Supplementary Online Content

McCullough M, Caraballo C, Ravindra NG, et al. Neurohormonal blockade and clinical outcomes in patients with heart failure supported by left ventricular assist devices. *JAMA Cardiol*. Published online November 18, 2019. doi: 10.1001/jamacardio.2019.4965

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Description of modified Charlson Comorbidities Index used for sensitivity analysis

The Charlson Comorbidities Index (CCI) was calculated using the comorbidities listed on the pre-implant data collection forms. Each comorbidity corresponds to a point value, and the sum of the points equals the CCI score. The INTERMACS data collection forms do not include every diagnosis that comprises the original CCI score. As such, we use a modified CCI score.

All patients received a point for congestive heart failure. To identify a history of myocardial infarction, we relied on the admitting diagnosis, planned reason for implant, or whether the patient had a major myocardial infarction event during hospitalization but prior to implant. For liver disease, we considered a history of hepatitis as mild (+1) and the presence of liver dysfunction as moderate to severe (+3). Patients received 2 points for severe diabetes if the presence of diabetes mellitus with end organ damage was listed on the pre-implant form. A history of uncomplicated diabetes was not present on the pre-implant form and so was not used to calculate the modified CCI score. We gave 2 points to patients with a history of solid tumor listed on the pre-implant form. The presence of metastasis was not on the forms; as such, no patients received 6 points for the presence of metastatic disease. We gave 4 points to patients with a history of lymphoma or leukemia rather than 2 points for leukemia or 2 points for lymphoma. Connective tissue disease and hemiplegia were not tracked in the pre-implant form and so these contributions to the CCI score were ignored. All other comorbidities were counted by referencing the INTERMACS pre-implant form and assigned the appropriate CCI score.

eTable 1: Characteristics of the study population based on medication group at 6 months

Data are presented as mean (SD) for continuous measures and n (%) for categorical variables. ACEi/ARB = angiotensin converting enzyme or angiotensin receptor blocker; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; New York Heart Association= NYHA; INTERMACS= Interagency Registry for Mechanically Assisted Circulatory Support; BUN= Blood urea nitrogen; BNP= Brain natriuretic peptide; NTproBNP = N-terminal brain natriuretic peptide; INR= International normalized ratio; ALT= Alanine aminotransferase; AST= Aspartate aminotransferase.

	ACEi/ARB + BB + MRA N = 1,967	ACEi/ARB +BB N=2,741	ACE/ARB + MRA N = 541	ACEi/ARB N=1035	BB + MRA N= 1,200	BB N = 2,359	MRA N=576	Not on NHB N=1,725	P-value
Age, Years	52.3 (14.1)	56.5 (12.6)	53.8 (13.4)	58.2 (12.5)	56.4 (12.4)	59.4 (12.2)	58.1 (12.5)	59.0 (12.5)	<0.001
Women	21.5%	20.9%	22.2%	22.9%	21.5%	18.5%	23.6%	20.6%	0.045
White	64.7%	65.9%	64.7%	65.7%	68.9%	67.1%	69.8%	67.8%	0.1
African American	25.1%	26.8%	26.8%	25.6%	24.0%	24.8%	21.2%	22.8%	0.033
Hispanic	7.0%	5.9%	6.3%	6.2%	5.8%	6.2%	4.0%	6.7%	0.32
Body mass index, kg/m^2	29.5 (7.0)	28.2 (6.4)	29.3(6.7)	28 (6.5)	29.6 (6.6)	28.3 (6.8)	29.1 (6.9)	28.2	<0.001
Body surface area	2.1 (0.3)	2.0 (0.3)	2.1(0.3)	2.1 (0.3)	2.1 (0.3)	2.0 (0.3)	2.1 (0.3)	2.0 (0.3)	<0.001
Comorbid conditions									
Diabetes	7.8%	7.3%	9.6%	7.1%	7.8%	7.4%	9.4%	8.9%	0.24
Peripheral Vascular Disease	3.8%	4.0%	4.3%	4.0%	4.2%	4.3%	3.1%	3.8%	0.93
Atrial Arrhythmia	16.2%	13.6%	16.5%	12.6%	16.0%	14.5%	16.7%	14.4%	0.039
Ischemic Heart Disease	4.7%	5.8%	5.2%	5.5%	7.5%	6.7%	5.9%	6.7%	0.027
Prior Cardiac Surgery	26.8%	31.2%	27.9%	30.9%	33.3%	36.2%	35.2%	35.7%	<0.001

Chronic Lung Disease	7.3%	6.9%	11.5%	8.2%	6.8%	17.4%	9.9%	7.4%	0.006
Active Smoker	5.3%	6.9%	3.5%	6.0%	4.6%	4.7%	3.6%	6.1%	0.001
Chronic Kidney Disease	14.8%	15.3%	16.1%	15.4%	19.8%	24.0%	22.9%	21.1%	<0.001
INTERMACS Profile									
1	11.9%	12.1%	13.3%	13.9%	13.4%	13.1%	15.5%	15.4%	<0.001
2	34.2%	32.4%	34.3%	38.6%	37.9%	34.8%	43.9%	37.8%	
3	36.6%	34.6%	34.6%	29.6%	32.4%	34.3%	28.3%	29.9%	
4	13.5%	3.8%	15.0%	13.2%	13.8%	14%	11.5%	12.5%	
5-7	3.8%	5.1%	2.8%	4.7%	2.5%	3.7%	0.8%	4%	
Modified Charlson Comorbidity Index	2 (3)	3 (2)	3 (3)	3 (2)	3 (2)	3 (3)	3 (3)	3 (3)	<0.001
Device Strategy									
Bridge to recovery	0.8%	0.3%	0.6%	0.3%	0.2%	0.2%	0.9%	0.3%	0.022
Bridge to transplant	48.4%	49.5%	51.6%	48.1%	46.7%	42.3%	51.6%	42.6%	<0.001
Destination therapy	39.9%	41.1%	39.4%	42.7%	43.8%	46.9%	38.4%	49.1%	<0.001
NYHA Class									
I-II	0.6%	1.0%	0.9%	0.9%	0.4%	0.7%	0.7%	0.6%	0.002
III	19.5%	19.6%	18.1%	16.7%	19.3%	17.4%	12.5%	15.9%	
IV	73.8%	73.6%	76.7%	76.2%	74.8%	75.8%	80.7%	75.6%	
Unknown	16.2%	5.9%	4.3%	6.2%	5.4%	6.1%	6.1%	7.9%	
Laboratory Values									
Sodium, meq/L	138 (3.0)	139 (3.0)	137 (3)	138 (3)	138 (3)	139(3)	137 (4)	138 (3)	<0.001
Potassium meq/L	4.3 (0.4)	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)	4.2 (0.5)	4.2 (0.5)	4.1 (0.5)	4.2 (0.5)	<0.001

Creatinine, mg/dL	1.18 (0.43)	1.21 (0.52)	1.20 (0.37)	1.23 (0.62)	1.3 (0.5)	1.49 (0.89)	1.32 (0.52)	1.49 (0.97)	<0.001
BUN, mg/dL	21 (11)	22 (11)	22 (11)	22 (11)	25 (12)	26 (14)	26 (15)	25 (15)	<0.001
BNP, pg/L	249 (298)	343 (451)	243 (253)	297 (311)	343 (419)	376 (457)	346 (340)	473 (590)	<0.001
proBNP, ng/L	1252 (1442)	1991 (2801)	1544 (1567)	1899 (3100)	2074 (2249)	2853 (4897)	3214 (5335)	3276 (4712)	<0.001
Total Bilirubin, mg/dL	0.8 (1.0)	0.8 (08)	0.8 (0.5)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)	0.9 (06)	0.8 (0.8)	0.13
Platelets (x10^3)	222 (68)	211 (66)	230 (72)	214 (65)	215 (69)	203 (67)	222 (80)	215 (76)	<0.001
INR	2.25 (0.71)	2.19 (0.74)	2.27 (0.69)	2.18 (0.70)	2.22 (0.72)	2.19 (0.73)	2.19 (0.77)	2.14 (0.77)	<0.001
Albumin, g/dL	4.0 (0.5)	3.9 (0.5)	4.0 (0.5)	3.9 (0.5)	3.9 (0.5)	3.8 (0.6)	3.9 (0.5)	3.7 (0.6)	<0.001
ALT, units/L	29 (20)	31 (43)	29 (27)	29 (22)	29 (28)	33 (130)	27 (17)	29 (24)	0.45
AST, units/L	31 (17)	33 (36)	32 (24)	33 (23)	34 (26)	34 (35)	32 (16)	37 (88)	0.061

eTable 2: Balance between covariate distributions for propensity-matched patients

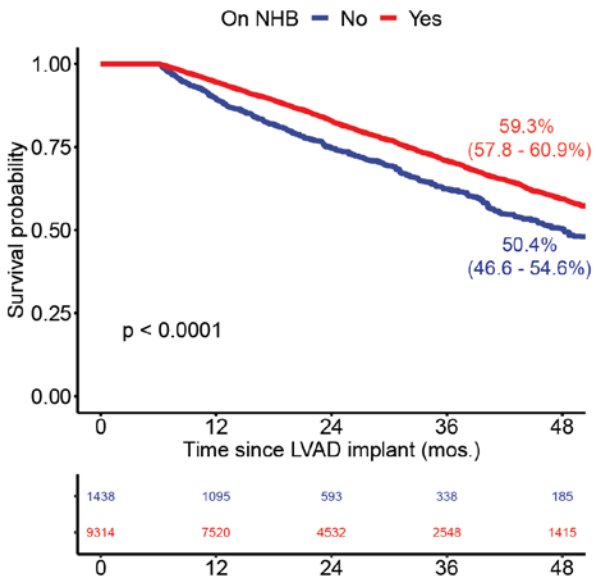
Data are presented as mean (SD). BMI= Body mass index; ICD= Implantable cardiac defibrillator; INTERMACS= Interagency Registry for Mechanically Assisted Circulatory Support; BUN= Blood urea nitrogen; BILI = total bilirubin.

	Covariate	Mean (SD) treated	Mean (SD) control	Mean difference	Mean difference after matching	Percent balance improvement
On NHB vs. Not on NHB	Propensity score (%)	86.4 (4.0)	85.1 (4.2)	1.3	0.03	97.62
	Age (y)	56.4 (13.1)	59.2 (12.6)	-2.82	-0.6	78.43
	Female	0.21 (0.41)	0.21 (0.41)	-0.005	0.0006	86.28
	BMI	28.7 (6.7)	28.1 (6.68)	0.64	0.14	78.04
	ICD	0.81 (0.39)	0.80 (0.40)	0.009	-0.002	76.42
	INTERMACS profile 1 or 2	0.48 (0.50)	0.53 (0.50)	-0.05	-0.001	97.75
	Albumin (g/dL)	3.44 (0.65)	3.33 (0.64)	.11	0.004	96.66
	Dialysis	0.01 (0.10)	0.02 (0.13)	-.006	0.002	76.63
	BUN (mg/dL)	28.41 (17.11)	31.34 (20.39)	-2.93	0.31	89.43
	BILI (total, mg/DL)	1.29 (1.42)	1.34 (1.27)	-0.05	0.06	-28.14
	History of cardiac surgery	0.32 (0.47)	0.35 (0.48)	-0.04	0.0001	99.71
	Concomitant cardiac surgery	0.38 (0.49)	0.43 (0.50)	-0.05	0.02	62.23
	Too sick to complete EQ5D assessment	0.44 (0.50)	0.48 (0.50)	-0.04	0.001	97.45
Triple therapy vs. Not on NHB	Propensity score (%)	59.5 (15.4)	48.9 (15.1)	10.61	0.2	89.14
	Age (y)	52.2 (14.1)	59.2 (12.6)	-7.0	-0.24	96.54
	Female	0.20 (0.40)	0.21 (0.41)	-.0.01	0.001	87.99
	BMI	29.5 (7.0)	28.1 (6.7)	1.44	0.28	80.81
	ICD	0.80 (0.40)	0.80 (0.40)	-.004	-0.002	59.77
	INTERMACS profile 1 or 2	0.46 (0.50)	0.53 (0.50)	-0.07	-0.02	76.89
	Albumin (g/dL)	3.51 (0.64)	3.33 (0.64)	0.18	0.03	84.06
	Dialysis	0.01 (0.08)	0.02 (0.13)	-0.01	0	100.00

	BUN (mg/dL)	25.54 (14.00)	31.34 (20.39)	-5.80	0.79	86.43
	BILI (total, mg/DL)	1.30 (1.30)	1.34 (1.27)	-0.04	0.03	18.0
	History of cardiac surgery	0.27 (0.44)	0.35 (0.48)	-0.09	0..02	77.78
	Concomitant cardiac surgery	0.38 (48)	0.43 (0.50)	-0.05	0.002	96.79
	Too sick to complete EQ5D assessment	0.43 (0.49)	0.48 (0.50)	-0.05	0.001	97.88

eFigure 1: **Propensity-matched cohort analysis**
Unadjusted Kaplan-Meier survival curve based on exposure to the various combinations of NHB therapy at 6 months post-LVAD implant. Results are displayed out to 48 months. Number at risk is shown below.

A



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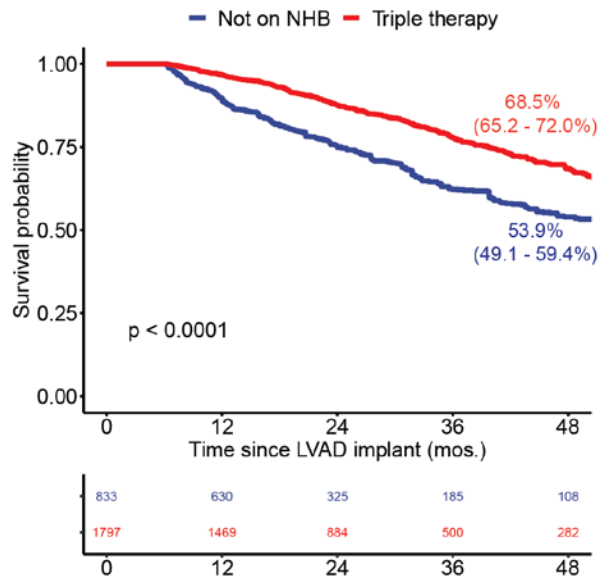
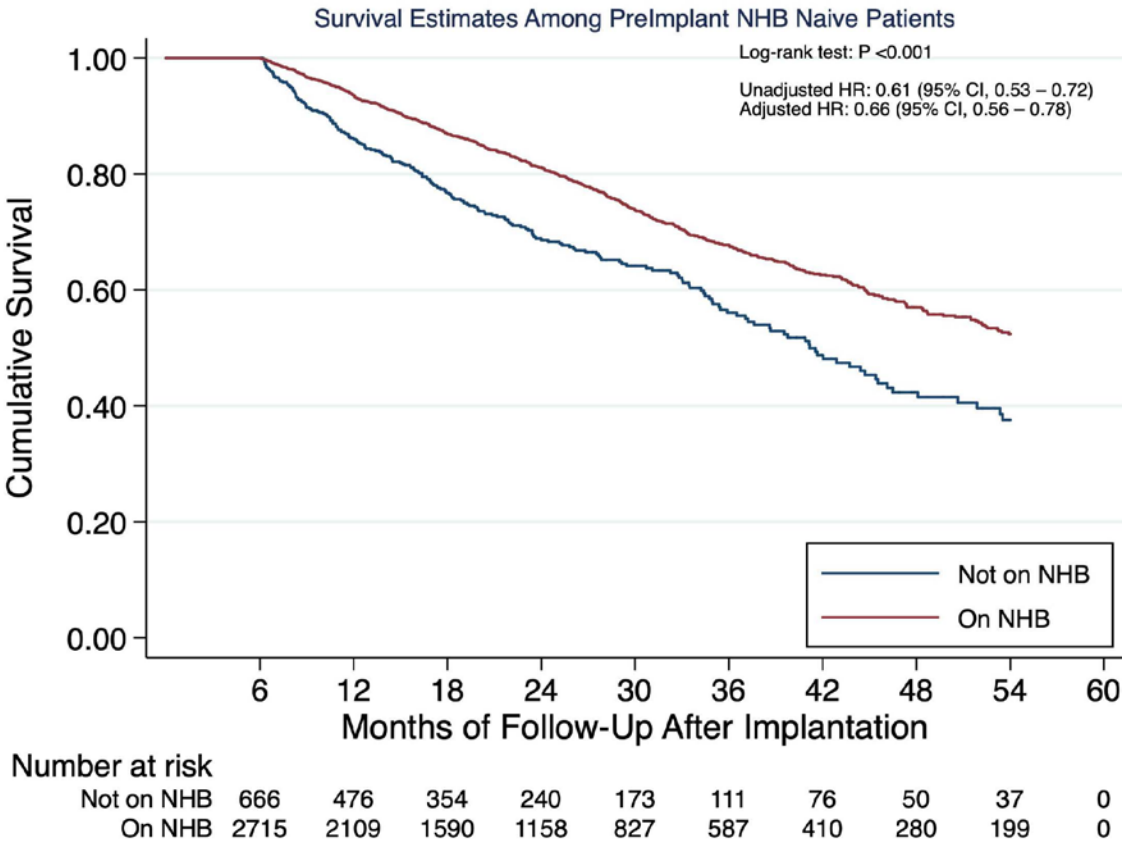


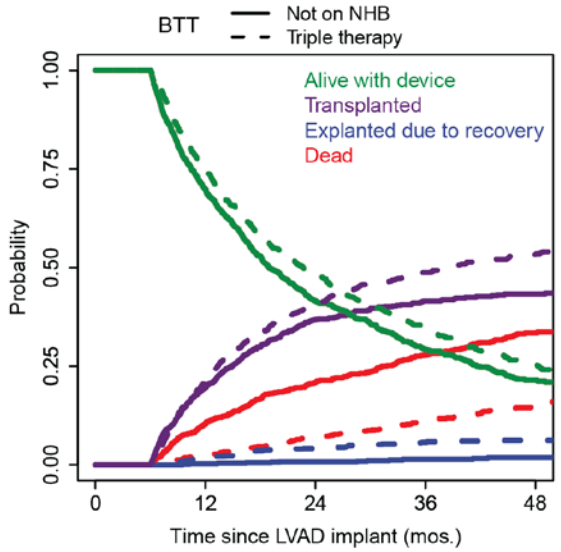
eFigure 2. **Survival Estimates Among Preimplant NHB Naïve Patients**
Effect of medical therapy on propensity-matched LVAD recipients. (A) Kaplan-Meier survival estimates weighted by covariate loading in propensity-matched analysis for patients receiving any NHB therapy vs no NHB therapy or patients receiving triple therapy vs no NHB therapy (B). Annotations show survival estimates and 95% CI at 48 months post-implant.



eFigure 3. Competing Risk Analysis for Patients with either BTT or DT as device strategy.

Hazard ratios (HR) were adjusted for early hazard risks from the INTERMACS 8th annual report (age, sex, body mass index, ICD, INTERMACS profile 1 or 2, albumin, dialysis, blood urea nitrogen, total bilirubin, history of cardiac surgery, concomitant cardiac surgery, and too sick to complete EQ5D). NHB = neurohormonal blockage; Triple = therapy with all three NHB drug classes.

A



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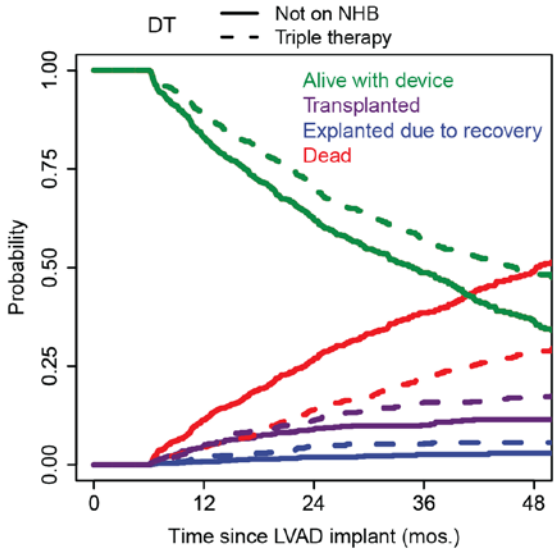

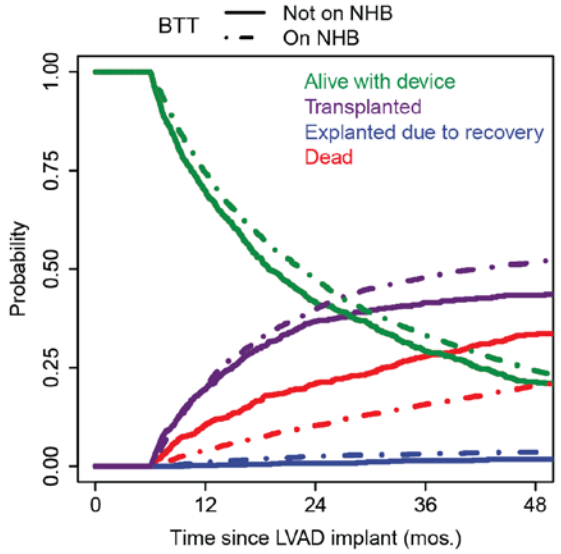

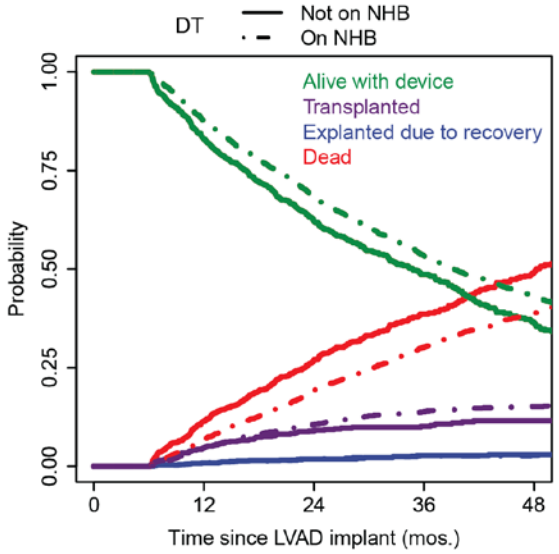

C

	@ Time=48 mos.	Dead	Explanted	Transplanted	Alive
BTT	Not on NHB	33.4 (30.0-37.2)	1.8 (1.0-3.2)	43.3 (39.9-47.1)	21.4 (18.4-25.0)
	On NHB	20.5 (19.3-21.7)	3.6 (3.1-4.1)	51.7 (50.3-53.1)	24.3 (23.0-25.6)
	Triple therapy	15.1 (12.9-17.7)	6.2 (4.8-7.9)	53.3 (50.2-56.6)	25.4 (22.6-28.6)
DT	Not on NHB	48.9 (44.8-53.3)	2.9 (1.9-4.6)	11.5 (9.4-14.2)	36.6 (32.6-41.1)
	On NHB	38.9 (37.2-40.6)	2.7 (2.2-3.3)	15.2 (14.1-16.4)	43.2 (41.5-45.0)
	Triple therapy	28.2 (24.7-32.3)	5.7 (4.2-7.7)	17.3 (14.5-20.5)	48.9 (44.8-53.3)

w