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Effect of Low-Dose Spironolactone on Proteinuria in Diabetic Kidney Disease: A Randomized Controlled Trial

Dr. H Hasan[1], Dr. M Mannan[2], Dr. M N Islam[3]
[1,2]Professor, Department of Nephrology, Dhaka Medical College Hospital Dhaka, Bangladesh
[3]Associate Professor, Department of Nephrology, Dhaka Medical College Hospital
Dhaka, Bangladesh

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Corresponding Author
Dr. M Mannan
Professor, Department of Nephrology, Dhaka Medical College Hospital Dhaka, Bangladesh

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ABS TRAC T

Background*:** Albuminuria persists in a substantial proportion of patients with diabetic kidney disease despite maximally tolerated renin-angiotensin system blockade, and aldosterone breakthrough is a recognised contributor to this residual risk. Conventional-dose mineralocorticoid receptor antagonism lowers proteinuria but carries an appreciable risk of hyperkalaemia, which limits its use in routine practice. This trial evaluated whether low-dose spironolactone added to standard care reduced proteinuria in diabetic kidney disease without unacceptable hyperkalaemia. ***Methods: A prospective, randomised, open-label, parallel-group trial was conducted at a tertiary care teaching hospital. One hundred and twenty adults with type 2 diabetes mellitus, urine albumin-to-creatinine ratio 30 to 3000 mg/g, estimated glomerular filtration rate of at least 45 mL/min/1.73 m² and serum potassium not exceeding 5.0 mmol/L, all receiving maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, were randomised in a 1:1 ratio to spironolactone 12.5 mg once daily or to standard care alone for 24 weeks. The primary outcome was the percentage change in urine albumin-to-creatinine ratio from baseline to 24 weeks. Secondary outcomes were 24-hour urinary protein excretion, office blood pressure, estimated glomerular filtration rate, serum potassium and treatment-emergent adverse events. ***Results*:** Baseline characteristics were comparable between arms. At 24 weeks the median percentage change in urine albumin-to-creatinine ratio was −41.8% (interquartile range −56.2 to −24.6) with spironolactone and −4.2% (interquartile range −14.8 to +7.6) with standard care ($p<0.001$). A reduction of at least 30% was achieved by 41 of 60 participants (68.3%) versus 9 of 60 (15.0%) respectively ($p<0.001$). Systolic blood pressure fell by 9.6±8.2 mmHg versus 2.1±7.9 mmHg ($p<0.001$). The decline in estimated glomerular filtration rate did not differ significantly (−3.2±6.4 versus −1.2±6.1 mL/min/1.73 m²; $p=0.082$). Serum potassium rose by 0.29±0.34 versus 0.03±0.31 mmol/L ($p<0.001$), with potassium above 5.5 mmol/L in 6.7% versus 1.7% ($p=0.36$). ***Conclusion*:** Low-dose spironolactone added to maximally tolerated renin-angiotensin system blockade produced a clinically meaningful reduction in proteinuria over 24 weeks, accompanied by a modest and manageable rise in serum potassium.

Keywords: *Spironolactone, Diabetic Nephropathies, Proteinuria, Albuminuria, Mineralocorticoid Receptor Antagonists, Randomized Controlled Trial.*

INTRODUCTION

Diabetes mellitus is the single largest contributor to chronic kidney disease worldwide, and diabetic kidney disease now accounts for a substantial and rising share of incident kidney failure requiring replacement therapy. Approximately one in three adults with type 2 diabetes mellitus develops evidence of kidney involvement during the course of the illness, most often heralded by a persistent increase in urinary albumin excretion [1]. Global burden estimates place chronic kidney disease among the leading causes of years of life lost, with diabetes-attributable disease accounting for a disproportionate fraction of that burden in South Asia, where diabetes occurs at younger ages

and at lower body mass indices than in Western populations [3]. The clinical consequence is a large and expanding cohort of relatively young patients who face decades of exposure to progressive nephron loss, accelerated cardiovascular risk and the economic burden of renal replacement therapy.

Albuminuria occupies a central position in this natural history. It is not merely a marker of established glomerular injury but an independent and modifiable determinant of subsequent decline in glomerular filtration rate and of cardiovascular events. Contemporary guidance therefore recommends systematic screening for albuminuria in all patients with diabetes and treats a sustained reduction in urinary albumin excretion as a legitimate therapeutic target rather than an incidental laboratory observation [1]. Blockade of the renin-angiotensin system with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, titrated to the maximally tolerated dose, remains the cornerstone of albuminuria-directed therapy and has been shown to delay progression across the spectrum of diabetic kidney disease [4].

Renin-angiotensin system blockade nevertheless leaves a considerable burden of residual proteinuria. A recognised mechanism is aldosterone breakthrough, whereby circulating aldosterone concentrations, initially suppressed by angiotensin blockade, return towards or above pretreatment values within months of therapy in a substantial minority of treated patients. Aldosterone exerts effects on the kidney that extend well beyond epithelial sodium handling. Activation of the mineralocorticoid receptor in podocytes, mesangial cells, fibroblasts, vascular endothelium and infiltrating inflammatory cells promotes oxidative stress, profibrotic signalling, extracellular matrix accumulation and podocyte injury, culminating in glomerulosclerosis and tubulointerstitial fibrosis [2]. These non-epithelial actions provide a coherent pathophysiological rationale for adding mineralocorticoid receptor antagonism to angiotensin blockade rather than relying on angiotensin blockade alone.

Clinical evidence supports this rationale. Early crossover and parallel-group studies demonstrated that spironolactone added to established antihypertensive therapy reduced albuminuria by approximately 30% to 60% in patients with diabetic nephropathy, with reductions that were largely independent of the accompanying fall in blood pressure [5]. A randomised comparison of spironolactone against an angiotensin receptor blocker, each added to maximal angiotensin-converting enzyme inhibition, showed that mineralocorticoid receptor antagonism produced the greater antialbuminuric effect [6]. These individual findings have been corroborated at the level of pooled evidence. A systematic review and meta-analysis of randomised trials in chronic kidney disease reported a weighted mean reduction in urinary protein or albumin excretion of close to 39% with mineralocorticoid receptor antagonism, together with a clear reduction in blood pressure [9]. A subsequent Cochrane review reached broadly concordant conclusions regarding proteinuria while emphasising the limited certainty of the evidence for hard kidney endpoints [10].

The principal barrier to translation has been hyperkalaemia. The same meta-analytic evidence that established the antiproteinuric benefit also documented an approximately threefold increase in the relative risk of trial withdrawal attributable to hyperkalaemia [9]. This risk is amplified in precisely the population most likely to benefit, namely patients with reduced glomerular filtration rate who are already receiving angiotensin blockade. The development of non-steroidal mineralocorticoid receptor antagonists was a direct response to this problem, and finerenone has since been shown in large outcome trials to reduce kidney and cardiovascular events in chronic kidney disease associated with type 2 diabetes with a comparatively favourable potassium profile [8]. Access to these agents, however, remains constrained by cost and availability in much of the developing world, and steroidal mineralocorticoid receptor antagonists continue to be the only affordable option for the majority of patients treated in public sector institutions in Bangladesh [2].

Against this background, dose reduction offers a pragmatic strategy to preserve antiproteinuric efficacy while attenuating the risk of hyperkalaemia. The proposition rests on the observation that the mineralocorticoid receptor is substantially occupied at doses well below those conventionally prescribed for heart failure or resistant hypertension, and that the antiproteinuric response to spironolactone appears to reach a plateau at relatively low exposures. A randomised trial of spironolactone 12.5 mg daily in adults with chronic kidney disease and type 2 diabetes reported a significant reduction in the urine albumin-to-creatinine ratio without an excess of clinically important hyperkalaemia, supporting the feasibility of this approach [7]. Data of this kind remain limited in number, are drawn largely from East Asian and European cohorts, and have rarely been generated in South Asian populations, in whom the phenotype of diabetic kidney disease, background dietary potassium intake and prevailing standards of ambulatory monitoring differ appreciably.

A clinically important evidence gap therefore persists. It is not established whether low-dose spironolactone, added to maximally tolerated renin-angiotensin system blockade in a Bangladeshi tertiary care setting, delivers a magnitude of proteinuria reduction comparable to that reported with conventional doses, and whether it does so with a potassium safety

profile acceptable for routine outpatient use. The present randomised controlled trial was designed to address that question by quantifying the effect of spironolactone 12.5 mg once daily on proteinuria over 24 weeks in adults with diabetic kidney disease, and by characterising the accompanying changes in blood pressure, glomerular filtration rate and serum potassium.

Aims and Objectives

The aim of the present study was to determine whether the addition of low-dose spironolactone to maximally tolerated renin-angiotensin system blockade reduced proteinuria in adults with type 2 diabetes mellitus and diabetic kidney disease, and to establish whether any such reduction was achieved at an acceptable cost in terms of hyperkalaemia and short-term change in glomerular filtration rate.

The primary objective was to compare the percentage change in the urine albumin-to-creatinine ratio from baseline to 24 weeks between participants who received spironolactone 12.5 mg once daily in addition to standard care and those who received standard care alone. The secondary objectives were to compare the change in 24-hour urinary protein excretion between the two groups over the same interval; to determine the proportion of participants in each group who achieved a reduction of at least 30% in the urine albumin-to-creatinine ratio, this threshold having been adopted because it corresponds to the magnitude of albuminuria change associated with a demonstrable reduction in the risk of subsequent kidney failure; to compare the change in office systolic and diastolic blood pressure; to compare the change in estimated glomerular filtration rate and serum creatinine; to quantify the change in serum potassium and to record the incidence of hyperkalaemia at predefined thresholds; and to document all treatment-emergent adverse events, including gynaecomastia, symptomatic hypotension, acute kidney injury and study drug discontinuation. An exploratory objective was to identify baseline clinical and biochemical characteristics that predicted the magnitude of the antiproteinuric response among participants allocated to spironolactone.

Materials and Methods

Study Design and Setting

This was a prospective, randomised, open-label, parallel-group, single-centre controlled trial conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka, Bangladesh. Participants were recruited from the diabetes and nephrology outpatient services over a period of 9 months, from September 2025 to May 2026, with the final follow-up visit completed in May 2026. The protocol was approved by the Institutional Ethics Committee of Dhaka Medical College Hospital (approval number DMC/IEC/2025/132, dated 05 Aug 2025) and the trial was prospectively registered with the appropriate Bangladesh clinical trial registry BMRC/CTR/2025/087. The study was conducted in accordance with the Declaration of Helsinki and applicable national ethical guidelines for biomedical and health research involving human participants. Written informed consent was obtained from every participant before any study procedure was performed. The report conforms to the CONSORT 2010 statement for parallel-group randomised trials.

Participants and Eligibility Criteria

Adults aged 18 to 70 years with a documented diagnosis of type 2 diabetes mellitus of at least one year in duration were screened for eligibility. Participants were included if they demonstrated a urine albumin-to-creatinine ratio between 30 and 3000 mg/g on at least two of three consecutive first-morning voided specimens obtained within the preceding three months; an estimated glomerular filtration rate of at least 45 mL/min/1.73 m² calculated by the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation; a serum potassium concentration not exceeding 5.0 mmol/L at screening; and stable treatment with a maximally tolerated dose of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker for a minimum of eight weeks before randomisation.

Participants were excluded if they had type 1 diabetes mellitus; a non-diabetic cause of kidney disease established clinically, serologically or histologically; an estimated glomerular filtration rate below 45 mL/min/1.73 m²; a serum potassium concentration above 5.0 mmol/L; known hypersensitivity or previous intolerance to spironolactone; concurrent or recent use of any mineralocorticoid receptor antagonist, potassium-sparing diuretic, potassium supplement, non-steroidal anti-inflammatory drug or trimethoprim within four weeks of screening; New York Heart Association class III or IV heart failure; decompensated chronic liver disease; active urinary tract infection, febrile illness, nephrotic syndrome or an episode of acute kidney injury within the preceding three months; uncontrolled hypertension defined as an office blood pressure of 180/110 mmHg or higher; systolic blood pressure below 110 mmHg; pregnancy, lactation or the intention to conceive during the study period; malignancy or any condition expected to limit survival to less than one year; and an inability or unwillingness to comply with scheduled follow-up and biochemical monitoring.

Sample Size Determination

The sample size was calculated for the primary outcome of percentage change in the urine albumin-to-creatinine ratio (UACR) at 24 weeks. Assuming a clinically meaningful between-group difference of 30 percentage points in the mean percentage change, a common standard deviation of 45 percentage points, a two-sided alpha level of 0.05, and a statistical power of 80%, the

required sample size was calculated using the formula for comparison of two independent means:

$$n = 2(Z\alpha/2 + Z\beta)^2\sigma^2 / \delta^2$$

where n represents the number of participants required in each group, $Z\alpha/2 = 1.96$ for a two-sided α of 0.05, $Z\beta = 0.84$ for 80% power, $\sigma = 45$ percentage points (common standard deviation), and $\delta = 30$ percentage points (expected between-group difference). Accordingly, the calculated sample size was approximately 36 participants per group. Allowing for an anticipated 15% attrition rate, the adjusted sample size was approximately 42 participants per group. However, to satisfy the sample size specified in the approved study synopsis and to provide adequate allowance for participant withdrawals and loss to follow-up, the final recruitment target was set at 60 participants per group, resulting in a total planned sample size of 120 participants.

Randomisation, Allocation Concealment and Blinding

A computer-generated randomisation sequence was prepared by an investigator not involved in recruitment or outcome assessment, using permuted blocks of variable size of four and six to achieve 1:1 allocation. Allocation was concealed using sequentially numbered, opaque, sealed envelopes that were opened only after a participant had completed all baseline assessments and had provided consent. The trial was open-label with respect to participants and treating clinicians, because a matching placebo could not be sourced. Bias was mitigated by blinding of the outcome assessors and of the laboratory personnel who processed and reported all urine and blood specimens, and by blinding of the statistician who conducted the analysis to group identity until the analysis was locked.

Intervention and Comparator

Participants allocated to the intervention group received spironolactone 12.5 mg orally once daily, taken after breakfast, in addition to their existing therapy, for a period of 24 weeks. Participants allocated to the control group continued their existing therapy without the addition of any mineralocorticoid receptor antagonist. In both groups, the background regimen of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, glucose-lowering therapy, statin therapy and other antihypertensive agents was maintained unchanged wherever clinically feasible. Where a change in background therapy became clinically necessary, it was documented in the case record form and accounted for in the sensitivity analysis. All participants received standardised dietary counselling regarding sodium and potassium intake and were advised to avoid potassium-rich salt substitutes, non-steroidal anti-inflammatory drugs and over-the-counter potassium supplements for the duration of the study.

Study Procedures and Data Collection

At the baseline visit, a structured history was recorded and a complete clinical examination was performed. Demographic details, duration of diabetes, duration of hypertension, smoking and alcohol history, complete drug history and the presence of diabetic retinopathy and neuropathy were documented in a predesigned case record form. Anthropometry included height, weight, body mass index and waist circumference. Office blood pressure was recorded as the mean of three readings obtained with a calibrated automated oscillometric device after five minutes of seated rest, with one minute between readings, using an appropriately sized cuff.

Laboratory investigations at baseline comprised fasting and postprandial plasma glucose, glycated haemoglobin measured by high-performance liquid chromatography, serum creatinine measured by the modified Jaffe kinetic method with isotope dilution mass spectrometry traceable calibration, blood urea, serum electrolytes including potassium and sodium, serum albumin, a fasting lipid profile, complete blood count and urine routine microscopy. The urine albumin-to-creatinine ratio was determined on a first-morning voided specimen using immunoturbidimetry for albumin and the modified Jaffe method for creatinine. A 24-hour urine collection was obtained for total protein estimation, with adequacy of collection verified by 24-hour urinary creatinine excretion. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation.

Follow-up Protocol

Participants were reviewed at weeks 2, 4, 12 and 24 after randomisation. Serum potassium and serum creatinine were measured at every visit in both groups to permit uniform safety surveillance. The urine albumin-to-creatinine ratio was repeated at weeks 12 and 24, and the 24-hour urinary protein estimation was repeated at week 24. Glycated haemoglobin was repeated at week 24. Blood pressure, weight, adherence and adverse events were assessed at each visit. Adherence was evaluated by pill count and by direct questioning, and participants who took fewer than 80% of the prescribed doses were classified as non-adherent. Predefined safety rules governed the management of hyperkalaemia. A serum potassium concentration between 5.5 and 5.9 mmol/L prompted reinforcement of dietary counselling, review of concomitant medication and repeat measurement within one week; a concentration of 6.0 mmol/L or above, or a confirmed value above 5.5 mmol/L on repeat testing, mandated permanent discontinuation of the study drug. A fall in estimated glomerular filtration rate exceeding 30% from baseline also mandated discontinuation and clinical evaluation for reversible causes.

Outcome Measures

The primary outcome measure was the percentage change in the urine albumin-to-creatinine ratio from baseline to 24 weeks. The secondary outcome measures were the change in 24-hour urinary protein excretion at 24 weeks; the proportion of participants achieving a reduction of at least 30% in the urine albumin-to-creatinine ratio at 24 weeks; the proportion achieving regression to a lower albuminuria category; the change in office systolic and diastolic blood pressure; the change in serum creatinine and estimated glomerular filtration rate; the change in serum potassium; and the incidence of predefined adverse events including hyperkalaemia at thresholds of 5.5 and 6.0 mmol/L, gynaecomastia or breast tenderness, symptomatic hypotension, acute kidney injury and study drug discontinuation for any reason.

Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and analysed using [SPSS version 26.0, IBM Corporation, Armonk, New York, United States]. The distribution of continuous variables was assessed using the Shapiro-Wilk test and by inspection of histograms and normal quantile-quantile plots. Normally distributed continuous variables were summarised as mean with standard deviation and compared between groups using the independent samples t test. Variables with a skewed distribution, including the urine albumin-to-creatinine ratio and 24-hour urinary protein excretion, were summarised as median with interquartile range and compared between groups using the Mann-Whitney U test; these variables were logarithmically transformed where parametric modelling was required. Categorical variables were expressed as frequencies with percentages and compared using the chi-square test, with the Fisher exact test applied where any expected cell frequency was below five.

Within-group changes from baseline were assessed using the paired t test for normally distributed variables and the Wilcoxon signed rank test for skewed variables. Changes across the three time points were examined using repeated measures analysis of variance for normally distributed variables and the Friedman test for skewed variables, with post hoc pairwise comparisons adjusted by the Bonferroni method. The primary outcome was analysed on an intention-to-treat basis with all randomised participants included and missing values at 24 weeks imputed by multiple imputation using chained equations under a missing at random assumption; a per-protocol analysis restricted to adherent participants who completed 24 weeks was performed as a sensitivity analysis. The relative risk and number needed to treat for the outcome of at least 30% reduction in the urine albumin-to-creatinine ratio were calculated with 95% confidence intervals. Multivariable linear regression was used to identify baseline predictors of the percentage change in the urine albumin-to-creatinine ratio among participants allocated to spironolactone, with candidate variables selected on the basis of a p value below 0.10 on univariate analysis and on biological plausibility, and with multicollinearity assessed by the variance inflation factor. A two-sided p value of less than 0.05 was considered statistically significant throughout.

RESULTS

A total of 200 patients were screened for eligibility, of whom 120 satisfied the inclusion and exclusion criteria and were randomised, 60 to the spironolactone group and 60 to the control group. Four participants in the spironolactone group and three in the control group did not complete the 24-week visit; the reasons were loss to follow-up in four instances, withdrawal of consent in one and permanent discontinuation of the study drug for hyperkalaemia in two. All 120 randomised participants were included in the intention-to-treat analysis of the primary outcome, and 113 participants contributed to the per-protocol analysis. Overall adherence to the study drug, assessed by pill count, was 94.2% in the spironolactone group.

The two groups were well matched at baseline with respect to demographic and clinical characteristics, as shown in Table 1. The mean age was 54.8±8.6 years in the spironolactone group and 55.6±9.1 years in the control group (p=0.62). Male participants constituted 61.7% and 58.3% of the two groups respectively (p=0.71). The mean body mass index was 27.4±3.8 kg/m² and 27.1±3.6 kg/m² (p=0.66), and the mean duration of diabetes was 9.6±4.2 years and 10.1±4.5 years (p=0.53). Hypertension was present in 80.0% and 76.7% of participants (p=0.66), diabetic retinopathy in 41.7% and 36.7% (p=0.58), and sodium-glucose cotransporter 2 inhibitors were in use in 43.3% and 40.0% respectively (p=0.71). No baseline demographic or clinical variable differed significantly between the two groups.

Table 1: Baseline demographic and clinical characteristics of the study population

Variable	Spironolactone (n=60)	Control (n=60)	p value
Age, years, mean ± SD	54.8 ± 8.6	55.6 ± 9.1	0.62
Male sex, n (%)	37 (61.7)	35 (58.3)	0.71
Body mass index, kg/m², mean ± SD	27.4 ± 3.8	27.1 ± 3.6	0.66
Waist circumference, cm, mean ± SD	96.4 ± 9.2	95.6 ± 8.8	0.63
Duration of diabetes, years, mean ± SD	9.6 ± 4.2	10.1 ± 4.5	0.53
Hypertension, n (%)	48 (80.0)	46 (76.7)	0.66
Duration of hypertension, years, mean ± SD	6.4 ± 3.8	6.8 ± 4.1	0.58

Current or ex-smoker, n (%)	14 (23.3)	12 (20.0)	0.66
Diabetic retinopathy, n (%)	25 (41.7)	22 (36.7)	0.58
Diabetic peripheral neuropathy, n (%)	21 (35.0)	19 (31.7)	0.70
ACE inhibitor use, n (%)	22 (36.7)	24 (40.0)	0.71
Angiotensin receptor blocker use, n (%)	38 (63.3)	36 (60.0)	0.71
SGLT2 inhibitor use, n (%)	26 (43.3)	24 (40.0)	0.71
Metformin use, n (%)	52 (86.7)	50 (83.3)	0.60
Insulin use, n (%)	23 (38.3)	26 (43.3)	0.58
Statin use, n (%)	51 (85.0)	49 (81.7)	0.62
Loop or thiazide diuretic use, n (%)	18 (30.0)	16 (26.7)	0.68

SD, standard deviation; ACE, angiotensin-converting enzyme; SGLT2, sodium-glucose cotransporter 2. Continuous variables compared using the independent samples t test; categorical variables compared using the chi-square test.

Baseline biochemical and renal parameters were likewise comparable between the two groups, as detailed in Table 2. Mean glycated haemoglobin was 8.1±1.2% in the spironolactone group and 8.3±1.3% in the control group (p=0.38). Mean serum creatinine was 1.14±0.26 mg/dL and 1.11±0.24 mg/dL (p=0.51), and mean estimated glomerular filtration rate was 68.4±14.2 mL/min/1.73 m² and 70.1±15.0 mL/min/1.73 m² (p=0.53). Mean serum potassium was 4.32±0.34 mmol/L and 4.28±0.31 mmol/L (p=0.50). The median urine albumin-to-creatinine ratio was 412 mg/g (interquartile range 188 to 746) and 396 mg/g (interquartile range 174 to 712) respectively (p=0.68), and median 24-hour urinary protein excretion was 0.86 g (interquartile range 0.42 to 1.42) and 0.81 g (interquartile range 0.39 to 1.36) respectively (p=0.72). Mean systolic blood pressure was 138.2±11.6 mmHg and 136.9±12.1 mmHg (p=0.55) and mean diastolic blood pressure was 82.4±7.2 mmHg and 81.8±7.6 mmHg (p=0.66).

Table 2: Baseline biochemical, renal and haemodynamic parameters

Parameter	Spironolactone (n=60)	Control (n=60)	p value
Fasting plasma glucose, mg/dL	148.6 ± 38.2	152.4 ± 40.1	0.60
Glycated haemoglobin, %	8.1 ± 1.2	8.3 ± 1.3	0.38
Serum creatinine, mg/dL	1.14 ± 0.26	1.11 ± 0.24	0.51
Blood urea, mg/dL	34.2 ± 9.6	33.1 ± 9.2	0.52
eGFR, mL/min/1.73 m²	68.4 ± 14.2	70.1 ± 15.0	0.53
Serum potassium, mmol/L	4.32 ± 0.34	4.28 ± 0.31	0.50
Serum sodium, mmol/L	138.6 ± 3.2	139.1 ± 3.4	0.41
Serum albumin, g/dL	3.94 ± 0.38	3.98 ± 0.36	0.55
Total cholesterol, mg/dL	178.4 ± 34.2	182.6 ± 36.8	0.52
LDL cholesterol, mg/dL	102.6 ± 28.4	105.2 ± 30.1	0.63
Haemoglobin, g/dL	12.4 ± 1.6	12.6 ± 1.5	0.48
UACR, mg/g, median (IQR)	412 (188–746)	396 (174–712)	0.68
24-hour urinary protein, g, median (IQR)	0.86 (0.42–1.42)	0.81 (0.39–1.36)	0.72
Microalbuminuria (30–299 mg/g), n (%)	26 (43.3)	28 (46.7)	0.71
Macroalbuminuria (≥300 mg/g), n (%)	34 (56.7)	32 (53.3)	0.71
Systolic blood pressure, mmHg	138.2 ± 11.6	136.9 ± 12.1	0.55
Diastolic blood pressure, mmHg	82.4 ± 7.2	81.8 ± 7.6	0.66

Values are mean ± standard deviation unless otherwise stated. eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; UACR, urine albumin-to-creatinine ratio; IQR, interquartile range. Skewed variables compared using the Mann-Whitney U test.

The primary outcome favoured spironolactone by a wide margin, as presented in Table 3. In the spironolactone group the median urine albumin-to-creatinine ratio fell from 412 mg/g (interquartile range 188 to 746) at baseline to 268 mg/g (interquartile range 124 to 498) at 12 weeks and to 214 mg/g (interquartile range 96 to 430) at 24 weeks, a within-group reduction that was highly significant on the Friedman test (p<0.001) and on post hoc Wilcoxon signed rank testing at both time points (p<0.001 for each comparison against baseline). In the control group the corresponding values were 396 mg/g (interquartile range 174 to 712) at baseline, 382 mg/g (interquartile range 168 to 698) at 12 weeks and 372 mg/g (interquartile range 162 to 690) at 24 weeks, and the within-group change was not significant (p=0.21). The median percentage change from baseline to 24 weeks was −41.8% (interquartile range −56.2 to −24.6) in the spironolactone group and −4.2% (interquartile range −14.8 to +7.6) in the control group, and the between-group difference was highly significant on the Mann-Whitney U test (p<0.001). The per-protocol analysis yielded a closely comparable estimate, with a median percentage change of −43.1% versus −4.6% (p<0.001).

A parallel pattern was observed for 24-hour urinary protein excretion. The median value fell from 0.86 g (interquartile range 0.42 to 1.42) to 0.49 g (interquartile range 0.24 to 0.88) in the spironolactone group, corresponding to a median reduction of 38.6%, whereas in the control group it changed from 0.81 g (interquartile range 0.39 to 1.36) to 0.78 g (interquartile range 0.36 to 1.32), corresponding to a median reduction of 2.8% (between-group p<0.001). A reduction of at least 30% in the urine albumin-to-creatinine ratio was achieved by 41 of 60 participants (68.3%) in the spironolactone group and by 9 of 60 (15.0%) in the control group (p<0.001), giving a relative risk of 4.56 (95% confidence interval 2.44 to 8.51) and a number needed to treat of 2 (95% confidence interval 1.5 to 2.6). Regression from macroalbuminuria to microalbuminuria, or from microalbuminuria to normoalbuminuria, occurred in 19 participants (31.7%) in the spironolactone group and in 4 participants (6.7%) in the control group (p=0.001).

Table 3: Proteinuria indices at baseline, 12 weeks and 24 weeks by treatment group

Parameter and group	Baseline	Week 12	Week 24	Within-group p
UACR, mg/g, median (IQR)				
Spironolactone (n=60)	412 (188–746)	268 (124–498)	214 (96–430)	<0.001
Control (n=60)	396 (174–712)	382 (168–698)	372 (162–690)	0.21
Between-group p	0.68	<0.001	<0.001	—
Percentage change in UACR at 24 weeks, median (IQR)				
Spironolactone	—	−34.6 (−48.2 to −18.4)	−41.8 (−56.2 to −24.6)	<0.001
Control	—	−2.8 (−12.4 to +8.2)	−4.2 (−14.8 to +7.6)	0.21
Between-group p	—	<0.001	<0.001	—
24-hour urinary protein, g, median (IQR)				
Spironolactone	0.86 (0.42–1.42)	Not measured	0.49 (0.24–0.88)	<0.001
Control	0.81 (0.39–1.36)	Not measured	0.78 (0.36–1.32)	0.34
Between-group p	0.72	—	<0.001	—
≥30% reduction in UACR at 24 weeks, n (%)				
Spironolactone	—	31 (51.7)	41 (68.3)	—
Control	—	7 (11.7)	9 (15.0)	—
Between-group p	—	<0.001	<0.001	—

UACR, urine albumin-to-creatinine ratio; IQR, interquartile range. Within-group comparisons across time points assessed by the Friedman test with post hoc Wilcoxon signed rank testing; between-group comparisons assessed by the Mann-Whitney U test for continuous variables and the chi-square test for proportions.

Haemodynamic and renal function outcomes are summarised in Table 4. Systolic blood pressure fell from 138.2±11.6 mmHg to 128.6±10.4 mmHg in the spironolactone group, a mean reduction of 9.6±8.2 mmHg, and from 136.9±12.1 mmHg to 134.8±11.2 mmHg in the control group, a mean reduction of 2.1±7.9 mmHg; the between-group difference in change was 7.5 mmHg (95% confidence interval 4.6 to 10.4; p<0.001). Diastolic blood pressure fell by 5.2±6.1 mmHg and 1.2±6.4 mmHg respectively, with a between-group difference of 4.0 mmHg (95% confidence interval 1.7 to 6.3; p=0.001). Mean serum creatinine rose from 1.14±0.26 mg/dL to 1.19±0.28 mg/dL in the spironolactone group and from 1.11±0.24 mg/dL to 1.13±0.26 mg/dL in the control group, and the between-group difference in change was not significant (p=0.21). The estimated glomerular filtration rate declined by 3.2±6.4 mL/min/1.73 m² in the spironolactone group and by 1.2±6.1 mL/min/1.73 m² in the control group, a difference that did not reach statistical significance (p=0.082). Glycated haemoglobin at 24 weeks was 8.0±1.1% and 8.2±1.2% respectively (p=0.34), indicating that glycaemic control did not differ materially between the groups over the study period. Importantly, the antiproteinuric effect persisted after adjustment for the change in systolic blood pressure in a multivariable model, with the treatment allocation remaining an independent predictor of percentage change in the urine albumin-to-creatinine ratio (adjusted β = −31.4; 95% confidence interval −40.2 to −22.6; p<0.001), indicating that the reduction in proteinuria was only partly attributable to blood pressure lowering.

Table 4: Blood pressure, renal function and glycaemic parameters at baseline and 24 weeks

Parameter	Spiro baseline	Spiro 24 wk	Control baseline	Control 24 wk	p value*
Systolic BP, mmHg	138.2 ± 11.6	128.6 ± 10.4	136.9 ± 12.1	134.8 ± 11.2	<0.001
Diastolic BP, mmHg	82.4 ± 7.2	77.2 ± 6.8	81.8 ± 7.6	80.6 ± 7.1	0.001
Mean arterial pressure, mmHg	101.0 ± 8.1	94.3 ± 7.4	100.2 ± 8.6	98.7 ± 8.0	<0.001
Serum creatinine, mg/dL	1.14 ± 0.26	1.19 ± 0.28	1.11 ± 0.24	1.13 ± 0.26	0.21
eGFR, mL/min/1.73 m²	68.4 ± 14.2	65.2 ± 14.8	70.1 ± 15.0	68.9 ± 15.4	0.082

Blood urea, mg/dL	34.2 ± 9.6	36.1 ± 10.2	33.1 ± 9.2	33.8 ± 9.6	0.28
Glycated haemoglobin, %	8.1 ± 1.2	8.0 ± 1.1	8.3 ± 1.3	8.2 ± 1.2	0.34
Body weight, kg	72.6 ± 11.4	71.8 ± 11.1	71.9 ± 10.8	71.6 ± 10.6	0.19

*Values are mean ± standard deviation. Spiro, spironolactone; BP, blood pressure; eGFR, estimated glomerular filtration rate. *p value refers to the between-group comparison of the change from baseline to 24 weeks, assessed by the independent samples t test.*

Safety outcomes are presented in Table 5. Serum potassium rose from 4.32±0.34 mmol/L to 4.61±0.42 mmol/L in the spironolactone group, a mean increase of 0.29±0.34 mmol/L, and from 4.28±0.31 mmol/L to 4.31±0.36 mmol/L in the control group, a mean increase of 0.03±0.31 mmol/L; the between-group difference in change was 0.26 mmol/L (95% confidence interval 0.14 to 0.38; p<0.001). A serum potassium concentration exceeding 5.5 mmol/L was recorded at any visit in 4 participants (6.7%) in the spironolactone group and in 1 participant (1.7%) in the control group (p=0.36 by the Fisher exact test). A value of 6.0 mmol/L or above occurred in 1 participant (1.7%) in the spironolactone group and in none in the control group (p=1.00). Permanent discontinuation of the study drug for hyperkalaemia was required in 2 participants (3.3%), both of whom had a baseline estimated glomerular filtration rate below 60 mL/min/1.73 m². No participant required emergency treatment for hyperkalaemia, and no arrhythmic event was recorded. Gynaecomastia or breast tenderness was reported by 3 male participants (5.0%) in the spironolactone group and by none in the control group (p=0.24), and was mild and self-limiting in all instances. Symptomatic dizziness or postural giddiness occurred in 5 participants (8.3%) and 3 participants (5.0%) respectively (p=0.72). A fall in estimated glomerular filtration rate exceeding 30% from baseline occurred in 2 participants (3.3%) and 1 participant (1.7%) respectively (p=1.00), and was reversible in all cases on withdrawal of the precipitating factor. No death and no hospitalisation attributable to the study intervention occurred during the trial.

Table 5: Serum potassium trajectory and treatment-emergent adverse events

Variable	Spironolactone (n=60)	Control (n=60)	p value
Serum potassium at baseline, mmol/L	4.32 ± 0.34	4.28 ± 0.31	0.50
Serum potassium at week 4, mmol/L	4.56 ± 0.40	4.30 ± 0.34	<0.001
Serum potassium at week 12, mmol/L	4.58 ± 0.41	4.29 ± 0.35	<0.001
Serum potassium at week 24, mmol/L	4.61 ± 0.42	4.31 ± 0.36	<0.001
Mean change in potassium, mmol/L	+0.29 ± 0.34	+0.03 ± 0.31	<0.001
Potassium >5.0 mmol/L at any visit, n (%)	11 (18.3)	3 (5.0)	0.023
Potassium >5.5 mmol/L at any visit, n (%)	4 (6.7)	1 (1.7)	0.36
Potassium ≥6.0 mmol/L at any visit, n (%)	1 (1.7)	0 (0.0)	1.00
Discontinuation for hyperkalaemia, n (%)	2 (3.3)	0 (0.0)	0.50
Gynaecomastia or breast tenderness, n (%)	3 (5.0)	0 (0.0)	0.24
Dizziness or postural giddiness, n (%)	5 (8.3)	3 (5.0)	0.72
Symptomatic hypotension, n (%)	2 (3.3)	1 (1.7)	1.00
eGFR decline >30% from baseline, n (%)	2 (3.3)	1 (1.7)	1.00
Menstrual irregularity (female participants), n (%)	1 (4.3)	0 (0.0)	1.00
Any adverse event, n (%)	16 (26.7)	7 (11.7)	0.038
Serious adverse event, n (%)	0 (0.0)	0 (0.0)	—

Values are mean ± standard deviation or n (%). eGFR, estimated glomerular filtration rate. Categorical comparisons by the chi-square test or the Fisher exact test as appropriate.

Exploratory multivariable linear regression conducted within the spironolactone group, presented in Table 6, identified independent predictors of the magnitude of the antiproteinuric response. A higher log-transformed baseline urine albumin-to-creatinine ratio was associated with a greater percentage reduction (β = −8.42 per unit increase in natural logarithm; 95% confidence interval −13.16 to −3.68; p=0.001), as was a higher baseline systolic blood pressure (β = −0.62 per mmHg; 95% confidence interval −1.04 to −0.20; p=0.004) and concomitant use of a sodium-glucose cotransporter 2 inhibitor (β = −6.24; 95% confidence interval −12.08 to −0.40; p=0.037). Baseline estimated glomerular filtration rate (p=0.24), glycated haemoglobin (p=0.26), duration of diabetes (p=0.39) and body mass index (p=0.61) were not independently predictive. The model explained approximately one-third of the variance in the antiproteinuric response (R^2 = 0.34; adjusted R^2 = 0.27; F = 4.58; p<0.001), and no variance inflation factor exceeded 2.1, indicating the absence of problematic multicollinearity.

Table 6: Multivariable linear regression for percentage change in urine albumin-to-creatinine ratio at 24 weeks

within the spironolactone group (n=60)

Predictor variable	β coefficient	95% confidence interval	p value
Baseline UACR (natural log)	−8.42	−13.16 to −3.68	0.001
Baseline systolic blood pressure (per mmHg)	−0.62	−1.04 to −0.20	0.004
Concomitant SGLT2 inhibitor use	−6.24	−12.08 to −0.40	0.037
Baseline eGFR (per mL/min/1.73 m²)	0.18	−0.12 to 0.48	0.24
Baseline glycated haemoglobin (per %)	1.86	−1.42 to 5.14	0.26
Duration of diabetes (per year)	−0.42	−1.38 to 0.54	0.39
Body mass index (per kg/m²)	0.31	−0.89 to 1.51	0.61
Age (per year)	0.14	−0.32 to 0.60	0.54
Male sex	2.06	−3.84 to 7.96	0.49

UACR, urine albumin-to-creatinine ratio; SGLT2, sodium-glucose cotransporter 2; eGFR, estimated glomerular filtration rate. A negative β coefficient denotes a greater percentage reduction in UACR. Model summary: $R^2 = 0.34$; adjusted $R^2 = 0.27$; $F = 4.58$; $p<0.001$.

DISCUSSION

This randomised controlled trial demonstrated that the addition of spironolactone 12.5 mg once daily to maximally tolerated renin-angiotensin system blockade produced a median reduction of approximately 42% in the urine albumin-to-creatinine ratio over 24 weeks in adults with type 2 diabetes mellitus and diabetic kidney disease, compared with a negligible change in participants who continued standard care alone. The effect was evident by 12 weeks, was accompanied by a modest reduction in blood pressure, persisted after statistical adjustment for that reduction, and was obtained at the cost of a mean rise in serum potassium of less than 0.3 mmol/L with a low incidence of clinically consequential hyperkalaemia.

The magnitude of the antiproteinuric effect observed here is consistent with the published experience of steroidal mineralocorticoid receptor antagonism in diabetic kidney disease. In a placebo-controlled parallel-group trial of one year's duration, the addition of spironolactone 25 mg daily to an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with type 2 diabetic nephropathy and macroalbuminuria produced a marked and sustained antiproteinuric response, although those investigators attributed a portion of the effect to a concomitant reduction in glomerular filtration rate [11]. An earlier double-blind crossover study reported a reduction in urinary albumin excretion of approximately 30% with spironolactone 25 mg daily added to established antihypertensive therapy in type 1 diabetic nephropathy, with an insignificant and reversible decline in glomerular filtration rate [5]. Aldosterone blockade with spironolactone 25 mg daily was also shown to reduce urinary albumin excretion by close to 40% in an earlier Japanese randomised study, again largely independently of blood pressure change [12]. The present finding of a 41.8% median reduction at a dose of 12.5 mg therefore sits comfortably within the range reported at twice that dose, which supports the contention that the antiproteinuric dose-response relationship for spironolactone flattens at relatively low exposures.

The most directly comparable published trial is the randomised study of spironolactone 12.5 mg daily in adults with chronic kidney disease and type 2 diabetes, which likewise demonstrated a significant reduction in the urine albumin-to-creatinine ratio without an excess of clinically important hyperkalaemia [7]. A subsequent post hoc analysis of that trial identified higher baseline albuminuria as a determinant of greater response, a finding replicated in the present regression analysis, in which the log-transformed baseline urine albumin-to-creatinine ratio was the strongest independent predictor of the magnitude of reduction [22]. This convergence across two geographically distinct cohorts suggests that the phenomenon reflects a genuine biological gradient of mineralocorticoid-driven injury rather than simple regression to the mean, although the latter cannot be excluded in either dataset.

A comparison with the trial of spironolactone against an angiotensin receptor blocker added to maximal angiotensin-converting enzyme inhibition is instructive. In that study, spironolactone 25 mg daily reduced the urine albumin-to-creatinine ratio by approximately 34% relative to placebo, whereas the addition of losartan achieved a reduction of about 17%, establishing that mineralocorticoid receptor antagonism is the more effective of the two strategies for residual albuminuria [6]. The present trial did not include an active comparator arm and cannot address that comparison directly, but the effect size observed is of a similar order, which suggests that dose reduction to 12.5 mg did not materially compromise efficacy. A long-term randomised study of mineralocorticoid receptor antagonism added to angiotensin receptor blockade in diabetic nephropathy similarly reported sustained antiproteinuric benefit over 18 months [13].

Contrasting results merit equal emphasis. The PRIORITY trial, which randomised patients with type 2 diabetes, normoalbuminuria and a high-risk urinary proteomic classifier score to spironolactone 25 mg daily or placebo, found no significant effect on progression to microalbuminuria over a median follow-up of 2.5 years

[14]. That negative result does not contradict the present findings so much as define their boundary. The participants in PRIORITY had no albuminuria at entry, whereas the present cohort had established albuminuria with a median urine albumin-to-creatinine ratio above 390 mg/g. The regression analysis reported here, in which the response was proportional to baseline albuminuria, offers a mechanistic explanation for the divergence: where there is little mineralocorticoid-mediated glomerular injury to reverse, there is correspondingly little for the drug to achieve. Similarly, the ACHIEVE trial found that spironolactone 25 mg daily did not reduce cardiovascular death or heart failure hospitalisation in patients receiving maintenance dialysis, a population in which residual kidney function and therefore any antiproteinuric mechanism is largely absent [17]. These trials collectively indicate that the benefit of mineralocorticoid receptor antagonism is concentrated in patients with established but not end-stage kidney disease and with measurable albuminuria.

Pooled analyses reinforce this interpretation while sounding a cautionary note. A systematic review and meta-analysis of nineteen randomised trials in chronic kidney disease reported a weighted mean reduction in protein or albumin excretion of 38.7% with mineralocorticoid receptor antagonism, closely matching the 38.6% median reduction in 24-hour urinary protein excretion observed in the present study, but also documented an approximately threefold relative risk of trial withdrawal because of hyperkalaemia [9]. A Cochrane review reached similar conclusions on proteinuria while noting that the certainty of evidence for kidney failure and mortality endpoints remained low [10]. A further meta-analysis restricted to proteinuric kidney disease likewise confirmed a substantial antiproteinuric effect with an accompanying increase in the risk of hyperkalaemia [19]. The relatively low rate of clinically important hyperkalaemia in the present trial, with only two permanent discontinuations across 60 exposed participants, is plausibly attributable to three features of the design: the halved dose, the restriction of eligibility to an estimated glomerular filtration rate of at least 45 mL/min/1.73 m² with a screening potassium not exceeding 5.0 mmol/L, and the schedule of potassium measurement at four separate visits with predefined discontinuation rules. This combination should be regarded as integral to the intervention rather than incidental to it.

The clinical context has been reshaped by the arrival of non-steroidal mineralocorticoid receptor antagonists. Finerenone reduced the composite of sustained decline in glomerular filtration rate, kidney failure and renal death in patients with chronic kidney disease and type 2 diabetes in the FIDELIO-DKD trial [8], and reduced cardiovascular events in the broader FIGARO-DKD population [15], in each case with a lower incidence of hyperkalaemia than has historically been reported with steroidal agents. Contemporary reviews have accordingly positioned non-steroidal agents as the preferred choice where they are available [2]. The relevance of the present trial lies precisely in that qualification. In publicly funded Bangladesh institutions, the acquisition cost of finerenone remains an order of magnitude greater than that of spironolactone, and sustained supply is not assured. Evidence that a low dose of an inexpensive, widely available steroidal agent delivers a substantial antiproteinuric effect under a defined monitoring protocol therefore addresses a practical therapeutic gap rather than duplicating existing evidence.

The observation that concomitant sodium-glucose cotransporter 2 inhibitor use independently predicted a greater antiproteinuric response merits comment. A randomised crossover trial demonstrated that the albuminuria-lowering effects of dapagliflozin and eplerenone are additive when the agents are combined, producing a reduction of approximately 53% and, importantly, a lower incidence of hyperkalaemia with combination therapy than with the mineralocorticoid receptor antagonist alone [16]. The present data are consistent with that mechanism, although the analysis was exploratory, was not stratified at randomisation and is therefore hypothesis-generating only. The finding nonetheless supports the prevailing guideline direction towards layered pillar-based therapy for diabetic kidney disease rather than sequential monotherapy [4].

The interpretation of albuminuria reduction as a therapeutic goal rests on evidence that a change in albuminuria functions as a valid surrogate for subsequent kidney disease progression. A meta-analysis of treatment effects across randomised trials established that a 30% reduction in albuminuria is associated with a clinically meaningful reduction in the risk of subsequent kidney failure, which provides the justification for the responder threshold adopted in the present study [21]. The modest, non-significant decline in estimated glomerular filtration rate observed in the spironolactone arm is consistent with the acute haemodynamic effect described with other agents that reduce intraglomerular pressure, and long-term data on spironolactone in chronic kidney disease suggest that the initial dip is not associated with an accelerated long-term trajectory [18]. Nonetheless, the present trial was neither designed nor powered to establish an effect on hard kidney endpoints, and the results should not be extrapolated to such outcomes.

Several limitations qualify these findings. The open-label design is the most important, as knowledge of allocation may have influenced adherence, lifestyle behaviour and the reporting of subjective adverse events; the blinding of outcome assessors, laboratory personnel and the statistician mitigates but does not eliminate this concern. The follow-up period of 24

weeks was sufficient to demonstrate an effect on proteinuria but far too short to address kidney or cardiovascular outcomes. The single-centre design and the recruitment of participants from a tertiary care outpatient population limit generalisability, particularly to primary care settings where potassium monitoring may be less reliable. Plasma aldosterone and renin concentrations were not measured, so the trial cannot confirm that participants with biochemical evidence of aldosterone breakthrough derived preferential benefit. Dietary sodium and potassium intake were addressed by counselling but were not quantified by 24-hour urinary electrolyte excretion. Finally, no active comparator arm was included, so the relative efficacy of low-dose spironolactone against conventional-dose spironolactone or against a non-steroidal agent cannot be inferred from these data. Adequately powered, blinded, multicentre trials with longer follow-up and hard kidney endpoints, ideally incorporating a direct comparison across doses and drug classes, are required before low-dose spironolactone can be recommended as standard therapy for residual albuminuria in diabetic kidney disease [25].

CONCLUSION

In adults with type 2 diabetes mellitus and diabetic kidney disease receiving maximally tolerated renin-angiotensin system blockade, the addition of spironolactone 12.5 mg once daily for 24 weeks produced a median reduction of 41.8% in the urine albumin-to-creatinine ratio and a 38.6% reduction in 24-hour urinary protein excretion, against negligible change with standard care alone. More than two-thirds of treated participants achieved a reduction of at least 30% in albuminuria, a threshold associated in pooled trial data with a meaningful reduction in the risk of subsequent kidney failure, and almost one-third regressed to a lower albuminuria category. The antiproteinuric effect was only partly explained by the accompanying 7.5 mmHg between-group difference in systolic blood pressure, which is consistent with a direct action on mineralocorticoid receptor mediated glomerular injury.

The safety profile was acceptable within the constraints of the eligibility criteria and monitoring schedule employed. The mean rise in serum potassium was 0.29 mmol/L, hyperkalaemia above 5.5 mmol/L occurred in 6.7% of treated participants, and permanent discontinuation for hyperkalaemia was required in 3.3%; no participant required emergency intervention. The decline in estimated glomerular filtration rate did not differ significantly between the groups over 24 weeks.

These findings suggest that low-dose spironolactone may be a pragmatic and inexpensive option for reducing residual proteinuria in selected patients with diabetic kidney disease when non-steroidal mineralocorticoid receptor antagonists are not accessible, provided that appropriate potassium and renal-function monitoring is available. Its applicability depends on adherence to the eligibility criteria and the structured potassium surveillance used in this trial. Longer, blinded, multicentre trials with hard kidney and cardiovascular endpoints are needed before low-dose spironolactone can be incorporated into routine practice.

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