Clinical Significance of Renal Function in Hypertensive Patients at High Risk

Results From the INSIGHT Trial

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Background: Increasing evidence suggests renal involvement in hypertension-related cardiovascular and cerebrovascular complications. To assess this role of renal function in more detail, we studied the evolution of renal function and the relationship of renal function with mortality and morbidity in the Intervention as a Goal in Hypertension Treatment (INSIGHT) study.

Methods: The INSIGHT study was a double-blind, randomized, multicenter trial in patients with hypertension and at least 1 additional cardiovascular risk factor. Treatment consisted of nifedipine gastrointestinal therapeutic system, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride). Primary outcome was a composite of cardiovascular death, myocardial infarction, heart failure, and stroke. Renal function was assessed by measuring creatinine clearance, serum creatinine level, and serum uric acid level and by the presence of proteinuria.

Results: Creatinine clearance fell more in nifedipine recipients than in hydrochlorothiazide-amiloride recipients. Renal insufficiency developed in 2% of nifedipine recipients and 5% of hydrochlorothiazide-amiloride recipients. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and 6% of patients with normal levels (odds ratio [OR] 2.89; 95% confidence interval [CI], 1.92-4.36; P <.001). Primary outcomes were more likely in patients with low creatinine clearance (<60 mL/min) than in those with higher clearances (9% vs 5%, respectively [OR, 1.51, 95%CI, 1.22-1.88; P <.001]).

Conclusions: Renal function is an important predictor of risk in hypertensive patients at high risk. Antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may better preserve renal function than would treatment with diuretics.

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Evidence is accumulating that the kidney contributes to the development of cardiac and cerebral complications. Recent data indicate that, besides microalbuminuria, serum creatinine level also acts as a marker of risk. Interestingly, the predictive power of serum creatinine is already demonstrable with relatively normal values. In hypertensive populations, relationships have been found between serum creatinine level and cardiovascular events, but in most of the studies either the type of treatment was not accounted for or patients were at relatively low risk. Consequently, only limited information is available regarding the effect of renal function on cardiovascular prognosis in patients who are already at high risk. We have addressed this question using the results from the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial. The INSIGHT trial was a large, prospective, double-blind, randomized, controlled trial that compared the effects of nifedipine gastrointestinal therapeutic system (GITS) with a diuretic combination (hydrochlorothiazide and amiloride hydrochloride) on cardiovascular outcome in hypertensive patients with additional cardiovascular risk factors. The main results of this trial have been described elsewhere. In the present study, we report on the evolution of renal function during treatment and on the post hoc analysis of the relationship between renal function at baseline and cardiovascular complications. As markers of renal function, serum creatinine, creatinine clearance, serum uric acid, and proteinuria were used.

METHODS

TRIAL DESIGN

Inclusion criteria for the INSIGHT trial were age 55 to 80 years, hypertension (blood pressure [BP]: ≥150 mm Hg systolic and ≥95 mm Hg...
diastolic, or \( \geq 160 \text{ mm Hg systolic regardless of diastolic BP} \), and at least 1 additional cardiovascular risk factor. The design of the trial has been described previously. Briefly, after 4 weeks of placebo treatment, during which baseline measurements of BP and laboratory values were obtained, patients from 8 countries in Western Europe and Israel were randomized to either treatment with nifedipine, 30 mg/d, or hydrochlorothiazide-amiloride (25 mg/d of hydrochlorothiazide and 2.5 mg/d of amiloride hydrochloride) (step 1). Patients whose BP fell by less than 20/10 mm Hg or remained higher than 140/90 mm Hg received 1 of 4 dose titration steps (steps 2-5): dose doubling of the randomized drug; addition of 25 mg/d of atenolol (or 5 mg/d of enalapril maleate if atenolol was contraindicated); dose doubling of the additional drug; and addition of any other antihypertensive drug except calcium channel blockers or diuretics. Renal function was never a contraindication to any of these drugs.

Blood pressure was always measured 3 times after a 5-minute rest, with a calibrated mercury sphygmomanometer. After dose titration, patients were seen 3 times a year for BP and heart rate assessment. Laboratory tests (including serum creatinine and serum uric acid measurements and urinalysis) were done during the titration phase and annually thereafter. The main marker of reduced renal function was a serum creatinine level higher than 1.5 mg/dL (\( \geq 133 \mu \text{mol/L} \)) in men or higher than 1.4 mg/dL (\( \geq 124 \mu \text{mol/L} \)) in women. Other markers included creatinine clearance below 60 mL/min (<1.00 mL/s) (as calculated with the Cockcroft and Gault formula), serum uric acid level of 7 mg/dL or higher (\( \geq 416 \mu \text{mol/L} \)), presence of proteinuria (defined as protein excretion \( \geq 0.5 \text{g/24h} \)) and any of these 4 measures.

The primary outcome of the trial was the composite end point of incidence of cardiovascular death, myocardial infarction, heart failure, and stroke. Secondary outcomes were all-cause mortality, death from a vascular cause, and death from a nonvascular cause, including transient ischemic attacks, angina, and renal failure. The latter was defined as a serum creatinine level of 2.94 mg/dL or higher (\( \geq 260 \mu \text{mol/L} \)) on 2 repeated measurements. All end points were validated from source documents by an independent critical events committee according to prespecified diagnostic criteria. The study complied with the principles of good clinical practice and the Declaration of Helsinki and was approved by the relevant ethics committees. All patients gave written informed consent.

**RESULTS**

Altogether, 6321 patients were included in the primary analysis of the INSIGHT trial. Baseline serum creatinine levels were missing in 4 patients (2 in each treatment group), leaving 6317 patients (2927 men and 3390 women) for analysis. Uric acid data were available for 6296 patients (2914 men and 3382 women) and data on protein excretion for all patients. Serum creatinine was elevated at baseline in 192 patients (3%), while creatinine clearance was below 60 mL/min (1.00 mL/s) in 1839 patients (29%). Increased serum uric acid level was present in 934 patients (15%) and proteinuria was observed in 170 patients (3%). In 2550 patients (40%), at least 1 of the 4 markers of renal impairment was found.

Patients with increased serum creatinine level were slightly older, but the difference was not statistically significant. While the prevalence of increased serum creatinine concentrations or of reduced creatinine clearance increased with age, hyperuricemia and proteinuria were not related to age. As given in Table 1, demographic characteristics and risk factors were well balanced between the nifedipine and hydrochlorothiazide-amiloride treatment groups, irrespective of renal function. Patients with increased serum creatinine levels were more often men and smokers. In addition, they had a higher prevalence of diabetes mellitus, coronary heart disease, previous myocardial infarction, left ventricular hypertrophy or strain, peripheral vascular disease, and proteinuria. Essentially, the same results were obtained with the other markers of kidney function.

**EVOLUTION OF CREATININE CLEARANCE DURING TREATMENT**

Estimated creatinine clearance at baseline averaged \( 74 \pm 24 \text{ mL/min (1.24±0.40 mL/s) in the nifedipine group and 73} \pm 22 \text{ mL/min (1.22±0.37 mL/s) in the hydrochlorothiazide-amiloride group. During the trial it decreased in both groups to 72} \pm 24 \text{ mL/min (1.20±0.40 mL/s) and 68} \pm 22 \text{ mL/min (1.14±0.37 mL/s), respectively (Figure 1). The difference between the groups was statistically significant (P<.05) and independent from baseline renal function. Renal insufficiency occurred in 2% of patients receiving nifedipine and 5% of patients receiving the diuretic combination (P<.01).**

**RENAL FUNCTION AND CONTROL OF BP AND HEART RATE**

At baseline, patients with increased serum creatinine levels had significantly higher values for systolic and diastolic BP compared with those with normal serum creatinine levels (Table 2). At the end of the trial, systolic BP was still higher in the patients with increased serum creatinine levels, but the difference in diastolic BP was no longer statistically significant. When creatinine clearance was used to classify patients as those with normal or reduced renal function, systolic BP was again significantly higher in the latter at the time of randomization (Table 2). Although the fall in systolic BP was greater in patients with reduced creatinine clearance, systolic BP remained higher in this group at the end of the trial. The opposite was found for diastolic BP, which was lower both at the start and at the end of the trial in patients with reduced creatinine clearance, with no difference in the changes of diastolic BP.

Both systolic and diastolic BPs were slightly higher in patients with increased serum uric acid levels than in those with normal concentrations, but the changes in BP during treatment were similar. When patients with or without proteinuria were considered, systolic BP was significantly higher in the former, both at the start (180±18 vs
172 ± 15 mm Hg; *P < .001) and at the end of the trial (146 ± 16 vs 142 ± 16 mm Hg; **P < .001). The fall in systolic BP was also greater in patients with proteinuria (34 ± 19 vs 30 ± 18 mm Hg; *P < .01), but no differences in baseline and final measurements or change in diastolic BP were observed.

During treatment, heart rate fell both in patients with normal and reduced renal function. Changes were significantly greater in patients with elevated serum creatinine levels (*P < .02), probably because more of these patients progressed to the atenolol treatment step. However, no significant differences emerged when patients were divided on the basis of creatinine clearance, serum uric acid level, or proteinuria.

Although changes in BP were similar in nifedipine- and hydrochlorothiazide-amiloride–treated patients, in both groups more drugs were needed in the patients with renal impairment. Indeed, while 30% of patients with normal renal function used 2 drugs and 9% used 3 drugs, these figures were 35% and 19%, respectively, in the other group (*P < .001), with a similar proportion of patients using an angiotensin-converting enzyme inhibitor. Moreover, in patients with reduced renal function there was no difference in add-on medication between the 2 treatment groups.

**Figure 2** shows the proportions of patients who reached a BP of 140/90 mm Hg or below at the end of the titration phase. Both proteinuria and an elevated serum creatinine concentration significantly reduced responses, whereas increased serum uric acid level or a creatinine clearance below 60 mL/min (<1.00 mL/s) had no effect. When all patients with at least 1 positive marker of renal impairment were considered, response rates were similar in those with or without such an abnormality (70% in both groups).

**CARDIOVASCULAR COMPLICATIONS IN RELATION TO BASELINE RENAL FUNCTION**

**Figure 3** summarizes risk estimates for increased serum creatinine level, reduced creatinine clearance, and presence of proteinuria when patients with such abnormalities were compared with those without. Primary outcomes occurred in 15% of patients with increased serum creatinine levels and in 6% of those with normal creatinine levels. This difference was highly significant (OR, 2.89;
95% CI, 1.92-4.36;  0.001). A similar difference was observed in the incidence of secondary outcomes (12% vs 33%;  0.001). In the group with increased serum creatinine levels at baseline, the percentages of patients with primary outcomes did not differ between the nifedipine- and hydrochlorothiazide-amiloride–treated groups (16% and 14%, respectively;  0.001).  

Primary outcomes were noted in 5% of the patients with a creatinine clearance above 60 mL/min (>1.00 mL/s) and 8% of the others (OR, 1.51; 95% CI, 1.22-1.88;  0.001). Nonrenal secondary outcomes were also more frequent in patients with reduced creatinine clearance (17% vs 10%;  0.001). When primary end points in patients receiving randomized treatment were compared, the results were slightly in favor of the nifedipine group (relative risk, 0.93; 95% CI, 0.92-0.94;  0.001). The risks of a primary event associated with increased serum uric acid concentration or the presence of proteinuria (OR, 3.82; 95% CI, 2.56-5.70;  0.001) showed similar patterns to those for creatinine. With regard to proteinuria, the comparison of end points in patients receiving randomized treatment proved nifedipine to be slightly worse than hydrochlorothiazide-amiloride (relative risk, 1.16; 95% CI, 1.01-1.32;  0.001). When cardiovascular complications were analyzed in relation to any abnormality of renal function, the same findings emerged as for the individual markers of renal function.

Logistic regression analysis was performed to evaluate the effect of renal impairment on primary outcome with adjustments for various other risk factors. In the first model, we tested whether baseline serum creatinine is a risk factor for primary events, independent of proteinuria. This, indeed, appeared to be the case, with an OR of 2.47 (95% CI, 1.68-3.93;  0.001) for the presence of proteinuria and an OR of 1.38 (95% CI, 1.27-1.49;  0.001) for each 0.2-mg/dL (20-µmol/L) increase in se-
The first conclusion from the present study is that renal function is better preserved with the calcium channel blocker nifedipine GITS than with the diuretic combination hydrochlorothiazide-amiloride. Few studies have addressed the effects of long-term antihypertensive therapy on renal function in large cohorts of patients. In the European Working Party on High Blood Pressure in the Elderly trial, more than 800 patients received either placebo or a diuretic combination. Serum creatinine increased much more in the actively treated group than in the placebo group, and the risk of mild renal dysfunction was substantially higher in actively treated patients.² The increase in serum creatinine level correlated inversely with the fall in systolic BP, suggesting that reduced renal perfusion during diuretic treatment may underlie this phenomenon.³ The same may be true for our data because the greatest disparity between the groups occurred during the first year with no evidence for a sustained damaging effect thereafter. Other trials in hypertensive patients, mostly using diuretics or β-blockers, also showed that active treatment is associated with a greater increase in serum creatinine level than in placebo treatment.⁴,⁵ However, Voyaki et al⁶ provided evidence that, compared with placebo, treatment with the calcium channel blocker nilnidipine had a renoprotective effect in patients with isolated systolic hypertension. Thus, it may be that the type of medication plays an important role in determining renal outcome during antihypertensive treatment.

Three trials have compared the effect of a calcium channel blocker with alternative treatment on renal function in hypertensive patients. In the National Intervention Cooperative Study in Elderly Hypertensives, serum urea nitrogen level increased similarly in patients treated with nicardipine hydrochloride or a diuretic.⁷ However, abnormally elevated levels were less frequent in the nicardipine group. In the Treatment of Mild Hypertension Study, hypertensive patients were randomized to placebo or 1 of 5 active drugs, which included chlorthalidone and amloidipine maleate.⁸ Serum creatinine concentration increased with chlorthalidone use but was reduced by the other types of treatment. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which concluded that thiazide-type diuretics should be considered first-line therapy in patients with hypertension, also included a post hoc analysis of the changes in estimated glomerular filtration rate.¹⁴ In this trial, the incidence of end-stage renal disease was similar for the 3 treatment arms (chlorthalidone, lisinopril, and amlodipine), but estimated creatinine clearance was significantly better preserved with amlodipine than with chlorthalidone or lisinopril. The present findings thus corroborate the data from the literature that antihypertensive treatment with a long-acting dihydropyridine calcium channel blocker may protect renal function more effectively compared with diuretics. This was true not only when changes in creatinine clearance over time were considered but also when comparing the percentage of patients in both groups who had progressive renal deterioration. Taken together, it is fair to state that dihydropyridine calcium channel blockers confer prognostic benefit in terms of renal function. However, the mechanisms whereby this may be accomplished remain uncertain.

The second conclusion from our analysis is that in hypertensive patients at high risk, renal function is an important predictor of risk. In this respect, serum creatinine level, creatinine clearance, and urinary protein excretion may all be taken as markers of renal function. Although serum uric acid level also predicted outcome in univariate analysis, it turned out not to be an independent risk factor. The observation that serum creatinine level predicted cardiovascular morbidity and mortality fits well with data from other studies that showed an independent association between serum creatinine level and cardiovascular or overall prognosis. For example, the investigators from the Hypertension Optimal Treatment trial recently reported that in treated hypertensive patients, an elevation in serum creatinine level above 1.5 mg/dL (>132.6 µmol/L) or a reduction in estimated creatinine clearance below 60 mL/min (<1.00 mL/s) at baseline are powerful predictors of cardiovascular events and death.¹ Similar results have been described in patients with isolated systolic hypertension.²,⁵,¹⁶ Importantly, in hypertensive patients, creatinine levels that are still in the normal range may already predict outcome.³ The INSIGHT trial, however, is the first trial to examine the prognostic significance of renal function in hypertensive patients at high risk. In addition, the impact of renal function was demonstrated for the 2 treatment groups separately. Moreover, raised serum creatinine level and presence of pro-

Table 3. Odds Ratios for Several Mutually Adjusted Risk Factors*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.66 (1.31-2.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.59 (1.24-2.03)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2.38 (1.73-3.32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.57 (1.24-1.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.35 (1.52-3.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Creatinine level</td>
<td>1.23 (1.12-1.34)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Odds ratios refer to having or not having the risk factor for the categorical variables (yes/no) or the odds ratios for a 1-unit change (1 year for age and 0.2 mg/dL [20 µmol/L] for creatinine level).
teinuria were independently related to the incidence of complications.

The 3 measurements (creatinine level, serum uric acid level, and protein excretion) that we used in this study are not very sensitive or very specific markers of renal function. Moreover, they differ in strength regarding their prognostic power (greatest for proteinuria). Indeed, serum concentrations of creatinine and uric acid are also dependent on extrarenal factors, and urinary protein excretion may reflect the hydraulic consequences of elevated (intrarenal) pressure rather than true glomerular damage. Despite this caveat, all markers were powerful predictors of future complications, suggesting that glomerular damage is somehow associated with progression of atherosclerotic lesions. While several investigators believe that proteinuria or elevated serum creatinine level reflects generalized endothelial dysfunction or a prothrombotic state, others argue (on equally reasonable grounds) against these possibilities.17,18 Progression of atherosclerotic lesions in patients with reduced renal function has also been linked to enhanced oxidative stress and inflammation. Finally, increased levels of homocysteine, which is normally cleared by the kidney, may play a role. Clearly, more work has to be done before the pathophysiological connection between renal function and atherosclerotic complications can be elucidated.

One of the limitations of this study is that there may be unmeasured confounders that could have influenced our results. Although the observed relationships between renal function and cardiovascular prognosis remained statistically significant after adjustment for the other risk factors, we did not account for obesity or the newer risk factors, such as hyperhomocysteinemia, inflammation, or oxidative stress. In addition, one should bear in mind that our results apply only to hypertensive patients at high risk, treated with nifedipine GITS or hydrochlorothiazide-amiloride. Whether similar results apply to other types of treatment remains unknown. Likewise, the population we studied was predominantly white and, therefore, the implications for other races/ethnicities (eg, African Americans) are difficult to define. Finally, we have to be aware that selection bias may have occurred in the sense that patients with more advanced renal impairment were not recruited for clinical reasons. Despite these limitations, the present findings suggest that antihypertensive treatment based on a long-acting dihydropyridine calcium channel blocker (nifedipine GITS) may offer better renoprotection compared with therapy based on the diuretic combination hydrochlorothiazide-amiloride.

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