

REVIEW ARTICLE

Telmisartan – A Potent Antihypertensive With Proven Cardio-Renal-Metabolic Beneficial Effects

Nirvana Sabanovic-Bajramovic¹, Mirna Aleckovic-Halilovic², Larisa Dizdarevic-Hudic³, Sevlata Avdic⁴, Ljiljana Kos^{5,6}, Bojan Stanetic^{5,6}, Ammar Brkic⁷, Bojan Pejovic⁸, Denaida Ovcina-Sabanovic⁹

¹ Clinic for Heart, Blood Vessels and Rheumatism, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

² Department for Nephrology, Dialysis and Renal Transplantation, Clinic for Internal Medicine, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

³ Department for Cardiology, Clinic for Internal Medicine, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

⁴ Bayer MIB, Tuzla, Bosnia and Herzegovina

⁵ Department of Cardiology, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina

⁶ Medical Faculty, University of Banja Luka, Banja Luka, Bosnia and Herzegovina

⁷ Intensive Care Unit, Clinic for Internal Medicine, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

⁸ Hospital "Serbia", East Sarajevo, Bosnia and Herzegovina

⁹ Health Care Institution, Sarajevo, Bosnia and Herzegovina

Corresponding Author: Nirvana Sabanovic-Bajramovic MD, MSc Clinic for Heart, Blood Vessels and Rheumatism, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina; E-mail: nirvana_sabanovic@yahoo.com; Phone: +387 61 361 231; ORCID ID: 0000-0003-3749-6073

Pages: - / Published online: 26 April 2025

Cite this article: Sabanovic-Bajramovic N, Aleckovic-Halilovic M, Dizdarevic-Hudic L, Avdic S, Kos LJ, Stanetic B, et al. Telmisartan – a Potent Antihypertensive with Proven Cardio-Renal-Metabolic Beneficial Effects. Sar Med J 2025; 2(1): Online ahead of print. doi 10.70119/0028-25

Original submission: 10 August 2024; **Revised submission:** 18 December 2024; **Accepted:** 06 April 2025

Abstract

Due to an epidemic of risk factors, such as hypertension, and an increase in life expectancy, cardiovascular disease (CVD) has an overwhelming morbidity and mortality burden worldwide.

Various treatment options are available to disrupt pathophysiological processes along the cardiovascular continuum by focusing on distinct regions of the renin-angiotensin-aldosterone system (RAAS). As a RAAS inhibition, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are recommended first-line treatments for hypertension and CVD. Both ACE inhibitors and ARBs prevent CVD by lowering blood pressure (BP). Furthermore, a number of studies have shown that RAAS blockade can lower cardiovascular risk in ways that go beyond what could be predicted from lowering blood pressure alone.

However, the ARBs are not all equally effective. Telmisartan is a long-lasting ARB that effectively controls BP over the full 24-hour period. In high cardiovascular risk patients, telmisartan reduces cardiovascular events in a manner comparable to that of the ACE inhibitor ramipril beyond lowering blood pressure alone, but with better tolerability.

Research points to possible benefits for adipose tissue activity, neurovascular function, and enhancements in glucose and lipid metabolism. According to several studies, telmisartan has partial peroxisome proliferator-activated receptor gamma (PPAR γ) agonist activity, which improves insulin resistance in diabetic patients by modifying adipokine levels.

The combination of telmisartan and indapamide as metabolically neutral diuretic has an additional positive antihypertensive as well as cardioprotective effects.

In addition to reviewing current CVD management guidelines, this article will examine important clinical trial and clinical practice data that assess the role of telmisartan/indapamide in CVD.

Keywords. arterial hypertension, angiotensin II receptor blocker, telmisartan, cardiovascular risk.

INTRODUCTION

Arterial hypertension is a leading factor in the global disease burden yet control of the condition remains inadequate (1). The initiation of antihypertensive therapy should be guided by blood pressure measurements and the presence of elevated atherosclerotic cardiovascular disease (CVD) risk. First-line pharmacologic management for hypertension typically includes an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), combined with thiazide or thiazide-like diuretic and/or a calcium channel blocker. Dosages of these medications should be titrated based on both office and home systolic and diastolic blood pressure readings to achieve a target systolic blood pressure (SBP) and diastolic blood pressure (DBP) of <130/80 mm Hg for treated individuals with the use of fixed-dose single-pill combination treatment (1, 2).

The choice of therapy should be in accordance with the systolic and diastolic function of the left ventricular heart, renal and liver function, the presence of comorbidities, primarily diabetes mellitus, all with the goal of impacting primary and secondary prevention of cardiovascular events (3). The selection of pharmacological agents should be based on the pharmacokinetic and pharmacodynamic properties of the drug, with careful consideration of the atherosclerotic process throughout the entire body, including its effects on cerebral and renal circulation (4).

The most recent international guidelines recommend using ACEIs or ARBs in patients with coexisting microalbuminuria, renal dysfunction, and chronic kidney disease (CKD), as well as those with metabolic syndrome, diabetes mellitus (DM), atherosclerosis, chronic stable angina, a history of myocardial infarction (MI), atrial fibrillation (AF), and heart failure (HF) (1, 5, 6).

Angiotensin Receptor Blockers

Guidelines recommend both angiotensin receptor blockers (ARBs) and ACE (angi-

otensin-converting enzyme) inhibitors as first-line treatments for hypertension. ACE inhibitors and ARBs did not differ statistically significantly in their effects on AMI, HF, stroke, or composite CVEs; however, ARBs exhibited a better safety profile with reduced risks for cough, GI bleeding, angioedema, and acute pancreatitis (3). ACE-Is are less likely to be tolerated than ARBs, besides that ARBs were shown to reduce withdrawal due to adverse effects. For patients unable to tolerate ACEI therapy due to side effects such as a cough or angioedema, ARBs are recommended as an alternative. The currently available angiotensin receptor blockers include azilsartan, candesartan, eprosartan, irbesartan, valsartan, losartan, telmisartan, and olmesartan (3).

Telmisartan

Telmisartan is indicated for treatment of arterial hypertension and for reducing cardiovascular mortality in adults with risk factors for serious cardiovascular events, especially in those who do not tolerate angiotensin-converting enzyme inhibitors (ACEIs) (3). Additionally, it is utilized for the prevention of stroke and myocardial infarction (3). Telmisartan acts by selectively blocking the binding of angiotensin II to AT1 receptors, resulting in vasodilation, decreased aldosterone production, and reduced sodium and water retention (7). Its long biological half-life allows for sustained 24-hour blood pressure control with a once-daily dosing regimen (8). At an 80 mg dose, telmisartan's antihypertensive efficacy is comparable to amlodipine and significantly superior to enalapril and ramipril (9).

Unlike ACE inhibitors, telmisartan does not inhibit angiotensin-converting enzyme (kinase II), which is responsible for the degradation of bradykinin. As a result, it does not induce bradykinin-mediated side effects, such as persistent cough (10). Beyond its antihypertensive effects, telmisartan offers additional cardiovascular benefits, including a reduction in the risk of myocardial infarcti-

on and a decrease in left ventricular hypertrophy (11). In terms of renal function, it effectively lowers blood pressure and reduces proteinuria, particularly in patients with diabetic nephropathy (12).

Several studies have indicated that telmisartan possesses partial peroxisome proliferator-activated receptor gamma (PPAR γ) agonist activity, which modulates adipokine levels to improve insulin resistance in diabetic patients. Furthermore, there is a growing body of evidence that activators of PPAR γ -gamma exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risks for atherosclerosis. This may provide additional therapeutic benefits for conditions such as diabetes mellitus, obesity, and hyperlipidemia, without the safety concerns typically associated with full PPAR γ agonists (13).

Additionally, indapamide that comes in a single-pill combination with telmisartan has positive metabolic effects. Because it has less of an effect on glucose tolerance and lipid metabolism than some other diuretics, it is a good choice for patients with metabolic issues like diabetes or dyslipidemia (14).

Consequently, a fixed-dose combination of telmisartan and indapamide may be a viable alternative for managing hypertension and all components of metabolic syndrome (13).

These pleiotropic effects position the telmisartan and indapamide combination as a promising therapeutic approach, offering comprehensive cardiovascular management beyond blood pressure control. This combination has been shown to decrease fasting plasma glucose (FBG), fasting plasma insulin, homeostasis model assessment (HOMA) index, and triglyceride (TG) levels (14).

Among angiotensin receptor blockers (ARBs), telmisartan has the longest duration of action, providing 24-hour blood pressure control. This extended effect is crucial, as the incidence of acute myocardial infarction and other cardiovascular events exhibits circadian variation, with higher incidence observed during the morning (15).

With multiple benefits for all elements of the metabolic syndrome, such as obesity, diabetes mellitus, hypertension, and hyperlipidemia, telmisartan may therefore be regarded as a multi-useful therapeutic option.

INDICATIONS

The indications based on clinical studies that evaluated the use of telmisartan are presented in Table 1.

TELMISARTAN AND INDAPAMIDE IN METABOLIC SYNDROME

Telmisartan, a partial peroxisome proliferation-activator receptor gamma (PPAR γ) agonist, is useful in prevention and treatment of type 2 diabetes mellitus because it can improve insulin sensitivity and decrease ectopic fat deposition (14). Data from numerous recent studies suggest that the AT-1 agonist telmisartan, either as a result of its AT-1 antagonistic and/or PPAR γ agonistic properties, may also have beneficial metabolic effects including improvements in glucose and lipid profiles, adipokine levels and/or fat distribution and body weight (16-19).

Peng et al. demonstrated in a study involving 221 patients that the combination of telmisartan and indapamide has an effect on the incidence rate of metabolic syndrome (14). Weidmann showed that indapamide did not significantly impact glucose and lipid metabolism (16). Imenshahidi et al. suggest that telmisartan is effective in preventing and improving metabolic syndrome, and this well-tolerated drug can be strongly recommended for treating various components of metabolic syndrome (16-19).

Telmisartan's ability to lower blood sugar has been attributed to a variety of mechanisms. One of these thought-to-be mechanisms is antioxidant activity. Another way telmisartan helps to restore insulin resistance is by reducing the inflammatory response in adipose tissue (13).

Table 1. Telmisartan in clinical trials

Study	Sample	Methodology	Findings
The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) (15)	25,620 pts HTN with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	Prospective, randomized 4.7 years Subgroup: Telmisartan 80 mg/day vs ramipril 10 mg/day	Mean blood pressure was lower in telmisartan group than in ramipril group. Telmisartan 80 mg was as effective as ramipril 10 mg in preventing new-onset diabetes in patients at high vascular risk. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema.
The Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) (15)	5926 pts Intolerance to ACE inhibitors + coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	Prospective, randomized 4.7 years Telmisartan 80 mg/day vs placebo	Patients who could not tolerate ACE inhibitors responded well to telmisartan. Telmisartan 80 mg was more effective than placebo in LVH reduction. The group taking telmisartan experienced a 37% decrease in new-onset LVH. Telmisartan modestly reduces the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke.
Telmisartan to Prevent Recurrent Stroke (PRoFESS) (17)	20,332 pts Age 50 years + recent ischemic stroke (120 days)	Prospective, randomized 2.5 years 80 mg/day vs placebo	Significant advantage for stroke and cardiovascular events was seen after 6 months (considerable time may be necessary to modify the atherosclerotic process).
The prospective, randomized investigation of the safety and efficacy of telmisartan versus ramipril using ambulatory blood pressure monitoring (PRISMA I) (18)	801 patients with mild-to-moderate hypertension	Prospective, randomized telmisartan 80 mg for 14 weeks or ramipril 5 mg for 8 weeks and then force titrated to ramipril 10 mg for the last 6 weeks.	Telmisartan is much more effective than ramipril at lowering blood pressure over the course of the 24-hour dosage period, especially in the final six hours, when there is a higher chance of cerebro- and cardiovascular events. Both drugs were well tolerated, although ramipril was associated with a higher incidence of cough.
Sanchez Muñoz-Torrero JFS et al. (12)	42 patients Homeostatic model assessment-insulin resistance (HOMA-IR) in hypertensive subjects with MS	Cytokines and metabolic parameters were analyzed before and after treatment with telmisartan	Telmisartan treatment reduced HOMA-IR by 35%. In MS patients with low serum cytokine levels, telmisartan had more positive effects on glucose homeostasis.
Jie Peng et al. (14)	221 subjects with high-normal blood pressure were randomly assigned to telmisartan, 213 to indapamide and 230 to placebo	Prospective 3 years Metabolism changes especially in abdominally obese individuals	The intervention for high-normal blood pressure with telmisartan and indapamide reduced the risk of metabolic syndrome Telmisartan was more effective, whereas indapamide had better pharmacoeconomic benefits.
Telmisartan vs. Ramipril in Renal Endothelial Dysfunction (TRENDY) (19)	87 patients HTN with type 2 diabetes	Prospective Randomised Telmisartan vs ramipril adiponectin levels at baseline and following 9 weeks treatment	There was a significant increase in adiponectin levels in the telmisartan but not in the ramipril group.
Dragos Vinereanu et al. (30)	56 patients (57 ± 9 years, 52% men) with mild-to-moderate hypertension and type 2 diabetes	Prospective, randomized compare the effects of 2 types of diuretics, indapamide and hydrochlorothiazide, on ventricular and arterial functions in patients with hypertension and diabetes	Indapamide improved measures of endothelial and arterial functions and increased longitudinal left ventricular function compared with hydrochlorothiazide.

ACEI, angiotensin-converting enzyme inhibitor; HTN, hypertension; LVH, left ventricular hypertrophy; HOMA-IR, homeostatic model assessment-insulin resistance; MS, metabolic syndrome.

In a double-blind, randomized study, hypertensive patients with metabolic syndrome showed improvements in fasting glucose, plasma insulin, insulin resistance, glycosylated hemoglobin insulin, and homeostasis after administration 80 mg/day of telmisartan for three months; however, administration of 50 mg/day of losartan did not demonstrate any appreciable positive effects in this study (16-19).

Telmisartan was found to significantly lower serum insulin levels in 36 patients with metabolic syndrome and hypertension. The HOMA-IR model (homeostasis model assessment of insulin resistance) was also used in this study to measure insulin resistance, and the results demonstrated that telmisartan significantly reduces insulin resistance (18, 19).

Apart from the mechanisms common to other ARBs, telmisartan also uses other mechanisms to exert its anti-obesity effects. In addition to its anti-hypertensive effects, telmisartan exhibits remarkable effects on the structure and function of adipose tissue. By partially activating the PPAR γ receptors, telmisartan reduces the buildup of visceral adipose tissues (20).

According to a meta-analysis of telmisartan's effects on body fat distribution in 651 participants who were overweight or obese, telmisartan improves fat distribution and lowers visceral fat, which may make it particularly helpful for obese hypertensive patients (21).

In dyslipidemic conditions, ARBs and statins may also have some additive effects that result in further effects on lipid metabolism. One of the likely mechanisms of telmisartan's anti-dyslipidemic effects is its hepatic partial PPAR γ agonist activity, which raises lipoprotein lipase expression through a PPAR γ -dependent pathway (22).

TELMISARTAN AND POST-CEREBROVASCULAR ACCIDENT

Telmisartan demonstrated effective antihypertensive activity in hypertensive patients with chronic-stage stroke, without altering hemispheric blood flow. In fact, it even enhanced regional cerebral blood flow in most regions studied (23). Kono et al. found that telmisartan significantly reduced inflammation and protected the neurovascular unit through its pleiotropic effects in hypertensive rats after ischemic stroke (24). Iwanami et al. suggested that the beneficial effects of telmisartan on stroke

are partly due to the activation of PPAR γ and the blockade of the angiotensin 1 receptor (25). Additionally, the post hoc analysis of the PROFESS trial, as well as the ONTARGET and TRANSCEND studies, indicated that telmisartan notably reduced the incidence of strokes compared to a placebo (26). Furthermore, it was demonstrated that telmisartan was superior to ramipril in lowering the incidence and severity of AF in hypertensive patients with metabolic syndrome, as well as in preventing recurrence of AF in hypertensive patients (46).

COMBINATION OF TELMISARTAN AND INDAPAMIDE – EFFECT ON DIASTOLIC DYSFUNCTION

The risk of cardiovascular morbidity and death is raised by left ventricular hypertrophy (LVH) and diastolic dysfunction, a common type of target organ damage linked to hypertension. Anomalies in neurohormonal systems, including the renin-angiotensin-aldosterone system, as well as metabolic disorders, can also lead to LVH. Regression of left ventricular mass (LVM) significantly lowers this risk, and LVM reduction is linked to antihypertensive medication. Telmisartan is a long-acting ARB that has shown regression of LVH and improved diastolic function in several clinical trials.

Chang et al. reported that telmisartan reversed left ventricular hypertrophy and the E/A ratio, suggesting that telmisartan can enhance LV remodeling and diastolic function in cardiorenal HF with preserved ejection fraction (HFpEF) (27). Cardiac fibrosis plays a key role in the pathophysiology of cardiorenal HFpEF, and modulation of the RAAS with telmisartan effectively reduces cardiac fibrosis and helps maintain diastolic function in this rat model (27). Given the evidence of telmisartan's effect on LV mass itself, this effect could lead to improvements in both systolic and diastolic function.

In the TRANSCEND trial, after 5 years of therapy LVH was reduced to 9.9% in the tel-

misartan group compared to 12.8% in the placebo group. Furthermore, telmisartan reduced new-onset LVH by 37% when compared with placebo. In the ONTARGET trial, telmisartan was also slightly more effective than ramipril in reducing LVH (28).

The diuretic's effect on diastolic function suggests that combining telmisartan with indapamide in patients with HFpEF, especially in those with metabolic syndrome who are likely to have undiagnosed HFpEF in a large percentage, could be beneficial. After 6 months of treatment, indapamide was shown to enhance endothelial and arterial function, as well as improve longitudinal left ventricular function, compared to hydrochlorothiazide in patients with hypertension and diabetes (29).

TELMISARTAN AND KIDNEY FUNCTION

Telmisartan has been tested in many different studies, in diverse patient cohorts, in comparison with placebo or other commonly used antihypertensives as presented in detail in Table 2.

It has been demonstrated that telmisartan in standard and especially higher doses safely and effectively lowers blood pressure (SBP and DBP, daytime and night-time) and reduces proteinuria, even independent of BP, in diabetic and nondiabetic hypertensive patients, with proteinuria and CKD of various degrees, preserves renal function, and potentially ameliorates atherosclerosis (24-26, 33-36).

Being a RAAS inhibitor and due to its aforementioned properties and effects, telmisartan should be one of the first logical choices for modern therapy of hypertension in wide spectrum of CKD patients, especially, and in accordance with recent guidelines (ESC 24) – in single-pill combinations. Such combination with indapamide is a very useful tool in nephrology practice for indapamide is a proven better choice of antihypertensive and diuretic than hydrochlorothiazide for its better preservation of renal function and reduction of morbidity and mortality (28,

37). It is even more pronounced in patients with metabolic disturbances because of its metabolic effects (14, 16, 17), and also preservation of renal function through reducing the often neglected but growing problem of renal calculosis (25,39).

Maximal tolerable dosage of ARB/ACEi in patients with elevated UACR or proteinuria irrespective of eGFR or even BP is used in the widest spectrum of renal patients as a recommended practice for lowering proteinuria as the most relevant renal prognostic factor, and also decreasing hyperfiltration (12, 41, 42). Telmisartan alone and in combination with indapamide might be very useful in this common scenario.

Regardless of its cause, CKD as a continuum and through all its stages, starting from subclinical kidney injury, endothelial dysfunction, from microalbuminuria to macroalbuminuria, from hyperfiltration to declining GFR and finally end-stage renal disease, represents independent and progressively increasing CV risk factor. Hence, contemporary treatment that warrants not only renal but CV and other benefits in a holistic manner should encompass lowering of blood pressure and proteinuria together with many pleiotropic renal, metabolic and CV protective effects described earlier in this manuscript (12). Telmisartan, and its combination with indapamide offers it all.

TELMISARTAN AFFECTS ENDOTHELIAL DYSFUNCTION, INFLAMMATION AND PROMOTES RISK REDUCTION IN CHRONIC CORONARY SYNDROME PATIENTS

Multiple randomized controlled trials demonstrated reduction of mortality and hospital admissions in high-risk patients with cardiovascular disease when treated with an ARB (43).

In the 2011 study by Akhras et al., it is reported that blocking the RAAS with telmisartan provides optimal cardio protection in high-risk patients and is well-tolerated (44).

Vascular homeostasis is primarily regulated by the endothelium, and hypertensi-

Table 2. Telmisartan and CKD (24-26, 33-36)

Study	Sample	Methodology	Findings
Rysava et al. 2005 (32)	92 (60 with DM) hypertensive proteinuric pts with CKD (including mild-to-moderate)	Prospective telmisartan 40 mg for 3 mo, followed by telmisartan 80 mg subsequent 3 mo (target SBP/DBP of <130/85 mmHg) antihypertensive and antiproteinuric efficacy and safety	-reduced BP (office and ABPM- SBP and DBP, daytime and night-time) -regression of proteinuria in DM and nonDM
Aranda et al. 2005 (35)	78 non-DM, hypertensive pts with biopsy-proven chronic proteinuric nephropathies	Prospective randomized telmisartan 80 mg once daily (40 pts) or 80 mg twice daily (38 pts) after 4-week wash-out mean follow-up 24.6 +/- 2.2 mo long-term renoprotective effects of "standard" vs "high" doses of telmisartan	No difference in BP, potassium and lipid profile Cr increased and eCrCl declined with standard but no change with high dose proteinuria decreased more with high dose
Nakamura et al. 2008 (31)	30 untreated hypertensive pts with moderate renal insufficiency	Prospective randomized 40 mg telmisartan (15 pts) vs 5 mg amlodipine (15 pts) 12 months follow-up Comparison of renal and vascular protective effects	-BP decreased equally -serum Cr, proteinuria, baPWV, IMT, IL-6 and MMP-9, Chol decreased and 24-h Ccr increased better with telmisartan
Bakris et al. 2008 (33)	860 hypertensive DM pts with UACR 700 or more	Prospective, randomized telmisartan or losartan difference in UACR at 52 weeks	Telmisartan more effective in reducing proteinuria despite no difference in reduction in BP
Mann et al. 2009 (37)	5927 pts with CV or DM with end-organ damage without macroalbuminuria or HF intolerant of ACEi	Prospective, randomized From 2001 to 2004, follow up until 2008 Telmisartan, 80 mg/d (n = 2954) placebo (n = 2972) plus standard treatment for a mean of 56 months long-term renal effects	No important difference in composite renal outcomes but with only 17 pts starting dialysis Albuminuria increased less with telmisartan than with placebo (32% [CI, 23% to 41%] vs. 63% [CI, 52% to 76%]; P < 0.001)
Agrawal et al. 2016 (36)	55 adult pts, mean 48.23 years (96.36% hypertensive; 63.61% diabetic)	Prospective, observational effects of 40 mg/day telmisartan on CKD in real-life setting	24-h urinary protein, spot urine protein-to-creatinine, Cr and BP significantly reduced at the end of 3 month treatment
Kitamura et al. 2020 (33)	61 non-nephrotic stage 3-4 CKD	Prospective, randomized from 2009 to 2014 (follow-up up to 104 weeks) telmisartan 40 mg (32 pts) or 80 mg (29) dose-dependent renoprotective effects	No significant difference in primary renal outcomes and eGFR after 24 weeks and in adverse events urinary protein level significantly lower with 80 mg

CKD – chronic kidney disease; DM – diabetes mellitus; Pts – patients; BP – blood pressure; SBP – systolic BP; DBP – diastolic BP; Mo – months; Cr – serum creatinine; HF – heart failure; ABPM – Ambulatory blood pressure monitoring; 24-h Ccr – 24-h creatinine clearance; eGFR – estimated Glomerular Filtration Rate; baPWV – brachial-ankle pulse wave velocity; IMT – intima-media thickness; IL-6 – plasma interleukin-6; MMP – plasma matrix metalloproteinase-9; Chol – total cholesterol.

on-associated vascular change is believed to be significantly influenced by endothelial dysfunction (45). Despite having comparable effects on lowering blood pressure, telmisartan had more positive effects on endothelial function-related functional parameters in hypertensive patients than valsartan. Furthermore, in hypertensive patients with type 2 diabetes, telmisartan decreased arterial stiffness more than a placebo (46).

Telmisartan has been demonstrated to lower inflammatory markers like C-reactive protein and interleukin-6 in patients with hypertension or diabetes at least as well as ACE inhibitors like ramipril or other ARBs like valsartan and olmesartan (47, 48).

Finally, based on the ONTARGET and TRANSCEND studies, RAAS blockade with telmisartan is shown to provide optimal cardio protection and significant reduction of cardiovascular morbidity and mortality in high-risk patients with CVD, diabetes mellitus and end-organ damage, along with a good tolerance profile (27, 37).

CONCLUSION

When choosing an antihypertensive treatment to prevent CVD, consideration should be given to agents whose actions extend beyond optimal BP lowering. Telmisartan is recommended for the prevention of cardi-

ovascular disease in addition to the potent treatment of hypertension.

Compared to other ARBs, telmisartan has distinct pharmacological characteristics that may have clinical implications. Telmisartan stands out among RAAS inhibitor medications due to its long duration of action, which allows for 24-hour blood pressure control, and its appropriate tolerability. Telmisartan has several therapeutic advantages, such as anti-diabetic, anti-inflammatory, and protective cardiovascular effects, due to its partial agonistic activity on PPAR γ receptors and antagonistic activity on AT1 receptors. The benefits of telmisartan's effects on endothelial dysfunction, metabolic factors, and inflammatory markers may contribute to its heart and kidney prevention effects in addition to its antihypertensive action.

Together, these characteristics make telmisartan a perfect multipurpose medication for patients with metabolic syndrome, diabetes mellitus, hypertension, CKD and other cardiovascular conditions who represent the majority of patients seen in primary and secondary care practices worldwide.

Through numerous studies indapamide has also demonstrated cardiovascular protective effects and its metabolic neutrality and no or minimal effect on potassium, creatinine, and

lipid and glucose profiles. The use of telmisartan with indapamide in a fixed dose combination has an additional positive effect on the metabolic profile of the patient, as well as on the diastolic function of the left ventricle, making it also a recommended option for hypertensive patients with left ventricular diastolic dysfunction.

The administration of telmisartan/indapamide combination to patients may also improve medication adherence by lowering the number of pills and polytherapy side effects.

Acknowledgment: None.

Authors' Contributions: Conceptualization: NS-B, MA-H. Formal analysis: NS-B, MA-H, LD-H, SA, LJK, BS, AB, BP, DO-S. Project administration: NS-B, MA-H. Resources: NS-B, MA-H. Software: NS-B, MA-H. Supervision: NS-B, MA-H. Visualization: NS-B, MA-H, LD-H, SA, LJK, BS, AB, BP, DO-S. Writing – original draft: NS-B, MA-H, LD-H, SA, LJK, BS, AB, BP, DO-S. Writing – review & editing: NS-B, MA-H, LD-H, SA, LJK, BS, AB, BP, DO-S.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

REFERENCES:

1. Brouwers S, Sudano I, Kokubo Y, Sulaica EM. Arterial hypertension. *Lancet*. 2021;398(10296):249-61. doi: 10.1016/S0140-6736(21)00221-X
2. Carey RM, Moran AE, Whelton PK. Treatment of Hypertension: A Review. *JAMA*. 2022;328(18):1849-61. doi: 10.1001/jama.2022.328(18):1849-61.
3. Hill RD, Vaidya PN. Angiotensin II Receptor Blockers (ARB). 2023 Mar 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. PMID: 30725712.
4. Chen R, Suchard MA, Krumholz HM, Schuemie MJ, Shea S, Duke J, et al. Comparative First-Line Effectiveness and Safety of ACE (Angiotensin-Converting Enzyme) Inhibitors and Angiotensin Receptor Blockers: A Multinational Cohort Study. *Hypertension*. 2021;78(3):591-603. doi: 10.1161/HYPERTENSIONAHA.120.16667.
5. Begic E, Causevic M. Glucagon-Like Peptide-1 Receptor Agonists and Brain Vascular Function. *Heart Lung Circ*. 2021;30(11):1675-80. doi: 10.1016/j.hlc.2021.07.024
6. Dézsi CA. The Different Therapeutic Choices with ARBs. Which One to Give? When? Why? *Am J Cardiovasc Drugs*. 2016;16(4):255-66. doi: 10.1007/s40256-016-0165-4
7. Parati G, Goncalves A, Soergel D, Bruno RM, Caiani EG, Gerds E, et al. New perspectives for hypertension management: progress in methodological and technological developments. *Eur J Prev Cardiol*. 2023;30(1):48-60. doi: 10.1093/eurjpc/zwac203
8. Baguet JP, Ormezzano O, Barone-Rochette G. Impact of telmisartan in modifying vascular risk. *Integr Blood Press Control*. 2010;3:81-9. doi: 10.2147/ibpc.s6707
9. Parra Carrillo JZ, Fernández M, Barrera M, Bahena J, Estrella M, Olivares Ruiz R, et al. Effect of telmisartan 80 mg once daily on 24-h blood pressure profile in patients with mild-to-moderate hypertension failing to respond to prior antihypertensive therapy. *Int J Clin Pract Suppl*. 2004;(145):9-15. doi: 10.1111/j.1742-1241.2004.00404.x.

10. White WB. Comparative effects of telmisartan in the treatment of hypertension. *J Clin Hypertens* (Greenwich). 2002;4(4 Suppl 1):20-5. doi: 10.1111/j.1524-6175.2002.01585.x.
11. Arendse LB, Danser AHJ, Poglitsch M, Touyz RM, Burnett JC Jr, Llorens-Cortes C, et al. Novel Therapeutic Approaches Targeting the Renin-Angiotensin System and Associated Peptides in Hypertension and Heart Failure. *Pharmacol Rev*. 2019;71(4):539-70. doi: 10.1124/pr.118.017129
12. Mattioli AV, Zennaro M, Bonatti S, Bonetti L, Mattioli G. Regression of left ventricular hypertrophy and improvement of diastolic function in hypertensive patients treated with telmisartan. *Int J Cardiol*. 2004;97(3):383-8. doi: 10.1016/j.ijcard.2003.10.018
13. Balakumar P, Bishnoi HK, Mahadevan N. Telmisartan in the management of diabetic nephropathy: a contemporary view. *Curr Diabetes Rev*. 2012;8(3):183-90. doi: 10.2174/157339912800563972
14. Ayza MA, Zewdie KA, Tesfaye BA, Gebrekirstos ST, Berhe DF. Anti-Diabetic Effect of Telmisartan Through its Partial PPAR γ -Agonistic Activity. *Diabetes Metab Syndr Obes*. 2020;13:3627-35. doi: 10.2147/DMSO.S265399
15. Peng J, Zhao Y, Zhang H, Liu Z, Wang Z, Tang M, et al. Prevention of metabolic disorders with telmisartan and indapamide in a Chinese population with high-normal blood pressure. *Hypertens Res*. 2015;38(2):123-31. doi: 10.1038/hr.2014.148
16. Zheng Z, Lin S, Shi H. A systematic review and meta-analysis of telmisartan versus valsartan in the management of essential hypertension. *J Clin Hypertens* (Greenwich). 2010;12(6):414-21. doi: 10.1111/j.1751-7176.2010.00287.x
17. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. *Drug Saf*. 2001;24(15):1155-65. doi: 10.2165/00002018-200124150-00006.
18. Imenshahidi M, Roohbakhsh A, Hosseinzadeh H. Effects of telmisartan on metabolic syndrome components: a comprehensive review. *Biomed Pharmacother*. 2024;171:116169. doi: 10.1016/j.biopha.2024.116169.
19. Vitale C, Mercuro G, Castiglioni C, Cornoldi A, Tulli A, Fini M, et al. Metabolic effect of telmisartan and losartan in hypertensive patients with metabolic syndrome. *Cardiovasc Diabetol*. 2005;4:6. doi: 10.1186/1475-2840-4-6
20. Kiyici S, Guclu M, Budak F, Sigirli D, Tuncel E. Even Short-Term Telmisartan Treatment Ameliorated Insulin Resistance But Had No Influence on Serum Adiponectin and Tumor Necrosis Factor-Alpha Levels in Hypertensive Patients with Metabolic Syndrome. *Metab Syndr Relat Disord*. 2019;17(3):167-12. doi: 10.1089/met.2018.0129
21. Nakagami H, Morishita R. Obesity and gastrointestinal hormones-dual effect of angiotensin II receptor blockade and a partial agonist of PPAR- γ . *Curr Vasc Pharmacol*. 2011;9(2):162-6. doi: 10.2174/157016111794519291
22. Choi GJ, Kim HM, Kang H, Kim J. Effects of telmisartan on fat distribution: a meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2016; 32(7):1303-9. doi: 10.1185/03007995.2016.1171204
23. Rizos CV, Liberopoulos EN, Tellis K, DiNicolantonio JJ, Tselepis AD, Elisaf MS. Combining rosuvastatin with angiotensin-receptor blockers of different PPAR γ -activating capacity: effects on high-density lipoprotein subfractions and associated enzymes. *Angiology*. 2015;66(1):36-42. doi: 10.1177/0003319713512556
24. Deguchi I, Furuya D, Fukuoka T, Tanahashi N. Effects of telmisartan on the cerebral circulation of hypertensive patients with chronic-stage stroke. *Hypertens Res*. 2012;35(12):1171-5. doi: 10.1038/hr.2012.105
25. Kono S, Kurata T, Sato K, Omote Y, Hishikawa N, Yamashita T, et al. Neurovascular protection by telmisartan via reducing neuroinflammation in stroke-resistant spontaneously hypertensive rat brain after ischemic stroke. *J Stroke Cerebrovasc Dis*. 2015;24(3):537-47. doi: 10.1016/j.jstrokecerebrovasdis.2014.09.037.
26. Iwanami J, Mogi M, Tsukuda K, Min LJ, Sakata A, Jing F, Iwai M, Horiuchi M. Low dose of telmisartan prevents ischemic brain damage with peroxisome proliferator-activated receptor- γ activation in diabetic mice. *J Hypertens*. 2010;28(8):1730-7. doi: 10.1097/HJH.0b013e32833a551a.
27. Diener HC. Preventing stroke: the PROFESS, ONTARGET, and TRANSCEND trial programs. *J Hypertens Suppl*. 2009;27(5):S31-6. doi: 10.1097/01.hjh.0000357906.60778.7f
28. Verdecchia P, Sleight P, Mancina G, Fagard R, Trimarco B, Schmieder RE; ONTARGET/TRANSCEND Investigators. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals at high vascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease. *Circulation*. 2009;120(14):1380-9. doi: 10.1161/CIRCULATIONAHA.109.865774.
29. Chang D, Xu TT, Zhang SJ, Cai Y, Min SD, Zhao Z, Lu CQ, Wang YC, Ju S. Telmisartan ameliorates cardiac fibrosis and diastolic function in cardiorenal heart failure with preserved ejection fraction. *Exp Biol Med* (Maywood). 2021;246(23):2511-21. doi: 10.1177/15353702211035058
30. Vinereanu D, Dulgheru R, Magda S, Dragoi Galrinho R, Florescu M, Cinteza M, Granger C, Ciobanu AO. The effect of indapamide versus hydrochlorothiazide on ventricular and arterial function in patients with hypertension and diabetes: results of a randomized trial. *Am Heart J*. 2014;168(4):446-56. doi: 10.1016/j.ahj.2014.06.010.
31. Nakamura T, Inoue T, Suzuki T, Kawagoe Y, Ueda Y, Koide H, et al. Comparison of renal and vascular protective effects between telmisartan and amlodipine in hypertensive patients with chronic kidney disease with mild renal insufficiency. *Hypertens Res*. 2008;31(5):841-50. doi: 10.1291/hypres.31.84
32. Rysavá R, Tesar V, Merta M; Czech Group for the Study of Glomerulonephritis. Effect of telmisartan on blood pressure control and kidney function in hypertensive, proteinuric patients with chronic kidney disease. *Blood Press Monit*. 2005 Aug;10(4):207-13. doi: 10.1097/01.mbp.0000172708.97534.15.

33. Bakris G, Burgess E, Weir M, Davidai G, Koval S; AMADEO Study Investigators. Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int.* 2008;74(3):364-9. doi: 10.1038/ki.2008.204
34. Kitamura M, Arai H, Abe S, Ota Y, Muta K, Furusu A, et al. Renal outcomes of treatment with telmisartan in patients with stage 3-4 chronic kidney disease: A prospective, randomized, controlled trial (JINNA-GA). *SAGE Open Med.* 2020;8:2050312120973502. doi: 10.1177/2050312120973502
35. Aranda P, Segura J, Ruilope LM, Aranda FJ, Frutos MA, López V, et al. Long-term renoprotective effects of standard versus high doses of telmisartan in hypertensive nondiabetic nephropathies. *Am J Kidney Dis.* 2005;46(6):1074-9. doi: 10.1053/j.ajkd.2005.08.034
36. Agrawal A, Kamila S, Reddy S, Lilly J, Mariyala MS. Effect of telmisartan on kidney function in patients with chronic kidney disease: an observational study. *J Drug Assess.* 2016;5(1):24-8. doi: 10.1080/21556660.2016.1252380
37. Mann JF, Schmieder RE, Dyal L, McQueen MJ, Schumacher H, Pogue J; TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) Investigators. Effect of telmisartan on renal outcomes: a randomized trial. *Ann Intern Med.* 2009;151(1):1-10, W1-2. doi: 10.7326/0003-4819-151-1-200907070-00122.
38. Madkour H, Gadallah M, Riveline B, Plante GE, Massry SG. Indapamide is superior to thiazide in the preservation of renal function in patients with renal insufficiency and systemic hypertension. *Am J Cardiol.* 1996;77(6):23B-25B. doi: 10.1016/s0002-
39. DiNicolantonio JJ, Bhutani J, Lavie CJ, O'Keefe JH. Evidence-based diuretics: focus on chlorthalidone and indapamide. *Future Cardiol.* 2015;11(2):203-17. doi: 10.2217/fca.14.83
40. Ceylan K, Topal C, Erkoc R, Sayarlioglu H, Can S, Yilmaz Y, et al. Effect of indapamide on urinary calcium excretion in patients with and without urinary stone disease. *Ann Pharmacother.* 2005;39(6):1034-8. doi: 10.1345/aph.1E544
41. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J.* 2024;45(38):3912-4018. doi: 10.1093/eurheartj/ehae178
42. Rossing P, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Khunti K, et al. Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. *Kidney Int.* 2022;102(5):990-9. doi: 10.1016/j.kint.2022.06.013
43. Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators; Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet.* 2008;372(9644):1174-83. doi: 10.1016/S0140-6736(08)61242-8.
44. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J.* 2024;45(36):3415-537. doi: 10.1093/eurheartj/ehae177
45. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol.* 2003;42(7):1149-60. doi: 10.1016/s0735-1097(03)00994-x.
46. Asmar R, Gosse P, Topouchian J, N'tela G, Dudley A, Shepherd GL. Effects of telmisartan on arterial stiffness in Type 2 diabetes patients with essential hypertension. *J Renin Angiotensin Aldosterone Syst.* 2002;3(3):176-80. doi: 10.3317/jraas.2002.038.
47. Koulouris S, Symeonides P, Triantafyllou K, Ioannidis G, Karabinos I, Katostaras T, et al. Comparison of the effects of ramipril versus telmisartan in reducing serum levels of high-sensitivity C-reactive protein and oxidized low-density lipoprotein cholesterol in patients with type 2 diabetes mellitus. *Am J Cardiol.* 2005;95(11):1386-8. doi: 10.1016/j.amjcard.2005.01.092.
48. Tian Q, Miyazaki R, Ichiki T, Imayama I, Inanaga K, Ohtsubo H, et al. Inhibition of tumor necrosis factor- α -induced interleukin-6 expression by telmisartan through cross-talk of peroxisome proliferator-activated receptor- γ with nuclear factor κ B and CCAAT/enhancer-binding protein- β . *Hypertension.* 2009;53(5):798-804. doi: 10.1161/HYPERTENSIONAHA.108.126656.