

## Pleiotropic Effects of Antihypertensive Drugs

Omran M.O. Alhamami<sup>1\*</sup>, Jabbar Y. AL-Mayah<sup>2</sup>, Najah R. AL-Mousawi<sup>2</sup>,  
Hayder I. J. AL- Mousawi<sup>2</sup>

1. Department of Pharmaceutics, College of Pharmacy and Medical Sciences, Amman University, P.O. Box 181, post code 19328, Amman. Jordan.
2. Department of Pharmacology, College of Medicine, Kufa University, Kufa, P.O Box 18, Najaf, Iraq.  
E-mail: [omalhamami@hotmail.com](mailto:omalhamami@hotmail.com)

*This work was done at the University of Kufa, Kufa, Iraq.*

**Abstract:** The haemostatic state and the lipid profile in hypertensive patients and the effects of antihypertensive drugs on these parameters were investigated. C-reactive protein (CRP) was also measured for its great role in detecting future cardiovascular events. One hundred and one patients with essential hypertension of mild to moderate grades were included in this study. Those patients were either on antihypertensive therapy, off-treatment or they were newly diagnosed hypertensives. Forty eight normotensive subjects were selected from the general population and acted as control. Serum lipids (total cholesterol, TC; triglyceride, TG; low density lipoprotein, LDL; high density lipoprotein, HDL and very low density lipoprotein, VLDL) and haemostatic parameters (prothrombin time, PT; partial thromboplastin time, PTT and platelets count) as well as renal and hepatic functions were assessed in all hypertensive and normal subjects. CRP was also measured. A two-tailed independent t-test at  $\alpha = 0.05$  level of significance was used. The results indicated that the HDL is significantly lower and VLDL is significantly higher in hypertensive patients than normotensive subjects. Hypertensives on atenolol and those on diuretics have significantly higher levels of TC, TG and LDL and significantly lower HDL levels than normotensives. Hypertensive patients on captopril have significantly higher levels of HDL and significantly lower levels of TC compared with patients on atenolol. Patients with longer duration of hypertension have greater possibility of having positive CRP and patients with positive CRP have higher LDL and lower HDL levels. No significant differences were found in PT, PTT and platelets count between hypertensives and normotensives. As a conclusion, antihypertensives do have an effect on lipids and CRP, namely  $\beta$ -selective blockers like atenolol which may induce a shift towards a more atherogenic lipid profile. This means careful choice of antihypertensives according to comorbid disease or risk factors.

(CRP)

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48

( TC,TG, LDL, HDL, VLDL)			
		(PT, PTT, platelet counts)	
(VLDL)		(HDL)	
(Atenolol)			
(HDL)		(TC, TG & LDL)	
(HDL)		(Captopril)	
		(Atenolol)	(TC)
( LDL)		(CRP)	(CRP)
	(PT, PTT, & Platelets count)		(HDL)
	(Atenolol)	(CRP)	
		( LDL)	(HDL)

**Keywords:** Antihypertensive drugs, serum lipids, haemostatic parameters, Pleiotropic effects

### 1. Introduction

The severity of target organ damage is markedly influenced by coexisting factors such as age, gender, obesity, diabetes and dyslipidemia [1]. Haemostatic system is directly involved in the atherosclerotic process and may affect the impact of hypertension on cardiovascular morbidity [2,3]. Because adverse metabolic effects probably reduce the benefit of blood pressure lowering therapy, researches have been concerned on the effects of different antihypertensive agents on serum lipid levels [4,5]. Many drugs adversely affect serum lipids like thiazides and non-selective beta-blockers[6]. Recently, essential hypertension has been linked to abnormalities in glucose and triglycerides metabolism [7]. This effect was ubiquitous and was seen with different classes of agents [6,8].

Endothelial damage, platelets hyperactivity and other changes of blood coagulation may play a role in the vascular complications of essential hypertension [9]. Undesirable changes of haemostasis induced by some antihypertensive drugs can encourage the acceleration of atherogenesis. Therefore, restoration of endothelial function and reduction of increased platelets aggregation in essential hypertension are one of the aims of modern

antihypertensive therapy [9]. Many antihypertensive drugs can influence the prothrombotic state in hypertension [10]. Antihypertensive drugs may perhaps act by influencing both the coagulation and fibrinolytic system in hypertension, adding to their protective potential with respect to cardiovascular end point [11]. Beyond their blood pressure lowering potential, some antihypertensive agents may exhibit a number of non-hemodynamic effects such as changes in serum electrolytes, lipid and carbohydrate metabolism, endothelial function, vascular smooth muscle and cardiomyocyte growth and possible fibrinolysis [10].

Predicting the future cardiovascular events in high-risk patients with advanced atherosclerosis remain challenging. This is because traditional risk factors account for only a part of the individual's susceptibility for an adverse outcome [12]. Among the panel of new biological markers indicative of impending cardiovascular events, compelling evidence suggests that high-sensitivity CRP represents a powerful cardiovascular risk predictor [13], with a predictive value exceeding that of LDL-C [14].

It was the purpose of this study to assess the haemostatic state and the lipid profile in hypertensive patients and to clarify the effects of antihypertensive drugs on these parameters. In addition, CRP was also measured for its great role in detecting future cardiovascular events. CRP, as a marker of inflammation, identifies a different high-risk group than the traditional parameters of the metabolic syndrome and provides additional information on the cardiovascular risk [14].

## **Materials and Methods**

### **Materials**

All the materials (unless otherwise stated) and reagents used in the study were obtained from Biomerieux Company ( France). Latex reagent was obtained from Plasmatec Company (UK). Liquid calcium-thromboplastin was obtained from Diaplastin ( Diamed).

### **Patients and study design**

One-hundred one patients (age:  $49\pm 9.9$  years, weight:  $76\pm 10.2$  Kg; 50 men and 51 women) with mild to moderate essential hypertension attending Al-Najaf Teaching Hospital ( Najaf, Iraq) in the period between Feb.14 to Dec. 3, 2004 were included in this study. Our investigations were performed after approval by our local health ethical committee at College of Medicine, Kufa University. A written and signed in-formed consents from all subjects (patients and controls) under study were provided. These patients were either on their antihypertensive treatment, off treatment (discontinued their

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treatment for at least 6 weeks or patients who are on no treatment) or they are newly diagnosed with essential hypertension. Diagnosis of hypertension was established by standard criteria[11]. The patients underwent full history and complete physical examination. Patients with the following criteria were excluded from the study:

1. Age > 75 year [15]
2. Patients with diabetes, pregnant ladies, obese patients and patients with advanced renal failure (because these conditions are known to affect haemostatic parameters) [15].
3. Patients on anticoagulant therapy [15].
4. Patients with secondary form of hypertension [16].
5. Patients with liver disease.

Forty eight normotensive subjects (age  $48 \pm 8.3$  years;  $73 \pm 9.8$  Kg) were selected from the general population and acted as control. They were not taking any medication and did not have any concomitant disease.

Hypertensive patients were divided into two groups; group I: patients on antihypertensive therapy. Group II: hypertensive patients taking no antihypertensive drugs or they are off-treatment. Group I further subdivided into: (a) Beta-blockers-treated patients, (b) ACEI-treated patients and (c) patients on multiple therapy.

Thirty three of the hypertensive patients included in this study were treated with monotherapy, and fifteen patients on multiple drug therapy. The doses used were: atenolol (50-100 mg daily), captopril (25 mg 3 times a day) and hydrochlorthiazide (50 mg daily).

### **Blood pressure measurement**

Blood pressure was measured in an office sitting by the conventional cuff-method with a mercury manometer. Patients remained seated for at least 10 min. before measurement. Systolic blood pressure measured at the first Korotkoff sound and diastolic blood pressure was determined at the 5<sup>th</sup>. Korotkoff sound [17].

### **Laboratory analysis**

Subjects fasted for at least 12-14 hours, after which the blood was drawn between 8.00 and 10.00 am with the participant in sitting position. 1.9 ml of the blood was added to 0.1 ml of trisodium citrate in a glass tubes to measure PT, PTT, platelets. 4 ml of blood was put in tube for biochemical analysis including : serum lipids, serum creatinine, liver function tests ( serum glutamic oxaloacetate transaminase, S.GOT, serum glutamic pyruvic transaminase, S.GPT, and serum alkaline phosphatase). These tests were

done to exclude hepatic dysfunction. The blood was immediately centrifuged at 3000 rpm for 10 min.

### Statistical analysis

Two tailed independent t-test was used in the determining the significant level at  $\alpha = 0.05$ .

### Reading of samples

Measurement of PTT, PT and platelet count [18]; TC, LDL-C and VLDL [19]; TG [20]; HDL-C [21] and CRP [22] were carried out.

### Results

Comparing study parameters between the different groups were performed, and the following results were obtained:

1. Significant decrease in HDL and significant increase in VLDL levels in hypertensive patients compared with control group (  $p < 0.05$ ), ( Table 1).

**Table 1:** Mean values of serum lipid levels (mmol/L) in normotensive subjects and hypertensive patients off treatment and on different mono and multiple therapy. Values as a mean  $\pm$  SEM.

Parameters	All hypertensives (n = 101)	Normotensives (n=48)	Hypertensives off treat (n = 53)	Hypertensives On treat (n=48)	Atenolol treated group (n=21)	Captopril treated group (n=12)	Hypertensives on multiple therapy (n=13)
TC	5.005 $\pm$ 1.013	4.733 $\pm$ 0.715 <sup>3</sup>	4.884 $\pm$ 0.986	5.132 $\pm$ 1.037 <sup>3</sup>	5.361 $\pm$ 1.084 <sup>4</sup>	<sup>4</sup> 4.550 $\pm$ 0.715 <sup>5</sup>	5.615 $\pm$ 0.943 <sup>5</sup>
TG	1.808 $\pm$ 0.69	1.597 $\pm$ 0.563 <sup>3</sup>	1.684 $\pm$ 0.593	1.942 $\pm$ 0.773 <sup>3</sup>	2.095 $\pm$ 1.007	1.858 $\pm$ 0.644	1.907 $\pm$ 0.422
HDL	1.008 $\pm$ 0.120 <sup>1</sup>	<sup>1</sup> 1.081 $\pm$ 0.163 <sup>2</sup>	0.969 $\pm$ 0.138 <sup>2</sup>	0.989 $\pm$ 0.106 <sup>3</sup>	0.952 $\pm$ 0.120 <sup>4</sup>	1.033 $\pm$ 0.780 <sup>4</sup>	0.992 $\pm$ 0.111
LDL	3.133 $\pm$ 1.006	3.004 $\pm$ 0.835	3.167 $\pm$ 1.004	3.145 $\pm$ 1.038	3.249 $\pm$ 1.158	2.646 $\pm$ 0.674 <sup>5</sup>	3.741 $\pm$ 0.922 <sup>5</sup>
VLDL	0.820 $\pm$ 0.323 <sup>1</sup>	<sup>1</sup> 0.707 $\pm$ 0.243 <sup>3</sup>	0.761 $\pm$ 0.261	0.883 $\pm$ 0.372 <sup>3</sup>	0.982 $\pm$ 0.526	0.836 $\pm$ 0.284	0.850 $\pm$ 0.209

- 1 significant difference ( $p < 0.05$ ) in HDL and VLDL between normotensives and all hypertensives.
- 2 significant difference ( $p < 0.05$ ) in HDL between normotensives and hypertensives off treatment.
- 3 significant difference ( $p < 0.05$ ) in TC, TG, HDL and VLDL between normotensives and hypertensives on treatment.
- 4 significant difference ( $p < 0.05$ ) in TC and HDL between Atenolol and Captopril treated groups.
- 5 significant difference ( $p < 0.05$ ) in TC and LDL between Captopril treated group and hypertensives on multiple therapy.

2. TC, TG and VLDL were significantly higher, and HDL was significantly lower in hypertensive patients on treatment (atenolol or captopril alone or combination of two or all of the following: atenolol, hydrochlorthiazide, amiloride) than in normotensive subjects (  $p < 0.05$ ), (Table 1).

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3. TC was significantly higher in patients on atenolol than patients on captopril while HDL was significantly lower in patients on atenolol compared with patients on captopril (  $p < 0.05$ ), (Table 1).
4. TC and LDL were significantly higher (  $p < 0.05$ ) in patients on multiple therapy (atenolol + diuretic or atenolol + captopril ) than patients on captopril. (Table 1).
5. There was a significant number of hypertensive patients who had positive C-reactive protein test, interestingly these patients had higher blood pressure levels, longer duration of hypertension, higher S.LDL and lower S.HDL levels (  $p < 0.05$ ) (Table 2).

**Table 2:** C- Reactive Protein determinations in hypertensive patients and normotensive controls.

Group	Positive	Negative	Total
Controls	1	47	48
Hypertensives	19	69	88
Total	20	116	136

$$X^2 = 14.14$$

$$d.f. = 2$$

$$P < 0.05$$

6. No significant difference (  $p > 0.05$ ) in serum lipid levels between; hypertensive patients on antihypertensive therapy and off-therapy hypertensive; patients off-therapy and normotensives (except HDL) and hypertensive patients on multiple therapy and patients on atenolol (Table 1).
7. No significant change in PT, PTT and platelets count between hypertensives and controls (  $p > 0.05$  ) (Table 3 ).

### Discussion:

Regarding serum lipids, this study revealed that there was a significant decrease in HDL-C level in all hypertensive patients in comparison with normotensive individuals (  $p < 0.05$ ) (Table 1). Possible explanation for these results might be due to the effect of antihypertensive drugs that lower HDL-C, the state of hyperlipidemia commonly associated with hypertension or the effect of hypertension on serum lipids. This suggestion is supported by the previous studies [16].

Another finding of this study concerning serum lipid levels is that TC was significantly higher and HDL was significantly lower in patients on atenolol than in patients on captopril (  $p < 0.05$ ) (Table 1).

**Table 3:** Mean values of coagulation parameters in normotensive subjects and hypertensive patients on different mono and multiple therapy. Values as a mean  $\pm$  SEM.

Parameters	All hypertensives (n=101)	Normotensives (n = 48)	Hypertensives off treat (n = 53)	Hypertensives on treat (n=48)	Atenolol treated group (n=21)	Captopril treated group (n=12)	Hypertensives on multiple therapy (n=13)
PT (sec.)	13.00 $\pm$ 0.714	13.745 $\pm$ 0.948	13.960 $\pm$ 0.999	14.021 $\pm$ 1.140	14.523 $\pm$ 0.845	13.500 $\pm$ 0.904	13.840 $\pm$ 0.550
PTT (sec.)	30.666 $\pm$ 2.066	30.931 $\pm$ 3.159	30.540 $\pm$ 3.210	30.265 $\pm$ 2.991	30.381 $\pm$ 2.499	28.666 $\pm$ 3.312	31.070 $\pm$ 0.801
Platelets count (c/mm <sup>3</sup> )	229098 $\pm$ 5288.100	233041 $\pm$ 5757.890	237452 $\pm$ 6709.850	225006 $\pm$ 8003.580	225285 $\pm$ 9459.279	198750 $\pm$ 11977	218158 $\pm$ 10305.900

No significant difference was found between any two groups ( $p > 0.05$ ). for all parameters.

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This result may be attributed to the effect of atenolol, as B-blocker, which is known to increase serum lipids. B-selective blockers, like atenolol, may induce a shift toward a more atherogenic lipid profile, namely a decrease in HDL-C and an increase in LDL-C (Table 1). These effects are attributed to inhibition of Lecithin Cholesterol Acyl Transferase (LCAT) enzyme [23] and a decrease in hepatic LDL-C receptors [24]. A controversy among researchers and studies regarding these effects have been reported. Lehtonen (1988) observed in a prospective study that atenolol significantly lowers HDL-C after six months of treatment while pindolol significantly increases HDL-C levels for the same treatment period [9]. Herrmann et al (1998) found that celiprolol has no effect on total cholesterol and LDL-C [25]. Al-Mousawi (2003) also observed that telmisartan and enalapril significantly increase HDL-C levels in hypertensive patients [16]. Lacourciere et al (1990) concluded that captopril and deliazem had deleterious effects on serum lipids [26].

Furhermore, TC, TGs and VLDL were significantly higher in hypertensive patients on treatment with atenolol and /or diuretic than in normotensive subjects ( $p < 0.05$ ) (Table 1). This result is in agreement with some of the previous studies that stated “ B-blockers and diuretics adversely affect serum lipid levels” [8,27] but conflict with Lehtonen (1988) [9]. The later study reported that pindolol or atenolol caused no significant changes in TC, TG, LDL, and VLDL in hypertensive patients after six months. This contrasting result might be due to the short period of treatment while most of the patients in the present study were taking these drugs for a longer period of time.

In addition, TC and LDL levels were significantly higher in patients on multiple antihypertensive therapies compared with patients on captopril alone ( $p < 0.05$ ) (Table 1). This is to be expected because most of the patients on multiple therapy were taking diuretic / B-blocker combination which are known to have adverse effects on serum lipids while ACEI have beneficial or no effects on serum lipids.

The present study showed that there were no significant changes in PT and PTT between hypertensive and normal subjects ( $p > 0.05$ ) (Table 3). In fact there was a difference in PT and PTT between those two groups ( i.e. they are lower in hypertensives) but it did not reach a statistical significance ( $p > 0.05$ ). Our result appears to conflict with the previous studies that stated “ hypertension per se is a hypercoagulable state” [28,29]. This contrasting results could be explained by the fact that the selected parameters in this study obviously can not be said to give the exact state of haemostatic system in hypertension and another markers, namely, PAI-1. VWF, fibrinogen

levels, thrombomodulin, fibrin dimmer and other factors of blood coagulation can give further clues.

Several studies were conducted to assess the function of haemostatic system in hypertension [15]. Increased activity of the coagulation system and decreased function of the fibrinolytic system have been consistently reported in comparison with normotensive subjects; which suggests the existence of prothrombotic state related to hypertension [11]. Similar results were demonstrated by several prospective investigations [15].

Concerning platelets count, our study showed no significant difference between both groups (  $p > 0.05$ ) (Table 3). This result is supported by a previous study[15].

Regarding CRP, in addition of being a risk marker for cardiovascular diseases, several lines of evidence point to a proarthrogenic role for CRP [30]. CRP has been shown to exert pro-inflammatory effects in endothelial cells [31]. Although atherosclerosis was formerly considered a bland lipid storage disease, substantial advances in basic and clinical studies have illuminated the role of inflammation and the underlying cellular and molecular mechanisms that contribute to atherogenesis [32]. In this context, accumulating epidemiological data evolved indicating that elevation of CRP heralds atherothrombotic events [33]. We have found that there were a significant number of patients having positive CRP test (Table 2). Nevertheless, those patients had higher blood pressure levels, longer duration of hypertension, higher LDL-C and lower HDL-C levels. This result might be attributed to the state of atherosclerosis and the associated inflammatory process as CRP is an inflammatory marker. Therefore, patients with positive CRP (with exclusion of other causes of high CRP) have greater possibility of having atherosclerosis and future cardiovascular complications. This result agrees with that found by Sridevi et al (2003) who concluded that CRP is elevated in patients with hypertension [31]. Many studies correlate the level of CRP with future cardiovascular events [9].

### **Conclusions**

Lipids and CRP are significantly affected by antihypertensive agents and therefore choice of antihypertensives should be made carefully according to comorbid disease or risk factors.

This study recommends further prospective studies on haemostatic state in hypertension and the effect of different antihypertensive agents on such a state are suggested. Furthermore, haemostatic state, CRP as well as lipid profile should be checked in hypertensive patients.

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