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ORIGINAL ARTICLE

The association between antihypertensive drug therapies and plasma lipid levels in the general population

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Objective: **To assess the association between different antihypertensive drug regimens and plasma lipid levels in the general population.**

Methods: **The Monitoring Project on Cardiovascular Risk Factors was conducted from 1987 to 1991 as a cross-sectional study in The Netherlands. Antihypertensive drug-users and untreated hypertensives were selected. After exclusion of users of cholesterol-lowering drugs 2997 subjects remained for the analysis. The plasma lipid concentrations of the users and non-users of antihypertensives were compared by multiple linear regression.**

Results: **In the univariate analysis patients using beta-blockers had lower high-density lipoprotein (HDL) concentrations (1.13 mmol/l, $P < 0.05$) and higher cholesterol ratios (5.74, $P < 0.05$) than untreated hypertensives (Total cholesterol = 6.07 mmol/l, HDL = 1.20 mmol/l and ratio = 5.44). Patients using diuretics had higher total cholesterol levels (6.34 mmol/l) and higher HDL levels (1.26 mmol/l) compared to untreated hypertensives. After adjustment for possible confounders these differences were smaller and no longer statistically significant. After adjustment we found a significant lower HDL cholesterol (mean difference of −0.10 mmol/l, $P < 0.05$) for users of a combination of a beta-blocker and a diuretic.**

Conclusions: **Although randomised, controlled trials have demonstrated that antihypertensive drugs may influence plasma lipid levels we observed no substantial association for single antihypertensive drug therapy in the general population. The combination of a diuretic and a beta-blocker was associated with a worse lipid profile.**

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Introduction

The effects of antihypertensive drug therapies on plasma lipid levels are well documented based on the results from randomised clinical trials (RCTs). Thiazide diuretics increase total cholesterol and low-density lipoprotein (LDL) levels but do not affect high-density lipoprotein (HDL) levels.[1] A recent study on diuretics demonstrated that during continuation of diuretics initially elevated lipid concentrations returned to the old level after 1 year.[2] The effects of thiazide diuretics on triglyceride and LDL levels were dose dependent.[3] Beta-blockers decrease HDL cholesterol and elevate serum triglycerides.[1,4,5] The beta1-selective beta-blockers may have less adverse effects than non-selective beta-blockers, and celiprolol may even improve the lipid pattern.[6]

A meta-analysis of 23 randomised trials published between 1988 and 1994 suggested that effects of beta-blockers sustain during 3 years of follow up[4] although a recent study by Lakhsman[2] found that 1 year after the start of beta-blockers the plasma lipid levels had returned to their original level. Angiotensin converting enzyme (ACE)-inhibitors and Ca-antagonists do not have adverse effects on the total cholesterol and HDL cholesterol levels.[1] ACE-inhibitors may reduce the concentration of triglycerides.[7,8] These effects of antihypertensive therapies on plasma lipid levels that have been demonstrated in RCTs may not be generalisable to the general population where patient characteristics and practice patterns can differ.

The effects of antihypertensive drug therapy on plasma lipid levels have been studied in a few popu-

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lation-based observational studies.[9–11] In most studies no distinction was made between the different antihypertensive drug classes[9,10] and some studies used a reference group that included both untreated hypertensives and normotensives.[9] This approach may lead to a biased comparison since hypertension itself is associated with higher total cholesterol levels and lower HDL cholesterol levels.[12] Our hypothesis is that the well known effects of antihypertensive drugs on lipid levels as demonstrated in randomised trials may be different in daily practice due to treatment of more heterogenous patient groups. Therefore the aim of the study was to assess the association between different antihypertensive drug regimens and plasma lipid levels in daily medical practice.

Methods

Data

The Monitoring Project on Cardiovascular Risk Factors was conducted from 1987 to 1991 as a cross-sectional population-based study in Amsterdam, Maastricht and Doetinchem, three cities in the Netherlands. Each year a new random sample of men and women 20–59 years of age in each city was selected. To obtain equal numbers in different sex and age categories, the sample was stratified according to gender and 5-year age classes. In Doetinchem and Maastricht 400 persons were selected per stratum; in Amsterdam 500 because of the lower response there. Overall response rate was about 40% for men and about 46% for women. All respondents completed a questionnaire which contained questions on demographic variables, presence and family history of cardiovascular diseases, history of hypertension and hypercholesterolaemia, presence of diabetes, presence of a number of chronic diseases, current use of medication, a prescribed diet status, use of alcohol, smoking habits, physical activity, psycho-social factors, selected dietary habits, and for women reproductive history. At the study centre the questionnaire was checked with the participant for completeness and, if necessary, further completed with the help of the field worker. Several characteristics such as educational level, smoking, alcohol use, height and weight of non-respondents and respondents have been evaluated in previous studies.[13] The results of these studies suggested that no substantial selection had taken place with respect to these characteristics.

During a physical examination blood pressure, weight and height were measured and blood was drawn for total cholesterol and HDL-cholesterol determination. A random zero sphygmomanometer was used to measure blood pressure twice with the subject in a sitting position. Trained technicians, who all received repeated instructions and who were all initially trained by the same physician, conducted the measurements. A standardised approach was used to determine cuff size. Systolic blood pressure, was recorded at the appearance of sounds (first-phase Korotkoff), and the diastolic blood pressure at the disappearance of sounds (fifth-phase Korotkoff). After the first measurement, the heart rate was measured for 30 s followed after 5 min by a second blood pressure measurement. For the analyses the mean of the two blood pressure measurements was used. Total and HDL cholesterol were determined in a non-fasting blood sample at the Clinical Chemistry Laboratory of the University Hospital 'Dijkzigt' in Rotterdam. The study is described in more detail elsewhere.[14] The medication data were obtained from the questionnaires. Previously it was demonstrated that agreement between questionnaire data on antihypertensive drug use and pharmacy records is high.[15]

Patient selection and definition

Patients who used antihypertensive drugs for the indication of hypertension and subjects, who had a high blood pressure, but did not use antihypertensive drugs, were considered hypertensive. The patients who used antihypertensive drugs had to be aware that those drugs were used for high blood pressure. High blood pressure was defined as a systolic blood pressure >160 mm Hg and/or a diastolic blood pressure >95 mm Hg. Patients using cholesterol-lowering agents were excluded. Antihypertensive drug therapy was divided into monotherapy (beta-blockers, diuretics, ACE-inhibitors and Ca-antagonists) and combination therapy (beta-blockers and ACE-inhibitors, Ca-antagonists and beta-blockers, beta-blockers and diuretics, ACE-inhibitors and diuretics). Other antihypertensive drug classes (alpha-blockers, alpha/beta-blockers and vasodilators) were not analysed due to the small numbers of subjects who used these drugs.

Analyses

Assuming a 4% increase in total cholesterol for diuretics and a 10% decrease in HDL cholesterol for beta-blockers (based on RCT's) we had more than 80% power ($\alpha = 0.05$) to detect these differences in our study.

Chi-square tests were used to compare proportious characteristics and *t*-tests to compare continuous characteristics of treated and untreated hypertensive patients. Linear regression was used to study the association between anihypertensive drug therapies and plasma lipid levels and to adjust for potential confounding factors. Untreated hypertensives served as the reference category.

We also performed separate analyses with untreated hypertensive patients who were aware and untreated hypertensive patients who were unaware of their hypertension as reference categories. Subjects aware of hypertension but without treatment may have a lower risk of coronary diseases, because this lower risk may have been the reason not to prescribe an antihypertensive drug. On

the other hand it is possible that subjects unaware of their hypertension are at lower risk. Maybe their hypertension was not detected because they never visited a physician because they were healthy. These analyses showed no important differences compared to the analysis that included all untreated hypertensives in the control group. Therefore we only present the results from the combined analyses.

Results

From 1987 to 1991 about 36 000 men and women were examined. Prevalence of hypertension was 8.5% ($n = 3056$). After exclusion of the cholesterol-lowering drug users ($n = 24$) and subjects who did not have a measurement of plasma lipid levels ($n = 35$), 2997 subjects remained for further analysis. A total of 1450 subjects used one or more antihypertensive drug(s) and 1547 subjects were not treated with antihypertensive drugs.

Table 1 Characteristics of hypertensive patients ($n = 2997$)

	n	*(%)*	*Tot chol*	*HDL chol*	*Ratio*
Sex					
Male	1574	52.5	6.04	1.08	5.95
Female	1423	47.5	6.17	1.29	5.07
Age (years)					
20–29	89	3.0	5.44	1.19	5.11
30–39	286	9.5	5.69	1.16	5.30
40–49	857	28.6	6.00	1.18	5.49
50–59	1765	58.9	6.25	1.19	5.61
Current cigarette smoking					
No	2021	67.5	6.08	1.21	5.34
Yes	971	32.5	6.15	1.12	5.93
Diabetes					
No	2899	97.0	6.10	1.19	5.51
Yes	90	3.0	6.04	1.04	6.14
Education					
Low	2272	75.8	6.15	1.18	5.59
Middle	388	12.9	5.98	1.19	5.42
High	322	10.7	5.90	1.20	5.24
History of CHD[a]					
No	2903	96.9	6.1	1.19	5.51
Yes	94	3.1	6.08	1.02	6.26
BMI (kg/m^2)					
<30	2204	73.5	6.07	1.21	5.39
>30	793	26.5	6.18	1.11	5.93
Hypertension (mm Hg)					
<90/140	715	23.9	6.10	1.16	5.59
90–95/140–160	406	13.5	6.09	1.17	5.59
>95/160	1876	62.6	6.10	1.20	5.50
Family history[b]					
No	2654	88.6	6.10	1.18	5.52
Yes	343	11.4	6.14	1.17	5.64
Alcohol (glasses per day)					
0–0.9	1780	59.4	6.05	1.17	5.53
1–2	461	15.4	6.11	1.20	5.47
>2	756	25.2	6.22	1.21	5.58
Sedentary					
No	1916	64.0	6.09	1.20	5.44
Yes	1077	36.0	6.13	1.16	5.71

[a]Self-reported history of myocardial infarction, heart/vascular surgery.
[b]Father or mother had a myocardial infarction before the age of 60.

Characteristics of the hypertensive population

In Table 1 the characteristics of the population and cholesterol parameters for different strata are presented. The cholesterol ratio (total cholesterol/HDL cholesterol) was associated with several factors. As expected we observed a higher HDL cholesterol level for women and an increasing cholesterol ratio with age. Smokers had a higher cholesterol ratio than non-smokers. Diabetic patients had a lower HDL-cholesterol than non-diabetic subjects did. Total cholesterol and cholesterol ratio decreased with a higher level of education.

Differences between treated and untreated subjects

In Table 2 several important baseline characteristics of treated and untreated subjects are shown. Treated subjects are more likely to be women and they have a higher mean age compared with untreated subjects. Untreated hypertensives have a much higher blood pressure at baseline. These differences were all statistically significant.

Effects of antihypertensive drugs on plasma lipids

In Table 3 the total cholesterol levels, HDL cholesterol levels and the ratios are shown for subjects using a single antihypertensive drug. The mean differences of plasma lipids between antihypertensive drug users and untreated hypertensives were assessed. In the univariate analyses we observed that subjects using a beta-blocker had a HDL-level that was 0.06 mmol/l lower compared to untreated hypertensives and that the ratio for beta-blocker users compared with non-users was 0.30 higher. Subjects using diuretics had a total cholesterol that was 0.26 mmol/l higher compared to untreated hypertensives and their HDL-level was 0.06 mmol/l higher. After adjustment for potential confounding factors in the multivariate analyses these differences were smaller and no longer statistically significant.

Table 2 Characteristics of treated ($n = 1450$) and untreated ($n = 1547$) patients

	Treated	*Untreated*
Female (*n* (%))	822 (56.7%)	601 (38.8%)*
Age (years), mean	51.9	47.9*
Smoking (*n* (%))	427 (29.4%)	541 (35.0%)**
Diabetes (*n* (%))	65 (4.5%)	25 (1.6%)*
History of CHD[a] (*n* (%))	71 (4.9%)	23 (1.5%)*
Body mass index (kg/m^2), mean	28.0	28.0
Blood pressure (mm Hg), mean		
SBP	135.8	151.6*
DBP	86.9	98.8*

[a]Self reported history of myocardial infarction, heart/vascular surgery.
*Statistically significant *P*-value <0.0001.
**Statistically significant *P*-value = 0.001.

Table 3 Association between monotherapy with antihypertensive drugs and plasma lipid levels. Compared with all untreated hypertensives[a]

	n	*Mean*	*Mean diff*	*95% CI*	*Mean diff*[b]	*95% CI*
Total cholesterol						
Diuretic	300	6.34	0.26	0.12–0.40*	0.13	–0.10–0.37
Ca-antagonist	45	5.89	–0.19	–0.52–0.14	–0.62	–1.3–0.08
Beta-blocker	475	6.02	–0.06	–0.17–0.18	0.02	–0.06–0.06
ACE-inhibitor	86	6.11	0.04	–0.21–0.29	0.09	–0.29–0.36
HDL-cholesterol						
Diuretic	300	1.26	0.06	0.02–0.10*	–0.01	–0.07–0.06
Ca-antagonist	45	1.16	–0.04	–0.13–0.13	0.03	–0.15–0.22
Beta-blocker	475	1.13	–0.07	–0.11 to –0.04*	–0.01	–0.13–0.52
ACE-inhibitor	86	1.19	–0.01	–0.03–0.11	–0.14	–0.28–0.01
Ratio (=Total chol/HDL chol)						
Diuretic	300	5.34	–0.10	–0.33–0.13	0.21	–0.17–0.59
Ca-antagonist	45	5.40	–0.04	–0.59–0.51	–0.76	–1.85–0.32
Beta-blocker	475	5.74	0.30	0.10–0.48*	0.20	–0.13–0.53
ACE-inhibitor	86	5.45	0.01	–0.20–0.61	0.33	–0.24–0.92

[a]Untreated hypertensives $n = 1547$; Total chol = 6.07 mmol/l; HDL chol = 1.20 mmol/l; Ratio = 5.44.
[b]Adjusted for sex, age, current cigarette smoking, diabetes, level of education, history of coronary heart diseases, BMI, severity of hypertension, physical inactivity, use of alcohol and family history of myocardial infarction.
*Statistically significant ($P < 0.05$).

Table 4 shows the results for subjects who used a combination of antihypertensive drugs. HDL cholesterol for users of the combination of a beta-blocker and a diuretic was both in univariate (–0.06 mmol/l) and in multivariate analysis (–0.10 mmol/l) significantly decreased. The ratio for users of this combination was significantly increased in the univariate analysis (0.24) and after the adjustment it was even more increased (0.30). This last value was not statistically significant probably due to missing covariate information. The combination of an ACE-inhibitor and a diuretic was associated with a lower HDL cholesterol level (difference = 0.15 mmol/l) compared to untreated hypertensives. Users of the combination of an ACE-inhibitor and a diuretic had after adjustment a decreased total cholesterol level (–0.58 mmol/l).

Discussion

In this population-based cross-sectional study we found no association between single antihypertensive drug therapy and plasma lipid levels. Subjects who used a combination of diuretics and beta-blockers (both known for adverse effects on plasma lipid levels) had a decreased HDL cholesterol and an

Table 4 Association between combination therapy with antihypertensive drugs and plasma lipid levels. Compared with all untreated hypertensives[a]

	n	*Mean*	*Mean diff*	*95% CI*	*Mean diff*[b]	*95% CI*
Total cholesterol						
Beta-blocker/ACE-inhibitor	26	6.21	0.13	–0.30–0.57	0.53	–0.21–1.27
Ca-antagonist/Beta-blocker	20	5.99	–0.09	–0.58–0.41	–0.48	–2.15–1.18
Beta-blocker/Diuretic	305	6.16	0.08	–0.05–0.22	–0.09	–0.34–0.16
ACE-inhibitor/Diuretic	47	5.83	–0.25	–0.57–0.08	–0.58	–1.13 to –0.03*
HDL-cholesterol						
Beta-blocker/ACE-inhibitor	26	1.12	–0.08	–0.21–0.05	–0.09	–0.29–0.10
Ca-antagonist/Beta-blocker	20	1.08	–0.12	–0.26–0.02	–0.03	–0.47–0.40
Beta-blocker/Diuretic	305	1.14	–0.06	–0.10 to –0.02*	–0.10	–0.16 to –0.03*
ACE-inhibitor/Diuretic	47	1.10	–0.15	–0.30 to –0.01*	–0.14	–0.89–0.82
Ratio (=Total chol/HDL chol)						
Beta-blocker/ACE-inhibitor	26	5.93	0.49	–0.23–1.22	0.91	–0.25–2.07
Ca-antagonist/Beta-blocker	20	5.73	0.29	–0.53–1.12	–0.76	–3.36–1.84
Beta-blocker/Diuretic	305	5.68	0.24	0.01–0.46*	0.30	–0.08–0.69
ACE-inhibitor/Diuretic	47	5.54	0.38	–0.42–1.19	–0.03	–1.16–1.12

[a]Untreated hypertensives $n = 1547$; Total chol = 6.07 mmol/l; HDL chol = 1.20 mmol/l; Ratio = 5.44.
[b]Adjusted for sex, age, current cigarette smoking, diabetes, level of education, history of coronary heart diseases, BMI, severity of hypertension, physical inactivity, use of alcohol and family history of myocardial infarction.
*Statistically significant ($P < 0.05$).

increased cholesterol ratio compared to untreated hypertensives. In trials those drugs are known for their negative effects on plasma lipid levels. It is not surprising that the combination of those two leads to a worse lipid profile.

Subjects using a combination of an ACE-inhibitor and a diuretic had a decreased total cholesterol level. This was an unexpected finding that was not found in trials. Although this decrease was significant, the power of our study was not sufficient to detect this difference. Therefore, this result may be due to chance and should be interpreted with caution. In our study we had limited power to rule out small (about 5%) but potentially clinical important effects of Ca-antagonists, ACE-inhibitors, and combinations of antihypertensive drugs on lipids.

Although, the cross-sectional design is not optimal to study changes in plasma lipid concentrations it may give a reasonable indication of the effects of antihypertensive medication on lipid profile in the general Dutch population. Another limitation of our study was that we had no information about the duration of drug use. We observed no apparent association between use of solely diuretics and plasma lipid levels. Other studies found that 1-year after initiation of diuretic therapy, lipid levels had returned to the level before treatment.[16] This may explain why we found no association between diuretic therapy and plasma lipid levels in this study.

In another population-based cross-sectional study by Helmert and Shea[11] adverse effects of beta-blockers on plasma lipid levels were found. Whether these effects were only temporary is uncertain.[2,4] The fact that the differences in plasma lipid levels between subjects who used beta-blockers compared to untreated hypertensives that we found in univariate analyses, disappeared after adjustment for potential confounding factors suggests that beta-blockers have no substantial impact on plasma lipid levels in the general Dutch population. Another explanation for not finding an expected relation between the use of solely diuretics or solely beta-blockers could be confounding by contra-indication. Physicians (aware of trial results) may have prescribed less beta-blockers and diuretics to patients who had a high total cholesterol.

However, the presumed advantage of selective non-prescribing of beta-blockers and diuretics to patients with a high total cholesterol should be carefully weighed against their proven benefit in reduction of cardiovascular morbidity and mortality.[17] Although experimental evidence demonstrated that diuretics and beta-blockers adversely affect plasma lipid levels, in daily practice we only observed this negative influence for the combination of those two drugs.

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