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REVIEW ON THE ROLE OF TELMISARTAN IN MANAGING HYPERTENSION WITH EMPHASIS ON EARLY MORNING BP CONTROL

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ABSTRACT

Hypertension remains a leading global contributor to cardiovascular morbidity and mortality, and growing evidence highlights the prognostic relevance of blood pressure (BP) variability and inadequate control during the early morning hours. Ambulatory blood pressure monitoring (ABPM) has demonstrated that many treated patients experience suboptimal trough-phase BP reduction, resulting in an exaggerated early morning BP surge (EMBS) that coincides with a peak incidence of myocardial infarction, stroke, and sudden cardiac events. In this context, the selection of long-acting antihypertensive agents with sustained 24-hour efficacy is clinically important. Telmisartan, a long-acting angiotensin II type-1 receptor (AT_1) blocker, exhibits a prolonged elimination half-life, high receptor affinity, slow dissociation kinetics, and a favourable trough-to-peak ratio, contributing to consistent end-of-dose BP control, including during the early morning "high-risk window." Beyond AT_1 receptor blockade, telmisartan demonstrates partial PPAR-γ and PPAR-α modulatory activity, conferring additional metabolic, vascular, anti-inflammatory, and anti-remouldeing benefits. Evidence from randomized clinical trials, PROBE-designed studies, and community-based ABPM investigations indicates that telmisartan provides

superior late-dose, nocturnal, and early-morning BP suppression compared with several other ARBs, ACE inhibitors, and calcium channel blockers, and maintains residual BP control even after a missed dose. Its favourable pharmacokinetic profile, minimal renal dose adjustment requirement, and good tolerability further support its therapeutic utility, particularly in patients with metabolic syndrome, diabetes, or cardiovascular risk. While contraindications include pregnancy and severe hepatic impairment, the overall evidence suggests that telmisartan is a reliable, metabolically advantageous, and long-acting antihypertensive agent with significant potential to attenuate early morning BP surge and reduce circadian-linked cardiovascular risk.

KEYWORDS: *angiotensin II receptor blocker, antihypertensive, cardiovascular disease, hypertension, morning, telmisartan.*

INTRODUCTION

Hypertension affects nearly one in four adults worldwide and remains a major contributor to cardiovascular morbidity and mortality. Treatment decisions are commonly guided by clinic-based blood pressure (BP) measurements; however, office readings often fail to reflect BP fluctuations that occur during daily activities. As a result, conditions such as masked or reversed white-coat hypertension may go unrecognized, with reported prevalence ranging from 9% to 23%. Importantly, masked hypertension is associated with a higher cardiovascular risk and, in elderly individuals, outcomes comparable to sustained hypertension.

This concern is further amplified in treated patients, since many once-daily antihypertensive agents demonstrate a weaker trough effect relative to peak activity. With morning administration, peak efficacy typically coincides with clinic measurement, whereas the trough phase often occurs during the early morning hours — a period when BP tends to rise. Consequently, treated individuals may exhibit inadequately controlled morning BP despite

apparently normal office readings. Evidence from ambulatory blood pressure monitoring (ABPM) has confirmed that a substantial proportion of such patients fail to achieve morning BP control. ABPM is therefore considered a superior assessment tool because it provides reproducible 24-hour BP data and is a better predictor of cardiovascular outcomes than clinic measurements. Circadian variation in cardiovascular events is well established, with a marked clustering of myocardial infarction, stroke, and sudden cardiac events in the early morning following awakening a period identified as a "high-risk window." This vulnerability is attributed to sympathetic activation, hormonal surges, and hemodynamic stress that collectively enhance cardiovascular load. Accordingly, current hypertension guidelinesemphasize the importance of sustained 24-hour BP control, particularly across the late-night and early morning dosing interval.

In this therapeutic context, long-acting antihypertensive agents capable of maintaining consistent trough-phase BP reduction are of particular relevance. Telmisartan, a long-acting angiotensin II type-1 (AT_1) receptor blocker, has gained clinical prominence due to its prolonged half-life, high receptor affinity, favorable trough–peak ratio, and sustained 24-hour antihypertensive efficacy. Unlike several shorter-acting agents, telmisartan provides effective BP control extending into the early morning period andadditionally exhibits partial PPAR-γ modulatory properties, which may confer metabolic and vascular advantages. This review evaluates the role of telmisartan in hypertension management, with special emphasis on its ability to attenuate the early morning blood pressure surge, evidence derived from ABPM studies, its pharmacological strengths relative to other ARBs, and its potential implications in reducing cardiovascular risk.

MEASUREMENT OF BP

Blood pressure represents the pressure exerted by circulating blood on arterial walls and is expressed as systolic (SBP) and diastolic (DBP) values. Accurate measurement is essential for the diagnosis and monitoring of hypertension, as well as for evaluating therapeutic response. BP can be assessed in the clinic, through ambulatory blood pressure monitoring (ABPM), or by home/self-monitoring.

Office / Clinic Blood Pressure Measurement

Clinic BP is measured by physicians or nurses using:

- Mercury sphygmomanometer (reference standard)
- Aneroid manometer

- Digital / oscillometric devices

In the auscultatory method, Korotkoff Phase I corresponds to SBP and Phase V to DBP. However, clinic BP has limitations such as white-coat effect, observer bias, improper cuff size, equipment calibration errors, and failure to capture 24-hour BP variation. It also does not reflect BP during sleep or the early morning surge. For most adults, ≥140/90 mmHg is considered hypertensive, while lower targets (<130/80 mmHg) are advised in diabetes and kidney disease.

Ambulatory Blood Pressure Monitoring (ABPM)

ABPM records BP automatically every 15–30 minutes over 24 hours and provides:

- Daytime (awake) BP
- Night-time (asleep) BP
- 24-hour mean BP
- Early morning BP surge (EMBS)

It is superior to office BP as it detects masked and nocturnal hypertension, offers better cardiovascular risk prediction, and helps evaluate trough–peak drug effects.

Diagnostic ABPM thresholds

- Daytime ≥ 135/85 mmHg
- Night-time ≥ 120/70 mmHg
- 24-hour ≥ 130/80 mmHg

2.3. Home Blood Pressure Monitoring (HBPM)

HBPM involves self-measurement using validated electronic devices.

Benefits

- Improves treatment adherence
- Detects morning BP levels
- Minimizes white-coat effect

Limitation

- Does not assess nocturnal BP pattern

Home readings are usually lower than clinic values, and self-monitoring has been shown to improve BP control and enhance patient participation in disease management.

PHARMACOLOGICAL PROPERTIES OF TELMISARTAN

Pharmacodynamics

Telmisartan is an orally active, non-peptide angiotensin II type-1 receptor (AT_1R) antagonist that acts as a major regulator of the renin–angiotensin system (RAS). AT_1 receptors are abundantly expressed in multiple organs, including vascular smooth muscle, kidneys, liver, myocardium, and brain tissue. Activation of AT_1R by angiotensin II (Ang II) produces a spectrum of physiological responses such as vasoconstriction, elevation of arterial pressure, sodium and water retention with reduced urine output, stimulation of thirst, increased sympathetic outflow, endothelial dysfunction, and promotion of vascular and myocardial hypertrophy.

By competitively inhibiting AT_1R, telmisartan suppresses these Ang II-mediated actions, thereby promoting vasodilation, improving endothelial function, and exerting anti-inflammatory and anti-remodeling effects. Telmisartan displays slow but reversible receptor binding with a prolonged dissociation profile, contributing to sustained receptor blockade. Among available ARBs, it demonstrates the highest binding affinity for AT_1R (telmisartan > olmesartan > candesartan > valsartan > losartan), which supports consistent 24-hour antihypertensive action and improved trough-phase BP control. In addition to classical AT_1R antagonism, telmisartan exhibits selective partial agonist activity at peroxisome proliferator-activated receptor-γ (PPAR-γ) a transcription factor involved in glucose metabolism, adipocyte differentiation, and enhancement of insulin sensitivity. Activation of PPAR-γ confers anti-inflammatory, antioxidant, and antiproliferative benefits, suggesting a potential therapeutic role in metabolic syndrome, type 2 diabetes, and vascular dysfunction. Compared with most ARBs, telmisartan demonstrates stronger PPAR-γ modulatory capacity.

Furthermore, telmisartan also acts as a PPAR-α activator, a nuclear receptor that regulates lipid oxidation and fatty acid metabolism, particularly in organs with high metabolic turnover such as the liver and skeletal muscle. Through combined AT_1R blockade and dual PPAR modulation, telmisartan provides additional cardiometabolic protection, extending its therapeutic relevance beyond blood pressure control.

Additional pharmacodynamic attributes include:

- improvement of arterial compliance and vascular elasticity
- reduction of oxidative stress and inflammatory cytokines
- inhibition of cardiac and vascular hypertrophy
- attenuation of early morning BP surge and circadian BP variability

These mechanisms collectively contribute to superior end-organ protection.

PHARMACOKINETIC

Following oral administration, telmisartan is efficiently absorbed from the gastrointestinal tract, exhibiting dose-dependent bioavailability (≈42% at 40 mg and ≈58% at 160 mg). Maximum plasma concentrations are achieved within 0.5–1 hour, and the elimination half-life of approximately 24 hours supports its prolonged and sustained antihypertensive activity. The drug demonstrates very high plasma protein binding (~99%) and undergoes primary elimination through biliary–fecal excretion, with negligible renal clearance.

Accordingly, hepatic impairment and biliary obstruction may delay drug clearance, whereas renal dysfunction has minimal pharmacokinetic impact making telmisartan suitable for use in patients with renal insufficiency.

Earlier imaging investigations underestimated its central penetration; however, more recent evidence confirms that telmisartan is capable of crossing the blood–brain barrier (BBB) and attaining pharmacologically meaningful concentrations within the CNS. Although brain uptake is lower than in peripheral tissues, telmisartan exhibits the highest BBB permeability among ARBs, enabling potential benefits in:

- neuroinflammation
- cerebrovascular protection
- prevention of hypertensive brain remodeling

Importantly, these CNS effects may occur at doses that do not significantly lower systemic blood pressure, highlighting a possible neuroprotective advantage.

Additional pharmacokinetic strengths include:

- consistent 24-hour trough concentration
- minimal pharmacokinetic drug–drug interactions
- sustained control during early morning high-risk period

Together, these characteristics reinforce telmisartan's suitability as a long-acting, metabolically favorable antihypertensive agent.

EARLY MORNING BLOOD PRESSURE CONTROL AND CLINICAL REVELANCE

Blood pressure follows a circadian rhythm characterized by:

- reduced levels during sleep, and
- a pronounced early morning surge between 4:00 and 10:00 AM.

This morning rise in BP is strongly associated with:

- increased risk of myocardial infarction
- higher incidence of stroke
- greater cardiovascular morbidity and mortality

Therefore, an ideal antihypertensive agent should maintain consistent 24-hour BP suppression, with particular effectiveness during the late-dosing interval and early morning hours when risk is highest

Monotherapy and 24-Hour Control with Telmisartan

The long elimination half-life of telmisartan has been extensively evaluated using ambulatory blood pressure monitoring (ABPM) to determine its ability to maintain BP reduction throughout the once-daily dosing period. In addition to double-blind trials, several prospective, randomized, open-label, blinded-endpoint (PROBE) studies have been conducted. Although treatment allocation is known to investigators in PROBE designs, automated ABPM minimizes observer bias, and meta-analytic data indicate that PROBE and double-blind studies yield comparable reliability in detecting clinically meaningful BP differences.

Comparison with Amlodipine

In patients with mild–moderate hypertension, telmisartan (40–120 mg) and amlodipine (5–10 mg) produced similar clinic BP reductions after 12 weeks. However, ABPM demonstrated that telmisartan produced:

- a significantly greater decrease in night-time DBP and
- superior BP control during the last 4 hours of the dosing interval, indicating stronger late-dose and nocturnal BP coverage.

Comparison with Ramipril – PRISMA Studies

The PRISMA program compared telmisartan 80 mg with ramipril 10 mg over 14 weeks in >1,200 patients. Across both North American and European cohorts, telmisartan achieved:

- greater reductions in last-6-hour mean SBP/DBP
- 12.0 / 8.4 mmHg vs
- 7.9 / 5.4 mmHg with ramipril
- *($p < 0.0001$)*

This confirmed superior end-of-dose BP control.

Comparison with Losartan

When compared with losartan 50 mg, telmisartan 40–80 mg produced:

- substantially greater reductions in last-6-hour mean SBP/DBP
- better early-morning BP values on home monitoring
- significantly lower morning DBP in Japanese patients

These findings highlight the longer duration of action of telmisartan relative to losartan.

Comparison with Valsartan

In PROBE and double-blind forced-titration studies:

- telmisartan 80 mg provided greater reductions in:
- last-6-hour SBP and DBP
- 24-hour mean BP after a missed dose

For example:

- last-6-hour DBP reduction
- 7.6 mmHg with telmisartan vs
- 5.8 mmHg with valsartan *($p = 0.0044$)*

Even after a missed dose:

- telmisartan maintained stronger residual BP control than valsartan

This effect is attributed to its longer half-life and higher receptor affinity, resulting in more sustained receptor blockade and improved protection in patients with suboptimal adherence.

Community-Based ABPM Evidence

To evaluate real-world effectiveness, the MICCAT-2 community ABPM study assessed telmisartan in routine practice and confirmed:

- robust 24-hour BP reduction
- preserved late-dosing-interval control
- clinically meaningful early-morning BP suppression

These outcomes further support telmisartan as a reliable once-daily antihypertensive agent with strong coverage across the circadian cycle.

DOSAGE AND ADMINISTRATION—TELMISARTAN

Telmisartan is indicated for the management of hypertension in adults and may be used either as monotherapy or in combination with other antihypertensive agents. The dosage should be individualized, with a usual starting dose of 40 mg once daily. For patients requiring greater blood pressure reduction, the dose may be increased to 80 mg once daily. If adequate control is not achieved at 80 mg, the addition of another antihypertensive agent may be considered.

Telmisartan may be taken with or without food. No dose adjustment is necessary in elderlypatients or in those with mild-to-moderaterenal impairment, including patients on haemodialysis. In the United States, caution is recommended in patients with biliary obstructive disorders or hepatic insufficiency, whereas in Europe, telmisartan is not

recommended in patients with obstructive biliary disease, cholestasis, or severe hepaticimpairment. Telmisartan is contraindicated during pregnancy. For full information regarding dosage, administration in special populations, precautions, and contraindications, clinicians should refer to the local prescribing information.

MERITS OF TELMISARTAN

Telmisartan, a non-peptide angiotensin II type-1 receptor blocker (ARB), exhibits several pharmacological and clinical properties that distinguish it within its class. It has a longterminal elimination half-life (~24 hours), which is the longest among available ARBs and supports once-daily dosing with sustained 24-hour blood pressure control, including during early-morning hours prone to cardiovascular events. This prolonged action contributes to consistent antihypertensive efficacy and may improve adherence. Telmisartan also demonstrates high binding affinity and slow dissociation from AT_1 receptors, potentially leading to more durable receptor blockade compared with several other ARBs. Additionally, it *uniquely* acts as a partial PPAR-γ agonist, which may favourably influence metabolic parameters such as insulin sensitivity and lipid metabolism; this property is not shared to the same degree by other ARBs and may offer added benefit in patients with concomitant metabolic disorders.

In clinical comparisons, telmisartan has been shown to provide superior or comparable blood pressure reduction and tolerability relative to other antihypertensive agents, including ACE inhibitors, with a lower incidence of class-specific adverse effects like cough Evidence also supports its cardiovascular risk-modifying potential in high-risk populations, as demonstrated in large trials such as ONTARGET. Furthermore, telmisartan's safety profile is favourable, with most adverse events being mild and similar to other ARBs, supporting its use as a first-line antihypertensive agent in appropriate patients.

Demerits of Telmisartan

Despite its advantages, telmisartan has limitations that must be considered. Like all ARBs, it is contraindicated during pregnancy due to risks of fetal toxicity, particularly in the second and third trimesters Use in patients with severe hepatic impairment or biliary obstruction is also not recommended, given its primary biliary elimination and altered pharmacokinetics in hepatic dysfunction. Additionally, caution is advised in individuals with bilateral renal artery stenosis or severe renal impairment because of the potential for worsening renal function.

Although generally well tolerated, telmisartan can cause adverse effects such as dizziness, headache, and hyperkalemia, and rare hypersensitivity reactions have been reported. While its metabolic effects are advantageous in many patients, they may also complicate management in certain subgroups and require monitoring. Furthermore, the incremental benefit of telmisartan's pharmacologic profile over other ARBs has been debated, with some meta-analyses indicating that class-wide RAAS blockade may be the dominant driver of cardiovascular protection rather than any single molecule's properties.

CONCLUSION

Telmisartan is a long-acting angiotensin II type-1 receptor blocker (ARB) with a prolonged half-life, high receptor affinity, and favorable trough-to-peak ratio, providing sustained 24-hour blood pressure control, including during the early morning surge. Its partial PPAR-γ and PPAR-α modulatory effects confer metabolic and vascular benefits, making it advantageous in patients with metabolic syndrome or type 2 diabetes. Clinical trials and ambulatory blood pressure monitoring (ABPM) demonstrate superior or comparable efficacy relative to other ARBs, ACE inhibitors, and calcium channel blockers, particularly in maintaining late-dose and early-morning BP control. Telmisartan is generally well tolerated, with low incidence of class-specific adverse effects, and requires minimal dose adjustment in renal impairment or elderly patients. Contraindications include pregnancy and severe hepatic impairment. Overall, telmisartan is a reliable, metabolically favorable, and long-acting antihypertensive agent that provides effective cardiovascular risk reduction across the circadian cycle.

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