/m ² , %	52.8	55.8	49.8	
<30 mL/min/m ² , %	21.7	14.6	28.6	
Haemodialysis, %	1.7	0.4	3.0	0.070
NT-proBNP, pg/mL	3818 (2067–7423)	3891 (2067–7706)	3634 (2083–7222)	0.756
Echocardiographic findings				
MR severity				0.990
3+, %	28.9	28.9	28.8	
4+, %	71.1	71.1	71.2	
EROA, mm ²	28.4 (20.0–38.2)	29.3 (20.4–39.7)	27.5 (20.0–35.7)	0.274
LVEF, %	32.2 (26.0–39.7)	30.3 (25.0–35.6)	34.4 (27.9–42.8)	<0.001
40%–50%, %	23.9	14.5	34.0	<0.001
LVEDV, mL	175 (135–222)	185 (152–230)	164 (124–207)	<0.001
LVESV, mL	119 (84–154)	127 (99–165)	104 (70–139)	<0.001
LA volume, mL	101 (79–126)	102 (79–123)	101 (79–129)	0.642
SPAP, mm Hg	48±17	49±16	48±16	0.603
TAPSE, mm	17±5	17±5	17±5	0.551
TR severe or more, %	25.2	24.7	25.8	0.803

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

BMI, body mass index; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GDMT, guideline-directed medical therapy; HR, heart rate; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Statistical significance was set as a two-sided $p < 0.05$. All analyses were conducted using Stata V.15.1 (StataCorp, College Station, Texas, USA).

RESULTS

Baseline characteristics

Among 463 included patients, the mean age was 74 ± 9 years and 72.6% were of male sex (table 1). The median LVEF was 32.2% (IQR: 26.0–39.7), and 23.3% of the patients had an LVEF between 40% and 50%. Technical success was achieved in 98.7%, and the rate of reduction in MR to 2+ or less was 94.6% (online supplemental table 2).

Of these, 228 patients (49.2%) were treated with GDMT at discharge (figure 1). The use of beta-blockers, RAS inhibitors, and MRAs was 92.0%, 79.9%, and 60.5%, respectively. Between sites of intervention (ie, University Hospitals of Bonn, Düsseldorf and Cologne), the proportion of GDMT was comparable (45.3%, 47.2% and 57.4%, respectively; $p = 0.089$). The detailed dose of each drug is summarised in table 2. In addition, medical therapy before the procedure is shown in online supplemental table 3.

Also, GDMT based on the 2016 ESC HF guidelines (ie, both RAS inhibitors and beta-blockers and, in patients with an LVEF of $\leq 35\%$, MRAs) was achieved in 292 patients (63.1%).

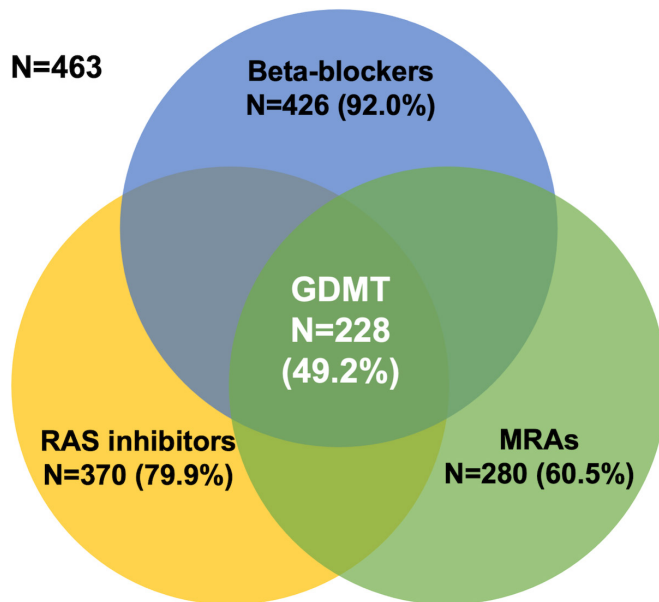


Figure 1 Prevalence of medical therapy in the study population. Venn diagram indicating the prevalence of medical therapy in the study population. GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system.

Baseline characteristics of patients with or without GDMT are shown in [table 1](#). Patients with GDMT were younger, more likely to be male, had lower LVEF, larger LV volumes and different patterns of comorbidities, compared with those without GDMT. In contrast, the rates of implantation success and reduction in MR to 2+ or less were comparable between the groups (online supplemental table 2). Consequently, propensity scores were differently distributed between patients with and without GDMT (online supplemental figure 2).

After IPTW adjustment, all variables were well balanced, with all absolute standardised differences less than 10% ([table 3](#) and online supplemental figure 3), and propensity score distribution

Table 2 Medical therapy for heart failure upon discharge

	All n=463	GDMT n=228	Non-GDMT n=235	P value
Beta-blocker, %				<0.001
None	8.0	0.0	15.8	
1%–24%	8.6	8.8	8.5	
25%–49%	26.8	29.8	23.8	
50%–99%	38.4	40.8	36.2	
100%	18.2	20.6	15.7	
RAS inhibitor, %				<0.001
None	20.1	0.0	39.6	
1%–24%	13.8	20.2	7.7	
25%–49%	30.7	37.3	24.3	
50%–99%	23.8	30.7	17.0	
100%	11.7	11.8	11.5	
MRA, %	60.5	100.0	22.1	<0.001
Loop diuretics, %	87.7	92.1	83.4	0.004
Standardised furosemide equivalent, mg/day	40 (20–60)	40 (20–60)	35 (20–60)	0.299

Values are either % or median (IQR).

GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system.

Table 3 Baseline characteristics after inverse probability of treatment weighting

	Weighted study population		Absolute standardised difference, %
	GDMT	Non-GDMT	
Age, year	74.2 (10.0)	74.0 (8.4)	2.1
Male, %	73.0	72.7	0.7
BMI, kg/m ²	26.1 (4.9)	26.2 (4.4)	1.5
DM, %	35.1	33.7	3.0
CAD, %	68.5	68.4	0.3
Prior MI, %	44.6	44.3	0.6
COPD, %	17.0	17.1	0.1
CIED, %	55.7	56.8	2.4
CRT, %	20.0	20.2	0.7
NYHA class III/IV, %	80.8	80.8	0.0
Atrial fibrillation, %	60.6	60.9	0.5
SBP <100 mm Hg, %	11.9	11.9	0.1
HR <60 bpm, %	10.2	9.9	1.3
Logistic EuroSCORE, %	23.4 (15.7)	22.9 (15.4)	3.7
Institutions			0.8
University Hospital Bonn, %	39.2	39.5	
University Hospital Düsseldorf, %	30.2	30.2	
University Hospital Cologne, %	30.6	30.3	
eGFR			1.1
>60 mL/min/m ² , %	23.7	21.0	
30–60 mL/min/m ² , %	49.9	52.5	
<30 mL/min/m ² , %	26.4	26.5	
Haemodialysis, %	2.2	1.8	3.0
Log NT-proBNP	8.3 (1.2)	8.3 (1.1)	2.4
MR severity: 4+, %			0.3
EROA, mm ²	29.7 (13.8)	29.8 (13.4)	0.6
LVEF, %	32.1 (8.2)	32.3 (9.6)	2.3
LVEDV, mL	185 (72)	183 (70)	2.0
SPAP, mm Hg	48.7 (15.6)	48.9 (15.8)	1.0
TAPSE, mm	16.9 (4.5)	17.0 (4.7)	0.4
TR severe or more, %	26.5	26.8	0.6
Standardised furosemide equivalent	72.0	72.1	1.5

Values are either mean (SD) or %.

BMI, body mass index; CAD, coronary artery disease; CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GDMT, guideline-directed medical therapy; HR, heart rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

between the two groups achieved adequate balance (online supplemental figure 2).

Clinical outcomes

The median follow-up period was 528 days (IQR: 348–842). Within 2 years, 92 patients (19.7%) died from all causes, including 76 due to cardiovascular causes. Two-year clinical follow-up was complete in 249 patients. IPTW-adjusted Kaplan-Meier curves showed that patients with GDMT had a lower incidence of all-cause mortality within 2 years after TEER, compared with those

Valvular heart disease

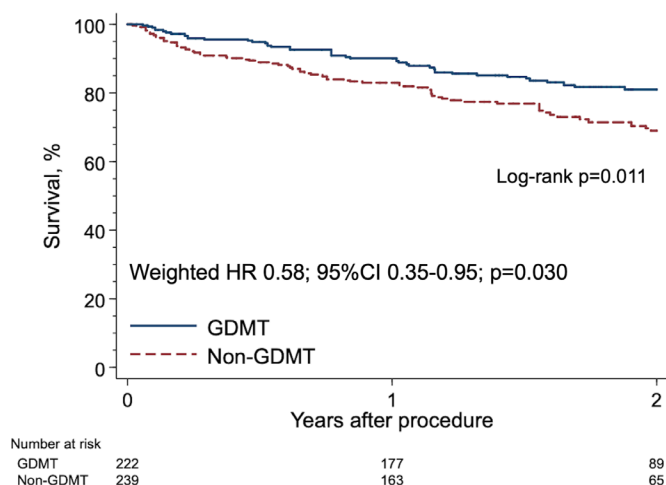


Figure 2 Inverse probability of treatment weighting-adjusted Kaplan-Meier analysis of all-cause mortality. An inverse probability of treatment weighting-adjusted Kaplan-Meier curve of all-cause mortality within 2 years after transcatheter edge-to-edge mitral valve repair for patients with guideline-directed medical therapy (GDMT) versus those without GDMT.

without GDMT (19.8% vs 31.1%, $p=0.011$; figure 2). In the IPTW-adjusted Cox proportional hazards analysis, GDMT was associated with a reduced risk of all-cause mortality within 2 years after TEER (weighted HR: 0.58; 95% CI: 0.35 to 0.95; $p=0.030$; figure 2). The association between GDMT and 2-year mortality was consistent across the subgroups, including pre-procedural LVEF ($\leq 40\%$ or $>40\%$; p for interaction=0.835; figure 3).

In the sensitivity analysis, the association between GDMT and all-cause mortality was consistent (non-weighted HR: 0.52; 95% CI: 0.33 to 0.81; $p=0.004$; online supplemental table 4).

Echocardiographic follow-up

Echocardiographic assessments at 1 year after TEER were available in 192 patients (41.5%) (online supplemental table 5). The

median LVEF was 33.2% (IQR: 25.8–41.6), and the median LV end-systolic volume was 117 mL (IQR: 79–172). LV reverse remodelling was observed in 64 patients (33.9%). Patients with GDMT had a higher rate of LV reverse remodelling than those without GDMT (40.2% vs 26.8%; $p=0.038$).

Medication follow-up

Detailed information about medical therapy at 3 months and 1 year after TEER is shown in online supplemental table 6. In both groups, the dose of beta-blockers and RAS inhibitors was comparable between baseline and follow-up, while the proportion of MRAs in patients with GDMT decreased at 3-month and 1-year follow-ups from baseline.

DISCUSSION

In the present study using a multicentre cohort of patients with SMR with LVEF $<50\%$ who underwent TEER, we investigated the prognostic benefit of GDMT, defined as triple therapy consisting of beta-blockers, RAS inhibitors and MRAs, using the IPTW analysis. The main findings can be summarised as follows:

1. Approximately half of patients with SMR who underwent TEER were treated with GDMT at discharge based on the 2021 ESC HF guidelines.
2. GDMT was associated with a reduced risk of mortality within 2 years after TEER, which was consistent among all pre-defined clinical subgroups, including pre-procedural LVEF ($\leq 40\%$ or $>40\%$).
3. Patients with a GDMT were likely to have LV reverse remodelling at 1 year after TEER.

Optimisation of medical therapy is the first-line therapy for patients with SMR.³ Numerous studies have demonstrated that medical therapy plays a pivotal role in the global range of patients with HF. Nevertheless, there is still a sizeable proportion of patients with SMR who do not receive optimal medical therapy in clinical practice, due to age, blood pressure, renal function and comorbidities.^{6,7} In the present cohort, approximately half of patients undergoing TEER for SMR were not treated with GDMT upon discharge, which was comparable with the COAPT

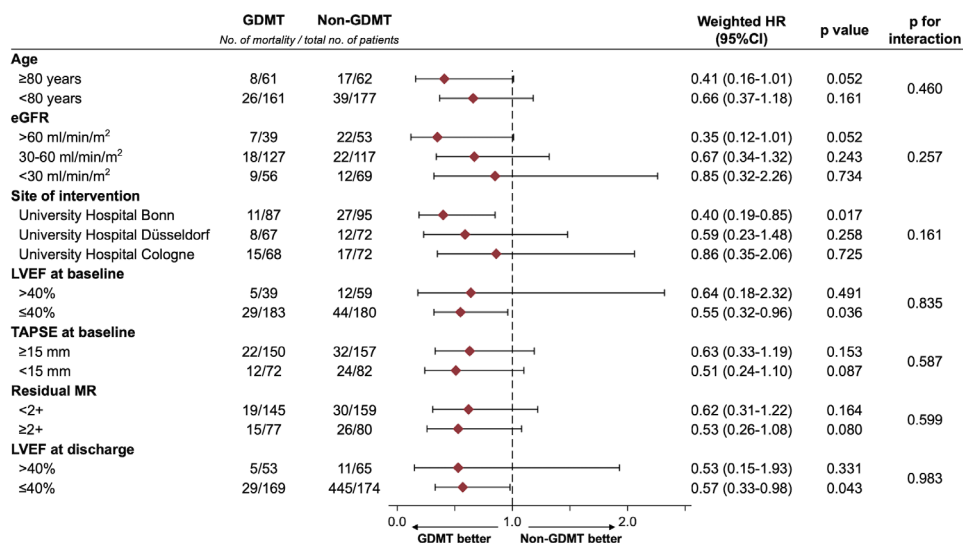


Figure 3 Subgroup analysis of the association between guideline-directed medical therapy (GDMT) and all-cause mortality within the inverse probability of treatment weighting-adjusted population. A forest plot illustrates the association between GDMT and all-cause mortality for prespecified subgroups within the inverse probability of treatment weighting-adjusted population. eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion.

trial and other previous studies.^{4 6 7 15} Nevertheless, it has been little known about the clinical relevance of GDMT after TEER.

We tested the hypothesis whether the optimisation of medical therapy based on the HF guidelines improves clinical outcomes of patients undergoing TEER for SMR. Since the adherence to GDMT is affected by various patient factors, the effects of optimising medical therapy have multiple potential confounders. To overcome the bias related to these potential confounders, we used IPTW analysis, which is a statistical approach to infer a causal association and allows increasing the weight of under-represented observations to reduce the imbalances related to treatment allocation, thereby mimicking the effect of randomisation on baseline characteristics.¹⁶ In the IPTW analysis, GDMT based on the 2021 ESC HF guidelines was associated with a reduced risk of 2-year mortality after TEER. Furthermore, this association was consistent with the subgroup analysis that was stratified by patient characteristics and post-procedural findings. Our findings collectively indicate the causal association of GDMT with mortality after TEER in patients with SMR.

The potential explanations for the association of GDMT with mortality are multifactorial. A plausible reason may be related to the higher rate of LV reverse remodelling in patients with GDMT. Reduction in MR by TEER can improve LV function and reduce LV volumes, which itself consequently might lead to improved clinical prognosis.¹¹ Furthermore, owing to the positive effects on LV reverse remodelling, GDMT may further ameliorate MR even after the initial reduction of MR and potentially reduce the risk of recurrent MR, thereby improving clinical outcomes.^{17–19}

The reduction in MR and the optimisation of medical therapy are two pivotal managements in patients with SMR. There might be synergistic benefits of TEER and medical therapy on clinical outcomes. Besides the GDMT upon discharge, we showed that patients with residual MR <2+ had a lower risk of mortality (unadjusted HR: 1.58; 95% CI: 1.04 to 2.41; $p=0.034$), indicating that the reduction of MR by TEER also plays a key role in clinical outcomes in patients with SMR. Our findings emphasise that TEER and GDMT should go ‘hand in hand’, and GDMT should not be neglected after TEER for SMR.

Owing to multiple options of neurohormonal antagonists for HF, there are various possible combinations of medical therapy, which have different prognostic benefits.²⁰ In the present study, the lack of RAS inhibitors or MRAs accounted for the majority of patients without GDMT, while the proportion of use of beta-blockers was relatively high (85%). The lack of RAS inhibitors or MRAs might be due to renal dysfunction, hyperkalaemia or hypotension; however, the association between GDMT and mortality was consistent after adjustment for the potential confounders. These findings may collectively indicate a possibility that the inferior results in the non-GDMT group were mainly driven by the lack of RAS inhibitors or MRAs. Nevertheless, larger studies are needed to investigate the clinical benefits of each neurohormonal antagonist and their combination in patients undergoing TEER for SMR.

There are limited data about the effect of neurohormonal antagonists on HF with an LVEF between 40% and 50%, which is referred to as ‘mildly reduced EF’. Recent retrospective analyses revealed the clinical benefits of neurohormonal antagonists for HF with mildly reduced EF as well as for that with reduced EF (ie, LVEF <40%).^{21–23} Accordingly, the 2021 ESC HF guidelines now provide recommendations on medical therapy for patients with mildly reduced EF, including beta-blockers, RAS inhibitors and MRAs. The present study revealed no significant interaction between the clinical benefits of GDMT and

pre-procedural LVEF ($\leq 40\%$ or $>40\%$). In settings of MR, due to the afterload-reducing effect of MR, LV systolic dysfunction is likely underestimated. Therefore, the severity of the underlying LV dysfunction in patients with SMR and mildly reduced EF may resemble that of patients with reduced EF but without MR. Thus, GDMT may have prognostic benefits in patients with mildly reduced EF who underwent TEER for SMR, as well as those with reduced EF.

Limitations

First, our results need to be interpreted within the limitations of a retrospective, observational study. The present analyses are subject to a selection bias, which we attempted to correct by using an IPTW-adjusted approach. Nonetheless, several unmeasured confounders may have affected our results. Second, the management of medical therapy was not adjudicated by a core laboratory, and we could not assess the patient compliance to the prescribed medical therapy. In the present analysis, approximately half of patients were not treated with GDMT, and the number of patients treated with medical therapy at the target dose was small, which might be partially explained by the ineligibility of medical therapy. Among patients without GDMT, 41.8% had any of the factors related to the ineligibility (ie, systolic blood pressure <100 mm Hg, heart rate <60 beats/min or eGFR <30 mL/min/m²),⁸ although detailed reasons for the intolerance of GDMT were not recorded. The present study was the analysis of data from the multicentre, real-world registry, and therefore, we believe that our findings are generalisable to the clinical practice in the real-world setting. Third, the present study did not have a control arm consisting of patients treated with medical therapy alone. Therefore, we could not evaluate the relative improvements in prognosis with TEER compared with medical therapy only. Fourth, we did not assess the effects of novel HF drugs, including SGLT2 inhibitors, although SGLT2 inhibitors have a class I indication for patients with HF with reduced EF in the current guidelines.⁸ Therefore, further investigation is necessary to examine the beneficial effects of the new drugs in patients undergoing TEER. Finally, approximately 45% of patients were lost to clinical follow-up within 2 years, and information about echocardiographic assessments and medications at follow-up was not fully available. However, the selection bias due to the loss to clinical follow-up might be limited since patient characteristics were comparable between patients with completed and lost follow-up (online supplemental table 7).

CONCLUSION

GDMT, defined as triple therapy consisting of beta-blockers, RAS inhibitors and MRAs, was associated with a reduced risk of all-cause mortality within 2 years after TEER for SMR. Furthermore, GDMT was linked to a greater LV reverse remodelling after TEER. Our findings suggest that optimisation of medical therapy is crucial to improve clinical outcomes in patients undergoing TEER for SMR.

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