

The Effect of Renin-Angiotensin-Aldosterone System Inhibition on Morbidity and Mortality during Long-term Continuous-flow Left Ventricular Assist Device Support

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Relevant Financial Relationship Disclosure Statement

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I will not discuss off label use and/or investigational use of drugs/devices.

The following relevant financial relationships exist related to this presentation:

Brinkley DM: No relationships to disclose

Wang L: No relationships to disclose

Chang Y: No relationships to disclose

Kiernan MS: Consultant - Medtronic, Scientific Medical Advisor - Medtronic, Other support - Abiomed

Background

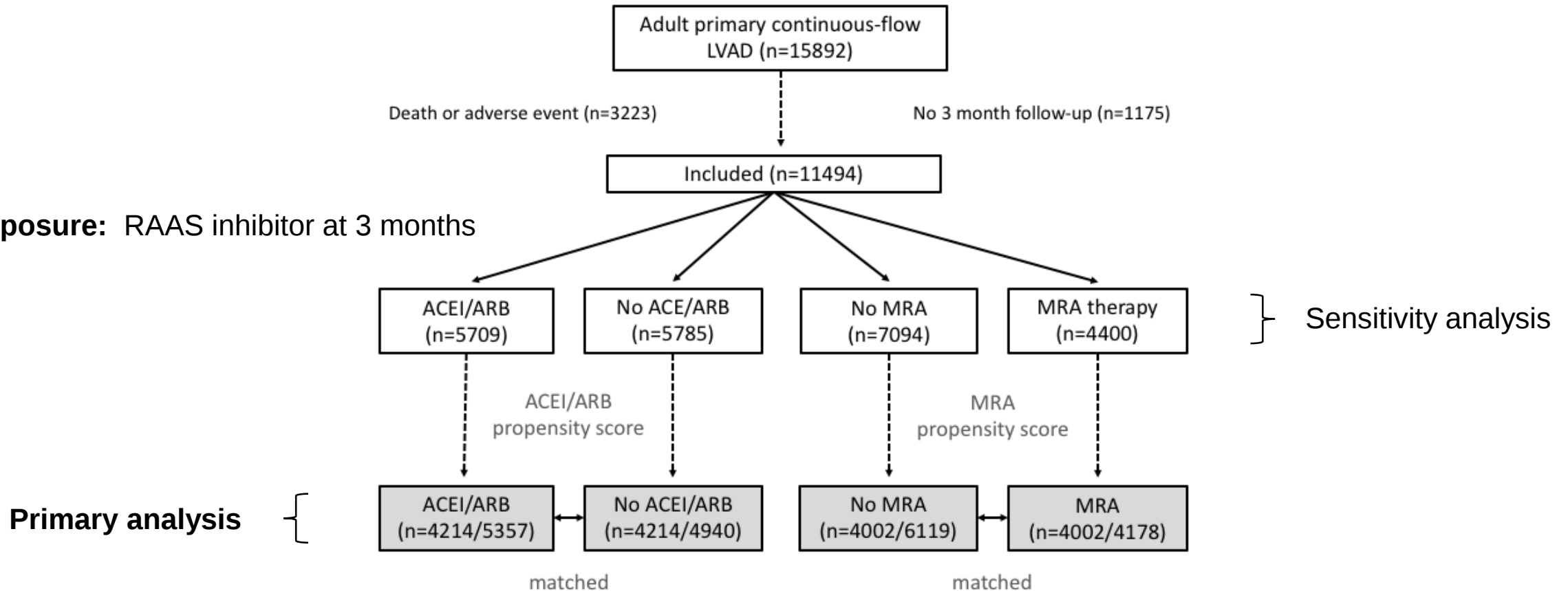
- Neurohormonal modulators including angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) and mineralocorticoid antagonists (MRA) decrease mortality, sudden cardiac death, and hospitalization among patients with heart failure
- Although LVAD therapy improves survival in select patients with advanced heart failure, cardiovascular events remain a major cause of morbidity and mortality during support
- We sought to determine the effect of renin-angiotensin-aldosterone inhibition on morbidity and mortality in patients with LVADs



Methods: Patient selection

Population: IMACS registry January 2013 - September 2017

Exposure: RAAS inhibitor at 3 months



Methods

- Propensity score matching* was performed separately for ACEI/ARB vs. none (n=4,214 each) and MRA vs. none (n=4,002 each) to reduce selection bias
- Matching substantially improved the standardized mean difference among variables in both cohorts
- Primary outcome: Survival, evaluated with Cox proportional hazards regression
- Secondary outcomes: Adverse events at 12 and 24-months

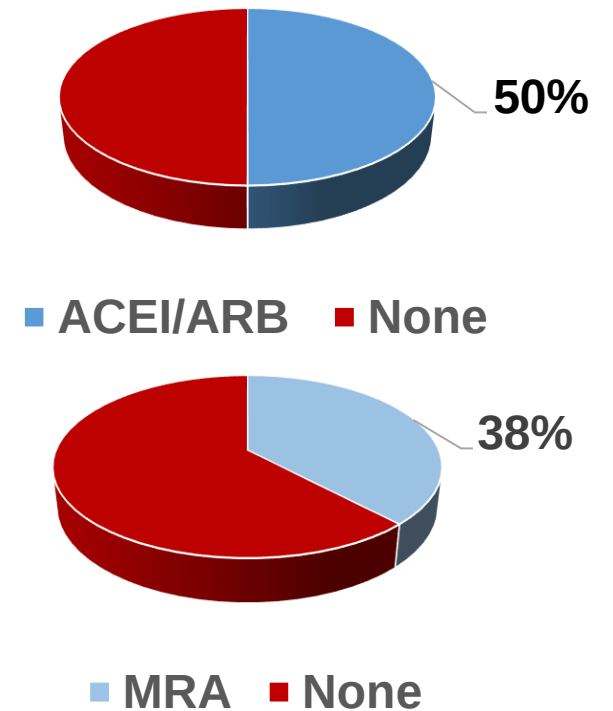
* Score included age, beta-blocker use, BUN, creatinine, diabetes, gender, implant strategy, INTERMACS profile, loop diuretic use, other antihypertensive use, potassium, and pre-implant use of a RAAS inhibitor



Results

- Patients treated with ACEI/ARB or MRA were more likely to have:
 - younger age
 - female gender
 - higher BMI
 - non-ischemic etiology
 - BTT or BTD strategy
 - less acute INTERMACS profile (less sick)
 - lower BUN, creatinine, and bilirubin
 - pre-implant of RAAS therapy

RAAS therapy at 3 months



Results: Baseline characteristics

Variable	No ACEI/ARB n=4214	ACEI/ARB n=4214	P
Pre-implant Clinical			
Age (years)	57 ± 13	56 ± 13	<0.001*
Gender (male)	79 (3331)	79 (3323)	0.83
BMI (kg/m ²)	28.4 ± 6.9	28.3 ± 6.9	0.65
Diabetes (severe)	9 (400)	10 (401)	0.97
INTERMACS profile			0.28
1	15 (613)	14 (573)	
2	35 (1465)	34 (1418)	
3	35 (1480)	36 (1535)	
4-7	16 (656)	16 (688)	
Ischemic	44 (1857)	42 (1783)	0.10
Non-ischemic	52 (2176)	53 (2228)	0.26
LVEF <20%	69 (2757)	70 (2758)	0.43
Prior cardiac surgery	32 (1303)	30 (1190)	<0.05*
Pulmonary disease	10 (407)	9 (359)	0.07
Renal disease	24 (987)	18 (725)	<0.001*
Smoking (current)	5 (208)	5 (214)	0.74
Strategy			0.16
Bridge to recovery	0 (4)	0 (9)	
Bridge to transplant	27 (1127)	28 (1184)	
Bridge to decision	26 (1079)	27 (1117)	
Destination	47 (1992)	45 (1892)	
Vascular disease	4 (182)	4 (167)	0.41

Variable	No ACEI/ARB n=4214	ACEI/ARB n=4214	P
Hemodynamics			
RA (mmHg)	13.4 ± 8.5	12.4 ± 8.0	<0.001*
PA systolic (mmHg)	50 ± 15	50 ± 15	0.38
PA diastolic (mmHg)	25.0 ± 9.0	24.7 ± 8.9	0.18
PCW (mmHg)	25.1 ± 9.3	24.8 ± 9.5	0.17
Cardiac output (L/min)	4.2 ± 1.4	4.1 ± 1.4	0.04
Post-implant Labs			
BUN (mg/dL)	22 ± 13	21 ± 13	<0.001*
Creatinine (mg/dL)	1.19 ± 0.47	1.14 ± 0.51	<0.001*
Potassium (mmol/dL)	4.10 ± 0.58	4.11 ± 0.72	<0.001*
Sodium (mEq/L)	138.2 ± 3.3	137.8 ± 3.2	<0.001*
Post-implant therapies			
ACEI	0 (0)	79 (3335)	
ARB	0 (0)	23 (985)	
MRA	37 (1540)	44 (1834)	<0.001*
Amiodarone	46 (1958)	44 (1861)	0.09
Beta-blocker	61 (2584)	64 (2717)	0.01*
Calcium channel	11 (452)	11 (462)	<0.001*
Hydralazine	21 (882)	18 (740)	<0.001*
Loop diuretic	72 (3053)	71 (2987)	0.22
PDE inhibitor	24 (1005)	21 (871)	<0.001*

Values represent % (number) or mean ± standard deviation. * two-tailed p<0.05



Results: Baseline characteristics

Variable	No MRA n=4002	MRA n=4002	P
Pre-implant Clinical			
Age (years)	55 ± 14	54 ± 14	<0.001*
Gender (male)	78 (3137)	78 (3105)	0.39
BMI (kg/m ²)	28.2 ± 7.0	28.8 ± 7.1	<0.001*
Diabetes (severe)	10 (386)	10 (385)	0.97
INTERMACS profile			0.69
1	14 (560)	13 (536)	
2	34 (1362)	35 (1381)	
3	36 (1424)	36 (1454)	
4-7	16 (656)	16 (631)	
Ischemic	41 (1659)	37 (1496)	<0.001*
Non-ischemic	54 (2154)	57 (2292)	<0.01*
LVEF <20%	70 (2624)	71 (2645)	0.47
Prior cardiac surgery	29 (1113)	28 (1079)	0.72
Pulmonary disease	9 (352)	9 (367)	0.56
Renal disease	20 (774)	19 (742)	0.54
Smoking (current)	5 (208)	5 (194)	0.49
Strategy			0.41
Bridge to recovery	0 (9)	0 (11)	
Bridge to transplant	29 (1171)	30 (1215)	
Bridge to decision	27 (1099)	28 (1138)	
Destination	43 (1713)	41 (1627)	
Vascular disease	4 (145)	4 (146)	0.95

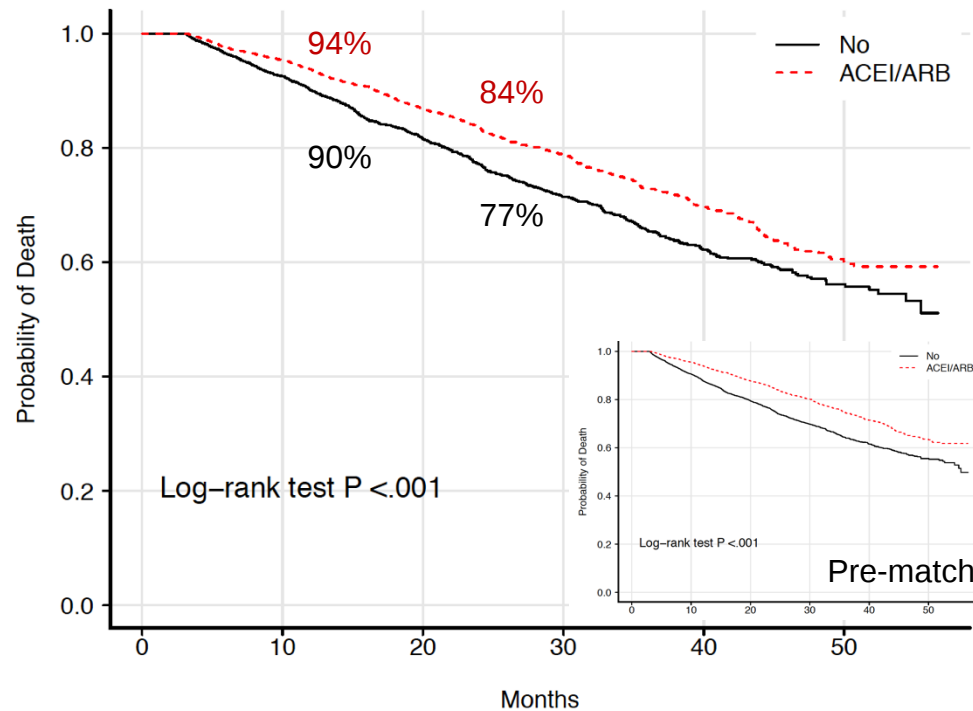
Variable	No MRA n=4002	MRA n=4002	P
Hemodynamics			
RA (mmHg)	12.8 ± 8.5	12.8 ± 8.0	0.38
PA systolic (mmHg)	50 ± 15	50 ± 15	0.19
PA diastolic (mmHg)	24.9 ± 9.3	25.2 ± 8.7	0.04*
PCW (mmHg)	24.9 ± 9.7	25.1 ± 9.2	0.2
Cardiac output (L/min)	4.2 ± 1.4	4.2 ± 1.4	0.1
Post-implant Labs			
BUN (mg/dL)	22 ± 16	22 ± 13	0.09
Creatinine (mg/dL)	1.15 ± 0.47	1.14 ± 0.46	0.92
Potassium (mmol/dL)	4.10 ± 0.62	4.10 ± 0.71	0.04*
Sodium (mEq/L)	138.4 ± 3.2	137.4 ± 3.3	<0.001*
Post-implant therapies			
ACEI	42 (1668)	46 (1826)	0.001*
ARB	11 (437)	14 (570)	<0.001*
MRA	0 (0)	100 (4002)	
Amiodarone	42 (1689)	45 (1792)	0.06
Beta-blocker	65 (2602)	67 (2672)	0.15
Calcium channel	10 (408)	9 (372)	<0.001*
Hydralazine	17 (684)	18 (707)	<0.001*
Loop diuretic	75 (2982)	75 (3000)	0.74
PDE inhibitor	22 (879)	23 (936)	<0.001*

Values represent % (number) or mean ± standard deviation. * two-tailed p<0.05



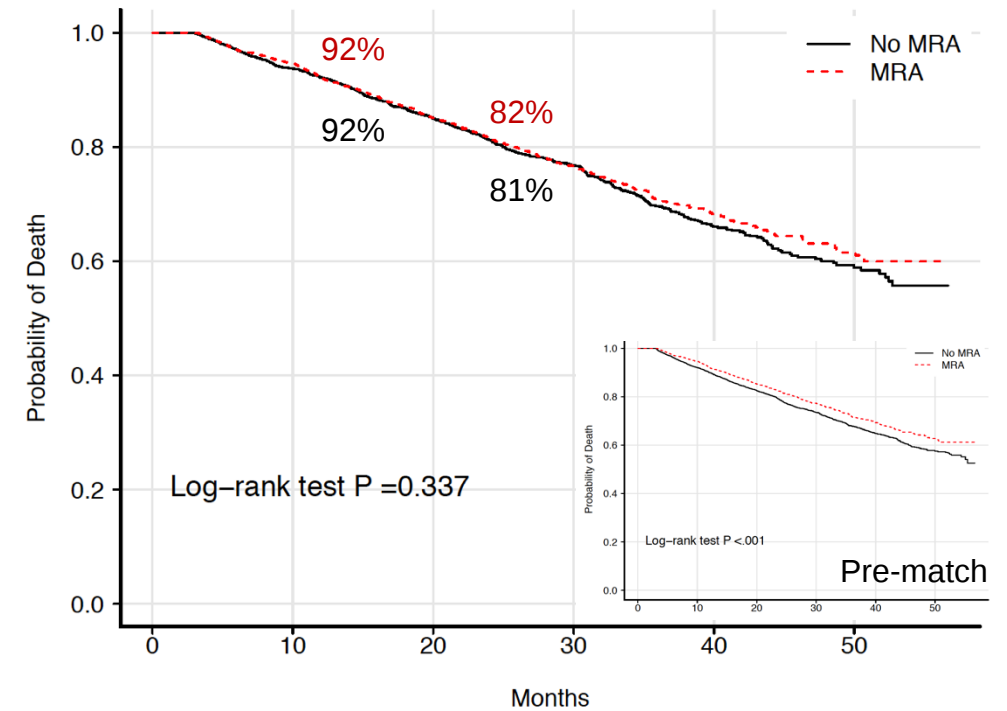
Results: Kaplan-Meier survival

Matched cohort survival by ACEI/ARB therapy



No	4214	2924	1651	896	401	149
ACEI/ARB	4214	3055	1791	991	450	142

Matched cohort survival by MRA therapy



No MRA	4002	2873	1697	929	423	135
MRA	4002	2784	1567	841	353	128



Results: Multivariate Predictors

ACEI/ARB
HR 0.81
[0.71-0.93]

Variable	ACEI/ARB matched		
	Wald	HR [95% CI]	P
ACEI/ARB	23.0	0.81 [0.71-0.93]	<0.0001*
MRA	1.6	1.05 [0.90-1.22]	0.46
Age	23.9	1.25 [1.06-1.47]	<0.0001*
Female:male	0.4	1.04 [0.91-1.20]	0.55
BMI	4.2	1.08 [0.94-1.24]	0.24
BUN	8.2	1.18 [1.03-1.36]	0.04*
Creatinine	2.3	1.09 [0.94-1.26]	0.51
Bilirubin	7.3	0.92 [0.82-1.02]	0.06
Strategy	18.4		0.001*
BTT:DT		0.73 [0.62-0.86]	
Possible BTT:DT		0.80 [0.69-0.92]	
INTERMACS Profile	4.7		0.20
Profile 1:3		1.11 [0.93-1.33]	
Profile 2 :3		1.06 [0.93-1.21]	
Profile 4-7:3		0.91 [0.78-1.07]	
Prior cardiac surgery	14.5	1.25 [1.11-1.40]	0.0001*
PVD	1.5	1.15 [0.92-1.44]	0.23
Smoking	3.7	1.26 [1.00-1.58]	0.05
Dialysis	18.8	2.49 [1.64-3.78]	<0.0001*

Cox proportional hazards analysis. HR – hazard ratio, CI – confidence interval, * two-tailed p<0.05



Results: Multivariate Predictors

Variable	MRA matched		P
	Wald	HR [95% CI]	
ACEI/ARB	27.5	0.79 [0.68-0.93]	<0.0001*
MRA	1.7	1.07 [0.92-1.25]	0.43
Age	30.6	1.36 [1.14-1.62]	<0.0001*
Female:male	4.1	1.16 [1.01-1.34]	0.04*
BMI	8.5	1.08 [0.93-1.25]	0.04*
BUN	10.7	1.24 [1.07-1.43]	0.01*
Creatinine	4.0	1.09 [0.94-1.27]	0.26
Bilirubin	3.9	0.93 [0.83-1.04]	0.27
Strategy	18.5		0.001*
BTT:DT		0.72 [0.61-0.85]	
Possible BTT:DT		0.81 [0.70-0.93]	
INTERMACS Profile	6.5		0.09
Profile 1:3		1.14 [0.95-1.38]	
Profile 2 :3		1.07 [0.93-1.22]	
Profile 4-7:3		0.89 [0.75-1.05]	
Prior cardiac surgery	11.7	1.24 [1.10-1.40]	<0.001*
PVD	1.7	1.18 [0.92-1.50]	0.19
Smoking	10.2	1.45 [1.16-1.83]	0.001*
Dialysis	23.0	2.87 [1.86-4.44]	<0.0001*

MRA

HR 1.07
[0.92-1.25]

ACEI/ARB

HR 0.79
[0.68-0.93]

Cox proportional hazards analysis. HR – hazard ratio, CI – confidence interval, * two-tailed p<0.05



Results: Adverse Events

	Variable	No ACEI/ARB n=4214	ACEI/ARB n=4214	P
Less CV death {	CV death			
	12 months	2.2 (94)	1.1 (46)	<0.001*
	24 months	3.6 (150)	2.3 (95)	<0.001*
	Late RV failure			
	12 months	1.1 (48)	0.8 (35)	0.15
	24 months	1.4 (59)	0.9 (40)	0.06
Less GI bleeding {	Stroke			
	12 months	6.5 (272)	6.8 (286)	0.54
	24 months	9.8 (415)	9.9 (416)	0.97
	GI bleeding			
	12 months	14.0 (589)	12.6 (533)	0.07
	24 months	18.5 (784)	16.7 (705)	0.02*
Lower creatinine {	Hemolysis			
	12 months	5.2 (220)	5.9 (249)	0.17
	24 months	8.3 (348)	9.3 (390)	0.11
	Dialysis			
	12 months	0.7 (28)	0.4 (16)	0.12
	24 months	0.3 (13)	0.2 (9)	0.07
	Creatinine			
	12 months	1.36 ± 0.64	1.29 ± 0.52	<0.001*
	24 months	1.38 ± 0.67	1.34 ± 0.58	0.06

Values represent % (number) or mean + standard deviation. * two-tailed p<0.05



Results: Sensitivity analysis without matching

ACEI/ARB

HR 0.81 [0.72-0.92]

MRA

HR 1.09 [0.95-1.25]

ACEI/ARB + MRA

HR 0.76 [0.65-0.88]

Variable	Wald	HR [95% CI]	P
RAAS therapy	27.8		<0.0001*
ACEI/ARB		0.81 [0.72-0.92]	
MRA		1.09 [0.95-1.25]	
ACEI/ARB + MRA		0.76 [0.65-0.88]	
Beta-blocker	13.7	0.83 [0.75-0.92]	0.001*
Other antihypertensive	0.01	1.00 [0.89-1.11]	0.93
Age	39.3	1.32 [1.14-1.53]	<0.0001*
Female:male	0.5	1.05 [0.92-1.18]	0.49
Diabetes, severe	1.0	1.08 [0.93-1.26]	0.32
BMI	7.8	1.12 [0.99-1.27]	0.05
BUN	13.8	1.22 [1.08-1.38]	<0.01*
Creatinine	2.2	1.04 [0.92-1.19]	0.53
Bilirubin	6.2	0.93 [0.85-1.02]	0.10
Strategy	16.9		<0.01*
BTT:DT		0.77 [0.66-0.88]	
Possible BTT:DT		0.84 [0.74-0.96]	
INTERMACS Profile	6.6		0.09
Profile 1:3		1.11 [0.95-1.30]	
Profile 2:3		1.05 [0.93-1.18]	
Profile 4-7:3		0.89 [0.77-1.03]	
Prior cardiac surgery	16.4	1.24 [1.12-1.37]	<0.0001*
PVD	6.1	1.28 [1.05-1.55]	0.01*
Smoking	6.4	1.31 [1.06-1.60]	0.01*
Dialysis	125.9	3.13 [2.56-3.83]	<0.0001*

Cox proportional hazards analysis. HR – hazard ratio, CI – confidence interval, * two-tailed p<0.05



Results: Limitations

- Use of registry data
- Treatment crossover (typically bias towards no effect)
- Possibility of residual bias/confounding despite matching and multivariate analysis
- Cannot conclude causality



Conclusion

- Among patients alive at 3 months, treatment with ACEI/ARB is associated with improved survival following continuous-flow LVAD implantation
- MRA use was not associated with improved survival
- Given the known mortality benefit and safety profile of ACEI/ARB therapy in other heart failure populations, these findings support continued use of these agents after LVAD implantation
- Prospective studies are needed to explore how RAAS inhibitors affect adverse outcomes



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- The reporting and interpretation of these data are the responsibility of the authors