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ORIGINAL RESEARCH ARTICLE

# Impact of Sacubitril/Valsartan Compared With Ramipril on Cardiac Structure and Function After Acute Myocardial Infarction: The PARADISE-MI Echocardiographic Substudy

Amil M. Shah<sup>1</sup> MD, MPH; Brian Claggett<sup>1</sup> PhD; Narayana Prasad<sup>1</sup> MD, MPH, RDCS; Guichu Li<sup>1</sup> PhD, RDCS; Mayra Volquez, RDCS; Karola Jering<sup>1</sup> MD; Maja Cikes<sup>1</sup> MD, PhD; Attila Kovacs<sup>1</sup> MD, PhD; Wilfried Mullens, MD, PhD; Jose C. Nicolau<sup>1</sup> MD; Lars Køber<sup>1</sup> MD, DMSc; Peter van der Meer<sup>1</sup> MD, PhD; Pardeep S. Jhund<sup>1</sup> MBChB, MSc, PhD; Ghionul Ibram, MD; Martin Lefkowitz, MD; Yinong Zhou, MD; Scott D. Solomon<sup>1</sup> MD; Marc A. Pfeffer<sup>1</sup> MD, PhD

**BACKGROUND:** Angiotensin-converting enzyme inhibitors attenuate left ventricular (LV) enlargement after acute myocardial infarction (AMI). Preclinical data suggest similar benefits with combined angiotensin receptor neprilysin inhibition, but human data are conflicting. The PARADISE-MI Echo Study (Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction) tested the effect of sacubitril/valsartan compared with ramipril on LV function and adverse remodeling after high risk-AMI.

**METHODS:** In a prespecified substudy, 544 PARADISE-MI participants were enrolled in the Echo Study to undergo protocol echocardiography at randomization and after 8 months. Patients were randomized within 0.5 to 7 days of presentation with their index AMI to receive a target dose of sacubitril/valsartan 200 mg or ramipril 5 mg twice daily. Echocardiographic measures were performed at a core laboratory by investigators blinded to treatment assignment. The effect of treatment on change in echo measures was assessed with ANCOVA with adjustment for baseline value and enrollment region. The primary end points were change in LV ejection fraction (LVEF) and left atrial volume (LAV), and prespecified secondary end points included changes in LV end-diastolic and end-systolic volumes.

**RESULTS:** Mean age was 64±12 years; 26% were women; mean LVEF was 42±12%; and LAV was 49±17 mL. Of 544 enrolled patients, 457 (84%) had a follow-up echo at 8 months (228 taking sacubitril/valsartan, 229 taking ramipril). There was no significant difference in change in LVEF ( $P=0.79$ ) or LAV ( $P=0.62$ ) by treatment group. Patients randomized to sacubitril/valsartan demonstrated less increase in LV end-diastolic volume ( $P=0.025$ ) and greater decline in LV mass index ( $P=0.037$ ), increase in tissue Doppler  $e'_{\text{lat}}$  ( $P=0.005$ ), decrease in  $E/e'_{\text{lat}}$  ( $P=0.045$ ), and decrease in tricuspid regurgitation peak velocity ( $P=0.024$ ) than patients randomized to ramipril. These differences remained significant after adjustment for differences in baseline characteristics. Baseline LVEF, LV end-diastolic volume, LV end-systolic volume, LV mass index, LAV, and Doppler-based diastolic indices were associated with risk of cardiovascular death or incident heart failure.

**CONCLUSIONS:** Treatment with sacubitril/valsartan compared with ramipril after AMI did not result in changes in LVEF or LAV at 8 months. Patients randomized to sacubitril/valsartan had less LV enlargement and greater improvement in filling pressure. Measures of LV size, systolic function, and diastolic properties were predictive of cardiovascular death and incident heart failure after AMI in this contemporary, well-treated cohort.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02924727.

**Key Words:** echocardiography ■ heart failure ■ myocardial infarction

Correspondence to: Amil M. Shah, MD, MPH, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02445. Email [ashah11@rics.bwh.harvard.edu](mailto:ashah11@rics.bwh.harvard.edu)

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## Clinical Perspective

### What Is New?

- Among patients with acute myocardial infarction complicated by left ventricular (LV) dysfunction or congestion, treatment with sacubitril/valsartan compared with ramipril did not result in changes in LV ejection fraction or left atrial volume at 8 months.
- Treatment with sacubitril/valsartan compared with ramipril resulted in less LV enlargement and greater improvement in measures of LV filling pressure at 8 months.
- In addition to measures of LV size and systolic function, baseline measures of LV diastolic properties were predictive of cardiovascular death and incident heart failure after acute myocardial infarction in this contemporary, well-treated cohort.

### What Are the Clinical Implications?

- Treatment with sacubitril/valsartan compared with ramipril early after acute myocardial infarction may beneficially affect LV size and diastolic properties, possibly as a result of reductions in LV filling pressure.
- Among patients with enhanced-risk AMI enriched for systolic dysfunction, measures of diastolic function and filling pressure during the index hospitalization are robustly prognostic of longer-term risk of cardiovascular death and incident heart failure

Left ventricular (LV) remodeling and systolic dysfunction are robust risk factors for heart failure (HF) and mortality after acute myocardial infarction (AMI).<sup>1,2</sup> Pharmacological agents that reduce the risk of adverse outcomes after high-risk AMI, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and  $\beta$ -blockers, also attenuate post-myocardial infarction (MI) LV remodeling and systolic dysfunction.<sup>1-3</sup> More recently, diastolic indices, including magnitude of left atrial (LA) enlargement, have been established as independent risk factors for adverse outcomes after AMI.<sup>4</sup> The angiotensin receptor neprilysin inhibitor sacubitril/valsartan has been shown to be superior to ACE inhibition for reduction of HF hospitalization or cardiovascular death in patients with HF with reduced ejection fraction (HFrEF),<sup>5</sup> among whom sacubitril/valsartan has also been associated with greater improvements in LV volume, LA volume (LAV), and LV diastolic function.<sup>6</sup> Preclinical models demonstrate improvements in LV remodeling and systolic function with sacubitril/valsartan after experimentally induced AMI,<sup>7-9</sup> although sacubitril/valsartan was not associated with improvements in LV or LA size or LVEF compared with valsartan in patients with LV dysfunction late after AMI.<sup>10</sup> Whether sacubitril/valsartan initiated early after high-

## Nonstandard Abbreviations and Acronyms

<b>ACE</b>	angiotensin-converting enzyme
<b>AMI</b>	acute myocardial infarction
<b>eGFR</b>	estimated glomerular filtration rate
<b>EVALUATE-HF</b>	Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction
<b>HF</b>	heart failure
<b>HFrEF</b>	heart failure with reduced ejection fraction
<b>LA</b>	left atrial
<b>LAV</b>	left atrial volume
<b>LAVi</b>	left atrial volume index
<b>LV</b>	left ventricular
<b>LVEDV</b>	left ventricular end-diastolic volume
<b>LVEDVi</b>	left ventricular end-diastolic volume index
<b>LVEF</b>	left ventricular ejection fraction
<b>LVESV</b>	left ventricular end-systolic volume
<b>MI</b>	myocardial infarction
<b>PARADISE-MI</b>	Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction
<b>PARAMOUNT</b>	Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction
<b>PRIME</b>	Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation

risk AMI improves cardiac structure and function compared with ACE inhibition is not known.

The PARADISE-MI trial (Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction) tested whether sacubitril/valsartan would be superior to ramipril in reducing the composite end point of cardiovascular death, HF hospitalization, or outpatient development of HF after AMI with LV systolic dysfunction or pulmonary congestion.<sup>11</sup> Sacubitril/valsartan was not superior to ramipril in reducing the incidence of the primary adjudicated composite outcome, although nominally significant reductions were observed in investigator reports of the primary outcome and in the composite of total (first and recurrent) HF hospitalizations, outpatient HF events, and cardiovascular death.<sup>12,13</sup> The PARADISE-MI Echo Substudy was designed to test the hypothesis that treatment with sacubitril/valsartan would improve LV function and

attenuate adverse remodeling compared with ramipril after high-risk AMI. Among patients randomized in the main PARADISE-MI trial, 544 were enrolled in the PARADISE Echo Substudy to undergo protocol echocardiography at randomization and 8 months. We report the findings of the PARADISE-MI Echo Substudy and the associations of cardiac structure and function with risk of incident HF and cardiovascular mortality in a large, contemporary cohort of patients with enhanced-risk AMI.

## METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results.

### Study Population

Clinical sites enrolling patients in the main PARADISE-MI trial were invited to participate in the Echo Substudy, and patients enrolled at these sites were eligible for inclusion in the PARADISE-MI Echo Substudy.<sup>11</sup> Major inclusion criteria in the Echo Substudy were equivalent to those for the main PARADISE-MI trial. Patients were within 0.5 to 7 days after presentation with a spontaneous AMI and were required to have either LVEF  $\leq 40\%$  or transient pulmonary congestion requiring intravenous treatment during the index event and at least 1 of the following 8 predefined risk-augmenting factors: (1) age  $\geq 70$  years; (2) estimated glomerular filtration rate (eGFR)  $< 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$  at screening; (3) diabetes; (4) previous MI; (5) atrial fibrillation associated with the index MI; (6) LVEF  $< 30\%$  associated with the index MI; (7) Killip class III or IV associated with index MI requiring temporary intravenous treatment; or (8) ST-segment-elevation MI without reperfusion therapy within the first 24 hours after presentation. Patients with previous HF were excluded. Additional inclusion criteria specific to the Echo Substudy included (1) sinus rhythm at the time of randomization, (2) adequate echocardiographic image quality on qualifying echocardiogram for determination of the study primary end point (LVEF, LAV) as determined by the site investigator, and (3) consent to participate in the Echo Substudy. Of the 5661 patients validly randomized in PARADISE-MI, 544 were enrolled in the Echo Substudy. Protocol echocardiographic studies were performed at  $\pm 2$  days of randomization (and within 7 days after index MI presentation) and at month 8 (or as close as possible). A total of 98 sites in 27 countries participated in the Echo Substudy. All patients provided signed informed consent for inclusion in the PARADISE-MI Echo Substudy, and institutional review board approval was obtained at each clinical site.

### Echocardiographic Analysis

All study echocardiograms were performed by sonographers at clinical sites who were certified in performance of the study imaging protocol by the Echocardiography Core Laboratory at Brigham and Women's Hospital (Boston, MA). Echocardiographic studies were sent in digital format to the Echocardiography Core Laboratory, where quantitative measures were performed in accordance with American Society of Echocardiography guidelines<sup>14,15</sup> by dedicated analysts blinded

to randomized treatment assignment and to temporal sequence of serial echocardiograms (baseline versus 8 months). Each measure was performed by the same analyst for all study participants. Each measure was performed on 3 separate cardiac cycles, and the average is reported.

LV volumes and LVEF were derived according to the modified biplane Simpson rule. LV mass was calculated by the American Society of Echocardiography–recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area (LV mass index).<sup>14</sup> LAV was assessed by the modified biplane Simpson method from apical 2- and 4-chamber views at end systole and was indexed to body surface area (LAV index [LAVi]). Peak early diastolic tissue velocity ( $e'$ ) was measured from the septal ( $e'_{\text{sept}}$ ) and lateral ( $e'_{\text{lat}}$ ) aspects of the mitral annulus, and their average was calculated ( $e'_{\text{ave}}$ ). Mitral inflow velocity was assessed by pulsed-wave Doppler from the apical 4-chamber view. Peak tricuspid regurgitation velocity was measured from the continuous-wave spectral Doppler envelope.

Reproducibility of echocardiographic measures at the Echocardiography Core Laboratory has been previously reported.<sup>16</sup> Intrareader reproducibility of key echocardiographic measures was also specifically assessed in a subset of 40 PARADISE-MI echocardiograms (Table S1). Results for primary and secondary echocardiographic end points are as follows: LVEF: bias,  $0.7 \pm 4.8\%$ , coefficient of variation, 11.0%, and intraclass correlation coefficient 0.90; LAV: bias,  $1.5 \pm 4.5 \text{ mL}$ , coefficient of variation, 8.4%, and intraclass correlation coefficient, 0.97; LV end-diastolic volume (LVEDV): bias,  $0 \pm 8 \text{ mL}$ , coefficient of variation, 6.7%, and intraclass correlation coefficient, 0.97; and LV end-systolic volume (LVESV): bias,  $1 \pm 8 \text{ mL}$ , coefficient of variation, 10.8%, and intraclass correlation coefficient, 0.98.

### Clinical Outcomes

Clinical outcomes included the composite of cardiovascular death, HF hospitalization, or outpatient episode of symptomatic HF. The primary analysis was performed with investigator-reported events; the sensitivity analysis was performed with Clinical End Point Committee–adjudicated events. All events were reported by the primary site investigator, and adjudicated end points were independently adjudicated by a Clinical Endpoints Center by investigators blinded to treatment assignment. Definitions of these end points have previously been published.<sup>11</sup>

### Statistical Methods

The coprimary end points for the Echo Substudy were change in LVEF from baseline to 8 months and change in LAV from baseline to 8 months. Prespecified secondary end points included change in LVESV from baseline to 8 months and change in LVEDV from baseline to 8 months. Change in absolute LAV, as opposed to LAVi, was selected because some patients may experience significant weight loss after AMI related partially to prescribed exercise and lifestyle modification that could change LAVi without appreciable changes in actual LA size. Additional exploratory end points included changes in LV mass, Doppler-based measures of LV diastolic function (peak early transmitral velocity [E wave], tissue Doppler peak early diastolic mitral annular velocity [ $e'$ ], and E/ $e'$  ratio), and the tricuspid

regurgitation velocity, which is an estimate of pulmonary artery systolic pressure. The primary efficacy analysis of change from baseline was performed using linear regression with treatment as a factor and the baseline value of the variable and region as covariates. Additional post hoc analyses were performed with adjustment for the following baseline characteristics there were found to differ significantly between patients randomized to sacubitril/valsartan and those randomized to ramipril in the Echo Substudy: age; eGFR; history of percutaneous coronary intervention or coronary artery bypass surgery, atrial fibrillation, and peripheral artery disease; and mineralocorticoid receptor antagonist use at randomization. A sample size of 488 patients was determined to be necessary to detect an absolute 2% treatment difference in LVEF change assuming an SD of 6%<sup>2,17</sup> and a 5-mL treatment difference in LAV change assuming an SD of 15 mL<sup>18</sup> with  $\alpha=0.025$  (2 sided) and 85% power, assuming 20% dropout in the sample size attributable to patient death or poor echo quality. The SDs of change in LVEF and LAV are based on those observed in previous randomized clinical trials.

The primary analysis was performed using raw data, even when some patients had missing values. An additional sensitivity analysis was performed using multiple imputation for missing data. Given the arbitrary missing value pattern of the echocardiographic measures among participants with available echocardiograms at randomization and month 8, we used multiple imputation by chained equations, an iterative imputation procedure (STATA `mi impute chained`).<sup>19,20</sup> Imputation was performed for each echocardiographic measure with any missing data and was based on linear regression using 37 baseline clinical variables (Table 1) and the 36 echocardiographic measures (baseline, month 8) as predictor variables and was derived over 40 imputations. To assess the potential impact of failure to obtain month 8 echocardiograms for some enrolled patients, additional sensitivity analysis was performed using inverse probability of attrition weighting.<sup>21,22</sup> Acquisition of month 8 echocardiograms was modeled among substudy participants alive at month 8 using 33 baseline clinical variables. The resulting calculated weights were incorporated into multivariable linear regression models relating treatment assignment to change in echocardiographic measures. An additional sensitivity analysis was performed using a linear mixed-effect model, accounting for site as a random effect.

Multivariable Cox proportional hazard models were used to study the association of echocardiographic measures with clinical outcomes. Echocardiographic exposures were modeled as continuous variables per SD. Two multivariable Cox models were used: model 1 adjusted for age, sex, randomized treatment, and region of enrollment; and model 2 adjusted for age, sex, randomized treatment, Killip class, site-reported LVEF <40%, and enrollment in Latin America. Model 1 covariates were defined a priori. Model 2 covariates were selected according to a forward selection procedure with a *P* threshold for retention of <0.05 and with age, sex, and randomized treatment forced into the model; indicator variables for each enrollment region were included as candidate covariates. We performed a sensitivity analysis using a mixed-effect model, accounting for site as a random effect. No echocardiographic predictors violated the proportional hazards assumption on the basis of Schoenfeld residuals. For echocardiographic measurements demonstrating a robust association with clinical outcomes in adjusted analyses, the flexible continuous relationship with first HF hospitalization or cardiovascular death

was further assessed using restricted cubic splines with the number of knots selected to minimize the model Akaike information criteria (3–7 knots considered). No compelling evidence to support nonlinearity was observed, so all associations are displayed linearly. All analyses were performed with STATA version 16.

## RESULTS

### Baseline Characteristics

The average age of the 544 PARADISE-MI Echo Substudy participants was  $64\pm 12$  years, and 26% were women (Table 1). The mean time from presentation to randomization was  $4.1\pm 1.7$  days; the index AMI was ST-segment–elevation MI in 75%; 52% received intravenous treatment for congestion; the site-assessed LVEF was  $\leq 40\%$  in 85%; and 92% underwent coronary revascularization. Compared with PARADISE-MI patients not in the Echo Substudy, those in the Echo Substudy were more likely to be enrolled in Central or Western Europe and to be of White race, had higher body mass index and shorter time from presentation to randomization, were more likely to undergo reperfusion with percutaneous coronary intervention and stenting, and were more likely to have been taking an ACE inhibitor or angiotensin receptor blocker before randomization and a mineralocorticoid receptor antagonist at randomization (Table 1). Among Echo Substudy participants, the 279 randomized to sacubitril/valsartan compared with the 265 randomized to ramipril tended to be older; had a lower eGFR and higher prevalence of previous percutaneous coronary intervention, coronary artery bypass graft surgery, history of atrial fibrillation, and peripheral artery disease; had a modestly longer time from presentation to randomization; and were less frequently taking a mineralocorticoid receptor antagonist at randomization (Table 1).

Baseline echocardiography was mostly performed on the day of randomization (median days from randomization, 0 [interquartile range, 0, 1]) and was similar in both treatment arms. The median time from AMI presentation to baseline echocardiography was 4.8 (interquartile range, 3.2, 6.1) days and was modestly longer among those randomized to sacubitril/valsartan compared with ramipril (5.0 [3.7, 6.1] and 4.5 [3.0, 6.1] days, respectively;  $P=0.023$ ). The mean baseline LVEF was  $42.4\pm 11.5\%$  and the mean LAV was  $49.4\pm 17.2$  mL (Table 2). Compared with patients randomized to ramipril, those randomized to sacubitril/valsartan demonstrated higher baseline LVEF and smaller LVEDV and LVESV. No significant differences were observed in LA size or Doppler-based diastolic measures.

### Changes in Cardiac Structure and Function From Baseline to 8 Months

Both baseline and month 8 echocardiograms were available in 457 Echo Substudy participants (Figure 1): 228 in the sacubitril/valsartan arm and 229 in the ramipril

**Table 1. Baseline Characteristic of PARADISE-MI Patients Not Enrolled Versus Enrolled in the Echo Substudy and Among Echo Substudy Participants by Randomized Treatment Allocation**

	Not Echo Study (n=5117)	Echo Study (n=544)	P value	Ramipril (n=265)	Sac/Val (n=279)	P value
<b>Demographics</b>						
Age, y	63.8±11.5	63.7±11.6	0.89	62.3±11.2	65.0±11.9	0.008
Female	1221 (24)	142 (26)	0.25	64 (24)	78 (28)	0.31
Racial/ethnic group			<0.001			0.62
Asian	923 (18)	30 (6)		12 (5)	18 (7)	
Black	66 (1)	9 (2)		4 (2)	5 (2)	
White	3786 (74)	477 (88)		233 (88)	244 (88)	
Other	342 (7)	28 (5)		16 (6)	12 (4)	
Region			<0.001			0.84
North America	476 (9)	52 (10)		25 (9)	27 (10)	
Latin America	624 (12)	55 (10)		27 (10)	28 (10)	
Western Europe	1638 (32)	215 (40)		108 (41)	107 (38)	
Central Europe	1308 (26)	191 (35)		93 (35)	98 (35)	
Asia/Pacific	1071 (21)	31 (6)		12 (5)	19 (7)	
<b>Comorbidities</b>						
Previous stroke	232 (5)	31 (6)	0.22	15 (6)	16 (6)	0.96
Previous MI	847 (17)	102 (19)	0.19	44 (17)	58 (21)	0.21
Previous PCI	736 (14)	91 (17)	0.14	34 (13)	57 (20)	0.018
Previous CABG	176 (3)	29 (5)	0.025	1 (3)	22 (8)	0.007
Hypertension	3322 (65)	354 (65)	0.94	164 (62)	190 (68)	0.13
Hyperlipidemia	2656 (52)	309 (57)	0.019	145 (55)	164 (59)	0.39
Diabetes	2165 (42)	236 (43)	0.63	112 (42)	124 (44)	0.61
Current smoker	1070 (21)	126 (23)	0.37	60 (23)	66 (24)	0.10
Former Smoker	1913 (37)	190 (35)		104 (39)	86 (31)	
A Fib	665 (13)	61 (11)	0.23	19 (7)	42 (15)	0.004
PAD	317 (6)	28 (5)	0.35	7 (3)	21 (8)	0.010
ICD	17 (0)	2 (0)	0.89	0 (0)	2 (1)	0.17
COPD	306 (6)	32 (6)	0.95	15 (6)	17 (6)	0.86
Cancer	298 (6)	31 (6)	0.93	13 (5)	18 (7)	0.46
Depression	289 (6)	40 (7)	0.10	19 (7)	21 (8)	0.90
<b>Index MI event</b>						
Time from presentation to randomization, d	4.3±1.8	4.1±1.7	0.009	4.0±1.7	4.3±1.7	0.040
STEMI	3883 (76)	408 (75)	0.65	199 (75)	209 (75)	0.96
Anterior	3483 (68)	370 (68)	0.98	182 (69)	188 (67)	0.75
Intravenous treatment for congestion	2772 (54)	284 (52)	0.38	142 (54)	142 (51)	0.53
Killip class			0.14			0.85
I	2045 (41)	236 (44)		117 (45)	119 (43)	
II	1612 (33)	152 (28)		72 (27)	80 (29)	
III	1016 (21)	125 (23)		59 (22)	66 (24)	
IV	269 (5)	27 (5)		15 (6)	12 (4)	
Revascularization						
Thrombolytics	245 (5)	8 (2)	<0.001	4 (2)	4 (2)	0.95
Stent	4273 (84)	489 (90)	<0.001	241 (91)	248 (89)	0.43
<b>Physical examination</b>						
HR, bpm	76±12	77±11	0.004	78±11	77±12	0.24

(Continued)

**Table 1. Continued**

	Not Echo Study (n=5117)	Echo Study (n=544)	P value	Ramipril (n=265)	Sac/Val (n=279)	P value
SBP, mmHg	121±13	119±13	<0.001	119±13	119±13	0.77
DBP, mmHg	74±10	73±10	0.004	73±9	73±11	0.85
BMI, kg/m <sup>2</sup>	28±5	28.8±5.1	0.002	28.8±5.1	28.7±5.2	0.84
eGFR, mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>	72±22	71±23	0.18	73±25	68±20	0.005
Medications						
DAPT	4723 (92)	499 (92)	0.64	247 (93)	252 (90)	0.22
β-Blocker	4368 (85)	459 (84)	0.54	226 (85)	233 (84)	0.57
MRA	2075 (41)	236 (48)	<0.001	141 (53)	122 (44)	0.027
Diuretics	2263 (44)	258 (47)	0.15	128 (48)	130 (47)	0.69
Statin	4855 (95)	515 (95)	0.83	252 (95)	263 (94)	0.67
Prior ACE inhibitor/ARB	3976 (78)	460 (85)	<0.001	222 (84)	238 (85)	0.62

Values are displayed as mean±SD for continuous variables and number (percent) for categorical variables. Between-group comparisons were performed with a *t* test for continuous variables and a  $\chi^2$  test for categorical variables. A Fib indicates atrial fibrillation; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PAD, peripheral artery disease; PARADISE-MI, Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction; PCI, percutaneous coronary intervention; Sac/Val, sacubitril/valsartan; SBP, systolic blood pressure; and STEMI, ST-segment-elevation myocardial infarction.

arm. Of the 87 patients without a follow-up echo, 22 died before month 8 and were not significantly different between the treatment arms. Compared with Echo Substudy participants with month 8 echocardiograms, those without month 8 studies were more frequently female and Asian; had lower body mass index, higher systolic blood pressure, and a higher prevalence of previous stroke; and were more likely to require intravenous treatment for congestion during the index AMI admission (Table S2). They also had higher LVEF, smaller LAV, lower tissue Doppler imaging  $e'$ , and higher  $E/e'$  ratio (Table S3).

The median time from baseline to the 8-month echocardiogram was 243 (240, 251) days and was similar between treatment arms. Overall, from baseline to 8 months, LVEF increased by  $6.0\pm 10.1\%$  ( $P<0.001$ ); LVEDV and LVESV decreased by  $2.5\pm 29.6$  mL ( $P=0.092$ ) and  $6.2\pm 26.3$  mL ( $P<0.001$ ), respectively; and LAV increased by  $2.6\pm 15.5$  mL ( $P<0.001$ ; Table 3). Among substudy participants with core laboratory LVEF <40% at randomization, LVEF at follow-up was  $\geq 40\%$  in 58%, was  $\geq 50\%$  in 22%, and increased by  $\geq 10\%$  in 44%. Among patients with baseline and follow-up studies, baseline differences in age, eGFR, and prevalence of previous coronary artery bypass graft surgery, history of atrial fibrillation, and peripheral artery disease (Table S4) and in baseline LVEF and LV volume (Table S5) by treatment arm persisted but were more modest in magnitude. The median treatment dose at month 8 among those with baseline and follow-up studies was 200 (interquartile range 100, 200) mg in the sacubitril/valsartan arm and 5 (2.5, 5) mg in the ramipril arm. No significant change in systolic blood pressure between baseline and follow-up echocardiographic studies was observed between treat-

ment groups (sacubitril/valsartan versus ramipril,  $-2.5$  [ $-5.7, 0.7$ ] mmHg;  $P=0.13$ ). Use of other cardiovascular medications was also similar between treatment arms at 8 months (Table S6).

No differences in change in LVEF or in change in LAV from baseline to month 8 were observed with sacubitril/valsartan compared with ramipril (Table 3, Table S7, and Figure 2). Among patients with LVEF <40% at randomization, the sacubitril/valsartan and ramipril arms demonstrated a similar proportion of patients recovering LVEF at follow-up to  $>40\%$  (57% versus 59%, respectively;  $P=0.78$ ) or  $>50\%$  (22% in both arms;  $P=0.99$ ) or increasing LVEF by  $\geq 10\%$  (40% versus 48%, respectively;  $P=0.26$ ). Patients randomized to sacubitril/valsartan demonstrated less increase in LVEDV and greater decline in LV mass index compared with those randomized to ramipril. They also demonstrated a greater increase in tissue Doppler  $e'_{\text{lat}}$  and decrease in  $E/e'_{\text{lat}}$ , increase in  $e'_{\text{ave}}$ , and decrease in tricuspid regurgitation peak velocity. Sacubitril/valsartan was not associated with changes in  $e'_{\text{septal}}$  compared with ramipril. These associations persisted after adjustment for differences in baseline age, history of percutaneous coronary intervention or coronary artery bypass graft surgery, atrial fibrillation, peripheral artery disease, eGFR, and mineralocorticoid receptor antagonist use at randomization. Similar treatment effects were observed in sensitivity analyses using multiple imputation to account for variable missing data among the 457 substudy participants with baseline and month 8 echocardiograms (Table S8) and in sensitivity analyses using inverse probability of attrition weighting to account for the 65 substudy patients who were alive at month 8 but did not undergo a month 8 echocardiogram (Table S9). Similar results were also observed in

**Table 2. Baseline Echocardiographic Measures of Echo Substudy Participants Overall and by Randomized Treatment Allocation**

	No.	Overall (n=544)	Ramipril (n=265)	Sac/Val (n=279)	P value
LV structure and systolic function					
LVEF, %	516	42.4±11.5	40.8±11.0	43.9±11.8	0.003
LVEDV, mL	516	128.4±42.8	132.7±46.2	124.3±38.74	0.025
LVEDVi, mL/m <sup>2</sup>	513	65.6±20.1	67.4±22.2	63.9±17.7	0.047
LVESV, mL	516	76.7±37.1	81.3±39.9	72.2±33.7	0.005
LVESVi, mL/m <sup>2</sup>	513	39.2±18.5	41.3±20.3	37.0±16.4	0.009
MWT, cm	517	1.07±0.16	1.07±0.16	1.08±0.17	0.36
LV mass, g	493	193.6±54.3	197.8±54.4	189.6±54.0	0.09
LVMi, g/m <sup>2</sup>	491	99.0±24.9	100.2±24.4	97.8±25.3	0.30
LA size					
LA volume, mL	517	49.4±17.2	49.3±16.3	49.4±18.1	0.95
LAVi, mL/m <sup>2</sup>	510	25.1±9.3	24.7±8.6	25.4±9.9	0.42
LA width, cm	508	3.69±0.57	3.70±0.55	3.68±0.59	0.76
Diastolic measures					
E wave, cm/s	517	69.4±23.2	70.3±23.0	68.6±23.5	0.41
TDI e' <sub>lat</sub> , cm/s	504	6.8±2.4	6.9±2.4	6.7±2.4	0.40
E/e' <sub>lat</sub>	493	11.3±5.0	11.3±5.2	11.3±4.9	0.83
TDI e' <sub>sept</sub> , cm/s	510	5.4±1.7	5.5±1.7	5.3±1.7	0.23
E/e' <sub>sept</sub>	497	13.8±5.9	13.7±6.1	13.9±5.7	0.75
TDI e' <sub>ave</sub> , cm/s	495	6.1±1.8	6.2±1.8	6.0±1.8	0.18
E/e' <sub>ave</sub>	484	12.1±4.9	12.0±5.0	12.2±4.7	0.71
TRV, m/s	201	2.58±0.36	2.59±0.34	2.57±0.39	0.70

Values are displayed as mean±SD. LA indicates left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVMi, left ventricular mass index; MWT, minimum wall thickness; Sac/Val, sacubitril/valsartan; TDI, tissue Doppler imaging; and TRV, tricuspid regurgitation velocity.

a sensitivity analysis using a linear mixed-effect model, accounting for site as a random effect (Table S10).

### Association of Echocardiographic Measures With Risk of Clinical Outcomes

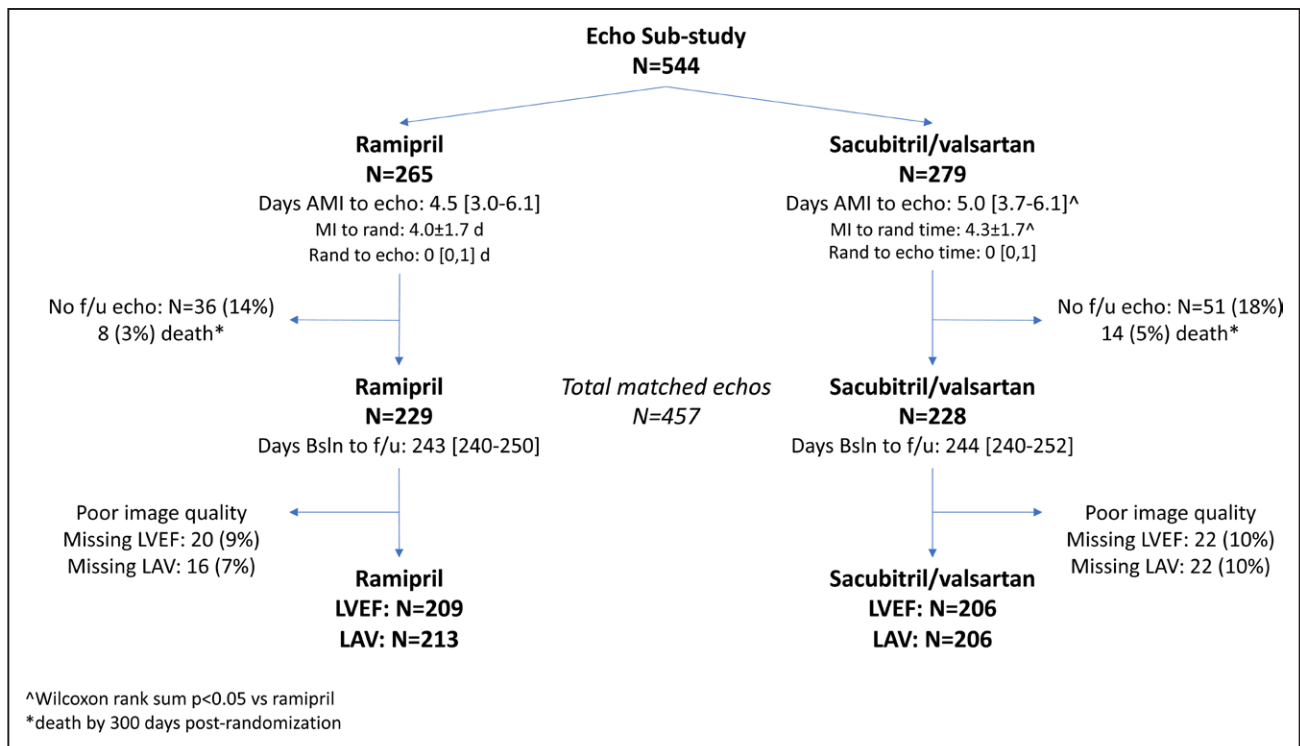
Over a median follow-up of 525 (346, 708) days, 78 patients experienced the composite of investigator-reported cardiovascular death, HF hospitalization, or outpatient HF. Lower LVEF, larger LVEDV and LVESV, greater LV mass index, greater LAV, and higher E wave and E/e' ratio were each associated with greater risk of the composite end point after adjustment for age, sex, treatment assignment, and region of enrollment (model 1; Figure 3 and Table S11). It is notable that standardized effect estimates were similar in magnitude across each of these measures. Key measures of LV and LA size and LV systolic and diastolic function were linearly related to risk (Figure 4). In models adjusted for age, sex, treatment assignment, Killip class, site-reported LVEF <40%, and enrollment in Latin America (model 2), larger LVEDV and LVESV, greater LAV, and higher E wave and E/e' ratio remained associated with the composite end point

(Table 4). In models including LVEDV, LAV, and E/e' together, higher LAV (standardized hazard ratio, 1.37 [95% CI, 1.09–1.74];  $P=0.008$ ) and higher E/e' (hazard ratio, 1.25 [95% CI, 1.01–1.54];  $P=0.039$ ) were associated with higher risk, whereas greater LVEDV was not (hazard ratio, 0.93 [95% CI, 0.72–1.19];  $P=0.56$ ). Similar findings were observed for the composite end point of Clinical End Point Committee–adjudicated cardiovascular death, HF hospitalization, or outpatient HF (n=52 events; Table S12). Similar results were also observed in a sensitivity analysis using a mixed-effect model, accounting for site as a random effect (Table S13).

### DISCUSSION

Among 457 patients enrolled in the PARADISE-MI trial with protocol echocardiograms at randomization and month 8, randomization to sacubitril/valsartan did not improve LVEF or mitigate LA enlargement compared with ramipril. Randomization to sacubitril/valsartan did result in less increase in LVEDV and greater decline in LV mass index, increase in tissue Doppler e'<sub>lat</sub>, decrease in E/e'<sub>lat</sub>, and decrease in tricuspid regurgitation peak velocity.





**Figure 1. Consolidated Standards of Reporting Trials diagram of patient flow for the PARADISE-MI Echo Substudy.**

AMI indicates acute myocardial infarction; f/u, follow-up; LAV, left atrial volume; LVEF, left ventricular ejection fraction; and PARADISE-MI, Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction.

These associations persisted after adjustment for differences in baseline characteristics between treatment arms and in sensitivity analyses accounting for missing data and absence of month 8 echocardiograms in a subset of patients enrolled in the PARADISE-MI Echo Substudy. Lower LVEF; larger LVEDV, LVESV, LV mass index, and LAV; and worse Doppler-based diastolic indices at baseline were each associated with risk of incident cardiovascular death, HF hospitalization, or outpatient HF after AMI in this contemporary, vigorously managed cohort. Measures reflective of elevated LV filling pressures (LAV, E/e') assessed at randomization were robustly prognostically independent of LV enlargement, emphasizing the long-term prognostic importance of these diastolic measures.

Although the incidence of HF after AMI may be declining in the context of procedural and pharmacological treatment advances,<sup>23</sup> AMI remains one of the most important causes of HF.<sup>24</sup> Post-MI LV remodeling, characterized by chamber enlargement and dysfunction, is a potent risk factor for the development of clinical HF that is modifiable with pharmacological interventions, including ACE inhibitors and  $\beta$ -blockers.<sup>1-3</sup> These agents have similarly been shown to be efficacious in HFrEF<sup>25-28</sup>; the impact of pharmacological or device interventions on LV remodeling (LV volumes and LVEF) correlates with the impact on relevant clinical outcomes.<sup>29</sup> Furthermore, findings of the VALIANT (Valsartan in Acute Myocardial Infarction) echocardiographic

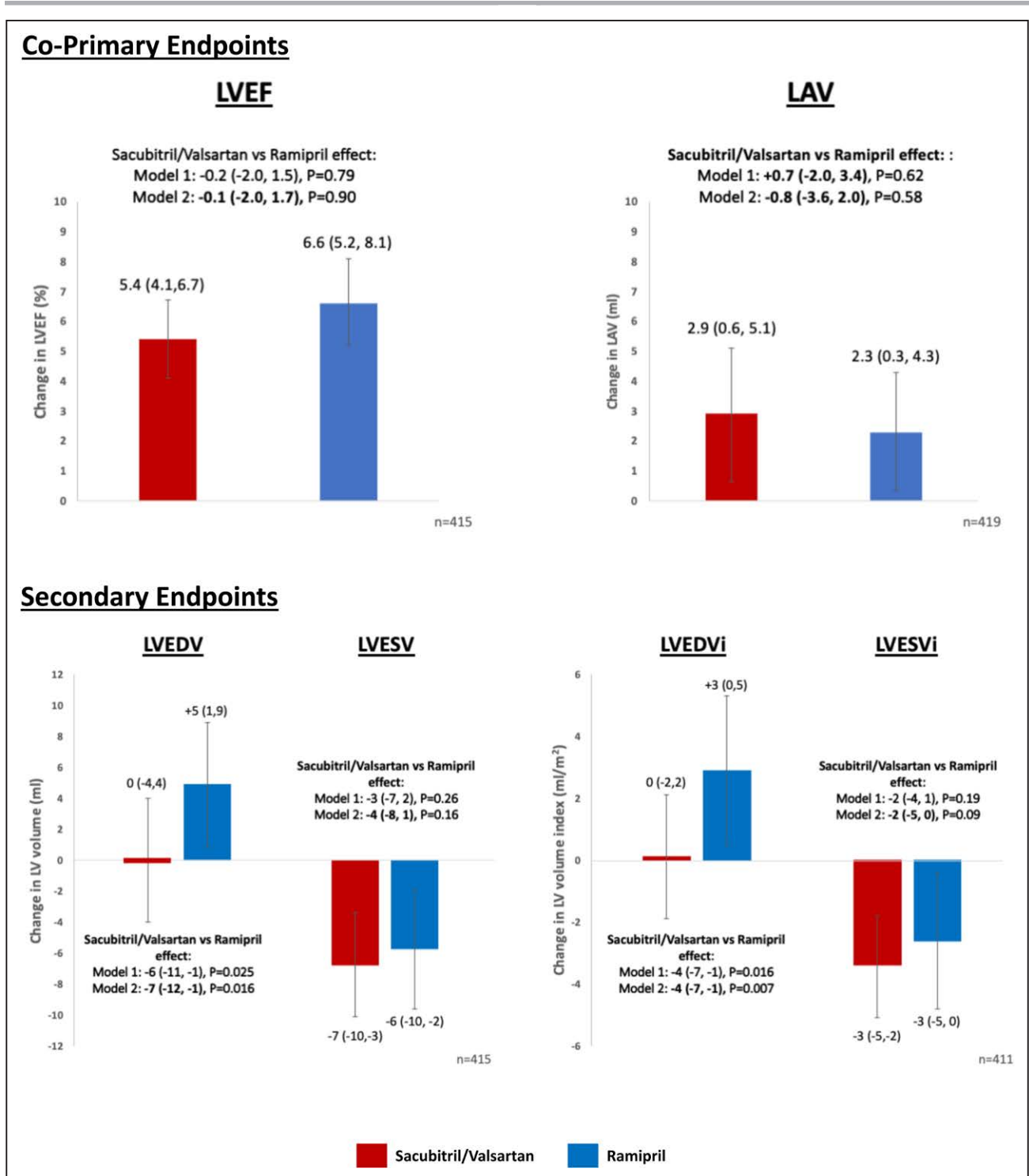
substudy suggest similar effects of ACE inhibitors and angiotensin receptor blockers on post-MI LV remodeling.<sup>2</sup> Preclinical data suggest similar beneficial effects of sacubitril/valsartan on LV remodeling after MI, with decreased LV size and mass and increased LVEF compared with placebo and nearly complete attenuation of angiotensin II stimulation-related myocyte fibrosis and hypertrophy.<sup>7-9</sup> In PARADISE-MI, reductions in LV size and LV mass were observed with sacubitril/valsartan, consistent with the preclinical data, although no effects were observed on LVEF or LAV. The treatment-related effect of sacubitril/valsartan versus ramipril in PARADISE-MI on changes in LV size was more modest than previously observed with the ACE inhibitor captopril versus placebo in the SAVE (Survival and Ventricular Enlargement) Echocardiographic Substudy (change in LV end-diastolic area,  $-0.9$  cm<sup>2</sup> [95% CI,  $-1.8$  to  $-0.0$ ] versus  $2.7 \pm 8.7$  cm<sup>2</sup>, respectively)<sup>1</sup> or the  $\beta$ -blocker metoprolol versus placebo in the CAPRICORN substudy (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; change in LVESV,  $-3$  [ $-7$ ,  $2$ ] versus  $-9$  [ $-17$ ,  $-1$ ] mL, respectively).<sup>3</sup> Compared with some preclinical studies and with these previous post-MI remodeling studies, PARADISE-MI used an active comparator as opposed to placebo, which may account for these differences. In addition, PARADISE-MI was performed in the era of reperfusion therapy, which itself is associated with functional improvement in the majority of patients with MI complicated by LV dysfunction,

**Table 3. Changes in Echocardiographic Measures From Baseline to Month 8 by Randomized Treatment Assignment**

Measure	Arm	No.	Baseline	Month 8	Delta	Model 1		Model 2	
						Treatment effect	P value	Treatment effect	P value
LV structure and function									
LVEF (n=415)*	Ramipril	209	40.6±10.8	47.2±11.2	6.6±10.7	-0.2 (-2.0, 1.5)	0.79	-0.1 (-2.0, 1.7)	0.90
	Sac/val	206	43.0±10.8	48.4±11.2	5.4±9.5				
LVEDV (n=415)	Ramipril	209	132±45	137±47	5±30	-6 (-11, -1)	0.025	-7 (-12, -1)	0.016
	Sac/val	206	127±39	127±35	0±29				
LVEDVi (n=411)	Ramipril	206	67.2±22.1	70.1±23.7	2.9±17.5	-3.6 (-6.5, -0.7)	0.016	-4.1 (-7.1, -1.1)	0.007
	Sac/val	205	64.2±18.0	64.3±16.0	0.1±14.8				
LVESV (n=415)	Ramipril	209	81±39	75±41	-6±28	-3 (-7, 2)	0.26	-4 (-8, 1)	0.16
	Sac/val	206	74±34	68±30	-7±24				
LVESVi (n=411)	Ramipril	206	41.3±20.3	38.7±21.8	-2.6±16.0	-1.7 (-4.3, 0.9)	0.19	-2.2 (-4.9, 0.4)	0.09
	Sac/val	205	37.7±16.2	34.2±14.3	-3.4±12.1				
LVEDD (n=403)	Ramipril	209	4.95±0.73	5.07±0.70	0.12±0.59	-0.06 (-0.16, 0.05)	0.28	-0.06 (-0.16, 0.05)	0.27
	Sac/val	194	4.79±0.59	4.91±0.63	0.13±0.54				
MWT (n=415)	Ramipril	211	1.06±0.15	0.98±0.16	-0.08±0.17	-0.01 (-0.04, 0.02)	0.49	-0.02 (-0.04, 0.01)	0.28
	Sac/val	204	1.08±0.16	0.97±0.16	-0.10±0.16				
LVM (n=383)	Ramipril	195	195±53	183±55	-12±44	-8 (-15, 0)	0.056	-9 (-17, -1)	0.023
	Sac/val	188	190±55	172±52	-18±40				
LVMi (n=380)	Ramipril	193	98.9±24.8	93.3±26.2	-5.6±23.4	-4.3 (-8.3, -0.3)	0.037	-5.5 (-9.7, -1.4)	0.009
	Sac/val	187	96.5±25.4	87.6±23.5	-8.9±20.3				
LA size									
LAV (n=419)*	Ramipril	213	49.8±16.2	52.1±17.2	2.3±14.7	0.7 (-2.0, 3.4)	0.62	-0.8 (-3.6, 2.0)	0.58
	Sac/val	206	50.1±18.8	53.0±19.1	2.9±16.3				
LAVi (n=408)	Ramipril	206	24.8±8.7	26.5±9.6	1.6±9.0	0.1 (-1.5, 1.8)	0.88	-0.9 (-2.6, 0.7)	0.28
	Sac/val	202	25.3±10.0	26.8±10.3	1.6±9.4				
LAD (n=399)	Ramipril	206	3.69±0.55	3.70±0.52	0.01±0.51	0.03 (-0.06, 0.12)	0.48	0.01 (-0.1, 0.10)	0.81
	Sac/val	193	3.70±0.59	3.73±0.58	0.03±0.50				
LV diastolic Doppler-based indices									
E wave (n=421)	Ramipril	215	71±23	70±21	0±23	1 (-3, 5)	0.57	-0 (-4, 4)	0.88
	Sac/val	206	68±24	70±23	2±23				
TDI e' lat (n=405)	Ramipril	203	7.0±2.4	7.7±2.3	0.7±2.7	0.7 (0.2, 1.1)	0.005	0.8 (0.3, 1.2)	0.002
	Sac/val	202	6.8±2.3	8.2±2.9	1.5±2.6				
E/e' lat (n=390)	Ramipril	198	10.7±4.4	9.7±3.8	-1.0±4.4	-0.7 (-1.4, 0.0)	0.045	-0.9 (-1.6, -0.2)	0.009
	Sac/val	192	11.0±4.8	9.1±3.8	-1.9±4.6				
TDI e' sept (n=411)	Ramipril	204	5.6±1.7	5.9±1.7	0.3±1.7	0.1 (-0.2, 0.4)	0.43	0.2 (-0.1, 0.5)	0.17
	Sac/val	207	5.5±1.7	6.0±1.9	0.5±1.9				
E/e' sept (n=394)	Ramipril	198	13.5±5.8	12.5±5.4	-1.0±5.8	0.2 (-0.7, 1.2)	0.62	-0.2 (-1.1, 0.8)	0.74
	Sac/val	196	13.2±5.0	12.6±5.6	-0.7±5.4				
TDI e' ave (n=396)	Ramipril	196	6.3±1.8	6.8±1.8	0.5±1.9	0.4 (0.1, 0.7)	0.022	0.5 (0.1, 0.8)	0.006
	Sac/val	200	6.1±1.7	7.1±2.1	1.0±1.9				
E/e' ave (n=382)	Ramipril	191	11.6±4.5	10.6±3.8	-1.0±4.3	-0.3 (-1.0, 0.3)	0.33	-0.6 (-1.3, 0.1)	0.073
	Sac/val	191	11.7±4.3	10.3±3.9	-1.4±4.1				
TRV (n=98)	Ramipril	50	2.54±0.31	2.62±0.50	0.08±0.56	-0.19 (-0.35, -0.03)	0.024	-0.23 (-0.41, -0.06)	0.010
	Sac/val	48	2.54±0.41	2.43±0.37	-0.11±0.30				

Model 1: adjusted for baseline value and region. Model 2: adjusted for baseline value, region, age, history of percutaneous coronary intervention or coronary artery bypass graft surgery, atrial fibrillation, pulmonary artery disease, estimated glomerular filtration rate, and use of mineralocorticoid antagonist at randomization. LA indicates left atrial; LAD, left atrial dimension; LAV, left atrial volume; LAVi, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVM, left ventricular mass; LVMi, left ventricular mass index; MWT, minimum wall thickness; Sac/Val, sacubitril/valsartan; TDI, tissue Doppler imaging; and TRV, tricuspid regurgitation volume.

\*LVEF and LAV were the study co-primary end points.

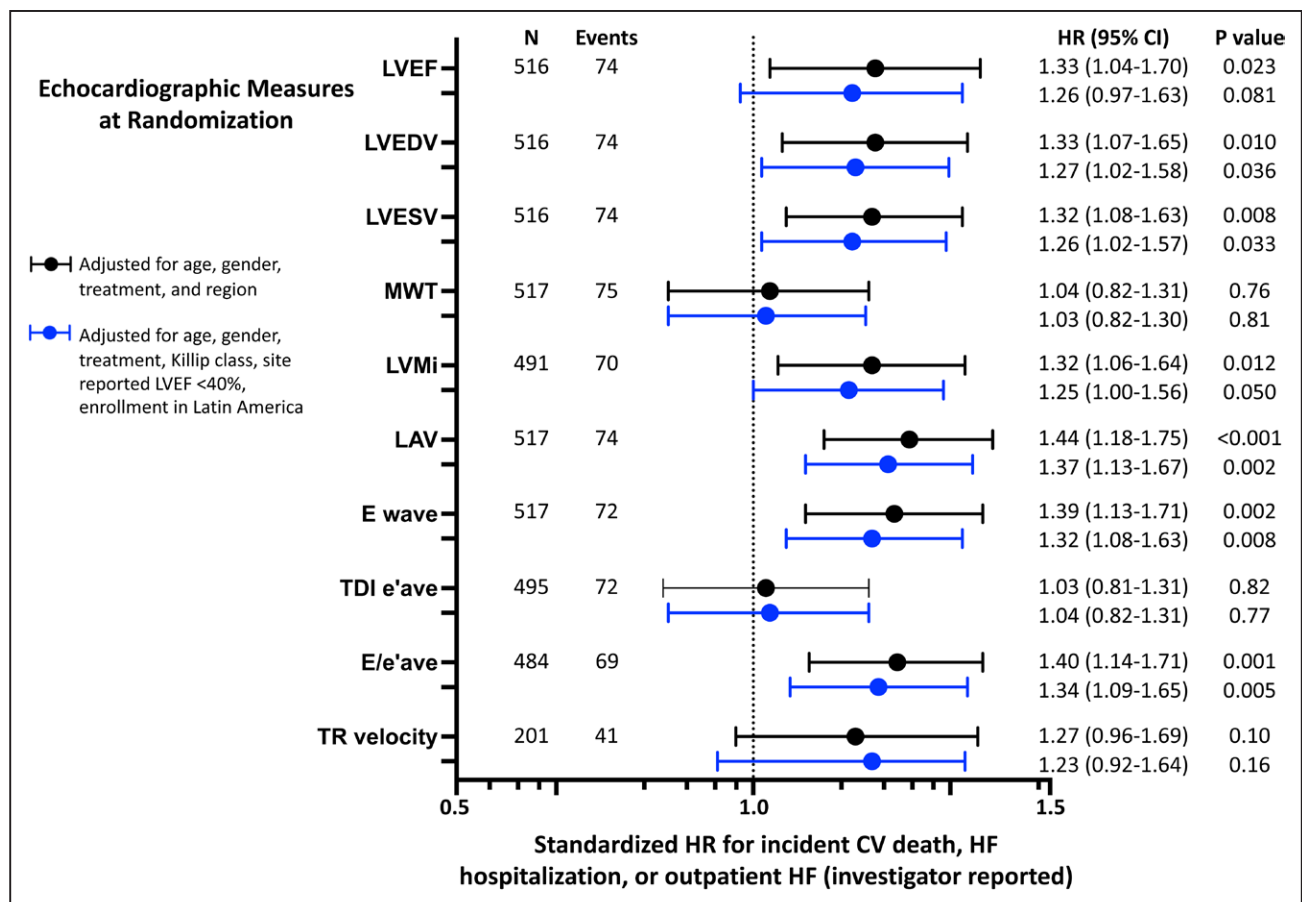


**Figure 2. Changes in primary and secondary study end points from randomization to 8 months by treatment arm.**

Bar graphs show mean and 95% CI. Model 1 is adjusted for baseline value and region. Model 2 is adjusted for baseline value, region, age, history of percutaneous coronary intervention or coronary artery bypass graft surgery, atrial fibrillation, pulmonary artery disease, estimated glomerular filtration rate, and use of magnetic resonance angiography at randomization. LAV indicates left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; and LVESVi, left ventricular end-systolic volume index.

and contemporary guideline-directed medical therapy, including  $\beta$ -blockers.<sup>30</sup> Ninety-one percent of substudy participants underwent revascularization during index

hospitalization; 84% were on a  $\beta$ -blocker at randomization; and 58% of those with LVEF <40% at baseline recovered to an LVEF  $\geq$ 40% by month 8.

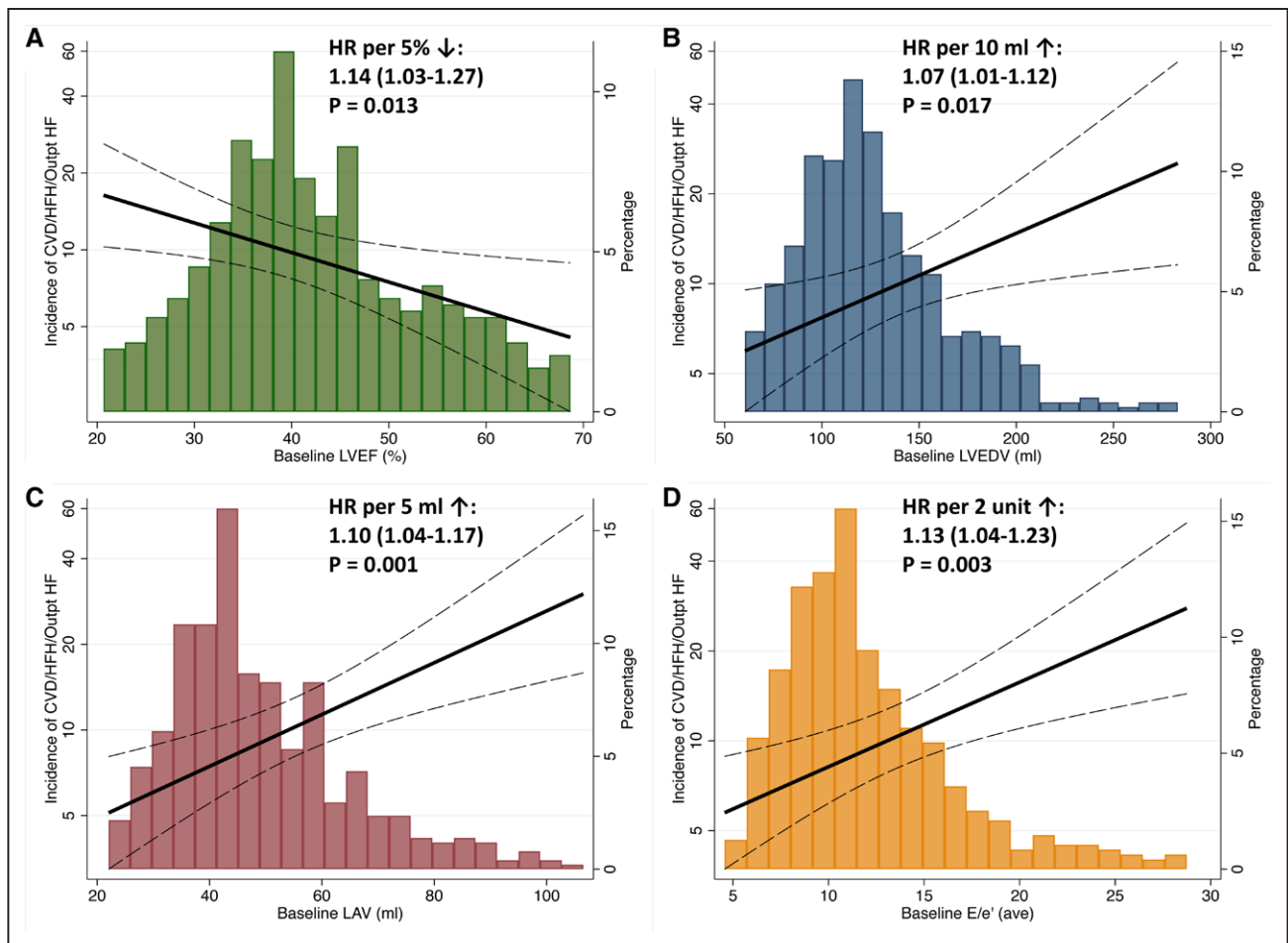


**Figure 3. Associations of baseline measures of cardiac structure and function with incidence of the composite of investigator-reported cardiovascular death, HF hospitalization, or outpatient HF.**

Hazard ratios (HRs) are shown per SD of measure to enable comparability between measures, as follows: left ventricular ejection fraction (LVEF), per 11.5% decrease; left ventricular end-diastolic volume (LVEDV), per 42.8-mL increase; left ventricular end-systolic volume (LVESV), per 37.1-mL increase; minimum wall thickness (MWT), per 0.16-cm increase; left ventricular mass index (LVMi), per 24.9-g/m<sup>2</sup> increase; left atrial volume (LAV), per 17.2-mL increase; E wave, per 23.2-cm/s increase; tissue Doppler imaging (TDI) e'ave, per 1.8-cm/s increase; E/e'ave, per 4.9-unit increase; and tricuspid regurgitation (TR) velocity, per 0.36-m/s increase. CV indicates cardiovascular; and HF, heart failure.

After an AMI, adverse LV remodeling can lead to the development of symptomatic HF and HFrEF in particular. Although the remodeling process is different in the context of AMI compared with chronic HFrEF, comparing our findings in AMI with studies evaluating the impact of sacubitril/valsartan in late post-MI LV dysfunction and chronic HFrEF provides important context within which to interpret our results. The PARADIGM-HF trial demonstrated significant reductions in cardiovascular death or HF hospitalization with sacubitril/valsartan compared with enalapril among symptomatic patients with HF with LVEF  $\leq$ 40%.<sup>5</sup> Among 464 stable patients with HFrEF randomized to sacubitril/valsartan or enalapril for 3 months, the EVALUATE-HF trial (Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction) demonstrated significant reductions in LVEDV index (LVEDVi), LVESV index, LAVi, and E/e' with randomization to sacubitril/valsartan (Table 3).<sup>6</sup> The PRIME trial (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) demonstrated significant reductions

in mitral regurgitation severity with sacubitril/valsartan compared with valsartan in 118 patients with HF with LVEF of 25% to 50% and significant functional mitral regurgitation.<sup>31</sup> In this sample of patients with more advanced HFrEF with significant functional mitral regurgitation, sacubitril/valsartan demonstrated even greater reductions in LV volumes, LAVi, and E/e' after 12 months compared with those seen after 3 months in EVALUATE-HF. Together with observational studies of changes in cardiac structure and function with sacubitril/valsartan initiation,<sup>32</sup> these findings support beneficial impacts on LV remodeling as one mechanism by which sacubitril/valsartan affects clinical outcomes in HFrEF. Recently, Docherty et al<sup>10</sup> evaluated the impact of sacubitril/valsartan compared with valsartan alone on LV remodeling in patients with asymptomatic LV dysfunction late after MI. Among 93 patients a median of 3.6 (interquartile range, 1.2–7.2) years after MI with LVEF  $\leq$ 40% and New York Heart Association class I to II, randomization to sacubitril/valsartan compared with valsartan for 12 months did not result in significant changes in LV volume, or LAV, or



**Figure 4.** Linear continuous associations of (A) left ventricular ejection fraction, (B) left ventricular end-diastolic volume, (C) left atrial volume, and (D) E/e' with incidence of investigator-reported cardiovascular death, HF hospitalization, or outpatient HF. Fitted lines, hazard ratios, and P values are adjusted for age, sex, and randomized treatment assignment. CVD indicates cardiovascular death; HF, heart failure; and HR, hazard ratio.

LVEF assessed by cardiac magnetic resonance imaging. A notable finding was that sacubitril/valsartan was associated with a trend toward reduction in LVEDVi similar in magnitude to that observed in EVALUATE-HF and the PARADISE-MI Echo Substudy and with a nonsignificant reduction in LAVi similar in magnitude to that observed in EVALUATE-HF. The PARADISE-MI Echo Substudy now provides data on the impact of sacubitril/valsartan on LV remodeling when initiated at the time of enhanced-risk AMI. PARADISE-MI is perhaps most notable for the modest degree of LV and LA enlargement and generally mildly reduced LVEF compared with these other randomized trials of sacubitril/valsartan (Table S14).

Sacubitril/valsartan did not improve LVEF compared with ramipril in the PARADISE-MI Echo Substudy. This contrasts with findings from a recent small Egyptian study of 200 patients with ST-segment-elevation MI randomized to sacubitril/valsartan or ramipril that found significant improvement in LVEF at 6 months with sacubitril/valsartan.<sup>33</sup> However, patients in this study were substantially younger with fewer comorbidities than those in PARADISE-MI, and use of other guideline-

directed therapies was not reported. Our finding with respect to LVEF is perhaps not surprising in the context of the aforementioned LV remodeling studies across the HF continuum, which were not available at the time the PARADISE-MI Echo Substudy was designed. Indeed, no effect of sacubitril/valsartan versus an active comparator was observed on measures of LV systolic function, including both LVEF and longitudinal strain, in PRIME,<sup>31</sup> EVALUATE-HF,<sup>6</sup> or the Docherty et al<sup>10</sup> study. Also consistent with the EVALUATE-HF and PRIME trials in HFrEF, we did observe significant reductions in LVEDVi with sacubitril/valsartan compared with ramipril. The  $\approx 3.6$ -mL/m<sup>2</sup> reduction in LVEDVi associated with sacubitril/valsartan in the PARADISE-MI Echo Substudy was similar to that in EVALUATE-HF but smaller than the  $\approx 7$ -mL/m<sup>2</sup> reduction seen in PRIME in which the baseline LVEDVi was substantially larger. This magnitude of reduction was also similar in magnitude to the study by Docherty et al,<sup>10</sup> although statistical significance was not achieved in that study. Reduction in E/e', a surrogate for LV filling pressure, with sacubitril/valsartan in the PARADISE-MI Echo Substudy is also consistent with

**Table 4. Randomized Controlled Trials of Cardiac Remodeling With Sacubitril/Valsartan Compared With Active Comparator**

RCT	Acute MI with LV dysfunction or congestion	Late post-MI asymptomatic LV dysfunction	Stable HFrEF	HFrEF with FMR
	PARADISE-MI Echo	Docherty et al <sup>10</sup>	EVALUATE-HF	PRIME
No.	457	93	464	118
Comparator	Ramipril	Valsartan	Enalapril	Valsartan
Duration, mo	8	12	3	12
Imaging modality	TTE	CMR	TTE	TTE
Impact of sacubitril/valsartan				
LVEF, %	−0.2 (−2.0, 1.5)	0.5 (−2.0, 0.9)	0.6 (−0.4, 1.7)	−0.2 (−2.0, 1.6)
LVEDVi, mL/m <sup>2</sup>	−3.6 (−6.5, −0.7)	−3.1 (−6.8, 0.6)	−2.0 (−3.7, −0.3)	−7.1 (−14.3, 0.2)
LVESVi, mL/m <sup>2</sup>	−1.7 (−4.3, 0.9)	−1.9 (−4.8, 1.0)	−1.6 (−3.1, −0.0)	−3.7 (−9.9, 2.4)
LVMi, g/m <sup>2</sup>	−4.3 (−8.3, −0.3)	−1.5 (−3.5, 0.6)	NA	NA
LAVi, mL/m <sup>2</sup>	0.1 (−1.5, 1.8)	−2.3 (−6.6, 2.0)	−2.8 (−4.0, −1.6)	−8.9 (−14.6, −3.3)
TDI e', cm/s	0.7 (0.2, 1.1)	NA	0.0 (−0.3, 0.3)	0.2 (−0.4, 0.7)
E/e'	−0.7 (−1.4, 0)	NA	−1.8 (−2.8, −0.8)	−2.7 (−5.1, −0.2)

EVALUATE-HF indicates Effects of Sacubitril/Valsartan vs Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction; CMR, cardiac magnetic resonance; FMR, functional mitral regurgitation; HFrEF, heart failure with reduced ejection fraction; LAVi, left atrial volume index; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMi, left ventricular mass index; MI, myocardial infarction; NA, not applicable; PARADISE-MI, Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction; PRIME, Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation; RCT, randomized controlled trial; TDI, tissue Doppler imaging; and TTE, transthoracic echocardiography.

findings from EVALUATE-HF and PRIME, although it was smaller in magnitude compared with those studies in which baseline E/e' was higher.

The reductions in LV volume in the absence of effects on LVEF or systolic blood pressure suggest effects of sacubitril/valsartan on filling pressure as opposed to load or systolic function. A primary effect on LV filling pressure is also consistent with the observed effect of sacubitril/valsartan on LVEDV but not ESV and on E/e' ratio. In this context, the lack of effect of sacubitril/valsartan on change in LAV is perhaps unexpected, especially given the greater reductions in LAVi with sacubitril/valsartan observed in HFrEF (EVALUATE-HF, PRIME)<sup>6,31</sup> and HF with preserved ejection fraction in the phase II PARAMOUNT trial (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction) comparing sacubitril/valsartan with valsartan.<sup>18</sup> The mean baseline LAVi was appreciably smaller in the PARADISE-MI Echo Substudy (25.1±9.3 mL/m<sup>2</sup>) compared with EVALUATE-HF (≈30 mL/m<sup>2</sup>), PRIME (≈67 mL/m<sup>2</sup>), or PARAMOUNT (≈35 mL/m<sup>2</sup>). LA enlargement, based on LAVi >34 mL/m<sup>2</sup>, was present in only 15% of participants in the PARADISE-MI Echo Substudy at baseline. This low prevalence of atrial enlargement may have limited our ability to detect an impact of randomized therapy on LA measures.

The prognostic importance of LV volumes and LVEF on HF risk and mortality after MI is well established.<sup>1,2,34</sup> Our findings corroborate their continued relevance in a contemporary cohort of patients with AMI treated with reperfusion and current guideline-directed medical ther-

apy. Although speculative, because larger LV volumes are important risk factors for mitral regurgitation after AMI, the attenuation of enlargement in LVEDV with sacubitril/valsartan may be expected to result in less subsequent mitral regurgitation.<sup>35</sup> It is notable that in this cohort of patients selected for post-MI LV systolic dysfunction or pulmonary congestion, measures reflective of elevated LV filling pressures (LAV, E/e') at randomization were robustly prognostic of incident cardiovascular death or incident HF independently of LV enlargement. These findings highlight the importance of LV diastolic measures in assessing longer-term HF risk in patients with AMI with LV systolic dysfunction.

This study has several limitations. Cardiac structure and LVEF were assessed with echocardiography as opposed to cardiac magnetic resonance imaging, which provides more precise quantification and is considered a gold standard. However, cardiac magnetic resonance imaging was not feasible given the international, multi-center nature of this study. Furthermore, all echocardiograms were performed by certified sonographers using a study-specific imaging protocol and were analyzed centrally at an experienced core laboratory. The greater measurement variability inherent in echocardiography was accounted for in our power calculations. The observed SD of change in LVEF was greater than anticipated for our prespecified power calculations (10% versus 6%, respectively). Despite this, we were able to rule out a benefit of sacubitril/valsartan compared with ramipril with respect to change in LVEF of 2% points or greater. Follow-up was incomplete; 12% of patients

enrolled in the Echo Study and alive at month 8 did not have a follow-up echocardiogram. However, baseline clinical and echocardiographic characteristics were generally comparable in these patients and in those who did have a follow-up study. Furthermore, sensitivity analysis incorporating inverse probability of attrition weights demonstrated results similar to those of our primary analysis. The 22 patients who died between baseline and month 8 were balanced between the ramipril and sacubitril/valsartan arms (3% and 5%, respectively). Last, variable missing data for echocardiographic measures were present at baseline and follow-up. Sensitivity analysis using multiple imputation to account for this missingness demonstrated consistent findings with our primary analysis.

## Conclusions

In a contemporary randomized clinical trial of enhanced-risk AMI aggressively managed with revascularization and contemporary guideline-directed medical therapy, treatment with sacubitril/valsartan compared with ramipril for 8 months after AMI did not result in greater improvement in LVEF or reduction in LAV. Patients randomized to sacubitril/valsartan demonstrated less LV enlargement and greater improvement in measures reflective of LV filling pressure. In addition to LV size and systolic function, measures reflective of elevated filling pressure at index hospitalization were robustly prognostic of risk of incident HF or cardiovascular mortality independently of LV volumes.

## ARTICLE INFORMATION

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### Affiliations

Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (A.M.S., B.C., N.P., G.L., M.V., K.J., S.D.S., M.A.P.). University of Zagreb School of Medicine and University Hospital Centre Zagreb, Croatia (M.C.). Heart and Vascular Center, Semmelweis University, Budapest, Hungary (A.K.). University Hasselt, Ziekenhuis Oost Limburg, Genk, Belgium (W.M.). Instituto do Coracao, Hospital das Clinicas, Faculdade de Medicina, Universidade de São Paulo, Brazil (J.C.N.). Rigshospitalet, Copenhagen, Denmark (L.K.). University of Groningen, The Netherlands (P.v.d.M.); University of Glasgow, Scotland (P.S.J.). Novartis Pharmaceutical Corporation, East Hanover, NJ (G.I., M.L., Y.Z.).

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## Supplemental Material

Tables S1–S14

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