Original Article

Efficacy and Safety of Combination therapy of Amlodipine along with Rosuvastatin versus Amlodipine Monotherapy in Hypertensive Patients with Dyslipidaemia: A Randomised Controlled Trial

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Received: 16-05-2024; **Revised:** 28-07-2024; **Accepted:** 10-08-2024; **Published on:** 15-08-2024.

ABSTRACT

Background: Even with the success of antihypertensive and lipid-lowering medications in reaching target values, the percentage of patients having blood pressure under control is still low. Patients with both ailments typically have low compliance since many require continuous treatment and take a long time to receive a diagnosis before the implications of both diseases manifest. The purpose of this study was to evaluate the safety and effectiveness of amlodipine monotherapy against combination therapy with amlodipine along with rosuvastatin in hypertensive patients with dyslipidaemia.

Methods: 120 hypertensive patients with dyslipidaemia were randomised into Group MT (monotherapy with Amlodipine 10 mg once daily) and Group CT (recombination therapy with rosuvastatin 20 mg along with amlodipine 10 mg once daily). At one and three months after randomization, all patients were asked to visit the institution in order to assess the safety and effectiveness. The unpaired t-test was used to evaluate end-points like mean SBP, DBP, LDL-C, total cholesterol (TC), triglyceride (TG), and HDL from baseline to one month as well as three months.

Results: SBP in CT group was significantly lesser (132.83 ± 8.26) as compared to MT group (137.2 ± 8.46) (p=0.005). There was significantly greater improvement in lipid profile in CT group as compared to MT group. However, there was also some slight improvement in lipid profile in patients receiving monotherapy with amlodipine. There was no significant difference between CT group and MT group with respect to ADRs.

Conclusion: The single-pill FDC "Rosuvastatin-Amlodipine" constitutes a sensible combination of two safe, well-tolerated, evidence-based, and effective medications to treat two major risk factors, such as hypertension and hypercholesterolemia.

Keywords: Rosuvastatin, Amlodipine, Hypertension, Dyslipidaemia.

INTRODUCTION

Globally, cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality, exerting a substantial impact on public health.[1]

This has led to a significant deal of work being done in recent years by scientific societies, health care providers within their clinical settings, and "National Healthcare Systems" to establish and implement effective preventative interventions with the aim of minimizing the monetary burden of CVD.

Current methods of preventing cardiovascular disease are based on the monitoring and management of cardiovascular risk factors on a scale, that expands the goals of therapy for each individual based on their expected global risk profile. Due to the clustering of three primary cardiovascular risk variables in one patient—dyslipidemia, diabetes, as well as hypertension—patients may require multiple drugs to achieve treatment goals. [2] In addition, the number of risk factors (RFs) increases exponentially with the likelihood of developing cardiovascular disease. [3] A comprehensive observational study discovered that the likelihood of major CVS events had been six times greater in hypertensive patients having increased total cholesterol as well as LDL in addition to smoking habits than in non-smoking subjects who have increased blood pressure (BP) as well as satisfactory cholesterol levels. [4]

A number of scientific investigations support the pretty reasonable hypothesis that prompt preventative therapy focused on reducing key RFs could potentially avoid or at least delay the advancement of organ damage in addition to lowering the elevated degree of CVS risk. [5]

Even with the success of antihypertensive and lipid-lowering medications in reaching target values, the percentage of patients with blood pressure under control is still low. In one study, only 9% of hypertension patients with dyslipidaemia achieved the target blood pressure and lipid profile levels.[6] Low compliance may be part of the cause of this inadequate state.[6] Patients with both ailments typically have low compliance since many require long-term medication and take a long time to receive a diagnosis before the implications of both diseases manifest. Moreover, polypharmacy and intricate treatment regimens are linked to decreased compliance.[7] Poor compliance increases the risk of CVD along with its death toll, increasing the yearly financial burden globally.[7-9]

Previous studies have shown that combined pharmacotherapy for dyslipidaemia as well as hypertension (HTN) seems to reduce the incidence of CVD-related events compared to standalone treatment. [8, 10] These results have brought attention to the importance of multimodal intervention in relation to CVD hazards in clinical settings. [11–13]

Previous studies have demonstrated the safety and efficacy of atorvastatin + amlodipine taken together as a single medication for patients with dyslipidaemia and hypertension. As a result, the FDC can now be purchased commercially and used in real clinical situations. [14–16] Even though rosuvastatin is one of the best statins for people with dyslipidaemia, very little study has been conducted regarding single-pill combinations of this medication.

The purpose of this study was to evaluate the safety and effectiveness of amlodipine monotherapy against combination therapy with amlodipine along with rosuvastatin in hypertensive patients with dyslipidaemia.

MATERIALS AND METHODS

This randomized controlled trial with parallel 1:1 allocation was conducted on hypertensive patients with dyslipidaemia in Department Pharmacology with collaboration from Department of General Medicine of a tertiary care healthcare facility of eastern India from November 2023 to March 2024. Informed consent was taken from hypertensive patients with dyslipidaemia in accordance with GCP and declaration of Helsinki.

Sample Size: With 22.8 mmHg mean change of SBP in combination therapy group as compared to 15.9 in amlodipine group with SD of 11 as per previous research [17], minimum sample size required to achieve 90% power with 0.05 alpha value was found to be 106. So, 120 hypertensive patients with dyslipidaemia were randomized into two groups to cope up with expected attrition rate of 5%.

Inclusion Criteria:

- Patients of any gender who are at least 19 years old
- Patients diagnosed with HTN according to JNC 8 norms, with a DBP of 90 to 99 mm Hg and an SBP of 140 to 159 mm Hg [18]
- Patients with dyslipidaemia and borderline high TG levels from 150 to 199 mg per dl as well as LDL-C from 130 to 159 mg per dL according to AHA/ACC recommendations [19]

Exclusion Criteria:

- Patients whose blood pressure differs in both arms
- Patients suffering from secondary hypertension
- Patients who have previously experienced an adverse reaction to rosuvastatin and amlodipine
- Patients suffering from valvular heart disease, ischemic stroke, and CAD

After a wash-out/run-in phase, patients who satisfied the randomization conditions were eventually enrolled and randomly assigned to either of 2 treatment arms using randomly generated numbers from the internet:

Group CT: Combination therapy of rosuvastatin 20 mg along with amlodipine 10 mg OD

Group MT: Amlodipine 10 mg OD

All patients were asked to visit the facility one and three months after randomization in order to assess the safety and effectiveness of the treatment, along with they were instructed to maintain adherence to prescription of a minimum 80 percent at each visit during the course of the study.

Outcome Measures:

- Mean change in SBP from baseline to 1 and 3 months
- Mean change in DBP from baseline to 1 and 3 months
- Mean change in LDL-C, TC, TG and HDL from baseline to 1 and 3 months

After getting allocated at random, patients were instructed to visit the study site on a monthly basis to have their blood pressure measured and have laboratory tests performed. It was instructed to the study participants to monitor their blood pressure each day. We assessed the degree of safety by compiling adverse event (AE) data, reviewing medical records, diagnostic test findings, ECG, as well as physical examination findings at each visit. The therapy groups were compared with respect to adverse medication responses. Additionally, a comparison was done among the proportion of individuals whose serum AST or ALT levels reached twice in a row over three times beyond the normal threshold and the overall incidence of myopathies.

Statistical Analysis:

Using Microsoft Excel 2019, results from hypertensive patients with dyslipidaemia were tabulated and then imported into Graph Pad version 8.4.3 for additional statistical analysis. Age, blood pressures, and lipid profile parameters were examples of continuous variables that were represented as mean ± SD (standard deviation). The unpaired t test was used to assess the statistical significance of the differences in continuous data between the CT and MT groups. Gender as well as adverse events were categorical data that were presented as percentages or frequencies, and they were compared using the Fisher's exact test or chi-square test. A statistically significant p-value of 0.05 or lower was considered to be the cut-off.

RESULTS

In this RCT, 50 patients each in CT group and MT group completed 3 months of follow-up.

Table 1: Comparison of Baseline Demographic and Clinical Characteristics between CT Group and MT Group

Parameter	Group CT (n = 60)	Group MT (n = 60)	P-Value
Age in years (mean ± SD)	61.1 ± 10.44	63.83 ± 11.33	0.1725
Gender (n) Male Female	 35 25	 32 28	0.7133**
BMI in kg/m^2 (mean ± SD)	26.27 ± 2.61	26.67 ± 2.94	0.4322*
Duration of Hypertension in months (mean ± SD)	111.92 ± 13.16	115.25 ± 13.92	0.1807*
Duration of Dyslipidaemia in months (mean ± SD)	70.22 ± 7.53	74.08 ± 8.58	0.01*

*Unpaired t-test **Fisher's Exact Test

Most of the hypertensive patients with dyslipidaemia were males of age group 50-70 years. There was no significant between CT group and MT group with respect to age, sex, BMI, duration of hypertension and dyslipidaemia (p>0.05).

Table 2: Comparison of Blood Pressure between CT Group and MT Group

Parameter	Time	Group CT (n = 50)	Group MT (n = 50)	P-Value (Unpaired t Test)
Systolic Blood Pressure	Baseline	155.05 ± 9.97	152.08 ± 9.78	0.1022
	1 Month	144.32 ± 8.86	148.12 ± 8.95	**0.0211**
	3 Months	132.83 ± 8.26	137.2 ± 8.46	**0.005**
Diastolic Blood Pressure	Baseline	94.03 ± 7.46	92.32 ± 9.11	0.2629
	1 Month	91.68 ± 7.6	90.27 ± 9.08	0.3582
	3 Months	87.01 ± 7.37	89.5 ± 8.61	0.0914

SBP in CT group was significantly lesser (132.83 ± 8.26) as compared to MT group (137.2 ± 8.46) (p=0.005).

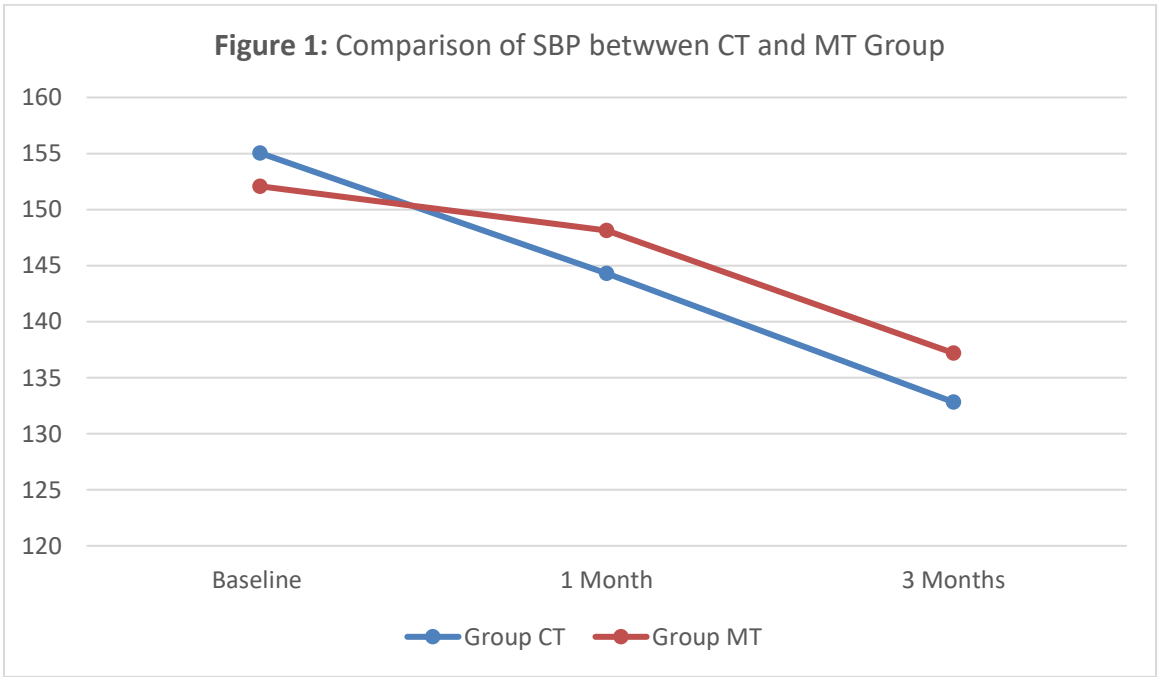

Figure 1: Comparison of SBP betwwen CT and MT Group

Table 3: Comparison of Lipid Profile between CT Group and MT Group

Parameter	Time	Group CT (n = 50)	Group MT (n = 50)	P-Value (Unpaired t Test)
LDL	Baseline	152.31 ± 17.79	153.42 ± 15.14	0.7135
	1 Month	141.49 ± 13.53	152 ± 14.93	**0.0001**
	3 Months	124.4 ± 12.23	148.9 ± 14.6	**<0.0001**
TC	Baseline	215.08 ± 21.53	220.27 ± 20.63	0.1802
	1 Month	199.07 ± 20.23	216 ± 20.39	**<0.0001**
	3 Months	173.97 ± 18.57	207.05 ± 19.61	**<0.0001**
TG	Baseline	177.81 ± 19.12	180.9 ± 18.11	0.3653
	1 Month	166.34 ± 15.81	178.33 ± 17.65	**0.0002**
	3 Months	147.75 ± 13.62	174.56 ± 17.72	**<0.0001**
HDL	Baseline	39.58 ± 6.02	37.46 ± 7.99	0.1034
	1 Month	42.11 ± 4.74	38.6 ± 7.49	**0.0027**
	3 Months	45.09 ± 4.55	40.77 ± 5.95	**<0.0001**

There was significantly greater improvement in lipid profile in CT group as compared to MT group. However, there was also some slight improvement in lipid profile in patients receiving monotherapy with amlodipine.

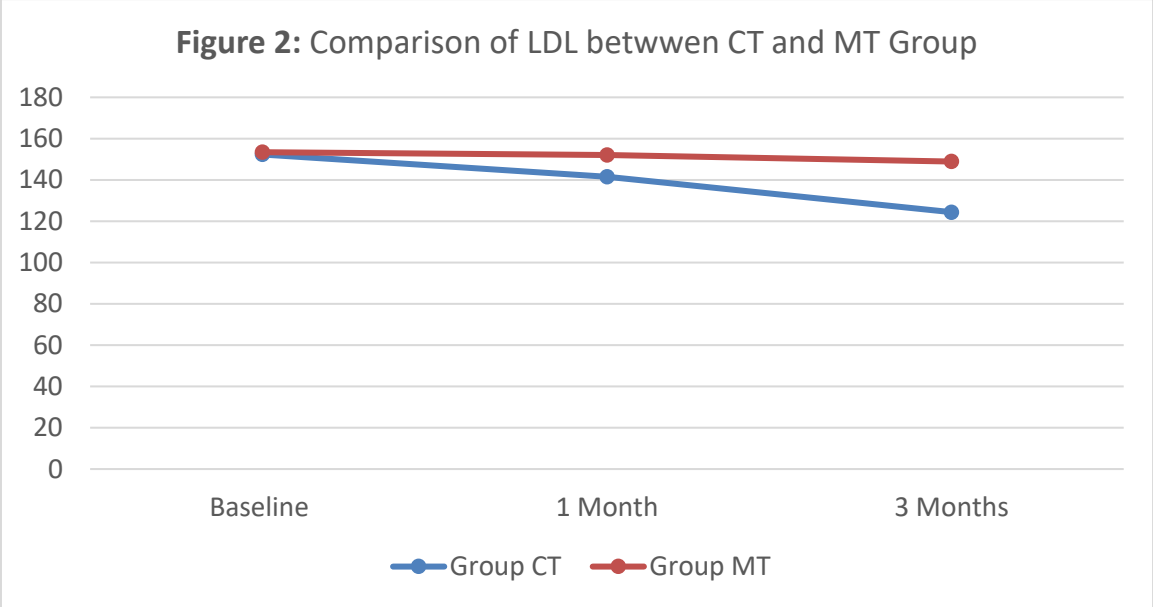

Table 4: Comparison of Adverse Drug Reactions between CT Group and MT Group

ADR	Group CT (n = 60)	Group MT (n = 60)
Peripheral Oedema	4	2
Headache	1	3
Dizziness	1	0
Total	6	5

There was no significant difference between CT group and MT group with respect to ADRs. During the trial duration, no group suffered adverse drug reactions (ADRs) that led to the study drug being stopped or to death. No patient developed myopathy and blood AST or ALT values that were more than three times higher than the standard threshold for two tests in a row. None of the patients had any clinically significant changes to their vital signs including ECG.

DISCUSSION

In hypertensive patients with dyslipidaemia, the combination of rosuvastatin along with amlodipine had superior lipid-modulating as well as blood pressure-lowering effects compared to amlodipine monotherapy in this randomized controlled trial. Furthermore, while maintaining a manageable level of safety, the

combination's goal level attainment rate was significantly greater as compared to monotherapy.

Many attempts are being made to create a free-drug conjugate (FDC) for the management of various disorders, as administering an FDC rather than using a regimen including free-drug components may increase efficacy through improved compliance. [20] When comparing a regimen containing free-drug components, the FDC reduced the likelihood of non-compliance by twenty-six percent per a previous meta-analysis. [20] It is well-established that combining amlodipine along with atorvastatin to patients with HTN with dyslipidemia is effective as well as safe. Additionally, single-pill FDC of both of these medications have been shown to improve compliance, which in turn reduces the risk of cardiovascular disease (CVD). [21]

Rosuvastatin is "a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor" and constitutes one of the most efficient statins. It is easily absorbed, reaches peak levels in the blood quickly, has a long half-life, and is used widely around the world.[22] A very few studies have looked at the administration of rosuvastatin along with amlodipine in a combination regimen for patients with HTN plus dyslipidemia, in contrast to atorvastatin along with amlodipine investigations. Interestingly, new studies have demonstrated the efficacy and safety of multiple combinations containing rosuvastatin plus amlodipine.[23, 24] It is crucial to determine both the safety and effectiveness of the single combination consisting of rosuvastatin along with amlodipine because results on the safety and effectiveness of an FDC can sometimes not be positive.[25]

It is unclear exactly how lipid alteration as well as blood pressure reduction together function in CT group, aside from the possible gain in compliance through reduced pill burden. Statins are thought to assist in restoring the function of endothelial cells and hence somewhat reduce arterial pressure by reducing oxidative stress, minimizing inflammatory reactions, and enhancing Nitric oxide (NO) bioavailability.[26] Comparatively, amlodipine has been demonstrated to possess anti-inflammatory properties as well as antioxidant stress characteristics in addition to lowering blood pressure; these features may aid in the management of lipids.[27]

It's interesting to note that following both one and three months, blood pressure dropped more in the trial subjects receiving amlodipine with rosuvastatin than in those getting amlodipine monotherapy. [28]

Research has demonstrated a little but notable reduction in blood pressure, along with the hypotensive properties of statins—aside from their cholesterol-lowering benefits—have continued to draw attention.[29, 30] However, there is a dispute that produces contradictory results. [31, 32] This is due to the fact that most trials featured small sample numbers and short research durations, making it difficult to determine with certainty how statins, when utilized in conjunction with concurrent antihypertensive drugs, affect blood pressure reduction. Moreover, no studies have examined the efficacy of rosuvastatin in relation to additional statin classes for the management of hypertension.

There are some issues with this study as well. A few of the study's shortcomings include its limited sample size and relatively brief follow-up period. Finding out if there is a stronger synergistic effect and if this combination maintains the CVD preventive advantage that has been shown for each separate medication is crucial in the end. Additional study in this field is necessary because it was challenging to show this influence on CVD based solely on the research methodology.

CONCLUSION

In hypertensive patients with dyslipidaemia, combination therapy of amlodipine 10 mg along with rosuvastatin 20 mg effectively and safely reduced blood pressure and levels of low-density lipoprotein (LDL-C). For the treatment of two main risk factors, like hypertension as well as high cholesterol levels, the single-pill FDC "Rosuvastatin-Amlodipine" is a rational FDC consisting of 2 drugs that have enough evidence for their efficacy and safety in their respective indications. Consequently, the burden related to cardiovascular events is reduced. It is not yet extensively used in clinical practice, though.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. GBD 2017 Causes of Death Collaborators Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–1788. doi: 10.1016/S0140-6736(18)32203-7.
2. Asia Pacific Cohort Studies Collaboration Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. Circulation. 2005;112(22):3384–3390. doi: 10.1161/CIRCULATIONAHA.105.537472.
3. Volpe M, Erhardt LR, Williams B. Managing cardiovascular risk: the need for change. J Hum Hypertens. 2008;22(2):154–157. doi: 10.1038/sj.jhh.1002273.
4. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple risk factor intervention trial research group. Arch Intern Med. 1992;152:56–64. doi: 10.1001/archinte.1992.00400130082009.
5. Volpe M, Gallo G, Tocci G. Is early and fast blood pressure control important in hypertension management? Int J Cardiol. 2018;254:328–332. doi: 10.1016/j.ijcard.2017.12.026.
6. Chapman RH, Yeaw J, Roberts CS. Association between adherence to calcium-channel blocker and statin medications

and likelihood of cardiovascular events among us managed care enrollees. BMC Cardiovasc Disord. 2010;10:29.

7. Messerli FH, Bakris GL, Ferrera D, et al. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. J Clin Hypertens (Greenwich, Conn.). 2006;8:571–581; quiz 582-573.
8. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet (London, England). 2005;365:434-441.
9. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34:2940-2948.
10. Wong ND, Pio JR, Franklin SS, L'Italien GJ, Kamath TV, Williams GR. Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome. Am J Cardiol. 2003;91:1421-1426.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults . Executive summary of the third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii). JAMA. 2001;285:2486-2497.
12. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press. 2014;23:3-16.
13. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289:2560-2572.
14. Neutel JM, Bestermann WH, Dyess EM, et al. The use of a single-pill calcium channel blocker/statin combination in the management of hypertension and dyslipidemia: a randomized, placebo-controlled, multicenter study. J Clin Hypertens (Greenwich, Conn.). 2009;11:22-30.
15. Oliver S, Jones J, Leonard D, Crabbe A, Delkhah Y, Nesbitt S. Improving adherence with amlodipine/atorvastatin therapy: IMPACT study. J Clin Hypertens (Greenwich, Conn.). 2011;13:598-604.
16. Preston RA, Harvey P, Herfert O, et al. A randomized, placebo-controlled trial to evaluate the efficacy, safety, and pharmacodynamic interaction of coadministered amlodipine and atorvastatin in 1660 patients with concomitant hypertension and dyslipidemia: the respond trial. J Clin Pharmacol. 2007;47:1555-1569.
17. Kim W, Chang K, Cho EJ, Ahn JC, Yu CW, Cho KI, Kim YJ, Kang DH, Kim SY, Lee SH, Kim U, Kim SJ, Ahn YK, Lee CH, Shin JH, Kim M, Park CG. A randomized, double-blind clinical trial to evaluate the efficacy and safety of a fixed-dose combination of amlodipine/rosuvastatin in patients with dyslipidemia and hypertension. J Clin Hypertens (Greenwich). 2020 Feb;22(2):261-269. doi: 10.1111/jch.13774. Epub 2020 Jan 31. PMID: 32003938; PMCID: PMC8029832.
18. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24352797/
19. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary. Circulation. 2019 Mar 17;140(11): 563-595
20. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120:713-719.
21. Curran MP. Amlodipine/atorvastatin: a review of its use in the treatment of hypertension and dyslipidaemia and the prevention of cardiovascular disease. Drugs. 2010;70:191-213.
22. Adams SP, Sekhon SS, Wright JM. Lipid-lowering efficacy of rosuvastatin. Cochrane Database Syst Rev. 2014;(11):Cd010254.
23. Hong SJ, Jeong HS, Cho JM, et al. Efficacy and safety of triple therapy with telmisartan, amlodipine, and rosuvastatin in patients with dyslipidemia and hypertension: The jeil telmisartan, amlodipine, and rosuvastatin randomized clinical trial. Clin Ther. 2019;41(2):233-248.e9.
24. Lee HY, Kim SY, Choi KJ, et al. A randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and the tolerability of a triple combination of amlodipine/losartan/rosuvastatin in patients with comorbid essential hypertension and hyperlipidemia. Clin Ther. 2017;39:2366-2379.
25. Elley CR, Gupta AK, Webster R, et al. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials. PLoS ONE. 2012;7:e52145.
26. Devaraj S, Siegel D, Jialal I. Statin therapy in metabolic syndrome and hypertension post-jupiter: what is the value of CRP? Curr Atheroscler Rep. 2011;13:31-42.
27. Yoshii T, Iwai M, Li Z, et al. Regression of atherosclerosis by amlodipine via anti-inflammatory and anti-oxidative stress actions. Hypertens Res. 2006;29:457-466.
28. Chopra V, Choksi PU, Cavusoglu E. Beyond lipid lowering: the anti-hypertensive role of statins. Cardiovasc Drugs Ther. 2007;21:161-169.
29. Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. Hypertension. 2007;49:792-798.
30. Briasoulis A, Agarwal V, Valachis A, Messerli FH. Antihypertensive effects of statins: a meta-analysis of prospective controlled studies. J Clin Hypertens (Greenwich, Conn.). 2013;15:310-320.
31. Feldstein CA. Statins in hypertension: are they a new class of antihypertensive agents? Am J Ther. 2010;17:255-262.
32. Banach M, Nikfar S, Rahimi R, et al. The effects of statins on blood pressure in normotensive or hypertensive subjects – a meta-analysis of randomized controlled trials. Int J Cardiol. 2013;168:2816-2824.