Antihypertensive Medication Use in Older Patients Transitioning from Chronic Kidney Disease to End-Stage Renal Disease on Dialysis

Tara I. Chang, Yuanchao Zheng,* Maria E. Montez-Rath,* and Wolfgang C. Winkelmayer†*

Abstract

Background and objectives The transition from CKD to ESRD can be particularly unstable, with high rates of death and hospitalizations. Few studies have examined medication use during this critical period. We examined patterns of antihypertensive medication use from the four quarters before and eight quarters after incident ESRD treated with maintenance dialysis.

Design, setting, participants, & measurements We used the US Renal Data System to identify patients aged ≥67 years initiating dialysis for ESRD between January 2008 and December 2010 with Medicare Part D and a low-income subsidy. We ascertained the incidence of AKI and hyperkalemia during each quarter on the basis of having at least 1 payment claim for the condition. We used Poisson regression with robust SEMs to formally test for changes in the trend and level of antihypertensive medication use in a series of intervention analyses.

Results The number of antihypertensive drugs used increased as patients neared ESRD, peaking at an average of 3.4 in the quarter immediately preceding dialysis initiation, then declining to 2.2 medications by 2 years later. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use was stable at approximately 40%, even among patients with coronary disease and systolic heart failure, and did not correlate with AKI or hyperkalemia. Dialysis initiation was associated with a 40% (95% confidence interval, 38% to 43%) lower adjusted level of diuretic use, which continued to decline after ESRD. Three- and four-drug combinations that included a diuretic were most common before ESRD, whereas after ESRD, one- and two-drug β-blocker or calcium-channel blocker–based combinations were most common.

Conclusions The use of antihypertensive medications, particularly angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and diuretics, may be suboptimal during the transition from CKD to ESRD, especially in patients with coronary disease or systolic heart failure. Future studies are needed to identify strategies to increase the appropriate use of antihypertensive medications during this critical transition period.

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Introduction

The transition from predialysis CKD to ESRD requiring initiation of maintenance dialysis can be a particularly unstable time, with high rates of death and hospitalizations (1,2). Although improving, the adjusted mortality rate in the first year of hemodialysis remains high, at 193 deaths per 1000 patient-years by month 12 (3). Cardiovascular events are common and account for the largest proportion of deaths (3). Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are the recommended first-line agents for hypertension in CKD and ESRD given their cardioprotective effects (4–8). Moreover, for patients with CKD and systolic heart failure or coronary heart disease (3), guidelines mirror those for the general population, recommending ACEIs or ARBs and β-blockers to reduce cardiovascular morbidity and mortality (6,9,10).

Despite these recommendations, patients with CKD are less likely than patients with preserved renal function to receive these medications (11,12), perhaps because of concerns about adverse side effects, such as hyperkalemia or bradycardia. However, most previous studies on medication use in CKD were cross-sectional and focused only on predialysis CKD or ESRD populations (13–16) and so could not examine changes in medication use during the critical transition from predialysis CKD to incident ESRD treated with dialysis. We therefore sought to examine patterns of antihypertensive medication use from the year before and up to 2 years after incident ESRD treated with maintenance dialysis. We further examined whether patterns of use differed by black race, diabetes mellitus, coronary heart disease, and systolic heart failure status.

Materials and Methods

Cohort Assembly

The institutional review board of Stanford University approved the study. We used data on all fee-for-service claims from Medicare Parts A and B reported to the US Renal Data System (USRDS) (17). Because Medicare eligibility begins at age 65 years, we selected patients age ≥67 years with incident ESRD initiating dialysis between January 1, 2008, and December 31, 2010, to allow for at least 2 years of Medicare eligibility to ascertain comorbid conditions and medication use. The index date was defined as the first date of ESRD treatment. We divided the time before and after incident ESRD into 90-day quarters, numbering the four quarters before ESRD as −Q4 to −Q1 and the eight quarters after ESRD as Q1–Q8. We excluded patients who received a kidney transplant within Q1, including on the index date (Figure 1).

To ascertain comorbid conditions based on payment claims, we required continuous Medicare Part A and B as primary payer for at least six quarters before the index date. We also required at least one valid claim during this time to ensure use of Medicare benefits. To exclude patients with relatively normal kidney function and then severe AKI or rapid progression leading to long-term dialysis, we required all patients to have at least one CKD diagnosis code in the 90–360 days before the index date (18).

We required continuous Medicare Part D coverage with a low-income subsidy for ≥360 days before and ≥90 after the index date, with at least one medication filled during this time. For patients to remain eligible for inclusion after Q1, we required ≥1 day of coverage with a low-income subsidy, which provides full or partial waivers for copayments even during the medication coverage gap, when pharmacy fill data may otherwise be unavailable. Patients were eligible to re-enter the cohort if a low-income subsidy was regained at any time. Patients who received a kidney transplant or died were no longer eligible for inclusion in any subsequent quarters.

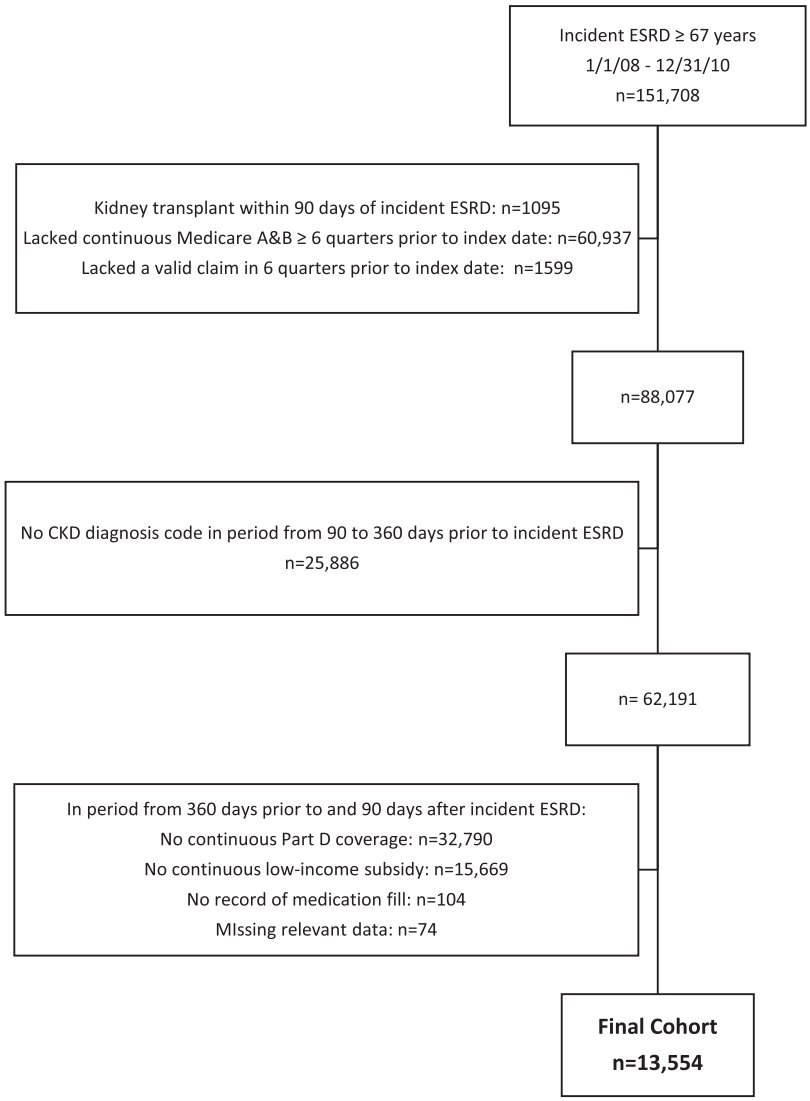

Figure 1. | Cohort assembly of patients age ≥67 years at dialysis initiation in the US Renal Data System from January 1, 2008, through December 31, 2010.

Medication Use

We defined medication use according to pharmacy fill information for four main classes of antihypertensive agents (ACEI/ARBs, β-blockers, calcium-channel blockers, and diuretics) and for four secondary antihypertensive agents (central α-2 agonists, α-blockers, nitrates, and vasodilators). We ascertained statin use to have a nonantihypertensive medication class for comparison. We ascertained the proportion of eligible patients within each quarter who filled a prescription for the antihypertensive medication of interest.

We stratified our analyses by black race, diabetes mellitus, coronary heart disease, and systolic heart failure, given certain indications for use of specific antihypertensive medication classes in these subgroups. We also examined the top five antihypertensive medications used alone or in combination among patients taking any antihypertensive medications in each quarter.

Covariates

We obtained patient age, sex, race, Hispanic ethnicity, initial dialysis modality, and cause of ESRD from the USRDS patient file on the index date. We defined the prevalence of comorbid conditions listed in Table 1 using International Classification of Diseases, Ninth Revision, codes and procedure codes from at least one inpatient or two or more outpatient encounters separated by at least 1 day (19,20). We ascertained baseline comorbid conditions for up to eight quarters before the index date and updated comorbid conditions in each quarter after the index date. We identified the number of non-nephrology outpatient visits and hospitalized days and any nursing home stay in the two quarters before the index date. We identified the incidence of AKI, acute hyperkalemia, or acute myocardial infarction during each quarter based on one inpatient or one outpatient claim.

Statistical Analyses

To formally test for changes in the trends and levels of use of the four main antihypertensive medications, we conducted a series of intervention analyses (21,22). Although the true model would be a log binomial, because of convergence problems when adjusting for covariates we instead used a log Poisson regression with robust standard errors (23):

$$log(E\{Y\}) = \beta_0 + \beta_1 quarter + \beta_2 * dialysis\_initiation + \beta_3 * time\_since\_dialysis\_initiation + other\_covariates$$

Y is a binary variable indicating medication use during that quarter; *quarter* is a continuous variable corresponding to quarters −Q4 to Q8, ranging from 1 to 12; *dialysis_initiation* is 0 in quarters −Q4 to −Q1 and 1 in quarters Q1–Q8; *time_since_dialysis_initiation* is 0 in quarters −Q4 to −Q1 and ranged from 1 to 8 after ESRD; β_1 is the linear trend in antihypertensive medication use prior to dialysis initiation (*i.e.*, incident ESRD), β_2 is the change in level of antihypertensive medication use at the time of dialysis initiation, and β_3 is the linear trend in antihypertensive medication use after dialysis initiation. The exponentiated coefficients

Table 1. Baseline characteristics of patients age ≥67 years with ESRD at dialysis initiation

Characteristic	Value
Age	
Mean±SD, yr	75.8±6.4
67–69 yr	2608 (19.2)
70–74 yr	3945 (29.1)
75–79 yr	3193 (23.6)
≥80 yr	3808 (28.1)
Sex	
Male	4700 (34.7)
Female	8854 (65.3)
Race/ethnicity	
White	7707 (56.9)
Black	4434 (32.7)
Asian	1157 (8.5)
Other	256 (1.9)
Hispanic	2514 (18.5)
Incident year	
2008	4549 (33.6)
2009	4439 (32.8)
2010	4566 (33.7)
Initial modality	
Hemodialysis	13,157 (97.1)
Peritoneal dialysis	397 (2.9)
Reported cause of ESRD	
Diabetes	7273 (53.7)
Hypertension	4641 (34.2)
GN	369 (2.7)
Other	1271 (9.4)
Cardiovascular comorbid conditions	
Coronary heart disease	8134 (60.0)
Heart failure	
Systolic	3096 (22.8)
Nonsystolic	6377 (47.0)
Unstable angina	2496 (18.4)
Valvular disease	4100 (30.2)
Hypertension	13,497 (99.6)
Atrial fibrillation	3321 (24.5)
Other arrhythmias	2772 (20.5)
Cerebrovascular disease	2722 (20.1)
Stroke/transient ischemic attack	2679 (19.8)
Peripheral vascular disease	4858 (35.8)
Other medical comorbidities	
Hyperlipidemia	9417 (69.5)
Diabetes mellitus	10,615 (78.3)
Liver disease	977 (7.2)
Rheumatologic disease	760 (5.6)
Lung disease	5874 (43.3)
Gastrointestinal bleeding	2829 (20.9)
Cancer	1861 (13.7)
Dementia	1759 (13.0)
Depression	2371 (17.5)
Alcohol use	188 (1.4)
Tobacco use	755 (5.6)
Hyperkalemia	4478 (33.0)
Health care use in the 2 quarters before dialysis initiation	
Had nursing home stay	2646 (19.5)
Median no. non-nephrology visits (p25–p75)	22 (13–32)
Median no. hospital days (p25–p75)	7 (1–17)

Unless otherwise noted, values are number (percentage) of patients. p25, 25th percentile; p75, 75th percentile.

can be interpreted as the relative rate of medication use per quarter if before ESRD [exp(β_1)], the change in relative rate of medication use after versus before dialysis initiation [exp (β_2)], and change in the relative rate of medication use per quarter after ESRD from the rate at dialysis initiation [exp (β_3)]. Models were adjusted for all variables listed in Table 1 and for AKI, acute hyperkalemia, and acute myocardial infarction. To account for multiple comparisons, we used a Bonferroni correction and considered $P<0.001$ as indicating statistical significance.

Given the very low level of missing data (<1% for any variable), we conducted complete case analyses. All analyses were conducted using SAS 9.4 (Cary, NC) and STATA 13.1.

Results

We identified 13,554 patients age ≥67 years at the time of incident ESRD meeting the inclusion and exclusion criteria (Figure 1). The cohort was diverse in terms of sex, race, and Hispanic ethnicity, with an average age of 76 years and a high prevalence of comorbid conditions (Table 1). The proportion of patients on peritoneal dialysis (2.9%) remained low over time (range, 2.9%–4.1% during Q1–Q8).

The number of antihypertensive medications used increased before incident ESRD, from an average of 2.4 in –Q4 to 3.4 in −Q1 (Figure 2). With initiation of dialysis, the mean number of antihypertensive classes dropped to 2.2 by Q8. Use of individual antihypertensive medication classes (except ACEIs/ARBs) followed a similar pattern of use (Figure 3, Supplemental Figure 1). By comparison, statin use increased before incident ESRD and remained relatively stable after ESRD (Supplemental Figure 1).

ACEIs/ARBs

The use of ACEIs or ARBs remained relatively stable throughout the transition from CKD to ESRD (Figure 3A [red line]). From the intervention analysis, we found no significant differences in ACEI/ARB use before ESRD and at the time of dialysis initiation, whereas after ESRD, there was a 4% (95% confidence interval [95% CI], 2% to 6%) decrease in the relative rate of ACEI/ARB use per quarter (Table 2). The use of ACEIs/ARBs was not associated with the incidence of AKI or acute hyperkalemia or with the prevalence of systolic heart failure and coronary heart disease (Figure 3B). We saw a sustained increase in ACEI use and corresponding drop in ARB use after incident ESRD, and few patients took ACEIs and ARBs concomitantly (Supplemental Figure 2).

More patients with diabetes mellitus used ACEIs or ARBs compared with patients without diabetes mellitus,

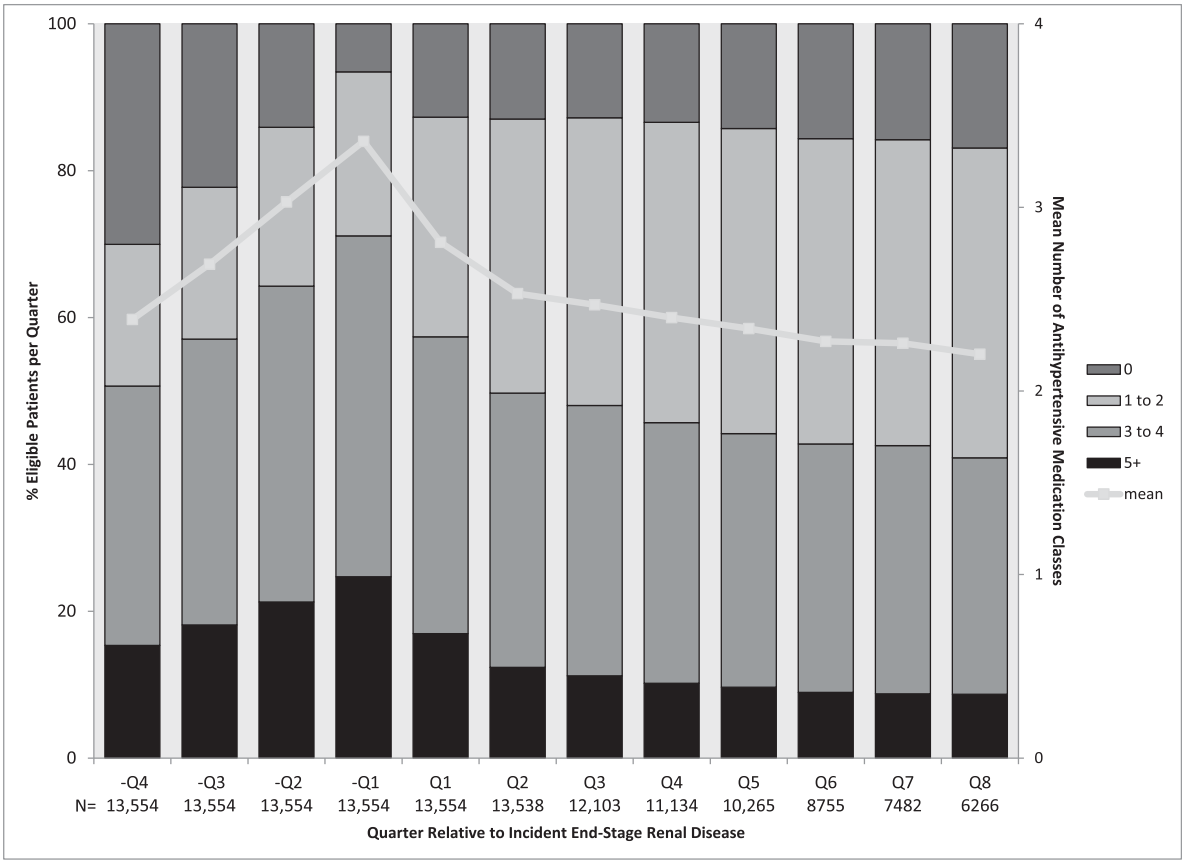

Figure 2. | Proportion of the study cohort of patients age ≥67 years at dialysis initiation using no, one to two, three to four, or five or more antihypertensive medications classes in the quarters before and after incident ESRD. Line indicates the mean number of antihypertensive medication classes taken per quarter. N indicates number of patients included within each quarter.

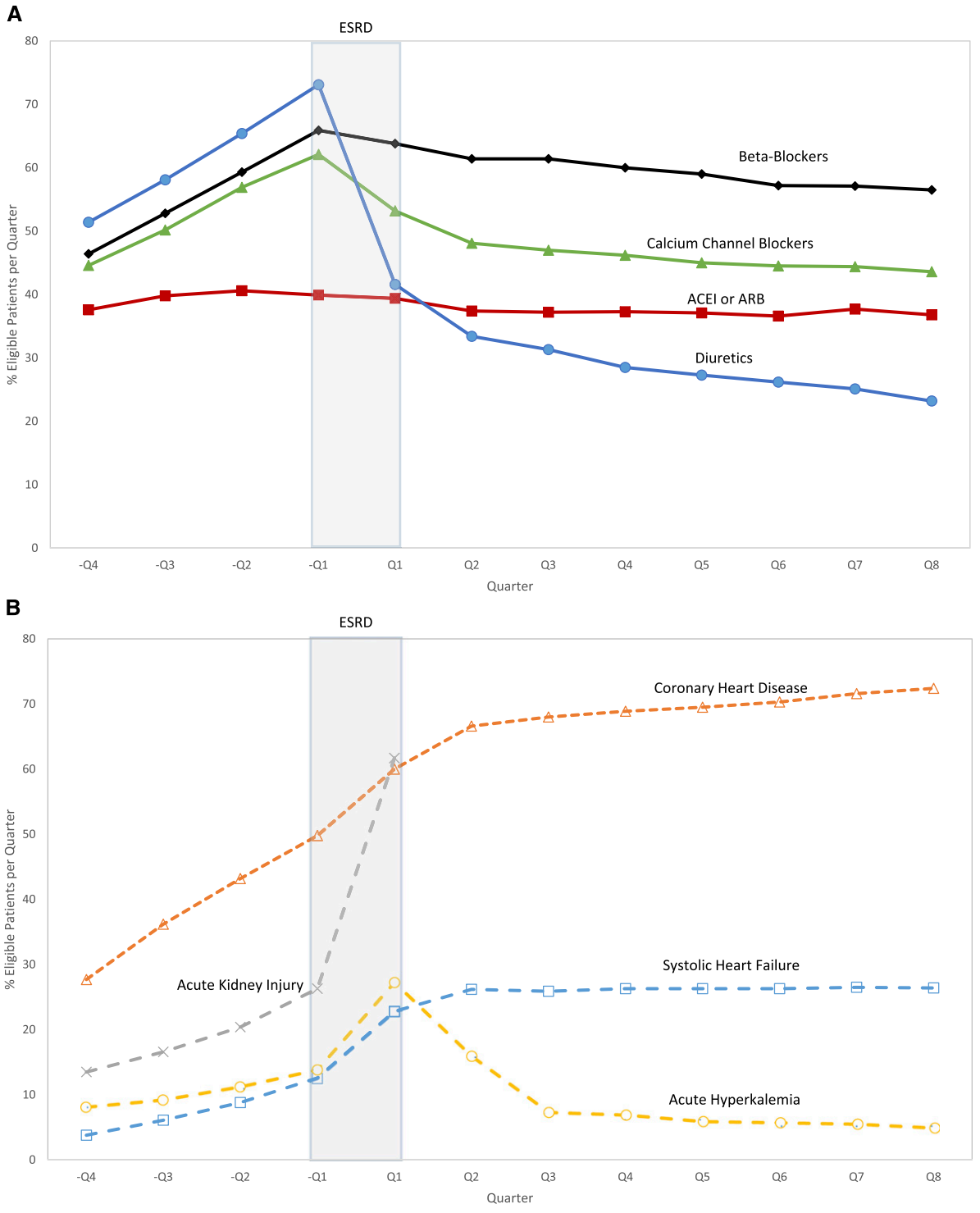

Figure 3. | Proportion of eligible patients age ≥67 years at dialysis initiation per prescription type and comorbidity. (A) Patients with a prescription filled for angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), β-blockers, calcium-channel blockers, or diuretics. (B) Patients with prevalent systolic heart failure or coronary heart disease, incident AKI or acute hyperkalemia in the four quarters before and eight quarters after incident ESRD.

but even among this subgroup the overall prevalence was only about 40%, and patterns of use were similar across subgroups (Figure 4A, Table 2). ACEI or ARB use was nearly identical among patients with and without coronary heart disease or systolic heart failure.

β-Blockers

β-Blocker use increased significantly before incident ESRD, from 46% in –Q4% to 66% in –Q1 (Figure 3A [black line]), mirroring an increase in the prevalence of systolic heart failure and coronary heart disease (Figure 3B). In the

Table 2. Results of intervention analysis for specified antihypertensive medications overall and within specified subgroups.

Variable	ACEI or ARB			β-Blockers		
	Pre-ESRD	Dialysis Initiation	Post-ESRD	Pre-ESRD	Dialysis Initiation	Post-ESRD
Entire cohort	1.01 (1.00 to 1.03)	1.04 (1.00 to 1.09)	0.96 (0.94 to 0.98)	1.08 (1.07 to 1.10)	0.98 (0.95 to 1.00)	0.89 (0.88 to 0.90)
Subgroups						
Black	1.01 (0.98 to 1.04)	1.12 (1.03 to 1.21)	0.97 (0.94 to 1.00)	1.09 (1.07 to 1.11)	1.00 (0.96 to 1.05)	0.89 (0.87 to 0.91)
Nonblack	1.01 (0.99 to 1.03)	1.01 (0.95 to 1.07)	0.95 (0.93 to 0.97)	1.08 (1.06 to 1.10)	0.97 (0.94 to 1.00)	0.89 (0.88 to 0.90)
Diabetes mellitus	1.02 (1.00 to 1.03)	1.05 (1.00 to 1.10)	0.96 (0.94 to 0.98)	1.08 (1.07 to 1.10)	0.98 (0.95 to 1.01)	0.89 (0.88 to 0.90)
No diabetes mellitus	1.01 (0.97 to 1.04)	1.00 (0.90 to 1.12)	0.97 (0.93 to 1.01)	1.08 (1.06 to 1.11)	0.96 (0.91 to 1.02)	0.89 (0.86 to 0.91)
Coronary heart disease	1.01 (0.99 to 1.04)	1.02 (0.96 to 1.08)	0.96 (0.94 to 0.99)	1.07 (1.05 to 1.09)	0.97 (0.94 to 1.00)	0.90 (0.89 to 0.92)
No coronary heart disease	1.01 (0.99 to 1.03)	1.08 (1.01 to 1.16)	0.95 (0.93 to 0.98)	1.09 (1.07 to 1.11)	1.00 (0.95 to 1.04)	0.88 (0.86 to 0.90)
Systolic heart failure	1.03 (0.97 to 1.11)	1.03 (0.92 to 1.16)	0.94 (0.88 to 1.01)	1.08 (1.03 to 1.12)	0.98 (0.92 to 1.04)	0.90 (0.86 to 0.93)
No systolic heart failure	1.01 (1.00 to 1.03)	1.05 (0.99 to 1.10)	0.96 (0.94 to 0.98)	1.08 (1.07 to 1.10)	0.98 (0.95 to 1.00)	0.89 (0.88 to 0.90)

The pre-ESRD and post-ESRD values indicate relative rate of medication use per quarter relative to the prior quarter (95% confidence intervals using a Bonferroni-corrected cutoff P value of <0.001). Values for dialysis initiation indicate the relative change in level of medication use associated with dialysis initiation (95% confidence interval). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

intervention analysis, before ESRD there was an 8% (95% CI, 7% to 10%) higher rate of β-blocker use per quarter (Table 2). β-Blocker use did not significantly change at the initiation of dialysis. After ESRD, each subsequent quarter was associated with an 11% (95% CI, 10% to 12%) decrease in the relative rate of use compared with the previous quarter (Table 2), dropping to 57% by Q8 (Figure 3A [black line]). More patients with coronary heart disease or systolic heart failure used β-blockers at each time point compared with patients without these conditions, but patterns of use were similar (Figure 4B, Table 2).

Calcium-Channel Blockers

Calcium-channel blocker use increased significantly before incident ESRD, from 45% in –Q4% to 62% in –Q1, significantly dropped at the initiation of dialysis, and continued to decline gradually after incident ESRD to 44% by Q8 (Figure 3A [green line], Table 2). More black patients and patients without coronary heart disease or systolic heart failure used calcium-channel blockers at each time point, but patterns of use were similar (Figure 4C, Table 2).

Diuretics

Diuretic use increased significantly before incident ESRD, peaking at 73% in −Q1 before dropping sharply at the initiation of dialysis, and continued to decline after incident ESRD (Figure 3A [blue line]). In the intervention analysis, each quarter before ESRD was associated with a 10% (95% CI, 9% to 12%) higher relative rate of use, but dialysis initiation was associated with a 40% (95% CI, 38% to 43%) lower rate of use, and rates of use continued to decline after ESRD by 18% (95% CI, 17% to 19%) per quarter. Loop diuretics constituted the vast majority of all diuretics used (Supplemental Figure 3). Before incident ESRD, more patients with diabetes mellitus, coronary heart disease, or systolic heart failure used diuretics than patients without these comorbid conditions, but the differences narrowed after incident ESRD (Figure 4D, Table 2).

Medication Combinations

We examined the top five antihypertensive medication classes used alone or in combination in each of the 12 quarters of interest, resulting in 11 unique combinations of ACEIs/ARBs, β-blockers, calcium-channel blockers, and diuretics. None of the secondary antihypertensive medication classes was used in these combinations. Three- and four-drug combinations that included a diuretic were most common before incident ESRD. After incident ESRD, one- and two-drug β-blocker and calcium-channel blocker–based combinations without a diuretic were most common (Figure 5).

Discussion

Our study provides insights into patterns of antihypertensive medication use in older patients during the critical transition from predialysis CKD to treated ESRD. We identified the following major findings. First, use of antihypertensive drugs increased considerably as patients neared ESRD, peaked immediately preceding initiation of dialysis, and declined swiftly over the first 2 quarters on dialysis. In contrast, the use of statins remained relatively stable, suggesting that the postdialysis decrease may have been related to improved volume and hence BP control, rather than to patient nonadherence or therapeutic nihilism. Second, ACEI/ARB use was consistent at approximately 40% before and after the initiation of maintenance dialysis, even among patients with coronary heart disease and systolic heart failure, and did not correlate with changes in the incidence of AKI or hyperkalemia. Third, a higher proportion of patients with coronary heart disease or systolic heart failure used β-blockers than patients without these conditions. Fourth, diuretic use increased in the quarters leading up to incident ESRD, which dropped precipitously at initiation of dialysis and continued to decline thereafter. Fifth, three- and four-drug antihypertensive medication combinations that included a diuretic were most common before ESRD,

Table 2. (Continued)

Variable	Calcium-Channel Blockers			Diuretics		
	Pre-ESRD	Dialysis Initiation	Post-ESRD	Pre-ESRD	Dialysis Initiation	Post-ESRD
Entire cohort	1.11 (1.09 to 1.12)	0.91 (0.88 to 0.94)	0.86 (0.85 to 0.88)	1.10 (1.09 to 1.12)	0.60 (0.57 to 0.62)	0.82 (0.81 to 0.83)
Subgroups						
Black	1.09 (1.07 to 1.12)	0.94 (0.89 to 0.98)	0.88 (0.86 to 0.90)	1.10 (1.08 to 1.12)	0.58 (0.54 to 0.63)	0.81 (0.79 to 0.83)
Nonblack	1.11 (1.10 to 1.13)	0.90 (0.86 to 0.93)	0.86 (0.84 to 0.87)	1.10 (1.09 to 1.12)	0.60 (0.57 to 0.63)	0.83 (0.81 to 0.84)
Diabetes mellitus	1.11 (1.09 to 1.13)	0.91 (0.88 to 0.95)	0.86 (0.85 to 0.88)	1.10 (1.09 to 1.11)	0.60 (0.57 to 0.63)	0.83 (0.81 to 0.84)
No diabetes mellitus	1.09 (1.07 to 1.12)	0.91 (0.85 to 0.97)	0.87 (0.84 to 0.90)	1.12 (1.09 to 1.15)	0.60 (0.54 to 0.66)	0.80 (0.77 to 0.83)
Coronary heart disease	1.09 (1.07 to 1.11)	0.89 (0.85 to 0.93)	0.88 (0.86 to 0.90)	1.10 (1.08 to 1.11)	0.58 (0.55 to 0.61)	0.83 (0.82 to 0.85)
No coronary heart disease	1.11 (1.09 to 1.13)	0.94 (0.89 to 0.98)	0.86 (0.84 to 0.88)	1.11 (1.09 to 1.13)	0.63 (0.59 to 0.68)	0.81 (0.79 to 0.83)
Systolic heart failure	1.10 (1.03 to 1.17)	0.89 (0.81 to 0.98)	0.88 (0.82 to 0.94)	1.10 (1.06 to 1.14)	0.56 (0.52 to 0.62)	0.84 (0.80 to 0.87)
No systolic heart failure	1.11 (1.09 to 1.12)	0.92 (0.89 to 0.96)	0.86 (0.85 to 0.88)	1.10 (1.09 to 1.12)	0.61 (0.58 to 0.64)	0.82 (0.80 to 0.83)

whereas one- and two-drug β-blocker or calcium-channel blocker–based combinations were most common after ESRD.

Our results extend the findings from the few previous studies to examine medication use around the time of incident ESRD. The USRDS Annual Data Report showed that in 2011, the use of renin-angiotensin system inhibitors decreased from approximately 45% to 35%, β-blocker use increased from 48% to 61%, and loop diuretic use increased from 45% to nearly 60% in the quarters leading up to ESRD in older patients with identified CKD (17). However, in contrast to our analysis, that report did not provide information on medication use beyond the first quarter after incident ESRD and did not adjust for difference in case mix. The 2015 USRDS Annual Data Report (24) examined medication use in patients transitioning from CKD to ESRD and showed a higher prevalence of ACEI/ARB use in the 12 months before incident ESRD (56%), which decreased in the 6 months after incident ESRD to 39%. Although our results are qualitatively similar, quantitative differences in the prevalence of ACEI/ARB use between our studies may stem from the fact that their study was conducted in a cohort of United States veterans, which was nearly all male (94%) and white (72%), whereas our study cohort was more diverse. Moreover, our study goes beyond that report by providing further details on antihypertensive medication combinations and differences in use by patient subgroup during the transition to ESRD. A separate study of 13,072 patients with incident ESRD (25) showed a monthly increase in the prevalence of ACEI/ARB and β-blocker use in the 6 months after initiation of dialysis. However, that study did not consider the pre-ESRD phase, did not conduct formal trends analysis, and did not provide information beyond 6 months of follow-up (25). Thus, our study provides novel longitudinal information on antihypertensive medication use during the transition of care from predialysis CKD to maintenance dialysis, which could be used to identify areas for future practice improvement among older, lower-income patients reaching ESRD.

The National Kidney Foundation (26) endorses ACEIs or ARBs to treat hypertension in patients with CKD and ESRD (6) and ACEIs or ARBs and β-blockers to treat patients with CKD and concomitant coronary heart disease or' systolic heart failure, as in the general population (6). We hypothesized that ACEI or ARB use would decrease leading up to incident ESRD because of hyperkalemia or acute-on-chronic kidney injury but would gradually increase after dialysis initiation when these issues would be of less concern. However, ACEI or ARB use remained relatively stable before incident ESRD and actually decreased slightly after incident ESRD. Moreover, ACEI/ARB use did not correlate with observed trends in AKI or episodes of acute hyperkalemia or with the prevalence of systolic heart failure and coronary heart disease. Interestingly, unlike our findings for ACEI or ARB use, we saw a 10%–15% higher prevalence of β-blocker use in patients with coronary heart disease or systolic heart failure throughout the period studied. Our claims-based analysis cannot tell whether the lower use of ACEIs or ARBs and higher use of β-blockers were clinically appropriate or a consequence of physician inertia or patient nonadherence. Moreover, evidence supporting the use of ACEIs/ARBs or β-blockers in patients with advanced CKD for cardioprotection is much weaker than for the general population. Future studies designed to elucidate factors driving decisions about ACEI/ARB and β-blocker use are needed to target effective interventions aimed at increasing their appropriate use in CKD and ESRD.

Diuretic use was the most volatile in our analysis, climbing to 73% in the quarter before incident ESRD, dropping sharply to 42% in the quarter after incident ESRD, and then steadily declining to 23% by Q8. Similarly, combinations that included a diuretic dropped after incident ESRD. We did not have information on residual renal function, but we hypothesize that the rapid dropoff in diuretic use likely outpaced the development of anuria in these patients. Our findings are consistent with a report from the Dialysis Outcome and Practice Patterns Study (27), which showed that diuretic use declined in patients with incident ESRD in the United States, Japan, and Europe. However, that study, in contrast to ours, did not have information on diuretic use before incident ESRD. That study also showed that diuretic use (versus nonuse) correlated with lower interdialytic weight gain and lower risk of cardiovascular mortality. Whether those results

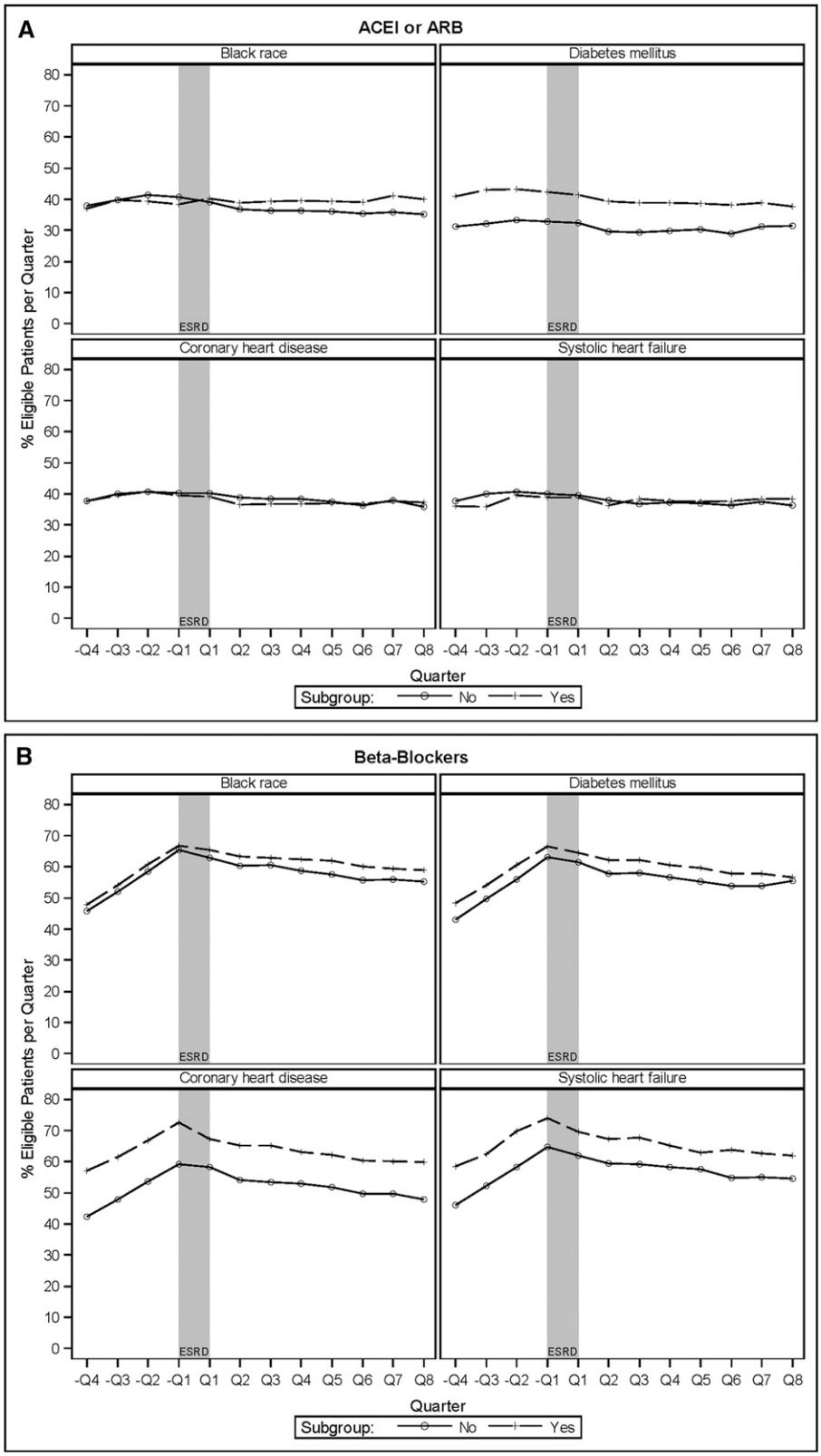

Figure 4. | Proportion of eligible patients age ≥67 years at dialysis initiation by specified subgroups with prescriptions filled for various drugs in the four quarters prior to and eight quarters after incident ESRD. (A) Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). (B) β-Blockers. (C) Calcium-channel blockers. (D) Diuretics.

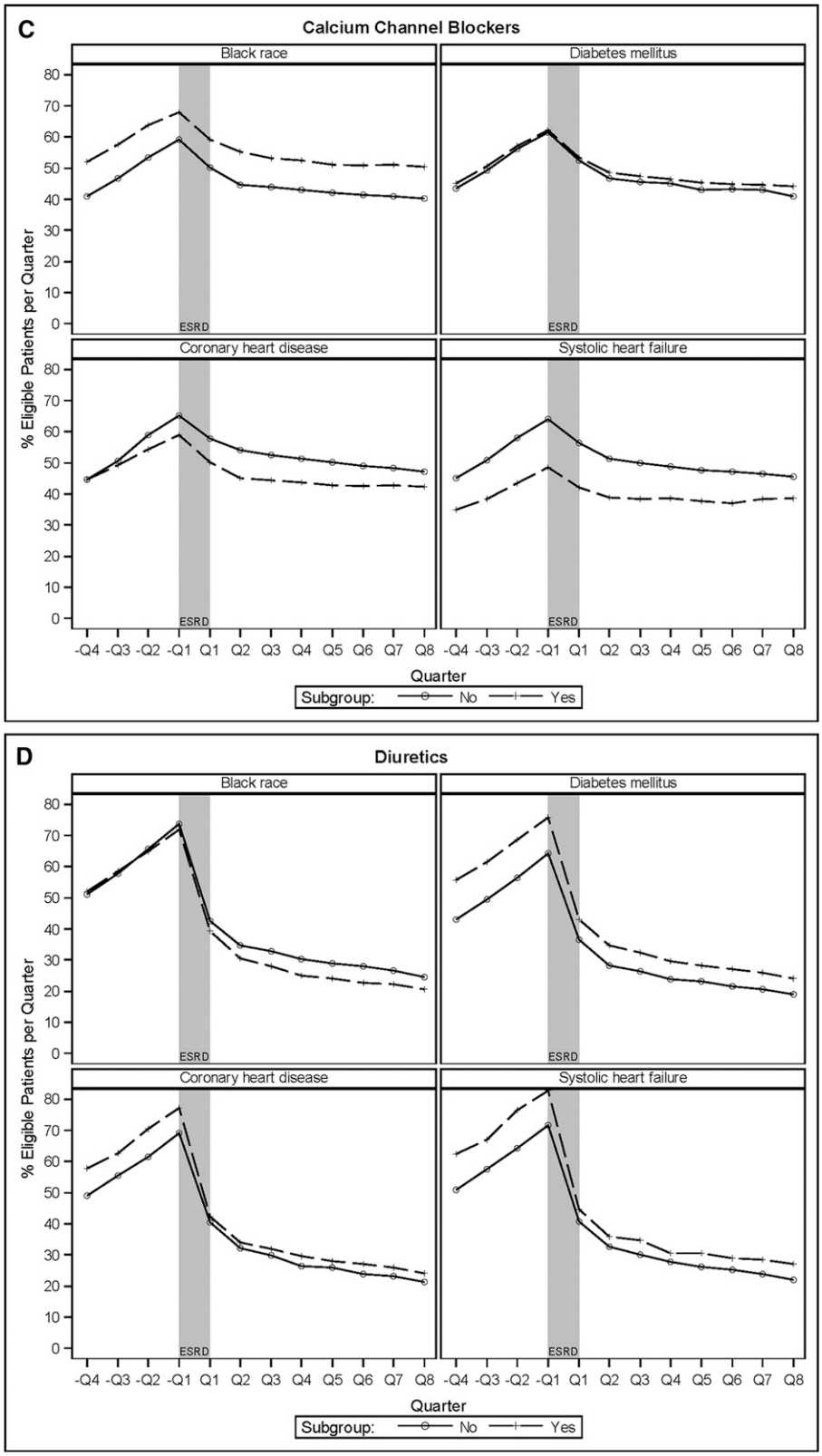

Figure 4. | Continued.

were a consequence of diuretic use remains to be proven, but the routine discontinuation of diuretics after dialysis initiation is probably not warranted.

Our analysis has some limitations to note. First, it was restricted to patients covered by a low-income subsidy, who are generally more adherent than patients who are at

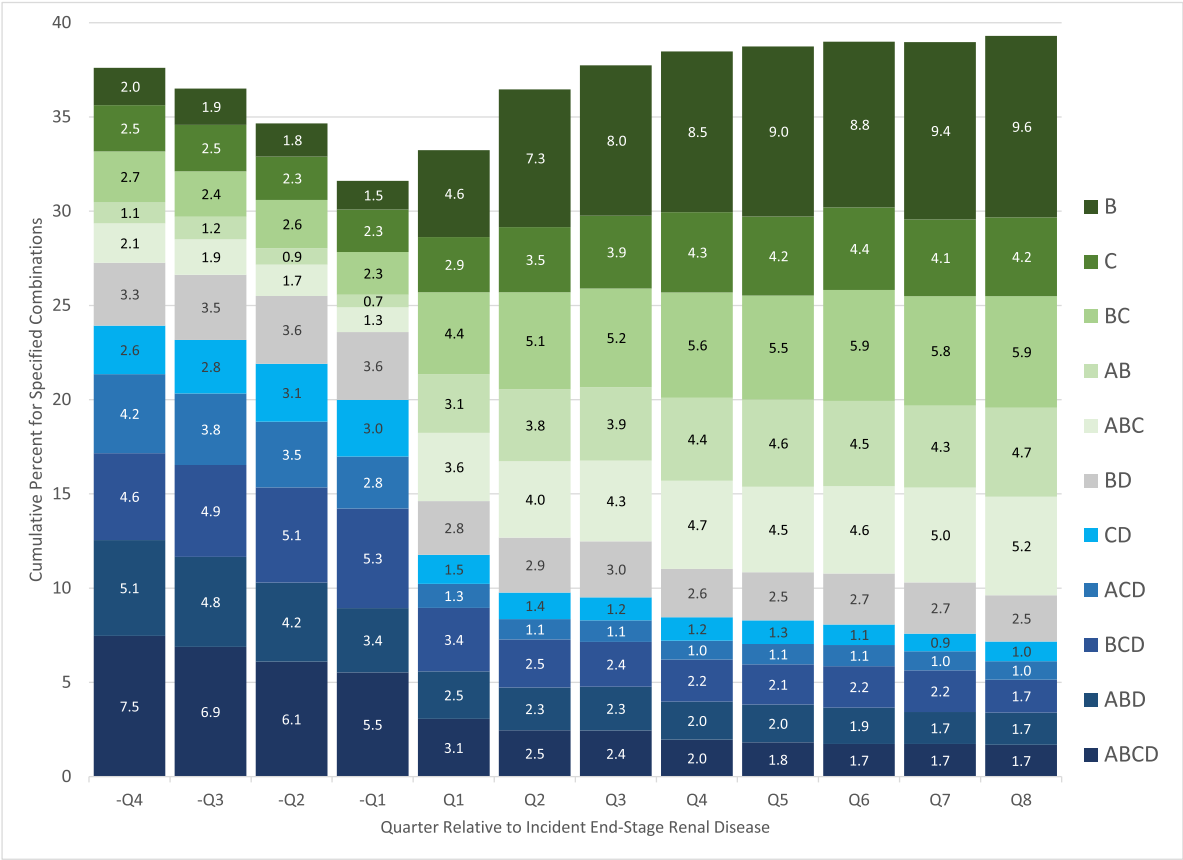

Figure 5. | Most common antihypertensive medication used alone or in combination among patients age ≥67 years at dialysis initiation taking any antihypertensive medication in the four quarters before and eight quarters after incident ESRD. Values indicated are percentages. A, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; B, β-blockers; C, calcium-channel blockers; D, diuretics.

risk of reaching the medication coverage gap (28). Our cohort included only older patients, with a high prevalence of comorbid conditions, and the findings may not be generalizable to the overall dialysis population. However, in 2013 approximately 49% of incident ESRD was among persons age ≥65 years, and the oldest age groups have the highest adjusted ESRD incident rates (24), underscoring the importance of understanding medication trends among an older cohort. Second, because this was an ecological study aimed at examining trends in medication use in the overall population during the transition from pre-ESRD to post-ESRD, we were unable to relate individual medication-taking behaviors with individual health events. Moreover, we did not have information on BP or residual renal function, both of which influence decisions about antihypertensive medication use. We did not have information on left ventricular ejection fraction, relying on diagnostic codes to identify systolic heart failure. However, these codes showed high specificity and positive predictive value in a cohort of older, lower-income patients (20), albeit with relatively preserved kidney function. Finally, we ascertained medication use through pharmacy claims information, which does not allow differentiation of whether lack of medication use was intentional (*e.g.*, physician discontinuation) or unintentional (*e.g.*, patient nonadherence), and does not capture medications filled without using Medicare benefits.

In conclusion, our study details trends in antihypertensive medication use during the transition from predialysis CKD to incident ESRD in older, low-income patients. This transition period is often a time of clinical instability, fraught with high risks of hospitalization and death (29,30), but it is therefore also a period with a large potential for practice improvement. We showed that ACEI/ARB and β-blocker use could be improved, particularly in subgroups in whom clinical guidelines recommend first-line treatment, such as patients with coronary heart disease or systolic heart failure. We also show a precipitous drop in diuretic use after incident ESRD, which may not always be appropriate if the patient still has significant residual renal function. Future prospective trials are needed to identify strategies aimed at increasing the appropriate use of antihypertensive medications in patients transitioning to ESRD treated with maintenance dialysis.

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Disclosures

None.

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