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Advancing Healthcare Innovation: Multidisciplinary Collaboration and Translational Research

# A systematic review of efficacy and safety for calcium channel blockers in the treatment of albuminuria in patients with diabetes and hypertension

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**Abstract** In individuals with diabetes mellitus (DM) and hypertension, renin-angiotensin system (RAS) inhibitors are advised for the therapy of albuminuria, although there is limited agreement on other treatments. Calcium channel blockers (CCB) are often used for hypertension patients, their effectiveness in those with albuminuria remains uncertain. Patients with diabetes, hypertension and nephropathy were evaluated for their response to CCB and inhibitors of the RAS to reduce albuminuria. We measured albuminuria before and after the intervention and compared CCB to RAS inhibitors by looking through records on MEDLINE, Embase and CENTRAL. Randomized controlled adult trials were identified using abstract screening were performed separately. 20 papers were selected from 800 records using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We evaluated data from 2,114 participants in the experiment who had the equivalent of pre-hypertension and diabetic mellitus of ≥31 days/mg of urine albumin excretion. The standardized mean difference in reducing albuminuria was 0.443. When analyzing the treatment impact on blood pressure, the research showed no significant difference between RAS inhibitors and CCB in terms of indications of renal function. RAS inhibitors could be superior to CCB in reducing albuminuria in hypertensive and diabetic nephropathy.

**Keywords:** Calcium Channel Blockers (CCB), albuminuria, diabetes, hypertension and Cardiovascular Diseases (CVD), Blood Pressure (BP)

## 1. Introduction

Diabetes mellitus (DM) is a prevalent metabolic disease. Due to diabetic nephropathy (DN), which causes irreversible proteinuria and kidney damage, people with diabetes have a high prevalence of advanced kidney disease. DN is followed by a gradual decline in renal function and a rise in blood pressure (BP) (Liang et al 2021). Lowering albuminuria can reduce the incidence of cardiovascular disease (CVD) and renal outcomes. The risk of CVD and renal catastrophes is elevated due to the increased incidence of hypertension in diabetic individuals (Fici et al 2020). One of the effects of diabetes mellitus is diabetic kidney disease (DKD), sometimes called nephropathy in medical circles. Glomerular hyperfiltration is the feature of the first stage of DKD, followed by the development of microalbuminuria, overt Albuminuria and nephritic syndrome. People with Chronic Kidney Disease (CKD) are less likely to develop nephritic syndrome as a result of advancements in diabetes management. (Uchida et al 2022). There is a dearth of knowledge on hypertension and practical treatment alternatives. People usually have a number of cardiovascular risk factors and their blood pressure varies depending on the season (Ram 2022). CVD are a common complication of hypertension, a chronic medical condition. Hypertension is a major contributor to cardiovascular disease therefore studies focusing on preventative measures are required. Despite the advent of various medicines for the management of hypertension, it remains a prevalent risk factor for CVD (Fu et al 2021).

CCBs are utilized in hypertension because of their efficiency, cost efficiency and safety. Amlodipine, a member of the CCB dihydropyridine family, has an imposing pharmacokinetic and pharmacodynamic profile (Srinath 2020). It was thought that the health benefits of antihypertensive drugs were attributable to their ability of reducing blood pressure (BP), but recent research has pointed to additional, less obvious processes at work (Jeonget al 2021). Management of patients with CKD and hypertension, CVD while widespread, is notoriously difficult to treat. Antihypertensive therapy is necessary to reduce the risk of cardiovascular events and to postpone the progression of CKD in patients with these diseases (Syamala 2023).

## 2. Methods

The purpose of this study is to investigate various scientific publications published on Scopus that are connected to the growth of employee empowerment. Furthermore, the review article in this study is focused on the notion of employee empowerment surveys, as described by the following questions: (1) What topics are related to employee empowerment? (2) What type of mapping is used in employee empowerment topics? (3) What concepts are used in employee empowerment learning? These questions are described based on the study topic, framework, and previous research findings indexed in the Scopus database.

Moreover, the articles reviewed in this study went through stages from (1) searching for items, (2) mapping topics, (3) analysing problems, and (4) creating employee empowerment concepts. Articles are searched through the following stages. First, identify the theme. This was done using the Scopus database. Furthermore, at this stage, the keyword "employee empowerment" was included in the article search field on Scopus, and the publication year was limited to between 2018 and 2022. The search returned 391 views. Accessible publications, visualizations, and bibliometric mappings were performed using VOSviewer and bibliometric software. The study analysed data collected through VOSviewer. This process was carried out to obtain data clusters and visualize the network of the research theme.

*2.1. Study participants*

The inclusion criterion was as follows: period >20 years, chronic 24-hour proteinuria *>2000* mg; this is compact to >500 mg after the initial tolerant was included and albuminuria at *>300* mg, BP of *>131/81* mm Hg while utilizing steady antihypertensive therapy that contains a RAS-blocker. There was no demand for continued RAS-blocking treatment**.** Plasma (p-) potassium, diabetic nephropathy and creatinine clearance below < 20 mL/min were ruled out. Millimoles-per-deciliter (>5.0 mEq/l), aldosterone antagonist allergy, chronic liver failure, constant use of CYP3A4-inhibitors, lithium, or immunosuppressive medications (such as steroids), incapacitating mental problems, other non-renal severe disease, failure to use efficient contraception by women of reproductive capacity and pregnancy or breast-feeding. The two departments' outpatient clinics served as a recruitment and monitoring hub for study participants.

*2.2. Study protocol*

Eplerenone treatment began with a 26-mg oral quantity given once a day as an adjunct to preexisting medication. The target BP was *<120/90* mm Hg. In the event of symptomatic hypotension, non-RAS-blocking antihypertensive drug dose reductions were prioritized, whereas, in the event of BP over the goal, non-RAS-blocking agent additions were made. Albuminuria, calculated from single 24-hour urine samples obtained at each potassium, phosphorus, fractional excretion of albumin, creatinine and BP clearance were the primary outcome variables (Coresh et al 2019).

*2.3. Data assembling, synthesis and evaluation*

To prevent publishing the same work again, we compared cited works based on their titles, authors, geographical origins and sample sizes. When research had several reports, we picked the one with the most up-to-date results; further data on methodology and baseline characteristics were obtained from the published works. We obtained the complete papers from the abstracts that met our first criteria and re-evaluated them using the PRISMA checklist. When possible, we used the measurement tool in Adobe Acrobat Reader, as outlined in the additional materials, to extract the data from the readily accessible visuals. UAE was expressed as mg/24 h when published in either $\mu$g/min or mg/24 h. To get the serum creatinine concentration in milligrams per deciliter (mg/dL), we multiplied the $\mu$mol/DL.

Graphic depictions of the UAE were employed in several researches. The geometrical averages and 95% confidence intervals (CIs) and the geometrical averages were converted into their corresponding measures on the logarithmic scale using the provided equations. We determined the SD by averaging the SDs from research with comparable starting populations, periods, dimension scales and methods, regardless of whether information was given as geometric methods and acceptance factors, inter-quartile ranges or values. We used the confidence interval to determine the SD when the mean was the only information provided.

The information is presented as a mean ± SD. There was a distinct pooling of papers that reported geometric means for the UAE that reported arithmetic metric standards. The Model for unpredictability can be used to combine the data and significance was defined as a 2-sided P value of less than p<.05; the findings are shown as the standardized mean difference (SMD) with 95% confidence intervals (CI). Chi-square tests, the gold standard for measuring differences, were performed. P≤ .1 was considered significant for indicating heterogeneity. Possible causes of heterogeneity were examined using prespecified subgroup analyses categorized by prevalence of diabetes baseline albuminuria, as well as studies by trial arm, number of participants, BP management and method of quantifying UAE. The potential for selection bias in the randomized and concealed assignments was evaluated. Partial reporting of findings for mortality bias, selective distribution of results for particular reporting bias and blinding the research personnel for accomplishment bias were considered. As a secondary factor, we looked at whether or not the study's financing came from the pharmaceutical sector to see whether it had a role in the results. When

ten or less papers were included in a meta-analysis, we utilized funnel plots to look for signs of publication bias and we conducted a test to see whether there was correlation between sample size and effect size.

*2.4. Statistical analyses*

At baseline, we projected that individuals would have an unimpeded effective renal plasma flow (ERPF) of 445 min/ml. It was projected that the ERPF would increase by 48 min/ml with DRI and 29mL/min with ACEi, the standard deviation in the ERPF response was estimated to be 18 min/ml and a sample size calculation was performed. To acquire 91% ability for identifying an essential rise in ERPF during ACEi and DRI (μ=0.04). They offered compensated T-tests since this study had no major impact on the outcomes. Renal hemodynamics and blood pressure measurements were almost equal across the baseline and wash-out periods. Hence, baseline data are shown. If the data are normally distributed, we offer a mean and SEM, we provide a geometric mean with 95% CI.

**3. Results**

*3.1. Study choosing, defining and evaluating*

There were 800 records from our searches of MEDLINE, Embassy and CENTRAL. After the screening process for evaluation, 260 full-text publications were chosen and obtained. We selected 20 clinical trial reports that met the selection standards, as shown in Figure 1.

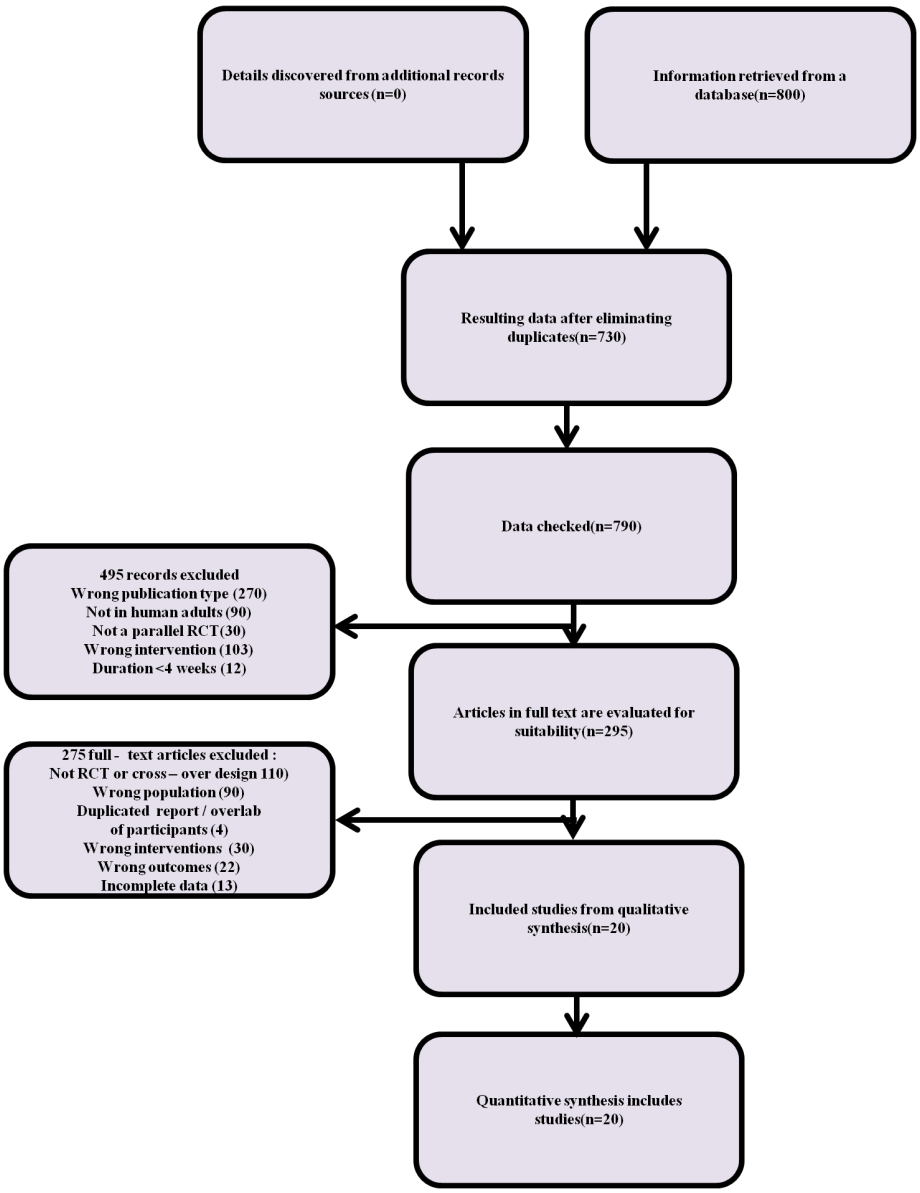


**Figure 1** Research selection procedure based on PRISMA.

Eight papers were excluded because they included proteinuria; two were excluded since the initial albuminuria levels in those investigations were under the cutoff point for this analysis (Khan et al 2023) and one was left out because their baseline BP wasn't in the hypertensive range (Loucks et al 2019). In three investigations, we could not contact the authors for clarification; therefore, we extrapolated the results from the data (Ng et al 2021). The investigated research's average age was 56 decades (array 38-63.1 decades) and body weight indices mean 27.5 $m^2$ per kg (array 22.8-31.1 $m^2$ per kg). People's BP was relatively normal, with diastolic readings of 93.6 mmHg (array, 51.0-104.5 mmHg) and systolic readings of 160.0 mmHg (array, 141.7-184.1 mmHg) (Zhao et al 2023). The average difference in BP decrease across groups throughout trials was 0.044% (95% CI: 0.056-0.142; P=.388; $I^2$=1.94%), except for study 31.4 (Brady et al 2021). Eight studies were able to reduce post-intervention BP to below 140/90 mmHg and two were able to reduce it to below 130/90 mmHg in both groups (Lu et al 2021).

Among research that satisfied the inclusion criteria, the median length of diabetes-related illness was 9.3 points (range 4.9-32.2 points) and the mean glycosylated hemoglobin was 7.3% (array 6.9%-9.7%) (Cativo et al 2021). Most study covered patients with type-2 diabetes, while five studies included persons with type-1 diabetes and two studies included people with both kinds of diabetes. In contrast, seven studies that used overnight urine samples found a significant difference. The albumin-to-creatinine ratio was determined using three timed urine samples from four probes. Amlodipine was the most studied CCB (ten studies), followed by nitrendipine (4 studies) and nifedipine (5 studies) (Muthamil2020).

*3.2. Quantitative analysis of CCB's impact on Urinary Albumin Excretion (UAE)*

Table 1 shows that during the Eplerenone supplementation treatment period compared to the placebo-controlled phase, albuminuria was decreased by 23% [95% CI: 15, 29], P<0.001. The control period 24-hour mean excretion was 1481 mg [CI: 1194, 1842], whereas the add-on eplerenone period means excretion was 1163 mg [CI: 922, 1469] (Chung et al 2020). There was no evidence that urine albumin excretion was affected by either time or carryover (P=0.3). Thirty-one out of forty individuals saw a decrease in albuminuria. After supplementing with eplerenone for two weeks, there was a significant drop (P=0.003) (Fulton et al 2023). A glomerular disease associated with resistance to aldosterone antagonists, Membranous nephropathy, was seen in three patients (Moroni and Ponticelli 2020). Add-on eplerenone reduced urine albumin excretion in two of these individuals, whereas in the third patient, it had no effect (Brandt-Jacobsen et al 2021). Table 1 shows that throughout the eplerenone treatment period, fractional albumin excretion was decreased (P<0.001). When accounting for the decrease in systolic BP, eplerenone therapy resulted in a 17% [CI: 9, 26] decrease in UAE (P<0.001) (Manolis et al 2019). Albumin excretion was reduced by 19% [CI: 11-28] throughout the therapy period due to reduced creatinine clearance (P=0.0003). The combined effect of BP and creatinine clearance on UAE was 14% [CI: 5, 25], P=0.008. Without these interventions, there was a 25% variance in UAE [CI: 19, 34], P<0.001. Albumin excretion did not change between the treatment and control periods or between visits 2 and 6, as well as no significant carry-over effect was seen (P=0.3) (Kolkhof et al 2021). When the ARB/ACEI dosage per day was ¼ of the maximum dose for the particular medication (n=12), when it was between ½ and ¼ of the maximum amount (n=19) and when it was, ½ high levels of blockage were achieved. Patients receiving mild RAS-blockade tended to respond better to eplerenone than the other groups, though this difference was not significant (Kawanami et al 2021).

**Table 1** Mathematical Average Features of the Research Considered at Baseline.

| Comparison (mg/day) | Treatment (mg/day) | Follow-Up (Month) | Men Age (Yer) | n | Baseline Blood Pressure (mm Hg) | Baseline GFR | Baseline SCr (mg*dL1) | CCB RASI | Baseline Albuminuria | CCB RASI | Post-intervention Albuminuria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Enalapril (5-20) | Nitrendipine (10-40) | 28 | NR | 24 | 153/97 | 66 | NR | 6.47 | 5.65 | 3.47 | 4.08 |
| Lisinopril (20-40) | Nifedipine (20-40) | 7 | 56.4 | 163 | 161/98 | 104 | NR | 6.67 | 6.14 | 6.72 | 7.53 |
| Lisinopril (10-20) | Nisoldipine (20-40) | 49 | 38.1 | 49 | 155/96 | 1.24 | 1.24 | 27.23 | 21,.42 | 20.54 | 23.19v |
| Losartan (25-100) | Amlodipine (2.5-10) | 4 | 61.4 | 88 | 161/95 | 1.22 | 1.22 | 18.37 | 18.14 | 15.94 | 18.344 |
| Enalapril (10-40) | Nifedipine (40-80) | 61 | 58.2 | 103 | 169/94 | 0.03 | 0.03 | 7.02 | 7.10 | 7.49 | 8.24 |

*3.3. The cumulative impact of CCB on Renal Function and BP Markers*

ARB/ACEI did not alter Glomerular filtration compared to CCB (CI, 0.321-0.169; P=.543; SMD 0.076). After accounting for methodological differences across the trials, we found that the effect of CCB and ARB/ACEI on this clinical measure was similar (CI, 0.148-0.216; P=.711; SMD 0.034).

Table 1 shows the significant decreases in systolic and diastolic BP that came from the addition of eplerenone to preexisting BP medication in comparison to the untreated phase (Adachi et al 2019). After two weeks of treatment with eplerenone, systolic BP dropped significantly (P=0.003). There had been a significant change in systolic BP at future visits. After four weeks of eplerenone therapy, the diastolic BP was lowered (P=0.002) and there was a notable distinction (P=0.004) between the treated group's and the untreated group's simultaneous systolic blood pressure (Wilson et al 2022). The final readings of diastolic blood pressure failed to vary among the two time periods. B-Prediction was similar in those with high, low, or moderate baseline RAS blockade. No significant temporal or carryover effects on systolic BP were seen (P=0.9 and P=0.4, respectively) (Arnold et al 2020).

*3.4. Bias potential in the collected research*

The majority of trials were double-masked. Four were open-label and fourteen did not disclose that outcome assessors were blinded. The origin of financing was unknown in 16 investigations (Lanfranconi et al 2023). Table 2 summarizing potential sources of bias are included in the Supplemental Material. The graphic compares the study weights versus the standardized difference in means for the change urine albumin excretion in studies having an arithmetic mean in Figure 2 showed no periodical bias by “Egger's test”, we found that this was the case (P=.2610). Three studies were found to be skewed to the left of the mean using the trim-and-fill approach, nonetheless, this had little impact on the predicted effects (0.512; CI, 0.629 to 0.427) (Tenorio-Pedraza et al 2023).

**Table 2** The Renal and BP Test Results.

| Bias Potential test results | Control | Treatment effect | Eplerenone | P-value |
|---|---|---|---|---|
| | Mean 95 percent CI | Mean difference Mean 95 percent CI | Mean Mean 95 percent CI | |
| Diastolic BP (mmHg) | 86 [82,90] | -5 [-7,-3] | 82 [81,87] | *0.02* |
| Systolic BP (mmHg) | 123 [121,129] | -3 [4,1] | 122 [118,125] | *0.002* |
| P- bicarbonate (mEq/L) | 24.4 [23.5,25.2] | -0.5 [-0.9,0.0] | 23.10 [23.1,27.8] | *0.05* |
| P- albumin (g/dL) | 4.01 [3.82,4.18] | +0.08 [0.03,0.12] | 4.09 [3.91,4.26] | *0.004* |
| P- potassium (mEq/L | 4.3 [4.2,4.4] | +0.1 [0.2,0.3] | 4.5 [4.4,4.6] | *<0.001* |
| P- urea nitrogen (mg/dL) | 26.86 [22.96,30.75] | +3.12 [1.32,4.93] | 29.98 [25.14,34.82] | *0.001* |
| P- creatinine (mg/dL) | 1.53 [1.33,1.71] | +0.06 [0.04,0.10] | 1.57 [1.37,1.77] | *<0.001* |
| Creatinine clearance | | | | |
| (mL/min)* | 87 [76,98] | 25% [22,28] | 82 [71,94] | *0.005* |
| log10-values | 1.94 [1.89,1.99] | -0.04 [-0.06,-0.03] | 1.93 [1.86,1.98] | *0.005* |
| Urine albumin | | | | |
| (mg/24hours)* | 1483 [1194,1842] | -23% [-29,-15] | 1164 [922,1469] | *<0.001* |
| log10-values | 3.18 [3.08,3.28] | -0.13 [-0.16,-0.07] | 3.08 [2.97,3.18] | *<0.001* |
| Fractional albumin excretion | | | | |
| (%)* | 0.031 [0.024,0.034] | -18% [-26,13] | 0.026 [0.020,0.034] | *<0.001* |
| log10-values | 21.54 [21.64,21.41] | -0.08 [-0.12,0.06] | 21.61 [21.74,21.49] | *<0.001* |

**4. Discussion**

Combining data from 2,114 individuals across 20 randomized clinical studies, we showed that angiotensin-II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) are more effective than Albuminuria in diabetic patients and CCB reduces hypertension. (Gallo et al 2022). Regardless of how much these drugs drop blood pressure; this conclusion seems to be accurate. Renal function was not improved by treatment with CCBs or ARB/ACEI (Arvanitis et al 2021).

A meta-analysis of randomized clinical trials found that individuals with increased blood sugar and diabetes without albuminuria, ARB/ACEI reduce cardiovascular risk compared to other antihypertensive medications (Zhang et al 2020). The study analysis is strong enough to back up these claims. The research was exhaustive and we employed clear qualifying criteria. Extraction of data and evaluation of bias were performed and evaluated in triplicate for the records (Martin et al 2021). They demonstrated that two factors beyond initial albuminuria extent that are known to affect ARB/ACEI response were variability in the albuminuria testing procedure and the mean age of study participants. The degree of albuminuria was measured in the vast majority of studies by collecting urine over 24 hours and this subgroup showed the most extraordinary heterogeneity ($I^2$ =

84.6%), which is in line with the recognized technical challenges of this measurement technique (Piperidou et al 2019). Concerns concerning the accuracy of the 24-hour urinalysis have been raised since studies that employed the urine albumin-creatinine ratio approach exhibited reduced heterogeneity ($I^2$=35.8%) and found that there was not an important variation among the two therapies for the main endpoint. Subgroup studies have their inherent limitations. Therefore, differences between these two groups cannot be considered definitive (Luo et al 2020).

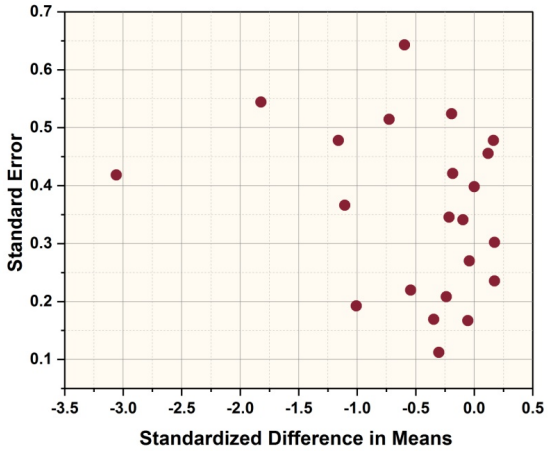


**Figure 2** outcomes of Bias Potential.

## 5. Final considerations

CCB shows promise in the treatment of albuminuria in people with diabetes and hypertension without posing any serious risks. CCBs are gaining favor as a treatment option for these conditions due to accumulating data suggesting that they can lower albuminuria without producing significant adverse effects. However, constant observation and tailored treatment programs are required for the best results. More studies are needed to determine the long-term safety of CCBs in this patient group. Regardless of albuminuria severity, the positive benefits persisted. In addition, esaxerenone is well tolerated in this population, with no increased risk of serum potassium or decreased eGFR. When a RAS inhibitor fails to reduce BP in hypertensive individuals with DKD, eplerenone can be effective.

## Ethical Considerations

Not Applicable.

## Conflict of Interest

The authors declare no conflicts of interest.

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