Amlodipine + Telmisartan: A Powerful Duo

Module 2

Content

Introduction

Hypertension is a major global public health issue and the leading risk factor for cardiovascular diseases, imposing a significant economic burden on society. Its epidemiological profile is marked by a high incidence, high rates of disability and mortality, and low levels of public awareness. In 2021, approximately 330 million people in China were affected by cardiovascular diseases, with 245 million of them diagnosed with hypertension. As the most critical risk factor, managing blood pressure is considered essential in preventing cardiovascular diseases. The primary medications for treating hypertension include angiotensin-converting enzyme inhibitors, angiotensin II (Ang II) receptor blockers, calcium channel blockers, β-blockers, and diuretics, among others. For patients whose blood pressure is poorly controlled, multiple antihypertensive medications are often required.

Despite advancements in drug treatments and the introduction of new surgical techniques, effective hypertension control remains inadequate. Enhancing the effectiveness of preventive medications and delaying the onset of hypertension-related cardiovascular diseases is a significant ongoing challenge. Hypertension is typically the result of a combination of genetic and environmental factors. The classic mechanisms of hypertension include overactivity of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, vascular endothelial dysfunction, insulin resistance, and dysregulation of neurohumoral factors. Recent studies continue to explore these pathways [Yang, Z, et al. 2023].

Cardiovascular diseases (CVD) are the primary cause of death and illness in both developed and developing nations. Although the occurrence of ischemic heart disease (IHD) has significantly decreased in developed countries, longer life expectancy and improved management of chronic conditions have made HF a significant public health concern, particularly among older adults [Chaturvedi V., et al.2016]. Telmisartan and amlodipine lower blood pressure through complementary mechanisms that work together synergistically to enhance their blood pressure-lowering effects. The specific mechanisms of action for each drug have been thoroughly discussed in other reviews. Telmisartan's chemical structure includes the biphenyl-tetrazole and imidazole groups, which are characteristic of all angiotensin II receptor blockers (ARBs) (Figure 1).

Figure 1. Chemical structures of telmisartan and amlodipine besylate

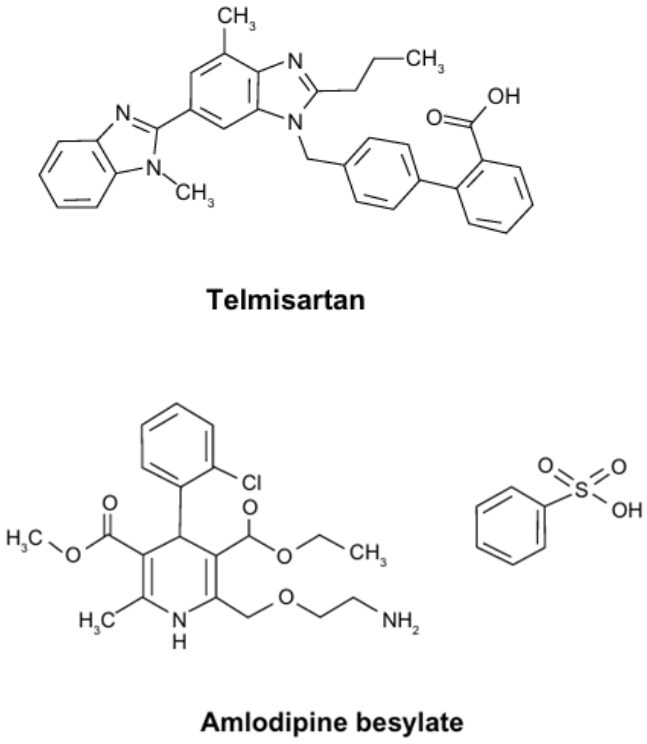

Figure adapted from: Billecke S, et. al 2013

Telmisartan and amlodipine have distinct pharmacokinetic profiles in terms of absorption rate, volume of distribution, and metabolism. Among the ARBs used to treat hypertension, telmisartan is the most lipophilic, which contributes to its longer half-life, highest affinity for AT1 receptors, and largest volume of distribution. Telmisartan's bioavailability ranges from 45% to 50%, while amlodipine's bioavailability is between 64% and 90%. Both drugs are highly bound to plasma proteins, with amlodipine binding at 93% and telmisartan at over 99%. Steady-state concentrations of amlodipine are reached within 7 to 8 days, while for telmisartan, this occurs in 5 to 7 days [Billecke S, et. al 2013.]. This situation highlights the significant challenges in achieving target blood pressure (BP) levels in patients with hypertension. Several factors contribute to these difficulties, including the ineffectiveness of using a single medication and issues related to patient adherence to prescribed treatment regimens.

Many individuals with hypertension do not reach their target BP when treated with monotherapy, prompting current clinical guidelines to recommend that patients whose systolic blood pressure (SBP) exceeds the target by 20 mmHg or whose diastolic blood pressure (DBP) is 10 mmHg above the target should be prescribed a combination of two antihypertensive medications.

These medications should have complementary mechanisms of action to enhance their effectiveness in managing blood pressure more successfully. This approach aims to improve the overall treatment outcomes for hypertensive patients by addressing the limitations associated with single-drug therapy and encouraging better compliance [Mancia G, et al. 2007, Billecke S, et al.2013].

2. Mechanism of action of amlodipine

Amlodipine, on the other hand, is a dihydropyridine calcium channel blocker (CCB) that attaches to a specific transmembrane site on L-type calcium channels found in cardiac and smooth muscle cells. By binding to these channels, amlodipine effectively inhibits the influx of calcium ions. This disruption of calcium entry interferes with the interactions between myosin and actin, leading to a decrease in muscle contractility. Consequently, the overall effect of amlodipine on the vascular system is vasodilation, which helps to lower peripheral resistance. This reduction in peripheral resistance ultimately contributes to a decrease in BP. Through this mechanism, amlodipine plays a significant role in managing hypertension and improving cardiovascular health.

Figure 2. MOA of amlodipine

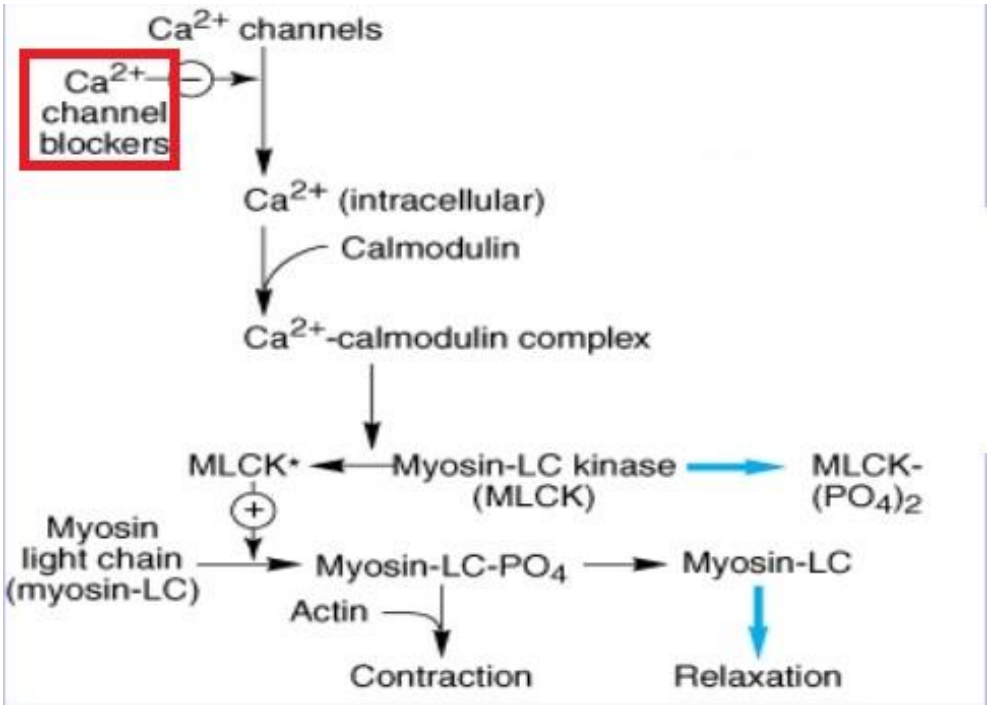

Figure adapted from: Mori H, et al. 2012

Amlodipine is a long-acting, lipophilic third-generation dihydropyridine (DHP) calcium channel blocker (CCB) that functions by inhibiting calcium influx into vascular smooth muscle and myocardial cells. This mechanism leads to a reduction in peripheral vascular resistance (PVR). It is prescribed for treating high blood pressure (hypertension) and angina. Numerous randomized trials have confirmed its effectiveness in managing angina pectoris [Taylor S., et al. 1994].

Due to its long half-life, amlodipine is typically administered once daily, which enhances patient compliance. The standard starting dose is 5 mg, with a maximum daily dose of 10 mg. For elderly patients or those with liver dysfunction, a lower starting dose of 2.5 mg is recommended. Amlodipine's gradual onset of action minimizes significant reflex neuroendocrine activation. Such reflex responses—such as increased PVR and heart rate—can adversely impact lipid and carbohydrate metabolism. These negative effects are often associated with other medications, including first-generation β-blockers (like atenolol and metoprolol) and earlier DHPs. Amlodipine boasts a high bioavailability of 60% to 80% and is metabolized in the liver. While its elimination is somewhat affected in patients with liver cirrhosis, there is no accumulation observed in cases of renal failure. The drug has a prolonged elimination half-life of 40 to 60 hours. When amlodipine is discontinued, blood pressure typically returns to baseline levels within a week, and there are no significant rebound increases in blood pressure, which differentiates it from medications like clonidine [Abernethy D., et al. 1992].

3. Mechanism of action of telmisartan

Telmisartan exhibits a high degree of selectivity for the angiotensin II type 1 receptor (AT1), effectively blocking the harmful effects of angiotensin II (Ang II). These detrimental effects include vasoconstriction, the activation of several intracellular signaling pathways such as protein kinase C, NADPH oxidase, and the Janus kinase/signal transducer and activator of transcription cascade. Additionally, Ang II promotes the release of catecholamines from the adrenal medulla, stimulates aldosterone secretion, and encourages cell proliferation, all of which can contribute to various cardiovascular problems. Moreover, at higher yet still clinically relevant doses, telmisartan functions as a partial agonist of the peroxisome proliferator-activated receptor γ (PPAR-γ). This action allows telmisartan to confer additional benefits to patients, particularly by improving conditions related to glucose intolerance and insulin resistance, as well as positively influencing lipid metabolism. These multifaceted actions make telmisartan a valuable therapeutic option for managing hypertension and its associated

risks, offering both cardiovascular protection and metabolic benefits [Tuck M, et al.2005, Mori H, et al. 2012].

Figure 3. MOA of telmisartan

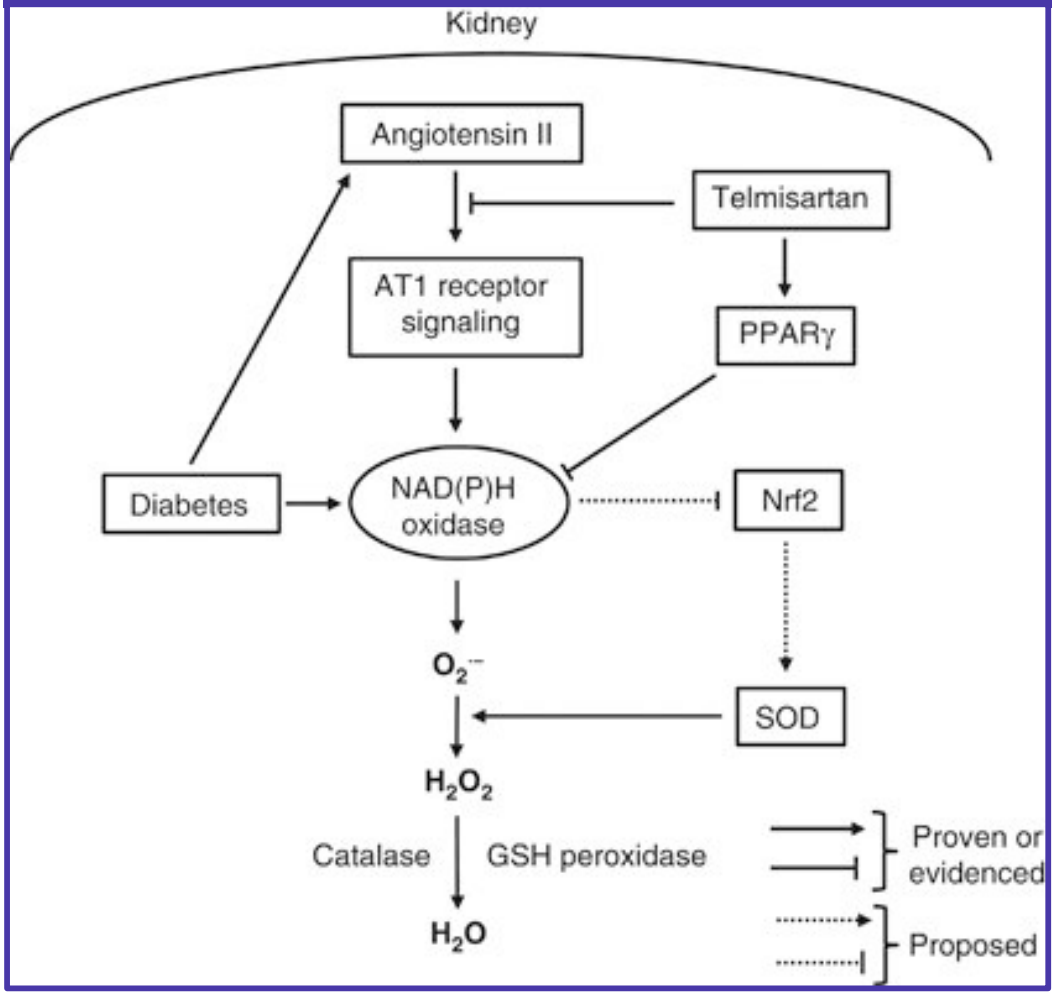

Figure adapted from: Fujita, H., et al. 2012

Telmisartan is not subject to significant first-pass metabolism, meaning that most of the drug remains unchanged as it circulates through the liver. Approximately 97% of telmisartan is excreted via the biliary-fecal route in its original, unaltered form. However, a small portion of the drug does undergo glucuronidation, a process where the drug is combined with glucuronic acid, making it more water-soluble and easier to excrete. This unique excretion pattern allows telmisartan to maintain its efficacy without extensive metabolic alteration, contributing to its favorable pharmacokinetic profile [Stangier, J., et al. 2000].

4. Rationale of combination therapy

Multi-drug therapy for hypertension can involve either fixed-dose combinations (FDCs) or the sequential addition of medications. The choice of therapy depends on the patient's ability to tolerate the treatment and the convenience of dosing and adjusting the regimen. FDCs have been shown to improve adherence to medication compared to administering two separate drugs, while also providing quicker reductions in blood pressure. Combination antihypertensive therapy began in the 1960s with the pairing of hydrochlorothiazide (HCTZ) and triamterene, a potassium-sparing diuretic, and has since evolved to include newer combinations over time [Weir, M., et al. 2008].

The rationale for combining agents that block the renin-angiotensin-aldosterone system (RAAS) with calcium channel blockers (CCBs) or diuretics is well-supported. Beyond lowering blood pressure, angiotensin receptor blockers (ARBs) and CCBs provide additional benefits for reducing morbidity and mortality in hypertensive patients with comorbid conditions. In the LIFE study, a losartan-based ARB regimen reduced the relative risk of cardiovascular morbidity and death in hypertensive patients with left ventricular hypertrophy by 13%, primarily due to a 25% reduction in stroke risk compared to atenolol, despite only a 1 mm Hg difference in systolic blood pressure. Telmisartan, an ARB with a distinct pharmacokinetic profile, has limited studies examining its combination with CCBs in hypertension management. In one study by Fogari et al., patients whose blood pressure remained above 130/80 mm Hg after initial treatment with 40 mg telmisartan and 2.5 mg amlodipine were randomized into two dose-titration regimens. One group received escalating doses of telmisartan, while the other received increasing doses of amlodipine. Although both regimens achieved similar blood pressure reductions, the group receiving higher telmisartan doses experienced greater reductions in urinary albumin excretion, a marker of kidney function. Overall, the combination of 80 mg telmisartan and 10 mg amlodipine proved most effective and well-tolerated, offering a strong therapeutic option for patients needing combination therapy [Kalra, S., et al. 2010].

Combining an angiotensin II receptor blocker (ARB) with a calcium channel blocker (CCB) is an effective strategy for managing hypertension. Studies, such as the ACCOMPLISH trial, have demonstrated that a combination of a renin-angiotensin system (RAS) inhibitor and a CCB is superior in reducing cardiovascular risk compared to a RAS inhibitor paired with a diuretic. This finding is reflected in the 2011 updated NICE guidelines for hypertension treatment. Additionally, there is evidence that the ARB telmisartan, when combined with the CCB amlodipine, achieves better blood pressure reduction than either drug used as a monotherapy.

This combination has also proven effective across all stages of hypertension, including in patients with additional risk factors such as obesity, diabetes, or metabolic syndrome [Neldam S., et al. 2013].

5. Telmisartan and amlodipine safety profile

Amlodipine and telmisartan are both generally well-tolerated, with a low incidence of adverse events (AEs) when used individually. Their combination is particularly suitable for patients with diabetes and/or metabolic syndrome, as neither medication exacerbates the metabolic issues associated with these conditions. Most studies assessing the safety of the telmisartan/amlodipine single-pill combination were short-term. In an 8-week placebo-controlled trial with a 4 × 4 factorial design, groups receiving varying doses (T40/A5, T40/A10, T80/A5, T80/A10, T40, T80, A5, A10, and placebo) experienced AEs at rates comparable to the placebo group, which had a 39% incidence of AEs. The highest incidence was 44% in the T80/A10 group, while the lowest was 33% in the T40/A5 group. Drug-related AEs ranged from 5.2% (T80) to 19% (T80/A10). The most common AE was peripheral edema, a known side effect of amlodipine due to its vasodilatory action. The incidence of edema was as high as 18% in the A10 group and 11% in the T80/A10 group. The lower occurrence of peripheral edema in the T80/A10 group compared to A10 monotherapy aligns with previous findings for this combination and other RAS inhibitors, further supporting the use of such combinations [Mallat S., et al. 2012, Fogari, R., 2011, Sica D., 2002].

Safety data from longer-term trials, as outlined in Tables 1 and 2, cover a total of 2,283 patients. The TEAMSTA study reported adverse event (AE) incidence per 100 patient-years, as the study design included dose increases for nonresponders. The same approach was used for trial NCT00618774, though patient-year data were unavailable for that trial. In three trials with AE data categorized by treatment group (Table 1), all-cause AEs occurred at rates as low as 12% (T40/A10; TEAMSTA-10), with incidence rates of 51 occurrences per 100 patient-years. Interestingly, in the unpublished NCT00618774 trial, the overall AE incidence was 77% in both study arms, but drug-related AEs did not exceed 8%, or 14 events per 100 patient-years, across any trial. Discontinuation rates due to AEs were low in all four studies, occurring in less than 2% of patients. Similar to short-term trials, peripheral edema was the most common AE, with higher amlodipine doses leading to increased incidence. Some cases of dizziness were also reported, and no deaths occurred during any of the trials [Billecke, S., et al. 2013].

Table 1. Safety profile for telmisartan/amlodipine combination therapy

	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) 95 per 100 PY	201 (51) 97 per 100 PY	102 (12) 50 per 100 PY	157 (26) 46 per 100 PY	163 (77)	37 (77)
Discontinuations due to AEs	12 (1.2) 3 per 100 PY	4 (1.0) 2 per 100 PY	6 (0.7) 3 per 100 PY	9 (1.5) 3 per 100 PY	–	–
SAE	22 (2.3) 4 per 100 PY	6 (1.5) 4 per 100 PY	4 (0.5) 3 per 100 PY	13 (2.1) 2 per 100 PY	9 (4.3)[a]	3 (6.3)[a]
Study-drug related AE	51 (5.2) 13 per 100 PY	30 (7.6) 14 per 100 PY	28 (3.3) 14 per 100 PY	38 (6.2) 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) 6 per 100 PY	11 (2.8) 5 per 100 PY	16 (1.9) 8 per 100 PY	24 (3.9) 7 per 100 PY	–	–
Dizziness	0	6 (1.5) 3 per 100 PY	0	0	–	–

Table adapted from: Billecke, S., et al. 2013.

6. Telmisartan and amlodipine efficacy profile

The efficacy results from three long-term studies are summarized in Table 2. Most of the telmisartan/amlodipine trials used DBP control (defined as DBP < 90 mmHg) as the primary efficacy measure. This target was achieved by at least 76% of participants who did not require maximal dose increases or additional therapy (T80/A5 + add-on, TEAMSTA-5) or dose escalation (T80/A5, trial 1235.16). In these groups, DBP control was achieved in 46.4% and 66.7% of patients, respectively. DBP response rates, defined as either DBP < 90 mmHg or a reduction of at least 10 mmHg, were consistently above 69%, while SBP response rates (SBP < 140 mmHg or a reduction of at least 15 mmHg) exceeded 70% in all groups.

Mean blood pressure reductions showed significant improvements across all treatment arms, with reductions of at least 12.6/9.5 mmHg. The changes in blood pressure did not always follow a typical dose-response pattern within each study, likely due to the study designs, which involved dose adjustments or the addition of therapy for nonresponders rather than straightforward randomization. None of these long-term studies were designed to compare telmisartan/amlodipine with monotherapy or other antihypertensive drugs, as such comparisons have generally been limited to shorter trials of around 8 weeks [Littlejohn T., et al. 2009, Neldam S., et al. 2011, White, W., et al. 2010].

Table 2. Efficacy profile for telmisartan/amlodipine combination therapy

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

Table adapted from: Billecke, S., et al. 2013.

7. Synergistic effect

7.1 Role as monotherapy in HTN:

Several hypertension (HTN) trials have evaluated the effectiveness of amlodipine monotherapy compared to other treatments, such as diuretics, ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). The results suggest that amlodipine has a neutral impact on certain pre-existing comorbidities, which are discussed below.

The Comparison of Amlodipine versus Enalapril to Limit Occurrence of Thrombosis (CAMELOT) trial involved 1,991 patients with coronary artery disease (CAD) confirmed by angiography. Participants were randomized to receive either 10 mg of amlodipine, 20 mg of enalapril, or a placebo, and were followed for 24 months. In a sub study of 274 patients, atherosclerotic progression was assessed using intravascular ultrasound. Despite starting with a relatively low baseline blood pressure (129/78 mmHg), both treatment groups experienced similar reductions in blood pressure, with decreases of 4.8/2.5 mmHg for amlodipine and 4.9/2.4 mmHg for enalapril. Amlodipine was found to significantly reduce the incidence of non-fatal myocardial infarction (MI) by 26% and stroke or transient ischemic attack by 50%, with a number needed to treat of 16. Enalapril, on the other hand, did not demonstrate a significant benefit compared to placebo. Additionally, hospitalizations due to angina were significantly lower with amlodipine than with enalapril (p=0.003). This study indicates that in normotensive patients, amlodipine reduces cardiovascular events and hospitalizations and may slow the progression of atherosclerosis compared to enalapril. A smaller Japanese study examined the effects of losartan and amlodipine on left ventricular (LV) diastolic function in patients with mild-to-moderate HTN. LV diastolic dysfunction is closely linked to LV hypertrophy (LVH) and myocardial fibrosis [Nissen S., et al. 2004].

7.2 Role of amlodipine in mild to moderate hypertension:

Randomized studies have shown that amlodipine outperforms diltiazem and hydrochlorothiazide in lowering systolic (SBP) and diastolic blood pressure (DBP) in individuals with mild to moderate hypertension. Additionally, amlodipine is just as effective as chlorthalidone in reducing average blood pressure in patients aged 50 and older. In Asian populations with mild to moderate hypertension, increasing the amlodipine dosage from 5 to 10 mg per day led to a significant decrease in SBP [Kario, K., et al. 2013].

7.3 Role of amlodipine in BPV, including the morning bp surge:

Blood pressure variability (BPV) over 24 hours is an important and independent predictor of cardiovascular morbidity and mortality. Different antihypertensive drug classes have varying effects on short-term 24-hour BPV. In patients receiving combination drug therapy, regimens that included calcium channel blockers (CCBs) demonstrated lower BPV compared to those without CCBs. A retrospective analysis of BPV data from five studies found that amlodipine was more effective than other antihypertensive drug classes in reducing BPV. In a randomized, double-blind, placebo-controlled trial, amlodipine significantly decreased daytime, nighttime, and 24-hour systolic BP (SBP) variability, while candesartan did not, as measured by ambulatory blood pressure monitoring (ABPM) after three months of treatment. Numerous studies have also highlighted the importance of long-term visit-to-visit BPV in predicting cardiovascular outcomes and mortality.

For instance, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), patients assigned to an amlodipine-based treatment regimen had significantly lower BPV, as indicated by SBP standard deviation and variability independent of the mean, compared to those on atenolol. This was largely due to lower within-individual visit-to-visit variability. Moreover, within-visit and ABPM SBP variability were also lower in the amlodipine group than in the atenolol group [Rothwell P., et al.2010].

7.4 Role of amlodipine in stroke prevention:

Numerous landmark trials have demonstrated the stroke-protective effects of amlodipine. For example, across nine key studies, amlodipine reduced the incidence of stroke by 40% compared to placebo, by 18% versus ACE inhibitors (ACEIs), by 16% versus ARBs, and by 14% compared to diuretics or beta-blockers. In the ASCOT study, amlodipine-based

treatment lowered the relative risk of stroke by 23% compared to atenolol-based therapy. Additionally, amlodipine provided superior protection against stroke (16%) and myocardial infarction (MI, 17%) when compared with ARBs in a quantitative review. A recent meta-analysis of 13 studies involving over 50,000 patients found that amlodipine reduced the incidence of MI by 13% when compared to other antihypertensive drugs.

Several mechanisms have been proposed to explain the stroke-protective benefits of calcium channel blockers (CCBs) like amlodipine:

(1) Amlodipine has a longer duration of action than most other antihypertensive medications;

(2) Carotid intima-media thickness (IMT), which is strongly associated with cardiovascular events, is reduced more effectively by CCBs than by diuretics, beta-blockers, or ACEIs, contributing to the superior stroke protection of CCBs;

(3) CCBs reduce inter-individual blood pressure variability (BPV).

A meta-analysis comparing various drug classes found that CCBs and non-loop diuretics reduced inter-individual SBP variability, whereas ACEIs and ARBs had little impact, and beta-blockers increased BPV. Compared to placebo, CCBs showed greater reduction in inter-individual BPV than other drug classes (figure 4) [Wang, J., et al. 2023].

Figure 4. Meta-analysis of antihypertensive drug effects on long-term BPV

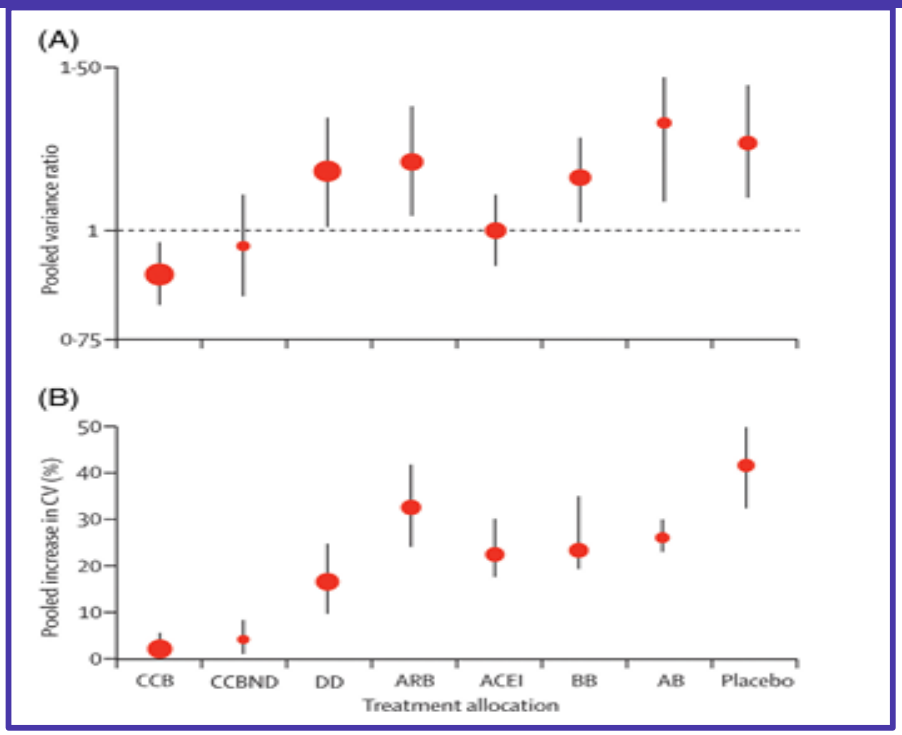

Figure adapted from: Wang, J., et al. 2023.

7.5 Amlodipine in specific populations

7.5.1. Patients with angina pectoris:

Approximately 47% of the risk for developing ischemic heart disease is linked to hypertension. Both the European Society of Cardiology and the American Heart Association (AHA) recommend calcium channel blockers (CCBs), either alone or combined with beta-blockers, as a first-line treatment for managing stable ischemic heart disease.

A prospective, double-blind study demonstrated that amlodipine reduced the occurrence of repeat percutaneous transluminal coronary angioplasty and related complications when administered two weeks before and for four months following the procedure. Additionally, in an open-label, randomized study involving patients with hypertension and type 2 diabetes, amlodipine therapy led to a significantly greater reduction in carotid intima-media thickness (IMT) compared to ARB therapy, indicating that amlodipine may inhibit the early stages of atherosclerosis. Furthermore, a prospective, randomized study found that amlodipine was associated with fewer hospitalizations for unstable angina (a 33% reduction) and fewer coronary revascularization procedures (a 43% reduction), regardless of concurrent use of beta-blockers, nitrates, or lipid-lowering therapy. Notably, in the ASCOT trial, amlodipine was shown to have a synergistic effect with atorvastatin in preventing coronary events, a synergy supported by other reports and a proposed molecular mechanism. Given these findings, amlodipine may be an effective option for preventing the progression of atherosclerotic vascular disease [Wang, J., et al. 2023].

7.5.2 Patients with diabetes mellitus:

The 2023 American Diabetes Association guidelines recommend calcium channel blockers (CCBs) as a first-line treatment for patients with diabetes who do not have albuminuria or coronary artery disease. The guidelines indicate that, in the absence of albuminuria, ACE inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) do not provide greater cardiovascular protection than CCBs or diuretics. Notably, β-blockers and diuretics can worsen insulin resistance and negatively impact lipoprotein metabolism, while ACE-Is, CCBs, and α-blockers remain neutral in these respects. A database analysis revealed that patients with type 2 diabetes treated with CCBs experienced lower morning home blood pressure variability (BPV) compared to those treated with ARBs or ACE-Is, with CCB treatment significantly linked to reduced BPV independent of other factors.

Additionally, a systematic review and meta-analysis found that the risk of stroke in diabetic patients was lower when treated with amlodipine compared to other treatments, such as diuretics, β-blockers, α-blockers, ACE-Is, or ARBs. In cases where diabetic patients did not adequately respond to 5 mg of amlodipine, a retrospective analysis demonstrated that increasing the dosage to 10 mg daily led to significant reductions in both systolic and diastolic blood pressure [Wang, J., et al. 2023].

7.1.4 Patients with chronic kidney disease:

Lowering blood pressure is an effective method for reducing cardiovascular events in patients with moderately decreased estimated glomerular filtration rate (eGFR). The long-term follow-up of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that patients with kidney dysfunction who were treated with amlodipine maintained higher average eGFR levels compared to those treated with chlorthalidone by the fourth year. Additionally, a retrospective post hoc analysis of patients in the ASCOT and ALLHAT trials revealed that systolic blood pressure variability (BPV) was consistently lower in patients taking amlodipine compared to those using other antihypertensive drugs like chlorthalidone or lisinopril, regardless of their eGFR levels. Moreover, a real-world study provided further evidence supporting the kidney-protective effects of amlodipine, comparable to those seen with other calcium channel blockers (CCBs). Notably, amlodipine demonstrated greater effectiveness in reducing blood pressure, even at lower doses, making it a potent option for managing hypertension in patients with renal concerns. This combination of kidney protection and blood pressure control highlights amlodipine's valuable role in treating patients with compromised kidney function and hypertension [Jadhav U., et al. 2021].

8. Study on amlodipine and telmisartan combination

A combination therapy using an angiotensin II receptor blocker (ARB) and a calcium channel blocker (CCB) offers an effective strategy for managing hypertension. This approach, particularly the pairing of a renin-angiotensin system (RAS) inhibitor with a CCB, has proven to provide better cardiovascular protection than combining a RAS inhibitor with a diuretic, as demonstrated in the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) trial. This evidence was a key factor in the 2011 update of the NICE guidelines for hypertension treatment. Research further supports that combining the ARB telmisartan with the CCB amlodipine achieves superior blood pressure reduction compared to either drug alone.

The telmisartan-amlodipine combination has been shown to effectively lower blood pressure across all stages of hypertension, making it a versatile option for patients. It is especially beneficial for those with additional risk factors such as obesity, diabetes, or metabolic syndrome. This combination provides a potent and reliable method for managing complex cases, improving outcomes in patients who might otherwise be at greater risk of cardiovascular events due to their comorbid conditions [White W., et al. 2010].

8.1 Method:

The Boehringer Ingelheim trial database was reviewed to identify studies that compared combination therapy with telmisartan and amlodipine to monotherapy using either drug, with data collected by week 4 or earlier. This search resulted in eight randomized, double-blind studies. These studies included designs without a run-in period involving protocol-defined antihypertensive medications, as well as studies on patients who did not respond to initial treatment with either telmisartan or amlodipine alone (as detailed in Table 3). From the identified studies, only treatment groups receiving dosages currently available for prescription—telmisartan at 40 mg and 80 mg, and amlodipine at 5 mg and 10 mg—were included in the analysis. The participants in these eight studies were selected based on various baseline blood pressure criteria, which are outlined in Table 3.

Table 3. study analysis

Study identifier	Study number	Pretreatment	Selection criteria	Randomised treatments	SPC or free dose	Weeks with BP measurements	Primary end-point
Studies with initial combination therapy							
Factorial study	NCT00281580 (15)	None	DBP ≥ 95 and ≤ 119 mmHg	Placebo, A5, A10, T40, T80, T40/A5, T40/A10, T80/A5, T80/A10	Free dose	2 (A5, T40/A5, T80/A5), 4, 8	Change from baseline in seated trough DBP at week 8
TEAMSTA Severe	NCT00860262 (20)	None	SBP ≤ 180 and DBP ≥ 95 mmHg	A10, T80, T80/A10	SPC	2 (A5, T80/A5), 4, 8	Change from baseline in trough seated SBP at week 8
TEAMSTA Diabetes	NCT00877929 (28)	None	Diabetes and SBP ≥ 150 mmHg	A10, T80/A10	SPC	1, 2 (A5, T80/A5), 4, 6, 8	Change from baseline in trough seated SBP at week 8
Studies in patients not controlled on monotherapy							
TEAMSTA-5	NCT00558428 (19)	A5 (6 weeks)	DBP ≥ 90 mmHg	A5, A10, T40/A5, T80/A5	SPC	4, 8	Change from baseline in trough seated DBP at week 8
TEAMSTA-10	NCT00553267 (27)	A5 (2 weeks), A10 (6 weeks)	DBP ≥ 90 mmHg	A10, T40/A10*, T80/A10	SPC	4, 8	Change from baseline in trough seated DBP at week 8
T40 non-responder	NCT00550953 (24)	T20 (2 weeks), T40 (4 weeks)	DBP ≥ 90 mmHg	T40, T40/A5	SPC	4, 8	Change from baseline in trough seated DBP at week 8
A5 non-responder	NCT01103960 (26)	A5 (6 weeks)	DBP ≥ 90 mmHg	A5, T80/A5	SPC	4, 8	Change from baseline in trough seated DBP at week 8
T80 non-responder	NCT01222520 (25)	T20 (2 weeks), T40 (2 weeks), T80 (4 weeks)	SBP ≤ 200 mmHg; DBP ≥ 90 and ≤ 114 mmHg	T80, T80/A5	SPC	4, 8	Change from baseline in trough seated DBP at week 8

Table adapted from: Neldam S., et al. 2013.
DBP, diastolic blood pressure; SBP, systolic blood pressure; SPC, single-pill combination.

Three of the studies did not involve protocol-defined antihypertensive pretreatment and are referred to as "studies with initial combination therapy." These included a single-blind, placebo run-in period lasting between 1 and 28 days to eliminate any previous antihypertensive medications. Baseline blood pressure (BP) was measured at the end of the washout period, prior to randomization (week 0). Patients assigned to high-dose treatment began with a low dose for the first two weeks, followed by an increase to the target study dose for the remaining six weeks. One of the studies (the "factorial study") used a free-dose combination of telmisartan and amlodipine, while the other two utilized a single-pill combination (SPC).

In the five studies with protocol-defined antihypertensive pretreatment, termed "studies in patients not controlled on monotherapy," patients underwent an open-label, 6- to 8-week run-in period with either telmisartan or amlodipine at various doses. Titration was included in this phase for those on high-dose monotherapy. At week 0, patients were randomized to either continue monotherapy or switch to SPC therapy with telmisartan and amlodipine for the study's 8-week duration.

The treatment regimens analyzed were: amlodipine 5 mg (A5), amlodipine 10 mg (A10), telmisartan 40 mg (T40), telmisartan 80 mg (T80), telmisartan 40 mg plus amlodipine 5 mg (T40/A5), telmisartan 80 mg plus amlodipine 5 mg (T80/A5), and telmisartan 80 mg plus amlodipine 10 mg (T80/A10). Patients took their treatments once daily in the morning. Seated trough BP was measured with a validated sphygmomanometer at baseline (week 0) and at week 8, with additional measurements at weeks 1, 2, 4, and 6 in some studies. The primary endpoints were changes in SBP and DBP after 8 weeks. This combined analysis, which included pooled and non-pooled post hoc analyses, focused on BP changes and goal attainment during the early weeks of combination therapy, particularly at weeks 1, 2, and 4 [Neldam S., et al. 2013].

8.2 Statistical analysis:

The different analyses, both pooled and separate, are outlined in Table 4. The mean changes in SBP and DBP from baseline were calculated, with adjustments made for baseline BP and the specific study. These changes were then compared across treatments using analysis of covariance (ANCOVA).

Additionally, the rates of patients achieving blood pressure goals—defined as overall BP less than 140/90 mmHg, SBP less than 140 mmHg, and DBP less than 90 mmHg—were compared between treatment groups. These goal attainment rates were analyzed using odds ratios, which were calculated through logistic regression, also adjusted for baseline BP and study.

Table 4. Analysis

Analysis number	Pooled (yes/no)	Study identifier	Comparative treatments	Week
Studies with initial combination therapy				
A1	Yes	Factorial study TEAMSTA Severe TEAMSTA Diabetes	T80/A10 vs. A10, T80	4
A2	No	Factorial study	T40/A5 vs. A5, T40	2
A3	Yes	Factorial study TEAMSTA Severe TEAMSTA Diabetes	T80/A5 vs. A5, T80	2
A4	Yes	Factorial TEAMSTA Severe TEAMSTA Diabetes	T80/A5 vs. A5	1
Studies in patients not controlled on monotherapy				
B1	Yes	TEAMSTA-5 A5 non-responder	T40/A5 vs. A5, A10 T80/A5 vs. A5, A10	4
B2	No	TEAMSTA-10	T80/A10 vs. A10	4
B3	No	T40 non-responder	T40/A5 vs. T40	4
B4	No	T80 non-responder	T80/A5 vs. T80	4

Table adapted from: Neldam S., et al. 2013.

8.3 Results Study

A total of 5,100 patients from eight studies were included in these analyses, with the groups showing a good match in terms of demographics and baseline characteristics. However, it is important to highlight that the 'TEAMSTA Diabetes' study specifically involved patients with diabetes mellitus. This study featured a slightly older population, with a longer mean duration of hypertension, higher baseline SBP, and lower baseline DBP compared to the other studies. Meanwhile, the 'TEAMSTA Severe' study focused solely on patients with severe hypertension (SBP of 180 mmHg), and similarly had an older population with a longer duration of hypertension. The studies designated as 'A5, T40, and T80 non-responder studies' were conducted exclusively with Asian patients (specifically Japanese and Chinese) and exhibited lower average body mass index (BMI) compared to their counterparts [Neldam S., et al. 2013].

8.3.1 Studies with initial combination therapy

A total of four analyses were conducted, labeled A1 to A4. Three of these were pooled analyses focusing on weeks 1, 2, and 4 (A1, A3, A4), while one specifically analyzed the factorial study at week 2 (A2) (refer to Table 5). An overall significant difference in treatment was observed for the reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as for blood pressure (BP), SBP, and DBP goal attainment across all treatment groups in each analysis ($p < 0.02$). In all four analyses, at every time point, patients receiving combination therapies experienced greater reductions in SBP and DBP from baseline compared to those on monotherapy (refer to Table 5).

This difference was statistically significant for all combination versus monotherapy doses across all analyses and time points ($p < 0.0001$). Additionally, the rates of achieving BP, SBP, and DBP goals were significantly higher in patients treated with combination therapy compared to those on monotherapy at all measured time points (refer to Table 5). There was also a noticeable trend toward improved BP goal attainment with longer treatment durations and higher doses across all analyses [Neldam S., et al. 2013].

7.4 Role of amlodipine in stroke prevention:

Numerous landmark trials have demonstrated the stroke-protective effects of amlodipine. For example, across nine key studies, amlodipine reduced the incidence of stroke by 40% compared to placebo, by 18% versus ACE inhibitors (ACEIs), by 16% versus ARBs, and by 14% compared to diuretics or beta-blockers. In the ASCOT study, amlodipine-based

Table 5: BP, SBP and DBP goals, and reduction in SBP/DBP therapy

	BP goal (%)	SBP goal (%)	DBP goal (%)	Change in SBP (mmHg)	Change in DBP (mmHg)
Analysis A1 (week 4)					
T80/A10	57.8	61.7	65.3	−33.4 (−34.4, −32.5)	−16.1 (−16.6, −15.5)
T80	30.1	38.5	52.2	−23.1 (−24.6, −21.6)	−10.9 (−11.8, −9.9)
A10	43.1	49.0	47.1	−28.0 (−29.1, −27.0)	−13.0 (−13.7, −12.4)
OR (95% CI) T80/A10 vs. T80	3.33 (2.43–4.60)	2.94 (2.16–4.03)	3.19 (2.34–4.36)	–	–
OR (95% CI) T80/A10 vs. A10	2.37 (1.88–2.98)	2.20 (1.75–2.77)	2.26 (1.77–2.88)	–	–
p-value T80/A10 vs. T80	–	–	–	< 0.0001	< 0.0001
p-value T80/A10 vs. A10	–	–	–	< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	< 0.0001	< 0.0001	< 0.0001	–	–
Analysis A2 (week 2)					
T40/A5	49.2	64.7	60.5	−17.9 (−19.3, −16.6)	−14.5 (−15.4, −13.5)
T40	32.5	50.4	41.5	−12.1 (−14.1, −10.1)	−11/1 (−12.5, −9.7)
A5	34.1	56.7	45.6	−13.9 (−15.3, −12.5)	−11.3 (−12.2, −10.3)
OR (95% CI) T40/A5 vs. T40	2.01 (1.25–3.27)	1.98 (1.19–3.32)	2.16 (1.36–3.47)	–	–
OR (95% CI) T40/A5 vs. A5	2.01 (1.37–2.96)	1.53 (1.01–2.34)	1.91 (1.32–2.79)	–	–
p-value T40/A5 vs. T40	–	–	–	< 0.0001	< 0.0001
p-value T40/A5 vs. A5	–	–	–	< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	0.0005	0.0201	0.0004	–	–
Analysis A3 (week 2)					
T80/A5	40.9	46.7	49.8	−26.6 (−27.4, −25.4)	−12.4 (−12.9, −12.0)
T80	22.3	29.4	44.6	−19.0 (−20.4, −17.6)	−9.4 (−10.3, −8.6)
A5	27.4	36.9	38.6	−21.6 (−22.5, −20.7)	−9.9 (−10.5, −9.4)
OR (95% CI) T80/A5 vs. T80	2.07 (1.50–2.88)	2.19 (1.59–3.03)	1.62 (1.22–2.16)	–	–
OR (95% CI) T80/A5 vs. A5	2.44 (1.96–3.06)	2.06 (1.65–2.57)	1.61 (1.30–2.00)	–	–
p-value T80/A5 vs. T80	–	–	–	< 0.0001	< 0.0001
p-value T80/A5 vs. A5	–	–	–	< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	< 0.0001	< 0.0001	< 0.0001	–	–
Analysis A4 (week 1)					
T80/A5	25.5	29.3	35.6	−24.6 (−25.6, −23.7)	−8.9 (−9.4, −8.4)
A5	16.0	18.7	24.9	−20.4 (−21.5, −19.3)	−7.1 (−7.7, −6.5)
OR (95% CI) T80/A5 vs. A5	2.44 (1.79, 3.36)	2.42 (1.81, 3.27)	1.66 (1.25, 2.20)	–	–
p-value T80/A5 vs. A5				< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	< 0.0001	< 0.0001	< 0.0004	–	–

Table adapted from: Neldam S., et al. 2013.

8.3.2 Studies in patients not controlled on monotherapy

A total of four analyses were conducted, labeled B1 to B4, all at week 4. One analysis was a pooled study (B1), while the others were post hoc evaluations of individual studies (B2–B4). In analyses B1, B3, and B4, a significant treatment difference was observed for reductions in SBP and DBP, as well as for overall blood pressure (BP) and goal attainment for both SBP and DBP among all treatment groups ($p < 0.0001$). For analysis B2, significant differences were found for SBP and DBP reductions, BP, and DBP goal attainment ($p < 0.05$), but not for SBP goal attainment. Across all four analyses, patients receiving combination therapies experienced greater reductions in SBP and DBP from baseline compared to those on monotherapy (refer to Table 5). This difference was statistically significant for all combinations versus monotherapy across all doses in every analysis ($p < 0.05$), with the exception of T40/A5 versus A10 in analysis B1, where the difference was not significant ($p = 0.1312$).

Aside from the SBP goal comparison between T80/A10 and A10, analysis B2 indicated that goal attainment rates for BP, SBP, and DBP were significantly higher in patients receiving combination therapy compared to those on monotherapy [Neldam S., et al. 2013].

Table 6: BP, SBP and DBP goals, and reduction in SBP/DBP (all analyses at week 4)

	BP goal (%)	SBP goal (%)	DBP goal (%)	Change in SBP (mmHg)	Change in DBP (mmHg)
Analysis B1					
A10	35.2	51.4	51.8	−11.0 (−12.5, −9.6)	−8.1 (−9.1, −7.1)
A5	29.0	42.8	42.8	−6.2 (−7.2, −5.2)	−6.1 (−6.8, −5.4)
T40/A5	42.9	56.3	56.7	−12.4 (−13.8, −11.0)	−9.4 (−10.4, −8.4)
T80/A5	48.0	61.8	62.5	−12.8 (−13.8, −11.7)	−9.9 (−10.6, −9.1)
OR (95% CI) T40/A5 vs. A5	2.50 (1.71–3.67)	2.91 (1.98–4.30)	2.13 (1.49–3.06)	–	–
OR (95% CI) T80/A5 vs. A5	2.56 (1.87–3.53)	2.59 (1.88–3.59)	2.49 (1.84–3.39)	–	–
p-value T40/A5 vs. A10	–	–	–	0.1312	0.0363
p-value T40/A5 vs. A5	–	–	–	< 0.0001	< 0.0001
p-value T80/A5 vs. A10	–	–	–	0.0454	0.0036
p-value T80/A5 vs. A5	–	–	–	< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	< 0.0001	< 0.0001	< 0.0001	–	–
Analysis B2					
A10	34.7	49.2	48.8	−6.2 (−7.1, −5.3)	−5.8 (−6.5, −5.1)
T80/A10	41.3	51.1	59.7	−8.3 (−9.3, −7.4)	−7.7 (−8.3, −7.0)
OR (95% CI) T80/A10 vs. A10	1.48 (1.03–2.13)	1.23 (0.86–1.78)	1.62 (1.16–2.28)	–	–
p-value T80/A10 vs. A10	–	–	–	0.0018	0.0002
Overall treatment difference between all groups (p-value)	0.0342	0.2632	0.0053	–	–
Analysis B3					
T40	34.8	55.7	42.4	−5.6 (−7.1, −4.0)	−4.2 (−5.2, −3.2)
T40/A5	63.4	79.1	69.3	−15.6 (−17.0, −13.8)	−10.8 (−11.8, −9.8)
OR (95% CI) T40/A5 vs. T40	4.71 (2.77–8.22)	5.06 (2.76–9.67)	4.98 (2.84–9.04)	–	–
p-value T40/A5 vs. T40	–	–	–	< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	< 0.0001	< 0.0001	< 0.0001	–	–
Analysis B4					
T80	19.8	43.0	22.1	−1.7 (−3.6, 0.2)	−2.9 (−4.2, −1.5)
T80/A5	52.9	78.2	56.3	−14.3 (−16.2, −12.4)	−9.6 (−11.0, −8.3)
OR (95% CI) T80/A5 vs. T80	7.79 (3.44–19.22)	11.02 (4.54–29.9)	8.12 (3.60–19.93)	–	–
p-value T80/A5 vs. T80	–	–	–	< 0.0001	< 0.0001
Overall treatment difference between all groups (p-value)	< 0.0001	< 0.0001	< 0.0001	–	–

Table adapted from: Neldam S., et al. 2013.

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