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ORIGINAL RESEARCH

# Left Atrial Improvement in Patients With Secondary Mitral Regurgitation and Heart Failure

## The COAPT Trial

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ABSTRACT

**BACKGROUND** Functional mitral regurgitation induces adverse effects on the left ventricle and the left atrium. Left atrial (LA) dilatation and reduced LA strain are associated with poor outcomes in heart failure (HF). Transcatheter edge-to-edge repair (TEER) of the mitral valve reduces heart failure hospitalization (HFH) and all-cause death in selected HF patients.

**OBJECTIVES** The aim of this study was to evaluate the impact of LA strain improvement 6 months after TEER on the outcomes of patients enrolled in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial.

**METHODS** The difference in LA strain between baseline and the 6-month follow-up was calculated. Patients with at least a 15% improvement in LA strain were labeled as "LA strain improvers." All-cause death and HFH were assessed between the 6 and 24-month follow-up.

**RESULTS** Among 347 patients (mean age 71 ± 12 years, 63% male), 106 (30.5%) showed improvement of LA strain at the 6-month follow-up (64 [60.4%] from the TEER + guideline-directed medical therapy [GDMT] group and 42 [39.6%] from the GDMT alone group). An improvement in LA strain was significantly associated with a reduction in the composite of death or HFH between the 6-month and 24-month follow-up, with a similar risk reduction in both treatment arms ($P_{interaction} = 0.27$). In multivariable analyses, LA strain improvement remained independently associated with a lower risk of the primary composite endpoint both as a continuous variable (adjusted HR: 0.94 [95% CI: 0.89-1.00]; $P = 0.03$) and as a dichotomous variable (adjusted HR: 0.49 [95% CI: 0.27-0.89]; $P = 0.02$). The best outcomes were observed in patients treated with TEER in whom LA strain improved.

**CONCLUSIONS** In symptomatic HF patients with severe mitral regurgitation, improved LA strain at the 6-month follow-up is associated with subsequently lower rates of the composite endpoint of all-cause mortality or HFH, both after TEER and GDMT alone. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [COAPT]; NCT01626079) (J Am Coll Cardiol Img 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**GDMT** = guideline-directed medical therapy

**HF** = heart failure

**HFH** = heart failure hospitalization

**LA** = left atrial

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**MR** = mitral regurgitation

**TEER** = transcatheter edge-to-edge repair

The presence of functional mitral regurgitation (MR) is associated with worse outcomes in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF).[1,2] Results from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated that symptomatic patients with HR and moderate to severe (3+) or severe (4+) functional MR randomized to transcatheter edge-to-edge repair (TEER) with the MitraClip device (Abbott) plus guideline-directed medical therapy (GDMT) had a significant reduction of heart failure hospitalization (HFH) and all-cause mortality compared with those randomized to GDMT alone.[3] However, mortality and HFH remain high among patients receiving TEER, which has often been attributed to the extent of concomitant left ventricular (LV) dysfunction. Therefore, current research has mainly focused on baseline parameters of LV dysfunction, as well as on LV remodeling during follow-up, to risk stratify patients with functional MR and to select patients who would benefit most from TEER.[2,4,5] However, significant MR does not only adversely affect the left ventricle but also the left atrium.[6] Left atrial (LA) dilatation has proven to be an important prognostic parameter in patients with HF and has shown a strong association with the severity of symptoms and poor outcomes.[7] Conversely, successful TEER can significantly reduce LA volumes.[8] Recently, LA reservoir strain, a measure of LA function rather than LA size, has also been shown to have a strong association with outcomes in patients with HF and reduced ejection fraction, patients with secondary MR, and patients undergoing surgical mitral valve repair and provides incremental prognostic value over LA volume.[9-11] Whether TEER can improve LA reservoir strain in patients with functional MR and whether such an improvement is associated with better outcomes has not been previously investigated. Accordingly, the aim of the current study was to assess the characteristics of patients with improvement of LA reservoir strain at 6 months after enrollment in the COAPT trial and to evaluate the impact of LA reservoir strain improvement on outcomes during the 24-month follow-up.

## METHODS

**STUDY DESIGN.** The COAPT trial design was previously published.[12] Briefly, patients with HF, reduced LVEF (ranging from 20% to 50%), and ≥3+ functional MR who remained symptomatic despite maximally tolerated GDMT were randomized to TEER plus GDMT vs GDMT 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 to the Cardiovascular Research Foundation 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 upon reasonable request to the corresponding author and approval by the COAPT Publications Committee.

**ECHOCARDIOGRAPHY.** Echocardiograms were acquired following a study-specific protocol at baseline and at 1, 6, 12, and 24 months of follow-up. Transthoracic echocardiograms were analyzed for conventional parameters by an independent echocardiographic core laboratory (MedStar Health Research Institute) as previously reported.[5] Strain measurements were taken by 2 investigators (S.M.P. and D.M.) using a semiautomated algorithm (Cardiac Performance Analysis, TomTec Imaging Systems) as described previously.[13] The median (Q1-Q3) frame

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rate of images analyzed for strain was 50 Hz (Q1-Q3: 46-53 Hz). Left and right ventricular dimensions and function were measured according to the current recommendations.[14,15] LA volumes were measured using the method of disks on 2- and 4-chamber views.[15] MR was quantified as per the current recommendations.[16] Tricuspid regurgitation was graded based on a multiparametric approach consisting of qualitative and semiquantitative parameters.[16]

**SPECKLE TRACKING MEASUREMENTS.** LA strain analysis was performed by 2 investigators (S.M.P. and D.M.) blinded to any clinical information. LA strain was measured at baseline and at the 6-month follow-up using vendor-neutral software that allowed analysis of 2-dimensional images obtained from multiple echocardiography machines (2D Cardiac Performance Analysis version 1.3, TomTec). First, 1 cardiac cycle was defined from R-wave to R-wave from which end-diastolic and end-systolic frames were selected. Next, speckle tracking LA strain was measured on the apical 4-chamber view according to the current guidelines.[17] The endocardium of the LA wall was traced manually and corrected by adjusting the region of interest or the width of the contour, excluding the pulmonary vein ostia and LA appendage.[18] Patients with poor image quality, inadequate border tracking, and missing images were excluded. LA reservoir strain was used for this analysis because this parameter showed a good correlation with LA wall fibrosis on cardiac magnetic resonance[19] and can still be assessed in patients with atrial fibrillation.[17] For the purposes of this analysis, LA reservoir strain values have been expressed as absolute values. The difference between LA reservoir strain at 6 months and baseline was calculated, and patients whose strain improved by at least 15% between baseline and 6 months were classified as "LA strain improvers," whereas patients who did not meet that threshold for improvement were classified as "LA strain nonimprovers."

**FOLLOW-UP.** Patients were followed for 24 months after randomization. For the present study, the primary outcome of interest was the combined endpoint of all-cause mortality or HFH between 6 and 24 months of follow-up (ie, landmarked after assessment of the change in LA strain). Secondary endpoints were all-cause mortality and HFH alone within this period.

**STATISTICAL ANALYSIS.** Continuous variables are presented as the mean ± SD when normally distributed or median (Q1-Q3) when non-normally distributed and were compared using the Student's *t*-test or the Mann-Whitney test, respectively. Normality for continuous variables was assessed using the Shapiro-Wilk test. Categoric variables are summarized as frequencies and percentages and were compared using the chi-square 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

**TABLE 1 Baseline Characteristics of LA Strain Improvers vs Nonimprovers in the Overall Population**

| | LA Strain Improvers (n = 106) | LA Strain Nonimprovers (n = 241) | *P* Value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, y | 71 ± 13 | 71 ± 11 | 0.87 |
| Male | 68 (64.2) | 150 (62.2) | 0.73 |
| Body mass index, kg/m$^2$ | 26.4 ± 5.4 | 27.3 ± 5.6 | 0.16 |
| Systolic blood pressure, mm Hg | 106 ± 14 | 112 ± 17 | 0.004 |
| Diastolic blood pressure, mm Hg | 65 ± 9 | 65 ± 10 | 0.57 |
| Ischemic cardiomyopathy | 61 (57.5) | 133 (55.2) | 0.68 |
| Hypertension | 83 (78.3) | 192 (79.7) | 0.77 |
| Diabetes mellitus | 31 (29.2) | 88 (36.5) | 0.19 |
| Hypercholesterolemia | 52 (49.1) | 131 (54.4) | 0.36 |
| Coronary artery disease | 75 (70.8) | 159 (66.0) | 0.38 |
| Previous myocardial infarction | 51 (48.1) | 109 (45.2) | 0.38 |
| Previous PCI | 46 (43.4) | 105 (43.6) | 0.98 |
| Previous stroke or TIA | 13 (12.3) | 41 (17.0) | 0.26 |
| Peripheral vascular disease | 13 (12.3) | 35 (14.5) | 0.57 |
| COPD | 22 (20.8) | 48 (19.9) | 0.86 |
| History of atrial fibrillation or flutter | 51 (48.1) | 124 (51.5) | 0.57 |
| HFH within prior year | 72 (67.9) | 133 (55.2) | 0.03 |
| Anemia | 23 (21.7) | 49 (20.3) | 0.77 |
| Creatinine clearance, mL/min | 49.3 ± 27.4 | 53.4 ± 27.2 | 0.66 |
| BNP with conversions, pg/mL | 516.5 (284.9-1,212.8) | 520.4 (299.0-1,032.0) | 0.99 |
| NYHA functional class | | | 0.44 |
| II | 43 (40.6) | 107 (44.6) | |
| III | 51 (48.1) | 116 (48.3) | |
| IV | 12 (11.3) | 16 (6.7) | |
| KCCQ score | 54.2 ± 22.3 | 54.7 ± 23.5 | 0.84 |
| 6MWD, m | 248.5 ± 124.6 | 263.6 ± 126.7 | 0.31 |
| Previous device implantation | 72 (67.9) | 167 (69.3) | 0.80 |
| Medications | | | |
| ACEI/ARB/ARNI | 74 (69.8) | 164 (68.0) | 0.74 |
| Aldosterone antagonist | 59 (55.7) | 120 (49.8) | 0.31 |
| Beta-blockers | 94 (88.7) | 221 (91.7) | 0.37 |
| Aspirin | 70 (66.0) | 142 (58.9) | 0.21 |
| Diuretic agents | 95 (89.6) | 217 (90.0) | 0.91 |
| Statin | 64 (60.4) | 152 (63.1) | 0.63 |
| Intervention | | | |
| MitraClip | 64 (60.4) | 124 (51.5) | 0.12 |
| Number of clips implanted | 1.7 ± 0.6 | 1.7 ± 0.7 | 0.73 |

Values are mean ± SD, n (%), or median (Q1-Q3).

6MWD = 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; HFH = heart failure hospitalization; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrium; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

**TABLE 2 Baseline Echocardiographic Characteristics of LA Strain Improvers vs Nonimprovers in the Overall Population**

| | LA Strain Improvers (n = 157) | LA Strain Nonimprovers (n = 192) | *P* Value |
|---|---|---|---|
| Heart rhythm at baseline scan | | | |
| Sinus rhythm | 48 (45.3) | 106 (44.0) | 0.82 |
| AF | 14 (13.2) | 34 (14.1) | 0.82 |
| Paced | 41 (38.7) | 98 (40.7) | 0.73 |
| LV end-diastolic diameter, cm | 6.1 ± 0.7 | 6.3 ± 0.7 | 0.051 |
| LV end-systolic diameter, cm | 5.3 ± 0.9 | 5.3 ± 0.9 | 0.53 |
| LV end-diastolic volume, mL | 173.5 (133.0-222.0) | 197 (148-242) | 0.02 |
| LV end-systolic volume, mL | 123 (90-161) | 134 (100-176) | 0.10 |
| LA volume, mL | 91.8 ± 36.4 | 91.7 ± 38.0 | 0.98 |
| LA volume end-systole, mL | 129.3 ± 51.6 | 136.0 ± 52.3 | 0.27 |
| LA volume end-diastole, mL | 94.2 ± 42.8 | 90.9 ± 42.4 | 0.51 |
| LVEF, % | 30.3 ± 9.1 | 31.2 ± 8.8 | 0.39 |
| LV global longitudinal strain | 11.6 ± 3.7 | 12.2 ± 3.3 | 0.13 |
| LA strain, % | 10.5 ± 3.8 | 13.8 ± 4.8 | <0.0001 |
| MR severity | | | |
| MR 3+ | 51 (48.1) | 124 (51.5) | 0.57 |
| MR 4+ | 55 (51.9) | 117 (48.5) | 0.57 |
| EROA, $cm^2$ | 0.40 ± 0.13 | 0.40 ± 0.15 | 0.97 |
| Tricuspid regurgitation | | | 0.35 |
| None | 0 (0) | 6 (2.5) | |
| 1+ | 92 (88.5) | 100 (84.4) | |
| 2+ | 12 (11.5) | 30 (12.7) | |
| 3+ | 0 (0) | 1 (0.4) | |
| 4+ | 0 (0) | 0 (0) | |
| RVSP, mm Hg | 42.7 ± 13.4 | 45.1 ± 14.0 | 0.17 |

Values are n (%), mean ± SD, or median (Q1-Q3).

AF = atrial fibrillation; EROA = effective regurgitant orifice area; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; RVSP = right ventricular systolic pressure; other abbreviation as in Table 1.

independently associated with 6-month to 24-month event rates in the overall population. The following covariates (in addition to LA strain improvement from baseline to 6 months and the randomization group) were entered into these models: baseline LA strain, LA volume (at end-diastole), LVEF, LV global longitudinal strain at baseline, change in LV global longitudinal strain from baseline to 6 months, history of atrial fibrillation, and MR 4+ (vs 3+). Because there is no established "optimal threshold" for improvement in LA strain, these models were repeated treating change in LA strain from baseline to 6 months as a continuous variable. A 2-sided value of $P < 0.05$ was considered significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

## RESULTS

### BASELINE CHARACTERISTICS.

Echocardiographic images feasible for LA strain measurements at baseline and 6 months were available in 347 patients (mean age 70.8 ± 11.8 years, 62.8% male), of whom 188 (54.2%) had been randomized to TEER + GDMT and 159 (45.8%) to GDMT alone. LA reservoir strains at baseline and 6 months were 12.8% ± 4.7% and 12.1% ± 5.2%, respectively, in the overall population ($P = 0.01$), representing a median change of −5.6% (Q1-Q3: −30.8% to 22.3%). In the TEER + GDMT group, LA reservoir strain was 12.6% ± 4.7% and 11.9% ± 5.1% at baseline and 6 months, respectively ($P = 0.06$) (median change: −5.3 [IQR: −31.1 to 26.5]), whereas in the GDMT-alone group, LA reservoir strain was 13.0% ± 4.8% and 12.3% ± 5.4% at baseline and 6 months, respectively ($P = 0.09$) (median change: −5.6 [IQR: −26.0 to 17.6]).

Improvement of LA reservoir strain by at least 15% from baseline was present in 106 of 347 (30.5%) patients (64/188 [34.0%] in the device group and 42/159 [26.4%] in the GDMT group) ($P = 0.12$). Tables 1 and 2 summarize the baseline clinical and echocardiographic characteristics, respectively, of the overall population according to LA strain improvers vs LA strain nonimprovers. LA strain nonimprovers had larger LV volumes. In addition, baseline values of LA reservoir strain were significantly lower in patients in whom a significant improvement in LA reservoir strain was present at follow-up. There were no significant differences between LA strain improvers and nonimprovers in either MR severity or LA volume.

Tables 3 and 4 summarize the baseline clinical and echocardiographic characteristics, respectively, according to LA strain improvers vs nonimprovers stratified by treatment arm. Baseline values of LA reservoir strain were lower in LA strain improvers in both the TEER and GDMT groups. The prevalence of atrial fibrillation at the time of the index echocardiography and a history of atrial fibrillation/flutter were not different between LA strain improvers and LA strain nonimprovers in either the TEER or the GDMT-alone group.

### SIX-MONTH ECHOCARDIOGRAPHIC CHARACTERISTICS OF LA STRAIN IMPROVERS.

Six-month echocardiographic characteristics of LA strain improvers vs nonimprovers are shown in Supplemental Table 1 (overall population) and Supplemental Table 2 (stratified by treatment arm). Among LA strain improvers, the mean values of LA volume (84.8 ± 35.8 mL vs 87.7± 40.4 mL; $P = 0.70$) and LA strain (15.4% ± 4.9% vs 15.9% ± 6.1%; $P = 0.62$) at 6 months were not significantly different between the TEER + GDMT and GDMT-alone groups, respectively. None or mild MR was more prevalent in the TEER + GDMT group, whereas MR ≥3+ was more prevalent in the

**TABLE 3** Baseline Clinical Characteristics of LA Strain Improvers vs Nonimprovers Stratified by Randomization Arm

| | TEER + GDMT (n = 188) | | | GDMT Alone (n = 159) | | |
|---|---|---|---|---|---|---|
| | LA GLS Improvers (n = 64) | LA GLS Nonimprovers (n = 124) | *P* Value | LA GLS Improvers (n = 42) | LA GLS Nonimprovers (n = 117) | *P* Value |
| Clinical characteristics | | | | | | |
| Age, y | 70 ± 14 | 71 ± 11 | 0.75 | 72 ± 12 | 71 ± 11 | 0.84 |
| Male | 42 (65.6) | 81 (46.8) | 0.97 | 26 (61.9) | 69 (59.0) | 0.74 |
| Body mass index, kg/m$^2$ | 26.2 ± 5.2 | 26.8 ± 5.1 | 0.44 | 26.7 ± 5.7 | 27.9 ± 6.0 | 0.28 |
| Systolic blood pressure, mm Hg | 105.6 ± 14.5 | 111.1 ± 16.9 | 0.03 | 107.7 ± 14.4 | 112.6 ± 16.2 | 0.08 |
| Diastolic blood pressure, mm Hg | 64.6 ± 9.3 | 65.4 ± 10.4 | 0.60 | 64.3 ± 9.1 | 64.8 ± 8.8 | 0.76 |
| Ischemic cardiomyopathy | 37 (57.8) | 71 (57.3) | 0.94 | 24 (57.1) | 62 (53.0) | 0.64 |
| Hypertension | 47 (73.4) | 102 (82.3) | 0.16 | 36 (85.7) | 90 (76.9) | 0.23 |
| Diabetes mellitus | 18 (28.1) | 42 (33.9) | 0.42 | 13 (31.0) | 46 (39.3) | 0.34 |
| Hypercholesterolemia | 35 (54.7) | 71 (57.3) | 0.74 | 17 (40.5) | 60 (51.3) | 0.23 |
| Coronary artery disease | 44 (68.8) | 83 (66.9) | 0.80 | 31 (73.8) | 76 (65.0) | 0.29 |
| Previous myocardial infarction | 33 (51.6) | 56 (45.2) | 0.40 | 18 (42.9) | 53 (45.3) | 0.78 |
| Previous PCI | 28 (43.8) | 48 (38.7) | 0.50 | 18 (42.9) | 57 (48.7) | 0.51 |
| Previous stroke or TIA | 8 (12.5) | 26 (21.0) | 0.15 | 5 (11.9) | 15 (12.8) | 0.88 |
| Peripheral vascular disease | 9 (14.1) | 17 (13.7) | 0.95 | 4 (9.5) | 18 (15.4) | 0.14 |
| COPD | 14 (21.9) | 25 (20.2) | 0.78 | 8 (19.0) | 23 (19.7) | 0.93 |
| History of atrial fibrillation/flutter | 28 (43.8) | 70 (56.5) | 0.10 | 23 (54.8) | 54 (46.2) | 0.34 |
| HFH within prior year | 44 (68.8) | 70 (56.5) | 0.10 | 28 (66.7) | 63 (53.8) | 0.15 |
| Anemia | 11 (17.2) | 26 (21.0) | 0.54 | 12 (28.6) | 23 (19.7) | 0.23 |
| Creatinine clearance, mL/min | 50.3 ± 28.0 | 53.6 ± 26.2 | 0.44 | 47.8 ± 26.7 | 53.2 ± 28.3 | 0.29 |
| BNP with conversions, pg/mL | 492.0 (307.9-1,107.0) | 468.7 (293.0-1,008.0) | 0.72 | 565.5 (247.1-1,318.6) | 604.0 (300.3-1,067.5) | 0.76 |
| NYHA functional class | | | 0.31 | | | 0.62 |
| II | 26 (40.6) | 62 (50.0) | | 17 (40.5) | 45 (38.8) | |
| III | 32 (50.0) | 56 (45.2) | | 19 (45.2) | 60 (51.7) | |
| IV | 6 (9.4) | 5 (4.0) | | 6 (14.3) | 11 (9.5) | |
| KCCQ overall summary score | 55.1 ± 22.1 | 55.6 ± 23.4 | 0.90 | 52.8 ± 22.8 | 53.8 ± 23.7 | 0.80 |
| 6MWD, m | 263.2 ± 115.7 | 265.8 ± 121.3 | 0.89 | 226.3 ± 135.2 | 261.3 ± 132.6 | 0.15 |
| Previous device[a] implantation | 39 (60.9) | 94 (75.8) | 0.03 | 33 (78.6) | 73 (62.4) | 0.06 |
| Medications | | | | | | |
| ACEI/ARB/ARNI | 48 (75.0) | 89 (71.8) | 0.64 | 26 (61.9) | 75 (64.1) | 0.80 |
| Aldosterone antagonist | 36 (56.3) | 61 (49.2) | 0.36 | 23 (54.8) | 59 (50.4) | 0.63 |
| Beta-blockers | 57 (89.1) | 114 (91.9) | 0.52 | 37 (88.1) | 107 (91.5) | 0.52 |
| Aspirin | 44 (68.8) | 65 (52.4) | 0.03 | 26 (61.9) | 77 (65.8) | 0.65 |
| Diuretic agents | 59 (92.2) | 111 (89.5) | 0.56 | 36 (85.7) | 106 (90.6) | 0.38 |
| Statin | 43 (67.2) | 79 (63.7) | 0.64 | 21 (50.0) | 73 (62.4) | 0.16 |
| Intervention | | | | | | |
| Number of clips implanted | 1.7 ± 0.6 | 1.7 ± 0.7 | 0.73 | – | – | – |

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Pacemaker, implantable cardioverter-defibrillator, CRT- P (CRT with pacing) CRT-D (CRT with defibrillator).
GLS = global longitudinal strain; GDMT = guideline-directed medical therapy; TEER = transcatheter edge-to-edge repair; other abbreviations as in Table 1.

GDMT-alone group. Patients in the TEER + GDMT group had lower 6-month LVEF compared with the GDMT-alone group (27.1% ± 10.6% vs 33.4% ± 11.5%; $P = 0.009$).

**OUTCOMES.** The estimated rate of the composite endpoint of death or HFH between the 6-month and 24-month follow-up was 23.7% for LA strain improvers and 38.6% for LA strain nonimprovers ($P = 0.02$) (Figure 1A). The rates of the composite endpoint of death or HFH at 2 years according to treatment arm were 19.7% for LA strain improvers in the TEER + GDMT group, 30.5% for LA strain nonimprovers in the TEER + GDMT group, 31.3% for LA strain improvers in the GDMT-alone group, and 49.3% for LA strain nonimprovers in the GDMT-alone group, with no evidence of interaction between LA improvement and treatment assignment ($P_{interaction} = 0.99$) (Figure 1B; Central Illustration, A). By Cox proportional hazards multivariable analysis (Table 5), LA strain improvement at 6 months (HR: 0.49 [95% CI: 0.27-0.89]; $P = 0.02$), LVEF at baseline (HR: 0.57 [95% CI: 0.40-0.79]; $P = 0.001$), and treatment with TEER (HR: 0.51 [95% CI: 0.33-0.80]; $P = 0.004$) were independently associated with a reduced risk of death or HFH

**TABLE 4** Baseline Echocardiographic Characteristics of LA Strain Improvers vs Nonimprovers Stratified by Randomization Arm

| | TEER + GDMT (n = 188) | | | GDMT Alone (n = 159) | | |
|---|---|---|---|---|---|---|
| | LA GLS Improvers (n = 64) | LA GLS Nonimprovers (n = 124) | *P* Value | LA GLS Improvers (n = 42) | LA GLS Nonimprovers (n = 117) | *P* Value |
| Heart rhythm at baseline echo | | | | | | |
| Sinus rhythm | 29 (45.3) | 48 (38.7) | 0.38 | 19 (45.2) | 58 (49.6) | 0.63 |
| AF | 10 (15.6) | 18 (14.5) | 0.38 | 4 (9.5) | 16 (13.7) | 0.49 |
| Paced | 23 (35.9) | 56 (45.2) | 0.22 | 18 (42.9) | 42 (35.9) | 0.42 |
| LV end-diastolic diameter, cm | 6.2 ± 0.7 | 6.3 ± 0.7 | 0.45 | 6.0 ± 0.7 | 6.3 ± 0.7 | 0.04 |
| LV end-systolic diameter, cm | 5.3 ± 0.8 | 5.3 ± 0.8 | 0.97 | 5.2 ± 0.9 | 5.4 ± 0.9 | 0.36 |
| LV end-diastolic volume, mL | 173.0 (139.0-219.0) | 187.5 (152.5-247.0) | 0.07 | 180.0 (119.5-231.0) | 202.0 (148.0-241.0) | 0.23 |
| LV end-systolic volume, mL | 122.0 (98.0-157.0) | 129.5 (100.5-181.0) | 0.22 | 129.0 (78.5-167.0) | 140.0 (99.0-175.0) | 0.30 |
| LA volume, mL | 91.0 ± 31.8 | 95.3 ± 41.6 | 0.46 | 93.1 ± 42.9 | 87.8 ± 33.5 | 0.42 |
| LA volume end-systole, mL | 127.0 ± 46.4 | 140.3 ± 53.9 | 0.10 | 132.8 ± 59.0 | 131.5 ± 50.3 | 0.89 |
| LA volume end-diastole, mL | 93.1 ± 38.8 | 94.5 ± 44.2 | 0.84 | 95.8 ± 48.8 | 87.1 ± 40.3 | 0.26 |
| LVEF, % | 30.6 ± 9.5 | 31.1 ± 8.2 | 0.71 | 29.8 ± 8.4 | 31.3 ± 9.5 | 0.37 |
| LV GLS, % | 11.6 ± 4.0 | 12.0 ± 3.1 | 0.49 | 11.6 ± 3.2 | 12.4 ± 3.5 | 0.17 |
| LA strain, % | 10.3 ± 3.5 | 13.8 ± 4.8 | <0.0001 | 10.8 ± 4.3 | 13.7 ± 4.8 | 0.0006 |
| MR severity | | | 0.61 | | | 0.81 |
| MR 3+ | 30 (46.9) | 63 (50.8) | | 21 (50.0) | 61 (52.1) | |
| MR 4+ | 34 (53.1) | 61 (49.2) | | 21 (50.0) | 56 (47.9) | |
| EROA, $cm^2$ | 0.41 ± 0.15 | 0.41 ± 0.15 | 0.98 | 0.40 ± 0.11 | 0.40 ± 0.14 | 1.00 |
| Tricuspid regurgitation | | | 0.15 | | | 0.74 |
| None | 0 (0) | 5 (4.0) | | 0 (0) | 1 (0.9) | |
| 1+ | 58 (92.1) | 103 (83.1) | | 34 (82.9) | 97 (85.8) | |
| 2+ | 5 (7.9) | 16 (12.9) | | 7 (17.1) | 14 (12.4) | |
| 3+ | 0 (0) | 0 (0) | | 0 (0) | 1 (0.9) | |
| 4+ | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| RVSP | 41.4 ± 12.2 | 45.0 ± 13.6 | 0.10 | 44.8 ± 14.9 | 45.2 ± 14.4 | 0.90 |

Values are n (%), mean ± SD, or median (Q1-Q3).
Abbreviations as in Tables 1 to 3.

between the 6-month and 24-month follow-up, whereas severe MR (4+) at baseline (HR: 1.66 [95% CI: 1.07-2.57]; $P = 0.02$) was independently associated with an increased risk of death or HFH in this period. These findings were consistent when change in LA strain was treated as a continuous variable rather than dichotomized at 15% change (Supplemental Table 3).

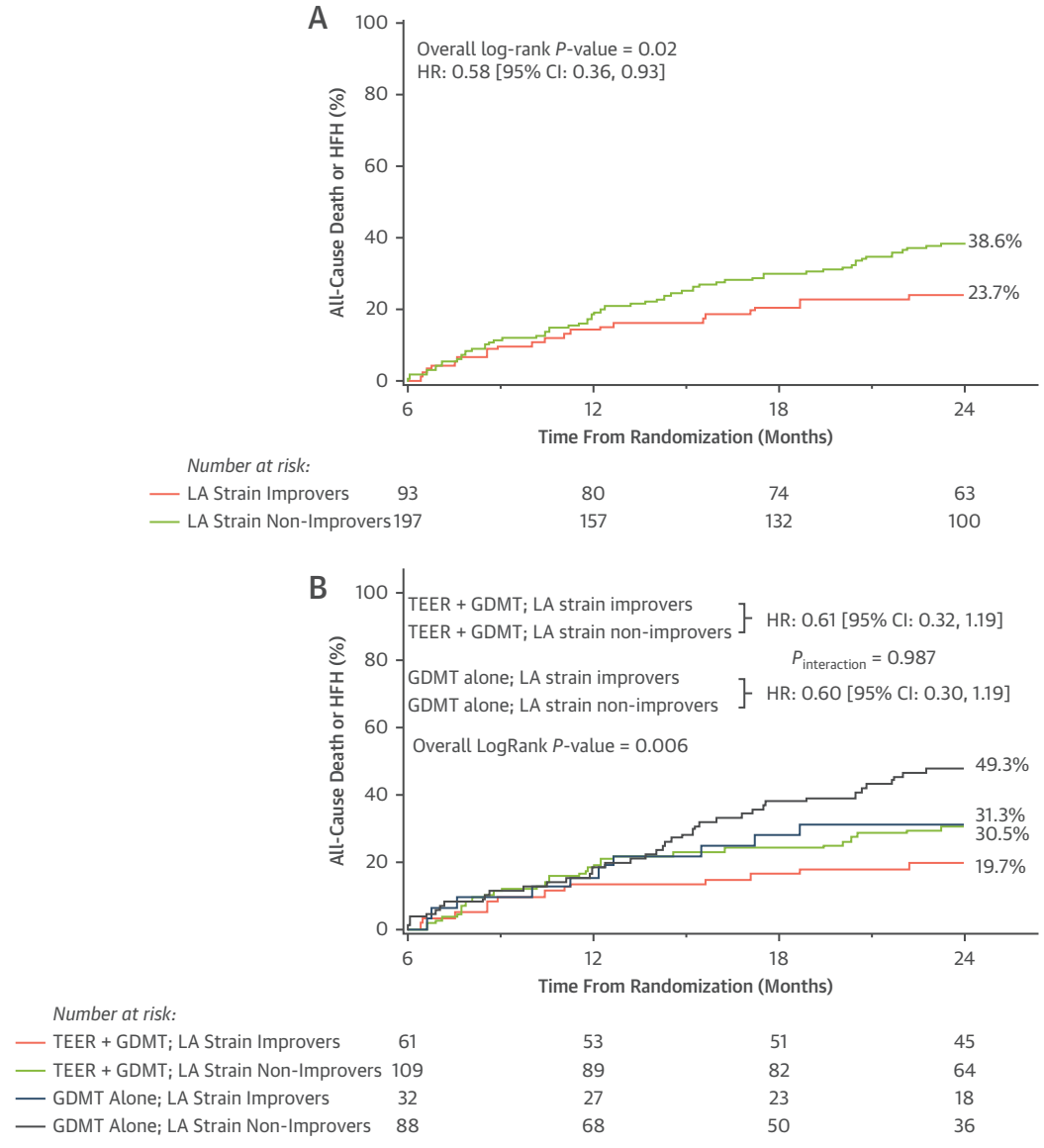
The estimated rate of all-cause death between the 6-month and 24-month follow-up was 17.9% for LA strain improvers and 24.3% for LA strain nonimprovers ($P = 0.22$) (**Figure 2A**). LA strain improvement conferred similar risk reductions in death in both treatment arms ($P_{interaction} = 0.30$) (**Figure 2B**; **Central Illustration, B**). After multivariable adjustment, only TEER treatment remained independently associated with a lower risk of death regardless of whether improvement in LA strain was dichotomized at 15% or treated as a continuous variable (Supplemental Table 4).

The estimated rate of HFH between the 6-month and 24-month follow-up was 19.8% for LA strain improvers and 31.2% for LA strain nonimprovers ($P = 0.07$) (**Figure 3A**). LA strain improvement conferred similar risk reductions in HFH in both treatment arms ($P_{interaction} = 0.66$) (**Figure 3B**; **Central Illustration, C**). When LA strain improvement was defined as an increase ≥15%, it was independently associated with a reduced risk of HFH by multivariable analysis (HR: 0.42 [95% CI: 0.21-0.84]; $P = 0.01$), as were treatment with TEER and greater baseline LVEF. MR grade 4+ was associated with an increased risk of HFH. The same directional trends were observed when LA strain improvement was treated as a continuous variable, although its statistical significance was borderline in this model (0.058) (Supplemental Table 5).

## DISCUSSION

The main findings of the present substudy from the COAPT trial can be summarized as follows: 1) LA reservoir strain improved from baseline to 6 months in 45% of patients with a similar degree of

**FIGURE 1** **Kaplan-Meier Curves for Death or HFH**




Estimates of the composite endpoint of all-cause death or HFH between the 6-month and 24-month follow-up according to left atrial (LA) strain improvement from baseline to 6 months in (A) all patients and (B) stratified by treatment arm. GDMT = guideline-directed medical therapy; HFH = heart failure hospitalization; TEER = transcatheter edge-to-edge repair.

improvement after TEER + GDMT and GDMT alone; 2) patients with severe secondary MR who had an improvement in LA reservoir strain from baseline to the 6-month follow-up had a significant reduction in the composite endpoint of all-cause mortality or HFH between the 6- and 24-month follow-up regardless of whether LA strain improvement was measured along a continuum or defined using a 15% improvement threshold; 3) improvement in LA reservoir strain during the 6-month follow-up conferred a similar prognostic benefit in patients treated with TEER + GDMT and GDMT alone; and 4) the lowest rates of

**TABLE 5** Characteristics Associated With All-Cause Death or HFH Between the 6-Month and 24-Month Follow-Up

| | Univariable Analysis | | Multivariable Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| LA strain improvement | 0.58 (0.36-0.93) | 0.02 | 0.49 (0.27-0.89) | 0.02 |
| LA strain at baseline, per 1 U | 0.97 (0.93-1.02) | 0.20 | 1.00 (0.93-1.07) | 0.90 |
| LA volume (end-diastole), per mL | 1.01 (1.00-1.01) | 0.008 | 1.01 (1.00-1.01) | 0.12 |
| LVEF at baseline, per 10% | 0.72 (0.56-0.93) | 0.01 | 0.57 (0.40-0.79) | 0.001 |
| LV GLS at baseline, per 1 U | 0.97 (0.92-1.03) | 0.35 | 1.66 (1.06-1.16) | 0.24 |
| Change in LV GLS to 6 mo, per 1 U | 0.95 (0.89-1.02) | 0.15 | 0.95 (0.87-1.03) | 0.19 |
| TEER + GDMT (vs GDMT alone) | 0.56 (0.38-0.84) | 0.005 | 0.51 (0.33-0.80) | 0.004 |
| History of atrial fibrillation or flutter | 1.32 (0.88-1.97) | 0.18 | 1.21 (0.75-1.97) | 0.44 |
| MR 4+ (vs 3+) | 1.52 (1.02-2.28) | 0.04 | 1.66 (1.07-2.57) | 0.02 |

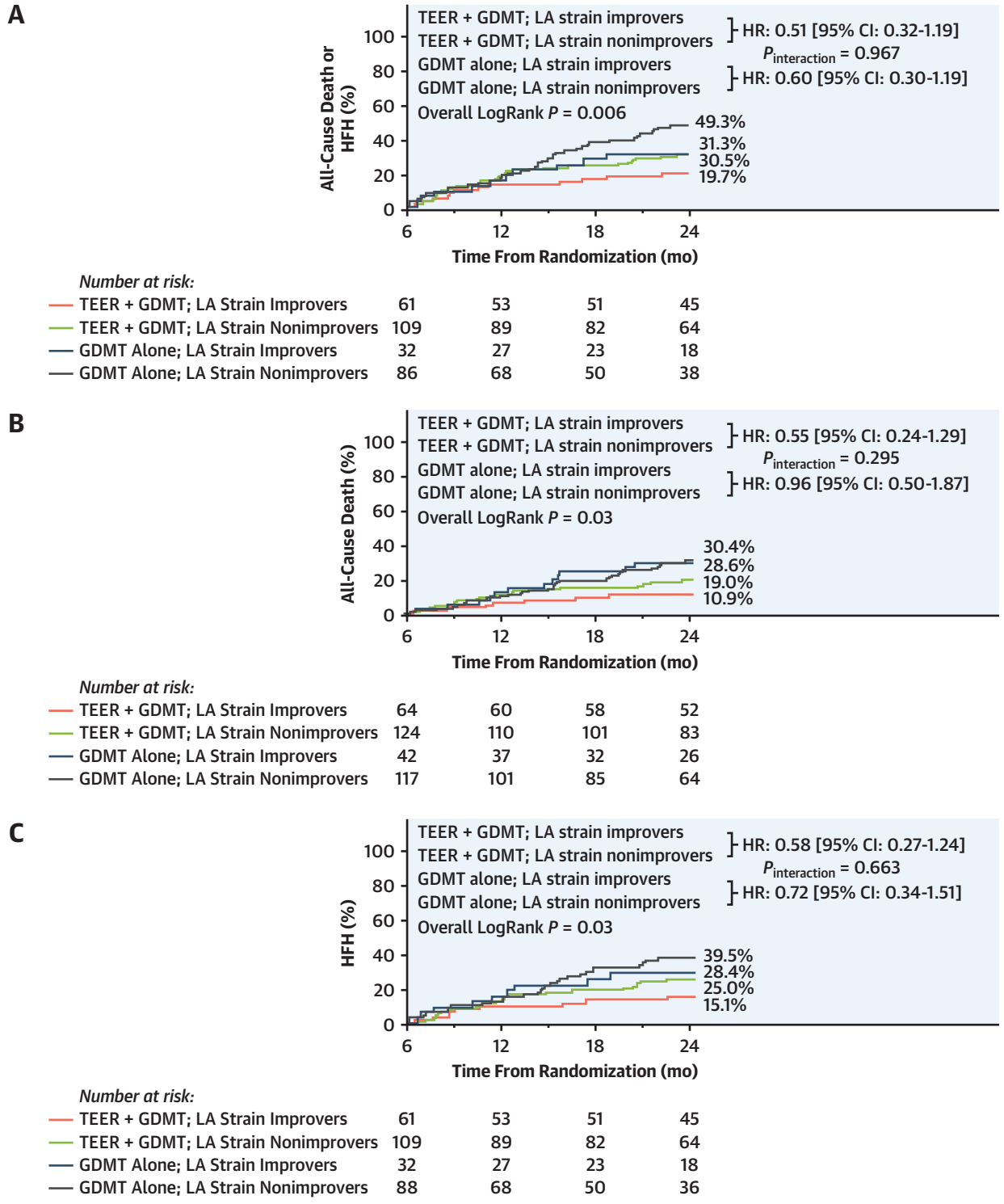
Abbreviations as in Tables 1 to 3.

death or HFH at 2 years occurred in patients treated with TEER in whom LA strain improved from baseline to 6 months.

**LA RESERVOIR STRAIN IN PATIENTS WITH HF AND FUNCTIONAL MR.** At least moderate secondary MR is common in patients with HF and reduced LVEF, with a prevalence ranging between 6% and 29%.[20,21] In these patients, additional volume overload may accelerate not only adverse LV remodeling but also LA remodeling. The assessment of LA size has become an essential part of the multiparametric evaluation of patients with HF and reduced LVEF. LA size has been demonstrated to be an important prognostic marker, showing a strong association with symptom severity and worse outcomes.[7] However, the evaluation of LA function may provide incremental prognostic information beyond LA size alone. LA reservoir strain (measured by 2-dimensional speckle tracking echocardiography) is a marker of LA function and is closely related to LA compliance and LA pressure.[22,23] Anatomically situated between the pulmonary circulation and the left ventricle, the left atrium acts as a buffer for an increase in LV pressure overload, which otherwise is directly transmitted to the pulmonary circulation.[7] In patients with HF and significant MR, a compliant left atrium may also partially compensate for the additional volume overload on the pulmonary circulation, thereby preventing pulmonary congestion and right ventricular-pulmonary arterial uncoupling.[24] However, during longer-term follow-up, excessive volume and pressure overload on the left atrium may cause LA fibrosis, which reduces LA compliance.[6,25] A reduction in LA compliance facilitates pulmonary congestion and right ventricular-pulmonary arterial uncoupling, which are strongly associated with worse survival in patients with HF and significant functional MR.[26,27] Because LA reservoir strain has shown a good correlation with the extent of atrial fibrosis on cardiac magnetic resonance,[19] it may provide a more thorough risk stratification of patients with functional MR. In particular, patients with more extensive LA fibrosis may display less benefit in survival/HF hospitalization independent of the therapy given. Patients with more extensive LA fibrosis may respond less to therapy (either TEER or GDMT).

**PROGNOSTIC IMPLICATIONS.** The COAPT trial demonstrated that HF patients with 3+ or 4+ functional MR who remain symptomatic despite maximally tolerated GDMT benefit from MR reduction with TEER, showing a significant reduction in HF hospitalization and all-cause mortality after MitraClip device implantation.[3] However, not all patients benefit from TEER. Event rates remain high in this high-risk cohort of patients with LV dysfunction despite successful TEER; thus, being able to provide an accurate prognosis as well as identify patients likely to derive benefit (or not) from TEER is of major clinical relevance. Although research has mainly focused on progressive adverse remodeling of the left ventricle after TEER,[5] assessment of serial changes in LA reservoir strain may provide additional prognostic information. In a limited sample of patients with moderate to severe MR, Toprak et al[28] showed that successful TEER was able to reverse LA remodeling within 12 months, but outcome data were lacking. The current study shows for the first time that patients who had an improvement in LA reservoir strain from baseline to the 6- follow-up had a significantly lower composite rate of all-cause mortality or HFH between the 6-month and 24-month follow-up compared with patients who had no improvement in LA reservoir strain. LA reservoir strain at the 6-month follow-up remained independently associated with a lower risk of HFH and the composite endpoint of all-cause mortality or HFH after adjustment for other

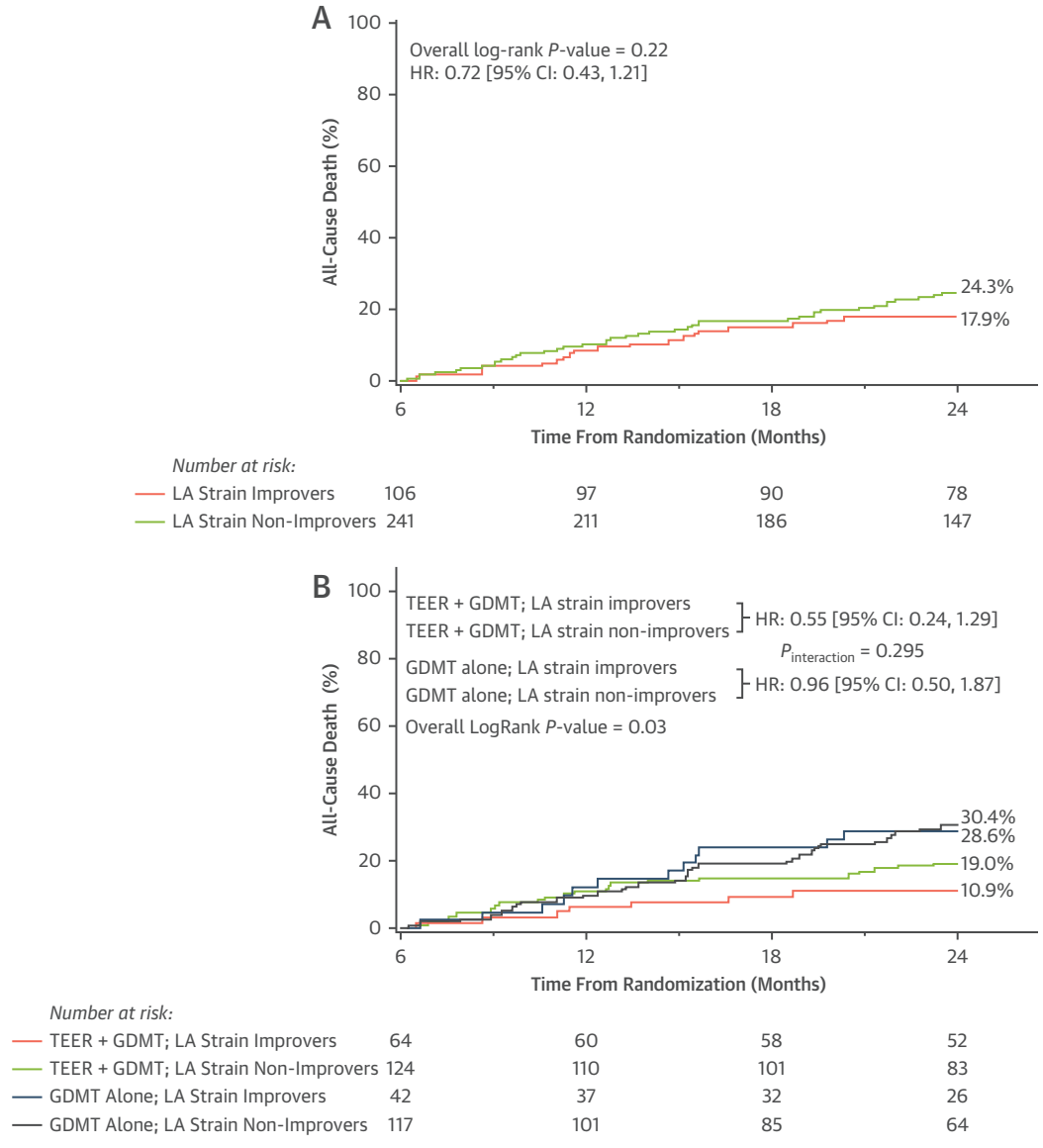
**CENTRAL ILLUSTRATION** **Kaplan-Meier Curves for the Composite Outcome of Death or HFH as Well as Its Individual Components Stratified by Treatment Arm**




**Pio SM, et al. J Am Coll Cardiol Img. 2024;■(■):■-■.**

GDMT = guideline-directed medical therapy; HFH = heart failure hospitalization; LA = left atrial; TEER = transcatheter edge-to-edge repair.

**FIGURE 2** Kaplan-Meier Curves for All-Cause Death

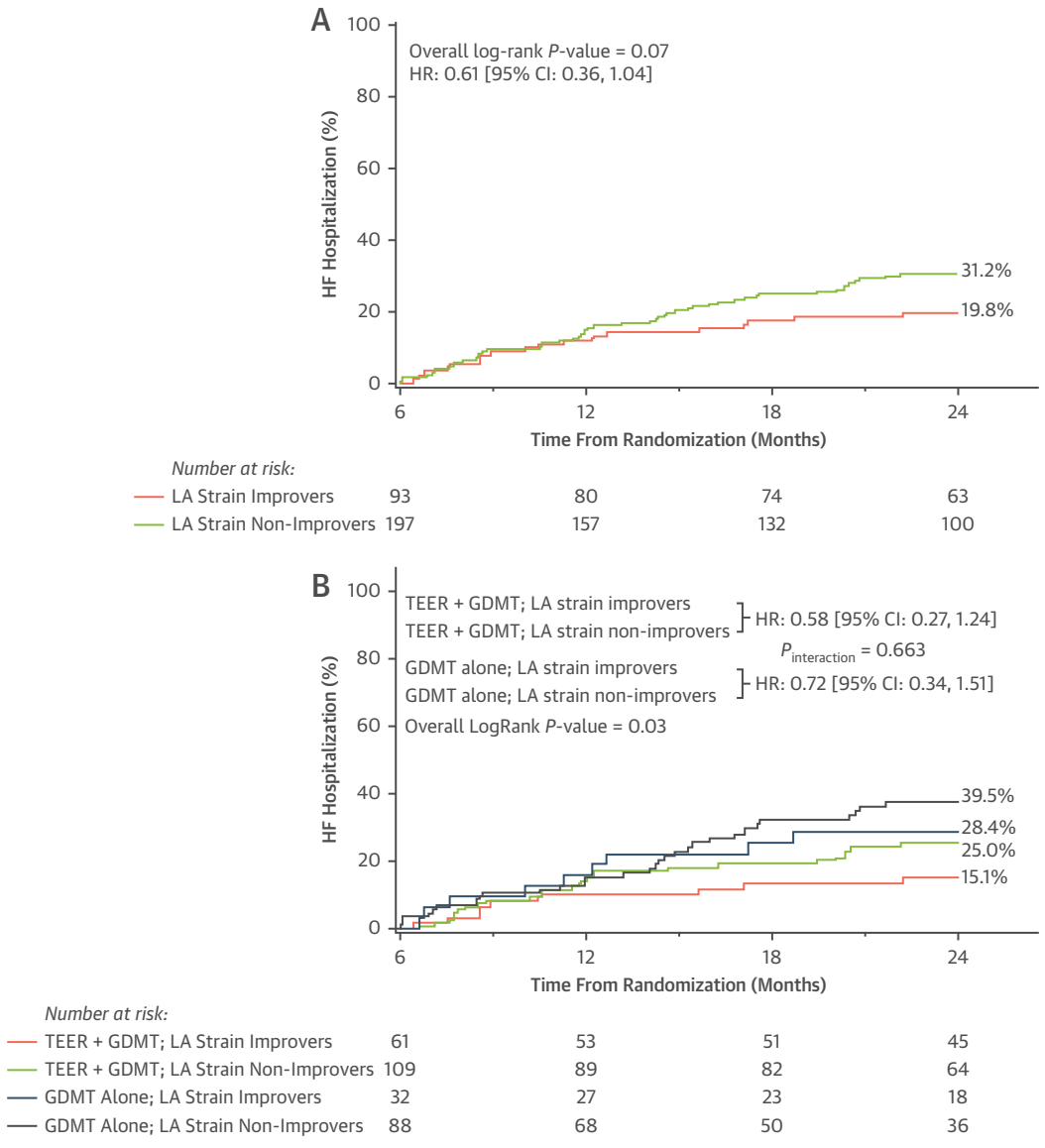



Estimates of all-cause death between the 6-month and 24-month follow-up according to LA strain improvement from baseline to 6 months in (A) all patients and (B) stratified by treatment arm. Abbreviations as in Figure 1.

clinical and echocardiographic covariates. This benefit was observed in both treatment arms with no evidence of interaction. Also of note, improvement in LA strain at the 6-month follow-up was independently associated with improvement in the subsequent rates of HFH and the composite of death or HFH, whereas baseline LA strain was not. Previous studies have demonstrated that optimization of GDMT could have an impact on LA reverse remodeling,[29,30] potentially explaining why a proportion of patients in the GDMT-alone group experienced an improvement in LA reservoir strain as well. Although the correlates of and mechanisms underlying LA reservoir strain improvement warrant further investigation, patients who presented with improved LA reservoir strain at follow-up may have had a greater LA myocardial reserve.

The current findings support serial measurements of LA reservoir strain during the follow-up of patients who undergo TEER given that the improvement of LA

**FIGURE 3** Kaplan-Meier Curves for HFH




Estimates of heart failure hospitalization between the 6-month and 24-month follow-up according to left atrial (LA) strain improvement from baseline to 6 months in (A) all patients and (B) stratified by treatment arm. Abbreviations as in Figure 1.

reservoir strain at 6 after TEER was associated with the lowest rates of events during 24 months of follow-up. In this regard, the composite rate of death or HFH between the 6-month and 24-month follow-up was 19.7% in patients treated with TEER + GDMT in whom LA strain had improved from baseline to 6 months vs 49.3% in patients treated with GDMT alone in whom LA strain had not improved from baseline to 6 months.

**STUDY LIMITATIONS.** The present analysis was post hoc and should therefore be considered hypothesis generating. The assessment of LA reservoir strain was performed with different echocardiography systems, which may have affected the results. Moreover, patients who died during the first 6 months after randomization could not be included; the impact of improving LA strain before 6 months on outcomes in this early period cannot be estimated from the

present study. Finally, more patients from the GDMT-alone arm than the TEER + GDMT arm were excluded from the analysis population because of both excess early deaths and more missingness of 6-month echocardiographic follow-up in the GDMT-alone arm. The potential impact of this imbalance in missingness of echocardiographic follow-up is unclear.

## CONCLUSIONS

In symptomatic HF patients with severe functional MR enrolled in the COAPT trial, improvement of LA reservoir strain from baseline to 6 months was associated with lower rates of the composite endpoint of all-cause mortality or HFH, both after TEER + GDMT and GDMT alone. The lowest rates of death or HFH at 2 years occurred in patients treated with TEER in whom LA strain improved from baseline to 6 months.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In symptomatic HF patients with severe functional MR enrolled in the COAPT trial, the improvement of LA reservoir strain from baseline to 6 months was associated with lower rates of the composite endpoint of all-cause mortality or HFH and the individual endpoint of HFH between the 6- and 24-month follow-up, both after TEER + GDMT and after GDMT alone.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** The current findings support serial measurements of LA reservoir strain during follow-up of patients who undergo TEER given that the improvement of LA reservoir strain at 6 months after TEER was associated with the lowest rates of events during 24 months of follow-up.

**TRANSLATIONAL OUTLOOK:** The correlates of, and mechanisms underlying, LA reservoir strain improvement warrant further investigation.

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**KEY WORDS** COAPT, heart failure, left atrial reservoir strain, secondary mitral regurgitation, transcatheter edge-to-edge repair

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