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Comparative Effectiveness of Antihypertensive Medications in Children With Chronic Kidney Disease

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IMPORTANCE Hypertension is a major modifiable factor for kidney function decline in chronic kidney disease (CKD). Comparative trials of antihypertensive medications in pediatric CKD are lacking.

OBJECTIVE To evaluate the comparative effectiveness of renin-angiotensin-aldosterone system inhibition (RAASi) vs calcium channel blockade (CCB), the most widely used first-line antihypertensive treatment approaches in pediatric CKD, on preservation of kidney function.

DESIGN, SETTING, AND PARTICIPANTS Using target trial emulation methods, this comparative-effectiveness study emulated a pragmatic, open-label clinical trial using electronic health record data from the Preserving Kidney Function in Children with CKD (PRESERVE) study from January 2009 through December 2020. Thirteen health care institutions from 5 PCORnet Clinical Research Networks were represented. Children and adolescents aged 2 to 20.9 years with CKD stage 2-4 and systolic blood pressure higher than the 90th percentile or with a hypertension diagnosis who initiated treatment with RAASi or CCB were included. Exclusion criteria included kidney replacement therapy, renal artery stenosis, malignancy, and pregnancy. Data analysis was completed in July 2025.

EXPOSURES Incident RAASi or CCB treatment. Randomization was emulated by propensity score weighting to balance groups on sociodemographic factors, institution, year, CKD etiology, proteinuria, CKD stage, obesity, health care use, medications, comorbidities, and blood pressure control (percentage of time at greater than the 90th percentile).

MAIN OUTCOMES AND MEASURES The primary outcome was progression to kidney replacement therapy within 2 years of follow-up, ascertained through linkage with the United States Renal Data System. The secondary outcome was a composite of kidney replacement therapy, 50% decline in estimated glomerular filtration rate, or estimated glomerular filtration rate less than 15 mL/min/1.73 m^2. Cox proportional hazards regression with propensity score stratification was used to estimate adjusted hazard ratios (aHRs) in the intention-to-treat analysis. Adjusted analyses also compared systolic blood pressure control within 2 years of follow-up.

RESULTS Of 2762 children and adolescents, 1757 initiated RAASi (median [IQR] age, 13.1 [9.2-15.5] years; 897 [51.1%] male) and 1005 initiated CCB (median [IQR] age, 12.6 [8.4-15.3] years; 500 [49.8%] male). In adjusted analyses, RAASi was associated with reduced risk of both kidney replacement therapy (aHR, 0.58; 95% CI, 0.40-0.84, P = .004) and the secondary composite outcome (aHR, 0.67; 95% CI, 0.53-0.83). Systolic blood pressure control was better with RAASi than CCB (29% vs 39% of time >90th percentile).

CONCLUSIONS AND RELEVANCE In this comparative-effectiveness study, RAASi was associated with lower risk of CKD progression and better blood pressure control compared to CCB. Findings support first-line use of RAASi for antihypertensive treatment in pediatric CKD.

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Supplemental content

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One of the most important outcomes for children with chronic kidney disease (CKD) and their families is preservation of kidney function.[1-3] Hypertension occurs in 50% of children with CKD[4,5] and is a major, modifiable contributor to kidney function decline.[5-8] While blood pressure (BP) control is a cornerstone of pediatric CKD management, control of hypertension for many remains suboptimal.[9] Clinical trial and observational data are limited, creating a thin evidence base for informing management.

Several clinical practice guidelines have provided recommendations for BP management in pediatric CKD.[10-15] These guidelines recommend that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers be the preferred initial antihypertensive medications, based on the central role of the renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of hypertension in CKD and their additional antiproteinuric effects.[16] However, the lack of clinical trial data, combined with concerns about potential adverse effects of RAAS inhibition (RAASi) in children with congenital anomalies of the kidney and urinary tract and advanced stage CKD, has limited the application of these guidelines. Available pediatric data for BP management in CKD comes largely from a single clinical trial (The Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients [ESCAPE][6]) and the observational Chronic Kidney Disease in Children (CKiD) study.[17] ESCAPE, a European trial of 385 children with CKD conducted from 1998 to 2007, provides some of the highest quality evidence in support of strict BP control in pediatric CKD, but all participants were treated with a single angiotensin-converting enzyme inhibitor (ramipril) and randomized to intensified or conventional BP control. CKiD, which has enrolled more than 1000 children across North America since 2003, showed that children who were treated with RAASi had better control of BP at baseline compared to those who received other classes of antihypertensive medications[4] and that use of RAASi was associated with a 21% to 37% reduction in the risk of kidney replacement therapy.[18] To date, there have been no comparative trials of antihypertensive medications in pediatric CKD.

Preserving Kidney Function in Children With CKD (PRESERVE) was a PCORnet[19] designated multi-institutional cohort study of more than 20 000 children and adolescents with CKD designed to address evidence gaps and generate new knowledge to inform shared decision-making for BP management in pediatric CKD.[20] Using electronic health record data from 13 health care institutions participating in PRESERVE, we used target trial emulation methods to evaluate the real-world comparative effectiveness of the most widely used first-line antihypertensive treatments in pediatric CKD, RAASi vs calcium channel blockade (CCB), on preservation of kidney function.

Key Points

Question What is the real-world comparative effectiveness of the most widely used first-line antihypertensive treatment approachess in pediatric chronic kidney disease (CKD), renin-angiotensin-aldosterone system inhibition (RAASi) and calcium channel blockade (CCB), on preservation of kidney function?

Findings This comparative-effectiveness study emulated a pragmatic trial comparing 2-year outcomes among a cohort of 2762 children and adolescents with CKD initiating antihypertensive therapy with RAASi or CCB. Compared to CCB, RAASi was associated with a statistically significant lower risk of the primary outcome of kidney replacement therapy.

Meaning The findings in this study support first-line use of RAASi for antihypertensive therapy in children with CKD.

Methods

Data Sources and Study Population

PRESERVE integrated electronic health record data from 15 health system partners across 5 PCORnet Clinical Research Networks (PEDSnet, Science, Technology and Research [STAR], Greater Plains Collaborative [GPC], PaTH, and OneFlorida+). The methods for PRESERVE have been previously published.[20] The PRESERVE study cohort included 20 100 children (aged 1 to 18 years) with at least 1 nephrologist encounter and mild-moderate CKD, defined as 2 or more eGFR values of 30 to less than 90 mL/min/1.73 m^2 (using the CKiD under 25 [U25] formula)[21] at least 90 days apart without an intervening eGFR result of 90 mL/min/1.73 m^2 or greater and without prior long-term dialysis or kidney transplant at cohort entrance. The study period for PRESERVE was January 2009 to December 2022. To produce a high-quality, research grade dataset, rigorous data quality evaluations were done, involving 3 data queries and 2 rounds of network remediation, as previously described.[22] The 13 institutions that contributed data to this analysis were Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Children's Hospital Colorado, Ann & Robert H. Lurie Children's Hospital, Nemours Children's Health, Seattle Children's Hospital, Stanford Children's Health, The University of North Carolina at Chapel Hill, Medical College of Wisconsin/Children's Wisconsin, University of Iowa Stead Family Children's Hospital, University of Michigan/C. S. Mott Children's Hospital, Johns Hopkins Children's Center, and University of Florida/Shands Children's Hospital. The minimum study cohort entrance date varied based on the start of data availability for each institutional data mart (eTable 1 in Supplement 1). To enable complete ascertainment of kidney replacement therapy, patients in PRESERVE were linked with the United States Renal Data System (USRDS), which includes Centers for Medicare & Medicaid Services data for patients of all ages who initiate maintenance dialysis or undergo kidney transplantation. The linked USRDS data were complete through December 31, 2020, which was therefore the end of the study period for this analysis. The work presented here was approved as part of the PRESERVE study protocol by the Children's Hospital of Philadelphia institutional review board, which serves as the central institutional review board for PRESERVE. This study is reported

Table 1. Renin-Angiotensin-Aldosterone System Inhibition (RAASi) vs Calcium Channel Blockade (CCB) to Preserve Kidney Function in Children and Adolescents With Chronic Kidney Disease

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	Aged 2.0-20.9 y at enrollment Chronic kidney disease stage 2-4 with eGFR between 15-89 mL/min/1.73 m^2 at enrollment (baseline) Elevated blood pressure determined by clinic systolic blood pressure of >90th percentile or clinician diagnosis of hypertension (baseline) No exposure to RAASi (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) or CCB in prior 547 d No renal artery stenosis No prior kidney transplant No prior chronic dialysis No pregnancy within a period of 280 d prior to baseline No prescription for both RAASi and CCB on the baseline date No cancer diagnosis	Same as target trial except: GFR is estimated (eGFR) using height and creatinine and computed using the CKiD study under 25 (U25) eGFR calculation Chronic kidney disease stage is determined by two eGFRs <90 mL/min/1.73 m^2 separated by 90 d with no intervening eGFR≥90 mL/min/1.73 m^2 The eGFR value between 15-89 mL/min/1.73 m^2 can be 180 d before or after baseline Elevated blood pressure determined by a clinic systolic blood pressure of >90th percentile or hypertension identified with diagnosis codes Kidney transplant and chronic dialysis used data linked from the United States Renal Data System No prescription for multiple antihypertensive medication ingredients No evidence for cancer (multiple cancer diagnoses or ≥1 cancer diagnosis and ≥1 chemotherapy exposure)
Baseline date	Day that a RAASi (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker) or CCB is first prescribed	Same as target trial
Treatment strategies	Prescribe RAASi Prescribe CCB For each of the 2 strategies, allow the clinician to choose the specific ingredient within the therapeutic class	Same as target trial
Treatment assignment	Patients are randomly assigned to a strategy at baseline within strata defined by etiology of chronic disease, either glomerular or nonglomerular disorder	Balancing of measured confounders via propensity score weighting
Outcomes	Primary outcome: kidney replacement therapy, either maintenance dialysis or kidney transplant Secondary outcomes: Composite outcome that is positive when any of the following occurs: kidney replacement therapy, 50% decline in eGFR from baseline, or eGFR <15 mL/min/1.73 m^2 Adverse events (see list of study variables)	Same as target trial, except data from the United States Renal Data System will be used to identify chronic dialysis and kidney transplant
Follow-up	For each patient, follow-up starts on the baseline day and ends on the day of the outcome of interest, death, 730 d (2 y) from the baseline day, or the end of the study period, whichever happens first	Same as target trial
Causal contrasts	Intention-to-treat effect As-treated effect	Same as target trial Sensitivity analysis excluding patients exposed to the other comparator agent within 90 d
Statistical analysis	Primary: hazard ratios Subgroup analyses by chronic kidney disease etiology	Same as target trial except with propensity score stratification to estimate adjusted hazard ratios

Abbreviations: CKiD, Chronic Kidney Disease in Children; eGFR, estimated glomerular filtration rate.

in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Design

We applied a target trial emulation approach, first specifying the protocol of a hypothesized pragmatic, active comparator randomized trial and then using observational methods and real-world data to emulate the trial.[23] **Table 1** summarizes the specification of the hypothesized trial and the emulated target trial. Detailed variable definitions are provided in eTable 2 in Supplement 1 with links to their respective code sets in the publicly available repository for PRESERVE. Patients were identified from the PRESERVE cohort based on the following eligibility criteria: at least 1 elevated BP measurement (systolic BP >90th percentile for age, sex, and height) or *International Classification of Diseases, Ninth Revision* (*ICD-9*) or *Tenth Revision* (*ICD-10*)-based diagnosis of hypertension or elevated BP during the study period, age 2.0 to 20.9 years at initiation of treatment with RAASi or CCB (baseline) and eGFR 15 to 89 mL/min/1.73 m^2 (CKD stage 2-4) within 180 days of baseline. BP values were only included for outpatient encounters (not inpatient or emergency department), and if multiple BP measurements were recorded on the same day, the average was used.

Patients were excluded if they met any of the following criteria: exposure to an antihypertensive drug (RAASi, CCB, or β blocker) in the 547 days (18 months) prior to baseline (to ensure new users), a diagnosis of renal artery stenosis at any time during the study period, kidney replacement therapy (maintenance dialysis and/or kidney transplant) prior to baseline, a pregnancy-related diagnosis at baseline or 280 days prior,

Table 2. Baseline Characteristics of Children and Adolescents With Chronic Kidney Disease Who Initiated Renin-Angiotensin-Aldosterone System Inhibition (RAASi) or Calcium Channel Blockade (CCB), 2009-2020

Characteristic	No. (%)			Standardized mean difference
	Overall (N = 2762)	Calcium channel blocker group (n = 1005)	Renin-angiotensin-aldosterone system inhibitor group (n = 1757)	
Age at baseline, median (IQR), y	12.9 (8.9-15.4)	12.6 (8.4-15.3)	13.1 (9.2-15.5)	0.10
Sex				
Female	1365 (49.4)	505 (50.2)	860 (48.9)	0.03
Male	1397 (50.6)	500 (49.8)	897 (51.1)	
Race and ethnicity[a]				
American Indian or Alaska Native, non-Hispanic	<11	<11	<11	0.12
Asian, non-Hispanic	101 (3.7)	40 (4.0)	61 (3.5)	
Black or African American, non-Hispanic	682 (24.7)	245 (24.4)	437 (24.9)	
Hispanic	491 (17.8)	185 (18.4)	306 (17.4)	
Multiple race, non-Hispanic	51 (1.8)	22 (2.2)	29 (1.7)	
Native Hawaiian or Other Pacific Islander, non-Hispanic	<15	<11	<11	
White, non-Hispanic	1281 (46.4)	457 (45.5)	824 (46.9)	
Other (unspecified)/unknown, non-Hispanic	133 (4.8)	47 (4.7)	86 (4.9)	
Insurance payer at baseline				
Medicaid	667 (24.1)	216 (21.5)	451 (25.6)	0.12
Commercial	508 (18.4)	177 (17.6)	331 (18.8)	
Other/unknown	1587 (57.5)	612 (60.9)	975 (55.5)	
Obesity at baseline	771 (27.9)	249 (24.8)	522 (29.7)	0.11
Short stature at baseline	381 (13.8)	148 (14.7)	233 (13.3)	0.04
Proteinuria at baseline				
Negative	1126 (40.8)	417 (41.5)	709 (40.4)	0.007
Positive	948 (34.3)	354 (35.2)	594 (33.8)	
Missing	688 (24.9)	234 (23.3)	454 (25.8)	
Chronic disease status[b]				
Noncomplex chronic disease	119 (4.3)	33 (3.3)	86 (4.9)	0.16
Complex chronic disease	1309 (47.4)	524 (52.1)	785 (44.7)	
Without chronic disease	1334 (48.3)	448 (44.6)	886 (50.4)	
Chronic kidney disease etiology				
Glomerular disease	530 (19.2)	167 (16.6)	363 (20.7)	0.1
Nonglomerular disease	2232 (80.8)	838 (83.4)	1394 (79.3)	
Adjusted clinical group quantile, %				
<50	1522 (55.1)	395 (39.3)	1127 (64.1)	0.59
50-75	688 (24.9)	281 (28.0)	407 (23.2)	
75-85	224 (8.1)	111 (11.0)	113 (6.4)	
85-95	243 (8.8)	164 (16.3)	79 (4.5)	
≥95	85 (3.1)	54 (5.4)	31 (1.8)	

[a] Race and ethnicity data were collected via the electronic health record and reported to evaluate representativeness and balance between comparator arms.

[b] Per the Pediatric Medical Complexity Algorithm; kidney diagnoses are excluded from chronic disease status.

exposure to more than 1 antihypertensive medication ingredient at baseline (ie, combination therapy), or malignancy at any time during the study period. eTable 3 in Supplement 1 provides the attrition table for the target trial emulation cohort, starting with the full PRESERVE study cohort.

Outcomes

The primary outcome was kidney replacement therapy (maintenance dialysis or kidney transplant from USRDS) within 730 days (2 years) of baseline. We also evaluated a secondary kidney function decline outcome that was a composite of kidney replacement therapy, 50% decline in eGFR from baseline, or eGFR<15 mL/min/1.73 m^2. Other secondary outcomes included a priori selected adverse events as well as BP control. The latter was defined by the percent of time for which the systolic BP was above the calculated 90th percentile for age, sex, and height based on outpatient encounters. For each patient, follow-up started with the baseline date (date RAASi or CCB was first prescribed) and ended with the earliest of: occurrence of the outcome of interest if applicable, death (from

Table 3. Primary and Secondary Outcomes With Renin-Angiotensin-Aldosterone System Inhibition (RAASi) vs Calcium Channel Blockade (CCB), 2009-2020

Outcome	No. (%)		HR (95% CI)	
	CCB	RAASi	RAASi vs CCB, unadjusted	RAASi vs CCB, adjusted
Primary outcome: kidney replacement therapy[a]	91 (9.1)	57 (3.2)	0.33 (0.24-0.46)	0.58 (0.40-0.84)
Maintenance dialysis	72 (7.2)	<50 (<2.8)[b]	NA	NA
Kidney transplant	19 (1.9)	<11 (<0.6)[b]	NA	NA
Secondary composite kidney function decline outcome[a]	230 (22.8)	161 (9.2)	0.35 (0.28-0.42)	0.67 (0.53-0.83)
Maintenance dialysis	<11 (<1.1)[b]	<11 (<0.6)[b]	NA	NA
Kidney transplant	<15 (<1.5)[b]	<11 (<0.6)[b]	NA	NA
50% eGFR decline	123 (12.2)	100 (5.7)	NA	NA
eGFR<15 mL/min/1.73 m^2	97 (9.7)	55 (3.1)	NA	NA
Adverse events				
Anemia	295 (29.4)	267 (15.2)	0.44 (0.37-0.51)	0.74 (0.62-0.89)
Cough	137 (13.6)	160 (9.1)	0.59 (0.47-0.74)	0.77 (0.60-0.99)
Dizziness	34 (3.4)	74 (4.2)	1.20 (0.80-1.80)	1.30 (0.84-2.01)
Edema	127 (12.6)	153 (8.7)	0.63 (0.50-0.80)	0.76 (0.59-0.99)
Elevated liver enzymes	147 (14.6)	127 (7.2)	0.45 (0.35-0.56)	0.71 (0.54-0.92)
Fatigue	112 (11.1)	131 (7.5)	0.60 (0.46-0.77)	0.87 (0.66-1.15)
Gastrointestinal symptoms	345 (34.3)	476 (27.1)	0.67 (0.59-0.77)	0.89 (0.77-1.04)
Hair loss	15 (1.5)	36 (2)	1.20 (0.66-2.16)	1.94 (1.02-3.69)
Hyperkalemia	238 (23.7)	347 (19.7)	0.75 (0.64-0.89)	1.07 (0.89-1.29)
Hypotension	40 (4)	76 (4.3)	1.00 (0.68-1.46)	1.55 (1.03-2.35)
Leukocytopenia	240 (23.9)	233 (13.3)	0.48 (0.40-0.57)	0.76 (0.62-0.93)
Nocturnal enuresis	32 (3.2)	69 (3.9)	1.14 (0.76-1.73)	1.06 (0.67-1.67)
Pericarditis	<11[b]	<15 (<0.9)[b]	0.60 (0.26-1.42)	0.93 (0.36-2.43)
Pyelonephritis	53 (5.3)	59 (3.4)	0.60 (0.42-0.87)	0.73 (0.48-1.09)
Respiratory infections	174 (17.3)	219 (12.5)	0.64 (0.52-0.78)	0.83 (0.67-1.03)
Stomatitis	50 (5)	28 (1.6)	0.27 (0.17-0.43)	0.41 (0.25-0.67)
Tonsillitis	13 (1.3)	14 (0.8)	0.57 (0.27-1.21)	0.50 (0.22-1.15)
Urinary tract infection	123 (12.2)	206 (11.7)	0.87 (0.70-1.09)	0.97 (0.76-1.24)
Any adverse event	725 (72.1)	1062 (60.4)	0.62 (0.57-0.69)	0.82 (0.74-0.90)

Abbreviations: eGFR, estimated glomerular filtration rate; NA, not applicable.

[a] Counts represent the earliest component event of the outcome and are not mutually exclusive (ie, if events occurred on the same date).

[b] Exact counts are suppressed due to small cell sizes.

USRDS), 730 days of follow-up, end of the study period (December 31, 2020), or the final encounter date prior to a 24-month gap between consecutive encounters (ie, loss to follow-up). eTable 4 in Supplement 1 provides expanded details on study time anchors.

Statistical Analysis

Propensity score stratification was used to balance populations on variables at initiation of RAASi or CCB, including sociodemographic factors (age, sex, race, ethnicity, payer), health care institution, calendar year, CKD etiology (glomerular vs nonglomerular), proteinuria, CKD stage, obesity, health care use, medications, health care utilization risk score (Johns Hopkins Adjusted Clinical Group system),[24] and BP control. BP control was quantified for each patient as the percentage of time for which the systolic BP was above their calculated 90th percentile in the year prior to baseline (based on outpatient encounters). eTable 5 in Supplement 1 provides further information about covariates used for propensity score stratification. Love plots of absolute standardized mean differences and density plots of preference score distributions were used to assess covariate balance. Cox proportional hazards regression with propensity score stratification was used to estimate adjusted hazard ratios (HRs) for outcomes in intention-to-treat analysis. Adjusted analyses also compared systolic BP control (percentage of time above the 90th percentile) within 2 years of follow-up for RAASi and CCB as well as a priori selected adverse effects.

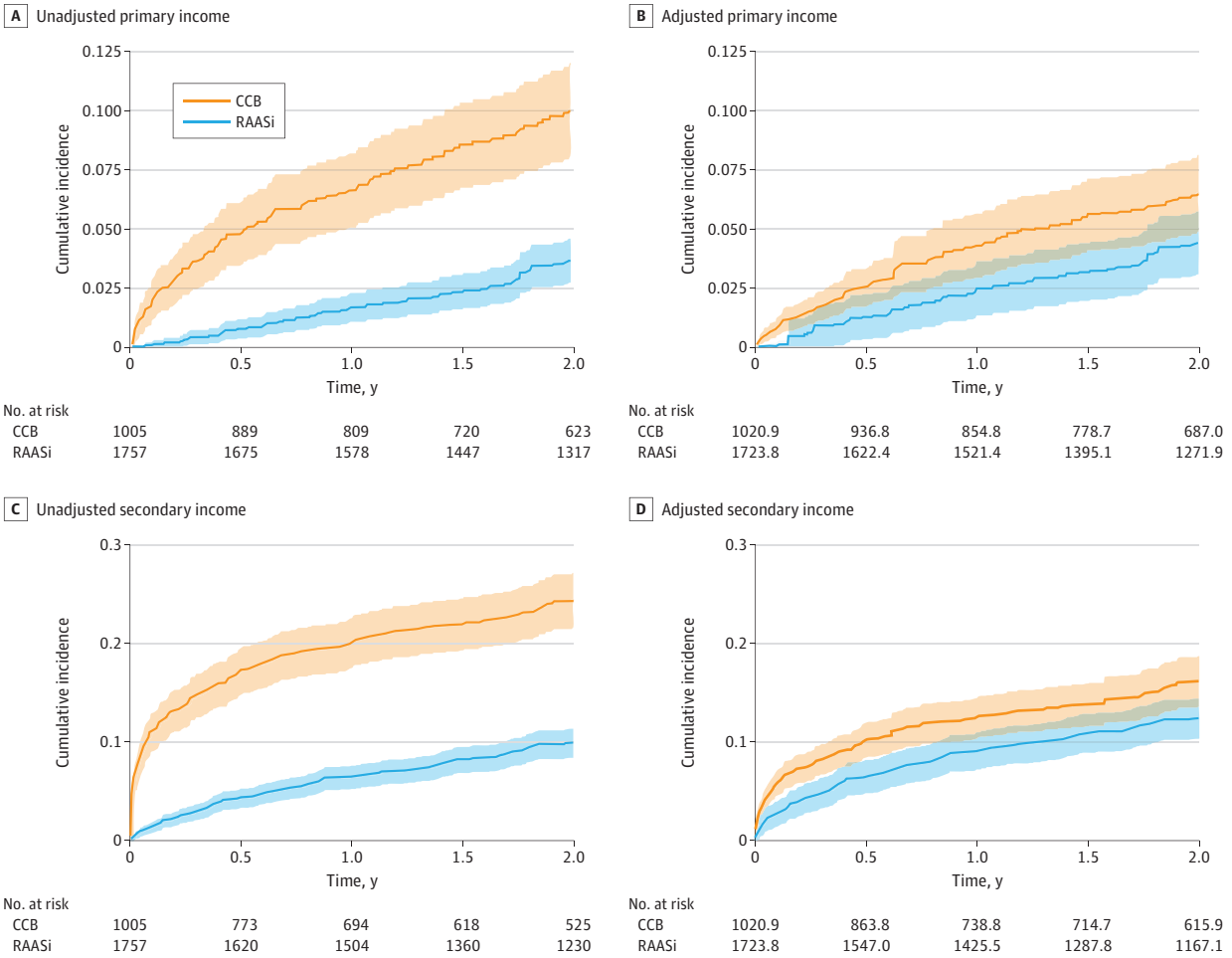
We examined treatment effects by subgroups of glomerular vs nonglomerular CKD etiology by allowing propensity scores and Cox models estimating the effect of RAASi vs CCB to be calculated within each etiology. In a sensitivity analysis, we removed patients who were initiated on one comparator agent but were exposed to the other comparator agent within 90 days (ie, a patient initiated on RAASi with an exposure to CCB within 90 days, and vice versa). The R statistical environment version 4.4.0 (R Core Team) was used to perform all statistical analyses. Data analysis was completed in July 2025.

Results

Baseline Characteristics

The final study population included 2762 children and adolescents, 1757 of whom initiated RAASi (median [IQR] age 13.1 [9.2-15.5] years, 860 [48.9%] female and 897 [51.1%] male) and 1005 of whom initiated CCB (median [IQR] age, 12.6 [8.4-

Figure 1. Cumulative Incidence Curves for the Primary and Secondary Kidney Function Decline Outcomes



The figure compares initiation of renin-angiotensin-aldosterone system inhibition (RAASi) vs calcium channel blockade (CCB). Panels A and B show the primary outcome of kidney replacement therapy. Panels C and D show the secondary composite outcome of kidney replacement therapy, estimated glomerular filtration rate <15 mL/min/1.73 m^2, or 50% decline in estimated glomerular filtration rate. Shaded areas represent the 95% CIs around each point estimate.

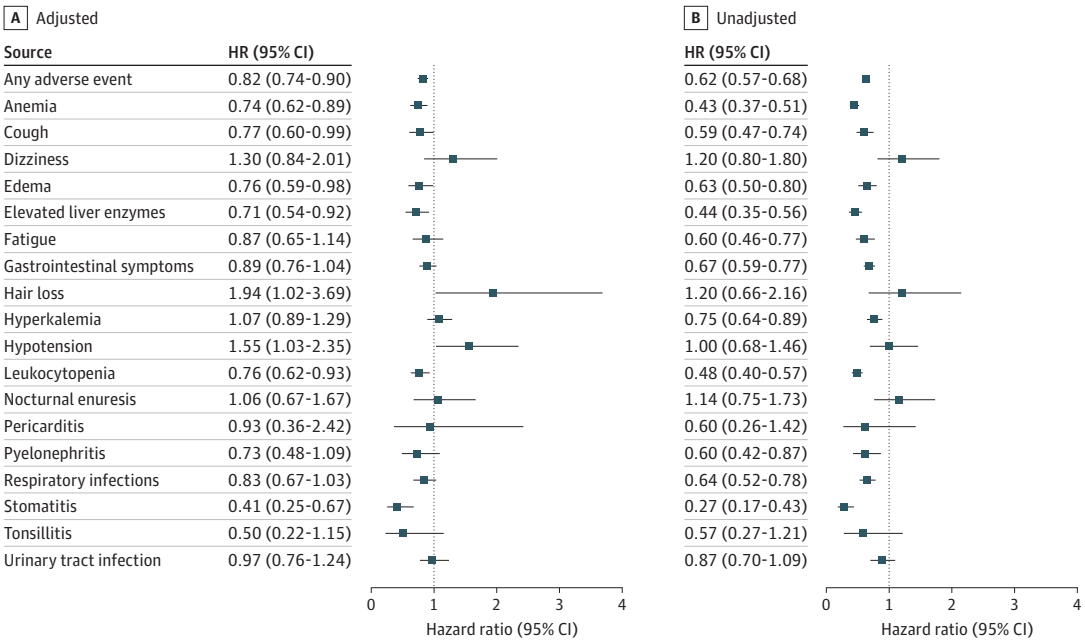
15.3] years; 505 [50.2%] female and 500 [49.8%] male). Most of the RAASi group received lisinopril (1114 [63.4%]); 427 (24.3%) received enalapril, 178 (10.1%) received losartan, and 38 (2.2%) received other agents, including benazepril, captopril, ramipril, candesartan, olmesartan, telmisartan, and valsartan (<1% each). Most of the CCB group received amlodipine (962 [95.7%]); 43 (4.3%) received extended-release nifedipine or isradipine. **Table 2** shows the baseline characteristics of the study sample. The standardized mean differences highlight that the CCB group had more advanced baseline CKD severity and greater medical complexity as assessed by both the Pediatric Medical Complexity Algorithm (which stratifies children into 3 levels of chronic disease status)[25] and Johns Hopkins Adjusted Clinical Group system (which provides a summary measure of an individual's morbidity burden based on their age, sex, and pattern of diagnoses). The Love plot in eFigure 1 in Supplement 1 demonstrates the balance of covariates between treatment groups after propensity score stratification, including BP control, proteinuria, CKD etiology and stage, and medical complexity, with all absolute standardized mean differences less than 0.1.

Kidney Function Decline Outcomes

Table 3 shows the frequencies and unadjusted and adjusted HRs for study outcomes at 2 years. The primary kidney replacement therapy end point was observed in 57 patients per thousand person-years in the CCB group and 18 patients per thousand person-years in the RAASi group. The secondary composite end point was observed in 160 and 54 patients per thousand person-years in the CCB and RAASi groups, respectively, with 88 in the CCB group and 34 in the RAASi group experiencing a 50% decline in eGFR from baseline and 69 of those in the CCB group and 18 in the RAASi group per thousand person-years reaching an eGFR less than 15 mL/min/1.73 m^2. There were 0 USRDS-reported deaths in the full cohort within the 2-year follow-up period.

Figure 1 shows unadjusted and adjusted cumulative incidence curves for the primary and secondary outcomes by treat-

Figure 2. Forest Plot Comparison of A Priori Selected Adverse Effects



The figure shows adverse effects among children with chronic kidney disease and elevated blood pressure treated with renin-angiotensin-aldosterone system inhibition (RAASi) vs calcium channel blockade (CCB).

ment group. There were notable differences between the curves for both outcomes, particularly the composite kidney function decline outcome. RAASi was associated with reduced risk of both kidney replacement therapy (HR, 0.33; 95% CI, 0.24-0.46; $P < .001$) and the secondary composite outcome (HR, 0.35; 95% CI, 0.28-0.42) in unadjusted Cox regression analyses. In Cox regressions stratified by propensity score quintile, RAASi was associated with reduced risk of both kidney replacement therapy (adjusted HR, 0.58; 95% CI, 0.40-0.84; $P = .004$) and the secondary composite outcome (adjusted HR, 0.67; 95% CI, 0.53-0.83). E-values were 3.7 for the primary outcome and 3.5 for the secondary composite outcome before propensity score adjustment; after adjustment, the E-values were 2.3 and 2.0 for the primary and secondary outcomes, respectively.

BP Control and Adverse Effects

BP control was better with RAASi than CCB in adjusted analyses: 29% vs 39% of time above the 90th percentile for systolic BP (mean difference, -11%; 95% CI, −15 to −8) (eTable 6 in Supplement 1). Table 3 and **Figure 2** show the unadjusted and adjusted HRs from stratified Cox models for a priori selected adverse effects. RAASi was associated with reduced risk of any adverse effect as well as lower risk of edema, cytopenias, and abnormal liver enzymes but a higher risk of hypotension and hair loss.

Subgroup Analysis by CKD Etiology

For propensity score weighting within the nonglomerular subgroup, baseline covariates were well balanced (eFigure 2 in Supplement 1). However, in the smaller glomerular subgroup, we were unable to achieve adequate statistical equipoise or covariate balance (eFigure 3 in Supplement 1), so results for this subgroup analysis should be considered exploratory and interpreted with caution. The magnitude of the unadjusted HRs for the primary outcome was highly similar for glomerular and nonglomerular disease: 0.35 (95% CI, 0.22-0.55) and 0.25 (95% CI, 0.15-0.40), respectively. In adjusted analyses, the protective effect of RAASi remained in the nonglomerular subgroup and was consistent with that observed in the full cohort (adjusted HR, 0.53; 95% CI, 0.32-0.88) but was attenuated in the glomerular subgroup: 0.94 (95% CI, 0.56-1.57).

For the secondary outcome, the unadjusted HRs were also similar for glomerular and nonglomerular disease: 0.43 (95% CI, 0.30-0.62) and 0.30 (95% CI, 0.23-0.38), respectively. In adjusted analysis, the protective effect of RAASi again persisted in the nonglomerular cohort (adjusted HR, 0.62; 95% CI, 0.41-0.81) but not in the glomerular cohort (adjusted HR, 1.17; 95% CI, 0.80-1.73).

Sensitivity Analyses

In a sensitivity analysis that removed patients who were initiated on one comparator agent but were exposed to the other comparator agent within 90 days, RAASi was associated with reduced risk of both kidney replacement therapy (adjusted HR, 0.55; 95% CI, 0.36-0.83; $P = .004$) and the secondary composite outcome (adjusted HR, 0.63; 95% CI, 0.49-0.81) in adjusted analyses. BP control was better with RAASi than CCB (28% vs 41% of time above the 90th percentile) in adjusted analyses (mean difference, −14%, 95% CI, −18 to −10) (eTable 7 in Supplement 1).

Discussion

To date, to our knowledge, there have been no comparative trials of antihypertensive medications in pediatric CKD. In this target trial emulation analysis of multi-institutional real-world electronic health record data from the PRESERVE cohort of children with CKD, RAASi was associated with lower risk of CKD progression, better BP control and a favorable adverse effect profile compared to CCB. In the absence of randomized clinical trial data, the target trial framework, unprecedented size of the study sample, unselected study population, and real-world setting of this study provide robust evidence in support of first-line use of RAASi. This is consistent with existing clinical practice guidelines and prior observational data from CKiD and uniquely addresses an evidence gap for nonglomerular CKD, which represents most of the pediatric CKD population.

The PRESERVE study data resource and results of this study exemplify the capacity of PCORnet to address evidence gaps in rare disease. An advantage of real-world data are that it reflects clinical practice, and the breadth of longitudinal data capture provides unprecedented opportunities for comparative effectiveness research using more robust causal inference methods. Comparison of baseline characteristics of the comparator treatment groups highlighted the greater medical complexity of the CCB group, underscoring the importance of accounting for this in the statistical analysis. Propensity score stratification achieved excellent balance of covariates and statistical equipoise, accounting for practice pattern variation across health care institutions and key potential confounders, such as baseline BP control, proteinuria, CKD severity, CKD etiology, and medical complexity. Both unadjusted and adjusted intention-to-treat analyses demonstrated lower risk of progression to the primary outcome of kidney replacement therapy and the secondary composite kidney function decline outcome with RAASi. The lower risk of progression with RAASi was confirmed in a sensitivity analysis designed to account for early switching or addition of the comparator therapeutic class.

The replication of findings from the main analysis within the nonglomerular subgroup is a particularly important contribution. The lack of consensus on first-line antihypertensive therapy in pediatric CKD applies predominantly to those with nonglomerular and nonproteinuric CKD, which represents most of pediatric CKD, as previously demonstrated by CKiD and confirmed by PRESERVE. Indeed, because of its antiproteinuric effect, RAASi is a mainstay of treatment for proteinuric glomerular disease even in the absence of elevated BP. In adults, RAASi is standard of care for mild to moderate CKD based on a large body of clinical trial data supporting its renoprotective and cardioprotective effects independent of BP lowering.[26-31] Most of these trials focused on proteinuric CKD, but an analysis of adults with nonproteinuric CKD in the Chronic Renal Insufficiency Cohort[32] found that, after accounting for time-updated use, RAASi was associated with lower risk of cardiovascular events and mortality compared to other antihypertensive agents.

Also consistent with existing observational data, RAASi was associated with better BP control compared to CCB, assessed using the time above target BP measure. Among 202 children in CKID with hypertension who were on antihypertensive therapy at baseline, RAASi use was independently associated with controlled BP (<90th percentile) compared to CCB and other classes of antihypertensive agents with a prevalence ratio of 0.72 (0.52-0.99).[4] In longitudinal analysis[33] of 754 CKiD participants with hypertension or BP at the 90th percentile or higher, any BP less than the 90th percentile was associated with decreased risk of progression to kidney replacement therapy or 30% decline in eGFR.

Limitations

Our study has several limitations. The nonrandomized observational study design used has inherent limitations for causal inference. Target trial emulation using propensity score stratification enabled us to balance many measured covariates that could affect assignment to the comparator groups and outcomes and to verify balance of these covariates, which represents an important advance over previously published observational data. Although we selected and evaluated a comprehensive list of covariates based on existing literature and clinician input, it is possible that unmeasured health status variables could have accounted for the observed differences between the RAASi and CCB groups. After adjustment, E-values, which are the estimated risk ratios for confounding factors associated with both predictor and outcome, [34] were 2.3 and 2.0 for the primary and secondary outcomes, respectively. These large E-values suggest that considerable unmeasured confounding would need to be present to explain away our effect estimates. PRESERVE leveraged electronic health record data and therefore, the comparator groups represent medications prescribed but not necessarily administered. Exact dosing was not ascertained in our data. Adverse effect outcomes ascertained through diagnosis codes were likely subject to misclassification and insensitivity. PRESERVE analyses did not incorporate degrees of quantitative proteinuria (eg, urine protein/creatinine or albumin/creatinine ratios). Urine dipstick results were prioritized over quantitative measures because these results were more consistently available for the cohort.

Conclusions

The size of the PRESERVE cohort enabled this target trial emulation study comparing the effectiveness of RAASi vs CCB, the most widely used first-line antihypertensive treatments. Over 2 years of follow-up, RAASi was more effective in reducing the risk of CKD progression and was associated with better BP control. These findings support first-line use of RAASi for antihypertensive therapy in children with CKD.

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