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

Antonio Coca, Luis Cea-Calvo, José V. Lozano, Verónica Inaraja, Cristina Fernández-Pérez, Jorge Navarro, Álvaro Bonet, and Josep Redón, on behalf of the research group of the RIMHA study

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


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 χ² 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...
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; χ² 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) (χ² 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%
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

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 \(\geq 150\) 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%; \(P<.001\)).
as compared with those with HDL cholesterol concentrations in the range of normality (24.7% vs 18.4%; \textit{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; \textit{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 obesity, blood pressure control, low-density lipoprotein cholesterol concentration, 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; \textit{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 cholesterol concentrations and cardiovascular disease.

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%; \textit{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; \textit{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 obesity; blood pressure control; low-density lipoprotein cholesterol concentration, 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; \textit{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 cholesterol concentrations and cardiovascular disease.

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

<table>
<thead>
<tr>
<th>Cardiovascular Disease, Any</th>
<th>Heart Disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>\textit{P}</td>
<td>\textit{P}</td>
</tr>
<tr>
<td>Model 1\textsuperscript{b}</td>
<td>1.42 (1.26-1.60) &lt;.001</td>
</tr>
<tr>
<td>Model 2\textsuperscript{c}</td>
<td>1.31 (1.15-1.49) &lt;.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
The dependent variable was cardiovascular disease and the same model was repeated for heart disease.
\textsuperscript{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).
\textsuperscript{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

<table>
<thead>
<tr>
<th>Quintiles of HDL Cholesterol, mg/dL</th>
<th>P \textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td></td>
</tr>
<tr>
<td>≤ 45</td>
<td>46-50</td>
</tr>
<tr>
<td>Established cardiovascular disease, total</td>
<td>25.5%</td>
</tr>
<tr>
<td>Heart disease\textsuperscript{b}</td>
<td>21.4%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4.9%</td>
</tr>
<tr>
<td>Angina</td>
<td>11.8%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12.1%</td>
</tr>
<tr>
<td>Stroke (cerebrovascular disease)</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

NS indicates not statistically significant.
\textsuperscript{a}\textsuperscript{c}2 test of linear trend.
\textsuperscript{b}Includes myocardial infarction, angina and heart failure.
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 (>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%), of 23.3% in hypertensive persons aged over 55 years (men, 13.3%; women, 31.1%) and lower in persons of working age, although with a prevalence >30% in women. Using these same criteria, the prevalence in patients with dyslipidemia was 35.4% (39% in women) in a European study, whereas in the United States, in the NHANES study, it was 37.1% (39.3% in women).

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, 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, 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.

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 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.

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. 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. 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 the HDL cholesterol concentration.
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\textsuperscript{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.

ACKNOWLEDGMENTS

The RIMHA study was supported by the Sociedad Española de Hipertensión-Liga Española para la Lucha contra la Hipertensión Arterial (SEH-LELHA) and the Sociedad Española de Medicina Rural y Generalista (SEMERGEN), and was financed by a research grant from Merck Sharp & Dohme de España. The authors of the manuscript wish to thank the study researchers for their participation.

REFERENCES