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Clinical Study

Differential Effects in Cardiovascular Markers between High-Dose Angiotensin II Receptor Blocker Monotherapy and Combination Therapy of ARB with Calcium Channel Blocker in Hypertension (DEAR Trial)

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Background/Aims. Arterial stiffness is an independent risk factor for cardiovascular morbidity and mortality. This study was conducted to determine the effect of olmesartan (OLM) and azelnidipine (AZL) on arterial stiffness using the cardio-ankle vascular index (CAVI), which is a novel blood pressure (BP)-independent marker for arterial stiffness in hypertensive patients. *Methods*. Fifty-two consecutive hypertensive patients were randomly assigned either to a group treated with OLM monotherapy or to a group treated with OLM and AZL combination therapy. Clinical and biological parameters were measured before and 12 months after the start of this study. *Results*. Both therapies significantly and similarly reduced BP, augmentation index, and plasma aldosterone levels. The combination therapy significantly decreased CAVI and serum low-density lipoprotein (LDL-C) levels and these reductions were significantly greater than those produced with monotherapy. No significant differences in metabolic parameters were observed between the two therapies. *Conclusion*. The combination therapy with OLM and AZL had beneficial effects on arterial stiffness assessed by CAVI, LDL-C, and metabolism, despite the similar BP reduction, compared with OLM monotherapy. Since these markers are known to influence the future risk of cardiovascular events, combination therapy with OLM and AZL could be a useful choice for treating hypertensive patients.

1. Introduction

Arterial stiffness is an important risk factor for cardiovascular morbidity and mortality [1] and can be assessed using several methods including pulse pressure (PP), the augmentation index (AI), and pulse wave velocity (PWV). These parameters are readily determined on an outpatient basis and are well correlated with the risk of cardiovascular events [1–3]. The cardioankle vascular index (CAVI) is a novel marker of arterial stiffness that is calculated from the PWV and adjusted according to the BP values. Therefore, CAVI is more independent of the BP effect than conventional markers [4]. In addition, CAVI has been shown to be a biomarker for the evaluation of the severity of arterial fibrosis with higher sensitivity and specificity than PWV [4].

Both experimental data and clinical evidence suggest that the renin-angiotensin system (RAS) contributes to the pathogenesis of a number of cardiovascular diseases. Angiotensin II type 1 receptor blockers (ARBs) are currently some of the most wildly used antihypertensive drugs. ARBs reduce BP and also affect cardiovascular properties to protect heart and kidney function [5]. We have demonstrated that losartan, candesartan, and telmisartan improve arterial stiffness as assessed by CAVI [6–8]. Olmesartan (OLM) significantly decreases CAVI in patients with hypertension and diabetes [9, 10], but whether it is more effective alone

than together with azelnidipine (AZL) treatment remains uncertain.

The aim of this study was to evaluate the protective effects of OLM and add-on AZL on arterial stiffness in patients with essential hypertension. Arterial stiffness was assessed by measuring CAVI, the augmentation index (AI), and the maximum of the carotid intima-media thickness (MAX-IMT).

2. Patients and Methods

2.1. Study Population and Design. The subjects of the present study were 52 consecutive hypertensive patients with arterial stiffness and untreated hypertension or uncontrollable hypertension treated with medications other than RAS inhibitors. In patients without comorbid illness, hypertension was defined as a clinic systolic BP of >140 mmHg at any time and/or a clinic diastolic BP of >90 mmHg at any time and/or a systolic BP of >130 mmHg in the morning and/or a diastolic BP of >85 mmHg in the morning. In patients with diabetes mellitus and chronic kidney disease, hypertension was defined as a clinic systolic BP of >130 mmHg at any time and/or a clinic diastolic BP of >80 mmHg at any time. In patients with metabolic syndrome, hypertension was defined as a clinic systolic BP of >130 mmHg at any time and/or a clinic diastolic BP of >85 mmHg at any time.

All of the patients were randomly assigned to either a group treated with OLM alone (monotherapy group) or a group treated with OLM combined with AZL (combination therapy group). The target BP was defined as <130/85 mmHg in patients without any complications and <130/80 mmHg in patients with diabetes mellitus, chronic kidney disease, or metabolic syndrome. Patients in the monotherapy group were first treated with 20 mg/day of OLM for 4 weeks, and the dose of the OLM was subsequently titrated up to 40 mg/day. If the target BP was not achieved, additional antihypertensive medications other than RAS inhibitors and calcium channel blockers were added. Patients treated with combination therapy were first treated with 20 mg/day of OLM for 4 weeks, and 16 mg/day of AZL was subsequently added.

The dose of the OLM was increased up to 40 mg/day until the target BP was attained. Additional antihypertensive agents other than RAS inhibitors and calcium channel blockers were further added unless the BP fell below the target BP despite treatment with 40 mg/day of OLM combined with 16 mg/day of AZL. Clinical and biological parameters were measured before and 12 months after the start of this study. During the study period, previous medications and therapies other than antihypertensive drugs were continued. The study was approved by the Review Board of Keio University Medical School Hospital and written informed consent was obtained from every subject.

Serum levels of creatinine (Cr), estimated glomerular filtration rate (eGFR), cystatin C, potassium (K), uric acid (UA), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glycoalbumin (GA), plasma levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), the active renin concentrations (ARC), and aldosterone were measured in venous blood samples. The albumin creatinine ratio (ACR) was measured in urinary samples drawn on the morning after an overnight fast on the same days as the ankle-brachial index (ABI), cardioankle brachial index (CAVI), augmentation index (AI), and BP measurements and the maximum of carotid intima-media thickness (MAX-IMT) measurements were performed.

2.2. Ambulatory Blood Pressure Monitoring. An oscillometric-based device (TM-2431; A&D Co., Tokyo, Japan) was used to perform 24-hour ambulatory BP monitoring. The BP was measured every 30 minutes during the day (between 6:00 AM and 10:00 PM) and every 60 minutes during the night (between 10:00 PM and 6:00 AM). The mean values and the standard deviations of the ambulatory BP for each subject were calculated for a 24-hour period. The standard deviation of the ambulatory BP values was recorded as the variability of ambulatory BP in this study. The nocturnal decrease in BP was calculated as the average systolic BP during the day minus the average systolic BP during the night. The morning BP surge was calculated as the highest systolic BP during the first 2 hours after waking minus the lowest systolic BP during the night.

2.3. Cardioankle Vascular Index. The CAVI was measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi Co. Ltd., Tokyo, Japan), as described previously [11]. Cuffs were applied to bilateral upper arms and ankles, with the subjects lying in a supine position and holding their heads along the midline. ECG electrodes were placed on both wrists, and a microphone for detecting heart sounds was placed over the sternum. The patients rested in this supine position for at least 10 minutes before the start of monitoring. The CAVI was calculated using the following formula:

$$\mathrm{CAVI} = a\left\{\left(\frac{2\rho}{\Delta P}\right)\times \ln\left(\frac{P_s}{P_d}\right)\mathrm{PWV}^2\right\} + b, \tag{1}$$

where, P_s is the systolic blood pressure, P_d is the diastolic blood pressure, ΔP is $P_s - P_d$, ρ is blood density, and a and b are constants.

2.4. Augmentation Index. The AI was measured using an automated tonometric device (HEM-9000AI; Omron Healthcare Co., Ltd., Kyoto, Japan), as described previously [7]. Peripheral pressure waveforms were recorded over 30 seconds from the radial artery at the wrist with the subjects in a sitting position after resting for at least 5 minutes. The AI was calculated using the following formula

$$\mathrm{AI} = \frac{(\text{late systolic BP} - \text{diastolic BP (DBP)})}{(\text{systolic BP} - \text{DBP})}\times 100\ (\%). \tag{2}$$

2.5. Albumin Creatinine Ratio (ACR). ACR was evaluated on the basis of the mean albumin-to-creatinine ratio in three nonconsecutive overnight urine samples. The urinary concentrations of albumin and creatinine were determined using a turbidimetric immunoassay with a Superior-Microalbumin kit (DPC Co., Tokyo, Japan) and with the Jaffé reaction using an autoanalyzer.

2.6. Carotid Intima-Media Thickness. Ultrasonography B-mode imaging of the carotid artery was performed using a PowerVision 6000 machine (Toshiba, Tokyo, Japan) at a transducer frequency of 7.5 MHz. Each subject was examined while in a supine position. Up to 4 cm of the common carotid artery and the carotid bulb were scanned bilaterally using longitudinal and transverse projections. The images were focused on the far wall of the artery. Intima-media thickness (IMT) was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall. The greatest IMT value in the bilateral longitudinal projections was recorded as the MAX-IMT. All measurements were performed under blind conditions. The mean intraobserver and interobserver coefficients of variation for the maximum IMT were 4.3% and 4.7%, respectively.

2.7. Statistical Analyses. Analyses were performed using Microsoft Office Excel 2007 and StatView 5.0. software (SAS Institute Inc., Cary, NC, USA). Fisher's exact test was used to analyze sex and the frequency of diabetes mellitus, smoking, and the use of statins. The Mann-Whitney U test was used to analyze the age and body mass index. The changes in the biological parameters were analyzed using a Student t-test and a two-way analysis of variance for repeated measures combined with Tukey-Kramer posthoc tests. The contributions of changes in variables to changes in CAVI were tested using a regression analysis and an analysis of covariance. A P value $< .05$ was considered significant. Data are presented as the means ± SEM.

3. Results

No significant differences were observed in the baseline patient characteristics between the monotherapy group and the combination therapy group, with the exception of the serum K level (Table 1).

During the 12-month treatment period, the clinic systolic BP, the clinic diastolic BP, the 24-hour ambulatory systolic BP, the 24-hour ambulatory diastolic BP, the daytime systolic BP, the daytime diastolic BP, and the nighttime systolic BP decreased significantly both after the monotherapy and combination therapy, although no significant difference was observed between the two groups (Table 2). The nighttime diastolic BP decreased significantly after combination therapy whereas it did not change significantly after monotherapy. The nocturnal decrease reduced significantly after monotherapy whereas it did not change significantly after combination therapy. No significant changes in the morning SBP surge or the SBP variability were seen during the 12-month observation period in either group.

Figure 1 shows the changes in primary outcomes including ACR, ANP, BNP, ABI, MAX-IMT, and arterial stiffness as assessed by CAVI and AI in both groups. The CAVI decreased significantly from 8.4 ± 0.2 to 7.8 ± 0.2 after combination therapy, whereas it did not change significantly after monotherapy. The reduction after the combination therapy was significantly greater than the monotherapy. The AI decreased significantly after both monotherapy and combination therapy, from 83.8 ± 2.8 to 71.9 ± 3.7, and from 75.2 ± 4.3 to 68.8 ± 3.3, respectively. The ACR, ANP, BNP, and MAX-IMT did not change significantly in either group.

During the 12-month observation period, the serum LDL-C level decreased significantly from 127 ± 6 to 109 ± 8 mg/dL after combination therapy whereas a significant change was not observed after monotherapy (Figure 2). The reduction after combination therapy was significantly greater than the monotherapy. The plasma aldosterone level decreased significantly after both monotherapy and combination therapy, from 205 ± 23 to 155 ± 20 pg/dL, from 194 ± 18 to 125 ± 9 pg/dL, respectively, but no significant difference was observed between the two groups.

During the 12-month observation period, the reduction in CAVI, ABI, and serum LDL-C level was significantly greater after the combination therapy than the monotherapy after adjustment by the baseline value (Figures 3 and 4).

An ANCOVA analysis to examine whether the changes in the LDL-C, plasma aldosterone, ABI, AI, clinical BP, 24-h BP, daytime BP, and nighttime BP affected the change in CAVI during the combination therapy (Table 3). The changes in the ABI and clinic SBP contributed significantly to the decrease in CAVI after combination therapy.

4. Discussion

The present study demonstrates that OLM plus AZL significantly improve the CAVI in hypertensive patients, which reflects arterial stiffness. Although the reduction in the CAVI in the combination therapy group was correlated with clinic SBP, the beneficial effect of OLM and AZL on arterial stiffness was independent of BP changes. There was no significant difference in the reduction of brachial systolic BP between the two treatments. It has been shown that the combination of OLM and AZL has beneficial effects on the properties of the cardiovascular system. Stimulation of the Angiotensin II type 1 receptor results in stimulation of L-type calcium channels and induces the influx of extracellular calcium through calcium channels. This calcium influx results in a sustained elevation of intracellular calcium [12]. The L-type calcium channel blocker (CCB) AZL enhances the effect of ARBs on vascular remodeling independently of blood pressure [13]. Moreover, AZL has been implicated in augmenting the inhibitory effect of ARB compared with other L-type CCBs such as nifedipine and amlodipine [14]. Coadministration of AZL and OLM synergistically blunts oxidative stress partly through the inhibition of Akt activity and exerts antiatherogenic actions by inhibiting VSMC migration and vascular remodeling. Combination therapy has a beneficial effect on central systolic BP and arterial stiffness, and enhances the effects of monotherapy with these drugs in treating atherosclerosis [14–17]. The combination of AZL with OLM acts to prevent hypertensive heart failure with preserved systolic function in a rat model of this disease. Combination therapy produces a greater reduction in cardiac fibrosis by inhibiting the increase in elastolytic activity induced by activation of NADPH oxidase [18, 19]. Simultaneous treatment with exercise and OLM plus AZL produces renal protective effects in the rat model. This suggests that the treatment may

Table 1: Patient characteristics at baseline.

Characteristics	Olmesartan	Olmesartan + Azelnidipine	P
Number	26	26	.999
Age (yr)	54.1 ± 2.2	51.7 ± 2.0	.423
Male gender (n)	21	21	.495
BMI (kg/m^2)	23.5 ± 0.7	25.8 ± 0.9	.052
WC (cm)	84.8 ± 2.3	91.9 ± 2.8	.053
DM (n)	3	1	.610
Smoker (n)	0	5	.051
Use of statin (n)	5	4	.999
Serum Cr (mg/dL)	0.92 ± 0.05	0.91 ± 0.06	.880
eGFR (mL/min/1.73 m^2)	67.7 ± 2.9	72.0 ± 4.0	.390
Cystatin C (mg/dL)	0.74 ± 0.03	0.80 ± 0.06	.450
Serum K (mEq/L)	4.4 ± 0.1	4.2 ± 0.1	.010
Serum UA (mg/dL)	6.6 ± 0.3	6.0 ± 0.2	.345
Serum TG (mg/dL)	154 ± 23	196 ± 23	.209
Serum HDL-C (mg/dL)	60 ± 4	53 ± 3	.176
Serum LDL-C (mg/dL)	115 ± 6	122 ± 5	.451
GA (%)	14.6 ± 0.3	14.0 ± 0.3	.173
ANP (pg/mL)	29.8 ± 5.1	28.0 ± 3.2	.758
BNP (pg/mL)	19.8 ± 6.9	24.1 ± 11.3	.755
Plasma ARC (pg/mL)	9.6 ± 1.5	15.6 ± 4.3	.201
Plasma aldosterone (pg/mL)	205 ± 16	209 ± 21	.866
UAE (mg/gCr)	27.4 ± 10.9	37.4 ± 13.8	.572
Clinic SBP (mmHg)	159 ± 2	166 ± 5	.247
Clinic DBP (mmHg)	102 ± 8	105 ± 3	.444
24-h SBP (mmHg)	144 ± 2	145 ± 3	.772
24-h DBP (mmHg)	90 ± 1	90 ± 2	.766
Daytime SBP (mmHg)	148 ± 2	149 ± 3	.732
Daytime DBP (mmHg)	92 ± 1	92 ± 2	.769
Nighttime SBP (mmHg)	130 ± 3	128 ± 3	.608
Nighttime DBP (mmHg)	83 ± 2	80 ± 2	.297
Nocturnal decrease (mmHg)	17 ± 2	20 ± 3	.436
Morning surge (mmHg)	29 ± 3	38 ± 4	.090
SBP variablity (mmHg)	20 ± 1	22 ± 1	.178
ABI	1.07 ± 0.04	1.11 ± 0.01	.386
CAVI	7.8 ± 0.4	8.3 ± 0.2	.192
AI (%)	81.0 ± 2.5	78.6 ± 3.1	.563
Mean IMT (mm)	0.9 ± 0.1	0.9 ± 0.1	.797

Data are the means ± SEM. BMI, body mass index; WC, waist circumference; DM, diabetes mellitus; Cr, creatinine; eGFR, estimated glomerular filtration rate; K, potassium; UA, uric acid; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GA, glycoalbumin; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; ARC, active renin concentration; UAE, urinary albumin excretion; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABI, ankle-brachial index; CAVI, cardioankle vascular index; AI, augmentation index; IMT, intima-media thickness.

affect macrophage infiltration to the glomerulus, fibroblast accumulation in the glomerulus, mesangial activation, and podocyte differentiation [20]. Combination therapy protects against cyst enlargement in polycystic kidney disease by suppressing interstitial inflammation, fibrosis, and oxidative stress through upregulating eNOS expression during the course of the disease [21]. Taken together, the combination of OLM plus AZL provides additional cardiovascular protective effects on arterial stiffness resulting in an improvement in the CAVI. Since arterial stiffness is a powerful and independent risk factor for mortality in cardiovascular events, OLM plus AZL could be a first-line antihypertensive drug [22].

The AI is another marker of arterial stiffness and reflects the central aortic pressure [23, 24]. Vascular stiffening causes an increase in the amplitude and early return of the reflected wave during systole, with augmentation of the central systolic BP and a resultant increase in AI [25]. We have shown that ARBs decrease the AI [7, 8] but there has not been any prior study focusing on the effect of OLM on AI. In the present study, OLM produced a reduction in the AI whereas AZL has

Table 2: Changes in blood pressure during the study period.

Therapy	Olmesartan		Olmesartan + Azelnidipine		P
	Baseline	12 months	Baseline	12 months	Between therapies
Clinic SBP	157 ± 2	141 ± 3*	165 ± 6	143 ± 4*	.430
Clinic DBP	100 ± 2	87 ± 3*	106 ± 4	91 ± 3*	.813
24-h SBP	144 ± 3	129 ± 3*	147 ± 4	134 ± 4*	.726
24-h DBP	90 ± 2	81 ± 2*	92 ± 2	82 ± 2*	.779
Daytime SBP	149 ± 4	133 ± 3*	152 ± 4	138 ± 4*	.708
Daytime DBP	93 ± 9	84 ± 2*	94 ± 3	85 ± 2*	.820
Nighttime SBP	128 ± 5	113 ± 3*	129 ± 4	116 ± 5*	.852
Nighttime DBP	81 ± 4	72 ± 2	83 ± 2	72 ± 2*	.684
Nocturnal decrease	17 ± 2	9 ± 2*	20 ± 3	15 ± 3	.472
Morning surge	33 ± 5	32 ± 3	40 ± 5	38 ± 4	.921
SBP variability	21 ± 2	21 ± 2	23 ± 1	22 ± 2	.738

Units are mmHg. Data are the means ± SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure. *$P < .05$ versus the baseline value.

Table 3: Effects of percent changes in LDL-C, plasma aldosterone, ABI, AI, clinical BP, 24-h BP, daytime BP, and nighttime BP on percent changes in CAVI after combination therapy.

ANCOVA	Coefficient	SE	t-value	P
Intercept	−17.930	9.220	−1.945	.0696
ΔLDL	0.547	10.422	0.052	.9588
Intercept	−48.479	26.262	−1.846	.0878
Δplasma aldosterone	30.080	27.760	1.084	.2982
Intercept	−0.061	0.021	−2.893	.0106
ΔABI	−0.052	0.024	−0.479	.0441
Intercept	−7.475	3.985	−1.876	.0852
ΔAI	−1.744	4.932	−0.354	.7298
Intercept	−8.027	7.571	−1.060	.3048
Δclinic SBP	21.792	8.558	2.546	.0216
Intercept	−10.428	4.509	−2.313	.0344
Δclinic DBP	6.750	5.096	1.325	.2039
Intercept	−7.595	4.425	−1.717	.1066
△24h SBP	8.584	4.896	1.753	.1000
Intercept	−8.952	3.175	−2.819	.0129
Δ24h DBP	1.042	3.513	0.297	.7708
Intercept	−9.199	4.478	−2.054	.0578
Δdaytime SBP	6.761	4.955	1.364	.1926
Intercept	−9.811	3.172	−3.093	.0074
Δdaytime DBP	−0.711	3.509	−0.203	.8422
Intercept	−6.706	4.743	−1.414	.1778
Δnighttime SBP	9.909	5.248	1.888	.0785
Intercept	−7.240	3.250	−2.228	.0416
Δnighttime DBP	5.993	3.596	1.666	.1164

LDL-C, low-density lipoprotein cholesterol; ABI, ankle-brachial index; AI: augmentation index; BP: blood pressure; CAVI: cardioankle vascular index; ANCOVA: analysis of covariance; SE: standard error.

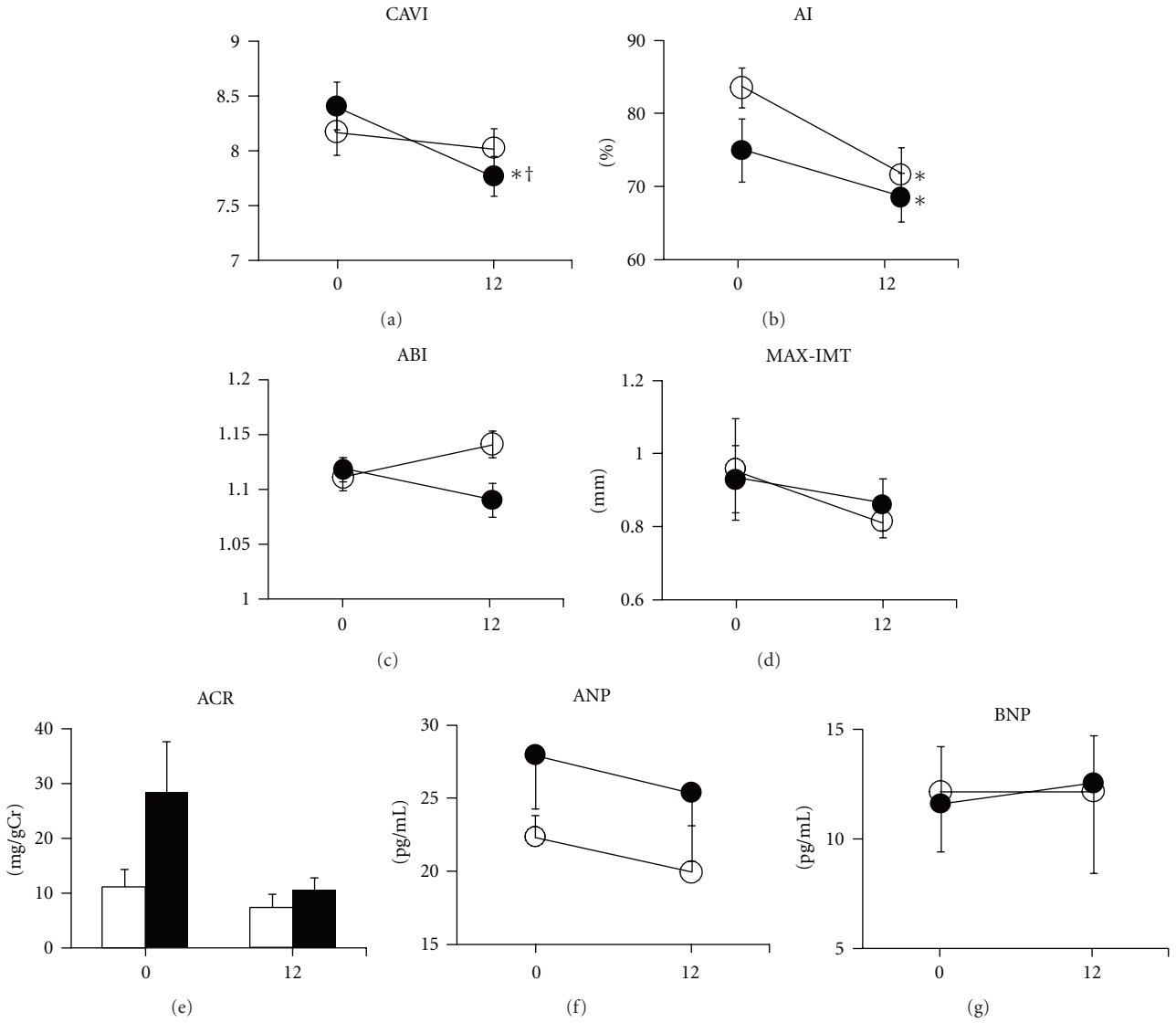

Figure 1: Cardioankle vascular index (CAVI), augmentation index (AI), ankle-brachial index (ABI), maximum of intima-media thickness (MAX-IMT), urinary albumin to creatinine ratio (ACR), serum atrial natriuretic peptide (ANP), and serum brain natriuretic peptide (BNP) at baseline and after 12 months of treatment with olmesartan monotherapy (open circles) or combination therapy with olmesartan and azelnidipine (closed circles). $^{*}P < .05$ versus the baseline value. $^{\dagger}P < .05$ versus the olmesartan monotherapy.

been previously shown to cause a significant reduction in AI in combination with ARBs [26]. This was confirmed in the present study indicating that combination therapy results in a reduction in AI. Since there was not any difference in the decrease in the AI between the two therapies, the reduction could be explained by the vascular protective effects of the OLM.

In this study a significant reduction in the serum LDL-C levels after the combination therapy was observed. This improvement in the serum LDL-C levels can be attributed to azelnidipine, since OLM monotherapy did not produce a decrease in the serum LDL-C levels. A previous study showed that the antioxidant effect of azelnidipine may have participated in the reduction of plasma malondialdehyde-modified LDL (MDA-LDL) levels [27]. The antioxidant effect of AZL possibly participated in the reduction of plasma MDA-LDL levels [28, 29]. In this respect, combination therapy would be preferable for hypertensive patients with comorbid dyslipidemia.

In the present study, the metabolic parameters were not significantly altered in either treatment group. This confirms previous reports that show that the incidence of adverse events is similar in the combination and the monotherapy groups [30]. Thus, the present study also confirmed the metabolic safety of OLM and AZL.

Some limitations in interpreting the results of the present study need to be recognized. These include that the trial population was comparatively small and the observation period was relatively short. A longer observation with a larger number of subjects might more clearly elucidate

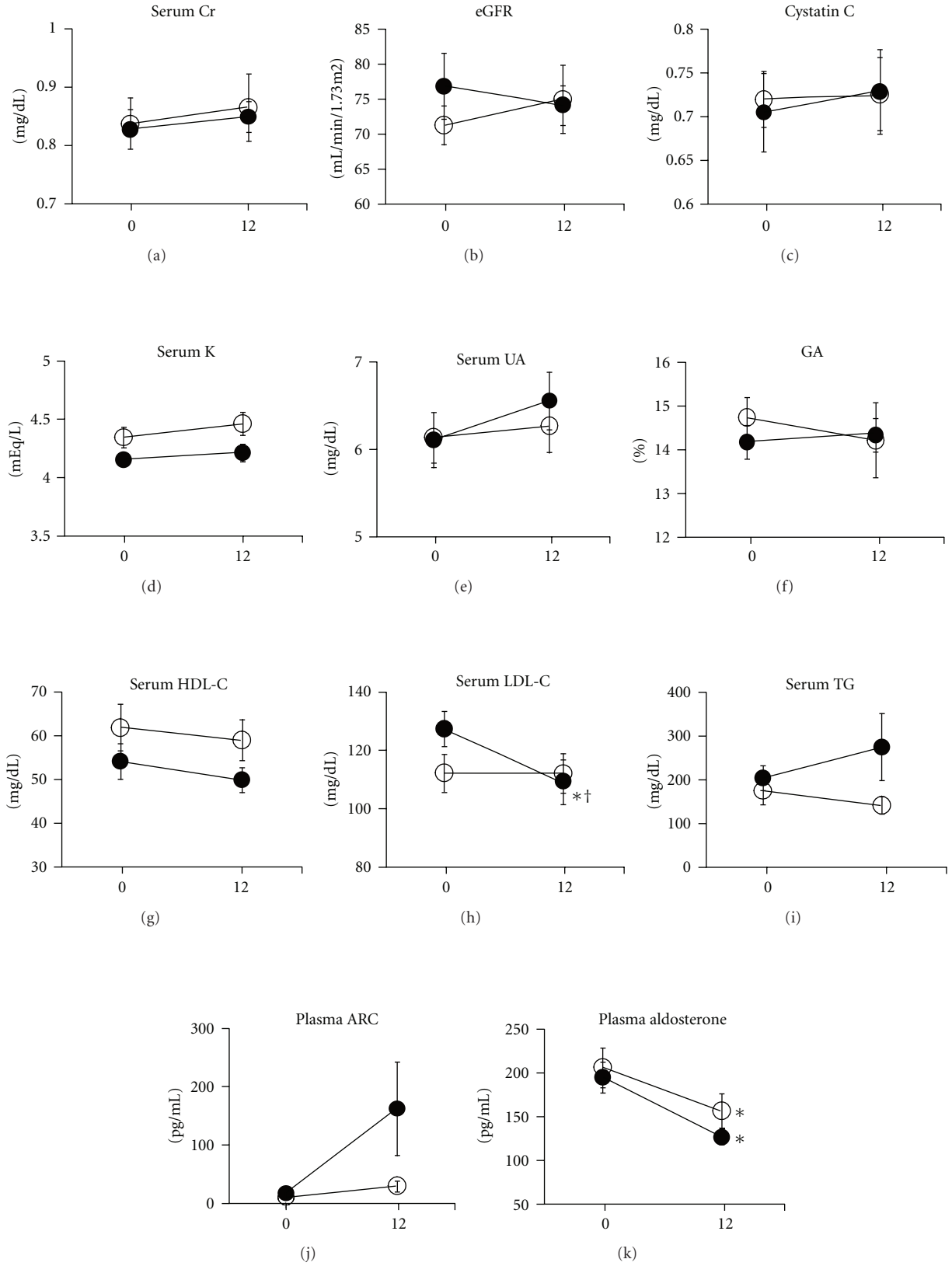

Figure 2: Serum creatinine (Cr), estimated glomerular filtration rate (eGFR), serum cystatin C, serum K, serum uric acid (UA), glycoalbumin (GA), serum high-density lipoprotein cholesterol (HDL), serum low-density lipoprotein cholesterol (LDL-C), serum triglyceride (TG), plasma active renin concentration (ARC), and plasma aldosterone at baseline and after 12 months of treatment with olmesartan monotherapy (open circles) or combination therapy with olmesartan and azelnidipine (closed circles). $^{*}P < .05$ versus the baseline value, $^{\dagger}P < .05$ versus the olmesartan monotherapy.

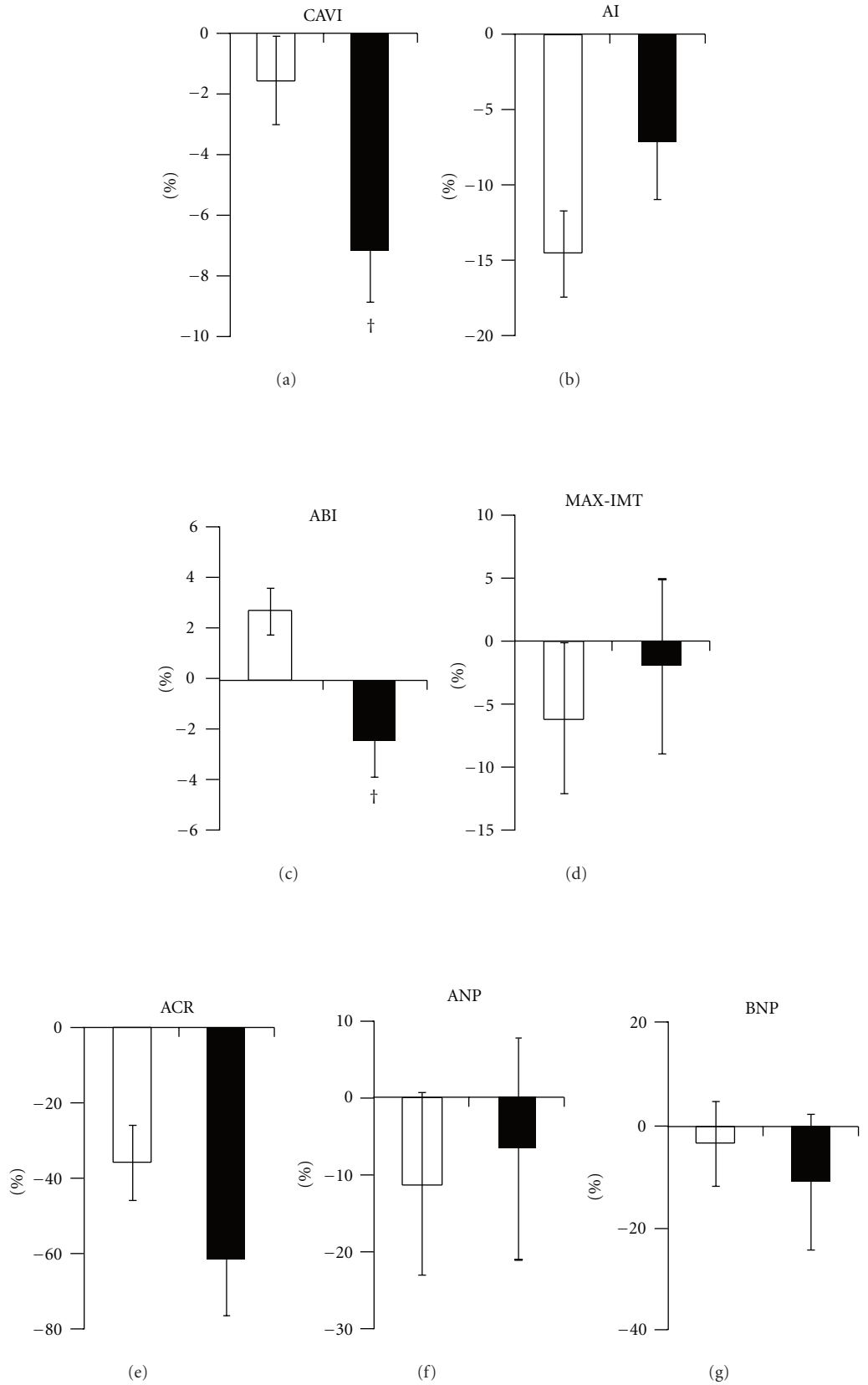

Figure 3: Changes from the baseline value for cardioankle vascular index (CAVI), augmentation index (AI), ankle-brachial index (ABI), maximum of intima-media thickness (MAX-IMT), urinary albumin to creatinine ratio (ACR), serum atrial natriuretic peptide (ANP), and serum brain natriuretic peptide (BNP) during 12 months of treatment with olmesartan monotherapy (open circles) or combination therapy with olmesartan and azelnidipine (closed circles). $^{\dagger}P < .05$ versus the group treated with olmesartan monotherapy.

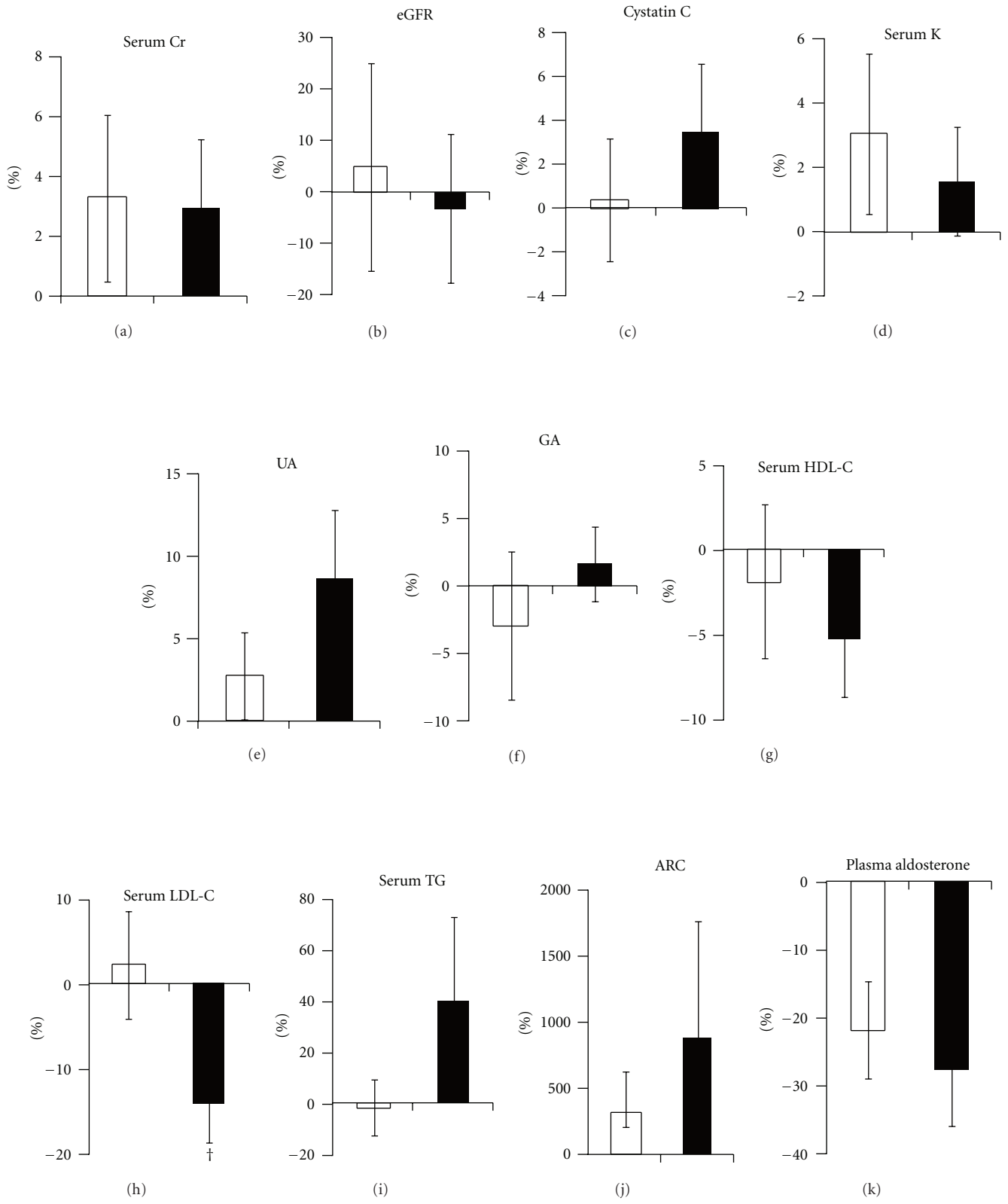

Figure 4: Changes from the baseline value for serum creatinine (Cr), estimated glomerular filtration rate (eGFR), serum cystatin C, serum K, serum uric acid (UA), glycoalbumin (GA), serum high density lipoprotein cholesterol (HDL), serum low density lipoprotein cholesterol (LDL-C), serum triglyceride (TG), plasma active renin concentration (ARC), and plasma aldosterone during 12 months of treatment with olmesartan monotherapy (open circles) or combination therapy with olmesartan and azelnidipine (closed circles). $^{\dagger}P < .05$ versus the olmesartan monotherapy.

the beneficial and adverse effects of OLM and AZL. In addition, prognostic events were not examined in the present study. Therefore, further studies are needed to confirm the benefits and safety of OLM and AZL therapy.

In conclusion, the combination treatment with OLM and AZL compared with OLM monotherapy produces beneficial effects on arterial stiffness as assessed by CAVI, as well as by the level of LDL-C, despite a similar reduction of BP. Since these markers are known to influence the future risk for cardiovascular events in hypertensive patients, the combination of OLM and AZL could well be a reasonable antihypertensive management for the treatment of hypertensive patients.

Conflict of Interests

The authors report no conflicts of interest.

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