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Guideline-directed medical treatment in patients undergoing transcatheter edge-to-edge repair for secondary mitral regurgitation

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Abstract

Introduction:

Guideline-directed medical therapy (GDMT), based on the combination of beta blockers (BB), renin-angiotensin system inhibitors (RAS-I), and mineralocorticoid-receptor antagonists (MRA), is known to have a major impact on the outcome of the patients with heart failure with reduced ejection fraction (HFrEF). Although GDMT is recommended prior to M-TEER, not all patients tolerate it. We studied the association of GDMT prescription with survival in HFrEF patients undergoing mitral valve transcatheter edge-to-edge repair (M-TEER) for secondary mitral regurgitation (SMR).

Methods and results:

EuroSMR, a European multicenter registry, included SMR patients with left ventricular ejection fraction of less than fifty percent. The outcome was 2-year all-cause mortality. Of 1344 patients, BB, RAS-I, and MRA were prescribed in 1169 (87%), 1012 (75%), and 765 (57%) patients at the time of M-TEER, respectively. Triple GDMT prescription was associated with a lower 2-year all-cause mortality compared to non-triple GDMT (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.60–0.91). The association persisted in patients with glomerular filtration rate of <30ml/min, ischemic etiology, or right ventricular dysfunction. Further, a positive impact of triple GDMT prescription on survival was observed in patients with residual MR of ≥2+ (HR, 0.62; 95% CI, 0.44–0.86), but not in patients with residual MR of ≤1+ (HR,

0.83; 95% CI, 0.64–1.08).

Conclusion:

Triple GDMT prescription is associated with higher 2-year survival after M-TEER in HFrEF patients with SMR. This association was consistent also in patients with major comorbidities or non-optimal results after M-TEER.

Key words: guideline-directed medical therapy; secondary mitral regurgitation; heart failure with reduced ejection fraction; transcatheter edge-to-edge-repair; comorbidities; residual mitral regurgitation

Introduction

Guideline-directed medical therapy (GDMT) including beta-blockers (BB), renin-angiotensin system inhibitors (RAS-I), and mineralocorticoid-receptor antagonists (MRA) reduces mortality in patients with systolic heart failure (HF) [1, 2]. The importance of GDMT is similar in patients with secondary mitral regurgitation (SMR) and such medical treatment is recommended prior to mitral valve transcatheter edge-to-edge repair (M-TEER)[3]. However, not all patients tolerate the intended medication with all 3 drug classes (triple GDMT), because of coexisting conditions such as low systemic blood pressure, hyperkalemia, bradycardia, and renal failure. Indeed, in 2 recent randomized clinical trials, MITRA–FR and COAPT, prescription rates for BB, RAS-I, and MRA were approximately 90%, 70%, and 50%, respectively, although GDMT was requested as study inclusion criteria [4, 5] and in COAPT a committee screened all potential individuals and required specific reasons if a drug class was not prescribed or if there was not maximal up-titration. The rigorous evaluation of HF medication for study inclusion in COAPT, which was not available in MITRA-FR, has been considered as one potential reason for the opposing results of both trials.

According to previous studies, M-TEER has been reported to be associated with reverse remodeling of the left ventricle [6, 7]. Nevertheless, the exact contribution of GDMT on survival after successful M-TEER has not been sufficiently investigated. Thus, this study aimed to investigate the impact of GDMT prescription at the time of M-TEER treatment on survival

and whether such impact differs based on CKD, HF etiology, and residual MR (resMR) in HF patients with reduced left ventricular ejection fraction (LVEF) undergoing M-TEER for SMR.

Methods

Study population

The EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry (registered at German Clinical Trials Register; DRKS00017428) is an international, multicenter, retrospective large patient cohort from eleven academic centers across Europe (France, Germany, Italy, Portugal, and Switzerland). The current study collected data on the clinical characteristics and outcomes of HF patients with SMR who underwent M-TEER between 2008 and 2020. This study protocol conforms to the 1975 Declaration of Helsinki and is in line with the local ethical guidelines. All patients were judged to be at high or prohibitive surgical risk. The recommendation for M-TEER was made by an interdisciplinary Heart Team at each center, considering SMR severity, cardiac function, symptoms, patient history, HF medication, and life expectancy. Up-titration of HF medication and cardiac resynchronization therapy were performed, if clinically indicated. Patient characteristics including age, sex, diabetes mellitus, atrial fibrillation and/or flutter, chronic obstructive pulmonary disease, history of myocardial infarction, stroke, New York Heart Association (NYHA) classification, estimated glomerular filtration rate (eGFR), device therapy, echocardiographic findings, and 2-year all-cause mortality were collected. CKD stage 3B was defined as eGFR <45 ml/min. The present analysis included patients with LVEF of <50%. Patients with missing data regarding GDMT were excluded. M-TEER was performed using

either MitraClip NT, NTR or XTR (Abbott Structural Heart, Santa Clara, California) by a standard protocol, as described previously [8].

Definition of GDMT

Triple GDMT was defined as concurrent prescription of 3 HF medication classes, i.e. BB, RAS-I, and MRA at the time of M-TEER after Heart Team evaluation. In the same way, double GDMT, prescription of two of three medication classes; single GDMT, prescription of one or no HF medication class. The sensitivity analysis has shown the highest c-index for defining GDMT as prescription of all three above-mentioned drugs (3/3 GDMT drugs, c=0.536; 2/3 GDMT drugs, c=0.529; 1/3 GDMT drugs, c=0.505). The prescription of an angiotensin receptor-neprilysin inhibitor (ARNI) became a guideline recommended medication in the later inclusion period of this registry. Consequently, ARNI was considered in the category of RAS-I for this analysis. The use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors was not analyzed in this registry due to their late adoption in recent HF guidelines.

Study Endpoint and follow-up

The study endpoint was all-cause mortality during follow-up up to two years. The follow-up was completed on the last medical interview date, the last examination date, or the date when an endpoint event was observed, whichever came first. All-cause mortality at thirty days was

also investigated to assess an association of GDMT with a short-term endpoint.

Echocardiographic analysis

Echocardiography was conducted and assessed by experienced investigators at each institute. All patients underwent transthoracic and transesophageal echocardiography before M-TEER. SMR severity was evaluated using an integrative approach according to the European recommendations for the assessment of native valvular regurgitation [9, 10]. Right ventricle-pulmonary artery coupling was defined as tricuspid annular plane systolic excursion-to-systolic pulmonary artery pressure ratio. Right ventricular dysfunction (RV-Dys) was defined as tricuspid annular plane systolic excursion-to-systolic pulmonary artery pressure ratio <0.274 mm/mmHg [11].

Statistical analysis

Continuous variables are displayed as mean ± standard deviation if the skewness-kurtosis test did not reject the hypothesis of normality. Otherwise, variables are presented as median and interquartile range values. Categorical variables are expressed as absolute numbers and percentages. Continuous variables were analyzed using unpaired Student's t-tests or Mann–Whitney U tests, while Fisher's exact test or the chi-squared test was used for categorical variables. The cumulative incidence of two-year all-cause mortality was assessed using

Kaplan-Meier-estimated curve. The risk of mortality was assessed using Cox regression analysis and expressed as hazard ratio (HR) with 95% confidence interval (CI). Predictors of triple GDMT prescription was assessed using logistic regression analyses and expressed as odds ratio (OR), 95% CI, and p value. Multivariate Cox or logistic regression analysis were conducted backward–forward stepwise selection. Variables with a $p < 0.25$ in the univariate Cox or logistic regression analysis were selected for multivariable Cox or logistic regression analysis. Effect estimation of GDMT was stratified by CKD, HF etiologies (ischemic or non-ischemic cardiomyopathy), RV-Dys, and resMR. For a subgroup-based analysis on renal impairment, study population was divided into two groups: CKD stages 1–3A (eGFR of ≥45 ml/min) and stage 3B–5 (eGFR of <45 ml/min), because the cutoff value was 44 ml/min according to the Liu method. Statistical significance was defined as p-value < 0.05. All statistical analyses were carried out using Stata version 14 (Stata Corp; College Station, TX, USA).

Results

Patient characteristics

Of 1626 EuroSMR patients, 282 (17.3%) patients were excluded from the current analysis due to either an LVEF ≥50% (272 patients) or missing medication data. Accordingly, 1344 patients (mean age: 73 ± 10 years; male: 70%) were included and analyzed. Patients' clinical and echocardiographic characteristics are shown in *Table 1* and *Table 2*. Baseline MR severity of 3+ and 4+ was observed in 644 (48%) and 656 (49%) patients, respectively. The mean LVEF was 31 ± 9 % and the number of patients with LVEF of <30% were 559 (42%). MR severity after M-TEER was ≤1+ in 886 (66%), 2+ in 378 (28%), 3+ in 55 (4%), and 4+ in 25 (2%) patients. At the time of M-TEER, BB, RAS-I, and MRA were prescribed in 1169 (87%), 1012 (75%), and 765 (57%) patients, respectively. *Table 3* compares the medication rates in EuroSMR with the published results from COAPT and MITRA-FR. In EuroSMR, triple, double, and single GDMT were prescribed in 536 (40%), 570 (42%), and 238 (18%) patients, respectively. Of patients with single GDMT, forty did not take any HF medication.

Impact of triple GDMT on 2-year survival

During a median follow-up duration of 602 (IQR: 327–1093) days, 403 (30%) patients died. Follow-up information on survival status was available in 87% and 72% of eligible patients at 1- and 2-year follow-up, respectively *Figure 1* demonstrated that the prescription of triple

GDMT was associated with a higher 2-year all-cause survival than non-triple GDMT (i.e. double or single GDMT) (HR, 0.74; 95% CI, 0.60–0.91; p=0.004). Uni- and multivariate Cox regression analyses for 2-year survival are shown in *Table 4*. Even after adjustment for age, NYHA class IV, CKD stage 3B, diabetes mellitus, previous coronary artery bypass graft (CABG), LVEF, RV-Dys, and resMR ≤1+, triple GDMT prescription was associated with a higher 2-year survival (HR, 0.76; 95% CI, 0.59–0.99; p = 0.045). Supplementary material online, *Figure S1* summarizes the survival curves for patients with triple vs double vs single GDMT prescription, which also reveals a better survival when two instead of one HF medication classes were prescribed. In a subgroup of patients with an LVEF <40% a consistent and comparable reduction of 2-year mortality was observed with triple vs non-triple GDMT (HR, 0.72; 95% CI, 0.57–0.90; p = 0.004), while such association was not statistically significant in patients with an LVEF of ≥40% (HR, 0.77; 95% CI, 0.45–1.33; p = 0.353). The impact of triple GDMT attenuated in patients with an LVEF <40% (HR, 0.77; 95% CI, 0.58–1.02; p = 0.070) after adjustment for age, previous CABG, diabetes mellitus, TR severity, RV-Dys, and resMR ≤1+.

Survival of patients with triple GDMT prescription was better than non-triple GDMT regardless of the omitted heart failure medication class (Supplementary material online, *Figure S2 A-C*). Compared to triple GDMT prescription, non-triple GDMT prescription without BB resulted in 13% lower estimated survival at 2-years (HR, 1.58; 95% CI, 1.18–2.13; p = 0.002).

Similarly, the estimated 2-year survival rates were both 9% lower for non-triple GDMT prescription without RAS-I (HR, 1.40; 95% CI, 1.08–1.80; p = 0.010) and for non-triple GDMT without MRA prescription (HR, 1.36; 95% CI, 1.09–1.69; p = 0.007), respectively, when compared with triple GDMT prescription.

Association of triple GDMT with thirty-day survival

Thirty-day all-cause mortality was observed in 48 patients (4%) and triple GDMT was not associated with 30-day mortality (HR, 0.58; 95% CI, 0.30–1.14; p = 0.114).

Predictors for prescription of triple GDMT

Uni- and multivariate logistic regression analyses for predictors of triple GDMT prescription are shown in *Table 5*. Multivariate logistic regression analysis demonstrated that higher eGFR, lower LVEF, and larger LA volume were significantly associated with a higher triple GDMT prescription rate.

Triple GDMT prescription and two-year survival in patients with chronic kidney disease

The strong association of kidney function with the probability of triple GDMT prescription is shown in more detail in Supplementary material online, Figure S3. In patients with CKD stages 1-3A, triple GDMT was prescribed in 48% of patients, while patients with CKD stages 3B–5

received triple GDMT in only 33% of patients ($p < 0.001$). Beta-blockers were prescribed at high rates regardless of CKD stages, but the prescription of RAS-I and MRA was significantly lower in patients with lower eGFRs (Supplementary material online, *Figure S4*).

While there was no difference in survival between triple and non-triple GDMT prescription in patients with CKD stages 1–3A (*Figure 2A*; HR, 0.92; 95% CI, 0.68–1.25; $p = 0.595$), the Kaplan-Meier analysis demonstrated that prescription of triple GDMT was associated with a significantly higher 2-year survival compared to non-triple GDMT in CKD stages 3B–5 (*Figure 2B*; HR, 0.67; 95% CI, 0.50–0.91; $p = 0.011$) (p for interaction = 0.141). In the subgroup of patients with CKD stages 3B-5, the mean eGFR were 33 ± 8 and 28 ± 10 ml/min for patients with triple and non-triple GDMT prescription, respectively ($p <0.001$).

Triple GDMT prescription and two-year survival in patients with ischemic vs non-ischemic heart failure

A non-ischemic etiology was present in 551 (44%) patients, of which 223 (40%) patients were treated with triple GDMT. In patients with a non-ischemic etiology, there was no difference in survival with respect to GDMT prescriptions (*Figure 2C*; HR, 0.95; 95% CI, 0.68–1.32; $p = 0.754$). An ischemic HF etiology was present in 714 (53%) patients, of which 275 (38.5%) patients were treated with a triple GDMT drug regimen. In patients with an ischemic HF, Kaplan-Maier analysis revealed a significantly lower 2-year survival rate in patients with non-

triple GDMT prescription when compared to patients with triple GDMT prescription (*Figure 2D*; HR, 0.64; 95% CI, 0.48–0.85; p = 0.002). P for interaction between triple GDMT and the etiologies was 0.082. After adjustment for age, NYHA class IV, eGFR, DM, previous coronary artery bypass graft, RV-Dys, and resMR ≤1+, the impact of triple GDMT in ischemic patients persisted (HR, 0.62; 95% CI, 0.43–0.89; p = 0.009).

Triple GDMT prescription and two-year survival in patients with and without RV-Dys

Figure 2E and 2F depicted association of triple GDMT prescription with two-year survival in patients with and without RV-Dys. Triple GDMT prescription was associated with a higher survival rate compared to non-triple GDMT prescription in patients with RV-Dys (*Figure 2F*; HR, 0.63; 95% CI, 0.42–0.94; p = 0.023); however, the association was not observed in patients without RV-Dys (*Figure 2E*; HR, 0.81; 95% CI, 0.59–1.12; p = 0.207) (p for interaction = 0.320).

Triple GDMT prescription and two-year survival according to resMR after M-TEER

M-TEER resulted in a significant MR reduction with resMR rates of 34% and 66% for ≥2+ and ≤1+ at hospital discharge, respectively. In patients with resMR ≤1+ at discharge, triple and non-triple GDMT were prescribed in 362 (40.9%) and 524 (59.1%) patients, respectively. In both patient groups, 2-year estimated survival rates did not differ (*Figure 2G*;

HR, 0.83; 95% CI, 0.64–1.08; p = 0.176). In patients with non-triple GDMT prescription, resMR ≤1+ was related to a lower mortality compared to resMR 2+ (HR, 0.69; 95% CI, 0.53–0.90; p = 0.006).

In patients with resMR ≥2+, triple and non-triple GDMT prescriptions were administered in 174 (38.0%) and 284 (62.0%) of patients, respectively. In these patients, triple GDMT prescription was associated with a significantly higher 2-year estimated survival rate of 68%, while the survival rate was only 54% in non-triple GDMT patients with resMR ≥2+ (*Figure 2H*; HR, 0.62; 95% CI, 0.44–0.86; p = 0.005) P for interaction between triple GDMT and resMR was 0.166.

Discussion

The EuroSMR registry is a large, retrospective, multicenter European registry, which investigates the outcomes of patients undergoing M-TEER for SMR in daily practice. The current analysis, which investigated the association of guideline-directed HF medication and survival in EuroSMR patients, revealed three important findings. First, the prescription rates of HF medication classes were comparable between EuroSMR, COAPT and MITRA-FR. This finding may suggest that a documented Heart Team approach in "daily clinical practice", which is required for procedure reimbursement in some European countries, is associated with the establishment of an optimized medical HF treatment before consideration of M-TEER similar to well controlled RCTs. Nonetheless, the resulting rate of concurrent triple GDMT prescription with BB, RAS-I and MRA appeared to be relatively low. Relevant comorbidities and/or low cardiac outputs in heart failure with reduced ejection fraction (HFrEF) patients with SMR make a triple GDMT prescription difficult or even contraindicated, which might impact survival.

Second, triple GDMT prescription is associated with better survival after M-TEER than non-triple GDMT. It is noteworthy that triple and double GDMT were associated with survival benefit compared to single GDMT. The importance of GDMT prescription and adherence to GDMT in patients with HFrEF has been confirmed in many RCTs to be associated with improved prognosis [12-15]. Indeed, GDMT may reduce SMR from 3+/4+ to ≤2+ in as many as 57% of patients - thus making M-TEER unnecessary[16]. Therefore, GDMT is recommended

before considering M-TEER in HFrEF patients with severe SMR [3, 17, 18]. The current analysis of the EuroSMR registry confirms the positive impact of triple GDMT prescription on mortality reduction and highlights its importance in specific vulnerable patient subgroups of EuroSMR with: (1) advanced CKD stages 4–5, (2) ischemic cardiomyopathies, and (3) RV-Dys. Advanced CKD is one of the strongest independent predictors for reduced survival in HFrEF patients and a major limitation to the administration of RAS-I and MRA [19]. Besides many pathophysiologic mechanisms leading to the cardio-renal syndrome, a sub-optimal GDMT prescription of HF medication is another important aspect for the observed increased mortality. The increased risk of hyperkalemia, bradycardia, and worsening renal failure hamper the prescription especially of RAS-I and MRA in HFrEF patients with CKD stages 3B–5, while the BB prescription was high and comparable in patients with CKD stages 1–3A and 3B–5. However, the current analysis reveals that a significant proportion of HFrEF patients with severe SMR and CKD stages 3B–5 still may benefit from GDMT prescription. In fact, 33% of patients with CKD stages 3B–5 were treated with triple GDMT prescription in EuroSMR, and their estimated 2-year survival rate was 11% higher (67% vs 56% for triple vs non-triple GDMT prescription) when all three HF drugs were prescribed. Thus, clinicians should not avoid RAS-I and MRA in general in HFrEF patients with advanced CKD stages, but should optimize GDMT on an individual basis. A similar approach appears to be warranted in patients with ischemic cardiomyopathies and patients with concomitant RV-Dys. The reduced efficacy of

triple GDMT in patients with less renal dysfunction, normal RV function and resMR 1+ might be explained by several reasons including a reduced statistical power. In such patient groups with lower risks for adverse events, larger sample sizes are needed to show potential statistical differences as compared to high-risk patient groups which suffer from higher event rates.

Third, triple GDMT prescription was strongly associated with survival in patients with resMR ≥2+, this association was less pronounced in patients with resMR ≤1+. Accordingly, clinicians should try to achieve triple GDMT prescription especially for patients with resMR ≥2+, unless patients have contraindications for any of the three key HF drugs. Therefore, triple GDMT appears to be particularly helpful in patients in whom optimal MR reduction to resMR ≤1+ could not be achieved. On the other hand, if patients were at high risk of adverse GDMT effects such as hypotension, bradycardia, hyperkalemia, or acute kidney injury, double GDMT prescription might be justified in patients with resMR ≤1+. The different impact of GDMT on survival based on resMR suggests that resMR ≤1+ might provide similar positive effects on survival equivalent to triple GDMT prescription. Since GDMT has been reported to lead to LV reverse remodeling in HFrEF patients [20, 21] and since recent cohort studies also suggested that M-TEER in HFrEF patients with SMR might be associated with LV reverse remodeling [6, 7], the two different pathophysiological mechanisms of GDMT plus M-TEER resulting in LV reverse remodeling might be the potential key for improved survival in HFrEF patients with severe SMR.

Future studies need to assess whether new HF drug classes such as ARNI and SGLT-2 inhibitors will add further benefits in HFrEF patients undergoing M-TEER for severe SMR. Since SGLT-2 inhibitors improve prognosis in HFrEF patients [22] and protect renal function in patients with CKD [23], SGLT-2 inhibitors should be considered especially in the majority of HFrEF patients with SMR, who suffer from advanced CKD. The impact of triple GDMT without full up-titration vs. double GDMT with up-titration is another important topic, which needs consideration for optimizing patient care in the future. Current guidelines have emphasized that the former approach could be the first choice in HF patients [18]. Furthermore, with the improved cardiac output after M-TEER, the ability to up-titrate HF medications after M-TEER should be evaluated because this might have a significant impact on the timing of M-TEER procedures in relation to the usually performed up-titration of GDMT before M-TEER.

A main limitation of this retrospective analysis of EuroSMR is the lack of information on the achieved up-titrated drug doses and on GDMT changes during follow-up. Due to the study period, the information regarding use of SGLT-2 inhibitors was not available. Further, there was no data on relevant comorbidities during follow-up period which could have affected GDMT prescription rates. The choice of an LVEF <50% for inclusion into our study may be criticized as there is evidence for GDMT only for patients with HFrEF, i.e. with an LVEF <40%. However, a 50% cut-off was chosen in COAPT [5] and the same neurohormonal antagonists indicated in patients with HFrEF may be considered for treatment also in the patients with an

LVEF between 41% and 49%, according to the most recent guidelines [18]. While the number of patients with triple or double GDMT was sufficient, there was a limited number of patients who took one or no HF medication drug; therefore, the statistical power did not allow for a meaningful evaluation of the prognosis in these patients. Finally, given the observational nature of the study, we cannot exclude the possibility that patients who tolerated triple GDMT were actually less severe than those who did not, explaining their better survival rate. However, the EuroSCORE was similar between triple and non-triple GDMT and multivariate analyses including main prognostic factors still showed a positive impact of triple GDMT.

Conclusion

The EuroSMR registry reveals that a "triple" GDMT prescription including the concomitant administration of BB, RAS-I, and MRA in HFrEF patients is associated with higher 2-year survival after M-TEER for severe SMR. The impact of triple GDMT prescription appears to be of particular relevance in patients with advanced kidney disease, ischemic cardiomyopathies, in the presence of additional right ventricular failure, and in patients in whom a resMR grade ≥2+ persisted after M-TEER.

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None.

Conflicts of interest

Dr. Higuchi has received lecture fees from Medtronic Japan, Daiichi Sankyo, and Ono Pharmaceutical Company. Dr. Orban has received speaker fees from Abbott Vascular and Tomtec Imaging Systems. Dr. Adamo has received payment from Abbott and Medtronic. Dr. Melica has received consulting fee and honoraria for lectures from Abbott and honoraria for lectures from Edwards. Dr. Karam has received consultant fees from Edwards Lifesciences and Medtronic and proctor fees from Abbott. Dr. Praz has received travel expenses from Abbott Vascular, Polares Medical and Edwards. LifesciencesDr. Kalbacher has received lecture fees and travel expenses by Abbott and proctor and lecture fees as well as travel expenses by Edwards Lifesciences. Dr. Ludwig has received travel compensation from Abbott Vascular. Dr. Braun has received speaker honoraria from Abbott Vascular. Dr. Windecker has received grants from Abbott, Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo, and V-wave. Dr. Pfister has received consulting fees from Edwards Lifesciences, honoraria for lectures and financial support for attending symposia by Abbott Vascular, and honoraria for lectures from Edwards Lifesciences. Dr. von Bardeleben has received speaker fees from Abbott Vascular and Edwards Lifesciences. Dr. Lurz has

received grants from Abbott Vascular, Edwards Lifesciences, and ReCor Medical. Dr. Petronio has received consulting fees and honoraria for lectures from Abbott and Medtronic, consulting fee from Boston, and honoraria fee from Daiichi Sankyo. Dr. Lindenfeld has received consulting fees from Abbott, AstraZeneca, Alleviant, Boehringer Ingelheim, Boston Scientific, CVRx, Edwards Lifesciences, Merck, and VWave and grants from AstraZeneca, Volumetrix, and Sensible Medical. Dr. Abraham has received consulting fees from Abbott and Edwards Lifesciences. Dr. Hausleiter has received research support and speaker honoraria from Abbott Vascular and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Legends

Structured graphical abstract

Triple GDMT prescription was associated with a lower two-year mortality compared to non-triple GDMT prescription (A). Such association was observed in patients with concomitant comorbidities (B).

CI, confidence interval; CKD, chronic kidney disease; CMP, cardiomyopathy; GDMT, guideline-directed medica; therapy; HR, hazard ratio; MRA, mineralocorticoid-receptor antagonists; M-TEER, mitral valve transcatheter edge-to-edge repair; RAS, renin-angiotensin system; resMR, residual mitral regurgitation; RV-Dys, right ventricular dysfunction; SMR, secondary mitral regurgitation

Figure 1. Association of triple GDMT with 2-year all-cause mortality

Triple GDMT was associated with lower 2-year all-cause mortality than non-triple GDMT in all patients –

CI, confidence interval; GDMT, guideline-directed medical therapy; HR, hazard ratio; M-TEER, mitral valve transcatheter edge-to-edge repair

Figure 2. Impact of GDMT on survival in EuroSMR subgroups

There was no significant difference of 2-year mortality between triple and non-triple GDMT in patients with CKD stages 1–3A (A), nonischemic etiology (C), no RV-Dys (E), and resMR ≤1+ (G). The prognosis in triple GDMT was better than that in non-triple GDMT in patients with CKD stages 3B–5 (B), ischemic etiology (D), RV-Dys (F), and resMR ≥2+ (H).

CI, confidence interval; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HR, hazard ratio; M-TEER, mitral valve transcatheter edge-to-edge repair; resMR, residual mitral regurgitation; RV-Dys, right ventricular dysfunction

Figure S1. Different survival rate dependent on number of key drugs

Compared to single GDMT, triple and double GDMT indicated higher survival rate at two years.

CI, confidence interval; GDMT, guideline-directed medical therapy; HR, hazard ratio; M-TEER, mitral valve transcatheter edge-to-edge repair

Figure S2 Comparison of prognosis between triple and non-triple GDMT

No prescription of BB (A), RAS-I (B), and MRA (C) were associated with worse prognosis in the current cohort.

BB, beta blockers; CI, confidence interval; GDMT, guideline-directed medical therapy; HR, hazard ratio; MRA, mineralocorticoid-receptor antagonists; M-TEER, mitral valve transcatheter edge-to-edge repair; RAS-I, renin-angiotensin system inhibitors

Figure S3. Association of eGFR with triple GDMT prescription

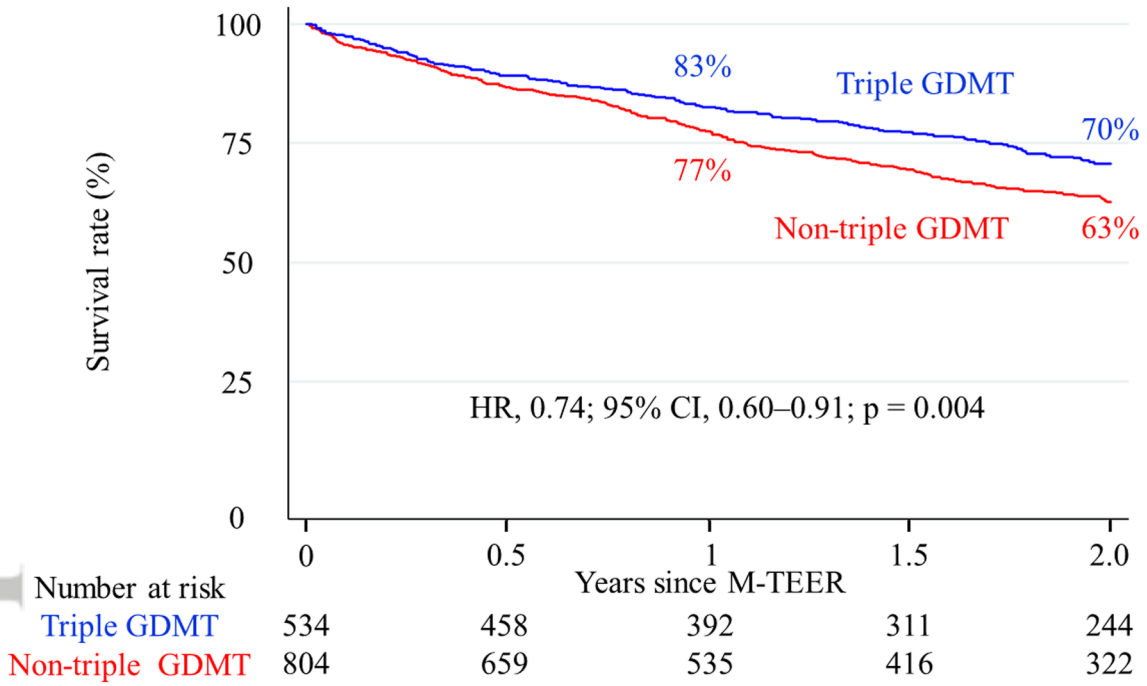
Triple GDMT was achieved more frequently in patients with higher eGFR.

CI, confidence interval; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy

Figure S4. Prescription rate of each GDMT based on CKD stages

Triple GDMT was observed more frequently in patients with CKD stages 1–3A than those with CKD stages 3B–5, due to high prescription rates of RAS-I and MRA. There was no significant difference of BB prescription rate between the groups.

BB, beta blockers; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid-receptor antagonists; RAS-I, renin-angiotensin system inhibitor



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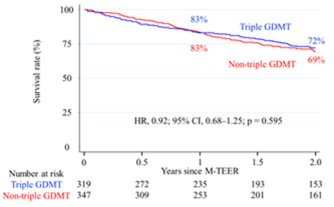
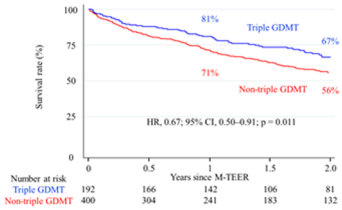
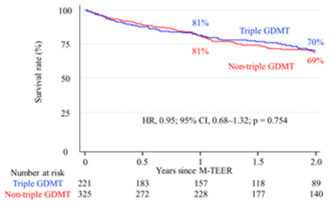
A) CKD stages 1–3A



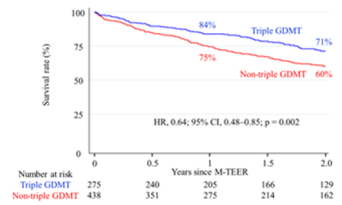
B) CKD stages 3B–5



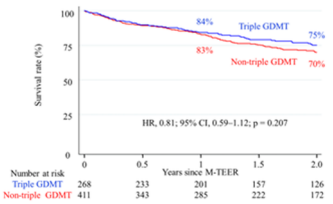
C) Non-ischemic cardiomyopathy



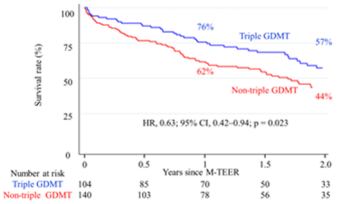
D) Ischemic cardiomyopathy



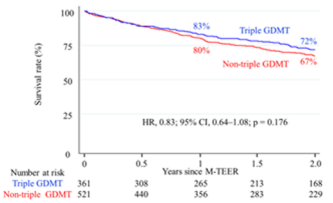
E) Without RV-Dys



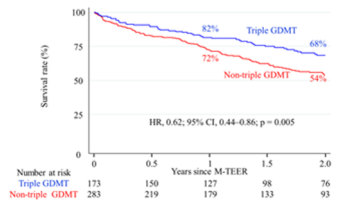
F) With RV-Dys



G) With resMR ≤1+



H) With resMR ≥2+



EJHF_2613_300 Fig 2.tif

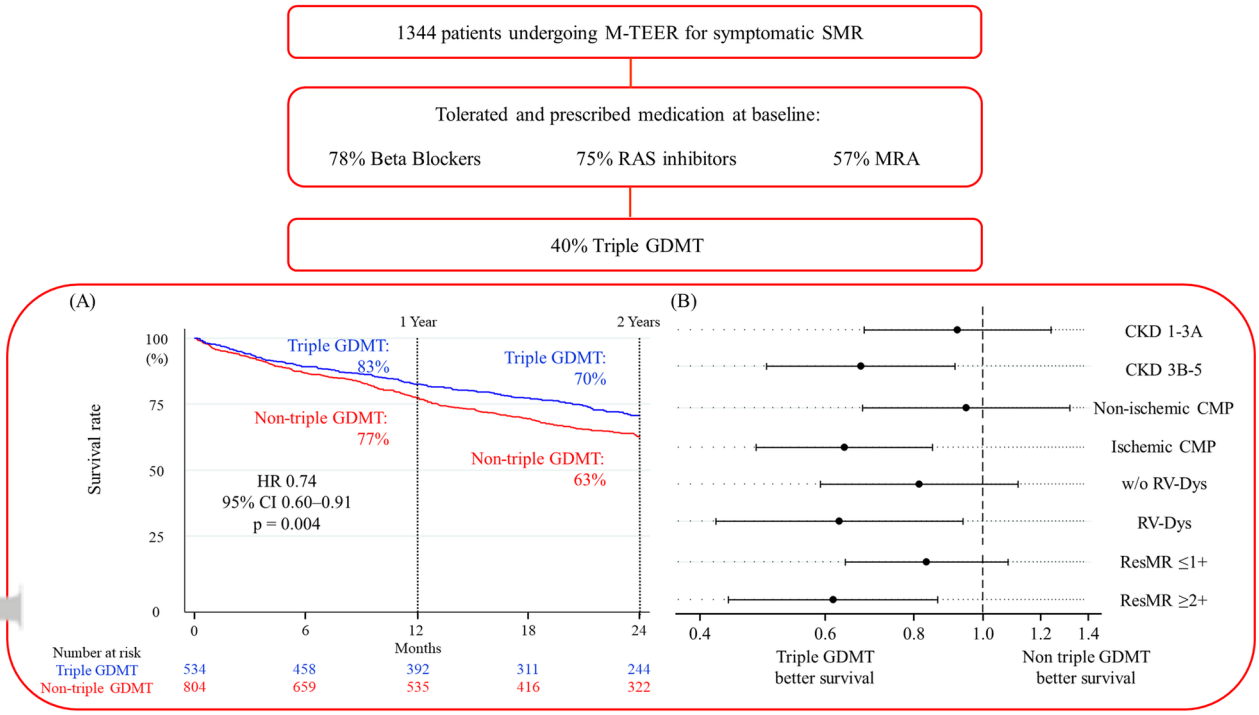


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Table 1. Patient characteristics

	All n = 1344	Triple GDMT n = 536	Non-triple GDMT n = 808	p value
Age, years	73 ± 10	71 ± 11	74 ± 9	<0.001
Body mass index, kg/m^2	26 ± 5	26 ± 5	26 ± 5	0.927
History of myocardial infarction, n (%)	443 (33)	166 (31)	277 (34)	0.206
History of PCI, n (%)	442 (33)	160 (30)	282 (35)	0.054
History of CABG, n (%)	264 (20)	99 (18)	165 (20)	0.378
History of ICD, n (%)	211 (16)	103 (19)	108 (13)	0.004
History of CRT, n (%)	344 (26)	136 (25)	208 (26)	0.879
History of AF or AFL, n (%)	783 (58)	299 (56)	484 (60)	0.134
Ischemic mitral regurgitation, n (%)	714 (53)	275 (51)	439 (54)	0.276
NYHA classification IV at baseline, n (%)	310 (23)	121 (23)	189 (23)	0.728
CKD stages 3B–5, n (%)	595 (44)	194 (36)	401 (50)	<0.001
Diabetes mellitus, n (%)	433 (32)	171 (32)	262 (32)	0.841
Chronic obstructive pulmonary disease, n (%)	219 (16)	80 (15)	139 (17)	0.268
History of stroke, n (%)	119 (9)	49 (9)	70 (9)	0.762
eGFR, ml/min/1.73m2	48 ± 22	54 ± 22	45 ± 22	<0.001
Logistic EuroSCORE	21 ± 16	20 ± 16	22 ± 17	0.068
RAS-I, n (%)	1012 (75)	536 (100)	476 (59)	<0.001
Beta blockers, n (%)	1169 (87)	536 (100)	633 (78)	<0.001
MRA, n (%)	765 (57)	536 (100)	229 (28)	<0.001

AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid-receptor antagonists; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAS-I, renin-angiotensin system inhibitors

Table 2. Echocardiographic characteristics

	All	Triple GDMT	Non-triple GDMT	p value
	n = 1344	n = 536	n = 808	
LVEF, %	31 ± 9	30 ± 8	32 ± 9	<0.001
LVEDV, ml	185 (142-233)	196 (152-248)	178 (135-223)	<0.001
MR severity at baseline				0.151
moderate (2+)	44 (3)	17 (3)	27 (3)	
moderate-to-severe (3+)	644 (48)	240 (45)	404 (50)	
severe (4+)	656 (49)	279 (52)	377 (47)	
MR EROA, cm^2	0.30 (0.20-0.40)	0.29 (0.20-0.39)	0.30 (0.20-0.40)	0.330
MR volume, ml	38 (26-54)	35 (25-51)	40 (27-55)	0.010
MR vena contracta, mm	6.5 (4.9-7.8)	6.7 (5.3-8.0)	6.3 (4.4-8.0)	0.018
LA volume, ml	100 (61-142)	109 (67-147)	94 (54-135)	0.002
TR severity at baseline moderate or higher	751 (56)	308 (57)	443 (55)	0.341
TR vena contracta, mm	5.0 (3.5-6.9)	5.0 (3.6-6.8)	5.0 (3.4-7.0)	0.904
RA area, cm^2	24 ± 8	24 ± 8	24 ± 8	0.542
TAPSE, mm	17 ± 5	17 ± 5	17 ± 5	0.989
sPAP, mmHg	47 ± 14	48 ± 14	47 ± 14	0.340
TAPSE/sPAP, mm/mmHg	0.39 ± 0.18	0.39 ± 0.19	0.39 ± 0.18	0.882
MR severity post TEER				0.652
none or mild (≤1+)	886 (66)	362 (68)	524 (65)	
moderate (2+)	378 (28)	144 (27)	234 (29)	
moderate-to-severe (3+)	55 (4)	23 (4)	32 (4)	
severe (4+)	25 (2)	7 (1)	18 (2)	

EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RA, right atrium; sPAP, systolic pulmonary artery pressure; TAPSE,

tricuspid annular plane systolic excursion; M-TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation

Table 3 Comparison of prescription rate of GDMT in the device group

	EuroSMR	COAPT	MITRA-FR
Beta blockers	87.0%	91.1%	88.2%
RAS-I	75.3%	71.5%	73.0%
MRA	56.9%	50.7%	56.6%

GDMT, guideline-directed medical therapy; MRA, mineralocorticoid-receptor antagonists; RAS-I, renin-angiotensin system inhibitors

Table 4. Survival analysis for 2-year all-cause mortality

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age (per year)	1.02	1.01-1.03	<0.001	1.02	1.01-1.04	0.002
Male	1.03	0.83-1.28	0.777			
Body mass index (an increase of 1 kg/m^2)	0.98	0.96-1.01	0.208			
History of myocardial infarction	1.23	1.00-1.51	0.045			
History of PCI	0.99	0.79-1.24	0.933			
History of CABG	1.38	1.09-1.74	0.006	1.29	0.97-1.73	0.081
History of ICD	1.03	0.76-1.39	0.864			
History of CRT	1.18	0.95-1.47	0.136			
History of AF or AFL	1.15	0.94-1.40	0.185			
Ischemic mitral regurgitation	1.19	0.96-1.47	0.104			
NYHA classification IV	1.75	1.41-2.17	<0.001	1.44	1.09-1.90	0.011
Diabetes mellitus	1.36	1.10-1.68	0.004	1.40	1.09-1.80	0.008
Chronic obstructive pulmonary disease	1.22	0.95-1.57	0.118			
History of stroke	1.29	0.93-1.78	0.128			
NT-proBNP (an increase of 1000 pg/ml)	1.04	1.03-1.05	<0.001			
eGFR (an increase of 10 ml/min)	0.88	0.83-0.92	<0.001			
CKD stage 3B–5	1.57	1.28-1.92	<0.001	1.29	0.99-1.67	0.057
Triple GDMT	0.74	0.60-0.91	0.004	0.76	0.59-0.99	0.045
LVEF (an absolute increase of 10%)	0.90	0.80-1.01	0.063	0.88	0.76-1.02	0.085
LVEDV (an increase of 10 ml)	1.00	0.99-1.01	0.853			
LA volume (an increase of 10 ml)	0.99	0.97-1.00	0.131			
TR severity at baseline of ≥2+	1.39	1.13-1.71	0.002			
RA area (an increase of 10 cm^2)	1.24	1.05-1.45	0.009			
RV dysfunction	2.12	1.66-2.70	<0.001	2.05	1.59-2.66	<0.001
Residual MR ≤1+	0.72	0.59-0.88	0.001	0.79	0.61-1.02	0.074

AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; CI, confidence interval; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid-receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RA, right atrium; RAS-I, renin-angiotensin system inhibitors; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; M-TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation

Table 5. Predictors for prescription of triple GDMT

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age (an increase of 1 year old)	0.97	0.96-0.98	<0.001	0.99	0.97-1.00	0.053
Male	1.23	0.97-1.56	0.093			
Body mass index (an increase of 1 kg/m^2)	1.00	0.98-1.03	0.927			
History of myocardial infarction	0.87	0.69-1.10	0.238			
History of PCI	1.00	0.78-1.30	0.982			
History of CABG	0.92	0.70-1.22	0.555			
History of ICD	1.75	1.27-2.41	0.001			
History of CRT	1.02	0.80-1.32	0.852			
History of AF or AFL	0.84	0.67-1.05	0.127			
Ischemic mitral regurgitation	0.92	0.73-1.16	0.480			
NYHA classification IV	0.96	0.74-1.24	0.751			
Diabetes mellitus	0.98	0.77-1.25	0.894			
Chronic obstructive pulmonary disease	0.84	0.63-1.14	0.269			
History of stroke	1.06	0.72-1.56	0.760			
NT-proBNP (an increase of 1000 pg/ml)	0.98	0.96-1.00	0.028			
eGFR (an increase of 10 ml/min)	1.22	1.15-1.28	<0.001	1.22	1.14-1.31	<0.001
MR at baseline (an increase of 1 stage)	1.20	0.98-1.45	0.075			
LVEF (an absolute increase of 10%)	0.70	0.61-0.79	<0.001	0.76	0.64-0.91	0.002
LVEDV (an increase of 10 ml)	1.04	1.02-1.05	<0.001			
LA volume (an increase of 10 ml)	1.02	1.00-1.04	0.019	1.02	1.00-1.04	0.035
TR severity at baseline of ≥2+	1.07	0.85-1.33	0.572			
RA area (an increase of 10 cm2)	1.06	0.88-1.28	0.541			
RV dysfunction	1.15	0.85-1.54	0.359			

AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft; CI, confidence interval; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate;

EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; RA, right atrium; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation