ORIGINAL RESEARCH

Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers for Geriatric Ischemic Stroke Patients: Are the Rates Right?

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***Background*—**Our objective is to estimate the effects associated with higher rates of renin-angiotensin system antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARBs), in secondary prevention for geriatric (aged >65 years) patients with new ischemic strokes by chronic kidney disease (CKD) status.

***Methods and Results*—**The effects of ACEI/ARBs on survival and renal risk were estimated by CKD status using an instrumental variable (IV) estimator. Instruments were based on local area variation in ACEI/ARB use. Data abstracted from charts were used to assess the assumptions underlying the instrumental estimator. ACEI/ARBs were used after stroke by 45.9% and 45.2% of CKD and non-CKD patients, respectively. ACEI/ARB rate differences across local areas grouped by practice styles were nearly identical for CKD and non-CKD patients. Higher ACEI/ARB use rates for non-CKD patients were associated with higher 2-year survival rates, whereas higher ACEI/ARB use rates for patients with CKD were associated with lower 2-year survival rates. While the negative survival estimates for patients with CKD were not statistically different from zero, they were statistically lower than the estimates for non-CKD patients. Confounders abstracted from charts were not associated with the instrumental variable used.

***Conclusions*—**Higher ACEI/ARB use rates had different survival implications for older ischemic stroke patients with and without CKD. ACEI/ARBs appear underused in ischemic stroke patients without CKD as higher use rates were associated with higher 2-year survival rates. This conclusion is not generalizable to the ischemic stroke patients with CKD, as higher ACEI/ARBS use rates were associated with lower 2-year survival rates that were statistically lower than the estimates for non-CKD patients. **(*J Am Heart Assoc*. 2018;7:e009137. DOI: 10.1161/JAHA.118.009137.)**

Key Words: angiotensin receptor • chronic kidney disease • instrumental variables • ischemic stroke • renin angiotensin system • secondary prevention • treatment effectiveness

It has been suggested that renin-angiotensin system antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARBs), are underutilized in secondary stroke prevention.[1] The current guideline recommends blood pressure reduction for all stroke patients to prevent recurrent stroke and other vascular events.[2] The guideline also adds that treatment choice including the use of ACEI/ARBs should be "individualized" in light of patient conditions such as renal impairment,[2] and "judicious" use of ACEI/ARBs has been stressed.[3] Although ACEI/ARBs are thought protective of renal function,[4] higher ACEI/ARB use rates have been associated with higher prevalence of acute kidney injury and end-stage kidney disease.[5–7] ACEI/ARBs may accelerate the progression of chronic kidney disease

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Clinical Perspective

What Is New?

- Although secondary stroke prevention guidelines recommend use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARB) therapy post-stroke and kidney guidelines recommend ACEI/ARB use in CKD, our study suggests that increasing rates of ACEI/ARB prescribing in a population with both indications for ACEI/ARB use (secondary stroke prevention and CKD) would not improve clinical outcomes and, in fact, may worsen outcomes.
- However, If ACEI/ARB treatment effects are heterogeneous across patients with both stroke and CKD and care is currently individualized across patients, extrapolating our estimates to ACEI/ARB use rates far outside our study ranges may not be appropriate.

What Are the Clinical Implications?

- Our estimates suggest, at a minimum, that a subset of patients exists post-stroke with CKD for whom ACEI/ARB use may worsen survival outcomes.
- Further research is needed to provide more specific guidance on which cohorts of stroke patients and which cohorts of CKD patients would benefit from more versus less ACEI prescribing, as these populations are diverse and current guidelines do not address this diversity.
- Until then, it appears that ACEI/ARB use in practice should be "individualized" and "judicious" as is stressed in the current guideline.

(CKD) to end-stage kidney disease through intrarenal hemodynamic effects.[8–13] ACEI/ARBs may also disrupt the capacity for auto-regulation in other vital organ systems which could be harmful in high-risk geriatric patients with cardiovascular comorbidities.[8–11]

The evidence guiding ACEI/ARB use for geriatric patients with comorbidities is sparse. Guidelines are based largely on studies of younger patients with well-preserved renal function,[13–18] that did not focus on long-term renal, cardiovascular, or survival outcomes.[19,20] Observational studies assessing ACEI/ARBs effects using risk-adjustment approaches have shown mixed results,[6,21–25] likely stemming from varying ability to control for confounders[26,27] and heterogeneity of ACEI/ARB effects across patients.[6,10,17,24,26–29]

If ACEI/ARB effects are heterogeneous across patients, the relevant question is not whether all geriatric ischemic stroke patients should be treated with an ACEI/ARB or not, but rather whether existing ACEI/ARB use rates for ischemic stroke patients are "right"?[30] The ACEI/ARB use rate for ischemic stroke patients may reflect the proper tradeoffs of ACEI/ARB benefits and detriments across individual patients. Estimates of ACEI/ARB effects for ischemic stroke patients on the "extensive margin"[31–33] are needed to address this question. Patients on the extensive margin are those who would be next to receive an ACEI/ARB if use rates increased, or the first not to receive an ACEI/ARB if rates fell.

Our objective is to estimate the effects of ACEI/ARBs on geriatric patients with ischemic stroke on the extensive margin. Instrumental variable (IV) estimators are applied to data from Medicare insurance system in the United States using measures of local area ACEI/ARB prescribing practice styles as instruments. This approach aligns our estimates with what might be expected from a policy intervention meant to change ACEI/ARB use rates for ischemic stroke patients.[33–35] Because of the postulated heterogeneity of ACEI/ARB effects, we contrasted IV estimates across patient subpopulations based on prior CKD. In addition, data from medical charts for a sample of patients with CKD in our study population were used to evaluate the assumptions underlying our IV estimator.

Methods

Data

Data from 2009 to 2012 for all Medicare fee-for-service enrollees diagnosed with stroke during 2010 were obtained from Chronic Conditions Data Warehouse (CCW). For these patients all Medicare claims and enrollment files were obtained. Also used were ZIP code level socioeconomic data from the US Census Bureau and a file developed by the project team containing driving distance between any 2 ZIP code centroids throughout the United States. Chart abstraction was performed for a stratified random sample of the ischemic stroke patients with CKD (see Data S1, Figures S1 and S2, Tables S1 and S2).[2,36–46] The data, analytical methods, and study materials will be made available to other researchers for the purpose of reproducing the results or replicating the procedures, but because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author. This study design was accepted by the University of South Carolina Institutional Review Board.

Population

Medicare fee-for-service enrollees with incident ischemic stroke during 2010 with sufficient observation windows to measure all study variables were included.[47] For each patient we found the first inpatient stay with a primary stroke diagnosis,[48] during 2010 and designated this as each patient's *index stroke stay*. The observation window was built around the admission date for the index stroke—referred to as the *index date*. Table 1 shows the impact of inclusion criteria on our study population: 35 769

patients were included, 9092 with a diagnosis of CKD (*International Classification of Diseases, Ninth Edition [ICD-9-CM]* diagnosis codes: 585.1, 585.2, 585.3 585.4 585.5, 585.9) in the period 12 months before index through the index stay, and 26 677 without a diagnosis of CKD.

Treatment

If a patient filled an ACEI/ARB prescription in the 30 days after discharge or had sufficient ACEI/ARBs at home before discharge to cover the 30 days after discharge, the ACEI/ARB treatment variable was set to one, zero otherwise. We used "days supplied" on prescriptions filled before discharge to estimate the days of supply remaining at discharge. Patients were excluded who died or had an inpatient stay during the 30 days after discharge to ensure a consistent treatment observation period.[47]

Outcomes

1. Two-year survival: 1 if the patient survived 2 years after index discharge, 0 otherwise;
2. Two-year secondary stroke-free survival: 1 if the patient survived 2 years after index discharge without a recurrent stroke,[48] 0 otherwise;
3. Two-year renal events: 1 if the patient had inpatient or outpatient claims with *ICD-9-CM* codes with acute kidney injury (584.xx and 580.xx) or end-stage renal disease (585.6) within 2 years of index discharge, 0 otherwise.

Table 1. Effects of Inclusion Rules on Study Population for Patients With Ischemic Stroke Who Were Medicare Fee-for-Service Enrollees in 2010

	Number of Patients
Inpatient hospital stay with a primary diagnosis of stroke in 2010	142 203
Aged 66+ years at diagnosis	140 385
Survived the index stroke inpatient stay and 30 days after discharge	113 785
Enrolled in Medicare Parts A (inpatient) and B (physician) from 12 months before index stay to 2-years after discharge or until death date	102 091
Enrolled in Part D (drugs) from 12 months before index stay to 1 month after discharge	94 343
Not in hospice from 12 months before index stay to 1 month after discharge	91 419
No stroke in 12 months before index stay	74 047
No inpatient admission in the 30 days after discharge	63 827
No diagnosis of end stage renal disease, or renal cancer and did not receive dialysis during the 12 months before index stay	62 151
Had index diagnosis as ischemic stroke	35 769
Had no diagnosis of CKD in the 12 months before index through the index stay	26 677
Had a diagnosis of CKD in the 12 months before index through the index stay	9092

CKD indicates chronic kidney disease.

Covariates

Covariates measured at baseline included patient demographics, financial and insurance variables, comorbidities, prior adverse events related to ACEI/ARB use, complications during the index stay, therapy during the index stay, lengths of stay by unit (eg, intensive care) and facility type (skilled nursing facility), medication use before index stroke, and other medications used after discharge. Definitions and data sources for the covariates are in Data S2.[48–64] For a stratified random sample of patients with CKD we measured confounders which are unmeasurable using Medicare data through chart abstraction (Data S1).

Instrument Strategy

We measured ACEI/ARB local area practice style measures around each patient residence ZIP code using a driving time approach refined in previous studies based on driving times (Data S3).[32,65–68] For each ZIP code, an area treatment ratio (ATR) was estimated as the ratio of the number of patients in the local area who used ACEI/ARBs after stroke over the sum of the predicted probabilities of these same patients receiving ACEI/ARBs after stroke. Larger ATR values indicate stronger provider preference in the local area for prescribing an ACEI/ARB after stroke. The instrument was specified in estimation models either using continuous variables (the patient's ZIP code ATR value and ATR value squared) or grouping patients into quintiles based on their ZIP code ATR values using dummy variables.

Analysis

Patients were stratified into CKD and non-CKD subpopulations. For each subpopulation we tested the association of the measured covariates with ACEI/ARB use and for trends in each covariate across patients grouped by ATR quintiles.[69] Linear 2-stage least squares (2SLS) IV estimators were used (Data S4).[29,70–80] In this study 2SLS yields estimates of the absolute average effect of ACEI/ARBs for the patients whose ACEI/ARB choice was sensitive to local area practice styles[71,80] or what is known as the local average treatment effect. Our large sample size ensures that our 2SLS estimates will be distributed normally via the central limit theorem.[76] All models were estimated with robust standard errors using

STATA software. We tested for differences in local average treatment effect estimates between the CKD and non-CKD patients.[77] To further contrast ACEI/ARB effects between CKD and non-CKD patients, we estimated empirical distributions of each effect using bootstrap methods by CKD status.[78] We created 3000 patient samples by randomly selecting from each subpopulation with replacement and applied the IV models to each of the 3000 samples for each subpopulation. To evaluate IV estimator assumptions, we grouped the patients from our abstraction sample based on local area ACEI/ARB practice styles and tested the mean differences in laboratory values (eg, blood pressure, kidney function, electrolytes) between groups.

Results

Tables S3 and S4 summarize the relationships between the covariates measured using Medicare data and ACEI/ARB use and local area practice styles, for CKD and non-CKD patients, respectively. ACEI/ARBs were used by 45.9% of CKD patients and 45.2% of non-CKD patients. ACEI/ARB users were younger, less frail, more likely a minority, lived in areas with lower socioeconomic conditions, and had fewer prior conditions thought to be adverse events of ACEI/ARBs, but had higher rates of obesity, diabetes mellitus, and hypertension. ACEI/ARB users were more likely to have used an ACEI/ARB before their stroke and other medications after discharge. Higher-staged CKD patients were less likely to use ACEI/ARB after stroke. For CKD patients in the first quintile of the instrument, 40.0% of patients had an ACEI/ARB available within 30 days of discharge compared with 53.5% of patients in the fifth quintile. For non-CKD patients the range across quintiles was 38.5% to 51.7%. Local areas with higher ACEI/ARB use rates had higher minority percentages and poverty rates.

Table 2 summarizes the IV estimates. Column 3 contains F-statistics testing whether the instrument had a statistically significant impact on ACEI/ARB use.[81] All F-statistics were much greater than 10 so that our instrumental variable is considered "non-weak".[79] Columns 4 to 6 contain the IV estimates of ACEI/ARB use on each study outcome. For non-CKD patients higher ACEI/ARB rates are associated with higher 2-year survival rates (column 4). ACEI/ARB effects on stroke-event-free survival rates were in the same range, but not statistically different from zero (column 5). Higher ACEI/ARB rates for non-CKD patients were associated with lower 2-year renal event rates that were also not statistically different from zero (column 6). For patients with CKD, higher ACEI/ARB rates were associated with *lower* 2-year survival rates, 2-year renal event rates but neither was statistically different from zero.

IV estimates using the entire population are clearly averages of the CKD and non-CKD IV estimates and hide the treatment effect heterogeneity across subpopulations. To investigate heterogeneity further, we tested for treatment effect *differences* between CKD and non-CKD patients (Table 3). The IV estimates of ACEI/ARB effects on 2-year survival were statistically different between subpopulations. Figure contains the empirical distributions of the treatment effect estimates across the bootstrapped samples by outcome, estimator, and subpopulation. A clear difference can be seen in the empirical distributions of ACEI/ARB survival effects by CKD status. The two-sample Komogorov-Smirnov goodness of fit test[82] statistic (0.458) rejects the null hypothesis that the distributions of ACEI/ARB survival effect estimates were the same across CKD status at the $P<0.01$ level.

Table 4 shows laboratory values found in the index inpatient stay for ischemic stroke patients with CKD from our abstraction sample. Patients are grouped by ACEI/ARB use after discharge and local area ACEI/ARB practice styles.

Table 2. IV Estimates of ACEI/ARB Effects on 2-Year Study Outcomes for Medicare Enrollees With Ischemic Stroke by Prior CKD

			Outcomes		
1	2	3	4	5	6
Population	IV Specification*	F-Statistic†	2-Year Survival	2-Year Stroke Free Survival	2-Year Renal Events
Non-CKD	Continuous*	270.5	0.086‡ (0.038)	0.083 (0.043)	−0.046 (0.025)
	Quintiles*	119.1	0.089‡ (0.041)	0.079 (0.046)	−0.046 (0.027)
CKD	Continuous*	108.3	−0.108 (0.069)	−0.083 (0.073)	−0.100 (0.060)
	Quintiles*	52.0	−0.116 (0.070)	−0.065 (0.074)	−0.106 (0.061)
Total	Continuous *	384.5	0.039 (0.033)	0.041 (0.037)	−0.055‡ (0.024)
	Quintiles*	172.8	0.034 (0.035)	0.042 (0.039)	−0.058‡ (0.026)

*Two-Stage Least Squares (2SLS) IV models with robust standard errors. Instrument specification in first-stage equation—Continuous: area treatment rate (ATR) and ATR-squared. Quintiles: 4 dummy variables grouping ZIP codes in 5 groups based on ATR values.
†F-statistic testing the significance of the instrument specification in the 2SLS first stage regression.
‡$P<0.05$.
ACEI/ARB indicates angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; CKD, chronic kidney disease; IV, instrumental variable.

Table 3. Differences in ACEI/ARB Absolute Treatment Effects Between CKD and Non-CKD Ischemic Stroke Patients

Estimator		Outcomes		
		2-Year Survival	2-Year Stroke Free Survival	2-Year Renal Events
Continuous*	Absolute difference†	0.194‡	0.166	0.053
	P-value on difference§	0.015	0.052	0.404
Quintiles*	Absolute difference†	0.203‡	0.142	0.060
	P-value on difference§	0.012	0.104	0.371

*Two-stage least squares (2SLS) IV models with robust standard errors. Instrument specification in first-stage equation—Continuous: area treatment rate (ATR) and ATR-squared. Quintiles: 4 dummy variables grouping ZIP codes in 5 groups based on ATR values.

†Difference between the CKD and non-CKD estimated treatment effects.

‡$P<0.05$.

§Based on Z-statistic $= \frac{\widehat{\alpha}_{nonCKD} - \widehat{\alpha}_{CKD}}{\sqrt{(SE\alpha_{nonCKD})^2 + (SE\alpha_{nonCKD})^2}}$

ACEI/ARB indicates angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; CKD, chronic kidney disease.

Patients using ACEI/ARBs after stroke had higher blood pressure and international normalized ratio levels, but lower serum creatinine than non-treated patients. No statistically significant differences in these values were found between patients grouped by local area ACEI/ARB practice styles.

Discussion

Controversy exists as to whether ACEI/ARBs are over- or underused for secondary prevention by stroke patients.[1] Guidelines highlight the benefits of blood pressure control from ACEI/ARBs[2] but the possibility of renal and survival risks from ACEI/ARBs for complex patients has been noted.[5–7] Previous observational studies assessing ACEI/ARB effects are susceptible to confounding bias[26,27] and have not addressed the over/underuse question directly. Instrumental variable (IV) estimators were used in this study to assess the average effects of ACEI/ARBs for ischemic stroke patients who were Medicare fee-for-service beneficiaries whose ACEI/ARB use was sensitive to local area practice styles. We stratified our analysis by CKD status. We assessed confounding assumptions underlying IV estimators through chart abstraction and the contrast of baseline laboratory values across patients grouped by local area ACEI/ARB practice styles.

We found comparable ACEI/ARB use patterns for ischemic stroke patients with and without CKD, suggesting providers had similar ACEI/ARB effect expectations for both subpopulations.

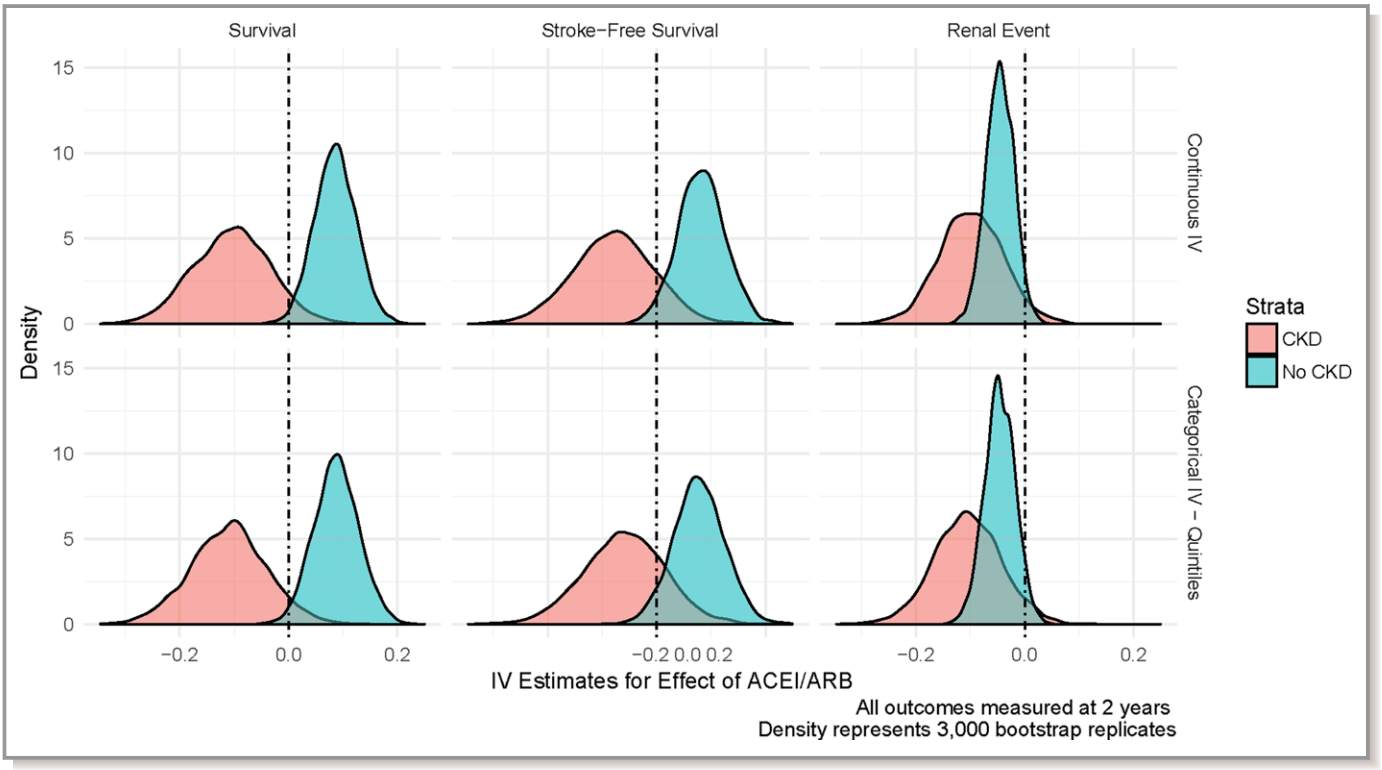

Figure. Bootstrap distributions of instrumental variable (IV) renin-angiotensin system antagonist (ACEI/ARB) effect estimates for geriatric stroke patients by chronic kidney disease (CKD) status. Continuous IV: instrumental variable specified as ZIP code specific area treatment rate (ATR) and ATR-squared. Categorical IV—Quintiles: instrumental variable specified as 4 dummy variables grouping ZIP codes in 5 groups based on area treatment rate (ATR) values. ACEI/ARB indicates renin-angiotensin system antagonist; CKD, chronic kidney disease; IV, instrumental variable.

Table 4. Differences in Laboratory Values Between Patients Using and Not Using ACEI/ARBs and Patients Living in Low and High ACEI/ARB Treatment Areas

	n=419		n=412			n=414		n=417		
	Not Using ACEI/ARBs*		Using ACEI/ARBs*			Living in a Low ACEI/ARB Area†		Living in a High ACEI/ARB Area†		
Values	Mean	# Missing	Mean	# Missing	*P* Value‡	Mean	# Missing	Mean	# Missing	*P* Value‡
Highest systolic blood pressure	176.23	0	183.75	1	<0.0001§	181.24	0	178.68	1	0.175
Highest diastolic blood pressure	92.62	0	95.63	1	0.004§	94.38	0	93.84	1	0.605
Highest BUN level, mg/dL	33.03	2	31.02	3	0.053	32.35	3	31.73	2	0.547
Highest serum creatinine level, mg/dL	1.72	2	1.56	2	0.004§	1.65	2	1.62	2	0.574
Highest INR value	1.36	74	1.56	87	0.005§	1.46	85	1.45	76	0.867
Latest GFR level, mL/min per 1.73 m^2	45.42	89	49.32	92	0.003§	47.38	88	47.3	93	0.951

*Based on either filling an ACEI/ARB prescription 30-days after discharge or having a 30-day supply of ACEI/ARBs upon discharge.
†Low: patient resided in ZIP code in the lowest quintile of ACEI/ARBS use based on area treatment ratios. High: patient resided in ZIP code in the highest quintile of ACEI/ARB use.
‡Student *t* test of difference in means.
§$P<0.05$.
ACEI/ARB indicates angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; BUN, blood urea nitrogen; GFR, glomerular filtration rate; INR, international normalized ratio.

Global ACI/ARB use rates were nearly the same for both subpopulations, along with the range in use rates across local areas. Despite these parallels, the survival effects associated with ACEI/ARB use variation across local areas differed dramatically by CKD status. Higher ACEI/ARB use rates for non-CKD stroke patients were associated with higher 2-year survival rates. For non-CKD patients with ischemic stroke, ACEI/ARBs appear underused, as higher rates would have improved survival rates with no increased renal risk. Perhaps providers overestimated the adverse-event risks of ACEI/ARBs for these patients. We can also assert from our results that higher ACEI/ARB use rates for older ischemic stroke patients have different implications for CKD and non-CKD patients. While the negative survival effects for patients with CKD were not statistically different from zero, they were statistically lower than the estimates for non-CKD patients. Our estimates suggest it would be inappropriate to generalize the relationships found for non-CKD ischemic stroke patients to patients with CKD.

IV estimates are consistent if unmeasured confounders related to study outcomes are unrelated to the instrument specified. We found no relationships in blood pressure levels, international normalized ratio values, creatinine levels, and glomerular filtration rates (GFR) across ischemic stroke patients with CKD grouped by local area ACEI/ARB practice styles. These results suggest that the local area ACEI/ARB practice styles provided a natural experiment in ACEI/ARB use and the bias risk in our IV estimates is minimal.

The IV estimates in this study should be interpreted *locally* to avoid improper generalization. These estimates apply directly to the ischemic stroke patients whose ACEI/ARB use in 2010 would have changed had they resided in areas with different ACEI/ARB practice styles. The ranges in ACEI/ARB use rates associated with our instrument, (38.5–51.7%) for non-CKD patients and (40.0–53.5%) for CKD patients, are those around which our results should be interpreted. Extrapolating our estimates to changes in ACEI/ARB use rates far outside these ranges is problematic if ACEI/ARB effects are heterogeneous across patients and ACEI/ARB use in practice was individualized across patients. Without additional information on how ACEI/ARBs are sorted across ischemic stroke patients in practice, policy-makers should be cautious using our estimates, or estimates from any observational study, as the basis guidelines on the *uniform use* ACEI/ARBs for CKD and non-CKD ischemic stroke patients.

Conclusions

Our study uses an instrumental variable (IV) estimator with a commonly used instrument to address the question of whether ACEI/ARBs were over- or underused in secondary prevention for ischemic stroke patients with and without CKD who were Medicare fee-for-service enrollees. The survival effects associated with higher ACEI/ARB use rates clearly differed between CKD and non-CKD patients. Higher ACEI/ARBS use rates for non-CKD patients were associated with higher 2-year survival rates. Whereas, 2-year survival estimates for CKD patients were negative and statistically distinct from the estimates for non-CKD patients. It would be a mistake to generalize the estimates for non-CKD ischemic stroke patients to CKD patients or to apply the estimates from the entire ischemic stroke population

to either subpopulation. Policies to increase ACEI/ARB uses rates for non-CKD ischemic stroke patients should be considered but these policies should be limited to only the non-CKD ischemic stroke patients.

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SUPPLEMENTAL MATERIAL

Data S1

Medical Chart Procurement, Abstraction, and Quality Measurement

To assess the assumptions underlying our IV estimator we selected a stratified random sample of patients with CKD from our study population based on (1) observed ACEI/ARB use after index stroke, (2) local area ACEI/ARB area treatment rates (ATRs) after stroke (high or low ACEI/ARB areas using patients from the highest and lowest quintiles, respectively), and (3) geographic region, using the four U.S. Census Geographical Regions: Northeast (NE), Midwest (MW), South (ST), and West (WT; US Census Bureau, 2014). To evaluate assumptions underlying the IV estimator, we grouped patients based on local area ACEI/ARB use rates and tested the mean differences in each abstracted measure between groups.

Medical Chart Procurement

Investigators randomly selected 1,424 patients based on the criteria described above. The sample was designed to obtain sufficient medical charts to ensure 840 completed abstractions. Our previous work indicated the need for at least 69% more abstraction requests to obtain the desired number of cases; therefore the initial sample included an oversample based on those response rates.[1]

The investigators worked with the Chronic Condition Data Warehouse (CCW) and Information Collection Enterprises (ICE) to obtain the medical charts for these patients. ICE disseminated chart requests for the initial sample on October 2, 2015. The inpatient claims for the index stroke for the abstraction subsample were linked to the Provider of Services (POS) file, a public use file made available by the Centers for Medicare & Medicaid Services (CMS), to obtain hospital contact information for requesting the medical charts. A patient finder file was sent by study investigators to CCW to obtain patient names for inclusion with the chart requests. The finder file also contained an encrypted identification number for each patient. The CCW provided patient information to ICE directly along with the encrypted identification number.

ICE mailed a chart request packet to each facility with a patient in the study. The packet included a cover letter from the Principal Investigator, a 2-page abstract describing the study objectives, a copy of the Center for Medicare and Medicaid Services (CMS) Data Use Agreement (DUA) to document approval to request medical charts, the approval letter from University of South Carolina Institutional Review Board (USC IRB), and medical chart coversheet that contained patient-specific identifiers (name, Social Security Number [SSN], and Medicare Health Insurance Claim [HIC]), and the admission date of the hospitalization chart being requested. The packet also included detailed instructions to photocopy the chart and send all components by secure package to ICE. Hospitals were reimbursed a standard amount per chart for photocopying and United States mail costs. Often the acute portion of an index stroke hospitalization occurred at two facilities if a patient was transferred to another hospital. For the 2% of cases in which a transfer occurred, charts were requested from both hospitals. Failure to obtain charts from both hospitals rendered the case incomplete and was not abstracted.

If the requested medical charts were not received by ICE within 30 days of the original request, the medical charts department was contacted by telephone to re-request the chart. In some cases, a copy of the original packet was mailed again. After these efforts to obtain charts from the initial sample were exhausted, and after abstractors successfully reviewed charts for the original sampling wave, 15 chart requests from a second wave (oversample) were disseminated on May 13, 2016 to obtain the necessary number of medical charts for each category.

Data Collection Tool

We created a structured data abstraction tool to obtain information from the medical charts of the sampled patients for the index hospital stay, which could have included treatment at two facilities if the patient was transferred during the acute stay. The data collection tool was based loosely on an instrument used for our previous AMI study.[1] We also leveraged key questions from other well-designed medical chart abstraction tools such as the Women's Health Initiative[2] and the Adult Comorbidity Evaluation (ACE-27).[3] We examined clinical practice guidelines for management of acute stroke patients[4] and secondary prevention of stroke[5] and included variables to capture important clinical assessment and treatment information. For

example, variables regarding stroke severity and functional status were based on the Modified Rankin Scale (MRS),[6] Barthel Index,[7] Stroke Scales: An Update,[8] and the Continuity and Assessment Record and Evaluation (CARE) item set.[9] Variables were modified and customized in consultation with the study team cardiologist, nephrologist, neurologist, pharmacist, and nurses. The abstraction tool was originally created in Microsoft (MS) Word to allow for ease of viewing the dimensions of care, variables, operational definitions, and to facilitate training, review, and revisions of the tool. After the tool was completed, ICE programmed the data elements into an electronic tool with a user-friendly front-end interface using MS Access. Operational definitions were documented for each variable, including a list of valid sources within a medical chart (e.g., admission face sheet, surgical report, and medication administration record), inclusion/exclusion criteria, time frame parameters, and medical terms/synonyms. To facilitate the collection of medications, a list of commonly prescribed medications and their corresponding dosages was imported into the tool so that a drop-down list could be offered to facilitate efficiency; the field also allowed for the entry of free text so that medications which did not appear on the drop-down list could be captured.

Testing and Fielding the Data Collection Tool

The abstraction tool was finalized by the study team nurses and the ICE lead abstractor. The ICE lead abstractor trained five additional ICE abstractors in December 2015. Collectively, the abstractors had extensive medical chart abstraction experience averaging more than ten years each and all were well-versed in medical terminology, though none were nurses or clinicians. During the training, the study objectives were described, each subsection of the tool was explained, and instructions for each variable were highlighted. Each abstractor received his/her own copy of the abstraction instruction manual for reference while abstracting the cases. Abstractions were completed at a secure, onsite location exclusively.

Prior to beginning abstraction, all abstractors initially reviewed the same set of 8 cases. The cases were sent to the study clinical co-investigators and “gold” answers were established. Inter-rater reliability scores were calculated for each data element by comparing each abstractor’s results to the gold answers. Feedback was given on all discrepancies so that the

collected data would be consistent across the abstractors. Feedback from this training exercise was used to make minor clarifications to the abstraction tool and the manual. When an abstractor demonstrated 95% agreement with the gold standard abstractor for all data elements, the abstractor began abstracting from the pool of charts available.

To coordinate activities between all study team members and facilitate resolution of any barriers to abstraction, the entire research team attended biweekly meetings during which project updates were provided by ICE. These updates included reports detailing the number of charts and full sets/cases requested, received, and refused by primary sample unit (PSU). They also highlighted the number of abstracted cases that were complete to date for each PSU. If, at any time during the data collection process, an abstractor had a question or concern about how to abstract a data element, the on-site lead abstractor was consulted. Questions that required a decision from the clinical team were evaluated (by e-mail or on the bi-weekly call) and responded to within approximately 48 hours. During the abstraction process, our study team clinicians were consulted when a clinical judgment was necessary. To maintain quality throughout the entire project, our protocol involved extensive quality control for the abstracted charts.

Abstraction and Quality Assurance

To maintain quality throughout the project, our protocol involved extensive quality control for the abstracted charts. In addition to the inter-rater agreement process used for all abstractors prior to launching the abstraction data collection effort, ongoing internal quality control (IQC) processes were instituted. Three rounds of IQC were performed, one at the start of study and two additional rounds, both of which occurred after 1/3 of the cases (i.e., approximately 280 charts) were abstracted. All rounds of IQC included re-abstraction of a random sample of cases; 18 cases for round 1, and 12 cases for both rounds 2 and 3. This approach yielded interrater agreement scores for 5% of the charts abstracted (42 cases). Each of the abstractors completed three cases that were re-abstracted by another abstractor. An accuracy-by-variable report was prepared, and abstractors who did not meet the 95% agreement per variable standard were retrained and charts they abstracted were re-abstracted by the lead abstractor to ensure

accuracy. To verify that data were abstracted accurately and uniformly across all members of the abstraction team, results from all three IQC rounds were aggregated by conceptual domains and agreement was calculated. We calculated a kappa statistic for each categorical variable and each associated domain; for continuous variables (e.g., lab values) we calculated intra-class correlations (ICC) – then also summarized them into domain scores.

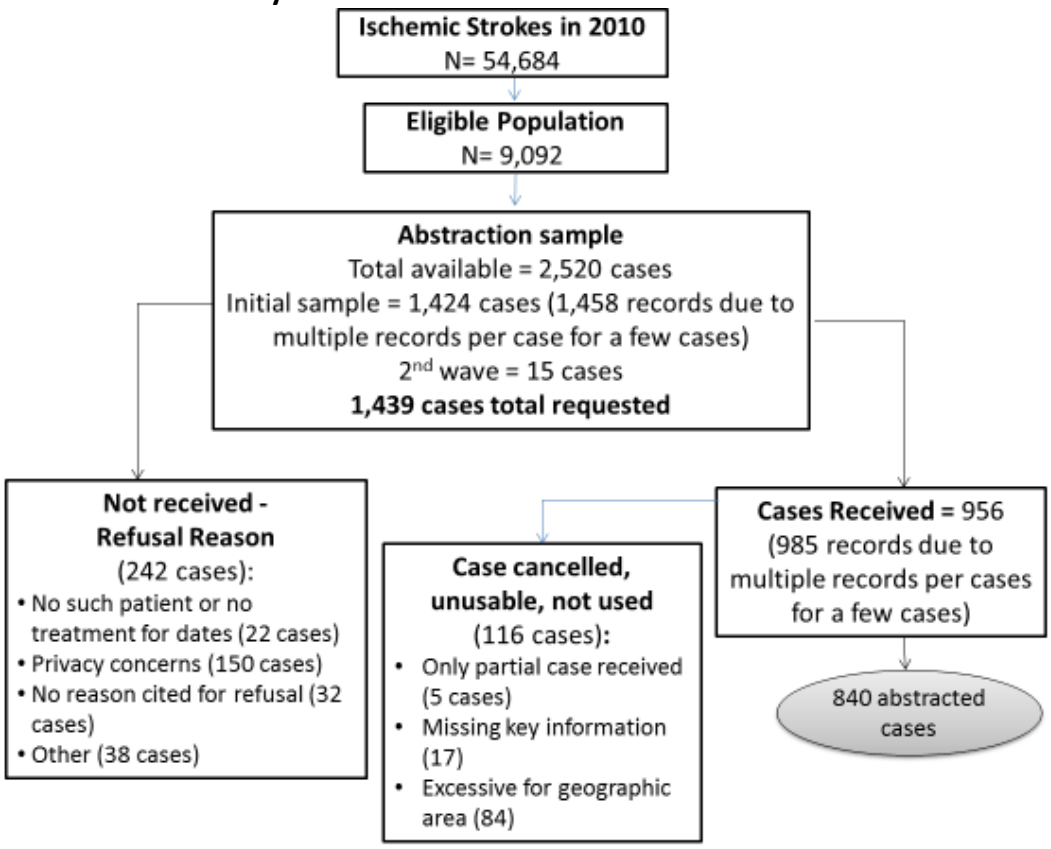
Analyses

Because of the voluntary nature of the response from the facilities, we analyzed the characteristics of patients for whom we received charts versus those for whom we did not by linking patient-level beneficiary and Medicare A and B claims from the index stroke stay to our requested and received medical charts. We also linked data from the CMS POS file to obtain geographic information and additional characteristics of the hospital facilities to allow for comparison of responding versus non-responding facilities.

Results

A total of 1,439 complete chart sets were requested and 956 were received for an overall response rate of 66.4%; of these, 840 were abstracted. Of the chart sets received, 17 of them were not abstracted due to missing information such as initial intake/history, medication administration list, or discharge instructions; and 84 were not abstracted because they came from a stratum for which the necessary number of charts had been received and abstracted (i.e., we obtained more charts than we needed for some of the strata). For five cases, a transfer occurred, and the other chart was not received, rendering the case unusable for abstraction. Figure S1 documents the medical chart sample requested, received, and abstracted.

Figure S1. Charts Requested, Received, Abstracted for Medicare Ischemic Stroke Patients with Chronic Kidney Disease in 2010



Nonresponse analysis revealed that very few differences between patients whose charts were received versus not received (Table S1). Examination of claims-based measures at the patient-level indicated that patients for whom we received charts were more likely white (83.2% versus 77.4%, p=.005), less likely to be dually enrolled in Medicare and Medicaid (33.6% versus 38.5%, $p < 0.05$), were less likely to have required an acute care transfer for the stroke hospitalization (0.9% versus 4.4%; $p < 0.0001$), and had shorter average acute care lengths of stay (LOS) (5.67 days versus 6.37 days; $p < 0.001$). Other demographics, as well as characteristics of the index stroke, prior comorbid conditions, and the complications of index stay were all comparable. Examination of the hospital facility-level nonresponse (Table S2) revealed that we were more likely to receive charts from facilities in the West region of the U.S. (26.7% versus 20.5%; $p < 0.01$). We were also less likely to receive charts from larger facilities (300+ beds) (45.1% versus 60.4%; $p < 0.001$).

Table S1. Comparison of Patient Characteristics Between Patients with Chart Requests Received and Those Not Received.			
	Full record received	Full record requested but not received	P-value
Number	956	483	
Demographics			
Percent female	60.8%	62.5%	0.064
Percent dual eligible for Medicaid	33.6%	38.5%	0.013*
Race			
White	83.2%	77.4%	0.005*
Black	9.8%	13.9%	0.006*
American Native	0.6%	0.4%	0.078
Asian	2.6%	3.3%	0.066
Other race	1.8%	1.2%	0.067
Mean age (at time of admission)	81.48	80.78	0.291
Baseline Comorbid conditions			
CKD			
CKD_STG_1	1.7%	2.1%	0.076
CKD_STG_2	3.5%	5.2%	0.025*
CKD_STG_3	26.8%	24.4%	0.060
CKD_STG_4	13.4%	9.9%	0.016*
CKD_STG_5	2.2%	1.5%	0.056
CKD_STG_NOS	52.4%	56.1%	0.030*
Cardiovascular disease	64.5%	60.5%	0.036*
Heart Failure	33.2%	32.7%	0.088
Hypertension			
Without complications	65.1%	65.8%	0.079
With complications	52.4%	50.5%	0.076
Obesity	5.8%	7.7%	0.032*
Function-related indicators (FRI)[10]			
FRI0	32.7%	32.5%	0.088
FRI1	25.7%	28.4%	0.046*
FRI2	16.3%	15.7%	0.086
FRI3plus	25.1%	22.6%	0.054
Characteristics of index institutional stay			
Multiple acute care facility/transfer (transfer)	0.9%	4.4%	<.0001*
Discharge disposition			
Discharged home	27.6%	25.9%	0.484
Transferred to inpatient hospital	0.3%	0.4%	0.760
Discharged to LTC/IRF/IPF	26.5%	22.6%	0.108
Discharged to SNF/NF	31%	32.1%	0.663

Discharged to Home Health	14.6%	19.1%	0.032*
Stay had an ICU component	16.1%	14.7%	0.487
Mean Length of Hospital Stay (LOS)	5.67	6.37	<.0001*
Chrischilles E, Schneider K, Wilwert J, et al. Beyond comorbidity: expanding the definition and measurement of complexity among older adults using administrative claims data. *Med Care.* 2014;52 Suppl 3:S75-84. * p<.05			

For internal quality control (IQC), we calculated a kappa statistic for each item and then summarized the kappa statistics for each conceptual area; for continuous variables (e.g., lab values) we calculated intra-class correlations (ICC) and summarized them for each conceptual area. Figure A2 illustrates the summary scores for each conceptual area, along with the error bars for the standard deviation. Since the kappa statistic corrects for agreement by chance, values 0.41-0.60 are often considered "moderate" agreement, 0.61 – 0.80 is "substantial agreement", and scores higher than this are considered "very high" or near perfect agreement.[11, 12] ICC are interpreted similarly. All conceptual areas had moderate or better agreement between raters, with four conceptual areas having very high agreement (administrative variables, vitals during stay, lab test values during stay and administration of medications).

Table S2. Comparison of Hospital Characteristics Between Patients with Chart Requests Received and Those Not Received.

Facility characteristics	Facility returned one or more records	Facility did not return any records	P-value
Number (%)	967 (65.8%)	503 (34.2%)	
Hospital Type			
For profit	103 (10.5%)	53 (10.7%)	0.946
NFP	450 (89.5%)	864 (89.4%)	0.946
Number of hospital beds			
Under 100	129 (13.3%)	50 (9.9%)	0.059
100-199	183 (18.9%)	77 (15.3%)	0.085
200-299	219 (22.7%)	72 (14.3%)	0.0001*
300+	436 (45.1%)	304 (60.4%)	<.0001*
Region			
Northeast	234 (24.2%)	139 (27.6%)	0.151
Midwest	247 (25.5%)	125 (24.9%)	0.772
South	228 (23.6%)	136 (27.0%)	0.145

West	258 (26.7%)	103 (20.5%)	0.009*
Metropolitan Status			
Urban/Metro	825 (85.3%)	452 (89.9%)	0.014*
Nonmetro	142 (14.7%)	51 (10.1%)	0.014*
* p<.05			

We originally asked abstractors to find and document use in the charts of standardized stroke severity scores that have been used in previous prospective clinical studies, such as the Modified Rankin Score or Barthel Index. Unfortunately, pilot testing revealed that these standardized scores were almost universally unreported. Therefore, instead, we identified the key concepts from these stroke assessment instruments, and directly measured each of the clinical domains with our abstraction tool to address items such as activities of daily living (ADLs) and functional deficits.

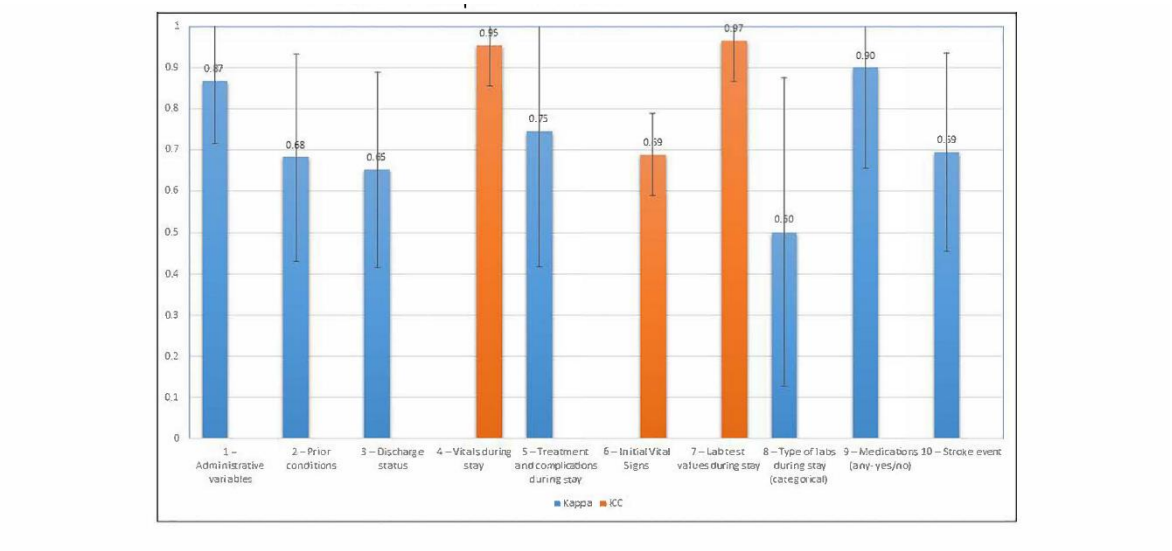
Limitations

Study abstractors found little consistent information in the charts with respect to measures of stroke severity. We originally asked abstractors to find and document use in the charts of standardized stroke severity scores that have been used in previous prospective clinical studies, such as the Modified Rankin Score or Barthel Index. Unfortunately, pilot testing revealed that these standardized scores were almost universally unreported. We attempted to isolate the conditions that underlie these measures in the charts. However, uncertainty remains as to whether individual conditions not reported in a chart did not actually exist for a patient or were simply not specifically recorded in the charts at individual institutions. For example, we feel confident that patients who were reported in the charts to have “problems with self-feeding” had this problem. We cannot be certain, though, because of reporting differences across institutions, whether patients who were not reported to have “problems with self-feeding” did not have these problems. As a result, our results are conditional on the assumption that chart reporting differences across institutions are not correlated with ACE/ARB treatment choices or local area ACE/ARB prescribing rates.

Future Research

Abstractors reported substantial variation in the quality and extent of information available in the charts across institutions. Future research requiring data abstracted from patient charts across institutions perhaps should also include measures of chart "completeness" to help ensure that conditions observed for a patient are recorded.

Figure S2. Average Kappa Statistics Indicating Consistency of Abstracting Across Conceptual Domains.



Data S2. Covariate Definitions for Medicare Claims Data Analysis of ACEI/ARB Effectiveness After Ischemic Stroke

Demographic characteristics (age at index stroke, sex, race) were obtained from the CCW Medicare Beneficiary File. Comorbidity concepts related to the use of ACEI/ARBs for secondary prevention of stroke were developed after a thorough review of available measures by the study clinical investigators. The Elixhauser Comorbidity Index (ECI) served as the basis for this effort because of its wide acceptance, common use, and broad spectrum of conditions.[13] Some conditions were separated out of the Elixhauser categories for emphasis (e.g., hyperkalemia). Several conditions in the ECI not considered relevant to this study by our clinical experts were not specified. Other conditions considered important by study clinicians were added using commonly accepted claims-based algorithms (e.g., Chronic Condition Data Warehouse[14], Mini-Sentinel[15]). Most comorbidities were identified using Medicare claims for the 12 months before the index inpatient stroke admission date through the index stroke institutional stay except for complications sepsis and pneumonia, which were assessed only during the index stroke institutional stay. The table below defines each covariate and measurement approach.

Covariate	Definition
Elix_Depress	Elixhauser Depression: 1 if patient had (ICD-9 codes 309, 311, 296.2, 296.3, 296.5, 300.4) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_FluElexDis	Elixhauser Fluid and Elextrolyte Disorders: 1 if patient had (ICD-9 codes 253.6, 276.0, 276.1, 276.2, 276.3, 276.4, 276.5, 276.6, 276.8, 276.9) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_Obesity	Elixhauser Obesity: 1 if patient had (ICD-9 code 278.0)[13]
ELIX_WL	Elixhauser Weight Loss: 1 if patient had (ICD-9 codes 260, 261, 262, 263, 783.2, 799.4) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]

ELIX_SubstanceAbuse	Elixhauser Drug Abuse combined with Alcohol Abuse: 1 if patient had (ICD-9 codes 980, 265.2, 291.1, 291.2, 291.3, 291.5, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, V113, 292, 304, 305.2, 305.3, 305.4, 305.5, 305.6, 305.7, 305.8, 305.9, V654) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_Coagu	Elixhauser Coagulopathy: 1 if patient had (ICD-9 codes 286, 287.1, 287.3, 287.4, 287.5) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_BLA	Elixhauser Blood Loss Anemia: 1 if patient had (ICD-9 code 280.0) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_DA	Elixhauser Deficiency Anemia: 1 if patient had (ICD-9 codes 281, 280.1, 280.8, 280.9) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
CCW_ExtraAnemia	CCW Anemia (2010) beyond Elixhauser Blood Loss Anemia and Deficiency Anemia: 1 if patient had (ICD-9 codes 282.0, 282.1, 282.2, 282.3, 282.5, 282.7, 282.8, 282.9, 283.0, 283.2, 283.9, 284.2, 284.9, 285.0, 285.1, 285.3, 285.8, 285.9, 282.40, 282.41, 282.42, 282.43, 282.44, 282.45, 282.46, 282.47, 282.49, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69, 283.10, 283.11, 283.19, 284.01, 284.09, 284.11, 284.12, 284.19, 284.81, 284.89, 285.21, 285.22, 285.29) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[14]
Sepsis_Index	Sepsis: 1 if patient had (Mini-Sentinel 2011) (ICD-9 code 995.91) on Medicare Part A claim for the index stay, 0 otherwise.[16]
ELIX_OthNeuro	Elixhauser Other Neurological Disorders: 1 if patient had (ICD-9 codes 334, 335, 340, 341, 345, 331.9, 332.0, 332.1, 333.4, 333.5, 336.2, 348.1, 348.3, 780.3, 784.3, 333.92) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_Paralysis	Elixhauser Paralysis: 1 if patient had (ICD-9 codes 342, 343, 334.1, 344.0, 344.1, 344.2, 344.3, 344.4, 344.5, 344.6, 344.9) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_METS	Elixhauser Metastatic Cancer: 1 if patient had (ICD-9 codes 196-199) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_CA	Elixhauser Cancer, general: 1 if patient had (ICD-9 codes 140-165, 170-176, 179-195, 200-208, 273.0, 273.3) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
AF	Atrial Fibrillation: 1 if patient had (2010) (Primary or Secondary ICD-9 codes - 427.31, 427.32) on a Medicare Part A or B claim in

	the period 1-year prior to the index though the index stay, 0 otherwise.[17]
Cardiac_Arrest	Cardiac Arrest: 1 if patient had (Aujesky 2006) (ICD-9 code 427.5) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[18]
ELIX_Cardiac_Arrhyth	Elixhauser Cardiac Arrhythmia: 1 if patient had (ICD-9 codes 427.0, 427.1, 427.2, 427.3, 427.4, 427.6, 427.9, 785.0, V450, V533, 996.01, 996.04) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_CHF	Elixhauser Congestive Heart Failure: 1 if patient had (ICD-9 codes 428, 425.4, 425.5, 425.7, 425.8, 425.9, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
CABG	Coronary Artery Bypass Graft: 1 if patient had (ICD-9 procedure codes 361, 362, 363; or HCPCS codes 35510, 35511, 35512, 35513, 35514, 35515, 35516, 35517, 35518, 35519, 35520, 35521, 35522, 35523, 35524, 35525, 35526, 35527, 35528, 35529, 35530, 35531, 35532, 35533, 35534, 35535, 355336) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[19, 20]
CCW_IHDnonAMI	CCW Ischemic Heart Disease - non-AMI: 1 if patient had (2010) (ICD-9 codes 412, 411.0, 411.1, 413.0, 413.1, 413.9, 414.2, 414.3, 414.4, 414.8, 414.9, 410.00, 410.02, 410.10, 410.12, 410.20, 410.22, 410.30, 410.32, 410.40, 410.42, 410.50, 410.52, 410.60, 410.62, 410.70, 410.72, 410.80, 410.82, 410.90, 410.92, 411.81, 411.89, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[14]
CCW_AMI	CCW Acute Myocardial Infarction: 1 if patient had (Primary or Secondary ICD-9 codes 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[14]
ELIX_VD	Elixhauser Valvular Disease: 1 if patient had (ICD-9 codes 394, 395, 396, 397, 424, 093.2, 746.3, 746.4, 746.5, 746.6, V422, V433) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_COPD	Elixhauser Chronic Pulmonary Disease: 1 if patient had (ICD-9 codes 490-496, 500-505, 416.8, 416.9, 506.4, 508.1, 508.8) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
Pneumonia_Index	Pneumonia: 1 if patient had (ICD-9 codes 481-483) on Medicare Part A claim for the index stay, 0 otherwise.[21]
ELIX_RHEUM_A	Elixhuauser Rheumatologic Disease: 1 if patient had (ICD-9 codes 446, 720, 725, 701.0, 710.0, 710.1, 710.2, 710.3, 710.8, 710.9, 711.2, 719.3, 728.5, 729.30) on a Medicare Part A claim in the

	period 1-year prior to the index though the index stay, 0 otherwise.[13]
CCW_RHEUM_O	CCW Rheumatoid and Osteoarthritis: 1 if patient had (ICD-9 codes 714.0, 714.1, 714.2, 720.0, 721.0, 721.1, 721.2, 721.3, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 721.90, 721.91) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[14]
ELIX_DMUC	Elixhauser Diabetes, uncomplicated: 1 if patient had (ICD-9 codes 250.0, 250.1, 250.2, 250.3) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_DMC	Elixhauser Diabetes, complicated: 1 if patient had (ICD-9 codes 250.4, 250.5, 250.6, 250.7, 250.8, 250.9) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_HPTN_C	Elixhauser Hypertension, complicated: 1 if patient had (ICD-9 codes 402 through 405) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_HPTN_UC	Elixhauser Hypertension, uncomplicated: 1 if patient had (ICD-9 codes 401) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
CCW_HyperLipid	CCW Hyperlipidemia: 1 if patient had (ICD-9 codes 272.0, 272.1, 272.2, 272.3, 272.4) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[14]
ELIX_HPOTHROID	Elixhauser Hypothyroidism: 1 if patient had (ICD-9 codes243, 244, 240.9, 246.1, 246.8) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_LiverDz	Elixhauser Liver Disease: 1 if patient had (ICD-9 codes 570, 571, 070.6, 0700.9, 456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8, 573.3, 573.4, 573.8, 573.9, V427, 070.22, 070.23, 070.32, 070.33, 070.44, 070.54) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_PUBNB	Elixhauser Peptic Ulcer Disease, Excluding Bleeding: 1 if patient had (ICD-9 codes 531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
ELIX_PVD	Elixhuaser Peripheral Vascular Disease/Disorders: 1 if patient had (ICD-9 codes 440, 441, 093.0, 437.3, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9, V434) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]

ELIX_PCD	Elixhauser Pulmonary Circulation Disorders: 1 if patient had (ICD-9 codes 416, 415.0, 415.1, 417.0, 417.8, 417.9) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
CHRS_CVD_nonstroke	Charlson Cerebrovascular Disease: 1 if patient had (ICD-9 codes 432, 433, 437, 438, 435.2; ICD-9 Procedure codes 3812, 3842; HCPCS codes 35001, 35002, 35005, 35301, 35501, 35508, 35509, 35515, 35642, 35645, 35691, 35693) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[22]
ELIX_Psycho	Elixhauser Psychoses: 1 if patient had (ICD-9 codes 295, 297, 298, 293.8, 296.04, 296.14, 296.44, 296.54) on a Medicare Part A claim in the period 1-year prior to the index though the index stay, 0 otherwise.[13]
TIA	Transient Ischemic Attack: 1 if patient had (ICD-9 code 435) during index stay, 0 otherwise.[23]
Hemorrhagic	Hemorrhagic stroke: 1 if patient had (ICD-9 codes 430, 431) during index stay, 0 othewise.[14]
CCW_AlzhDemetia	CCW Alzheimer's Disease and Related Disorders or Senile Dementia: 1 if patient had (ICD-9 codes 797, 331.0, 331.2, 331.7, 290.0, 290.3, 294.0, 294.8, 331.11, 331.19, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.40, 290.41, 290.42, 290.43, 294.10, 294.11, 294.20, 294.21) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[14]
Angioedema	Angioedema: 1 if patient had (ICD-9 code 995.1) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.
Hyperkalemia	Hyperkalemia: 1 if patient had (ICD-9 code 276.7) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[24]
ARF	Acute renal failure: 1 if patient had (ICD-9 code 584) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.
HPOTN	Hypotension: 1 if patient had (ICD-9 codes 458.0, 785.5, 988.0) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[25, 26]
Bradycardia	Bradycardia: 1 if patient had (ICD-9 code 427.8) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[27]
HrtBlock	Heart Block: 1 if patient had (ICD-9 code 426) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[27]
Myopathy	Myopathy serious: 1 if patient had (Primary or Secondary ICD-9 codes 791.3, 729.1, 359.4, 359.8, 359.9, 710.4, 728.9, 729.8, 728.89, E942.2; HCPCS codes 82550, 82552, 82554, 80012, 80016, 80018, 80019) combined with Myopathy non-serious

	(Primary or Secondary ICD-9 codes 791.3, 729.1, 359.4, 359.8, 359.9, 710.4, 728.9, 729.8, 728.89, E942.2) on a Medicare Part A or B claim in the period 1-year prior to the index though the index stay, 0 otherwise.[28]
age66to70	1 if patient in age group 66 years to 70 years at index admission from CCW Medicare Beneficiary File, 0 otherwise.
age71to75	1 if patient in age group 71 years to 75 years at index admission from CCW Medicare Beneficiary File, 0 otherwise.
age76to80	1 if patient in age group 76 years to 80 years at index admission from CCW Medicare Beneficiary File, 0 otherwise.
age81to85	1 if patient in age group 81 years to 85 years at index admission from CCW Medicare Beneficiary File, 0 otherwise.
age85over	1 if patient in age group 85 years and over at index admission from CCW Medicare Beneficiary File, 0 otherwise.
male	1 if patient Sex is male, 0 otherwise.
female	1 if patient Sex is female, 0 otherwise.
white	1 if patient Race is Non-Hispanic White, 0 otherwise.
black	1 if patient Race is Black (or African-American), 0 otherwise.
race_other	1 if patient Race is Not otherwise specified, 0 otherwise.
asian	1 if patient Race is Asian / Pacific Islander, 0 otherwise.
hispanic	1 if patient Race is Hispanic, 0 otherwise.
american_native	1 if patient Race is American Indian / Alaska Native, 0 otherwise
ruca_metro	1 if patient zip code in metropolitan area based on Rural-Urban Commuting Area (RUCA) , 0 otherwise.
ruca_nonmetro	1 if patient zip code in non-metropolitan area based on Rural-Urban Commuting Area (RUCA) , 0 otherwise
ruca_unknown	1 if patient zip code rural-urban status unknown, 0 otherwise.
LIS_ind	1 if p atient has low income subsidy from CCW Medicare Beneficiary File, 0 otherwise.
dual_elig_strokemonth	1 if patient had Medicaid dual eligibility in the index stroke month from CCW Medicare Beneficiary File, 0 otherwise.
dual_elig_diff	1 if patient had different Medicaid eligibility status in the index stroke month and the month before, 0 otherwise.
highIMMarea	1 if patient zip code has a higher percentage of immigrants than the median zip code according to the Census, 0 otherwise.
highnoENGarea	1 if patient zip code has a higher percentage of residence how do not speak English than the median zip code according to the Census, 0 otherwise.
lowincomearea	1 if patient zip code has a lower per capita income than the median zip code according to the Census, 0 otherwise.
noHSedarea	1 if patient zip code has a higher percentage residence who did not complete high school than the median zip code according to the Census, 0 otherwise.
pctpovertyhigh	1 if patient zip code has a higher poverty rate than the median zip code according to the Census, 0 otherwise.

le_first_quart	1 if patient county of residence in the lowest survival quartile, 0 otherwise. [29]
le_second_quart	1 if patient county of residence in the second lowest survival quartile, 0 otherwise. [29]
le_third_quart	1 if patient county of residence in the highest survival quartile, 0 otherwise. [29]
le_fourth_quart	1 if patient county of residence in the highest survival quartile, 0 otherwise. [29]
deductible_phase	1 if patient in Part D deductible phase at index date from CCW Medicare Beneficiary File, 0 otherwise.
pre_ICL_phase	1 if patient in Part D pre-Initial Coverage Limit (ICL) phase at index date from CCW Medicare Beneficiary File, 0 otherwise.
ICL_phase	1 if patient in Part D Initial Coverage Limit (ICL) phase (donut hole) at index date from CCW Medicare Beneficiary File, 0 otherwise.
catastrophic_phase	1 if patient in Part D catastrophic phase at index date from CCW Medicare Beneficiary File, 0 otherwise.
unknown_phase	1 if patient in Part D phase at index date unknown from CCW Medicare Beneficiary File, 0 otherwise.
PLAN_PREMIUM_under25th	1 if patient Part D Plan Premium for 2010 under 25th percentile of study cohort from CCW Medicare Beneficiary File, 0 otherwise.
PLAN_PREMIUM_25thto50th	1 if patient Part D Plan Premium for 2010 between 25th and 50th percentile of study cohort from CCW Medicare Beneficiary File, 0 otherwise.
PLAN_PREMIUM_50thto75th	1 if patient Part D Plan Premium for 2010 between 50th and 75th percentile of study cohort from CCW Medicare Beneficiary File, 0 otherwise.
PLAN_PREMIUM_over75th	1 if patient Part D Plan Premium for 2010 over 75th percentile of study cohort from CCW Medicare Beneficiary File, 0 otherwise.
cum_bene_rspns_amt_under25th	1 if patient out-of-pocket drug costs in 2010 up to index date from Part D claims -- under 25th percentile of study cohort, 0 otherwise.
cum_bene_rspns_amt_25thto50th	1 if patient out-of-pocket drug costs in 2010 up to index date from Part D claims -- between 25th and 50th percentile of study cohort, 0 otherwise.
cum_bene_rspns_amt_50thto75th	1 if patient out-of-pocket drug costs in 2010 up to index date from Part D claims -- between 50th and 75th percentile of study cohort
cum_bene_rspns_amt_over75th	1 if patient out-of-pocket drug costs in 2010 up to index date from Part D claims – over 75th percentile of study cohort, 0 otherwise.
cum_total_cost_under25th	1 if patient total drug costs in 2010 up to index date from Part D claims -- under 25th percentile of study cohort, 0 otherwise.
cum_total_cost_25thto50th	1 if patient total drug costs in 2010 up to index date from Part D claims -- between 25th and 50th percentile of study cohort, 0 otherwise.

cum_total_cost_50thto75th	1 if patient total drug costs in 2010 up to index date from Part D claims -- between 50th and 75th percentile of study cohort, 0 otherwise.
cum_total_cost_over75th	1 if patient total drug costs in 2010 up to index date from Part D claims – over 75th percentile of study cohort, 0 otherwise.
FRI0	1 if the sum of 16 conditions related to patient frailty identified using Part A and Part B Medicare claims during the year prior to the index stroke period[10] equaled 0, 0 otherwise.
FRI1	1 if the sum of 16 conditions related to patient frailty identified using Part A and Part B Medicare claims during the year prior to the index stroke period[10] equaled 1, otherwise.
FRI2	1 if the sum of 16 conditions related to patient frailty identified using Part A and Part B Medicare claims during the year prior to the index stroke period[10] equaled 2, 0 otherwise.
FRI3plus	1 if the sum of 16 conditions related to patient frailty identified using Part A and Part B Medicare claims during the year prior to the index stroke period[10] equaled 3 or more, 0 otherwise.
CKD_STG_1_NOS	1 if CKD stage I (ICD-9 585.1) is the severest stage of CKD found from 1-year prior index through the index stay or if CKD NOS (ICD-9 585.9), 0 otherwise.
CKD_STG_2	1 if CKD stage II (ICD-9 585.2) is the severest stage of CKD found from 1-year prior index through the index stay, 0 otherwise.
CKD_STG_3	1 if CKD stage III (ICD-9 585.3) is the severest stage of CKD found from 1-year prior index through the index stay, 0 otherwise.
CKD_STG_4	1 if CKD stage IV (ICD-9 585.4) is the severest stage of CKD found from 1-year prior index through the index stay, 0 otherwise.
CKD_STG_5	1 if CKD stage V (ICD-9 585.5) is the severest stage of CKD found from 1-year prior index through the index stay, 0 otherwise.
PRE180_ACEARB	1 if patient had an ACEI/ARB prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_ALDO_RECEPT_ANTAG	1 if patient had an Aldosterone receptor antagonist prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_ALPHA_AGNOIST_CENTRAL	1 if patient had an Antiadrenergic agent (centrally acting) prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_ALPHA_BLOCKER_PERIPHERAL	1 if patient had an Antiadrenergic agent (peripherally acting) prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_ANTICOAG_OTH	1 if patient had a non-warfarin and non-heparin anticoagulant prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_ANTIHYPERTENSIVE_OTH	1 if patient had an antihypertensive prescription for a class not specifically designated in the 180 days prior to the index admission in Part D claims, 0 otherwise.

PRE180_ANTIPLATELET_OTH	1 if patient had an antiplatelet prescription for a class not specifically designated in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_ASPIRIN	1 if patient had an aspirin prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_BACTRIM	1 if patient had a bactrim prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_BETA_BLOCKER	1 if patient had a beta blocker prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_BILE_ACID	1 if patient had a bile acid prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_CC_BLOCKER	1 if patient had a calcium channel blocker in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_CLOPIDOGREL	1 if patient had a clopidogrel prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_DIURETIC_OTH	1 if patient had a non k-sparing diuretic prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_EZETIMIBE	1 if patient had an ezetimibe prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_FIBRATE	1 if patient had a fibrate prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_HEPARIN	1 if patient had a heparin prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_K_SPARING	1 if patient had a K-sparing diuretic in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_K_SUPP	1 if patient had a potassium supplement in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_LIPID_OTH	1 if patient had a lipid lowering product prescription not otherwise specified in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_LITHIUM	1 if patient had a lithium prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_NIACIN	1 if patient had a niacin prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_NSAID	1 if patient had a nsaid prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_PP_INHIBITOR	1 if patient had a proton pump inhibitor prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_RENIN_INHIB	1 if patient had a renin inhibitor prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_STATIN	1 if patient had a statin prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_TICLOPIDINE	1 if patient had a ticlopidine prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
PRE180_VASODILATOR	1 if patient had a vascodilator prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.

PRE180_WARFARIN	1 if patient had a wafarin prescription in the 180 days prior to the index admission in Part D claims, 0 otherwise.
POST30_ALDO_RECEPT_ANTAG	1 if patient had an Aldosterone receptor antagonist prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_ALPHA_AGNOIST_CENTRAL	1 if patient had an Antiadrenergic agent (centrally acting) prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_ALPHA_BLOCKER_PERIPHERAL	1 if patient had an Antiadrenergic agent (peripherally acting) prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_ANTICOAG_OTH	1 if patient had a non-warfarin and non-heparin anticoagulant prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_ANTIHYPERTENSIVE_OTH	1 if patient had an antihypertensive prescription for a class not specifically designated in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_ANTIPLATELET_OTH	1 if patient had an antiplatelet prescription for a class not specifically designated in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_ASPIRIN	1 if patient had an aspirin prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_BACTRIM	1 if patient had a bactrim prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_BETA_BLOCKER	1 if patient had a beta blocker prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_BILE_ACID	1 if patient had a bile acid prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_CC_BLOCKER	1 if patient had a calcium channel blocker in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_CLOPIDOGREL	1 if patient had a clopidogrel prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_DIURETIC_OTH	1 if patient had a non k-sparing diuretic prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_EZETIMIBE	1 if patient had an ezetimibe prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_FIBRATE	1 if patient had a fibrate prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_HEPARIN	1 if patient had a heparin prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_K_SPARING	1 if patient had a K-sparing diuretic in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_K_SUPP	1 if patient had a potassium supplement in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_LIPID_OTH	1 if patient had a lipid lowering product prescription not otherwise specified in the 30 days after the index discharge in Part D claims, 0 otherwise.

POST30_LITHIUM	1 if patient had a lithium prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_NIACIN	1 if patient had a niacin prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_NSAID	1 if patient had a nsaid prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_PP_INHIBITOR	1 if patient had a proton pump inhibitor prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_RENIN_INHIB	1 if patient had a renin inhibitor prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_STATIN	1 if patient had a statin prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_TICLOPIDINE	1 if patient had a ticlopidine prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_VASODILATOR	1 if patient had a vascodilator prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
POST30_WARFARIN	1 if patient had a wafarin prescription in the 30 days after the index discharge in Part D claims, 0 otherwise.
NDC_admission_0	1 if patient had 0 prescriptions with positive days supplied at index date based on days-supplied in Part D claims, 0 otherwise.
NDC_admission1to3	1 if patient had 1-3 prescriptions with distinct National Drug Codes (NDCs) with positive days supplied at index date based on days-supplied in Part D claims, 0 otherwise.
NDC_admission4plus	1 if patient had 4 or more prescriptions with distinct National Drug Codes (NDCs) with positive days supplied at index date based on days-supplied in Part D claims, 0 otherwise.
OT_acute	1 if patient had occupational therapy during acute stroke inpatient stay (revenue center code = 0430, 0431, 0432, 0433, 0434, 0439), 0 otherwise.
PT_acute	1 if patient had physical therapy during acute stroke inpatient stay (revenue center code = 0420, 0421, 0422, 0423, 0424, 0429), 0 otherwise.
ST_acute	1 if patient had speech therapy during acute stroke inpatient stay (revenue center code = 0440, 0441, 0442, 0443, 0444, 0449), 0 otherwise.
ier	1 if patient entered the acute stroke inpatient stay through the emergency room (revenue center code =0450, 0451, 0452, 0456, 0459), 0 otherwise.
transfer	1 if patient was transferred to another acute facility during the acute stroke inpatient stay, 0 otherwise.
days_imc	Days patient stayed in an Intermediate Care Unit (revenue center code = 0206) during index stroke institutional stay prior to discharge home.
days_icu	Days patient stayed in an Intensive Care Unit (revenue center code = 0200, 0201, 0202, 0203, 0204, 0207, 0208, 0209) during index stroke institutional stay prior to discharge home.

days_ccu	Days patient stayed in a Critical Care Unit (revenue center code = 0210, 0211, 0212, 0213, 0214, 0215, 0216, 0217, 0218, 0219) during index stroke institutional stay prior to discharge home.
days_SNF_sum	Days patient stayed in a Skilled Nursing Facility during index stroke institutional stay prior to discharge home.
days_reg_IP	Days patient stayed in an acute inpatient facility but not in a IMC, ICU, or CCU during index stroke institutional stay prior to discharge home.
days_IRF_sum	Days patient stayed in an Inpatient Rehabilitation Facility during index stroke institutional stay prior to discharge home.

Data S3. Instrument Strategy Background.

"Instruments" in instrumental variable estimation are measured factors having a strong relationship with treatment choice and are assumed to have no direct relationship to study outcomes or other unmeasured factors related to study outcomes. With these characteristics, instruments provide a natural experiment of treatment choice across patients.[30] Measures of local area practice styles have been shown to be a practical and rich source for instrument development.[31-33] The approach used here to measure local area practice styles has explained larger portions of treatment variation than other approaches and effectively balanced measured confounding variables.[34] We produced ZIP code-specific practice style measures reflecting the ACEI/ARB treatment choices for Medicare stroke patients living within a driving distance of each patient's ZIP code. Driving times were expanded around each ZIP code adding patients from additional ZIP codes until a defined threshold number of patients were found. For the patients around each ZIP code, an area treatment ratio (ATR) was estimated as the ratio of the number of these patients that used ACEI/ARBs after stroke over the sum of the predicted probabilities of these same patients receiving ACEI/ARBs after stroke. Predicted treatment probabilities were estimated for each patient based on a logistic model of treatment choice over all the stroke patients in our study using baseline covariates in Supplement A as dependent variables. A ZIP code with an ATR greater than 1 suggests greater provider preference in the local area for prescribing an ACEI/ARB after stroke than the average ZIP code area, and an ATR less than 1 suggests lower preference than average.

Data S4.

2-Stage Least Squares (2SLS) Instrumental Variable Estimator Background

2SLS estimation involved estimation of first-stage treatment choice equation of the form:

(1) $A_i = \beta_0 + \beta_1 \cdot X_i + \beta_2 \cdot R_i$, where

A_i equals 1 if patient "i" used an ACEI/ARB in the 30 days after index stroke discharge, 0 otherwise; X_i is vector containing all measured covariates; and R_i represents a set of variables describing the ACEI/ARB area treatment ratio (ATR) in ZIP code of the residence of patient "i". As robustness checks we used several approaches to specify R_i. We used standard F-test to assess the statistical significance of variables used to specify the instruments in equation (1). [35] The second stage outcome models were specified as follows:

(2) $Y_i = \alpha_0 + \alpha_1 \cdot \acute{A}_\iota + \alpha_2 \cdot X_i$, where

Y_i equals 1 of the outcome occurs for patient "i", 0 otherwise; and X_i is defined as above. $\acute{A}_\iota$ equals the predicted probability that patient "i" received an ACEI/ARB from equation (1). The parameter α_1 equals the absolute effect of ACEI/ARB use on the probability of outcome Y_i occurring, and is an estimate of the local average treatment effect (LATE) of ACEI/ARB use for those patients whose choice of ACEI/ARB was sensitive to local area practice styles.[36-39] We estimated α_1 for the full sample and on the subsets based on CKD status. As each dependent variable in this study is a binary variable, these linear specifications yield direct estimates of absolute LATEs.[40] Because of our large sample size, our parameter estimates will be distributed normally via the central limit theorem regardless of the distribution of the underlying error term.[41-43] Each 2SLS model was estimated with robust standard error methods using STATA software. We tested for differences in ACEI/ARB LATE estimates between the CKD and non-

CKD patients[44] and used bootstrapping to contrast the empirical distributions of treatment effects between CKD and non-CKD patients.[45] Over-identification tests were performed to assess whether our assumed exclusion of the instruments (R_i) from equation (2) was appropriate.[46]

Table S3. Means of Outcomes, Treatments, and Covariates for Medicare Patients in 2010 with an Index Ischemic Stroke and Chronic Kidney Disease by ACEI/ARB Treatment Choice and Instrument Values

Variables (See Supplement B for Definitions)	Total Popula-tion	ACE/ARB use					Quantiles of Local Areas Based Area Treatment Ratios (ATRs) Based on Actual and Predicted ACE/ARB Use[a]					
		No	Yes	p[b]	F-statistic[c]	p[d]	1st	2nd	3rd	4th	5th	p[e]
N	9,092	4,918	4,174	NA	NA	NA	1,817	1,865	1,816	1,821	1,773	NA
Treatment												
post_acearb	0.459	0.000	1.000	NA	NA	NA	0.400	0.408	0.448	0.508	0.535	<0.0001*
Outcomes												
Angioedema_2yr	0.005	0.005	0.005	0.930	NA	NA	0.007	0.006	0.006	0.002	0.003	0.025*
Hyperkalemia_2yr	0.107	0.101	0.113	0.060	NA	NA	0.104	0.108	0.110	0.105	0.106	0.961
HPOTN_2yr	0.053	0.055	0.050	0.325	NA	NA	0.053	0.057	0.051	0.053	0.049	0.482
renalevnt_2yr	0.177	0.171	0.184	0.095	NA	NA	0.186	0.177	0.177	0.172	0.172	0.260
recurstroke_2yr	0.065	0.067	0.062	0.417	NA	NA	0.067	0.064	0.067	0.063	0.062	0.515
surv_out2yr	0.678	0.662	0.697	0.001*	NA	NA	0.668	0.694	0.673	0.668	0.686	0.793
Baseline Covariates												
Elix_Depress	0.154	0.158	0.151	0.348	Comorbid-ities: 2.33	<0.0001*	0.151	0.159	0.163	0.143	0.156	0.779
ELIX_FluElexDis	0.357	0.367	0.345	0.029*			0.353	0.351	0.349	0.367	0.366	0.237
ELIX_Obesity	0.069	0.063	0.076	0.020*			0.066	0.069	0.074	0.061	0.073	0.745
ELIX_WL	0.077	0.085	0.067	0.0020*			0.076	0.071	0.084	0.076	0.076	0.820
ELIX_SubstanceAbuse	0.007	0.008	0.005	0.150			0.008	0.006	0.006	0.006	0.008	0.991
ELIX_Coagu	0.048	0.052	0.043	0.037*			0.051	0.050	0.042	0.046	0.051	0.763
ELIX_BLA	0.018	0.020	0.016	0.104			0.017	0.013	0.020	0.017	0.023	0.140
ELIX_DA	0.065	0.068	0.062	0.276			0.055	0.074	0.062	0.065	0.071	0.232
CCW_ExtraAnemia	0.405	0.417	0.390	0.008*			0.394	0.392	0.415	0.409	0.415	0.113
Sepsis_Index	0.041	0.047	0.034	0.001*			0.036	0.040	0.042	0.043	0.045	0.185
ELIX_OthNuro	0.271	0.271	0.271	0.993			0.268	0.287	0.252	0.274	0.273	0.916
ELIX_Paralysis	0.282	0.283	0.282	0.945			0.277	0.270	0.282	0.285	0.300	0.073
ELIX_METS	0.012	0.015	0.008	0.003*			0.013	0.011	0.013	0.008	0.013	0.656

ELIX_CA	0.163	0.176	0.148	0.0003*			0.172	0.160	0.167	0.146	0.169	0.450
AF	0.286	0.308	0.260	<0.0001*			0.290	0.289	0.283	0.279	0.290	0.764
Cardiac_Arrest	0.008	0.009	0.007	0.151			0.009	0.010	0.009	0.007	0.005	0.054
ELIX_Cardiac_Arrhyth	0.379	0.400	0.355	<0.0001*			0.385	0.387	0.378	0.377	0.368	0.220
ELIX_CHF	0.344	0.343	0.346	0.823			0.346	0.338	0.342	0.344	0.351	0.633
CABG	0.045	0.043	0.047	0.467			0.048	0.040	0.041	0.047	0.048	0.668
CCW_IHDnonAMI	0.525	0.522	0.527	0.638			0.524	0.544	0.502	0.514	0.539	0.991
CCW_AMI	0.042	0.042	0.042	0.864			0.042	0.044	0.036	0.045	0.043	0.808
ELIX_VD	0.122	0.123	0.121	0.814			0.123	0.128	0.126	0.109	0.125	0.525
ELIX_COPD	0.264	0.278	0.247	0.001*			0.258	0.256	0.262	0.280	0.264	0.259
Pneumonia_Index	0.022	0.022	0.022	0.794			0.017	0.021	0.025	0.019	0.028	0.077
ELIX_RHEUM_A	0.016	0.016	0.015	0.588			0.019	0.015	0.013	0.017	0.014	0.339
CCW_RHEUM_O	0.377	0.373	0.383	0.321			0.381	0.379	0.382	0.364	0.381	0.676
ELIX_DMUC	0.404	0.366	0.450	<0.0001*			0.399	0.398	0.408	0.422	0.397	0.571
ELIX_DMC	0.137	0.127	0.150	0.001*			0.146	0.134	0.136	0.129	0.142	0.590
ELIX_HPTN_C	0.523	0.530	0.514	0.118			0.534	0.501	0.519	0.532	0.527	0.666
ELIX_HPTN_UC	0.663	0.627	0.707	<0.0001*			0.674	0.655	0.655	0.674	0.659	0.772
CCW_HyperLipid	0.723	0.700	0.749	<0.0001*			0.705	0.735	0.713	0.716	0.743	0.089
ELIX_HPOTHROID	0.181	0.178	0.185	0.354			0.186	0.184	0.181	0.169	0.188	0.727
ELIX_LiverDz	0.017	0.019	0.014	0.103			0.014	0.022	0.014	0.017	0.016	0.962
ELIX_PUBNB	0.019	0.019	0.019	0.959			0.016	0.021	0.017	0.020	0.022	0.266
ELIX_PVD	0.152	0.150	0.155	0.531			0.176	0.146	0.139	0.148	0.154	0.121
ELIX_PCD	0.067	0.070	0.064	0.209			0.072	0.070	0.062	0.061	0.071	0.531
CHRS_CVD_nonstroke	0.639	0.628	0.652	0.017*			0.648	0.637	0.621	0.630	0.660	0.671
ELIX_Psycho	0.031	0.030	0.033	0.387			0.030	0.035	0.027	0.034	0.031	0.971
TIA	0.394	0.389	0.400	0.253			0.393	0.402	0.382	0.402	0.391	0.915
Hemorrhagic	0.043	0.046	0.040	0.179			0.040	0.043	0.044	0.044	0.045	0.448
CCW_AlzhDemetia	0.243	0.252	0.232	0.025*			0.253	0.237	0.238	0.250	0.237	0.556
Angioedema	0.003	0.005	0.002	0.0130*	ARCARB Side	<0.0001*	0.002	0.002	0.003	0.003	0.006	0.045*
Hyperkalemia	0.122	0.134	0.109	0.0003*			0.124	0.130	0.113	0.131	0.114	0.416

ARF	0.488	0.512	0.460	<0.0001*	Effects: 12.65		0.479	0.509	0.464	0.515	0.473	0.863
HPOTN	0.060	0.071	0.047	<0.0001*			0.062	0.064	0.060	0.057	0.057	0.314
Bradycardia	0.278	0.282	0.274	0.412	Other Med Side Effects: 0.036	0.783	0.269	0.270	0.287	0.280	0.285	0.208
HrtBlock	0.157	0.160	0.154	0.451			0.152	0.170	0.163	0.146	0.155	0.496
Myopathy	0.346	0.343	0.349	0.607			0.345	0.334	0.350	0.344	0.357	0.343
age66to70	0.108	0.097	0.121	0.0002*	Age Group: 1.09	0.358	0.111	0.097	0.113	0.111	0.109	0.644
age71to75	0.153	0.146	0.160	0.067			0.145	0.149	0.161	0.153	0.156	0.329
age76to80	0.187	0.182	0.192	0.226			0.179	0.205	0.189	0.186	0.173	0.273
age81to85	0.230	0.232	0.228	0.674			0.233	0.233	0.225	0.224	0.235	0.879
age85over	0.323	0.343	0.299	<0.0001*			0.332	0.316	0.312	0.327	0.327	0.995
male	0.379	0.398	0.356	<0.0001*	Sex: 0.54	0.462	0.375	0.374	0.382	0.373	0.390	0.425
female	0.621	0.602	0.644	<0.0001*			0.625	0.626	0.618	0.627	0.610	0.425
white	0.790	0.807	0.770	<0.0001*	Race: 2.25	0.047*	0.807	0.832	0.784	0.749	0.777	<0.0001*
black	0.144	0.133	0.158	0.0005*			0.143	0.121	0.153	0.167	0.139	0.138
race_other	0.012	0.012	0.013	0.687			0.007	0.009	0.013	0.020	0.014	0.002*
asian	0.024	0.020	0.029	0.0050*			0.021	0.026	0.020	0.030	0.023	0.521
hispanic	0.023	0.021	0.025	0.229			0.015	0.010	0.024	0.029	0.038	<0.0001*
american_native	0.006	0.007	0.005	0.125			0.007	0.003	0.006	0.005	0.010	0.133
ruca_metro	0.763	0.772	0.752	0.026*	RUCA: 0.176	0.838	0.756	0.745	0.756	0.774	0.785	0.006*
ruca_nonmetro	0.237	0.228	0.248	0.026*			0.243	0.255	0.245	0.225	0.215	0.006*
ruca_unknown	0.000	0.000	0.000	0.908			0.001	0.000	0.000	0.001	0.000	0.626
LIS_ind	0.053	0.050	0.055	0.276	SES: 1.16	0.307	0.054	0.049	0.053	0.058	0.049	0.945
dual_elig_strokemonth	0.368	0.339	0.402	<0.0001*			0.359	0.331	0.378	0.408	0.365	0.013*
dual_elig_diff	0.049	0.044	0.054	0.030*			0.053	0.050	0.046	0.047	0.048	0.396
highIMMarea	0.503	0.493	0.516	0.029*			0.473	0.493	0.515	0.533	0.503	0.007*
highnoENGarea	0.480	0.485	0.475	0.336			0.411	0.452	0.492	0.512	0.538	<0.0001*
lowincomearea	0.506	0.486	0.530	<0.0001*			0.492	0.505	0.510	0.515	0.510	0.207
noHSedarea	0.504	0.488	0.523	0.001*			0.452	0.490	0.528	0.545	0.508	<0.0001*
pctpovertyhigh	0.507	0.488	0.529	0.0001*			0.477	0.481	0.516	0.559	0.503	0.0005*
le_first_quart	0.250	0.244	0.258	0.143			0.235	0.230	0.275	0.278	0.234	0.139

le_second_quart	0.245	0.240	0.251	0.193			0.238	0.276	0.225	0.216	0.270	0.968
le_third_quart	0.244	0.253	0.234	0.042*			0.306	0.248	0.212	0.232	0.224	<0.0001*
le_fourth_quart	0.260	0.264	0.257	0.469			0.221	0.247	0.288	0.274	0.273	<0.0001*
deductible_phase	0.132	0.138	0.125	0.072	Insur-ance: 0.709	0.756	0.141	0.127	0.126	0.143	0.124	0.487
pre_ICL_phase	0.647	0.654	0.639	0.135			0.647	0.651	0.648	0.652	0.636	0.558
ICL_phase	0.136	0.123	0.152	<0.0001*			0.133	0.137	0.138	0.129	0.144	0.573
catastrophic_phase	0.030	0.026	0.035	0.018*			0.025	0.028	0.031	0.025	0.043	0.012*
unknown_phase	0.055	0.060	0.049	0.029*			0.055	0.057	0.057	0.051	0.054	0.629
PLAN_PREMIUM_under25th	0.244	0.231	0.259	0.002*			0.271	0.232	0.232	0.261	0.223	0.0400*
PLAN_PREMIUM_25thto50th	0.226	0.229	0.222	0.449			0.225	0.203	0.247	0.229	0.226	0.356
PLAN_PREMIUM_50thto75th	0.257	0.265	0.249	0.090			0.242	0.270	0.256	0.242	0.278	0.179
PLAN_PREMIUM_over75th	0.273	0.275	0.270	0.571			0.263	0.295	0.265	0.268	0.273	0.841
cum_bene_rspns_amt_under25th	0.204	0.221	0.184	<0.0001*			0.214	0.186	0.204	0.227	0.188	0.795
cum_bene_rspns_amt_25thto50th	0.258	0.244	0.274	0.001*			0.250	0.246	0.256	0.280	0.258	0.130
cum_bene_rspns_amt_50thto75th	0.256	0.254	0.258	0.694			0.255	0.258	0.258	0.237	0.271	0.801
cum_bene_rspns_amt_over75th	0.282	0.280	0.285	0.638			0.281	0.309	0.283	0.256	0.283	0.138
cum_total_cost_under25th	0.210	0.231	0.185	<0.0001*			0.215	0.213	0.209	0.221	0.190	0.157
cum_total_cost_25thto50th	0.251	0.254	0.248	0.497			0.246	0.238	0.259	0.257	0.258	0.191
cum_total_cost_50thto75th	0.268	0.263	0.274	0.213			0.280	0.280	0.258	0.265	0.257	0.063
cum_total_cost_over75th	0.271	0.252	0.293	<0.0001*			0.259	0.269	0.274	0.258	0.296	0.061
FRI0	0.332	0.318	0.349	0.002*	FRI: 1.68	0.168	0.341	0.337	0.337	0.331	0.316	0.117
FRI1	0.250	0.248	0.251	0.778			0.264	0.238	0.254	0.244	0.248	0.408
FRI2	0.170	0.173	0.166	0.406			0.156	0.187	0.164	0.168	0.174	0.573
FRI3plus	0.248	0.261	0.234	0.003*			0.239	0.239	0.245	0.258	0.262	0.183
CKD_STG_1_NOS	0.566	0.545	0.591	<.0001*	CKD Stage: 4.91	<0.0006*	0.560	0.579	0.567	0.559	0.566	0.3590
CKD_STG_2	0.037	0.036	0.038	0.4881			0.032	0.031	0.042	0.042	0.038	0.5769
CKD_STG_3	0.267	0.268	0.266	0.8588			0.286	0.253	0.257	0.272	0.267	0.5838
CKD_STG_4	0.113	0.130	0.093	<.0001*			0.104	0.122	0.120	0.108	0.112	0.4799
CKD_STG_5	0.017	0.021	0.012	0.0010*			0.019	0.016	0.015	0.019	0.018	0.4695
PRE180_ACEARB	0.582	0.379	0.822	<0.0001*		<0.0001*	0.566	0.581	0.581	0.589	0.595	0.080

PRE180_ALDO_RECEPT_ANTAG	0.052	0.059	0.045	0.004*			0.043	0.062	0.051	0.050	0.056	0.369
PRE180_ALPHA_AGNOIST_CENTRAL	0.078	0.069	0.089	0.0003*			0.074	0.073	0.083	0.082	0.077	0.432
PRE180_ALPHA_BLOCKER_PERIPHERAL	0.107	0.112	0.101	0.090			0.101	0.109	0.118	0.099	0.106	0.944
PRE180_ANTICOAG_OTH	0.013	0.014	0.012	0.360			0.011	0.015	0.015	0.012	0.015	0.527
PRE180_ANTIPLATELET_OTH	0.015	0.012	0.018	0.019*			0.014	0.017	0.012	0.012	0.021	0.301
PRE180_ASPIRIN	0.023	0.022	0.024	0.396			0.022	0.023	0.023	0.023	0.025	0.486
PRE180_BACTRIM	0.080	0.078	0.082	0.473			0.081	0.082	0.079	0.075	0.083	0.860
PRE180_BETA_BLOCKER	0.593	0.573	0.617	<0.0001*			0.592	0.605	0.589	0.572	0.606	0.871
PRE180_BILE_ACID	0.011	0.010	0.012	0.605			0.012	0.015	0.012	0.006	0.010	0.067
PRE180_CC_BLOCKER	0.390	0.364	0.421	<0.0001*			0.385	0.379	0.373	0.406	0.410	0.032*
PRE180_CLOPIDOGREL	0.169	0.155	0.185	0.0001*			0.157	0.170	0.171	0.176	0.170	0.239
PRE180_DIURETIC_OTH	0.544	0.512	0.582	<0.0001*			0.525	0.550	0.562	0.538	0.546	0.421
PRE180_EZETIMIBE	0.038	0.036	0.040	0.292	Pre 180 days drugs: 74.44		0.031	0.037	0.043	0.035	0.043	0.118
PRE180_FIBRATE	0.056	0.050	0.062	0.011*			0.050	0.055	0.054	0.055	0.064	0.102
PRE180_HEPARIN	0.002	0.002	0.002	0.411			0.002	0.001	0.002	0.004	0.001	0.705
PRE180_K_SPARING	0.045	0.047	0.042	0.250			0.043	0.048	0.045	0.046	0.043	0.941
PRE180_K_SUPP	0.206	0.206	0.207	0.864			0.186	0.205	0.214	0.218	0.210	0.037*
PRE180_LIPID_OTH	0.001	0.000	0.001	0.527			0.000	0.001	0.001	0.000	0.002	0.107
PRE180_LITHIUM	0.002	0.001	0.002	0.399			0.001	0.003	0.001	0.001	0.003	0.425
PRE180_NIACIN	0.012	0.010	0.014	0.124			0.014	0.012	0.012	0.008	0.015	0.661
PRE180_NSAID	0.125	0.116	0.136	0.003*			0.113	0.128	0.113	0.132	0.138	0.030*
PRE180_PP_INHIBITOR	0.307	0.293	0.324	0.002*			0.307	0.294	0.302	0.309	0.326	0.120
PRE180_RENIN_INHIB	0.011	0.010	0.012	0.352			0.011	0.008	0.009	0.012	0.016	0.071
PRE180_STATIN	0.482	0.448	0.523	<0.0001*			0.462	0.491	0.474	0.474	0.512	0.029*
PRE180_TICLOPIDINE	0.001	0.001	0.001	0.561			0.000	0.001	0.002	0.002	0.001	0.459
PRE180_VASODILATOR	0.113	0.107	0.120	0.062			0.118	0.096	0.118	0.115	0.118	0.399
PRE180_WARFARIN	0.139	0.144	0.134	0.198			0.151	0.145	0.139	0.131	0.130	0.029*
POST30_ALDO_RECEPT_ANTAG	0.029	0.029	0.029	0.882	Post 30 days drugs: 17.99	<0.0001*	0.024	0.032	0.029	0.023	0.036	0.310
POST30_ALPHA_AGNOIST_CENTRAL	0.064	0.054	0.076	<0.0001*			0.058	0.064	0.066	0.068	0.064	0.371
POST30_ALPHA_BLOCKER_PERIPHERAL	0.082	0.081	0.082	0.796			0.071	0.083	0.089	0.084	0.082	0.245

POST30_ANTICOAG_OTH	0.024	0.024	0.025	0.681			0.025	0.027	0.023	0.017	0.030	0.892
POST30_ANTIPLATELET_OTH	0.010	0.008	0.014	0.003*			0.008	0.014	0.008	0.008	0.015	0.260
POST30_ASPIRIN	0.083	0.078	0.088	0.070			0.088	0.071	0.090	0.079	0.085	0.916
POST30_BACTRIM	0.027	0.028	0.025	0.505			0.032	0.021	0.026	0.027	0.027	0.661
POST30_BETA_BLOCKER	0.475	0.426	0.532	<0.0001*			0.476	0.459	0.466	0.475	0.500	0.085
POST30_BILE_ACID	0.005	0.005	0.006	0.250			0.005	0.010	0.004	0.002	0.006	0.290
POST30_CC_BLOCKER	0.339	0.299	0.387	<0.0001*			0.341	0.335	0.327	0.356	0.338	0.662
POST30_CLOPIDOGREL	0.294	0.265	0.328	<0.0001*			0.280	0.295	0.301	0.303	0.290	0.416
POST30_DIURETIC_OTH	0.335	0.267	0.414	<0.0001*			0.331	0.340	0.339	0.337	0.327	0.743
POST30_EZETIMIBE	0.024	0.019	0.030	0.0005*			0.014	0.026	0.025	0.026	0.027	0.024*
POST30_FIBRATE	0.035	0.028	0.043	<0.0001*			0.035	0.035	0.030	0.038	0.036	0.789
POST30_HEPARIN	0.003	0.003	0.003	0.980			0.007	0.001	0.002	0.002	0.003	0.139
POST30_K_SPARING	0.017	0.016	0.018	0.532			0.019	0.016	0.019	0.020	0.012	0.307
POST30_K_SUPP	0.142	0.135	0.151	0.0409*			0.137	0.137	0.151	0.151	0.136	0.627
POST30_LIPID_OTH	0.000	0.000	0.000	0.662			0.000	0.001	0.000	0.001	0.001	0.402
POST30_LITHIUM	0.001	0.001	0.001	0.346			0.001	0.001	0.001	0.001	0.002	0.434
POST30_NIACIN	0.009	0.007	0.012	0.012*			0.009	0.008	0.010	0.006	0.012	0.626
POST30_NSAID	0.037	0.030	0.044	0.0003*			0.035	0.033	0.036	0.036	0.045	0.106
POST30_PP_INHIBITOR	0.259	0.240	0.282	<0.0001*			0.253	0.233	0.258	0.267	0.287	0.002*
POST30_RENIN_INHIB	0.008	0.004	0.012	<0.0001*			0.007	0.005	0.007	0.008	0.013	0.014*
POST30_STATIN	0.529	0.460	0.610	<0.0001*			0.526	0.511	0.526	0.537	0.546	0.076
POST30_TICLOPIDINE	0.001	0.001	0.001	0.930			0.001	0.001	0.001	0.001	0.002	0.225
POST30_VASODILATOR	0.089	0.086	0.094	0.190			0.100	0.078	0.089	0.088	0.093	0.913
POST30_WARFARIN	0.207	0.204	0.211	0.362			0.211	0.219	0.202	0.200	0.203	0.228
NDC_admission_0	0.344	0.366	0.319	<0.0001*	NDC drugs at admission : 4.27	0.014*	0.339	0.341	0.357	0.357	0.328	0.906
NDC_admission1to3	0.416	0.422	0.409	0.196			0.401	0.413	0.409	0.419	0.438	0.029*
NDC_admission4plus	0.240	0.212	0.272	<0.0001*			0.261	0.246	0.234	0.224	0.234	0.017*
OT_acute	0.671	0.674	0.668	0.564	Therapy days during	0.329	0.685	0.689	0.664	0.657	0.661	0.020*
PT_acute	0.891	0.887	0.897	0.111			0.902	0.892	0.892	0.882	0.889	0.118
ST_acute	0.619	0.622	0.615	0.504			0.614	0.610	0.611	0.624	0.635	0.127

					acute stay: 1.14							
ier	0.871	0.872	0.869	0.635	Admission Type: 0.076	0.927	0.869	0.871	0.884	0.862	0.868	0.609
transfer	0.023	0.022	0.024	0.675			0.026	0.023	0.019	0.021	0.026	0.881
days_imc	1.062	1.045	1.083	0.499	Institutional stay divisions: 2.96	0.007*	1.068	1.068	1.033	1.013	1.133	0.429
days_icu	0.603	0.578	0.632	0.311			0.579	0.537	0.554	0.641	0.706	0.217
days_ccu	0.666	0.703	0.622	0.082			0.643	0.584	0.677	0.738	0.690	0.047*
days_reg_IP	3.714	3.752	3.668	0.476			3.909	3.618	3.768	3.563	3.712	0.014*
days_SNF_sum	17.664	17.701	17.622	0.909			18.478	17.246	17.955	16.936	17.721	0.526
days_IRF_sum	4.051	4.046	4.057	0.945			4.220	4.126	3.962	3.929	4.016	0.376

a. Based on Area Treatment Ratio (ATR) of actual ACE/ARB treatment rate over predicted ACE/ARB treatment rate for the 50 AMI patients living closest to each patient's residence ZIP code.

b. P value of T-test of characteristic difference between treated and non-treated patients.

c. Chow F-statistic used to test the exclusion restrictions of the specified set of covariates in the ARC/ARB choice equations. Chow GC. Tests of equality between sets of coefficients in two linear regressions. *Econometrica: Journal of the Econometric Society*. 1960:591-605.

d. P value for Chow F-tests.

e. Cochran-Armitage two-sided test of trend in characteristic value across patients grouped into quintiles based on local area ACE/ARB Area Treatment Ratios (ATRs). For example, the p value for age66to70 tests whether a linear trend in the percentage of patients in this age group exists across quintiles of the ACE/ARB choice ATR-based patient groups.

*p<0. _____ signifies positive relationship with ACE/ARB choice or positive association with local area ACE/ARB Area Treatment rates. _____ signifies negative relationship with ACE/ARB choice or positive association with local area ACE/ARB Area Treatment rates.

Table S4. Means of Outcomes, Treatments, and Covariates for Medicare Patients in 2010 with an Index Ischemic Stroke and No Prior Chronic Kidney Disease by ACEI/ARB Treatment Choice and Instrument Values

Variables (See Supplement B for Definitions)	Total population	ACE/ARB use					Quantiles of Local Areas Based Area Treatment Ratios (ATRs) Based on Actual and Predicted ACE/ARB Use[a]					
		No	Yes	p[b]	F-statistic[c]	p[d]	1st	2nd	3rd	4th	5th	p[e]
N	**26,677**	**14,609**	**12,068**	**NA**	**NA**	**NA**	**5,335**	**5,290**	**5,337**	**5,333**	**5,382**	**NA**
Treatments												
post_acearb	**0.452**	**0.000**	**1.000**	**NA**	**NA**	**NA**	**0.385**	**0.423**	**0.452**	**0.484**	**0.517**	**<0.0001***
Outcomes												
Angioedema_2yr	0.004	0.003	0.006	0.001*	NA	NA	0.004	0.005	0.004	0.005	0.005	0.874
Hyperkalemia_2yr	0.044	0.038	0.051	<0.0001*	NA	NA	0.044	0.042	0.051	0.042	0.040	0.375
HPOTN_2yr	0.048	0.047	0.049	0.293	NA	NA	0.046	0.047	0.050	0.049	0.047	0.635
renalevnt_2yr	0.063	0.054	0.075	<0.0001*	NA	NA	0.065	0.061	0.062	0.064	0.065	0.785
recurstroke_2yr	0.068	0.065	0.072	0.020*	NA	NA	0.070	0.071	0.063	0.071	0.066	0.457
surv_out2yr	0.795	0.778	0.814	<0.0001*	NA	NA	0.788	0.793	0.800	0.798	0.794	0.324
Baseline Covariates												
Elix_Depress	0.140	0.141	0.139	0.522	Comorobid-ities: 8.23	<0.0001*	0.140	0.141	0.136	0.136	0.146	0.620
ELIX_FluElexDis	0.208	0.202	0.215	0.008*			0.214	0.210	0.209	0.202	0.202	0.069
ELIX_Obesity	0.054	0.045	0.065	<0.0001*			0.051	0.048	0.060	0.055	0.055	0.118
ELIX_WL	0.038	0.042	0.032	<0.0001*			0.038	0.040	0.035	0.038	0.037	0.697
ELIX_SubstanceAbuse	0.006	0.006	0.005	0.424			0.007	0.005	0.005	0.006	0.006	0.572
ELIX_Coagu	0.027	0.029	0.025	0.023*			0.031	0.027	0.025	0.028	0.025	0.131
ELIX_BLA	0.007	0.007	0.008	0.631			0.008	0.006	0.009	0.006	0.009	0.578
ELIX_DA	0.033	0.033	0.033	0.886			0.032	0.030	0.037	0.032	0.033	0.653
CCW_ExtraAnemia	0.185	0.190	0.180	0.032*			0.186	0.167	0.177	0.196	0.200	0.001*
Sepsis_Index	0.012	0.013	0.011	0.056			0.012	0.014	0.013	0.013	0.010	0.227
ELIX_OthNuro	0.244	0.250	0.236	0.010*			0.245	0.242	0.236	0.242	0.255	0.283
ELIX_Paralysis	0.277	0.269	0.286	0.002*			0.268	0.269	0.280	0.289	0.277	0.044*
ELIX_METS	0.009	0.011	0.007	0.0010*			0.012	0.008	0.008	0.007	0.011	0.643
ELIX_CA	0.142	0.153	0.128	<0.0001*			0.143	0.127	0.145	0.143	0.150	0.048*
AF	0.241	0.257	0.222	<0.0001*			0.253	0.244	0.236	0.247	0.227	0.008*

Cardiac_Arrest	0.003	0.002	0.004	0.047*			0.003	0.004	0.002	0.002	0.003	0.496
ELIX_Cardiac_Arrhyth	0.322	0.340	0.299	<0.0001*			0.331	0.313	0.318	0.327	0.320	0.663
ELIX_CHF	0.164	0.154	0.177	<0.0001*			0.158	0.164	0.169	0.159	0.171	0.201
CABG	0.038	0.038	0.039	0.639			0.044	0.042	0.035	0.034	0.036	0.007*
CCW_IHDnonAMI	0.375	0.362	0.390	<0.0001*			0.363	0.371	0.380	0.374	0.385	0.025*
CCW_AMI	0.020	0.017	0.023	0.002*			0.019	0.020	0.019	0.019	0.022	0.429
ELIX_VD	0.111	0.114	0.108	0.104			0.114	0.113	0.114	0.108	0.108	0.215
ELIX_COPD	0.199	0.204	0.193	0.028*			0.205	0.194	0.201	0.199	0.196	0.440
Pneumonia_Index	0.009	0.010	0.008	0.031*			0.009	0.007	0.010	0.010	0.009	0.559
ELIX_RHEUM_A	0.015	0.015	0.014	0.804			0.017	0.017	0.015	0.011	0.013	0.012*
CCW_RHEUM_O	0.354	0.354	0.355	0.764			0.358	0.343	0.352	0.352	0.368	0.163
ELIX_DMUC	0.286	0.240	0.342	<0.0001*			0.288	0.278	0.286	0.288	0.293	0.316
ELIX_DMC	0.050	0.040	0.063	<0.0001*			0.051	0.049	0.049	0.052	0.052	0.677
ELIX_HPTN_C	0.041	0.033	0.050	<0.0001*			0.035	0.038	0.042	0.041	0.046	0.004*
ELIX_HPTN_UC	0.832	0.772	0.904	<0.0001*			0.835	0.831	0.833	0.832	0.828	0.387
CCW_HyperLipid	0.686	0.663	0.713	<0.0001*			0.689	0.676	0.688	0.687	0.687	0.765
ELIX_HPOTHROID	0.177	0.184	0.169	0.002*			0.177	0.178	0.171	0.180	0.178	0.779
ELIX_LiverDz	0.009	0.010	0.007	0.008*			0.011	0.006	0.008	0.008	0.010	0.969
ELIX_PUBNB	0.011	0.011	0.010	0.149			0.009	0.009	0.013	0.012	0.010	0.245
ELIX_PVD	0.092	0.092	0.092	0.791			0.091	0.085	0.094	0.096	0.092	0.313
ELIX_PCD	0.040	0.041	0.039	0.431			0.041	0.038	0.041	0.040	0.039	0.766
CHRS_CVD_nonstroke	0.565	0.549	0.585	<0.0001*			0.569	0.561	0.562	0.573	0.560	0.805
ELIX_Psycho	0.027	0.027	0.026	0.629			0.026	0.027	0.026	0.027	0.029	0.388
TIA	0.403	0.407	0.399	0.164			0.411	0.405	0.398	0.402	0.400	0.281
Hemorrhagic	0.039	0.040	0.038	0.506			0.038	0.041	0.036	0.039	0.041	0.677
CCW_AlzhDemetia	0.196	0.200	0.191	0.063			0.197	0.193	0.188	0.201	0.200	0.464
Angioedema	0.003	0.003	0.003	0.284	ARC/ARB Side Effects: 7.99	<0.0001*	0.004	0.003	0.002	0.002	0.004	0.974
Hyperkalemia	0.025	0.025	0.026	0.539			0.025	0.022	0.023	0.026	0.029	0.070
ARF	0.003	0.003	0.004	0.122			0.004	0.003	0.004	0.002	0.005	0.574
HPOTN	0.031	0.037	0.024	<0.0001*			0.032	0.030	0.032	0.032	0.030	0.837

Bradycardia	0.209	0.205	0.213	0.087	Other Med Side Effects: 2.45	0.061	0.202	0.209	0.215	0.210	0.209	0.410
HrtBlock	0.117	0.116	0.118	0.642			0.115	0.121	0.111	0.113	0.123	0.475
Myopathy	0.295	0.290	0.299	0.111			0.289	0.299	0.303	0.290	0.292	0.945
age66to70	0.128	0.122	0.135	0.002*	Age Group: 2.46	0.043*	0.122	0.127	0.129	0.134	0.127	0.247
age71to75	0.183	0.174	0.194	<0.0001*			0.187	0.174	0.191	0.187	0.175	0.481
age76to80	0.198	0.196	0.199	0.580			0.199	0.196	0.201	0.199	0.193	0.565
age81to85	0.213	0.214	0.212	0.811			0.214	0.217	0.208	0.208	0.217	0.815
age85over	0.279	0.294	0.261	<0.0001*			0.277	0.286	0.271	0.273	0.288	0.638
male	0.337	0.353	0.317	<0.0001*	Sex: 9.98	0.002*	0.335	0.326	0.345	0.334	0.344	0.207
female	0.663	0.647	0.683	<0.0001*			0.665	0.674	0.655	0.666	0.656	0.207
white	0.849	0.868	0.826	<0.0001*	Race: 0.433	0..826	0.866	0.866	0.835	0.836	0.843	<0.0001*
black	0.088	0.075	0.104	<0.0001*			0.084	0.082	0.100	0.094	0.081	0.594
race_other	0.011	0.011	0.011	0.724			0.008	0.011	0.013	0.010	0.013	0.079
asian	0.022	0.020	0.025	0.004*			0.021	0.017	0.023	0.027	0.022	0.077
hispanic	0.025	0.021	0.030	<0.0001*			0.018	0.021	0.023	0.029	0.036	<0.0001*
american_native	0.005	0.005	0.005	0.986			0.003	0.004	0.007	0.005	0.005	0.062
ruca_metro	0.736	0.745	0.725	0.0002*	RUCA: 4.19	0.015*	0.752	0.702	0.721	0.740	0.765	0.001*
ruca_nonmetro	0.263	0.254	0.274	0.0002*			0.248	0.298	0.278	0.259	0.235	0.001*
ruca_unknown	0.001	0.000	0.001	0.238			0.000	0.000	0.001	0.001	0.000	0.705
LIS_ind	0.052	0.047	0.059	<0.0001*	SES: 2.43	0.005*	0.047	0.057	0.056	0.050	0.052	0.700
dual_elig_strokemonth	0.304	0.274	0.340	<0.0001*			0.292	0.286	0.306	0.312	0.323	<0.0001*
dual_elig_diff	0.040	0.039	0.041	0.418			0.042	0.041	0.037	0.041	0.037	0.293
highIMMarea	0.501	0.499	0.504	0.471			0.497	0.478	0.489	0.527	0.515	0.0001*
highnoENGarea	0.478	0.474	0.482	0.193			0.428	0.439	0.491	0.483	0.549	<0.0001*
lowincomearea	0.495	0.476	0.518	<0.0001*			0.464	0.490	0.493	0.510	0.517	<0.0001*
noHSedarea	0.480	0.456	0.510	<0.0001*			0.442	0.455	0.493	0.510	0.501	<0.0001*
pctpovertyhigh	0.488	0.465	0.516	<0.0001*			0.453	0.462	0.495	0.521	0.509	<0.0001*
le_first_quart	0.245	0.234	0.259	<0.0001*			0.247	0.244	0.263	0.263	0.210	0.004*
le_second_quart	0.247	0.244	0.250	0.249			0.229	0.274	0.246	0.221	0.264	0.360
le_third_quart	0.243	0.247	0.238	0.067			0.293	0.235	0.204	0.240	0.244	<0.0001*

le_fourth_quart	0.265	0.274	0.253	0.0001*			0.231	0.247	0.287	0.276	0.282	<0.0001*
deductible_phase	0.163	0.172	0.153	<0.0001*	Insurance: 2.29	0.005*	0.166	0.170	0.166	0.161	0.154	0.036*
pre_ICL_phase	0.661	0.657	0.667	0.114			0.661	0.664	0.655	0.660	0.668	0.594
ICL_phase	0.094	0.088	0.101	0.0002*			0.090	0.086	0.095	0.096	0.101	0.007*
catastrophic_phase	0.021	0.017	0.025	<0.0001*			0.018	0.020	0.020	0.024	0.020	0.161
unknown_phase	0.061	0.066	0.055	0.0002*			0.066	0.061	0.063	0.059	0.057	0.055
PLAN_PREMIUM_under25th	0.231	0.218	0.246	<0.0001*			0.242	0.234	0.236	0.224	0.218	0.002*
PLAN_PREMIUM_25thto50th	0.220	0.220	0.221	0.850			0.213	0.219	0.232	0.214	0.224	0.318
PLAN_PREMIUM_50thto75th	0.277	0.289	0.263	<0.0001*			0.285	0.277	0.260	0.280	0.284	0.954
PLAN_PREMIUM_over75th	0.272	0.274	0.270	0.444			0.261	0.271	0.272	0.282	0.274	0.049*
cum_bene_rspns_amt_under25th	0.233	0.245	0.218	<0.0001*			0.232	0.229	0.233	0.237	0.234	0.532
cum_bene_rspns_amt_25thto50th	0.261	0.251	0.273	0.0001*			0.262	0.262	0.255	0.253	0.272	0.566
cum_bene_rspns_amt_50thto75th	0.262	0.265	0.258	0.240			0.257	0.262	0.263	0.265	0.262	0.541
cum_bene_rspns_amt_over75th	0.245	0.239	0.251	0.029*			0.248	0.247	0.249	0.246	0.232	0.068
cum_total_cost_under25th	0.296	0.320	0.267	<0.0001*			0.306	0.309	0.288	0.289	0.286	0.003*
cum_total_cost_25thto50th	0.268	0.270	0.265	0.282			0.269	0.269	0.270	0.266	0.265	0.580
cum_total_cost_50thto75th	0.244	0.231	0.259	<0.0001*			0.238	0.240	0.247	0.245	0.248	0.206
cum_total_cost_over75th	0.193	0.179	0.210	<0.0001*			0.187	0.181	0.195	0.200	0.201	0.006*
FRI0	0.448	0.432	0.466	<0.0001*	FRI: 6.52	0.0002*	0.453	0.465	0.454	0.440	0.426	0.0003*
FRI1	0.266	0.270	0.261	0.088			0.264	0.256	0.265	0.280	0.266	0.146
FRI2	0.143	0.144	0.142	0.587			0.136	0.139	0.142	0.142	0.154	0.009*
FRI3plus	0.143	0.153	0.131	<0.0001*			0.147	0.140	0.139	0.138	0.153	0.495
PRE180_ACEARB	0.476	0.265	0.732	<0.0001*	Pre 180 days drugs: 213.74	<0.0001*	0.465	0.461	0.488	0.481	0.487	0.003*
PRE180_ALDO_RECEPT_ANTAG	0.025	0.025	0.024	0.460			0.025	0.022	0.028	0.024	0.025	0.831
PRE180_ALPHA_AGNOIST_CENTRAL	0.038	0.028	0.050	<0.0001*			0.039	0.035	0.039	0.037	0.038	0.984
PRE180_ALPHA_BLOCKER_PERIPHERAL	0.072	0.072	0.071	0.753			0.070	0.068	0.073	0.075	0.071	0.409
PRE180_ANTICOAG_OTH	0.009	0.010	0.007	0.021*			0.008	0.009	0.008	0.009	0.009	0.349
PRE180_ANTIPLATELET_OTH	0.010	0.010	0.011	0.359			0.011	0.011	0.010	0.011	0.009	0.275
PRE180_ASPIRIN	0.016	0.016	0.016	0.768			0.017	0.016	0.016	0.016	0.016	0.467
PRE180_BACTRIM	0.050	0.049	0.050	0.7826			0.053	0.048	0.045	0.053	0.049	0.708

PRE180_BETA_BLOCKER	0.454	0.430	0.484	<0.0001*			0.454	0.459	0.455	0.454	0.449	0.486
PRE180_BILE_ACID	0.010	0.009	0.011	0.160			0.011	0.010	0.010	0.009	0.011	0.783
PRE180_CC_BLOCKER	0.300	0.279	0.325	<0.0001*			0.308	0.295	0.303	0.297	0.295	0.257
PRE180_CLOPIDOGREL	0.122	0.111	0.135	<0.0001*			0.110	0.112	0.132	0.126	0.129	0.0002*
PRE180_DIURETIC_OTH	0.369	0.318	0.431	<0.0001*			0.372	0.371	0.376	0.359	0.366	0.221
PRE180_EZETIMIBE	0.031	0.028	0.035	0.0003*			0.032	0.030	0.028	0.029	0.037	0.225
PRE180_FIBRATE	0.031	0.029	0.033	0.027*			0.029	0.033	0.030	0.036	0.027	0.916
PRE180_HEPARIN	0.001	0.001	0.001	0.380			0.001	0.001	0.001	0.001	0.001	0.538
PRE180_K_SPARING	0.035	0.040	0.029	<0.0001*			0.032	0.041	0.036	0.034	0.035	0.873
PRE180_K_SUPP	0.149	0.145	0.153	0.052			0.148	0.151	0.150	0.147	0.148	0.823
PRE180_LIPID_OTH	0.001	0.001	0.001	0.019*			0.000	0.001	0.001	0.001	0.002	0.013*
PRE180_LITHIUM	0.001	0.002	0.001	0.011*			0.001	0.001	0.001	0.002	0.001	0.890
PRE180_NIACIN	0.010	0.010	0.009	0.536			0.011	0.010	0.007	0.010	0.011	0.942
PRE180_NSAID	0.141	0.135	0.147	0.006*			0.134	0.136	0.144	0.146	0.143	0.063
PRE180_PP_INHIBITOR	0.239	0.233	0.247	0.007*			0.238	0.238	0.236	0.249	0.234	0.814
PRE180_RENIN_INHIB	0.006	0.004	0.007	0.001*			0.004	0.006	0.005	0.007	0.005	0.439
PRE180_STATIN	0.404	0.375	0.440	<0.0001*			0.403	0.407	0.410	0.396	0.405	0.702
PRE180_TICLOPIDINE	0.001	0.001	0.001	0.376			0.001	0.000	0.001	0.001	0.000	0.471
PRE180_VASODILATOR	0.054	0.047	0.063	<0.0001*			0.055	0.049	0.057	0.053	0.055	0.679
PRE180_WARFARIN	0.119	0.121	0.116	0.183			0.126	0.123	0.119	0.114	0.113	0.010*
POST30_ALDO_RECEPT_ANTAG	0.016	0.014	0.018	0.023*	Post 30 days drugs: 64.89	<0.0001*	0.016	0.017	0.018	0.014	0.015	0.529
POST30_ALPHA_AGNOIST_CENTRAL	0.039	0.027	0.055	<0.0001*			0.040	0.040	0.036	0.041	0.040	0.918
POST30_ALPHA_BLOCKER_PERIPHERAL	0.055	0.051	0.060	0.002*			0.052	0.053	0.058	0.059	0.053	0.388
POST30_ANTICOAG_OTH	0.027	0.030	0.024	0.005*			0.029	0.025	0.031	0.024	0.027	0.581
POST30_ANTIPLATELET_OTH	0.008	0.007	0.009	0.104			0.007	0.008	0.009	0.008	0.009	0.233
POST30_ASPIRIN	0.088	0.086	0.091	0.185			0.091	0.084	0.088	0.093	0.086	0.963
POST30_BACTRIM	0.022	0.023	0.021	0.408			0.028	0.020	0.021	0.022	0.020	0.049*
POST30_BETA_BLOCKER	0.375	0.326	0.434	<0.0001*			0.369	0.373	0.377	0.375	0.381	0.233
POST30_BILE_ACID	0.006	0.005	0.007	0.262			0.006	0.005	0.006	0.005	0.007	0.360
POST30_CC_BLOCKER	0.271	0.223	0.330	<0.0001*			0.263	0.274	0.266	0.285	0.269	0.214

POST30_CLOPIDOGREL	0.299	0.270	0.334	<0.0001*			0.278	0.282	0.305	0.318	0.309	<0.0001*
POST30_DIURETIC_OTH	0.250	0.169	0.349	<0.0001*			0.247	0.257	0.256	0.248	0.243	0.400
POST30_EZETIMIBE	0.021	0.016	0.026	<0.0001*			0.021	0.019	0.020	0.022	0.022	0.483
POST30_FIBRATE	0.023	0.018	0.029	<0.0001*			0.022	0.023	0.023	0.025	0.021	0.859
POST30_HEPARIN	0.002	0.001	0.002	0.215			0.002	0.001	0.001	0.003	0.002	0.200
POST30_K_SPARING	0.017	0.020	0.013	<0.0001*			0.014	0.020	0.020	0.013	0.016	0.537
POST30_K_SUPP	0.117	0.106	0.131	<0.0001*			0.114	0.122	0.112	0.123	0.116	0.758
POST30_LIPID_OTH	0.001	0.000	0.001	0.001*			0.001	0.000	0.000	0.001	0.001	0.855
POST30_LITHIUM	0.001	0.001	0.000	0.001*			0.001	0.001	0.001	0.001	0.000	0.527
POST30_NIACIN	0.009	0.008	0.009	0.259			0.010	0.010	0.006	0.008	0.009	0.240
POST30_NSAID	0.050	0.045	0.057	<0.0001*			0.050	0.046	0.047	0.056	0.051	0.210
POST30_PP_INHIBITOR	0.205	0.185	0.229	<0.0001*			0.200	0.200	0.203	0.213	0.207	0.131
POST30_RENIN_INHIB	0.004	0.002	0.006	<0.0001*			0.003	0.004	0.003	0.005	0.004	0.390
POST30_STATIN	0.534	0.465	0.616	<0.0001*			0.545	0.530	0.530	0.527	0.537	0.395
POST30_TICLOPIDINE	0.000	0.000	0.001	0.740			0.001	0.000	0.001	0.001	0.000	0.408
POST30_VASODILATOR	0.037	0.028	0.047	<0.0001*			0.035	0.034	0.038	0.038	0.039	0.124
POST30_WARFARIN	0.200	0.200	0.200	0.886			0.207	0.208	0.195	0.192	0.199	0.067
NDC_admission_0	0.406	0.429	0.378	<0.0001*	NDC drugs at admission: 6.27	0.002*	0.405	0.401	0.411	0.411	0.402	0.830
NDC_admission1to3	0.416	0.418	0.413	0.460			0.422	0.427	0.410	0.405	0.414	0.075
NDC_admission4plus	0.178	0.153	0.209	<0.0001*			0.173	0.173	0.179	0.184	0.184	0.044*
OT_acute	0.628	0.618	0.639	0.0004*	Therapy days during acute stay: 4.16	0.006*	0.626	0.630	0.618	0.625	0.638	0.312
PT_acute	0.853	0.843	0.866	<0.0001*			0.853	0.849	0.848	0.859	0.858	0.163
ST_acute	0.572	0.564	0.582	0.003*			0.567	0.565	0.562	0.574	0.593	0.004*
ier	0.845	0.844	0.847	0.562	Admission Type: 0.446	0.640	0.853	0.835	0.850	0.851	0.838	0.328
transfer	0.016	0.015	0.017	0.479			0.018	0.017	0.015	0.017	0.013	0.103
days_imc	0.795	0.780	0.812	0.168	Institu-tional stay LOS divisions: 3.03	0.006*	0.857	0.741	0.755	0.793	0.826	0.869
days_icu	0.381	0.378	0.385	0.695			0.376	0.380	0.358	0.400	0.391	0.973
days_ccu	0.475	0.459	0.494	0.063			0.453	0.432	0.489	0.484	0.516	0.002*
days_reg_IP	2.721	2.708	2.737	0.515			2.636	2.840	2.759	2.714	2.658	0.348

days_SNF_sum	12.048	11.571	12.624	0.002*			12.386	11.920	11.447	12.161	12.321	0.138
days_IRF_sum	3.468	3.114	3.896	<0.0001*			3.565	3.333	3.575	3.409	3.456	0.628

a. Based on Area Treatment Ratio (ATR) of actual ACE/ARB treatment rate over predicted ACE/ARB treatment rate for the 50 AMI patients living closest to each patient's residence ZIP code.

b. P value of T-test of characteristic difference between treated and non-treated patients.

c. Chow F-statistic used to test the exclusion restrictions of the specified set of covariates in the ARC/ARB choice equations. Chow GC. Tests of equality between sets of coefficients in two linear regressions. *Econometrica: Journal of the Econometric Society*. 1960:591-605.

d. P value for Chow F-tests.

e. Cochran-Armitage two-sided test of trend in characteristic value across patients grouped into quintiles based on local area ACE/ARB Area Treatment Ratios (ATRs). For example, the p value for age66to70 tests whether a linear trend in the percentage of patients in this age group exists across quintiles of the ACE/ARB choice ATR-based patient groups.

*p<0. _____ signifies positive relationship with ACE/ARB choice or positive association with local area ACE/ARB Area Treatment rates. _____ signifies negative relationship with ACE/ARB choice or positive association with local area ACE/ARB Area Treatment rates.

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