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Renal Safety of Telminuvo, a Single Pill Combination of Telmisartan and S-amlodipine, in Korean Hypertensive Patients: A Multicenter, Retrospective Cohort Study

ORCID iDs
Hongran Moon
https://orcid.org/0000-0002-0076-9413
Sohyun Bae
https://orcid.org/0000-0002-0206-7108
Donghwan Yun
https://orcid.org/0000-0003-1800-319X
Hyung-Kwan Kim
https://orcid.org/0000-0001-7950-2131
Sung Uk Kwon
https://orcid.org/0000-0003-3435-3819
Min Su Hyon
https://orcid.org/0000-0002-8202-7535
Seung Seok Han
https://orcid.org/0000-0003-0137-5261

Hongran Moon [1], Sohyun Bae [2], Donghwan Yun [2], Hyung-Kwan Kim [3], Sung Uk Kwon [4], Min Su Hyon [5], Seung Seok Han [2]

[1]Department of Internal Medicine and Hospital Medicine Center, Seoul National University Hospital, Seoul, Republic of Korea
[2]Division of Nephrology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[3]Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[4]Department of Cardiology, Ilsan-Paik Hospital, Inje University College of Medicine, Goyang, Korea
[5]Division of Cardiology, Department of Internal Medicine, Soonchunhyang University Hospital Seoul, Soonchunhyang University College of Medicine, Seoul, Republic of Korea

ABSTRACT

Background: Effective blood pressure (BP) control is vital for preventing target organ damage, and combination therapy offers added benefits when single-agent treatment is insufficient. This cohort study examined whether Telminuvo, a single-pill combination of telmisartan and S-amlodipine, effectively maintains kidney function as a target organ in a large cohort of Korean patients.

Methods: A total of 4,934 patients from 30 hospitals were treated with Telminuvo for over six months, with BP, estimated glomerular filtration rate (eGFR), electrolyte levels, and adverse events monitored throughout the study period.

Results: Among the participants, 1,463 (29.7%) used Telminuvo for less than 1 year, while the remainder used it for longer. At baseline, the systolic and diastolic BP averaged 140.2 ± 18.4 mmHg and 82.1 ± 13.4 mmHg, respectively, which significantly decreased to approximately 130 and 75 mmHg after the initiation of treatment. The baseline eGFR of 79.3 mL/min/1.73 m^2 remained stable over three years, regardless of the initial eGFR levels. Within the first six months, acute kidney injury (defined as either a ≥ 0.3 mg/dL increase in serum creatinine or a $\geq 50\%$ increase from baseline) occurred in 6.6% of patients, while hyperkalemia (defined as serum potassium levels > 5.5 mmol/L) was observed in 3.2% of patients.

Conclusion: This cohort study demonstrates that Telminuvo effectively reduces blood pressure without compromising kidney function. Furthermore, the findings provide additional insights into drug-related adverse events, which will be valuable for clinicians in the real-world prescribing of Telminuvo.

Keywords: Combination therapy; Hypertension; Kidney function; Safety

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INTRODUCTION

Hypertension is a significant global health issue, affecting over 30% of adults and playing a major role in cardiovascular morbidity and mortality, particularly in developed countries [1,2]. Effective management of blood pressure (BP) is crucial, especially in high-risk patients, as it can substantially improve their prognosis [3]. Numerous studies have shown that adequate control of hypertension is vital for reducing the risk of cardiovascular events and associated mortality [4,5]. Since more than two-thirds of hypertensive patients do not achieve adequate control with monotherapy, combining medications that have different mechanisms of action is often necessary. For patients with stage 2 or high-risk hypertension, starting combination therapy from the outset is recommended [6-11].

Key classes of antihypertensive agents include those targeting the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), as well as calcium channel blockers (CCBs) [12]. ACE inhibitors and ARBs are particularly recommended for patients with type 1 or type 2 diabetes who have hypertension and albuminuria [13,14]. These agents are effective in reducing proteinuria and preserving kidney function in conditions like diabetic kidney disease [15]. According to guidelines for managing chronic kidney disease (CKD), ARBs are the preferred choice for patients with stages 1 to 4 CKD, especially when diabetes and hypertension coexist [13]. In contrast, CCBs work by blocking the influx of calcium ions into cardiac and peripheral vascular smooth muscle cells, providing both antihypertensive and antianginal effects [16].

With a wide range of antihypertensive medications available, various combination therapies can be employed [10,11]. 2018 European Society of Hypertension/European Society of Cardiology hypertension guidelines recommend pairing an ARB with a CCB as a first-line combination due to its effectiveness in controlling BP and its ability to alleviate common side effects associated with CCBs, such as peripheral edema [17].

The combination of telmisartan (as an ARB) and S-amlodipine (as a CCB), marketed as Telminuvo, was specifically developed to treat essential hypertension that is inadequately controlled by either agent alone. Considering the importance of monitoring renal function in hypertensive patients, we conducted an observational cohort study—TRUST (a multicenter retrospective study evaluating the renal safety of the Telmisartan/S-Amlodipine combination in patients with essential hypertension treated for over six months)—utilizing data from multiple centers in Korea. In addition to assessing renal safety, we monitored the incidence of major and minor drug-related adverse events not associated with renal function.

METHODS

Ethics statements

The protocol for this multicenter retrospective study, evaluating the renal safety of the telmisartan/S-amlodipine combination in patients with essential hypertension treated for more than six months (the TRUST study), was reviewed and approved by the institutional review boards of all participating centers. These include Seoul National University Hospital (H-2003-165-1112; H-2003-149-1111), Changwon Fatima Hospital (CFH-2020-07), Kyung Hee University Hospital at Gangdong (2020-03-013; 2020-03-014; 2020-03-022; 2020-06-025), Andong Medical Group Hospital (2020-005), Bongseng Memorial Hospital (BSIRB-2021-005;

BSIRB-2021-010), CHA University Bundang Medical Center (2020-01-036), Chonnam National University Hospital (2020-236), Dong-A University Hospital (DAUHIRB-20-053; DAUHIRB-20-054; DAUHIRB-20-066), Dongguk University Medical Center (2020-11-040; 2020-12-015; 2020-12-020), Gachon University Gil Medical Center (GDIRB2020-265; GDIRB2021-420), Gangnam Severance Hospital (2020-1043-006), Haeundae Bumin Hospital (202103-CTDG-029), Hallym University Gangnam Sacred Heart Hospital (2020-05-005; 2020-05-006; 2020-05-007; 2020-08-007), Hanyang University Seoul Hospital (2019-12-016; 2020-03-032; 2020-06-011), Inje university Busan Paik Hospital (2020-01-087; 2020-01-089), Inje University Ilsan Paik Hospital (2020-01-016; 2020-02-038; 2020-02-039), Kangdong Sacred Heart Hospital (2020-02-007; 2020-02-009; 2020-05-006; 2020-05-007; 2020-08-002; 2020-10-002; 2020-10-003), Konkuk University Medical Center (2020-11-010; 2020-11-011; 2021-02-005; 2021-03-009), Korea University Anan Hospital (2020AN0144; 2020AN0151; 2020AN0234), Korea University Guro Hospital (2020GR0578), Kosin University Gospel Hospital (2020-02-026; 2020-03-001), Maryknoll Hospital (MMC/2021-303), Myongji Hospital (2020-08-018), National Health Insurance Service Ilsan Hospital (2020-05-012), Pusan National University Yangsan Hospital (02-2020-046), Seoul National University Bundang Hospital (B-2005-613-103; B-2012-652-103; B-2204-748-401), Soon Chun Hyang University Hospital Bucheon (2020-08-007; 2020-08-011; 2020-10-025), Soonchunhyang University Hospital Seoul (2020-02-014), Yeungnam University Hospital (2020-12-016), and Yongin Severance Hospital (2020-0361-008). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and the requirement for written consent was waived due to the retrospective nature of the study.

Study design and patients

This study was designed as a multicenter observational cohort, incorporating demographic and biochemical parameters, with a focus on patients with essential hypertension. Patients were included if they met the following criteria: diagnosed with essential hypertension according to clinical guidelines, at least 19 years old at the start of Telminuvo treatment, on Telminuvo for at least 6 months, and had serum creatinine data available both before and after starting the medication. Exclusion criteria included patients with hypersensitivity to the main components or dihydropyridine derivatives of telmisartan and S-amlodipine, those who were pregnant or possibly pregnant at the start of Telminuvo treatment, or those who were breastfeeding. Additionally, patients who had previously undergone dialysis or received a kidney transplant, or who were otherwise deemed unsuitable for the study at the investigator's discretion, were also excluded.

Study variables

The demographic data collected at the time of Telminuvo administration included age, sex, height, weight, smoking history, comorbidities, Telminuvo dosage, and concomitant medications. Body mass index (BMI) was calculated by dividing weight by height squared. BP measurements were taken at multiple centers during patient visits using a standardized method, which involved taking several readings in the sitting position. Blood tests included measurements of blood urea nitrogen, creatinine, sodium, potassium, chloride, hemoglobin A1c, and lipid panel components such as total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [18]. These variables were extracted from electronic medical records.

Outcome data focused on adverse events following Telminuvo administration. Monitoring occurred at 3, 6, 12, 24, and 36 months post-administration, with particular attention to

kidney dysfunction-related events, such as acute kidney injury (AKI). AKI was defined as either a ≥ 0.3 mg/dL increase in serum creatinine or a ≥ 50% increase from baseline [19]. Hyperkalemia was defined as a serum potassium level > 5.5 mmol/L. Additionally, we monitored other adverse events, including cardiovascular events, peripheral edema, headache, facial flushing, gum hypertrophy, leukopenia, angioedema, and rash, throughout the study period.

Statistical analysis

Categorical data were presented as frequencies and percentages, while continuous data were presented as means (± standard deviations) or medians (interquartile ranges). Each patient's medical history was coded using MedDRA software (version 22.1; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland). Concomitant medications were classified according to the World Health Organization's Anatomical Therapeutic Chemical index, and the corresponding numbers and percentages were provided based on therapeutic categories. As this was an observational study, no imputation was performed for missing data. Patients could be included in more than one time group, depending on the timing of data collection, which varied among participants. Safety and other data analyses were conducted based on the duration of Telminuvo administration, divided into pre-administration and 3, 6, 12, 24, and 36 months post-administration. If data did not align with the predefined time points, the closest available time point was used. In cases where multiple measurements were taken within the same visit window, the value closest to the designated time point was selected for analysis. Paired t-tests were used to analyze changes in BP over time, comparing baseline values with measurements taken at 3, 6, 12, 24, and 36 months. Differences in variables between pre- and post-administration were estimated using paired t-tests or Wilcoxon signed-rank tests if the assumption of normality was not met. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 4,934 patients from 30 hospitals across South Korea were included in the analysis. Of these, 1,463 (29.7%) used Telminuvo for less than one year, while the remaining patients used it for longer periods. The average age of the patients was 63.3 ± 12.8 years, and 56.8% were male. The median duration of hypertension was 6.4 years (interquartile range: 1.3–12.1 years). The prescribed doses of Telminuvo (telmisartan and S-amlodipine) were 40/2.5 mg, 40/5 mg, 80/2.5 mg, and 80/5 mg, used by 53.1%, 18.8%, 25.8%, and 2.3% of patients, respectively. **Table 1** provides additional clinical details.

The most common comorbidities were metabolism and nutrition disorders, affecting 61.71% of patients, followed by cardiac disorders (30.34%) and nervous system disorders (14.13%). Within the metabolism and nutrition category, hyperlipidemia (26.90%) and diabetes mellitus (26.39%) were the most prevalent. Additional details on comorbidities can be found in **Supplementary Table 1**. Information on transitions from previous medications to Telminuvo is presented in **Supplementary Table 2**, with the most common transitions being from ACE inhibitors or ARBs (22.1%), β-blockers (20.8%), and no prior hypertensive medications (11.6%).
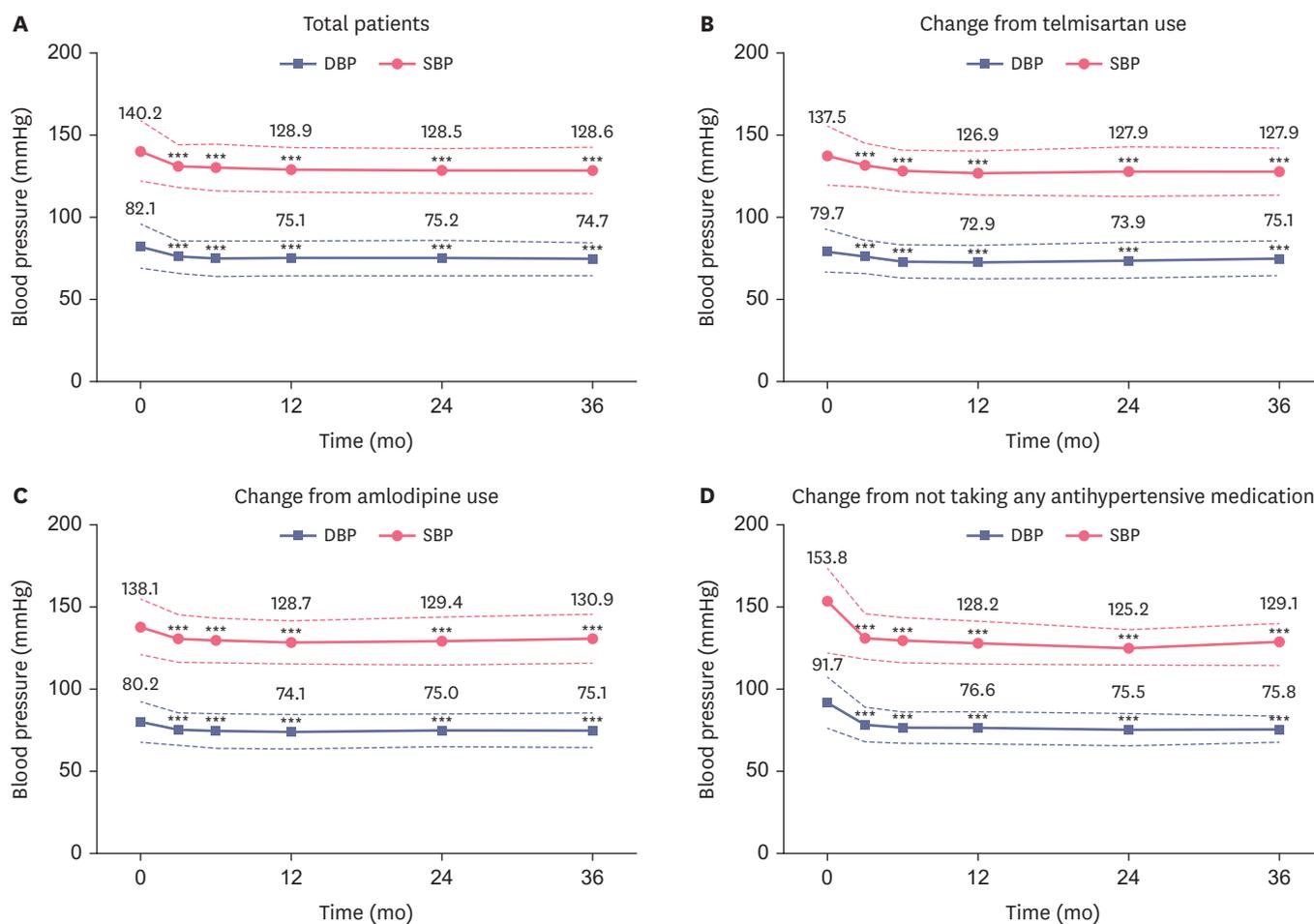
Table 1. Demographics and baseline characteristics of patients

Variables	Values (n = 4,934)
Male	2,804 (56.8)
Age (yr)	63.3 ± 12.8
Height (cm)	162.8 ± 9.4
Weight (kg)	68.6 ± 13.6
Body mass index (kg/m²)	25.7 ± 3.8
Duration of hypertension (yr)	8.0 ± 7.7
Smoking history	
Never smoker	2,001 (40.6)
Ex-smoker	488 (9.9)
Current smoker	544 (11.0)
Unknown	1,901 (38.5)

Data are presented as mean ± standard deviation for continuous variables and the number (%) for categorical variables.

BP after Telminuvo administration

At baseline, the systolic and diastolic BPs averaged 140.2 ± 18.4 mmHg and 82.1 ± 13.4 mmHg, respectively. After starting Telminuvo, systolic BP remained at approximately 130 mmHg, while diastolic BP stabilized around 75 mmHg over a 3-year period (**Fig. 1**). Among patients

Fig. 1. Blood pressure after administration of Telminuvo.
(A) All patients; (B) Patients previously treated with telmisartan; (C) Patients previously treated with amlodipine; (D) Patients not previously treated with antihypertensive medication.
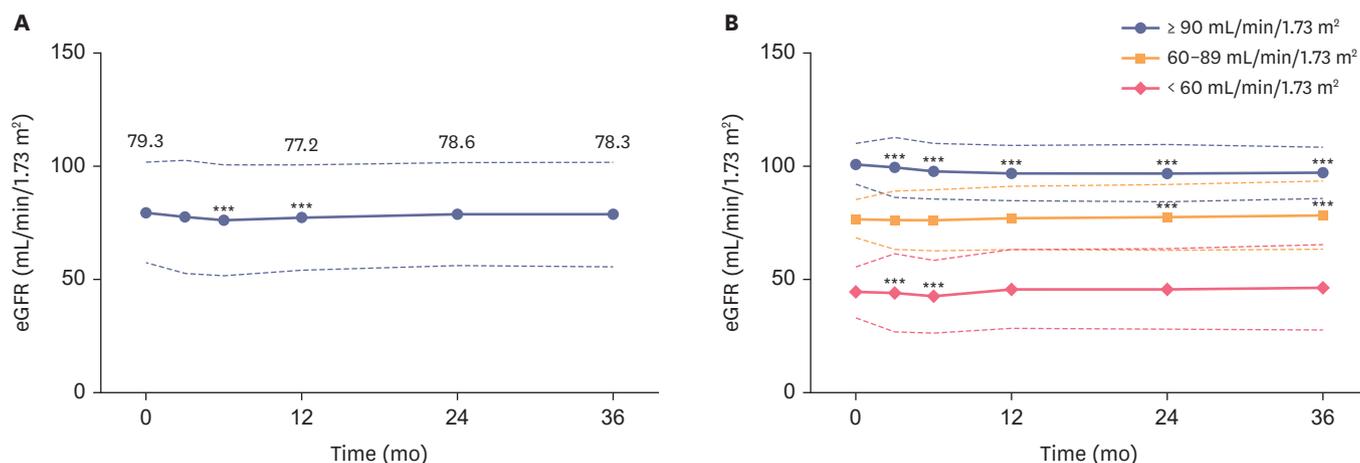DBP, diastolic blood pressure; SBP, systolic blood pressure.
***p < 0.001 compared with values at baseline.

who transitioned from renin-angiotensin system agents or CCBs to Telminuvo, systolic BP decreased by about 9 mmHg and diastolic BP by 5 mmHg over the 3 years. For those transitioning from no prior antihypertensive medication to Telminuvo, the reduction was more pronounced, with systolic BP decreasing by 25 mmHg and diastolic BP by 16 mmHg over the same period (**Fig. 1**). Patients were stratified by baseline eGFR, and temporal trends in serum potassium, eGFR, and blood pressure were analyzed separately (**Supplementary Fig. 1**). In this stratified analysis, both SBP and DBP showed statistically significant reductions across all time points.

Renal safety after Telminuvo administration

The baseline eGFR was 79.3 ± 22.1 mL/min/1.73 m^2, with 80.9% of patients having an eGFR of 60 mL/min/1.73 m^2 or higher. While eGFR initially decreased after 6 and 12 months of Telminuvo administration, it returned to baseline levels after one year (**Fig. 2**), suggesting a protective effect from long-term ARB use or effective BP control on target organs [20,21]. The overall annual change in eGFR was less than 1 mL/min/1.73 m^2, consistent with the natural decline in eGFR seen in healthy aging [22]. Notably, no significant decrease in eGFR was observed in patients with reduced kidney function at baseline (e.g., eGFR of 60–89 mL/min/1.73 m^2 or below 60 mL/min/1.73 m^2) (**Table 2**). However, a significant reduction was noted in patients with an eGFR above 90 mL/min/1.73 m^2, though the maximum decrease was only 4 mL/min/1.73 m^2, and eGFR levels remained above 90 mL/min/1.73 m^2 (**Fig. 2**).

Fig. 2. Kidney function parameters after administration of Telminuvo.
(A) All patients; (B) Stratified analysis by baseline kidney function.
eGFR, estimated glomerular filtration rate.
***p < 0.001 compared with values at baseline.

Table 2. Changes in kidney function parameters after the administration of Telminuvo

Variables	Baseline		3 mo		6 mo		12 mo		24 mo		36 mo	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Total	4,934	79.3 ± 22.1	801	77.4 ± 25.1	1,422	75.9 ± 24.5***	1,696	77.2 ± 23.3***	1,395	78.6 ± 22.6	894	78.3 ± 23.0
eGFR (mL/min/1.73 m^2)												
≥ 90	1774	100.9 ± 9.2	293	99.5 ± 13.2**	474	97.9 ± 12.3***	577	96.9 ± 12.2***	466	97.0 ± 12.6***	284	97.3 ± 11.4***
60–89	2,220	76.7 ± 8.7	324	76.4 ± 12.8	630	76.2 ± 13.5	759	77.2 ± 13.9	687	77.6 ± 14.5*	437	78.6 ± 15.0***
< 60	940	44.7 ± 11.5	184	44.2 ± 17.2*	318	42.6 ± 16.2*	360	45.8 ± 17.3	242	45.9 ± 17.8	173	46.6 ± 18.9

Comparison analyses are performed when the baseline group serving as a reference.
eGFR, estimated glomerular filtration rate; SD, standard deviation.
*p < 0.05, **p < 0.01, and ***p < 0.001.

Table 3. Changes in the serum potassium concentration after the administration of Telminuvo

Variables	Baseline		3 mo		6 mo		12 mo		24 mo		36 mo	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Total	2,931	4.32 ± 0.48	452	4.42 ± 0.48	821	4.45 ± 0.49***	1,049	4.38 ± 0.48**	820	4.34 ± 0.43	555	4.38 ± 0.47*
eGFR (mL/min/1.73 m²)												
≥ 90	969	4.19 ± 0.39	147	4.22 ± 0.38	229	4.26 ± 0.36*	337	4.26 ± 0.37***	259	4.25 ± 0.38	159	4.19 ± 0.35
60–89	1,301	4.29 ± 0.44	178	4.38 ± 0.43	362	4.38 ± 0.44*	451	4.31 ± 0.40	395	4.31 ± 0.40	267	4.35 ± 0.43*
< 60	661	4.57 ± 0.56	127	4.68 ± 0.54	230	4.74 ± 0.56	261	4.64 ± 0.57	166	4.57 ± 0.49	129	4.69 ± 0.54***

Comparison analyses are performed when the baseline group serving as a reference.
eGFR, estimated glomerular filtration rate; SD, standard deviation.
*p < 0.05, **p < 0.01, and ***p < 0.001.

AKI occurred in 6.6% of patients within the first 6 months of Telminuvo administration, increasing slightly to 7.4% within 3 years. Hyperkalemia was observed in 1.6% and 3.2% of patients within 3 and 6 months, respectively, while 2.0% experienced this condition over 3 years. Long-term increases in serum potassium were primarily observed in patients with an eGFR below 90 mL/min/1.73 m², rather than those with an eGFR ≥ 90 mL/min/1.73 m² (**Table 3**). No kidney-related events were linked to the dosage of Telminuvo (**Supplementary Table 3**).

Other safety events after Telminuvo administration

Adverse events unrelated to kidney dysfunction were also recorded (**Supplementary Table 4**). A total of 1,463 patients received Telminuvo for less than 1 year, during which 61 adverse events were reported. The most common was peripheral edema (n = 8, 0.55%), followed by generalized edema and dizziness, which occurred in 2 (0.14%) and 3 (0.21%) patients, respectively. A total of 15 patients (2.43%) discontinued treatment, with dizziness and hypotension being the primary adverse events leading to discontinuation. No deaths were reported during the study period. Further details on other adverse events can be found in **Supplementary Table 4**.

DISCUSSION

Clinicians require detailed evaluations of individual medications, as efficacy and the frequency of complications can vary even among drugs within the same class. This study focused on kidney-related outcomes and complications associated with Telminuvo, a single-pill combination of telmisartan and S-amlodipine. Over 3 years of use, kidney function remained largely stable, with rates of AKI and hyperkalemia recorded at 7.4% and 2.0%, respectively. Notably, patients with pre-existing kidney impairment did not experience a decline in eGFR. These findings suggest that the appropriate use of Telminuvo may help prevent further deterioration of kidney function in hypertensive patients [23]. Additionally, various complications were investigated, and common adverse effects such as edema and dizziness, which are frequently seen with drugs in the same class, occurred at very low rates. This may be due to the specific characteristics of the study population. On the other hand, BP control was notably effective. These findings provide valuable data for anticipating and addressing potential issues when using Telminuvo in real-world clinical practice.

Antihypertensive drugs are among the most commonly prescribed medications worldwide [24]. There is a well-established positive correlation between BP and the risk of stroke, coronary artery disease, heart failure, and the development and progression of kidney dysfunction [25-28], a relationship that applies across all age groups and ethnicities [29]. While improving lifestyle habits can lower BP and reduce overall cardiovascular

risk, most hypertensive patients require antihypertensive medications alongside lifestyle interventions [30]. Several classes of antihypertensive drugs are available, with ARBs being the most commonly prescribed in Korea, followed by CCBs [12]. In this study, we focused on Telminuvo, a single-pill combination that may enhance patient compliance and lead to improved clinical outcomes [6]. However, before this study, no reports had explored the use of Telminuvo in real clinical settings, particularly in relation to kidney outcomes.

Over the 3-year period of Telminuvo use, no significant deterioration in kidney function was observed. Although eGFR may decrease in the early phase of treatment due to the effects of ARBs, long-term follow-up showed sustained kidney function [31]. This is likely attributable to BP-lowering effect of Telminuvo. The incidence of AKI and hyperkalemia was low, at around 7% and 2%, respectively, indicating that these events are rare. Furthermore, since these complications mainly occurred in patients with advanced kidney dysfunction, Telminuvo appears to be very safe for hypertensive patients with preserved kidney function.

This study also discusses several other events associated with the use of Telminuvo. Peripheral edema is a common complication linked to CCBs, with rates exceeding 5% in various cohort studies. This side effect may be influenced by the molecular structure of CCBs. Telminuvo contains S-amlodipine, which has a lower incidence of edema compared to amlodipine, which consists of both S- and R-amlodipine [32]. Additionally, the inclusion of telmisartan in Telminuvo may further reduce the risk of peripheral edema typically associated with CCBs. These findings suggest that Telminuvo could be a beneficial option for patients who experience peripheral edema, whether or not it is related to other drug use.

While the study provides valuable insights, it also has several limitations. As a retrospective study, it cannot definitively establish causal relationships, particularly regarding Telminuvo use and the rise in potassium levels. Hyperkalemia can be influenced by various factors, including underlying diseases, dietary habits, concomitant medications, and the use of potassium-lowering agents, which were not fully accounted for. The lack of proteinuria data limits the comprehensive evaluation of renal outcomes. These limitations highlight the need for future prospective studies to address such variables. Moreover, the inclusion criteria required patients to have been on Telminuvo therapy for at least six months, which could introduce bias, as patients who experienced early onset of AKI or hyperkalemia and discontinued treatment were excluded, potentially leading to lower observed incidence rates.

Since the cohort consisted solely of Korean patients and hospitals, the results may reflect specific characteristics of this population, and the findings may not be directly applicable to other countries or ethnic groups. Additionally, the lack of imputation for missing data could introduce bias and reduce the statistical power of the study. Furthermore, the absence of a comparison between Telminuvo and other ARB-CCB combination therapies limits the study to descriptive observations, highlighting the need for future studies with comparison groups to draw stronger conclusions.

Conclusions

This study provides evidence supporting the use of Telminuvo in hypertensive patients by thoroughly analyzing its renal safety. Additionally, the findings offer valuable insights for clinical practice, demonstrating effectiveness of Telminuvo in lowering BP and its low incidence of associated complications. Future research will focus on investigating its impact on other target organs beyond the kidneys.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Comorbidities at baseline

Supplementary Table 2
Information on antihypertensive medications

Supplementary Table 3
Occurrence of major adverse events based on the Telminuvo dose

Supplementary Table 4
Occurrence of other adverse events according to the period of Telminuvo administration

Supplementary Fig. 1
Comparative trends.

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