A multicenter, non-comparative study to evaluate the efficacy and safety of fixed-dose olmesartan/amlodipine in hypertensive patients

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Abstract

Background: Uncontrolled blood pressure (BP) is a major healthcare issue and responsible for high risk of cardiovascular disease (CVD) mortality and morbidity. P*hysicians of Bangladesh had been using* amlodipine and Olmesartan combination for a long period of time but have very limited evidence-based information regarding the efficacy and safety of this combination. The aim of this study was to evaluate the efficacy and safety of fixed dose combination of olmesartan/amlodipine in hypertensive patients.

Methods: This open-label, non-randomized, non-comparative observational study was conducted in different centers of Bangladesh during the period from January 2020 to November 2020. In total 443 Bangladeshi adult patients with hypertension were selected as the study population. Proper written consent was taken from all the participants before collecting data. Inter-group differences in the baseline characteristics were compared using analysis of variance (ANOVA). Two-tailed p-values of less than 0.05 were considered to be statistically significant. Statistical analyses were conducted by using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, USA).

Results: Among all the participants, more than 70% were above 46 years of age and 55% were male. More than 60% of them were either overweight or obese. Among them, dyslipidemia, diabetes, and Chronic renal failure (CRF) was found among 14.22%, 28.44%, and 4.29% participants respectively Mean systolic (SBP) and diastolic blood pressures (DBP) were reduced to 36.61 and 18.69 mm of Hg respectively after 12 weeks of therapy. Besides these, the targeted SBP was achieved among 92% and targeted DBP was achieved among 98.3% of participants after 12 weeks. Achievement of BP goal in respect to Body mass index (BMI) of the patient (*P-value 0.019*), family history of hypertension (*P-value 0.028*),

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and dose of the drug in initial visit (*P-value 0.001*) was found statistically significant. There was no discontinuation of study medication due to intolerance or adverse events.

Conclusion: Olmesartan/Amlodipine is an effective combination for reducing the blood pressure along with achievement of BP goal. Future studies on Olmesartan/Amlodipine in Bangladesh could be conducted with a longer treatment duration to examine the maintenance of effect and long-term safety.

Keywords: Efficacy; Safety; Olmesartan; Amlodipine; Hypertension

1. Introduction

Uncontrolled blood pressure (BP) is a major healthcare issue and responsible for high risk of cardiovascular disease (CVD) mortality and morbidity. Physicians had been using amlodipine for a long period of time in Bangladesh to manage hypertensive patient. The global prevalence of hypertension is projected to increase from 26% in 2000 to 29.2% by 2025 [1], which will be approximately 29% of the world's population. Hypertension is one of the major non-communicable diseases (NCDs) in the world. In 2019 an estimated 17.9 million people died from CVDs, representing 32% of all global deaths, among them 85% were due to heart attack and stroke [2]. Lowering the BP is prime target to prevent organ damage and consequence of hypertension [3]. It was found that every 2 mm Hg decrease in mean SBP results into 7% reduction in the risk of ischemic heart disease mortality, and a 10% reduction in the risk of stroke mortality. [4] Achieving blood pressure (BP) goals is a continuing challenging task. To control BP, most patients require more than one medication, as reported in large-scale clinical trials, including the Hypertension Optimal Treatment (HOT) study [5], the Anti- hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [6] and Anglo-Scandinavian Cardiac Outcomes Trials (ASCOT)[7]. Combining medications with different mechanisms of action provides an additive BP-lowering effect through complementary mechanisms [8]. Furthermore, combination therapy provides a better protective effect against coronary heart disease and stroke than monotherapy [9]. Combination therapy can be two or more agents administered separately or in a fixed-dose combination dosing, and the latter seems to be more popular in clinical practice based on its advantages in terms of convenience, cost, compliance, efficacy and safety. Meta-analysis of 68 studies of fixed-dose combinations involving a total of 11925 patients found a 26% decrease in the risk of non-adherence compared with free-drug combination strategies, with a 24% reduction in studies specific to antihypertensive medication. Consequently, as better adherence can translate into improved clinical outcomes, [10] fixed-dose combinations should be considered in patients with hypertension. Among the various combinations of anti-hypertensive agents, the renin-angiotensin system (RAS) inhibitors plus calcium channel blockers (CCBs) are superior to other combinations or higher dose single therapy for reducing cardiovascular events in patients with hypertension who are at high risk [11].

Olmesartan medoxomil (OM) is a prodrug of the non-peptide drug olmesartan, an angiotensin II (Ang II) receptor blocker (ARB). The affinity of olmesartan for the Ang II type 1 receptor (AT1) is 12,500-fold higher than for the Ang II type 2 (AT2) receptor [12]. Ang II exerts its powerful vasoconstrictive and cell growth effects through its binding to the AT1 receptor. Olmesartan negates this action of Ang II by binding to this receptor. Administration of OM at 2.5–40 mg was effective in blocking the pressure response after the infusion of Ang I (a precursor of Ang II). This effect was dose-dependent and still present (90%) at 24h with the administration of 40 mg dose of OM [13]. Single or multiple doses of OM lead to increased levels of Ang II and plasma renin activity (PRA), without affecting its antihypertensive potency. In addition, chronic administration of OM provides sustained BP control and protects end organ damage in animals and humans [14]. Amlodipine is a dihydropyridine calcium channel blocker (CCB) which reduces the BP by inhibiting the entry of calcium through the L channels into the cardiac and vascular smooth muscle cells and thus blocking their contractile effects. This action results in arteriolar vascular relaxation, decrease in peripheral vascular resistance and reduction of BP [15]. The BP lowering effect of amlodipine (AML) is gradual and lasts over 24h after its administration. Prolonged administration of AML does not significantly increase the catecholamine levels and heart rate, and does not cause negative cardiac inotropic effects, or interferes with the myocardial conduction system. The ARB olmesartan medoxomil (OM) and the CCB amlodipine (AML) are one such combination which is very much popular in our country. The Combination of Olmesartan medoxomil and Amlodipine in Controlling High BP (COACH) study demonstrated that the OM/AML combination had significantly greater efficacy in reducing systolic and diastolic BP after 8 weeks of therapy than monotherapy with either compound [16]. This combination has been found to be safe and well tolerated over both short and long-term treatments [17]. However, there has been no report on the clinical efficacy of this combination in Bangladeshi patients. Therefore, we intend to evaluate the efficacy and safety of the olmesartan/amlodipine FDC in Bangladeshi patients with hypertension.

2. Methods

This open-label, non-randomized, non-comparative observational study was conducted in different centers of Bangladesh during the period from January 2020 to November 2020. In total 443 Bangladeshi adult patients with hypertension were selected as the study population. Proper written consent was taken from all the participants before collecting data. Adult male or female patients with a prescription of tablet olmesartan/amlodipine for hypertension and also previously never treated or not treated for at least 4 weeks before entry into the trial, or patients who were uncontrolled by monotherapy were included. On the other hand, patients with, secondary hypertension or malignant hypertension, severe heart failure, malignancy requiring treatment, known serious hepatic or renal dysfunction (serum creatinine ≥ 2.5 mg), any compelling indication for any other Anti-hypertensive drugs, history of a serious adverse drug reaction to an angiotensin II receptor blocker or calcium channel blocker and with any other condition that makes a patient unsuitable for the study in the opinion of the investigators were excluded.

All patients were followed up for a period of 12 weeks. Patient visits were done at baseline (Visit 1), at week 2 (Visit 2), at week 6 (Visit 3), and week 12 (Visit 4) of the study. Patients who showed significant progress as judged by the physician at week 2 had continued the same dosage prescribed before. Patients who failed to show progress at week 2 received an escalated dose of olmesartan/amlodipine 40/5 mg for an additional 4 weeks. After that, patients failed to meet significant progress as judged by the physician at week 6, the dosage was escalated once again to olmesartan/amlodipine 40/10 for another 6 weeks. Patients were instructed not to take other anti-hypertensive medications, tricyclic anti-depressants, or long-acting nitrates.

At the time of patient recruitment and several visits from the patients, information regarding the date of consultation, duration of hypertension, demographic features, blood pressure (BP), medical & drug history, electrolyte, creatinine, drug taken/missed, treatment stopped and reason for premature discontinuation (if any) were taken and recorded. Efficacy was assessed on the basis of clinical response to therapy. The primary efficacy variable was the mean change from baseline in the seated Diastolic Blood Pressure (seDBP) from baseline to week 12. The secondary efficacy variables were the 'mean change from baseline in seated systolic BP (SeSBP) and SeDBP from baseline to week 2, 6 and 12' and the proportion of patients achieving the target BP. In safety assessment, the primary safety variable was the percentage of patients who withdraw from the study due to adverse events. The secondary safety variables were 'the total number of treatment-emergent adverse events (TEAEs), adverse drug responses (ADRs) and serious adverse events (SAEs) among the patients. All information regarding the adverse events was collected and analyzed. Inter-group differences in the baseline characteristics were compared using analysis of variance (ANOVA) for parametric continuous variables and the chi-square test for categorical variables. Two-tailed p-values of less than 0.05 were considered to be statistically significant. Statistical analyses were conducted by using SPSS for Windows, version 24 (SPSS Inc., Chicago, IL, USA).

3. Results

Among the participants, the highest number of patients were from the 46-59 years' age group (45%) and their mean ± SD of SBP and DBP were 168.3 ± 16.6 and 98 ±9 respectively. Among total participants, 55% were male and 45% were female. We observed that 5(1.13%), 162 (36.6%), 228 (51.5%), and 48 (10.8%) participants were underweighted, optimal, overweight and obese respectively. The majority of the participants were non-smokers (62%) (Table 1). Family history of HTN was found among 48% of participants. Besides these, the medical history of dyslipidemia, diabetes, and CRF was found among 14.22%, 28.44%, and 4.29% participants respectively (Table 2). Around three-fourths (75.62%) of the patients received 5/20 mg once daily olmesartan and amlodipine combination whereas 21.9% received 5/40 mg once daily dose.

Table 1 Demographic status of the participants (N=443)

Variables	n	%	SBP	DBP
			Mean ± SD	Mean ± SD
Age distribution (Years)				
<35 years	38	8.58	165.5±20.3	99.7±9.0
36-45 years	91	20.54	165.7±16.6	100.0±7.8
46-59 years	199	44.92	168.3±16.6	98.0±9.0
>60 years	115	25.96	171.8±19.1	96.4±11.1
Gender distribution				
Female	198	44.70	167.8±18.0	98.2±9.7
Male	245	55.30	168.7±17.4	98.2±9.1
BMI distribution				
Underweight	5	1.13	179±12.4	98.0±13.0
Optimal	162	36.57	166.1±17.4	97.5±9.4
Overweight	228	51.47	166.3±17.0	97.7±9.5
Obesity	48	10.84	167.5±14.3	96.0±8.9
Smoking History				
Smoker	131	29.57	168.3±16.7	98.8±8.7
Non-Smoker	274	61.85	166.7±18.1	97.9±9.7
Ex-Smoker	38	8.58	173.3±17.6	99.6±9.7

Table 2 Baseline clinical findings of the participants (N=443)

Variables	n	%	SBP	DBP
			Mean ± SD	Mean ± SD
Family H/O HTN				
Yes	213	48.08	168.1±16.7	99.0±9.4
No	230	51.92	166.9±17.9	97.8±9.7
Dose of Study drugs				
5/20 mg OD	335	75.62	164.91±15.052	97.0±8.203
5/40 mg OD	97	21.90	178.40±20.942	101.95±11.6
5/20 mg BD	11	2.48	185.7±17.959	102.5±12.0
Medical History				
Dyslipidemia	63	14.22	167.5±18.3	97.1±10.4
Diabetes	126	28.44	166.2±16.4	96.4±8.9
CRF	19	4.29	176.7±24.4	99.81±9.9

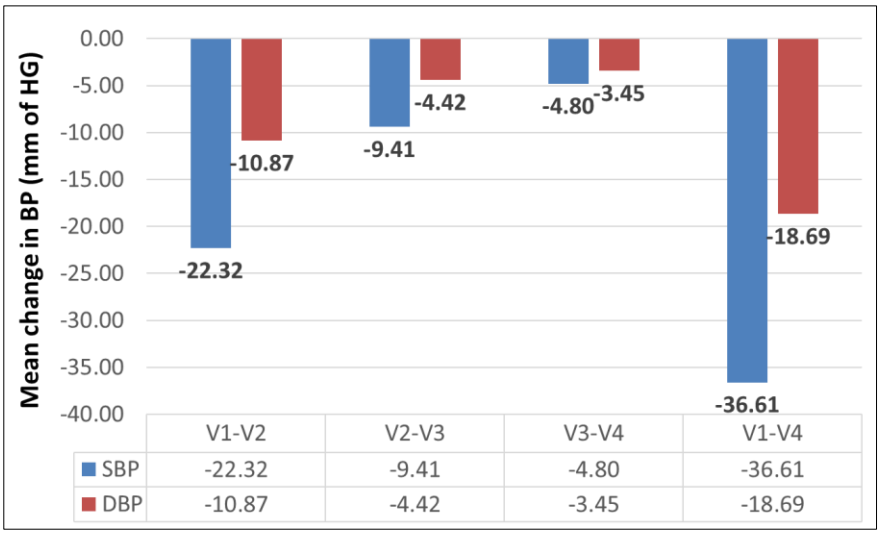

Figure 1 Change in BP over time (Visit wise) among the participants (N=443)
V1-Visit 1; V2-Visit 2; V3- Visit-3; V4- Visit 4

In our study, visit-wise changes in BP over time among the participants we observed that the mean changes of systolic and diastolic blood pressures (mmHg) were found 36.61 and 18.69 mm of Hg respectively (Figure 1) between visit 1 and visit 4. The targeted SBP was achieved among 92% and DBP was achieved among 98.3% of participants (Figure 2). Achievement of BP goal in respect to BMI of the patient (*P-value 0.019*), Family history of hypertension (P-value 0.028), Dose of the drug in initial visit (*P-value 0.001*) were found statistically significant (Figure 3). Among all the patients, a total 15.2% reported treatment emergent adverse events (TEAEs). There was no discontinuation of study medication due to intolerance or adverse events and there were no serious adverse events.

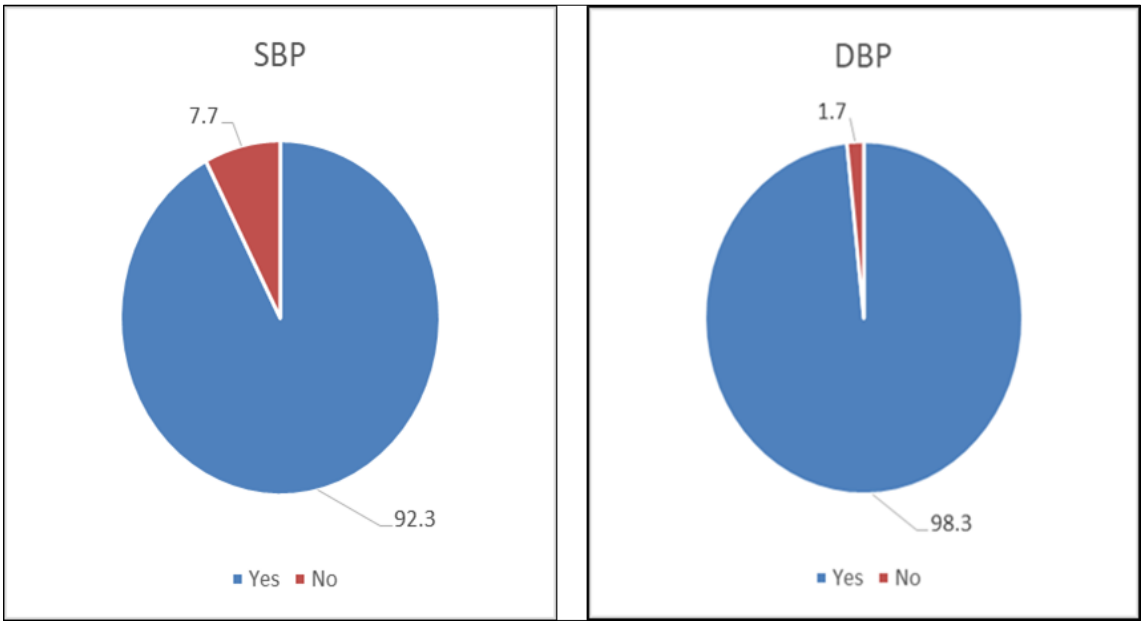

Figure 2 Target BP achievement among the participants (N=443)

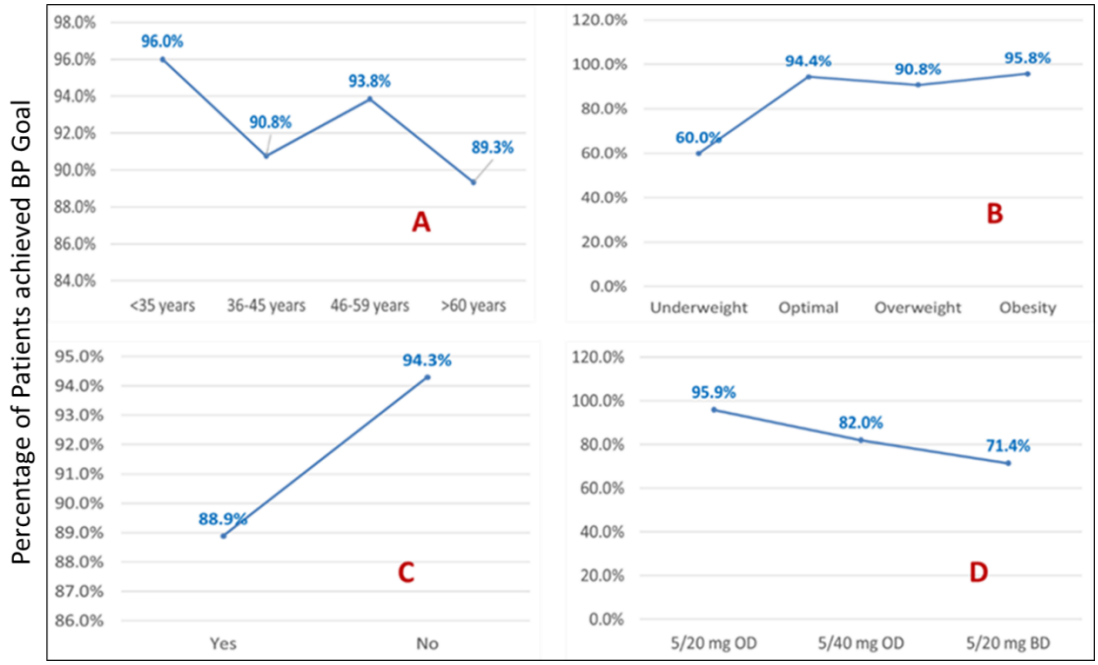

Figure 3 Achievement of BP Goal in respect to A. Age of the patients B. BMI of the patients (The result was found statistically significant, *P-value 0.019*); C. Family History of Hypertension (The result was found statistically significant, *P-value 0.028*); D. Dose of Drugs in initial visit (The result was found statistically significant, *P-value < 0.001*) (N=443)

4. Discussion

Current guidelines recommend stepwise treatment regimens, typically with more than one antihypertensive agent for controlling blood pressure [18]. It has been confirmed by various epidemiological studies for the last few decades that even minimally elevated systolic BPs (SBPs) or diastolic BPs (DBPs) increased cardiovascular risk [19]. In this study, we found that the fixed dose combination (FDC) of olmesartan/amlodipine was effective in controlling systolic and diastolic BP in Bangladeshi patients. In 12 weeks, mean changes of systolic and diastolic blood pressures (mmHg) were found 36.61 and 18.69 mm of Hg respectively. Also, the targeted SBP was achieved among 92% and DBP was achieved among 98.3% of participants. Furthermore, the study medication was well tolerated, and there were no unexpected adverse events associated with the study medication. A Renin-Angiotensin-Aldosterone System (RAAS) inhibitor plus CCB combination therapy is most commonly used in many countries. In Bangladesh, the FDC of angiotensin receptor blockers (ARBs) plus CCB is frequently prescribed in daily clinical practice. However, there has been no report regarding the efficacy and safety of olmesartan/amlodipine in Bangladeshi population. The effect of olmesartan/amlodipine in BP reduction in this study showed similar trends to other previous studies. In the Combination of Olmesartan medoxomil and Amlodipine besylate in Controlling High blood pressure (COACH) study, the systolic and diastolic BP reduction by olmesartan/amlodipine 20/5 mg were 23.6±14.9 mm of Hg and 14.0±9.1 mm of Hg at week 8, respectively (20). In the AZOR Trial Evaluating blood pressure reductions and Control study, which used ABPM to measure the efficacy of olmesartan/amlodipine titrated from 20/5 mg to 40/10 mg every 3 weeks in 185 patients, the reductions in mean 24h systolic BP and diastolic BP at week 12 from baseline were 21.4±0.8 mm of Hg and 12.7±0.5 mm of Hg (21).

In our study, almost three-fourth participants were more than 45 years of age and 55% were male. The majority of the participants were non-smokers (62%). Family history of HTN was found among 48% of participants. Besides these, the medical history of dyslipidemia, diabetes, and CRF was found among 14.22%, 28.44%, and 4.29% participants respectively. In another study conducted in Bangladesh, where diabetes mellitus was similar between male & female, smoking was most commonly found in men (50.3%) [22]. In another study, among hypertensive patients, some findings revealed that 31.7% had hyperglycemia, 68.8% low high-density lipoprotein (LDL) cholesterol and 55.3% high triglycerides. Prevalence of tobacco consumption was stated 26.2% for smoking [23]. Mean age of the respondents was found 67.1 ± 6.6 where mean SBP and DBP measured were 126 ± 2 mm of Hg and 72 ±12 SD mm of Hg respectively. There was a tendency of being hypertensive with overweight/obese &the result was narrated statistically significant ($p<0.05$). Prevalence of hypertension was found higher among the seniors of the study areas especially among those who were affected by overweight/obese [24]. Mean age group was found in between 40-60 years 49.77±7.70 [25]. In a study the overall prevalence of hypertension, obesity, dyslipidemia, and chronic kidney diseases were found 57.5%, 62.6%, 72.7%, & 21.3% respectively, for SBP mean ± SD was 131.56± 17.60, for DBP mean ± SD was 79.38 ± 10.10. [26].

For most of the patients with hypertension, treatment goals cannot be achieved with monotherapy. Moreover, combination therapy results in more rapid control of blood pressure. This pathway may facilitate improvements in long-term clinical outcomes, compared with more traditional and time-consuming processes [27]. Achievement of BP goal in respect to BMI of the patient (P- value 0.019), Family history of hypertension (P-value 0.028), Dose of drug in initial visit (P-value 0.001) was found statistically significant.

Furthermore, there were only a few reports of edema in the present study. This observation is in accordance with another study showing decreased leg edema combined therapy of valsartan and amlodipine compared with amlodipine monotherapy (20). As proposed by a study combining enalapril with amlodipine (21), antagonism to RAS can be helpful through microvascular mechanisms in preventing leg edema associated with CCB.

There were a few limitations with our study. This was conducted as a real-world study in clinical practice settings, therefore detailed information regarding screen failures was not captured. Additionally, this was a relatively short study; whilst 12 weeks were sufficient to demonstrate the benefit of Antihypertensive, a longer treatment period may have helped to better observe the outcomes of hypertension, including target organ damage and adverse outcomes. Furthermore, because there was no control group and the study was conducted with an open-label design, it was impossible to compare the effects of olmesartan/amlodipine to those of other regimens or placebo. Despite these limitations, we believe the study fulfilled the purpose of assessing the efficacy and safety of fixed dose olmesartan/amlodipine in hypertensive patients.

5. Conclusion

Olmesartan/Amlodipine is an effective combination for the management of hypertensive patients of Bangladesh. Future studies on Olmesartan/Amlodipine in Bangladesh could be conducted with a longer treatment duration to examine the maintenance of effect and long-term safety and could attempt to examine the dose-response relationship and factors associated with response in further detail.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

This is to certify that the Investigators do not have any matters which might give rise to a real or perceived conflict of interest. There is no existence of any personal interest, pressure of biasness and involvement with any organization which can mislead during the study procedure. The study was conducted by Cardiology Study group which was supported by the unconditional unrestricted educational grant from Beximco Pharmaceuticals Ltd.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012; 380(9859): 2224–60.

[2] World Health Organization. (n.d.). *Cardiovascular diseases (cvds)*. World Health Organization. Retrieved August 2, 2022, from https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

[3] Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002; 359: 995–1003.

[4] Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data of one million adults in 61 prospective studies. Lancet. 2002; 360: 1903–13.

[5] Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005; 36: 1218–1226.

[6] Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003; 349: 1893–1906.

[7] Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001; 345: 1667–1675.

[8] Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003; 362: 759–766.

[9] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N EnglJMed. 2001; 345: 861–869.

[10] Waeber B, Detry JM, Dahlof B, et al. Felodipine-metoprolol combination tablet: a valuable option to initiate antihypertensive therapy? Am J Hypertens. 1999; 12 (9 Pt 1): 915-20.

[11] Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001; 345: 870–878.

[12] Deeks ED. Olmesartanmedoxomil/amlodipine/hydrochlorothiazide fixed-dose combination in hypertension. Drugs. 2011; 71: 209–220.

[13] Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004; 363: 2022–2031.

[14] Scott LJ, Mc Cormack PL. Olmesartanmedoxomil: a review of its use in the management of hypertension. Drugs. 2008; 68, 1239–1272.

[15] Haria M, Wagstaff AJ. Amlodipine: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. Drugs. 1995; 50: 560–566.

[16] Chrysant SG, S Oparil, M Melino, S Karki, J Lee, R. Heyrman. Efficacy and safety of long-term treatment with the combination of amlodipine besylate and olmesartanmedoxomil in patients with hypertension. The Journal of Clinical Hypertension. 2009; 11: 475–482.

[17] Oparil S, J Lee, S Karki, M Melino. Subgroup analyses of an efficacy and safety study of concomitant administration of amlodipine besylate and olmesartanmedoxomil: Evaluation by baseline hypertension stage and prior antihypertensive medication use. Journal of Cardiovascular Pharmacology. 2009; 54: 427–436.

[18] Benjamin J. Epstein, PharmD, BCPS, Niren K. Shah, PharmD, Nancy L. Borja-Hart; Management of Hypertension with Fixed-Dose Triple-Combination Treatments. TherAdvCardiovasc Dis. 2013; 7(5): 246-259.

[19] Moser M. From JNC 1-JNC 7: what have we learned? Prog. Cardiovasc. Dis. 2006; 48: 303–315.

[20] Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebocontrolled, 8-week factorial efficacy and safety study. Clin Ther. 2008; 30: 587–604.

[21] Punzi H, Neutel JM, Kereiakes DJ, et al. Efficacy of amlodipine and olmesartan medoxomil in patients with hypertension: the AZOR Trial evaluating blood pressure reductions and control (AZTEC) study. Ther Adv Cardiovasc Dis. 2010; 4: 209–21.

[22] Zaman MM, Yoshiike N, Rouf MA, Syeed MH, Khan MR, Haque S, Mahtab H, Tanaka H. Cardiovascular risk factors: distribution and prevalence in a rural population of Bangladesh. Journal of cardiovascular risk. Apr 2001; 8(2): 103-8.

[23] Islam AK, Majumder AAS. Hypertension in Bangladesh: a review. Indian Heart J. 2012 May-Jun;64(3):319-23.

[24] Moni M, Rahman M, Haque M, Islam M, Ahmed K: Blood pressure in relation to selected anthropometric measurements in senior citizens. MMJ. 2010; 19(2): 254-258.

[25] Tabassum R, Begum N, Ferdousi S, Begum S, Ali T: Heart rate variability in patients with essential hypertension. Journal of Bangladesh Society of Physiologist. 2010; 5(1): 1-7.

[26] Islam, S. M., Alam, D. S., Wahiduzzaman, M., Niessen, L. W., Froeschl, G., Ferrari, U., Seissler, J., Rouf, H. M., & Lechner, A. (2015). Clinical characteristics and complications of patients with type 2 diabetes attending an urban hospital in Bangladesh. *Diabetes & metabolic syndrome*, *9*(1), 7–13. https://doi.org/10.1016/j.dsx.2014.09.014

[27] Gradman AH. Rationale for triple-combination therapy for management of high blood pressure. J ClinHypertens (Greenwich). 2010; 12(11): 869-78.