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Association between Higher Rates of Cardioprotective Drug Use and Survival in Patients on Dialysis

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Abstract

Background—While cardiovascular (CV) disease is a leading cause of morbidity and mortality in patients on chronic dialysis, utilization rates of cardioprotective drugs for dialysis patients remain low. This study sought to determine whether higher rates of cardioprotective drug use among dialysis patients might increase survival.

Methods—A retrospective cohort of incident dialysis patients ($n = 50,468$) with dual eligibility for U.S. Medicare and Medicaid was constructed using USRDS data linked with billing claims. Medication exposures included angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), β -blockers, calcium channel blockers (CCBs), and HMG-CoA reductase inhibitors (statins) prescribed within 90 days of dialysis initiation. The outcomes were one- and two-year survival and CV event-free survival. Variation in treatment rates based on local area practice styles were used as instruments in instrumental variable (IV) estimation, yielding average treatment effect estimates for patients whose treatment choices were affected by local area practice styles.

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Compliance and protection of human research participants

The research protocol was approved by the institutional review board at the University of Kansas Medical Center (KUMC) and the University of Iowa. Data use agreements were in place with the Centers for Medicare & Medicaid Services and the USRDS.

Results—Patients aged 65 years and older comprised 47.4% of the sample, while 59.5% were female and 35.0% were white. The utilization rate was 40.7% for ACEIs/ARBs, 43.0% for β -blockers, 50.7% for CCBs and 26.4% for statins. The local area practice style instruments were highly significantly related to cardioprotective drug use in dialysis patients (Chow-F values > 10). IV estimates showed only that higher rates of β -blockers increased one-year survival ($\beta = 0.161$, P -value = 0.020) and CV event-free survival ($\beta = 0.189$, P -value = 0.033), but that higher rates of CCBs decreased two-year CV event-free survival ($\beta = -0.520$, P -value = 0.009).

Conclusions—This study suggests that higher utilization rates of β -blockers might yield higher survival rates for dialysis patients. However, higher rates of the other drugs studied had no correlations with survival, and higher CCB rates might actually reduce CV-event free survival. Since the benefits of cardiovascular drugs may vary across dialysis patients, the study findings should be interpreted only with respect to changes of utilization rates around the rates observed in this study.

Keywords

dialysis; end stage renal disease; cardioprotective drugs; instrumental variables

Introduction

Cardiovascular (CV) disease is a leading cause of morbidity and mortality among patients with end stage renal disease (ESRD) undergoing chronic dialysis.¹ Evidence from randomized clinical trials (RCTs) in the non-dialysis population suggests that cardioprotective medications [angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), β -adrenergic blockers (β -blockers), calcium channel blockers (CCBs), and HMG-CoA reductase inhibitors (statins)] increase survival²⁻¹⁰ and reduce CV-related events.²⁻¹⁵ However, relatively little RCT evidence exists on the effects of cardioprotective drug use in dialysis patients specifically, who generally have been systematically excluded from large RCTs.¹⁶⁻¹⁹ The few RCTs conducted in dialysis patients to assess the efficacy of cardioprotective drugs on CV outcomes have yielded contradictory results.²⁰⁻³³

Due to the paucity of evidence of cardioprotective drug effectiveness for dialysis patients, the current U.S. National Kidney Foundation Clinical Practice Guidelines generally default to guidelines for blood pressure and cholesterol management established for non-dialysis patients.³⁴ Even so, previous studies have shown relatively low utilization rates of cardioprotective drugs in dialysis patients. For example, in 2005, 49% received an ACEI/ARB, 64% a β -blocker, 49% a CCB, and 42% a statin,^{35, 36} and in 2007, 52% had an ACEI/ARB, 64% a β -blocker, 51% a CCB, and 40% a statin.³⁷ These modest use rates suggest continuing uncertainty in this area. Appropriate prescription of these agents is particularly important given the side effect profiles of these drugs: ACEIs/ARBs may cause hyperkalemia even in dialysis patients, while β -blockers may cause bradycardia or precipitate acute heart failure, and CCBs may cause heart block and peripheral edema.³⁸ The case for statins may be even more uncertain, with newly published guidelines by American College of Cardiology/American Heart Association recommending neither initiation nor continuation of statins for dialysis patients.³⁹ Given contradictory results on the effect of

statins on patient CV benefits,²⁴⁻²⁷ statins use is not without risk, as these agents can cause increased liver transaminases and, particularly in older patients with comorbidities, myopathy.⁴⁰

Given the potential benefit/risk tradeoff associated with using cardioprotective drugs in dialysis patients, it is uncertain whether treatment rates in dialysis patients reflect the correct allocation, or “sorting”, of treatments across patients. This study addressed the question by assessing whether higher rates of cardioprotective drug use might be associated with improved patient health outcomes. To do so, a large retrospective cohort was created for newly initiated dialysis patients with dual eligibility for Medicare and Medicaid. An instrumental variable (IV) estimator with a novel instrument strategy was employed that exploits the variation in cardioprotective drug use across dialysis patients associated with general usage patterns of these drugs across local areas. IV estimators yield treatment estimates that are averages over the subset of patients in the study whose treatment choices were influenced by the instrument used in the study.^{41, 42} This patient subset is often referred to as the “marginal patients” in IV research.^{30,31} Because the instruments here are derived from the variation in local area practice styles, our estimates over marginal patients directly address the study question. If cardioprotective drugs were underused across dialysis patients, one would expect to see positive correlations between treatment rates and outcomes. Alternatively, if cardioprotective drugs were appropriately prescribed in dialysis patients, one would expect that higher utilization rates would be associated with little added benefit. While the local average treatment effect estimates generated from IV analysis properly apply only to the subset of dialysis patients whose cardioprotective drug use is affected by the instrument, such patients are likely to be the ones who would be potentially responsive to changes in policy or treatment paradigms that affect treatment rates at the population level,^{41, 42} and are therefore important to study.

Methods

Data and study sample

A retrospective cohort was created for patients with dual eligibility for Medicare and Medicaid who initiated dialysis during 2000-2005 using data from the U.S. Renal Data System (USRDS) and the Centers for Medicare and Medicaid Services (CMS). Information on patient demographic characteristics, functional status, comorbidities, dialysis modality, and date and cause of death, were obtained from the USRDS Core CD (representing data captured through the CMS 2728 Medical Evidence Form, which is completed upon dialysis initiation). Medicare Part A and B claims were used to identify CV events. Medicaid Analytic eXtract (MAX) personal summary files were used to determine Medicaid enrollment, while Medicaid MAX prescription claims were used to measure cardioprotective drug utilization after dialysis initiation. Individuals were excluded if they were not dialyzing within the date range, did not have dual eligibility for the first 90 days of dialysis, were age < 18, were previously transplanted, had < 90 days of follow-up, or had multi-state Medicaid enrollment. Additional exclusions were lack of a filled prescription during the first 90 days, absence of multiple CMS 2728 data fields, and continuous admission to a hospital or skilled nursing facility based upon analysis of Medicare Part A claims. To ensure a complete one-

year follow-up window, the study sample was restricted to patients who initiated dialysis in 2000-2004 and had at least one year of follow up. To assess whether the effects of cardioprotective drug use at the onset of dialysis appeared to be maintained over a greater duration, repeated analyses were conducted on the sample of patients who initiated dialysis in 2000-2003, allowing a two-year follow-up period. In addition, because the IV estimation strategy is based on driving time between ZIP (postal) codes, the sample was restricted to patients living in the continental United States and with ZIP codes in Microsoft's MapPoint software.

This study used a novel approach of driving area for clinical care (DACC) to measure local area practice styles based on adjusted geographic variation in cardioprotective drug use in the IV method (see below for full details).

Covariates

USRDS data from the CMS 2728 form were used to create baseline covariates. Patient demographic characteristics included age, gender, race/ethnicity, and employment status. Body mass index (BMI) was categorized as $< 20\text{kg/m}^2$, $20\text{--}24.9\text{kg/m}^2$, $25\text{--}29.9\text{kg/m}^2$, and 30kg/m^2 . Patient health behavior measures were smoking and substance abuse, and functional status measures were inability to ambulate and inability to transfer. Comorbid conditions included hypertension (HTN), diabetes (DM), coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), and peripheral vascular disease (PVD). Dialysis type was categorized as in-center hemodialysis vs self-care dialysis (home hemodialysis and peritoneal dialysis). Hemoglobin (Hgb) category was divided into $< 11\text{gm/dL}$ and $\geq 11\text{gm/dL}$. Lastly, state-level indicators were included to capture variation in Medicaid policy across states.

Medication Exposures

The National Drug Codes (NDCs) for cardioprotective drug classes were identified using Multum Lexicon (Cerner Corp, www.cerner.com). Use of each cardioprotective medication was determined for each patient by linking the NDCs in each drug class to Medicaid pharmacy claims during the first 90 days after dialysis initiation following an intention-to-treat study design. A binary variable for each cardioprotective drug class was set to “1” if the patient received a prescription for that class within that timeframe, and “0” otherwise.

Outcomes

Outcomes assessed included one- and two-year survival (all-cause mortality) and CV event-free survival (survival without any CV hospitalization). CV events were defined as an inpatient hospitalization (Medicare Part A claims) for myocardial infarction (410.x0, 410.x1), ischemic heart disease (411.xx), revascularization (procedure codes 36.xx except 36.9), congestive heart failure (428.xx, 402.x1, 404.x1, or 404.x3), cerebrovascular accident (433.xx, 434.xx, 435.x), or peripheral vascular disease (440.2-4, 443.1, 443.81, 443.9, 444.2x, 444.81, 445.0x).⁴³

Geographic Variation Measures

IV estimators utilize treatment variation associated with “instruments” to assess treatment effects. Instruments are factors that are related to treatment decisions but are theorized to be unrelated to outcomes directly or other unmeasured confounders.³⁶ In this study, a novel instrument was derived based on local area cardioprotective medication practice styles across *all* Medicare/Medicaid dually eligible patients. A broader sample of patients was deliberately used to estimate local practice styles to help ensure that the measures are not based on idiosyncratic unmeasured characteristics of local dialysis populations. A valid instrument must have (1) a strong relationship with treatment choice and (2) a sound theoretical basis to support the assumption that the instrument has no direct effect on outcomes and is unrelated to other unmeasured confounders.⁴⁴ Local area treatment variation has been used as instruments in previous research to assess the outcomes associated with higher treatment rates.⁴⁵⁻⁴⁹ The Chow F-test is used to assess this first property, the strength of the relationship between instruments and treatment choices.⁵⁰ However, the second property of a valid instrument is an assumption. Use of local area practice style as an instrument here postulates that (1) dialysis patients living in areas with physicians having stronger preferences for a particular cardioprotective drug class in general were more apt to receive medications in that class, and (2) that unmeasured characteristics of the dialysis patients in each local area were not related to the general physician prescribing preferences in each area – a plausible assumption, since most individuals are not likely to choose to reside in a given area based on future physician prescribing practices.^{41, 51}

All Medicare and Medicaid dually eligible patients were selected across the United States in six years (2000-2005) using Medicaid MAX data personal summary files and pharmacy claims. Dually eligible patients were included if they had at least one month of Medicaid fee-for-service eligibility during this period or at least one Medicaid prescription claim. Using the Medicaid pharmacy claims for these individuals, ZIP code-specific measures of local area practice styles were estimated for each cardioprotective drug class.

Local areas on ZIP code level were defined using the DACC approach which expands the area around the centroid of each ZIP code until a threshold number of beneficiaries are found.⁴⁷ For the dually eligible patients living around each ZIP code, area treatment ratios (ATRs) for each cardioprotective drug class were calculated, defined as the ratio of the number of beneficiaries receiving each class of drugs within a driving-time area ZIP code divided by the sum of the predicted probabilities for each beneficiary in the local area of receiving that class of drugs. Logistic regressions for each drug class based on the entire national data were used to estimate the probabilities for each beneficiary, given patient demographics, pharmacy-claim based comorbidities⁵², annual healthcare utilization, and state residence binary variables. An ATR > 1 indicates a local area practice style that uses more of a cardioprotective drug than expected given patient characteristics in the area, while an ATR < 1 indicates the reverse.⁴⁷ ATR-based instrument values for the four cardioprotective drug classes were linked to dialysis patients by ZIP code.

Statistical Analysis

Instrument Approach—Two-stage least squares (2SLS) estimators were used to yield consistent estimates of the local average treatment effects (LATEs) for the dialysis patients whose choices of cardioprotective drugs were affected by the instrument in this study.^{41, 42} LATE estimates are properly generalized to the subset of patients whose treatment choices were influenced by the instrument used in the study.^{53, 54} Here the instruments were derived from general local area variation in cardiovascular drug utilization rates so the estimates can be interpreted tangibly as what might be expected from higher utilization rates, and so is well-suited to address the research objective. In the first stage of 2SLS, individual linear probability models of treatment choice were estimated for each cardioprotective drug class, adjusting for ATR-based instruments and measured covariates. For each cardioprotective drug class, dialysis patients were divided into five groups based on quintiles of the ATR values associated with their respective ZIP codes. Binary variables were specified in the first stage models indicating these five groups. Unadjusted utilization rates for each cardioprotective drug class were calculated across the ATR-based instrument groups as a simple unadjusted assessment of whether treatment rates varied across levels of instrument groups. Furthermore, a propensity score analysis was conducted to estimate the predicted probabilities of receiving cardioprotective drugs for each class based on measured covariates excluding the ATR-based instruments. If the IV assumption of no relationship between instruments and unmeasured confounders is valid, one would expect the average values of predicted treatment rates to have fairly similar distributions across the ATR-based instrument groups. In the first stage models, Chow F-tests were also performed to examine whether the instruments described a statistically significant portion of variation in cardioprotective drug use.⁵⁰ A common convention for a strong instrument relationship is a Chow F-value > 10.⁵⁵

In the second stage of 2SLS, linear probability models were estimated for one- and two-year survival and CV event-free survival. The independent variables in the second stage were each patient's predicted probabilities of receiving each of the four drug classes from the first stage and the non-instrument covariates from the first-stage models. Thus, the treatment effect estimates in the second stage used only the treatment variation associated with the ATR-based instruments. Treatment effect estimates from 2SLS were reported with robust standard errors. In addition to comparing adjusted treatment rates across the ATR-based instrument groups in the first stage to assess the IV assumption, Basmann over-identification tests were used to examine whether excluding the ATR-based instruments from the second stage of 2SLS was appropriate.⁵⁶ A smaller value of the Basmann statistic indicates less risk of relationships between the instruments and either outcomes or potential unmeasured confounders. To assess whether the IV estimates were sensitive to model specifications, the estimation was repeated using area size thresholds from 100 to 1000 persons around each ZIP code and used decile categories of ATRs instead of quintiles.

All analyses were conducted using SAS version 9.3 and Stata 11.

Results

After applying initial exclusion criteria to the linked USRDS-Medicare-Medicaid data, 84,670 persons had observable data, making them eligible for cohort entry (Figure 1). Additional exclusions required for the IV analysis resulted in a final study sample of 50,468 dialysis patients for assessment of one-year outcomes, of which 37,547 were available for assessment of two-year outcomes.

Table 1 summarizes patient characteristics across each cardioprotective drug class. Those aged 65 years and older comprised 47.4% of the cohort. Overall, 59.5% of the study sample was female and 35.0% was white. Percentages using the various medication classes within 90 days of dialysis initiation were 40.7% for ACEIs/ARBs, 43.0% for β -blockers, 50.7% for CCBs, and 26.4% for statins.

Variation in use of cardioprotective drug classes

Figure 2 shows maps of ATR quintile groups for each cardioprotective drug class; the northeastern U.S. is shown as a representative example. As seen by the color variation, the ATR-based instruments captured substantial small area variation in local area practice styles of cardioprotective drugs both within and across states. Other regions of the U.S. demonstrated similar findings (data not shown).

Local area variation in cardioprotective drug exposure was found across dialysis patients grouped by ATR instrument values (Table 2). From the first to fifth quintile groups for each drug class, cardioprotective drug utilization rates varied from 36.4% to 43.5% for ACEIs/ARBs, 37.5% to 46.1% for β -blockers, 46.6% to 54.4% for CCBs, and 23.6% to 28.5% for statins (all P -value < 0.01). These are average utilization rates across ATR quintile groups; some areas had a 100% utilization rate, while some had 0%. Although statistically significant, the values of average propensity scores (adjusted utilization rates) were evenly distributed across the ATR-based instrument groups for ACEIs, β -blockers, and statins. As shown in Table 2, the average predicted probabilities of receiving CCBs had an increasing trend progressing from the first to the fifth CCB quintile groups, indicating potential unmeasured confounders associated with the CCB ATR groups (49.1% to 52.8%, P -value < 0.01).

IV analysis

The right side of Table 3 contains the results of diagnostic tests used to assess the performance of the analytic approach, namely the results for the Chow test F-statistics from each first stage treatment choice equation and the Basermann over-identification tests using 500-person sized local areas. The Chow-test F values were all >10, suggesting that the ATR-based instruments in the first stage of IV models were highly significantly related to use of each of the four drug classes by dialysis patients.⁵⁵ The Basermann over-identification test for the second stage of the IV models indicates that the ATR-based instruments did not have a direct effect on one-year outcomes and two-year CV event-free survival.⁵⁶ The Basermann test did suggest the possibility of a direct effect in the two-year survival model and that the

interpretation of the two-year survival requires caution due to the possible violation of the IV assumption (i.e., no direct relationship between instruments and outcomes/instruments).

The IV analysis showed that only higher rates of β -blocker use had a positive relationship with one-year survival (P -value = 0.020) and one-year CV event-free survival (P -value = 0.033). Higher medication use rates of other classes were not associated with improved one-year and two-year outcomes. In contrast, a higher rate of CCB use was associated with statistically significant decrease in two-year CV event-free survival (P -value = 0.009).

Sensitivity analyses showed that IV estimates were consistent in terms of magnitude and statistical significance across the variety of instrument specifications employed (e.g., by varying local area size and the number of binary variables used). These results are shown in Appendix 1a-d. Therefore, this study reports only the results for 500 person-sized local areas with patients grouped into ATR-based quintile groups.

Discussion

Given the high rate of CV disease in dialysis patients, understanding how medications with cardioprotective properties affect outcomes in this population is important. This study used a novel IV analytical approach exploiting general local area variation in cardioprotective drug use to investigate whether higher utilization rates of cardioprotective drugs might have improved survival in dually eligible dialysis patients. IV estimators revealed different relationships across cardioprotective drug classes between higher utilization rates and outcomes in dialysis patients.

Interpreting the study findings in light of treatment-effect heterogeneity necessarily depends on the validity of the assumptions underlying IV estimators.⁵⁷ The IV estimators revealed tangible evidence that higher rates of only two of the study drugs would have affected patient outcome rates. The estimates suggest that higher β -blocker utilization rates were associated with increased one-year survival (P -value = 0.020) and CV event-free survival rates (P -value = 0.033), with no significant association with two-year outcomes. It is possible that higher β -blockers rates only yield short-term benefits. However, the non-significant relationships between higher β -blocker utilization rates and two-year outcomes might result from large standard errors in two-year outcome sample, as the Chow F-value was somewhat smaller than for the sample used to assess one-year outcomes. For this reason, the IV estimator might lack precision to obtain statistically significant relationships between β -blocker utilization rates and two-year outcomes. Our IV estimates are absolute effects of cardioprotective drug use for the marginal patients whose treatment choices varied with different levels of ATR-based instruments. Therefore, for one year, it would require treating seven more marginal patients to save one more patient (number needed to treat = 6.21) and six more marginal patients to save one more patients without CV events (number needed to treat = 5.29).

Furthermore, no associations were found between higher rates of ACEI/ARB and statin use and study outcomes. Therefore, clinician decisions about use of ACEIs/ARBs and statins in the spectrum of dialysis patients appear appropriate. However, it should be noted that the

standard errors associated with IV estimates are often an order of magnitude larger than those produced by other estimators, which makes it hard to detect statistically what might be clinically significant estimates for these agents.⁵⁸

The estimates also showed that higher utilization rates of CCBs were negatively associated with CV event-free survival at two years. It may be that CCBs have untoward effects such as heart block and peripheral edema (a marker for water retention, or “volume overload” in clinical parlance) which may be the cause of this negative association.³⁸ In local areas with high CCB utilization rates, patients with these higher risks of CCB-related adverse events may have been aggressively treated, leading the observed “negative” relationship. Therefore, dialysis patients might have been over-treated with CCBs in these areas with particularly high utilization. Alternatively, the distributions of unmeasured factors affecting both CCB use and survival might not be similar across the ATR-based instrument groups. Such a difference was not apparent in the propensity scores for cardioprotective drugs across the instrument groups for ACEIs/ARBs, β -blockers, and statins. However, higher propensity scores for CCBs were observed from the first to the fifth CCB ATR groups, signifying imbalance in unmeasured confounders and indicating the possibility of residual confounding.

Large RCTs have demonstrated the survival²⁻¹⁰ and CV benefits²⁻¹⁵ of cardioprotective drug use on the non-dialysis population. However, RCTs on dialysis patients suggest uncertainty of the efficacy of cardioprotective drugs on survival and CV-related outcomes. For ACEIs/ARBs, the benefit on survival is mixed, with one RCT suggesting benefit,²¹ one demonstrating a trend towards improved outcomes (which included mortality as part of a combined primary outcome) in treated patients (who were sicker, on average, than untreated patients),²² and one showing no benefit.²⁸ Collectively, the results of these studies indicate that clinical equipoise for ACEI/ARB use exists in dialysis patients.²⁹ For CCBs, only one small RCT has been conducted for CCBs in dialysis patients, which appeared to demonstrate a modest benefit of CCBs on survival.⁵⁹ In the case of statins, three major trials have been conducted, only one of which demonstrated CV benefits from statins.³ However, the other two RCTs did not show the benefits,^{24, 26} and recent meta-analyses have suggested little evidence for beneficial effects of statins in dialysis patients.^{30, 32, 33} It is always difficult to compare the results on an RCT to any type of observational study, in part because all of these RCT yields the estimates of average treatment effects for patients in the trial, while an IV approach yields the estimates of local average treatment effects for the marginal patients whose treatment effects are affected by the local practice style instrument in the “real world” and directly address our research question on.

Given the uncertainty of cardioprotective drug use among dialysis patients and their side effect profiles, this study showed that the utilization rates of these medications remained low as reported in previous studies and might reflect clinical equipoise as to the benefits of these drugs.^{35, 36, 60-62} As noted, prior research^{35, 36, 60} using data since 2005 showed higher utilization rates of ACEIs/ARBs, β -blockers, and statins than the current study using 2000-2004 Medicaid data and even lower utilization rates^{61, 62} of ACEIs/ARBs, β -blockers in studies using early data in 2000-2001. It is possible that healthcare providers have increased awareness of the benefits of cardioprotective drugs over their risks, which led to

higher utilization rates of these drugs. On the other hand, only half of dialysis patients were prescribed with CCBs, indicating that healthcare providers might not believe a higher utilization rate of CCBs would benefit dialysis patients. This was consistent with this study demonstrating higher utilization rate of CCBs associated with decreased CV event-free survival in two years.

This study has several important limitations. First, if physicians are individually prescribing to patients based upon expected benefits,⁶³ it is not wise to generalize the estimates beyond the rate variations that served at the basis of the instruments of local area practice of cardioprotective drug use. For example, observers should be careful not to generalize the estimated benefits of β -blocker use in the IV models to treatment rates higher than observed in the fifth quintile (46.1%). Second, this study included prevalent users of cardioprotective drugs which might result in more favorable results for those received drugs.⁶⁴ Third, this study considered each class effect regardless of the number of other treatments a patient is receiving (some patients might have been on multiple cardioprotective drugs). As such, one cannot distinguish between the benefits from using a drug as a single treatment from adding the same drug to an existing drug combination. The effectiveness of each cardioprotective drug class may be higher than the estimates when used as a single treatment. Fourth, this study focused on evaluating the class effects of cardioprotective drugs. Individual drugs within each cardioprotective drug class have different pharmacokinetic and pharmacodynamics properties.^{65, 66} Therefore, the study findings on the effects of cardioprotective drug classes might not be extrapolated to individual drugs. Lastly, like all observational studies, our study findings might suffer from unmeasured confounding issues, even though IV approach is likely to attenuate this problem more than other statistical methods. For example, dialysis patients living in areas with higher utilization rates of cardioprotective drugs may be more likely sicker in unmeasured ways and have lower survival. In this case, our IV estimates of cardioprotective drugs on survival and CV-event free survival might provide a lower bound of the true effects for the marginal patients whose treatment choices were affected by the instrument of local area practice styles. Future studies with more detailed patient health information are needed to assess the bias direction of the IV estimates.

The study also featured counterbalancing strengths. The number patients studied was large and geographically diverse. The local area-based instruments were specifically created using a broader sample of all Medicare and Medicaid dual eligible patients, helping to ensure the validity of the instruments by lessening the likelihood that they are related to idiosyncratic unmeasured characteristics of local dialysis populations. Confidence in this instrument strategy is bolstered because patient characteristics were found to be more evenly distributed across patients grouped by local area practice styles than by treatment groups and the adjusted treatment rates were fairly similar across the ATR quintile groups, suggesting that the unmeasured factors are also likely to be well-balanced across patients grouped by the instruments (except possibly residual confounding issue for CCB use).

Conclusion

This study suggests that higher utilization rates of ACEIs/ARBs and statins by dialysis patients would likely not increase survival or CV event-free survival rates. Higher utilization rates of β -blockers might yield higher survival rates for dialysis patients. In contrast, higher CCB rates might actually reduce CV-event free survival. Since the benefits of cardiovascular drugs may vary across dialysis patients, the results should be interpreted only with respect to changes of utilization rates around the rates observed in this study. Future research is needed to further determine the optimal use of cardioprotective drugs in patients on dialysis.

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Appendix

Appendix 1a

Instrumental variables estimates of cardioprotective drug use on survival (area treatment ratio-quintile groups)

Local area sizes		100	200	300	400	500	600	700	800	900	1000
One-year survival											
ACEI/ARB	Estimate	0.069	0.071	0.088	0.081	0.078	0.060	0.064	0.040	0.084	0.090
	Standard error	-0.068	-0.066	-0.065	-0.066	-0.066	-0.068	-0.068	-0.069	-0.068	-0.066
	P value	0.311	0.280	0.177	0.219	0.233	0.375	0.347	0.564	0.217	0.173
β -blocker	Estimate	0.135	0.122	0.138*	0.157*	0.161*	0.179*	0.141*	0.120	0.133	0.112
	Standard error	-0.069	-0.066	-0.067	-0.069	-0.069	-0.073	-0.071	-0.071	-0.070	-0.070
	P value	0.052	0.063	0.040	0.023	0.020	0.014	0.048	0.089	0.057	0.107
CCB	Estimate	0.024	-0.038	-0.010	0.022	0.021	-0.016	-0.047	-0.100	-0.047	-0.106
	Standard error	-0.111	-0.106	-0.104	-0.105	-0.110	-0.113	-0.106	-0.102	-0.098	-0.099
	P value	0.830	0.723	0.921	0.833	0.850	0.885	0.656	0.328	0.631	0.285
Statins	Estimate	-0.020	-0.032	-0.010	0.003	-0.003	-0.049	-0.053	-0.049	-0.037	-0.044
	Standard error	-0.087	-0.092	-0.096	-0.097	-0.096	-0.098	-0.098	-0.097	-0.094	-0.098
	P value	0.819	0.730	0.914	0.977	0.977	0.618	0.592	0.612	0.694	0.654
Two-year survival											
ACEI/ARB	Estimate	0.050	0.032	0.020	0.007	0.047	0.035	0.049	0.063	0.098	0.096
	Standard error	-0.090	-0.086	-0.084	-0.087	-0.089	-0.092	-0.092	-0.095	-0.089	-0.085
	P value	0.577	0.713	0.813	0.936	0.595	0.706	0.593	0.505	0.273	0.261
β -blocker	Estimate	0.222	0.211	0.167	0.161	0.112	0.117	0.080	0.062	0.118	0.118
	Standard error	-0.121	-0.108	-0.110	-0.112	-0.115	-0.121	-0.117	-0.115	-0.115	-0.111
	P value	0.067	0.052	0.131	0.153	0.333	0.333	0.496	0.589	0.304	0.287
CCB	Estimate	0.127	0.049	0.006	-0.021	-0.091	-0.151	-0.203	-0.187	-0.098	-0.130
	Standard error	-0.174	-0.162	-0.160	-0.157	-0.172	-0.177	-0.174	-0.162	-0.153	-0.148
	P value	0.466	0.761	0.972	0.891	0.596	0.393	0.244	0.249	0.523	0.378
Statins	Estimate	0.007	-0.020	0.085	0.101	0.143	0.108	0.084	0.068	0.106	0.053
	Standard error	-0.109	-0.114	-0.116	-0.117	-0.117	-0.119	-0.123	-0.122	-0.121	-0.123
	P value	0.951	0.860	0.461	0.386	0.221	0.364	0.494	0.576	0.385	0.663

Appendix 1b

Instrumental variables estimates of cardioprotective drug use on survival (area treatment ratio-decile groups)

Local area sizes		100	200	300	400	500	600	700	800	900	1000
One-year survival											
ACEI/ARB	Estimate	0.022	0.031	0.054	0.069	0.079	0.051	0.080	0.052	0.052	0.075
	Standard error	-0.063	-0.062	-0.058	-0.057	-0.059	-0.059	-0.058	-0.059	-0.058	-0.057
	P value	0.720	0.614	0.352	0.231	0.177	0.394	0.171	0.379	0.366	0.184
β-blocker	Estimate	0.075	0.059	0.087	0.123*	0.108	0.140*	0.126*	0.165**	0.144*	0.130*
	Standard error	-0.061	-0.060	-0.060	-0.061	-0.062	-0.062	-0.058	-0.058	-0.062	-0.060
	P value	0.219	0.324	0.145	0.043	0.081	0.025	0.031	0.005	0.020	0.029
CCB	Estimate	-0.056	-0.124	-0.077	-0.021	-0.055	-0.046	-0.023	0.002	-0.009	-0.020
	Standard error	-0.093	-0.092	-0.086	-0.090	-0.091	-0.093	-0.084	-0.081	-0.083	-0.077
	P value	0.551	0.180	0.369	0.817	0.550	0.621	0.783	0.984	0.910	0.795
Statins	Estimate	-0.038	-0.007	0.035	0.035	0.027	0.002	-0.008	-0.010	-0.013	-0.010
	Standard error	-0.079	-0.082	-0.087	-0.087	-0.089	-0.089	-0.090	-0.088	-0.086	-0.087
	P value	0.628	0.930	0.688	0.690	0.759	0.979	0.932	0.912	0.877	0.911
Two-year survival											
ACEI/ARB	Estimate	0.027	0.023	0.041	0.054	0.078	0.095	0.108	0.121	0.132	0.104
	Standard error	-0.082	-0.081	-0.077	-0.077	-0.078	-0.077	-0.079	-0.081	-0.078	-0.073
	P value	0.747	0.773	0.591	0.484	0.316	0.220	0.171	0.133	0.088	0.155
β-blocker	Estimate	0.162	0.068	0.056	0.132	0.129	0.195*	0.188*	0.232**	0.265**	0.189*
	Standard error	-0.099	-0.091	-0.092	-0.091	-0.095	-0.094	-0.086	-0.089	-0.096	-0.089
	P value	0.102	0.454	0.541	0.148	0.175	0.038	0.028	0.009	0.006	0.034
CCB	Estimate	0.043	-0.125	-0.138	-0.046	-0.090	0.018	-0.031	0.064	0.062	-0.016
	Standard error	-0.137	-0.132	-0.122	-0.121	-0.128	-0.129	-0.120	-0.120	-0.124	-0.110
	P value	0.754	0.343	0.260	0.704	0.484	0.886	0.797	0.597	0.615	0.883
Statins	Estimate	0.023	0.099	0.167	0.146	0.149	0.146	0.097	0.091	0.094	0.054
	Standard error	-0.098	-0.097	-0.105	-0.104	-0.107	-0.108	-0.108	-0.109	-0.112	-0.110
	P value	0.813	0.307	0.111	0.161	0.165	0.178	0.366	0.406	0.402	0.625

Appendix 1c

Instrumental variables estimates of cardioprotective drug use on cardiovascular event-free survival (area treatment ratio-quintile groups)

Local area sizes		100	200	300	400	500	600	700	800	900	1000
One-year cardiovascular event-free survival											
ACEI/ARB	Estimate	0.070	0.062	0.092	0.109	0.119	0.108	0.119	0.108	0.153	0.168*
	Standard error	-0.086	-0.084	-0.083	-0.084	-0.084	-0.086	-0.086	-0.087	-0.086	-0.083
	P value	0.417	0.458	0.265	0.193	0.155	0.210	0.170	0.213	0.077	0.042
β -blocker	Estimate	0.134	0.125	0.151	0.185*	0.189*	0.182*	0.152	0.143	0.169	0.158
	Standard error	-0.088	-0.085	-0.086	-0.089	-0.089	-0.092	-0.090	-0.089	-0.089	-0.089
	P value	0.125	0.140	0.077	0.037	0.033	0.047	0.092	0.108	0.056	0.075
CCB	Estimate	-0.136	-0.219	-0.169	-0.139	-0.137	-0.130	-0.162	-0.176	-0.109	-0.177
	Standard error	-0.140	-0.137	-0.133	-0.135	-0.141	-0.142	-0.135	-0.129	-0.125	-0.126
	P value	0.331	0.111	0.205	0.303	0.332	0.358	0.230	0.175	0.384	0.160
Statins	Estimate	-0.109	-0.147	-0.184	-0.206	-0.167	-0.127	-0.108	-0.059	-0.062	-0.091
	Standard error	-0.109	-0.117	-0.123	-0.124	-0.123	-0.123	-0.124	-0.122	-0.119	-0.124
	P value	0.315	0.210	0.135	0.097	0.175	0.301	0.386	0.631	0.606	0.464
Two-year cardiovascular event-free survival											
ACEI/ARB	Estimate	-0.020	-0.077	-0.040	0.004	0.018	0.011	0.027	0.043	0.122	0.147
	Standard error	-0.091	-0.092	-0.091	-0.094	-0.103	-0.102	-0.106	-0.103	-0.095	-0.091
	P value	0.825	0.399	0.659	0.969	0.864	0.911	0.800	0.676	0.200	0.108
β -blocker	Estimate	0.138	0.043	0.039	0.064	-0.026	0.000	-0.045	0.003	0.075	0.101
	Standard error	-0.123	-0.116	-0.119	-0.122	-0.133	-0.135	-0.135	-0.125	-0.123	-0.118
	P value	0.261	0.708	0.745	0.599	0.842	0.999	0.739	0.982	0.543	0.396
CCB	Estimate	-0.086	-0.311	-0.327	-0.334*	-0.520**	-0.468*	-0.554**	-0.422*	-0.332*	-0.327*
	Standard error	-0.176	-0.174	-0.171	-0.169	-0.199	-0.198	-0.201	-0.177	-0.164	-0.159
	P value	0.625	0.074	0.056	0.048	0.009	0.018	0.006	0.017	0.044	0.040
Statins	Estimate	-0.192	-0.201	-0.151	-0.207	-0.186	-0.148	-0.162	-0.161	-0.167	-0.195
	Standard error	-0.111	-0.122	-0.124	-0.126	-0.135	-0.132	-0.140	-0.132	-0.131	-0.132
	P value	0.082	0.098	0.222	0.101	0.168	0.264	0.248	0.223	0.200	0.139

Appendix 1d

Instrumental variables estimates of cardioprotective drug use on cardiovascular event-free survival (area treatment ratio-decile groups)

Local area sizes		100	200	300	400	500	600	700	800	900	1000
One-year cardiovascular event-free survival											
ACEI/ARB	Estimate	0.052	0.068	0.122	0.129	0.142	0.114	0.117	0.089	0.091	0.146 [*]
	Standard error	−0.079	−0.079	−0.073	−0.073	−0.075	−0.076	−0.075	−0.076	−0.074	−0.072
	P value	0.513	0.391	0.096	0.078	0.057	0.132	0.119	0.239	0.216	0.045
β-blocker	Estimate	0.063	0.081	0.118	0.164 [*]	0.158 [*]	0.207 ^{**}	0.171 [*]	0.160 [*]	0.137	0.168 [*]
	Standard error	−0.077	−0.077	−0.076	−0.078	−0.079	−0.079	−0.074	−0.074	−0.079	−0.076
	P value	0.414	0.291	0.121	0.036	0.047	0.009	0.021	0.031	0.082	0.027
CCB	Estimate	−0.181	−0.269 [*]	−0.175	−0.129	−0.141	−0.106	−0.145	−0.199	−0.216 [*]	−0.150
	Standard error	−0.118	−0.119	−0.109	−0.115	−0.117	−0.119	−0.108	−0.104	−0.106	−0.099
	P value	0.125	0.023	0.108	0.262	0.227	0.373	0.178	0.055	0.043	0.132
Statins	Estimate	−0.103	−0.098	−0.094	−0.160	−0.149	−0.156	−0.147	−0.083	−0.074	−0.112
	Standard error	−0.099	−0.104	−0.110	−0.112	−0.113	−0.114	−0.115	−0.112	−0.110	−0.112
	P value	0.299	0.343	0.395	0.153	0.190	0.169	0.201	0.460	0.500	0.317
Two-year cardiovascular event-free survival											
ACEI/ARB	Estimate	−0.040	−0.065	−0.013	0.050	0.056	0.069	0.121	0.100	0.151	0.165 [*]
	Standard error	−0.085	−0.086	−0.082	−0.080	−0.084	−0.080	−0.083	−0.082	−0.080	−0.077
	P value	0.639	0.449	0.875	0.533	0.503	0.391	0.146	0.225	0.058	0.031
β-blocker	Estimate	0.101	0.016	0.002	0.123	0.042	0.122	0.132	0.149	0.165	0.207 [*]
	Standard error	−0.103	−0.097	−0.099	−0.095	−0.102	−0.097	−0.090	−0.090	−0.098	−0.093
	P value	0.326	0.871	0.982	0.194	0.684	0.209	0.143	0.098	0.093	0.025
CCB	Estimate	−0.125	−0.320 [*]	−0.371 ^{**}	−0.216	−0.376 ^{**}	−0.250	−0.282 [*]	−0.201	−0.225	−0.169
	Standard error	−0.142	−0.141	−0.131	−0.126	−0.138	−0.133	−0.127	−0.122	−0.127	−0.115
	P value	0.378	0.023	0.005	0.087	0.007	0.061	0.026	0.100	0.076	0.139
Statins	Estimate	−0.199 [*]	−0.130	−0.086	−0.179	−0.151	−0.138	−0.142	−0.131	−0.160	−0.162
	Standard error	−0.101	−0.102	−0.111	−0.108	−0.115	−0.112	−0.113	−0.111	−0.115	−0.116
	P value	0.049	0.202	0.437	0.096	0.188	0.214	0.207	0.237	0.164	0.162

Notes:

All models adjusted for patient demographic characteristics, comorbidities, functional status, and state differences.

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; β -blockers: β -adrenergic blockers; CCB: calcium channel blocker; Statins: HMG-CoA reductase inhibitors.

* significant at 95% CI

** significant at 99% CI.

REFERENCES

1. Collins AJ, Foley RN, Chavers B, et al. US renal data system 2013 annual data report. *Am J Kidney Dis.* 2014; 63:A7. doi: 10.1053/j.ajkd.2013.11.001 [doi]. [PubMed: 24360288]
2. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: A systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol.* 2006; 47:1576–1583. doi: 10.1016/j.jacc.2005.11.073. [PubMed: 16630993]
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005; 366:1267–1278. doi: 10.1016/S0140-6736(05)67394-1. [PubMed: 16214597]
4. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension.* 2003; 42:1206–1252. doi: 10.1161/01.HYP.0000107251.49515.c2. [PubMed: 14656957]
5. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med.* 1998; 339:489–497. doi: 10.1056/NEJM199808203390801. [PubMed: 9709041]
6. Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: An overview of long-term randomized controlled trials. *Arch Intern Med.* 2006; 166:787–796. doi: 10.1001/archinte.166.7.787. [PubMed: 16606817]
7. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J.* 2003; 146:848–853. doi: 10.1016/S0002-8703(03)00403-4. [PubMed: 14597934]
8. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: Angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med.* 2004; 141:693–704. [PubMed: 15520426]
9. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: Blood pressure goals, choice of agents, and setting priorities in diabetes care. *Ann Intern Med.* 2003; 138:593–602. [PubMed: 12667032]
10. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med.* 2003; 348:583–592. doi: 10.1056/NEJMoa021716. [PubMed: 12584366]
11. Black HR, Elliott WJ, Grandits G, et al. Principal results of the controlled onset verapamil investigation of cardiovascular end points (CONVINCE) trial. *JAMA.* 2003; 289:2073–2082. doi: 10.1001/jama.289.16.2073. [PubMed: 12709465]
12. Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: Meta-analysis of randomised controlled trials. *BMJ.* 2006; 332:1115–1124. doi: 10.1136/bmj.38793.468449.AE. [PubMed: 16585050]
13. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: A systematic review. *Stroke.* 2003; 34:2741–2748. doi: 10.1161/01.STR.0000092488.40085.15. [PubMed: 14576382]
14. Smith SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: Endorsed by the nation heart, lung, and blood institute. 2006
15. Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension.* 2005; 46:386–392. doi: 10.1161/01.HYP.0000174591.42889.a2. [PubMed: 16009786]
16. Cohn JN, Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001; 345:1667–1675. doi: 10.1056/NEJMoa010713. [PubMed: 11759645]
17. Fox KM, EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients

- with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003; 362:782–788. [PubMed: 13678872]
18. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001; 344:1651–1658. doi: 10.1056/NEJM200105313442201. [PubMed: 11386263]
 19. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. the heart outcomes prevention evaluation study investigators. *N Engl J Med*. 2000; 342:145–153. doi: 10.1056/NEJM200001203420301. [PubMed: 10639539]
 20. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: A randomized controlled trial. *Nephrol Dial Transplant*. 2014 doi: 10.1093/ndt/gft515.
 21. Cice G, Di Benedetto A, D'Isa S, et al. Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2010; 56:1701–1708. doi: 10.1016/j.jacc.2010.03.105; 10.1016/j.jacc.2010.03.105. [PubMed: 21070920]
 22. Zannad F, Kessler M, Leheret P, et al. Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of foscipril and implications for future studies. *Kidney Int*. 2006; 70:1318–1324. doi: 10.1038/sj.ki.5001657. [PubMed: 16871247]
 23. Wetmore JB, Shireman TI. The ABCs of cardioprotection in dialysis patients: A systematic review. *Am J Kidney Dis*. 2009; 53:457–466. doi: 10.1053/j.ajkd.2008.07.037; 10.1053/j.ajkd.2008.07.037. [PubMed: 19022545]
 24. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005; 353:238–248. doi: 10.1056/NEJMoa043545. [PubMed: 16034009]
 25. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): A randomised placebo-controlled trial. *Lancet*. 2011; 377:2181–2192. doi: 10.1016/S0140-6736(11)60739-3; 10.1016/S0140-6736(11)60739-3. [PubMed: 21663949]
 26. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009; 360:1395–1407. doi: 10.1056/NEJMoa0810177; 10.1056/NEJMoa0810177. [PubMed: 19332456]
 27. Holdaas H, Holme I, Schmieder RE, et al. Rosuvastatin in diabetic hemodialysis patients. *J Am Soc Nephrol*. 2011; 22:1335–1341. doi: 10.1681/ASN.2010090987; 10.1681/ASN.2010090987. [PubMed: 21566054]
 28. Iseki K, Arima H, Kohagura K, et al. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: A randomized controlled trial. *Nephrol Dial Transplant*. 2013; 28:1579–1589. doi: 10.1093/ndt/gfs590; 10.1093/ndt/gfs590. [PubMed: 23355629]
 29. Chang TI, Shilane D, Brunelli SM, Cheung AK, Chertow GM, Winkelmayer WC. Angiotensin-converting enzyme inhibitors and cardiovascular outcomes in patients on maintenance hemodialysis. *Am Heart J*. 2011; 162:324–330. doi: 10.1016/j.ahj.2011.05.004; 10.1016/j.ahj.2011.05.004. [PubMed: 21835294]
 30. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: A systematic review and meta-analysis. *Ann Intern Med*. 2012; 157:263–275. doi: 10.7326/0003-4819-157-4-201208210-00007; 10.7326/0003-4819-157-4-201208210-00007. [PubMed: 22910937]
 31. Tepel M, Giet MV, Park A, Zidek W. Association of calcium channel blockers and mortality in haemodialysis patients. *Clin Sci (Lond)*. 2002; 103:511–515. doi: 10.1042/. [PubMed: 12401125]
 32. Baryliski M, Nikfar S, Mikhailidis DP, et al. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy--a meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res*. 2013; 72:35–44. doi: 10.1016/j.phrs.2013.03.007; 10.1016/j.phrs.2013.03.007. [PubMed: 23542730]

33. Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: A systematic review and meta-analysis. *Eur Heart J*. 2013; 34:1807–1817. doi: 10.1093/eurheartj/ehd065; 10.1093/eurheartj/ehd065. [PubMed: 23470492]
34. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. 2005; 45:S1–153.
35. Wetmore JB, Mahnken JD, Mukhopadhyay P, et al. Geographic variation in HMG-CoA reductase inhibitor use in dialysis patients. *J Gen Intern Med*. 2012; 27:1475–1483. doi: 10.1007/s11606-012-2112-7; 10.1007/s11606-012-2112-7. [PubMed: 22696256]
36. Wetmore JB, Mahnken JD, Mukhopadhyay P, et al. Geographic variation in cardioprotective antihypertensive medication usage in dialysis patients. *Am J Kidney Dis*. 2011; 58:73–83. doi: 10.1053/j.ajkd.2011.02.387; 10.1053/j.ajkd.2011.02.387. [PubMed: 21621889]
37. Frankenfield DL, Weinhandl ED, Powers CA, Howell BL, Herzog CA, St Peter WL. Utilization and costs of cardiovascular disease medications in dialysis patients in medicare part D. *Am J Kidney Dis*. 2012; 59:670–681. doi: 10.1053/j.ajkd.2011.10.047. [PubMed: 22206743]
38. Saseen, JJ.; MacLaughlin, EJ. Chapter 19. hypertension.. In: DiPiro, JT.; Talbert, RL.; Yee, GC.; Matzke, GR.; Wells, BG.; Posey, LM., editors. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed.. McGraw-Hill; New York: 2011.
39. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the american college of Cardiology/American heart association task force on practice guidelines. *Circulation*. 2013 doi: 10.1161/01.cir.0000437738.63853.7a.
40. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation*. 2002; 106:3143–3421. [PubMed: 12485966]
41. Angrist JD. Estimation of limited dependent variable models with dummy endogenous regressors. *Journal of business economic statistics*. 2001; 19:2. doi: 10.1198/07350010152472571.
42. Imbens GW, Angrist JD. Identification and estimation of local average treatment effects. *Econometrica: Journal of the Econometric Society*. 1994:467–475.
43. Kestenbaum B, Gillen DL, Sherrard DJ, Seliger S, Ball A, Stehman-Breen C. Calcium channel blocker use and mortality among patients with end-stage renal disease. *Kidney Int*. 2002; 61:2157–2164. doi: 10.1046/j.1523-1755.2002.00355.x. [PubMed: 12028456]
44. Stock, JH.; Watson, MW. *Introduction to Econometrics: Global Edition*. Pearson Education; 2012.
45. Brooks JM. Was breast conserving surgery underutilized for early stage breast cancer? instrumental variables evidence for stage II patients from iowa. *Health Serv Res*. 2003; 38:1385. [PubMed: 14727779]
46. Brooks JM, Chrischilles EA, Landrum MB, et al. Survival implications associated with variation in mastectomy rates for early-staged breast cancer. *Int J Surg Oncol*. 2012; 2012:127854. doi: 10.1155/2012/127854. [PubMed: 22928097]
47. Fang G, Brooks JM, Chrischilles EA. A new method to isolate local-area practice styles in prescription use as the basis for instrumental variables in comparative effectiveness research. *Med Care*. 2010; 48:710. [PubMed: 20613655]
48. McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? analysis using instrumental variables. *JAMA*. 1994; 272:859–866. [PubMed: 8078163]
49. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: Effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007; 297:278–285. doi: 10.1001/jama.297.3.278. [PubMed: 17227979]
50. Chow GC. Tests of equality between sets of coefficients in two linear regressions. *Econometrica: Journal of the Econometric Society*. 1960:591–605.

51. Newhouse JP, McClellan M. Econometrics in outcomes research: The use of instrumental variables. *Annu Rev Public Health*. 1998; 19:17–34. doi: 10.1146/annurev.publhealth.19.1.17. [PubMed: 9611610]
52. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol*. 1992; 45:197–203. doi: 0895-4356(92)90016-G [pii]. [PubMed: 1573438]
53. Harris KM, Remler DK. Who is the marginal patient? understanding instrumental variables estimates of treatment effects. *Health Serv Res*. 1998; 33:1337. [PubMed: 9865223]
54. McClellan MB, Newhouse JP. Overview of the special supplement issue. *Health Serv Res*. 2000; 35:1061–1069. [PubMed: 11130810]
55. Staiger D, Stock JH. Instrumental variables regression with weak instruments. *Econometrica*. 1997;557–586.
56. Basmann RL. On finite sample distributions of generalized classical linear identifiability test statistics. *Journal of the American Statistical Association*. 1960; 55:650–659.
57. Fang G, Brooks JM, Chrischilles EA. Apples and oranges? interpretations of risk adjustment and instrumental variable estimates of intended treatment effects using observational data. *Am J Epidemiol*. 2012; 175:60–65. doi: 10.1093/aje/kwr283; 10.1093/aje/kwr283. [PubMed: 22085626]
58. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data*. 2002
59. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant*. 2008; 23:3605–3612. doi: 10.1093/ndt/gfn304; 10.1093/ndt/gfn304. [PubMed: 18511605]
60. Frankenfield DL, Weinhandl ED, Powers CA, Howell BL, Herzog CA, St Peter WL. Utilization and costs of cardiovascular disease medications in dialysis patients in medicare part D. *Am J Kidney Dis*. 2012; 59:670–681. doi: 10.1053/j.ajkd.2011.10.047 [doi]. [PubMed: 22206743]
61. Manley HJ, Garvin CG, Drayer DK, et al. Medication prescribing patterns in ambulatory haemodialysis patients: Comparisons of USRDS to a large not-for-profit dialysis provider. *Nephrol Dial Transplant*. 2004; 19:1842–1848. doi: 10.1093/ndt/gfh280. [PubMed: 15128886]
62. Rahman M, Griffin V. Patterns of antihypertensive medication use in hemodialysis patients. *Am J Health Syst Pharm*. 2004; 61:1473–1478. [PubMed: 15332695]
63. Heckman JJ, Urzua S, Vytlačil EJ. Understanding instrumental variables in models with essential heterogeneity. *Rev Econ Stat*. 2006; 88:389. doi: 10.1162/rest.88.3.389.
64. Ray WA. Evaluating medication effects outside of clinical trials: New-user designs. *Am J Epidemiol*. 2003; 158:915–20. [PubMed: 14585769]
65. Hanif K, Bid HK, Konwar R. Reinventing the ACE inhibitors: Some old and new implications of ACE inhibition. *Hypertens Res*. 2010; 33:11–21. doi: 10.1038/hr.2009.184 [doi]. [PubMed: 19911001]
66. Lopez-Sendon J, Swedberg K, McMurray J, et al. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. the task force on ACE-inhibitors of the european society of cardiology. *Eur Heart J*. 2004; 25:1454–1470. doi: 10.1016/j.ehj.2004.06.003 [doi]. [PubMed: 15302105]

Cardiovascular disease is a leading cause of death and morbidity in dialysis patients. However, utilization rates of cardioprotective drugs for dialysis patients remain low. We assess whether higher utilization rates of cardioprotective drugs would improve survival in a large retrospective cohort of chronic dialysis patients. We employed instrumental variables analytical approach with a linked database of incident, dually-eligible (Medicare-Medicaid) beneficiaries on dialysis. Our study showed that β -blockers might be underused for dialysis patients, because higher utilization rates could provide additional benefit. CCBs might be overused, as higher CCB utilization rates were associated with lower cardiovascular event-free survival for dialysis patients.

Figure 1.
Exclusion criteria for the analytical sample

Figure 2.

Northeastern United States area treatment ratios (ATRs)-based on local areas defined by 500 Medicare/Medicaid dual eligible around each ZIP code for cardioprotective drugs

Note: For the purpose of mapping, the area treatment ratios (ATRs) shown in the maps did not adjust for state indicators; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; β -blockers: β -adrenergic blockers; CCB: calcium channel blocker; Statins: HMG-CoA reductase inhibitors.

Table 1

Patient characteristics across cardioprotective drug use for dialysis patients

Variables	ACEIs/ARBs within 90 days of dialysis initiation		β-blocker within 90 days of dialysis initiation		CCBs within 90 days of dialysis initiation		Statins within 90 days of dialysis initiation		Total
	No	Yes	No	Yes	No	Yes	No	Yes	
Number of patients (%)	29904 (59.3%)	20564 (40.7%)	28760 (57%)	21708 (43%)	24889 (49.3%)	25579 (50.7%)	37141 (73.6%)	13327 (26.4%)	50468 (100%)
Age									
< 50	21.5	22.2 *	22.1	21.4	21.6	22.0	24.1	15.3 **	10994(21.8%)
50-65	29.5	32.6 **	30.0	31.8 **	30.2	31.3 *	29.1	35.3 **	15528(30.8%)
65-75	26.1	26.7	26.0	26.8 *	26.1	26.5	24.6	31.0 **	13288(26.3%)
75	22.9	18.5 **	22.0	20.0 **	22.0	20.2 **	22.1	18.4 **	10658(21.1%)
Sex (female)	58.6	60.8 **	59.6	59.2	57.1	61.7 **	57.7	64.4 **	30005(59.5%)
Race									
Black	39.2	42.0 **	38.8	42.3 **	35.4	45.1 **	42.1	35.3 **	20353(40.3%)
Hispanic	17.9	20.0 **	20.0	17.2 **	18.3	19.2 **	18.5	19.6 **	9483(18.8%)
Others	5.6	6.2 **	6.0	5.7	5.5	6.2 **	5.4	7.1 **	2956(5.9%)
White	37.3	31.8 **	35.1	34.9	40.7	29.5 **	33.9	38.1 **	17676(35%)
Full/part-time employed	1.8	1.7	1.8	1.8	1.8	1.8	1.9	1.3 **	887(1.8%)
BMI category									
<20 kg/m2	11.1	9.3 **	10.9	9.7 **	10.8	9.9 **	11.7	6.7 **	5229(10.4%)
20-24.9 kg/m2	29.2	29.5	29.1	29.6	28.7	29.9 **	30.7	25.5 **	14789(29.3%)
25-29.9 kg/m2	25.8	26.9 **	25.8	26.8 *	25.6	26.9 **	25.7	27.7 **	13245(26.2%)
30 kg/m2	32.7	33.1	32.8	32.8	33.6	32.1 **	30.7	38.9 **	16572(32.8%)
Missing	1.2	1.3	1.3	1.1 *	1.3	1.2	1.3	1.2	633(1.3%)
Smoke	6.1	6.5 *	6.2	6.3	6.1	6.4	6.5	5.4 **	3151(6.2%)

Variables	ACEIs/ARBs within 90 days of dialysis initiation		β-blocker within 90 days of dialysis initiation		CCBs within 90 days of dialysis initiation		Statins within 90 days of dialysis initiation		Total
	No	Yes	No	Yes	No	Yes	No	Yes	
Substance abuse	3.0	2.5**	2.8	2.7	3.0	2.6*	3.4	1.1**	1403(2.8%)
Inability to ambulate	6.5	4.6**	6.1	5.2**	6.5	4.9**	6.1	4.7**	2884(5.7%)
Inability to transfer	2.4	1.3**	2.2	1.7**	2.4	1.5**	2.2	1.3**	999(2%)
Comorbidities									
Hypertension	83.0	87.2**	82.6	87.5**	80.9	88.4**	84.1	86.5**	42747(84.7%)
Diabetes	59.8	70.8**	63.2	65.8**	62.9	65.7**	59.4	78.1**	32460(64.3%)
Coronary artery disease	24.9	26.4**	21.7	30.4**	28.2	22.8**	22.5	33.8**	12855(25.5%)
Congestive heart failure	33.1	36.5**	32.5	37.2**	37.4	31.7**	33.3	37.8**	17414(34.5%)
Cerebrovascular accident	11.4	10.8*	10.5	12.0**	11.0	11.2	10.7	12.5**	5625(11.1%)
Peripheral vascular disease	14.7	15.2	14.2	15.8**	16.2	13.6**	13.8	17.9**	7512(14.9%)
Dialysis type (self care)	4.8	4.9	5.1	4.6*	4.9	4.8	4.6	5.8**	2465(4.9%)
Hemoglobin									
<11	68.9	68.2	68.9	68.3	68.2	69.1*	69.5	66.2**	34637(68.6%)
11	22.7	23.3	22.5	23.5*	23.5	22.4**	22.0	25.6**	11582(22.9%)
Missing	8.4	8.5	8.6	8.2	8.3	8.6	8.5	8.2	4249(8.4%)
Outcomes									
One-year survival	78.9	83.1**	79.9	81.6**	77.0	84.1**	79.3	84.4*	40688(80.6%)
One-year CV event-free survival	57.1	57.5	58.5	55.7**	54.4	60.1**	57.5	56.7	28898(57.3%)

Notes: Chi-square test was used to examine differences in characteristic value across patients grouped by cardioprotective drug classes. For example, the p value for hypertension tests whether the difference in hypertension rates exists across treatment group.

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; β-blocker: β-adrenergic blocker; CCB: calcium channel blocker; Statins: HMG-CoA reductase inhibitors; BMI: body mass index.

* significant at 95% CI

** significant at 99% CI.

Patient characteristics across local area practice styles of cardioprotective drug use in dialysis patients

Table 2

Variables	ATR of ACEIs/ARBs [#]		ATR of β -blockers [#]		ATR of CCBs [#]		ATR of statins [#]	
	Quintile 1 ^a (%)	Quintile 5 ^a (%)	Quintile 1 ^a (%)	Quintile 5 ^a (%)	Quintile 1 ^a (%)	Quintile 5 ^a (%)	Quintile 1 ^a (%)	Quintile 5 ^a (%)
Unadjusted rates (corresponding treatment)	36.4	43.5**	37.5	46.1**	46.6	54.4**	23.6	28.5**
Propensity score adjusted rates ^b (corresponding treatment)	39.6	41.0**	42.2	42.9**	49.1	52.8**	26.2	26.0**
Age								
< 50	24.0	20.4**	20.5	21.7*	21.9	20.5*	23.1	19.3**
50-65	31.5	30.5	31.5	29.9**	31.4	29.5**	32.2	28.3**
65-75	24.7	28.0**	27.2	25.7	25.9	27.5**	25.2	27.2**
75	19.8	21.1	20.7	22.7**	20.8	22.4**	19.5	25.3**
Sex (female)	59.9	58.3**	59.9	59.2	59.9	59.3	60.3	59.3
Race								
Black	40.3	33.4**	40.5	37.5**	30.4	45.2**	36.1	37.9**
Hispanic	11.0	31.1**	22.3	16.6**	16.3	23.5**	16.2	21.9**
Others	5.5	6.1	5.2	6.9**	4.8	8.0**	3.9	9.7**
White	43.2	29.5**	31.9	39.0**	48.5	23.4**	43.8	30.4**
Full/part-time employed	2.0	1.6	1.5	2.0*	2.0	1.7	2.0	1.7
BMI category								
<20 kg/m2	10.7	9.5**	10.1	10.6	10.0	10.6*	10.2	10.7
20-24.9 kg/m2	28.4	29.2	29.6	29.2	28.0	30.1**	27.8	30.4**
25-29.9 kg/m2	25.6	27.5**	26.2	26.1	26.3	26.4	26.0	26.5
30 kg/m2	34.1	32.4*	32.8	32.6	34.4	31.4**	34.8	31.2**

Variables	ATR of ACEIs/ARBs [#]		ATR of β -blockers [#]		ATR of CCBs [#]		ATR of statins [#]	
	Quintile 1 ^a (%)	Quintile 5 ^d (%)	Quintile 1 ^a (%)	Quintile 5 ^d (%)	Quintile 1 ^a (%)	Quintile 5 ^d (%)	Quintile 1 ^a (%)	Quintile 5 ^d (%)
Missing	1.2	1.4	1.4	1.4	1.3	1.6 ^{**}	1.2	1.2
Smoke	7.4	5.2 ^{**}	6.3	6.4	7.3	4.8 ^{**}	7.7	5.3 ^{**}
Substance abuse	3.4	2.3 ^{**}	2.9	2.8	2.5	2.5	2.9	2.4
Inability to ambulate	5.8	5.5	5.7	6.1	5.8	5.5 [*]	6.2	5.7
Inability to transfer	2.2	1.8 [*]	2.2	2.2	2.1	1.8	2.0	2.0
Comorbidities								
Hypertension	84.0	84.5	85.0	85.0	83.2	85.9 ^{**}	84.1	85.1
Diabetes	63.4	66.7 ^{**}	65.8	64.2 [*]	65.2	64.4 [*]	65.0	64.3
Coronary artery disease	27.6	26.0 ^{**}	24.6	28.8 ^{**}	28.9	24.1 ^{**}	26.9	26.2 [*]
Congestive heart failure	34.9	35.3	34.2	36.7 ^{**}	36.4	33.0 ^{**}	36.1	35.1 [*]
Cerebrovascular accident	11.6	10.7 [*]	10.6	11.9 ^{**}	11.4	10.4 ^{**}	11.0	10.8
Peripheral vascular disease	15.7	16.0	14.0	17.3 ^{**}	17.2	14.1 ^{**}	17.3	15.1 ^{**}
Dialysis type (self care)	4.8	5.1	4.8	4.9	5.4	4.6 ^{**}	5.1	5.0
Hemoglobin								
<11	67.2	69.8 ^{**}	69.1	68.8	67.3	69.6 ^{**}	68.5	68.1
11	22.8	23.2	23.1	22.6 [*]	24.1	22.6 ^{**}	22.8	23.8
Missing	10.0	7.0 ^{**}	7.9	8.6 ^{**}	8.6	7.8	8.8	8.1 [*]
Outcomes								
One-year survival	80.2	81.7 ^{**}	79.6	80.5	79.7	81.6 ^{**}	80.0	80.3
One-year CV event free survival	56.5	57.8 [*]	56.6	57.2	56.3	57.7 [*]	56.4	56.4

Notes:

Cochran-Armitage test was used to examine trend in characteristic value across patients grouped into quintiles based on local area practice style measures of each cardioprotective drug. For example, the p value for hypertension tests whether a linear trend in hypertension rates exists across the instrument-based patient groups.

Abbreviations: ATR, area treatment ratio ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; β -blocker; β -adrenergic blocker; CCB: calcium channel blocker; Statins: HMG-CoA reductase inhibitors; BMI: body mass index.

Area treatment ratio (ATR) of that drug was adjusted for patient-level characteristics. Patients were grouped using ATR quintiles of each drug.

^a Area treatment ratios (ATR) measuring local area practice styles were divided into 5 groups. The ATR-based instruments used in the IV models were a series of binary variables indicating each patient residence ZIP code ATR within the quintiles of the distribution of ATRs across dialysis patients. Quintile1 represents the lowest ATR group, while Quintile5 represents the highest ATR group.

^b Propensity scores (Adjusted rates) were calculated as the average predicted probabilities of receiving cardioprotective drugs for each class across the ATR quintile groups, based on measured covariates (excluding instruments). For example, in the first β -blocker quintile group, the adjusted treatment rate for β -blocker use was 42.2%, while in the fifth β -blocker quintile group, the adjusted rate was 42.9%.

* significant at 95% CI

** significant at 99% CI.

Table 3

Instrumental variables estimates of cardioprotective drug use on survival and cardiovascular event-free survival for dialysis patients

	Instrumental variables models				
	Estimate	Standard Error	P value	Chow-F test ^a	Basman over-identification test ^b
One-year survival				F value	P value
ACEI/ARB	0.078	0.066	0.233	33.63	0.671
β-blocker	0.161 [*]	0.069	0.020	42.04	
CCB	0.021	0.110	0.850	15.73	
Statins	-0.003	0.096	0.977	24.3	
Two-year survival					
ACEI/ARB	0.047	0.089	0.595	28.8	0.036
β-blocker	0.112	0.115	0.333	29.58	
CCB	-0.091	0.172	0.596	11.63	
Statins	0.143	0.117	0.221	22.59	
One-year CV event-free survival					
ACEI/ARB	0.119	0.084	0.155	33.63	0.649
β-blocker	0.189 [*]	0.089	0.033	42.04	
CCB	-0.137	0.141	0.332	15.73	
Statins	-0.167	0.123	0.175	24.3	
Two-year CV event-free survival					
ACEI/ARB	0.018	0.103	0.864	28.8	0.614
β-blocker	-0.026	0.133	0.842	29.58	
CCB	-0.520 ^{**}	0.199	0.009	11.63	
Statins	-0.186	0.135	0.168	22.59	

Notes:

All models adjusted for patient demographic characteristics, comorbidities, functional status, and state differences.

Abbreviations: ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; β-blockers: β-adrenergic blockers; CCB: calcium channel blocker; Statins: HMG-CoA reductase inhibitors; CV: cardiovascular.

^{*} significant at 95% CI

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significant at 99% CI.

^a Chow F-tests examined whether the instruments described a statistically significant portion of variation in CV drug use.

^b Basmann over-identification tests were used to examine whether excluding the ATR-based instruments from the second stage of 2SLS was appropriate (null hypothesis).