Impact of Sacubitril/Valsartan compared to Ramipril on cardiac structure and function following acute myocardial infarction: The PARADISE-MI Echocardiographic Sub-Study

Running Title: PARADISE-MI Echo Sub-Study

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Abstract

Background: Angiotensin-converting enzyme (ACE) inhibitors attenuate left ventricular (LV) enlargement following acute myocardial infarction (AMI). Preclinical data suggest similar benefits with combined angiotensin receptor neprilysin inhibition, but human data is conflicting. The Prospective ARNI versus ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI) Echo Study tested the effect of sacubitril/valsartan compared to ramipril on LV function and adverse remodeling following high risk AMI.

Methods: In a prespecified sub-study, 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 sacubitril/valsartan 200 mg or ramipril 5 mg twice daily. Echocardiographic measures were performed at a core laboratory blinded to treatment assignment. The effect of treatment on change in echo measures was assessed using ANCOVA adjusting for baseline value and enrollment region. The primary endpoints were change in LV ejection fraction (LVEF) and left atrial volume (LAV), and prespecified secondary endpoints included changes in LV end-diastolic (LVEDV) and end-systolic volumes (LVESV).

Results: Mean age was 64±12 years, 26% were women, mean LVEF was 42±12%, and LAV 49±17 ml. Of 544 enrolled patients, 457 (84%) had a follow-up echo at 8 months (228 sacubitril/valsartan, 229 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 LVEDV (p=0.025) and greater decline in LV mass index (p=0.037), increase in tissue Doppler e'_{lat} (p=0.005), decrease in E/e'_{lat} (p=0.045), and decrease in tricuspid regurgitation peak velocity (p=0.024) than patients randomized to ramipril. These differences remained significant after adjusting for differences in baseline characteristics. Baseline LVEF, LVEDV, LVESV, LV mass index, LAV, and Doppler-based diastolic indices were associated with risk of cardiovascular (CV) death or incident heart failure (HF).

Conclusions: Treatment with sacubitril/valsartan compared to ramipril following 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 CV death and incident HF post-AMI in this contemporary, well-treated cohort.

Clinical Trial Registration: Clinicaltrials.gov Identifier NCT02924727

Key words: Acute myocardial infarction, heart failure, echocardiography

Clinical Perspectives

What is New?

- Among patients with acute myocardial infarction (AMI) complicated by LV dysfunction and/or congestion, treatment with sacubitril/valsartan compared to ramipril did not result in changes in LVEF or LAV at 8 months
- Treatment with sacubitril/valsartan compared to ramipril did result 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 CV death and incident HF post-AMI in this contemporary, well-treated cohort.

What are the Clinical Implications?

- Treatment with sacubitril/valsartan compared to ramipril early following AMI may beneficially impact LV size and diastolic properties, possibly due to reductions in LV filling pressure
- Among enhanced risk AMI patients enriched for systolic dysfunction, measures of diastolic function and filling pressure during the index hospitalization are robustly prognostic of longer-term risk of CV death and incident HF.

Nonstandard Abbreviations

ACE – angiotensin converting enzyme

AMI – acute myocardial infarction

ASE – American Society of Echocardiography

CoV – coefficient of variation

CV – cardiovascular

HF – heart failure

HFrEF – heart failure with reduced ejection fraction

LA – left atrium

LAV – left atrial volume

LAVi – left atrial volume index

LV – left ventricle

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

PARADISE-MI – Prospective ARNI versus ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction trial

TR – tricuspid regurgitation

Introduction

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

The Prospective ARNI versus ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI) trial tested whether sacubitril/valsartan would be superior to ramipril in reducing the composite endpoint of cardiovascular death, HF hospitalization or outpatient development of HF following AMI with LV systolic dysfunction and/or pulmonary congestion.[11] 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 CV death.[12, 13] The PARADISE-MI Echo Sub-Study was designed to test the hypothesis that treatment with sacubitril/valsartan would improve LV function and attenuate adverse remodeling compared to ramipril following high risk AMI. Among patients randomized in the main PARADISE-MI trial, 544 were enrolled in the PARADISE Echo Sub-Study to undergo protocol echocardiography at randomization and 8 months. We report the findings of the PARADISE-MI Echo Sub-Study and the associations of cardiac structure and function with risk of incident HF and CV mortality in a large, contemporary cohort of patients with enhanced risk AMI.

Methods

The data, analytic 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 Sub-Study, and patients enrolled at these sites were eligible for inclusion in the PARADISE-MI Echo Sub-Study.[11] Major inclusion criteria in the Echo Sub-Study 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 ≤40% and/or transient pulmonary congestion requiring intravenous treatment during the index event, and at least one of the following 8 predefined risk-augmenting factors: 1) age ≥ 70 years; 2) eGFR <60 mL/min/1.73 m^2 at screening; 3) diabetes mellitus; 4) prior 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 prior HF were excluded. Additional inclusion criteria specific to the Echo Sub-Study included: (1) sinus rhythm at the time of randomization; (2) adequate echocardiographic image quality on qualifying echocardiogram for determination of the study primary endpoint (LVEF, LAV) as determined by the site investigator; and (3) consented to participate in the Echo Sub-Study. Of the 5,661 patients validly randomized in PARADISE-MI, 544 were enrolled in the Echo Sub-Study. Protocol echocardiographic studies were performed at ±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 Sub-Study. All patients provided signed informed consent for inclusion in the PARADISE-MI Echo Sub-study, 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 (ASE) guidelines,[14, 15] by dedicated analysts blinded to randomized treatment assignment and to temporal sequence of serial echocardiograms (baseline vs 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's rule. LV mass was calculated by the ASE recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area (LV mass index, LVMi).[14] LA volume was assessed by the modified biplane Simpson's method from apical 2- and 4-chamber views at end-systole, and was indexed to body surface area (LA volume index, LAVi). Peak early diastolic tissue velocity (e') was measured from the septal (e'_{sept}) and lateral (e'_{lat}) aspects of the mitral annulus, and their average was calculated (e'_{ave}). Mitral inflow velocity was assessed by pulsed-wave Doppler from the apical 4-chamber view. Peak tricuspid regurgitation (TR) velocity was measured from the continuous wave spectral Doppler envelope.

Reproducibility of echocardiographic measures at the Echocardiography Core Laboratory has been previously reported.[16] Intra-reader 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 endpoints are as follows: LVEF: bias: 0.7±4.8%, coefficient of variation (CoV) 11.0%, intraclass correlation coefficient (ICC) 0.90; LAV: bias: 1.5±4.5 ml, CoV 8.4%, ICC 0.97; left ventricular end-diastolic volume (LVEDV): bias: 0±8 ml, CoV 6.7%, ICC 0.97; left ventricular end-systolic volume (LVESV): bias: 1±8 ml, CoV 10.8%, ICC 0.98.

Clinical Outcomes

Clinical outcomes included the composite of CV death, HF hospitalization or outpatient episode of symptomatic HF. The primary analysis was performed using investigator-reported

events, while sensitivity analysis was performed using clinical endpoints committee adjudicated events. All events were reported by the primary site investigator and adjudicated endpoints were independently adjudicated by a Clinical Endpoints Center, blinded to treatment assignment. Definitions of these endpoints have been previously published.[11]

Statistical methods

The co-primary endpoints for the Echo Sub-Study were: (1) Change in LVEF from baseline to 8 months; (2) Change in LAV from baseline to 8 months. Prespecified secondary endpoints included: (1) Change in LVESV from baseline to 8 months; and (2) Change in LVEDV from baseline to 8 months. Change in absolute LAV, as opposed to LAVi, was selected as some patients may experience significant weight loss following AMI partially related to prescribed exercise and lifestyle modification that could change LAVi without appreciable changes in actual LA size. Additional exploratory endpoints 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 [TDI 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 compared to ramipril in the Echo Sub-Study: age, eGFR, history of percutaneous coronary intervention or coronary artery bypass surgery, atrial fibrillation, and peripheral arterial disease, and mineralocorticoid receptor antagonist use at randomization. A sample size of 488 patients

was determined as necessary to detect an absolute 2% treatment difference in LVEF change assuming a standard deviation (SD) of 6%[2, 17] and 5 ml treatment difference in LAV change assuming a SD of 15 ml[18] with alpha = 0.025 (2-sided) and 85% power, assuming 20% dropout in the sample size due to patient death or poor echo quality. The SD of change in LVEF and LAV are based on those observed in prior 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 employed multiple imputation by chained equations, an iterative imputation procedure (STATA mi impute chained).[19, 20] 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.[21, 22] Acquisition of Month 8 echocardiograms was modeled among sub-study 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 employed to study the association of echocardiographic measures with clinical outcomes. Echocardiographic exposures were modeled as continuous variables per standard deviation. Two multivariable Cox models were

employed: (1) Model 1 adjusted for age, sex, randomized treatment, and region of enrollment; (2) 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 based on a forward selection procedure with a p threshold for retention of <0.05, and with age, sex, and randomized treatment forced into the model and 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 CV death was further assessed using restricted cubic splines with the number of knots selected to minimize the model Akaike information criteria (3 to 7 knots considered). No compelling evidence to support non-linearity was observed so all associations are displayed linearly. All analyses were performed using STATA version 16.

Results

Baseline characteristics

The average age of the 544 PARADISE-MI Echo Sub-Study participants was 64±12 years and 26% were women (Table 1). The mean time from presentation to randomization was 4.1±1.7 days, the index AMI was STEMI in 75%, 52% received IV treatment for congestion, the site-assessed LVEF was ≤40% in 85%, and 92% underwent coronary revascularization. Compared to PARADISE-MI patients not in the Echo Sub-Study, those in the Echo Sub-Study were more likely to be enrolled in Central or Western Europe and to be of White race, had higher

BMI and shorter time from presentation to randomization, were more likely to undergo reperfusion with PCI and stenting, and were more likely to have been taking an ACE inhibitor or ARB prior to randomization and a mineralocorticoid receptor antagonist at randomization (Table 1). Among Echo Sub-Study participants, the 279 randomized to sacubitril/valsartan compared to the 265 randomized to ramipril tended to be older, had a lower eGFR and higher prevalence of prior PCI, CABG, history of atrial fibrillation and peripheral arterial 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 [IQR 0, 1]), and was similar in both treatment arms. The median time from AMI presentation to baseline echocardiography was 4.8 [IQR 3.2, 6.1] days, and was modestly longer among those randomized to sacubitril/valsartan compared to 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±11.5% and the mean LAV was 49.4±17.2 ml (Table 2). Compared to patients randomized to ramipril, those randomized to sacubitril/valsartan demonstrated higher baseline LVEF, and smaller LV end-diastolic and end-systolic volumes. 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 Sub-study participants (Figure 1), 228 in the sacubitril/valsartan arm and 229 in the ramipril 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 to Echo Sub-Study participants with Month 8

echocardiograms, those without Month 8 studies were more frequently female and Asian, had lower BMI, higher systolic blood pressure, and a higher prevalence of prior stroke, and were more likely to require IV treatment for congestion during the index AMI admission (Table S2). They also had higher LVEF, smaller LAV, lower TDI e', and higher E/e' ratio (Table S3).

The median time from baseline to 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±10.1% ($p < 0.001$), LVEDV and LVESV decreased by 2.5±29.6 ($p=0.092$) and 6.2±26.3 ml ($p < 0.001$) respectively, and LAV increased by 2.6±15.5 ml ($p<0.001$; Table 3). Among sub-study participants with core lab LVEF <40% at randomization, LVEF at follow-up was ≥40% in 58%, was ≥50% in 22%, and increased by ≥10% if 44%. Among patients with baseline and follow-up studies, baseline differences in age, eGFR, and prevalence of prior CABG, history of atrial fibrillation and peripheral arterial 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 mg [interquartile range 100, 200] in the sacubitril/valsartan arm and 5 mg [2.5, 5] in the ramipril arm. No significant change in systolic blood pressure between baseline and follow-up echocardiographic studies was observed between treatment groups (sacubitril/valsartan vs ramipril: -2.5 [-5.7,0.7] mmHg, $p = 0.13$). Use of other cardiovascular medications were 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 to ramipril (Table 3; Table S7; Figure 2). Among patients with LVEF <40% at randomization, sacubitril/valsartan and ramipril arms demonstrated similar proportion of patients recovering LVEF at follow-up to >40% (57 vs 59% respectively,

p= 0.78) or >50% (22% in both arms, p=0.99), or increasing LVEF by ≥10% (40 vs 48% respectively, p=0.26). Patients randomized to sacubitril/valsartan demonstrated less increase in LV end-diastolic volume and greater decline in LV mass index compared to those randomized to ramipril. They also demonstrated greater increase in tissue Doppler e'_{lat} and decrease in E/e'_{lat}, increase in e'_{ave}, and decrease in tricuspid regurgitation peak velocity. Sacubitril/valsartan was not associated with changes in e'_{septal} compared to ramipril. These associations persisted after adjusting for differences in baseline age, history of PCI or CABG, atrial fibrillation, peripheral arterial disease, eGFR, and MRA use at randomization. Similar treatment effects were observed in sensitivity analyses employing 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 employing inverse probability of attrition weighting to account for the 65 sub-study patients who were alive at Month 8 but did not undergo a Month 8 echocardiogram (Table S9). Similar results were also observed in 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 CV death, HF hospitalization, or outpatient HF. Lower LVEF, larger LVEDV and LVESV, greater LVMi, greater LAV, and higher E wave and E/e' ratio were each associated with greater risk of the composite endpoint after adjustment for age, sex, treatment assignment, and region of enrollment (Model 1; Figure 3, Table S11). Notably, 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 endpoint (Table 4). In models including LVEDV, LAV, and E/e'$_{ave}$ together, higher LAV (standardized HR 1.37 [95% CI 1.09-1.74], p = 0.008) and higher E/e'$_{ave}$ (1.25 [1.01-1.54], p=0.039) were associated with higher risk while greater LVEDV was not (0.93 [0.72-1.19], p=0.56). Similar findings were observed for the composite endpoint of CEC adjudicated CV 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 to ramipril. Randomization to sacubitril/valsartan did result in less increase in LVEDV and greater decline in LV mass index, increase in tissue Doppler e'$_{lat}$, decrease in E/e'$_{lat}$, and decrease in tricuspid regurgitation peak velocity. These associations persisted after adjusting 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 sub-study. 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 CV death, HF hospitalization, or outpatient HF post-AMI in this contemporary, vigorously managed cohort. Measures reflective of elevated LV filling

pressures (LAV, E/e') assessed at randomization were robustly prognostic independent of LV enlargement, emphasizing the long-term prognostic importance of these diastolic measures.

Although the incidence of HF following AMI may be declining in the context of procedural and pharmacologic treatment advances,[23] AMI remains one of the most important causes of HF.[24] 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 pharmacologic interventions including ACE inhibitors and beta-blockers.[1-3] These agents have similarly been shown to be efficacious in HFrEF,[25-28] where the impact of pharmacologic or device interventions on LV remodeling (LV volumes and LVEF) correlates with impact on relevant clinical outcomes.[29] Furthermore, findings of the VALIANT echocardiographic sub-study suggest similar effects of ACE inhibitors and angiotensin receptor blockers on post-MI LV remodeling.[2] Preclinical data suggest similar beneficial effects of sacubitril/valsartan on LV remodeling post-MI, with decreased LV size and mass and increased LVEF compared to placebo, and near complete attenuation of angiotensin II stimulation related myocyte fibrosis and hypertrophy.[7-9] 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 LA volume. The treatment related effect of sacubitril/valsartan versus ramipril in PARADISE-MI on changes in LV size were more modest than those previously observed with the ACE inhibitor captopril versus placebo in the SAVE Echocardiographic sub-study (change in LV end-diastolic area -0.9 [95% CI -1.8 to -0.0] vs 2.7±8.7 cm2 respectively)[1] or the beta-blocker metoprolol versus placebo in the CAPRICORN sub-study (change in LVESV -3 [-7, 2] vs -9 [-17, -1] ml respectively).[3] Compared to some preclinical studies and to these prior 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, and contemporary guideline-directed medical therapy including beta-blockers.[30] Ninety-one percent of sub-study 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 ≥40% by Month 8.

Following an AMI, adverse LV remodeling can lead to the development of symptomatic HF, and HFrEF in particular. While the remodeling process is different in the context of AMI compared to chronic HFrEF, comparing our findings in AMI to 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 CV death or HF hospitalization with sacubitril/valsartan compared to enalapril among symptomatic HF patients with LVEF ≤40%.[5] Among 464 stable HFrEF patients randomized to sacubitril/valsartan or enalapril for 3 months, the EVALUATE-HF trial demonstrated significant reductions in LVEDVi, LVESVi, LAVi, and E/e' with randomization to sacubitril/valsartan (Table 3).[6] The PRIME trial demonstrated significant reductions in mitral regurgitation severity with sacubitril/valsartan compared to valsartan in 118 HF patients with LVEF 25-50% and significant functional mitral regurgitation.[31] In this sample of more advanced HFrEF patients with significant functional mitral regurgitation, sacubitril/valsartan demonstrated even greater reductions in LV volumes, LAVi, and E/e' after 12 months compared to those seen after 3 months in EVALUATE-HF. Together with observational studies of changes in cardiac structure and function with sacubitril/valsartan initiation,[32] these findings support beneficial impacts on LV remodeling as one mechanism by which sacubitril/valsartan impacts clinical

outcomes in HFrEF. Recently, Docherty et al evaluated the impact of sacubitril/valsartan compared to valsartan alone on LV remodeling in patients with asymptomatic LV dysfunction late following myocardial infarction.[10] Among 93 patients a median of 3.6 [interquartile range, 1.2-7.2] years post-MI with LVEF ≤40% and NYHA class I-II, randomization to sacubitril/valsartan compared to valsartan for 12 months did not result in significant changes in LV or LA volumes or LVEF assessed by cardiac MRI. Notably, sacubitril/valsartan was associated with a trend toward reduction in LVEDVi similar in magnitude to that observed in EVALUATE-HF and in the PARADISE-MI Echo sub-study, and with non-significant reduction in LAVi similar in magnitude to that observed in EVALUATE-HF. The PARADISE-MI Echo sub-study 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 to these other randomized trials of sacubitril/valsartan (Table S14).

Sacubitril/valsartan did not improve LVEF compared to ramipril in the PARADISE-MI Echo Sub-Study. This contrasts with findings from a recent small Egyptian study of 200 patients with STEMI randomized to sacubitril/valsartan or ramipril, which found significant improvement in LVEF at 6 months with sacubitril/valsartan.[33] However, patients in this study were substantially younger with fewer co-morbidities 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 above LV remodeling studies across the HF continuum, which were not available at the time the PARADISE-MI Echo Sub-Study 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, EVALUATE-HF,

or Docherty et al's study.[6, 10, 31] Also consistent with the EVALUATE-HF and PRIME trials in HFrEF, we did observe significant reductions in LVEDVi with sacubitril/valsartan compared to ramipril. The ~3.6 ml/m2 reduction in LVEDVi associated with sacubitril/valsartan in the PARADISE-MI Echo Sub-Study was similar to EVALUATE-HF, but smaller than the ~7 ml/m2 reduction seen in PRIME where the baseline LVEDVi was substantially larger. This magnitude of reduction was also similar in magnitude to the study by Docherty et al, 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 Sub-Study is also consistent with findings from EVALUATE-HF and PRIME, although was smaller in magnitude compared to those studies where baseline E/e' was higher.

The reductions in LV volume in the absence of effects on LVEF or SBP 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 LV end-diastolic – but not end-systolic – volume 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)[6, 31] and HFpEF in the phase II PARAMOUNT trial comparing sacubitril/valsartan to valsartan.[18] The mean baseline LAVi was appreciably smaller in the PARADISE-MI Echo Sub-Study (25.1 ± 9.3 ml/m2) compared to EVALUATE-HF (~30 ml/m2), PRIME (~67 ml/m2), or PARAMOUNT (~35 ml/m2). LA enlargement, based on LAVi >34 ml/m2 was present in only 15% of participants in the PARADISE-MI Echo Sub-Study 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 left ventricular volumes and ejection fraction for HF risk and mortality post-MI is well established.[1, 2, 34] Our findings corroborate their continued relevance in a contemporary cohort of AMI patients treated with reperfusion and current guideline-directed medical therapy. Although speculative, as larger left ventricular volumes are important risk factors for mitral regurgitation post-AMI, the attenuation of enlargement in LV end-diastolic volume with sacubitril/valsartan may be expected to result in less subsequent mitral regurgitation.[35] It is notable that in this cohort of patients selected for post-MI LV systolic dysfunction and/or pulmonary congestion, measures reflective of elevated LV filling pressures (LAV, E/e') at randomization were robustly prognostic of incident CV death or incident HF independent of LV enlargement. These findings highlight the importance of LV diastolic measures in assessing longer-term HF risk in AMI patients with LV systolic dysfunction.

This study has several limitations. Cardiac structure and LVEF were assessed using echocardiography as opposed to cardiac MRI, which provides more precise quantification and is considered a gold standard. However, cardiac MRI was not feasible given the international, multicenter 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 standard deviation of change in LVEF was greater than anticipated for our pre-specified power calculations (10% vs 6% respectively). Despite this, we were able to rule out a benefit of sacubitril/valsartan compared to ramipril on change in LVEF of 2% points or greater. Follow-up was incomplete, such that 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 compared to those who did have a follow-up study. Furthermore, sensitivity analysis incorporating inverse probability of attrition weights demonstrated similar results to 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). Finally, 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 to ramipril for 8 months following 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 CV mortality independent of LV volumes.

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Supplemental Materials

Tables S1-14

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Tables and Figures

Figure 1. Consort diagram of patient flow for the PARADISE-MI Echo sub-study.

Figure 2. Changes in primary and secondary study endpoints 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 prior PCI or CABG, AF, PAD, eGFR, and use of MRA at randomization. LVEF – left ventricular ejection fraction; LAV – left atrial volume; LVEDV – LV end-diastolic volume; LVESV – LV end-systolic volume; LVEDVi – LV end-diastolic volume index; LVESVi – LV end-systolic volume index

Figure 3. Associations of baseline measures of cardiac structure and function with incidence of the composite of investigator-reported CV death, HF hospitalization, or outpatient HF. Hazard ratios are shown per standard deviation of measure to enable comparability between measures, as follows: LVEF – per 11.5% decrease; LVEDV – per 42.8 ml increase; LVESV – per 37.1 ml increase; MWT – per 0.16 cm increase; LVMi – per 24.9 g/m^2 increase; LA volume – per 17.2 ml increase; E wave – per 23.2 cm/s increase; TDI e'$_{ave}$ – per 1.8 cm/s increase; E/e'$_{ave}$ – per 4.9 unit increase; TR velocity – per 0.36 m/s increase.

Figure 4. Linear continuous associations of (A) LVEF, (B) LVEDV, (C) LAV, and (D) E/e' with incidence of investigator reported CV death, HF hospitalization, or outpatient HF. Fitted lines, hazard ratios, and p values are adjusted for age, sex, and randomized treatment assignment.

Table 1. Baseline characteristic of PARADISE-MI patients not enrolled vs enrolled in the Echo sub-study, and among Echo sub-study participants by randomized treatment allocation.

	Non-Echo Study (n=5,117)	Echo Study (n=544)	P value	Ramipril (n=265)	Sac/Val (n=279)	P value
Demographics						
Age	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
Race 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)	
Co-Morbidities						
Prior Stroke	232 (5)	31 (6)	0.22	15 (6)	16 (6)	0.96
Prior MI	847 (17)	102 (19)	0.19	44 (17)	58 (21)	0.21
Prior PCI	736 (14)	91 (17)	0.14	34 (13)	57 (20)	0.018
Prior 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
Index MI event						
Time from presentation to randomization (days)	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
IV treatment for congestion	2772 (54)	284 (52)	0.38	142 (54)	142 (51)	0.53
Killip class			0.14			0.85
Class I	2045 (41)	236 (44)		117 (45)	119 (43)	
Class II	1612 (33)	152 (28)		72 (27)	80 (29)	
Class III	1016 (21)	125 (23)		59 (22)	66 (24)	

Class 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
Physical Exam						
HR	76 ± 12	77 ± 11	0.004	78 ± 11	77 ± 12	0.24
SBP	121 ± 13	119 ± 13	<0.001	119 ± 13	119 ± 13	0.77
DBP	74 ± 10	73 ± 10	0.004	73 ± 9	73 ± 11	0.85
BMI	28 ± 5	28.8 ± 5.1	0.002	28.8 ± 5.1	28.7 ± 5.2	0.84
eGFR	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
Beta 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 ACEi/ARB	3976 (78)	460 (85)	<0.001	222 (84)	238 (85)	0.62

Values are displayed as mean ± standard deviation for continuous variables, and number (percent) for categorical variables. Between group comparisons were performed using a t-test for continuous variables and a Chi-squared test for categorical variables.

Table 2. Baseline echocardiographic measures of Echo sub-study participants overall, and by randomized treatment allocation

	N	Overall (n=544)	Ramipril (n=265)	Sac/Val (n=279)	P value
LV structure & 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/m2)	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/m2)	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/m2)	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/m2)	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'_{lat} (cm/s)	504	6.8 ± 2.4	6.9 ± 2.4	6.7 ± 2.4	0.40
E/e'_{lat}	493	11.3 ± 5.0	11.3 ± 5.2	11.3 ± 4.9	0.83
TDI e'_{sept} (cm/s)	510	5.4 ± 1.7	5.5 ± 1.7	5.3 ± 1.7	0.23
E/e'_{sept}	497	13.8 ± 5.9	13.7 ± 6.1	13.9 ± 5.7	0.75
TDI e'_{ave} (cm/s)	495	6.1 ± 1.8	6.2 ± 1.8	6.0 ± 1.8	0.18
E/e'_{ave}	484	12.1 ± 4.9	12.0 ± 5.0	12.2 ± 4.7	0.71
TR velocity (m/s)	201	2.58 ± 0.36	2.59 ± 0.34	2.57 ± 0.39	0.70

Values are displayed as mean ± standard deviation

Table 3. Changes in echocardiographic measures from baseline to Month 8 by randomized treatment assignment

Measure	Arm	N	Baseline	Month 8	Delta	Model 1		Model 2	
						Treatment Effect	P value	Treatment Effect	P value
LV Structure and Function									
LVEF	**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**
N=415	**Sac/val**	**206**	**43.0±10.8**	**48.4±11.2**	**5.4±9.5**				
LVEDV	Ramipril	209	132±45	137±47	5±30	-6 (-11, -1)	0.025	-7 (-12, -1)	0.016
N=415	Sac/val	206	127±39	127±35	0±29				
LVEDVi	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
N=411	Sac/val	205	64.2±18.0	64.3±16.0	0.1±14.8				
LVESV	Ramipril	209	81±39	75±41	-6±28	-3 (-7, 2)	0.26	-4 (-8, 1)	0.16
N=415	Sac/val	206	74±34	68±30	-7±24				
LVESVi	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
N=411	Sac/val	205	37.7±16.2	34.2±14.3	-3.4±12.1				
LVEDD	Ramipril	209	4.95±0.73	5.07±0.70	0.12±0.59	-0.06 (-0.16, 0.05)	0.28		0.27

N=403	Sac/val	194	4.79±0.59	4.91±0.63	0.13±0.54			-0.06 (-0.16, 0.05)	
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				
LV mass 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'_{sep} 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

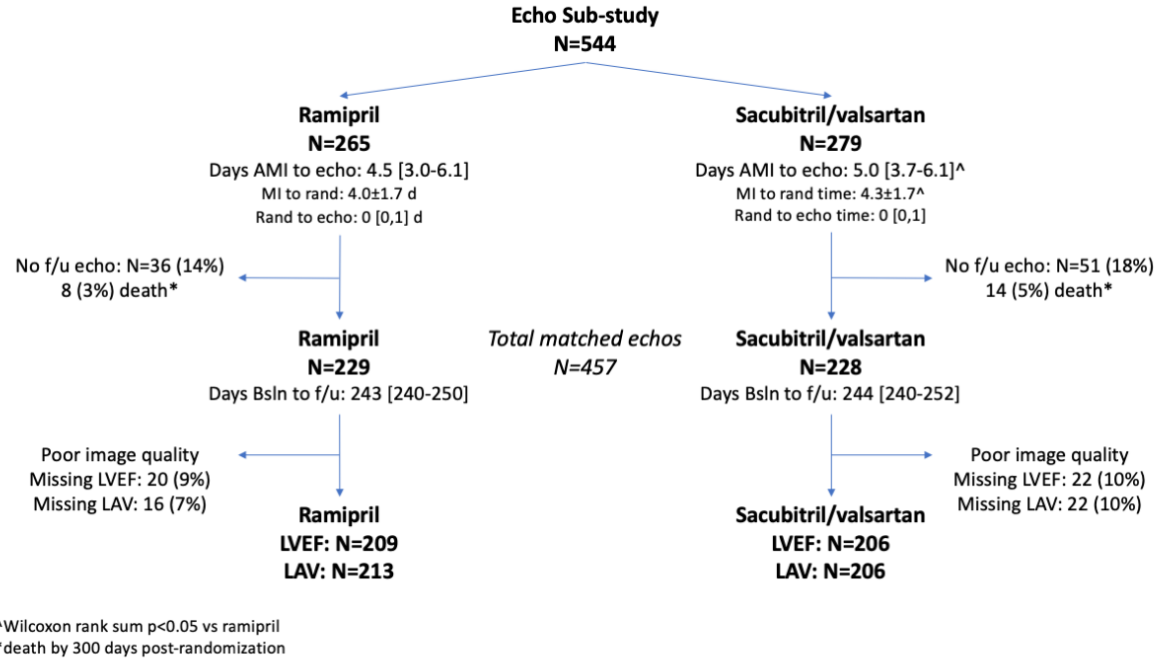
Model 2 – adjusted for baseline value, region, age, history of prior PCI or CABG, AF, PAD, eGFR, and use of MRA at randomization

Table 4. Randomized controlled trials of cardiac remodeling with sacubitril/valsartan compared to active comparator.

	Acute MI with LV dysfunction and/or congestion	Late post-MI asymptomatic LV dysfunction	Stable HFrEF	HFrEF with FMR
RCT	**PARADISE-MI Echo**	**Docherty et al.**	**EVALUATE-HF**	**PRIME**
N	457	93	464	118
Comparator	Ramipril	Valsartan	Enalapril	Valsartan
Duration	8 months	12 months	3 months	12 months
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^2)	-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^2)	-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^2)	-4.3 (-8.3, -0.3)	-1.5 (-3.5, 0.6)	NA	NA
LAVi (ml/m^2)	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)

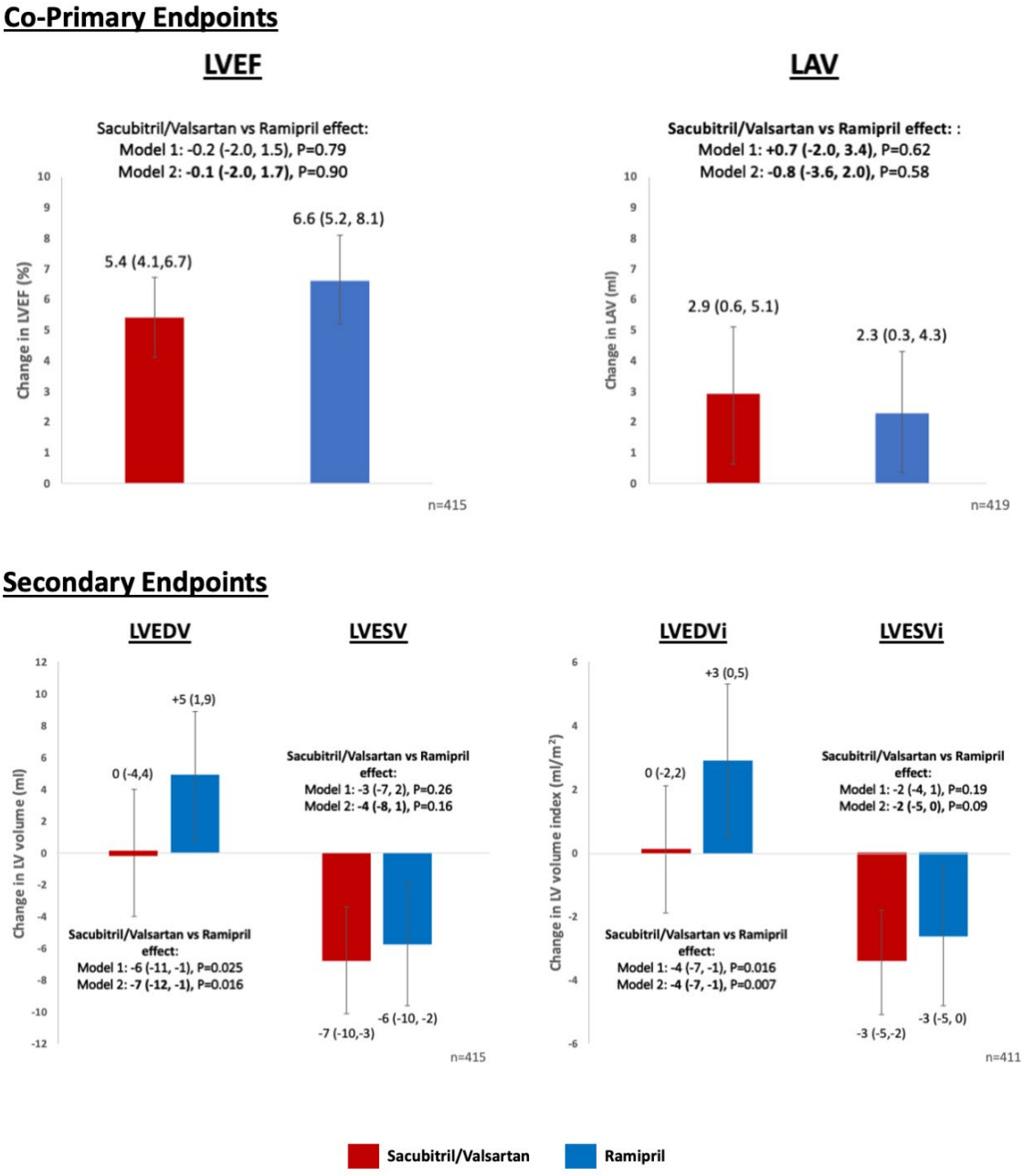
RCT – randomized control trial; LVEF – left ventricular (LV) ejection fraction; LVEDVi – LV end-diastolic volume index; LVESVi – LV end-systolic volume index; LVMi – LV mass index; LAVi – left atrial volume index

Figure 1.



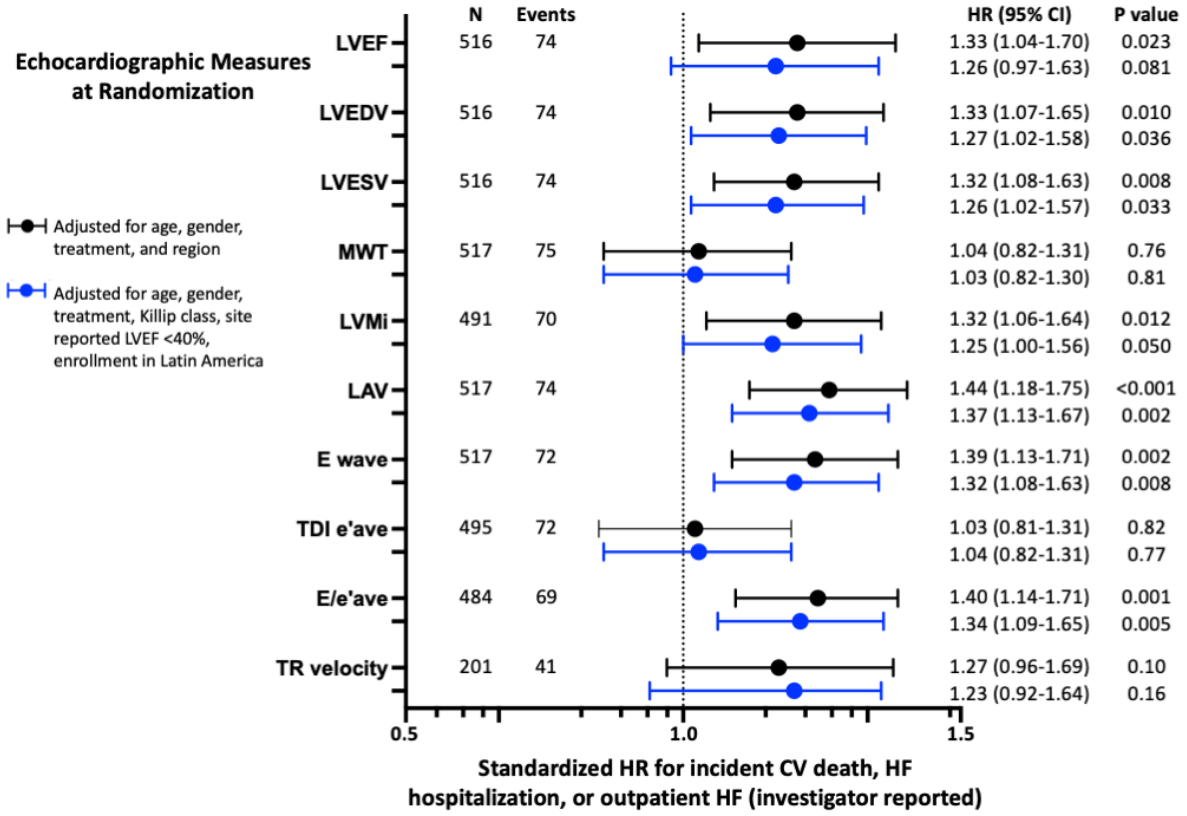
^Wilcoxon rank sum p<0.05 vs ramipril
*death by 300 days post-randomization

Figure 2.



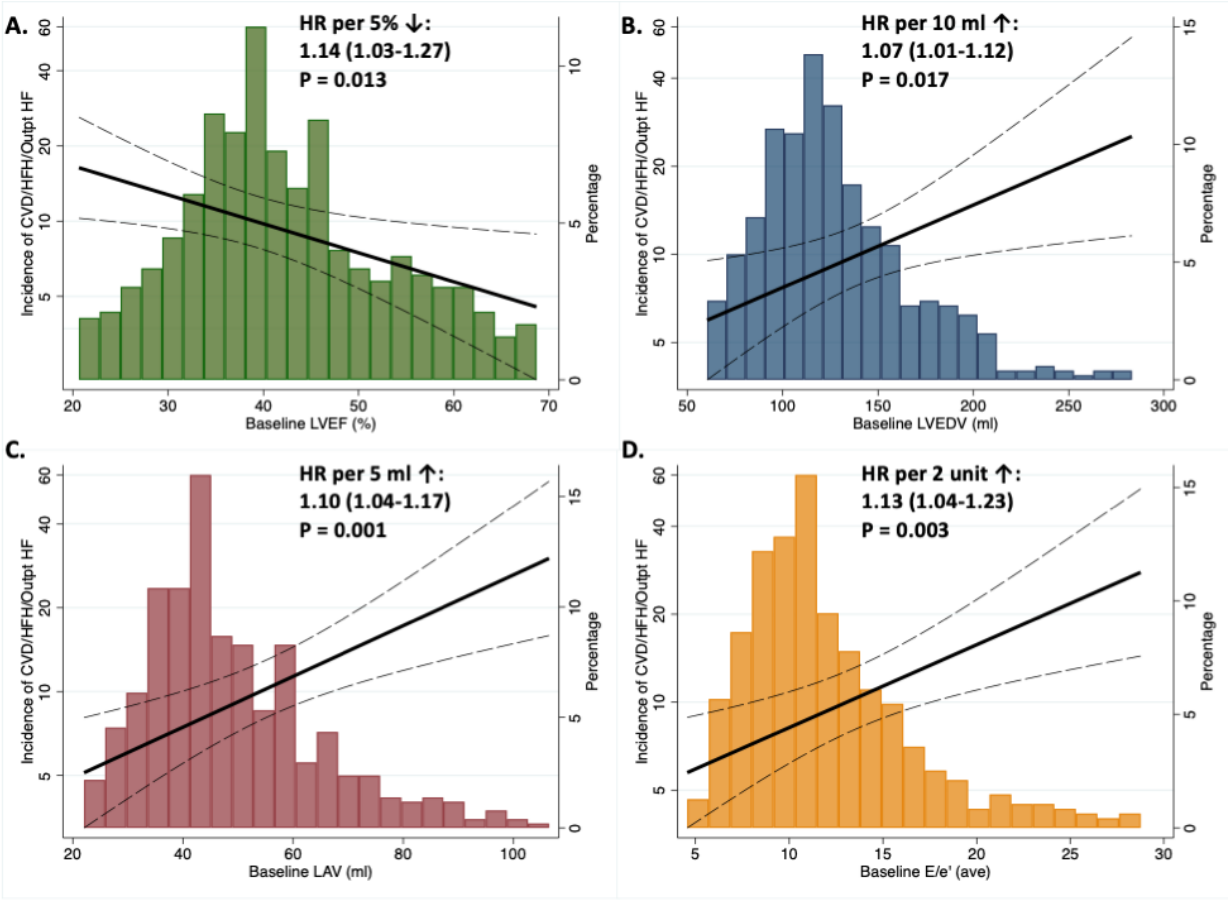
Bar graphs show mean and 95% CI. Model 1 is adjusted for baseline value and region. Model 2 is adjusted for baseline value, region, age, history of prior PCI or CABG, AF, PAD, eGFR, and use of MRA at randomization. LVEF – left ventricular ejection fraction; LAV – left atrial volume; LVEDV – LV end-diastolic volume; LVESV – LV end-systolic volume; LVEDVi – LV end-diastolic volume index; LVESVi – LV end-systolic volume index

Figure 3.



HR are shown per standard deviation of measure to enable comparability between measures, as follows: LVEF – per 11.5% decrease; LVEDV – per 42.8 ml increase; LVESV – per 37.1 ml increase; MWT – per 0.16 cm increase; LVMi – per 24.9 g/m^2 increase; LA volume – per 17.2 ml increase; E wave – per 23.2 cm/s increase; TDI e'$_{ave}$ – per 1.8 cm/s increase; E/e'$_{ave}$ – per 4.9 unit increase; TR velocity – per 0.36 m/s increase

Figure 4.


A.
HR per 5% ↓:
1.14 (1.03-1.27)
P = 0.013
Incidence of CVD/HFH/Outpt HF
Percentage
Baseline LVEF (%)
B.
HR per 10 ml ↑:
1.07 (1.01-1.12)
P = 0.017
Incidence of CVD/HFH/Outpt HF
Percentage
Baseline LVEDV (ml)
C.
HR per 5 ml ↑:
1.10 (1.04-1.17)
P = 0.001
Incidence of CVD/HFH/Outpt HF
Percentage
Baseline LAV (ml)
D.
HR per 2 unit ↑:
1.13 (1.04-1.23)
P = 0.003
Incidence of CVD/HFH/Outpt HF
Percentage
Baseline E/e' (ave)