

Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction

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Background—Guidelines recommend continuation or initiation of guideline-directed medical therapy, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARB), in hospitalized patients with heart failure with reduced ejection fraction.

Methods and Results—Using the Get With The Guidelines–Heart Failure Registry, we linked clinical data from 16 052 heart failure with reduced ejection fraction (ejection fraction $\leq 40\%$) patients with Medicare claims data. We divided ACEi/ARB-eligible patients into 4 categories based on admission and discharge ACEi/ARB use: continued (reference group), started, discontinued, or not started on therapy. A multivariable Cox proportional hazard model was used to determine the association between ACEi/ARB category and outcomes. Most, 90.5%, were discharged on ACEi/ARB (59.6% continued and 30.9% newly started). Of those discharged without ACEi/ARB, 1.9% were discontinued, and 7.5% were eligible but not started. Thirty-day mortality was 3.5% for patients continued and 4.1% for patients started on ACEi/ARB. In contrast, 30-day mortality was 8.8% for patients discontinued (adjusted hazard ratio [HR_{adj}] 1.92; 95% CI 1.32–2.81; $P < 0.001$) and 7.5% for patients not started (HR_{adj} 1.50; 95% CI 1.12–2.00; $P = 0.006$). The 30-day readmission rate was lowest among patients continued or started on therapy. One-year mortality was 28.2% for patients continued and 29.7% for patients started on ACEi/ARB compared to 41.6% for patients discontinued (HR_{adj} 1.35; 95% CI 1.13–1.61; $P < 0.001$) and 41.7% (HR_{adj} 1.28; 95% CI 1.14–1.43; $P < 0.001$) for patients not started on therapy.

Conclusions—Compared with continuation, withdrawal of ACEi/ARB during heart failure hospitalization is associated with higher rates of postdischarge mortality and readmission, even after adjustment for severity of illness. (*J Am Heart Assoc.* 2017;6:e004675. DOI: 10.1161/JAHA.116.004675.)

Key Words: angiotensin II receptor blockers • angiotensin-converting enzyme inhibitors • heart failure • outcomes research • quality of care

Almost 6 million Americans suffer from heart failure (HF). By 2030, that figure is projected to surpass 8 million. Over the past decade, HF has accounted for over 1 million hospitalizations annually.¹ Readmission rates are also high, with over 50% of discharged patients readmitted within the

next 6 months.² The age-adjusted mortality, after an admission for acute decompensated heart failure (ADHF), is ~10% at 30 days, 30% at 1 year, and as high as 50% by 5 years.¹

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) have been shown in

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Accompanying Tables S1 through S6 and Figure S1 are available at <http://jaha.ahajournals.org/content/6/2/e004675/DC1/embed/inline-supplementary-material-1.pdf>

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multiple large clinical trials to improve symptoms, reduce hospitalizations, and improve survival in patients with HF with reduced ejection fraction (HFrEF).³⁻⁷ The American College of Cardiology (ACC)/American Heart Association (AHA) clinical guidelines make it a Class I, Level A recommendation to use ACEi/ARB therapy in patients with HFrEF both to “prevent symptomatic heart failure” and to “reduce morbidity and mortality.”⁸ In addition, the ACC/AHA HF Performance Measures recommend ACEi/ARB for outpatients with HFrEF and ACEi/ARB therapy at the time of hospital discharge for inpatients with HFrEF.⁹ These clinical guidelines and quality metrics, along with their associated incentives, have led to significant improvements in the rates of ACEi/ARB use over time.

Continuation of β -blocker therapy at the time of hospital discharge has been shown to reduce both readmission and mortality rates after ADHF admissions.¹⁰⁻¹² The impact of continuing or discontinuing ACEi/ARB after ADHF hospitalization has not been as well studied. This study aims to define the relationship between the continuation or withdrawal of ACEi/ARB therapy and the outcomes of patients with HFrEF hospitalized for ADHF.

Methods

Data Source

Data for this analysis are from the Get With The Guidelines Heart Failure (GWTG-HF) registry linked with Medicare inpatient data. Medicare Part A (inpatient) claims and the associated denominator file from January 1, 2005, through December 31, 2013 were linked with data from the GWTG-HF registry using previously described methods and indirect identifiers.¹³ Standardized data collection variables and methods for GWTG-HF have been previously described as well.¹⁴ GWTG-HF is a hospital-based, voluntary data collection and quality improvement initiative that began in 2005. Participating hospitals submit clinical information regarding in-hospital care and outcomes of consecutive patients hospitalized for ADHF using an online Patient Management Tool (Outcome Sciences, Inc, Cambridge, MA). Linkage of GWTG-HF data with Medicare claims data allows for both short- and long-term mortality and readmission assessment.

Study Population

Patients were eligible to be included if they had a diagnosis of HF based on their GWTG records and if their GWTG record could be linked with Medicare claims. To ensure high-quality data, we excluded patients from hospitals with $\geq 25\%$ missing data for past medical history. This left us with a starting population of 130 155 patients from 339 hospitals. The

complete study population derivation algorithm is provided in Figure S1. We excluded patients with ejection fractions that were missing or $>40\%$ (N=79 986) and patients with contraindications to ACEi/ARB therapy (N=13 268, contraindication frequencies listed in Table S1) or patients who had missing ACEi/ARB contraindication data (N=13 379). We also excluded patients who were started on inotropes, transplanted, discharged to hospice, placed on comfort measures only, died during admission, left against medical advice, were transferred to another short-term hospital, or who were not enrolled in Medicare fee-for-service. If multiple hospitalizations existed for a patient, the first hospitalization was selected as the index hospitalization. The remaining population of 16 052 was used for all analyses.

Primary Measures and Definitions

Among those eligible for the study and without a contradiction to ACEi/ARB therapy, we created and defined 4 patient groups for comparison: patients on ACEi/ARB at admission and discharge (continued), those not on ACEi/ARB at admission but who were discharged on ACEi/ARB (started), those on ACEi/ARB at admission but not at discharge (discontinued), and those not on ACEi/ARB at admission or discharge (not started).

The primary endpoint of this study was the difference in all-cause mortality at 30 days between those who continued versus discontinued ACEi/ARB at the time of discharge. Secondary endpoints included differences between those who continued and those who discontinued ACEi/ARB therapy in 90-day and 1-year mortality rates and differences in 30-day, 90-day and 1-year readmission rates. Tertiary endpoints include differences between those who continued and those who discontinued ACEi/ARB therapy in rates of the composite endpoint of all-cause death and all-cause readmission at 30 days, 90 days, and 1 year.

All participating institutions are required to comply with local regulatory and privacy guidelines and to submit the GWTG protocol for review and approval by their institutional review board. Because data are used mainly at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. The Duke Clinical Research Institute served as the primary analytic center for the aggregate de-identified data. The Duke University Institutional Review Board approved the study.

Statistical Analysis

Patient characteristics and hospital characteristics are described by mean \pm standard deviation for normally distributed data and or median and 25th and 75th percentiles for non-normally distributed data. Categorical variables are

Table 1. Baseline Characteristics of GWTG-HF Subjects Meeting Eligibility Criteria

	Total	Continued ACEi/ARB	Started ACEi/ARB	Discontinued ACEi/ARB	Not Started ACEi/ARB
N	16 052	9572	4963	308	1209
% total N		59.63%	30.92%	1.92%	7.53%
Demographics					
Age, y	78.34±7.92	77.99±7.82	78.65±8.1	78.97±7.77	79.58±7.85
Sex (% female)	41.85	41.19	43.2	44.48	40.78
Race (% white)	77.97	78.02	77.31	76.3	80.73
Body mass index	27.65±6.83	27.91±6.82	27.34±6.84	27.38±7.32	26.8±6.62
Past medical history					
Atrial fibrillation/flutter, %	36.19	37.33	32.77	33.66	41.4
Diabetes mellitus— insulin-treated, %	16.8	17.52	15.21	15.18	17.78
Diabetes mellitus— non-insulin-treated, %	24.85	26.24	21.99	29.04	24.12
Hyperlipidemia, %	51.18	53.65	46.81	46.2	50.17
Hypertension, %	76.51	79.59	71.6	75.58	71.79
ICD, %	14.9	16.55	11.35	13.2	16.44
Ischemic heart disease, %*	67.09	70.23	59.71	68.32	71.2
PVD, %	13.51	13.86	12.56	11.22	15.11
Renal insufficiency, %	14.63	13.77	13.86	19.47	23.37
Smoking, %	12.05	11.35	13.82	10.71	10.75
Stroke, %	15.72	16.16	14.5	16.83	16.78
HF characteristics					
History of HF, %	67.91	72.79	58.8	63.31	67.91
Ejection fraction, % [†]	26.36±7.33	26.34±7.28	26.27±7.41	26.35±7.29	26.9±7.37
Number of hospital admissions in prior 1 year for HF (n)					
Unknown (%)	21.99	23.03	18.56	27.6	26.47
>2 (%)	2.21	2.44	1.51	2.92	3.06
2 (%)	3.11	3.45	2.16	2.6	4.55
1 (%)	12.46	13.59	10.03	12.99	13.32
0 (%)	37.07	39.77	32.66	37.66	33.66
Vital signs (at admission)					
Heart rate, bpm	85.3±19.91	83.66±19.29	88.67±20.69	84.85±20.39	84.99±19.81
Systolic blood pressure, mm Hg	137.67±26.86	137.58±26.8	139.29±27.12	134.27±26.47	132.72±25.6
% with systolic blood pressure <90 mm Hg	1.44%	1.57%	1.03%	0.97%	2.23%
Diastolic blood pressure, mm Hg	76.94±17.18	76.25±17.07	79.06±17.44	74.9±17.65	74.39±15.95
Vital signs (at discharge)					
Heart rate, bmp	74.77±12.81	74.14±12.55	75.61±13.01	76.1±13.32	76.26±13.65
Systolic blood pressure, mm Hg	119.82±19.29	120.22±19.55	119.13±18.95	119.23±20.34	119.64±18.17
% with systolic blood pressure <90 mm Hg	2.63%	2.80%	2.42%	3.90%	1.82%

Continued

Table 1. Continued

	Total	Continued ACEi/ARB	Started ACEi/ARB	Discontinued ACEi/ARB	Not Started ACEi/ARB
Diastolic blood pressure, mm Hg	65.46±11.63	65.42±11.73	65.51±11.63	65.31±11.56	65.61±10.72
Labs (at admission) [‡]					
BNP, pg/mL	1078 (552, 2010)	1032 (521, 1928)	1136 (590, 2150)	1170 (577, 2061)	1190 (632, 2142)
NT-proBNP, pg/mL	7315 (3284, 15 310)	7205 (3107, 14 115)	7155 (3594, 16 017)	7306 (4297, 19 602)	9693 (4065, 20 896)
Creatinine, mg/dL	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)	1.2 (1.0, 1.6)	1.5 (1.1, 2.1)	1.5 (1.1, 2.0)
% with creatinine >2 mg/dL	11.15%	10.31%	9.39%	23.38%	21.92%
eGFR, mL/[min·1.73 m ²]	52.7 (38.7, 69.4)	52.7 (39.1, 69.2)	55.9 (41.3, 72.3)	41.7 (29.8, 61.3)	45.0 (30.4, 61.4)
% with CKD Stage IV or V [§]	10.09%	9.31%	8.36%	22.40%	20.26%
Labs (at discharge) [‡]					
Potassium, mEq/L	4.1 (3.8, 4.4)	4.1 (3.8, 4.4)	4.1 (3.8, 4.4)	4.1 (3.7, 4.4)	4.1 (3.7, 4.4)
% with potassium >5 mEq/L	2.16%	2.37%	1.59%	3.90%	2.40%
BNP, pg/mL	706 (348, 1417)	671 (334, 1350)	717 (344, 1480)	906 (414, 1582)	974 (501, 1700)
NT-proBNP, pg/mL	5419 (2787, 12 019)	5470 (2839, 10 556)	5049 (2629, 12 611)	4656 (4142, 14 231)	8471 (3172, 15 356)
Creatinine, mg/dL	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.2 (1.0, 1.6)	1.5 (1.2, 2.0)	1.5 (1.1, 2.1)
% with creatinine >2 mg/dL	9.89%	9.02%	8.54%	19.16%	19.93%
eGFR, mL/[min·1.73 m ²]	51.6 (37.9, 68.3)	51.6 (37.9, 68.0)	54.9 (40.5, 70.8)	43.7 (30.5, 61.3)	44.2 (30.7, 61.5)
% with CKD stage IV or V [§]	9.11%	8.33%	8.04%	17.86%	17.54%
% with worsening renal function	11.87%	11.84%	11.38%	15.58%	13.23%

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; bpm, beats per minute; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GWTG, Get With the Guidelines; HF, heart failure; ICD, implantable cardiac defibrillator; NT-proBNP, N-terminal prohormone BNP; PVD, peripheral vascular disease.

*Ischemic heart disease: a history of myocardial infarction, coronary artery disease, percutaneous coronary intervention or coronary artery bypass grafting.

[†]Ejection fraction: defined as original variable (%) when present or, if categorized only, imputed to 30% if described as moderate/severe or 50% if described as mild/moderate.

[‡]Labs at admission and discharge are displayed as median with interquartile ranges. There is a high rate of missing data among some variables: admission BNP 37.2% missing, admission NT-proBNP 88.1% missing, and admission creatinine 11.6% missing; discharge BNP 67.8% missing, discharge NT-proBNP 97.1% missing, and discharge creatinine 24.6% missing.

[§]Chronic kidney disease (CKD) stage IV or V: defined as eGFR <30 mL/(min·1.73 m²).

^{||}Worsening renal function: defined as a rise of ≥0.3 mg/dL in serum creatinine between admission and discharge.

described using percentages. Categorical variables are compared using a chi-squared test, and continuous variables are compared using the Kruskal-Wallis test. A multivariable Cox proportional hazard model was constructed to assess whether there were differences in clinical outcomes (30-day, 90-day, and 1-year mortality, readmission, and composite endpoints) among the ACEi/ARB groups (continued, started, discontinued, not started). Patients continued on ACEi/ARB are the reference group for all hazard ratio assessments unless otherwise specified.

The covariates adjusted for in the model are specified in Table S2, and a sensitivity analysis using discharge vital signs and laboratory values is displayed in Table S3 and confirms the study's main findings. Robust standard errors are estimated in Cox models to account for the clustering of patients within hospitals. For readmission outcomes, the Fine-Gray model¹⁵ was used to account for the competing risk of mortality. Formal tests and graphical methods (cumulative

instance plots and plots of residuals vs time) were used to assess the proportional hazards assumptions in Cox and Fine-Gray models. There was no major violation detected from the data. All *P*-values are 2-sided, with values less than 0.05 considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

The baseline patient characteristics of the 16 052 patients included in this study are displayed in Table 1. The average age was 78.3 years, 42% were women, and 78% were white. The median ejection fraction was 26% (interquartile range 20% to 33%). A total of 14 535 (90.5%) of patients were discharged on ACEi/ARB. There were 9572 (59.6%) continued on ACEi/

Table 2. Baseline Hospital Characteristics

Hospital characteristics					
Number of beds, n	443.77±280.13	447.53±285.13	440.03±270.97	442.33±289.78	429.71±274.31
Academic hospital, %	64.38	63.37	66.63	68.51	62.03
Rural hospital, %	6.77	6.48	6.27	8.77	10.67
Region					
West, %	5.86	5.87	6.04	4.87	5.21
South, %	37.78	38.65	35.16	46.43	39.37
Midwest, %	27.96	28.4	27.34	20.78	28.87
Northeast, %	28.41	27.08	31.45	27.92	26.55
Primary PCI performed for MI, %	82.09	81.84	82.01	82.47	84.28
Interventional capabilities, %	73.6	73.57	74.57	70.45	70.72
Cardiac surgery on site, %	73.95	74.03	74.87	72.08	70.06
Cardiac transplant center	10.37	11.31	9.17	6.17	8.85
Performance measures					
Discharge instructions provided, %	89.81	90.7	91.02	77.18	79.98
HF patients with LVSD discharged on β -blocker, %	93.59	94.96	94.79	75.95	82.38
HF patients with smokers with smoking cessation, %	94.63	95.03	95.34	87.88	89.23
HF patients with follow-up appointment at discharge, %	61.99	64.46	59.77	50	46.27
HF patients with LVSD with ICD placed/prescribed at discharge, %	61.06	65.25	52.56	64.29	48.89

HF signifies heart failure; ICD, implantable cardiac defibrillator; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

ARB, 4963 (30.9%) newly started on ACEi/ARB, 308 (1.9%) discontinued from ACEi/ARB, and 1209 (7.5%) not started. Although there was a higher rate of hypotension (defined as systolic blood pressure <90 mm Hg) at admission among those discontinued or not started on ACEi/ARB, there was no difference in the rate of hypotension at discharge. Those discontinued or not started on ACEi/ARB did have higher rates of renal dysfunction as evidenced by higher rates of creatinine >2 mg/dL, potassium >5 mg/dL, rates of chronic kidney disease stage IV and V, and lower estimated glomerular filtration rates. There was no difference in the rate of hyperkalemia.

Hospital characteristics are displayed in Table 2. The rates of in-hospital procedures were low and are presented in Table S4. The rates of conformity with hospital performance measures were lower among patients discontinued or not started on ACEi/ARB. In addition to lower rates of β -blocker and ACEi/ARB prescription at discharge, those discontinued or not started on ACEi/ARB also had lower rates of being provided discharge instructions, smoking cessation counseling, timely follow-up appointments, and ICD counseling.

Mortality

The unadjusted results for 30-day, 90-day, and 1-year mortality, readmission, and composite mortality or readmission rates are displayed in Table 3. The adjusted hazard ratios (HR_{adj}) and corresponding 95% CI from the multivariate Cox proportional hazard model are displayed in Table 4.

The unadjusted 30- and 90-day mortality rates were higher among those who discontinued or did not start ACEi/ARB therapy, compared to those who continued or started therapy. After adjustment, the HR_{adj} for 30-day mortality among patients who discontinued ACEi/ARB was 1.92 (95% CI 1.32, 2.81; $P<0.001$) compared to patients continued on therapy. Among those not started on therapy, it was 1.50 (95% CI 1.12, 2.06; $P=0.006$). By 1 year, patients discontinued from ACEi/ARB had an HR_{adj} of 1.35 (95% CI 1.13, 1.61; $P=0.001$), and those not started on ACEi/ARB had an HR_{adj} of 1.28 (95% CI 1.14, 1.43; $P<0.001$). Estimates for 1-year mortality are displayed in Figure – panel A.

In addition, although it did not reach statistical significance, we observed a trend toward increased mortality at 30 and 90 days among those who discontinued compared with

Table 3. 30-Day, 90-Day, and 1-Year Mortality, Readmission, and Composite Mortality and Readmission Rates by Group, Observed

	Continued	Started	Discontinued	Not Started	P Value
N	9572	4963	308	1209	
30-day mortality	338 (3.5%)	202 (4.1%)	27 (8.8%)	90 (7.5%)	<0.0001
90-day mortality	950 (10.0%)	550 (11.2%)	64 (20.8%)	215 (18.0%)	<0.0001
1-year mortality	2590 (28.2%)	1413 (29.7%)	126 (41.6%)	492 (41.7%)	<0.0001
30-day readmission	1738 (18.3%)	941 (19.1%)	88 (28.6%)	281 (23.3%)	<0.0001
90-day readmission	3301 (35.0%)	1687 (34.5%)	132 (43.0%)	488 (40.9%)	<0.0001
1-year readmission	5639 (61.6%)	2827 (59.6%)	198 (66.0%)	753 (64.3%)	<0.0001
30-day mortality/readmission	1910 (20.1%)	1042 (21.1%)	102 (33.1%)	331 (27.5%)	<0.0001
90-day mortality/readmission	3652 (38.7%)	1888 (38.6%)	153 (49.9%)	579 (48.5%)	<0.0001
1-year mortality/readmission	6202 (67.7%)	3144 (66.2%)	225 (74.9%)	886 (75.6%)	<0.0001

those not started on ACEi/ARB (Table S5). In addition, there was a slight mortality advantage for those who continued on ACEi/ARB compared with those started on therapy at the time of discharge.

Readmission

The unadjusted 30-day, 90-day, and 1-year readmission rates were higher in patients discontinued or not started on ACEi/ARB therapy compared with patients who continued or started on ACEi/ARB. After adjustment, the HR_{adj} for 30-day readmission was 1.40 (95% CI 1.16, 1.71, $P<0.001$) among those who discontinued and 1.14 (95% CI 1.01, 1.29, $P=0.038$) among those who did not start ACEi/ARB. There was no difference in 30-day readmission rates between those who continued and those who started ACEi/ARB therapy. By 90 days, after adjustment, there was no difference in readmission rates between the groups. Estimates for 1-year readmission are displayed in Figure – panel B.

Composite Endpoint (Mortality or Readmission)

Similar to mortality and readmission rates, the unadjusted 30-day, 90-day, and 1-year composite endpoint of mortality and readmission was higher among those discontinued or not started on ACEi/ARB, compared with patients who continued or started on therapy. As observed with mortality, patients who were continued or started on ACEi/ARB had lower 30- and 90-day composite endpoint rates. By 1 year, those who were not started on ACEi/ARB had higher rates of the composite endpoint compared to patients continued on ACEi/ARB, and there was a trend toward higher rates among those discontinued from ACEi/ARB. Estimates for 1-year composite endpoint rates are displayed in Figure – panel C.

Discussion

In this study of 16 052 patients with HF_{rEF} admitted for ADHF, we found that discontinuation of ACEi/ARB at the time of hospital discharge was associated with higher 30-day, 90-day, and 1-year mortality compared with continuation of ACEi/ARB among eligible patients. We also found that continuation or initiation of ACEi/ARB was associated with lower 30- and 90-day readmission and composite endpoint rates. Patients who had ACEi/ARB discontinued during hospitalization had the highest rates of mortality and readmission.

These findings are consistent with prior cardiovascular work demonstrating improved outcomes with greater adherence to clinical guidelines. The REACH investigators examined 37 154 outpatients diagnosed with atherothrombotic disease and found that nonadherence was associated with an increased risk of cardiovascular death, myocardial infarction, or stroke.¹⁶ In this study we similarly found improved outcomes for patients when clinicians adhered closely to guidelines and continued or initiated ACEi/ARB therapy.

Compared to some prior studies, we found higher rates of ACEi/ARB prescription at discharge, 90.6%.¹⁷⁻¹⁹ This rate, however, is consistent with a prior GWTG-HF study.²⁰ The high rates of ACEi/ARB prescription in this study may reflect the impact of including ACEi/ARB as a performance measure^{9,21} and the results of quality improvement efforts made during this time (2005-2013). The percentage may also be high due to selection bias, and hospitals that choose to participate in GWTG may be different from those that do not.

This study confirms and extends prior work regarding patterns of guideline-directed medical therapy use and outcomes in HF patients. Data from Tran et al using the Atherosclerosis Risk in Communities Study found that the initiation or cessation of guideline-directed medical therapy

Table 4. Multivariate Cox Proportional Hazard Model Comparing Mortality, Readmission, and Composite Mortality and Readmissions Between Groups

Outcome	Groups Compared	Adjusted Hazard Ratio and 95% CI	Adjusted <i>P</i> Value
Mortality rates			
30-day mortality	Started vs continued	1.15 (0.96, 1.38)	0.134
	Discontinued vs continued	1.92 (1.32, 2.81)	<0.001
	Not started vs continued	1.50 (1.12, 2.00)	0.006
90-day mortality	Started vs continued	1.13 (1.01, 1.25)	0.026
	Discontinued vs continued	1.68 (1.31, 2.15)	<0.001
	Not started vs continued	1.37 (1.17, 1.60)	0.000
1-year mortality	Started vs continued	1.09 (1.01, 1.17)	0.019
	Discontinued vs continued	1.35 (1.13, 1.61)	0.001
	Not started vs continued	1.28 (1.14, 1.43)	<0.001
Readmission rates			
30-day readmission	Started vs continued	1.07 (0.98, 1.17)	0.148
	Discontinued vs continued	1.40 (1.16, 1.71)	<0.001
	Not started vs continued	1.14 (1.01, 1.29)	0.038
90-day readmission	Started vs continued	1.01 (0.94, 1.08)	0.769
	Discontinued vs continued	1.18 (0.98, 1.41)	0.074
	Not started vs continued	1.09 (1.00, 1.20)	0.061
1-year readmission	Started vs continued	0.98 (0.93, 1.03)	0.434
	Discontinued vs continued	1.07 (0.92, 1.25)	0.353
	Not started vs continued	1.01 (0.93, 1.09)	0.836
Composite mortality or readmission rates			
30-day mortality/readmission	Started vs continued	1.08 (0.99, 1.17)	0.091
	Discontinued vs continued	1.47 (1.21, 1.79)	<0.001
	Not started vs continued	1.20 (1.07, 1.36)	0.003
90-day mortality/readmission	Started vs continued	1.02 (0.96, 1.09)	0.509
	Discontinued vs continued	1.24 (1.04, 1.49)	0.020
	Not started vs continued	1.18 (1.08, 1.29)	<0.001
1-year mortality/readmission	Started vs continued	0.99 (0.95, 1.04)	0.803
	Discontinued vs continued	1.14 (0.96, 1.34)	0.130
	Not started vs continued	1.12 (1.03, 1.22)	0.008

for HF occurs in roughly 12% of hospitalized patients and that cessation of guideline-directed medical therapy was associated with higher mortality rates.²² Our work is also consistent with prior work analyzing continuation versus withdrawal of β -blocker therapy. Data from the OPTIMIZE-HF study found a significant benefit (HR 0.60, 95% CI 0.37, 0.99) for all-cause mortality at 60 to 90 days associated with β -blocker continuation at the time of discharge among HFrEF patients.¹²

This study also confirms and extends prior work regarding ACEi/ARB use patterns. Data from over 17 000 patients enrolled in the National Health Care Project found that a discharge prescription for ACEi/ARB was associated with a

17% relative reduction in mortality (RR 0.83, 95% CI 0.79, 0.88).¹⁹ Work by Sanam et al analyzing 1384 Medicare beneficiaries in Alabama found lower 30-day and 1-year readmission and mortality rates among patients with HF discharged on ACEi/ARB.²³

In contrast to prior work this study separated patients not discharged on ACEi/ARB into discontinued and not started categories and separated patients discharged on ACEi/ARB into continued and newly started categories. By doing this we were able to observe a trend toward increased mortality at 30 and 90 days among those discontinued from ACEi/ARB, compared with those not started on ACEi/ARB. This trend

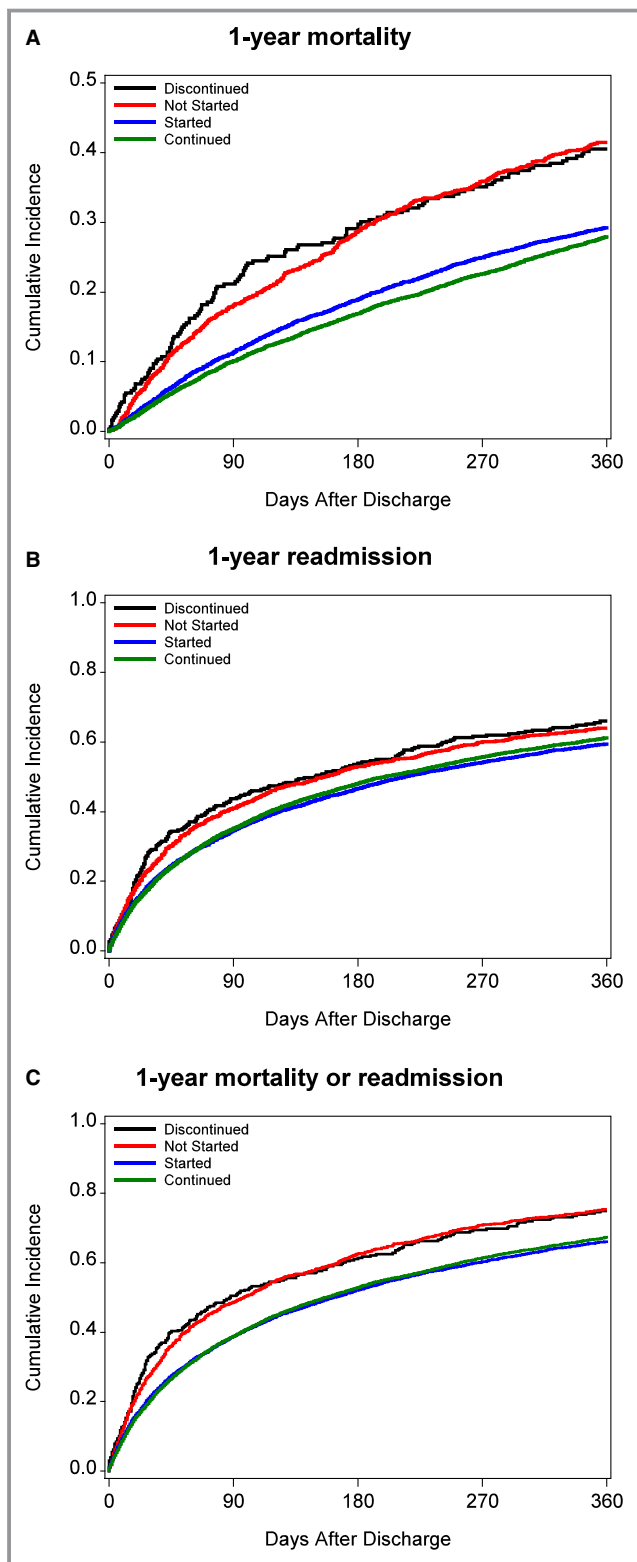


Figure. A, One-year mortality. B, One-year readmission rates. C, One-year composite endpoint (mortality or readmission) rates.

may merit further investigation. We also observed a mortality advantage for those who continued on ACEi/ARB compared with those started on therapy at discharge.

Based on the results of this study, additional work adequately powered to determine if there is indeed a true disadvantage to discontinuing versus not starting therapy or if there is a true advantage to continuing versus starting therapy, should be considered. In addition, using a different data set, exploring the clinical reasons underlying the decision not to follow clinical guidelines and whether these reasons affect clinical outcomes would be very helpful.

Limitations

Certain limitations should be considered when interpreting the results of this study. First, because of the retrospective design of this study, we are unable to make any comments on causation. This study reports associations only. Because the data come from a registry, many patients were excluded because of missing data. These results should therefore only be applied to patients meeting the study's inclusion/exclusion criteria. However, to address concern regarding excluded patients, we compared baseline characteristics of the study population and those excluded due to missing data. The results are displayed in Table S6. Although their interpretation is limited by a high rate of missing data in the excluded group, the only notable differences are a higher rate of prior HF diagnosis, higher number of prior HF hospitalizations, and higher B-type natriuretic peptide and N-terminal prohormone B-type natriuretic peptide in the excluded group.

Although we have adjusted for many relevant clinical characteristics, it is possible that some of the associations we observe are due to unmeasured or residual confounding. We are also unable to track patient adherence, a powerful predictor of cardiovascular outcomes in a registry such as this.²⁴ Prior studies of HF patients have demonstrated that patients discharged on ACEi/ARB therapy have relatively high persistence rates, whereas those discharged not on therapy have low rates of outpatient initiation.²⁵ Finally, these findings are from hospitals participating in GWTG and may not necessarily generalize to other settings and populations.

Conclusions

In this large, multicenter cohort of 16 052 patients with HFREF, we found that continuation or initiation of ACEi/ARB at the time of discharge after admission for ADHF was associated with lower 30-day, 90-day, and 1-year mortality rates. In addition, patients who continued or initiated ACEi/ARB therapy had lower readmission rates at 30 and 90 days compared with those who discontinued or did not start therapy. Additional research to better understand the determinants of guideline adherence and ACEi/ARB initiation and discontinuation may be warranted.

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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

		Primary Analysis (from Table 4)		Sensitivity Analysis using Complete Discharge Data (n=4,011)	
Outcome	Groups Compared	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

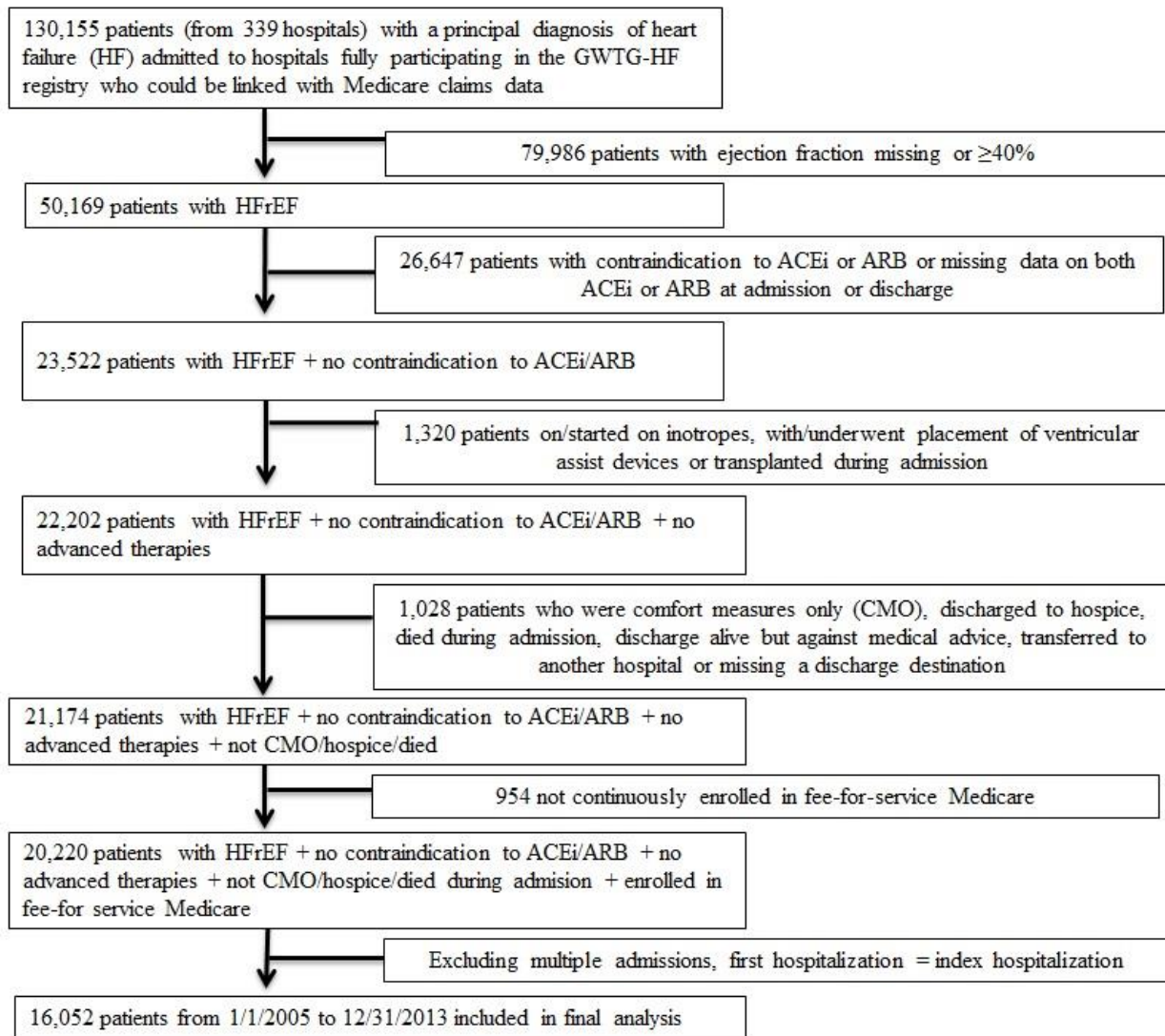
Table S6. Comparison of Baseline Characteristics between Patients Excluded due to Missing Data and those Included in the Study Population

	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	22.05
2 (%)	4.79	9.30	
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^l

Figure S1. Study Population Derivation



Supplemental Reference:

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