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ORIGINAL RESEARCH

Changes in Left Ventricular Global Longitudinal Strain in Patients With Heart Failure and Secondary Mitral Regurgitation: The COAPT Trial

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BACKGROUND: Left ventricular (LV) global longitudinal strain (GLS) provides incremental prognostic information over LV ejection fraction in patients with heart failure (HF) and secondary mitral regurgitation. We examined the prognostic impact of LV GLS improvement in this population.

METHODS AND RESULTS: The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial randomized symptomatic patients with HF with severe (3+/4+) mitral regurgitation to transcatheter edge-to-edge repair with the MitraClip device plus maximally tolerated guideline-directed medical therapy (GDMT) versus GDMT alone. LV GLS was measured at baseline and 6-month follow-up. The relationship between the improvement in LV GLS from baseline to 6 months and the composite of all-cause death or HF hospitalization between 6- and 24-month follow-up were assessed. Among 383 patients, 174 (45.4%) had improved LV GLS at 6-month follow-up (83/195 [42.6%] with transcatheter edge-to-edge repair+GDMT and 91/188 [48.4%] with GDMT alone; P=0.25). Improvement in LV GLS was strongly associated with reduced death or HF hospitalization between 6 and 24 months (P<0.009), with similar risk reduction in both treatment arms ($P_{interaction}$=0.40). By multivariable analysis, LV GLS improvement at 6 months was independently associated with a lower risk of death or HF hospitalization (hazard ratio [HR], 0.55 [95% CI, 0.36–0.83]; P=0.009), death (HR, 0.48 [95% CI, 0.29–0.81]; P=0.006), and HF hospitalization (HR, 0.50 [95% CI, 0.31–0.81]; P=0.005) between 6 and 24 months.

CONCLUSIONS: Among patients with HF and severe mitral regurgitation in the COAPT trial, improvement in LV GLS at 6-month follow-up was associated with improved outcomes after both transcatheter edge-to-edge repair and GDMT alone between 6 and 24 months.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01626079.

Key Words: COAPT trial ■ heart failure ■ left ventricular global longitudinal strain ■ secondary mitral regurgitation ■ transcatheter edge-to-edge repair

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CLINICAL PERSPECTIVE

What Is New?

- In patients with heart failure and severe secondary mitral regurgitation enrolled in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, improvement of left ventricular global longitudinal strain from baseline to 6-month follow-up was associated with lower rates of subsequent all-cause death, heart failure hospitalization, or both through 24-month follow-up, both after transcatheter edge-to-edge repair plus guideline-directed medical therapy and guideline-directed medical therapy alone.

What Are the Clinical Implications?

- The current findings support serial measurements of left ventricular global longitudinal strain during follow-up of patients who undergo transcatheter edge-to-edge repair, given that the improvement of left ventricular global longitudinal strain at 6 months after transcatheter edge-to-edge repair was associated with the lowest rates of events during subsequent follow-up through 24 months.

Nonstandard Abbreviations and Acronyms

COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
GDMT	guideline-directed medical therapy
GLS	global longitudinal strain
HFH	heart failure hospitalization
MR	mitral regurgitation
TEER	transcatheter edge-to-edge repair

Secondary mitral regurgitation (MR) is common in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF), with a reported prevalence of at least moderate MR ranging between 6% and 29%.[1,2] The presence of significant secondary MR is strongly associated with an increased risk of all-cause mortality, cardiovascular mortality, and HF hospitalization (HFH).[3-5] Patients with severe secondary MR who remain symptomatic despite maximally tolerated guideline-directed medical therapy (GDMT) are often at high risk for surgical treatment of MR.[6,7] As shown in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, in both surgical high- and low-risk patients with HF, transcatheter edge-to-edge repair (TEER) with the MitraClip device (Abbott, Santa Clara, CA) reduces the degree of MR and improves prognosis compared with GDMT alone.[8] However, mortality and HFH rates remained high in the COAPT trial, even after TEER. This observation may be related in part to the severity of concomitant left ventricular (LV) systolic dysfunction. Although LVEF is often used to risk stratify patients, this parameter underestimates the degree of LV systolic dysfunction in patients with HF and significant MR[9] because calculation of LVEF is based on the difference between LV end-diastolic and end-systolic volumes, which combines the forward stroke volume and the backward regurgitant flow into the left atrium.[10] LV global longitudinal strain (GLS) is an alternative echocardiographic parameter to measure LV systolic function and may be a more robust marker of LV performance than LVEF.[11] Previous studies have found that impaired LV GLS was independently associated with all-cause mortality in patients with secondary MR, whereas LVEF was not.[12] Whether improvement in LV GLS after TEER is associated with better outcomes has not been previously investigated. Accordingly, the aim of the current study was to evaluate the characteristics of patients with improvement of LV GLS at 6 months after enrollment in the COAPT trial and the impact of LV GLS improvement on subsequent outcomes.

METHODS

Study Design

The COAPT trial design and end point definitions have been previously published.[13] Briefly, patients with HF, reduced LVEF (range, 20%–50%), and severe secondary MR (≥3+ by echocardiographic core laboratory analysis) who remained symptomatic despite maximally tolerated GDMT were randomized to TEER plus GMDT or GMDT alone. The protocol was approved by the investigational board at each participating center, and all patients provided written informed consent. The trial was sponsored by Abbott. The sponsor participated in site selection and management and provided funding for data analysis. The investigators had unrestricted access to the data and accept the responsibility for the integrity of the present report. The data that support the findings of this report may be made available to qualified investigators on reasonable request to the corresponding author and approval of the COAPT trial Publications Committee.

Table 1. Clinical Baseline Characteristics of LV GLS Improvers Versus Nonimprovers in the Overall Population

Variables	Overall population (N=383)	LV GLS improvers (N=174)	LV GLS nonimprovers (N=209)	*P* value
Clinical characteristics				
Age, y	71±12	72±12	71±11	0.61
Sex, male	236 (61.6)	108 (62.1)	128 (61.2)	0.87
Body mass index, kg/m^2	26.8±5.3	26.3±4.7	27.2±5.7	0.10
Systolic blood pressure, mm Hg	111.1±17.0	111.2±17.4	111.0±16.7	0.90
Diastolic blood pressure, mm Hg	65±9	64±9	66±10	0.10
Ischemic cardiomyopathy	218 (56.9)	108 (66.1)	110 (52.6)	0.06
Hypertension	306 (79.9)	135 (77.6)	171 (81.8)	0.30
Diabetes	127 (33.2)	51 (29.3)	76 (36.4)	0.14
Hypercholesterolemia	200 (52.2)	90 (51.7)	110 (52.6)	0.86
Coronary artery disease	263 (68.7)	128 (73.6)	135 (64.6)	0.06
Previous MI	178 (46.5)	87 (50.0)	91 (43.5)	0.21
Previous PCI	168 (43.9)	80 (46.0)	88 (42.1)	0.45
Previous stroke or TIA	63 (16.4)	30 (17.2)	33 (15.8)	0.70
Peripheral vascular disease	56 (14.6)	31 (17.8)	25 (12.0)	0.11
COPD	81 (21.1)	36 (20.7)	45 (21.5)	0.84
History of atrial fibrillation or flutter	197 (51.4)	92 (52.9)	105 (50.2)	0.61
HFH within prior year	218 (56.9)	101 (58.0)	117 (56.0)	0.68
Anemia	85 (22.2)	35 (20.1)	50 (23.9)	0.37
Creatinine clearance, mL/min	51.4±27.9	52.0±29.4	50.9±26.7	0.70
BNP with conversions*, pg/mL	553.3 (307.9–1059.0)	604.0 (317.0–1131.3)	501.0 (300.0–1046.0)	0.40
NYHA class				
II	161 (42.1)	74 (42.5)	87 (41.9)	0.89
III	188 (49.2)	86 (49.4)	102 (49.0)	0.94
IV	32 (8.4)	14 (8.0)	18 (8.7)	0.83
KCCQ score	55.1±23.2	55.6±24.4	54.6±22.2	0.68
6MWD, m	225.3±123.5	251.6±126.8	258.3±121.0	0.60
Previous device implantation†	258 (67.4)	121 (69.5)	137 (65.6)	0.41
Medications				
ACEi/ARB/ARNi	265 (69.2)	124 (71.3)	131 (67.5)	0.42
Aldosterone antagonist	195 (50.9)	92 (52.9)	103 (49.3)	0.48
β-Blockers	350 (91.4)	160 (92.0)	190 (90.9)	0.72
Aspirin	237 (61.9)	108 (62.1)	129 (61.7)	0.94
Diuretic	346 (90.3)	161 (92.5)	185 (88.5)	0.19
Statin	237 (61.9)	110 (63.2)	127 (60.8)	0.62
Intervention				
MitraClip arm	195 (50.9)	83 (47.7)	112 (53.6)	0.25
No. of clips implanted	1.6±0.6	1.6±0.6	1.6±0.7	0.96

Data are presented as number (percentage), mean±SD, or median (quartile 1–quartile 3), where applicable. 6MWD indicates 6-minute walk distance; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; GLS, global longitudinal strain; HFH, heart failure hospitalization; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*In patients with only baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) values, NT-proBNP was converted to BNP by dividing by 7.

†Pacemaker, implantable cardioverter-defibrillator, cardiac resynchronization therapy-defibrillator (CRT-D), or cardiac resynchronization therapy- pacemaker (CRT-P).

Echocardiography

Echocardiograms were acquired following a study-specific protocol at baseline and at 1, 6, and 12 months of follow-up. Transthoracic echocardiograms were analyzed for conventional parameters by an independent echocardiographic core laboratory (MedStar Health Research Institute, Washington, DC), as previously reported.[14] Left and right ventricular dimensions

Table 2. Echocardiographic Baseline Characteristics in the Overall Population

Variables	Overall population (N=383)	LV GLS improvers (N=174)	LV GLS nonimprovers (N=209)	*P* value
LV end-diastolic diameter, cm	6.2±0.7	6.2±0.7	6.2±0.7	0.39
LV end-systolic diameter, cm	5.3±0.8	5.3±0.8	5.3±0.9	0.60
LV end-diastolic volume, mL	185.0 (140.0–234.0)	185.0 (140.0–234.0)	187.0 (141.5–234.5)	0.65
LV end-systolic volume, mL	128.0 (95.0–170.0)	130.0 (99.0–167.0)	126.0 (93.5–175.0)	0.76
LVEF, %	30.7±8.8	29.5±8.3	31.8±9.2	0.01
LV GLS, %	12.0±3.4	10.8±3.1	12.9±3.3	<0.001
MR severity				0.62
3+	195 (50.9)	91 (52.3)	104 (49.8)	
4+	188 (49.1)	83 (47.7)	105 (50.2)	
EROA, cm^2	0.40±0.14	0.40±0.14	0.41±0.14	0.34
Tricuspid regurgitation				0.20
None	8 (2.1)	6 (3.5)	2 (1.0)	
1+	320 (85.1)	146 (85.9)	174 (84.5)	
2+	47 (12.5)	18 (10.6)	29 (14.1)	
3+	1 (0.3)	0 (0)	1 (0.5)	
4+	0 (0)	0 (0)	0 (0)	
RVSP, mmHg	44.1±13.7	44.1±14.5	44.1±13.0	0.98
RV FAC, %	31.9±8.9	31.7±9.5	32.0±8.4	0.76

Data are presented as number (percentage), mean±SD, or median (quartile 1–quartile 3), where applicable. EROA indicates effective regurgitant orifice area; GLS, global longitudinal strain; LV, left ventricular; LVEF, LV ejection fraction; MR, mitral regurgitation; RV FAC, right ventricular fractional area change; and RVSP, right ventricular systolic pressure.

and function were measured according to current recommendations.[15-17] LV volumes were calculated by the Simpson biplane method, and LVEF was calculated as follows: [left ventricular end-diastolic volume – left ventricular end-systolic volume]/left ventricular end-diastolic volume.[15-17] MR and tricuspid regurgitation were graded using a multiparametric approach consisting of qualitative and semiquantitative parameters.[18]

LV GLS Measurements

LV myocardial strain analysis was performed in the research laboratory at MedStar Health in a collaboration with the Department of Cardiology at Leiden University Medical Center (Leiden, the Netherlands) by 2 investigators (S.M.P. and D.M.), blinded to any clinical information. LV GLS was measured at baseline and at 6-month follow-up using vendor-neutral software that allowed analysis of 2-dimensional images obtained from multiple echocardiographic machines (2D Cardiac Performance Analysis version 1.3; TomTec, Unterschleissheim, Germany). First, 1 cardiac cycle was defined from R wave to R wave, and the end-diastolic and end-systolic frames were selected by the closure of the mitral and aortic valves, respectively. Next, 2 reference points were placed at the mitral annulus, and 1 was placed at the apex, with automated border tracing and adjustments at the observer's discretion if needed. LV GLS was measured in selected apical 4-, 2-, and 3-chamber views. Patients with poor image quality, inadequate border tracking, foreshortened views, and missing images were excluded. LV GLS values are reported as absolute numbers. By convention, GLS is expressed as a negative number (normal range, –19% to –20%), and more negative LV GLS values represent better systolic performance. To avoid confusion, in the present study, GLS is expressed as positive values. Interobserver and intraobserver variabilities of LV GLS were tested by reanalyzing 42 random studies by 2 cardiologists (S.M.P. and D.M.) who were blinded to the results of the first analysis. The interobserver intraclass correlation coefficient was 0.92 (95% CI, 0.87–0.95), and the intraobserver intraclass correlation coefficient was 0.96 (95% CI, 0.92–0.98), representing low variability.

The difference between LV GLS at 6 months and baseline was calculated, and patients with values >0 were classified as LV GLS improvers, whereas patients with values ≤0 were classified as LV GLS nonimprovers.

Follow-Up

Patients were followed up for clinical, echocardiographic, and functional outcomes for 24 months after randomization. For the present study, the

primary outcome of interest was the combined end point of all-cause mortality or HFH between 6 and 24 months of follow-up (ie, after assessment of the change in LV GLS from baseline to 6 months). Secondary end points were all-cause mortality and HFH alone within this period. To preserve the intention-to-treat assessment of outcomes after treatment, follow-up in this study was truncated at 24 months because, after this time, patients randomized to GDMT alone were allowed to cross over and be treated with the MitraClip.

Statistical Analysis

Continuous variables are presented as mean and SD when normally distributed or median and interquartile range when nonnormally distributed and were compared using the Student *t* test or Mann-Whitney *U* test, respectively. Categorical variables are summarized as percentages and were compared using the χ^2 or Fisher exact test, as appropriate. Time-to-event curves were generated using the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Multivariable Cox proportional hazards regression was performed to identify baseline variables that were independently associated with event rates between 6- and 24-month follow-up in the overall analysis population. The following baseline covariates (in addition to change in LV GLS from baseline to 6 months and randomization group) were entered into these models: baseline LV GLS, age, sex, diabetes, baseline LVEF, improvement in LVEF from baseline to 6 months, MR 4+ (versus 3+), left ventricular end-diastolic diameter, left ventricular end-diastolic volume, effective regurgitant orifice area, and B-type natriuretic peptide. A 2-sided $P<0.05$ was considered significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Of the 614 patients enrolled in the COAPT trial, 63 had died before 6 months and an additional 168 were missing baseline LV strain, 6-month LV strain, or both, resulting in an analysis cohort of 383 (62.4%) of the COAPT trial randomized patients (mean age, 71±12 years; 61.6% men), of whom 195 (50.9%) were randomized to TEER+GDMT and 188 (49.1%) were randomized to GDMT alone. In the overall population, LV GLS was 12.0±3.4% at baseline and 11.7±3.7% at 6 months ($P=0.09$). In the TEER+GDMT group, LV GLS was 11.8±3.3% and 11.4±3.7% at baseline and 6 months, respectively ($P=0.09$), whereas in the GDMT alone group, LV GLS was 12.1±3.5% and 12.0±3.6% at baseline and 6 months, respectively ($P=0.55$). An improvement of LV GLS at 6 months was present in 174 (45.4%) patients, including 83 (42.6%) in the TEER+GDMT group and 91 (48.4%) in the GDMT alone group ($P=0.25$). Tables 1 and 2 summarize the baseline clinical and echocardiographic characteristics of the overall population according to LV GLS improvement from baseline to 6 months. Baseline values of LVEF and LV GLS were significantly lower in LV GLS improvers, whereas no other baseline measure distinguished patients in whom LV GLS was likely to improve over 6 months.

Tables S1 and S2 summarize the baseline clinical and echocardiographic characteristics of LV GLS improvers versus nonimprovers, stratified by treatment arm. Baseline LVEF values were slightly lower in LV GLS improvers in the TEER+GDMT group, whereas no significant difference was present in the GDMT alone group. Values of baseline LV GLS were lower in improvers in both the TEER+GDMT and GDMT alone groups. Effective regurgitant orifice area values were slightly lower in LV GLS improvers in the TEER+GDMT

Table 3. Six-Month Echocardiographic Characteristics of LV GLS Improvers Versus Nonimprovers in the Overall Population

Variable	LV GLS improvers (N=174)	LV GLS nonimprovers (N=209)	*P* value
LV end-diastolic diameter, cm	6.1±0.8	6.2±0.8	0.17
LV end-systolic diameter, cm	5.2±0.9	5.4±0.9	0.06
LV end-diastolic volume, mL	181.0±65.0	182.1±71.0	0.89
LV end-systolic volume, mL	124.0±55.6	133.8±61.6	0.39
LVEF, %	30.7±10.8	28.1±10.1	0.02
LV GLS, %	13.0±3.6	10.6±3.3	<0.0001
ΔLVEF from baseline to 6 mo	1.3±9.2	−3.1±7.5	<0.0001
ΔLV GLS from baseline to 6 mo	2.3±2.0	−2.4±1.9	<0.0001
MR severity			0.47
≤1+	63 (37.1)	78 (38.2)	
2+	105 (24.7)	141 (30.9)	
3+	46 (27.1)	40 (19.6)	
4+	19 (11.2)	23 (11.3)	
Tricuspid regurgitation			0.67
None	3 (1.8)	3 (1.5)	
1+	136 (81.9)	155 (77.9)	
2+	23 (13.9)	37 (18.6)	
3+	4 (2.4)	4 (2.0)	
4+	0 (0)	0 (0)	
RVSP, mm Hg	41.5±13.9	41.9±13.8	0.79
RV FAC, %	39.9±10.2	37.8±9.8	0.06

Data are presented as number (percentage) or mean±SD. GLS indicates global longitudinal strain; LV, left ventricular; LVEF, LV ejection fraction; MR, mitral regurgitation; RV FAC, right ventricular fractional area change; and RVSP, right ventricular systolic pressure.

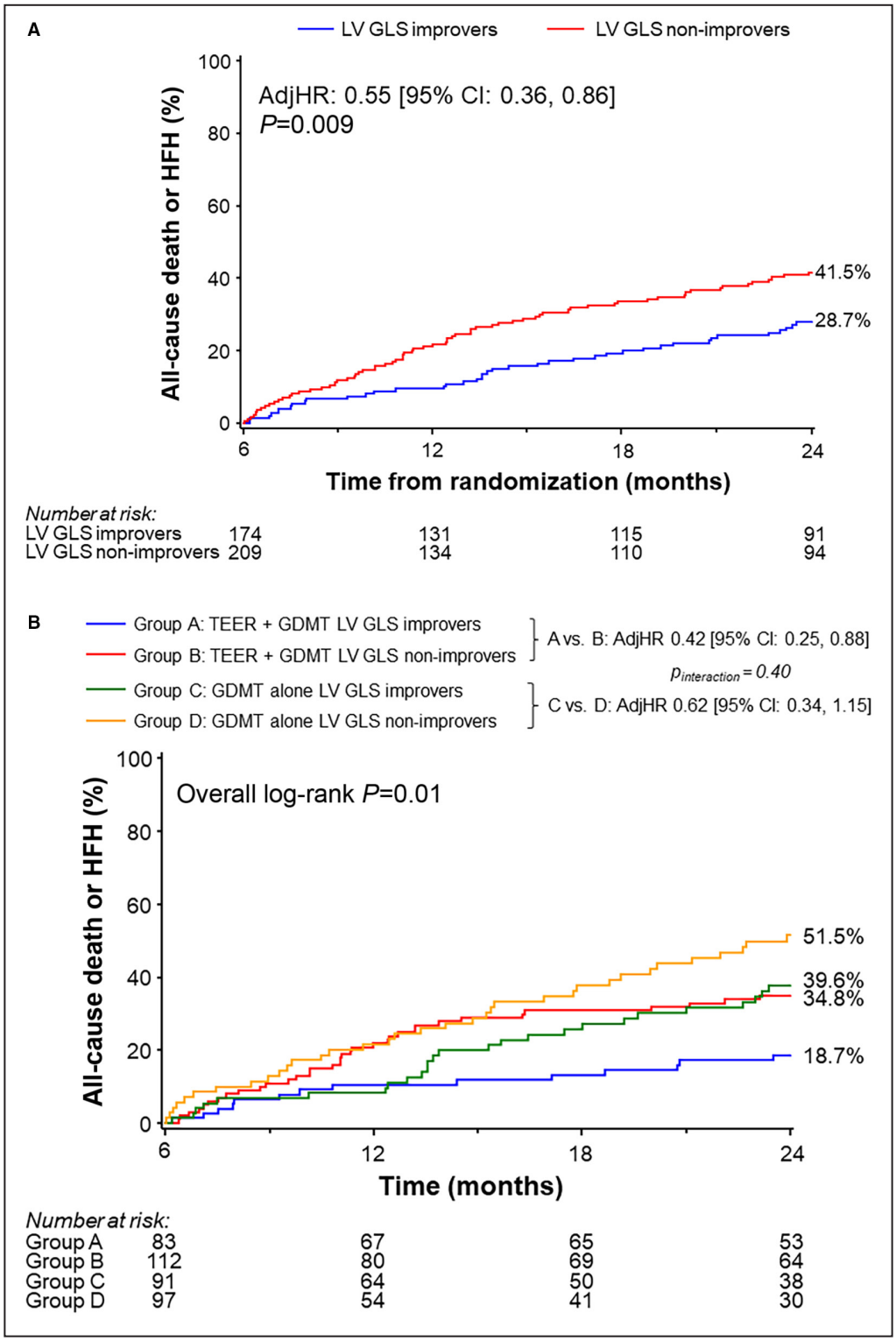

Figure 1. Kaplan-Meier (KM) curves for all-cause death or heart failure hospitalization (HFH). Estimates of the composite end point of all-cause death or HFH between 6- and 24-month follow-up according to left ventricular (LV) global longitudinal strain (GLS) improvement at 6 months in all patients (**A**) and according to treatment arm (**B**). *P* values associated with adjusted hazard ratios (AdjHRs) are from the multivariable Cox proportional hazards model. Overall log-rank *P* value refers to the log-rank *P* value for the unadjusted comparison of the KM rates. GDMT indicates guideline-directed medical therapy; and TEER, transcatheter edge-to-edge repair.

Table 4. Covariates Associated With All-Cause Death or HFH Between 6- and 24-Month Follow-Up

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LV GLS improvement	0.61 (0.41–0.89)	0.011	0.57 (0.37–0.90)	0.015
Baseline LV GLS, per 1%	1.02 (0.97–1.08)	0.42	0.99 (0.91–1.07)	0.76
LVEF improvement	0.89 (0.59–1.33)	0.57	0.72 (0.45–1.16)	0.18
LVEF, per 10%	0.75 (0.60–0.94)	0.014	0.72 (0.53–1.00)	0.048
Age, per 5 y	1.03 (0.95–1.12)	0.46	1.04 (0.93–1.15)	0.53
TEER+GDMT (vs GDMT alone)	0.59 (0.40–0.85)	0.005	0.47 (0.31–0.73)	0.0007
Sex, male	1.27 (0.85–1.88)	0.24	1.12 (0.69–1.82)	0.65
Diabetes	1.49 (1.01–2.18)	0.042	1.39 (0.91–2.11)	0.12
MR 4+ (vs 3+)	1.52 (1.05–2.21)	0.028	1.32 (0.81–2.16)	0.27
LVEDD, per cm	1.31 (1.01–1.71)	0.041	0.97 (0.61–1.55)	0.90
BNP with conversions, per 10 pg/mL	1.00 (1.00–1.00)	0.003	1.00 (1.00–1.00)	0.046
LVEDV, per 10 mL	1.02 (0.99–1.05)	0.13	1.01 (0.96–1.05)	0.71
EROA, per cm^2	2.93 (0.91–9.40)	0.07	1.82 (0.32–10.33)	0.50

BNP indicates brain natriuretic peptide; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; GLS, global longitudinal strain; HFH, heart failure hospitalization; HR, hazard ratio; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; MR, mitral regurgitation; and TEER, transcatheter edge-to-edge repair.

group, despite similar prevalence of patients with MR grade 4+ in improvers and nonimprovers.

Echocardiographic Characteristics of LV GLS Improvers at 6-Month Follow-Up

Mean LVEF values and LV GLS at 6-month follow-up were not significantly different between the TEER+GDMT and GDMT alone groups (29.3±11.6% versus 32.2±10.0%, respectively [*P*=0.11]; and 11.4±3.7% versus 12.0±3.6%, respectively [*P*=0.64]). No or mild (≤1+) MR at 6-month follow-up was more prevalent in the TEER+GDMT group than the GDMT alone group (65.9% versus 10.2%; *P*<0.001), whereas MR ≥3+ was more prevalent in the GDMT alone group (62.5% versus 12.2%; *P*<0.001). Patients in the TEER+GDMT group also had better right ventricular systolic function (assessed by fractional area change) compared with the GDMT group (42.3±8.1% versus 37.6±11.6%; *P*=0.006). Echocardiographic characteristics in LV GLS improvers versus nonimprovers at 6-month follow-up are shown in Table 3 for the overall population and in Table S3 stratified by treatment.

Outcomes

The estimated rate of the composite end point of death or HFH between 6- and 24-month follow-up was 28.7% for LV GLS improvers and 41.5% for LV GLS nonimprovers (*P*=0.009; Figure 1A). LV GLS improvement was associated with similar risk reductions in the composite end point in both treatment arms ($P_{interaction=}$0.40; Figure 1B). By multivariable analysis (Table 4), LV GLS improvement at 6 months (hazard ratio [HR], 0.57 [95% CI, 0.37–0.90]; *P*=0.015) and treatment with TEER (HR, 0.47 [95% CI, 0.31–0.73]; *P*=0.0007) were independently associated with the composite end point of death or HFH between 6- and 24-month follow-up.

The estimated rate of all-cause death between 6 and 24 months was 19.2% for LV GLS improvers and 25.6% for LV GLS nonimprovers (*P*=0.006; Figure 2A). LV GLS improvement was associated with similar risk reductions in death in both treatment arms ($P_{interaction=}$0.27; Figure 2B). Age, TEER treatment, male sex, creatinine clearance, anemia, New York Heart Association class IV, 6-minute walk distance, MR grade 4+, and B-type natriuretic peptide were also associated with all-cause death in univariable analysis. By multivariable analysis, LV GLS improvement from baseline to 6 months was independently associated with a lower risk of death between 6- and 24-month follow-up (HR, 0.49 [95% CI, 0.29–0.82]; *P*=0.007), as were treatment with TEER, longer 6-minute walk distance, and female sex (Table 5).

The estimated rate of HFH between 6 and 24 months was 22.9% for LV GLS improvers and 35.1% for nonimprovers (*P*=0.005; Figure 3A). LV GLS improvement was associated with similar risk reductions in HFH in both treatment arms ($P_{interaction=}$0.99; Figure 3B). LV GLS improvement at 6 months, LVEF at baseline, TEER, MR grade 4+, left ventricular end-diastolic diameter, left ventricular end-diastolic volume, and effective regurgitant orifice area were associated with HFH on univariate analysis. LV GLS improvement (0.55 [95% CI, 0.34–0.89]; *P*=0.014), treatment with TEER, greater baseline LVEF, and improvement in LVEF were independently associated with a reduced risk of HFH between 6- and 24-month follow-up by multivariate analysis (Table 6).

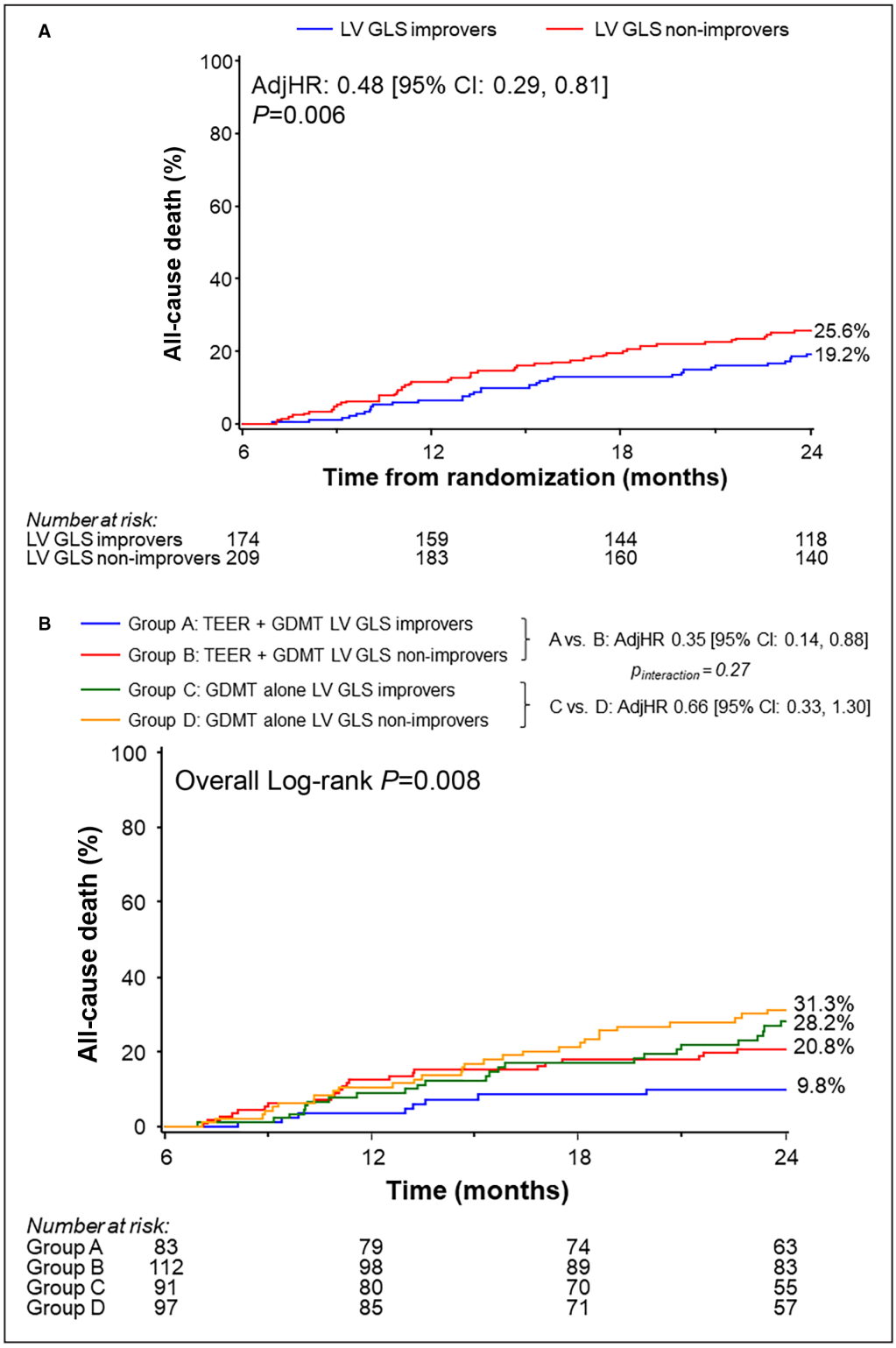

Figure 2. Kaplan-Meier (KM) curves for all-cause death.
Estimates of all-cause death between 6- and 24-month follow-up according to left ventricular (LV) global longitudinal strain (GLS) improvement at 6 months in all patients (**A**) and according to treatment arm (**B**). *P* values associated with adjusted hazard ratios (AdjHRs) are from the multivariable Cox proportional hazards model. Overall log-rank *P* value refers to the log-rank *P* value for the unadjusted comparison of the KM rates. GDMT indicates guideline-directed medical therapy; and TEER, transcatheter edge-to-edge repair.

Table 5. Covariates Associated With All-Cause Death Between 6- and 24-Month Follow-Up

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LV GLS improvement	0.70 (0.45–1.09)	0.12	0.49 (0.29–0.82)	0.007
Baseline LV GLS, per 1%	1.06 (0.99–1.13)	0.09	1.00 (0.90–1.10)	0.92
LVEF improvement	1.14 (0.73–1.79)	0.56	0.95 (0.57–1.59)	0.84
LVEF, per 10%	0.77 (0.59–1.00)	0.051	0.76 (0.53–1.09)	0.13
Age, per 5 y	1.15 (1.03–1.28)	0.010	1.03 (0.90–1.18)	0.67
TEER+GDMT (vs GDMT alone)	0.53 (0.34–0.82)	0.004	2.45 (1.36–4.40)	0.003
Sex, male	1.84 (1.13–2.99)	0.014	0.53 (0.33–0.86)	0.010
CrCl, per 10 mL/min per 1.73 m^2	0.83 (0.75–0.93)	<0.001	0.90 (0.79–1.01)	0.08
Anemia	1.65 (1.04–2.63)	0.033	1.54 (0.93–2.55)	0.09
NYHA class IV	2.15 (1.17–3.96)	0.014	1.09 (0.52–2.31)	0.82
6MWD, per 50 m	0.85 (0.77–0.93)	<0.001	0.86 (0.77–0.97)	0.013
MR 4+ (vs 3+)	1.83 (1.18–2.84)	0.007	1.37 (0.85–2.20)	0.20
BNP with conversions, per 10 pg/mL	1.00 (1.00–1.01)	<0.001	1.00 (1.00–1.00)	0.24

6MWD indicates 6-minute walk distance; BNP, brain natriuretic peptide; CrCl, creatinine clearance; GDMT, guideline-directed medical therapy; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricular; LVEF, LV ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; and TEER, transcatheter edge-to-edge repair.

Kaplan-Meier event rates for the primary composite end point and its components, stratified by both treatment arm and LV strain improvement status, are shown in Table S4.

DISCUSSION

The major finding from the current COAPT trial substudy is that patients with HF with severe secondary MR who had improvement in LV GLS from baseline to 6-month follow-up had lower rates of all-cause mortality, HFH, and the composite of mortality or HFH between 6- and 24-month follow-up, whether treated with TEER plus GDMT or GDMT alone.

LVEF is an important diagnostic and prognostic parameter in patients with HF.[19] Current guidelines recommend assessment of LVEF to classify patients into different groups according to the degree of LV systolic dysfunction, and therapeutic strategies differ in their use and effectiveness according to LVEF.[20] LVEF has been shown to be a powerful predictor of cardiovascular outcomes in patients with HF across a broad spectrum of LV systolic dysfunction.[21] However, calculation of LVEF is based on the total volume of blood ejected from the LV, not taking into consideration the percentage of blood that leaks backward through the mitral valve into the left atrium (and therefore does not contribute to forward cardiac output). In patients with HF and severe secondary MR, the amount of backward flow into the left atrium during LV contraction can significantly contribute to LVEF and can be >40% of the amount of blood that fills the LV during diastole.[22] Therefore, LVEF in patients with severe MR often overestimates LV systolic function. In contrast, LV GLS measures the active longitudinal shortening of myocardial fibers, and it is less load dependent than LVEF in patients with MR.[23] Kamperidis et al showed that LV GLS is reduced in patients with nonischemic cardiomyopathy and severe MR compared with those with no or mild MR with comparable values of LVEF, demonstrating incremental value of LV GLS compared with LVEF to accurately define LV systolic function.[10] LV GLS is also strongly associated with outcomes in patients with HF and secondary MR. Chasapi et al reported lower survival rates in patients with HF and secondary MR who had more impaired LV GLS, whereas no difference in survival was present according to LVEF tiers (LVEF <30%, 30%–40%, and 40%–50%).[24] Moreover, Namazi et al demonstrated that LV GLS (before TEER) was independently associated with all-cause mortality in patients with secondary MR, whereas LVEF was not.[12] Finally, Medvedofsky et al found that although baseline LV GLS was not associated with early outcomes in the COAPT trial, it was significantly associated with death and HFH after 10 months.[25] Summarizing, LVEF does not directly measure LV myocardial function but rather chamber function, whereas LV GLS more directly measures myocardial function. Lower values of GLS may also represent greater myocardial fibrosis/scar, which could influence the response of the myocardium to GDMT or TEER.

Reduction in MR severity after TEER decreases LV volume overload in an already injured LV, thereby potentially reducing diastolic wall stress with attenuation of the adverse LV remodeling process. Previous studies from the COAPT trial have shown that LVEF

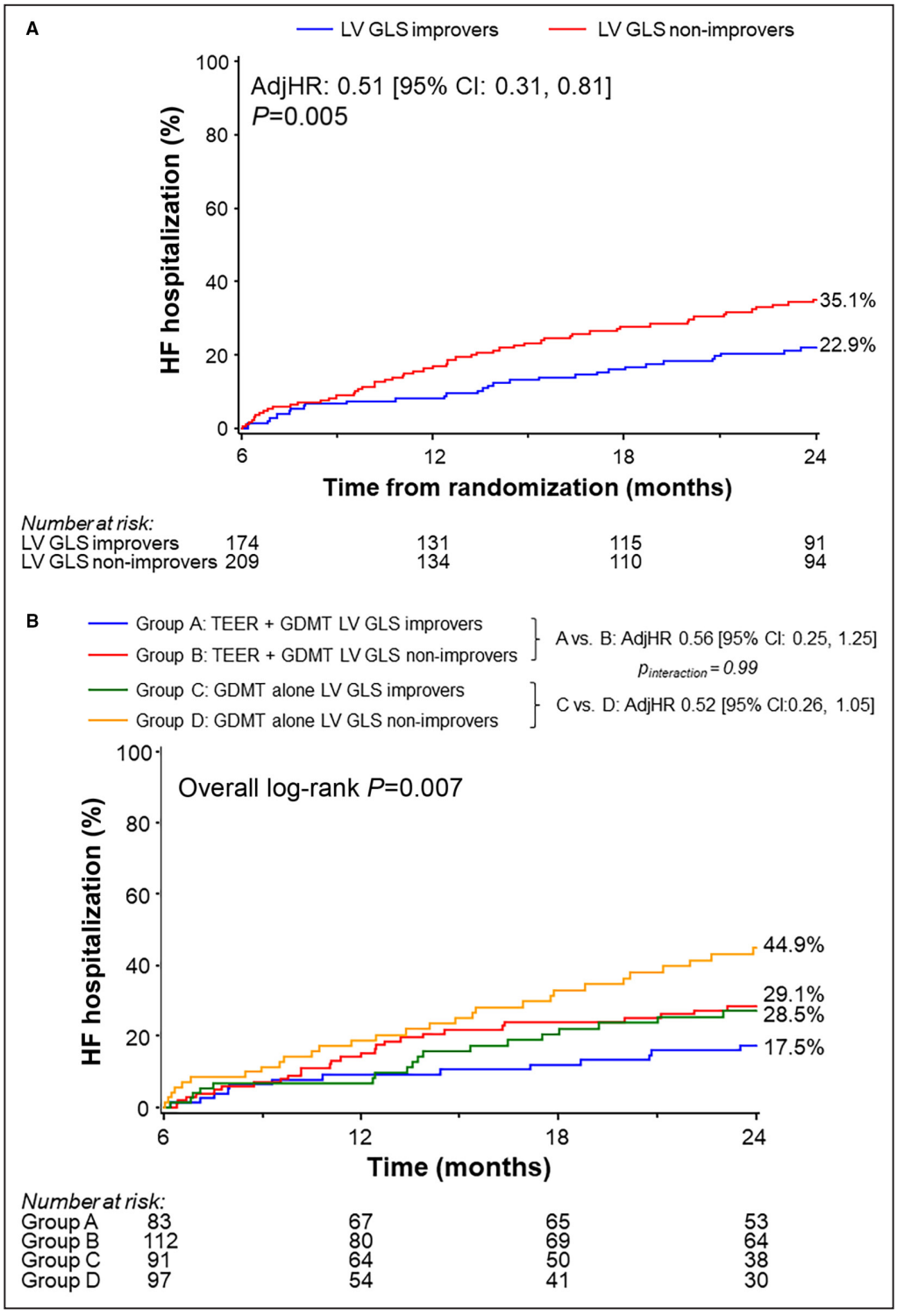

Figure 3. Kaplan-Meier (KM) curves for heart failure (HF) hospitalization.
Estimates of HF hospitalization between 6- and 24-month follow-up according to left ventricular (LV) global longitudinal strain (GLS) improvement at 6 months in all patients (**A**) and according to treatment arm (**B**). *P* values associated with adjusted hazard ratios (AdjHRs) are from the multivariable Cox proportional hazards model. Overall log-rank *P* value refers to the log-rank *P* value for the unadjusted comparison of the KM rates. GDMT indicates guideline-directed medical therapy; and TEER, transcatheter edge-to-edge repair.

Table 6. Covariates Associated With HFH Between 6- and 24-Month Follow-Up

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LV GLS improvement	0.59 (0.38–0.91)	0.018	0.55 (0.34–0.89)	0.014
Baseline LV GLS, per 1%	1.02 (0.96–1.08)	0.59	0.97 (0.89–1.05)	0.47
LVEF improvement	0.76 (0.47–1.21)	0.24	0.59 (0.35–0.99)	0.044
LVEF, per 10%	0.75 (0.58–0.97)	0.027	0.63 (0.44–0.89)	0.010
Age, per 5 y	1.01 (0.92–1.10)	0.90	1.02 (0.91–1.14)	0.73
TEER+GDMT (vs GDMT alone)	0.62 (0.41–0.94)	0.024	1.05 (0.63–1.74)	0.86
Sex, male	1.17 (0.75–1.81)	0.49	0.46 (0.29–0.74)	0.001
MR 4+ (vs 3+)	1.70 (1.11–2.59)	0.014	1.57 (0.93–2.66)	0.09
LVEDD, per cm	1.45 (1.08–1.95)	0.013	0.98 (0.60–1.61)	0.94
LVEDV, per 10 mL	1.04 (1.01–1.07)	0.018	1.02 (0.98–1.07)	0.38
EROA, per cm^2	3.81 (1.10–13.20)	0.035	2.62 (0.48–14.29)	0.26

EROA indicates effective regurgitant orifice area; GDMT, guideline-directed medical therapy; GLS, global longitudinal strain; HFH, heart failure hospitalization; HR, hazard ratio; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; MR, mitral regurgitation; and TEER, transcatheter edge-to-edge repair.

decreases immediately after MR correction and during follow-up,[14] reflecting the early increase in afterload the LV experiences when MR is reduced, and more chronically the natural history of the underlying cardiomyopathy. However, the worsening in LVEF over 12 months was more pronounced in the GDMT alone group than the TEER plus GDMT group,[14] a reflection of reduced systemic vascular resistance with increased forward stroke volume after TEER and the long-term effects that reducing LV volume overload with TEER may have in slowing the progression of the underlying disease process. However, as previously mentioned, LVEF may not be the optimal marker to assess LV systolic function in patients with secondary MR, and assessment of changes in LV GLS may be more accurate. Although a limited number of studies have described the evolution of LV GLS after TEER,[26,27] the prognostic implications of LV GLS improvement have not been previously analyzed. The current study shows that an improvement of LV GLS from baseline to 6-month follow-up was independently associated with a subsequently lower risk of the combined end point of all-cause mortality or HFH after 6 months, as well as with death and HFH separately. Improvement of LV GLS at 6-month follow-up was independently associated with improved rates of all-cause mortality and the composite end point of all-cause mortality or HFH, whereas baseline LVEF and LV GLS were not. Although factors contributing to LV GLS improvement at follow-up warrant further investigation, patients who had improved LV GLS during follow-up may have a greater LV contractile reserve (explaining the lower values of LVEF and LV GLS at baseline). LV contractile reserve (assessed with dobutamine stress echocardiography) has been associated with a lower risk of adverse events in patients with secondary MR undergoing TEER with the MitraClip implant.[28]

Previous studies have shown that patients with HF and reduced LVEF who experience improvement in LVEF at follow-up may represent a distinct phenotype (termed HF with improved ejection fraction), and those patients seem to have better clinical outcomes than other phenotypes.[29] Early assessment of the evolution of LV systolic function after HF therapy (either medical or device related) therefore seems important for risk stratification and may identify patients without such improvement who are at increased risk of adverse events, warranting especially close follow-up. The current findings support serial measurements of LV GLS during follow-up of patients who undergo TEER, given that the improvement of LV GLS at 6 months after TEER was associated with the lowest rates of events during subsequent follow-up through 24 months.

More importantly, clinical benefits of TEER treatment between 6 and 24 months were observed in patients in whom both LV GLS improved and did not improve during the first 6 months. The lowest 6- to 24-month rates of death and HFH were present in TEER-treated patients in whom LV GLS improved in this period. This fact is also notable as the difference in mortality between TEER and GDMT alone at 24 months in the COAPT trial did not emerge until after 6-month follow-up.

Study Limitations

The present post hoc study was not prespecified and thus should be considered hypothesis generating. Assessment of LV GLS is vendor dependent, and values cannot be compared directly across different echocardiographic platforms. Paired baseline and 6-month LV GLS data were only present for analysis in 62.4% of patients, in part because of suboptimal image quality in some patients and deaths before 6 months in others. Table S5 shows the baseline characteristics

of patients included versus excluded from the analysis. The necessary exclusion of patients who died during the first 6 months after TEER may have introduced survival bias, although the utility of assessing improvement in LV GLS from baseline to 6 months is only applicable to survivors beyond 6 months. Finally, although regression to the mean may have contributed to the greater 6-month improvement in LV GLS in patients with lower baseline LVEF, it is unlikely that this phenomenon contributed to the improved prognosis in this cohort.

CONCLUSIONS

In patients with HF and severe secondary MR enrolled in the COAPT trial, improvement of LV GLS from baseline to 6-month follow-up was associated with lower rates of all-cause death, HFH, or both between 6- and 24-month follow-up, after both TEER plus GDMT and GDMT alone.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5

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