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Citation
Lindman, B. R., Asch, F. M., Grayburn, P. A., Mack, M. J., Bax, J. J., Gonzales, H., ... Stone, G. W. (2023). Ventricular remodeling and outcomes after mitral transcatheter edge-to-edge repair in heart failure. *Jacc: Cardiovascular Interventions*, *16*(10), 1160-1172. doi:10.1016/j.jcin.2023.02.031

Version:	Publisher's Version
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Downloaded from:	https://hdl.handle.net/1887/3762058

Note: To cite this publication please use the final published version (if applicable).

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 10, 2023
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PUBLISHED BY ELSEVIER

NEW RESEARCH PAPER

STRUCTURAL

Ventricular Remodeling and Outcomes After Mitral Transcatheter Edge-to-Edge Repair in Heart Failure

The COAPT Trial

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ABSTRACT

BACKGROUND The relationship between left ventricular (LV) remodeling and clinical outcomes after treatment of severe mitral regurgitation (MR) in heart failure (HF) has not been examined.

OBJECTIVES The aim of this study was to evaluate the association between LV reverse remodeling and subsequent outcomes and assess whether transcatheter edge-to-edge repair (TEER) and residual MR are associated with LV remodeling in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial.

METHODS Patients with HF and severe MR who remained symptomatic on guideline-directed medical therapy (GDMT) were randomized to TEER plus GDMT or GDMT alone. Baseline and 6-month core laboratory measurements of LV end-diastolic volume index and LV end-systolic volume index were examined. Change in LV volumes from baseline to 6 months and clinical outcomes from 6 months to 2 years were evaluated using multivariable regression.

RESULTS The analytical cohort comprised 348 patients (190 treated with TEER, 158 treated with GDMT alone). A decrease in LV end-diastolic volume index at 6 months was associated with reduced cardiovascular death between 6 months and 2 years (adjusted HR: 0.90 per 10 mL/m^2 decrease; 95% CI: 0.81-1.00; $P = 0.04$), with consistent results in both treatment groups ($P_{interaction} = 0.26$). Directionally similar but nonsignificant relationships were present for all-cause death and HF hospitalization and between reduced LV end-systolic volume index and all outcomes. Neither treatment group nor MR severity at 30 days was associated with LV remodeling at 6 or 12 months. The treatment benefits of TEER were not significant regardless of the degree of LV remodeling at 6 months.

CONCLUSIONS In patients with HF and severe MR, LV reverse remodeling at 6 months was associated with subsequently improved 2-year outcomes but was not affected by TEER or the extent of residual MR. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [The COAPT Trial] and COAPT CAS [COAPT]; NCT01626079) (J Am Coll Cardiol Intv 2023;16:1160–1172) © 2023 by the American College of Cardiology Foundation.

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ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2023.02.031

Studies in patients with heart failure (HF) with reduced left ventricular (LV) ejection fraction have reported a significant association between adverse LV remodeling and subsequent mortality.[1-5] For example, Kramer et al[1] examined 30 mortality trials of 25 drugs and devices and 88 remodeling trials of the same therapies and found that the odds for death correlated with the drug and device effects on LV end-diastolic volume (LVEDV) ($r = 0.44$; $P = 0.002$) and LV end-systolic volume (LVESV) ($r = 0.48$; $P = 0.002$).[1] As such, LV remodeling is considered by some to be a surrogate for adverse clinical outcomes in patients with HF with reduced ejection fraction. However, these trials typically have excluded patients with severe mitral regurgitation (MR), and the link between LV remodeling and clinical outcomes after interventions specifically targeting MR has not been examined.

The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial demonstrated reduced rates of death and HF hospitalization (HFH) in select patients with HF and severe secondary MR (SMR) treated with transcatheter edge-to-edge repair (TEER)[6]; as such, the number of devices being developed to treat MR is increasing.[6,7] The safety and effectiveness of new therapies for MR are typically evaluated in randomized trials. However, given the resources and time required to execute randomized mitral valve trials with primary clinical endpoints (more than 7 years for COAPT), using surrogate measures of clinical outcomes as a sole endpoint or as part of a composite endpoint in future studies may be desirable to enable smaller sample sizes and shorten trial duration. For example, a trial from the Cardiothoracic Surgical Network compared mitral valve surgical repair with replacement for severe ischemic MR with a primary endpoint of LVESV index (LVESVi) at 12 months, affording adequate power with 251 patients (compared with 614 patients in COAPT).[8] However, MR reduction increases afterload, which may paradoxically increase LV volumes, at least in the short term.[9] Whether LV remodeling is a predictor of subsequent clinical outcomes specifically in patients with severe MR in HF and, if so, whether such effects differ according to MR treatment with TEER have to our knowledge never been examined. Accordingly, from the randomized COAPT trial, we evaluated the association between LV remodeling and subsequent clinical outcomes and examined whether TEER intervention or residual MR severity at 30 days was associated with LV remodeling.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The COAPT trial has been previously described in detail.[7] Briefly, COAPT was a multicenter, randomized controlled trial which assigned patients with HF and echocardiography core laboratory-confirmed moderate to severe (3+) or severe (4+) SMR who remained symptomatic despite maximally tolerated guideline-directed medical therapy (GDMT) to TEER with the MitraClip device (Abbott) plus GDMT or GDMT alone. Key enrollment criteria included valve anatomy amenable to TEER, LV ejection fraction between 20% and 50%, New York Heart Association functional class ≥2, LV end-systolic diameter ≤70 mm, and the absence of severe pulmonary hypertension or moderate or severe right ventricular dysfunction. Patients were randomized 1:1 to treatment with the MitraClip plus GDMT vs GDMT alone. The analysis was performed according to actual treatment received rather than intention-to-treat. Quality of life and functional capacity were measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and 6-minute walk distance at baseline, 30 days, and 6, 12, 18, and 24 months. Clinical follow-up is ongoing through 5 years. The trial was approved by the institutional review committee at each site, and all subjects provided written informed consent.

ECHOCARDIOGRAPHY. Transthoracic echocardiography was performed in all patients at baseline; discharge (TEER group only); 30 days; 6, 12, 18, and 24 months; and then annually through 5 years. Echocardiograms were obtained at the enrolling centers following a study-specific acquisition protocol. Pertinent to this analysis, 2-dimensional images from the apical window (2- and 4-chamber views) were obtained, with an emphasis on avoiding LV

ABBREVIATIONS AND ACRONYMS

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle/ventricular

LVEDV = left ventricular end-diastolic volume

LVEDVi = left ventricular end-diastolic volume index

LVESV = left ventricular end-systolic volume

LVESVi = left ventricular end-systolic volume index

MR = mitral regurgitation

SMR = secondary mitral regurgitation

TEER = transcatheter edge-to-edge repair

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 10, 2022; revised manuscript received February 13, 2023, accepted February 21, 2023.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 10, 2023
MAY 22, 2023:1160–1172

TABLE 1 Baseline Characteristics According to Treatment Received

	MitraClip Plus GDMT (n = 190)	GDMT Alone (n = 158)	*P* Value
Clinical parameters			
Age, y	70.8 ± 12.3	71.2 ± 10.6	0.78
Female	63 (33.2)	63 (39.9)	0.19
Black or African American	34 (17.9)	31 (19.6)	0.68
Hispanic or Latino	14 (7.4)	7 (4.4)	0.25
Body mass index, kg/m^2	26.7 ± 5.3	27.6 ± 6.1	0.18
Diabetes	62 (32.6)	59 (37.3)	0.36
Hypertension	147 (77.4)	129 (81.6)	0.33
Systolic blood pressure, mm Hg	111 ± 18	111 ± 16	0.73
Previous myocardial infarction	90 (47.4)	77 (48.7)	0.80
Previous percutaneous coronary intervention	81 (42.6)	74 (46.8)	0.43
Previous coronary artery bypass graft surgery	68 (35.8)	54 (34.2)	0.75
Previous stroke or TIA	36 (18.9)	23 (14.6)	0.28
Peripheral vascular disease	27 (14.2)	27 (17.1)	0.46
Chronic obstructive pulmonary disease	44 (23.2)	30 (19.0)	0.34
History of atrial fibrillation or flutter	100 (52.6)	80 (50.6)	0.71
Creatinine clearance, mL/min	53.4 ± 27.3	50.3 ± 27.2	0.29
Anemia[a]	40 (21.1)	33 (20.9)	0.97
STS risk score for MV replacement, %	7.0 ± 4.9	7.6 ± 5.7	0.26
Extremely high risk for surgery	122 (64.9)	103 (65.2)	0.95
Ischemic cardiomyopathy	111 (58.4)	89 (56.3)	0.69
NYHA functional class III or IV	108 (56.8)	95 (60.5)	0.49
Hospitalization for HF within prior 1 y	110 (57.9)	90 (57.0)	0.86
Previous cardiac resynchronization therapy	74 (38.9)	55 (34.8)	0.43
Previous implantable cardioverter defibrillator	61 (32.1)	62 (39.2)	0.17
BNP, pg/mL	925 ± 1,020	1,028 ± 887	0.42
NT-proBNP, pg/mL	4,455 ± 4,939	5,656 ± 6,775	0.33
Echocardiographic parameters (core laboratory)			
Severity of mitral regurgitation			
Moderate to severe (3+)	90 (47.4)	81 (51.3)	0.47
Severe (4+)	100 (52.6)	77 (48.7)	0.47
Effective regurgitant orifice area by PISA, cm^2	0.42 ± 0.15	0.39 ± 0.13	0.06
Moderate to severe tricuspid regurgitation (≥3+)	0 (0.0)	1 (0.7)	0.27
LV end-systolic dimension, cm	5.3 ± 0.8	5.4 ± 0.8	0.58
LV end-diastolic dimension, cm	6.2 ± 0.7	6.3 ± 0.7	0.66
LV end-systolic dimension index, mL/m^2	2.8 ± 0.5	2.9 ± 0.5	0.62
LV end-diastolic dimension index, mL/m^2	3.3 ± 0.4	3.3 ± 0.4	0.72
LV end-systolic volume, mL	138 ± 59	142 ± 63	0.52
LV end-diastolic volume, mL	198 ± 72	200 ± 76	0.79
LV end-systolic volume index, mL/m^2	73 ± 29	74 ± 30	0.63
LV end-diastolic volume index, mL/m^2	104 ± 35	104 ± 34	0.98
LV ejection fraction, %	31.3 ± 8.9	30.0 ± 8.9	0.18
LV global longitudinal strain, %	−11.8 ± 3.4	−11.7 ± 3.2	0.85
Forward stroke volume, mL	50.8 ± 17.0	51.5 ± 17.5	0.70
Left atrial volume, mL	93.6 ± 37.2	89.0 ± 35.3	0.24
Right ventricular systolic pressure, mm Hg	44 ± 13	45 ± 14	0.72

Values are mean ± SD or n (%). [a]Defined as a hemoglobin level at initial presentation of <13 g/dL in men and <12 g/dL in women.

BNP = B-type natriuretic peptide; HF = heart failure; GDMT = guideline-directed medical therapy; LV = left ventricular; NT-proBNP; N-terminal pro-B-type natriuretic peptide; MV = mitral valve; PISA = proximal isovelocity surface area; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

foreshortening. All echocardiograms were analyzed at an independent echocardiographic core laboratory (MedStar Health Research Institute), as previously described.[7,10] All measurements were made in accordance with recommendations from the American Society of Echocardiography. Specifically, LVESV and LVEDV measurements were made using the biplane method of disks (Simpson's rule) by tracing the endocardial border (trabeculations were considered within the LV cavity) and indexed to body surface area (LVESVi and LVEDV index [LVEDVi]). LV global longitudinal strain was measured from the apical views (4, 2, and 3 chamber) in a semiautomated manner using a vendor-neutral workstation (2D

TABLE 2 Changes in Left Ventricular Volumes During 1-Year Follow-Up According to Treatment

	All Patients (N = 348)	MitraClip Plus GDMT (n = 190)	GDMT Alone (n = 158)	*P* Value
LVEDVi measurements, mL/m^2				
At 30 d				
Number with paired measurements	426	216	210	
Baseline measurement	103.0 ± 34.3	104.4 ± 34.3	101.7 ± 34.5	0.42
30-d follow-up measurement	93.9 ± 31.0	92.9 ± 30.7	94.9 ± 31.4	0.50
Change from baseline	−9.1 ± 24.2[a]	−11.4 ± 23.4[a]	−6.8 ± 24.8[a]	0.045
Adjusted difference in change from baseline	—	−3.8 (−7.8 to 0.2)		0.07
At 6 mo				
Number with paired measurements	348	190	158	
Baseline measurement	104.1 ± 34.5	104.0 ± 34.9	104.1 ± 34.1	0.98
6-mo follow-up measurement	95.7 ± 32.3	95.3 ± 32.2	96.3 ± 32.3	0.77
Change from baseline	−8.4 ± 27.5[a]	−8.8 ± 28.4[a]	−7.9 ± 26.4[a]	0.76
Adjusted difference in change from baseline	—	−1.0 (−6.1 to 4.2)		0.71
At 1 y				
Number with paired measurements	290	159	131	
Baseline measurement	102.5 ± 34.7	103.8 ± 34.5	100.9 ± 35.0	0.48
1-y follow-up measurement	95.2 ± 33.1	96.4 ± 34.6	93.8 ± 31.3	0.50
Change from baseline	−7.3 ± 29.0[a]	−7.5 ± 28.2[a]	−7.2 ± 27.8[a]	0.93
Adjusted difference in change from baseline	—	0.8 (−5.0 to 6.6)		0.79
LVESVi measurements, mL/m^2				
At 30 d				
Number with paired measurements	426	216	210	
Baseline measurement	72.8 ± 29.4	73.2 ± 28.9	72.3 ± 29.9	0.77
30-d follow-up measurement	67.4 ± 27.4	67.9 ± 27.0	66.9 ± 27.8	0.69
Change from baseline	−5.4 ± 19.8[a]	−5.3 ± 19.0[a]	−5.5 ± 20.6[a]	0.91
Adjusted difference in change from baseline	—	0.5 (−2.9 to 3.9)		0.79
At 6 mo				
Number with paired measurements	348	190	158	
Baseline measurement	73.4 ± 29.3	72.7 ± 29.3	74.2 ± 29.5	0.63
6-mo follow-up measurement	69.0 ± 28.7	69.6 ± 29.9	68.3 ± 27.3	0.66
Change from baseline	−4.4 ± 21.8[a]	−3.1 ± 22.7	−6.0 ± 20.8[a]	0.22
Adjusted difference in change from baseline	—	2.4 (−1.8 to 6.7)		0.26
At 1 y				
Number with paired measurements	290	159	131	
Baseline measurement	71.8 ± 29.2	72.3 ± 28.4	71.1 ± 30.3	0.73
1-y follow-up measurement	69.7 ± 30.0	71.6 ± 32.2	67.4 ± 27.0	0.22
Change from baseline	−2.1 ± 24.5	−0.7 ± 25.6	−3.7 ± 23.1	0.29
Adjusted difference in change from baseline	—	3.4 (−1.8 to 8.7)		0.20

Values are mean ± SD or median (IQR). Data represent paired changes from baseline to each follow-up time period. Note, however, that having an echocardiogram at all follow-up time points was not required. [a]$P < 0.05$ for paired-sample *t*-test used to compare follow-up value to baseline value.

LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index.

Cardiac Performance Analysis version 1.3, TomTec Imaging Systems) to allow analysis of images from multiple vendors, as previously described.[11]

CLINICAL ENDPOINTS. Endpoints of interest for the present study included 1) all-cause death or HFH; 2) all-cause death; 3) HFH; and 4) cardiovascular death, each as previously defined.[7] All endpoints were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation).

STATISTICAL ANALYSIS. Baseline characteristics are summarized as mean ± SD for continuous variables and as proportions for categorical variables. Continuous data were compared using Student's *t*-test, and categorical variables were compared using the chi-square or Fisher exact test as appropriate. Comparisons across 3 groups were assessed with analysis of variance. Changes in echocardiographic measures of LV volume (LVEDVi and LVESVi) over time were determined using paired baseline and follow-up measurements at 30 days, 6 months, and 1 year, without imputation for missing data. Differences in LV volume changes over time between groups were estimated by analysis of covariance, adjusting for the

TABLE 3 Changes in Left Ventricular Volumes During 1-Year Follow-Up According to MR Severity at 30 Days in All Study Patients

	0-1+ MR at 30 d	2+ MR at 30 d	3-4+ MR at 30 d	P Value
LVEDVi measurements, mL/m^2				
At 6 mo				
Number with paired measurements	133	74	101	
30-d measurement	92.5 ± 30.9	89.4 ± 30.7	105.3 ± 33.6	0.001
6-mo follow-up measurement	93.5 ± 31.8	90.0 ± 31.0	104.0 ± 34.3	0.009
Change from 30 d to 6 mo	1.0 ± 23.6	0.6 ± 15.7	−1.2 ± 24.8	0.74
	0-1+ vs 2+	**0-1+ vs 3-4+**	**2+ vs 3-4+**	
Adjusted difference in change from 30 d	1.1 (−5.0 to 7.2)	−0.7 (−6.3 to 4.9)	−1.8 (−8.3 to 4.7)	
At 1 y				
Number with paired measurements	119	67	78	
30-d measurement	91.1 ± 29.4	87.5 ± 33.1	101.0 ± 32.3	0.022
1-y follow-up measurement	92.5 ± 30.6	88.8 ± 34.9	101.4 ± 33.3	0.053
Change from 30 d to 1 y	1.5 ± 28.6	1.3 ± 21.3	0.3 ± 23.0	0.95
	0-1+ vs 2+	**0-1+ vs 3-4+**	**2+ vs 3-4+**	
Adjusted difference in change from 30 d	1.2 (−6.0 to 8.3)	−1.7 (−8.6 to 5.1)	−2.9 (−10.8 to 5.0)	
LVESVi measurements, mL/m^2				
At 6 mo				
Number with paired measurements	133	74	101	
30-d measurement	68.0 ± 27.4	64.7 ± 26.3	74.4 ± 30.0	0.06
6-mo follow-up measurement	69.4 ± 29.4	63.5 ± 27.6	74.0 ± 29.2	0.059
Change from 30 d to 6 mo	1.4 ± 20.3	−1.3 ± 14.0	−0.4 ± 19.7	0.58
	0-1+ vs 2+	**0-1+ vs 3-4+**	**2+ vs 3-4+**	
Adjusted difference in change from 30 d	3.3 (−1.8 to 8.4)	0.6 (−4.1 to 5.2)	−2.7 (−8.2 to 2.7)	
At 1 y				
Number with paired measurements	119	67	78	
30-d measurement	66.9 ± 26.6	62.3 ± 28.6	71.2 ± 29.1	0.16
1-y follow-up measurement	69.2 ± 28.8	63.5 ± 30.0	73.7 ± 30.5	0.12
Change from 30 d to 1 y	2.3 ± 25.1	1.2 ± 18.4	2.5 ± 20.6	0.93
	0-1+ vs 2+	**0-1+ vs 3-4+**	**2+ vs 3-4+**	
Adjusted difference in change from 30 d	2.3 (−4.1 to 8.7)	−1.3 (−7.4 to 4.8)	−3.6 (−10.6 to 3.4)	

Values are mean ± SD or median (IQR).
MR = mitral regurgitation; other abbreviations as in Table 2.

baseline volume measurements. Multivariable linear regression was used to model the relationship between covariates and the change in LV volumes over time. Covariates with univariable associations ($P < 0.10$) with change in LV volume were included in each model.

The principal study objective was to examine the relationship between LV remodeling from baseline to 6 months and subsequent clinical outcomes. We chose to look at LV remodeling at 6 months rather than at 30 days to allow more time for remodeling and rather than at 1 year to minimize survivor bias. The present report is restricted to 2-year follow-up, as crossovers from control to device treatment were allowed after this time. Time-to-first event rates between 6 months and 2 years were estimated in a landmark analysis using the Kaplan-Meier method and compared using Cox proportional hazards models. There were 57 subjects with HFH before 6 months. So as not to overfit the multivariable models, we included 26 covariates selected a priori on the basis of their previously established impact on prognosis in patients with HF and SMR (Supplemental Table 1). Among these, any variable with ≥10% missingness was eliminated. We then identified those variables with univariable associations ($P < 0.20$) with death or HFH between 6 months and 2 years. Those variables remaining were entered in a stepwise selection model (with a leave/stay criterion of 0.10) to identify the covariates to include in all multivariable models regardless of the clinical endpoint. Actual treatment (MitraClip vs GDMT alone) was also included as a covariate. The relationship between the changes in LV volumes from baseline to 6 months as a continuous variable and clinical outcomes between 6 months and 2 years was also modeled using spline analysis with a knot at 50%. Finally, the associations between change in LV volumes from baseline to 6 months and change in 6-minute walk distance or KCCQ overall summary score from 6 months to 2 years were assessed using linear regression, adjusted for baseline LV volume, baseline 6-minute walk

TABLE 4 Adjusted Associations Between Changes in Left Ventricular Volumes From Baseline to 6 Months and Clinical Outcomes Between 6 Months and 2 Years in All Study Patients

	Death or HFH		All-Cause Death		HFH		CV Death	
	AdjHR (95% CI)	*P* Value	AdjHR (95% CI)	*P* Value	AdjHR (95% CI)	*P* Value	AdjHR (95% CI)	*P* Value
All patients								
Change in LVEDVi at 6 mo								
Δ in LVEDVi (per 10 mL/m^2 decrease)	0.94 (0.87-1.02)	0.12	0.92 (0.84-1.02)	0.11	0.92 (0.84-1.00)	0.06	0.90 (0.81-1.00)	0.04
Δ in LVEDVi × treatment group interaction		0.73		0.14		0.75		0.26
Baseline LVEDVi (per 10 mL/m^2 higher)	1.11 (1.04-1.18)	0.002	1.06 (0.98-1.14)	0.12	1.15 (1.07-1.24)	<0.001	1.06 (0.98-1.15)	0.15
Change in LVESVi at 6 mo								
Δ in LVESVi (per 10 mL/m^2 decrease)	0.93 (0.84-1.02)	0.11	0.93 (0.83-1.04)	0.20	0.91 (0.82-1.01)	0.07	0.91 (0.81-1.04)	0.16
Δ in LVESVi × treatment group interaction		0.82		0.06		0.87		0.18
Baseline LVESVi (per 10 mL/m^2 higher)	1.14 (1.06-1.22)	<0.001	1.07 (0.98-1.16)	0.13	1.18 (1.09-1.28)	<0.001	1.07 (0.97-1.17)	0.17
MitraClip-treated patients								
Change in LVEDVi at 6 mo								
Δ in LVEDVi (per 10 mL/m^2 decrease)	0.90 (0.82-1.00)	0.052	0.85 (0.74-0.98)	0.022	0.88 (0.79-0.99)	0.032	0.85 (0.72-1.00)	0.050
Baseline LVEDVi (per 10 mL/m^2 higher)	1.17 (1.06-1.29)	0.001	1.07 (0.96-1.20)	0.23	1.23 (1.10-1.37)	<0.001	1.02 (0.89-1.17)	0.76
Change in LVESVi at 6 mo								
Δ in LVESVi (per 10 mL/m^2 decrease)	0.91 (0.81-1.02)	0.11	0.83 (0.71-0.97)	0.019	0.90 (0.79-1.03)	0.12	0.84 (0.70-1.01)	0.07
Baseline LVESVi (per 10 mL/m^2 higher)	1.18 (1.06-1.31)	0.002	1.04 (0.91-1.19)	0.55	1.23 (1.09-1.39)	<0.001	0.99 (0.85-1.17)	0.94
GDMT alone-treated patients								
Change in LVEDVi at 6 mo								
Δ in LVEDVi (per 10 mL/m^2 decrease)	0.97 (0.85-1.10)	0.62	0.99 (0.87-1.12)	0.82	0.94 (0.81-1.09)	0.42	0.94 (0.82-1.08)	0.39
Baseline LVEDVi (per 10 mL/m^2 higher)	1.07 (0.97-1.17)	0.16	1.05 (0.95-1.16)	0.31	1.12 (1.01-1.24)	0.025	1.08 (0.98-1.20)	0.12
Change in LVESVi at 6 mo								
Δ in LVESVi (per 10 mL/m^2 decrease)	0.95 (0.80-1.13)	0.56	1.02 (0.87-1.20)	0.76	0.90 (0.74-1.09)	0.27	0.97 (0.82-1.15)	0.72
Baseline LVESVi (per 10 mL/m^2 higher)	1.11 (0.99-1.24)	0.07	1.06 (0.95-1.19)	0.29	1.17 (1.04-1.33)	0.010	1.10 (0.98-1.23)	0.12

All models were adjusted for treatment group, systolic blood pressure, creatine clearance, history of atrial arrhythmia, and diabetes in addition to the baseline value of the left ventricular volume parameter of interest.

AdjHR = adjusted HR; CV = cardiovascular; HFH = heart failure hospitalization; other abbreviations as in Table 2.

distance or KCCQ score (respectively), and 6-month 6-minute walk distance or KCCQ score (respectively).

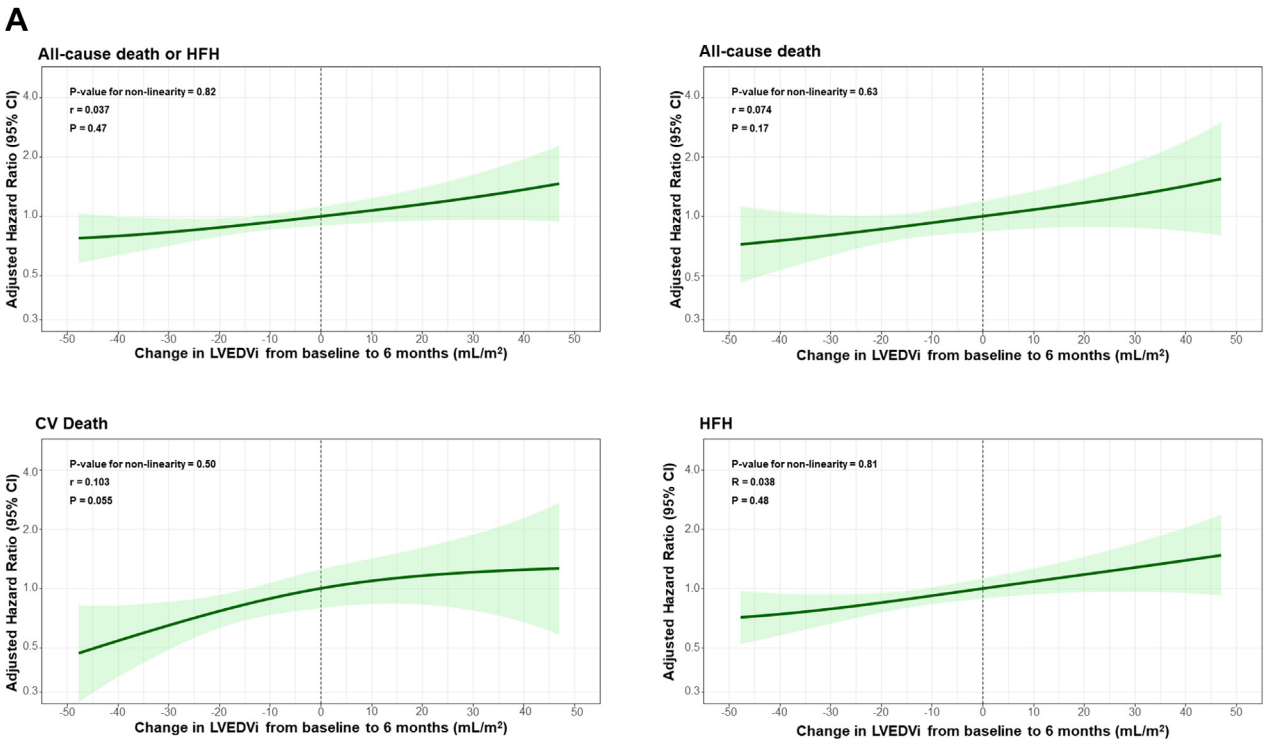
A 2-sided *P* value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute).

RESULTS

PATIENT POPULATION. Among 614 randomized patients, 47 were excluded for missing baseline LV volume measurements, 57 were excluded who died prior to 6 months, and 162 were excluded because of missing 6-month LV volume measurements. Thus, 348 patients (190 treated with the MitraClip and 158 treated with GDMT alone) were alive at 6 months with both baseline and 6-month LV volume measurements available for analysis, constituting the analytical study cohort (Supplemental Figure 1). In addition to excluded patients more commonly having been treated with GDMT alone rather than MitraClip plus GDMT (because of their higher rates of death and disability during follow-up with GDMT treatment alone), there were modest differences in several other baseline clinical and echocardiographic characteristics of the 348 included patients compared with the 266 excluded patients (Supplemental Table 2). There were no significant differences, however, in the baseline clinical or echocardiographic characteristics between patients treated with the MitraClip vs GDMT alone in the analytical study cohort (Table 1).

CHANGE IN LV VOLUMES DURING FOLLOW-UP AND ACCORDING TO TREATMENT GROUP AND MR SEVERITY AT 30 DAYS. Table 2 shows paired analyses between baseline and each follow-up time point (30 days, 6 months, and 1 year). Among all patients, small but significant reductions in LVEDVi from baseline were noted at all follow-up time points and in LVESVi at 30 days and 6 months. There were no significant differences between treatment groups in adjusted changes in LV volumes from baseline to any follow-up time point. The distributions of the changes in LVEDVi and LVESVi from baseline to 6 months were also similar for patients in both treatment groups; slightly more than 50% of patients in both groups had reductions in LV volumes, whereas the remainder had increases in LV volumes (Supplemental Figure 2). A sensitivity analysis that included only patients with echocardiograms at baseline and all follow-up time points at 30 days, 6 months, and 1 year (121 treated with the MitraClip, 92 treated with GDMT alone) similarly showed no differences in the change in LV volumes between 30 days and 1 year

FIGURE 1 Relationships Between Changes in LV Volumes From Baseline to 6 Months and Clinical Outcomes Between 6 Months and 2 Years



(A) Left ventricular (LV) end-diastolic volume index (LVEDVi). **(B)** LV end-systolic volume index (LVESVi). Using penalized splines with 2 degrees of freedom, the adjusted hazards for events between 6 months and 2 years after randomization are shown according to change in LV volume between baseline and 6 months for all-cause death or heart failure hospitalization (HFH) **(top left graph)**, all-cause death **(top right graph)**, cardiovascular (CV) death **(bottom left graph)**, and HFH **(bottom right graph)**. Outcomes are adjusted for treatment group, systolic blood pressure, creatinine clearance, history of atrial fibrillation or flutter, diabetes, and baseline LVEDVi or LVESVi as appropriate.

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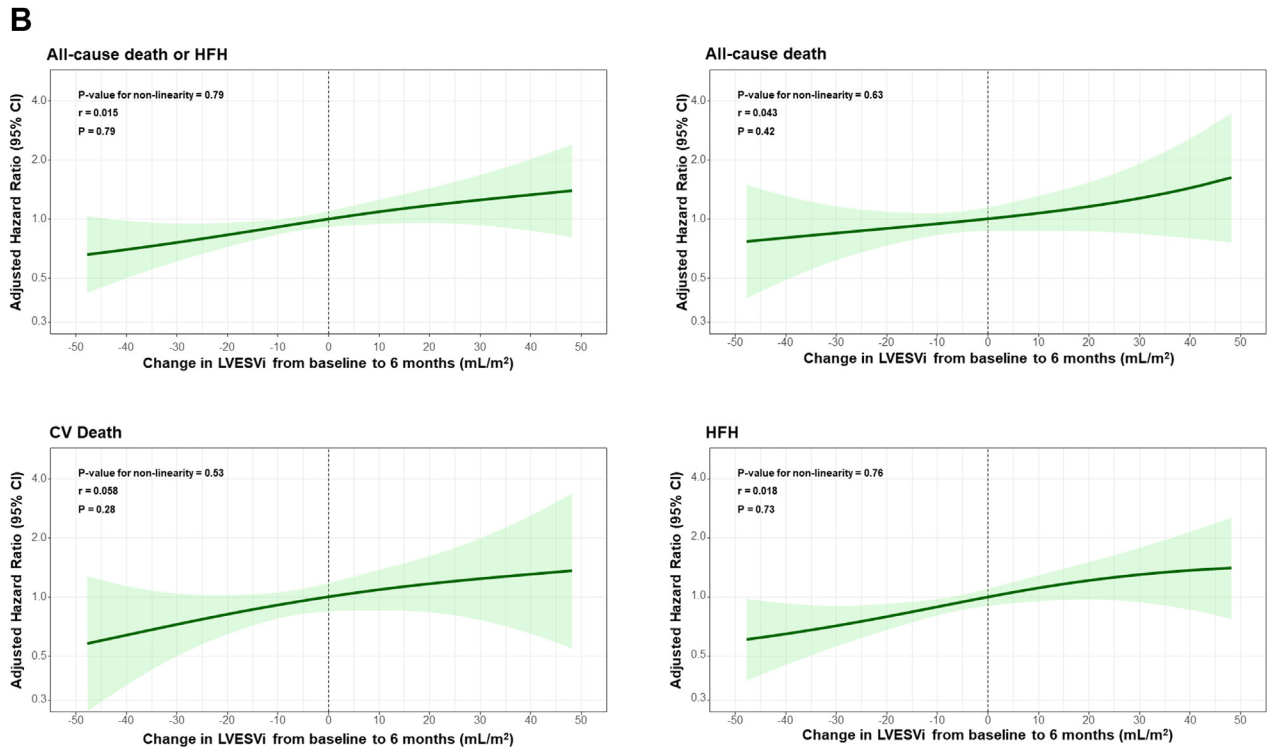
or between treatments at each time period (Supplemental Figure 3).

The factors related to change in LV volumes from baseline to 6 months are shown in Supplemental Tables 3 and 4. For both LVEDVi and LVESVi, larger baseline LV volumes were independently associated with a greater decrease in follow-up LV volumes, and more impaired (less negative) baseline LV global longitudinal strain was independently associated with a greater increase in follow-up LV volumes. No other factors were independently associated with change in LVEDVi, although baseline B-type natriuretic peptide and MR severity were independently associated with change in LVESVi.

MR severity at 30 days was not significantly associated with change in LVEDVi or LVESVi from 30 days to 6 months or from 30 days to 1 year in all patients (**Table 3**) or in the 2 treatment groups separately (Supplemental Tables 5 and 6).

CHANGES IN LV VOLUMES AND CLINICAL OUTCOMES. The adjusted associations between the changes in LVEDVi and LVESVi from baseline to 6 months and the subsequent risk for clinical events between 6 months and 2 years are shown in **Table 4**. Among all patients, a greater decrease in LVEDVi at 6 months was associated with a lower risk for cardiovascular death between 6 months and 2 years (adjusted HR: 0.90 per 10 mL/m^2 decrease; 95% CI: 0.81-1.00; $P = 0.04$). The associations between reduced LVEDVi from baseline to 6 months and improved outcomes between 6 months and 2 years for all-cause death and HFH and between reduced LVESVi and all outcomes were directionally similar but nonsignificant. These relationships were also evident in spline analysis (**Figure 1**). There were no significant interactions between change in LV volumes and treatment for any of the clinical outcomes ($P_{\text{interaction}} > 0.05$ for all) (**Table 4**). In addition, larger baseline LVEDV and

FIGURE 1 Continued



LVESV were associated with an increased risk for HFH and for the composite outcome of death or HFH between 6 months and 2 years (Table 4). Although it was not our primary research question, we performed a sensitivity analysis, which showed that LVESVi and LVEDVi as time-varying covariates were each independently associated with each of the 4 clinical outcomes of interest without and with additional adjustment for baseline LV volume (Supplemental Table 7).

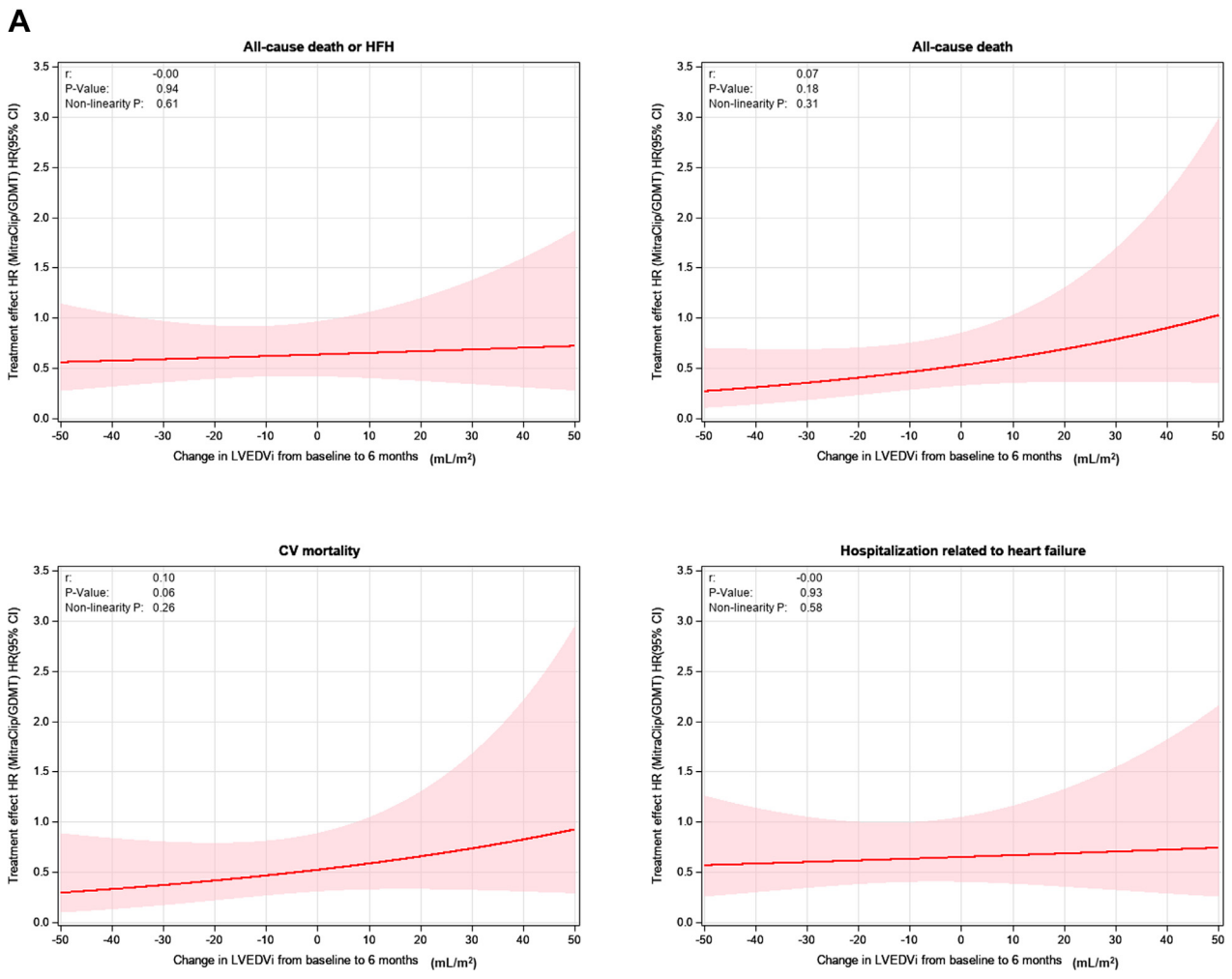
There were no associations between baseline LVEDVi or LVESVi or the change in LVEDVi or LVESVi from baseline to 6 months and the improvement in KCCQ overall summary score or 6-minute walk distance from 6 months to 2 years (Supplemental Table 8).

TREATMENT EFFECT OF MitraClip IMPLANTATION ACCORDING TO CHANGE IN LV VOLUMES. Across the spectrum of change in LV volumes between baseline and 6 months, the point estimate for the treatment effect of MitraClip plus GDMT compared with GDMT alone in reducing death and HFH remained <1.0, indicating a preserved benefit of MitraClip implantation regardless of the extent of LV remodeling at 6 months (Figure 2).

DISCUSSION

In the present post hoc analysis from the COAPT trial, we evaluated the association between LV reverse remodeling and subsequent clinical outcomes. There were small overall changes in LVEDVi during 1-year follow-up in both treatment groups, although individual patients varied substantially from positive to negative (reverse) LV remodeling over time. Among all patients, a decrease in LVEDVi from baseline to 6 months was associated with a lower adjusted hazard of cardiovascular death between 6 months and 2 years, with nonsignificant trends in the same direction for the outcomes of all-cause death, HFH, and the composite of death or HFH. Of note, however, neither treatment with MitraClip compared with GDMT alone nor MR severity at 30 days was associated with the extent of LV remodeling at 6 or 12 months. The 2-year treatment benefits of MitraClip implantation in reducing death and HFH were consistent regardless of the degree of LV remodeling at 6 months. Collectively, these data indicate that although LV reverse remodeling at 6 months was associated with subsequent clinical outcomes, as it was not greater after MitraClip treatment, nor was it

FIGURE 2 Treatment Effect of MitraClip Implantation on Clinical Outcomes Between 6 Months and 2 Years According to Change in LV Volumes From Baseline to 6 Months



(A) LVEDVi. **(B)** LVESVi. Treatment effect of MitraClip implantation compared with guideline-directed medical therapy (GDMT) alone across the range of changes in LV volumes from baseline to 6 months for clinical outcomes between 6 months and 2 years for all-cause death or HFH **(top left graph)**, all-cause death **(top right graph)**, CV death **(middle left graph)**, and HFH **(middle right graph)**. Outcomes are adjusted for systolic blood pressure, creatinine clearance, history of atrial fibrillation or flutter, diabetes, and baseline LVEDVi or LVEDVi as appropriate. Abbreviations as in Figure 1.

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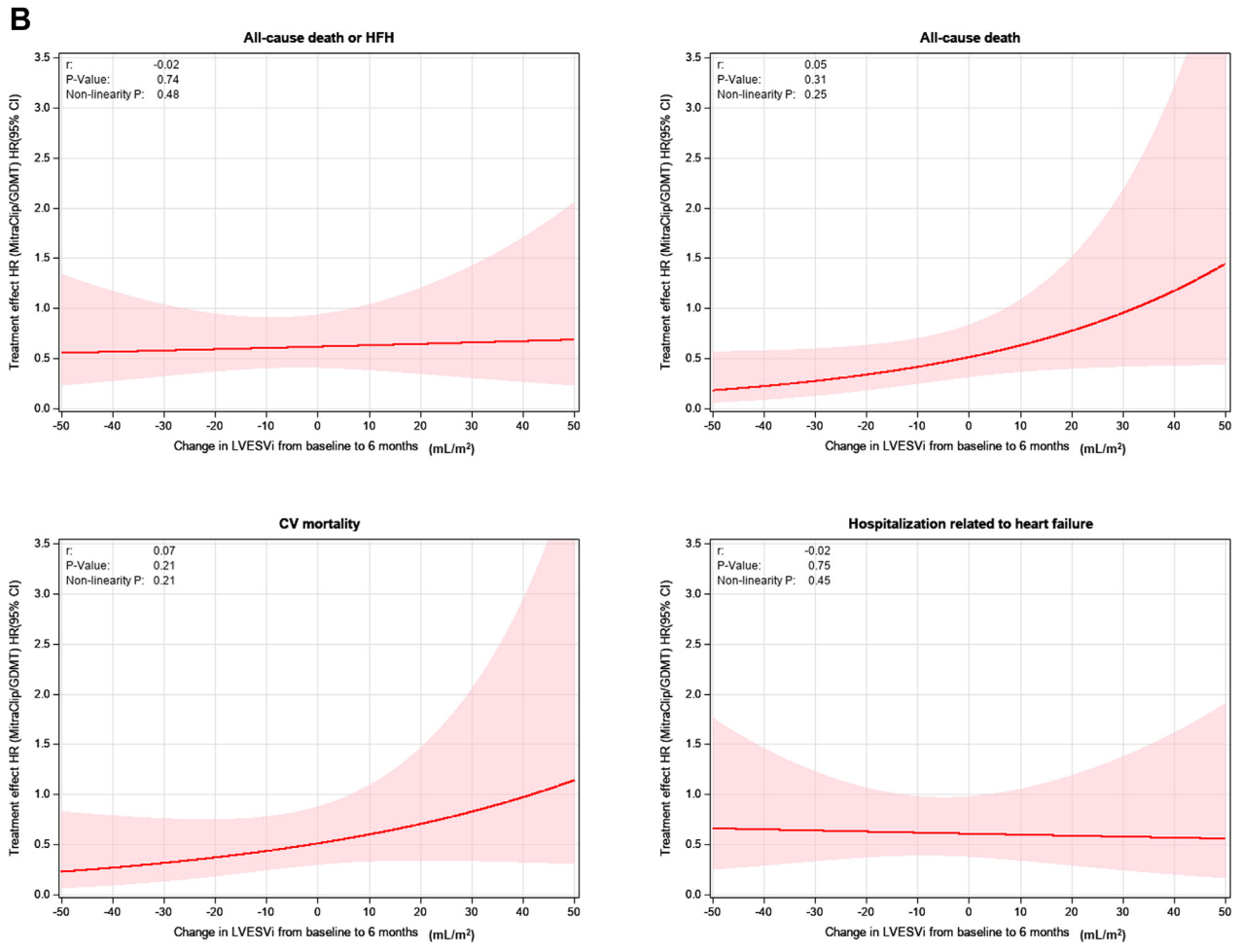
influenced by the severity of residual MR, LV reverse remodeling does not appear to have mediated the beneficial effects of TEER on clinical outcomes. Accordingly, these data do not support the use of LV remodeling as a surrogate endpoint when comparing treatments for SMR in HF (Central Illustration).

Most prior studies of medical therapies and cardiac resynchronization therapy in patients with HF with reduced ejection fraction have demonstrated associations between LV volumes and subsequent clinical outcomes and that the effects of these interventions on LV volumes correlated with their effects on clinical outcomes.[1-5] These observations have supported the notion that the change in LV volumes after an intervention can serve as a clinically relevant surrogate endpoint in smaller, earlier phase trials testing novel interventions. However, the use of LV volumes as a surrogate endpoint for trials testing therapies that reduce MR has not, to our knowledge, been previously assessed.

In this regard, some prior studies have shown significant decreases in LV volumes after MitraClip

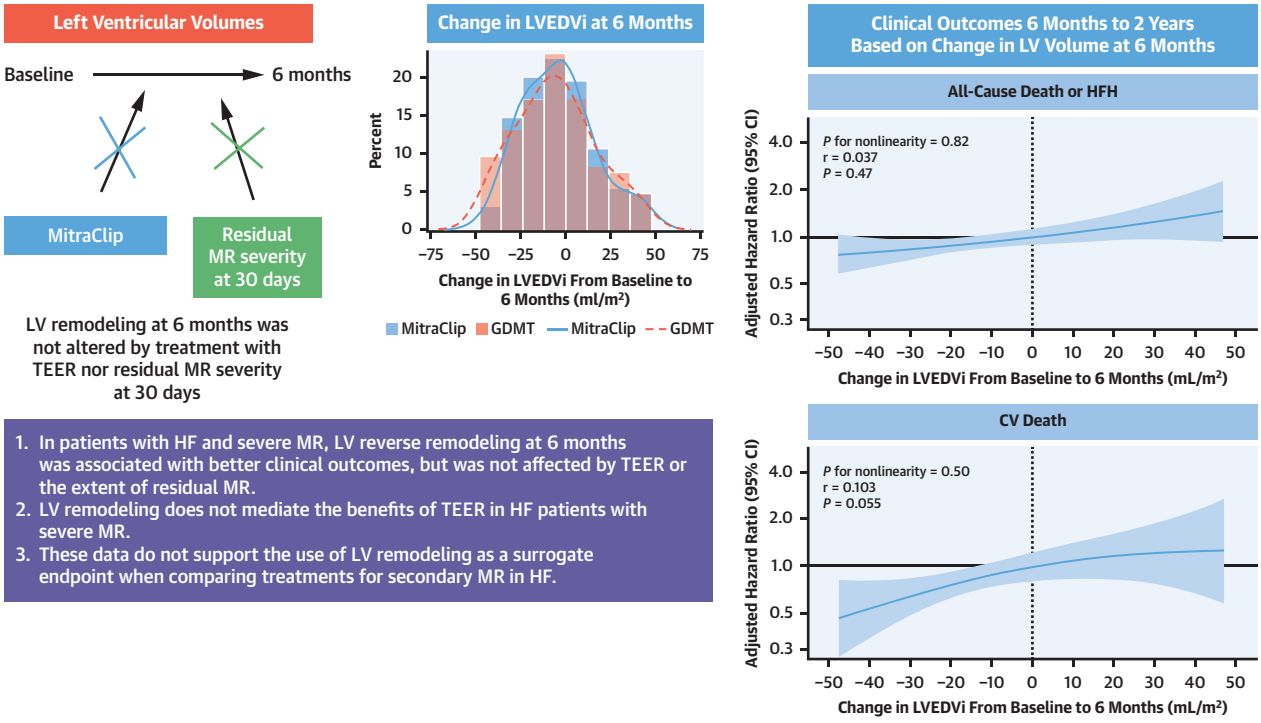
FIGURE 2 Continued



treatment,[12-15] and one study showed an association between LV reverse remodeling at 6 months after MitraClip and subsequent clinical outcomes between 6 months and 2 years.[16] However, the lack of a control group in these reports precluded evaluation of whether the reduction in LV volumes was more than what would have been observed with optimal medical therapy alone or whether the change in LV volume mediated the clinical benefit of MitraClip. Accordingly, our findings extend prior observations by demonstrating that: 1) the reduction in LV volumes during 1-year follow-up was not greater after TEER than GDMT alone; and 2) whereas changes in LV volumes during follow-up after MitraClip device treatment were associated with subsequent clinical outcomes, the same was true in patients treated with GDMT alone. As such, a greater degree of reverse remodeling did not mediate the marked clinical benefits observed with TEER in the randomized COAPT trial that appeared as early as 30 days after MitraClip device treatment.[7]

The relationship between residual MR and LV reverse remodeling after MitraClip has been previously examined.[12,13] Grayburn et al[12] showed a significant decrease in nonindexed LVEDV and LVESV 1 year after MitraClip implantation among individuals with primary (degenerative) MR and SMR, which was greater among those with less residual MR. This observation contrasts with our findings, which showed no association between residual MR and LV reverse remodeling among all patients with SMR and in stratified analyses by treatment group. However, Grayburn et al[12] studied residual MR severity at 1 year, which was the same time when they evaluated LV volumes, thus introducing potential bias (LV reverse remodeling may have affected reduced MR during follow-up rather than the converse). In our study, we overcame this bias by studying whether

CENTRAL ILLUSTRATION **LV Remodeling and Clinical Outcomes From the COAPT Trial**



1. In patients with HF and severe MR, LV reverse remodeling at 6 months was associated with better clinical outcomes, but was not affected by TEER or the extent of residual MR.
2. LV remodeling does not mediate the benefits of TEER in HF patients with severe MR.
3. These data do not support the use of LV remodeling as a surrogate endpoint when comparing treatments for secondary MR in HF.

Lindman BR, et al. J Am Coll Cardiol Intv. 2023;16(10):1160–1172.

COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; CV = cardiovascular; HF = heart failure; HFH = heart failure hospitalization; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; MR = mitral regurgitation; TEER = transcatheter edge-to-edge repair.

residual MR at an early follow-up time point (30 days) was associated with subsequent remodeling (ie, changes in LV volumes from 30 days to 6 months or 1 year). Similar to our findings, Adamo et al[16] did not find an association between residual postprocedural MR and LV reverse remodeling. Mechanistically, the increased afterload to LV ejection that occurs when MR is reduced (which in some patients may increase LVESVi and reduce LV ejection fraction) may paradoxically offset some of the benefits of increasing forward stroke volume with MR correction that might otherwise reduce LV dimensions.

Notably, a prior analysis from the COAPT trial showed that the severity of residual MR at 30 days was an independent predictor of subsequent clinical outcomes (although the association between reduced MR and subsequent death or HFH was independent of treatment group) and that MitraClip treatment reduced MR at 30 days much more effectively than GDMT alone.[17] Thus, residual MR severity at an early follow-up time point appears to be a more useful surrogate endpoint than LV reverse remodeling in studies testing therapies to reduce MR. However, the CTSN trial (CardioThoracic Surgical trials Network) compared surgical repair vs replacement for patients with severe ischemic MR and showed a clear benefit of mitral valve replacement in terms of MR reduction, but this did not translate into improved clinical outcomes (although the study was not powered for clinical endpoints).[8] Accordingly, these relationships remain poorly understood and may be influenced by the type of intervention targeting MR and other factors.

Our analytical approach differed from prior COAPT echocardiographic analyses, which reported smaller nonindexed LV volumes during follow-up among those treated with MitraClip implantation plus GDMT compared with GDMT alone.[7,10] These prior studies used multiple imputation to account for missing LV volumes during follow-up. Because the primary goal of our analysis was to evaluate the association between change in LV volumes and subsequent clinical outcomes, we chose to include only those patients with available measurements, as others have done for

similar analyses.[16,18] In addition, for these reasons, we analyzed the treatment groups according to actual treatment received rather than intention-to-treat. This may also explain some differences in outcomes between the present and prior COAPT reports.

STUDY LIMITATIONS. First, about 43% of study participants did not have paired baseline and 6-month echocardiograms because of death or other reasons (eg, failure to undergo the later examination) and were not included in the analytical cohort. Patients excluded were more commonly treated with GDMT alone and had smaller LV volumes and better LV function.

Second, as noted earlier, we chose not to impute values for LV volumes for 1) patients who died prior to 6 months, because they fell outside the scope of the analysis relating LV remodeling to outcomes; and 2) those alive but missing LV volume data at 6 months, as assumptions underlying imputation may be flawed.[16,18] Therefore, we cannot exclude worse LV remodeling in patients who did not survive to 6 months or were too ill to undergo the follow-up echocardiographic examination(s).

Third, the lack of statistically significant interactions between LV remodeling and subsequent clinical outcomes according to treatment group should be interpreted with caution given the modest sample size. In addition, no adjustments were made for multiple testing.

Fourth, despite instructions to minimize LV foreshortening during echocardiographic acquisition, foreshortening of dilated LVs may be unavoidable in some patients and may have influenced the present outcomes.[9] Whether the results would have been different had LV volumes been assessed by a true quantitative 3-dimensional volumetric technique such as magnetic resonance imaging is unknown. Finally, longer term follow-up and echocardiographic analyses at later time points may reveal an association between late remodeling and long-term prognosis. We plan on examining these relationships after the final 5-year report from the COAPT trial.

CONCLUSIONS

In the present analysis from the COAPT trial, we found that greater decreases in LV volumes from baseline to 6 months were associated with subsequently improved clinical outcomes through 2-year follow-up, especially freedom from cardiovascular death. However, neither treatment with the MitraClip device compared with GDMT alone nor the severity of residual MR at 30 days was associated with LV reverse remodeling. Given the marked improvement in clinical outcomes with TEER compared with GDMT alone in the randomized COAPT trial, these findings suggest that a reduction in LV volume does not mediate the clinical benefits of MR reduction by MitraClip device treatment and that use of LV remodeling as a surrogate endpoint in trials testing interventions for SMR in patients with HF may not be appropriate.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The COAPT trial was sponsored by Abbott Vascular. Dr Lindman has received investigator-initiated research grants from Edwards Lifesciences. Dr Asch is the director of an academic echocardiography core laboratory (MedStar Health Research Institute) with institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, Foldax, InnovHeart, Polares Medical, and Corcyn. Dr Grayburn has received consulting fees from Abbott Vascular, Edwards Lifesciences, W.L. Gore, Medtronic, and 4C Medical; and has received grant support from Abbott Vascular, Boston Scientific, Cardiovalve, Edwards Lifesciences, W.L. Gore, Medtronic, and NeoChord. Dr Mack has served as a co-primary investigator for the PARTNER trial for Edwards Lifesciences and the COAPT trial for Abbott; and has served as study chair for the APOLLO trial for Medtronic. Dr Bax's employer, the Department of Cardiology (Leiden University Medical Center), has received research grants from Medtronic, Biotronik, Edwards Lifesciences, and Boston Scientific; and Dr Bax has received speaker fees from Abbott Vascular. Dr Gonzales has received speaker honoraria from Abbott. Dr Barker has received consultant honoraria from Edwards Lifesciences; and is an advisory board member for Medtronic and Boston Scientific. Dr Weissman is the associate director of an academic echocardiography core laboratory (MedStar Health Research Institute) with institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and Livanova. Dr Abraham has received research grant support from Abbott Vascular and the National Heart, Lung, and Blood Institute; has received consulting income from Abbott Vascular; and has received speaker honoraria from Impulse Dynamics. Dr Lindenfeld has received research grant support from AstraZeneca and VoluMetrix; and has received consulting income from Abbott Vascular, AstraZeneca, Alleviant, Bayer, CVRx, Cytokinetics, Edwards Lifesciences, Boehringer Ingelheim, Merck, Medtronic, Vascular Dynamics, VoluMetrix, and V-Wave. Dr Stone has received speaker honoraria from Medtronic, Pulnovo, and Infraredx; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore, Amgen, Adona Medical; and has equity or options in Ancora, Cagent, Applied Therapeutics, the Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter. Dr Stone's daughter is an employee of Medtronic. Dr Stone's employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems, Phillips, Biosense Webster, Shockwave, Vascular Dynamics, and V-Wave. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: CARDIOVASCULAR INTERVENTIONS VOL. 16, NO. 10, 2023
MAY 22, 2023:1160–1172

PERSPECTIVES

WHAT IS KNOWN? Studies in patients with HF with reduced LV ejection fraction have reported a significant association between adverse LV remodeling and subsequent mortality. The relationship between LV remodeling and clinical outcomes after treatment of severe MR in patients with HF has not been examined.

WHAT IS NEW? In a post hoc analysis of the COAPT trial, a greater decrease in LV volumes from baseline to 6 months was associated with lower clinical events rates between 6 months and 2 years. Neither treatment with MitraClip implantation compared with GDMT alone nor the severity of residual MR at 30 days was associated with LV reverse remodeling. The 2-year treatment benefits of MitraClip device implantation in reducing death and HFH were consistent regardless of the degree of LV remodeling at 6 months.

WHAT IS NEXT? These findings suggest that a reduction in LV volume does not mediate the clinical benefits of MR reduction by MitraClip treatment and that use of LV remodeling as a surrogate endpoint in trials testing interventions for SMR in patients with HF may not be appropriate.

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KEY WORDS edge-to-edge repair, left ventricular volume, left ventricular remodeling, mitral regurgitation, outcomes

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