Mathematical Modeling for the Effect of Single-Pill Amlodipine and Valsartan Combination Therapy on Biochemical Markers of Atherosclerosis

Tek-Tablet Amlodipin ve Valsartan Kombinasyon Tedavisinin Aterosklerozun Biyokimyasal Belirteçleri Üzerine Etkisinin Matematiksel Modelleme ile Belirlenmesi

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ABSTRACT Objective: The primary aim of this study was to construct a model that could predict the overall effect of concomitant administration of amlodipine and valsartan on biochemical markers of atherosclerosis. **Material and Methods:** The medical literature was systematically reviewed by searching the PubMed, Embase and Biosis databases using the terms hypertension and "amlodipine or valsartan" and "atherosclerosis or insulin resistance or insulin sensitivity or inflammation". In total, 39 publications, in which atherosclerotic risk parameters before and after treatment were reported, were identified and included in this analysis. The percentage difference between pre- and post-treatment values was calculated by weighting the values by the number of patients. The additive effect of amlodipine and valsartan was also calculated using a formula postulated on the basis of a previous study. **Results:** According to the criteria given above, data from 1765 patients from 39 studies were analyzed. The median duration of treatment was 16 weeks (range, 4–156 weeks). Amlodipine and valsartan treatment produced a decrease in HOMA, hsCRP, TNF-alpha and IL-6 levels, and an increase in adiponectin and triglyceride levels. Concomitant use of amlodipine and valsartan is estimated to decrease HOMA, hsCRP, TNF-alpha and IL-6 levels while increasing adiponectin, triglyceride, HDL-C and BMI levels. **Conclusion:** In conclusion, both amlodipine and valsartan have positive effects on atherosclerotic risk parameters, and the combination of amlodipine/valsartan is predicted to be more effective than either drug administered individually for reduction of atherosclerosis risk, using mathematical modeling. This study provides preliminary results based on mathematical modeling, which need to be confirmed with prospective and controlled clinical studies.

Key Words: Models, theoretical; atherosclerosis; amlodipine; valsartan

ÖZET Amaç: Çalışmanın birincil amacı amlodipin ve valsartan'ın birlikte kullanılmasının aterosklerozun biyokimyasal belirteçleri üzerine etkisini değerlendirmek amacıyla bir model oluşturmaktır. **Gereç ve Yöntemler:** Mevcut literatür PubMed, Embase ve Biosis veritabanları üzerinden "hipertansiyon" ve "amlodipine" veya "valsartan" ve "ateroskleroz" veya "insulin direnci" veya "insulin hassasiyeti" veya inflamasyon terimleri kullanılarak sistematik olarak taranmıştır. Aterosklerotik risk parametrelerin tedaviden önce ve sonra bildirildiği toplam 39 yayın belirlenmiş ve analize dahil edilmiştir. Tedavi öncesi ve sonrası değerler arasındaki yüzde fark, değerler hasta sayılarına göre ağırlıklandırılarak hesaplanmıştır. Amlodipin ve valsartan'ın additif etkisi de önceki bir çalışmaya dayanarak oluşturulan formül ile hesaplanmıştır. **Bulgular:** Bu kriterlere göre 39 çalışmadan 1765 hasta analize dahil edilmiştir. Medyan tedavi süresi 16 haftadır (4-156 hafta). Amlodipin ve valsartan tedavisi ile HOMA, hsCRP, TNF-alfa ve IL-6 düzeylerinde düşme, adiponektin ve trigliserit düzeylerinde ise yükselme belirlenmiştir. Amlodipin ve valsartan'ın birlikte kullanımının adiponektin, trigliserit, HDL-C ve BKİ değerlerini artırırıken; HOMA, hsCRP, TNF-alfa ve IL-6 düzeylerini düşürdüğü öngörülmektedir. **Sonuç:** Sonuç olarak, hem amlodipin hem de valsartan aterosklerotik risk parametreleri üzerine olumlu etki oluşturmaktadır. Kurulan matematiksel modellemeye göre amlodipin/valsartan kombine tedavisinin aterosklerotik risk azaltımında her bir ilacın ayrı ayrı kullanımından daha etkili olduğu belirlenmiştir. Matematisel modellemeye dayalı bu çalışmanın bir öncalışma olduğu dikkate alınarak, elde edilen sonuçların prospektif çalışmalar ile doğrulanması şarttır.

Anahtar Kelimeler: Modeller, teorik; ateroskleroz; amlodipin; valsartan

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Hypertension is a common disorder associated with cardiovascular mortality and morbidity. It is widely known that adequate lowering of blood pressure reduces hypertension-induced cardiovascular events.[1,2] Currently, there are many antihypertensive drugs with a wide-range of mechanisms. However, effective, long-term control of blood pressure is insufficient in the treatment of patients with hypertension. To overcome this problem, the combination of two or more antihypertensive drugs, separately or as a single pill, is suggested by most guidelines and applied in clinical practice.[1,3] Compared to monotherapy, a single-pill, fixed-dose combination therapy for the control of blood pressure is more effective, while decreasing adverse effects and healthcare costs.[4,5]

Single-pill combinations of renin-angiotensin-aldosterone system inhibitors and other antihypertensive drugs (*e.g.*, calcium channel blockers, diuretics) are commonly used for the treatment of hypertension, due to their advantage of increased patient compliance due to the reduced number of tablets.[6] The combination of valsartan, an angiotensin II receptor blocker, and amlodipine, a calcium channel blocker, is among the most preferred initial treatments used in clinical practice to obtain optimum control of blood pressure.[7,8] The antihypertensive efficacy of oral amlodipine and valsartan administered as separate agents or as a combination has been demonstrated in several clinical trials.[4,9,10] Single-pill, fixed-dose amlodipine and valsartan combinations have shown improved blood pressure control compared with the respective monotherapies in diverse patient populations, together with a favorable tolerability profile.[11]

Although many large and randomized clinical studies have shown that the antihypertensive efficacy and safety of fixed-dose combinations and the presence of mortality and morbidity studies of single molecules in combinations, long-term mortality and morbidity studies have not been conducted or planned due to the need for long-duration follow-up and the high cost.[12-15] It is, therefore, possible only to estimate the effect of combination regimens on cardiovascular damage by means of systemic analysis and modeling studies using mortality and morbidity data of individual drugs in combinations.[15,16]

The primary aim of this study was to construct a model predictive of the overall effect of concomitant administration of amlodipine and valsartan on biochemical markers of atherosclerosis (glycemic, inflammatory, lipid, and anthropometric parameters). Furthermore, the relationship between blood pressure reduction and atherosclerotic risk parameters was evaluated. This study will provide a basis for future evaluations and modeling of the effectiveness of combination treatments for hypertension and other chronic diseases using the data of the individual agents.

MATERIAL AND METHODS

STUDY DESIGN

The study was a systematic review with a mathematical model, which utilized the data of published clinical studies to predict the effect of concomitant administration of amlodipine and valsartan on atherosclerotic risk parameters. A systematic literature review was performed to identify the clinical studies to be included in the analysis.

The study was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

SYSTEMATIC REVIEW AND SELECTED ARTICLES

To determine the studies that would be included in the analysis, we searched the PubMed, Embase and Biosis databases. The search terms used were hypertension and (amlodipine or valsartan) and (atherosclerosis or insulin resistance or insulin sensitivity or inflammation). The search was limited to studies published in English after 2000. In total, 103 articles fulfilled the search criteria. Two investigators separately reviewed the abstracts of these articles and those with at least one study arm treated with amlodipine or valsartan or both, including blood pressure values, and evaluating the effect of treatment on metabolic and inflammatory parameters, were identified. The full text of 46 articles meeting these criteria, confirmed by

both investigators, were obtained and re-reviewed against the selection criteria. Of these 46 articles, 39 were selected for inclusion in the analysis: 27 amlodipine monotherapy, 14 valsartan monotherapy, and 1 combination therapy.[16,18-55] A flow diagram of the selection process is presented (Figure 1).

ATHEROSCLEROTIC RISK PARAMETERS

The included studies had 42 patient groups in which systolic and diastolic blood pressures (mmHg); glycemic [homeostatic model assessment (HOMA) index as %, adiponectin (mg/mL)], inflammatory [high sensitivity C reactive protein (hsCRP, mg/L), tumor necrosis factor alpha (TNF-alpha, pg/mL), interleukin 6 (IL-6, pg/mL)], lipid [triglycerides (mg/dL), high density lipoproteins (HDL, mg/dL)] and anthropometric [body mass index (BMI, kg/m^2)] parameters were recorded before and after treatment and reported as means, standard deviations, and absolute and percentage changes. Among the parameters, those not reported in some of the articles (*e.g.*, absolute or percent changes) were calculated. The units of parameters were standardized by converting into molar-mass-based units. In addition to the analysis parameters, the demographic data of the populations in the articles were summarized.

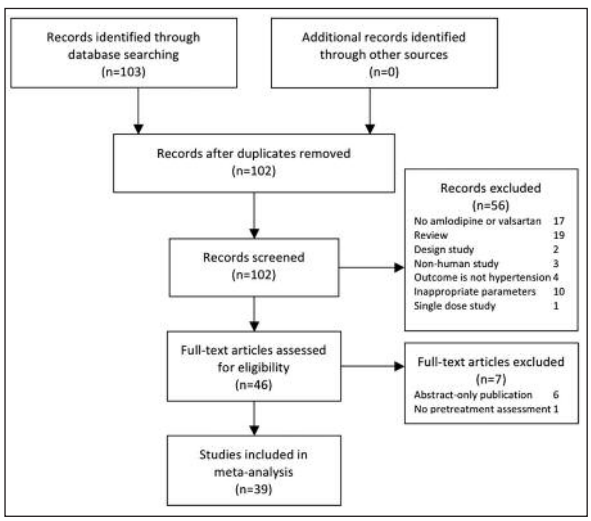

FIGURE 1: The flow diagram that shows the flow of information through the different phases of a systematic review.

STATISTICAL METHODS

Postulation of the Mathematical Model

Based on the study by Fogari et al., the effects of amlodipine or valsartan monotherapy, or a single-tablet combination of amlodipine and valsartan, were evaluated.[16] A formula was postulated to calculate the effect of the amlodipine and valsartan combination on the above-mentioned atherosclerotic risk parameters.

Fogari et al. reported the glucose and insulin values of the patients.[16] Using these values, the HOMA index of the study groups was calculated using the following formula:

$$\text{HOMA: } \frac{\text{fasting insulin } (\mu u/mL) \text{x} \text{fasting plasma glucose } (mg/dL)}{405}$$

Afterwards, for each study arm, the absolute and percentage changes in the HOMA index were calculated according to the initial values. The percentage changes in the amlodipine and valsartan monotherapy groups were summed, and the total percentage change of the monotherapy groups was compared to that of the combination therapy group. The ratio of the percentage change of the combination therapy group to those of the monotherapy groups was calculated as 1.065. Thus the combination therapy was 1.065 times more effective than sum of the monotherapies for the HOMA parameter. On the basis of this calculation, the formula used to estimate the effect of the amlodipine and valsartan combination therapy was as follows:

$$1{,}065 \text{x} \sum \overline{\chi}_{\text{amlodipin}} \overline{\chi}_{\text{valsartan}}$$

According to this formula, the average results of any parameter for amlodipine and valsartan monotherapies will be summed mathematically and multiplied by 1.065 to obtain the result of the combination therapy.

METHOD USED TO OVERCOME THE HETEROGENEITY OF THE STUDIES

The initial, before-treatment values of the parameters evaluated in the analysis showed variations

among the studies. If the initial value in a particular study was markedly lower or higher than the overall value of that parameter obtained from all studies, the treatment-related effect of this parameter may be misleading. To overcome this problem, rather than absolute initial values, the percentage change of each parameter from baseline was calculated and analyzed.

In addition to different initial values, the direction of the effect differed among the studies, which makes evaluating the outcomes of the studies problematic. The changes in parameters upon treatment were expressed as percentages to overcome this issue.

STATISTICAL ANALYSIS

The normality of the distributions of all parameters included in the analysis were evaluated; all parameters except hsCRP, TNF alpha, and IL-6 showed a normal distribution. The data for each parameter are presented as means, standard deviations and 95% confidence intervals. Non-normally distributed parameters are presented as medians and interquartile ranges.

The statistical level of significance was set to the 95% interval for comparisons of the treatment groups. The correlations between the parameters were tested by Pearson's correlation analysis for normally distributed data and by Spearman's nonparametric correlation analysis for non-normally distributed data.

The effect of blood pressure on other parameters was evaluated using linear regression models. Since all values of the corresponding parameters are required for a regression analysis, fewer patients are presented in the regression results than in the main analysis.

All statistical analyses were performed using the SPSS software (Statistical Package for Social Sciences, version 12.0; SPSS Inc., Chicago, Illinois, USA).

RESULTS

ANALYSIS POPULATION

In total, 954 patients received amlodipine and 811 received valsartan treatments in the studies included in the analysis. The mean durations of treatment were 39.1±37.5 and 20.9±21.9 months in the amlodipine and the valsartan groups, respectively. Blood pressure was evaluated in 1731 patients; the systolic and diastolic blood pressures were significantly decreased by treatment in both the amlodipine and the valsartan groups (Table 1).

ATHEROSCLEROTIC RISK PARAMETERS

The available data regarding the effects of amlodipine and valsartan on atherosclerotic risk parameters are given (Table 2). The following parameters decreased with both amlodipine and valsartan treatment: HOMA index, hsCRP, TNF-alpha and IL-6. The decrease in HDL cholesterol and BMI was significant only with valsartan. HDL cholesterol was significantly increased in the amlodipine group, while triglyceride was increased in the valsartan group. The adiponectin level increased with both amlodipine and valsartan treatment. The percentage changes in the atherosclerotic parameters with amlodipine and valsartan alone or in combination calculated using the mathematical model are presented (Table 3). According to the model, valsartan had a greater effect than amlodipine on glycemic and anthropometric parameters, while amlodipine was more advantageous in terms of its effect on inflammatory and lipid parameters. The

TABLE 1: Blood pressure of amlodipine and valsartan groups before and after treatment.

	Pretreatment mean±SD	Posttreatment mean±SD	Difference mean±SD (95%CI)
Amlodipine (n=920)			
SBP (mmHg)	157.0±8.4	137.4±5.9	-19.9±6.6 (-20.3 – -19.4)
DBP (mmHg)	93.8±5.9	83.7±3.9	-10.2±4.3 (-10.5 – -9.9)
Valsartan (n=811)			
SBP (mmHg)	151.3±7.1	137.1±6.2	-14.1±5.6 (-14.5 – -13.7)
DBP (mmHg)	90.8±7.4	82.0±3.8	-8.7±4.9 (-9.1 – -8.4)

SD: Standard deviation; CI: Confidence interval; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

TABLE 2: Atherosclerotic risk parameters of amlodipine and valsartan groups before and after treatment.

	n	Pretreatment mean±SD	Posttreatment mean±SD	Difference mean±SD (95%CI)	%Difference mean±SD (95%CI)
Amlodipine					
HOMA index (%)	500	3.64±1.79	3.31±1.7	-0.47±0.88 (-0.55 – -0.38)	-9.65±24.39 (-11.89 – -7.42)
Adiponectin (mg/mL)	202	7.26±2.73	7.71±2.48	0.43±1.16 (0.27 – 0.59)	10.15±26.96 (6.41 – 13.9)
hsCRP (mg/L)	354	3.12±2.94	2.90±3.00	-0.22±0.43 (-0.27 – -0.18)	-14.05±17.49 (-15.88 – -12.23)
TNF-alpha (pg/mL)	161	11.87±11.06	8.62±5.68	-3.25±6.99 (-4.34 – -2.16)	-15.3±17.7 (-18.06 – -12.54)
IL-6 (pg/mL)	104	16.46±13.77	15.95±14.07	-0.08±1.39 (-0.35 – 0.19)	-7.09±14.43 (-9.9 – -4.29)
Triglyceride (mg/dL)	793	160.18±43.42	163.04±49.75	-1.07±23 (-3.03 – 0.89)	-0.04±12.93 (-1.14 – 1.06)
HDL cholesterol (mg/dL)	706	46.65±10.07	45.43±12.04	1.69±2.15 (1.49 – 1.89)	3.48±4.82 (3.03 – 3.93)
BMI (kg/m^2)	791	27.21±3.44	26.89±2.75	0.04±0.33 (0 – 0.07)	0.1±1.18 (-0.03 – 0.23)
Valsartan					
HOMA index (%)	653	3.76±1.54	3.31±1.25	-0.46±0.69 (-0.51 – -0.4)	-10.54±14.58 (-11.66 – -9.42)
Adiponectin (mg/mL)	420	7.0±0.79	7.84±1.33	0.82±1.56 (0.67 – 0.97)	13.08±25.08 (10.67 – 15.48)
hsCRP (mg/L)	420	2.95±1.75	2.91±2.19	0.09±0.71 (0.02 – 0.16)	-2.61±13.42 (-3.9 – -1.32)
TNF-alpha (pg/mL)	190	3.34±2.45	2.71±1.44	-0.63±1.01 (-0.77 – -0.48)	-12.4±8.75 (-13.65 – -11.15)
IL-6 (pg/mL)	190	3.28±2.56	3.14±2.45	-0.15±0.11 (-0.16 – -0.13)	-4.51±0.09 (-4.52 – -4.5)
Triglyceride (mg/dL)	688	154.86±20.21	156.52±16.74	2.02±8.33 (1.32 – 2.72)	1.8±5.54 (1.34 – 2.27)
HDL cholesterol (mg/dL)	688	52.20±4.40	53.40±3.16	-0.67±2.16 (-0.89 – -0.44)	-1.07±4.17 (-1.5 – -0.63)
BMI (kg/m^2)	771	28.94±5	28.88±3.34	-0.65±0.75 (-0.76 – -0.54)	-1.96±2.26 (-2.28 – -1.64)

SD: Standard deviation; CI: Confidence interval; HOMA: Homeostatic model assessment; hsCRP: High sensitivity C reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin 6; HDL: High density lipoproteins; BMI: Body mass index.

combination of amlodipine and valsartan changed atherosclerotic parameters in the desired direction to a greater degree than did either amlodipine or valsartan alone.

CORRELATIONS BETWEEN CHANGES IN BLOOD PRESSURE AND ATHEROSCLEROTIC PARAMETERS

The correlation analysis revealed that amlodipine and valsartan induced changes in all of the atherosclerotic risk parameters except TNF-alpha and IL-6. Amlodipine and valsartan induced changes were positively correlated with the decrease in either systolic or diastolic blood pressure, except the effects of amlodipine on the HOMA index, adiponectin, hsCRP, and TNF-alpha, which were negatively correlated with a decrease in blood pressure (Table 4).

TABLE 3: The percent changes in atherosclerotic parameters with amlodipine and valsartan alone or in combination obtained from study model.

	Amlodipine	Valsartan	Amlodipine+Valsartan
Glycemic parameters			
HOMA index	↓ 9.7%	↓ 10.5%	↓ 21.5%
Adiponectin	↑ 10.2%	↑ 13.1%	↑ 24.7%
Inflammatory parameters			
hsCRP	↓ 14.1%	↓ 2.6%	↓ 17.8%
TNF-alpha	↓ 15.3%	↓ 12.4%	↓ 29.5%
IL-6	↓ 7.1%	↓ 4.5%	↓ 12.4%
Lipid parameters			
Triglyceride	↓ 0.04%	↑ 1.8%	↑ 1.9%
HDL cholesterol	↑ 3.5%	↓ 1.1%	↑ 2.6%
Antropometric parameters			
BMI	↑ 0.1%	↓ 2.0%	↓ 2.0%

↑: increase; ↓: decrease; HOMA: Homeostatic model assessment; hsCRP: High sensitivity C reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin 6; HDL: High density lipoproteins; BMI: Body mass index.

REGRESSION MODELING

Regression modeling was postulated to predict the percentage change in atherosclerotic risk parameters with a 10% decrease in the systolic or diastolic blood pressure. The percentage change in each parameter along with the mathematical model and *p*

TABLE 4: Correlation coefficients (r) for the relation between change in blood pressure and change in atherosclerotic parameters.

Change in atherosclerotic risk parameters	Treatment groups	Change in SBP	Change in DBP
HOMA index	Amlodipine (n=427)	r=-0.062 (p=0.202)	r=-0.276 (p<0.001)
	Valsartan (n=653)	r=0.444 (p<0.001)	r=0.490 (p<0.001)
Adiponectin	Amlodipine (n=182)	r=-0.556 (p<0.001)	r=-0.716 (p<0.001)
	Valsartan (n=420)	NA	NA
hsCRP	Amlodipine (n=334)	r=-0.143 (p=0.009)	r=0.219 (p<0.001)
	Valsartan (n=420)	r=0.218 (p<0.001)	r=0.218 (p<0.001)
TNF-alpha	Amlodipine (n=161)	NA	r=-0.370 (p<0.001)
	Valsartan	NA	NA
IL-6	Amlodipine	NA	NA
	Valsartan	NA	NA
Triglyceride	Amlodipine (n=513)	r=0.025 (p=0.567)	r=0.114 (p=0.010)
	Valsartan (n=545)	r=0.387 (p<0.001)	r=0.383 (p<0.001)
HDL cholesterol	Amlodipine (n=446)	r=0.205 (p<0.001)	r=0.365 (p<0.001)
	Valsartan (n=357)	r=0.207 (p<0.001)	r=0.367 (p<0.001)
BMI	Amlodipine (n=298)	r=0.422 (p<0.001)	r=0.387 (p<0.001)
	Valsartan (n=192)	r=0.125 (p=0.085)	r=0.161 (p=0.026)

NA: not analyzed due to insufficient data.

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HOMA: Homeostatic model assessment; hsCRP: High sensitivity C reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin 6; HDL: High density lipoproteins; BMI: Body mass index.

value are given (Table 5). According to the regression modeling, the greatest percentage change with a 10% decrease in blood pressure with amlodipine treatment was obtained for IL-6 (54.2% decrease) and TNF-alpha (40.7% decrease). A 10% decrease in blood pressure with valsartan treatment induced the greatest changes in TNF-alpha (212.8% decrease) and adiponectin (67.0% decrease) levels.

DISCUSSION

In this mathematical modeling study, we evaluated the benefits of amlodipine and valsartan monotherapies on atherosclerotic parameters and predicted the potential of the combination therapy to reduce the risk of atherosclerosis. We suggested that the combination of amlodipine/valsartan is more effective than either drug individually in terms of reducing the risk of atherosclerosis.

Previous large-scale studies confirmed the superiority of combinations of renin-angiotensin-aldosterone system inhibitors and calcium channel blockers to other combination regimens. In the ASCOT-BPLA study, the amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than an atenolol-based regimen.[56] Similarly, in the ACCOMPLISH study the benazepril-amlodipine combination was found to be superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension.[57]

Single-pill, fixed-dose amlodipine/valsartan is the first available combination of an angiotensin II receptor blocker and a calcium channel blocker and has been available for clinical use since 2008. The efficacy of the single-pill amlodipine/valsartan combination in terms of hypertension end-points and safety has been reported.[7-11] However, the long-term morbidity and mortality along with cardiovascular and atherosclerotic parameters have not been investigated.

It is well-known that insulin resistance is a risk factor for hypertension and atherosclerosis and is closely associated with other atherosclerotic parameters.[58,59] In the present study, the model was constructed based on a previous report of the effects of single and combination therapies of am-

TABLE 5: Results of regression modelling to predict percentage change in atherosclerotic parameters with 10% decrease in blood pressure with amlodipine or valsartan.

		10% decrease in SBP	10% decrease in DBP
Amlodipine			
HOMA	% change	16.90	-0.96
	Mathematical model	ΔHOMA%=10.141+(1.69×ΔSBP%)	ΔHOMA% =12.495+(-0.096×ΔDPB%)
	p	<0.001	<0.001
Adiponectin	% change	-5.07	-6.23
	Mathematical model	ΔAdiponectin%=-4.568+(-0.507×ΔSBP%)	ΔAdiponektin% =-4.450+(-0.623×ΔDPB%)
	p	<0.001	<0.001
hsCRP	% change	5.68	23.47
	Mathematical model	ΔhsCRP%=-5.652+(0.568⑨ΔSBP%)	ΔhsCRP%=10.859+(2.347×ΔDPB%)
	p	0.121	<0.001
TNF-alpha	% change	-40.70	-37.54
	Mathematical model	ΔTNF-alpha%=-63.24+(-4.07×ΔSBP%)	ΔTNF-alpha%=-59.398+(-3.754×ΔDPB%)
	p	<0.001	<0.001
IL-6	% change	-13.55	-54.23
	Mathematical model	ΔIL-6%=-17.762+(-1.355×ΔSBP%)	ΔIL-6%=-81.927+(-5.423×ΔDPB%)
	p	<0.001	<0.001
Triglyceride	% change	2.27	8.03
	Mathematical model	ΔTriglyceride%=3.125+(0.227×ΔSBP%)	ΔTriglyceride%=8.57+(0.803×ΔDPB%)
	p	0.187	<0.001
HDL cholesterol	% change	1.26	4.53
	Mathematical model	ΔHDL%=5.094+(0.126×ΔSBP%)	ΔHDL%=8.27+(0.453×ΔDPB%)
	p	0.118	<0.001
BMI	% change	-2.14	1.91
	Mathematical model	ΔBMI%=2.425+(-0.214×ΔSBP%)	ΔBMI%=1.905+(0.191×ΔDPB%)
	p	<0.001	<0.001
Valsartan			
HOMA	% change	10.52	1.11
	Mathematical model	ΔHOMA%=-0.28+(1.052×ΔSBP%)	ΔHOMA%=-6.362+(0.111×ΔDPB%)
	p	<0.001	<0.001
		10% decrease in SBP	10% decrease in DBP
Adiponectin	% change	-67.00	-45.36
	Mathematical model	ΔAdiponektin%=-45.711+(-6.7×ΔSBP%)	ΔAdiponektin%=-23.936+(-4.536×ΔDPB%)
	p	<0.001	<0.001
hsCRP	% change	-13.65	-4.472
	Mathematical model	ΔhsCRP%=-14.483+(-1.365×ΔSBP%)	ΔhsCRP%=-6.168+(-0.447×ΔDPB%)
	p	<0.001	0.052
TNF-alpha	% change	NA	-212.83
	Mathematical model	-	ΔTNF-alpha%=-218.036+(-21.283×ΔDPB%)
	p	-	<0.001
IL-6	% change	NA	2.14
	Mathematical model	-	ΔIL-6%=-2.438+(0.214×ΔDPB%)
	p	-	<0.001
Triglyceride	% change	5.75	4.37
	Mathematical model	ΔTriglyceride%=7.101+(0.575×ΔSBP%)	ΔTriglyceride%=5.719+(0.437×ΔDPB%)
	p	<0.001	<0.001
HDL cholesterol	% change	3.21	4.42
	Mathematical model	ΔHDL%=1.692+(0.321×ΔSBP%)	ΔHDL%=2.255+(0.442×ΔDPB%)
	p	<0.001	<0.001
BMI	% change	0.83	0.66
	Mathematical model	ΔBMI%=-1.111+(0.083×ΔSBP%)	ΔBMI%=-1.14+(0.066×ΔDPB%)
	p	0.065	<0.001

NA: not analyzed due to insufficient data, Δ: change.

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HOMA: Homeostatic model assessment; hsCRP: High sensitivity C reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin 6; HDL: High density lipoproteins; BMI: body mass index.

lodipine and valsartan on insulin sensitivity.[16] In that study, Fogari et al. suggested that the amlodipine/valsartan combination improved insulin sensitivity, a key factor for atherosclerosis, independently of the antihypertensive effects of the individual drugs in combination.[16] The reduction in insulin resistance by the single-pill combination of amlodipine/valsartan was calculated to be 6.5% greater than that caused by each individual drug; the formula we used here was postulated on the basis of this calculation.

Our results show that both amlodipine and valsartan treatments significantly lower blood pressure when administered individually. In terms of the effects of amlodipine and valsartan separately on each atherosclerotic parameter, both drugs improved the glycemic and inflammatory parameters. Valsartan had a more advantageous effect on BMI than amlodipine; however, the triglyceride level was increased in the valsartan group.

Amlodipine and valsartan decreased the HOMA index, a glycemic index indicative of insulin resistance, by 9.7% and 10.5%, and increased the level of adiponectin, an adipocyte-derived insulin sensitizer that is negatively correlated with insulin resistance, by 10.2% and 13.1%, respectively.[60] As calculated by the study formula, the combination of amlodipine and valsartan decreased the HOMA index by 21.5% and increased the adiponectin level by 24.7%. Our glycemic parameter results are in line with those obtained by Fogari et al.[16] Therefore, we suggest that a single-pill combination of valsartan and amlodipine has a favorable effect on insulin resistance, thus helping to prevent atherosclerosis and other cardiovascular events.

Obesity is among the etiological factors of insulin resistance, and is thus also a risk factor for atherosclerosis. We found that amlodipine increased BMI by 0.1%, valsartan decreased it by 2.0% and the combination regimen decreased it by 2.0%, showing that a fixed-dose combination of amlodipine and valsartan has an overall decreasing effect on BMI. Regarding lipid parameters, we evaluated the HDL cholesterol and triglyceride levels. HDL cholesterol was increased by amlodipine by 3.5% and decreased by valsartan by 1.1%, and adiponectin, an insulin sensitizer, was increased by 10.2% and 13.1%, respectively. As calculated using the study formula, the combination of amlodipine and valsartan increased HDL cholesterol by 2.6%. The strengthening effect of the combination therapy in the present study is similar to previous reports.[61] However, we found conflicting results regarding triglyceride levels. Amlodipine decreased the level of triglyceride by 0.04% and valsartan increased it by 1.18%. The overall effect of the combination was unfavorable in terms of atherosclerosis risk as it increased triglycerides by 1.19%.

Previous studies indicated a positive effect of renin-angiotensin-aldosterone system inhibitors and calcium channel blockers on lipid parameters and BMI.[62] The inconsistency between our data and previous reports for some findings may be due to the marked heterogeneity among the studies included in the model. Heterogeneity is a common problem in meta-analyses and modeling studies.

The analysis of the effects of valsartan and amlodipine on inflammatory parameters such as hsCRP, TNF-alpha and IL-6, revealed that both drugs individually decreased these parameters. Also, the reducing effect of the combination regimen on inflammatory parameters was greater than the sum of the reduction caused by each agent individually.

We performed correlation and regression analyses to evaluate the relationship between antihypertensive and anti-atherosclerotic effects of amlodipine and valsartan therapy and to quantify the anti-atherosclerotic benefit of each agent in addition to its blood pressure lowering effect. The effect on the atherosclerotic risk parameters of each agent was significantly correlated in a favorable direction with its primary effect-a reduction in blood pressure. According to regression modeling, a 10% decrease in blood pressure resulted in the highest percentage changes in inflammatory and glycemic parameters under amlodipine treatment (IL-6 and TNF-alpha with amlodipine, TNF-alpha and adiponectin with valsartan).

The greater anti-inflammatory, anti-glycemic, anti-atherogenic effects of the amlodipine/valsartan combination over its antihypertensive effect can be explained by the additive oxidative-stress-reducing effect of the combination therapy.[63]

Therefore, we suggest that the data of individual drugs used in combination therapies can be used to predict the effect of the combination regimen. Therefore, in addition to randomized clinical trials, modeling studies with appropriate endpoints would provide data for decision-making.

The present study had a number of limitations. First, not all atherosclerosis parameters were evaluated. The final conclusion regarding the atherosclerotic risk reduction by using a single-pill fixed-dose amlodipine and valsartan combination should be investigated further; such work should include other atherosclerosis parameters, such as insulin resistance. Second, it should be kept in mind that the mathematical formula used here was based on a previous study of the HOMA index parameter.[16] Although the HOMA index is closely related to insulin resistance, calculating the effect of the single-pill amlodipine/valsartan combination on atherosclerotic parameters other than the HOMA index using a HOMA index-based formula may not be appropriate. Another limitation is the heterogeneity of source studies in terms of the number of patients and the baseline values of the parameters evaluated. It was noted that the changes in parameters in this study were more marked, particularly for studies with high baseline values compared to those with low baseline values. To overcome these heterogeneity-related problems, percentage changes were calculated and used in all analyses, including the regression analysis. Taken together these limitations and characteristics of mathematical modeling, results of the present study should be considered preliminary, which must be validated by further prospective clinical studies.

CONCLUSION

In conclusion, the mathematical modeling of the effects of a single-pill combination of antihypertensive amlodipine/valsartan on atherosclerotic risk factors presented here was a pilot study. This study provides preliminary results on single-pill combination of antihypertensive amlodipine/valsartan, which need to be confirmed with prospective and controlled clinical studies. Therefore, our data will provide a basis for planning future similar studies of single-pill combination regimens used for treatment of hypertension or other chronic diseases.

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