Add-On Antihypertensive Medications to Angiotensin-Aldosterone System Blockers in Diabetes

A Comparative Effectiveness Study

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Abstract

Background and objectives In individuals with diabetes, the comparative effectiveness of add-on antihypertensive medications added to an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker on the risk of significant kidney events is unknown.

Design, setting participants, & measurements We used an observational, multicenter cohort of 21,897 individuals with diabetes to compare individuals who added β-blockers, dihydropyridine calcium channel blockers, loop diuretics, or thiazide diuretics to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. We examined the hazard of significant kidney events, cardiovascular events, and death using Cox proportional hazard models with propensity score weighting. The composite significant kidney event end point was defined as the first occurrence of a ≥30% decline in eGFR to an eGFR<60 ml/min per 1.73 m^2, initiation of dialysis, or kidney transplant. The composite cardiovascular event end point was defined as the first occurrence of hospitalization for acute myocardial infarction, acute coronary syndrome, stroke, or congestive heart failure; coronary artery bypass grafting; or percutaneous coronary intervention, and it was only examined in those free of cardiovascular disease at baseline.

Results Over a maximum of 5 years, there were 4707 significant kidney events, 1498 deaths, and 818 cardiovascular events. Compared with thiazide diuretics, hazard ratios for significant kidney events for β-blockers, calcium channel blockers, and loop diuretics were 0.81 (95% confidence interval, 0.74 to 0.89), 0.67 (95% confidence interval, 0.58 to 0.78), and 1.19 (95% confidence interval, 1.00 to 1.41), respectively. Compared with thiazide diuretics, hazard ratios of mortality for β-blockers, calcium channel blockers, and loop diuretics were 1.19 (95% confidence interval, 0.97 to 1.44), 0.73 (95% confidence interval, 0.52 to 1.03), and 1.67 (95% confidence interval, 1.31 to 2.13), respectively. Compared with thiazide diuretics, hazard ratios of cardiovascular events for β-blockers, calcium channel blockers, and loop diuretics compared with thiazide diuretics were 1.65 (95% confidence interval, 1.39 to 1.96), 1.05 (95% confidence interval, 0.80 to 1.39), and 1.55 (95% confidence interval, 1.05 to 2.27), respectively.

Conclusions Compared with thiazide diuretics, calcium channel blockers were associated with a lower risk of significant kidney events and a similar risk of cardiovascular events.

Clin J Am Soc Nephrol 13: 727–734, 2018. doi: https://doi.org/10.2215/CJN.09510817

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Introduction

Diabetic kidney disease (DKD) is a major cause of morbidity, mortality, and higher heath care costs, and it is the leading cause of CKD and ESKD in the United States and worldwide (1–3). DKD occurs in 20%–40% of individuals with diabetes (4), and individuals with both diabetes and CKD have higher rates of mortality and cardiovascular disease than individuals with either diabetes or CKD alone (5). Even small impairments in kidney function are associated with higher mortality and cardiovascular disease (2,6–8). BP control can prevent or slow DKD progression (1,9,10), although the most appropriate BP goal for individuals with diabetes is the subject of ongoing debate (1,11–14).

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, and calcium channel blockers (CCBs) are recommended as first BP medications for individuals with diabetes (1,14). However, because ACE inhibitors and ARBs provide a selective class benefit in slowing progression of proteinuria and decline in eGFR, they are commonly used as the first agent for BP control in individuals with diabetes, hypertension, and albuminuria (1,9,14). Multiple BP agents are often necessary for management of hypertension in DKD. In clinical trials, on average, more than two different BP medications have been required to achieve target BPs of <130/80 mm Hg (9). However, few studies have compared the effect of different classes of BP medications when added to ACE inhibitors or ARBs on the risk of significant kidney events and cardiovascular events.

The purpose of this study was to examine the comparative effectiveness of four classes of BP

medications when added to an ACE inhibitor or ARB on risk of significant kidney events, cardiovascular events, and mortality in a population of individuals receiving routine clinical care for diabetes. We examined β-blockers, dihydropyridine CCBs, loop diuretics, and thiazide diuretics.

Materials and Methods

Study Population

This study was on the basis of the Surveillance, Prevention, and Effectiveness of Management in Diabetes Mellitus cohort of individuals with diabetes at four integrated health systems (Health Partners [Minnesota], Kaiser Permanente Colorado [KPCO], Kaiser Permanente Northern California [KPNC], and Kaiser Permanente Northwest [KPNW; Oregon]) from 2005 to 2013. Research institutions embedded in these health systems have developed a distributed virtual data warehouse that contains information on demographics, outpatient pharmacy dispensing, laboratory tests and results, and diagnostic and procedure codes from outpatient and inpatient health care encounters from their electronic health record and administrative data systems (15–17).

Diabetes was defined using diagnosis codes, medications, and laboratory results as previously described (Supplemental Table 1) (15,16). Individuals with diabetes were included in these analyses if they were on monotherapy with an ACE inhibitor or ARB and then started a second BP medication while continuing the ACE inhibitor or ARB. The date of initiation of the second BP medication was considered the index date. Index dates were between January 1, 2005 and December 31, 2012 (Health Partners, KPCO, and KPNW) or between January 1, 2008 and December 31, 2012 (KPNC; due to lack of routine availability of granular BP data in the electronic health record before January 1, 2008). We additionally required that, at the index date, individuals (*1*) have at least 6 months of continuous prior enrollment; (*2*) have at least one elevated BP (>130/80) in the 6 months prior; (*3*) have been diagnosed with diabetes; (*4*) not be pregnant; (*5*) be at least 21 years old; (*6*) have not been on dialysis, had a prior kidney transplant, or had a most recent eGFR <15 ml/min per 1.73 m^2; and (*7*) have a serum creatinine available on or within 365 days prior (Figure 1). Individuals were followed from the index date until development of the study outcome or the earliest censoring event (disenrollment for >90 consecutive days, death, pregnancy, 5 years of follow-up, or end of study period on January 31, 2013).

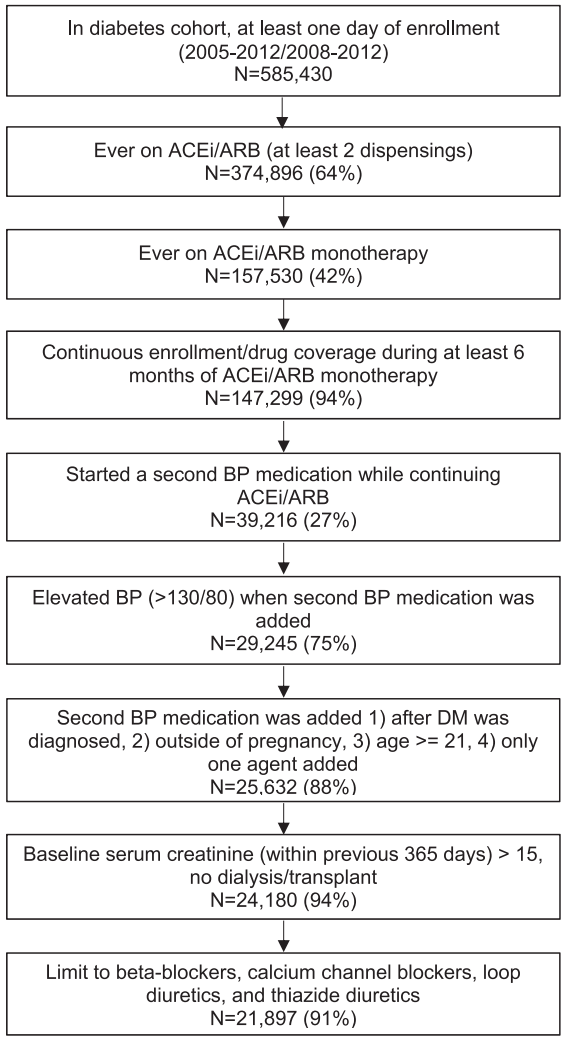

Figure 1. | Cohort construction. ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; DM, diabetes mellitus.

Exposures

We limited our analyses to the four most common classes of add-on antihypertensive medications in our cohort: β-blockers, dihydropyridine CCBs, loop diuretics, and thiazide diuretics. As the largest group, thiazide diuretics were treated as the referent group.

Outcomes

The composite significant kidney event end point was defined as the first occurrence of a ≥30% decline in eGFR to an eGFR60 ml/min per 1.73 m^2, initiation of dialysis, or kidney transplant. The composite cardiovascular event end point was defined as the first occurrence of hospitalization for acute myocardial infarction, acute coronary syndrome, stroke, or congestive heart failure; coronary artery bypass grafting; or percutaneous coronary intervention. We also examined all-cause mortality. Dialysis, kidney transplant, and cardiovascular events were defined using ICD-9 and CPT codes (Supplemental Table 1) (18–22). All eGFRs were estimated from outpatient serum creatinine values using the Chronic Kidney Disease Epidemiology Collaboration estimating equation (23).

Covariates

Important covariates were selected *a priori* using data from the index date or up to 365 days prior. Covariates included age, sex, race/ethnicity, insurance type, index date, smoking status, overall Quan Elixhauser comorbidity score and individual comorbidities (Supplemental Table 2) (22), retinopathy, coronary artery disease or stroke, laboratory values (baseline eGFR, albuminuria, hemoglobin A1c, LDL cholesterol, HDL cholesterol, and potassium), vital signs (body mass index and systolic and diastolic BP),

utilization (number of inpatient, outpatient, and emergency room encounters in the previous 365 days), medication use (insulin, metformin, baseline ACE inhibitor versus ARB use, and number of generic medications using dispensing within the prior 365 days), and census track–level measures of poverty and education.

Measurements of BPs during follow-up were used in time-varying covariate models to determine if changes in BP over time mediated the relationship between medication exposures and outcomes. We determined the average of all BPs taken during each month. We then used two different BP adjustment methods. In the first method, we adjusted for the mean BP each month to capture any short-term BP effects. In the second method, we adjusted for the average of the monthly BPs over all preceding months to capture any long-term BP effects.

For missing baseline covariates, we used Markov Chain Monte Carlo imputation methods (SAS 9.4) to create ten imputation datasets (24). All covariates, survival time, and an outcome indicator were included in the ten imputation models, which were stratified by study site.

Statistical Analyses

To characterize the study population at baseline, we calculated descriptive statistics using mean and SD for continuous variables and percentages for categorical variables. To adjust for differences in baseline demographic and clinical factors, we performed a propensity score analysis and created inverse probability of treatment-weighted estimators (25). Propensity scores were created using the covariates in Table 1 and Supplemental Table 2, and they were stratified by study site (24–31). Because we had four treatment groups, we used multinomial regression to estimate multiple propensity scores (26,27). Graphic comparisons confirmed that the distributions of the propensity scores for treatment groups largely overlapped. Generalized stabilized inverse probability weights were created and used to adjust for covariates in the outcome models (25,28). We trimmed the propensity score weights by recoding a small number of extreme weights to 50. Sensitivity analyses with untrimmed weights had similar results. After weighting by the propensity score, we assessed balance of each covariate by the absolute standardized difference (30,31). Most variables were balanced (absolute standardized difference <0.1), and variables with larger differences were additionally included in the outcome models (29) together with age, race, sex, and study site. We used Cox proportional hazard models for the outcome models using three dummy independent variables to represent the four treatment groups (26,27). For cardiovascular events, the cohort was restricted to individuals without heart disease at baseline (coronary artery disease, stroke, cardiac arrhythmias, and congestive heart failure), and separate propensity score weights were created for this subcohort.

We conducted three sensitivity analyses. For the first sensitivity analysis, we assessed for effect modification by baseline eGFR (<60 and ≥ 60 ml/min per 1.73 m^2) by including interaction terms with the index medications in the outcome models. For the second analysis, we required that eGFR declines be sustained (*i.e.*, after the first eGFR with a $\geq 30\%$ decline in eGFR to an eGFR<60 ml/min per 1.73 m^2, there was another eGFR 90–365 days later that also had a similar decline from baseline). For the third sensitivity analysis, we examined the significant kidney event outcome after excluding the initial 3 months of follow-up time. This was done to exclude the initial hemodynamic effects that can be seen after starting diuretics, which may not represent true eGFR changes (32). We used the propensity score from the original index date, because those are the factors that influenced the treatment decision. We used the first available eGFR obtained between index date and 12 months (as long as it was >15 ml/min per 1.73 m^2) after the original baseline as the new baseline eGFR for calculating change in eGFR.

This study was reviewed by the KPCO Institutional Review Board, and informed consent was not required.

Results

The total sample size was of 21,897 (Figure 1), of whom 9768 (45%) were started on thiazide diuretics, 7343 (34%) were started on β-blockers, 2705 (12%) were started on CCBs, and 2081 (10%) were started on loop diuretics. Baseline characteristics of individuals in all groups are shown in Table 1 and Supplemental Table 2. In general, individuals receiving thiazide diuretics were younger and had fewer comorbidities, whereas the loop diuretic group was the oldest and had the most comorbidities. After propensity score weighting, the majority of variables had an absolute standardized difference <0.1. Variables with an absolute standardized difference of ≥ 0.1 were included in the outcome models to adjust for any residual confounding (Table 1).

Significant Kidney Events

There were 4707 significant kidney events (one kidney transplant, 43 dialysis initiations, and 4663 eGFR declines $\geq 30\%$ to an eGFR<60 ml/min per 1.73 m^2: 2111 in the thiazide diuretic group, 1468 in the β-blocker group, 511 in the CCB group, and 617 in the loop diuretic group). Individuals in the CCB group and the β-blocker group had a lower risk of a significant kidney event compared with those in the thiazide diuretic group, with hazard ratios of 0.67 (95% confidence interval [95% CI], 0.58 to 0.78) and 0.81 (95% CI, 0.74 to 0.89), respectively (Table 2). The loop diuretic group had a higher risk of a significant kidney event compared with the thiazide diuretic group, with a hazard ratio of 1.19 (95% CI, 1.00 to 1.41). Adjusting for BP as a time-varying covariate using the two different methods did not affect the results (Table 2). Interaction terms between the index medications and baseline eGFR were not statistically significant, but there was an attenuation of the association for loop diuretics in those with an eGFR≥ 60 ml/min per 1.73 m^2 (Supplemental Table 3).

In the second sensitivity analysis that required a sustained eGFR decline, we had fewer significant kidney events (2198) and a slightly higher hazard ratio for loop diuretics of 1.43 (95% CI, 1.12 to 1.82). Otherwise, the results were not appreciably changed (Supplemental Table 4). In the third sensitivity analysis, we excluded the initial 3 months of follow-up time. This decreased the cohort size to 17,178 and the number of significant kidney events to 2836, but did not appreciably change the results (Supplemental Table 5).

Table 1. Baseline characteristics of individuals with diabetes receiving four classes of antihypertensive medications added on to angiotensin-aldosterone system blockers (*n*=21,897)

Variable	Overall	β-Blockers	Calcium Channel Blockers	Loop Diuretics	Thiazide Diuretics
N	21,897	7343	2705	2081	9768
Demographic characteristics					
Age, mean±SD	62±12	63±12	64±12	66±13	60±12
Women, *n* (%)	10,768 (49)	3464 (47)	1307 (48)	1267 (61)	4730 (48)
Race/ethnicity, *n* (%)					
White	12,649 (58)	4507 (61)	1348 (50)	1464 (70)	5330 (55)
Other	6761 (31)	2187 (30)	980 (36)	434 (21)	3160 (32)
Black	1665 (8)	388 (5)	289 (11)	132 (6)	856 (9)
Missing	822 (4)	261 (4)	88 (3)	51 (2)	422 (4)
Year of index date,[a] *n* (%)					
2005–2008	7735 (35)	2808 (38)	697 (26)	676 (32)	3554 (36)
2009	4489 (21)	1366 (19)	598 (22)	380 (18)	2145 (22)
2010	3728 (17)	1097 (15)	624 (23)	299 (14)	1708 (17)
2011	2825 (13)	949 (13)	409 (15)	356 (17)	1111 (11)
2012	3120 (14)	1123 (15)	377 (14)	370 (18)	1250 (13)
Medicare, *n* (%)	9472 (43)	3519 (48)	1324 (49)	1224 (59)	3405 (35)
Commercial insurance,[a] *N* (%)	16,070 (73)	5147 (70)	1938 (72)	1327 (64)	7658 (78)
Smoking, *n* (%)					
Current	1839 (8)	640 (8)	203 (8)	163 (8)	833 (9)
Former/never	14,399 (66)	4961 (68)	1765 (65)	1472 (71)	6201 (63)
Missing	5659 (26)	1742 (24)	737 (27)	446 (21)	2734 (28)
Body mass index,[b] mean±SD	33.0±7.7	31.9±7.1	31.5±7.2	36.5±9.5	33.4±7.7
No. (%) missing	444 (2)	93 (1)	69 (3)	42 (2)	240 (2)
Baseline BP,[b] mm Hg, mean±SD					
Systolic BP, most recent	142±17	138±18	148±17	135±17	145±15
Diastolic BP, most recent	79±11	78±11	81±12	74±11	81±11
Systolic BP,[a] maximum	153±17	151±17	158±18	150±16	154±16
Diastolic BP, maximum	86±11	85±10	86±11	82±10	87±10
Baseline laboratory values[c]					
eGFR, ml/min per 1.73 m^2, mean±SD	81±21	80±21	77±22	75±23	85±19
eGFR<60 ml/min per 1.73 m^2, *n* (%)	3713 (17)	1382 (19)	637 (24)	582 (28)	1112 (11)
A1c, %, mean±SD	7.5±1.6	7.5±1.6	7.4±1.5	7.4±1.6	7.6±1.6
No. (%) missing	894 (4)	332 (5)	118 (4)	116 (6)	328 (3)
HDL, mg/dl, mean±SD	47±13	46±13	48±13	48±14	47±13
No. (%) missing	1570 (7)	553 (8)	188 (7)	217 (10)	612 (6)
LDL, mg/dl, mean±SD	92 (33)	91 (33)	92 (32)	90 (34)	93 (32)
No. (%) missing	961 (4)	349 (5)	106 (4)	152 (7)	354 (4)
Potassium,[a] mEq, mean±SD	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)	4.5 (0.4)
No. (%) missing	884 (4)	273 (4)	111 (4)	52 (3)	448 (5)
Albuminuria,[a,d] *n* (%)					
Normal	11,692 (53)	4052 (55)	1310 (48)	1097 (53)	5233 (54)
Microalbuminuria	3646 (17)	1201 (16)	499 (18)	340 (16)	1606 (16)
Macroalbuminuria	1621 (7)	473 (6)	242 (9)	212 (10)	694 (7)
Missing	4938 (23)	1617 (22)	654 (24)	432 (21)	2235 (23)
Comorbidities					
Total no. of comorbidities Quan[a] (22), mean±SD	4±2	4±2	4±2	5±2	4±1
Retinopathy,[a,e] *n* (%)	3588 (16)	1154 (16)	456 (17)	455 (22)	1523 (16)
Coronary artery disease and stroke,[e] *n* (%)	2945 (13)	1863 (25)	253 (9)	335 (16)	494 (5)
Baseline medication use					
Insulin, *n* (%)	5010 (23)	1626 (22)	543 (20)	705 (34)	2136 (22)
Metformin, *n* (%)	11,945 (55)	3907 (53)	1311 (48)	934 (45)	5793 (59)
Statin, *n* (%)	15,903 (73)	5454 (74)	1914 (71)	1416 (68)	7119 (73)
ARB, *n* (%)	5902 (27)	2021 (28)	947 (35)	576 (28)	2348 (24)
No. of medications,[a] mean±SD	11±5	11±5	10±5	14±6	10±4.4
Utilization within the prior 12 mo, mean±SD					
Outpatient encounters	11.4±11.5	12.7±12.5	11.0±11.1	15.7±14.1	9.6±9.8
Inpatient encounters[a]	0.2±0.7	0.4±0.8	0.2±0.7	0.5±1.0	0.1±0.4
Emergency department encounters[a]	0.6±1.4	0.8±1.6	0.6±1.3	1.1±2.0	0.4±1.0

Table 1. (Continued)

Variable	Overall	β-Blockers	Calcium Channel Blockers	Loop Diuretics	Thiazide Diuretics
Socioeconomic status[f]					
Poverty	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
No. (%) missing	154 (0.7)	55 (0.7)	19 (0.7)	13 (0.6)	67 (0.7)
Education[a]	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
No. (%) missing	154 (0.7)	55 (0.7)	19 (0.7)	13 (0.6)	67 (0.7)

ARB, angiotensin II receptor blocker.
[a]Variables with absolute standardized differences after propensity score weighting of ≥0.1.
[b]Most recent within the past 6 months.
[c]Most recent within the past 12 months.
[d]Albuminuria was calculated from spot albumin-to-creatinine ratios (normal: 0–29 mg/g; microalbuminuria: 30–299 mg/g; macroalbuminuria: ≥300 mg/g), spot protein-to-creatinine ratios (normal: 0–149 mg/g; microalbuminuria: 150–499 mg/g; macroalbuminuria: ≥500mg/g), and urine protein dipsticks (normal: negative, trace; microalbuminuria: 1+; macroalbuminuria: 2+ and above) (44).
[e]Retinopathy was defined as two outpatient encounters or one inpatient encounter in the 365 days before the index date with the following ICD-9 codes (250.5X or 362.0X). Coronary artery disease and stroke were defined by any of the following codes in the 365 days before the index date (ICD-9: 410–414, 429.2, or 429.7 for coronary artery disease and 430.X, 431.X, 433.X1, or 434.X1 for stroke) or primary discharge diagnosis for acute myocardial infarction or stroke (Supplemental Table 1) in the 365 days before the index date.
[f]Socioeconomic status was defined at the census track level. Poverty reflects the proportion of households with below poverty-level income in the census track, and education reflects the proportion of households with a high school degree or less in the census track.

Mortality

There were 1498 deaths (377 in the thiazide diuretic group, 595 in the β-blocker group, 162 in the CCB group, and 364 in the loop diuretic group). The loop diuretic group had a higher risk of death compared with the thiazide diuretic group, with a hazard ratio of 1.67 (95% CI, 1.31 to 2.13) (Supplemental Table 3). The hazard ratios for β-blockers and CCBs did not differ from those of thiazide diuretics. However, after including BP as a time-varying covariate, the hazard ratio for CCBs was significantly lower than for thiazide diuretics at 0.64 (95% CI, 0.42 to 0.98). Interaction terms between the index medications and baseline eGFR were not statistically significant (Supplemental Table 3).

Cardiovascular Events

There were 818 cardiovascular events (185 acute myocardial infarction, 180 stroke, 86 acute coronary syndrome, 153 congestive heart failure, and 214 revascularization: 320 in the thiazide diuretic group, 301 in the β-blocker group, 105 in the CCB group, and 92 in the loop diuretic group) in patients without prevalent coronary artery disease, stroke, cardiac arrhythmias, or congestive heart failure at baseline (n=17,271). Individuals in the β-blocker and loop diuretic groups had a higher risk of cardiovascular events compared with those in the thiazide diuretic group, with hazard ratios of 1.65 (95% CI, 1.39 to 1.96) and 1.55 (95% CI, 1.05 to 2.27), respectively (Table 2). Limiting the outcome to acute myocardial infarction and stroke resulted in no statistically significant differences between the medication classes (Supplemental Table 6). Interaction terms between the index medications and baseline eGFR were statistically significant for β-blockers and CCBs. There was attenuation of the β-blockers association in individuals with lower eGFR (hazard ratio, 1.14; 95% CI, 0.76 to 1.69 for baseline eGFR <60 ml/min per 1.73 m^2 and hazard ratio, 1.84; 95% CI, 1.51 to 2.23 for baseline eGFR ≥60 ml/min per 1.73 m^2). For CCBs, there was a higher risk of cardiovascular events in individuals with lower eGFR (hazard ratio, 1.73; 95% CI, 1.01 to 2.96 for baseline eGFR <60 ml/min per 1.73 m^2 and hazard ratio, 0.86; 95% CI, 0.63 to 1.16 for baseline eGFR ≥60 ml/min per 1.73 m^2) (Supplemental Table 3).

Discussion

In this large comparative effectiveness study from four integrated health care systems, we found that, over 5 years of follow-up, compared with thiazide diuretics, CCBs were associated with a lower risk of significant kidney events, similar risk of cardiovascular events, and a suggestion of a lower risk of death. Although β-blockers were associated with a lower risk of significant kidney events compared with thiazide diuretics, they were also associated with a higher risk of cardiovascular events. Loop diuretics were associated with a higher risk of a significant kidney event compared with thiazide diuretics. These results persisted after several sensitivity analyses, including (*1*) excluding the initial period of rapid hemodynamic changes after new medication initiation and (*2*) requiring a persistent decline in eGFR or cardiovascular events. For cardiovascular events, CCBs seemed similar to thiazide diuretics overall and in individuals with baseline eGFR >60 ml/min per 1.73 m^2, but they were worse in individuals with baseline eGFR ≤60 ml/min per 1.73 m^2.

Our results for CCBs and thiazide diuretics are consistent with those of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) Study, a randomized trial that compared benazepril plus amlodipine with benazepril plus hydrochlorothiazide among 11,506 individuals at high risk for cardiovascular events. The benazepril-amlodipine group had a lower risk of cardiovascular events and kidney events, with no statistically different risk of mortality, both overall and among the 60% of participants with diabetes (33–35). Similarly, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), participants in the amlodipine group had a 3- to 6-ml/min per 1.73 m^2 higher eGFR at the end of follow-up than those in the chlorthalidone group (36). In our study, we did not

Table 2. Hazard ratios (95% confidence intervals) for kidney events, mortality, and cardiovascular events by class of antihypertensive medication added on to angiotensin-aldosterone system blockers compared with thiazide diuretics

Outcomes	β-Blockers	Calcium Channel Blockers	Loop Diuretics
Significant kidney events			
No. (total =21,897)	7343	2705	2081
No. of events (total =4707)	1468	511	617
Crude	0.94 (0.88 to 1.00)	0.88 (0.80 to 0.97)	1.70 (1.55 to 1.87)
Propensity score analysis	0.81 (0.74 to 0.89)	0.67 (0.58 to 0.78)	1.19 (1.00 to 1.41)
Propensity score analysis adjusting for current BP	0.80 (0.73 to 0.88)	0.63 (0.54 to 0.74)	1.21 (1.01 to 1.44)
Propensity score analysis adjusting for cumulative BP	0.76 (0.69 to 0.84)	0.60 (0.52 to 0.70)	1.22 (1.03 to 1.46)
Mortality			
No. (total =21,897)	7343	2705	2081
No. of events (total =1498)	595	162	364
Crude	2.18 (1.92 to 2.48)	1.62 (1.34 to 1.94)	5.35 (4.63 to 6.18)
Propensity score analysis	1.19 (0.97 to 1.44)	0.73 (0.52 to 1.03)	1.67 (1.31 to 2.13)
Propensity score analysis adjusting for current BP	1.13 (0.86 to 1.47)	0.65 (0.43 to 0.99)	1.61 (1.19 to 2.18)
Propensity score analysis adjusting for cumulative BP	1.13 (0.86 to 1.48)	0.64 (0.42 to 0.98)	1.62 (1.20 to 2.19)
Cardiovascular events			
No. (total =17,271)[a]	4593	2320	1374
No. of events (total =818)	301	105	92
Crude	1.88 (1.61 to 2.20)	1.31 (1.05 to 1.63)	2.13 (1.69 to 2.69)
Propensity score analysis	1.65 (1.39 to 1.96)	1.05 (0.80 to 1.39)	1.55 (1.05 to 2.27)
Propensity score analysis adjusting for current BP	1.69 (1.42 to 2.01)	1.06 (0.80 to 1.41)	1.62 (1.12 to 2.35)
Propensity score analysis adjusting for cumulative BP	1.55 (1.30 to 1.85)	1.00 (0.75 to 1.32)	1.57 (1.08 to 2.27)

Reference group is thiazide diuretics. Significant kidney events were ≥30% eGFR decline from baseline and eGFR<60 ml/min per 1.73 m^2, initiation of dialysis, or kidney transplant (Supplemental Table 1). Cardiovascular events were hospitalization for acute myocardial infarction, acute coronary syndrome, stroke, congestive heart failure, coronary artery bypass grafting, or percutaneous coronary intervention (Supplemental Table 1). Propensity score analyses were weighted using generalized stabilized inverse probability weights, with outcomes models including study site, age, sex, race, and variables with absolute standardized differences after propensity score weighting of ≥0.1. For the current BP adjustment, we adjusted for the mean BP each month as a time-varying covariate to capture any short-term BP effects. For the cumulative BP adjustment, we adjusted for the average of the monthly BP over all preceding months to capture any long-term BP effects.

[a]Excludes individuals with prevalent coronary artery disease, stroke, cardiac arrhythmias, or congestive heart failure at baseline.

find an overall difference between CCBs and thiazide diuretics in the risk of cardiovascular events. However, the ACCOMPLISH Study included individuals with prevalent cardiovascular disease, whereas we excluded them. This observational study complements the ACCOMPLISH Study in that we assessed β-blockers and loop diuretics and had a larger diabetic population (21,897 versus 6946). In addition, we used an eGFR-based event definition for kidney disease progression (≥30% decline in eGFR to an eGFR<60 ml/min per 1.73 m^2, initiation of dialysis, or kidney transplant) instead of a serum creatinine–based definition (doubling of serum creatinine concentration or ESKD with eGFR<15 ml/min per 1.73 m^2).

In our study, β-blockers also seemed more kidney protective than thiazide diuretics, but they were associated with a higher risk of cardiovascular disease. We are not aware of clinical trials that have compared the combination of ACE inhibitors/ARBs and β-blockers with ACE inhibitors/ARBs and thiazide diuretics. However, β-blockers are generally not recommended for initial monotherapy for hypertension in the absence of a compelling indication because of concerns that they may be associated with higher rates of cardiovascular events as we observed (12,14,37,38). Additionally, many β-blockers have adverse metabolic effects, including increasing triglycerides, decreasing HDL cholesterol, and increasing insulin resistance, and they may mask symptoms of hypoglycemia (39). β-Blockers also reduce renin secretion, and therefore, they are not physiologically complementary to ACE inhibitors and ARBs (40).

Diuretics are often used when a second BP medication is required, and the physiologic actions of diuretics and ACE inhibitors/ARBs are complementary (41,42). However, diuretics may worsen hyperglycemia, dyslipidemia, and hyperuricemia (32,41,43). In general, thiazide diuretics are more effective in lowering BP than loop diuretics, and therefore, they are typically favored in patients with normal kidney function or early-stage CKD. In contrast, loop diuretics have a greater natriuretic effect, and thus, they are often used in advanced CKD when edema is more of a problem (41). These practice patterns are reflected in our data, where the loop diuretic group generally had lower baseline eGFR and more comorbidities. We did not have information on volume status, and we were unable to compare specific medications within a class (for example, hydrochorothiazide and chlorthalidone).

Strengths of this study include a large population of patients receiving routine clinical care from multiple study

sites with assessment of a wide range of potential confounders that might lead to differential prescribing of BP medications and might differentially affect study outcomes. We used complex statistical techniques supplemented with sensitivity analyses to examine the four most common classes of second-line BP medications in diabetes.

As in any observational study, there is the potential for residual confounding, and thus, these results should be interpreted cautiously. To address this concern, we used propensity score weighting and included unbalanced covariates in the outcomes models. Residual confounding is of the greatest concern for the loop diuretic group, because it was the most different from the other groups at baseline; additionally, loop diuretics are often used selectively in individuals with more advanced CKD. We used an intention to treat analysis and did not examine duration of treatment, and therefore, there is a possibility that our results are due to differential adherence, length of time on specific medications, or BP control among the different medication groups. However, adjusting for achieved BP using two different methods did not substantially change the results. Although acute hemodynamic changes can also affect eGFR measurements, results from a sensitivity analysis excluding the first 3 months of follow-up did not substantially change our results.

In conclusion, our results complement recent guidelines (1,14) and suggest benefits to the use of CCBs on kidney function in individuals with diabetes who are already on an ACE inhibitor or ARB and require a second BP medication.

Acknowledgments

This project was supported by grant 1K23DK099237-01 from the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and grants 1R01HS022963-01 and R01HS019859 from the Agency for Healthcare Research and Quality. J.A.S. and P.J.O. received additional support from NIDDK-funded Health Delivery Systems Center for Diabetes Translational Research grant 1P30DK92924.

The study sponsors had no role in the study design, collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Agency for Healthcare Research and Quality.

Because Michel Chonchol is a Deputy Editor of the Clinical Journal of the American Society of Nephrology, he was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript.

Disclosures

None.

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Received: August 30, 2017 **Accepted:** February 2, 2018

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.09510817/-/DCSupplemental.