

# A review of the benefits of early treatment initiation with single-pill combinations of telmisartan with amlodipine or hydrochlorothiazide

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**Abstract:** This review discusses the rationale for earlier use of single-pill combinations (SPCs) of antihypertensive drugs, with a focus on telmisartan/amlodipine (T/A) and telmisartan/hydrochlorothiazide (T/H) SPCs. Compared with the respective monotherapies, the once-daily T/A and T/H SPCs have been shown to result in significantly higher blood pressure (BP) reductions, BP goal rates, and response rates in patients at all stages of hypertension. As expected, BP reductions are highest with the highest dose (T80/A10 and T80/H25) SPCs. Subgroup analyses of the telmisartan trials have reported the efficacy of both SPCs to be consistent, regardless of the patients' age, race, and coexisting diabetes, obesity, or renal impairment. In patients with mild-to-moderate hypertension, the T/A combination provides superior 24-hour BP-lowering efficacy compared with either treatment administered as monotherapy. Similarly, the T/H SPC treatment provides superior 24-hour BP-lowering efficacy, especially in the last 6 hours relative to other renin-angiotensin system inhibitor-based SPCs. The T/A SPC is associated with a lower incidence of edema than amlodipine monotherapy, and the T/H SPC with a lower incidence of hypokalemia than hydrochlorothiazide monotherapy. Existing evidence supports the use of the T/A SPC for the treatment of hypertensive patients with prediabetes, diabetes, or metabolic syndrome, due to the metabolic neutrality of both component drugs, and the use of the T/H SPC for those patients with edema or in need of volume reduction.

**Keywords:** calcium-channel blocker, essential hypertension, diuretic, primary care physician, renin-angiotensin system inhibitor

## Introduction

The treatment and control of hypertension remain less than optimal, despite the proven benefits of treatment in reducing cardiovascular morbidity and mortality.<sup>1,2</sup> Therapeutic inertia, ie, the treating physician's failure to increase therapy when treatment goals are unmet, is one of the reasons for the high prevalence of uncontrolled hypertension. A retrospective cohort study of a large number of patients showed that reducing treatment inertia by 50% led to improvement in goal-rate attainment from 45% to 66% over a 1-year period.<sup>3</sup> Similarly, in a cross-sectional observational study in an outpatient setting, adherence to treatment guidelines and involvement of the physician were observed to result in a significantly higher percentage of patients achieving blood pressure (BP) goals.<sup>4</sup>

At least 75% of patients with hypertension require combination therapy to achieve BP targets.<sup>5</sup> Treatment initiation with combination therapy has been shown to result in

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higher goal rates and reduction in the risk of cardiovascular (CV) events and death in a population-based, nested, case-control study and a retrospective analysis of electronic medical charts.<sup>6,7</sup>

Renin-angiotensin system (RAS) inhibitors are commonly used as a part of combination therapy,<sup>8,9</sup> because of their proven CV benefits<sup>10,11</sup> and the reduced risk of new-onset diabetes.<sup>12</sup> RAS inhibitors offer benefits in patients with a greater risk of renal damage, such as those with diabetes and high-normal BP or overt hypertension, due to their superior protective effect against initiation and progression of nephropathy,<sup>8,11</sup> and in patients with renal disease, to reduce and slow progression to end-stage renal disease and CV events.<sup>9</sup>

Angiotensin-receptor antagonists (ARBs) have better treatment adherence than angiotensin-converting enzyme inhibitors,<sup>13</sup> better tolerability, and significantly lower rates of cough and angioedema.<sup>10,14</sup> Among the ARBs, telmisartan has the most favorable pharmacokinetic profile, providing consistent BP reductions over 24 hours and beyond,<sup>15</sup> and offers CV risk prevention in patients at high CV risk.<sup>10</sup> Telmisartan is the only ARB approved for the reduction of CV morbidity in patients with manifest atherothrombotic CV disease (history of coronary heart disease, stroke, or peripheral artery disease) or diabetes mellitus, with documented target-organ damage.<sup>16,17</sup>

This review discusses the rationale for earlier use of telmisartan-based therapies, and in particular the evidence for choosing between calcium-channel blocker (CCB) and hydrochlorothiazide (HCTZ) combinations.

## **RAS inhibitors, CCBs, and HCTZ: the cornerstones of combination antihypertensive therapy**

The American Society of Hypertension recommends an RAS inhibitor in addition to either a CCB or a diuretic, preferably as a single-pill combination (SPC) when convenience outweighs all other considerations.<sup>18</sup> In the ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients LIVING with Systolic Hypertension) trial involving 11,506 high-risk patients assigned to an RAS inhibitor plus a diuretic or CCB, RAS inhibitors plus a CCB reduced CV morbidity and mortality more than an RAS inhibitor plus a diuretic combination;<sup>19</sup> the RAS inhibitor plus CCB combination also slowed the progression of nephropathy in a subgroup of patients with chronic kidney disease and minimal or no albuminuria.<sup>20</sup> The combination is also beneficial in high-risk hypertensive patients, such as those

with diabetes and/or existing CV disease.<sup>21</sup> The beneficial effects of a RAS inhibitor plus a thiazide diuretic combination in lowering CV risk were shown in ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), PROGRESS (Perindopril Protection Against Recurrent Stroke Study), and HYVET (Hypertension in the Very Elderly Trial) studies.<sup>22–25</sup>

## **Achieving BP control with combination therapy: evidence from telmisartan clinical trials**

The once-daily telmisartan/amlodipine (T/A) combination has been shown to result in significantly higher BP reductions, BP goal rates, and response rates in patients at all stages of hypertension, compared with the respective monotherapies; the reductions were greatest with telmisartan 80 mg plus amlodipine 10 mg (T80/A10).<sup>26–28</sup> In a subgroup analysis of patients with moderate-to-severe hypertension, the T80/A10 combination provided significantly greater BP lowering than A10 monotherapy, with 85% of patients achieving their diastolic BP (DBP) goal. The incidence of peripheral edema was also lower in the combination group.<sup>29</sup> In a large, combined analysis of 5,100 patients (24% with diabetes mellitus, 56% with obesity) from eight studies of 8 weeks' duration, T80/A10 combination therapy was associated with significantly higher BP goal-attainment rates and significantly greater reductions in BP compared with telmisartan or amlodipine monotherapy. The most significant differences were noted in patients whose treatment was initiated with combination therapy, and as early as 1 week after treatment initiation.<sup>30</sup>

Similarly, the once-daily telmisartan plus HCTZ (T/H) combination has been shown to result in significantly higher BP reductions and response rates in patients with mild-to-moderate hypertension, compared with the respective monotherapies after 7–8 weeks of treatment.<sup>27,31–34</sup> Significantly higher reductions in BP and a higher proportion of patients reaching target BP were observed with the highest dose of telmisartan 80 mg plus HCTZ 25 mg (T80/H25) than with telmisartan 80 mg plus HCTZ 12.5 mg (T80/H12.5) after 8 weeks of treatment.<sup>35</sup> In patients with moderate-to-severe hypertension (stage 2, defined as mean seated trough cuff systolic BP [SBP]  $\geq 160$  mmHg and DBP  $\geq 100$  mmHg),<sup>36</sup> initial antihypertensive treatment with T80/H25 resulted in significantly greater reductions in BP and in more patients achieving BP target and SBP response (defined as  $<140$  mmHg or  $\geq 15$  mmHg reduction from baseline) after 7 weeks compared with T80 monotherapy.

The antihypertensive efficacy of T80/H25 was observed as early as 2 weeks after the start of treatment.<sup>37</sup>

The telmisartan SPCs are also effective in providing 24-hour BP-lowering efficacy. In patients with mild-to-moderate hypertension, the T/A combination provided significantly higher 24-hour BP-lowering efficacy compared with the respective monotherapies after 8 weeks of treatment.<sup>38</sup> In previously untreated and treated patients with hypertension, 8 weeks of treatment with telmisartan and the T/H combination resulted in significant reductions in mean morning ambulatory BP, daytime ambulatory BP, 24-hour ambulatory BP, and clinic BP.<sup>39</sup>

## Comparison with other SPCs

There are currently no studies directly comparing the T/A SPC with SPCs of other antihypertensive drugs. However, in patients who failed to achieve BP goals after at least 2 months' treatment with 5 mg amlodipine plus 80 mg valsartan or 8 mg candesartan, replacement of valsartan or candesartan with telmisartan 40 mg was reported to reduce significantly both mean clinic SBP and DBP at 4, 8, and 12 weeks of treatment.<sup>40</sup> Similarly, replacement of valsartan 80 mg or candesartan 8 mg after at least 2 months of treatment with telmisartan 40 mg in amlodipine 5 mg-treated elderly patients with hypertension resulted in significant reduction in morning home SBP and evening home SBP and DBP at 12 weeks, and a significant increase in serum adiponectin level, suggesting beneficial cardiometabolic effects with T/A in elderly patients with hypertension.<sup>41</sup>

In two large placebo-controlled trials of 8 weeks' duration in patients with stage 1 or 2 hypertension, T/H treatment resulted in significantly higher BP reduction than valsartan/HCTZ.<sup>42,43</sup> A pooled analysis of the two studies showed that the significant difference in BP reduction in favor of T80/H25 was maintained, regardless of age, sex, or race of the patients.<sup>44</sup> In patients with essential hypertension, the T/H SPC was significantly more efficacious than the losartan/HCTZ SPC in reducing BP during the last 6 hours of the dosing interval, as well as in reducing 24-hour ambulatory BP after 6 weeks of treatment.<sup>45-47</sup> Similarly, 6 weeks' treatment with the T/H SPC resulted in significantly greater reductions in mean ambulatory BP over the entire 24-hour dosing interval and during the last 6 hours compared with valsartan/HCTZ, in the SMOOTH (Study of Micardis [telmisartan] in Overweight/Obese Patients with Type 2 Diabetes and Hypertension) trial.<sup>48</sup> A recent meta-analysis of head-to-head randomized controlled trials of T/H versus other ARBs plus HCTZ therapy for reduction of BP in hypertension showed that telmisartan/HCTZ therapy may reduce SBP and DBP

by an additional 2.9 and 1.9 mmHg, respectively, over other ARB/HCTZ therapy.<sup>49</sup>

## Which combination for which patient?

The selection of a specific combination is dependent on individual patient factors, including additional CV risk factors and comorbidities.<sup>9</sup> Subgroup analyses of the telmisartan trials have shown consistent efficacy for both combinations across a range of patient types.

In hypertensive diabetes patients with microalbuminuria, treatment with T/A reduced urinary albumin-excretion rate, in addition to lowering BP.<sup>50</sup> In a multicenter, open-label clinical trial in the People's Republic of China, involving 13,542 high-risk patients with at least one CV risk factor, long-term T/A treatment was found to be efficacious and well tolerated.<sup>51</sup> In patients with stage 1 or 2 hypertension and diabetes uncontrolled on amlodipine monotherapy, 8 weeks of treatment with the T/A SPC resulted in a significantly higher reduction in SBP and in more patients achieving their BP goal. The results were similar in the subpopulation of obese patients.<sup>52</sup> In a post hoc analysis of data from patients stratified into subpopulations based on age, race, coexisting diabetes, obesity, metabolic syndrome, renal impairment, and elevated baseline SBP, it was seen that BP reductions, goal-attainment rate, and response rate obtained with T80/A10 in these added-risk patients were similar to those observed in the overall population.<sup>53</sup> Another post hoc analysis of data pooled from clinical studies of the T/A SPC on hypertensive patients with metabolic risk factors (obesity, diabetes, or both), showed that in patients uncontrolled on monotherapy, BP reductions and goal-rate achievement with T/A were similarly high among patients with and without the presence of metabolic risk factors; particularly large reductions were recorded among patients with severe hypertension (defined as SBP  $\geq$  180 mmHg).<sup>54</sup> The same post hoc analysis also showed that in hypertensive patients with metabolic risk factors, BP reductions with the T/A SPC were maintained throughout the 24-hour dosing period, and 24-hour goal rates were obtained in a high proportion of patients.<sup>54</sup>

In patients with moderate-to-severe hypertension, a pre-specified analysis showed that the T80/H25 SPC treatment resulted in significantly higher BP reductions than T80 monotherapy, regardless of the patients' sex, age, race, hypertension severity, and previous treatment history (treatment-naïve or treated with one or  $\geq$  2 antihypertensive agents).<sup>55</sup> Furthermore, a retrospective analysis showed that in black patients with hypertension and hypertensive patients with concomitant type

2 diabetes mellitus or moderate or severe renal impairment, T80/H25 resulted in greater reductions in SBP and DBP than telmisartan monotherapy, irrespective of baseline BP.<sup>27</sup> A prespecified subgroup analysis of data from patients with stage 2 or 3 hypertension and CV disease risk factors, such as diabetes mellitus, low estimated glomerular filtration rate, high body mass index, and high coronary heart disease risk, reported that 6 weeks' treatment with T80/H25 consistently provided greater BP reductions and increased BP goal-attainment rates compared with T80 monotherapy.<sup>56</sup> A pooled analysis of data from seven studies showed that the efficacy and tolerability of the T/H SPC was similar between younger patients and patients older than 65 years (who may have added CV risk factors and are generally difficult to treat to goal).<sup>57</sup>

Thus, the important consideration in choosing the combination of an ARB plus a CCB versus an ARB plus HCTZ is the risk for associated adverse events with CCBs or HCTZ, and their effect on comorbidities in patients with hypertension. The SPC of an ARB with a CCB is preferable for the treatment of hypertensive patients with prediabetes,<sup>58,59</sup> diabetes, or metabolic syndrome, due to the metabolic neutrality of both component drugs.<sup>60</sup> The International Society on Hypertension in Blacks recommends an RAS inhibitor-CCB over an RAS inhibitor-thiazide combination in patients with BP >15/>10 mmHg above the goal, in the absence of edema and/or volume-overload states.<sup>61</sup>

The combination of an ARB plus HCTZ should be considered for patients in need of volume reduction, as the combination, in addition to maintaining the volume-reducing efficacy of HCTZ, results in additive BP reduction, and a decrease in the adverse metabolic effects of either drug alone.<sup>62</sup> Similarly, coadministration of an ARB tends to reverse the potassium loss associated with thiazide diuretics, and thiazide-induced reduction in extracellular fluid-volume reduction and peripheral resistance, and the resultant RAS activation may increase the sensitivity of the angiotensin II type 1 receptor, thereby enhancing response to ARBs.<sup>63</sup> Diuretics are reported to increase the risk for new-onset diabetes,<sup>64,65</sup> and RAS inhibitors are known to prevent or delay new-onset diabetes.<sup>66</sup> An ARB/HCTZ combination is particularly useful for patients with high salt consumption,<sup>67</sup> common in countries such as the People's Republic of China.<sup>68</sup>

In all the T/A SPC treatment trials, the T/A SPC was associated with a lower incidence of edema than amlodipine monotherapy.<sup>26-29,69</sup> Similarly, the rates of adverse events with T/H combination therapy were comparable with or lower than those reported for placebo or telmisartan monotherapy.<sup>27,70</sup> A retrospective analysis of 50 studies confirmed that as

with telmisartan monotherapy, T/H is well tolerated in adult patients of all ages and has a favorable safety and tolerability profile.<sup>71</sup> In a prespecified analysis of data from patients with moderate-to-severe hypertension, it was observed that mean serum potassium levels were unchanged in older, black, and Asian patient subpopulations receiving T80/H25, and other patient subpopulations receiving T80/H25 had small mean reductions in serum potassium, of -0.1 mmol/L.<sup>55</sup>

## Discussion

Telmisartan with either amlodipine or HCTZ in an SPC is equally efficacious and well tolerated at all stages of hypertension and in a wide variety of patient subpopulations, and the rationale for selection of one combination over the other is based on the accompanying comorbidities in hypertensive patients. The results from clinical trials and planned and post hoc pooled analysis of data from these trials show the T/A SPC to be efficacious and well tolerated in hypertensive patients with added risk factors including obesity, diabetes, metabolic syndrome, renal impairment, and elevated SBP,<sup>52-54</sup> and the T/H SPC to be efficacious and well tolerated in hypertensive patients with CV risk factors including obesity, diabetes, high coronary heart disease risk, and renal impairment.<sup>27,55-57</sup>

Also, in a real-life clinical practice setting, most of the patients on combination therapy were found to be on a combination of an RAS inhibitor with a CCB or a diuretic; of the 552 patients on combination therapy, equal proportions were on a combination of RAS inhibitor plus a CCB or a diuretic.<sup>72</sup> At the end of the follow-up, the BP-lowering efficacy was similar between the two combinations, but the incidence of new-onset diabetes was higher with the RAS inhibitor plus diuretic combination.<sup>72</sup>

Due to the nature of existing antihypertensives, and in most cases their single site of action, BP responses are largely unpredictable and wide ranging when administered to a heterogeneous population encompassing many hypertensive phenotypes.<sup>73</sup> In patients not adequately responding to monotherapy, uptitration or substitution of medication is not always as effective as combination therapy, especially where the phenotype is not known.<sup>73</sup> Combination therapy works better in these patients because of the pharmacological action on two or more different physiological sites, and the blocking of the counterregulatory responses that occur with monotherapy.<sup>73</sup> For example, RAS inhibitors may also reduce the unfavorable metabolic side effects of thiazide monotherapy<sup>74</sup> and CCB-induced peripheral edema.<sup>75,76</sup> The postcapillary dilation and normalization of hydrostatic pressure induced by RAS inhibitors<sup>77</sup> compensates for the



increased capillary pressure and flow with CCBs, which leads to increased permeability and fluid hyperfiltration.<sup>78</sup> An SPC of an RAS inhibitor plus a CCB is the preferred combination over an RAS inhibitor plus HCTZ in CV high-risk patients and those with evidence of renal disease.<sup>19–21</sup> The adverse electrolytic changes, including hypokalemia associated with diuretic use, may also be offset with concomitant use of RAS inhibitors.

The benefit of early achievement of BP goal in preventing CV events was seen in the Valsartan Antihypertensive Long term Use Evaluation (VALUE) study, which showed significant benefits for major CV outcomes when BP goals were achieved within 6 months of treatment initiation.<sup>79</sup> Early use of an SPC, including as first-line treatment, is suggested to help to reduce the gap between antihypertensive use and achievement of BP target control.<sup>80</sup> Indeed, a retrospective analysis of 106,621 patients showed improved CV outcomes with SPCs compared with monotherapy during the first year of treatment.<sup>81</sup>

In addition to early treatment initiation with combination therapy and selection of the most suitable combination based on patient needs, treatment adherence and compliance are also crucial for BP control, to reduce long-term CV morbidity and mortality and to improve quality of life.<sup>82</sup> Compared with free-drug combinations, SPCs of antihypertensive agents are associated with a significant improvement in compliance,<sup>83</sup> adherence rates,<sup>59,84,85</sup> lower health-care costs,<sup>86</sup> and significantly higher goal rates.<sup>87</sup> The reduced pill burden, simplified treatment regimens, and improved treatment adherence with SPCs is expected to result in better BP control and long-term CV risk reduction.<sup>88</sup>

## Conclusion

SPCs of telmisartan with amlodipine or HCTZ provide better efficacy than the respective monotherapies in patients at all stages of hypertension, as well as in those with added risk factors, including obesity, diabetes, or metabolic syndrome. The SPCs are associated with a lower incidence of adverse effects, such as edema and hypokalemia, compared with amlodipine and HCTZ monotherapy.

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