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CLINICAL RESEARCH
Valvular heart disease

Association of transcatheter edge-to-edge repair with improved survival in older patients with severe, symptomatic degenerative mitral regurgitation

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Background Randomized clinical trials demonstrated transcatheter edge-to-edge repair (TEER) efficacy in improving outcome vs. medical management for functional mitral regurgitation, but limited randomized data are available for the treatment of degenerative mitral regurgitation (DMR). We aimed to compare the outcome of older patients treated with TEER vs. unoperated DMR.

Methods and results Registries including consecutive patients ≥65 years with symptomatic severe DMR treated with TEER (MitraSwiss and Minneapolis Heart Institute registries) or unoperated (MIDA registry) were analysed. Survival was compared overall and after matching for age, sex, EuroSCORE II, and ejection fraction. The study included 1187 patients (872 treated with TEER and 315 unoperated). During 24 ± 17 months of follow-up, 430 patients died, 18 ± 1% at 1 year and 50 ± 2% at 4 years. Patients undergoing TEER had similar age (82 ± 6 vs. 82 ± 7 years) and sex to unoperated patients, but higher surgical risk/comorbidity (EuroSCORE II 3.98 ± 4.28% vs. 2.77 ± 2.46%), more symptoms, and atrial fibrillation ($P < 0.0001$). Transcatheter edge-to-edge repair was associated with lower mortality accounting for age, sex, EuroSCORE II, New York Heart Association class, atrial fibrillation, and ejection fraction [hazard ratio (HR): 0.47, 95% confidence interval (CI): 0.37–0.58; $P < 0.0001$]. After propensity matching (247 pairs of patients), TEER consistently showed better survival compared with unoperated patients (49 ± 6% vs. 37 ± 3% at 4 years, $P < 0.0001$) even in comprehensive multivariable analysis (HR: 0.60, 95% CI: 0.40–0.91; $P = 0.03$). Procedural failure was infrequent but post-procedural mitral regurgitation, remaining moderate-to-severe in 66 (7.6%) patients, was associated with excess mortality vs. trivial residual regurgitation (30 ± 6% vs. 11 ± 1% at 1 year, $P < 0.0001$).

Conclusion Amongst older patients with severe symptomatic DMR at high surgical risk, mitral TEER was associated with higher survival vs. unoperated patients. Successful control of mitral regurgitation was key to survival improvement with mitral TEER, which should be actively considered in patients deemed inoperable.

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Key question

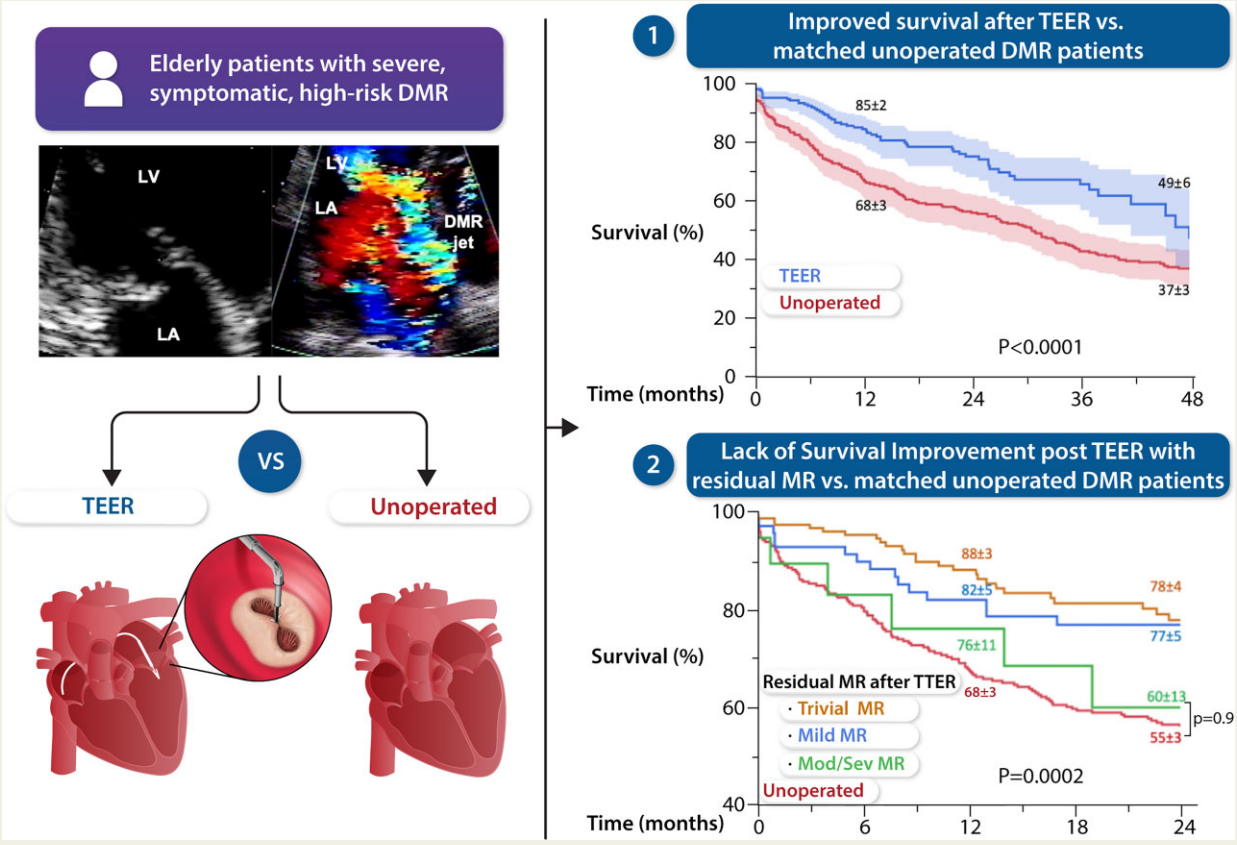
In the absence of randomized clinical trials, survival benefit of transcatheter edge-to-edge repair (TEER) vs. medical management for degenerative mitral regurgitation (DMR) remains unclear. With TEER approved clinical use, randomized trials are not possible, warranting the use of established registries.

Key finding

The study included 1187 patients (872 treated with TEER and 315 unoperated) from 3 registries. After propensity matching (247 pairs), TEER-treated DMR was associated with higher survival than unoperated DMR, also on multivariable analysis. Procedural failure was infrequent but post-procedural mitral regurgitation (moderate-to-severe in 7.6%) was associated with excess mortality.

Take-home message

Among older patients with severe symptomatic DMR at high surgical risk, mitral TEER was associated with higher survival vs. unoperated DMR. Successful control of mitral regurgitation was key to survival improvement with TEER.



Structured Graphical Abstract Comparison of patients with degenerative mitral regurgitation treated with transcatheter edge-to-edge mitral valve repair vs. unoperated.

Keywords Degenerative mitral regurgitation • Transcatheter edge-to-edge repair • Survival

Introduction

Degenerative mitral regurgitation (DMR), anatomically caused by mitral valve prolapse, is the most frequent cause of organic mitral regurgitation in western countries.[1] It is a serious condition associated with excess mortality and cardiovascular morbidity,[2–4] effectively treated with surgical mitral valve repair,[5] which restores life expectancy of affected patients[6] and provides improved outcomes vs. valve replacement in all age strata.[7] Hence, valve repair is now recommended for patients with DMR at low risk for surgery in expert hands, even with no or minimal symptoms.[8]

However, mitral regurgitation, including DMR, is a disease of the aging, often elderly patient[1,9] in whom surgical risk is not minimal and can be substantial,[10] leading to hesitancy in indicating surgery. This hesitancy, compounded by concerns with frequently

associated comorbidity and possibly other factors, leads to considerable undertreatment,[11] even for highly reparable DMR.[1] In turn, surgical undertreatment has led to the development of transcatheter tools aimed at treating mitral regurgitation.[12] Edge-to-edge mitral valve repair conceived initially as a bailout approach during difficult surgical DMR repairs[13] has subsequently been developed as standalone transcatheter therapy (transcatheter edge-to-edge repair, TEER).[12] Randomized clinical trials demonstrated TEER efficacy in improving 2-year clinical outcome of functional mitral regurgitation,[14] but limited randomized data are available for the treatment of DMR. Patients with DMR were partly enrolled in the EVEREST II trial, which compared TEER with mitral surgery and showed improved safety but reduced efficacy,[15] confirmed at long-term follow-up.[16] No other randomized trial has been conducted but 'acceptable' outcome in high-risk (mostly functional mitral regurgitation) patients,[17] yielded TEER approval for treating patients with DMR considered at high-risk for surgical repair. Subsequent registries of patients treated with TEER for DMR have demonstrated that 30-day mortality is not inconsequential with notable 1-year mortality.[18–20] Hence, beyond symptom improvement, it remains difficult to verify[21] whether TEER provides treated DMR patients with improved survival vs. unoperated patients or whether comorbidity is so high in high-risk patients that survival is unaffected. Therefore, current guidelines mention TEER consideration in severely symptomatic patients with DMR and prohibitive risk for surgery, but only as Class II indication, reflecting uncertainty regarding TEER survival benefit, even in the context of patients with no other therapeutic option.[8] To address this conundrum despite lacking randomized trials, the only option is to gather registries of patients, specifically with DMR, TEER-treated or unoperated, and to compare outcome without and with matching for baseline characteristics. We gathered large and well-defined DMR registries in Europe/USA and hypothesized that TEER for DMR in older, symptomatic patients, is associated with improved survival vs. unoperated patients.

Methods

Participating registries and design

In view of lacking clinical trials of TEER vs. medical treatment, comparison of patients enrolled in DMR registries is warranted. Comparing TEER-treated to unoperated DMR patients requires their enrollment with selective surgical indications and as non-TEER-rejects patients. For this purpose, the following registries were used: the MIDA registry is an international registry enrolling consecutive patients from the USA (Mayo Clinic, Rochester, MN) and Europe (France, Italy, and Belgium listed in Supplementary material online, Appendix) tertiary care centres, based on the routine clinical practice of DMR diagnosed by Doppler echocardiography, irrespective of treatment received, between 1985 and 2011. Detailed enrolment criteria and outcomes were presented in detail previously,[3,6,7,22,23] whilst TEER was not available and mitral valve surgery was a selective therapeutic option during the years of the study. The Minneapolis Heart Institute Foundation (MHIF) registry includes prospectively consecutive patients who received TEER for mitral regurgitation enrolled in three hospitals of Minneapolis, St. Paul, MN, USA (Abbott Northwestern Hospital, Minneapolis, MN; United Hospital, St. Paul, MN; Mercy Hospital, Coon Rapids, MN).[24] The prospective MitraSwiss registry involves referral cardiac centres in Switzerland (Supplementary material online, Appendix) enrolling consecutive patients diagnosed with mitral regurgitation and treated with TEER in each centre.[25]

Patients

The patients enrolled represent the consecutive experience of participating centres. Eligibility criteria were (i) DMR diagnosis by transthoracic echocardiography with mitral valve prolapse with or without flail segment; (ii) moderate-to-severe or severe DMR at diagnosis by integrative grading; (iii) age at diagnosis ≥65 years; and (iv) presence of symptoms attributed to DMR (Class II–IV). The exclusion criteria were (i) active endocarditis; (ii) ischaemic mitral regurgitation with flail leaflet due to ruptured papillary muscle; (iii) rheumatic valve disease; (iv) previous valvular surgery; (v) associated mitral stenosis with gradient ≥5 mmHg; (vi) associated ≥ moderate aortic valve disease; (vii) pericardial, myocardial, endocardial disease independent of the DMR; and (viii) patients referred for mitral valve surgery (repair or replacement) as the primary therapeutic approach for DMR after diagnosis. The therapeutic arm assigned was medical in the unoperated patients of the MIDA registry and interventional in patients in whom TEER was attempted, therefore, enrolling patients diagnosed with DMR in Europe and the USA in both arms of the present study. In patients undergoing TEER, the success of the procedure was not an eligibility criterion whilst medical controls were all unoperated patients who did not receive TEER during follow-up. All enrolled patients were consecutively diagnosed or intervened upon in the institution participating in the registries and none was excluded based on criteria different from the listed eligibility.

Clinical data

Clinical evaluation was performed by the patients' personal physician at the tertiary centre of enrolment with assessment of symptoms, comorbid conditions, physical examination, and vital signs. Therapeutic decisions (to remain unoperated or to proceed to TEER) were made by consensus of patient and personal physician after discussion of risks and goals of intervention/surgery and medical treatment. Atrial fibrillation was diagnosed on ECG.

Doppler echocardiography

Transthoracic echocardiography was performed in routine clinical practice in each participating centre with standard windows and views and measurements guided by scientific societies guidelines.[26,27] DMR diagnosis was based on the systolic movement of at least one scallop of a mitral leaflet within the left atrium and by the absence of features other than myxomatous disease. Left ventricular (LV) and left atrial (LA) dimensions were assessed from parasternal views by 2D-guided linear or M-mode measurements at end-diastole and end-systole. Left ventricular ejection fraction (LVEF) was then calculated or estimated visually. Degenerative mitral regurgitation severity was assessed integratively (of specific, supportive, and quantitative signs/measures) as per society guidelines.[27] Haemodynamics measured right ventricular systolic pressure using tricuspid regurgitant velocity by continuous-wave Doppler and estimated right atrial pressure. Residual mitral regurgitation was defined as mitral regurgitation grade at hospital discharge after the procedure.

Follow-up and outcome measures

The primary endpoint was all-cause mortality after DMR diagnosis/intervention. The secondary endpoint was cardiovascular mortality. Patients were followed by their primary physicians at the participating or referral institutions. Data were collected through direct review of

Table 1 Clinical and echocardiographic characteristics in patients with severe symptomatic degenerative mitral regurgitation treated with transcatheter edge-to-edge repair or unoperated

	Overall DMR cohorts			Matched DMR cohort		
	TEER-treated ($n = 872$)	Unoperated ($n = 315$)	*P*-value	TEER-treated ($n = 247$)	Unoperated ($n = 247$)	*P*-value
Age (years)	82 ± 6	82 ± 7	0.5	81 ± 7	81 ± 7	0.09
Female sex (%)	44	42	0.5	43	43	0.9
Body mass index (kg/m^2)	25 ± 4	24 ± 5	0.2	25 ± 5	24 ± 5	0.1
Hypertension Hx (%)	76	46	<0.0001	75	47	<0.0001
Diabetes (%)	15	13	0.02	12	13	0.1
Ischaemic heart disease Hx (%)	48	28	<0.0001	49	31	<0.0001
Atrial fibrillation (%)	58	43	<0.0001	52	43	0.05
EuroSCORE II	3.98 ± 4.28	2.77 ± 2.46	<0.0001	3.00 ± 2.62	3.01 ± 2.61	0.1
NYHA Class III/IV (%)	76	50	<0.0001	77	55	<0.0001
Ejection fraction (%)	58 ± 11	60 ± 12	0.0001	59 ± 10	60 ± 13	0.1
LV end-diastolic diameter (mm)	51 ± 9	55 ± 7	<0.0001	52 ± 8	56 ± 7	<0.0001
LV end-systolic diameter (mm)	34 ± 10	34 ± 9	0.1	36 ± 8	35 ± 9	0.2
Left atrial diameter (mm)	49 ± 11	51 ± 9	<0.0001	49 ± 10	52 ± 9	0.009
sPAP (mmHg)	48 ± 16	51 ± 20	0.03	46 ± 16	52 ± 19	0.003

DMR, degenerative mitral regurgitation; Hx, history; LV, left ventricular; sPAP, systolic pulmonary artery pressure; TEER, transcatheter edge-to-edge repair; NYHA, New York Heart Association.

clinical records, patient/family interviews, local physician communication, and/or follow-up letters and questionnaires, by investigators of each centre.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on distribution normalcy. Variable distributions were assessed visually and with Shapiro–Wilk and Kolmogorov–Smirnov–Lilliefors test. Group comparisons used Student's *t*-test, Mann–Whitney *U* test, or χ^2 test as appropriate for each variable. Outcomes were displayed using Kaplan–Meier method, compared using log-rank test with survival estimates ± standard error reported in figures. Mortality at 30 days and 6 months was compared between TEER-treated vs. unoperated DMR by logistic regression. Cox proportional-hazard models adjusting for baseline characteristics were also conducted to assess long-term outcome. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI) between TEER-treated vs. unoperated DMR. Due to baseline differences in EuroSCORE II between groups, TEER cases were also matched to unoperated patients using the greedy nearest propensity-score matching algorithm, with 0.1 SD calliper, using age, sex (to maintain similarity), and EuroSCORE II. Success of propensity matching was assessed by comparing distributions in matched subsets (using standardized mean differences), followed by univariable and multivariable Cox proportional-hazard models adjusted for covariates of prognostic importance [age, sex, EuroSCORE II, New York Heart Association (NYHA) class, cardiac rhythm, ejection fraction] as well as DMR-related variables (LV/LA diameters, pulmonary pressure) and then individual variables remaining different between TEER-treated and unoperated DMR. To verify that the matching process does not cause bias, other matching modalities (different calipers/input variables/method) were tested and HRs of TEER in these alternative matched subsets were reported. Sensitivity analysis used forest plots displaying corresponding HRs (95% CI) with interaction reported. Analyses were performed using JMP v.14, SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and R version 3.6.2 (R Foundation, Vienna, Austria). A two-tailed a priori alpha level <0.05 was considered significant.

Results

Baseline characteristics

A total of 872 eligible consecutive patients treated with TEER (633 MitraSwiss, 239 Minneapolis Heart Institute) were enrolled in the present study. Their baseline characteristics are reported in *Table 1*. These patients were quite advanced in age (average 82 years), predominantly male with a high frequency of cardiovascular comorbid conditions and high risk with considerably elevated EuroSCORE II. From the DMR point of view, severe symptoms (NYHA Class III/IV) and atrial fibrillation were largely predominant with markedly enlarged left atrium and somewhat reduced ejection fraction. Thus, patients treated with TEER in the cohorts examined present with DMR at a very advanced stage, similarly to all TEER registries. There was no significant difference between the two included TEER registries in regard to baseline patients' characteristics. The characteristics of the 315 patients with severe symptomatic DMR unoperated from the MIDA registry are shown in *Table 1*. Compared with TEER-treated patients, age, sex, body mass index, and LV end-systolic diameter showed no clinical difference. Other baseline characteristics were statistically different, although diabetes, LVEF, and pulmonary pressure did not reach clinically significant difference. Main medications used are reported in Supplementary material online, *Table S1*.

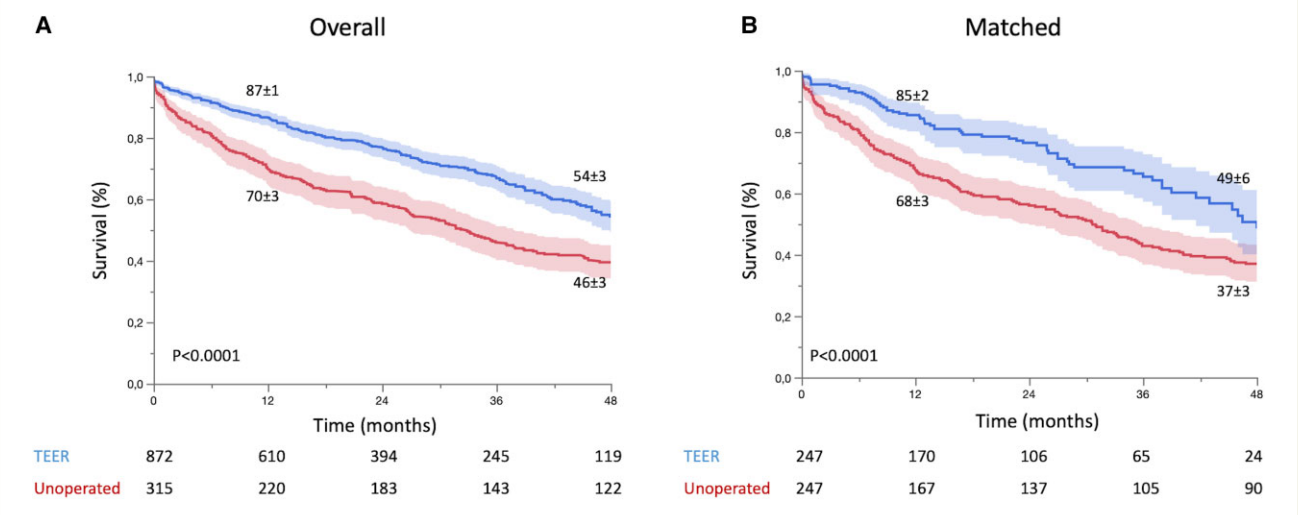


Figure 1 Survival of older patients with severe symptomatic degenerative mitral regurgitation treated with transcatheter edge-to-edge repair compared with those unoperated. (*A*) Comparison involving the entire cohorts. Note the higher survival associated with transcatheter edge-to-edge repair despite baseline higher EuroSCORE II, symptoms, and atrial fibrillation frequency. (*B*) Comparison between matched cohorts. Higher survival associated with transcatheter edge-to-edge repair remains present early and sustained at long term.

Matching of TEER-treated and unoperated patients resulted in 247 pairs with baseline characteristics listed in *Table 1* and was successful with almost identical EuroSCORE II and LVEF in addition to age and sex (standardized differences are presented in Supplementary material online, *Figure S2*). However, matching minimized but did not abolish the more severe symptoms and more frequent atrial fibrillation in the TEER-treated cohort potentially penalizing its survival. Amongst echocardiographic variables, only LV end-diastolic diameter showed notable TEER-treated vs. unoperated DMR difference, but was unassociated with survival (HR: 1.02, 95% CI: 0.99–1.03; $P = 0.2$). Although statistically significant, the difference in systolic pulmonary artery pressure did not reach clinical significance.

Survival of transcatheter edge-to-edge repair-treated and unoperated degenerative mitral regurgitation

In the 1187 patients included amongst all registries, during 24 ± 17 months of follow-up 430 patients died, with combined survival 82 ± 1% at 1 year and 50 ± 2% at 4 years. Of note, survival of unoperated DMR remained stable across years of the MIDA registry (Supplementary material online, *Figure S1*). Overall, 30-day mortality was 3.6% in the TEER-treated vs. 6.3% in unoperated DMR (odds ratio 0.55, 95% CI: 0.31–0.98; $P = 0.04$). Six-month mortality was 8.2% vs. 17.5% (odds ratio 0.42, 95% CI: 0.29–0.62; $P < 0.0001$). Amongst matched patients, 6-month mortality was 6.9% vs. 19.4% (odds ratio 0.31, 95% CI: 0.17–0.55; $P < 0.0001$).

In the entire cohort, long-term survival was much higher in TEER-treated (54 ± 3% at 4 years) vs. unoperated DMR (46 ± 3%, $P < 0.0001$; *Figure 1A*). Cox proportional-hazard models showed univariably >40% mortality reduction (*Table 2*) and in multivariable analysis TEER-treated (vs. unoperated DMR) remained, with any adjustment, associated with markedly reduced mortality with adjusted HR: 0.47 (95% CI: 0.37–0.58; $P < 0.0001$) in the main model and HR: 0.54 (95% CI: 0.39–0.74; $P = 0.002$) adjusting incrementally for echocardiographic characteristics. The effect was stable after inclusion of any other individual baseline characteristic (*Table 2*).

In the matched cohorts, there were 233 deaths observed over a mean follow-up of 24 ± 17 months with survival of 76 ± 2% at 1 year and 44 ± 3% at 4 years.

Direct comparison of matched TEER-treated vs. unoperated DMR of similar age, sex, and EuroSCORE II showed survival at 1 year of 85 ± 2% for TEER-treated vs. 68 ± 3% in unoperated DMR, a difference that remained stable at 4 years (49 ± 6% vs. 37 ± 3%, $P = 0.002$). Matched TEER-treated vs. unoperated DMR survival curves are presented in *Figure 1B*. Cox proportional-hazard models confirmed TEER treatment association with improved survival vs. unoperated DMR (adjusted HR: 0.53, 95% CI: 0.39–0.72; $P < 0.0001$ unadjusted). Further multivariable analysis using progressively extended models showed that results remained stable (adjusted HR: 0.47, 95% CI: 0.34–0.63; $P < 0.0001$ in the main model and after further adjustment for LV/LA dimensions and pulmonary pressure and for any individual baseline characteristic) (*Table 2*). Analysis of alternative matching processes (Supplementary material online, *Figure S3*) showed mostly satisfactory matching range and demonstrated significant TEER-treated vs. unoperated DMR survival benefit in all and remarkably with similar HRs to the main matching process analysis persisted. Thus, irrespective of the matching process selected, TEER was uniformly associated with reduced mortality and by a magnitude uniformly within 40–50%.

Furthermore, survival free from cardiovascular mortality (Supplementary material online, *Figure S4*), confirmed the survival advantage of TEER-treated vs. unoperated DMR, overall and in the matched cohorts.

Subgroup analysis and interaction test are presented as a forest plot. Improved survival associated with TEER was confirmed in all subgroups of patients including those stratified by age (<85 and

Table 2 Multivariable analysis of survival in Cox proportional-hazards models

	Overall cohorts		Matched cohorts	
	TEER-treated vs. unoperated DMR, HR (95% CI)	*P*-value	TEER-treated vs. unoperated DMR, HR (95% CI)	*P*-value
Unadjusted	0.56 (0.46–0.68)	<0.0001	0.53 (0.39–0.72)	<0.0001
Model 1: age, sex, ESII, AF, NYHA Class, LVEF	0.47 (0.37–0.58)	<0.0001	0.47 (0.34–0.63)	<0.0001
Model 2: Model 1 + LV end-diastolic diameter, left atrial diameter, systolic pulmonary artery pressure	0.54 (0.39–0.74)	0.002	0.60 (0.40–0.91)	0.03
Additional adjustment for diabetes	0.56 (0.40–0.77)	0.0004	0.59 (0.37–0.93)	0.03
Additional adjustment for hypertension	0.55 (0.39–0.75)	0.0003	0.63 (0.40–0.98)	0.04
Additional adjustment for ischaemic heart disease	0.56 (0.40–0.79)	0.0008	0.61 (0.39–0.96)	0.04
Additional adjustment for European/US centres	0.55 (0.40–0.75)	0.0002	0.61 (0.39–0.97)	0.04

DMR, degenerative mitral regurgitation; AF, atrial fibrillation; CI, confidence interval; EF, ejection fraction; ESII, EuroSCORE II; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association; TEER, transcatheter edge-to-edge repair; US, United States.

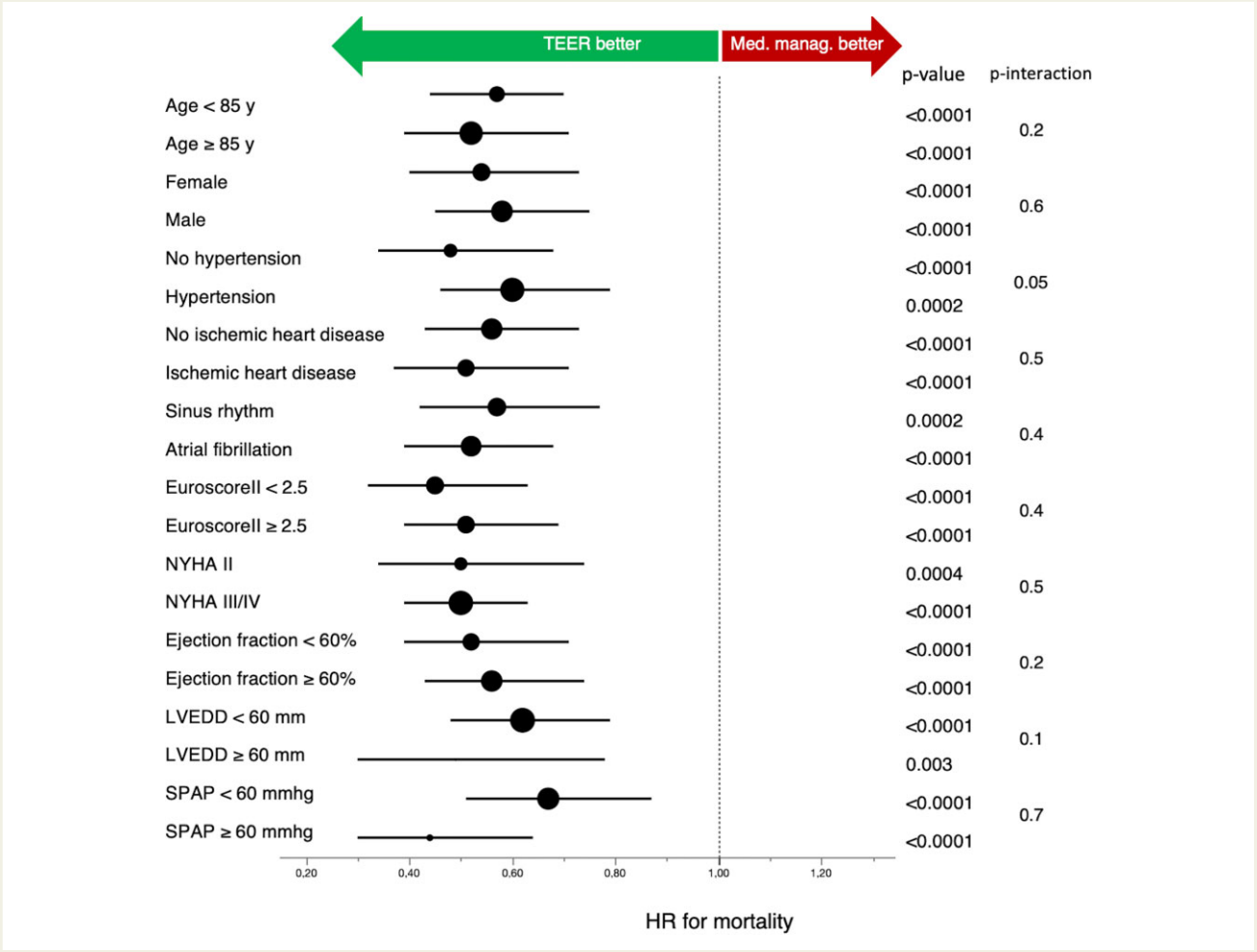


Figure 2 Subgroup analysis of the association of transcatheter edge-to-edge repair with reduced mortality in forest-plot display. Each couple of lines indicates the subgroups with and without a clinical characteristic (e.g. age ≥85 and <85 years) with the bars representing hazard ratios and 95% confidence intervals associated with transcatheter edge-to-edge repair. The size of the dot indicates the relative size of each subset. Note that in all subgroups, transcatheter edge-to-edge repair is always associated with reduced mortality.

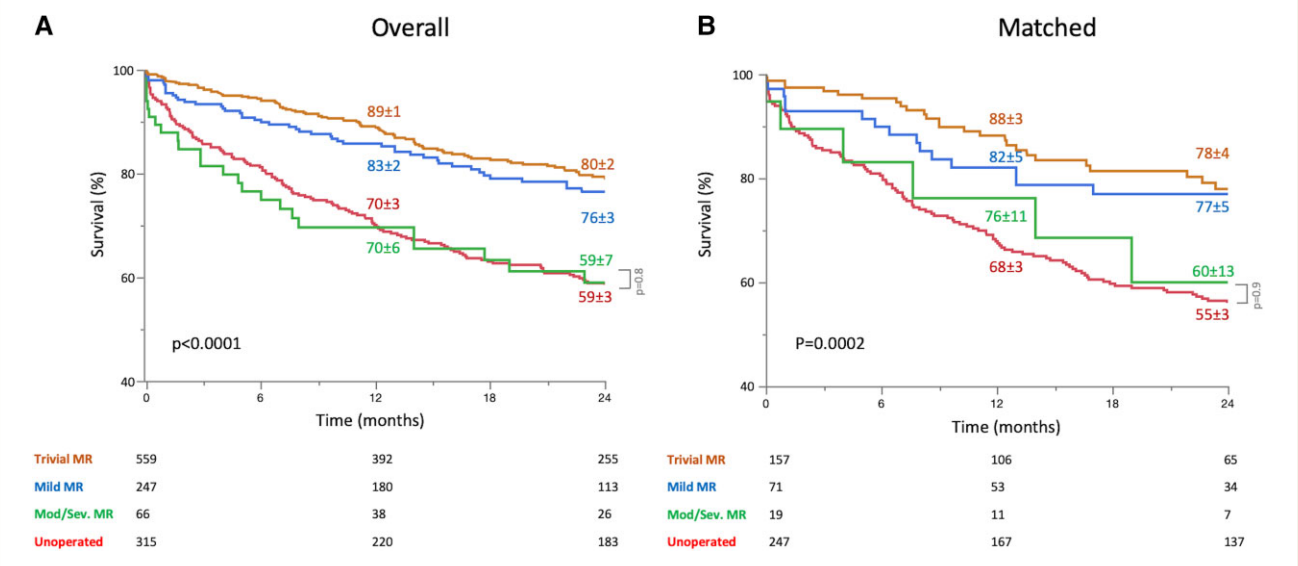


Figure 3 Survival according to the severity of mitral regurgitation after transcatheter edge-to-edge repair in the overall cohort. (*A*) and in the matched cohort. (*B*) Note that moderate or severe post-procedural mitral regurgitation is associated with excess mortality appearing early and sustained similar to that of unoperated patients.

≥85), sex (male and female), NYHA class (Class II and III/IV), rhythm (atrial fibrillation and sinus rhythm), comorbidity/risk (EuroSCORE II <2.5 and ≥2.5), and by a variety of clinical and echocardiographic characteristics such as LV size and elevated pulmonary artery pressures (*Figure 2*). Therefore, the association of TEER treatment with survival benefit over unoperated DMR was confirmed in all specific subgroups.

Procedural success

Amongst the entire TEER cohort, 41/872 patients (4.7%) had procedural complications of various severity (12 device-related complications, 5 cardiac tamponade, 9 complications related to transeptal puncture, 4 vascular perforations, 8 bleeding requiring transfusion, and 3 other types of complications). Overall, procedural failure was immediately diagnosed in 17 patients (2%) and overall, on post-procedural echocardiograms residual, mitral regurgitation at hospital discharge was trivial in 559 (64%), mild in 247 (28%), and remained moderate-to-severe in 66 (7.6%) patients. Median transmitral gradient post-TEER was 3 (2–5) mmHg, with severe mitral stenosis present post-TEER in only 1% of patients.

Residual mitral regurgitation was strongly associated with excess mortality post-TEER: at 1 year 11 ± 1% for trivial residual mitral regurgitation, 17 ± 2% for mild residual mitral regurgitation, and 30 ± 6% for moderate-to-severe residual mitral regurgitation ($P < 0.0001$), and 20 ± 2%, 24 ± 3%, and 41 ± 7%, respectively, 2 years after the procedure ($P = 0.006$). Survival curves (*Figure 3A*) according to residual post-procedural MR demonstrate the immediate mortality toll associated with unsuccessful DMR elimination, sustained medium-/long-term post-intervention; of note, patients with significant residual mitral regurgitation present comparable outcome vs. unoperated DMR. In multivariable analysis, adjusted HR for mortality associated with moderate-to-severe residual DMR was 4.32 (95% CI: 2.16–8.67; $P < 0.0001$) vs. trivial DMR and 1.79 (95% CI: 1.12–2.75; $P = 0.02$) vs. mild DMR, comprehensively adjusted model for age, sex, EuroSCORE II, EF, atrial fibrillation, NYHA class, LV and LA size, and pulmonary artery pressure. Similarly, in the matched subgroup (*Figure 3B*), 19 (7.7%) patients had moderate-to-severe residual MR post-TEER, associated with dismal outcome comparable to unoperated DMR (40 ± 13% vs. 45 ± 3 mortality at 2 years; $P = 0.9$).

Discussion

The present study by coalescing and matching DMR registries, encompassing older patients from Europe and the USA diagnosed with severe, symptomatic DMR provides new and unique insights into the outcome of DMR treatment in such high-risk population and fills the knowledge gap related to lacking randomized clinical trials. First, patients gathered in the registries represent a true therapeutic challenge, quite elderly with frequent heart failure symptoms, atrial fibrillation and high risk for mitral valve surgery, even valve repair. Second, TEER-treated vs. unoperated DMR patients, matching and adjusting for any characteristic, particularly EuroSCORE II, benefit markedly from higher survival, appearing early and sustained at long term. The association of TEER with improved survival persists in all subgroups with mortality reduction ranging from 40% to 50%. An important point of caution is that unsuccessful TEER with residual mitral regurgitation grade three-fourth is associated with considerable excess mortality during follow-up, similar to unoperated DMR, directly linking TEER survival benefit to effective DMR treatment. In elderly patients with severe, symptomatic, high-risk DMR, this results in improved outcomes associated with TEER and a deleterious impact of 'imperfect' procedural success with residual DMR post-TEER (*Structured Graphical Abstract*). These improved outcomes emphasize the

importance of addressing the significant undertreatment of older patients with DMR.

Degenerative mitral regurgitation outcome and undertreatment

Degenerative mitral regurgitation, the most prevalent form of primary mitral regurgitation in the population,[1] is highly surgically reparable,[5,10] generally with low risk, excellent durability,[28] and favourable long-term outcomes in expert hands.[6] Whilst patients with heart failure symptoms or ventricular dysfunction (Class I triggers) should be referred to surgery promptly,[8] the best outcomes are observed in patients operated before the occurrence of LV dysfunction and with no/minimal symptoms.[29] Hence, clinical guidelines have evolved in suggesting prompt consideration of mitral valve surgery even without Class I triggers.[8] Improved quantitative tools for diagnosing severe DMR, strongly associated with clinical outcome, were developed to facilitate diagnosis in routine practice.[4,27,30] However, the recommended early surgery remains underused in community practice,[11] where patients are first evaluated, and undertreatment, whilst not as pronounced as for functional mitral regurgitation, remains pervasive.[1,31] Thus, most patients with DMR are left to endure the natural history of the condition with high incidence of heart failure and atrial fibrillation and excess mortality after diagnosis.[1–3,31] Exhaustive reasons for undertreatment are not enumerated but fear of open-heart surgery in older patients is probably paramount.[32] Indeed, whilst surgical risks have markedly declined for older patients,[10] they remain much higher than in younger patients and can be considered prohibitive. Thus, it is essential to consider transcatheter interventions with the caveat of still unproven survival benefits in patients with DMR.

Transcatheter interventions and their impact on degenerative mitral regurgitation outcome

Traditional treatment of valvular heart diseases is by cardiac surgery and transcatheter valvular therapies first addressed 'inoperable' patients with aortic stenosis, in whom considerable survival benefit firmly established their clinical value.[33] Unfortunately, with mitral regurgitation this has not been the selected approach. The only randomized clinical trial with partial DMR enrolment compared TEER to surgery and left many questions unresolved, with its conclusion of improved safety and reduced efficacy.[15,16] Whilst the COAPT trial has now established TEER superiority vs. medical therapy for functional mitral regurgitation due to LV dysfunction,[14] no such randomized data are available for DMR. Registries of single-arm TEER therapy are encouraging, but are not focusing on DMR and cannot ascertain survival benefit vs. unoperated DMR.[21,34–36] Furthermore, as TEER is now approved for use in clinical practice, the conduct of clinical trials of TEER in patients with DMR appears all but impossible. Hence evaluating potential clinical benefits of TEER in DMR is left to match comparison in registries involving DMR in clinical practice. We assembled patients from the USA/Europe in both TEER and unoperated registries, specifically focused on DMR and routine clinical practice, with widely applicable results. Our data show that TEER treatment for DMR is mostly reserved for patients quite elderly, symptomatic, at an advanced stage of the disease. Similar unoperated DMR patients incur notable excess mortality vs. those treated with TEER despite persistent excess symptoms and arrhythmias with TEER. The link between effective DMR treatment and higher survival post-TEER is strongly suggested by persistent excess mortality in patients with residual DMR post-TEER.[36] Our results strongly support treating DMR patients considered 'inoperable' or 'at very high-risk' with TEER to improve survival. Indeed, despite the advanced age in our cohorts, there is a significant gain in survival after TEER overall and in all subgroups, even in the very elderly beyond the age of 85. Hence, TEER can undoubtedly reduce undertreatment and mortality of high-risk patients with DMR. Indicating TEER is a complex judgement requiring careful evaluation of comorbid conditions, best performed in a heart team setting with diverse specialists of valve diseases. In the quest to reduce DMR undertreatment and its related poor outcome, referral from primary care to specialized teams is essential. Team experience in treating DMR is crucial, as unsuccessful/incomplete TEER with residual regurgitation results in considerable mortality, emphasizing the goal of 'perfect' TEER result. This stringent requirement, not different from surgical repair,[28] probably limits TEER applicability to expert mitral teams. With crucial 'perfection' proviso, improved survival with TEER vs. medical therapy suggests that no patient with DMR should be labelled 'untreatable' and that full consideration of mitral valve surgery and TEER should be widely offered in expert centres by specialized heart teams.

Strengths and limitations

Our study is not a randomized clinical trial, the ultimate method for affirming with certainty therapeutic benefit of an intervention. However, the only randomized trial that included patients with DMR compared TEER vs. mitral valve surgery and cannot address benefit vs. medical therapy.[15,16] With TEER available in routine practice, there is no ethical possibility of withholding treatment and a randomized approach is now impossible. The only registry comparing TEER to conservative management mainly included patients with functional mitral regurgitation and cannot apply to DMR.[21] Our study compares patients enrolled in several registries, but all patients are consecutive. Registries of TEER-treated DMR have baseline characteristics quite similar to the US National Mandatory TVT registry,[18] confirming representativity whilst providing superior data ascertainment and longer follow-up. Furthermore, the MIDA registry is a large and unique consecutive experience with DMR in numerous centres in Europe/USA.[3,6,7,22,23] Finally, matching TEER-treated and unoperated DMR allowed comparison of cohorts at similar risk, although more severe clinical characteristics (functional class and atrial fibrillation) would penalize TEER treatment, further supporting TEER survival benefit. Serum creatinine was not available for all, but renal failure, as categorical variable, showed no difference between groups (15.7% vs. 14.8% in matched unoperated vs. transcatheter edge-to-edge repair-treated DMR, $P = 0.8$). Combination of TEER registries may concern for inhomogeneity, but similar baseline characteristics (age 81 $\pm$ 6 vs. 83 $\pm$ 6, female 45% vs. 44%, hypertension 75% vs. 76%, diabetes 14% vs. 16%, LVEF 58 $\pm$ 9% vs. 57 $\pm$ 12%) and similar outcome (mortality at 1 and 4 years 16 $\pm$ 3%

and 45 ± 6% for TEER-treated patients at MHIF and 13 ± 1% and 46 ± 3% for MitraSwiss, $P = 0.4$) do not reveal differences.

Conclusion

The present study compares for the first time older patients with severe, symptomatic DMR treated with TEER vs. unoperated, overall and matched, and shows post-TEER reduced mortality appearing early and sustained at long term. Unsuccessful TEER with significant residual mitral regurgitation is associated with considerable excess mortality, underscoring the importance of aiming at 'perfect' intervention result. These novel outcome data are crucial to reduce the pervasive undertreatment of mitral regurgitation.

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All the contributors are listed in the Supplementary material online, Appendix.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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