Clinical Research

Effects of Antihypertensive Treatment with Angiotensin II Receptor Blockers on Lipid Profile: An Open Multi-Drug Comparison Trial

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Introduction: Dyslipidaemia is associated with high risk for cardiovascular disease and lipid management is arguably necessary, especially in hypertensive subjects. There is an implication that angiotensin receptor blockers (ARB) are characterised by a beneficial effect on lipid profile in addition to their blood pressure lowering properties. This study was conducted to evaluate blood pressure control and the plasma lipid profile in hypertensive patients after six months' treatment with ARB.

Methods: We studied 2438 consecutive, untreated patients with uncomplicated essential hypertension (mean blood pressure [BP] 167/100 mmHg). All patients underwent full lab and echo examination at drug-free baseline, which was repeated after at least 6 months of ARB monotherapy.

Results: Overall, ARB treatment reduced BP levels significantly ($p<0.0001$). Evaluating lipid profile changes, a significant ($p<0.0001$) reduction was noted in total cholesterol (TC: from 220 ± 39 to 216 ± 36 mg/dL), low density lipoprotein cholesterol (LDL: from 146 ± 35 to 141 ± 33 mg/dL), ratio of TC to high density lipoprotein cholesterol (HDL) (from 4.80 ± 1.35 to 4.64 ± 1.25), apolipoprotein (Apo) B (from 129 ± 32 to 124 ± 28 mg/dL), and triglyceride levels (from 130 ± 63 to 128 ± 61 mg/dL, $p=0.015$), while $ApoA_1$ and lipoprotein(a) levels were not significantly affected (149 ± 23 vs. 149 ± 22 and 24.9 ± 26.3 vs. 24.7 ± 26.4 mg/ dL, respectively, p=NS). Additionally, HDL levels increased from 48.2 ± 12.2 to 48.8 ± 11.9 mg/ dL, $p<0.0001$. According to the individual agent used, a different effect on lipid indices was observed.

Conclusions: ARB antihypertensive therapy may have a uniquely beneficial metabolic effect in addition to blood pressure lowering.

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Two of the major determinants of cardiovascular disease, hypertension and hyperlipidaemia, commonly coexist. There is a high prevalence (5-25%) of low high density lipoprotein (HDL) cholesterol and a higher prevalence of elevated triglyceride (TGL) levels in hypertensive compared to normotensive individuals.[1] Elevated total cholesterol (TC) levels augment the risk of cardiovascular disease associated with hypertension. In fact, a large proportion of the cardiovascular risk in patients with hypertension can be attributed to dyslipidaemia. The high attendant cardiovascular risk when these two conditions coexist warrants a strict emphasis on dietary and pharmacological therapy to successfully achieve blood pressure control. Contrary to the goal, it is reported that only 32% of hypertensive patients manage to improve their lipid profile, while this percentage falls to 11% for control of both blood pressure (BP) and lipids.[2]

Patients with the common lipid triad (hypertriglyceridaemia, high low-density lipoprotein cholesterol [LDL] and low HDL)

are at high risk for cardiovascular disease. This risk is even greater when the lipid triad is accompanied by hypertension and diabetes. The Heart Protection Study (HPS),[3] which included 20,536 patients, reported a 24% relative reduction in the risk of major cardiovascular events after active lipid treatment. In the same study, as predicted from the observational data, there was a 25% reduction in the relative risk of stroke.

The antihypertensive drugs in use today were designed primarily to affect cellular and biochemical mechanisms contributing to increased blood pressure, and not to address the disordered lipid metabolism that often accompanies hypertension. Angiotensin II receptor blockers (ARB) are efficient antihypertensive agents that act through inhibition of AT_1 receptors.[4] In experimental models, as well as some human studies, ARB have demonstrated the ability to affect lipid metabolism in a modest but significant way. More precisely, ARB improved the overproduction and accumulation of TGL in the liver, in experimental models, through mechanisms independent of their hypotensive action.[5] Furthermore, there are preclinical studies showing that telmisartan has a beneficial effect on metabolic parameters, including lipid abnormalities, due to its partial activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ).[6] In another study the administration of losartan to children of essential hypertensive parents, with early metabolic abnormalities, was followed by a significant reduction in the levels of TC and TGL.[7] Moreover, in a 12-month comparison study of telmisartan versus eprosartan a significant improvement in plasma lipids was noted and was attributed to varying pharmacokinetic/pharmacodynamic properties of telmisartan.[8] In humans, recently, a decrease in total cholesterol and LDL-cholesterol was seen in 60 hypertensive patients after 12-weeks' treatment with 80 mg valsartan daily, whereas no change was observed in apoprotein B lipoprotein.[9] According to the JNCVII guidelines ARB have little effect on lipid profile.[8] However, further studies need to be conducted in order to establish a clear relation between ARB antihypertensive treatment and lipid profile amelioration.

In our study, we explored the possible beneficial effect of ARB on the lipid profile of hypertensive patients with metabolic disorders.

Material and methods

From a total cohort of 22,000 patients who were treated in our clinic during the last two decades, 5000 patients with essential hypertension and no damage to target organs were recruited in this study, after informed consent was obtained. Full clinical and laboratory evaluation was carried out to exclude patients with acute or chronic inflammatory diseases, endocrine disorders, chronic obstructive pulmonary disease, malignancy, renal failure (creatinine >1.3 mg/dL), heart failure, recent (<6 months) cerebrovascular event, coronary artery disease (history of stable or unstable angina), ventricular arrhythmia, sinus bradycardia (<55 beats/min), sinus tachycardia (>100 beats/min) or atrioventricular conduction disturbance and severe hypercholesteraemia (TC levels >220 mg/dl). Patients on hypolipidaemic therapy, patients with poor compliance or drug-related side effects were also excluded from the study.

The diagnosis of arterial hypertension was based upon elevations of either systolic (>140 mmHg) or diastolic (>90 mmHg) blood pressure on three visits, one week apart, and mean values were calculated. A two-week washout period preceded the measurements for every patient already receiving antihypertensive treatment. In each visit, blood pressure was measured three times at one-minute intervals and with the patient resting comfortably, back supported in the sitting position after a 10-15 minute relaxation period. A mercury sphygmomanometer was used for all measurements, with a medium or a large size cuff according to the patient's arm circumference.

The present study included 2850 patients, who were responders to ARB monotherapy. Monotherapy was defined as treatment with one antihypertensive medication for at least 4 weeks. To achieve goal BP a low dose of chlorthalidone (12.5 mg once daily) was also added in 30% of participants. Patients who did not normalise blood pressure levels under ARB, even after the addition of low-dose chlorthalidone, were excluded from the study.

Thus, the study finally comprised 2438 patients (mean age 58.8 ± 12.9 years, 1371 men, 26.8% smokers and 12.5% diabetics). All patients underwent full laboratory examination at drug-free baseline, which was repeated after at least 6 months of ARB antihypertensive treatment at maximal dose. Patients were randomly treated with candesartan (n=470, 16 mg once daily), eprosartan (n=208, 600 mg once daily), telmisartan (n=274, 80 mg once daily), losartan (n=577, 50 mg once daily), irbesartan (n=508, 300 mg once daily), and valsartan (n=401, 1600 mg once daily). Study population characteristics in each drug group are presented in Table 1. Women as well as smokers were represented to similar degrees in all six groups. The differences in

Table 1. Study population characteristics.

	Candesartan	Eprosartan	Telmisartan	Losartan	Irbesartan	Valsartan	Total
n (M)	470 (233)	208 (106)	274 (165)	577 (328)	508 (316)	401 (223)	2438 (1371)
Age (y)	57.6±12.1	62.2±13.4	60.0±12.5	57.3±12.4	58.0±12.9	59.1±12.9	58.8±12.9
BMI (kg/m^2)	28.3±4.4	28.4±4.2	28.1±4.1	28.6±4.4	28.7±4.1	28.3±4.2	28.4±4.3
Obesity (%)†	57.9	58.7	56.6	60.1	63.0	57.6	59.4
Waist/Hip ratio	0.865±0.072	0.858±0.063	0.868±0.062	0.873±0.073	0.879±0.066	0.872±0.072	0.871±0.069
High W/H ratio (%)‡	45.5	40.9	44.5	54.9	51.0	51.4	49.3
Smokers (%)	26.8	19.7	20.4	32.8	28.5	24.2	26.8
IGT (%)	17.4	20.7	22.6	21.0	23.0	19.7	20.7
Diabetes melitus (%)	12.8	11.5	10.9	13.5	13.0	11.5	12.5

† Body mass index >27
‡ W/H – waist/hip ratio >0.9 in men, >0.8 in women
BMI – body mass index; IGT – impaired glycose tolerance; M – males

body mass index (BMI), waist-to-hip (W/H) ratio and plasma renin activity between the six groups were not significant. Lipid factors were measured before and six months after ARB treatment. The blood samples were collected from the antecubital vein between 8 a.m. and 10 a.m., with the patient in a sitting position, after 12 hours of fasting and avoiding alcohol. The biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories. All biochemical examinations (serum TC, HDL and TGL) were measured using a chromatographic enzymic method in a Technicon automatic analyser RA-1000 (Dade Behring, Marburg, Germany). Oxidised LDL was measured in plasma using an enzyme-linked immunosorbent assay (ELISA) kit (Mercodia AB, Uppsala, Sweden). HDL-cholesterol was determined after precipitation of the apolipoprotein B-containing lipoproteins with dextran-magnesium-chloride. Non-HDL-cholesterol was calculated by the formula: total cholesterol minus HDL-cholesterol. Lipoprotein(a) [Lp(a)] was measured by latex enhanced turbidimetric immunoassay. Serum for the measurement of these lipids was harvested immediately after admission. LDL-cholesterol was calculated using the Friedewald formulae: {total cholesterol} - {HDL-cholesterol} - (1/5) (triglycerides). Plasma renin activity was measured by radioimmunoassay of angiotensin I after timed incubation of plasma under optimised conditions. The baseline values in each drug group are listed in Table 2.

Mean values and standard deviations of variables, at baseline and after therapy, were calculated and compared using the paired Student t-test. Significance was assumed at a two-tailed probability value of <0.05. Statistical analysis was done using SPSS for Windows statistical software, version 10.0 (SPSS, Chicago, IL).

Results

BP response

In all patients, after six months' therapy blood pressure levels had dropped to within the normal range (from

Table 2. Baseline lipid profile of the study population.

	Candesartan	Eprosartan	Telmisartan	Losartan	Irbesartan	Valsartan	Total
n (M)	470	208	274	577	508	401	2438
TC (mg/dL)	220±40	212±35	217±36	225±41	221±38	218±42	220±39
TGL (mg/dL)	132±69	121±48	126±58	132±64	133±62	132±65	130±63
HDL (mg/dL)	48.7±11.8	50.7±12.7	49.0±12.8	47.6±11.8	47.7±12.3	47.4±12.1	48.2±12.2
LDL (mg/dL)	145±35	137±31	143±31	151±37	147±34	144±37	146±35
TC/HDL	4.74±1.35	4.39±1.15	4.67±1.24	4.98±1.44	4.89±1.39	4.83±1.30	4.80±1.35
ApoA, (mg/dL)	148±23	151±24	148±22	150±24	148±23	149±23	149±23
ApoB (mg/dL)	127±31	118±23	124±26	135±33	129±32	129±33	129±32
Lp(a) (mg/dL)	23.3±25.6	24.2±28.0	24.3±26.7	27.6±27.4	24.5±24.3	24.4±26.6	24.9±26.3

TC – total cholesterol; TGL – triglycerides lipoprotein; HDL – high density lipoprotein; LDL – low density lipoprotein; ApoA – apolipoprotein A
ApoB – apolipoprotein B; Lp(a) – lipoprotein A

Table 3. Systolic and diastolic blood pressure changes according to the specific agent used.

		Candesartan	Eprosartan	Telmisartan	Losartan	Irbesartan	Valsartan	Total
	n	470	208	274	577	508	401	2438
SBP	Pre	168.5±13.5	165.8±11.3	166.8±13.2	166.1±13.2	168.9±14.1	166.1±12.7	167.2±13.3
	Post	130±9.0	131.7±8.0	132.5±8.4	132.0±9.1	132.1±8.3	130.7±8.6	131.6±8.7
	Δ	-38.5±13.1	-34.7±13.2	-34.3±9.7	-34.2±9.6	-37.0±11.6	-37.4±18.4	-36.2±12.9
DBP	Pre	100.5±8.3	98.07±8.1	100.3±7.5	101.0±7.0	101.4±8.6	100.5±7.4	100.6±7.8
	Post	81.4±5.5	80.9±5.8	81.7±5.6	81.9±5.4	82.0±5.4	81.7±5.4	81.7±5.5
	Δ	-19.5±7.7	-18.2±7.8	-18.6±5.1	-19.1±4.8	-19.6±7.1	-20.1±10.2	-19.3±7.3
PRA	Pre	1.23±1.40	1.21±1.49	1.20±1.47	1.14±1.125	1.29±1.57	2.31±20.7	1.39±8.53
	Post	3.96±4.16	4.19±5.33	3.38±4.41	3.05±3.40	4.24±5.52	3.72±5.36	3.72±4.68
	Δ	2.72±3.34	2.98±4.91	2.18±3.66	1.91±2.92	2.94±4.75	1.43±21.5	2.33±9.28

SBP – systolic blood pressure; DBP – diastolic blood pressure; PRA – plasma renin activity.

167.2 ± 13.3 / 100.6 ± 7.8 to 131.6 ± 8.7 / 81.7 ± 5.5), while plasma renin activity levels increased during the same period (from 1.39 ± 8.53 to 3.72 ± 4.68) (Table 3). Candesartan was the most effective in reducing systolic BP (-38.5 ± 13.1, p<0.0001), followed by valsartan (-37.4 ± 18.4), irbesartan (-37.0 ± 11.6), eprosartan (-34.7 ± 13.2), telmisartan (-34.3 ± 9.7) and losartan (-34.2 ± 9.6). Diastolic BP was most reduced with valsartan (-20.1 ± 10.2), followed by irbesartan (-19.6 ± 7.1), candesartan (-19.5 ± 7.7), losartan (-19.1 ± 4.8), telmisartan (-18.6 ± 5.1) and finally eprosartan (-18.2 ± 7.8).

Lifestyle modifications

All patients received the same dietary hypolipidaemic recommendations, but there was no significant difference in patients' BMI after six months' treatment with losartan (from 28.57 ± 4.38 to 28.56 ± 4.36), irbesartan (from 28.64 ± 4.13 to 28.57 ± 4.56), valsartan (from 28.34 ± 4.21 to 28.3 ± 4.66), candesartan (from 28.31 ± 4.38 to 28.28 ± 4.69), eprosartan (from 28.36 ± 4.21 to 28.35 ± 4.32) or telmisartan (from 28.11 ± 4.12 to 28.09 ± 4.11). Furthermore, no difference was noted in the patients' smoking habits during the six months.

Whole study cohort

Overall, a statistically significant (p<0.0001) reduction was noted in TC (from 220 ± 39 to 216 ± 36 mg/dL), LDL (from 146 ± 35 to 141 ± 33 mg/dL), TC/HDL (from 4.80 ± 1.35 to 4.64 ± 1.25) and apolipoprotein (Apo) B levels (from 129 ± 32 to 124 ± 28 mg/dL). TGL levels also decreased (from 130 ± 63 to 128 ± 61 mg/dL, p=0.015), while $ApoA_1$ and Lp(a) levels were not significantly affected (149 ± 23 vs. 149 ± 22 and 24.9 ± 26.3 vs. 24.7 ± 26.4 mg/ dL, respectively). Additionally, HDL levels increased (from 48.2 ± 12.2 to 48.8 ± 11.9 mg/dL, p<0.0001).

Lipid parameter changes according to the specific agent used are presented in Figures 1 and 2. TC levels were decreased most by candesartan (from 220 ± 40 to 213 ± 37 mg/dL, p<0.0001) followed by valsartan (from 218 ± 42 to 214 ± 35 mg/dL, p<0.0001), irbesartan (from 221 ± 38 to 216 ± 34 mg/dL, p<0.0001) and losartan (from 225 ± 41 to 221 ± 37 mg/dL, p=0.0005), but not with telmisartan and eprosartan (217 ± 36 vs. 216 ± 38 and 212 ± 35 vs. 211 ± 37 mg/dL, respectively, p=NS). LDL levels were considerably affected by candesartan (from 145 ± 35 to 139 ± 33 mg/dL, p<0.0001), irbesartan (from 147 ± 34 to 141 ± 32 mg/dL, p<0.0001), valsartan (from 144 ± 37 to 140 ± 32 mg/dL, p<0.0001), losartan (from 151 ± 37 to 147 ± 34 mg/dL, p<0.0001), but again no change was seen with telmisartan and eprosartan (143 ± 31 vs. 141 ± 32 and 137 ± 31 vs. 136 ± 32 mg/dL, p=NS). ApoB levels were also significantly (p<0.0001) reduced by valsartan (from 129 ± 33 to 123 ± 27 mg/dL), followed by irbesartan (from 129 ± 32 to 123 ± 28 mg/dL), candesartan (from 127 ± 31 to 122 ± 28 mg/dL) and losartan (from 135 ± 33 to 131 ± 29 mg/dL); however, no significant alterations were observed with telmisartan and eprosartan (124 ± 26 vs. 122 ± 27 and 118 ± 28 vs. 119 ± 30 mg/dL). The TC/HDL ratio was also strongly affected by valsartan (from 4.83 ± 1.30 to 4.62 ± 1.14, p<0.0001), losartan (from 4.98 ± 1.44 to 4.77 ± 1.28, p<0.0001), irbesartan (from 4.89 ± 1.39 to 4.69 ± 1.25, p<0.0001) and candasartan (from 4.74 ± 1.35

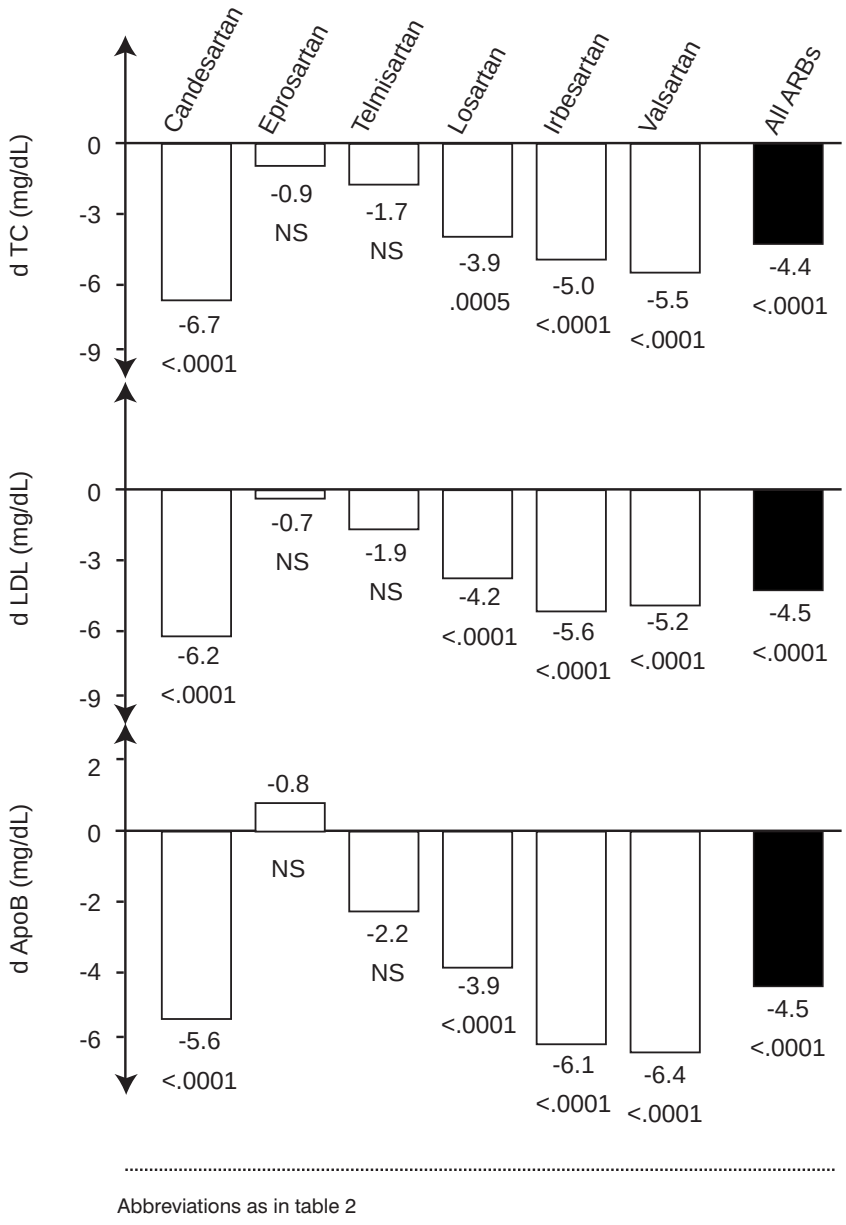

Figure 1. TC, lDL and ApoB alterations according to the specific agent used.

to 4.55 ± 1.32, p<0.0001), but not by telmisartan and eprosartan (4.67 ± 1.24 vs. 4.66 ± 1.27 and 4.39 ± 1.15 vs. 4.38 ± 1.14, p=NS). TGL levels decreased only in the valsartan and losartan groups (from 132 ± 65 to 127 ± 57 mg/dL, p=0.02 and from 132 ± 64 to 128 ± 54 mg/dL, p=0.04, respectively) and not (p=NS) in the candesartan (132 ± 69 vs. 128 ± 67 mg/dL), irbesartan (133 ± 62 vs. 132 ± 67), eprosartan (121 ± 48 vs. 121 ± 49 mg/dL) and telmisartan (126 ± 58 vs. 129 ± 63 mg/dL) groups. Finally, HDL levels increased significantly with losartan (from 47.6 ± 11.8 to 48.6 ± 11.8 mg/dL, p=0.0009), valsartan (from 47.4 ± 12.1 to 48.3 ± 11.4 mg/dL, p=0.003) and irbesartan (from 47.7 ± 12.3 to 48.4 ± 11.9 mg/dL, p=0.006), but not (p=NS) with candesartan (48.7 ± 11.8 vs. 49.1 ± 11.7 mg/dL), telmisartan (49.0 ± 12.8 vs. 48.7 ± 12.5 mg/dL) and eprosartan (50.7 ± 12.7 vs. 50.6 ± 13.1 mg/dL).

Discussion

Hypertension is not the only determinant of cardiovascular damage and the propensity of a subject to devel-

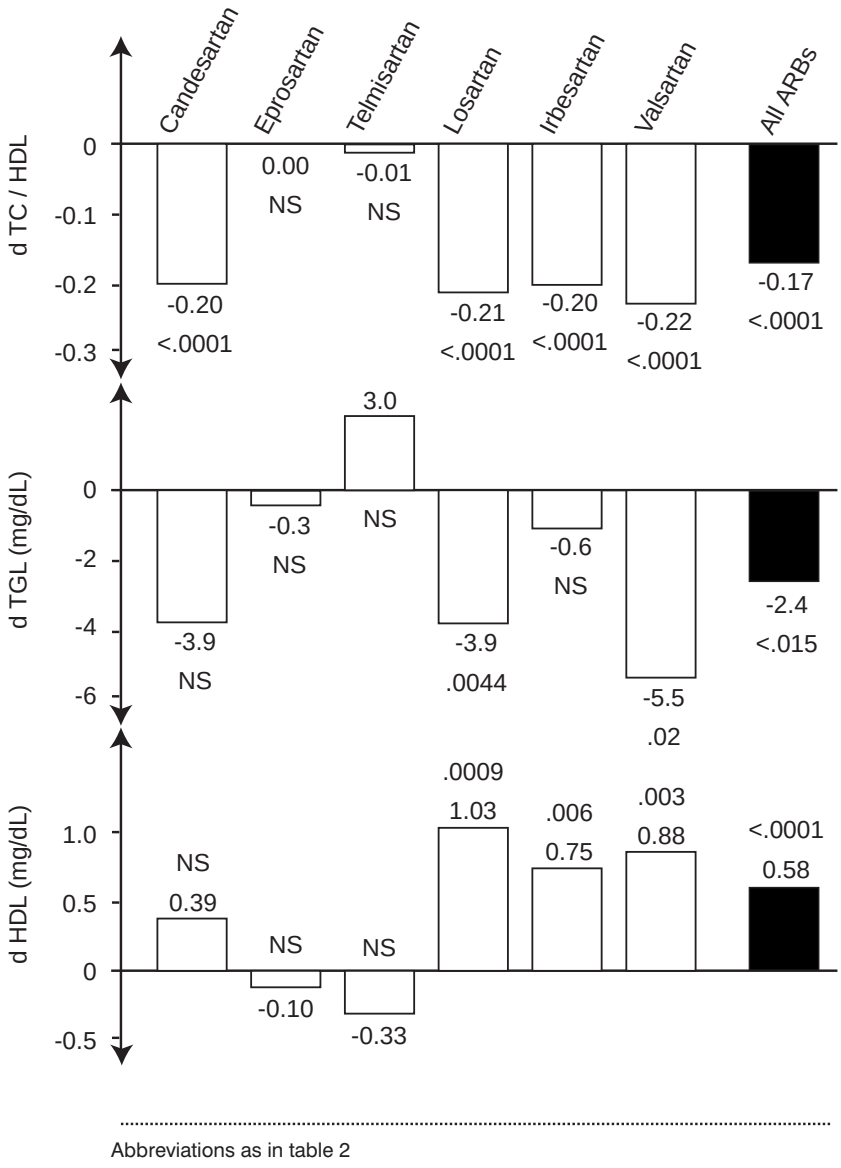

Figure 2. TC/HDL ratio, TGL and HDL changes in each drug group.

op atherosclerotic vascular disease is markedly affected by the presence of traditional risk factors, such as age, gender, obesity, smoking, diabetes and dyslipidaemia.[9] Epidemiological studies provide a large body of evidence for the independent relationship between lipid profile and cardiovascular risk.[10] Treating hypertension along with dietary and lifestyle modifications is the cornerstone of successful clinical management of these patients.[11] There is no doubt that the management of lipid disorders in hypertensive patients ameliorates their total cardiovascular risk. Clinical trials suggest that some antihypertensive agents may have a beneficial effect on lipid metabolism, through various possible mechanisms.[12]

The main findings of our study are as follows. First, ARB administration regulated blood pressure to within the normal range, without any additional agent, in 70% of our patients. Candesartan was the most effective in lowering SBP ($p<0.0001$), while DBP regulation was better achieved with valsartan ($p<0.0001$). The percentages of patients in each drug group who needed the addition of chlorthalidone to achieve opti-

mal BP control were not different. The ability of ARB to lower blood pressure in patients with hypertension is unquestionable. In our study ARB administration was based upon plasma renin activity levels, which significantly increased after 6 months' therapy ($p<0.0001$). Accumulating scientific data suggests that antihypertensive treatment with angiotensin II antagonists significantly reduces a range of novel risk determinants, including inflammation and haemostatic markers. The results of some of these trials have expanded the indications for ARB.[13]

Secondly, we evaluated the patients' full lipid profile before and after 6 months of ARB monotherapy at maximal dose. We noted a positive effect of ARB on most lipid indices, as well as different alterations in lipid levels according to the individual agent used. More precisely, TC and LDL levels were mostly decreased in the candesartan subgroup ($p<0.0001$), while the reduction in ApoB levels and TC/HDL ratio was best in the valsartan subgroup ($p<0.0001$). TGL levels were decreased only in the valsartan ($p=0.02$) and losartan ($p=0.04$) subgroups. No significant alteration was noted in $ApoA_1$ and Lp(a) levels. Finally, ARB affected HDL levels positively, especially losartan ($p=0.0009$) This improvement in lipid profile could not be explained by confounding factors, such as nutrition, body weight or smoking habits, which were similar in all drug groups during the six-month period of ARB monotherapy. Although the changes in lipid levels were small, which dictates a cautious interpretation, this finding is consistent with the possibility of an ARB-induced, angiotensin II-receptor-dependent amelioration of the lipid profile in essential hypertensive patients.

It is possible that the lipid lowering property of ARB is due to numerous different mechanisms. There are studies[14] suggesting that some ARB activate PPAR-γ, which regulates lipid metabolism. It seems that some ARB can activate PPAR-γ and therefore reduce TGL and LDL levels. Furthermore, there is experimental evidence suggesting an interaction between the angiotensin system and lipid metabolism. More precisely, it has been suggested that dyslipidaemia may activate angiotensin II endothelial injury and lipid peroxidation via an AT_1 receptor-mediated mechanism.[15] In rabbits a marked increase of AT_1 receptor density has been shown in hypercholesterolaemia,[16] while in humans a close relationship has been found between AT_1 receptor density and plasma LDL-cholesterol, while the use of statins to lower cholesterol was associated with AT_1 receptor downregulation.[17] The whole spectrum of possible mechanisms through which ARB exert a beneficial effect on lipid metabolism remains unknown.

We conclude that ARB antihypertensive treatment may result in an amelioration of cardiovascular risk factors, not only through arterial pressure regulation but also through the reduction of lipid markers, in a range depending on the individual agent used.

Study Limitations

Our study had some limitations. First the design of the study does not allow us to support any possible explanation for these results. Perhaps PPAR-γ activation and AT1 blockade are possible mechanisms explaining the beneficial effect of some ARB on lipid metabolism. The fact that agents such as telmisartan and eprosartan did not manage to affect HDL, TC/HDL, TC and ApoB levels implies that not all ARB have the same action on these indices, pointing to different pharmacodynamic and pharmacokinetic properties. Second, no comparison of ARB with other antihypertensive agents, regarding their impact on lipid profile, was attempted. This will be a possible target of future studies.

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