High-Density Lipoprotein Cholesterol and Cardiovascular Disease in Spanish Hypertensive Women. The RIMHA Study

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Introduction and objectives. To determine the prevalence of a low high-density lipoprotein cholesterol (HDL-C) concentration in 11 042 hypertensive Spanish women aged ≥55 years, to identify factors associated with a low concentration, and to evaluate its relationship with cardiovascular disease (CVD).

Methods. Analysis of RIMHA cross-sectional study findings. Data on demographic, biochemical and clinical variables were obtained. Relationships between a low HDL-C concentration (<46 mg/dL) and CVD and between the HDL-C concentration (in quintiles) and CVD were studied by multivariate logistic regression modeling.

Results. The prevalence of a low HDL-C concentration was 24.3% (95% confidence interval [CI], 23.5–25.1), and was higher in women with diabetes or CVD. A low HDL-C concentration was independently associated with excess weight, smoking, diabetes, and the presence of CVD, and inversely associated with age. The prevalence of CVD was higher in women with a low HDL-C concentration (24.7% vs 18.4% in those with a normal concentration; P<.001). There was an independent association between a low HDL-C concentration and CVD after adjustment for other risk factors (odds ratio [OR]=1.42; 95% CI, 1.26–1.60; P<.001) and with silent target organ damage (OR=1.31; 95% CI, 1.15–1.49; P<.001). Similarly, there was an independent inverse association between the HDL-C concentration (in quintiles) and the prevalence of CVD, particularly for HDL-C concentrations <58 mg/dL.

Conclusions. One in 4 hypertensive women aged ≥55 years had a low HDL-C concentration, which was independently associated with the presence of CVD. Moreover, there was an inverse association between the HDL-C concentration and the prevalence of CVD, even at normal HDL-C concentrations.

Key words: *Women. High-density lipoprotein cholesterol. Prevalence. Cardiovascular disease. Cross-sectional studies.*

Colesterol HDL y enfermedad cardiovascular en mujeres hipertensas de España. Estudio RIMHA

Introducción y objetivos. Evaluar la prevalencia de concentración baja de colesterol de las lipoproteínas de alta densidad (cHDL), los factores asociados y la relación con la enfermedad cardiovascular (ECV), en 11.042 mujeres hipertensas de 55 o más años de edad.

Métodos. Análisis del estudio transversal RIMHA. Se recogieron datos demográficos, bioquímicos, y clínicos. Se analizó la relación entre cHDL bajo (< 46 mg/dl) y ECV, y entre concentración de cHDL (quintiles) y ECV mediante modelos multivariables de regresión logística.

Resultados. La prevalencia de cHDL bajo fue del 24,3% (intervalo de confianza [IC] del 95%, 23,5-25,1), y fue mayor en mujeres diabéticas o con ECV. El cHDL bajo se asoció a exceso de peso, tabaquismo, diabetes y ECV, e inversamente con la edad. La prevalencia de ECV fue mayor en mujeres con cHDL bajo (el 24,7 frente al 18,4% con cHDL normal; p < 0,001). Se observó una asociación independiente entre cHDL bajo y ECV tras ajustar por otros factores de riesgo (odds ratio [OR] = 1,42; IC del 95%, 1,26-1,60; p < 0,001) y por la lesión asintomática de órgano diana (OR = 1,31; IC del 95%, 1,15-1,49; p < 0,001). Del mismo modo, se observó una asociación independiente e inversa entre la concentración de cHDL (quintiles) y la presencia de ECV, en especial para concentraciones de cHDL < 58 mg/dl.

Conclusiones. En esta muestra de mujeres hipertensas de 55 años o más, una de cada 4 tenía cHDL bajo, y esto se relacionó independientemente con la presencia de ECV. Además, encontramos una asociación inversa

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entre la concentración de cHDL y la prevalencia de ECV también en cifras de cHDL consideradas normales.

Palabras clave: *Mujer. Colesterol de las lipoproteínas de alta densidad. Prevalencia. Enfermedad cardiovascular. Estudios transversales.*

ABBREVIATIONS

CVD: cardiovascular disease
HDL: high-density lipoprotein
LDL: low-density lipoprotein

IINTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in older women in developed societies, and the number of deaths is expected to increase by 30% from the 1990s to 2020.[1] Ischemic heart disease becomes more common after the menopause, and could therefore be partly related with the associated metabolic changes, in particular increases in concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and reductions in the concentration of high-density lipoprotein (HDL) cholesterol, which can contribute to the increased cardiovascular risk in women aged 60 years or older.[2,3]

For several years now low concentrations of HDL cholesterol have been known to be associated with an increased risk of developing CVD, especially coronary heart disease.[4,5] This increased risk remains in persons treated with statins,[6] even when very low concentrations of LDL cholesterol are achieved.[7] Thus, the low concentration of HDL cholesterol may be a conditioning factor for the persistence of the cardiovascular risk, at least in certain patients, in spite of treatment with statins. In addition, HDL cholesterol seems to have a greater impact in women. In the Framingham study, the risk of developing myocardial infarction associated with a low HDL cholesterol concentration was far greater in women than in men,[8] and in 4 American studies an increase in HDL cholesterol produced a greater cardiovascular benefit in women than in men.[9]

Only a few series have studied the prevalence of low concentrations of HDL cholesterol in Spanish women and the transverse association between HDL cholesterol and CVD. The aim of this study was to evaluate the prevalence of low concentrations of HDL cholesterol and the association between the HDL cholesterol concentration and the prevalence of CVD in a wide sample of women aged ≥55 years with hypertension included in the RIMHA study (Riesgo de Ictus en las Mujeres con Hipertensión Arterial—Risk of stroke in women with hypertension).[10]

METHODS

This study is an analysis of the RIMHA study, which is a cross-sectional, multicenter, epidemiological study undertaken in primary care centers in Spain.[10] The study was approved by an independent clinical research ethics committee and the data were collected between June and December 2004. Each researcher collected information about the first 8 non-selected hypertensive women who attended their office, after being duly informed and providing signed consent to participation in the study.

The primary endpoint of the study was to estimate the risk of stroke in this particular population, and the results have already been published.[10] Amongst the secondary aims of the study was the evaluation of other cardiovascular risk factors. The study included women who had had hypertension for at least 6 months (according to the diagnosis in their clinical histories) and were aged ≥55 years. Patients were excluded if they refused to give informed consent or had a disease or psychological disorder advising against their participation. Information was gathered about demographic and anthropometric data, cardiovascular risk factors and diseases.

The blood pressure was measured with an OMRON® M5 automatic device following the recommendations in force at the time.[11] All the patients underwent an electrocardiogram. Left ventricular hypertrophy was considered to be present when the Cornell voltage criteria for women were fulfilled.[12] A woman was considered to be diabetic if this diagnosis was reflected in the clinical history or if her baseline fasting glucose level was above 125 mg/dL.

The biochemical data were obtained from a blood test undergone within the 6 months prior to data collection. If this had not been done, or if the patient had started a new treatment since then that could affect the result, a new blood test was carried out. The glomerular filtration rate was calculated with the shortened MDRD (Modification of Diet in Renal Disease) equation.[13]

The measurement of the lipids was done at the usual laboratory for each office, not centralized. In general, the total cholesterol and the triglycerides were measured by enzymatic assays, the HDL cholesterol by a direct in vitro enzymatic method, and the LDL cholesterol was calculated from the Friedewald formula. To define the HDL cholesterol
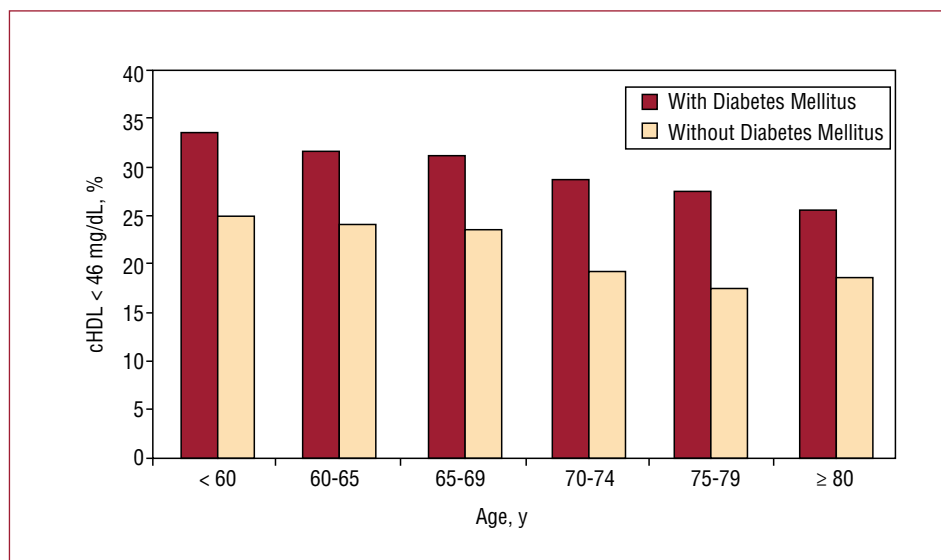
concentration as low, we used a concentration of <46 mg/dL, a concentration that the European Guidelines on Cardiovascular Prevention define as a marker of increased cardiovascular risk in women.[14]

Statistical Analysis

The sample size was calculated according to the primary endpoint of the study.[10] According to the likelihood of the expected risk of stroke taken from the Framingham study, with a 95% confidence interval and a maximum sampling error of 0.41%, we estimated a sample of 9200 women.[10]

The qualitative variables are presented as their frequency distribution. The quantitative variables are summarized as their mean and standard deviation (SD). For the comparison of the means between the groups, we used the Student t test for independent groups, and for the association between categorical variables we used the χ^2 test or Fisher's exact test. HDL cholesterol was managed as a binary variable ("normal" or "low" HDL cholesterol) to make the comparison between the two groups, and then in quintiles according to the HDL cholesterol concentration.

The variables associated with a low concentration of HDL cholesterol were evaluated with a multivariate logistic regression model that included demographic and metabolic variables and CVD. Another two models were used to study the association between low concentrations of HDL cholesterol and CVD, with CVD being the dependent variable; the variable HDL cholesterol was again binary ("normal" or "low" HDL cholesterol) and, alternatively, as quintiles of HDL cholesterol. The adjustment variables selected were statins and those variables that could affect the presence of CVD. These models were also repeated taking as the dependent variable the presence of heart disease (excluding cerebrovascular disease). The odds ratios (OR) and their 95% confidence intervals (CI) are given. In all the comparisons, a null hypothesis was rejected if the alpha error was less than 0.05. The data were processed using the statistical program SPSS 13.0.

RESULTS

Population Characteristics

In total, 11 042 women (85.8% of the total sample) had a complete lipid profile available (mean age, 67.9 years; 20% with established CVD) (Table 1). No significant differences were found between the women included and those excluded from the analysis.

HDL Cholesterol Concentration and Prevalence of Low HDL Cholesterol

The mean (SD) concentration of HDL cholesterol was 55.9 (14.6) mg/dL. This concentration was lower in the diabetic women (53.5 [14.7] vs 56.9 [14.5] mg/dL in the non-diabetic women; $P<.001$), in women with prior CVD (54.3 [15.7] vs 56.3 [14.3] mg/dL in women without CVD; $P<.001$) and in women treated with statins (55.2 [15] vs 56.5 [14.5] mg/dL in the non-treated women; $P<.001$).

The prevalence of low concentrations of HDL cholesterol (<46 mg/dL) was 24.3% (95% CI, 23.5-25.1). The prevalence was higher in the diabetic women as compared with the non-diabetic women (29.9% vs 21.9%; $P<.001$), in the women with CVD (30.1% vs 22.8% in the women without CVD; $P<.001$) and in the women treated with statins as compared

TABLE 1. Characteristics of the Total Sample, and Stratified According to Whether the Serum Concentration of High-Density Lipoprotein (HDL) Cholesterol Was Normal or Low

	Total (n=11 042)	HDL cholesterol normal (n=8359)	HDL cholesterol low (n=2683)	P
Demographic data and risk factors				
Age, y	67.9 (8.5)	68.2 (8.5)	67.2 (8.4)	<.001
Menopause	95.5	95.8	94.8	.037
Active smokers	9.9	9.1	12.5	<.001
BMI	29.2 (4.9)	29 (4.8)	29.7 (5.1)	<.001
Obesity (BMI=30)	38.4	37.3	42	<.001
Abdominal circumference, cm	97 (16)	97 (15)	98 (17)	.001
SBP, mm Hg	143 (16)	143 (16)	142 (16)	<.001
DBP, mmHg	82 (9)	82 (9)	83 (9)	<.001
BP controlled[a]	69.5	31.8	26.5	<.001
Diabetes mellitus	29.4	27.2	36.3	<.001
Lipids				
Total cholesterol, mg/dL	219 (38)	221 (37)	216 (42)	<.001
LDL cholesterol, mg/dL	137 (34)	136 (33)	138 (37)	.001
HDL cholesterol, mg/dL	56 (15)	61 (13)	40 (5)	<.001
Triglycerides, mg/dL	139 (65)	131 (62)	163 (69)	<.001
Non-HDL cholesterol, mg/dL	163 (39)	160 (37)	176 (42)	<.001
Non-HDL cholesterol ≥150 mg/dL	62.8	59	74.5	<.001
Ratio total cholesterol/HDL cholesterol	4.2 (1.3)	3.7 (0.8)	5.5 (1.5)	<.001
Ratio total cholesterol/HDL cholesterol >5	19.7	7	59.2	<.001
Metabolic syndrome and its components				
Metabolic syndrome	59.6	49.2	91.4	<.001
Abdominal circumference >88 cm	75.4	75	76.9	.001
Glycemia ≥110 mg/dL or diabetes mellitus	37.6	35.4	44.4	<.001
Triglycerides ≥150 mg/dL	38.2	32.3	56.5	<.001
HDL cholesterol <50 mg/dL	36	13.2	100	<.001
BP ≥135/85 mm Hg or hypertension	100	100	100	–
Target organ damage				
Left ventricular hypertrophy	19.4	17.9	24	<.001
Glomerular filtration rate <60 mL/min/1.73 m^2	37.3	35.4	43.4	<.001
Cardiovascular diseases				
Cardiovascular disease (any)	20	18.4	24.7	<.001
Heart disease[b]	16.1	14.5	20.6	<.001
Myocardial infarction	3.3	2.9	4.6	<.001
Angina	8.5	7.7	11.3	<.001
Heart failure	9	8.1	11.7	<.001
Stroke (cerebrovascular disease)	6.2	5.9	7.1	.034
Treatment with statins	45.3	43.8	50.1	<.001

BMI indicates body mass index; BP, blood pressure; DBP, diastolic BP; LDL, low-density lipoprotein; SBP, systolic BP.
[a]<140/90 or <130/80 mm Hg if diabetes or cardiovascular disease present.
[b]Includes myocardial infarction, angina, and heart failure. The values express the mean (SD) or percentage.

with the women not treated with statins (26.9% vs 22.2%; *P*<.001). For a cut-off point of <50 mg/dL, the prevalence was 36% (95% CI, 35.1-36.9).

The prevalence was greater for the age range of 55-69 years (26.9%, 26.2%, and 25.8%, respectively, in the women younger than 60, aged 60-64, and 65-69 years), and lower in the older women (22.5%, 20.9%, and 20.6%, respectively, in the women aged 70-74, 75-79 years, and 80 years or over; χ^2 for the linear trend <0.001). In each age range the prevalence was greater in diabetic women and in women with CVD

(Figures 1 and 2) (χ^2 for the linear trend <0.001 in all cases, except in the women with diabetes, *P*=.004).

Among the women without CVD, the prevalence of low concentrations of HDL cholesterol was similar in those with and without treatment with diuretics or beta-blockers (22.9% and 22.8%, respectively; *P*=.919), whereas in the women with CVD the prevalence was numerically superior in the treated women, though the difference was not statistically significant (31.6% vs 27.8%; *P*=.062). In the non-diabetic women, the prevalences were 21.9%
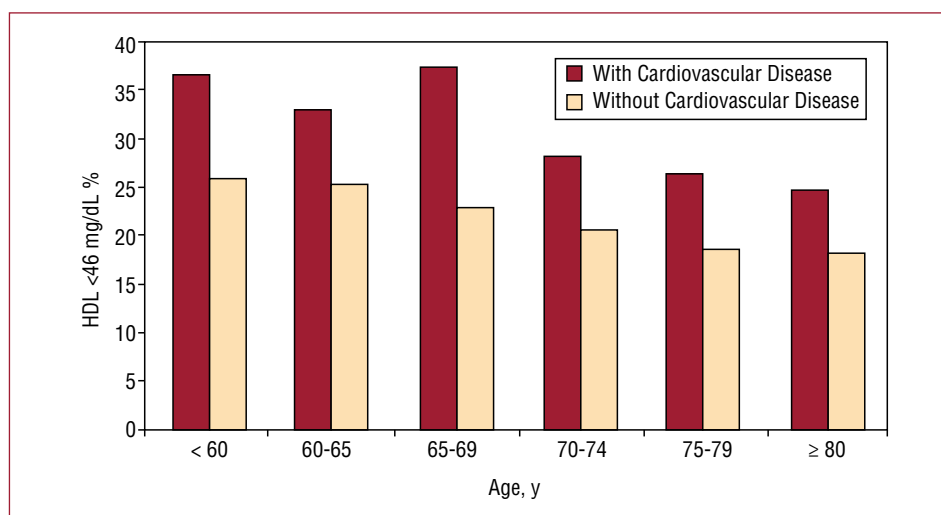
Figure 2. Percentage of hypertensive women with high-density lipoprotein (HDL) cholesterol concentrations <46 mg/dL, stratified according to age and the presence or absence of cardiovascular disease.

TABLE 2. **Multivariate Analysis. Variables Independently Associated With the Presence of Low Concentrations of High-Density Lipoprotein Cholesterol**

	OR (95% CI)	P
Model for all the women		
Age (for each increment of 1 year)	0.98 (0.98-0.99)	<.001
BMI (overweight vs normal weight)	1.17 (1.01-1.36)	.034
BMI (obesity vs normal weight)	1.34 (1.15-1.55)	<.001
Smoker versus non-smoker	1.30 (1.10-1.53)	.002
Diabetes mellitus	1.42 (1.28-1.58)	<.001
Cardiovascular disease	1.46 (1.29-1.65)	<.001
Model for the women with no history of cardiovascular disease		
Age (for each increment of 1 year)	0.98 (0.97-0.99)	<.001
BMI (overweight versus normal weight)	1.14 (0.98-1.35)	.115
BMI (obesity versus normal weight)	1.39 (1.13-1.58)	.001
Smoker versus non-smoker	1.33 (1.11-1.60)	.002
Diabetes mellitus	1.46 (1.29-1.60)	<.001

IBMI indicates body mass index; CI, confidence interval; OR, odds ratio.
The following variables were included in the model (dependent variable: low HDL cholesterol concentration): age, menopause, BMI categorized as normal, overweight or obesity, waist circumference (normal or enlarged), diabetes mellitus, smoker, and cardiovascular disease. The second model included the same variables except for cardiovascular disease, and it was restricted to the women with no cardiovascular history.

and 22% (without and with treatment with diuretics or beta-blockers; P=.894), and for the diabetic women the figures were 27.8% and 31.6% (without and with treatment with diuretics or beta-blockers, respectively, P=.032).

Prevalence of High Triglyceride Levels

Triglyceride levels were ≥150 mg/dL in 38.2% of the patients, a prevalence that was greater in the women with low concentrations of HDL cholesterol (56.5% vs 32.3% in the women with normal HDL cholesterol; P<.001), in the diabetic women (48.3% vs 34%; P<.001) and in the women with CVD (44.7% vs 36.5%; P<.001).

Characteristics Related With Low HDL Cholesterol Concentrations

Table 1 shows the characteristics of the women with normal and low HDL cholesterol concentrations. The group with low HDL cholesterol concentrations contained a greater percentage of women who were smokers, or who had obesity, a large abdominal circumference and diabetes mellitus, and a worse blood pressure control. In the women with low HDL cholesterol concentrations, the concentration of total cholesterol was slightly lower, that of LDL cholesterol slightly higher and that of triglycerides higher. The prevalence of high concentrations of triglycerides was much greater in the women with low HDL cholesterol concentrations. Finally, the women

TABLE 3. Odds Ratio (OR) of Cardiovascular Disease and Heart Disease in Women With Low Concentrations of High-Density Lipoprotein (HDL) Cholesterol Compared With Women With Normal Concentrations of HDL Cholesterol. Multivariate Analysis

	Cardiovascular Disease, Any		Heart Disease[a]	
	OR (95% CI)	P	OR (95% CI)	P
Model 1[b]	1.42 (1.26-1.60)	<.001	1.47 (1.30-1.67)	<.001
Model 2[c]	1.31 (1.15-1.49)	<.001	1.35 (1.18-1.56)	<.001

CI indicates confidence interval.
The dependent variable was cardiovascular disease and the same model was repeated for heart disease.
[a]Includes myocardial infarction, angina, and heart failure.
[b]The adjustment variables included in model 1 were age, smoking, diabetes, body mass index categorized as normal, overweight or obesity, blood pressure control, low-density lipoprotein cholesterol concentration, treatment with statins, and HDL cholesterol concentration (low or normal).
[c]Model 2 also included left ventricular hypertrophy and the glomerular filtration rate (normal or reduced).

TABLE 4. Prevalence of Cardiovascular Disease by Quintiles of High-Density Lipoprotein (HDL) Cholesterol

	Quintiles of HDL Cholesterol, mg/dL					P[a]
	≤ 45	46-50	51-58	59-66	≥ 66	
Established cardiovascular disease, total	25.5%	21%	18.7%	17.2%	17.4%	<.001
Heart disease[b]	21.4%	17.3%	14.9%	13.6%	13%	<.001
Myocardial infarction	4.9%	3.5%	3.3%	2.7%	2%	<.001
Angina	11.8%	8.9%	8%	6.7%	7.3%	<.001
Heart failure	12.1%	10.3%	8.2%	7.8%	6.5%	<.001
Stroke (cerebrovascular disease)	7.2%	5.8%	6.1%	5.5%	6.4%	NS

NS indicates not statistically significant.
[a]χ^2 test of linear trend.
[b]Includes myocardial infarction, angina and heart failure.

with low HDL cholesterol concentrations had a greater prevalence of left ventricular hypertrophy, a low glomerular filtration rate, overall CVD and heart disease.

The variables related with low concentrations of HDL cholesterol were evaluated in a multivariate model with the following variables: age, menopause, body mass index, waist circumference, diabetes mellitus, smoking and CVD (Table 2). The presence of low concentrations of HDL cholesterol was associated with excess weight, diabetes, smoking and CVD and, inversely, with age. In the women without CVD, the related variables were the same and the magnitude of the association was similar (Table 2). The inclusion in the multivariate models of treatment with diuretics or beta- blockers did not modify the associations, and the presence of a low concentration of HDL cholesterol was not related with these treatments.

Relation Between Low HDL Cholesterol Concentrations and Cardiovascular Disease

The prevalence of overall CVD was greater in the women with low HDL cholesterol concentrations as compared with those with HDL cholesterol concentrations in the range of normality (24.7% vs 18.4%; P<.001) (Table 1). After excluding cerebrovascular disease, the prevalences of heart disease were 20.6% (women with low HDL cholesterol concentrations) and 14.5% (women with normal HDL cholesterol concentrations; P<.001). Table 3 shows the OR of CVD and heart disease in the women with low HDL cholesterol concentrations compared with the women with normal HDL cholesterol concentrations obtained from the multivariate models. The first model included the variables age; smoking; diabetes; body mass index, categorized as normal, overweight or obese; blood pressure control; LDL cholesterol; treatment with statins and HDL cholesterol concentration (low or normal). There was an independent association between a low HDL cholesterol concentration and CVD (OR of CVD in women with a low HDL cholesterol concentration =1.42; 95% CI, 1.26-1.60, as compared with women with a normal HDL cholesterol concentration; P<.001). The OR of heart disease, excluding cerebrovascular disease, was similar (Table 3). The inclusion in this model of triglycerides (normal or raised) did not modify the relation between low HDL

TABLE 5. Multivariate Analysis. Odds Ratio (OR) of Cardiovascular Disease and Heart Disease According to the Concentration of High-Density Lipoprotein (HDL) Cholesterol

	Cardiovascular disease, Any		Heart Disease[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Model 1[b]				
First quintile, ≤45 mg/dL	1.59 (1.35-1.88)	<.001	1.71 (1.43-2.05)	<.001
Second quintile, 46-50 mg/dL	1.29 (1.09-1.53)	.003	1.39 (1.16-1.67)	<.001
Third quintile, 51-58 mg/dL	1.13 (0.95-1.35)	.160	1.17 (0.97-1.42)	.097
Fourth quintile, 59-66 mg/dL	1.04 (0.87-1.23)	.690	1.08 (0.90-1.31)	.408
Fifth quintile, >66 mg/dL	1 (reference)		1 (reference)	
Model 2[c]				
First quintile, ≤45 mg/dL	1.59 (1.25-2.04)	<.001	1.57 (1.29-1.93)	<.001
Second quintile, 46-50 mg/dL	1.54 (1.22-1.94)	<.001	1.36 (1.11-1.67)	.004
Third quintile, 51-58 mg/dL	1.26 (1.00-1.60)	.049	1.23 (1.00-1.52)	.056
Fourth quintile, 59-66 mg/dL	1.06 (0.85-1.33)	.586	1.09 (0.88-1.34)	.440
Fifth quintile, >66 mg/dL	1 (reference)		1 (reference)	

CI indicates confidence interval.
The dependent variable was cardiovascular disease and the same model was repeated for heart disease.
[a]Includes myocardial infarction, angina and heart failure.
[b]The following variables were included in model 1: age, body mass index categorized as normal, overweight or obesity, smoking, diabetes mellitus, blood pressure control, low-density lipoprotein cholesterol concentration, treatment with statins, and HDL cholesterol concentration (divided into quintiles).
[c]Model 2 includes the same variables, plus left ventricular hypertrophy and the glomerular filtration rate (normal or low). In both models the reference group is the group with the highest HDL cholesterol concentration (>66 mg/dL).

cholesterol concentrations and CVD, although there was a slight relation between triglycerides ≥150 mg/dL and CVD (OR=1.14; 95% CI, 1.02-1.27).

The second model included the same variables together with left ventricular hypertrophy and glomerular filtration rate (normal or reduced). The associations between low HDL cholesterol concentrations and CVD and between low HDL cholesterol concentrations and heart disease remained significant (Table 3). Nor did the inclusion of triglycerides change the association between low HDL cholesterol concentrations and CVD, but in this second model no association was seen between high concentrations of triglycerides and CVD.

Relation Between HDL Cholesterol Concentration and Cardiovascular Disease

To evaluate the association between the concentration of HDL cholesterol and CVD, the population was divided into the following quintiles of HDL cholesterol: <45 mg/dL (first), 45-50 mg/dL (second), 51-58 mg/dL (third), 59-66 mg/dL (fourth), and >66 mg/dL (fifth). The prevalence of CVD was highest in the lowest quintile of cholesterol (25.5%) and lowest in the higher quintiles of HDL cholesterol (χ^2 for the linear trend, <0.001). The prevalence of heart disease showed the same linear trend, as did the prevalence of each individual entity, except for stroke (Table 4).

Finally, the association between the concentration of HDL cholesterol and the prevalence of CVD or heart disease was analyzed using the same multivariate models, introducing the HDL cholesterol in quintiles. Taking as the reference the women with the highest HDL cholesterol concentration (fifth quintile, >66 mg/dL), the OR of CVD and heart disease increased progressively with lower concentrations of HDL cholesterol (Table 5). Compared with the women with the highest concentrations of HDL cholesterol (>66 mg/dL), those with the lowest HDL cholesterol concentration (<45 mg/dL) had an adjusted OR of CVD that was 60% greater (OR=1.59; 95% CI, 1.35-1.88; *P*<.001). The addition of left ventricular hypertrophy and glomerular filtration rate barely modified the relation (Table 4), which began to be significant for an HDL cholesterol concentration <58 mg/dL.

DISCUSSION

One out of every 4 women with hypertension aged ≥55 years had a low concentration of HDL cholesterol, and this was associated with a greater prevalence of overall CVD, and heart disease in particular. The variables associated with a low HDL cholesterol concentration were excess weight, diabetes, smoking and a history of CVD. In spite of the effect of diuretics and beta-blockers on the lipids, we found no relation between treatment with

these drugs and the presence of low HDL cholesterol concentrations, probably because, in the context of the effect of multiple variables, their influence is lower.

Most studies that have reported the prevalence of low HDL cholesterol concentrations in our setting have done so in the context of the metabolic syndrome (cut-off point in women of <50 mg/dL). Given this, the studies have reported prevalences of low HDL cholesterol concentrations of 34.4% in patients with CVD (men, 27.8%; women, 52%),[15] of 23.3% in hypertensive persons aged over 55 years (men, 13.3%; women, 31.1%)[16] and lower in persons of working age, although with a prevalence >30% in women.[17] Using these same criteria, the prevalence in patients with dyslipidemia was 35.4% (39% in women) in a European study,[18] whereas in the United States, in the NHANES study, it was 37.1% (39.3% in women).[19]

We found a prevalence of low HDL cholesterol concentrations of 24.3% for a cut-off point of <46 mg/dL and 36% for a cut-off point of <50 mg/dL, in line with earlier studies. The prevalence was higher in the women who had a greater cardiovascular risk (in diabetics and women with a history of CVD). Although persons living in Mediterranean areas have higher concentrations of HDL cholesterol, probably related with their dietary habits,[20] specific groups with a high cardiovascular risk, such as those described, have a considerably higher prevalence of low HDL cholesterol concentrations.

The association between low HDL cholesterol concentrations and CVD or heart disease was independent of other risk factors. Moreover, the association between the HDL cholesterol concentration and CVD or heart disease was also seen for a few HDL cholesterol concentrations situated within the range of normality (in particular, below 58 mg/dL) where the OR of CVD increased significantly after adjusting the model for all the risk factors and target organ damage. The inverse continuous relation between the HDL cholesterol concentration and the risk of CVD has been described in follow-up studies such as the Framingham study,[4] particularly in women. In the women of the Framingham study the adjusted risk of having a myocardial infarction in the lowest quartile of HDL cholesterol (<47 mg/dL) was 6 times greater than in the top quartile (≥67 mg/dL), with the risk increasing much more than that for the men.[8]

The cardiovascular risk associated with low concentrations of HDL cholesterol should be interpreted in the context of the high prevalence of the metabolic syndrome in the group of hypertensive women with low HDL cholesterol concentrations (91.4%) (Table 1). Many studies have shown that this particular group of metabolic anomalies increases

the risk of developing CVD[21-23] and, in addition, the low HDL cholesterol concentration usually coincides with high concentrations of triglycerides. In our study, the inclusion in the models of triglycerides did not modify the relation between low HDL cholesterol concentrations and CVD; in fact, the relation between triglycerides and CVD was weaker, and even disappeared when target organ damage was added to the model. Whereas a low HDL cholesterol concentration is a well-established cardiovascular risk factor, studies on triglycerides and CVD have found less consistent relations, although postprandial hypertriglyceridemia is emerging as an independent risk factor, especially in women.[24,25]

The protective properties of HDL cholesterol are well-known. As well as participating in the inverse transport of cholesterol for its hepatic elimination, HDL particles possess antioxidant, anti-inflammatory and antithrombotic properties that protect against the development of atherosclerosis and CVD.[26-29] A combined analysis of 4 follow-up studies showed that an increment of 1 mg/dL in levels of HDL cholesterol was associated with a reduction in the incidence of coronary heart disease of 2% in men and 3% in women.[9] Even so, the evidence that increasing HDL cholesterol concentrations by the use of drugs can reduce cardiovascular risk is modest. Earlier studies with gemfibrozil[30] and with niacin (the most effective drug for increasing HDL cholesterol)[31] indicate that the cardiovascular benefits of these drugs are closely related with the increase in HDL cholesterol. A recent meta-analysis of 23 clinical trials found that the trials in which LDL cholesterol decreased at the same time as HDL cholesterol increased were those that achieved the greatest reduction in cardiovascular risk.[32] Large clinical trials are currently in progress involving patients with a high cardiovascular risk in order to assess whether the addition of fenofibrate[33] or extended-release niacin[34,35] to statins reduces the incidence of cardiovascular complications. These clinical trials may determine whether the pharmacologic increase in HDL cholesterol reduces the incidence of CVD in patients already receiving statins, and what is the most suitable concentration of HDL cholesterol to achieve with drugs in high cardiovascular risk patients.

Several limitations should be considered concerning this study. The first is its cross-sectional nature, which prevents the establishment of a cause-effect relation between the associations found. The second limitation concerns the sample selection method, which was consecutive and not random, resulting in the greater likelihood of inclusion of patients with disease processes. Thirdly, the original study did not collect data about treatment with fibrates or physical activity, which may slightly

increase HDL cholesterol concentrations, and we were not therefore able to analyze their importance in the multivariate model. However, these limitations should have no impact on the relation seen between HDL cholesterol concentrations and the prevalence of CVD. Finally, the analyses were not performed at a centralized laboratory. We cannot therefore rule out the possibility of a certain degree of variability in the measurements or that this may have influenced the results. Nevertheless, we believe that the sample size analyzed and the analysis methods used strengthen the study, and that the results complement the information from follow-up studies and clinical trials, as they highlight the problems faced by physicians in their daily clinical practice. In spite of having been undertaken in a sample of women with hypertension, the prevalence of hypertension is so high in the age group studied[36,37] that the results of this study can be applied to most women of a similar age.

CONCLUSIONS

One out of every 4 hypertensive women aged 55 years or over seen in primary care offices had low HDL cholesterol concentrations. The prevalence of low HDL cholesterol concentrations was greater in women with an increased cardiovascular risk and was independently associated with the presence of CVD and heart disease. Moreover, the inverse association between HDL cholesterol concentrations and the prevalence of CVD was found at figures currently considered to be normal. The results of large ongoing clinical trials with HDL cholesterol-raising drugs should better determine the effect on CVD of pharmacologically increasing HDL cholesterol concentrations, and the attitude to follow in patients with low HDL cholesterol concentrations, particularly in those with a high cardiovascular risk.

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