

Supplementary Table S1. Characteristics of ARNI Initiators vs ACE Inhibitors/ARB Initiators for Heart Failure with Reduced Ejection, Replacing Frailty (binary) with Frailty Index

Characteristics	Initiation of ARNI (vs ACE Inhibitor or ARB) ^a		
	ARNI	ACE Inhibitor or ARB	OR (95% CI)
Sample size, n	4,547	33,868	
Age category, %			
65 to <75 years old	43.5	44.5	Reference
75 to <85 years old	43.2	39.9	1.07 (1.00, 1.15)
≥85 years old	13.3	15.7	0.88 (0.79, 0.98)
Male, %	79.5	75.8	1.23 (1.13, 1.34)
Race, %			
White	82.5	80.9	Reference
Black	11.4	12.7	0.97 (0.87, 1.08)
Hispanic/Asian/Other/Unknown	6.1	6.5	1.00 (0.87, 1.15)
Dual eligibility, %	17.4	23.8	0.78 (0.71, 0.85)
Gagne combined comorbidity index (per 1 point), mean (SD)	7.2 (3.3)	7.3 (3.5)	0.98 (0.97, 0.99)
Frailty Index (per 0.1 point), mean (SD)	0.21 (0.05)	0.23 (0.06)	0.71 (0.66, 0.78)
Comorbidities, %			
Alzheimer's disease or dementia	20.8	25.4	0.95 (0.87, 1.04)
Acute myocardial infarction	27.2	29.0	0.99 (0.92, 1.07)
Anemia	80.5	80.3	1.10 (1.01, 1.2)
Atrial fibrillation	64.6	60.4	1.07 (1.00, 1.14)
Cancer	19.8	20.3	0.99 (0.91, 1.07)
Chronic kidney disease	78.7	76.2	1.12 (1.03, 1.23)
Chronic obstructive pulmonary disease	58.4	58.0	1.10 (1.03, 1.18)
Depression	42.4	44.5	1.06 (0.98, 1.13)
Diabetes	66.7	68.5	0.95 (0.88, 1.02)
Hip or pelvic fracture	3.8	5.1	0.86 (0.73, 1.02)
Hypertension	98.0	98.3	0.85 (0.66, 1.08)
Osteoporosis	13.6	15.5	1.02 (0.92, 1.13)
Rheumatoid arthritis or osteoarthritis	69.3	68.3	1.09 (1.01, 1.18)
Stroke or Transient Ischemic Attack	27.1	30.3	0.97 (0.9, 1.05)

Cardiovascular care, %			
Cardiology visit within 30 days	72.5	68.2	1.24 (1.15, 1.33)
HF hospitalization ≥ 2 in prior year	15.8	14.3	1.44 (1.3, 1.6)
HF hospitalization within 30 days	10.1	12.4	0.62 (0.55, 0.69)
Other heart failure medications, %			
Mineralocorticoid receptor antagonists	43.1	29.8	1.68 (1.57, 1.79)
Beta-blockers	88.9	87.7	1.03 (0.93, 1.14)
Hydralazine	12.5	12.1	0.94 (0.84, 1.05)
Isosorbide dinitrate	5.7	4.4	1.37 (1.17, 1.6)
Loop diuretics	82.3	74.4	1.51 (1.38, 1.65)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; HF, heart failure; OR, odds ratio; SD, standard deviation.

^a Initiators were defined as beneficiaries who filled the prescription of ARNI vs ACE inhibitors or ARB without prior fills of any drug in ARNI, ACE inhibitor, or ARB classes in the previous year

Supplementary Table S2. Trend of Heart Failure Medications in Patients with Heart Failure with Reduced Ejection Fraction, 2015 to 2019, by Sex

Medications	2015	2016	2017	2018	2019	P-value for yearly trend ^b	P for yearly trend by sex ^b
ARNI							
Male	0.4%	3.7%	8.3%	12.1%	15.8%	<.0001	0.364
Female	0.3%	3.3%	7.3%	10.6%	13.8%	<.0001	
ACE inhibitors							
Male	55.4%	53.5%	49.6%	46.2%	43.1%	<.0001	0.233
Female	59.2%	56.5%	52.4%	48.8%	46.0%	<.0001	
ARB							
Male	22.4%	23.4%	23.0%	23.1%	22.2%	<.0001	<.0001
Female	24.2%	25.7%	26.0%	26.0%	25.0%	0.677	
MRA							
Male	26.0%	28.7%	29.9%	30.2%	31.0%	<.0001	<.0001
Female	34.8%	37.2%	38.1%	38.7%	39.5%	<.0001	
Evidence-based beta-blockers^a							
Male	84.8%	86.3%	87.1%	87.3%	87.1%	<.0001	0.423
Female	89.1%	90.2%	90.7%	90.5%	90.7%	<.0001	
Hydralazine + Isosorbide dinitrate							
Male	1.5%	1.7%	1.9%	1.8%	1.7%	0.001	0.123
Female	1.9%	2.2%	2.3%	2.1%	2.0%	<.0001	
Loop diuretics							
Male	63.6%	68.3%	68.6%	67.9%	66.7%	0.003	<.0001
Female	74.4%	77.6%	77.3%	76.2%	75.5%	<.0001	
All 3 of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
Male	18.9%	21.1%	22.0%	22.5%	22.9%	<.0001	<.0001
Female	26.5%	28.6%	29.4%	29.7%	30.3%	<.0001	
2 of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
Male	53.1%	52.8%	52.3%	52.1%	51.5%	<.0001	0.126
Female	53.4%	52.0%	51.5%	50.9%	50.2%	0.000	
1 of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
Male	22.7%	21.6%	21.5%	21.1%	21.2%	<.0001	0.002
Female	17.2%	16.9%	16.5%	16.8%	17.1%	<.0001	
None of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
Male	5.3%	4.6%	4.3%	4.3%	4.4%	<.0001	0.126
Female	2.9%	2.5%	2.6%	2.6%	2.5%	<.0001	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists.

^a Evidence-based beta-blockers include carvedilol, metoprolol succinate, and bisoprolol.

^b The receipt of a heart failure medication class or GDMT was modeled as a function of year (continuous variable), sex, and their interaction term, adjusting for age, race, dual eligibility, frailty, Alzheimer's disease and related dementias, anemia, atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, hip or pelvic fracture, hypertension, myocardial infarction, osteoporosis, rheumatoid arthritis or osteoarthritis, and stroke or transient ischemic attack, Gagne combined comorbidity index, cardiology visit within the past 30 days, ≥ 2 heart failure hospitalizations within the past year, and heart failure hospitalization within the past 30 days, using generalized estimating equation logistic regression with exchangeable correlation structure to account for correlation within the same individuals.

Supplementary Table S3. Trend of Heart Failure Medications in Patients with Heart Failure with Reduced Ejection Fraction, 2015 to 2019, by Race

Medications	2015	2016	2017	2018	2019	P-value for yearly trend ^b	P for yearly trend by race ^b
ARNI							
White	0.4%	3.6%	8.0%	11.5%	15.0%	<.0001	0.186
Black	0.4%	3.7%	8.0%	12.5%	16.3%	<.0001	
Other	0.5%	4.0%	8.6%	13.6%	17.4%	<.0001	
ACE inhibitors							
White	56.5%	54.5%	50.8%	47.4%	44.3%	<.0001	<.0001
Black	57.3%	54.3%	49.1%	44.6%	41.2%	<.0001	
Other	52.3%	50.8%	46.4%	43.9%	41.8%	<.0001	
ARB							
White	22.2%	23.3%	23.1%	23.2%	22.4%	<.0001	<.0001
Black	25.1%	26.1%	25.8%	26.0%	25.1%	0.000	
Other	30.2%	31.8%	30.7%	29.3%	26.9%	<.0001	
MRA							
White	28.2%	30.9%	32.1%	32.4%	33.1%	<.0001	<.0001
Black	30.8%	32.9%	33.5%	34.6%	35.1%	<.0001	
Other	26.1%	29.3%	30.1%	29.9%	30.9%	<.0001	
Evidence-based beta-blockers^a							
White	85.7%	87.1%	87.9%	88.0%	87.9%	<.0001	0.029
Black	88.2%	89.2%	89.6%	89.6%	89.0%	0.041	
Other	86.3%	87.6%	87.6%	88.3%	88.2%	0.003	
Hydralazine + Isosorbide dinitrate							
White	0.9%	1.1%	1.1%	1.2%	1.1%	0.007	0.000
Black	7.5%	8.0%	8.5%	7.8%	7.4%	0.000	
Other	1.7%	1.9%	2.1%	1.8%	1.9%	0.079	
Loop diuretics							
White	66.2%	70.7%	70.8%	70.1%	68.9%	0.522	<.0001
Black	71.4%	74.0%	74.1%	73.0%	71.9%	0.267	
Other	61.9%	66.7%	66.4%	65.1%	64.5%	0.758	
All 3 of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
White	20.6%	22.8%	23.8%	24.2%	24.5%	<.0001	<.0001
Black	24.6%	25.9%	26.3%	27.0%	27.3%	0.010	
Other	19.8%	22.8%	23.2%	23.5%	24.6%	<.0001	
2 of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
White	53.2%	52.7%	52.2%	52.0%	51.4%	<.0001	0.097
Black	52.1%	51.4%	50.4%	49.6%	48.4%	<.0001	
Other	55.0%	53.8%	53.0%	53.2%	51.8%	0.001	

1 of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
White	21.5%	20.5%	20.2%	20.0%	20.1%	<.0001	<.0001
Black	19.2%	19.1%	19.6%	19.6%	20.4%	0.491	
Other	21.0%	19.9%	20.1%	19.8%	19.9%	0.043	
None of ARNI/ACE inhibitors/ARB + beta-blockers + MRA							
White	4.7%	4.1%	3.8%	3.8%	3.9%	<.0001	0.060
Black	4.1%	3.6%	3.7%	3.8%	3.9%	0.038	
Other	4.3%	3.6%	3.7%	3.5%	3.8%	0.019	

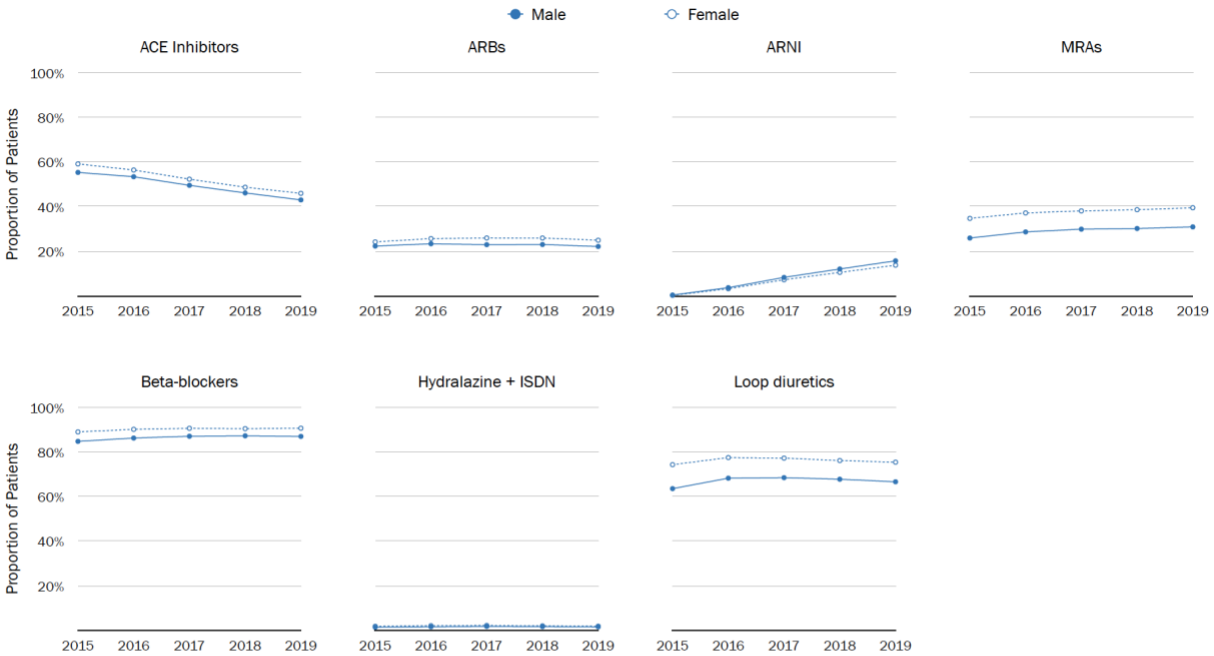
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists.

^a Evidence-based beta-blockers include carvedilol, metoprolol succinate, and bisoprolol.

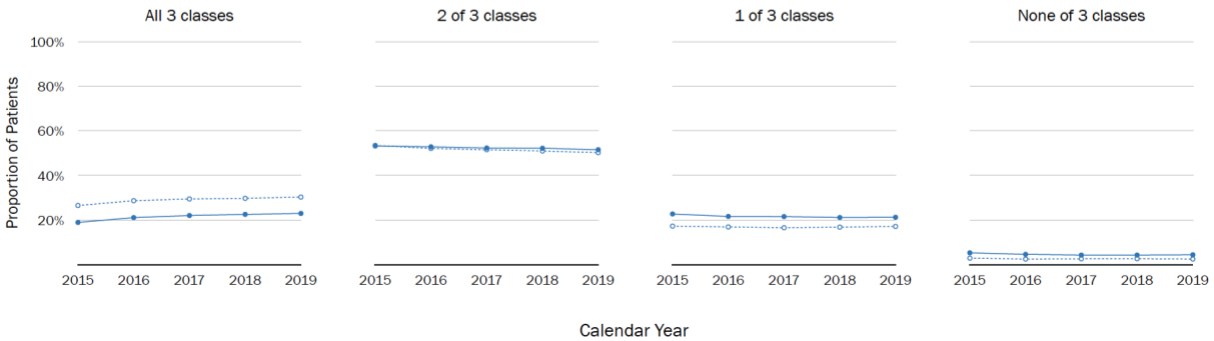
^b The receipt of a heart failure medication class or GDMT was modeled as a function of year (continuous variable), race, and their interaction term, adjusting for age, sex, dual eligibility, frailty, Alzheimer's disease and related dementias, anemia, atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, hip or pelvic fracture, hypertension, myocardial infarction, osteoporosis, rheumatoid arthritis or osteoarthritis, and stroke or transient ischemic attack, Gagne combined comorbidity index, cardiology visit within the past 30 days, ≥ 2 heart failure hospitalizations within the past year, and heart failure hospitalization within the past 30 days, using generalized estimating equation logistic regression with exchangeable correlation structure to account for correlation within the same individuals.

Supplementary Figure S4. Temporal Trends of Heart Failure Medications and Guideline-Directed Medical Therapy in Medicare Beneficiaries with Heart Failure with Reduced Ejection Fraction, 2015-2019, by Sex^a

A. Use of Heart Failure Medications



B. Guideline-Directed Medical Therapy

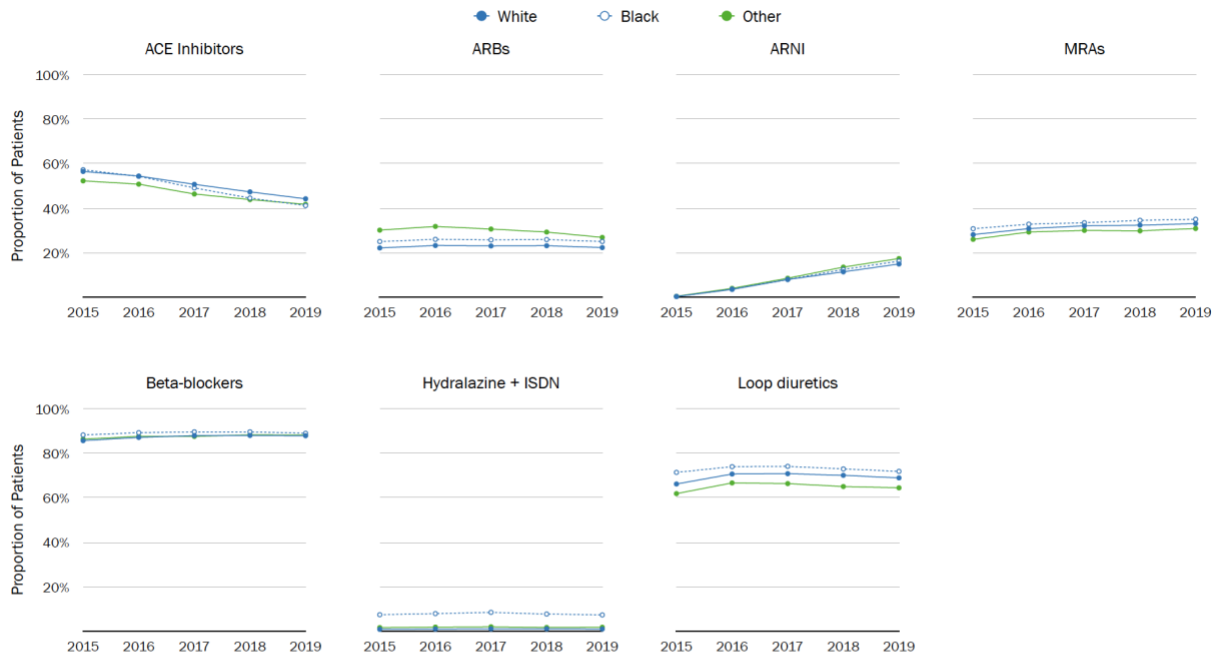


Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ISDN, isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist.

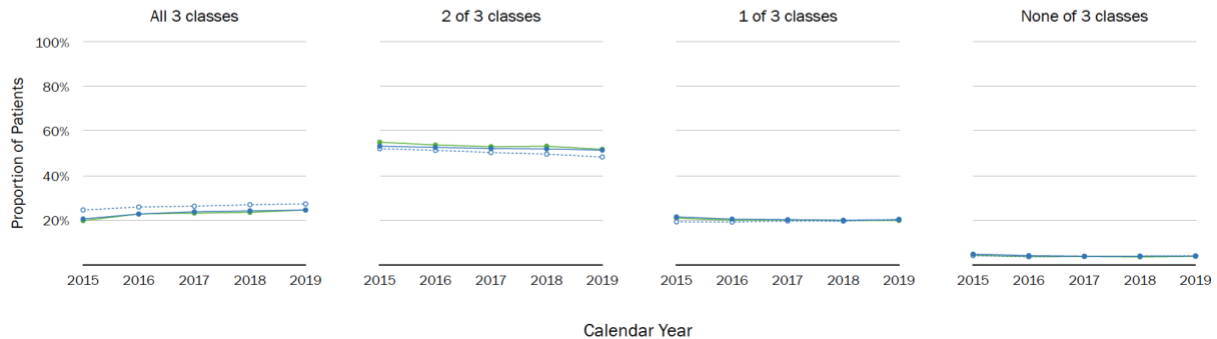
^a Figure S4 shows the proportion of Medicare beneficiaries with heart failure and reduced ejection fraction receiving heart failure medications and guideline-directed medical therapy (GDMT) by sex in each year. Heart failure medication use was defined as any prescription fill in part D claims in a given calendar year for ARNI, ACE inhibitor, ARB, evidence-based beta-blockers (bisoprolol, carvedilol, or metoprolol), MRA (spironolactone and eplerenone), hydralazine and ISDN, and loop diuretics. GDMT was defined as filling of a prescription for drugs in the following 3 classes within a given year: 1) an ARNI, ACE inhibitor, or ARB; 2) a beta-blocker; or 3) a MRA.

Supplementary Figure S5. Temporal Trends of Heart Failure Medications and Guideline-Directed Medical Therapy in Medicare Beneficiaries with Heart Failure with Reduced Ejection Fraction, 2015-2019, by Race^a

A. Use of Heart Failure Medications



B. Guideline-Directed Medical Therapy

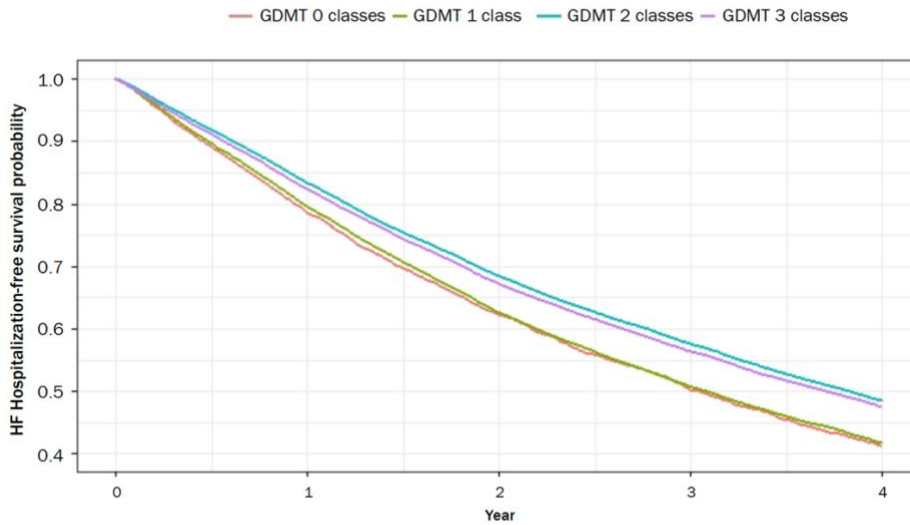


Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ISDN, isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist.

^a Figure S5 shows the proportion of Medicare beneficiaries with heart failure and reduced ejection fraction receiving heart failure medications and guideline-directed medical therapy (GDMT) by race in each year. Heart failure medication use was defined as any prescription fill in part D claims in a given calendar year for ARNI, ACE inhibitor, ARB, evidence-based beta-blockers (bisoprolol, carvedilol, or metoprolol), MRA (spironolactone and eplerenone), hydralazine and ISDN, and loop diuretics. GDMT was defined as filling of a prescription for drugs in the following 3 classes within a given year: 1) an ARNI, ACE inhibitor, or ARB; 2) a beta-blocker; or 3) a MRA.

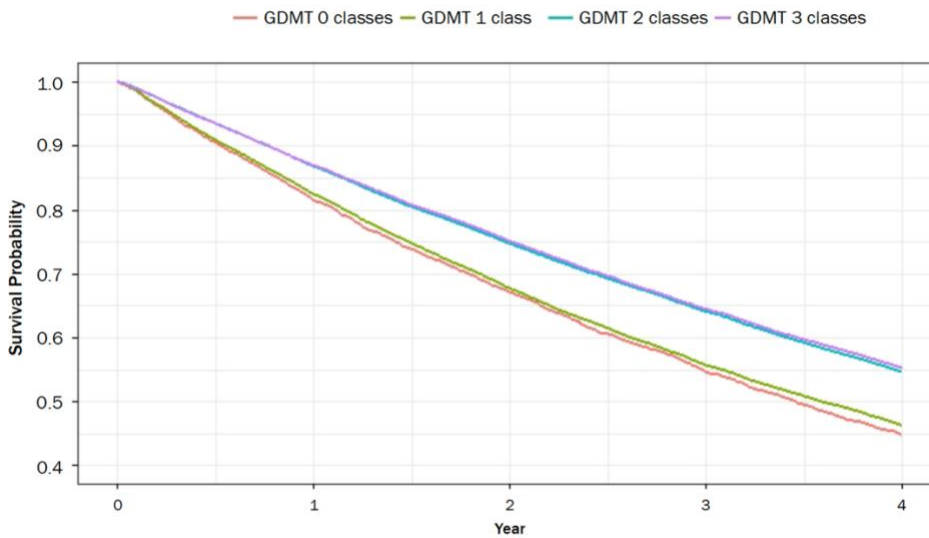
Supplementary Figure S6. Use of Guideline-Directed Medical Therapy and Kaplan-Meier Curves of Heart Failure Hospitalization-Free and Overall Survival Over 4 Years

A. Death or HF Hospitalization



GDMT	0	1	2	3	4
0 Classes	5970	4590	3022	2129	1567
1 Class	30028	23475	15908	11475	8579
2 Classes	78302	64108	45960	34529	26529
3 Classes	32699	26399	19054	14415	11144

B. Death



GDMT	0	1	2	3	4
0 Classes	5970	4766	3282	2332	1715
1 Class	30028	24344	17312	12684	9599
2 Classes	78302	66784	50474	38729	30185
3 Classes	32699	27895	21473	16645	13095

Abbreviations: GDMT, guideline-directed medical therapy; HF, heart failure.

Cox proportional hazards regression was used to estimate the hazard ratio and 95% confidence interval for the clinical outcomes associated with the number of GDMT class received. We adjusted for age, sex, race, dual eligibility, Alzheimer's disease and related dementias, anemia, atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease,

depression, diabetes, hip or pelvic fracture, hypertension, myocardial infarction, osteoporosis, rheumatoid arthritis or osteoarthritis, and stroke or transient ischemic attack, Gagne combined comorbidity index, frailty, cardiology visit within the past 30 days, ≥ 2 heart failure hospitalizations within the past year, and heart failure hospitalization within the past 30 days.