

Supplementary Tables

Supplementary Table S1: HFrEF Identification

Step 1: Classification based on index admission diagnosis codes whenever possible:

ICD-9	ICD-10
Automatically <i>include</i> HFrEF cohort if the primary/secondary diagnosis code is the following: 1) 428.2x, 428.4x	Automatically <i>include</i> HFrEF cohort if the primary/secondary diagnosis code is the following: 1) I50.2x, I50.4x
Automatically <i>exclude</i> HFpEF cohort if the primary/secondary diagnosis code is the following: 2) 428.3x	Automatically <i>exclude</i> HFpEF cohort if the primary/secondary diagnosis code is the following: 2) I50.3x
If the primary or secondary diagnosis code is for undifferentiated HF, apply the *algorithm below: 3) 428.0, 428.1, 428.9	If the primary secondary dx code is for undifferentiated HF, apply the **algorithm below: 3) I50.1, I50.9

Step 2: If primary or secondary diagnosis code from the index admission is for undifferentiated HF apply the following algorithms:

*Algorithm to Differentiate HFrEF from HFpEF (ICD-9)

Look back 1 year at all claims (inpatient and outpatient, in any position) for HF (428.x)

1. If they have ≥ 1 code for HFrEF (428.2x, 428.4x) and no codes for HFpEF (428.3x) \rightarrow include as a HFrEF admission
2. If they have ≥ 1 code for HFpEF (428.3x) and no codes for HFrEF (428.2x, 428.4x) \rightarrow exclude as a HFpEF admission
3. If they have ≥ 1 code for HFrEF (428.2x, 428.4x) and ≥ 1 code HFpEF (428.3x) \rightarrow include them as a HFrEF admission the number of HFrEF codes is greater than the number of HFpEF codes but if the number of HFpEF codes is greater than the number of HFrEF codes, exclude them as a HFpEF admission
4. If they have no codes for either HFrEF (428.2x, 428.4x) or HFpEF (428.3x) and only have codes for “undetermined HF” (428.0, 428.1, 428.9) in the year prior to the index admission \rightarrow exclude them because their HF type cannot be determined

**Algorithm to Differentiate HFrEF from HFpEF (ICD-10)

Look back 1 year at all claims (inpatient and outpatient, in any position) for HF (I50.x)

1. If they have ≥ 1 code for HFrEF (I50.2x, I50.4x) and no codes for HFpEF (I50.3x) \rightarrow include as a HFrEF admission
2. If they have ≥ 1 code for HFpEF (I50.3x) and no codes for HFrEF (I50.2x, I50.4x) \rightarrow include as a HFrEF admission
3. If they have ≥ 1 code for HFrEF (I50.2x, I50.4x) and ≥ 1 code HFpEF (I50.3x) \rightarrow include them as a HFrEF admission the number of HFrEF codes is greater than the number of HFpEF codes but if the number of HFpEF codes is greater than the number of HFrEF codes, exclude them as a HFpEF admission
4. If they have no codes for either HFrEF (I50.2x, I50.4x) or HFpEF (I50.3x) and only have codes for “undetermined HF” (I50.1, I50.9) \rightarrow exclude them because their HF type cannot be determined

Supplementary Table S2: Pre/Post Weighting for Short- and Long-Term Analyses

Pre/Post Weighting for Short-Term Analysis

Variables	Unweighted				Weighted			
	No 30d Fill	30d Fill	Standardized Difference	Variance Ratio	No 30d Fill	30d Fill	Standardized Difference	Variance Ratio
	Mean/Percent	Mean/Percent			Mean/Percent	Mean/Percent		
Demographic Characteristics								
Age 66-74	24.82	31.79	-0.16	0.86	25.37	29.42	-0.09	0.91
Age 75-84	38.01	39.56	-0.03	0.99	38.28	39.38	-0.02	0.99
Age 85+	37.17	28.65	0.18	1.14	36.35	31.21	0.11	1.08
Female	54.38	52.80	0.03	1.00	54.12	52.71	0.03	1.00
Race/Ethnicity								
Black	8.34	9.97	-0.06	0.85	8.41	9.23	-0.03	0.92
White	84.61	81.43	0.08	0.86	84.51	82.91	0.04	0.92
Hispanic	4.55	5.64	-0.05	0.81	4.59	5.16	-0.03	0.89
Socioeconomic Characteristics								
Dual Enrollment	33.93	34.73	-0.02	0.99	33.45	32.81	0.01	1.01
% Bachelor's Degree*	27.16	26.67	-0.03	1.01	26.97	26.88	-0.01	1.12
% below Federal Poverty Line*	15.49	16.03	0.06	0.94	15.71	15.79	0.01	1.08
Geography								
Midwest	25.98	26.45	-0.01	0.99	26.02	26.33	-0.01	0.99
Northeast	21.47	20.93	0.01	1.02	21.42	21.10	0.01	1.01
South	39.53	39.50	0.00	1.00	39.55	39.41	0.00	1.00
West	13.02	13.12	0.00	0.99	13.02	13.16	0.00	0.99
Medical Comorbidities								
Valvular heart disease	23.39	20.85	0.06	1.09	23.30	22.00	0.03	1.04
Pulmonary circulatory disease	8.18	6.27	0.07	1.28	8.01	6.97	0.04	1.14
Peripheral vascular disease	26.04	22.82	0.07	1.09	25.68	23.73	0.05	1.05
Hypertension	83.04	81.43	0.04	0.93	82.90	81.98	0.02	0.96
Paralysis	3.09	2.44	0.04	1.26	3.00	2.52	0.03	1.18
Neurodegenerative disorder	14.37	10.62	0.11	1.30	14.02	11.49	0.08	1.19
Chronic lung disease	34.45	29.71	0.10	1.08	34.00	31.19	0.06	1.05
Diabetes	26.46	27.77	-0.03	0.97	26.39	27.21	-0.02	0.98
Complicated Diabetes	17.50	16.59	0.02	1.04	17.30	16.79	0.01	1.02
Hypothyroidism	22.41	19.24	0.08	1.12	22.20	20.32	0.05	1.07
Renal failure	27.62	25.37	0.05	1.06	27.56	26.24	0.03	1.03
Liver disease	1.55	1.30	0.02	1.18	1.55	1.40	0.01	1.10
Lymphoma	1.60	1.66	-0.01	0.96	1.62	1.68	0.00	0.96
Metastatic cancer	1.66	1.53	0.01	1.08	1.67	1.65	0.00	1.01
Solid tumor without metastasis	9.12	8.75	0.01	1.04	9.15	8.95	0.01	1.02

Coagulopathy	7.83	6.65	0.05	1.16	7.79	7.12	0.03	1.09
Obesity	8.83	8.30	0.02	1.06	8.66	8.36	0.01	1.03
Weight Loss	7.15	5.59	0.06	1.26	7.06	6.05	0.04	1.15
Fluid and electrolyte disorder	29.10	24.74	0.10	1.11	28.73	25.87	0.06	1.07
Blood loss anemia	2.85	2.30	0.03	1.23	2.81	2.50	0.02	1.12
Anemia	36.35	31.87	0.09	1.07	36.05	33.31	0.06	1.04
Psychiatric Disease	6.14	4.92	0.05	1.23	6.01	5.11	0.04	1.17
Depression	12.48	10.42	0.06	1.17	12.30	10.86	0.04	1.11
Implanted cardiac defibrillator	13.54	13.18	0.01	1.02	13.70	13.71	0.00	1.00
Frailty Score	0.22	0.21	-0.22	1.09	0.21	0.21	-0.03	1.04
Index Admission Comorbidities								
Bradycardia	5.25	5.24	0.00	1.00	5.34	5.46	-0.01	0.98
Acute Kidney Injury	19.73	19.34	0.01	1.02	19.71	19.49	0.01	1.01
Hypotension	7.20	6.93	0.01	1.04	7.21	7.03	0.01	1.02
Drug Use Prior to Admission (90d)								
0 PDC	57.35	38.16	0.39	1.04	54.79	46.31	0.17	1.00
1-80 PDC	33.87	41.74	-0.16	0.92	35.07	38.96	-0.08	0.96
80+ PDC	8.79	20.10	-0.33	0.50	10.14	14.73	-0.14	0.73
Total number of Drugs at Discharge	3.90	7.38	1.17	2.10	5.68	6.32	0.20	1.95
Hospitalizations in Year Prior	1.15	0.99	-0.11	1.15	1.07	1.05	-0.01	1.12
Days Inpatient or in Post-Acute Care in Year Prior	8.83	5.74	-0.12	1.54	7.03	6.22	-0.03	1.36

* ZCTA-level characteristics derived from linking beneficiary zip codes with US Census Data

Pre/Post Weighting Long-Term Analysis

Variable	Unweighted				Weighted			
	PDC 0%	PDC 1-80%	PDC 80+%	P-Value	PDC 0%	PDC 1-80%	PDC 80+%	P-Value
Demographic Characteristics								
66-74	21.56	30.55	31.02	<0.001	26.92	28.06	27.96	<0.001
75-84	36.54	39.61	39.64	<0.001	38.80	38.76	38.94	0.670
85+	41.90	29.85	29.34	<0.001	34.28	33.18	33.10	<0.001
Female	0.56	0.52	0.53	<0.001	0.54	0.54	0.54	0.066
Race/Ethnicity								
White	0.85	0.81	0.84	<0.001	0.84	0.83	0.83	0.001
Black	0.08	0.11	0.09	<0.001	0.09	0.09	0.09	0.074
Hispanic	0.04	0.06	0.05	<0.001	0.05	0.05	0.05	0.058
Socioeconomic Characteristics								
Dual Eligibility	35.43	34.22	33.58	<0.001	33.58	34.44	33.75	<0.001
% Bachelor's Degree*	26.83	26.71	27.20	<0.001	27.12	26.94	27.09	0.020
% below Federal Poverty Line*	15.71	16.01	15.54	<0.001	15.65	15.74	15.63	0.009
Geography								
Midwest	0.25	0.25	0.28	<0.001	0.26	0.26	0.26	0.033
Northeast	0.21	0.20	0.22	<0.001	0.21	0.21	0.21	0.149
South	0.40	0.41	0.37	<0.001	0.40	0.40	0.39	0.027
West	0.13	0.13	0.13	<0.001	0.13	0.13	0.13	0.101
Medical Comorbidities								

Anemia	37.36	34.54	31.38	<0.001	34.83	34.44	34.34	0.079
Blood blood anemia	3.02	2.58	2.24	<0.001	2.66	2.62	2.57	0.498
Chronic lung disease	36.76	32.25	28.53	<0.001	32.51	32.37	31.90	0.010
Coagulopathy	7.87	7.45	6.59	<0.001	7.46	7.31	7.33	0.429
Depression	12.91	11.52	10.34	<0.001	11.83	11.58	11.61	0.211
Diabetes	25.32	27.56	27.99	<0.001	26.48	27.13	27.11	0.002
Complicated Diabetes	16.31	18.09	16.63	<0.001	17.05	17.12	17.20	0.681
Hypertension	81.50	83.19	81.92	<0.001	82.12	82.42	82.63	0.016
Hypothyroidism	22.87	20.67	19.53	<0.001	21.25	21.00	21.06	0.409
Implanted cardiac defibrillator	9.93	15.17	14.21	<0.001	12.36	13.35	13.27	<0.001
Liver disease	1.65	1.51	1.17	<0.001	1.49	1.44	1.41	0.455
Lymphoma	1.69	1.60	1.61	<0.001	1.75	1.64	1.66	0.170
Fluid and electrolyte disorder	30.42	27.01	24.31	<0.001	27.74	27.34	27.02	0.002
Metastatic cancer	1.95	1.46	1.47	<0.001	1.79	1.62	1.62	0.004
Neurodegenerative disorder	15.99	11.95	10.49	<0.001	12.96	12.70	12.34	<0.001
Obesity	8.28	9.08	8.30	<0.001	8.52	8.59	8.70	0.401
Paralysis	3.16	2.82	2.43	<0.001	2.90	2.85	2.69	0.015
Peripheral vascular disease	26.21	24.79	22.84	<0.001	24.93	24.63	24.44	0.054
Psychiatric disease	6.59	5.37	4.92	<0.001	5.76	5.60	5.56	0.155
Pulmonary circulatory disease	8.72	7.21	6.17	<0.001	7.52	7.35	7.30	0.171
Renal failure	27.08	27.48	25.17	<0.001	26.87	26.83	26.67	0.561
Solid tumor without metastasis	9.09	9.03	8.74	0.012	9.15	8.96	8.99	0.319
Valvular heart disease	23.01	22.51	21.15	<0.001	22.41	22.33	22.28	0.797
Frailty Score	0.22	0.21	0.20	<0.001	0.21	0.21	0.21	<0.001
Index Admission Comorbidities								
Hypotension	7.62	6.82	6.88	<0.001	7.98	6.86	7.25	<0.001
Bradycardia	5.35	5.02	5.39	<0.001	5.80	5.07	5.53	<0.001
Acute Kidney Injury	20.11	19.56	19.09	<0.001	20.89	19.59	19.92	<0.001
Drug Use Prior to Admission (90d)								
0 PDC	76.45	39.81	34.32	<0.001	53.85	48.01	48.13	<0.001
1-79 PDC	18.35	46.53	43.84	<0.001	35.03	37.66	37.69	<0.001
80+ PDC	5.21	13.65	21.84	<0.001	11.12	14.33	14.18	<0.001
Total number of Drugs at Discharge	4.04	5.49	6.87	<0.001	5.22	5.55	5.71	<0.001
Hospitalizations in Year Prior	1.19	1.12	0.94	<0.001	1.10	1.09	1.07	<0.001
Number of days Inpatient or in Post-Acute Care in Year Prior	9.76	6.88	5.90	<0.001	7.84	7.45	7.27	<0.001

* ZCTA-level characteristics derived from linking beneficiary zip codes with US Census Data

Supplementary Table S3: Sensitivity Analysis for Short- and Long-Term Analyses

Sensitivity Analysis of Short-Term Analysis: “Target Trial” with 7-day Exposure Window and Mortality between Days 8 and 30

Drug Fill within 7-days of Discharge	Odds Ratio	95% Confidence Interval	P-Value
Beta Blocker Fill			
Age 66-74	0.827	0.756, 0.904	<0.001
Age 75-84	0.773	0.724, 0.825	<0.001
Age 85+	0.769	0.727, 0.814	<0.001
ACEi/ARB/ARNI Fill			
Age 66-74	0.686	0.618, 0.761	<0.001
Age 75-84	0.609	0.563, 0.658	<0.001
Age 85+	0.688	0.645, 0.734	<0.001

* Deaths that occur during the first week are excluded

Sensitivity Analysis of Long-Term Analysis: Among Beneficiaries that Survive to 6 months, Evaluation of Mortality between Day 180 and 360 based on PDC during the first 6 months

PDC during first 6 months	Hazard Ratio for death between days 180-365 after discharge	95% Confidence Interval	P-Value
Beta Blocker Fill			
Age 66-74			
1-80 PDC	0.371	0.336, 0.411	<0.001
80+ PDC	0.409	0.377, 0.444	<0.001
Age 75-84			
1-80 PDC	0.441	0.409, 0.476	<0.001
80+ PDC	0.476	0.447, 0.507	<0.001
Age 85+			
1-80 PDC	0.489	0.454, 0.527	<0.001
80+ PDC	0.554	0.521, 0.589	<0.001
ACEi/ARB Fill			
Age 66-74			
1-80 PDC	0.444	0.399, 0.493	<0.001
80+ PDC	0.531	0.486, 0.580	<0.001
Age 75-84			
1-80 PDC	0.491	0.453, 0.532	<0.001
80+ PDC	0.558	0.521, 0.597	<0.001
Age 85+			
1-80 PDC	0.548	0.507, 0.592	<0.001
80+ PDC	0.657	0.615, 0.701	<0.001

0 PDC is the reference group

Supplementary Table S4: E-Values for Short and Long Analyses

Drug Fill within 30-days of Discharge	E-Value*	E-value for the Upper Limit of the Confidence Interval
Beta Blocker Fill		
Age 66-74	1.72	1.60
Age 75-84	1.79	1.71
Age 85+	1.94	1.86
ACEi/ARB Fill		
Age 66-74	2.10	1.96
Age 75-84	2.32	2.22
Age 85+	2.29	2.20

* Residual confounding could explain the observed association if there exists an unmeasured covariate that has a relative risk association at least as large as the E-value with both the outcome (30-day mortality) and the exposure (receipt of neurohormonal therapy).

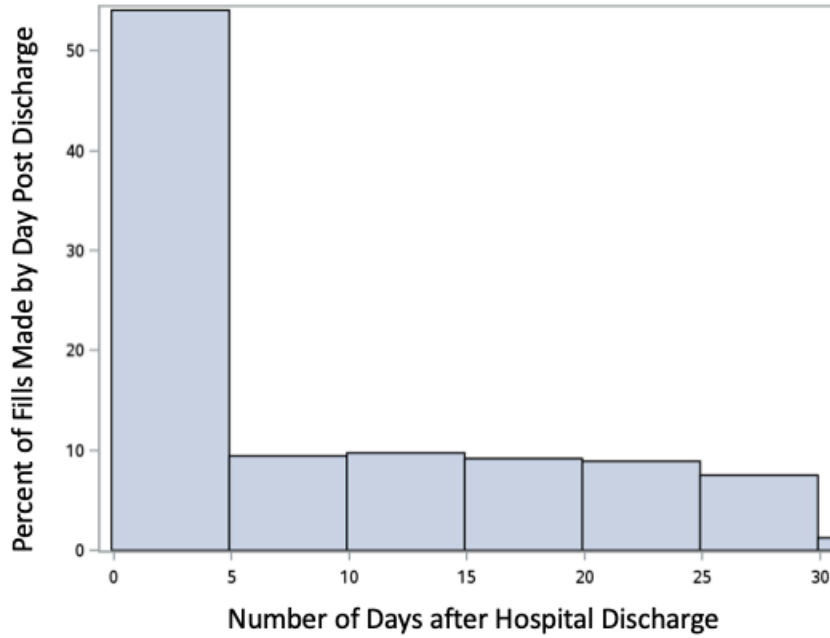
Drug Use in 1 year After Discharge	E-Value*	E-value for Confidence Interval
Beta Blocker Exposure		
Age 66-74		
1-80 PDC	2.78	2.68
80+ PDC	3.38	3.26
Age 75-84		
1-80 PDC	2.67	2.59
80+ PDC	3.27	3.18
Age 85+		
1-80 PDC	2.35	2.28
80+ PDC	2.97	2.89
ACEi/ARB Exposure		
Age 66-74		
1-80 PDC	2.95	2.85
80+ PDC	3.26	3.14
Age 75-84		
1-80 PDC	2.84	2.77
80+ PDC	3.29	3.20
Age 85+		
1-80 PDC	2.47	2.41
80+ PDC	2.85	2.77

* Residual confounding could explain the observed association if there exists an unmeasured covariate that has a relative risk association at least as large as the E-value with both the outcome (30-day mortality) and the exposure (receipt of neurohormonal therapy).

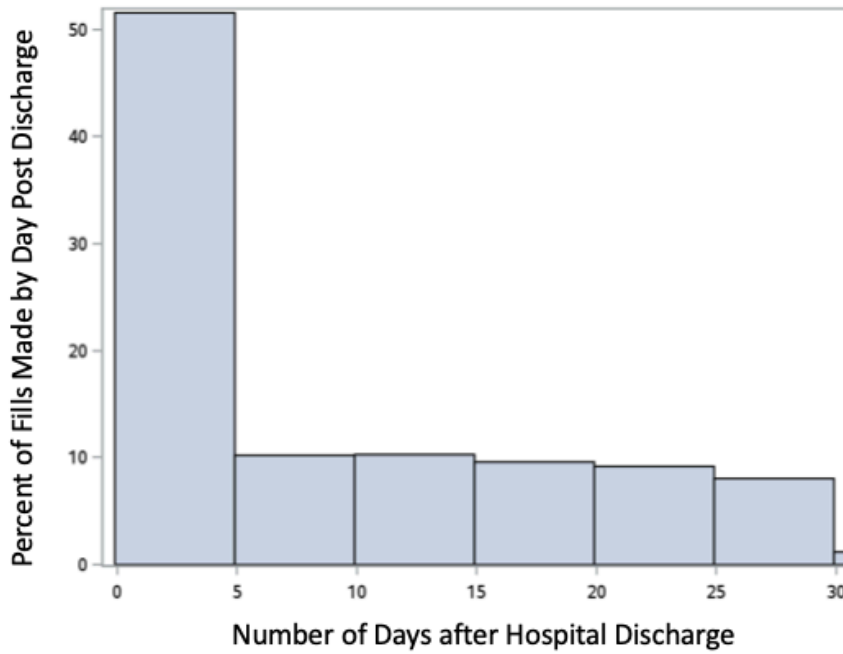
Supplementary Figures

Supplementary Figure S1: Distribution of Days to Drug fill for those Exposed to Neurohormonal Therapy after Hospital Discharge

Beta Blocker Fills



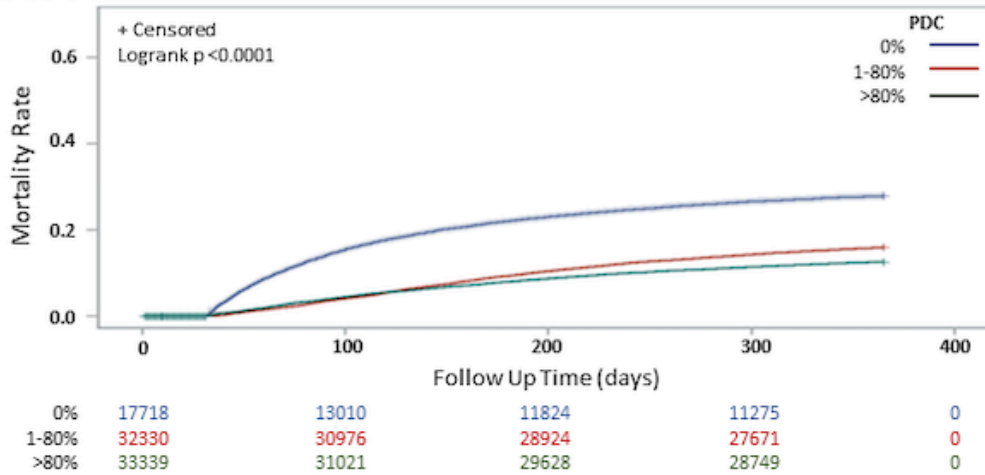
ACEi/ARB/ARNI Fills



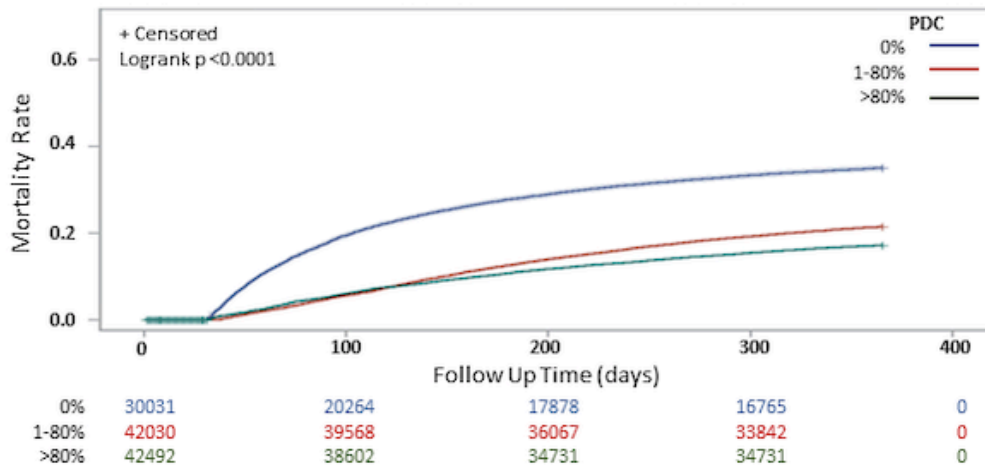
Supplementary Figure S2: Survival Curves for Death within 1 Year after Hospital Discharge based on Beta-Blocker and ACEi/ARB/ARNI Exposure, Stratified by Age, 2008-2015

Beta-Blockers

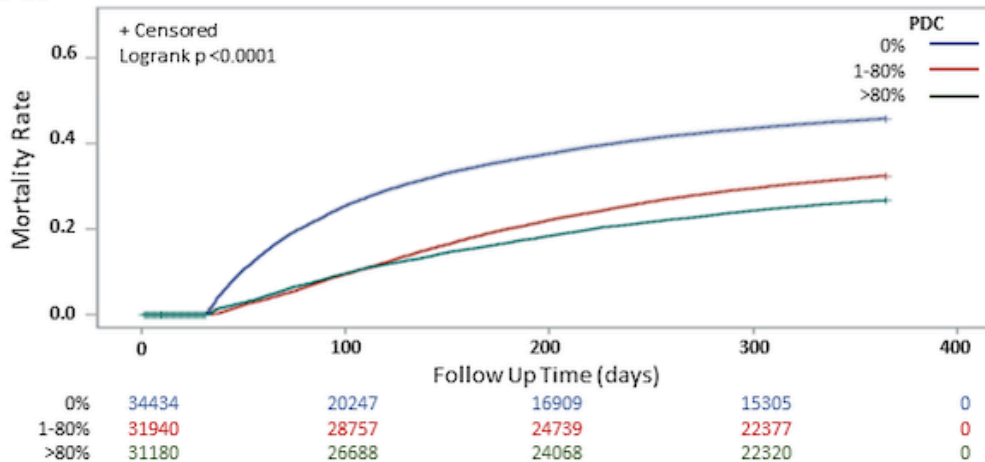
A) Age 66-74



B) Age 75-85



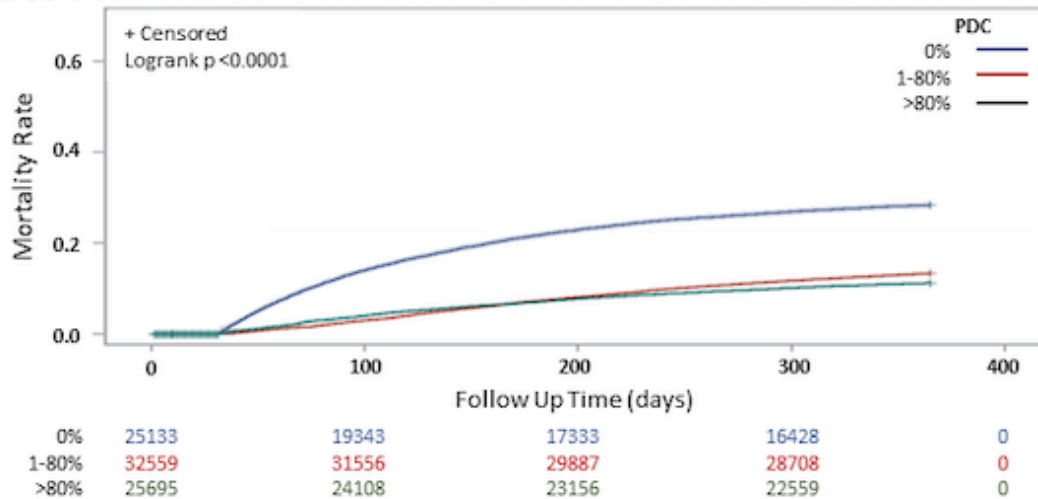
C) Age 85+



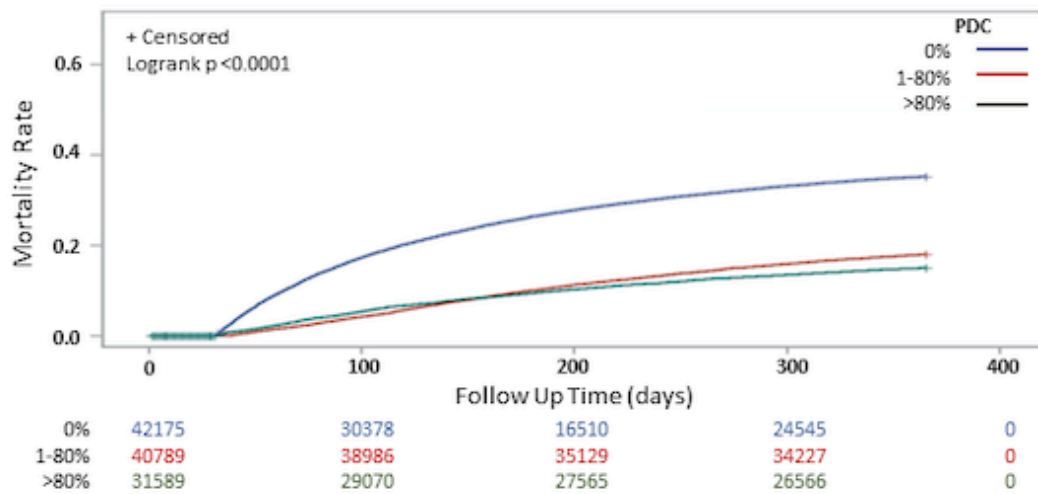
This figure shows the survival curves for beneficiaries based on exposure to beta-blockers after admission for decompensated heart failure. (A) shows the survival curves for beneficiaries aged 66-74. (B) shows the survival curves for beneficiaries aged 75-85 and (C) shows the survival curves for beneficiaries aged 85+. In each panel, patients are stratified based on the proportion of days covered (PDC) by beta-blockers: “no exposure” 0 PDC (blue), “moderate” exposure 1-80 PDC (red) and “high exposure” 80+ PDC (green).

ACEi/ARB/ARNI

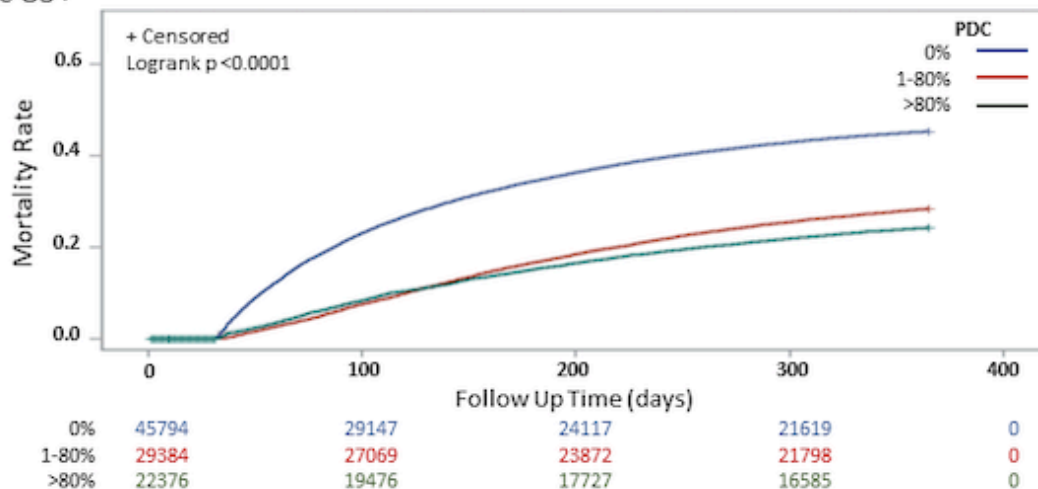
A) Age 66-74



B) Age 75-85



C) Age 85+



This figure shows the survival curves for beneficiaries based on exposure to ACEi/ARB/ARNI after admission for decompensated heart failure. (A) shows the survival curves for beneficiaries aged 66-74. (B) shows the survival curves for beneficiaries aged 75-85 and (C) shows the survival curves for beneficiaries aged 85+. In each panel, patients are stratified based on the proportion of days covered (PDC) by ACEi/ARB/ARNI: “no exposure” 0 PDC (blue), “moderate” exposure 1-80 PDC (red) and “high exposure” 80+ PDC (green).