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High-Dose Versus Standard-Dose Manidipine for Albuminuria Reduction in Hypertensive Patients With Chronic Kidney Disease: A Triple-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Background

Albuminuria predicts CKD progression and cardiovascular risk. Randomized evidence on manidipine dose escalation in CKD is limited. We evaluated the efficacy and safety of increasing manidipine from 20 to 40 mg/day in hypertensive adults with albuminuric CKD.

Methods

This single-center, randomized, placebo-controlled trial was conducted in Thailand. Adults aged 35–80 years with hypertension, eGFR ≥ 30 mL/min/1.73 m², persistent UACR > 30 mg/g, and background manidipine 20 mg/day were randomized 1:1 to add-on manidipine 20 mg/day (total 40 mg/day) or matching placebo for 6 months. Participants, treating investigators, outcome assessors, and the statistician responsible for the final analysis were masked to treatment allocation. The primary outcome was a ≥ 30% reduction in UACR from baseline to 6 months, analyzed in all randomized participants using non-responder imputation and Pearson's chi-square test.

Results

Ninety-four participants were randomized (46 high-dose; 48 standard-dose); five had no post-baseline assessments. The primary outcome occurred in 32/46 (69.6%) and 15/48 (31.3%) participants, respectively (risk ratio, 2.23; 95% CI, 1.40–3.53; risk difference, 38.3 percentage points; 95% CI, 19.6–57.0; P < 0.001). In the observed-case modified intention-to-treat population, the baseline-adjusted geometric mean ratio for high-dose versus standard-dose UACR at 6 months was 0.48 (95% CI, 0.31–0.74; P = 0.001). No statistically significant between-group differences were observed in blood pressure or kidney function. Among 89 participants with post-baseline safety data, adverse events occurred in 10/44 (22.7%) versus 5/45 (11.1%) (risk difference, 11.6 percentage points; 95% CI, − 4.2 to 27.2; P = 0.167); ankle edema occurred in 18.2% versus 8.9%. One high-dose participant discontinued study medication because of an adverse event; no serious adverse events occurred.

Conclusions

Escalating manidipine from 20 to 40 mg/day increased the probability of achieving a ≥ 30% UACR reduction and lowered UACR at 6 months. The albuminuria effect was observed without statistically significant between-group differences in blood pressure or kidney function, although blood-pressure lowering may have contributed. Adverse events were numerically more frequent with high-dose therapy. Larger, longer-term trials are needed to clarify safety and clinical kidney or cardiovascular benefit.

Clinical trial registration:

Thai Clinical Trials Registry, TCTR20260411008. Retrospectively registered on 11 April 2026.

Background

Albuminuria is a key marker of kidney damage and a strong predictor of chronic kidney disease (CKD) progression, kidney failure, cardiovascular events, and mortality [1, 2]. Beyond its prognostic value, changes in albuminuria are clinically informative. Large observational and trial-level meta-analyses have shown that reductions in albuminuria are associated with a lower subsequent risk of kidney disease progression, particularly among individuals with elevated baseline albuminuria [3, 4]. Scientific evaluations involving the National Kidney Foundation, the US Food and Drug Administration, and the European Medicines Agency have therefore supported early change in albuminuria as a candidate surrogate endpoint for CKD progression under appropriate conditions [5]. Experimental evidence also suggests that filtered albumin and other plasma proteins may contribute to tubulointerstitial inflammation and fibrosis, providing biological plausibility for targeting albuminuria in CKD [6].

Renin–angiotensin system (RAS) inhibition remains a foundation of therapy for albuminuric CKD, and sodium–glucose cotransporter-2 (SGLT2) inhibitors have subsequently become established disease-modifying therapies for many patients with CKD [7–9]. Nevertheless, additional antihypertensive therapy is frequently required to achieve blood-pressure targets, and calcium channel blockers (CCBs) are commonly used for this purpose. The present trial commenced in 2018, before SGLT2 inhibitors became established as routine kidney-protective therapy for CKD. As these agents entered clinical practice during the extended recruitment period, the protocol was amended to exclude patients receiving SGLT2 inhibitors from subsequent enrollment. Manidipine 20 mg was included in the 2018 Thai National List of Essential Medicines [10], providing context for its use within the Thai public healthcare system. Accordingly, evaluation of the kidney-related effects of adjunctive antihypertensive agents remains relevant, while the therapeutic context in which this trial was conducted should be distinguished from contemporary CKD management.

CCBs differ in their effects on the renal microcirculation. Predominantly L-type dihydropyridine CCBs, such as amlodipine, act primarily on preglomerular vessels and may therefore have less favorable effects on intraglomerular pressure despite effective systemic blood-pressure lowering [11, 12]. Manidipine is a dihydropyridine CCB with inhibitory activity at both L-type and T-type calcium channels [12]. In experimental models, manidipine reduces resistance in both afferent and efferent renal arterioles, an effect that may relate in part to T-type calcium-channel blockade [13, 14]. In a randomized human renal hemodynamic study, manidipine was associated with a more favorable intrarenal hemodynamic profile than amlodipine [15]. These findings provide a plausible mechanistic basis for albuminuria lowering that may reflect both systemic blood-pressure reduction and favorable intrarenal hemodynamic effects.

Previous clinical studies have reported reductions in urinary albumin excretion with manidipine in hypertensive patients with diabetes and albuminuria [16–18]. In patients with type 2 diabetes and albuminuria, adding manidipine to candesartan reduced urinary albumin excretion more than adding hydrochlorothiazide despite similar blood-pressure reductions [17]. In the AMANDHA trial, addition of manidipine produced a greater reduction in albuminuria than amlodipine at 6 months in patients receiving background RAS blockade, with the difference maintained during extended follow-up [18]. However, previous studies predominantly evaluated manidipine at doses of 10–20 mg/day or compared manidipine with alternative antihypertensive strategies rather than with a higher dose of manidipine itself. A 40-mg daily dose had previously been evaluated in a randomized dose-ranging hypertension study; however, albuminuria was not assessed [19]. Whether escalation from 20 to 40 mg/day provides additional albuminuria reduction in patients with CKD who are already receiving manidipine 20 mg/day has therefore not been established.

We therefore conducted a triple-blind, randomized, placebo-controlled trial comparing high-dose manidipine (40 mg/day) with continued standard-dose manidipine (20 mg/day) in hypertensive patients with albuminuric CKD who were already receiving manidipine 20 mg/day. We hypothesized that dose escalation to 40 mg/day would increase the proportion of participants achieving the prespecified primary response, defined as a ≥ 30% reduction in urinary albumin-to-creatinine ratio (UACR) from baseline to 6 months. Secondary objectives were to evaluate changes in UACR over time and the effects of treatment on blood pressure, kidney function, glycemic and laboratory parameters, and safety.

Methods

Study design and setting

This was a single-center, parallel-group, triple-blind, randomized, placebo-controlled superiority trial conducted at the outpatient internal medicine clinic of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. The trial evaluated whether increasing the total daily dose of manidipine from 20 mg/day to 40 mg/day provided additional albuminuria reduction in hypertensive patients with albuminuric chronic kidney disease (CKD) who were already receiving manidipine 20 mg/day. Participants were allocated in a 1:1 ratio.

The first participant was enrolled on 2 April 2018, and the last participant was randomized on 15 May 2023. Each participant was followed for 6 months after randomization, with scheduled assessments at Months 1, 3, and 6. The last participant completed the 6-month follow-up on 13 November 2023. Study-related data verification was completed on 4 February 2024 under continuing institutional ethics approval.

Ethics approval and trial registration

The study protocol was approved by the Institutional Review Board/Ethics Committee of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA no. 018/2561; project no. 156/60; initial approval date, 5 February 2018), before enrollment of the first participant. Continuing ethics approval was maintained throughout participant recruitment, follow-up, and study-related data verification. All participants provided written informed consent before enrollment. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles.

The trial was retrospectively registered with the Thai Clinical Trials Registry (TCTR20260411008) on 11 April 2026. The primary efficacy outcome—the proportion of participants achieving a ≥ 30% reduction in urinary albumin-to-creatinine ratio (UACR) from baseline to 6 months—was prespecified in the ethics-approved trial protocol before enrollment of the first participant and formed the basis of the sample size calculation. The final statistical analysis plan (SAP) was finalized and date-stamped before database lock and before disclosure of treatment allocation.

Protocol, statistical analysis plan, and protocol changes

The trial was conducted according to the ethics-approved protocol and approved amendments. The final SAP specified the analysis populations, handling of missing data, primary and supportive analyses, sensitivity analyses, and operational rules for selecting follow-up measurements.

The trial commenced in 2018, before sodium–glucose cotransporter-2 (SGLT2) inhibitors became established as routine kidney-protective therapy for CKD. As these agents entered clinical practice during the extended recruitment period, the protocol was amended, with institutional ethics approval, to exclude patients receiving SGLT2 inhibitors from subsequent enrollment. This amendment was intended to minimize potential confounding of albuminuria outcomes by concomitant SGLT2 inhibitor therapy.

Before treatment-code disclosure, the analysis dataset underwent masked data review, including assessment of protocol deviations, missing data, and eligibility for the prespecified analysis populations. Treatment groups were provided to the statistician responsible for the final analysis using masked group codes. Prespecified analyses were performed according to the SAP, and treatment identities were disclosed only after the relevant analysis decisions had been documented. Analyses introduced after treatment-code disclosure were identified as post hoc where applicable.

No interim efficacy analyses were planned or performed, and no formal trial-level statistical stopping guidelines were specified. The protocol and SAP are available from the corresponding author on reasonable request.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, analysis, or reporting of the trial.

Participants and eligibility criteria

Potentially eligible patients attending the outpatient internal medicine clinic were identified using the hospital electronic medical record system, based on diagnostic and medication records for hypertension, diabetes mellitus, CKD, and current manidipine treatment.

Participants were eligible if they were 35–80 years of age; had treated hypertension with a seated systolic blood pressure ≥ 120 and < 150 mmHg at screening; were receiving manidipine 20 mg/day before enrollment; had persistent albuminuria, defined as UACR > 30 mg/g documented on at least two independent measurements within the preceding 6 months in the absence of active urinary tract infection; and had an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m² based on a serum creatinine measurement obtained within the preceding 3 months. There was no upper eGFR eligibility limit.

eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [20]. For reporting, kidney function was categorized as G1 (eGFR ≥ 90 mL/min/1.73 m²), G2 (60–89 mL/min/1.73 m²), and G3 (30–59 mL/min/1.73 m²), consistent with the KDIGO 2012 GFR categories, with G3a and G3b combined [21].

Concomitant treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, other antihypertensive agents, and clinically indicated treatments for controlled comorbid conditions was permitted. RAS inhibitor therapy was not required for eligibility, and the protocol did not require a run-in to maximally tolerated RAS inhibitor therapy. Following the ethics-approved protocol amendment, patients receiving an SGLT2 inhibitor were not eligible for subsequent enrollment.

Exclusion criteria included bedridden status; inability to provide reliable clinical information or attend scheduled follow-up visits; refusal to participate; severe liver disease; ischemic heart disease or stroke within the preceding 3 months; pregnancy; and use of medications considered to have clinically important interactions with manidipine metabolism.

Randomization and allocation concealment

The random allocation sequence was generated by an independent statistician who was not involved in participant recruitment, clinical care, outcome assessment, or the subsequent blinded statistical analysis. Participants were randomly assigned in a 1:1 ratio using computer-generated permuted-block randomization with a fixed block size of four.

An independent pharmacist prepared the study medication according to the randomization sequence and placed it in sequentially numbered, opaque, sealed containers with identical external packaging. After written informed consent had been obtained and eligibility confirmed, study personnel dispensed the next sequentially numbered study-medication package.

Personnel responsible for participant enrollment and treatment assignment had no access to the randomization sequence and therefore could not foresee upcoming treatment assignments. The allocation code was maintained separately in a sealed record and stored securely in the pharmacy.

Blinding

Participants, treating investigators, outcome assessors, and the statistician responsible for the blinded final analysis were unaware of treatment allocation.

Active add-on manidipine (20 mg) and matching placebo tablets were manufactured to be identical in physical appearance, dimensions, shape, color, weight, surface characteristics, and organoleptic properties, including taste and odor. They were supplied in identically packaged, sequentially numbered study-medication containers to preserve treatment masking.

The allocation code remained inaccessible to participants, investigators, treating clinicians, outcome assessors, and the statistician responsible for the blinded final analysis until database lock and completion of the prespecified masked analysis procedures. Before treatment-code disclosure, treatment groups were identified only by masked group codes, and the allocation code was disclosed only after the relevant analysis decisions had been documented. The independent statistician who generated the randomization sequence was distinct from the statistician who performed the blinded final analyses.

Interventions

All participants continued their pre-existing manidipine dose of 20 mg/day throughout the randomized treatment period.

Participants assigned to the high-dose group received one additional manidipine 20-mg tablet once daily after the evening meal, resulting in a total manidipine dose of 40 mg/day. Participants assigned to the standard-dose group received one matching placebo tablet once daily after the evening meal while continuing background manidipine 20 mg/day, resulting in a total active manidipine dose of 20 mg/day.

Thus, the randomized comparison was background manidipine 20 mg/day plus add-on manidipine 20 mg/day versus background manidipine 20 mg/day plus matching placebo.

Concomitant antihypertensive and other clinically indicated therapies, including renin–angiotensin system inhibitor therapy, were permitted according to the study protocol.

Follow-up, assessments, and treatment adherence

Participants underwent scheduled assessments at baseline and at Months 1, 3, and 6 after randomization.

Baseline assessments included demographic and clinical characteristics, comorbidities, concomitant medications, systolic (SBP) and diastolic blood pressure (DBP), UACR, serum creatinine and eGFR, serum potassium, serum albumin, fasting plasma glucose, and glycated hemoglobin (HbA1c).

At scheduled follow-up visits, blood pressure, UACR, kidney function, treatment adherence, and adverse events were assessed according to the study protocol. Laboratory and glycemic measurements were obtained according to the scheduled study assessments.

Treatment adherence was assessed by counting returned study tablets at each follow-up visit. Acceptable adherence was defined as taking at least 80% of the prescribed study medication.

For analyses of Month 6 kidney-function, laboratory, and glycemic outcomes, the SAP prespecified that measurements obtained between 5 and 8 months after randomization could represent the Month 6 assessment. When more than one eligible measurement was available within this interval, the measurement closest to 6 months after randomization was selected.

Outcomes

The prespecified primary efficacy outcome was the proportion of randomized participants achieving a ≥ 30% reduction in UACR from baseline to 6 months.

Other albuminuria outcomes included UACR at Months 1, 3, and 6; absolute change in UACR from baseline to Month 6; percentage change in UACR from baseline to Month 6; the proportion of participants achieving a ≥ 50% reduction in UACR; and the proportion achieving any reduction in UACR.

Percentage change in UACR was calculated as [(Month 6 UACR − baseline UACR)/baseline UACR] × 100.

Secondary clinical and laboratory outcomes included systolic and diastolic blood pressure, serum creatinine, eGFR, serum potassium, serum albumin, and HbA1c at Month 6 and their changes from baseline, where applicable.

There were no changes to the prespecified primary or secondary outcomes after trial commencement.

Harms

Adverse events were systematically evaluated at each scheduled post-randomization visit throughout each participant's 6-month follow-up using a standardized two-step assessment. Participants were first asked an open-ended question regarding any new or unexpected health problems or symptoms since the preceding visit, followed by a structured review of recognized adverse effects associated with dihydropyridine calcium channel blockers.

Targeted clinical assessment included evaluation for ankle edema, dizziness, flushing, palpitations, and orthostatic symptoms. Lower-extremity edema and seated blood pressure were routinely assessed at each visit, and serum potassium was monitored as part of the scheduled laboratory safety assessments.

Hyperkalemia was defined as a laboratory-confirmed serum potassium concentration > 5.5 mmol/L or an elevated serum potassium concentration requiring clinical intervention or modification of concomitant medication. Symptomatic hypotension was defined as a seated systolic blood pressure < 90 mmHg accompanied by symptoms attributable to hypotension, including dizziness, lightheadedness, presyncope, diaphoresis, or postural symptoms. Dizziness occurring in the absence of hypotension was classified separately as dizziness.

Prespecified safety outcomes were the occurrence of at least one adverse event, ankle edema, dizziness, symptomatic hypotension, hyperkalemia, study-drug discontinuation due to an adverse event, and serious adverse events. Each participant was counted once within each adverse-event category if one or more events of that type occurred; an individual participant could contribute to more than one category.

Serious adverse events and suspected unexpected serious adverse reactions were reported in accordance with institutional ethics committee requirements.

Sample size calculation

The sample size calculation was based on the prespecified primary efficacy outcome, defined as the proportion of participants achieving a ≥ 30% reduction in UACR from baseline to 6 months.

Because no previous trial had directly compared high-dose with standard-dose manidipine using this binary responder definition, anticipated response proportions were based on conservative planning assumptions informed by previous studies evaluating the antiproteinuric effects of manidipine and related antihypertensive strategies in patients with albuminuria [17, 18].

Response rates of 60% in the high-dose manidipine group ($p_1 = 0.60$) and 30% in the standard-dose group ($p_2 = 0.30$) were assumed, corresponding to an absolute between-group difference of 30 percentage points. Using the standard normal approximation for comparison of two independent proportions, a two-sided significance level of 0.05, and 80% statistical power, a minimum of 42 participants per group (84 participants in total) was required.

A total of 94 participants were randomized, including 46 to the high-dose manidipine group and 48 to the standard-dose manidipine group, exceeding the prespecified minimum sample size.

Statistical analysis

Baseline demographic and clinical characteristics were summarized by randomized treatment group. Continuous variables are presented as mean ± standard deviation (SD) or median with first and third quartiles (Q1–Q3), as appropriate, and categorical variables as frequencies and percentages. Formal significance testing of baseline characteristics between randomized treatment groups was not performed.

Analysis populations

The intention-to-treat (ITT) population comprised all 94 randomized participants, analyzed according to their assigned treatment groups: 46 in the high-dose group and 48 in the standard-dose group.

The observed-case modified intention-to-treat (mITT) population comprised randomized participants with baseline and evaluable post-baseline UACR data: 44 participants in the high-dose group and 45 in the standard-dose group. All participants in this population had evaluable Month 6 UACR data.

The safety-evaluable population comprised randomized participants with at least one post-baseline safety assessment: 44 participants in the high-dose group and 45 in the standard-dose group.

Five participants—two in the high-dose group and three in the standard-dose group—were lost to follow-up immediately after randomization and had no post-baseline assessments.

Primary efficacy analysis

The primary efficacy outcome was analyzed in the ITT population. Participants without evaluable 6-month responder status were classified as non-responders using non-responder imputation; this applied to the five participants who had no post-baseline assessments. No last-observation-carried-forward imputation was used.

Between-group differences were tested using Pearson's chi-square test. Treatment effects were reported as risk ratios (RRs) with 95% confidence intervals (CIs) calculated using the log method and as absolute risk differences (RDs) with 95% CIs calculated using the Wald method.

Binary albuminuria outcomes

The proportions of participants achieving a ≥ 50% reduction in UACR and any reduction in UACR were analyzed in the observed-case mITT population.

Between-group comparisons were performed using Pearson's chi-square test. Effects were reported as RRs with 95% CIs calculated using the log method and RDs with 95% CIs calculated using the Wald method.

Continuous albuminuria outcomes

Because UACR was right-skewed, UACR values were summarized as medians (Q1–Q3).

At Months 1, 3, and 6, baseline-adjusted treatment effects were estimated using linear regression models with log-transformed follow-up UACR as the dependent variable and treatment group and log-transformed baseline UACR as covariates. The treatment coefficient and its 95% CI were exponentiated and reported as a geometric mean ratio (GMR), with values < 1 favoring high-dose manidipine.

Absolute and percentage changes in UACR from baseline to Month 6 were summarized as medians (Q1–Q3). Between-group comparisons were performed using the Mann–Whitney U test. Between-group

differences in medians and their 95% CIs were estimated using a nonparametric bias-corrected and accelerated (BCa) bootstrap procedure with 5,000 resamples.

No imputation was performed for the observed-case albuminuria analyses.

Supportive and sensitivity analyses

A supportive observed-case analysis of the primary responder outcome was performed in the mITT population without imputation.

A baseline-adjusted logistic regression model was fitted in the observed-case mITT population, with treatment group and baseline log-transformed UACR included as covariates. The treatment effect was reported as an adjusted odds ratio with a 95% CI.

A worst-case sensitivity analysis included all randomized participants. Participants with missing 6-month responder status in the high-dose group were classified as non-responders, whereas those with missing responder status in the standard-dose group were classified as responders.

Secondary clinical and laboratory analyses

Blood pressure, kidney-function, laboratory, and glycemic outcomes were analyzed in the mITT population. Continuous outcomes were summarized as mean ± SD. Between-group treatment effects were reported as unadjusted mean differences with 95% CIs and compared using two-sided independent-samples Student's t tests assuming equal variances.

Change-from-baseline analyses included participants with both baseline and the corresponding follow-up measurement. For outcomes with incomplete follow-up measurements, available-case analysis was used and no imputation was performed. Accordingly, baseline values used for change calculations were restricted to participants contributing paired baseline and follow-up measurements and could differ from baseline values reported for the complete randomized population.

For Month 6 kidney-function, laboratory, and glycemic analyses, the prespecified 5–8-month assessment window defined in the SAP was applied, with the measurement closest to 6 months selected when multiple eligible measurements were available.

Safety analyses

Safety analyses included randomized participants with at least one post-baseline safety assessment.

For each safety outcome, the absolute RD was calculated as the event proportion in the high-dose group minus that in the standard-dose group and expressed in percentage points. Ninety-five percent CIs for RDs were calculated using the Newcombe method based on Wilson score intervals. P values were obtained using two-sided Fisher's exact tests. No P value was calculated when no events occurred in either treatment group.

All statistical tests were two-sided. A P value < 0.05 was considered statistically significant for the primary efficacy analysis. No adjustment for multiplicity was applied to non-primary outcomes; these analyses were interpreted as exploratory. Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

Reporting guideline

The trial is reported in accordance with the CONSORT 2010 statement [22]. A completed CONSORT checklist and participant flow diagram accompany the manuscript.

Use of generative artificial intelligence

Generative artificial intelligence tools were used during manuscript preparation to assist with language editing, manuscript organization, consistency checking, and alignment with reporting guidelines. All AI-assisted content was critically reviewed, fact-checked, and revised by the authors, who take full responsibility for the accuracy, interpretation, and integrity of the manuscript.

Results

Participant flow and recruitment

Of 156 patients assessed for eligibility, 62 were excluded before randomization: 36 did not proceed to consent or enrollment, and 26 consented but were not randomized. Among the latter, 6 had UACR below the eligibility threshold on repeat testing, 3 had eGFR below the eligibility threshold on confirmatory testing, 6 had blood pressure outside the protocol-specified range at baseline, 2 had other laboratory exclusions, 2 withdrew consent, and 7 were lost to contact or missed the baseline visit (Fig. 1).

The first participant was enrolled on 2 April 2018, and the last participant was randomized on 15 May 2023. The last participant completed the 6-month follow-up on 13 November 2023. The trial was completed as planned after the final participant completed the prespecified follow-up and was not stopped early.

A total of 94 participants were randomized: 46 to high-dose manidipine (40 mg/day) and 48 to standard-dose manidipine (20 mg/day). All 94 randomized participants received the allocated study medication (46 and 48, respectively). Two participants in the high-dose group and three in the standard-dose group were lost to follow-up immediately after randomization and had no post-baseline assessments. One participant in the high-dose group discontinued study medication because of an adverse event but remained in follow-up.

The primary efficacy outcome was analyzed in all 94 randomized participants according to the intention-to-treat (ITT) principle, with participants missing 6-month responder status classified as non-responders. Other albuminuria outcomes were analyzed in the observed-case modified intention-to-treat (mITT) population, comprising 44 participants in the high-dose group and 45 in the standard-dose group with

baseline and evaluable post-baseline UACR data. Safety analyses included 44 and 45 participants, respectively, with at least one post-baseline safety assessment. Participant flow is shown in Fig. 1.

Treatment adherence, concomitant therapy, and blinding

The prespecified adherence threshold of at least 80% of prescribed study medication was met by 39 of 44 participants (88.6%) in the high-dose group and 39 of 45 participants (86.7%) in the standard-dose group.

Changes in concomitant antihypertensive therapy during follow-up were infrequent. RAS inhibitor therapy was initiated in 1 of 44 participants (2.3%) in the high-dose group and 1 of 45 (2.2%) in the standard-dose group and was discontinued in no participants and 1 participant (2.2%), respectively. Other antihypertensive therapy was added in 2 participants (4.5%) in the high-dose group and 3 (6.7%) in the standard-dose group and was reduced in 2 participants (4.5%) and none, respectively. No participant initiated SGLT2 inhibitor therapy during follow-up.

No emergency unblinding was requested or performed during the 6-month follow-up. Treatment allocation remained concealed from participants, investigators, outcome assessors, and the statistician responsible for the blinded final analysis until database lock and completion of the prespecified masked analysis procedures.

Baseline characteristics

Baseline demographic and clinical characteristics are summarized in Table 1. Mean age was 59.5 ± 7.3 years in the high-dose group and 58.6 ± 5.0 years in the standard-dose group. Women comprised 16 of 46 participants (34.8%) and 14 of 48 (29.2%), respectively. Diabetes mellitus was present in 34 participants (73.9%) in the high-dose group and 35 (72.9%) in the standard-dose group. CKD category G3 accounted for 21 participants (45.7%) and 20 participants (41.7%), respectively.

Table 1
Baseline demographic and clinical characteristics of randomized participants

Parameter	High-dose manidipine (40 mg) group (N = 46)	Standard-dose manidipine (20 mg) group (N = 48)
Age, years	59.5 ± 7.3	58.6 ± 5.0
Sex, female, n (%)	16 (34.8%)	14 (29.2%)
BMI, kg/m²	25.8 ± 4.0	25.5 ± 4.1
CKD G category, n (%)		
G1	11 (23.9%)	10 (20.8%)
G2	14 (30.4%)	18 (37.5%)
G3	21 (45.7%)	20 (41.7%)
Diabetes mellitus, n (%)	34 (73.9%)	35 (72.9%)
Blood pressure, mmHg		
Systolic (SBP)	136.2 ± 11.6	135.2 ± 10.4
Diastolic (DBP)	73.2 ± 12.1	74.6 ± 13.8
Creatinine, mg/dL	1.14 ± 0.41	1.12 ± 0.45
eGFR, mL/min/1.73 m²	69.3 ± 24.0	71.7 ± 25.0
UACR, median (Q1–Q3), mg/g	346 (210–688)	274 (165–503)
Albumin, g/dL	3.91 ± 0.56	3.94 ± 0.31
Fasting plasma glucose, mg/dL	152.1 ± 37.8	147.2 ± 39.3
HbA1c, %	7.32 ± 1.14	7.17 ± 1.02
Serum potassium, mmol/L	4.28 ± 0.38	4.31 ± 0.41
Concomitant antihypertensive drugs, n (%)		
RAS inhibitor use	25 (54.3%)	26 (54.2%)
Diuretics	16 (34.8%)	15 (31.2%)
Beta-blockers	11 (23.9%)	10 (20.8%)
Other antihypertensives	4 (8.7%)	5 (10.4%)
Statin use, n (%)	42 (91.3%)	43 (89.6%)

Note: Data are presented as mean ± SD, median (Q1–Q3), or n (%), as appropriate. Participants could receive more than one class of concomitant antihypertensive medication.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; Q1, first quartile; Q3, third quartile; RAS, renin–angiotensin system; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

Baseline SBP was 136.2 ± 11.6 mmHg in the high-dose group and 135.2 ± 10.4 mmHg in the standard-dose group; corresponding DBP values were 73.2 ± 12.1 and 74.6 ± 13.8 mmHg. Mean baseline eGFR was 69.3 ± 24.0 and 71.7 ± 25.0 mL/min/1.73 m², respectively.

Median baseline UACR in the randomized population was numerically higher in the high-dose group than in the standard-dose group: 346 mg/g (Q1–Q3, 210–688) versus 274 mg/g (Q1–Q3, 165–503). Concomitant RAS inhibitor therapy was used by 25 participants (54.3%) in the high-dose group and 26 (54.2%) in the standard-dose group.

Primary efficacy outcome

In the primary ITT analysis, 32 of 46 participants (69.6%) in the high-dose manidipine group achieved the primary outcome of a ≥ 30% reduction in UACR from baseline to 6 months, compared with 15 of 48 participants (31.3%) in the standard-dose group (Table 2; Fig. 3).

Table 2
Efficacy and albuminuria outcomes during the 6-month follow-up period

Outcome	High-dose manidipine (40 mg) group	Standard-dose manidipine (20 mg) group	Effect estimate (95% CI)	P value
Primary efficacy outcome (ITT population)a	**n = 46**	**n = 48**		
Participants achieving ≥ 30% reduction in UACR at 6 months, n/N (%)	32/46 (69.6%)	15/48 (31.3%)	RR, 2.23 (1.40–3.53); RD, 38.3 percentage points (19.6–57.0)	< 0.001
Albuminuria outcomes (observed-case mITT population)b	**n = 44**	**n = 45**		
UACR at baseline, median (Q1–Q3), mg/g	312 (210–692)	284 (165–536)	—	—
UACR at 1 month, median (Q1–Q3), mg/gc	286.8 (185–520)	231.2 (140–410)	Adjusted GMR, 1.11 (0.83–1.47)	0.474
UACR at 3 months, median (Q1–Q3), mg/gc	210.0 (130–410)	235.0 (145–420)	Adjusted GMR, 0.81 (0.61–1.07)	0.142
UACR at 6 months, median (Q1–Q3), mg/gc	130.0 (90–290)	242.3 (150–490)	Adjusted GMR, 0.48 (0.31–0.74)	0.001
Absolute UACR change from baseline to 6 months, median (Q1–Q3), mg/gd	−216.0 (− 398 to − 60)	−31.7 (− 115 to 45)	Median difference, − 184 mg/g (− 288 to − 81)	< 0.001
Percentage UACR change from baseline to 6 months, median (Q1–Q3), %d	−62.4 (− 78.5 to − 41.2)	−11.6 (− 32.5 to 12.4)	Median difference, − 50.8 percentage points (− 66 to − 36)	< 0.001
Participants achieving ≥ 50% reduction in UACR, n/N (%)	26/44 (59.1%)	10/45 (22.2%)	RR, 2.66 (1.46–4.84); RD, 36.9 percentage points (17.9–55.8)	< 0.001
Participants with any reduction in UACR, n/N (%)	40/44 (90.9%)	28/45 (62.2%)	RR, 1.46 (1.14–1.87); RD, 28.7 percentage points (12.2–45.2)	0.001

Notes: □ The primary outcome was analyzed in the intention-to-treat population (46 high-dose; 48 standard-dose). Two and three participants, respectively, were lost to follow-up immediately after randomization with no post-baseline assessments and were classified as non-responders using non-responder imputation.

□ Other albuminuria outcomes were analyzed in the observed-case modified intention-to-treat population (44 and 45 participants, respectively) with baseline and post-baseline UACR measurements. UACR

measurements at Months 1, 3, and 6 were available for all participants in this population; no imputation was performed. Baseline UACR therefore differs from Table 1, which includes all randomized participants.

 Adjusted GMRs at Months 1, 3, and 6 were estimated by linear regression of log-transformed follow-up UACR on treatment group and log-transformed baseline UACR. The treatment coefficient and 95% CI were exponentiated; GMRs <1 favor high-dose manidipine.

 Absolute change was Month 6 minus baseline UACR. Percentage change was [(Month 6 UACR − baseline UACR)/baseline UACR] × 100. Between-group median differences (high-dose minus standard-dose) and 95% CIs were estimated using the nonparametric BCa bootstrap with 5000 resamples; negative values indicate greater reductions with high-dose manidipine. P values were obtained using the Mann–Whitney U test.

RR confidence intervals were calculated using the log method and RD confidence intervals using the Wald method. P values for binary outcomes were obtained using Pearson's chi-square test. All tests were two-sided; no multiplicity adjustment was applied to non-primary outcomes.

Abbreviations: BCa, bias-corrected and accelerated; CI, confidence interval; GMR, geometric mean ratio; ITT, intention-to-treat; mITT, modified intention-to-treat; Q1, first quartile; Q3, third quartile; RD, risk difference; RR, risk ratio; UACR, urinary albumin-to-creatinine ratio.

High-dose manidipine was associated with a higher probability of achieving the primary outcome (RR, 2.23; 95% CI, 1.40–3.53; P < 0.001). The corresponding absolute RD was 38.3 percentage points (95% CI, 19.6–57.0; P < 0.001).

Prespecified supportive and sensitivity analyses yielded treatment-effect estimates in the same direction as the primary analysis (Supplementary Table S1); the RR-based analyses are also shown in Fig. 3.

In the supportive observed-case analysis, the primary outcome was achieved by 32 of 44 participants (72.7%) in the high-dose group and 15 of 45 (33.3%) in the standard-dose group (RR, 2.18; 95% CI, 1.39–3.43; RD, 39.4 percentage points; 95% CI, 20.3–58.4; P < 0.001).

In the baseline-adjusted logistic regression analysis of the observed-case mITT population, high-dose manidipine was associated with higher odds of achieving the primary outcome after adjustment for baseline log-transformed UACR (adjusted OR, 6.42; 95% CI, 2.48–16.64; P < 0.001).

In the worst-case sensitivity analysis, participants with missing 6-month responder status in the high-dose group were classified as non-responders, whereas those with missing responder status in the standard-dose group were classified as responders. Response rates were 32 of 46 (69.6%) and 18 of 48 (37.5%), respectively (RR, 1.86; 95% CI, 1.23–2.80; RD, 32.1 percentage points; 95% CI, 13.0–51.2; P = 0.002).

Albuminuria outcomes over follow-up

In the observed-case mITT population, UACR measurements at Months 1, 3, and 6 were available for all 44 participants in the high-dose group and all 45 participants in the standard-dose group. No imputation was performed for these analyses.

Median baseline UACR was 312 mg/g (Q1–Q3, 210–692) in the high-dose group and 284 mg/g (Q1–Q3, 165–536) in the standard-dose group (Table 2; Fig. 2).

There was no evidence of a between-group difference in baseline-adjusted UACR at Month 1 (adjusted GMR, 1.11; 95% CI, 0.83–1.47; P = 0.474) or Month 3 (adjusted GMR, 0.81; 95% CI, 0.61–1.07; P = 0.142). At Month 6, the adjusted GMR was 0.48 (95% CI, 0.31–0.74; P = 0.001), corresponding to a 52% lower adjusted geometric mean UACR in the high-dose group relative to the standard-dose group.

Median UACR at Month 6 was 130.0 mg/g (Q1–Q3, 90–290) in the high-dose group and 242.3 mg/g (Q1–Q3, 150–490) in the standard-dose group.

The median absolute change in UACR from baseline to Month 6 was − 216.0 mg/g (Q1–Q3, − 398 to − 60) in the high-dose group and − 31.7 mg/g (Q1–Q3, − 115 to 45) in the standard-dose group. The between-group median difference was − 184 mg/g (95% CI, − 288 to − 81; P < 0.001).

The median percentage change in UACR was − 62.4% (Q1–Q3, − 78.5% to − 41.2%) in the high-dose group and − 11.6% (Q1–Q3, − 32.5% to 12.4%) in the standard-dose group, corresponding to a median between-group difference of − 50.8 percentage points (95% CI, − 66 to − 36; P < 0.001).

A ≥ 50% reduction in UACR was achieved by 26 of 44 participants (59.1%) in the high-dose group and 10 of 45 (22.2%) in the standard-dose group (RR, 2.66; 95% CI, 1.46–4.84; RD, 36.9 percentage points; 95% CI, 17.9–55.8; P < 0.001).

Any reduction in UACR was observed in 40 of 44 participants (90.9%) in the high-dose group and 28 of 45 (62.2%) in the standard-dose group (RR, 1.46; 95% CI, 1.14–1.87; RD, 28.7 percentage points; 95% CI, 12.2–45.2; P = 0.001).

Secondary blood pressure, kidney function, and laboratory outcomes

Blood pressure

Blood pressure changes were small, and no statistically significant between-group differences in SBP or DBP were observed during follow-up (Table 3; Supplementary Figure S1).

Table 3
Secondary blood pressure, kidney function, laboratory, and glycemic outcomes during follow-up

Outcome	High-dose manidipine (40 mg) group (N = 44)	Standard-dose manidipine (20 mg) group (N = 45)	Unadjusted mean difference (95% CI)	P value
Blood pressure outcomes				
SBP at 1 month, mmHg	134.1 ± 16.3	134.7 ± 13.6	−0.6 (− 6.9 to 5.8)	0.858
SBP at 3 months, mmHg	132.5 ± 14.1	135.3 ± 14.5	−2.8 (− 8.8 to 3.2)	0.359
SBP at 6 months, mmHg	132.3 ± 13.3	136.0 ± 15.2	−3.7 (− 9.8 to 2.3)	0.219
Change in SBP from baseline to 6 months, mmHg	−3.7 ± 13.4	0.6 ± 14.1	−4.3 (− 10.1 to 1.5)	0.144
DBP at 1 month, mmHg	77.3 ± 14.4	78.1 ± 14.3	−0.8 (− 6.9 to 5.2)	0.780
DBP at 3 months, mmHg	76.5 ± 12.2	78.2 ± 13.4	−1.7 (− 7.1 to 3.7)	0.534
DBP at 6 months, mmHg	75.8 ± 12.4	78.3 ± 13.5	−2.5 (− 8.1 to 2.9)	0.351
Change in DBP from baseline to 6 months, mmHg	2.3 ± 12.9	4.1 ± 13.8	−1.8 (− 7.4 to 3.8)	0.527
Kidney function outcomes				
Serum creatinine at 6 months, mg/dL	1.20 ± 0.48	1.18 ± 0.51	0.02 (− 0.19 to 0.23)	0.849
Change in serum creatinine from baseline to 6 months, mg/dL	0.06 ± 0.22	0.07 ± 0.21	−0.01 (− 0.10 to 0.08)	0.827
eGFR at 6 months, mL/min/1.73 m²	66.1 ± 22.5	68.9 ± 23.8	−2.8 (− 12.6 to 7.0)	0.570
Change in eGFR from baseline to 6 months, mL/min/1.73 m²	−3.2 ± 7.8	−2.9 ± 7.2	−0.3 (− 3.4 to 2.9)	0.886
Other laboratory and glycemic outcomes				
Serum potassium at 6 months, mmol/L	4.30 ± 0.42 (n = 42)	4.35 ± 0.45 (n = 43)	−0.05 (− 0.24 to 0.14)	0.598

Outcome	High-dose manidipine (40 mg) group (N = 44)	Standard-dose manidipine (20 mg) group (N = 45)	Unadjusted mean difference (95% CI)	P value
Blood pressure outcomes				
Change in serum potassium from baseline to 6 months, mmol/L	0.02 ± 0.41 (n = 42)	0.04 ± 0.44 (n = 43)	−0.02 (− 0.20 to 0.16)	0.829
Serum albumin at 6 months, g/dL	3.93 ± 0.52 (n = 41)	3.96 ± 0.35 (n = 40)	−0.03 (− 0.23 to 0.17)	0.762
Change in serum albumin from baseline to 6 months, g/dL	0.02 ± 0.31 (n = 41)	0.02 ± 0.32 (n = 40)	0.00 (− 0.14 to 0.14)	1.000
HbA1c at 6 months, %	7.03 ± 1.20 (n = 39)	7.33 ± 1.12 (n = 41)	−0.30 (− 0.82 to 0.22)	0.251
Change in HbA1c from baseline to 6 months, percentage points	−0.33 ± 1.12 (n = 39)	0.12 ± 1.02 (n = 41)	−0.45 (− 0.93 to 0.03)	0.064

Note: Data are presented as mean ± SD. Analyses were conducted in the modified intention-to-treat population, comprising 44 participants in the high-dose manidipine group and 45 participants in the standard-dose manidipine group. Unless otherwise indicated by an *n* value, analyses included all 44 and 45 participants, respectively. For outcomes with incomplete data, available-case analysis was used; the corresponding *n* is shown and no imputation was performed. For 6-month kidney function, laboratory, and glycemic outcomes, the prespecified statistical analysis plan window of 5 to 8 months after randomization was applied; when multiple eligible measurements were available, the measurement closest to 6 months was selected. Unadjusted mean differences were calculated as the mean in the high-dose group minus the mean in the standard-dose group. Changes were calculated as the follow-up value minus the baseline value among participants with both measurements. Baseline values used for change calculations were restricted to participants contributing paired baseline and follow-up measurements and may therefore differ from the randomized-population baseline values reported in Table 1. P values were obtained using two-sided independent-samples Student's *t* tests assuming equal variances. No adjustment was made for multiple comparisons; these secondary analyses should therefore be interpreted as exploratory.

Abbreviations:CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; mITT, modified intention-to-treat; SBP, systolic blood pressure; SD, standard deviation.

At Month 6, mean SBP was 132.3 ± 13.3 mmHg in the high-dose group and 136.0 ± 15.2 mmHg in the standard-dose group (mean difference, − 3.7 mmHg; 95% CI, − 9.8 to 2.3; P = 0.219). Mean change in SBP from baseline to Month 6 was − 3.7 ± 13.4 mmHg and 0.6 ± 14.1 mmHg, respectively (mean difference, − 4.3 mmHg; 95% CI, − 10.1 to 1.5; P = 0.144).

At Month 6, mean DBP was 75.8 ± 12.4 mmHg in the high-dose group and 78.3 ± 13.5 mmHg in the standard-dose group (mean difference, − 2.5 mmHg; 95% CI, − 8.1 to 2.9; P = 0.351). Mean change in DBP from baseline was 2.3 ± 12.9 mmHg and 4.1 ± 13.8 mmHg, respectively (mean difference, − 1.8 mmHg; 95% CI, − 7.4 to 3.8; P = 0.527).

Kidney function and laboratory outcomes

Kidney-function measures did not differ significantly between groups at Month 6 (Table 3). Mean serum creatinine was 1.20 ± 0.48 mg/dL in the high-dose group and 1.18 ± 0.51 mg/dL in the standard-dose group (mean difference, 0.02 mg/dL; 95% CI, − 0.19 to 0.23; P = 0.849).

Mean eGFR at Month 6 was 66.1 ± 22.5 mL/min/1.73 m² in the high-dose group and 68.9 ± 23.8 mL/min/1.73 m² in the standard-dose group (mean difference, − 2.8 mL/min/1.73 m²; 95% CI, − 12.6 to 7.0; P = 0.570). Mean change in eGFR from baseline was − 3.2 ± 7.8 versus − 2.9 ± 7.2 mL/min/1.73 m² (mean difference, − 0.3 mL/min/1.73 m²; 95% CI, − 3.4 to 2.9; P = 0.886).

Among participants with available measurements, serum potassium at Month 6 was 4.30 ± 0.42 mmol/L (n = 42) in the high-dose group and 4.35 ± 0.45 mmol/L (n = 43) in the standard-dose group (mean difference, − 0.05 mmol/L; 95% CI, − 0.24 to 0.14; P = 0.598).

Serum albumin at Month 6 was 3.93 ± 0.52 g/dL (n = 41) in the high-dose group and 3.96 ± 0.35 g/dL (n = 40) in the standard-dose group (mean difference, − 0.03 g/dL; 95% CI, − 0.23 to 0.17; P = 0.762). Mean change from baseline was 0.02 ± 0.31 and 0.02 ± 0.32 g/dL, respectively (mean difference, 0.00 g/dL; 95% CI, − 0.14 to 0.14; P = 1.000).

Glycemic outcomes

Among participants with available HbA1c measurements, mean HbA1c at Month 6 was 7.03 ± 1.20% (n = 39) in the high-dose group and 7.33 ± 1.12% (n = 41) in the standard-dose group (mean difference, − 0.30 percentage points; 95% CI, − 0.82 to 0.22; P = 0.251).

Mean change in HbA1c from baseline was − 0.33 ± 1.12 percentage points in the high-dose group and 0.12 ± 1.02 percentage points in the standard-dose group (mean difference, − 0.45 percentage points; 95% CI, − 0.93 to 0.03; P = 0.064).

Adverse events and safety

At least one adverse event occurred in 10 of 44 participants (22.7%) in the high-dose group and 5 of 45 participants (11.1%) in the standard-dose group (RD, 11.6 percentage points; 95% CI, − 4.2 to 27.2; P = 0.167) (Table 4).

Table 4
Safety outcomes during the 6-month follow-up period

Safety outcome	High-dose manidipine (40 mg) group (N = 44)	Standard-dose manidipine (20 mg) group (N = 45)	Risk difference (95% CI), percentage points	P value
Participants with at least one adverse event	10 (22.7%)	5 (11.1%)	11.6 (− 4.2 to 27.2)	0.167
Ankle edema	8 (18.2%)	4 (8.9%)	9.3 (− 5.4 to 24.1)	0.230
Dizziness	3 (6.8%)	1 (2.2%)	4.6 (− 5.8 to 16.1)	0.361
Symptomatic hypotension	1 (2.3%)	0 (0.0%)	2.3 (− 5.8 to 11.8)	0.494
Hyperkalemia	0 (0.0%)	1 (2.2%)	−2.2 (− 11.6 to 6.0)	1.000
Study-drug discontinuation due to adverse events	1 (2.3%)	0 (0.0%)	2.3 (− 5.8 to 11.8)	0.494
Serious adverse events	0 (0.0%)	0 (0.0%)	0.0 (− 7.9 to 8.0)	—

Note: Data are presented as number (percentage). The safety-evaluable population comprised randomized participants with at least one post-baseline safety assessment: 44 participants in the high-dose group and 45 participants in the standard-dose group. Five participants (2 in the high-dose group and 3 in the standard-dose group) who were lost to follow-up immediately after randomization and had no post-baseline safety data were excluded from the safety analysis. Each adverse-event category represents participants with at least one event of that type; participants could therefore contribute to more than one category. Risk differences were calculated as the event proportion in the high-dose group minus that in the standard-dose group and are expressed as percentage points. Confidence intervals for risk differences were calculated using the Newcombe method based on Wilson score intervals. P values were calculated using two-sided Fisher's exact tests; no P value was calculated when no events occurred in either group. No adjustment was made for multiple comparisons.
Abbreviations: CI, confidence interval.

Ankle edema was the most frequently reported adverse event, occurring in 8 of 44 participants (18.2%) in the high-dose group and 4 of 45 (8.9%) in the standard-dose group (RD, 9.3 percentage points; 95% CI, − 5.4 to 24.1; P = 0.230).

Dizziness occurred in 3 participants (6.8%) in the high-dose group and 1 participant (2.2%) in the standard-dose group (RD, 4.6 percentage points; 95% CI, − 5.8 to 16.1; P = 0.361). Symptomatic hypotension occurred in 1 participant (2.3%) in the high-dose group and none in the standard-dose group (RD, 2.3 percentage points; 95% CI, − 5.8 to 11.8; P = 0.494).

Hyperkalemia occurred in no participants in the high-dose group and in 1 participant (2.2%) in the standard-dose group (RD, − 2.2 percentage points; 95% CI, − 11.6 to 6.0; P = 1.000).

One participant (2.3%) in the high-dose group discontinued study medication because of an adverse event, compared with none in the standard-dose group (RD, 2.3 percentage points; 95% CI, − 5.8 to 11.8; P = 0.494); this participant remained in follow-up. No serious adverse events occurred in either group.

No events of flushing, palpitations, or orthostatic symptoms occurring in the absence of hypotension were recorded in either group during follow-up.

Discussion

In this triple-blind, randomized, placebo-controlled trial of hypertensive patients with albuminuric CKD who were already receiving manidipine 20 mg/day, escalation to 40 mg/day substantially increased the proportion of participants achieving the prespecified primary response of a ≥ 30% reduction in UACR at 6 months. In the primary ITT analysis, the response occurred in 69.6% of participants assigned to high-dose manidipine and 31.3% assigned to standard-dose manidipine, corresponding to an RR of 2.23 (95% CI, 1.40–3.53) and an absolute RD of 38.3 percentage points (95% CI, 19.6–57.0). The direction of effect was preserved in the observed-case and worst-case analyses. Importantly, despite the numerically higher baseline UACR in the high-dose group, adjustment for baseline log-transformed UACR also supported the primary finding (adjusted OR, 6.42; 95% CI, 2.48–16.64). Continuous UACR analyses were consistent with these findings; at Month 6, the baseline-adjusted GMR for high-dose versus standard-dose manidipine was 0.48 (95% CI, 0.31–0.74). Together, these analyses support an additional albuminuria-lowering effect of increasing manidipine from 20 to 40 mg/day over 6 months.

These results extend previous clinical observations of albuminuria lowering with manidipine. Earlier studies evaluated manidipine predominantly at doses of 10–20 mg/day or compared manidipine with other antihypertensive strategies [16–18]. In patients with type 2 diabetes and albuminuria, addition of manidipine to candesartan reduced urinary albumin excretion more than addition of hydrochlorothiazide despite similar blood-pressure reductions [17]. The AMANDHA study likewise reported greater albuminuria reduction with manidipine than with amlodipine in patients receiving background RAS blockade [18]. A 40-mg dose of manidipine has previously been studied for blood-pressure lowering in essential hypertension, but albuminuria was not assessed [19]. The present trial therefore adds direct randomized evidence comparing continued manidipine 20 mg/day with dose escalation to 40 mg/day in patients with CKD and persistent albuminuria.

A plausible explanation for the observed albuminuria lowering relates to the renal microvascular effects of manidipine. Unlike predominantly L-type dihydropyridine CCBs, manidipine inhibits both L-type and T-type calcium channels [12]. Experimental studies have shown effects on both afferent and efferent renal arteriolar resistance [13, 14], and a randomized human renal hemodynamic study reported a more favorable intrarenal hemodynamic profile with manidipine than with amlodipine [15]. These observations provide biological plausibility for an effect on intrarenal hemodynamics. However, the present trial did not directly measure intraglomerular pressure or renal arteriolar resistance, and the mechanism underlying the observed UACR reduction therefore cannot be determined from these data.

The relationship between albuminuria reduction and systemic blood pressure also warrants cautious interpretation. No statistically significant between-group differences in SBP or DBP were observed during follow-up. At Month 6, the between-group difference in change from baseline was − 4.3 mmHg (95% CI, − 10.1 to 1.5) for SBP and − 1.8 mmHg (95% CI, − 7.4 to 3.8) for DBP. The reduction in albuminuria was therefore observed without a statistically significant between-group difference in blood pressure. Nevertheless, the confidence intervals do not exclude a clinically relevant difference in blood-pressure lowering, and blood pressure was not incorporated into a formal mediation analysis. A contribution from systemic blood-pressure reduction to the UACR effect cannot therefore be excluded. The findings are compatible with, but do not establish, an additional contribution from intrarenal hemodynamic effects.

Kidney function and laboratory parameters showed no statistically significant between-group differences during the 6-month follow-up. Changes in serum creatinine and eGFR were small in both groups, and hyperkalemia occurred in no participant receiving high-dose manidipine and in one participant receiving standard-dose therapy. Approximately 54% of randomized participants were receiving a RAS inhibitor at baseline, and changes in concomitant antihypertensive therapy during follow-up were infrequent. RAS inhibitor therapy was permitted rather than required by the protocol, and participants were not required to undergo a run-in to maximally tolerated RAS blockade. Accordingly, these results should not be interpreted as demonstrating efficacy specifically on top of optimized RAS inhibition. The trial was also not designed to determine whether the treatment effect differed according to baseline RAS inhibitor use.

The therapeutic context of the trial should also be considered. Recruitment began in 2018, before SGLT2 inhibitors became established as routine disease-modifying therapy for CKD. As evidence and clinical use of SGLT2 inhibitors evolved during the extended recruitment period, the protocol was amended with ethics approval to exclude patients receiving SGLT2 inhibitors from subsequent enrollment, and no participant initiated an SGLT2 inhibitor during trial follow-up. The study therefore largely reflects a treatment context preceding widespread contemporary SGLT2 inhibitor use. Current CKD management increasingly incorporates SGLT2 inhibitors in eligible patients [7–9], and whether escalation of manidipine provides additional albuminuria lowering when added to contemporary SGLT2 inhibitor-based therapy remains unknown and should be evaluated prospectively.

Safety findings should be interpreted in the context of the modest sample size. At least one adverse event occurred in 22.7% of participants in the high-dose group and 11.1% in the standard-dose group, an absolute difference of 11.6 percentage points (95% CI, − 4.2 to 27.2). Ankle edema was the most frequently reported adverse event and was numerically more common with high-dose manidipine (18.2% vs 8.9%). One participant receiving high-dose manidipine discontinued study medication because of an adverse event but remained in follow-up, and no serious adverse events occurred in either group. Treatment adherence was similar between groups, with the prespecified adherence threshold of at least 80% achieved by 88.6% and 86.7% of participants, respectively. These data do not demonstrate a statistically significant difference in adverse events, but the trial was not powered to establish equivalence or to exclude clinically important differences in uncommon harms. Larger studies are needed to characterize the safety of 40-mg manidipine more precisely.

Several features strengthen the interpretation of this trial. The randomized, placebo-controlled, triple-blind design minimized the potential for allocation and ascertainment bias, and no emergency unblinding occurred during follow-up. Both groups continued background manidipine 20 mg/day, allowing the randomized comparison to evaluate addition of a further 20 mg/day of manidipine against matching placebo. The primary outcome was prespecified in the ethics-approved protocol before enrollment and formed the basis of the sample-size calculation. The primary ITT analysis included all randomized participants using prespecified non-responder imputation, and its findings were supported by observed-case, baseline-adjusted, and worst-case analyses. Baseline-adjusted analyses also specifically addressed the numerical imbalance in baseline UACR between the randomized groups.

Several limitations should be acknowledged. First, the trial was conducted at a single academic center and included 94 randomized participants, limiting precision and generalizability, particularly for safety outcomes. Second, follow-up was limited to 6 months and the study was not designed to evaluate long-term changes in eGFR, kidney failure, cardiovascular events, or mortality. Although changes in albuminuria have been associated with subsequent kidney outcomes and have been supported as a candidate surrogate endpoint for CKD progression under appropriate conditions [3–5], the binary ≥ 30% UACR reduction used as the primary outcome should not be interpreted as proof of long-term individual clinical benefit. Third, UACR is biologically variable, although persistent albuminuria was required for eligibility and randomization should reduce systematic effects of this variability.

Fourth, median baseline UACR was numerically higher in the high-dose group than in the standard-dose group (346 vs 274 mg/g in the randomized population), raising the possibility that regression to the mean could have contributed to the magnitude of the observed reduction. However, the treatment effect remained evident in the baseline-adjusted logistic regression analysis, and the baseline-adjusted continuous UACR analysis at Month 6 similarly favored high-dose manidipine. Fifth, only approximately 54% of participants were receiving RAS inhibitors, and the protocol did not require maximally tolerated RAS inhibition, limiting direct applicability to patients receiving fully optimized contemporary CKD therapy. Sixth, SGLT2 inhibitor therapy was not part of the treatment context evaluated in this trial, further limiting generalizability to contemporary multidrug kidney-protective regimens. Seventh, multiple secondary outcomes were evaluated without adjustment for multiplicity and should therefore be interpreted as exploratory.

An additional important limitation is the retrospective registration of the trial. Formal prospective registration was not completed. The trial was registered with the Thai Clinical Trials Registry on 11 April 2026, after completion of participant follow-up and before manuscript submission. Retrospective registration limits the ability to verify prespecified outcomes against a contemporaneous public trial registry. To mitigate concerns regarding selective outcome reporting, the primary ≥ 30% UACR reduction outcome and the sample-size calculation were documented in the ethics-approved protocol before enrollment of the first participant, and the final SAP was finalized and date-stamped before database lock and disclosure of treatment allocation. The protocol and SAP are available from the corresponding author on reasonable request.

Overall, these findings provide randomized evidence that escalating manidipine from 20 to 40 mg/day can produce additional albuminuria reduction beyond continued standard-dose therapy, while underscoring the need for larger and longer-term trials—particularly in patients receiving contemporary kidney-protective therapies—to determine the durability, safety, and clinical relevance of this effect.

Conclusions

In hypertensive patients with albuminuric CKD already receiving manidipine 20 mg/day, dose escalation to 40 mg/day increased the proportion of participants achieving a ≥ 30% reduction in UACR and produced greater albuminuria reduction over 6 months compared with continued standard-dose manidipine. The albuminuria effect was observed without statistically significant between-group differences in blood pressure or kidney function, although a contribution from blood-pressure lowering cannot be excluded. Adverse events, particularly ankle edema, were numerically more frequent with high-dose therapy, and the trial was not powered for definitive safety conclusions. Larger multicenter trials with longer follow-up are needed to determine the durability and safety of this effect, whether albuminuria reduction translates into improved kidney or cardiovascular outcomes, and whether similar effects occur when high-dose manidipine is used alongside contemporary CKD therapies, including SGLT2 inhibitors.

Abbreviations

BCa
bias-corrected and accelerated
BMI
body mass index
CCB
calcium channel blocker
CI
confidence interval
CKD
chronic kidney disease
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
CONSORT
Consolidated Standards of Reporting Trials
DBP
diastolic blood pressure
eGFR
estimated glomerular filtration rate
GMR
geometric mean ratio

HbA1c
glycated hemoglobin
ITT
intention-to-treat
mITT
modified intention-to-treat
OR
odds ratio
Q1
first quartile
Q3
third quartile
RAS
renin–angiotensin system
RD
risk difference
RR
risk ratio
SAP
statistical analysis plan
SBP
systolic blood pressure
SD
standard deviation
SGLT2
sodium–glucose cotransporter-2
UACR
urinary albumin-to-creatinine ratio.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board/Ethics Committee of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand (COA no. 018/2561; project no. 156/60; initial approval date, 5 February 2018), before enrollment of the first participant. Continuing ethics approval was maintained throughout participant recruitment, follow-up, and study-related data verification. All participants provided written informed consent before enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable participant confidentiality, institutional data-protection, and ethics requirements. The ethics-approved trial protocol and final statistical analysis plan are also available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WS: investigation, participant recruitment, data collection, and drafting of the manuscript. SJ, TN, WP, and TT: participant recruitment, clinical data collection, interpretation of the findings, and critical revision of the manuscript. SK: conceptualization, methodology, supervision, interpretation of the findings, and drafting and critical revision of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for the work.

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References

1. van der Matsushita K, Astor BC, Woodward M, Levey AS, de Jong PE, Chronic Kidney Disease Prognosis Consortium, et al. Association of estimated glomerular filtration rate and albuminuria

with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073–81.

2. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286(4):421–6.
3. Coresh J, Heerspink HJL, Sang Y, Matsushita K, Arnlov J, Astor BC, Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol. 2019;7(2):115–27.
4. Heerspink HJL, Greene T, Tighiouart H, Gansevoort RT, Coresh J, Simon AL, et al. Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol. 2019;7(2):128–39.
5. Levey AS, Gansevoort RT, Coresh J, Inker LA, Heerspink HJL, Grams ME, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. Am J Kidney Dis. 2020;75(1):84–104.
6. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol. 2006;17(11):2974–84.
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4S):S117–314.
8. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306.
9. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
10. National Drug System Development Committee. Notification of the National Drug System Development Committee: National List of Essential Medicines B.E. 2561 (2018). Royal Thai Government Gazette. 2018;135(Special Part 14 Ng):4. Published January 19, 2018.
11. Epstein M. Calcium antagonists and renal disease. Kidney Int. 1998;54(5):1771–84.
12. Hayashi K, Wakino S, Sugano N, Ozawa Y, Homma K, Saruta T. Ca2 + channel subtypes and pharmacology in the kidney. Circ Res. 2007;100(3):342–53.
13. Tojo A, Kimura K, Matsuoka H, Sugimoto T. Effects of manidipine hydrochloride on the renal microcirculation in spontaneously hypertensive rats. J Cardiovasc Pharmacol. 1992;20(6):895–9.
14. Hayashi K, Ozawa Y, Fujiwara K, Wakino S, Kumagai H, Saruta T. Role of actions of calcium antagonists on efferent arterioles—with special references to glomerular hypertension. Am J

Nephrol. 2003;23(4):229–44.

15. Ott C, Schneider MP, Raff U, Ritt M, Striepe K, Alberici M, Schmieder RE. Effects of manidipine vs. amlodipine on intrarenal haemodynamics in patients with arterial hypertension. Br J Clin Pharmacol. 2013;75(1):129–35.
16. Fogari R, Mugellini A, Zoppi A, Lazzari P, Destro M, Rinaldi A, Preti P. Effect of successful hypertension control by manidipine or lisinopril on albuminuria and left ventricular mass in diabetic hypertensive patients with microalbuminuria. Eur J Clin Pharmacol. 2005;61(7):483–90.
17. Fogari R, Corradi L, Zoppi A, Lazzari P, Mugellini A, Preti P, Rinaldi A. Addition of manidipine improves the antiproteinuric effect of candesartan in hypertensive patients with type II diabetes and microalbuminuria. Am J Hypertens. 2007;20(10):1092–6.
18. Martinez-Martin FJ, Saiz-Satjes M. Add-on manidipine versus amlodipine in diabetic patients with hypertension and microalbuminuria: the AMANDHA study. Expert Rev Cardiovasc Ther. 2008;6(10):1347–55.
19. Fogari R, Zoppi A, Lusardi P, Preti P, Poletti L, Mugellini A. Evaluation by 24-hour ambulatory blood pressure monitoring of efficacy of manidipine hydrochloride 10, 20 or 40 mg once daily as compared to placebo in treating mild to moderate essential hypertension: a double-blind, randomized, parallel group, placebo-controlled study. Blood Press Suppl. 1996;5:16–23.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
21. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.
22. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

Figures

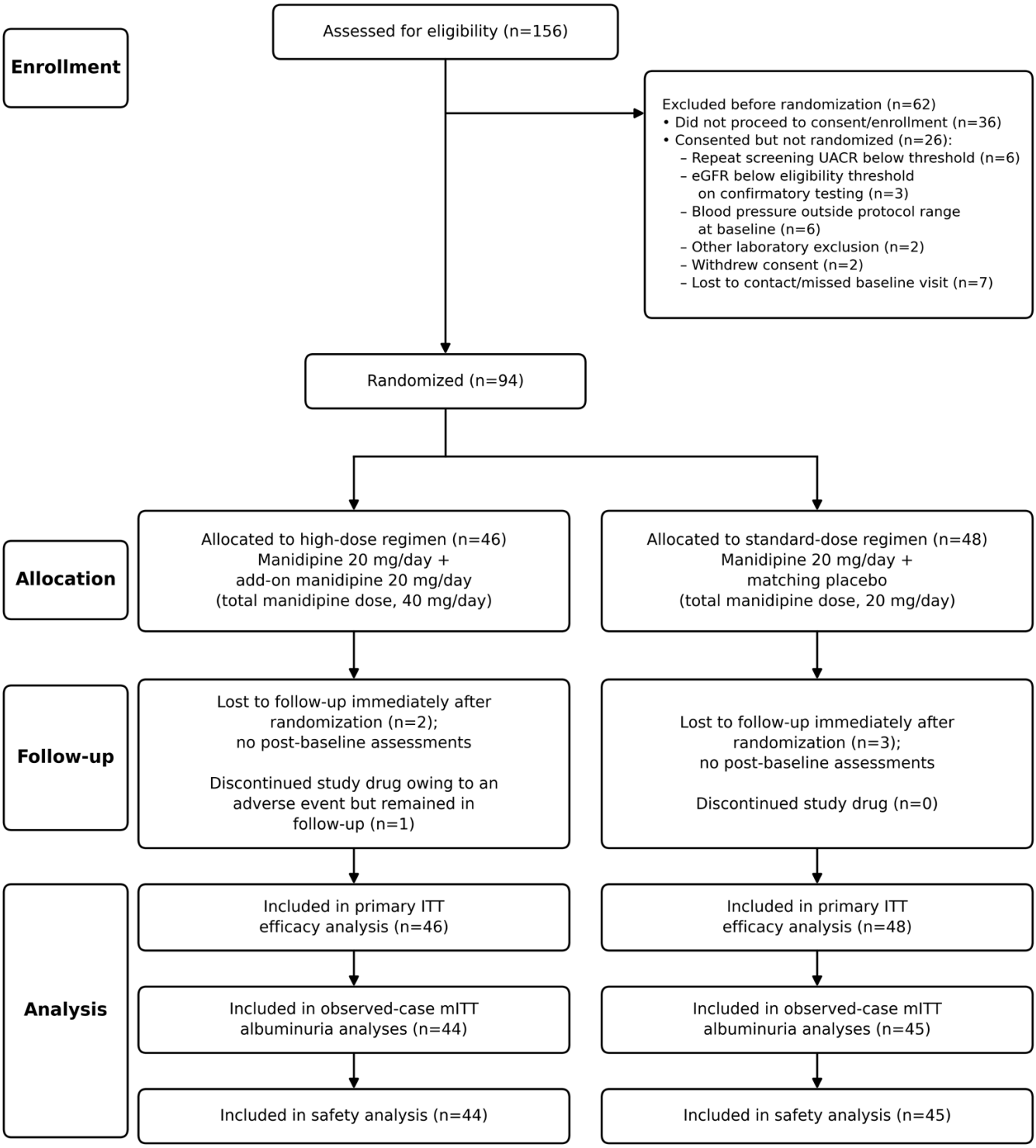


Figure 1

CONSORT flow diagram of participant progress through the trial

Note: Of 156 patients assessed for eligibility, 62 were excluded before randomization, and 94 were randomized to high-dose manidipine (40 mg; n=46) or standard-dose manidipine (20 mg; n=48). Two participants in the high-dose group and three in the standard-dose group were lost to follow-up

immediately after randomization and had no post-baseline assessments. The primary efficacy outcome was analyzed in the intention-to-treat population using non-responder imputation for missing 6-month responder status. Other albuminuria outcomes were analyzed in the observed-case modified intention-to-treat population, comprising 44 participants in the high-dose group and 45 in the standard-dose group with baseline and post-baseline UACR measurements; all had evaluable 6-month UACR data, and no imputation was performed. Safety analyses included participants with at least one post-baseline safety assessment. One participant in the high-dose group discontinued study medication because of an adverse event but remained in follow-up and was included in the applicable analyses.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; ITT, intention-to-treat; mITT, modified intention-to-treat; UACR, urinary albumin-to-creatinine ratio.

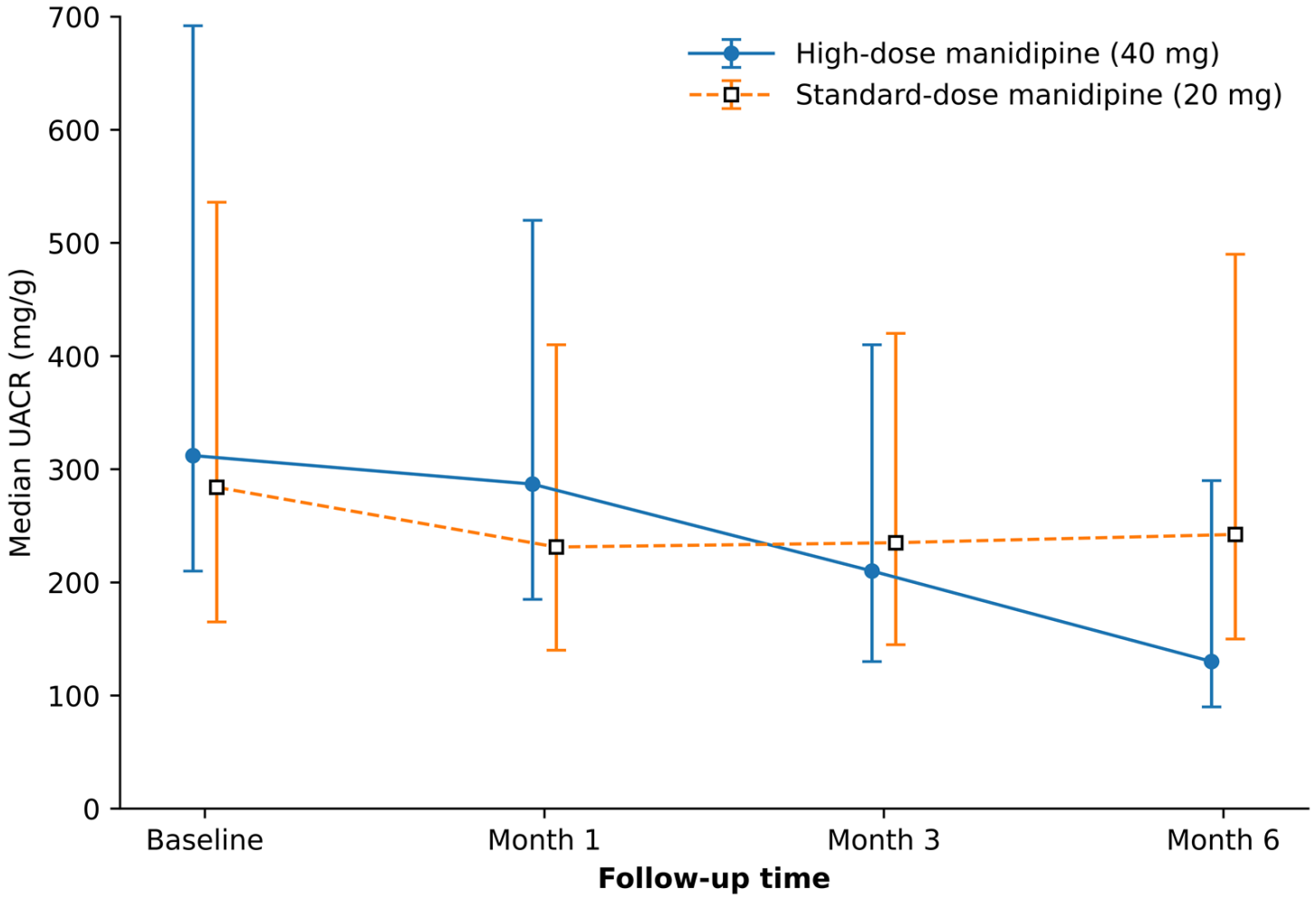


Figure 2

Median UACR trajectories during the 6-month follow-up period

Note: Data are presented as median UACR with Q1–Q3 in the observed-case modified intention-to-treat (mITT) population (44 participants in the high-dose manidipine group and 45 in the standard-dose manidipine group). UACR measurements at Months 1, 3, and 6 were available for all participants

included in this analysis; no imputation was performed. Adjusted GMRs for high-dose versus standard-dose manidipine were 1.11 (95% CI, 0.83–1.47; P=0.474) at Month 1, 0.81 (95% CI, 0.61–1.07; P=0.142) at Month 3, and 0.48 (95% CI, 0.31–0.74; P=0.001) at Month 6. Adjusted GMRs were estimated from linear regression models of log-transformed follow-up UACR on treatment group and log-transformed baseline UACR. GMRs <1 favor high-dose manidipine.

Abbreviations: CI, confidence interval; GMR, geometric mean ratio; mITT, modified intention-to-treat; Q1, first quartile; Q3, third quartile; UACR, urinary albumin-to-creatinine ratio.

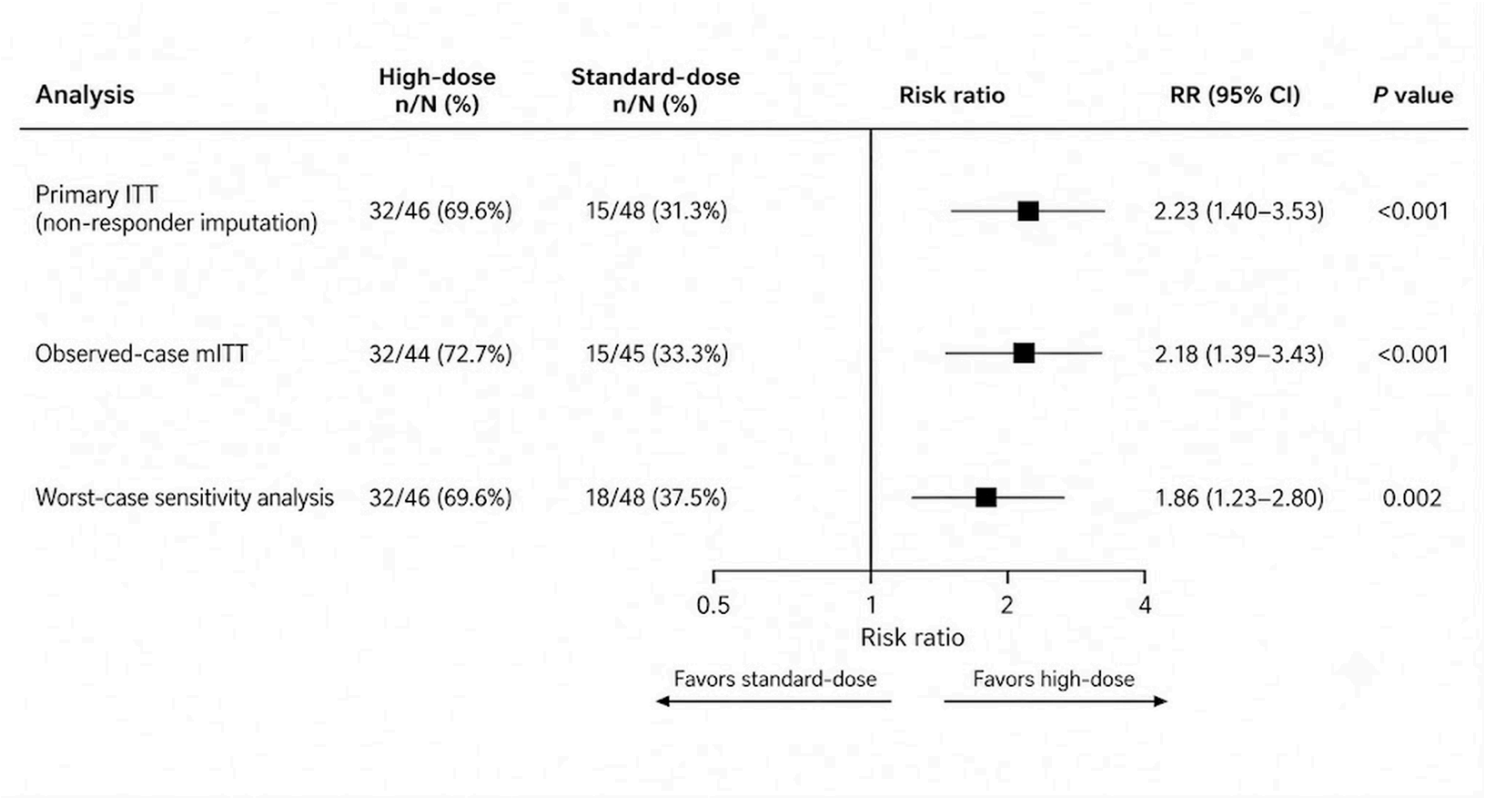


Figure 3

Risk ratios for the primary ≥30% UACR reduction outcome across primary, supportive, and sensitivity analyses

Note: The primary outcome was a ≥30% reduction in UACR from baseline to 6 months. Squares represent risk ratios (RRs), and horizontal lines represent 95% confidence intervals. The primary intention-to-treat analysis included all randomized participants, with participants missing 6-month responder status classified as non-responders. The supportive observed-case modified intention-to-treat analysis included participants with baseline and evaluable post-baseline UACR measurements and used no imputation. In the worst-case sensitivity analysis, participants with missing responder status in the high-dose group were classified as non-responders, whereas those with missing responder status in the standard-dose group were classified as responders. RRs >1 favor high-dose manidipine. Confidence intervals for RRs were calculated using the log method, and P values were obtained using Pearson's chi-

square test. The baseline-adjusted logistic regression analysis is reported separately in Supplementary Table S1 because it provides an odds ratio rather than a risk ratio.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; mITT, modified intention-to-treat; RR, risk ratio; UACR, urinary albumin-to-creatinine ratio.

Supplementary Files

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- SupplementarymaterialManidipineBMC.docx