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

Shah: PARADISE-MI Echo Sub-Study

SUPPLEMENTAL MATERIAL

Table S1. Intra-observer reproducibility metrics for 40 PARADISE-MI Echocardiographic studies randomly selected for remeasurement in a blinded fashion.

	Mean value	**Bias ± SD**	**CV**	**ICC**
LVEF	43.5±10.6%	0.7±4.8%	11.0%	0.90
LAV	53.3±19.0 ml	1.5±4.5 ml	8.4%	0.97
LVEDV	127±30 ml	0±8 ml	6.7%	0.97
LVESV	73±25 ml	1±8 ml	10.8%	0.98
MWT	1.04±0.15 cm	0.05±0.08 cm	8.1%	0.88
LVEDD	5.00±0.76 cm	0.07±0.23 cm	4.5%	0.98
E wave	68±20 cm/s	2±3 cm/s	3.8%	0.99
TDI e'lat	7.4±2.6 cm/s	0.2±0.5 cm/s	7.3%	0.99
TDI e'sept	5.8±1.6 cm/s	0.2±0.5 cm/s	8.5%	0.97
TR velocity	2.49 m/s	0.03±0.11 m/s	4%	0.98

Table S2. Baseline characteristic of Echo sub-study participants overall, and among those with versus without Month 8 (M8) echo data

	Overall (n=544)	With M8 data (n=457)	Without M8 data (n=87)	P value
Demographics				
Age	63.7 ± 11.6	63.4 ± 11.5	65.4 ± 12.3	0.14
Female	142 (26)	111 (24)	31 (36)	0.03
Race group				0.003
Asian	30 (6)	19 (4)	11 (13)	
Black	9 (2)	9 (2)	0 (0)	
White	477 (88)	408 (89)	69 (79)	
Other	28 (5)	21 (5)	7 (8)	
Region				0.06
North America	52 (10)	43 (9)	9 (10)	
Latin America	55 (10)	41 (9)	14 (16)	
Western Europe	215 (40)	190 (42)	25 (29)	
Central Europe	191 (35)	160 (35)	31 (36)	
Asia/Pacific	31 (6)	23 (5)	8 (9)	
Co-Morbidities				
Prior Stroke	31 (6)	19 (4)	12 (14)	<0.001
Prior MI	102 (19)	80 (18)	22 (25)	0.09
Prior PCI	91 (17)	73 (16)	18 (21)	0.28

Prior CABG	29 (5)	24 (5)	5 (6)	0.85
Hypertension	354 (65)	290 (64)	64 (74)	0.07
Hyperlipidemia	309 (57)	263 (58)	46 (55)	0.62
Diabetes	236 (43)	192 (42)	44 (51)	0.14
Current smoker	126 (23)	105 (23)	21 (24)	0.94
Former Smoker	190 (35)	161 (35)	29 (33)	
A Fib	61 (11)	52 (11)	9 (10)	0.78
PAD	28 (5)	21 (5)	7 (8)	0.17
ICD	2 (0)	1 (0)	1 (1)	0.19
COPD	32 (6)	25 (6)	7 (8)	0.32
Cancer	31 (6)	26 (6)	5 (6)	0.95
Depression	40 (7)	32 (7)	8 (9)	0.44
Index MI event				
Time from presentation to randomization	4.1 ± 1.7	4.1 ± 1.7	4.3 ± 1.6	0.32
STEMI	408 (75)	349 (76)	59 (68)	0.09
Anterior	370 (68)	304 (67)	66 (76)	0.09
IV treatment for congestion	284 (52)	230 (50)	54 (62)	0.044
Killip class				0.14
Class I	236 (44)	207 (46)	29 (34)	
Class II	152 (28)	120 (26)	32 (37)	

Class III	125 (23)	104 (23)	21 (24)	
Class IV	27 (5)	23 (5)	4 (5)	
Revascularization				
Thrombolytics	8 (2)	8 (2)	0 (0)	0.22
Stent	489 (90)	414 (91)	75 (86)	0.21
Physical Exam				
HR	77 ± 11	77 ± 11	79 ± 13	0.11
SBP	119 ± 13	118 ± 13	122 ± 16	0.014
DBP	73 ± 10	73 ± 10	73 ± 12	0.91
BMI	28.8 ± 5.1	29.0 ± 5.2	27.9 ± 5.0	0.07
eGFR	71 ± 23	72 ± 23	66 ± 21	0.03
Medications				
DAPT	499 (92%)	418 (92%)	81 (93%)	0.61
Beta Blocker	459 (84%)	388 (85%)	71 (82%)	0.44
MRA	263 (48%)	217 (48%)	46 (53%)	0.36
Diuretics	258 (47%)	217 (48%)	41 (47%)	0.95
Statin	515 (95%)	432 (95%)	83 (95%)	0.74
Prior ACEi/ARB	460 (85%)	386 (85%)	74 (85%)	0.89

Table S3. Baseline echocardiographic measures of Echo sub-study participants overall, and among those with versus without Month 8 (M8) echo data

	N	Overall (n=544)	With M8 data (n=457)	Without M8 data (n=87)	P value
LV structure & systolic function					
LVEF (%)	516	42.4 ± 11.5	41.8 ± 10.8	45.3 ± 14.5	0.011
LVEDV (ml)	516	128.4 ± 42.8	129.7 ± 42.5	121.6 ± 43.7	0.12
LVEDVi (ml/m2)	513	65.6 ± 20.1	65.6 ± 20.1	65.5 ± 20.2	0.94
LVESV (ml)	516	76.7 ± 37.1	77.9 ± 36.7	70.2 ± 38.8	0.08
LVESVi (ml/m2)	513	39.2 ± 18.5	39.4 ± 18.3	37.7 ± 19.7	0.44
MWT (cm)	517	1.07 ± 0.16	1.07 ± 0.16	1.10 ± 0.19	0.08
LV mass (g)	493	193.6 ± 54.3	193.3 ± 54.8	195.3 ± 52.2	0.77
LVMi (g/m2)	491	99.0 ± 24.9	98.0 ± 25.1	104.5 ± 22.7	0.04
LA size					
LA volume (ml)	517	49.4 ± 17.2	50.0 ± 17.5	45.7 ± 15.2	0.034
LAVi (ml/m2)	510	25.1 ± 9.3	25.1 ± 9.3	24.8 ± 9.1	0.79
LA width (cm)	508	3.69 ± 0.57	3.68 ± 0.57	3.73 ± 0.58	0.47
Diastolic measures					
E wave (cm/s)	517	69.4 ± 23.2	69.3 ± 23.3	70.0 ± 23.2	0.81
TDI e'$_{lat}$ (cm/s)	504	6.8 ± 2.4	6.9 ± 2.3	6.3 ± 2.5	0.04
E/e'$_{lat}$	493	11.3 ± 5.0	11.0 ± 4.8	12.7 ± 6.0	0.01

TDI e'$_{sept}$ (cm/s)	510	5.4 ± 1.7	5.5 ± 1.7	4.9 ± 1.6	0.002
E/e'$_{sept}$	497	13.8 ± 5.9	13.4 ± 5.4	16.1 ± 7.6	<0.001
TDI e'$_{ave}$ (cm/s)	495	6.1 ± 1.8	6.2 ± 1.8	5.6 ± 1.8	0.01
E/e'$_{ave}$	484	12.1 ± 4.9	11.8 ± 4.5	13.9 ± 6.2	<0.001
TR velocity (m/s)	201	2.58 ± 0.37	2.58 ± 0.36	2.59 ± 0.38	0.84

Table S4. Baseline characteristic of Echo sub-study participants overall, and by randomized treatment allocation among 457 participants with matched baseline and Month 8 echocardiograms

	Overall (n=457)	Ramipril (n=229)	Sac/Val (n=228)	P value
Demographics				
Age	63.4 ± 11.5	62.1 ± 11.3	64.6 ± 11.6	0.02
Female	111 (24)	51 (22)	60 (26)	0.31
Race group				0.71
Asian	19 (4)	9 (4)	10 (4)	
Black	9 (2)	4 (2)	5 (2)	
White	408 (89)	203 (89)	205 (90)	
Other	21 (5)	13 (6)	8 (4)	
Region				0.83
North America	43 (9)	20 (9)	23 (10)	
Latin America	41 (9)	23 (10)	18 (8)	
Western Europe	190 (42)	98 (43)	92 (40)	
Central Europe	160 (35)	78 (34)	82 (36)	
Asia/Pacific	23 (5)	10 (4)	13 (6)	
Co-Morbidities				
Prior Stroke	19 (4)	10 (4)	9 (4)	0.82
Prior MI	80 (18)	37 (16)	43 (19)	0.45
Prior PCI	73 (16)	30 (13)	43 (19)	0.09

Prior CABG	24 (5)	7 (3)	17 (8)	0.04
Hypertension	290 (64)	139 (61)	151 (66)	0.22
Hyperlipidemia	263 (58)	130 (57)	133 (58)	0.78
Diabetes	192 (42)	92 (40)	100 (44)	0.42
Current smoker	105 (23)	50 (22)	55 (24)	0.13
Former Smoker	161 (35)	91 (40)	70 (31)	
A Fib	52 (11)	18 (8)	34 (15)	0.02
PAD	21 (5)	5 (2)	16 (7)	0.014
ICD	1 (0)	1 (0)	1 (0)	0.32
COPD	25 (6)	13 (6)	12 (5)	0.84
Cancer	26 (6)	12 (5)	14 (6)	0.69
Depression	32 (7)	14 (6)	18 (8)	0.46
Index MI event				
Time from presentation to randomization	4.1 ± 1.7	4.0 ± 1.8	4.2 ± 1.7	0.12
STEMI	349 (76)	173 (76)	176 (77)	0.68
Anterior	304 (67)	152 (66)	152 (67)	0.95
IV treatment for congestion	230 (50)	121 (53)	109 (48)	0.28
Killip class				0.66
Class I	207 (46)	102 (45)	105 (46)	
Class II	120 (26)	62 (27)	58 (26)	

Class III	104 (23)	49 (22)	55 (24)	
Class IV	23 (5)	14 (6)	9 (4)	
Revascularization				
Thrombolytics	8 (2)	4 (2)	4 (2)	0.98
Stent	414 (91)	210 (92)	204 (90)	0.41
Physical Exam				
HR	77 ± 11	77 ± 10	76 ± 12	0.34
SBP	118 ± 13	118 ± 13	119 ± 13	0.75
DBP	73 ± 10	73 ± 9	72 ± 10	0.62
BMI	29.0 ± 5.2	28.9 ± 5.2	29.0 ± 5.2	0.80
eGFR	72 ± 23	74 ± 26	69 ± 20	0.03
Medications				
DAPT	418 (92%)	212 (93%)	206 (90%)	0.39
Beta Blocker	388 (85%)	195 (85%)	193 (85%)	0.88
MRA	217 (48%)	119 (52%)	98 (43%)	0.05
Diuretics	217 (48%)	110 (48%)	107 (47%)	0.81
Statin	432 (95%)	216 (94%)	216 (95%)	0.85
Prior ACEi/ARB	386 (85%)	192 (84%)	194 (85%)	0.71

Table S5. Baseline echocardiographic measures of Echo sub-study participants overall, and by randomized treatment arm restricted to 457 participants with matched baseline and Month 8 echocardiograms

	N	Overall (n=457)	Ramipril (n=229)	Sac/Val (n=228)	P value
LV structure & systolic function					
LVEF (%)	434	41.8 ± 10.8	40.7 ± 10.8	43.0 ± 10.7	0.023
LVEDV (ml)	434	129.7 ± 42.5	132.8 ± 45.5	126.5 ± 39.1	0.13
LVEDVi (ml/m2)	432	65.6 ± 20.1	67.1 ± 22.0	64.1 ± 17.8	0.13
LVESV (ml)	434	77.9 ± 36.7	81.5 ± 39.5	74.3 ± 33.3	0.041
LVESVi (ml/m2)	432	39.4 ± 18.3	41.2 ± 20.1	37.6 ± 16.0	0.041
MWT (cm)	434	1.07 ± 0.16	1.06 ± 0.15	1.07 ± 0.16	0.41
LV mass (g)	416	193.3 ± 54.8	197.9 ± 54.0	188.7 ± 55.3	0.09
LVMi (g/m2)	415	98.0 ± 25.1	99.7 ± 24.8	96.3 ± 25.4	0.17
LA size					
LA volume (ml)	435	50.0 ± 17.5	49.9 ± 16.2	50.2 ± 18.8	0.81
LAVi (ml/m2)	429	25.1 ± 9.3	24.9 ± 8.6	25.4 ± 10.0	0.59
LA width (cm)	428	3.68 ± 0.57	3.69 ± 0.55	3.68 ± 0.59	0.78
Diastolic measures					
E wave (cm/s)	435	69.3 ± 23.3	70.6 ± 22.9	68.1 ± 23.7	0.27
TDI e' lat (cm/s)	422	6.9 ± 2.3	7.0 ± 2.4	6.7 ± 2.3	0.23

E/e' lat	414	11.0 ± 4.8	11.0 ± 4.8	11.1 ± 4.8	0.84
TDI e' septal (cm/s)	430	5.5 ± 1.7	5.6 ± 1.7	5.5 ± 1.7	0.43
E/e' septal	420	13.4 ± 5.4	13.5 ± 5.8	13.2 ± 5.0	0.57
TDI e' ave (cm/s)	417	6.2 ± 1.8	6.3 ± 1.8	6.1 ± 1.7	0.22
E/e' ave	409	11.8 ± 4.5	11.8 ± 4.7	11.7 ± 4.3	0.90
TR velocity (m/s)	169	2.58 ± 0.36	2.58 ± 0.34	2.57 ± 0.38	0.88

Table S6. Cardiovascular medication use at Month 8 by treatment arm.

	Sacubitril/valsartan	Ramipril	P value
Beta blocker	86%	89%	0.40
MRA	49%	54%	0.35
Diuretics	41%	48%	0.19
Statin	93%	93%	0.72

Table S7. Changes in echocardiographic measures from baseline to Month 8 by randomized treatment assignment. 'Adj Delta' is the within treatment arm change from baseline to Month 8 adjusted for the relevant model covariates.

Measure	Arm	N	Baseline	Month 8	Delta	Model 1 Adj Delta	Model 2 Adj Delta
LVEF	**Ramipril**	**209**	**40.6±10.8**	**47.2±11.2**	**6.6±10.7**	**6.1±0.6**	**6.1±0.6**
N=415	**Sac/val**	**206**	**43.0±10.8**	**48.4±11.2**	**5.4±9.5**	**5.9±0.6**	**6.0±0.7**
LVEDV	Ramipril	209	132±45	137±47	5±30	5.5±1.9	5.6±1.9
N=415	Sac/val	206	127±39	127±35	0±29	-0.6±1.9	-1.2±2.0
LVEDVi	Ramipril	206	67.2±22.1	70.1±23.7	2.9±17.5	3.3±1.0	3.4±1.1
N=411	Sac/val	205	64.2±18.0	64.3±16.0	0.1±14.8	-0.3±1.0	-0.7±1.1
LVESV	Ramipril	209	81±39	75±41	-6±28	-4.9±1.7	-4.7±1.7
N=415	Sac/val	206	74±34	68±30	-7±24	-7.6±1.7	-8.2±1.7
LVESVi	Ramipril	206	41.3±20.3	38.7±21.8	-2.6±16.0	-2.2±0.9	-2.0±0.9
N=411	Sac/val	205	37.7±16.2	34.2±14.3	-3.4±12.1	-3.9±0.9	-4.3±0.9
LVEDD	Ramipril	209	4.95±0.73	5.07±0.70	0.12±0.59	0.15±0.04	0.15±0.04
N=403	Sac/val	194	4.79±0.59	4.91±0.63	0.13±0.54	0.09±0.04	0.09±0.04

MWT N=415	Ramipril	211	1.06±0.15	0.98±0.16	-0.08±0.17	-0.09±0.01	-0.08±0.01
	Sac/val	204	1.08±0.16	0.97±0.16	-0.10±0.16	-0.10±0.01	-0.10±0.01
LV mass N=383	Ramipril	195	195±53	183±55	-12±44	-11±3	-10±3
	Sac/val	188	190±55	172±52	-18±40	-19±3	-19±3
LVMi N=380	Ramipril	193	98.9±24.8	93.3±26.2	-5.6±23.4	-5.1±1.4	-4.4±1.5
	Sac/val	187	96.5±25.4	87.6±23.5	-8.9±20.3	-9.4±1.5	-9.9±1.5
LAV **N=419**	**Ramipril**	**213**	**49.8±16.2**	**52.1±17.2**	**2.3±14.7**	**2.3±1.0**	**2.9±1.0**
	Sac/val	**206**	**50.1±18.8**	**53.0±19.1**	**2.9±16.3**	**3.0±1.0**	**2.1±1.0**
LAVi N=408	Ramipril	206	24.8±8.7	26.5±9.6	1.6±9.0	1.5±0.6	2.0±0.6
	Sac/val	202	25.3±10.0	26.8±10.3	1.6±9.4	1.7±0.6	1.1±0.6
LAD N=399	Ramipril	206	3.69±0.55	3.70±0.52	0.01±0.51	0.01±0.03	0.02±0.03
	Sac/val	193	3.70±0.59	3.73±0.58	0.03±0.50	0.04±0.03	0.03±0.03
E wave N=421	Ramipril	215	71±23	70±21	0±23	0±1.3	1±1.3
	Sac/val	206	68±24	70±23	2±23	1±1.4	1±1.4
TDI e'$_{lat}$ N=405	Ramipril	203	7.0±2.4	7.7±2.3	0.7±2.7	0.7±0.2	0.7±0.2
	Sac/val	202	6.8±2.3	8.2±2.9	1.5±2.6	1.4±0.2	1.5±0.2

E/e'$_{lat}$	Ramipril	198	10.7±4.4	9.7±3.8	-1.0±4.4	-1.1±0.2	-1.0±0.2
N=390	Sac/val	192	11.0±4.8	9.1±3.8	-1.9±4.6	-1.8±0.2	-2.0±0.2
TDI e'$_{sep}$	Ramipril	204	5.6±1.7	5.9±1.7	0.3±1.7	0.4±0.1	0.3±0.1
N=411	Sac/val	207	5.5±1.7	6.0±1.9	0.5±1.9	0.5±0.1	0.5±0.1
E/e'$_{sept}$	Ramipril	198	13.5±5.8	12.5±5.4	-1.0±5.8	-0.9±0.3	-0.8±0.3
N=394	Sac/val	196	13.2±5.0	12.6±5.6	-0.7±5.4	-0.7±0.3	-0.9±0.3
TDI e'$_{ave}$	Ramipril	196	6.3±1.8	6.8±1.8	0.5±1.9	0.6±0.1	0.5±0.1
N=396	Sac/val	200	6.1±1.7	7.1±2.1	1.0±1.9	1.0±0.1	1.0±0.1
E/e'$_{ave}$	Ramipril	191	11.6±4.5	10.6±3.8	-1.0±4.3	-1.1±0.2	-1.0±0.2
N=382	Sac/val	191	11.7±4.3	10.3±3.9	-1.4±4.1	-1.4±0.2	-1.6±0.2
TRV	Ramipril	50	2.54±0.31	2.62±0.50	0.08±0.56	0.08±0.06	0.10±0.06
N=98	Sac/val	48	2.54±0.41	2.43±0.37	-0.11±0.30	-0.11±0.06	-0.13±0.06

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 S8. Changes in echocardiographic measures from baseline to Month 8 by randomized treatment assignment using MICE to account for variable missing data (total n=457; Ramipril n=229, sac/val n=228)

Measure	Arm	Baseline	Month 8	Delta	Model 1		Model 2	
					Treatment effect	P value	Treatment effect	P value
LVEF	Ramapiril	40.6 ± 0.7	47.2 ± 0.8	6.6 ± 0.7	-0.05 [-1.83 – 1.73]	0.96	-0.01 [-1.84 – 1.82]	0.99
	Sac/val	43.0 ± 0.8	48.6 ± 0.8	5.6 ± 0.7				
LVEDV	Ramapiril	133 ± 3	138 ± 3	4 ± 2	-6 [-11 - 0]	0.046	-6 [-12 - -1]	0.031
	Sac/val	126 ± 3	127 ± 2	1 ± 2				
LVEDVi	Ramapiril	67.1 ± 1.5	69.7 ± 1.6	2.5 ± 1.2	-3.1 [-6.0 - -0.1]	0.041	-3.6 [-6.6 - -0.6]	0.018
	Sac/val	63.9 ± 1.2	64.4 ± 1.1	0.4 ± 1.1				
LVESV	Ramapiril	82 ± 3	76 ± 3	-6 ± 2	-3 [-8 – 2]	0.25	-4 [-9 – 1]	0.16
	Sac/val	74 ± 2	67 ± 2	-7 ± 2				
LVESVi	Ramapiril	41.2 ± 1.3	38.4 ± 1.4	-2.8 ± 1.1	-1.6 [-4.2 – 1.0]	0.22	-2.2 [-4.8 – 0.5]	0.11
	Sac/val	37.5 ± 1.1	34.1 ± 1.0	-3.4 ± 0.9				

LVEDD	Ramapiril	4.96 ± 0.05	5.07 ± 0.05	0.10 ± 0.04	-0.06 [-0.16 – 0.04]	0.23	-0.06 [-0.16 – 0.04]	0.23
	Sac/val	4.80 ± 0.04	4.91 ± 0.04	0.11 ± 0.04				
MWT	Ramapiril	1.06 ± 0.01	0.98 ± 0.01	-0.08 ± 0.01	-0.01 [-0.04 – 0.02]	0.42	-0.02 [-0.05 – 0.01]	0.24
	Sac/val	1.08 ± 0.01	0.98 ± 0.01	-0.10 ± 0.01				
LV mass	Ramapiril	198 ± 4	185 ± 4	-13 ± 3	-7 [-15 – 1]	0.085	-9 [-17 - 0]	0.041
	Sac/val	191 ± 4	174 ± 4	-18 ± 3				
LVMi	Ramapiril	99.9 ± 1.7	93.7 ± 1.8	-6.2 ± 1.7	-3.9 [-8.0 – 0.1]	0.058	-5.0 [-9.2 - -0.9]	0.018
	Sac/val	97.2 ± 1.7	88.3 ± 1.7	-8.9 ± 1.6				
LAV	**Ramapiril**	49.7 ± 1.1	52.0 ± 1.2	2.3 ± 1.0	1.0 [-1.7 – 3.7]	0.46	-0.4 [-3.2 – 2.4]	0.78
	Sac/val	49.9 ± 1.3	53.1 ± 1.3	3.2 ± 1.1				
LAVi	Ramapiril	24.7 ± 0.6	26.3 ± 0.7	1.6 ± 0.6	0.3 [-1.3 – 1.9]	0.32	-0.7 [-2.3 – 1.0]	0.43
	Sac/val	25.2 ± 0.7	26.8 ± 0.7	1.7 ± 0.7				
LAD	Ramapiril	3.70 ± 0.04	3.70 ± 0.04	0.00 ± 0.03	0.03 [-0.06 – 0.12]	0.54	0.01 [-0.08 – 0.09]	0.90
	Sac/val	3.67 ± 0.04	3.71 ± 0.04	0.03 ± 0.04				
E wave	Ramapiril	70 ± 2	70 ± 1	-1 ± 2	1 [-3 – 5]	0.68	0 [-4 – 3]	0.85

	Sac/val	68 ± 2	69 ± 2	2 ± 2				
TDI e'$_{lat}$	Ramapiril	6.9 ± 0.2	7.6 ± 0.2	0.6 ± 0.2	0.7 [0.3 – 1.2]	0.002	0.8 [0.4 – 1.3]	0.001
	Sac/val	6.7 ± 0.2	8.2 ± 0.2	1.5 ± 0.2				
E/e'$_{lat}$	Ramapiril	11.1 ± 0.3	9.9 ± 0.3	-1.2 ± 0.3	-0.6 [-1.3 – 0.1]	0.09	-0.9 [-1.6 - -0.2]	0.013
	Sac/val	11.0 ± 0.3	9.3 ± 0.3	-1.7 ± 0.3				
TDI e'$_{sept}$	Ramapiril	5.5 ± 0.1	5.9 ± 0.1	0.3 ± 0.1	0.2 [-0.1 – 0.5]	0.29	0.2 [-0.1 – 0.5]	0.12
	Sac/val	5.4 ± 0.1	6.0 ± 0.1	0.6 ± 0.1				
E/e'$_{sept}$	Ramapiril	13.6 ± 0.4	12.8 ± 0.4	-0.9 ± 0.4	0.0 [-0.9 – 0.9]	0.98	-0.3 [-1.3 – 0.6]	0.47
	Sac/val	13.1 ± 0.3	12.5 ± 0.4	-0.7 ± 0.4				
TDI e'$_{ave}$	Ramapiril	6.3 ± 0.1	6.8 ± 0.1	0.5 ± 0.1	0.4 [0.1 – 0.7]	0.022	0.5 [0.1 – 0.8]	0.006
	Sac/val	6.1 ± 0.1	7.1 ± 0.2	1.0 ± 0.1				
E/e'$_{ave}$	Ramapiril	11.6 ± 0.3	10.6 ± 0.3	-1.0 ± 0.3	-0.3 [-1.0 – 0.3]	0.33	-0.6 [-1.3 – 0.1]	0.073
	Sac/val	11.7 ± 0.3	10.3 ± 0.3	-1.4 ± 0.3				
TRV	Ramapiril	2.47 ± 0.05	2.51 ± 0.06	0.04 ± 0.07	-0.11 [-0.28 – 0.05]	0.17	-0.14 [-0.30 -0.04]	0.12
	Sac/val	2.49 ± 0.06	2.39 ± 0.05	-0.09 ± 0.07				

Baseline, Month 8, and change values are shown as mean and standard error. 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 S9. Changes in echocardiographic measures from baseline to Month 8 associated with randomization to sac/val compared to Ramipril using IPAW to account for missing follow-up echo data in a subset of enrolled participants.

Measure	Model 1		Model 2	
	Treatment effect	P value	Treatment effect	P value
LV structure and systolic function				
LVEF (%)	-0.31 [-2.06 – 1.45]	0.73	-0.14 [-1.95 – 1.68]	0.88
LVEDV (ml)	-6 [-11 –0]	0.038	-7 [-12 – -1]	0.024
LVEDVi (ml/m^2)	-3.2 [-6.1 – -0.3]	0.031	-3.9 [-7.0 – -0.8]	0.015
LVESV (ml)	-3 [-7 – 2]	0.27	-3.5 [-8.4 – 1.5]	0.17
LVESVi (ml/m^2)	-1.5 [-4.0 – 0.9]	0.21	-2.2 [-4.9 – 0.5]	0.11
LVEDD (cm)	-0.06 [-0.16 – 0.04]	0.23	-0.07 [-0.17 – 0.04]	0.22
MWT (cm)	-0.01 [-0.04 – 0.02]	0.46	-0.02 [-0.04 – 0.01]	0.27
LV mass (g)	-8 [-16 – 0]	0.053	-9 [-18 – -1]	0.022
LVMi (g/m^2)	-4.3 [-8.3 – -0.2]	0.038	-5.6 [-9.7 – -1.5]	0.008

LA size				
LAV (ml)	1.0 [-1.8 – 3.8]	0.50	-0.5 [-3.4 – 2.5]	0.76
LAVi (ml/m^2)	0.2 [-1.4 – 1.8]	0.79	-0.8 [-2.5 – 0.9]	0.35
LAD (cm)	0.03 [-0.06 – 0.12]	0.50	0.01 [-0.08 – 0.09]	0.84
LV Diastolic function				
E wave (cm/s)	2 [-2 – 6]	0.36	0 [-3 – 4]	0.82
TDI e'$_{lat}$ (cm/s)	0.7 [0.2 – 1.2]	0.003	0.8 [0.3 – 1.2]	0.002
E/e'$_{lat}$	-0.7 [-1.4 – 0.0]	0.055	-0.8 [-1.5 – -0.2]	0.015
TDI e'$_{sept}$ (cm/s)	0.1 [-0.2 – 0.5]	0.33	0.2 [-0.1 – 0.5]	0.17
E/e'$_{sept}$	0.2 [-0.7 –1.2]	0.60	-0.1 [-1.0 – 0.9]	0.86
TDI e'$_{ave}$ (cm/s)	0.4 [0.1 – 0.7]	0.013	0.5 [0.1 – 0.8]	0.006
E/e'$_{ave}$	-0.3 [-1.0 – 0.4]	0.37	-0.5 [-1.2 – 0.1]	0.11
TR Velocity (cm/sec)	-0.22 [-0.37 – -0.07]	0.005	-0.25 [-0.43 – -0.08]	0.006

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 S10. Changes in echocardiographic measures from baseline to Month 8 by randomized treatment assignment using a linear mixed-effect model.

Measure	Model 1		Model 2	
	Treatment effect	**P value**	**Treatment effect**	**P value**
LV Structure and Function				
LVEF, N=415				
LVEDV, N=415	-6 (-11, -1)	0.025	-7 (-12, -1)	0.014
LVEDVi, N=411	-3.5 (-6.4, -0.7)	0.016	-4.1 (-7.0, -1.2)	0.006
LVESV, N=415	-3 (-7, 2)	0.25	-3 (-8, 1)	0.16
LVESVi, N=411	-1.7 (-4.3, 0.8)	0.18	-2.3 (-4.9, 0.3)	0.08
LVEDD, N=403	-0.05 (-0.15, 0.05)	0.29	-0.05 (-0.15, 0.05)	0.33
MWT, N=415	-0.01 (-0.04, 0.02)	0.50	-0.02 (-0.04, 0.01)	0.27
LV mass, N=383	-8 (-15, 0)	0.049	-9 (-17, -1)	0.022
LVMi, N=380	-4.3 (-8.2, -0.4)	0.033	-5.5 (-9.5, -1.5)	0.007
LA Size				
LAV, N=419	**0.7 (-2.0, 3.4)**	**0.62**	**-0.7 (-3.5, 2.0)**	**0.60**

LAVi, N=408	0.1 (-1.5, 1.7)	0.90	-0.9 (-2.5, 0.7)	0.28
LAD, N=399	0.03 (-0.06, 0.11)	0.55	0.01 (-0.08, 0.09)	0.87
LV Diastolic Doppler-based indices				
E wave, N=421	1 (-3, 5)	0.61	-1 (-4, 3)	0.78
TDI e'$_{lat}$, N=405	0.7 (0.2, 1.2)	0.003	0.8 (0.3, 1.2)	0.001
E/e'$_{lat}$, N=390	-0.7 (-1.4, 0.0)	0.037	-0.9 (-1.6, -0.3)	0.007
TDI e'$_{sep}$, N=411	0.1 (-0.2, 0.4)	0.36	0.2 (-0.1, 0.5)	0.13
E/e'$_{sept}$, N=394	0.2 (-0.8, 1.1)	0.71	-0.2 (-1.1, 0.8)	0.72
TDI e'$_{ave}$, N=396	0.4 (0.1, 0.8)	0.018	0.5 (0.2, 0.8)	0.003
E/e'$_{ave}$, N=382	-0.4 (-1.0, 0.3)	0.28	-0.6 (-1.3, 0.0)	0.059
TRV, N=98	-0.18 (-0.34, -0.03)	0.021	-0.20 (-0.36, -0.05)	0.011

Model 1 – adjusted for baseline value and incorporating site as a random effect

Model 2 – adjusted for baseline value, age, history of prior PCI or CABG, AF, PAD, eGFR, and use of MRA at randomization, and incorporating site as a random effect

Table S11. Standardized Hazard Ratios demonstrating the association of baseline measures of cardiac structure and function with incidence of the composite of investigator-reported CV death, HF hospitalization, or outpatient HF.

	N	Events	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value
LV structure & systolic function						
LVEF (per 11.5%)	516	74	1.33 (1.04 – 1.70)	0.023	1.26 (0.97 – 1.63)	0.081
LVEDV (per 42.8 ml)	516	74	1.33 (1.07 – 1.65)	0.010	1.27 (1.02 – 1.58)	0.036
LVEDVi (per 20.1 ml/m2)	513	73	1.26 (1.04 – 1.53)	0.018	1.20 (0.98 – 1.47)	0.072
LVESV (per 37.1 ml)	516	74	1.32 (1.08 – 1.63)	0.008	1.26 (1.02 – 1.57)	0.033
LVESVi (per 18.5 ml/m2)	513	73	1.28 (1.06 – 1.55)	0.011	1.22 (1.00 – 1.50)	0.05
MWT (per 0.16 cm)	517	75	1.04 (0.82 – 1.31)	0.76	1.03 (0.82 – 1.30)	0.81
LV mass (per 54.3 g)	493	70	1.33 (1.05 – 1.67)	0.017	1.26 (0.99 – 1.59)	0.059
LVMi (per 24.9 g/m2)	491	70	1.32 (1.06 – 1.64)	0.012	1.25 (1.00 – 1.56)	0.05
LA size						
LA volume (per 17.2 ml)	517	74	1.44 (1.18 – 1.75)	<0.001	1.37 (1.13 – 1.67)	0.002

LAVi (per 9.3 ml/m2)	510	72	1.42 (1.16 – 1.73)	0.001	1.35 (1.11 – 1.64)	0.003
LA width (per 0.57 cm)	508	74	1.62 (1.30 – 2.02)	<0.001	1.56 (1.25 – 1.94)	<0.001
Diastolic measures						
E wave (per 23.2 cm/s)	517	72	1.39 (1.13 – 1.71)	0.002	1.32 (1.08 – 1.63)	0.008
TDI e'$_{lat}$ (per 2.4 cm/s)	504	73	0.99 (0.79 - 1.25)	0.94	1.01 (0.80 - 1.26)	0.96
E/e'$_{lat}$ (per 5 units)	493	70	1.32 (1.07 - 1.62)	0.009	1.27 (1.03-1.57)	0.023
TDI e'$_{septal}$ (per 1.7 cm/s)	510	73	1.10 (0.85 – 1.43)	0.047	1.09 (0.84 – 1.40)	0.51
E/e'$_{septal}$ (per 5.9 units)	497	70	1.45 (1.20 – 1.75)	<0.001	1.39 (1.14 – 1.68)	0.001
TDI e'$_{ave}$ (per 1.8cm/s)	495	72	1.03 (0.81 – 1.31)	0.82	1.04 (0.82 – 1.31)	0.77
E/e'$_{ave}$ (per 4.9 units)	484	69	1.40 (1.14 – 1.71)	0.001	1.34 (1.09 – 1.65)	0.005
TR velocity (per 0.36 m/s)	201	41	1.27 (0.96 – 1.69)	0.10	1.23 (0.92 – 1.64)	0.16

All HRs are displayed per 1-standard deviation of the echo measure baseline distribution, as specified above

Model 1: adjusted for age, gender, randomized treatment assignment, and region

Model 2: adjusted for age, gender, randomized treatment assignment, Killip class, LVEF <40% per site investigator, and enrollment in Latin America

Table S12. Standardized Hazard Ratios demonstrating the association of baseline measures of cardiac structure and function with incidence of the composite of CEC adjudicated CV death, HF hospitalization, or outpatient HF.

			Model 1		Model 2	
	N	Events	HR (95% CI)	P value	HR (95% CI)	P value
LV structure & systolic function						
LVEF (per 11.5%)	516	48	1.53 (1.12 – 2.09)	0.007	1.41 (1.01 – 1.96)	0.042
LVEDV (per 42.8 ml)	512	48	1.45 (1.11 – 1.89)	0.006	1.36 (1.03 – 1.78)	0.029
LVEDVi (per 20.1 ml/m2)	513	47	1.41 (1.12 – 1.77)	0.003	1.32 (1.04 – 1.68)	0.021
LVESV (per 37.1 ml)	516	48	1.46 (1.14 – 1.87)	0.003	1.37 (1.05 – 1.78)	0.020
LVESVi (per 18.5 ml/m2)	513	47	1.43 (1.14 – 1.79)	0.002	1.35 (1.06 – 1.71)	0.014
MWT (per 0.16 cm)	517	50	0.87 (0.65 – 1.17)	0.35	0.87 (0.65 – 1.16)	0.35
LV mass (per 54.3 g)	493	45	1.23 (0.90 – 1.66)	0.19	1.12 (0.82 – 1.52)	0.48
LVMi (per 24.9 g/m2)	491	45	1.29 (0.98 – 1.69)	0.08	1.17 (0.88 – 1.54)	0.28
LA size						
LA volume (per 17.2 ml)	517	48	1.37 (1.07 – 1.77)	0.013	1.29 (1.01 – 1.66)	0.05
LAVi (per 9.3 ml/m2)	510	46	1.36 (1.06 – 1.75)	0.015	1.29 (1.00 – 1.65)	0.05

LA width (per 0.57 cm)	508	48	1.79 (1.37 – 2.35)	<0.001	1.70 (1.28 – 2.23)	<0.001
Diastolic measures						
E wave (per 23.2 cm/s)	517	48	1.29 (1.01 – 1.66)	0.044	1.21 (0.94 – 1.56)	0.13
TDI e'$_{lat}$ (per 2.4 cm/s)	504	47	1.11 (0.82-1.50)	0.51	1.13 (0.84 – 1.51)	0.43
E/e'$_{lat}$ (per 5 units)	493	46	1.44 (1.13-1.84)	0.003	1.39 (1.08 - 1.77)	0.010
TDI e'$_{septal}$ (per 1.7 cm/s)	507	46	1.48 (1.04 – 2.10)	0.03	1.44 (1.02 – 2.03)	0.04
E/e'$_{septal}$ (per 5.9 units)	497	45	1.55 (1.25 – 1.93)	<0.001	1.49 (1.19 – 1.86)	0.001
TDI e'$_{ave}$ (per 1.8cm/s)	495	45	1.23 (0.89 – 1.69)	0.21	1.21 (0.90 – 1.66)	0.21
E/e'$_{ave}$ (per 4.9 units)	484	44	1.51 (1.19 – 1.92)	0.001	1.43 (1.12 – 1.83)	0.004
TR velocity (per 0.36 m/s)	201	25	1.20 (0.83 – 1.73)	0.32	1.12 (0.76 – 1.63)	0.57

All HRs are displayed per 1-standard deviation of the echo measure baseline distribution, as specified above

Model 1: adjusted for age, gender, randomized treatment assignment, and region

Model 2: adjusted for age, gender, randomized treatment assignment, Killip class, LVEF <40% per site investigator, and enrollment in Latin America

Table S13. Standardized hazard ratios demonstrating the association of baseline measures of cardiac structure and function with incidence of the composite of investigator-reported CV death, HF hospitalization, or outpatient HF using mixed-effect model accounting for Site as a random effect.

Echo Measures at Randomization	Model 1		Model 2	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
LVEF	1.35 (1.05-1.73)	0.018	1.23 (0.83-1.84)	0.31
LVEDV	1.30 (1.04-1.63)	0.021	1.17 (0.91-1.52)	0.22
LVEDVi	1.27 (1.04-1.56)	0.019	1.17 (0.92-1.47)	0.20
LVESV	1.32 (1.07-1.63)	0.011	1.19 (0.91-1.56)	0.21
LVEDVi	1.30 (1.07-1.58)	0.009	1.19 (0.93-1.54)	0.17
MWT	1.04 (0.82-1.32)	0.74	1.02 (0.80-1.31)	0.86
LV mass	1.34 (1.05-1.70)	0.017	1.28 (1.00-1.64)	0.055
LVMi	1.34 (1.07-1.68)	0.010	1.28 (1.02-1.61)	0.036
LAV	1.47 (1.20-1.80)	<0.001	1.39 (1.13-1.71)	0.002
LAVi	1.50 (1.22-1.84)	<0.001	1.42 (1.15-1.76)	0.001
E wave	1.39 (1.13-1.71)	0.002	1.28 (1.03-1.58)	0.023

TDI e'$_{ave}$	0.98 (0.76-1.27)	0.89	0.97 (0.75-1.25)	0.79
E/e'$_{ave}$	1.34 (1.09-1.65)	0.005	1.25 (1.01-1.55)	0.038
TR velocity	1.43 (1.05-1.95)	0.024	1.40 (1.02-1.92)	0.035

Model 1 adjusts for age, gender, and treatment and incorporates site as a random effect; Model 2 adjusts for age, gender, treatment, Killip class, and site reported LVEF <40% and incorporates site as a random effect. 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; LVEDVi – per 20.1 ml/m^2 increase; LVESV – per 37.1 ml increase; LVESVi – per 18.5 ml/m^2 increase; MWT – per 0.16 cm increase; LV mass – per 54.3 g increase; LVMi – per 24.9 g/m^2 increase; LA volume – per 17.2 ml increase; LAVi – per 9.3 ml/m^2 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

Table S14. Baseline measures of cardiac structure and function in 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
Baseline measures:				
LVEF (%)	42±12	37±7	34±10	34±7
LVEDVi (ml/m^2)	66±20	117±21	77±26	116±39
LVESVi (ml/m^2)	39±19	75±20	52±23	78±32
LVMi (g/m^2)	99±25	52±9	NA	NA

LAVi (ml/m^2)	25±9	47±14	30±9	69±32
TDI e' (cm/s)	6.1±1.8	NA	6±2	5.2±1.7
E/e'	12.1±4.9	NA	13.6±7.2	17.2±6.7

*Values for the trial population overall are estimated from primary publications. 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