SUPPLEMENTAL MATERIAL

Table S1. Documented Reasons for ACEi/ARB Contraindication

ACEi Contraindication	N=6753	
Hypotension/Risk for Cardiogenic Shock	588	8.71%
Azotemia	1589	23.53%
Other	4023	59.57%
Patient Reason	796	11.79%
System Reason	58	0.86%

ARB Contraindication	N=6739	
Hypotension/Risk for Cardiogenic Shock	587	8.71%
Azotemia	1610	23.89%
Other	3983	59.10%
Patient Reason	765	11.35%
System Reason	56	0.83%

Table S2. Covariates Included in Multivariable Cox Regression

Variable Type	Covariates
Demographic	Age, sex, race (African American, Hispanic, Asian, other vs. white)
Past Medical History	Atrial fibrillation/flutter, diabetes, hyperlipidemia, hypertension, history of an implantable defibrillator, cardiac resynchronization therapy, ischemic heart disease (defined as a history of: coronary artery disease, myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting), number of heart failure hospitalizations during prior year, renal insufficiency, anemia, peripheral vascular disease, depression, chronic obstructive pulmonary disease, prior diagnosis of heart failure, number of heart failure hospitalizations in the prior year, dialysis, stroke, valvular heart disease, smoking status and admission weight
Vital Signs	Admission heart rate, systolic blood pressure and respiratory rate
Laboratory Values	Admission sodium, hemoglobin, creatinine, blood urea nitrogen, and estimated glomerular filtration rate, discharge potassium
Heart Failure Characteristics	Ejection fraction (treated as continuous if available, documented moderate/severe dysfunction set to 30% and normal/mild dysfunction set to 50%) and discharge on a beta blocker
In-Hospital Procedures	Cardiac catheterization with or without revascularization, cardiac surgery, mechanical ventilation, dialysis/ultrafiltration and cardioversion
Hospital Characteristics	Teaching status, number of beds, region, rural location and capability of performing percutaneous coronary intervention, cardiac surgery or cardiac transplantation

Multiple imputation was used to handle missing variables. Age and sex were complete variables. Race has 0.5% missing. Weight at admission had 10% missing. Past medical histories had only 1.4% missing. Heart rate and blood pressure had 4% missing. Respiratory rate at admission had 13% missing. In terms of labs, sodium had 17% missing, hemoglobin had 19% missing, creatinine had 11% missing, BUN had 17% missing and eGFR had 20% missing. Procedures had 7% missing. Hospital level variable number of beds and teaching status had <0.5% missing. Capability of PCI, surgery and transplant had 6-7% missing.

Table S3. Comparison of Primary Analysis and Sensitivity Analysis using Complete Discharge Data

Outcome	Groups Compared	Primary Analysis (from Table 4)		Sensitivity Analysis using Complete Discharge Data (n=4,011)	
		Adjusted HR and 95% CI	Adjusted P-value	Adjusted HR and 95% CI	Adjusted P-value
Mortality Rates					
30-day mortality	Started vs. continued	1.15 (0.96, 1.38)	0.134	1.02 (0.65, 1.60)	0.925
30-day mortality	Discontinued vs. continued	1.92 (1.32, 2.81)	<0.001	2.41 (1.15, 5.05)	0.020
30-day mortality	Not started vs. continued	1.50 (1.12, 2.00)	0.006	1.48 (0.89, 2.47)	0.131
90-day mortality	Started vs. continued	1.13 (1.01, 1.25)	0.026	0.97 (0.79, 1.19)	0.759
90-day mortality	Discontinued vs. continued	1.68 (1.31, 2.15)	<0.001	1.61 (0.94, 2.78)	0.085
90-day mortality	Not started vs. continued	1.37 (1.17, 1.60)	0.000	1.51 (1.20, 1.88)	<0.001
1-year mortality	Started vs. continued	1.09 (1.01, 1.17)	0.019	1.01 (0.87, 1.16)	0.915
1-year mortality	Discontinued vs. continued	1.35 (1.13, 1.61)	0.001	1.26 (0.81, 1.98)	0.306
1-year mortality	Not started vs. continued	1.28 (1.14, 1.43)	<0.001	1.30 (1.10, 1.52)	0.002
Readmission Rates					
30-day readmission	Started vs. continued	1.07 (0.98, 1.17)	0.148	1.07 (0.92, 1.26)	0.371
30-day readmission	Discontinued vs. continued	1.40 (1.16, 1.71)	<0.001	1.49 (0.91, 2.46)	0.114
30-day readmission	Not started vs. continued	1.14 (1.01, 1.29)	0.038	1.10 (0.81, 1.50)	0.526
90-day readmission	Started vs. continued	1.01 (0.94, 1.08)	0.769	0.99 (0.87, 1.12)	0.828
90-day readmission	Discontinued vs. continued	1.18 (0.98, 1.41)	0.074	1.22 (0.81, 1.85)	0.344

90-day readmission	Not started vs. continued	1.09 (1.00, 1.20)	0.061	1.01 (0.81, 1.25)	0.960
1-year readmission	Started vs. continued	0.98 (0.93, 1.03)	0.434	0.94 (0.85, 1.05)	0.274
1-year readmission	Discontinued vs. continued	1.07 (0.92, 1.25)	0.353	1.18 (0.83, 1.69)	0.360
1-year readmission	Not started vs. continued	1.01 (0.93, 1.09)	0.836	0.98 (0.81, 1.17)	0.795
Composite Mortality & Readmission Rates					
30-day mortality/ readmission	Started vs. continued	1.08 (0.99, 1.17)	0.091	1.04 (0.91, 1.20)	0.554
30-day mortality/ readmission	Discontinued vs. continued	1.47 (1.21, 1.79)	<0.001	1.74 (1.15, 2.62)	0.008
30-day mortality/ readmission	Not started vs. continued	1.20 (1.07, 1.36)	0.003	1.14 (0.87, 1.49)	0.359
90-day mortality/ readmission	Started vs. continued	1.02 (0.96, 1.09)	0.509	0.95 (0.85, 1.07)	0.392
90-day mortality/readmission	Discontinued vs. continued	1.24 (1.04, 1.49)	0.020	1.40 (1.00, 1.97)	0.051
90-day mortality/ readmission	Not started vs. continued	1.18 (1.08, 1.29)	<0.001	1.13 (0.95, 1.34)	0.173
1-year mortality/ readmission	Started vs. continued	0.99 (0.95, 1.04)	0.803	0.91 (0.83, 1.01)	0.069
1-year mortality/ readmission	Discontinued vs. continued	1.14 (0.96, 1.34)	0.130	1.37 (1.00, 1.86)	0.047
1-year mortality/ readmission	Not started vs. continued	1.12 (1.03, 1.22)	0.008	1.14 (0.98, 1.33)	0.099

Table S4. Rates of In-Hospital Procedures

	Total	Continued	Started	Discontinued	Not Started
N	16052	9572	4963	308	1209
% total N		59.63%	30.92%	1.92%	7.53%
In Hospital Procedures					
No Procedure (%)	70.06	68.44	70.84	73.45	78.92
Cardiac catheterization/ angiography (%)	11.52	10.79	15	7.59	4.72
Cardioversion (%)	1.37	1.53	1.19	0.69	0.96
CRT-P or CRT-D (%)	8	9.85	4.98	6.9	5.42
Pacemaker (%)	0.87	0.95	0.68	0.34	1.14
ICD only (%)	6.72	8.02	3.9	11.03	6.39
CABG (%)	0.32	0.21	0.36	1.03	0.79
Cardiac valve surgery (%)	0.15	0.1	0.2	0.34	0.26
CABG or cardiac valve surgery (%)	0.4	0.27	0.52	1.03	0.87
Dialysis (%)	1.54	1.44	1.55	1.72	2.27
Dialysis or ultrafiltration (%)	2.43	2.17	2.54	2.76	3.94
ABP (%)	0.08	0.07	0.09	0.34	0.09
Mechanical ventilation (%)	1.43	1.29	1.89	1.03	0.87
PCI or PCI with stent (%)	1.88	2.05	1.91	0.69	0.7
Stress testing (%)	3.22	3.03	4.19	1.03	1.57
Right Heart Cardiac Catheterization (%)	2.65	2.52	3.38	1.72	1.14

CRT-D: cardiac resynchronization therapy + defibrillator, CRT-P: cardiac resynchronization therapy + pacemaker, ICD: implantable cardiac defibrillator, CABG: Coronary artery bypass grafting, LVAD: Left ventricular assist device, IABP: Intra-aortic balloon pump, PCI: percutaneous coronary intervention

Table S5. Multivariate Cox Proportional Hazard Model Comparing Mortality, Readmission and Composite Mortality and Readmissions between Patients Discontinued from and Not Started on ACEi/ARB

Outcome	Groups Compared	Adjusted HR and 95% CI	Adjusted P-value
30-day mortality	Discontinued vs. Not Started	1.37 (0.83, 2.24)	0.218
30-day readmission	Discontinued vs. Not Started	1.17 (0.96, 1.44)	0.115
30-day composite (mortality or readmission)	Discontinued vs. Not Started	1.21 (1.00, 1.46)	0.056
90-day mortality	Discontinued vs. Not Started	1.27 (0.95, 1.69)	0.104
90-day readmission	Discontinued vs. Not Started	1.07 (0.89, 1.29)	0.449
90-day composite (mortality or readmission)	Discontinued vs. Not Started	1.07 (0.89, 1.28)	0.459
1-year mortality	Discontinued vs. Not Started	1.07 (0.88, 1.30)	0.513
1-year readmission	Discontinued vs. Not Started	1.05 (0.91, 1.20)	0.539
1-year composite (mortality or readmission)	Discontinued vs. Not Started	1.02 (0.88, 1.19)	0.794

Table S6. Comparison of Baseline Characteristics between Patients Excluded due to Missing Data and those Included in the Study Population
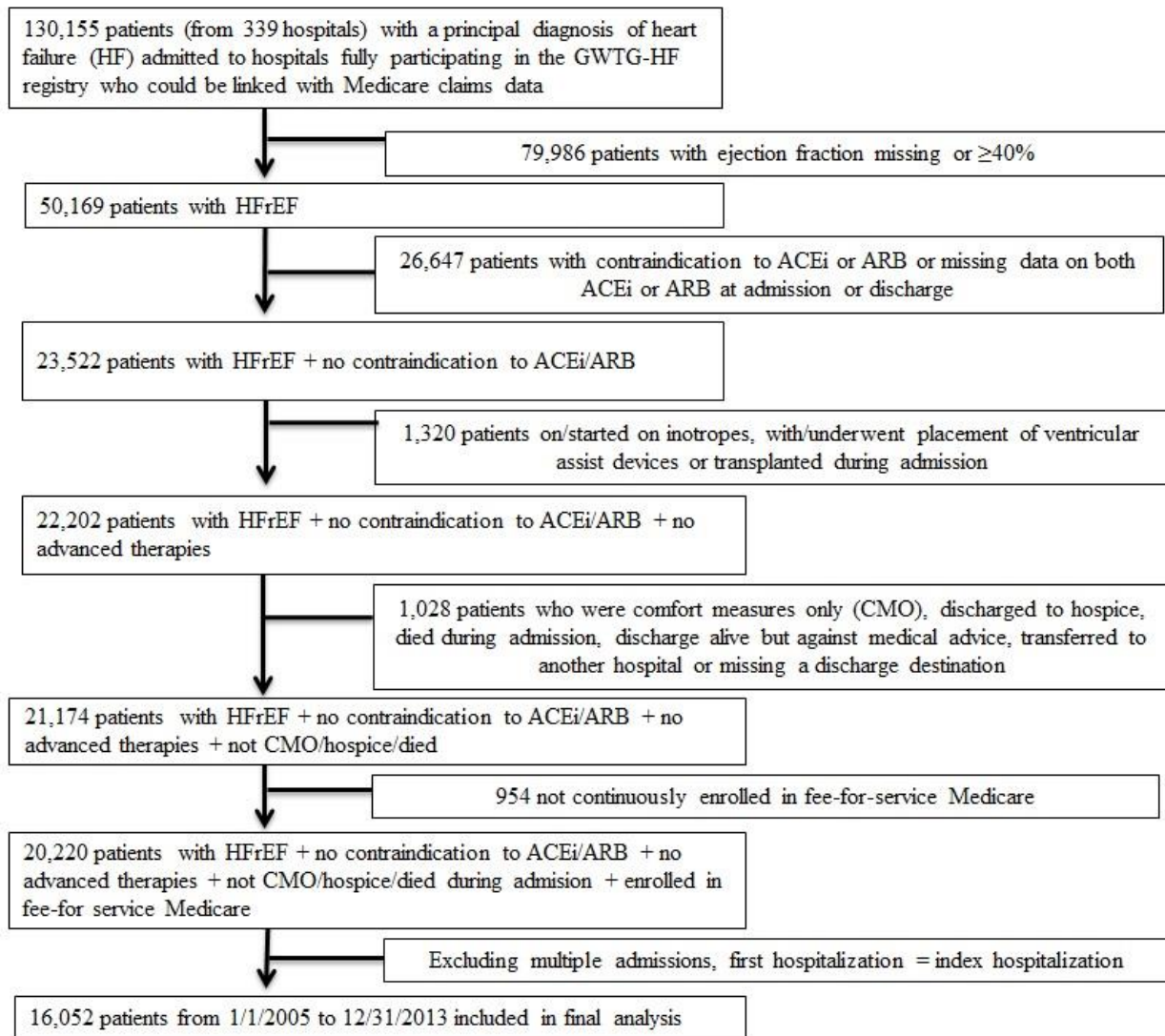
	Included Study Population	Excluded due to Missing Data	Standardized Differences*
N	16052	15727	
Demographics			
Age	78.34 ± 7.92	79.01 ± 8.25	8.3
Sex (% female)	41.85	41.74	0.21
Race (% white)	77.97	75.56	5.11
Body Mass Index (BMI)	27.65 ± 6.83	26.96 ± 6.57	10.29
Past Medical History			
Atrial Fibrillation/Flutter (%)	36.19	39.98	7.82
Diabetes - Insulin Treated (%)	16.8	17.54	1.96
Diabetes - Non-insulin Treated (%)	24.85	22.25	6.13
Hyperlipidemia (%)	51.18	48.4	5.55
Hypertension (%)	76.51	71.02	12.49
ICD (%)	14.90	17.49	7.01
Ischemic Heart Disease (%)	67.09	67.19	0.21
PVD (%)	13.51	13.85	0.97
Renal Insufficiency (%)	14.63	24.27	24.54
Smoking (%)	12.05	10.87	2.49
Stroke (%)	15.72	16.29	1.56
Heart Failure Characteristics			
History of HF	62.38	70.3	20.2
Ejection fraction (%)	25.39 ± 7.46	25.41 ± 7.56	14.96
Number of hospital admission in 1 year prior to admission (n)			
>2 (%)	3.20	7.97	
2 (%)	4.79	9.30	22.05
1 (%)	16.99	22.35	
0 (%)	75.01	60.37	

Vital Signs (at admission)			
Heart rate (bmp)	85.30 ± 19.91	85.90 ± 19.98	3.02
Systolic blood pressure (mmHg)	137.67 ± 26.86	129.44 ± 27.17	30.45
Vital signs (at discharge)			
Heart rate (bmp)	74.77 ±12.81	77.09 ± 14.34	17.05
Systolic blood pressure (mmHg)	119.82 ± 19.29	116.86 ± 19.43	15.17
Labs (at admission)			
BNP (pg/ml)	1078 (552, 2010)	1385 (718, 2556)	20.42
NT-proBNP (pg/ml)	7315 (3284, 15310)	11154 (5535, 25000)	34.45
Creatinine (mg/dl)	1.3 (1.0, 1.6)	1.4 (1.1, 1.9)	14.78
eGFR	52.65 (38.68, 69.40)	46.94 (32.63, 63.72)	1.77
Labs (at discharge)			
Potassium (mEq/L)	4.1 (3.8, 4.4)	4.1 (3.7, 4.5)	2.99
BNP (pg/ml)	706 (348, 1417)	1088 (519, 2187)	34.47
NT-proBNP (pg/ml)	5419 (2787, 12019)	9995 (5178, 16498)	43.95
Creatinine (mg/dl)	1.3 (1.0, 1.7)	1.5 (1.1, 2.1)	15.8

A standardized difference greater than 10% is typically considered meaningful[1]

Figure S1. Study Population Derivation

130,155 patients (from 339 hospitals) with a principal diagnosis of heart failure (HF) admitted to hospitals fully participating in the GWTG-HF registry who could be linked with Medicare claims data

→ 79,986 patients with ejection fraction missing or ≥40%

50,169 patients with HFrEF

→ 26,647 patients with contraindication to ACEi or ARB or missing data on both ACEi or ARB at admission or discharge

23,522 patients with HFrEF + no contraindication to ACEi/ARB

→ 1,320 patients on/started on inotropes, with/underwent placement of ventricular assist devices or transplanted during admission

22,202 patients with HFrEF + no contraindication to ACEi/ARB + no advanced therapies

→ 1,028 patients who were comfort measures only (CMO), discharged to hospice, died during admission, discharge alive but against medical advice, transferred to another hospital or missing a discharge destination

21,174 patients with HFrEF + no contraindication to ACEi/ARB + no advanced therapies + not CMO/hospice/died

→ 954 not continuously enrolled in fee-for-service Medicare

20,220 patients with HFrEF + no contraindication to ACEi/ARB + no advanced therapies + not CMO/hospice/died during admision + enrolled in fee-for service Medicare

→ Excluding multiple admissions, first hospitalization = index hospitalization

16,052 patients from 1/1/2005 to 12/31/2013 included in final analysis

Supplemental Reference:

1. Mamdani M, Sykora K, Li P, Normand SL, Streiner DL, Austin PC, Rochon PA, Anderson GM. Reader's guide to critical appraisal of cohort studies: Assessing potential for confounding. *BMJ*. 2005;330:960-2.