# Amlodipine + Telmisartan: A Powerful Duo


Module 4

## Content

# Introduction

Hypertension (HTN) is recognized as a significant independent risk factor for the onset of symptomatic cardiovascular disease (CVD). Research indicates that the risk of developing CVD doubles for every 20 mm Hg rise in systolic blood pressure (SBP) or a 10 mm Hg rise in diastolic blood pressure (DBP). Despite advancements, managing HTN effectively poses considerable challenges both in the United States and globally, largely due to the increasing prevalence of HTN, which is primarily driven by an aging population [Egan BM et al. 2010].

Although there has been a notable increase in the proportion of patients who successfully achieve blood pressure (BP) control within the recommended guidelines in recent years, approximately half of individuals with HTN do not reach these targets. This issue extends to nearly one-third of patients currently undergoing antihypertensive therapy. Evidence from clinical studies strongly indicates that most individuals diagnosed with HTN will likely need to use two or more antihypertensive medications to achieve the desired BP control that aligns with established guidelines. Various combination therapy approaches have been employed in managing HTN [Weir MR et al 2007].

These often involve the use of medications that operate through different mechanisms, either administered separately or in the form of single-pill combinations. Some of the commonly used agents include diuretics, β-blockers, α-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists.

One promising strategy involves the combination of an ARB with the CCB amlodipine, a method supported by both clinical evidence and considerations of their mechanisms of action. Recently, the United States approved a single-dose combination therapy featuring the ARB telmisartan and amlodipine for treating HTN, particularly for patients who may require multiple antihypertensive medications to effectively reach their BP targets. This single-dose formulation is available in several combinations: 40 mg telmisartan with 5 mg amlodipine (40/5), 40 mg telmisartan with 10 mg amlodipine (40/10), 80 mg telmisartan with 5 mg amlodipine (80/5), and 80 mg telmisartan with 10 mg amlodipine (80/10). The clinical significance of the telmisartan–amlodipine single-dose combination in managing hypertensive patients is profound [Twynsta 2010].

Hypertension remains the leading cardiovascular disease (CVD) risk factor, with increasing prevalence worldwide. In the United States, over 30% of adults—approximately 76.4 million individuals aged 20 and older—are affected by hypertension, based on 2008 data. According to the National Health and Nutrition Examination Survey, around 8% of these adults are unaware they have hypertension. Among those diagnosed, only about 75% are on antihypertensive medications, and of those receiving treatment, only half have their blood pressure (BP) adequately controlled. Projections indicate a 10% rise in hypertension prevalence by 2030, exacerbating its societal and financial burdens. This is particularly alarming since elevated BP (over 140/90 mmHg) precedes serious cardiovascular events, such as myocardial infarction (MI) and stroke, in at least 69% of cases. Therefore, enhancing awareness and treatment effectiveness is crucial for both patients and healthcare providers [Roger VL et al 2012].

The risk associated with high BP is influenced by various factors, including race, gender, and comorbid conditions. In the U.S., hypertension is notably prevalent in black communities, with African American adults experiencing a rate of 41.4% compared to 28.1% for white adults. This disparity leads to significantly higher rates of nonfatal and fatal strokes and a much greater incidence of end-stage kidney disease in African Americans. Hypertension typically affects men more than women until the age of 64, after which women have a higher incidence. Despite this, women have historically been underrepresented in antihypertensive drug trials; for instance, only 31% of participants in key trials for the 2007 American Heart Association guidelines were female. Additionally, BP control rates for women can be up to 15% lower than for men [Lloyd-Jones DM et al 2005].

Individuals with diabetes face particular challenges in managing hypertension, often requiring three or more antihypertensive medications to meet the target BP of less than 130/80 mmHg recommended by the American Diabetes Association. Many patients struggle to achieve target BP due to factors such as ineffective monotherapy and poor medication adherence. Recommendations for those with significantly elevated systolic or diastolic BP include using two antihypertensive medications with complementary mechanisms. Noncompliance with medication is a leading cause of failure to reach BP goals, largely due to the chronic, asymptomatic nature of hypertension, side effects, and other physician-related factors. Research indicates that increasing medication dosage can reduce adherence by nearly 20%, while decreasing dosage can improve compliance by a similar amount. The number of medications prescribed is also correlated with higher discontinuation rates, which can be mitigated through the use of single-pill combinations that can enhance adherence by up to 25% [Bangalore S et al. 2007].

Using single-pill combination drugs not only improves adherence but also leads to better BP control compared to higher doses of a single drug. Combining lower doses of two medications can reduce side effects, provided they have different side-effect profiles. Additionally, single-pill combinations can lower costs by improving BP management, thus reducing the need for more physician visits and hospitalizations. Recent trials have shown significant improvements in cardiovascular outcomes with certain antihypertensive combinations. For instance, the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension trial revealed that patients taking a combination of an ACE inhibitor (benazepril) with either a calcium channel blocker (CCB, amlodipine) or a diuretic (hydrochlorothiazide) achieved comparable BP improvements, with the amlodipine group experiencing greater reductions in cardiovascular mortality and morbidity [Bramlage P et al 2009].

One promising recent dual antihypertensive single-pill combination is Twynsta (telmisartan/amlodipine), approved by the FDA in 2009. Amlodipine has been widely used since its approval in 1993, while telmisartan was approved in 2000. This combination is unique because it pairs telmisartan, the only ARB indicated for preventing CVD progression, with amlodipine, one of the most commonly used CCBs. The complementary mechanisms of action of telmisartan and amlodipine and highlight the long-term safety and efficacy of this combination, particularly concerning populations that have been underrepresented in clinical trials and the implications of this knowledge gap [Epstein BJ et al 2007].

## 2. Pharmacology of Amlodipine and Telmisartan

This section summarizes the pharmacokinetics of telmisartan and amlodipine as separate entities (detailed discussions are available in other sources). Two studies involving healthy volunteers (with sample sizes of 12 and 38) explored the pharmacokinetics of these individual agents and their combination. Additional information has been derived from the manufacturer's prescribing guidelines.

### a. Telmisartan

Telmisartan is rapidly absorbed, achieving peak plasma concentrations (Cmax) roughly 0.5 to 1 hour post oral intake. Its bioavailability is dose-dependent (42% for 40 mg and 58% for 160 mg) and is slightly influenced by food, though this effect is not deemed clinically significant. Non-linear pharmacokinetics are observed for doses between 20 and 160 mg. With once-daily dosing, steady-state plasma levels are attained in about 5 to 7 days, displaying an accumulation index of 1.5 to 2.0.

In a study where healthy volunteers received 80 mg of telmisartan daily for 9 days, the geometric mean Cmax on day 9 was 272 mg/mL, with the peak occurring approximately 0.69 hours after the last dose. The mean area under the plasma concentration-time curve (AUC) at steady state was 1020 mg·h/mL. Telmisartan shows high plasma protein binding (>99.5%), primarily associating with albumin and α1-acid glycoprotein. It has a substantial volume of distribution (around 500 L) and is mainly eliminated via biliary-fecal pathways as unchanged drug (>97% of a radiolabeled dose). The only identified metabolite in human plasma or urine is an inactive acylglucuronide. The mean terminal elimination half-life (t½g) of telmisartan is approximately 24 hours [Tanswell P et al 2009].

**b. Amlodipine**

The absorption of oral amlodipine is slower compared to telmisartan, with Cmax occurring between 6 to 12 hours post-administration. Steady-state plasma concentrations typically are reached after 7 to 8 days of multiple doses. The estimated bioavailability of amlodipine ranges from 64% to 90%. Following a single oral dose of 10 mg, the geometric mean Cmax is 5.4 ng/mL, occurring at a median of 7.0 hours. After 9 days of taking 10 mg daily, a mean Cmax of 17.7 ng/mL was observed, with the peak occurring at a median of 6.0 hours, and the accumulation ratio for Cmax was 3.3. Amlodipine exhibits high plasma protein binding (about 93% in hypertensive individuals) and a large volume of distribution (21 L/kg). Approximately 90% of amlodipine undergoes extensive hepatic metabolism to inactive metabolites. It is mainly eliminated as the parent drug (10%) or metabolites (60%) through urine, with a long t½g of around 30 to 50 hours. In healthy volunteers taking 10 mg daily for 9 days, the geometric mean t½g of amlodipine was 55.9 hours [Strangier J et al. 2000].

c. Telmisartan/Amlodipine Combination

The pharmacokinetics of amlodipine remain unaffected by the concurrent administration of telmisartan in healthy volunteers. The Cmax and AUC ratios for the combination therapy compared to amlodipine alone at steady state were both 1.06 (90% CI: 0.97, 1.14 for Cmax and 0.98, 1.16 for AUC), falling within the established bioequivalence limits (90% CI: 0.8, 1.25). The clearance ratio was 1.09 (90% CI: 0.79, 1.50), which did not meet bioequivalence criteria, likely due to the variability in amlodipine renal excretion, although it was not considered clinically significant. Another study indicated that administering amlodipine did not alter telmisartan's pharmacokinetics. The AUC ratio for the combination versus telmisartan monotherapy was 0.976 (90% CI: 0.895, 1.065), meeting bioequivalence standards

Although the Cmax ratio for the combination therapy (0.890 [90% CI: 0.763, 1.037]) did not meet standard bioequivalence criteria, the 90% CI was within the predefined wider acceptance range of 0.75 to 1.33 for drugs exhibiting high variability in Cmax [Haria M et al 1995].

### 2.1 Fixed-Dose Combination of Amlodipine + Telmisartan

The selection of a specific combination therapy for hypertension is influenced by various patient factors, including cardiovascular (CV) risk factors and comorbid conditions. Subgroup analyses from trials involving telmisartan combinations have shown consistent efficacy across a broad range of patient profiles. For hypertensive patients with diabetes and micro albuminuria, treatment with telmisartan and amlodipine (T/A) not only lowered blood pressure (BP) but also reduced the urinary albumin excretion rate, highlighting its dual benefit. In a large-scale, multicenter, open-label trial conducted in China involving 13,542 high-risk patients—each with at least one CV risk factor—long-term T/A treatment was found to be both effective and well-tolerated over time.

For patients with stage 1 or 2 hypertension and diabetes who were previously uncontrolled on amlodipine monotherapy, 8 weeks of treatment with the single-pill combination (SPC) of T/A significantly lowered systolic blood pressure (SBP) and helped a higher proportion of patients reach their BP goals. These results were also observed in obese patient subgroups, reflecting the broad efficacy of this combination. Furthermore, a post hoc analysis involving patients stratified by factors such as age, race, coexisting diabetes, obesity, metabolic syndrome, renal impairment, and elevated baseline SBP found similar improvements in BP reduction and goal achievement across these varied subpopulations, mirroring the outcomes seen in the overall study population. Another analysis of pooled data from clinical trials investigating hypertensive patients with metabolic risk factors—such as obesity, diabetes, or both—demonstrated that those uncontrolled on monotherapy experienced significant BP reductions and a high rate of goal achievement with the T/A SPC. In patients with severe hypertension, defined as having an SBP ≥ 180 mmHg, even greater reductions in BP were recorded. Additionally, BP control with T/A SPC was sustained throughout the 24-hour dosing period, with a significant proportion of patients achieving 24-hour BP goals [Ley L et al 2013].

For individuals with moderate-to-severe hypertension, a prespecified analysis revealed that treatment with the telmisartan and hydrochlorothiazide (T80/H25) SPC provided significantly greater BP reductions compared to telmisartan monotherapy.

These results held true regardless of patient demographics, including sex, age, race, hypertension severity, and prior treatment history (whether treatment-naive or previously treated with one or more antihypertensive agents). A retrospective analysis also showed that black patients with hypertension and hypertensive patients with concomitant type 2 diabetes mellitus or moderate to severe renal impairment experienced more significant reductions in both SBP and diastolic blood pressure (DBP) with T80/H25 compared to telmisartan monotherapy, regardless of baseline BP levels. In another subgroup analysis of patients with stage 2 or 3 hypertension and additional CV disease risk factors such as diabetes mellitus, low estimated glomerular filtration rate (eGFR), high body mass index (BMI), and high coronary heart disease risk, six weeks of treatment with T80/H25 consistently resulted in greater BP reductions and higher BP goal-attainment rates than telmisartan monotherapy [Kjeldson SE et al 2013].

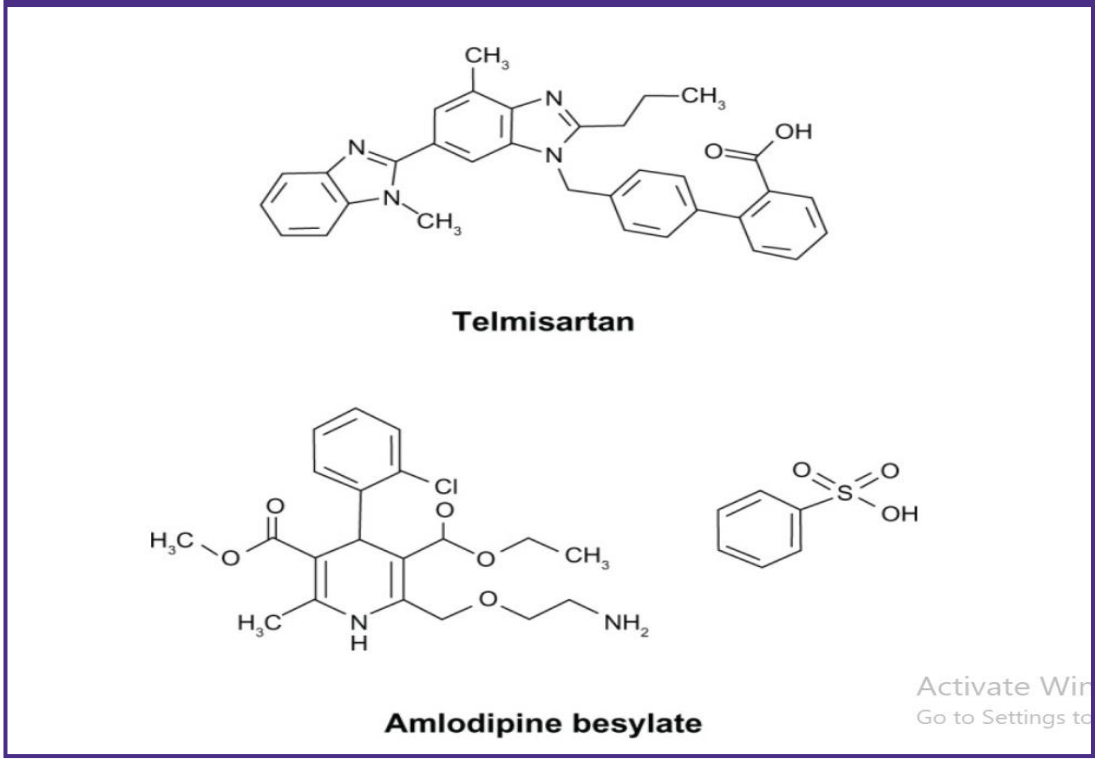
A pooled analysis of data from seven studies demonstrated that the efficacy and tolerability of the T/H SPC were comparable between younger patients and those older than 65 years—an age group generally considered more difficult to treat due to the presence of added CV risk factors. These findings underscore the broader applicability of the combination therapy. When choosing between an angiotensin II receptor blocker (ARB) plus a calcium channel blocker (CCB) versus an ARB plus hydrochlorothiazide (HCTZ) combination, the decision depends on the risk of adverse events associated with CCBs or HCTZ and how these drugs impact comorbid conditions in hypertensive patients. For instance, the SPC of an ARB and CCB is particularly preferred in hypertensive patients with prediabetes, diabetes, or metabolic syndrome due to the metabolic neutrality of both drugs. Moreover, the International Society on Hypertension in Blacks recommends the use of a renin-angiotensin system (RAS) inhibitor–CCB combination over a RAS inhibitor–thiazide combination in patients with BP more than 15/10 mmHg above the target, provided there is no presence of edema or volume overload [Liu Z et al 2009].

In contrast, the combination of an ARB with HCTZ should be considered for patients who require volume reduction. This combination not only maintains the volume-reducing efficacy of HCTZ but also results in additive BP reductions while mitigating the adverse metabolic effects seen with either drug when used alone. Furthermore, coadministration of an ARB can reverse the potassium loss typically associated with thiazide diuretics.

The thiazide-induced reduction in extracellular fluid volume and peripheral resistance, along with the resultant RAS activation, may enhance sensitivity to angiotensin II type 1 receptor activation, thus increasing the efficacy of ARBs. It is important to note that diuretics have been associated with an increased risk of new-onset diabetes, whereas RAS inhibitors have been shown to prevent or delay its onset. The ARB/HCTZ combination is particularly beneficial for patients with high salt consumption, a common dietary habit in countries like China.

Lastly, clinical trials of T/A SPC treatments have reported a lower incidence of edema compared to amlodipine monotherapy. Similarly, adverse event rates with T/H combination therapy were comparable to or lower than those seen with telmisartan monotherapy or placebo. A retrospective analysis of 50 studies confirmed the favorable safety and tolerability profile of T/H in adult patients across all age groups. For patients with moderate-to-severe hypertension, serum potassium levels remained stable in older, black, and Asian patient subgroups receiving T80/H25. In other subpopulations, minor mean reductions in serum potassium were observed, with the reduction averaging −0.1 mmol/L.

**Figure 1: Chemical structure of telmisartan and amlodipine**




Adapted from [Billecke SS et al 2013]

## 2.2 Telmisartan/amlodipine efficacy

Fixed-dose combinations (FDCs) of antihypertensive agents, such as amlodipine (a calcium channel blocker, CCB) and valsartan (an angiotensin II receptor blocker, ARB), have become essential in the treatment of hypertension, especially for patients who are inadequately controlled with monotherapy. These combinations are widely used in Europe, the United States, and other regions due to their ability to address the multifaceted pathophysiology of hypertension. The efficacy of FDC therapies lies in their complementary mechanisms of action. While amlodipine works by relaxing blood vessels through calcium channel blockade, valsartan reduces the effects of angiotensin II, leading to vasodilation and reduced fluid retention. This dual approach not only improves blood pressure (BP) control but also minimizes the risk of side effects that may arise from higher doses of single agents. Clinical trials have consistently shown the superior efficacy of amlodipine/valsartan FDC therapy compared to monotherapy with either drug alone. For instance, a study evaluating amlodipine/valsartan 5 mg/80 mg demonstrated significantly better BP control than valsartan 160 mg monotherapy. This indicates that the combination achieves the desired therapeutic effect at lower doses of each component, reducing the likelihood of dose-dependent adverse effects. Patients treated with the FDC also tend to experience better adherence due to the convenience of a single-pill regimen, as opposed to taking multiple medications separately [Nixon RM et al 2009].

Moreover, two pivotal studies involving over 3161 patients with mild-to-moderate hypertension revealed the benefits of amlodipine/valsartan across various dose combinations, such as 5 mg/160 mg and 10 mg/320 mg. The most commonly used dose, 5 mg/160 mg , resulted in a mean reduction in systolic BP by 19.5 mmHg and diastolic BP by 14.2 mmHg over eight weeks of treatment. Notably, patients receiving this combination therapy showed higher rates of achieving BP control (defined as diastolic BP < 90 mmHg), with rates exceeding 80% in some cases. This efficacy was particularly significant when compared to monotherapy or placebo, where BP control rates were much lower. These studies highlight the dose-dependent nature of FDC therapy, with greater BP reductions observed at higher doses [Lacourciere Y et al 2004].

The rational design of these FDCs is based on the principle of targeting different pathways involved in BP regulation. While amlodipine works primarily by inhibiting calcium ion influx into vascular smooth muscle cells, leading to vasodilation, valsartan blocks the binding of angiotensin II to its receptors, reducing vasoconstriction and aldosterone secretion.

The 2009 European Guidelines for the management of hypertension recommend using a RAAS inhibitor, a CCB, and a diuretic when two-drug therapy fails to achieve target BP levels. In line with this recommendation, a triple-combination therapy of amlodipine, valsartan, and hydrochlorothiazide is also available and has been proven effective for patients requiring additional BP control. The additive effects of these drugs mean that lower doses of each can be used to achieve the same or greater therapeutic benefit than higher doses of monotherapy. This synergistic interaction reduces the risk of side effects such as peripheral edema, a common issue with high-dose amlodipine monotherapy, while still providing substantial BP reductions. Furthermore, FDCs offer the advantage of convenience, which is crucial for medication adherence, a significant factor in long-term hypertension management. Studies show that simplifying the treatment regimen through single-pill combinations leads to better patient compliance and, consequently, better clinical outcomes [Lu F et al 2012].

Subgroup analyses from the pivotal trials showed that amlodipine/valsartan FDC was effective across various patient populations, including those with stage 2 hypertension , elderly patients (age ≥ 65 years), and younger adults. The FDC was particularly beneficial for patients with more severe hypertension, where monotherapy often falls short in controlling elevated BP. Additionally, the tolerability of the combination was high, with adverse effects generally being mild and consistent with those expected from either drug component. In clinical practice, this translates to a high success rate in achieving BP control without a significant increase in the risk of side effects, even in more vulnerable patient groups (Table 1).

The introduction of fixed-dose amlodipine/valsartan combinations has significantly advanced the management of hypertension by providing a potent, well-tolerated, and patient-friendly option. Clinical trials support the use of these combinations as first-line therapy for patients with inadequate BP control on monotherapy, demonstrating their ability to provide greater BP reductions while minimizing adverse effects. The availability of triple-combination therapies further enhances treatment options for those who require additional agents to reach their target BP. Overall, the use of FDCs aligns with current hypertension management guidelines, offering a rational and effective approach to improving BP control and reducing the risk of cardiovascular events [Twynsta et al 2011].

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**Table 1: Efficacy results of telmisartan/amlodipine**

Efficacy results from long-term (≥6 months) telmisartan/amlodipine single pill clinical trials

| Study | Duration, week | Regimen[a], mg/day | No | DBP control[b], % | DBP response[c], % | SBP response[d], % |
|---|---|---|---|---|---|---|
| Telmisartan plus amlodipine study-amlodipine 5 mg Long-term follow-up[71] | 34 | T40/A5 | 553 | 91.1 | 91.1 | 88.6 |
| | | T80/A5 | 206 | 77.7 | 83.0 | 86.9 |
| | | T40/A5+Add-on[e] | 25 | 76.0 | 76.0 | 72.0 |
| | | T80/A5+Add-on[e] | 181 | 46.4 | 59.7 | 70.7 |
| Telmisartan plus amlodipine study-amlodipine 10 mg Long-term follow-up[71] | 34 | T40/A10 | 216 | 93.1 | 93.1 | 88.0 |
| | | T80/A10 | 436 | 92.2 | 92.9 | 92.0 |
| | | T80/A10 (uptitrated)[f] | 91 | 79.1 | 78.0 | 82.4 |
| | | T40-80/A10+Add-on[e] | 92 | 76.1 | 79.3 | 75.0 |
| Trial no 1235.16[89] | 56 | T40/A5 | 211 | 92.8 | 98.6 | 97.6 |
| | | T80/A5 | 48 | 66.7 | 87.5 | 93.8 |



Adapted from [Billecke SS et al 2013]

## 2.3 Telmisartan/amlodipine safety

The combination of amlodipine and telmisartan is known to be well tolerated, with both drugs generally causing a low frequency of adverse events (AEs) when used individually (Table 2). This makes the combination particularly beneficial for patients dealing with conditions such as diabetes or metabolic syndrome, as these medications do not negatively impact the metabolic issues typically seen in these patients. Several clinical trials, mostly short-term, have been conducted to assess the safety of this combination. One specific study, which lasted for eight weeks and used a placebo-controlled, 4 × 4 factorial design, evaluated the safety of various dosages of telmisartan and amlodipine. The overall AE rate for the placebo group was 39%, with rates ranging from 33% to 44% in the treatment groups (Table 2). The drug-related AEs ranged from as low as 5.2% to as high as 19%, depending on the dosage. The most commonly reported AE was peripheral edema, especially due to the vasodilator effects of amlodipine, with occurrences as high as 18% in the A10 group and 11% in the T80/A10 group. Longer-term studies involving a total of 2,283 patients showed that AEs were generally consistent with short-term findings. These trials reported AE rates as low as 12% for some combinations, and drug-related AEs did not exceed 8%. Discontinuation rates due to AEs were very low, under 2% in all trials, and no deaths occurred throughout the studies. The most frequent AE was peripheral edema, especially with higher doses of amlodipine, though some instances of dizziness were also noted [Sica DA et al 2002].

**Table 2: Safety profile of telmisartan/amlodipine**

| | TEAMSTA-5 | | TEAMSTA-10 | | Trial no 1235.16 | |
|---|---|---|---|---|---|---|
| | T40/A5 n = 976 n (%) | T80/A5 n = 397 n (%) | T40/A10 n = 838 n (%) | T80/A10 n = 611 n (%) | T40/A5 n = 211 n (%) | T80/A5 n = 48 n (%) |
| All-cause AEs | 381 (39)<br>95 per 100 PY | 201 (51)<br>97 per 100 PY | 102 (12)<br>50 per 100 PY | 157 (26)<br>46 per 100 PY | 163 (77) | 37 (77) |
| Discontinuations due to AEs | 12 (1.2)<br>3 per 100 PY | 4 (1.0)<br>2 per 100 PY | 6 (0.7)<br>3 per 100 PY | 9 (1.5)<br>3 per 100 PY | – | – |
| SAE | 22 (2.3)<br>4 per 100 PY | 6 (1.5)<br>4 per 100 PY | 4 (0.5)<br>3 per 100 PY | 13 (2.1)<br>2 per 100 PY | 9 (4.3)[a] | 3 (6.3)[a] |
| Study-drug related AE | 51 (5.2)<br>13 per 100 PY | 30 (7.6)<br>14 per 100 PY | 28 (3.3)<br>14 per 100 PY | 38 (6.2)<br>11 per 100 PY | 4 (1.9) | 2 (4.2) |
| **Treatment-related AE occurring in >1% of patients in any treatment group** | | | | | | |
| Peripheral Edema | 23 (2.4)<br>6 per 100 PY | 11 (2.8)<br>5 per 100 PY | 16 (1.9)<br>8 per 100 PY | 24 (3.9)<br>7 per 100 PY | – | – |
| Dizziness | 0 | 6 (1.5)<br>3 per 100 PY | 0 | 0 | – | – |

**Notes:** Number of participants (n) represents the number analyzed for the primary efficacy endpoints with the exception of TEAMSTA-10, which analyzed all participants exposed to study drug. An en-dash (–) indicates no data were provided. [a]Not considered related to study drug.

**Abbreviations:** T, telmisartan; A, amlodipine; TEAMSTA, TElmisartan plus AMlodipine Study–Amlodipine; AE, adverse event; PY, patient years; SAE, serious adverse event.



Adapted from [Billecke SS et al 2013]

## 2.4 Indications for use of Amlodipine and telmisartan

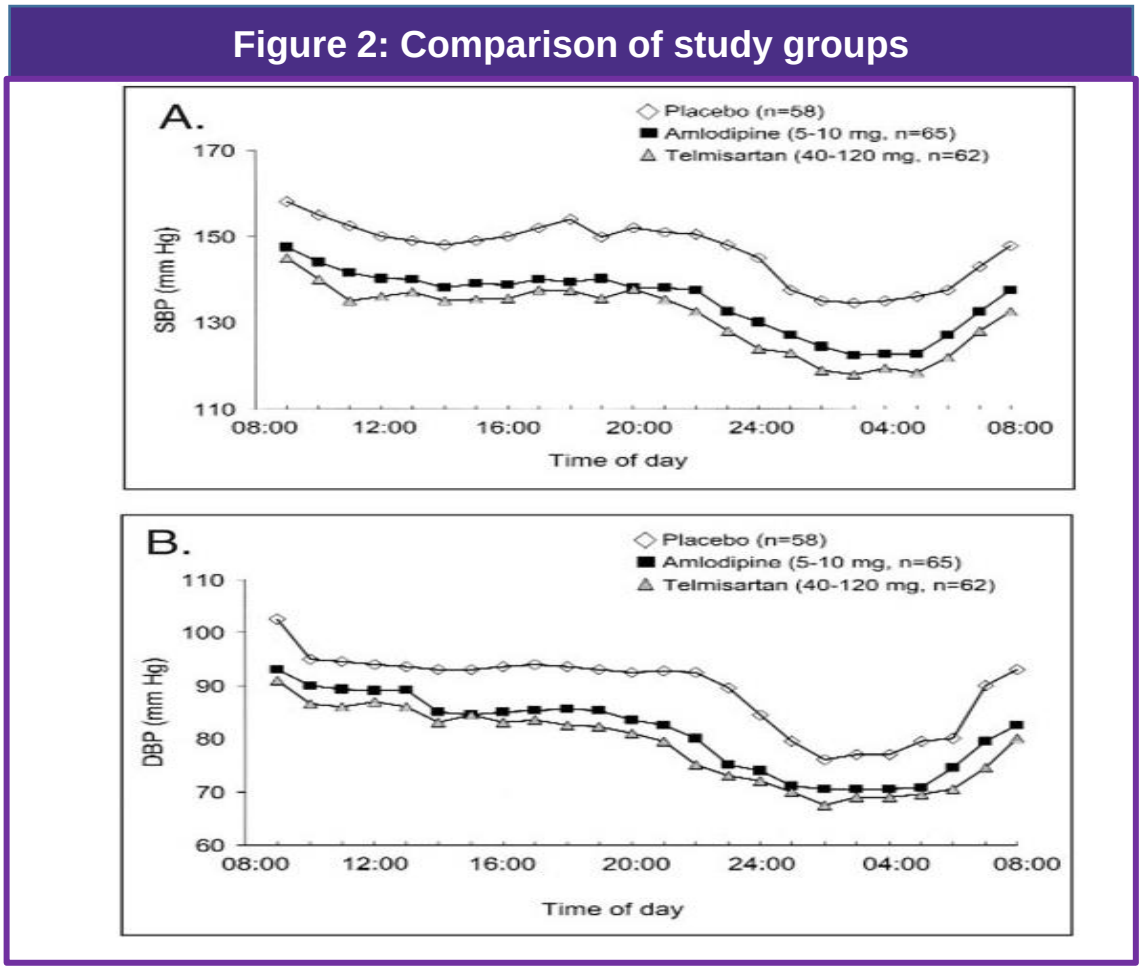
Amlodipine, one of the most widely prescribed calcium channel blockers for hypertension management, shares a long half-life of roughly 24 hours, similar to telmisartan. A clinical study was conducted to compare the safety and effectiveness of these two medications. This study included patients aged 28 to 80 years with stage 1 to 3 hypertension, characterized by a sitting diastolic blood pressure (DBP) ranging from 95 to 114 mm Hg. Participants were enrolled in a double-blind, randomized, placebo-controlled, parallel-group trial. The trial consisted of a 4-week placebo run-in period followed by a 12-week treatment phase. The study involved 232 patients, with two-thirds of them being male (65%) and nearly all identifying as white (96%). The average age of participants was 54.3 years, with an age range between 28 and 78 years. After randomization, patients were divided into three groups: 81 received a placebo, 73 were given telmisartan, and 78 were treated with amlodipine.

Initial dosing was telmisartan at 40 mg and amlodipine at 5 mg. For patients taking telmisartan who's DBP remained above 90 mm Hg after 4 weeks, the dose could be increased to 80 mg, and after 8 weeks, it could be further increased to 120 mg if necessary. Similarly, patients in the amlodipine group could have their dose increased to 10 mg if DBP levels exceeded 90 mm Hg after 8 weeks. The study monitored changes in systolic blood pressure (SBP) and DBP, particularly during the last 4 hours before the next dose. These changes were tracked through ambulatory blood pressure monitoring, conducted at hourly intervals over a 24-hour period, with the final assessment performed at 12 weeks.

Both the telmisartan and amlodipine groups showed comparable reductions in SBP and DBP at trough. Specifically, telmisartan resulted in mean reductions of −13.1 mm Hg in SBP and −7.1 mm Hg in DBP, while amlodipine produced mean reductions of −14.0 mm Hg in SBP and −7.1 mm Hg in DBP. These reductions were significantly greater compared to the placebo group ($p<0.001$). However, telmisartan showed greater reductions in SBP and DBP during the last 4 hours before dosing, especially during night-time intervals. Adverse events were reported by 56 placebo recipients (69.1%), 51 telmisartan recipients (69.9%), and 61 amlodipine recipients (78.2%). Amlodipine was associated with more cases of edema (21.8%) and headaches, in contrast to telmisartan (5.5%) and placebo (6.2%) (Figure 2). The frequency of other adverse events was relatively similar across the groups. In summary, both telmisartan and amlodipine proved effective in reducing blood pressure, though telmisartan provided superior control during the last 4 hours of the dosing period. Amlodipine, however, had a higher incidence of side effects, particularly edema [Lacourcière Y et al 1998].

In the trial comparing amlodipine and telmisartan, the effectiveness of both medications in managing blood pressure over a 24-hour period was analysed using a dose-adjustment approach to optimize results. Amlodipine, similar to telmisartan, is suitable for once-daily administration, as pharmacokinetic studies reveal that both drugs have half-lives exceeding 24 hours. The study's ambulatory blood pressure monitoring revealed that telmisartan consistently achieved a more significant reduction in blood pressure across each hour of the day. Notably, during the last four hours before the next dose, patients treated with telmisartan had significantly lower systolic and diastolic blood pressure compared to those on amlodipine. This finding is especially important because the early morning hours represent a period of elevated risk for cardiovascular and cerebrovascular events. Therefore, better control of blood pressure during these hours has critical clinical implications for reducing the incidence of such adverse events. Telmisartan ability to offer superior blood pressure management in this critical period highlights its potential advantage over amlodipine in certain patients, especially those with heightened cardiovascular risk in the morning hours [Chasen C et al 1998].

**Figure 2: Comparison of study groups**




Adapted from [White WB et al 2002]

### 3. Dosing for telmisartan/amlodipine

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, and among the most significant treatable risk factors for these diseases is hypertension. Research shows that the risk of developing cardiovascular conditions is lowest when blood pressure (BP) is maintained around 115/75 mmHg. When BP rises above this level, every 20 mmHg increase in systolic blood pressure (SBP) or every 10 mmHg increase in diastolic blood pressure (DBP) leads to a doubling of the risk of major cardiovascular events, including strokes and heart attacks. Therefore, keeping BP within the recommended range plays a critical role in reducing the risk of cardiovascular mortality. However, managing hypertension often requires more than just a single medication. In fact, over two-thirds of hypertensive patients need a combination of two or more drugs to achieve optimal BP control. The rationale for using multiple drugs stems from the ability of different classes of antihypertensive medications to act through distinct mechanisms, which helps offset the potential side effects of each drug when used in isolation (Figure 3).

To improve treatment adherence and ease the burden of multiple medications, fixed-dose combination therapies have become increasingly popular. These combinations package two or more antihypertensive agents into a single formulation, simplifying the treatment regimen for patients. Among the most effective combinations are those that target the renin-angiotensin system, such as combinations involving angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) alongside diuretics or calcium channel blockers. These drug combinations have shown superior efficacy compared to other types of antihypertensive therapies. The combination of a renin-angiotensin system blocker with a calcium channel blocker is especially recommended due to its effectiveness in lowering BP and its capacity to address specific side effects. For instance, ARBs or ACE inhibitors are known to reduce peripheral edema, a common adverse effect associated with calcium channel blockers [ESH/ESC 2013].

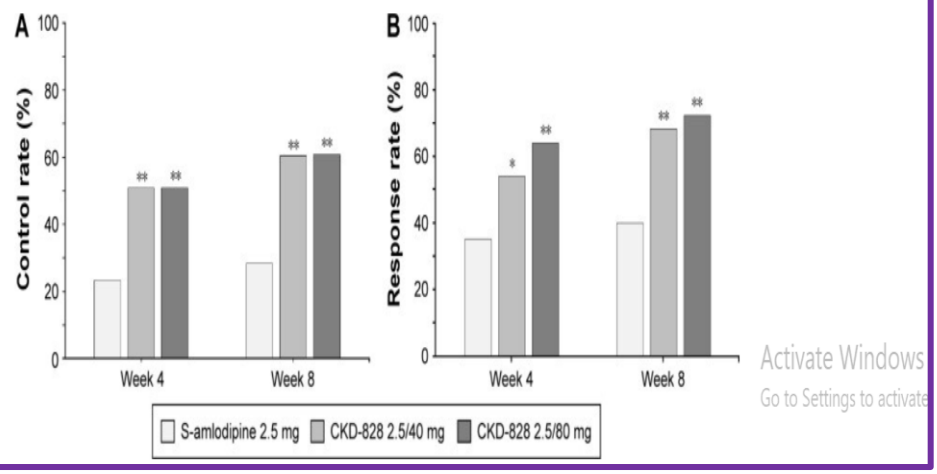
Amlodipine besylate, a well-known third-generation dihydropyridine calcium channel blocker, is widely used in treating high blood pressure. It's more active isomer, S-amlodipine besylate, has been approved for managing conditions such as hypertension, stable angina, and variant angina. Notably, S-amlodipine also displays efficacy in treating hypertension caused by fluid retention, thanks to its added natriuretic properties. Telmisartan, another component in some combination therapies, is an ARB that specifically targets the angiotensin II receptor.

This receptor is pivotal in regulating blood vessel constriction, a key factor in BP regulation. Telmisartan has an extended antihypertensive effect that lasts for over 24 hours, providing continuous BP control even during periods when morning BP surges can occur. Importantly, telmisartan is eliminated by the kidneys at a rate of less than 2%, meaning it does not require dose adjustments in patients with mild to moderate kidney impairment. This makes it particularly useful in individuals with renin-dependent hypertension [Noh YH et al 2012].

Fixed-dose combination therapies, such as those that include a calcium channel blocker and an ARB, have demonstrated better BP control compared to high-dose monotherapy regimens. These combinations help improve adherence and reduce the incidence of side effects, leading to better overall outcomes for patients. Among these combinations, those involving telmisartan and S-amlodipine besylate have shown superior efficacy due to their complementary mechanisms of action. S-amlodipine besylate, in particular, offers more potent BP-lowering effects compared to its parent drug, amlodipine, and when combined with telmisartan, the resulting formulation provides a dual-action approach to hypertension management. For instance, fixed-dose combinations of S-amlodipine besylate (2.5 mg) and telmisartan (available in 40 or 80 mg doses) have been developed for the treatment of patients whose hypertension is not adequately controlled with S-amlodipine alone. These formulations, identified as CKD-828, offer enhanced therapeutic outcomes by combining two drugs with different modes of action. A clinical trial was conducted to assess the efficacy and safety of these fixed-dose combinations in hypertensive patients, specifically those who were inadequately managed on S-amlodipine monotherapy [Neldam S et al 2011].

**Figure 3: Comparison of doses**

Abbreviation: CKD-828, a fixed-dose combination of S-amlodipine and telmisartan.




Adapted from [Woo youl kang et al 2018]

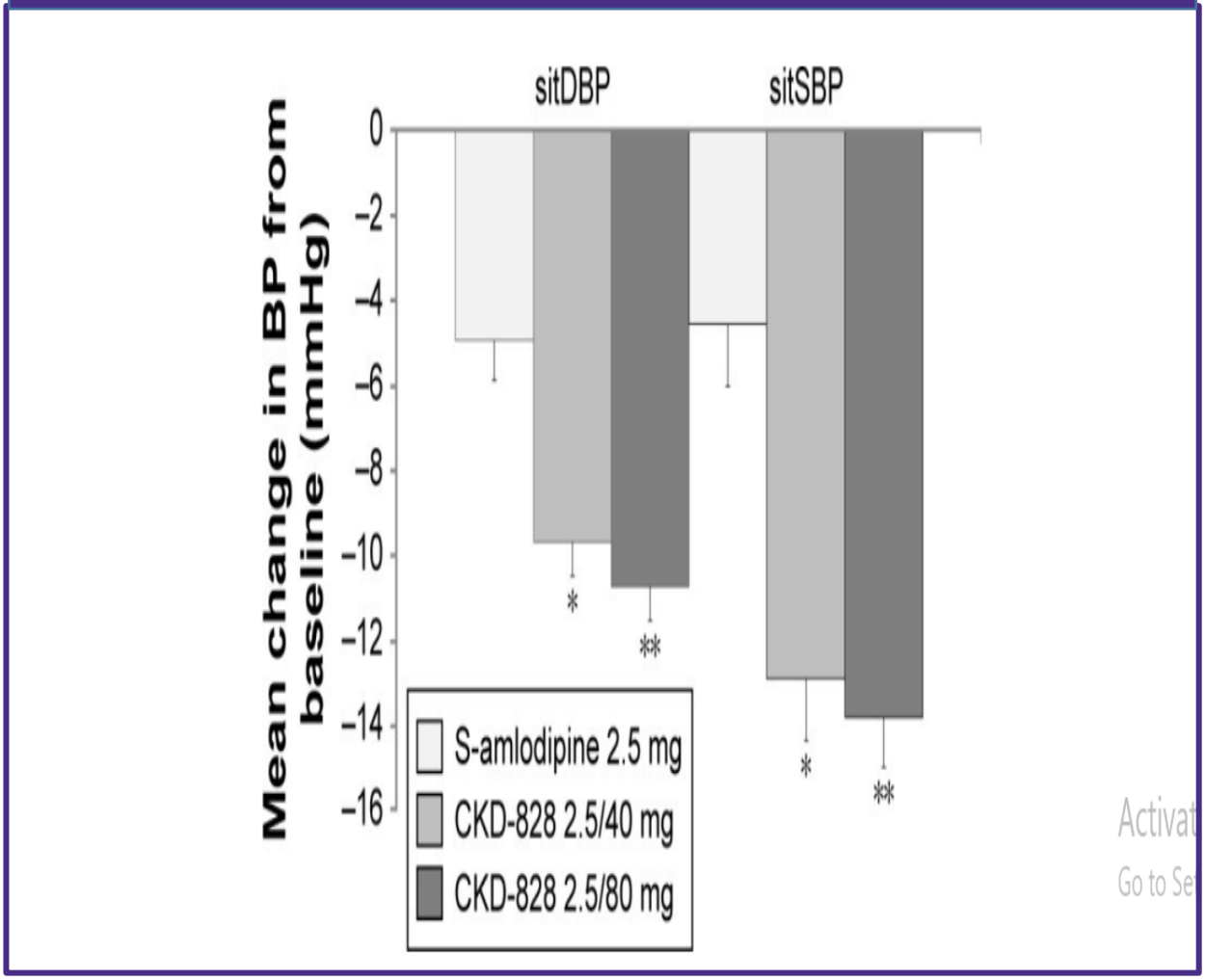
### 3.1 Clinical trial on amlodipine/telmisartan dosing

CKD-828, a fixed-dose combination of telmisartan and S-amlodipine besylate, has demonstrated superior efficacy in lowering blood pressure (BP) compared to conventional amlodipine besylate in Korean patients with hypertension inadequately controlled by S-amlodipine 2.5 mg monotherapy. In an 8-week study, CKD-828 at doses of 2.5/80 mg and 2.5/40 mg significantly reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) more effectively than S-amlodipine monotherapy. Specifically, the 2.5/80 mg dose led to reductions of -10.72/13.79 mmHg, while the 2.5/40 mg dose resulted in reductions of -9.67/12.89 mmHg. Both doses showed significant control and response rates at 4 and 8 weeks, with a slight but non-significant trend towards greater reductions with the higher dose (Figure 4).

The combination of telmisartan, an angiotensin receptor blocker (ARB), and S-amlodipine, a calcium channel blocker, is supported by clinical evidence for its antihypertensive benefits. ARBs like telmisartan are often preferred over angiotensin-converting enzyme inhibitors (ACE inhibitors) due to fewer side effects, such as cough. Notably, the reduced dose of S-amlodipine in CKD-828 helps minimize common side effects like edema, while telmisartan's natriuretic properties further contribute to this benefit [Kim SA et al 2008].

The study highlighted the safety of CKD-828, showing a lower incidence of adverse events such as headaches and respiratory issues, compared to S-amlodipine monotherapy. Interestingly, edema, a typical side effect of amlodipine, was not observed in any CKD-828 group. However, the study's limitations include a focus on Korean patients, mild-to-moderate hypertension cases, and a short duration, which limits the generalizability of the results to other populations and longer-term outcomes. In summary, CKD-828 is a promising therapeutic option for hypertension, offering superior BP control and a favourable safety profile compared to traditional monotherapies. However, further research involving diverse populations and longer durations is needed to fully assess its long-term benefits and broader applicability [Ferrarini A et al. 2013].

**Figure 4: Mean change in BP**



## 4 Patient-focused perspectives

Hypertension, or high blood pressure, is a chronic condition that significantly impacts cardiovascular health. While there is currently no cure for hypertension, antihypertensive medications are effective in managing blood pressure when patients adhere to their prescribed treatment plans. Adherence, or the extent to which patients follow medical advice, is crucial; non-adherence is a prevalent issue that leads to ineffective treatment. Factors contributing to non-compliance include lack of understanding about the condition, side effects of medications, and the perception of the medication's necessity. Moreover, if patients and healthcare providers view initial treatment failures negatively, this can create a discouraging cycle, reducing the patient's motivation to continue therapy. As a result, blood pressure management deteriorates, increasing the risk of serious health complications, such as heart disease and stroke [Corrao G et al 2008].

Adherence rates vary significantly among different classes of antihypertensive medications. For example, patients who are prescribed angiotensin receptor blockers (ARBs) typically demonstrate better persistence with treatment compared to those starting with other classes like ACE inhibitors, calcium channel blockers, alpha-blockers, beta-blockers, and diuretics. This variance is influenced by multiple factors, including the complexity of treatment regimens. Patients who receive multiple prescriptions or those who must manage complex dosing schedules often struggle with compliance. Research indicates that simpler dosing regimens—particularly medications taken once daily—are associated with higher adherence rates. To address adherence issues, healthcare providers can consider strategies such as consolidating multiple medications into a single pill, a method known as fixed-dose combination therapy. This approach not only simplifies the treatment process but has also been shown to improve compliance significantly. Guidelines recommend this strategy to enhance patient adherence, ultimately improving overall health outcomes. By fostering a supportive environment that encourages communication and understanding, healthcare providers can better assist patients in managing their hypertension effectively [Gupta AK et al 2010].

## 5 Comparison of telmisartan/amlodipine single pill combinations

Currently, no studies directly compare the T/A single-pill combination (SPC) with other antihypertensive drug SPCs. However, in patients who did not meet blood pressure (BP) targets after two months on 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan, switching to telmisartan 40 mg significantly lowered both systolic and diastolic BP at 4, 8, and 12 weeks.

In elderly patients on 5 mg amlodipine, replacing valsartan 80 mg or candesartan 8 mg with telmisartan 40 mg after two months also led to significant reductions in morning and evening home SBP and DBP after 12 weeks, along with an increase in serum adiponectin levels, indicating favourable cardio metabolic effects of T/A [Ley L et al 2013].

In two large placebo-controlled trials lasting 8 weeks, T/H treatment resulted in a more significant BP reduction compared to valsartan/hydrochlorothiazide (HCTZ). A pooled analysis confirmed this advantage across different demographics. Furthermore, in patients with essential hypertension, T/H was found to be more effective than the losartan/HCTZ combination in reducing BP during the last 6 hours of the dosing interval and lowering 24-hour ambulatory BP after 6 weeks. The SMOOTH trial also showed that T/H therapy produced greater reductions in mean ambulatory BP compared to valsartan/HCTZ. A recent meta-analysis indicated that telmisartan/HCTZ could reduce SBP and DBP by an additional 2.9 and 1.9 mmHg, respectively, compared to other ARB/HCTZ therapies. The choice of a specific medication combination is influenced by individual patient characteristics, including additional cardiovascular risk factors and comorbidities. Subgroup analyses from telmisartan trials indicate consistent efficacy for various combinations across diverse patient demographics. In patients with hypertension and diabetes who have micro albuminuria, the telmisartan/amlodipine (T/A) combination not only lowered blood pressure (BP) but also decreased the urinary albumin excretion rate. A large multicentre trial in China, which involved over 13,500 high-risk patients with at least one cardiovascular risk factor, demonstrated that long-term treatment with T/A was effective and well tolerated [Chrysant SG et al 2008].

For patients with stage 1 or 2 hypertension and diabetes who were not adequately controlled on amlodipine alone, eight weeks of treatment with the T/A combination led to a significantly greater reduction in systolic blood pressure (SBP) and increased the proportion of patients reaching their BP targets. Similar results were observed among obese patients. In post hoc analyses stratified by factors like age, race, and coexisting conditions (such as diabetes and obesity), the reductions in BP and the rate of achieving BP goals with the T80/A10 combination were comparable to the overall population. Notably, patients with severe hypertension (defined as SBP ≥180 mmHg) showed particularly significant reductions. In those with moderate to severe hypertension, a predefined analysis indicated that the T80/H25 combination resulted in more significant BP reductions than T80 monotherapy, regardless of patient demographics or previous treatment history.

Furthermore, retrospective analyses showed that in Black patients and those with type 2 diabetes or significant renal impairment, T80/H25 produced greater reductions in both SBP and diastolic BP (DBP) compared to telmisartan alone, irrespective of their baseline BP levels [Liu Z et al 2009].

Additional analyses highlighted that in patients with stage 2 or 3 hypertension and cardiovascular risk factors, treatment with T80/H25 for six weeks led to greater BP reductions and higher goal attainment rates compared to T80 alone. Pooled data from several studies showed that the efficacy and tolerability of the T/H combination were consistent across younger and older patients, including those over 65 who often have additional cardiovascular risks and are more challenging to treat. When selecting between an angiotensin receptor blocker (ARB) combined with a calcium channel blocker (CCB) versus one combined with hydrochlorothiazide (HCTZ), the potential adverse effects of each are crucial to consider, particularly their impact on patients with hypertension and comorbidities. The combination of an ARB with a CCB is generally favoured for patients with prediabetes, diabetes, or metabolic syndrome due to the metabolic neutrality of both drugs. The International Society on Hypertension in Blacks advocates for an RAS inhibitor–CCB combination in patients whose BP significantly exceeds targets without edema or volume overload.

Conversely, an ARB and HCTZ combination is beneficial for patients requiring volume reduction, as this combination not only enhances BP reduction but also mitigates the adverse metabolic effects associated with either drug used alone. Additionally, using an ARB can counteract potassium loss linked to thiazide diuretics, and thiazides can inadvertently heighten the sensitivity of the angiotensin II type 1 receptor, improving ARB efficacy. Diuretics may elevate the risk of developing new-onset diabetes, whereas RAS inhibitors can help delay or prevent this occurrence. The ARB/HCTZ combination is particularly advantageous for patients with high salt intake, which is common in regions like China. In all trials involving the T/A combination, there was a lower incidence of edema compared to amlodipine monotherapy. A comprehensive retrospective analysis of 50 studies confirmed that the T/H combination, like telmisartan monotherapy, is well tolerated across all age groups and boasts a favourable safety and tolerability profile. In a specific analysis of patients with moderate to severe hypertension, it was noted that average serum potassium levels remained stable in older Black and Asian patients receiving T80/H25, while other subpopulations had minor reductions in serum potassium levels averaging −0.1 mmol/L [Schumacher H et al 2008].

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