Interaction Between Renal Function and Microalbuminuria for Cardiovascular Risk in Hypertension

The Nordic Diltiazem Study

Patrik Färbom, Björn Wahlstrand, Peter Almgren, Stanko Skrtic, Jan Lanke, Lars Weiss, Sverre Kjeldsen, Thomas Hedner, Olle Melander

Abstract—We investigated whether renal function and microalbuminuria are independent predictors and whether any interaction exists between them, regarding future cardiovascular disease in hypertensive patients (n=10 881) followed for 4.5 years. The primary end points (PEs) were fatal and nonfatal myocardial infarction and stroke and other cardiovascular deaths. Creatinine and glomerular filtration rate (GFR), estimated using the formulas of the Modification of Diet in Renal Disease study group and Cockroft and Gault and in a subsample (n=4929) of microalbuminuria and interaction terms of microalbuminuria and renal function, were related to the risk of the PE using Cox proportional hazards model after full adjustment. Increased creatinine (P<0.001), decreased GFR from Cockroft and Gault (P=0.001), and decreased GFR from the Modification of Diet in Renal Disease study group (P=0.001) were all independent risk factors for the PE. Stepwise exclusion of patients with the poorest renal function excluded the possibility that the relationship between decreasing renal function and the PE was driven only by patients with severely impaired renal function. Microalbuminuria and all 3 of the indices of renal function predicted the PE independent of each other. There was a significant interaction between microalbuminuria and GFR from Cockroft and Gault (P=0.040) in prediction of the PE. Both renal function and microalbuminuria add independent prognostic information regarding cardiovascular risk in hypertensive patients. The cardiovascular risk associated with microalbuminuria increases with a decline in GFR, as demonstrated by a significant interaction between microalbuminuria and GFR from Cockroft and Gault. Because estimation of the total cardiovascular risk is essential for the aggressiveness of risk factor interventions, simultaneous inclusion of GFR and microalbuminuria in global cardiovascular risk assessment is essential. (Hypertension. 2008;52:1-8.)

Key Words: hypertension □ microalbuminuria □ creatinine □ glomerular filtration rate □ interaction □ cardiovascular risk

Hypertension is the most common of the classical cardiovascular risk factors, with a prevalence of 27% in the adult Swedish population.1 The beneficial effect of antihypertensive treatment is well documented with regard to primary and secondary prevention of cardiovascular disease (CVD). Based on solid scientific evidence, there is now international consensus that the level of blood pressure at which pharmacological antihypertensive treatment is to be initiated, as well as the level of the target blood pressure, should take the individual total cardiovascular risk into account.2,3 This has increased the need for an introduction of new and easy-to-use cardiovascular risk markers that add prognostic information in the cardiovascular risk assessment of hypertensive patients.

The presence of microalbuminuria (MA) is well established as a cardiovascular risk factor in diabetes mellitus, and today there is evidence that MA predicts CVD also in hypertensive patients without diabetes.4–6 As for MA, reduced glomerular filtration rate (GFR) has been shown to also predict CVD in nondiabetic patients with hypertension.7–9 There are different methods for estimating GFR, such as plasma creatinine and the use of formulas/equations of estimated GFR according to Cockroft and Gault (GFR_{Cockroft}) and the Modifications of Diet in Renal Disease study group (GFR_{MDRD}).10

It is not yet known which of these estimates of renal function is to be preferred in cardiovascular risk assessment of hypertensive patients and whether the relationship between

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the decline in renal function and the risk of CVD is linear or not. Furthermore, the presence of MA and the decline in GFR both indicate glomerular dysfunction, and they are tightly correlated with classical cardiovascular risk factors; however, it is yet unclear what the relationships are between MA and GFR in relation to future CVD in hypertensive patients. The aims of this study were to assess the following in a large cohort of hypertensive patients: (1) whether renal function (estimated with creatinine, GFR\textsubscript{CRG}, and GFR\textsubscript{MDRD}) predicts CVD after full adjustment for classical cardiovascular risk factors and to exclude that such a relationship, if any, is driven by patients with markedly reduced renal function; (2) whether MA predicts CVD and whether MA and renal function predict CVD independently of each other, after full adjustment for classical cardiovascular risk factors; and (3) whether renal function and MA interact regarding prediction of CVD in hypertensive patients.

Methods

Design and Patients

The design and main results of the Nordic Diltiazem Study have been described previously in detail.\textsuperscript{11} In brief, the Nordic Diltiazem Study included 10,881 Swedish and Norwegian hypertensive patients who were randomly assigned to receive either diltiazem-based (n = 5410) or diuretic- and/or \beta-blocker–based (n = 5471) antihypertensive treatment to compare the 2 treatment regimens with regard to the development of cardiovascular events during a mean follow-up time of 4.5 years (Tables 1 and 2). Hypertension was defined as a diastolic blood pressure of $\geq 100$ mm Hg on $\geq 2$ occasions. The combined primary end points (PEs) in the Nordic Diltiazem Study were fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular deaths.\textsuperscript{11} All of the PEs were assessed by an independent end point committee, according to prespecified criteria. PE occurred in 403 patients in the diltiazem group and in 400 patients in the diuretic and \beta-blocker group. There was no difference in the incidence of PE between the 2 groups ($P = 0.97$).\textsuperscript{11} Of the total number of PEs (n = 803), 434 were myocardial infarction, 335 were stroke, and 34 were other cardiovascular deaths.

The present substudy was performed in 2 parts. First, all of the patients were studied regarding the relationship between renal function and PE (n = 10,881). Second, the subset of the patients who had given urine samples for MA testing, all from the Swedish cohort, were studied regarding the relationships among MA, renal function, and PE (n = 4929; Tables 1 and 2).

Determination of renal function was based on analysis of plasma creatinine and on estimated GFR\textsubscript{MDRD} and GFR\textsubscript{CRG}. The formula for GFR\textsubscript{MDRD} was (mL/min per 1.73 m$^2$)=$\frac{186.3 \times \text{creatinine} \times \text{age} \times 0.203}{\text{weight} \times \text{height}^2}$, where F is 0.8 if male and F is 0.85 if female. The formula was for body surface area (BSA) (m$^2$)=$\sqrt{\frac{\text{weight} \times \text{height}}{10}}$. MA was tested in morning urine samples, using the MICRAL test (Roche Diagnostics), an immunologic semiquantitative dipstick test.\textsuperscript{12} A value of $\geq 20$ µg/L defined the presence of MA in the absence of concomitant factors known to cause temporary proteinuria, such as urinary tract infection, excessive exercise, and menstruation.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Patients in the MA Study With Clinical Data According to the Presence of MA or Not (n = 4929)</th>
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</thead>
<tbody>
<tr>
<td>Baseline Variables</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Sex, % male</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<tr>
<td>Serum cholesterol, mmol/L</td>
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<tr>
<td>Blood glucose, mmol/L</td>
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<tr>
<td>Plasma creatinine, µmol/L</td>
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<tr>
<td>GFR\textsubscript{MDRD}, mL/min per 1.73 m$^2$</td>
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<tr>
<td>GFR\textsubscript{CRG}, mL/min per 1.73 m$^2$</td>
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<tr>
<td>Smoking, %</td>
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<tr>
<td>Previous cardiovascular disease, %</td>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>MA, %</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
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</tbody>
</table>

MA+ indicates the presence of MA; MA−, absence of MA; NA, not applicable. Continuous variables are shown as means±SDs.
The definition of diabetes was based on repeated (≥2) fasting blood glucose values of ≥6.7 mmol/L or history of previous diabetes diagnosis and/or antidiabetic treatment. Smokers were defined by current smoking. Previous CVD was defined by a standardized report form, checked by the local study physician, where patients reported whether they had had acute myocardial infarction or stroke, verified and diagnosed by a physician, before the Nordic Diltiazem Study.

Statistics
The Cox proportional hazards model was used to calculate relative risks for PE in crude and adjusted models. The covariates included in the adjusted models were as follows: previous CVD (myocardial infarction and/or stroke), age, sex, systolic blood pressure, smoking, diabetes, serum cholesterol, and treatment allocation (diltiazem-versus β-blocker/diuretic-based treatment). Covariates were included in the model if the P value was <0.10. In contrast to MA and the other continuous indices of renal function, GFRMDRD did not fulfill the assumption of linearity in the Cox proportional hazards model (P=0.2). Hence, GFRMDRD was instead analyzed as a dichotomized variable (at 40 mL/min per 1.73 m²). Analyses of interaction between the effects of GFR (G), defined GFRMDRD, and an indicator of MA (M) (1=present and 0=not present) on time to PE were performed using the following Cox proportional hazards model: \( h(t) = h_0(t)\exp(\beta_M+N + \beta_{GM}\times G) \), \( h_0(t) \) being the hazard function and \( h_0(t) \) the baseline hazard function, with \( \beta_M \) and \( \beta_{GM} \) measuring the main effects and \( \beta_1 \) measuring the interaction. If there is an interaction (\( \beta_1 \neq 0 \)), the hazard ratio (HR) for those with MA versus those without will be \( \text{HR} = \exp(\beta_M+N + \beta_{GM}\times G) \). Thus, the HR will be a function of GFR, as visualized in Figure 5.

Statistical calculations were performed using the Stata software version 8.0 (Stata Corp). Tests were considered significant if the 2-sided P value was <0.05.

Results
Renal Function in Prediction of CVD
The relative risks of PE associated with increased baseline creatinine and decreased GFRCRG (analyzed as continuous variables) and GFRMDRD (dichotomized at 40 mL/min per 1.73 m²) are shown in Table 3. In crude models, these indices of renal function were highly significant predictors of PE. All of the classical risk factors (previous CVD, diabetes, age, sex, smoking, systolic blood pressure, and cholesterol) were independent predictors of PE (data not shown). After adjustment for these established cardiovascular risk factors and treatment allocation, each of the 3 markers of renal function (creatinine, GFRCRG, and GFRMDRD) significantly predicted PE (Table 3). The relationship between renal function and PE was evident also when diabetic patients were excluded (Table 3). The numbers of PEs that occurred per 1000 patient-years in our study population when they were was categorized into groups according to various degrees of renal function show that the relationship between decline in renal function and increased risk of CVD starts well within the reference range of serum creatinine and GFRCRG, whereas this is not the case for GFRMDRD (Figures 1 to 3). It should be emphasized that these incidence rates are not standardized for differences in classical risk factors between the strata of renal function.

To exclude the possibility that the relationship between renal function and PE was driven only by patients with severely impaired renal function, we performed a stepwise exclusion of groups of patients with the poorest renal function, and comparisons were made between patients with various ranges of moderately reduced renal function and patients having renal function better than this range. The results from these analyses showed that we could exclude that the relationship among the 3 continuous indices of renal function and CVD risk was driven solely by patients with severely impaired renal function. The mildest ranges of impairment in renal function that significantly (P≤0.05) predicted PE after full adjustment for classical cardiovascular risk factors were for creatinine 90 to 111 μmol/L versus <90 μmol/L, for GFRCRG, 52 to 80 mL/min per 1.73 m² body surface versus >80 mL/min per 1.73 m² body surface, and for GFRMDRD, 57 to 70 mL/min per 1.73 m² body surface versus >70 mL/min per 1.73 m² body surface.

MA and Prediction of CVD in Subsample With MA Testing Available
In both the crude and fully adjusted models, the presence of MA significantly predicted future risk of PE. This was also true when nondiabetic patients (n=4929) were analyzed separately (Table 4). The proportion of patients free from PE as a function of follow-up time in patients with and without MA is shown in Figure 4 (note, only crude analysis).

Renal Function and MA in Prediction of CVD
In both a crude model and after full adjustment for classical cardiovascular risk factors, MA and renal function predicted PE independently of each other (Table 5). The risk associated with MA corresponded approximately with the risk associated with a decline of 50 mL/min per 1.73 m² in GFR. There was a significant interaction between MA and GFRCRG regarding future CVD (Table 5 and Figure 5). As shown in Figure 5, the relative risk of CVD in hypertensive patients

<table>
<thead>
<tr>
<th>Renal Function Parameter</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>All patients (n=10 881; No. of PEs=803)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine crude*</td>
<td>1.10</td>
<td>1.08 to 1.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine adjusted*</td>
<td>1.05</td>
<td>1.02 to 1.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFRCRG crude†</td>
<td>1.13</td>
<td>1.10 to 1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFRCRG adjusted†</td>
<td>1.06</td>
<td>1.02 to 1.10</td>
<td>0.001</td>
</tr>
<tr>
<td>GFRMDRD crude‡</td>
<td>4.21</td>
<td>2.43 to 7.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFRMDRD adjusted‡</td>
<td>2.63</td>
<td>1.51 to 4.58</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Adjusted models include adjustment for age, sex, systolic blood pressure, smoking, diabetes, previous cardiovascular disease, cholesterol, and treatment allocation.

*Data are per 10-mmol/L increase.
†Data are per 10-mL/min per 1.73 m² decrease.
‡Data are GFRCRG expressed as a dichotomized variable with cutoff at 40 mL/min per 1.73 m² of body surface.

Table 3. Renal Function in Relation to Future Cardiovascular Events

FAßBOM ET AL GFR, MA, AND CARDIOVASCULAR DISEASE

3
with MA, relative to those without MA, increased steeply with decreasing GFR_{CRG}. Because GFR_{MDRD} did not meet the assumption of linearity in the Cox proportional hazards model, we did not include this index of renal function in interaction analyses. There was no significant interaction between creatinine and MA regarding CVD risk (Table 5). Although the presence of MA and decline in renal function were significantly associated with increased risk of stroke in both crude and fully adjusted models, they were only significant in crude models regarding the risk of myocardial infarction (data not shown).

**Discussion**

We show here in a large population of patients with quite severe hypertension (diastolic blood pressure $\geq$100 mm Hg), based on a prospective intervention trial, that slightly reduced renal function and presence of MA, respectively, predict a primary composite end point of fatal and nonfatal myocardial infarction and stroke and other cardiovascular deaths. These results cannot be generalized to the population at large; however, they are in agreement with previous prospective studies of hypertensive patients.\textsuperscript{5,13–16} Despite the fact that most of the classical risk factors for CVD, especially diabetes, are associated with the presence of MA and reduced renal function, we clearly show that MA and renal function, respectively, predict CVD independent of age, sex, smoking, previous CVD, systolic blood pressure, diabetes, and cholesterol level. Furthermore, we show that MA and reduced renal function, which both reflect glomerular dysfunction, predict CVD independently of each other. In addition, for the first time, it is shown that, despite their separate prognostic information, MA and GFR interact significantly in predicting CVD in hypertensive patients. Thus, the risk associated with having MA depends on GFR.

Our findings may have several clinical implications. Because the level of blood pressure at which pharmacological blood pressure–lowering therapy should be initiated, as well as the treatment target blood pressure level, depends on the total CVD risk, our data strongly support routine measurement of GFR and MA in all hypertensive patients to obtain a more accurate assessment of total CVD risk. Importantly, our data show that the measure of renal function and MA is

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**Figure 1.** Unadjusted incidence rates of the PE with increasing creatinine in steps of 10 $\mu$mol/L, events per 1000 patient-years ($n=10,881$, total number of PEs=803).

**Figure 2.** Unadjusted incidence rates of the PE with decreasing GFR_{CRG} in steps of 10 mL/min per 1.73 m$^2$, events per 1000 patient-years ($n=10,881$, total number of PEs=803).
informative regarding CVD prediction not only in hypertensive patients with diabetes, where routine measurement of the 2 markers is more established because of their prognostic value for diabetic nephropathy, but also in hypertensive patients who do not have diabetes. The interaction that we describe between GFR and MA shows a synergistic effect between the 2 on future risk of CVD, meaning that the risk of CVD associated with the presence of MA increases steeply with the decline in GFR (Figure 5). Thus, the biological mechanisms underlying each of the 2 phenotypes seem to amplify each other in the development of CVD. For example, as demonstrated by Figure 5, the relative risk of CVD associated with MA at a GFR_{CRG} of 125 mL/min per 1.73 m² increases to 2 at a GFR_{CRG} of 60 mL/min per 1.73 m² and to 3.5 at a GFR_{CRG} of 30 mL/min per 1.73 m². Because the effect of MA and reduced GFR on cardiovascular risk was independent of diabetes mellitus and because of the fact that type 2 diabetes today is recognized as a major cardiovascular risk factor by itself, the direct clinical consequences of our findings, ie, on how early and how aggressively blood pressure should be lowered in individual patients, are probably most important for nondiabetic hypertensive patients. Of note, the strengths of the increased relative risks for PE associated with the presence of MA and lower renal function were unchanged and remained highly significant when the covariate of diabetes was exchanged with fasting blood glucose.

It is well established that patients with severely impaired renal function and renal insufficiency have increased cardiovascular risk. One possible explanation behind our finding of a relationship between renal function, analyzed as a continuous variable, and CVD could potentially be that this relationship is solely driven by markedly increased CVD in a minor segment of our hypertensive population with severely impaired renal function. To explore this possibility, we plotted the crude incidence rates of CVD according to segments of successively decreasing renal function (Figures 1 to 3). These graphs show that, although there is a tendency of a steepening of the CVD relative risk at renal function expressed as GFR_{CRG} < 60 mL/min per 1.73 m² and serum creatinine > 110 μmol/L, the relationship between renal function and CVD risk seems to stretch all over the continuous range of GFR_{CRG} values.

![Figure 3.](attachment:image.png) Unadjusted incidence rates of the PE with decreasing GFR_{CRG} in steps of 10 mL/min per 1.73 m², events per 1000 patient-years (n=10 881, total number of PEs=803).

![Figure 4.](attachment:image.png) Kaplan-Meier failure estimates

**Table 4. Relative Risks for the PEs in Patients Having MA Among All of the Patients (n=10 881; No. of PEs=803) and in Nondiabetic Patients (n=10 155; No. of PEs=715)**

<table>
<thead>
<tr>
<th>Risk Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA in all patients, crude</td>
<td>1.77</td>
<td>1.41 to 2.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MA in all patients, adjusted*</td>
<td>1.35</td>
<td>1.06 to 1.71</td>
<td>0.014</td>
</tr>
<tr>
<td>MA in nondiabetic subjects, crude</td>
<td>1.67</td>
<td>1.29 to 2.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data were adjusted for age, sex, systolic blood pressure, previous cardiovascular disease, smoking and diabetes (cholesterol and treatment allocation were not significant [P>0.10] and, therefore, were not included in the model).

†Data were adjusted as above, but diabetes was not included.
The curve shows the relative risk for the PE (in patients with MA as compared with patients without MA) as a function of GFR-CRG, illustrating the interaction between MA and GFR-CRG.
early systemic atherosclerosis, also involving the kidney. However, it may well be that reduced renal function is a primary cause of atherosclerosis.

From a treatment perspective, blockade of the renin-angiotensin-aldosterone system, using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockade, has been shown to be more effective than other antihypertensive drugs in preventing MA,20,21 as well as the transition from MA to macroalbuminuria22 and decline in renal function in patients with established diabetic nephropathy.23,24 However, whether such a superior effect of renin-angiotensin-aldosterone system blockade in preventing kidney damages translates into a superior effect regarding CVD is still controversial. In terms of antihypertensive treatment, we can conclude that patients with modestly reduced renal function or MA and, in particular, those with the combination of the 2, should be treated at lower levels of blood pressure and have lower blood pressure treatment targets than if these risk markers are absent.

In conclusion, in patients with hypertension, GFR and MA both add independent prognostic information regarding cardiovascular risk. Importantly, the cardiovascular risk associated with MA increases with the decline in GFR as demonstrated by a significant interaction between MA and GFR. Because estimation of total cardiovascular risk is essential for how aggressively blood pressure and other cardiovascular risk factors should be treated, simultaneous inclusion of GFR and MA in global cardiovascular risk assessment is essential.

Perspectives

Because indications for treatment and target blood pressure in modern antihypertensive therapy are based on estimation of global CVD risk, novel, and easy-to-use CVD risk factors have become increasingly important. Our findings show that, not only are renal function and MA independent CVD risk factors, but they also interact on future CVD risk, meaning that the CVD risk associated with one of them (MA) depends on the level of the other one (GFR). Future goals related to our findings should be to test whether more exact measures of renal function, such as cystatin C, and glomerular permeability are even better predictors of CVD, with the ultimate goal being to develop novel pharmacological therapies targeted at these potentially basic etiologic factors of CVD.

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Disclosures

None.

References


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