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ORIGINAL ARTICLE

Association of hypertensive status and its drug treatment with lipid and haemostatic factors in middle-aged men: the PRIME Study

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***Aims*: To assess the association of hypertensive status and antihypertensive drug treatment with lipid and haemostatic levels in middle-aged men.**

***Methods and results*: Hypertensive status, antihypertensive drug treatment, total and high-density lipoprotein (HDL) cholesterol, triglyceride, apoproteins A-I and B, lipoparticles LpA-I, LpE:B and Lp(a), fibrinogen, plasminogen activator inhibitor-1 (PAI-1) activity and factor VII were assessed in a sample of men 50–59 years living in France ($n = 7050$) and Northern Ireland ($n = 2374$). After adjustment for age, body mass index, smoking status, educational level, country, alcohol drinking and hypolipidaemic drug treatment, untreated hypertensive subjects had higher levels of total cholesterol, triglyceride, apoproteins A-I and B and PAI-I activity than normotensive subjects. On univariate analysis, diuretics decreased total and HDL-cholesterol and apoproteins A-I and B; those differences remained after multivariate adjustment. Treatment with beta-blockers decreased total and HDL-cholesterol, apoprotein A-I and LpA-I, and this effect remained after multivariate adjustment. Calcium channel blockers decreased total cholesterol and apoproteins A-I and B; those differences remained significant after multivariate adjustment. ACE inhibitors decreased total cholesterol, triglycerides, apoprotein B and LpE:B; and this effect remained after multivariate adjustment. Analysis of the subjects on monotherapy showed beta-blockers to decrease total cholesterol and HDL parameters and angiotersin-converting enzyme (ACE) inhibitors to decrease low-density lipoprotein (LDL)-related parameters, while no effect was found for the other antihypertensive drugs.**

***Conclusions*: Hypertensive status is associated with an unfavourable lipid and haemostatic profile in middle-aged men. Antihypertensive treatment with beta-blockers decreases HDL parameters, whereas treatment with ACE inhibitors appears to decrease total cholesterol and LDL-related parameters.**

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Introduction

Cardiovascular diseases (CVD) are the leading cause of premature death in industrialised countries.[1] The association of hypertension with CVD is well documented, and several clinical studies have shown that reduction in high levels of blood pressure leads to a decrease in the incidence of stroke and myocardial infarction (MI).[2–5] Nevertheless, the decrease in myocardial infarction rates is somewhat less than expected from the magnitude of the decrease in blood pressure levels.[4,6] A possible explanation for this discrepancy is a deleterious effect of antihypertensive drug treatment on blood lipids, and it has been shown that some of the most commonly used antihypertensive drugs tend to increase total cholesterol and triglyceride levels.[4,7,8] This increase would reduce the beneficial effects of blood pressure lowering. Furthermore, although the effects of the older antihypertensive drugs (thiazide diuretics and beta-blockers) on serum lipids are well documented,[7] there is still controversy on the effects of these drugs in haemostatic variables.[9] Finally, there is some controversy on the effects of the other classes of antihypertensive drugs such as calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors on lipid and haemostatic variables.[9–12]

Hence, we used the baseline data from the PRIME (Prospective Epidemiological Study of Myocardial Infarction) Study to assess the association of hypertensive status and of different antihypertensive drugs with serum lipid and haemostatic variables.

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Patients and methods

Population sampling

The PRIME Study was established in 1991 in the populations of four WHO-MONICA collaborating centres in Belfast (UK), Lille, Strasbourg and Toulouse (France). The target was to recruit 2500 men, aged 50–59 years, in each centre and to follow them for a minimum of 5 years. The sample was recruited to broadly match the social class structure of the background population. The sampling frame was based on industry and various employment groups, and on health screening centres and general practice. Participation was voluntary. Subjects were informed of the aim of the study and those who agreed to take part were given a morning appointment and asked to fast for a minimum of 10 h.

Personal and medical history

Self-administered questionnaires relating to demographic, socio-economic factors and diet were completed at home by the participants and checked by the interviewer at the clinic. Additional questionnaires on medical history were administered by the interviewers at the clinic. Data on level of education, occupational activity, personal and family history, tobacco and alcohol consumption, drug intake and physical activity were also collected.

Definition of hypertension

Blood pressure was measured once at the end of the examination after a 5-min rest in the sitting position. Measurements were performed with an automatic device (Spengler SP9), which also recorded heart rate. A standard cuff size was used, but a large cuff was available when necessary. At least three measuring devices were available at any time in each centre and all three were used equally. In order to avoid systematic differences between centres, the devices were circulated between them. The devices were also recalibrated every 3 months in the coordinating centre in Paris.

Hypertension was defined according to WHO criteria, ie, when a subject had a systolic blood pressure (SBP) $\geqslant$160 mm Hg and/or a diastolic blood pressure (DBP) $\geqslant$95 mm Hg and/or was taking antihypertensive drugs. Awareness of hypertension was defined by a positive answer to the question: 'Did a doctor ever tell you that you had high blood pressure levels?' Medical treatment was considered if the subject answered positively to the question: 'Are you currently being treated for hypertension?' Based on these data, four distinct categories were obtained:

Category 1: Normotensive subjects: subjects for which SBP $<$160 mm Hg and DBP $<$95 mm Hg, without antihypertensive drug therapy.

Category 2: Unaware hypertensive subjects: subjects for which SBP $\geqslant$160 mm Hg or DBP $\geqslant$95 mm Hg, who had never been told that they were hypertensive.

Category 3: Aware untreated hypertensive subjects: subjects for which SBP $\geqslant$160 mm Hg or DBP $\geqslant$95 mm Hg, who had been told that they were hypertensive, but without antihypertensive drug therapy.

Category 4: Treated hypertensive subjects: subjects currently on antihypertensive drug therapy.

Blood sampling and assay procedures

Venous blood was collected between 9 and 10 am into siliconised vacutainer tubes (Vacutainer, Becton Dickinson, Franklin Lakes, NJ, USA) containing 0.11 M trisodium citrate. Platelet-poor plasma was obtained by centrifugation at 3000 *g* and 4°C (PAI-1 activity measurements) or 20°C (fibrinogen and factor VII assay) for 15 min. Aliquots of plasma were immediately transferred into plastic tubes and frozen at –80°C. The frozen aliquots were then shipped in batches to the central laboratory in Lille.

Haemostatic variables were measured in the central haemostasis laboratory of La Timone Hospital at Marseille, France. Fibrinogen was measured according to the method of Clauss (Fibriprest automate, Diagnostica Stago, Asnières, France). Factor VIIc was assayed in a regular one-stage system using rabbit thromboplastin. Factor VII-deficient substrate plasma was prepared from absorbed bovine plasma and concentrate of human factors IX, X and II as described previously.[13] Results were expressed as a percentage of reference plasma. PAI-1 activity was measured by a two-stage amidolytic method using a commercially available kit (Spectrolyse/pl, Biopool, Umea, Sweden). All the haemostatic tests were performed between January 1991 and January 1994. Accuracy and precision of haemostatic assays were assured by a strict internal quality control programme. A single batch of normal plasma pool prepared from 50 healthy subjects was used as control material. For each assay, two to four controls were included in each run of PRIME study samples. Analysis of internal quality control data showed that the laboratory coefficient of variation ranged from 4.3% (fibrinogen) to 9.5% (PAI-1).

Plasma prepared with EDTA was used for analysis of lipids. Plasma total cholesterol and triglycerides were measured by enzymatic methods using reagents from Boerhinger Mannheim (Mannheim, Germany). The inter-assay coefficient of variation for total cholesterol and triglyceride were 2% and 3%, respectively. High density lipoprotein (HDL) cholesterol was measured after precipitation of apoprotein B-containing lipoproteins with sodium phosphotungstate-magnesium chloride (Boerhinger Mannheim). Apoproteins A-I and B were measured by a nephelometric method (Behringwerke, Marburg, Germany). Lipoparticles LpE:B and Lp(a) were assessed using double-site immunoenzymatic tests. Lipoparticles LpA-I were assessed by electroimmunoassay on ready-to-use plates.[14]

Statistical analysis

Out of the 10 596 subjects initially included in the study, 593 were excluded from the analysis because

of a personal history of angina pectoris, myocardial infarction or possible coronary heart disease. Statistical analysis was conducted using SAS (SAS Institute, Cary, NC, USA) software. As a first step, the levels of the lipid, lipoprotein and haemostatic variables were assessed between the categories 2 and 3 defined previously. The association of blood lipid and haemostatic levels with hypertension was then assessed pooling categories 2 and 3 and comparing them with category 1, whereas the association of blood lipid and haemostatic levels with antihypertensive drug therapy was assessed pooling categories 2 and 3 and comparing them with subjects treated with different types of antihypertensive drugs within category 4. The impact of certain types of antihypertensive drugs (thiazide diuretics *vs* non-thiazide, beta-blockers with and without intrinsic sympathomimetic activity) was assessed between subjects in category 4. For certain analyses, treated subjects (category 4) were further separated according to hypertension control into controlled (SBP <160 mm Hg and DBP <95 mm Hg) and uncontrolled (SBP $\geqslant 160$ mm Hg or DBP $\geqslant 95$ mm Hg) subjects. Data are presented as mean ± s.d., as adjusted mean ± s.e.m. or as number of subjects (percentage). Comparisons were performed by χ^2 test for qualitative variables and by Student's *t*-test for quantitative variables. The effects of each antihypertensive drug class were further assessed comparing subjects on monotherapy with untreated hypertensive subjects (categories 2 + 3) using Dunnett's test. Multivariate analysis was performed using the general linear models (Proc GLM) of SAS. Since alcohol drinking patterns and the type of hypolipidaemic drug prescription differ between France and Northern Ireland[15] and that those variables might affect lipid and lipoprotein values,[16] the interactions country*alcohol drinking and country*hypolipidaemic drug were introduced in the multivariate model. Due to the number of tests performed, statistical significance was considered for $P < 0.01$, except for Dunnett's test, for which statistical significance was considered for $P < 0.05$.

Results

Population

In all data from 9424 subjects corresponding to categories 1 to 4 defined previously were analysed: 7050 from France and 2374 from Northern Ireland. Table 1 gives the distribution of the different categories of blood pressure and of the main cardiovascular risk factors between France and Northern Ireland. Subjects from France were significantly older and had a higher body mass index (BMI) than subjects from Northern Ireland. Prevalence of ex-smokers was higher in France whereas prevalence of non-smokers was higher in Northern Ireland. Prevalence of normotensive subjects was higher in Northern Ireland whereas the prevalence of aware, treated hypertensive subjects was higher in France. Finally, alcohol drinking and hypolipidaemic drug treatment was more frequent in France than in Northern Ireland.

Table 1 Distribution of the different categories of blood pressure and of the main cardiovascular risk factors between France and Northern Ireland

	France (n = 7050)	*N. Ireland (n = 2374)*	*Test*
Age	54.9 ± 2.9	54.7 ± 2.9	$P < 0.001$
Body mass index	26.7 ± 3.5	26.2 ± 3.4	$P < 0.001$
Blood pressure categories			
Normotensive	4901 (70)	1831 (77)	
Unaware hypertensive	853 (12)	281 (12)	$P < 0.001$
Aware, untreated	291 (4)	70 (3)	
Aware, treated	999 (14)	193 (8)	
Smoking status			
Current smoker	1868 (27)	747 (31)	
Ex-smoker	3229 (46)	798 (34)	$P < 0.001$
Non-smoker	1953 (27)	829 (35)	
Alcohol drinking	6387 (91)	1443 (61)	$P < 0.001$
Hypolipidaemic drug treat.	814 (12)	23 (1)	$P < 0.001$

Results are expressed as number of subjects and (percentage) or as mean ± standard deviation. Analysis by χ^2 or Student's *t*-test.

Association of lipid and haemostatic variables with hypertensive status

Since categories 2 and 3 did not differ regarding lipid, lipoprotein and haemostatic levels (not shown), they were pooled into a single category named 'untreated hypertensive subjects'. The association of blood lipid and haemostatic factors with hypertension was then assessed using normotensive subjects (category 1) and untreated hypertensive subjects (category 2 + 3). On univariate analysis, untreated hypertensive subjects had higher levels of total cholesterol (5.86 ± 1.00 *vs* 5.65 ± 0.98 mmol/L, $P < 0.001$), triglycerides (1.95 ± 1.43 *vs* 1.61 ± 1.05 mmol/L, $P < 0.001$), apoproteins A-I (1.52 ± 0.25 *vs* 1.49 ± 0.24 g/L, $P < 0.002$) and B (1.35 ± 0.35 *vs* 1.26 ± 0.33 g/L, $P < 0.001$), lipoparticles LpE:B (0.29 ± 0.22 *vs* 0.25 ± 0.20 g/L, $P < 0.001$), PAI-1 activity (17 ± 12 *vs* 12 ± 10 mU/ml, $P < 0.001$) and factor VII (1.37 ± 0.46 *vs* 1.30 ± 0.41 g/L, $P < 0.001$). Those differences persisted after multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment and the interactions country*hypolipidaemic drug treatment and country*alcohol drinking (Table 2).

Association of different antihypertensive drugs with lipid and haemostatic variables

The association of blood lipid and haemostatic levels with antihypertensive drug therapy was then assessed comparing category (2 + 3) with subjects treated with different types of antihypertensive drugs within category 4.

Diuretics

On univariate analysis, hypertensive subjects taking diuretics had significantly lower levels of total cholesterol (5.56 ± 0.95 *vs* 5.84 ± 1.00 mmol/L, $P < 0.001$), HDL-cholesterol (1.15 ± 0.31 *vs* 1.25 ± 0.36 mmol/L, $P < 0.001$), apoprotein A-I

Table 2 Lipid, lipoprotein and haemostatic levels in normotensive and untreated hypertensive male subjects

	Normotensive (n = 6503)	*Untreated hypertensive (n = 1495)*	*Test*
Total cholesterol (mmol/L)	5.94 ± 0.05	6.12 ± 0.07	$P < 0.001$
HDL cholesterol (mmol/L)	1.20 ± 0.03	1.23 ± 0.03	$P < 0.001$
Triglyceride (mmol/L)	1.89 ± 0.07	2.13 ± 0.07	$P < 0.001$
Apoprotein A-I (g/L)	1.46 ± 0.01	1.50 ± 0.02	$P < 0.001$
Apoprotein B (g/L)	1.38 ± 0.02	1.44 ± 0.02	$P < 0.001$
LpA-I (g/L)	0.42 ± 0.01	0.43 ± 0.01	$P < 0.001$
LpE:B (g/L)	0.29 ± 0.01	0.31 ± 0.01	$P < 0.001$
Lp(a):B (g/L)	0.21 ± 0.02	0.21 ± 0.02	NS
Fibrinogen (g/L)	3.38 ± 0.06	3.42 ± 0.07	NS
PAI-1 activity	14 ± 1	17 ± 1	$P < 0.001$
Factor VII	1.35 ± 0.03	1.41 ± 0.03	$P < 0.001$

Results are expressed as adjusted mean ± s.e.m. Multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment and the following interactions: country*hypolipidaemic drug treatment and country*alcohol drinking: NS, not significant. To obtain mg/dL from mmol/L, multiply by 39.06 for cholesterol and by 87.72 for triglycerides.

(1.44 ± 0.24 *vs* 1.52 ± 0.25 g/L, $P < 0.001$), apoprotein B (1.29 ± 0.29 *vs* 1.35 ± 0.35 g/L, $P < 0.01$), LpA-I (0.44 ± 0.11 *vs* 0.46 ± 0.12 g/L, $P < 0.01$) and higher levels of PAI-1 activity (19 ± 14 *vs* 17 ± 12 Ui/mL) than untreated hypertensive subjects. Those differences remained after multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment, presence of other antihypertensive drug treatment and the interactions country*hypolipidaemic drug treatment and country*alcohol drinking, although differences in LpA-I and PAI-1 activity were no longer significant Table 3). Conversely, no differences were found between hypertensive subjects treated with thiazide diuretics and subjects treated with other types of diuretics (not shown).

Table 3 Lipid, lipoprotein and haemostatic levels in hypertensive subjects taking diuretics compared to untreated hypertensive subjects

	Untreated (n = 1495)	*Diuretics (n = 419)*	*Test*
Total cholesterol (mmol/L)	5.99 ± 0.10	5.68 ± 0.13	$P < 0.001$
HDL cholesterol (mmol/L)	1.15 ± 0.05	1.10 ± 0.05	$P < 0.001$
Triglyceride (mmol/L)	1.98 ± 0.15	1.89 ± 0.16	NS
Apoprotein A-I (g/L)	1.47 ± 0.03	1.41 ± 0.03	$P < 0.001$
Apoprotein B (g/L)	1.41 ± 0.04	1.34 ± 0.04	$P < 0.001$
LpA-I (g/L)	0.42 ± 0.01	0.40 ± 0.01	NS
LpE:B (g/L)	0.29 ± 0.03	0.29 ± 0.03	NS
Lp(a):B (g/L)	0.22 ± 0.03	0.20 ± 0.03	NS
Fibrinogen (g/L)	3.55 ± 0.11	3.50 ± 0.11	NS
PAI-1 activity	18 ± 1	20 ± 2	NS
Factor VII	1.44 ± 0.05	1.42 ± 0.06	NS

Results are expressed as adjusted mean ± s.e.m. Multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment, other antihypertensive drug treatment and the following interactions: country*hypolipidaemic drug treatment and country*alcohol drinking: NS, not significant. To obtain mg/dL from mmol/L, multiply by 39.06 for cholesterol and by 87.72 for triglycerides.

Beta-blockers

On univariate analysis, hypertensive subjects taking beta-blockers had significantly lower levels of total cholesterol (5.63 ± 1.00 *vs* 5.84 ± 0.95 mmol/L, $P < 0.001$), HDL-cholesterol (1.13 ± 0.28 *vs* 1.25 ± 0.36 mmol/L, $P < 0.001$), apoprotein A-I (1.43 ± 0.22 *vs* 1.52 ± 0.25 g/L, $P < 0.001$) and LpA-I (0.43 ± 0.12 *vs* 0.46 ± 0.12 g/L, $P < 0.001$) than untreated hypertensive subjects. Those differences persisted after multivariate adjustment, which also showed a significant difference regarding LpE:B (Table 4). Finally, no differences were found between beta-blockers with or without intrinsic sympathomimetic activity (not shown).

Calcium channel blockers

On univariate analysis, hypertensive subjects taking calcium channel blockers had significantly lower levels of total cholesterol (5.56 ± 0.92 *vs* 5.86 ± 1.00 mmol/L, $P < 0.01$) and apoprotein A-I (1.45 ± 0.23 *vs* 1.52 ± 0.25 g/L, $P < 0.01$) than untreated hypertensive subjects. Those differences remained significant after multivariate adjustment, which also showed a lower level of apoprotein B in subjects taking calcium channel blockers (adjusted mean ± s.e.m.: 2.24 ± 0.05 *vs* 2.37 ± 0.04 g/L, F test = 7.97, $P < 0.01$). Finally, no differences were found between nifedipine and verapamil derivatives (not shown).

ACE inhibitors

On univariate analysis, hypertensive subjects taking ACE inhibitors had significantly lower levels of total cholesterol (5.58 ± 0.84 *vs* 5.86 ± 1.00 mmol/L,

Table 4 Lipid, lipoprotein and haemostatic levels in hypertensive subjects taking beta-blockers compared to untreated hypertensive subjects

	Untreated (n = 1495)	*Beta-blockers (n = 523)*	*Test*
Total cholesterol (mmol/L)	5.96 ± 0.10	5.76 ± 0.10	$P < 0.001$
HDL cholesterol (mmol/L)	1.18 ± 0.03	1.05 ± 0.03	$P < 0.001$
Triglyceride (mmol/L)	2.17 ± 0.15	2.20 ± 0.15	NS
Apoprotein A-I (g/L)	1.46 ± 0.03	1.39 ± 0.03	$P < 0.001$
Apoprotein B (g/L)	1.42 ± 0.04	1.40 ± 0.04	NS
LpA-I (g/L)	0.43 ± 0.01	0.40 ± 0.01	$P < 0.001$
LpE:B (g/L)	0.29 ± 0.02	0.32 ± 0.02	$P < 0.01$
Lp(a):B (g/L)	0.21 ± 0.03	0.20 ± 0.03	NS
Fibrinogen (g/L)	3.54 ± 0.10	3.52 ± 0.10	NS
PAI-1 activity	19 ± 1	20 ± 1	NS
Factor VII	1.44 ± 0.05	1.39 ± 0.05	NS

Results are expressed as adjusted mean ± s.e.m. Multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment, other antihypertensive drug treatment and the following interactions: country*hypolipidaemic drug treatment and country*alcohol drinking: NS, not significant. To obtain mg/dL from mmol/L, multiply by 39.06 for cholesterol and by 87.72 for triglycerides.

$P < 0.001$), triglycerides (1.74 ± 1.36 vs 1.96 ± 1.43 mmol/L, $P < 0.01$), apoprotein A-I (1.48 ± 0.23 *vs* 1.51 ± 0.25 g/L, $P < 0.01$), apoprotein B (1.27 ± 0.31 *vs* 1.35 ± 0.35 g/L, $P < 0.001$), LpE:B (0.26 ± 0.18 *vs* 0.29 ± 0.22 g/L, $P < 0.01$) and factor VII (1.30 ± 44 *vs* 1.37 ± 0.46 mg/L) than untreated hypertensive subjects. Most of those differences persisted after multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment, presence of other antihypertensive drug treatment and the interactions country*hypolipidaemic drug treatment and country*alcohol drinking, with the exception of apoprotein A-I which was borderline significant (adjusted mean ± s.e.m.: 1.43 ± 0.03 *vs* 1.46 ± 0.03, F test = 5.85, $P < 0.02$).

Subjects on monotherapy

Since several subjects had a combination of antihypertensive drugs, the relationships between antihypertensive drug treatment and blood lipid, lipoprotein and haemostatic levels were further analysed using subjects receiving only one of the antihypertensive drugs. After excluding 486 hypertensive subjects who were not on monotherapy, the levels of cardiovascular risk factors were compared between each pharmacological group (diuretics, beta-blockers, calcium channel blockers and ACE inhibitors) by Dunnett's test using untreated hypertensive subjects as a control. The results indicated that treatment with beta-blockers was associated with a significant decrease in total cholesterol and all HDL-related parameters (HDL cholesterol, apoprotein A-I and LpA-I), whereas treatment with ACE inhibitors was associated with a significant decrease in total cholesterol, triglycerides, apoprotein B and LpE:B (Table 5). Conversely, no effect on cardiovascular risk factors was found for diuretics or calcium channel blockers (not shown). Finally, restricting the analysis to each country led to similar results, excepting that some differences were no longer significant due to the reduced sample size (not shown).

Table 5 Mean differences in lipid and lipoprotein levels between subjects taking beta-blockers or ACE inhibitors as a monotherapy and untreated hypertensive subjects

	Beta-blockers (n = 353)	*ACE inhibitors (n=241)*
Total cholesterol (mmol/L)	−0.15 (−0.28; −0.03)*	−0.18 (−0.33; −0.03)*
HDL cholesterol (mmol/L)	−0.10 (−0.15; −0.05)*	−0.03 (−0.08; 0.05)^{NS}
Triglyceride (mmol/L)	0.01 (−0.18; 0.22)^{NS}	−0.25 (−0.49; −0.02)*
Apoprotein A-I (g/L)	−0.06 (−0.09; −0.03)*	−0.00 (−0.04; 0.04)^{NS}
Apoprotein B (g/L)	−0.01 (−0.06; 0.04)^{NS}	−0.07 (−0.12; −0.01)*
LpA-I (g/L)	−0.02 (−0.04; −0.01)*	−0.00 (−0.02; 0.02)^{NS}
LpE:B (g/L)	0.03 (−0.01; 0.06)^{NS}	−0.04 (−0.08; −0.01)*

Results are expressed as difference between means and (95% confidence limits) of subjects treated with beta-blockers or ACE inhibitors relative to untreated hypertensive subjects. Analysis by Dunnett's test: ^{NS}Not significant; *$P < 0.05$. To obtain mg/dL from mmol/L, multiply by 39.06 for cholesterol and by 87.72 for triglycerides.

Table 6 Lipid, lipoprotein and haemostatic levels in controlled and uncontrolled treated hypertensive subjects

	Uncontrolled (n = 631)	*Controlled (n = 532)*	*Test*
Total cholesterol (mmol/L)	5.71 ± 0.10	5.56 ± 0.10	$P < 0.001$
HDL cholesterol (mmol/L)	1.13 ± 0.03	1.05 ± 0.03	$P < 0.001$
Triglyceride (mmol/L)	2.20 ± 0.14	2.13 ± 0.14	NS
Apoprotein A-I (g/L)	1.36 ± 0.03	1.33 ± 0.03	NS
Apoprotein B (g/L)	1.38 ± 0.02	1.44 ± 0.02	NS
LpA-I (g/L)	0.45 ± 0.01	0.43 ± 0.01	NS
LpE:B (g/L)	0.30 ± 0.02	0.32 ± 0.02	NS
Lp(a):B (g/L)	0.18 ± 0.03	0.17 ± 0.03	NS
Fibrinogen (g/L)	3.50 ± 0.10	3.43 ± 0.10	NS
PAI-1 activity	21 ± 1	19 ± 1	NS
Factor VII	1.34 ± 0.05	1.33 ± 0.05	NS

Results are expressed as adjusted mean ± s.e.m. multivariate adjustment on age, BMI, smoking status, educational level, country, alcohol drinking, hypolipidaemic drug treatment and the following interactions: country*hypolipidaemic drug treatment and country*alcohol drinking: NS, not significant. To obtain mg/dL from mmol/L, multiply by 39.06 for cholesterol and by 87.72 for triglycerides.

Effect of hypertension control

On univariate analysis, controlled treated hypertensive subjects had lower levels of total cholesterol (5.53 ± 0.87 *vs* 5.71 ± 0.92 mmol/L, $P < 0.001$), apoprotein B (1.27 ± 0.30 *vs* 1.32 ± 0.32 g/L, $P < 0.01$) and PAI-1 activity (17 ± 12 *vs* 19 ± 13 Ui/L, $P < 0.001$) than uncontrolled treated hypertensive subjects. Those differences remained after adjusting on country, age, BMI, smoking status, educational level, alcohol drinking, hypolipidaemic drug treatment and the interactions country*hypolipidaemic drug treatment and country*alcohol drinking (Table 6). The differences regarding HDL-cholesterol and PAI-1 activity were of borderline significance ($P < 0.012$ and $P < 0.011$, respectively).

Discussion

In this study, lipid and lipoprotein levels were significantly higher in untreated hypertensive subjects than in normotensive subjects. Those findings are in agreement with other studies[17,18] and indicate that hypertensive subjects are characterised by an unfavourable lipid profile. Since the combined effect of an unfavourable lipid profile and elevated blood pressure on the development of atherosclerotic heart disease is known to be multiplicative rather than additive,[19–21] our observations should therefore contribute to the general recognition of the need to screen hypertensive patients for lipid disturbances. The finding of higher levels of apoprotein A-I among untreated hypertensive subjects is not a classical one and could be attributable to a higher alcohol consumption in this group. Indeed,

untreated hypertensive drinkers had a higher alcohol consumption than normotensive drinkers (372 ± 290 *vs* 307 ± 260 gr ethanol/week, Wilcoxon test $P < 0.001$), which could partly explain the difference in apoprotein A-I levels. Notwithstanding, this difference remained statistically significant after further adjustment on the total amount of alcohol consumed, indicating that other factors (different from BMI, smoking, age, hypolipidaemic drug treatment or alcohol consumption) might be responsible for the higher apoprotein A-I levels among untreated hypertensive subjects. Another possibility would be that untreated hypertensive patients had adopted a healthier lifestyle, which would have led to the observed increase in apo A-I levels. Nevertheless, no differences were found between unaware hypertensives and aware untreated hypertensives regarding BMI and tobacco smoking, indicating that the impact of those lifestyle changes (if any) is limited.

Untreated hypertensive subjects also had higher PAI-I activity levels than normotensive subjects. Those findings are in agreement with other studies,[22–24] and indicate that among hypertensive subjects there is a relative impairment of fibrinolysis. Nevertheless, since most hypertensive subjects also present with other metabolic disturbances (obesity and dyslipidaemia) and since PAI-I activity levels are correlated with lipids and obesity, it is not clear whether the changes in the fibrinolytic and haemostatic systems are linked to hypertension or to the concomitant metabolic disturbances of the disease.[25] The levels of factor VII were also significantly increased among untreated hypertensive subjects. Again, those findings indicate a possible impairment of the haemostratic system among hypertensive subjects, which might favour the development of premature coronary heart disease or stroke. Finally, no difference in fibrinogen levels was found between normotensive and untreated hypertensive subjects. Those findings do not confirm previously reported data[24,26] and might indicate that, at least in this study, fibrinogen levels are not influenced by hypertensive status.

The univariate comparison of lipid levels between treated and untreated hypertensive subjects showed a negative effect of diuretic and beta-blocker treatment on HDL-cholesterol levels, and those differences persisted after multivariate adjustment. Our findings are in agreement with other studies,[27–29] and indicate that the already high risk lipid profile of the hypertensive subjects can be further swelled by antihypertensive drug therapy. Indeed, although in this study treatment compliance could not be assessed, adequately controlled hypertensive subjects had lower HDL-cholesterol levels than uncontrolled (and possibly less compliant) hypertensive subjects.

The biochemical mechanisms by which diuretics and beta-blockers decrease HDL parameters are poorly known. A possible explanation might be that beta-blockers stimulate the production of very low density lipoproteins (VLDL), thus increasing triglyceride levels at the expense of HDL levels.[30] Another possibility is that beta-blockers inhibit lipoprotein lipase activity, thus decreasing the production of HDL via the lipolysis of VLDL,[31] although those findings have been assessed in animal experiments and no such data is available for humans. Similarly, the metabolic effect of diuretics might be related to sodium depletion since reduced sodium intake has been shown to increase total and LDL-cholesterol levels.[32] Nevertheless, it should be noted that although diuretics and beta-blockers might possess deleterious effects that lessen the beneficial effects from blood pressure lowering, those drugs have consistently been shown to effectively reduce cardiovascular mortality[5] and, in the case of the diuretic chlorthalidone, to be associated with a high quality of life rating.[4] Thus, it is our belief that despite their slight effect on lipid and lipoprotein levels, those drugs can still be prescribed as a first choice for hypertension.

In this study, no differences were found between thiazide diuretics and other types of diuretics, as well as between beta-blockers with and without intrinsic sympathomimetic activity. Several reasons can explain those findings, which do not replicate previous results.[11,12] First, the number of subjects treated which each class of antihypertensive drug was relatively low, thus decreasing the statistical power of the study. Second, as stated previously, it was not possible to assess compliance and thus to control for a possible differential intake of those types of drugs. Nevertheless, our data indicate that, at least at a populational level, the prescription of a non-thiazide diuretic or of a beta-blocker with intrinsic sympathomimetic activity appears not to lead to a better lipid profile relative to other classes of diuretics or beta-blockers.

Although the effects of diuretic and/or beta-blocker treatment on lipid levels are currently well assessed,[4,28,29,33] less is known about the effects of other antihypertensive drugs such as calcium channel blockers and ACE inhibitors.[4,11] Based on our current findings, it seems that calcium channel blockers exert only a moderate effect on lipid, lipoprotein and haemostatic factors, while the effect of ACE inhibitors on total cholesterol and LDL parameters (apoprotein B and LpE:B) appears to be more consistent, namely when it is prescribed as a monotherapy. Those findings are in agreement with some authors[11] but not with others.[12] Thus, our data indicate that ACE inhibitors might be the best choice for hypertensive subjects who also have dyslipidaemia.

The fact that only beta-blockers and ACE inhibitors had an effect on lipid variables among subjects on monotherapy might also be due to the small number of subjects receiving solely diuretics and calcium channel blockers ($n = 114$ and $n = 39$, respectively, *vs* $n = 353$ and $n = 241$ for beta-blockers and ACE inhibitors, respectively). Thus, although the analysis did not show a significant effect for diuretics and calcium channel blockers, this does not imply that those drugs do not possess such effect. Indeed, on univariate and multivariate analysis, both types of drugs had a small effect on total cholesterol, and diuretics were also associated with a significant decrease in HDL parameters.

Data on the effect of antihypertensive drugs on the fibrinolytic and haemostatic systems is scant and

controversial.[9,10,34–36] Several experimental studies have shown that PAI-1 activity is stimulated by angiotensin II, or associated with ACE gene polymorphism,[37] although this latter association has been questioned by others.[38] Thus, antihypertensive drugs acting within the renin-angiotensin system should also exert effects within the fibrinolytic system. Indeed, on univariate analysis, a positive effect on PAI-1 levels was found for diuretics, but this difference disappeared after multivariate adjustment. Also, no consistent effect on the levels of fibrinogen, PAI-1 activity and factor VII was found for all antihypertensive drugs studied. Those findings are in agreement with other studies[39] and indicate that, at least in this observational study, the effects of antihypertensive drugs on the fibrinolytic and haemostatic system appear to be negligible. Still, although adjusting for smoking status was performed, it is possible that data on fibrinogen be subject to residual confounding and misclassification of smokers.

Since this was an observational study, possible biases must be considered. First, the prescription of antihypertensive drugs must take into account not only hypertensive status but also other clinical and biological features. Although adjustment for those variables might partly correct the results, it is clear that only double-blind studies can adequately assess the metabolic effect of the newer antihypertensive drugs.[4] Further, our survey relied on a single visit with one blood pressure measurement, leading to an overestimation of the prevalence of hypertension.[40] Still, for epidemiological studies, it would be impractical and costly to perform multiple blood pressure measurements in several visits. Also, this possible bias will only apply to the comparisons between normotensive and untreated hypertensive subjects, since the other analyses were performed in subjects with personal history of hypertension. Thus, supposing that the levels of cardiovascular risk factors are increased among hypertensive subjects, the overestimation of the number of hypertensive subjects would tend to decrease the differences between normotensive and untreated hypertensive subjects. Thus, it is likely that the differences observed in our study between those two groups would increase if a better evaluation of blood pressure levels was performed. Further, since this study used two centres with different populations, a possible bias was that the effects of antihypertensive drugs on cardiovascular risk factors would be different according to country; nevertheless, restricting the analysis to each country gave similar results, indicating that this is a general effect of antihypertensive drugs. Finally, there is a possible selection bias since medicine prescription can be influenced by both physician and patient preferences, Nevertheless, no differences were found regarding the characteristics of subjects according to the type of medicine prescribed (age, BMI, smoking and drinking status) and the effects of drugs were comparable in both countries. Thus, although the prescription patterns are different between France and Northern Ireland (French practitioners prescribe more ACE inhibitors than their Northern Irish counterparts), it seems that this pattern does not take into account the characteristics of the patients.

In summary, our results confirm that in middle-aged men hypertensive status is associated with an unfavourable lipid and haemostatic profile. They also indicate that antihypertensive treatment with beta-blockers is associated with lower levels of HDL-related parameters, whereas treatment with ACE inhibitors appears to exert a small beneficial effect on total cholesterol and LDL-related parameters.

The PRIME Study

The PRIME Study is organised under an agreement between INSERM and the Merck, Sharp and Dohme-Chibret laboratory, with the following participating Laboratories:

- Strasbourg MONICA Project, Department of Epidemiology and Public Health, Faculty of Medicine, Strasbourg, France (D Arveiler, B Haas)
- Toulouse MONICA Project, INSERM U518, Department of Epidemiology, Paul-Sabatier-Toulouse Purpan University, Toulouse France (J Ferriéres, JB Ruidavets)
- Lille MONICA Project, INSERM U508, Pasteur Institute, Lille, France (P Amouyel, M Montaye)
- Department of Epidemiology and Public Health, The Queen's University of Belfast, Belfast, Northern Ireland (A Evans, J Yarnell)
- Department of Atherosclerosis, SERLIA-INSERM U325, Lille, France (G Luc, JM Bard)
- Laboratory of Haematology, La Timone Hospital, Marseilles, France (I Juhan-Vague)
- Laboratory of Endocrinology, INSERM U326, Toulouse, France (B Perret)
- Vitamin Research Unit, The University of Bern, Bern, Switzerland (F Gey)
- Trace Element Laboratory, Department of Medicine, The Queen's University of Belfast, Belfast, Northern Ireland (D McMaster)
- DNA Bank, INSERM U525/SC7, Paris, France (F Cambien)
- Coordinating Center, INSERM U258, Villejuif, France (P Ducimetière, PY Scarabin, A Bingham).

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