# Coronary Disease Risk and Prevalence of Heart Disease in Primary Care Patients With Hypertension and Renal Disease

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**Introduction and objectives.** The presence of renal disease significantly alters the cardiovascular risk of patients with high blood pressure. However, few studies have examined renal parameters in primary care patients. The objectives of this study were to investigate cardiovascular risk and the factors influencing it in hypertensive patients with renal disease and to compare the findings with those in hypertensive patients without renal disease.

**Methods.** The CORONARIA study involved primary care patients with hypertension from all regions of Spain and included 2 groups with different degrees of renal disease.

**Results.** In total, 703 patients (9.8%) had renal disease. Hypertensive patients with renal disease had a worse cardiovascular risk profile than other hypertensives. The prevalence of diabetes was double in patients with renal disease. Moreover, the risk of a coronary event was significantly higher in those with renal disease. One-third of hypertensives with renal disease had another previously diagnosed cardiovascular disease. In addition, they more frequently had a history of angina, were twice as likely to have had a myocardial infarction, and were more than twice as likely to have undergone revascularization or to have peripheral vascular disease or cerebrovascular disease. Heart failure was four times more frequent in these patients with renal disease than in other hypertensives.

**Conclusions.** Patients with hypertension and renal disease have a higher risk of cardiovascular disease, exhibit an increased prevalence of diabetes, and suffer from more extensive target organ damage.

**Key words:** *Systemic hypertension. Cardiovascular risk. Renal damage.*

## Riesgo coronario y prevalencia de cardiopatías en pacientes hipertensos con afectación renal en asistencia primaria

**Introducción y objetivos.** La afectación renal supone un cambio importante en la evolución de la enfermedad cardiovascular del hipertenso, pero la frecuencia con que las manifestaciones renales se estudian en el paciente ambulatorio es muy escasa. Se ha estudiado el riesgo cardiovascular y los factores que intervienen en él en una población de hipertensos con afectación renal y se han comparado con los de otros hipertensos.

**Métodos.** En el estudio CORONARIA, realizado en pacientes hipertensos ambulatorios de todas las regiones de España, se incluyeron 2 apartados relativos a los grados de afectación renal.

**Resultados.** Un total de 703 pacientes incluidos (9,8%) presentaban afectación renal. Los hipertensos con afectación renal tuvieron peor perfil de factores de riesgo cardiovascular en comparación con los demás hipertensos. La prevalencia de la diabetes fue el doble en los grupos de pacientes renales. El riesgo de presentar un accidente coronario fue significativamente mayor en los pacientes con afectación renal. Un tercio de los hipertensos con afectación renal tenía otra enfermedad cardiovascular diagnosticada. Además, estos pacientes presentaban una mayor incidencia de angina de pecho, el doble de infartos, y más del doble tenía el antecedente de revascularización o enfermedad vascular periférica y/o cerebral. La insuficiencia cardiaca llegaba a ser 4 veces más frecuente en los pacientes con afectación renal grave que en los otros hipertensos.

**Conclusiones.** Los pacientes hipertensos con afectación renal presentan un riesgo cardiovascular más elevado, una prevalencia mayor de diabetes y una mayor afectación de los órganos diana.

**Palabras clave:** *Hipertensión arterial sistémica. Riesgo cardiovascular. Afectación renal.*

## INTRODUCTION

The World Health Organization reports of 1996[1] and 1999[2] on the control of hypertension consider three stages of evolution. Stage 2 corresponds to

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ABBREVIATIONS

HDL-C: high density lipoprotein cholesterol.
LDL-C: low density lipoprotein cholesterol.
CVD: cardiovascular disease.
DBP: diastolic blood pressure.
SBP: systolic blood pressure.

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hypertension that has caused detectable damage in a target organ. In Stage 3, the hypertension falls within the clinical context of cardiovascular disease, which is referred to as hypertension with associated clinical disorders. The prognosis in both stages worsens, especially in Stage 3, in which secondary prevention is involved.

The kidney is a target organ and is considered to be affected (Stage 2) if there is gross proteinuria or a mild increase in creatinine (from 1.2 to 2.0 mg/dL), and damaged (Stage 3) if there is diabetic nephropathy or a plasma creatinine >2 mg/dL.

Chronic renal failure in a 25-year old man represents a 100-fold rise in the risk of death due to vascular disease.[3] Likewise, death of a person on dialysis usually corresponds to a premature death of cardiovascular origin.[4] Even the mildest kidney disease represents an important worsening of the prognosis due to the increased cardiovascular risk. A creatinine value >1.29 mg/dL (114 µmol/L) in a general middle-aged population represented a 60% increase in the risk for stroke after 15 years of follow-up. When the creatinine was >1.59 mg/dL (141 µmol/L) the increased risk for cardiovascular death and coronary event rose by 20%.[5] The hypertensive patients in the HOT study who had creatinine >1.49 mg/dL (132 µmol/L) had double the number of events over 5 years, including cardiovascular death,[6] than those participants who had lower plasma creatinine concentrations.

Proteinuria also indicates a greater risk. In patients with diabetes it means a four-fold increase in the risk for cardiovascular disease and death.[7] Microalbuminuria forms part of the metabolic syndrome and it is a marker of cardiovascular risk in the general population, in persons with hypertension and in persons with diabetes. It is also a marker of worsening renal function, especially in diabetic patients.[8] Indeed, in the general population, concentrations as low as 5 µg/min (measured during nocturnal diuresis) indicate patients who are at greater risk for ischemic heart disease and cardiac death.[9]

Kidney disease implies a very marked qualitative change in the evolution of cardiovascular disease in a patient with hypertension.[10,11] Nevertheless, very few studies have actually examined renal manifestations in persons with hypertension who are not hospitalized. The CORONARIA study,[12] undertaken in non-hospitalized hypertensive patients from all over Spain, included two sections[2] concerning the two stages of renal disease mentioned above. This report provides the analysis of these data, undertaken in order to determine the differences between these hypertensive patients with renal disease and other hypertensive patients.

## METHODS

This study analyzed the baseline data corresponding to persons with renal disease who formed part of a study of pharmacovigilance in persons with hypertension (CORONARIA study). The primary aim of the study, which has been the subject of other reports,[12-14] was to obtain significant reductions in coronary risk, as calculated with the Framingham equation, induced by treatment with amlodipine for 12 months.

### Population

The CORONARIA study was undertaken by 1720 primary care physicians from 17 autonomous regions of Spain. The number and distribution of the physicians was proportional to the inhabitants of each region and also contemplated the rural and urban distribution of each region. Each physician included data from a maximum of 5 consecutive patients, older than 18 years of age, of either sex and with a blood pressure (BP) ≥140/90 mm Hg and with at least one other risk factor. The selection period was limited to 2 months.

For study inclusion purposes, risk factors were considered to be age (women over 65 years and men over 55 years), smoking, cholesterol >250 mg/dL, diabetes, pre-existing cardiovascular disease (CVD), and a history of heart disease in first degree male members of the family younger than 55 years of age or coronary heart disease in female family members younger than 65 years of age.

A total of 7187 patients were included in this analysis, of whom 6484 had no renal disease, 371 had raised creatinine concentrations between 1.2 and 2 mg/dL or proteinuria >1 g per 24 h (=1 mg/min = +/++++), and 332 had more severe renal disease, defined as diabetic nephropathy or chronic kidney failure (creatinine >2 mg/dL).

### Procedures

All the patients underwent a medical examination which included measurements of weight, height, BP and heart rate, as well as recording any history of diabetes, dyslipidemia, hypertension, smoking,

myocardial infarction, angina, myocardial revascularization procedures, congestive heart failure, cerebrovascular disease, peripheral vascular disease, retinopathy, and chronic nephropathy. Damage to other target organs was also recorded from the clinical history of each patient, as was left ventricular hypertrophy, diagnosed by any technique (electrocardiogram, echocardiogram, or radiology). The body mass index was calculated. A venous blood sample was drawn for study of lipids, glycemia and constants. All the procedures and questionnaires were performed by the corresponding primary care physician.

The coronary risk for each patient was considered to be the percentage risk of having a coronary event over the following 10 years, calculated according to the model proposed in the Framingham study.[15,16] The risk for coronary death was considered to be the percentage risk of having a fatal coronary disease in the following 10 years, and the risk of vascular death was calculated as the percentage risk of having a fatal, non-coronary vascular disease over the following 10 years, in both cases according to the proposal of the SCORE project.[17] The calculations of the average risk for the primary care patients were done for patients aged 30 to 64 years in the case of risk calculations according to SCORE and 30 to 74 years for risk calculations according to the Framingham and corrected Framingham equations.

### Statistical Analysis

The estimation of the 10-year risk for coronary disease for each patient was obtained from the Framingham equation detailed in the appendix to the article by Wilson et al,[15] calibrated for Spain according to the appendix of the article by Marrugat et al.[16] The following coronary risk factors were used for the calculation: sex, age, total cholesterol, high density lipoprotein (HDL) cholesterol, BP, diabetes, and smoking. The estimation of the 10-year risks for coronary death and vascular death was done from the SCORE equation, described in the appendix of the article by Conroy et al,[17] which includes all those risk factors included in the Framingham equation except diabetes. Models for a low-risk region were followed as well as a model that uses the association between cholesterol and HDL cholesterol (HDL-C) as a risk factor instead of just total cholesterol.

The quantitative variables were summarized as their means ± standard deviations (SD) and the qualitative variables with their percentages. The comparison of renal disease between each regional autonomous community in Spain was done using an analysis of variance (ANOVA) that included the effects of age, sex, and the autonomous community. The lineal trend in the quantitative variables was compared between the different degrees of renal disease using the Spearman correlation for ordinal data, and the qualitative variables with the $\chi^2$ of Mantel-Haenszel. The results were considered to be statistically significant when the P-values were ≤.05. The models were analyzed using the statistical package SAS, version 8.2.[18]

## RESULTS

Renal disease, most commonly mild, was detected in 703 hypertensive patients, representing 9.8% of those assessed. Table 1 shows the percentage of patients with the two stages of kidney disease in each regional autonomous community. With the exception of the Basque Country, the percentage of patients with one or other of the two stages of kidney disease was similar in all the autonomous regions. The rates of kidney disease were similar in both men and women. Kidney disease was more common in older patients with hypertension and in those with a previous diagnosis of hypertension; it was not associated with a family history of cardiovascular disease.

### Cardiovascular Risk and Renal Disease
(Tables 2 and 3)

The presence of cardiovascular risk factors was more common in the patients with some degree of kidney disease. These patients had a higher systolic BP (SBP), higher average concentrations of triglycerides and lower HDL cholesterol (HDL-C) concentrations in comparison with the other hypertensive patients, although the quantitative differences between the average SBP and HDL-C values were not clinically important. The prevalence of diabetes was twice as high in the patients with renal disease, especially in those who already had chronic renal failure; a similar situation was seen with the presence of left ventricular hypertrophy. No significant differences were detected, however, in the diastolic BP (DBP) or heart rate, nor in obesity, as considered from the body mass index. No significant differences were noted in the average concentrations of total cholesterol or low density lipoprotein (LDL) cholesterol (LDL-C). Strangely, those patients with some degree of renal disease had a lower prevalence of smoking, which was even less in the patients who had more severe renal disease.

The 10-year risk of having a coronary event was greater in the primary care patients with kidney disease, calculated from both the uncalibrated Framingham system (P<.0001) as well as after correction for the Spanish population (P<.0001). The differences were clinically important in both calculations. However, no significant differences were

**TABLE 1. Distribution of Kidney Disease According to Regional Autonomous Community**

| | Overall Number | No Renal Disease | | Proteinuria and/or Increased Creatinine | | Kidney Disease | | P |
|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | |
| Spain | 7187 | 6484 | 90.2 | 371 | 5.2 | 332 | 4.6 | >.05 |
| Andalusia | 1302 | 1165 | 89.5 | 76 | 5.8 | 61 | 4.7 | >.05 |
| Aragon | 216 | 191 | 88.4 | 15 | 6.9 | 10 | 4.6 | >.05 |
| Asturias | 176 | 160 | 90.9 | 10 | 5.7 | 6 | 3.4 | >.05 |
| Balearic Isles | 149 | 130 | 87.2 | 7 | 4.7 | 12 | 8.1 | >.05 |
| Canary Isles | 363 | 329 | 90.6 | 16 | 4.4 | 18 | 5.0 | >.05 |
| Cantabria | 92 | 87 | 94.6 | 2 | 2.2 | 3 | 3.3 | >.05 |
| Castilla-La Mancha | 272 | 247 | 90.8 | 9 | 3.3 | 16 | 5.9 | >.05 |
| Castilla and Leon | 460 | 414 | 90.0 | 20 | 4.3 | 26 | 5.7 | >.05 |
| Catalonia | 1209 | 1094 | 90.5 | 61 | 5.0 | 54 | 4.5 | >.05 |
| Extremadura | 261 | 236 | 90.4 | 16 | 6.1 | 9 | 3.4 | >.05 |
| Galicia | 540 | 478 | 88.5 | 35 | 6.5 | 27 | 5.0 | >.05 |
| La Rioja | 98 | 89 | 90.8 | 6 | 6.1 | 3 | 3.1 | >.05 |
| Madrid | 684 | 621 | 90.8 | 32 | 4.7 | 31 | 4.5 | >.05 |
| Murcia | 212 | 199 | 93.9 | 7 | 3.3 | 6 | 2.8 | >.05 |
| Navarre | 84 | 76 | 90.5 | 7 | 8.3 | 1 | 1.2 | >.05 |
| Basque Country | 283 | 268 | 94.7 | 7 | 2.5 | 8 | 2.8 | < .05 |
| Valencia | 786 | 700 | 89.1 | 45 | 5.7 | 41 | 5.2 | >.05 |

**TABLE 2. Distribution of the Risk Factors According to Renal Disease[*]**

| | No Renal Disease (N=6484) | Proteinuria and/ or Increased Creatinine (N=371) | Renal Disease (N=332) | P |
|---|---|---|---|---|
| Age, y | 62.7±11.4 | 67.0±11.0 | 67.1±11.1 | <.0001 |
| BMI | 28.6±4.0 | 28.9±4.2 | 28.9±4.7 | .0772 |
| SBP, mm Hg | 162.3±13.0 | 163.7±13.8 | 163.6±14.5 | .0092 |
| DBP, mm Hg | 95.3±8.4 | 94.7±7.8 | 94.6±9.2 | .0602 |
| HR, bpm | 77.3±9.3 | 78.2±9.2 | 77.2±9.2 | .5392 |
| Total cholesterol, mg/dL | 236±39 | 236±42 | 234±41 | .2750 |
| LDL cholesterol, mg/dL | 157±36 | 155±37 | 154±34 | .1128 |
| HDL cholesterol, mg/dL | 50±13 | 49±12 | 48±13 | .0161 |
| Triglycerides, mg/dL | 154±67 | 164±67 | 168±71 | <.0001 |
| Male | 51.5% | 53.3% | 48.8% | .5846 |
| Diabetes | 26.5% | 46.4% | 51.0% | <.0001 |
| Smokers | 36.1% | 33.8% | 26.1% | .0002 |
| LVH | 22.5% | 37.4% | 40.9% | <.0001 |
| Family history of CVD | 42.6% | 44.1% | 48.5% | .1006 |
| Newly diagnosed HT | 44.5% | 22.0% | 13.0% | <.0001 |

[*]HDL indicates high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease; HR, heart rate; HT, hypertension; LVH, left ventricular hypertrophy; BMI: body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

found for the risk of cardiovascular death, either coronary or non-coronary, according to the SCORE project.

## Cardiovascular Disease and Renal Disease (Table 4)

One third of the hypertensive patients with renal disease had another cardiovascular disease; this represented 10 percentage points above the frequency of the association that was found in the other patients with hypertension. The patients with renal disease more often had angina; they also had twice the rate of myocardial infarction and were more than twice as likely to have undergone coronary revascularization or to have peripheral or cerebral vascular disease. Heart failure was four times more frequent in the patients with severe renal disease as compared with the hypertensive patients with no signs of renal disease.

TABLE 3. **Cardiovascular Risk According to the Different Organ Systems and Renal Disease in Primary Care**

| | No Renal Disease (N=4391) | | Proteinuria and/or Increased Creatinine (N=191) | | Renal Disease (N=193) | | P* |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | |
| Framingham: 10 year risk of CVD, without calibrating† | 23.0 | 13.5 | 27.7 | 13.8 | 26.4 | 15.0 | <.0001 |
| P versus no renal disease | | | | <.0001 | | .0014 | |
| Framingham: 10 year risk of CVD, calibrated according to REGICOR† | 9.1 | 5.7 | 11.3 | 6.2 | 10.7 | 6.7 | <.0001 |
| P versus no renal disease | | | | <.0001 | | .0004 | |
| SCORE: 10 year risk of death due to coronary disease‡ | 2.8 | 2.9 | 3.0 | 2.8 | 2.7 | 2.9 | .6991 |
| P versus no renal disease | | | | .4183 | | .8245 | |
| SCORE: 10 year risk of death due to vascular disease‡ | 1.4 | 1.2 | 1.6 | 1.3 | 1.4 | 1.4 | .2878 |
| P versus no renal disease | | | | .1147 | | .9263 | |

*Linear trend statistical significance.
†Age range of 30 to 74 years.
‡Age range of 30 to 64 years.

TABLE 4. **Distribution of the Associated Clinical Entities According to Renal Disease**

| | No Renal Disease (N=6484), % | Proteinuria and/or Increased Creatinine (N=371), % | Renal Disease (N=332), % | P |
|---|---|---|---|---|
| Myocardial infarction | 5.6% | 10.7% | 9.4% | <.0001 |
| Angina | 12.3% | 17.9% | 17.7% | .0001 |
| Revascularization | 1.9% | 5.6% | 5.1% | <.0001 |
| Congestive heart failure | 3.2% | 9.2% | 12.6% | <.0001 |
| Any* | 19.7% | 30.7% | 29.4% | <.0001 |
| Cerebrovascular disease | 5.6% | 12.5% | 10.0% | <.0001 |
| Peripheral artery disease | 12.8% | 28.3% | 28.3% | <.0001 |

*Patients with any of the following disorders: myocardial infarction, angina, revascularization, or congestive heart failure.

## DISCUSSION

This study showed that renal disease in patients with hypertension coincides with a greater severity of their cardiovascular disease. Symptoms in target organs and the onset of vascular disease associated with hypertension are considered prognostic markers in hypertensive patients.[1,2] When the target organ is the kidney and the associated disease is chronic nephropathy, not only are they markers of poor prognosis, but they also involve pathophysiological mechanisms that have a very negative influence on the evolution of the hypertension. In our study, one third of the hypertensive patients with renal disease (as defined in the Methods section) had at least one other cardiovascular disease (ischemic heart disease, cerebral vascular disease or peripheral artery disease) and some 10% had chronic heart failure. Not surprisingly, therefore, these patients have a much higher coronary risk than those with hypertension but no associated renal disease, and follow-up studies have shown a greater true mortality in these patients.[3-7,19]

Our hypertensive patients with renal disease were seen to have a significant increase in triglycerides, a slight reduction in HDL-C and, very especially, a marked increase in the prevalence of diabetes. As seen in other studies,[20] these patients were older, with slightly higher average SBP figures and more often had left ventricular hypertrophy; the control of the hypertension is worse than in patients with no accompanying renal disease.[21] In our study the number of hypertensive patients who were not controlled was higher when they had renal disease.

An interesting point was the notable reduction in smoking in relation to renal disease and its severity. This could reflect a true reduction as a consequence of identifying smoking as a collaborative cause of vascular disease or be the result of a greater mortality in the subgroup of patients with kidney disease who also smoked.

The risk of having a coronary event is raised in primary care patients with kidney disease, both according to the uncorrected Framingham equation and to the equation corrected for the Spanish population. These differences are mainly based on the increased prevalence of diabetes in hypertensive patients with kidney disease. However, the risk of coronary death and non-coronary cardiovascular

death, calculated in accordance with the SCORE project, showed no differences between the groups with and without renal disease. This apparent paradox can be explained by the inability of the SCORE method to detect differences in population risk when these differences are derived from a varying prevalence of diabetes. This point has been the subject of an earlier communication.[13]

## Limitations of the Study

The prevalence of renal disease in the group of hypertensive patients studied was 9.8%, a low percentage in comparison with that of other studies. In fact, the prevalence of renal disease in groups of persons from the general population without hypertension or diabetes is already estimated to be 6.6%.[22] Considering the "uncorrected" general population, the prevalence is from 7.2% to 11.8%,[22-24] and for the population of patients with hypertension it reaches 16.5% to 18%.[20,25] The highest prevalence is seen in groups of patients with diabetes, in whom it can be as high as 32.6%.[26,27] The key to these differences resides in the recent changes affecting the definition of renal risk and in the diagnostic techniques used. The statistics quoted above are based on the presence of microalbuminuria measured with radioimmunoassays, which consider disease to be present with values from 30 mg/24 h, and which, together with glomerular filtration rates <60 mL/min, are the criteria considered by the VII Joint National Committee (JNC).[28] Our study was undertaken in accordance with the norms of the 1999 WHO/ISH subcommittee[2] (selection for the CORONARIA study commenced at the end of 1999) which, in turn, were from the 1996 and 1997 reports (V[1] and VI JNC[29]), in which renal disease was considered to be present with a proteinuria ≥1 g/24 h or the equivalent (see the Methods section) measured by turbimetry or colorimetry, or with a blood creatinine value ≥1.2 mg/dL. Consequently, the patients with just microalbuminuria were not considered to have renal disease for the purposes of this study. In the general population it is estimated that for each patient with gross proteinuria there are 11 with microalbuminuria,[23] and that half the patients with diabetes have some degree of proteinuria, half gross and the other half microalbuminuria.[26] Thus, among hypertensive patients, as well as the 9% with gross proteinuria there may be at least a similar percentage with microalbuminuria.

Our results are applicable to hypertensive patients with proteinuria according to the terms of this study. We now know that the differences between pathological and physiological values of albuminuria are not so clearly defined because the physiological variation in the urinary excretion of proteins is very great (and, consequently, its measurement), and also because increased risks have been described in the general population with microabuminuria (5 μg/min) that were considered physiological.[9,10] So many and such rapid changes in the concept, together with the multiple units used to measure albuminuria, may well be hindering the systematic use of albuminuria as a marker of cardiovascular risk.

Could our results be extended to other populations with hypertension in whom renal disease is considered based solely on the presence of microalbuminuria or an increase in the glomerular filtration rate? Qualitatively, we believe so; that the increases in cardiovascular risk, the greater involvement of other organs and the increased association with other cardiovascular diseases, which were shown in this study, are in fact common to all groups of hypertensive patients with kidney disease. Quantitatively, however, we think not, as the percentages of patients with an increased risk and cardiovascular involvement were significantly greater in relation to the amount of proteinuria. Relevant data exist concerning this aspect; microalbuminuria is known to be a previous step to proteinuria.[8] A recent study showed that, at the same time as the percentage of kidney disease in persons with hypertension and diabetes rose two-fold over 2 years, the values of renal excretion in the group went from microalbuminuria to proteinuria.[30] A report involving Spanish persons with hypertension and microalbuminuria[25] showed the percentage of persons with diabetes to be 25.5%, whereas in our study it reached 46% and 51%, depending on the degree of involvement. The patients with gross proteinuria, detectable at the bedside, had a greater cardiovascular risk than those who only had microalbuminuria. On the other hand, the high prevalence of diabetes in patients with kidney disease may be an expression that the diabetes itself is, together with the hypertension, the origin of the kidney disease.

## CONCLUSIONS

Hypertensive patients with gross proteinuria or increased blood creatinine, or both, had symptoms of the metabolic syndrome, a very increased prevalence of diabetes, and a significantly increased risk for a coronary event. These patients were more than twice as likely to have ischemic heart disease or cerebrovascular disease or peripheral artery disease than patients with no accompanying renal disease, and 10% had heart failure.

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