COMPARISON OF EFFICACY IN RENOPROTECTION BETWEEN AZILSARTAN AND ENALAPRIL: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) are reported to improve renal outcomes among patients with hypertension and chronic kidney disease (CKD), but there might be substantial differences in their renoprotective effects. Azilsartan medoxomil is a relatively new available ARB, highly specific angiotensin type 1 receptor and superior in terms of blood pressure reduction, with respect to other ARBs.

Methods: The study employed a randomized controlled trial; hypertensive subjects with albuminuria >30 mg/g creatinine at the outpatient clinic, Phramongkutklao Hospital, Bangkok, Thailand were randomly assigned to azilsartan 40-80 mg/day (n=27) or enalapril 10-40 mg/day (n=23) for 24 weeks. The primary outcome was the change in urine albumin creatinine ratio (UACR). UACR, estimated glomerular filtration rate (GFR), blood pressure and serum electrolytes were evaluated at baseline, 12 and 24 weeks.

Results: A total of 50 patients with hypertension and albuminuria were recruited. At the end of treatment, systolic blood pressure level was significantly reduced in the azilsartan group compared with the enalapril group (-12.2 mmHg [95%CI -18.9 to -5.5] vs. -1.1 mmHg [95% -7.8 to 5.7], p=0.021). In addition, at 24 weeks, significantly reduced median UACR was observed in the azilsartan group compared with that of the enalapril group (-59.9 mg/g Cr [95% CI -284.6 to -31.0] vs. -40.4 mg/gCr [95% CI -129.4 to 88.3], p=0.026)). No statistically significant difference was found between the two groups in hyperkalemia, estimated GFR, acute kidney injury and serious adverse events.

Conclusion: This study demonstrated that azilsartan had superior antihypertensive and albuminuric efficacy compared with the standard dose of enalapril without increasing adverse events.

Keywords: Hypertension, Antihypertensive therapy, Azilsartan Medoxomil, Enalapril, Microalbuminuria, Macroalbuminuria, Renoprotective effect

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Introduction

Activation of the renin-angiotensin-aldosterone system (RAAS) promotes systemic hypertension with kidney disease and excessive angiotensin II leading to intraglomerular hypertension, salt retention and profibrotic, inflammatory activation of fibrogenic mediators causing long term adverse effects to the kidneys.[1, 2] RAAS inhibitors including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are first-line antihypertensives to slow chronic kidney disease (CKD) progression.[3] Clinical studies indicated that novel ARBs especially azilsartan medoxomil has a tighter and longer-lasting binding to the angiotensin II subtype-1 (AT1) receptor than other ACEIs or ARBs, leading to more effectively reduced blood pressure. [4, 5] An observational study demonstrated that a blood pressure target of <140/90 mmHg was achieved by a significantly greater proportion of patients in the azilsartan treatment than that of the ACEIs treatment.[6] An initial trial also showed that azilsartan had significantly greater reduced proteinuria than other ARBs among patients with CKD.[7]

Azilsartan medoxomil more selectively inhibits angiotensin II-induced activation of AT1 receptors. Its affinity is greater than 10,000-fold for AT1 receptors than for AT2 receptors.[8] Azilsartan medoxomil at its maximal dose has more benefit on blood pressure control over olmesartan and valsartan at their maximal, approved doses without increasing adverse events.[9] Moreover, azilsartan demonstrated antihypertensive effects with improved vascular endothelial function and lower albuminuria along with reduced tubular cast formation and glomerular injury in an animal model.[10] However, limited studies have been conducted regarding the effects of azilsartan on urine albumin among patients with hypertension. This study aimed to compare efficacy regarding renoprotective effect between azilsartan medoxomil and enalapril, which is commonly used and available worldwide.

Methods

Study population

This constituted an open-label, randomized controlled study conducted among patients with hypertension and albuminuria, Phramongkutklao Hospital, Bangkok, Thailand. This study was reviewed and approved by the Royal Thai Army Medical Department Institutional Review Board. Written informed consent was obtained from the participants following the WMA Declaration of Helsinki Ethics principles for medical research involving human subjects (approval number: R221h/60). The study was registered in the Thai Clinical Trials Registry and obliged to disclose details of the 24 mandatory items of the WHO International Clinical Trials Registry Platform (Trial identification number was TCTR20220426002, First submitted date: 22/04/2022). Treatment protocol patients were selected using a method of block randomization by a research pharmacist. Randomization was performed using a central computerized randomization program.

From April 2018 to May 2019, patients attending the outpatient clinic in medicine were recruited and screened for eligibility. All eligible patients were required to be over 18 years of age and have essential hypertension with albuminuria more than 30 mg/day for more than three months, stable systolic blood pressure of 140 to 160 mmHg in more than three screening visits or to be taking antihypertensive medication other than ACEIs/ARBs without adjusting glucose lowering medications or lipid lowering agents within three months. No treatment was given with RAAS inhibitors within three months before starting the study. Exclusion criteria included hyperkalemia, secondary or malignant hypertension, chronic alcohol consumption, known hypersensitivity to ARBs or ACEIs, pregnancy, kidney transplantation and end stage kidney disease (ESKD). All patients were required to provide written informed consent before the initiating any study-related procedures.

Intervention

During the 24-week treatment period, all patients in each group received the assigned study drug once daily after breakfast. Patients in the azilsartan group received a dosage of 40 mg daily for the first 8 weeks and then 80 mg daily for the subsequent 16 weeks. Patients in the

enalapril group received a dosage of 20 mg daily for the first 8 weeks and then 40 mg daily for the subsequent 16 weeks to control blood pressure less than 130/80 mmHg. Both treatments were given for 24 weeks. A complete medical history and physical examination were performed on all subjects. Adherence was monitored by pill counting during each visit. Once a patient was given the assigned medication, the use of other anti-hypertensive medications was prohibited.

All patients were scheduled for first followed-up visits at four weeks in the run-in period. After the run-in period, patients were scheduled to follow-up at 8, 12 and 24 weeks. Adjusting the medications to reach the systolic blood pressure target was based on office blood pressure measurements (Omron HBP-9020 Kentaro Automatic sphygmomanometer blood pressure monitor AC 100V, Japan).

At the time of recruitment, baseline characteristics were collected by physician's face-to-face visits using a questionnaire. At each follow-up visit, the office blood pressure and heart rate were measured and information was gathered regarding concomitant medication use and adverse events. Measurement of the office blood pressure was performed three times at one-to two-minute intervals by the patients themselves with recommendation from trained physicians. Patients were required to rest for at least five minutes in a seated position, without consuming alcohol or caffeine, exercising or smoking at least 30 minutes before recording blood pressure. The laboratory tests including blood urea nitrogen, serum creatinine, calculation of estimated glomerular infiltration rate using the 2009 Chronic Kidney Disease Epidemiology Collaboration Equation, serum potassium level and urine albumin creatinine ratio (UACR) were measured at baseline and during treatment at weeks 12 and 24. Thirty milliliters of fresh urine were centrifuged at 4,000 rpm for 10 minutes. UACR were measured using immunonephelometric assay method.

The primary outcome was the change of urinary albumin level after 24 weeks in the azilsartan group, compared with that of the enalapril group. The following secondary outcomes were prespecified: change of estimated glomerular filtation rate (GFR) and blood pressure.

Statistical analysis

The sample size was determined on the basis of the results of a related study provided to detect a 20% lower albuminuria in the ARBs group than in the ACEIs group (11). A sample-size of 22 subjects per group was required to verify the statistical difference between azilsartan and enalapril with at least a 90% power and a two-sided type I error α of 5%. Accordingly, the number of subjects evaluable for the primary endpoint was determined to be 50 in total. All analyses were based on the intention-to-treat approach.

Normal data distribution was confirmed using the Kolmogorov-Smirnov test. Differences between groups were comparing using Chi-square test or Fischer's exact test for categorical data. For the primary efficacy endpoint, summary statistics and two-sided 95% confidence intervals (CI) of the mean ± standard deviation (SD) or medians with interquartile range (IQR) values were determined and Student's t test or Mann-Whitney U test was performed. Within group changes were evaluated using paired t-tests. All statistical analyses were performed using SPSS Inc., Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.

Results

A total of 80 patients provided informed consent to participate in the trial, of whom 50 were randomized, 23 patients in the enalapril group and 27 patients in the azilsartan group (**Figure 1**). The baseline characteristics were similar between the two groups (**Table 1**). The mean age and estimated GFR was 69.5± 10.4 years and 60.8±23.4 mL/min/1.73 m^2, respectively. Comorbid illnesses included dyslipidemia (84%), type 2 diabetes mellitus (80%), CKD stages 3 to 4 (56%) and cardiovascular disease (16%). Mean systolic and diastolic blood pressure was 142.2±13.1 and 75.3±10.2 mmHg, respectively. The medications prescribed before this study to all patients in both groups did not differ significantly. During study in the treatment

group, the average dose of enalapril was 34 mg/day and average dose of azilsartan was 70 mg/day. Treatment compliance was 90% in the enalapril group and 100% in the azilsartan group.

Changes in renal function and albuminuria over period of the study

Estimated GFR, biochemical profiles and UACR are shown in **Table 2.** During the follow-up period of 24 weeks, median UACR decreased from baseline in the azilsartan -treated group at 12 weeks (-59.3 (95%CI -376.8 to -24.8), $p<0.05$) and 24 weeks (-59.9 (95%CI -284.6 to -31.0), $p<0.05$), whereas they did not significantly change in the enalapril group. These changes significantly differed between the two groups (**Figure 2**). No difference was found between the two groups regarding estimated GFR and serum potassium at baseline or the end of study.

Changes in blood pressure during the study

Blood pressure during the study is shown in **Table 3.** Comparing between groups, the azilsartan-treated group exhibited a greater decrease in systolic blood pressure than that in the enalapril-treated group (12.2 (95% CI= -18.87 to -5.53) vs. -1.05 (95%CI= -7.76 to 5.65) mmHg, $p=0.021$) at 24 weeks whereas change of diastolic blood presssure at 24 weeks did not significantly differ between the two groups (-6.65 (-15.85, 2.55) vs. -8.64 (-14.54, -2.74) mmHg, $p=0.696$).

Safety profile

During the 24-week study, the drugs were equally well-tolerated and no differences were observed in the incidence of treatment-emergent adverse events including acute kidney injury, cardiac arrhythmia and hyperkalemia between the two treatment groups (**Table 4**). Overall incidence of hypotension-related events was comparable to the two drugs: 2 of 23 patients (8.6%) in the enalapril group compared with 3 of 27 patients (11.1%) in the azilsartan group. Two patients in the enalapril group developed chronic cough.

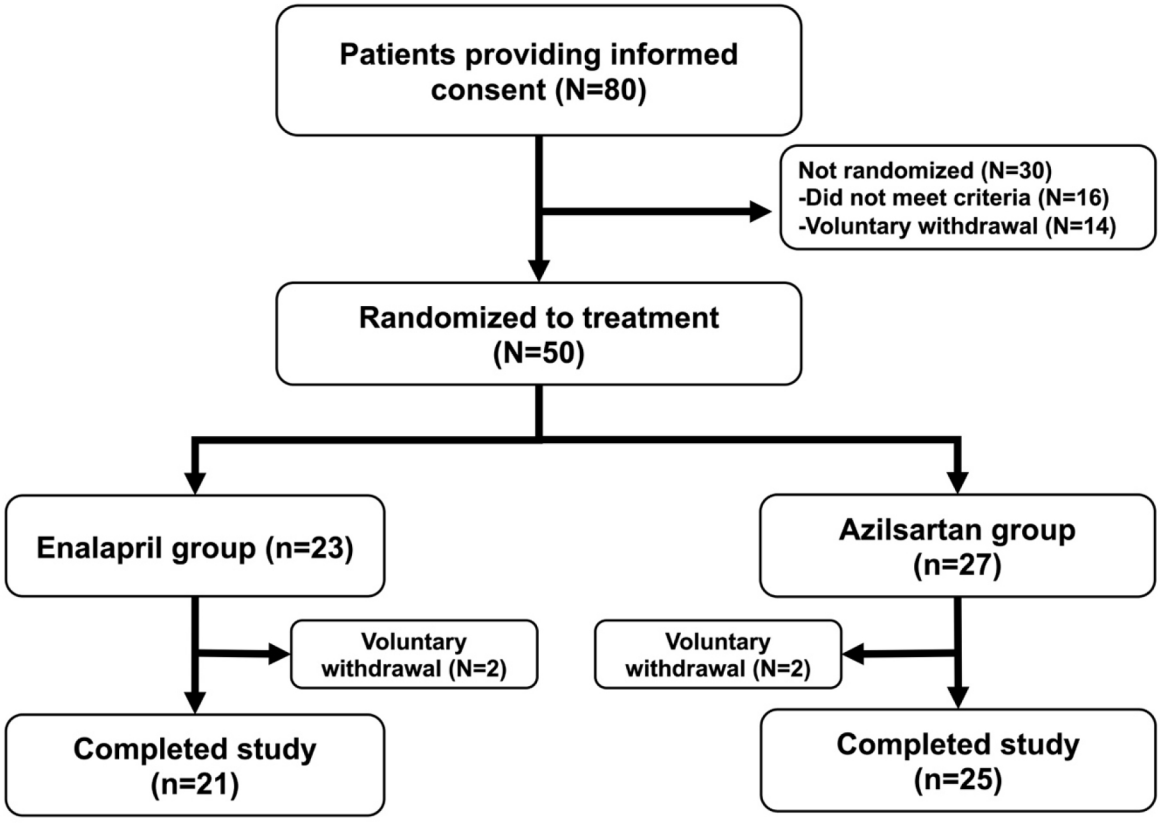

Figure 1. Flow chart of enrolled patients

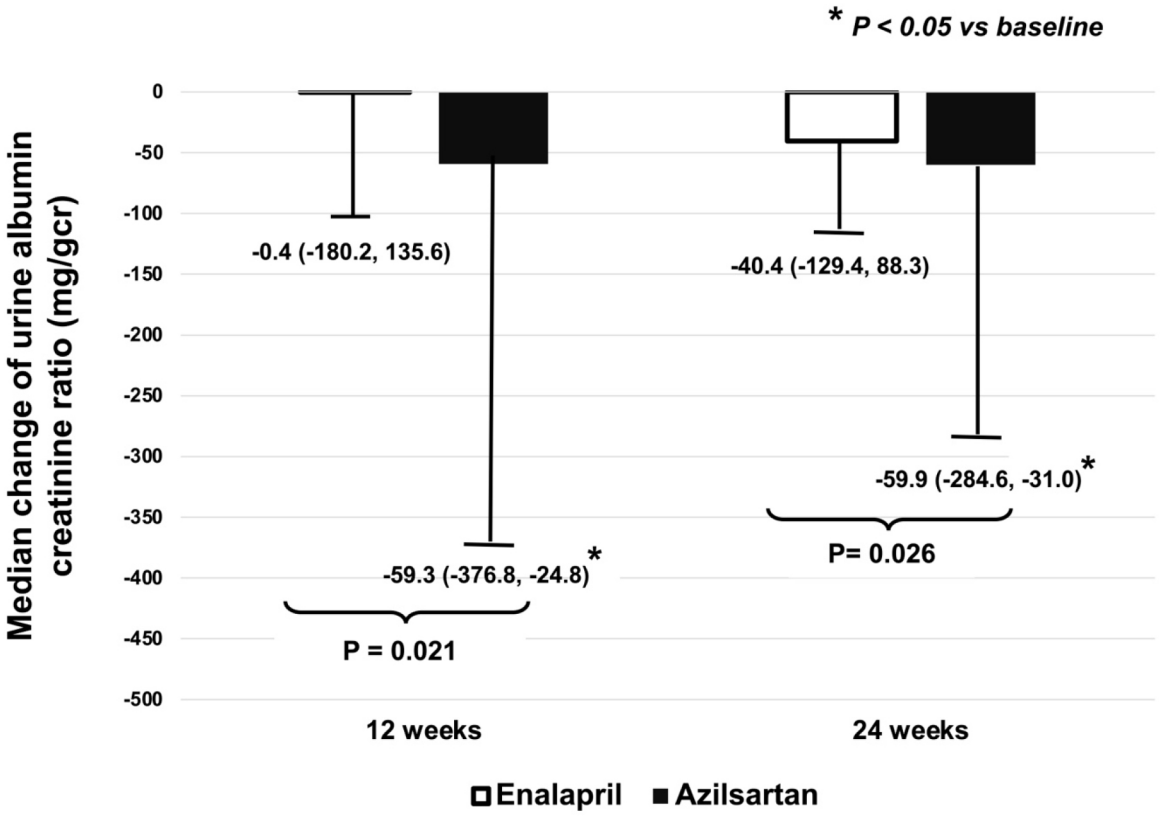

Figure 2. Urine albumin creatinine ratios in the enalapril group (open bar) and azilsartan group (closed bar)

Table 1. Baseline characteristics of the study population

Variables	Enalapril (N=23)	Azilsartan (N=27)
Male (N, %)	8 (34.8%)	13 (48.1%)
Age (years)	70.0±9.3	68.3±12.3
Body weight (kg)	61.4±10.9	66.2±12.9
Systolic blood pressure (mmHg)	143.3±12.1	141.8±14.0
Diastolic blood pressure (mmHg)	74.7±9.2	75.7±12.8
Estimated glomerular filtration (mL/min/1.73 m^2)	60.35 ± 24.11	61.15 ± 25.04
Urine albumin creatinine ratio (mg/gCr)	165.3 (76.3, 581.5)	154.8 (72.2, 1000)
Serum potassium (mEq/L)	4.54 ± 0.53	4.32 ± 0.37
Co-morbid diseases (N, %)		
- Type 2 diabetes	18 (78.2%)	22 (81.5%)
- Dyslipidemia	19 (82.6%)	23 (85.2%)
- Cardiovascular disease	5 (21.7%)	3 (11.1%)

Table 1. Baseline characteristics of the study population (Cont.)

Variables	Enalapril (N=23)	Azilsartan (N=27)
Previous medications (N, %)		
- Calcium channel blockers	17 (73.9%)	19 (70.4%)
- Beta-blockers	9 (39.1%)	7 (25.9%)
- Diuretics	7 (30.4%)	8 (29.6%)

Data are mean ± SD and median with interquartile range

Table 2. Comparison of the changes of renal function, serum potassium and albuminuria before and after treatment between two groups

Mean changes	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Median urine albumin creatinine ratio (mg/gCr)			
Baseline	165.3 (76.3, 581.5)	154.8 (72.2, 1000)	0.876
Week 12	186.9 (62.9, 385.5)	85.2 (31.1, 565.8)	0.224
Change from baseline with 95% CI at week 12	-0.4 (-180.2, 135.6)	-59.3 (-376.8, -24.8)*	0.021
Week 24	120.7 (38.6, 236.2)	65 (26.6, 98.7)	0.197
Change from baseline with 95% CI at week 24	-40.4 (-129.4, 88.3)	-59.9 (-284.6, -31.0)*	0.026
Mean estimated glomerular filtration rate (mL/min/1.73 m^2)			
Baseline	60.4±24.1	61.2±25.0	0.909
Week 12	63.9±22.2	60.7±27.0	0.679
Change from baseline with 95% CI at week 12	-0.7 (-4.32, 2.91)	-0.41 (-4.54, 3.72)	0.917
Week 24	62.9±23.6	55.7±27.4	0.360
Change from baseline with 95% CI at week 24	-1.62 (-6.76, 3.52)	-3.12 (-7.21, 0.97)	0.632
Mean serum potassium (mEq/L)			
Baseline	4.5±0.5	4.3±0.4	0.102
Week 12	4.5±0.4	4.5±0.4	0.991
Change from baseline with 95% CI at week 12	-0.01 (-0.25, 0.24)	0.16 (-0.01, 0.32)	0.232
Week 24	4.4±0.4	4.5±0.4	0.439
Change from baseline with 95% CI at week 24	-0.11 (-0.34, 0.13)	0.13 (-0.03, 0.29)	0.080

Data are mean ± SD and median with interquartile range (IQR); Weeks 12 and 24 value compared with baseline; $^*p<0.05$

Table 3. Comparison of the changes of blood pressure before and after treatment between two groups

Mean changes	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Mean systolic blood pressure (mmHg)			
Baseline	143.3±12.1	141.8±14.04	0.692
Week 12	136.8±17.4	132.9±10.5	0.376

Table 3. Comparison of the changes of blood pressure before and after treatment between two groups (Cont.)

Mean changes	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Change from baseline with 95% CI at week 12	-5.35 (-12.91, 2.21)	-8.96 (-14.31, -3.62)*	0.409
Week 24	141.6±13.2	128.9±10.8	0.001
Change from baseline with 95% CI at week 24	-1.05 (-7.76, 5.65)	12.2 (-18.87, -5.53)*	0.021
Mean diastolic blood pressure (mmHg)			
Baseline	74.7±9.2	75.7±12.8	0.745
Week 12	76.0±13.1	72.2±9.8	0.263
Change from baseline with 95% CI at week 12	0.8 (-5.25, 6.85)	-3.48 (-8.24, 1.27)	0.248
Week 24	68.8±19.2	67.9±9.8	0.844
Change from baseline with 95% CI at week 24	-6.65 (-15.85, 2.55)	-8.64 (-14.54, -2.74)*	0.696

Data are mean ± SD and mean± 95%CI. Week 12 and 24 value compared with baseline; $^{*}p<0.05$

Table 4. Adverse events during the study

	Enalapril (N=23)	Azilsartan (N=27)	*p*-value
Acute kidney injury	1 (4.3%)	0 (0%)	0.460
Hyperkalemia	5 (21.7%)	3 (11.1%)	0.444
Cough	2 (8.6%)	0 (0%)	0.207
Cardiac arrhythmia	0	0	NA
Hypotension-related events	2 (8.6%)	3 (11.1%)	0.815

Discussion

The results indicated that treatment with azilsartan for 24 weeks significantly augmented improved albuminuria among patients with CKD and that this effect occurred by a mechanism dependent on reducing blood pressure. However, renal function did not significantly differ between groups. This study provided evidence of potent blood pressure and albuminuria lowering effects with azilsartan among patients with CKD.

Azilsartan is a new ARB exhibiting a higher affinity and selectively on AT1 receptors than other ARBs(12) and azilsartan provides significantly more effectiveness in lowering blood pressure than other ARBs.[9, 13, 14] Similarly, in a double-blind, controlled, randomized trial, patients with hypertension, treated with azilsartan medoxomil indicated significantly more effectiveness than ramipril in lowering clinic systolic blood pressure and better tolerance.[5] Our results supported that azilsartan (40 to 80 mg once daily) provided a significantly greater reduction from baseline of clinic-measured systolic blood pressure than enlalapril (20 to 40 mg once daily) among patients with albuminuria and hypertension at week 24 after the treatment period. The results from our study demonstrated that azilsartan was significantly superior to enlalapril in reducing clinic systolic blood pressure with high rate of treatment compliance in the both groups (90% in the enalapril group and 100% in the azilsartan group).

Among antihypertensive agents, both ACEIs and ARBs demonstrated a renoprotective effect attributable to both antihypertensive and antiproteinuric effects. The positive effect of azil-

sartan on albuminuria in this study was consistent with a related study, showing that inhibition of angiotensin II action improved albuminuria and inhibited an intrarenal renin-angiotensin system activity marker among patients with uncontrolled hypertension.[15] Limited studies have directly compared the renoprotective effects, including protection against kidney injury and albuminuria of ARBs and ACEIs among patients with hypertension. One study demonstrated that telmisartan and enalapril significantly reduced proteinuria, urinary liver-type fatty acid-binding protein (L-FABP) and urinary endothelin-1 levels, but telmisartan appeared to be more potent than enalapril in protecting against kidney injury among patients with CKD.[16] Recently, another study reported that azilsartan treatment significantly decreased proteinuria and blood pressure compared with candesartan among patients with CKD.[7] This was consistent to our study; azilsartan reduced albuminuria compared with enalapril during 24 weeks of treatment. In addition, the severity of albuminuria correlated with blood pressure levels and responded to lowering blood pressure.[17] Therefore, significantly reduced albuminuria induced by azilsartan might be related to reduced systolic blood pressure. Finally, the albuminuric effects of azilsartan may be related to strong RAAS inhibition to AT1 receptors with long and strong antihypertensive effects in a clinical setting.

In the meta-analysis of randomized controlled trials comparing ACEIs or ARBs with placebo among patients with diabetes and albuminuria, ARBs reduced risks of ESKD, but ACEIs failed to reduce risks of ESKD.[18] Based on the renoprotective effects, ARBs may be preferred for diabetic patients with albuminuria. Our findings support the notion that azilsartan 40 to 80 mg/day had potent antihypertensive and albuminuria effects by blocking the inhibitory effect of angiotensin II on kidney damage by reducing renal oxidative stress and inflammation.[19] Further, ESKD risk showed a clear dependence on albuminuria and blood pressure reduction.[20] Therefore, the RAAS blockers regimen require a dual strategy, targeting both systolic blood pressure and albuminuria reduction. The potent and long acting of antihypertensive efficacy of azilsartan did not increase risk of adverse events, as the two groups were equally well tolerated in the study. A slightly higher incidence was observed of postural dizziness with azilsartan and candesartan (11.1 vs. 8.6%). However, these events were generally of mild intensity and resolved without intervention.

Several limitations were encountered in the present study. First, the long term outcomes of ARBs treatment concerning patients with CKD were not demonstrated in this study, making these agents undesirable for long term renoprotective effects. Second, a significant decrease in systolic blood pressure was observed in the azilsartan-treated group. The significantly reduced albuminuria from azilsartan might be related to tight blood pressure control. Finally, the present study was a -single center trial and the results might not be generalizable to patients with hypertensive patients and all CKD stages. Moreover, the sample size of this study was small and the trial was underpowered to demonstrate an effect.

In conclusion, this study demonstrated improved systolic blood pressure and albuminuria after a short course of azilsartan treatment among patients with hypertension compared with enalapril without severe adverse events. Thus, azilsartan could be useful for treating patients with hypertension for their antihypertensive capacity and for their albuminuric actions.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PT and BS designed the study, reviewed the manuscript and shared first authorship. BS and NN acquired most of the data and drafted

the manuscript. PT, OS and NN confirmed the authenticity of all the raw data, analyzed the data and revised the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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