Relationship between Ankle-Brachial Index and Chronic Kidney Disease in Hypertensive Patients with No Known Cardiovascular Disease

Jose M. Mostaza,* Carmen Suarez,† Luis Manzano,‡ Marc Cairols,§ Francisca García-Iglesias,* Julio Sanchez-Alvarez,‖ Javier Ampuero,¶ Diego Godoy,** Andrés Rodriguez-Samaniego,†† and Miguel A. Sanchez-Zamorano;‡‡ on behalf of the MERITO Study Group

*Atherosclerosis Unit, Hospital Carlos III, †Internal Medicine Department, Hospital de la Princesa, ‡Internal Medicine Department, Hospital Ramón y Cajal, Madrid, §Vascular Surgery Department, Hospital Bellvitge, Barcelona, ‖Internal Medicine Department, Hospital Virgen del Camino, Pamplona, ¶Internal Medicine Department Hospital Provincial, Córdoba, **Internal Medicine Department, Hospital General Valencia, Valencia, ††Internal Medicine Department, Hospital Rio Carrión, Palencia, and ‡‡Medical Department, Bristol Myers-Squibb, Madrid, Spain

Both decreased GFR and albuminuria are associated with an elevated prevalence of peripheral artery disease. However, the combined effects of these alterations previously were not evaluated. Patients with hypertension and with no known vascular disease (n = 955; mean age 66 yr; 56% male) were selected from internal medicine outpatient clinics throughout Spain. Cardiovascular risk factors, urinary albumin excretion, and the ankle-brachial index (ABI) were assessed in all participants. GFR was estimated according to the Cockcroft-Gault equation. Of the study population, 62% had diabetes, 23.8% had a GFR <60 ml/min per 1.73 m², and 43.8% had albuminuria. The prevalence of ABI <0.9 was greater in patients with a GFR <60 ml/min per 1.73 m² (37.4 versus 24.3%; P < 0.0001) and in those who had albuminuria (32.2 versus 23.3%; P = 0.001). In patients with both alterations, the prevalence of ABI <0.9 was 45.7%. Multivariate analysis indicated that the factors that were associated independently with low ABI were age (odds ratio [OR] 1.06; 95% confidence interval [CI] 1.03 to 1.08; P < 0.0001), triglyceride concentration (OR 1.003; 95% CI 1.001 to 1.005; P = 0.001), presence of albuminuria (OR 1.61; 95% CI 1.18 to 2.20; P = 0.003), smoking habit (OR 1.72; 95% CI 1.13 to 2.63; P = 0.012), and a GFR <60 ml/min per 1.73 m² (OR 1.47; 95% CI 1.01 to 2.17; P = 0.049). In patients with hypertension and without known vascular disease, reduced GFR and albuminuria are associated independently with an ABI <0.9. Their combined presence characterizes a subgroup of the population who have an elevated prevalence of peripheral artery disease and could benefit from early diagnosis and treatment.


Patients

Patients with peripheral artery disease (PAD) of the lower limbs, whether symptomatic or not, have an elevated risk for cardiovascular disease and premature death (1,2). Early detection of PAD identifies a group of patients who would benefit from aggressive cardiovascular risk factor modification and from antiplatelet therapy. Several factors have been associated with the development of PAD, among which are age, gender, diabetes, smoking habit, dyslipidemia, and hypertension. High BP is an important risk factor in the progressive deterioration of renal function and in the development of albuminuria, particularly in patients of advanced age. Although both a decreased GFR (3–7) and the presence of albuminuria (8,9) have been associated independently with an elevated prevalence of PAD, their combined effects were not evaluated previously. This is of considerable importance given that not only PAD but also chronic renal disease is additive, and both are independent risk factors for the development of cardiovascular disease (10,11). Their simultaneous presence characterizes a subgroup of patients who have very high risk for cardiovascular disease and could benefit from early diagnosis and treatment (12). The objective of the present study was to determine the association between the GFR and albuminuria with the presence of subclinical PAD of the lower limbs in a large population of hypertensive patients with no known cardiovascular disease.

Materials and Methods

Patients

Participants in the Modificacion de le Estratificacio n del Riesgo con el Indice Tobillo-brazo (MERITO) study were of both genders, were between the ages of 50 and 85 yr, and attended internal medicine outpatient clinics in hospitals throughout Spain. Each investigator was required to measure the ankle-brachial index (ABI) in 20 consecutive patients who attended the clinic; 10 had type 2 diabetes, and 10 did not have diabetes but had a risk for death from cardiovascular disease ≥3% over the next 10 yr, calculated according to the equation of the System-
The diagnosis of hypertension required that the patient had had such a diagnosis made previously by the treating physician, a BP \( \geq 140/90 \) mmHg in patients without diabetes or \( \geq 130/80 \) mmHg in patients with diabetes recorded on two separate occasions, or treatment with antihypertensive drugs. Of the participants in the MERITO study, 85% were hypertensive and were selected for the current study. The diagnosis of diabetes was established in accordance with the criteria of the American Diabetes Association (14). All individuals with a definitive or suspected diagnosis of vascular disease, including coronary, cerebral, or PAD, were excluded from the study.

On entry into the study, a clinical history was taken and a thorough physical examination was made. Fasting venous blood was taken for biochemical analyses. Plasma concentrations of glucose, glycated hemoglobin, creatinine, lipids, and lipoproteins were measured using standardized biochemical methods. Estimated creatinine clearance was calculated by the Cockroft-Gault equation standardized to body surface area (15). Urinary albumin excretion was estimated using one or more of the following methods: Quantification of 24-h albumin excretion (54.8% of study patients), albumin-to-creatinine ratio on a spot urine specimen (36.5% of study patients), or quantification of albumin in an overnight sample (8.6% of study patients). Albuminuria was present when the albumin-to-creatinine ratio was \( \geq 30 \) mg/g, the 24-h albumin excretion was \( \geq 30 \) mg/24 h, or the concentration of albumin in the overnight sample was \( \geq 20 \) \( \mu \)g/min.

The ABI was determined with a bidirectional portable echo-Doppler of 8 MHz (Mini Doppler HADECO ES-100, Kawasaki, Japan) and a calibrated mercury sphygmomanometer. The systolic BP (SBP) was measured in the posterior tibial and pedal arteries of both lower limbs and the brachial artery of both upper limbs. The value of the ABI was calculated using the greater SBP obtained in the lower limbs divided by the SBP of whichever was the higher in the upper limbs. The lowest ABI so obtained for each patient was used in the subsequent statistical analyses. A value of ABI \(<0.9\) was considered pathologically low. All patients gave written informed consent, and the study was approved by the Committee on Ethics and Research of the Hospital Ramón y Cajal in Madrid.

### Table 1. Characteristics of the study population as a function of creatinine clearance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Creatinine Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;60 \text{ml/min per 1.73 m}^2) ((n = 227); 23.8%)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>41</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>71.8 (6.5)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.8 (5)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>11.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>63.4</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>151 (24)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79 (12)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>123 (41)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54 (29)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>154 (98)</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m(^2))</td>
<td>46.4 (10.5)</td>
</tr>
<tr>
<td>Antihypertension treatment (%)</td>
<td>91.6</td>
</tr>
<tr>
<td>Hypolipemic treatment (%)</td>
<td>61.9</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>51.1</td>
</tr>
<tr>
<td>ABI (&lt;0.9)</td>
<td>37.4</td>
</tr>
</tbody>
</table>

*ABI, ankle-brachial index; DBP, diastolic BP; SBP, systolic BP.*

### Statistical Analyses

The quantitative variables are presented as the mean (SD), and the qualitative variables are presented as percentages. The comparisons between the quantitative variables were with the \(t\) test, and the comparisons between the qualitative variables were with the \(\chi^2\) test. To evaluate the independent association between ABI (dependent variable) and renal disease, we performed logistic regression analyses in which the independent variables such as age, gender, and classical risk factors all were entered into the model. Statistic software program used for all analyses was the SAS package (version 8.2; SAS Institute, Cary, NC).

### Results

There were 955 white patients included in the study, 56% were male, and the overall mean age was 66 yr (8.1). Of these, 62% had diabetes, 21% were current smokers, 85% were receiving antihypertensive treatment, and 65% were receiving hypolipemic agents. Of the participants, 34.3% had a creatinine clearance \(>90\) ml/min per 1.73 m\(^2\), 41.9% had a mildly decreased GFR (between 60 and 89 ml/min per 1.73 m\(^2\)), 21.8% had a moderately decreased GFR (between 30 and 59 ml/min per 1.73 m\(^2\)), and 2% had a severely decreased GFR (<30 ml/min per 1.73 m\(^2\)). Albuminuria was noted in 43.8% of patients. Patients without diabetes had a poorer risk profile. They were older and had a greater proportion of cardiovascular disease risk factors. However, the percentage of those with albuminuria and/or a decreased GFR did not differ between patients with and without diabetes (data not shown). The mean ABI of the overall population was 0.97 (0.16); 27.4% of the participants had an ABI \(<0.9\), 22.6% between 0.7 and 0.9, and 4.7% between 0.4 and 0.7, and only one participant had an ABI \(<0.4\).

The patients with a GFR \(<60\) ml/min per 1.73 m\(^2\) (Table 1) were predominantly female, older, and on antihypertensive...
treatment. Conversely, body mass index, diastolic BP and LDL cholesterol were lower, and there was a lower prevalence of smoking habit. Also, the presence of albuminuria was greater in these patients with a decreased GFR (51.1 versus 41.5%; \( P = 0.007 \)).

The percentage of patients with low ABI was greater among participants with a GFR <60 ml/min per 1.73 m² (37.4 versus 24.3%; \( P < 0.0001 \)), with a significant positive correlation between the GFR and the ABI (\( r = 0.097, P = 0.003 \)). The prevalence of ABI <0.9 as a function of the grade of deterioration of the GFR can be seen in Table 2: The lower the GFR, the higher the prevalence of PAD. The patients with albuminuria had, as well, a greater prevalence of low ABI (32.2 versus 23.3%; \( P = 0.001 \)).

We performed multivariate analysis to assess the factors that were related to a low ABI. The continuous variables that were included in the model were age in years; body mass index in kg/m²; and LDL cholesterol, HDL cholesterol, and triglycerides in mg/dl. The categorical variables that were included in the model were age in years; body mass index in kg/m²; and LDL cholesterol, HDL cholesterol, and triglycerides. The factors that were associated independently with a low ABI were age (odds ratio [OR] 1.06; 95% confidence interval [CI] 1.03 to 1.08; \( P < 0.0001 \)), triglyceride concentration (OR 1.003; 95% CI 1.001 to 1.005; \( P = 0.001 \)), the presence of albuminuria (OR 1.61; 95% CI 1.18 to 2.20; \( P = 0.003 \)), being a current smoker (OR 1.72; 95% CI 1.13 to 2.63; \( P = 0.012 \)), and the presence of GFR <60 ml/min per 1.73 m² (OR 1.47; 95% CI 1.01 to 2.17; \( P = 0.049 \)). The inclusion of the use of inhibitors of the renin-angiotensin system into the model did not alter the findings.

The prevalence of a low ABI in patients who had a GFR ≥60 ml/min per 1.73 m² and did not have albuminuria was 21.8%; in patients who had only a GFR <60 ml/min per 1.73 m², the prevalence was 27.2%; in patients with only albuminuria, the prevalence was 28.8%; and in patients with both a GFR <60 ml/min per 1.73 m² and albuminuria, the prevalence was 45.7% (\( P < 0.001 \); Figure 1).

Discussion

Although the presence of chronic kidney disease, either as reduction in the GFR or as albuminuria, was shown previously to be associated independently with the risk for PAD (3–6), cardiovascular disease, and premature death (3,16–19), the combined effects of small decreases in GFR and albuminuria were not evaluated previously in relation to arteriosclerosis of the lower limbs. Our present data, obtained in a population of patients with hypertension and with no known cardiovascular disease, demonstrated that a GFR <60 ml/min per 1.73 m² and the presence of albuminuria both were associated with a reduced ABI and that these relationships were independent of other classical risk factors of cardiovascular disease. More than one quarter of the participants with a reduced GFR or with albuminuria had a low ABI, and this prevalence increased up to 50% in the group of patients with both disorders. The percentage of patients with a low ABI increased with decreasing GFR, and this was apparent even in patients with a modest reduction in renal function.

Our results are useful because they enable the identification of a section of the population with a high prevalence of PAD and, as such, with an elevated risk for developing coronary artery disease, cerebrovascular disease, or premature death. This elevated prevalence would justify the recommendation to perform an ABI measurement in patients with a reduced GFR and/or albuminuria so that if a low ABI is recorded, then aggressive measures of secondary prevention of cardiovascular disease can be implemented. Given the additive and independent cardiovascular disease risk that is conferred by both PAD and chronic renal disease, particularly in patients with hypertension (11), further studies would be warranted to determine

![Figure 1. Prevalence of a low ankle-brachial index (ABI) as a function of the presence or absence of a GFR <60 ml/min per 1.73 m² and of albuminuria.](image)

<table>
<thead>
<tr>
<th>Table 2. OR (95% CI) for an ABI &lt;0.9 segregated with respect to GFRa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Creatinine Clearance Rate</td>
</tr>
<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>&gt;90 ml/min per 1.73 m²</td>
</tr>
<tr>
<td>60 to 89 ml/min per 1.73 m²</td>
</tr>
<tr>
<td>30 to 59 ml/min per 1.73 m²</td>
</tr>
<tr>
<td>&lt;30 ml/min per 1.73 m²</td>
</tr>
</tbody>
</table>

aCI, confidence interval; OR, odds ratio.

bThe continuous variables that were included in the model were age in years; body mass index in kg/m²; and LDL cholesterol, HDL cholesterol, and triglycerides in mg/dl. The categorical variables that were included in the model were gender, current smoking, and presence or absence of diabetes.
the efficacy of recommending a routine evaluation of the presence of atherosclerosis in other vascular beds in these patients. Several mechanisms can be hypothesized to explain the association between a reduction in GFR and vascular disease. Despite that the two entities have risk factors in common, our results indicate that the relationship is independent of the presence of other classical risk factors. In patients with diabetes and a reduced GFR and without albuminuria, the underlying cause of the renal insufficiency could be the presence of atherosclerosis in the renal artery or in arteries of narrow diameter (20). Other factors that are present in patients with chronic kidney disease, such as hyperhomocystinemia, increase in inflammation activity, oxidative stress, and endothelial dysfunction, also could underlie the higher prevalence of PAD in patients with impaired renal function. Factors that link albuminuria to vascular disease have not been ascertained unambiguously. Albuminuria seems to identify individuals with generalized endothelial dysfunction and also may be a marker of a prothrombotic state (21,22). What is clear, however, is that it acts as a risk factor that is independent of renal function. Our present results demonstrate that low GFR and albuminuria are alterations that are associated independently with a low ABI, suggesting that the underlying routes of their association with vascular disease may be different.

In our study, reduced GFR was highly prevalent as a result of the advanced age of the patients, of all participants’ having hypertension, and of there being an elevated prevalence of diabetes. These observations coincide with other data that have been published on similar populations (23).

Our study has several limitations. The number of participants is relatively small in epidemiologic terms, which suggests that there may not have been sufficient numbers of patients representing the whole range of renal function deterioration. Other shortcomings of the study are that the albuminuria was measured using only one sample of urine, that a urinary sedimentation analysis was not performed simultaneously, and that the analyses were not conducted centrally. Nevertheless, all of these limitations would have served to reduce the possibilities of finding significant associations.

Conclusion
Our data indicate that both a reduction in the GFR and albuminuria are independent as well as additive factors for the presence of subclinical PAD in hypertensive patients with no known cardiovascular disease. Given our findings of an elevated prevalence of PAD in asymptomatic patients with an estimated creatinine clearance <60 ml/min per 1.73 m² and with albuminuria, we suggest that routine measurement of ABI be performed in these patients to identify individuals who are at very high risk and would benefit from the early implementation of appropriate therapeutic strategies.

Acknowledgments
This study was funded, in part, by a grant from Bristol Myers Squibb. The funding source had no involvement in the collection of the data or in their analyses and interpretation.

Members of the MERITO study group: P. Abizanda Soler (Albacete), A. Acosta Socorro (Las Palmas de Gran Canaria), O. Arámburu Bodas (Sevilla), C. Argüello Martin (Arriandad), A. Baamonde Carrasco (El Bierzo), J.M. Baucells Azcona (Barcelona), M. Beltrán Salvador (Castellón de la Plana), J.L. Bianchi Lláves (Algeciras), J.C. Blázquez Encinar (Alicante), P. Burillo Fuertes (Alcañiz), M. Cabre Roure (Mataró), J.M. Calbo Mayo (Albacete), E. Calderón Sandubete (Sevilla), L. Caminal Montero (Asturias), R. Cañizares Navarro (Alicante), F. Carrasco Miras (Huercal-Oliva), J. Cebollada del hoyo (Huesca), J.M. Cepeda Rodrigo (Orihuela), F. Civeira Murillo (Zaragoza), L. Comas Montgall (Vic), P. Conte Gutiérrez (Madrid), A. Costa Campooamor (Cáceres), J.I. Cuende Melero (Palencia), A. de la Peña Fernández (Palma de Mallorca), J. del Valle Gutiérrez (Madrid), F. Diosdado Fernández (Jerez de la Frontera), D. Liz Loiz Martinez (A Coruña), C. Dueñas Gutiérrez (Burgos), O. Fernández Álvarez (Ourense), I. Fernández Galante (Valadolid), F. Fernández Monras (Barcelona), J. Fernández Pardo (Murcia), J.L. Fernández Reyes (Jaén). J. Ferrando Vela (Zaragoza), E.M. Ferreire Pasos (Segovia), P. Férez Moreno (Elda), M.J. Forner Giner (Valencia), F. Fuentes Lopez (Córdoba), J.D. García Díaz (Alcalá de Henares), I. García Polo (Madrid), V. Giner Galván (Valencia), P. González Blanco (Don Benito), J.J. González Igal (Barbastro), E. González Sarmiento (Valladolid), J.L. Griera Borrás (Sevilla), A. Grilo Reina (Sevilla), J.I. Hernández Hernández (Santander), P. Horcajo Aranda (Guadalajara), E. Iranzo Gómez (Valencia), M. Jiménez Pascual (Murcia), J. Lapaza Andueza (San Sebastián), J.J. Linares Linares (Granada), E. Llarges Rocabruna (Granollers), F. López Fernández (Jarrio), E. Luna Heredia (Móstoles), G. Luna Rodrigo (Salamanca), F. Luque Ruiz (Jaén), A. Mangas Rojas (Cádiz), J. Maraver Delgado (Jerez de la Frontera), J.M. Marco Lattur (Castellón), L. Mateos Polo (Salamanca), M. Mauri Pont (Terrassa), J.D. Mediavilla García (Granada), M. Monreal Bosch (Barcelona), F. Montaner Batlle (Martorell), R. Monte Secade (Lugo), M. Montero Perez-Barquero (Córdoba), J. Montes Santiago (Lugo), J. Moreno Palomares (Segovia), J.L. Mulero Condé (Murcia), M. Muñoz Rodríguez (León), A.I. Muñoz Ruiz (Talavera), I. Otero Mayo (Elche), G. Penades Cervera (Alicante), L. Pérez Alonso (Madrid), A.I. Pérez Caballero (Pozoblanco), A. Pérez del Molino Castellanos (Torrelavega), N. Plana Gil (Reus), A. Pose Reino (Santiago de Compostela), G. Ramirez Olivencia (Madrid), R. Redondo Fernández (Madrid), A. Ribera Gallego (Vigo), M.A. Rico Corral (Sevilla), E. Rodilla Salas (Segunto), M. Rodríguez Gaspar (Las Palmas de Gran Canarias), P. Román Sánchez (Requena), E. Rovira Daudí (Valencia), M. Ruiz Climente (Cuenca), D. Sánchez Fuentes (Ávila), H. Sánchez Huelva (Sevilla), A. Sánchez Purificación (Fuenlabrada), M.V. Sánchez Simonet (Málaga), J.L. Sanpedro Villasanz (Jaén), F. Sena Ferrer (Tortosa), M. Tasiás Pittarch (Valencia), S. Tenes Rodrigo (Castellón de la Plana), I. Tinoco Bernal (Cádiz), R. Tirado Miranda (Cabra), I. Trouillhet Manso (Sanlúcar de Barrameda), M. Ulla Anes (Lanzarote), P. Valdivieso Felices (Málaga), J.M. Varela Aguilar (Sevilla), J.A. Vargas Núñez (Madrid), F. Vega Rollán (El Bierzo), J.M. Vega Vázquez (Sevilla), D. Vinuesa García (Granada), and M.A. Zarraga Fernández (Avilés).

References
2. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG: Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to con-


5. O’Hare AM, Vittinghoff E, Hsia J, Shlipak MG: Renal insufficiency and the risk of lower extremity peripheral arterial disease: Results from the Heart and Estrogen/Progestin Replacement Study (HERS). J Am Soc Nephrol 15: 1046–1051, 2004


