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The efficacy of olmesartan/amlodipine combination in hypertension treatment – a systematic review



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ABSTRACT

Introduction: Hypertension is the most common non-communicable disease, which persists as a major risk factor of cardiovascular diseases such as stroke, myocardial infarction, and heart failure. Another major problem in clinical practice was the patients' adherence to treatment, directly related to the number of hypertension pills to be taken. Thus, determining the appropriate time duration and action of a hypertensive drug to maintain the blood pressure is needed. Olmesartan is one of the drug compounds frequently used for long-acting anti-hypertensive treatment. It is often combined with amlodipine; however, their combination remains unclear to provide equal efficacy and safety. Thus, in this article, we systematically summarize the combination of Olmesartan with amlodipine.

Methods: This systematic literature review was extracted from Science Direct and Pubmed to identify randomized clinical trials (RCT) of the outcome of the Olmesartan/amlodipine effect compared with other hypertension regimens by using PRISMA guideline 2009. The methodological quality of the included

studies was assessed independently by two reviewers using The Cochrane Collaboration's RoB 2 tool.

Results: We evaluated twelve studies in the last ten years, and there were four studies with an intention-to-treat protocol (25% of articles had some concern, and 75% had a low risk of bias.) and eight studies with per-protocol analysis (37,5% of articles were concerned, and the rest had a low risk of overall bias). We also presented the efficacy and safety outcomes of the study reviewed.

Conclusion: Hypertension is a common non-communicable disease, and treatment approaches for hypertension vary widely. Administration of combination drugs is a good approach in reducing the dose of drug administration and reducing the incidence of side effects in monotherapy. Inhibiting the RAA system by olmesartan and reducing vascular smooth muscle tone by amlodipine gives better results and can be a safe and effective option for lowering blood pressure in hypertensive patients. The side effects observed were not severe and only observed in a few cases, making it an option to treat hypertension.

Keywords: amlodipine, efficacy, olmesartan, hypertensive drugs .

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INTRODUCTION

Hypertension is the most common non-communicable disease, which persists as a significant risk factor of cardiovascular diseases such as stroke, myocardial infarction, and heart failure.¹ An analysis of data from several countries reported that the global trend of hypertension as the most life-threatening disease in South-East Asia increased. In 2009, Myanmar reported around 30.1% the prevalence of hypertension, in the same year, Sri Lanka established patient hypertension around ≥ 18 years in 2005-2006 was 23.7%, Malaysia in 2011 was around 43.5% among ≥ 30 years old, Vietnam was 25.1%

(≥ 25 years in 2002-2008). Meanwhile, in Indonesia, the prevalence rate of hypertension has dramatically increased from 25.8% in 2013 to 34.1% in 2018.² Other studies conducted by Hussain *et al.* found that around 47.8% of patients diagnosed with hypertension in 40 years older.³ Data hypertension in Indonesia from 2013 until 2018 has dramatically increased from 25.8% to 34.1%.⁴

Hypertension was high risk around people that concerned about some comorbidities such as diabetes.² It was already proven by the National Health and Nutrition Examination. Their survey reported that hypertension is much higher in patients with diabetes (77%).

A significant concern in hypertension patients because type 2 diabetes mellitus (T2DM) is also associated with an increased risk of developing coronary heart disease. Moreover, achieving BP control in hypertension and comorbid diabetes patients can be more complicated than hypertensive patients without this additional risk factor.¹ Another major problem in clinical practice was the patients' adherence to treatment, which is directly related to the number of hypertension pills to be taken.⁵ Result of study in Palangkaraya, Indonesia, showed that patients' adherence to treatment was moderate using Morisky Medication Adherence Scale (MMAS) evaluation.⁶

Boratas and Kilic's study showed patients with a once-daily intake of hypertensive medication in line with higher adherence rates. It was proven by a high proportion of status patients with regularly intake anti-hypertensive drugs.⁷

Reducing the number of pills taken using fixed-dose combinations improved adherence by reducing the total number of pills. Thus, determining the appropriate time duration and action of a hypertensive drug to maintain the blood pressure is needed. Anti-hypertensive drugs with a mechanism of action over 24 hours (long-acting drugs effect) are beneficial to the patients. Olmesartan is one of the drug compounds frequently used for long-acting anti-hypertensive treatment.⁵ Olmesartan acts as a reversible and selective angiotensin-II receptor blocker to undermine the renin-angiotensin-aldosterone system. It binds to angiotensin type I receptors (AT-I) and angiotensin type II receptors (AT-II). The competitive binding of Olmesartan antagonizes helps lower blood pressure by reducing arteriolar resistance through vasodilation, lowering blood pressure.⁸

In a recent study, Olmesartan was combined with amlodipine. Its combination provides a better outcome. According to the Derosa *et al.* study, Olme/Amlo combination can be a safe and effective option for reducing blood pressure, improving insulin sensitivity, and decreasing inflammatory markers.⁹ This study in line with Ram *et al.* and Bramlage *et al.*^{10,11} However, combination olmesartan with amlodipine remains unclear to provide equal efficacy and safety. Thus, in this article, we systematically summarize the combination of Olmesartan with amlodipine. We hope this article could conclude an appropriate dosage and its outcome.

METHODS

Systematic Literature Review

This systematic literature review (SLR) was collected from Science Direct and Pubmed to identify randomized clinical trials (RCT) of the outcome of the Olmesartan/amlodipine effect compared with other hypertension regimens. This SLR accords with PRISMA guideline 2009, with the study's time frame, is the

last ten years. In addition, several inclusion criteria for this SLR, such as the study, were using a human sample diagnosed with primary hypertension, evaluating baseline blood pressure or blood pressure before the olmesartan/amlodipine intervention. After the intervention, a minimal intervention was two months. In contrast, exclusion criteria in this study were full-text inaccessible, sample less than fifty, high risk of bias articles, and using the English language.

Eligibility Criteria and data extraction

The conditions for the inclusion of the analysis included: (1) randomized controlled trials (RCTs), (2) evaluating the efficacy of Olmesartan/amlodipine in primary hypertension patients, (3) Research in the last ten years, (4) providing sufficient data of blood pressure before intervention. However, the following requirements were found: (1) an insignificant subject was identified; (2) research variables are not available in the results section; (3) the result section is not available. Data extraction information was derived from each analysis concerning (1) first author's name and year of publication, (2) study type, (3) mean age, (4) number of sample, (5) race, (6) BMI and (7) condition of hypertension (duration of hypertension, comorbid disease, SBP/DBP

pre-treatment and post-treatment, dose of Olmesartan/amlodipine, and adverse event). Two independent authors carried out data extraction to prevent human mistakes. In the event of disagreements, a consensus or debate has been established.

Quality Assessment

The methodological quality of the included studies was assessed independently by two reviewers using The Cochrane Collaboration's RoB 2 tool for Randomised Controlled Trials (RCTs), which has five domains of bias assessment, including randomization process, deviations from intended intervention, missing outcomes data, measurement of the outcomes, and selection of the reported result. We also assessed the overall bias based on the mark at five domains. All analysis percentages are presented using a graph (Figure 1 and 2).

Risk of Bias Assessment

Our risk of bias analysis was using Cochrane RoB 2 tools. The risk of bias analysis compared the outcome of olmesartan/amlodipine intervention and other hypertension drugs with or without comorbidities. All of the articles enroll based on inclusion and exclusion criteria that mostly have a low risk of bias in each clinical trial study. We evaluated

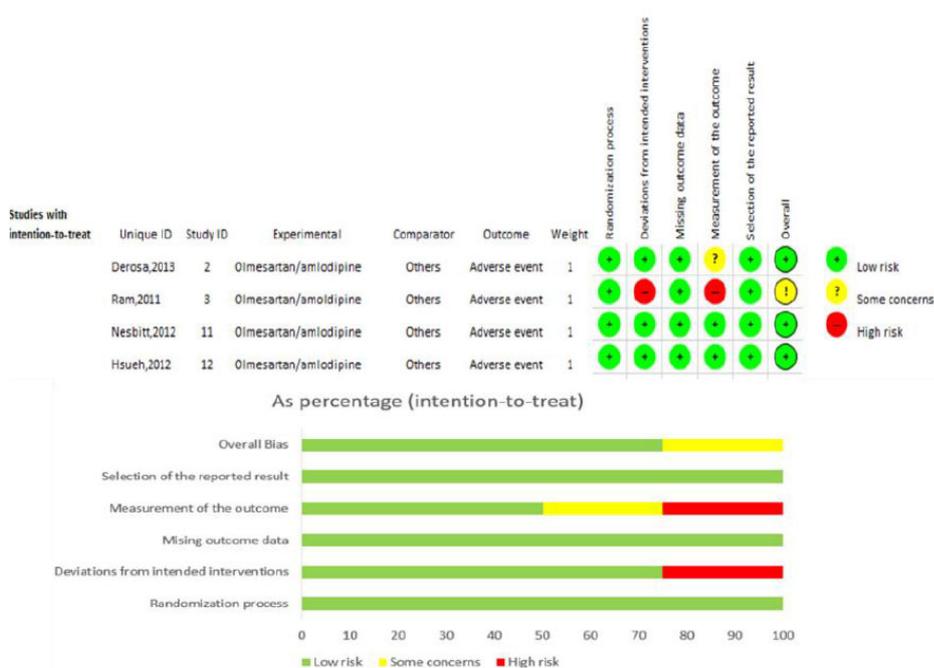


Figure 1. RoB 2 tools risk of bias analysis in intention-to-treat studies.

twelve studies in the last ten years, and there were four studies with an intention-to-treat protocol (Figure 1) and eight studies with per-protocol analysis (Figure 2). Overall bias in intention-to-treat

protocol there were 25% articles had some concern, and 75% had a low risk of bias. According to each journal, 25% of articles in high risk at domain 2 (deviation from intended interventions) due to deviation of intervention likely to have affected the

outcome probably existed. In the per-protocol study, there were 25% articles high risk and 25% articles some concerns at domain 4 (measurement of the outcome. On the other hand, 37,5% of articles were concerned, and the rest had a low risk of overall bias. Specifically, 25% had some concern in domain 1 (randomization process), which does not explain the randomization technique, and 25% of articles had some concern in domain 4 (measurement of the outcome).

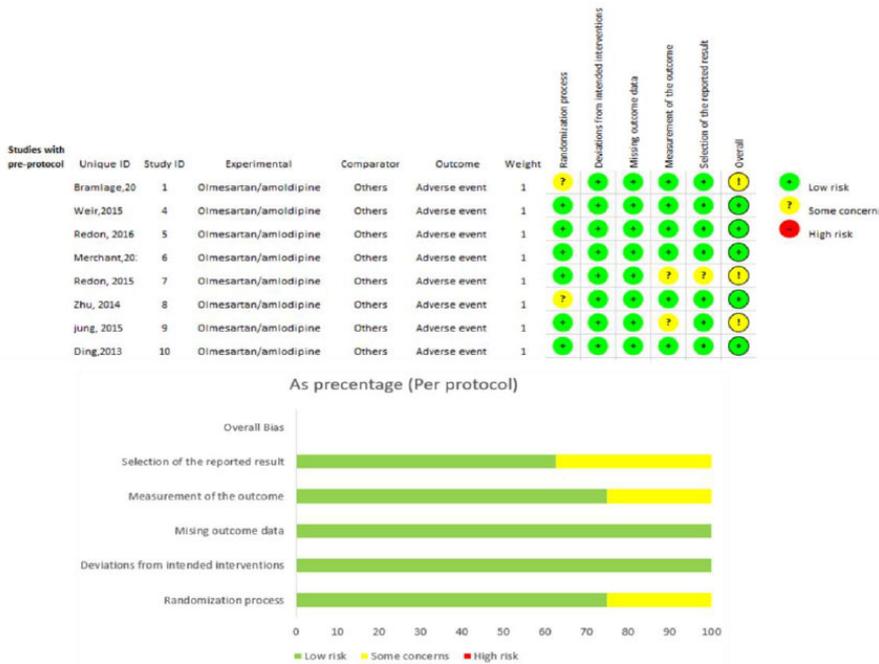


Figure 2. RoB 2 tools risk of bias analysis in per-protocols studies.

RESULTS

We identified articles from PUBMED (42 articles) and ScienceDirect (63 articles). Thus, the total number of articles was 105. After removing the duplicate, we found that the articles were 97. The articles were screened three times, the first screen by the title or abstract related to the topic, the second screen by the accessibility of the full text and the third screen matching the inclusion and exclusion criteria. Finally, there were 12 studies enrolled (Figure 3).

Baseline characteristics of the sample from included studies

According to the review, most of the articles' study design was RCT (10 articles) after that clinical trial (2 articles). All trials evaluated the use of Olmesartan (OLM) and amlodipine (AML) as a combination therapy. There were various sample sizes and ages but similar outcomes. This study presents data on characteristics associated with treatment outcomes for hypertensive patients, namely race, BMI, duration of hypertension, and comorbid disease (Table 1).

Primary efficacy and Safety Outcomes

In some different studies, the treatment (Olmesartan/amiodipine) was mainly similar (20-40 mg/5-10 mg). We present pre and post-treatment SBP and DBP data to show the patient's blood pressure changes. Direct treatment effects of combination OLM/AML for primary efficacy and safety outcome are synthesized and presented in (Table 2).

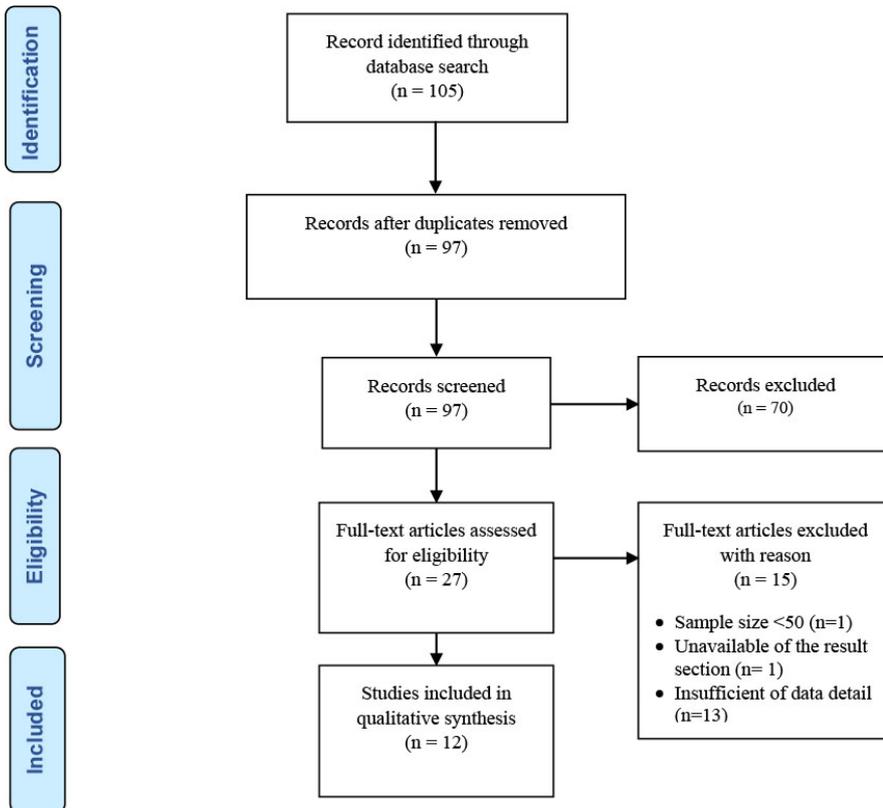


Figure 3. PRISMA flowchart of systematic literature review.

DISCUSSION

Mechanism of Action of Olmesartan and Amlodipine

Olmesartan is a hypertension drug from the Angiotensin Receptor Blocker (ARB) class. Olmesartan works by inhibiting the Renin-Angiotensin-Aldosterone (RAA) system by inhibiting Angiotensin II type I receptors (AT₁-R).¹² Olmesartan administered in the form of prodrug ester, which will rapidly undergo de-esterification through the help of the arylesterase enzyme. Olmesartan has a bioavailability of 26% with a half-life of about 13 hours. Olmesartan also has good plasma protein binding (99%) with a high volume distribution rate of around 17 Liters.¹³

In general, Olmesartan works by inhibiting AT₁-R. Inhibition of AT₁-R can inhibit the effect of vasoconstriction, reduce sodium and water retention, and reduce cell proliferation and hypertrophy. Inhibition of AT₁-R provides an opportunity for AT₂-R receptors with the opposite system of action. Inhibition of AT₁-R by Olmesartan will allow AT₂-R to

bind to Angiotensin II, which can cause inhibition of cell hypertrophy, inhibition of cell proliferation, and vasodilation through the formation of nitric oxide. This mechanism causes a decrease in blood pressure.¹²⁻¹⁴

On the other hand, Amlodipine is a calcium channel blocker (CCB) dihydropyridine type hypertension drug. Amlodipine has good bioavailability (80%) and a long half-life that allows administration in a single daily dose. Amlodipine also has a gradual action and does not provide significant reflex neuroendocrine activation. Amlodipine inhibits calcium influx into vascular smooth muscle by blocking voltage-dependent L-type calcium channels. This action causes intracellular calcium levels to decrease so that the contractility of vascular smooth muscle decreases, there is an increase in vascular smooth muscle relaxation and vasodilation, causing a decrease in blood pressure.^{15,16}

The use of combinations of several types of anti-hypertensives with different mechanisms of action has shown better blood pressure results than the use of

single anti-hypertensives. Several previous studies have shown that the administration of additional anti-hypertensives can reduce blood pressure by 10-15 mmHg. In addition, the administration of a combination of anti-hypertensives can also increase compliance and reduce cardiovascular morbidity and mortality.¹⁷

Side Effects

The adverse events arising from the combined use of olmesartan and amlodipine are highly variable. Some of the most common adverse events found in patients were peripheral edema, headache, and dizziness.^{1,9,11,18-22} Peripheral edema is an adverse event caused by the consumption of calcium channel blockers (CCB), which in this case is amlodipine. Amlodipine is known to cause peripheral edema due to arteriolar dilatation leading to an increase in the pressure gradient between arteriolar and venular capillaries, leading to extravasation of intravascular fluid.²³ Peripheral edema caused by amlodipine and other CCBs of the dihydropyridine group is also known not to be associated with water and salt

Table 1. An overview of characteristic sample.

Study (years)	Study types	Age (mean)	Sample Size	Race	BMI	Duration of HT (month)	Comorbid
Ding (2013)	RCT	66.5 ± 8.8	157	-	28.5 ± 4.4	6	DMT2, CKD, albuminuria
Hsueh (2012)	Clinical Trial	58.0 ± 11.1	494	Caucasian, Black, Asian	26.1 ± 2.7	-	DMT2, metabolic syndrome
Jung (2015)	RCT	52.4 ± 11.7	376	-	25.3 ± 3.2	39.4 ± 52.2	DMT2
Nesbit (2012)	Clinical Trial	55.1 ± 11.8	807	White, black, Asian, American-Indian, Alaskan native	30.7 ± 6.4	-	DMT2
Zhu (2014)	RCT	53.2 ± 9.6	258	-	26.3 ± 3.1	100.4 ± 101.2	DMT2, dyslipidemia
Redon (2015)	RCT	58.91 ± 7.47	128	-	28.69 ± 3.38	74.46 ± 11.46	DMT2, dyslipidemia
Redon (2016)	RCT	58.7 ± 8.3	88	-	29.7 ± 3.3	102.7 ± 98.5	DMT2, dyslipidemia
Weir (2013)	RCT	51.3 ± 9.0	771	White, black, Asian, American-Indian, Alaskan native	31.7 ± 6.6	-	DMT2
Merchant (2013)	RCT	50.0 ± 12.5	66	African-American	36.4 ± 5.3	-	Metabolic syndrome
Ram (2011)	RCT	59.1 ± 9.5	164	Caucasian, Black, Asian	32.8 ± 5.9	-	DMT2
Bramlage (2013)	RCT	56 ± 15	50	Caucasian	29 ± 5	-	DMT2
Derosa (2013)	RCT	55.9 ± 5.8	95	Caucasian	26.4 ± 0.9	-	Dyslipidemia, CHD, stroke

retention; this is because these drugs are natriuretic. Previous study have shown that vasodilation of the venules and combination therapy using an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) can reduce the incidence of peripheral edema due to CCB use.²⁴ The use of olmesartan is known to cause headaches and dizziness commonly; this was found in several studies that we reviewed.^{1,9,11,18–22,25} In addition to the three adverse events found from the combination of olmesartan and amlodipine, there were other adverse events in much smaller amounts, including nausea and muscle pain, hypotension, hypokalemia, polyuria, and others that were not severe.

Study Advantages and Limitations

This systematic review has the advantage of discussing various studies that discuss the effectiveness of the combined administration of Olmesartan and Amlodipine in hypertensive patients of varying degrees without taking into account racial differences and comorbid background. This study allows a broader picture of the effectiveness of this combination in its application in various communities and various comorbid disease background conditions. This systematic review also has potential limitations. The exclusion of non-English manuscripts allows for the different results obtained not to be recorded in this review so that the data collected becomes more limited. Our review is also based on the criteria of adult age only. It does not distinguish it from the elderly, so the efficacy and side effects found cannot be generalized to the elderly group.

CONCLUSION

Hypertension is a common non-communicable disease, and treatment approaches for hypertension vary widely. Administration of combination drugs is a good approach in reducing the dose of drug administration and reducing the incidence of side effects in monotherapy. Inhibiting the RAA system with olmesartan and reducing vascular smooth muscle tone by amlodipine gives better results and can be a safe and effective option for lowering

blood pressure in hypertensive patients. The side effects observed were not severe and only observed in a few cases, making it an option to treat hypertension.

CONFLICT OF INTEREST

We declare that there was no conflict of interest in this study.

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None.

AUTHOR CONTRIBUTION

All authors contributed equally in this study.

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Table 2. An overview of Olmesartan/Amlodipine to decrease SBP/DBP among hypertension patient.

Study (years)	Study types	Sample Size	Pre-Treatment		Post-Treatment		Dose Olmesartan/Amlodipine	Duration of Intervention (month)	Adverse Event	Outcome
			SBP	DBP	SBP	DBP				
Ding (2013)	RCT	157	138.8 (137.0-140.6)	-	124.1 (121.9-126.3)	-	40/10 mg	2	<ul style="list-style-type: none"> • Edema, • Headache, • dizziness/vertigo • Hypotension • diarrhea 	Patients receiving combination therapy (OLM/AML) achieved BP goal than those treated with placebo or monotherapy. An OLM/AML treatment regimen provided effective and safe BP control in obese patients with hypertension uncontrolled.
Hsueh (2012)	Clinical Trial	494	153.5	93.5	135	83.2	40/10 mg	5	<ul style="list-style-type: none"> • Peripheral edema, • Dizziness, • Hypotension • Headache 	OLM/AML was significantly decreased SBP and was well tolerated with no serious adverse events associated with medication.
Jung (2015)	RCT	376	154.6 ± 11.9	103.3 ± 3.0	120.3 ± 13.0	80.2 ± 8.1	20/5 mg	3	<ul style="list-style-type: none"> • Headache, dizziness • Palpitation, chest pain, flushing, orthostatic hypotension • Cough • Hematuria • Dyspepsia, abdominal discomfort, diarrhea, dry mouth, gastritis, nausea, reflux esophagitis • Respiratory infection • Musculoskeletal disorder • Pruritus • Insomnia 	OLM/AML was significantly decreased SBP and was well tolerated with no serious adverse events associated with medication.
Nesbit (2012)	Clinical Trial	807	154.2	92.5	139.5	84.5	20/5 mg	5	-	After failed monotherapy, treatment algorithm based on OLM/AML was safe and improved BP control in patients with hypertension and DMT2.

Study (years)	Study types	Sample Size	Pre-Treatment		Post-Treatment		Dose Olmesartan/Amlodipine	Duration of Intervention (month)	Adverse Event	Outcome
			SBP	DBP	SBP	DBP				
Zhu (2014)	RCT	258	143	94.7	128.4	82.8	20/5 mg	2	<ul style="list-style-type: none"> Increased bilirubinemia, blood creatine phosphokinase, blood cholesterol and blood triglycerides Hypokalemia Decreased WBC count Dizziness, headache, cough Peripheral edema 	OLM/AML was effective for decrease BP in mild to moderate hypertensive patients with inadequate BP control on monotherapy
Redon (2015)	RCT	128	155.17 ± 10.22	96.31 ± 4.99	138.57 ± 13.77	84.61 ± 8.41	20/5 mg for 6 weeks, 40/10 mg for 18 weeks	6	-	OLM/AML is safe, well-tolerated, and as effective as the combination in the control of essential hypertension in patients with diabetes mellitus.
Redon (2016)	RCT	88	157 ± 10	96 ± 5	137 ± 14	83 ± 9	20/5 mg	4.5	-	The OLM/AML combination is safe and well-tolerated in diabetic patients. OLM/AML provides longer-lasting efficacy in terms of CBP reduction
Weir (2013)	RCT	771	153.5	94.1	133.4	82.8	40/10 mg	5	-	Fixed-dose OLM/AML combination therapy effectively lowered BP and achieved BP goals in patients aged ≥ 65 and 65 years with hypertension previously uncontrolled on monotherapy. The treatment regimen was well tolerated irrespective of patient age.

Study (years)	Study types	Sample Size	Pre-Treatment		Post-Treatment		Dose Olmesartan/ Amlodipine	Duration of Intervention (month)	Adverse Event	Outcome
			SBP	DBP	SBP	DBP				
Merchant (2013)	RCT	66	166 ± 16	100 ± 16	130 ± 18	83 ± 14	20/5 mg for 2 weeks, 40/10 mg for 12 weeks	3.5	-	Treatment with OLM/AML has good efficacy in reducing reactive oxygen species generation and production of inflammatory and oxidative biomarkers in a hypertensive African- American population with features of the metabolic syndrome
Ram (2011)	RCT	164	144.3 ± 0.9	81.6 ± 0.7	124.3 ± 0.9	70.4 ± 0.6	40/10 mg	3	<ul style="list-style-type: none"> • Peripheral edema • Dizziness, • Headache, • Presyncope, • Hypotension, • Orthostatic hypotension 	OLM/AML-based titration regimen was well tolerated and effectively lowered BP throughout the 24-hour dosing interval in patients with hypertension and DMT2
Bramlage (2013)	RCT	50	160 ± 12	94 ± 9	140 ± 18	84 ± 11	40/10 mg	3	<ul style="list-style-type: none"> • Peripheral edema, • Hypotension, • Muscle pain 	Patients of Caucasian ethnicity with moderate essential hypertension, uncontrolled on candesartan monotherapy, experienced a further drop in BP when receiving a fixed-dose combination of OLM/AML
Derosa (2013)	RCT	95	148.8 ± 7.5	98.6 ± 6.4	120.7 ± 4.2	77.4 ± 2.5	20/5 mg	12	<ul style="list-style-type: none"> • Edema, • Cough, • Hypotension, headache, • Rush, • Stomach pain 	OLM/AML combination can be a safe and effective option to reduce blood pressure, improve insulin sensitivity and decrease inflammatory markers.